SYNTHETIC STUDIES TOWARDS SULPHUR AND NITROGEN CONTAINING NOVEL ANTIFUNGAL AGENTS

A THESIS

SUBMITTED TO THE

UNIVERSITY OF PUNE

FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

IN

CHEMISTRY

BY

Mr. SANGMESHWER P. SAWARGAVE

UNDER THE SUPERVISION OF

DR. H. B. BORATE

ORGANIC CHEMISTRY DIVISION
NATIONAL CHEMICAL LABORATORY
PUNE–411008, INDIA

DECEMBER–2011

SYNTHETIC STUDIES TOWARDS SULPHUR AND NITROGEN CONTAINING NOVEL ANTIFUNGAL AGENTS

A THESIS

SUBMITED FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

IN

CHEMISTRY

TO

UNIVERSITY OF PUNE

BY

SANGMESHWER P. SAWARGAVE

RESEARCH SUPERVISOR

DR. H. B. BORATE

ORGANIC CHEMISTRY DIVISION

NATIONAL CHEMICAL LABORATORY

DR. HOMI BHABHA ROAD

PUNE–411008 (INDIA)

DECEMBER–2011

Dedicated To MY Parents

राष्ट्रीय रासायनिक प्रयोगशाला
(वैज्ञानिक तथा औद्योगिक अनुसंधान परिषद)
डॉ. होमी भाभा मार्ग पुणे - 411 008. भारत
NATIONAL CHEMICAL LABORATORY
(Council of Scientific & Industrial Research)
Dr. Homi Bhabha Road, Pune - 411 008. India.

Dr. H. B. Borate
Scientist F
Division of Organic Chemistry

Telephone: +91-20-25902546
Telefax : +91-20-25902629
E mail: hb.borate@ncl.res.in

CERTIFICATE

This is to certify that the work presented in this thesis entitled **"SYNTHETIC STUDIES TOWARDS SULPHUR AND NITROGEN CONTAINING NOVEL ANTIFUNGAL AGENTS"** submitted by Mr. Sangmeshwer P. Sawargave, has been carried out by the candidate at National Chemical Laboratory, Pune, India, under my supervision. Such materials as obtained from other sources have been duly acknowledged in the thesis. This work is original and has not been submitted for any other degree or diploma of this or any other university.

DECEMBER 2011

Dr. H. B. BORATE

CANDIDATE'S DECLARATION

I hereby declare that the research work presented in the thesis entitled **"SYNTHETIC STUDIES TOWARDS SULPHUR AND NITROGEN CONTAINING NOVEL ANTIFUNGAL AGENTS"** was carried out by me at the National Chemical Laboratory, Pune, India, under the supervision of **Dr. H. B. BORATE**, Sci. F, Division of Organic Chemistry, National Chemical Laboratory, Pune, India and submitted for the degree of Doctor of Philosophy in Chemistry to the University of Pune. This work is original and has not been submitted in part or full by me for any other degree or diploma of this or any other university.

DECEMBER 2011 **SANGMESHWER P. SAWARGAVE**

Acknowledgements

As I complete my journey to the most cherished dream, it gives me immense pleasure and sense of satisfaction to record my sincere thanks to all those persons who have made this possible for me. I wish to express my heartfelt gratitude to my teacher and research supervisor ***Dr. H. B. Borate*** *at the first place for believing in my abilities and providing me an incredible opportunity to pursue my career as a Ph. D. student. I thank him for his excellent guidance, constant encouragement, sincere advice, understanding and unstinted support during all the time of my Ph.D. life. My interactions with him have improved my belief towards research as well as real life. I consider very fortunate for my association with him, which has given a decisive turn and a significant boost in my career.*

My feelings go beyond the limit of my language in acknowledging ***Dr. U. R. Kalkote****, who indeed patiently helped me in research as well as personal life with his expertise. I owe a special word of gratitude to* ***Dr. Subhash P. Chavan*** *for his time to time discussions, suggestions, help and encouragement.*

I am thankful to Dr. M. K. Gurjar, (Former Head, Organic Chemistry Division), Dr. Ganesh Pandey (Head, Organic Chemistry Division), Dr. Sivram, (Former Director, NCL) and Dr. Sourav Pal Director, NCL, for giving me the opportunity to carry out my research in NCL and providing all necessary infrastructure and facilities.

My thanks are due to ***Dr. D. Srinivas,*** *Dr. (Mrs.) S. P. Joshi, Dr. (Mrs.) R. D. Wakharkar,* ***Dr. (Mrs.) V. S. Pore****,* ***Dr. M. N. Deshmukh****, Dr. S. B. Mhaske, Dr. C. V. Ramana, Dr. Sonawane, Dr. Sawaikar, Dr. Gajbhiye, and all other scientists of NCL.*

I wish to express a great sense of gratitude for Prof. S. P. Pachaling, Prof. Peshawe and Dr. Jadhav (N. S. B. College, Nanded) for valuable guidance during my M. Sc. studies and Dr. Mote, Dr. Sankaye and Dr. Dhonde (M. G. M College, Ahmedpur) during my B. Sc. studies. I am greatly indebted to my school teachers specially Mr. Yerme sir for igniting the spark of science in me.

I would like to extend my thanks to Mrs. Kunte madam for recording HPLC, Dr. (Mrs.) Tambe for mass spectroscopy, Mr. Kalal K. and Dr. Borikar for recording GCMS, Dr. Rajmohanan, Jima, Dipak and Mr. Sathe for their timely help with NMR spectra recording and Dr. Rajesh Gonnade, Ms. Shobhana and Dr. Mrs. Puranik for the X-ray analysis. Help from microanalytical and IR facility is also acknowledged.

I thank Mr. Shambhuji, Organic Chemistry office staff (Mrs. Pooja Kulkarni and Mrs. Catherine), library staff, chemical stores and purchase staff and glass blowing section, NCL for their co-operation. I gratefully acknowledge the training and support extended by my senior colleagues ***Dr. Suleman****, Dr. Deepa Dumre, Dr. Santosh and Mr. Lahore during the tenure of my Ph.D. life.*

With much appreciation I would like to mention the crucial role of my charming junior labmates Pankaj, Suresh, Sanil, Nilesh, Mahesh, ***Dhiraj****, Gopi, Shankar, Pratap, Prem, Jayant, Rohit, Manisha,* ***Sandip****, Ananda, Jaydeep, Datta, Jaysingh, Ranjeet, Jyoti, Yogesh, Pramod and Milind for their cooperation, friendly attitude and cheerful atmosphere in lab. It has been a great learning experience for me through our group seminar.*

No words can suffice to acknowledge my prized friends ***Dr. Suleman****, Dr. Abasaheb and Dr. Manmath for helping me in various aspects of life as well as work. Also Dr. Attrimuni and Mr. Birajdar were always with me during my studies with helping hands. I am equally indebted to my friend Mr. Tuptewar for his support and encouragement. Help from my seniors friends Dr. Nagendra, Dr. Kotkar, Dr. Namdev, Dr. Jayprakash, Dr. Giri, Dr. Sharad, Dr. Haval, Dr. R. Srinivas, Dr. Shetty, and Dr. Lakshi is gratefully and sincerely appreciated.*

I am deeply indebted to M.Sc. friends Kiran, Mallikarjun, Pramod, Desai, Chandure, Pandurang and Pratap for their support and encouragement.

I feel fortunate to have a lot of friends in and out of NCL who have helped me at various stages of my work in NCL and I wish to thank Anand Haibindu, Ankush, Rahul, Pitamber, Kishor, Lalit, Nilesh, Prakash, Pradeeep, Kailash, Harshali,

Nagesh, Ravi, Sutar and Bharat …..… for providing a helping hand and cheerful moments which made my stay in Pune and NCL a memorable one.

I wish to thank my school friends Balaji, Mallikarjun, Amol, Ambrish, Sandesh and Younus. Also, I would like to thank Ratanamala, Kanta and Suman.

*Without understanding what I am doing, my beloved parents (**Akka** and **Tatya**) have supported me throughout my career with lots of patience. I am indeed very much grateful to them for constant love, care, support and encouragement which have been the main force and motivation so far and will continue to be so in the days to come. The best wishes of my parents-in-law (Mallikarjun Bhume and Chayya Bhume) helped me to complete this work. My special thanks to my uncles-in-law (Dr. Janardhan Bhume, Dr. Ramesh Bhume, Mr. Sachin Munde, Mr. Chapule and Mr. Banale) for their sacrifice, support and encouragement. I thank my sisters-in-law (Shubhada, Madhumita, Smita, and Dr. Amruta) for their love and blessings. I am indebted to **Dr. Shobha Bhume** for her support and encouragement.*

*I can't find the right words for one person whom I like most, my wife **Sucheta**. She has experienced all my ups and downs. Without her patience, love and endless support this thesis wouldn't have been written. My baby-**Gayatri (Gargi)** is really a blessing to us. I just can not imagine that she is almost seven months old now. To watch her growing up makes me happy everyday. Being a daddy is not only changing diapers, feeding, but to spend a lot of time together and have fun. I love them both very much.*

*Finally, my acknowledgement would not be completed without thanking the **God Ganesha**, for giving me the strength and the determination to overcome the hardship faced in my life.*

Sangmeshwer

CONTENTS

Chapter 2: Section II: Hybrid fluconazole analogues containing furanones as novel antifungal agents

Chapter 3: Section I: A short synthesis of 3,6-disubstituted N-2-thienyl/aryl-indoles

Chapter 3: Section II: One-step synthesis of 4-alkyl-3-aryl-2,6-dicyanoanilines and their use in the synthesis of highly functionalized 1,2,3,5,6,7- and 1,2,3,4,5,7-hexasubstituted indoles

GENERAL REMARKS

- ^{1}H NMR spectra were recorded on Bruker AC-200 MHz, Bruker AC-400 MHz and DRX–500 MHz spectrometer using tetramethylsilane (TMS) as an internal standard. Chemical shifts have been expressed in ppm units downfield from TMS.
- ^{13}C NMR spectra were recorded on Bruker AC-200, Bruker AC-400 and DRX-500 instruments operating at 50 MHz, 100 MHz and 125 MHz respectively.
- EI Mass spectra were recorded on Finngan MAT-1020 spectrometer at 70 *eV* using a direct inlet system and API QSTAR Pulsar Mass Spectrometer (Electrospray ionization, direct infusion method, solvents used were acetonitrile/methanol).
- The X-Ray crystal data were collected on *Bruker SMART APEX* CCD diffractometer using Mo K_{α} radiation with fine focus tube with 50 kV and 30 mA.
- Infrared spectra were scanned on Shimadzu IR 470 and Perkin-Elmer 683 or 1310 spectrometers with sodium chloride optics and measured in cm^{-1}.
- Optical rotations were measured with a JASCO DIP 370 digital polarimeter.
- All reactions were monitored by Thin Layer Chromatography (TLC) carried out on 0.25 mm E-Merck silica gel plates (60F-254) with UV light, I_2 or *p*-anisaldehyde in ethanol as developing agents.
- All dry reactions were carried out under nitrogen or argon atmosphere with dry, freshly distilled solvents under anhydrous conditions unless otherwise specified. Yields refer to chromatographically and spectroscopically homogeneous materials unless otherwise stated.
- All evaporations were carried out under reduced pressure on Buchi rotary evaporator below 45 °C unless otherwise specified.
- Silica gel (60-120, 100-200 or 230-400 mesh) was used for column chromatography.

ABBREVIATIONS

Ac	Acetyl
Ac_2O	Acetic anhydride
$AlCl_3$	Aluminium chloride
AIBN	2,2'-Azobisisobutyronitrile
aq	Aqueous
ATCC	American type culture collection
b	Broad
Bn	Benzyl
BnBr	Benzyl bromide
$CDCl_3$	Deuterated chloroform
cm	Centimeter
$(COCl)_2$	Oxalyl chloride
DCM	Dichloromethane
d	Doublet
dm	Decimeter
DMF	Dimethylformamide
DMSO	Dimethyl sulfoxide
DMSO-d_6	Deuterated dimethyl sulfoxide
EDC	Ethylene dichloride
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
EtOAc	Ethyl acetate
Et_3N	Triethyl amine
g	Grams
h	Hour/s
HPLC	High performance liquid chromatography
HCOOH	Formic acid
IR	Infrared
K_2CO_3	Potassium carbonate
L	Liter
m	Multiplet

M^+	Molecular ion
mg	Milligrams
MHz	Megahertz
min	Minutes
ml	Milliliter
mmol	Millimole
MP	Melting point
MTCC	Microbial type culture collection
n-BuLi	*n*-Butyllithium
Na_2SO_4	Sodium sulfate
$NaHCO_3$	Sodium bicarbonate
NaH	Sodium hydride
NaI	Sodium iodide
NBS	*N*-Bromosuccinimide
NMR	Nuclear Magnetic Resonance
NCPF	National Collection of Pathogenic Fungi
psi	Per square inch
P-TSA	para toluene sulfonic acid
q	Quartet
rt	Room temperature
RT	Retention time
R_f	Retention factor
s	Singlet
t	Triplet
TBAB	Tetrabutylammonium bromide
TBDMS	*tert*-Butyldimethylsilyl
TBTH	Tributyltin hydride
TEA	Triethyl amine
THF	Tetrahydrofuran
TLC	Thin layer chromatography

ABSTRACT

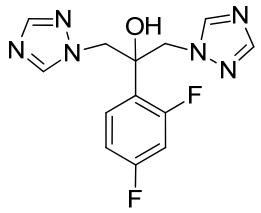
The thesis entitled **"Synthetic Studies Towards Sulphur and Nitrogen Containing Novel Antifungal Agents"** consists of three chapters. The first chapter deals with the synthesis of fluconazole analogues containing substituted 2-aminothiophenes and their bioevaluation. The second chapter is divided into two sections wherein the first section describes the synthesis of hybrid fluconazole analogues containing chalcone moieties and their bioevaluation while the second section deals with hybrid fluconazole analogues containing furanones as novel antifungal agents. The third chapter is divided into three sections wherein the first section deals with a short synthesis of 3,6-disubstituted N-2- thienyl/aryl-indoles, second section describes the multicomponent synthesis of 3,4-disubstituted-2,6 dicyanoanilines and a short synthesis of highly substituted and highly functionalized indoles while third section deals with the facile synthesis of α-chlorostilbenes mediated by a heterogeneous Si-Fe catalyst.

Chapter 1

Synthesis of fluconazole analogues containing substituted 2-aminothiophenes and their bioevaluation

Introduction

The frequency of life-threatening fungal infections has tremendously increased in recent years due to greater use of immunosuppressive drugs, prolonged use of broad-spectrum antibiotics, wide-spread use of indwelling catheters, and also in cancer and AIDS patients. The presently marketed antifungal drugs are either highly toxic (amphotericin B) or becoming ineffective due to appearance of drug resistant strains (flucytosine and azole antifungals).[1] Azole antifungals are strong inhibitors of lanosterol 14α-demethylase which is involved in the biosynthesis of ergosterol, a major component of fungal cell membrane[2] and fluconazole (**1**) is one of the best drugs of this class. It is an orally effective, potent, and safe triazole based antifungal drug, with favorable pharmacokinetic characteristics and low toxicity[3]. Also, it has excellent oral bioavailability and half-life period of 30 hours so it is used safely for treatment of systemic infections in cancer, leukemia, transplant and AIDS patients.



1

Figure 1. Fluconazole

Although fluconazole shows a very significant efficacy against *Candida albicans* and *C. neoformans*, it is not very effective against *Aspergillus niger* and *Aspergillus fumigatus*. In addition, extensive use of fluconazole has increased the number of fluconazole-resistant fungal strains. Therefore, due to toxicity concerns, limited spectrum, and the emergence of fungi resistant to currently available antifungal drugs, worldwide efforts to obtain analogues of fluconazole effective against resistant strains have resulted in synthesis of many novel azole antifungals[2-6].

Present work

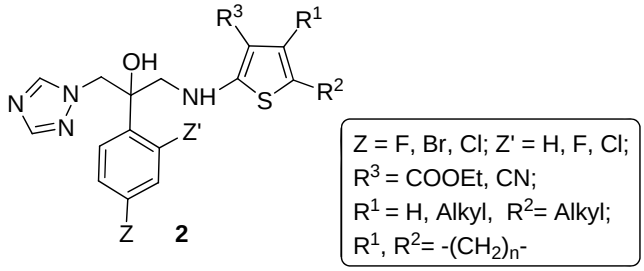
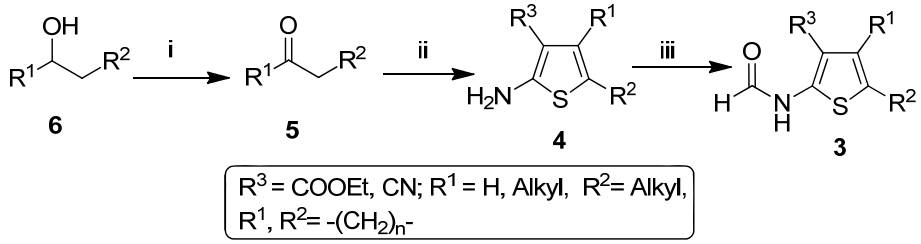


Figure 2. General structure of compounds synthesized in present work

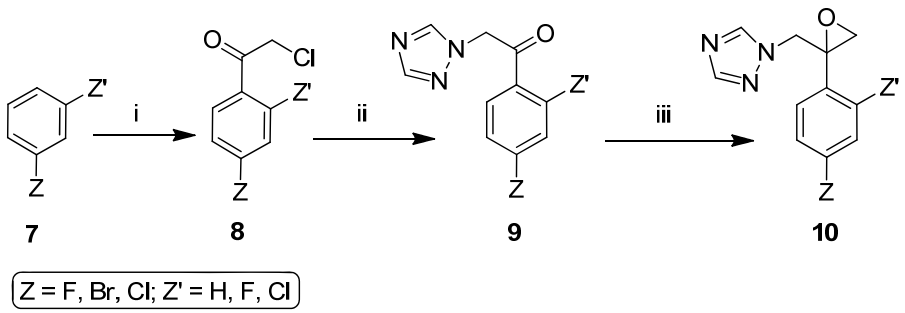
The structure-activity relationship study of fluconazole has revealed that the left half portion of the molecule is essential for the high antifungal activity and a number of analogues have been reported in literature, in an attempt to develop better antifungal agents wherein one of the triazole rings of fluconazole is replaced by other groups. Substituted aminothiophenes exhibit different biological activities like anticancer, herbicidal, antibacterial and antifungal activity[7]. In order to synthesize new triazole antifungal agents, we designed a series of novel compounds depicted by general formula **2** wherein efforts were directed towards replacement of triazole moiety with variously substituted aminothiophenes in order to make a number of compounds available for screening of antifungal activity.

The various substituted aminothiophenes were prepared by the synthetic route shown in Scheme 1.



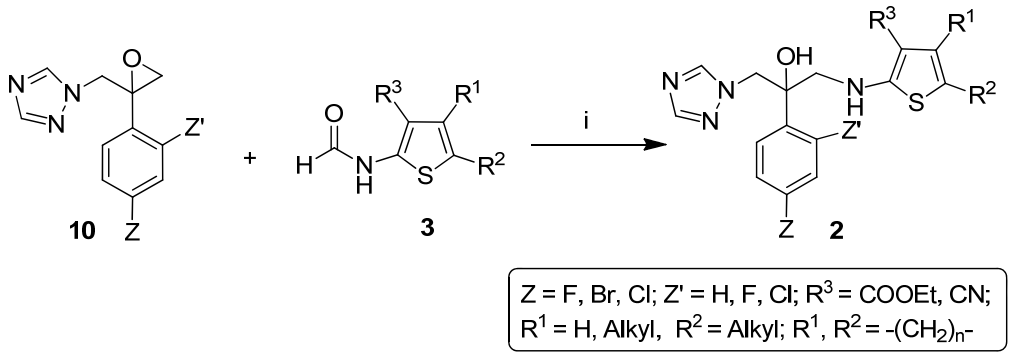
Scheme 1. Reagents and conditions: i) DMSO, $(COCl)_2$, Et_3N, DCM, -78 °C, 3-4 h, 82-90% ii) a) for R^3= COOEt: Ethyl cyanoacetate, sulphur, ethanol, morpholine, 80 °C, 10-15 h, 85-93% b) for R^3= CN: Malononitrile, sulphur, DMF, Et_3N, rt, 10-15 h, 40-75% iii) a) For R^3= COOEt: HCOOH, NH_4OAc, 120-140 °C, 5-7 h, 71-83% b) For R^3 = CN: HCOOH, NH_4OAc, rt, 2-4 h, 70-78%.

A substituted alcohol **6** was subjected for oxidation to get aldehyde/ketone **5** which was subjected to Gewald synthesis[8] to afford 4- and/or 5-substituted 2-aminothiophene-3-carboxylate/carbonitrile **4** which was then formylated to get the key intermediate, a substituted N-formylated aminothiophene **3**. Synthesis of the epoxide **10** was carried out by known method[9] as shown in Scheme 2. 1,3-Dihalobenzene was acylated with chloroacetyl chloride in presence of aluminium chloride. The acylated product **8** thus obtained was treated with 1*H*-1,2,4-triazole in presence of potassium carbonate to get ketone **9**. These triazole containing ketones **9** were converted into respective epoxides **10** by reaction with trimethylsulphoxonium iodide and aq. potassium hydroxide.



Scheme 2. Reagents and conditions: i) Chloroacetyl chloride, $AlCl_3$, DCM, 0 °C, 10-12 h, 80-90% ii) K_2CO_3, 1*H*-1,2,4-triazole, EtOAc, 80 °C, 10 h, 69-76% iii) Trimethylsulphoxonium iodide, aq. KOH, DCM, 12 h, 81-91%.

The N-formylated aminothiophenes **3** were then reacted with the epoxide **10** in presence of potassium carbonate and TBAB (tetrabutylammonium bromide) in ethyl acetate at refluxing temperature to afford the target molecules **2** as shown in Scheme 3.



Scheme 3. Reagents and conditions: i) K_2CO_3, TBAB, EtOAc, 80 °C, 12 h, 70-85%.

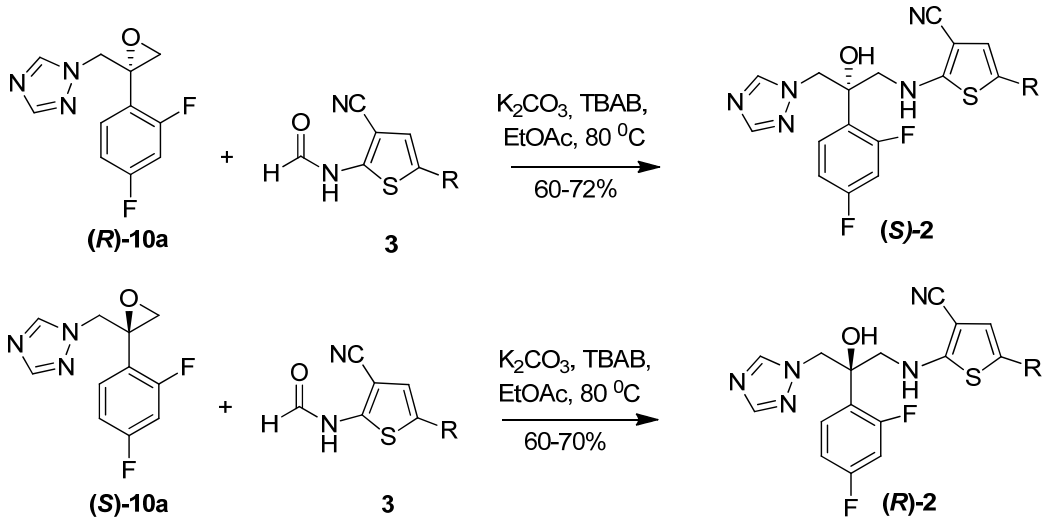
Using above synthetic strategy, a library of compounds **2** was synthesized and tested[10,11] for antifungal activity against various fungi including *Candida albicans* ATCC 24433, *Aspergillus niger* ATCC 16404 and *Fusarium proliferatum* ATCC 10052. Known antifungal agents, fluconazole and amphotericin B, were used as positive control. The activity data indicated following points regarding the structure-activity relationship of the compounds studied in the present section.

1. The compounds with 2-aminothiophene carbonitrile are more active than with 2-aminothiophene carboxylate.
2. In case of the compounds with aliphatic side chain at R^2, activity is observed with compounds having shorter side chains and reaches maximum for $R^2 = (CH_2)_3CH_3$ after which the activity decreases rapidly.
3. The compounds with substitutions at both R^1 and R^2 show less activity, when compared with the compounds with no substituents at R^1.
4. The compounds with R^1, R^2 forming a carbocyclic ring show very less activity when compared with the compounds with R^1 = H, R^2 = alkyl chain and activity vanishes in larger rings.

In continuation to the above work, we prepared the *R* and *S* enantiomers of compound **2** to examine the influence of absolute configuration on antifungal activity. The enantioselective preparation of this class of antifungal agents was achieved from chiral epoxides **(*R*)-10a** and **(*S*)-10a**. These two chiral epoxides were synthesized by known method[12].

The N-formylated aminothiophene carbonitriles **3** were then reacted with the chiral epoxides **(*R*)-10a** and **(*S*)-10a** in presence of potassium carbonate and TBAB (tetrabutyl

ammonium bromide) in ethyl acetate at refluxing temperature to afford the target molecules **(*S*)-2** and **(*R*)-2** as shown in Scheme 4.



Scheme 4. Synthesis of enantiomers **(*S*)-2** and **(*R*)-2**

We also accomplished direct optical resolution of compound **2** by chiral HPLC providing each enantiomer in high optical purity (>95% ee). These enantiopure compounds were evaluated for antifungal activity and it was found that the *S*-enantiomer of this class of antifungal agents has higher antifungal activity than the *R*-enantiomer.

References

1. (a) Johnson, E. M.; Warnock, D. W.; Liker, J.; Porter, S. R.; Scully, C. *J. Antimicrob. Chemother.* **1995**, *35*,103-114; (b) Rex, J. H.; Rinaldi, M. G.; Pfallar, M. A. *Antimicrob. Agents Chemother.* **1995**, *39*, 1-8.

2. Asai, K.; Tsuchimori, N.; Okonogi, K.; Prefect, J. R.; Gotoh, O.; Yoshida, Y. *Antimicrob. Agents Chemother*. **1999**, *43*, 1163-1169.

3. (a) Zervos, M.; Meunier, F. *Int. J. Antimicrob. Agents* **1993**, *3*, 147-170; (b) Kauffman, C. A.; Carver, P. L. *Drugs* **1997**, *53*, 539-549; (c) Andriole, V. T. *J. Antimicrob. Chemother.* **1999**, *44*, 151-162.

4. (a) Richardson, M. D. *J. Antimicrob. Chemother.* **1991**, *28*, 1-11; (b) Ablordeppy, S. Y.; Fan, P.; Ablordeppy, J. H.; Mardenborough, L. *Curr. Med. Chem.* ***1999***, *6, 1151-1196*; (c) Fridkin, S. K.; Jarvos, W. R. *Clin. Microbiol. Rev.* **1996**, *9*, 499-511; (d) Larocco, M.

T.; Burgert, S. J. *Clin. Microbiol. Rev.* **1997**, *10*, 277-297; (e) *Patel, R.; Paya, C. V. Clin. Microbiol. Rev.* **1997**, *10*, 86-124.

5. (a) Bartroli, J.; Turmo, E.; Alguero, M.; Boncompte, E.; Vericat, M. L.; Garcia- Rafanell, J.; Forn, J. *J. Med. Chem.* **1995**, 38, 3918-3932 and references cited therein; (b) Bartroli, J.; Turmo, E.; Alguero, M.; Boncompte, E.; Vericat, M. L.; Conte, L.; Ramis, J.; Merlos, M.; Garcia-Rafanell, J.; Forn, J. *J. Med. Chem.* **1998**, 41, 1855-1868 and references cited therein; (c) Bartroli, J.; Turmo, E.; Anguita, M. USP 5807854, **1998**; (d) Heravi, M. M.; Motamedi, R. *Phosphorus, Sulphur and Silicon* **2004**, 179, 2329-2334; (e) Upadhayaya, R. S.; Sinha, N.; Jain, S.; Kishore, N.; Chandra, R.; Arora, S. K. *Bioorg. Med. Chem.* **2004**, 12, 2225-2238.

6. (a) Dickinson, R. P.; Bell, A. S.; Hitchcock, C. A.; Narayanaswami, S.; Ray, S. J.; Richardson, K.; Troke, P. F. *Bioorg. Med. Chem. Lett.* **1996**, 6, 2031-2036; (b) Herbrecht, R. *Expert Review of Anti-Infective Therapy* **2004**, 2, 485-497.

7. (a) Kazutaka, N.; Itaru, T.; Keigo, T.; Toru, H.; Satoshi, I.; Norio, M.; Shinya, A.; Norihiro, U.; Mamiko, M.; Naoaki, W.; Makoto, A.; Kentaro, Y.; Katsura, H. *Bioorg. Med. Chem. Lett.* **2010**, *20,* 4624-4626; (b) Pillai, A.; Rathod, P.; Xavier, F.; Vasu, K.; Padh, H.; Sudarsanam, V. *Bioorg. Med. Chem.* **2004**, *12,* 4667-4671.

8. (a) Gewald, K. *Chem. Ber.* **1965**, 98, 3571-3577; (b) Gewald, K.; Scmnke, E.; Bottcher, H. *Chem. Ber.* **1966**, 99, 94-100.

9. (a) Mo, A.; Zhang, H.; Pan, H. CN 1995-111510, **1995**; CA 131:228724; (b) Antoni, S.; Marcial, M.; Roser, P. *ARKIVOC* **2007**, *(iv)*, 234-250.

10. CLSI: Reference method for broth dilution antifungal susceptibility testing of yeasts; Approved standard, second edition M27-A2, **2002**.

11. CLSI: Reference method for broth dilution antifungal susceptibility testing of filamentous fungi; Approved standard M38-A, **2002**.

12. (a) Saksena, A. K.; Girijavallabhan, V. M.; Lovey, R. G.; Pike, R. E.; Desai, J. A.; Ganguly, A. K.; Hare, R. S.; Loebenberg, D.; Cacciapuoti, A.; Parmegiani, R. M. *Bioorg. Med. Chem. Lett.* **1994**, *16*, 2023-2028; (b) Murakami, K.; Mochizuki, H. Eur. Pat. Appl. EP0472392A2, **1991**.

Chapter 2: Section-I

Synthesis of hybrid fluconazole analogues containing chalcone moieties and their bioevaluation

Introduction

The combination drug therapy is necessary in many cases because a single drug is not always able to cure the illness. The principle of combination drug therapy can be achieved by either using concomitant administration of two or more single active drugs or by drugs in which the single active agents are combined in one molecule, i.e. hybrid molecules and there are some reports describing the incorporation of pharmacophores of two drugs in a single molecule with the intention of exerting dual drug action[1]. For example, one of the hybrid parts may be incorporated to counterbalance the known side effects associated with the other hybrid part, or to amplify its effects through action on another biological target. Encouraging examples of molecules like **1-3** with potential as drugs in case of systemic heart disease, malaria, cancer, fungal infections *etc* were recently published in the literature[2-4] and the concept of "hybrid drugs" has been gaining more popularity in medicine as a part of efforts to develop drugs with more activity or less toxicity.

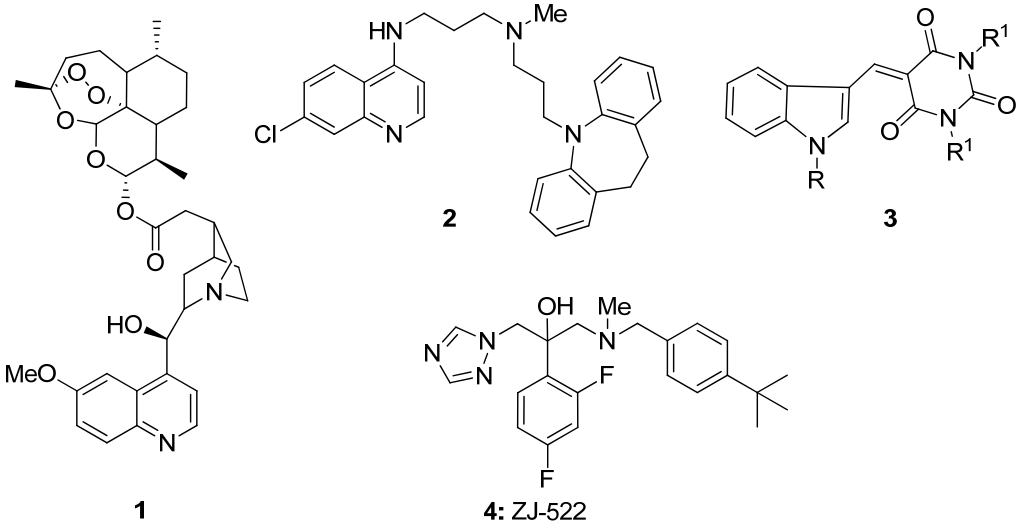


Figure 1. Structures of hybrid molecules

Yuan-Ying[5] reported the synthesis of antifungal hybrid molecule ZJ-522 (**4)** restructured from fluconazole and butenafine wherein the hybrid compound **4** was found to

be 50-fold more potent than the fluconazole itself. The use of hybrid drugs shows some advantages compared with a cocktail of drugs, including a lower risk of drug-drug interactions, improved compliance by the patient, and a more predictable pharmacokinetic profile. During the work presented in this chapter, efforts were made to synthesize hybrid fluconazole analogues containing chalcone moieties depicted by general formulae **5** and **6** as shown in Figure 2.

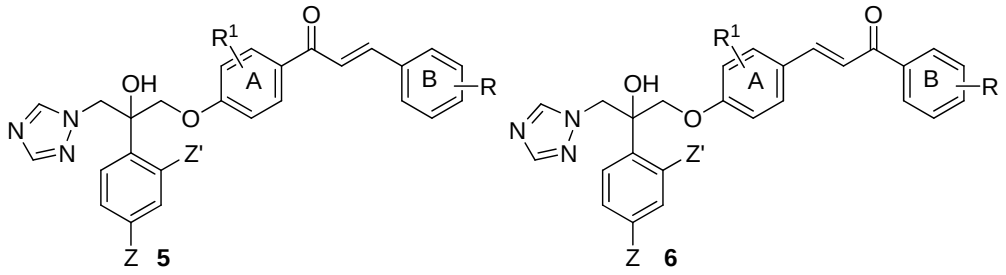
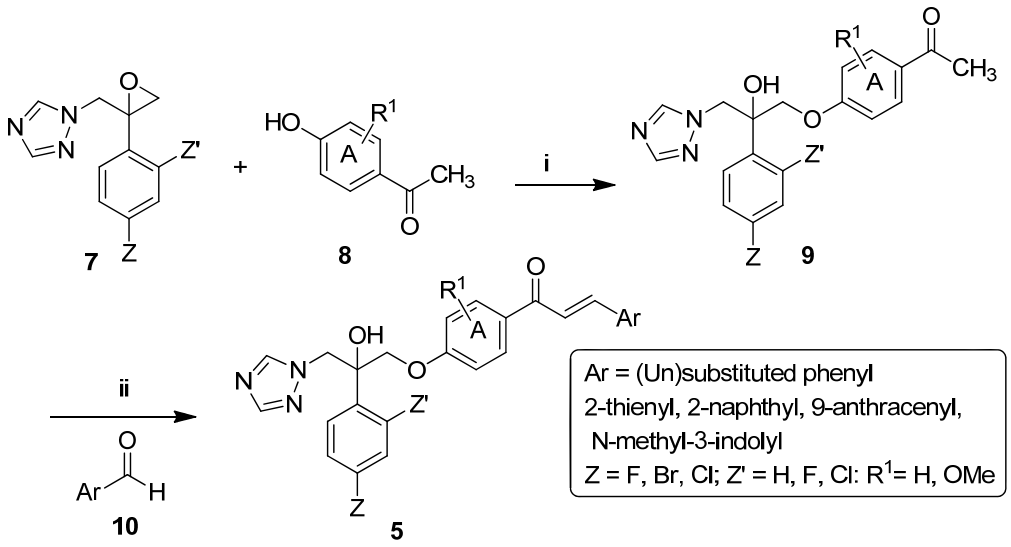


Figure 2. Hybrid fluconazole analogues **5** and **6** containing chalcone moieties

Present work

Fluconazole inhibits the fungal enzyme lanosterol 14 α-demethylase, thereby blocking the biosynthesis of ergosterol, an essential component of fungal cell membranes.[6] Chalcones have been shown to inhibit the growth of various fungi and yeasts, including representatives of the *Candida* species[7]. It is known that the mode of the antifungal action of chalcones relates to inhibition of the fungal cell wall[8]. The new hybrid antifungal agents **5** and **6** (Figure 2) restructured from fluconazole and substituted chalcones were designed and synthesized. It was thought that these molecules would be an inhibitor of both fungal enzyme lanosterol 14α-demethylase and the fungal cell wall, and have antifungal activity like fluconazole and chalcones.

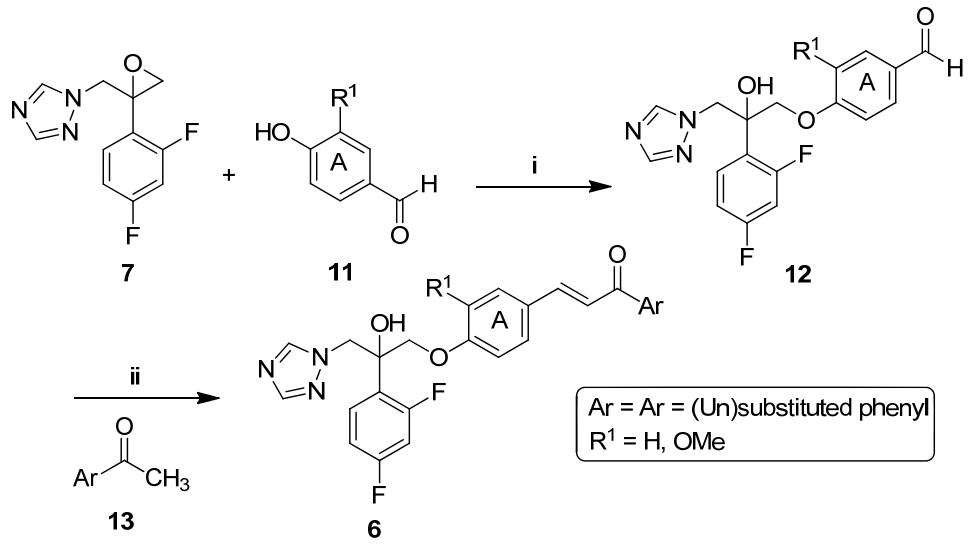
Syntheses of the hybrid molecules **5** were carried out *via* the route shown in Scheme 1.



Scheme 1. Reagents and conditions: i) K_2CO_3, TBAB, EtOAc, 80 °C, 12 h, 80-86 % ii) 10% NaOH, MeOH, rt, 12-20 h, 70-85%.

The 4-hydroxy acetophenone **8** was reacted with the epoxide **7** in presence of potassium carbonate in ethyl acetate at refluxing temperature for 10-12 h to give the intermediate compound **9** in good yields, which on Claisen–Schmidt condensation[10] using 10% NaOH in methanol with various substituted aromatic aldehydes **10** afforded target molecules **5.**

The compounds with general structure **6** were synthesized as shown in Scheme 2.



Scheme 2. Reagents and conditions: i) K_2CO_3, TBAB, EtOAc, 80 °C, 12 h, 80-86 % ii) 10% NaOH, MeOH, rt, 12-20 h, 80-85%.

A library of hybrid fluconazole analogues was synthesized by using above synthetic route and was screened for antifungal activity as described in Chapter 1. The activity data indicated following points regarding the structure-activity relationship of the compounds studied in the present work:

1. The hybrid compounds **5** and **6** having same substituent on the corresponding aromatic rings showed almost same antifungal activity.

2. The hybrid compounds showed broader spectrum of antifungal activity than the individual compounds.

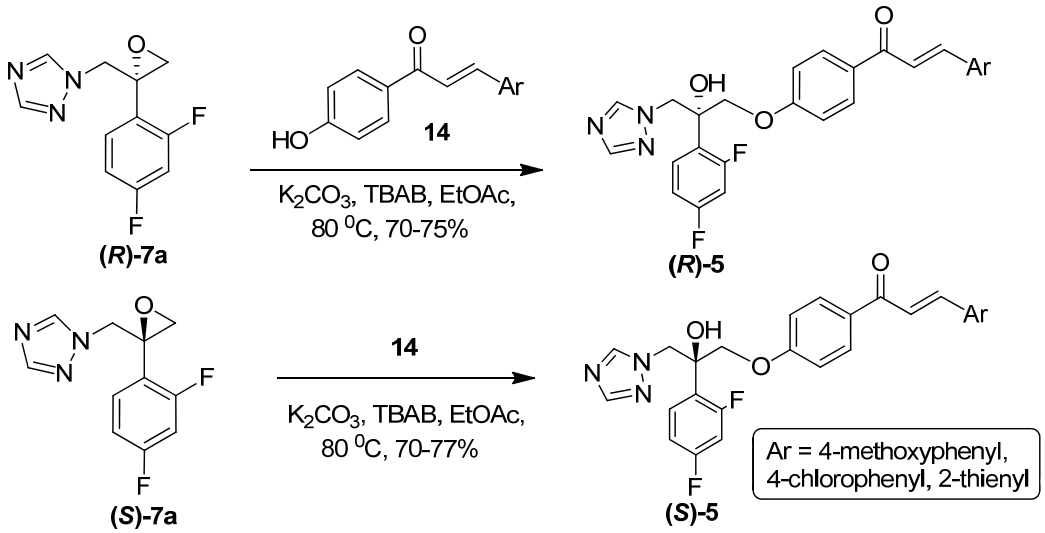
3. The compounds with difluorophenyl moieties showed higher antifungal activity than compounds with 4-fluoro and 4-bromophenyl moieties.

4. As number of substituents on **A** or **B** ring of hybrid molecule **5** increases, its activity decreases.

5. The replacement of the **B** ring with alternative aromatic systems like naphthyl, thienyl and indolyl was tolerated while bulky ring like 9-anthracenyl resulted in loss of activity.

6. Also, it was observed that along with α-β unsaturated functionality, tertiary hydroxyl group is an essential functional group for antifungal activity.

In continuation to the above work, we have synthesized the (*R*) and (*S*) enantiomers of compound **5** by reacting chiral epoxides **(*R*)-7a** and **(*S*)-7a** with hydroxy chalcones **14** in presence of potassium carbonate and TBAB (tetrabutyl ammonium bromide) in ethyl acetate at refluxing temperature to afford the target molecules **(*R*)-5** and **(*S*)-5** as shown in Scheme 3.



Scheme 3. Synthesis of enantiomers **(*R*)-5** and **(*S*)-5**

These enantiopure compounds were then evaluated for antifungal activity and it was found that the *R*-enantiomers of this class of antifungal agents have higher antifungal activity than the *S*-enantiomers.

References

1. Schellenberg, D.; Abdulla, S.; Roper, C. *Curr. Mol. Med.* **2006**, *6*, 253-260.

2. Walsh, J. J.; Coughlan, D.; Heneghan, N.; Gaynor, C.; Bell, A. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 3599-3602.

3. Burgess, S. J.; Selzer, A.; Kelly, J. X.; Smilkstein, M. J.; Riscoe, M.; Peyton, D. H. *J. Med. Chem.* **2006**, *49*, 5623-5625.

4. Kengo, O.; Haruaki, I.; Koshi, O.; Hiroyasu, N.; Jun'ichi, K. *Bioorg. Med. Chem*. **2007**, *15*, 3235-3240.

5. Gao, P.-H.; Cao, Y-B.; *Xu, Z.;* Zang, J.-D.; Zheng Gu, J.; Cao,Y.-Y.; Li, R.-Y.; Jiang, Y.-Y. *Biol. Pharm. Bull.* **2005**, *28*, 1414-1417.

6. Morrow, J. D. *Am. J. Med. Sci. Rev.* **1991**, *302*, 129-132.

7. Ni**,** L.; Meng , C. Q.; Sikorski , J. A. Expert Opin. Ther. Pat. **2004**, *14*, 1669.

8. Boeck, P.; Leal, P. C.; Yunes, R. A.; Fiiho, V. C.; Lopez, S.; Sortino , M.; Escalante, A.; Furlan, R. L. E.; Zacchino, S.; *Arch. Pharm. Chem. Life Sci*. **2005**, *338*, 87-92.

9. (a) Mo, A.; Zhang, H.; Pan, H. CN 1995-111510, **1995**; CA 131:228724; (b) Antoni, S.; Marcial, M.; Roser, P. *ARKIVOC* **2007**, *(iv)*, 234-250.

10. Patil, C. B.; Mahajan, S. K.; Katti, S. A. *J. Pharm. Sci. Res.* **2009**, 1, 11-22.

Chapter 2: Section-II

Hybrid fluconazole analogues containing furanones as novel antifungal agents

Introduction

Functionalized furanones are important subunits present in a large variety of natural products and biologically active compounds such as alkaloids, lignan lactones and sex attractant insect pheromones. Many of these compounds exhibit a variety of biological properties including antifungal, anticancer, antibacterial etc and some of them act as antibiotics, cyclooxygenase inhibitors etc. The natural product incrustoporin (**2**)[1] exhibits antifungal activity and a number of analogues with structures **3** and **4** have been reported as antifungal agents. Because of their unique structural features and wide range of biological activities, furanones have attracted attention of organic as well as medicinal chemists.

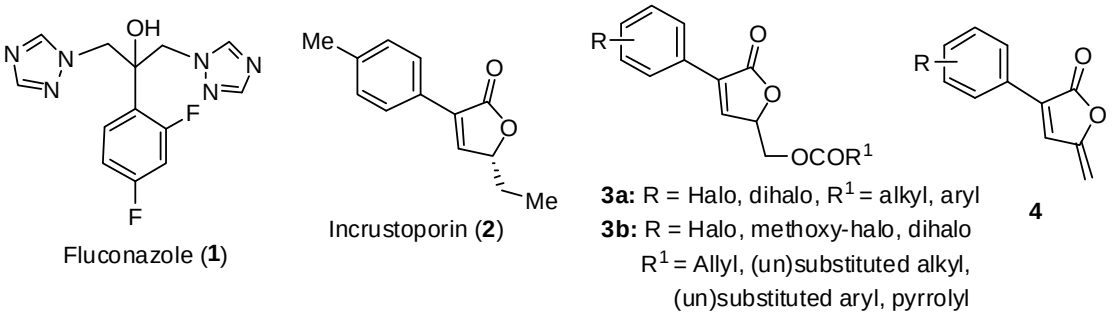


Figure 1. Structures of fluconazole (**1**), incrustoporin (**2**) and incrustoporin analogues **3** and **4**

In the present work efforts were directed towards the synthesis of new antifungal agents wherein a series of substituted furanone containing hybrid fluconazole analogues were designed and synthesized.

Present work

In order to study the activity of hybrid molecules containing furanones and fluconazole pharmacophores, new chemical entities with general structures **5, 6** and **7** (Figure 2) were designed. It was found that some of the synthesized molecules exhibited significant antifungal activity against *Candida.*

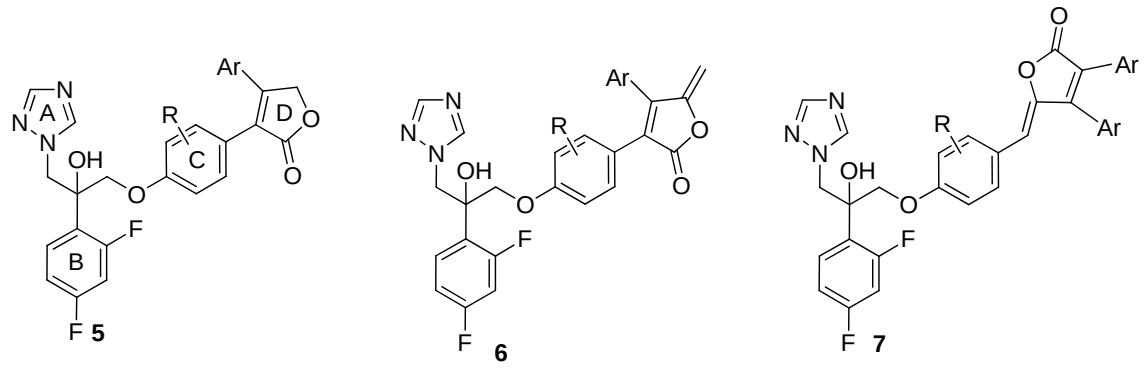
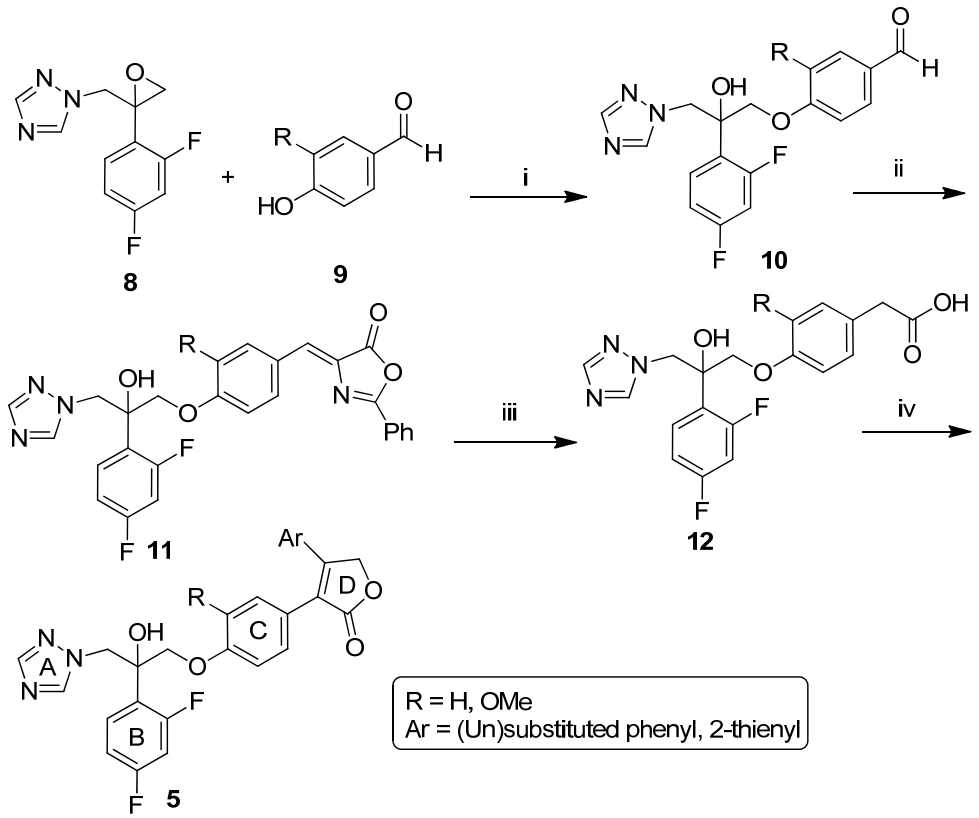


Figure 2. Structures of fluconazole analogues **5**, **6** and **7**

1) Synthesis of fluconazole analogues 5 containing furanones

The synthetic sequence used for preparation of hybrid molecules **5** is shown in Scheme 1.

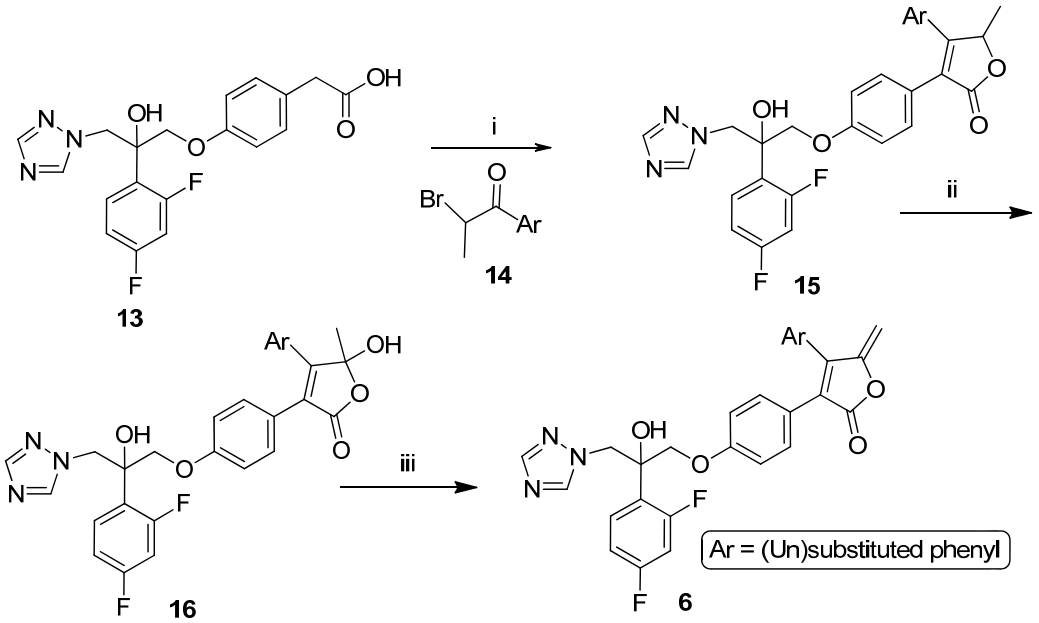


Scheme 1. Reagents and conditions: i) K_2CO_3, TBAB, EtOAc, 80 ^{0}C, 12 h, 64-73% ii) Hippuric acid, AC_2O, NaOAc, 80 ^{0}C, 2 h, 90-95% iii) Aq. NaOH, 85 ^{0}C; b) H_2O_2, aq. NaOH, rt, 15 h, 30-35% iv) $ArCOCH_2Cl$, K_2CO_3, MeCN, reflux, 1-6 h, 65-75%.

Thus, the known epoxide **8**[2] was reacted with hydroxybenzaldehydes **9** to afford the fluconazole analogues **10** which upon reaction[3] with hippuric acid in presence of acetic anhydride and sodium acetate provided the azlactones **11**. The substituted phenylacetic acids **12** were obtained by subjecting the azlactones **11** to heating with sodium hydroxide followed by reaction with hydrogen peroxide in presence of sodium hydroxide at room temperature[3]. The reaction[4] of phenylacetic acids **12** with suitable chloroketones in presence of potassium carbonate in acetonitrile afforded the desired hybrid molecules **5**. These compounds were screened for their antifungal activity.

2) Synthesis of fluconazole analogues 6 containing furanones with exocyclic double bond

The significant antifungal activity exhibited by compounds with general structure **4** with exocyclic double bond prompted us to synthesize the hybrid molecules **6** employing the synthetic strategy shown in Scheme 2.



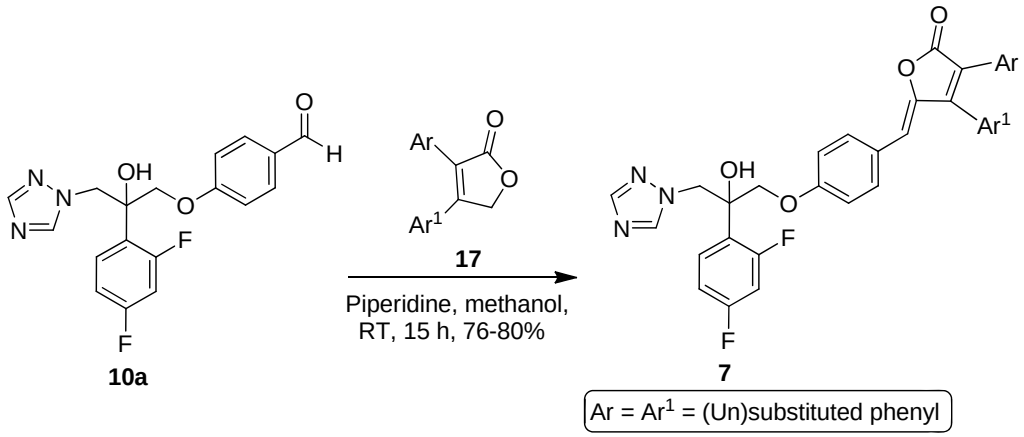
Scheme 2. Reagents and conditions: i) K_2CO_3, MeCN, 80 ^{0}C, 6 h, 60-65% ii) DBU, MeCN, air, rt, 2 h, 65-70% iii) *P*-TSA, toluene, reflux, 1-6 h, 50-57%.

The compounds **6** were found to be not enough stable to check their antifungal activity.

3) Synthesis of fluconazole analogues 7 containing trisubstituted furanones

The synthetic strategy employed for the preparation of the fluconazole analogues **7** containing trisubstituted furanones is shown in Scheme 3. The reaction[5] of aldehyde **10a**

with furanones **17** in methanol in presence of piperidine afforded the desired fluconazole analogues **7**.



Scheme 3. Synthesis of fluconazole analogues **7**

All the newly synthesized compounds were tested for antifungal activity against various fungi as described in Chapter 1. The activity data indicated following points regarding the structure-activity relationship of the compounds studied in the present work.

1. The hybrid compounds with general structure **5** showed higher antifungal activity than the compounds with general structure **7**.

2. The hybrid compounds **5** with substituent R^1= OMe exhibited less activity than those with R^1= H. Also it was observed that as the number of substituents on aromatic ring **C** increased the activity decreased.

References

1. Petr, S.; Lucie, T.; Ivan, V.; Vladimir, B.; Marcel S.; Jiri, K.; Milan, N.; Ondrej, K.; Milan, P. *Bioorg. Med. Chem. Lett.* **2010**, 18, 1988-2000.

2. (a) Mo, A.; Zhang, H.; Pan, H. CN 1995-111510, **1995**; CA 131:228724; (b) Antoni, S.; Marcial, M.; Roser, P. *ARKIVOC* **2007**, *(iv)*, 234-250.

3. Mahajan, S. S.; Pikle, R. P. *Ind. J. Chem.* **2006**, *45B*, 1554-1556.

4. (a) Black, W. C.; Brideau, C.; Chan, C.-C.; Hughes, Wang, Z.; Xu, L.-J.; Prasit, P. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 1195-1198; (b) Caturla, F.; Amat, M.; Reinoso, R. F.; Córdoba, M.; Warrellow, G. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 3209-3212; (c) Zargi, A.; Praveen Rao, P. N.; Knaus, E. E. *Bioorg. Med. Chem.* **2007**, *15*, 1056-1059.

5. Chavan, S. P.; Pathak, A. B.; Pandey, A.; Kalkote, U. R. *Synth. Commun.* **2007**, *37*, 4253-4263.

Chapter 3: Section-I

A short synthesis of 3,6-disubstituted N-2- thienyl/aryl-indoles

Introduction

The work described in this section involved a short synthesis of substituted indoles from substituted styrene epoxides. Indole ring system is present in many natural products and there are various methods reported for synthesis of indole framework[1-2]. We have developed a short synthesis of substituted indoles from substituted styrene epoxides and the results are presented in this section.

Present work

We desired to study the antifungal activity[3] of the compounds **1** wherein the substituted benzyl group was to be replaced with various structural units and imidazolyl moiety was to be replaced with various heterocycles (Figure 1).

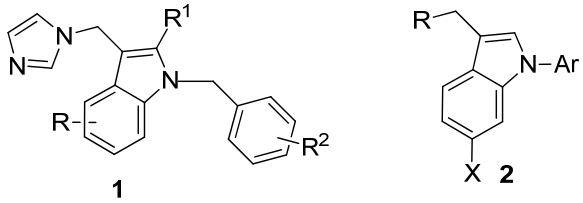
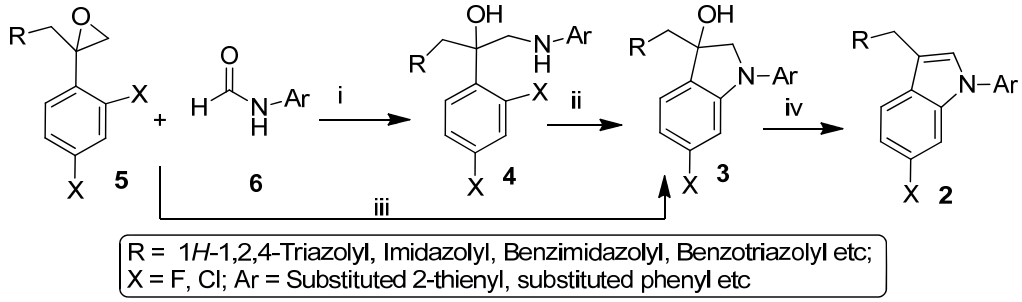


Figure 1. General structures of substituted indoles **1** and **2**

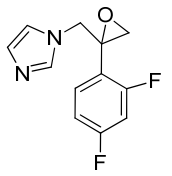
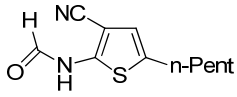
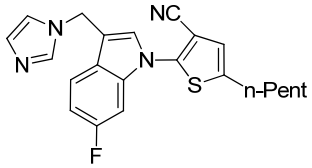
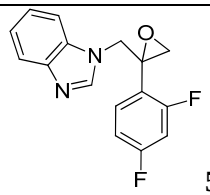
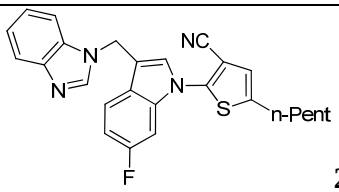
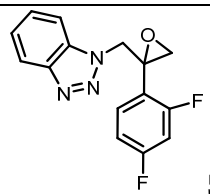
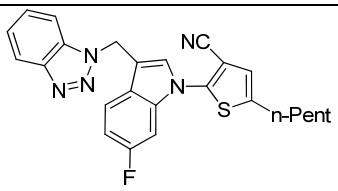
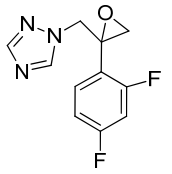
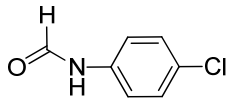
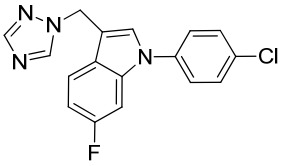
Accordingly, we synthesized a series of N-2- thienyl/aryl-indoles depicted by general formula **2**. The synthesis of desired N-2- thienyl/aryl-indoles **2** was effected by reaction of epoxides **5** with the N-formylated aryl amines **6**, to give the intermediate 2,3-dihydro-3- hydroxyindolines **3** followed by subsequent dehydration with hydrochloric acid as shown in Scheme 1.



Scheme 1. Reagents and conditions: for Ar = phenyl: i) K_2CO_3, DMF, 80 ^{0}C; 80-90% ii) tBuOK, DMF, 90 ^{0}C, iv) 50% HCl, EtOAc, 65-70%; for Ar = thienyl: iii) a) K_2CO_3, DMF, 80 ^{0}C; b) 50% HCl, 58-85%

Using above synthetic strategy a library of compounds was synthesized (a few examples shown in Table 1) and checked for antifungal activity against various fungal strains but none of the compounds showed good antifungal activity.

Table 1: Synthesis of substituted indoles

Entry	Reactant **5**	Reactant **6**	Product **2**	Yield %
1	 **5a**	 **6a**	 **2a**	70.5
2	 **5b**	**6a**	 **2b**	63
3	 **5c**	**6a**	 **2c**	84
4	 **5d**	 **6b**	 **2d**	67

References

1. (a) Fischer, E.; Jourdan, F.; *Chem. Ber.* **1883**, *16*, 2241-2245; (b) E. Fischer, O. Hess *Chem. Ber.* **1884**, *17*, 559-568.

2. (a) Hughes, D. L. *Org. Prep. Proced. Int.* **1993**, *25*, 607-632; (b) Robinson, B. *Chem. Rev.* **1963**, *63*, 373-401; (c) Robinson, B. *Chem. Rev.* **1969**, *69*, 227-250.

3. Na,Y.-M.; Le Borgne, M.; Pagniez, F.; Le Baut, G.; Le Pape, P. *Eur. J. Med. Chem.* **2003**, *38*, 75-87.

Chapter 3: Section-II

One-step synthesis of 4-alkyl-3-aryl-2,6-dicyanoanilines and their use in the synthesis of highly functionalized 1,2,3,5,6,7- and 1,2,3,4,5,7-hexasubstituted indoles

Introduction

Dicyanoanilines exhibit various biological activities and they are useful as important substrates for non-linear optical materials[1]. They are also reported to be used in the field of molecular electronic devices[2]. The amino and cyano groups in 2,6-dicyanoanilines can be converted into various other functional groups so these compounds can be used as starting materials for a large number of aromatic compounds with various functional groups. There are a number of methods reported for the synthesis of substituted 2,6-dicyanoanilines[3] but most of the reports describe synthesis of 3,5-disubstituted-2,6-dicyanoanilines **1** (Figure 1).

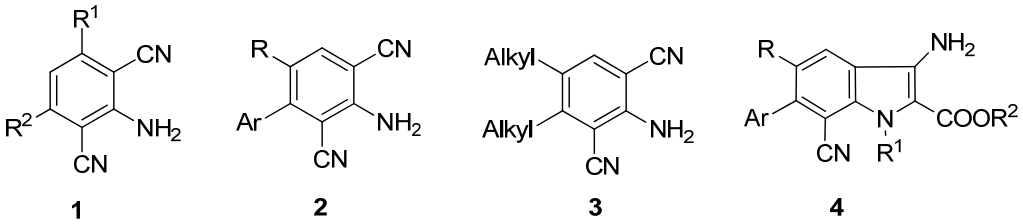


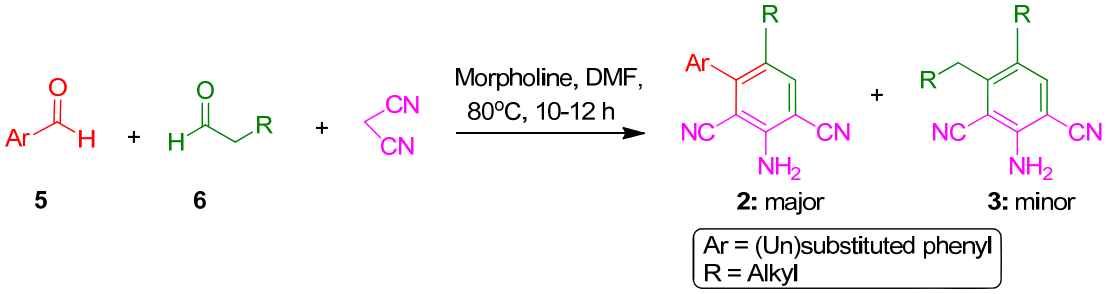
Figure 1. General structures of 2,6-dicyanoanilines and hexasubstituted indoles.

Present work

This section describes a synthetic strategy for the preparation of highly substituted, highly functionalized indoles **4** in two steps. The first step involved a facile synthesis of 3,4-disubstituted-2,6-dicyanoanilines **2** *via* three-component reaction of aliphatic aldehyde, aryl aldehyde and malononitrile in presence of base while the second step involved reaction of 3,4-disubstituted-2,6-dicyanoanilines **2** with ethyl bromoacetate in presence of base.

The reaction of aryl aldehyde **5**, malononitrile and aliphatic aldehyde **6** was attempted in presence of various bases like potassium carbonate, triethylamine, morpholine, basic alumina *etc* with solvent (dimethylformamide, ethyl acetate, acetonitrile) or without solvent at various temperatures ranging from room temperature to 100 ^{o}C and it was observed that the reaction in presence of morpholine in DMF at 80 ^{o}C afforded the desired 4-alkyl-3-aryl-2,6-dicyanoanilines **2** as major product and 3,4-dialkyl-2,6-dicyanoanilines **3**[4]

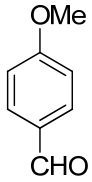
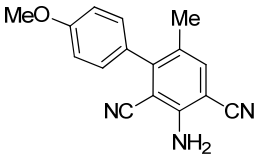
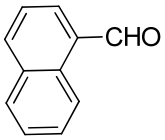
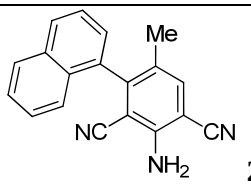
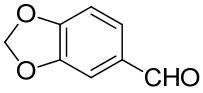
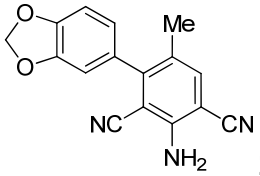
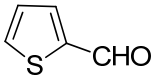
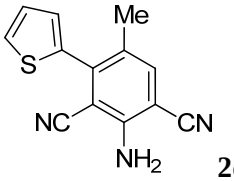
as a minor product (Scheme 1). These two products were easily separated by column chromatography.



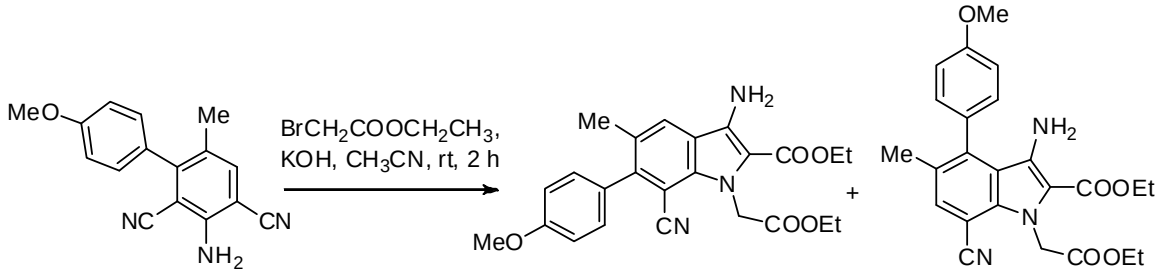
Scheme 1. Synthesis of 4-alkyl-3-aryl-2,6-dicyanoanilines **2**

A number of 3-aryl-4-alkyl-2,6-dicyanoanilines **2** were prepared in order to check the generality of the reaction (a few examples are shown in Table 1).

Table 1. Synthesis of 4-alkyl-3-aryl-2,6-dicyanoanilines **2**

Entry	Aromatic aldehyde	Aliphatic aldehyde	Product **2**	Yield %
1	 **5a**	CH_3CH_2CHO **6a**	 **2a**	77
2	 **5b**	CH_3CH_2CHO **6a**	 **2b**	77
3	 **5c**	CH_3CH_2CHO **6a**	 **2c**	75
4	 **5d**	CH_3CH_2CHO **6a**	 **2d**	56

We desired to prepare functionalized indoles to be used as intermediates in the synthesis of new chemical entities to be developed as antifungal agents. Accordingly, reaction[5] of the 3-amino-4'-methoxy-6-methyl-[1,1'-biphenyl]-2,4-dicarbonitrile (**2a**) with ethyl bromoacetate in presence of potassium hydroxide pellets in acetonitrile at room temperature afforded ethyl 3-amino-7-cyano-1-(2-ethoxy-2-oxoethyl)-6-(4-methoxyphenyl)-5-methyl-1*H*-indole-2-carboxylate **4a** as major product in 69% yield and ethyl 3-amino-7-cyano-1-(2-ethoxy-2-oxoethyl)-4-(4-methoxyphenyl)-5-methyl-1*H*-indole-2-carboxylate **7a** as minor product in 12% yield (Scheme 2).

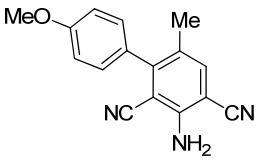
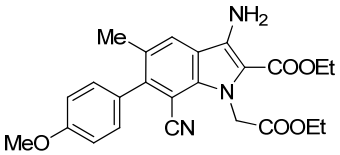
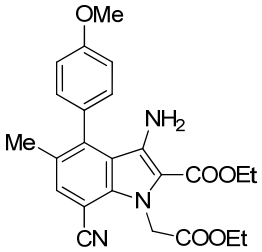
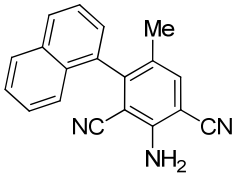
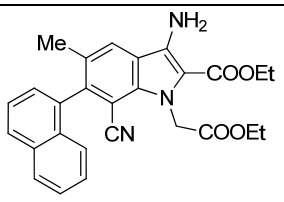
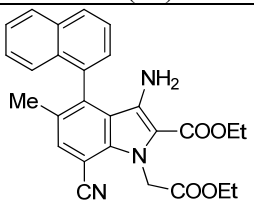


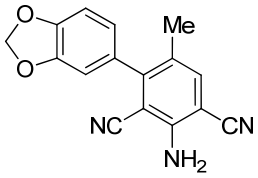
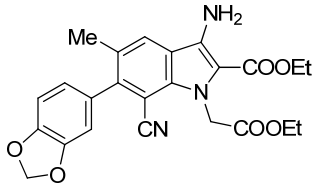
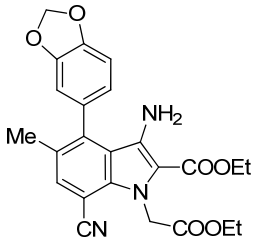
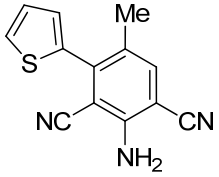
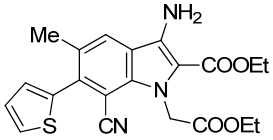
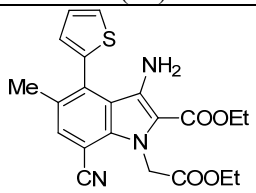
2a **4a:** 69% **7a:** 12%

Scheme 2. Synthesis of 1,2,3,5,6,7-and 1,2,3,4,5,7-hexasubstituted indoles **4a** and **7a**

These two products were easily separated by column chromatography. The various novel 2,6-dicyanoanilines synthesized earlier were subjected to above reaction conditions and a few examples are shown in Table 2.

Table 2. Synthesis of 1,2,3,5,6,7- and 1,2,3,4,5,7-hexasubstituted indoles **4** and **7**

Entry	Substituted aniline **2**	Product **4** (Yield %)	Product **7** (Yield %)
1	 **2a**	 **4a** (69)	 **7a** (12)
2	 **2b**	 **4b** (62)	 **7b** (18)

3	 **2c**	 **4c** (69)	 **7c** (23)
4	 **2d**	 **4d** (64)	 **7d** (12)

Thus, highly functionalized 5-alkyl-3-amino-6-aryl-2-carboethoxy-7-cyano-N-carboethoxymethyl indoles **4** and 5-alkyl-3-amino-4-aryl-2-carboethoxy-7-cyano-N-carboethoxymethyl indoles **7** were prepared by a short route using 3-aryl-4-alkyl-2,6-dicyanoanilines **2** as intermediates which in turn were prepared by one-step method involving three-component reaction of aliphatic aldehyde, aryl aldehyde and malononitrile in presence of base.

References

1. Cardozo, T. M.; Nascimento, M. A. C. *J. Mater. Sci.* **2005**, *40*, 3549-3551.

2. Bendikov, M.; Wudl, F.; Perepichka, D. F. *Chem. Rev.* **2004**, *104*, 4891-4945.

3. (a) Blum Yi, C.; Liu, C.; Frei, S.-X.; Neels, G. A.; Renaud, P. ; Leutwyler, S.; Decurtins, S. *J. Org. Chem.* **2008**, *73*, 3596-3599; (b) Milart, P.; Wilamowski, J.; Sepiol, J. J. *Tetrahedron* **1998**, *54*, 15643-15656.

4. Dyachenko, V. D. *Russ. J. Gen. Chem.* **2004**, *74*, 1135-1136.

5. Maitraie, D.; Reddy, G. V.; Rao, V. V. V. N. S. R.; Ravikanth, S.; Narsaiah, B.; Rao, P. S.; Ravikumar, K.; Sridhar, B. *Tetrahedron* **2005**, 61, 3999-4008.

Chapter 3: Section-III

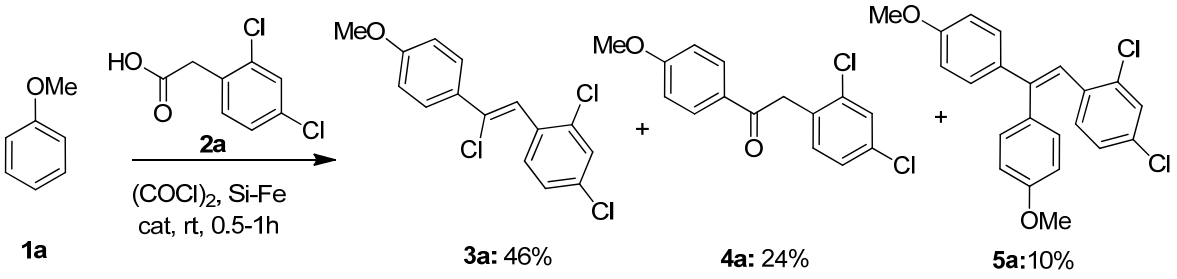
One-step synthesis of α-chlorostilbenes mediated by a heterogeneous Si-Fe catalyst

Introduction

During the previous research in our group, involving Friedel-Crafts acylation of aromatic substrates with acid chlorides in the presence of a heterogeneous Si-Fe catalyst, we found that α-chlorostyrenes were obtained in good yields in addition to the normal Friedel-Crafts acylation products[1]. We envisioned that these results could be extended further to obtain α-chlorostilbenes by reaction of phenylacetic acid chlorides with aromatic substrates. The α-chlorostilbenes could then be converted into *cis* or *trans*-stilbenes. Dechlorination of properly substituted α-chlorostilbenes could then lead to various important molecules like DMU-212.

Present work

We undertook the present work to develop efficient method for preparation of α-chlorostilbenes and DMU-212. Accordingly, when anisole (**1a**) was reacted with 2,4-dichlorophenylacetyl chloride (generated *in situ* from 2,4-dichlorophenylacetic acid (**2a**) and oxalyl chloride) in the presence of the heterogeneous Si-Fe catalyst[1] at room temperature, the α-chlorostilbene **3a** was obtained as a major product in 46% isolated yield. The normal Friedel-Crafts acylation product **4a** and aryl stilbene **5a** were obtained as side products in 24% and 10% yields respectively (Scheme 1).

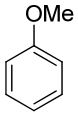
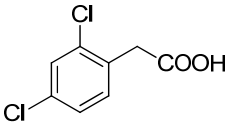
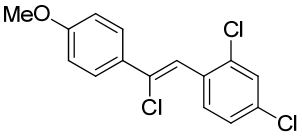
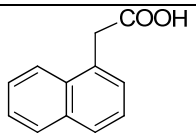
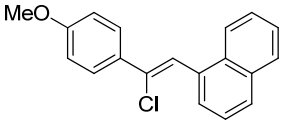
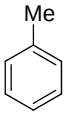
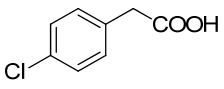
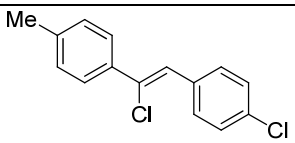
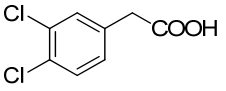
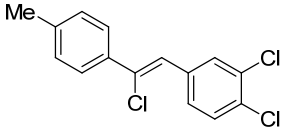
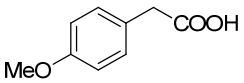
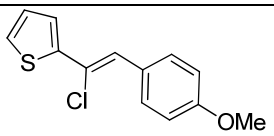


Scheme 1. Synthesis of α-chlorostilbene **3a**

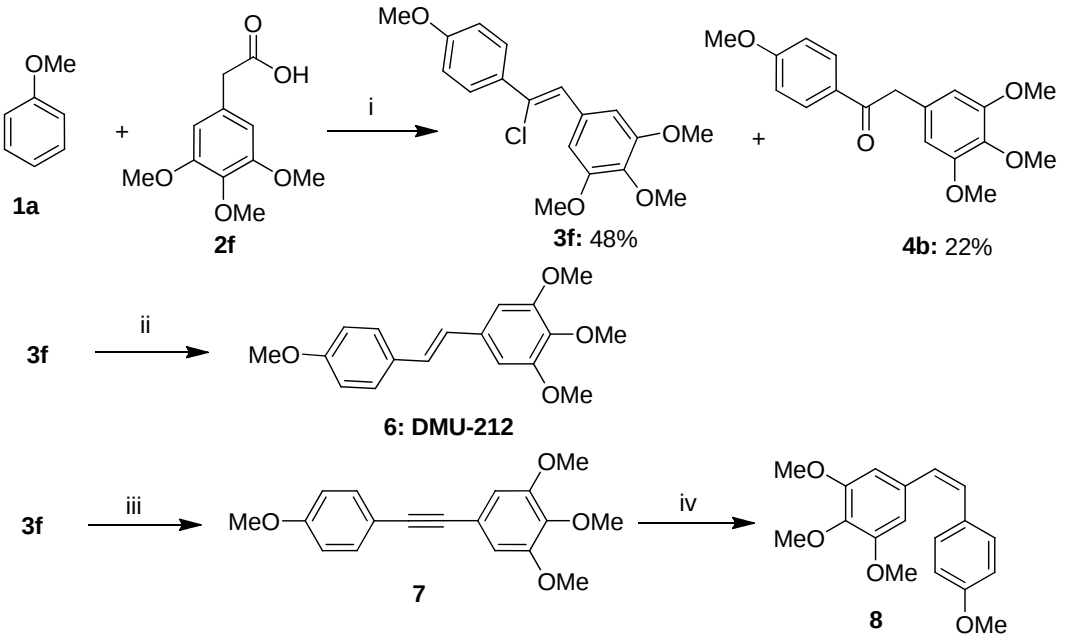
A number of α-chlorostilbenes were prepared in 46-55% isolated yields, when anisole or toluene was reacted with various arylacetic acid chlorides in the presence of the heterogeneous Si-Fe catalyst at room temperature for 0.5 to 2 h, demonstrating the

generality of the method and a few examples are shown in Table 1. Reaction with thiophene afforded the desired product in low yields.

Table 1. Synthesis of α-chlorostilbenes

Entry	Aromatic substrate	Arylacetic acid	Product **3**	Yield %
1	 **1a**	 **2a**	 **3a**	46
2	**1a**	 **2b**	 **3b**	50
3	 **1b**	 **2c**	 **3c**	55
4	**1b**	 **2d**	 **3d**	54
5	 **1c**	 **2e**	 **3e**	28

This synthetic strategy was used to prepare DMU-212, an anticancer agent, and its *cis* isomer **8** as shown in Scheme 2.



Scheme 2. i) $(COCl)_2$, Si-Fe cat, rt, 0.5-1 h ii) TBTH, AIBN, toluene, reflux, 1 h, 88% iii) n-BuLi, THF, rt, 2 h, 90% iv) H_2, Lindlar catalyst, EtOAc, quinoline, rt, 2 h, 72%.

In conclusion, we have developed a short synthetic strategy mediated by a heterogeneous catalyst for the preparation of α-chlorostilbenes which can lead to *trans*-stilbenes, diaryl acetylenes or *cis*-stilbenes. The utility of the present methodology has been demonstrated by successful synthesis of a number of substituted α-chlorostilbenes, DMU-212 and its *cis*-isomer.

References

1. Borate, H. B.; Gaikwad, A. G.; Maujan, S. R.; Sawargave, S. P.; Kalal, K. M. *Tetrahedron Lett.* **2007**, *48*, 4869-4872.

Chapter 1

Synthesis of fluconazole analogues containing substituted 2-aminothiophenes and their bioevaluation

Chapter 1

Synthesis of fluconazole analogues containing substituted 2-aminothiophenes and their bioevaluation

Synthesis of fluconazole analogues containing substituted 2-aminothiophenes and their bioevaluation

1.1 Abstract

A series of novel triazole antifungal agents was synthesized based on structural features of fluconazole by replacing one of the triazole moieties in fluconazole (**6**) with various substituted 2-aminothiophenes. The strategy developed can be used for the synthesis of a number of such compounds with very good to excellent yields. Efforts to vary substituents on thiophene ring led to a library of compounds for SAR study. The enantiomers of the substituted 2-aminothiophene-containing fluconazole analogues were synthesized by utilizing Sharpless epoxidation reaction. All the synthesized compounds containing triazole moiety were screened against different fungal strains and it was observed that some of the newly synthesized compounds exhibited better antifungal activity than the standard drugs like fluconazole and/or potent antifungal agent amphotericin B. The antifungal activity data obtained suggest that these compounds have potential to be developed as antifungal agents in the treatment of infections caused by various fungal strains.

1.2 Introduction

Fungi are microorganisms that exist as yeasts (single-cell, round, grow by division or budding), molds (multicellular filamentous) or a combination of both (dimorphic). Although there are some 300,000 different fungal species[1], only 600 species are pathogenic to humans and of these, 20 species account for 99% of all infections. In human beings infections due to fungi range from the very common to critical diseases, such as dermatophytoses and onycomycoses to deeply invasive and disseminated, such as candidiasis and aspergillosis. Recently used antifungal agents are associated with severe side effects mainly due to the lower degree of specificity towards the desired target. Due to longer use of these drugs, resistance gets developed, especially in the opportunistic fungi active during the immunosuppressive stage. The main factor for the increase of fungal infections is the increased population of severely immunocompromised patients either with AIDS, undergoing cancer chemotherapy or immunosuppressive therapy for organ transplantation. The additional factors include treatment with broad-spectrum antibacterial drugs or glucocorticosteroids, invasive procedures such as surgery, in-dwelling catheters or prosthetic devices and parenteral nutrition or dialysis. However, as medical science has progressed in other disease areas, many more patients are immunocompromised[2], which have resulted in a greater incidence of systemic fungal infections. Clinically, candidosis, aspergillosis and

cryptococcosis are the three major infections in the immunocompromised individuals.[3] Due to the increasing frequency of fungal infections and development of resistance to the current treatment,[4] mycology is today undergoing a true renaissance. Fungi cause a number of illnesses (mycoses) ranging from the chronic to the serious infections. Invasive fungal infections are nowadays a major cause of morbidity and mortality in patients such as with neutropenia, AIDS, organ transplantation, *etc*.[5]

The term mycosis (plural: *mycoses*) refers to conditions in which fungi occupy the resistance barriers of the human body and establish infections. These mycoses can manifest themselves in a variety of ways. Infections can be superficial, i.e. situated at or close to the surface of the skin, or systemic, which means they can affect the body as a whole rather than individual parts or organs.[6]

Mycoses are classified according to the tissue levels initially colonized[6,7]:

1) Superficial mycoses.
2) Cutaneous mycoses.
3) Subcutaneous mycoses.
4) Systemic mycoses due to primary pathogens.
5) Systemic mycoses due to opportunistic pathogens.

Factors responsible for the development of fungal infections are as follows[1, 5, 7c,]:

- ❖ Use of drugs that suppress the immune system, e.g. anticancer drugs, corticosteroids.
- ❖ Diseases and conditions, such as AIDS, kidney failure, lung diseases, diabetes, leukemia, organ transplantation *etc*.
- ❖ Fungal infections are extremely difficult to diagnose and therefore delays in initiation of treatment.

1.3 Review of literature

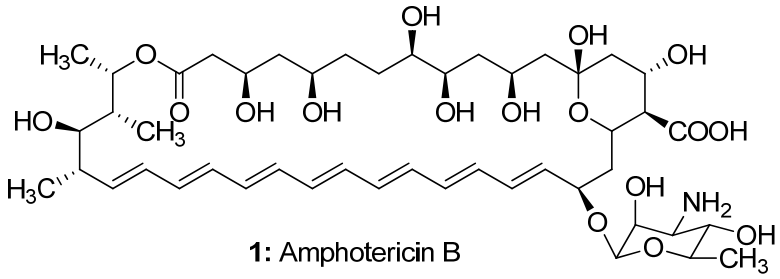
Antifungal agents (Existing antifungal drugs)

There has been extensive research on the development of antifungal drugs including human, agriculture as well as veterinary medicine, but only some of them are licensed for human medicine use. They can be broadly classified into five major types[7b].

- ➢ The polyene antibiotics
- ➢ Allylamines and thiocarbamates
- ➢ The azole derivatives

- Morpholines
- Miscellaneous classes

The polyene antifungals comprise a large family of drugs but only two [amphotericin B (**1)** and nystatin (**2**)] are used as antifungal agents (Figure 1). These drugs bind to ergosterol within the fungal membrane disrupting its integrity. This makes the membrane leaky, causing loss of small molecules from the fungal cell leading to lysis and finally death of fungal cell. Amphotericin B is a very successful and widely used antifungal drug but its use has been curtailed due to its toxicity. It causes unpleasant side effects including chills, fever and lowering of blood pressure. It may also cause kidney damage. But still amphotericin B remains the drug of choice for life threatening fungal infections and may often be administered in lower doses together with other antifungal agents, reducing the risk of therapeutic complications.



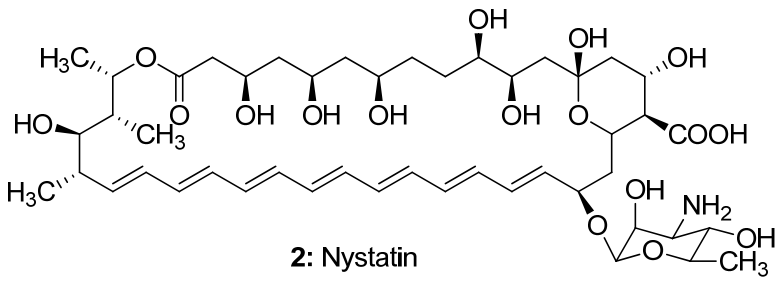


Figure 1. Polyene antifungals amphotericin B (**1)** and nystatin (**2)**.

Azole derivatives such as imidazoles and triazoles are emerging groups of antifungal agents. The first group developed is imidazoles, which contains large number of compounds primarily aimed at topical use. It includes miconazole (**3)**, clotrimazole (**4),** ketoconazole (**5)**, *etc* (Figure 2). These compounds have broad spectrum of antifungal activity. Some of them are also active against Gram-positive bacteria. One of the potential disadvantages of these compounds is interference with human cytochrome P-450. The newer triazole series includes fluconazole (**6)**, itraconazole (**7)**, terconazole and very recent ones voriconazole,

posaconazole *etc*. They act by the same mechanism as the imidazoles but show less affinity for the mammalian cytochrome P-450.

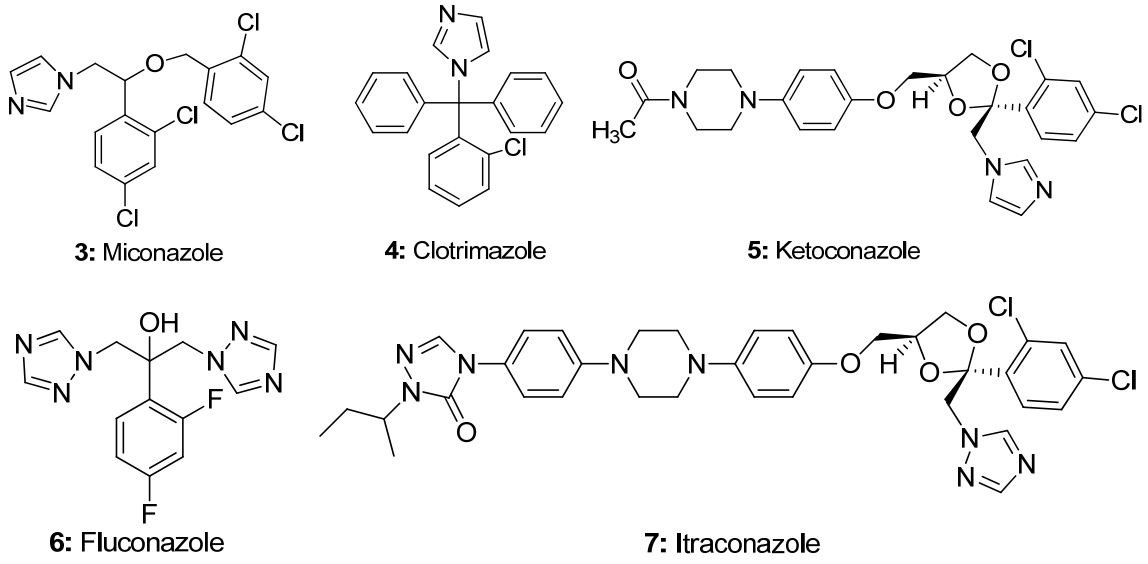


Figure 2. Azole antifungals containing imidazoles and triazoles.

The mode of action of azole antifungals is inhibition of ergosterol biosynthesis by inhibiting the fungal cytochrome P450 3-A dependent enzyme, lanosterol 14-α- demethylase, thereby interrupting the synthesis of ergosterol and inhibition of the cell growth as shown in Figure 3.

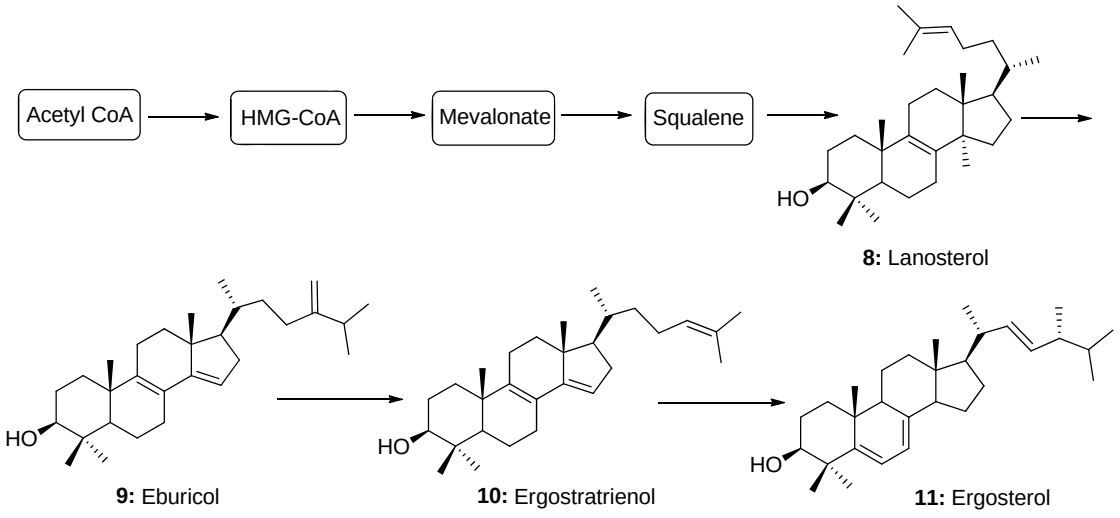


Figure 3. The steps illustrated for ergosterol biosynthesis.

Azole antifungals can also inhibit mammalian cytochrome P450-dependent enzymes involved in hormone synthesis or drug metabolism; therefore, azole antifungals cause hepatotoxicity. Sensitivity of other P450-dependent enzymes accounts for their primary mode of toxicity. Although azoles demonstrate a broad spectrum of activity with less toxicity than amphotericin B, they are not generally fungicidal but they are only fungistatic[6c].

There are three allylamine antifungals in current use namely terbinafine **12**, naftifine **13** and butenafine **14** (Figure 4). Allylamines act by inhibiting squalene epoxidase, which is an important enzyme in the membrane synthesis of fungi. Naftifine is active against dermatophytes and some yeasts. Terbinafine is active against wider range of fungi. Its *tert*-butyl side chain is essential for the specific activity.

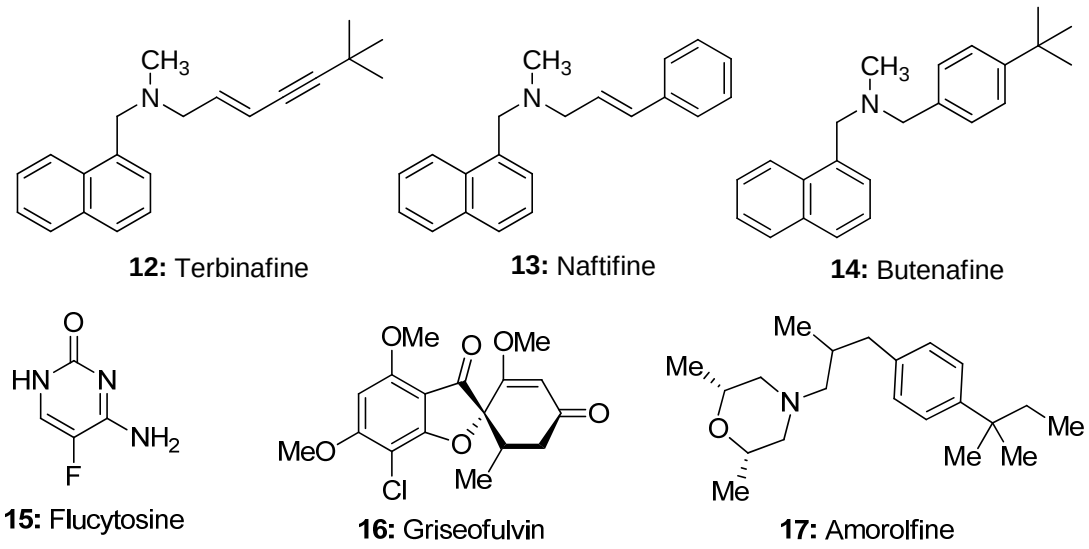


Figure 4. Other antifungal agents.

Flucytosine **15** interferes with the formation of fungal RNA/DNA. It can be used alone or with amphotericin B. It derives selective toxicity from inability of human cells to convert it into 5-fluorouracil. Its major drawback is the ease with which resistance develops against it. Other antifungal agents include griseofulvin **16**, which is a natural antibiotic and acts by inhibition of microtubule formation, thus inhibiting fungal mitosis. It is used in the treatment of ringworm, dermatophytis and fungal infections of nails.

Morpholine antifungal amorolfine **17** is known to inhibit sterol synthesis. There are also cell wall antagonists like echinocandins *e.g.* cilofungin or nikkomycins. The

echinocandins are fungal secondary metabolites comprising a cyclic hexapeptide core with a lipid sidechain responsible for antifungal activity. Antifungal activity in the prototypes, echinocandin B and aculeacin A was discovered by random screening in the 1970s. The target for the echinocandins is the complex of proteins responsible for synthesis of cell wall β-1,3 glucan polysaccharides. The sordarin antifungal class, although not developed for clinical use, merits mention among the new mechanisms of action. Sordarins inhibit protein synthesis by blocking the function of fungal translation Elongation Factor 2 (EF2).

The field of antifungal drugs has become static and there are only a few new groups of antifungals under development. Due to emergence of new fungal pathogens, nephrotoxicity to polyene antifungals and development of resistance to emerging azole antifungals, there is always need for new antifungal compounds with novel modes of action for treating or preventing fungal infections.

Need for further research in antifungal agents

There are mainly three challenging problems for the development of an effective drug in combating severely invasive mycosis.

1. Resistance of yeasts to clinically useful antifungal agents: There are three different resistance mechanisms known in pathogenic yeasts.[8]

- First, the reduced access of the agents to the target cytochrome P450 enzyme because of increased efflux of antifungals, caused by the action of resistance gene products.
- Second, the overproduction of cytochrome P450 enzyme, possibly by gene amplification.
- Third, resistance mechanism due to a structural alteration in cytochrome P450 enzyme which results in lower susceptibility to azole antifungals.

2. Emergence of newer strains by mutation:

The treatment of immunosuppressed and immunocompromised patients such as cancer and AIDS patients needs long term administration of antifungal drugs to treat the invasive infections caused by opportunistic pathogenic fungi. The consequence leads to the development of resistance of fungi to these drugs by mutation in the genes leading to newer resistant strains.

3. Toxicity of currently used antifungal agents:

The majority of the currently administered drugs are only fungistatic and cause several side effects such as nephrotoxicity (polyenes) and hepatotoxicity (azoles), as the fungi share similar cellular components and mechanism as that of mammalian cells.

New potential targets for antifungal developments

There is a great challenge to find sensitive fungicidal targets with potential for selectivity over mammalian cells, some of them are discussed below.

1. The fungal cell wall: A unique target

The fungal cell wall is a complex structure composed of chitin, glucans, and other polymers (Figure 5). This structure is very dynamic as it changes during various processes. Beyond serving as a protective shell and providing cell morphology, the fungal cell wall is a critical site for exchange and filtration of ions and proteins, as well as metabolism and catabolism of complex nutrients. The fungal cell wall is a unique target since mammalian cells lack a cell wall; it represents an ideal, safe and specific target for antifungal therapy. Cell wall is present in all fungi, therefore cell wall biosynthesis inhibitors would exhibit broad spectrum of antifungal activity.[4,7] These features make it an ideal antifungal target.

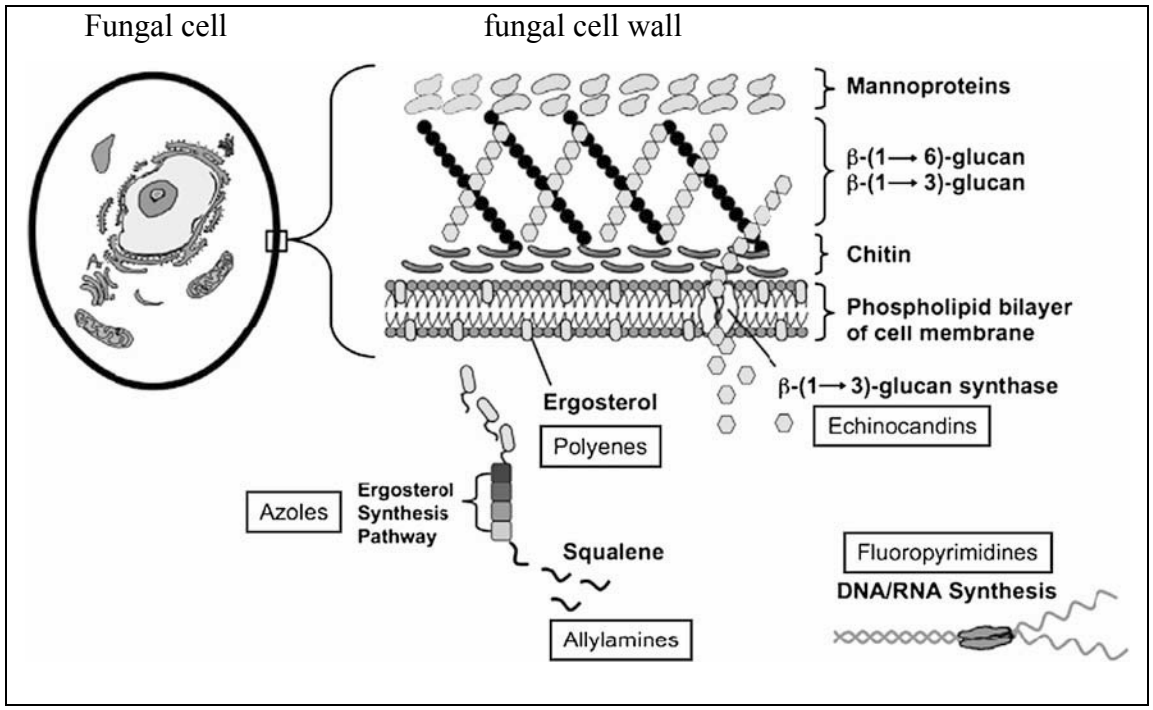


Figure 5. Targets of systemic antifungal agents.

2. (1, 3)-β-D-Glucan synthase

The β-glucans are an abundant class of polysaccharides that are involved in structural, functional and certain morphological roles at the fungal cell surface. The membrane-bound enzyme (1, 3)-β-D-glucan synthase catalyses the synthesis of (1,3)-β-D glucan, an essential glucose polymer found in fungi. It forms a fibril composed of three helically entwined linear polysaccharides, which provide rigidity and integrity to the cell structure. Since the (1, 3)-β-glucan is not found in mammalian cells, the glucan synthase has become a target for research in antifungal agent development.

3. Chitin synthase

Chitin is the major structural component of the cell walls of many fungi. It is a (1-4)-β-linked homopolymer of N-acetyl-D-glucosamine, and is produced by chitin synthase from the nucleotide uridine diphosphate N-acetylglucosamine (UDP-GlcNAc). Chitin synthesis is cell cycle regulated, and the amount and distribution of chitin in the cell wall changes as the cell proceeds from vegetative growth to diploid formation and then sporulation. Since chitin is not present in mammalian cells, it has the potential to be a highly selective target for therapeutic use.

4. Mannoproteins

Mannose constitutes a major portion of the cell wall of many fungi, as well as the glycoproteins that form the protective capsule in *C. neoformans.* The biosynthetic pathway of this polysaccharide may be important to its survival in the host. Mannoproteins are formed by O-linkages joining mannose and small oligosaccharides to the hydroxyl groups of the amino acid serine. A second type of linkage connects high molecular weight and highly branched mannoproteins to the protein moiety *via* an N-acetyl-glucosamine and asparagines. Once mannose has been synthesized, dolichol phosphate mannose (Dol-P-mannose) transfers mannose from GDP-mannose (Guanosine diphosphomannose) to dolichol phosphate, forming Dol-P-mannose, a key intermediate in protein glycosylation. The glycosylation of proteins occurs in the rough endoplasmic reticulum, after which they are transported to the cell wall. All these steps might become antifungal drugs targets.

Fluconazole and its analogues

There have been many new developments in antifungal therapy in the past few years. Some antifungal drugs have been reformulated to reduce toxicity (e.g. new lipid formulations of polyenes), and new derivatives of drugs have been developed to enhance

potencies of the presently marketed drugs. In spite of significant research on antifungal agents, the azoles remain the mainstay of therapy for systemic life threatening fungal infections as they have fungistatic, orally active and broad-spectrum activities against yeasts and filamentous fungi. Azole antifungals are strong inhibitors of lanosterol 14α-demethylase, a cytochome P-450-dependent enzyme which is essential for conversion of lanosterol into ergosterol (Figure 3), a major component of fungal cell membrane[6]. Among all azole antifungal agents, fluconazole (**6**) (1,2,4-triazole based drug) is the most important antifungal agent. It is an antifungal agent of choice for the treatment of infections by *Candida albicans* and *Cryptococcus neoformans* due to its potent activity, excellent safety profile and favorable pharmacokinetic properties[9].

Fluconazole is an orally effective azole-based antifungal drug with low toxicity,[10] but it has a limited antifungal spectrum and is not fungicidal. Although fluconazole shows a very significant efficacy against *Candida albicans* and *C. neoformans*[11], it is not very effective against *Aspergillus niger*[12,13] and *Aspergillus fumigatus*[14]. In addition, extensive use of fluconazole has increased the number of fluconazole-resistant *C. albicans* isolates[15]. Therefore, toxicity concerns, limited spectrum, and the emergence of fungi resistant to currently available agents has created a need for new and effective antifungal agents against life-threatening systemic mycoses caused by *C. neoformans, Aspergillus* species, and *Candida* species[16].

The efforts in the development of new antifungal agents led to discovery of several new azole and triazole antifungals such as voriconazole (**18**), ravuconazole (**19**), albaconazole (**20**), posaconazole (**21**), *etc* (Figure 6) which are active against *Aspergillus*.[17] Other modified fluconazole analogues **22**-**24** are reported in literature (Figure 6). Azoles exert antifungal activity through inhibition of CYP51 by a mechanism in which the heterocyclic nitrogen (N-3 of imidazole or N-4 of 1,2,4-tiazole) binds to the sixth coordination of heme iron atom of the porphyrin in the substrate binding site of the enzyme.[18]

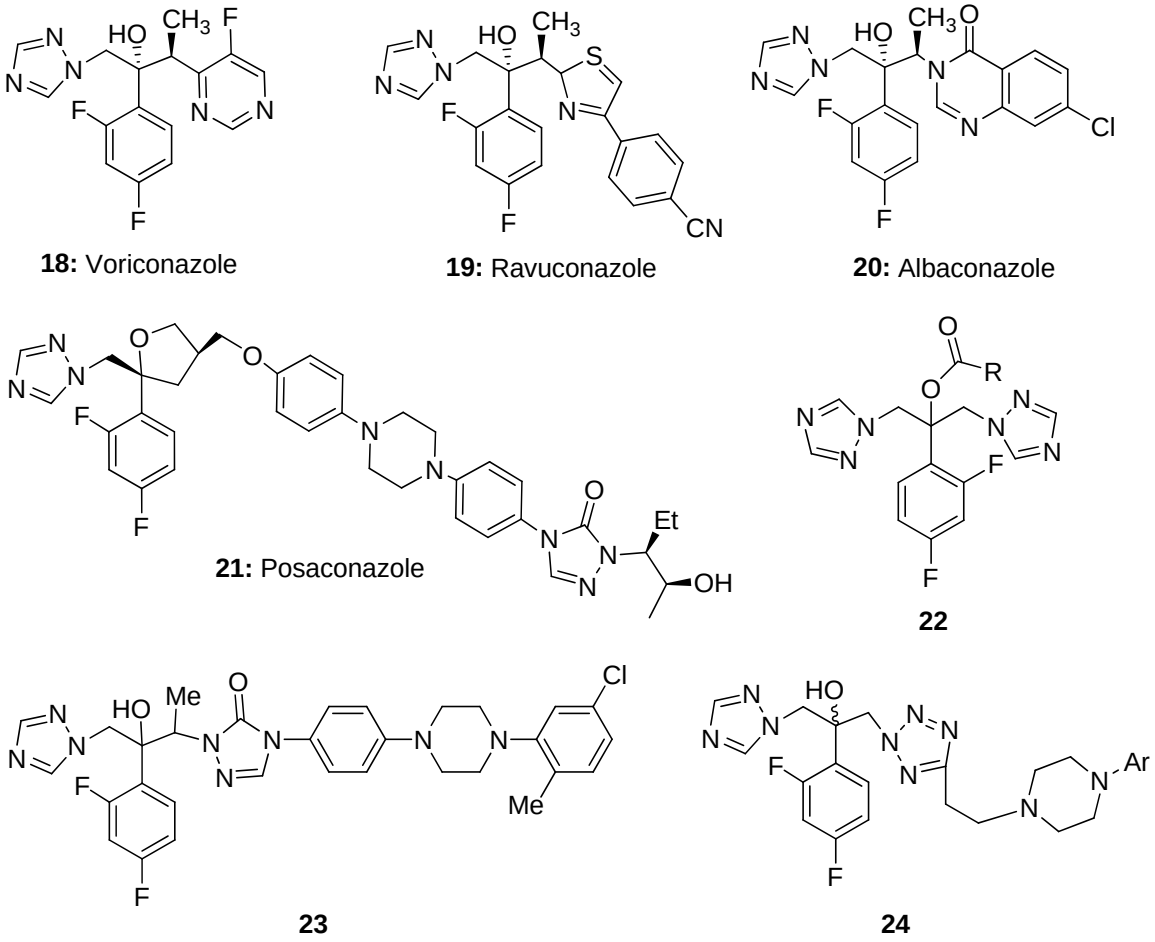
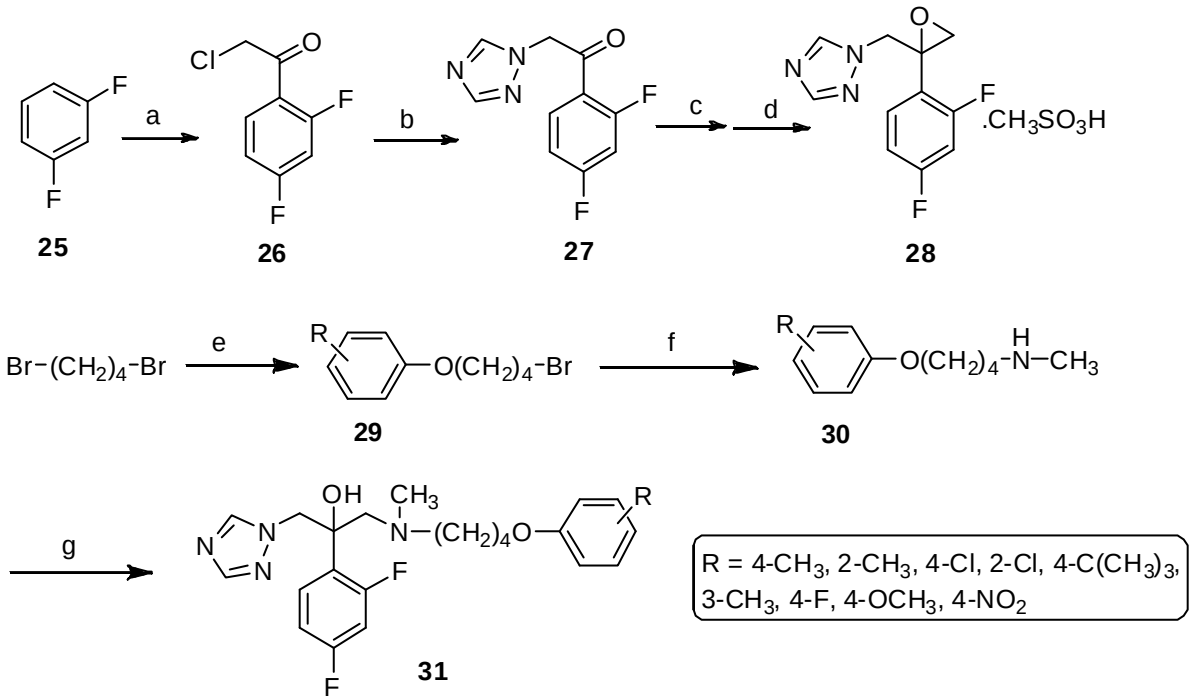


Figure 6. Azole antifungals containing 1,2,4-triazole

Based on the structure of the active site of CYP51 and the extensive investigation of the structure-activity relationships of azole antifungals, it was found that 1,2,4-triazole ring and 2,4-difluorophenyl group are essential for the high antifungal activity. Several papers on the synthesis and biological activity of structurally modified new analogues of fluconazole have been published in the literature[19-41] and some of them are discussed below.

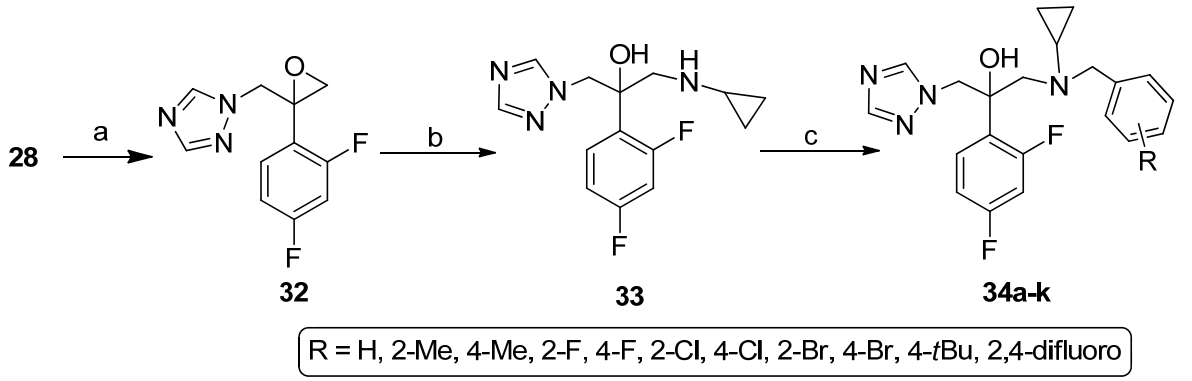
Wang and coworkers reported[23] fluconazole analogues with general formula **31.** The compound **31** was synthesized by using chemistry shown in Scheme 1. The intermediate oxirane **28** was synthesized by known procedure and was allowed to react with N-methyl-substituted phenoxybutan-1-amine **30** (which was synthesized by reacting 1-(4-bromobutoxy)-substituted benzene with methylamine in EtOH at room temperature) in the presence of triethylamine in ethanol at 80 ^{0}C to get the target compound **31** with moderate to high yields.



Scheme 1. Reagents and conditions: (a) $ClCH_2COCl$, $AlCl_3$, CH_2Cl_2, 40 ^{0}C, 3 h, 50%; (b) 1,2,4-(1*H*)-Triazole, K_2CO_3, CH_2Cl_2, rt, 24 h, 70%; (c) $(CH_3)_3SOI$, NaOH, toluene, 60 ^{0}C, 3 h, 62%; (d) CH_3SO_3H, 0 ^{o}C, 1 h, 89% (e) Substituted phenol, K_2CO_3, DMF, 70 ^{0}C, 2 h, 91-92%; (f) Methylamine, EtOH, rt, 12 h, 97–98%; (g) **28**, Et_3N, EtOH, reflux, 9 h, 51-60%.

In vitro antifungal activity assay indicated that the new azoles **31** showed excellent activity against both systemic pathogenic fungi and dermatophytes. Most of the compounds show higher activity than fluconazole and itraconaozle with MIC_{80} values in the range of 0.0156–0.001 μg/mL.

Based on the model study carried out by Ji *et al.*[24], Qui-Ye Wu and coworkers[25] designed fluconazole analogues **34a-k** by computational docking experiments to the active site of the cytochrome P450 demethylase (CYP51). They synthesized the compounds **34a-k** as shown in Scheme 2. The compound **33** was obtained by reacting epoxide **32** (a known intermediate) with cyclopropylamine in EtOH in the presence of Et_3N as base. Finally, the target compounds **34a-k** were obtained in 40–60 % of yields by reacting **33** with differently substituted benzyl bromides in acetonitrile in the presence of potassium carbonate.



Scheme 2. Reagents and conditions**:** a) Et_3N, EtOH; b) Cyclopropylamine, Et_3N, EtOH, 80 ^oC, 6–8 h, 60 %; c) $ArCH_2Br$, MeCN, K_2CO_3, 70–90 ^oC, 6–10 h, 40 –60 %.

Preliminary biological tests showed that most of the target compounds **34** exhibit significant activities against the eight most-common pathogenic fungi. The most potent derivative, 1-[(4-*tert*-butylbenzyl)(cyclopropyl)amino]-2-(2,4-difluorophenyl)-3-(1*H*-1,2,4-triazol-1-yl)propan-2-ol (**34j**), was found to have a broad antifungal spectrum, being more active against *Candida albicans*, *Candida tropicalis*, *Cryptococcus neoformans*, *Microsporum canis* and *Trichophyton rubrum* than the standard clinical drug itraconazole.

Bartroli *et al.* reported[26] a series of azole derivaties carrying *N*-acylmorpholine ring depicted by general formula **35** which were lactones, lactols and cyclic ethers. One of the compounds from the series exhibited excellent activity, and in vaginal model of murine systemic candidosis, it was observed to be superior in potency when compared with fluconazole. Triazole compounds (shown with general formula **36**, Figure 7) with an oxazolidine ring were reported[27] by S. Oida and co-workers as the potential inhibitors of fungal cytochrome P450 14α-demethylase.

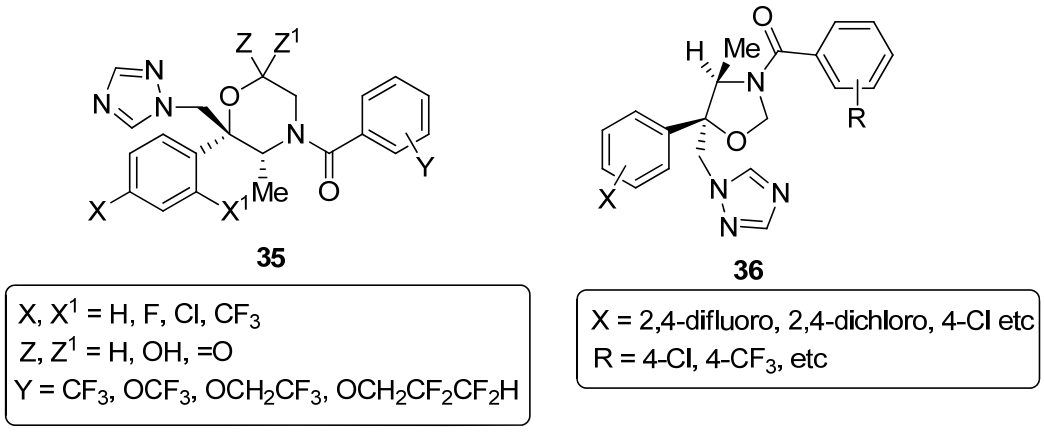


Figure 7. General structures of fluconazole analogues containing *N*-acylmorpholine and oxazolidine

Furthermore, some of the methyloxazolidine derivatives **36** exhibited remarkably high efficacy against a mouse systemic *Candida albicans* infection.

Chai *et al.*[28] reported the synthesis of fluconazole analogues **37** containing substituted benzylamine based on the results of computational docking to the active site of the cytochrome P450 14α-demethylase (CYP51) (Figure 8). Zang and coworkers also reported[29a] the synthesis of a series of substituted benzylamine-containing azole molecules depicted by general formulae **38** and **39** and studied the antifungal activity and calculated the interaction energies for the complexes of compounds **38** and **39** with the active site of CYP51. Pharmacological and toxicological evaluation of these compounds may help in discovery and optimization of the lead compounds. Compounds depicted by general formula **37** with free primary amine (X, X^1 = Cl, R = H, R^1 = 4-amino) were also studied and reported[29b] by F. Giraud *et al.*

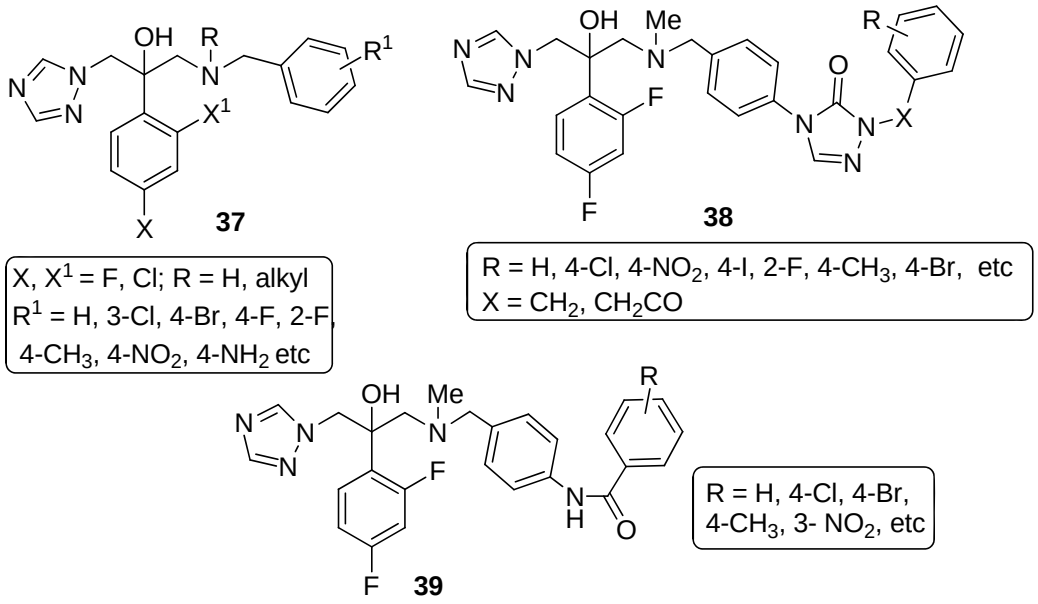


Figure 8. Fluconazole analogues **37, 38** and **39**

Furthermore, P. Liu *et al.* reported[30] a series of 1-(substituted biaryloxy)-2-(2,4-difluorophenyl)-3-(1*H*-1,2,4-triazol-1-yl) propan-2-ols **40, 41** and **42** as analogues of fluconazole and their antifungal activities were evaluated against eight human pathogenic fungi *in vitro*. Seventeen compounds showed activity 4-to 64-fold higher than voriconazole against *Candida albicans*. SAR study clearly suggested that introduction of a biaryloxy side chain greatly enhanced the antifungal activity of triazole analogous against *Candida* species.

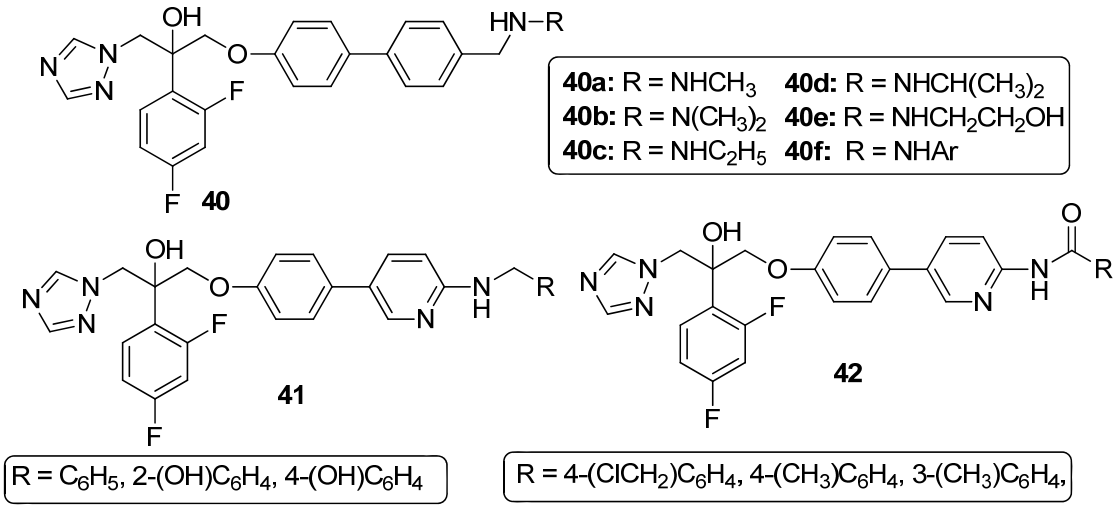


Figure 9. Structure of biaryloxy triazole derivatives.

N-H. Nam *et al.* reported[31] two classes of fluconazole derivatives, (a) carboxylic acid esters and (b) phosphate esters of carbohydrates and fatty alcohols, and evaluated *in vitro* against *Cryptococcus neoformans*, *Candida albicans*, and *Aspergillus niger*. All carboxylic acid ester derivatives of fluconazole such as *O*-2-bromooctanoylfluconazole (**43e**, MIC = 111 μg/mL) and *O*-11-bromoundecanoylfluconazole (**43g**, MIC = 198 μg/mL), exhibited higher antifungal activity than fluconazole (MIC = 444 μg/mL) against *C. albicans* ATCC 14053 in Sabouraud dextrose broth (SDB) medium. Several fatty alcohol phosphate triester derivatives of fluconazole exhibited enhanced antifungal activities against *C. albicans* and/or *A. niger* compared to fluconazole in SDB medium. These results demonstrate the potential of these antifungal agents.

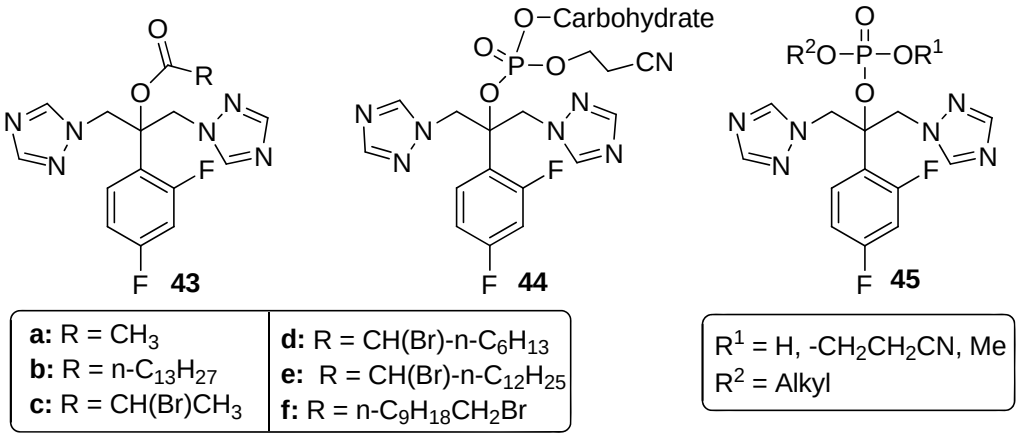


Figure 10. Carboxylic acid and phosphate ester derivatives of fluconazole

Le Borgne and co-workers reported[32] a series of fluconazole analogues **46** incorporating azaindole and indole moieties using oxirane intermediates. They synthesized these fluconazole analogues under microwave irradiation. All of the compounds were evaluated *in vitro* against two clinically important fungi, *Candida albicans* and *Aspergillus fumigatus*. Most of the derivatives exerted high antifungal activity against *C. albicans* with MIC_{80} values 3- to 28-fold lower than those of fluconazole.

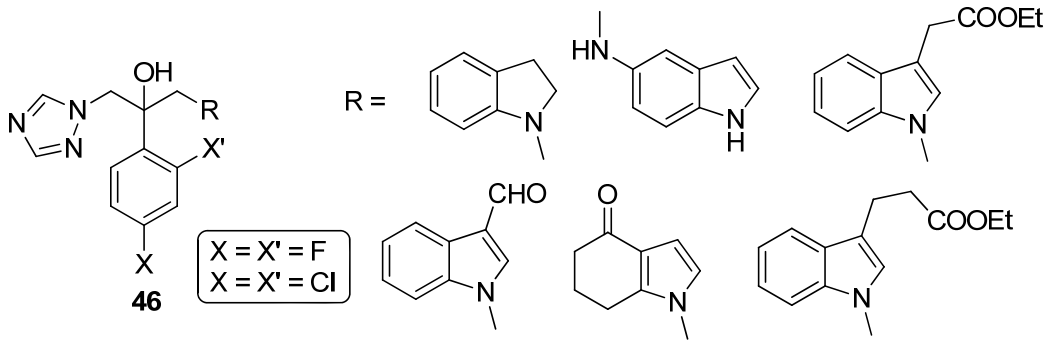


Figure 11. Azaheterocycle analogues of fluconazole

Chai *et al.* reported[33] the synthesis and *in vitro* antifungal activity of various N-substituted piperazine-containing fluconazole analogues **47**.

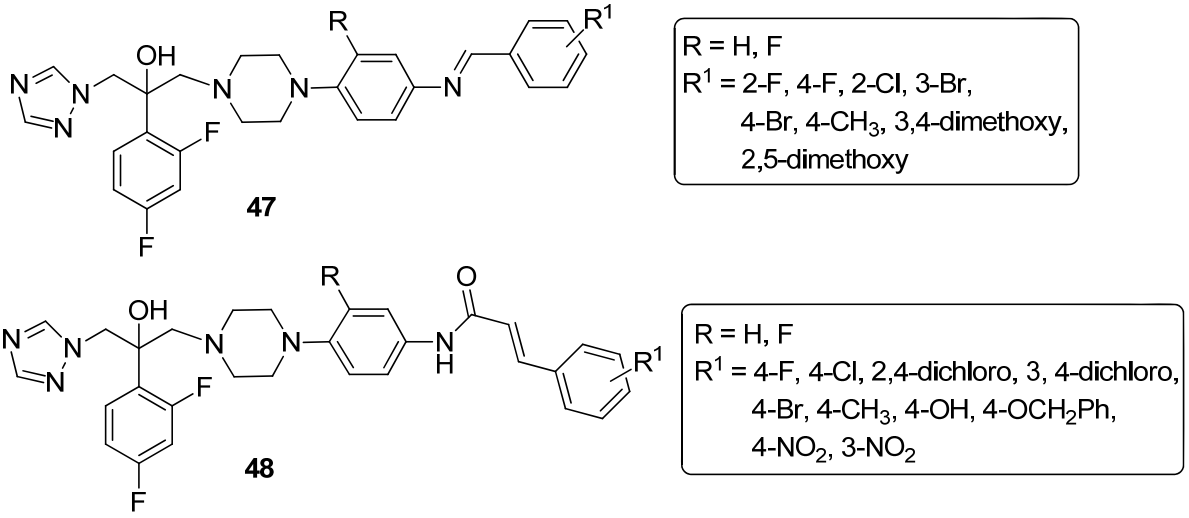


Figure 12. Fluconazole analogues containing piperazinyl moiety

Antifungal activity studies of the synthetic compounds indicated that the piperazinyl side chain greatly enhanced the antifungal activity of these analogues against *Candida* species. Q-Y. Sun *et al.* also reported[34] piperazine-containing fluconazole analogues 1-(1*H*-

1,2,4-triazol-1-yl)-2-(2,4-difluorophenyl)-3-[(4-substitutedphenyl)-piperazin-1-yl]-propan-2-ols **48** on the basis of the structure activity relationships and antimycotic mechanism of azole antifungal agents. All the 19 compounds, synthesized and tested for antifungal activity against 6 different strains of fungi, exhibited good to excellent activities.

Pore and co-workers reported[35] fluconazole analogues having general formulae **49** and **50** with (un)substituted 1,2,3-triazole ring which are isosteres of fluconazole. They also reported bile acid conjugates of fluconazole isosteres as shown in Figure 13.

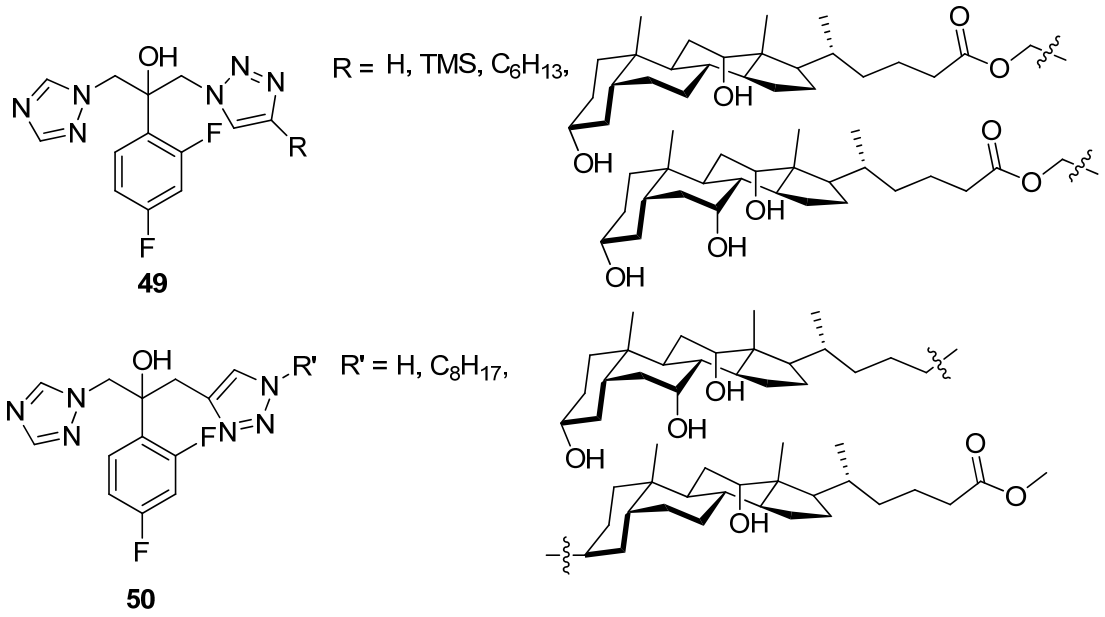


Figure 13. Fluconazole analogues and their bile acid conjugates

These molecules were evaluated *in vivo* against *Candida albicans* in Swiss mice model and antiproliferative activities were tested against human hepatocellular carcinoma Hep3B and human epithelial carcinoma A431. It was observed that one of the compound (**50**, R = C_8H_{17}) resulted in 97.4 % reduction in fungal load in mice and did not show any profound proliferative effect at lower dose. Some of the compounds were observed to be more toxic than fluconazole but less toxic than ketoconazole.

On the basis of the active site of lanosterol 14α-demethylase from *Candida albicans* (CACYP51), Jiang and coworkers reported[36a-b] the synthesis and antifungal activity of a series of 1-(2-(2,4-difluoro-phenyl)-2-hydroxy-3-(1*H*-1,2,4-triazol-1-yl)propyl)-1*H*-1,2,4-triazol-5(4*H*)-ones **51** and **52**.

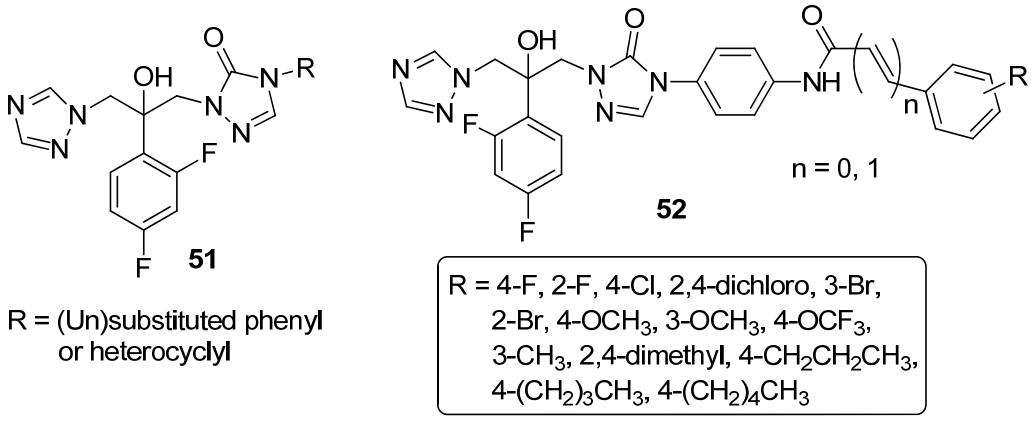


Figure 14. Fluconazole analogues containing 1*H*-1,2,4-triazol-5(4*H*)-one moiety

All compounds were evaluated by *in vitro* test against eight human pathogenic species. Preliminary results showed that some compounds displayed better antifungal activities than reference drug fluconazole against tested strains.

Zhang and coworkers reported[37] new azoles with piperidin-4-one O-substituted oxime side chains depicted by general formula **53** by using computer modeling. *In vitro* antifungal assay indicated that most of the synthesized compounds showed good activity against tested fungal pathogens in comparison with fluconazole, itraconazole and voriconazole, suggesting that they are promising leads for the development of novel antifungal agents. Sheng *et al.* reported[38] that fluconazole analogues with phenylacetamide side chain showed by general formula **54** exhibited good antifungal activity against *Candida albicans* and *C. neoformans.*

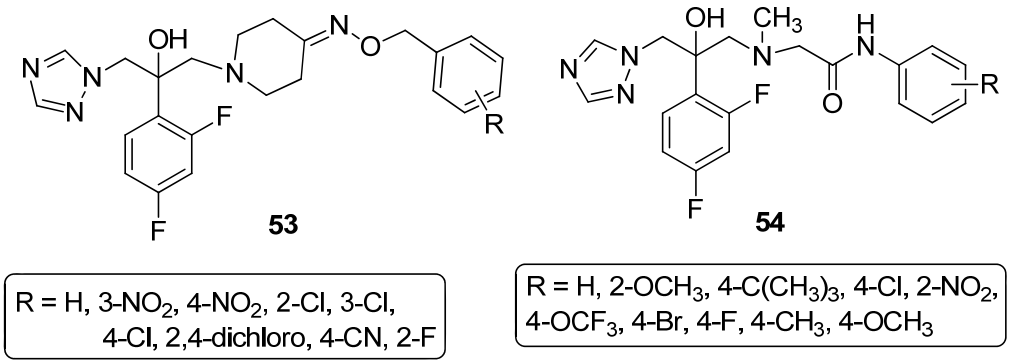


Figure 15. Fluconazole analogues **53** and **54**

Apart from this, in our group efforts have been made for the synthesis of number of fluconazole analogues containing thieno-[3,2-*d*]pyrimidin-4(3*H*)-one[39], thieno-[2,3-*d*]pyrimidin-4(3*H*)-one[40] and 2*H*-1,4-benzothiazin-3(4*H*)-one or 2*H*-1,4-benzoxazin-3(4*H*)-one[41] moieties shown by general formulae **55, 56** and **57.** Most of the synthesized compounds exhibited very good to excellent antifungal activity against different fungal strains. This made us to design and synthesize novel fluconazole analogues described in this chapter.

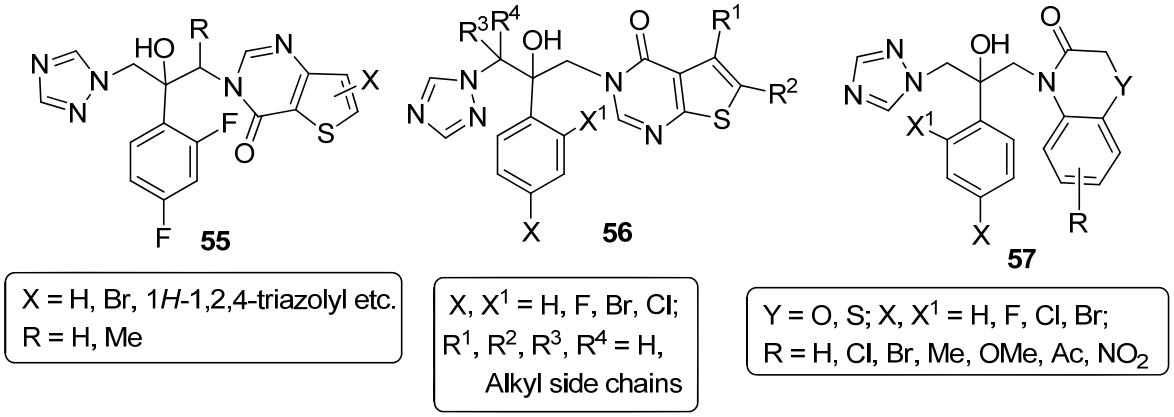


Figure 16. Fluconazole analogues containing thienopyrimidinone, benzothiazinone and benzoxazinone moieties

Thiophenes: biologically important channel (feed)

Thiophene is the backbone of several important products, including pharmaceuticals[42], dyes[43], and agrochemicals[44]. In addition, this S-heterocyclic core is

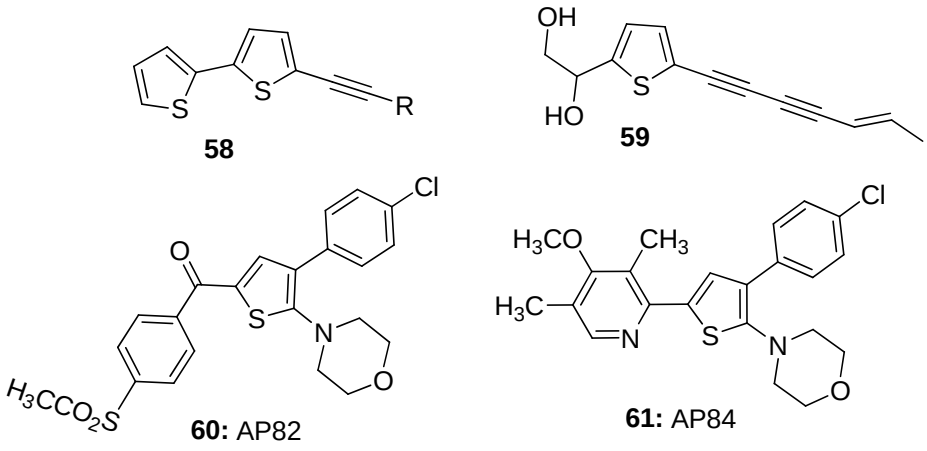


Figure 17. Thiophenes exhibiting antifungal and anti-inflammatory activity

present in many natural products, several of which show antibacterial, antifungal, antiamoebic, antioxidant, antitumor, anticoagulant and antithrombotic activities[45a-g]. Within this family, the 2-aminothiophenes occupy a special position as important intermediates in synthesis because they provide building blocks for several types of heterocyclic systems. Fokialakis *et al.* reported[46] thiophene moieties **58** and **59** (Figure 17) present in some natural products and it was found that they exhibited significant antifungal activity.

A. D. Pillai *et al.* reported[47] trisubstituted thiophenes AP82 and AP84 (representative examples **60** and **61)** as anti-inflammatory agents (Figure 17). AP82 had an aroyl substitution at the fifth position of the thiophene and AP84 had a pyridyl substitution at the fifth position. These compounds were synthesized from thioacrylic acid morpholide intermediate, which in turn was synthesized from α-halo carbonyl compound or halomethylene compound.

Burns and co-workers discovered[48] that 2-amino-3-benzoylthiophenes (**62, 63, 64** and **65**) are allosteric enhancer of agonist binding to the A_1 adenosine receptor (A_1AR). Substituted 2-aminothiophenes of structures **62-65**, with alkyl, aryl and cycloalkyl substituents in C-4 and C-5 position and aroyl subtituent in C-3 position (Figure 18), maintained the best allosteric enhancer activity. They have prepared some more derivatives of 2-aminothiophene, out of which the compounds represented in Figure 18 showed excellent activities.

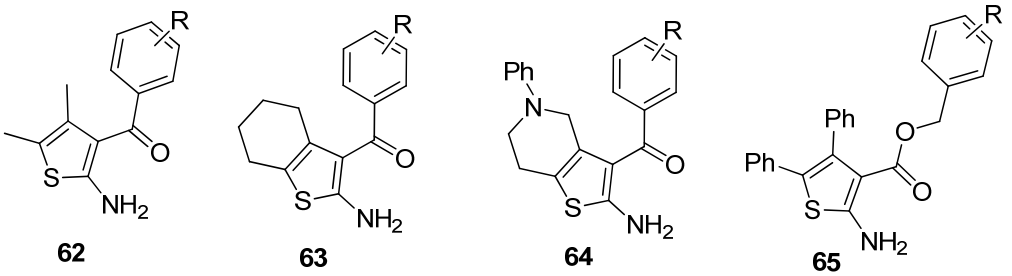


Figure 18. Structures of some aminothiophene-based allosteric enhancers

K. Nakamoto *et al.* reported[49] new quinoline, azaindole, and pyridine amide derivatives **66**, **67** and **68** that show potent antifungal activity against *C. albicans* and *A. fumigatus* that act by inhibiting the function of the glycosyl wall transferase 1 (Gwt1) protein in an early step of the glycosylphosphatidylinositol (GPI) biosynthetic pathway. Glycosylphosphatidylinositols (GPIs) are glycolipids that play a role in attaching cell

surface proteins to eukaryotic plasma membranes, including those in fungi. Also these GPI-proteins play important roles in cell wall biosynthesis and maintenance of homeostasis. The syntheses of these analogues began with 5-nitro-2-thiophenecarbonitrile and substituted phenols respectively.

