STUDIES ON SYNTHESIS OF NATURALLY OCCURRING BIOACTIVE QUINAZOLINONE ALKALOIDS: (–)-VASICINONE, LUOTONINS, RUTAECARPINES AND CIRCUMDATINS

THESIS

SUBMITTED TO THE

UNIVERSITY OF PUNE

FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

IN

CHEMISTRY

BY

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DIVISION OF ORGANIC CHEMISTRY (SYNTHESIS)

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PUNE - 411 008, INDIA

. . …To My Parents

CERTIFICATE

This is to certify that the work incorporated in the thesis entitled "***Studies on Synthesis of Naturally Occurring Bioactive Quinazolinone Alkaloids: (–)-Vasicinone, Luotonins, Rutaecarpines and Circumdatins***" which is being submitted to the ***University of Pune*** for the award of ***Doctor of Philosophy*** in ***Chemistry*** by ***Mr. Santosh B. Mhaske*** was carried out by him under my supervision at the National Chemical Laboratory, Pune. Such material as has been obtained from other sources has been duly acknowledged in the thesis.

June 2004

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Candidate's Declaration

I hereby declare that the thesis entitled "***Studies on Synthesis of Naturally Occurring Bioactive Quinazolinone Alkaloids:* (–)-*Vasicinone, Luotonins, Rutaecarpines and Circumdatins***" submitted for the degree of ***Doctor of Philosophy*** in ***Chemistry*** to the ***University of Pune*** has not been submitted by me for a degree to any other university or institution. This work was carried out at the Division of Organic Chemistry (Synthesis), National Chemical Laboratory, Pune, India.

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Acknowledgements

It gives me great pleasure to express my heartfelt gratitude to my research supervisor Dr. N. P. Argade for his astute guidance, invaluable suggestions and keen criticism while carrying out the present work. His enduring passion, moral support and help out of the way led me to overcome all the difficulties I encountered during this endeavor. I am certain that the guidance and training provided by him has laid a foundation for future success.

It is my privilege to thank Dr. K. N. Ganesh, Head, OCS Division, for his constant encouragement and ardent interest shown during the progress of the work. I sincerely acknowledge CSIR, New Delhi for the award of research fellowship and thanks are due to the Director, NCL for providing the infrastructure and necessary facilities. I owe tremendous debt to Dr. S. P. Vernekar, former Head, Polymer Division, for introducing me to the fascinating field of research. I am also thankful to Dr. S. D. Patil, Mr. A. S. Patil, Dr. P. P. Wadgoankar, Dr. M. B. Sabne, Dr. A. R. A. S. Deshmukh and Dr. S. S. Bhosale for their help and encouragement.

The work would not have been complete without the help provided by the analytical groups. My sincere thanks to Dr. Rajmohanan, Mrs. Phalgune, Mr. Sathe, Rupali, Pratiksha and Sachin for providing NMR training as well as for recording the spectra. I would like to thank Mrs. Shantakumari, Dr. Mrs. Bhalerao, Mrs. Kale and Dr. Mrs. Joshi for recording the Mass and IR spectra and all the library staff for excellent facilities. I thank the members of elemental analysis, SMIS, glass blowing, stores, workshop and administrative group for technical support.

My special thanks to lab-friends Kishan, Sanjib, Sunil, Mehrajuddin, Manoj, Mukulesh, Easwar, Anirban, Mangaleswaran, Revaiah**,** Sachin, Drs. Vinay, Ramesh, Anil and Vallabh for their cheerful co-operation and help in every aspect throughout this work. Thanks are due to Vrushali, Govind, Senthilkumar, Vijay, Twarita and Nilesh for the help during their project tenure in our laboratory.

My warm thanks are due to my friends Navanath, Balkrishna, Kiran, Shreekant, Abhijit, Paresh, Augustin, Rahul, Snehalata, Radhika, Ranjit, Avinash, Sachin, Madhav, Nitin, Yogesh, Vijay, Dnyaneshwer, Ravi, Anil, Sudhir, Milind, Vivek, Pandurang, Arvind, Shivkalyan, Arun, Siddhesh and Swathi. I would like to extend my thanks to Girish, Subbu, Jayanthi, Sony, Sanjay, Shriniwas, Rani, Harshada, Vidyesh, Bidhan, Anand, Shriram, Nandu, Bapu, Deepak, Dr. Gumaste and my other colleagues for making my stay at NCL a very comfortable and memorable one. I thank Mr. Pawar, Mr. Shelar, Mr. Patil and Mr. Chavan for their help and assistance.

Finally, no words can express the feelings towards my Aai, Anna and sisters Sunita, Sanjaya and Vijaya, who have contributed and sacrificed a lot for me to accomplish this stage and will always remain a sole source of inspiration in my life to achieve higher goals.

Santosh B. Mhaske

CONTENTS

General Remarks

- All the solvents used were purified according to the literature procedures.
- Petroleum ether used in the experiments was of 60-80 °C boiling range.
- Column chromatographic separations were carried out by gradient elution with light petroleum ether-ethyl acetate mixture, unless otherwise mentioned and silica gel (60-120 mesh/100-200 mesh).
- TLC was performed on E-Merck pre-coated 60 F_{254} plates and the spots were rendered visible by exposing to UV light, iodine, phosphomolybdic acid (in ethanol), bromocresol green (in ethanol).
- IR spectra were recorded on Shimadzu FTIR instrument, for solid either as nujol mull or in chloroform solution (conc. 1 μM) and neat in case of liquid compounds.
- NMR spectra were recorded on Brucker ACF 200 (200 MHz for ^{1}H NMR and 50 MHz for ^{13}C NMR), MSL 300 (300 MHz for ^{1}H NMR and 75 MHz for ^{13}C NMR) and DRX 500 (500 MHz for ^{1}H NMR and 125 MHz for ^{13}C NMR) spectrometers. Chemical shifts (δ) reported are referred to internal reference tetramethyl silane.
- Mass spectra were recorded on Finnigan-Mat 1020C mass spectrometer and were obtained at an ionization potential of 70 eV.
- Microanalytical data were obtained using a Carlo-Erba CHNS-O EA 1108 Elemental Analyser. Elemental analyses observed for all the newly synthesized compounds were within the limits of accuracy (± 0.3%).
- All the melting points reported are uncorrected and were recorded using an electro-thermal melting point apparatus.
- All the compounds previously known in the literature were characterized by comparison of their R_f values on TLC, IR and NMR spectra as well as melting point (in case of solid) with authentic samples.
- All the new experiments were repeated two or more times.
- Starting materials were obtained from commercial sources or prepared using known procedures.

Abbreviations

AIBN	2,2’-Azobisisobutyronitrile
BINAP	2,2’-Bis(diphenylphosphino)1,1’-binaphthyl
BOP	Benzotriazol-1-yloxytris(dimethylamino)-phosphoniumhexaflurophosphate
CAN	Ceric ammonium nitrate
m-CPBA	*meta*-Chloroperoxybenzoic acid
DBP	Dibenzoyl peroxide
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCC	1,3-Dicyclohexylcarbodiimide
DCM	Dichloromethane
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DEAD	Diethyl azodicarboxylate
DMAP	4-(Dimethylamino)pyridine
DMF	Dimethylformamide
DMP	Dess-Martin periodinate
DMSO	Dimethyl sulphoxide
EDAC	1-Ethyl-3(3-dimethylaminopropyl)carbodiimide
HMDS	Hexamethyldisilazane
HMPA	Hexamethylphosphoramide
o-IBX	*ortho*-Iodoxybenzoic acid
IC	Inhibitory concentration
KHMDS	Potassium hexamethyldisilazide
LAH	Lithium aluminum hydride

LDA	Lithium diisopropylamide
LTMP	Lithium tetramethylpiperidine
MOM	Methoxymethyl
NBS	*N*-Bromosuccinimide
PCC	Pyridinium chlorochromate
PCy_3	Tricyclohexylphosphine
$Pd_2(dba)_3$	Tris(dibenzylideneacetone)dipalladium
PMB	*p*-Methoxybenzyl
PPA	Polyphosphoric acid
PPTS	Pyridinium *p*-toluenesulfonate
TBAF	Tetrabutylammonium fluoride
TEA	Triethylamine
TEP	Triethylphosphite
TFA	Trifluoroacetic acid
TFAA	Trifluroacetic anhydride
THF	Tetrahydrofuran
TMEDA	Tetramethylethylenediamine
TMSCl	Trimethylchlorosilane
TMSI	Trimethyliodosilane
TMSOTf	Trimethylsilyl trifluoromethanesulfonate
TPP	Triphenylphosphine
p-TsCl	*p*-Toluenesulfonyl chloride
p-TsOH	*p*-Toluenesulfonic acid

Abstract of the thesis

Note: Compound numbers in the abstract are different from those in the thesis.

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Title of the Thesis: "***Studies on Synthesis of Naturally Occurring Bioactive Quinazolinone Alkaloids:* (–)-*Vasicinone, Luotonins, Rutaecarpines and Circumdatins***"
Registration No.: 294/2k, **Date of Registration:** 28/12/2000
Place of work: Division of Organic Chemistry (Synthesis), NCL, Pune - 411 008, India

Abstract

The present dissertation describes studies on total synthesis of several bioactive quinazolinone alkaloids (Figure 1) and it is divided into five chapters. The first chapter reports a concise account on the chemistry of the recently isolated naturally occurring bioactive quinazolinone alkaloids. The second chapter describes the use of cyclic anhydrides as potential starting materials for the synthesis of quinazolinone alkaloids, wherein the first section describes total synthesis of pegamine, deoxyvasicinone and (–)-vasicinone whereas the second section describes total synthesis of rutaecarpine and studies on synthesis of 7,8-dehydrorutaecarpine. The third chapter is also divided into two sections. The first section deals with the total synthesis of luotonin alkaloids A, B and E via regioselective directed ortho lithiation strategy as a key step and the second section describes biogenetic total synthesis of luotonin F. The fourth chapter describes our studies on total synthesis of circumdatin C & F and explains its logical application for the synthesis of asperlicin C and asperlicin. The fifth chapter is divided into two sections wherein, the first section presents tabulated spectral and analytical data of the compounds synthesized and section second presents ^{1}H and ^{13}C NMR spectra of selected compounds.

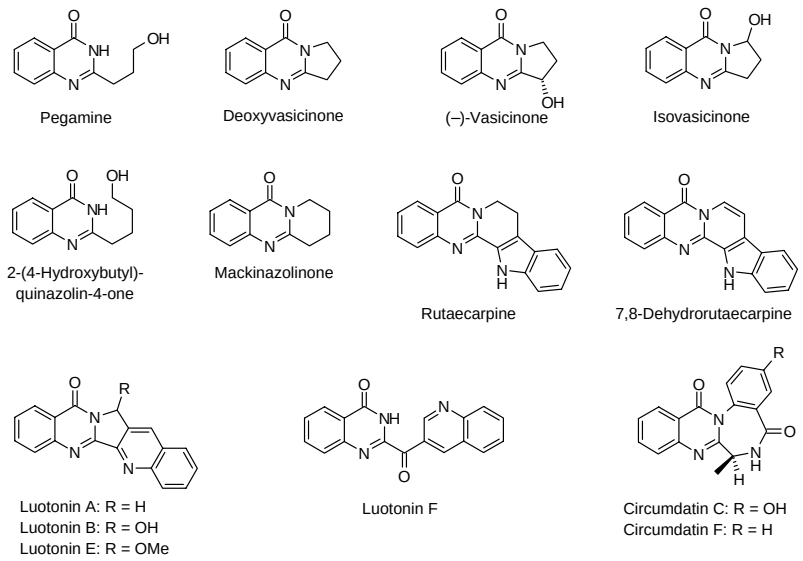


Figure 1: Synthesis of naturally occurring bioactive quinazolinone alkaloids

Chapter One

A Concise Account on the Chemistry of the Naturally Occurring Bioactive Quinazolinone Alkaloids

Large numbers of quinazolinone alkaloids have been isolated from a number of plants, animals and microorganisms and synthesized in view of their well-established pharmacological activities. This chapter portrays a concise account on isolation, bioactivity and synthesis of recently isolated bioactive quinazolinone based natural products and the recent developments in the area of complex quinazolinone natural products with an emphasis on new synthetic routes and strategies.

Chapter Two

Synthesis of Pegamine, Deoxyvasicinone, (–)-Vasicinone, Rutaecarpine and Studies on Synthesis of 7,8-Dehydrorutaecarpine

This chapter is divided into two sections. The first section presents synthesis of pegamine, deoxyvasicinone and (–)-vasicinone and the second section describes an efficient total synthesis of rutaecarpine and an attempted synthesis of 7,8-dehydrorutaecarpine. All these natural products have been synthesized using cyclic anhydrides as building block.

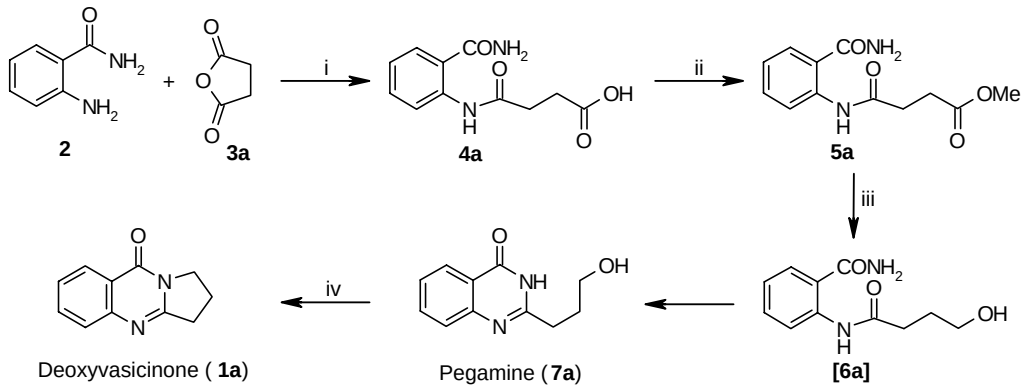
2.1 Section A

Concise and Efficient Synthesis of Bioactive Natural Products Pegamine, Deoxyvasicinone and (–)-Vasicinone

Pegamine [2-(3-hydroxypropyl)quinazolin-4(1*H*)-one, **7a**], deoxyvasicinone [2,3-dihydropyrrolo[2,1-*b*]quinazolin-9(1*H*)-one, **1a**] and (–)-vasicinone [2,3-dihydro-3(*S*)-hydroxypyrrolo[2,1-*b*]quinazolin-9(1*H*)-one, **1b**] have been isolated as bioactive natural products. Pegamine (**7a**) has been isolated from *Peganum harmala* and it exhibits cytotoxic activity. Deoxyvasicinone (**1a**) and (–)-vasicinone (**1b**) have been isolated from aerial parts of an evergreen subherbaceous bush *Adhatoda vasica*. Deoxyvasicinone (**1a**) possesses anti-microbial, anti-inflammatory and anti-depressant activities. Several synthetic routes to deoxyvasicinone (**1a**) are known in the literature. (–)-Vasicinone (**1b**) exhibits anti-tumor, bronchodilating, hypotensive, anthelmintic and antianaphylactic activities. It is used in "*The Indian Ayurvedic System of Medicine*" as a remedy for cold, cough, bronchitis, rheumatism, phthisis and asthma. Three synthetic routes to vasicinone are known and (±)-vasicinone has been obtained from

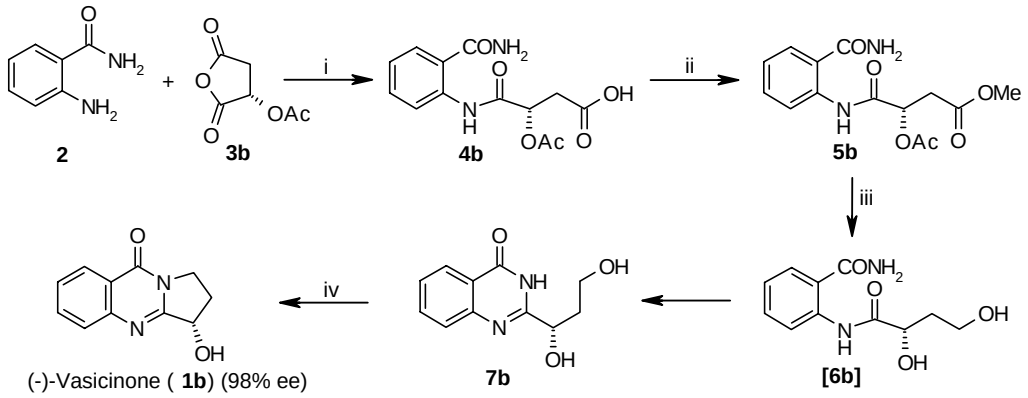
deoxyvasicinone via NBS-bromination, while (–)-vasicinone has been synthesized from deoxyvasicinone via asymmetric oxidation using (1*R*)-(–)-(10-camphorsulfonyl)oxaziridine with 62% ee. (±)-Vasicinone and (–)-vasicinone have been also synthesized via the tandem Staudinger/intramolecular aza-Wittig reaction and an efficient enzymatic resolution of (±)-vasicinone is known in the literature.

This section presents a convenient first synthesis of pegamine (**7a**) with 89% overall yield and a new route to deoxyvasicinone (**1a**) with 85% overall yield via acylation of anthranilamide (**2**) with succinic anhydride (**3a**), followed by diazomethane esterification of formed succinanilic acid **4a**, chemoselective LAH-reduction of ester **5a**, in situ LiOH-catalyzed dehydrative cyclization and intramolecular Mitsunobu ring closure reaction pathway (Scheme 1).



Scheme 1: (i) Et_2O/C_6H_6/1,4-dioxane (2:2:1), rt, 2 h (98%); (ii) CH_2N_2, Et_2O, rt, 1 h (98%); (iii) LAH, THF, 90 min., aqueous workup (93%); (iv) PPh_3, DEAD, THF, rt, 1 h (95%).

Total synthesis of (–)-vasicinone (**1b**) with 80% overall yield (97-98% ee) has been accomplished



Scheme 2: (i) Et_2O/C_6H_6/1,4-dioxane (2:2:1), rt, 2 h (98%); (ii) CH_2N_2, Et_2O, rt, 1 h (98%); (iii) LAH, THF, 90 min., aqueous workup (92%); (iv) PPh_3, DEAD, THF, rt, 1 h (90%).

via highly regioselective ring opening of 2(*S*)-acetoxysuccinic anhydride at the more reactive electron-deficient carbonyl carbon, followed by repetition of the same reaction sequence as

depicted in Scheme 1, without using any protection-deprotection chemistry. The present synthesis of (–)-vasicinone with chiral pool strategy directly confirms the stereochemistry of the natural product (Scheme 2).

2.2 Section B

Facile Zeolite Induced Fischer-Indole Synthesis: A New Approach to Bioactive Natural Product Rutaecarpine and Studies on Synthesis of 7,8-Dehydrorutaecarpine

The dried fruits of *Evodia rutaecarpa* have been used in traditional Chinese medicine under the name Wu-Chu-ru and Shih-Hu as a remedy for headache, dysentery, cholera, worm infections and postpartum. The drug extract contains quinazolinocarboline alkaloids rutaecarpine (**1a**) and

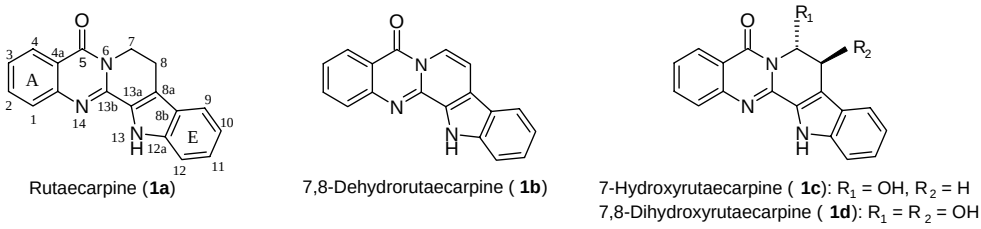
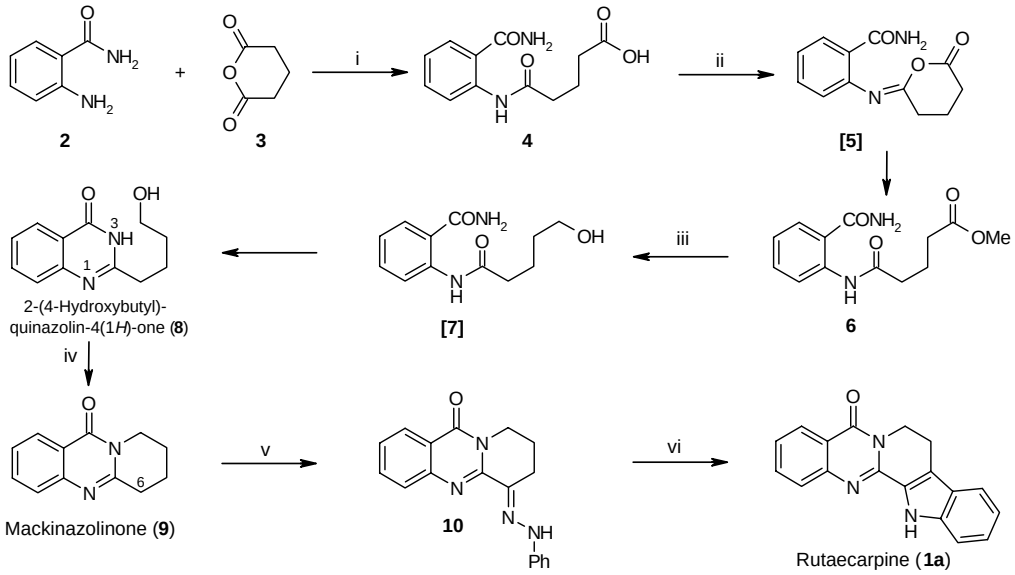


Figure 2 : Naturally occurring bioactive rutaecarpines

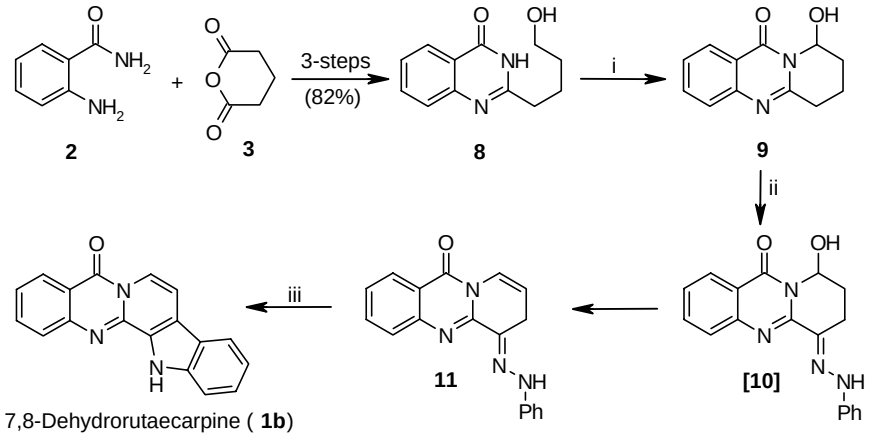
evodiamine. Recently callus tissue cultured from the stem of *Phellodendron amurense* has been shown to produce **1a** along with a variety of other alkaloids (Figure 2). In recent literature, **1a** and its derivatives have been reported to possess strong analgesic, anti-emetic, astringent, anti-hypertensive, uterotonic, TCDD-receptor, anti-nociceptive, anti-inflammatory and cycloxygenase (COX-2) inhibitory activities. Rutaecarpine (**1a**) was also found to suppress platelet plug formation in mesenteric venules and increase intracellular Ca^{2+} in endothelial cells. Robinson et al reported the first total synthesis of this important bioactive natural product **1a** in 1927 and since then several routes to **1a** and its derivatives have been developed.

This section demonstrates a new practical synthesis of bioactive natural product rutaecarpine (**1a**). We felt that it would be possible to design the five carbon six membered ring C in **1a** from glutaric anhydride (**3**) and a facile six-step synthesis of **1a** has been completed, starting from glutaric anhydride (**3**), via *o*-amidoglutaranilic acid (**4**) formation, esterification, chemoselective ester reduction, intramolecular dehydrative cyclizations, hydrazone formation and zeolite induced Fischer-indole synthesis with 53% overall yield. The conditions employed in the present synthesis are mild, efficient and general (Scheme 3).



Scheme 3: (i) C_6H_6/1,4-dioxane (2:1), rt, 2 h (98%); (ii) MeOH, H_2SO_4 (cat.), rt, 8 h (96%); (iii) $NaBH_4$, THF, reflux, 3 h, aqueous workup (86%); (iv) NaH, *p*-TsCl, THF, rt, 30 min. (81%); (v) Aniline, 30% HCl, $NaNO_2$, AcOH, – 5 to 5 ^oC, 8 h (98%); (vi) Zeolite (H-Mordenite), AcOH, reflux, 5 h (82%).

The indolopyridoquinazoline alkaloid 7,8-dehydrorutaecarpine (**1b**) was isolated from callus tissues of *Phellodendron amurense* (Rutaceae), which is used in a crude form as a drug in Japan and China as an anti-stomachic, anti-inflammatory and anti-pyretic agent. The agonist activity of 7,8-dehydrorutaecarpine (**1b**) towards TCDD-receptor was found to be more than that of rutaecarpine. Bergman et al completed the first synthesis of this important molecule by DDQ oxidation of rutaecarpine. This section presents our results on synthesis of 7,8-dehydrorutaecarpine (**1b**) (Scheme 4). The alcohol **8** was synthesized using our own method,



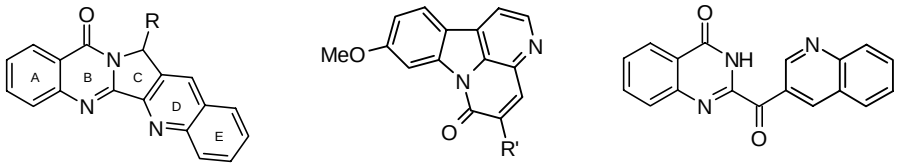
Scheme 4: (i) PCC, CH_2Cl_2, rt, 1h (72%); (ii) Aniline, 30% HCl, $NaNO_2$, AcOH, -5 to 5 ^oC, 8 h (98%); (iii) in progress.

used in the synthesis of rutaecarpine. Oxidation of **8** using PCC gave compound **9**, which on diazonium coupling reaction directly furnished hydrazone **11**, plausibly via dehydration of intermediate **10**. We tried several reagents/reaction conditions such as PPA, $ZnCl_2$, BF_3-ether, neat heating, heating in high boiling solvent, zeolite and acidic resin for conversion of **11** to 7,8-dehydrorutaecarpine (**1b**) but all of them met with failure (Scheme 4). We are in search of a suitable reagent/reaction condition and the work is under active progress. Protection of the secondary alcohol in **9**, followed by hydrazone formation, Fischer-indolization and deprotection may provide a way to the natural product (±)-7-hydroxyrutaecarpine (**1c**) and further dehydration under acidic conditions would provide 7,8-dehydrorutaecarpine (**1b**). We feel that the alkaloid 7,8-dehydrorutaecarpine (**1b**) would be a potential precursor for the enantioselective synthesis of 7-hydroxyrutaecarpine (**1c**) and 7,8-dihydroxyrutaecarpine (**1d**) (Figure 2).

Chapter Three

Total Synthesis of Quinazolinone Natural Products Luotonins A, B, E and F

The species from plant kingdom *Peganum nigellastrum* Bunge (Zygophyllaceae) is found all over Asia and is more common in the northwest region of China. The same plant with Chinese name "Luo-Tuo-Hao" has been used in the Chinese traditional medicine system as a remedy for a rheumatism, abscess and inflammation. Recently, Nomura and co-workers from Japan in their collaborative work with scientists from China isolated six new alkaloids luotonin A, B, C, D, E and F from aerial parts of *P. nigellasturm* (Figure 3). Luotonin C and D are unusual canthin-6-one derivatives. These bioactive natural products exhibit an anti-tumor activity. This chapter



Luotonin A (**1a**): R = H
Luotonin B (**1b**): R = OH
Luotonin E (**1c**): R = OMe

Luotonin C: R' = Me
Luotonin D: R' = Et

Luotonin F (**1d**)

Figure 3: Naturally occurring luotonin alkaloids

presents our studies on the synthesis of luotonin A, B, E and F in two sections. The first section deals with the total synthesis of luotonin alkaloids A, B and E via directed ortho lithiation strategy as a key step and the second section describes biogenetic total synthesis of luotonin F.

3.1 Section A

Regioselective Directed Ortho Lithiation: A Practical Total Synthesis of Quinazolinone Natural Products Luotonins A, B and E

Luotonin A is cytotoxic towards the murine leukemia P-388 cell line (IC_{50} 1.8 µg/mL). Very recently, Hecht et al have demonstrated that despite the lack of lactone ring functionality, luotonin A stabilizes the human DNA topoisomerase I-DNA covalent binary complex and mediates topoisomerase I-dependant cytotoxicity in intact cells (IC_{50} 5.7-12.6 µm/mL), alike camptothecin and its analogues (Figure 4). Due to similarity in structure and biological activity

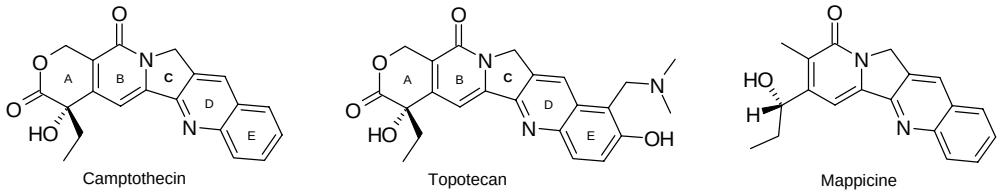
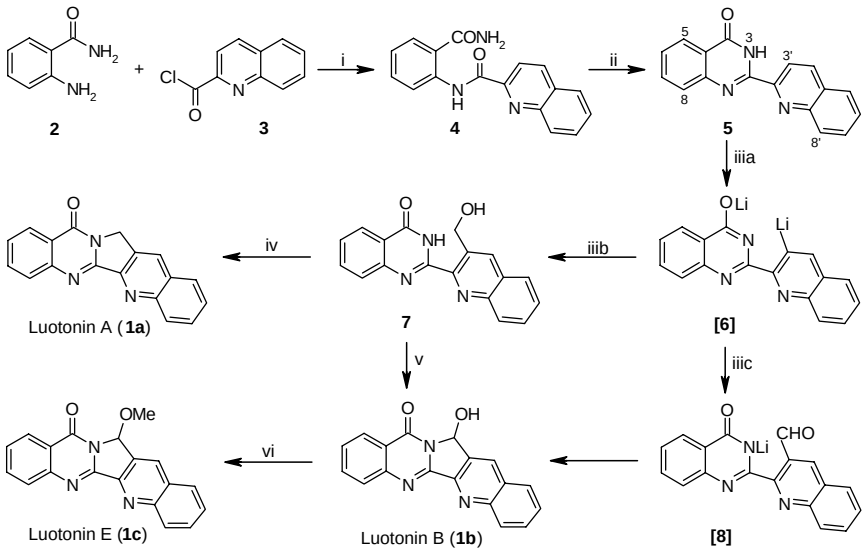


Figure 4: Camptothecin and its analogues of clinical importance

with camptothecin, in a very short span of time (6-years) eleven syntheses of luotonin A have been reported from different laboratories using variety of elegant synthetic strategies. Out of eleven known syntheses, ten multi-step syntheses of linear penta-cyclic luotonin A have been completed using two suitable building blocks with construction of ring B or D, wherein the construction of these building blocks demand more number of steps. Recently, Harayama et al completed the synthesis of luotonin A with construction of middle ring C using a similar reported Pd-assisted bi-aryl coupling reaction. Till date, four syntheses of luotonin B and two syntheses of luotonin E are known in the literature.

This section presents a practical approach for the synthesis of luotonin A, B and E. Acylation of anthranilamide (**2**) with quinaldic acid chloride (**3**) followed by aqueous potassium hydroxide catalyzed dehydrative cyclization gave the 2-quinolinoquinazolinone **5** in quantitative yield, which can undergo lithiation at carbon number 8, 3' and 8'. We reasoned that alike carboxamide, the amide unit in quinazolinones will be useful to perform directed-metalation reactions on adjacent 2-aryl/heteroaryl groups. In order to perform the quinazolinone-directed ortho lithiation selectively at the 3'-poisiton of adjacent quinoline nucleus with the assistance of amide moiety in quinazolinone skeleton, we tried several reaction conditions using different alkyllithiums and their combination with TMEDA. Finally, use of in situ generated non-nucleophilic mesityl lithium at – 20°C furnished the desired dilithiated species **6** via lithiation of quinazolinone nitrogen at 3-position as a first step followed by directed ortho lithiation at the 3'-position. The

reaction of dilithiated intermediate **6** with formaldehyde followed by Mitsunobu cyclization of the compound **7** furnished the bioactive natural product luotonin A (**1a**) in 95% yield. The reaction of dilithiated species **6** with *N*,*N*-dimethylformamide directly furnished luotonin B (**1b**) in 81%. The PCC oxidation of **7** in CH_2Cl_2 also furnished luotonin B (**1b**) in 61% yield. Luotonin B (**1b**) on treatment with *p*-TsOH/methanol provided luotonin E (**1c**) in 82% yield (Scheme 5). The present bridging of two segments using quinazolinone-directed ortho metalation strategy is note-worthy and useful. We feel that our present approach is general in nature and such type of regioselective directed-lithiation of aryl and heteroaryl substituted quinazolinone systems will be highly useful for the synthesis of a large number of desired complex quinazolinone alkaloids,



luotonins and camptothecin like analogues for structure activity relationship studies.

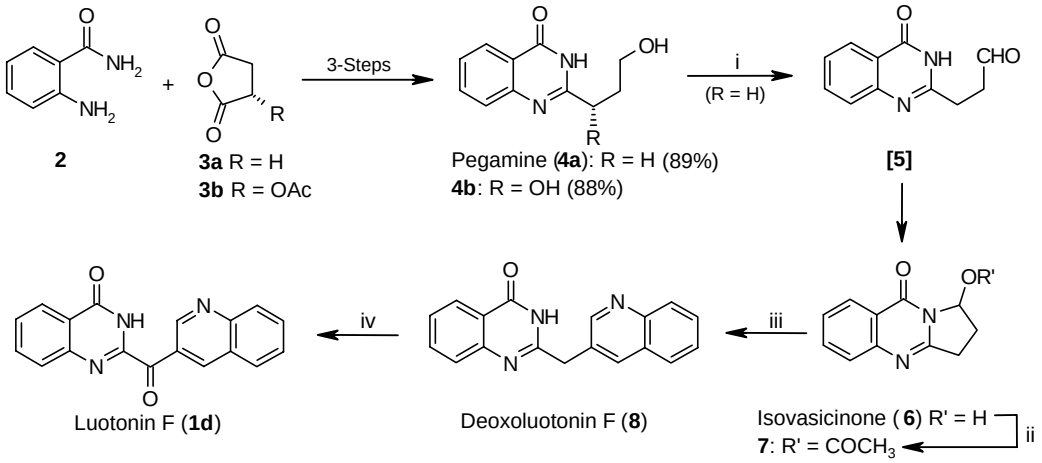
Scheme 5: (i) Et_3N (2 eq.), THF, rt, 3 h (96%); (ii) 5% aq. KOH, EtOH, reflux, 5 min. (98%); (iiia) mesityl lithium (2.2 eq.), – 78 ^oC, 30 min. to – 20 ^oC (gradually), (iiib) THF solution of HCHO (5 eq.), – 30 ^oC, 20 min., saturated aq. solution of NH_4Cl (86%), (iiic) DMF (5 eq.), – 20 ^oC, 30 min., saturated aq. solution of NH_4Cl (81%); (iv) PPh_3 (1.3 eq.), DEAD (1.2 eq.), THF, rt, 1 h (95%); (v) PCC (1.2 eq.), powdered 4 Å molecular sieves, CH_2Cl_2, rt, 1 h (61%); (vi) *p*-TsOH (5 eq.), MeOH, reflux, 3 h (82%).

3.2 Section B

Biogenetic Synthesis of Luotonin F

Till date, two syntheses of the structurally interesting and biologically important luotonin F (**1d**) are known in the literature. Very recently Ma et al reported that luotonin F (**1d**) and its analogue deoxoluotonin F (**8**) are cytotoxic (IC_{50} 1.8-40.0 μg/mL) and inhibit DNA topoisomerase at a concentration of 25 μM. This section demonstrates an efficient biogenetic type synthesis of the recently isolated bioactive natural product luotonin F (**1**) starting from succinic anhydride (**3a**) via

PCC-oxidation of the natural product pegamine (**4a**), Friedländer condensation and Yamazaki's CrO_3-H_5IO_6 oxidation reaction sequence. The overall yield of **1d** starting from **4a** was 38% and starting from succinic anhydride (**3a**), luotonin F (**1d**) was obtained in six steps with 34% overall yield. In our hands, all attempts to oxidize hydroxypegamine **4b** to the corresponding desired keto-aldehyde or its ring closed form like **6**, using a variety of oxidizing agents failed and hence we were unable to complete the short two step synthesis of **1d** starting from **4b** (Scheme 6).