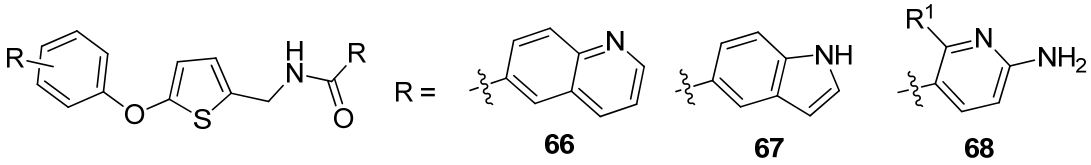


Figure 19. Thiophene-containing compounds exhibiting antifungal activity

Furthermore, some drug candidates and marketed drugs[50] **69, 70, 71** and **72** developed from 2-aminothiophene scaffold (Figure 20) show diverse pharmacological profiles with antimicrobial, anticonvulsant, and anti-inflammatory activities, and as potent c-Jun N-terminal kinase 2 and c-Jun N-terminal kinase 3 (JNK2 and JNK3) inhibitors and adenosine agonists.

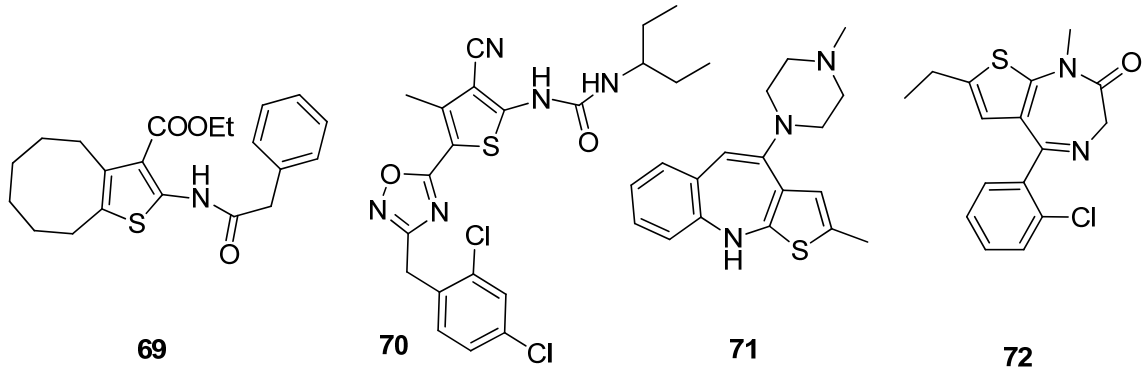


Figure 20. Examples of substituted 2-aminothiophenes having different biological activities

1.4 Present work

1.4.1 Objective

As discussed above, fluconazole is one of the most important drugs used as antifungal agent in treatment of various fungal infections. It is an orally effective azole-based antifungal drug with broad antifungal activity and low toxicity. Although fluconazole shows a very significant efficacy against *Candida albicans* and *C. neoformans*, it is not very effective against *Aspergillus niger* and *Aspergillus fumigatus*. In addition, extensive use of fluconazole has increased the number of fluconazole-resistant fungal strains. Therefore, it is

necessary to develop new and effective antifungal agents with broad spectrum of antifungal activity against life-threatening systemic mycoses including those caused by *C. neoformans, Aspergillus* species, and *Candida* species.

In search for new antifungal agents with improved antifungal profiles, we designed a series of novel antifungal compounds depicted by general formula **73** (Figure 21), wherein efforts were directed towards replacement of triazole moiety with variously substituted 2-aminothiophenes to explore the possibility of getting new antifungal agents active against the fluconazole-resistant fungal strains and with less toxicity. Since the salts of aminothiophene moieties would make molecule more water soluble than simple hydrocarbon moieties, the compounds could be more easily delivered to the target enzyme. Also since many other triazole antifungal agents have heteroatoms at the corresponding part of the molecule, complementary structure of the target enzyme would be implied and a variety of substituted 2-aminothiophenes could be made available for structure-activity relationship study.

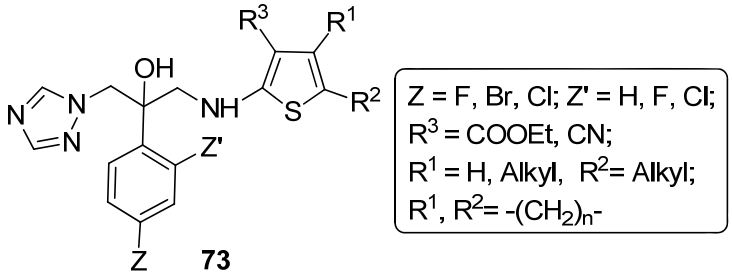
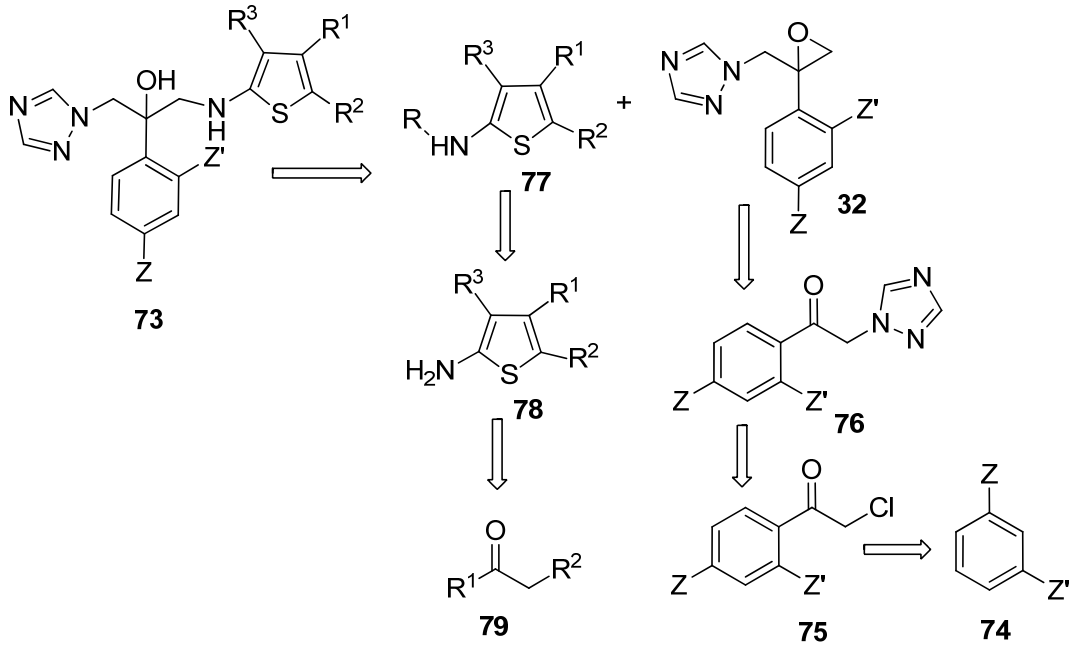


Figure 21. General structure of compounds synthesized in present work

Furthermore, the stereoselective interaction of the enzyme with stereoisomeric azoles has become an intriguing field of study. The relationship between stereochemistry and antifungal activity showed that the target enzyme, cytochrome P-45014-α- demethylase, recognized the configuration of the chiral centres[51]. So in continuation to the above work, efforts were also directed towards the synthesis of enantiopure compounds to examine the influence of absolute configuration upon antifungal activity. The structure-activity relationship study is also presented in this chapter.

1.4.2 Results and discussion

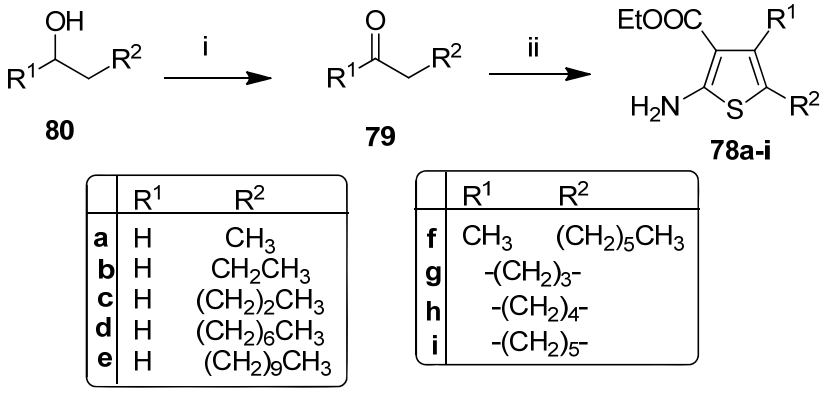
The retrosynthetic analysis for preparation of compounds depicted by general formula **73** is shown in Scheme 3.



Scheme 3. Retrosynthetic analysis for preparation of compounds **73**

Compound **73** could be synthesized by the opening of epoxide **32** with suitable aminothiophene **77** which could be synthesized from substituted 2-aminothiophene **78**, which in turn could be synthesized from respective aldehyde or ketone **79** by Gewald reaction[52]. The epoxide **32** could be synthesized from triazolyl ketone compound **76**, which can be synthesized from (di)halobenzene **74** *via* its acylated intermediate **75** by a known method[53].

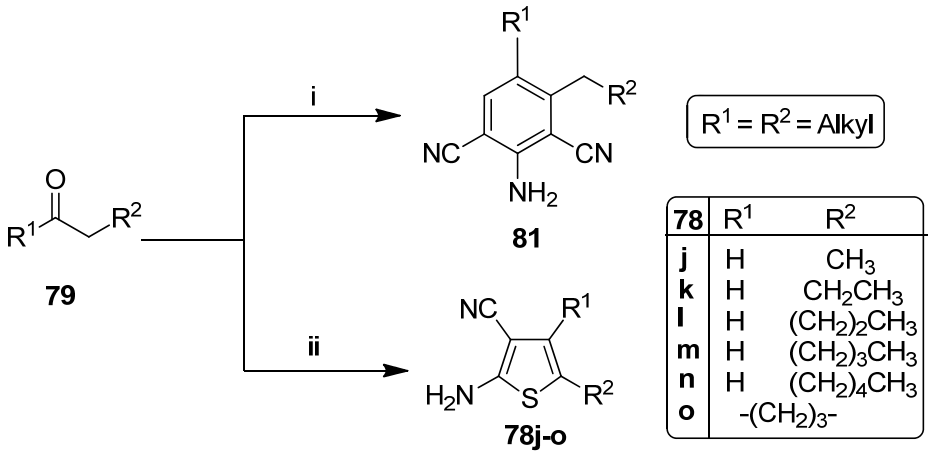
The various substituted 2-aminothiophenes **78a-i** were prepared by the synthetic route shown in Scheme 4.



Scheme 4. Reagents and conditions: i) DMSO, $(COCl)_2$, Et_3N, DCM, -78 °C, 3-4 h, 82-90% ii) Ethyl cyanoacetate, sulphur, ethanol, morpholine, 80 °C, 10-15 h, 85-93%.

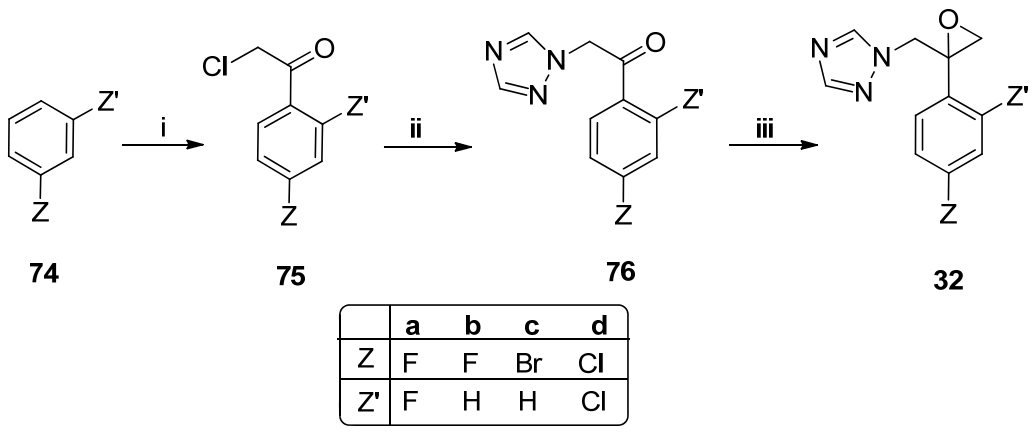
Thus, a substituted alcohol **80** (depending on side chain in thiophene) was subjected for oxidation to get aldehyde/ketone **79,** which was reacted with ethyl cyanoacetate and molecular sulphur under Gewald reaction condition[52] using morpholine as a base and ethanol as solvent (Scheme 4) to afford the desired 4 and/or 5-substituted 2-aminothiophene-3-carboxylate **78a-i.**

When aldehydes **79** were reacted with malononitrile under same reaction condition (Scheme 5), instead of getting the corresponding 5-substituted 2-aminothiophene-3-carbonitriles **78j-n**, 2,6-dicyano-3,4-dialkyl-anilines **81**[54] were obtained as major product in 80-87% yield. Thus, when propionaldehyde was reacted with malononitrile and sulphur in presence of morpholine using ethanol as solvent, 2,6-dicyano-3-ethyl-4-methyl-aniline[54] was obtained as a major product in 84% of yield. But when cyclopentanone was reacted with malononitrile under Gewald reaction condition[52] (as used for the synthesis of compounds **78a-i**) the desired compound **78o** was obtained in good yield. In order to get the 5-substituted 2-aminothiophene-3-carbonitriles from the aldehydes, we changed the reaction condition as shown in Scheme 5. The aldehydes were reacted with malononitrile and sulphur in presence of triethyl amine as base in dry DMF to get the desired compounds **78j-n** along with the minor side products 2,6-dicyano-3,4-dialkyl-anilines **81** in 10-30% of yields.



Scheme 5. Reagents and conditions: i) Malononitrile, sulphur, ethanol, morpholine, 80 °C, 10-15 h, 80-87% ii) Malononitrile, sulphur, DMF, Et_3N, 0 ^{0}C-rt, 10-15 h, 40-75%

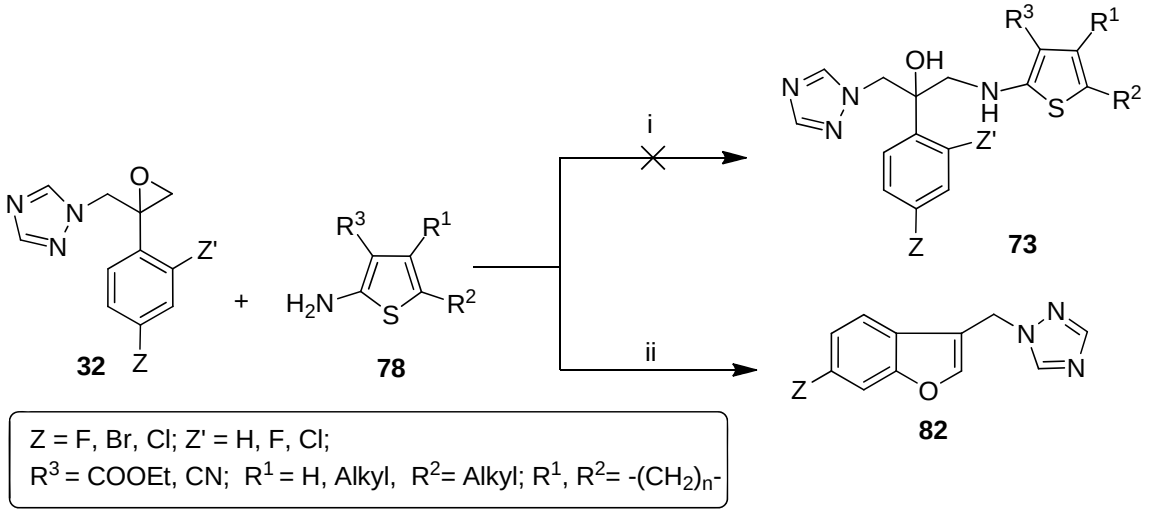
Synthesis of the epoxide **32** was carried out by known method[53] as shown in Scheme 6.



Scheme 6. Reagents and conditions: i) Chloroacetyl chloride, $AlCl_3$, DCM, 0 °C-rt, 10-12 h, 80-90 %; ii) K_2CO_3, 1*H*-1,2,4-triazole, EtOAc, 80 °C, 10 h, 69-76 %; iii) Trimethylsulphoxonium iodide, aq. KOH, DCM, 45 ^{o}C, 12 h, 81-91 %.

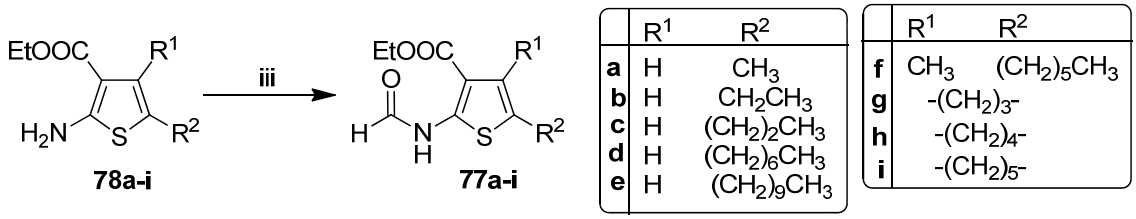
Halobenzenes **74a-d** were acylated with chloroacetyl chloride in presence of aluminium chloride. The acylated products **75a-d** thus obtained were treated with 1*H*-1,2,4-triazole in presence of potassium carbonate to get ketones **76a-d** respectively. These triazole containing ketones **76a-d** were converted into respective epoxides **32a-d** under Corey-Chaykovsky reaction conditions[53e-f] using trimethylsulphoxonium iodide and aq. potassium hydroxide. The comparison of the spectroscopic data of epoxides **32a-d** with the literature values confirmed the product formation in the reaction.

The substituted aminothiophenes **78** were then reacted with the epoxides **32** in presence of potassium carbonate and tetrabutyl ammonium bromide (TBAB) in ethyl acetate at refluxing temperature but we failed to get desired compounds **73.** For the synthesis of target compound **73,** substituted aminothiophenes **78** were then reacted with the epoxides **32a-d** in presence of strong bases such as potassium tert-butoxide, sodium hydride *etc* in different solvents such as dimethylsulfoxide, dimethylformamide *etc*. and also at varying temperatures, but none of the above reaction conditions resulted in product formation. Every reaction resulted in either recovery of starting material or a complex reaction mixture. In case of epoxides **32a** and **32d** the reaction resulted in the formation of the substituted benzofuran[53b] **82** along with the recovery of compound **78** (Scheme 7).



Scheme 7. Reagents and conditions: i) K_2CO_3, TBAB, EtOAc ii) a) NaH, DMF, rt b) *t*BuOK, DMF and/or *t*BuOH, rt.

After the failure in the reaction of substituted aminothiophenes **78** with epoxides **32**, we thought to make the amine proton of substituted aminothiophenes **78** more active and then react with epoxides **32** in presence of mild base. Accordingly, we formylated the substituted 2-aminothiophenes **78a-i** by using formic acid and ammonium acetate at 120-140 ^{0}C to get the the substituted N-formylated aminothiophene carboxylates **77a-i** as shown in Scheme 8. Evidences for the formation of N-formylated aminothiophene carboxylates **77a-i** were shown by the presence of amide proton in the range of δ 9.00 to 11.00 in ^{1}H NMR. Furthermore, IR spectra in chloroform/nujol showed band at 1680 to 1690 cm^{-1} indicating the presence of amide carbonyl, in addition to the band at 1660 to 1675 cm^{-1} for ester carbonyl.

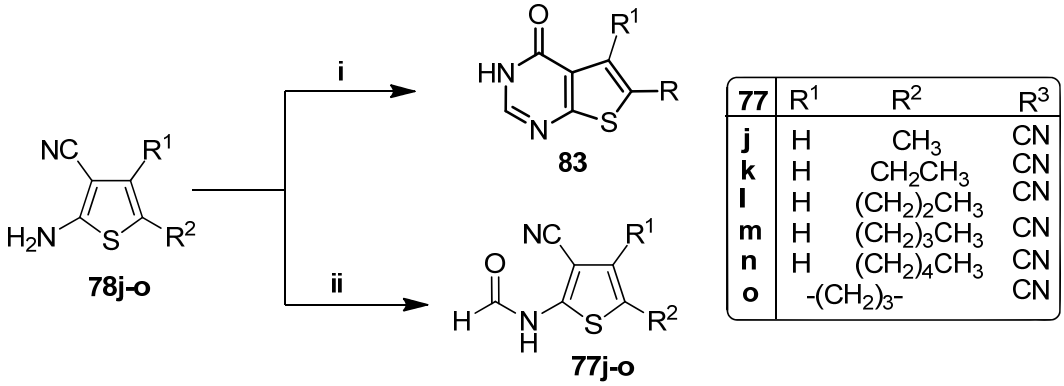


	R^1	R^2
a	H	CH_3
b	H	CH_2CH_3
c	H	$(CH_2)_2CH_3$
d	H	$(CH_2)_6CH_3$
e	H	$(CH_2)_9CH_3$

	R^1	R^2
f	CH_3	$(CH_2)_5CH_3$
g	$-(CH_2)_3-$	
h	$-(CH_2)_4-$	
i	$-(CH_2)_5-$	

Scheme 8. Reagents and conditions: i) HCOOH, NH_4OAc, 120-140 °C, 5-7 h, 71-83%.

The 5-substituted 2-aminothiophene-3-carbonitriles **78j-o** were then subjected to formylation by using same reaction condition as used for the preparation of compounds **77a-i** but instead of getting the desired products **77j-o**, thieno-[2,3-*d*]pyrimidin-4(3*H*)-ones[55] **83** were obtained (Scheme 9). For the synthesis of N-formylated compounds **77j-o**, we attempted the reaction at different temperatures like 80 or 60 ^{0}C, which also resulted in the formation of compound **83.** To obtain the desired N-formylated compound, finally the reaction was carried out at room temperature to afford the N-formylated aminothiophene carbonitriles **77j-o**. Formations of N-formylated aminothiophene carbonitriles **77j-o** were confirmed by the ^{1}H NMR value of amide proton in the range of δ 9.00 to 11.00. Furthermore, IR band at 1680 to 1690 cm^{-1} confirmed the formation of formylated products.

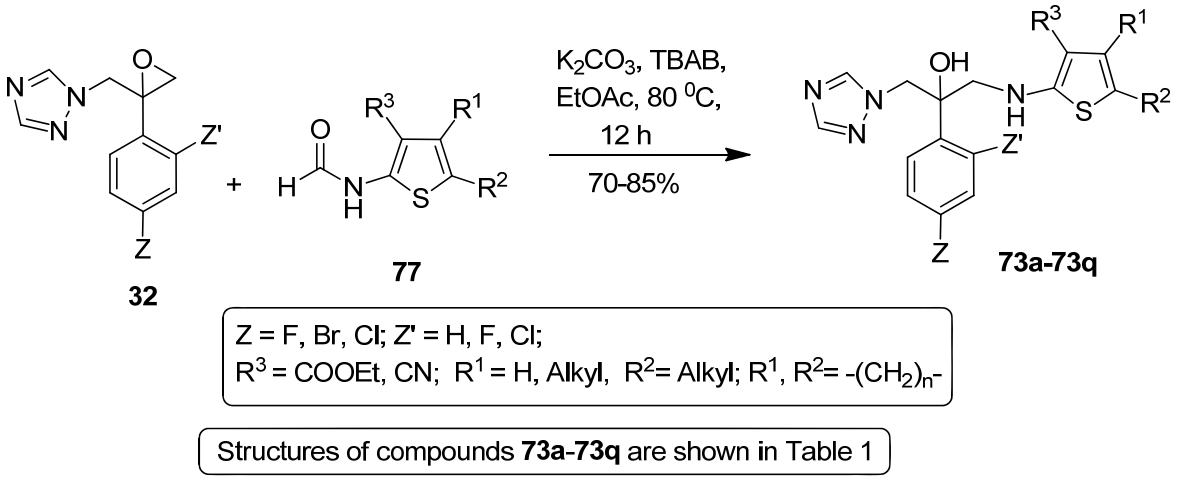


77	R^1	R^2	R^3
j	H	CH_3	CN
k	H	CH_2CH_3	CN
l	H	$(CH_2)_2CH_3$	CN
m	H	$(CH_2)_3CH_3$	CN
n	H	$(CH_2)_4CH_3$	CN
o		$-(CH_2)_3-$	CN

Scheme 9. Reagents and conditions: i) HCOOH, NH_4OAc, 120-140 °C, 5-7 h, 78-90% ii) HCOOH, NH_4OAc, rt, 2-4 h, 70-78%.

So as to achieve the synthesis of target molecules, the N-formylated aminothiophenes **77a-o** were then reacted with the epoxides **32** in presence of potassium carbonate and tetrabutylammonium bromide (TBAB) in ethyl acetate at refluxing temperature to afford the target molecules **73a-o** as shown in Scheme 10. Four successive doublets, each for one proton in the range of δ 4.04-4.98 with coupling constant in the range

of J = 10-14 Hz in ^{1}H NMR spectrum confirmed the formation of product. These four protons are diastereotopic in nature hence showed doublets in ^{1}H NMR spectrum. The structures of the products were further confirmed with the help of ^{13}C NMR, IR and mass spectroscopy.



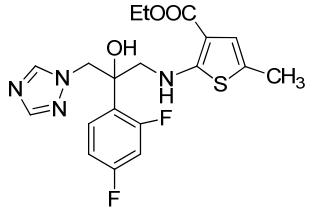
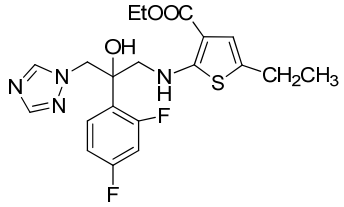
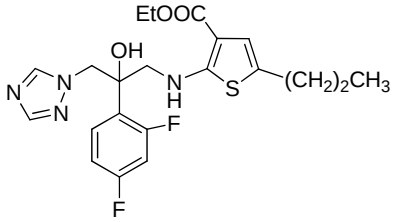
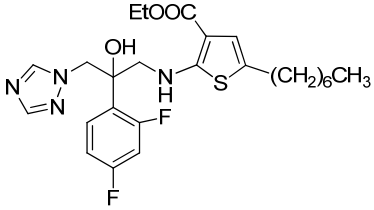
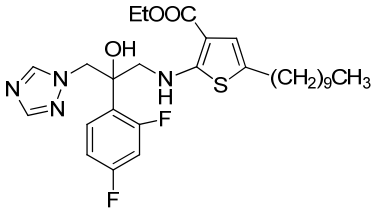
Scheme10. Synthesis of fluconazole analogues **73**

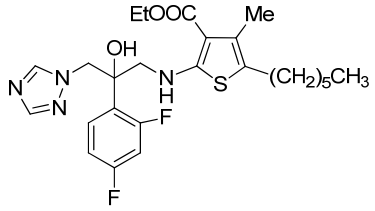
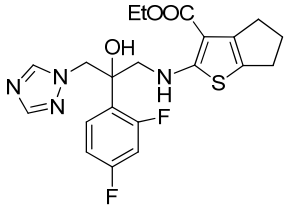
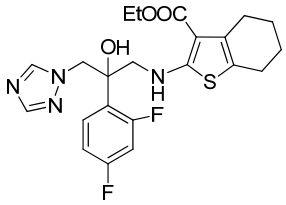
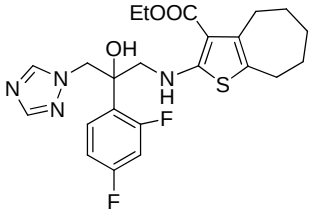
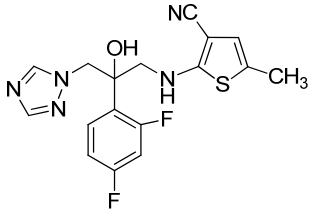
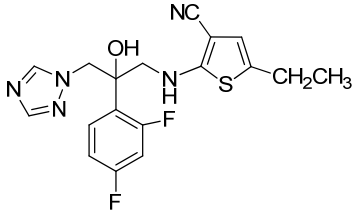
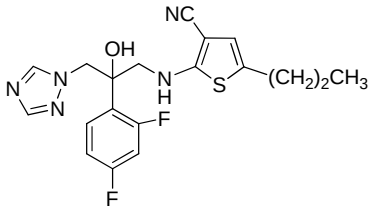
Using above synthetic strategy, a number of compounds were synthesized and structure activity relationship was studied. The synthesized fluconazole analogues containing 4 and/or 5-substituted 2-aminothiophene-3-carboxylates/carbonitriles **73a-q** described in this chapter were screened for antifungal activity at FDC Ltd., Mumbai and the results are presented in the following paragraphs.

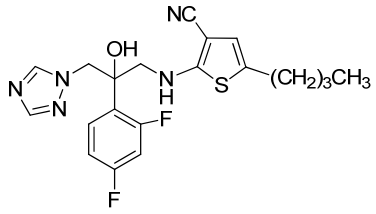
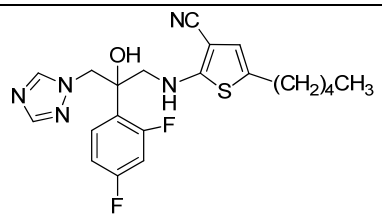
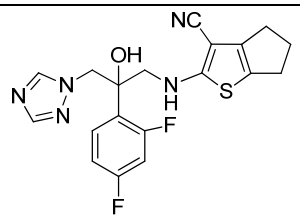
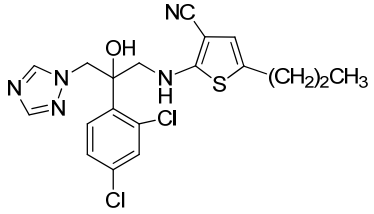
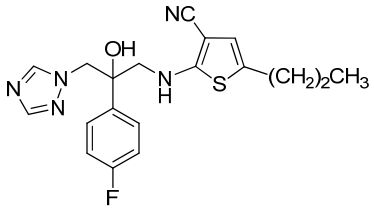
Antifungal evaluation

All the newly synthesized compounds **73** were tested for antifungal activity against various fungi including *Candida albicans* ATCC 24433, *Aspergillus niger* ATCC 16404 and *Fusarium proliferatum* ATCC 10052. *In vitro* evaluation of antifungal activity was performed by determining the minimum inhibitory concentration (MIC) following standard methods[55,56]. Antifungal susceptibility testing of these compounds was done by broth dilution method using RPMI 1640 medium (RPMI = Roswell Park Memorial Institute) with MOPS (3-(N-morpholino) propanesulfonic acid) buffer. Known antifungal agents like fluconazole and amphotericin B were used as positive control. End points were determined after 48 hours visually and by using spectrophotometer wherever necessary. Different dilutions were tried and various sets of experiments were performed. The activity parameters are enumerated in Table 1.

Table 1: MIC obtained by broth macro-dilution method

Sr No	Comp. Code	Structures	MIC_{80} in µg/mL		
			C. albicans ATCC 24433	*A. niger* ATCC 16404	*F. proliferatum* ATCC 10052
A		Fluconazole	**1**	128	128
B		Amphotericin-B	**0.25**	1	2
1	**73a**		2	NI till 16	NI till 16
2	**73b**		2	NI till 4	NI till 4
3	**73c**		2	NI till 16	NI till 16
4	**73d**		NI till 16	NI till 16	NI till 16
5	**73e**		NI till 4	NI till 4	NI till 4

6	**73f**		NI till 2	NI till 2	NI till 2
7	**73g**		2	NI till 8	NI till 8
8	**73h**		4	NI till 4	NI till 4
9	**73i**		8	NI till 4	NI till 4
10	**73j**		**0.5**	> 64	> 64
11	**73k**		**0.25**	> 32	> 32
12	**73l**		**0.12**	> 16	> 16

13	**73m**		**0.5**	> 4	> 4
14	**73n**		**0.25**	> 8	> 8
15	**73o**		**0.5**	NI till 16	NI till 16
16	**73p**		**0.12**	> 4	> 4
17	**73q**		**2**	> 16	> 16

NI: No inhibition

For azoles: For fluconazole and the synthetic compounds, MIC is recorded as the concentration exhibiting 80% inhibition as compared to the positive control.

For amphotericin B: MIC is recorded as the concentration exhibiting complete inhibition.

The antifungal activity exhibited by the compounds with 2-aminothiophene carbonitrile in the present work was confirmed by secondary screening of **73j-n** against various strains of *Candida* and it was observed that activity of **73l** and **73m** is excellent against the *C. albicans* ATCC 24433, *C. albicans* ATCC 90028 and *C. albicans* ATCC 90030 when compared with amphotericin B and fluconazole as shown in Table 2.

Table 2: MIC_{50} obtained by broth micro-dilution method

Fungus	Activity against organisms (MIC_{50} in µg/mL)						
	AMB	**FLU**	**73j**	**73k**	**73l**	**73m**	**73n**
C.albicans ATCC 24433	**0.25**	**0.25**	**0.25**	**0.12**	**0.06**	**0.25**	**0.5**
C.albicans ATCC 10231	**0.5**	1	1	**0.5**	**0.25**	**0.25**	**0.5**
C.albicans ATCC 90028	**0.5**	**0.5**	**0.5**	**0.12**	**0.12**	**0.12**	**0.25**
C. glabrata ATCC 90030	**0.25**	1	**0.5**	**0.25**	**0.12**	**0.25**	**0.5**
C. glabrata NCPF 8018	**0.5**	1	1	**0.5**	**0.12**	**0.25**	**0.5**
C. krusei ATCC 6258	**0.5**	32	64	16	8	>4	8
C. krusei NCPF 3876	**0.5**	16	>64	32	8	4	>8
C. tropicalis ATCC 750	**0.5**	1	4	4	2	2	4
C. tropicalis ATCC 13803	**0.5**	**0.25**	**1**	**0.5**	**0.25**	**0.25**	1
C. neoformans ATCC 34664	**0.5**	2	4	2	1	**0.25**	2
C. neoformans MTCC 4424	**0.25**	2	4	4	1	**0.25**	2

For azoles**:** For fluconazole and the synthetic compounds, MIC is recorded as the concentration exhibiting 50% inhibition as compared to the positive control.
For amphotericin B**:** MIC is recorded as the concentration exhibiting complete inhibition.

The activity data indicated following points regarding the structure-activity relationship of the compounds studied in the present chapter.

1. The compounds with 2-aminothiophene carbonitrile are more active than with 2-aminothiophene carboxylate e.g. **73a-c** v/s **73j-l**.

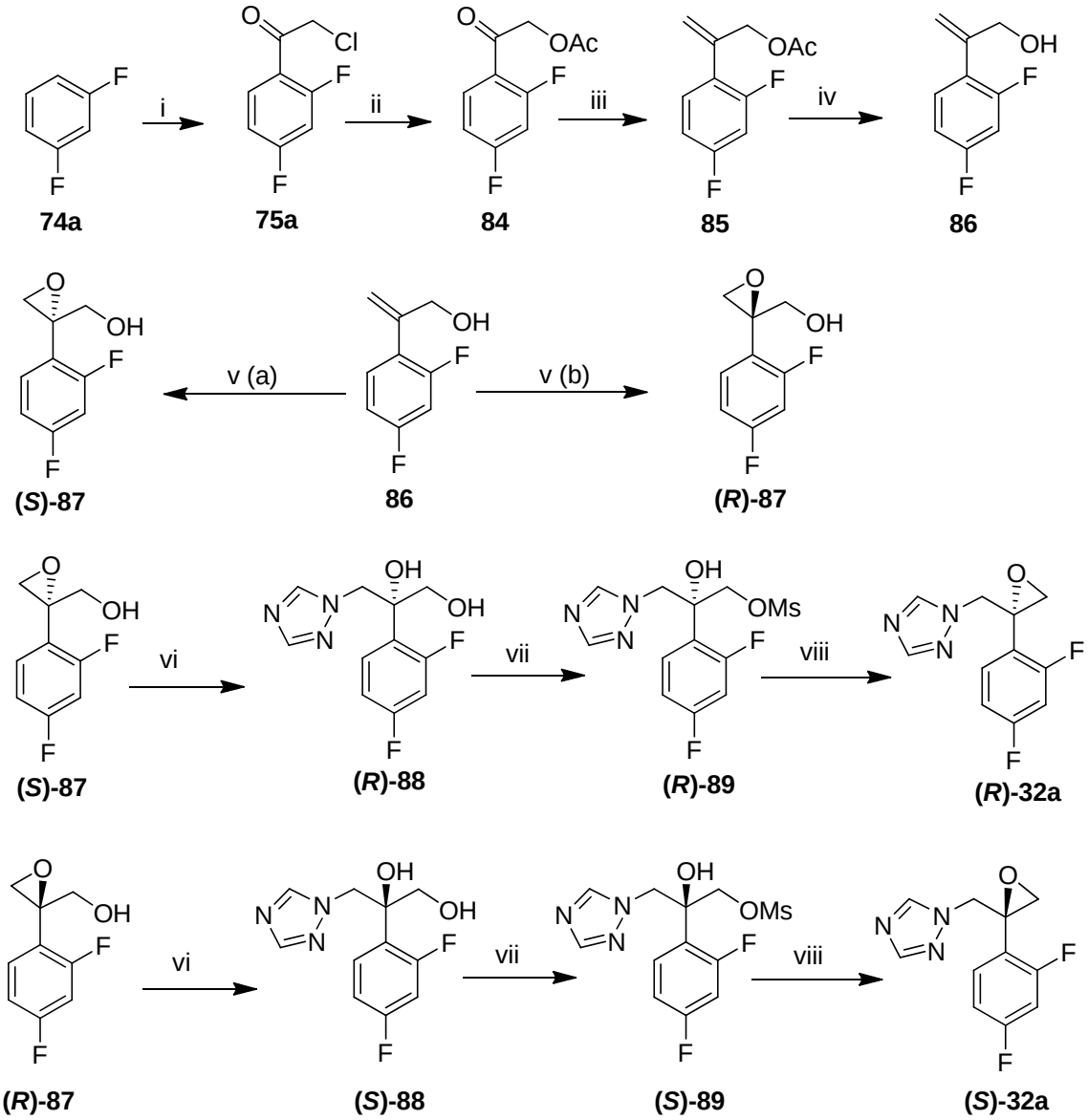
2. In case of the compounds **73j-n** with aliphatic side chain at R^2, activity is observed with compounds having shorter side chains and reaches maximum for $R^2 = (CH_2)_3CH_3$ after which the activity decreases rapidly e.g. **73j < 73k < 73l ≈ 73m > 73n**.

3. The compounds with substitutions at both R^1 and R^2 show less activity, when compared with the compounds with no substitutents at R^1 e.g. **73a-c** v/s **73f**.

4. The compounds with R^1, R^2 forming a carbocyclic ring show less activity when compared with the compounds with R^1= H, R^2= alkyl chain, and activity vanishes in larger rings e.g. **73j-n** v/s **73o and 73g > 73h > 73i**.

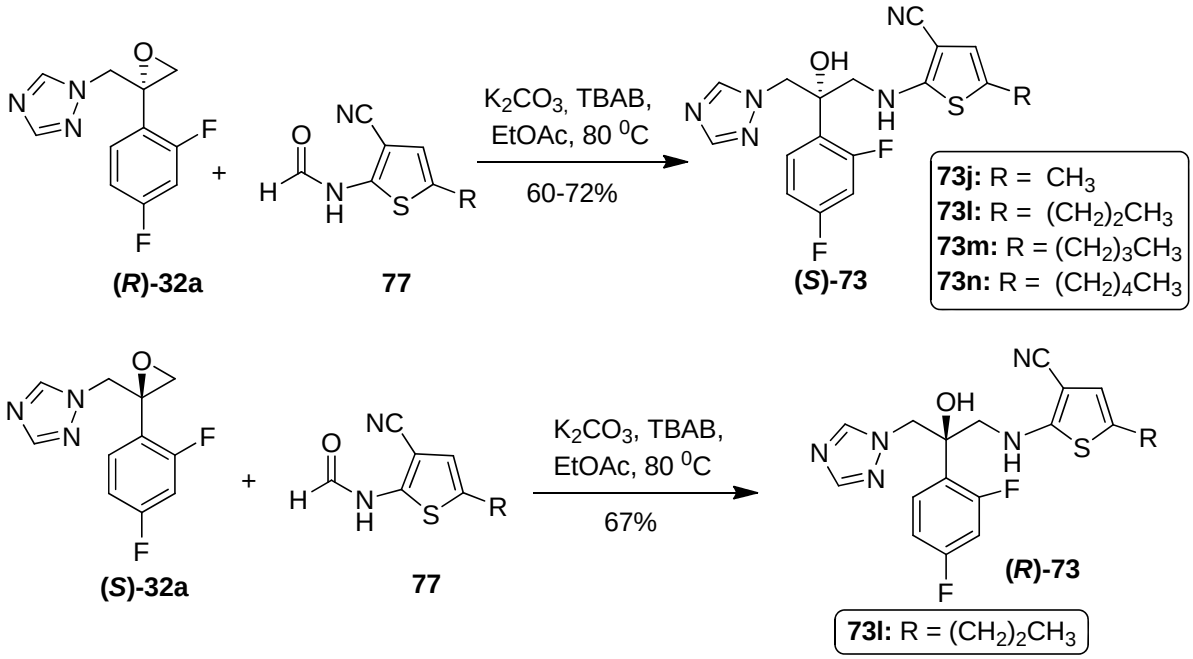
In continuation to the above work, the *R* and *S* enantiomers of compound **73** were prepared to examine the influence of absolute configuration upon antifungal activity. From the antifungal activity results of racemic compounds **73** it was observed that the compounds with 2-aminothiophene carbonitriles (**73j-o**) are more active than compounds with 2-aminothiophene carboxyalate, so the compounds **73j-o** containing 2-aminothiophene carbonitriles were chosen for preparation of their enantiomers. The preparation of enantiomers of this class of antifungal agents was achieved from chiral epoxides **(*R*)-32a** and **(*S*)-32a**. These two chiral epoxides were synthesized by known method[57] as shown in Scheme 11.

The chiral epoxides **(*R*)-32a** and **(*S*)-32a** were synthesized by known method[57] wherein 1,3-difluorobenzene was acylated with chloroacetyl chloride to obtain the chloroketone **75a** and then reacted with sodium acetate in DMF to afford acetoxy ketone **84**. The acetoxy ketone **84** was then subjected to Wittig reaction followed by deprotection of acetoxy group to give allylic alcohol **86**, which on Sharpless epoxidation[57] using (+)-diethyl L-tartarate and (-)-diethyl d-tartarate provided the hydroxyepoxides (*R*)-**87** and (*S*)-**87** respectively. The chiral hydroxyepoxides **87** were then reacted with 1,2,4-triazole in presence of sodium hydride to get diols (*R*)-**88** and (*S*)-**88** which were protected as mesylates (*R*)-**89** and (*S*)-**89** and subjected to reaction with sodium hydride in dry DMF, to afford the chiral epoxides **(*R*)-32a** and **(*S*)-32a** respectively.



Scheme 11. Reagents and conditions: i) $ClCH_2COCl$, DCM, $AlCl_3$, 75% ii) NaOAc, NaI, DMF, 12 h, 77% iii) Ph_3PCH_3Br, NaHMDS, THF, 3-4 h, 44% iv) KOH, 1,4-dioxane: H_2O (1:1), 12 h, 87% v) (a) (+)-DET, $Ti\{OCH(CH_3)_2\}_4$, TBHP, DCM, -23 ^{0}C, 24 h, 44%; (b) (-)-DET, $Ti\{OCH(CH_3)_2\}_4$, TBHP, DCM, -23 ^{0}C, 24 h, 45% vi) 1,2,4 -Triazole, NaH, DMF, 0 ^{0}C-rt, 12 h, 37% vii) CH_3SO_2Cl (MsCl), Et_3N, DCM, 0 ^{0}C, 2 h viii) NaH, DMF, 0 ^{0}C-rt, 3-5 h, 30% over two steps.

The N-formylated aminothiophene carbonitriles **77** were then reacted with the chiral epoxides **(*R*)-32a** and **(*S*)-32a** in presence of potassium carbonate and TBAB (tetrabutyl ammonium bromide) in ethyl acetate at refluxing temperature to afford the target enantiopure molecules **(*S*)-73** and **(*R*)-73** as shown in Scheme 12.



Scheme 12. Synthesis of enantiomers **(*S*)-73** and **(*R*)-73**

After synthesis of enantiomers of **73j**, **73m** and **73n,** specific rotations of enantiomers were calculated from the observed rotations as shown in Table 3.

Table 3. Specific rotations of enantiomers of **73j**, **73m** and **73n**.

Comp. No.	Chem. Purity	Peak In Chiral HPLC Chromatogram	Retention Time (RT) min	Enantiomeric Excess (% ee)	Specific Rotation $[\alpha]_D^{24} = \frac{\text{Obs. Rotation X 100}}{\text{Conc. X Length}}$
(*S*)-73j	100%	B	45.65	98.99	-10 ^{o} (c = 1.01, MeOH)
(*S*)-73m	100%	B	26.24	98.34	-10 ^{o} (c = 1.03, MeOH)
(*S*)-73n	100%	B	26.09	99.89	-12 ^{o} (c = 1.02, MeOH)

We also accomplished direct optical resolution of compound **73l** by chiral HPLC (High Performance Liquid Chromatography) providing each enantiomer in high optical purity.

Resolution of racemic compounds 73 by using chiral HPLC

Out of the above compounds synthesized, a few compounds were chosen for resolution using chiral HPLC wherein compounds **73j**, **73k, 73l, 73m** and **73n** were resolved

using chiral analytical HPLC (High Performance Liquid Chromatography), under the following conditions:

HPLC Column	Kromasil 5-Cellucoat (250 x 4.6 mm)
Mobile Phase	IPA: PE: TFA (20:80:0.1)
Wavelength	254 nm
Flow rate	0.5 mL/min (330 psi)

The retention times of the various enantiomers **73j**, **73k, 73l, 73m** and **73n** in chiral HPLC are shown in Table 4.

Table 4. Retention times of the enantiomers of **73j**, **73k**, **73l**, **73m** and **73n**.

Comp. No.	Peak In Chiral HPLC Chromatogram	Retention Time (RT) min	Peak In Chiral HPLC Chromatogram	Retention Time (RT) min
73j	A	34.35	B	45.97
73k	A	24.01	B	26.51
73l	A	25.46	B	28.85
73m	A	23.70	B	26.57
73n	A	23.45	B	26.09

Since **73l** was observed to be the most active compound within this group, it was resolved into *R* and *S* enantiomers using chiral preparative HPLC under following conditions:

HPLC Column	Chiralcel-OD (250 x 4.6 mm) (DAICEL)
Mobile Phase	IPA: PE: TFA (20:80:0.1)
Wavelength	254 nm

The chiral HPLC chromatograms for racemic **73l** and its (S) and (R) enantiomers are shown in Figure 22.

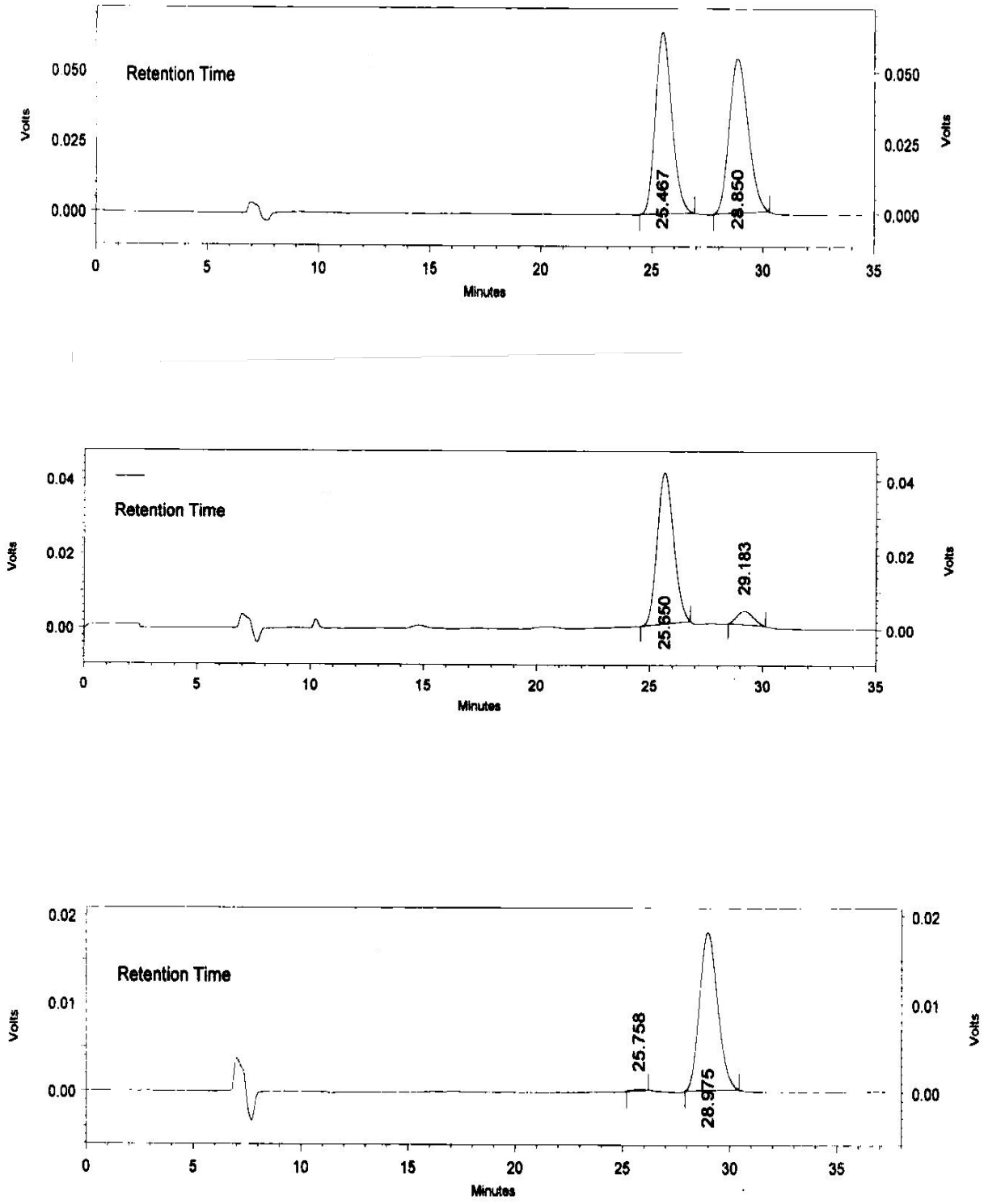


Figure 22. Resolution of **73l** using chiral HPLC

After resolution and separation of enantiomers of **73l**, specific rotations of enantiomers were calculated from the observed rotations as shown in Table 5.

Table 5. Specific rotations of enantiomers of **73l**.

Comp No.	Peaks In Chromatogram	Retention Time (RT) min	Enantiomeric excess (% *ee*)	Specific Rotation $[\alpha]_D^{24} = \frac{\text{Obs. Rotation X 100}}{\text{Conc. X Length}}$
73l	A	25.65	83.48	+10 ^{o} (c = 1.0, THF)
	B	28.97	98.91	-12 ^{o} (c = 1.0, THF)

All the newly synthesized and resolved *R* and *S* enantiomers of compound **73** were tested for antifungal activity against various fungi and results are enumerated in Table 6.

Table 6. MIC obtained by broth micro-dilution method

Fungus	**Activity against organisms (MIC_{50} in µg/mL)**										
	AMB	**FLU**	**73l**	**(*R*)-73l**	**(*S*)-73l**	**73m**	**(*S*)-73m**	**73n**	**(*S*)-73n**	**73j**	**(*S*)-73j**
C. albicans ATCC 24433	**0.25**	**0.5**	**0.06**	**0.5**	**0.25**	**0.12**	**0.06**	**0.25**	**0.12**	**0.25**	**0.12**
C. albicans ATCC 10231	**0.5**	**0.5**	**0.12**	1	**0.5**	**0.12**	**0.06**	1	**0.5**	**0.5**	**0.25**
C. albicans ATCC 2091	**0.5**	**0.5**	**0.12**	1	**0.5**	**0.25**	**0.12**	1	**0.5**	**0.5**	**0.25**
C. albicans ATCC 90028	**0.5**	**0.5**	**0.12**	**0.5**	**0.5**	**0.12**	**0.06**	**0.5**	**0.25**	**0.5**	**0.25**
C. glabrata ATCC 90030	**0.25**	4	**0.12**	**0.5**	**0.25**	**0.12**	**0.06**	**0.25**	**0.12**	**0.25**	**0.12**
C. krusei ATCC 6258	**0.5**	64	8	>8	**0.5**	8	4	8	4	64	32
C.tropicalis ATCC 750	**0.5**	2	2	>8	**0.5**	1	0.5	2	1	4	2

For azoles**:** For fluconazole and the synthetic compounds, MIC is recorded as the concentration exhibiting 50% inhibition as compared to the positive control.
For amphotericin B**:** MIC is recorded as the concentration exhibiting complete inhibition.

From the antifungal activity results of these enantiopure compounds it was found that the *S*-enantiomer of this class of antifungal agents has higher antifungal activity than the *R*-enantiomer.

1.5 Conclusion

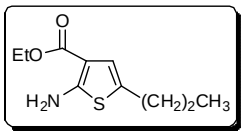
A novel series of fluconazole analogues having general structure **73** containing substituted 2-aminothiophenecarboxylates and 2-aminothiophenecarbonitriles were synthesized by a short route with good to excellent yields. Variation in the side chains can be done by varying the starting materials, most of which are cheap and readily available. These reactions can be carried out conveniently on large scales and various new chemical entities (NCEs) were prepared for SAR studies. A few compounds were prepared in enantiomerically pure form to examine the influence of absolute configuration on antifungal activity. This work will be very helpful in development of more potent antifungal agents.

1.6 Experimental Section

Preparation of ethyl 2-amino-5-propylthiophene-3-carboxylate (78c)

Valeraldehyde (10.0 g, 0.116 mol) was taken in two-necked round bottom flask equipped with reflux condenser and guard tube, absolute ethanol (100 mL) was added followed by sulphur powder (3.72 g, 0.116 mol), ethyl cyanoacetate (13.1 g, 0.116 mol) and triethyl amine (8.08 mL, 0.058 mol). The reaction mixture was stirred at 70-80 ºC for 12 h, cooled to room temperature and diluted with excess of water, extracted with ethyl acetate, dried over Na_2SO_4 and concentrated under vacuum. Purification by column chromatography yielded pure product ethyl 2-amino-5-propylthiophene-3-carboxylate **78c** as redish brown oil (23.08 g, 93.2 %).

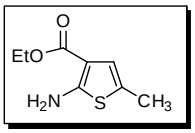
Nature: Reddish brown oil; **Yield:** 93.2 %; **^{1}H NMR** (200 MHz, $CDCl_3$)**:** δ 0.95 (t, *J* = 7 Hz, 3H), 1.34 (t, *J* = 7 Hz, 3H), 1.51-1.71 (m, 2H), 2.56 (t, *J* = 7 Hz, 2H), 4.26 (q, *J* = 7 Hz, 2H), 4.75 (bs, 2H), 6.64 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$)**:** δ 13.4, 13.9, 24.2, 41.0, 58.3, 125.6, 127.6, 143.8, 158.4, 162.8.; **IR** (Chloroform)**:** 1673, 3287, 3343 cm^{-1}; **MS** (ESI) *m*/*z***:** 214.22 (M + 1).



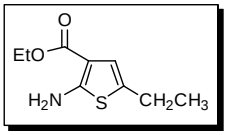
The amino esters 7**8a, 78b, 78d-78i** were prepared from the corresponding aldehydes or ketones **79** using the procedure given for the preparation of compound 7**8c**.

Ethyl 2-amino-5-methylthiophene-3-carboxylate (78a)[58]

Nature: Dark brown oil; **Yield:** 85.2 %; **^{1}H NMR** (200 MHz, $CDCl_3$)**:** δ 1.28 (t, *J* = 8 Hz, 3H), 2.36 (s, 3H), 4.31 (q, *J* = 8 Hz, 2H), 5.43 (bs, 2H), 6.66 (s, 1H). **^{13}C NMR** (50 MHz, $CDCl_3$)**:** δ 14.4, 15.3, 59.4, 124.9, 128.1, 138.2, 158.4, 164.5; **IR** (Chloroform)**:** 1672, 3294, 3449 cm^{-1}; **MS** (ESI) *m*/*z***:** 186.16 (M +1).



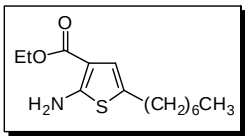
Ethyl 2-amino-5-ethyl-thiophene-3-carboxylate (78b)[59,60]



Nature: Reddish brown oil; **Yield:** 94.6 %; **^{1}H NMR** (200 MHz, $CDCl_3$)**:** δ 1.23 (t, *J* = 7 Hz, 3H), 1.34 (t, *J* = 7 Hz, 3H), 2.62 (q, *J* = 7 Hz, 2H), 4.26 (q, *J* = 7 Hz, 2H), 4.62 (bs, 2H), 6.64 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$)**:** δ 14.1, 16.3, 22.8, 60.3, 125.3, 127.6, 136.8, 157.8, 163.7; **IR** (Chloroform)**:** 1669, 3350, 3483 cm^{-1}; **MS** (ESI) *m*/*z***:** 238.99 (M + K).

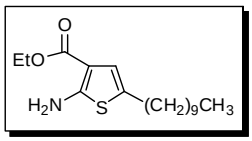
Ethyl 2-amino-5-heptyl-thiophene-3-carboxylate (78d)

Nature: Red oil; **Yield:** 93.5 %; **^{1}H NMR** (200 MHz, $CDCl_3$)**:** δ 0.88 (t, *J* = 6 Hz, 3H), 1.29-1.37 (m, 11H), 1.50-1.65 (m, 2H), 2.57 (t, *J* = 8 Hz, 2H), 4.26 (q, *J* = 8 Hz, 2H), 5.31 (bs, 1H), 6.63 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$)**:** δ 14.0, 14.4, 22.5, 28.8, 28.9, 29.6, 31.0, 31.7, 59.5, 106.6, 121.3, 127.3, 160.5, 165.3; **IR** (Chloroform)**:** 1674, 3358, 3440 cm^{-1}; **MS** (ESI) *m*/*z***:** 308.27 (M + K).



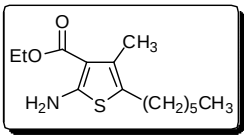
Ethyl 2-amino-5-n-decyl-thiophene-3-carboxylate (78e)

Nature: Brown semisolid; **Yield:** 89.5 %; **^{1}H NMR** (200 MHz, $CDCl_3$)**:** δ 0.88 (t, *J* = 6 Hz, 3H), 1.22-1.37 (m, 17H), 1.50-1.65 (m, 2H), 2.56 (t, *J* = 6 Hz, 2H), 4.25 (q, *J* = 8 Hz, 2H), 5.40 (bs, 2H), 6.63 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$)**:** δ 13.8, 14.2, 22.4, 28.8, 29.1, 29.2, 29.3, 29.4, 29.5, 30.8, 31.7, 59.2, 105.7, 121.1, 126.4, 161.3, 165.2; **IR** (Chloroform)**:** 1670, 3347, 3481 cm^{-1}; **MS** (ESI) *m*/*z***:** 350.32 (M + K).



Ethyl 2-amino-5-hexyl-4-methylthiophene-3-carboxylate (78f)

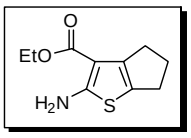
Nature: Brown semisolid; **Yield:** 90.3%; **^{1}H NMR** (200 MHz, $CDCl_3$)**:** δ 0.88-0.95 (m, 6H), 1.17-1.30 (m, 8H), 2.20 (s, 3H), 2.60 (t, *J* = 8 Hz, 2H), 4.25 (q, *J* = 8 Hz, 2H), 5.43 (bs,



2H); **^{13}C NMR** (50 MHz, $CDCl_3$)**:** δ 13.7, 14.1, 14.5, 21.9, 27.5, 28.3, 30.8, 31.5, 61.2, 112.7, 120.4, 137.1, 161.1, 165.3; **IR** (Chloroform)**:** 1669, 3345, 3456 cm^{-1}; **MS** (ESI) *m*/*z***:** 270.07 (M + 1).

Ethyl 2-amino-5,6-dihydro-4*H*-cyclopenta[b]thiophene-3-carboxylate (78g)[60]

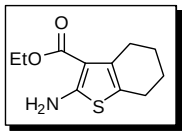
Nature: Dark brown oil; **Yield:** 84.3 %; **^{1}H NMR** (200 MHz, $CDCl_3$)**:** δ 1.32 (t, *J* = 7 Hz,



3H), 2.22-2.38 (m, 2H), 2.65-2.90 (m, 4H), 4.24 (q, *J* = 7 Hz, 2H), 5.85 (bs, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$)**:** δ 14.4, 25.5, 26.7, 29.3, 59.1, 104.8, 127.7, 139.2, 161.3, 165.6; **IR** (Chloroform)**:** 1666, 3341, 3476 cm^{-1}; **MS** (ESI) *m*/*z***:** 250.09 (M + K).

Ethyl 2-amino-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate (78h)[60, 61]

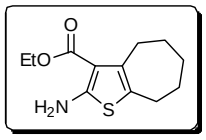
Nature: Brown semisolid; **Yield:** 93.8 %; **^{1}H NMR** (200 MHz, $CDCl_3$ + CCl_4)**:** δ 1.27 (t, *J*



= 7 Hz, 3H), 1.62-1.78 (m, 4H), 2.35-2.50 (m, 2H), 2.54-2.70 (m, 2H), 4.19 (q, *J* = 7 Hz, 2H), 5.87 (bs, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$ + CCl_4)**:** δ 14.4, 22.8, 23.2, 24.5, 26.9, 59.3, 105.7, 117.5, 132.4, 161.7, 166.1; **IR** (Chloroform)**:** 1659, 3345, 3483 cm^{-1}; **MS** (ESI) *m*/*z***:** 226.13 (M + 1).

Ethyl 2-amino-5,6,7,8-tetrahydro-4*H*-cyclohepta[b]thiophene-3-carboxylate (78i)

Nature: Brown semisolid; **Yield:** 92.6 %; **^{1}H NMR** (200 MHz, $CDCl_3$ + CCl_4)**:** δ 1.30 (t, *J*

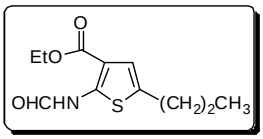


= 8 Hz, 3H), 1.58-1.76 (m, 4H), 2.41-2.52 (m, 4H), 2.54-2.61 (m, 2H), 4.27 (q, *J* = 8 Hz, 2H), 5.83 (bs, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$ + CCl_4)**:** δ 14.7, 23.3, 23.8, 25.2, 26.7, 28.5, 60.3, 106.3, 117.9, 133.1, 160.4, 165.7; **IR** (Chloroform)**:** 1659, 3345, 3483 cm^{-1}; **MS** (ESI) *m*/*z***:** 240.11 (M + 1).

Preparation of ethyl 2-formamido-5-propylthiophene-3-carboxylate (77c)

A mixture of compound 7**8c** (2.13 g, 0.01 mol), ammonium acetate (0.77g, 0.01 mol) and formic acid (7.56 mL, 0.2 mol) was refluxed at 120-140 ^{0}C for 7 h, cooled to room temperature and diluted with water, extracted with ethyl acetate, dried over Na_2SO_4, concentrated and purified by column chromatography to give pure compound ethyl 2-formamido-5-propylthiophene-3-carboxylate **77c** as brown semisolid (1.82 g, 75.4 %).

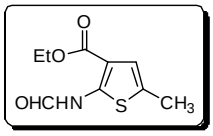
Nature: Brown semisolid; **Yield:** 75.4%; **^{1}H NMR** (200 MHz, $CDCl_3$)**:** δ 0.96 (t, *J* = 8 Hz, 3H), 1.38 (t, *J* = 8 Hz, 3H), 1.61-1.73 (m, 2H), 2.69 (t, *J* = 8 Hz, 2H), 4.33 (q, *J* = 8 Hz, 2H), 6.88 (s, 1H), 8.49 (s, 1H), 10.93 (s, 1H); **^{13}C NMR** (200 MHz, $CDCl_3$)**:** δ 13.3, 14.1, 24.2, 31.3, 60.5, 113.1, 119.9, 135.7, 144.6, 157.1, 165.1; **IR** (Chloroform)**:** 1670, 1685, 3289 cm^{-1}; **MS** (ESI) *m*/*z***:** 242.06 (M + 1), 264.01 (M + Na).



The following compounds **77a, 77b, 77d-77i** were prepared using the procedure given for the preparation of compound **77c**.

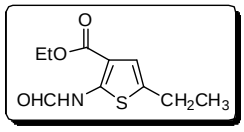
Ethyl 2-formamido-5-methylthiophene-3-carboxylate (**77a**)

Nature: Brown semisolid; **Yield:** 71.7%; **^{1}H NMR** (200 MHz, $CDCl_3$)**:** δ 1.37 (t, *J* = 8 Hz, 3H), 2.39 (s, 3H), 4.33 (q, *J* = 8 Hz, 2H), 6.87 (s, 1H), 8.48 (s, 1H), 10.91 (bs, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$)**:** δ 14.1, 14.6, 60.1, 112.3, 130.3, 135.3, 143.7, 157.1, 166.2; **IR** (Chloroform)**:** 1673, 1690, 3290 cm^{-1}; **MS** (ESI) *m*/*z***:** 214.08 (M + 1).



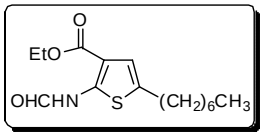
Ethyl 5-ethyl-2-formamidothiophene-3-carboxylate (**77b**)

Nature: Brown semisolid; **Yield:** 73.5%; **^{1}H NMR** (200 MHz, $CDCl_3$)**:** δ 1.27-1.42 (m, 6H), 2.76 (q, *J* = 8 Hz, 2H), 4.33 (q, *J* = 8 Hz, 2H), 6.87 (s, 1H), 8.50 (s, 1H), 11.05 (bs, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$)**:** δ 14.5, 15.3, 23.1, 59.5, 112.7, 130.9, 136.3, 143.8, 156.8, 165.7; **IR** (Chloroform)**:** 1673, 1684, 3292 cm^{-1}; **MS** (ESI) *m*/*z***:** 228.17 (M + 1).



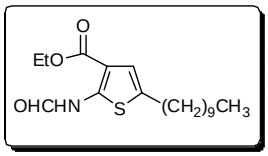
Ethyl 2-formamido-5-heptylthiophene-3-carboxylate (77d)

Nature: Brown semisolid; **Yield:** 79.3%; **^{1}H NMR** (200 MHz, $CDCl_3$)**:** δ 0.88 (t, *J* = 6 Hz, 3H), 1.28-1.42 (m, 10H), 1.66 (t, *J* = 8 Hz, 3H), 2.71 (t, *J* = 8 Hz, 2H), 3.34 (q, *J* = 8 Hz, 2H), 6.88 (s, 1H), 8.49 (s, 1H), 10.92 (bs, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$)**:** δ 14.0, 14.3, 22.6, 28.9 (2C), 29.4, 31.2, 31.6, 60.7, 113.2, 119.8, 136.3, 144.6, 157.0, 165.3; **IR** (Chloroform)**:** 1670, 1685, 3292 cm^{-1}; **MS** (ESI) *m*/*z***:** 298.06 (M + 1), 320.09 (M + Na).



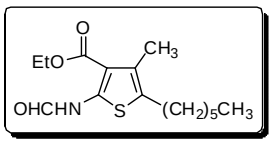
Ethyl 5-decyl-2-formamidothiophene-3-carboxylate (77e)

Nature: Brown semisolid; **Yield:** 83.1%; **^{1}H NMR** (200 MHz, $CDCl_3$)**:** δ 0.88 (t, *J* = 6 Hz, 3H), 1.18-1.32 (m, 14H), 1.38 (t, *J* = 8 Hz, 3H), 1.58-1.71 (m, 2H), 2.70 (t, *J* = 8 Hz, 2H), 4.33 (q, *J* = 8 Hz, 2H), 6.87 (s, 1H), 8.49 (s, 1H), 10.92 (bs, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$)**:** δ 14.0, 14.2, 22.6, 28.9, 29.2 (2C), 29.4 (2C), 29.5, 31.2, 31.8, 60.6, 113.2, 119.8, 136.2, 144.6, 157.0, 165.3; **IR** (Chloroform)**:** 1670, 1686, 3292 cm^{-1}; **MS** (ESI) *m*/*z***:** 340.09 (M + 1).



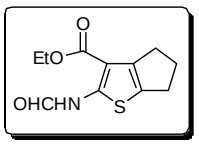
Ethyl 2-formamido-5-hexyl-4-methylthiophene-3-carboxylate (77f)

Nature: Brown semisolid; **Yield:** 81.4%; **^{1}H NMR** (200 MHz, $CDCl_3$)**:** δ 0.83-0.95 (m, 6H), 1.18-1.29 (m, 8H), 2.18 (s, 3H), 2.56 (t, *J* = 8 Hz, 2H), 4.26 (q, *J* = 8 Hz, 2H), 8.67 (s, 1H), 10.82 (bs, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$)**:** δ 14.0, 14.3, 14.8, 22.5, 27.3, 27.9, 31.3, 31.7, 60.4, 112.9, 119.7, 136.3, 144.6, 157.1, 165.6; **IR** (Chloroform)**:** 1665, 1685, 3274 cm^{-1}; **MS** (ESI) *m*/*z***:** 298.19 (M + 1).



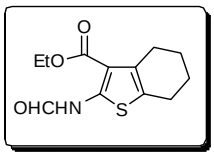
Ethyl 2-formamido-5,6-dihydro-4*H*-cyclopenta[b]thiophene-3-carboxylate (77g)

Nature: Brown semisolid; **Yield:** 76.3%; **^{1}H NMR** (200 MHz, $CDCl_3$)**:** δ 1.33 (t, *J* = 8 Hz, 3H), 2.25-2.43 (m, 2H), 2.74-2.89 (m, 4H), 4.26 (q, *J* = 8 Hz, 2H), 8.48 (s, 1H), 11.16 (bs, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$)**:** δ 14.1, 22.5, 24.1, 26.1, 60.4, 112.3, 127.2, 130.7, 145.1, 152.2, 166.1; **IR** (Chloroform)**:** 1662, 1683, 3273 cm^{-1}; **MS** (ESI) *m*/*z***:** 240.06 (M + 1).



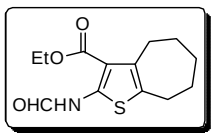
Ethyl 2-formamido-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate (**77h**)

Nature: Brown semisolid; **Yield:** 80.6%; **^{1}H NMR** (200 MHz, $CDCl_3$)**:** δ 1.35 (t, *J* = 8 Hz, 3H), 1.72-1.78 (m, 4H), 2.59-2.76 (m, 4H), 4.30 (q, *J* = 8 Hz, 2H), 8.46 (s, 1H), 11.25 (bs, 1H). **^{13}C NMR** (50 MHz, $CDCl_3$)**:** δ 14.2, 22.7, 22.8, 24.2, 26.2, 60.4, 112.3, 127.3, 130.8, 145.3, 157.1, 166.2. **IR** (Chloroform)**:** 1669, 1686, 3270 cm^{-1}; **MS** (ESI) *m*/*z***:** 254.09 (M + 1).



Ethyl 2-formamido-5,6,7,8-tetrahydro-4*H*-cyclohepta[b]thiophene-3-carboxylate (77i)

Nature: Brown semisolid; **Yield:** 77.8%; **^{1}H NMR** (200 MHz, $CDCl_3$)**:** δ 1.39 (t, *J* = 8 Hz, 3H), 1.55-1.71 (m, 4H), 1.79-1.90 (m, 2H), 2.72 (t, *J* = 6 Hz, 2H), 3.03 (t, *J* = 6 Hz, 2H),

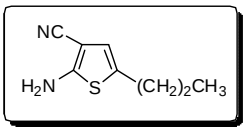


4.35 (q, *J* = 8 Hz, 2H), 8.46 (s, 1H), 11.15 (bs, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$)**:** δ 14.1, 26.8, 27.6, 28.1, 28.5, 32.1, 60.7, 113.8, 131.5, 136.5, 143.1, 157.1, 166.3; **IR** (Chloroform)**:** 1668, 1683, 3271 cm^{-1}; **MS** (ESI) *m*/*z***:** 268.04 (M + 1).

Preparation of 2-amino-5-propylthiophene-3-carbonitrile (78l)

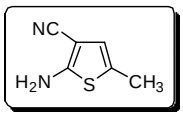
To the mixture of valeraldehyde (10.0 g, 0.116 mol), malononitrile (7.67 g, 0.116 mol) and sulfur (3.72 g, 0.116 mol) in DMF (100 mL) was added morpholine (5.03 mL, 0.058 mol) slowly at 0 ^{0}C. The resulting mixture was stirred at room temperature for 10 h, diluted with excess of water, extracted with diethyl ether, dried over Na_2SO_4, concentrated and purified by column chromatography to give pure product 2-amino-5-propylthiophene-3-carbonitrile **78l** as white solid (10.67 g, 55.3 %).

Nature: White solid; **Yield:** 55.3%; **MP:** 107 ^{0}C; **^{1}H NMR** (200 MHz, $CDCl_3$)**:** δ 0.94 (t, *J* = 8 Hz, 3H), 1.48-1.68 (m, 2H), 2.54 (t, *J* = 8 Hz, 2H), 4.77 (bs, 2H), 6.34 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$)**:** δ 13.2, 23.9, 31.4, 86.2, 116.0, 120.8, 129.9, 161.3; **IR** (Chloroform)**:** 1616, 2193, 3335, 3436 cm^{-1}; **MS** (ESI) *m*/*z***:** 167.08 (M + 1).



The following compounds **78j, 78k, 78m-o** were prepared by using the procedure given for the preparation of compound **78l.**

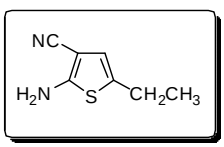
2-Amino-5-methylthiophene-3-carbonitrile (**78j**)



Nature: Pale brown solid; **MP:** 184 ^{0}C; **Yield:** 40.3%; **^{1}H NMR** (200 MHz, $CDCl_3$)**:** δ 2.18 (s, 3H), 4.65 (bs, 2H), 6.25 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$ + DMSO-d_6)**:** δ 14.6, 85.7, 115.8, 121.6, 123.5, 161.6; **IR** (Nujol)**:** 1617, 2198, 3345, 3438 cm^{-1}; **MS** (ESI) *m*/*z***:** 139.06 (M + 1).

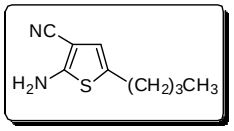
2-Amino-5-ethylthiophene-3-carbonitrile (**78k**)

Nature: White solid; **MP:** 167 ^{0}C; Yield: 48.5%; **^{1}H NMR** (200 MHz, $CDCl_3$)**:** δ 1.17 (t, *J* = 8 Hz, 3H), 2.56 (q, *J* = 8 Hz, 2H), 4.80 (bs, 2H), 6.30 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$ + DMSO-d_6)**:** δ 15.4, 21.9, 86.1, 115.8, 121.1, 122.7, 158.8. IR (Chloroform)**:** 1614, 2195, 3334, 3436 cm^{-1}; **MS** (ESI) *m*/*z***:** 153.16 (M + 1).

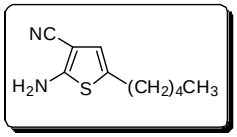


2-Amino-5-butylthiophene-3-carbonitrile (**78m**)

Nature: Off-white solid; **MP:** 143 ^{0}C; **Yield:** 57.2%; **^{1}H NMR** (200 MHz, $CDCl_3$)**:** δ 0.97 (t, *J* = 8 Hz, 3H), 1.25-1.31 (m, 2H), 1.42-1.53 (m, 2H), 2.63 (t, *J* = 8 Hz, 2H), 4.76 (bs, 2H), 6.33 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 13.3, 21.5, 29.8, 33.9, 87.2, 115.8, 120.6, 130.2, 158.9; **IR** (Nujol): 1622, 2203, 3309, 3442 cm^{-1}; **MS** (ESI) *m*/*z*: 181.10 (M + 1).



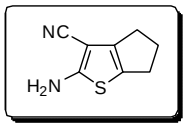
2-Amino-5-pentylthiophene-3-carbonitrile (**78n**)



Nature: White solid; **MP:** 134 ^{0}C; Yield: 60.6%; **^{1}H NMR** (200 MHz, $CDCl_3$)**:** δ 0.88 (t, *J* = 8 Hz, 3H), 1.23-1.36 (m, 4H), 1.48-1.63 (m, 2H), 2.56 (t, *J* = 8 Hz, 2H), 4.70 (bs, 2H), 6.34 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$)**:** δ 13.6, 22.0, 29.3, 30.3, 30.7, 85.8, 116.0, 120.5, 129.9, 161.4; **IR** (Chloroform)**:** 1616, 2197, 3327, 3445 cm^{-1}; **MS** (ESI) *m*/*z***:** 195.26 (M + 1).

2-Amino-5,6-dihydro-4*H*-cyclopenta[b]thiophene-3-carbonitrile (**78o**)

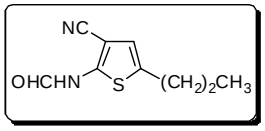
Nature: White solid; M. p. 159 ^{0}C; **Yield:** 76.3%; **^{1}H NMR** (200 MHz, $CDCl_3$+ DMSO-d_6)**:** 2.02-2.16 (m, 2H), 2.38-2.50 (m, 4H), 4.75 (bs, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$)**:** δ 26.6, 27.7, 28.5, 80.7, 115.6, 122.3, 140.8, 166.9; **IR** (Nujol)**:** 1615, 2196, 3304, 3444 cm^{-1}; **MS** (ESI) *m*/*z***:** 165.17 (M + 1).



Preparation of N-(3-cyano-5-propylthiophen-2-yl)formamide (**77l**):

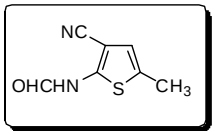
A mixture of compound **78l** (4.98 g, 0.03 mol), ammonium acetate (2.31g, 0.03 mol) and formic acid (22.6 mL, 0.6 mol) was stirred at room temperature for 3 h and diluted with water. The precipitate obtained was filtered through Whatman filter paper, washed with excess of water followed by ethyl acetate-pet ether (5:95) to give pure product N-(3-cyano-5-propylthiophen-2-yl)formamide **77l** as white solid (4.55 g, 78.2 %).

Nature: White solid; **Yield:** 78.2%; **MP:** 128 ^{0}C; **^{1}H NMR** (200 MHz, $CDCl_3$)**:** δ 0.97 (t, *J* = 8 Hz, 3H), 1.59-1.78 (m, 2H), 2.70 (t, *J* = 8 Hz, 2H), 6.65 (s, 1H), 8.48 (s, 1H), 9.42 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$)**:** δ 13.6, 24.5, 31.6, 90.9, 117.6, 121.1, 136.8, 144.1, 157.5; **IR** (Chloroform)**:** 1647, 1682, 2215, 3168 cm^{-1}; **MS** (ESI) *m*/*z***:** 193.03 (M - 1).



The following compounds were prepared by using the procedure given for the preparation of compound **77l**.

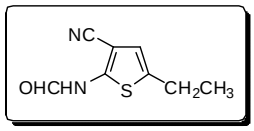
N-(3-Cyano-5-methylthiophen-2-yl)formamide (**77j**)



Nature: Pale yellow solid; **MP:** 209 ^{0}C; **Yield:** 71.3%; **^{1}H NMR** (200 MHz, $CDCl_3$ + DMSO-d_6)**:** δ 2.12 (s, 3H), 6.36 (s, 1H), 8.13 (s, 1H), 11.24 (bs, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$ + DMSO-d_6)**:** δ 13.7, 91.8, 113.9, 120.3, 131.1, 145.4, 157.8; **IR** (Chloroform)**:** 1650, 1678, 2214, 3173 cm^{-1}; **MS** (ESI) *m*/*z***:** 165.16 (M - 1).

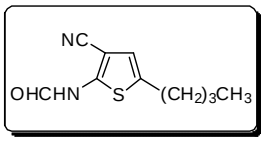
N-(3-Cyano-5-ethylthiophen-2-yl)formamide (**77k**)

Nature: Brown solid; **MP:** 148 ^{0}C; **Yield:** 76.4%; **^{1}H NMR** (200 MHz, $CDCl_3$)**:** δ 1.29 (t, *J* = 8 Hz, 3H), 2.76 (q, *J* = 8 Hz, 2H), 6.65 (s, 1H), 8.48 (s, 1H), 9.80 (bs, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$ + DMSO-d_6)**:** δ 14.4, 22.9, 92.3, 116.2, 124.4, 137.5, 143.0, 157.1; **IR** (Chloroform)**:** 1645, 1683, 2217, 3170 cm^{-1}; **MS** (ESI) *m*/*z***:** 179.03 (M - 1).



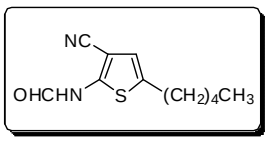
N-(5-Butyl-3-cyanothiophen-2-yl)formamide (**77m**)

Nature: Pale brown solid; **MP:** 121 ^{0}C; **Yield:** 73.3%; **^{1}H NMR** (200 MHz, $CDCl_3$)**:** δ 0.93 (t, *J* = 8 Hz, 3H), 1.29-1.48 (m, 2H), 1.57-1.72 (m, 2H), 2.73 (t, *J* = 8 Hz, 2H), 6.65 (s, 1H), 8.47 (s, 1H), 9.46 (bs, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$)**:** δ 13.6, 21.9, 29.0, 33.0, 92.4, 114.7, 119.7, 138.7, 146.3, 157.7; **IR** (Chloroform)**:** 1647, 1677, 2211, 3171 cm^{-1}; **MS** (ESI) *m*/*z***:** 207.05 (M - 1).



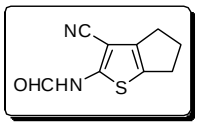
N-(3-Cyano-5-pentylthiophen-2-yl)formamide (**77n**)

Nature: Off-white solid; **MP:** 107 ^{0}C; **Yield:** 78.5%; **^{1}H NMR** (200 MHz, $CDCl_3$)**:** δ 0.90 (t, *J* = 8 Hz, 3H), 1.24-1.45 (m, 4H), 1.58-1.75 (m, 2H), 2.72 (t, *J* = 8 Hz, 2H), 6.65 (s, 1H), 8.47 (s, 1H), 9.34 (bs, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$+ DMSO-d_6)**:** δ 13.1, 24.4, 28.6, 30.0, 30.2, 95.1, 114.3, 118.3, 134.8, 141.9, 156.7; **IR** (Chloroform)**:** 1651, 1678, 2214, 3173 cm^{-1}; **MS** (ESI) *m*/*z***:** 221.04 (M - 1).



N-(3-Cyano-5,6-dihydro-4*H*-cyclopenta[b]thiophen-2-yl)formamide (**77o**)

Nature: Brown solid; **MP:** 217 ^{0}C; **Yield:** 76.3%; **^{1}H NMR** (200 MHz, $CDCl_3$+ DMSO-d_6)**:** 1.72-1.86 (m, 2H), 2.16-2.38 (m, 4H), 8.23 (s, 1H). **^{13}C NMR** (50 MHz, $CDCl_3$+ DMSO-d_6)**:** δ 26.3 (2C), 27.6, 87.7, 112.8, 132.6, 139.4, 148.7, 157.0. **IR** (Chloroform)**:** 1650, 1678, 2213, 3170 cm^{-1}; **MS** (ESI) *m*/*z***:** 191.03 (M - 1).

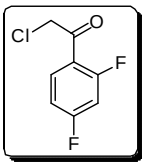


Preparation of 2-chloro-1-(2,4-difluorophenyl)ethanone (75a)[20]

To a solution of 1,3-difluorobenzene **74** (5.7 g, 50 mmol) in dichloromethane (30 mL), anhydrous aluminum chloride (7.98 g, 60 mmol) was added at 25-30 °C and stirred for 30 min. The reaction mixture was then cooled to 0 °C and chloroacetyl chloride (6.21 g, 54 mmol) in DCM (15 mL) was added over a period of 30 min at 0-10 °C. The reaction mixture was stirred at 25-30 °C for 7 h and diluted with DCM (30 mL) and poured into chilled water (150 mL). The product was extracted with DCM (2 X 50 mL) and the combined organic layer was washed with water (2 X 20 mL) followed by brine (20 mL) and dried over anhydrous Na_2SO_4. The solvent was concentrated under reduced pressure to yield the product 2-chloro-1-(2,4-difluorophenyl)ethanone **75a** as yellow solid (7.60 g, 80 %).

Caution: Product **75a** is highly lachrymatory and skin irritating hence reaction must be carried out under vacuum hood and use of hand gloves is essential during reaction work-up.

Nature: Yellow solid; **MP:** 47.5 ºC; **Yield:** 80 %; **^{1}H NMR** (200 MHz, $CDCl_3$)**:** δ 4.70 (d, *J* = 2 Hz, 2H), 6.86-7.06 (m, 2H), 7.96-8.08 (m, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$)**:** δ 49.7 (d), 104.5 (t), 112.5 (d), 119.2 (d), 133.0 (d), 161.6 (dd), 166.7 (dd), 187.4.

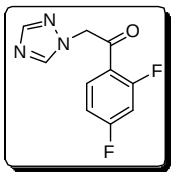


Compounds **75b, 75c** and **75d** were prepared from fluorobenzene, bromobenzene and dichlorobenzene using the procedure given for the compound **75a**. All these compounds were lachrymatory and skin irritating, hence they were used for further reactions without purification.

Preparation of 1-(2,4-difluorophenyl)-2-(1*H*-1,2,4-triazol-1-yl)ethanone (76a)[20, 53c]

2-Chloro-1-(2,4-difluorophenyl)ethanone **75a** (9.05 g, 47.5 mmol), 1*H*-1,2,4-triazole (3.93 g, 57.01 mmol) and potassium carbonate (7.88 g, 57.00 mmol) were taken in round bottom

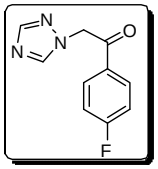
flask equipped with a condenser and guard tube, containing ethyl acetate (50 mL) and the reaction mixture was refluxed for 10 h. It was then cooled to room temperature, diluted with water (100 mL) and extracted with ethyl acetate (2 X 50 mL). The combined organic layer was washed with water (2 X 20 mL), brine (20 mL) and dried over anhydrous Na_2SO_4. The solvent was concentrated under reduced pressure on rotary evaporator. Purification by column chromatography yielded pure product **76a** as white solid (7.30 g, 69.3 %).



Nature: White solid; **MP:** 105 ºC; **Yield:** 69.3 %; **^{1}H NMR** (200 MHz, $CDCl_3$)**:** δ 5.59 (d, *J* = 2 Hz, 2H), 6.93-7.10 (m, 2H), 7.99-8.11 (m, 1H), 8.21 (bs, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$)**:** δ 58.3 (d), 104.8 (t), 112.9 (d), 118.9 (d), 132.9 (d), 144.7, 151.7, 162.1 (dd), 168.7 (dd), 187.4; **IR** (Chloroform)**:** 1688 cm^{-1}.

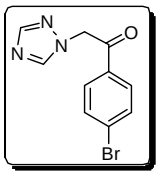
Compounds **76b, 76c** and **76d** were prepared by reacting **75b**, **75c** and **75d** with 1*H*-1,2,4-triazole using the procedure given for the preparation of compound **76a**.

1-(4-Fluorophenyl)-2-(1*H*-1,2,4-triazol-1-yl)ethanone (76b)[53c]



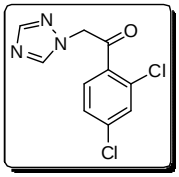
Nature: White solid; **MP:** 76 ºC; **Yield:** 68 % (over two steps); **^{1}H NMR** (200 MHz, $CDCl_3$)**:** δ 6.10 (s, 2H), 7.48-7.52 (m, 2H), 8.05 (s, 1H), 8.12-8.22 (m, 2H), 8.41 (s, 1H).

1-(4-Bromophenyl)-2-(1*H*-1,2,4-triazol-1-yl)ethanone (76c)[53c]



Nature: Off-white solid; **MP:** 172-174 ºC; **Yield:** 63 % (over two steps); **^{1}H NMR** (200 MHz, $CDCl_3$)**:** δ 5.98 (s, 2H), 7.79 (d, *J* = 8 Hz, 2H), 7.98 (d, *J* = 8 Hz, 2H), 8.10 (s, 1H), 8.48 (s, 1H).

1-(2,4-Dichlorophenyl)-2-(1*H*-1,2,4-triazol-1-yl)ethanone (76d)[53c]



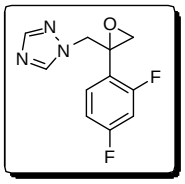
Nature: White solid; **MP:** 116-117 ºC; **Yield:** 71 % (over two steps); **^{1}H NMR** (200 MHz, $CDCl_3$)**:** δ 5.85 (s, 2H), 7.59-7.65 (m, 1H), 7.82 (d, *J* = 2 Hz, 1H), 8.02 (d, *J* = 6 Hz, 1H), 7.89 (s, 1H), 8.67 (s, 1H).

Preparation of 1-[2-(2,4-difluorophenyl)-oxiranylmethyl]-1*H*-[1,2,4]triazole (32a)[53c]

A mixture of 1-(2,4-difluorophenyl)-2-(1*H*-1,2,4-triazolyl)-ethanone **76a** (15.00 g, 0.067 mol), trimethylsulfoxonium iodide (22.20 g, 0.1 mol) and cetrimide (0.245 g, 0.00067 mol)

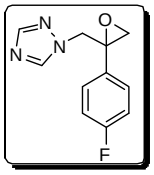
in dichloromethane (150 mL) was stirred at room temperature for 10 min. Then a solution of KOH (9.42 g, 0.168 mol) in water (20 mL) was added to it. This mixture was refluxed at 40-45 ^{o}C for 12 h, cooled to room temperature and diluted with water (60 mL). The two layers were separated, the aqueous layer was extracted with dichloromethane (3 X 150 mL) and the combined organic extracts were dried over Na_2SO_4. After the solvent was concentrated *in vacuo*, the residue was subjected to chromatography on silica gel to afford pure 1-[2-(2,4-difluorophenyl)-oxiranylmethyl]-1*H*-[1,2,4]triazole **32a** as colourless thick liquid (13.55 g, 85 %).

Nature: Colourless thick liquid, **Yield:** 85 %; **^{1}H NMR** (200 MHz, $CDCl_3$)**:** δ 2.85 (d, *J* = 6 Hz, 1H), 2.95 (d, *J* = 6 Hz, 1H), 4.50 (d, *J* = 16 Hz, 1H), 4.80 (d, *J* = 16 Hz, 1H), 6.76-6.89 (m, 2H), 7.12-7.26 (m, 1H), 7.83 (s, 1H), 8.07 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$)**:** δ 52.1, 53.5, 56.2, 104.0 (t), 111.7 (d), 119.5 (d), 129.54 (t), 144.0, 151.8, 159.3 (dd), 164.3 (dd).



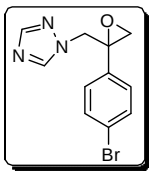
Compounds **32b, 32c** and **32d** were prepared from **76b**, **76c** and **76d** using the procedure given for the preparation of epoxide **32a**.

1-[(2-(4-Fluorophenyl)-oxiranylmethyl]-1*H*-[1,2,4]-triazole (32b)[53c]



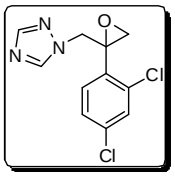
Nature: Red thick liquid, **Yield:** 81 %; **^{1}H NMR** (200 MHz, $CDCl_3$)**:** δ 2.87 (d, *J* = 6 Hz, 1H), 3.10 (d, *J* = 6 Hz, 1H), 4.66 (d, *J* = 16 Hz, 1H), 4.97 (d, *J* = 16 Hz, 1H), 7.15-7.24 (m, 2H), 7.39-7.48 (m, 2H), 7.98 (s, 1H), 8.39 (s, 1H).

1-[(2-(4-Bromophenyl)oxiranylmethyl]-1*H*-[1,2,4]-triazole (32c)[53c]



Nature: Red thick liquid, **Yield:** 84 %; **^{1}H NMR** (200 MHz, $CDCl_3 + CCl_4$)**:** δ 2.81 (d, *J* = 6 Hz, 1H), 2.87 (d, *J* = 6 Hz, 1H), 4.59 (d, *J* = 14 Hz, 1H), 4.80 (d, *J* = 14 Hz, 1H), 7.20 (d, *J* = 8 Hz, 2H), 7.47 (d, *J* = 8 Hz, 2H), 7.89 (s, 1H), 8.08 (s, 1H).

1-[2-(2,4-Dichlorophenyl)-oxiranylmethyl]-1*H*-[1,2,4]triazole (32d)[53c]

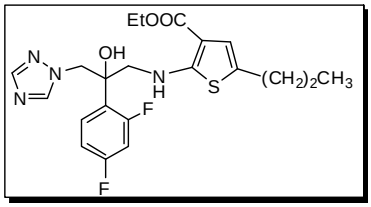


Nature: Red thick liquid, **Yield:** 91 %; **^{1}H NMR** (200 MHz, $CDCl_3 + CCl_4$)**:** δ 2.92 (d, *J* = 4 Hz, 1H), 3.01 (d, *J* = 4 Hz, 1H), 4.53 (d, *J* = 14 Hz, 1H), 4.90 (d, *J* = 14 Hz, 1H), 7.16-7.46 (m, 3H), 7.92 (s, 1H), 8.13 (s, 1H).

Preparation of ethyl 2-((2-(2,4-difluorophenyl)-2-hydroxy-3-(1*H*-1,2,4-triazol-1-yl)propyl)amino)-5-propylthiophene-3-carboxylate (73c)

To the flame-dried K_2CO_3 (0.97 g, 0.007 mol), tetra-butylammonium bromide (150 mg) was added followed by the addition of compound **77c** (1.0 g, 0.004 mol) in dry ethyl acetate (10 mL). Reaction mixture was stirred at reflux for 30 min. Then epoxide **32a** (1.18 g, 0.005 mol) dissolved in dry ethyl acetate (20 mL) was added to the refluxing mixture drop wise over a period of 10 min and stirring was continued for further 12 h at the same temperature. It was then cooled to room temperature, diluted with water, extracted with ethyl acetate, dried over Na_2SO_4, concentrated and purified by column chromatography to give pure product ethyl 2-((2-(2,4-difluorophenyl)-2-hydroxy-3-(1*H*-1,2,4-triazol-1-yl)propyl)amino)-5-propylthiophene-3-carboxylate **73c** as brown semisolid (1.54 g, 82.7 %).

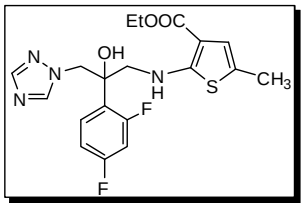
Nature: Brown semisolid; **Yield:** 82.7%; **^{1}H NMR** (200 MHz, $CDCl_3$)**:** δ 0.92 (t, *J* = 8 Hz, 3H), 1.29 (t, *J* = 8 Hz, 3H), 1.48- 1.67 (m, 2H), 2.53 (t, *J* = 8 Hz, 2H), 3.64 (s, 2H), 4.20 (q, *J* = 8 Hz, 2H), 4.67 (d, *J* = 14 Hz, 1H), 4.86 (d, *J* = 14 Hz, 1H), 6.63 (s, 1H), 6.71-6.81 (m, 2H), 7.45-7.56 (m, 2H), 7.79 (s, 1H), 8.00 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$ + CCl_4)**:** δ 13.4, 14.4, 24.1, 31.6, 54.6, 59.5, 75.7, 77.2, 103.6, 104.3 (t), 111.7 (d), 122.0, 123.0 (d), 125.8, 130.1 (d), 144.1, 151.5, 158.2 (dd), 163.0 (dd), 163.9, 165.4; **IR** (Chloroform)**:** 1618, 1661, 3324, 3395 cm^{-1}; **MS** (ESI) *m*/*z***:** 451.2612 (M + 1), 473.2156 (M + Na).



The fluconazole analogues **73a, 73b, 73d-73q** were prepared by using the procedure given for the preparation of compound **73c**.

Ethyl 2-((2-(2,4-difluorophenyl)-2-hydroxy-3-(1*H*-1,2,4-triazol-1-yl)propyl)amino)-5-methylthiophene-3-carboxylate (73a)

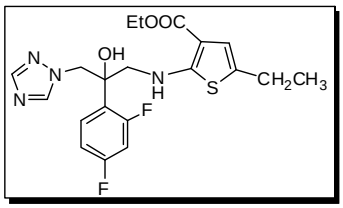
Nature: Brown sticky solid; **Yield:** 83.5%; **^{1}H NMR** (200 MHz, $CDCl_3$)**:** δ 1.25 (t, *J* = 8 Hz, 3H), 2.20 (s, 3H), 3.61 (s, 2H), 4.16 (q, *J* = 8 Hz, 2H), 4.63 (d, *J* = 14 Hz, 1H), 4.79 (d, *J* = 14 Hz, 1H), 5.11 (s, 1H), 6.58 (s, 1H) 6.68-6.80 (m, 2H), 7.42-7.54 (m, 1H), 7.72 (s, 1H), 8.00 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$)**:** δ 13.8, 14.4, 59.0, 58.4, 60.1, 75.1,



103.8, 104.2 (t), 111.2 (d), 119.5, 122.7 (d), 129.8, 132.4 (d), 144.1, 150.8, 156.4 (dd), 163.7 (dd), 165.2, 168.8; **IR** (Chloroform)**:** 1617, 1659, 3326, 3384 cm^{-1}; **MS** (ESI) *m*/*z***:** 423.2314 (M + 1).

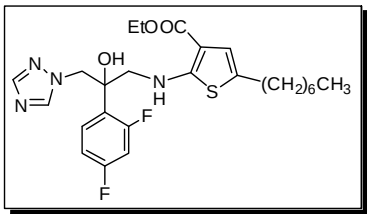
Ethyl 2-((2-(2,4-difluorophenyl)-2-hydroxy-3-(1*H*-1,2,4-triazol-1-yl)propyl)amino)-5-ethylthiophene-3-carboxylate (73b)

Nature: Brown sticky solid; **Yield:** 85.1%; **^{1}H NMR** (200 MHz, $CDCl_3$)**:** δ 1.16-1.32 (m, 6H), 2.58 (q, *J* = 8 Hz, 2H), 3.61 (s, 3H), 4.18 (q, *J* = 8 Hz, 2H), 4.65 (d, *J* = 14 Hz, 1H), 4.83 (d, *J* = 14 Hz, 1H), 6.60 (s, 1H), 6.71-6.80 (m, 2H), 7.44-7.57 (m, 1H), 7.76 (s, 1H), 8.01 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$)**:** δ 14.4, 14.5, 20.0, 54.6, 54.7, 59.4, 75.8, 104.1 (t), 104.3, 111.8 (d), 121.2, 123.3 (d), 127.3, 130.2 (d), 144.1, 151.4, 158.3 (dd), 163.5 (dd), 163.8, 168.3; **IR** (Chloroform)**:** 1618, 1660, 3132, 3403 cm^{-1}; **MS** (ESI) *m*/*z***:** 459.6368 (M + 1).



Ethyl 2-((2-(2,4-difluorophenyl)-2-hydroxy-3-(1*H*-1,2,4-triazol-1-yl)propyl)amino)-5-heptylthiophene-3-carboxylate (73d)

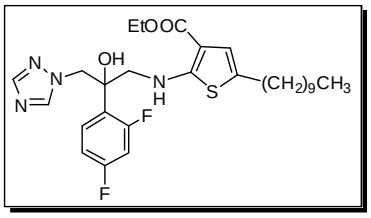
Nature: Brown semisolid; **Yield:** 82.7%; **^{1}H NMR** (200 MHz, $CDCl_3$ + CCl_4)**:** δ 0.88 (t, *J* = 6 Hz, 3H), 1.24-1.34 (m, 12H), 1.52-1.59 (m, 2H), 2.55 (t, *J* = 6 Hz, 2H), 3.63 (s, 2H), 4.20 (q, *J* = 8 Hz, 2H), 4.67 (d, *J* = 14 Hz, 1H), 4.85 (d, *J* = 14 Hz, 1H), 4.96 (bs, 1H), 6.61 (s, 1H), 6.72-6.82 (m, 2H), 7.46-7.59 (m, 1H), 7.79 (s, 1H), 8.05 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$)**:** δ 14.1, 14.5, 22.6, 29.0 (2C), 29.7, 31.1, 31.7, 54.6, 54.7, 59.4, 75.7, 77.2, 103.6, 104.3 (t), 111.8 (d), 122.0, 123.1 (d), 125.9, 130.2 (d), 144.1, 151.3, 158.1 (dd), 163.0 (dd), 163.9, 165.4; **IR** (Chloroform)**:** 1618, 1662, 3131, 3324 cm^{-1}; **MS** (ESI) *m*/*z***:** 507.3260 (M + 1), 529.2630 (M + Na), 545.2398 (M + K).



Ethyl 5-decyl-2-((2-(2,4-difluorophenyl)-2-hydroxy-3-(1*H*-1,2,4-triazol-1-yl)propyl)amino)thiophene-3-carboxylate (73e)

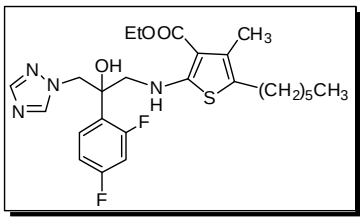
Nature: Brown sticky solid; **Yield:** 79.8%; **^{1}H NMR** (200 MHz, $CDCl_3$)**:** δ 0.82-0.91 (m, 6H), 1.20-1.34 (m, 14H), 1.50-1.57 (m, 2H), 2.56 (t, *J* = 8 Hz, 2H), 3.65 (s, 2H), 4.21 (q, *J* = 8 Hz, 2H), 4.70 (d, *J* = 14 Hz, 1H), 4.90 (d, *J* = 14 Hz, 1H), 6.63 (s, 1H), 6.76-6.84 (m,

2H), 7.46-7.58 (m, 1H), 7.84 (s, 1H), 8.10 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$)**:** δ 14.0, 14.4, 22.6, 28.9, 29.2, 29.4, 29.5, 29.6, 29.7, 31.0, 31.8, 54.5, 54.6, 59.5, 75.9, 104.1 (t), 104.3, 111.8 (d), 121.8, 123.0 (d), 126.1, 130.2 (d), 144.1, 151.6, 158.3 (dd), 163.2 (dd), 163.9, 165.4; **IR** (Chloroform)**:** 1618, 1661, 3231, 3348 cm^{-1}; **MS** (ESI) *m*/*z***:** 549.2214 (M + 1).



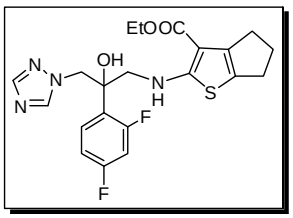
Ethyl 2-((2-(2,4-difluorophenyl)-2-hydroxy-3-(1*H*-1,2,4-triazol-1-yl)propyl)amino)-5-hexyl-4-methylthiophene-3-carboxylate (73f)

Nature: Brown sticky solid; **Yield:** 83.6%; **^{1}H NMR** (400 MHz, $CDCl_3$)**:** δ 0.83-0.93 (m, 6H), 1.20-1.34 (m, 8H), 2.16 (s, 3H), 2.54 (t, *J* = 8 Hz, 2H), 3.64 (d, *J* = 12 Hz, 1H), 3.67 (d, *J* = 12 Hz, 1H), 4.23 (q, *J* = 8 Hz, 2H), 4.70 (d, *J* = 16 Hz, 1H), 4.88 (d, *J* = 16 Hz, 1H), 5.83 (bs, 1H), 6.74-6.81 (m, 2H), 7.49-7.55 (m, 1H), 7.83 (s, 1H), 8.11 (s, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$)**:** δ 14.0, 14.4, 14.7, 22.5, 27.0, 28.0, 31.2, 31.5, 54.2, 54.7, 59.3, 75.7, 104.1 (t), 105.0, 111.7 (d), 119.6, 123.2 (d), 130.1 (d), 130.6, 144.1, 151.3, 158.6 (dd), 162.2 (dd), 163.8, 166.3; **IR** (Chloroform)**:** 1619, 1659, 3130, 3331 cm^{-1}; **MS** (ESI) *m*/*z***:** 507.3215 (M + 1).

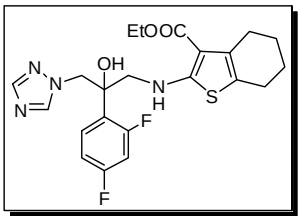


Ethyl 2-((2-(2,4-difluorophenyl)-2-hydroxy-3-(1*H*-1,2,4-triazol-1-yl)propyl)amino)-5,6-dihydro-4*H*-cyclopenta[b]thiophene-3-carboxylate (73g)

Nature: Brown sticky solid; **Yield:** 76.2%; **^{1}H NMR** (200 MHz, $CDCl_3$)**:** δ 1.22 (t, *J* = 8 Hz, 3H), 2.13-2.27 (m, 2H), 2.59-2.75 (m, 4H), 3.60 (s, 2H), 4.10 (q, *J* = 8 Hz, 2H), 4.61 (d, *J* = 14 Hz, 1H), 4.76 (d, *J* = 14 Hz, 1H), 5.37 (bs, 1H), 6.67-6.77 (m, 2H), 7.47-7.54 (m, 1H), 7.67 (s, 1H), 7.98 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$)**:** δ 14.0, 26.8, 28.5, 30.4, 53.8, 54.6, 59.0, 75.3, 100.4, 103.9 (t), 111.4 (d), 120.0, 123.2 (d), 130.0 (d), 143.0, 144.0, 150.9, 158.0 (dd), 163.1 (dd), 165.6, 168.9; **IR** (Chloroform)**:** 1617, 1660, 3227, 3412 cm^{-1}; **MS** (ESI) *m*/*z***:** 449.9304 (M + 1), 471.9344 (M + Na), 487.9152 (M + K).

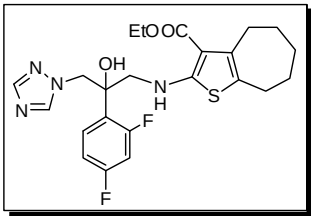


Ethyl 2-((2-(2,4-difluorophenyl)-2-hydroxy-3-(1*H*-1,2,4-triazol-1-yl)propyl)amino)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate (73h)



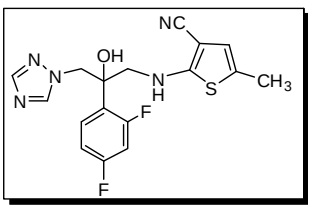
Nature: Brown sticky solid; **Yield:** 78.4%; **^{1}H NMR** (200 MHz, $CDCl_3$)**:** δ 1.30 (t, *J* = 8 Hz, 3H), 1.70-1.78 (m, 4H), 2.48-2.56 (m, 4H), 3.65 (s, 2H), 4.20 (q, *J* = 8 Hz, 2H), 4.68 (d, *J* = 14 Hz, 1H), 4.89 (d, *J* = 14 Hz, 1H), 4.96 (bs, 1H), 6.73-6.83 (m, 2H), 7.45-7.57 (m, 1H), 7.84 (s, 1H), 8.15 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$)**:** δ 14.3, 22.7, 23.1, 24.5 (2C), 26.7, 54.3, 59.3, 75.8, 103.9, 104.9 (t), 111.5 (d), 116.8, 123.2 (d), 130.2 (d), 133.2, 144.1, 151.4, 156.2 (dd), 161.1 (dd), 164.4, 166.3; **IR** (Chloroform)**:** 1618, 1663, 3135, 3324, cm^{-1}; **MS** (ESI) *m*/*z***:** 485.3185 (M + Na).

Ethyl 2-((2-(2,4-difluorophenyl)-2-hydroxy-3-(1*H*-1,2,4-triazol-1-yl)propyl)amino)-5,6,7,8-tetrahydro-4*H*-cyclohepta[b]thiophene-3-carboxylate (73i)



Nature: Brown sticky solid; **Yield:** 77.7%; **^{1}H NMR** (200 MHz, $CDCl_3$)**:** δ 1.30 (t, *J* = 8 Hz, 3H), 1.50-1.85 (m, 6H), 2.60 (t, *J* = 6 Hz, 2H), 2.95 (t, *J* = 6 Hz, 2H), 3.61 (s, 2H), 4.22 (q, *J* = 8 Hz, 2H), 4.67 (d, *J* = 14 Hz, 1H), 4.87 (d, *J* = 14 Hz, 1H), 6.71-6.82 (m, 2H), 7.44-7.58 (m, 1H), 7.80 (s, 1H), 8.04 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$)**:** δ 14.2, 23.1, 23.9, 24.5, 24.7 (2C), 25.8, 54.2, 58.9, 76.7, 104.1, 104.3 (t), 111.3 (d), 116.8, 122.8 (d), 131.8 (d), 134.8, 144.4, 151.7, 158.2 (dd), 162.3 (dd), 165.1, 165.7; **IR** (Chloroform)**:** 1620, 1663, 3138, 3390 cm^{-1}; **MS** (ESI) *m*/*z***:** 477.4964 (M + 1).

2-((2-(2,4-Difluorophenyl)-2-hydroxy-3-(1*H*-1,2,4-triazol-1-yl)propyl)amino)-5-methylthiophene-3-carbonitrile (73j)

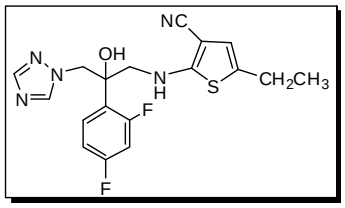


Nature: Pale brown solid; **MP:** 153 ^{0}C; **Yield:** 68.2%; **^{1}H NMR** (200 MHz, $CDCl_3$)**:** δ 2.28 (s, 3H), 3.64 (d, *J* = 8 Hz, 1H), 3.68 (d, *J* = 8 Hz, 1H), 4.65 (d, *J* = 14 Hz, 1H), 4.87 (d, *J* = 14 Hz, 1H), 5.30 (bs, 1H), 6.36 (s, 1H), 6.37-6.87 (m, 2H), 7.45-7.57 (m, 1H), 7.86 (s, 1H), 7.92 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$)**:** δ 14.8, 54.7 (2C), 75.6, 84.4, 104.2 (t), 111.9 (d), 116.1, 122.5, 122.7 (d), 123.2, 130.1 (d), 144.3, 151.1, 158.3 (dd), 163.3 (dd), 163.9; **IR** (Nujol)**:** 1615, 2198, 3170, 3434 cm^{-1}; **MS** (ESI) *m*/*z***:** 376.28 (M + 1),

398.25 (M + Na). **Anal. Calcd. for** $C_{17}H_{15}F_2N_5OS$**:** C, 54.39; H, 4.03; N, 18.66 %. **Found:** C, 54.22; H, 4.18; N, 18.49 %.

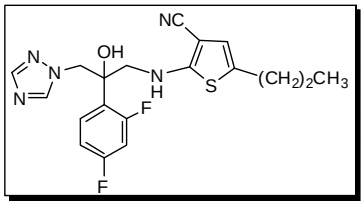
2-((2-(2,4-Difluorophenyl)-2-hydroxy-3-(1*H*-1,2,4-triazol-1-yl)propyl)amino)-5-ethylthiophene-3-carbonitrile (73k)

Nature: White solid; **MP:** 137 ^{0}C; **Yield:** 70.5%; **^{1}H NMR** (200 MHz, $CDCl_3$)**:** δ 1.20 (t, *J* = 8 Hz, 3H), 2.60 (q, *J* = 8 Hz, 2H), 3.60 (d, *J* = 10 Hz, 1H), 3.70 (d, *J* = 10 Hz, 1H), 4.67 (d, *J* = 14 Hz, 1H), 4.85 (d, *J* = 14 Hz, 1H), 5.35-5.41 (m, 2H), 6.35 (s, 1H), 6.72-6.85 (m, 2H), 7.44-7.57 (m, 1H), 7.82 (s, 1H), 7.95 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$)**:** δ 15.1, 22.9, 54.6 (2C), 75.6, 84.1, 104.2 (t), 111.8 (d), 116.1, 120.7, 122.7 (d), 130.1 (d), 130.7, 144.2, 151.8, 158.2 (dd), 163.2 (dd), 163.7; **IR** (Nujol)**:** 1615, 2200, 3179, 3445 cm^{-1}; **MS** (ESI) *m*/*z***:** 390.34 (M + 1), 412.04 (M + Na). **Anal. Calcd. for** $C_{18}H_{17}F_2N_5OS$**:** C, 55.52; H, 4.40; N, 17.98 %. **Found:** C, 55.73; H, 4.27; N, 17.83 %.



2-((2-(2,4-Difluorophenyl)-2-hydroxy-3-(1*H*-1,2,4-triazol-1-yl)propyl)amino)-5-propylthiophene-3-carbonitrile (**73l**)

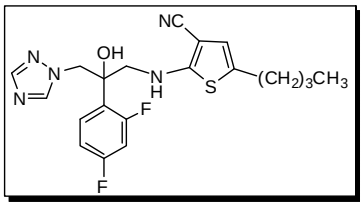
Nature: White solid; **MP:** 117 ^{0}C; **Yield:** 73.3%; **^{1}H NMR** (200 MHz, $CDCl_3$)**:** δ 0.92 (t, *J* = 8 Hz, 3H), 1.47-1.66 (m, 2H), 2.53 (t, *J* = 8 Hz, 2H), 3.62 (d, *J* = 8 Hz, 1H), 3.69 (d, *J* = 8 Hz, 1H), 4.67 (d, *J* = 14 Hz, 1H), 4.84 (d, *J* = 14 Hz, 1H), 5.39-5.44 (m, 2H), 6.34 (s, 1H), 6.71-6.85 (m, 2H), 7.44-7.57 (m, 1H), 7.81 (s, 1H), 7.96 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$)**:** δ 13.2, 24.0, 31.5, 54.6 (2C), 75.5, 83.9, 104.1 (t), 111.8 (d), 116.1, 121.4, 122.8 (d), 128.8, 130.0 (d), 144.2, 151.6, 158.2 (dd), 163.6 (dd), 163.9; **IR** (Nujol)**:** 1614, 2200, 3178, 3445 cm^{-1}; **MS** (ESI) *m*/*z***:** 404.14 (M + 1). **Anal. Calcd. for** $C_{19}H_{19}F_2N_5OS$**:** C, 56.56; H, 4.75; N, 17.36 %. **Found:** C, 56.69; H, 4.66; N, 17.23 %.



5-Butyl-2-((2-(2,4-difluorophenyl)-2-hydroxy-3-(1*H*-1,2,4-triazol-1-yl)propyl)amino)thiophene-3-carbonitrile (**73m**)

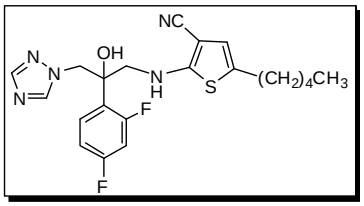
Nature: Off-white solid; **MP:** 107 ^{0}C; **Yield:** 75.1%; **^{1}H NMR** (200 MHz, $CDCl_3$)**:** δ 0.89 (t, *J* = 8 Hz, 3H), 1.22-1.40 (m, 2H), 1.44-1.59 (m, 2H), 2.55 (t, *J* = 8 Hz, 2H), 3.61 (d, *J* = 8 Hz, 1H), 3.68 (d, *J* = 8 Hz, 1H), 4.66 (d, *J* = 16 Hz, 1H), 4.82 (d, *J* = 16 Hz, 1H), 5.43-5.49

(m, 2H), 6.32 (s, 1H), 6.71-6.84 (m, 2H), 7.44-7.56 (m, 1H), 7.79 (s, 1H), 7.97 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$)**:** δ 13.5, 21.7, 29.1, 32.9, 54.6 (2C), 75.5, 83.9, 104.1 (t), 111.8 (d), 116.1, 121.3, 122.7 (d), 129.1, 130.0 (d), 144.2, 151.6, 158.2 (dd), 163.7 (dd), 163.9; **IR** (Nujol)**:** 1615, 2199, 3181, 3444 cm^{-1}; **MS** (ESI) *m*/*z***:** 418.06 (M + 1). **Anal. Calcd. for** $C_{20}H_{21}F_2N_5OS$**:** C, 57.54; H, 5.07; N, 16.78 %. **Found:** C, 57.71; H, 5.23; N, 16.61 %.



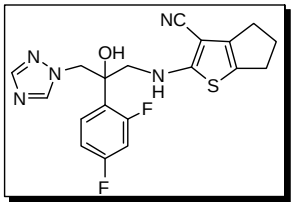
2-((2-(2,4-Difluorophenyl)-2-hydroxy-3-(1*H*-1,2,4-triazol-1-yl)propyl)amino)-5-pentylthiophene-3-carbonitrile (**73n**)

Nature: Brown solid; **MP:** 110 ^{0}C; **Yield:** 78.4%; **^{1}H NMR** (500 MHz, $CDCl_3$)**:** δ 0.90 (t, *J* = 10 Hz, 3H), 1.26-1.35 (m, 4H), 1.52-1.58 (m, 2H), 2.57 (t, *J* = 10 Hz, 2H), 3.62 (d, *J* = 10 Hz, 1H), 3.68 (d, *J* = 10 Hz, 1H), 4.67 (d, *J* = 12 Hz, 1H), 4.86 (d, *J* = 12 Hz, 1H), 5.27-5.31 (m, 2H), 6.36 (s, 1H), 6.75-6.83 (m, 2H), 7.49-7.54 (m, 1H), 7.85 (s, 1H), 7.93 (s, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$)**:** δ 13.9, 22.2, 29.5, 30.6, 30.9, 54.6 (2C), 75.8, 84.6, 104.2 (t), 112.0 (d), 116.0, 121.5, 122.7 (d), 129.5, 130.2 (d), 144.1, 152.1, 158.4 (dd), 163.5 (dd), 163.9; **IR** (Nujol)**:** 1615, 2196, 3188, 3448 cm^{-1}; **MS** (ESI) *m*/*z***:** 432.34 (M + 1), 454.25 (M + Na). **Anal. Calcd. for** $C_{21}H_{23}F_2N_5OS$**:** C, 58.45; H, 5.37; N, 16.23 %. **Found:** C, 58.33; H, 5.51; N, 16.40 %.



2-((2-(2,4-Difluorophenyl)-2-hydroxy-3-(1*H*-1,2,4-triazol-1-yl)propyl)amino)-5,6-dihydro-4*H*-cyclopenta[b]thiophene-3-carbonitrile (**73o**)

Nature: Brown solid; **MP:** 125 ^{0}C; Yield: 72.7%; **^{1}H NMR** (200 MHz, $CDCl_3$)**:** δ 2.24-2.38 (m, 2H), 2.60-2.75 (m, 4H), 3.62 (d, *J* = 14 Hz, 1H), 3.71 (d, *J* = 14 Hz, 1H), 4.70 (d, *J* = 14 Hz, 1H), 4.84 (d, *J* = 14 Hz, 1H), 5.23 (bs, 1H), 6.71-6.83 (m, 2H), 7.43-7.55 (m, 1H), 7.82 (s, 1H), 8.11 (s, 1H). **^{13}C NMR** (125 MHz, $CDCl_3$)**:** δ 27.2, 28.3, 29.2, 54.2, 54.8, 75.6, 81.5, 104.2 (t), 111.9 (d), 116.1, 122.8 (d), 123.6, 130.0 (d), 142.4, 144.2, 151.1, 158.6 (dd), 164.0 (dd), 165.3; **IR** (Nujol)**:** 1614, 2204, 3187, 3462 cm^{-1}; **MS** (ESI) *m*/*z***:** 402.23 (M + 1). **Anal. Calcd. for** $C_{19}H_{17}F_2N_5OS$**:** C, 56.85; H, 4.27; N, 17.45 %. **Found:** C, 56.71; H, 4.47; N, 17.61 %.



2-((2-(2,4-Dichlorophenyl)-2-hydroxy-3-(1*H*-1,2,4-triazol-1-yl)propyl)amino)-5-propylthiophene-3-carbonitrile (**73p**)

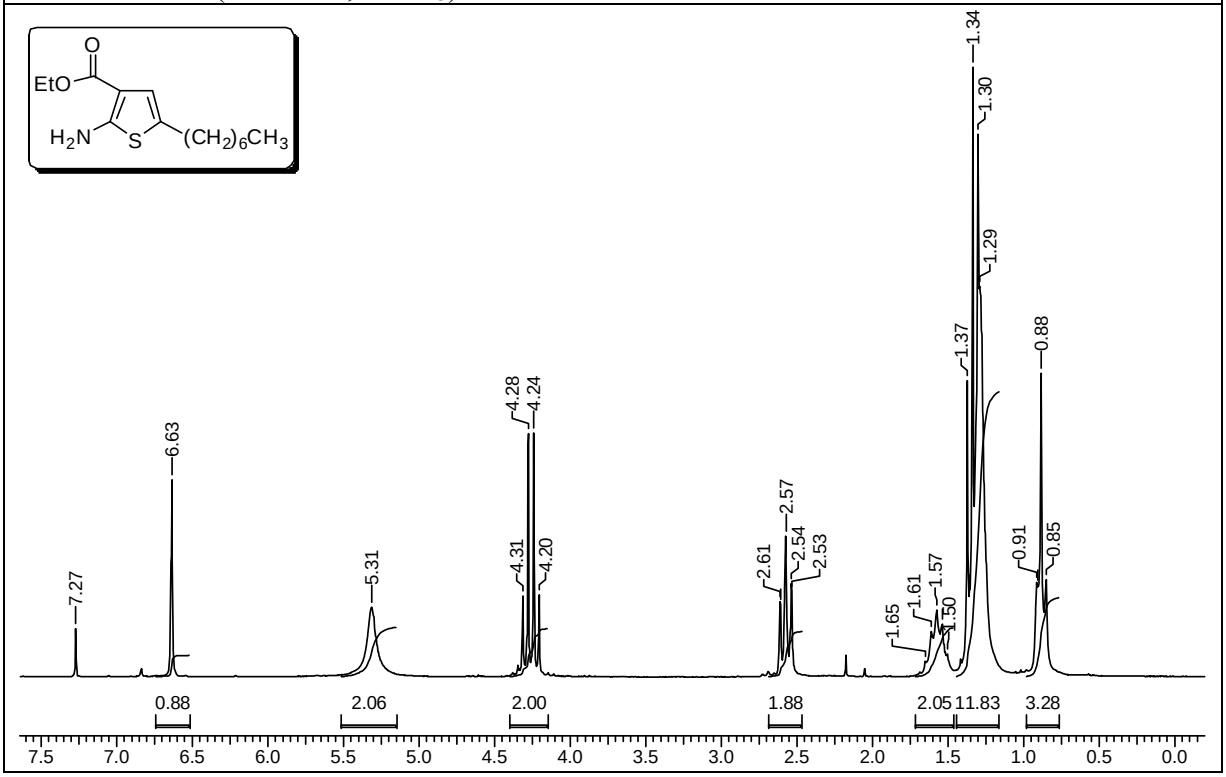
Nature: White solid; **MP:** 143 ^{0}C; **Yield:** 77.1%; **^{1}H NMR** (200 MHz, $CDCl_3$)**:** δ 0.93 (t, *J* = 7 Hz, 3H), 1.48-1.65 (m, 2H), 2.54 (t, *J* = 7 Hz, 2H), 3.83 (d, *J* = 14 Hz, 1H), 4.02 (d, *J* = 14 Hz, 1H), 4.92 (d, *J* = 14 Hz, 1H), 5.44 (d, *J* = 14 Hz, 1H), 6.34 (s, 1H), 7.16 (dd, *J* = 8, 2 Hz, 1H), 7.35 (d, *J* = 2 Hz, 1H), 7.61 (d, *J* = 8 Hz, 1H), 8.04 (s, 1H), 8.91 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$)**:** δ 13.4, 24.2, 31.6, 53.3, 54.4, 77.2, 104.2, 116.3, 121.6, 124.8, 127.8, 129.0, 130.6, 130.8, 135.0, 135.2, 146.9, 151.4, 163.9; **IR** (Chloroform)**:** 1617, 2203, 3131, 3434 cm^{-1}; **MS** (ESI) *m*/*z***:** 458.01 (M + Na). **Anal. Calcd. for**: $C_{19}H_{19}Cl_2N_5OS$**:** C, 52.30; H, 4.39; N, 16.05 %. **Found:** C, 52.46; H, 4.21; N, 15.91 %.

2-((2-(4-Fluorophenyl)-2-hydroxy-3-(1*H*-1,2,4-triazol-1-yl)propyl)amino)-5-propylthiophene-3-carbonitrile (**73q**)

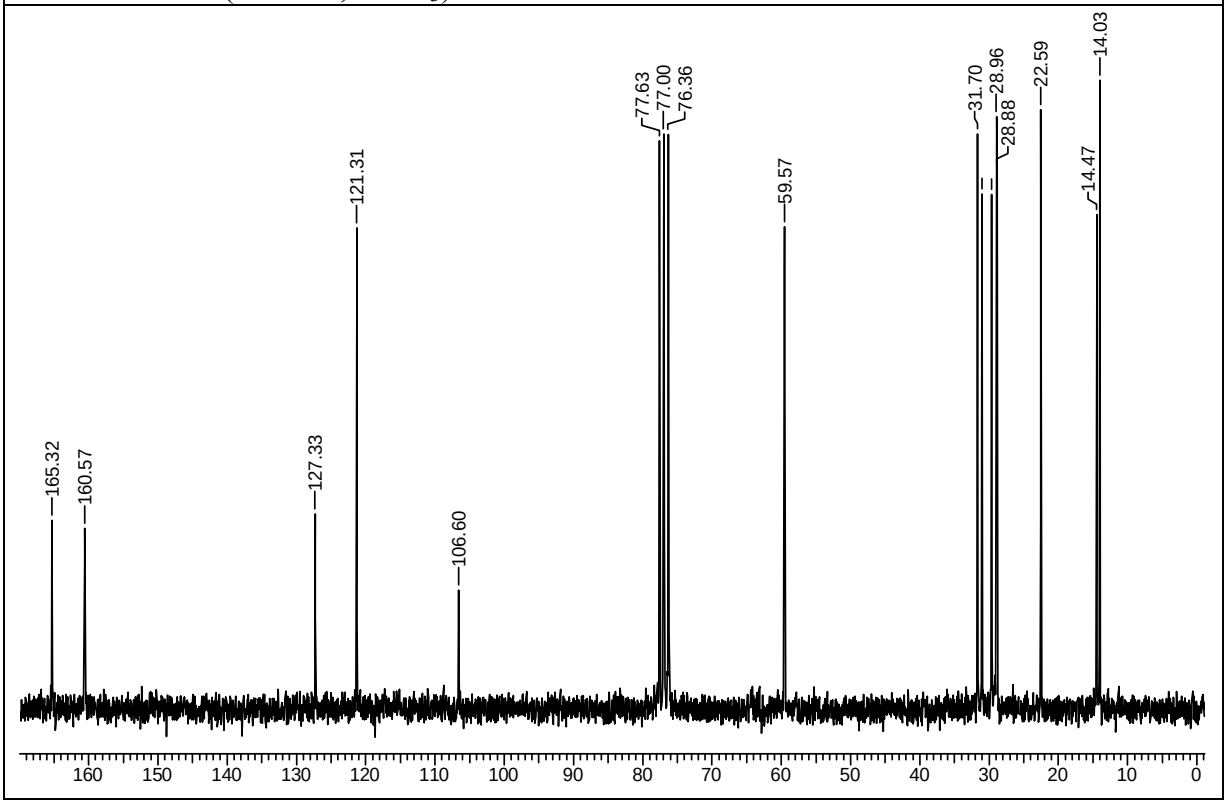
Nature: Brown sticky solid; **Yield:** 76.3%; **^{1}H NMR** (200 MHz, $CDCl_3$)**:** δ 0.91 (t, *J* = 7 Hz, 3H), 1.46-1.61 (m, 2H), 2.51 (t, *J* = 8 Hz, 2H), 3.54 (d, *J* = 14 Hz, 1H), 3.61 (d, *J* = 14 Hz, 1H), 4.57 (d, *J* = 14 Hz, 1H), 4.71 (d, *J* = 14 Hz, 1H), 5.12 (bs, 2H), 6.32 (s, 1H), 6.92-7.06 (m, 2H), 7.33-7.44 (m, 2H), 7.89 (s, 1H), 8.28 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$)**:** δ 13.3, 24.0, 31.5, 55.9, 56.7, 75.7, 84.0, 115.6 (d, 2C), 116.4, 121.5, 127.0 (d, 2C), 129.0, 136.5, 144.5, 150.9, 162.3 (d), 163.8; **IR** (Chloroform)**:** 1616, 2199, 3180, 3447 cm^{-1}; **MS** (ESI) *m*/*z***:** 386.11 (M + 1). **Anal. Calcd. for** $C_{19}H_{20}FN_5OS$**:** C, 59.20; H, 5.23; N, 18.17 %. **Found:** C, 59.39; H, 5.07; N, 18.37 %.

1.7 Selected spectra

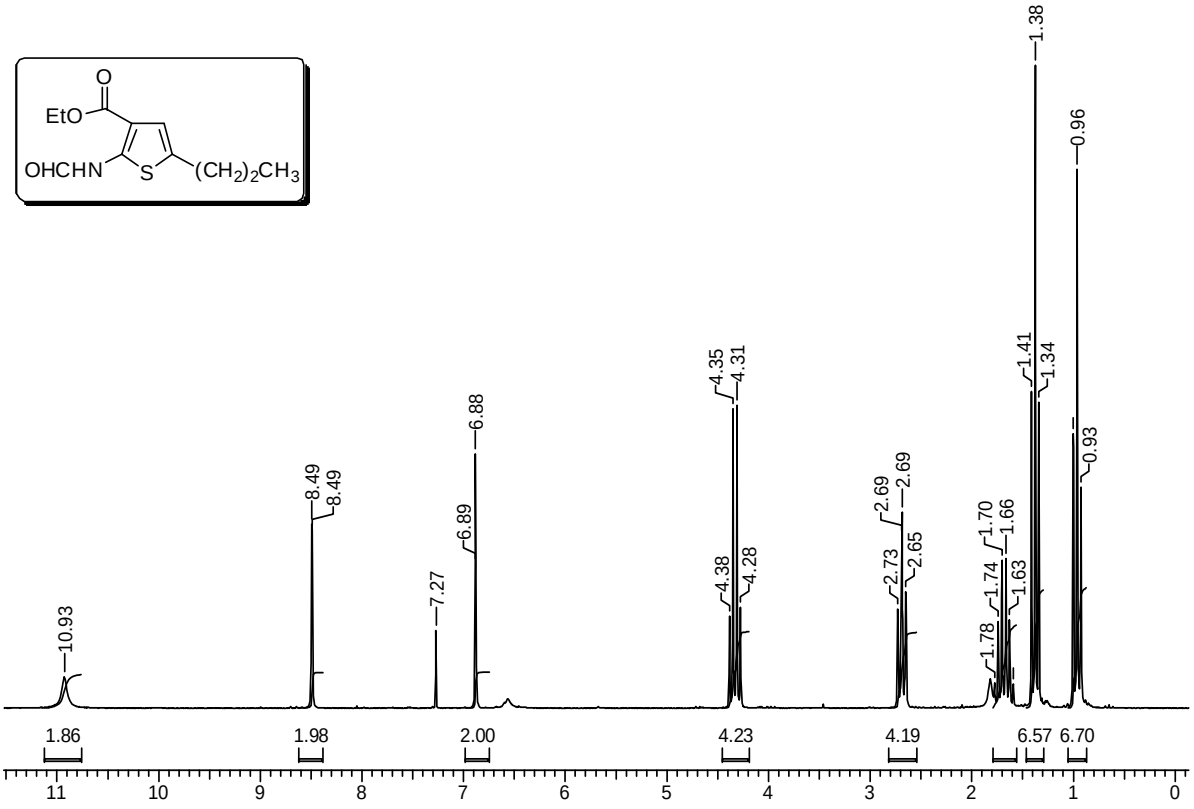
78d: ^{1}H NMR (200 MHz, $CDCl_3$)



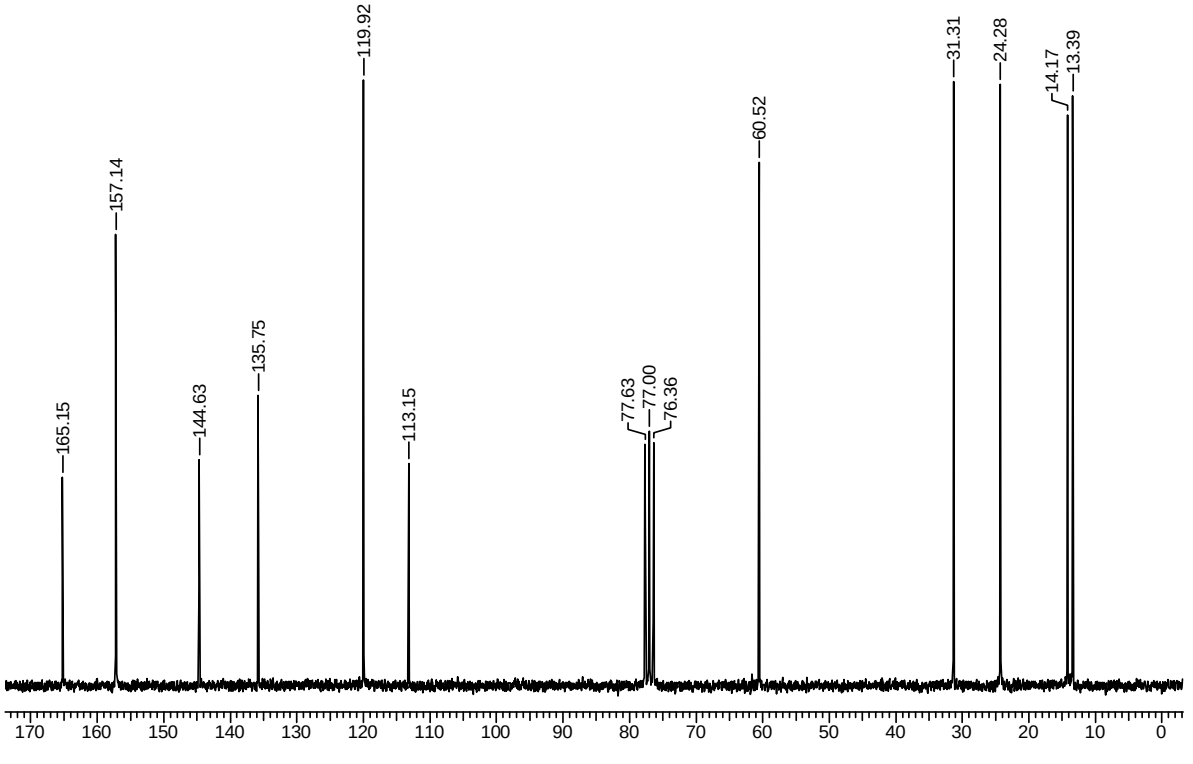
78d: ^{13}C NMR (50 MHz, $CDCl_3$)



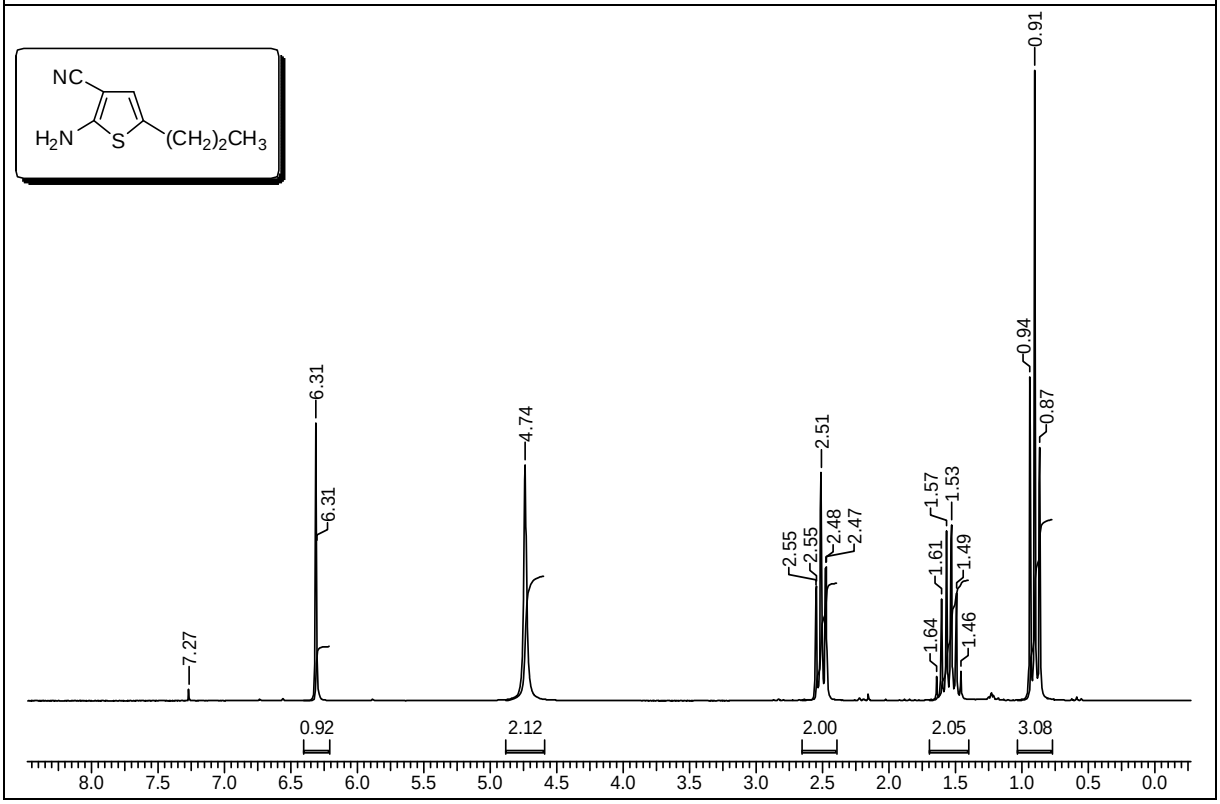
77c: ^{1}H NMR (200 MHz, $CDCl_3$)



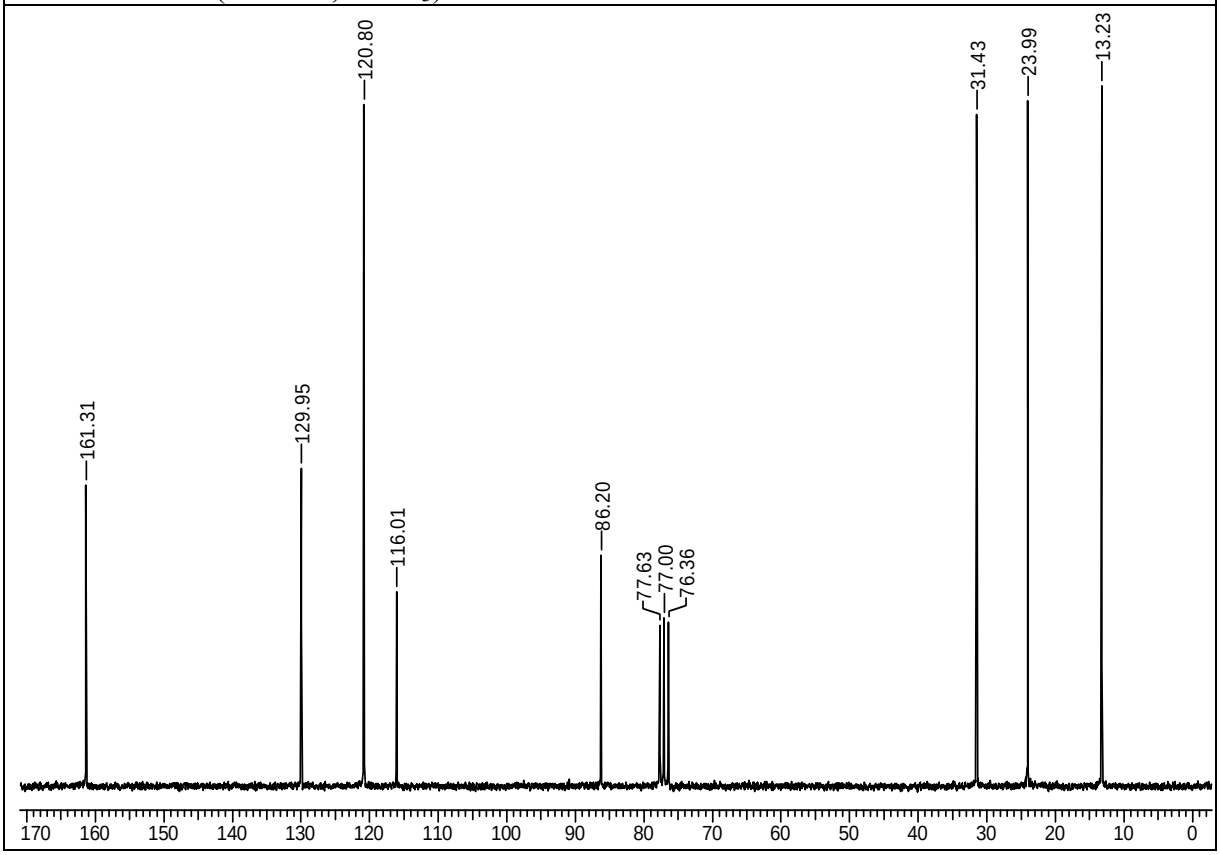
77c: ^{13}C NMR (50 MHz, $CDCl_3$)



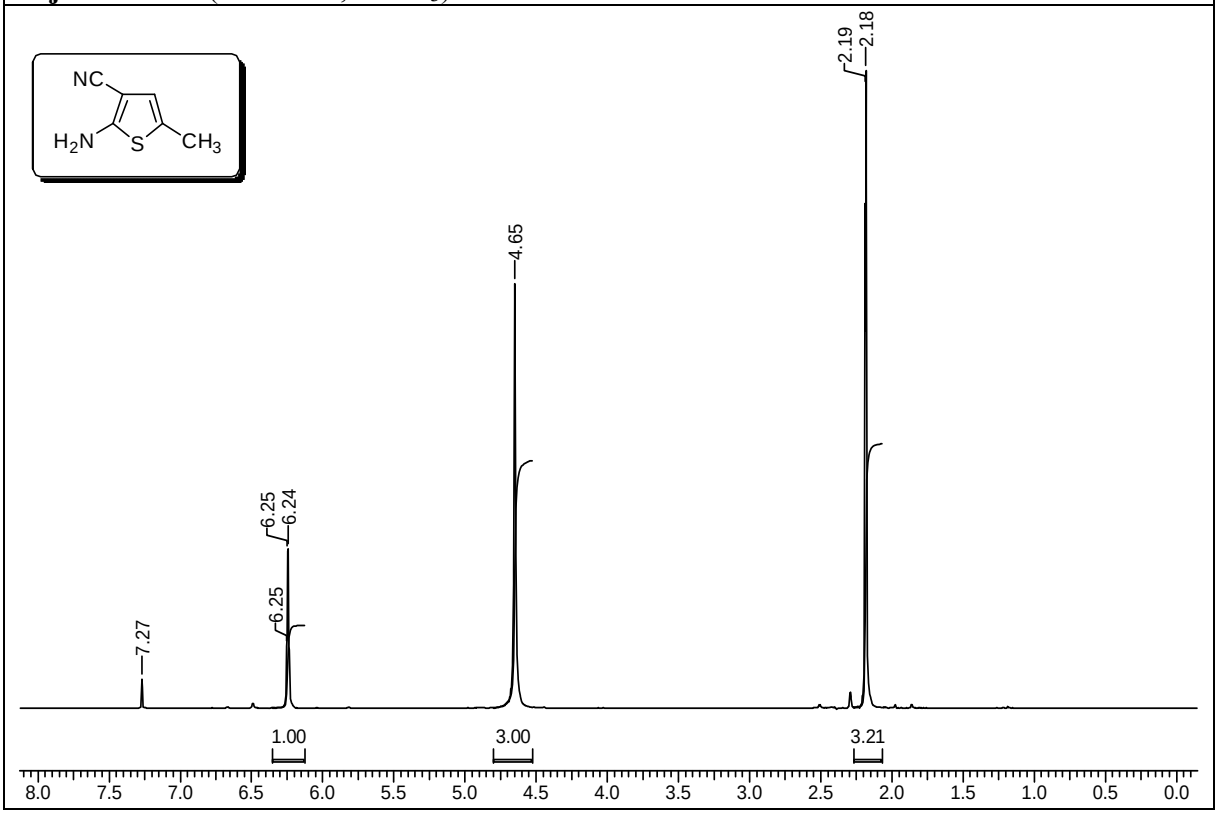
78l: ^{1}H NMR (200 MHz, $CDCl_3$)



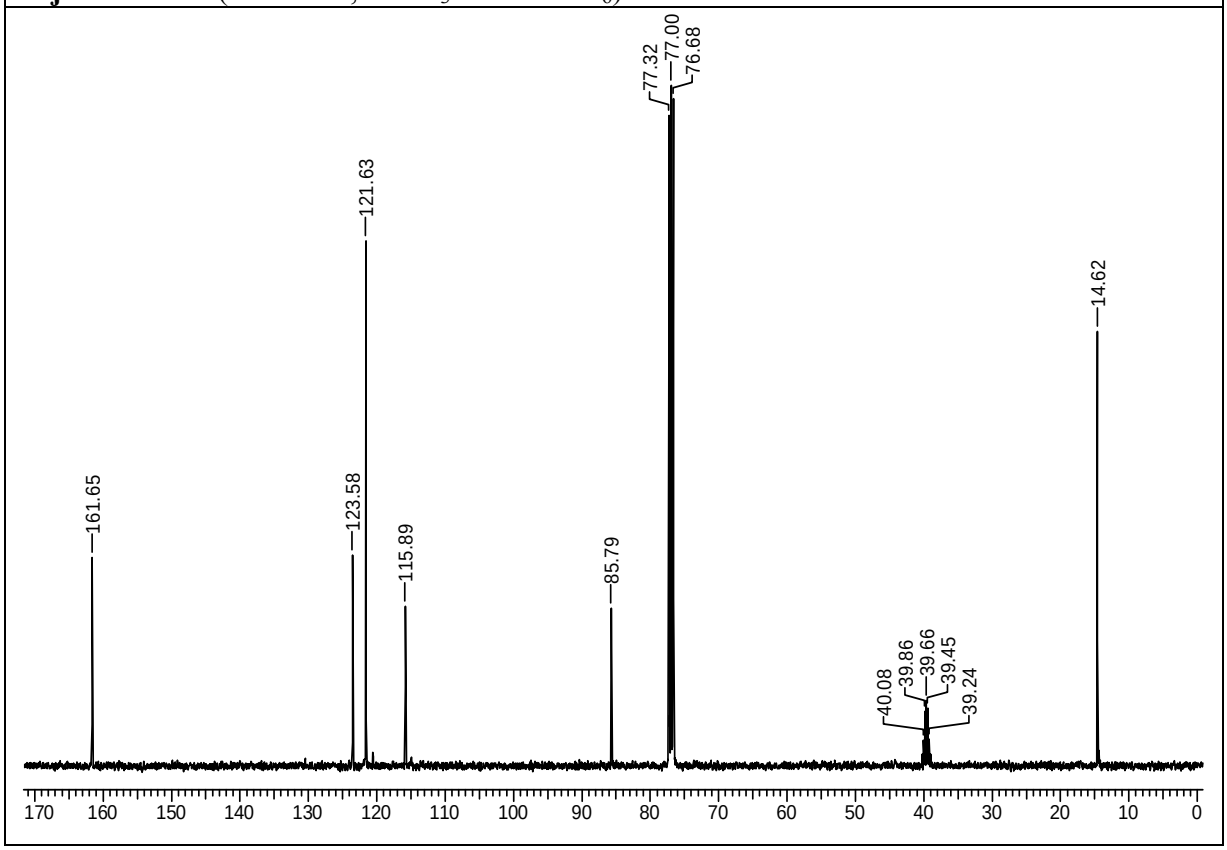
78l: ^{13}C NMR (50 MHz, $CDCl_3$)



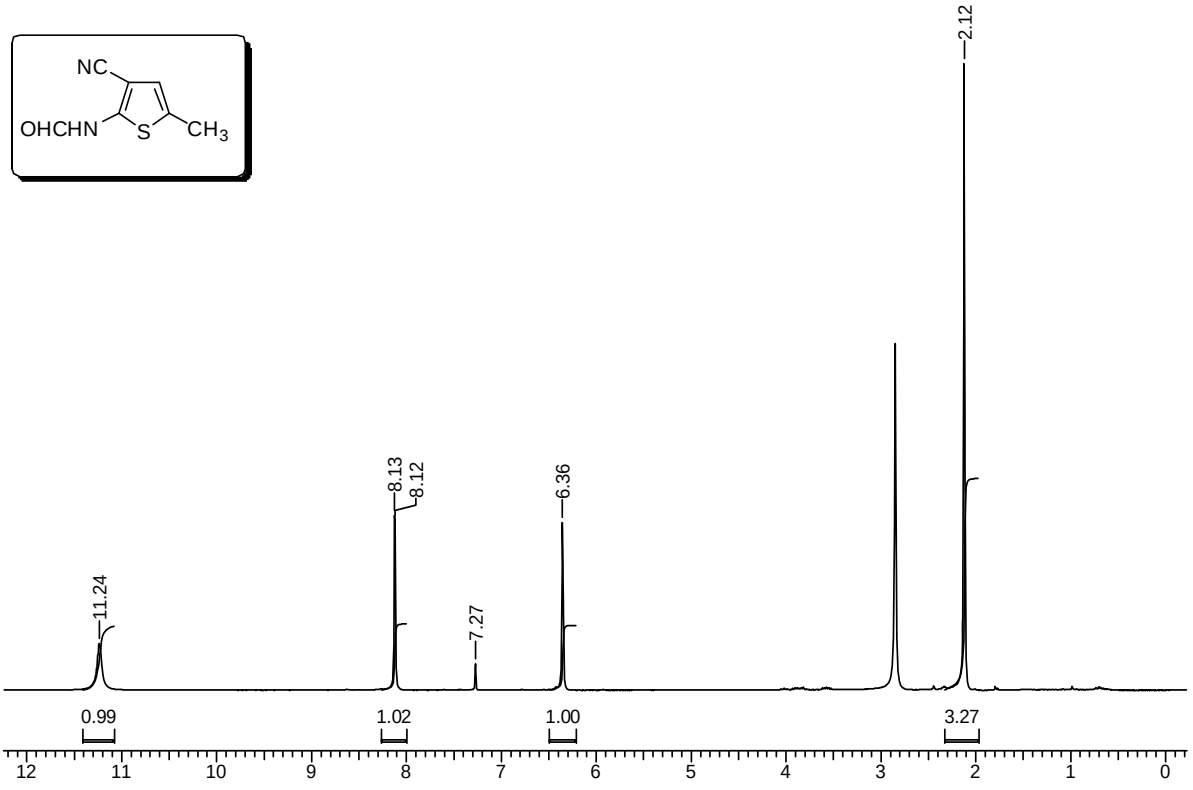
78j: ^{1}H NMR (200 MHz, $CDCl_3$)



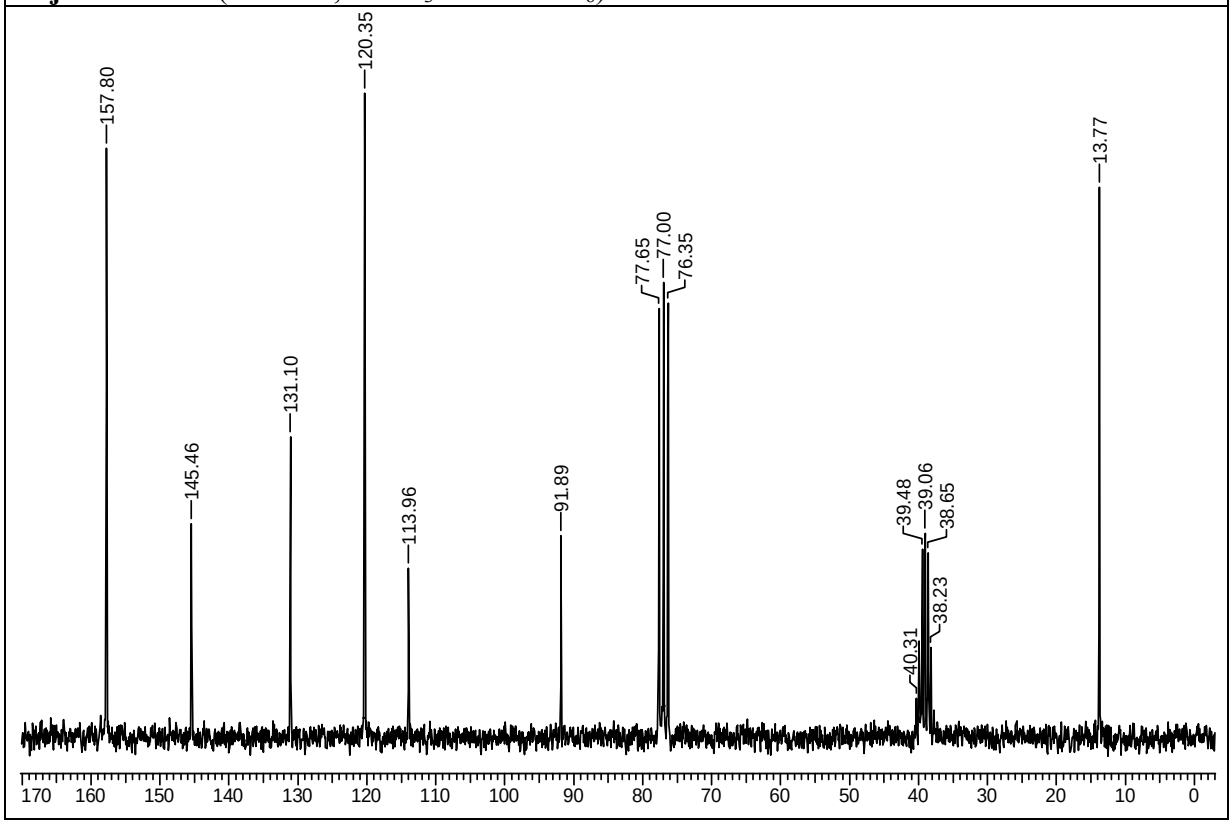
78j: ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6)



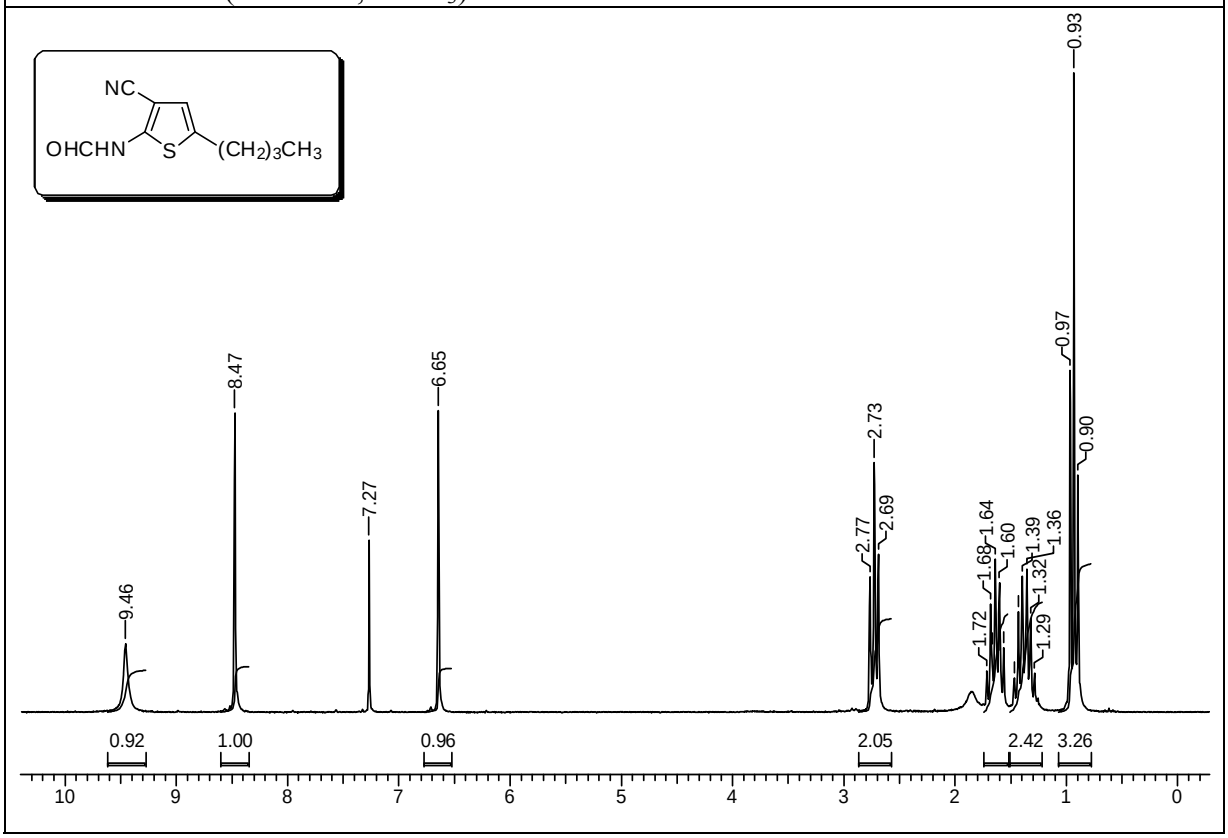
77j: ^{1}H NMR (200 MHz, $CDCl_3$ + DMSO-d_6)



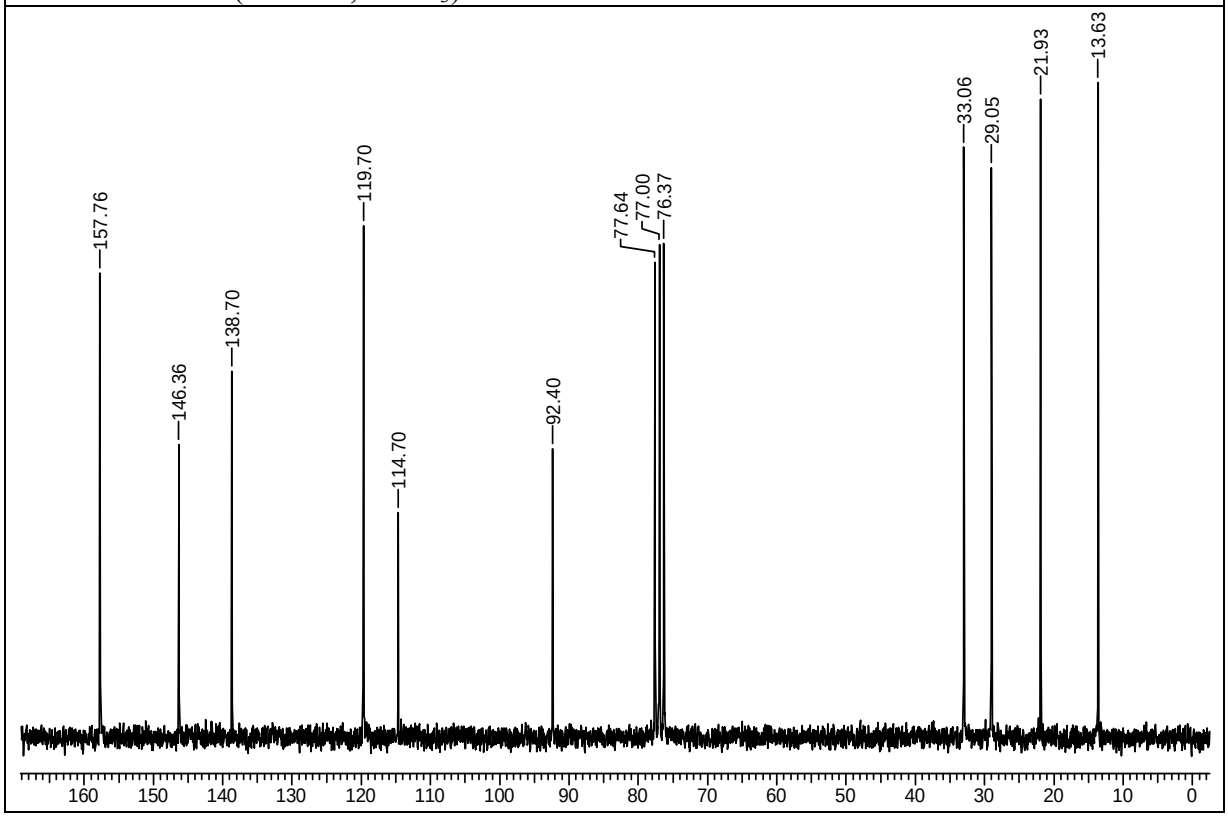
77j: ^{13}C NMR (50 MHz, $CDCl_3$ + DMSO-d_6)



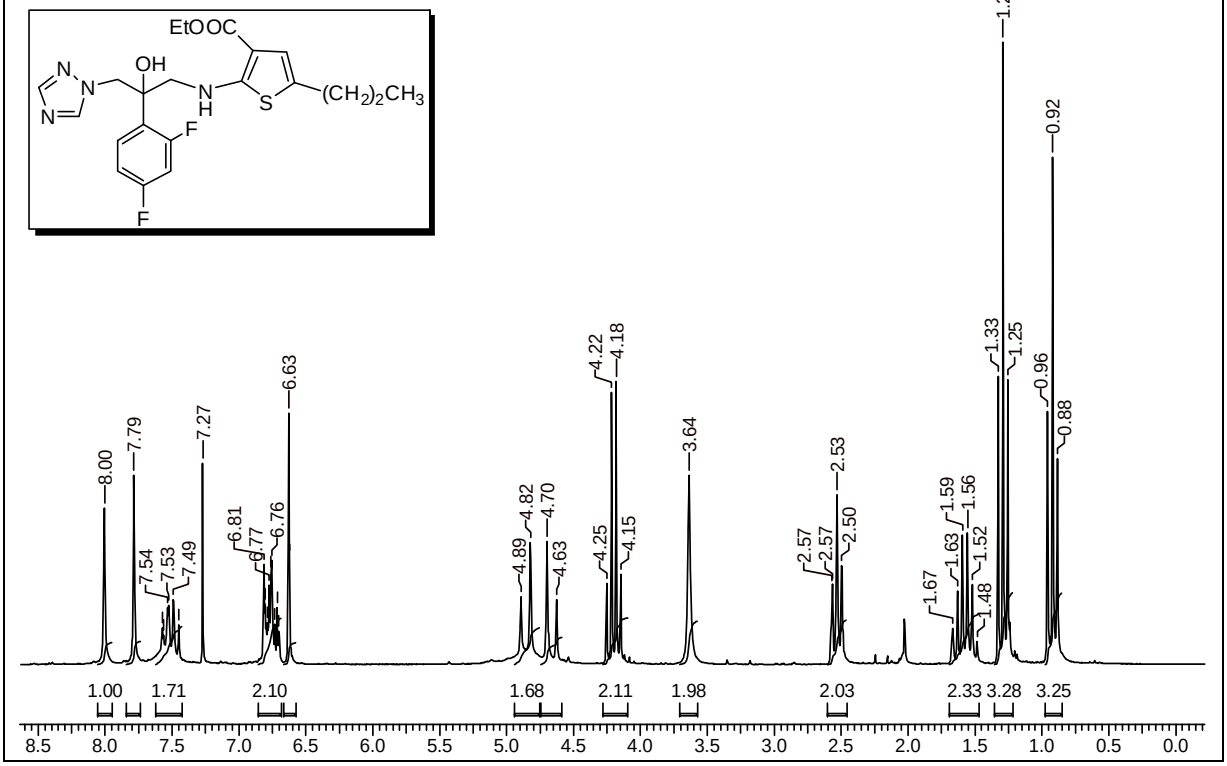
77m: ^{1}H NMR (200 MHz, $CDCl_3$)



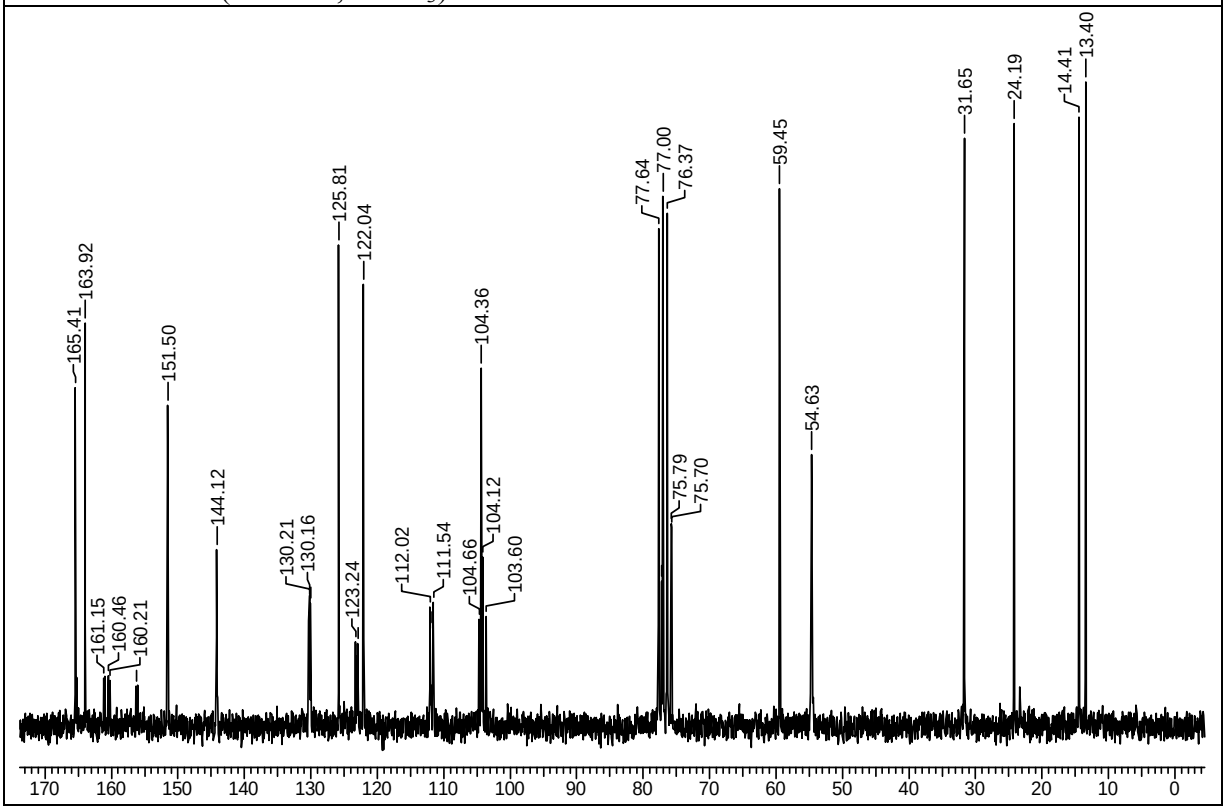
77m: ^{13}C NMR (50 MHz, $CDCl_3$)



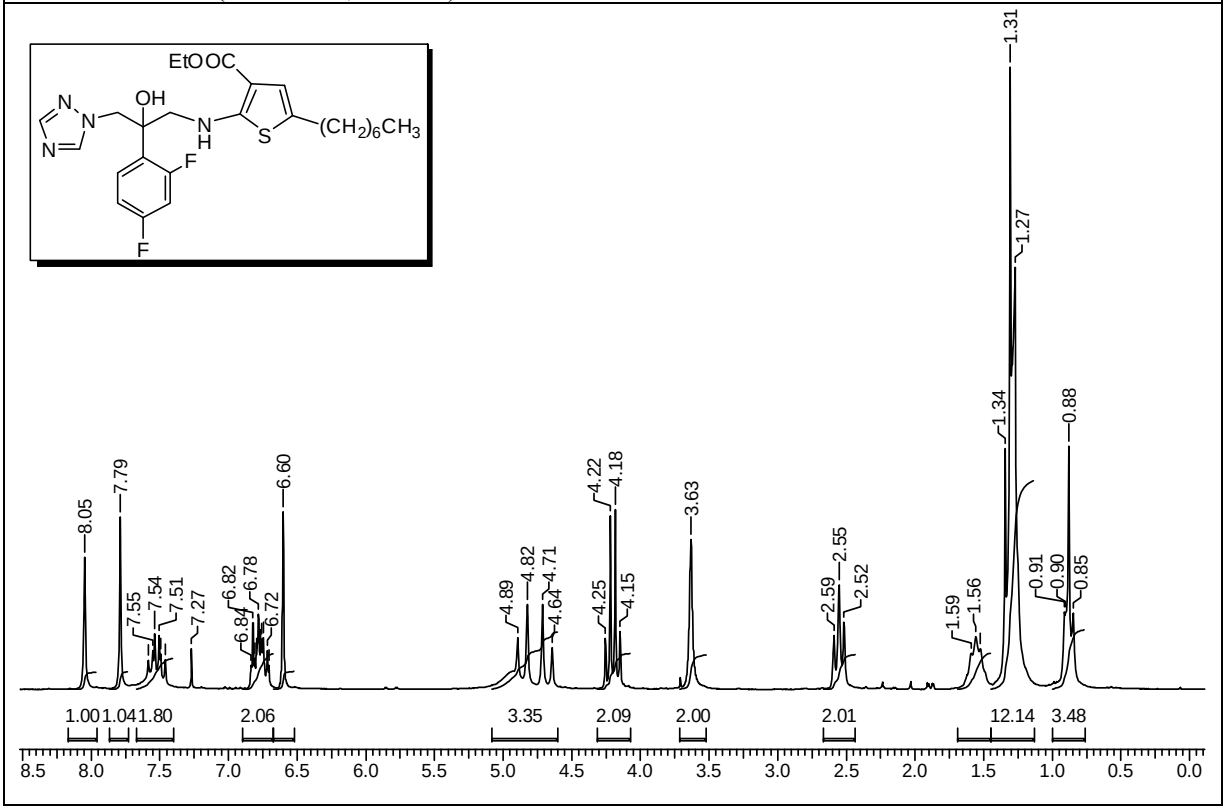
73c: ^{1}H NMR (200 MHz, $CDCl_3$)



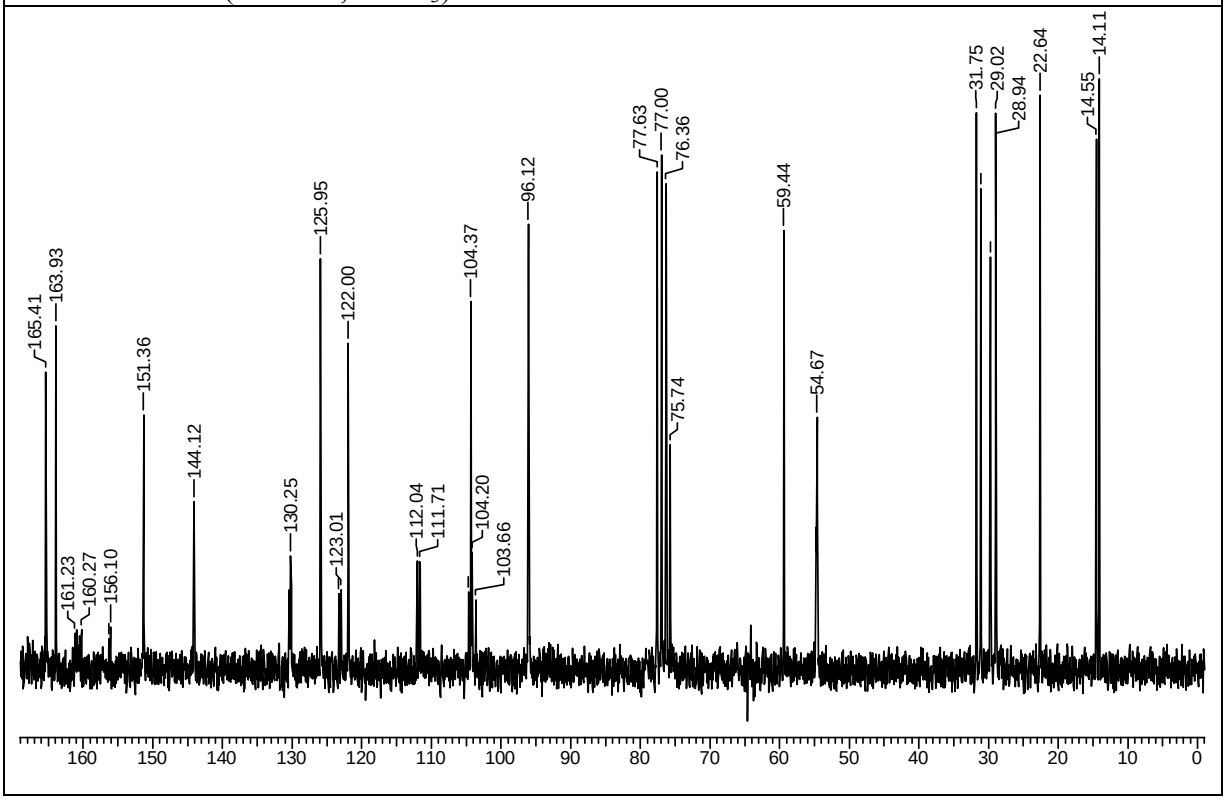
73c: ^{13}C NMR (50 MHz, $CDCl_3$)



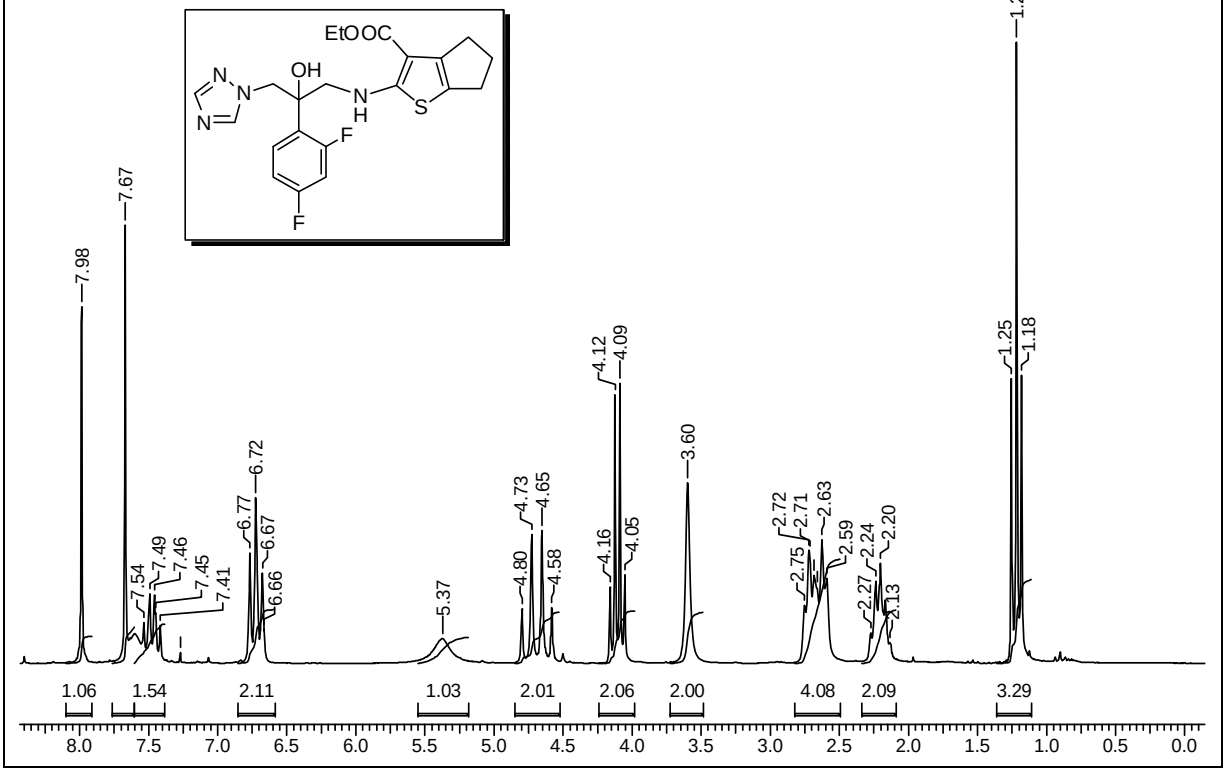
73d: ^{1}H NMR (200 MHz, $CDCl_3$)



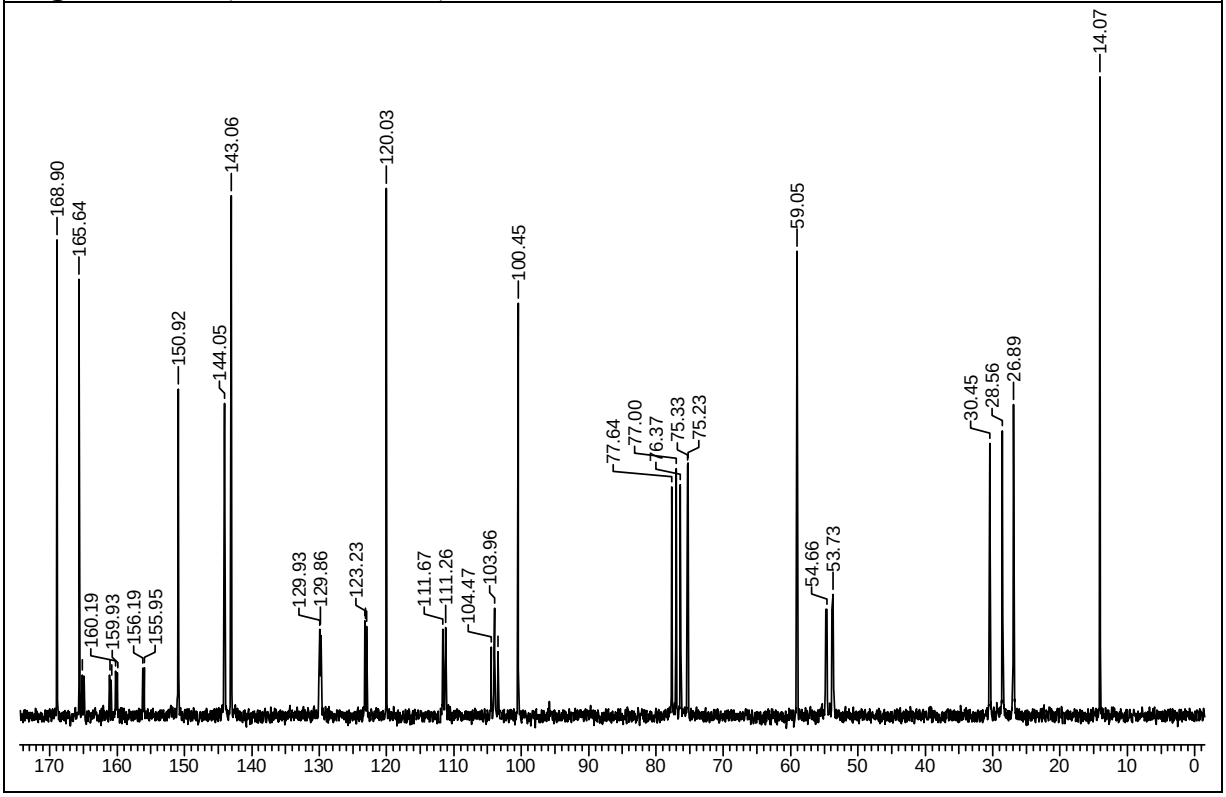
73d: ^{13}C NMR (50 MHz, $CDCl_3$)



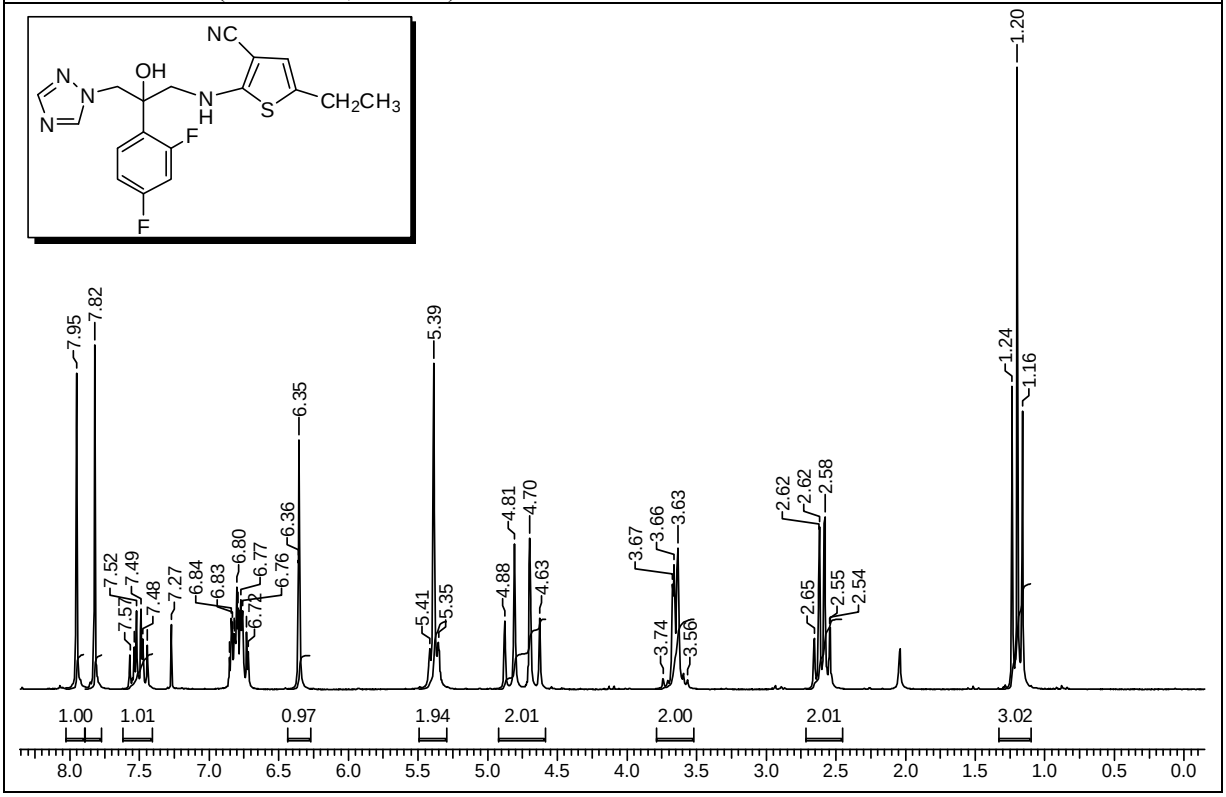
73g: ^{1}H NMR (200 MHz, $CDCl_3$)



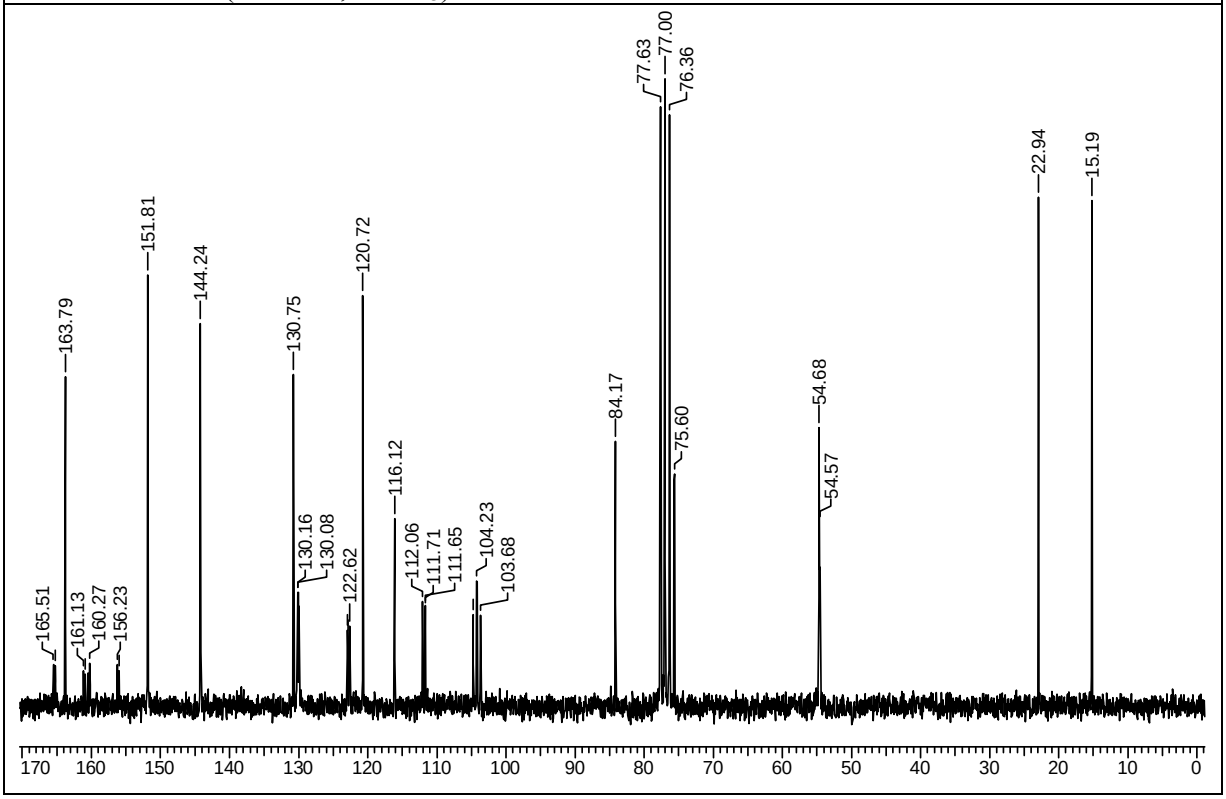
73g: ^{13}C NMR (50 MHz, $CDCl_3$)



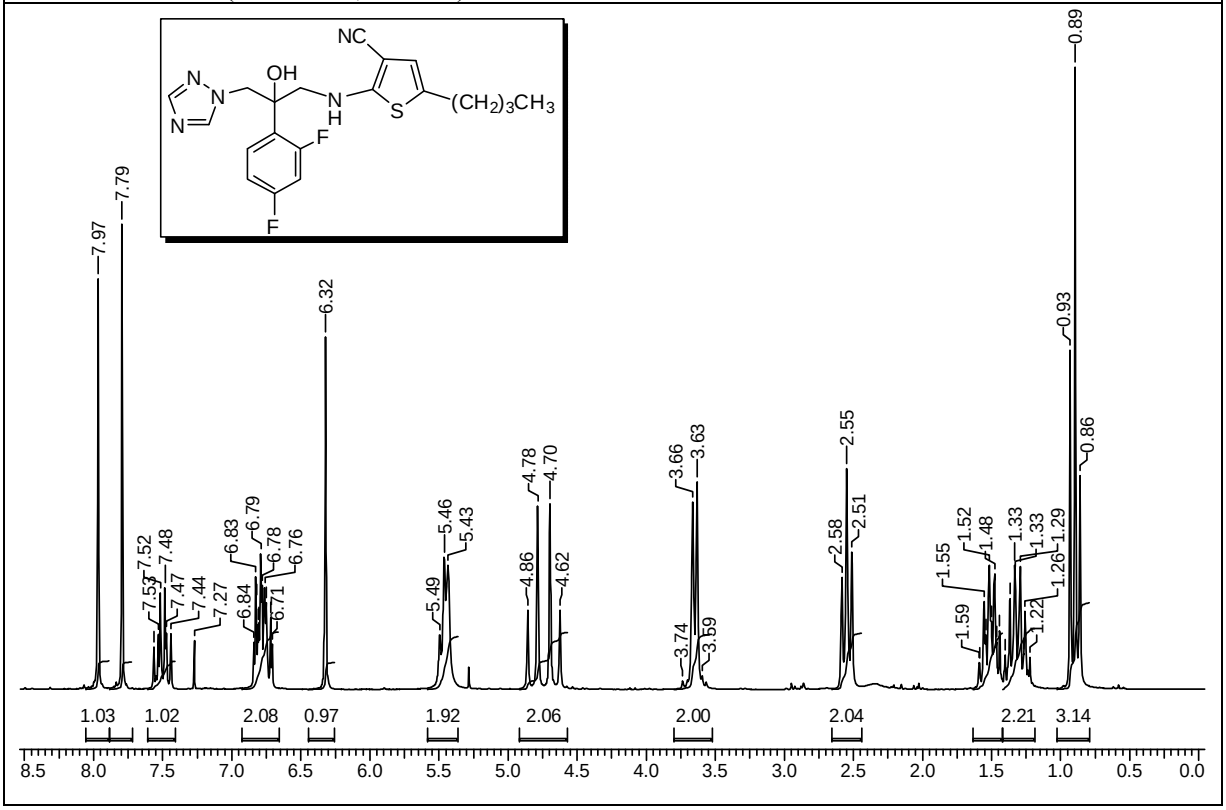
73k: ^{1}H NMR (200 MHz, $CDCl_3$)



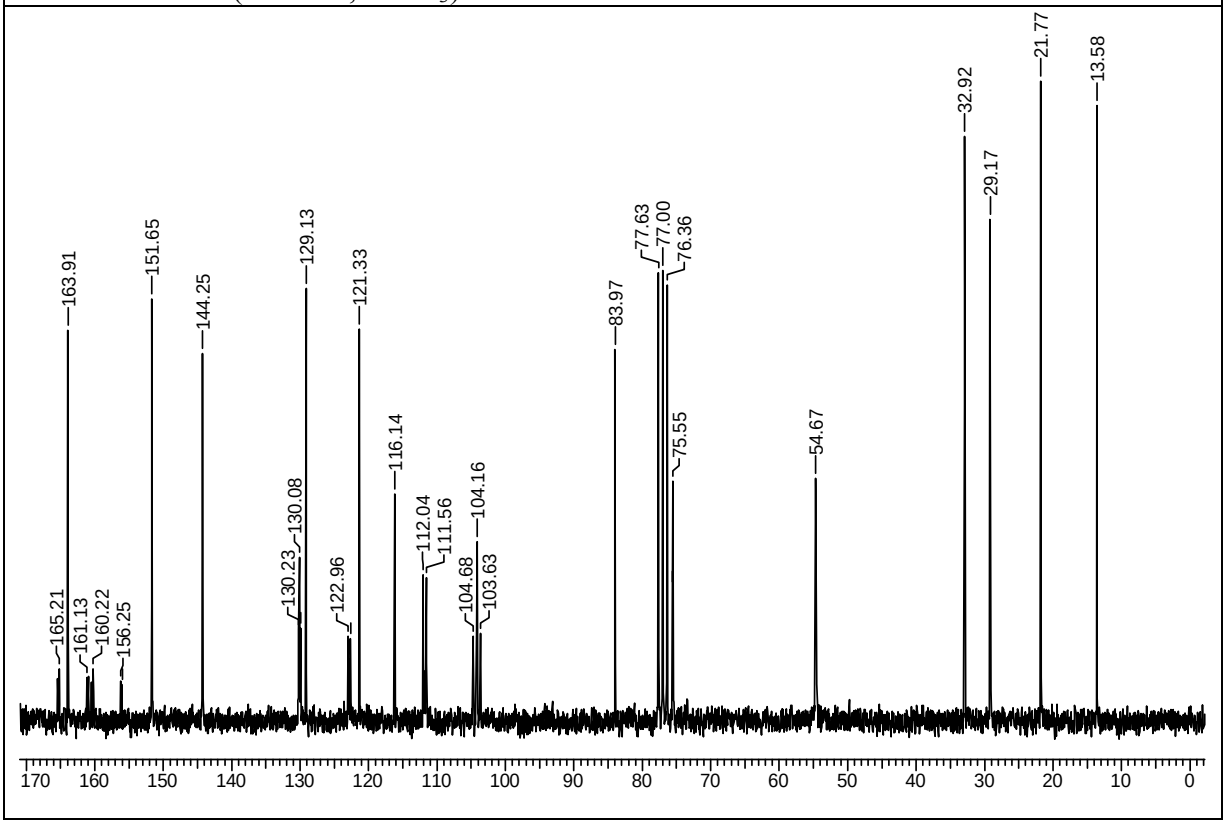
73k: ^{13}C NMR (50 MHz, $CDCl_3$)



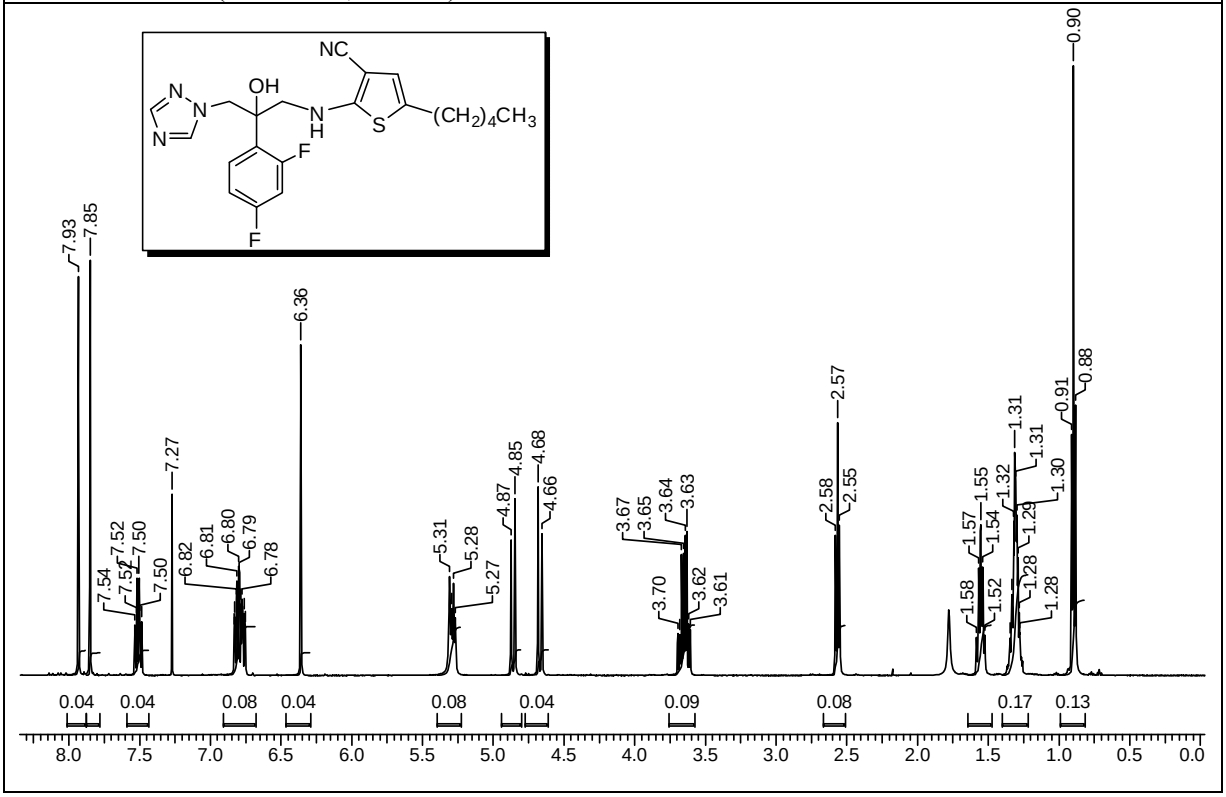
73m: ^{1}H NMR (200 MHz, $CDCl_3$)



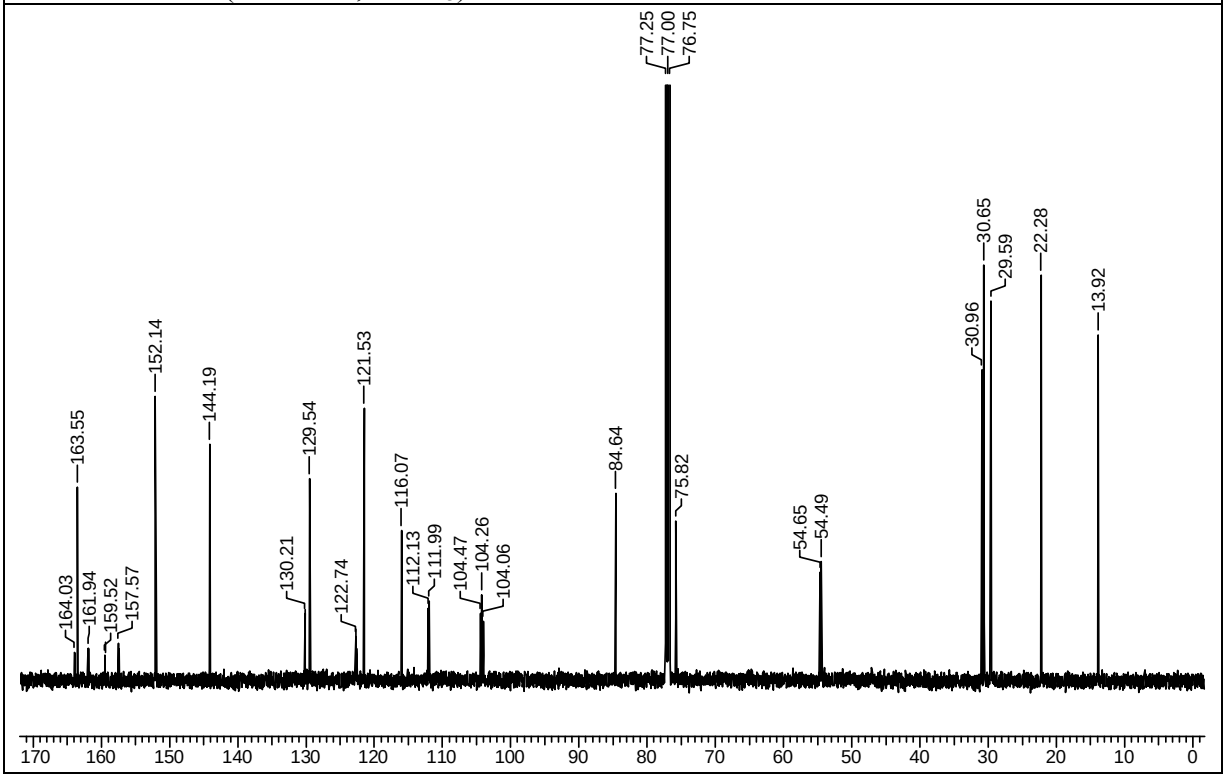
73m: ^{13}C NMR (50 MHz, $CDCl_3$)



73n: ^{1}H NMR (500 MHz, $CDCl_3$)



73n: ^{13}C NMR (125 MHz, $CDCl_3$)



1.8 References

1. Hawksworth, D. L. *Studies in Mycology* **2004**, *50*, 9-17.
2. (a) Fridkin, S. K.; Jarvis, W. R. *Clin. Microbiol. Rev*. **1996**, *9*, 499-511; (b) Larocco, M. T.; Burgert, S. J. *Clin. Microbiol. Rev.* **1997**, *10*, 277-297; (c) Patel, R.; Paya, C. V. *Clin. Microbiol. Rev*. **1997**, *10*, 86-124.
3. (a) Latge, J. P. *Clin. Microbiol. Rev.* **1999**, *12*, 310-350; (b) Steenbergen, J. N.; Casabevall, A. *J. Clin. Microbiol.* **2000**, *38*, 1974-1976.
4. Fostel, J. M.; Lartey, P. A. *Drug Discov. Today* **2000**, *5*, 25-32.
5. Meunier, F. *Inter. J. Antimicrob. Agents* **1996**, *6,* 135-140.
6. (a) Watkins, W. J.; Renau, T. E. Antifungal agents in *Burger's Medicinal Chemistry and Drug Discovery* 6th Edition, *vol. 5*, p 881; (b) Frost, D. J.; Brandt, K. D.; Cugier, D.; Goldman, R. *J. Antibiotics* **1995**, *48,* 306-310; (c) Sheehan, D. J.; Hitchcock, C. A.; Sibley, C. M. *Clin. Microbiol. Rev.* **1999**, *12*, 40-79.
7. (a) Georgopapadakou, N. H.; Tkacz, J. S. *Trends in Microbiology* **1995**, *3*, 98-104; (b) Odds, F. C.; Brown, A. J. P.; Gow, N. A. R. *Trends in Microbiology* **2003**, *11*, 272-279; (c) Barrett, D. *Biochimica et Biophysica Acta* **2002**, *1587*, 224-233.
8. Odds, F. C. *Inter. J. Antimicrob. Agents* **1996**, *6*, 145.
9. (a) Richardson, K.; Brammer, K. W.; Marriott, M. S.; Troke, P. F. *Antimicrob. Agents Chemother.* **1985**, *27*, 832-835; (b) Richardson, K.; Cooper, K.; Marriott, M. S.; Tarbit, M. H.; Troke, P. F.; Whittle, P. J. *Ann. N.Y. Acad. Sci.* **1988**, *544*, 4-11.
10. Kauffman, C. A.; Carver, P. L. *Drugs* **1997**, *53*, 539-549.
11. Rex, J. H.; Rinaldi, M. G.; Pfaller, M. *Antimicrob. Agents Chemother.* **1995**, *39*, 40-44.
12. Schmitt, H. J.; Edwards, F.; Andrade, J.; Niki, Y.; Armstrong, D., *Chemotherapy* **1992**, *38*, 118-126.
13. Zakula, D.; Capobianco, J. O.; *J. Antimicrob. Chemotherapy* **1997**, *39*, 261-264.
14. Tsukuda, T.; Shiratori, Y.; Watanabe, M.; Ontsuka, H.; Hattori, K.; Shirai, M.; Shimma, N. *Bioorg. Med. Chem. Lett*. **1998**, *8*, 1819-1824.
15. Rex, J. H.; Rinaldi, M. G.; Pfaller, M. A. *Antimicrob. Agents Chemother* **1995**, *39*, 1-8.
16. Hitchcock, C. A.; Dickinson, K.; Brown, S. B.; Evans, E. G. V.; Adams, D. J. *Biochem. Journal* **1990**, *266*, 475-480.
17. Wong-Beringer, A.; Kriengkauykiat, J. *Pharmacotherapy* **2003**, *23*, 1441-1462.

18. Lebouvier, N.; Pagniez, F.; Duflos, M.; Le Pape, P.; Na, Y. M.; Le Baut, G.; Le Borgne, M. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 3686-3689.

19. (a) Nam, N.-H.; Sardari, S.; Selecky, M.; Parang, K. *Bioorg. Med. Chem*. **2004**, *12*, 6255-6269; (b) Gao, P.-H.; Cao, Y.-B.; Xu, Z.; Zhang, J.-D.; Zhang, W.-N.; Wang, Y.; Gu, J.; Cao, Y.-Y.; Li, R.; Jia, X.-M.; Jiang, Y.-Y. *Biol. Pharm. Bull*. **2005**, *28*, 1414-1417 and references cited therein.

20. Upadhayaya, R. S.; Jain, S.; Sinha, N.; Kishore, N.; Chandra, R.; Arora, S. K. *Eur. J. Med. Chem*. **2004**, *39*, 579-592.

21. (a) Park, J. S.; Yu, K. A.; Kang, T. H.; Kim, S.; Suh, Y.-G. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 3486-3490; (b) Sun, Q.-Y.; Xu, J.-M.; Cao, Y.-B.; Zhang, W.-N.; Wu, Q.- Y.; Zhang, D.-Z.; Zhang, J.; Jiang, Y.-Y. *Eur. J. Med. Chem.* **2007**, *42*, 1226-1233.

22. Hosni, H. M.; Basyouni, W. M.; El-Nahas, H. A. *J. Chem. Res. (S)* **1999**, *11*, 646-647.

23. Wang, W.; Sheng, C.; Che, X.; Ji, H.; Cao, Y.; Miao, Z.; Yao, J.; Zhang, W. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 5965-5969.

24. Ji, H.; Zhang, W.; Zhou, Y.; Zhang, M.; Zhu, J.; Song, Y.; Lu, J.; Zhu, J. *J. Med. Chem.* **2000**, *431*, 2493-2505.

25. Zhao, Q.; Hu, H.; Li, Y.; Song, Y.; Cai, L.; Wu, Q.; Jiang, Y. *Chemistry & Biodiversity* **2007**, *4*, 1472-1479.

26. Bartroli, J.; Turmo, E.; Alguero, M.; Boncompte, E.; Vericat, M. L.; Garcia-Rafanell, J. *J. Med. Chem.* **1995**, *38*, 3918-3932 and references cited therein.

27. Konosu, T.; Tajima, Y.; Takeda, N.; Miyaoka, T.; Kasahara, M.; Yasuda, H.; Oida, S. *Chem. Pharm. Bull.* **1990**, *38*, 2476-2486.

28. Chai, X.; Zhang, J.; Yu, S.; Hu, H.; Zou, Y.; Zhao, Q.; Dan, Z.; Zhang, D.; Wu, Q. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 1811-1814.

29. (a) Sheng, C.; Zhang, W.; Ji, H.; Zhang, M.; Song, Y.; Xu, H.; Zhu, J.; Miao, Z.; Jing, Q.; Yao, J.; Zhou, Y.; Zhu, J.; Lu, J. *J. Med. Chem.* **2006**, *49*, 2512-2525; (b) Giraud, F.; Loge, C.; Pagniez, F.; Crepin, D.; Pape, P. L.; Borgne, M. L. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 1820-1824.

30. Liu, P.; Zhu, S.; Li, P.; Xie, W.; Jin,Y.; Qingyan Sun, Q.; Wu, Q.; Sun, P.; Zhang, Y.; Yang, X.; Jiangc, Y.; Zhang, D. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 3261-3265.

31. Nam, N.-H.; Sardari, S.; Selecky, M.; Parang, K. *Bioorg. Med. Chem. Lett.* **2004**, *12*, 6255-6269.

32. Lebouvier, N.; Pagniez, F.; Duflos, M.; Le Pape, P.; Min Na, Y.; Le Bauta, G.; Le Borgne, M. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 3686-3689.

33. Chai, X.; Zhang, J.; Cao Y.; Zou Y.; Wua, Q.; Zhang D.; Jiang, Y.; Sun Q. W. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 686-689.

34. Sun, Q.-Y.; Zhang, W.-N.; Xu, J.-M.; Cao, Y.-B.; Wu, Q.-Y.; Zhang, D.-Z.; Liu, C.-M.; Yu, S.-C.; Jiang, Y.-Y. *Eur. J. Med. Chem.* **2007**, *42*, 1151-1157.

35. Aher, N. G.; Pore, V. S.; Mishra, N. N.; Kumar, A.; Shukla, P. K.; Sharma, A.; Bhat, M. K. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 759-763.

36. (a) Jiang, Y.; Cao, Y.; Zhang, J.; Zou, Y.; Chai, X.; Hu, H.; Zhao, Q.; Wu, Q.; Zhang, D.; Sun, Q. *Eur. J. Med. Chem.* **2011**, *46*, 3135-3141; (b) Jiang, Y.; Zhang, J.; Cao, Y.; Chai, X.; Zhang, D.; Jiang Y.; Sun, Q. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 4471-4475.

37. Zhang, W.; Wang, W.; Sheng, C.; Che, X.; Ji, H.; Cao, Y.; Miao, Z.; Yao, J. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 2942-2945.

38. Sheng, C.; Che, X.; Wang, W.; Wang, S.; Cao, Y.; Yao, J.; Miao, Z.; Zhang, W. *Chem. Biol. Drug Des.* **2011**, *78*, 309-313.

39. Chandavarkar, M. A.; Joshi, S. V.; Gurjar, M. K.; Wakharkar, R. D.; Kelkar, R. G.; Murugan, A. Indian Pat. Appl. IN 2005MUM01424 A **2007**.

40. Borate, H. B.; Maujan, S. R.; Sawargave, S. P.; Chandavarkar, M. A.; Vaiude, S. R.; Joshi, S. V. Ind. Patent Appl. No. 438/MUM/2008 (3-3-2008); PCT International Application No. PCT/IN08/000571 dated 05/09/2008; WO 2009/109983 A1.

41. Borate, H. B.; Maujan, S. R.; Sawargave, S. P.; Chandavarkar, M. A.; Vaiude, S. R.; Joshi, V. A.; Wakharkar, R. D.; Iyer, R.; Kelkar, R. G.; Chavan, S. P.; Kunte, S. S. *Bioorg. Med. Chem. Lett.* **2010**, *20,* 722-725.

42. Briel, D.; Ribak, A.; Kronbach, C. *Eur. J. Med. Chem.* **2010**, *45*, 69-77.

43. Maradiya, H. R. *Turk. J. Chem.* **2001**, *25*, 441-450.

44. Sabnis, R. W.; Rangnekar, D. W. *J. Heterocycl. Chem.* **1999**, *36*, 333-345.

45. (a) Koike, K.; Jia, Z.; Nikaido, T.; Liu, Y.; Zhao, Y.; Guo, D. *Org. Lett.* **1999**, *1*, 197; (b) Foroumadi, A.; Mansouri, S.; Kiani, Z.; Rahmani, A. *Eur. J. Med. Chem.* **2003**, *38,* 851-854; (c) Al-Omran, F.; Mohareb, R. M.; El-Khair, A. A. *J. Heterocycl. Chem.* **2002**, *39*, 877-883; (d) Bharti, N.; Shailendra.; Sharma, S.; Naqvi, F.; Azam, A. *Bioorg. Med. Chem.* **2003***, 11*, 2923-2929; (e) Meotti, F. C.; Silva, D. O.; dos Santos, A. R. S.; Zeni, G.; Rocha, J. B. T.; Nogueira, C.W. *Environ. Toxicol. Pharmacol.* **2003**, *37,* 37-44; (f)

Gobbi, S.; Rampa, A.; Bisi, A.; Belluti, F.; Piazzi, L.; Valenti, P.; Caputo, A.; Zampiron, A.; Carrara, M. *J. Med. Chem.* **2003**, *46*, 3662-3669; (g) Lee, K.; Park, C. W.; Jung, W.-H.; Park, H. D.; Lee, S. H.; Chung, K. H.; Park, S. K.; Kwon, O. H.; Kang, M.; Park, D.-H.; Kim, E. E.; Yoon, S. K.; Kim, A. *J. Med. Chem.* **2003**, *46*, 3612-3622.

46. (a) Fokialakis, N.; Cantrell, C. L.; Duke, S. O.; Skaltsounis, A. L.; Wedge, D. E. *J. Agric. Food Chem.* **2006**, *54*, 1651-1655; (b) Chobot, V.; Buchta, V.; Jahodarova, H.; Pour, M.; Opletal, L.; Jahodar, L.; Harant, P. *Fitoterapia* **2003**, *74*, 288-290.
47. Pillai, A. D.; Rathod, P. D.; Franklin, P. X.; Vasu, K. K.; Harish, P. *Bioorg. Med. Chem. Lett.* **2004**, *12*, 4667-4671.
48. (a) Bruns, R. F.; Fergus, J. H. *Mol. Pharmacol.* **1990**, *38*, 939-949; (b) Bruns, R. F.; Fergus, J. H.; Coughenour, L. L.; Courtland, G. G.; Pugsley, T. A.; Dodd, J. H.; Tinney, F. *J. Mol. Pharmacol.* **1990**, *38*, 950-958.
49. Nakamoto, K.; Tsukada I.; Tanaka, K.; Haneda, T.; Murai, N.; Ueda, N.; Watanabe. N.; Asada, M.; Hata, K. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 4624-4626.
50. Wang, T.; Xian-Gui, H.; Liu, J.; Li, B.; Zeng, B.-B. *Synlett* **2010**, *9*, 1351-1354.
51. (a) Konosu, T.; Tajima, Y.; Takeda, N.; Miyaoka, T.; Kasahara, M.; Yasuda, H.; Oida, S. *Chem. Pharm. Bull.* **1991**, *39*, 2581-2589; (b) Bartroli, J.; Turmo, E.; Alguero, M.; Boncompte, E.; Vericat, M. L.; Conte, L.; Ramis, J.; Merlos, M.; Garcia-Rafanell, J.; Forn, J. *J. Med. Chem.* **1998**, *41*, 1869-1882.
52. (a) Gewald, K. *Chem. Ber.* **1965**, *98*, 3571-3577; (b) Gewald, K.; Scmnke, E.; Bottcher, H. *Chem. Ber.* **1966**, *99*, 94-100.
53. (a) Mo, A.; Zhang, H.; Pan, H. CN 1995-111510, **1995**; CA 131:228724; (b) Antoni, S.; Marcial, M.; Roser, P. *ARKIVOC* **2007**, *(iv)*, 234-250; (c) Lebouvier, N.; Giraud, F.; Corbin, T.; Na, Y. M.; Baut, G. L.; Marchand, P.; Borgne, M. L. *Tetrahedron Lett.* **2006**, *47*, 6479-6483; (d) Tamoto, K.; Tanaka, Y.; Miyauchi, H.; Fujimoto, K.; Ohashi, N. *Bull. Chem. Soc. Jpn.* **1994**, *67*, 1427-1433; (e) Corey, E. J.; Chaykovsky, M., *J. Am. Chem. Soc.*, **1962**, *84*, 3782-3783; (f) Corey, E. J.; Chaykovsky, M., *J. Am. Chem. Soc.* **1965**, *87*, 1353-1364; (g) Richardson, K.; Narayanaswami, S. Eur. Pat. Appl. EP0122056, **1984**; (h) Richardson, K.; Gymer, G. E. Eur. Pat. Appl. EP0153803, **1985**.
54. Dyachenko, V. D. *Russ. J. Gen. Chem.* **2004**, *74*, 1135-1136.
55. CLSI: Reference method for broth dilution antifungal susceptibility testing of yeasts; Approved standard, second edition M27-A2, **2002**.

56. CLSI: Reference method for broth dilution antifungal susceptibility testing of filamentous fungi; Approved standard M38-A, **2002**.

57. (a) Saksena, A. K.; Girijavallabhan, V. M.; Lovey, R. G.; Pike, R. E.; Desai, J. A.; Ganguly, A. K.; Hare, R. S.; Loebenberg, D.; Cacciapuoti, A.; Parmegiani, R. M. *Bioorg. Med. Chem. Lett.* **1994**, *16*, 2023-2028; (b) Murakami, K.; Mochizuki, H. Eur. Pat. Appl. EP0472392A2, **1991**.

58. Gangjee, A.; Qiu, Y.; Li, W.; Kisliuk, R. L. *J. Med. Chem.* **2008**, *51*, 5789-5797.

59. Gangjee, A.; Li, W.; Kisliuk, R. L.; Cody, V.; Pace, J.; Piraino, J.; Makin, J. *J. Med. Chem.* **2009**, *52*, 4892-4902.

60. Kathiravan, M. K.; Shishoo, C. J.; Chitre, T. S.; Mahadik, K. R.; Jain, K. S. *Synth. Commun.* **2007**, *37*, 4273-4279.

61. Phoujdar, M. S.; Kathiravan, M. K.; Bariwal, J. B.; Shah, A. K.; Jain, K. S. *Tetrahedron Lett.* **2008**, *49*, 1269-1273.

Chapter 2: Section I

Synthesis of hybrid fluconazole analogues containing chalcone moieties and their bioevaluation

Chapter 2: Section I

Synthesis of hybrid fluconazole analogues containing chalcone moieties and their bioevaluation

Synthesis of hybrid fluconazole analogues containing chalcone moieties and their bioevaluation

2.1.1 Abstract

New class of hybrid antifungal agents was synthesized with various substituted chalcone (1,3-diphenyl-2-propen-1-one) moieties in place of one of the triazoles in fluconazole since it is known that various substituted chalcones and their derivatives exhibit a variety of biological activities against various pests, pathogens and micro-organisms. A number of such compounds were synthesized with good to excellent yield using the strategy developed and the synthesized hybrid fluconazole analogues containing chalcone moieties were screened against different fungal strains. It was observed that most of the newly synthesized hybrid compounds exhibited better antifungal activity than the fluconazole. The enantiomers of some of the substituted chalcone-containing hybrid fluconazole analogues were synthesized by utilizing Sharpless epoxidation reaction. The structure-activity relationship study was carried out to identify the most active compounds of this class.

2.1.2 Introduction

As mentioned in the Chapter 1, in recent years there is an increase in the number of immunocompromised patients such as those infected with HIV and undergoing organ transplantations or cancer chemotherapy and they have to undergo long term antifungal therapy to fight against opportunistic fungi. Though there are effective antifungal agents available in the market, they have quite a few shortcomings such as toxicity, limited range of activity for the fungal strains, high price and limited penetration through central nervous system. Also, the extensive use of antifungal agents like fluconazole[1,2] has increased the number of resistant fungi due to mutations. This has made it necessary to design and synthesize new drugs which can be used in place of current antifungal drugs like amphotericin B, fluconazole *etc*, against the mutated resistant fungal strains and as a result various fluconazole derivatives and analogues have been synthesized and checked for the antifungal activity against different fungal strains. This included derivatisation at tertiary alcohol of fluconazole as ethers, esters, phosphates and so on or the replacement of one of the triazole units by different moieties.[3] In the present work, efforts were directed towards the synthesis of new antifungal agents wherein a series of substituted chalcone-containing hybrid fluconazole analogues were designed and synthesized.

2.1.3 Review of literature

Hybrids as New Leads for Drug Discovery:

The concept of "hybrid drugs" has been gaining more popularity in medicine because of their multitargeted action. The principle of combination drug therapy (hybrid drugs) can be achieved by either using concomitant administration of two or more single active drugs or by drugs in which the single active agents are combined in one molecule i.e. "hybrid molecules". Most of the commonly used drugs in therapy are developed on the basis of the "one target-one disease approach." They are able to address individual targets, and consequently they are successfully used in single-target therapy. They are also used in combination with other drugs for the treatment of complex diseases, such as cardiovascular and inflammatory diseases, cancer and AIDS, which require addressing more than one target. Since a single drug is not always able to adequately control the illness, the combination of drugs with different pharmacotherapeutic profile may be needed[4]. In this regard, there is great interest in the use of multitarget drugs, also called polyvalent or multifunctional drugs, namely, single products capable of interacting simultaneously with multiple targets, directly or following metabolism[5, 6].

There are many reports[7] describing the incorporation of two drug pharmacophores in a single molecule with the intention of exerting dual drug action. For example, one of the hybrid parts may be incorporated to counterbalance the known side effects associated with the other hybrid part, or to amplify its effects through action on another biological target. Encouraging examples of hybrid drug use on systemic heart disease, malaria and on fungal infections were recently published in the literature.

Peyton and co-workers synthesized[8] hybrid molecule **92 (**Figure 1) termed as "reversed chloroquine" by combining chloroquine and des N-methyl imipramine and this drug was found to be 10 times more effective than chloroquine against both chloroquine-sensitive and chloroquine-resistant strains of *Plasmodium falciparum*.

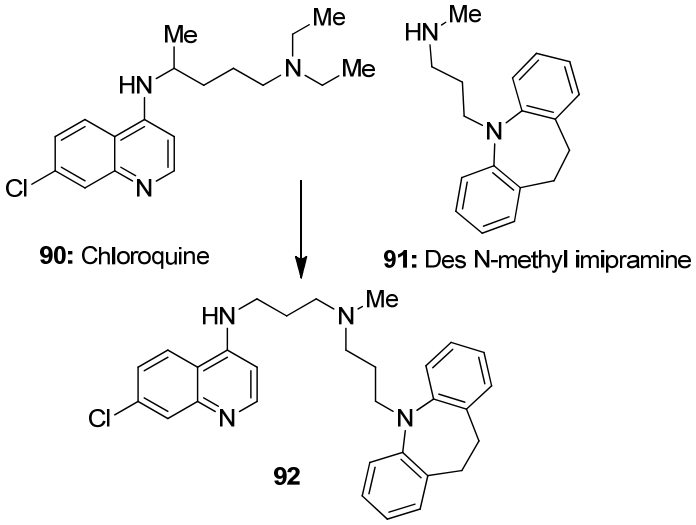


Figure 1. Structures of chloroquine (**90**), des N-methyl imipramine (**91**) and hybrid molecule **92**

Artemisinin (**93**) is a drug used to treat multi-drug resistant strains of falciparum malaria. This compound is isolated from the plant *Artemisia annua*. In addition to its well-known antimalarial activity, artemisinin derivatives possess potent activity against cancer cells. Walsh and coworkers[9] combined fast-acting artemisinin and slow-acting quinine into a hybrid drug **95** (Figure 2) for malaria (for which drug resistance is a barrier to effective treatment).

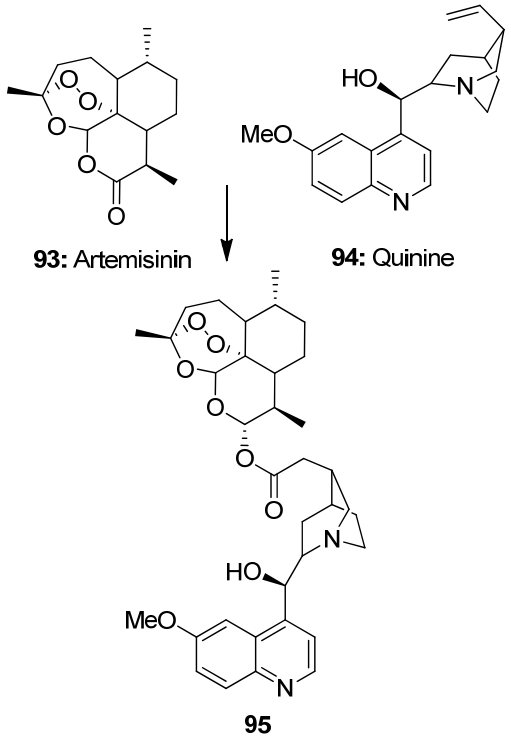


Figure 2. Structures of artemisinin (**93**), quinine (**94**) and hybrid molecule **95**

In vitro assays showed that the hybrid compound **95** is more effective against drug-sensitive and drug-resistant malaria than the individual drugs alone or a cocktail made of a 1:1 molar ratio of the two. Walsh also suggested that the hybrid drug may increase cellular uptake which improves the efficacy of the treatment.

Furthermore, Francisca *et al.* reported[10] a series of artemisinin–vinyl sulfone hybrid molecules **97** (Figure 3) with the potential to act in the parasite food vacuole *via* endoperoxide activation and falcipain inhibition. A number of compounds were synthesized and screened for antiplasmodial activity and falcipain-2 inhibition. All hybrid molecules were active against the *Plasmodium falciparum* W2 strain in the low nanomolar range.

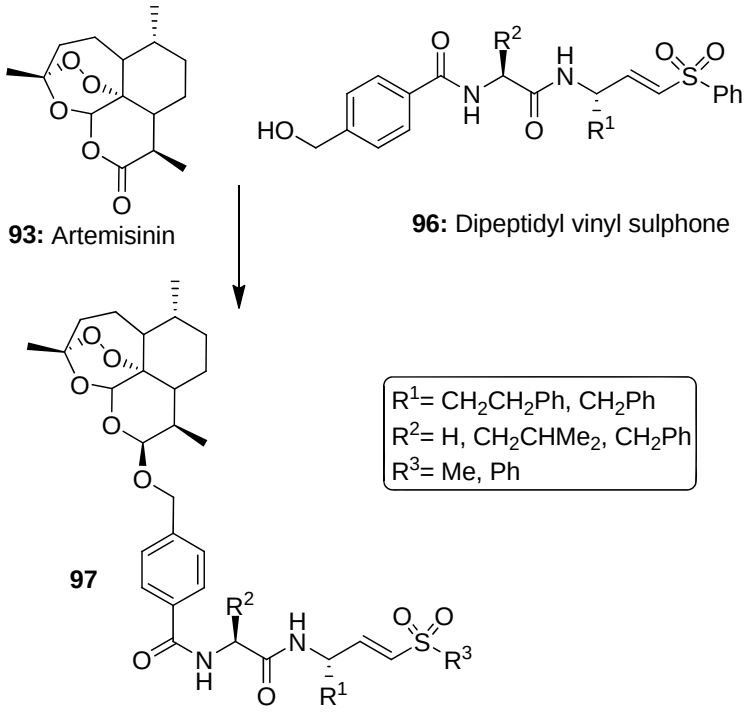


Figure 3. Structures of artemisinin (**93**), dipeptidyl vinyl sulfone (**96**) and hybrid molecules **97**

Singh and coworkers[11] designed hybrid molecules **100** on the basis of the biological significance of indoles and barbituric acid and evaluated their anticancer activities. Out of a set of 10 molecules, two compounds (**100g** and **100h**) (Figure 4) exhibited significant anticancer activities and could be used as leads for further investigations.

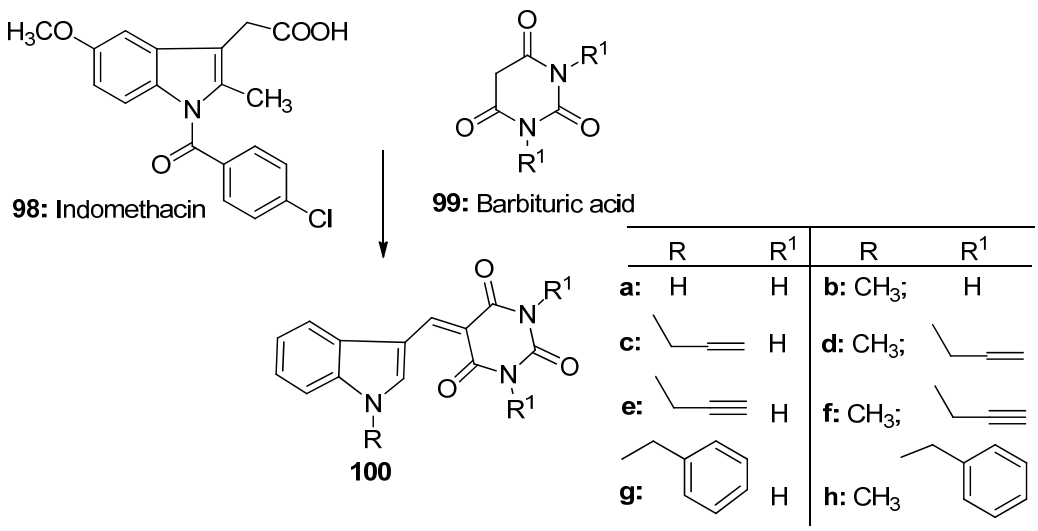


Figure 4. Structures of indomethacin **(98)**, barbituric acid **(99)** and hybrid molecules **100**

Jun'ichi *et al.* reported[12] hybrid molecules **103a** and **103b** of caffeine (**101**) and eudistomin D (**102**), a β-carboline alkaloid from a marine tunicate, and their affinity and selectivity for adenosine receptors A_1, A_{2A}, and A_3 were examined (Figure 5). It was found that both the compounds showed better potency as adenosine receptor ligands as compared with caffeine.

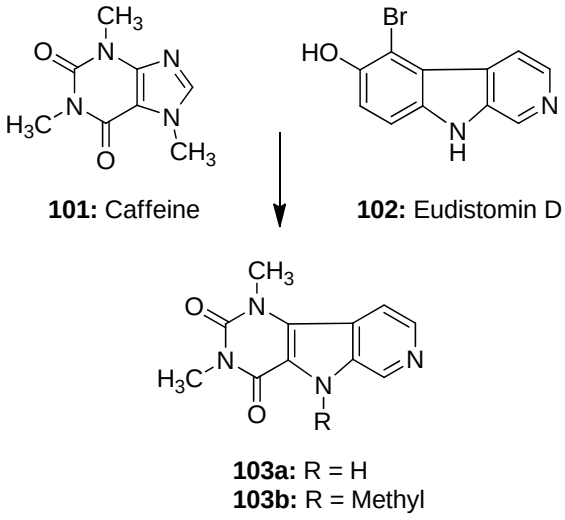


Figure 5. Structures of caffeine **(101)**, eudistomin D **(102)** and hybrid molecule **103**

Bisi and coworkers reported[4] the synthesis and pharmacological profile of some hybrid compounds bearing benzazepinone moiety present in Zatebradine (**104**). In these new hybrid molecules **105**, the presence of aryloxypropanol moiety produces high affinity and selectivity for β_1-adrenoreceptors. Moreover, the investigation on the

enantiomers of the most potent hybrid compound has revealed a different cardiovascular profile, i.e., (+)-(*R*)-enantiomer displays affinity for cardiac β_1-adrenoreceptors, while (−)-(*S*)- enantiomer shows specificity for vessel smooth muscle. The trend noted in this series of hybrid molecules might help in developing useful structure-activity relationships to differentiate and to understand structural elements which give selectivity for β_1 versus β_2-adrenoreceptors.

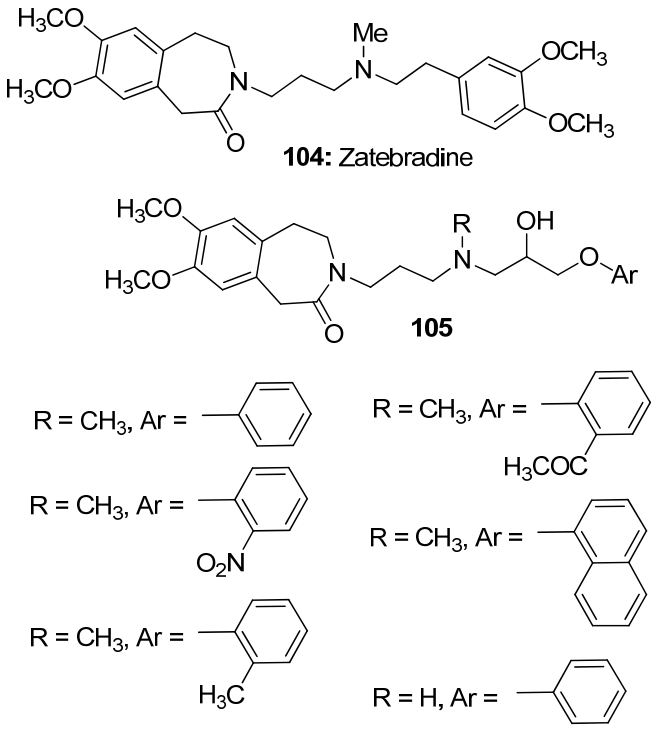


Figure 6. Structures of zatebradine **(104)** and hybrid molecules **105**

Pier *et al.* reported[13] the hybrid molecule **108** (Figure 7) by the combination of the natural antibiotic distamycin A **106** and the antineoplastic agent uramustine **107.** Uramustine (uracil mustard) **107** is an inexpensive oral alkylating agent that has been effective in the treatment of patients with lymphosarcoma, chronic lymphatic leukaemia and thrombocythemia. Uramustine interacts in guanine-cytosine (GC) rich regions being able to alkylate guanine-N7 in 5'-PyGCC-3' (Py= pyrimidine; GCC= guanine-cytosine content) sequences. All the hybrid compounds in this series exhibit enhanced activity compared both to distamycin A and uramustine, giving IC_{50} values in the range of 7.26-0.07 μM on human leukemic K562 cells, with maximal activity shown when n= 6.

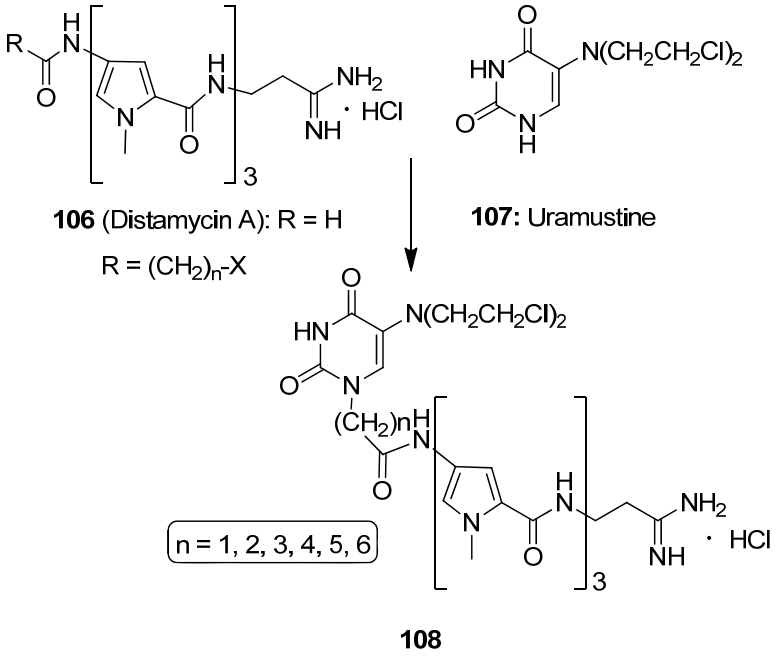


Figure 7. Structures of distamycin A (**106**), uramustine (**107**) and hybrid molecules **108**

Singh *et al.* reported[14] hybrid molecules **111** and **112** on the basis of the structural features of pyrazole-based drugs **109** and multidrug resistance (MDR) modulator propafenone **110** (Figure 8). The synthesized hybrid molecules were evaluated for their interactions with permeability glycoprotein (P-glycoprotein). Some of the molecules show considerable interactions with P-glycoprotein and some of the compounds are potential candidates for their use as MDR modulators.

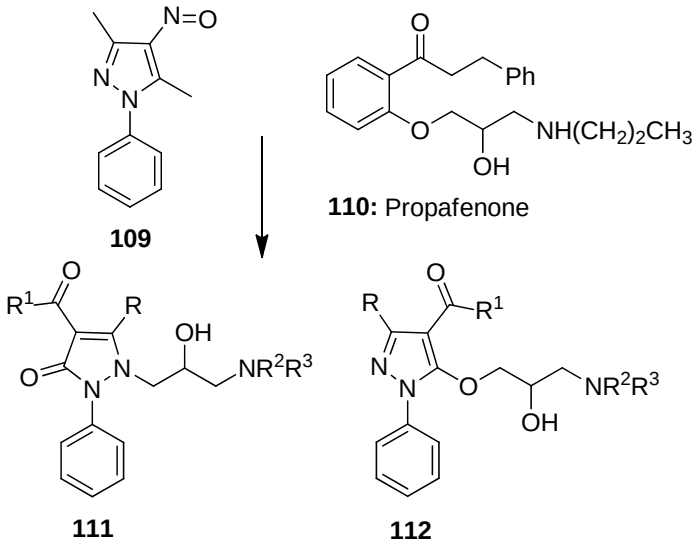


Figure 8. Structures of **109**, **110** and the hybrid molecules **111** and **112**

Recently Jiang and coworkers reported[15] a hybrid molecule ZJ-522 (**114**) restructured from fluconazole (**6**) and butenafine (**113**) (Figure 9) exhibiting antifungal activity.

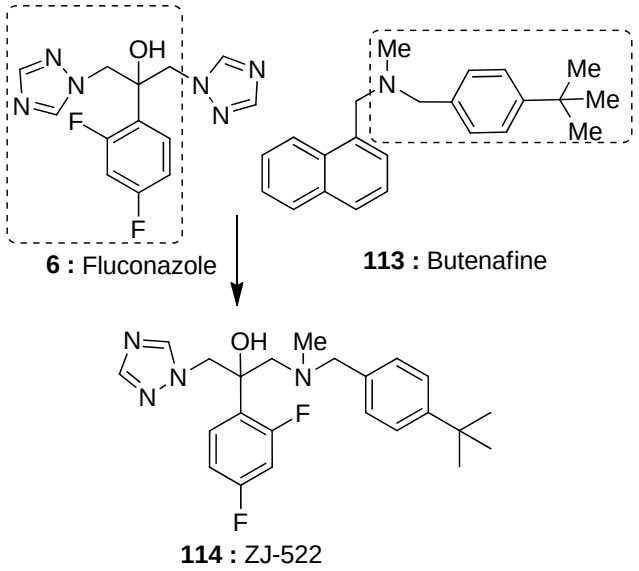


Figure 9. Structures of fluconazole (**6**), butenafine (**113**) and hybrid molecule **ZJ-522**

ZJ-522 was tested against 43 strains of fungi representing 13 fungal species and it was observed to exhibit about 50-fold and 2 to 16-fold more activity than fluconazole against yeasts and filamentous fungi respectively. This research demonstrated that hybrid molecules having pharmacophores/structural features of two molecules of different classes may have potential to exhibit superior activity than the parent molecules. Moreover, the use of hybrid drugs shows some advantages compared with a cocktail of drugs, including a lower risk of drug-drug interactions, improved compliance by the patient, and a more predictable pharmacokinetic profile.

Chalcone: biologically important lead

Chalcones constitute an important group of natural products and serve as valuable precursors for the synthesis of different classes of flavonoids which are common substances in plants[16]. Chalcones are open-chain flavonoids in which two aromatic rings are joined by a three carbon α,β-unsaturated carbonyl system (1,3-diphenyl-2-propen-1-ones)[16]. Natural and synthetic chalcone derivatives have received a great deal of attention due to their relatively simple structures, and wide variety of pharmacological activities reported for these compounds including anti-inflammatory,[17] anti-bacterial[16], anti-

fungal[18-20], and anti-tumor activities[21–24]. Naturally occurring chalcones have been reported to have multiple biological and pharmacological activities. For example, xanthoangelol (**115**) has been reported to induce apoptosis (death of cell) and to inhibit tumor promotion and metastasis in several cancer cell lines.[25,26] Broussochalcone A **(116)**[27], dimethylaminochalcone **117**[28], and cardamonin (**118**)[29,30] possess anti-inflammatory activity. Licochalcone A (**119**), a substance found in the roots of the Chinese liquorice, showed antimalarial activity[31] (Figure 10). 4,4'-Dichlorochalcone exhibits antilipidemic activity[32]. There are other chalcones with very interesting biological activity such as isoliquiritigenin (**120**)[29] and butein (**121**)[33]. These chalcones, like *trans*-resveratrol[34], remarkably activate sirtuin[35] enzymatic activity, mimic the beneficial effects of caloric restriction (CR), retard the aging process, and increase longevity in the budding yeast *Saccharomyces cerevisiae*.

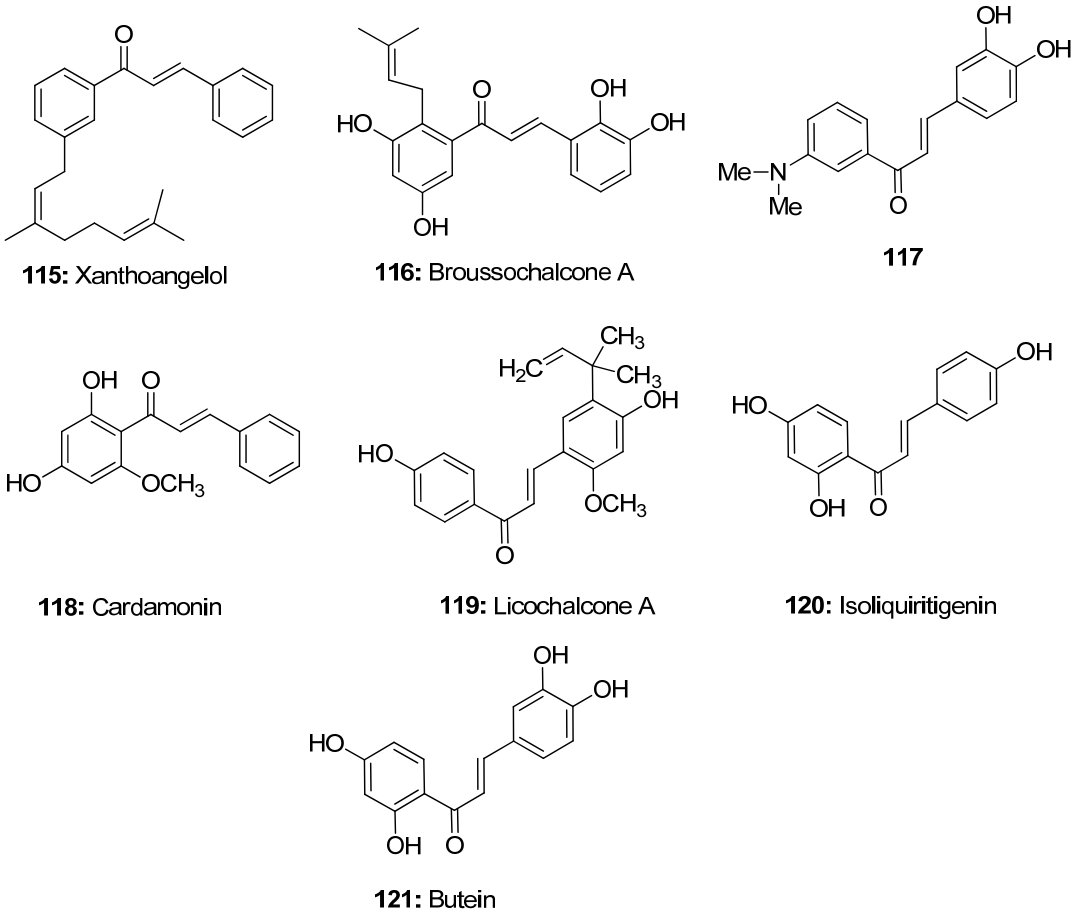


Figure 10. Naturally occurring chalcones exhibiting different biological activities

Apart from this, chalcones are well known intermediates for synthesizing various heterocyclic compounds. Cyclization of chalcones, leading to thiazines, pyrimidines,

pyrazolines *etc* has been a developing field within the realm of heterocyclic chemistry for the past several years because of their ready accessibility and the broad spectrum of biological activity of the products as antibacterial, antifungal, antiprotozoal and anti-inflammatory substances. Also chalcones (1,3-diaryl-2-propen-1-ones) seem to be promising antifungal drug candidates and antifungal activity of chalcones (Figure 11) has been investigated by a number of researchers.

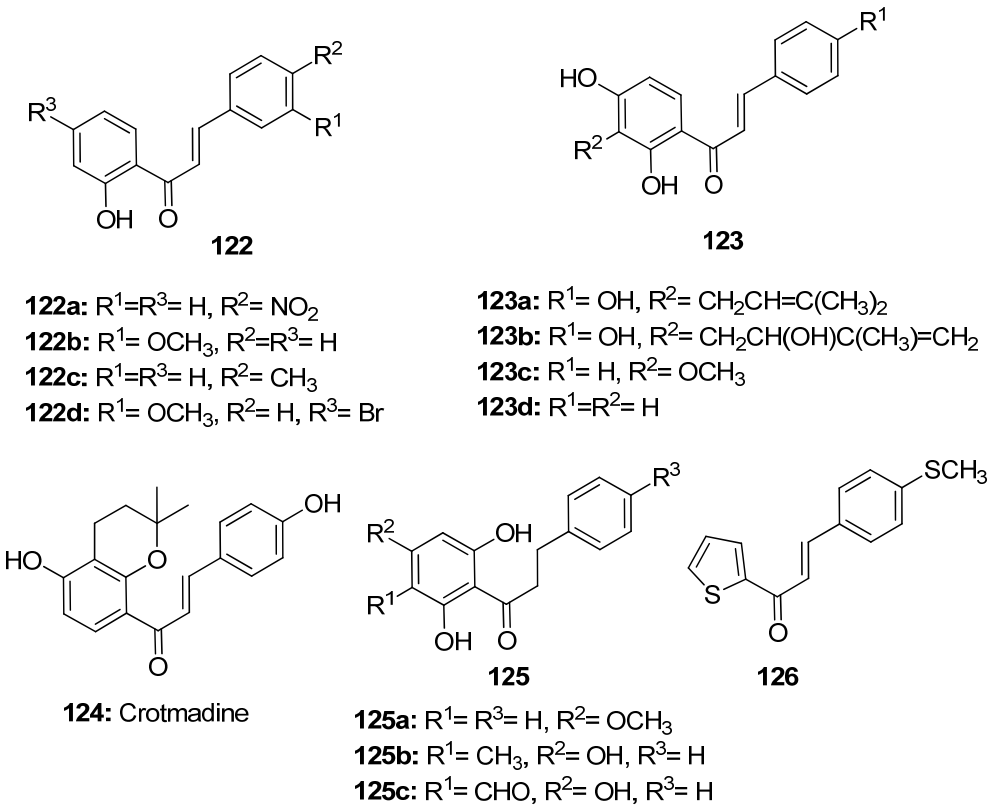


Figure 11. Substituted chalcones exhibiting antifungal activity

Lopez *et al.*[36] tested chalcones **122a-d** against a panel of human opportunistic pathogenic fungi, using the agar dilution method and these compounds showed strong antifungal activities against different fungal strains. The prenylated chalcones isobavachalcone (**123a**) and **123b**[37] isolated from the leaves of *Maclura tinctoria* were active against both fungal pathogens *Candida albicans* (IC_{50} of 3 and 15 µg/ml, respectively) and *Cryptococcus neoformans* (IC_{50} of 5 and 7 µg/ml). The methanolic extract of *Zuccagnia punctata*[38] consisting of 2, 4-dihydroxy-3-methoxychalcone **123c** and 2, 4-dihydroxychalcone **123d** displayed very good activities against *Phomopsis longicolla* CE117 and *Colletotrichum truncatum* CE175.

Suman *et al.*[39] tested some substituted chalcones for their antifungal activity against *Rhizoctonia solani*, *Fusarium oxysporum* and *Colletotrichum capsicum* strains of phytopathogenic fungi. The study showed that α,β-dibromo-3,3'-dinitrochalcone had the activity against all three fungi with MIC = 6.25 μg/ml, and 4,4'-dimethylchalcone showed activity against *C. capsicum* (MIC = 6.25 μg/ml).

Crotmadine **124** isolated from the leaves and stems of *Crotalaria madurensis*[40] exhibited antifungal activity against *T. mentagrophytes* at a concentration of 62.5 μg/ml. Geranyl chalcone derivatives isolated from *Artocarpus nobilis* by Jayasinghe *et al.*[41] showed good fungicidal activity against *Cladosporium cladosporioides.*

Biological screening of dihydrochalcone derivatives by Okunade *et al.*[42] showed that **125a** demonstrated relatively good activity against the two leading AIDS-related fungal pathogens *C. albicans* and *C. neoformans*, and marginal activity against the acid-fast bacterium *Mycobacteria intracellulare.* This is the first report of evaluation of this species for activity against these important AIDS-related pathogens. Additionally, 2,4,6-trihydroxy-3-methyldihydrochalcone **125b**[43] showed promising bioactivity in antimicrobial assays. It showed very good activity against *B. subtilis and T. mentagrophytes*. Extract from the leaves of the Peruvian plant *Psidium acutangulum*[44] containing dihydrochalcone **125c** revealed potent antifungal activities against *Rhizoctonia solani* and *Helminthosporium teres* and antibacterial activity against *Xanthomonas campestris*. Bag and co-workers reported[45] a series of chalcones incorporating sulfur either as part of a hetero-aromatic ring (thiophene) or as a side chain (thiomethyl group) and tested for their *in vitro* activity. Some of the compounds e.g. 3-(4-(methylthio)phenyl)-1-(thiophen-2-yl)prop-2-en-1-one **126** showed appreciable activity against fluconazole-sensitive and fluconazole-resistant strains. The antifungal activity exhibited by various compounds containing chalcone moiety prompted us to design new hybrid molecules with chalcones and fluconazole pharmacophores.

2.1.4 Present work

2.1.4.1 Objective

Keeping in view the advantages of hybrid molecules over the individual drugs or the cocktail of the two drugs, we planned to synthesize the hybrid molecules restructured from the fluconazole and biologically active chalcone moieties (described as above) in such a way that the important part of fluconazole molecule which is responsible for the antifungal activity (that is triazole ring, difluorophenyl group and the hydroxyl group)

does not get disturbed. As we know, fluconazole inhibits the fungal enzyme lanosterol 14α-demethylase, thereby blocking the biosynthesis of ergosterol, an essential component of fungal cell membranes[46]. Chalcones (1,3-diaryl-2-propen-1-ones) seem to be promising antifungal drug candidates. They have been shown to inhibit the growth of various fungi and yeasts, including representatives of the Candida species[47,48]. It is known that the mode of the antifungal action of chalcones is related to inhibition of the fungal cell wall[49]. From a therapeutic standpoint it is also interesting that chalcones can inhibit glutathione-S-transferases (GSTs), enzymes that appear to be involved in drug resistance[48]. So, the new hybrid antifungal agents, **127** and **128** (Figure 12), restructured from fluconazole and substituted chalcones, were designed and synthesized. It was thought that these molecules would be inhibitors of both fungal enzyme lanosterol 14α-demethylase and the fungal cell wall, and have antifungal activity better than fluconazole and corresponding chalcones.

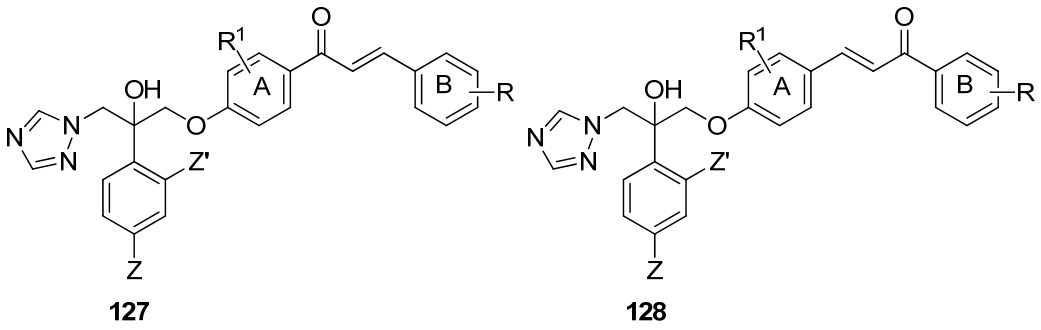


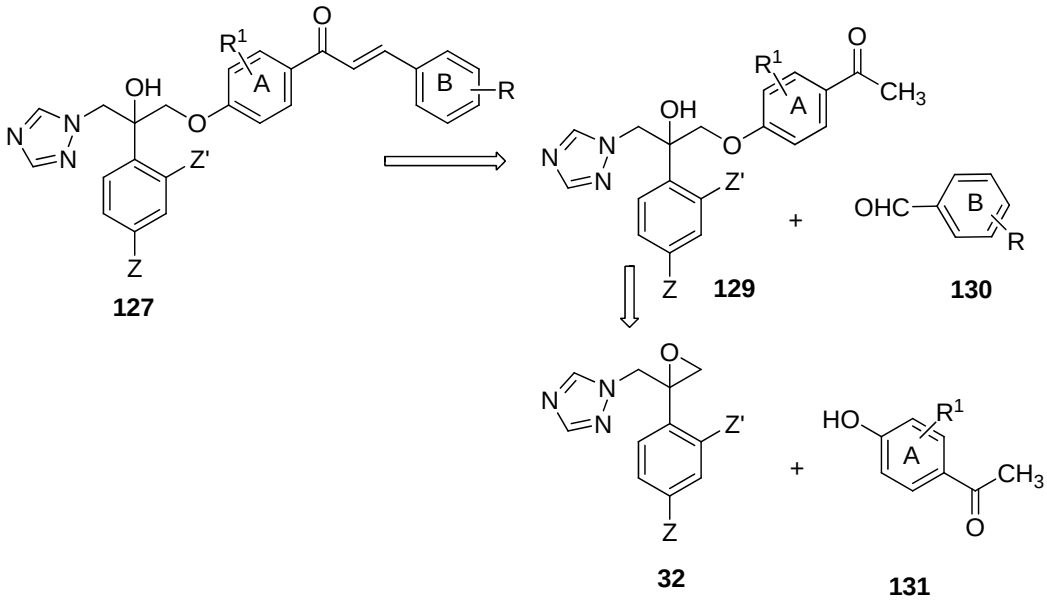
Figure 12. Hybrid fluconazole analogues containing chalcone moieties

During the work described in this section, efforts were directed towards replacement of one of the triazole moieties present in fluconazole with various substituted chalcones in order to make a number of compounds available for biological activity. So we targeted to synthesize a molecule where pharmacophore of fluconazole was attached to the biologically active chalcone moieties so that we could get hybrid molecules with enhanced antifungal activity. The newly synthesized molecules were tested against various fungi and the structure-activity relationship study was carried out.

Furthermore, the stereoselective interaction of the enzyme with stereoisomeric azoles has become an intriguing field of study and therefore in continuation to the above work, efforts were also directed towards the synthesis of enantiopure compounds to examine the influence of absolute configuration on antifungal activity. The structure-activity relationship study is also presented in this section.

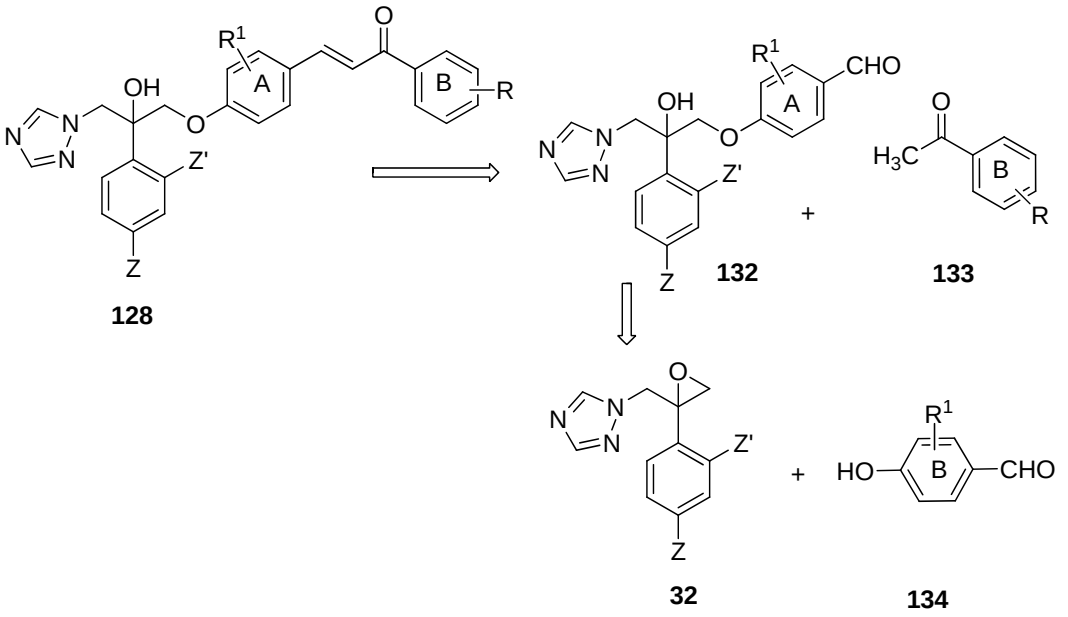
2.1.4.2 Results and discussion

The retrosynthetic route for the preparation of compounds depicted by the general formula **127** is shown in Scheme 1. The compound **127** could be synthesized by the Claisen-Schmidt condensation[50] of compound **129** and substituted benzaldehyde **130.** The compound **129** could be synthesized from the opening of epoxide **32** with substituted 4-hydroxyacetophenone **131**.



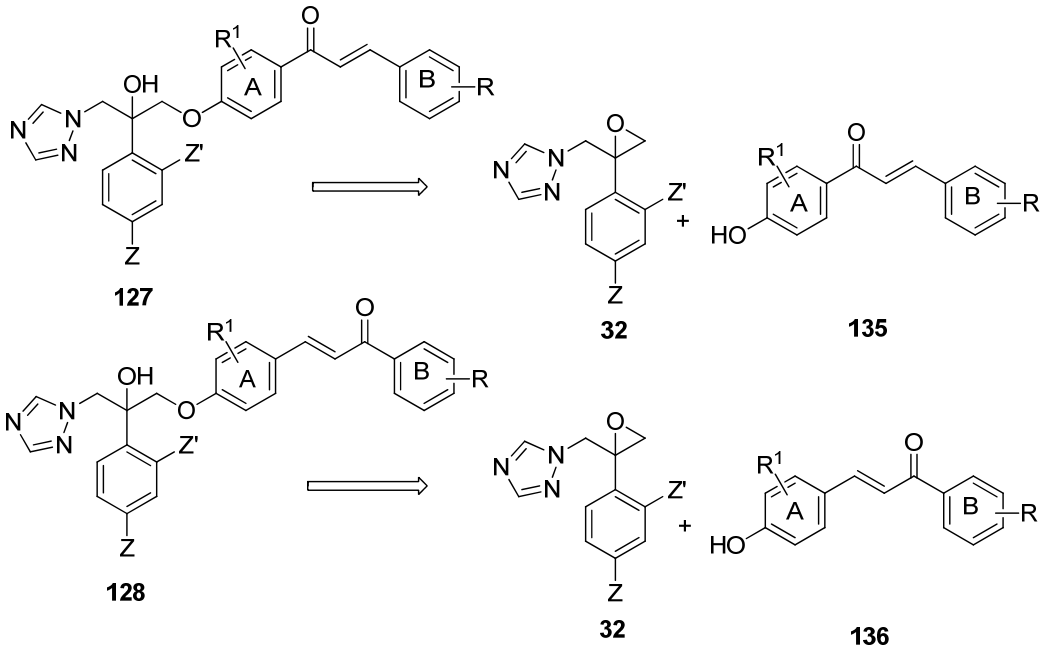
Scheme 1. Retrosynthetic analysis for the preparation of hybrid compounds **127**

The retrosynthetic route for the preparation of compounds **128** is shown in Scheme 2. The compound **128** could be prepared from the compound **132** and substituted acetophenone **133** as depicted above for the synthesis of compound **127**. The compound **132** could be obtained from the opening of epoxide **32** with 4-hydroxybenzaldehyde **134**.



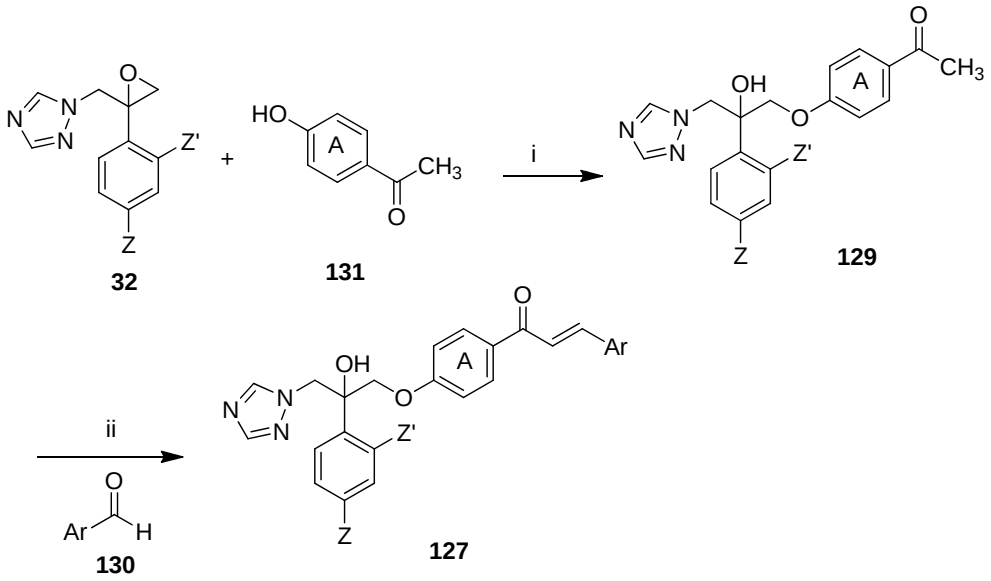
Scheme 2. Retrosynthetic analysis for preparation of hybrid compounds **128**

The compounds **127** and **128** could also be synthesized by the alternate route shown in Scheme 3 by the opening of epoxide **32** with regioisomeric hydroxychalcones **135** and **136** respectively.



Scheme 3. Alternate approach for preparation of hybrid compounds **127** and **128**

The synthesis of the hybrid molecule **127** was carried out *via* the route shown in Scheme 4. The 4-hydroxyacetophenone **131** was reacted with the epoxide **32** (Synthesis of epoxide **32**[51] has been described in Chapter 1, Scheme 6**)** in presence of potassium carbonate in ethyl acetate at refluxing temperature for 10-12 h to get the intermediate compound **129** in good yields, which on Claisen-Schmidt condensation[50] with various substituted aromatic aldehydes **130** afforded target molecules **127**.



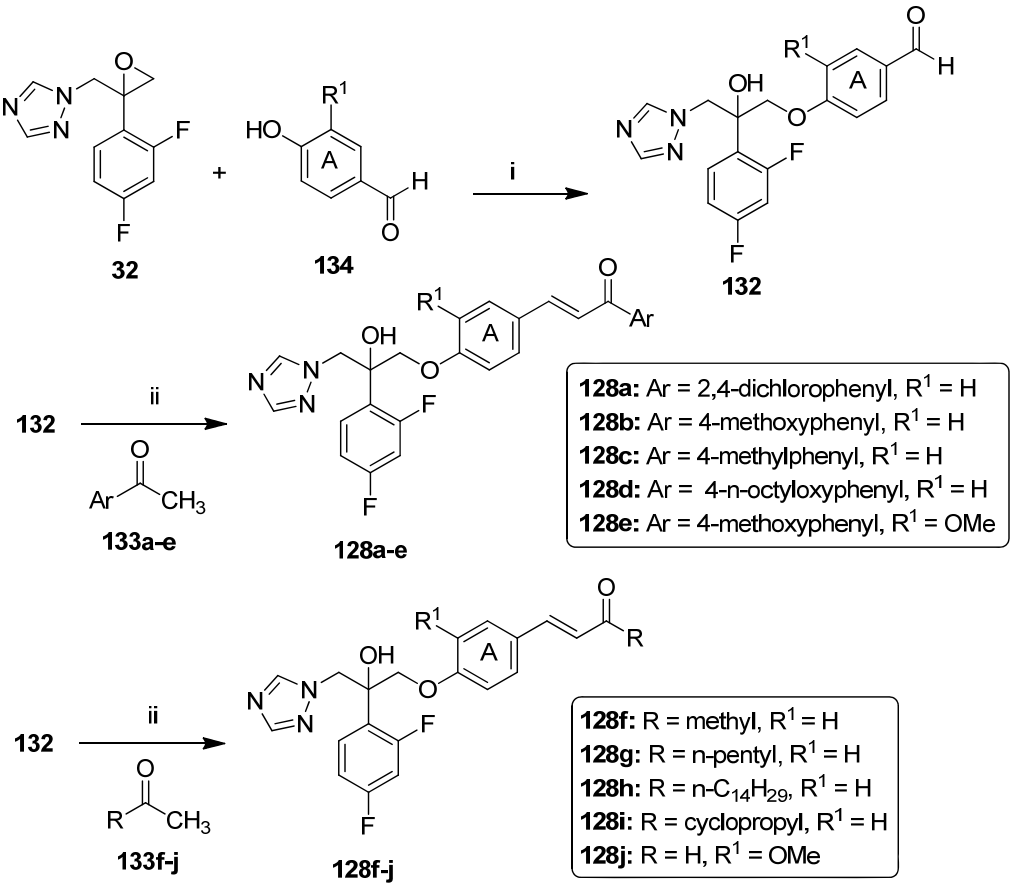
127a: Ar = phenyl, Z = Z'= F
127b: Ar = 4-methoxyphenyl, Z = Z'= F
127c: Ar = 2-methoxyphenyl, Z = Z'= F
127d: Ar = 3,5-dimethoxyphenyl, Z = Z'= F
127e: Ar = 3,4,5-trimethoxyphenyl, Z = Z'= F
127f: Ar = 4-chlorophenyl, Z = Z'= F
127g: Ar = 2,4-dichlorophenyl, Z = Z'= F
127h: Ar = 4-n-octyloxyphenyl, Z = Z'= F
127i: Ar = 2-fluorophenyl, Z = Z'= F
127j: Ar = 2-thienyl, Z = Z'= F
127k: Ar = 2-naphthyl, Z = Z'= F
127l: Ar = 9-anthracenyl, Z = Z'= F
127m: Ar = N-methyl-3-indolyl, Z = Z'= F
127n: Ar = 4-methoxyphenyl, Z = F, Z' = H
127o: Ar = 4-chlorophenyl, Z = F, Z' = H
127p: Ar = 4-methoxyphenyl, Z = Br, Z' = H
127q: Ar = 2-thienyl, Z = F, Z' = H

Scheme 4. Reagents and conditions: i) K_2CO_3, TBAB, EtOAc, 80 °C, 12 h, 80-86 %; ii) 10% NaOH, MeOH, rt, 12-20 h, 70-85%.

The structures of the products **127** were assigned based on ^{1}H NMR, ^{13}C NMR, IR and mass spectroscopy. In ^{1}H NMR spectrum, two doublets (each for one proton in the range of δ 6.00-8.00 with coupling constant in the range of J = 14-16 Hz) were observed along with four successive doublets (each for one proton in the range of δ 4.04-4.98 with coupling constant in the range of J = 10-14 Hz) which confirmed the formation of product. The coupling constant J = 14-16 Hz for olefinic enone protons indicated that the products consisted of E isomer. It is noteworthy that availability of a wide variety of substituted 4-hydroxyacetophenones **131** and aromatic aldehydes **130** as

well as easy preparation of a number of epoxides **32** makes the present reaction sequence effective in getting a large number of compounds for screening against various fungi.

Similarly, the synthesis of the hybrid molecule **128** was carried out *via* the route shown in Scheme 5.

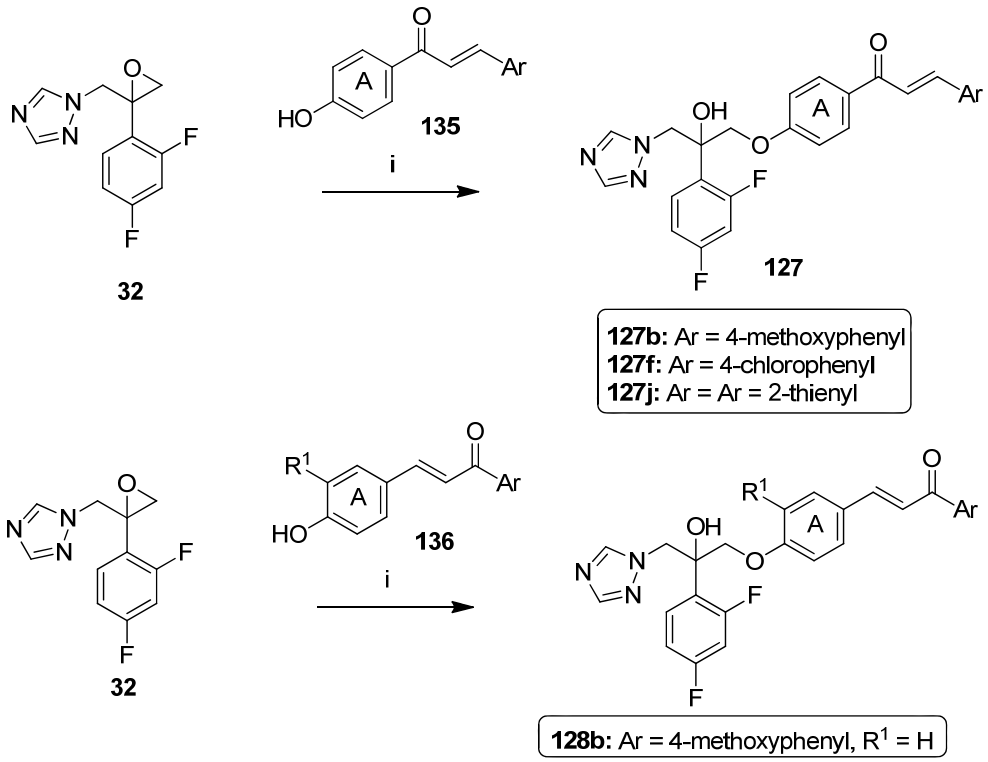


Scheme 5. Reagents and conditions: i) K_2CO_3, TBAB, EtOAc, 80 °C, 12 h, 80-90 %; ii) 10% NaOH, MeOH, rt, 12-20 h, 68-84%.

The 4-hydroxybenzaldehyde (**134**, R^1 = H) was reacted with the epoxide **32** under the same reaction conditions which were used for the synthesis of hybrid compounds **127** to give the intermediate compound **132** in good yields, which on Claisen-Schmidt condensation[50] with various substituted aromatic acetophenones **133** afforded target molecules **128** as shown in Scheme 5.

The hybrid molecules **127** and **128** were also synthesized by the alternate route as shown in Scheme 6. The regioisomeric hydroxychalcones **135** and **136** synthesized from 4-hydroxyacetophenones and substituted benzaldehydes and 4-hydroxybenzaldehyde and substituted acetophenones respectively by using Claisen-Schmidt condensation[50], were reacted with epoxide **32** in presence of potassium carbonate and tetrabutylammonium

bromide (TBAB) in ethyl acetate at refluxing temperature for 5-7 h to yield **127** and **128** in good yields.



Scheme 6. Reagents and conditions: i) K_2CO_3, TBAB, EtOAc, 80 °C, 5-7 h, 75-85 %.

In order to evaluate the antifungal activity of hybrid fluconazole analogues **127** and **128**, study of the effect of different structural modifications was undertaken and following points were considered while synthesizing different molecules: (a) variations of the substitution pattern on the benzene rings A and B (b) replacement of the benzene ring B with alternative aromatic systems such as thienyl, naphthyl, indolyl, anthracenyl *etc* and (c) structural modifications of the enone linkage.

Using above synthetic strategy, a number of compounds were synthesized. All the compounds synthesized were fully characterized by ^{1}H NMR, ^{13}C NMR, IR and mass spectroscopic methods and showed satisfactory spectral data as described in the experimental section.

Antifungal evaluation

All the newly synthesized hybrid compounds **127** were tested for antifungal activity against various fungi including *Candida albicans*, *Aspergillus niger, Fusarium*

proliferatum etc at FDC Ltd., Mumbai as described in Chapter 1. The activity parameters are depicted in Table 1 as MIC_{50} values.

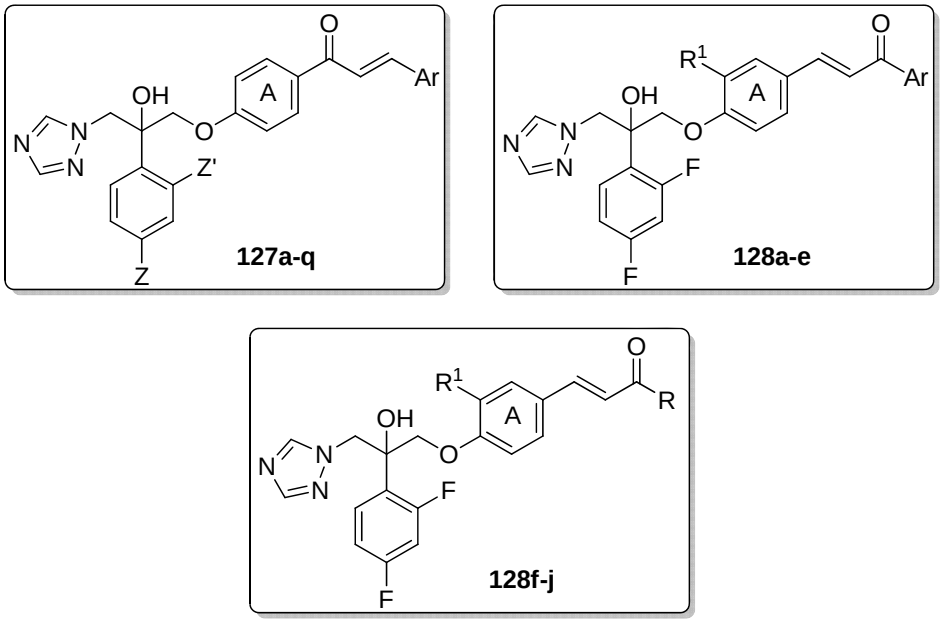


Table 1: MIC obtained by broth micro-dilution method

Sr. no.	Comp. no.	Structure	Activity against organisms (MIC_{50} in µg/ml)							
			Ca 01	**Cg 01**	**Ck 01**	**Ct 01**	**Cn 01**	**An 01**	**Afm01**	**Fp 01**
	FLU		**0.25**	1	32	1	2	>128	>128	>128
	AMB		**0.25**	**0.25**	**0.5**	**0.5**	**0.5**	**0.25**	**0.5**	2
1	**127a**	Ar = phenyl, Z = Z'= F	**0.06**	**0.25**	>2	**0.5**	1	>2	>2	>2
2	**127b**	Ar = 4-methoxyphenyl, Z = Z'= F	**0.06**	**0.25**	4	**0.25**	1	4	>4	>4
3	**127c**	Ar = 2-methoxyphenyl, Z = Z'= F	**0.25**	**0.5**	>8	2	8	>8	>8	>8
4	**127d**	Ar = 3,5-dimethoxyphenyl, Z = Z'= F	**0.25**	2	>4	2	2	>4	>4	>4
5	**127e**	Ar = 3,4,5-trimethoxyphenyl, Z = Z'= F	**0.25**	**1**	>4	1	>4	>4	>4	>4

6	**127f**	Ar = 4-chlorophenyl, Z = Z'= F	**0.5**	**0.5**	2	**0.5**	**0.5**	>4	>4	>4
7	**127g**	Ar = 2,4-dichlorophenyl, Z = Z'= F	**0.25**	**0.5**	2	1	2	>4	>4	>4
8	**127h**	Ar = 4-n-octyloxyphenyl, Z = Z'= F	>2	>2	>2	>2	>2	>2	>2	>2
9	**127i**	Ar = 2-fluorophenyl, Z = Z'= F	**0.12**	**0.25**	4	**0.5**	2	>4	>4	>4
10	**127j**	Ar = 2-thienyl, Z = Z'= F	**0.12**	**0.25**	8	**0.5**	1	>8	>8	>8
11	**127k**	Ar = 2-naphthyl, Z = Z'= F	**0.25**	**0.5**	**1**	**0.5**	**0.5**	>4	>4	>4
12	**127l**	Ar = 9-anthracenyl, Z = Z'= F	>2	2	>2	>2	2	>2	>2	>2
13	**127m**	Ar = N-methyl -3-indolyl, Z = Z'= F	**0.25**	2	>4	2	4	>4	>4	>4
14	**127n**	Ar = 4-methoxyphenyl, Z = F, Z' = H	**0.25**	**0.5**	4	4	**0.5**	>4	>4	>4
15	**127o**	Ar = 4-chlorophenyl, Z = F, Z' = H	**0.5**	**0.5**	4	4	**0.5**	>4	>4	>4
16	**127p**	Ar = 4-methoxyphenyl, Z = Br, Z' = H	**0.5**	**1**	>4	>4	1	>4	>4	>4
17	**127q**	Ar = 2-thienyl, Z = F, Z' = H	**0.25**	**0.25**	8	2	1	>8	>8	>8
18	**128a**	Ar = 2,4-dichlorophenyl, R^1 = H	**0.12**	**0.5**	2	1	1	>4	>4	>4
19	**128b**	Ar = 4-methoxyphenyl, R^1 = H	**0.12**	**0.25**	4	1	1	>4	8	>4
20	**128c**	Ar = 4-methylphenyl, R^1 = H	**0.12**	**0.25**	2	1	1	>4	8	>4
21	**128d**	Ar = 4-n-octyloxyphenyl, R^1 = H	**4**	**0.12**	>4	>4	>4	>4	>4	>4
22	**128e**	Ar = 4-methoxyphenyl, R^1 = OMe	**0.03**	**0.5**	4	2	2	>4	>4	>4
23	**128f**	R = methyl, R^1 = H	**0.12**	**0.12**	8	2	4	8	8	>128

24	**128g**	R = n-pentyl, R^1 = H	**0.12**	**0.06**	**1**	**2**	**0.5**	>4	>4	>4
25	**128h**	R = n-$C_{14}H_{29}$, R^1 = H	>1	>1	>1	>1	>1	>1	>1	>1
26	**128i**	R = cyclopropyl, R^1 = H	**0.015**	**0.03**	**1**	**0.25**	2	8	16	>16
27	**128j**	R = H, R^1 = OMe	**0.25**	**1**	32	8	16	>64	>64	>64

*** Ca01**: *C. albicans* ATCC 24433, **Cg01**: *C. glabrata* ATCC 90030, **Ck01**: *C. krusei* ATCC 6258, **Ct01**: *C. tropicalis* ATCC 750, **Cn01**: *C. neoformans* ATCC 34664, **An01**: *A. niger* ATCC 16404, **Afm01**: *A. fumigatus* ATCC 46645, **Fp01**: *F. proliferatum* ATCC 10052

From the antifungal activity data it was observed that most of the hybrid fluconazole analogues restructured from fluconazole and chalcone exhibited good antifungal activity. The activity data indicated following points regarding the structure-activity relationship of the compounds **127** and **128** studied in the present section of this chapter:

1. The hybrid compounds with general structures **127** and **128** having same substituents on corresponding aromatic rings showed almost same antifungal activity e.g. **127b** v/s **128b** and **127f** v/s **128a**.

2. The hybrid compounds showed broader spectrum of antifungal activity than fluconazole and many compounds from these two classes exhibited better antifungal activity than fluconazole against *C. albicans, C. glabrata, C. krusei, C. tropicalis* and *C. neoformans.*

3. The compounds with difluorophenyl moieties showed higher antifungal activity than compounds with 4-fluoro and 4-bromophenyl moieties e.g. **127b** v/s **127n**, **127g** v/s **127o** and **127j** v/s **127q**.

4. As number of substituents on phenyl ring B of hybrid molecule **127** increased, its antifungal activity decreased (e.g. **127b** v/s **127d**, **127b** v/s **127e** and **127f** v/s **127g**).

5. The replacement of 4-methoxyphenyl group with 4-n-octyloxyphenyl group resulted in the loss of antifungal activity e.g. **127b** v/s **127h**.

6. The replacement of the phenyl ring with alternative aromatic systems like thienyl or naphthyl was tolerated (e.g. **127a** v/s **127j** or **127a** v/s **127k**), replacement with indolyl ring resulted in decrease in antifungal activity (**127a** v/s **127m**) while replacement with bulky rings like 9-anthracenyl resulted in complete loss of activity (**127a** v/s **127l**).

7. In case of the compounds with general structure **128**, when phenyl ring was replaced with alkyl side chain (**128f-h**) activity was observed with compounds having shorter side

chains (e.g. **128f** and **128g**) while the compounds with longer side chains (e.g. **128h**) exhibited negligible activity.

8. The replacement of phenyl ring with cyclopropyl ring (compound **128i**) resulted in maximum antifungal activity in this group of compounds.

The significant results obtained in case of the hybrid molecules **127** and **128** made us to undertake the synthesis of dimeric molecules. The proposed dimeric molecules are depicted with general formulae **137** and **138**, wherein the two monomeric molecules are linked with the enone linkers (Figure 13). The monomeric molecules **127** or **128** exhibiting good antifungal activity could be further modified to get dimeric molecules and this may lead to the synthesis of new fluconazole analogues exhibiting enhanced antifungal activity.

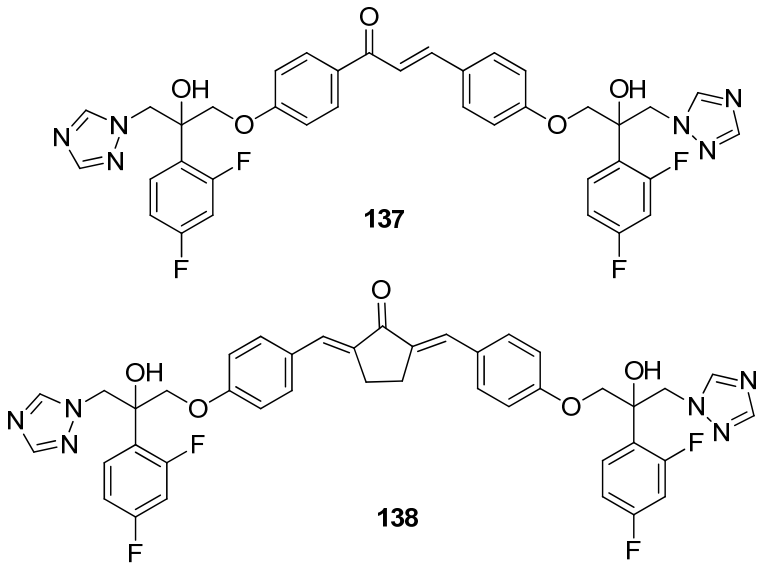
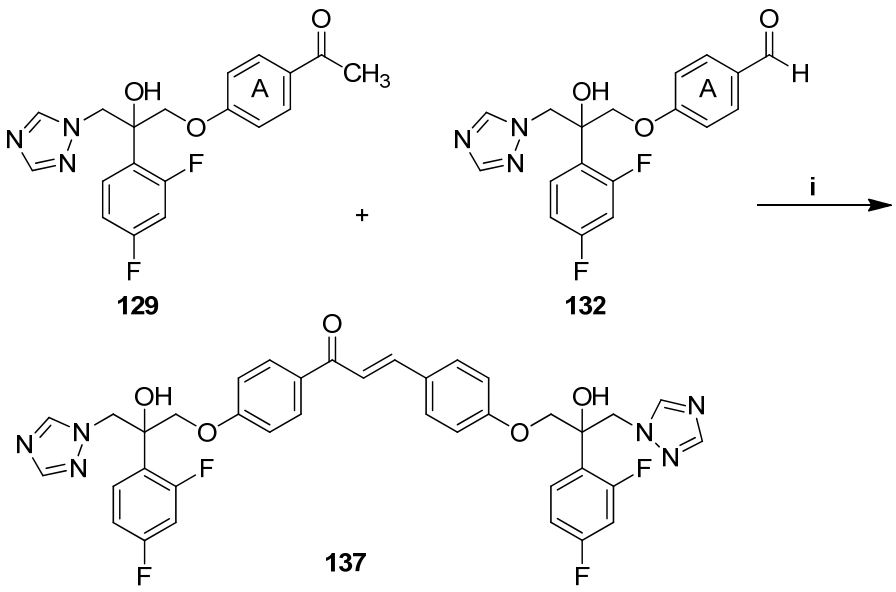


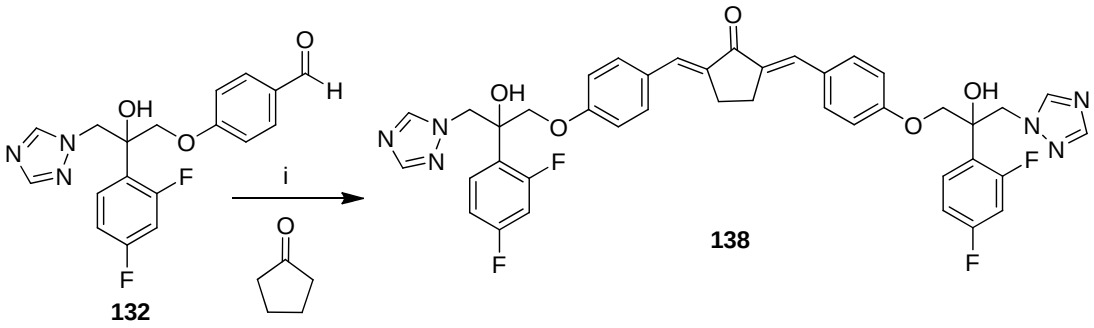
Figure 13. Dimeric fluconazole analogues containing enone moieties

The compound **137** was synthesized by the condensation of compounds **129** and **132** under Claisen-Schmidt reaction conditions[50] as shown in Scheme 7.



Scheme 7. i) 10% NaOH, MeOH, rt, 18 h, 80%.

The compound **138** was synthesized by the reaction of cyclopentanone with two equivalents of compound **132**, under the same reaction conditions as used for synthesis of compound **137**, as shown in Scheme 8.



Scheme 8. i) 10% NaOH, MeOH, rt, 18 h, 77%.

After the successful synthesis of hybrid molecules **127** and **128** and dimeric molecules **137** and **138**, we undertook synthesis of a new class of antifungal agents depicted by general formula **139** (Figure 14) by replacing one of the triazole moieties of fluconazole with (un)substituted enone.

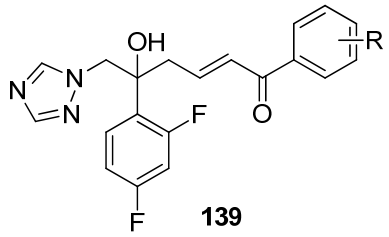
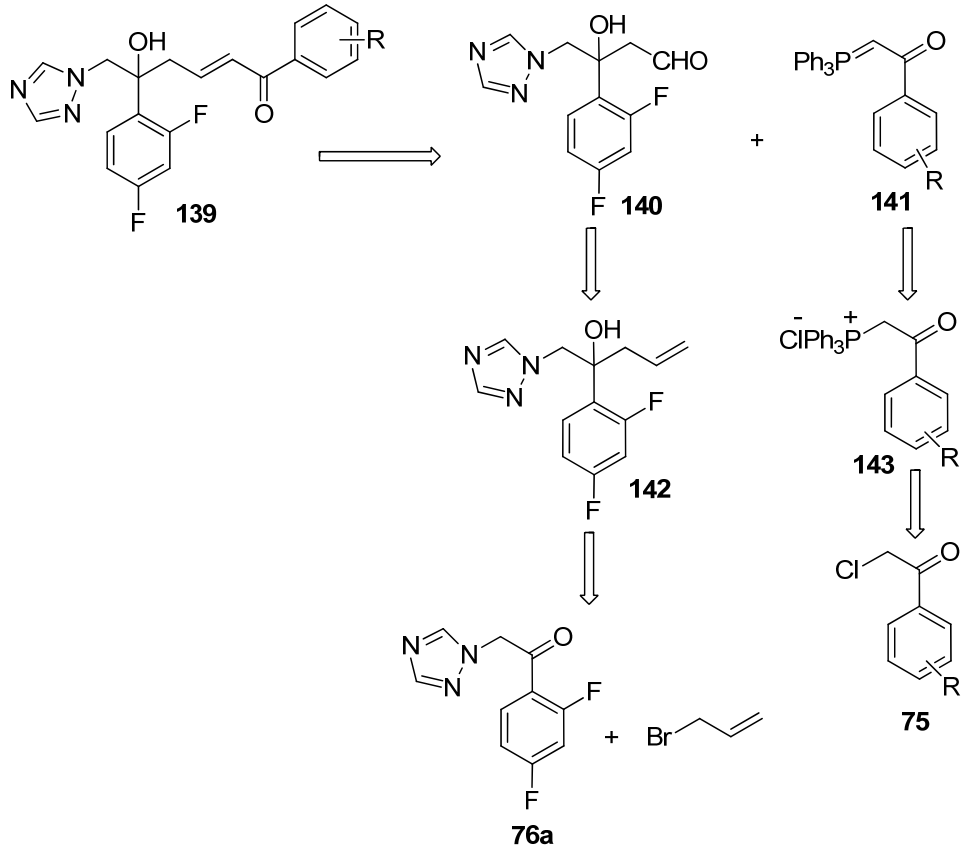


Figure 14. Structure of fluconazole analogues **139**

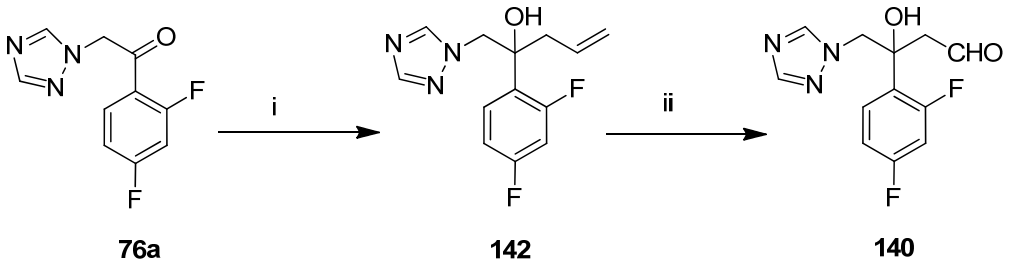
The retrosynthetic analysis for the preparation of compounds depicted by general formula **139** is shown in Scheme 9.



Scheme 9. Retrosynthetic analysis for preparation of compounds **139**.

Compound **139** could be obtained by the Wittig reaction of compound **140** with phosphorane **141**. The compound **140** could be prepared from the homoallylic alcohol **142**, which in turn could be obtained from triazolyl ketone compound **76a** and allyl bromide by using the Barbier reaction condition[54]. The phosphoranes **141** could be prepared by known method[55] from the substituted chloroacetophenones **75** *via* the intermediate Wittig salts **143**. The conversion of triazolyl ketone compound **76a** into the

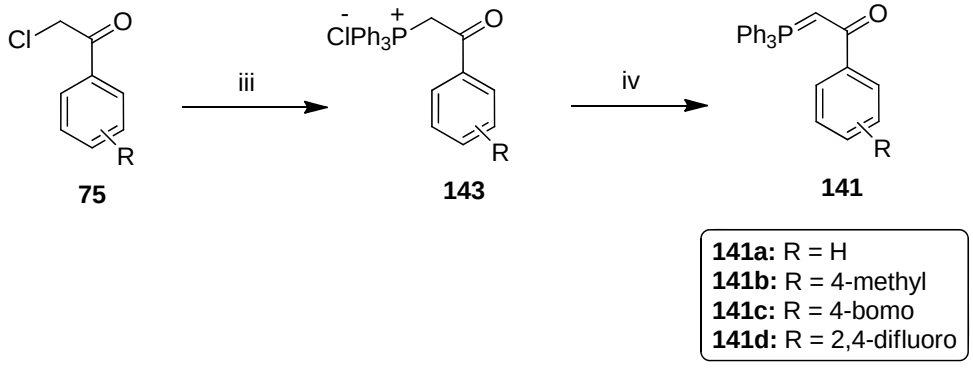
desired hydroxyaldehyde **140** was achieved by the reaction sequence shown in Scheme 10.



Scheme 10. Reagents and conditions: i) Allyl bromide, Zn, THF, rt, 3-5 h, 88% ii) OsO_4, t-BuOH-H_2O (1:1), $NaIO_4$, $NaHCO_3$, rt, 10-12 h, 76%.

The Barbier reaction[54] of ketone **76a** with allyl bromide and zinc in THF afforded the homoallylic alcohol **142** which was characterized by spectral methods. The ^{1}H NMR spectrum showed multiplets at δ 2.36-2.47 and 2.72-2.82 for one proton each which were assigned to methylene protons adjacent to double bond while the multiplets at δ 5.07-5.15 and 5.03-5.70 for 2 protons and one proton respectively were assigned to allylic double bond protons. The homoallylic alcohol **142** on dihydoxylation by using OsO_4 in t-BuOH-H_2O (1:1) followed by cleavage using $NaIO_4$ afforded the desired hydroxyaldehyde **140**.

The various substituted phosphoranes **141** were prepared by the synthetic route shown in Scheme 11.

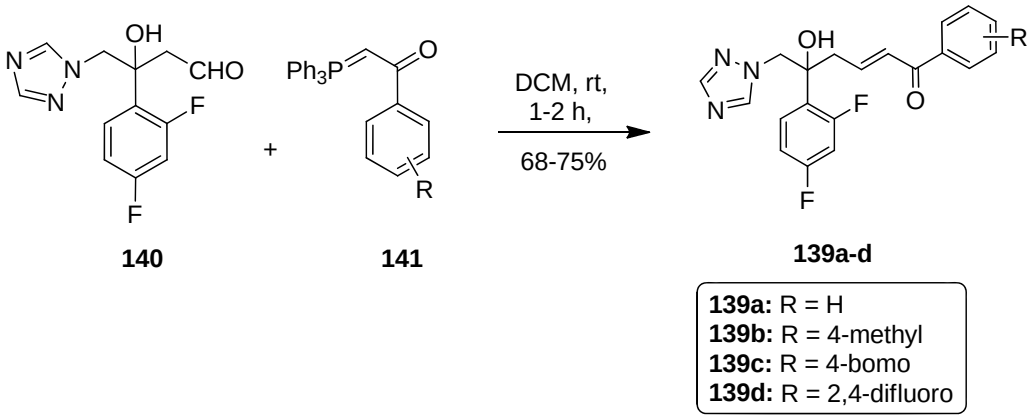


Scheme 11. Reagents and conditions: i) PPh_3, toluene, reflux, 12 h, 82-90% ii) Na_2CO_3, DCM-H_2O (1:1), rt, 8-10 h, 74-83%.