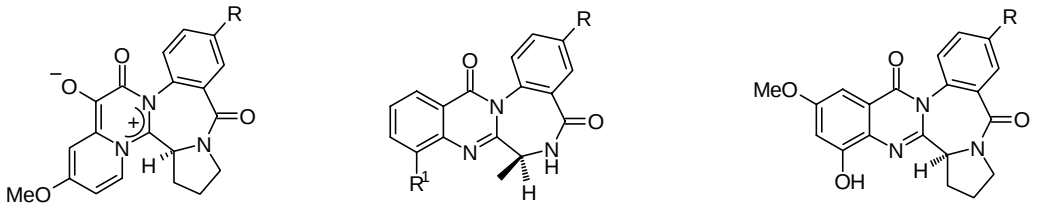


Scheme 6: (i) PCC, CH_2Cl_2, rt, 3 h (64%); (ii) Ac_2O, Py, rt, 8 h (98%); (iii) *o*-aminobenzaldehyde, KOH, EtOH, reflux, 15 h (62%); (iv) CrO_3, H_5IO_6, DMF, rt, 1 h (96%).

Chapter Four

Studies on Total Synthesis of Circumdatin C and F

The crude extract of the broth of fungus *Aspergillus ochraceus* was found to inhibit the final stage of polyprotein processing during hepatitis C virus replication and recently, seven benzodiazepine alkaloids circumdatin A-G (Figure 5) have been isolated from its terrestrial isolate, which are active against CNS disorders and also belong to psychoactive drug category. Structurally related bioactive natural quinazolinone alkaloids include sclerotigenin, benzomalvin A-C, asperlicin C



Circumdatin A: R = OMe
Circumdatin B: R = H

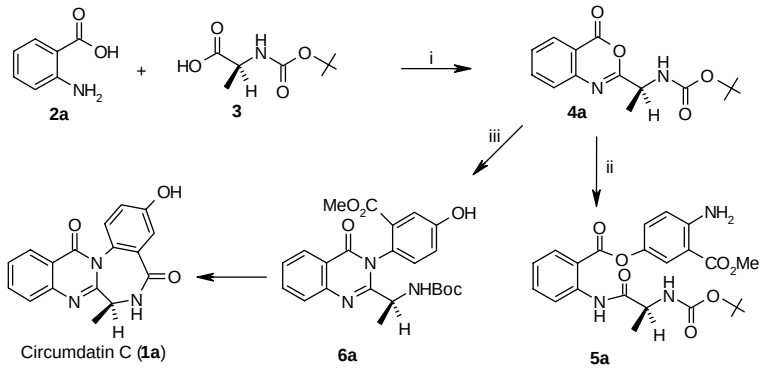
Circumdatin C (**1a**): R = OH, R^1 = H
Circumdatin F (**1b**): R = H, R^1 = H
Circumdatin G: R = H, R^1 = OH

Circumdatin D: R = OMe
Circumdatin E: R = H

Figure 2: Naturally occurring circumdatin alkaloids

and asperlicin. Only one 10-step synthesis of circumdatin C has been reported recently by Bergman & co-workers with 0.9% overall yield and three syntheses of circumdatin F are known in the literature.

This section presents our studies on the synthesis of circumdatin C (**1a**) and F (**1b**) via benzoxazinone pathway. In literature, ring opening of benzoxazinone with aromatic amines is



Scheme 7: (i) DCC, CH_2Cl_2, rt, 1 h (97%); (ii) DCC, heptane, reflux, 3 h (85%); (iii) in progress.

reported to be difficult and ends up in a complex reaction mixture but we feel that this would be the most straightforward way to obtain quinazolinone derivatives. Benzoxazinone **4a** was synthesized in quantitative yield from the reaction of anthranilic acid (**2a**) and Boc-L-alanine (**3**) in presence of DCC. Benzoxazinone **4a** is unstable and transforms to the corresponding diamide **4a'**. In our hands, several attempts using different reaction conditions for the condensation of benzoxazinone with aromatic amines met with failure. To keep the benzoxazinone ring intact, we

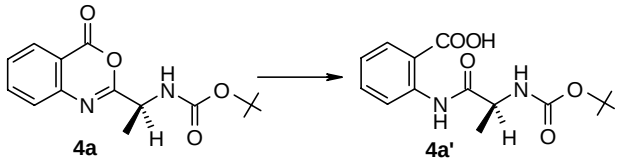
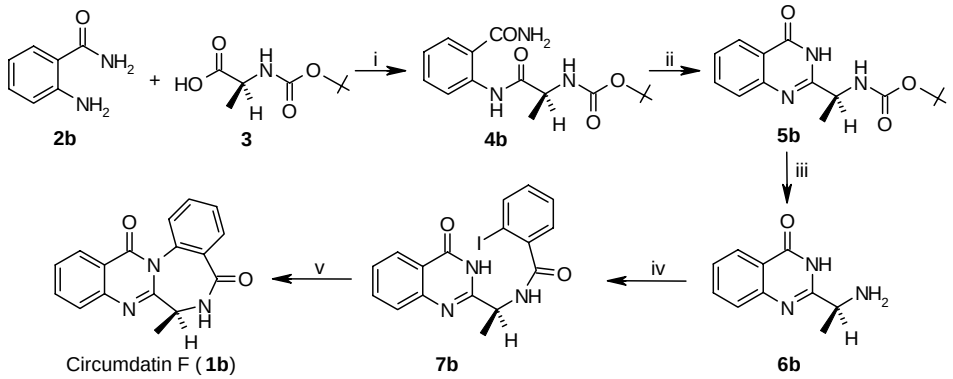


Figure 6: Unstable benzoxazinone **4a** transforms to diamide **4a'**

performed the reaction of **4a** and 5-hydroxy methyl anthranilate in presence of DCC but unfortunately the benzoxazinone ring was opened by phenolic – OH rather than the amino group to furnish compound **5a** instead of quinazolinone **6a**. Our efforts to find a suitable condition to react aromatic amines with benzoxazinone **4a** for the efficient synthesis of circumdatin C (**1a**) & F (**1b**) are under active progress (Scheme 7). The ^{1}H & ^{13}C NMR spectrum revealed that **4a'** exists in two rotameric forms. We have also proved by 2D, COSY, NOSY, ^{15}N-NMR, variable temperature NMR that this molecule exists in two different locked conformations. This conclusion is in agreement with the MOPAC calculations (Figure 6).

In our second approach for the synthesis of circumdatin C (**1a**) & F (**1b**) we planned to use copper or palladium catalyzed intramolecular Ullmann type coupling reaction as a key step (Scheme 8). Condensation of Boc-L-alanine (**3**) with anthranilamide (**2b**) in presence of EDAC gave amide **4b**, which was transformed to quinazolinone **5b** by using a base catalyzed dehydrative cyclization. Boc-deprotection of quinazolinone **5b** furnished amine **6b**, which was condensed with 2-iodo benzoic acid to obtain compound **7b**. Our work on conversion of **7b**



Scheme 8: (i) EDAC, THF, rt, 2 h (87%); (ii) aq. LiOH/THF (1:1), rt, 1 h (98%); (iii) $AlCl_3$, CH_2Cl_2, rt, 3 h (95%); (iv) 2-iodo benzoic acid, EDAC, THF, rt, 1 h (96%); (v) in progress.

to circumdatin F (**1b**) is under active progress and we feel that Ullman type coupling will provide an easy access to **1b**. The same strategy would be applicable for the synthesis of circumdatin family of natural products, other quinazolinone natural products like sclerotigenin, benzomalvins and its logical extension for the synthesis of asperlicin C and asperlicin would be possible.

Chapter Five

Spectral and Analytical Data of Compounds Synthesized and Spectra of Selected Compounds

This chapter is divided into two sections. The first section presents tabulated spectral and analytical data of the compounds synthesized and section second presents ^{1}H and ^{13}C NMR spectra of selected compounds.

In summary, we have accomplished synthesis of several quinazolinone based bioactive natural products using a variety of new and elegant synthetic strategies, which can be generalized. During these studies we have also developed a simple, efficient and general approach to the potential building blocks alkoxysuccinic acids and alkoxymaleic anhydrides.

Chapter One

A Concise Account on the Chemistry of the Naturally Occurring Bioactive Quinazolinone Alkaloids

This chapter portrays a concise account on isolation, bioactivity and synthesis of recently isolated bioactive quinazolinone based natural products and the recent developments in the area of complex quinazolinone natural products with an emphasis on new synthetic routes and strategies.

1.1 Introduction

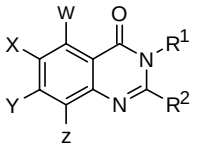
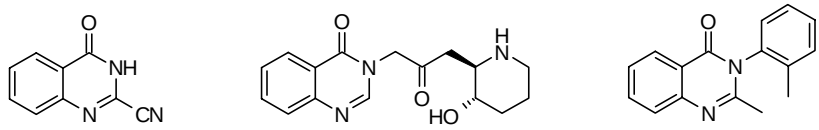


Figure 1: Quinazolinone general structure

Quinazolinone (Figure 1) is a building block for approximately 120 naturally occurring alkaloids isolated till date from a number of families of the plant kingdom, from microorganisms and from animals. The first quinazolinone was synthesized in the late 1860's from anthranilic acid and cyanogens to give the 2-cyanoquinazolinone[1] (**1,** Figure 2). Interest in the medicinal chemistry of quinazolinone derivatives was stimulated in the early 1950's with the elucidation of a quinazolinone alkaloid 3-[β-keto-γ(3-hydroxy-2-piperdyl)-propyl]-4-quinazolone [febrifugine[2] (**2**), Figure 2] from an Asian plant *Dichroa febrifuga*, which is an ingredient of a traditional Chinese herbal remedy, effective against



2-Cyanoquinazolinone (**1**) Febrifugine (**2**) Methaqualone (**3**)

Figure 2: Synthetic and natural quinazolinones

malaria. In a quest to find additional potential quinazolinone based drugs, various substituted quinazolinones have been synthesized, which led to the synthesis of the derivative 2-methyl-3-*o*-tolyl-4-(3*H*)-quinazolinone [methaqualone (**3**), Figure 2]. Methaqualone (**3**) was synthesized[3] for the first time in 1951 and it is the most well known synthetic quinazolinone drug, famous for its sedative-hypnotic effects.[4] The introduction of methaqualone and its discovery as a hypnotic triggered the research activities towards the isolation, synthesis and the studies on the pharmacological properties of the quinazolinones and related compounds. Quinazolinones and the derivatives thereof are now known to have

a wide range of biological properties, including hypnotic, sedative, analgesic, anti-convulsant, anti-tussive, anti-bacterial, anti-diabetic, anti-inflammatry, anti-tumor and several other useful and interesting properties.[5] The chemistry of the quinazolinone alkaloids is well documented[5,6] in a number of comprehensive reviews & monographs and continuously updated in Natural Product Reports.[7]

The review by Johne et al[6b] covered the literature of all the quinazolinone natural products isolated upto the middle of 1983. This chapter portrays a concise account on the isolation, bioactivity & the synthesis of the naturally occurring bioactive quinazolinone alkaloids (either isolated or synthesized after the middle of 1983 to the beginning of 2004) pertaining strictly to the basic structure shown in Figure 1 and the recent developments in the area of the complex quinazolinone natural products with an emphasis on new synthetic routes and strategies. The chemistry of quinazolinone alkaloids is published in a broad range of scientific journals. We have tried our best to assemble and present the information here, but no pretension of completeness is claimed. In order to simplify and understand the chemistry of the naturally occurring quinazolinone alkaloids, they have been divided according to their structures. Each group contains information about the natural products in tabular form, which shows the natural product's structure, name, bioactivity, the species from which it was isolated, references pertaining to its synthesis and its molecular formula. The table is followed by discussion and illustration of the synthesis of the important quinazolinone alkaloids from the list. In the last part, biological activity of quinazolinones and their application in clinical treatments has been discussed followed by summary and references.

Quinazolin-4-(3*H*)-one derivatives are of considerable interest because of their pharmacological properties;[8] e.g., protein tyrosine kinase inhibitor, cholecystokinin

inhibitor, antimicrobial, anticonvulsant, sedative and hypotensive, antidepressant and anti-inflammatory as well as antiallergy. Some of these have interesting biological properties[8] such as antimalarial activity and biofungicide and diuretic properties. Our literature survey revealed that there are about 73 new quinazolinone based natural products isolated under the present review period which were characterized by IR, ^{1}H-NMR, ^{13}C-NMR and Mass spectroscopic methods and also by UV, 2-D NMR and X-ray analysis data wherever necessary. In view of the importance of quinazolinones and their derivatives, many classical methods for their synthesis were reported in the literature.[5,8,9] The main synthetic routes to such compounds utilize 2-aminobenzoic acid or its derivatives, 2-aminobenzamide, 2-aminobenzonitrile, isatoic anhydride, 2-carbomethoxyphenyl isocyanate, *N*-arylnitrilium salts and 4*H*-3,1-benzoxazinones. Recently in the solid-phase synthesis, lithium reagents and transition metals have been used in the preparation of these compounds. Other important methods are coupling of *O*-methylbutyrolactim with anthranilic acid, cycloaddition of anthranilic acid iminoketene to methylbuyrolactam (via sulfonamide anhydride), anthranilic acid derivatives together with a wide range of substrates including imidates and iminohalides, the reaction of anthranilic acid and the appropriately substituted imidate in a facile one-pot procedure, microwaves promoted reaction of anthranilic acid with amine & formic acid (or ortho ester) and isatoic anhydride.[9]

All the important methods for the synthesis of the quinazolinone alkaloids are described in detail in the following sections with relation to the corresponding structural type of the naturally occurring quinazolinone alkaloids. These alkaloids have been divided into six different categories according to their structural features.

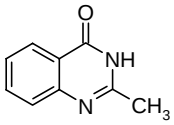
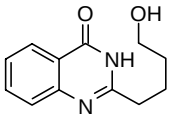
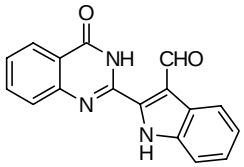
1.2 Quinazolinones substituted either at 2/3 or at 2 & 3 positions

These are simple quinazolinones substituted at either 2/3 or 2 & 3 positions. They are further divided into subclasses depending on the position of the substituents.

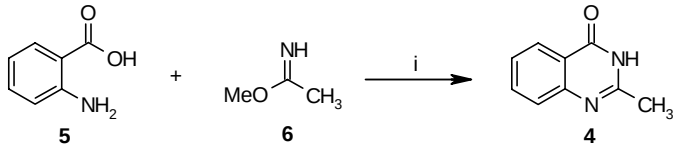
1.2.1 Simple 2-substitued quinazolin-4-ones:

Three new simple 2-substitued quinazolin-4-ones isolated from various species under the review period are listed in the table (Table 1, entries 1-3).

Table 1: Simple 2-substitued quinazolin-4-ones

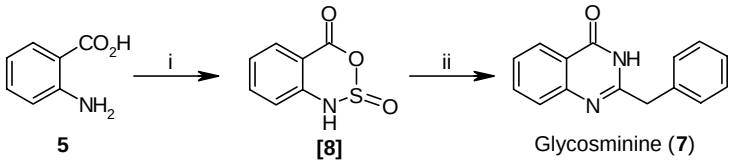
No.	Quinazolinone alkaloid	Source[Ref.] and activity	Synthesis[Ref.]
1.	 2-Methyl-4(3*H*)-quinazolinone	*Bacillus cereus*[10] BMH225-mF1 Low acute toxicity in mice	$C_9H_8N_2O$ Synthesis known before isolation[10] Connolly et al[11]
2.	 2-(4-Hydroxybutyl)quinazolin-4-one	*Dichroa febrifuga*[12]	$C_{12}H_{14}N_2O_2$ Synthesis known before isolation[13] Argade et al[17b]
3.	 Bouchardatine	*Bouchardatia neurococca*[14]	$C_{17}H_{11}N_3O_2$

2-Methyl-4(3*H*)-quinazolinone (**4**) was isolated from culture of the micro-organism *Bacillus cereus*[10] and it was prepared synthetically before its isolation.[10] Recently it was synthesized by Connolly et al[11] in their general approach for the synthesis of these type of alkaloids (Scheme 1), wherein a straightforward condensation between anthranilic acid (**5**) and various imidates of general formula RC(=NH)OMe in boiling methanol produced range of 2-substitued quinazolin-4(3*H*)-ones. Among them the condensation with the



Scheme 1: (i) MeOH, 25 ^{o}C, 30 min., then 80 ^{o}C, 6 h (42%).

imidate **6** produced the alkaloid **4** (entry 1) in 42% overall yield. One more efficient one-pot approach to this type of moiety was provided by Kametani et al[15] wherein they have synthesized a natural product glycosminine (**7**) starting from anthranilic acid via a sulfonamide anhydride **8** in 40% overall yield (Scheme 2).



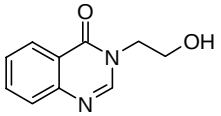
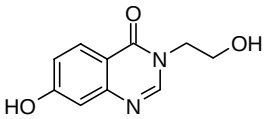
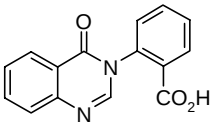
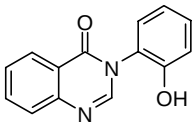
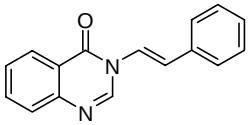
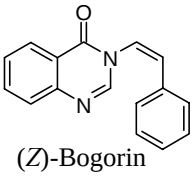
Scheme 2: (i) $SOCl_2$, benzene, reflux, 2 h; (ii) phenylacetamide, benzene, rt 12 h (40% overall yield).

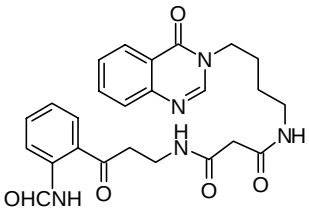
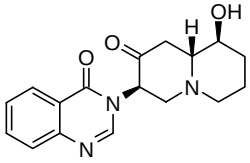
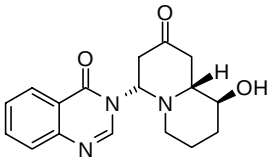
The natural product 2-(4-hydroxybutyl)-quinazolin-4-one (entry 2) is having almost similar structure with that of the cytotoxic alkaloid pegamine i.e. 2-(3-hydroxyproply)-quinazolin-4-one, a natural product isolated from *Peganum harmala.*[16] We have recently synthesized[17] both these natural products in our laboratory and further transformed them into the natural products mackinazolinone and deoxyvasicinone respectively, which will be discussed in chapter 2, as a part of this dissertation. Till date no synthetic method for the synthesis of bouchardatine (entry 3) is known in the literature. Natural product luotonin F also comes under this structural class of alkaloids, which will be discussed under the luotonin class of compounds (Section 1.4).

1.2.2 3-Substituted quinazolin-4-ones:

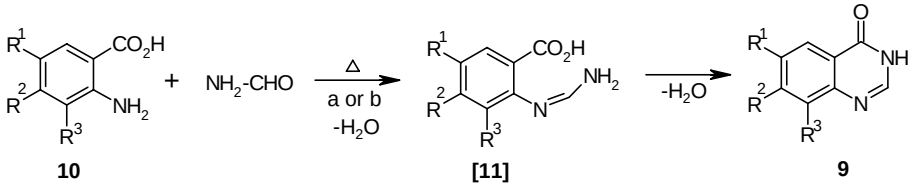
There are nine 3-substituted quinazolin-4-ones isolated from various species (Table 2, entries 1-9).

Table 2: 3-substituted quinazolin-4-ones

No.	Quinazolinone alkaloid	Source[Ref.] and activity	Synthesis[Ref.]
1.	 Echinozolinone	*Echinops echinatus*[18]	$C_{10}H_{10}N_2O_2$ Synthesis known before isolation[18]
2.	 7-Hydroxyechinozolinone	*Echinops echinatus*[19]	$C_{10}H_{10}N_2O_3$
3.	 3-(2-Carboxyphenyl)-4(3*H*)-quinazolinone	*Isatis indigotica*[20] Anti-endotoxic	$C_{15}H_{10}N_2O_3$ Synthesis known before isolation[20]
4.	 3-(2-Hydroxyphenyl)-4(3*H*)-quinazolinone	*Isatis indigotica*[21]	$C_{14}H_{10}N_2O_2$ Synthesis known before isolation[21]
5.	 (*E*)-Bogorin	*Glycosmis cf. chlorosperma*[22] Cytotoxic, antifungal	$C_{16}H_{12}N_2O$ Seger et al[22]
6.	 (*Z*)-Bogorin	*Glycosmis cf. chlorosperma*[22] Cytotoxic, antifungal	$C_{16}H_{12}N_2O$ Seger et al[22]

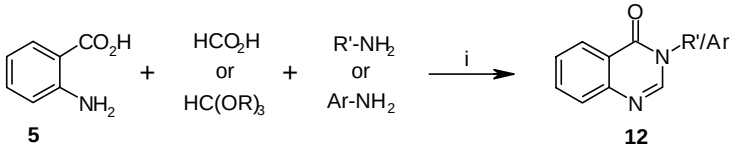
7.	 Monodontamide F	*Monadonta labio*[23]	$C_{25}H_{27}N_5O_5$ Niwa et al[23]
8.	 (+)-Neodichroine	*Dichroa febrifuga*[12]	$C_{17}H_{19}N_3O_3$ Deng et al[12]
9.	 (+)-Hydrachine A	*Hydrangea chinensis*[24d]	$C_{17}H_{19}N_3O_3$

A general route to this structural type can be exemplified by two recent approaches. In a search to speed up an aspect of drug discovery processes, Besson et al[25] have reinvestigated the Niementowski synthesis of the 3*H*-quinazolin-4-one core using microwave irradiation and improved the yields and reduced the reaction time (Scheme 3). The product **9** can be further transformed into the structural type shown in Table 2 by reaction with corresponding alkyl/aryl halide or epoxide.



Scheme 3: The Niementowski reaction: (a) conventional conditions: 130-150 ^{o}C, average time 6 h (40-60%), (b) microwave conditions: MW (60W), 150 ^{o}C, average time 20 min. (70-90%).

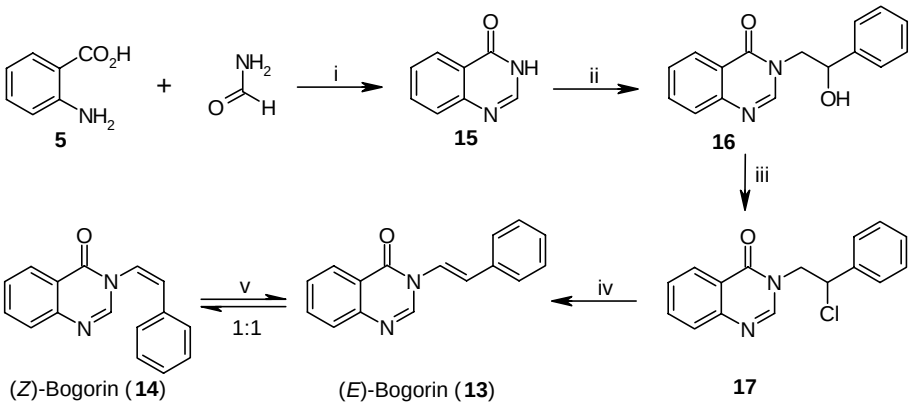
The other approach describes an efficient synthesis of an array of quinazolin-4-(3*H*)-ones from anthranilic acid, ortho esters (or formic acid) and amines using $Yb(OTf)_3$ in one-pot under solvent-free conditions. Compared with the classical reaction conditions, this new synthetic method has the advantage of excellent yields (75-99%), shorter reaction time (few minutes) and reusability of the catalyst (Scheme 4).



Scheme 4: (i) $Yb(OTf)_3$, heat under solvent-free conditions (75-99%).

I] Bogorin *E* and *Z*:

(*Z*)-Bogorin (**14**, entry 6), a new quinazolone alkaloid isolated from Javanese *Glycosmis cf. chlorosperma*, was obtained in quantities too small for confirmation of its structure by two-dimensional NMR spectroscopic experiments.[22] The putative structure was therefore substantiated by the short synthesis shown in Scheme 5. Base-induced elimination of hydrogen chloride from **17** produced exclusively (*E*)-bogorin (**13**, entry 5), which proved

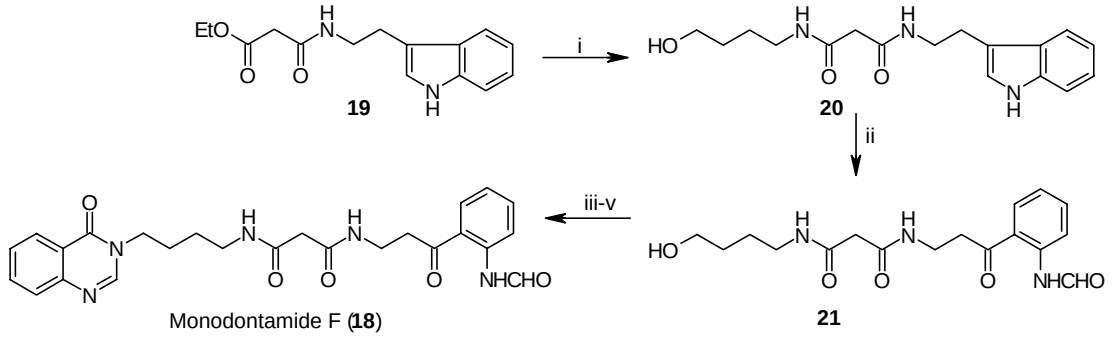


Scheme 5: (i) 130 ^{o}C, 2.5 h (83%); (ii) styrene oxide, pyridine (cat.), $Pr^{i}OH$, reflux (43%); (iii) $SOCl_2$, C_6H_6, reflux (93%); (iv) DBU, C_6H_6, reflux (65%); (v) *hv* (high pressure Hg lamp), cyclohexane, rt (50%).

to be identical to another trace alkaloid in the plant extract. Photochemical isomerisation of **13** yielded a separable 1:1 mixture of (*E*)- and (*Z*)-bogorins, the latter of which gave ^{1}H and ^{13}C NMR spectroscopic signals identical to those of natural **14**. (*Z*)-Bogorin showed antifungal activity towards *Cladosporum herbarium* (IC_{50} 40 µg cm^{-3}), and was moderately cytotoxic towards *Artemia salina* (brine shrimp). The corresponding (*E*)-isomer and the synthetic precursors were found significantly less active.

II] Monodontamide F:

The gastropod mollusc *Monodonta labio* is the unusual source of monodontamide F (**18**, entry 7), only the second quinazoline alkaloid to have been isolated[23] from a marine source. The structure of monodontamide F was determined spectroscopically, and confirmed by a synthesis,[23] the key steps of which are shown in Scheme 6.



Scheme 6: (i) 4-Aminobutan-l-ol, 70 ^{o}C (90%); (ii) O_3, $NaHCO_3$, MeOH, -78 ^{o}C, then Me_2S, -78 ^{o}C to rt (62%); (iii) *p*-TsC1, py, 0 ^{o}C; (iv) NaI, $CaCO_3$, acetone, 50 ^{o}C; (v) 4-hydroxyquinazoline, KOH, EtOH, rt to reflux (43% over iii-v).

III] (+)-Neodichroine:

Chinese researchers isolated the interesting new quinazolinone-quinolizidine dimer (+)-neodichroine (entry 8), which was isolated as a crystalline solid[12] as principal components from extracts of the leaves of *Dichroa febrifuga*. Evidence for the structure of neodichroine came from ^{1}H and ^{13}C NMR spectra, recorded in deuterated pyridine, together with COSY

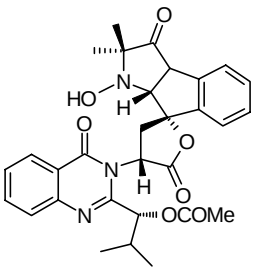
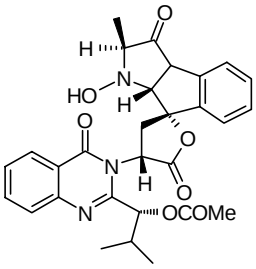
and NOE data. Neodichroine also formed an acetate that gave a well-resolved ^{1}H spectrum. A short synthesis of neodichroine by a Mannich reaction between the natural product febrifugine (**2**) and formaldehyde at pH 4 provided a definitive evidence for the structure of the isolated natural product.

For 7-hydroxyechinozolinone (entry 2) and Hydrachine (entry 9), no synthetic method is reported till date, but their synthesis should be possible by using the strategies as used for the synthesis of the other members of this class.

1.2.3. 2,3-Di-substituted quinazolin-4-ones:

There are only two quinazolinone natural products (Table 3, entries 1,2) isolated under the review period, substituted both at 2 and 3 positions and they are tryptoquivaline analogs. 27-*epi*-Tryptoquivaline (entry 1) and 27-*epi*-nortryptoquivaline (entry 2) are the epimers of the previously known quinazolinone alkaloids tryptoquivaline and nortryptoquivaline respectively, which were isolated from *Aspergillus clavatus*.[24a,b] The first total synthesis of

Table 3: 2,3-Di-substituted quinazolin-4-ones (Tryptoquivaline analogs)

No.	Quinazolinone alkaloid	Source[Ref.] and activity	Synthesis[Ref.]
1.	 27-epi-tryptoquivaline	*Corynascus setous*[84] Tremorgenic	$C_{29}H_{30}N_4O_7$
2.	 27-epi-Nortryptoquivaline	*Corynascus setous*[84] Tremorgenic	$C_{28}H_{28}N_4O_7$

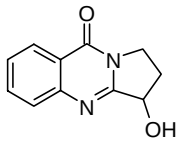
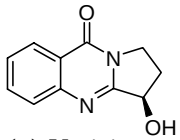
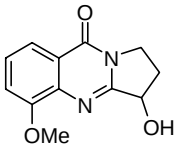
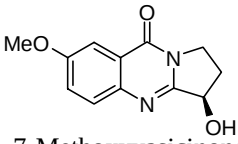
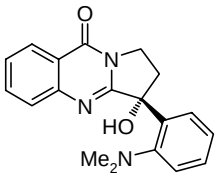
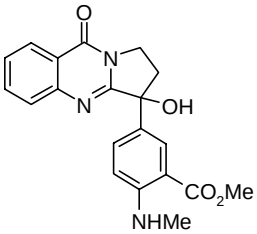
tryptoquivaline was achieved by Nakagawa et al[24c] which can be extended for the synthesis of the new tryptoquivalines by using a starting material with appropriate stereochemistry.

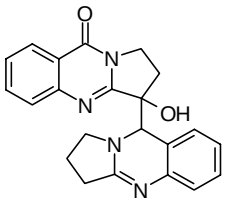
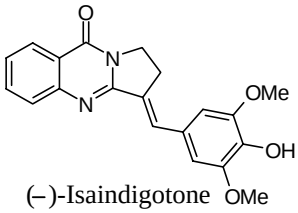
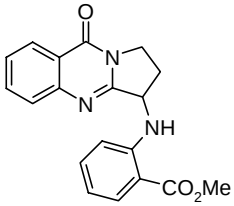
In conclusion the quinazolinones substituted at either 2/3 or 2 & 3 positions (Table 1,2 & 3) are structurally quite simple alkaloids with wide range of bioactivity and most of them have been synthesized using various synthetic strategies. We feel that the synthesis of bouchardatine (Table 1, entry 3) should be possible by using *ortho*-directed lithiation strategy, developed by us[51b] in the synthesis of luotonin A, B & E. Synthesis of (*Z*)-bogorin (Scheme 5) can probably be improved by performing a chemoselective Wittig reaction on the *N*-formyl derivative of compound **15** (alike imides) or by using a better *trans-cis* isomerization catalyst for converting **13** to **14**. The lower yields for the last two steps in the synthesis of monodontamide F (Scheme 6) may be possibly due to the feasible intramolecular cyclization in the compound **21**. Besson et al[25] made the 3-substitued quinazolinones more readily accessible by improving the classical and famous Niementowski reaction in terms of reaction temperature, time and yield. We feel that, 1,3-benzoxazinones will be potential precursors for the synthesis of 3-substitued quinazolinones (Table 2, entries 1-9) and tryptoquivaline analogs (Table 3).

1.3 Quinazolinones fused with a pyrrole ring system

There are nine naturally occurring quinazolinone alkaloids having quinazolinone ring fused with a pyrrole ring system. They all are analogs or derivatives of deoxyvasicinone or vasicinone isolated (entries 1-9) from various species and are tabulated in Table 4. The synthetic methods to this structural type can be understood by illustrating various approaches to deoxyvasicinone and vasicinone which is a basic structural unit for all these alkaloids (entries 1-9).

Table 4: Pyrroloquinazolinones (deoxyvasicinone/vasicinone and their derivatives)

No.	Quinazolinone alkaloid	Source[Ref.] and activity	Synthesis[Ref.]
1.	 (±)-Vasicinone	*Galium aparine*[26a] *Peganum multisectum*[26b,c] *Nitraria schoberi*[26d]	$C_{11}H_{10}N_2O_2$ Eguchi et al[27] Kamal et al[28]
2.	 (+)-Vasicinone	*Adhatoda vasica*[29]	$C_{11}H_{10}N_2O_2$ Eguchi et al[27] Kamal et al[28]
3.	 Adhavasinone	*Adhatoda vasica*[30]	$C_{12}H_{12}N_2O_3$ Chowdhury et al[30]
4.	 7-Methoxyvasicinone	*Adhatoda vasica*[31]	$C_{12}H_{12}N_2O_3$
5.	 Desmethoxyaniflorine	*Adhatoda vasica*[31]	$C_{19}H_{19}N_3O_2$
6.	 3-Hydroxyanisotine	*Adhatoda vasica*[32]	Synthesis known before isolation[33] $C_{20}H_{19}N_3O_4$

7.	 Dipeginol	*Peganum harmala*[34]	$C_{22}H_{20}N_4O_2$
8.	 (–)-Isaindigotone	*Isatis indigotica*[21,35a] *Isatis tinctoria*[35b] Scavnger of superoxide Anti-oxidant	$C_{20}H_{18}N_2O_4$ Molina et al[35c]
9.	 Vasnetine	*Adhatoda vasica*[32]	$C_{19}H_{17}N_3O_3$

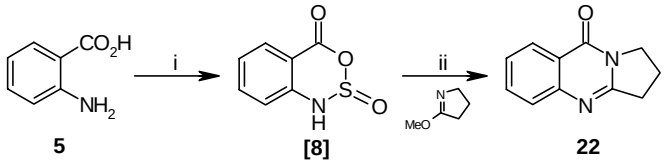
I] Deoxyvasicinone:

Deoxyvasicinone [2,3-dihydropyrrolo[2,1-*b*]quinazolin-9(1*H*)-one, **22**] has been isolated from aerial parts of an evergreen subherbaceous bush *Adhatoda vasica*[36] and possesses anti-microbial, anti-inflammatory and anti-depressant acitivities.[37] Several synthetic routes to deoxyvasicinone (**22**) are known in the literature.[15,38] Two efficient and easy approaches are discussed in detail below and the selected methods are tabulated in Table 4a.

A] Kametani's approach:

Kametani et al[38e] synthesized deoxyvasicinone (**22**) in good yields by reaction of unstable sulfonamide anhydride **8** with *O*-methylpyrrolidone (Scheme 7), thus affording

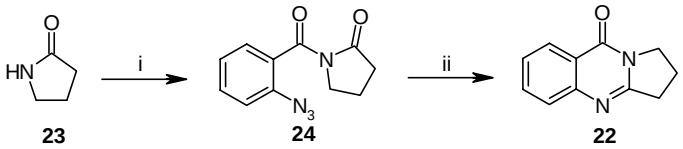
deoxyvasicinone in 65% overall yield. Later, they improved[15] these conditions by using simple 2-pyrrolidone to obtain **22** in 93% overall yield.



Scheme 7: (i) $SOCl_2$, benzene, reflux, 2 h; (ii) 2-methylpyrrolidone, benzene, rt, 1-2 h (65%).