The synthesis of phosphorane [1-aryl-2-(triphenylphosphoranylidene)ethanone] **141** was achieved by the reaction of chloroketones **75** with triphenylphosphine in toluene at reflux

temperature to afford the Wittig salt **143** which was then reacted with sodium carbonate in DCM-H_2O (1:1) at room temperature to get the phosphorane **141**.

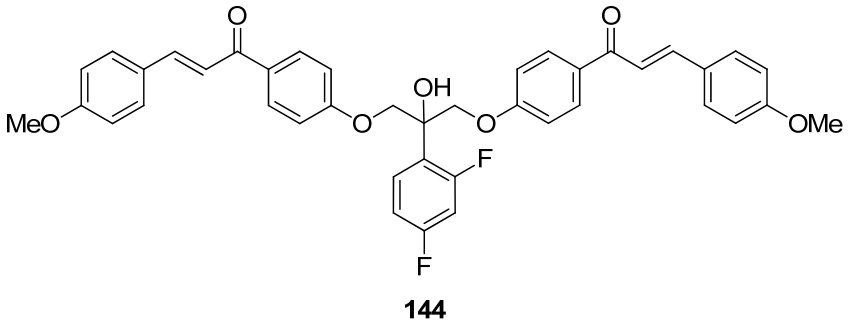
The compounds **140** and **141** were then reacted in dichloromethane at room temperature to afford the target molecules **139** in 68-75% of yields as shown in Scheme 12.



Scheme 12. Synthesis of the compound **139**

All the compounds synthesized in these reaction sequences were fully characterized by ^{1}H NMR, ^{13}C NMR, IR and mass spectroscopic methods and showed satisfactory spectral data described in experimental section.

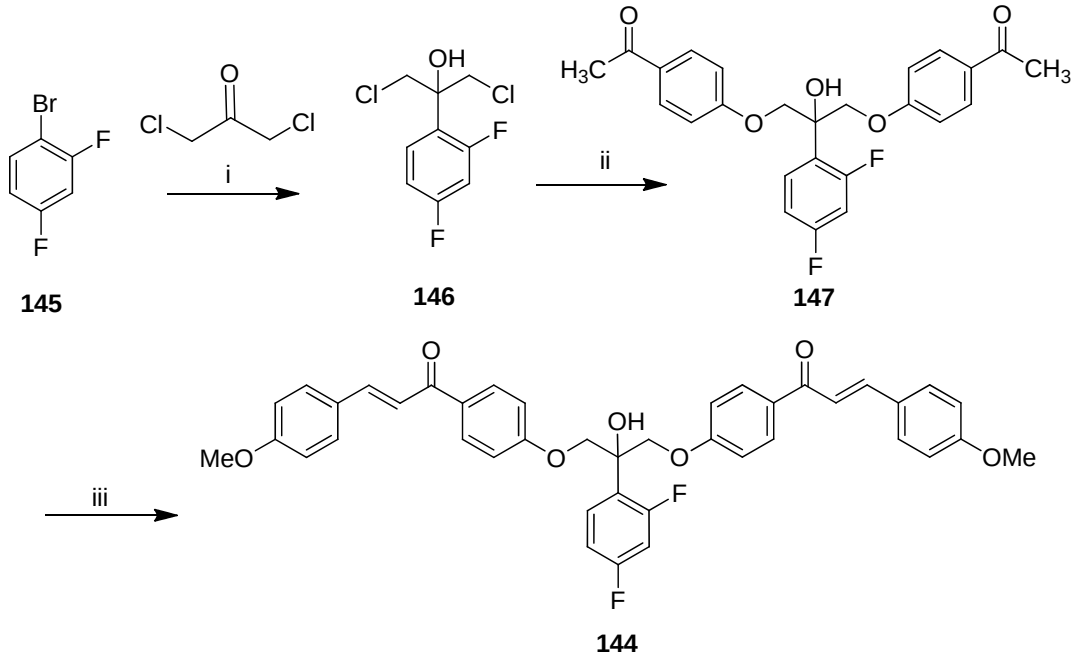
Apart from the above compounds (**127, 128, 137, 138** and **139**) synthesized for the structure activity relationship (SAR) study, we directed our efforts towards the synthesis of compound **144** where we replaced both the triazole moieties of fluconazole (**6**) with chalcone moiety as shown in Figure 15.



144

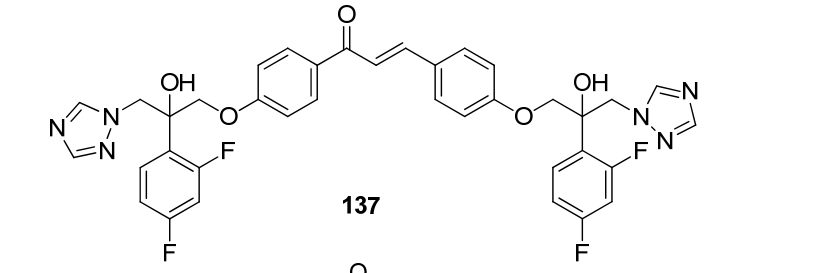
Figure 15. Fluconazole analogue **144** containing chalcone moieties

The synthesis of the compound **144** was carried out *via* the route shown in Scheme 13. 1-Bromo-2,4-difluorobenzene **145** was reacted with 1,3-dichloroacetone in presence of Mg powder in dry THF under Grignard condition[56] to get the dichloroalcohol **146.** The condensation of dichloroalcohol **146** with 4-hydroxyacetophenone **131** in presence of potassium carbonate and tetrabutylammonium bromide (TBAB) in acetonitrile at refluxing temperature for 8 h afforded 1,1'-(((2-(2,4-difluorophenyl)-2-hydroxypropane-1,3-diyl)bis(oxy))bis(4,1-phenylene))diethanone **147**, which on Claisen-Schmidt condensation[50] with 4-methoxybenzaldehyde afforded target molecule **144** as shown in Scheme 13.

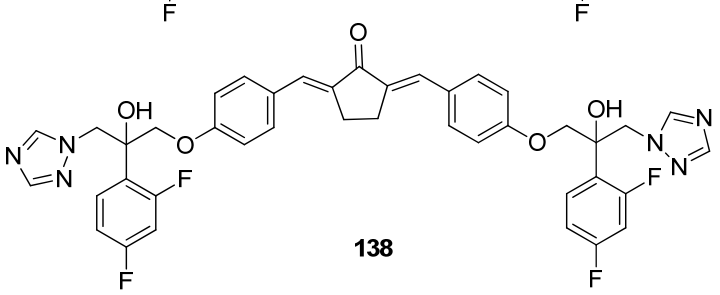


Scheme 13. Reagents and conditions: i) Mg, dry THF, 0 ^{0}C-rt, 7 h, 30% ii) 4-Hydroxy acetophenone, K_2CO_3, TBAB, CH_3CN, reflux, 8 h, 88% iii) 4-Methoxybenzaldehyde, 10% NaOH, MeOH, rt, 20 h, 68%.

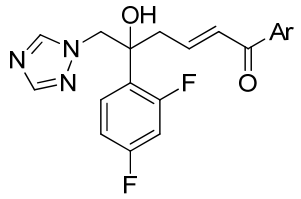
All the newly synthesized compounds **137**, **138**, **139** and **144** were tested for antifungal activity against various fungal strains and the activity parameters are depicted in Table 2 as MIC_{50} values.



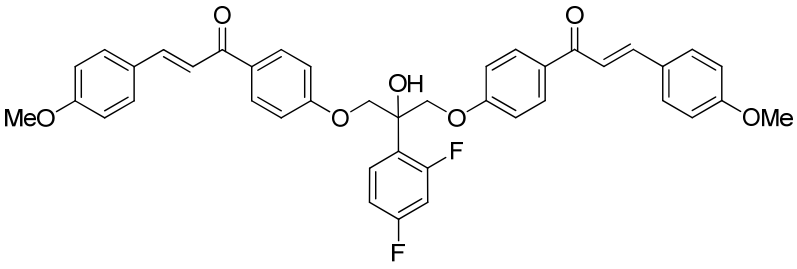
137



138



139a-d



144

Table 2. MIC obtained by broth micro-dilution method

Sr. no.	Comp. no.	Structure	Activity against organisms (MIC_{50} in µg/ml)							
			Ca 01	**Cg 01**	**Ck 01**	**Ct 01**	**Cn 01**	**An 01**	**Afm01**	**Fp 01**
	FLU		**0.25**	1	32	1	2	>128	>128	>128
	AMB		**0.25**	**0.25**	**0.5**	**0.5**	**0.5**	**0.25**	**0.5**	2
1	**137**		**0.06**	**0.5**	**1**	**0.5**	**1**	>4	>4	>4
2	**138**		**0.25**	**0.25**	4	1	>4	>4	4	>4
3	**139a**	Ar = phenyl	**0.5**	8	>32	>32	>32	>32	>32	>32
4	**139b**	Ar = 4-bromophenyl	**0.25**	2	>32	8	32	>32	>32	>32
5	**139c**	Ar = 2,4-difluorophenyl	**0.25**	1	>16	32	32	>16	>16	>16
6	**139d**	Ar =4-methylphenyl	**0.25**	2	>32	8	32	>32	>32	>32
7	**144**		>2	>2	>2	>2	>2	>2	>2	>2

The activity data indicated following points regarding the structure-activity relationship of the compounds **137**, **138**, **139** and **144** studied in the present chapter.

1. The hybrid compounds **137** and **138** containing two fluconazole moieties and central chalcone or aryl enone moiety showed antifungal activity lower than that of the corresponding compounds **127b** or **128b** containing one fluconazole unit and chalcone moiety.

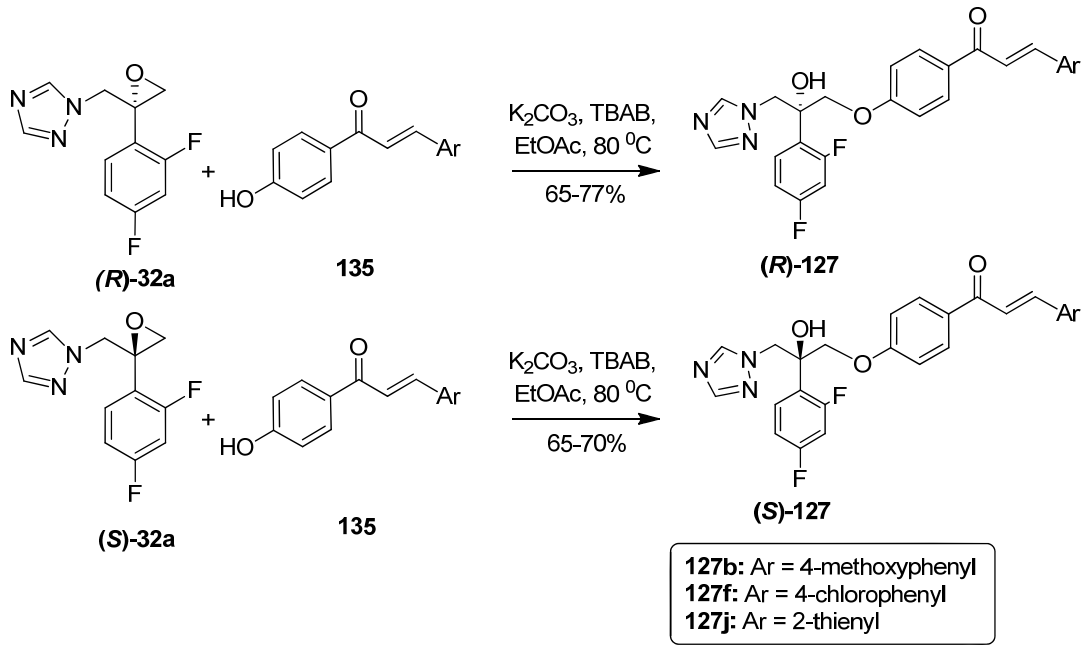
2. When the chalcone moiety was replaced with the olefinic enone linkage (e.g. **139a-d**) the antifungal activity decreased e.g. **139d** v/s **128c**.

3. The difluorophenyl substituted compound (e.g. **139c**) showed higher antifungal activity than the compounds with phenyl, 4-bromophenyl and 4-methylphenyl moieties. (e.g. **139a**, **139b** and **139d**).

4. Also, it was observed that when both the triazole rings were replaced with chalcone moieties, it resulted in the loss of antifungal activity (e.g. **144**).

In continuation to the above work, the *R* and *S* enantiomers of the active compounds **127** were prepared to examine the influence of absolute configuration on antifungal activity. From the antifungal activity results of racemic compounds **127** and **128** it was observed that the hybrid compounds **127** and **128** having same substituent on corresponding aromatic rings showed almost same antifungal activity so the compounds **127** were chosen for preparation of their enantiomers. The preparation of enantiomers of this class of antifungal agents was achieved from chiral epoxides **(*R*)-32a** and **(*S*)-32a** (Synthesis of chiral epoxides **(*R*)-32a** and **(*S*)-32a**[57] has been described in Chapter 1, Scheme 11**)**.

The *R* and *S* enantiomers of compound **127** were prepared by the synthetic route shown in Scheme 14. The hydroxychalcone **135** was reacted with chiral epoxides **(*R*)-32a** and **(*S*)-32a** in presence of potassium carbonate and tetrabutylammonium bromide (TBAB) in ethyl acetate at refluxing temperature for 5-7 h to afford the target enantiopure molecules **(*R*)-127** and **(*S*)-127**.



Scheme 14. Synthesis of enantiomers **(*R*)-127** and **(*S*)-127**

The chiral HPLC chromatogram for racemic **127f** and its (*S*) enantiomer is shown in Figure 16.

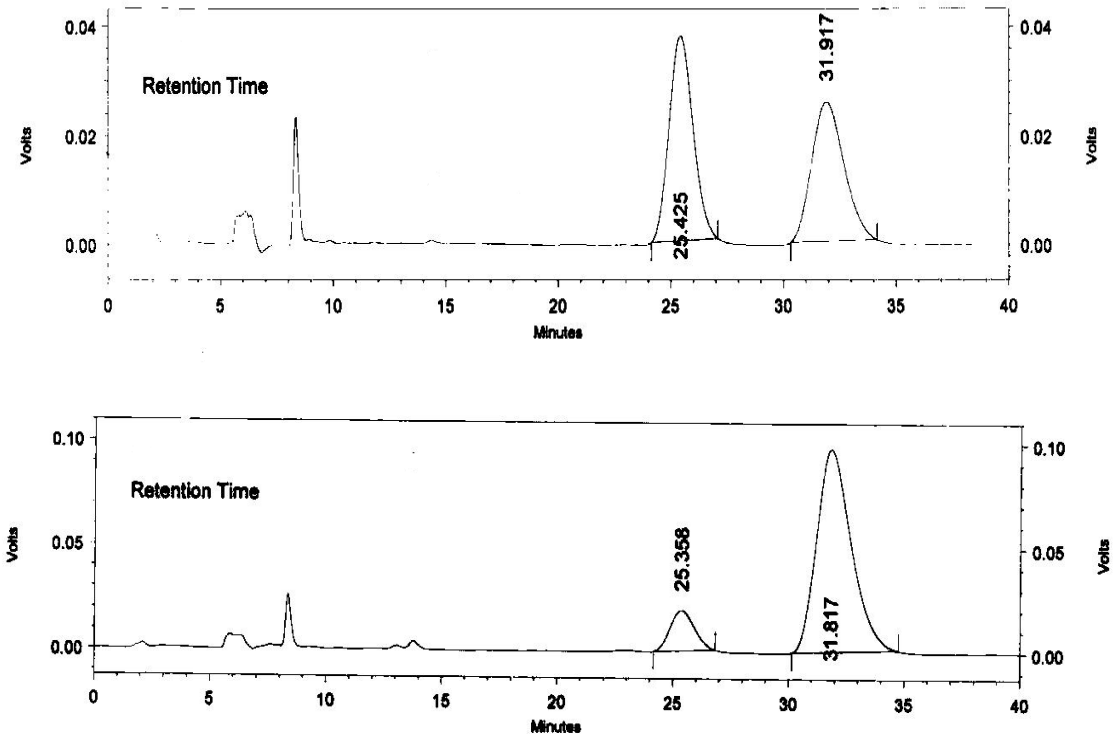


Figure 16. (*S*) enantiomer of **127f**

After synthesis of enantiomers of **127** specific rotations of enantiomers were calculated from the observed rotations as shown in Table 2.

Table 3. Specific rotations of enantiomers of **127b, 127f** and **127j**.

Comp. No.	Chem. Purity	Peak In Chiral HPLC Chromatogram	Retention Time (RT) min	Enantiomeric Excess (% *ee*)	Specific Rotation $[\alpha]_D^{24} = \frac{\text{Obs. Rotation X 100}}{\text{Conc. X Length}}$
(*R*)-127b	99.4	A	32.80	71.80	-11.28 ^{o} (c = 1.06, THF)
(*S*)-127b	96.7	B	40.76	95.2	+13.80 ^{o} (c = 1.01, THF)
(*R*)-127f	98.8	A	30.39	97.8	-12.30 ^{o} (c = 1.02, THF)
(*S*)-127f	92.0	B	31.81	77.92	+11.90 ^{o} (c = 1.00, THF)
(*R*)-127j	97.8	B	41.56	94.2	-13.01 ^{o} (c = 1.00, THF)
(*S*)-127j	98.7	A	28.31	94.7	+13.59 ^{o} (c = 1.03, THF)

All the newly synthesized *R* and *S* enantiomers of compounds **127** were tested for antifungal activity against various fungi and results are enumerated in Table 4.

Table 4: MIC obtained by broth micro-dilution method

Organism	**Activity against organisms (MIC_{50} in µg/ml)**										
	AMB	**FLU**	**127b**	**(*R*)-127b**	**(*S*)-127b**	**127f**	**(*R*)-127f**	**(*S*)-127f**	**127j**	**(*R*)-127j**	**(*S*)-127j**
C. albicans ATCC 24433	**0.25**	**0.5**	**0.06**	**0.06**	**0.5**	**0.12**	**0.06**	**1**	**0.06**	**0.03**	**0.25**
C. albicans ATCC 10231	**0.5**	**0.5**	**0.12**	**0.06**	**0.5**	**0.12**	**0.06**	**0.5**	**0.06**	**0.03**	**0.5**
C. albicans	**0.5**	**0.5**	**0.06**	**0.3**	**0.5**	**0.25**	**0.12**	**0.5**	**0.06**	**0.03**	**0.5**

ATCC 2091											
C. albicans ATCC 90028	**0.5**	**0.5**	**0.06**	**0.3**	**1**	**0.12**	**0.06**	**0.5**	**0.03**	**0.015**	**0.25**
C. glabrata ATCC 90030	**0.25**	**4**	**0.12**	**0.06**	**1**	**0.25**	**0.12**	**0.5**	**0.12**	**0.03**	**0.25**
C. krusei ATCC 6258	**0.5**	**64**	**2**	**2**	>4	**2**	**1**	4	4	**2**	>4
C. tropicalis ATCC 750	**0.5**	**2**	**0.25**	**0.25**	**2**	**1**	**0.5**	**2**	**0.5**	**0.12**	**2**
C. neoformans ATCC 34664	**0.5**	**2**	**0.5**	**0.5**	**2**	**0.5**	**0.25**	**2**	**1**	**0.5**	4
A. niger ATCC 16404	**0.25**	**>128**	4	**2**	>4	>4	>4	>4	>4	>4	>4
A. fumigatus ATCC 46645	**0.5**	**>128**	>4	>4	>4	>4	>4	>4	>4	>4	>4
F. proliferatum ATCC 10052	**2**	**>128**	>4	>4	>4	>4	>4	>4	>4	>4	>4

From the antifungal activity results of these enantiopure compounds it was found that the *R*-enantiomer of this class of antifungal agents has higher antifungal activity than the *S*-enantiomer.

2.1.5 Conclusion

Hybrid fluconazole analogues **127** and **128** containing substituted chalcones were synthesized using two routes with good to excellent yields. Variation in the substituents on phenyl ring was done by varying the starting materials, most of which are readily available. Also, the terminal phenyl ring was replaced with alternative aromatic systems like thienyl, naphthyl, indolyl and anthracenyl *etc*. These reactions can be carried out on large scales and various new chemical entities (NCEs) were prepared for SAR studies. Many compounds from both the classes of compounds having general structures **127** and **128** exhibited very good antifungal activity against various fungal strains. Furthermore, we prepared a few compounds **127** in enantiomerically pure form to examine the

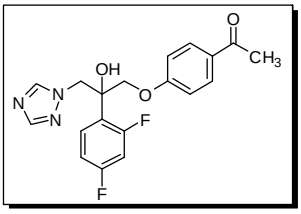
influence of absolute configuration upon antifungal activity and it was observed that *R* enantiomers were more active than *S* enantiomers This work will be very helpful in development of more potent antifungal agents with superior antifungal activity.

2.1.6 Experimental Section

Preparation of 1-(4-(2-(2,4-difluorophenyl)-2-hydroxy-3-(1*H*-1,2,4-triazol-1-yl)propoxy)phenyl)ethanone (129a)

To the flame-dried K_2CO_3 (33.9 g, 245.9 mmol), 4-hydoxyacetophenone **24a** (10.0 g, 81.96 mmol), tetra-butylammonium bromide (TBAB, 300 mg) and epoxide **23** (19.4 g, 81.96 mmol) dissolved in dry ethyl acetate (150 mL) were added. The reaction mixture was allowed to stir at reflux temperature for 12 h under nitrogen atmosphere. It was then cooled to room temperature, diluted with water, extracted with ethyl acetate, dried over Na_2SO_4, concentrated and purified by column chromatography to give pure compound 1-(4-(2-(2,4-difluorophenyl)-2-hydroxy-3-(1*H*-1,2,4-triazol-1-yl)propoxy)phenyl)ethanone **129a** as white solid (13.78 g, 87.6%).

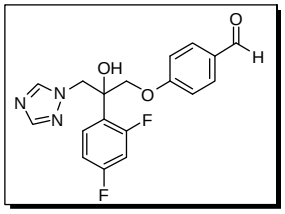
Nature: White solid; **MP:** 157 ^{0}C; **Yield:** 87.6 %; **^{1}H NMR** (200 MHz, $CDCl_3$)**:** δ 2.55 (s, 3H), 4.31 (s, 2H), 4.76 (s, 1H), 4.80-4.96 (m, 2H), 6.75-6.94 (m, 4H), 7.57-7.70 (m, 1H), 7.85 (s, 1H), 7.92 (d, *J*= 10 Hz, 2H), 8.03 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$)**:** δ 26.0, 54.5, 71.6, 74.6, 104.0 (t), 111.5 (d), 114.0 (2C), 122.3 (d), 129.9 (d), 130.3 (2C), 130.6, 144.2, 151.0, 158.2 (dd), 161.7, 163.2 (dd), 196.6; **IR** (Chloroform)**:** 1601, 1674, 3336 cm^{-1}; **MS** (ESI) *m*/*z***:** 374.08 (M + 1), 396.06 (M + Na).



The following compounds **132a-b** were prepared by using the procedure given for the preparation of compound **129a**.

4-(2-(2,4-Difluorophenyl)-2-hydroxy-3-(1*H*-1,2,4-triazol-1-yl)propoxy)benzaldehyde (132a)

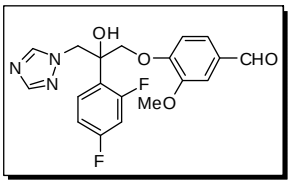
Nature: Pale yellow solid; **MP:** 140 ^{0}C; **Yield:** 73%; **^{1}H NMR** (200 MHz, $CDCl_3$)**:** δ 4.30 (d, *J* = 8 Hz, 1H), 4.38 (d, *J* = 10 Hz, 1H), 4.97 (s, 2H), 5.64 (bs, 1H), 6.77-6.91 (m, 2H), 7.00 (d, *J* = 8 Hz, 2H), 7.55-7.68 (m, 1H), 7.82 (d, *J* = 8 Hz, 2H), 7.91 (s, 1H), 8.55 (s, 1H), 9.88 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$)**:** δ 54.4, 71.9, 74.9, 104.2 (t), 111.8 (d), 114.8 (2C), 122.2 (d), 130.2 (d), 130.4,



131.8 (2C), 144.3, 151.5, 158.4 (dd), 162.8, 163.3 (dd), 190.6; **IR** (Nujol)**:** 1603, 1673, 3405 cm^{-1}; **MS** (ESI) *m*/*z***:** 360.03 (M + 1).

4-(2-(2,4-Difluorophenyl)-2-hydroxy-3-(1*H*-1,2,4-triazol-1-yl)propoxy)-3-methoxybenzaldehyde (132b)

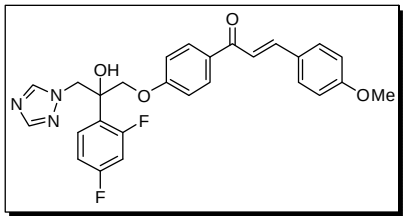
Nature: Yellow semisolid; **Yield:** 68%; **^{1}H NMR** (200 MHz, $CDCl_3$)**:** δ 3.90 (s, 3H), 4.32 (d, *J*= 10 Hz, 1H), 4.45 (d, *J*= 10 Hz, 1H), 4.93 (d, *J*= 14 Hz, 1H), 5.03 (d, *J*= 14 Hz, 1H), 5.11 (bs, 1H), 6.76-6.90 (m, 2H), 6.99 (d, *J*= 8 Hz, 1H), 7.40-7.44 (m, 2H), 7.54-7.66 (m, 1H), 7.92 (s, 1H), 8.69 (s, 1H), 9.85 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 54.3, 55.7, 73.1, 74.8, 104.0 (t), 109.6, 111.6 (d), 113.3, 122.2 (d), 126.2, 130.0 (d), 130.9, 144.3, 149.9, 151.2, 152.9, 158.3 (dd), 163.3 (dd), 190.7; **IR** (Chloroform): 1617, 1682, 3360 cm^{-1}; **MS** (ESI) *m*/*z*: 390.45 (M + 1).



Preparation of (*E*)-1-(4-(2-(2,4-difluorophenyl)-2-hydroxy-3-(1*H*-1,2,4-triazol-1-yl)propoxy)phenyl)-3-(4-methoxyphenyl)prop-2-en-1-one (127b)

To a solution of 1-(4-(2-(2,4-difluorophenyl)-2-hydroxy-3-(1*H*-1,2,4-triazol-1-yl)propoxy)phenyl)ethanone **129a** (1.0 g, 2.68 mmol) in methanol (20 ml), 4-methoxybenzaldehyde **130a** (0.437 g, 3.21 mmol) was added. To this mixture, aq. sodium hydroxide (10%, 7.5 mL, 0.75 g, 13.5 mmol) was added gradually while stirring. The mixture was kept at room temperature for 18 h with continuous stirring. After the reaction reached completion, it was quenched with ice-cold water, the precipitate obtained was filtered and washed with water followed by aq. HCl (30%). The precipitate was washed again with water, dried and recrystallized from methanol to get pure compound (*E*)-1-(4-(2-(2,4-difluorophenyl)-2-hydroxy-3-(1*H*-1,2,4-triazol-1-yl)propoxy)phenyl)-3-(4-methoxyphenyl)prop-2-en-1-one **127b** as yellow fluffy solid (1.09 g, 83.4%).

Nature: Yellow fluffy solid; **MP:** 62 ^{0}C; **Yield:** 83.4%; **^{1}H NMR** (200 MHz, $CDCl_3$)**:** δ 3.85 (s, 3H), 4.33 (s, 2H), 4.89 (s, 2H), 6.76-7.03 (m, 6H), 7.39 (d, *J* = 16 Hz, 1H), 7.55-7.73 (m, 3H), 7.81-7.88 (m, 2H), 7.99 (d, *J* = 10 Hz, 2H), 8.06 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$)**:** δ 54.4, 55.0, 71.5, 74.4, 103.9 (t), 111.4 (d), 114.0, 114.1 (2C), 118.8, 122.2 (d), 127.2, 129.9 (2C), 130.2 (d), 130.3, 131.5, 143.9, 144.2, 150.8, 158.2 (dd), 161.3 (2C), 161.4 (2C), 163.4 (dd), 188.4; **IR** (Chloroform)**:** 1601, 1656, 3327 cm^{-1}; **MS**

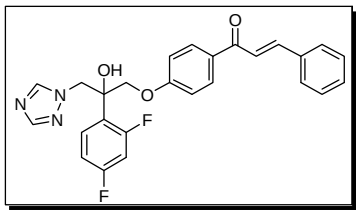


(ESI) *m/z***:** 492.17 (M + 1), 514.11 (M + Na). **Anal. Calcd. for** $C_{27}H_{23}F_2N_3O_4$**:** C, 65.98; H, 4.72; N, 8.55 %. **Found:** C, 65.86; H, 4.86; N, 8.70 %.

The following compounds **127a, 127c-127q, 128a-j, 137** and **138** were prepared by using the procedure given for the preparation of compound **127b**.

(*E*)-1-(4-(2-(2,4-Difluorophenyl)-2-hydroxy-3-(1*H*-1,2,4-triazol-1-yl)propoxy)phenyl)-3-phenylprop-2-en-1-one (127a)

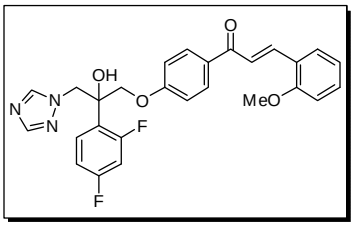
Nature: Pale yellow solid; **MP:** 77 ^{0}C; **Yield:** 80.6%; **^{1}H NMR** (200 MHz, $CDCl_3$)**:** δ



4.33 (s, 2H), 4.85 (s, 2H), 5.29 (bs, 1H), 6.73-6.95 (m, 4H), 7.16-7.39 (m, 4H), 7.48 (d, *J* = 16 Hz, 1H), 7.57-7.79 (m, 4H), 7.96 (d, *J* = 8 Hz, 2H), 8.06 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$)**:** δ 54.5, 71.6, 74.7, 104.1 (t), 111.6 (d), 114.2 (2C), 121.3, 122.3 (d), 128.2 (2C), 128.7 (2C), 129.1, 130.0 (d), 130.3, 130.6, 131.4, 134.6, 144.1, 144.2, 151.2, 158.3 (dd), 161.6, 163.4 (dd), 188.5; **IR** (Chloroform)**:** 1601, 1657, 3373 cm^{-1}; **MS** (ESI) *m/z***:** 462.06 (M + 1). **Anal. Calcd. for** $C_{26}H_{21}F_2N_3O_3$**:** C, 67.67; H, 4.59; N, 9.11 %. **Found:** C, 67.53; H, 4.71; N, 9.28 %.

(*E*)-1-(4-(2-(2,4-Difluorophenyl)-2-hydroxy-3-(1*H*-1,2,4-triazol-1-yl)propoxy)phenyl)-3-(2-methoxyphenyl)prop-2-en-1-one (127c)

Nature: Pale yellow fluffy solid; **MP:** 84 ^{0}C; **Yield:** 81.3%; **^{1}H NMR** (200 MHz,

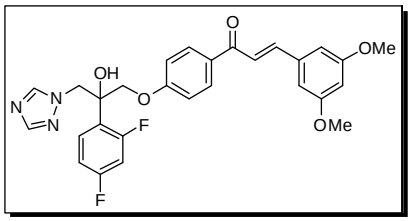


$CDCl_3$)**:** δ 3.89 (s, 3H), 4.25-4.33 (m, 2H), 4.73 (bs, 2H), 4.84 (d, *J* = 14 Hz, 1H), 4.92 (d, *J* = 14 Hz, 1H), 6.75-7.07 (m, 6H), 7.24 (d, *J* = 16 Hz, 1H), 7.43-7.69 (m, 5H), 7.85 (s, 1H), 8.04 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$)**:** δ 54.4, 55.2, 71.4, 74.4, 103.8 (t), 111.2, 111.3 (d), 114.6 (2C), 120.0, 120.2, 122.4 (d), 124.8, 128.0, 128.8, 129.7 (2C), 129.9 (d), 132.4, 142.7, 144.1, 150.7, 157.5, 158.1 (dd), 159.6, 163.0 (dd), 192.7; **IR** (Chloroform)**:** 1601, 1656, 3424 cm^{-1}; **MS** (ESI) *m/z***:** 492.04 (M + 1), 514.06 (M + Na). **Anal. Calcd. for** $C_{27}H_{23}F_2N_3O_4$**:** C, 65.98; H, 4.72; N, 8.55 %. **Found:** C, 65.85; H, 4.83; N, 8.73 %.

(*E*)-1-(4-(2-(2,4-Difluorophenyl)-2-hydroxy-3-(1*H*-1,2,4-triazol-1-yl)propoxy)phenyl)-3-(3,5-dimethoxyphenyl)prop-2-en-1-one (127d)

Nature: Off-white solid; **MP:** 93 ^{0}C; **Yield:** 79.7%; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 3.82 (s, 6H), 4.32 (bs, 2H), 4.95 (bs, 2H), 5.43 (bs, 1H), 6.75-7.01 (m, 6H), 7.43 (d, *J*= 16 Hz,

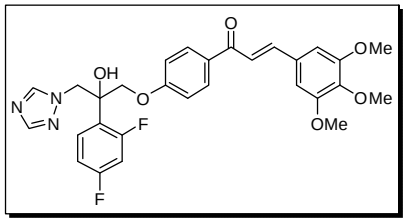
1H), 7.58-7.72 (m, 2H), 7.86-7.98 (m, 3H), 8.59 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$)**:** δ



54.9, 55.3 (2C), 71.7, 74.7, 102.5, 104.2 (t), 106.2 (2C), 111.8 (d), 114.4 (2C), 122.0 (d), 122.1, 130.1 (d), 130.7 (2C), 131.6, 136.7, 137.3, 144.2, 149.4, 158.9 (dd), 160.9 (2C), 161.7, 162.9 (dd), 188.6; **IR** (Chloroform)**:** 1602, 1660, 3363 cm^{-1}; **MS** (ESI) *m*/*z*: 522.10 (M + 1). **Anal. Calcd. for** $C_{28}H_{25}F_2N_3O_5$**:** C, 64.49; H, 4.83; N, 8.06 %. **Found:** C, 64.59; H, 4.91; N, 8.25 %.

(*E*)-1-(4-(2-(2,4-Difluorophenyl)-2-hydroxy-3-(1*H*-1,2,4-triazol-1-yl)propoxy)phenyl)-3-(3,4,5-trimethoxyphenyl)prop-2-en-1-one (127e)

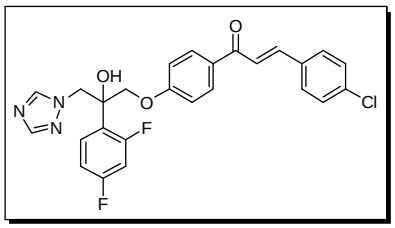
Nature: Yellow fluffy solid; **MP:** 78 ^{0}C; **Yield:** 78.7%; **^{1}H NMR** (200 MHz, $CDCl_3$)**:** δ



3.89 (s, 3H), 3.91 (s, 6H), 4.33 (s, 2H), 4.84 (bs, 1H), 4.88 (s, 2H), 6.75-6.96 (m, 6H), 7.38 (d, *J* = 16 Hz, 1H), 7.58-7.74 (m, 2H), 7.84 (s, 1H), 7.96-8.04 (m, 3H); **^{13}C NMR** (50 MHz, $CDCl_3$)**:** δ 54.3, 55.0 (2C), 60.7, 71.6, 74.7, 104.1 (t), 105.3 (2C), 111.6 (d), 114.2 (2C), 120.7, 122.3 (d), 130.2, 130.4 (d), 130.6 (2C), 131.5, 140.4, 144.3, 151.3, 153.2 (2C), 158.1 (dd), 161.5 (2C), 163.3 (dd), 188.4; **IR** (Chloroform)**:** 1602, 1658, 3393 cm^{-1}; **MS** (ESI) *m*/*z***:** 574.10 (M + Na). **Anal. Calcd. for** $C_{29}H_{27}F_2N_3O_6$**:** C, 63.15; H, 4.93; N, 7.62 %. **Found:** C, 63.33; H, 4.79; N, 7.49 %.

(*E*)-3-(4-Chlorophenyl)-1-(4-(2-(2,4-difluorophenyl)-2-hydroxy-3-(1*H*-1,2,4-triazol-1-yl)propoxy)phenyl)prop-2-en-1-one (127f)

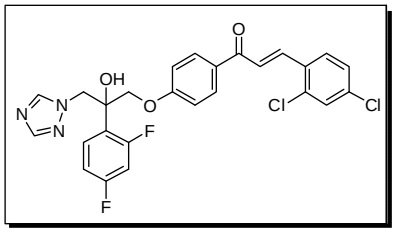
Nature: White solid; **MP:** 132 ^{0}C; **Yield:** 81.4%; **^{1}H NMR** (200 MHz, $CDCl_3$)**:** δ 4.11



(s, 2H), 4.65 (s, 2H), 6.53-6.71 (m, 4H), 7.13 (d, *J* = 8 Hz, 2H), 7.23 (d, *J* = 16 Hz, 1H), 7.29-7.52 (m, 4H), 7.59 (s, 1H), 7.74 (d, *J* = 10 Hz, 2H), 7.85 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$ + DMSO-d_6)**:** δ 54.2, 71.5, 74.0, 103.7 (t), 111.1 (d), 114.1 (2C), 121.6, 122.5 (d), 128.7 (2C), 129.1 (2C), 129.8 (d), 130.3 (2C), 130.8, 132.9, 135.6, 142.2, 150.7, 158.2 (dd), 161.7 (2C), 163.4 (dd), 187.7; **IR** (Nujol)**:** 1602, 1655, 3334 cm^{-1}; **MS** (ESI) *m*/*z***:** 497.11 (M + 1). **Anal. Calcd. for** $C_{26}H_{20}ClF_2N_3O_3$**:** C, 62.97; H, 4.07; N, 8.47 %. **Found:** C, 62.83; H, 4.29; N, 8.29 %.

(*E*)-3-(2,4-Dichlorophenyl)-1-(4-(2-(2,4-difluorophenyl)-2-hydroxy-3-(1*H*-1,2,4-triazol-1-yl)propoxy)phenyl)prop-2-en-1-one (127g)

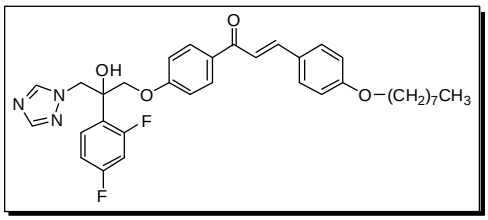
Nature: White fluffy solid; **MP:** 78 ^{0}C; **Yield:** 82.3%; **^{1}H NMR** (200 MHz, $CDCl_3$)**:** δ



4.32 (bs, 2H), 4.84 (bs, 2H), 5.40 (bs, 1H), 6.72-6.90 (m, 5H), 7.18-7.42 (m, 3H), 7.54-7.75 (m, 3H), 7.87-8.02 (m, 3H); **^{13}C NMR** (50 MHz, $CDCl_3$)**:** δ 54.3, 71.3, 73.7, 103.5 (t), 110.9 (d), 113.9 (2C), 122.3 (d), 123.8, 126.9, 127.9, 129.2, 129.6 (d), 130.2, 130.3, 131.0, 135.1, 135.5, 137.6, 144.1, 150.2, 157.8 (dd), 161.6 (2C), 162.8 (dd), 187.2; **IR** (Chloroform)**:** 1602, 1660, 3392 cm^{-1}; **MS** (ESI) *m*/*z***:** 531.05 (M + 1), 553.06 (M + Na). **Anal. Calcd. for** $C_{26}H_{19}Cl_2F_2N_3O_3$**:** C, 58.88; H, 3.61; N, 7.92 %. **Found:** C, 58.97; H, 3.73; N, 7.83 %.

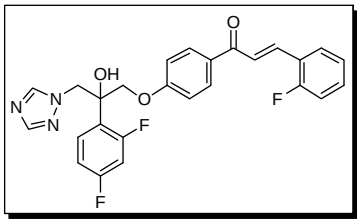
(*E*)-1-(4-(2-(2,4-Difluorophenyl)-2-hydroxy-3-(1*H*-1,2,4-triazol-1-yl)propoxy)phenyl)-3-(4-(octyloxy)phenyl)prop-2-en-1-one (127h)

Nature: White solid; **MP:** 134 ^{0}C; **Yield:** 82.4%; **^{1}H NMR** (200 MHz, $CDCl_3$)**:** δ 0.90



(t, *J* = 6 Hz, 3H), 1.26-1.50 (m, 10H), 1.74-1.87 (m, 2H), 4.00 (t, *J* = 8 Hz, 2H), 4.33 (s, 2H), 4.71 (bs, 1H), 4.82-4.98 (m, 2H), 6.76-6.98 (m, 6H), 7.40 (d, *J* = 16 Hz, 1H), 7.57-7.71 (m, 3H), 7.78 (d, *J* = 16 Hz, 1H), 7.86 (s, 1H), 7.99-8.04 (m, 3H); **^{13}C NMR** (50 MHz, $CDCl_3$)**:** δ 14.0, 22.5, 25.8, 29.1 (3C), 31.6, 54.4, 68.0, 71.7, 74.9, 104.2 (t), 111.7 (d), 114.2 (2C), 114.7 (2C), 118.9, 122.3 (d), 127.2, 130.0 (2C), 130.3 (d), 130.5 (2C), 132.0, 144.2 (2C), 151.5, 158.2 (dd), 161.1, 161.5, 163.1 (dd), 186.6; **IR** (Chloroform)**:** 1601, 1655, 3420 cm^{-1}; **MS** (ESI) *m*/*z***:** 590.33 (M + 1).

(*E*)-1-(4-(2-(2,4-Difluorophenyl)-2-hydroxy-3-(1*H*-1,2,4-triazol-1-yl)propoxy)phenyl)-3-(2-fluorophenyl)prop-2-en-1-one (127i)

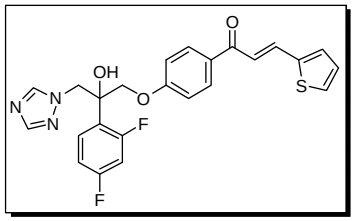


Nature: Pale yellow solid; **MP:** 145 ^{0}C; **Yield:** 82.5%; **^{1}H NMR** (200 MHz, $CDCl_3$)**:** δ 4.33 (s, 2H), 4.86 (s, 2H), 6.73-6.83 (m, 2H), 6.89 (d, *J* = 8 Hz, 2H), 7.04-7.19 (m, 2H), 7.29-7.40 (m, 1H), 7.54-7.68 (m, 3H), 7.80 (s, 1H), 7.82 (d, *J* = 16 Hz, 1H), 7.95 (d, *J* = 8 Hz, 2H), 8.07 (s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$)**:** δ 54.43, 71.8, 75.0, 104.2 (t), 111.8

(d), 114.4 (2C), 122.3 (d), 122.8, 123.0, 124.3 (d), 129.7, 130.2 (d), 130.8 (2C), 131.5, 131.6, 131.7, 136.9, 144.3, 151.6, 158.9 (dd), 161.6 (d), 161.7, 162.9 (dd), 188.6; **IR** (Chloroform)**:** 1604, 1658, 3362 cm^{-1}; **MS** (ESI) *m*/*z***:** 480.12 (M + 1), 502.08 (M + Na). **Anal. Calcd. for** $C_{26}H_{20}F_3N_3O_3$**:** C, 65.13; H, 4.20; N, 8.76 %. **Found:** C, 65.27; H, 4.07; N, 8.66 %.

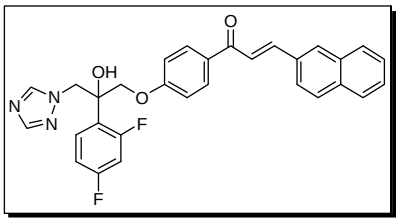
(*E*)-1-(4-(2-(2,4-Difluorophenyl)-2-hydroxy-3-(1*H*-1,2,4-triazol-1-yl)propoxy)phenyl)-3-(thiophen-2-yl)prop-2-en-1-one (127j)

Nature: Off-white fluffy solid; **MP:** 72 ^{0}C; **Yield:** 83.3%; **^{1}H NMR** (200 MHz, $CDCl_3$)**:**



δ 4.33 (s, 2H), 4.87 (s, 2H), 5.03 (bs, 1H), 6.74-6.93 (m, 4H), 7.04-7.09 (m, 1H), 7.25-7.41 (m, 3H), 7.57-7.89 (m, 1H), 7.82 (s, 1H), 7.86-7.98 (m, 3H), 8.05 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$)**:** δ 54.5, 71.8, 75.0, 104.2 (t), 111.8 (d), 114.3 (2C), 120.2, 122.3 (d), 128.2, 128.6, 130.1 (d), 130.6 (2C), 131.6, 131.9, 136.7, 140.2, 144.3, 151.3, 158.4 (dd), 161.6, 162.8 (dd), 187.9; **IR** (Chloroform)**:** 1602, 1651, 3392 cm^{-1}; **MS** (ESI) *m*/*z***:** 468.12 (M + 1). **Anal. Calcd. for** $C_{24}H_{19}F_2N_3O_3S$**:** C, 61.66; H, 4.10; N, 8.99 %. **Found:** C, 61.56; H, 4.22; N, 8.89 %.

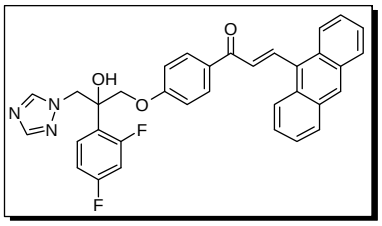
(*E*)-1-(4-(2-(2,4-Difluorophenyl)-2-hydroxy-3-(1*H*-1,2,4-triazol-1-yl)propoxy)phenyl)-3-(naphthalen-2-yl)prop-2-en-1-one (127k)



Nature: Yellow solid; **MP:** 103 ^{0}C; **Yield:** 83.2%; **^{1}H NMR** (200 MHz, $CDCl_3$)**:** δ 4.28 (d, *J* = 8 Hz, 1H), 4.43 (d, *J* = 10 Hz, 1H), 5.01 (d, *J* = 14 Hz, 1H), 5.18 (d, *J* = 14 Hz, 1H), 6.79-6.88 (m, 2H), 6.96 (d, *J* = 8 Hz, 2H), 7.47-7.61 (m, 5H), 7.71-8.00 (m, 8H), 8.22 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$)**:** δ 54.8, 71.7, 74.8, 104.3 (t), 111.9 (d), 114.4 (2C), 121.6, 122.0 (d), 123.6, 126.6, 127.2, 127.7, 128.5 (2C), 128.6, 130.3 (d), 130.5, 130.7 (2C), 131.8, 132.3, 133.2, 134.2, 144.3, 149.5, 158.2 (dd), 161.6, 163.3 (dd), 188.5; **IR** (Chloroform)**:** 1603, 1658, 3421 cm^{-1}; **MS** (ESI) *m*/*z***:** 512.09 (M + 1). **Anal. Calcd. for** $C_{30}H_{23}F_2N_3O_3$**:** C, 70.44; H, 4.53; N, 8.21%. **Found:** C, 70.34; H, 4.69; N, 8.39 %.

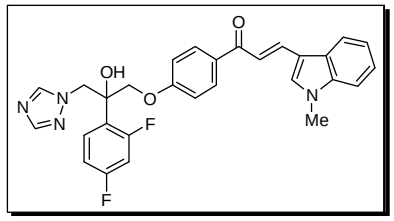
(*E*)-3-(Anthracen-9-yl)-1-(4-(2-(2,4-difluorophenyl)-2-hydroxy-3-(1*H*-1,2,4-triazol-1-yl)propoxy)phenyl)prop-2-en-1-one (127l)

Nature: Bright yellow fluffy solid; **MP:** 92 ^{0}C; **Yield:** 77.2%; **^{1}H NMR** (200 MHz, $CDCl_3$)**:** δ 4.08-4.19 (m, 2H), 4.56 (bs, 1H), 4.72-4.90 (m, 2H), 6.55 (d, *J* = 8 Hz, 2H), 6.74-6.91 (m, 2H), 7.34-7.63 (m, 8H), 7.83-7.96 (m, 4H), 7.99 (s, 1H), 8.03-8.12 (m, 2H), 8.31 (s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$)**:** δ 54.3, 71.6, 75.1, 104.3 (t), 111.9 (d), 113.7 (2C), 114.6, 122.2 (d), 125.0, 125.4 (2C), 125.7, 126.3, 127.1, 128.3, 128.7 (2C), 128.8, 129.6, 130.2 (d), 130.5 (2C), 130.6, 131.0, 131.3, 138.6, 141.4, 144.3, 151.8, 159.6 (dd), 161.2, 162.3 (dd), 190.8; **IR** (Chloroform)**:** 1602, 1658, 3421 cm^{-1}; **MS** (ESI) *m*/*z***:** 562.10 (M + 1). **Anal. Calcd. for** $C_{34}H_{25}F_2N_3O_3$**:** C, 72.72; H, 4.49; N, 7.48 %. **Found:** C, 72.63; H, 4.61; N, 7.36 %.



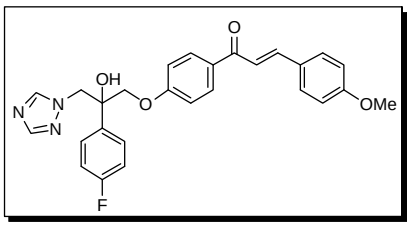
(*E*)-1-(4-(2-(2,4-Difluorophenyl)-2-hydroxy-3-(1*H*-1,2,4-triazol-1-yl)propoxy)phenyl)-3-(1-methyl-1*H*-indol-3-yl)prop-2-en-1-one (127m)

Nature: Yellow solid; **MP:** 123 ^{0}C; **Yield:** 80.7%; **^{1}H NMR** (200 MHz, $CDCl_3$)**:** δ 3.82 (s, 3H), 4.31-4.39 (m, 2H), 4.85 (d, *J* = 10 Hz, 1H), 4.94 (d, *J* = 10 Hz, 1H), 6.76-6.97 (m, 4H), 7.28-7.39 (m, 4H), 7.52 (d, *J* = 16 Hz, 1H), 7.59-7.71 (m, 1H), 7.85 (s, 1H), 7.98-8.10 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$)**:** δ 32.9, 54.3, 71.6, 74.2, 103.7 (t), 109.8, 111.2 (d), 112.4, 114.0 (2C), 115.9, 120.2, 121.1, 122.5 (d), 122.7, 125.6, 130.0 (3C), 130.2 (d), 132.0, 134.3, 137.8, 144.3, 150.8, 158.7 (dd), 161.2, 162.6 (dd), 188.4; **IR** (Nujol)**:** 1601, 1642, 3395 cm^{-1}; **MS** (ESI) *m*/*z***:** 515.04 (M + 1), 537.06 (M + Na). **Anal. Calcd. for** $C_{29}H_{24}F_2N_4O_3$**:** C, 67.70; H, 4.70; N, 10.89 %. **Found:** C, 67.81; H, 4.55; N, 10.79%.



(*E*)-1-(4-(2-(4-Fluorophenyl)-2-hydroxy-3-(1*H*-1,2,4-triazol-1-yl)propoxy)phenyl)-3-(4-methoxyphenyl)prop-2-en-1-one (127n)

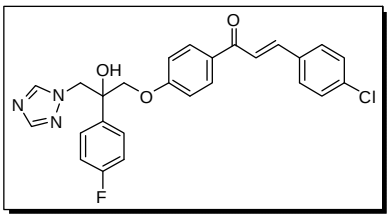
Nature: Pale brown solid; **MP:** 121 ^{0}C; **Yield:** 80.1%; **^{1}H NMR** (200 MHz, $CDCl_3$)**:** δ 3.86 (s, 3H), 4.14 (d, *J* = 10 Hz, 1H), 4.21 (d, *J* = 10 Hz, 1H), 4.47 (bs, 1H), 4.62 (d, *J* = 14 Hz, 1H), 4.78 (d, *J* = 14 Hz, 1H), 6.91-6.98 (m, 4H), 7.01-7.13 (m, 2H), 7.40 (d, *J* = 16 Hz, 1H), 7.49-7.64 (m, 4H), 7.78 (d, *J* = 16 Hz, 1H), 7.89-8.04 (m, 4H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 55.3, 55.9, 72.2, 74.8, 114.2 (2C), 114.3 (2C), 115.2, 115.6, 119.1,



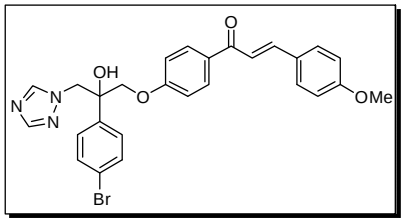
127.1, 127.3, 127.4, 130.1 (2C), 130.6 (2C), 132.0, 135.8, 144.2 (2C), 151.5, 161.3, 161.5, 162.3 (d), 188.7; **IR** (Chloroform)**:** 1600, 1656, 3393 cm^{-1}; **MS** (ESI) *m*/*z***:** 474.13 (M + 1). **Anal. Calcd. for** $C_{27}H_{24}FN_3O_4$**:** C, 68.49; H, 5.11; N, 8.87 %. **Found:** C, 68.56; H, 5.20; N, 8.79 %.

(*E*)-3-(4-Chlorophenyl)-1-(4-(2-(4-fluorophenyl)-2-hydroxy-3-(1*H*-1,2,4-triazol-1-yl)propoxy)phenyl)prop-2-en-1-one (127o)

Nature: Yellow solid; **MP:** 130 ^{0}C; **Yield:** 79.2%; **^{1}H NMR** (200 MHz, $CDCl_3$)**:** δ 4.14 (d, *J* = 10 Hz, 1H), 4.21 (d, *J* = 10 Hz, 1H), 4.50 (bs, 1H), 4.62 (d, *J* = 14 Hz, 1H), 4.78 (d, *J*= 14 Hz, 1H), 6.93-7.11 (m, 4H), 7.35-7.60 (m, 7H), 7.75 (d, *J* = 16 Hz, 1H), 7.89-8.03 (m, 4H); **^{13}C NMR** (50 MHz, $CDCl_3$)**:** δ 55.9, 72.2, 74.7, 114.3 (2C), 115.1, 115.5, 121.7, 127.1, 127.3, 129.0 (2C), 129.4 (2C), 130.7 (2C), 131.4, 133.1, 135.8, 136.1, 142.7, 144.3, 151.3, 161.5, 162.2 (d), 188.2; **IR** (Chloroform)**:** 1606, 1659, 3420 cm^{-1}; **MS** (ESI) *m*/*z***:** 478.04 (M + 1). **Anal. Calcd. for** $C_{26}H_{21}ClFN_3O_3$**:** C, 65.34; H, 4.43; N, 8.79 %. **Found:** C, 65.48; H, 4.31; N, 8.89 %.



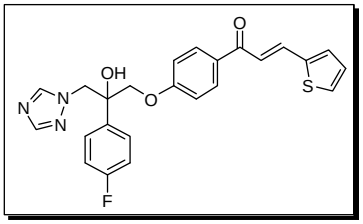
(*E*)-1-(4-(2-(4-Bromophenyl)-2-hydroxy-3-(1*H*-1,2,4-triazol-1-yl)propoxy)phenyl)-3-(4-methoxyphenyl)prop-2-en-1-one (127p)



Nature: Yellow solid; **MP:** 134 ^{0}C; **Yield:** 79.3%; **^{1}H NMR** (200 MHz, $CDCl_3$)**:** δ 3.86 (s, 3H), 4.11-4.21 (m, 2H), 4.60 (d, *J* = 14 Hz, 1H), 4.77 (d, *J* = 14 Hz, 1H), 6.90-6.96 (m, 4H), 7.34-7.53 (m, 5H), 7.59 (d, *J* = 8 Hz, 2H), 7.77 (d, *J* = 16 Hz, 1H), 7.91 (s, 1H), 7.99 (s, 1H), 8.00 (d, *J* = 8 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$)**:** δ 55.3, 55.7, 72.1, 75.0, 114.3 (3C), 119.2, 122.5, 127.2 (2C), 127.6, 130.1 (2C), 130.7 (2C), 131.7 (2C), 132.2, 139.1, 140.3, 144.4, 151.9 (2C), 161.2, 161.6, 188.7; **IR** (Chloroform)**:** 1600, 1660, 3420 cm^{-1}; **MS** (ESI) *m*/*z***:** 557.07 (M + Na). **Anal. Calcd. for** $C_{27}H_{24}BrN_3O_4$**:** C, 60.68; H, 4.53; N, 7.86 %. **Found:** C, 60.82; H, 4.38; N, 7.92 %.

(*E*)-1-(4-(2-(4-Fluorophenyl)-2-hydroxy-3-(1*H*-1,2,4-triazol-1-yl)propoxy)phenyl)-3-(thiophen-2-yl)prop-2-en-1-one (127q)

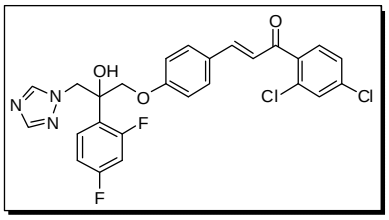
Nature: Golden solid; **MP:** 108 ^{0}C; **Yield:** 78.4%; **^{1}H NMR** (200 MHz, $CDCl_3$)**:** δ 4.14



(d, *J* = 10 Hz, 1H), 4.21 (d, *J* = 10 Hz, 1H), 4.62 (d, *J* = 14 Hz, 1H), 4.78 (d, *J* = 14 Hz, 1H), 6.93 (d, *J* = 10 Hz, 2H), 7.02-7.12 (m, 3H), 7.35-7.43 (m, 3H), 7.47-7.57 (m, 2H), 7.88-8.03 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$)**:** δ 55.9, 72.2, 74.8, 114.3 (2C), 115.3, 115.5, 120.2, 127.2, 127.3, 128.2, 128.6, 130.6 (2C), 131.6, 132.0, 135.8, 136.8, 140.2, 144.2, 151.5, 161.4, 162.3 (d), 188.0; **IR** (Chloroform)**:** 1602, 1650, 3393 cm^{-1}; **MS** (ESI) *m*/*z***:** 450.12 (M + 1), 472.14 (M + Na). **Anal. Calcd. for** $C_{24}H_{20}FN_3O_3S$**:** C, 64.13; H, 4.48; N, 9.35 %. **Found:** C, 64.26; H, 4.30; N, 9.49 %.

(*E*)-1-(2,4-Dichlorophenyl)-3-(4-(2-(2,4-difluorophenyl)-2-hydroxy-3-(1*H*-1,2,4-triazol-1-yl)propoxy)phenyl)prop-2-en-1-one (128a)

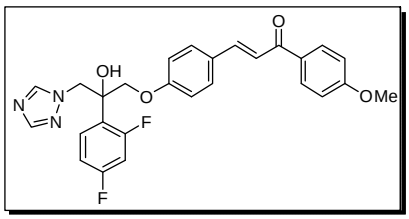
Nature: Yellow fluffy solid; **MP:** 78 ^{0}C; **Yield:** 81.1%; **^{1}H NMR** (200 MHz, $CDCl_3$)**:** δ



4.27 (s, 2H), 4.82 (s, 2H), 5.22 (bs, 1H), 6.71-6.84 (m, 4H), 6.92 (d, *J* = 16 Hz, 1H), 7.25-7.46 (m, 6H), 7.53-7.62 (m, 1H), 7.75 (s, 1H), 8.04 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$)**:** δ 54.4, 71.6, 74.7, 104.0 (t), 111.6 (d), 114.9 (2C), 122.3 (d), 123.9, 127.0, 127.5, 129.9, 130.0 (d), 130.1, 130.2 (2C), 132.0, 136.5, 137.2, 144.2, 146.0, 151.2, 158.3 (dd), 160.2, 163.2 (dd), 192.3; **IR** (Chloroform)**:** 1603, 1660, 3382 cm^{-1}; **MS** (ESI) *m*/*z***:** 531.06 (M + 1). **Anal. Calcd. for** $C_{26}H_{19}Cl_2F_2N_3O_3$**:** C, 58.88; H, 3.61; N, 7.92 %. **Found:** C, 58.76; H, 3.74; N, 7.83 %.

(*E*)-3-(4-(2-(2,4-Difluorophenyl)-2-hydroxy-3-(1*H*-1,2,4-triazol-1-yl)propoxy)phenyl)-1-(4-methoxyphenyl)prop-2-en-1-one (128b)

Nature: White solid; **MP:** 128 ^{0}C; **Yield:** 82.7%; **^{1}H NMR** (200 MHz, $CDCl_3$)**:** δ 3.89

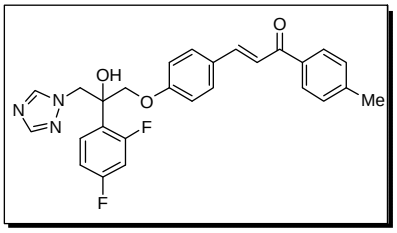


(s, 3H), 4.25-4.33 (m, 2H), 4.71 (bs, 1H), 4.81-4.96 (m, 2H), 6.76-7.00 (m, 6H), 7.43 (d, *J* = 16 Hz, 1H), 7.56-7.66 (m, 3H), 7.75 (d, *J* = 16 Hz, 1H), 7.86 (s, 1H), 8.00-8.05 (m, 3H); **^{13}C NMR** (50 MHz, $CDCl_3$)**:** δ 54.3, 55.4, 71.5, 74.3, 104.2 (t), 111.6 (d), 114.0, 114.2 (2C), 118.9, 122.5 (d), 127.1, 129.2 (2C), 130.1 (d), 130.3, 131.7, 143.7, 144.1, 151.2, 158.3 (dd), 161.3 (2C), 161.9 (2C), 163.2 (dd), 188.6; **IR** (Chloroform)**:**

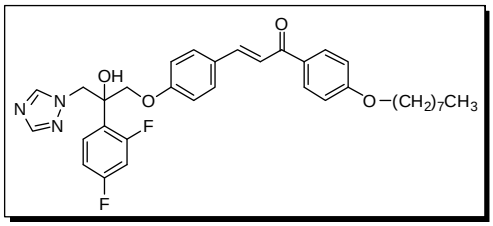
1601, 1657, 3379 cm^{-1}; **MS** (ESI) *m*/*z***:** 492.10 (M + 1). **Anal. Calcd. for** $C_{27}H_{23}F_2N_3O_4$**:** C, 65.98; H, 4.72; N, 8.55 %. **Found:** C, 65.87; H, 4.86; N, 8.67 %.

(*E*)-3-(4-(2-(2,4-Difluorophenyl)-2-hydroxy-3-(1*H*-1,2,4-triazol-1-yl)propoxy)phenyl)-1-(p-tolyl)prop-2-en-1-one (128c)

Nature: White solid; **MP:** 124 ^{0}C; **Yield:** 83.4%; **^{1}H NMR** (200 MHz, $CDCl_3$)**:** δ 2.43 (s, 3H), 4.25-4.34 (m, 2H), 4.77 (s, 1H), 4.80-4.96 (m, 2H), 6.75-6.93 (m, 4H), 7.30 (d, *J* = 10 Hz, 2H), 7.41 (d, *J* = 16 Hz, 1H), 7.55-7.66 (m, 3H), 7.75 (d, *J* = 16 Hz, 1H), 7.85 (s, 1H), 7.92 (d, *J* = 8 Hz, 2H), 8.04 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$)**:** δ 21.5, 54.5, 71.7, 75.0, 104.2 (t), 111.6 (d), 114.9 (2C), 120.1, 122.3 (d), 128.4 (3C), 129.2 (2C), 130.0 (2C), 130.2 (d), 135.8, 143.4, 143.7, 144.3, 151.8, 158.3 (dd), 159.8, 163.4 (dd), 189.9; **IR** (Chloroform)**:** 1603, 1657, 3363 cm^{-1}; **MS** (ESI) *m*/*z***:** 476.06 (M + 1). **Anal. Calcd. for** $C_{27}H_{23}F_2N_3O_3$**:** C, 68.20; H, 4.88; N, 8.84 %. **Found:** C, 68.37; H, 4.69; N, 8.91 %.



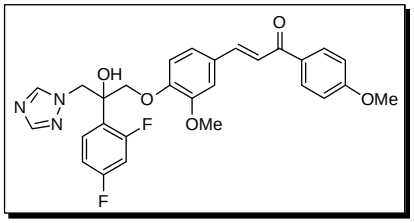
(*E*)-3-(4-(2-(2,4-Difluorophenyl)-2-hydroxy-3-(1*H*-1,2,4-triazol-1-yl)propoxy)phenyl)-1-(4-(octyloxy)phenyl)prop-2-en-1-one (128d)



Nature: Off-white solid; **MP:** 108 ^{0}C; **Yield:** 81.3%; **^{1}H NMR** (200 MHz, $CDCl_3$)**:** δ 0.89 (t, *J* = 6 Hz, 3H), 1.28-1.51 (m, 10H), 1.75-1.88 (m, 2H), 4.04 (t, *J* = 8 Hz, 2H), 4.25-4.35 (m, 2H), 4.72 (bs, 1H), 4.80-4.96 (m, 2H), 6.75-6.98 (m, 6H), 7.43 (d, *J* = 16 Hz, 1H), 7.55-7.65 (m, 3H), 7.75 (d, *J* = 16 Hz, 1H), 7.85 (s, 1H), 7.99-8.04 (m, 3H). **^{13}C NMR** (50 MHz, $CDCl_3$)**:** δ 13.9, 22.5, 25.8, 28.9, 29.1 (2C), 31.6, 54.5, 68.1, 71.7, 74.9, 104.1 (t), 111.7 (d), 114.1 (2C), 114.9 (2C), 119.9, 122.4 (d), 128.5, 129.9 (2C), 130.0 (d), 130.6 (2C), 130.7, 143.2, 144.3, 151.4, 158.2 (dd), 159.7, 162.9, 163.2 (dd), 188.5; **IR** (Chloroform)**:** 1599, 1657, 3406 cm^{-1}; **MS** (ESI) *m*/*z***:** 590.13 (M + 1). **Anal. Calcd. for** $C_{34}H_{37}F_2N_3O_4$**:** C, 69.25; H, 6.32; N, 7.13 %. **Found:** C, 69.12; H, 6.47; N, 7.29 %.

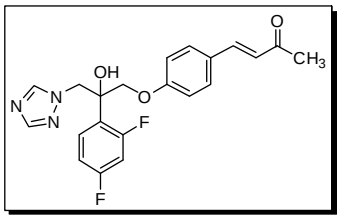
(*E*)-3-(4-(2-(2,4-Difluorophenyl)-2-hydroxy-3-(1*H*-1,2,4-triazol-1-yl)propoxy)-3-methoxyphenyl)-1-(4-methoxyphenyl)prop-2-en-1-one (128e)

Nature: Bright green fluffy solid; **MP:** 87 ^{0}C; **Yield:** 78.1%; **^{1}H NMR** (200 MHz, $CDCl_3$)**:** δ 3.85 (s, 6H), 4.30 (d, *J* = 8 Hz, 1H), 4.33 (d, *J* = 8 Hz, 1H), 4.83 (d, *J* = 12 Hz, 1H), 4.88 (d, *J* = 12 Hz, 1H), 5.11 (bs, 1H), 6.75-6.83 (m, 2H), 6.87 (d, *J* = 8 Hz, 1H), 6.95 (d, *J* = 8 Hz, 2H), 7.10-7.16 (m, 2H), 7.39 (d, *J* = 15 Hz, 1H), 7.56-7.61 (m, 1H), 7.69 (d, *J* = 15 Hz, 1H), 7.77 (s, 1H), 8.00 (d, *J* = 8 Hz, 2H), 8.08 (s, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$)**:** δ 54.5, 55.3, 55.8, 73.7, 74.9, 104.0 (t), 111.1, 111.6 (d), 113.6 (2C), 115.3, 120.4, 122.3, 122.4 (d), 129.7 (2C), 130.0 (d), 130.6, 130.9, 143.5, 144.3, 149.6, 149.8, 151.3, 158.9 (dd), 162.7 (dd), 163.2, 188.5; **IR** (Chloroform): 1601, 1656, 3442 cm^{-1}; **MS** (ESI) *m*/*z***:** 522.16 (M + 1). **Anal. Calcd. for** $C_{28}H_{25}F_2N_3O_5$**:** C, 64.49; H, 4.83; N, 8.06 %. **Found:** C, 64.56; H, 4.70; N, 8.22 %.



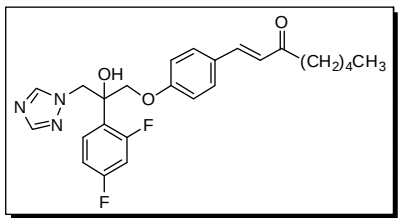
(*E*)-4-(4-(2-(2,4-Difluorophenyl)-2-hydroxy-3-(1*H*-1,2,4-triazol-1-yl)propoxy)phenyl)but-3-en-2-one (128f)

Nature: Pale yellow semisolid; **Yield:** 47.3%; **^{1}H NMR** (200 MHz, $CDCl_3$)**:** δ 2.35 (s, 3H), 4.28 (s, 2H), 4.79-4.94 (m, 2H), 6.59 (d, *J* = 16 Hz, 1H), 6.74-6.89 (m, 5H), 7.40-7.48 (m, 2H), 7.56-7.69 (m, 1H), 7.82 (s, 1H), 8.04 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$)**:** δ 27.2, 54.5, 71.7, 74.8, 104.2 (t), 111.7 (d), 114.9 (2C), 122.3 (d), 125.3, 127.8, 129.8 (2C), 130.0 (d), 142.8, 144.3, 151.5, 158.2 (dd), 159.8, 163.2 (dd), 198.3; **IR** (Chloroform)**:** 1601, 1664, 3363 cm^{-1}; **MS** (ESI) *m*/*z***:** 422.12 (M + Na). **Anal. Calcd. for** $C_{21}H_{19}F_2N_3O_3$**:** C, 63.15; H, 4.80; N, 10.52 %. **Found:** C, 63.28; H, 4.68; N, 10.41 %.



(*E*)-1-(4-(2-(2,4-Difluorophenyl)-2-hydroxy-3-(1*H*-1,2,4-triazol-1-yl)propoxy)phenyl)oct-1-en-3-one (128g)

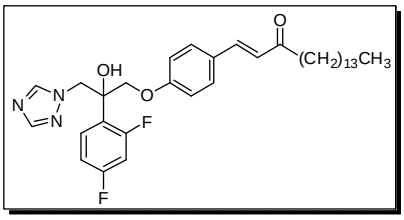
Nature: Pale pink semisolid; **Yield:** 28.3%; **^{1}H NMR** (200 MHz, $CDCl_3$)**:** δ 0.91 (t, *J* = 6 Hz, 3H), 1.22-1.38 (m, 4H), 1.60-1.71 (m, 2H), 2.63 (t, *J* = 8 Hz, 2H), 4.26-4.32 (m, 2H), 4.65 (s, 1H), 4.80-4.96 (m, 2H), 6.63 (d, *J* = 16 Hz, 1H), 6.78-6.92 (m, 4H), 7.46-7.54 (m, 3H), 7.57-7.67 (m, 1H), 7.86 (s, 1H), 8.03 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$)**:** δ



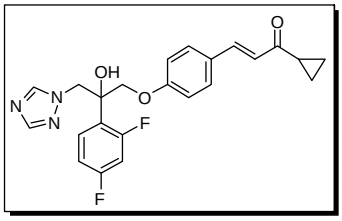
13.8, 22.4, 24.0, 31.4, 40.7, 54.4, 71.7, 75.0, 104.2 (t), 111.8 (d), 114.9 (2C), 122.3 (d), 124.5, 128.1, 129.8 (2C), 130.2 (d), 141.6, 144.3, 151.6, 158.8 (dd), 159.7, 162.8 (dd), 200.6; **IR** (Chloroform)**:** 1600, 1642, 3420 cm^{-1}; **MS** (ESI) *m*/*z***:** 456.13 (M + 1).

(*E*)-1-(4-(2-(2,4-Difluorophenyl)-2-hydroxy-3-(1*H*-1,2,4-triazol-1-yl)propoxy)phenyl)heptadec-1-en-3-one (128h)

Nature: White solid; **MP:** 78 ^{0}C; **Yield:** 26.7%; **^{1}H NMR** (200 MHz, $CDCl_3$)**:** δ 0.87 (t, *J* = 6 Hz, 3H), 1.19-1.30 (m, 22H), 1.61-1.66 (m, 2H), 2.61 (t, *J* = 6 Hz, 2H), 4.27 (s, 2H), 4.85 (s, 2H), 4.90 (bs, 1H), 6.63 (d, *J* = 16 Hz, 1H), 6.77-6.87 (m, 4H), 7.45-7.49 (m, 3H), 7.59-7.65 (m, 1H), 7.81 (s, 1H), 8.04 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$)**:** δ 14.07, 22.6, 24.3, 29.2 (2C), 29.3, 29.4, 29.5 (5C), 31.8, 40.8, 54.4, 71.7, 75.0, 104.2 (t), 111.8 (d), 114.9 (2C), 122.3 (d), 124.5, 128.0, 129.8 (2C), 130.1 (d), 141.6, 144.3, 151.6, 158.8 (dd), 159.7, 162.8 (dd), 200.7; **IR** (Chloroform)**:** 1600, 1647, 3393 cm^{-1}; **MS** (ESI) *m*/*z***:** 582.28 (M + 1).



(*E*)-1-Cyclopropyl-3-(4-(2-(2,4-difluorophenyl)-2-hydroxy-3-(1*H*-1,2,4-triazol-1-yl)propoxy)phenyl)prop-2-en-1-one (128i)

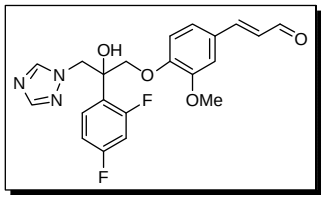


Nature: Yellow solid; **MP:** 60 ^{0}C; **Yield:** 41.3%; **^{1}H NMR** (200 MHz, $CDCl_3$)**:** δ 0.91-1.03 (m, 2H), 1.11-1.19 (m, 2H), 2.16-2.26 (m, 1H), 4.23-4.33 (m, 2H), 4.71 (s, 1H), 4.80-4.95 (m, 2H), 6.72-6.92 (m, 5H), 7.50 (d, *J* = 8 Hz, 2H), 7.57-7.69 (m, 2H), 7.85 (s, 1H), 8.04 (s, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$)**:** δ 11.8 (2C), 19.5, 54.5, 71.7, 75.0, 104.2 (t), 111.8 (d), 114.9 (2C), 122.4 (d), 124.6, 128.1, 129.8 (2C), 130.1 (d), 141.3, 144.3, 151.5, 158.8 (dd), 159.7, 162.8 (dd), 200.0; **IR** (Chloroform)**:**, 1600, 1670, 3365 cm^{-1}; **MS** (ESI) *m*/*z***:** 426.10 (M + 1). **Anal. Calcd. for** $C_{23}H_{21}F_2N_3O_3$**:** C, 64.93; H, 4.98; N, 9.88 %. **Found:** C, 64.86; H, 5.13; N, 9.96 %.

(*E*)-3-(4-(2-(2,4-Difluorophenyl)-2-hydroxy-3-(1*H*-1,2,4-triazol-1-yl)propoxy)-3-methoxyphenyl)acrylaldehyde (128j)

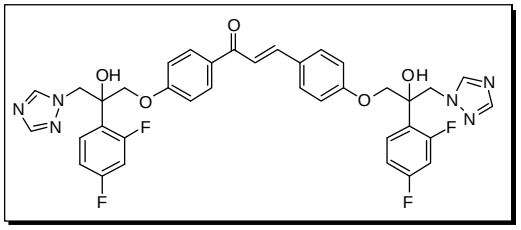
Nature: Golden solid; **MP:** 135 ^{0}C; **Yield:** 48.5%; **^{1}H NMR** (200 MHz, $CDCl_3$)**:** δ 3.88 (s, 3H), 4.28-4.38 (m, 2H), 4.77-4.95 (m, 3H), 6.56-6.67 (dd, *J* = 16, 8 Hz, 1H), 6.75-6.89 (m, 2H), 6.93 (d, *J* = 8 Hz, 1H), 7.07-7.15 (m, 2H), 7.40 (d, *J* = 16 Hz, 1H), 7.55-

7.67 (m, 1H), 7.82 (s, 1H), 8.06 (s, 1H), 9.67 (d, *J* = 8 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$)**:** δ 54.5, 55.8, 73.5, 74.9, 104.1 (t), 110.7, 111.7 (d), 115.0, 122.3 (d), 122.9, 127.2, 128.5, 130.0 (d), 149.9, 150.4, 151.4, 152.2, 158.7 (dd), 160.5, 162.6 (dd), 193.4; IR (Chloroform)**:** 1620, 1672, 3328 cm^{-1}; **MS** (ESI) *m*/*z***:** 416.02 (M + 1).



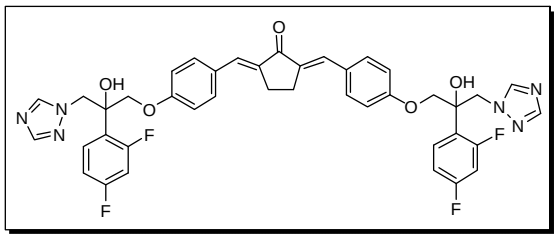
(*E*)-1,3-Bis(4-(2-(2,4-difluorophenyl)-2-hydroxy-3-(1*H*-1,2,4-triazol-1-yl)propoxy)phenyl)prop-2-en-1-one (137)

Nature: Yellow fluffy solid; **MP:** 97 ^{0}C; **Yield:** 80.7%; **^{1}H NMR** (200 MHz, $CDCl_3$)**:** δ 4.19-4.34 (m, 4H), 4.79-4.88 (m, 4H), 5.16 (bs, 2H), 6.73-6.93 (m, 8H), 7.53 (d, *J* = 16 Hz, 1H), 7.49-7.75 (m, 5H), 7.79 (s, 2H), 7.94 (d, *J* = 8 Hz, 2H), 8.05 (s, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$)**:** δ 54.6 (2C), 71.7 (2C), 74.7 (2C), 104.2 (t, 2C), 111.7 (d, 2C), 114.2 (2C), 114.8 (2C), 119.6, 122.4 (d, 2C), 128.3, 130.0 (2C), 130.3 (d, 2C), 130.5 (2C), 131.7, 143.7, 144.2 (2C), 151.2 , 158.3 (dd, 2C), 159.8, 161.6 (2C), 163.3 (dd, 2C), 188.5; **IR** (Chloroform)**:** 1601, 1657, 3379 cm^{-1}; **MS** (ESI) *m*/*z***:** 715.03 (M + 1), 737.03 (M + Na).



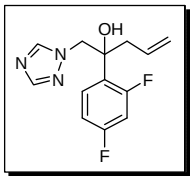
(2*E*,5*E*)-2,5-Bis(4-(2-(2,4-difluorophenyl)-2-hydroxy-3-(1*H*-1,2,4-triazol-1-yl)propoxy)benzylidene)cyclopentanone (138)

Nature: Bright yellow fluffy solid; **MP:** 105 ^{0}C; **Yield:** 83.3%; **^{1}H NMR** (200 MHz, $CDCl_3$)**:** δ 3.05 (s, 4H), 4.18-4.35 (m, 4H), 4.80-4.95 (m, 6H), 6.76-6.94 (m, 8H), 7.45-7.70 (m, 6H), 7.85 (s, 2H), 8.05 (s, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$)**:** δ 26.2 (2C), 54.6 (2C), 71.7 (2C), 75.0 (2C), 104.2 (t, 2C), 111.8 (d, 2C), 114.8 (4C), 122.4 (d, 2C), 129.4 (2C), 130.1 (d, 2C), 132.4 (2C), 133.0 (2C), 135.5 (2C), 144.3 (2C), 151.5 (2C), 158.3 (dd, 2C), 158.8 (4C), 163.3 (dd, 2C), 196.1; **IR** (Chloroform)**:** 1618, 1689, 3329 cm^{-1}; **MS** (ESI) *m*/*z***:** 789.10 (M + Na). **Anal. Calcd. for** $C_{41}H_{34}F_4N_6O_5$**:** C, 64.23; H, 4.47; N, 10.96 %. **Found:** C, 64.41; H, 4.59; N, 11.15 %.



Preparation of 2-(2,4-difluorophenyl)-1-(1*H*-1,2,4-triazol-1-yl)pent-4-en-2-ol (142)

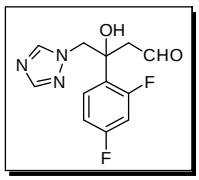
In a round bottom flask, allyl bromide (8.02 ml, 0.095 mol) was added to a stirred zinc powder (14.33 gm, 0.219 mol) suspended in THF (150 mL) and after stirring for 10-15 minutes at RT, 1-(2,4-difluorophenyl)-2-(1*H*-1,2,4-triazol-1-yl)ethanone (15.00 gm, 0.073 mol) was added. The mixture was stirred at RT for 3 hours and reaction was monitored by TLC (ethyl acetate-pet ether, 80:20). After completion of reaction, it was quenched with 15 mL sat NH_4Cl solution followed by addition of water (50 mL). It was then extracted with ethyl acetate (3 x 40 mL), the organic layer was dried over Na_2SO_4, concentrated and purified by column chromatography to give pure 2-(2,4-difluorophenyl)-1-(1*H*-1,2,4-triazol-1-yl)pent-4-en-2-ol **142** as pale yellow semisolid (15.6 g, 86.3%).



Nature: Pale yellow semisolid; **Yield:** 86.3%; **^{1}H NMR** (200 MHz, $CDCl_3$)**:** δ 2.51 (dd, *J* = 14, 2 Hz, 1H), 2.82 (dd, *J* = 8, 2 Hz, 1H), 4.43 (bs, 1H), 4.50 (d, *J* = 14 Hz, 1H), 4.75 (d, *J* = 14 Hz, 1H), 5.04-5.15 (m, 2H), 5.56-5.77 (m, 1H), 6.70-6.83 (m, 1H), 7.38-7.50 (m, 1H), 7.82 (s, 1H), 7.95 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$)**:** δ 42.6, 57.0, 74.8, 103.9 (t), 111.2 (d), 119.5, 124.7 (d), 129.6 (d), 131.6, 144.1, 150.8, 157.9 (dd), 162.2. **IR** (Chloroform)**:** 1618, 3429 cm^{-1}; **MS** (ESI) *m*/*z***:** 266.03 (M + 1).

Preparation of 3-(2,4-difluorophenyl)-3-hydroxy-4-(1*H*-1,2,4-triazol-1-yl)butanal (140)

To a stirred solution of 2-(2,4-difluorophenyl)-1-(1*H*-1,2,4-triazol-1-yl)pent-4-en-2-ol (**142**) (2.65 g, 0.01 mol) dissolved in 20 mL of t-butanol and water (1:1), was added 0.039 molar OsO_4 in t-butanol (0.5 mL). The mixture was stirred for five minutes, then $NaHCO_3$ (3.36 g, 0.04 mol) was added followed by $NaIO_4$ (21.3 g, 0.1 mol) and allowed to stirr at RT for 7 h. After completion of reaction, it was quenched with 10 ml sat NH_4Cl solution followed by addition of water (30 mL). It was then extracted with ethyl acetate (3 x 30 mL), the organic layer was dried over Na_2SO_4, concentrated and purified by column chromatography to give pure compound 3-(2,4-difluorophenyl)-3-hydroxy-4-(1*H*-1,2,4-triazol-1-yl)butanal **140** as pale yellow semisolid (2.33 g, 87.3%).

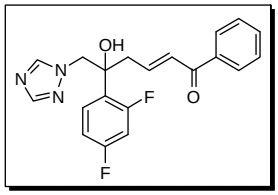


Nature: Pale yellow semisolid; **Yield:** 87.3%; **^{1}H NMR** (200 MHz, $CDCl_3$)**:** δ 2.82 (d, *J* = 16 Hz, 1H), 3.23 (d, *J* = 16 Hz, 1H), 4.58 (s, 2H), 5.23 (bs, 1H), 6.75-6.90 (m, 2H), 7.50-7.63 (m, 1H), 7.85 (s, 1H), 8.01 (s, 1H), 9.65 (t, *J* = 2 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$)**:** δ 49.6, 56.8, 73.3, 104.3 (t), 111.7 (d), 123.8 (d), 129.3 (d), 144.3, 151.4, 158.0 (dd), 163.0 (dd), 200.8; **IR** (Chloroform)**:** 1617, 1723, 3417 cm^{-1}; **MS** (ESI) *m*/*z***:** 268.10 (M + 1).

Preparation of (*E*)-5-(2,4-difluorophenyl)-5-hydroxy-1-phenyl-6-(1*H*-1,2,4-triazol-1-yl)hex-2-en-1-one (139a)

A mixture of 3-(2,4-difluorophenyl)-3-hydroxy-4-(1*H*-1,2,4-triazol-1-yl)butanal **140** (266 mg, 1 mmol) and 1-phenyl-2-(triphenylphosphoranylidene)ethanone **141a** (380 mg, 1 mmol) was stirred in dichloromethane (8 mL) at RT for 3 h. After completion of reaction, it was extracted with dichloromethane and purified by column chromatography to give pure compound (*E*)-5-(2,4-difluorophenyl)-5-hydroxy-1-phenyl-6-(1*H*-1,2,4-triazol-1-yl)hex-2-en-1-one **139a** as off-white solid (238 mg, 64.4%).

Nature: Off-white solid; **MP:** 97 ^{0}C; **Yield:** 64.4%; **^{1}H NMR** (200 MHz, $CDCl_3$)**:** δ

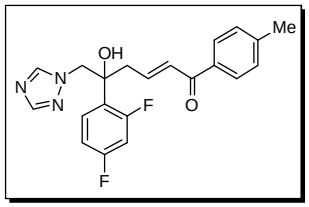


2.78 (dd, *J* = 14, 8 Hz, 1H), 3.02 (dd, *J* = 14, 8 Hz, 1H), 4.55 (d, *J* = 14 Hz, 1H), 4.78 (d, *J* = 14 Hz, 1H), 5.12 (bs, 1H), 6.73-6.87 (m, 4H), 7.37-7.58 (m, 4H), 7.75-7.81 (m, 2H), 7.83 (s, 1H), 7.97 (s, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$)**:** δ 41.5, 56.8, 75.3, 104.1 (t), 111.7 (d), 124.2, (d), 128.4 (2C), 128.5 (2C), 129.5, 129.9 (d), 132.8, 137.3, 142.2, 144.1, 151.1, 158.2 (dd), 162.6 (dd), 190.4; **IR** (Chloroform)**:** 1618, 1669, 3422 cm^{-1}; **MS** (ESI) *m*/*z***:** 370.06 (M + 1). **Anal. Calcd. for** $C_{20}H_{17}F_2N_3O_2$**:** C, 65.03; H, 4.64; N, 11.38 %. **Found:** C, 65.19; H, 4.49; N, 11.27 %.

The following compounds **139b-139d** were prepared by using the procedure given for the preparation of compound **139a**.

(*E*)-5-(2,4-Difluorophenyl)-5-hydroxy-1-(p-tolyl)-6-(1*H*-1,2,4-triazol-1-yl)hex-2-en-1-one (139b)

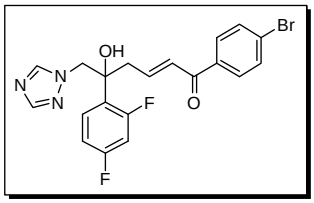
Nature: White solid; **MP:** 90 ^{0}C; **Yield:** 65.8%; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.39 (s,



3H), 2.72-2.82 (m, 1H), 2.97-3.06 (m, 1H), 4.54 (d, *J* = 14 Hz, 1H), 4.78 (d, *J* = 14 Hz, 1H), 5.08 (bs, 1H), 6.72-6.86 (m, 4H), 7.22 (d, *J* = 8 Hz, 2H), 7.42-7.54 (m, 1H), 7.69 (d, *J* = 8 Hz, 2H), 7.83 (s, 1H), 7.97 (s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 21.5, 41.5, 56.8, 75.3, 104.1 (t), 111.7 (d), 124.3 (d), 128.6 (2C), 129.1 (2C), 129.5, 129.9 (d), 134.7, 141.5, 143.7, 144.0, 151.9, 158.2 (dd), 162.7 (dd), 189.8; **IR** (Chloroform): 1617, 1671, 3428 cm^{-1}; **MS** (ESI) *m*/*z*: 384.10 (M + 1). **Anal. Calcd. for** $C_{21}H_{19}F_2N_3O_2$**:** C, 65.79; H, 5.00; N, 10.96%. **Found:** C, 65.87; H, 4.91; N, 11.10 %.

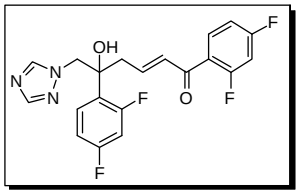
(*E*)-1-(4-Bromophenyl)-5-(2,4-difluorophenyl)-5-hydroxy-6-(1*H*-1,2,4-triazol-1-yl)hex-2-en-1-one (139c)

Nature: Pale yellow semisolid; **Yield:** 63.2%; **^{1}H NMR** (200 MHz, $CDCl_3$)**:** δ 2.78 (dd, *J* = 14, 8 Hz, 1H), 3.01 (dd, *J* = 14, 8 Hz, 1H), 4.54 (d, *J* = 14 Hz, 1H), 4.78 (d, *J* = 14 Hz, 1H), 5.16 (bs, 1H), 6.72-6.94 (m, 4H), 7.40-7.69 (m, 5H), 7.84 (s, 1H), 7.96 (s, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$)**:** δ 41.7, 56.7, 75.4, 104.3 (t), 112.0 (d), 122.2 (d), 128.1 (2C), 128.6 (2C), 129.4, 130.2 (d), 133.3, 137.6, 141.9, 144.5, 150.5, 158.3 (dd), 163.1 (dd), 187.3; **IR** (Chloroform)**:** 1618, 1670, 3420 cm^{-1}; **MS** (ESI) *m*/*z***:** 449.07 (M + 1). **Anal. Calcd. for** $C_{20}H_{16}BrF_2N_3O_2$**:** C, 53.59; H, 3.60; N, 9.37 %. **Found:** C, 53.46; H, 3.69; N, 9.45 %.



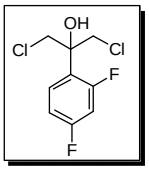
(*E*)-1,5-Bis(2,4-difluorophenyl)-5-hydroxy-6-(1*H*-1,2,4-triazol-1-yl)hex-2-en-1-one (139d)

Nature: Yellow thick liquid; **Yield:** 60.7%; **^{1}H NMR** (400 MHz, $CDCl_3$)**:** δ 2.76 (dd, *J* = 14, 8 Hz, 1H), 2.99 (dd, *J* = 14, 8 Hz, 1H), 4.53 (d, *J* = 16 Hz, 1H), 4.75 (d, *J* = 16 Hz, 1H), 5.11 (bs, 1H), 6.67-6.94 (m, 5H), 7.43-7.55 (m, 1H), 7.60-7.71 (m, 2H), 7.82 (s, 1H), 7.95 (s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$)**:** δ 41.4, 56.8, 75.3, 104.1 (t), 104.5 (t), 111.6 (d), 112.0 (d), 122.7 (d), 124.2 (d), 129.8 (d), 132.2, 132.7 (d), 142.7, 144.0, 151.8, 158.2 (dd), 161.8 (dd), 163.5 (dd), 165.4 (dd), 186.9; **IR** (Chloroform)**:** 1617, 1670, 3417 cm^{-1}; **MS** (ESI) *m*/*z***:** 428.10 (M + Na). **Anal. Calcd. for** $C_{20}H_{15}F_4N_3O_2$**:** C, 59.26; H, 3.73; N, 10.37 %. **Found:** C, 59.41; H, 3.60; N, 10.29 %.



Preparation of 1,3-dichloro-2-(2,4-difluorophenyl)propan-2-ol (146)[58]

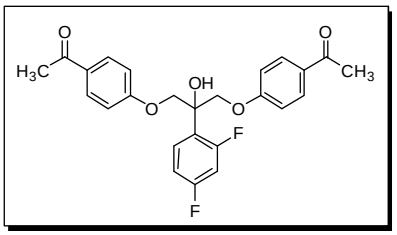
A solution of 1-bromo-2,4-difluorobenzene **145** (5.0 g, 25.9 mol) in THF (20 mL) was added to magnesium powder (0.621 g, 25.9 mol) at 0°C over 2 minutes. After stirring at 0°C for 5-10 minutes, dichloroacetone (3.29 g, 25.9 mol) dissolved in THF (10 mL) was slowly added at 0°C over 5 minutes. The reaction mixture was allowed to stir at RT for 4 h. After completion of reaction, it was quenched with 10-15 mL of sat NH_4Cl solution followed by addition of water (30 mL). It was then extracted with ethyl acetate (3 x 30 ml), the organic layer was dried over Na_2SO_4, concentrated and purified by column chromatography to give 1,3-dichloro-2-(2,4-difluorophenyl)propan-2-ol **146** as off-white semisolid (1.83 g, 29.4%).



Nature: Off-white semisolid; **Yield:** 29.4%; **^{1}H NMR** (200 MHz, $CDCl_3$)**:** δ 4.04 (s, 4H), 6.78-7.00 (m, 2H), 7.63-7.55 (m, 1H).

Preparation of 1,1'-(((2-(2,4-difluorophenyl)-2-hydroxypropane-1,3-diyl)bis(oxy))bis(4,1-phenylene))diethanone (147)

To the flame-dried K_2CO_3 (2.14 g, 15.56 mmol), 1,3-dichloro-2-(2,4-difluorophenyl)propan-2-ol **146** (1.5 g, 6.22 mmol) and 4-hydoxyacetophenone **131** (1.69 g, 12.44 mmol) dissolved in dry ethyl acetate (15 mL) were added. The reaction mixture was allowed to stir at reflux temperature for 8 h under nitrogen atmosphere. It was then cooled to room temperature, diluted with water, extracted with ethyl acetate, dried over Na_2SO_4, concentrated and purified by column chromatography to give pure compound 1,1'-(((2-(2,4-difluorophenyl)-2-hydroxypropane-1,3-diyl)bis(oxy))bis(4,1-phenylene))diethanone **147** as colorless semisolid (2.39 g, 87.3%).

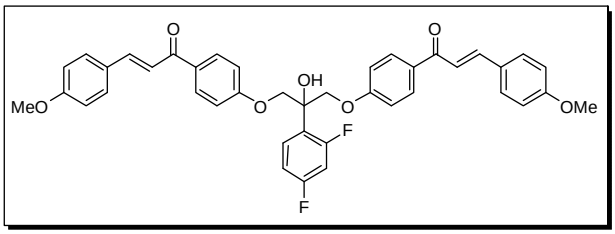


Nature: Colorless semisolid; **Yield:** 87.3%; **^{1}H NMR** (200 MHz, $CDCl_3$)**:** δ 2.51 (s, 6H), 4.46-4.57 (m, 4H), 6.76-7.11 (m, 6H), 7.61-7.89 (m, 5H).

The compound **144** was prepared by using the procedure given for the preparation of compound **127b**.

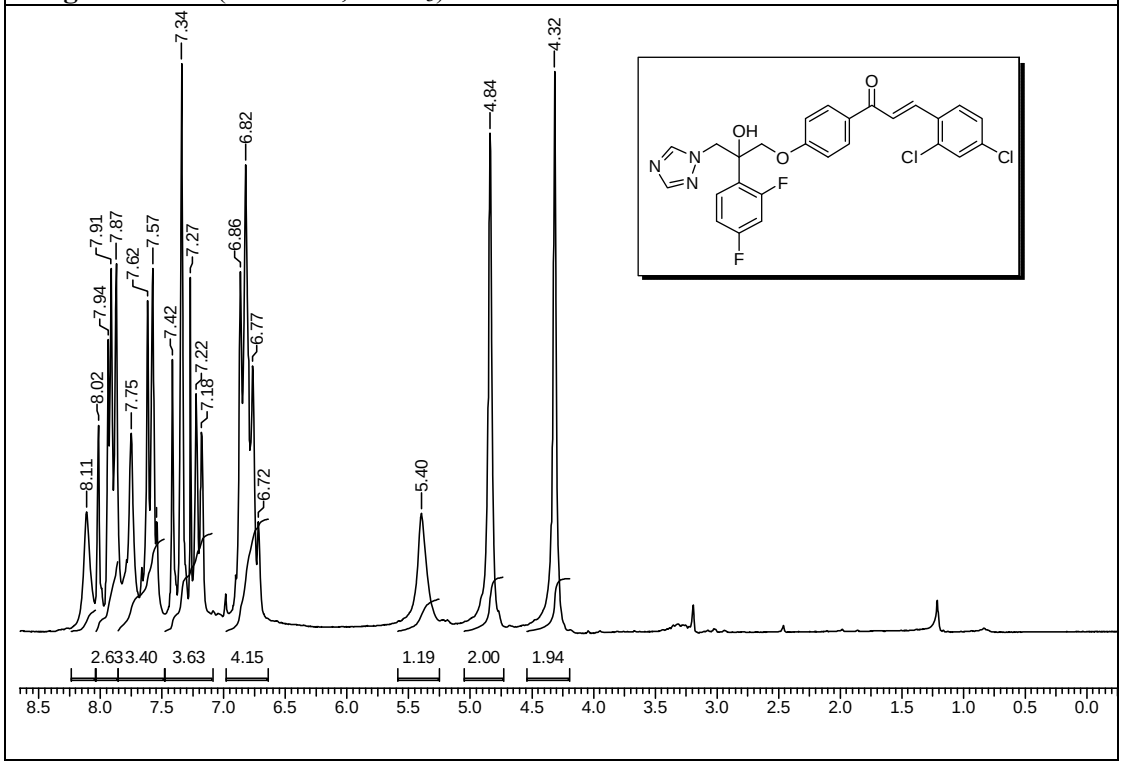
(2*E*,2'*E*)-1,1'-(((2-(2,4-Difluorophenyl)-2-hydroxypropane-1,3-diyl)bis(oxy))bis(4,1-phenylene))bis(3-(4-methoxyphenyl)prop-2-en-1-one) (144)

Nature: Pale yellow fluffy solid; **MP:** 86 ^{0}C; **Yield:** 83.7%; **^{1}H NMR** (200 MHz, $CDCl_3$)**:** δ 3.85 (s, 6H), 4.49-4.60 (m, 4H), 6.82-7.03 (m, 10H), 7.40 (d, *J* = 16 Hz, 2H), 7.59 (d, *J* = 10 Hz, 4H), 7.77 (d, *J* = 16 Hz, 2H), 7.84-7.92 (m, 1H), 8.00 (d, *J* = 8 Hz, 4H); **^{13}C NMR** (100 MHz, $CDCl_3$)**:** δ 55.3 (2C), 71.4 (2C), 74.7, 104.3 (t), 111.6 (d), 114.3 (4C), 114.4 (4C), 119.3 (2C), 123.1 (d), 127.6 (2C), 130.1 (4C), 130.4 (d), 130.6 (4C), 132.0 (2C), 144.1 (2C), 159.5 (dd), 161.5 (2C), 161.8 (2C), 162.9 (dd), 188.6 (2C); **IR** (Chloroform)**:** 1601, 1654, 3422 cm^{-1}; **MS** (ESI) *m*/*z***:** 677.09 (M + 1). **Anal. Calcd. for** $C_{41}H_{34}F_2O_7$**:** C, 72.77; H, 5.06 %. **Found:** C, 72.64; H, 5.17 %.

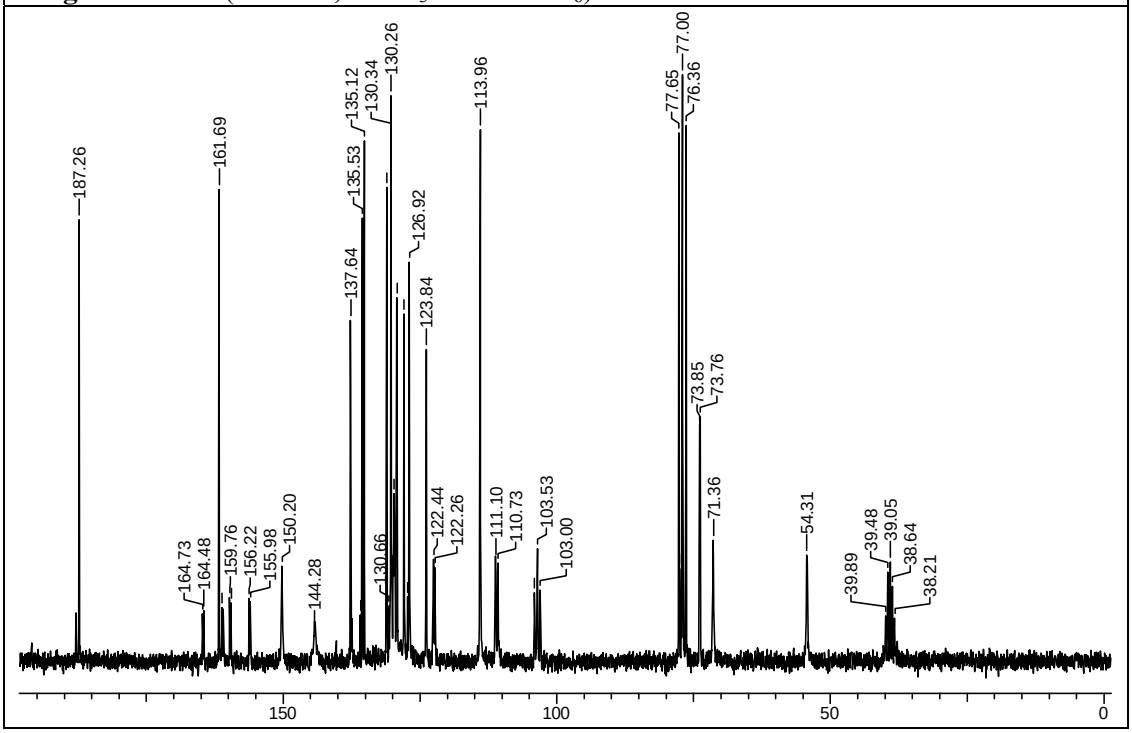


2.1.7. Selected spectra

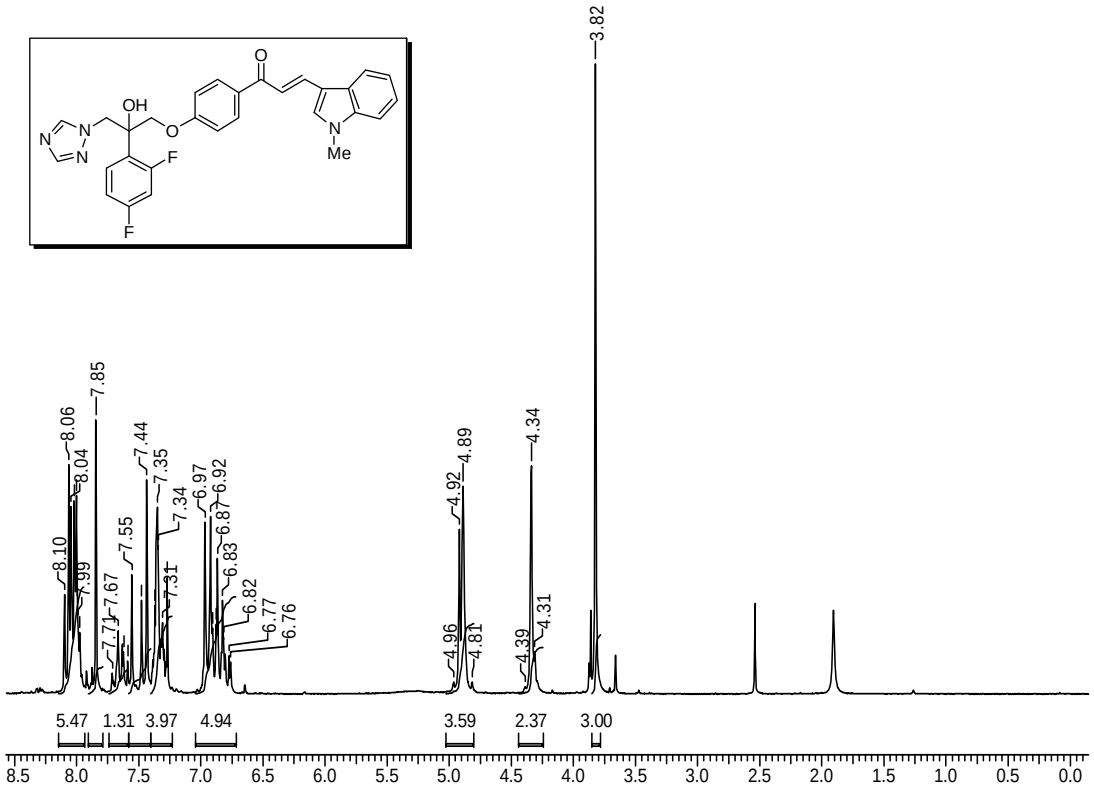
127g: ^{1}H NMR (200 MHz, $CDCl_3$)



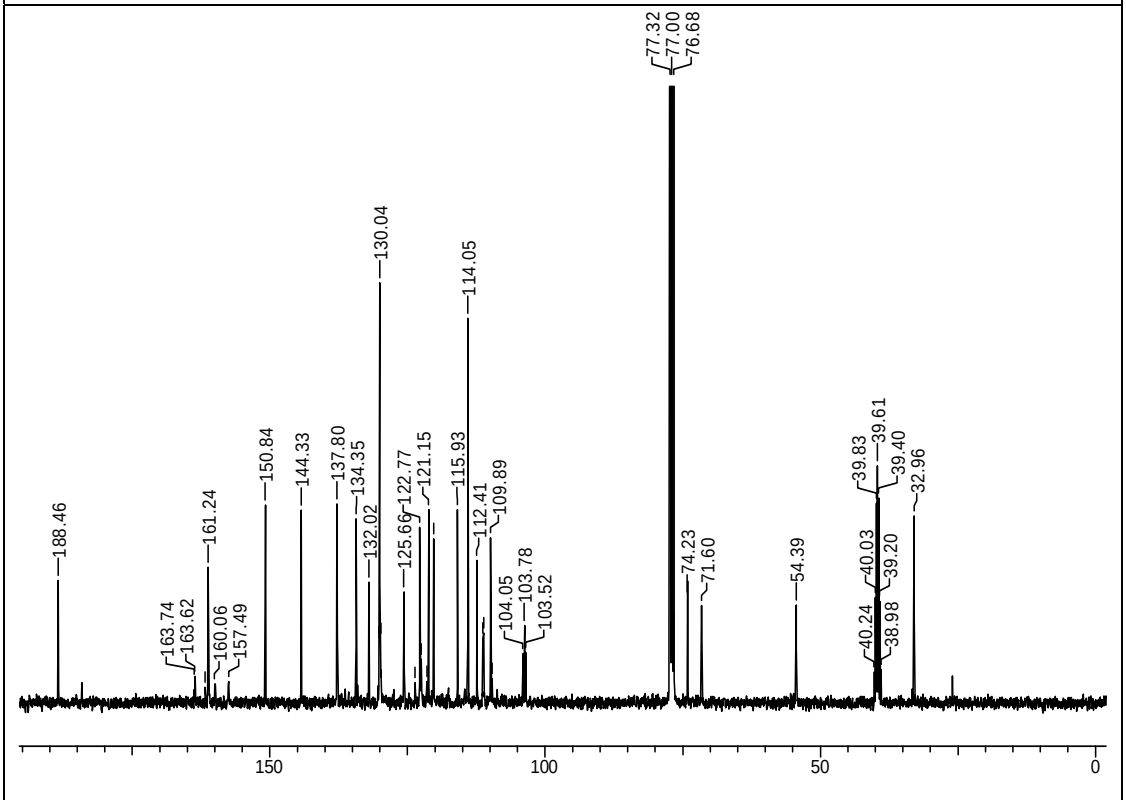
127g: ^{13}C NMR (50 MHz, $CDCl_3$ + DMSO-d_6)



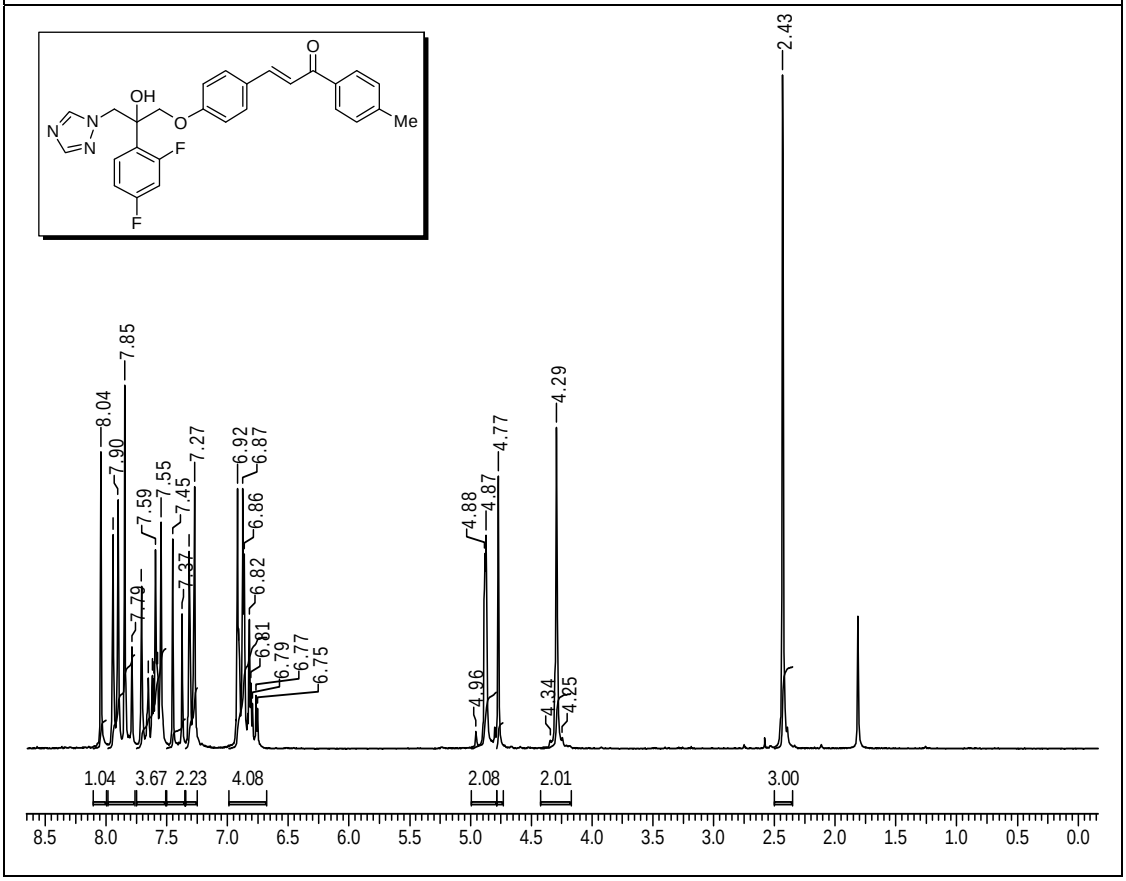
127m: ^{1}H NMR (200 MHz, $CDCl_3$)



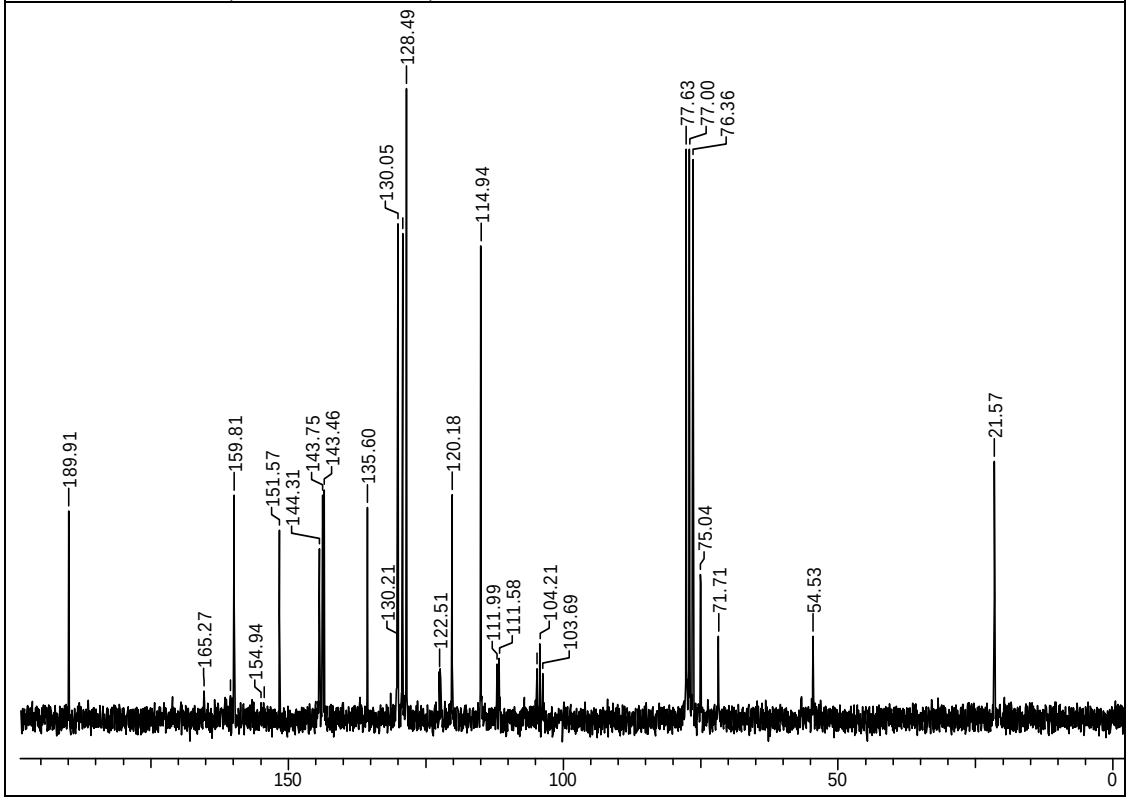
127m: ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6)



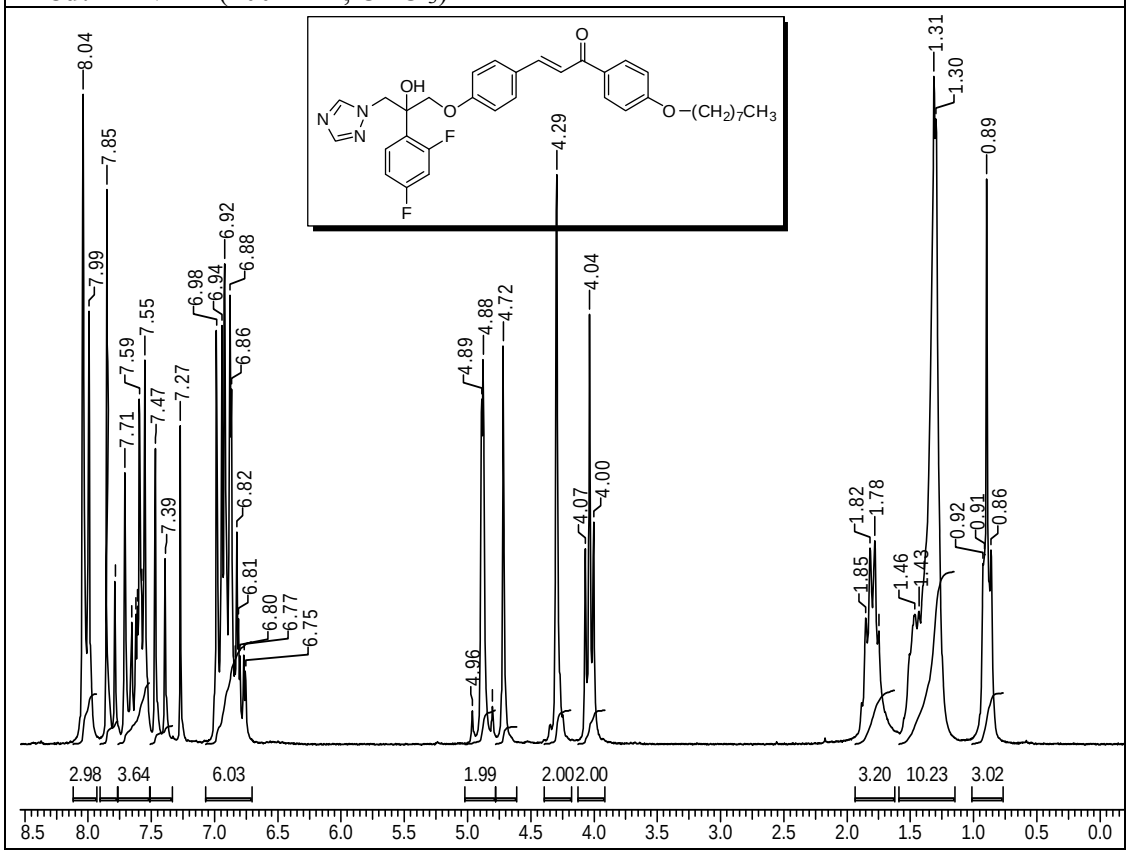
128c: ^{1}H NMR (200 MHz, $CDCl_3$)



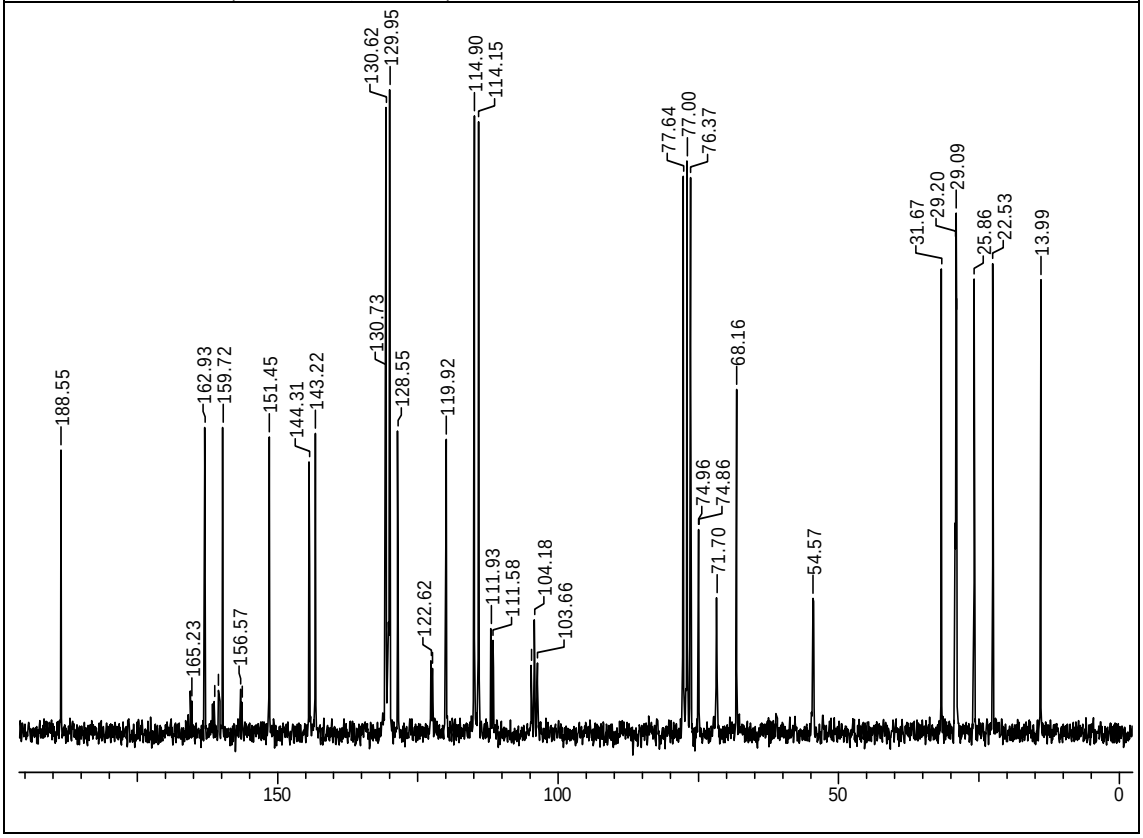
128c: ^{13}C NMR (50 MHz, $CDCl_3$)



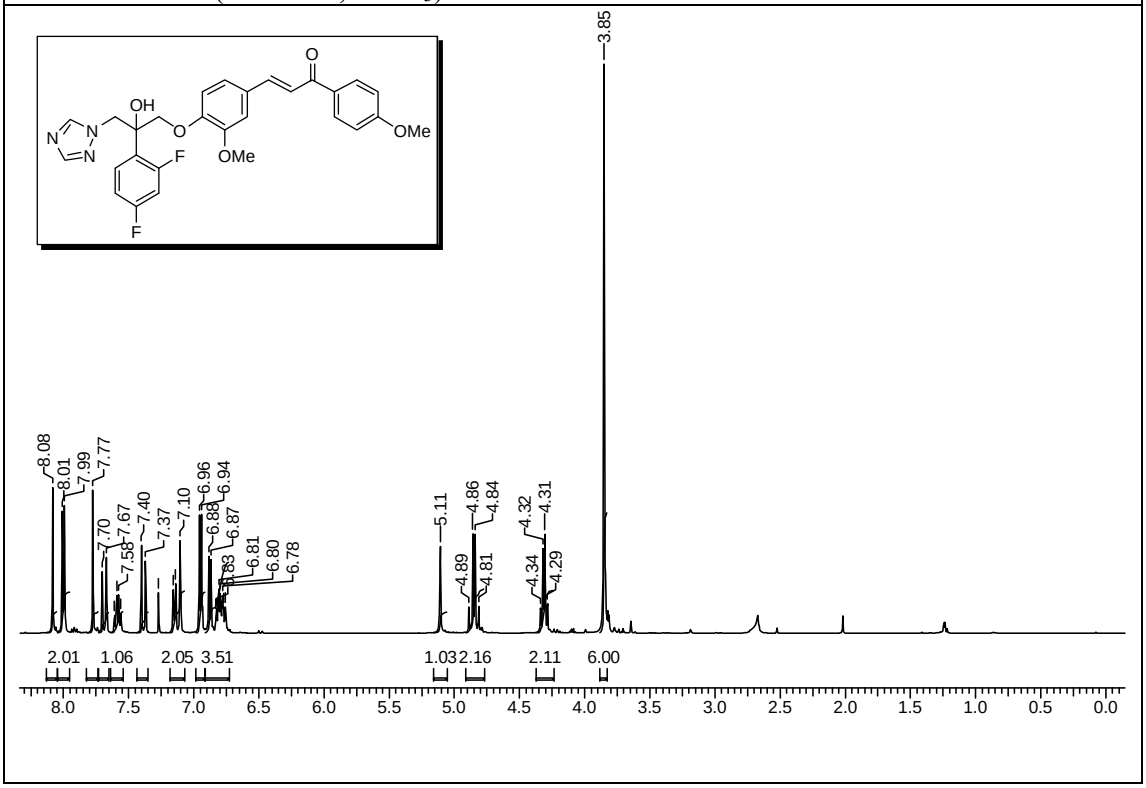
128d: ^{1}H NMR (200 MHz, $CDCl_3$)



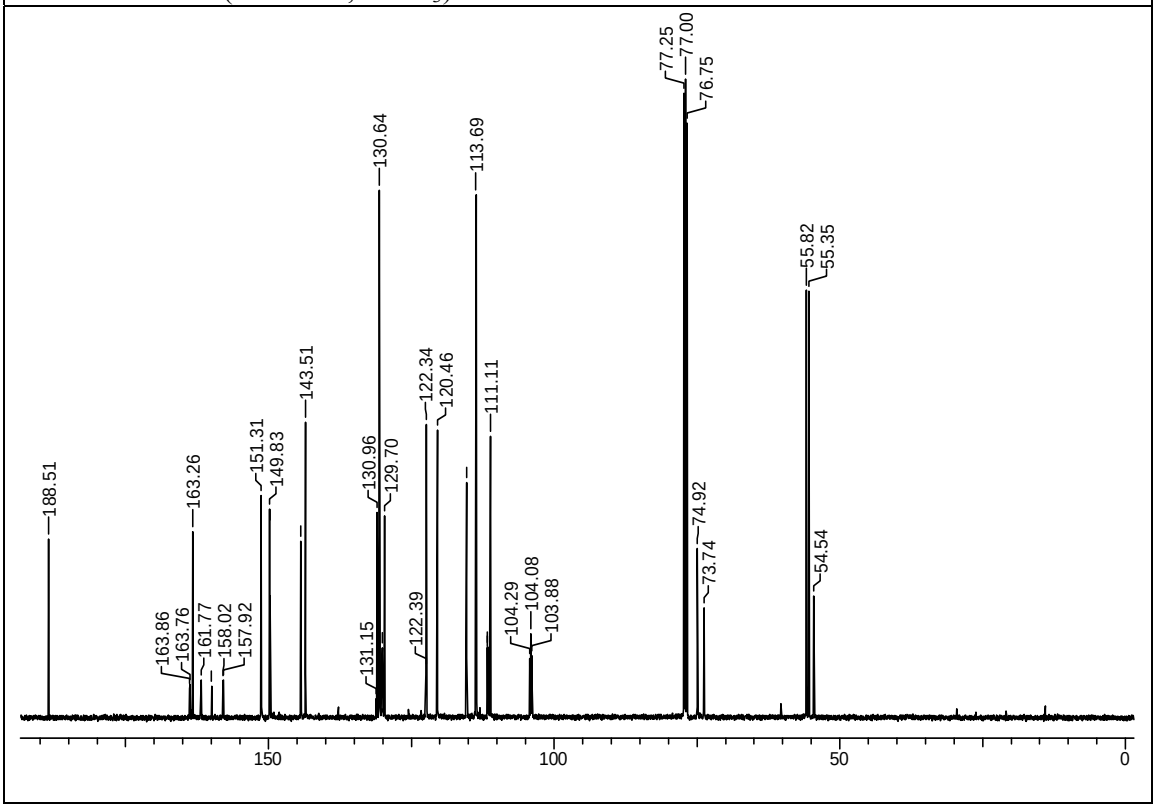
128d: ^{13}C NMR (100 MHz, $CDCl_3$)



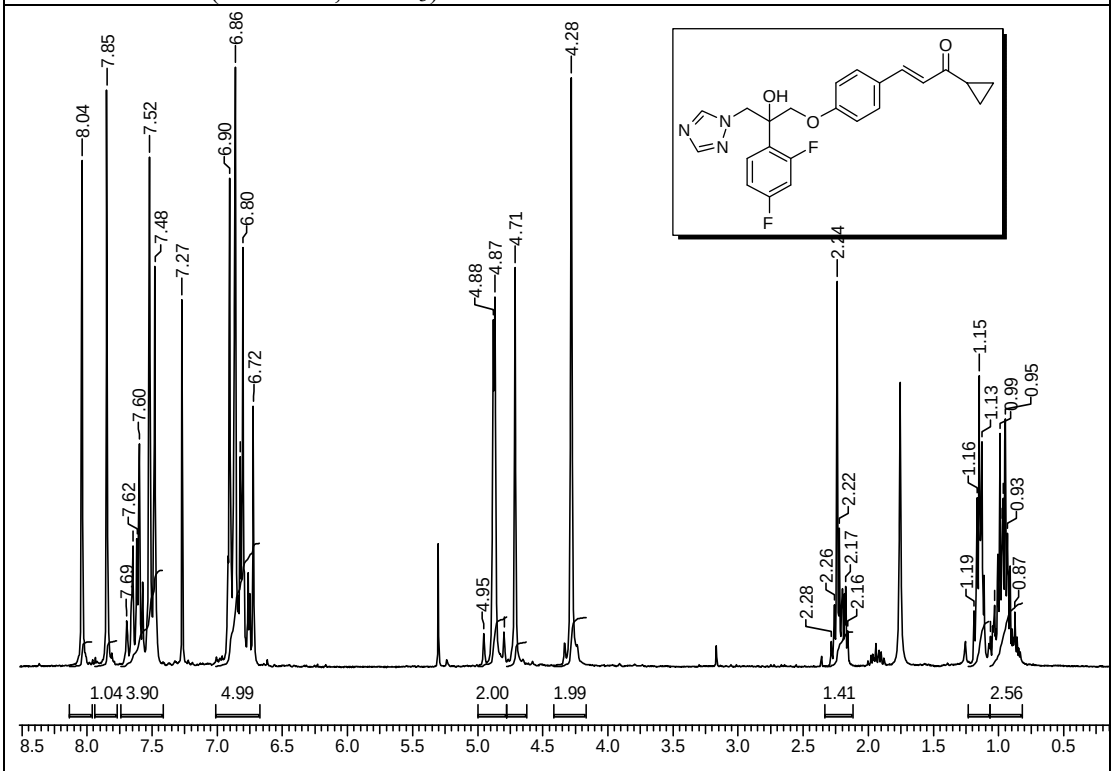
128e: ^{1}H NMR (500 MHz, $CDCl_3$)



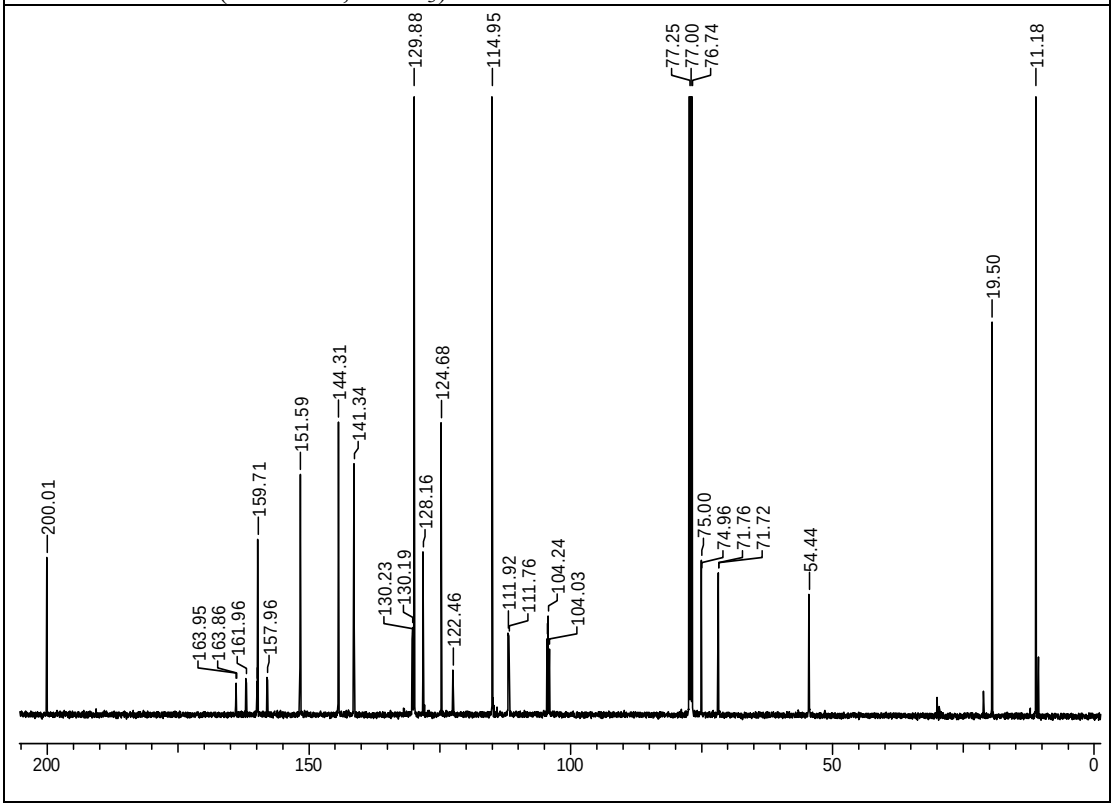
128e: ^{13}C NMR (125 MHz, $CDCl_3$)



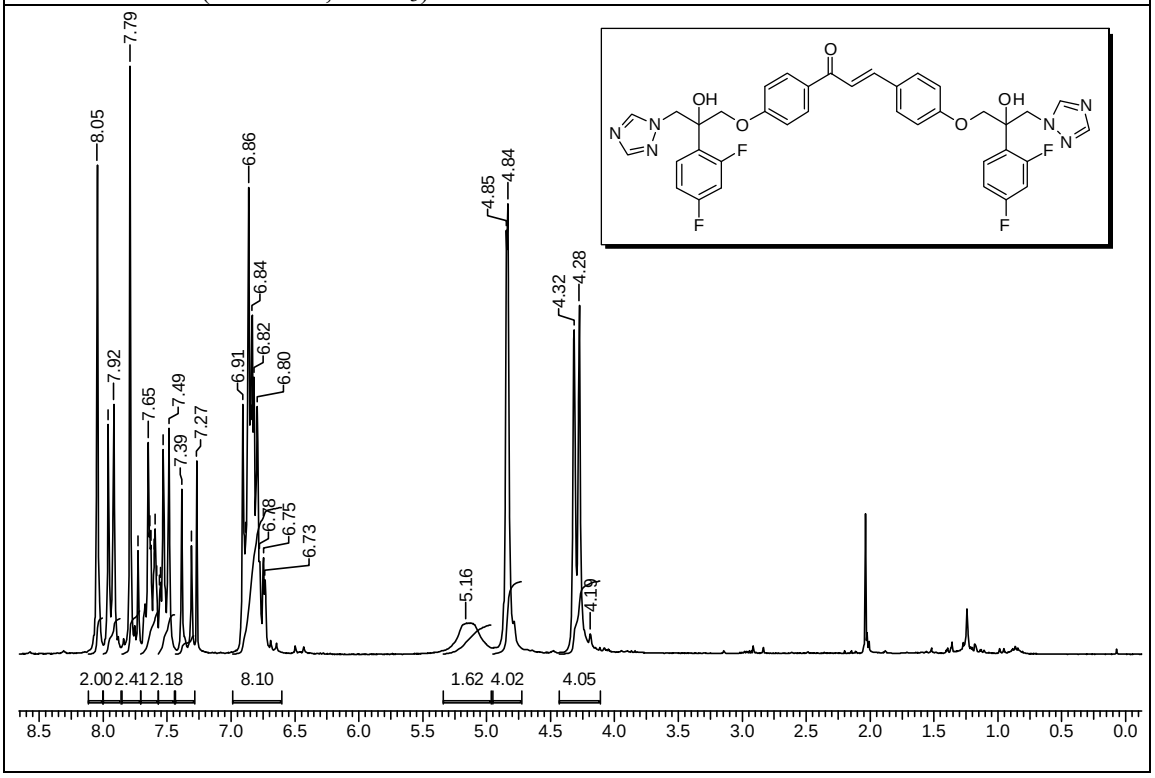
128i: ^{1}H NMR (200 MHz, $CDCl_3$)



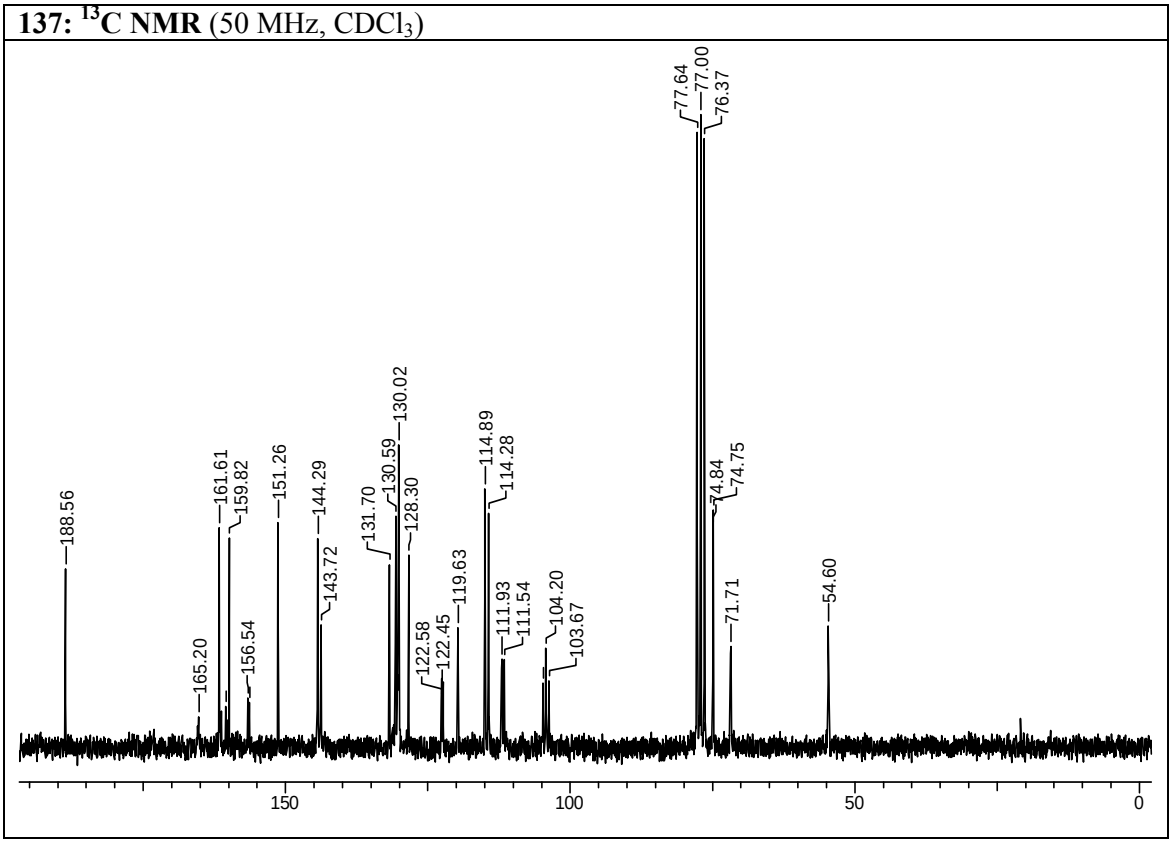
128i: ^{13}C NMR (125 MHz, $CDCl_3$)



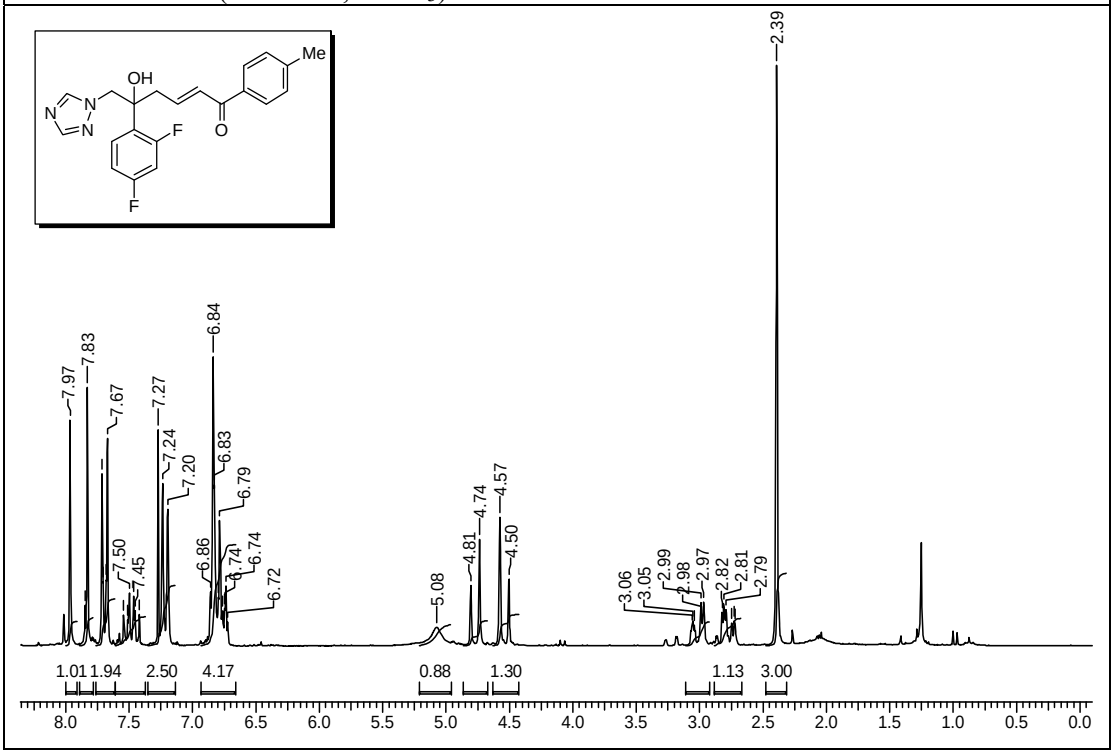
137: ^{1}H NMR (200 MHz, $CDCl_3$)



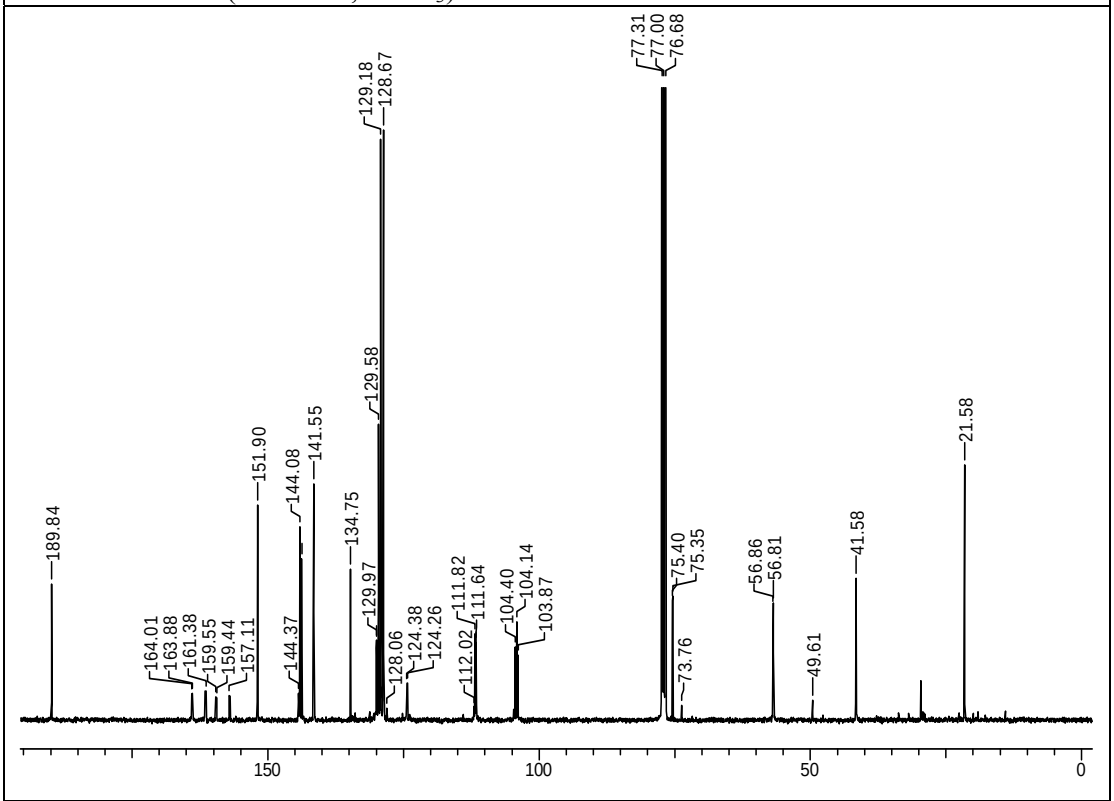
137: ^{13}C NMR (50 MHz, $CDCl_3$)



139b: ^{1}H NMR (200 MHz, $CDCl_3$)



139b: ^{13}C NMR (100 MHz, $CDCl_3$)



2.1.8 References

1. Richardson, K.; Brammer, K. W.; Marriott, M. S.; Troke, P. F. *Antimicrob. Agents Chemother.* **1985**, *27*, 832-835.
2. Kauffman, C. A.; Carver, P. L. *Drugs* **1997**, *53*, 539-549.
3. (a) Giraud, F.; Guillon, R.; Logé, C.; Pagniez, F.; Picot, C.; Le Borgne, M.; Le Pape, P. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1893-1895; (b) Lebouvier, N.; Pagniez, F.; Duflos, M.; Pape, P. L.; Na, Y. M.; Baut, G. L.; Borgne, M. L. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 3686-3689; (c) Zhao, Q.-J.; Hu, H.-G.; Li, Y.-W.; Song, Y.; Cai, L.-Z.; Wu, Q.-Y.; Jiang, Y.-Y. *Chem. Biodivers.* **2007**, *4*, 1472-1479; (d) Katritzky, A. R.; Slavov, S. H.; Dobchev, D. A.; Karelson, M. *Bioorg. Med. Chem.* **2008**, *16*, 7055-7069; (e) Uchida, T.; Somada, A.; Kagoshima, Y.; Konosu, T.; Oida, S. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 6538-6541; (f) Uchida, T.; Kagoshima, Y.; Konosu, T. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 2013-2017; (g) Liu, P.; Zhu, S.; Li, P.; Xie, W.; Jin, Y.; Sun, Q.; Wu, Q.; Sun, P.; Zhang, Y.; Yang, X.; Jiang, Y.; Zhang, D. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 3261-3265; (h) Uchida, T.; Kagoshima,Y.; Konosu, T. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 2013-2017; (i) Borate, H. B.; Maujan, S. R.; Sawargave, S. P.; Chandavarkar, M. A.; Vaiude, S. R.; Joshi, V. A.; Wakharkar, R. D.; Kelkar, R. G.; Chavan S. P.; Kunte, S. S. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 722-725.
4. Bisi, A.; Rampa, A.; Budriesi, R.; Gobbi, S.; Belluti, F.; Ioan, P.; Valoti, E.; Chiarini, A.; Valenti, P. *Bioorg. Med. Chem*. **2003**, *11*, 1353-1361.
5. Morphy, R.; Kay, C.; Rankovic, Z. *Drug Discov. Today* **2004**, *9*, 641-651.
6. Morphy, R.; Rankovic, Z. *J. Med. Chem.* **2005**, *48*, 6523-6543 and references cited therein.
7. Schellenberg, D.; Abdulla, S.; Roper, C. *Curr. Mol. Med.* **2006**, *6*, 253-260.
8. Burgess, S. J.; Selzer, A.; Kelly, J. X.; Smilkstein, M. J.; Riscoe, M.; Peyton, D. H. *J. Med. Chem.* **2006**, *49,* 5623-5625.
9. Walsh, J. J.; Coughlan, D.; Heneghan, N.; Gaynor, C.; Bell, A. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 3599-3602.
10. Rita, C.; Rudi, O.; Lídia, M.; Ana, D.; Jiri, G.; Philip, J.; Francisca, L.; Rui, M.; *Bioorg. Med. Chem*. *Lett.* **2009**, *19*, 3229-3232.
11. Singh, P.; Kaur, M.; Verma, P. *Bioorg. Med. Chem*. *Lett.* **2009**, *19*, 3054-3058.
12. Kengo, O.; Haruaki, I.; Koshi, O.; Hiroyasu, N.; Jun'ichi, K. *Bioorg. Med. Chem*. **2007**, *15*, 3235-3240.