B] Eguchi's approach:

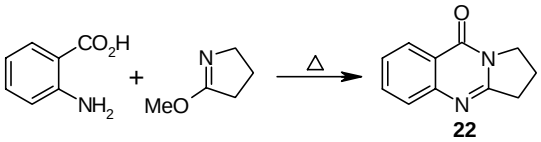
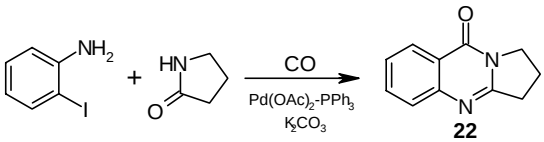
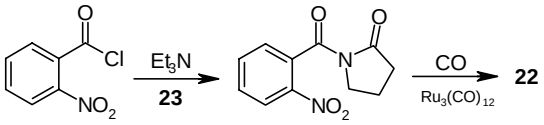
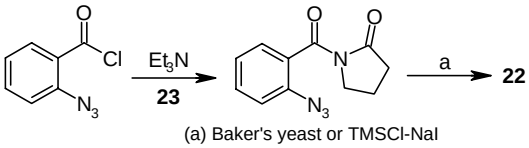
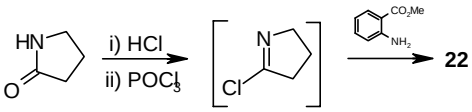
The azide **24** obtained from pyrrolidone (**23**) was treated with triphenylphosphine but the cyclization required heating at higher temperature and for longer time. When tributylphosphine was used instead, the reaction was complete in shorter time at room temperature with good yield (Scheme 8).[38i] This aza-Wittig reaction protocol is now



Scheme 8: (i) NaH, benzene, o-azidobenzoyl chloride, rt (75%); (ii) PPh_3, 140 ^oC, 5 h or PBu_3, rt, 3 h (99%).

famous as Eguchi's protocol. Morris et al[38a] completed a semi synthesis of deoxyvasicinone by oxidation of deoxyvasicine which is also a natural product. Kamal et al[38l] recently developed a route for the synthesis of deoxyvasicinone as shown in Table 4a, entry 4, wherein they have used $FeCl_3$-NaI as a regent for the last reductive cyclization step. Nishiyama et al[38m] used selenium as a catalyst for the reductive cyclization step and could synthesize deoxyvasicinone in good yield by following the same strategy as used by Watanabe et al[38k] (Table 4a, entry 3).

Table 4a: Various approaches to deoxyvasicinone

No.	Brief Scheme	Overall yield (%)	Reference
1.		82% (1-step)	Onaka[38c]
2.		52% (1-step)	Mori et al[38g]
3.		55% (2-steps)	Watanabe et al[38k]
4.		~ 82% (2-steps)	Kamal et al[28]
5.		88% (2-steps)	Lee et al[38n]

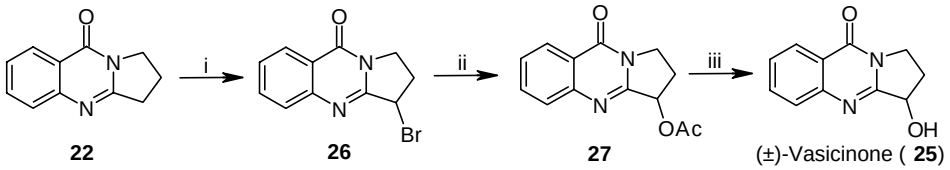
Recently we have completed[17a] the synthesis of deoxyvasicinone starting from succinic anhydride and these results will be discussed in chapter 2, as a part of this dissertation.

II] Vasicinone:

(–)-Vasicinone (**25a**) exhibits antitumor, bronchodilating, hypotensive, anthelmintic, and antianaphylactic activities.[26b,39] It is used in *The Indian Ayurvedic System of Medicine* as a remedy for cold, cough, bronchitis, rheumatism, phthisis and asthma.[36,40] Recently, Joshi and co-workers[32,41] reversed the previously assigned[42] 3(*R*)-configuration of **25a** on the basis of X-ray crystallographic analysis[41a] and by using the Mosher ester analysis method.[41b] Three synthetic routes to vasicinone are known in the literature.[38c,g,27,28]

A] Onaka's approach:

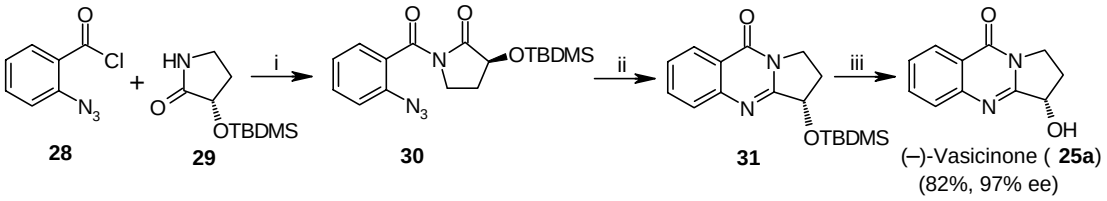
Onaka et al[38c] completed the synthesis of (±)-vasicinone (**25**) from deoxyvasicinone (**22**) (Scheme 9). Deoxyvasicinone (**22**), obtained by following their own scheme as shown in Table 4a (entry 1), was brominated using NBS and the monobromo product **26** was converted to acetylvasicinone **27** by treatment with AcONa-AcOH. Acetylvasicinone was then hydrolyzed under basic conditions to obtain (±)-vasicinone (**25**) in 17% overall yield starting from anthranilic acid. Mori et al[38g] synthesized (±)-vasicinone by modification of Onaka's method,[38c] employing the less expensive AcONa instead of AcOAg.



Scheme 9: (i) NBS, benzoyl peroxide, CCl_4, reflux (57%); (ii) AcONa-AcOH, reflux (33%); (iii) aq. KOH, rt (17% overall yield from anthranilic acid).

B] Eguchi's approach:

Eguchi et al[27] completed the synthesis of (±)-vasicinone (**25**), (–)-vasicinone (**25a**) and (+)-vasicinone (**25b**) via aza-Wittig reaction as the key step (Scheme 10). The sequence of the reactions shown in Scheme 10 was first carried out by using racemic 3-hydroxy γ-lactam to obtain (±)-vasicinone (**25**). Both optical isomers of the quinazolinone alkaloid, vasicinone, were synthesized by two different methods. The first method used 3(*S*)-3-hydroxy-γ-lactam (derived from L-aspartic acid in six steps)[43] as a chiral synthon, which was, after *O*-

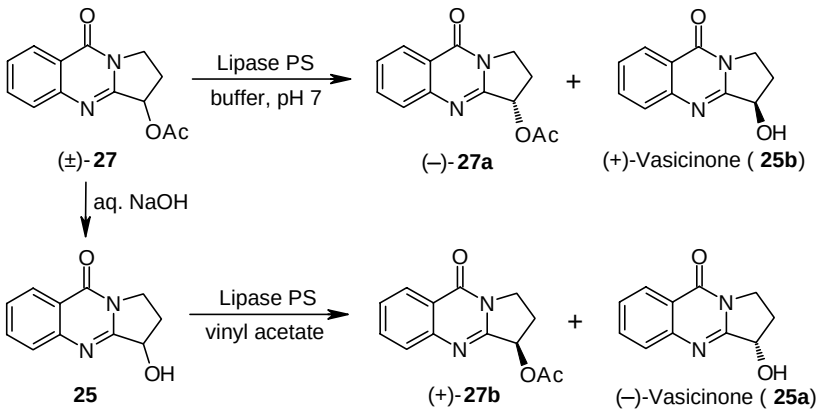


Scheme 10: (i) NaH, THF, 0 °C to rt, 3 h (83% from *o*-azidobenzoic acid); (ii) *n*-Bu_3P, toluene, rt, 1 h then reflux, 2 h (76%); (iii) TBAF, THF, 0 °C to rt, 15 h (97%).

TBDMS protection, *o*-azidobenzoylated followed by treatment with tri-*n*-butylphosphine to afford (*S*)-(–)-vasicinone via the tandem Staudinger/intramolecular aza-Wittg reaction (Scheme 10). The second method utilized asymmetric oxygenation of deoxyvasicinone (**22**) with (1*S*)-(+)- or (1*R*)-(–)-(10-camphorsulfonyl)oxaziridine (the Davis reagent). The aza-enolate anion of deoxyvasicinone was treated with (*S*)-(+)-reagent to afford (*R*)-(+)-vasicinone in 71% ee, while the reaction with (*R*)-(–)-reagent gave (*S*)-(–)-vasicinone in 62% ee. These results provided a good method to prepare both the enantiomers of vasicinone and confirmed the recently reversed[32,41] stereochemistry of natural (–)-vasicinone.

C] Kamal's approach:

Kamal et al[28] have reported an efficient enzymatic resolution of (±)-acetyl vasicinone **27** and (±)-vasicinone (**25**) to obtain both enantiomers of vasicinone (Scheme 11). Deoxyvasicinone (**22**) was synthesized using their own scheme (Table 4a, entry 4) and it was converted in good yields to (±)-acetyl vasicinone **27** and (±)-vasicinone (**25**) by bromination followed by displacement with acetate and hydrolysis reaction sequence.



Scheme 11: Enzymatic resolution of (±)-acetyl vasicinone (**27**) and (±)-vasicinone (**25**).

Acetyl vasicinone thus obtained has been enzymatically hydrolyzed employing lipase PS "Amano" to its (*R*)-alcohol and (*S*)-acetate in 98% ee. Alternatively, racemic vasicinone

has been resolved by transesterification with different lipases. It was observed that THF, followed by toluene and di-isopropyl ether, provide good selectivity with good conversions and, interestingly, (*R*)-acetate is obtained in >99% ee employing lipase PS in THF.

Recently we have demonstrated[17a] a concise, efficient and practical chiral pool synthesis of (–)-vasicinone (**25a**) starting from readily available (*S*)-malic acid as a chiral synthon. These results will be discussed in chapter 2, as a part of this dissertation.

Adhavasicinone (entry 3) has been synthesized by Chowdhury et al[30] starting from 2-methoxy aminobenzaldehyde. 7-Methoxyvasicinone (entry 4) can be very easily synthesized by using the various methods available for the synthesis of vasicinone. Desmethoxyaniflorine (entry 5), 3-hydroxyanisotine (entry 6, whose semi-synthesis[33] by oxidation of the natural product anisotine is known) and dipeganol (entry 7) can be synthesized using Kokosi's[44] synthetic route. This route was originally developed for the synthesis of quinazolinone natural product vasicolinone whose structure is similar to that of the alkaloids in entries 5-7. Straightforward condensation of deoxyvasicinone (**22**) with 4-acetoxy-3,5dimethoxybenazaldehyde in acetic anhydride followed by hydrolysis of the ester completed the first synthesis[35c] of isaindigotone (entry 8) in 64% overall yield. Vasnetine (entry 9), having a similar structure as that of the natural alkaloid anisessine (the only difference being the alkoxycarbonyl moiety), was synthesized by Onaka et al[38c] by nucleophilic displacement of bromine atom in bromovasicinone **26** with ethyl anthranilate. Synthesis of vasnetine will also be easily possible following Onaka's procedure for anisessine.

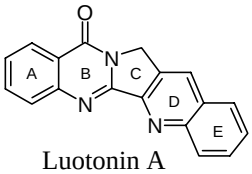
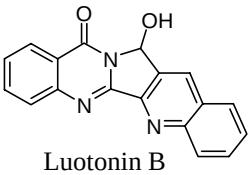
In conclusion, the new pyrroloquinazolinone alkaloids presented in Table 4 (entries 1-9) are deoxyvasicinone/vasicinone analogs and synthesis of some of them is known. Synthesis of these alkaloids should be possible by employing various synthetic strategies

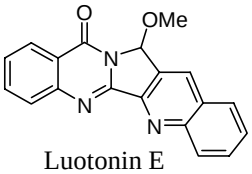
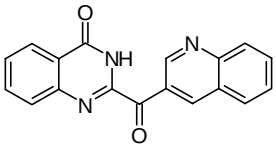
available for the synthesis of deoxyvasicinone/vasicinone (Scheme 7-11 & see Table 4a) and by their transformations like oxidation, substitution or condensation. The reductive cyclization using various catalysts developed for this class of compounds provided an easy access to these alkaloids and the use of Baker's yeast for this purpose is novel and interesting. To the best of our knowledge, the enzymatic resolution of (–)-vasicinone is the first example of quinazolinone resolution using lipases and it seems possible to apply it for the resolution of other alkaloids like isovasicione, luotonin B and 7-hydroxyrutaecarpine.

1.4 Quinazolinones fused with a pyrroloquinoline ring system

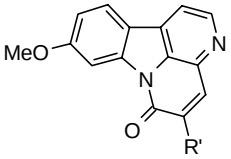
The species from plant kingdom *Peganum nigellastrum* Bunge (Zygophyllaceae) is found all over Asia and is more common in the northwest region of China. The same plant with Chinese name 'Luo-Tuo-Hao'[45] has been used in the Chinese traditional medicine system as a remedy for a rheumatism, abscess and inflammation.[45] Recently, Nomura and co-

Table 5: Pyrroloquinalinoquinazolinones (Luotonin alkaloids)

No.	Quinazolinone alkaloid	Source[Ref.] and activity	Synthesis[Ref.]
1.	 Luotonin A	*Pegaum nigellastrum*[46a] Cytotoxic towards the murine leukemia P-388 cell line (IC_{50} 1.8 µg/mL)	$C_{18}H_{12}N_3O$ Eleven syntheses Refs.[35c,38n,46b,50] Argade et al[51b]
2.	 Luotonin B	*Pegaum nigellastrum*[46a] Cytotoxic towards leukaemia P388 cells	$C_{18}H_{12}N_3O_2$ Ma et al[46a,b, 50c] Harayama et al[50h] Argade et al[51b]

3.	 Luotonin E	*Peganum nigellastrum*[16b]	$C_{19}H_{13}N_3O_2$ Ma et al[16b,46b] Argade et al[51b]
*4.	 Luotonin F	*Peganum nigellastrum*[16b] Antitumor	$C_{18}H_{11}N_3O_2$ Ma et al[16b, 46b] Argade et al[51a]

*Though it comes under different class, it is described here along with other luotoinin alkaloids.



Luotonin C (R' = Me)
Luotonin D (R' = Et)

Figure 3: Luotonin C & D

workers from Japan in their collaborative work with scientists from China isolated six new alkaloids:[16b,46] Luotonin A, B, C, D, E and F (Table 5 & Figure 3) from aerial parts of *P. nigellasturm*. Luotonin C and D are unusual canthin-6-one derivatives. The structural assignments of luotonin A-F have been done on the basis of analytical and spectral data,[16b,46] and these bioactive natural products exhibit an anti-tumor activity.[46a,47] Recently Ma et al[48b] reported a good bioactivity study of luotonin A and F analogues and Hecht et al[48c] reported synthesis & biochemical properties of A-ring modified luotonin A derivatives.

I] Luotonin A:

Luotonin A (**32**, entry 1) is cytotoxic towards the murine leukemia P-388 cell line (IC_{50} 1.8 μg/mL).[16b,46] Recently, Hecht et al[48a] have demonstrated that despite the lack of lactone ring functionality, luotonin A stabilizes the human DNA topoisomerase I-DNA covalent

binary complex and mediates topoisomerase I-dependant cytotoxicity in intact cells (IC_{50} 5.7-12.6 µm/mL), like camptothecin and its analogs[49] (Figure 4). In a very short span of time (6-years) eleven syntheses (Scheme 12-14, Table 5a) of luotonin A have been reported from different laboratories using variety of elegant synthetic strategies.[35c,38n,46b,50] Two approaches are illustrated below and the remaining have been tabulated in Table 5a.

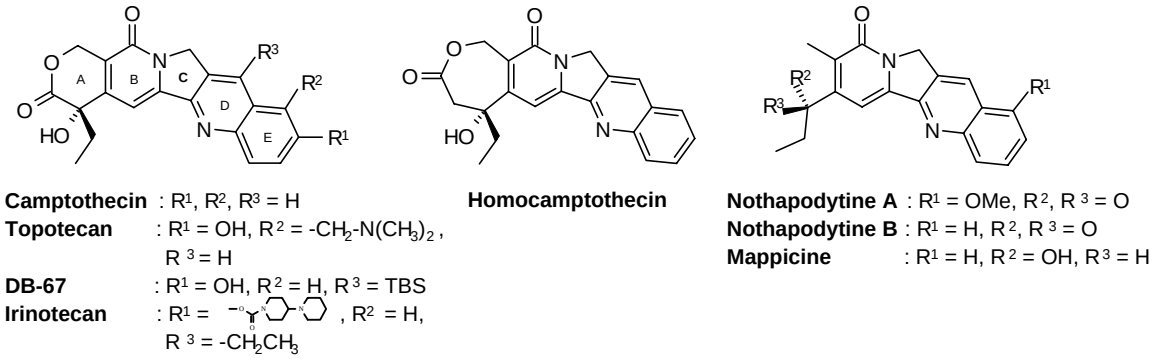
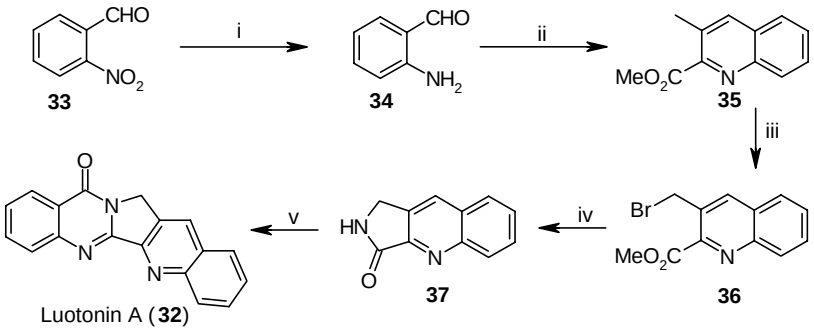


Figure 4: Camptothecin and its analogs

A] Ganesan's approach:

The structure of luotonin A (**32**) was unambiguously confirmed by Ganesan's total synthesis (Scheme 12). 3-Oxo-1*H*-pyrrolo[3,4-b]quinoline (**37**) was synthesized starting from *o*-nitrobenzaldehyde (**33**) via quinoline **36** in 5-steps. Deprotonation of quinoline **37**

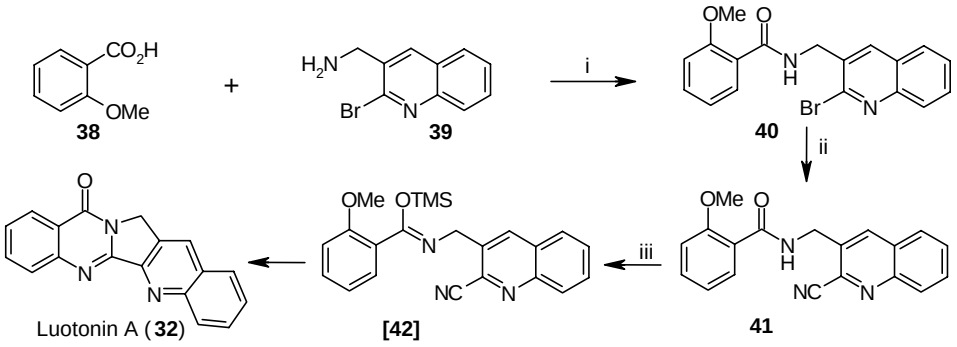


Scheme 12: (i) $FeSO_4$, NH_4OH (57%); (ii) (a) $CH_3CH_2COCO_2H$, NaOEt, MeOH, reflux, 16.5 h. (b) H_2SO_4, MeOH, reflux, 24.5 h. (60%); (iii) NBS, AIBN, CCl_4, reflux, 7 h (34%); (iv) NH_3, MeOH (74%); (v) $LiN(TMS)_2$, 2-sulfinylaminobenzoyl chloride (85%).

gave an anion which was coupled with 2-sulfinylaminobenzoyl chloride (prepared from the reaction of anthranilic acid with thionyl chloride) to afford the natural product luotonin A (**32**) in 7% overall yield starting from *o*-nitrobenzaldehyde (**33**) in 5-steps (Scheme 12).

B] Toyota's approach:

In Toyota's approach[50d,i] the intramolecular hetero Diels-Alder reaction of an aryl imino ether (diene) with an aryl nitrile (dienophile) has been used as the key reaction for an efficient approach to the pyrroquinozolino-quinoline alkaloid, luotonin A (**32**) (Scheme 13). Activation of the diene moiety by the incorporation of a methoxy group played an important role for the hetero Diels-Alder reaction. Acylation of amine **39** with acid **38** provided the bromo-amide **40**, which was converted to the cyano-amide **41** by using palladium-catalyzed coupling reaction with CuCN. Cyanide **41** was next subjected to intramolecular hetero Diels-Alder reaction by heating it with TMSCl and Et_3N in the presence of $ZnCl_2$ to obtain luotonin A (**32**) in 35% overall yield in 3-steps (Scheme 13).

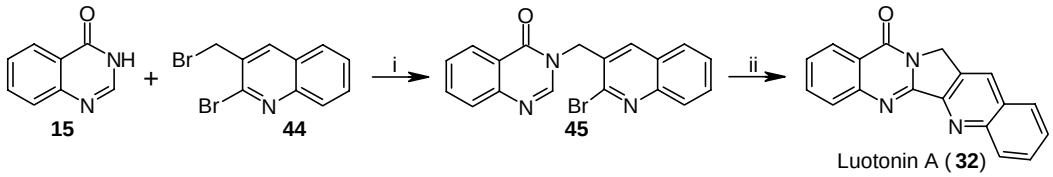


Scheme 13: (i) BOP, Et_3N, DCM (91%); (ii) $Pd_2(dba)_3$, DPPF, CuCN, Et_4NCN, 1,4-dioxane, reflux (84%); (iii) TMSCl, $ZnCl_2$, Et_3N, toluene, 150 ^oC in a sealed tube (46%).

C] Harayama's approach:

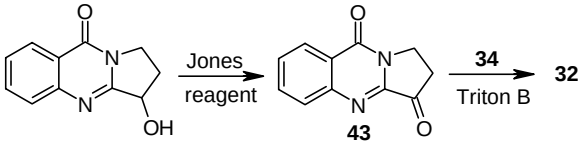
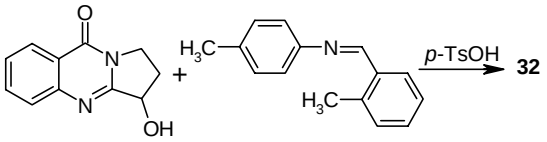
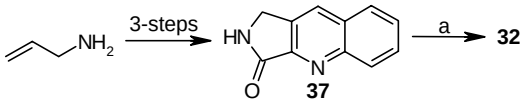
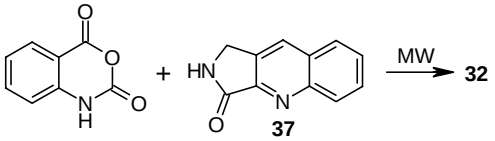
Out of eleven known syntheses, ten multi-step syntheses of linear penta-cyclic luotonin A have been completed using two suitable building blocks with construction of ring B or D.

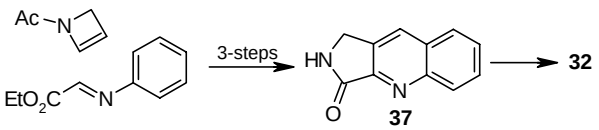
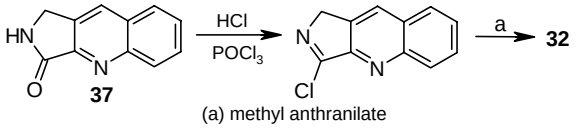
Recently, Harayama et al[50h] completed the synthesis of luotonin A (**32**) with construction of middle ring C using a Pd-assisted bi-aryl coupling reaction, wherein quinazolinone **45** was synthesized by coupling of quinazolinone **15** and bromo-quinoline **44**. Total synthesis of luotonin A (**32**) was completed by using a Pd-assisted biaryl coupling reaction of compound **45** in overall 79% yield over 2-steps (Scheme 14). Both such couplings have been used earlier by Comins et al[49b] in the total synthesis of camptothecin.



Scheme 14: (i) *t*-BuOK, DMF, rt, 1.5 h (92%); (ii) $Pd(OAc)_2$, tricyclohexylphosphine (Cy_3P), KOAc, DMF, reflux, 30 min (86%).

Table 5a: Various approaches to luotonin A

No.	Brief Scheme	Overall yield (%)	Reference
1.		5% (7-steps)	Kelly et al[50b]
2.		24% (3-steps)	Ma et al[50c]
4.	 (a) NaH, 2-nitrobenzoylchloride; then Fe, AcOH/EtOH	8% (6-steps)	Dallavalle et al[50e]
5.		85% (1-step)	Yadav et al[50f]

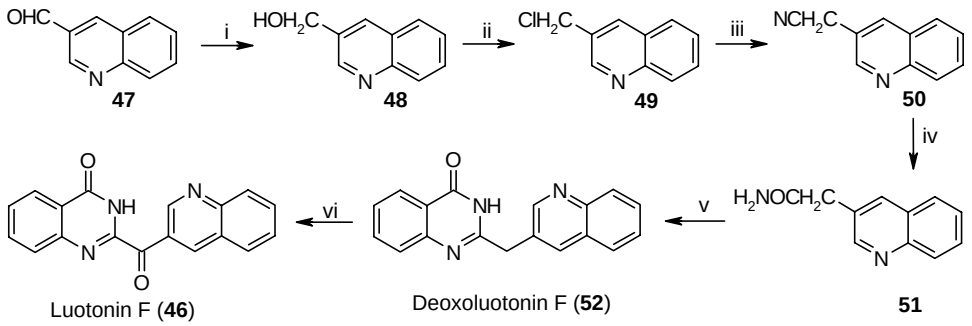
6.		Formal synthesis	Osborne et al[50g]
7.		88% (2-steps)	Lee et al[38n]

Molina et al[35c] in their formal synthesis of luotonin A (**32**), directly oxidized deoxyvasicinone to the precursor dione **43** which can be transformed to luotonin A (**32**) by Friedlander condensation with 2-amino benzaldehyde using Kelly's procedure.[50b]

Till date, four syntheses of luotonin B[46a,b,50c,h] and two syntheses of luotonin E[16b, 46b] & F[16b, 46b] are known. Ma et al[46a] exposed a chloroform solution of luotonin A (**32**) to sunlight for two weeks to obtain luotonin B (entry 2) whereas reaction of luotonin A (**32**) with cerric ammoniumnitrate (CAN) also gave luotonin B in 15% yield.[50c] Harayama et al[50h] brominated luotonin A with NBS under irradiation from a tungsten lamp, followed by solvolysis with silver nitrate in aqueous acetone to obtain luotonin B in 59% yield. Ma et al[16b] confirmed the structure of luotonin E (entry 3) by its synthesis from luotonin B, wherein luotonin B was treated with BF_3-etherate in a methanol solution to obtain luotonin E in 70% yield.

II] Luotonin F:

Ma et al[16b] completed the first total synthesis of luotonin F (Table 5, entry 4) starting from 3-formylquinoline with 5.6% overall yield in 6-steps (Scheme 15). This molecule comes under a different class but has been described here along with other members of luotonins. Quinoline **51** obtained in 4-steps from formylquinoline **47** via alcohol **48**, chloride **49** and the cyano-quinoline **50** was reacted with isatoic anhydride to obtain the bioactive precursor



Scheme 15: (i) $NaBH_4$, MeOH (85%); (ii) $SOCl_2$, benzene (96%); (iii) KCN, KI, 80% EtOH (62%); (iv) Conc. H_2SO_4 (71%); (v) isatoic anhydride, 200-210 ^oC (43%); (vi) MnO_2, $CHCl_3$, sunlight (36%).

deoxoluotonin F (**52**). Ma et al[48b] recently reported that the synthetic compound deoxoluotonin F has cytotoxic activity (IC_{50} 2.3 µg/mL) and shows DNA topoisomerase II inhibition at a concentration of 25 µM. Deoxoluotonin F was oxidized with MnO_2 in presence of sunlight to obtain luotonin F (Scheme 15).

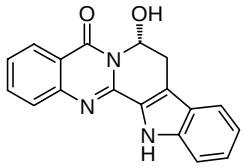
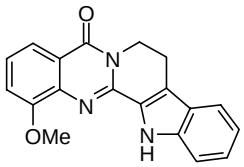
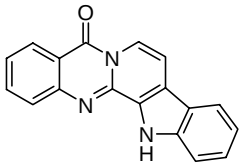
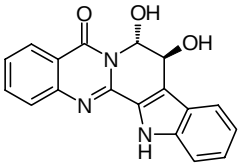
Recently we have completed[51b] the total synthesis of luotonin A, B and E via a novel ortho directed-lithiation as a key step. We have also completed a biogenetic total synthesis[51a] of luotonin F via deoxoluotonin F using Friedlander condensation. All these studies will be described in detail in chapter 3, as a part of this dissertation.

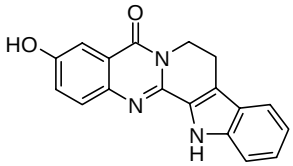
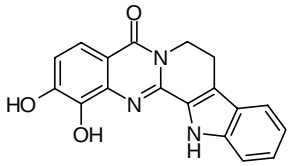
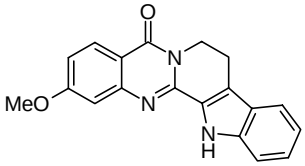
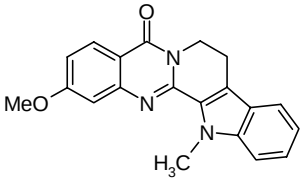
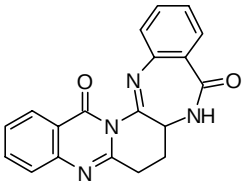
In conclusion, the pyrroloquinazolinoquinoline alkaloids luotonin A, B & E and 2-substitued quinazolino-quinoline alkaloid luotoin F (Table 5, entries 1-4) isolated by Nomura and Co-workers are important alkaloids having antitumor activity. Various elegant synthetic methods for all these alkaloids are known. Several syntheses of the alkaloid luotonin A in a short span of time and its correlation with camptothecin prove the importance of luotonin class of alkaloids for clinical purposes.

1.5 Quinazolinones fused with a piperidine ring system

Rutaecarpine (**53**) and its analogs (Table 6, entries 1-8) are derivatives of mackinazolinone (**54**), the simplest quinazolinone alkaloid having quinazolinone ring fused with a piperidine ring system, which was isolated[52] from *Mackinalaya* species, for which several syntheses[15,38l,m,52,61b] are known. It was synthesized[28,38k,n] by repeating the same scheme as shown in Table **3a** (entries 3-5) using 2-piperidone instead of 2-pyrrolidone. Spath et al[62] synthesized compound **54** by reduction of pyridoquinazoline **55** (Scheme 16).

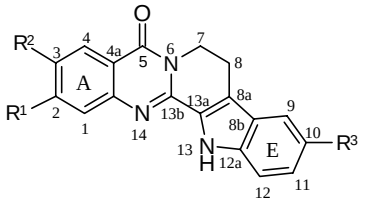
Table 6: Quinazolinones fused with a piperidine ring system (Rutaecarpines & auranthine)

No.	Quinazolinone alkaloid	Source[Ref.] and activity	Synthesis[Ref.]
1.	 (+)-7-Hydroxyrutaecarpine	*Tetradium glabrifolium*[53a] (*Evodia meliaefolia*) *Tetradium ruticarpum*[53a] *Phellodendron amurense*[53c]	$C_{18}H_{13}N_3O_2$
2.	 1-Methoxyrutaecarpine	*Zanthoxylum integrifolium*[53b] Antiplatelet aggregation activity	$C_{19}H_{15}N_3O_2$ Sheen et al[53b]
3.	 7,8-Dehydrorutaecarpine	*Phellodendron amurense*[53d]	$C_{18}H_{11}N_3O$ Synthesis known before isolation[59]
4.	 (−)-7,8-Dihydroxyrutaecarpine	*Phellodendron amurense*[53c]	$C_{18}H_{13}N_3O_3$

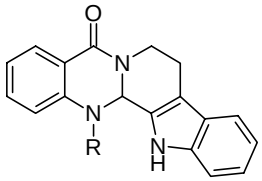
5.	 3-Hydroxyrutaecarpine	*Leptothyrsa sprucei*[53e] (*Rutaceae*)	$C_{18}H_{13}N_3O_2$
6.	 1,2-Dihydroxyrutaecarpine	*Bouchardatia neurococca*[53f]	$C_{18}H_{13}N_3O_3$
7.	 2-Methoxyrutaecarpine	*Araliopsis tabouensis*[53g] Antimalarial	$C_{19}H_{15}N_3O_2$
8.	 2-Methoxy-13-methyl-rutaecarpine	*Araliopsis tabouensis*[53g] Antimalarial	$C_{20}H_{17}N_3O_2$
9.	 Auranthine	*Penicillium aurantiogriseum*[55b]	$C_{19}H_{14}N_4O_2$

The first known representatives of the quinazolinocarboline alkaloids were rutaecarpine and evodiamine. The dried fruits of *Evodia rutaecarpa* have been used in the traditional Chinese medicine under the name Wu-Chu-ru[54b] and Shih-Hu[54c] as a remedy for headache, dysentery, cholera, worm infections and postpartum.[54a,d] The drug extract contains

quinazolinocarboline alkaloids rutaecarpine (**53**) and evodiamine.[55a] Recently callus tissue cultured from the stem of *Phellodendron amurense* has been shown to produce **53**, along with a variety of other alkaloids[7b(ix),53c,56] (Figure 5). In recent literature, **53** and its derivatives have been reported to possess strong analgesic, antiemetic, astringent, antihypertensive, uterotonic, TCDD-receptor, anti-nociceptive, anti-inflammatory and cycloxygenase (COX-2) inhibitory activities.[57] Rutaecarpine (**53**) was also found to suppress platelet plug formation in mesenteric venules and increase intracellular Ca^{2+} in



Rutaecarpine (**53**) ($C_{18}H_{13}N_3O$): $R^1 = R^2 = R^3 = H$
Hortiacine ($C_{19}H_{15}N_3O_2$): $R^1 = R^2 = H$, $R^3 = OMe$
Euxylophoricine ($C_{19}H_{13}N_3O_3$): $R^1 = R^2 = -O-CH_2-O-$, $R^3 = H$
Euxylophoricine A ($C_{20}H_{17}N_3O_3$): $R^1 = R^2 = OMe$, $R^3 = H$
Euxylophoricine D ($C_{21}H_{19}N_3O_4$): $R^1 = R^2 = R^3 = OMe$



(13*b*,14)-Dihydrorutaecarpine ($C_{18}H_{15}N_3O$): R = H
Evodiamine ($C_{19}H_{17}N_3O$): R = Me
14-Formyl-13*b*, 14-dehydrorutaecarpine: R = CHO ($C_{19}H_{15}N_3O_2$)

Figure 5: Naturally occurring bioactive rutaecarpines and analogs

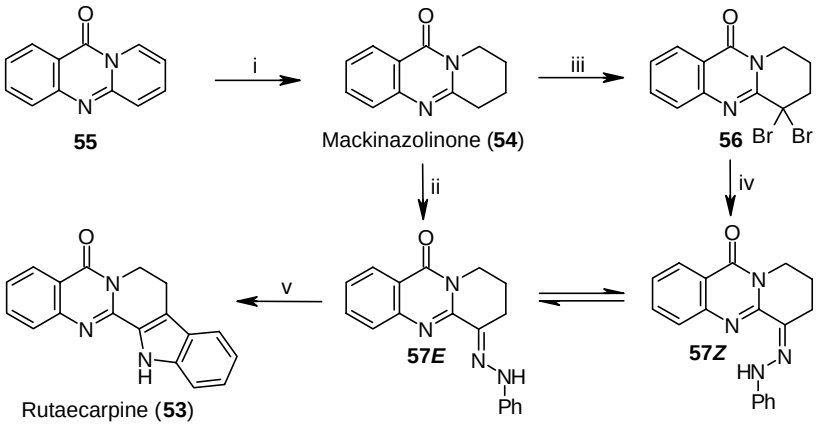
endothelial cells.[58] Recently Don et al[57g] reported their studies on the effect of structural modification on the inhibitory selectivity of rutaecarpine derivatives on human CYP1A1, CYP1A2 & CYP2B1 and found few of them to be most selective inhibitors. Rutaecarpines shown in Table 6 (entries 1-8) are new quinazolinocarboline alkaloids isolated form various species.[53] 1-Methoxyrutaecarpine (Table 6, entry 2) was prepared[53b] by methylating 1-hydroxyrutaecarpine with diazomethane and 7,8-dehydrorutaecarpine was synthesized by Bergman et al[59] from rutaecarpine by its oxidation with DDQ. There are no synthetic methods reported for the rutaecarpines presented in Table 6, entries 1, 4-8. A synthetic route could be designed for these molecules utilizing the various approaches available for the synthesis of rutaecarpine.

I] Rutaecarpine:

The first total synthesis of this important bioactive natural product **53** was reported[60] by Robinson et al in 1927 and since then several routes to **53** and its derivatives have been developed.[5,15,38e,g,n,44,59,61] Few syntheses are described below in detail and the remaining are listed in Table 6a.

A] Hermecz's approach:

Hermecz et al[61b] completed an efficient synthesis of rutaecarpine via the natural product mackinazolinone (**54**). Mackinazolinone (**54**) was synthesized either from 2-piperidone and anthranilic acid[38e] or by reduction[62] of compound **55**. Compound **54** was converted to hydrazone **57** by two different ways. In one of the methods, **54** was brominated to dibromo



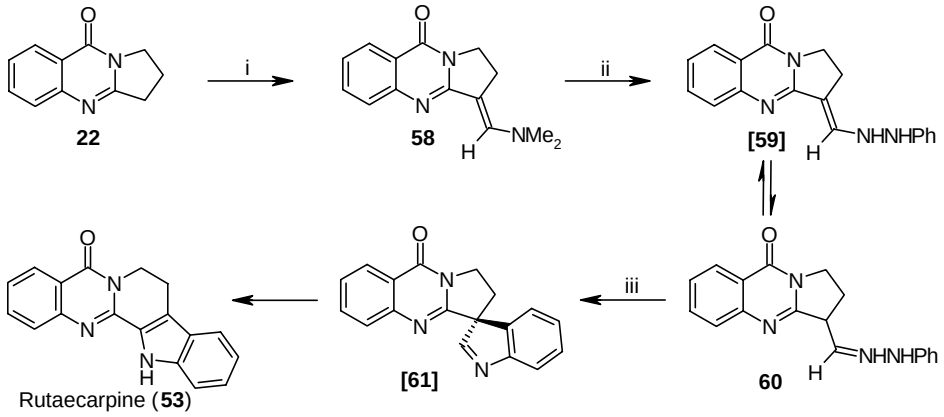
Scheme 16: (i) H_2, cat. (92%); (ii) Ph-$N_2^+Cl^-$, AcOH, pH-4, -5 to 10 ^oC, 12 h (98%); (iii) Br_2, AcOH-AcONa, 50 ^oC, 1 h (98%); (iv) phenylhydrazine, EtOH, reflux, 4 h (81%); (v) polyphosphoric acid, 180 ^oC, (92%).

compound **56**, which was then treated with phenylhydrazine to obtain hydrazone **57** in good yield. In the other method, which was later generalized by the authors,[63] the compound **54** was treated with phenyldiazonium chloride obtained from aniline to obtain directly the hydrazone **57** in quantitative yield. Interestingly, hydrazone **57** shows solvent

dependant geometric isomerism. Hydrazone **57** under PPA catalyzed Fischer indolization gave them rutaecarpine (**53**) in good yield, thus completing its total synthesis in 3-steps and 83% overall yield (Scheme 16).

B] Kokosi's approach:

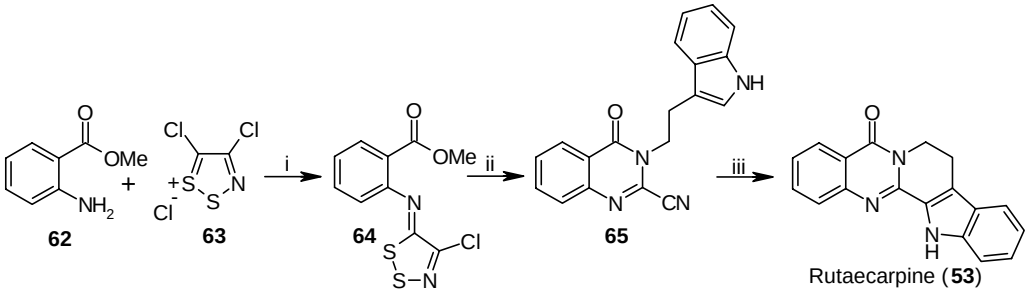
Kokosi's[44] rutaecarpine synthesis starts with deoxyvasicinone (**22**). The treatment of active methylene group of deoxyvasicinone (**22**) with Vilsmeier-Haack reagent afforded amino derivative **58**, which on treatment with phenylhydrazine gave hydrazone **60** via the intermediate **59**. Heating the hydrazone **60** in Dowtherm A, gave rutaecarpine (**53**) in 49% yield and in 40% overall yield from deoxyvasicinone (Scheme 17).



Scheme 17: (i) $POCl_3$, DMF, rt, 1 h; (ii) $PhNH_2$, EtOH, heat, 3 h; (iii) Dowtherm A, 160-190 ^oC, 0.5 h (49%).

C] Kim's approach:

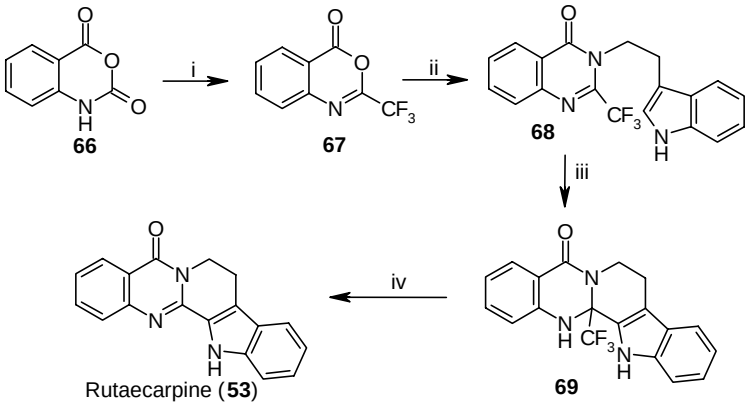
Kim et al[61e] developed an efficient general approach for the synthesis of rutaecarpine (**53**) and its analogs (Scheme 18), starting from the reaction of methylanthranilate (**62**) with 4,5-dichloro-1,2,3-dithiazolium chloride (Appel's salt)[64] to obtain derivative **64**. The anthranilate derivative **64** was then treated with tryptamine to obtain cyano quinazolinone **65**. Quinazolinone **65** was then converted to rutaecarpine (**53**) by treatment with trifluroacetic anhydride and HCl gas thus completing total synthesis of rutaecarpine (**53**) in 2-steps with 59% overall yield from **64**.



Scheme 18: (i) CH_2Cl_2, pyridine, rt, 3 h; (ii) tryptamine, CH_2Cl_2, rt, 31 h (62%); (iii) TFAA, HCl (g), 120-130 ^oC, 4 h (95%).

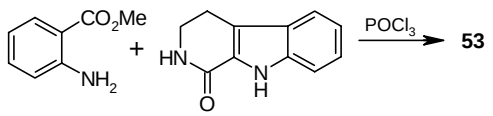
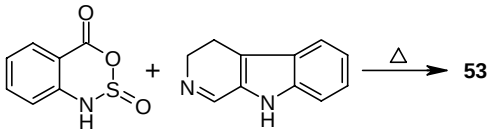
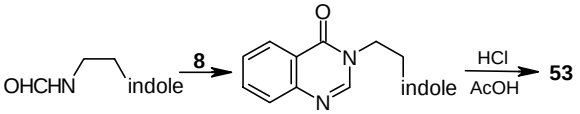
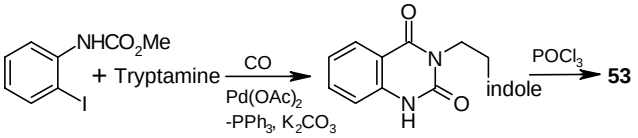
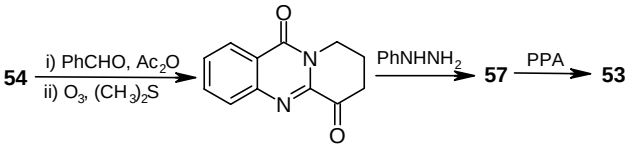
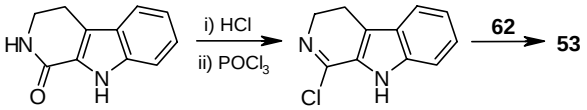
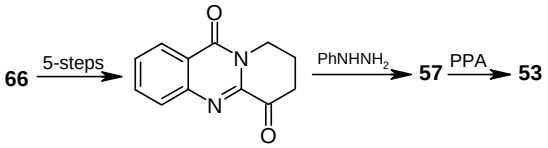
D] Bergaman's approach:

Bergaman et al[59] provided the most efficient approach for the synthesis of rutaecarpine (**53**). Isatoic anhydride (**66**) was converted to fluoromethyl-benzoxazinone **67** and then treated with tryptamine under mild conditions to obtain **68**. Quinazolinone **68** was cyclized under acidic conditions to compound **69** which, on refluxing in aq. EtOH, gave rutaecarpine (**53**), thus completing the total synthesis in 93% overall yield from benzoxazinone **67**.



Scheme 19: (i) TFAA, pyridine, 25 ^oC/15 min. + 115 ^oC/5 min.; (ii) tryptamine, 30 min. (98%); (iii) HCl, AcOH (95%); (iv) H_2O, EtOH (100%).

Table 6a: Various approaches to rutaecarpine

No.	Brief Scheme	Overall yield (%)	Reference
1.		24% (1-step)	Asahina et al[60]
2.		80% (1-step)	Kametani et al[38e]
3.		27% (2-steps)	Kametani et al[15]
4.		31% (2-steps)	Mori et al[38g]
5.		78% (4-steps)	Lee et al[61d]
6.		92% (2-steps)	Lee et al[38n]
7.		45% (7-steps)	Chavan et al[61g]

Kaneko et al[61c] completed the synthesis of rutaecarpine (**53**) by following almost the same strategy as described by Bergman et al[59] (Scheme 19). They have replaced the -CF_3 group by -Cl in order to study the mechanism of the reaction and to obtain rutaecarpine in better

yields. Their studies also gave evidence for the participation of the spiro intermediate in the cyclization step of Bergman's[59] rutaecarpine synthesis. Chang et al[61f] extended the approach for the synthesis of rutaecarpine analogs for COX-2 inhibitory activity studies developed by their own group.[61d]

In continuation of our research in synthesis of quinazolinone natural products, recently, we have completed[17b] a total synthesis of rutaecarpine (**53**) via the natural products 2-(4-hydroxybutyl)-quinazolin-4-one (Table 1, entry 2) and mackinazolinone (**54**) starting from glutaric anhydride by using zeolite induced Fischer-indole reaction as a key step. Our approach will be discussed in chapter 2, as a part of this dissertation.

II] Auranthine:

Auranthine (Table 6, entry 9), a derivative of mackinazolinone (**54**), is a structurally quite different quinazolinone alkaloid in this class and till date no synthetic method is known for the same. Recently Bergman et al[55c] reported studies towards the synthesis of alkaloid

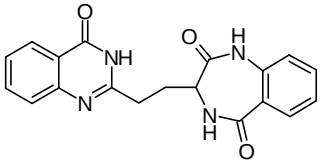


Figure 6: Auranthine precursor

auranthine, wherein different approaches have been discussed. The auranthine precursor (Figure 6) synthesized was treated with 50% polyphosphonic acid anhydride in ethyl acetate and DMA for the dehydration to occur but unfortunately instead of auranthine a C-acetyl derivative of auranthine was obtained.

In conclusion, rutaecarpine analogs (Table 6, entries 1-8) isolated from various species have moderate to good bioactivity and their synthesis should be possible by extending the several approaches available for rutaecarpine (Scheme 16-19 and Table 6a). Some

approaches to rutaecarpine used tryptamine as a starting material, wherein the indole moiety was carried forward from the beginning, whereas in many approaches the indole moiety was built up in the last step by using Fischer-indole reaction. Several publications on the synthesis and bioactivity of rutaecarpine and its analogs reveal that they are molecules of pharmaceutical importance. We feel that synthesis of auranthine (Table-6, entry 9) should be possible by further functionalization of the natural product mackinazolinone.

1.6 Quinazolinones fused with a piperazine ring system

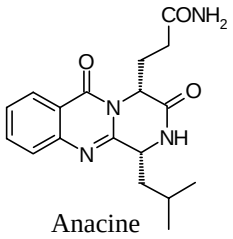
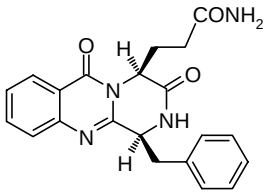
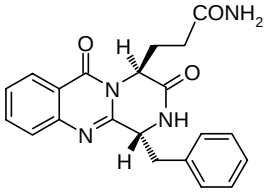
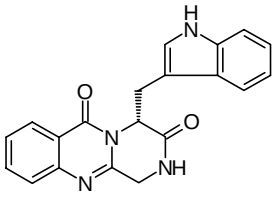
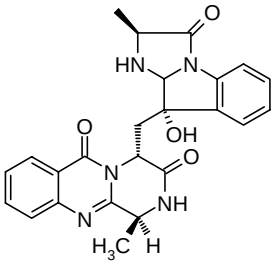
The quinazolinones fused with a piperazine ring system are subdivided into three classes. Class one consists of quinazolinones fused with just a piperazine ring, the ones fused with a piperazine ring along with a spiro-ring functionality form the second, while the last one comprises quinazolinones fused with a piperazine along with a prenyl substituted indole moiety, i.e. the alkaloids ardeemins.

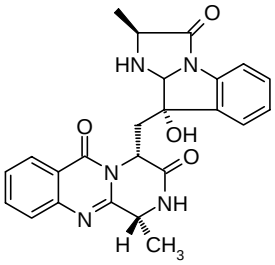
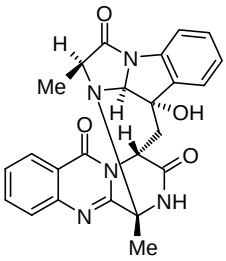
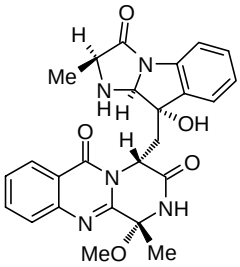
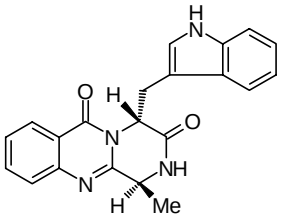
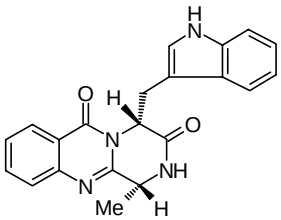
1.6.1 Quinazolinones fused with a simple piperazine ring system:

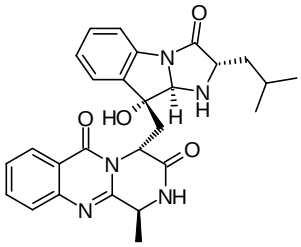
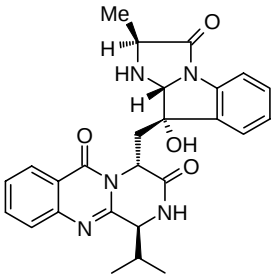
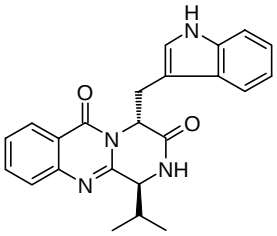
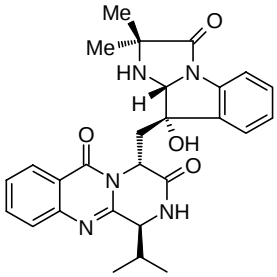
Under the review period, there are fourteen (Table 7, entries 1-14) quinazolinones isolated from various species, which are having a quinazolinone ring fused with piperazine ring system. Some of the representative syntheses are discussed in this section.

Table 7: Quinazolinones fused with a simple piperazine ring system

No.	Quinazolinone alkaloid	Source[Ref.] and activity	Synthesis[Ref.]
1.		*Penicillium verrucosum*[65] *Penicillium aurantiogriseum*[66]	$C_{18}H_{22}N_4O_3$ Wang et al[67]

	 Anacine		
2.	 (+)-Verrucine A	*Penicillium verrucosum*[65]	$C_{21}H_{20}N_4O_3$ Wang et al[67]
3.	 (+)-Verrucine B	*Penicillium verrucosum*[65]	$C_{21}H_{20}N_4O_3$ Wang et al[67]
4.	 (–)-Glyantrypine	*Aspergillus clavatus*[68]	$C_{20}H_{16}N_4O_2$ Five syntheses Refs.[69-73]
5.	 Fumiquinazoline A	*Aspergillus fumigatus*[74,75] Cytotoxic	$C_{24}H_{23}N_5O_4$ Snider et al[76]
6.		*Aspergillus fumigatus*[74,75] Cytotoxic	$C_{24}H_{23}N_5O_4$

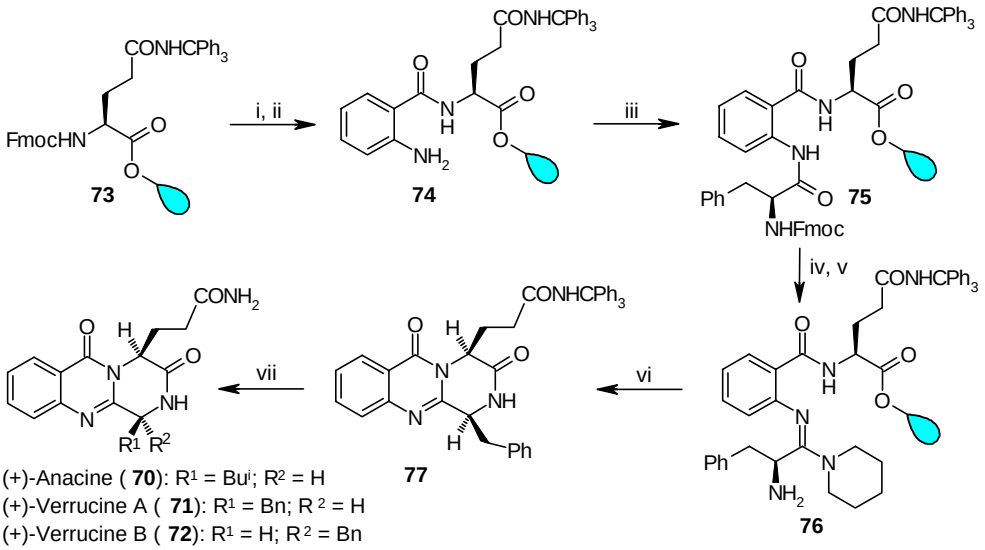
	 Fumiquinazoline B		Snider et al[76]
7.	 Fumiquinazoline D	*Aspergillus fumigatus*[75] Cytotoxic in P388 lymphocytic leukaemia test system	$C_{23}H_{21}N_5O_4$
8.	 Fumiquinazoline E	*Aspergillus fumigatus*[75] Cytotoxic in P388 lymphocytic leukaemia test system	$C_{29}H_{25}N_5O_5$ Snider et al[76,77]
9.	 Fumiquinazoline F	*Aspergillus fumigatus*[75] *Penicillium thymicola*[78] Cytotoxic in P388 lymphocytic leukaemia test system	$C_{21}H_{18}N_4O_2$ Wang et al[70,71] Hernández et al[73]
10.	 Fumiquinazoline G	*Aspergillus fumigatus*[75] Cytotoxic in P388 lymphocytic leukaemia test system	$C_{21}H_{18}N_4O_2$ Six syntheses Refs.[70,71,73,79-81]

11.	 (−)-Fumiquinazoline I	*Acremonium sp.*[82] Antifungal	$C_{27}H_{29}N_5O_4$ Snider et al[76]
12.	 Fiscalin A	*Neosartorya fischeri*[83]	$C_{26}H_{27}N_5O_4$
13.	 Fiscalin B	*Neosartorya fischeri*[83] *Corynascus setous*[84]	$C_{23}H_{22}N_4O_2$ Four syntheses Refs. [70,71,73,85]
14.	 Fiscalin C	*Neosartorya fischeri*[83]	$C_{27}H_{29}N_5O_4$

I] Anacine, Verrucine A and Verrucine B:

The first reported synthesis of the three related pyrazino[2,1-*b*]-quinazoline-3,6-dione alkaloids, anacine, verrucine A and verrucine B (entries 1-3) have been accomplished by exploiting the peptide assembly on Sasrin resin (Scheme 20).[67] For example, the resin-

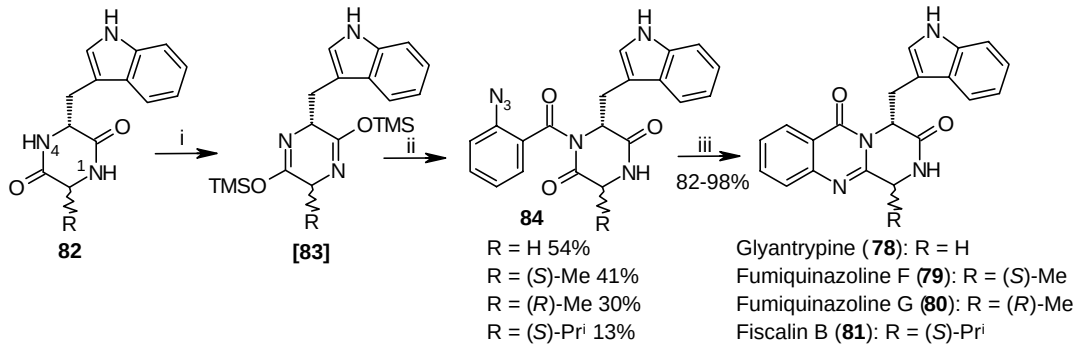
bound L-glutamine derivative **73** was sequentially condensed with anthranilic acid and Fmoc-protected L-phenylalanine chloride to give the resin-bound tripeptide **75**. Intramolecular dehydration followed by treatment with piperidine, a general procedure developed by Ganesan et al[70] and improved by Snider et al,[80] afforded amidine **76**. Cyclization with concomitant detachment from the resin was effected by overnight heating in a mixture of acetonitrile and 1,2-dichloroethane to give *N*-tritylverrucine A (**77**) in 17% overall yield from **73**; only 0.8% of the corresponding 1,4-*anti*-disubstituted isomer was isolated. The removal of the trityl group was achieved reductively with triethylsilane in trifluoroacetic acid to give (+)-verrucine A (**71**). Similar reaction sequences employing D-phenylalanine and L-leucine afforded (+)-verrucine B (**72**) and (+)-anacine (**70**), respectively, in overall yields of 14.5% and 9.3% based on **73** (Scheme 20). The absolute configuration of the former, not assigned when it was isolated, has thus been established unambiguously.



Scheme 20: (i) 20% piperidine in DMF, 15 min.; (ii) EDC, anthranilic acid, DMF or NMP, rt, 19 h; (iii) Fmoc-L-Phe-Cl, pyridine, CH_2Cl_2, rt, 13 h, workup, repeat condition (i); (iv) PPh_3, I_2, EtN^iPr_2, CH_2Cl_2, rt, 15 h; (v) 20% piperidine in CH_2Cl_2, rt, 30 min.; (vi) MeCN-$(CH_2Cl)_2$ (1:1), reflux overnight (17% over six-steps); (vii) TFA-Et_3SiH-CH_2Cl_2 (2:2:1), rt, 15 min. (84%).

II] Glyantrypine, Fumiquinazoline F & G and Fiscanlin B:

The other members of this family like glyantrypine, fumiquinazoline F & G and fiscanlin B have been synthesized as shown in scheme 21.[73] Avendaño and co-workers[73] have



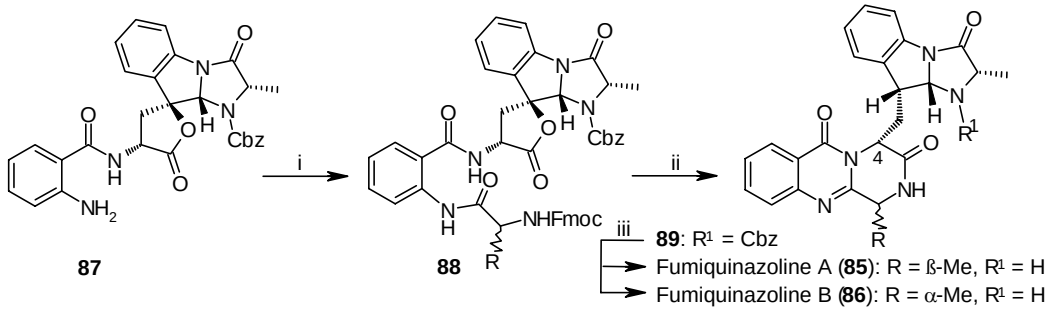
Scheme 21: (i) TMSCl, Et_3N, CH_2Cl_2, rt; (ii) 2-$N_3C_6H_4COCl$, CH_2Cl_2, rt; (iii) Bu_3P, PhMe, rt.

investigated the acylation of a range of diketopiperazines **82**, prepared by standard methods from the respective *N*-Boc dipeptides, with 2-azidobenzoyl chloride *via* the silyl imidates **83** (Scheme 21).[73] With the glycine derivative of **82** (*i.e.*, R = H), selective monoacylation on *N*(4) nitrogen atom to give **84** was ascribed to a boat-like conformation of the silylated intermediate, with the indolyl substituent folding in such a way that *N*(1) gets blocked. Selectivity was also good with the (*S*)-alanine derivative of **82** [R = (*S*)-Me], but less impressive with the (*R*)-alanine and (*S*)-valine analogues [R = (*R*)-Me and (*S*)-Pr^i], which gave almost equal amounts of the *N*(1)-acylated products. All of the acylated products **84** could be cyclized by an intramolecular Staudinger reaction upon treatment with tributylphosphine to complete syntheses of (–)-glyantrypine (**78**), (–)-fumiquinazoline F (**79**), fumiquinazoline G (**80**) and fiscalin B (**81**), respectively.

III] Fumiquinazoline A, B & I:

The more complex (–)-fumiquinazolines A, B and I (entries 5,6 & 11) have also been synthesized by Snider's group[76] using routes in which most of the effort was,

understandably, devoted to constructing the 3-oxotetrahydro-1*H*-imidazo[1,2-*a*]indol-9-yl substituents.[76] Formation of the 2*H*-pyrazino[2,1-*b*]quinazoline-3,6(1*H*,4*H*)-dione moieties was left to the final stages of the synthesis, and involved a methodology similar to that shown in Scheme 20 (see steps **74** to **77**). In the case of fumiquinazoline A, for



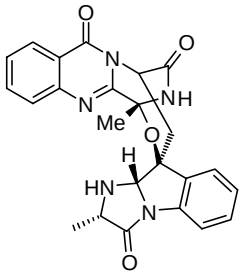
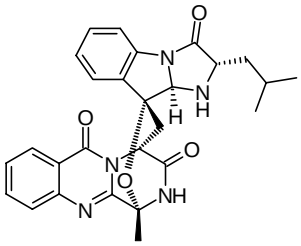
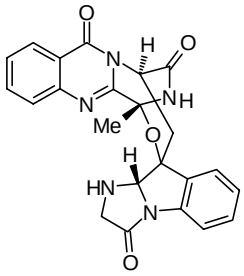
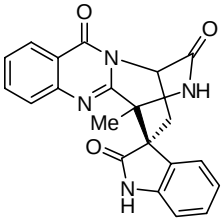
Scheme 22: (i) Fmoc-L-Ala/D-Ala, EDAC, CH_3CN; (ii) (a) PPh_3, Br_2, Et_3N, (b) piperidine, EtOAc (c) CH_3CN, reflux; (iii) H_2, Pd/C.

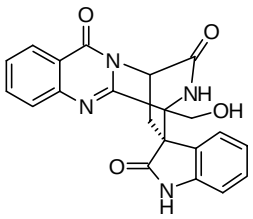
example, treatment of the precursor **88** with triphenylphosphine and bromine in the presence of triethylamine followed by aminolysis of the resulting benzoxazine with piperidine and final cyclization gave a mixture of the Cbz-protected product **89** and its C-4 epimer in overall yields of 49% and 14%, respectively. Removal of the Cbz protecting group from the former by hydrogenolysis over palladium completed the synthesis of (–)-fumiquinazoline A in 90% yield. The overall yields for (–)-fumiquinazolines B and I from the appropriate precursors similar to **88** were 42% and 52%, respectively. The first total synthesis of fumiquinazoline E (**91**, entry 8) was completed by using the intermediate **87** and following almost the same transformations with the appropriate amino acid (Scheme 23).

1.6.2 Quinazolinopiperazines with a spiro-ring system:

There are five alkaloids (Table 8, entries 1-5) isolated from various species, having quinazolinone ring fused with a piperazine ring along with a spiro-ring system.

Table 8: Quinazolinones fused with a piperazine ring along with a spiro-ring system

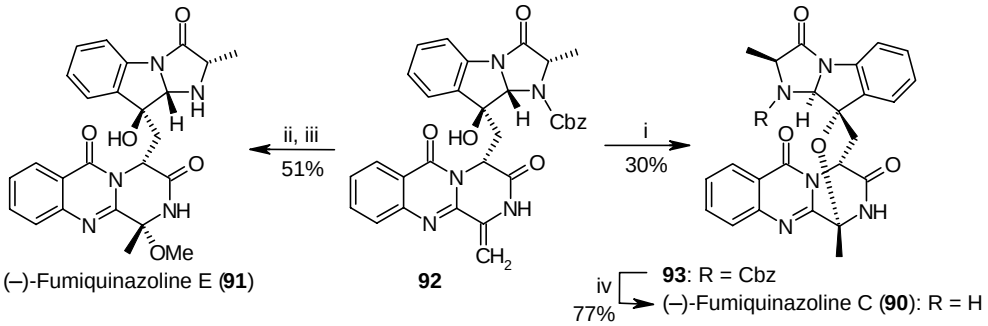
No.	Quinazolinone alkaloid	Source[Ref.] and activity	Synthesis[Ref.]
1.	 Fumiquinazoline C	*Aspergillus fumigatus*[74,75] Cytotoxic	$C_{24}H_{21}N_5O_4$ Snider et al[76,77]
2.	 (−)-Fumiquinazoline H	*Acremonium sp.*[82] Anti-fungal	$C_{27}H_{27}N_5O_4$ Snider et al[76,77]
3.	 (–)-Spiroquinazoline	*Aspergillus flavipes*[86] Inhibits binding of substance P to human astrocytoma cells	$C_{23}H_{19}N_5O_4$
4.	 (+)-Alantrypinone	*Penicillium thymicola*[78]	$C_{21}H_{16}N_4O_3$ Hart et al[87,88a] Kende et al[88b]

5. 
(–)-Serantrypinone

Penicillium thymicola[89] (IBT 5891) $C_{21}H_{16}N_4O_4$

I] Fumiquinazoline C, E, H:

The advanced intermediate **87** (Scheme 22), previously used by Snider et al[76] in a synthesis of the *Aspergillus* metabolite fumiquinazoline A (**85**), has been nicely transformed into two other complex fumiquinazolines by the same group (Scheme 23).[77]



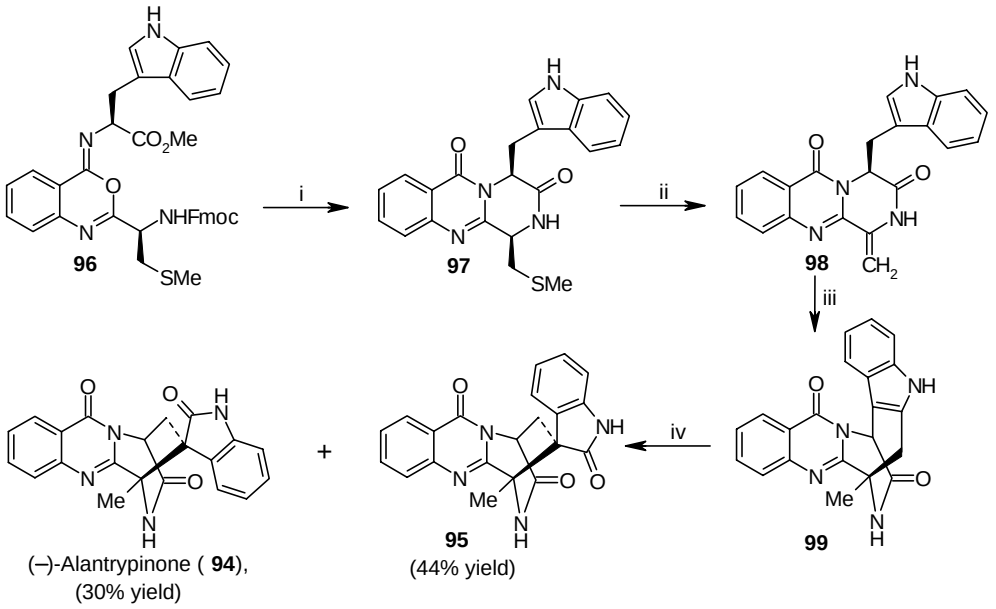
Scheme 23: (i) CH_3CN-HOAc (100:1), reflux, 2 h; (ii) HCl (0.2 M), MeOH, 25 ^oC; (iii) H_2 (1 atm), Pd/C, 30 min.; (iv) H_2, Pd/C, 30 h.

Condensation of **87** with a selenocysteine derivative, (*R*)-FmocNHCH(CH_2SePh)CO_2H, yielded the quinazoline precursor of the type **88** (Scheme 22), which was subjected to the Ganesan's cyclization condition to sequentially afford the benzoxazine and amidine (of the type **76**, Scheme 20) intermediates. Heating crude amidine in acetonitrile-acetic acid (25:1) at reflux set off a cascade of reactions that culminated in the formation of a mixture of **92** and its oxygen-bridged isomer **93** in yields of 56% and 14%, respectively, based on benzoxazine. Compound **92** could be partially converted into **93** by further heating, and recovered **92** was recycled. Finally, standard transformations on both products completed the first reported total syntheses of (–)-fumiquinazolines C (**90**) and E (**91**), respectively. A

Similar set of reactions on the appropriate analogue of **87**, designed to produce (–)-fumiquinazoline H (Table 8, entry 2), was accomplished, and required replacement of the Cbz protecting group by Fmoc in the benzoxazine intermediate before satisfactory cyclization could be effected.

II] Alantrypinone:

The principles implicit in the Wang and Ganesan[70,71] route to fumiquinazolines have been applied by Hart and Magomedov[87,88a] to a synthesis of the structurally complex alkaloid alantrypinone (**94**) (Scheme 24).[87,88a]

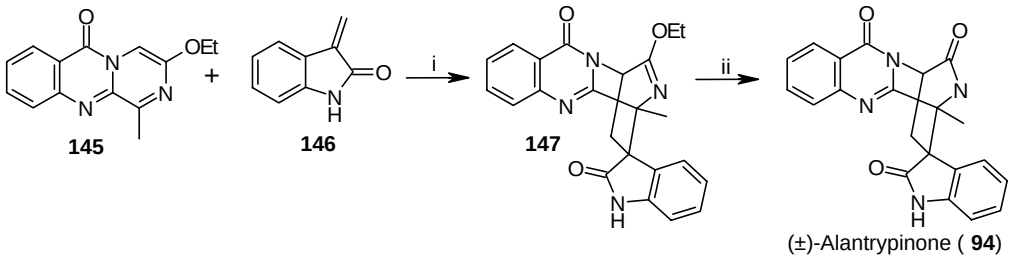


Scheme 24: (i) (a) $(Me_3AlSPh)Li$, THF, -78 to -10 ^oC, (b) piperidine, THF, 0 ^oC (71%); (ii) (a) *m*-CPBA, CH_2Cl_2, -78 ^oC, (b) Ph_3P, C_6H_6, reflux (79%); (iii) TFA, 70 ^oC (89%); (iv) (a) NBS, TFA-THF-H_2O, (b) H_2, Pt/C, MeOH.

In this case, dehydration of the precursor tripeptide of the type **88** (Scheme 22) gave the benzoxazine intermediate **96** in 80% yield. Treatment with ten equivalents of $(Me_3AlSPh)Li$ in THF at low temperature gave the expected pyrazino[2,1-*b*]quinazoline-3,6-dione **97** in 46% yield. However, with five equivalents of the reagent, the intermediate

quinazolinone was isolated and efficiently cyclized to **97** (94% yield) when treated with piperidine in THF at 0 ^{o}C. Oxidative elimination of the methylthio group then yielded the *exo*-methylene product **98** (79%), which cyclized in trifluoroacetic acid to the bridged hexacyclic compound (–)-**99** (89%). Oxidative rearrangement of this indole to an oxindole produced a mixture of (–)-alantrypinone **94** (the unnatural enantiomer) and its C-17 epimer (–)-**95** in yields of 30% and 44%, respectively. The synthesis confirmed the absolute configuration of natural alantrypinone, previously determined by the anomalous dispersion technique.

Recently Kende et al[88b] accomplished an efficient synthesis of (±)-alantrypinone and its 17-*epi*-isomer by employing a novel aza-Diels-Alder reaction between compound **145** and **146**, as the key step. The reaction sequence comprises 8-steps starting from anthranilic acid and proceeds in 13.5% yield (Scheme 25).



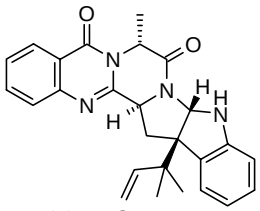
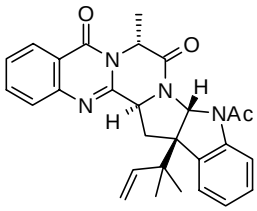
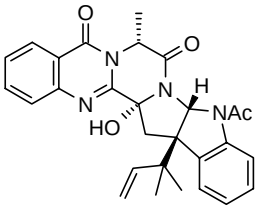
Scheme 25: (i) $CHCl_3$, rt, 24 h (55%); (ii) EtOAc, 1.0 N HCl, rt, 5 h (85%).

1.6.3 Quinazolinopiperazines with a prenylated indole moiety:

As part of a screening program for biologically active metabolites, McAlpine and co-workers[90,91] found that extracts of the fungus *Aspergillus fischeri* (var. brasiliensis) demonstrated the ability to restore vinblastine sensitivity to a tumor cell line that was otherwise insensitive.[90,91] Isolation of the active components from the fermentation mixture led to the characterization of three structurally related agents, which were called the

"ardeemins" for their ability to reverse drug insensitivity (vide infra). The major and most active constituent was named 5-*N*-acetylardeemin (**101**) and two other constituents isolated from the product mixture were termed ardeemin (**100**) and 15*b*-*β*-hydroxy-5-*N*-acetylardeemin (Table 9, entries 1-3).