13. Pier, B.; Abdel, Z.; Delia, P.; Francesca, F.; Mojgan, T.; Antonietta, I.; Maria, P.; Maria, C.; Carlota, C.; Romeo R. *ARKIVOK* **2006**, (vii), 20-34.

14. Singh, P.; Kaur, M.; Verma, P. *Bioorg. Med. Chem*. **2006**, *14*, 5061-5071.

15. Gao, P.-H.; Cao, Y.-B.; Xu, Z.; Zhang, J.-D.; Gu, J.; Cao, Y. Y.; Li, R.-Y.; Jiang.; Y.-Y. *Biol. Pharm. Bull.* **2005**, *28,* 1414-1417.

16. Avila, H. P.; Smania, E. F.; Monache, F. D.; Smania, A. *Bioorg. Med. Chem.* **2008**, *16*, 9790-9794.

17. Cheng, J. H.; Hung, C. F.; Yang, S. C.; Wang, J. P.; Won, S. J.; Lin, C. N. *Bioorg. Med. Chem*. **2008**, *16*, 7270-7276.

18. (a) Sortino, M.; Delgado, P.; Juarez, S.; Quiroga, J.; Abonia, R.; Insuasty, B.; Nogueras, M.; Rodero, L.; Garibotto, F. M.; Enriz, R. D.; Zacchino, S. A. *Bioorg. Med. Chem.* **2007**, *15*, 484-494; (b) Lahtchev, K. L.; Batovska, D. I.; Parushev, P.; Ubiyvovk, V. M.; Sibirny, A. A. *Eur. J. Med. Chem.* **2008**, *43*, 2220-2228.

19. Vargas, M. L. Y.; Castelli, M. V.; Kouznetsov, V. V.; Urbina, G. J. M.; Lopez, S. N.; Sortino, M.; Enriz, R. D.; Ribas, J. C.; Zacchino, S. *Bioorg. Med. Chem.* **2003**, *11*, 1531-1550.

20. Lopez, S. N.; Castelli, M. V.; Zacchino, S. A.; Dominguez, J. N.; Lobo, G.; Charris-Charris, J.; Cortes, J. C.; Ribas, J. C.; Devia, C.; Rodriguez, A. M.; Enriz, R. D. *Bioorg. Med. Chem.* **2001**, *8*, 1999-2013.

21. Katsori, A. M.; Hadjipavlou-Litina, D. *Curr. Med. Chem.* **2009**, *16*, 1062-1081.

22. Achanta, G.; Modzelewska, A.; Feng, L.; Khan, S. R.; Huang, P. *Mol. Pharmacol.* **2006**, *70*, 426-433.

23. Modzelewska, A.; Pettit, C.; Achanta, G.; Davidson, N. E.; Huang, P.; Khan, S. R. *Bioorg. Med. Chem.* **2006**, *14*, 3491-3495.

24. Kumar, S. K.; Hager, E.; Pettit, C.; Gurulingappa, H.; Davidson, N. E.; Khan, S. R. *J. Med. Chem.* **2003**, *46*, 2813-2815.

25. Tabata, K.; Motani, K.; Takayanagi, N.; Nishimura, R.; Asami, S.; Kimura, Y.; Ukiya, M.; Hasegawa, D.; Suzuki, T. *Biol. Pharm. Bull.* **2005**, *28*, 1404- 1407.

26. Kimura, Y.; Baba, K. *Int. J. Cancer 2003*, *106*, 429-37.

27. Cheng, Z. J.; Lin, C. N.; Hwang, T. L.; Teng, C. M. *Biochem. Pharmacol.* **2001**, *61*, 939-946.

28. Rojas, J.; Domı´nguez, J. N.; Charris, J. E.; Lobo, G.; Paya´, M.; Ferrandiz, M. L. *Eur. J. Med. Chem.* **2002**, *37*, 699-705.

29. Takahashi, T. T.; Takasuka, N.; Ligo, M.; Baba, M.; Nishino, H.; Tsuda, H.; Okuyama, T. *Cancer Sci.* **2004**, *95*, 448-453.

30. Israf, D. A.; Khaizurin, T. A.; Syhida, A.; Lajis, N. H.; Khozirah, S. *Mol. Immunol.* **2007**, *44*, 673–679.

31. Kim, Y. H.; Kim, J.; Park, H.; Kim, H. P. *Biol. Pharm. Bull.* **2007**, *30*, 1450-1455.

32. Ngameni, B.; Watchueng, J.; Boyom, F. F.; Keumedjio, F.; Ngadjui, B. T.; Gut, J.; Abegaz, B. M.; Rosenthal, P. J. *ARKIVOC* **2007**, (*xiii)*, 116-123.

33. Santos, L.; Curi Pedrosa, R.; Correa, R.; Filho, V. C.; Nunes, R. J.; Yunes, R. A. *Arch. Pharm. Chem. Life Sci.* **2006**, *339*, 541-546.

34. Orallo, F. *Curr. Med. Chem.* **2008**, *15*, 1887-1898.

35. Howitz, K. T.; Bitterman, K. J.; Cohen, H. Y.; Lamming, D. W.; Lavu, S.; Wood, J. G.; Zipkin, R. E.; Chung, P.; Kisielewski, A.; Zhang, L. L.; Scherer, B.; Sinclair, D. A. *Nature* **2003**, *425*, 191-196.

36. Lopez, S.; Castelli, M. V.; Zacchino, S.; Dominguez, J. N.; Lobo, G.; Charris-Charris, J.; Coetrs, J. C. C.; Ribas, J. C.; Devia, C.; Rodrigues, A. M.; Enriz, R. D. *Bioorg. Med. Chem.* **2001**, *9*, 1999-2013.

37. Eisohly, H. N.; Joshi, A. S.; Nimrod, A. C.; Walker, L. A.; Clark, A. M. *Planta Med.* **2001**, *67*, 87-89.

38. Svetaz, L.; Tapia, A.; Lopez, S. N.; Furlan, R. L. E.; Petenatti, E.; Pioli, R; Schmeda-Hirschmann, G.; Zacchino, S. A. *J. Agric. Food Chem.* **2004**, *52*, 3297-3300.

39. Suman, R. S., Malik, M. S.; Kathpal, T. S.; Malik, O. P.; *Indian J. Chem.* **1995**, *34B,* 743-746.

40. Bhakuni, D. S.; Chaturvedi, R. *J. Nat. Prod.* **1984**, *47*, 585-591.

41. Jayasinghe, L.; Balasooriya, B. A. I. S.; Chintha P. W.; Hara, N.; Fujimoto, Y. *Phytochemistry* **2004**, *65*, 1287-1290.

42. Okunade, A. L.; Hufford, D. C.; Clark, A. L.; Lentz, D. *Phytother. Res.* **1997**, *11*, 142-144.

43. Mustafa, K. A.; Kjaergaard, H. G.; Perry, N. B.; Weavers, R. T. *Tetrahedron* **2003**, *59*, 6113-6120.

44. Miles, D. H.; Del Medeiros, J. M. R.; Chittawong, V; Hedin, P. A.; Swithenbank, C.; Lidert, Z. *Phytochemistry* **1991**, *30*, 1131-1132.

45. Bag, S.; Ramar, S.; Degani, M. S. *Med. Chem. Res.* **2009**, *18*, 309-316.

46. Morrow, J. D. *Am. J. Med. Sci. Rev.* **1991**, *302*, 129-132.

47. Ni, L.; Meng, C. Q.; Sikorski, J. A. *Expert Opin. Ther. Pat.* **2004**, *14*, 1669-6991.

48. Dimmock, J. R.; Elias, D. W.; Beazely, M. A.; Kandepu, N. M. *Curr. Med. Chem.* **1999**, *6*, 1125-1149.

49. Boeck, P.; Leal, P. C.; Yunes, R. A.; Fiiho, V. C.; Lopez, S.; Sortino, M.; Escalante, A.; Furlan, R. L. E.; Zacchino, S. *Arch. Pharm. Chem. Life Sci.* **2005**, *338*, 87-92.

50. (a) Tu, H.-Y.; Huang, A-M.; Hour, T.-C.; Yang, S.-C.; Pu, Y.-S.; Lin, C.-N. *Bioorg. Med. Chem. Lett.* **2010**, *18*, 2089-2098; (b) Patil, C. B.; Mahajan, S. K.; Katti, S. A. *J. Pharm. Sci. Res.* **2009,** *1,* 11-22; (c) Won, S.-J.; Liu, C.-T.; Tsao, L.-T.; Weng, J.-R.; Ko, H.-H.; Wang, J.-P.; Lin, C.-N. *Eur. J. Med. Chem.* **2005**, *40*, 103-108; (d) Xia, Y.; Yang, Z.; Xia, P.; Bastow, K. F.; Nakanishi, Y.; Lee, K. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 699-706 and references cited therein.

51. (a) Mo, A.; Zhang, H.; Pan, H. CN 1995-111510, **1995**; CA 131:228724; (b) Antoni, S.; Marcial, M.; Roser, P. *ARKIVOC* **2007**, *(iv)*, 234-250; (c) Lebouvier, N.; Giraud, F.; Corbin, T.; Na, Y. M.; Baut, G. L.; Marchand, P.; Borgne, M. L. *Tetrahedron Lett.* **2006**, *47*, 6479-6483; (d) Tamoto, K.; Tanaka, Y.; Miyauchi, H.; Fujimoto, K.; Ohashi, N. *Bull. Chem. Soc. Jpn.* **1994**, *67*, 1427-1433; (e) Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1962**, *84*, 3782-3783; (f) Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1965**, *87*, 1353-1364; (g) Richardson, K.; Narayanaswami, S. Eur. Pat. Appl. EP0122056, **1984**; (h) Richardson, K.; Gymer, G. E. Eur. Pat. Appl. EP0153803, **1985**.

52. CLSI**:** Reference method for broth dilution antifungal susceptibility testing of yeasts; Approved standard, second edition M27-A2, **2002**.

53. CLSI**:** Reference method for broth dilution antifungal susceptibility testing of filamentous fungi; Approved standard M38-A, **2002**.

54. (a) Li, C. J. *Tetrahedron* **1996**, *52*, 5643-5668; (b) Li, C. J.; Chan, T.-H. *Tetrahedron* **1999**, *55*, 11149-11176; (c) Jõgi, A.; Mäeorg, U. *Molecules* **2001**, *6*, 964-968.

55. (a) Suresh Babu, K.; Li, X.-C.; Jacob, M. R.; Zhang, Q.; Khan, S. I.; Ferreira, D.; Clark, A. M. *J. Med. Chem.* **2006,** *49,* 7877-7886; (b) Leung, P. S.-W.; Teng, Y.; Toy, P. H. *Synlett* **2010**, 1997-2001.

56. (a) Pugia, M. J.; Knudsen, B. E.; Cason, C. V.; Bartsch, R. A. *J. Org. Chem*. **1987**, *52*, 536-541; (b) Tanyeli, C.; Demir, A. S.; Akhmedov, I. M.; Özgül, E.; Kandemir, C. G. *Synth. Commun*. **1996**, *26*, 2967-2970; (c) Yosohara, Y.; Miyamoto, K.; Kizaki, N.; Hasegawa, J.; Ohashi, T. *Tetrahedron Lett*. **2001**, *42*, 3331-3333.

57. (a) Saksena, A. K.; Girijavallabhan, V. M.; Lovey, R. G.; Pike, R. E.; Desai, J. A.; Ganguly, A. K.; Hare, R. S.; Loebenberg, D.; Cacciapuoti, A.; Parmegiani, R. M. *Bioorg. Med. Chem. Lett.* **1994**, *16*, 2023-2028; (b) Murakami, K.; Mochizuki, H. Eur. Pat. Appl. EP0472392A2, **1991**.

58. Yoshihiko, Y.; Kenji, M.; Noriyuku, K.; Junzo, H.; Takehisa, O. *Tetrahedron Lett.* **2001**, *42*, 3331-3333.

Chapter 2: Section II

Hybrid fluconazole analogues containing furanones as novel antifungal agents

Chapter 2: Section II

Hybrid fluconazole analogues containing furanones as novel antifungal agents

2.2.1 Abstract

A number of hybrid fluconazole analogues containing substituted furanones were designed and synthesized. The new chemical entities thus synthesized were tested for their potential as antifungal agents against various fungal strains and it was observed that some of the compounds were potent inhibitors of *C. albicans*. The structure-activity relationship for these compounds is discussed. The enantiomers of the substituted furanone-containing fluconazole analogues were synthesized by utilizing Sharpless epoxidation reaction. The synthetic strategies used in the present work have potential to prepare a large number of compounds for further refinement of structures to obtain molecules suitable for development as antifungal drugs.

2.2.2 Introduction

As described in the first section of this chapter, hybrid molecules having pharmacophores/structural features of two molecules of different classes may have potential to exhibit superior activity than the parent molecules. Most of the racemic hybrid molecules synthesized in the first section of this chapter (containing pharmacophores of fluconazole combined with chalcone) showed 4-8 fold enhanced antifungal activity than fluconazole against different fungal strains. Some of the hybrid molecules also exhibited good antifungal activity against the fluconazole-resistant fungal strains like *C. glabrata*. Further, the resolution of racemic molecules to get the enantiomers and screening of the individual enantiomers for antifungal activity showed that *R* enantiomers of all the screened molecules of this class exhibited 8 to 16 fold more antifungal activity than fluconazole. These results prompted us to synthesize the novel hybrid fluconazole analogues containing various substituted furanones as a replacing unit in place of one of the triazole rings in fluconazole.

2.2.3 Review of literature

Furanone: biologically important lead

Functionalized furanones[1] are important subunit present in a large variety of natural products and biologically active compounds such as alkaloids[2], lignan lactones,[3] sex attractant insect pheromones[4] *etc*. Many of these compounds exhibit a variety of biological properties including antifungal[5], anticancer[6], antibacterial[7] *etc* and some of them act as antibiotics[8], cyclooxygenage inhibitors[9] *etc*. Because of their unique structural features and wide range of biological activities, furanones have attracted

attention of organic as well as medicinal chemists. Some of the examples of naturally occurring as well as pharmaceutically relevant furanones are shown in Figure 1.

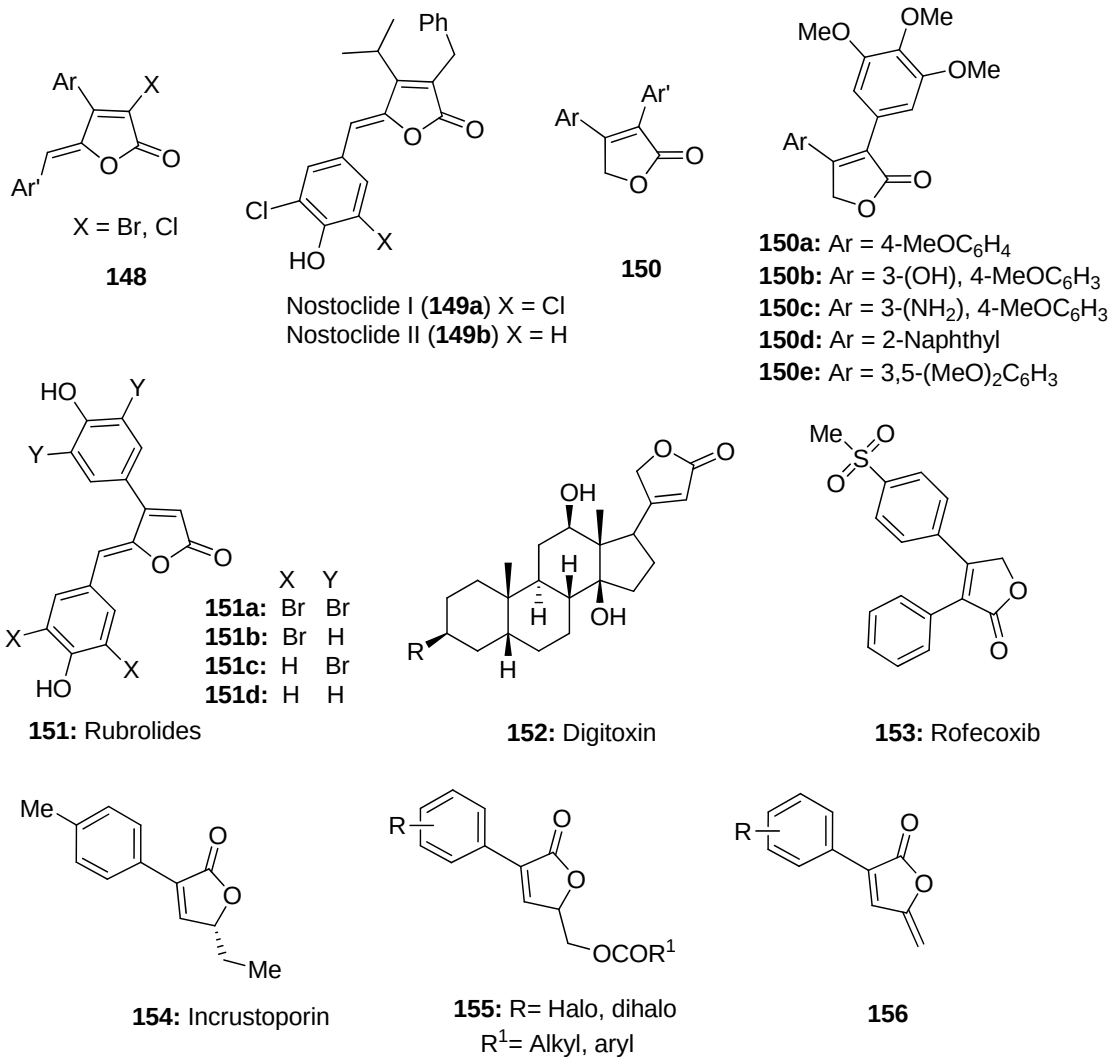


Figure 1. Examples of naturally occurring and pharmaceutically relevant furanones.

2(5*H*)-Furanone derivatives include 3,4,5-trisubstituted compounds, such as natural and unnatural (Z)-4-aryl-5-[1-(aryl)methylidene]-3-halo-2(5*H*)-furanones **148**[10-13] and naturally-occurring nostoclides I (**149a**) and II (**149b**)[14], that exhibit cytotoxicity against human cancer cell lines. 3,4-Diaryl-2(5*H*)-furanones **150** have also been reported as cytotoxic agents.[13,15] Thus, compounds **150a-d** have been found to have significant cytotoxic activities against A549, SK-MEL-2 (skin melanoma) and MCF-7 (Michigan Cancer Foundation-7) cell lines[15] and compounds **150d** and **150e**, which were tested in the *in vitro* human disease-oriented tumor cell lines, were found to exhibit potent cytotoxicity, especially against human leukemia cell lines. Rubrolides **151**[16] were also

found to exhibit significant cytotoxicities against human cancer cell lines. Digitoxin (**152**)[17] and rofecoxib (**153**)[18] are used mainly as the cardiac glycoside and nonsteroidal anti-inflammatory drugs respectively. Zapf *et al.* reported[5a] the isolation of an interesting fungal metabolite from the family of butenolides, incrustoporin **154**. The incrustoporin (**154**) was found to possess activity against a wide array of phytopathogenic fungi as well as some cytotoxic activity[5a]. Pour and coworkers reported[5b-d] various analogues **155** and **156** based on the structural features of incrustoporin with good antifungal activity against different fungal strains. Apart from this, there are numerous reports describing isolation, structure determination, biological activity and synthesis of various furanones. In the present work efforts were directed towards the synthesis of new antifungal agents wherein a number of substituted furanone-containing hybrid fluconazole analogues were designed and synthesized.

2.2.4 Present work

2.2.4.1 Objective

In the first section of this chapter, efforts were made to develop hybrid antifungal agents and a series of hybrid fluconazole analogues were designed and synthesized wherein one of the triazole moieties in fluconazole was replaced with various substituted chalcone moieties. The new chemical entities thus synthesized were screened against various strains of fungi and it was observed that most of the compounds were potent inhibitors of *Candida* strains. Exploring the chemistry used for the synthesis, and extending the utilization of the molecules for further development, we thought to synthesize the new hybrid fluconazole analogues restructured from the fluconazole and substituted furanones. As mentioned before, the furanones are known to exhibit different biological activities. The natural product incrustoporin **(154)** has very good antifungal activity against different fungal strains and there are a number of reports[5b-d] describing syntheses and structure-activity relationship study of various furanones **155** and **156** as antifungal agents. A recent publication[19] by Pour *et al.* describing antifungal activity of 5-methylene-3-aryl-2,5-dihydrofuran-2-ones **156** encouraged us to synthesize hybrids between fluconazole and furanone moieties. Furthermore, it is known in literature that structural features of molecules from two different classes having a particular biological activity can be combined to generate hybrid molecules with increase in that particular biological activity.[20,21] Accordingly, in the present work efforts were directed towards the synthesis of new antifungal agents wherein a series of substituted furanone-containing

hybrid fluconazole analogues depicted by general formulae **157**, **158** and **159** (Figure 2) were designed and synthesized.

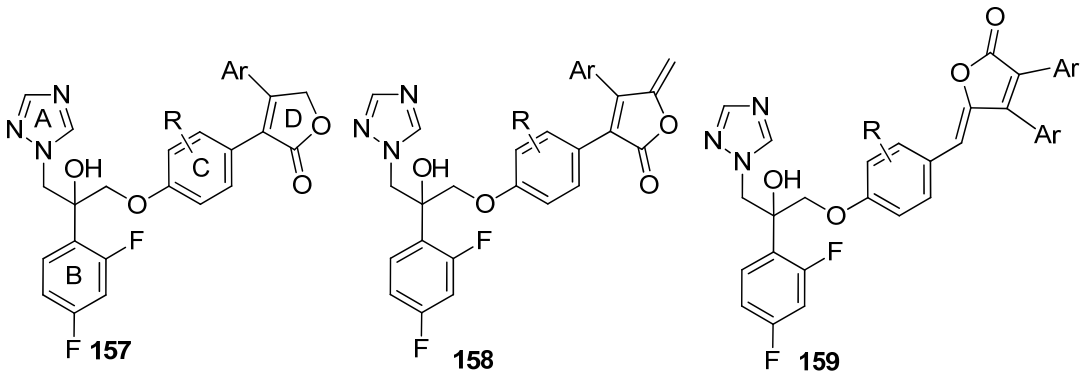


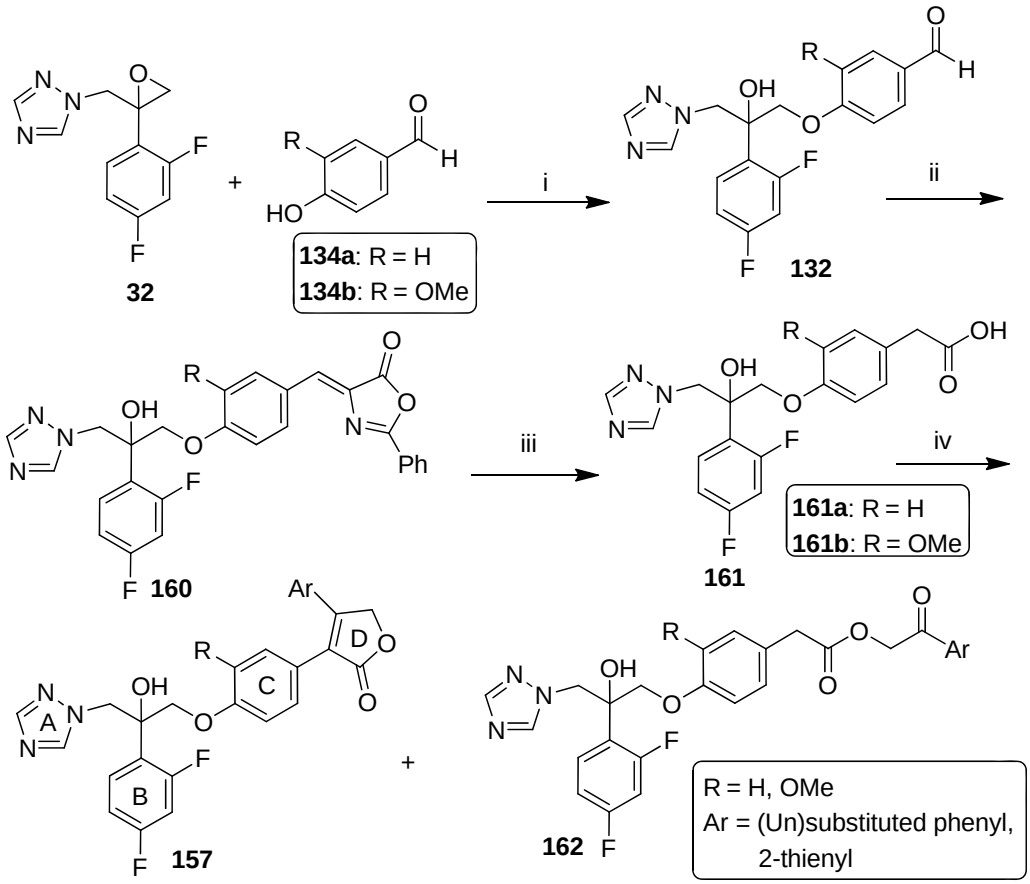
Figure 2. Structures of hybrid fluconazole analogues **157**, **158** and **159.**

In order to seek new triazole antifungal agents, efforts were directed towards replacement of one of the triazole moieties present in fluconazole with various substituted furanones to make a number of compounds available for biological activity. First of all we focused our attention on the synthesis of target molecule **157** wherein one of the triazoles from the fluconazole molecule was replaced with substituted furanone. The significant results obtained in case of molecules represented by general structure **157** made us to undertake synthesis of compounds with general structures **158** and **159** wherein newly synthesized molecules **157** were modified further. Furthermore, efforts were also directed towards the synthesis of enantiopure compounds to study the influence of absolute configuration on antifungal activity. The structure-activity relationship study for this class of compounds is also presented in this chapter.

2.2.4.2 Results and discussion

The synthetic sequence used for preparation of hybrid molecules **157** is shown in Scheme 1. Thus, the known epoxide **32** (Synthesis of epoxide **32**[22] described in Chapter 1, Scheme 6**)** was reacted with 4-hydroxybenzaldehydes **134** to afford the fluconazole analogues **132** which upon reaction[23a] with hippuric acid in presence of acetic anhydride and sodium acetate provided the azlactones **160**. The substituted phenylacetic acids **161** were obtained in 30-35% by subjecting the azlactones **160** to heating with sodium hydroxide followed by reaction with hydrogen peroxide in presence of sodium hydroxide at room temperature[23a]. The reaction[24] of phenylacetic acids **161** with suitable chloroketones in presence of potassium carbonate afforded the desired hybrid molecules **157**. It was observed that when less than 4 equivalents of potassium carbonate was used,

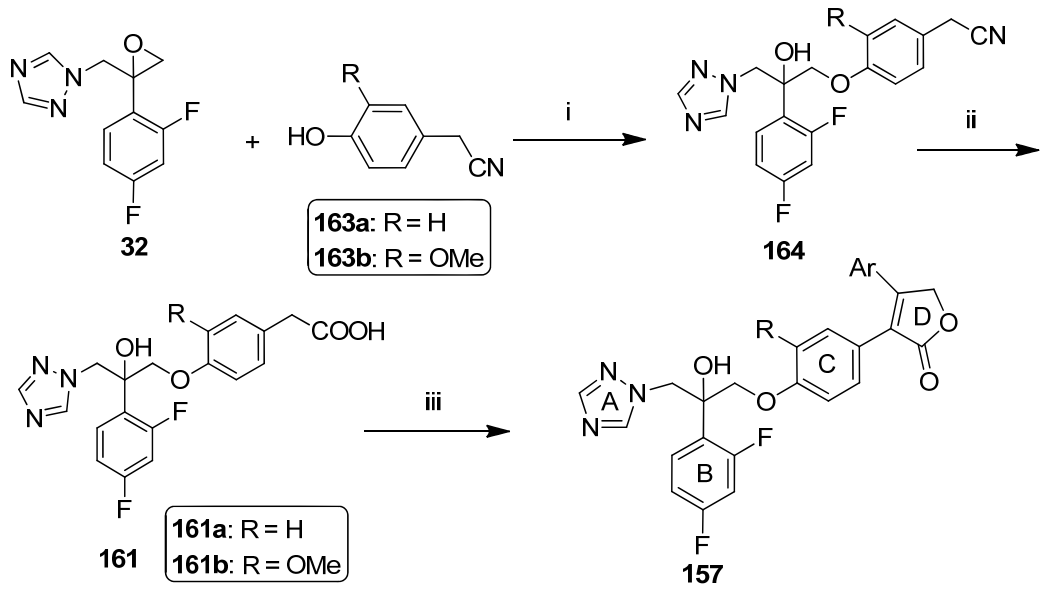
the desired product **157** was obtained along with the intermediate ester **162** in minor amount (15-20%) while use of 5-6 equivalents of potassium carbonate afforded the desired product **157** in excellent yields as shown in Scheme 1. Four successive doublets, each for one proton in the range of δ 4.04-4.98 with coupling constant in the range of J = 10-14 Hz in ^{1}H NMR spectrum, assigned to two methylene groups adjacent to carbon bearing tertiary hydroxyl group, indicated the formation of product. Furthermore, one singlet in the region of δ 5.10-5.20 for furanone methylene protons in ^{1}H NMR spectrum and C=O band in IR spectrum in the range of 1745 to 1755 cm^{-1} confirmed the formation of furanone products **157**. ^{13}C NMR and mass spectra of the products supported the assigned structures.



157a: R= H, Ar = phenyl
157b: R = H, Ar = 4-methoxyphenyl
157c: R = H, Ar = 4-methylphenyl
157d: R = H, Ar = 4-fluorophenyl
157e: R = H, Ar = 2,4-difluorophenyl
157f: R = H, Ar = 4-bromophenyl
157g: R = OMe, Ar = 4-fluorophenyl
157h: R = OMe, Ar = 4-bromophenyl
157i: R = OMe, Ar = 2,4-difluorophenyl
157j: R = H, Ar = 2-thienyl

Scheme 1. Reagents and conditions: i) K_2CO_3, TBAB, EtOAc, 80 ^{0}C, 12 h, 64-73% ii) Hippuric acid, Ac_2O, NaOAc, 80 ^{0}C, 2 h, 90-95% iii) a) Aq. NaOH, 85 ^{0}C; b) H_2O_2, aq. NaOH, rt, 15 h, 30-35% iv) $ArCOCH_2Cl$, K_2CO_3, MeCN, reflux, 1-6 h, 65-75%.

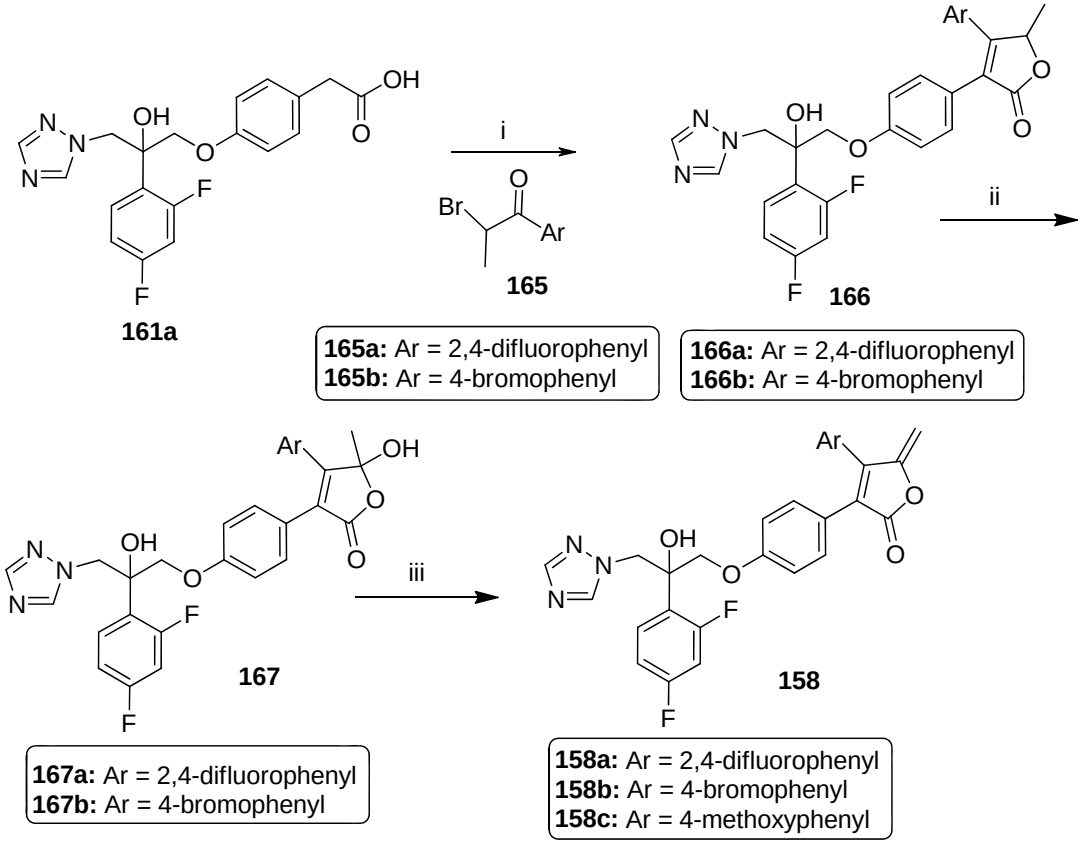
So as to achieve the synthesis of target molecule 1**57,** synthesis of intermediate compound **161** was important but the synthesis of intermediate compound **161** was lengthy and the yield was very low (30-35%) for the step involving conversion of azlactone **160** into the desired phenylacetic acid **161** shown in Scheme 1. In order to synthesize the compounds **161** in short route with good yields, we planned to utilize alternate route. Accordingly, the epoxide **32** was reacted with 4-hydroxyphenylacetonitrile **163** in presence of potassium carbonate in ethyl acetate at reflux temperature to afford the fluconazole analogues **164** in 85-90% of yield. The phenyl acetonitriles **164** were then hydrolyzed by using 30% sulphuric acid at 80-100 ^{0}C to provide the intermediate phenylacetic acids **161** in 80-88% of yield as shown in Scheme 2. The reaction[24] of phenylacetic acids **161** with suitable chloroketones in presence of excess potassium carbonate in acetonitrile afforded the desired hybrid molecules 1**57** in good yields (Scheme 2).



Scheme 2. Reagents and conditions: i) K_2CO_3, TBAB, EtOAc, 80 ^{0}C, 12 h, 85-90% ii) 30% H_2SO_4, 80-100 ^{0}C, 10-12 h, 80-88% iii) $ArCOCH_2Cl$, K_2CO_3, MeCN, reflux, 1-6 h, 65-75%.

The successful synthesis of hybrid molecules **157** and the significant antifungal activity exhibited by compounds with general structure **156**[5] with exocyclic double bond prompted us to synthesize the hybrid molecules **158** having exocyclic double bonds

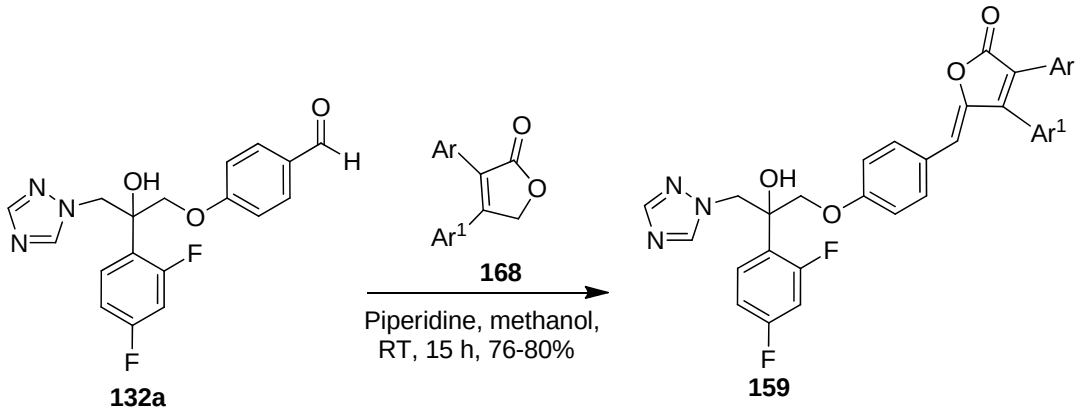
employing the synthetic strategy shown in Scheme 3. The phenylacetic acids **161** were reacted with suitable bromoketones **165** in presence of potassium carbonate to afford the fluconazole analogues **166**, which were then subjected to air oxidation[24a] using 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in acetonitrile at room temperature to provide the hydroxy lactones **167**. The hydroxy lactones **167** on dehydration in presence *p*-toluenesulfonic acid (PTSA) in toluene afforded the desired fluconazole analogues **158** in very good yield. Evidence for the formation of compound **158** was provided by the ^{1}H NMR wherein two doublets each for one proton in the region of δ 4.90-5.30 were seen for exocyclic double bond. Furthermore, ^{13}C NMR, IR and mass spectra confirmed the structures of furanone products **158**.



Scheme 3. Reagents and conditions: i) K_2CO_3, MeCN, 80 ^{0}C; 6 h, 60-65% ii) DBU, MeCN, air, rt, 2 h, 65-70% iii) *P*-TSA, toluene, reflux, 1-6 h, 50-57%.

The compound **158a** was found to decompose in a few days at room temperature. The other compounds from this class (**158b** and **158c**) also decomposed slowly at room temperature. In order to stabilize these compounds and to make available for the screening of antifungal activity, we planned to put a substituent on the exocyclic double bond of these compounds **158**. The synthetic strategy employed for the preparation of the

fluconazole analogues **159** containing trisubstituted furanones is shown in Scheme 4. The reaction[25] of aldehyde **132** (Scheme 1) with furanones **168** (prepared from phenylacetic acids and chloroketones) in methanol in presence of piperidine at room temperature afforded the desired fluconazole analogues **159**. These compounds were found to be stable to evaluate for antifungal activity.



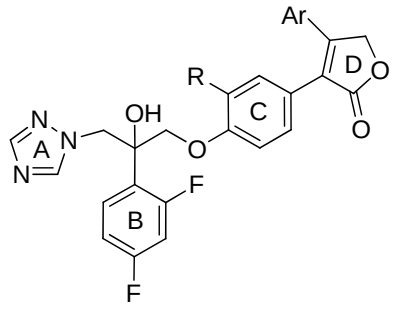
	Ar	Ar^1
159a:	4-chlorophenyl	2,4-difluorophenyl
159b:	3,4-dichlorophenyl	2,4-difluorophenyl
159c:	4-methoxyphenyl	4-bromophenyl

Scheme 4. Synthesis of fluconazole analogues **159**.

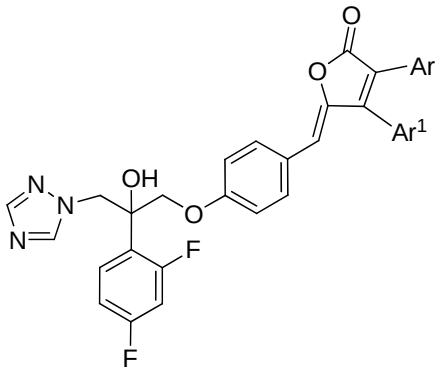
Using above synthetic strategy, a number of compounds were synthesized. All the compounds synthesized were fully characterized by ^{1}H NMR, ^{13}C NMR, IR and mass spectroscopic methods and showed satisfactory spectral data as described in the experimental section.

Antifungal evaluation

All the newly synthesized hybrid compounds **157** and **159** were tested for antifungal activity against various fungi including *Candida albicans*, *Aspergillus niger, Fusarium proliferatum etc* at FDC Ltd., Mumbai as described in Chapter 1. The activity parameters are depicted in Table 1 as MIC_{50} values.



157



159

Table 1. MIC obtained by broth micro-dilution method

Sr. no.	Comp. no.	Structure	Activity against organisms (MIC_{50} in µg/ml)							
			Ca 01	**Cg 01**	**Ck 01**	**Ct 01**	**Cn 01**	**An 01**	**Afm01**	**Fp 01**
	FLU		**0.25**	1	32	1	2	>128	>128	>128
	AMB		**0.25**	**0.25**	**0.5**	**0.5**	**0.5**	**0.25**	**0.5**	2
1	**157a**	Ar = phenyl, R = H	**0.5**	**0.5**	>4	**2**	>4	>4	>4	>4
2	**157b**	Ar = 4-methoxyphenyl, R = H	**1**	**1**	>8	4	**2**	>8	>8	>8
3	**157c**	Ar = 4-methylphenyl, R = H	**0.5**	**1**	>4	**2**	**2**	>4	>4	>4
4	**157d**	Ar = 4-fluorophenyl, R = H	**0.25**	**0.5**	8	**1**	**1**	>8	>8	>8
5	**157e**	Ar = 2,4-difluorophenyl, R = H	**0.5**	**0.5**	8	**2**	**2**	>8	>8	>8
6	**157f**	Ar = 4-bromophenyl, R = H	**0.5**	**2**	8	4	**1**	>8	>8	>8
7	**157g**	Ar = 4-fluorophenyl, R = OMe	**0.5**	**0.5**	16	**2**	**2**	>8	>8	>8
8	**157h**	Ar = 4-bromophenyl, R = OMe	**1**	**2**	>4	4	8	>4	>4	>4
9	**157i**	Ar = 2,4-difluorophenyl, R = OMe	**1**	**1**	>8	>8	>8	>8	>8	>8

10	**157j**	Ar = 2-thienyl, R = H	**0.5**	**0.5**	>8	**2**	>8	>8	>8	>8
11	**159a**	Ar = 4-chlorophenyl, Ar^1 = 2,4-difluorophenyl	>4	>4	>4	>4	>4	>4	>4	>4
12	**159b**	Ar = 3,4-dichlorophenyl, Ar^1 = 2,4-difluorophenyl	>4	>4	>4	>4	>4	>4	>4	>4
13	**159c**	Ar = 4-methoxyphenyl, Ar^1 = 4-bromophenyl	>2	>2	>2	>2	>2	>2	>2	>2

*** Ca01**: *C. albicans* ATCC 24433, **Cg01**: *C. glabrata* ATCC 90030, **Ck01**: *C. krusei* ATCC 6258, **Ct01**: *C. tropicalis* ATCC 750, **Cn01**: *C. neoformans* ATCC 34664, **An01**: *A. niger* ATCC 16404, **Afm01**: *A. fumigatus* ATCC 46645, **Fp01**: *F. proliferatum* ATCC 10052

The activity data indicated following points regarding the structure-activity relationship of the compounds studied in the present section of this chapter.

1. The hybrid molecules with general structure **157** exhibited very good antifungal activity against *C. albicans* ATCC 24433 and *C. glabrata* ATCC 90030 and significant antifungal activity against *C. tropicalis* ATCC 750 and *C. neoformans* ATCC 34664.

2. The introduction of methoxy group on the aromatic ring C adjacent to fluconazole pharmacophores in the molecules with general structure **157** decreased the antifungal activity (e.g. **157d** v/s **157g**, **157e** v/s **157i** and **157f** v/s **157h**).

3. The substituents on the phenyl ring at 4-position of the furanone ring D in compounds **157** also affected the antifungal activity to some extent. The 4-fluoro or 2,4-difluoro groups on this phenyl ring were tolerated and the resultant compounds exhibited antifungal activity similar to the parent compound **157a** (e.g. **157a** v/s **157d** or **157a** v/s **157e**) while the 4-methoxy, 4-methyl or 4-bromo substituent reduced the antifungal activity slightly (e.g. **157a** v/s **157b**, **157a** v/s **157c**, **157a** v/s **157f**).

4. The replacement of phenyl ring at 4-position of the furanone ring D in **154** with a thiophene ring did not have any effect on antifungal activity showing that the phenyl and thienyl moieties are bioisosteric (e.g. **157a** v/s **157j**).

5. The fluconazole analogues with general structure **159** did not exhibit any antifungal activity (e.g. **159a-c**).

6. None of the molecules prepared in the present work exhibited antifungal activity against *C. krusei* ATCC 6258, *A. niger* ATCC 16404, *A. fumigatus* ATCC 46645 and *F. proliferatum* ATCC 10052.

Apart from the above compounds (**157, 158** and **159**) synthesized, which were available for the structure activity relationship (SAR) study as described above, we targeted towards the synthesis of fluconazole analogues containing azlactone **160** as well as those containing 2-thioxothiazolidin-4-one moieties **170**. It is known in literature[23b] that compounds having azlactone moiety exhibit antifungal activity. It was therefore appropriate to synthesize a number of fluconazole analogues **160** containing azlactone moieties (Scheme 1) and screen them for antifungal activity. Accordingly, the azlactones **160a-d** (Figure 3) were synthesized by synthetic sequence elucidated for **160** in Scheme 1, by employing required substituted benzaldehyde *i.e.* 4-hydroxybenzaldehyde, 4-hydroxy-3-methoxybenzaldehyde, 3,5-dimethoxy-4-hydroxybenzaldehyde and 3-hydroxy-4-methoxybenzaldehyde respectively. The spectral data for all these compounds were in full agreement with the assigned structures.

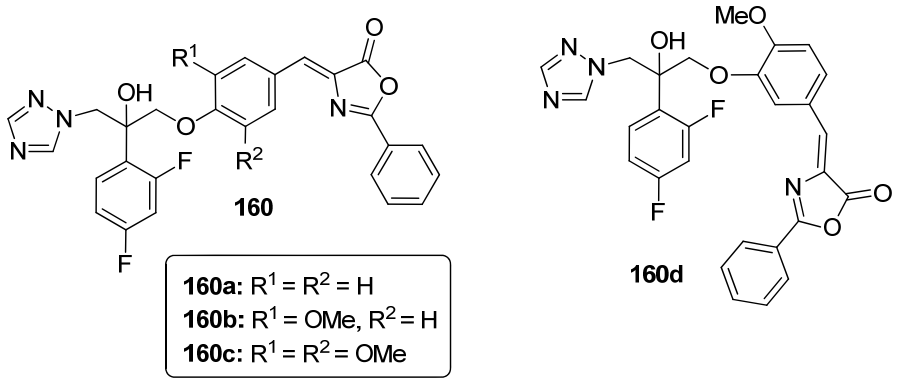
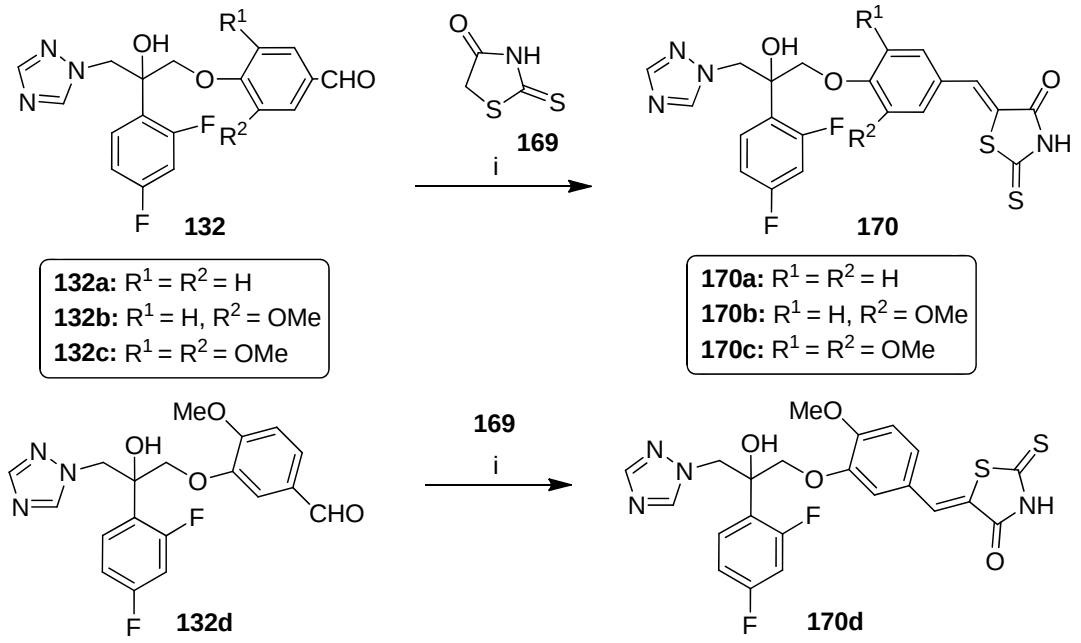


Figure 3. Structures of fluconazole analogues 1**60** containing azlactone moiety

For further structure-activity relationship study, hybrid molecules **170** containing 2-thioxothiazolidin-4-one moiety were prepared[26a] as there are reports[26b,c] that the molecules containing this structural feature exhibit antifungal activity. The reactions used for preparation of these molecules are shown in Scheme 5. The reaction[23a] of fluconazole analogues **132** with rhodanine **169** in presence of acetic acid and sodium acetate provided the 2-thioxothiazolidin-4-one containing fluconazole analogues **170**.



Scheme 5. Reagents and conditions: i) CH_3COOH, CH_3COONa, 80-85 ^0C, 2 h, 90-96%.

All the newly synthesized compounds **132**, **160**, **161, 166, 167** and **170** were tested for antifungal activity against various fungal strains and the activity parameters are depicted in Table 2 as MIC_{50} values.

Table 2. MIC obtained by broth micro-dilution method

Sr. no.	Comp. no.	Structure	Activity against organisms (MIC_{50} in µg/ml)							
			Ca 01	Cg 01	Ck 01	Ct 01	Cn 01	An 01	Afm 01	Fp 01
	FLU		**0.25**	1	32	1	2	>128	>128	>128
	AMB		**0.25**	**0.25**	**0.5**	**0.5**	**0.5**	**0.25**	**0.5**	2
1	**132a**		**0.5**	**0.5**	16	4	2	128	>128	>128
2	**132b**		**0.5**	**1**	128	8	16	128	>128	>128
3	**132c**		**1**	**1**	>128	64	8	>128	>128	>128
4	**132d**		**2**	**2**	>128	>128	16	>128	>128	>128
5	**160a**	$R^1 = R^2 = H$	4	4	>4	>4	>4	>4	>4	>4
6	**160b**	R^1 = OMe, R^2 = H	>4	>4	>4	>4	>4	>4	>4	>4
7	**160c**	$R^1 = R^2$ = OMe	>2	32	>2	>2	>2	>2	>2	>2

8	**160d**		>4	>4	>4	>4	>4	>4	>4	>4
9	**161a**	R = H	8	8	>128	64	64	>128	>128	>128
10	**161b**	R = OMe	>128	>128	>128	>128	>128	>128	>128	>128
11	**166a**	Ar = 2,4-difluorophenyl	**1**	**1**	>8	8	4	>8	>8	>8
12	**167a**	Ar = 2,4-difluorophenyl	**2**	**2**	>16	8	>16	>16	>16	>16
13	**170a**	$R^1 = R^2 = H$	**0.5**	4	>32	8	>32	>32	>32	>32
14	**170b**	$R^1 = H$, $R^2 = OMe$	**1**	8	>16	>16	>16	>16	>16	>16
15	**170c**	$R^1 = R^2 = OMe$	>16	>16	>16	>16	>16	>16	>16	>16
16	**170d**		>8	>8	>8	>8	>8	>8	>8	>8

From the antifungal activity data it was observed that the fluconazole analogues with general structure **132a-d** exhibited antifungal activity against *C. albicans* ATCC 24433 and *C. glabrata* ATCC 90030 (Table 2, Entry nos 1-4) while the corresponding azlactones **160a-d** showed no antifungal activity (Table 2, Entry nos 5-8). The fluconazole analogues **170a-b** exhibited marginal antifungal activity against *C. albicans* ATCC 24433 (Table 2, Entry nos 13 and 14) while the compounds **170c-d** did not show any antifungal activity against the fungal strains studied in the present work (Table 2, Entry nos 15 and 16). The furanones **166a** and **167a** (Table 2, Entry nos 11 and 12) exhibited marginal antifungal activity against *C. albicans* ATCC 24433 and *C. glabrata* ATCC 90030 but they did not exhibit any antifungal activity against rest of the fungal strains studied in the present work.

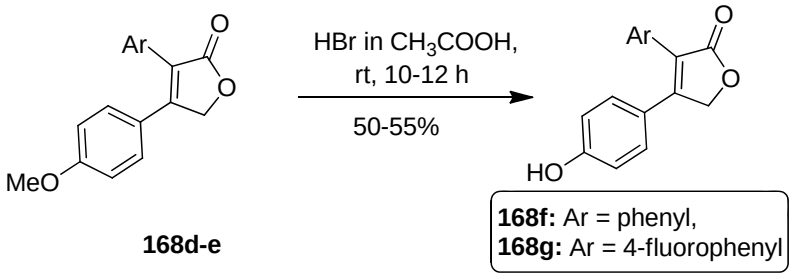
The above results indicated following points regarding the stability and structure-activity relationship of the compounds studied in the present work.

1. The fluconazole analogues **132** exhibited antifungal activity. The compounds **132a-c** containing phenyl ring with aldehyde functionality at *para* position exhibited antifungal activity against *C. albicans* ATCC 24433 and *C. glabrata* ATCC 90030 while the analogue **132d** with phenyl ring having aldehyde functionality at *meta* position exhibited less antifungal activity (e.g. **132a** ≥ **132b** > **132c** > **132d**).

2. The antifungal activity of compounds **132a-d** was lost completely when the aldehyde functionality was converted into an azlactone moiety (e.g. **132a** v/s **160a**, **132b** v/s **160b**, **132c** v/s **160c** and **132d** v/s **160d**).

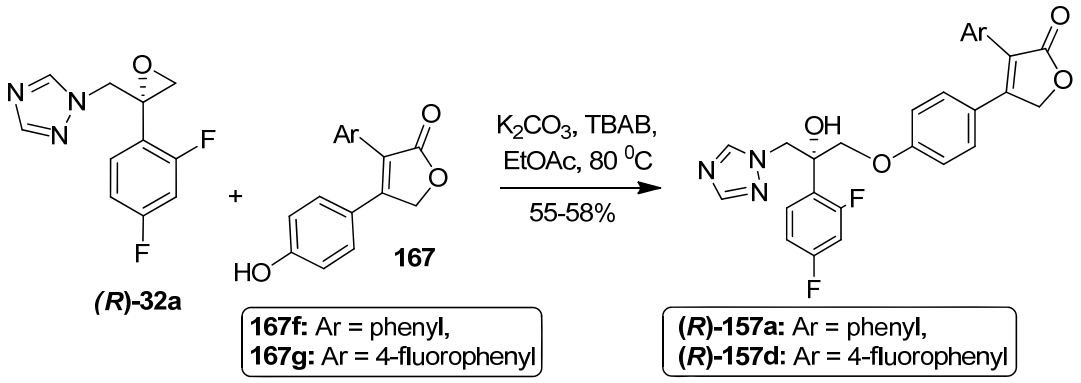
3. The conversion of the aryl aldehyde functionality of compounds **132** into arylacetic acid **161** resulted into complete loss of activity (e.g. **132a** v/s **161a** and **132b** v/s **161b**).
4. The antifungal activity of compounds **132a-d** was decreased or lost completely when the aldehyde functionality was converted into 2-thioxothiazolidin-4-one moiety (e.g. **132a** v/s **170a**, **132b** v/s **170b**, **132c** v/s **170c** and **132d** v/s **170d**).

From the antifungal activity results of racemic compounds synthesized in the present section of this chapter it was observed that the hybrid compounds **157** exhibited good antifungal activity so these compounds **157** were chosen for preparation of their enantiomers in order to examine the influence of absolute configuration on the antifungal activity. The enantiomers of this class of antifungal agents could be synthesized from chiral epoxides **(*R*)-32a** and **(*S*)-32a** (Synthesis of chiral epoxides **(*R*)-32a** and **(*S*)-32a**[28] has been described in Chapter 1, Scheme 11**)**. Accordingly, the hydroxyfuranones **168f** and **168g** were synthesized by the deprotection of methoxy group of furanones **168d** and **168e** by using excess of HBr in acetic acid at room temperature as shown in Scheme 6.



Scheme 6. Synthesis of hydroxyfuranones **168f** and **168g**

The hydroxyfuranones **168f** and **168g** were reacted with chiral epoxide **(*R*)-32a** in presence of potassium carbonate and tetrabutylammonium bromide (TBAB) in ethyl acetate at refluxing temperature for 5-7 h to afford the target enantiopure molecules **(*R*)-157** as shown in Scheme 7.



Scheme 7. Synthesis of **(*R*)-157a** and **(*R*)-157d**.

The chiral HPLC chromatogram for racemic **157d** and its (*R*) enantiomer is shown in Figure 4.

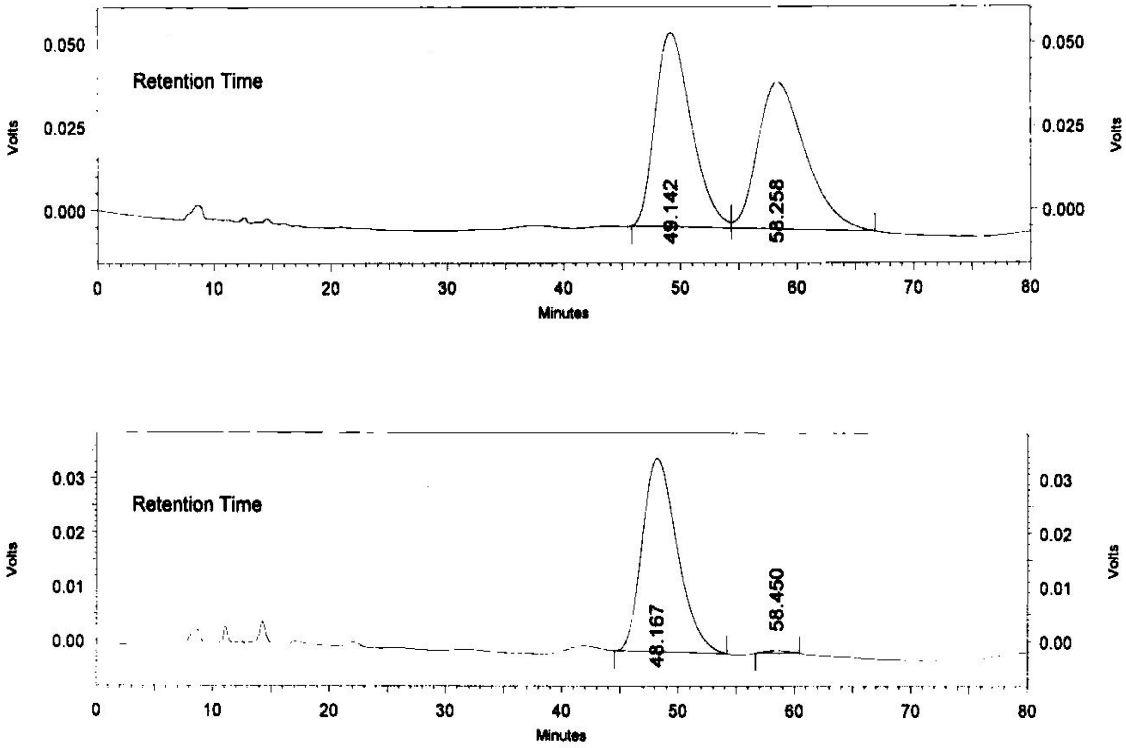


Figure 4. (*R*) enantiomer of **157d**

After synthesis of enantiomers **(*R*)-157a** and **(*R*)-157d** specific rotations were calculated from the observed rotations as shown in Table 3.

Table 3. Specific rotations of enantiomers of **157a** and **157d**

Comp. No.	Chem. Purity	Peak In Chiral HPLC Chromatogram	Retention Time (RT) min	Enantiomeric Excess (% ee)	Specific Rotation $[\alpha]_D^{24} = \frac{\text{Obs. Rotation X 100}}{\text{Conc. X Length}}$
(*R*)-157a	96.4%	A	49.07	98.64	-20 ^{o} (c = 1.02, THF)
(*R*)-157d	95.0%	A	48.16	98.00	-30 ^{o} (c = 1.01, THF)

The chiral compounds **157a** and **157d** were tested for antifungal activity against various fungi and results are enumerated in Table 4.

Table 4: MIC obtained by broth micro-dilution method

Organism	Activity against organisms (MIC_{50} in µg/ml)					
	AMB	**FLU**	**157a**	**(*R*)-157a**	**157d**	**(*R*)-157d**
C. albicans ATCC 24433	**0.25**	**0.5**	**0.25**	**0.25**	**0.5**	**0.5**
C. albicans ATCC 10231	**0.5**	**0.5**	**0.5**	**0.5**	**0.5**	**0.5**
C. albicans ATCC 2091	**0.5**	**0.5**	**0.5**	**0.25**	**1**	**0.5**
C. albicans ATCC 90028	**0.5**	**0.5**	**0.5**	**0.25**	**0.5**	**0.25**
C. glabrata ATCC 90030	**0.25**	4	**0.12**	**0.12**	**0.5**	**0.25**
C. krusei ATCC 6258	**0.5**	64	>8	>8	8	8
C. tropicalis ATCC 750	**0.5**	**2**	**2**	**1**	4	**2**
C. neoformans ATCC 34664	**0.5**	**2**	>8	>8	8	8
A. niger ATCC 16404	**0.25**	>128	>8	>8	>8	>8
A. fumigatus ATCC 46645	**0.5**	>128	>8	>8	>8	>8
F. proliferatum ATCC 10052	**2**	>128	>8	>8	>8	>8

From the antifungal activity results of these enantiopure compounds **157a** and **157d** it was found that the *R*-enantiomers of this class of antifungal agents has higher antifungal activity.

2.2.5 Conclusion

We have synthesized a number of compounds with different structural features and evaluated their antifungal activity against various fungal strains using fluconazole and amphotericin B as standards. The hybrid molecules **157a-j** exhibited significant antifungal activity against *C. albicans* ATCC 24433, *C. glabrata* ATCC 90030, *C. tropicalis* ATCC 750 and *C. neoformans* ATCC 34664 with MIC_{50} values comparable to fluconazole. The fluconazole analogues **158** were not enough stable to study their antifungal activity while the fluconazole analogues **159** did not show antifungal activity against any fungal strains. Furthermore, we prepared few compounds **157** in enantiomerically pure form to examine the influence of absolute configuration on

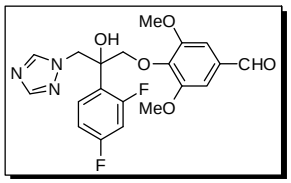
antifungal activity and observed that the *R* enantiomers of **157a** and **157d** have higher antifungal activity. These observations will be very useful in design and synthesis of new antifungal agents.

2.2.6 Experimental Section

The compounds **132c-d** were prepared by using the procedure given for the preparation of compound **129a** as described in the Section I of this chapter.

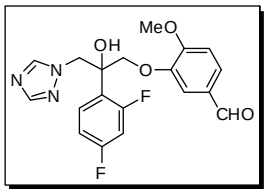
4-(2-(2,4-Difluorophenyl)-2-hydroxy-3-(1*H*-1,2,4-triazol-1-yl)propoxy)-3,5-dimethoxybenzaldehyde (132c)

Nature: White solid; **MP:** 124 ^{0}C; **Yield:** 66%; **^{1}H NMR** (200 MHz, $CDCl_3$)**:** δ 3.94 (s, 6H), 4.30 (d, *J* = 10 Hz, 1H), 4.46 (d, *J* = 10 Hz, 1H), 4.74 (d, *J* = 14 Hz, 1H), 4.83 (d, *J* = 14 Hz, 1H), 5.00 (bs, 1H), 6.74-6.86 (m, 2H), 7.10 (s, 2H), 7.49-7.61 (m, 1H), 7.78 (s, 1H), 8.11 (s, 1H), 9.86 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$)**:** δ 54.6, 56.1 (2C), 74.7, 77.2, 103.9 (t), 106.2 (2C), 111.3 (d), 122.3 (d), 129.9 (d), 132.2, 141.8, 144.3, 151.0, 152.9 (2C), 158.4 (dd), 163.3 (dd), 190.6; **IR** (Chloroform)**:** 1617, 1685, 3400 cm^{-1}; **MS** (ESI) *m*/*z***:** 420.03 (M + 1).



3-(2-(2,4-Difluorophenyl)-2-hydroxy-3-(1*H*-1,2,4-triazol-1-yl)propoxy)-4-methoxybenzaldehyde (132d)

Nature: Yellow semisolid; **Yield:** 64%; **^{1}H NMR** (200 MHz, $CDCl_3$)**:** δ 3.93 (s, 3H), 4.28 (d, *J* = 10 Hz, 1H), 4.41 (d, *J* = 10 Hz, 1H), 4.91 (d, *J* = 14 Hz, 1H), 5.00 (d, *J* = 14 Hz, 1H), 5.24 (bs, 1H), 6.75-6.89 (m, 2H), 6.98 (d, *J* = 8 Hz, 1H), 7.40 (s, 1H), 7.49-7.65 (m, 2H), 7.89 (s, 1H), 8.52 (s, 1H), 9.81 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$)**:** δ 54.6, 55.9, 73.3, 74.8, 104.1 (t), 111.0, 111.6 (d), 112.8, 122.2 (d), 127.6, 129.9, 130.0 (d), 144.2, 148.0, 150.7, 154.8, 158.4 (dd), 163.3 (dd), 190.5; **IR** (Chloroform)**:** 1619, 1678, 3412 cm^{-1}; **MS** (ESI) *m*/*z***:** 390.05 (M + 1).

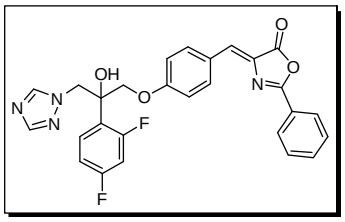


Preparation of (4*Z*)-4-(4-(2-(2,4-difluorophenyl)-2-hydroxy-3-(1*H*-1,2,4-triazol-1-yl)propoxy)benzylidene)-2-phenyloxazol-5(4*H*)-one (160a)

A mixture of aldehyde **132a** (15.0 g, 41.7 mmol), hippuric acid (7.47 g, 41.7 mmol) and sodium acetate (3.42 g, 41.7 mmol) dissolved in acetic anhydride (11.8 ml, 125 mmol) was allowed to stir at 85 ^{0}C for 2 h under nitrogen atmosphere. It was then cooled to

room temperature, quenched with ice in ethanol and allowed to stir at room temperature overnight. The precipitate obtained was filtered through Whatman filter paper, washed with excess water and dried to give pure (4*Z*)-4-(4-(2-(2,4-difluorophenyl)-2-hydroxy-3-(1*H*-1,2,4-triazol-1-yl)propoxy)benzylidene)-2-phenyloxazol-5(4H)-one **160a** as yellow solid (19.92 g, 95%).

Nature: Yellow solid; **MP:** 158 ^{0}C; Yield: 95%; **^{1}H NMR** (200 MHz, $CDCl_3$)**:** δ 4.30 (d,

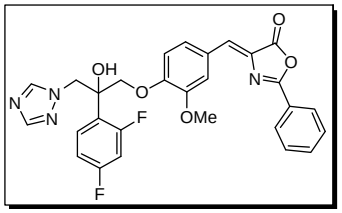


J = 10 Hz, 1H), 4.40 (d, *J* = 10 Hz, 1H), 4.99 (s, 2H), 6.78-6.93 (m, 2H), 6.99 (d, *J* = 8 Hz, 2H), 7.18 (s, 1H), 7.48-7.69 (m, 4H), 7.95 (s, 1H), 8.13-8.19 (m, 4H), 8.62 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$)**:** δ 54.5, 71.7, 74.9, 104.2 (t), 111.8 (d), 114.9 (2C), 122.3 (d), 125.5, 127.2, 128.0 (2C), 128.8 (2C), 130.1 (d), 131.2, 131.4, 133.0, 134.4 (2C), 144.3, 151.4, 158.4 (dd), 160.3, 162.5, 163.3 (dd), 167.7; **IR** (Chloroform)**:** 1602, 1651, 1788, 3435 cm^{-1}; **MS** (ESI) *m*/*z***:** 503.13 (M + 1).

The following compounds **160b-d** were prepared by using the procedure given for the preparation of compound **160a**.

(4*Z*)-4-(4-(2-(2,4-Difluorophenyl)-2-hydroxy-3-(1*H*-1,2,4-triazol-1-yl)propoxy)-3-methoxybenzylidene)-2-phenyloxazol-5(4*H*)-one (160b)

Nature: Yellow solid; **MP:** 100^{0}C; **Yield:** 95.5%; **^{1}H NMR** (200 MHz, $CDCl_3$)**:** δ 3.84

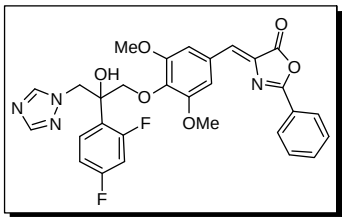


(s, 3H), 4.26 (d, *J* = 10 Hz, 1H), 4.33 (d, *J* = 10 Hz, 1H), 4.74 (d, *J* = 14 Hz, 1H), 4.85 (d, *J* = 14 Hz, 1H), 6.11 (bs, 1H), 6.75 (t, *J* =8 Hz, 2H), 6.88 (d, *J* = 10 Hz, 1H), 7.08 (s, 1H), 7.41-7.54 (m, 5H), 7.61 (s, 1H), 7.98-8.05 (m, 3H), 8.21 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$)**:** δ 52.7, 54.0, 71.3, 72.2, 102.1 (t), 109.2 (d), 112.0, 113.3, 122.0 (d), 123.5, 125.4, 125.7, 125.9 (2C), 127.3 (2C), 128.7 (d), 129.1, 129.7, 131.4, 143.2, 147.5, 148.7, 149.3, 158.9 (dd), 160.2, 164.1 (dd), 165.2; **IR** (Chloroform)**:** 1651, 1787, 3532 cm^{-1}; **MS** (ESI) *m/z***:** 533.11 (M + 1).

(4*Z*)-4-(4-(2-(2,4-Difluorophenyl)-2-hydroxy-3-(1*H*-1,2,4-triazol-1-yl)propoxy)-3,5-dimethoxybenzylidene)-2-phenyloxazol-5(4*H*)-one (160c)

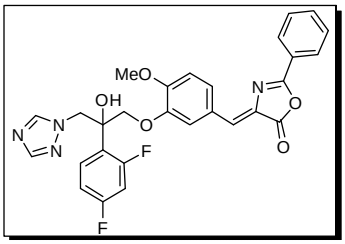
Nature: Yellow solid; **MP:** 173 ^{0}C; **Yield:** 93%; **^{1}H NMR** (200 MHz, $CDCl_3$)**:** δ 3.98 (s, 6H), 4.34 (d, *J* = 10 Hz, 1H), 4.43 (d, *J* = 10 Hz, 1H), 4.77 (d, *J* = 14 Hz, 1H), 4.86 (d, *J*

= 14 Hz, 1H), 5.09 (bs, 1H), 6.75-6.86 (m, 2H), 7.13 (s, 1H), 7.51-7.78 (m, 6H), 7.78 (s, 1H), 8.09-8.13 (m, 3H); **^{13}C NMR** (50 MHz, $CDCl_3$)**:** δ 54.7, 56.0 (2C), 60.3, 74.8, 104.0 (t), 109.3 (2C), 111.4 (d), 122.4 (d), 125.3, 128.1 (2C), 128.9 (2C), 129.6, 129.9 (d), 131.0, 132.7, 133.4, 139.5, 144.4, 151.1, 152.4 (2C), 158.6 (dd), 163.4, 164.8 (dd), 167.3; **IR** (Chloroform)**:** 1643, 1786, 3476 cm^{-1}; **MS** (ESI) *m*/*z***:** 563.05 (M + 1).



(*Z*)-4-(3-(2-(2,4-Difluorophenyl)-2-hydroxy-3-(1*H*-1,2,4-triazol-1-yl)propoxy)-4-methoxybenzylidene)-2-phenyloxazol-5(4*H*)-one (160d)

Nature: Yellow solid; **MP:** 130 ^{0}C; **Yield:** 92%; **^{1}H NMR** (200 MHz, $CDCl_3$)**:** δ 3.93 (s, 3H), 4.39 (d, *J* = 10 Hz, 1H), 4.50 (d, *J* = 10 Hz, 1H), 4.80 (bs, 1H), 4.88 (d, *J* = 16 Hz, 1H), 4.96 (d, *J* = 16 Hz, 1H), 6.78-6.91 (m, 2H), 6.95 (d, *J* = 8 Hz, 1H), 7.17 (s, 1H), 7.46-7.71 (m, 5H), 7.82 (s, 1H), 8.07-8.21 (m, 3H); **^{13}C NMR** (50 MHz, $CDCl_3$)**:** δ 53.6, 54.8, 73.3, 77.2, 102.7 (t), 110.1 (d), 110.7, 116.3, 122.3 (d), 124.3, 125.5, 126.8 (2C), 127.5, 127.8 (2C), 129.3 (d), 129.9, 130.3, 132.1, 143.7, 146.9, 149.5, 151.4, 158.7 (dd), 161.1, 163.8 (dd), 166.2; **IR** (Chloroform)**:** 1650, 1784, 3417 cm^{-1}; **MS** (ESI) *m*/*z***:** 533.09 (M + 1).



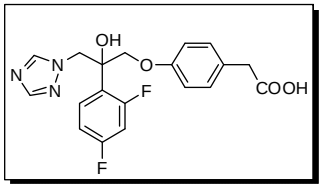
Preparation of 2-(4-(2-(2,4-difluorophenyl)-2-hydroxy-3-(1*H*-1,2,4-triazol-1-yl)propoxy)phenyl)acetic acid (161a)

Procedure 1:

The compound **160a** (15.0 g, 29.8 mmol) dissolved in 10% NaOH (3.5 g, 89.4 mmol) was heated at 80-90 ^{0}C for 7 h. It was then cooled to room temperature, 40% NaOH solution (40 mL) was added followed by addition of 30% hydrogen peroxide (100 mL) slowly at 0 ^{0}C with constant stirring at such a rate that the temperature did not rise above 15 ^{0}C. The reaction mixture was allowed to stand at room temperature for 15 h, acidified with dilute hydrochloric acid (150 mL), extracted with ethyl acetate and purified by column chromatography to give the pure compound 2-(4-(2-(2,4-difluorophenyl)-2-hydroxy-3-(1*H*-1,2,4-triazol-1-yl)propoxy)phenyl)acetic acid **161a** as white fluffy solid (3.83 g, 33%).

Nature: White fluffy solid; **MP:** 93 ^{0}C; **Yield:** 33%; **^{1}H NMR** (200 MHz, $CDCl_3$ + DMSO-d_6)**:** δ 3.57 (s, 2H), 4.20 (d, *J* = 10 Hz, 1H), 4.25 (d, *J* = 10 Hz, 1H), 4.82 (s, 2H),

6.74-6.89 (m, 4H), 6.77-6.96 (m, 2H), 7.18 (d, *J* = 10 Hz, 2H), 7.52-7.64 (m, 1H), 7.83 (s, 1H), 8.10 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$ + DMSO-d_6)**:** δ 39.9, 54.4, 71.4, 74.0, 103.6 (t), 111.0 (d), 114.2 (2C), 122.6 (d), 127.1, 129.7 (d), 130.0 (2C), 144.1, 150.3, 156.7, 158.0 (dd), 162.9 (dd), 173.6; **IR** (Chloroform)**:** 1615, 1713, 3418 cm^{-1}; **MS** (ESI) *m*/*z***:** 390.12 (M + 1).



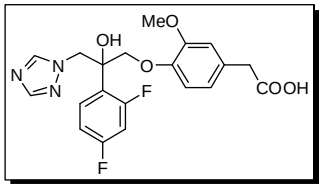
Procedure 2:

To a flame-dried K_2CO_3 (8.73 g, 63.29 mmol), 2-(4-hydroxyphenyl)acetonitrile **163a** (5.61 g, 81.96 mmol), tetra-butyl ammonium bromide (TBAB, catalytic) and epoxide **32a** (10.0 g, 42.19 mmol) dissolved in dry ethyl acetate (150 mL) were added. The reaction mixture was allowed to stir at reflux temperature for 12 h under nitrogen atmosphere. It was then cooled to room temperature, diluted with water, extracted with ethyl acetate, dried over Na_2SO_4 and concentrated to give crude compound **164a**. The crude compound **164a** was then heated at 80-100 ^{0}C in 30% H_2SO_4 for 10 h, cooled to room temperature and extracted with ethyl acetate and purified by column chromatography to give the pure compound 2-(4-(2-(2,4-difluorophenyl)-2-hydroxy-3-(1*H*-1,2,4-triazol-1-yl)propoxy)phenyl)acetic acid **161a** as white fluffy solid (13.95 g, 85%). The spectral data were identical with the product obtained in procedure 1.

The compound **161b** was prepared by using the procedure 1 given for the preparation of compound **161a**.

2-(4-(2-(2,4-Difluorophenyl)-2-hydroxy-3-(1*H*-1,2,4-triazol-1-yl)propoxy)-3-methoxyphenyl)acetic acid (161b)

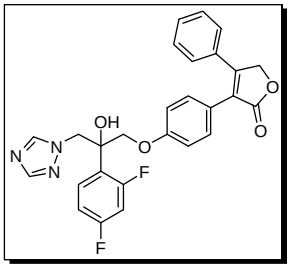
Nature: White solid; **MP:** 118 ^{0}C; **Yield:** 30%; **^{1}H NMR** (200 MHz, $CDCl_3$ + DMSO-d_6)**:** δ 3.23 (s, 2H), 3.53 (s, 3H), 3.93 (d, *J* = 10 Hz, 1H), 4.03 (d, *J* = 10 Hz, 1H), 4.51 (d, *J* = 14 Hz, 1H), 4.61 (d, *J* = 14 Hz, 1H), 5.08 (bs, 1H), 6.48-6.59 (m, 5H), 7.20-7.33 (m, 1H), 7.41 (s, 1H), 7.98 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$ + DMSO-d_6)**:** δ 38.9, 52.6, 53.0, 54.2, 72.7, 102.2 (t), 109.4 (d), 112.3, 114.1, 120.1, 122.2 (d), 127.4, 128.8 (d), 143.3, 145.3, 148.0, 148.9, 156.7 (dd), 161.5 (dd), 171.5; **IR** (Nujol)**:** 1615, 1711, 3431 cm^{-1}; **MS** (ESI) *m*/*z***:** 420.08 (M + 1).



Preparation of 3-(4-(2-(2,4-difluorophenyl)-2-hydroxy-3-(1*H*-1,2,4-triazol-1-yl)propoxy)phenyl)-4-phenylfuran-2(5*H*)-one (157a)

To a flame dried K_2CO_3 (5.52 g, 0.04 mol), 2-chloro-1-phenylethanone (1.84 g, 0.012 mol) and 2-(4-(2-(2,4-difluorophenyl)-2-hydroxy-3-(1*H*-1,2,4-triazol-1-yl)propoxy)phenyl)acetic acid **161a** (3.89 g, 0.01 mol) were added in acetonitrile at room temperature and the reaction mixture was refluxed for 4 h. It was then cooled to room temperature, diluted with water and extracted with ethyl acetate, dried over Na_2SO_4, concentrated and purified by column chromatography to give pure compound 3-(4-(2-(2,4-difluorophenyl)-2-hydroxy-3-(1*H*-1,2,4-triazol-1-yl)propoxy)phenyl)-4-phenylfuran-2(5*H*)-one (**157a**) as pale yellow fluffy solid (3.56 g, 73%).

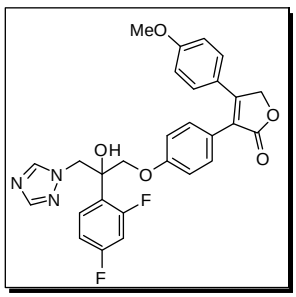
Nature: Pale yellow fluffy solid; **MP:** 86 ^{0}C; **Yield:** 73%; **^{1}H NMR** (200 MHz, $CDCl_3$)**:**



δ 4.26 (s, 2H), 4.84 (s, 2H), 4.88 (bs, 1H), 5.13 (s, 2H), 6.74-6.89 (m, 4H), 7.30-7.37 (m, 6H), 7.55-7.67 (m, 1H), 7.80 (s, 1H), 8.05 (s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$)**:** δ 54.5, 70.5, 71.6, 74.9, 104.2 (t), 111.7 (d), 114.7 (2C), 122.5 (d), 123.2, 125.2, 127.3 (2C), 128.9 (2C), 130.1 (d), 130.4, 130.6 (2C), 130.8, 144.3, 151.4, 155.3, 158.3, 158.9 (dd), 162.8 (dd), 173.6; **IR** (Chloroform)**:** 1608, 1748, 3419 cm^{-1}; **MS** (ESI) *m*/*z***:** 490.27 (M + 1). **Anal. Calcd. for** $C_{27}H_{21}F_2N_3O_4$**:** C, 66.25; H, 4.32; N, 8.58 %. **Found:** C, 66.36; H, 4.47; N, 8.47 %.

The following compounds **157b-j** were prepared by using the procedure given for the preparation of compound **157a.**

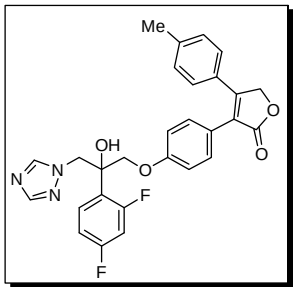
3-(4-(2-(2,4-Difluorophenyl)-2-hydroxy-3-(1*H*-1,2,4-triazol-1-yl)propoxy)phenyl)-4-(4-methoxyphenyl)furan-2(5*H*)-one (157b)



Nature: Yellow fluffy solid; **MP:** 97 ^{0}C; **Yield:** 75%; **^{1}H NMR** (200 MHz, $CDCl_3$)**:** δ 3.83 (s, 3H), 4.28 (s, 2H), 4.76 (bs, 1H), 4.88 (s, 2H), 5.14 (s, 2H), 6.77-6.97 (m, 6H), 7.29 (d, *J* = 8 Hz, 2H), 7.37 (d, *J* = 8 Hz, 2H), 7.57-7.70 (m, 1H), 7.84 (s, 1H), 8.07 (s, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$)**:** δ 54.5, 55.3, 70.3, 71.6, 75.0, 104.2 (t), 111.8 (d), 114.3 (2C), 114.8 (2C), 122.5 (d), 123.0, 123.4, 123.8, 128.9 (2C), 130.2 (d), 130.7 (2C), 144.3, 151.6, 154.9, 158.1, 158.9 (dd), 161.3, 162.9 (dd), 174.0; **IR** (Chloroform)**:** 1606, 1746, 3422 cm^{-1}; **MS** (ESI) *m*/*z***:** 520.24 (M + 1). **Anal. Calcd. for** $C_{28}H_{23}F_2N_3O_5$**:** C, 64.74; H, 4.46; N, 8.09 %. **Found:** C, 64.81; H, 4.23; N, 8.21 %.

3-(4-(2-(2,4-Difluorophenyl)-2-hydroxy-3-(1*H*-1,2,4-triazol-1-yl)propoxy)phenyl)-4-p-tolylfuran-2(5*H*)-one (157c)

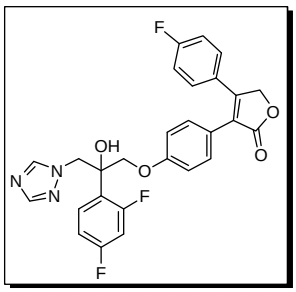
Nature: Yellow fluffy solid; **MP:** 89 ^{0}C; **Yield:** 70%; **^{1}H NMR** (200 MHz, $CDCl_3$)**:** δ



2.35 (s, 3H), 4.22 (d, *J* = 10 Hz, 1H), 4.29 (d, *J* = 10 Hz, 1H), 4.84 (s, 2H), 4.92 (bs, 1H), 5.11 (s, 2H), 6.74-6.91 (m, 4H), 7.13 (d, *J* = 8 Hz, 2H), 7.21 (d, *J* = 8 Hz, 2H), 7.34 (d, *J* = 10 Hz, 2H), 7.55-7.67 (m, 1H), 7.80 (s, 1H), 8.05 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$)**:** δ 21.2, 54.6, 70.4, 71.5, 74.6, 103.9 (t), 111.4 (d), 114.5 (2C), 122.5 (d), 123.1, 124.2, 127.1 (2C), 127.6, 129.4 (2C), 130.0 (d), 130.4 (2C), 140.8, 144.2, 150.9, 155.4, 158.1, 158.2 (dd), 163.2 (dd), 173.8; **IR** (Chloroform)**:** 1607, 1748, 3420 cm^{-1}; **MS** (ESI) *m*/*z***:** 504.14 (M + 1). **Anal. Calcd. for** $C_{28}H_{23}F_2N_3O_4$**:** C, 66.79; H, 4.60; N, 8.35 %. **Found:** C, 66.87; H, 4.50; N, 8.25 %.

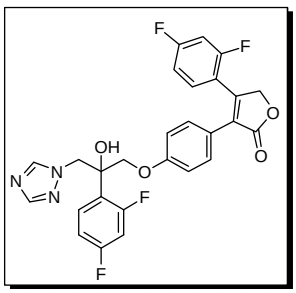
3-(4-(2-(2,4-Difluorophenyl)-2-hydroxy-3-(1*H*-1,2,4-triazol-1-yl)propoxy)phenyl)-4-(4-fluorophenyl)furan-2(5*H*)-one (157d)

Nature: Light yellow fluffy solid; **MP:** 90 ^{0}C; **Yield:** 73%; **^{1}H NMR** (200 MHz,



$CDCl_3$): δ 4.26 (s, 2H), 4.81 (bs, 1H), 4.86 (s, 2H), 5.12 (s, 2H), 6.75 -6.93 (m, 4H), 6.98-7.10 (m, 2H), 7.28-7.37 (m, 4H), 7.56-7.68 (m, 1H), 7.82 (s, 1H), 8.04 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 54.6, 70.4, 71.6, 74.8, 104.1 (t), 111.6 (d), 114.8 (2C), 115.9, 116.3, 122.5 (d), 122.8, 125.1, 126.8 (d), 129.3, 129.5, 130.1 (d), 130.5 (2C), 144.3, 151.2, 154.0, 158.3, 158.4 (dd), 163.3 (dd), 163.5 (d), 173.5; **IR** (Chloroform): 1604, 1751, 3422 cm^{-1}; **MS** (ESI) *m*/*z*: 508.15 (M + 1). **Anal. Calcd. for** $C_{27}H_{20}F_3N_3O_4$**:** C, 63.90; H, 3.97; N, 8.28 %. **Found:** C, 63.79; H, 4.10; N, 8.19 %.

3-(4-(2-(2,4-Difluorophenyl)-2-hydroxy-3-(1*H*-1,2,4-triazol-1-yl)propoxy)phenyl)-4-(2,4-difluorophenyl)furan-2(5*H*)-one (157e)

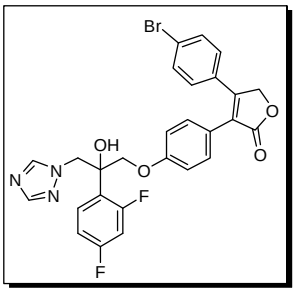


Nature: Yellow fluffy solid; **MP:** 82 ^{0}C; **Yield:** 71%; **^{1}H NMR** (50 MHz, $CDCl_3$): δ 4.17 (s, 2H), 4.77 (s, 2H), 5.07 (s, 2H), 6.66-6.88 (m, 6H), 7.08-7.28 (m, 3H), 7.47-7.59 (m, 1H), 7.73 (s, 1H), 7.97 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 54.5, 71.0, 71.5, 74.7, 104.0 (t), 104.9 (t), 111.5 (d), 112.2 (d),

114.6 (2C), 115.2 (d), 122.5 (d, 2C), 127.2, 129.9 (d), 130.1 (2C), 131.1 (d), 144.3, 149.8, 151.0, 157.0 (dd), 158.4, 160.6 (dd), 162.1 (dd), 165.7 (dd), 172.7; **IR** (Chloroform): 1608, 1751, 3420 cm^{-1}; **MS** (ESI) *m*/*z*: 526.09 (M + 1). **Anal. Calcd. for** $C_{27}H_{19}F_4N_3O_4$**:** C, 61.72; H, 3.64; N, 8.00 %. **Found:** C, 61.66; H, 3.71; N, 8.11 %.

4-(4-Bromophenyl)-3-(4-(2-(2,4-difluorophenyl)-2-hydroxy-3-(1*H*-1,2,4-triazol-1-yl)propoxy)phenyl)furan-2(5*H*)-one (157f)

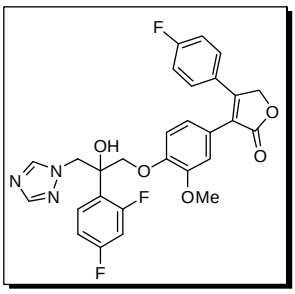
Nature: Pale yellow fluffy solid; **MP:** 98 ^{0}C; **Yield:** 74%; **^{1}H NMR** (400 MHz, $CDCl_3$)**:**



δ 4.26 (s, 2H), 4.69 (bs, 1H), 4.83 (d, *J* = 14 Hz, 1H), 4.92 (d, *J* = 14 Hz, 1H), 5.12 (s, 2H), 6.75-6.94 (m, 4H), 7.19 (d, *J* = 8 Hz, 2H), 7.35 (d, *J* = 10 Hz, 2H), 7.50 (d, *J* = 10 Hz, 2H), 7.56-7.69 (m, 1H), 7.84 (s, 1H), 8.05 (s, 1H). **^{13}C NMR** (50 MHz, $CDCl_3$): δ 54.5, 70.2, 71.7, 75.1, 104.2 (t), 111.9 (d), 114.9 (2C), 122.6 (d), 122.9, 124.9, 125.9, 128.8 (2C), 129.7, 130.2 (d), 130.6 (2C), 132.3 (2C), 144.3, 151.6, 153.7, 158.5, 158.9 (dd), 162.9 (dd), 173.2; **IR** (Chloroform)**:** 1606, 1750, 3418 cm^{-1}. **MS** (ESI) *m*/*z***:** 568.07 (M + 1). **Anal. Calcd. for** $C_{27}H_{20}BrF_2N_3O_4$**:** C, 57.06; H, 3.55; N, 7.39%. **Found:** C, 57.17; H, 3.66; N, 7.28 %.

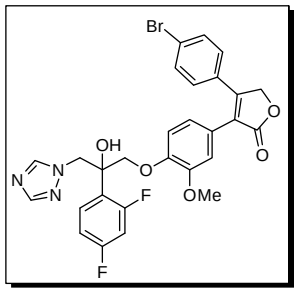
3-(4-(2-(2,4-Difluorophenyl)-2-hydroxy-3-(1*H*-1,2,4-triazol-1-yl)propoxy)-3-methoxyphenyl)-4-(4-fluorophenyl)furan-2(5*H*)-one (157g)

Nature: Yellow solid; **MP:** 78 ^{0}C; **Yield:** 70%; **^{1}H NMR** (200 MHz, $CDCl_3$)**:** δ 3.74 (s,



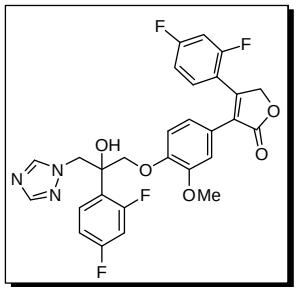
3H), 4.29 (d, *J* = 10 Hz, 1H), 4.34 (d, *J* = 10 Hz, 1H), 4.82 (d, *J* = 14 Hz, 1H), 4.89 (d, *J* = 14 Hz, 1H), 5.14 (s, 2H), 6.75-7.10 (m, 7H), 7.30-7.37 (m, 2H), 7.53-7.86 (m, 1H), 7.81 (s, 1H), 8.10 (s, 1H) ; **^{13}C NMR** (50 MHz, $CDCl_3$)**:** δ 54.6, 55.8, 70.4, 73.9, 74.9, 104.1 (t), 112.3 (d), 112.9, 116.0, 116.2, 116.3, 122.2, 122.4 (d), 124.4, 126.9 (d), 129.5, 129.6, 130.1 (d), 130.5 (d), 144.3, 148.2, 149.8, 151.3, 154.3, 159.0 (dd), 162.9 (dd), 163.7 (d), 173.2 ; **IR** (Chloroform)**:** 1603, 1748, 3461 cm^{-1}; **MS** (ESI) *m*/*z***:** 538.07 (M + 1). **Anal. Calcd. for** $C_{28}H_{22}F_3N_3O_5$**:** C, 62.57; H, 4.13; N, 7.82; %. **Found:** C, 62.44; H, 4.25; N, 7.90 %.

3-(4-(2-(2,4-Difluorophenyl)-2-hydroxy-3-(1*H*-1,2,4-triazol-1-yl)propoxy)-3-methoxyphenyl)-4-(4-bromophenyl)furan-2(5*H*)-one (157h)



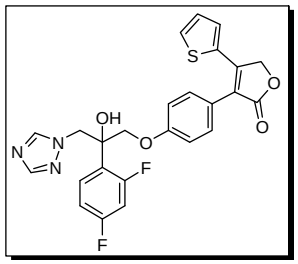
Nature: Yellow solid; **MP:** 84 ^{0}C; **Yield:** 75%; **^{1}H NMR** (200 MHz, $CDCl_3$)**:** δ 3.75 (s, 3H), 4.28 (d, *J* = 10 Hz, 1H), 4.33 (d, *J* = 10 Hz, 1H), 4.82 (d, *J* = 14 Hz, 1H), 4.89 (d, *J* = 14 Hz, 1H), 4.90 (bs, 1H), 5.13 (s, 2H), 6.75-6.96 (m, 5H), 7.20 (d, *J* = 8 Hz, 2H), 7.50 (d, *J* = 8 Hz, 2H), 7.54-7.66 (m, 1H), 7.81 (s, 1H), 8.08 (s, 1H) ; **^{13}C NMR** (50 MHz, $CDCl_3$)**:** δ 54.6, 55.7, 70.2, 73.6, 74.6, 104.0 (t), 111.5 (d), 112.7, 115.4, 122.1, 122.3 (d), 123.9, 124.9, 125.8, 128.8 (2C), 129.5, 130.0 (d), 132.1 (2C), 144.2, 148.1, 149.6, 150.4, 154.2, 158.9 (dd), 162.7 (dd), 173.0; **IR** (Chloroform)**:** 1619, 1754, 3448 cm^{-1}; **MS** (ESI) *m*/*z***:** 599.96 (M + 1). **Anal. Calcd. for** $C_{28}H_{22}BrF_2N_3O_5$**:** C, 56.20; H, 3.71; N, 7.02 %. **Found:** C, 56.37; H, 3.59; N, 7.19 %.

3-(4-(2-(2,4-Difluorophenyl)-2-hydroxy-3-(1*H*-1,2,4-triazol-1-yl)propoxy)-3-methoxyphenyl)-4-(2,4-difluorophenyl)furan-2(5*H*)-one (157i)



Nature: Yellow solid; **MP:** 91 ^{0}C; **Yield:** 68%; **^{1}H NMR** (200 MHz, $CDCl_3$)**:** δ 3.73 (s, 3H), 4.29 (d, *J* = 10 Hz, 1H), 4.31 (d, *J* = 10 Hz, 1H), 4.81 (d, *J* = 14 Hz, 1H), 4.88 (d, *J* = 14 Hz, 1H), 5.17 (s, 2H), 6.74-6.98 (m, 7H), 7.17-7.29 (m, 1H), 7.52-7.65 (m, 1H), 7.80 (s, 1H), 8.09 (s, 1H) ; **^{13}C NMR** (50 MHz, $CDCl_3$)**:** δ 54.6, 55.6, 71.0, 73.5, 74.6, 104.0 (t), 105.0 (t), 111.7 (d), 112.4 (d), 115.1, 115.2 (d), 121.9 (2C), 122.6 (d), 123.7, 127.2, 130.0 (d), 131.2 (d), 144.3, 148.1, 149.4, 150.2, 150.7, 157.1 (dd), 160.7 (dd), 162.0 (dd), 165.8 (dd), 172.5; **IR** (Chloroform)**:** 1611, 1752, 3468 cm^{-1}; **MS** (ESI) *m*/*z***:** 556.03 (M + 1). **Anal. Calcd. for** $C_{28}H_{21}F_4N_3O_5$**:** C, 60.54; H, 3.81; N, 7.56 %. **Found:** C, 60.46; H, 3.73; N, 7.49 %.

3-(4-(2-(2,4-Difluorophenyl)-2-hydroxy-3-(1*H*-1,2,4-triazol-1-yl)propoxy)phenyl)-4-(thiophen-2-yl)furan-2(5*H*)-one (157j)



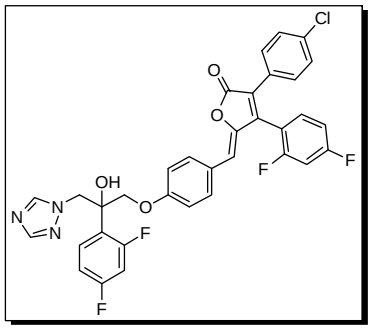
Nature: Pale yellow fluffy solid; **MP:** 94 ^{0}C; **Yield:** 65%; **^{1}H NMR** (200 MHz, $CDCl_3$)**:** δ 4.28 (s, 2H), 4.85 (s, 2H), 4.12 (s, 2H), 5.17 (bs, 1H), 6.74-7.06 (m, 5H), 7.23-7.49 (m, 4H), 7.55-7.67 (m, 1H), 7.80 (s, 1H), 8.06 (s, 1H). **^{13}C NMR** (100

MHz, $CDCl_3$)**:** δ 54.6, 70.2, 71.6, 74.8, 104.1 (t), 111.6 (d), 114.7, 114.9, 122.5 (d), 125.7, 126.7, 127.5, 130.1 (d), 130.6, 130.8, 131.7, 132.4, 144.3, 149.2, 150.2, 151.1, 158.3 (dd), 158.6, 163.3 (dd), 173.9; **IR** (Chloroform)**:** 1606, 1747, 3418 cm^{-1}; **MS** (ESI) *m*/*z***:** 496.13 (M + 1). **Anal. Calcd. for** $C_{25}H_{19}F_2N_3O_4S$**:** C, 60.60; H, 3.86; N, 8.48 %. **Found:** C, 60.76; H, 3.69; N, 8.38 %.

Preparation of 5-(4-(2-(2,4-difluorophenyl)-2-hydroxy-3-(1*H*-1,2,4-triazol-1-yl)propoxy)benzylidene)-3-(4-chlorophenyl)-4-(2,4-difluorophenyl)furan-2(5*H*)-one (159a)

To a stirred solution of compound **168a** (0.85 g, 2.78 mmol) and 4-(2-(2,4-difluorophenyl)-2-hydroxy-3-(1*H*-1,2,4-triazol-1-yl)propoxy)benzaldehyde **132a** (1.0 g, 2.78 mmol) in methanol, piperidine (0.2 mL, 1.94 mmol) was added slowly under nitrogen atmosphere at room temperature and the reaction mixture was stirred for another 15 h. The precipitate obtained was filtered through Whatman filter paper, washed with 10% HCl followed by excess of water and finally by ethyl acetate in petroleum ether (10:90) to give pure compound 5-(4-(2-(2,4-difluorophenyl)-2-hydroxy-3-(1*H*-1,2,4-triazol-1-yl)propoxy)benzylidene)-3-(4-chlorophenyl)-4-(2,4-difluorophenyl)furan-2(5*H*)-one **159a** as bright yellow solid (1.37 g, 76%).

Nature: Bright yellow solid; **MP:** 95 ^{0}C; **Yield:** 76%; **^{1}H NMR** (200 MHz, $CDCl_3$)**:** δ

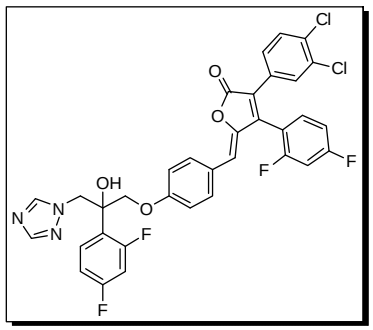


4.26 (d, *J* = 10 Hz, 1H), 4.31 (d, *J* = 10 Hz, 1H), 4.84 (d, *J* = 14 Hz, 1H), 4.89 (d, *J* = 14 Hz, 1H), 4.93 (bs, 1H), 5.81 (s, 1H), 6.74-7.10 (m, 6H), 7.22-7.38 (m, 5H), 7.56-7.65 (m, 1H), 7.70 (d, *J* = 8 Hz, 2H), 7.80 (s, 1H), 8.05 (s, 1H) ; **^{13}C NMR** (50 MHz, $CDCl_3$)**:** δ 54.4, 71.6, 74.9, 104.2 (t), 105.3 (t), 111.8 (d), 112.9, 113.7, 114.2 (d), 114.9 (2C), 122.3 (d), 124.9 (d), 126.5, 127.8, 128.6, 128.7 (2C), 129.5 (2C), 130.2 (d), 131.8 (d), 132.4, 135.0, 143.6, 144.3, 146.1, 151.5, 157.9 (dd), 158.8, 160.4 (dd), 162.1 (dd), 164.6 (dd), 167.9; **IR** (Chloroform)**:** 1602, 1759, 3421 cm^{-1}; **MS** (ESI) *m*/*z***:** 649.19 (M + 1). **Anal. Calcd. for** $C_{34}H_{22}ClF_4N_3O_4$**:** C, 63.02; H, 3.42; N, 6.48 %. **Found:** C, 63.19; H, 3.29; N, 6.33 %.

The following compounds **159b-c** were prepared by using the procedure given for the preparation of compound **159a.**

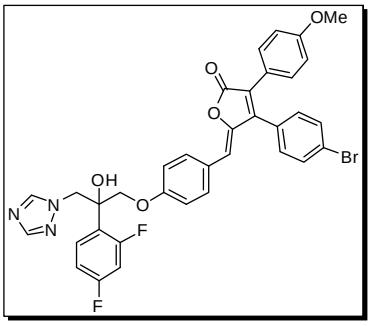
5-(4-(2-(2,4-Difluorophenyl)-2-hydroxy-3-(1*H*-1,2,4-triazol-1-yl)propoxy)benzylidene)-3-(3,4-dichlorophenyl)-4-(2,4-difluorophenyl)furan-2(5*H*)-one (159b)

Nature: Bright yellow fluffy solid; **MP:** 97 ^{0}C; **Yield:** 78%; **^{1}H NMR** (200 MHz, $CDCl_3$)**:** δ 4.24 (d, *J* = 10 Hz, 1H), 4.37 (d, *J* = 10 Hz, 1H), 4.80 (bs, 1H), 4.97 (d, *J* = 14 Hz, 1H), 5.07 (d, *J* = 14 Hz, 1H), 5.84 (s, 1H), 6.78-6.95 (m, 4H), 6.99-7.22 (m, 3H), 7.29-7.41 (m, 2H), 7.48-7.65 (m, 2H), 7.72 (d, *J* = 8 Hz, 2H), 7.97 (s, 1H), 8.93 (s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$)**:** δ 54.7, 71.6, 74.8, 104.2 (t), 105.4 (2C, t), 111.8 (d), 112.6 (d), 113.7, 113.8 (d), 115.0 (2C), 122.1 (d), 123.6, 126.4, 127.3, 129.3, 130.0, 130.1 (d), 130.4, 131.7 (d), 132.6 (2C), 132.7, 133.1, 144.1, 144.3, 145.9, 150.3, 158.9 (dd), 159.0, 159.4 (dd), 162.2 (dd), 164.7 (dd), 167.6; **IR** (Chloroform)**:** 1613, 1755, 3422 cm^{-1}; **MS** (ESI) *m*/*z***:** 683.11 (M + 1), 705.09 (M + Na). **Anal. Calcd. for** $C_{34}H_{21}Cl_2F_4N_3O_4$**:** C, 59.84; H, 3.10; N, 6.16 %. **Found:** C, 59.70; H, 3.22; N, 6.33 %.



4-(4-Bromophenyl)-5-(4-(2-(2,4-difluorophenyl)-2-hydroxy-3-(1*H*-1,2,4-triazol-1-yl)propoxy)benzylidene)-3-(4-methoxyphenyl)furan-2(5*H*)-one (159c)

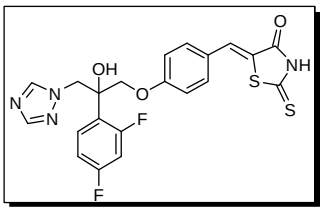
Nature: Bright yellow solid; **MP:** 113 ^{0}C; **Yield:** 80%; **^{1}H NMR** (200 MHz, $CDCl_3$)**:** δ 3.78 (s, 3H), 4.26 (d, *J* = 10 Hz, 1H), 4.31 (d, *J* = 10 Hz, 1H), 4.83 (d, *J* = 14 Hz, 1H), 4.91 (d, *J* = 14 Hz, 1H), 5.82 (s, 1H), 6.75-6.91 (m, 7H), 7.22 (d, *J* = 10 Hz, 2H), 7.56-7.73 (m, 5H), 7.71 (d, *J* = 10 Hz, 2H), 7.83 (s, 1H), 8.05 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$)**:** δ 54.5, 55.1, 71.6, 74.8, 77.2, 104.1 (t), 111.7 (d), 111.9, 113.8 (2C), 114.8 (2C), 122.4 (d), 123.7, 126.8, 129.6, 130.1 (d), 130.4 (2C), 130.7, 132.1 (2C), 132.2 (2C), 144.2, 146.8, 147.1, 151.4, 158.5, 158.8 (dd), 159.8 (2C), 162.8 (dd), 164.9 (dd), 168.8; **IR** (Chloroform)**:** 1603, 1754, 3421 cm^{-1}; **MS** (ESI) *m*/*z***:** 687.09 (M + 1). **Anal. Calcd. for** $C_{35}H_{26}BrF_2N_3O_5$**:** C, 61.23; H, 3.82; N, 6.12 %. Found: C, 61.43; H, 3.69; N, 6.01 %.



Preparation of 5-(4-(2-(2,4-difluorophenyl)-2-hydroxy-3-(1*H*-1,2,4-triazol-1-yl)propoxy)benzylidene)-2-thioxothiazolidin-4-one (170a)

A mixture of aldehyde **132a** (2.0 g, 5.57 mmol), rhodanine **169** (0.735 g, 5.57 mmol) and sodium acetate (0.450 g, 5.57 mol) in acetic acid (0.84 mL, 16.7 mmol) was allowed to stir at 85 ^{0}C for 2 h under nitrogen atmosphere. It was then cooled to room temperature, quenched with ice in ethanol and allowed to stir overnight. The precipitate obtained was filtered through Whatman filter paper and washed with excess water to give pure compound 5-(4-(2-(2,4-difluorophenyl)-2-hydroxy-3-(1*H*-1,2,4-triazol-1-yl)propoxy)benzylidene)-2-thioxothiazolidin-4-one **170a** as yellow solid (2.53 g, 96%).

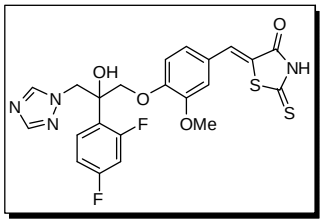
Nature: Yellow solid; **MP:** 193 ^{0}C; **Yield:** 96%; **^{1}H NMR** (200 MHz, $CDCl_3$ + DMSO-d_6)**:** δ 3.83 (s, 2H), 4.21 (d, *J* = 14 Hz, 1H), 4.34 (d, *J* = 14 Hz, 1H), 6.30-6.40 (m, 2H), 6.49 (d, *J* = 10 Hz, 2H), 6.92 (d, *J* = 10 Hz, 2H), 7.00 (s, 1H), 7.02-7.11 (m, 1H), 7.32 (s, 1H), 8.01 (s, 1H), 9.33 (bs, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$ + DMSO-d_6)**:** δ 53.5, 71.0, 73.0, 102.8 (t), 110.1 (d), 114.4 (2C), 122.0, 122.2 (d), 125.1, 129.2 (d), 130.4, 131.2 (2C), 143.7, 149.6, 157.2 (dd), 159.2, 162.4 (dd), 168.6, 194.1; **IR** (Chloroform)**:** 1630, 1739, 3455 cm^{-1}; **MS** (ESI) *m*/*z***:** 475.06 (M + 1).



The following compounds **170b-d** were prepared by using the procedure given for the preparation of compound **170a**.

5-(4-(2-(2,4-Difluorophenyl)-2-hydroxy-3-(1*H*-1,2,4-triazol-1-yl)propoxy)-3-methoxybenzylidene)-2-thioxothiazolidin-4-one (170b)

Nature: Yellow solid; **MP:** 168 ^{0}C; **Yield:** 95.8%; **^{1}H NMR** (200 MHz, $CDCl_3$ + DMSO-d_6): δ 3.85 (s, 3H), 4.36 (s, 2H), 4.78 (d, *J* = 14 Hz, 1H), 4.89 (d, *J* = 14 Hz, 1H), 6.26 (bs, 1H), 6.82-6.93 (m, 2H), 6.99-7.11 (m, 3H), 7.53-7.63 (m, 2H), 7.70 (s, 1H), 7.87 (bs, 1H), 8.31 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$ + DMSO-d_6): δ 53.1, 54.6, 71.9, 72.8, 102.4 (t), 109.7 (d), 112.4, 113.1, 122.0 (d, 2C), 123.3, 125.5, 129.0 (d), 130.4, 143.5, 148.3, 148.9, 149.2, 158.1 (dd), 162.0 (dd), 168.2, 193.8; **IR** (Chloroform): 1633, 1737, 3494 cm^{-1}; **MS** (ESI) *m*/*z*: 505.04 (M + 1).



5-(4-(2-(2,4-Difluorophenyl)-2-hydroxy-3-(1*H*-1,2,4-triazol-1-yl)propoxy)-3,5-dimethoxybenzylidene)-2-thioxothiazolidin-4-one (170c)

Nature: Yellow solid; **MP:** 172 ^{0}C; **Yield:** 94%; **^{1}H NMR** (200 MHz, $CDCl_3$ + DMSO-d_6)**:** δ 3.74 (s, 6H), 4.14 (d, *J* = 10 Hz, 1H), 4.21 (d, *J* = 10 Hz, 1H), 4.64 (d, *J* = 14 Hz, 1H), 4.75 (d, *J* = 14 Hz, 1H), 6.51 (s, 2H), 6.58-6.69 (m, 2H), 7.29-7.41 (m, 3H), 7.65 (s, 1H), 8.23 (bs, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$ + DMSO-d_6)**:** δ 53.3, 55.0 (2C), 73.6, 75.8, 102.6 (t), 106.3 (2C), 109.9 (d), 121.4 (d), 124.1, 128.1, 129.1 (d), 130.5, 137.5, 143.6, 149.5, 151.9 (2C), 157.5 (dd), 162.3 (dd), 168.4, 193.9; **IR** (Chloroform)**:** 1632, 1740, 3413 cm^{-1}; **MS** (ESI) *m*/*z***:** 535.06 (M + 1).

5-(3-(2-(2,4-Difluorophenyl)-2-hydroxy-3-(1*H*-1,2,4-triazol-1-yl)propoxy)-4-methoxybenzylidene)-2-thioxothiazolidin-4-one (170d)

Nature: Yellow solid; **MP:** 242 ^{0}C; **Yield:** 90%; **^{1}H NMR** (200 MHz, $CDCl_3$)**:** δ 3.64 (s, 3H), 4.09 (d, *J* = 10 Hz, 1H), 4.14 (d, *J* = 10 Hz, 1H), 4.56 (d, *J* = 16 Hz, 1H), 4.68 (d, *J* = 16 Hz, 1H), 6.60-6.69 (m, 3H), 6.77-6.96 (m, 3H), 7.31-7.43 (m, 2H), 7.54 (s, 1H), 8.15 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$ + DMSO-d_6)**:** δ 53.2, 54.9, 73.2, 74.8, 104.5 (t), 109.2 (d), 111.8 (2C), 116.2, 118.8, 122.1 (d), 125.4, 129.3 (d), 130.6, 143.7, 147.9, 151.6 (2C), 158.3 (dd), 162.2 (dd), 168.3, 193.5; **IR** (Chloroform)**:** 1634, 1738, 3425 cm^{-1}; **MS** (ESI) *m*/*z***:** 505.06 (M + 1).

3-(4-(2-(2,4-Difluorophenyl)-2-hydroxy-3-(1*H*-1,2,4-triazol-1-yl)propoxy)phenyl)-4-(2,4-difluorophenyl)-5-methylfuran-2(5*H*)-one (166a)

The compound **166a** was prepared by using the procedure given for the preparation of compound **157a.**

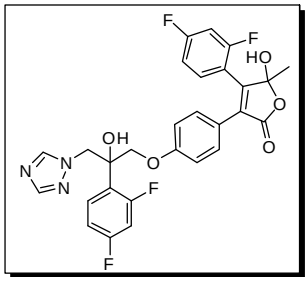
Nature: Off-white fluffy solid; **MP:** 76 ^{0}C; **Yield:** 63%; **^{1}H NMR** (200 MHz, $CDCl_3$)**:** δ 1.39 (d, *J* = 6 Hz, 3H), 4.22 (d, *J* = 10 Hz, 1H), 4.26 (d, *J* = 10 Hz, 1H), 4.61 (bs, 1H), 4.82 (d, *J* = 14 Hz, 1H), 4.90 (d, *J* = 14 Hz, 1H), 5.47-5.58 (q, *J* = 6 Hz, 1H), 6.73-6.98 (m, 6H), 7.07-7.18 (m, 1H), 7.73 (d, *J* = 8 Hz, 2H), 7.55-7.67 (m, 1H), 7.83 (s, 1H), 8.04 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$)**:** δ 18.4, 54.6, 71.5, 74.9, 78.2, 104.2 (t), 105.0 (t), 111.7 (d),

112.4 (d), 114.6 (2C), 122.4 (d), 122.6, 122.7 (d), 127.5, 129.9 (d), 130.2 (2C), 131.3 (d), 144.3, 151.2, 154.7, 158.3 (dd), 158.4, 159.2 (dd), 163.4 (dd), 164.2 (dd), 171.8; **IR** (Chloroform)**:** 1608, 1750, 3421 cm^{-1}; **MS** (ESI) *m*/*z***:** 540.08 (M + 1).

Preparation of 3-(4-(2-(2,4-difluorophenyl)-2-hydroxy-3-(1*H*-1,2,4-triazol-1-yl)propoxy)phenyl)-4-(2,4-difluorophenyl)-5-hydroxy-5-methylfuran-2(5*H*)-one (167a)

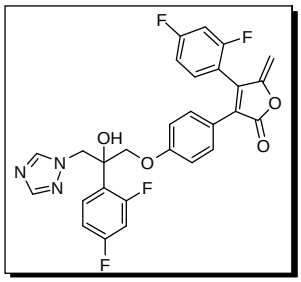
To a stirred solution of compound **167a** (0.539 g, 1 mmol) in acetonitrile (15 mL), was added DBU (0.228 g, 1.5 mmol) in presence of air and allowed to stir at room temperature for 3 h. The acetonitrile was evaporated and the product was extracted with ethyl acetate and purified by column chromatography to give the pure compound 3-(4-(2-(2,4-difluorophenyl)-2-hydroxy-3-(1*H*-1,2,4-triazol-1-yl)propoxy)phenyl)-4-(2,4-difluorophenyl)-5-hydroxy-5-methylfuran-2(5*H*)-one **167a** as off-white fluffy solid (366 mg, 66%).

Nature: Off-white fluffy solid; **MP:** 104 ^{0}C; **Yield:** 66%; **^{1}H NMR** (200 MHz, $CDCl_3$)**:** δ 1.65 (s, 3H), 4.17 (d, *J* = 12 Hz, 1H), 4.23 (d, *J* = 12 Hz, 1H), 4.81 (s, 2H), 6.73 (d, *J* = 10 Hz, 2H), 6.77-7.03 (m, 4H), 7.28 (d, *J* = 10 Hz, 2H), 7.54-7.69 (m, 3H), 7.79 (s, 1H), 8.08 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$)**:** δ 23.9, 54.7, 71.4, 74.7, 77.2, 104.2 (t), 105.3 (t), 105.5, 111.7 (d), 112.2 (d), 114.4 (2C), 122.3 (d), 122.6 (d), 122.7, 129.0, 129.8 (2C), 130.1 (d), 131.0 (d), 144.4, 150.8, 158.4, 158.5 (dd), 159.7 (dd), 163.6 (dd), 165.2 (dd), 170.1; **IR** (Chloroform)**:** 1607, 1755, 3406 cm^{-1}; **MS** (ESI) *m*/*z***:** 556.17 (M + 1).



Preparation of 3-(4-(2-(2,4-difluorophenyl)-2-hydroxy-3-(1*H*-1,2,4-triazol-1-yl)propoxy)phenyl)-4-(2,4-difluorophenyl)-5-methylenefuran-2(5*H*)-one (158a)

A mixture of compound **167a** (0.770 g, 1.38 mmol) and PTSA (0.346 g, 1.80 mmol) dissolved in toluene was allowed to stir at 110 ^{0}C for 5 h under nitrogen atmosphere. It was then cooled to room temperature, toluene was evaporated and the product was extracted with ethyl acetate and purified by column chromatography to give the pure compound **158a** as yellow fluffy solid (406 mg, 53%).

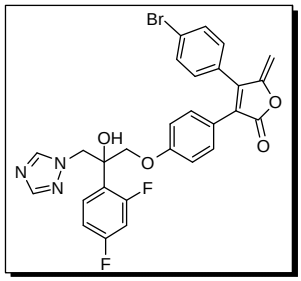


Nature: Yellow fluffy solid; **MP:** 91 ^{0}C; **Yield:** 53%; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 4.21 (d, *J* = 10 Hz, 1H), 4.26 (d, *J* = 10 Hz, 1H), 4.55 (bs, 1H), 4.73 (d, *J* = 4 Hz, 1H),

4.81 (d, *J* = 14 Hz, 1H), 4.90 (d, *J* = 14 Hz, 1H), 5.30 (d, *J* = 4 Hz, 1H), 6.74-7.06 (m, 6H), 7.24-7.32 (m, 1H), 7.40 (d, *J* = 8 Hz, 2H), 7.54-7.67 (m, 1H), 7.85 (s, 1H), 8.02 (s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$)**:** δ 54.4, 71.6, 75.1, 96.4, 104.2 (t), 105.2 (t), 111.9 (d), 112.3 (d), 114.4 (d), 114.6 (2C), 122.3 (d, 2C), 128.8, 130.0 (d), 130.1 (2C), 131.8 (d), 140.0, 144.3, 151.7, 154.1, 158.3 (dd), 158.8, 160.5 (dd), 162.1 (dd), 164.6 (dd), 168.0; **IR** (Chloroform)**:** 1606, 1766, 3431 cm^{-1}; **MS** (ESI) *m*/*z***:** 538.17 (M + 1).

4-(4-Bromophenyl)-3-(4-(2-(2,4-difluorophenyl)-2-hydroxy-3-(1*H*-1,2,4-triazol-1-yl)propoxy)phenyl)-5-methylenefuran-2(5*H*)-one (158b)

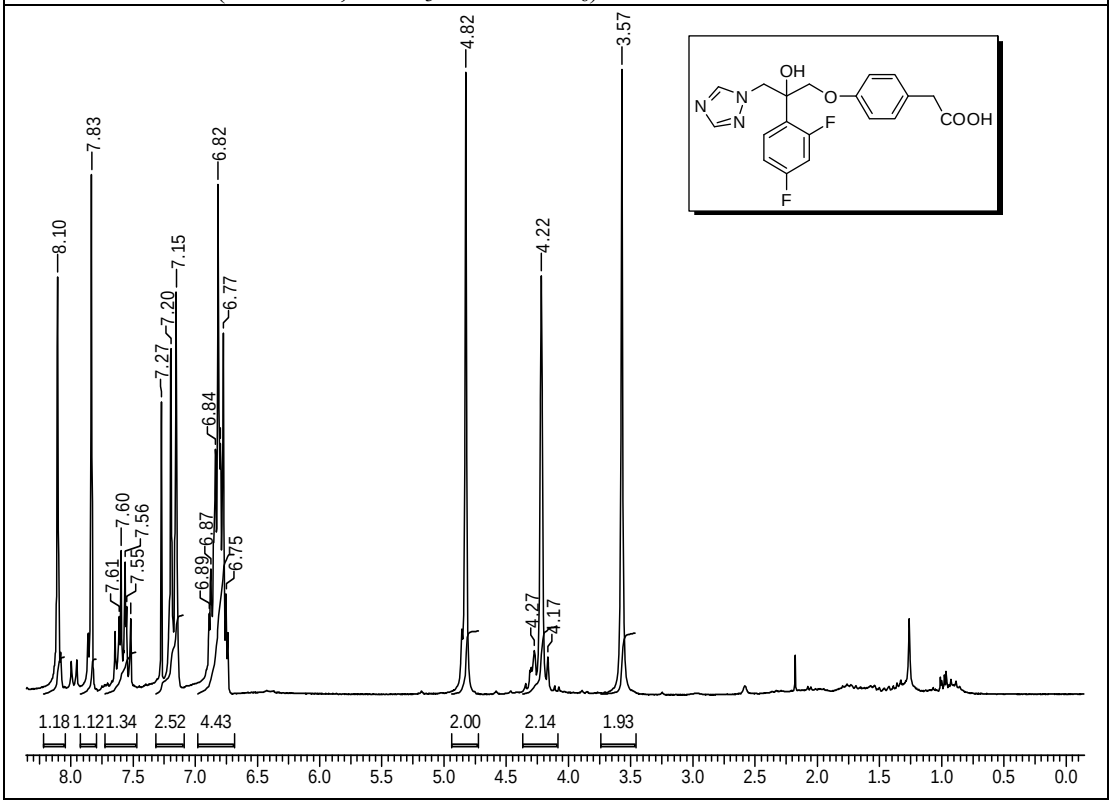
The compound **158b** was prepared by using the procedure given for the preparation of compound **158a**.



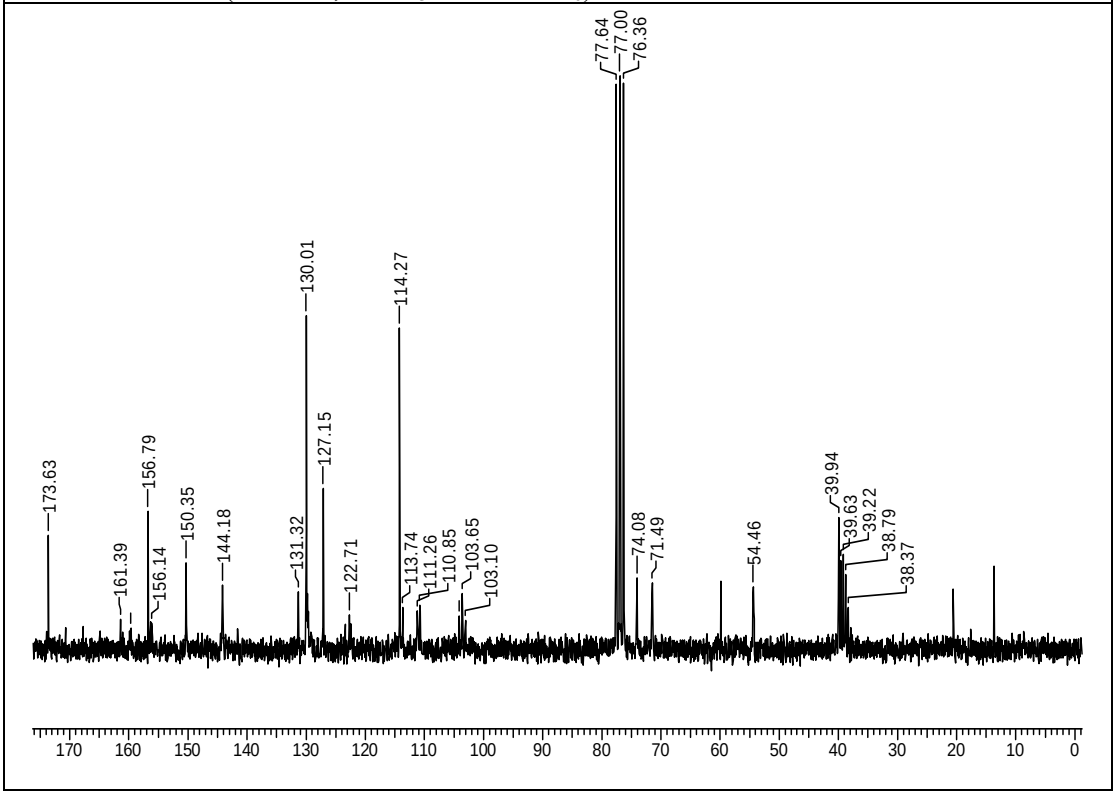
Nature: Pale yellow fluffy solid; **MP:** 87 ^{0}C; **Yield:** 57%; **^{1}H NMR** (200 MHz, $CDCl_3$)**:** δ 4.23 (s, 2H), 4.77-4.91 (m, 3H), 5.32 (d, *J* = 4 Hz, 1H), 6.74-6.90 (m, 4H), 7.18 (d, *J* = 8 Hz, 2H), 7.36 (d, *J* = 10 Hz, 2H), 7.55-7.62 (m, 3H), 7.84 (s, 1H), 8.05 (s, 1H) ; **IR** (Chloroform)**:** 1608, 1767, 3421 cm^{-1}; **MS** (ESI) *m*/*z***:** 581.22 (M + 1).