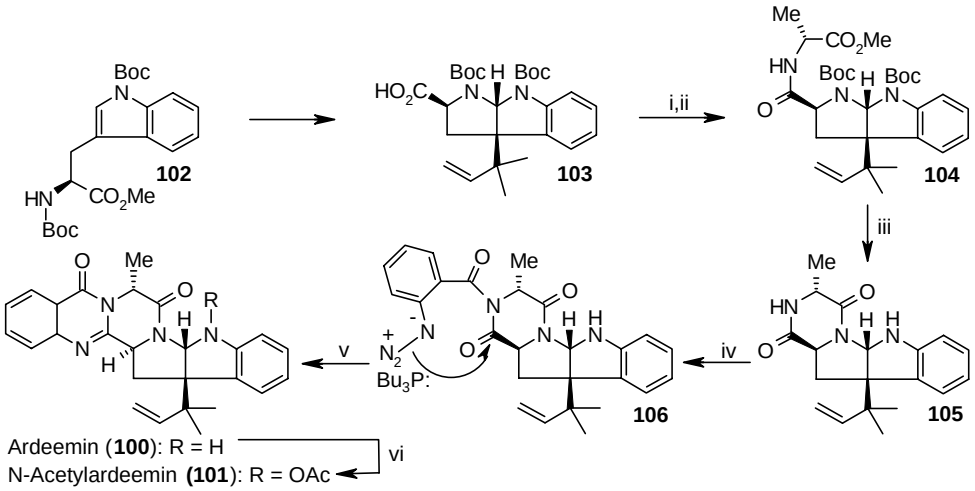
Table 9: Quinazolinopiperazines with a prenylated indole moiety (Ardeemin alkaloids)

No.	**Quinazolinone alkaloid**	**Source[Ref.] and activity**	**Synthesis[Ref.]**
1.	 (−)-Ardeemin	*Aspergillus fischeri*[90,91] var. brasiliensis	$C_{26}H_{26}N_4O_2$ Danishefsky et al[92.93]
2.	 (−)-5-*N*-Acetylardeemin	*Aspergillus fischeri*[90,91] var. brasiliensis Reversed multiple drug resistance (MDR) in human tumor cell lines and sensitized cells to anticancer vinblastine	$C_{28}H_{28}N_4O_3$ Danishefsky et al[92.93]
3.	 (−)-15b-*β*-Hydroxy-5-*N*-acetylardeemin	*Aspergillus fischeri*[90,91] var. brasiliensis	$C_{28}H_{28}N_4O_4$

I] (–)-Ardeemin and (–)-5-*N*-Acetylardeemin:

Structurally, the ardeemins belong to an interesting class of natural products, which are termed "reverse prenyl" hexahydropyrrolo[2,3-*b*]indole alkaloids. Danishefsky et al[92,93]

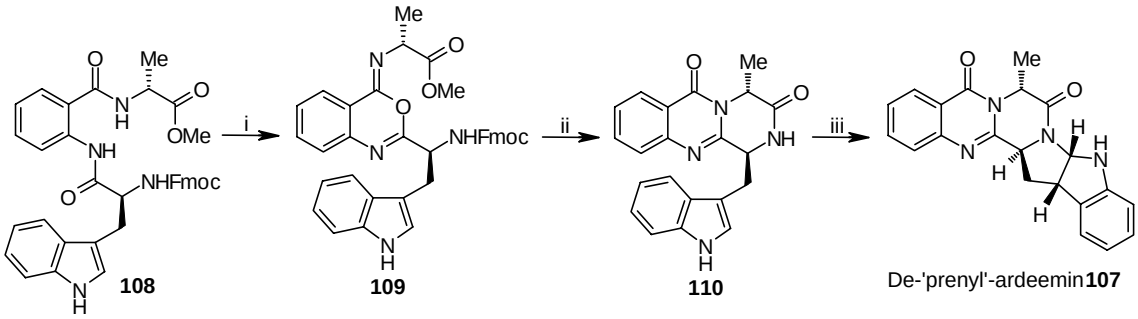
completed first the total synthesis of these structurally complex quinazolinones. The starting material was bis(Boc)tryptophan methyl ester **102** (Scheme 26),[92,93] which was transformed to the diketopiperazine **105** via the prenyl-acid **103** and prenyl-ester **104** by using standard transformations. The diketopiperazine **105** was obtained in 76% yield



Scheme 26: (i) FCN, pyridine, CH_2Cl_2, -15 ^oC; (ii) D-Ala-OMe.HCl, $NaHCO_3$, H_2O, CH_2Cl_2 (71%); (iii) TMSI, MeCN, 0 ^oC, then NH_3, DMAP, MeOH (76%); (iv) KHMDS, *o*-$N_3C_6H_4COCl$, THF, -78 ^oC (80%); (v) Bu_3P, C_6H_6 (72%); (vi) LDA, THF, -78 ^oC to rt, then AcCl, reflux (82%).

upon deprotection of **104** and ammonia-DMAP-induced intramolecular cyclization. An intramolecular variant of the aza-Wittig reaction was used for efficient fusion of the (3*H*)-quinazolin-4-one sector. Following acylation of **105** with *o*-azidobenzoyl chloride, the resultant **106** reacted with tributylphosphine in benzene to afford ardeemin (**100**) in 56% yield from **105**. Finally, acylation of **100** provided 5-*N*-acetylardeemin (**101**) in 11% overall yield for the total synthesis. In summary, the core structure of the three reverse prenylated hexahydropyrroloindole alkaloids was assembled rapidly and stereoselectively (through thermodynamic control) from a suitably protected tryptophan in two steps. Synthesis of (–)-15*b*-*β*-hydroxy-*N*-acetylardeemin appears possible following the same strategy.

Recently Sollhuber et al[94] have developed a new method for the synthesis of framework of ardeemin without the prenyl group (Scheme 27). De-'prenyl'-ardeemin was synthesized[94] in four steps with 45% overall yield, starting from *N*-2-aminobenzoyl-*α*-amino ester using



Scheme 27: (i) PPh_3, I_2, EtN^iPr_2, 3 h; (ii) (a) 20% piperidine/CH_2Cl_2, rt, 3 h (b) CH_3CN, reflux, 2 h; (iii) TFA, rt (45% overall yield).

standard transformations (Scheme 27). In the last step, the acid promoted cyclization of the dione **110** occurs in an irreversible and stereocontrolled fashion.

In conclusion, it appears that the two important protocols; Eguchi protocol and Ganesan's protocol have been used extensively for the synthesis of this class of alkaloids (Table 7,8 & 9). We feel that the most difficult and challenging task in the synthesis of complex alkaloids fumiquinazoline A, B, C, E, H & I was further functionalization of the indole moiety. Snider et al, in their elegant approaches to various fumiquinazolines, have developed an easy and straightforward access to these structurally complex and strained moieties.

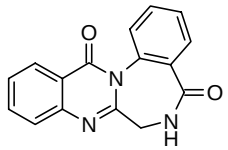
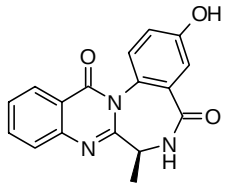
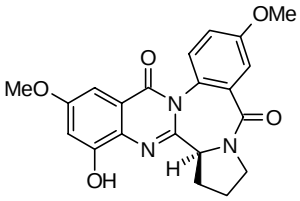
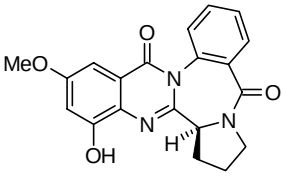
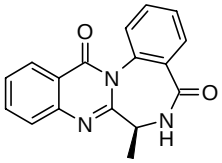
1.7 Quinazolinones fused with a diazepine ring system

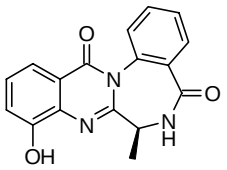
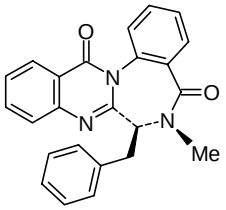
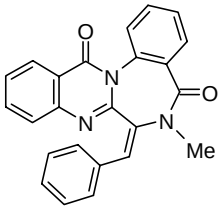
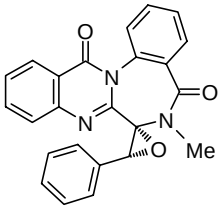
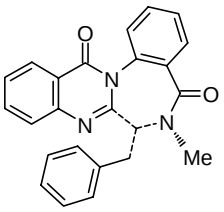
This class of quinazolinones is again subdivided into two classes. One presents simple benzodiazepines like sclerotigenin, circumdatins and benzomalvins, while the second class comprises the more complex asperlicins.

1.7.1 Sclerotigenin, Circumdatins and Benzomalvins:

The ten quinazolinones isolated from various species (Table 10) have a diazepine ring fused with a quinazolinone system.

Table 10: Quinazolinobenzodiazepines (Sclerotigenin, circumdatins and benzomalvins)

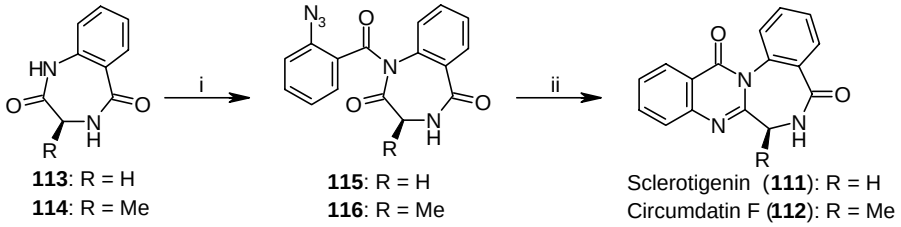
No.	Quinazolinone alkaloid	Source[Ref.] and activity	Synthesis[Ref.]
1.	 Sclerotigenin	*Penicillium sclerotigenum*[95] Anti-insectan	$C_{16}H_{11}N_3O_2$ Synthesis known before isolation[96] Snider et al[81] Witt et al[97] Grieder et al[98]
2.	 (–)-Circumdatin C	*Aspergillus ochraceus*[99]	$C_{17}H_{13}N_3O_3$ Witt et al[101]
3.	 (–)-Circumdatin D	*Aspergillus ochraceus*[99]	$C_{21}H_{19}N_3O_5$
4.	 (–)-Circumdatin E	*Aspergillus ochraceus*[99]	$C_{20}H_{17}N_3O_4$
5.	 (–)-Circumdatin F	*Aspergillus ochraceus*[99]	$C_{17}H_{13}N_3O_2$ Witt et al[97,101] Snider et al[81]

6.	 (–)-Circumdatin G	*Aspergillus ochraceus*[100]	$C_{17}H_{13}N_3O_3$
7.	 Benzomalvin A	*Penicillium culture*[102] Inhibitor of substance P, the endogenous ligand for neurokinin-1 receptor	$C_{24}H_{19}N_3O_2$ Sun et al[103] Eguchi et al[104,105]
8.	 Benzomalvin B	*Penicillium culture*[102]	$C_{24}H_{17}N_3O_2$ Sugimori et al[105]
9.	 Benzomalvin C	*Penicillium culture*[102]	$C_{24}H_{17}N_3O_3$
10.	 Benzomalvin D	*Penicillium culture*[103]	$C_{24}H_{19}N_3O_2$

I] Sclerotigenin:

Sclerotigenin (**111**) was known as a synthetic compound before its isolation.[96] After its isolation many syntheses have been reported.[96-98] Recently Snider et al[81] provided an

efficient general synthetic method for the synthesis of sclerotigenine and other members of benzodiazepine class (Scheme 28). Benzodiazepinedione **113** was selectively acylated at the more acidic anilide nitrogen, followed by aza-Wittig cyclization of the resulting imide **115** with Bu_3P afforded 43% of sclerotigenine (**111**) from dione **113** in 2-steps, without



Scheme 28: (i) (a) Et_3N, DMAP, DMSO-CH_2Cl_2, then 2-$N_3C_6H_4COCl$, CH_2Cl_2, 20 ^oC (for R = H), (b) Et_3N, DMAP, THF, then 2-$N_3C_6H_4COCl$, THF, 20 ^oC (for R = Me); (ii) Bu_3P, C_6H_6, rt to 60 ^oC.

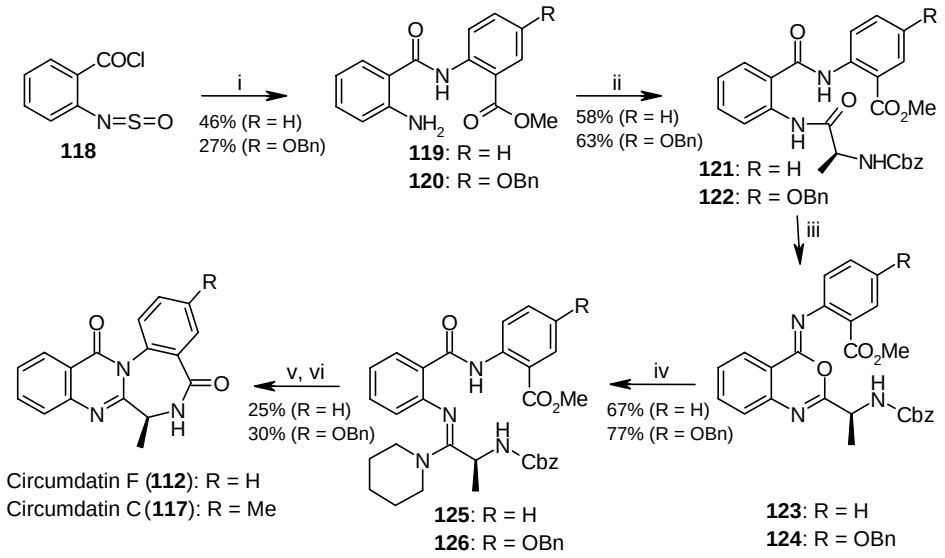
using any protection-deprotection chemistry. This strategy is general and can be applied for the synthesis of other quinazolinones (Table 10, entries 2, 5 & 6) of this class.

II] Circumdatins:

Circumdatins are the new fused benzodiazepine alkaloids isolated from terrestrial isolate of the fungus *Aspergillus ochraceus*.[99,100] Circumdatin C, F and G are prototypical members, while others such as circumdatin D and E contain an additional tetrahydropyrrole ring (Table 10, entries 2-6). Benzodiazepines constitute a widely prescribed class of psychoactive drugs.[99] First total synthesis of circumdatin C (**117**) and F (**112**) was recently reported by Bergman et al[101] (Scheme 29).

N-Sulfinylanthraniloyl chloride (**118**) was the preferred starting material for Witt and Bergman's assembly of the tripeptides **121** & **122**, key intermediates in a route to the fungal metabolites circumdatin F (**112**) and circumdatin C (**117**) (Scheme 29) respectively. Cyclization of **121** & **122** with triphenylphosphine and iodine in the presence of Hunig's

base gave the benzoxazines **123** & **124** respectively. Aminolysis of benxoxazines with piperidine produced the amidines **125** & **126**. The target alkaloids **112** and **117** were obtained after deprotection with HBr in acetic acid followed by treatment with a tertiary amine and silica gel.



Scheme 29: (i) Methyl anthranilate (R = H) or methyl 5-benzyloxyanthranilate (R = OBn), toluene, rt; 48 h; (ii) *N*-Cbz-L-Ala, DCC, CH_2Cl_2, 0 ^oC to rt; (iii) Ph_3P, I_2, Pr^i_2NEt, CH_2Cl_2, rt[57% (R = H, 36% (R = OBn)]; (iv) 20% piperidine in EtOAc, rt; (v) 45% HBr in HOAc, 60 ^oC; (vi) Et_3N (for R = H) or Pr^i_2NEt (for R = OH), EtOAc, rt.

An efficient total synthesis of circumdatin F was reported by Snider et al[81] in 69% yield from dione **114**, following selective acylation and aza-Wittig cylization reaction sequence (Scheme 28). A new synthesis of circumdatin F arose from the work of Bergman et al[97] where bezoxazinone was used as a potential intermediate. Recently Grieder et al[98] developed a concise building block approach to a diverse multi-arrayed library of the

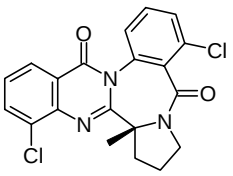


Figure 7: Circumdatin analogue

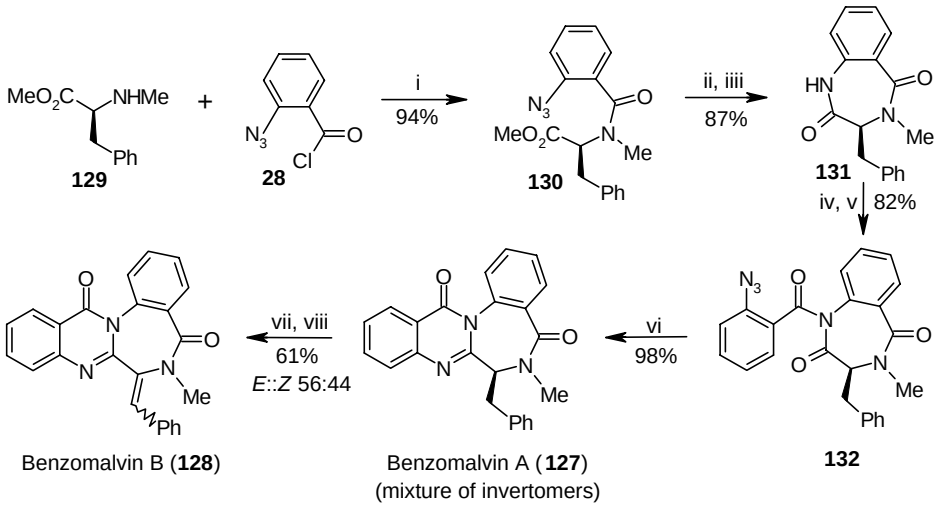
circumdatin family of natural products using a polymer-supported phosphine-mediated intramolecular aza-Wittig reaction as a key step of the reaction sequence. For example an analogue of the type shown in Figure 7 has been prepared using a novel modified Eguchi protocol. The multi arrayed library generation strategy commenced from readily accessible benzodiazepinedione derivatives.

We have attempted for the synthesis of circumdatin F using Ullman type coupling as a key step. These results and our studies on synthesis of circumdatin C via bezoxazinone intermediate will be described in chapter 4, as a part of this dissertation.

III] Benzomalvins:

Benzomalvins (Table 10, entries 7-8) are another class of benzodiazepine fused quinazolinones isolated from the fungus *Penicillium culture.*[102] A further unstable new metabolite, (+)-benzomalvin D (entry 10), has now been extracted from the same culture.[103] On standing overnight in a chloroform solution at room temperature, benzomalvin D was converted into benzomalvin A; similarly, benzomalvin A interconverted with benzomalvin D. Storage of the solid compounds at – 40 ^{o}C retarded their equilibration. The structural differences between the two compounds were confirmed by the first total synthesis[103] of benzomalvin A from isatoic anhydride, L-phenylalanine and methyl anthranilate following the same reaction sequence as used by Bock et al[109] in the synthesis of asperlicin C & E (Scheme 31). The enantiomerically pure synthetic benzomalvin A (3.7% overall yield) equilibrated in the same way as the natural product. Eventually, variable temperature NMR revealed that the two compounds are conformational isomers, in fact, atropisomers. Syntheses of (–)-benzomalvin A (**127**) and

benzomalvin B (**128**) by Eguchi and co-workers[104,105] utilized their own famous 'Eguchi protocol' (acylation of suitable precursors with 2-azidobenzoyl chloride (**28**) followed by intramolecular aza-Wittig reaction) to construct both heterocyclic rings (Scheme 30).[105] In brief, reaction of **28** with *N*-methyl-L-phenylalanine methyl ester **129** yielded the



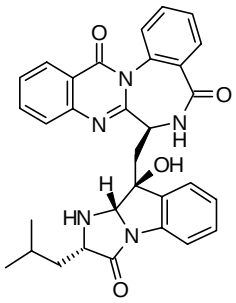
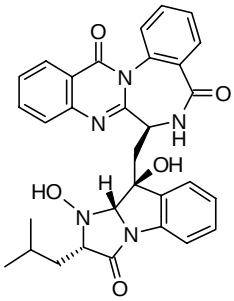
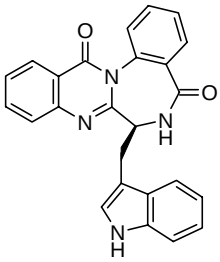
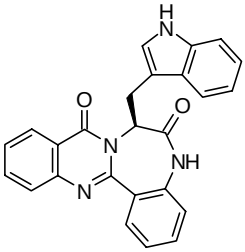
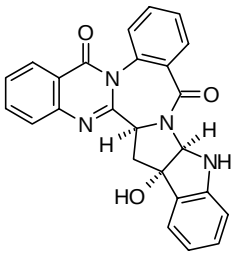
Scheme 30: (i) Et_3N, THF, 0 ^oC to rt; (ii) Bu_3P, PhMe, rt to reflux; (iii) TFA-H_2O-THF (1:1:12.5), rt; (iv) $KN(SiMe_3)_2$, THF, -78 ^oC; (v) **28**, THF, -78 ^oC to rt; (vi) Ph_3P, PhMe, rt to reflux; (vii) NBS, AIBN, CCl_4, reflux; (viii) DBU, PhMe, reflux.

intermediate azide **130** (ee 99.7%), after which treatment with tributylphosphine in boiling toluene followed by acidic work-up yielded the (–)-benzodiazepinedione **131** in 87% yield and high optical purity. A second application of the "Eguchi protocol" completed the synthesis of (–)-benzomalvin A (**127**). Benzomalvin B (**128**) was prepared from benzomalvin A (**127**) as a mixture of (*E*)- and (*Z*)-isomers by a benzylic bromination-dehydrobromination sequence.

1.7.2 Asperlicin alkaloids:

Table 11: Quinazolinobezodiazepines (Asperlicin alkaloids)

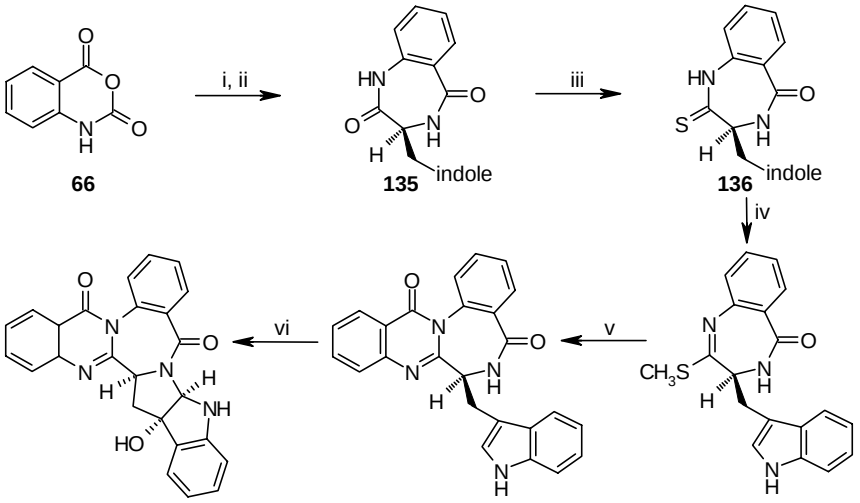
No.	Quinazolinone alkaloid	Source[Ref.] and activity	Synthesis[Ref.]

1.	 (–)-Asperlicin	*Aspergillus alliaceus*[106] Antagonist of the peptide hormone cholecystokinin	$C_{31}H_{29}N_5O_4$ Snider et al[110]
2.	 Asperlicin B	*Aspergillus alliaceus*[107] Agonist of cholecystokinin (CCK), selectivity affecting peripheral CCK receptors	$C_{31}H_{29}N_5O_5$
3.	 Asperlicin C	*Aspergillus alliaceus*[108] Agonist of the peptide hormone cholecystokinin	$C_{25}H_{17}N_4O_2$ Bock et al[109] Snider et al[81,110]
4.	 Asperlicin D	*Aspergillus alliaceus*[108]	$C_{25}H_{18}N_4O_2$
5.	 Asperlicin E	*Aspergillus alliaceus*[108]	$C_{25}H_{18}N_4O_3$ Bock et al[109]

Asperlicins A-E are competitive, nonpeptide cholecystokinin (CCK) antagonists isolated from the fungus *Aspergillus alliaceus*.[107,108]

I] Asperlicin C and E:

Asperlicin has 300-400 times more affinity for pancreatic, gastrointestinal and gallbladder CCK receptors than proglumide, a standard agent of this class. Moreover, asperlicin is highly selective for peripheral CCK receptors relative to brain CCK and gastrin receptors. Bock and co-workers[109] reported the first total synthesis of potentially important asperlicin C and asperlicin E (Scheme 31). Compound **135** was synthesized starting form isatoic



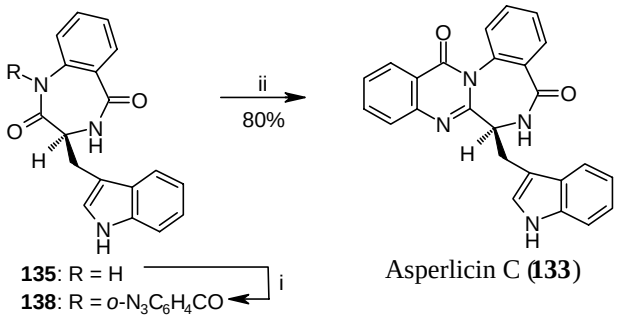
Scheme 31: (i) L-Trp, NEt_3, H_2O, 23 ^oC, 5 h; (ii) HOAc, 118 ^oC, 5 h (90% from **66**); (iii) $(CH_3OC_6H_4)_2P_2S_4$, THF, 23 ^oC, 2 h (33%); (iv) CH_3I, $(n\text{-Bu})_4NHSO_4$, NaOH (40%), $PhCH_3$, 23 ^oC, 20 min. (74%); (v) methyl anthranilate, 135 ^oC, 1 h (83%); (vi) (a) O_2, rose Bengal, CH_3OH-pyridine (5%), 0 ^oC, 5 h, (b) dimethyl sulfide (32%).

anhydride (**66**) & L-tryptophan and then it was reacted with Lawesson's reagent to give a 1:1 mixture of monothioamides which were separated. The desired thioamide **136** was elaborated to asperlicin C (**133**) in two steps and further transformed into asperlicin E

(**134**) by rose bengal sensitized photooxygenation and in situ reduction with dimethyl sulfide (Scheme 31).

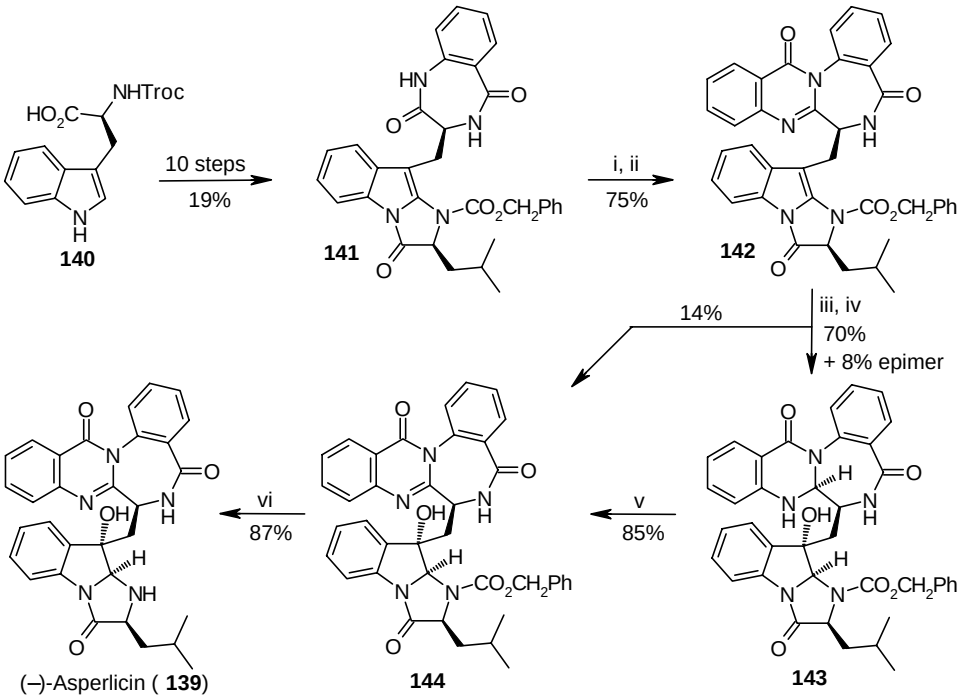
II] Asperlicin C and asperlicin:

Recently Snider et al[110] in their communication reported an efficient synthesis of asperlicin C (Scheme 32) and further successfully extended for the first total synthesis of (–)-asperlicin (Scheme 33). The most challenging aspect of the synthesis of the more complex antibiotic (–)-asperlicin (**139**) was the construction of the tryptophan-derived 1*H*-imidazo



Scheme 32: (i) *o*-$N_3C_6H_4COCl$, Et_3N, DMAP (83%); (ii) Bu_3P, benzene, 60 ^oC (80%).

[1,2-*a*]indol-3-one moiety in the intermediate **141**, following which the Eguchi protocol yielded the fused quinazolinone **142** (75%). Hydroxylation of the indole ring with an oxaziridine followed by reductive work-up with sodium borohydride competitively reduced the quinazolinone to the dihydroquinazolinone **143**, but reoxidation with DDQ restored the unsaturated linkage to give **144**. Removal of the benzyloxycarbonyl protecting



Scheme 33: (i) *o*-$N_3C_6H_4COCl$, Et_3N, DMAP, CH_2Cl_2, rt; (ii) Bu_3P, C_6H_6, 60 ^oC; (iii) 3-butyl-2,3-epoxy-1,2-benzisothiazole-1,1-dione, MeOH-CH_2Cl_2 (4:1), 25 ^oC; (iv) $NaBH_4$, HOAc, 25 ^oC; (v) DDQ, $CHCl_3$, rt; (vi) H_2 (1 atm), 5% Pd/C, MeOH, rt.

group completed a stereospecific synthesis of (–)-asperlicin (**139**) in fifteen steps and 8% overall yield from Troc-protected tryptophan (**140**). Authors have elegantly shortened and improved the synthesis of asperlicin C (**133**). They have developed a general route to the hydroxyimidazoindolone ring system, and applied it for the first synthesis of (–)-asperlicin (**139**), which proceeds stereospecifically and efficiently.

In conclusion, structurally interesting new benzodiazepine alkaloids isolated from various species, tabulated in Table 10 and 11 have good bioactivity and important alkaloids from this class have been synthesized by various groups. Synthesis of sclerotigenin, circumdatin F and asperlicin by Snider et al and an efficient synthesis of asperlicin E by Bock et al

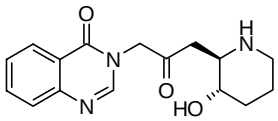
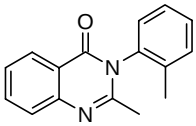
provided an easy access to these bioactive natural products and also generated a good amount of new chemistry.

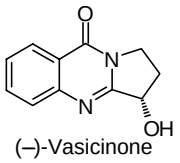
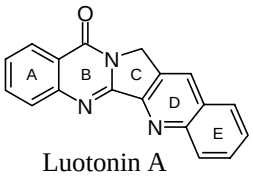
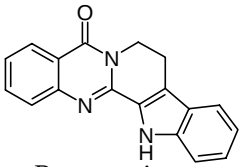
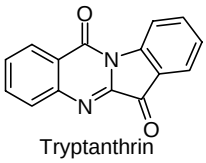
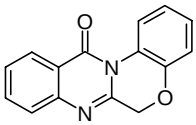
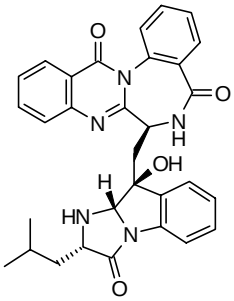
1.8 Quinazolinones in clinical treatments

Several quinazolinone alkaloids are known to elicit a wide variety of biological responses. This has spurred the preparation and pharmacological evaluation of a great number of quinazolinone derivatives and intensive research in the quinazolinone area is still in active progress. This topic has been very well reviewed in the literature.[4,111,112] Only a few quinazolinone natural products and derivatives of pharmaceutical importance are tabulated (Table 12) here.

Quinazolinone alkaloid luotonin A has attracted the attention of chemists and pharmacists world wide, because it is strikingly reminiscent of the cytotoxic alkaloid camptothecin, whose derivatives are clinically useful anticancer agents. Cagir et al[48a] recently increased the importance by demonstrating that despite the lack of A-ring functionality, luotonin A stabilizes the human DNA topoisomerase I-dependent cytotoxicity in intact cells.

Table 12: Natural/synthetic quinazolinones of therapeutic importance.[4,111,112]

No.	Natural/synthetic quinazolinones	Activity
1.	 Febrifugine	Anti-malarial Ingredient in *A traditional Chinese herbal remedy* effective against malaria
2.	 Methaqualone	Sedative-hypnotic

3.	 (–)-Vasicinone	Antitumor, bronchodilating, hypotensive, anthelmintic, antianaphylactic. Used in *The Indian Ayurvedic System of Medicine* as a remedy for cold, cough, bronchitis, rheumatism, phthisis & asthma.
4.	 Luotonin A	Anti-tumor Cytotoxic towards the murine leukemia P-388 cell line (IC_{50} 1.8 µg/mL)
5.	 Rutaecarpine	Strong analgesic, antiemetic, astringent, antihypertensive, uterotonic, TCDD-receptor, anti-nociceptive, anti-inflammatory and cycloxygenase (COX-2) inhibitory activities
6.	 Tryptanthrin	Antibiotic
7.		Antifertility
8.	 (–)-Asperlicin	300-400 times more affinity for pancreatic, gastrointestinal and gallbladder CCK receptors than proglumide, a standard agent of this class. Highly selective for peripheral CCK receptors relative to brain CCK and gastrin receptors.

It is important to note that the quinazolinone alkaloids are a class of natural compounds with very diverse structures and hence at present approximately fifty quinazolinone derivatives with a wide variety of biological activities are available for clinical use.

1.9 Summary

In this chapter we have presented a brief account of the natural quinazolinone alkaloids isolated under the review period along with their bioassay and various synthetic approaches. The combination of unique structural features, extensive functionalization and high biological activity found in quinazolinone alkaloids have presented an elegant challenge to the synthetic chemists. During the last 20 years, a number of research groups have reported a variety of synthetic approaches to biologically active natural/synthetic quinazolinone alkaloids.

There are approximately 73 new quinazolinone alkaloids isolated under the review period. All these alkaloids have been classified under six different classes according to their structural variations. The information about the isolation, bioactivity and synthesis has been tabulated in eleven tables. Various synthetic approaches to these quinazolinone alkaloids and their analogs have been explained and discussed by providing 33 complete schemes and 19 brief schemes tabulated in three tables. Wherever necessary, the illustration was made clearer with the help of 7 figures. The importance of natural and synthetic quinazolinones for clinical purposes has been reviewed in the last section along with a table presenting structure, name and activity of selected quinazolinone alkaloids of pharmaceutical interest. (–)-Vasicinone, luotonin A, rutaecarpine and (–)-asperlicin are the important quinazolinone natural products from a structural and therapeutic point of view. We strongly feel that luotonin A or its derivative will be a lead molecule for the treatment of cancer and it may replace the clinically useful anticancer agents, the camptothecin derivatives. All the information collected and presented here has been well supported by providing more than 200 references from various monographs and international journals.

It should be obvious that investigations over the last few years have demonstrated that the natural quinazolinone alkaloids and their synthetic derivatives exhibit a wide variety of pharmacological activities. The continuously increasing stream of publications on this subject permits the hope that even in the foreseeable future an answer must be found to the general philosophical question of the place and role in nature of alkaloids in general and of the quinazolinone alkaloids in particular. In the continuing search for the compounds producing interesting biological activities, the quinazolinone alkaloids should provide an excellent starting point for further investigations.

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Chapter Two

Synthesis of Pegamine, Deoxyvasicinone, (–)-Vasicinone, Rutaecarpine and Studies on Synthesis of 7,8-Dehydrorutaecarpine

This chapter describes the use of cyclic anhydrides as potential starting materials for the synthesis of quinazolinone alkaloids and is divided into two sections. The first section presents the synthesis of quinazolinone natural products pegamine, deoxyvasicinone and (−)-vasicinone and the second section describes the synthesis of the natural products 2-(4-hydroxybutyl)-quinazolin-4-one, mackinazolinone, rutaecarpine and an attempted synthesis of 7,8-dehydrorutaecarpine. All these natural products have been synthesized using cyclic anhydrides as building blocks (Figure 1).

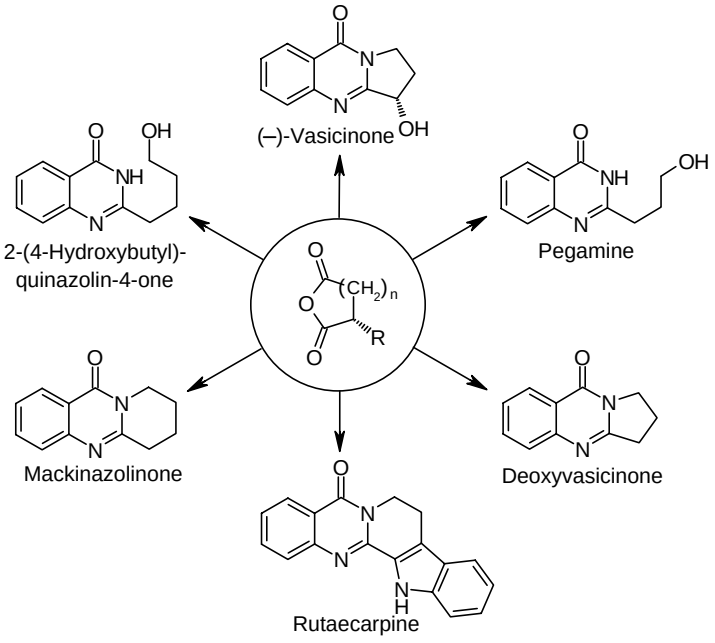


Figure 1: Quinazolinone natural products synthesized, starting from cyclic anhydrides

2.1 Section A

Concise and Efficient Synthesis of Bioactive Natural Products Pegamine, Deoxyvasicinone and (–)-Vasicinone

2.2 Section B

Facile Zeolite Induced Fischer-Indole Synthesis: A New Approach to Bioactive Natural product Rutaecarpine and Studies on Synthesis of 7,8-Dehydrorutaecarpine

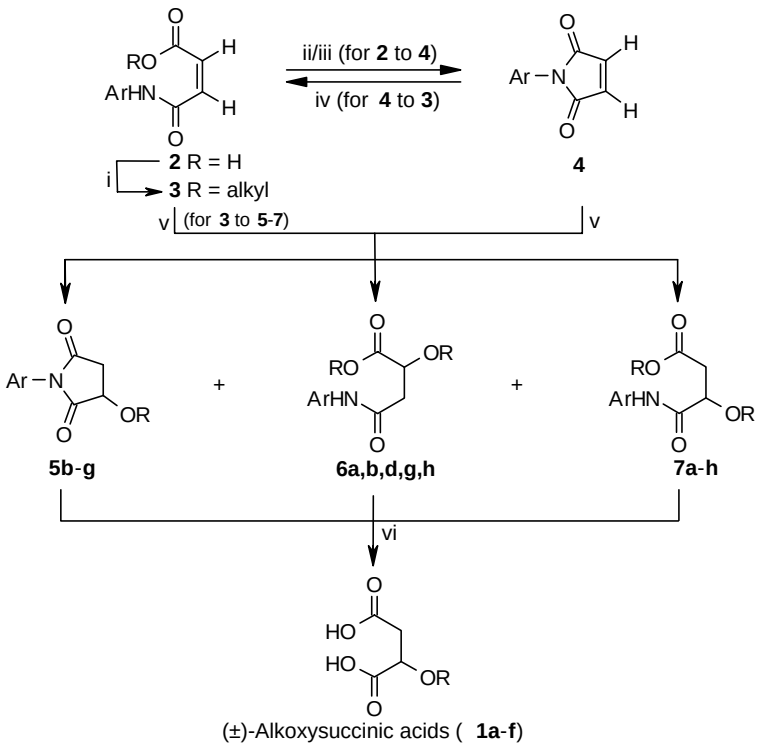
2.1.1 Background

Large numbers of quinazolinone alkaloids have been isolated from a number of plants, animals & microorganisms and synthesized in view of their well-established pharmacological activities.[1] Development of new elegant synthetic strategies to these bioactive quinazolinone alkaloids and their precursors is a challenging task of current interest.[2] Pegamine [2-(3-hydroxypropyl)-quinazolin-4(1*H*)-one, **30**], deoxyvasicinone [2,3-dihydropyrrolo[2,1-*b*]quinazolin-9(1*H*)-one, **24**], and (–)-vasicinone [2,3-dihydro-3(*S*)-hydroxypyrrolo[2,1-*b*]quinazolin-9(1*H*)-one, **31**] have been isolated as bioactive natural products. Pegamine (**30**) has been isolated from *Peganum harmala* and exhibits cytotoxic activity.[3] Deoxyvasicinone (**24**) and (–)-vasicinone (**31**) have been isolated from the aerial parts of an evergreen subherbaceous bush *Adhatoda vasica*.[4] Deoxyvasicinone (**24**) possesses anti-microbial, anti-inflammatory and anti-depressant acitivities.[5] Several synthetic routes to deoxyvasicinone (**24**) are known in the literature.[6] (–)-Vasicinone (**31**) exhibits antitumor,[7] bronchodilating,[8] hypotensive,[8] anthelmintic,[9] and antianaphylactic[10] activities. It is used in *The Indian Ayurvedic System of Medicine* as a remedy for cold, cough, bronchitis, rheumatism, phthisis, and asthma.[4,11] Recently, Joshi and co-workers[12,13] reversed the previously assigned[14] 3(*R*)-configuration of **31** on the basis of X-ray crystallographic analysis[12a] and by using the Mosher ester analysis method.[12b] Three synthetic routes to vasicinone are known; (±)-vasicinone has been obtained from deoxyvasicinone via NBS-bromination,[6c] while (–)-vasicinone has been synthesized[15] from deoxyvasicinone via asymmetric oxidation using (1*R*)-(–)-(10-camphorsulfonyl) oxaziridine (the Davis reagent) with 62% enantiomeric excess (ee). (±)-Vasicinone and (–)-vasicinone have been also synthesized[15] by coupling *o*-azidobenzoyl chloride with *O*-protected 3-hydroxy-γ-lactam and 3(*S*)-hydroxy-γ-lactam (derived from L-aspartic acid in

six steps),[16] respectively, via the tandem Staudinger/intramolecular aza-Wittig reaction. Recently, Kamal et al have reported[17] an efficient enzymatic resolution of (±)-vasicinone and its acetyl derivative.

Cyclic anhydrides and imides are potential starting materials for the synthesis of structurally interesting and biologically important heterocycles,[18] bioactive natural products[19,53] and their potential building blocks.[20] We planned to use succinic anhydride (**26**) for the synthesis of pegamine (**30**) and deoxyvasicinone (**24**) and (*S*)-acetoxysuccinic anhydride (**21**) for the synthesis of (–)-vasicinone (**31**).

The vast arrays of nucleophilic reactions undergone by the symmetrical and unsymmetrical cyclic anhydrides confer on them a high synthetic potential. The possible pathways in nucleophilic reactions of symmetrical and unsymmetrical cyclic anhydrides includes, nucleophilic addition to carbonyl without ring opening or nucleophilic attack at carbonyl with ring opening and an added variant of the reaction in case of maleic anhydride and its derivatives will be Michael type addition to the activated carbon-carbon double bond. As such cyclic anhydrides and their derivatives have been exclusively used to model a variety of (i) heterocyclic skeletons, (ii) natural products and their precursors, (iii) bioactive molecules, (iv) compounds highlighting regio-chemical dichotomy and (v) a series of polymers with tailored material characteristics.[18-21] Recently we have demonstrated the use of cyclic anhydrides as starting materials for the synthesis of important building blocks of natural products and bioactive molecules; alkoxysuccinic acids and alkoxymaleic anhydrides.[20] We have developed a simple, efficient and general two-step, one-pot approach to alkoxysuccinic acids[20b] starting from maleic anhydride (Scheme 1). The potassium carbonate-catalyzed reaction of alcohols with *N*-*p*-tolylmaleimide (**4**, prepared from maleic anhydride and *p*-toludine) followed by an acid-induced hydrolysis of the



Scheme 1: (i) MeOH, H^+/H_2SO_4, rt, 8 h (82%), for **3a**; (ii) Ac_2O, NaOAc, 60 ^oC, 1 h (85%); (iii) $ZnCl_2$, HMDS, benzene, reflux 2 h (98%); (iv) ROH, K_2CO_3, rt, 2-3 h (94-95%), for **3e** and **3g**; (v) ROH, K_2CO_3, rt/heat; (vi) H^+/HCl, reflux (91-98% for **1a-f**).

intermediate products furnished alkoxysuccinic acids **1a-f** in 90-98% yields. All the intermediates from the reaction of imide **4** with alcohols have been isolated and characterized, proving that the in situ formed alkyl maleanilates **3** are the actual Michael acceptors (Scheme 1). The structures of the intermediate regiomers, for example **6a** and **7a**,

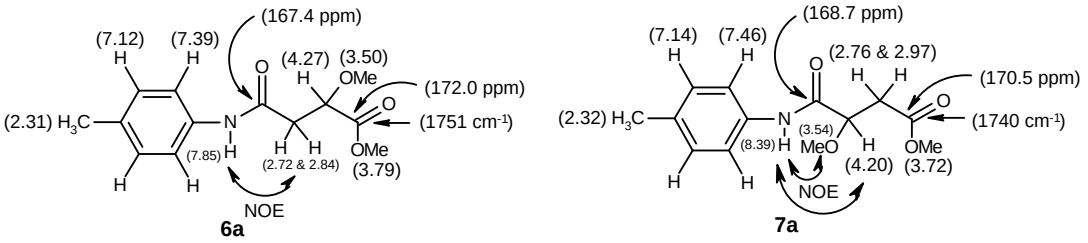
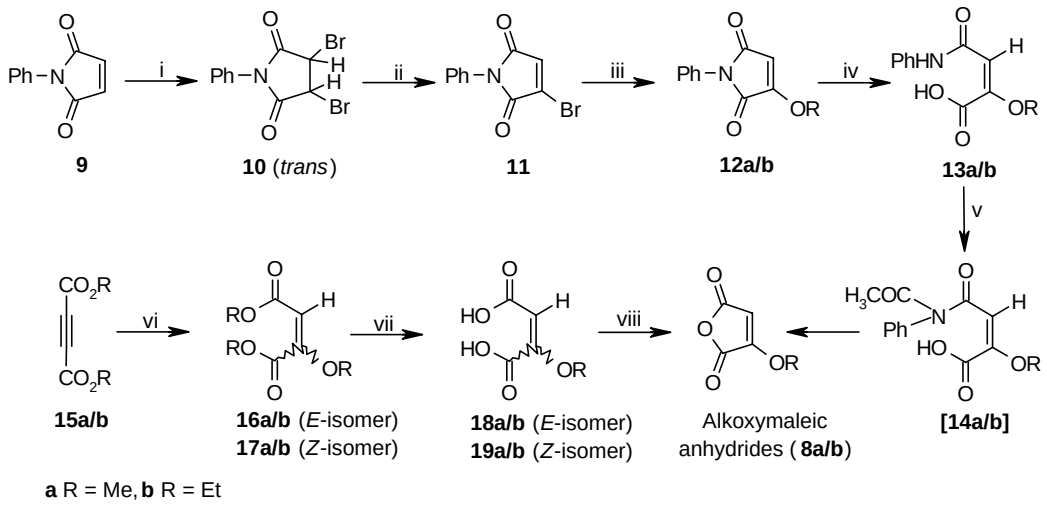


Figure 2: ^1H NMR & ^{13}C NMR signal assignments and NOE interactions for **6a** and **7a**

were confirmed by using IR, ^{1}H NMR, ^{13}C NMR spectroscopic analysis and special COSY and NOESY experiments (Figure 2). Methoxysuccinic acid (*O*-methylmalic acid, **1a**) thus synthesized has been earlier detected by GC-MS as a natural product from *Triticum aestivum* (wheat), *Secale cereale* (rye), *Hordeum vulgare* (barley), human urine and recently from *Rewarewa* honey of New Zealand as a proposed floral marker. It has been used in laundry as a disinfectant and also in the synthesis of succinimide derivatives possessing fungicidal activity.[20b] In view of the importance of the enantiomerically pure methoxysuccinic acids in asymmetric synthesis, we also repeated the above reaction sequence with a chiral base or by using a chiral substrate i.e. imide, but we were unable to improve the stereoselectivity. Although all our attempts for enantioselective/diastereoselective oxa-Michael addition did not meet with satisfactory results, a very clean fractional crystallization of (±)-**1a** to optically pure (+)-**1a** and (–)-**1b** at gram levels is well known.[20b]

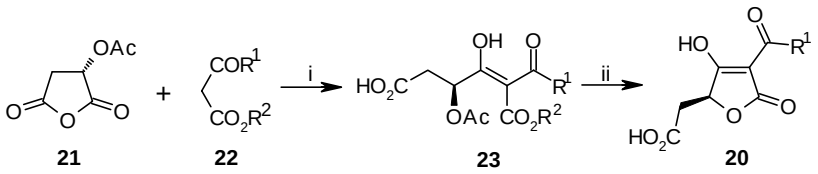
Recently we have also provided[20a] a new route to alkoxymaleic anhydrides **8a/b** in good



Scheme 2: (i) Br_2, CCl_4, reflux, 1 h (98%); (ii) TEA, THF, 0 ^{o}C, 2 h (98%); (iii) Et_3N, ROH, reflux, 1 h (70-75%); (iv) (a) aq. KOH, MeOH, rt, 1 h, (b) H^+/HCl (96%); (v) Ac_2O-AcOH (1:1), 80 ^{o}C, 4 h (95%); (vi) Et_3N, ROH, rt, 2 h (94-96%); (vii) (a) aq. KOH, MeOH, rt, 6 h, (b) H^+/HCl (93-96%); (viii) $SOCl_2$, reflux, 24 h (64-65%).

yields via base induced chemoselective vinylic substitution of bromo atom in bromo-maleimide **11** (prepared starting from maleic anhydride and aniline) with alkanols and base induced oxa-Micahel addition of alkanols to dialkyl acetylenedicarboxylates **15a/b** as key steps. An unusual acyl exchange in the conversion of **13a/b** to **8a/b** under very simple and mild reaction conditions is noteworthy (Scheme 2). Methoxymaleic anhydride (3-methoxy-2,5-furandione, **8a**) thus synthesized is useful building block for natural products and it has been used for the synthesis of bioactive natural products narthigenine, penicillic acid and lucidone.[20a] We feel that the various alkoxysuccinic acids and alkoxymaleic anhydrides synthesized by us will be useful building blocks for the synthesis of several natural products including the structurally interesting and biologically active quinazolinone based natural products.

In yet another application of ring opening of cyclic anhydrides for the synthesis of natural products and their intermediates, a regioselective ring opening of malic acid anhydride by carbon nucleophiles has been used by Mitsos et al (Scheme 3)[21e] for the synthesis of chiral



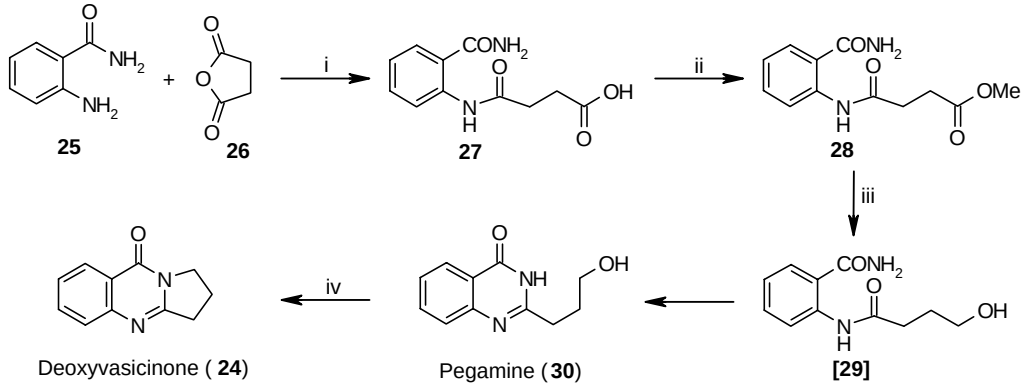
Scheme 3: (i) NaH, THF; (ii) NaOH, H_2O, MeOH (51-79%).

tetronic acids. Various tetronic acids **20** have been thus obtained in 51-79% yields. The reaction of **21** with the anions of β-keto-esters **22** leads to β-hydroxy-γ-acetoxybuenoates of type **23**, which are useful intermediates for the synthesis of certain tetronic acid natural products.

The utilities of various cyclic anhydrides have been well proved in research laboratories as well as in industrial practice.[19,21] For example, methyl and dimethylmaleic anhydrides have been used for the synthesis of important bioactive natural products like showdomycin,[19a] (±)-merrilactone,[19j] chaetomellic anhydride A,[19c-e,i] tyromycin A,[19g] (±)-piliformic acid,[19f] (±)-*erythro*-roccellic acid[19h] and pulchellalactam.[19l] We feel that, with proper control on the reactivity and selectivity, one can use cyclic anhydrides as potential building blocks for the short and efficient synthesis of several bioactive natural products in general and quinazolinone alkaloids in particular.

2.1.2 Present Work: Results and Discussion

The reaction of anthranilamide (**25**) with succinic anhydride (**26**) in a benzene-dioxane mixture furnished the *o*-amidosuccinanilic acid (**27**) in quantitative yield. The obtained compound **27** was used for the next step without any further purification and the analytically pure sample was obtained by recrystallization from methanol. The reaction of succinanilic acid **27** with diazomethane in ether at room temperature furnished the corresponding ester **28** in quantitative yield. The ester **28** can be obtained in good yields by

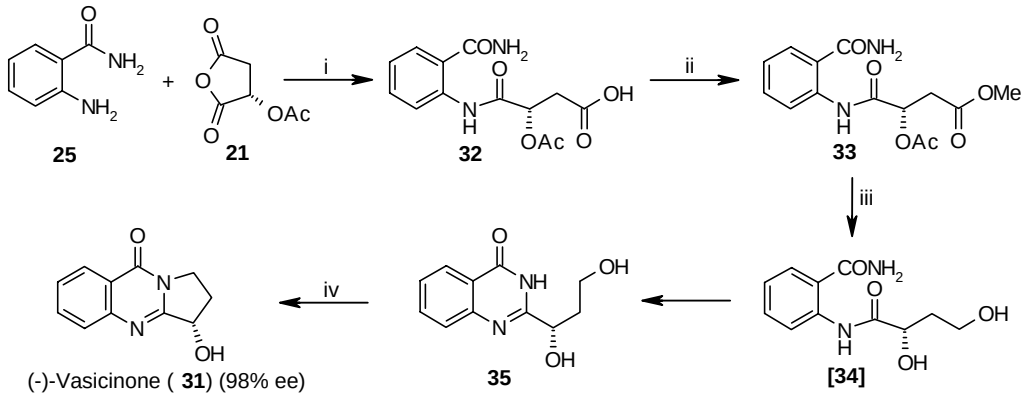


Scheme 4: (i) Et_2O/C_6H_6/1,4-dioxane (2:2:1), rt, 2 h (98%); (ii) CH_2N_2, Et_2O, rt, 1 h (98%); (iii) LAH, THF, 90 min., aqueous workup (93%); (iv) PPh_3, DEAD, THF, rt, 1 h (95%).

stirring the acid **27** in methanol with catalytic amount of H_2SO_4, at room temperature. The ester **28** on chemo-selective reduction with two equiv. of LAH in THF at room temperature furnished the reduced intermediate compound **29**. It is possible to isolate the intermediate **29** by quenching the reaction with dry ethyl acetate. Quenching of the reaction with H_2O generated LiOH in the reaction mixture, which further catalyzed dehydrative ring closure between the two amide units, to furnish quinazolinone derivative **30** in 93% yield, after silica gel column chromatographic purification, completing the first synthesis of bioactive natural product pegamine (**30**) in three steps with 89% overall yield. The analytical and spectral data obtained for **30** were in complete agreement with reported data.[3] The in situ generated LiOH catalyzed cyclization between the two amide units in compound **29**, observed here is mild and efficient as compared to the previous conditions, wherein such type of cyclizations have been effected at refluxing temperature in a mixture of ethanol and 5% aqueous KOH.[22] Mitsunobu reaction[23] is a very versatile protocol for the condensation of diols and interestingly application of the intramolecular Mitsunobu ring-closure reaction on pegamine (**30**) with DEAD-TPP reagent gave the thermodynamically more stable linear tricyclic compound deoxyvasicinone (**24**). Purification of the crude product by silica gel column chromatography furnished pure deoxyvasicinone (**24**) in 95% yield, completing the four step synthesis of **24** with 85% overall yield (Scheme 4).[24] Formation of the corresponding angular tricyclic compound was not observed. The conversion of deoxyvasicinone (**24**) to bioactive natural products (–)-vasicinone (**31**),[15] rutaecarpine[27] and isaindigotone[28] is known.

With the successful synthesis of the simple quinazolinone alkaloid deoxyvasicinone, we planned to extend our strategy for the chiral pool synthesis of (–)-vasicinone using (*S*)-acetoxysuccinic anhydride as a chiral synthon. (*S*)-Acetoxysuccinic anhydride (**21**) was

synthesized according to the Henrot's[25] procedure, by refluxing (*S*)-malic acid in freshly distilled acetyl chloride. In a benzene-dioxane mixture, the anthranilamide (**25**) reacted with (*S*)-acetoxysuccinic anhydride (**21**) in a 100% regioselective[21] fashion at the more reactive electron-deficient carbonyl (though hindered) to yield the ring-opened product *β* (*S*)-acetoxy-*o*-amidosuccinanilic acid (**32**) in a quantitative yield. Such regioselectivity on **21** with carbon, nitrogen and oxygen nucleophiles is known.[21] The obtained compound **27** was used for the next step without any further purification and the analytically pure sample was obtained by recrystallization from ethyl acetate. The reaction of succinanilic acid **32** with diazomethane in ether at room temperature furnished the corresponding ester **33** in a quantitative yield. In this case, on treatment of the acid **32** with methanol and catalytic amount of H_2SO_4, we couldn't get the desired ester **33** in good amount, instead a complex TLC pattern was observed, probably due to the alcoholysis/hydrolysis of acetyl group and



Scheme 5: (i) Et_2O/C_6H_6/1,4-dioxane (2:2:1), rt, 2 h (98%); (ii) CH_2N_2, Et_2O, rt, 1 h (98%); (iii) LAH, THF, 90 min., aqueous workup (92%); (iv) PPh_3, DEAD, THF, rt, 1 h (90%).

other side reactions. The ester **33** on chemo-selective reduction with two equiv. of LAH in THF at room temperature formed the reduced intermediate compound **34**, which during the aqueous workup underwent a smooth in situ LiOH catalyzed[22] dehydrative ring closure between the two amide units to yield quinazolinone derivative **35** in 92% yield, after silica

gel column chromatographic purification. The (*S*)-hydroxypegamine (**35**) on treatment with equivalent amount of DEAD-TPP reagent in THF at room temperature underwent a selective facile intramolecular Mitsunobu ring-closure reaction[23] with the primary alcohol to furnish the desired thermodynamically favored naturally occurring linear tricyclic system (–)-vasicinone (**31**) in 90% yield (Scheme 5).[24] We didn't observe any other possible cyclizations like, cyclization between the two alcohols or cyclization between the amide -NH and secondary alcohol probably because the formation of a five membered ring is favored over the formation of a strained four membered ring. The overall yield of (–)-vasicinone (**31**) in four steps was 80%, and the analytical and spectral data obtained for **31** were in complete agreement with the reported data.[12,13,15,17] For the synthesis of (–)-vasicinone (**31**) we started with the chiral synthon (*S*)-malic acid of 98% enantiomeric purity. In order to determine enantiomeric purity of (–)-vasicinone and to check whether there was any recemization during the reaction sequence, MTPA-esters of authentic (±)-vasicinone and (–)-vasicinone synthesized by us were prepared and their ^{1}H NMR spectra were scanned. The peaks at 3.57 & 3.65 (-OCH_3) as well as 6.37 & 6.43 (-CH) with clean and clear separations were compared by using their integral values, which revealed that (–)-vasicinone (**31**) possesses 97-98% ee and there was no recemization during the reaction sequence. The specific rotation observed for **31** and the comparison of the ^{1}H NMR spectra of MTPA-ester of our sample with that of the reported MTPA-ester spectra[26] also confirmed our observations. Our synthesis with a chiral pool strategy directly proved that the naturally occurring (–)-vasicinone (**31**) has the (*S*)-configuration. The conversion of vasicinone to luotonin A[29] and luotonin B[30] is known.

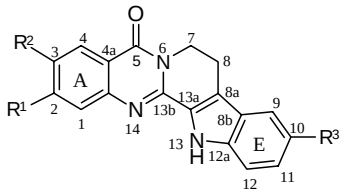
In Scheme 4 & 5, it may also be possible to obtain compounds **29**/**34** or **30**/**35** directly from the reaction of anthranilamide (**25**) with γ-lactone and (*S*)-hydroxy γ-lactone. We

reasoned that the readily available cyclic anhydrides **21** & **26** are better starting materials as these lactone preparations require more number of steps; nucleophilic ring opening using primary aromatic amines is relatively more easy with cyclic anhydrides than lactones, and these lactones have well-proven propensities for polymerization reactions.

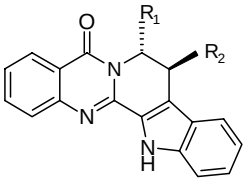
In conclusion, we have demonstrated[24] a concise, efficient and practical total synthesis of naturally occurring bioactive quinazolinone alkaloids pegamine (**30**), deoxyvasicinone (**24**) and (–)-vasicinone (**31**), for the first time starting from succinic anhydride (**26**) and (*S*)-acetoxysuccinic anhydride (**21**). The present approach also provides a new general method for designing several quinazolinone derivatives using a variety of cyclic anhydrides for structure activity relationship studies.

2.2.1 Background

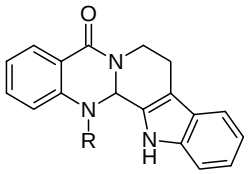
Several quinazolinone natural products being isolated from various living sources of nature with excellent bioactivity[1] are the center of attraction for the synthetic chemists world wide.[2] The dried fruits of *Evodia rutaecarpa* have been used in the traditional Chinese medicine under the name Wu-Chu-ru[31] and Shih-Hu[32] as a remedy for headache, dysentery, cholera, worm infections and postpartum.[33] The drug extract contains quinazolinocarboline alkaloids rutaecarpine (**36a**) and evodiamine (**38b**).[34] Recently callus tissue cultured from the stem of *Phellodendron amurense* has been shown to produce **36a**, along with a variety of other alkaloids[35-38] like 7,8-dehydrorutaecarpine,[37b] hortiacines and euxylophoricines etc. (Figure 3). This plant is being used in Japan and China in a crude form as a drug showing anti-stomachic, anti-inflammatory and anti-pyretic activities. The agonist activity of 7,8-dehydrorutaecarpine (**36b**) towards TCDD- receptor was found[39b] to



36a: $R^1 = R^2 = R^3 = H$; Rutaecarpine ($C_{18}H_{13}N_3O$, 287.32)
36b: $R^1 = R^2 = R^3 = H$; Carbon-carbon double bond between 7 and 8 position; Dehydrorutaecarpine ($C_{18}H_{11}N_3O$, 285.31)
36c: $R^1 = R^2 = H$, $R^3 = OMe$; Hortiacine ($C_{19}H_{15}N_3O_2$, 317.35)
36d: $R^1 = R^2 = -O-CH_2-O-$, $R^3 = H$; Euxylophoricine ($C_{19}H_{13}N_3O_3$, 331.33)
36e: $R^1 = R^2 = OMe$, $R^3 = H$; Euxylophoricine A ($C_{20}H_{17}N_3O_3$, 347.37)
36f : $R^1 = R^2 = R^3 = OMe$; Euxylophoricine D ($C_{21}H_{19}N_3O_4$, 377.4)



37a: $R^1 = OH$, $R^2 = H$; 7-Hydroxyrutaecarpine ($C_{18}H_{13}N_3O_2$, 303.32)
37b: $R^1 = R^2 = OH$; 7,8-Dihydroxyrutaecarpine ($C_{18}H_{13}N_3O_3$, 319.32)



38a: R = H; (13*b*,14)-Dihydrorutaecarpine ($C_{18}H_{15}N_3O$, 289.34)
38b: R = Me; Evodiamine ($C_{19}H_{17}N_3O$, 303.36)
38c: R = CHO; 14-Formyl-13*b*,14-dehydrorutaecarpine ($C_{19}H_{15}N_3O_2$, 317.35)

Figure 3: Naturally occurring bioactive rutaecarpines and analogs

be more than that of rutaecarpine (**36a**). In recent literature, **36a** and its derivatives have been reported to possess strong analgesic, anti-emetic, astringent, anti-hypertensive, uterotonic, TCDD-receptor, anti-nociceptive, anti-inflammatory and cycloxygenase (COX-2) inhibitory activities.[39] Rutaecarpine (**36a**) was also found to suppress platelet plug formation in mesenteric venules and increase intracellular Ca^{2+} in endothelial cells.[40] Recently, Don et al[41] reported their studies on the effect of structural modification on the inhibitory selectivity of rutaecarpine derivatives on human CYP1A1, CYP1A2 & CYP2B1 and found few of them to be most selective inhibitors. The first total synthesis of the important bioactive natural product **36a** was reported[42] by Robinson et al in 1927 and since then several routes to **36a** and its derivatives have been developed.[1e,6e,g,h,o,43]

In our on-going studies on the synthesis of bioactive natural products[24] and their building blocks[20] using cyclic anhydrides as potential precursors, we became interested in total synthesis of rutaecarpine (**36a**). We felt that it would be possible to design the five carbon six membered ring C in **36a** from glutaric anhydride (**45**) and further Fischer-indolization of the hydrazone using zeolite as an acid-catalyst should provide a new route to rutaecarpine.

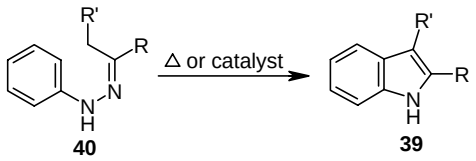


Figure 4: Fischer indole reaction.

The indole nucleus is an important moiety in many pharmacologically active compounds. The Fischer-indole synthesis is the most widely used method for the preparation of indoles.[44] In the Fischer-indole synthesis, arylhydrazones of aldehyde or ketone are treated with a catalyst, elimination of ammonia takes place and an indole is formed (Figure 4).

Zinc chloride and polyphosphoric acid are the catalysts most frequently employed, but several others, including other metal halides, mineral acids, Lewis acids and certain transition-metals have also been used.[44] Arylhydrazones are easily prepared by the treatment of aldehydes or ketones with phenylhydrazine or by aliphatic diazonium coupling. However, it is not necessary to isolate the arylhydrazone. The aldehyde or ketone can be treated with a mixture of phenylhydrazine and the catalyst; this is a common practice. In order to obtain an indole, the aldehyde or ketone must be of the form $RCOCH_2R'$ (R = alkyl, aryl, or hydrogen). The mechanism (Figure 5) of this important reaction has been proposed by Robinson[45] and there are many evidences for this

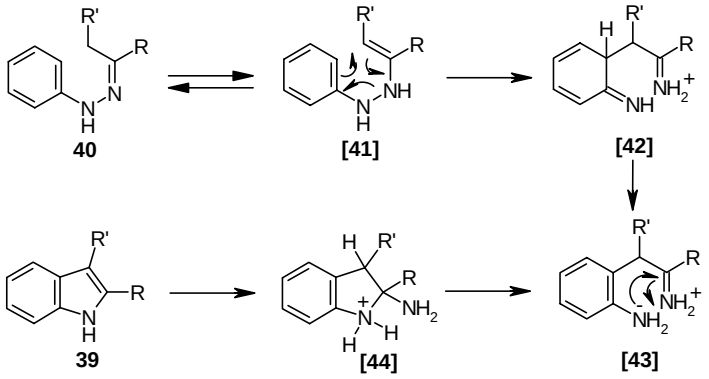


Figure 5: A pictorial representation of Fischer indole reaction mechanism

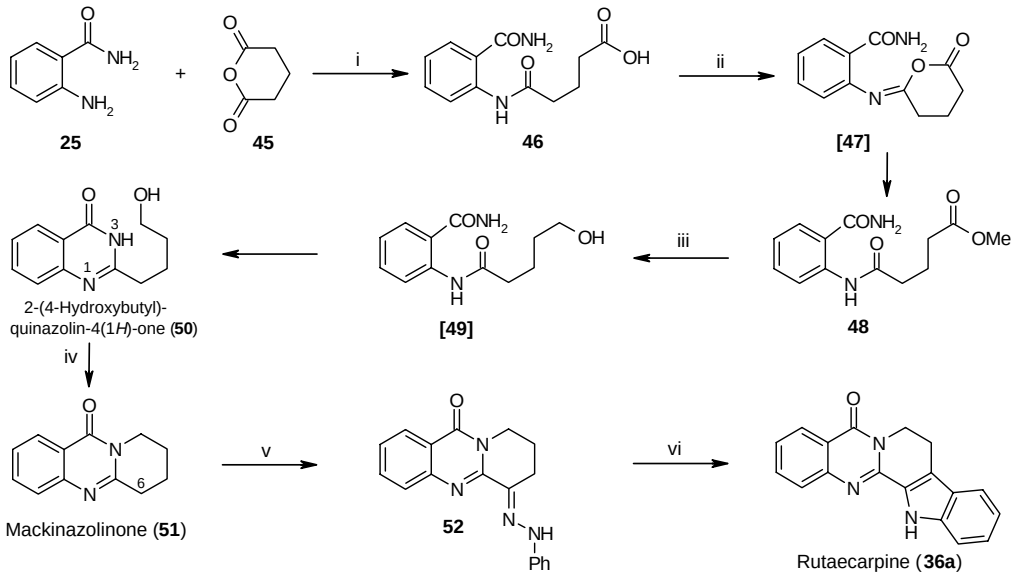
mechanism, e.g., (i) the isolation of **44**, (ii) the detection of **43** by ^{13}C and ^{15}N nmr, (iii) the isolation of side products that could only have come from **42** and (iv) ^{15}N labeling experiments that showed that it was the nitrogen farther from the ring that is eliminated as ammonia. The main function of the catalyst seems to be to speed up the conversion of **40** to **41**. In the acid-catalyzed formation of the enamine-intermediate, the more-substituted enamine is usually formed. The key step of the mechanism is [3,3]-sigmatropic rearrangement.[45] This reaction can be performed without a catalyst at very high temperature, but with poor yield.[44] Now a days, use of zeolites is gaining more importance

in chemical industries because of clean reaction, easy work-up and reusability of the catalyst. There are few reports on the use of zeolites for the Fischer-indole reaction, wherein zeolites like H-ZSM-12, H-beta, H-mordenite, H-Y, H-ZSM-22, H-EU-1, H-ZSM-5 have been used,[46,47] but use of zeolite induced Fischer-indole reaction for the synthesis of natural products was found to be limited.[44-47] We feel that the use of zeolite for the Fischer-indolization should provide a new entry to the bioactive rutaecarpine alkaloids.