2.2.7 Selected spectra

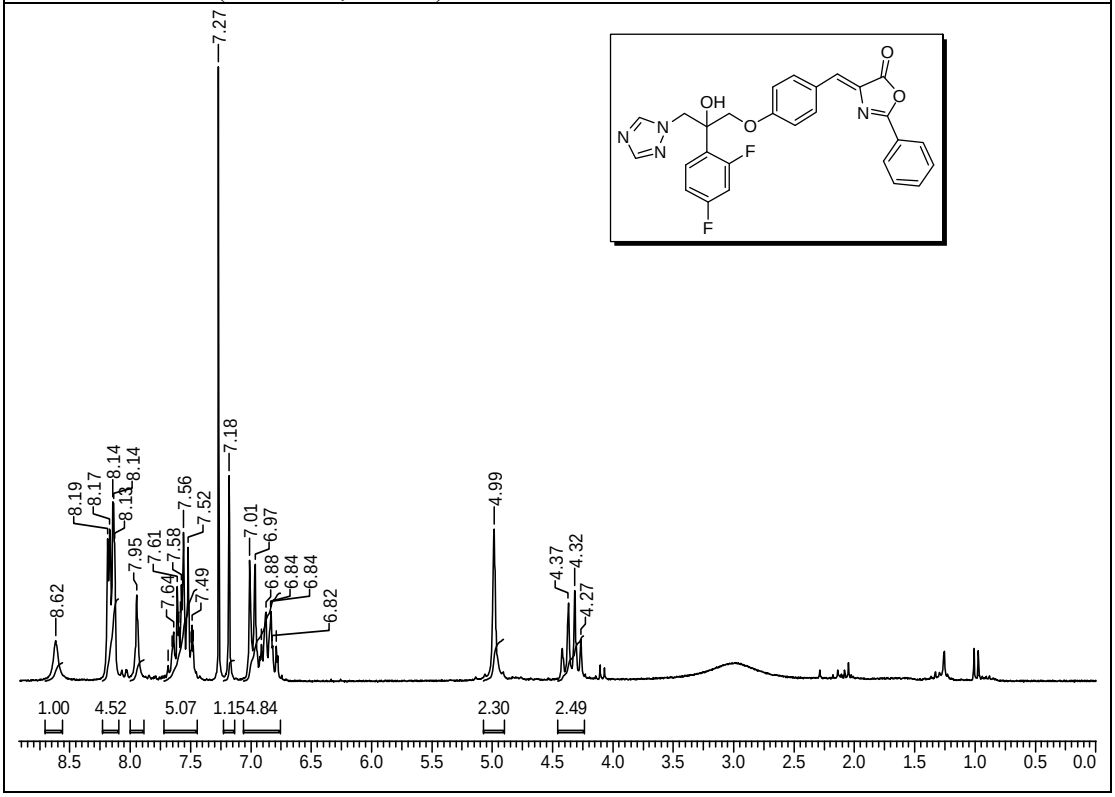
161a: ^{1}H NMR (200 MHz, $CDCl_3$ + DMSO-d_6)



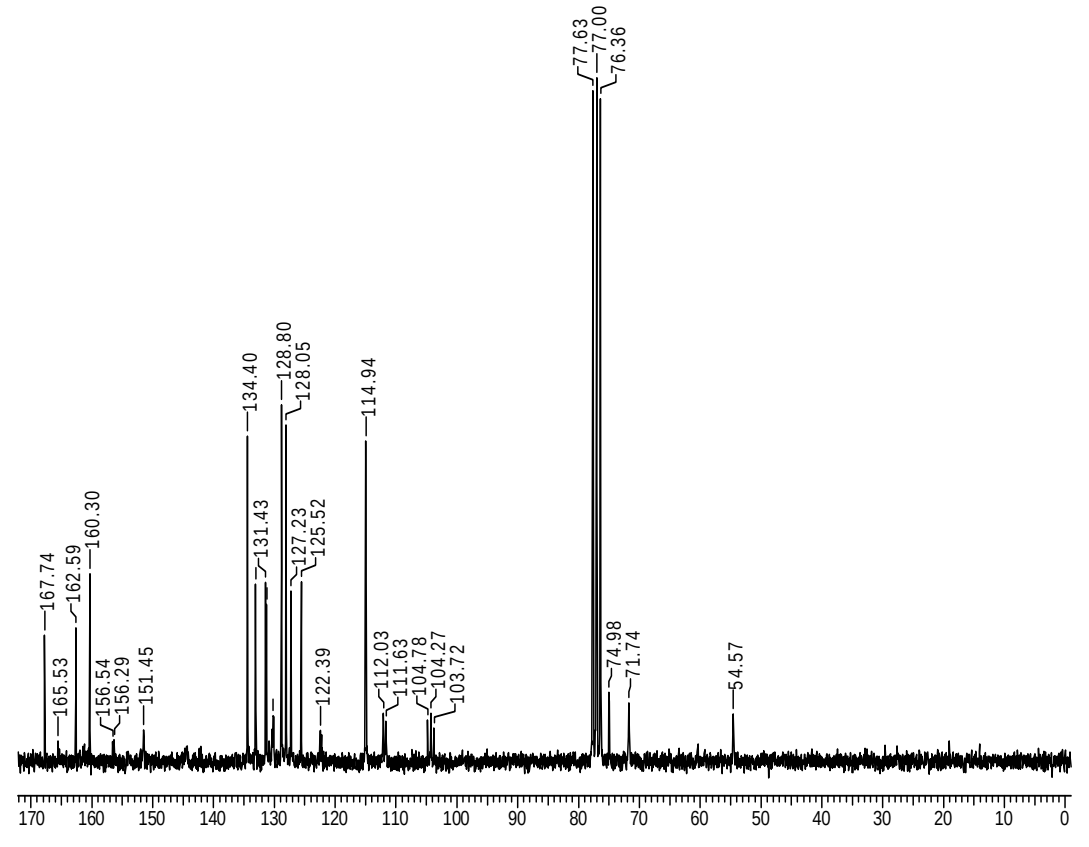
161a: ^{13}C NMR (50 MHz, $CDCl_3$ + DMSO-d_6)



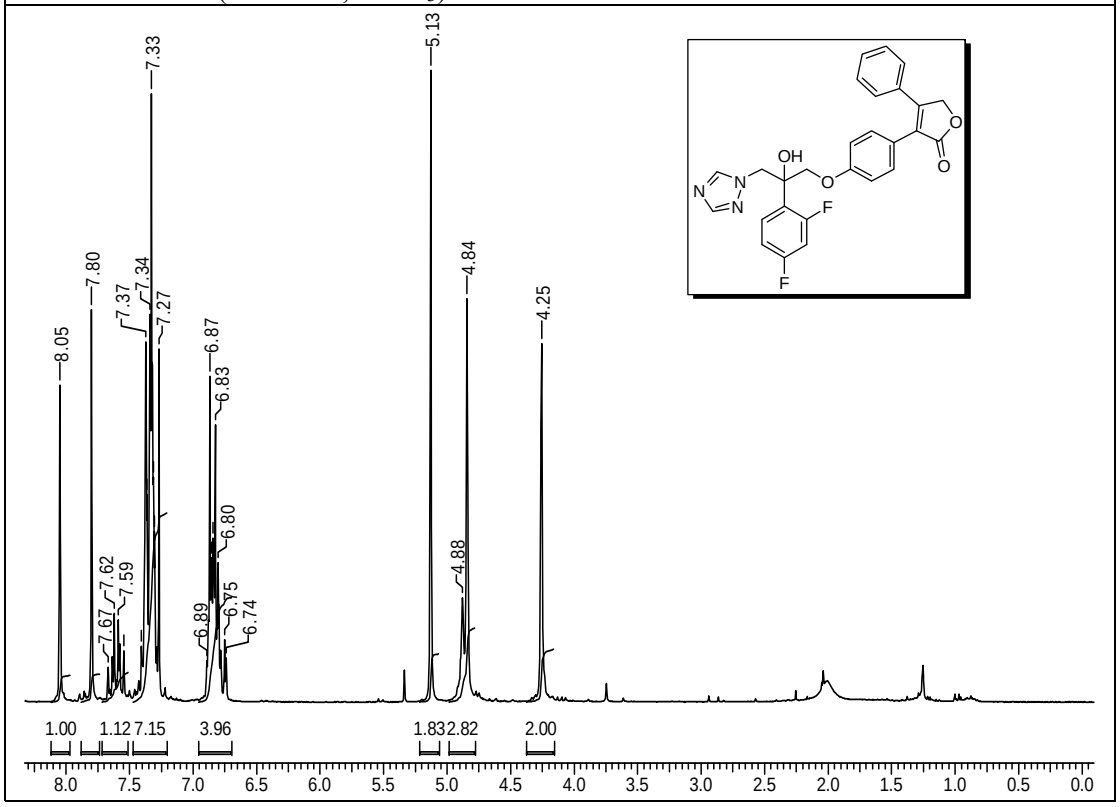
160a: ^{1}H NMR (200 MHz, $CDCl_3$)



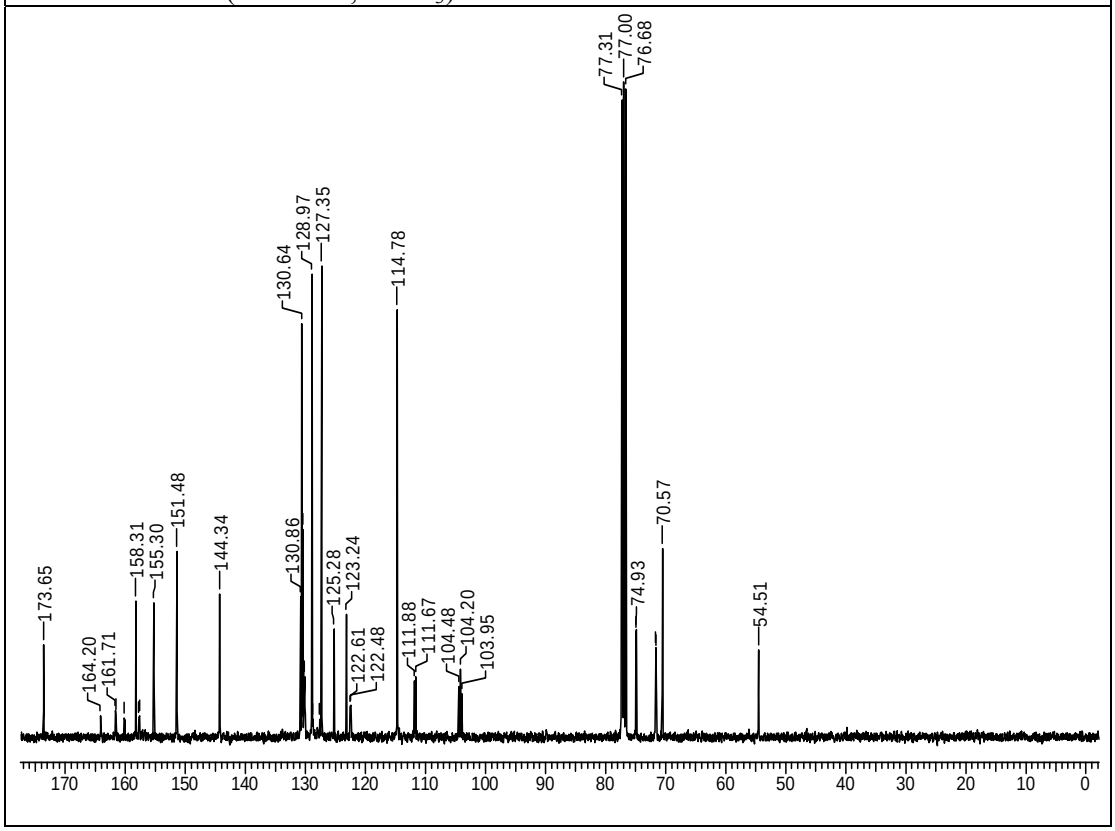
160a: ^{13}C NMR (50 MHz, $CDCl_3$)



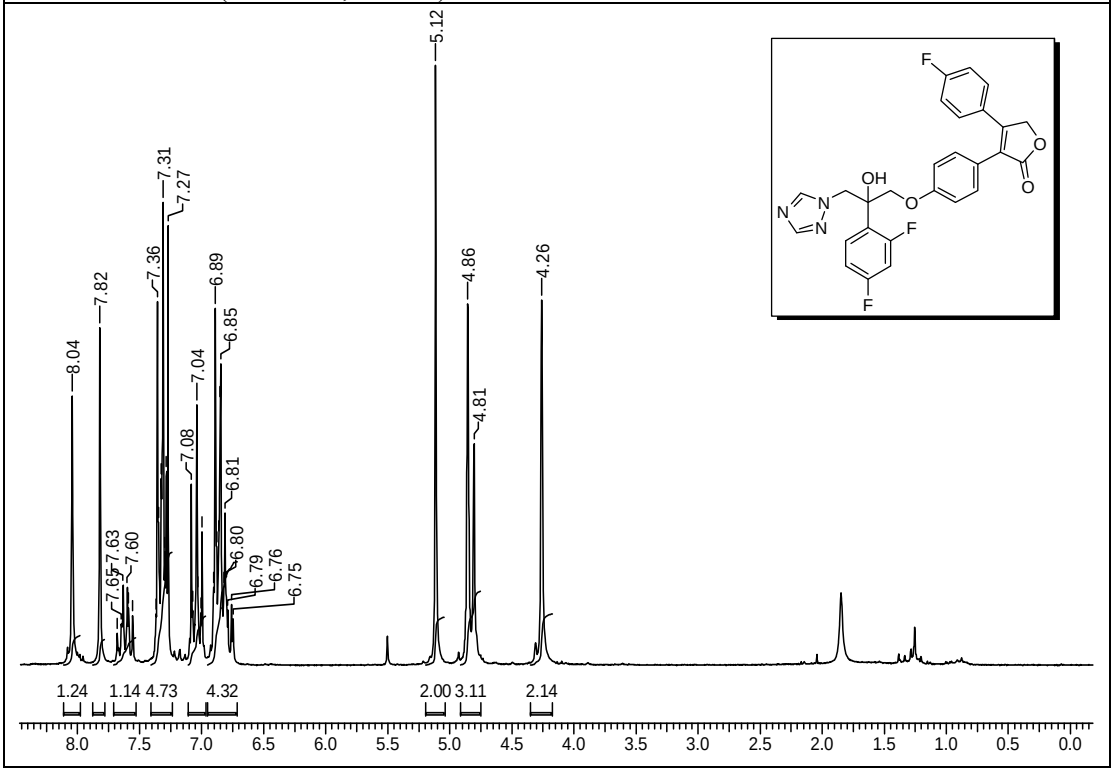
157a: ^{1}H NMR (200 MHz, $CDCl_3$)



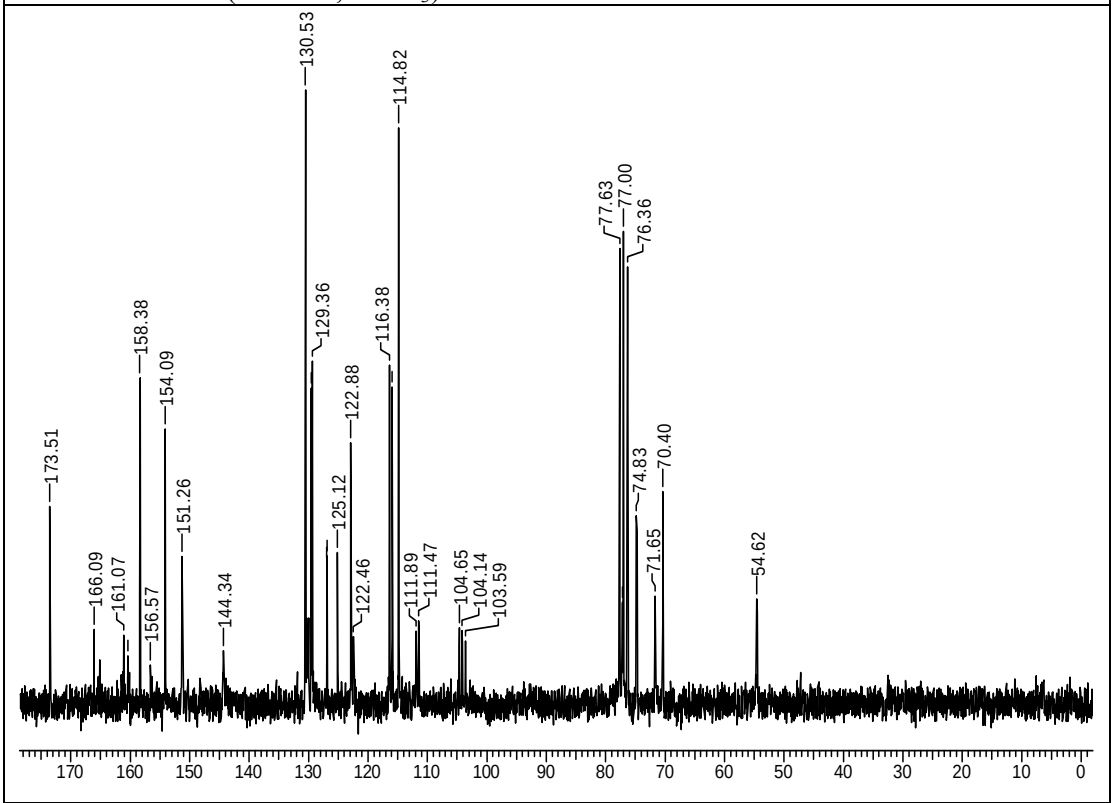
157a: ^{13}C NMR (100 MHz, $CDCl_3$)



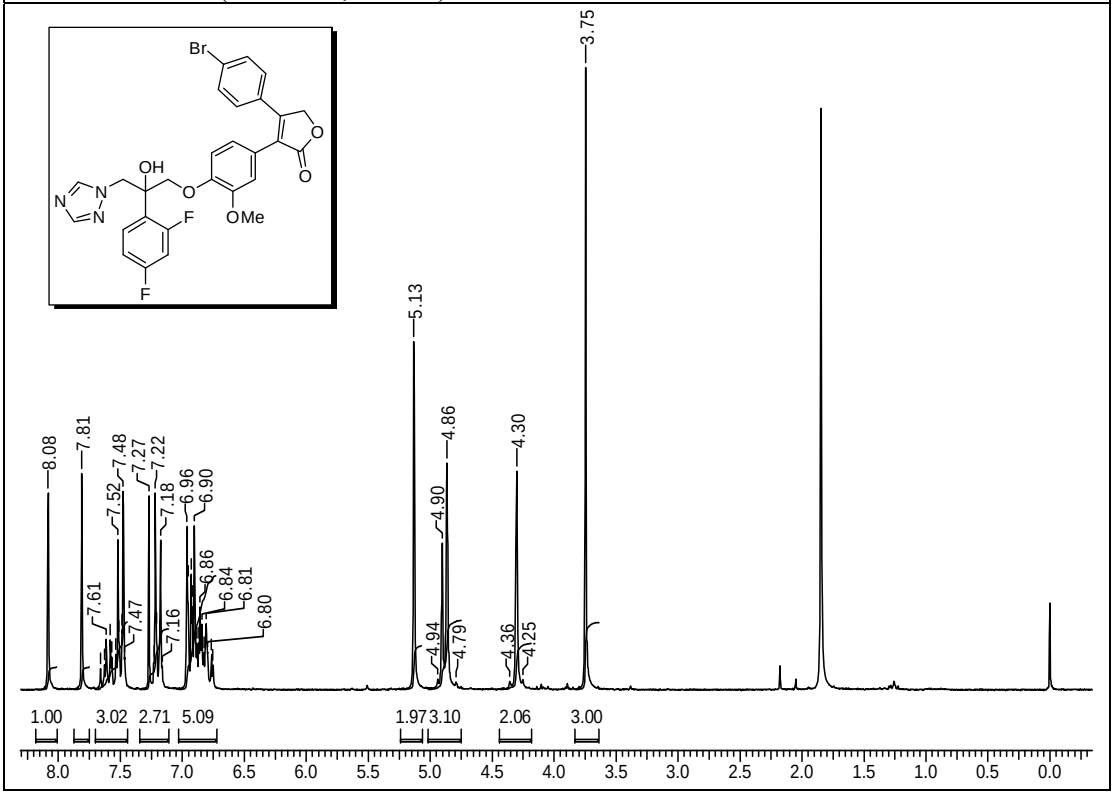
157d: ^{1}H NMR (200 MHz, $CDCl_3$)



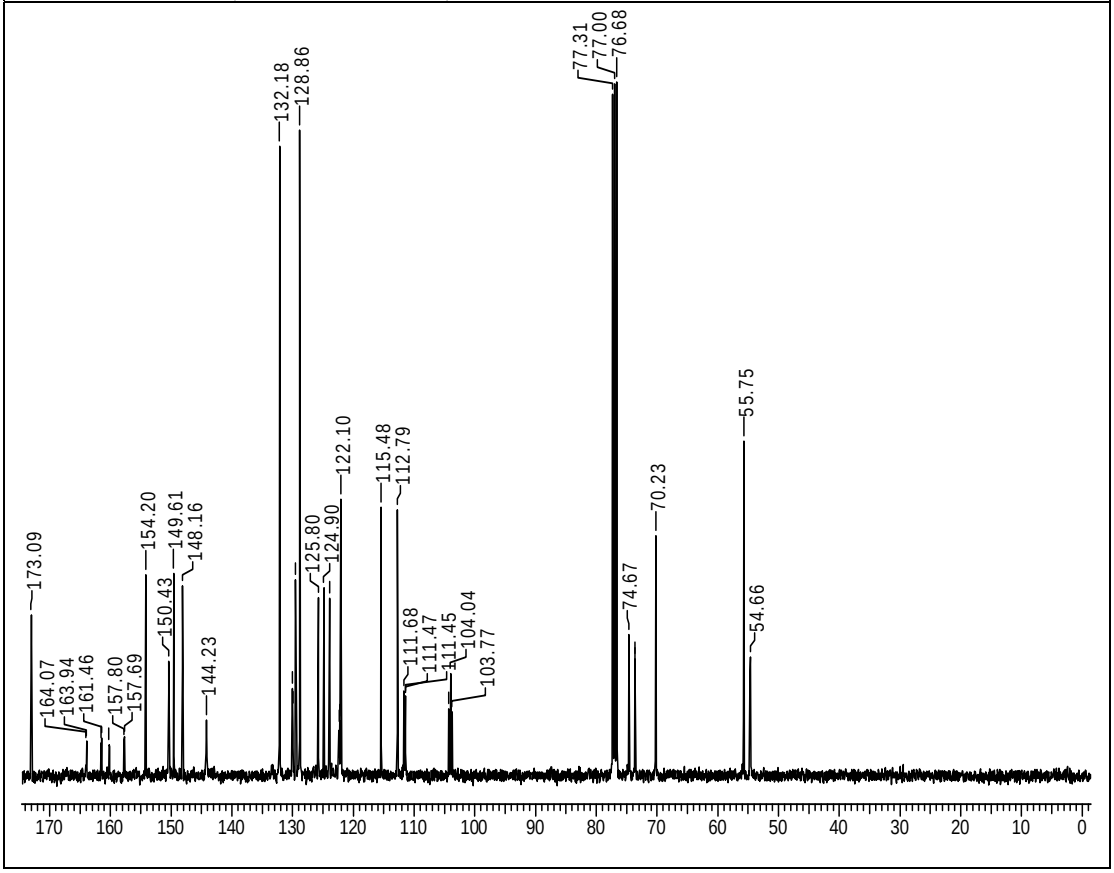
157d: ^{13}C NMR (50 MHz, $CDCl_3$)



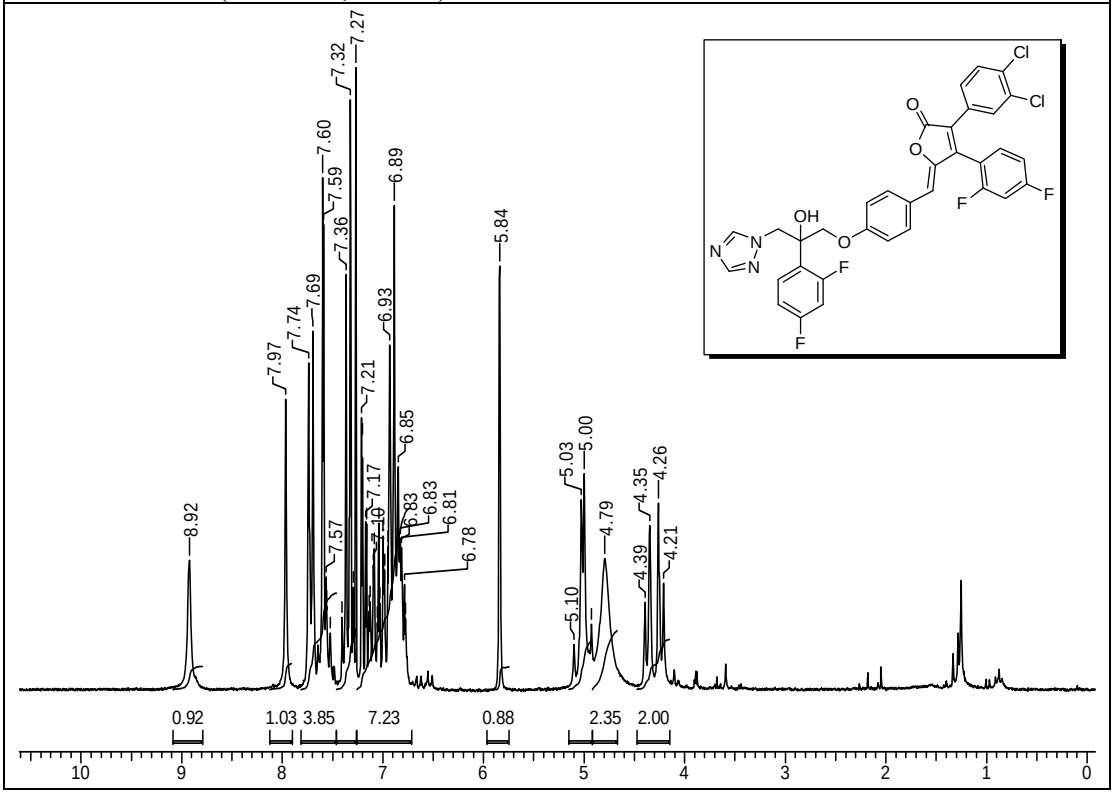
157h: ^{1}H NMR (200 MHz, $CDCl_3$)



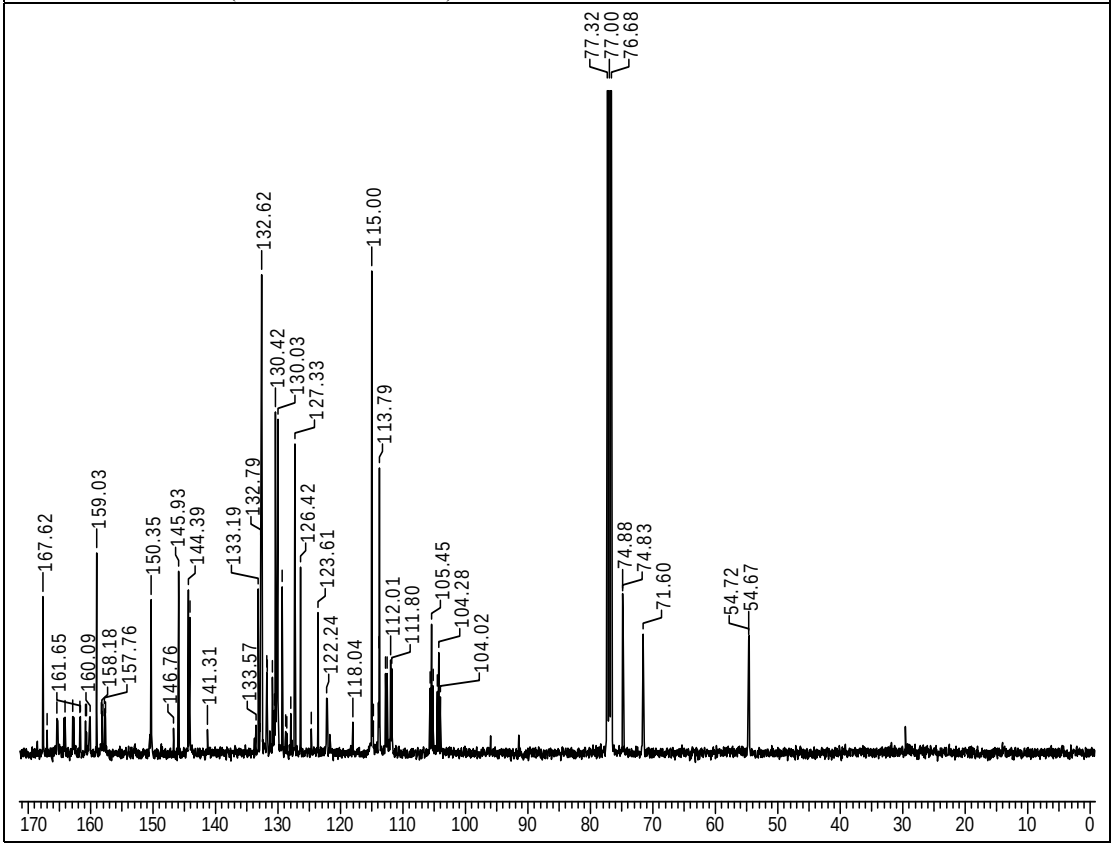
157h: ^{13}C NMR (100 MHz, $CDCl_3$)



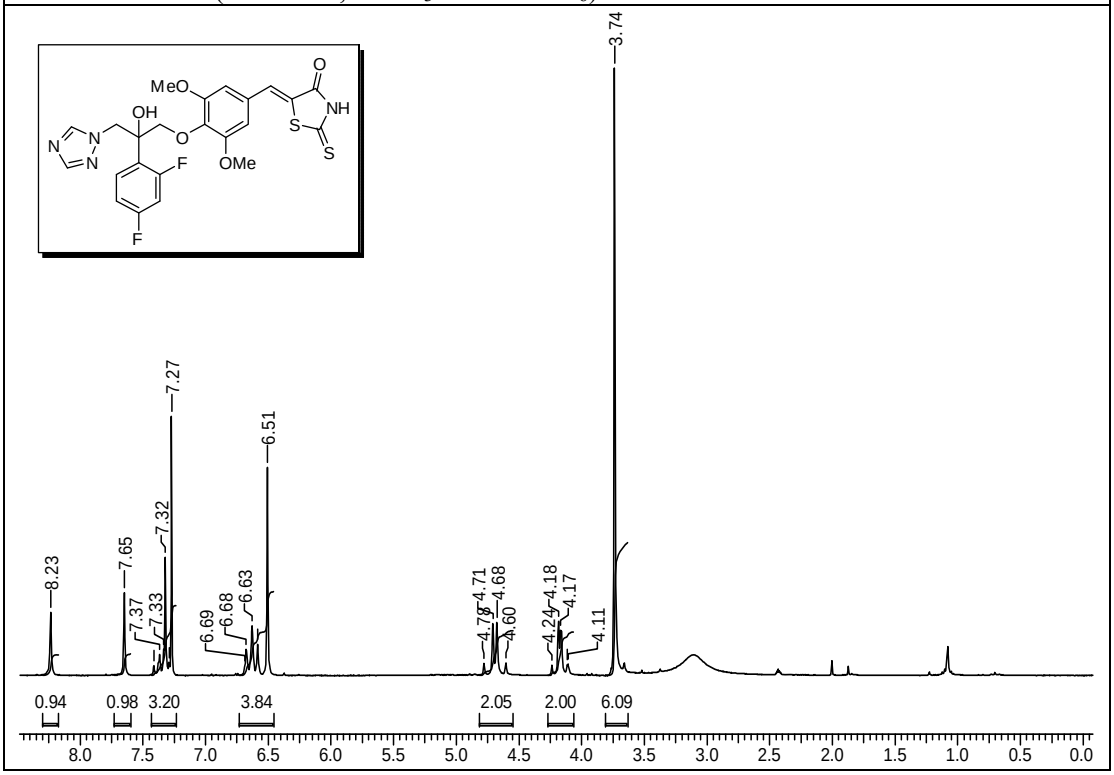
159b: ^{1}H NMR (200 MHz, $CDCl_3$)



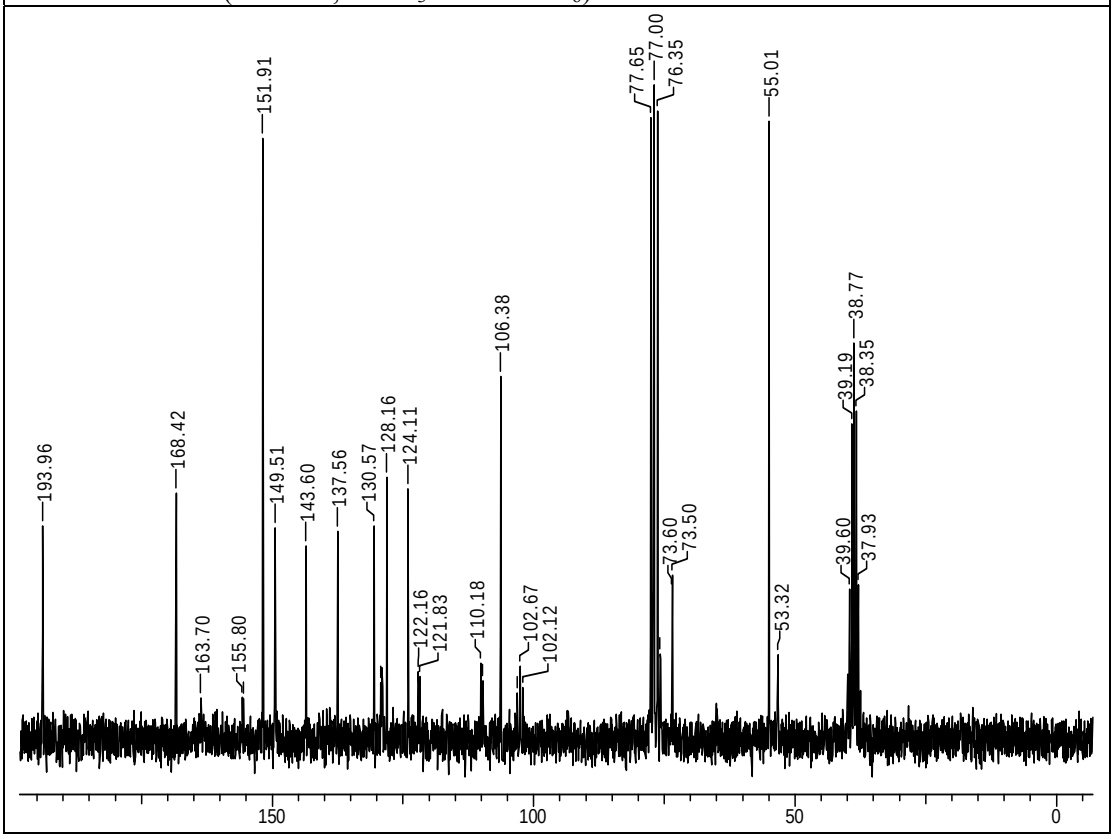
159b: ^{13}C NMR (100 MHz, $CDCl_3$)



170c: ^{1}H NMR (200 MHz, $CDCl_3$ + DMSO-d_6)



170c: ^{13}C NMR (50 MHz, $CDCl_3$ + DMSO-d_6)



2.2.8 References

1. (a) Zhang, R.; Iskander, G.; Silva, P.; Chan, D.; Vignevich, V.; Mohan, V. N.; Bhadbhade, V.; Black, D. S.; Kumar, N. *Tetrahedron* **2011**, *67,* 3010-3016; (b) Zang, T.; Lee, B. W. K.; Cannon, L. M.; Ritter, K. A.; Dai, S.; Ren, D.; Woodd, T. K.; Zhou, Z. S. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 6200-6204; (c) Poon, S. F.; Stock, S.; Payne, J. E.; McGuire, A. R.; Stearns, B.; Yang, X.; Chen, W.; Munoz, B.; Smith, N. D. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 2259-2263; (d) Zarghi, A.; Praveen Rao, P. N.; Knaus, E. E. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 1957-1960; (e) Ma, S.; Shi, Z.; Yu, Z. *Tetrahedron Lett*. **1999**, *40*, 2393-2396.
2. (a) Takadoi, M.; Katon, T.; Ishiwata, A.; Terashima, S. *Tetrahedron Lett.* **1999**, *40*, 3399-3402; (b) Bruggemann, M.; McDonald, A. I.; Overmann, L. E.; Rosen, M. D.; Schiwink, L.; Scott, J. P. *J. Am. Chem. Soc.* **2003**, *125*, 15284-15285.
3. (a) Rao, C. B. S. 'Chemistry of lignans', Andhra university press. Waltair, **1978**; (b) Ward, R. S. *Tetrahedron* **1990**, *46*, 5029-5041.
4. (a) Brown, H. C.; Kulkarni, S. V.; Racherla, V. S. *J. Org. Chem*. **1994**, *59*, 365-369; (b) Koch, S. C.; Chamberlin, A. R. *J. Org. Chem*. **1993**, *58*, 2725-2737.
5. (a) Zapf, S.; Anke, T.; Sterner, O. *Acta Chem. Scand.* **1995**, *49,* 233-234; (b) Pour, M.; Špulák, M.; Balšánek, V.; Kuneš, J.; Buchta, V.; Waisser, K. *Bioorg. Med. Chem. Lett.* **2000,** *10,* 893-898; (c) Pour, M.; Špulák, M.; Buchta, V.; Kubanová, P.; Vopršalová, M.; Wsól, V.; Fáková, H.; Koudelka, P.; Pourová, H.; Schiller, R. *J. Med. Chem*. **2001**, *44***,** 2701-2706; (d) Vale-Silva, L. A.; Buchta, V.; Vokurková, D.; Pour, M. *Bioorg. Med. Chem. Lett.* **2006**, *16,* 2492-2495.
6. Lattmann, E.; Ayuko, W.; Kinchinaton, D.; Langley, C.; Singh, H.; Karimi, L.; Tisdale M. *J. pharm. Pharmacol.* **2003**, *55*, 1259-1265.
7. Baveja, J. K.; Willcox, M. D. P.; Hume, E. B. H.; Kumar, N.; Odell, R.; Poole-Warren, L. A. *Biomaterials* **2004**, *25*, 5003-5012.
8. Wu, H.; Song, Z.; Hentzer, M.; Andersen, J. B.; Molin, S.; Givskov, M.; Hoiby1, N. *J. Antimicrob. Chemother.* **2004**, *53*, 1054-1061.
9. David, V. S.; Fabio, E. S.; Alex, G. F. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 2057-2060.
10. Ortega, M. J.; Zubia, E.; Ocana, J. M.; Naranjo, S.; Salva, J. *Tetrahedron* **2000**, *56*, 3963-3967.
11. Bellina, F.; Anselmi, C.; Viel, S.; Mannina, L.; Rossi, R. *Tetrahedron* **2001**, *57*, 9997-10007.
12. Bellina, F.; Anselmi, C.; Rossi, R. *Tetrahedron Lett.* **2002**, *43*, 2023-2027.

13. Bellina, F.; Anselmi, C.; Martina, F.; Rossi, R. *Eur. J. Org. Chem*. **2003**, *22*, 2290-2302.

14. Yang, X.; Shimizu, Y.; Steiner, J. R.; Clardy, J. *Tetrahedron Lett.* **1993**, *34*, 761-764.

15. Kim, Y.; Nam, N.-H.; You, Y.-J.; Ahn, B.-Z. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 719-722.

16. (a) Ortega, M. J.; Zubia, E.; Ocana, J. M.; Naranjo, S.; Salva, J. *Tetrahedron* **2000**, 56, 3963-3967; (b) Bellina, F.; Anselmi, C.; Rossi, R. *Tetrahedron Lett.* **2002**, *43*, 2023-2027.

17. Marie, J.; Steffen, S.; Natalya, U. F.; Jan, M.; Henrik, H. J. *Bioorg. Med. Chem. Lett.* **2011**, *19*, 2407-2417.

18. (a) Zarghi, A.; Praveen Rao, P. N.; Edward, E. K. *Bioorg. Med. Chem.* **2007**, *15*, 1056-1061; (b) Chen, Q.-H.; Praveen Rao, P. N.; Edward, E. K. *Bioorg. Med. Chem.* **2006**, *14*, 7898-7909.

19. Senel, P.; Tichotová, L.; Votruba, I.; Buchta, V.; Špulák, M.; Kuneš, J.; Nobilis, M.; Krenk, O.; Pour, M. *Bioorg. Med. Chem.* **2010**, *18,* 1988-2000.

20. Tietze, L. F.; Bell, H. P.; Chandrasekhar, S. *Angew. Chem. Int. Ed.* **2003**, *42,* 3996-4028.

21. Gao, P.-H.; Cao, Y.-B.; Xu, Z.; Zhang, J.-D.; Zhang, W.-N.; Wang, Y.; Gu, J.; Cao, Y.-Y.; Li, R.-Y.; Jia, X.-M.; Jiang, Y.-Y. *Biol. Pharm. Bull.* **2005**, *28,* 1414-1417.

22. (a) Mo, A.; Zhang, H.; Pan, H. CN 1995-111510, **1995**; CA 131:228724; (b) Antoni, S.; Marcial, M.; Roser, P. *ARKIVOC* **2007**, *(iv)*, 234-250; (c) Lebouvier, N.; Giraud, F.; Corbin, T.; Na, Y. M.; Baut, G. L.; Marchand, P.; Borgne, M. L. *Tetrahedron Lett.* **2006**, *47*, 6479-6483; (d) Tamoto, K.; Tanaka, Y.; Miyauchi, H.; Fujimoto, K.; Ohashi, N. *Bull. Chem. Soc. Jpn.* **1994**, *67*, 1427-1433; (e) Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1962**, *84*, 3782-3783; (f) Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1965**, *87*, 1353-1364; (g) Richardson, K.; Narayanaswami, S. Eur. Pat. Appl. EP0122056, **1984**; (h) Richardson, K.; Gymer, G. E. Eur. Pat. Appl. EP0153803, **1985**.

23. (a) Mahajan, S. S.; Pikle. R. P. *Indian. J. Chem.* **2006**, *45B,* 1554-1556; (b) Sandhar, R. K.; Sharma, J. R.; Manrao, M. R. *Indian. J. Heterocycl. Chem.* **2003**, *13*, 119-122.

24. (a) Black, W. C.; Brideau, C.; Chan, C.-C.; Charleson, S.; Cromlish, W.; Gordon, R.; Grimm, E. L.; Hughes, G.; Leger, S.; Li, C.-S.; Riendeau, D.; Thérien, M.; Wang, Z.; Xu, L.-J.; Prasit, P. *Bioorg. Med. Chem. Lett.* **2003**, *13,* 1195-1198; (b) Wakharkar,

R. D.; Deshpande, V. H.; Landage, A. B.; Upadhyaya, B. K. *Synth. Commun.* **1987**, *17,* 1513-1516; (c) Caturla, F.; Amat, M.; Reinoso, R. F.; Córdoba, M.; Warrellow, G. *Bioorg. Med. Chem. Lett.* **2006**, *16,* 3209-3212.

25. Chavan, S. P.; Pathak, A. B.; Pandey, A.; Kalkote, U. R. *Synth. Commun.* **2007**, *37,* 4253-4263.
26. (a) Julian, P. L.; Sturg, B. M. *J. Am. Chem. Soc.* **1935**, *57,* 1126-1128; (b) Brown, F. C.; Bradsher, C. K.; Morgan, E. C.; Tetenbaum, M.; Wilder Jr, P. *J. Am. Chem. Soc.* **1956**, *78,* 384-388; (c) Sortino, M. P.; Juárez, S.; Quiroga, J.; Abonía, R.; Insuasty, B.; Nogueras, M.; Rodero, L.; Garibotto, R.; Enriz, D.; Zacchino, S. A. *Bioorg. Med. Chem.* **2007**, *15,* 484-494.
27. (a) CLSI: Reference method for broth dilution antifungal susceptibility testing of yeasts, Approved standard, second edition M27-A2, **2002**; (b) CLSI: Reference method for broth dilution antifungal susceptibility testing of filamentous fungi, Approved standard M38-A, **2002**.
28. (a) Saksena, A. K.; Girijavallabhan, V. M.; Lovey, R. G.; Pike, R. E.; Desai, J. A.; Ganguly, A. K.; Hare, R. S.; Loebenberg, D.; Cacciapuoti, A.; Parmegiani, R. M. *Bioorg. Med. Chem. Lett.* **1994**, *16*, 2023-2028; (b) Murakami, K.; Mochizuki, H. Eur. Pat. Appl. EP0472392A2, **1991**.

Chapter 3: Section I

A short synthesis of 3,6-disubstituted N-2- thienyl/aryl-indoles

Chapter 3: Section I

A short synthesis of 3,6-disubstituted N-2- thienyl/aryl-indoles

3.1.1 Abstract

A short synthetic strategy for 3,6-disubstituted-*N*-2-thienyl/aryl-indoles, involving reaction of substituted 2,4-difluoro/dichloro-styrene epoxide with substituted 2-formylaminothiophenes or substituted *N*-formylanilines in presence of a base followed by treatment with an acid, has been developed. The method was applied for the synthesis of a number of indoles with a variety of substituents at 1, 3 and 6 positions of the indole moiety.

3.1.2 Introduction

Substituted indoles are the most common and important heterocycles in nature[1]. Additionally, the indole motif is represented within a range of pharmaceutical agents and materials (Figure 1). In nature, substituted indoles serve various purposes that range from cell signaling agents and biological function (seratonin **171**), to the structural building blocks of proteins (tryptophan **172**). Many indole-containing natural products, including well-known indole plant alkaloids such as strychnine **173** and yohimbine **174** have been identified for their biological uses. Of the many types of substituted indoles, one particular sub-class of interest is those indoles bearing substitution at the C(2) and C(3) positions, and several promising therapeutic agents belong to this class. Gonadotropin releasing hormone antagonist **175** was identified for the treatment of developmental disorders.[2] Compound **176** is a glycine receptor antagonist that was identified for the treatment of stroke[3], and fluvastatin **177** is a drug for the treatment of primary hypercholesterolemia[4].

The natural rareness of such important substances and the chemical challenges that their structures pose, have created a great deal of interest in the development of fully synthetic routes to these indole alkaloids. Therefore the search for efficient synthesis of indoles has inspired chemists to design and synthesize a variety of indoles and indole derivatives.

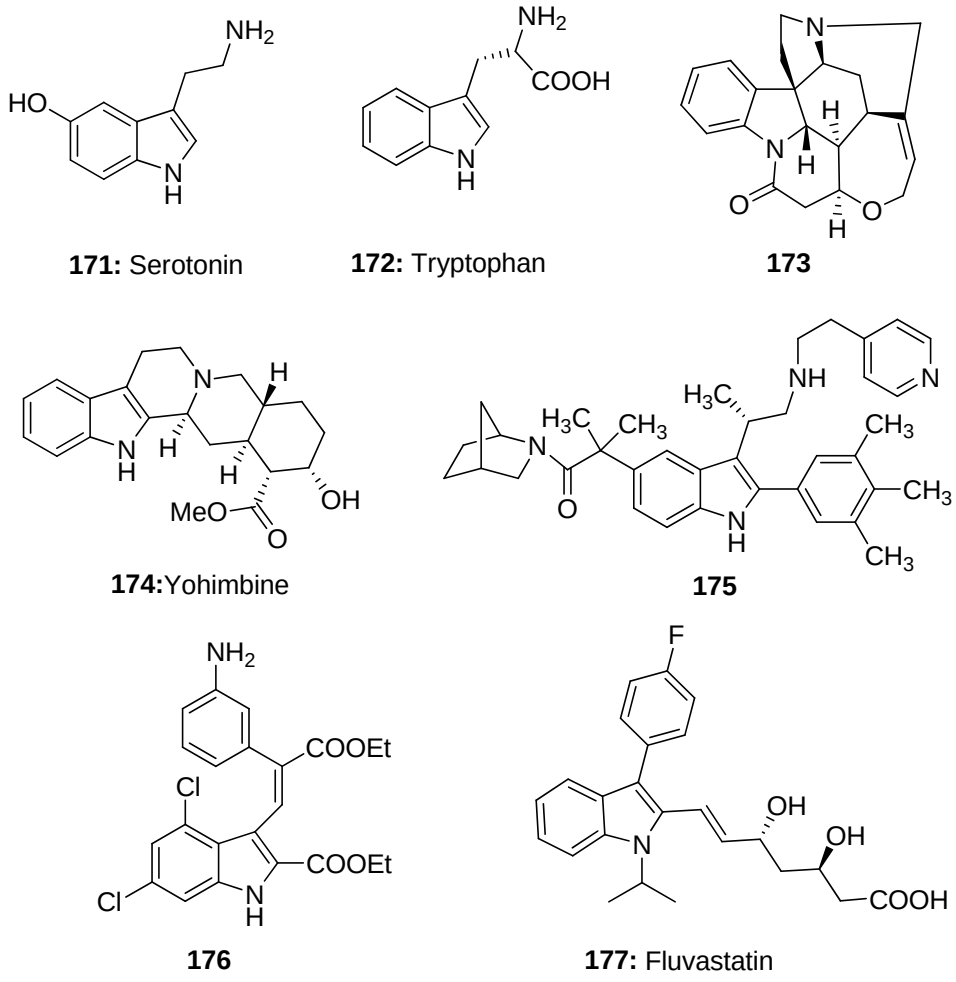


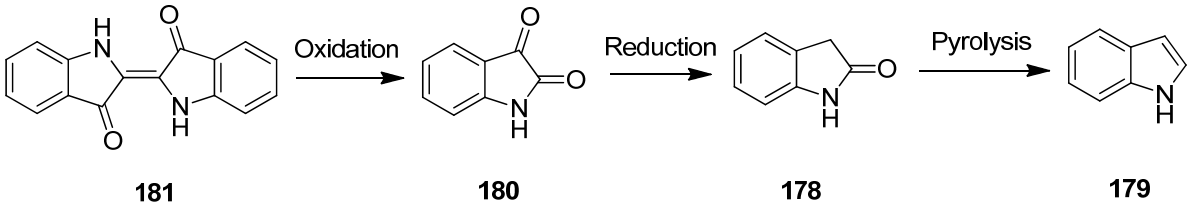
Figure 1. Selected examples of biologically active indoles.

3.1.3 Review of literature

Preparation of indoles

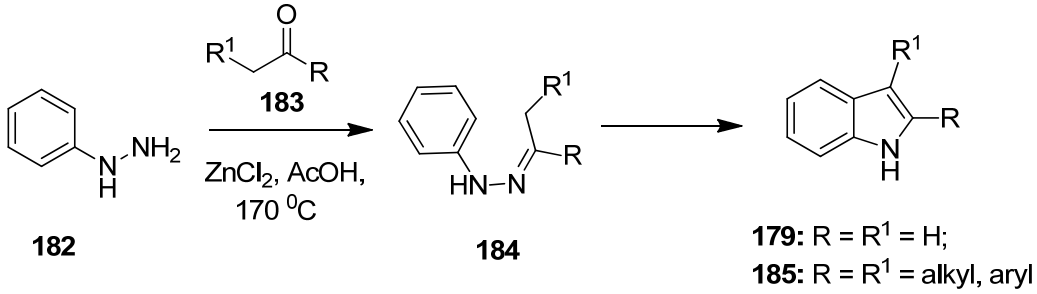
There is an immense volume of literature available on indole synthesis and is summarized in many excellent reviews so brief outlines of the most significant developments are revealed here. The first preparation of indole dates from 1866 but the Fisher indole synthesis, which remains one of the most versatile methods for preparing indoles, was first reported in 1883[5]. The principal commercial source of indole is extraction from coal tar, although the feasibility of industrial synthesis from starting materials such as aniline, ethylene glycol and others has also been demonstrated[5]. Indole **(179**) itself was first obtained by Adolf Baeyer by pyrolysis of oxindole (**178**) with zinc dust in 1886. Oxindole

(**178**) was obtained from the reduction of isatin (**180**) which was obtained from oxidizing the natural insoluble dark blue dye called indigo (**181**) as shown in Scheme 1.



Scheme 1. Synthesis of indole

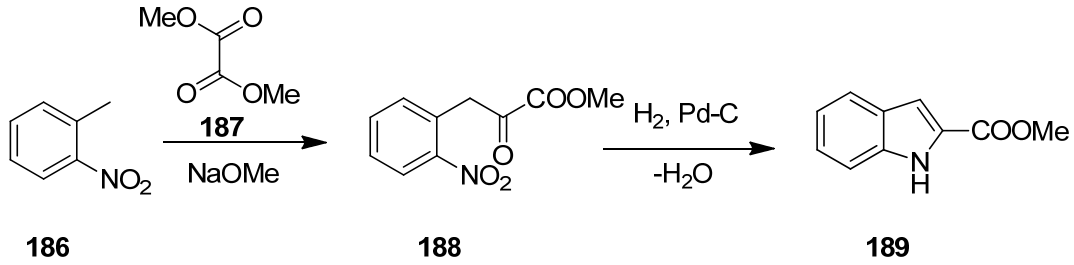
Although the main source of indole is extraction from coal tar, many researchers have reported synthetic methods for the preparation of various substituted indoles from readily available starting materials owing to their importance in natural products synthesis and pharmaceutical chemistry. One of the most widely used methods as mentioned previously is the Fischer indole synthesis[5]. This method involves heating phenylhydrazine (**182**) with aldehyde or ketone **183** in presence of zinc chloride in acetic acid, forming phenylhydrazone **184** which subsequently rearranges with the loss of ammonia to give indole (**179)** or 2, 3-disubstituted indoles **185** as outlined in Scheme 2.



Scheme 2. Fischer indole synthesis

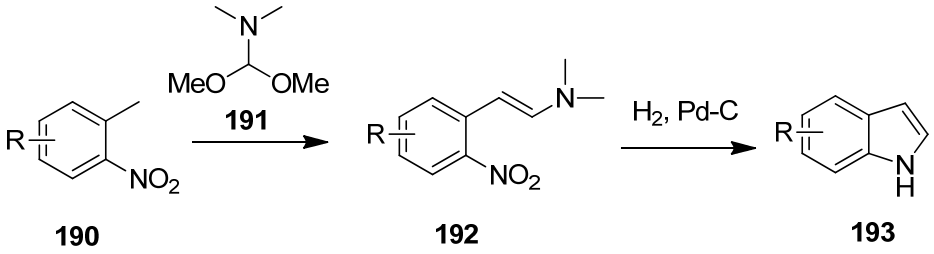
Other methods include the Gassman indole synthesis[6], Reissert indole synthesis[7], Leimgruber-Batcho indole synthesis[8], Madelung indole synthesis[9] and Bischler indole synthesis[10] to name a few. Both the Reissert and Leimgruber-Batcho syntheses depend on the acidity of methyl group *ortho* to an aromatic nitro group while Madelung synthesis proceeds *via* a Wittig-type reaction[11]. The Reissert synthesis is suitable for the preparation of 2-substituted indoles. For example, when 1-methyl-2-nitrobenzene (**186**) is treated with

dimethyl oxalate (**187**) in the presence of sodium methoxide as a base, it gave methyl 3-(2-nitrophenyl)-2-oxopropanoate (**188**), which upon catalytic hydrogenation (H_2, Pd-C) reduced the nitro group to an amino group followed by a spontaneous cyclodehydration to give indole-2-carboxylic acid methyl ester (**189**) (Scheme 3)[12].



Scheme 3. Synthesis of methyl 1*H*-indole-2-carboxylate

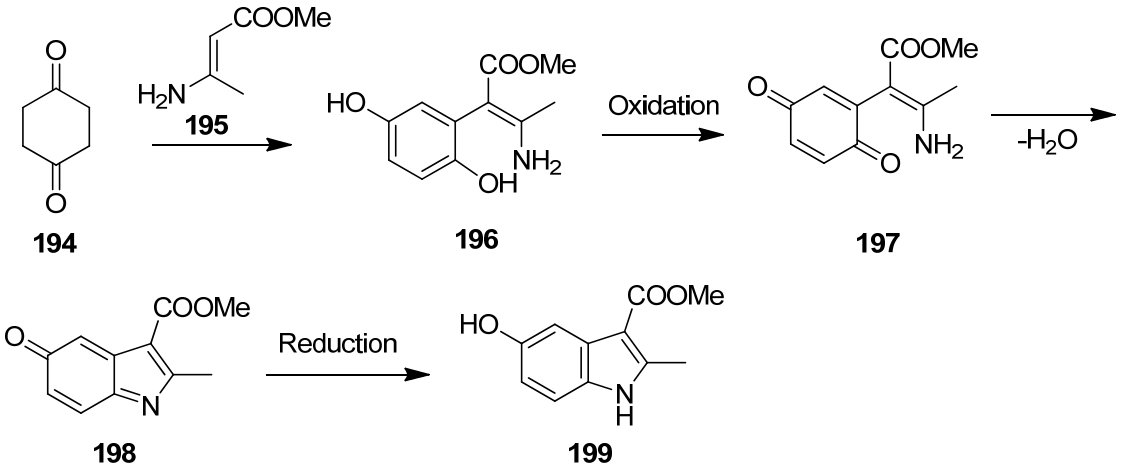
On the other hand, the Leimgruber-Batcho synthesis is particularly suitable for the synthesis of indoles with substituents on the benzene ring but no substituents on the pyrrole moiety. In this method, substituted 1-methyl-2-nitrobenzene **190** is treated with *N*,*N*-dimethylformamide dimethyl acetal **191** to give substituted 1-dimethylamino-2-(*o*-nitrophenyl)ethene **192**, which on reductive cyclization yielded substituted indole **193** (Scheme 4). Madelung synthesis (not illustrated) is essentially limited to the preparation of 2-alkylindoles due to the vigorous reaction conditions, while Bischler synthesis (not illustrated) is particularly suitable for 2- and 3-disubstituted indoles[12].



Scheme 4. Synthesis of substituted indoles

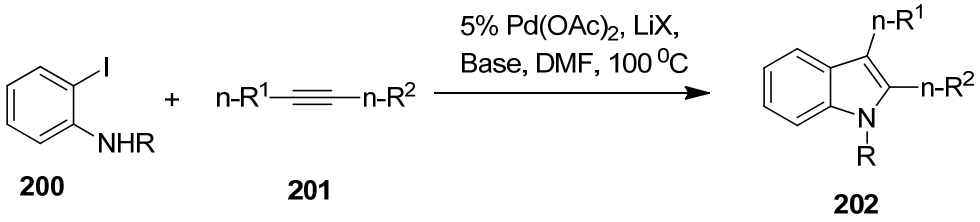
Up until now the methods discussed in the synthesis of indole have nitrogen atom bonded directly to an arene. Only a few indole syntheses make use of building blocks in which the nitrogen atom is not directly bonded to arene. The Nenitzescu synthesis is an example of this type. In this synthesis, 1,4-quinone **194** is condensed with (*E*)-methyl 3-aminobut-2-enoate (**195**) by a Michael addition to give (*E*)-methyl 3-amino-2-(2,5-

dihydroxyphenyl)but-2-enoate (**196**). When the compound **196** was subjected to oxidation, it gave (*E*)-methyl 3-amino-2-(3,6-dioxocyclohexa-1,4-dienyl)but-2-enoate (**197**) which was followed by a cyclodehydration to give methyl 2-methyl-5-oxo-5*H*-indole-3-carboxylate (**198**) and the reduction of the compound **198** furnished 2,3-disubstituted indole, methyl 5-hydroxy-2-methyl-1*H*-indole-3-carboxylate (**199**) (Scheme 5)[12]. This method provides a rapid resource of preparing functionalized 5-hydroxyindoles from simple, readily accessible starting materials[13], and the hydroxyl group can also be introduced onto the indole nucleus[14].



Scheme 5. synthesis of 2,3- substituted indoles

In addition, more modern approaches to the synthesis of substituted indoles have emerged that take advantage of the current advances in transition metal chemistry[15]. Some newer methods to construct 2,3-disubstituted indoles include the radical cyclization of 2-alkenylisocyanides[16], reductive cyclization of acylamido carbonyl compounds[17], cyclization of *N*-(2-halophenyl)allenamides[18], palladium-catalyzed cyclization of 2-alkynyltrifluoroanilines in the presence of an alkenyl- or aryl halide[19], and palladium-catalyzed cyclization of 2-iodoanilines **200** with disubstituted alkynes **201**. Among these, the Larock indole synthesis[20] has emerged as a versatile and powerful method for the formation of substituted indoles **202** (Scheme 6).



Scheme 6. Larock indole synthesis

However, many of these methods suffer from several drawbacks (e.g., the use of either unstable diazo compounds or moisture-sensitive organometallic reagents or expensive catalysts) and are only useful for the synthesis of specific indole derivatives. Moreover, some of them involve multistep synthesis and are not suitable for the preparation of these compounds in large quantity. The diversity of indoles as well as their biological and pharmaceutical relevance is still motivating academic and industrial researchers to look for new and improved syntheses for indole derivatives. In the present work, we have developed a short synthesis of substituted indoles from substituted styrene epoxides and the results are presented in this section.

3.1.4 Present work

3.1.4.1 Objective

N-Substituted 3-((1*H*-imidazol-1-yl)methyl)-1*H*-indoles of general structure **203** (Figure 2) are known to exhibit antifungal activity [21]. We desired to develop a general method for the synthesis of the compounds with general structure **204** wherein the substituted benzyl group in compound **203** would be replaced with various structural units for the study of the antifungal activity.

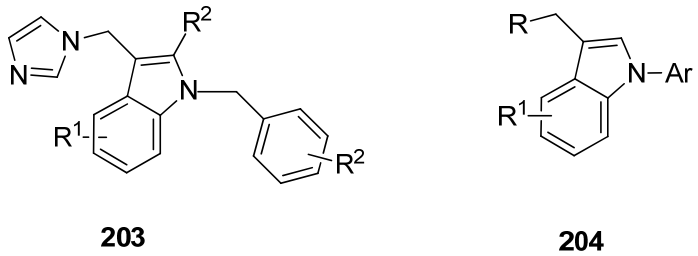
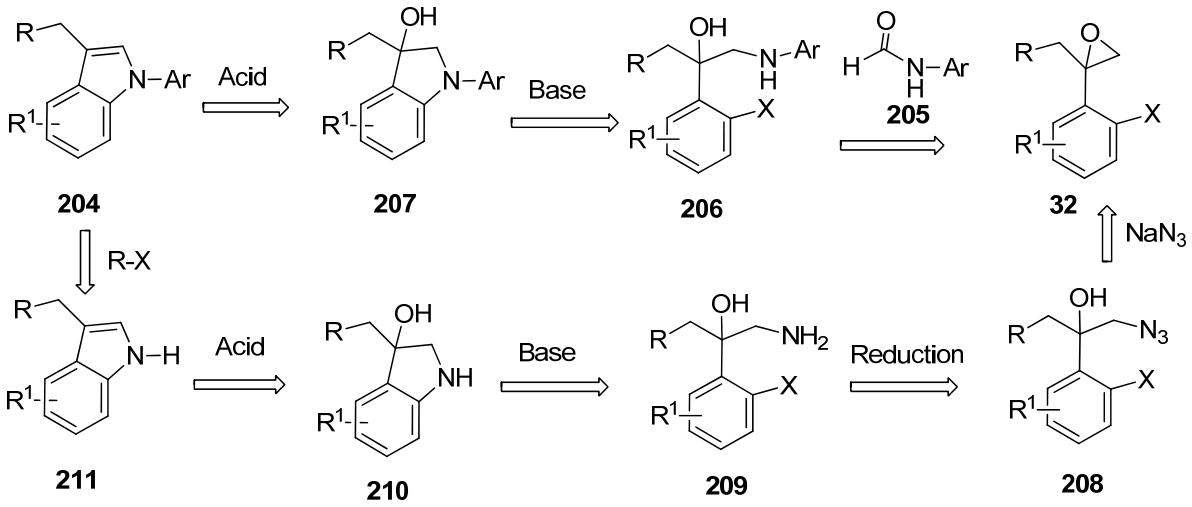


Figure 2. General structures of substituted indoles **203** and **204**

3.1.4.2 Results and discussion

The retrosynthetic analysis for the preparation of compounds depicted by general formulae **204** and **211** is shown in Scheme 7.

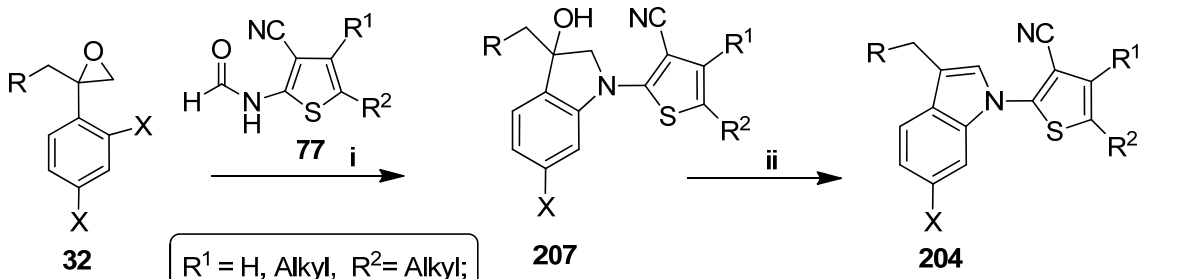


Scheme 7. Retrosynthetic analysis for substituted indoles **204** and **211**

Compound **204** could be synthesized by the opening of epoxide **32** with suitable nitrogen nucleophile **205** to give intermediate hydroxy amine **206** which in turn would react with halogen on aromatic ring in an intramolecular fashion to give the resultant 2,3-dihydro-3-hydroxyindole system **207** which upon treatment with an acid would result in dehydration providing the desired indole moiety **204** as depicted in Scheme 7. Alternatively, the epoxide **32** could be converted into the haloaminoalcohol **209** *via* the azide **208** and the indole moiety **211** could be constructed by treatment of **209** with a base followed by an acid. The indole **211** could then be alkylated[22] to get the desired chemical entities **204**. Our efforts in this direction resulted in the development of a method for the synthesis of substituted indoles and the results are presented in this section.

The synthesis of the N-thienyl-substituted indoles **204** was carried out *via* the route shown in Scheme 8. The reaction of epoxide **32** (Synthesis of epoxide **32**[23] has been described in Chapter 1, Scheme 6**)** with n-formylated substituted aminothiophene **77** (Synthesis of n-formylated aminothiophene **77** has been described in Chapter 1, Scheme 9**)** was attempted under various conditions and it was found that the reaction in presence of potassium carbonate and tetra-n-butylammonium bromide in DMF afforded the alcohol **207** which on treatment with dilute hydrochloric acid gave the desired indole **204**. It was

observed that the *N*-2-thienyl-3-hydroxyindolines **207** with imidazolylmethyl substituents were stable while the 3-hydroxyindolines **207** with triazolylmethyl or benzotriazolylmethyl substituents were prone to dehydration, resulting in the corresponding *N*-2-thienylindoles, on silica gel during column chromatography or in solution (The NMR samples kept for a few days showed complete conversion into indoles).



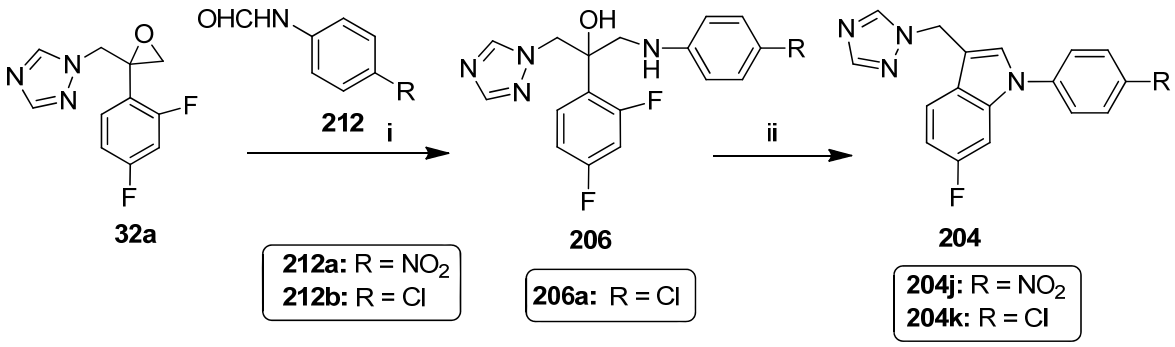
32a: 1*H*-1,2,4-triazol-1-yl, X = F
32e: imidazolyl, X = F
32f: benzimidazolyl, X = F
32g: benzotriazolyl, X = F

204	R	R^1	R^2	X
a	1*H*-1,2,4-triazol-1-yl	H	$(CH_2)_4CH_3$	F
b	1*H*-1,2,4-triazol-1-yl	-$(CH_2)_3$-		F
c	1*H*-1,2,4-triazol-1-yl	H	$(CH_2)_4CH_3$	Cl
d	imidazolyl	H	$(CH_2)_2CH_3$	F
e	imidazolyl	H	$(CH_2)_4CH_3$	F
f	imidazolyl	-$(CH_2)_5$-		F
g	imidazolyl	Me	$(CH_2)_5CH_3$	F
h	benzimidazolyl	H	$(CH_2)_4CH_3$	F
i	benzotriazolyl	H	$(CH_2)_4CH_3$	F

Scheme 8. Reagents and conditions: i) K_2CO_3, TBAB, DMF, 80 ^{0}C, 80-90% ii) 50% HCl, EtOAc, rt, 0.5-1 h, 58-85%.

The structures of the products **204** were assigned based on ^{1}H NMR, ^{13}C NMR, IR and mass spectroscopy. In ^{1}H NMR spectrum, a singlet in the range of δ 5.30-5.80 was observed for methylene protons attached to indole. The formation of compound **204** was further confirmed by the ^{13}C NMR in which the compound showed intricacies of various ^{19}F-^{13}C couplings. The CH carbon flanked between two fluorine atoms in epoxide **32** showed triplet in the range of δ 103-104 which appeared as a doublet in the range of δ 103-104, indicating the formation of compound **204**. Also it was observed that the carbons attached to fluorine atoms in epoxide **32** showed two doublet of doublets in the range of δ 156-165 while in case of the compound **204** only one doublet of doublet was seen, clearly indicating the formation of compound **204**. This was further supported by mass spectroscopy.

It was observed that the reaction sequence tolerated replacement of imidazole moiety in the epoxide by benzimidazole, benzotriazole, triazole *etc* and the 2,4-difluorophenyl group could be replaced by 2,4-dichlorophenyl group to afford various *N*-2-thienyl-indoles. Alkyl or cycloalkyl substituents on thiophene ring were also tolerated making the synthetic sequence suitable for generating molecules having varied functionalities. It is noteworthy that this synthetic strategy is also important from the point of synthesis of highly functionalized indolines **207** which can be used[24] in the synthesis of biologically active compounds and their analogues. The epoxide **32a** could be reacted with *N*-formyl-4-nitroaniline **212a** to generate *N*-aryl-indole **204j**. In the case of *N*-formyl-4-chloroaniline **212b**, the intermediate **206a** was isolated which on treatment with potassium t-butoxide in DMF followed by treatment with aq. HCl in ethyl acetate afforded the corresponding indole **204k** as shown in Scheme 9.

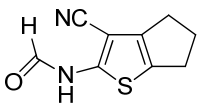
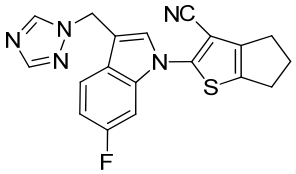
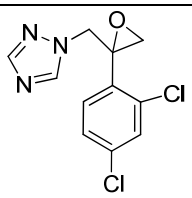
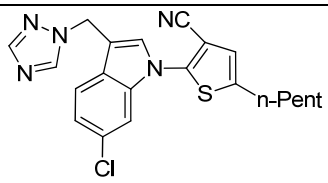
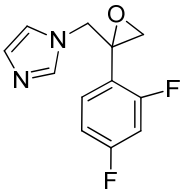
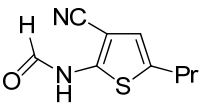
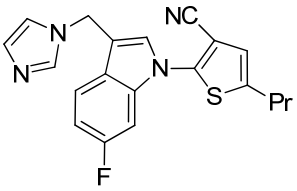
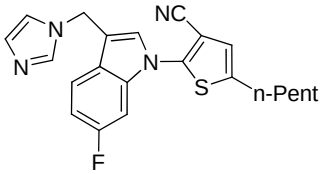
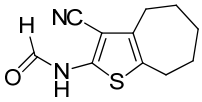
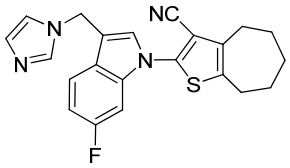
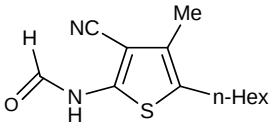
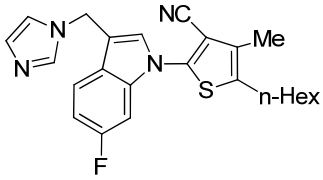
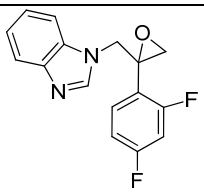
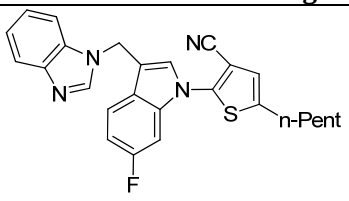
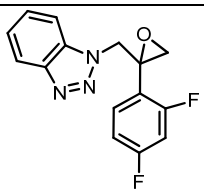
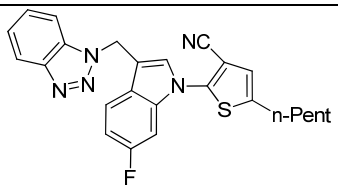


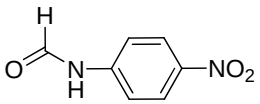
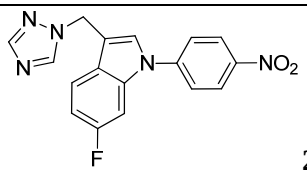
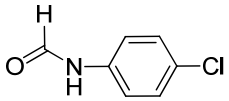
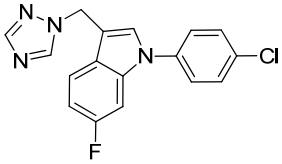
Scheme 9. Reagents and conditions: i) K_2CO_3, DMF, 80 ^{0}C; 80-90% ii) a) t-BuOK, DMF, 90-100 ^{0}C; b) 50% HCl, EtOAc, rt, 0.5-1 h, 60-70%.

Using the above synthetic strategy, a number of compounds were prepared to check the generality of the reaction sequence as shown in Table 1.

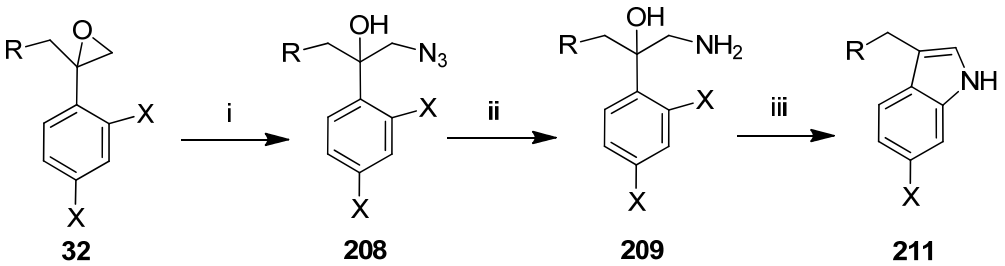
Table 1: Synthesis of substituted indoles.

Sr no	Epoxide **32**	Reactant **77** or **212**	Indole **204**	Yield %
1	**32a**	**77n**	**204a**	**80**

2	**32a**	 **77o**	 **204b**	**82**
3	 **32d**	**77n**	 **204c**	**58**
4	 **32e**	 **77l**	 **204d**	**65**
5	**32e**	**77n**	 **204e**	**70.5**
6	**32e**	 **77p**	 **204f**	**57.5**
7	**32e**	 **77q**	 **204g**	**62**
8	 **32f**	**77n**	 **204h**	**63**
9	 **32g**	**77n**	 **204h**	**84**

10	**32a**	 **212a**	 **204j**	**69**
11	**32a**	 **212b**	 **204k**	**67**

After the successful synthesis of 3,6-disubstituted-*N*-2-thienyl/aryl-indoles **204**, the synthesis of 3,6-disubstituted indoles **211** was achieved as shown in Scheme 10.



Scheme 10. i) a) NaN_3, MeOH, NH_4Cl, reflux, 12-15 h; ii) H_2, Pd-C, EtOH, rt, 6-8 h, 80-85% over 2 steps iii) a) t-BuOK, dry DMF, 90 ^oC, 3-5 h; b) HCl, H_2O, EtOAc, rt, 0.5-1 h, 56- 85% over 2 steps.

The epoxide **32**[23a-c] was converted into the aminoalcohol **209** by reaction with sodium azide followed by hydrogenation[23a]. Reaction of the halogenated aminoalcohol **209** with potassium t-butoxide followed by acidic work up afforded the desired substituted indole **211** in good yields. These indoles **211** could be used as intermediates to prepare analogues of various compounds exhibiting antifungal activity[25]. The substituted indoles **211** could be alkylated[22] by known methods to get the *N*-substituted indoles **204**.

3.1.5 Conclusion

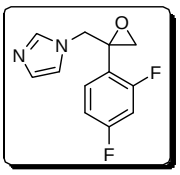
In conclusion, a two-step method for the synthesis of *N*-2-thienyl/aryl-indoles **204** from easily prepared 2-formylaminothiophenes **77** or *N*-formylanilines **212** and the styrene epoxides **32** has been developed. The benzotriazole moiety in compounds of the type **204h**

could be replaced[25a,26] with different structural units to get various other compounds. The reaction sequence has a potential to generate a large number of novel indoles and hydroxyindolines with a wide variety of functional groups.

3.1.6 Experimental Section

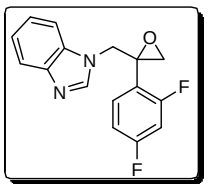
The epoxides **32e-h** were prepared by using the procedures[23] given for the preparation of epoxide **32a** as described in Chapter 1.

1-((2-(2,4-Difluorophenyl)oxiran-2-yl)methyl)-1*H*-imidazole (32e)[23c]



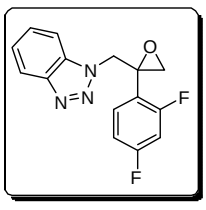
Nature: Brown sticky solid; **Yield:** 78%; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.80 (d, *J* = 6 Hz, 1H), 2.89 (d, *J* = 6 Hz, 1H), 4.07 (d, *J* = 15 Hz, 1H), 4.58 (d, *J* = 15 Hz, 1H), 6.69-6.86 (m, 3H), 6.93 (s, 1H), 7.03-7.15 (m, 1H), 7.33 (s, 1H). **^{13}C NMR** (50 MHz, $CDCl_3$): δ 50.9, 51.7, 56.6, 76.8, 103.5 (t), 111.8 (d), 119.3, 129.0, 129.6 (d), 137.2, 158.9 (dd), 163.1 (dd); **IR** (Chloroform)**:** 1138, 1272, 1617 cm^{-1}; **MS** (ESI) *m*/*z*: 237.10 (M + 1).

1-((2-(2,4-Difluorophenyl)oxiran-2-yl)methyl)-1*H*-benzo[*d*]imidazole (32f)[23c]



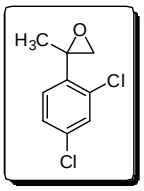
Nature: Brown sticky solid; **Yield:** 76%; **^{1}H NMR** (200 MHz, $CDCl_3$)**:** δ 2.73 (d, *J* = 6 Hz, 1H), 2.79 (d, *J* = 6 Hz, 1H), 4.30 (d, *J* = 16 Hz, 1H), 4.79 (d, *J* = 16 Hz, 1H), 6.57-6.80 (m, 2H), 6.96-7.07 (m, 1H), 7.17-7.22 (m, 2H), 7.35-7.42 (m, 1H), 7.64-7.69 (m, 2H), 7.76 (s, 1H). **^{13}C NMR** (50 MHz, $CDCl_3$)**:** δ 49.0, 51.8, 56.7, 103.8 (t), 109.8, 111.9 (d), 119.6 (d), 120.0, 122.4, 123.3, 129.3 (d), 133.8, 142.7, 143.3, 159.1 (dd), 164.0 (dd); **MS** (ESI) *m*/*z***:** 287.06 (M + 1).

1-((2-(2,4-Difluorophenyl)oxiran-2-yl)methyl)-1*H*-benzo[*d*][1,2,3]triazole (32g)[23c]



Nature: Brown solid; **MP:** 115 ^{0}C; **Yield:** 78%; **^{1}H NMR** (200 MHz, $CDCl_3$)**:** δ 2.90 (d, *J* = 4 Hz, 1H), 3.02 (d, *J* = 4 Hz, 1H), 4.83 (d, *J* = 15 Hz, 1H), 5.43 (d, *J* = 15 Hz, 1H), 6.60-6.85 (m, 2H), 6.94-7.05 (m, 1H), 7.30-7.52 (m, 2H), 7.65 (d, *J* = 9 Hz, 1H), 7.98 (d, *J* = 9 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$)**:** δ 51.6, 52.4, 56.7, 103.9 (t), 109.9, 111.6 (d), 119.5 (d), 119.6, 123.9, 127.6, 129.4 (d), 133.4, 145.6, 159.3 (dd), 163.3 (dd); **MS** (ESI) *m*/*z***:** 288.05 (M + 1).

2-(2,4-Dichlorophenyl)-2-methyloxirane (32h)

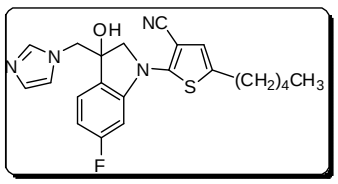


Nature: Pale yellow oil; **Yield:** 67%; **^{1}H NMR** (200 MHz, $CDCl_3$)**:** δ 1.63 (s, 3H), 2.78 (d, *J* = 6 Hz, 1H), 2.99 (d, *J* = 6 Hz, 1H), 7.22 (dd, *J* = 2, 8 Hz, 1H), 7.35 (d, *J* = 2 Hz, 1H), 7.41 (d, *J* = 10 Hz, 1H); **^{13}C NMR** ($CDCl_3$, 50 MHz)**:** δ 22.4, 54.9, 57.2, 127.1, 128.9, 129.3, 132.8, 133.9, 138.2; **MS** (ESI) *m*/*z***:** 170.05 (M + 1).

Preparation of 2-(3-((1*H*-imidazol-1-yl)methyl)-6-fluoro-3-hydroxyindolin-1-yl)-5-pentylthiophene-3-carbonitrile (207b)

To the flame dried K_2CO_3 (3.10 g, 22.52 mmol), tetrabutylammonium bromide (300 mg) was added followed by the addition of compound **77n** (Synthesis of n-formylated aminothiophene **77** has been described in Chapter 1, Scheme 9**)** (1.0 g, 4.50 mmol) in dry DMF (30 mL). Reaction mixture was stirred at 90 ^{0}C for 30 min. Then epoxide **32e** (1.06 g, 4.50 mmol) dissolved in dry ethyl acetate (10 mL) was added to the refluxing mixture drop wise over a period of 10 min and stirring was continued for further 12 h at the same temperature. It was then cooled to room temperature, diluted with water (60 mL), extracted with ethyl acetate (3 x 50 mL), dried over Na_2SO_4, concentrated and purified by column chromatography to give pure compound 2-(3-((1*H*-imidazol-1-yl)methyl)-6-fluoro-3-hydroxyindolin-1-yl)-5-pentylthiophene-3-carbonitrile (**207b)** as off-white solid.

Nature: Off-white solid; **MP:** 117 ^{0}C; **Yield:** 85%; **^{1}H NMR** (200 MHz, $CDCl_3$)**:** δ 0.91 (t,

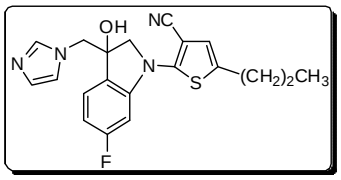


J = 7 Hz, 3H), 1.26-1.42 (m, 4H), 1.57-1.68 (m, 2H), 2.70 (t, *J* = 7 Hz, 2H), 4.05 (d, *J* = 12 Hz, 1H), 4.14 (d, *J* = 12 Hz, 1H), 4.29 (s, 2H), 4.88 (bs, 1H), 6.55 (dt, *J* = 2, 8 Hz, 1H), 6.67 (s, 1H), 6.75 (dd, *J* = 2, 10 Hz, 1H), 6.84-7.00 (m, 3H), 7.73 (s, 1H). **^{13}C NMR** (50 MHz, $CDCl_3$)**:** δ 13.9, 22.2, 30.0, 30.6, 31.0, 54.7, 66.1, 98.3 (d), 99.0, 108.5 (d), 115.2, 121.1, 122.5, 124.9, 125.6 (d), 126.6, 126.9, 135.1, 138.3, 147.3, 153.3, 164.4 (d); **IR** (Chloroform)**:** 1617, 2211, 3384 cm^{-1}; **MS** (ESI) *m*/*z***:** 411.5300 (M + 1).

The following compounds **207a**, **207c-207e** were prepared by using procedure given for the preparation of compound **207b**.

2-(3-((1*H*-Imidazol-1-yl)methyl)-6-fluoro-3-hydroxyindolin-1-yl)-5-propylthiophene-3-carbonitrile (207a)

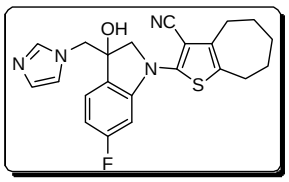
Nature: Off-white solid; **MP:** 188 ^{0}C; **Yield:** 88 %; **^{1}H NMR** (500 MHz, $CDCl_3$)**:** δ 0.99 (t,



J = 10 Hz, 3H), 1.64-1.71 (m, 2H), 2.70 (t, *J* = 10 Hz, 2H), 3.93 (d, *J* = 10 Hz, 1H), 4.16 (d, *J* = 10 Hz, 1H), 4.45 (d, *J* = 15 Hz, 1H), 4.64 (d, *J* = 15 Hz, 1H), 5.59 (bs, 1H), 6.58 (dt, *J* = 5, 10 Hz, 1H), 6.69 (s, 1H), 6.72 (dd, *J* = 5, 10 Hz, 1H), 7.18-7.22 (m, 3H), 8.88 (s, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$)**:** δ 13.5, 24.2, 32.1, 55.2, 65.5, 98.3 (d), 100.2, 108.4 (d), 115.2, 122.0 (2C), 122.5, 125.8 (d), 126.5, 137.3, 139.0, 147.5 (2C), 153.4, 164.5 (d); **IR** (Chloroform)**:** 1618, 2225, 3374 cm^{-1}; **MS** (ESI) *m*/*z***:** 383.2284 (M + 1).

2-(3-((1*H*-Imidazol-1-yl)methyl)-6-fluoro-3-hydroxyindolin-1-yl)-5,6,7,8-tetrahydro-4*H*-cyclohepta[b]thiophene-3-carbonitrile (207c)

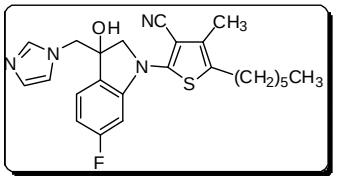
Nature: Off-white solid; **MP:** 218 ^{0}C; **Yield:** 81%; **^{1}H NMR** (200 MHz, $CDCl_3$)**:** δ 1.56-



1.72 (m, 4H), 1.82-1.92 (m, 2H), 2.68-2.76 (m, 4H), 3.98 (d, *J* = 12 Hz, 1H), 4.06 (d, *J* = 12 Hz, 1H), 4.20 (d, *J* = 16 Hz, 1H), 4.27 (d, *J* = 16 Hz, 1H), 6.14 (bs, 1H), 6.49 (dt, *J* = 2, 10 Hz, 1H), 6.69 (dd, *J* = 4, 12 Hz, 1H), 6.78-6.86 (m, 2H), 6.98 (s, 1H), 7.60 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$)**:** δ 26.9, 27.6, 29.1, 29.7, 31.8, 54.7, 66.1, 98.1 (d), 103.3, 107.8 (d), 115.1, 121.1, 125.3 (d), 126.6, 127.0, 132.1, 137.8, 138.4, 147.5, 147.7, 150.5, 164.2 (d); **IR** (Chloroform)**:** 1614, 2225, 3368 cm^{-1}; **MS** (ESI) *m*/*z***:** 409.1248 (M + 1).

2-(3-((1*H*-Imidazol-1-yl)methyl)-6-fluoro-3-hydroxyindolin-1-yl)-5-hexyl-4-methylthiophene-3-carbonitrile (207d)

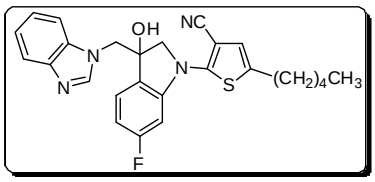
Nature: Brown solid; **MP:** 175 ^{0}C; **Yield:** 83%; **^{1}H NMR** (200 MHz, $CDCl_3$)**:** δ 0.90 (t, *J*



= 6 Hz, 3H), 1.31-1.43 (m, 6H), 1.56-1.62 (m, 2H), 2.20 (s, 3H), 2.66 (t, *J* = 8 Hz, 2H), 3.93 (d, *J* = 12 Hz, 1H), 4.15 (d, *J* = 12 Hz, 1H), 4.42 (d, *J* = 14 Hz, 1H), 4.60 (d, *J* = 14 Hz, 1H), 5.62 (bs, 1H), 6.58 (dt, *J* = 2, 10 Hz, 1H), 6.74 (dd, *J* = 2, 10 Hz, 1H), 7.13-7.20 (m, 3H), 8.74 (s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$)**:** δ 12.9, 14.0, 22.5, 28.0, 28.7, 31.0, 31.4, 55.6, 65.2, 98.3 (d), 103.9, 108.0 (d), 115.5, 119.9 (d), 120.6, 122.6, 123.3, 125.9 (d), 126.4, 135.1, 138.2, 143.9, 151.8, 161.6 (d); **IR** (Chloroform)**:** 1619, 2224, 3368 cm^{-1}; **MS** (ESI) *m*/*z***:** 439.1034 (M + 1).

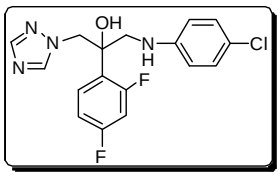
2-(3-((1*H*-Benzo[d]imidazol-1-yl)methyl)-6-fluoro-3-hydroxyindolin-1-yl)-5-pentylthiophene-3-carbonitrile (207e)

Nature: White solid; **MP:** 132 ^{0}C; **Yield:** 85%; **^{1}H NMR** (200 MHz, $CDCl_3$)**:** δ 0.91 (t, *J* = 6 Hz, 3H), 1.30-1.39 (m, 4H), 1.56-1.70 (m, 2H), 2.70 (t, *J* = 8 Hz, 2H), 4.00 (d, *J* = 11 Hz, 1H), 4.14 (d, *J* = 11 Hz, 1H), 4.67 (s, 2H), 5.50 (bs, 1H), 6.42 (dt, *J* = 2, 8 Hz, 1H), 6.64-6.70 (m, 2H), 6.92 (dd, *J* = 4, 8 Hz, 1H), 7.28-7.30 (m, 3H), 7.69-7.74 (m, 1H), 8.81 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$)**:** δ 13.9, 22.2, 30.0, 30.6, 31.0, 52.2, 66.3, 78.0, 98.4 (d), 100.4, 108.3 (d), 110.7, 114.9, 118.0, 122.5, 123.9, 124.7, 125.7 (d), 126.7, 133.5, 137.7, 139.4, 143.4, 147.7, 153.4, 163.3 (d); **IR** (Chloroform)**:** 1613 2221, 3425 cm^{-1}; **MS** (ESI) *m*/*z***:** 461.1124 (M + 1).



1-(4-Chlorophenylamino)-2-(2,4-difluorophenyl)-3-(1*H*-1,2,4-triazol-1-yl)propan-2-ol (206a)

Nature: Brown sticky solid; **Yield:** 85%; **^{1}H NMR** (200 MHz, $CDCl_3$)**:** δ 3.46 (d, *J* = 14 Hz, 1H), 3.61 (d, *J* = 14 Hz, 1H), 4.54 (bs, 1H), 4.66 (d, *J* = 14 Hz, 1H), 4.78 (d, *J* = 14 Hz, 1H), 6.54 (d, *J* = 8 Hz, 2H), 6.72-6.83 (m, 2H), 7.09 (d, *J* = 8 Hz, 2H), 7.43-7.56 (m, 1H), 7.80 (s, 1H), 7.95 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$)**:** 50.6, 54.9, 75.7, 104.2 (t), 111.7 (d), 114.5 (2C), 122.9 (d), 129.0 (2C), 129.4 (d), 144.1, 146.2, 146.9, 151.4, 158.0 (dd), 163.0 (dd) ; **IR** (Chloroform)**:** 1625, 3127, 3345 cm^{-1}; **MS** (ESI) *m*/*z***:** 365.2315 (M + 1).

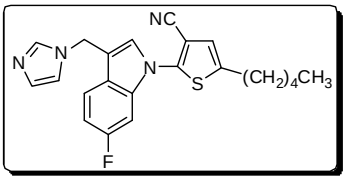


Preparation of 2-(3-((1*H*-imidazol-1-yl)methyl)-6-fluoro-1*H*-indol-1-yl)-5-pentylthiophene-3-carbonitrile (204e)

To a solution of compound **207b** (500 mg, 1.21 mmol) in ethyl acetate (15 mL), was added 50 % hydrochloric acid (10 mL) at room temperature and the reaction mixture was stirred at room temperature for 1 h. It was then diluted with excess of water and extracted with ethyl acetate (3 x 10 mL). Then the aqueous layer was basified with 10% NaOH, extracted with ethyl acetate (3 x 10 mL), dried over Na_2SO_4 and concentrated to give pure compound 2-(3-((1*H*-imidazol-1-yl)methyl)-6-fluoro-1*H*-indol-1-yl)-5-pentylthiophene-3-carbonitrile **204e**.

Nature: White solid; **MP:** 107 ^{0}C; **Yield:** 83%; **^{1}H NMR** (200 MHz, $CDCl_3$)**:** δ 0.93 (t, *J* = 7 Hz, 3H), 1.33-1.46 (m, 4H), 1.65-1.80 (m, 2H), 2.83 (t, *J* = 8 Hz, 2H), 5.43 (s, 2H), 6.91

(s, 1H), 6.99 (dt, *J* = 2, 8 Hz, 1H), 7.06 (s, 1H), 7.15 (s, 1H), 7.22 (dd, *J* = 2, 10 Hz, 1H),

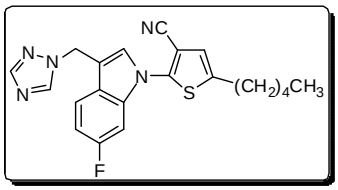


7.35-7.41 (m, 2H), 8.19 (s, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$)**:** δ 13.8, 22.2, 30.1, 30.6, 30.9, 42.7, 98.1 (d), 104.5, 111.1 (d), 113.5 (2C), 119.4, 120.0 (d), 123.5, 126.8, 128.3, 136.5, 137.4, 137.5, 144.3, 145.8, 160.9 (d); **IR** (Chloroform)**:** 1617, 2225 cm^{-1}; **MS** (ESI) *m*/*z***:** 393.1017 (M + 1). **Anal. Calcd. for** $C_{22}H_{21}FN_4S$**:** C, 67.32; H, 5.39; N, 14.27 %. **Found:** C, 67.46; H, 5.21; N, 14.44 %.

The following compounds **204a-d**, **204f-i** were prepared by using the procedure given for the preparation of compound **204e**.

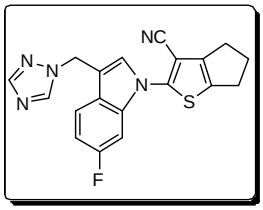
2-(3-((1*H*-1,2,4-Triazol-1-yl)methyl)-6-fluoro-1*H*-indol-1-yl)-5-pentylthiophene-3-carbonitrile (204a)

Nature: Brown solid; **MP:** 74 ^{0}C; **Yield:** 84%; **^{1}H NMR** (200 MHz, $CDCl_3$)**:** δ 0.87 (t, *J* =



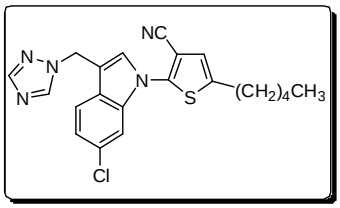
6 Hz, 3H), 1.26-1.40 (m, 4H), 1.58-1.73 (m, 2H), 2.76 (t, *J* = 6 Hz, 2H), 5.47 (s, 2H), 6.85 (s, 1H), 6.92 (dt, *J* = 2, 9 Hz, 1H), 7.17 (dd, *J* = 2, 9 Hz, 1H), 7.41-7.48 (m, 2H), 7.91 (s, 1H), 8.14 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$)**:** δ 13.7, 22.0, 29.9, 30.5, 30.8, 44.7, 97.8 (d), 104.2, 110.8 (d), 112.8, 113.3, 120.1 (d), 123.4 (2C), 128.4, 137.2 (d), 142.7, 144.1, 145.7, 151.3, 160.7 (d); **IR** (Chloroform)**:** 1621, 2226, 3390 cm^{-1}; **MS** (ESI) *m*/*z***:** 394.2864 (M + 1). **Anal. Calcd. for** $C_{21}H_{20}FN_5S$**:** C, 64.10; H, 5.12; N, 17.80 %. **Found:** C, 64.29; H, 5.01; N, 17.93 %.

2-(3-((1*H*-1,2,4-Triazol-1-yl)methyl)-6-fluoro-1*H*-indol-1-yl)-5,6-dihydro-4*H*-cyclpenta[b] thiophene-3-carbonitrile (204b)



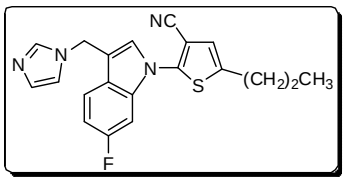
Nature: Off-white solid; **MP:** 194 ^{0}C; **Yield:** 82%; **^{1}H NMR** (200 MHz, $CDCl_3$ + DMSO-d_6)**:** δ 2.14-2.25 (m, 2H), 2.57-2.72 (m, 4H), 5.38 (s, 2H), 6.74 (dt, *J* = 2, 8 Hz, 1H), 6.82 (dd, *J* = 2, 8 Hz, 1H), 7.31-7.46 (m, 2H), 7.93 (s, 1H), 8.81 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$ + DMSO-d_6)**:** δ 25.4, 26.3, 28.1, 42.3, 98.8 (d), 100.0, 108.6 (d), 111.4, 112.0, 119.1 (d), 122.1, 127.8, 135.2 (2C), 137.9, 141.1, 142.2, 149.1, 160.8 (d); **IR** (Chloroform)**:** 1618, 2220, 3391 cm^{-1}; **MS** (ESI) *m*/*z***:** 364.04 (M + 1). **Anal. Calcd. for** $C_{19}H_{14}FN_5S$**:** C, 62.79; H, 3.88; N, 19.27 %. **Found:** C, 62.66; H, 3.92; N, 19.43 %.

2-(3-((1*H*-1,2,4-Triazol-1-yl)methyl)-6-chloro-1*H*-indol-1-yl)-5-pentylthiophene-3-carbonitrile (204c)



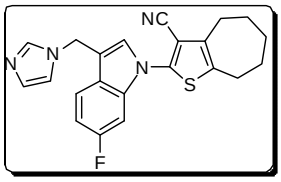
Nature: White solid; **MP:** 93 ^{0}C; **Yield:** 74%; **^{1}H NMR** (200 MHz, $CDCl_3$)**:** δ 0.92 (t, *J* = 6 Hz, 3H), 1.36-1.43 (m, 4H), 1.64-1.76 (m, 2H), 2.83 (t, *J* = 6 Hz, 2H), 5.61 (s, 2H), 6.91 (s, 1H), 7.22 (dd, *J* = 2, 8 Hz, 1H), 7.48-7.55 (m, 3H), 8.07 (s, 1H), 8.60 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$)**:** δ 13.9, 22.2, 29.6, 30.7, 31.0, 45.3, 104.9, 111.2, 112.3, 113.3, 120.2, 123.1, 123.6, 125.7, 129.2, 130.6, 137.6, 142.4, 144.7, 145.5, 149.7; **IR** (Chloroform)**:** 1620, 2226 cm^{-1}; **MS** (ESI) *m*/*z***:** 410.3943 (M + 1). **Anal. Calcd. for** $C_{21}H_{20}ClN_5S$**:** C, 61.53; H, 4.92; N, 17.08 %. **Found:** C, 61.68; H, 4.81; N, 17.20 %.

2-(3-((1*H*-Imidazol-1-yl)methyl)-6-fluoro-1*H*-indol-1-yl)-5-propylthiophene-3-carbonitrile (204d)



Nature: Pale brown solid; **MP:** 137 ^{0}C; **Yield:** 74%; **^{1}H NMR** (500 MHz, $CDCl_3$)**:** δ 1.05 (t, *J* = 10 Hz, 3H), 1.76 (q, *J* = 10 Hz, 2H), 2.82 (t, *J* = 10 Hz, 2H), 5.67 (s, 2H), 6.92 (s, 1H), 7.02 (dt, *J* = 5, 10 Hz, 1H), 7.17 (s, 1H), 7.22 (dd, *J* = 5, 10 Hz, 1H), 7.31 (s, 1H), 7.50-7.53 (m, 1H), 7.61 (s, 1H), 9.33 (s, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$)**:** δ 13.5, 24.3, 32.1, 44.0, 98.2 (d), 105.0, 111.5 (d), 111.7, 113.5, 120.1 (d), 120.2, 121.4, 123.3, 123.7, 129.5, 137.6 (2C), 144.5, 145.6, 161.1 (d); **IR** (Chloroform)**:** 1614, 2210 cm^{-1}; **MS** (ESI) *m*/*z***:** 365.1073 (M + 1). **Anal. Calcd. for** $C_{20}H_{17}FN_4S$**:** C, 65.91; H, 4.70; N, 15.37 %. **Found:** C, 65.82; H, 4.55; N, 15.49 %.

2-(3-((1*H*-Imidazol-1-yl)methyl)-6-fluoro-1*H*-indol-1-yl)-5,6,7,8-tetrahydro-4*H*-cyclohepta[b]thiophene-3-carbonitrile (204f)

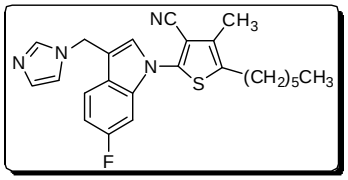


Nature: White solid; **MP:** 168 ^{0}C; **Yield**: 71%; **^{1}H NMR** (200 MHz, $CDCl_3$)**:** δ 1.68-1.79 (m, 4H), 1.90-1.98 (m, 2H), 2.82-2.89 (m, 4H), 5.31 (s, 2H), 6.91-7.01 (m, 2H), 7.10 (s, 1H), 7.20-7.35 (m, 3H), 7.72 (s, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$)**:** δ 26.9, 27.5, 29.3, 29.8, 31.8, 42.3, 98.0 (d), 107.7, 110.8 (d), 113.7, 113.9, 119.1, 119.9 (d), 123.5, 127.9, 129.0, 136.9, 137.5, 137.9, 139.8, 142.7, 160.8 (d); **IR** (Chloroform)**:** 1617, 2225,

cm^{-1}; **MS** (ESI) *m*/*z*: 391.0348 (M + 1). **Anal. Calcd. for** $C_{22}H_{19}FN_4S$**:** C, 67.67; H, 4.90; N, 14.35 %. **Found:** C, 67.46; H, 4.73; N, 14.47 %.

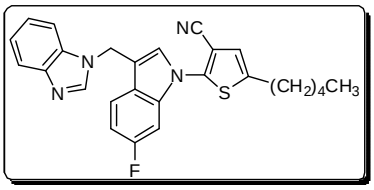
2-(3-((1*H*-Imidazol-1-yl)methyl)-6-fluoro-1*H*-indol-1-yl)-5-hexyl-4-methylthiophene-3-carbonitrile (204g)

Nature: Brown solid; **MP:** 137 ^{0}C; **Yield:** 75%; **^{1}H NMR** (200 MHz, $CDCl_3$)**:** δ 0.90 (t, *J* = 6 Hz, 3H), 1.28-1.48 (m, 6H), 1.59-1.72 (m, 2H), 2.29 (s, 3H), 2.76 (t, *J* = 8 Hz, 2H), 5.80 (s, 2H), 6.95-7.33 (m, 4H), 7.57-7.69 (m, 2H), 9.81 (s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$)**:** δ 12.8, 13.9, 22.4, 28.0, 28.7, 30.9, 31.3, 44.3, 98.2 (d), 107.8, 111.1 (d), 112.3, 113.6, 119.8, 120.1 (d), 120.5, 123.3, 129.9, 132.1, 135.3, 137.4, 138.1, 143.9, 161.0 (d); **IR** (Chloroform)**:** 1621, 2226 cm^{-1}; **MS** (ESI) *m*/*z***:** 421.0455 (M + 1). **Anal. Calcd. for** $C_{24}H_{25}FN_4S$**:** C, 68.54; H, 5.99; N, 13.32 %. **Found:** C, 68.41; H, 6.18; N, 13.21 %.



2-(3-((1*H*-Benzo[*d*]imidazol-1-yl)methyl)-6-fluoro-1*H*-indol-1-yl)-5-pentylthiophene-3-carbonitrile (204h)

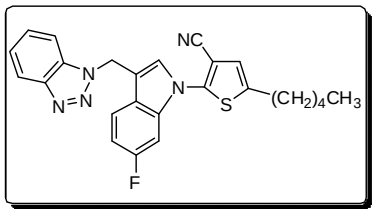
Nature: White solid; **MP:** 103.5 ^{0}C; **Yield:** 74%; **^{1}H NMR** (200 MHz, $CDCl_3$)**:** δ 0.86 (t, *J* = 8 Hz, 3H), 1.27-1.39 (m, 4H), 1.57-1.72 (m, 2H), 2.75 (t, *J* = 8 Hz, 2H), 5.46 (s, 2H), 6.83-6.94 (m, 2H), 7.13-7.32 (m, 5H), 7.42-7.46 (m, 1H), 7.75-7.80 (m, 1H), 8.02 (s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$)**:** δ 13.8, 22.2, 30.1, 30.7, 31.0, 41.3, 98.2 (d), 104.6, 110.8, 111.2 (d), 112.6, 113.5, 118.7, 120.1 (d), 123.6, 124.1, 124.6, 128.5, 132.7, 137.5 (2C), 138.9, 141.9, 144.4, 145.8, 161.0 (d); **IR** (Chloroform)**:** 1618, 2227 cm^{-1}; **MS** (ESI) *m*/*z***:** 443.0095 (M + 1). **Anal. Calcd. for** $C_{26}H_{23}FN_4S$**:** C, 70.56; H, 5.24; N, 12.66 %. **Found:** C, 70.44; H, 5.39; N, 12.44 %.



2-(3-((1*H*-Benzo[*d*][1,2,3]triazol-1-yl)methyl)-6-fluoro-1*H*-indol-1-yl)-5-pentylthiophene-3-carbonitrile (204i)

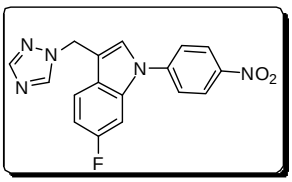
Nature: White solid; **MP:** 126 ^{0}C; **Yield:** 84%; **^{1}H NMR** (200 MHz, $CDCl_3$)**:** δ 0.85 (t, *J* = 6 Hz, 3H), 1.26-1.35 (m, 4H), 1.56-1.70 (m, 2H), 2.74 (t, *J* = 8 Hz, 2H), 5.97 (s, 2H), 6.80-6.90 (m, 2H), 7.09-7.39 (m, 3H), 7.47-7.52 (m, 3H), 7.97 (d, *J* = 8 Hz, 1H); **^{13}C NMR** (125

MHz, $CDCl_3$)**:** δ 13.7, 22.1, 29.9, 30.5, 30.8, 43.8, 98.8 (d), 104.0, 109.8, 110.8 (d), 113.0, 113.5, 119.6, 120.6, 123.4, 123.6 (d), 124.0, 127.4, 128.0, 132.5, 137.2, 144.0, 145.8 (2C), 160.7 (d); **IR** (Chloroform)**:** 1619, 2223 cm^{-1}; **MS** (ESI) *m*/*z***:** 444.3695 (M + 1). **Anal. Calcd. for** $C_{25}H_{22}FN_5S$**:** C, 67.70; H, 5.00; N, 15.79 %. **Found:** C, 67.58; H, 5.22; N, 15.67 %.



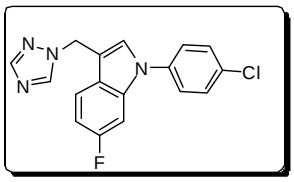
3-((1*H*-1,2,4-Triazol-1-yl)methyl)-6-fluoro-1-(4-nitrophenyl)-1*H*-indole (204j)

Nature: Yellow solid; **MP:** 190 ^{0}C; **Yield:** 78%; **^{1}H NMR** (200 MHz, $CDCl_3$ + DMSO-d_6)**:** δ 5.63 (s, 2H), 7.14 (dt, *J* = 2, 10 Hz, 1H), 7.35 (dd, *J* = 2, 10 Hz, 1H), 7.60-7.79 (m, 4H), 7.91 (s, 1H), 8.41-8.45 (m, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$ + DMSO-d_6)**:** δ 42.3, 96.0 (d), 108.2 (d), 111.9, 119.1 (d), 121.8 (2C), 123.1, 123.7 (2C), 126.5 (d), 133.6, 142.2, 143.3, 149.5, 157.3, 165.1 (d); **IR** (Chloroform)**:** 1613, 2878, 3019 cm^{-1}; **MS** (ESI) *m*/*z***:** 338.5522 (M + 2). **Anal. Calcd. for** $C_{17}H_{12}FN_5O_2$**:** C, 60.53; H, 3.59; N, 20.76 %. **Found:** C, 60.32; H, 3.65; N, 20.53 %.



3-((1*H*-1,2,4-Triazol-1-yl)methyl)-1-(4-chlorophenyl)-6-fluoro-1*H*-indole (204k)

Nature: White solid; **MP:** 172 ^{0}C; Yield: 67%; **^{1}H NMR** (200 MHz, $CDCl_3$ + CD_3OD)**:** δ 5.67 (s, 2H), 6.91 (dt, *J* = 2, 8 Hz, 1H), 7.09 (dd, *J* = 2, 8 Hz, 1H), 7.33-7.57 (m, 6H), 8.30 (s, 1H), 9.42 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$)**:** δ 45.2, 97.4 (d), 109.8, 110.6 (d), 119.9 (d), 123.7, 125.4 (2C), 127.8, 130.0 (2C), 132.9, 136.3, 137.1, 142.5, 151.9, 164.1 (d); **IR** (Chloroform)**:** 1611, 2846, 3018 cm^{-1}; **MS** (ESI) *m*/*z***:** 327.0034 (M + 2). **Anal. Calcd. for** $C_{17}H_{12}ClFN_4$**:** C, 62.49; H, 3.70; N, 17.15 %. **Found:** C, 62.58; H, 3.56; N, 17.29 %.

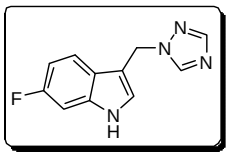


Preparation of 3-((1*H*-1,2,4-triazol-1-yl)methyl)-6-fluoro-1*H*-indole (211a)

To a solution of potassium t-butoxide (1.32 g, 11.81 mmol) in dry DMF (25 mL), was added slowly 1-amino-2-(2,4-difluorophenyl)-3-(1*H*-1,2,4-triazol-1-yl)propan-2-ol **209a** (1.0 g, 3.93 mmol) dissolved in dry DMF (10 mL) under nitrogen atmosphere and the solution was stirred at 90 ^{0}C for 5 h. Mixture was diluted with water and extracted with ethyl

acetate, dried over anhydrous Na_2SO_4, concentrated and purified by column chromatography to give pure compound 3-((1*H*-1,2,4-triazol-1-yl)methyl)-6-fluoro-1*H*-indole **211a** as brown sticky solid (663 mg, 78%).

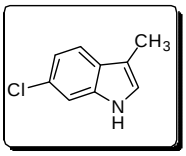
Nature: Brown sticky solid; **Yield:** 78%; **^{1}H NMR** (500 MHz, $CDCl_3$)**:** δ 5.49 (s, 2H), 6.88 (dt, *J* = 5, 10 Hz, 1H), 7.03 (dd, *J* = 2, 10 Hz, 1H), 7.25 (s, 1H), 7.38 (dd, *J* = 5, 10 Hz, 1H), 7.97 (s, 1H), 8.00 (s, 1H), 9.25 (s, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$)**:** δ 45.4, 97.9 (d), 108.7, 109.1 (d), 119.1 (d), 122.6, 124.9, 136.4 (d), 142.60, 151.5, 162.0 (d); **IR** (Chloroform)**:** 1618, 3337 cm^{-1}; **MS** (ESI) *m*/*z***:** 217.09.



6-Chloro-3-methyl-1*H*-indole (211b)

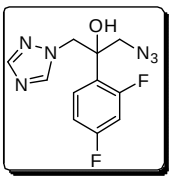
The compound **211b** was prepared using the procedure given for the preparation of compound **211a**.

Nature: White solid; **MP:** 97 ^{0}C; **Yield:** 56%; **^{1}H NMR** (400 MHz, $CDCl_3$)**:** δ 2.33 (s, 3H), 6.96 (s, 1H), 7.11 (d, *J* = 8 Hz, 1H), 7.33 (s, 1H), 7.49 (d, *J* = 8 Hz, 1H), 7.88 (bs, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$)**:** δ 9.53, 110.8, 111.8, 119.7 (2C), 122.2, 126.8, 127.7, 136.5; **IR** (Chloroform)**:** 1615, 3409 cm^{-1}; **MS** (ESI) *m*/*z***:** 166.03 (M + 1). **Anal. Calcd. for** C_9H_8ClN**:** C, 65.27; H, 4.87; N, 8.46 %. **Found:** C, 65.11; H, 4.69; N, 8.61 %.



Preparation of 1-azido-2-(2,4-difluorophenyl)-3-(1*H*-1,2,4-triazol-1-yl)propan-2-ol (208a)[25c]

To a solution of 1-((2-(2,4-difluorophenyl)oxiran-2-yl)methyl)-1*H*-1,2,4-triazole **32a** (5 g, 21.09 mmol) in 50 mL of methanol, was added sodium azide (4.11 g, 63.29 mmol) and ammonium chloride (1.45 g, 27.42 mmol) and the solution was refluxed for 15 h. It was then diluted with water, extracted with dichloromethane, dried over anhydrous Na_2SO_4, concentrated and purified by column chromatography to give pure compound 1-azido-2-(2,4-difluorophenyl)-3-(1*H*-1,2,4-triazol-1-yl)propan-2-ol **208** as pale yellow semisolid (6.93 g, 92%).



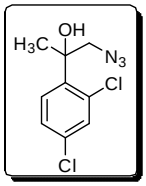
Nature: Pale yellow semisolid; **Yield:** 92 %; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 3.53 (d, *J* = 14 Hz, 1H), 3.69 (d, *J* = 14 Hz, 1H), 4.69 (d, *J* = 16 Hz, 1H), 4.78 (d, *J* = 16 Hz, 1H), 5.09 (bs, 1H), 6.73-6.87 (m, 2H), 7.46-7.59 (m,

1H), 7.84 (s, 1H), 8.08 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$)**:** δ 54.6, 56.8, 76.2, 104.2 (t), 111.7 (d), 122.5 (d), 130.1 (d), 144.1, 151.2, 160.5 (dd), 165.4 (dd); **IR** (Chloroform)**:** 2112, 3339 cm^{-1}; **MS** (ESI) *m*/*z***:** 281.0231 (M + 1).

1-Azido-2-(2,4-dichlorophenyl)propan-2-ol (208b)

The compound **208b** was synthesized by using the procedure given for the preparation of compound **208a**.

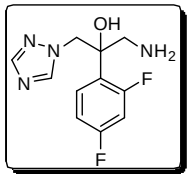
Nature: Colourless liquid; **Yield:** 92%; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.74 (s, 3H), 3.74 (d, *J* = 12 Hz, 1H), 4.10 (d, *J* = 12 Hz, 1H), 7.32 (dd, *J* = 2, 10 Hz, 1H), 7.43 (d, *J* = 2 Hz, 1H), 7.79 (d, *J* = 8 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 24.8, 58.8, 74.9, 127.3, 129.3, 130.8, 131.1, 134.0, 139.7; **IR** (Chloroform): 1617, 2107, 3393 cm^{-1}; **MS** (ESI) *m*/*z*: 247.0501 (M + 1).



Preparation of 1-amino-2-(2,4-difluorophenyl)-3-(1*H*-1,2,4-triazol-1-yl)propan-2-ol (209a)[25c]

To a solution of 1-azido-2-(2,4-difluorophenyl)-3-(1*H*-1,2,4-triazol-1-yl)propan-2-ol **208a** (3.5 g, 12.5 mmol) in 40 mL of ethanol, was added 10% active charcoal-supported palladium (350 mg). The solution was stirred overnight at room temperature under a hydrogen atmosphere (60 psi) and filtered through celite. It was then concentrated, the residue was washed with ethyl acetate-pet ether (50:50) and oven dried to get the desired product 1-amino-2-(2,4-difluorophenyl)-3-(1*H*-1,2,4-triazol-1-yl)propan-2-ol **209a** as white powder (3.04 g, 96%).

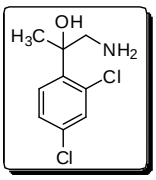
Nature: White powder; **MP:** 253 ^{0}C; **Yield:** 96%; **^{1}H NMR** (200 MHz, $CDCl_3$ + DMSO-d_6)**:** δ 3.35 (d, *J* = 10 Hz, 1H), 3.55 (d, *J* = 10 Hz, 1H), 4.79 (d, *J* = 14 Hz, 1H), 4.88 (d, *J* = 14 Hz, 1H), 7.07-7.28 (m, 2H), 7.56-7.67 (m, 1H), 7.94 (s, 1H), 8.20 (bs, 2H), 8.61 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$ + DMSO-d_6)**:** δ 42.8, 52.9, 70.4, 102.4 (t), 109.3 (d), 120.3 (d), 128.6 (d), 143.3, 148.6, 160.2 (dd), 165.3 (dd); **IR** (Nujol)**:** 1616, 3315, 3447 cm^{-1}; **MS** (ESI) *m*/*z***:** 255.04 (M + 1).



1-Amino-2-(2,4-dichlorophenyl)propan-2-ol (209b)

The compound **209b** was synthesized by using the procedure given for the preparation of compound **209a**.

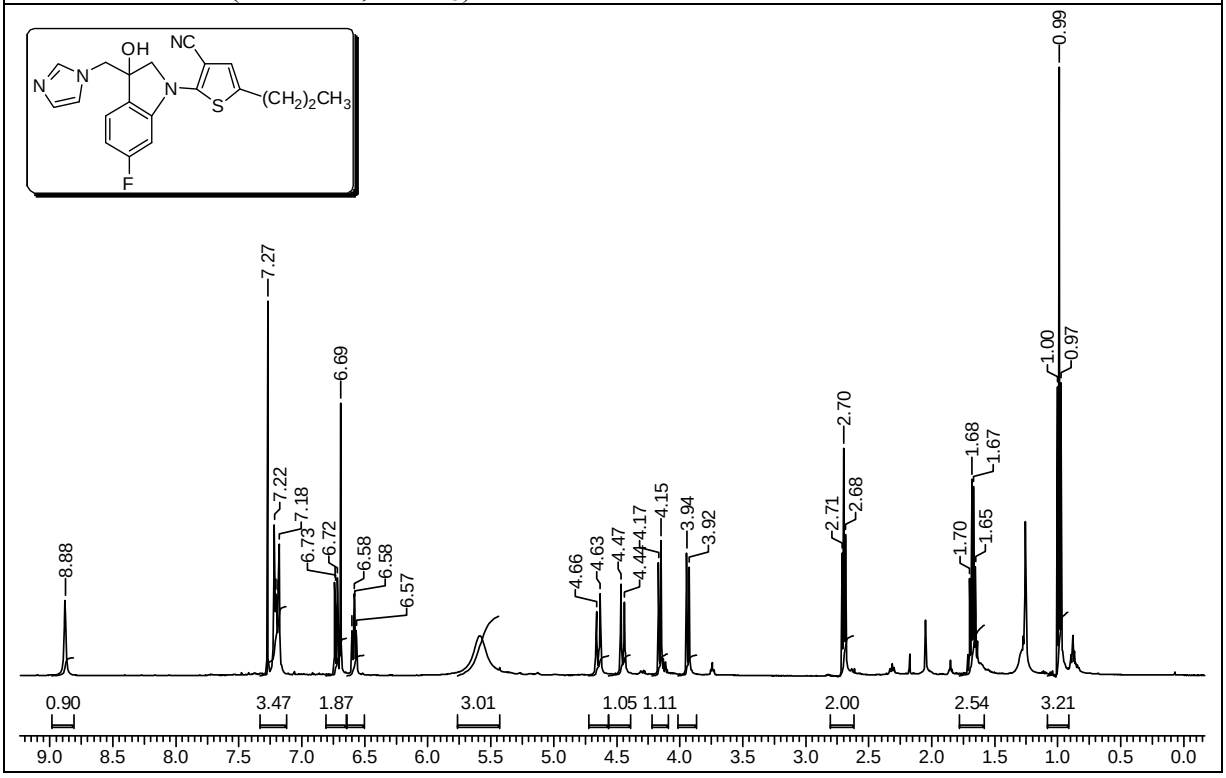
Nature: White solid; **MP:** 210 ^{0}C; **Yield:** 85%; **^{1}H NMR** (200 MHz, $CDCl_3$ + DMSO-d_6)**:** δ



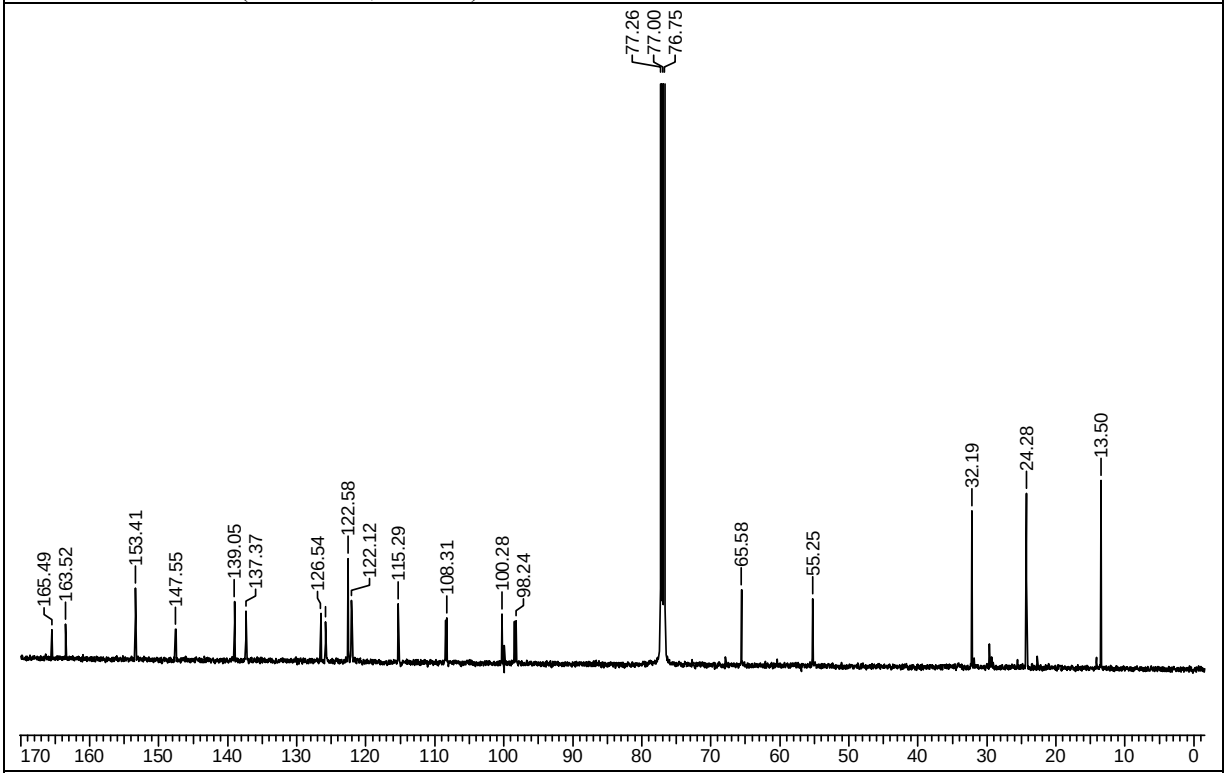
1.31 (s, 3H), 3.01 (s, 2H), 5.71 (bs, 1H), 6.85 (dd, *J* = 2, 10 Hz, 1H), 6.93 (d, *J* = 2 Hz, 1H), 7.45 (d, *J* = 10 Hz, 1H), 7.64 (bs, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$ + DMSO-d_6)**:** δ 24.0, 46.2, 70.6, 124.2, 126.9, 128.0, 129.2, 130.3, 138.7; **IR** (Nujol)**:** 1616, 3351, 3448 cm^{-1}; **MS** (ESI) *m*/*z***:** 220.0807 (M + 1).

3.1.7 Selected spectra

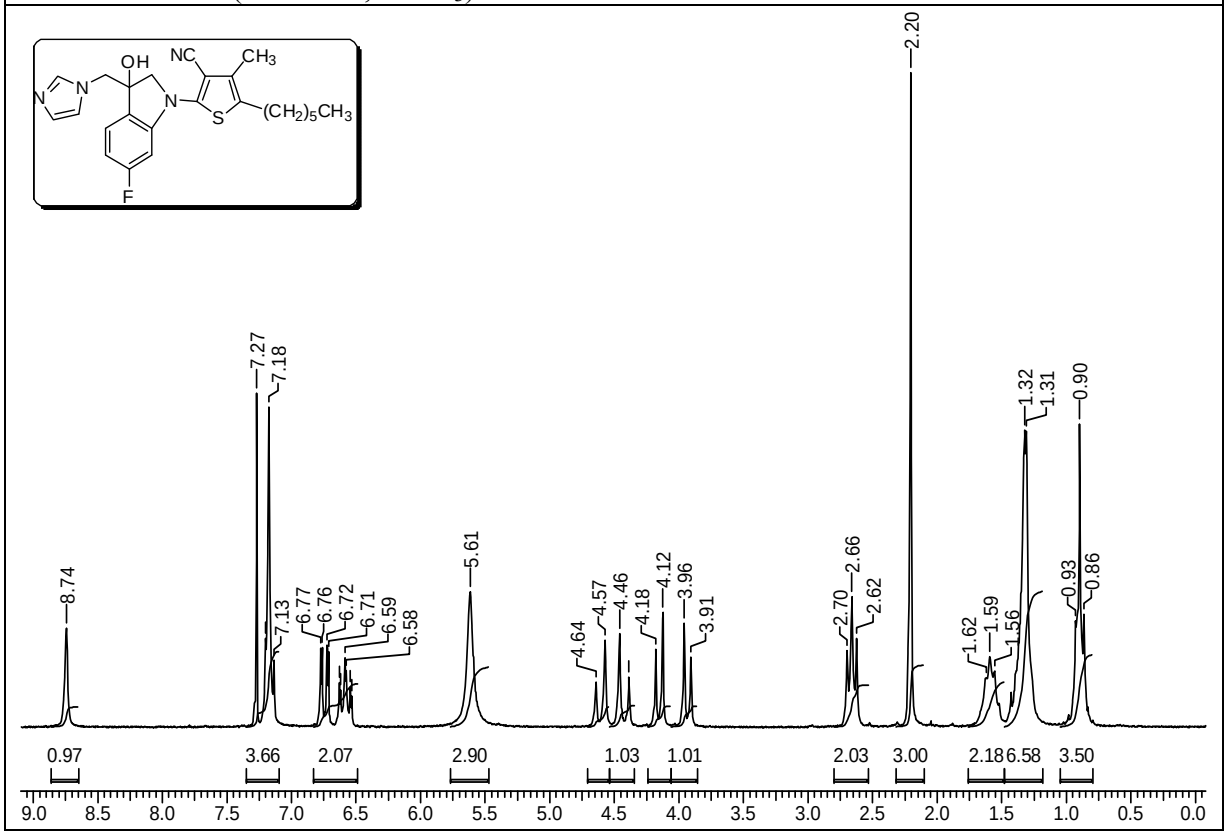
207a: ^{1}H NMR (500 MHz, $CDCl_3$)



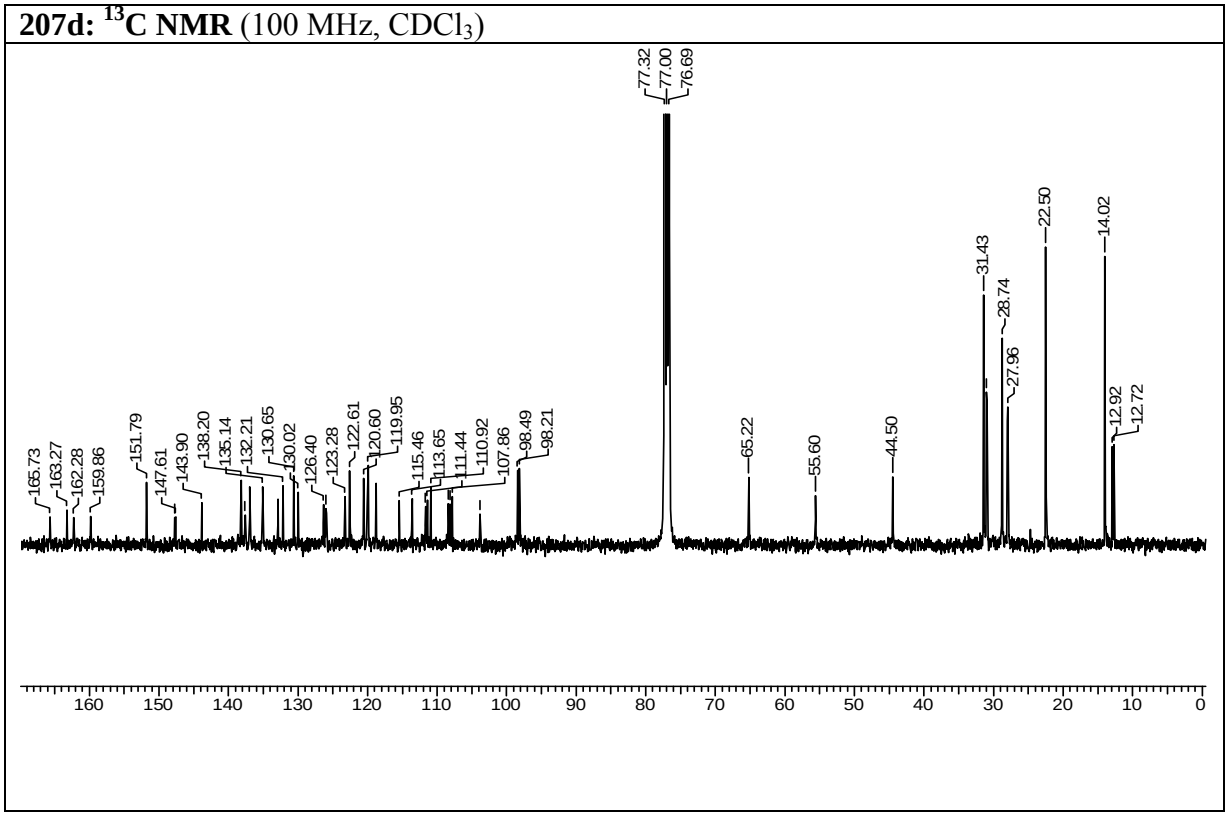
207a: ^{13}C NMR (125 MHz, $CDCl_3$)



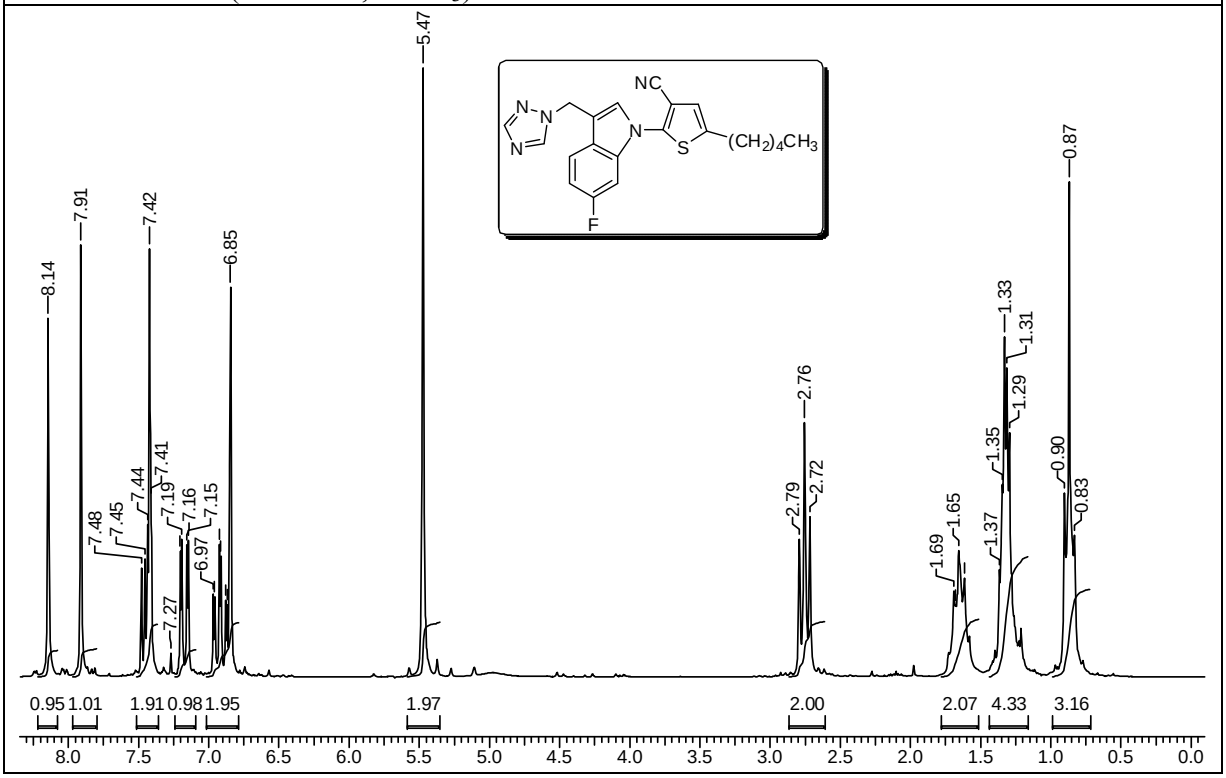
207d: ^{1}H NMR (400 MHz, $CDCl_3$)



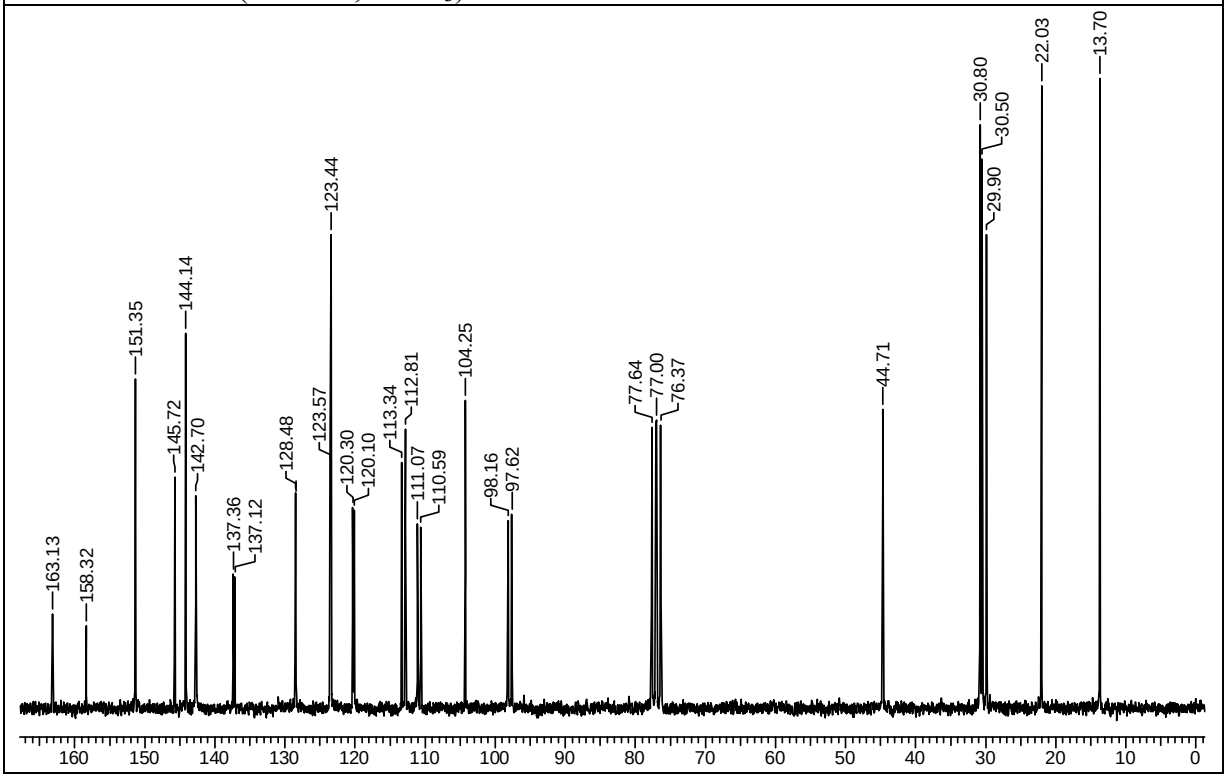
207d: ^{13}C NMR (100 MHz, $CDCl_3$)



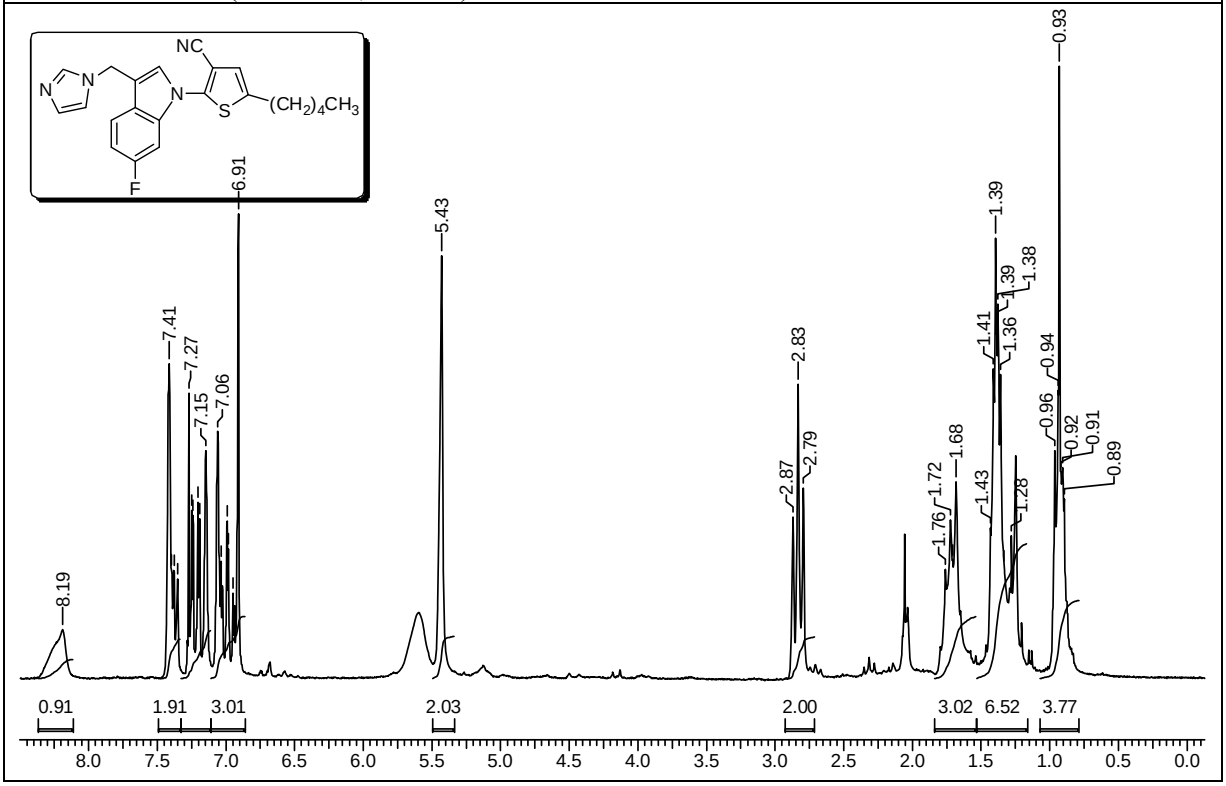
204a: ^{1}H NMR (200 MHz, $CDCl_3$)



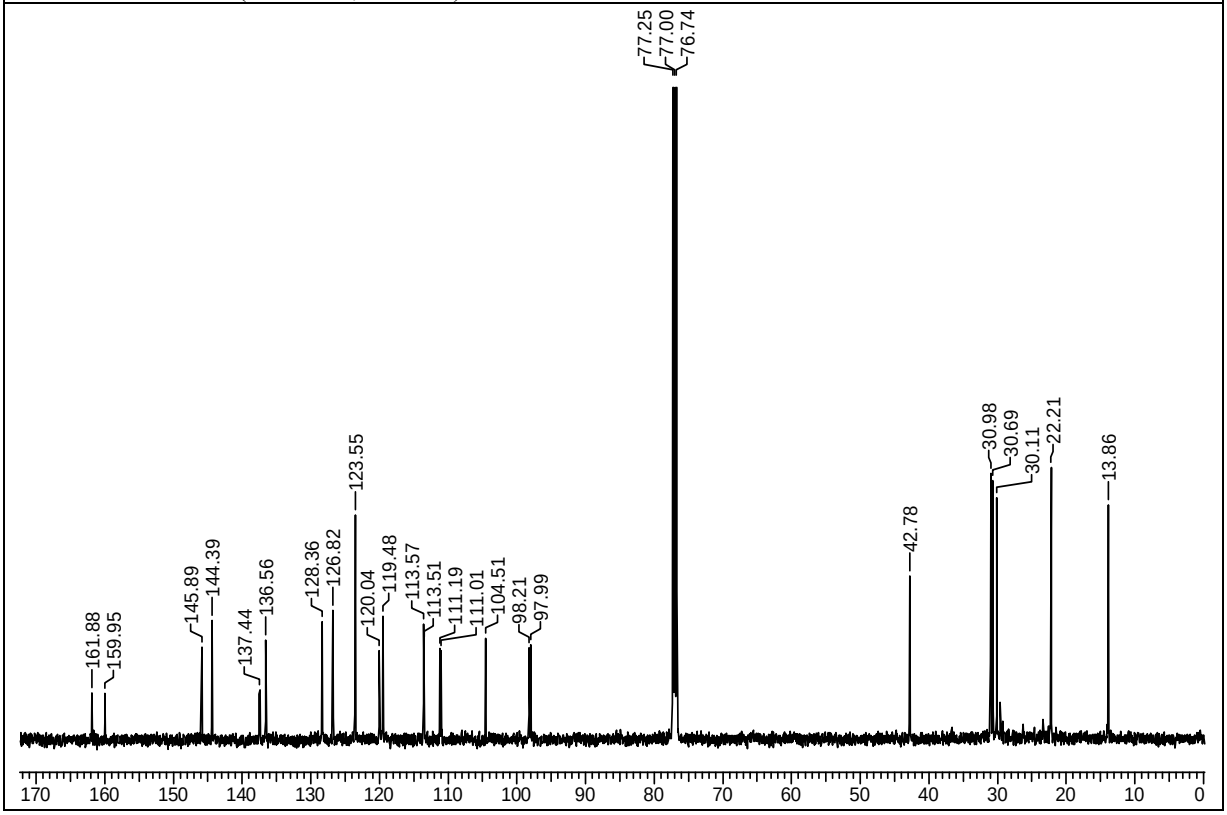
204a: ^{13}C NMR (50 MHz, $CDCl_3$)



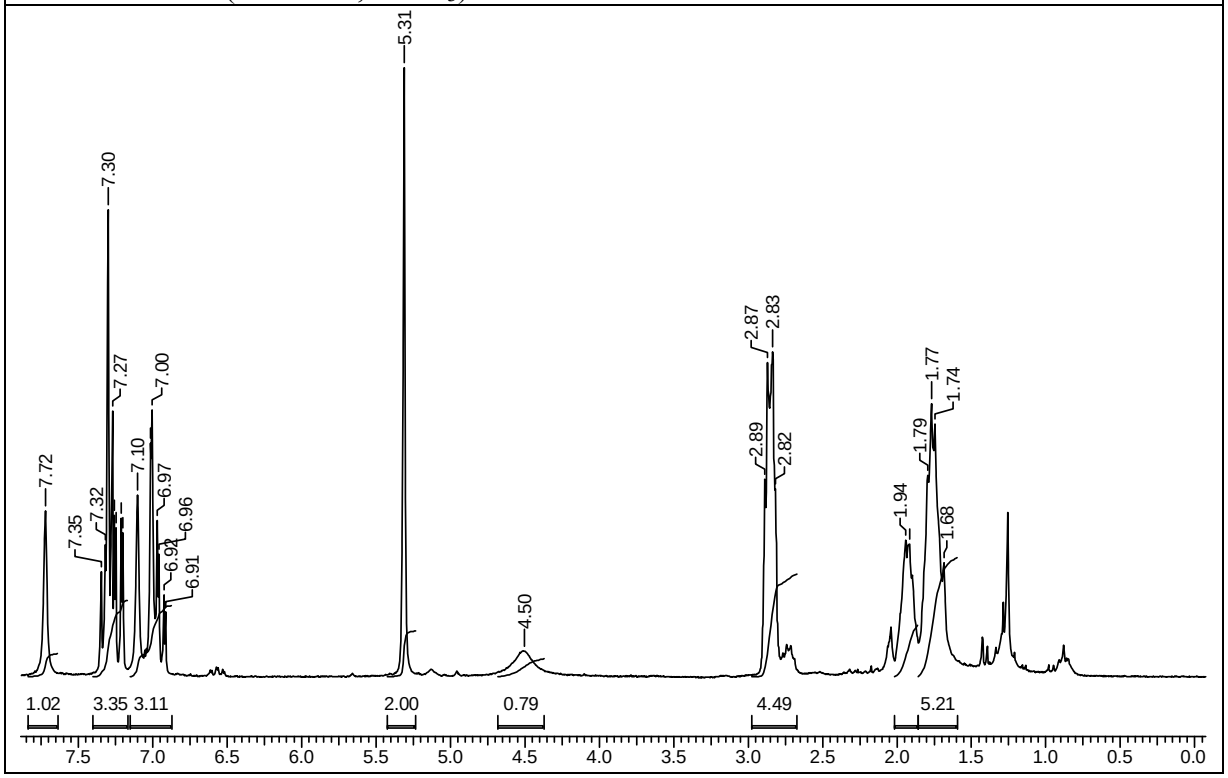
204e: ^{1}H NMR (400 MHz, $CDCl_3$)



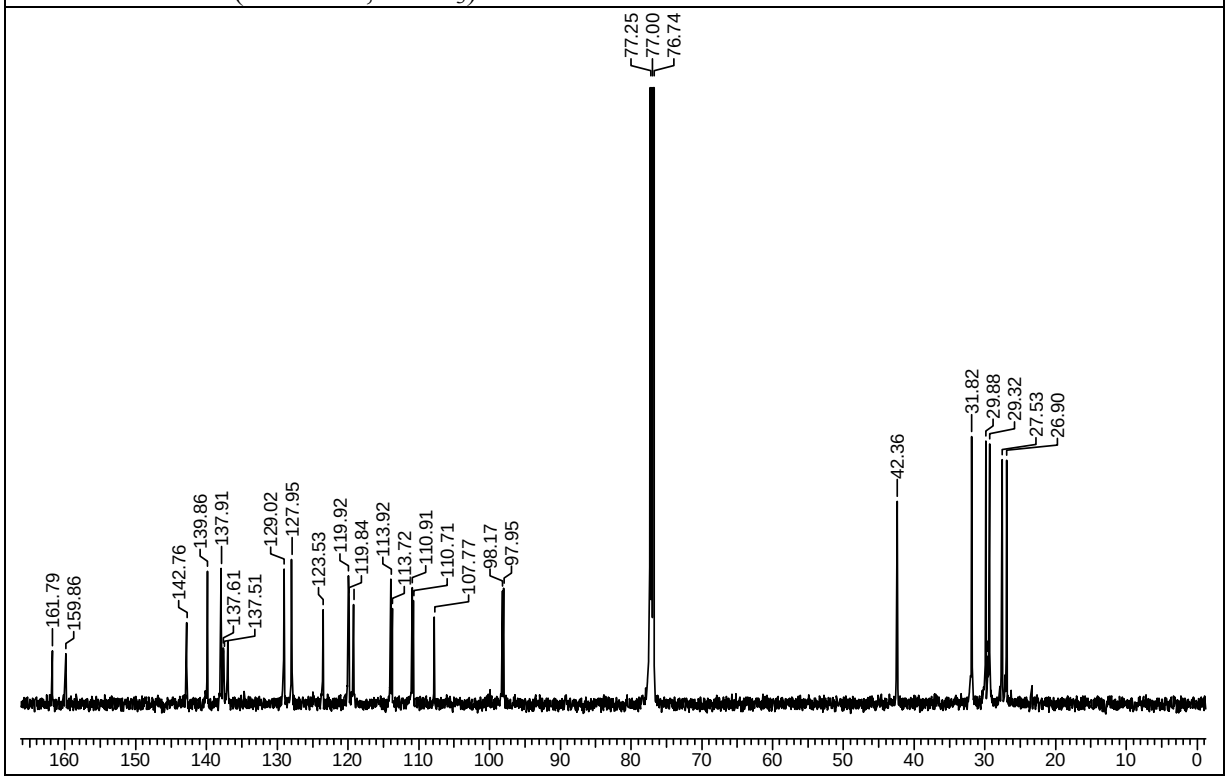
204e: ^{13}C NMR (50 MHz, $CDCl_3$)



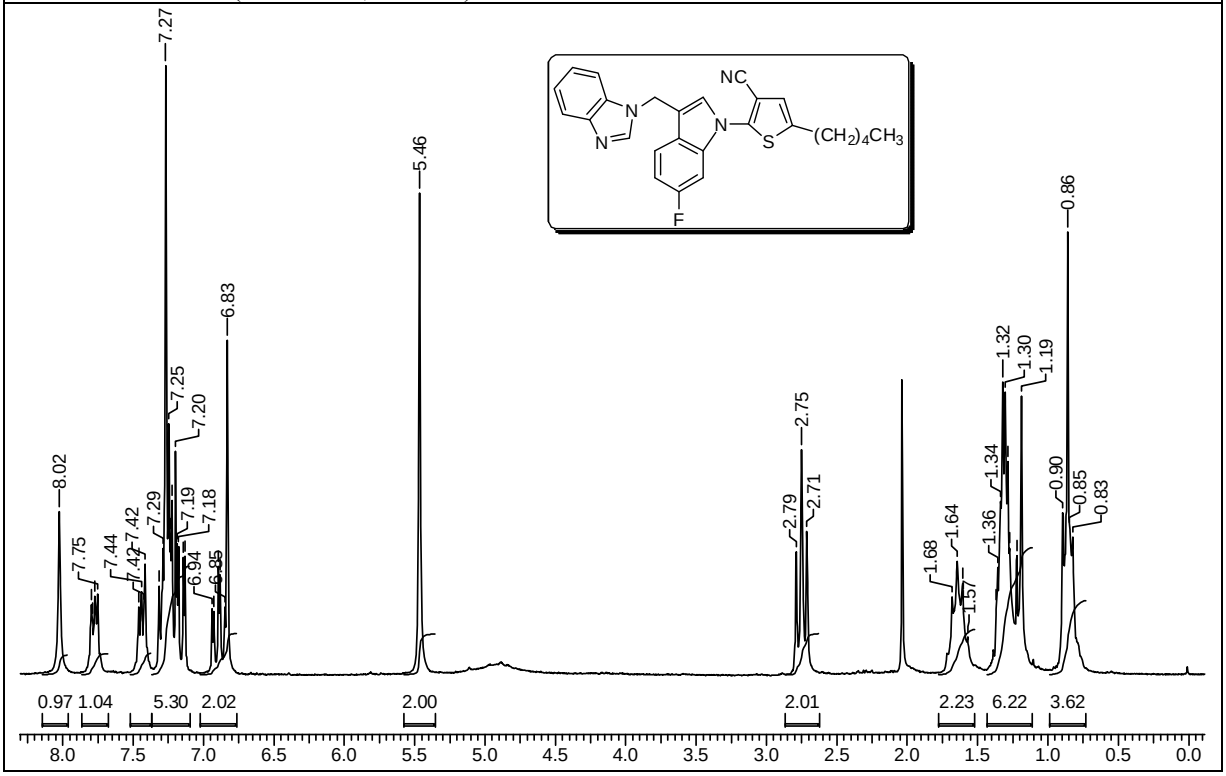
204f: ^{1}H NMR (400 MHz, $CDCl_3$)



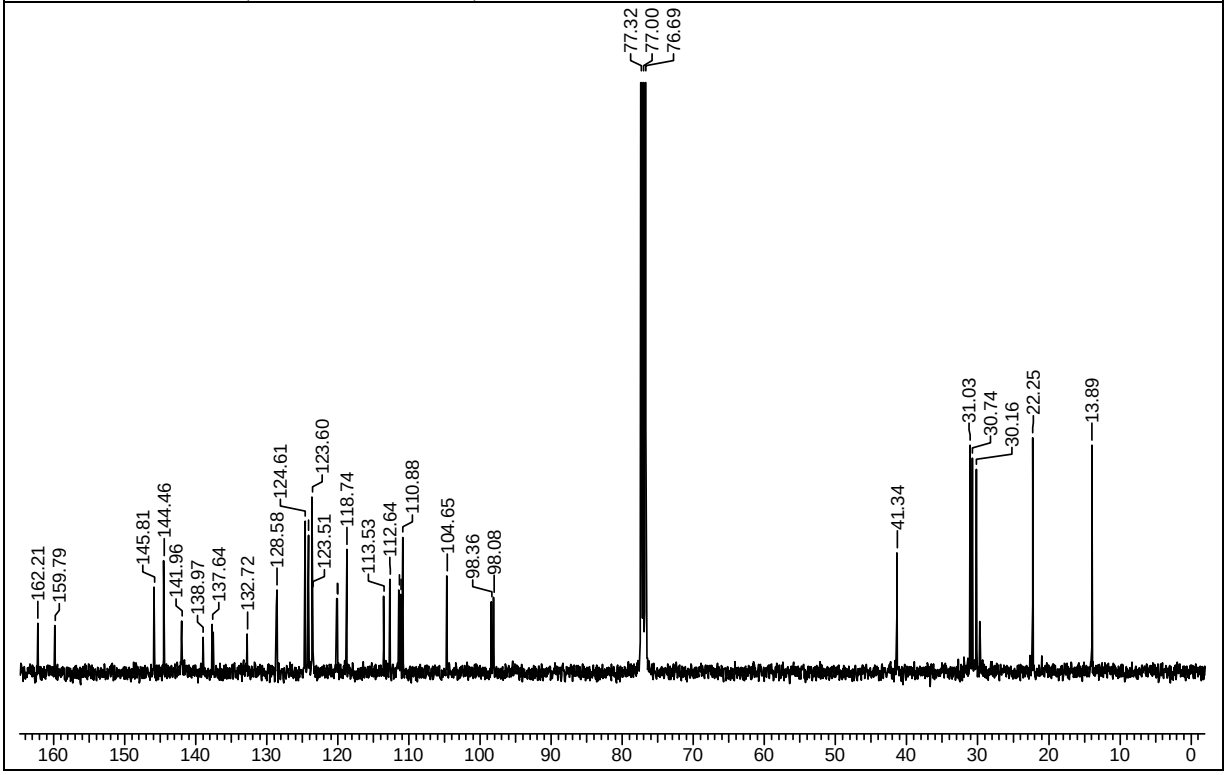
204f: ^{13}C NMR (100 MHz, $CDCl_3$)



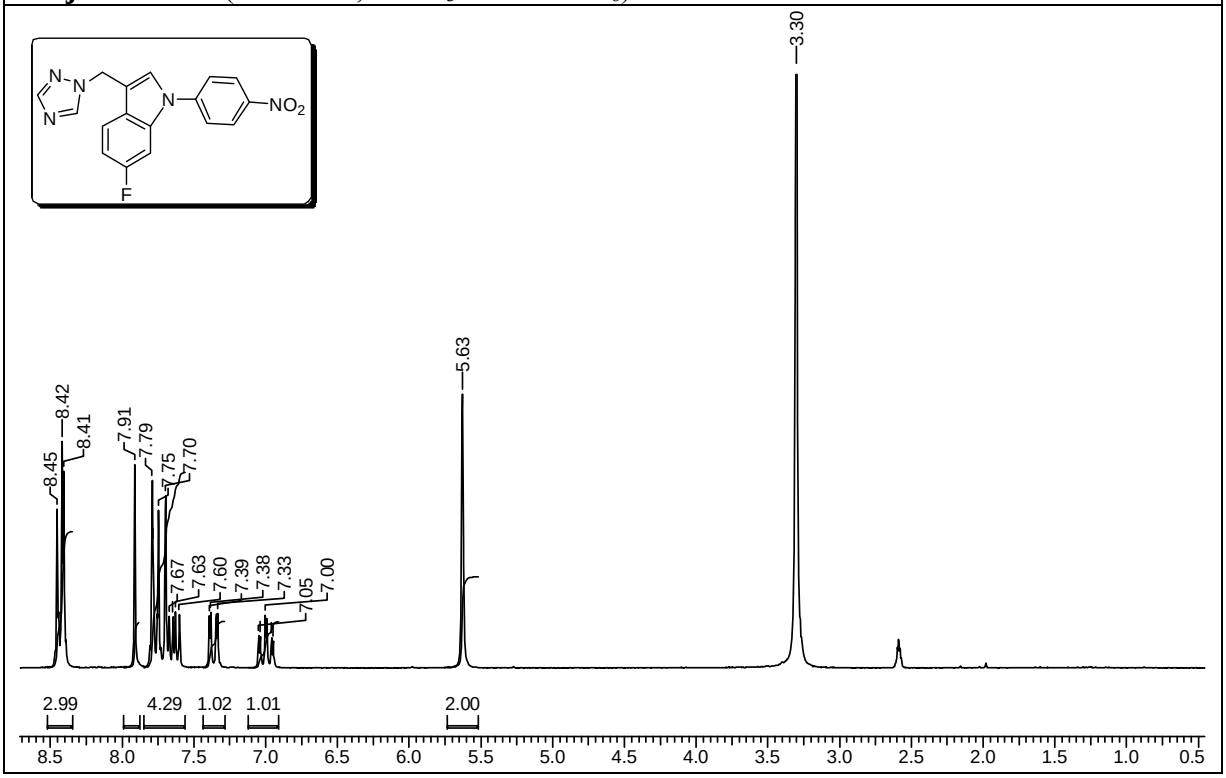
204h: ^{1}H NMR (400 MHz, $CDCl_3$)



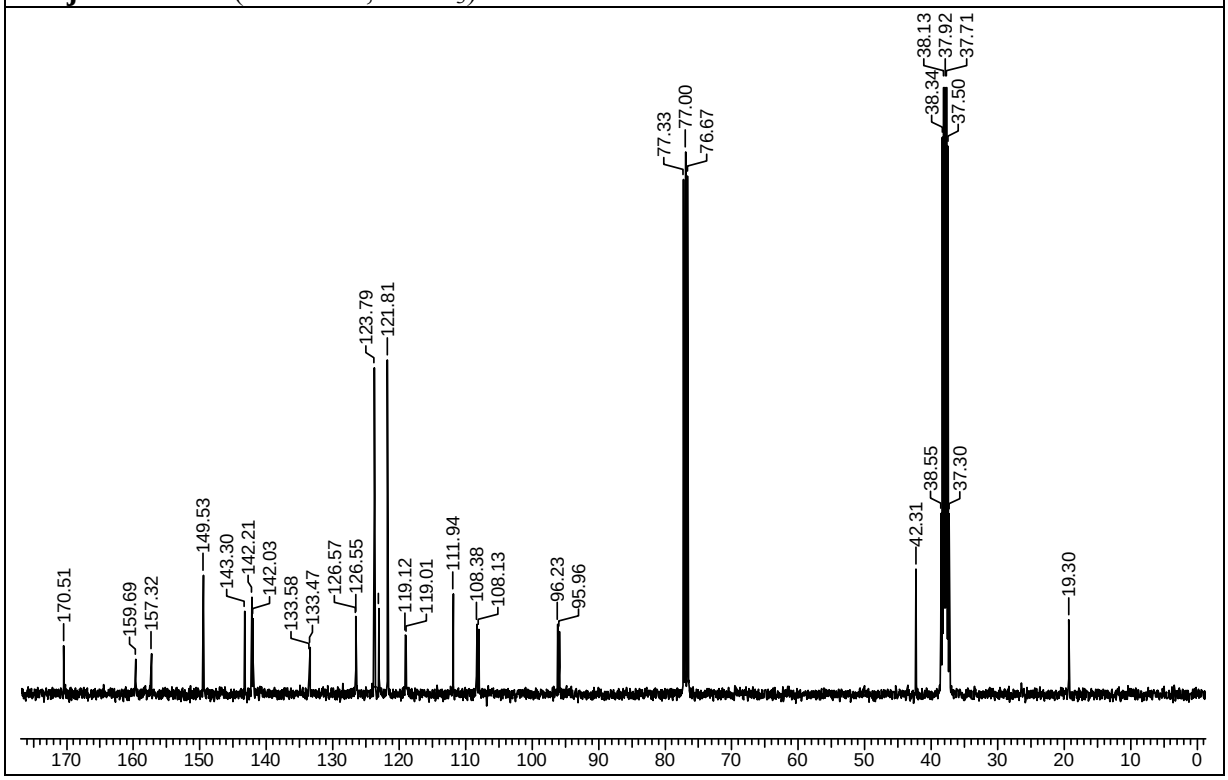
204h: ^{13}C NMR (100 MHz, $CDCl_3$)



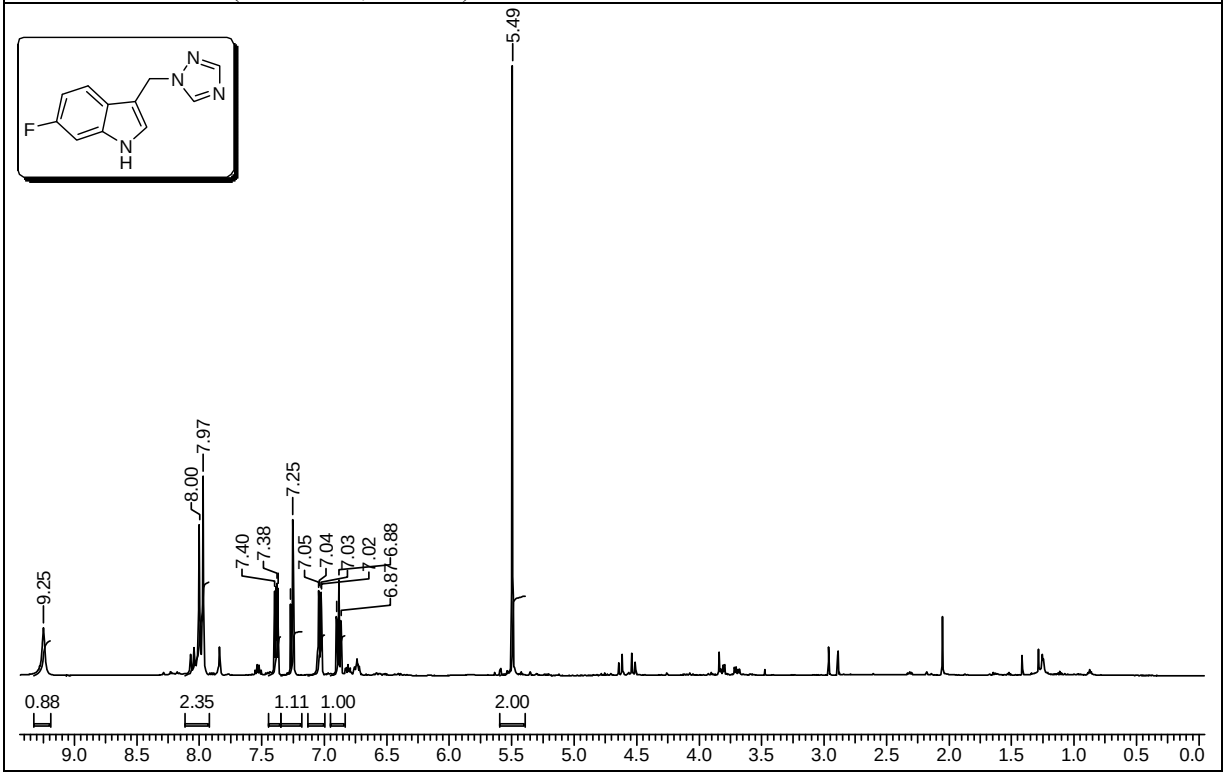
204j: ^{1}H NMR (200 MHz, $CDCl_3$ + DMSO-d_6)



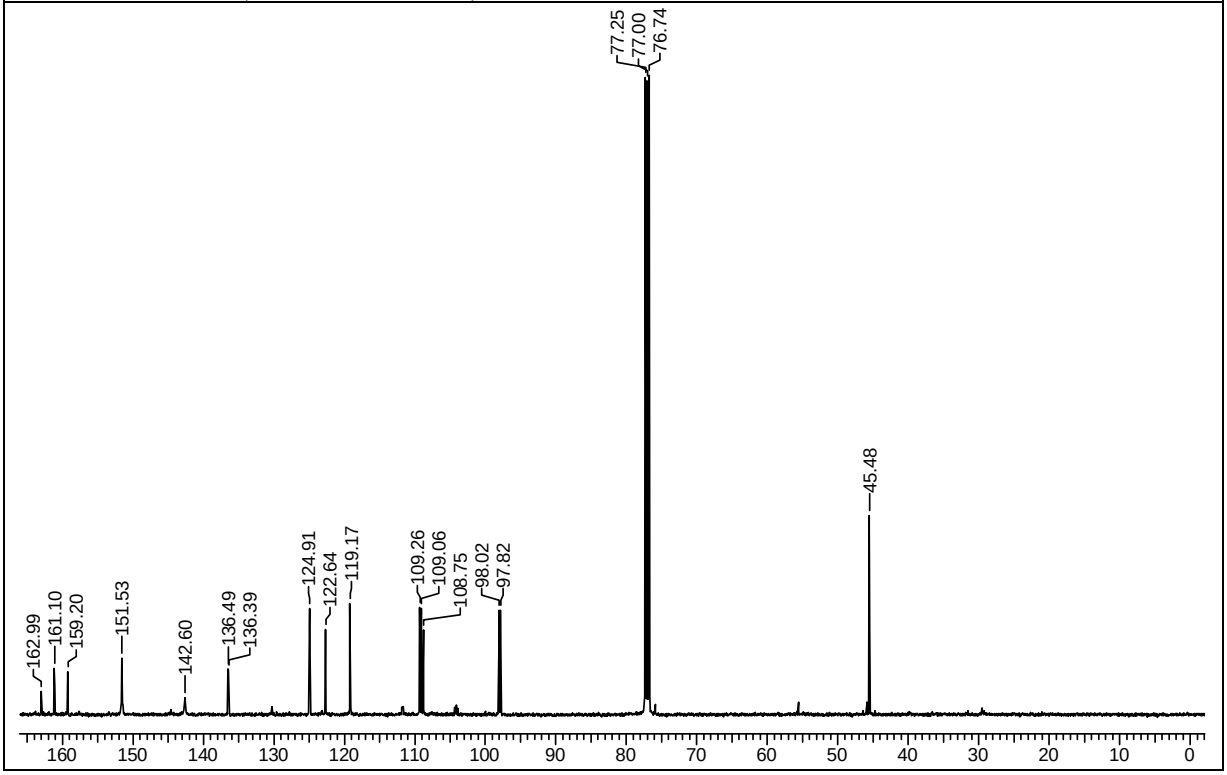
204j: ^{13}C NMR (125 MHz, $CDCl_3$)



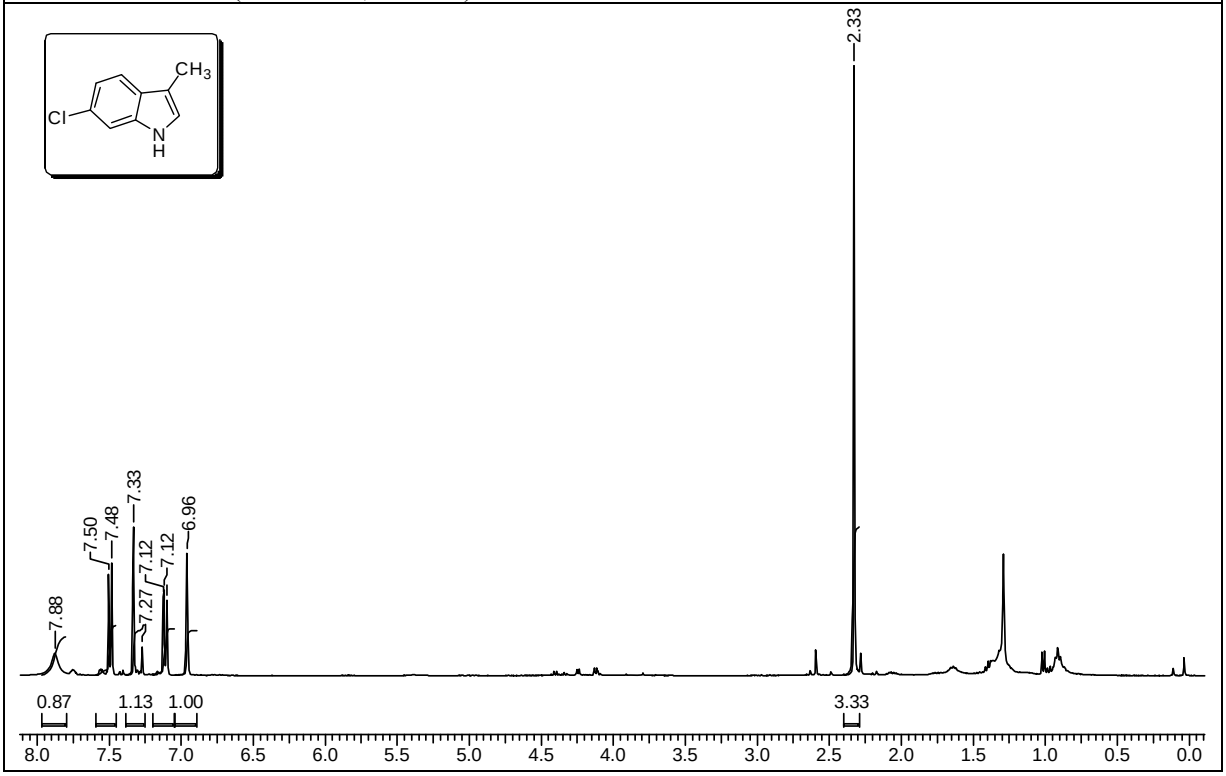
211a: ^{1}H NMR (500 MHz, $CDCl_3$)



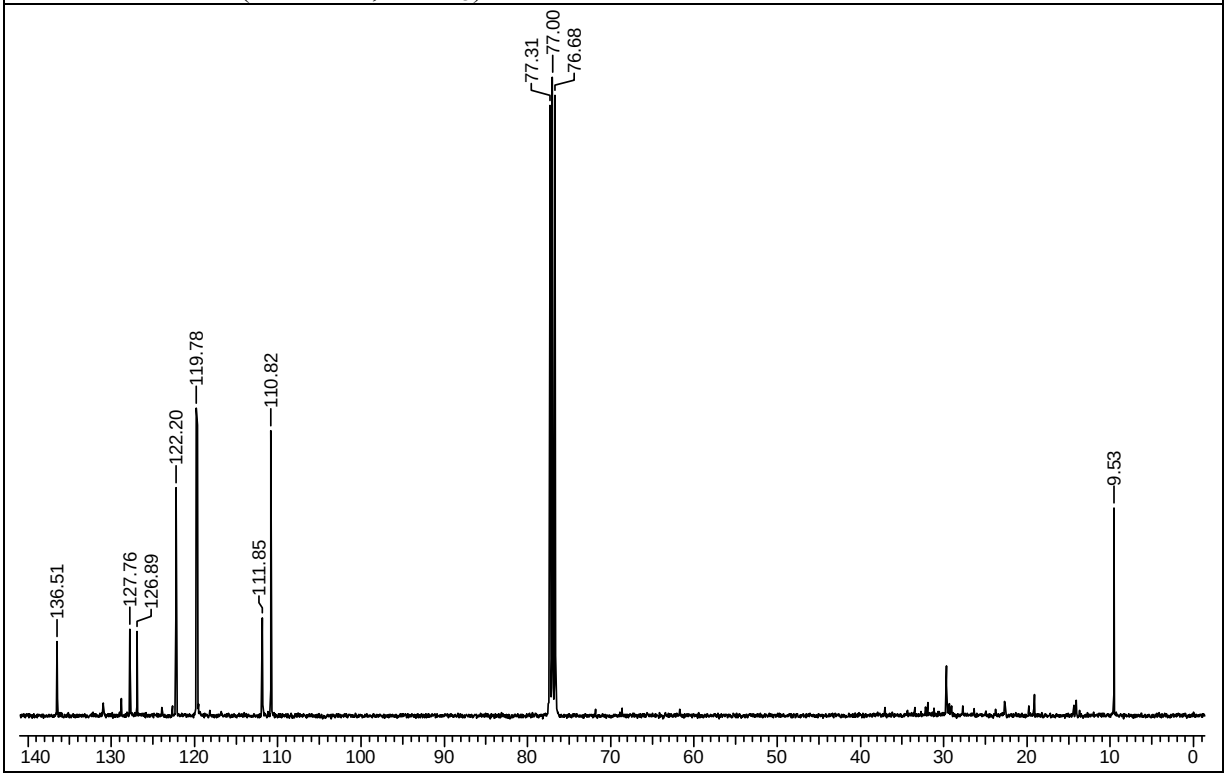
211a: ^{13}C NMR (125 MHz, $CDCl_3$)



211b: ^{1}H NMR (400 MHz, $CDCl_3$)



211b: ^{13}C NMR (100 MHz, $CDCl_3$)



3.1.8 References

1. Kawasaki, T.; Higuchi, K. *Nat. Prod. Rep*. **2005**, *22*, 761-793.
2. Walsh, T. F.; Toupence, R. B.; Ujjainwalla, F.; Young J. R; Goulet M. T. *Tetrahedron* **2001**, *57*, 5233-5241.
3. Watson, T. J. N.; Horgan, S. W.; Shah, R. S.; Farr, R. A; Schnettler, R. A.; Nevill, C. R.; Weiberth, F. J.; Huber, E. W.; Baron, B. M.; Webster, M. E.; Mishra, R. J.; Harrison, B. L.; Nyce, P. L.; Rand, C. L.; Gorlaski, C. T. *Org. Process Res. Dev.* **2000**, *4*, 477-487.
4. Jacotot, B.; Banga, J. D.; Pfister, P.; Mehra, M. *Br. J. Clin. Pharmac.* **1994**, *38*, 257-263.
5. **(**a) Fischer, E.; Jourdan, F.; *Chem. Ber.* **1883**, *16*, 2241-2245; (b) Fischer, E.; Hess, O. *Chem. Ber.* **1884**, *17*, 559568.
6. Gassman, P. G.; Gruetzmacher, G.; van Bergen, T. J. *J. Am. Chem. Soc.* **1973**, *95*, 6508-6509.
7. (a) Reissert, A. *Ber.* **1897**, *30*, 1030-1053; (b) Noland, W. E.; Baude, F. *J. Organic syntheses* **1963**, 43, 40-44.
8. Batcho, A. D.; Leimgruber, W. *Org. Synth.* **1985**, *63*, 214-220.
9. Madelung, W. *Ber.* **1912**, *45*, 1128-1134.
10. Bischler, A.; Brion, H. *Ber.* **1892**, *25*, 2860-2879.
11. Joule, J. A.; Mills, K. *Heterocyclic Chemistry*, Blackwell Science Ltd, 4th edition, Oxford, **2000**, 353-361.
12. Eicher, T.; Hauptmann, S. *The Chemistry of Heterocycles* George Thieme Verlag **1995**, 99-110.
13. Humphrey, G. R.; Kuethe, J. T. *Chem. Rev*. **2006**, *106*, 2875-2911.
14. Nakatsuka, S.; Asano, O.; Ueda, K. Goto, T. *Heterocycles* **1987**, *26*, 1471-1474.
15. Cacchi, S.; Fabrizi, G. *Chem. Rev.* **2005**, 105, 2873-2920.
16. Fukuyama, T.; Chen, X.; Peng, G. *J. Am. Chem. Soc.* **1994**, *116*, 3127-3128.
17. Fürstner, A.; Hupperts, A. J.; *J. Am. Chem. Soc.* **1995**, *117*, 4468-4475.
18. Fuwa, H.; Sasaki, M.; *Org. Biomol. Chem.* **2007**, *5*, 2214-2218.
19; (a) Arcadi, A.; Cacchi, S.; Marinelli, F.; *Tetrahedron Lett.* **1992**, *33*, 3915-3918; (b) Lu, B. Z.; Zhao, W.; Wei, H.; Dufour, M.; Farina, V.; Senanayake, C. H. *Org. Lett.* **2006**, *8*, 3271-3274.