2.2.2 Present Work: Results and Discussion

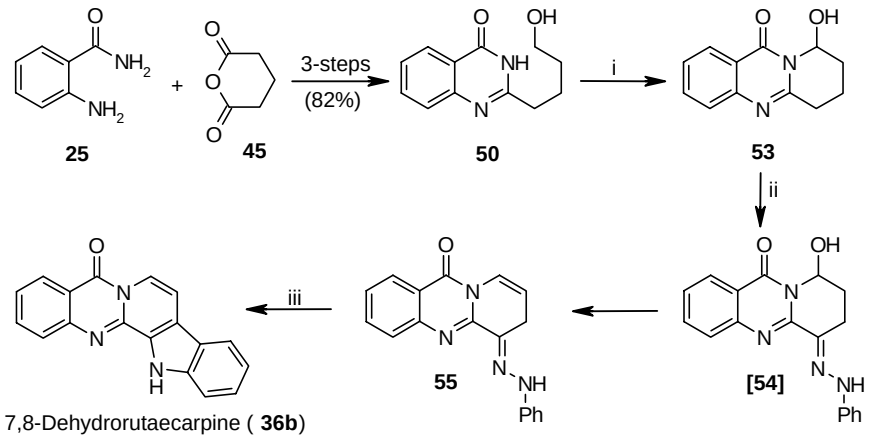
The reaction of anthranilamide (**25**) with glutaric anhydride (**45**) in benzene/1,4-dioxane (2:1) at room temperature furnished the corresponding *o*-amidoglutaranilic acid (**46**) in a quantitative yield. The obtained compound **46** was used for the next step without any further purification. The glutaranilic acid **46**, on treatment with methanol and catalytic amount of sulfuric acid at room temperature, gave the corresponding methyl ester **48** in 96% yield. We feel that the present esterification at room temperature is plausibly taking place via the corresponding isoimide **47**. The ester **48** in refluxing dry THF underwent smooth chemoselective sodium borohydride reduction to yield the intermediate alcohol **49**. Quenching of this reaction by adding water, generated NaOH in the reaction mixture, which catalyzed dehydrative ring closure between the two amide units to yield a natural product, 2-(4-hydroxybutyl)quinazolin-4(1*H*)-quinazolinone (**50**, originally isolated[48] from *Dichroa febrifuga* and its synthesis[49] was known before isolation) in 86% yield (Scheme 6), after silica gel column chromatographic purification. The analytical and spectral data obtained for **50** was in complete agreement with the reported data.[48,49] The quinazolinone **50**, on treatment with *p*-TsCl and sodium hydride in THF at room temperature, underwent a facile intramolecular dehydrative cyclization at *N*-3 nitrogen atom and furnished the

linear bioactive natural product mackinazolinone (**51**, originally isolated from *Mackinalaya* species[50]) in 81% yield (Scheme 6), after column chromatographic purification. The analytical and spectral data obtained for **51** was in complete agreement with the reported data.[50] We didn't observe formation of any angular compound which is possible due to cyclization between the alcohol and *N*-1 nitrogen atom in possible tautomeric form of quinazolinone **50**. Although several routes to **51** are known,[6g,l-o,17,43b,50,51] this is the first approach starting from glutaric anhydride and has several advantages like easily available low cost starting material and very facile reaction of amine with anhydrides than the corresponding lactones. The reactivity of the allylic active 6-methylene group in quinazolinone **51** towards the electrophilic reagents is well studied,[43b] which permitted the direct diazonium coupling and proved to be the most simple means of preparation of



Scheme 6: (i) C_6H_6/1,4-dioxane (2:1), rt, 2 h (98%); (ii) MeOH, H_2SO_4 (cat.), rt, 8 h (96%); (iii) $NaBH_4$, THF, reflux, 3 h, aqueous workup (86%); (iv) NaH, *p*-TsCl, THF, rt, 30 min. (81%); (v) Aniline, 30% HCl, $NaNO_2$, AcOH, – 5 to 5 ^oC, 8 h (98%); (vi) Zeolite (H-Mordenite), AcOH, reflux, 5 h (82%).

arylhydrazones.[52] The mackinazolinone, on reaction with in situ generated benzenediazonium chloride (prepared from aniline in water) at – 5 to 5 ^{o}C, gave the corresponding hydrazone **52** in 98% yield.[43b,52] The obtained hydrazone **52** was used further without any purification. Fisher-indole cyclization is a well established reaction for the conversion of the hydrazones to the indoles by using various acidic catalysts. The hydrazone **52** on zeolite (H-Mordenite) induced Fischer-indole synthesis[44-47] in refluxing glacial acetic acid yielded the bioactive natural product rutaecarpine (**36a**) in 82% yield, after silica gel column chromatographic purification. The analytical and spectral data obtained for **36a** was in complete agreement with the reported data.[6e,43c] The overall yield of **36a** in six-steps was 53% (Scheme 6). Rutaecarpine (**36a**) on DDQ-oxidation is known to give 7,8-dehydrorutaecarpine (**36b**) in 77% yield.[43c] We also planned to synthesize **36b** starting from the natural product **50**, obtained in the rutaecarpine synthesis. The primary alcohol in **50** was converted to the corresponding intermediate aldehyde by oxidation using PCC in CH_2Cl_2 and in the possible ring-chain tautomerism the isolated compound prefers to stay in ring-closed form **53**. The compound **53** was isolated in 72% yield, after column



Scheme 7: (i) PCC, DCM, rt, 1 h (72%); (ii) Aniline, 30% HCl, $NaNO_2$, AcOH, – 5 to 5 ^{o}C, 8 h (98%); (iii) in progress.

chromatographic purification, which on diazonium coupling reaction directly furnished hydrazone **55** in quantitative yield, plausibly via dehydration of the intermediate **54**. We tried several reagents/reaction conditions such as PPA, $ZnCl_2$, BF_3-ether, neat heating, heating in high boiling solvent, zeolite and acidic resins for conversion of **55** to 7,8-dehydrorutaecarpine (**36b**) but all of them met with failure (Scheme 7). Probably, according to the mechanism, compound **55** on treatment with the catalyst or on heating is forming the intermediate of the type **41** (Figure 5) which leads to a stable quasi-aromatic ring because of the presence of a double bond and thus plausibly inhibits the further indolization process. Protection of the secondary alcohol in **53**, followed by hydrazone formation, Fischer-indolization and deprotection may provide a way to the natural product (±)-7-hydroxyrutaecarpine (**37a**) and further dehydration under acidic conditions would provide 7,8-dehydrorutaecarpine (**36b**). We feel that the alkaloid 7,8-dehydrorutaecarpine (**36b**) would be a potential precursor for the enantioselective synthesis of 7-hydroxyrutaecarpine (**37a**) and 7,8-dihydroxyrutaecarpine (**37b**) (Figure 3).

In conclusion, starting from glutaric anhydride, we have demonstrated an elegant six-step total synthesis of the bioactive natural product rutaecarpine (**36a**) with 53% overall yield via zeolite induced Fischer-indole synthesis.[53] In this sequence we also have synthesized the bioactive natural products 2-(4-hydroxybutyl)quinazolin-4(1*H*)-one (**50**) and mackinazolinone (**51**) in 81% and 66% yields respectively[53] and attempted the synthesis of 7,8-dehydrorutaecarpine (**36b**). Synthesis of natural products from two intermediate natural products is noteworthy. The present zeolite induced Fischer-indole synthesis conditions used in the synthesis of rutaecarpine (**36a**) are mild and efficient compared to earlier known conditions and will be useful to design several naturally occurring indole skeletons. The present practical approach to quinazolinone alkaloids **36a**, **50** and **51** is

efficient, general and can be used to design libraries of rutaecarpine analogs and derivatives.

In summary, in this chapter we have presented an efficient synthesis of bioactive quinazolinone natural products pegamine, deoxyvasicinone, (–)-vasicinone, 2-(4-hydroxybutyl)quinazolin-4(1*H*)-one, mackinazolinone and rutaecarpine by effectively using cyclic anhydrides as potential starting materials. It is important to note that the natural products deoxyvasicinone, mackinazolinone and rutaecarpine have been synthesized via the natural products pegamine, 2-(4-hydroxybutyl)quinazolin-4(1*H*)-one and mackinazolinone respectively. The synthesis of natural product from another natural product is noteworthy because it reduces the total number of steps and also highlights their probable biological precursors. We feel that our approaches to various quinazolinone natural products are general and have the potential to generate libraries of quinazolinone alkaloids for the search of a bioactive lead molecule.

2.3 Experimental Section

Melting points are uncorrected. Column chromatographic separations were carried out on ACME silica gel (60-120 mesh). Commercially available anthranilamide, (*S*)-malic acid, lithium aluminum hydride (LAH), triphenylphosphine (TPP), diethyl azodicarboxylate (DEAD), glutaric anhydride, sodium borohydride, sodium hydride, *p*-toluenesulfonyl chloride and aniline were used. Zeolite H-Mordenite was obtained from PQ Zeolites (Netherlands) and was heated at 500 ^{o}C for 6 h before using.

2(*S*)-Acetoxysuccinic anhydride (21). A mixture of (*S*)-malic acid (8.04 g, 60 mmol) and freshly distilled acetyl chloride (60 mL) was heated at 40 ^{o}C with stirring for 2 h. Excess of acetyl chloride and acetic acid/acetic anhydride formed were distilled off in vacuo. The obtained solid residue was used for the next step without any further purification. The analytically pure compound **21** was obtained by recrystalisation from benzene. **21**: 9.28 g (98% yield); mp 56 ^{o}C (lit.[25] mp 55 ^{o}C); $[\alpha]^{20}_{D}$ = – 26.4 (*c* 5.0, $CHCl_3$) [lit.[25] $[\alpha]^{20}_{D}$ = – 26.0 (*c* 5.0, $CHCl_3$)].

β (*S*)-Acetoxy-*o*-amidosuccinanilic acid (32). To a solution of **21** (7.90 g, 50 mmol) in ether (50 mL) was added a solution of anthranilamide (**25**, 6.80 g, 50 mmol) in benzene-1,4-dioxane mixture (75 mL, 2:1), in a dropwise fashion with constant stirring at room temperature. Reaction mixture was further stirred for 2 h and the formed precipitate was filtered under vacuo and washed with ether (50 mL). The obtained compound **32** was used for the next step without any further purification. Analytically pure **32** was obtained by recrystalization from ethyl acetate. **32**: 14.4 g (98% yield); mp 152-153 ^{o}C; $[\alpha]^{20}_{D}$ = – 88.7 (*c* 0.6, acetone).

Similarly the reaction of succinic anhydride (**26**) with anthranilamide (**25**) furnished *o*-amidosuccinanilic acid (**27**): 98% yield; mp 197-198 ^{o}C (MeOH).

Methyl β (*S*)-acetoxy-*o*-amidosuccinanilate (33). To a solution of diazomethane in ether (50 mL) was added acid **32** (5.0 g, 17 mmol) at 0 ^{o}C and the reaction mixture was further stirred at room temperature till complete consumption of starting acid (1 h). Excess of diazomethane was quenched with acetic acid and the organic layer was washed with water,

brine and dried over Na_2SO_4. The organic layer was concentrated in vacuo followed by silica gel column chromatographic purification of the residue using petroleum ether and ethyl acetate mixture (3:1) gave pure **33**. **33**: 5.13 g (98% yield); mp 80-82 ^oC (C_6H_6); $[\alpha]^{20}_D = -65.7$ (*c* 1.2, $CHCl_3$).

Similarly **27** furnished **28**: 98% yield; mp 133-135 ^oC (C_6H_6).

2-[1(*S*),3-Dihydroxypropyl]quinazolin-4(1*H*)-one (35). To the slurry of LAH (0.76 g, 20 mmol) in THF (20 mL) was added a solution of ester **33** (3.08 g, 10 mmol) in THF (30 mL) in a dropwise fashion at 0-5 ^oC over a period of 30 min with continuous stirring. The reaction mixture was further stirred at room temperature for 1 h. The reaction mixture was slowly quenched with water (25 mL) and further stirred for 1 h at room temperature. Saturated NH_4Cl solution (10 mL) was added to the reaction mixture and then it was completely concentrated under vacuo and dried to the pump. The residue was stirred with THF (75 mL) for 1 h and the organic layer was filtered through celite, dried over Na_2SO_4 and concentrated in vacuo. The obtained crude product was purified by silica gel column chromatography using a mixture of ethyl acetate and methanol (99:1) to furnish pegamine derivative **35**. **35**: 2.03 g (92% yield); mp 134-136 ^oC (ethyl acetate); $[\alpha]^{20}_D = -22.6$ (*c* 1.0, MeOH).

Similarly **28** gave pegamine (**30**): 93% yield; mp 163-165 ^oC (ethyl acetate) (lit.[3a] mp 160-161 ^oC).

2,3-Dihydro-3(*S*)-hydroxypyrrolo[2,1-*b*]quinazolin-9(1*H*)-one [(–)-vasicinone, 31]. To the solution of **35** (0.55 g, 2.50 mmol) and TPP (0.85 g, 3.25 mmol) in THF (7 mL) was added a solution of DEAD (0.48 g, 2.75 mmol) in THF (5 mL) in a dropwise fashion with

continuous stirring at room temperature and the reaction mixture was further stirred for 1 h. The reaction mixture was concentrated in vacuo and the residue was chromatographed on silica gel using petroleum ether and ethyl acetate (1:1) to obtain (–)-vasicinone (**31**). **31**: 0.455 g (90% yield); mp 205-207 ^{o}C (EtOH) (lit.[17] mp 200-201 ^{o}C); $[\alpha]^{20}_{D}$ = – 105.6 (*c* 1.0, $CHCl_3$) [lit.[17] $[\alpha]^{20}_{D}$ = – 105.0 (*c* 1.0, $CHCl_3$)].

Similarly the reaction of **30** furnished deoxyvasicinone (**24**): 95% yield; mp 106-108 ^{o}C (C_6H_6) (lit.[17] mp 104-106 ^{o}C).

MTPA-ester of (±)-vasicinone. To a solution of (±)-vasicinone (10 mg, 0.05 mmol) and pyridine (0.1 mL) in DCM (1 mL) was added (*S*)-MTPA-Cl solution in DCM (0.08 M, 1 mL) and the reaction mixture was refluxed for 15 h. The reaction mixture was concentrated in vacuo and the residue was dissolved in diethyl ether (15 mL). The organic layer was washed with $CuSO_4$ solution, water, aqueous bicarbonate, water, brine and dried over Na_2SO_4. Concentration of organic layer in vacuo furnished the product as thick oil (16 mg).

Similarly MTPA-ester of (–)-vasicinone (**31**) was prepared: mp 172-174 ^{o}C.

***o*-Amidoglutaranilic acid (46).** To a solution of glutaric anhydride (**45**, 2.28 g, 20 mmol) in benzene (50 mL) was added a solution of anthranilamide (**25**, 2.72 g, 20 mmol) in 1,4-dioxane (25 mL), in a dropwise fashion with constant stirring at room temperature. Reaction mixture was further stirred for 2 h and the formed precipitate was filtered in vacuo and washed with benzene (2 x 25 mL). The obtained compound **46** was used for the next step without any further purification. Analytically pure **46** was obtained by

recrystalization from ethyl acetate. **46**: 4.90 g (98% yield); crystalline solid; mp 131-133 ^{o}C.

Methyl *o*-amidoglutaranilate (48). To a solution of acid **46** (4.50 g, 18 mmol) in methanol (50 mL) was added two drops of H_2SO_4 and the reaction mixture was stirred at room temperature for 8 h. The reaction mixture was concentrated in vacuo. The residue was dissolved in ethyl acetate and washed with aqueous sodium bicarbonate solution, water, brine and the organic layer was dried over Na_2SO_4. The organic layer was concentrated in vacuo to obtain ester **48**. The obtained ester **48** was used for the next step without any further purification. Analytically pure **48** was obtained by recrystalization from benzene. **48**: 4.56 g (96% yield); crystalline solid; mp 98-100 ^{o}C (C_6H_6).

2-(4-Hydroxybutyl)quinazolin-4(1*H*)-one (50). To a solution of ester **48** (4.00 g, 15 mmol) in THF (50 mL) was added $NaBH_4$ (2.88 g, 76 mmol) and the reaction mixture was refluxed for 3 h under an argon atmosphere. The reaction mixture was allowed to cool to rt and slowly quenched with water (50 mL). The reaction mixture was further stirred for 1 h at rt and then acidified with acetic acid. The reaction mixture was then concentrated and dried in vacuo. The residue was stirred with THF (100 mL) for 1 h and the organic layer was filtered through celite, dried over Na_2SO_4 and concentrated in vacuo. The obtained crude product was purified by silica gel column chromatography using a mixture of ethyl acetate and methanol (99:1) to furnish **50**. **50**: 2.84 g (86% yield); crystalline solid; mp 175-177 ^{o}C (ethyl acetate).

6,7,8,9-Tetrahydropyrido[2,1-*b*]quinazolin-11-one (Mackinazolinone, 51). To a stirred slurry of NaH (607 mg, 25.3 mmol) in THF (10 mL) was added a solution of alcohol **50** (2.5 g, 11.5 mmol) in THF (20 mL). To the above reaction mixture a solution of *p*-toluenesulfonyl chloride (2.63 g, 14 mmol) in THF (10 mL) was added in a drop-wise fashion over a period of 15 min and the reaction mixture was further stirred at rt for 30 min. Reaction was quenched with water (10 mL), concentrated in vacuo and extracted with ethyl acetate (100 mL). The organic layer was washed with aqueous sodium bicarbonate solution, water and brine. The organic layer was dried over Na_2SO_4 concentrated and dried in vacuo. The crude product was purified by silica gel column chromatography using a mixture of ethyl acetate and petroleum ether (1:1) to furnish **51**. **51**: 1.86 g (81% yield); crystalline solid; mp 99-101 ^{o}C (Hexane) (lit.[50] mp 98.5-99.5 ^{o}C).

6-Phenylhydrazono-6,7,8,9-tetrahydro-11*H*-pyrido[2,1-*b*]quinazolin-11-one (52). Phenyldiazonium chloride was prepared from aniline (512 mg, 5.5 mmol) in 20% hydrochloric acid (5 mL) at 0 ^{o}C using a solution of sodium nitrite (380 mg, 5.5 mmol) in water (5 mL). The reaction mixture was diluted with acetic acid (5 mL) and then was adjusted to pH 4 using sodium acetate. To this solution of phenyldiazonium chloride was added drop-wise a solution of the quinazolinone **51** (1.00 g, 5.0 mmol) in 50% acetic acid (10 mL) at 0 ^{o}C over a period of 15 min. The reaction mixture was further stirred at 0 ^{o}C for 3 h and then allowed to stand overnight in a refrigerator. The precipitated crystalline compound was filtered off, washed with water, dried in vauco to obtain pure **52**. **52**: 1.50 g (98 % yield); yellow crystalline solid; mp 184-186 ^{o}C (*n*-PrOH) (lit.[43b] mp 182-184 ^{o}C).

Similarly the reaction of hydroxymackinazolinone **53** with phenyldiazonium chloride directly furnished hydrazone **55**: 98% yield; mp 186-188 ^{o}C (ethyl acetate).

8,13-Dihydroindolo[2',3':3,4]pyrido[2,1-*b*]quinazolin-5(7*H*)-one (Rutaecarpine, 36a). To a solution of hydrazone **52** (500 mg, 1.65 mmol) in freshly distilled glacial acetic acid (10 mL) was added zeolite H-Mordenite (2 g) and the stirred reaction mixture was refluxed for 5 h under argon atmosphere. Acetic acid was distilled off in vacuo and the residue was dried to the pump and then stirred with THF (50 mL) for 1 h. The above reaction mixture was filtered and dried over Na_2SO_4. The organic layer was concentrated in vacuo and the obtained crude product was purified by silica gel column chromatography using a mixture of ethyl acetate and methanol (98:2) to furnish **36a**. **36a**: 387 mg (82 % yield); crystalline solid; mp 257-259 ^{o}C (Ethyl acetate) (lit.[43b] mp 258 ^{o}C).

9-Hydroxy-6,7,8,9-tetrahydropyrido[2,1-*b*]quinazolin-11-one (53). To the reaction mixture containing alcohol **50** (2.18 g, 10 mmol) and powdered 4 Å molecular sieves (2.00 g) in CH_2Cl_2 (60 mL) was added PCC (2.60 g, 12 mmol) in two portions with constant stirring at rt and it was further stirred for 1 h. Reaction mixture was diluted with ether (60 mL) and again stirred for next 15 min. Reaction mixture was then filtered through a bed of cellite and silica gel, washed with ether (3 x 50 mL) and the filtrate was concentrated in vacuo. Silica gel column chromatographic purification of the residue using a mixture of PE-EtOAc (1:1) gave pure compound **53**. **53**:1.44 g (72% yield). Mp 139-141 °C (C_6H_6).

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Chapter Three

Total Synthesis of Quinazolinone Natural Products Luotonins A, B, E and F

This chapter describes total synthesis of four luotonin alkaloids and is divided into two sections. The first section deals with the short, efficient and practical synthesis of the human DNA topoisomerase I poison luotonin A and luotonin B & E, wherein a regioselective quinazolinone-directed ortho lithiation on an adjacent quinoline moiety has been used as a key step. The second section describes a biogenetic synthesis of the recently isolated bioactive natural product luotonin F starting from the natural product pegamine via a Friedländer condensation (Figure 1).

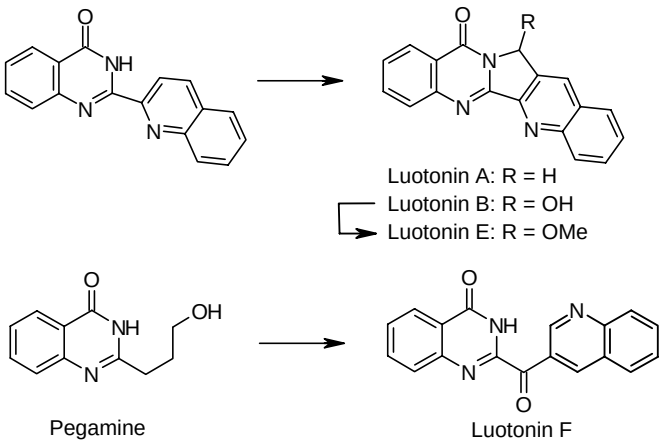


Figure 1: Total synthesis of quinazolinone alkaloids, luotonins A, B, E and F

3.1 Section A

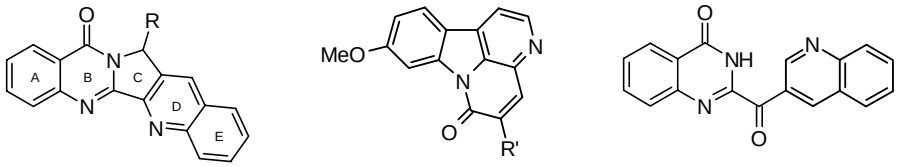
Regioselective Directed Ortho Lithiation: A Practical Total Synthesis of Quinazolinone Natural Products Luotonins A, B and E

3.2 Section B

Biogenetic Synthesis of Luotonin F

3.1.1 Background

The species from the plant kingdom *Peganum nigellastrum* Bunge (Zygophyllaceae) is found all over Asia and is more common in the northwest region of China. The same plant with Chinese name 'Luo-Tuo-Hao'[1] has been used in the Chinese traditional medicine system as a remedy for rheumatism, abscess and inflammation.[1] Recently, Nomura and co-workers from Japan in their collaborative work with scientists from China isolated six new alkaloids:[2-5] luotonin A, B, C, D, E and F (Figure 2) from aerial parts of *P. nigellasturm*. Luotonin C and D are unusual canthin-6-one derivatives (Figure 2). The structural



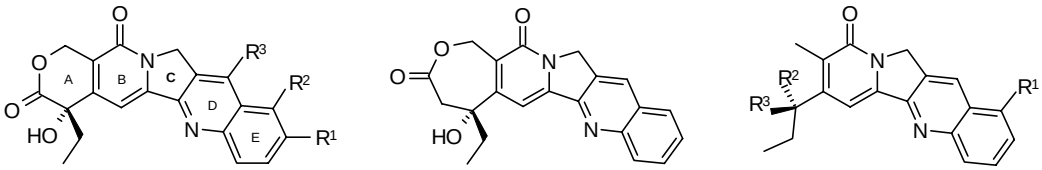
Luotonin A (**1a**): R = H
Luotonin B (**1b**): R = OH
Luotonin E (**1c**): R = OMe

Luotonin C: R' = Me
Luotonin D: R' = Et

Luotonin F (**1d**)

Figure 2: Naturally occurring luotonin alkaloids

assignments of luotonin A-F has been done on the basis of analytical and spectral data,[2-5] and these bioactive natural products exhibit anti-tumor activity.[2,6] Recently Ma et al[7] reported a good bioactivity study of luotonin A and F analogues and Hecht et al[8] reported synthesis & biochemical properties of A-ring modified luotonin A derivatives. Luotonin A (**1a**) is cytotoxic towards the murine leukemia P-388 cell line (IC_{50} 1.8 µg/mL).[2-5] Very recently, Hecht et al[9] have demonstrated that despite the lack of lactone ring functionality, luotonin A stabilizes the human DNA topoisomerase I-DNA covalent binary complex and mediates topoisomerase I-dependant cytotoxicity in intact cells (IC_{50} 5.7-12.6 µm/mL), like camptothecin and its analogs[10] (Figure 3). In a very short span of time (6-years) eleven syntheses of luotonin A have been reported from different laboratories using a variety of



Camptothecin (2) : R^1, R^2, R^3 = H
Topotecan : R^1 = OH, R^2 = $-CH_2-N(CH_3)_2$, R^3 = H
DB-67 : R^1 = OH, R^2 = H, R^3 = TBS
Irinotecan : R^1 = , R^2 = H, R^3 = $-CH_2CH_3$

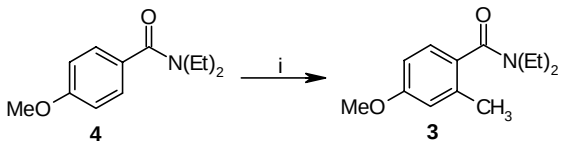
Homocamptothecin

Nothapodytine A : R^1 = OMe, R^2, R^3 = O
Nothapodytine B : R^1 = H, R^2, R^3 = O
Mappicine : R^1 = H, R^2 = OH, R^3 = H

Figure 3: Camptothecin and its analogs

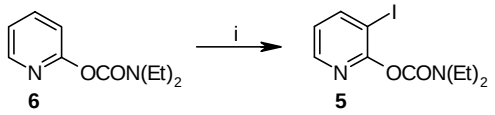
elegant synthetic strategies.[3,11-21] Out of eleven known syntheses, ten multi-step syntheses of linear penta-cyclic luotonin A have been completed using two suitable building blocks with construction of ring B or D. Recently, Harayama et al[20] completed the synthesis of luotonin A with construction of middle ring C using a Pd-assisted bi-aryl coupling reaction. Till date, four syntheses of luotonin B (**1b**)[2,3,13,20] and two syntheses of luotonin E (**1c**)[3,4] & F (**1d**)[3,4] are known. In continuation of our studies[39] on total synthesis of bioactive quinazolinone natural products, we planned for the synthesis of luotonin A, B and E using directed ortho lithiation strategy.

The use of directing groups to facilitate lithiation, followed by the reaction of the organolithium reagents thus obtained with electrophiles, has found wide range of applications in a variety of synthetic transformations.[22] Directed-metalation of anisole with *n*-BuLi was discovered independently in 1939-1940 by Gilman[23] and Wittig,[24] which led to the discovery of more than forty directing groups.[22] The process of directed ortho metalation using carboxamides, carbamates, carboxylic acids, hydrazides and oxazolines as directing groups is one of the better known methods for introducing various ortho substituents to the aromatic nucleus.[25] The great majority of studies on ortho metalation has been carried out on benzene rings.[25-27] For example Mills et al[27] demonstrated that



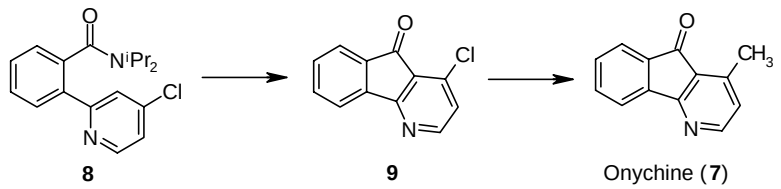
Scheme 1: (i) (a) *sec*-BuLi, TMEDA, (b) MeI, THF, – 78 ^{o}C (97%).

lithiation occurs *ortho* to a stronger directing group in cases where two lithiation sites are available (Scheme 1). In case of compound **4** there are two directing groups; methoxy and tertiary amide. The amide groups are generally stronger directing groups and hence methylation takes place at the *ortho*-position of the amide moiety in **4** to form compound **3** in quantitative yield (Scheme 1). Metallation of heteroaromatic systems has also been well studied.[22,25,28] Miah et al[28] studied the lithiation of pyridine ring system and found that



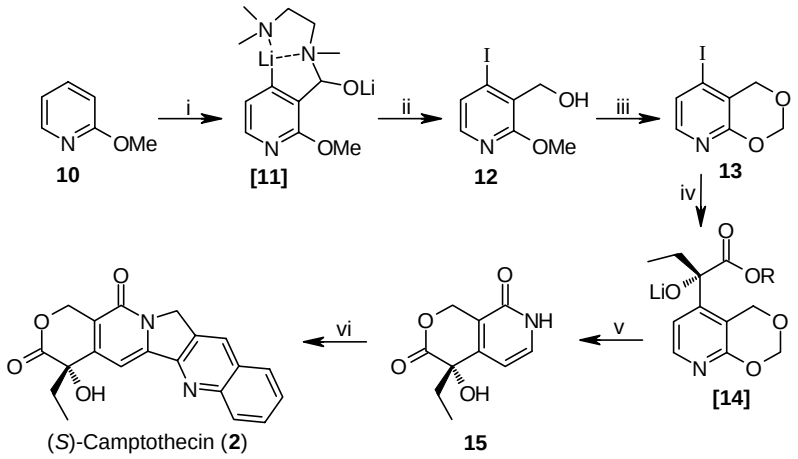
Scheme 2: (i) (a) *sec*-BuLi, TMEDA, (b) I_2, THF, – 78 ^{o}C (68%).

metalation of pyridine with simple *n*-BuLi reagent is complicated due to 1,2-addition of the organometalic reagent to the C=N moiety, but with an appropriate directing group and by using a hindered alkyllithium reagent, lithiation of the pyridine ring can be effected (Scheme 2). Pyridine derivative **6** was lithiated using *sec*-BuLi and TMEDA by avoiding the addition to C=N group. The lithiated species thus obtained was then treated with iodine to obtain the corresponding *ortho*-substituted iodo product **5** in 68% yield (Scheme 2). Recently, Rebstock et al[29] used amide directed lithiation strategy for the synthesis of natural product onychine (**7**), an alkaloid endowed with anti-candidal activity. The 2-substituted pyridine derivative **8** on treatment with LTMP followed by aqueous workup directly gave them the cyclized compound **9** in 66%, which was further transformed to onychine (**7**) in 96% yield by cross-coupling of the chloride with methylboronic acid under



Scheme 3: (i) (a) LTMP, THF, – 50 ^{o}C, (b) H_2O (66%); (ii) $MeB(OH)_2$, $Pd(PPh_3)_4$ 10 mol%, K_2CO_3, 1,4-dioxane, reflux (96%).

palladium catalysis. All these examples show that the directed ortho metalation is a strong tool for introducing a functional group at the desired position and hence it has been very well utilized in the synthesis of various bioactive natural products.[30-33] Comins et al[32,33] effectively used the directed ortho lithiation strategy for a practical six-step synthesis of (*S*)-camptothecin (Scheme 4), which is an important lead compound for the preparation of selective anticancer agents. 2-Methoxypyridine was lithiated at C-3 with mesityllithium[34]

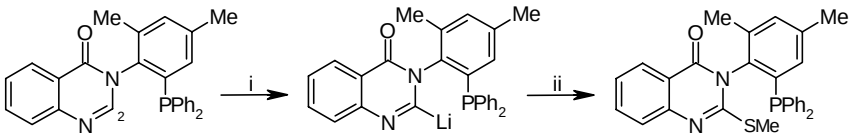


Scheme 4: (i) (a) MesLi, (b) *N*-formyl-*N,N',N*'-trimethylethylenediamine, (c) *n*-BuLi; (ii) I_2, $NaBH_4$, H_2O (one pot, 46%); (iii) TMSCl/NaI, $(CH_2O)_n$, CH_3CN (87%); (iv) (a) *n*-BuLi, (b) ketoester; (v) HCl, ^{i}PrOH (one pot, 60%); (vi) (a) 2-chloro-3-iodomethyl-quinoline, *t*-BuOK, DME, heat (81%), (b) $(Ph_3P)_2Pd(OAc)_2$, KOAc, CH_3CN, reflux (64%).

and treated with *N*-formyl-*N,N',N'*-trimethylethylenediamine to give an α-amino alkoxide in situ. Addition of *n*-BuLi effected α-amino alkoxide directed-lithiation at C-4 to give the intermediate dianion **11**. Addition of iodine and workup with aq. $NaBH_4/CeCl_3$ provided

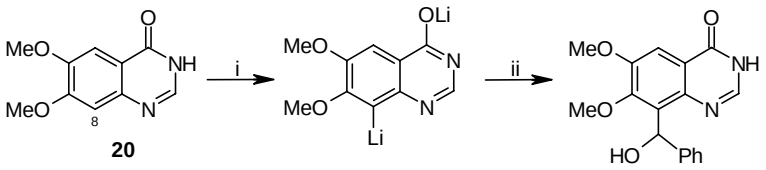
alcohol **12** in 46% yield. Alcohol **12** was converted directly to 1,3-dioxane **13**, which on treatment with *n*-BuLi followed by chiral ketoester[35] gave alkoxide **14** in situ. Treatment of **14** with HCl effected protonation, acetal hydrolysis and lactonization to afford intermediate **15**. Compound **15** was further transformed to (*S*)-camptothecin (**2**) in two steps, via Heck coupling reaction as a key step (Scheme 4).

Relatively few examples of the use of group-directed lithiation of more complex heterocyclic systems[26,36] are known in the literature. Quinazolinones are known to undergo selective lithiation at the 2 (Scheme 5) and 8 (Scheme 6) positions.[37] 2-Methyl/alkyl substituted quinazolinones are known to undergo lithiation at the 2-alkyl position[38]



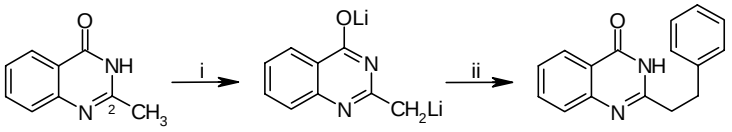
17 **[18]** **16**

Scheme 5: (i) LDA (1.05 eq.), THF, – 78 ^{o}C; (ii) (a) $(MeS)_2$, THF, – 78 ^{o}C, 1 h, (b) H_2O (88%).



20 **[21]** **19**

Scheme 6: (i) (a) *n*-BuLi (1 eq.), THF, – 78 ^{o}C, 15 min., (b) LTMP (4 eq.), – 78 ^{o}C, 1-2 h; (ii) (a) PhCHO (1 eq.), (b) H_2O (95%).



23 **[24]** **22**

Scheme 7: (i) *n*-BuLi (2 eq.), THF, – 78 ^{o}C, 15 min.; (ii) (a) $PhCH_2Cl$ (1eq.), (b) H_2O (58%).

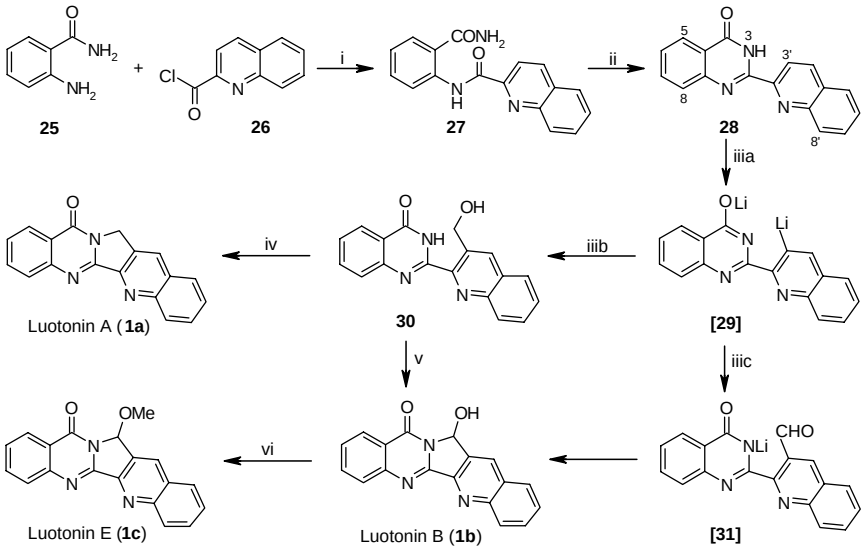
(Scheme 7). However, to the best of our knowledge, ortho lithiation of aryl and heteroaryl substituents on quinazolinones have not been reported in the literature and will be highly useful for the introduction of ortho substituents for the facile synthesis of several bioactive

quinazolinone natural products like luotonin A, B & E, unnatural quinazolinones and related compounds (Figure 2 & 3).