20. (a) Larock, R. C.; Yum, E. K.; Refvik, M. D. *J. Org. Chem.* **1998,** *63,* 7652-7662; (b) Zeni, G.; Larock, R. C. *Chem. Rev.* **2004**, *104*, 2285-2309; (c) Larock, R. C. *Top. Organomet. Chem.* **2005**, *14*, 147-182.

21. Na, Y.-M.; Le Borgne, M.; Pagniez, F.; Le Baut, G.; Le Pape, P. *Eur. J. Med. Chem.* **2003**, *38*, 75-87.

22. Tiwari, R. K.; Singh, J.; Singh, D.; Verma, A. K.; Chandra, R. *Tetrahedron* **2005**, *61*, 9513-9518.

23. (a) Konosu, T.; Tajima, Y.; Takeda, N.; Miyaoka, T.; Kasahara, M.; Yasuda, H.; Oida, S. *Chem. Pharm. Bull.* **1990**, *38*, 2476-2486; b) Upadhayaya, R. S.; Jain, S.; Sinha, N.; Kishore, N.; Chandra, R.; Arora, S. K. *Eur. J. Med. Chem.* **2004**, *39*, 579-592; (c) Santamaria, A.; Moreno-Mañas, M.; Pleixats, R. *ARKIVOC* **2007**, *iv*, 234-250.

24. (a) Hlasta, D. J.; Luttinger, D.; Perrone, M. H.; Silbernagel, M. J.; Ward, S. J.; Haubrich, D. R. *J. Med.Chem.* **1987**, *30*, 1555-1562; (b) Bermudez, J.; Dabbs, S.; Joiner, K. A.; King, F. D. *J. Med. Chem.* **1990**, *33*, 1929-1932; (c) Michaelis, D. J.; Dineen, T. A. *Tetrahedron Lett.* **2009**, *50*, 1920-1923.

25. (a) Tiwari, R. K.; Verma, A. K.; Chhillar, A. K.; Singh, D.; Singh, J.; Sankar, V. K.; Yadav, V.; Sharma, G. L.; Chandra, R. *Bioorg. Med. Chem.* **2006**, *14*, 2747-2752; (b) Lebouvier, N.; Pagniez, F.; Duflos, M.; Le Pape, P.; Na, Y. M.; Le Baut, G.; Le Borgne, M. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 3686-3689. (c) Giraud, F.; Guillon, R.; Logé, C.; Pagniez, F.; Picot, C.; Le Borgne, M.; Le Pape, P. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 301-304.

26. Katritzky, A. R.; Henderson, S. A.; Yang, B. *J. Heterocyclic Chem.* **1998**, *35*, 1123-1159.

Chapter 3: Section II

One-step synthesis of 4-alkyl-3-aryl-2,6-dicyanoanilines and their use in the synthesis of highly functionalized 1,2,3,5,6,7- and 1,2,3,4,5,7-hexasubstituted indoles

Chapter 3: Section II

One-step synthesis of 4-alkyl-3-aryl-2,6-dicyanoanilines and their use in the synthesis of highly functionalized 1,2,3,5,6,7- and 1,2,3,4,5,7-hexasubstituted indoles

One-step synthesis of 4-alkyl-3-aryl-2,6-dicyanoanilines and their use in the synthesis of highly functionalized 1,2,3,5,6,7-and 1,2,3,4,5,7-hexasubstituted indoles

3.2.1 Abstract

A three-component, one-step method for the synthesis of 4-alkyl-3-aryl-2,6-dicyanoanilines involving reaction of alkyl aldehyde, malononitrile and aryl aldehyde in presence of morpholine is reported. Highly functionalized 1,2,3,5,6,7- and 1,2,3,4,5,7-hexasubstituted indoles were prepared from these dicyanoanilines by reaction with ethyl bromoacetate in presence of potassium hydroxide. These substituted dicyanoanilines and indoles have a potential to be converted into various other compounds taking advantage of various functional groups present in these molecules.

3.2.2 Introduction

Polysubstituted benzenes are very useful compounds in organic chemistry, natural product chemistry, analytical chemistry and materials science. The regioselective preparation of these compounds is a challenging problem in organic synthesis[1]. Classical methods for the synthesis of substituted aromatics are based on aromatic substitution reactions which introduce a substituent to an existing arene. The most common procedures based on this approach involve electrophilic[2] or nucleophilic[3] substitution, catalyzed coupling reactions[4] and metalation-functionalization reactions[5]. However, these methods frequently suffer from disadvantages including multi-step reaction sequences, low yields, and serious regiochemical ambiguity originating from the activating, deactivating and directing effects of the substituents. On the other hand, modern approaches lead to the regioselective construction of the aromatic skeleton starting from acyclic precursors in which the substitution pattern of the final product is dictated by the structures and functional groups of the precursors[6].

Multi-functionalized benzenes possessing electron-donor and/or acceptor substituents such as 2,6-dicyanoanilines are of considerable interest. They are key constituents of a large number of bioactive natural and synthetic compounds[7] and are useful as versatile precursors for asymmetric syntheses[8] and as important substrates for nonlinear optical materials[9] and molecular electronic devices[10]. The amino and cyano groups can be converted into various other functional groups so these 2,6-dicyanoanilines can be used as starting materials for a large number of aromatic compounds.

There are a large number of methods reported for the synthesis of substituted 2,6-dicyanoanilines by using a multicomponent reaction wherein most of the methods describe

synthesis of 3,5-disubstituted-2,6-dicyanoanilines **213** (Figure 1). 2,6-Dicyanoanilines are typically prepared from (arylidene)malononitriles and (1-arylethylidene)malononitriles in the presence of a base[11]. Other synthetic routes include: reaction of malononitrile and α,β-unsaturated ketones[12], one-pot tandem reaction of (alkylidene)malononitriles with nitroolefins in the presence of a base[13], reaction of ynones and malononitrile[14], reaction of α-methylene ketones or enamino ketones with malononitrile[15], ring transformation of functionalized 2*H*-pyran-2-ones with malononitrile[16], the three-component reaction of aldehydes, ketones and malononitrile under solvent-free conditions[17] or microwave irradiation[18] and reaction between (arylidene)malononitriles, dialkyl acetylenedicarboxylates and malononitrile catalyzed by 1-methylimidazole[6]. In the present work, we have developed a short synthesis of 4-alkyl-3-aryl-2,6-dicyanoanilines from substituted aromatic and aliphatic aldehydes and malononitrile and the results are presented in this section.

3.2.3 Present work

3.2.3.1 Objective

Due to the interesting chemistry of 2,6-dicyanoanilines, the development of synthetic methods which enable easy access to these useful compounds is desirable. As a part of our studies on the development of efficient and straightforward methods for the preparation of 2, 6-dicyanoanilines (Figure 1) we report herein a three-component one-step method for the synthesis of 4-alkyl-3-aryl-2,6-dicyanoanilines **214**. These results were further extended for the synthesis of highly functionalized 1,2,3,5,6,7- and 1,2,3,4,5,7-hexasubstituted indoles from these dicyanoanilines **214** by reaction with ethyl bromoacetate.

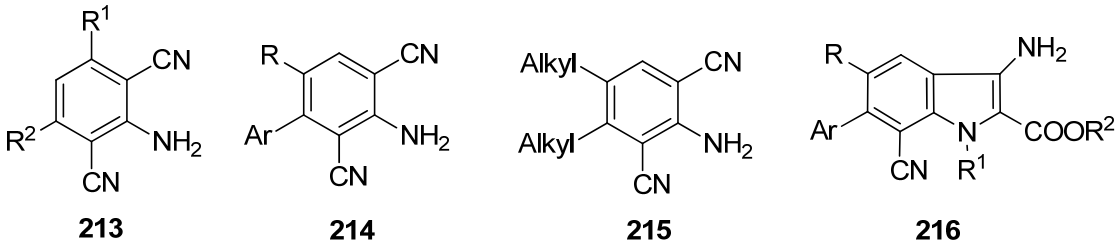
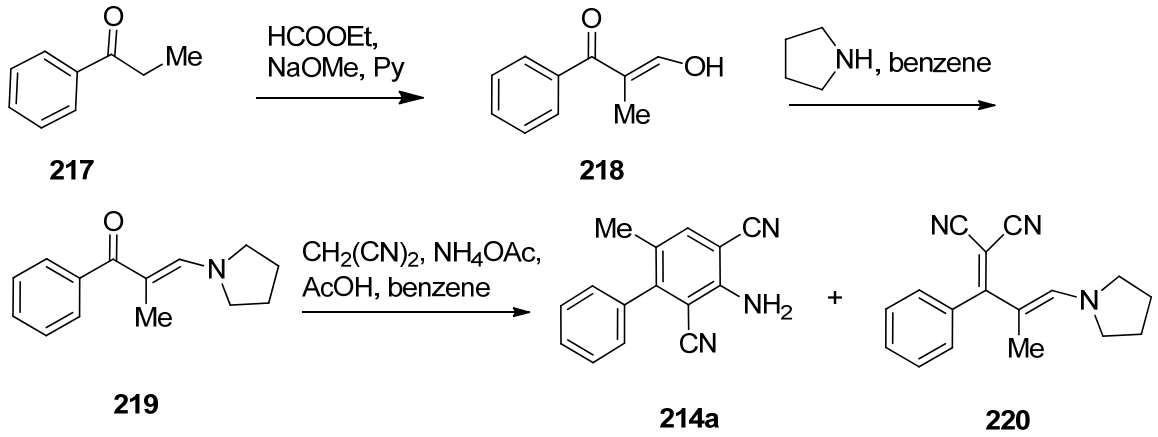


Figure 1. General structures of 2,6-dicyanoanilines and hexasubstituted indoles.

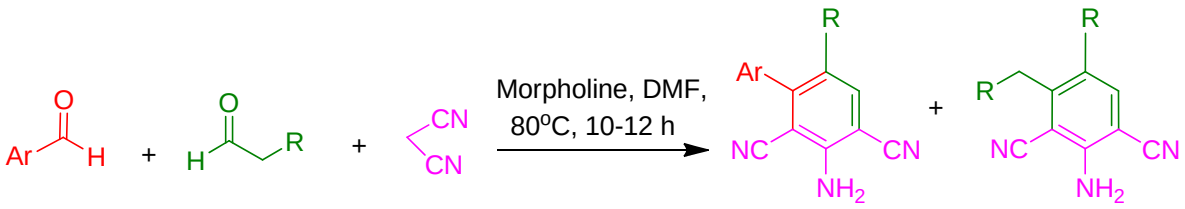
3.2.3.2 Results and discussion

A literature survey showed that there are a number of methods reported[11-18] for the synthesis of substituted 2,6-dicyanoanilines, among them most of the methods describe synthesis of 3,5-disubstituted-2,6-dicyanoanilines **213**. There are a very few reports describing synthesis of 3,4-dialkyl-2,6-dicyanoanilines **215**[19] and there is only one method[15] reported by Khaidem *et al.* for the synthesis of 4-alkyl-3-aryl-2,6-dicyanoaniline (4-methyl-3-phenyl-2,6-dicyanoaniline) **214a** by a three-step reaction sequence in very low yields (36%) as shown in Scheme 1.



Scheme 1. Reported preparation of 4-methyl-3-phenyl-2,6-dicyanoaniline

In order to improve the synthesis of 4-alkyl-3-aryl-2,6-dicyanoaniline **214**, we developed a practical three-component reaction that significantly reduces the reaction time and increases the yields as shown in Scheme 2.



221 **222** **214** **215**

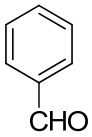
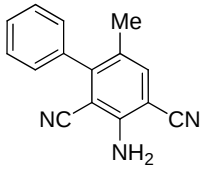
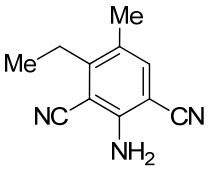
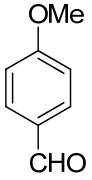
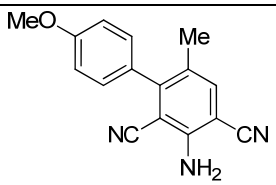
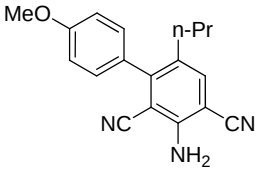
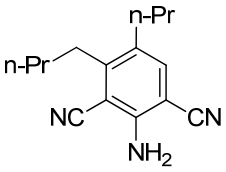
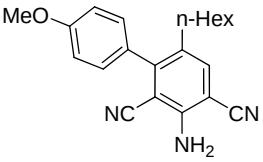
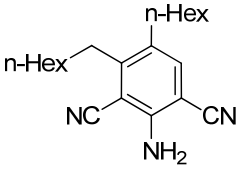
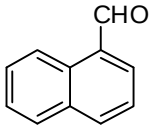
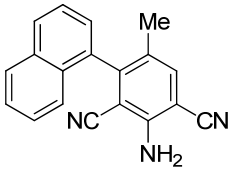
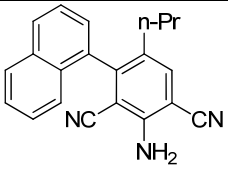
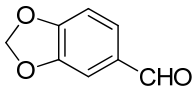
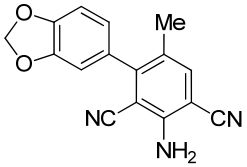
Ar	R
214a: Phenyl	Me
214b: 4-Methoxyphenyl	Me
214c: 4-Methoxyphenyl	n-Pr
214d: 4-Methoxyphenyl	n-Hex
214e: 1-Naphthyl	Me
214f: 1-Naphthyl	n-Pr
214g: 3,4-(Methylenedioxy)phenyl	Me
214h: 2-Thienyl	Me
214i: 2-Thienyl	n-Hex
214j: 2-Furanyl	Me
214k: 2-Furanyl	n-Hex
214l: 4-Hydroxyphenyl	Me

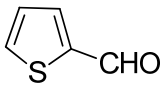
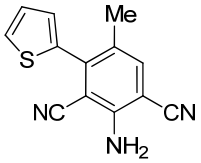
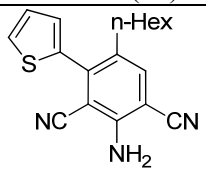
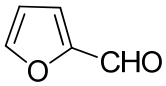
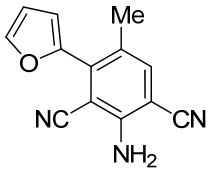
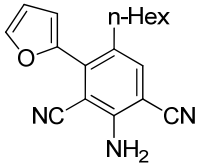
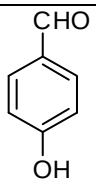
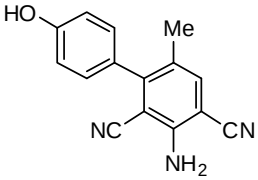
Scheme 2. Preparation of 4-alkyl-3-aryl-2,6-dicyanoanilines **214**.

The reaction of aliphatic aldehyde, malononitrile and aryl aldehyde was attempted in presence of various bases like potassium carbonate, triethylamine, morpholine, basic alumina *etc* with (dimethylformamide, ethyl acetate, acetonitrile) or without solvent at various temperatures ranging from room temperature to 100 ^{o}C and it was observed that the reaction in presence of morpholine in DMF at 80 ^{o}C afforded the desired 4-alkyl-3-aryl-2,6-dicyanoanilines **214** as major product and 3,4-dialkyl-2,6-dicyanoanilines **215**[19c] as a minor product (Scheme 2). These two products were easily separated by column chromatography. The structures of the products **214** were assigned based on ^{1}H NMR, ^{13}C NMR, IR and mass spectroscopy. In ^{1}H NMR spectrum, two singlets (one singlet for two NH_2 protons in the range of δ 5.00-5.20 and other for one aromatic CH proton in the range of δ 7.00-8.00) were observed and cyanide band in IR spectrum in the range of 2200 to 2222 cm^{-1} was seen which confirmed the formation of product. Furthermore, mass spectra confirmed the structures of 2,6-dicyanoaniline products **214**. Formation of compound **215** was confirmed by ^{1}H NMR, ^{13}C NMR, IR and mass spectroscopy and the comparison of the spectroscopic data with the literature values[19c].

The reaction was done with various combinations of aryl and aliphatic aldehydes to see the generality and the various compounds prepared are shown in Table 1.

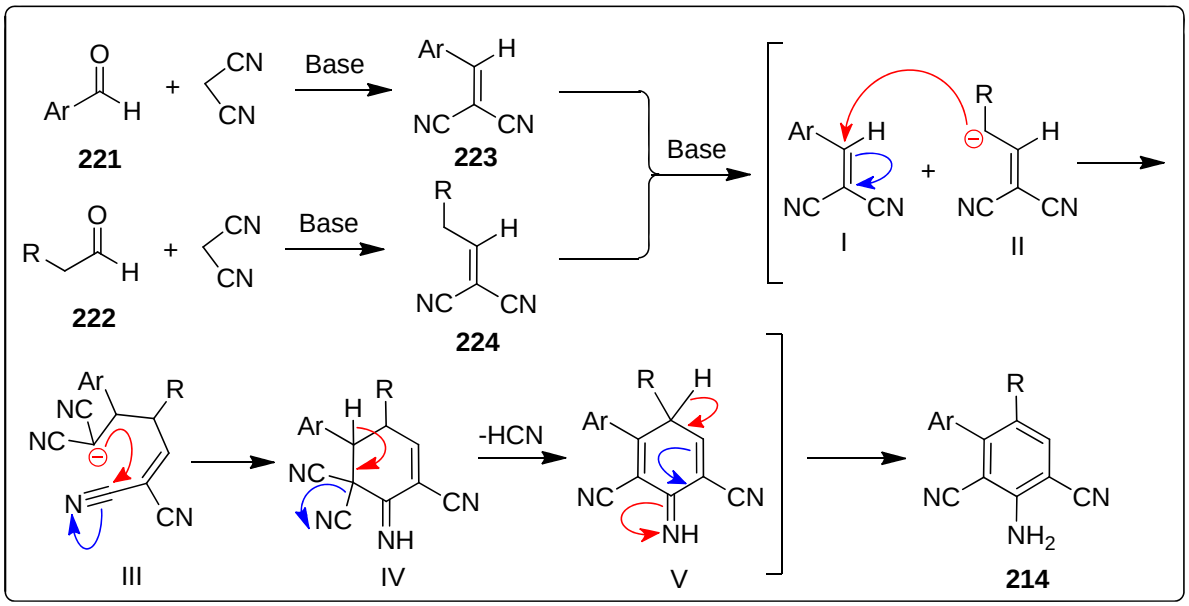
Table 1. Synthesis of 4-alkyl-3-aryl-2,6-dicyanoanilines **214**

Entry	Aromatic Aldehyde **221**	Aliphatic Aldehyde **222**	Product **214** (Yield %)*	Product **215** (Yield %)*
1	 **221a**	CH_3CH_2CHO **222a**	 **214a** (67)	 **215a** (12)
2	 **221b**	**222a**	 **214b** (77)	**215a** (8)
3	**221b**	$CH_3(CH_2)_3CHO$ **222b**	 **214c** (64)	 **215b** (10)
4	**221b**	$CH_3(CH_2)_6CHO$ **222c**	 **214d** (69)	 **215c** (13)
5	 **221c**	**222a**	 **214e** (77)	**215a** (11)
6	**221c**	**222b**	 **214f** (52)	**215b** (15)
7	 **221d**	**222a**	 **214g** (75)	**215a** (10)

8	 **221e**	**222a**	 **214h** (56)	**215a** (14)
9	**221e**	**222c**	 **214i** (70)	**215c** (9)
10	 **221f**	**222a**	 **214j** (10)	**215a** (18)
11	**221f**	**222c**	 **214k** (17)	**215c** (17)
12	 **221g**	**222a**	 **214l** (53)	**215a** (13)

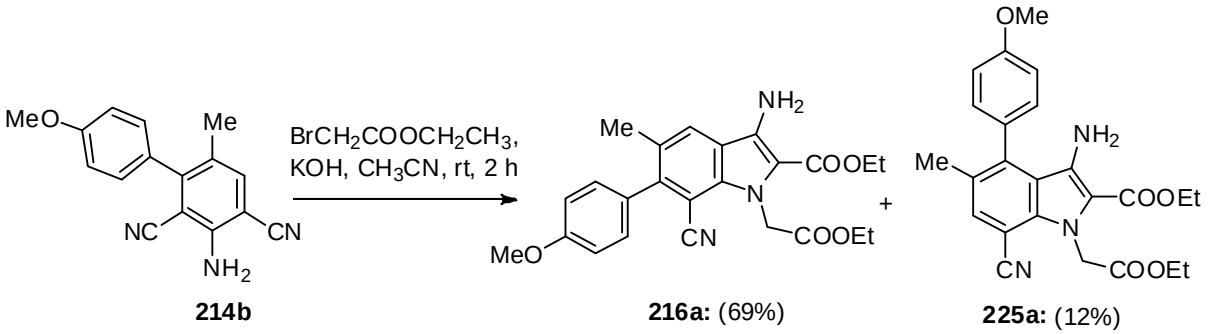
*The yields given are for the isolated products.

It was observed that dicyanoanilines with a wide variety of substituents could be prepared by this method. This protocol provides easy access to a regiospecific synthesis of unsymmetrical, polyfunctional biaryls, which would be difficult to make by conventional methods. It is also noteworthy that the present method makes use of easily available starting materials, use of expensive catalyst/reagents is not required and the conditions are mild. The proposed mechanism for formation of 4-alkyl-3-aryl-2,6-dicyanoanilines **214** is shown in Scheme 3.



Scheme 3. The proposed mechanism for formation of 4-alkyl-3-aryl-2,6-dicyanoanilines **214**.

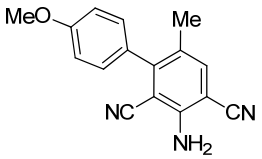
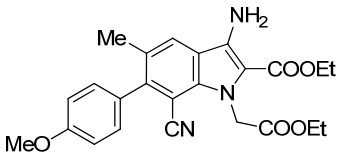
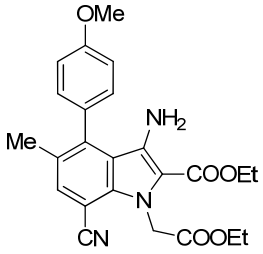
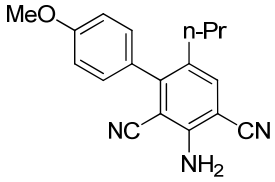
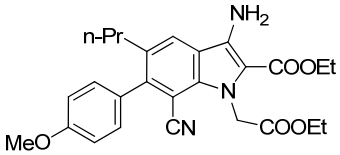
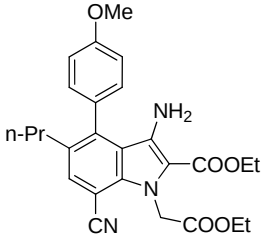
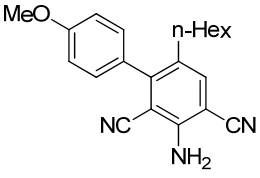
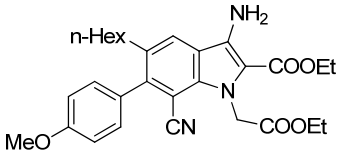
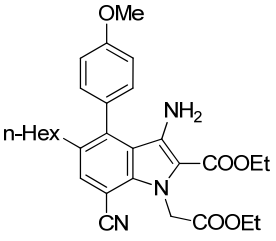
Narsaiah *et al.* have reported[8a] that reaction of 2,6-dicyanoanilines with ethyl bromoacetate in presence of potassium carbonate and potassium iodide affords substituted indoles. Taking into consideration the importance of substituted indoles, reaction of the 3-amino-4'-methoxy-6-methyl-[1,1'-biphenyl]-2,4-dicarbonitrile (**214b**) with ethyl bromoacetate was carried out in presence of bases like potassium carbonate, potassium hydroxide pellets, sodium hydroxide pellets *etc* in different solvents like ethyl acetate, acetonitrile, dimethyl formamide *etc* at various temperatures in order to get the corresponding substituted indole and it was observed that the reaction in presence of potassium hydroxide pellets in acetonitrile at room temperature afforded ethyl 3-amino-7-cyano-1-(2-ethoxy-2-oxoethyl)-6-(4-methoxyphenyl)-5-methyl-1*H*-indole-2-carboxylate **216a** as major product in 69% yield and ethyl 3-amino-7-cyano-1-(2-ethoxy-2-oxoethyl)-4-(4-methoxyphenyl)-5-methyl-1*H*-indole-2-carboxylate **225a** as minor product in 12% yield (Scheme 4). The structures of the isomers were assigned based on spectral data and literature precedent[8a] that the reaction is governed by the steric factors.

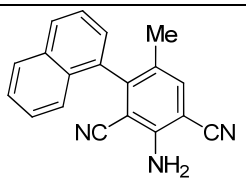
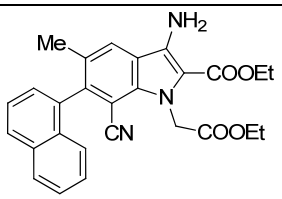
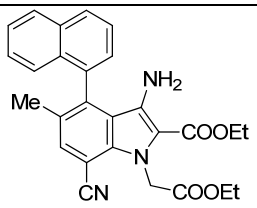
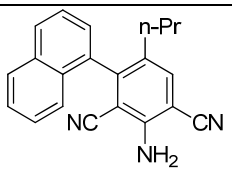
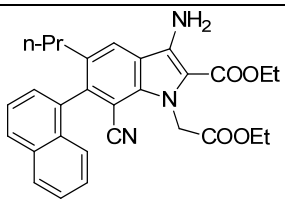
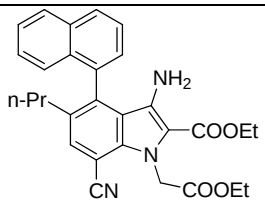
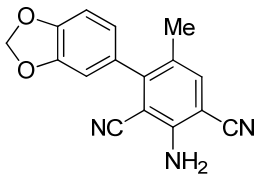
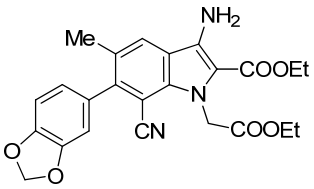
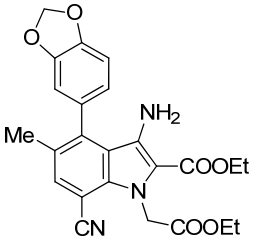
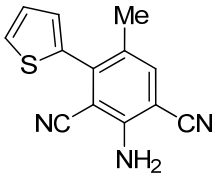
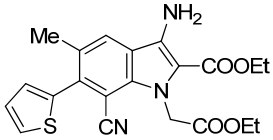
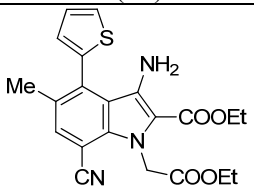
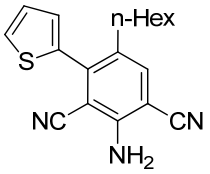
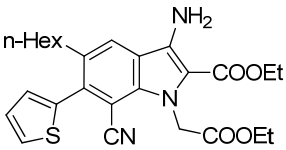
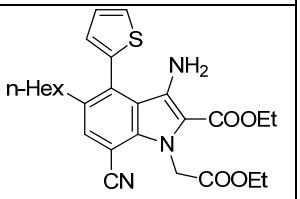
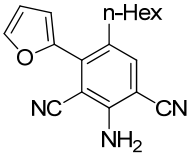
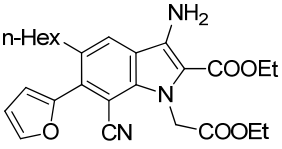
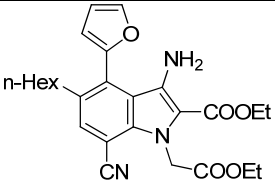


Scheme 4. Synthesis of 1,2,3,5,6,7-and 1,2,3,4,5,7-hexasubstituted indoles **216a** and **225a**

The various novel 2,6-dicyanoanilines **214** were subjected to above reaction conditions and the results are shown in Table 2.

Table 2. Synthesis of 1,2,3,5,6,7- and 1,2,3,4,5,7-hexasubstituted indoles **216** and **225**

Entry	Substituted aniline **214**	Product **216** (Yield %)*	Product **225** (Yield %)*
1	 **214b**	 **216a** (69)	 **225a** (12)
2	 **214c**	 **216b** (65)	 **225b** (15)
3	 **214d**	 **216c** (85)	 **225c** (9)

4	 **214e**	 **216d** (62)	 **225d** (18)
5	 **214f**	 **216e** (61)	 **225e** (13)
6	 **214g**	 **216f** (69)	 **225f** (23)
7	 **214h**	 **216g** (64)	 **225g** (12)
8	 **214i**	 **216h** (77)	 **225h** (11)
9	 **214j**	 **216i** (69)	 **225i** (15)

*The yields given are for the isolated products.

It is interesting to note that all the substituents on indoles **216** prepared in the present work are different and these compounds can be used as intermediates in the preparation of a large number of substituted indoles, and compounds derived from indoles, taking advantage

of different reactivities of various groups present in these molecules. The same is true with the compounds **225**.

3.2.4 Conclusion

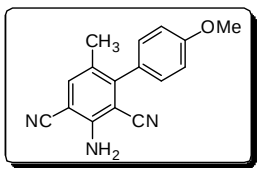
In conclusion, the present work describes a three-component, one-step method for the synthesis of 4-alkyl-3-aryl-2,6-dicyanoanilines **214** using easily available starting materials. The dicyanoanilines prepared above were utilized for the preparation of highly functionalized 1,2,3,5,6,7- and 1,2,3,4,5,7-hexasubstituted indoles **216** and **225** in one step under mild conditions. The present method has a potential to generate a large number of new compounds for structure-property studies in order to explore their utility as new substrates for non-linear optical materials or molecular electronic devices. Also, these molecules exhibit strong fluorescence in UV light (except **214l**) and may have utility as fluorescent materials.

3.2.5 Experimental Section

Preparation of 3-amino-4'-methoxy-6-methyl-[1,1'-biphenyl]-2,4-dicarbonitrile (214b)

To a mixture of propionaldehyde **222a** (2.00 g, 34.48 mmol), 4-methoxybenzaldehyde **221b** (2.81 g, 20.66 mmol) and malononitrile (3.40 g, 51.51 mmol) in dry DMF (15 mL) taken in a round bottom flask equipped with reflux condenser and guard tube, was added morpholine (2.1 mL, 2.11 g, 24.25 mmol) at 0 ^{0}C. The mixture was allowed to come to RT and then stirred at 80 ^{0}C for 12 h. It was then cooled to room temperature, diluted with ice-cold water (50 mL), extracted with ethyl acetate (3 x 50 mL), dried over Na_2SO_4, concentrated and purified by column chromatography on silica gel using pet ether-ethyl acetate (3% to 20% ethyl acetate in pet ether) as eluent to give 3-ethyl-4-methyl-2,6-dicyanoaniline (**215a**)[19c] as a white solid in initial fractions (0.255 g, 8%). Further elution afforded pure 3-amino-4'-methoxy-6-methyl-[1,1'-biphenyl]-2,4-dicarbonitrile **214b** as white solid (4.16 g, 77%).

Nature: White solid; **MP:** 199 ^{o}C; **Yield:** 77%; **^{1}H NMR** (200 MHz, $CDCl_3$)**:** δ 2.05 (s, 3H), 3.87 (s, 3H), 5.07 (bs, 2H), 7.01 (d, *J* = 9 Hz, 2H), 7.21 (d, *J* = 9 Hz, 2H), 7.47 (s, 1H); **^{13}C NMR** (50 MHz, DMSO-d_6)**:** δ 18.8, 55.3, 96.1, 98.0, 114.1 (2C), 116.1, 116.7, 124.7, 129.4, 130.1 (2C), 138.9, 150.5, 151.1, 159.6; **IR** (Chloroform)**:** 1644, 2218, 3349, 3434 cm^{-1};

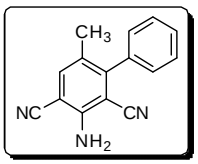


MS (ESI) *m/z:* 262.14 (M - 1). **Anal. Calcd. for** $C_{16}H_{13}N_3O$**:** C, 72.99; H, 4.98; N, 15.96 %. **Found:** C, 72.87; H, 5.16; N, 15.89 %.

The following compounds **214a, 214c-214l** were prepared by using the procedure given for the preparation of compound **214b.**

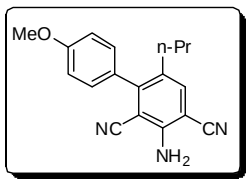
3-Amino-6-methyl-[1,1'-biphenyl]-2,4-dicarbonitrile (214a)

Nature: Off-white solid; **MP:** 187 ^oC; **Yield:** 67%; **^{1}H NMR** (200 MHz, $CDCl_3$)**:** δ 2.07 (s, 3H), 5.17 (bs, 2H), 7.11 (d, *J* = 8 Hz, 2H), 7.14-7.29 (m, 3H), 7.47 (s, 1H); **^{13}C NMR** (50 MHz, DMSO-d_6)**:** δ 18.6, 95.7, 99.1, 113.7 (2C), 115.4, 116.3, 124.6, 128.9, 129.0 (2C), 139.1, 150.7, 150.8, 159.5; **IR** (Chloroform)**:** 1639, 2220, 3351, 3458 cm^{-1}; **MS** (ESI) *m/z:* 232.05 (M - 1). **Anal. Calcd. for** $C_{15}H_{11}N_3$**:** C, 77.23; H, 4.75; N, 18.01 %. **Found:** C, 77.35; H, 4.66; N, 18.13 %.



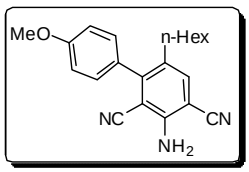
3-Amino-4'-methoxy-6-propyl- [1,1'-biphenyl]-2,4-dicarbonitrile (214c)

Nature: White solid; **MP:** 150 ^0C; **Yield:** 64%; **^{1}H NMR** (200 MHz, $CDCl_3$)**:** δ 0.77 (t, *J* = 6 Hz, 3H), 1.28-1.47 (m, 2H), 2.33 (t, *J* = 6 Hz, 2H), 3.88 (s, 3H), 5.07 (bs, 2H), 7.01 (d, *J* = 10 Hz, 2H), 7.18 (d, *J* = 8 Hz, 2H), 7.48 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$)**:** δ 13.5, 23.8, 33.7, 55.1, 95.8, 99.0, 113.9 (2C), 115.5, 116.1, 128.8, 129.6 (2C), 131.5, 136.9, 149.7, 150.3, 159.7; **IR** (Chloroform)**:** 1638, 2219, 3363, 3453 cm^{-1}; **MS** (ESI) *m/z:* 290.13 (M - 1). **Anal. Calcd. for** $C_{18}H_{17}N_3O$**:** C, 74.20; H, 5.88; N, 14.42 %. **Found:** C, 74.34; H, 5.77; N, 14.35 %.

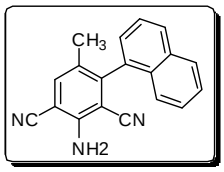


3-Amino-6-hexyl-4'-methoxy- [1,1'-biphenyl]-2,4-dicarbonitrile (214d)

Nature: White crystalline solid; **MP:** 121 ^oC; **Yield:** 69%; **^{1}H NMR** (200 MHz, $CDCl_3$)**:** δ 0.83 (t, *J* = 8 Hz, 3H), 1.05-1.40 (m, 8H), 2.34 (t, *J* = 8 Hz, 2H), 3.87 (s, 3H), 5.06 (s, 2H), 7.00 (d, *J* = 10 Hz, 2H), 7.18 (d, *J* = 8 Hz, 2H), 7.48 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$)**:** δ 13.7, 22.1, 28.4, 30.5, 31.1, 31.6, 55.0, 95.7, 98.9, 113.8 (2C), 115.5, 116.0, 128.7, 129.6 (2C), 131.1, 136.8, 149.7, 150.1, 159.7; **IR** (Chloroform)**:** 1655, 2221, 3354, 3411 cm^{-1}; **MS** (ESI) *m/z:* 333.18 (M - 1). **Anal. Calcd. for** $C_{21}H_{23}N_3O$**:** C, 75.65; H, 6.95; N, 12.60 %. **Found:** C, 75.73; H, 6.81; N, 12.49 %.

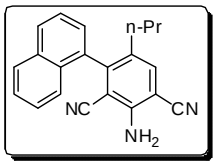


2-Amino-5-methyl-4- (naphthalen-1-yl) isophthalonitrile (214e)



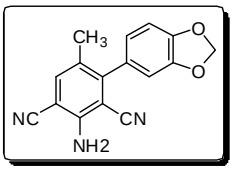
Nature: White crystalline solid; **MP:** 193 ^{o}C; **Yield:** 77%; **^{1}H NMR** (200 MHz, $CDCl_3$)**:** δ 1.87 (s, 3H), 5.12 (s, 2H), 7.30-7.65 (m, 6H), 7.92-8.01 (m, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$)**:** δ 18.2, 95.9, 98.6, 115.7, 116.7, 124.4, 125.4, 125.9, 126.6, 126.7, 127.4, 128.8, 129.2, 130.3, 133.3, 135.0, 139.1, 149.2, 151.2; **IR** (Chloroform)**:** 1612, 2225, 3241, 3357, 3478 cm^{-1}; **MS** (ESI) *m/z:* 282.13 (M - 1). **Anal. Calcd. for** $C_{19}H_{13}N_3$**:** C, 80.54; H, 4.62; N, 14.83 %. **Found:** C, 80.66; H, 4.55; 14.90 %.

2-Amino-4- (naphthalen-1-yl)-5-propylisophthalonitrile (214f)



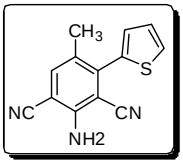
Nature: White solid; **MP:** 151 ^{0}C; **Yield:** 52%; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.67 (t, *J* = 8 Hz, 3H), 1.23-1.42 (m, 2H), 1.99-2.28 (m, 2H), 5.11 (bs, 2H), 7.33-7.63 (m, 6H), 7.96 (t, *J* = 6 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$)**:** δ 13.4, 23.5, 33.7, 96.5, 99.6, 115.0, 116.0, 124.5, 125.1, 126.2, 126.5, 126.8, 128.5, 129.3, 130.8, 131.8, 133.3, 134.0, 136.8, 148.9, 149.7; **IR** (Chloroform)**:** 1627, 2223, 3244, 3401 cm^{-1}; **MS** (ESI) *m/z:* 310.17 (M - 1). **Anal. Calcd for** $C_{21}H_{17}N_3$**:** C, 81.00; H, 5.50; N, 13.49 %. **Found:** C, 81.16; H, 5.39; N, 13.56 %.

2-Amino-4- (benzo[d][1,3]dioxol-5-yl)-5-methylisophthalonitrile (214g)



Nature: Yellow solid; **MP:** 207 ^{0}C; **Yield:** 75%; **^{1}H NMR** (200 MHz, $CDCl_3$)**:** δ 2.06 (s, 3H), 5.07 (bs, 2H), 6.05 (s, 2H), 6.71-6.74 (m, 2H), 6.93 (d, *J* = 8 Hz, 1H), 7.47 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$)**:** δ 19.1, 95.9, 99.0, 101.4, 108.6, 108.7, 115.4, 115.9, 122.2, 126.3, 130.3, 137.6, 147.8, 148.2, 149.8, 150.2; **IR** (Chloroform): 1613, 2226, 3347, 3419 cm^{-1}; MS (ESI) *m/z:* 276.1 (M - 1). **Anal. Calcd. for** $C_{16}H_{11}N_3O_2$**:** C, 69.31; H, 4.00; N, 15.15 %. **Found:** C, 69.19; H, 4.14; N, 15.28 %.

2-Amino-5-methyl-4- (thiophen-2-yl)isophthalonitrile (214h)

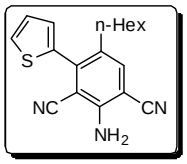


Nature: Off-white crystalline solid; **MP:** 165 ^{o}C; **Yield:** 56%; **^{1}H NMR** (200 MHz, $CDCl_3$)**:** δ 2.17 (s, 3H), 5.10 (s, 2H), 7.10-7.22 (m, 2H), 7.50-7.57 (m including s at 7.48, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$)**:** δ 19.3, 96.4, 99.4, 115.2, 117.7, 127.3, 127.7, 128.6, 129.3, 136.1, 137.5, 143.0, 149.9;

IR (Chloroform)**:** 1635, 2220, 2924, 3241, 3357, 3465 cm^{-1}; **MS** (ESI) *m/z:* 238.09 (M - 1). **Anal. Calcd. for** $C_{13}H_9N_3S$**:** C, 65.25; H, 3.79; N, 17.56 %. **Found:** C, 65.33; H, 3.68; 17.49 %.

2-Amino-5-hexyl-4-(thiophen-2-yl)isophthalonitrile (214i)

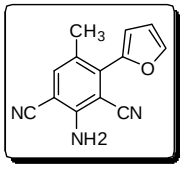
Nature: White crystalline solid; **MP:** 106 ^oC; **Yield:** 70%; **^{1}H NMR** (200 MHz, $CDCl_3$)**:** δ



0.85 (t, *J* = 8 Hz, 3H), 1.10-1.15 (m, 8H), 2.45 (t, *J* = 10 Hz, 2H), 5.13 (s, 2H), 7.07-7.20 (m, 2H), 7.54 (m including s at 7.49, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$)**:** δ 13.8, 22.2, 28.6, 30.9, 31.2, 32.1, 96.9, 99.8, 115.1, 115.8, 127.2, 127.5, 128.7, 132.5, 135.9, 136.9, 142.7, 149.7; **IR** (Chloroform)**:** 1635, 2222, 3241, 3349, 3465 cm^{-1}; **MS** (ESI) *m/z:* 308.11 (M - 1). **Anal. Calcd. for** $C_{18}H_{19}N_3S$**:** C, 69.87; H, 6.19; N, 13.58 %. **Found:** C, 69.77; H, 6.31; N, 13.47 %.

2-Amino-4- (furan-2-yl)-5-methylisophthalonitrile (214j)

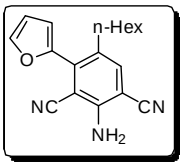
Nature: Off-white crystalline solid; **MP:** 178 ^oC; **Yield:** 10%; **^{1}H NMR** (400 MHz,



$CDCl_3$)**:** δ 2.30 (s, 3H), 5.14 (s, 2H), 6.57-6.64 (m, 1H), 6.86 (d, *J* = 4 Hz, 1H), 7.46 (s, 1H), 7.64 (s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$)**:** δ 20.2, 111.6, 112.7, 112.9, 113.8, 114.5, 115.8, 126.2, 136.5, 138.4, 143.9, 144.6, 150.3; **IR** (Chloroform)**:** 1637, 2214, 3368, 3467 cm^{-1}; MS (ESI) *m/z:* 222.06 (M - 1). **Anal. Calcd. for** $C_{13}H_9N_3O$**:** C, 69.95; H, 4.06; N, 18.82 %. **Found:** C, 69.86; H, 4.21; N, 18.75 %.

2-Amino-4- (furan-2-yl)-5-hexylisophthalonitrile (214k)

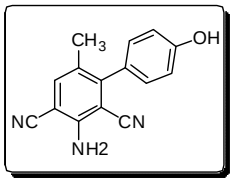
Nature: Off-white crystalline solid; **MP:** 89 ^oC; **Yield:** 17%; **^{1}H NMR** (200 MHz, $CDCl_3$)**:**



δ 0.87 (t, *J* = 6 Hz, 3H), 1.17-1.50 (m, 8H), 2.58 (t, *J* = 8 Hz, 2H), 5.12 (s, 2H), 6.59 (dd, *J* = 4, 2 Hz, 1H), 6.80 (dd, *J* = 4, 2 Hz, 1H), 7.48 (s, 1H), 7.52-7.60 (m, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$)**:** δ 13.9, 22.3, 28.7, 30.5, 31.3, 32.6, 96.5, 97.1, 111.5, 113.1, 115.7, 115.8, 131.5, 137.6, 137.7, 143.7, 148.1, 150.1; **IR** (Chloroform)**:** 1644, 2222, 3350, 3441 cm^{-1}; **MS** (ESI) *m/z:* 292.17 (M - 1). **Anal. Calcd. for** $C_{18}H_{19}N_3O$**:** C, 73.69; H, 6.53; N, 14.32 %. **Found:** C, 73.58; H, 6.66; N, 14.18 %.

3-Amino-4'-hydroxy-6-methyl- [1,1'-biphenyl]-2,4-dicarbonitrile (214l)

Nature: Yellow solid; **MP:** 204 ^{0}C; **Yield:** 53%; **^{1}H NMR** (200 MHz, DMSO-d_6)**:** δ 0.94 (s, 3H), 5.47 (bs, 2H), 5.89 (d, *J* = 8 Hz, 2H), 6.12 (d, *J* = 8 Hz, 2H), 6.67 (s, 1H), 8.82 (bs, 1H); **^{13}C NMR** (50 MHz, DMSO-d_6)**:** δ 18.9, 94.9, 98.1, 115.5 (2C), 115.6, 116.2, 116.8, 124.8, 127.8, 130.0 (2C), 138.8, 151.1, 157.9; **IR** (Nujol): 1607, 1644, 2218, 3355, 3369 cm^{-1}. **MS** (ESI) *m*/*z***:** 248.14 (M - 1). **Anal. Calcd. for** $C_{15}H_{11}N_3O$**:** C, 72.28; H, 4.45; N, 16.86 %. **Found:** C, 72.40; H, 4.57; N, 16.74 %.

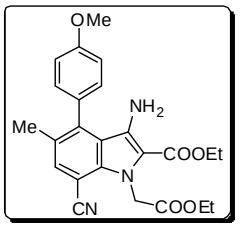


Preparation of ethyl 3-amino-7-cyano-1-(2-ethoxy-2-oxoethyl)-6-(4-methoxyphenyl)-5-methyl-1*H*-indole-2-carboxylate (216a) and ethyl 3-amino-7-cyano-1-(2-ethoxy-2-oxoethyl)-4-(4-methoxyphenyl)-5-methyl-1*H*-indole-2-carboxylate (225a)

The 3-amino-4'-methoxy-6-methyl-[1,1'-biphenyl]-2,4-dicarbonitrile **214b** (263 mg, 1 mmol) and ethyl bromoacetate (0.34 mL, 3 mmol) were dissolved in acetonitrile (5 mL) in a 2-necked RB flask equipped with guard tube at RT and the pellets of potassium hydroxide (336 mg, 6 mmol) were added. The reaction mixture was stirred at room temperature for 2 h. It was then diluted with excess of cold water and extracted with ethyl acetate (3 x 10 mL), dried over Na_2SO_4, concentrated and purified by column chromatography on silica gel using pet ether-ethyl acetate as eluent. Ethyl 3-amino-7-cyano-1-(2-ethoxy-2-oxoethyl)-4-(4-methoxyphenyl)-5-methyl-1*H*-indole-2-carboxylate **225a** was obtained as yellow solid (53 mg, 12.15 %).

Ethyl 3-amino-7-cyano-1-(2-ethoxy-2-oxoethyl)-4-(4-methoxyphenyl)-5-methyl-1*H*-indole-2-carboxylate (225a)

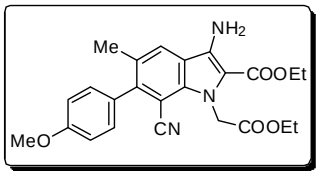
Nature: Yellow solid; **MP:** 167^{0}C; **Yield:** 12.15 %; **^{1}H NMR** (200 MHz, $CDCl_3$)**:** δ 1.33 (t, *J* = 6 Hz, 6H), 2.09 (s, 3H), 3.90 (s, 3H), 4.23- 4.37 (m, 4H), 4.49 (bs, 2H), 5.57 (s, 2H), 7.05 (d, *J* = 8 Hz, 2H), 7.23 (d, *J* = 8 Hz, 2H), 7.56 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$)**:** δ 14.1, 14.2, 18.6, 46.9, 55.2, 60.1, 61.4, 92.7, 109.5, 114.1 (2C), 118.1, 118.5, 127.0, 129.1, 129.6 (2C), 135.4, 135.9, 137.9, 141.2, 159.5, 162.4, 169.3; **IR** (Chloroform)**:** 1609, 1672, 1751, 2219, 3374, 3476 cm^{-1}; **MS** (ESI) *m*/*z***:** 458.20 (M + Na). **Anal. Calcd. for** $C_{24}H_{25}N_3O_5$**:** C, 66.19; H, 5.79; N, 9.65 %. **Found:** C, 66.30; H, 5.66; N, 9.73 %.



Further elution provided ethyl 3-amino-7-cyano-1-(2-ethoxy-2-oxoethyl)-6-(4-methoxyphenyl)-5-methyl-1*H*-indole-2-carboxylate **216a** as yellow solid (301 mg, 69.2 %).

Ethyl 3-amino-7-cyano-1-(2-ethoxy-2-oxoethyl)-6-(4-methoxyphenyl)-5-methyl-1*H*-indole-2-carboxylate (**216a)**

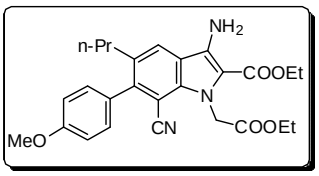
Nature: Yellow solid; **MP:** 188 ^{0}C; **Yield:** 69.2 %; **^{1}H NMR** (200 MHz, $CDCl_3$)**:** δ 1.28 (t, *J* = 6 Hz, 3H), 1.41 (t, *J* = 6 Hz, 3H), 2.18 (s, 3H), 3.87 (s, 3H), 4.28 (q, *J* = 8 Hz, 2H), 4.39 (q, *J* = 6 Hz, 2H), 4.97 (bs, 2H), 5.60 (s, 2H), 7.00 (d, *J* = 10 Hz, 2H), 7.22 (d, *J* = 10 Hz, 2H), 7.62 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$)**:** δ 14.0, 14.3, 20.6, 46.7, 55.1, 60.3, 61.4, 95.0, 110.2, 113.8 (2C), 117.3, 119.5, 124.9, 127.5, 130.2 (2C), 130.4, 136.2 (2C), 147.4, 159.4, 162.4, 169.6; **IR** (Chloroform)**:** 1621 1682, 1733, 2215, 3370, 3476 cm^{-1}; **MS** (ESI) *m/z***:** 458.14 (M + Na). **Anal. Calcd. for** $C_{24}H_{25}N_3O_5$**:** C, 66.19; H, 5.79; N, 9.65 %. **Found:** C, 66.30; H, 5.65; N, 9.73 %.



The following compounds **216b-216i** and **225b-225i** were prepared by using the procedure given for the preparation of compounds **216a** and **225a.**

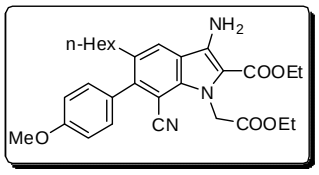
Ethyl 3-amino-7-cyano-1-(2-ethoxy-2-oxoethyl)-6-(4-methoxyphenyl)-5-propyl-1*H*-indole-2-carboxylate (216b)

Nature: Yellow solid; **MP:** 135 ^{0}C; **Yield:** 65%; **^{1}H NMR** (200 MHz, $CDCl_3$)**:** δ 0.79 (t, *J* = 8 Hz, 3H), 1.25-1.49 (m, 8H), 2.46 (t, *J* = 8 Hz, 2H), 3.88 (s, 3H), 4.24 (q, *J* = 8 Hz, 2H), 4.40 (q, *J* = 8 Hz, 2H), 4.99 (bs, 2H), 5.59 (s, 2H), 6.98 (d, *J* = 10 Hz, 2H), 7.22 (d, *J* = 8 Hz, 2H), 7.63 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$)**:** δ 13.7, 14.0, 14.3, 24.2, 35.2, 46.7, 55.1, 60.3, 61.4, 95.3, 110.3, 113.6 (2C), 117.2, 119.6, 124.2, 130.2, 130.4 (2C), 132.3, 136.1, 136.3, 147.3, 159.3, 162.4, 169.6; **IR** (Chloroform)**:** 1672, 1739, 2217, 3366, 3467 cm^{-1}; **MS** (ESI) *m/z:* 486.29 (M + Na). **Anal. Calcd. for** $C_{26}H_{29}N_3O_5$**:** C, 67.37; H, 6.31; N, 9.07 %. **Found:** C, 67.26; H, 6.44; N, 8.94 %.



Ethyl 3-amino-7-cyano-1-(2-ethoxy-2-oxoethyl)-5-hexyl-6-(4-methoxyphenyl)-1*H*-indole-2-carboxylate (216c)

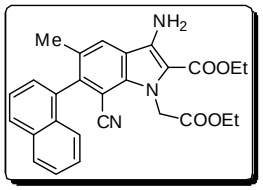
Nature: Yellow powder; **MP:** 131 ^{o}C; **Yield:** 85%; **^{1}H NMR** (200 MHz, $CDCl_3$)**:** δ 0.83 (t,



J = 8 Hz, 3H), 1.04-1.15 (m, 14H), 2.48 (t, *J* = 8 Hz, 2H), 3.88 (s, 3H), 4.24 (q, *J* = 8 Hz, 2H), 4.40 (q, *J* = 8 Hz, 2H), 4.99 (s, 2H), 5.59 (s, 2H), 6.99 (d, *J* = 9 Hz, 2H), 7.22 (d, *J* = 9 Hz, 2H), 7.62 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$)**:** δ 13.8, 14.0, 14.2, 22.29, 28.7, 31.0, 31.2, 33.0, 46.7, 55.0, 60.2, 61.3, 95.1, 110.1, 113.6 (2C), 117.2, 119.6, 124.2, 130.1, 130.3 (2C), 132.5, 136.0, 136.4, 147.1, 159.3, 162.3, 169.6; **IR** (Chloroform)**:** 1610, 1676, 1746, 2216, 3367, 3468 cm^{-1}; **MS** (ESI) *m/z:* 504.41 (M - 1). **Anal. Calcd for** $C_{29}H_{35}N_3O_5$**:** C, 68.89; H, 6.98; N, 8.31 %. **Found:** C, 68.78; H, 7.14; N, 8.16 %.

Ethyl 3-amino-7-cyano-1-(2-ethoxy-2-oxoethyl)-5-methyl-6-(naphthalen-1-yl)-1*H*-indole-2-carboxylate (216d)

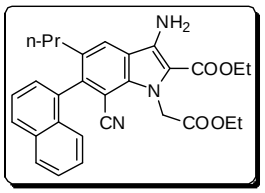
Nature: Yellow solid; **MP:** 135 ^{0}C; **Yield:** 62%; **^{1}H NMR** (200 MHz, $CDCl_3$)**:** δ 1.25 (t, *J* =



6 Hz, 3H), 1.43 (t, *J* = 6 Hz, 3H), 2.01 (s, 3H), 4.23 (q, *J* = 6 Hz, 2H), 4.42 (q, *J* = 6 Hz, 2H), 5.03 (bs, 2H), 5.60 (s, 2H), 7.25-7.63 (m, 5H), 7.72 (s, 1H), 7.92-7.98 (m, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$)**:** δ 14.0 14.3, 20.0, 46.8, 60.4, 61.4, 95.8, 110.5, 116.7, 120.1, 124.8 (2C), 124.9, 125.6, 126.0, 126.6, 127.0, 128.3, 128.4, 128.6, 131.4, 133.5, 135.8, 136.3, 145.9, 162.4, 169.4; **IR** (Chloroform)**:** 1681, 1759, 2217, 3379, 3476 cm^{-1}; **MS** (ESI) *m*/*z***:** 478.21 (M + Na). **Anal. Calcd for** $C_{27}H_{25}N_3O_4$**:** C, 71.19; H, 5.53; N, 9.22 %. **Found:** C, 71.28; H, 5.41; N, 9.39 %.

Ethyl 3-amino-7-cyano-1-(2-ethoxy-2-oxoethyl)-6-(naphthalen-1-yl)-5-propyl-1*H*-indole-2-carboxylate (216e)

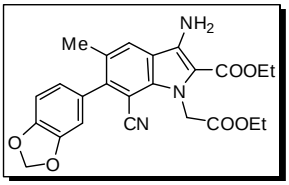
Nature: Yellow solid; **MP:** 168 ^{0}C; **Yield:** 61%; **^{1}H NMR** (200 MHz, $CDCl_3$)**:** δ 0.68 (t, *J* =



6 Hz, 3H), 1.21-1.46 (m, 7H), 1.43 (t, *J* = 8 Hz, 3H), 2.06-2.41 (m, 2H), 4.22 (q, *J* = 6 Hz, 2H), 4.42 (q, *J* = 8 Hz, 2H), 5.58 (bs, 2H), 7.35-7.62 (m, 5H), 7.74 (s, 1H), 7.94 (t, *J* = 6 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$)**:** δ 13.6, 14.0, 14.3, 24.1, 35.0, 46.9, 60.4, 61.4, 96.0, 110.5, 116.7, 120.2, 124.1, 125.0, 125.1, 126.0, 126.5, 127.5, 128.4, 128.9, 131.9, 133.0, 133.4, 135.5, 136.2, 136.3, 145.6, 162.5, 169.5; **IR** (Chloroform)**:** 1615, 1674, 1739, 2219, 3328, 3442 cm^{-1}; **MS** (ESI) *m*/*z***:** 506.32 (M + Na). **Anal. Calcd. for** $C_{29}H_{29}N_3O_4$**:** C, 72.03; H, 6.04; N, 8.69 %. **Found:** C, 72.18; H, 5.92; N, 8.77 %.

Ethyl 3-amino-6-(benzo[*d*][1,3]dioxol-5-yl)-7-cyano-1-(2-ethoxy-2-oxoethyl)-5-methyl-1*H*-indole-2-carboxylate (216f)

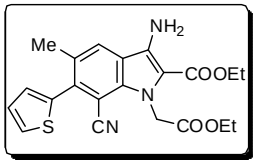
Nature: Bright green solid; **MP:** 179 ^{0}C; **Yield:** 69%; **^{1}H NMR** (200 MHz, $CDCl_3$)**:** δ 1.25-



1.45 (m, 6H), 2.18 (s, 3H), 4.19-4.45 (m, 4H), 4.97 (bs, 2H), 5.59 (s, 2H), 6.03 (s, 2H), 6.73 (s, 1H), 6.75 (d, *J* = 7 Hz, 1H), 6.92 (d, *J* = 7 Hz, 1H), 7.62 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$)**:** δ 14.0, 14.2, 20.5, 46.7, 60.2, 61.4, 94.9, 101.1, 108.3, 109.4, 110.2, 117.1, 119.6, 122.6, 125.0, 127.4, 131.7, 136.1, 136.2, 147.0, 147.5 (2C), 162.5, 166.5; **IR** (Chloroform)**:** 1620, 1731, 1749, 2215, 3324, 3452 cm^{-1}; **MS** (ESI) *m*/*z***:** 472.21 (M + Na). **Anal. Calcd. for** $C_{24}H_{23}N_3O_6$**:** C, 64.13; H, 5.16; N, 9.35 %. **Found:** C, 64.00; H, 5.27; N, 9.22 %.

Ethyl 3-amino-7-cyano-1- (2-ethoxy-2-oxoethyl)-5-methyl-6-(thiophen-2-yl)-1*H*-indole-2-carboxylate (216g)

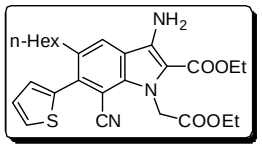
Nature: Yellow powder; **MP:** 199 ^{o}C; **Yield:** 64%; **^{1}H NMR** (200 MHz, $CDCl_3$)**:** δ 1.15-



1.50 (m, 6H), 2.26 (s, 3H), 4.15-4.50 (m, 4H), 4.97 (s, 2H), 5.59 (s, 2H), 7.00-7.21 (m, 2H), 7.44-7.73 (m, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$)**:** δ 14.0, 14.3, 20.6, 46.7, 60.3, 61.5, 96.2, 110.5, 116.7, 120.4, 124.9, 127.1 (2C), 128.4 (2C), 128.7, 136.1, 137.9, 139.5, 162.3, 169.6; **IR** (Chloroform)**:** 1667, 1716, 1762, 2215, 3356, 3460 cm^{-1}; **MS** (ESI) *m/z:* 410.21 (M - 1). **Anal. Calcd for** $C_{21}H_{21}N_3O_4S$**:** C, 61.30; H, 5.14; N, 10.21 %. **Found:** C, 61.19; H, 5.21; N, 10.09 %.

Ethyl 3-amino-7-cyano-1-(2-ethoxy-2-oxoethyl)-5-hexyl-6-(thiophen-2-yl)-1*H*-indole-2-carboxylate (216h)

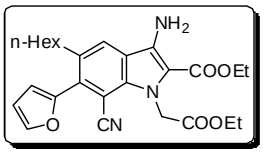
Nature: Yellow powder; **MP:** 105 ^{o}C; **Yield:** 77%; **^{1}H NMR** (200 MHz, $CDCl_3$)**:** δ 0.85 (t,



J = 6 Hz, 3H), 1.12-1.65 (m, 14H), 2.57 (t, *J* = 8 Hz, 2H), 4.24 (q, *J* = 8 Hz, 2H), 4.40 (q, *J* = 8 Hz, 2H), 4.99 (bs, 2H), 5.60 (s, 2H), 7.04-7.20 (m, 2H), 7.45-7.53 (m, 1H), 7.63 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$)**:** δ 13.9, 14.0, 14.2, 22.2, 28.8, 31.3, 31.5, 33.3, 46.7, 60.3, 61.4, 96.4, 110.4, 116.7, 120.5, 124.2, 126.9 (2C), 128.7, 133.8, 135.8, 136.2, 137.6, 139.1, 162.2, 169.5; **IR** (Chloroform)**:** 1615, 1688, 1746, 2217, 3373, 3475; **MS** (ESI) *m/z:* 480.31 (M - 1). **Anal.**

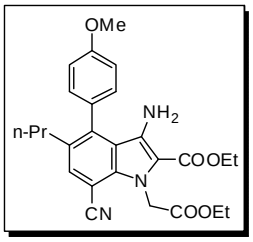
Calcd. for $C_{26}H_{31}N_3O_4S$**:** C, 64.84; H, 6.49; N, 8.72 %. **Found:** C, 64.91; H, 6.37; N, 8.83 %.

Ethyl 3-amino-7-cyano-1-(2-ethoxy-2-oxoethyl)-6-(furan-2-yl)-5-hexyl-1*H*-indole-2-carboxylate (216i)



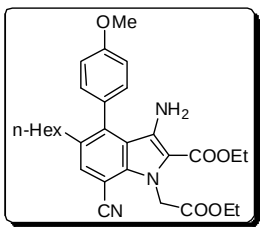
Nature: Yellow powder; **MP:** 105 ^{o}C; **Yield:** 69%; **^{1}H NMR** (200 MHz, $CDCl_3$)**:** δ 0.86 (t, *J* = 6 Hz, 3H), 1.17-1.56 (m, 14H), 2.63 (t, *J* = 8 Hz, 2H), 4.25 (q, *J* = 8 Hz, 2H), 4.40 (q, *J* = 8 Hz, 2H), 4.97 (bs, 2H), 5.61 (s, 2H), 6.54-6.60 (m, 1H), 6.63-6.68 (m, 1H), 7.58-7.65 (m, 2H); **^{13}C NMR** (50 MHz , $CDCl_3$)**:** δ 13.9, 14.0, 14.3, 22.4, 28.9, 31.0, 31.4, 33.5, 46.8, 60.4, 61.5, 95.0, 110.8, 111.0, 112.0 (2C), 117.0, 120.6, 124.8, 133.7, 135.2, 136.1, 143.0, 149.3, 162.3, 169.6; **IR** (Chloroform)**:** 1617, 1686, 1743, 2217, 3367, 3471 cm^{-1}; **MS** (ESI): *m/z**:*** 464.30 (M - 1). **Anal. Calcd for** $C_{26}H_{31}N_3O_5$**:** C, 67.08; H, 6.71; N, 9.03 %. **Found:** C, 67.21; H, 6.64; N, 9.17 %.

Ethyl 3-amino-7-cyano-1-(2-ethoxy-2-oxoethyl)-4-(4-methoxyphenyl)-5-propyl-1*H*-indole-2-carboxylate (225b)



Nature: Yellow solid; **MP:** 147 ^{0}C; **Yield:** 15%; **^{1}H NMR** (200 MHz, $CDCl_3$)**:** δ 0.80 (t, *J* = 8 Hz, 3H), 1.26-1.36 (m, 8H), 2.36 (t, *J* = 8 Hz, 2H), 3.90 (s, 3H), 4.26-4.36 (m, 4H), 4.43 (bs, 2H), 5.56 (s, 2H), 7.03 (d, *J* = 8 Hz, 2H), 7.23 (d, *J* = 8 Hz, 2H), 7.56 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$)**:** δ 13.7, 14.1, 14.2, 24.7, 33.6, 47.0, 55.2, 60.1, 61.5, 92.9, 109.5, 113.9 (2C), 118.2, 118.5, 128.8, 129.9 (2C), 131.8, 135.0, 135.6, 138.2, 141.0, 159.4, 162.4, 169.4; **IR** (Chloroform)**:** 1610, 1681, 1759, 2219, 3379, 3476 cm^{-1}; **MS** (ESI) *m*/*z***:** 486.26 (M + Na).

Ethyl 3-amino-7-cyano-1-(2-ethoxy-2-oxoethyl)-5-hexyl-4-(4-methoxyphenyl)-1*H*-indole-2-carboxylate (225c)

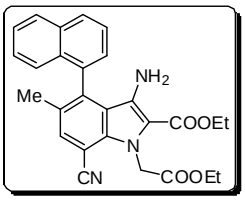


Nature: Yellow powder; **MP:** 103 ^{o}C; **Yield:** 9%; **^{1}H NMR** (400 MHz, $CDCl_3$)**:** δ 0.83 (t, *J* = 8 Hz, 3H), 1.09-1.50 (m, 14H), 2.37 (t, *J* = 8 Hz, 2H), 3.90 (s, 3H), 4.22-4.34 (m, 4H), 4.44 (s, 2H), 5.56 (s, 2H), 7.03 (d, *J* = 8 Hz, 2H), 7.23 (d, *J* = 8 Hz, 2H), 7.56 (s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$)**:** δ 13.9, 14.1, 14.3, 22.3, 28.8, 31.3, 31.5

(2C), 47.0, 55.2, 60.1, 61.5, 93.0, 109.5, 113.9 (2C), 118.2, 118.5, 128.8, 129.9 (2C), 132.2, 135.0, 135.6, 138.2, 140.9, 159.5, 162.4, 169.4; **IR** (Chloroform)**:** 1610, 1685, 1754, 2219, 3363, 3448 cm^{-1}; **MS** (ESI) *m/z***:** 504.38 (M - 1).

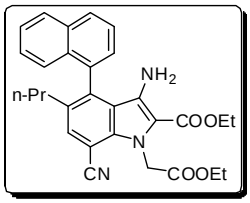
Ethyl 3-amino-7-cyano-1-(2-ethoxy-2-oxoethyl)-5-methyl-4-(naphthalen-1-yl)-1*H*-indole-2-carboxylate (225d)

Nature: Yellow solid; **MP:** 135 ^{0}C; **Yield:** 18%; **^{1}H NMR** (200 MHz, $CDCl_3$)**:** δ 1.24-1.38



(m, 6H), 1.97 (s, 3H), 4.14 (bs, 2H), 4.19-4.36 (m, 4H), 5.60 (s, 2H), 7.30-7.65 (m, 6H), 7.99 (t, *J* = 8 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$)**:** δ 14.1, 14.2, 18.2, 47.0, 60.1, 61.5, 93.2, 109.7, 118.1, 119.0, 125.3 (2C), 126.3, 126.6, 127.0, 127.6, 128.4, 128.9, 131.0, 133.3, 134.5, 135.4, 135.9, 137.6, 139.5, 162.3, 169.4; **IR** (Chloroform)**:** 1610, 1681, 1759, 2217, 3379, 3476 cm^{-1}; **MS** (ESI) *m*/*z***:** 478.28 (M + Na).

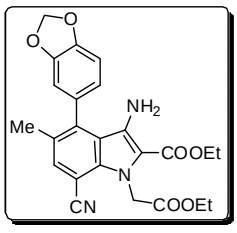
Ethyl 3-amino-7-cyano-1-(2-ethoxy-2-oxoethyl)-4-(naphthalen-1-yl)-5-propyl-1*H*-indole-2-carboxylate (225e)



Nature: Yellow solid; **MP:** 168 ^{0}C; **Yield:** 13%; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.69 (t, *J* = 6 Hz, 3H), 1.24-1.46 (m, 8H), 2.06-2.35 (m, 2H), 4.07 (bs, 2H), 4.20-4.37 (m, 4H), 5.60 (s, 2H), 7.33-7.68 (m, 6H), 7.99 (t, *J* = 8 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$)**:** δ 13.7, 14.1, 14.2, 24.4, 33.6, 47.1, 60.1, 61.5, 93.5, 109.7, 118.2, 118.8, 125.1, 125.6, 126.6, 126.7, 126.9, 128.3, 128.9, 131.5, 132.3, 133.2, 134.2, 134.9, 135.7, 137.8, 139.2, 162.3, 169.4; **IR** (Chloroform)**:** 1604, 1682, 1752, 2219, 3399, 3491 cm^{-1}; **MS** (ESI) *m*/*z***:** 506.31 (M + Na).

Ethyl 3-amino-4- (benzo[*d*][1,3]dioxol-5-yl)-7-cyano-1-(2-ethoxy-2-oxoethyl)-5-methyl-1*H*-indole-2-carboxylate (225f)

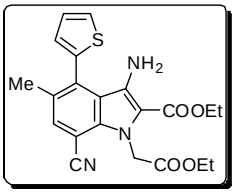
Nature: Light orange solid; **MP:** 108 ^{0}C; **Yield:** 23%; **^{1}H NMR** (200 MHz, $CDCl_3$)**:** δ 1.26-



1.38 (m, 6H), 2.11 (s, 3H), 4.23-4.36 (m, 4H), 4.58 (bs, 2H), 5.57 (s, 2H), 6.08 (s, 2H), 6.74 (s, 1H), 6.75 (d, *J* = 8 Hz, 2H), 7.55 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$)**:** δ 14.0, 14.2, 18.5, 46.9, 60.1, 61.5, 92.9, 101.4, 108.6, 109.1, 109.6, 118.0, 118.4, 121.7, 127.0, 130.5, 135.4, 136.0, 137.7, 140.9, 147.6, 147.9, 162.3, 169.3; **IR** (Chloroform)**:** 1681, 1750, 2220, 3348, 3489 cm^{-1}; **MS** (ESI) *m*/*z***:** 472.21 (M + Na).

Ethyl 3-amino-7-cyano-1-(2-ethoxy-2-oxoethyl)-5-methyl-4-(thiophen-2-yl)-1*H*-indole-2-carboxylate (225g)

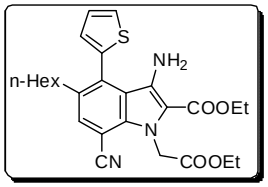
Nature: Yellow powder; **MP:** 156 ^{o}C; **Yield:** 12%; **^{1}H NMR** (200 MHz, $CDCl_3$)**:** δ 1.28-



1.46 (m, 6H), 2.19 (s, 3H), 4.24-4.47 (m, 4H), 4.63 (s, 2H), 5.58 (s, 2H), 7.04-7.12 (m, 1H), 7.20-7.28 (m, 1H), 7.55-7.63 (m, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$)**:** δ 13.9, 14.1, 18.4, 46.8, 60.1, 61.3, 93.8, 109.8, 117.6, 119.2, 127.2 (2C), 127.5, 129.0, 133.4, 134.9, 135.4, 136.8, 137.4, 162.1, 169.1; **IR** (Chloroform)**:** 1602, 1673, 1750, 2220, 3362, 3480 cm^{-1}; **MS** (ESI) m/z**:** 410.21 (M - 1).

Ethyl 3-amino-7-cyano-1-(2-ethoxy-2-oxoethyl)-5-hexyl-4-(thiophen-2-yl)-1*H*-indole-2-carboxylate (225h)

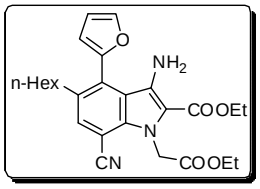
Nature: Yellow solid powder; **MP:** 99 ^{o}C; **Yield:** 11%; **^{1}H NMR** (200 MHz, $CDCl_3$)**:** δ



0.80 (t, *J* = 6 Hz, 3H), 1.10-1.58 (m, 14H), 2.45 (t, *J* = 8 Hz, 2H), 4.18-4.40 (m, 4H), 4.58 (s, 2H), 5.57 (s, 2H), 7.02-7.10 (m, 1H), 7.16-7.24 (m, 1H), 7.52-7.60 (m, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$)**:** δ 13.8, 14.0, 14.1, 22.2, 28.8, 31.2, 31.6, 31.9, 46.8, 60.1, 61.4, 94.2, 109.8, 117.7, 119.1, 127.0, 127.1, 128.0, 132.9, 134.2, 134.4, 135.1, 136.5, 137.6, 162.2, 169.1; **IR** (Chloroform)**:** 1602, 1686, 1754, 2219, 3367, 3393, 3486 cm^{-1}; **MS** (ESI) *m/z:* 480.31 (M - 1).

Ethyl 3-amino-7-cyano-1-(2-ethoxy-2-oxoethyl)-4-(furan-2-yl)-5-hexyl-1*H*-indole-2-carboxylate (225i)

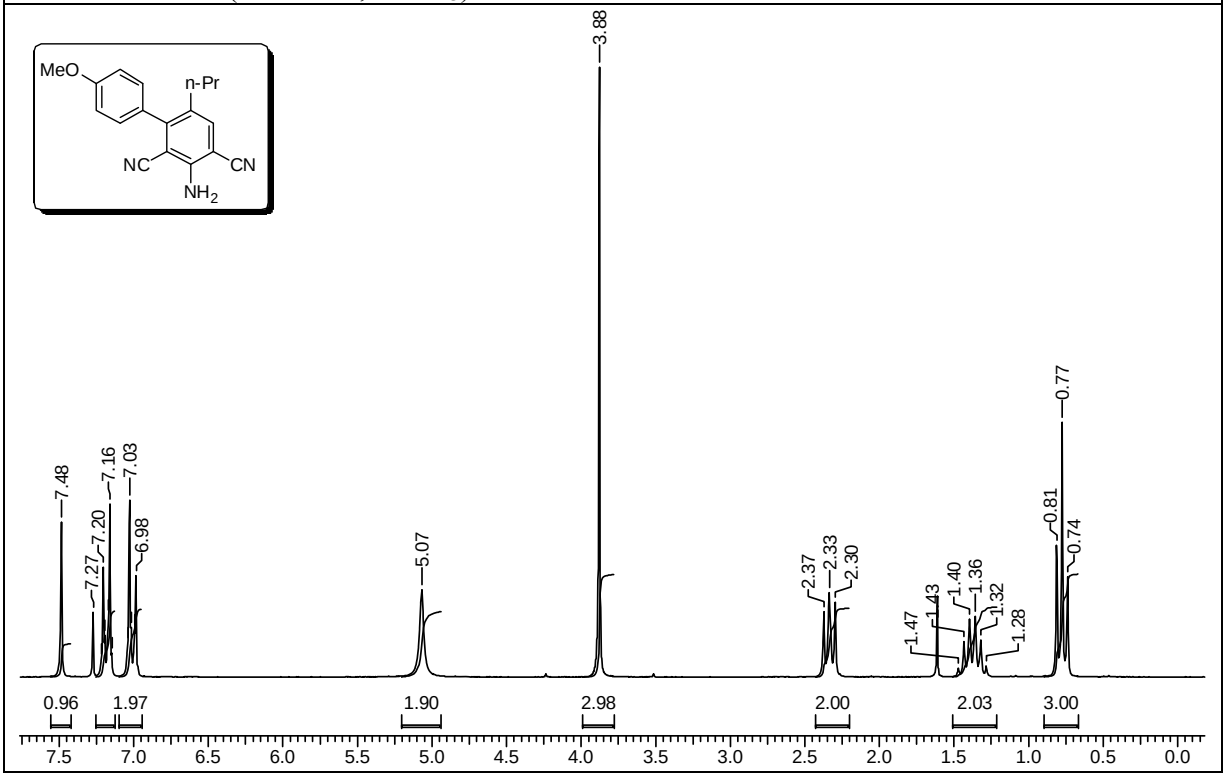
Nature: Yellow semisolid; **Yield:** 15%; **^{1}H NMR** (400 MHz, $CDCl_3$)**:** δ 0.80-0.92 (m, 6H),



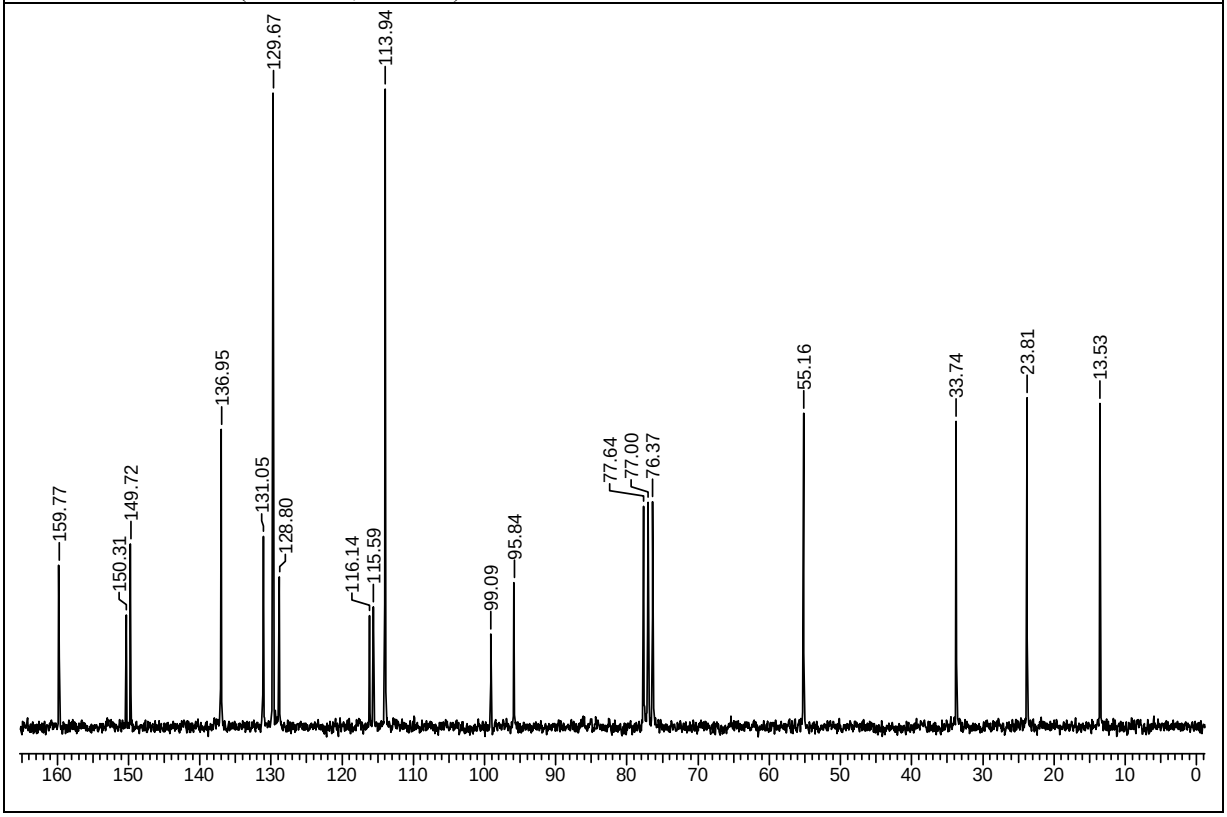
1.15-1.52 (m, 10H), 2.49 (t, *J* = 8 Hz, 2H), 4.20-4.37 (m, 4H), 4.70 (s, 2H), 5.56 (s, 2H), 6.52-6.56 (m, 2H), 6.62-6.67 (m, 1H), 7.57 (s, 1H), 7.65 (s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$)**:** δ 13.9, 14.1, 14.2, 22.4, 28.8, 29.6, 31.4, 31.7, 32.3, 47.0, 60.3, 61.5, 94.9, 110.3, 111.1, 111.2, 117.8, 119.3, 129.1, 134.7, 134.8, 135.4, 143.0, 148.2, 162.4, 169.2; **IR** (Chloroform)**:** 1608, 1685, 1753, 2220, 3336, 3488 cm^{-1}; **MS** (ESI) *m/z:* 464.29 (M - 1).

3.2.6 Selected spectra

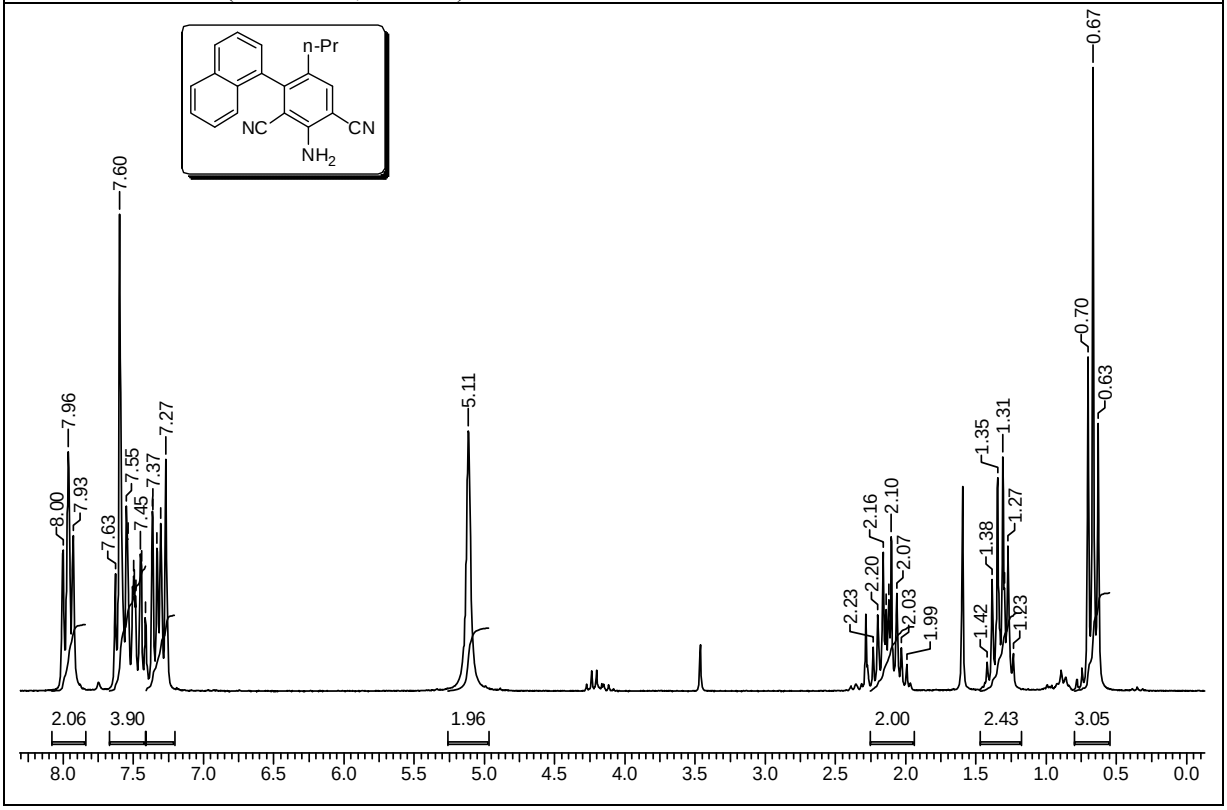
214c: ^{1}H NMR (200 MHz, $CDCl_3$)



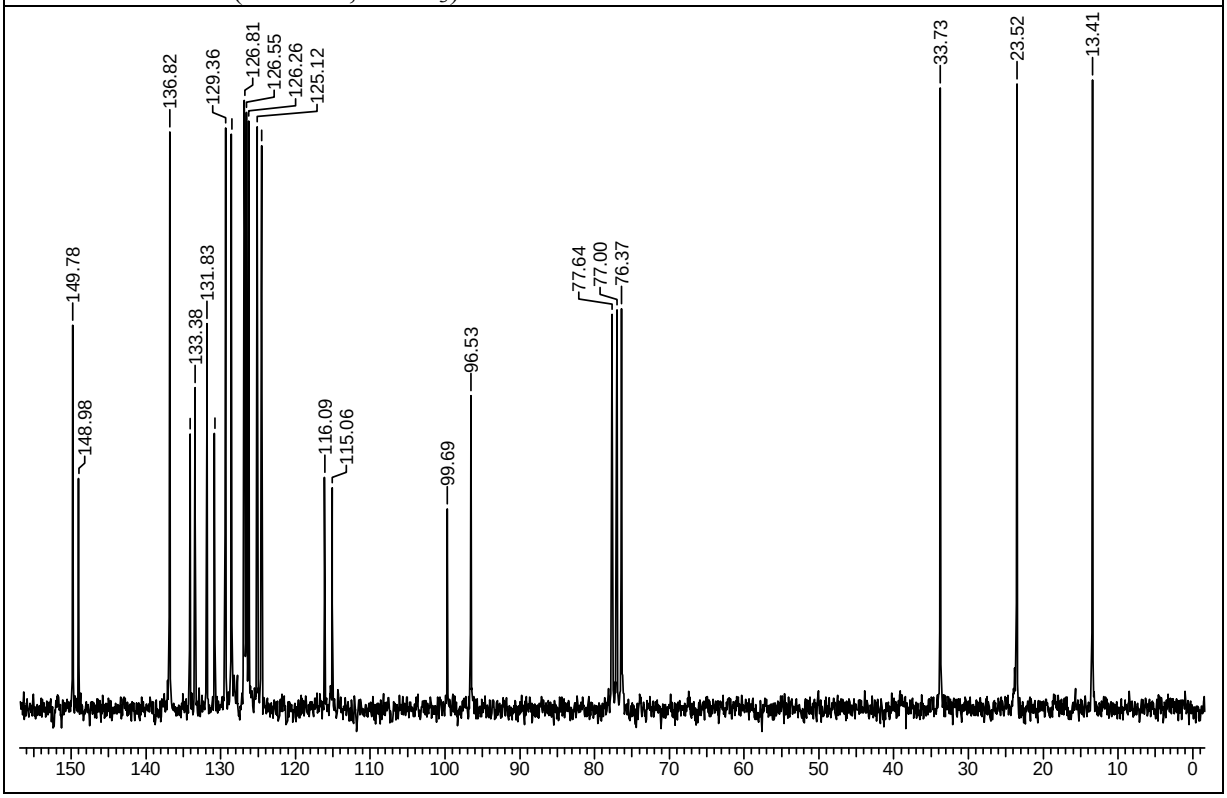
214c: ^{13}C NMR (50 MHz, $CDCl_3$)



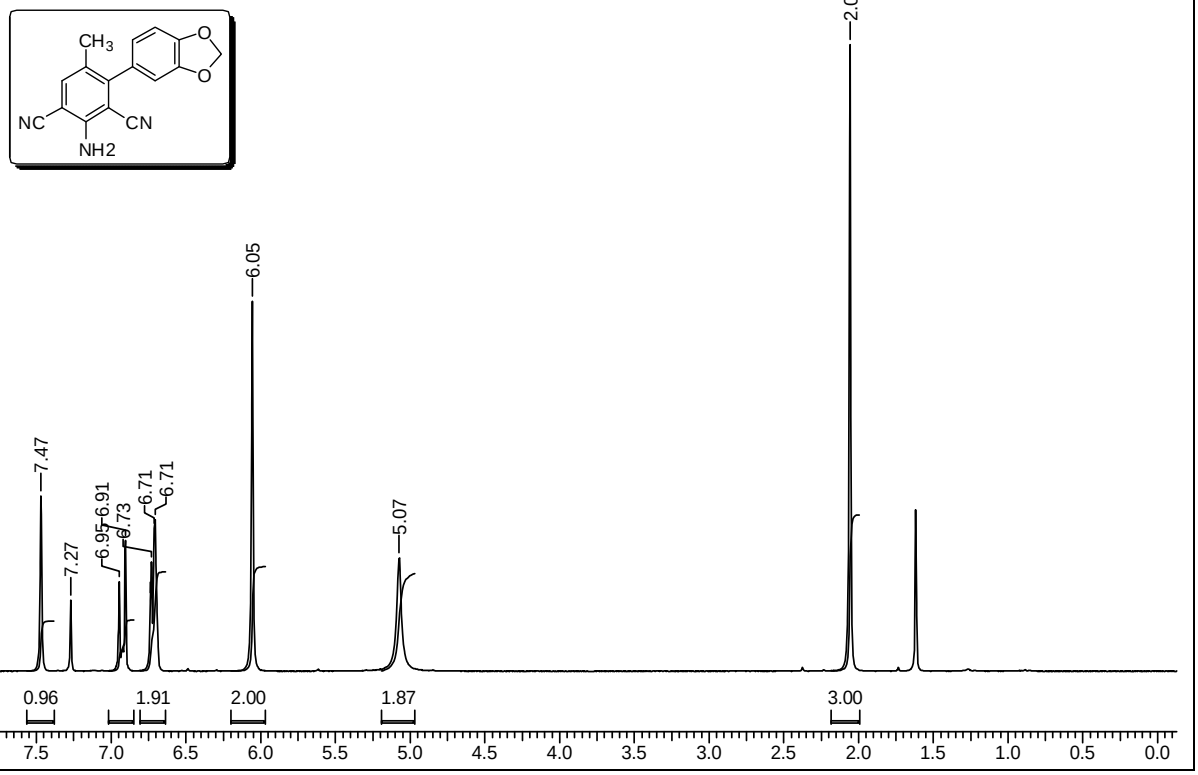
214f: ^{1}H NMR (200 MHz, $CDCl_3$)



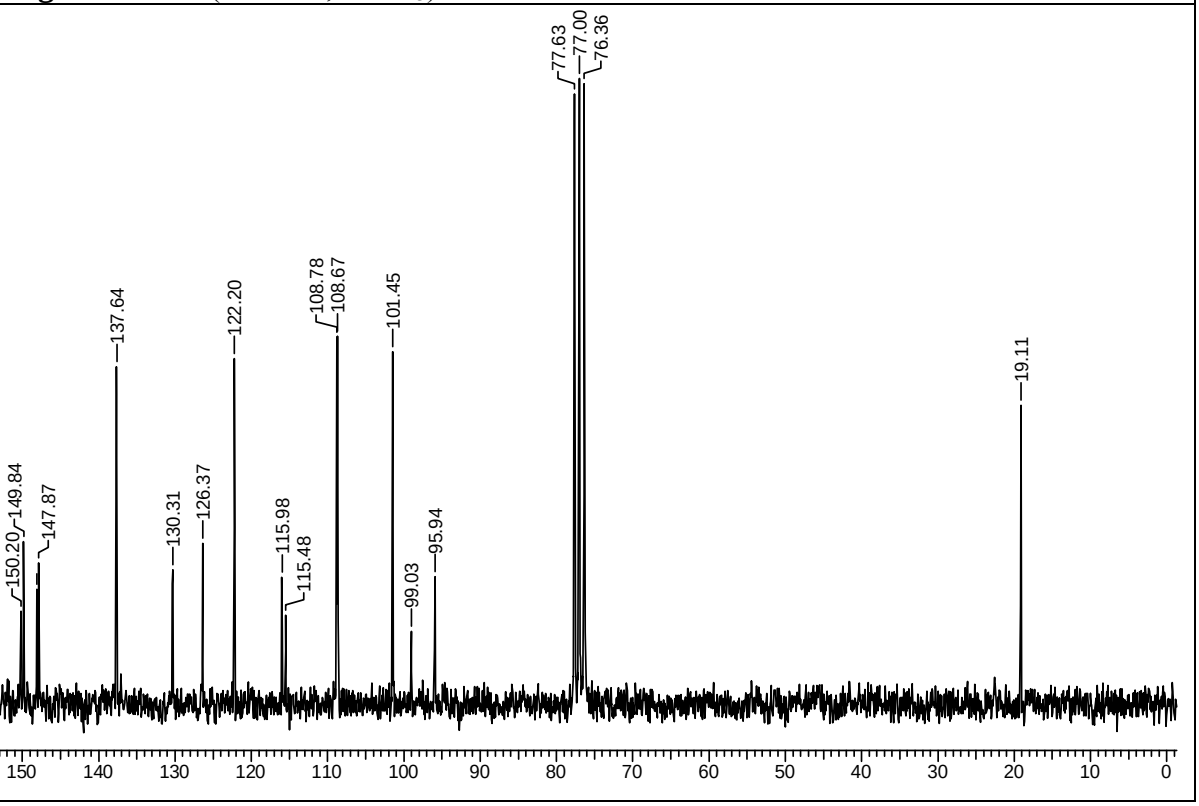
214f: ^{13}C NMR (50 MHz, $CDCl_3$)



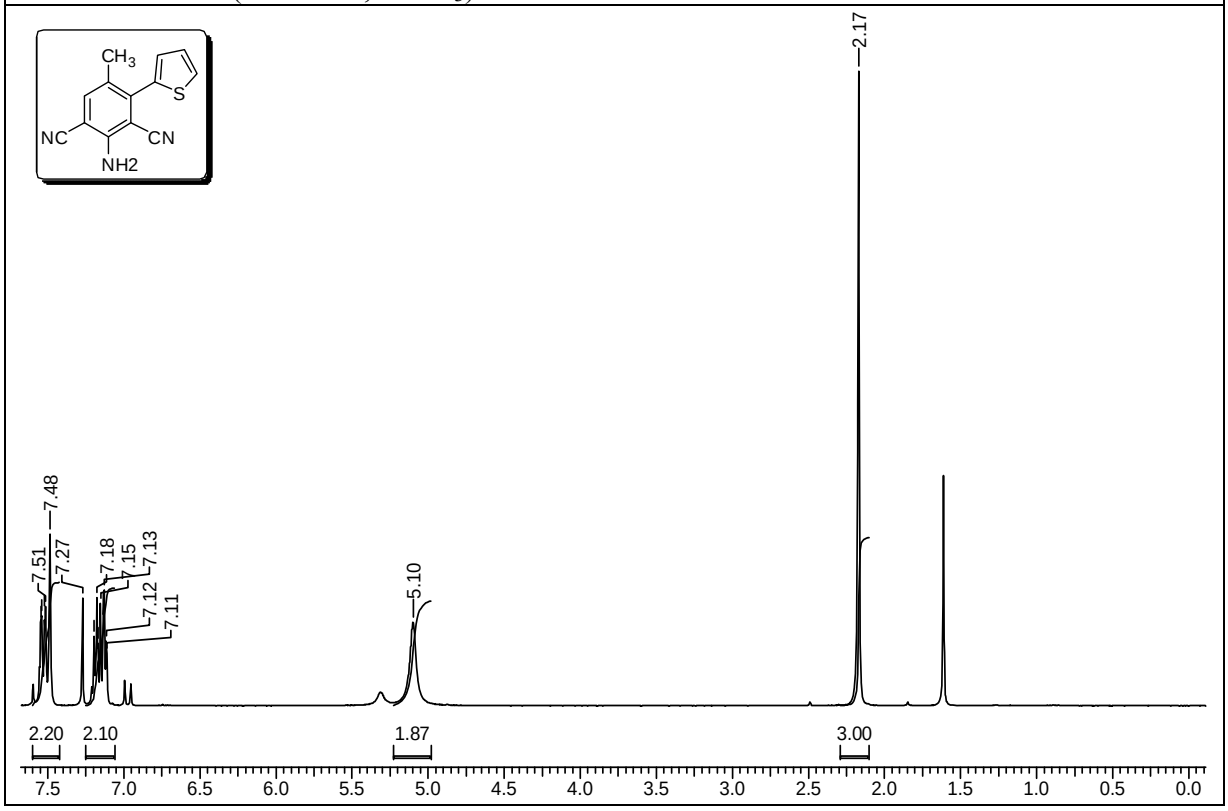
214g: ^{1}H NMR (200 MHz, $CDCl_3$)



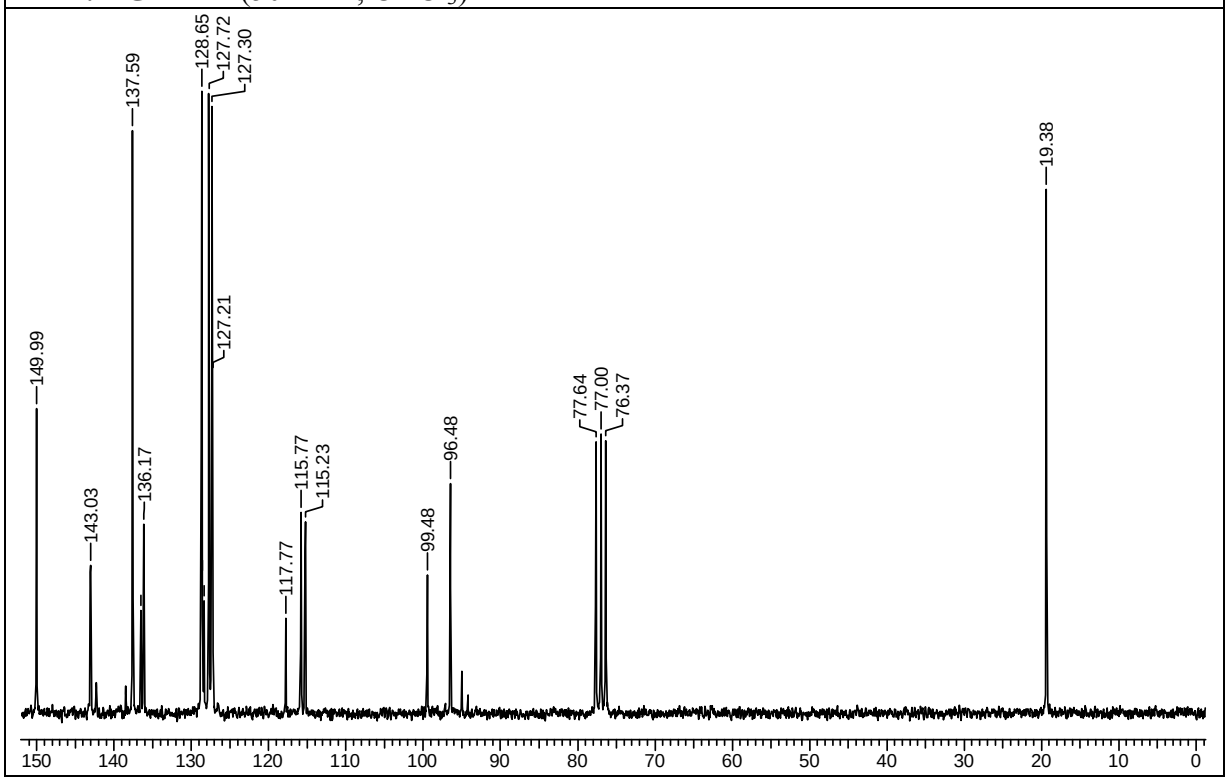
214g: ^{13}C NMR (50 MHz, $CDCl_3$)



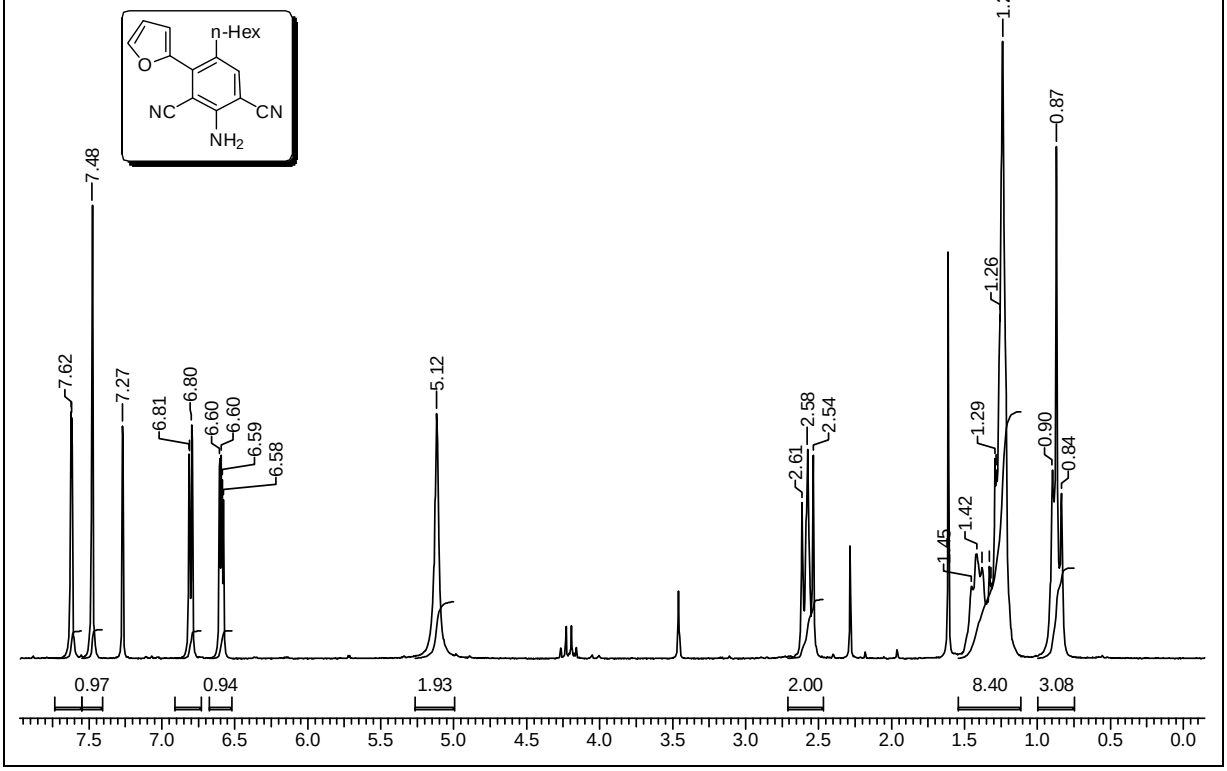
214h: ^{1}H NMR (200 MHz, $CDCl_3$)



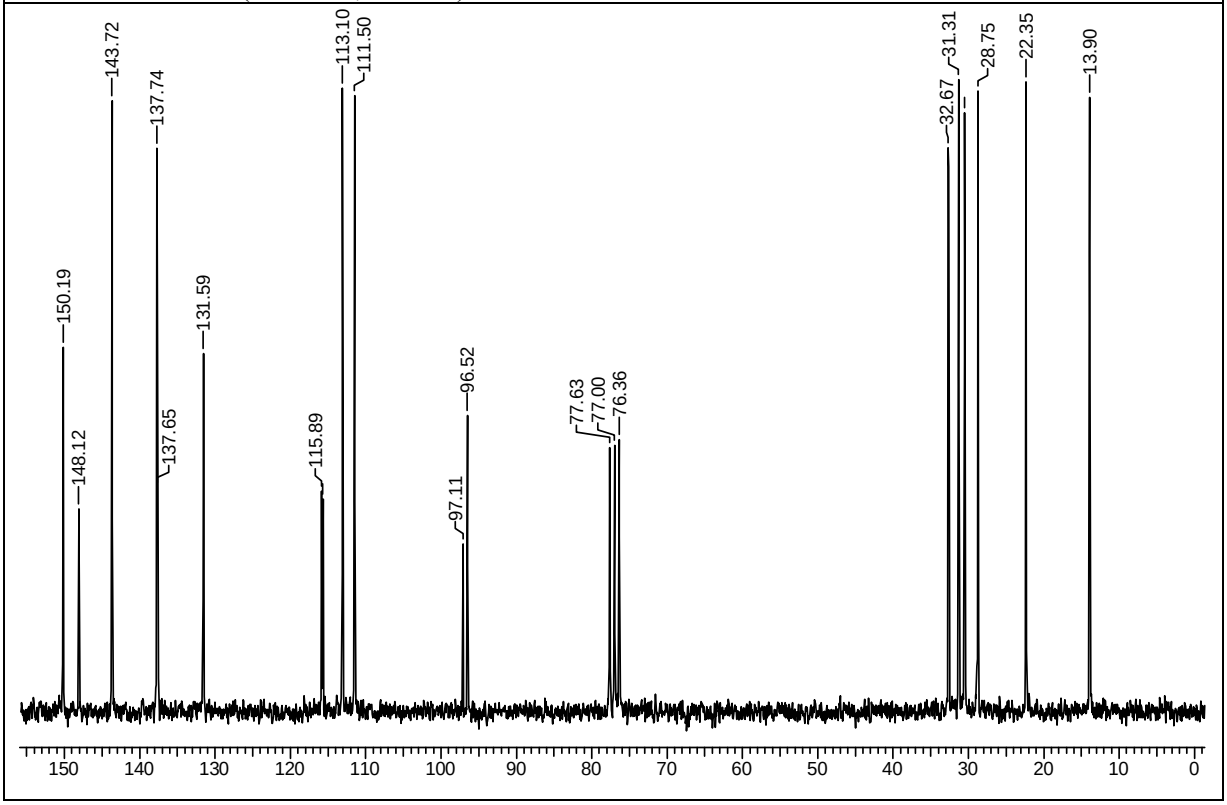
214h: ^{13}C NMR (50 MHz, $CDCl_3$)



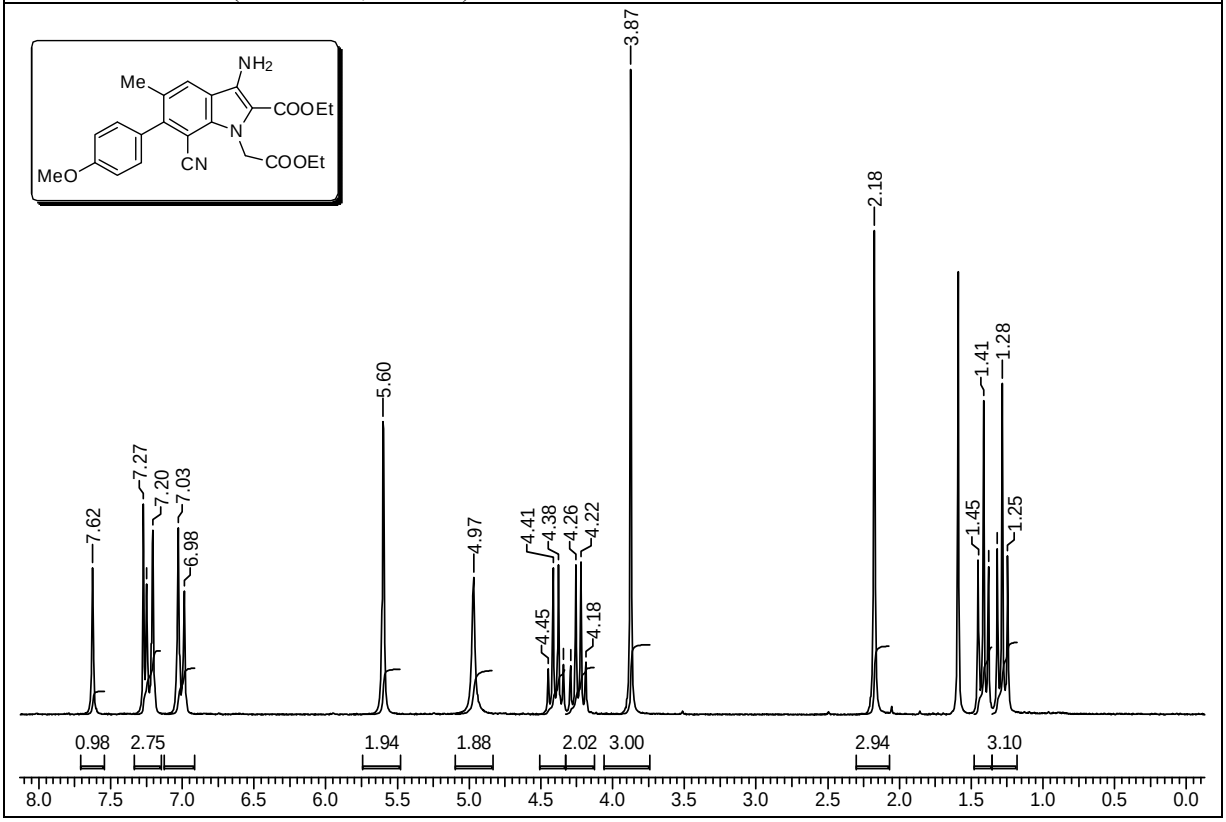
214k: ^{1}H NMR (200 MHz, $CDCl_3$)



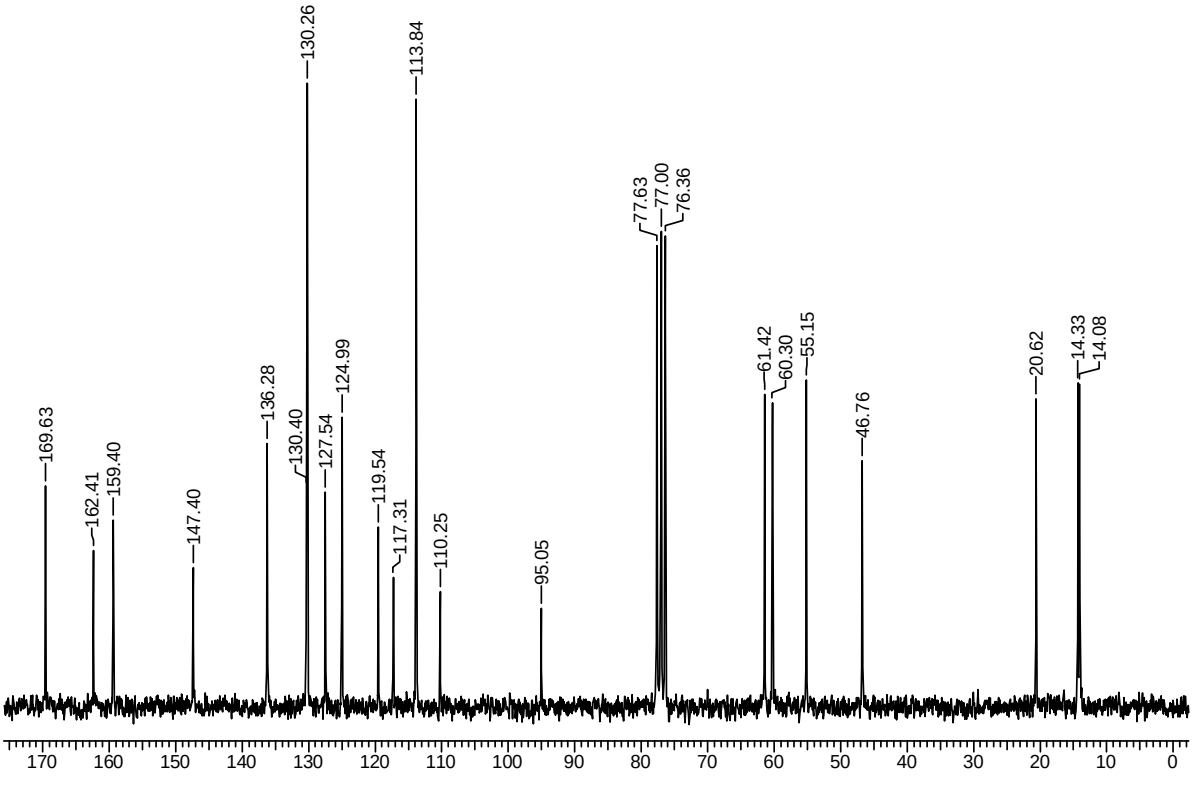
214k: ^{13}C NMR (50 MHz, $CDCl_3$)



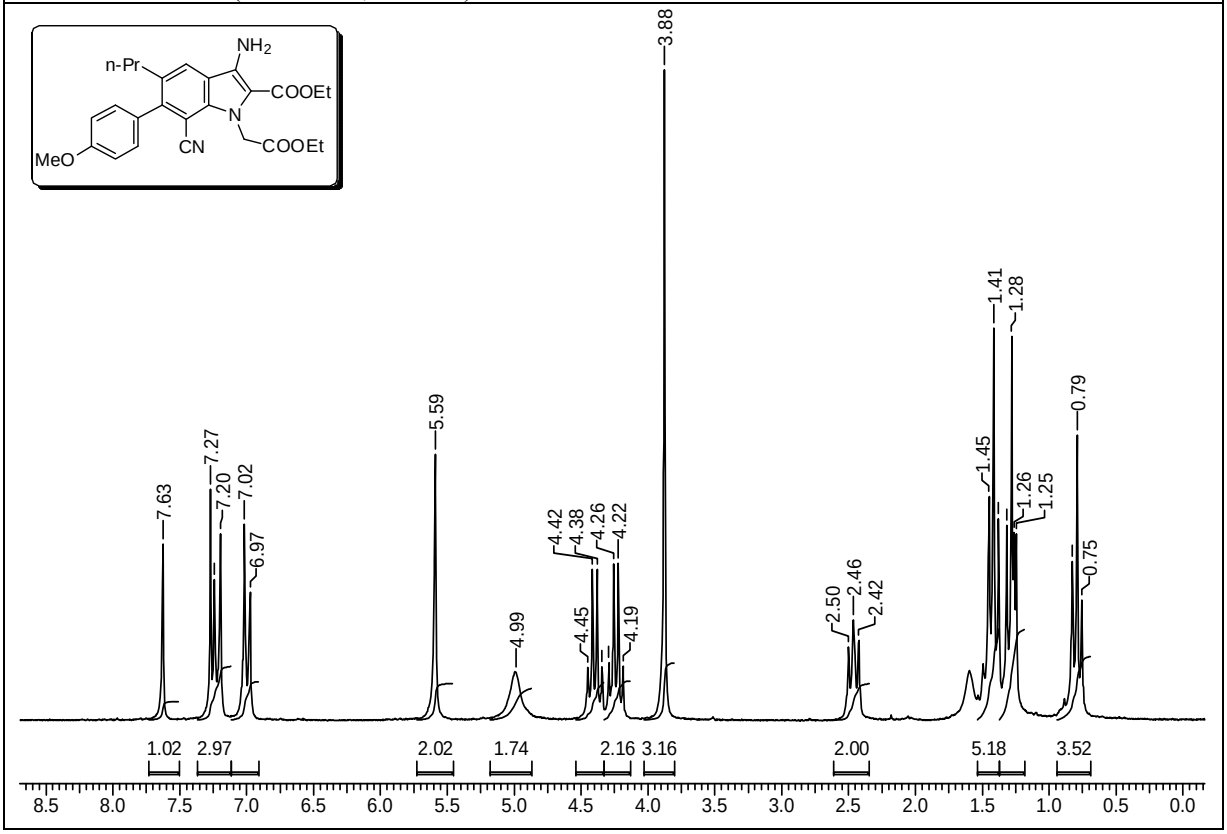
216a: ^{1}H NMR (200 MHz, $CDCl_3$)



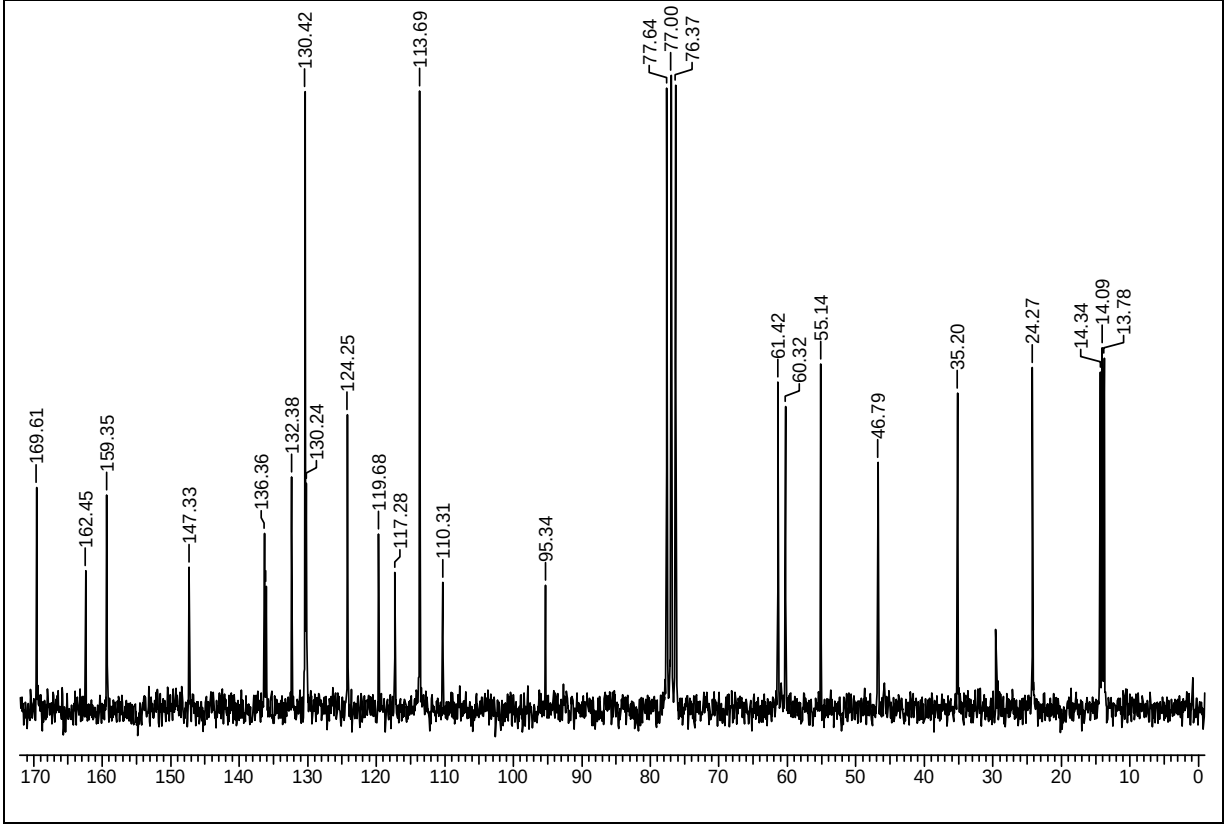
216a: ^{13}C NMR (50 MHz, $CDCl_3$)



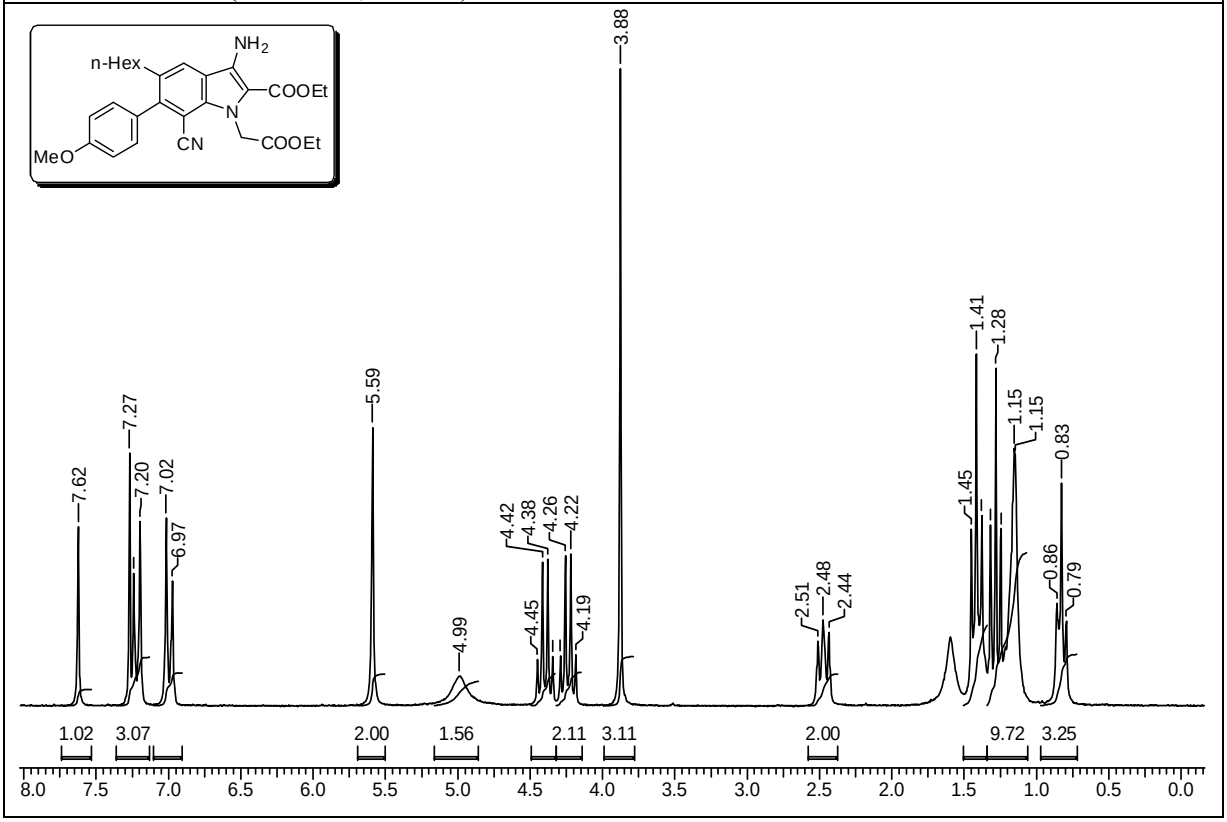
216b: ^{1}H NMR (200 MHz, $CDCl_3$)



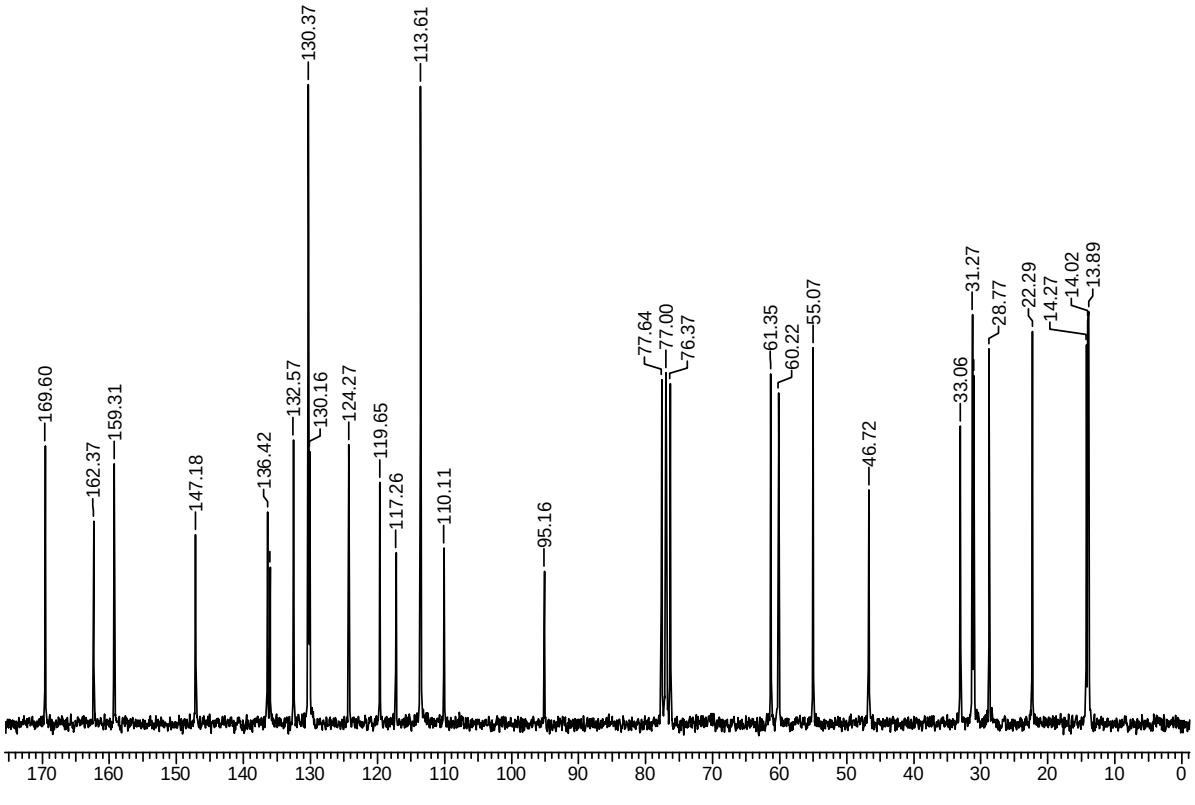
216b: ^{13}C NMR (50 MHz, $CDCl_3$)



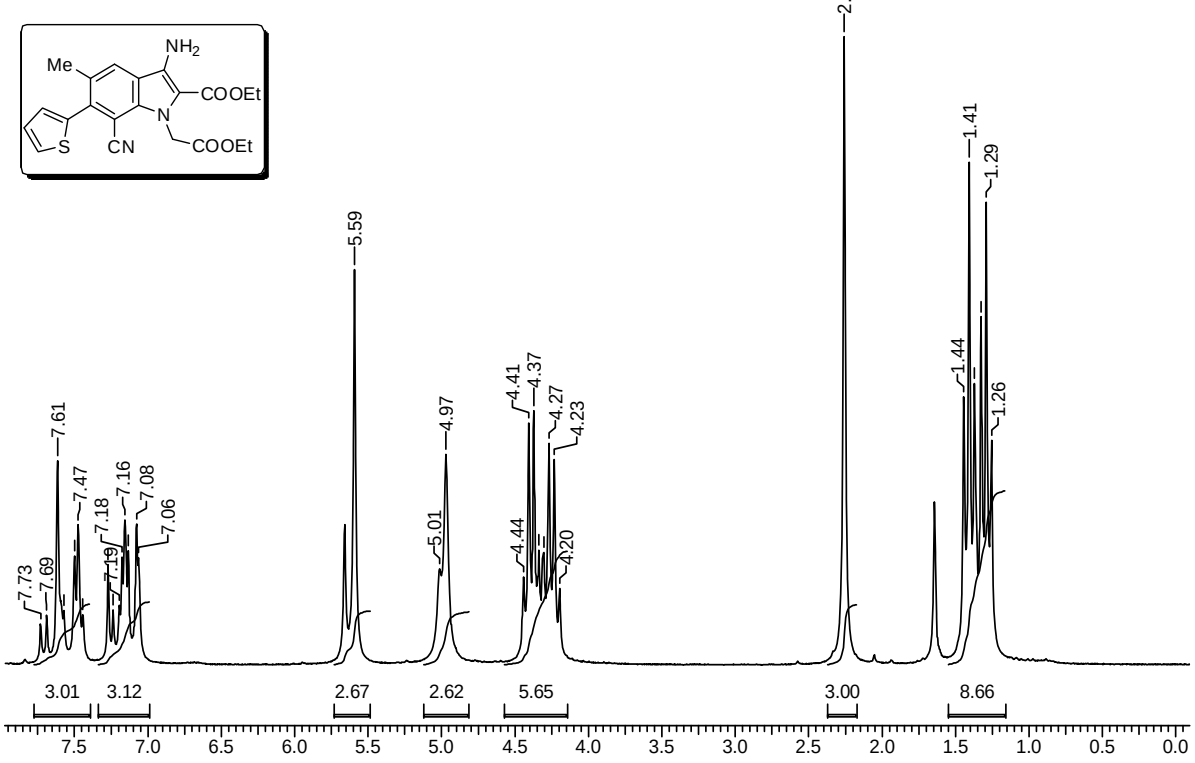
216c: ^{1}H NMR (200 MHz, $CDCl_3$)



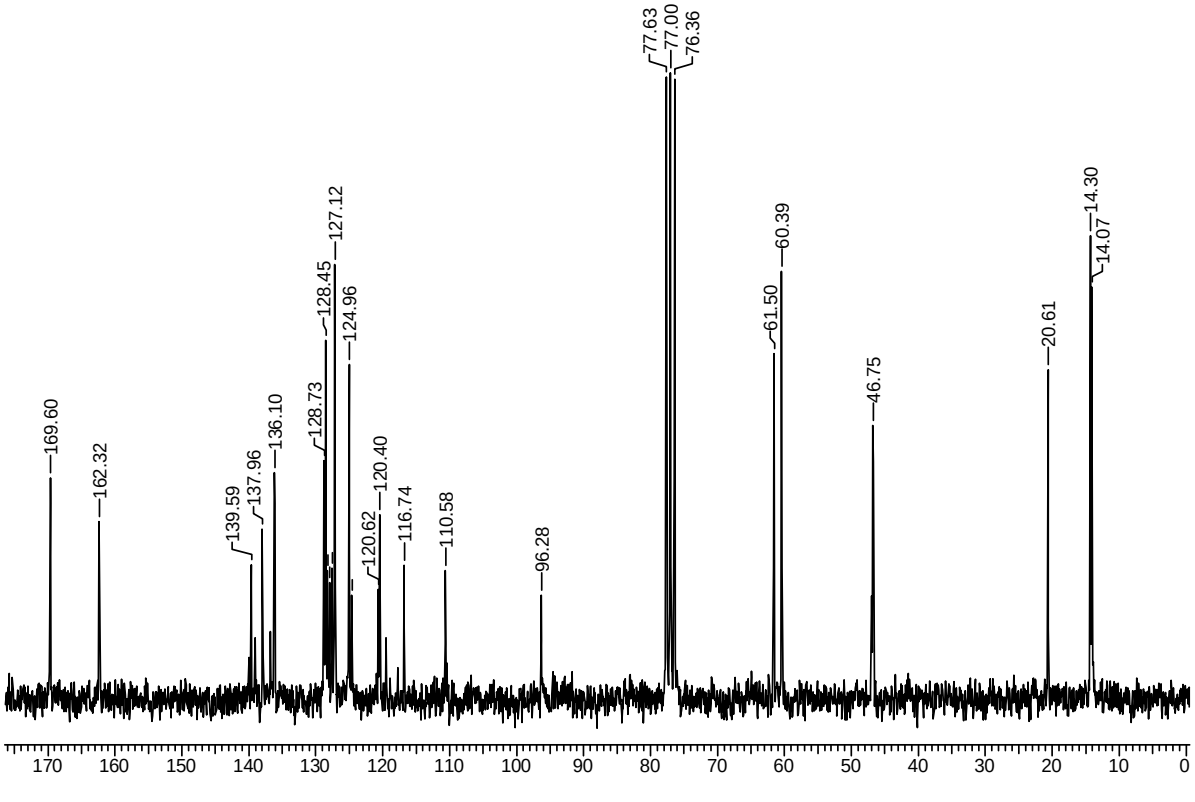
216c: ^{13}C NMR (50 MHz, $CDCl_3$)



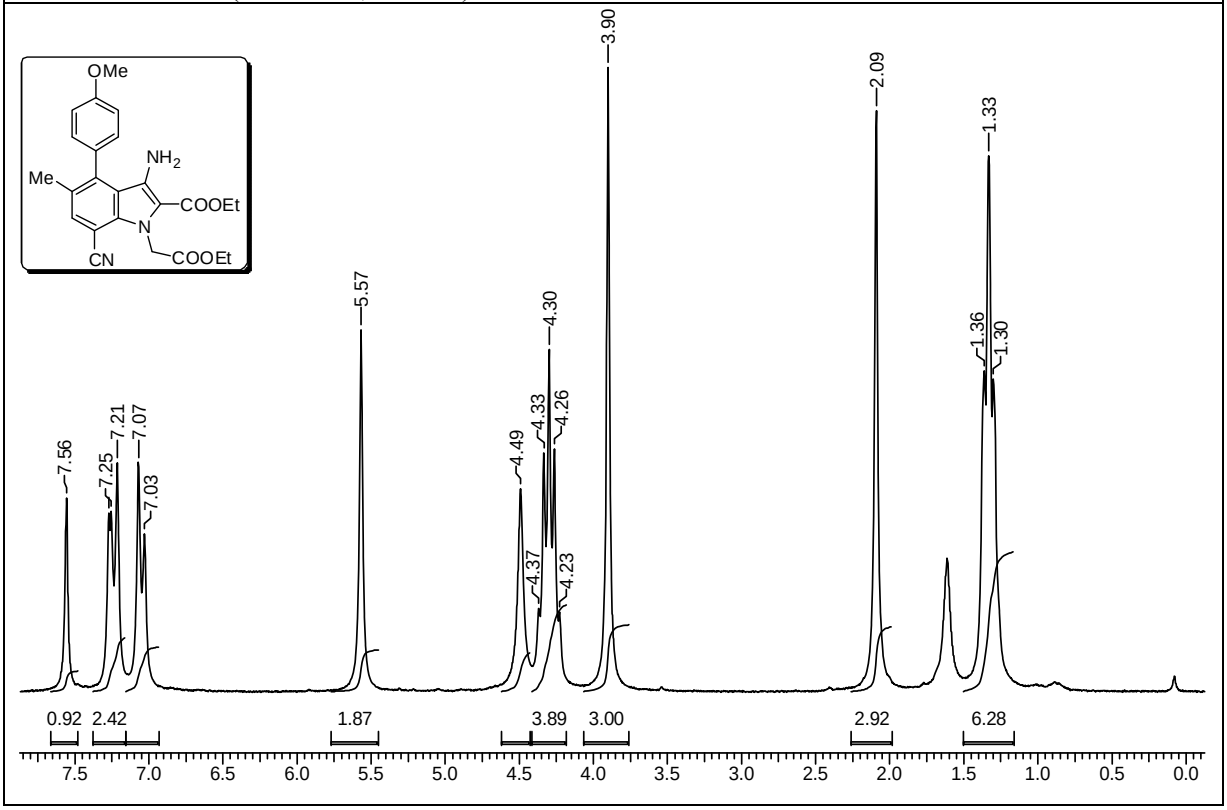
216g: ^{1}H NMR (200 MHz, $CDCl_3$)



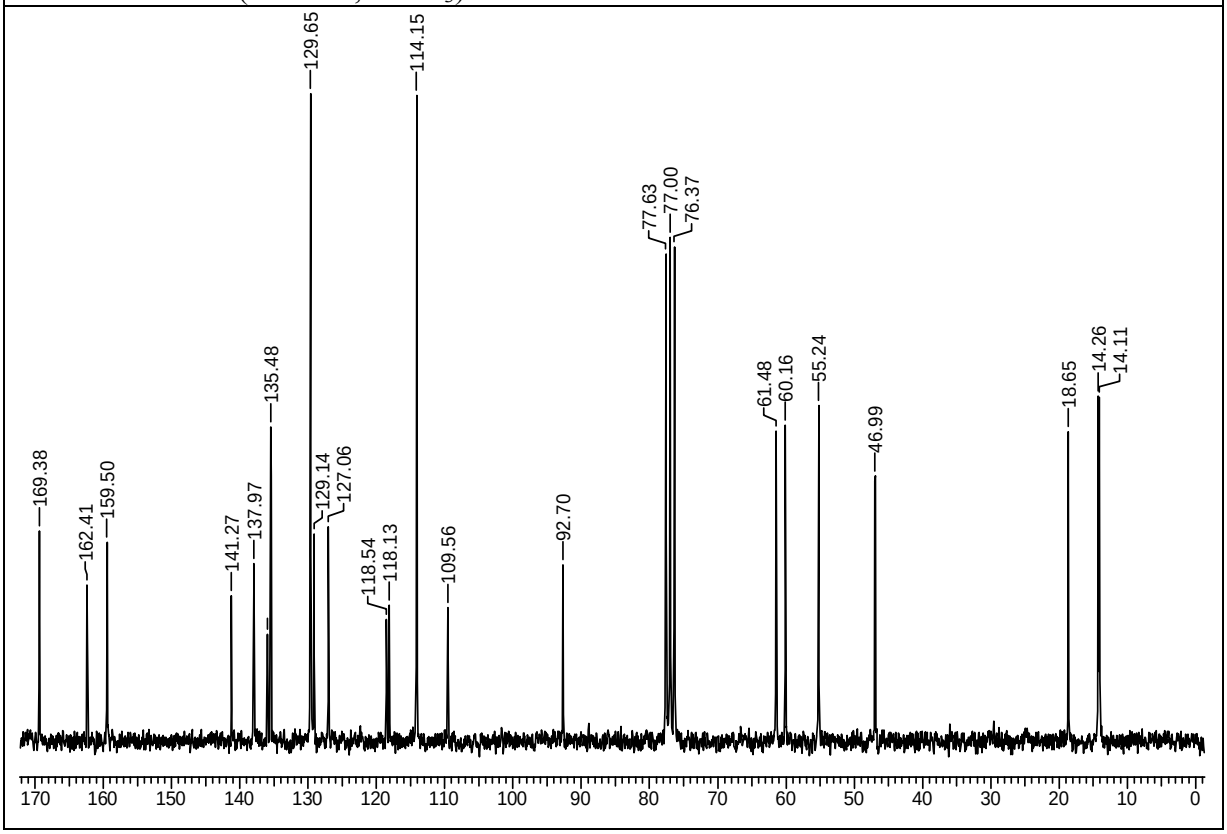
216g: ^{13}C NMR (50 MHz, $CDCl_3$)



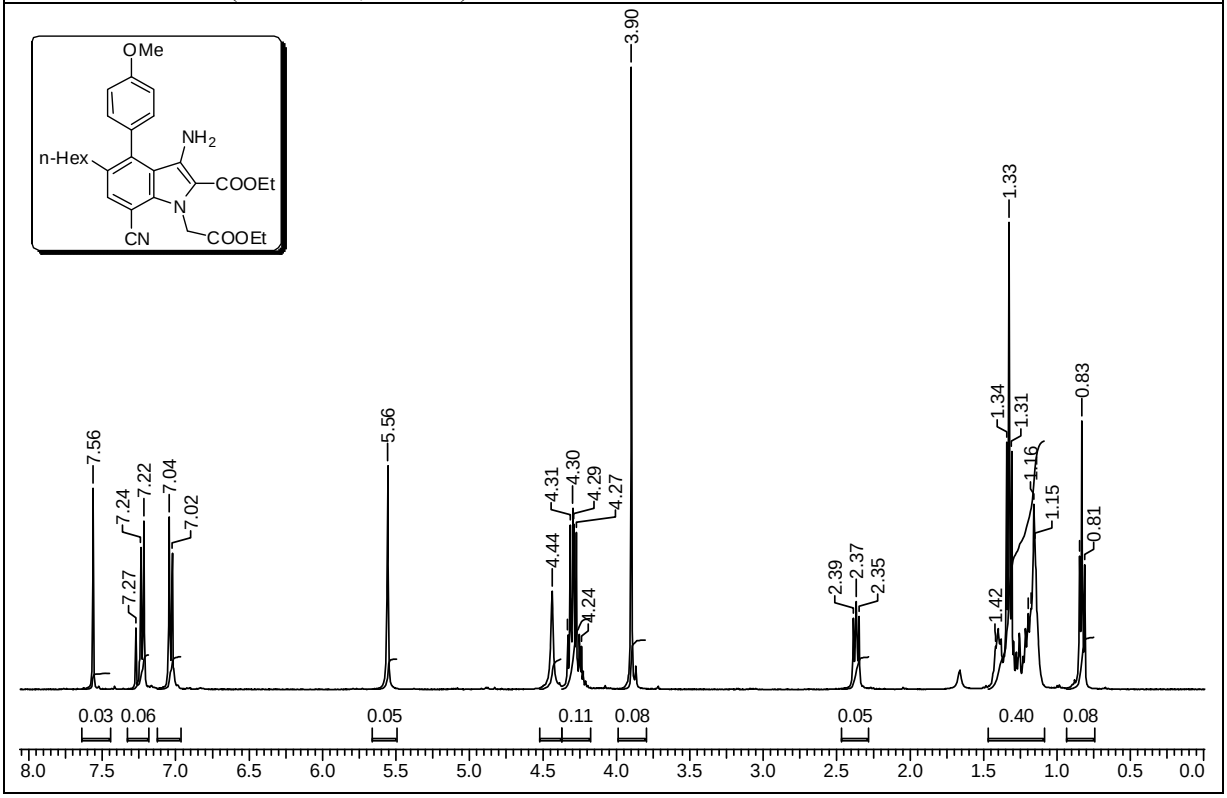
225a: ^{1}H NMR (200 MHz, $CDCl_3$)



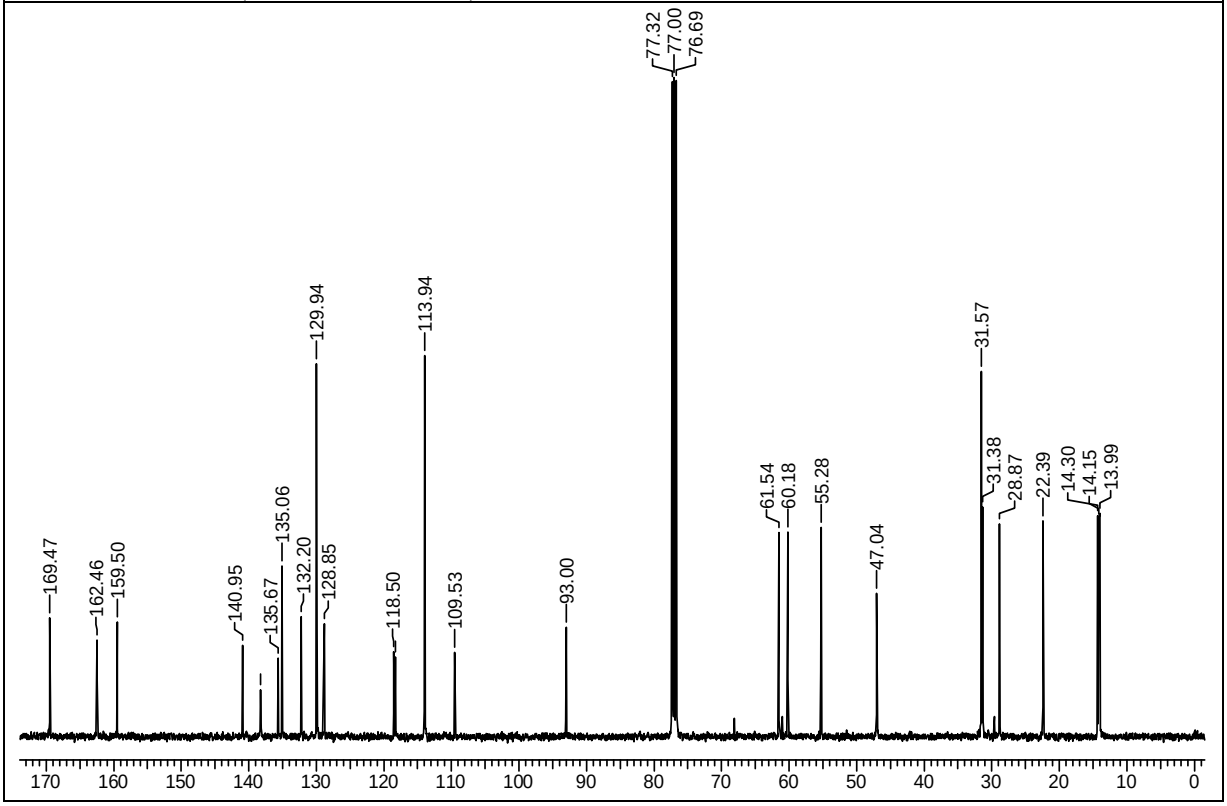
225a: ^{13}C NMR (50 MHz, $CDCl_3$)



225c: ^{1}H NMR (400 MHz, $CDCl_3$)



225c: ^{13}C NMR (100 MHz, $CDCl_3$)



3.2.7 References

1. (a) *Modern Arene Chemistry*; Astruc, D., Ed.; Wiley-VCH: Weinheim, **2002**; (b) Xi, C.; Chen, C.; Lin, J.; Hong, X. *Org. Lett.* **2005**, *7*, 347-349.
2. Taylor, R. *Electrophilic Aromatic Substitution*; Wiley: New York, **1990**.
3. Zoltewicz, J. A. *Top. Curr. Chem.* **1975**, *59*, 33-64.
4. Dyker, G. *Angew. Chem. Int. Ed. Eng.* **1999**, *38*, 1698-1712.
5. Lin, W. W.; Baron, O.; Knochel, P. *Org. Lett.* **2006**, *8*, 5673-5676 and references cited therein.
6. Adib, M.; Mohammadi, B.; Mahdavi, M.; Abbasi, A.; Riazati Kesheh, M. *Synlett* **2007**, 16, 2497-2500 and references cited therein.
7. (a) Muller, T. J. J.; Bunz, U. H. F. *Functional Organic Materials, Synthesis, Strategies and Applications*; Wiley-VCH: Weinheim, **2007**; (b) Thomson, R. H. *The Chemistry of Natural Products*; Blackie: Glasgow, **1985**; (c) Singh, F. V.; Vatsyayan, R.; Roy, U.; Goel, A. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 2734-2737.
8. (a) Maitraie, D.; Reddy, G. V.; Rao, V. V. V. N. S. R.; Ravikanth, S.; Narsaiah, B.; Rao, P. S.; Ravikumar, K.; Sridhar, B. *Tetrahedron* **2005**, *61*, 3999-4008; (b) Andersen, N. G.; Maddaford, S. P.; Keay, B. A. *J. Org. Chem.* **1996**, *61*, 9556-9559.
9. (a) Cardozo, T. M.; Nascimento, M. A. C. *J. Mater. Sci.* **2005**, *40*, 3549-3551; (b) Kanis, D. R.; Ratner, M. A.; Marks, T. J. *Chem. Rev.* **1994**, *94*, 195-242; (c) Murugan, P.; Shanmugasundaram, P.; Ramakrishnan, V. T.; Srividya, N.; Ramamurthy, P. *Indian J. Chem.* **1998**, *37B*, 737-741.
10. (a) Carroll, R. L.; Gorman, C. B. *Angew. Chem. Int. Ed. Eng.* **2002**, *41*, 4378-4400; (b) van Mullekom, H. A. M.; Vekemans, J. A. J. M.; Meijer, E. W. *Chem. Eur. J.* **1998**, *4*, 1235-1243; (c) Bendikov, M.; Wudl, F.; Perepichka, D. F. *Chem. Rev.* **2004**, *104*, 4891-4945.
11. (a) Wang, X. S.; Zhang, M. M.; Li, Q.; Yao, C. S.; Tu, S. J. *Tetrahedron* **2007**, *63*, 5265-5273; (b) Sepiol, J.; Milart, P. *Tetrahedron* **1985**, *41*, 5261-5265; (c) Griffiths J.; Lockwood, M.; Roozpeikar, B. *J. Chem. Soc., Perkin Trans.* **1977**, *2*, 1608-1610.
12. Victory, P.; Borrel, J. I.; Vidal-Ferran, A.; Seoane, C.; Soto, J. L. *Tetrahedron Lett.* **1991**, *32*, 5375-5378.
13. Xue, D.; Li, J.; Zhang, Z. T.; Deng, J. G. *J. Org. Chem.* **2007**, *72*, 5443-5447.

14. Yi, C.; Blum, C.; Liu, S. X.; Frei, G.; Neels, A.; Renaud, P.; Leutwyler, S.; Decurtins, S. *J. Org. Chem.* **2008**, *73*, 3596-3599.
15. Khaidem, I. S.; Singh, S. L.; Singh, L. R.; Khan, M. Z. R. *Indian J. Chem.* **1996**, *35B*, 911-914.
16. Singh, F. V.; Kumar, V.; Kumar, B.; Goel, A. *Tetrahedron* **2007**, *63*, 10971-10978.
17. (a) Rong, L.; Han, H.; Yang, F.; Yao, H.; Jiang, H.; Tu, S. *Synth. Commun.* **2007**, *37*, 3767-3772; (b) Rong, L.; Han, H.; Jiang, H.; Shi, D.; Tu, S. *Synth. Commun.* **2008**, *38*, 1044-1050.
18. Cui, S. L.; Lin, X. F.; Wang, Y. G. *J. Org. Chem.* **2005**, *70*, 2866-2889.
19. (a) Klaus, K. *Ger. Offen.* **1975**, DE2340569 A1; (b) Klaus, K. *Ger. Offen.* **1976**, DE2448911 A1; (c) Dyachenko, V. D. *Russ. J. Gen. Chem.* **2004**, *74*, 1135-1136.

Chapter 3: Section III

One-step synthesis of α-chlorostilbenes mediated by a heterogeneous Si-Fe catalyst

Chapter 3: Section III

One-step synthesis of α-chlorostilbenes mediated by a heterogeneous Si-Fe catalyst

3.3.1 Abstract

A short synthetic strategy mediated by a heterogeneous Si-Fe catalyst for the preparation of α-chlorostilbenes was developed by reaction of phenylacetic acid chlorides with various aromatic substrates. The α-chlorostilbenes were converted into *cis* or *trans*-stilbenes and diaryl acetylenes. Furthermore, the dechlorination of properly substituted α-chlorostilbenes led to various important molecules like DMU-212.

3.3.2 Introduction

Stilbenes constitute a family of compounds exhibiting various biological activities like anticancer activity[1], antifungal activity[2], cyclooxygenase-2 inhibitory activity[3] *etc.* as well as they are used as intermediates in the synthesis of various useful molecules including antibiotics, fluorescent brighteners, polymers *etc*. They are found in a number of plants[4] and are generally prepared by Wittig reaction[1a,1d,5a-b] or Heck reaction[6]. The stilbenes have potential in the medicinal field demonstrated by a number of publications describing synthesis and biological activity of DMU-212 (**226**)[1e,6b,7a-c], resveratrol (**227**)[1e,7b,7c,8], piceantannol (**228**)[4d], combretastatin A-4 (**229**)[1a-d,7a,9] and many other substituted stilbenes[6a,7b,10] (Figure 1).

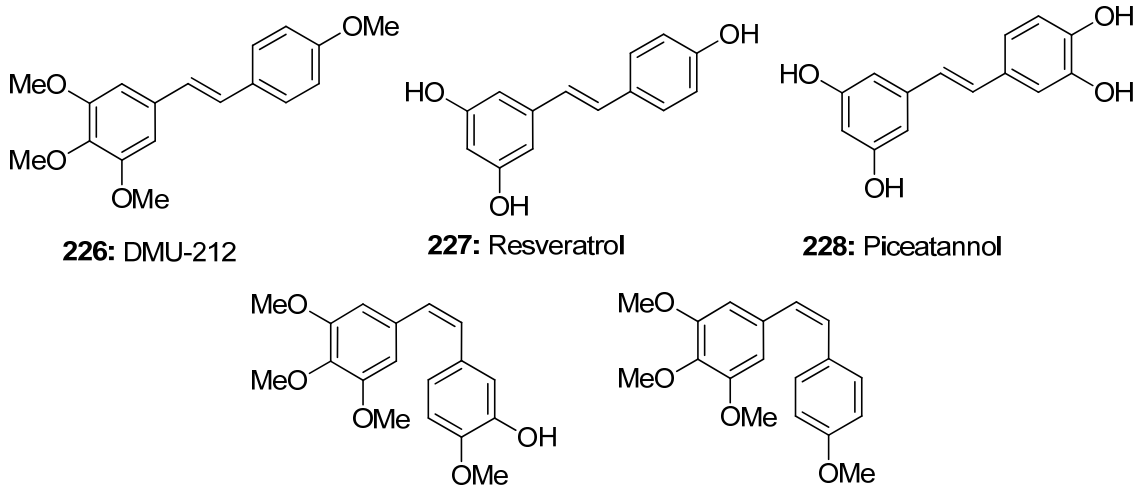


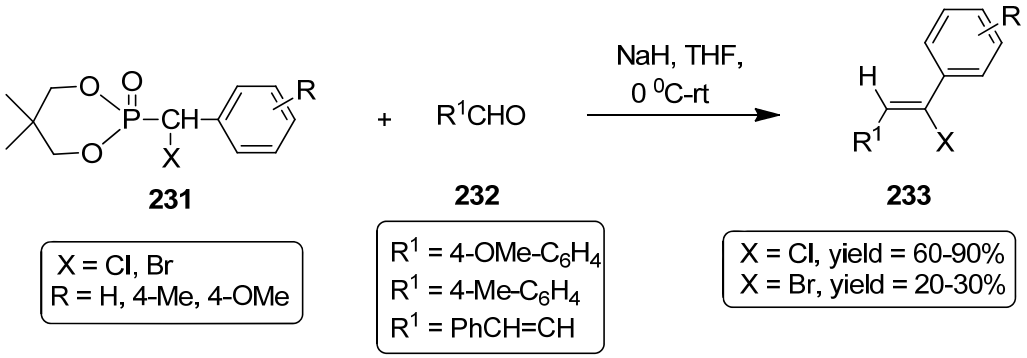
Figure 1. Structures of DMU-212 (**226**), resveratrol (**227**), piceatannol (**228**), combretastatin A-4 (**229**) and cis-isomer of DMU-212 (**230**)

DMU-212 (**226)** has received special interest in synthetic chemists as it has showed better anticancer activity than resveratrol[1e]. Its *cis*-isomer (**230**)[10a] also exhibits significant anticancer activity. Recent publications describing synthesis of DMU-212 (**226)**[6b,7a-c] prompted us to explore the possibility to develop a short synthetic strategy for substituted stilbenes based on our recent findings[11] and the results are described in this section.

3.3.3 Review of literature

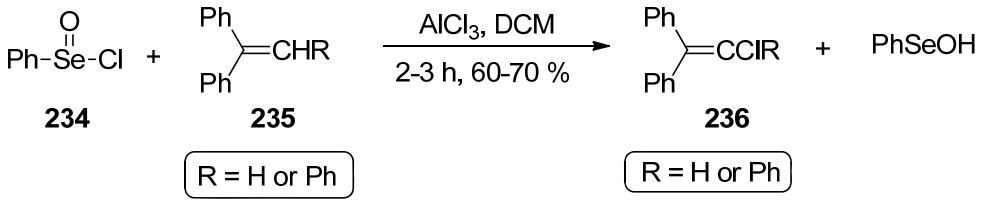
Preparation of α-halostilbenes

Aryl-substituted halo olefins are important intermediates in organic synthesis. There are so many methods reported in the literature for the synthesis of substituted halo olefins. One of the most preferred routes to prepare substituted olefins is by reacting a phosphonate carbanion with a carbonyl compound *via* the Horner–Wadsworth–Emmons reaction[12]. Synthesis of aryl-substituted halo olefins **233**[13] by this route would require the corresponding halogenophosphonates **231** as shown in scheme 1.



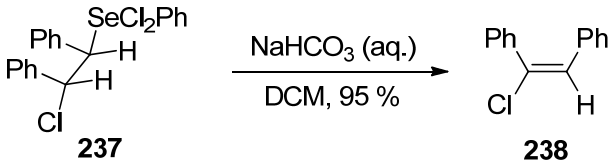
Scheme 1. Preparation of α-chloro-olefins **233** *via* Horner–Wadsworth–Emmons reaction

Other methods such as Wittig reaction of ketones with Ph_3P=CHCl or addition of HCl to acetylenes in the presence of zinc chloride are reported[14] by M. Hanack *et al.* Use of selenium reagent in presence of aluminum chloride for the preparation of α-chloro-olefins was reported[15] by N. Kamigata *et al.* They observed that the reaction of benzeneseleninyl chloride (**234**) with olefins **235** in the presence of aluminum chloride in DCM afforded chloro-olefins **236** as shown in Scheme 2.



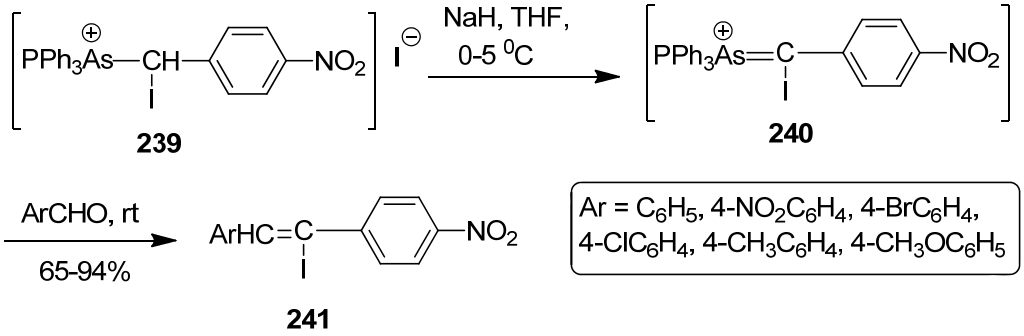
Scheme 2. Preparation of α-chloro-olefins **236** using aluminum chloride

L. Engman *et al.* reported[16] the addition of phenylselenium trichloride to number of olefinic compounds to produce (β-chloroalkyl)phenylselenium dichlorides (**237**), which on treatment with aqueous sodium hydrogen carbonate in DCM readily hydrolyzed to selenoxide, which underwent the usual selenoxide elimination reaction to produce an allylic or a vinylic chloride **238** as shown in Scheme 3.



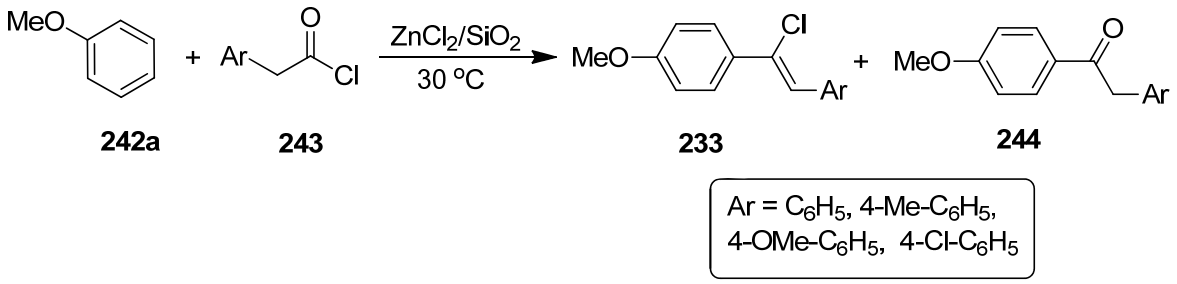
Scheme 3. Preparation of α-chloro-stilbene **238**

X. Haung *et al.* reported[17] the preparation of vinyl halides **241** by reacting arsonium ylides **240** with aromatic aldehydes through Wittig reaction as shown in Scheme 4. However, all of these ylides are limited to *α* -halo- *α* -electron withdrawing group substituted arsonium ylides, i.e. stabilized arsonium ylides.



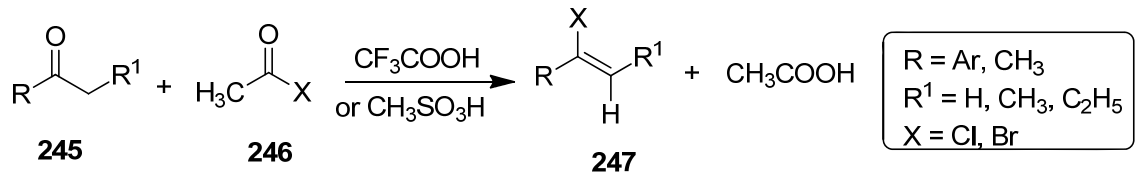
Scheme 4. Preparation of α-chloro-stilbenes **241** using arsonium ylides

M. Kodomari and co-workers reported[18] the use of silica gel-supported zinc chloride for the preparation of □-chlorostilbenes as shown in Scheme 5. Author observed that when anisole (**242a**) was treated with arylacetyl chloride (**243**) using silica gel-supported zinc chloride as a catalyst, □-chlorostilbene **233** as well as the expected acylated product **244** were obtained as shown in Scheme 5. Similar products have been seen in the Montmorillonite-supported $FeCl_3$-catalyzed Friedel-Crafts acylation reaction[19].



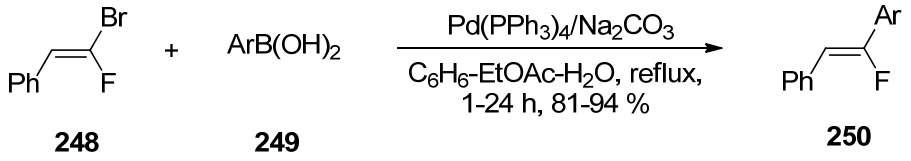
Scheme 5. Preparation of α-chlorostilbenes **233**

Furthermore, when aryl or alkyl ketones **245** were reacted with acetyl halides **246** in strongly acidic solvents such as trifluoroacetic acid or methanesulfonic acid, the products formed were aryl/alkyl-substituted halo olefins **247** as shown in Scheme 6. The reaction proceeds through the addition of acetyl halides to the carbonyl, resulting in the formation of □-haloacetate, followed by elimination of acetic acid[20].



Scheme 6. Preparation of α-chlorostyrenes/α-chlorostilbenes **247**

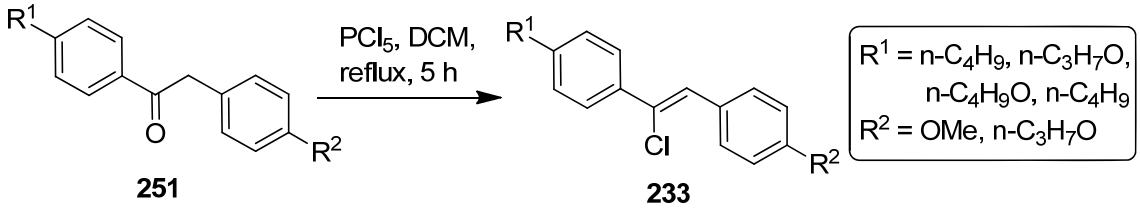
C. Chen *et al.* reported[21] the synthesis of □-fluorostilbenes using Suzuki coupling reaction. When 1-fluoro-2-phenylvinyl bromide (**248**) was coupled with arylboronic acid **249** in the presence of $Pd(PPh_3)_4$ under Suzuki conditions, □-fluorostilbenes **250** were obtained in 81-94% yields as shown in Scheme 7.



248 **249** **250**

Scheme 7. Preparation of α-fluorostilbenes **250**

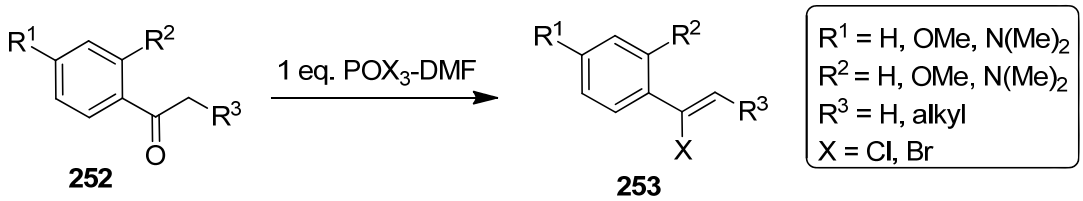
Young *et al.* also reported[22] the synthesis of α-chlorostilbene **233** by reacting substituted benzyl phenyl ketone **251** in presence of PCl_5 in DCM at reflux temperature as shown in Scheme 8.



251 **233**

Scheme 8. Preparation of α-chlorostilbenes **233**

Furthermore, Annamaria and coworkers reported[23] a very efficient method for the synthesis of (*Z*)-1-aryl-1-haloalkenes **253** by reacting aryl ketones **252** with Vilsmeier-Haack reagents (Vilsmeier reagents are halomethyliminium salts best known for their use in the Vilsmeier-Haack formylation of activated aromatic rings) as shown in Scheme 9. One of the drawbacks of this reaction is the presence of an electron-donating group at the ortho- or para-position to the carbonyl group in the aromatic ring.



252 **253**

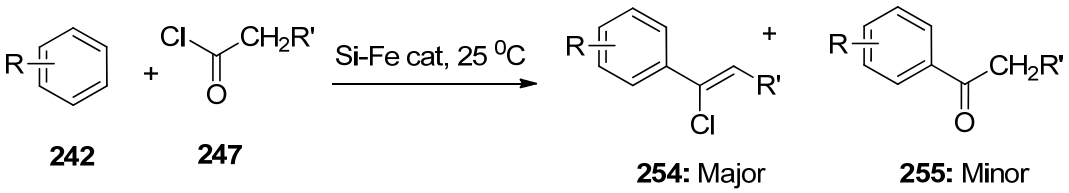
Scheme 9. Preparation of α-chlorostyrenes **253** by using Vilsmeier reagent

However, these methods frequently suffer from disadvantages including multi-step reaction sequences, low yields and serious regiochemical ambiguity originating from the activating, deactivating and directing effects of the substituents. In the present work, we developed a short synthesis of substituted α-chlorostilbenes from commercially available

substituted benzenes and phenyl acetic acids in presence of heterogeneous Si-Fe catalyst and the results are presented in this section.

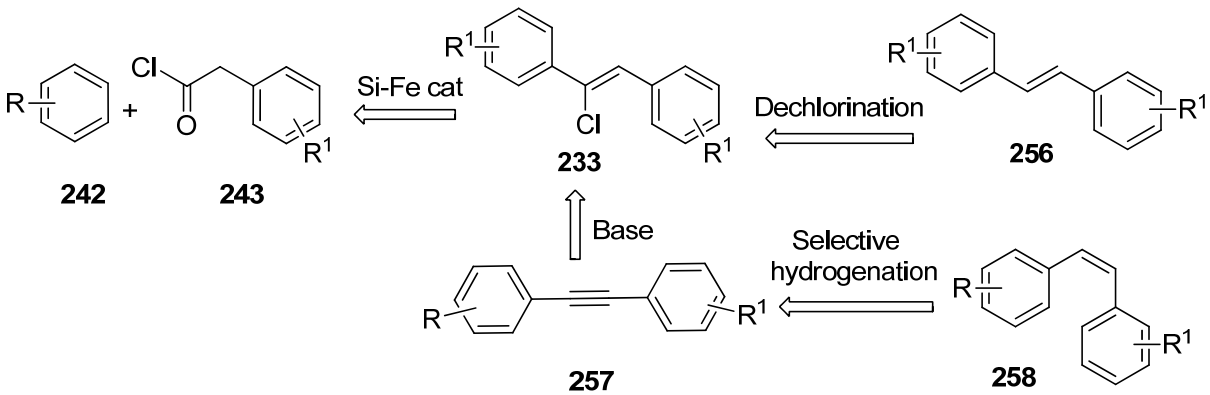
3.3.4 Present work

During previous research in our group[11], involving Friedel-Crafts acylation of aromatic substrates with acid chlorides in the presence of a heterogeneous Si-Fe catalyst, we found that α-chlorostyrenes **254** were obtained as major product in addition to the normal Friedel-Crafts acylation products **255** as shown in Scheme 10.



Scheme 10. Preparation of α-chlorostyrenes **254**

Based on these results, we envisioned that if instead of alkyl acyl chlorides we react aromatic acyl chlorides with aromatic substrates in presence of the same heterogeneous Si-Fe catalyst, it could serve as a simple method for synthesizing α-chlorostilbenes **233**. The α-chlorostilbenes could then be converted into *cis* or *trans*-stilbenes as depicted in the retrosynthetic strategy shown in Scheme 11. Dechlorination of properly substituted α-chlorostilbenes **233** could lead to various important molecules like DMU-212 (**226**). The results on the feasibility of the above strategy are presented in this section.



Scheme 11. Retrosynthesis of compounds **233**, **256**, **257** and **258**

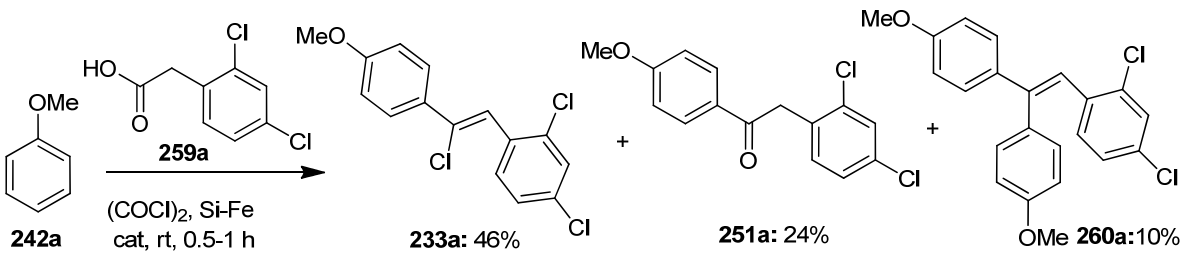
Preparation of Si-Fe catalyst

Heterogeneous Si-Fe catalyst was synthesized based on the procedure used for the synthesis of hydrotalcites[24]. Hydrotalcites are nothing but layered double hydroxides (LDH) and comprise an unusual class of layered materials with positively charged layers and charge balancing anions located in the interlayer region.

The Si–Fe catalyst was prepared from sodium trisilicate as a source of silica and ferric nitrate as source of iron in the presence of ammonia and ammonium carbonate at room temperature. The solid mass formed in the aqueous solution was stirred for 12 h, filtered, dried at 120 ^{o}C for 12 h, calcined at 500 ^{o}C for 3 h, powdered and used for reactions. The detailed procedure of preparation is described in experimental section. The acidity of this iron silicate type catalyst was determined by the ammonia method[25], and it was observed to be 0.4 mmol/g. Surface area was measured using BET method[29] and was found to be 271 m^2/g while the atomic weight ratio was calculated using EDAX (Energy Dispersive X-ray analysis) and was observed to be as follows: C = 4.14 %, O = 64.6 %, Si = 18.11% and Fe = 13.15 %. During synthesis of Si-Fe catalyst, we assumed that the product of the reaction will result into the formation of hydrotalcites, but we observed that nature of the catalyst synthesized was amorphous and not crystalline. This indicated that the catalyst synthesized falls in the category of a hydrotalcite-type anionic clays[24b].

Preparation of α-chlorostilbenes

Initially, anisole (**242a**) was reacted with 2,4-dichlorophenylacetyl chloride (generated *in situ* from 2,4-dichlorophenylacetic acid **259a** and oxalyl chloride) in the presence of the heterogeneous Si-Fe catalyst[11] at room temperature wherein the α-chlorostilbene **233a** was obtained as a major product. The normal Friedel-Crafts acylation product **251a** and aryl stilbene **260a** were obtained as side products in 24% and 10% yields respectively (Scheme 12).



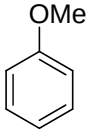
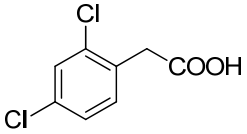
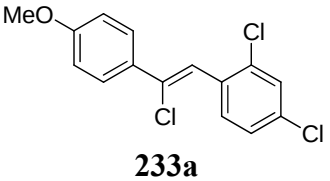
Scheme 12. Synthesis of α-chlorostilbene **233a**

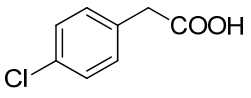
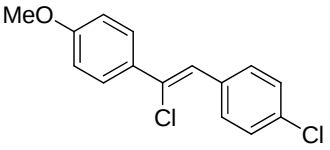
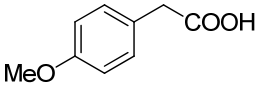
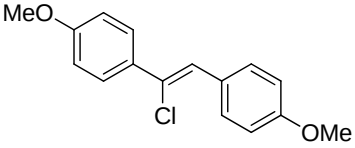
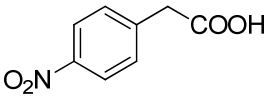
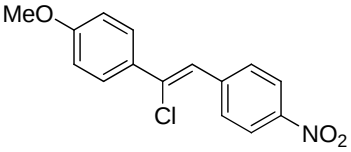
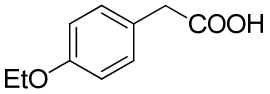
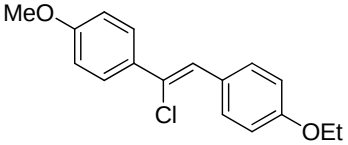
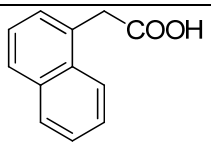
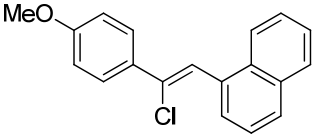
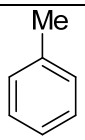
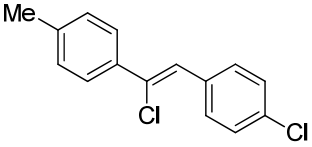
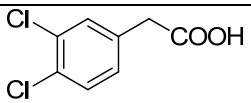
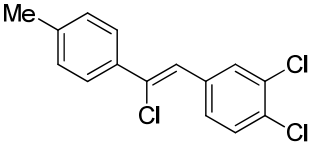
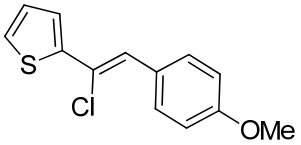
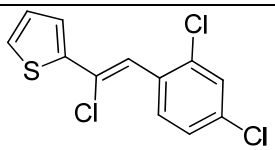
The TLC of the reaction mixture (Pet ether) indicated the presence of these compounds when viewed in UV light wherein the R_f (retention factor) values of the α-chlorostilbene **233a**, aryl stilbene **260a** and the Friedel-Crafts acylation product **251a** were 0.65, 0.5 and 0.25 respectively. The reaction mixture was purified by column chromatography on silica gel to get the pure products. Formation of compound **233a** was confirmed by ^{1}H NMR, ^{13}C NMR, IR and mass spectroscopy and the comparison of the spectroscopic data with the literature values[13,18]. All the compounds synthesized showed satisfactory spectral data as described in the experimental section.

A number of α-chlorostilbenes **233** were prepared in 46-55% isolated yields, when anisole (**242a**) or toluene (**242b**) was reacted with various arylacetic acid chlorides in the presence of the heterogeneous Si-Fe catalyst at room temperature for 0.5 to 1 h, demonstrating the generality of the method as shown in Table 1 (Entries 1 to 8). The normal Friedel-Crafts acylation product **251** was obtained as a minor product. When anisole (**242a**) was used as one of the reactants, the corresponding aryl stilbene **260a** was obtained as a side product which was not observed in case of toluene (**242b**) or thiophene (**242c**). The α-chlorostilbenes **233** could be easily isolated from the reaction mixture as they were the first compounds to elute during the column chromatography using pet ether as an eluent.

In case of reactions wherein thiophene (**242c**) was used as one of the reactants (Table 1, Entries 9 and 10), the α-chlorostilbenes **233i** and **233j** were obtained as minor products. When furan (**242d**) was reacted with various phenylacetic acid chlorides (generated *in situ* from phenylacetic acids **259** and oxalyl chloride) in the presence of the heterogeneous Si-Fe catalyst at 0 ^{0}C to room temperature for 0.5 to 1 h, it resulted in the polymerization of furan and thickening of the reaction mixture (Table 1, Entry 11).

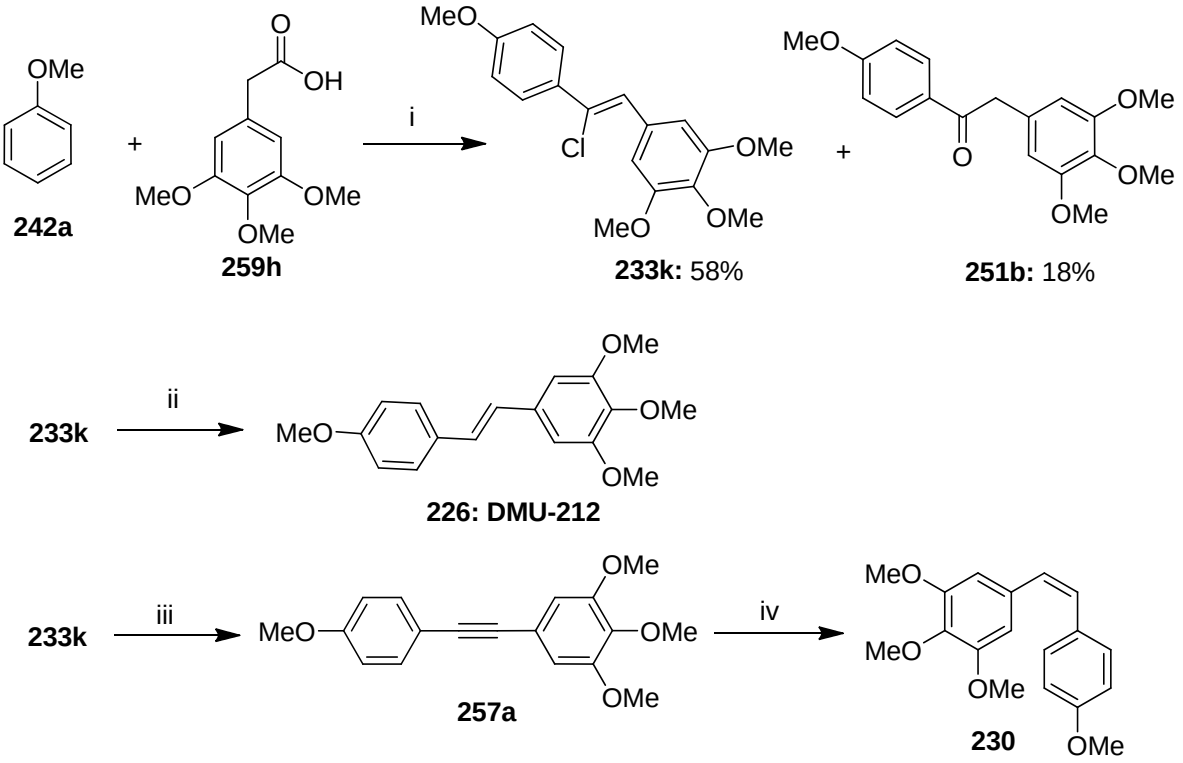
Table 1. Synthesis of α-chlorostilbenes

Entry	Aromatic substrate	Arylacetic acid	Product **233**	Yield %
1	 **242a**	 **259a**	 **233a**	46

2	**242a**	 **259b**	 **233b**	52
3	**242a**	 **259c**	 **233c**	54
4	**242a**	 **259d**	 **233d**	55
5	**242a**	 **259e**	 **233e**	53
6	**242a**	 **259f**	 **233f**	50
7	 **242b**	**259b**	 **233g**	54
8	**242b**	 **259g**	 **233h**	55
9	 **242c**	**259c**	 **233i**	28
10	**242c**	**259a**	 **233j**	25

11	 **242d**	**259a**	**Polymerization**	-

This synthetic strategy was used to prepare DMU-212 (**226**), an anticancer agent, as shown in Scheme 13. The reaction of 3,4,5-trimethoxyphenylacetic acid chloride, generated *in situ* from 3,4,5-trimethoxyphenylacetic acid (**259h**) and oxalyl chloride, with anisole (**242a**) in presence of the heterogeneous Si-Fe catalyst[11] afforded the α-chlorostilbene **233k** in 48% yield along with the minor product **251b**[26] which was easily separated by column chromatography. Dechlorination of the α-chlorostilbene **233k** with tributyltin hydride in presence of 2,2'-azobis(isobutyronitrile) afforded the desired DMU-212 (**226)** in 88% yield as shown in Scheme 13, spectral data of which were in full agreement with the reported values[27].

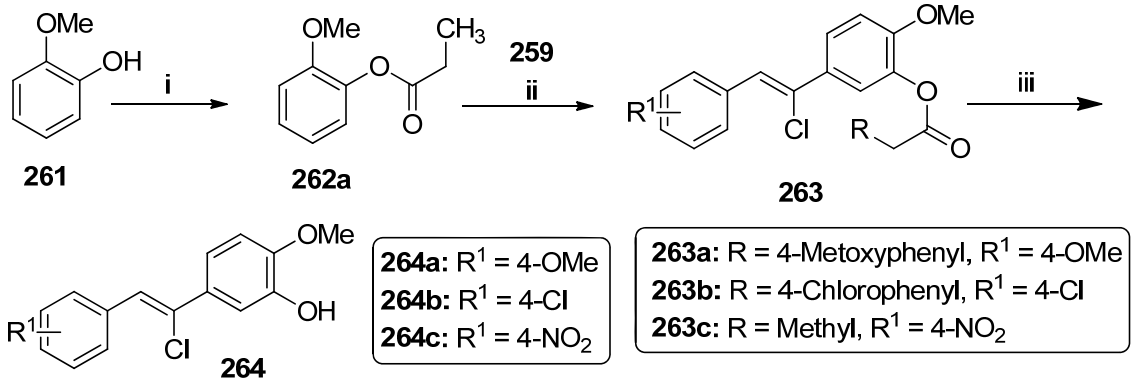


Scheme 13. Reagents and conditions: i) $(COCl)_2$, Si-Fe cat, rt, 0.5-1 h ii) TBTH, AIBN, toluene, reflux, 1 h, 88% iii) n-BuLi, THF, rt, 2 h, 90% iv) H_2, Lindlar catalyst, EtOAc, quinoline, rt, 2 h, 72%.

The utility of the present methodology was further extended to the synthesis of *cis*-stilbenes **230**. The reaction of chlorostilbene **233k** with n-butyllithium in THF at room temperature afforded the corresponding diarylacetylene **257a**[28] in 90% yield. This conversion was also effected using potassium *t*-butoxide in *t*-butanol under reflux but the reaction was not clean and 50% yield of **257a** was obtained. Selective hydrogenation[29] of **257a** using Lindlar catalyst in presence of quinoline in ethyl acetate gave the required *cis*-stilbene **230**[27] in 72% yield as shown in Scheme 13.

In order to extend the utility of this method of preparation of α-chlorostilbenes for the preparation of molecules with various other substituents e.g. combretastatin A-4 (**229**), piceatannol (**228**) *etc.* and their analogues, various substituted anisoles were subjected to the reaction with substituted phenylacetic acid chlorides (generated *in situ* from the corresponding phenylacetic acids **259** and oxalyl chloride) in presence of the heterogeneous Si-Fe catalyst and the results are shown in Scheme 14 and Table 2.

It was observed that in case of reaction of 2-methoxyphenyl propionate **262a** (which in turn synthesized by reacting guaiacol **261** with propionyl chloride in presence of pyridine as base in DCM at room temperature) with 4-methoxyphenylacetic acid or 4-chlorophenylacetic acid (Table 2, Entries 1 and 2) in presence of oxalyl chloride and the heterogeneous Si-Fe catalyst, the propionate group was replaced with the corresponding phenyl acetate group simultaneously with the formation of α-chlorostilbenes **263a-b**. The hydrolysis of the ester group of α-chlorostilbene **263a-b** with methanolic sodium hydroxide afforded the required α-chlorostilbene **264a-b** with phenolic hydroxy group.

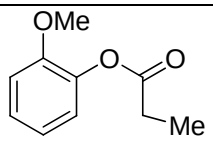
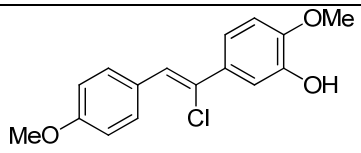
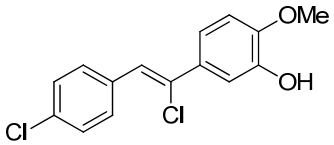
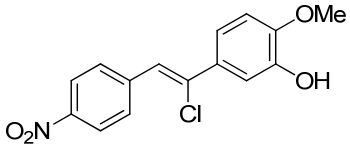


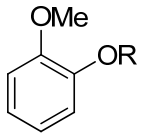
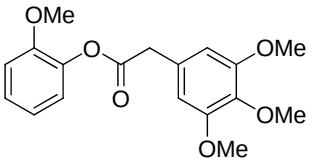
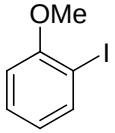
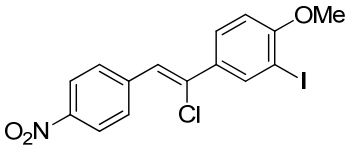
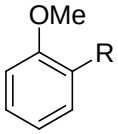
Scheme 14. Reagents and conditions: i) CH_3CH_2COCl, pyridine, DCM, 0 ^{0}C-rt, 2 h, 96% ii) $(COCl)_2$, Si-Fe cat, rt, 0.5-1 h iii) 10% NaOH, MeOH, 62-64% .

In case of 4-nitrophenylacetic acid **259d** (Table 2, Entry 3), the propionate group survived giving the corresponding α-chlorostilbene **263c** with propionate which on hydrolysis afforded the required α-chlorostilbene **264c** with phenolic hydroxy group. 3,4,5-Trimethoxyphenylacetic acid **259h** was subjected to reaction with 2-methoxyphenyl propionate **262a** in presence of oxalyl chloride and the heterogeneous Si-Fe catalyst in order to get the combretastatin A-4 (**229**) and its analogues, but instead of getting the corresponding α-chlorostilbene **264**, 2-methoxyphenyl 2-(3,4,5-trimethoxyphenyl)acetate **265** was obtained (Table 2, Entry 4).

The replacement of propionate group with O-TBDMS, O-Bn or O-allyl group (**263b-d**) also resulted in the formation of the same product **265**. There was no reaction when 3,4,5-trimethoxyphenylacetic acid chloride was reacted with 2-methoxybenzaldehyde (**267**) or 2-nitroanisole (**268**) (Table 2, Entry 6). The reaction of 2-iodoanisole (**266**) with 4-nitrophenylacetic acid chloride afforded the corresponding α-chlorostilbene **264d** in 73% yield (Table 2, Entry 5). This study showed that though the efforts to prepare combretastatin A-4 (**229**) were not successful, a number of α-chlorostilbenes with various substituents could be prepared using the present short synthetic strategy.

Table 2. Synthesis of α-chlorostilbenes using substituted anisoles

Entry	Substituted anisole	Acid	Product	Yield %
1	 **262a**	**259c**	 **264a**	62[a]
2	**262a**	**259b**	 **264b**	64[a]
3	**262a**	**259d**	 **264c**	63[a]

4	 **263a:** R = $COCH_2CH_3$ **263b:** R = TBDMS **263c:** R = Bn **263d:** R = allyl	**259h**	 **265**	86
5	 **266**	**259c**	 **264d**	73
6	 **267:** R = CHO **268:** R = NO_2	**259h**	**No Reaction**	-

[a]Yield over two step

Structure confirmation

All the compounds synthesized in reaction sequences in this section were fully characterized by ^{1}H NMR, ^{13}C NMR, IR and mass spectroscopic methods and showed satisfactory spectral data described in experimental section. So as to confirm the structure of one of the compounds from the series of **233a-j**, compound **233h** was recrystallised from hot ethanol. Using X-ray crystallography the structure of **233h** was confirmed as shown in the ORTEP diagram in Figure 2.

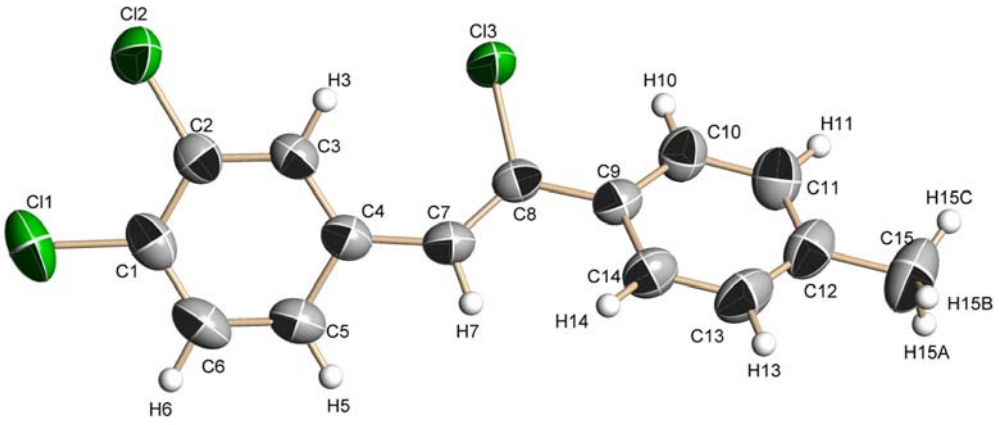


Figure 2. ORTEP diagram of compound **233h**

Table 3. Crystal data structure refinement for **233h**

Identification code	**233h**
Empirical formula	$C_{15}H_{11}Cl_3$
Formula weight	297.59
Temperature	297(2) K
Wavelength	0.71073Å
Crystal system, space group	MONOCLINIC, C2/c
Unit cell dimensions	a = 18.306(8) Å, α = 90º. b = 6.481(3) Å, β = 90.537(12)º. c = 23.568(9) Å, γ = 90º.
Volume	2795.9(19) $Å^3$
Z, Calculated density	8, 1.414 Mg/m^3
Absorption coefficient	0.633 mm^{-1}
F(000)	1216
Crystal size	0.40 x 0.19 x 0.12 mm
Theta range for data collection	2.83 to 25.99º.
Limiting indices	-21<=h<=22, -7<=k<=7, -29<=l<=15
Reflections collected / unique	7299 / 2703 [R(int) = 0.0230]
Completeness to theta = 26.00	98.9 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9256 and 0.7840
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2703 / 0 / 164
Goodness-of-fit on F^2	1.042
Final R indices [I>2sigma(I)]	R1 = 0.0477, wR2 = 0.1135
R indices (all data)	R1 = 0.0610, wR2 = 0.1240
Largest diff. peak and hole	0.432 and -0.290 $eÅ^{-3}$

Table 4. Bond lengths [Å] and angles [º] for **233h**

Cl(1)-C(1)	1.726(3)
Cl(2)-C(2)	1.728(3)
Cl(3)-C(8)	1.739(2)
C(1)-C(2)	1.380(4)
C(1)-C(6)	1.379(4)
C(2)-C(3)	1.373(3)
C(3)-C(4)	1.391(4)
C(4)-C(5)	1.394(4)
C(4)-C(7)	1.462(4)
C(5)-C(6)	1.365(4)
C(7)-C(8)	1.328(4)
C(8)-C(9)	1.464(3)
C(9)-C(10)	1.380(4)
C(9)-C(14)	1.392(3)
C(10)-C(11)	1.381(4)
C(11)-C(12)	1.368(4)
C(12)-C(13)	1.380(4)
C(12)-C(15)	1.507(4)
C(13)-C(14)	1.374(4)
C(2)-C(1)-C(6)	119.6(3)
C(2)-C(1)-Cl(1)	121.1(3)
C(6)-C(1)-Cl(1)	119.3(2)
C(3)-C(2)-C(1)	120.4(3)
C(3)-C(2)-Cl(2)	119.1(2)
C(1)-C(2)-Cl(2)	120.5(2)
C(2)-C(3)-C(4)	120.9(2)
C(3)-C(4)-C(5)	117.5(3)
C(3)-C(4)-C(7)	125.2(2)
C(5)-C(4)-C(7)	117.4(2)
C(6)-C(5)-C(4)	121.7(3)
C(5)-C(6)-C(1)	119.9(3)
C(8)-C(7)-C(4)	133.9(2)
C(7)-C(8)-C(9)	124.9(2)
C(7)-C(8)-Cl(3)	120.6(2)
C(9)-C(8)-Cl(3)	114.46(18)
C(10)-C(9)-C(14)	117.3(3)
C(10)-C(9)-C(8)	122.0(2)
C(14)-C(9)-C(8)	120.6(2)
C(9)-C(10)-C(11)	120.9(3)
C(12)-C(11)-C(10)	122.2(3)
C(11)-C(12)-C(13)	116.7(3)
C(11)-C(12)-C(15)	122.2(3)
C(13)-C(12)-C(15)	121.0(3)
C(14)-C(13)-C(12)	122.2(3)
C(13)-C(14)-C(9)	120.6(3)

Symmetry transformations used to generate equivalent atoms:

Table 5. Torsion angles [º] for **233h**

C(6)-C(1)-C(2)-C(3)	0.5(4)
Cl(1)-C(1)-C(2)-C(3)	179.77(19)
C(6)-C(1)-C(2)-Cl(2)	-179.7(2)
Cl(1)-C(1)-C(2)-Cl(2)	-0.5(3)
C(1)-C(2)-C(3)-C(4)	0.1(4)
Cl(2)-C(2)-C(3)-C(4)	-179.69(19)
C(2)-C(3)-C(4)-C(5)	-0.9(4)
C(2)-C(3)-C(4)-C(7)	-179.1(2)
C(3)-C(4)-C(5)-C(6)	1.1(4)
C(7)-C(4)-C(5)-C(6)	179.5(3)
C(4)-C(5)-C(6)-C(1)	-0.5(4)
C(2)-C(1)-C(6)-C(5)	-0.3(4)
Cl(1)-C(1)-C(6)-C(5)	-179.5(2)
C(3)-C(4)-C(7)-C(8)	-21.5(5)
C(5)-C(4)-C(7)-C(8)	160.3(3)
C(4)-C(7)-C(8)-C(9)	179.9(2)
C(4)-C(7)-C(8)-Cl(3)	-2.2(4)
C(7)-C(8)-C(9)-C(10)	147.4(3)
Cl(3)-C(8)-C(9)-C(10)	-30.6(3)
C(7)-C(8)-C(9)-C(14)	-30.9(4)
Cl(3)-C(8)-C(9)-C(14)	151.1(2)
C(14)-C(9)-C(10)-C(11)	1.5(4)
C(8)-C(9)-C(10)-C(11)	-176.8(2)
C(9)-C(10)-C(11)-C(12)	-0.7(4)
C(10)-C(11)-C(12)-C(13)	-0.3(4)
C(10)-C(11)-C(12)-C(15)	-179.5(3)
C(11)-C(12)-C(13)-C(14)	0.4(4)
C(15)-C(12)-C(13)-C(14)	179.6(3)
C(12)-C(13)-C(14)-C(9)	0.4(5)
C(10)-C(9)-C(14)-C(13)	-1.4(4)
C(8)-C(9)-C(14)-C(13)	177.0(2)

Symmetry transformations used to generate equivalent atoms:

3.3.5 Conclusion

α-Chlorostilbenes were prepared by a one-step method from various aromatic substrates and acid chlorides using a heterogeneous, Si–Fe catalyst at room temperature. The

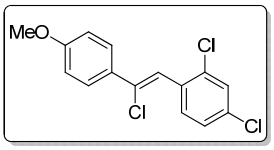
α-chlorostilbenes were then converted into *cis* or *trans*-stilbenes. The utility of the present methodology has been demonstrated by successful synthesis of DMU-212 (**226**), its *cis*-isomer and attempted synthesis of combretastatin A-4 (**229**).

3.3.6 Experimental Section

Preparation of (*Z*)- 2,4-dichloro-1-(2-chloro-2-(4-methoxyphenyl)vinyl)benzene (233a)

To 2,4-dichlorophenylacetic acid **259a** (2.05 g, 10 mmol) taken in a two-neck RB flask equipped with a calcium chloride guard tube, oxalyl chloride (1.73 mL, 20 mmol) was added at room temperature and the reaction mixture was stirred for 5 min. Then anisole **242a** (1.08 mL, 10 mmol) was added followed by activated (150 ^{0}C, 2 h) Si-Fe catalyst (10% by weight, 100 mg). The reaction mixture was allowed to stir at room temperature for 2 h. It was then filtered to remove the catalyst and washed with dichloromethane (50 mL). The filtrate and washings were combined, washed with water followed by saturated $NaHCO_3$ solution, dried over Na_2SO_4, concentrated and purified by column chromatography to give (*Z*)-2,4-dichloro-1-(2-chloro-2-(4-methoxyphenyl)vinyl)benzene **233a** as a compound to elute the first (1.43 g, 46%).

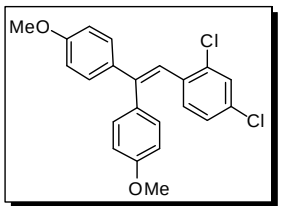
Nature: White solid; **MP:** 73 ^{0}C; **Yield:** 46 %; **^{1}H NMR** (200 MHz, $CDCl_3$)**:** δ 3.83 (s, 3H), 6.91 (d, *J* = 9 Hz, 2H), 7.05 (s, 1H), 7.26 (dd, *J* = 2, 9 Hz, 1H), 7.42 (d, *J* = 2 Hz, 1H), 7.64 (d, *J* = 9 Hz, 2H), 7.83 (d, *J* = 9 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$)**:** δ 55.3, 113.7 (2C), 120.0, 126.6, 128.2 (2C), 129.1, 130.7, 131.4, 132.4, 133.7, 134.6, 134.8, 160.4; **IR** (Chloroform)**:** 1184, 1618 cm^{-1}; **MS** (ESI) *m/z***:** 314.03 (M + 1). **Anal. Calcd. for** $C_{15}H_{11}Cl_3O$**:** C, 57.45; H, 3.54 %. **Found:** C, 57.56; H, 3.41 %.



The compound to elute after **233a** was found to be 4,4'-(2-(2,4-dichlorophenyl)ethene-1,1-diyl)bis(methoxybenzene) **260a**.

4,4'-(2-(2,4-Dichlorophenyl)ethene-1,1-diyl)bis(methoxybenzene) (260a)

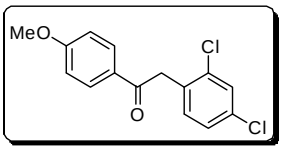
Nature: White solid; **MP:** 88 ^{0}C; **Yield:** 10 %; **^{1}H NMR** (200 MHz, $CDCl_3$)**:** δ 3.80 (s, 3H), 3.82 (s, 3H), 6.74-6.88 (m, 7H), 7.04 (d, *J* = 8 Hz, 2H), 7.28 (d, *J* = 8 Hz, 2H), 7.35 (d, *J* = 2 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$)**:** δ 55.1, 55.3, 113.5 (2C), 113.7 (2C), 121.5, 126.3, 128.9, 129.3 (2C), 131.7 (4C), 132.1, 134.9, 135.1, 135.5, 144.4, 159.0, 159.6; **IR** (Chloroform)**:** 1151, 1606 cm^{-1}; **MS** (ESI) *m/z***:** 386.03 (M + 1). **Anal. Calcd. for** $C_{22}H_{18}Cl_2O_2$**:** C, 68.58; H, 4.71 %. **Found:** C, 68.67; H, 4.63 %.



The compound to elute at last was found to be 2-(2,4-dichlorophenyl)-1-(4-methoxyphenyl)ethanone **251a**.

2-(2,4-Dichlorophenyl)-1-(4-methoxyphenyl)ethanone (251a)

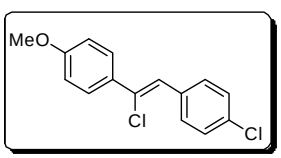
Nature: White solid; **MP:** 94 ^{0}C; **Yield:** 24%; **^{1}H NMR** (200 MHz, $CDCl_3$ + CCl_4)**:** δ 3.83 (s, 3H), 4.31 (s, 2H), 6.86-6.95 (m, 2H), 7.04-7.13 (m, 2H), 7.29 (s, 1H), 7.39 (dd, *J* = 2, 8 Hz, 1H), 7.67 (d, *J* = 8 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$ + CCl_4)**:** δ 44.6, 55.3, 113.8 (2C), 127.0, 127.6, 129.4, 129.6, 129.7, 130.9 (2C), 134.4, 136.8, 163.6, 194.8; **IR** (Chloroform)**:** 1163, 1676 cm^{-1}; **MS** (ESI) *m/z***:** 296.09 (M + 1). **Anal. Calcd. for** $C_{15}H_{12}Cl_2O_2$**:** C, 61.04; H, 4.10 %. **Found:** C, 61.17; H, 4.00 %.



The following compounds **233b-j** were prepared by using the procedure given for the preparation of compound **233a.**

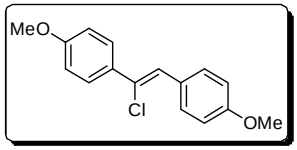
(*Z*)-1-Chloro-4-(2-chloro-2-(4-methoxyphenyl)vinyl)benzene (233b)

Nature: White solid; **MP:** 97 ^{0}C; Yield: 52 %; **^{1}H NMR** (200 MHz, $CDCl_3$ + CCl_4)**:** δ 3.83 (s, 3H), 6.87-6.91 (m, 3H), 7.33 (d, *J* = 8 Hz, 2H) 7.58-7.66 (m, 4H); **^{13}C NMR** (50 MHz, $CDCl_3$ + CCl_4)**:** δ 55.2, 113.7 (2C), 123.0, 128.0 (2C), 128.4 (2C), 130.6 (2C), 131.4, 132.6, 133.3, 133.9, 160.2; **IR** (Chloroform): 1182, 1612 cm^{-1}; **MS** (ESI) *m/z***:** 302.02 (M + Na). **Anal. Calcd. for** $C_{15}H_{12}Cl_2O$**:** C, 64.54; H, 4.33 %. **Found:** C, 64.46; H, 4.48 %.



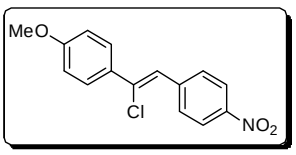
(*Z*)-4,4'-(1-Chloroethene-1,2-diyl)bis(methoxybenzene) (233c):

Nature: White solid; **MP:** 110 ^{0}C; Yield: 54 %; **^{1}H NMR** (200 MHz, $CDCl_3$)**:** δ 3.81 (s, 6H), 6.87-6.93 (m, 5H), 7.60 (d, *J* = 8 Hz, 2H) 7.69 (d, *J* = 8 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 55.1, 55.2, 113.6 (4C), 123.9, 127.8 (2C), 128.0, 129.7, 130.7 (2C), 131.9, 158.9, 159.7; **IR** (Nujol)**:** 1180, 1298, 1604 cm^{-1}; **MS** (ESI) *m*/*z***:** 297.02 (M + Na). **Anal. Calcd. for** $C_{16}H_{15}ClO_2$**:** C, 69.95; H, 5.50 %. **Found:** C, 69.85; H, 5.59 %.



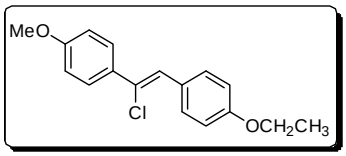
(*Z*)-1-(2-Chloro-2-(4-methoxyphenyl)vinyl)-4-nitrobenzene (233d)

Nature: Yellow solid; **MP:** 95 ^{0}C; Yield: 55 %; **^{1}H NMR** (200 MHz, $CDCl_3$)**:** δ 3.84 (s, 3H), 6.86 (d, *J* = 8 Hz, 2H), 6.99 (s, 1H), 7.63 (d, *J* = 8 Hz, 2H), 7.83 (d, *J* = 8 Hz, 2H), 8.20 (d, *J* = 8 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$)**:** δ 55.4, 113.8 (2C), 122.1, 123.5 (2C), 128.2 (2C), 129.9 (2C), 130.8, 135.9, 142.0, 146.4, 160.7; **IR** (Chloroform)**:** 1033, 1612 cm^{-1}; **MS** (ESI) *m*/*z***:** 312.08 (M + Na). **Anal. Calcd. for** $C_{15}H_{12}ClNO_3$**:** C, 62.19; H, 4.17; N, 4.83 %. **Found:** C, 62.07; H, 4.30; N, 4.97 %.



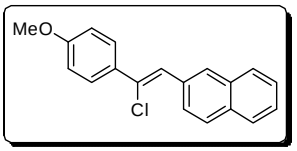
(*Z*)-1-(1-Chloro-2-(4-ethoxyphenyl)vinyl)-4-methoxybenzene (233e)

Nature: White solid; **MP:** 88 ^{0}C; **Yield:** 53 %; **^{1}H NMR** (200 MHz, $CDCl_3$)**:** δ 1.47 (t, *J* = 8 Hz, 3H), 3.86 (s, 3H), 4.08 (q, *J* = 8 Hz, 2H), 6.92-6.97 (m, 5H), 7.65 (d, *J* = 8 Hz, 2H), 7.74 (d, *J* = 8 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$)**:** δ 14.7, 55.2, 63.3, 113.6 (2C), 114.1 (2C), 123.9, 127.7 (2C), 127.8, 129.6, 130.7 (2C), 132.0, 158.4, 159.7; **IR** (Chloroform)**:** 1116, 1609 cm^{-1}; **MS** (ESI) *m*/*z***:** 289.03 (M + 1). **Anal. Calcd. for** $C_{17}H_{17}ClO_2$**:** C, 70.71; H, 5.93 %. **Found:** C, 70.87; H, 5.78 %.



(*Z*)-1-(2-Chloro-2-(4-methoxyphenyl)vinyl)naphthalene (233f)

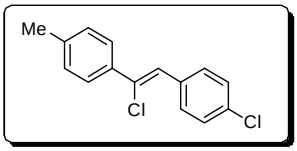
Nature: White solid; **MP:** 86 ^{0}C; **Yield:** 50 %; **^{1}H NMR** (200 MHz, $CDCl_3$)**:** δ 3.90 (s, 3H), 7.01 (d, *J* = 8 Hz, 2H), 7.53-7.62 (m, 4H), 7.80 (d, *J* = 8 Hz, 2H), 7.87-8.08 (m, 4H); **^{13}C NMR** (50 MHz, $CDCl_3$)**:** δ 55.3, 113.7 (2C), 122.3, 124.4, 125.2, 125.8, 126.1, 127.1, 128.1 (2C), 128.5,



129.3, 131.0, 131.6, 132.8, 133.4, 134.5, 160.1; **IR** (Chloroform)**:** 1084, 1616 cm^{-1}; **MS** (ESI) *m*/*z***:** 295.11 (M + 1). **Anal. Calcd. for** $C_{19}H_{15}ClO$**:** C, 77.42; H, 5.13 %. **Found:** C, 77.28; H, 5.26 %.

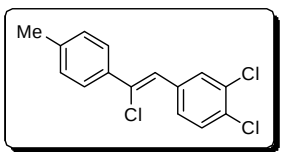
(*Z*)-1-Chloro-4-(2-chloro-2-p-tolylvinyl)benzene (233g)

Nature: White solid; **MP:** 97 ^{0}C; **Yield:** 54 %; **^{1}H NMR** (200 MHz, $CDCl_3$ + CCl_4)**:** δ 2.46 (s, 3H), 7.03 (s, 1H), 7.27 (d, *J* = 8 Hz, 2H), 7.42 (d, *J* = 8 Hz, 2H), 7.65 (d, *J* = 8 Hz, 2H), 7.73 (d, *J* = 8 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$)**:** δ 21.1, 123.9, 126.5 (2C), 128.4 (2C), 129.1 (2C), 130.6 (2C), 132.8, 133.4, 133.8, 136.1, 139.0; **IR** (Chloroform)**:** 1610 cm^{-1}; **MS** (ESI) *m*/*z***:** 264.03 (M + 1). **Anal. Calcd. for** $C_{15}H_{12}Cl_2$**:** C, 68.46; H, 4.60 %. **Found:** C, 68.51; H, 4.48 %.



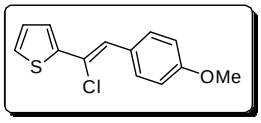
(*Z*)-1,2-Dichloro-4-(2-chloro-2-*p*-tolylvinyl)benzene (233h)

Nature: White solid; **MP:** 115 ^{0}C; **Yield:** 54 %; **^{1}H NMR** (200 MHz, $CDCl_3$ + CCl_4)**:** δ 2.48 (s, 3H), 6.95 (s, 1H), 7.26 (d, *J* = 8 Hz, 2H), 7.49 (d, *J* = 8 Hz, 1H), 7.58- 7.65 (m, 3H), 7.90 (d, *J* = 2 Hz, 1H); **^{13}C NMR** ((50 MHz, $CDCl_3$ + CCl_4)**:** δ 21.2, 122.6, 126.5 (2C), 128.5, 129.1 (2C), 130.0, 131.0, 131.5, 132.4, 134.2, 135.2, 135.7, 139.2; **IR** (Chloroform)**:** 1604 cm^{-1}; **MS** (ESI) *m*/*z***:** 298.02 (M + 1). **Anal. Calcd. for** $C_{15}H_{11}Cl_3$**:** C, 60.54; H, 3.73 %. **Found:** C, 60.42; H, 3.49 %.



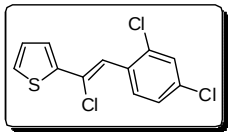
(*Z*)-2-(1-Chloro-2-(4-methoxyphenyl)vinyl)thiophene (233i)

Nature: Brown sticky solid; **Yield:** 28 %; **^{1}H NMR** (200 MHz, $CDCl_3$)**:** δ 3.82 (s, 3H), 6.91 (d, *J* = 8 Hz, 2H), 6.98-7.07 (m, 2H), 7.23 (dd, *J* = 2, 5 Hz, 1H), 7.34 (dd, *J* = 2, 5 Hz, 1H), 7.70 (d, *J* = 8 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$)**:** δ 55.2, 113.7 (2C), 123.7, 125.4, 125.5, 127.3, 127.4, 130.0, 130.9 (2C), 143.3, 159.3; **IR** (Chloroform)**:** 1051, 1606 cm^{-1}; **MS** (ESI) *m*/*z***:** 251.06 (M + 1).



(*Z*)-2-(1-Chloro-2-(2,4-dichlorophenyl)vinyl)thiophene (233j)

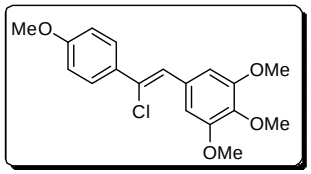
Nature: Pale yellow solid; **MP:** 74 ^{0}C; Yield: 25 %; **^{1}H NMR** (200 MHz, $CDCl_3$)**:** δ 7.04-



7.09 (m, 1H), 7.23 (s, 1H), 7.27-7.36 (m, 2H), 7.43-7.46 (m, 2H), 7.87 (d, *J* = 8 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$)**:** δ 119.6, 126.7 (2C), 126.9, 127.6, 128.2, 129.2, 131.3, 131.6, 134.0, 134.7, 142.1; **IR** (Chloroform)**:** 1610 cm^{-1}; **MS** (ESI) *m*/*z***:** 290.07 (M + 1). **Anal. Calcd. for** $C_{12}H_7Cl_3S$**:** C, 49.77; H, 2.44 %. **Found:** C, 49.81; H, 2.33 %.

(*Z*)-5-(2-Chloro-2-(4-methoxyphenyl)vinyl)-1,2,3-trimethoxybenzene (233k)

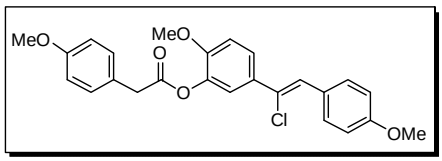
Nature: White solid; **MP:** 93.5 ^{0}C; Yield: 58 %; **^{1}H NMR** (500 MHz, $CDCl_3$)**:** δ 3.86 (s,



3H), 3.90 (s, 3H), 3.91 (s, 6H), 6.91 (s, 1H), 6.93 (d, *J* = 8 Hz, 2H), 7.02 (s, 2H), 7.63 (d, *J* = 8 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$)**:** δ 55.3, 56.0 (2C), 60.8, 106.6 (2C), 113.6 (2C), 124.2, 127.9 (2C), 129.3, 130.8, 131.1, 131.7, 137.7, 152.8, 159.9; **IR** (Chloroform)**:** 1033, 1611 cm^{-1}; **MS** (ESI) *m*/*z***:** 357.03 (M + Na). **Anal. Calcd. for** $C_{18}H_{19}ClO_4$**:** C, 64.57; H, 5.72 %. **Found:** C, 64.64; H, 5.60 %.

(*Z*)-5-(1-Chloro-2-(4-methoxyphenyl)vinyl)-2-methoxyphenyl 2-(4-methoxyphenyl)acetate (263a)

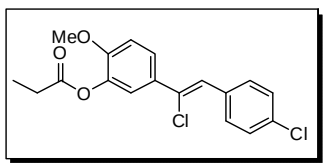
Nature: White solid; **MP:** 122 ^{0}C; **Yield:** 68 %; **^{1}H NMR** (200 MHz, $CDCl_3$)**:** δ 3.73 (s,



3H), 3.74 (s, 3H), 3.76 (s, 3H), 3.80 (s, 2H), 6.82-6.90 (m, 6H), 7.28 (d, *J* = 9 Hz, 2H), 7.32 (s, 1H), 7.46 (dd, *J* = 2, 9 Hz, 1H), 7.64 (d, *J* = 9 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$)**:** δ 39.8, 55.1 (2C), 55.8, 111.8, 113.5 (2C), 113.8 (2C), 120.9, 124.5, 124.9, 125.4, 127.7, 128.5, 130.3 (2C), 130.7 (2C), 132.1, 139.4, 151.1, 158.6, 159.0, 169.7; **IR** (Chloroform)**:** 1018, 1627, 1768 cm^{-1}; **MS** (ESI) *m*/*z***:** 439.21 (M + 1).

(*Z*)-5-(1-Chloro-2-(4-chlorophenyl)vinyl)-2-methoxyphenyl 2-(4- chlorophenyl)acetate (263b)

Nature: White solid; **MP:** 107 ^{0}C; **Yield:** 70 %; **^{1}H NMR** (200 MHz, $CDCl_3$)**:** δ 1.28 (t, *J* =

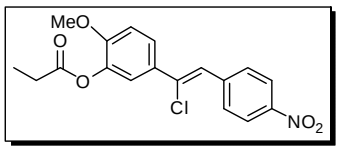


8 Hz, 3H), 2.60 (q, *J* = 8 Hz, 2H), 3.81 (s, 3H), 6.15 (d, *J* = 8 Hz, 2H), 6.92 (s, 1H), 7.55 (dd, *J* = 2, 9 Hz, 1H) 7.84 (d, *J* = 8 Hz, 2H), 8.22 (d, *J* = 8 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$)**:** δ 8.7,

27.4, 56.2, 112.1, 121.3, 122.5, 123.8 (2C), 124.9, 130.3 (2C), 131.2, 134.8, 139.2, 142.1, 146.1, 152.2, 172.3; **IR** (Chloroform)**:** 1124, 1613, 1765 cm^{-1}; **MS** (ESI) *m*/*z***:** 352.08 (M + 1).

(*Z*)-5-(1-Chloro-2-(4-nitrophenyl)vinyl)-2-methoxyphenyl propionate (263c)

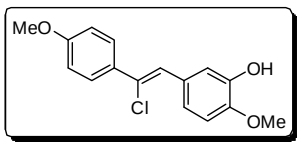
Nature: Yellow sticky solid; **Yield:** 71 %; **^{1}H NMR** (200 MHz, $CDCl_3$)**:** δ 1.30 (t, *J* = 8 Hz, 3H), 2.65 (q, *J* = 8 Hz, 2H), 3.88 (s, 3H), 6.10 (d, *J* = 9 Hz, 1H), 7.03 (s, 1H), 7.42 (d, *J* = 2 Hz, 1H), 7.58 (dd, *J* = 2, 9 Hz, 1H), 7.85 (d, *J* = 9 Hz, 2H), 8.23 (d, *J* = 9 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$)**:** δ 9.0, 27.2, 56.0, 111.9, 121.4, 122.7, 123.5 (2C), 125.3, 129.9 (2C), 130.9, 134.8, 139.5, 141.7, 146.5, 152.2, 172.4; **IR** (Chloroform)**:** 1164, 1633, 1760 cm^{-1}; **MS** (ESI) *m*/*z***:** 362.07 (M + 1).



The following compounds **264a-c** were obtained by the hydrolysis of compounds **263a-c** using 10% NaOH in methanol.

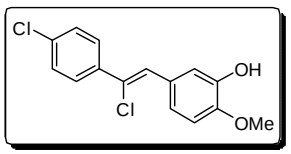
(*Z*)-5-(1-Chloro-2-(4-methoxyphenyl)vinyl)-2-methoxyphenol (264a)

Nature: Brown sticky solid; **Yield:** 52 %; **^{1}H NMR** (200 MHz, $CDCl_3$)**:** δ 3.80 (s, 3H), 3.85 (s, 3H), 5.69 (bs, 1H), 6.84-6.96 (m, 3H), 7.19-7.29 (m, 3H), 7.71 (d, *J* = 8 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$)**:** δ 55.2, 56.0, 110.1, 112.8, 119.3, 123.5, 127.9 (2C), 129.8, 130.7 (2C), 132.6, 133.8, 137.8, 145.4, 147.8; **IR** (Chloroform)**:** 1031, 1612, 3516 cm^{-1}; **MS** (ESI) *m*/*z***:** 291.21 (M + 1).



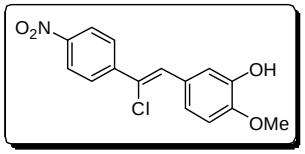
(*Z*)-5-(1-Chloro-2-(4-chlorophenyl)vinyl)-2-methoxyphenol (264b)

Nature: Off-white solid; **MP:** 54 ^{0}C; **Yield:** 54 %; **^{1}H NMR** (200 MHz, $CDCl_3$)**:** δ 3.85 (s, 3H), 5.63 (bs, 1H), 6.77 (d, *J* = 8 Hz, 1H), 6.84 (s, 1H), 7.14 (dd, *J* = 2, 8 Hz, 1H), 7.21 (d, *J* = 2 Hz, 1H), 7.27 (d, *J* = 8 Hz, 2H) 7.57 (d, *J* = 8 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$)**:** δ 55.9, 110.1, 112.8, 118.8, 123.4, 128.3 (2C), 128.8, 130.6 (2C), 132.2, 133.2, 133.8, 145.2, 147.1; **IR** (Chloroform)**:** 1091, 1618, 3537 cm^{-1}; **MS** (ESI) *m*/*z***:** 295.97 (M + 1). **Anal. Calcd. for** $C_{15}H_{12}Cl_2O_2$**:** C, 61.04; H, 4.10 %. **Found:** C, 61.19; H, 4.27 %.



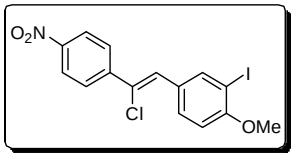
(*Z*)-5-(1-Chloro-2-(4-nitrophenyl)vinyl)-2-methoxyphenol (264c)

Nature: Pale yellow solid; **MP:** 73 ^{0}C; **Yield:** 53 %; **^{1}H NMR** (200 MHz, $CDCl_3$)**:** δ 3.93 (s, 3H), 5.67 (bs, 1H), 6.86 (d, *J* = 8 Hz, 1H), 7.00 (s, 1H), 7.23 (dd, *J* = 2, 6 Hz, 1H), 7.26 (d, *J* = 2 Hz, 1H), 7.84 (d, *J* = 8 Hz, 2H), 8.22 (d, *J* = 8 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$)**:** δ 56.0, 110.2, 113.0, 119.2, 122.4, 123.5 (2C), 129.3, 129.9 (2C), 131.7, 135.7, 141.9, 145.4, 147.7; **IR** (Chloroform)**:** 1030, 1606, 3531 cm^{-1}; **MS** (ESI) *m*/*z***:** 306.05 (M + 1). **Anal. Calcd. for** $C_{15}H_{12}ClNO_4$**:** C, 58.93; H, 3.96 %. **Found:** C, 58.81; H, 4.09 %.



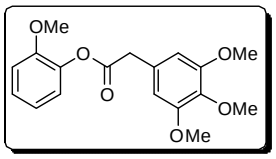
(*Z*)-4-(1-Chloro-2-(4-nitrophenyl)vinyl)-2-iodo-1-methoxybenzene (264d)

Nature: Yellow solid; **MP:** 90 ^{0}C; **Yield:** 63 %; **^{1}H NMR** (200 MHz, $CDCl_3$)**:** δ 3.95 (s, 3H), 6.86 (d, *J* = 8 Hz, 1H), 7.02 (s, 1H), 7.69 (dd, *J* = 2, 8 Hz, 1H), 7.87 (d, *J* = 8 Hz, 2H), 8.14 (d, *J* = 2 Hz, 1H), 8.26 (d, *J* = 8 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$)**:** δ 55.5, 85.9, 110.2, 122.9, 123.5 (2C), 123.6, 128.3, 129.3, 129.9 (2C), 137.6, 139.8, 146.5, 159.0; **IR** (Chloroform)**:** 1049, 1618 cm^{-1}; **MS** (ESI) *m*/*z***:** 438.20 (M + Na).



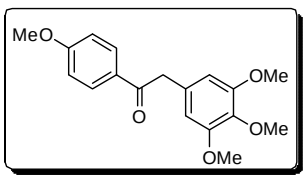
2-Methoxyphenyl 2-(3,4,5-trimethoxyphenyl)acetate (265)

Nature: Brown sticky solid; **Yield:** 66 %; **^{1}H NMR** (200 MHz, $CDCl_3$)**:** δ 3.77 (s, 3H), 3.83 (s, 2H), 3.85 (s, 3H), 3.87 (s, 6H), 6.64 (s, 2H), 6.88-7.05 (m, 3H), 7.15-7.24 (m, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$)**:** δ 40.8, 55.5, 55.8 (3C), 60.6, 106.2 (2C), 112.2, 120.5, 122.4, 126.7, 136.8, 139.5, 150.8, 152.9 (2C), 169.3; **IR** (Chloroform)**:** 1144, 1628, 1761 cm^{-1}; **MS** (ESI) *m*/*z***:** 333.07 (M + 1).



1-(4-Methoxyphenyl)-2-(3,4,5-trimethoxyphenyl)ethanone (251b)

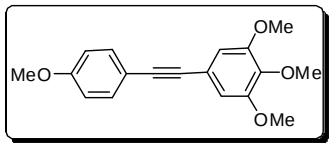
Nature: White solid; **MP:** 83 ^{0}C; **Yield:** 22 %; **^{1}H NMR** (400 MHz, $CDCl_3$)**:** δ 3.83 (s, 3H), 3.84 (s, 6H), 3.88 (s, 3H), 4.18 (s, 2H), 6.49 (s, 2H), 6.95 (d, *J* = 9 Hz, 2H), 8.01 (d, *J* = 9 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$)**:** δ 45.4, 55.4, 56.0 (2C), 60.7, 106.2 (2C), 113.7 (2C), 129.4, 130.4, 130.8 (2C), 132.2, 136.6, 153.2, 163.5, 196.1; **IR** (Chloroform)**:** 1128, 1605, 1678 cm^{-1}; **MS** (ESI) *m*/*z***:** 317.07 (M + 1).



Preparation of 1,2,3-trimethoxy-5-((4-methoxyphenyl)ethynyl)benzene (257a)

To a stirred solution of (*Z*)-5-(2-chloro-2-(4-methoxyphenyl)vinyl)-1,2,3-trimethoxybenzene **233k** (500 mg , 1.49 mmol) in dry THF (20 mL), was added n-BuLi (2.35 m, 0.89 mL, 2.09 mmol) drop wise at room temperature under nitrogen atmosphere. The reaction mixture was allowed to stir at same temperature for two hours, quenched with saturated solution of ammonium chloride (5 mL), the THF was evaporated *in vacuo* and the mixture was extracted with ethyl acetate. The organic layer was dried over Na_2SO_4 and concentrated to get the pure compound 1,2,3-trimethoxy-5-((4-methoxyphenyl)ethynyl)benzene **257a** as white sticky solid (404 mg, 90%).

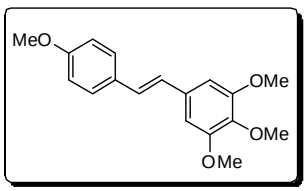
Nature: White sticky solid; **Yield:** 90 %; **^{1}H NMR** (200 MHz, $CDCl_3$)**:** δ 3.83 (s, 3H), 3.87 (s, 3H), 3.88 (s, 6H), 6.76 (s, 2H), 6.88 (d, *J* = 9 Hz, 2H), 7.47 (d, *J* = 9 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$)**:** δ 55.2, 56.1 (2C), 60.9, 80.0, 88.4, 108.5 (2C), 113.9 (2C), 115.1, 118.5, 132.9 (2C), 138.5, 153.0 (2C), 159.5; **IR** (Chloroform)**:** 1107, 1604, 2247 cm^{-1}; **MS** (ESI) *m*/*z***:** 299.03 (M + 1).



Preparation of (*E*)-1,2,3-trimethoxy-5-(4-methoxystyryl)benzene (DMU-212) (226)

A mixture of (*Z)*-5-(2-chloro-2-(4-methoxyphenyl)vinyl)-1,2,3-trimethoxybenzene **233k** (334 mg, 1 mmol), 2,2'-azobis (3-methylpropionitrile) (AIBN, 20 mg) and tri-n-butyltin hydride (436 mg, 1.5 mmol) in dry toluene was refluxed for one hour under nitrogen atmosphere. After cooling, the toluene was evaporated *in vacuo* and extracted with ethyl acetate (3 x 10 mL). The combined organic extracts were dried over Na_2SO_4, concentrated and then the residual syrup was washed with pet ether to remove the excess of tri-n-butyltin hydride. The traces of pet ether were removed under vacuum to get the pure (*E*)-1,2,3-trimethoxy-5-(4-methoxystyryl)benzene (DMU-212) **226** as white solid (293 mg, 88%).

Nature: White solid; **MP:** 158 ^{0}C; Yield: 88 %; **^{1}H NMR** (400 MHz, $CDCl_3$)**:** δ 3.84 (s, 3H), 3.87 (s, 3H), 3.93 (s, 6H), 6.73 (s, 2H), 6.91 (d, *J* = 16 Hz, 1H), 6.93 (d, *J* = 9 Hz, 2H), 6.98 (d, *J* = 16 Hz, 1H), 7.46 (d, *J* = 9 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$)**:** δ 55.3, 56.0 (2C), 60.9, 103.2 (2C), 114.1 (2C), 126.5, 127.6 (2C), 127.7, 129.9, 133.4,

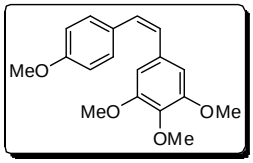


137.5, 153.3 (2C), 159.2; **IR** (Chloroform)**:** 1035, 1606 cm^{-1}; **MS** (ESI) *m*/*z***:** 301.23 (M + 1). **Anal. Calcd. for** $C_{18}H_{20}O_4$**:** C, 71.98; H, 6.71 %. **Found:** C, 71.87; H, 6.83 %.

Preparation of (*Z*)-1,2,3-trimethoxy-5-(4-methoxystyryl)benzene (230)

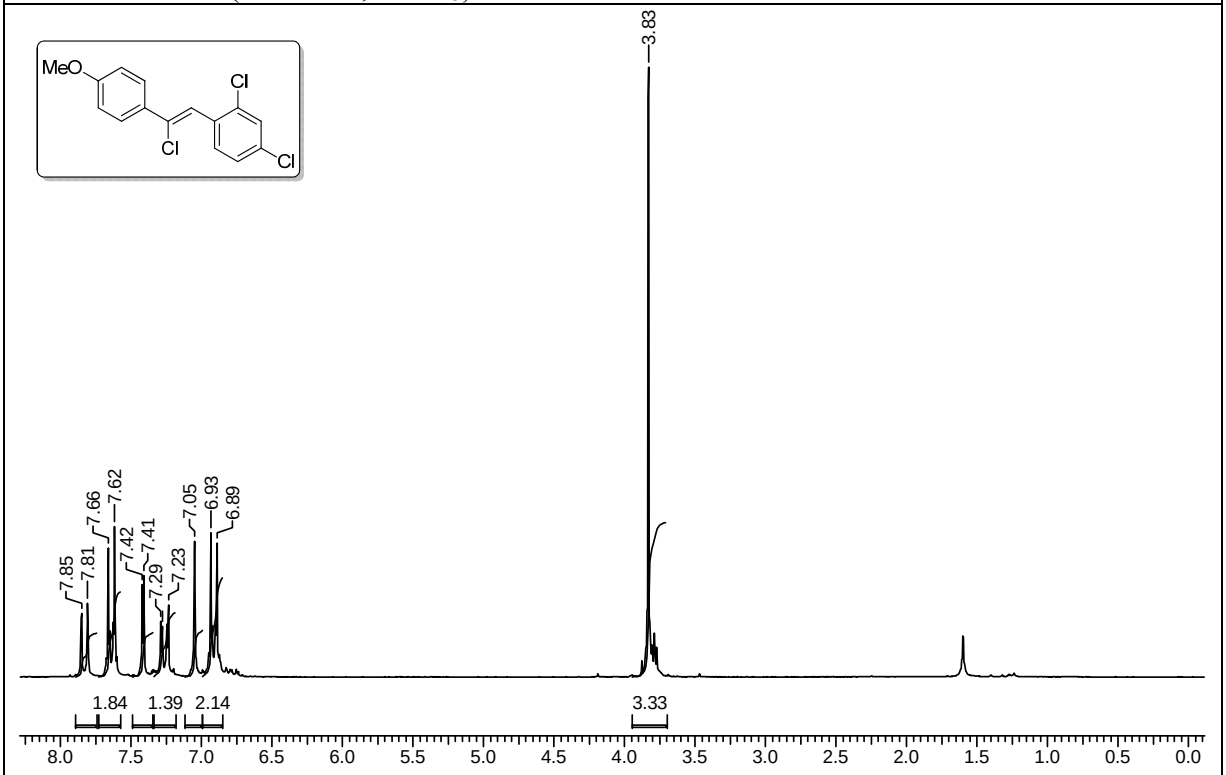
To a solution of 1,2,3-trimethoxy-5-((4-methoxyphenyl)ethynyl)benzene **257a** (100 mg, 0.335 mmol) in dry ethyl acetate (10 mL), was added quinoline (116 mg, 0.90 mmol) and Lindlar catalyst (10% by weight, 10 mg). The solution was stirred at room temperature under a hydrogen atmosphere for two hours and filtered through celite. It was then concentrated and purified by column chromatography to give (*Z*)-1,2,3-trimethoxy-5-(4-methoxystyryl)benzene **230** as colourless thick liquid (72 mg, 72%).

Nature: Colourless thick liquid; **Yield:** 72 %; **^{1}H NMR** (200 MHz, $CDCl_3$)**:** δ 3.69 (s, 6H), 3.79 (s, 3H), 3.84 (s, 3H), 6.41 (d, *J* = 12 Hz, 1H), 6.51 (s, 2H), 6.52 (d, *J* = 12 Hz, 1H), 6.79 (d, *J* = 9 Hz, 2H), 7.24 (d, *J* = 9 Hz, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$)**:** δ 55.2, 55.8 (2C), 60.8, 105.8 (2C), 113.5 (2C), 128.6, 129.4, 129.6, 130.2 (2C), 132.8, 136.9, 152.8 (2C), 158.6; **IR** (Chloroform)**:** 1033, 1611 cm^{-1}; **MS** (ESI) *m*/*z***:** 301.08 (M + 1).

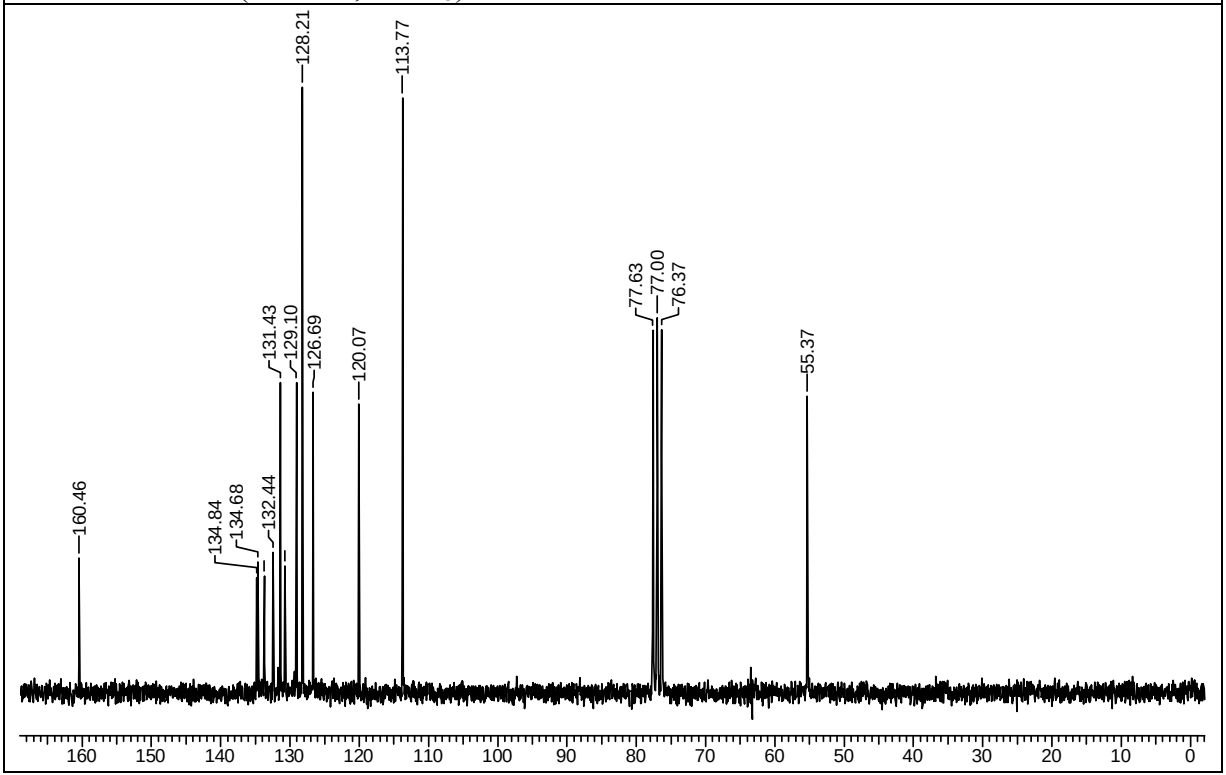


3.3.7 Selected spectra

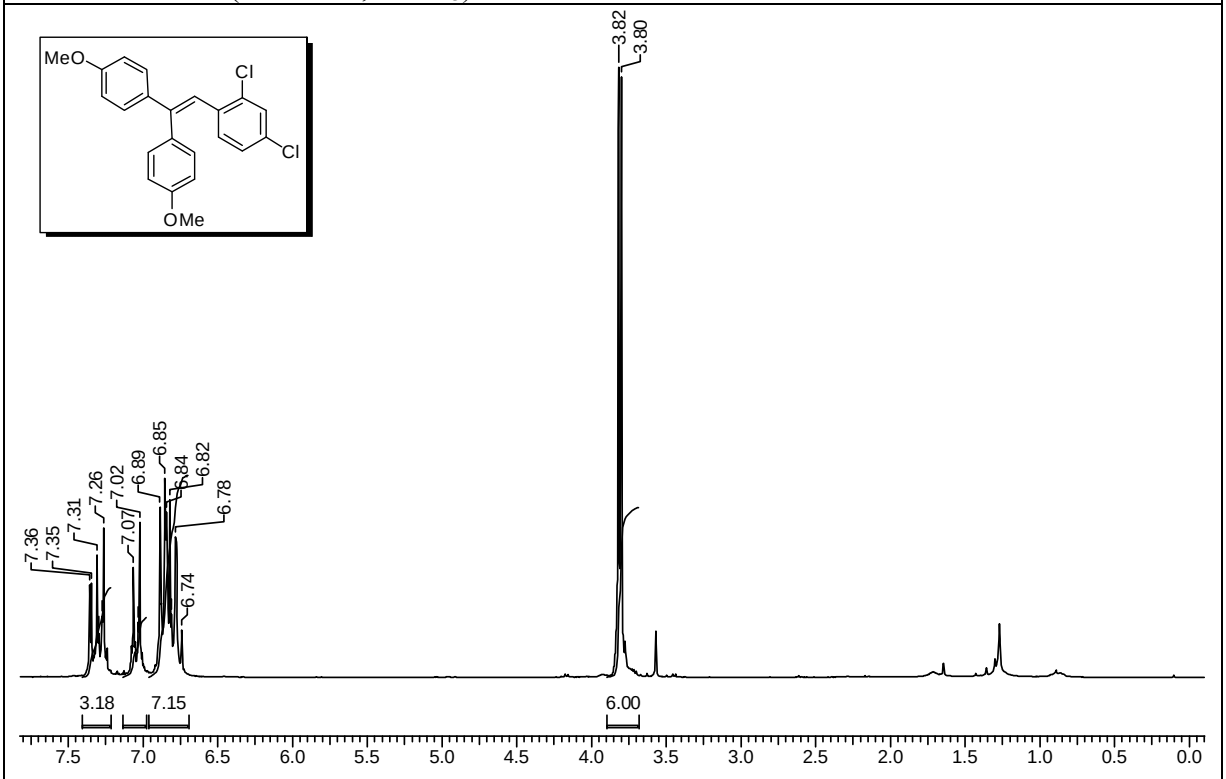
233a: ^{1}H NMR (200 MHz, $CDCl_3$)



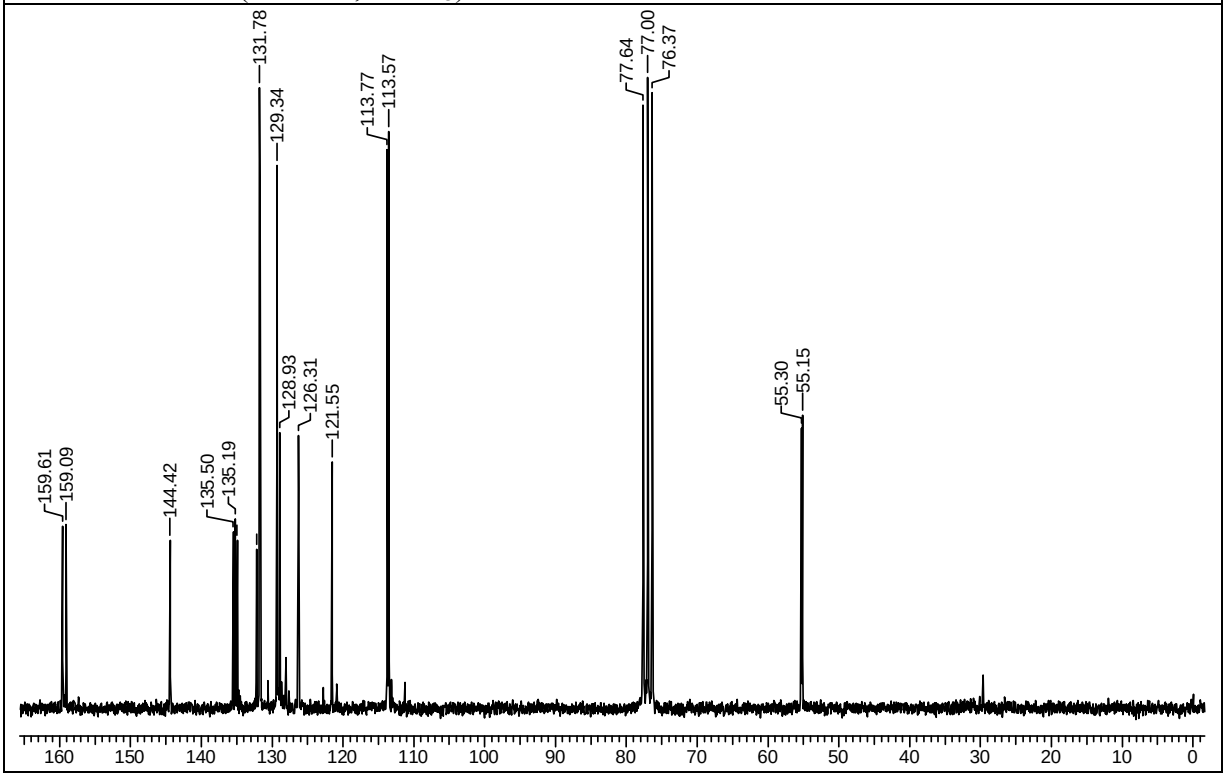
233a: ^{13}C NMR (50 MHz, $CDCl_3$)



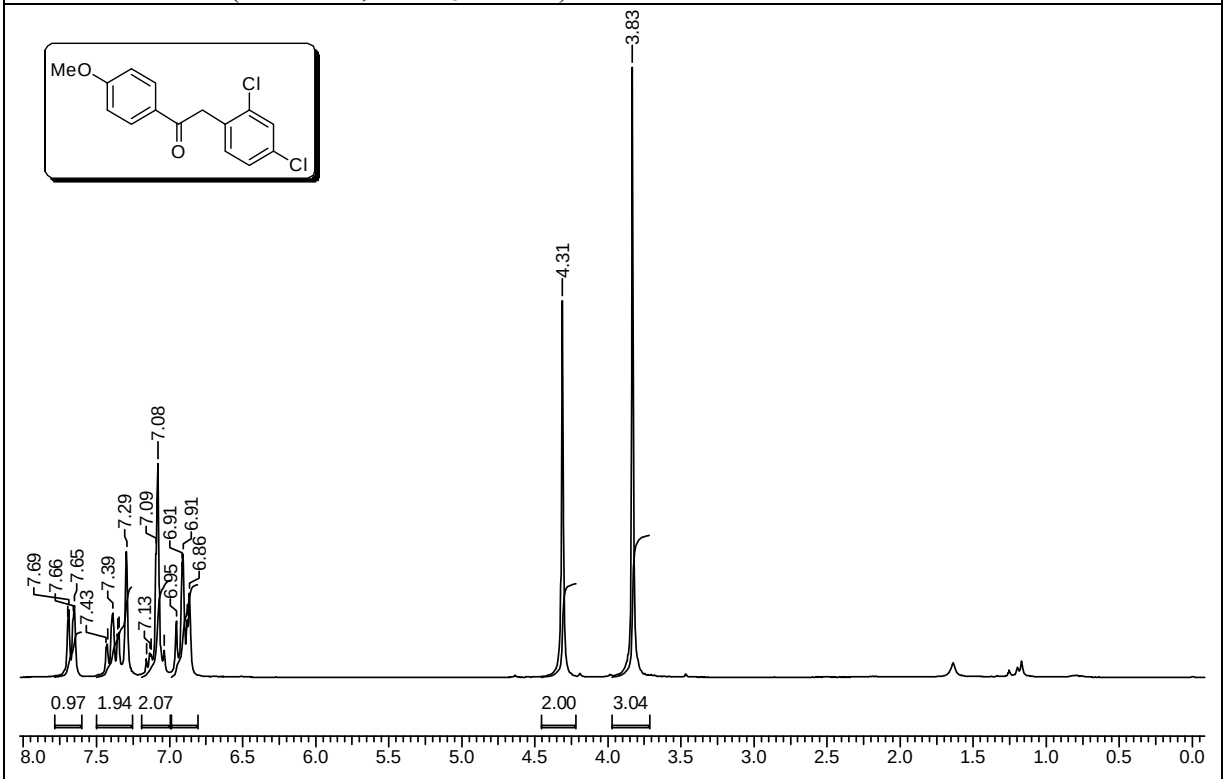
260a: ^{1}H NMR (200 MHz, $CDCl_3$)



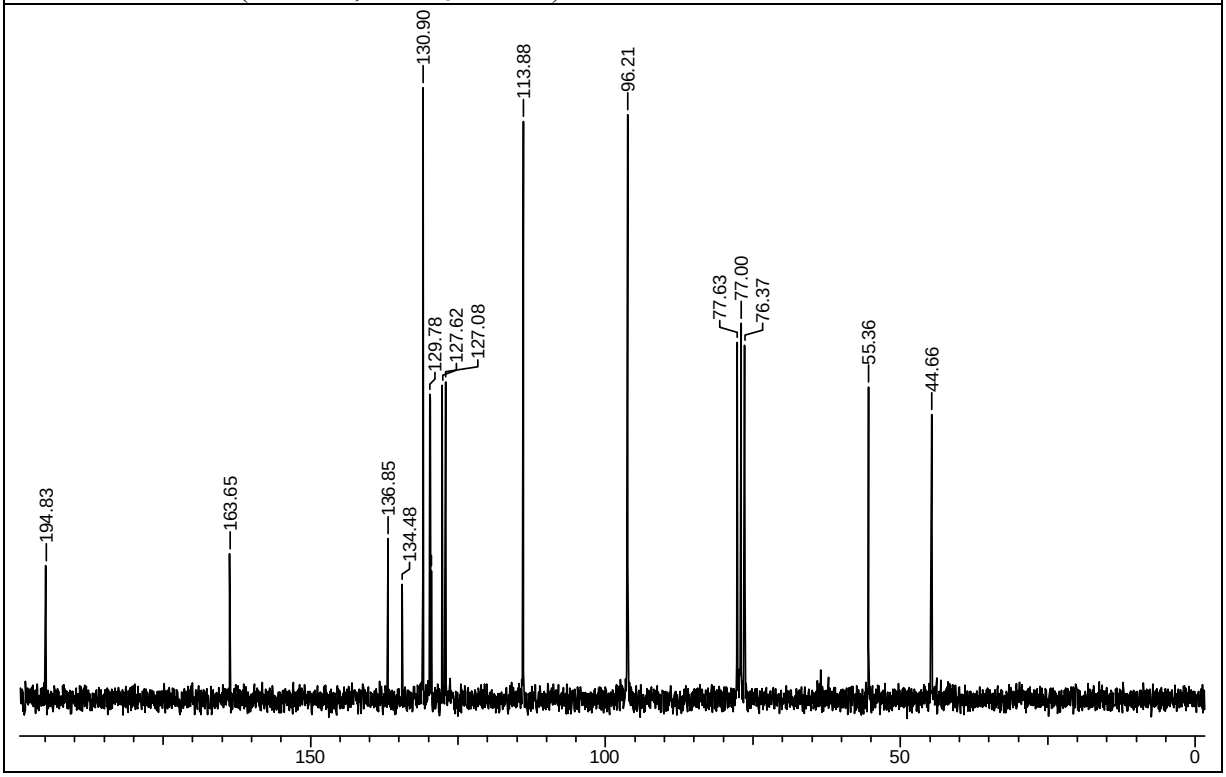
260a: ^{13}C NMR (50 MHz, $CDCl_3$)



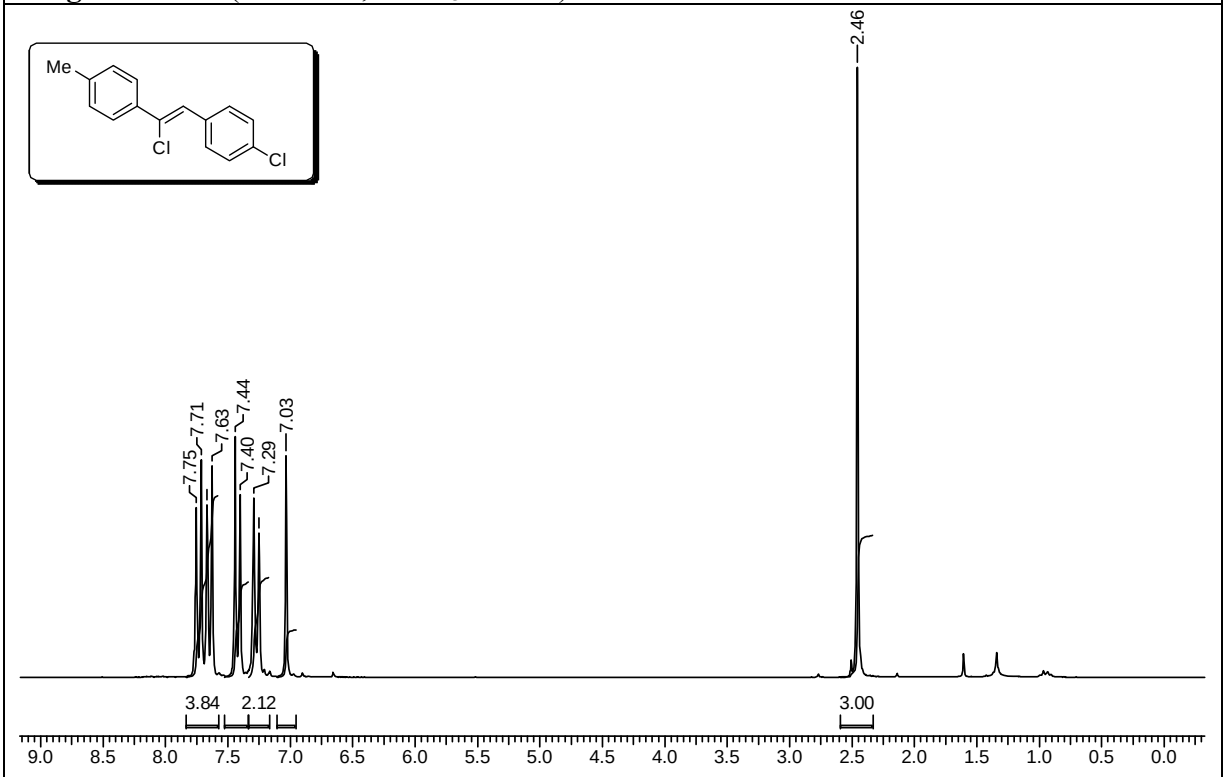
251a: ^{1}H NMR (200 MHz, $CDCl_3$ + CCl_4)



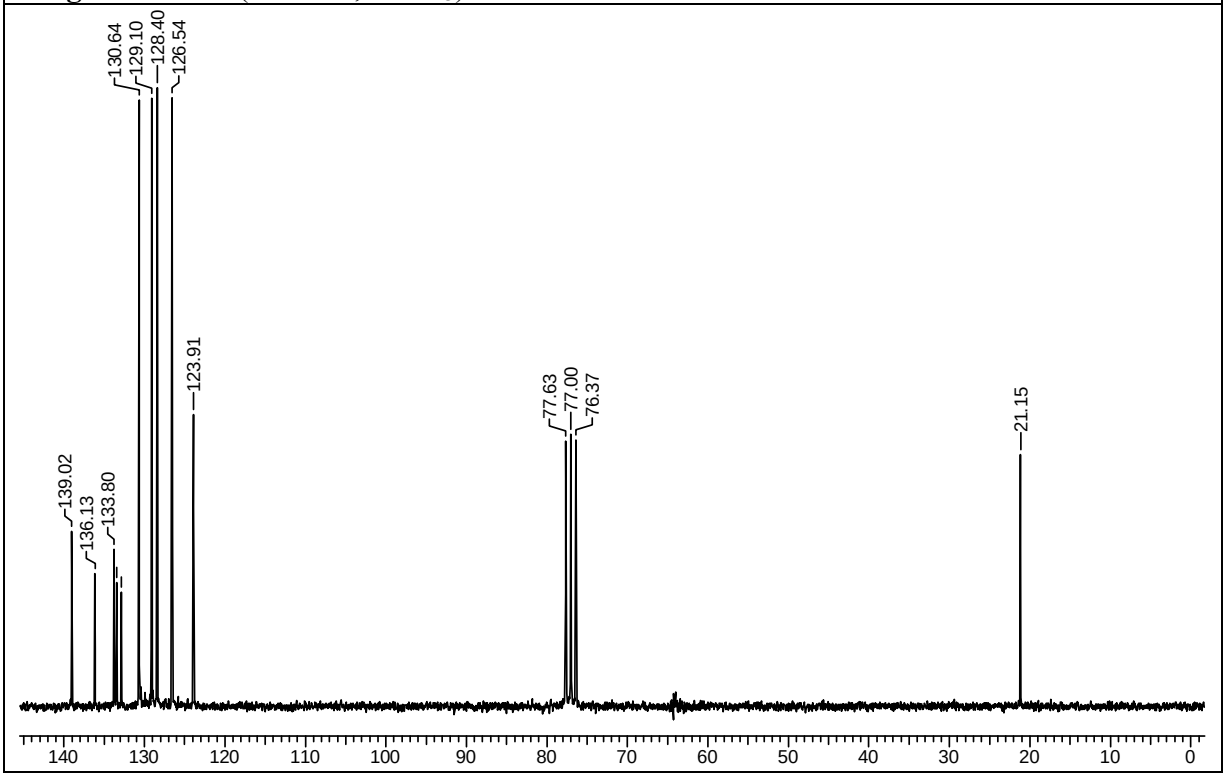
251a: ^{13}C NMR (50 MHz, $CDCl_3$ + CCl_4)



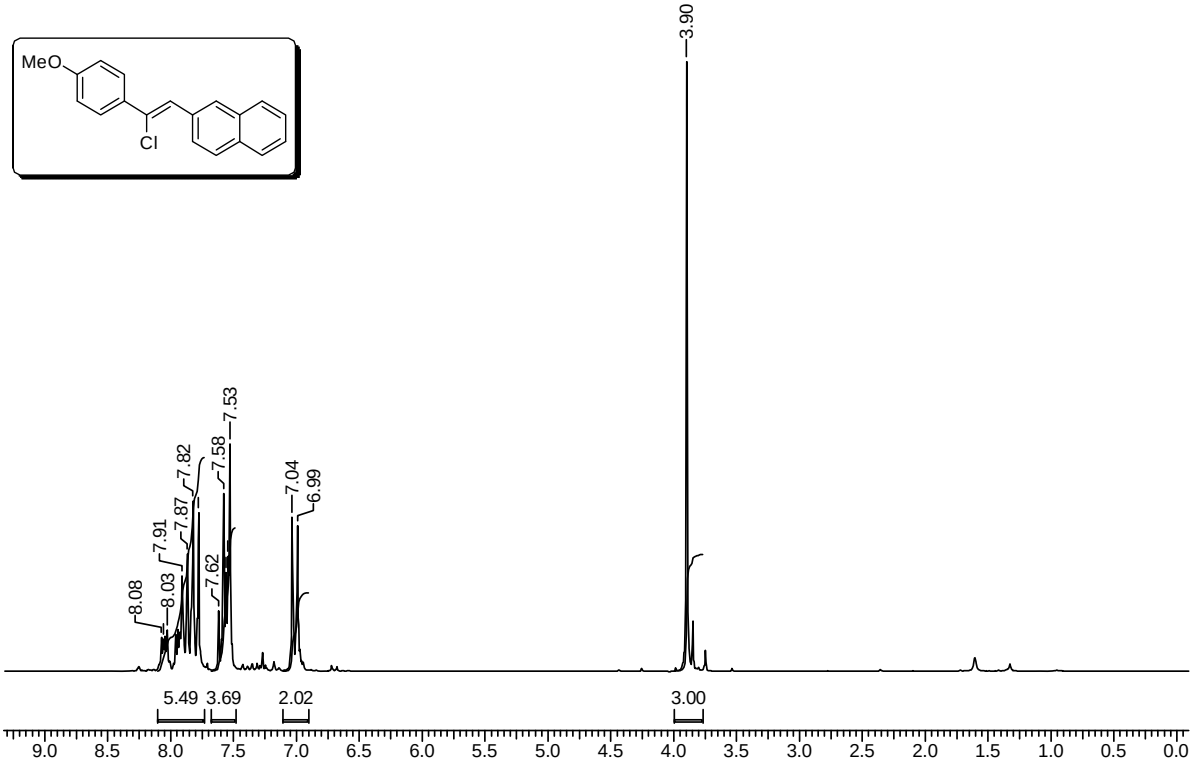
233g: ^{1}H NMR (200 MHz, $CDCl_3$ + CCl_4)



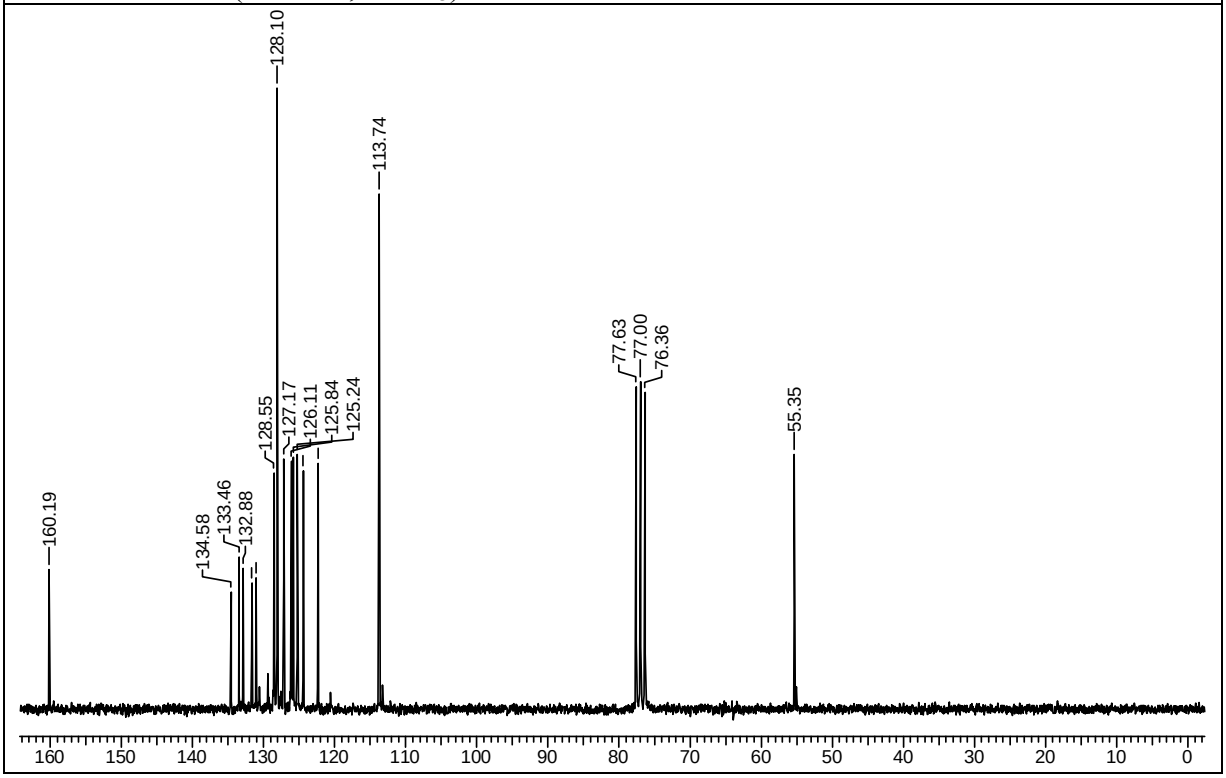
233g: ^{13}C NMR (50 MHz, $CDCl_3$)



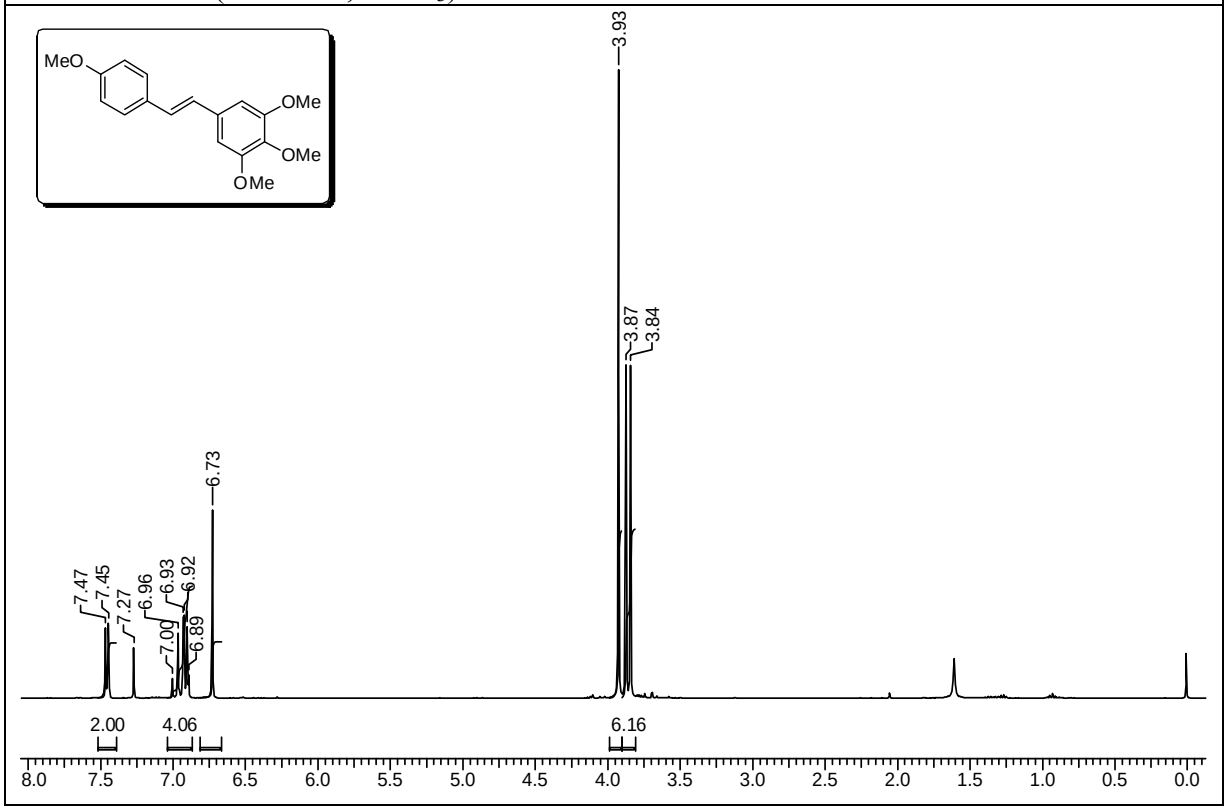
233f: ^{1}H NMR (200 MHz, $CDCl_3$)



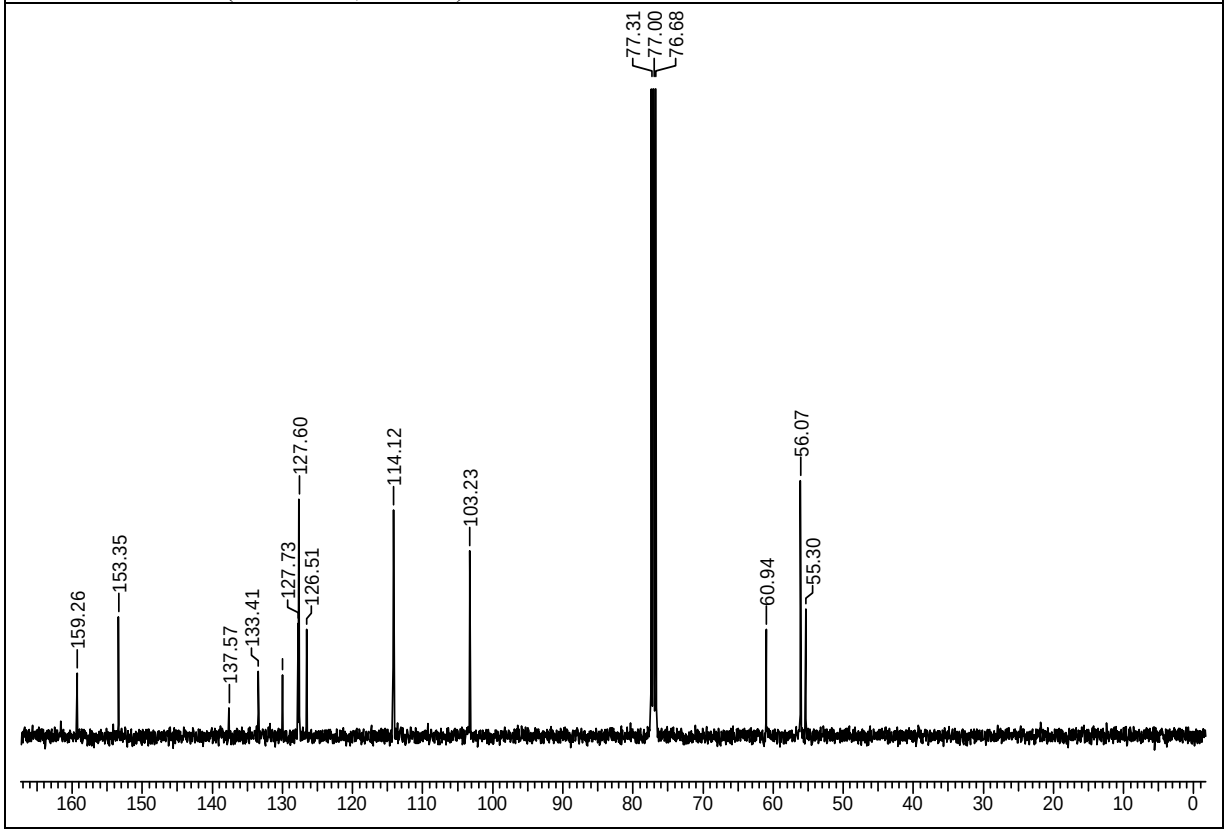
233f: ^{13}C NMR (50 MHz, $CDCl_3$)



226: ^{1}H NMR (400 MHz, $CDCl_3$)



226: ^{13}C NMR (100 MHz, $CDCl_3$)



3.3.8 References

1. (a) Pettit, G. R.; Singh, S. B.; Niven, M. L.; Hamel, E.; Schmidt, J. M. *J. Nat. Prod.* **1987**, *50*, 119-131; (b) Pettit, G. R.; Lippert, J. W.; Herald, D. L.; Hamel, E.; Pettit, R. K. *J. Nat. Prod.* **2000**, *63*, 969-974; (c) Lee, S. K.; Nam, K. A.; Hoe, Y. H.; Min, H.-Y.; Kim, E.-Y.; Ko, H.; Song, S.; Lee, T.; Kim, S. *Arch. Pharm. Res.* **2003**, *26*, 253-257; (d) Lion, C. J.; Matthews, C. S.; Stevens, M. F. G.; Westwell, A. D. *J. Med. Chem.* **2005**, *48*, 1292-1295; (e) Ma, Z.; Molavi, O.; Haddadi, A.; Lai, R.; Gossage, R. A.; Lavasanifar, A. *Cancer Chemother. Pharmacol.* **2008**, *63*, 27-35.
2. Dikshit, A.; Singh, K. P.; Chaudhuri, P. K. *Natl. Acad. Sci. Lett. (India)* **1990**, *13*, 43-48.
3. Kang, S. S. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 719-722.
4. (a) Boonlaksiri, C.; Oonanant, W.; Kongsaeree, P.; Kittakoop, P.; Tanticharoen, M.; Thebtaranonth, Y. *Phytochemistry* **2000**, *54*, 415-417; (b) Matsuda, H.; Tewtrakul, S.; Morikawa, T.; Yoshikawa, M. *Bioorg. Med. Chem.* **2004**, *12*, 4871-4876; (c) Adams, M.; Pacher, T.; Greger, H.; Bauer, R. *J. Nat. Prod.* **2005**, *68*, 83-86; (d) Ferrigni, N. R.; McLaughlin, J. L.; Powell, R. G.; Smith, C. R. *J. Nat. Prod.* **1984**, *47*, 347-352.
5. (a) Mintas, M.; Jakopcic, K.; Klasinc, L. *Z. Naturforsch., B: Anorg. Chem. Org. Chem*. **1977**, *32B*, 181-183; (b) Tsukamoto, M.; Schlosser, M. *Synlett* **1990**, *10*, 605-608.
6. (a) Botella, L.; Najera, C. *Tetrahedron* **2004**, *60*, 5563-5570; (b) Cross, G. G.; Eisnor, C. R.; Gossagea, R. A.; Jenkinsb, H. A. *Tetrahedron Lett.* **2006**, *47*, 2245-2247.
7. (a) Robinson, J. E.; Taylor, R. J. K. *Chem. Commun.* **2007**, *28*,1617-1619; (b) Moro, A. V.; Cardoso, F. S. P.; Correia, C. R. D. *Tetrahedron Lett.* **2008**, *49*, 5668-5671; (c) Alonso, F.; Riente, P.; Yus, M. *Tetrahedron Lett.* **2009**, *50*, 3070-3073.
8. Xu, J.; Xia, J.; Lan, Y. *Syn. Commun.* **2005**, *35*, 2347-2353.
9. Pettit, G. R.; Singh, S. B.; Boyd, M. R.; Hamel, E.; Pettit, R. K.; Schmidt, J. M.; Hogan, F. *J. Med. Chem.* **1995**, *38*, 1666-1672.
10. (a) Cushman, M.; Nagarathnam, D.; Gopal, D.; Chakraborti, A. K.; Lin, C. M.; Hamel, E. *J. Med. Chem.* **1991**, *34*, 2579-2588; (b) Kang, S. S.; Cuendet, M.; Endringer, D. C.; Croy, V. L.; Pezzuto, J. M.; Lipton, M. A. *Bioorg. Med. Chem.* **2009**, *17*, 1044-1054.
11. Borate, H. B.; Gaikwad, A. G.; Maujan, S. R.; Sawargave, S. P.; Kalal, K. M. *Tetrahedron Lett.* **2007**, *48*, 4869-4872.
12. Boutagy, J.; Thomas, R. *Chem. Rev*. **1974**, 74, 87-99.
13. Kumaraswamy, S.; Kumara Swamy, K. C. *Tetrahedron Lett*. **1997**, 38, 2183-2184.

14. Hanack, M.; Weber, E. *Chem. Ber.* **1983**, *116*, 777-797.
15. Kamigata, N.; Satoh, T.; Yoshida, M.; Kobayashi, M. *Chem. Lett.* **1987**, 345-346.
16. Engman, L. *J. Org. Chem.* **1987**, *52*, 4086-4094.
17. Huang, Z. Z.; Lan, G. C.; Haung, X. *Synth*. *Commun*. **1998**, 28, 633-637.
18. Kodomari, M.; Nagaoka, T.; Furusawa, Y. *Tetrahedron Lett.* **2001**, *42*, 3105-3107.
19. Bastock, T. W.; Clark, J. H.; Landon, P.; Martin, K. *J. Chem*. *Res*. (*S*) **1994**, 104-107.
20. (a) Moughamir, K.; Mezgueldi, B.; Atmani, A.; Mestdagh, H.; Rolando, C. *Tetrahedron Lett.* **1999**, *40*, 59-62; (b) Bigler, P.; Muhler, H.; Neuenschwander, M. *Synthesis* **1978**, 593-594.
21. Chen, C.; Wilcoxen, K.; Strack, N.; McCarthy, J. R. *Tetrahedron Lett.* **1999**, *40*, 827-830.
22. Young, W. R.; Aviram, A.; Cox, R. J. *J. Chem. Soc*. **I972,** *94,* 3976-3981.
23. Annamaria, L.; Mikael, P. J.; Kristiina, W. *Org. Lett.* **2003**, *5*, 3387-3390.
24. (a) Velu, S.; Swamy, C. S. *Appl. Catal. A**:** Gen.* **1994**, *119,* 241-252; (b) Cavani, F.; Trifiro, F.; Vaccari, A. *Catal. Today* **1991**, *11,* 173-301; (c) Velu, S.; Sabde, D. P.; Shah, N.; Sivasanker, S. *Chem. Mater.* **1998**, *10,* 3451-3458; (d) Recent catalytic applications of hydrotalcite type anionic clays. in**:** D. Tichit, A. Vacari, (Eds.), *Applied Clay Science* **1998**, *13*, 311-512.
25. Brown, D. R.; Rhodes, C. N. *Thermochim. Acta*. **1997**, *294*, 33-37.
26. Angle, S. R.; Neitzel, M. L. *J. Org. Chem.* **2000,** *65,* 6458-6461.
27. Cushman, M.; Nagarathnam, D.; Gopal, D.; Chakraborti, A. K.; Lin, C. M.; Hamel, E. *J. Med. Chem.* **1991**, *34*, 2579-2588.
28. Hadfield, J. A.; Mcgown, A. T. *Synth. Commun.* **1998**, *28*, 1421-1431.
29. Kumar, P.; Gupta, P. *Eur. J. Org. Chem.* **2008**, *2008*, 1195-1202.

List of publications:

Research papers published/ communicated in peer reviewed international journals

1. "Transesterification of α-haloesters and β-ketoesters over Mg–Al-hydrotalcites (HT)-like anionic Clays''
   Vivek J. Bulbule, Hanumant B. Borate, Yogesh S. Munot, Vishnu H. Deshpande, **Sangmeshwer P. Sawargave**, Abaji G. Gaikwad, *Journal of Molecular Catalysis* **2007**, 276, 158-161.

2. "One-step preparation of α -chlorostyrenes"
   Hanumant B. Borate, Abaji G. Gaikwad, Suleman R. Maujan, **Sangmeshwer P. Sawargave** and Kamalakar M. Kalal, *Tetrahedron Letters* **2007**, *48*, 4869-4872.

3. "A short synthesis of 3,6-disubstituted N-2-thienyl/aryl-indoles"
   Hanumant B. Borate, **Sangmeshwer P. Sawargave**, Suleman R. Maujan *Tetrahedron Letters* **2009**, *50*, 6562-6566.

4. "Fluconazole analogues containing 2*H*-1,4-benzothiazin-3(4*H*)-one or 2*H*-1,4-benzoxazin-3(4*H*)-one moieties, a novel class of anti-Candida agents"
   Hanumant B. Borate, Suleman R. Maujan, **Sangmeshwer P. Sawargave**, Mohan A. Chandavarkar, Sharangi R. Vaiude, Vinay A. Joshi, Radhika D. Wakharkar, Ramki Iyer, Ramesh G. Kelkar, Subhash P. Chavan, Sunita S. Kunte, *Bioorganic & Medicinal Chemistry Letters* **2010**, *20*, 722–725.

5. "Novel hybrids of fluconazole and furanones: Design, synthesis and antifungal activity'
   Hanumant B. Borate, **Sangmeshwer P. Sawargave**, Mohan A. Chandavarkar, Sharangi R. Vaiude, Vinay A. Joshi, Subhash P. Chavan, *Bioorganic and Medicinal Chemistry Letters* **2011,** *21,* 4873-4878.

6. "One-step synthesis of 4-alkyl-3-aryl-2,6-dicyanoanilines and their use in the synthesis of highly functionalized 2,3,5,6,7-and 2,3,4,5,7-substituted indoles"

Sangmeshwer P. Sawargave, Ananada S. Kudale, Jaydeep V. Deore, Dattatry S. Bhosale, Jaisingh M. Divse, Subhash P. Chavan and Hanumant B. Borate; *Tetrahedron Letters* **2011**, *52*, 5491-5493.

7. "Facile synthesis of α-chlorostilbenes mediated by a heterogeneous Si-Fe catalyst: short and stereoselective synthesis of DMU-212"
   Sangmeshwer P. Sawargave, Suleman R. Maujan, Hanumant B. Borate; **(*to be communicated*)**.

8. "Design, synthesis and evaluation of thiophene and thienopyrimidinone containing fluconazole analogues as antifungal agents'' Hanumant B. Borate, Suleman R. Maujan, **Sangmeshwer P. Sawargave**, Pankaj A. Bhole, Subhash P. Chavan, Mohan A. Chandavarkar, Ramki Iyer, Amit C. Tawte, Deepali D. Rao and Vinay A. Joshi **(*to be communicated*)**.

Patents

1. "Thieno-[2,3-*d*]pyrimidin-4(3*H*)-one compounds with antifungal properties and process thereof" Hanumant B. Borate, Suleman R. Maujan, **Sangmeshwer P. Sawargave**, Mohan A. Chandavarkar, Shreerang V. Joshi, Sharangi R. Vaiude
   Ind. Patent Appl. No. 438/MUM/2008 (3-3-2008); PCT International Application No. PCT/IN08/000571 dated 05/09/2008; WO 2009/109983 A1.

2. "Thiophene containing analogues of fluconazole as antifungal agents and process thereof" Hanumant B. Borate, **Sangmeshwer P. Sawargave**, Suleman R. Maujan, Mohan A. Chandavarkar, Sharangi R. Vaiude, Vinay A. Joshi Ind. Patent Appl. No. 1595/MUM/2007 (27-8-2007); PCT/IN2009/000543; WO 2010/046912 (published on 29-4-2010).

3. "Antifungal compounds containing benzothiazinone, benzoxazinone or benzoxazolinone and process thereof" Hanumant B. Borate, Suleman R. Maujan, **Sangmeshwer P. Sawargave**, Ramesh G. Kelkar, Radhika D. Wakharkar, Mohan A.

Chandavarkar, Sharangi R. Vaiude, Vinay A. Joshi Ind. Patent Appl. No. 2306/MUM/2008 (24-10-2008); WO 2010/046931 (published on 29-4-2010).

4. "Enantiomers of fluconazole analogues containing thieno-[2,3-d]pyrimidin-4(3H)-one moiety as antifungal agents; H. B. Borate, S. R. Maujan, **Sangmeshwer P. Sawargave**, S. P. Chavan, M. A. Chandavarkar, R. Iyer, V. Nawathye, G. Chavan. A. C. Tawte Ind. Patent Appl. No. 735/MUM/2011 (15-3-2011); Invention Disclosure No. INV-2011-12.

5. "Hybrid molecules containing pharmacophores of fluconazole as antifungal agents and their preparation" Hanumant B. Borate, **Sangmeshwer P. Sawargave**, S. P. Chavan, M. A. Chandavarkar, R. Iyer, A. C. Tawte, D. D. Rao; Appl. No 1750/MUM/2011 (15-06-2011).

6. "Optically active fluconazole analogues containing thiophenes as antifungal agents'' Hanumant B. Borate, **Sangmeshwer P. Sawargave**, S. P. Chavan, M. A. Chandavarkar, R. Iyer, A. C. Tawte, D. D. Rao; Appl. No 3063/MUM/2011 (31-10-2011)

Posters presentated at national/ international symposia and conferences/ symposia attended

- Attended Joint International Conference on Building Bridges, Forging Bonds for 21st Century, Organic Chemistry and Chemical Biology *(ACS-CSIR-OCCB Symposium)*, January 7−9, 2006 conducted at National Chemical Laboratory, Pune, India.

- Attended Intrernational Conference on the Biology of Yeasts and Filamentous Fungi from 15th February to 17th February 2007 conducted at National Chemical Laboratory, Pune, India.
- Presented poster entitled "Facile synthesis of α-chlorostilbenes mediated by a heterogeneous Si-Fe catalyst: short and stereoselective synthesis of DMU-212" during 10th RSC-CRSI National Symposium in Chemistry, February 1–3, 2008 conducted at Indian Institute of Science, Bangalore, India.

- Presented poster during entitled "A short synthesis of 3,6-disubstituted N-2-thienyl/aryl-indoles" 11th RSC-CRSI National Symposium in Chemistry, February 6–8, 2009 conducted at National Chemical Laboratory, Pune, India.

- Attended 4th INSA-KOSEF symposium in Organic Chemistry: Contemporary Organic Chemistry and its Future directions, Jan 12−13, 2009 conducted at National Chemical Laboratory, Pune, India.

- Attended 12th RSC-CRSI National Symposium in Chemistry, February 5–7, 2010 conducted at Indian Institute of Chemical Technology, Hyderabad, India.

- Attended UGC-SAP National Symposium on Advances in Synthetic Methodologies and New Materials, January 21–22, 2011 conducted at Shivaji University, Kolhapur, India.

- Presented poster entitled "One-step synthesis of 4-alkyl-3-aryl-2,6-dicyanoanilines and their use in the synthesis of highly functionalized 2,3,5,6,7-and 2,3,4,5,7-substituted indoles" during at 1st CRSI Zonal Meeting, May 13–14, 2011 conducted at National Chemical Laboratory, Pune, India.

- Attended Indo-French Conference in Organic Synthesis, December 8-9, 2011 conducted at National Chemical Laboratory, Pune, India.