3.1.2 Present Work: Results and Discussion

Potassium salt of quinoline-2-carboxylic acid was refluxed with oxalyl chloride in benzene. The resulting wine-red/black solution, containing in situ generated quinaldic acid chloride **26**, was allowed to cool to room temperature and added drop-wise to a solution of anthranilamide (**25**) & triethylamine in chloroform and stirred at room temperature for 3 h.[40] The precipitated solid was filtered and washed with ethanol to obtain the corresponding diamide **27** in 96% yield. It was used for the next step without any further purification and the analytically pure sample was obtained by recrystallization form methanol. In order to effect the base catalyzed dehydrative cyclization[41] between the two amide units, a mixture of benzamide **27** in 5% aqueous sodium hydroxide and ethanol (2:1 v/v) was refluxed for 5 min. Usual workup followed by silica gel column chromatographic purification furnished quinazolinone **28** in quantitative yield. The 2-quinolinoquinazolinone **28** can undergo lithiation at carbon number 8, 3' and 8'.[22] The key issue of our present approach lies in the di-lithiation of the quinoline-quinazolinone skeleton with high specificity. We reasoned that alike carboxamide,[42] the amide unit in quinazolinones will be useful to perform directed-metalation reactions on adjacent 2-aryl/heteroaryl groups. As expected, the first lithiation of compound **28** would take place at the 3-position nitrogen atom of quinazolinone ring and the mono-lithiated species formed may direct the second lithiation at the proximal 3'-position of quinoline ring. In order to perform the quinazolinone-directed ortho lithiation at the 3'-position of the adjacent quinoline nucleus with the assistance of the amide moiety in the quinazolinone skeleton,

we tried several reaction conditions. The reaction of **28** with *n*-BuLi, *s*-BuLi and *t*-BuLi with or without TMEDA at 0 to – 78 ^{o}C always ended up with the formation of a complex mixture, which was probably arising from the addition of alkyllithium to the carbon-nitrogen double bond[22] in **28**. The use of, hindered alkyllithium, LDA also ended up with the formation of complex mixtures. Finally, use of 2.2 equivalents of in situ generated non-nucleophilic mesityllithium, (prepared from 2-bromomesitylene by its reaction with *t*-BuLi



Scheme 8: (i) Et_3N (2 eq.), THF, rt, 3 h (96%); (ii) 5% aq. KOH, EtOH, reflux, 5 min. (98%); (iiia) mesityllithium (2.2 eq.), – 78 ^{o}C, 30 min. to – 20 ^{o}C (gradually), (iiib) THF solution of HCHO (5 eq.), – 30 ^{o}C, 20 min., saturated aq. solution of NH_4Cl (86%), (iiic) DMF (5 eq.), – 20 ^{o}C, 30 min., saturated aq. solution of NH_4Cl (81%); (iv) PPh_3 (1.3 eq.), DEAD (1.2 eq.), THF, rt, 1 h (95%); (v) PCC (1.2 eq.), powdered 4 Å molecular sieves, CH_2Cl_2, rt, 1 h (61%); (vi) *p*-TsOH (5 eq.), MeOH, reflux, 3 h (82%).

in THF at – 78 ^{o}C for 1 h)[34] at – 20 ^{o}C furnished the desired dilithiated species **29** via lithiation of the quinazolinone nitrogen at the 3-position as the first step followed by directed ortho lithiation at the 3'-position. Herein the formation of deep brown color in the reaction mixture at near about – 20 ^{o}C indicates the in situ generation of the dilithiated

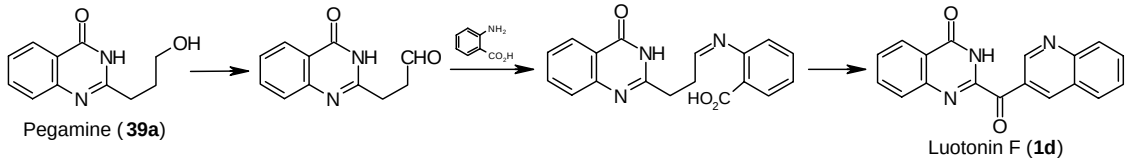
intermediate **29**, which was treated with THF solution of formaldehyde (prepared by thermal cracking of paraformaldehyde) and the reaction was quenched with saturated solution of NH_4Cl. Usual workup followed by silica gel column chromatographic purification exclusively yielded the desired *o*-hydroxymethylquinolinoquinazolinone 30 in 86% yield. The Mitsunobu intramolecular cyclization[43] of **30** with DEAD/TPP reagent in THF at room temperature furnished the bioactive natural product luotonin A in 95% yield with an overall insertion of a methylene group between the 3 and 3'-positions of **28**. The reaction of dilithiated species **29** with *N*,*N*-dimethylformamide directly furnished luotonin B (**1b**) in 81% yield via intermediate **31**, with insertion of a hydroxymethine group, thus generating an asymmetric centre in the molecule. We feel that due to the possible ring-chain tautomerism, luotonin B (**1b**) was isolated from its natural source in a reacemic form and probably it is a biological precursor of luotonin E (**1c**), which also did not show any optical activity. The PCC oxidation of **30** in CH_2Cl_2 also furnished luotonin B in 61% yield. We did not observe the formation of any further oxidation product in this reaction. Luotonin B on treatment with *p*-TsOH/methanol provided luotonin E (**1c**) in 82% yield. All these natural products were purified by silica gel column chromatography and the analytical and spectral data obtained for all the luotonin alkaloids were in complete agreement with the reported data.[2-5,11-21] We feel that the dilithiated species like **29** can be reacted with several types of electrophiles for generation of a library of quinazolinone alkaloids.

In conclusion, we have demonstrated[44] a facile quinazolinone-directed regioselective ortho lithiation of quinazolinoylquinoline and applied it for the short, efficient and practical synthesis of naturally occurring promising anti-cancer agents luotonin A, B and E. We feel that our present approach is general in nature and such type of regioselective directed-

lithiation of aryl and heteroaryl substituted quinazolinone systems will be highly useful for the synthesis of a large number of desired complex quinazolinone alkaloids, luotonin & camptothecin like analogs for structure activity relationship studies.

3.2.1 Background

Luotonin F (**1d**) was isolated[3,4] from the plant species *Peganum nigellastrum* along with four other alkaloids luotonin A-E (Figure 2). The structure of the alkaloid luotonin F (**1d**) was determined by its synthesis and spectroscopic methods.[3,4] Structurally luotonin F is a quinazolinoylquinolinyl ketone and it lacks a pyrrole ring system which is present in the structurally related pyrroloquinazolinoquinoline alkaloids luotonin A, B and E. Luotonin F (**1d**) exhibits anti-tumor activity.[6] Recently Ma et al reported[7] bioactivity studies of luotonin F analogs and showed that the synthetic analog deoxoluotonin F (**43**) is cytotoxic (IC_{50} 2.3 μg/mL) and inhibits DNA topoisomerase II at a concentration of 25 μM. The first six-step synthesis of luotonin F (**1d**) has been reported by Nomura's group[4] starting from 3-formylquinoline with 5.6% overall yield. Luotonin F (**1d**) was isolated[4] along with the naturally occurring quinazolinone alkaloid pegamine (**39a**) and hence the

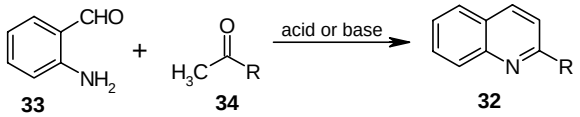


Scheme 8: A schematic representation of a plausible biosynthetic route to luotonin (**1d**) from pegamine (**39a**), proposed by Nomura et al.[4]

authors assumed **39a** as a potential starting material and proposed a hypothetical biosynthetic route to **1d** from **39a** (Scheme 8). Provision of a facile synthetic approaches to the naturally occurring bioactive quinazolinone alkaloids is a challenging task of our current interest.[39,44] Recently, we have completed[39a] a concise and efficient total synthesis of pegamine, hydroxypegamine, deoxyvasicinone and (–)-vasicinone. We planned two biogenetic type approaches for synthesis of structurally interesting and biologically

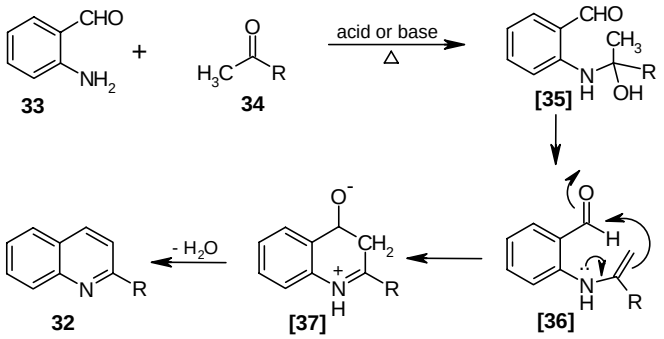
important alkaloid luotonin F (**1d**) starting from pegamine (**39a**) and hydroxypegamine **39b**, using Friedländer condensation reaction.

Friedländer quinoline synthesis[45] is a condensation reaction between 2-amino-benzaldehyde and ketone or aldehyde to generate a substituted quinoline moiety. This



Scheme 9: General scheme showing Friedländer condensation reaction.

reaction can be catalyzed by base or an acid (Scheme 9). The mechanism of the reaction has been proposed (Scheme 10)[45] and it goes through imine formation as the first step, followed by isomerization to enamine, intramolecular cyclization and dehydration (Scheme 10). This useful reaction has been not been used extensively because of the limited availability of 2-aminobenzaldehydes.

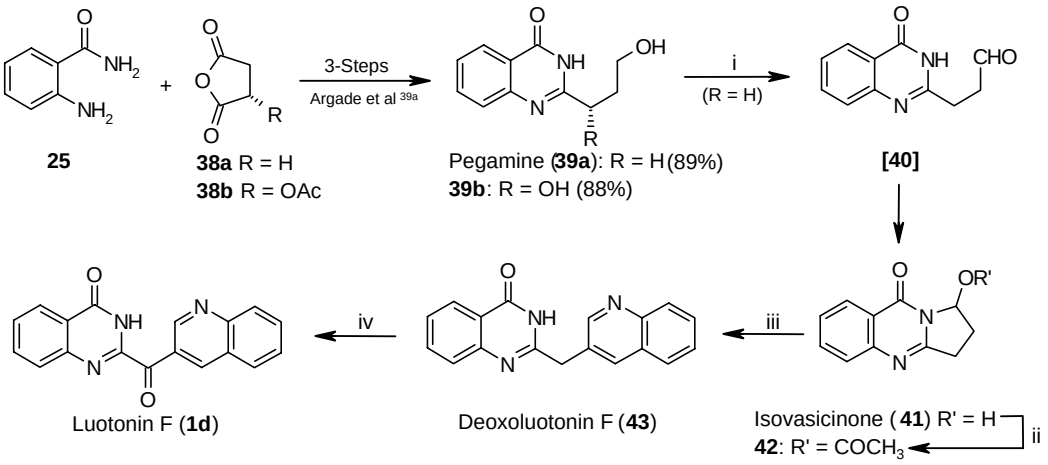


Scheme 10: Schematic representation of mechanism of Friedländer quinoline synthesis.

We felt that Friedländer condensation reaction of *o*-aminobenzaldehyde with lactol under basic conditions will be useful for constructing quinoline moiety in luotonin F (**1d**) for its efficient total synthesis starting from the natural product pegamine (**39a**).

3.2.2 Present work: Results and Discussion

The natural product pegamine (**39a**) was synthesized using our own procedure,[39a] starting from anthranilamide (**25**) and succinic anhydride (**38a**) in 89% yield over three-steps. Pegamine (**39a**) upon oxidation with PCC in dichloromethane at room temperature in 3 hours directly furnished isovasicinone (**41**) in 64% yield, after the silica gel column chromatographic purification. Isovasicinone (**41**) has been identified earlier[46] as a drug metabolite of deoxyvasicinone. We were unable to isolate the formed intermediate aldehyde **40** and in this possible ring-chain tautomerism, the isolated compound prefers to stay in ring-closed form **41**. It was also characterized as its acetyl derivative **42**.



Scheme 11: i) PCC, CH_2Cl_2, rt, 3 h (64%); ii) Ac_2O, Py, rt, 8 h (98%); iii) *o*-aminobenzaldehyde, KOH, EtOH, reflux, 15 h (62%); iv) CrO_3, H_5IO_6, DMF, rt, 1 h (96%).

Isovasicinone (**41**) on Friedländer condensation[45] with *o*-aminobenzaldehyde (prepared by the reduction of *o*-nitrobenzaldehyde),[47] using ethanolic potassium hydroxide under reflux for 15 hours gave deoxoluotonin F (**43**) in 62% yield via in situ ring opening of **41**, imine formation and intramolecular condensation reaction pathway. Our attempt to oxidize deoxoluotonin F (**43**) using chromium(VI) oxide catalyzed benzylic oxidation with periodic acid i.e. Yamazaki's[48] oxidation, in acetonitrile could not provide **1d** in

better yields, probably due to the low solubility of **43** in acetonitrile even at refluxing temperature. Better results were obtained by Yamazaki's[48] oxidation in DMF at room temperature in 1 hour to furnish the bioactive natural product luotonin F (**1d**) in 96% yield, after the silica gel column chromatographic purification. The overall yield of **1d** in three-steps was 38% and starting from succinic anhydride (**38a**), luotonin F was obtained in 34% yield over six-steps, which includes formation of both the quinazolinone and quinoline moiety and oxidation of methylene group. The analytical and spectral data obtained for **1d** were in complete agreement with the reported data.[4] In our hands, all attempts to oxidize hydroxypegamine (**39b**) to the corresponding desired keto-aldehyde or its ring closed form like **41**, using variety of oxidizing agents such as ceric ammonium nitrate, pyridinium chlorochromate, selenium dioxide, manganese dioxide, oxalyl chloride-DMSO and iodoxybenzoic acid (IBX)[49] failed and only decomposition products or polymeric gums were obtained. Hence we were unable to complete the short two step synthesis of **1d** starting from **39b**.

In conclusion, a three-step biogenetic type synthesis of recently isolated bioactive natural product luotonin F (**1d**) with 38% overall yield has been demonstrated,[50] starting from the natural product pegamine (**39a**). Synthesis of natural product luotonin F starting from the natural product pegamine is noteworthy because it directly proved that pegamine is a biological precursor of luotonin F and the number of steps are reduced to complete the short and efficient synthesis.

In summary, in this chapter we have presented an efficient synthesis of quinazolinone natural products luotonin A, B & E, metabolite isovasicinone and luotonin F. We feel that the quinazolinone directed regioselective ortho lithiation strategy developed for the

synthesis of luotonin A, B & E can be extended for the synthesis of library of quinazolinone compounds and camptothecin like analogs for the structure activity relationship studies. We have widened the scope of the quinazolinone directed ortho lithiation strategy by exploring its application for the synthesis of few pyrroloquinazolinoquinoline natural products and we are sure that in future quinazolinone directed ortho lithiation on aryl/heteroaryl systems will be widely used for the synthesis of more complex bioactive molecules. Our biogenetic synthesis of luotonin F starting from pegamine, via the metabolite isovasicinone is a good example of reproducing the nature's biosynthetic way of synthesizing the natural products, thus providing a direct proof of their genesis.

3.3 Experimental Section

Melting points are uncorrected. Column chromatographic separations were carried out on ACME silica gel (60-120 mesh). Petroleum ether had a bp range of 60-80 ^{o}C. Commercially available anthranilamide, quinolin-2-carboxylic acid, *t*-butyllithium, 2-bromomesitylene, PCC, triphenylphosphine (TPP), diethyl azodicarboxylate (DEAD), CAN, CrO_3, H_5IO_6, SeO_2, MnO_2, $(COCl)_2$ and Ac_2O were used.

2-(2'-Aminocarbonylquinolinyl)benzamide (27). 2-Quinolinecarboxylic acid (2.08 g, 12.00 mmol) and potassium hydroxide (692 mg, 12.36 mmol) were dissolved in distilled water (20 mL). The water was removed in vacuo and the resulting white solid residue was dried under high vacuum. To the resulting potassium salt suspended in benzene (30 mL) was added oxalyl chloride (1.26 mL, 14.40 mmol) dropwise at 5 - 10 ^{o}C. The reaction mixture was allowed to warm to rt and slowly heated to a gentle reflux. The

resulting wine-red/black solution was allowed to cool to rt and added drop-wise to a solution of anthranilamide (**25**) (1.63 g, 12.00 mmol) and triethylamine (3.34 mL, 24.00 mmol) in chloroform (20 mL) and stirred at rt for 3 h. The precipitated solid was filtered, washed with ethanol to obtain compound **27** and it was used for the next step without any further purification. The analytically pure sample was obtained by recrystallization from methanol. **27**: 3.35 g (96% yield); mp 269-271 ^{o}C (methanol).

2-(2'-Quinolinyl)-3*H*-quinazolin-4-one (28). A mixture of benzamide **27** (2.91 g, 10.00 mmol) in 5% aqueous NaOH (50 mL) and EtOH (25 mL) was heated to reflux for 5 min. Ethanol was removed in vacuo and the aqueous layer was extracted with chloroform (50 mL x 3). The organic layer was washed with water and brine and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by silica gel column chromatographic purification of the residue using ethyl acetate as an eluant gave pure **28**. **28**: 2.68 g (98% yield); mp 229-231 ^{o}C (ethyl acetate).

2-(3'-Hydroxymethyl-2'-quinolinyl)-3*H*-quinazolin-4-one (30). To a solution of *t*-BuLi (1.5 M in pentane, 2.69 mL, 4.03 mmol) in THF (10 mL) at – 78 ^{o}C was added a solution of 2-bromomesitylene (0.62 mL, 4.03 mmol) in THF (5 mL) over a period of 10 min. and the reaction mixture was stirred for 1 h. To the above reaction mixture was added a solution of quinazolinone **28** (500 mg, 1.83 mmol) in THF (30 mL) and then it was stirred for 30 min. at – 78 ^{o}C. The reaction mixture turned deep brown in color on gradually allowing it to reach – 20 ^{o}C. A solution of HCHO (9.16 mmol) in THF (1 mL) (formaldehyde solution in THF was prepared by thermal cracking of paraformaldehyde) was added to the reaction mixture and stirring was continued for further 20 min. at – 20

^{o}C. The reaction was quenched with a saturated solution of NH_4Cl and the reaction mixture was extracted with $CHCl_3$ (25 mL x 3). The organic layer was washed with water, brine and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by silica gel column chromatographic purification of the residue using a mixture of ethyl acetate/methanol (9:1) as an eluant furnished compound **30**. **30**: 477 mg (86% yield); mp 212-214 ^{o}C (benzene).

Quino[2',3':3,4]pyrrolo[2,1-*b*]quinazolin-11(13*H*)-one (luotonin A, 1a). To the solution of compound **30** (200 mg, 0.66 mmol) and TPP (225 mg, 0.86 mmol) in THF (10 mL) was added solution of DEAD (0.144 mL, 0.79 mmol) in THF (5 mL) dropwise over a period of 10 min. at rt and further stirred for 1 h. The reaction mixture was concentrated in vacuo. The column chromatographic purification of the residue using ethyl acetate as an eluant furnished luotonin A (**1a**). **1a**: 179 mg (95% yield); mp 284-285 ^{o}C (ethyl acetate) (lit.[20] mp 283-285 ^{o}C).

Quino[2',3':3,4]pyrrolo[2,1-*b*]quinazolin-13-hydroxy-11-one (luotonin B, 1b). (A) To a solution of *t*-BuLi (1.5 M in pentane, 2.69 mL, 4.03 mmol) in THF (10 mL) at – 78 ^{o}C was added a solution of 2-bromomesitylene (0.62 mL, 4.03 mmol) in THF (5 mL) over a period of 10 min. and the reaction mixture was stirred for 1 h. To the above reaction mixture was added a solution of quinazolinone **28** (500 mg, 1.83 mmol) in THF (30 mL) and then it was stirred for 30 min. at – 78 ^{o}C. The reaction mixture turned deep brown in color on gradually allowing it to reach – 20 ^{o}C. A solution of DMF (0.71 mL, 9.16 mmol) in THF (1 mL) was added to the reaction mixture and stirring was continued for further 30 min. at – 20 ^{o}C. The reaction was quenched with a saturated solution of NH_4Cl and

the reaction mixture was extracted with $CHCl_3$ (25 mL x 3). The organic layer was washed with water and brine and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by silica gel column chromatographic purification of the residue using a mixture of ethyl acetate/methanol (9:1) as an eluant furnished luotonin B (**1b**). **1b**: 447 mg (81% yield).

(B) To the reaction mixture containing powdered 4 Å molecular sieves (200 mg) and compound **30** (100 mg, 0.33 mmol) in DCM (20 mL) was added PCC (85 mg, 0.40 mmol) in two portions and the reaction mixture was stirred for 1 h at rt. The reaction mixture was then diluted with ether (20 mL) and stirred for another 15 min. Reaction mixture was then filtered through a bed of celite and silica gel and washed with ether (15 mL x 3). The filtrate was concentrated under vacuum and the residue was purified by silica gel column chromatography using a mixture of ethyl acetate/methanol (9:1) as an eluant to furnish luotonin B (**1b**). **1b**: 61 mg (61% yield); mp 274-276 ^{o}C (ethyl acetate) (lit.[20] mp 271-274 ^{o}C).

Quino[2',3':3,4]pyrrolo[2,1-*b*]quinazolin-13-methoxy-11-one (luotonin E, 1c). The solution of Luotonin B (**1b**) (350 mg, 1.16 mmol) and *p*-toluenesulfonic acid (1.11 g, 5.81 mmol) in methanol (20 mL) was refluxed for 3 h. The reaction mixture was concentrated in vacuo and the residue was dissolved in ethyl acetate (50 mL) and washed with aqueous solution of $NaHCO_3$, water and brine. The ethyl acetate layer was dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by silica gel column chromatographic purification of the residue using a mixture of ethyl acetate/petroleum ether (1:1) as an eluant furnished luotonin E (**1c**). **1c**: 300 mg (82% yield); mp 225-227 ^{o}C (benzene) (lit.[4] mp 222-225 ^{o}C).

1-Hydroxy-2,3-dihydro-1*H*-pyrrolo[2,1-*b*]quinazolin-9-one (Isovasicinone, 41). To a mixture of pegamine (**39a**, 1.02 g, 5 mmol), PCC (1.62 g, 7.5 mmol) and 4 Å molecular sieves (1.00 g) was added DCM (30 mL) with constant stirring at room temperature and the reaction mixture was further stirred for 3 h. Reaction mixture was diluted with diethyl ether (60 mL) and stirred for next 30 min. Reaction mixture was then filtered through a bed of celite and silica gel, washed with ether (100 mL) and the filtrate was concentrated in vacuo. Silica gel column chromatographic purification of the residue using a mixture of petroleum ether and ethyl acetate (1:1) gave pure isovasicinone **41**. **41**: 650 mg (64 % yield); mp 176-178 ^{o}C (C_6H_6).

1-Acetoxy-2,3-dihydro-1*H*-pyrrolo[2,1-*b*]quinazolin-9-one (42). To a mixture of acetic anhydride (2 mL) and pyridine (2 mL) was added isovasicinone (**41**, 60 mg, 0.3 mmol) at room temperature and the reaction mixture was kept in dark for 8 h. Reaction mixture was then concentrated in vacuo and dried under vacuum. The residue was dissolved in ethyl acetate and washed with brine (10 mL x 3). The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The crude product was chromatographed on silica gel column using petroleum ether and ethyl acetate (85:15) to obtain pure acetyl derivative **42**. **42**: 71 mg (98% yield); mp 89-91 ^{o}C (C_6H_6 + pet. ether).

2-(Quinolin-3-ylmethyl)-3*H*-quinazolin-4-one (43). To a solution of isovasicinone (**41**, 404 mg, 2 mmol) and *o*-aminobenzaldehyde (363 mg, 3 mmol) in absolute ethanol (5 mL) was added saturated ethanolic KOH (0.2 mL) and reaction mixture was refluxed for 15 h. The reaction mixture was concentrated in vacuo and the obtained residue was dissolved in ethyl acetate and washed with brine (15 mL x 3). The organic layer was

dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by silica gel column chromatography using a mixture of petroleum ether and ethyl acetate (1:1) to obtain pure deoxoluotonin F **43**. **43**: 356 mg (62 % yield); mp 263-265 ^oC ($CHCl_3$ + acetone) (lit.[4] mp 246-248 ^oC).

2-(Quinoline-3-carbonyl)-3*H*-quinazolin-4-one [Luotonin F, 1d]. To the reaction mixture containing CrO_3 (100 mg, 1 mmol) and periodic acid (570 mg, 2.5 mmol) in DMF (3 mL) was added a solution of deoxoluotonin F **43** (287 mg, 1 mmol) in DMF (1 mL) at room temperature over a period of 5 min. Reaction mixture was further stirred for 1 h and concentrated in vacuo and dried under vacuum. The residue was dissolved in ethyl acetate and washed with brine (10 mL x 3). The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The crude product obtained was purified by silica gel column chromatography using a mixture of petroleum ether and ethyl acetate (60:40) to furnish pure luotonin F (**1d**). **1d**: 290 mg (96 % yield); mp 241-242 ^oC ($CHCl_3$) (lit.[4] mp 238-240 ^oC).

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Chapter Four

Studies on Total Synthesis of Circumdatin C and F

This chapter presents our studies on the synthesis of recently isolated bioactive quinazolinone natural products circumdatin C (**1**) and F (**2**) using two different approaches. One approach comprises the use of benzoxazinone as a potential intermediate, while the other demonstrates the use of copper or palladium catalyzed intramolecular Ullman type coupling reaction for the attempted construction of these structurally interesting quinazolinone natural products (Figure 1). On completion these strategies would be applicable for the synthesis of circumdatin family of natural products, other quinazolinone natural products like sclerotigenin, benzomalvins and its logical extension for the synthesis of asperlicin C and asperlicin would be possible.

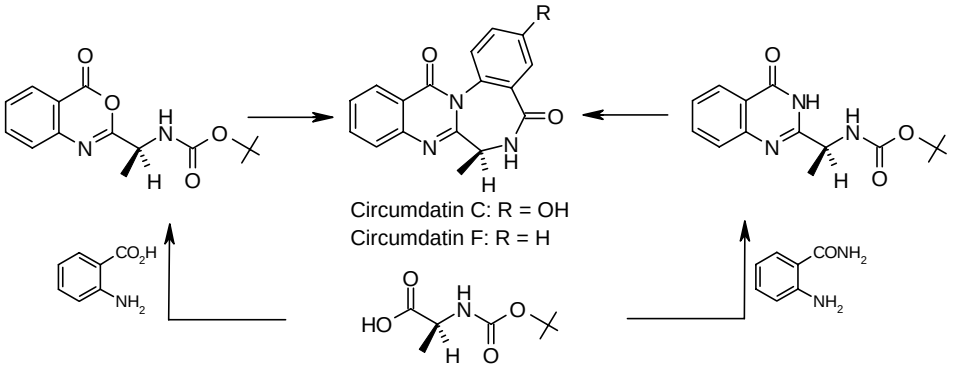


Figure 1: Two approaches for the synthesis of circumdatin C and F

4.1 Background

The crude extract of the broth of fungus *Aspergillus ochraceus* was found to inhibit the final stage of polyprotein processing during hepatitis C virus replication and recently, seven benzodiazepine alkaloids circumdatin A-G (Figure 2) have been isolated[1-3] from its terrestrial isolate, which are suggested to be suitable chemotaxonomic markers for this species. Structure of all these alkaloids were determined by spectroscopic methods and

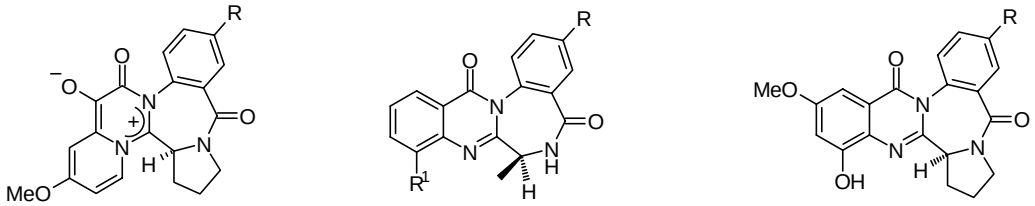


Figure 2: Naturally occurring circumdatin alkaloids

recently developed ^{1}H-detected INEPT2- and HMBC-INADEQUATE NMR experiments were used to solve the structures of the two zwitterionic benzodiazepines circumdatin A & B. Structurally related bioactive quinazolinone natural products include sclerotigenin (**3**),[4] benzomalvin A (**4**)[5,6] asperlicin C (**5**)[7] and asperlicin (**6**)[8] (Figure 3). Sclerotigenin

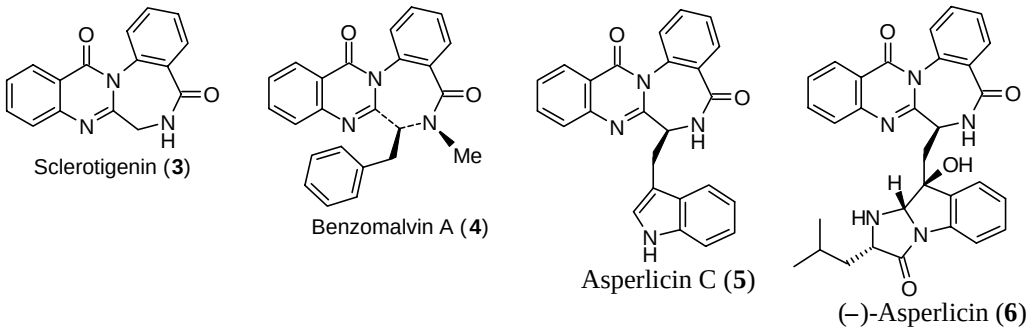


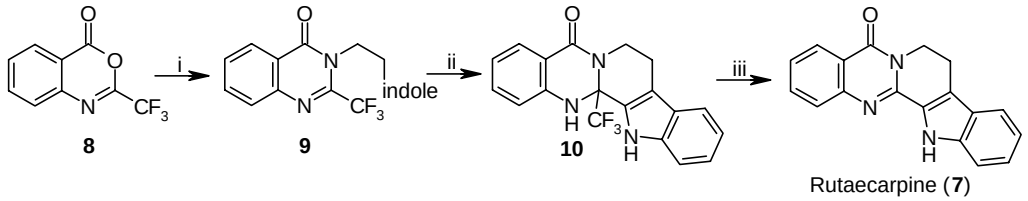
Figure 3: Isolated members of the circumdatin related benzodiazepine alkaloids

(**3**) has shown promising anti-insectan activity,[4] benzomalvins showed potent inhibitory activity[5,6] against substance P at the guineau pig, rat and human neurokinin NK1 receptor

and the asperlicins are known as potent cholescystokinin antagonists.[7-10] Asperlicin (**6**) is used for the treatment of gastrointestinal and CNS disorders.[11] Benzodiazepines constitute a widely prescribed class of psychoactive drugs,[12] and numerous compounds have been synthesized and tested for bioactivity. The benzodiazepine moiety has received much attention in the synthetic community, in part due to representation as a member of the family of 'privileged scaffolds'.[13,14] The unique characteristics that allow it to mimic endogenous ligands towards a number of different receptor targets have promoted its selection as a key scaffold in lead generation for many pharmaceutical programs through solution and solid phase chemistry. Till date only one synthesis of circumdatin C[15] in 10 steps with 0.9% overall yield is known, whereas three syntheses[15-17] of circumdatin F have been reported in the literature. Recently Grieder et al[18] developed a concise building block approach to a diverse multi-arrayed library of the circumdatin family of natural products using a polymer-supported phosphine-mediated intramolecular aza-Wittig reaction as a key step of the reaction sequence. In continuation of our studies[19-22] on total synthesis of bioactive quinazolinone natural products, we aimed to provide new efficient synthetic methods for the synthesis of circumdatin C and F using two different approaches. One of the approaches includes use of benzoxazinone as a potential intermediate and the other is based on the use of copper or palladium catalyzed Ullman type coupling as a key step.

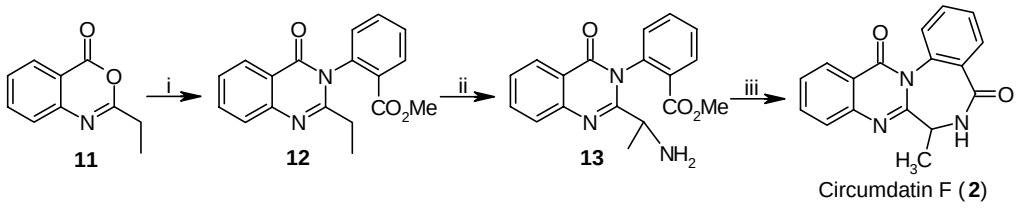
Benzoxazin-4-ones are potential precursors for the synthesis of natural and unnatural quinazolinones. The presence of reactive imino lactone moiety in benzoxazin-4-ones has been widely utilized[23-29] in synthetic organic chemistry to obtain a variety of novel heterocyclic skeletons, natural products and bioactive molecules. The most common method used for the synthesis of benzoxazinones is dehydrative cyclization of *N*-acyl

derivatives of anthranilic acids. A few less common approaches[30-32] to benzoxazinones are also known in the literature. Use of benzoxazin-4-one as an intermediate for the synthesis of quinazolinone natural products can be exemplified by the Bergman's rutaecarpine[24] and circumdatin F[29] synthesis. Isatoic anhydride was converted to tri-



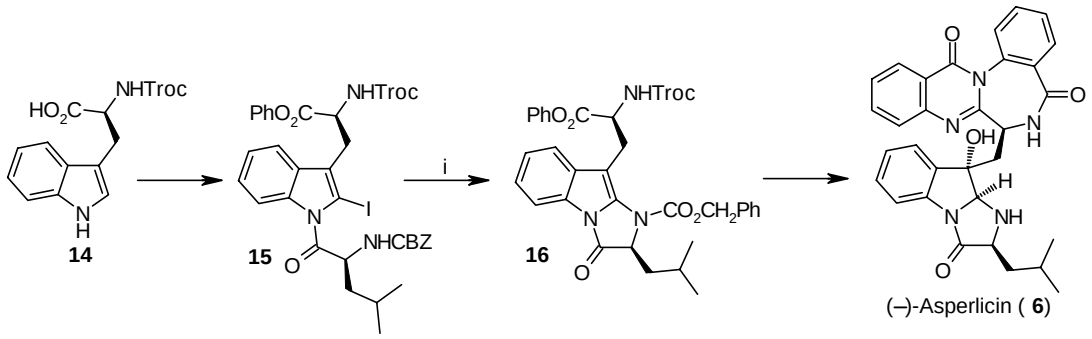
Scheme 1: (i) Tryptamine, 30 min. (98%); (ii) HCl, AcOH (95%); (iii) H_2O, EtOH (100%).

fluoromethyl-benzoxazinone **8** and then treated with tryptamine under mild conditions to obtain **9**, which was further cyclized under acidic conditions to obtain pentacyclic system **10**. Compound **10** on refluxing in aq. EtOH, gave rutaecarpine (**7**), thus completing the total synthesis[24] in 93% overall yield from benzoxazinone **8**. Bergman's[29] synthesis of circumdatin F commenced with the benzoxazinone **11**. The reaction of **11** with methyl anthranilate followed by thermal recylization gave them quinazolin-4-one **12**. Electrophilic bromination of **12** followed by its conversion to amine **13** and further thermally-induced lactam formation completed the synthesis of (±)-circumdatin F (**2**) in 1.3% overall yield from **11**. Similar transformations also gave them sclerotigenin (**3**).



Scheme 2: (i) (a) Methyl anthranilate, AcOH, reflux, (b) DMF, reflux (4.7%); (ii) (a) Br_2, NaOAc, HOAc, 60 ^oC, (b) NaN_3, H_2O-^{i}PrOH (1:5), reflux, (c) H_2 (220 psi), 5% Pd/C, EtOH, rt; (iii) MeCN, reflux (28% over ii & iii).

During the past few years significant advances have occurred in the development of cross-coupling methodology. By far, however, the largest application of cross-coupling chemistry, particularly C-N bond-forming processes, occurs in the medicinal and discovery groups of pharmaceutical companies and in academic laboratories. Despite significant improvements, the scope of cross-coupling methodology to form aryl and heteroaryl C-N bonds lags that of analogous C-C bond-forming processes such as Suzuki, Stille and Negishi coupling reactions. Several publications on the C-N bond-forming cross-coupling reactions are known by using palladium[33-40] or copper[41-45] catalyzed Ullman type coupling reactions. These reactions have been nicely utilized for the synthesis of natural products. Buchwald's[34] palladium-catalyzed Ullman type coupling reaction has been effectively used as one of the key steps for the synthesis of quinazolinone natural product asperlicin[35] (Scheme 3). Iodo-indole **15** was synthesized



Scheme 3: (i) $Pd_2(dba)_3$, P(*o*-tolyl)$_3$, K_2CO_3, toluene, reflux (28% from **14**).

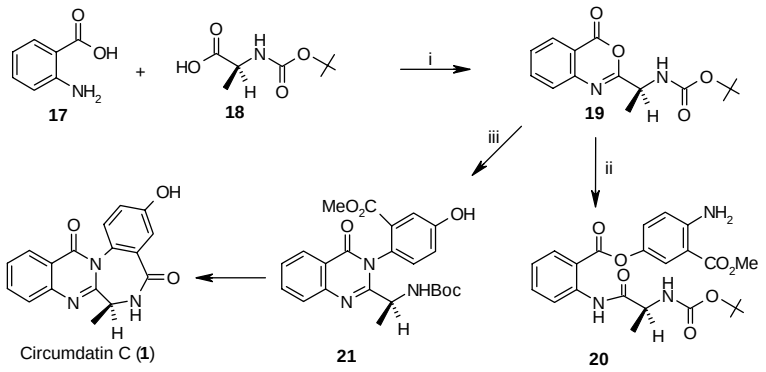
from Troc-protected-L-tryptophan **14**. Intramolecular cyclization of **15**, using palladium-catalyzed Ullman type C-N bond forming coupling reaction provided them the desired imidazoindolone **16**, which was further transformed smoothly to bioactive natural product (–)-asperlicin (**6**), thus completing its first total synthesis in 15 steps and 8% overall yield. Buchwald et al recently reported that[44] such type of C-N cross-coupling

reactions can be very efficiently carried out using less expensive copper catalyst. They have described a vastly enhanced version of the venerable Goldberg reaction, the copper-catalyzed amidation of aryl and heteroaryl halides.

In view of the literature survey we thought that the use of benzoxazinone as an intermediate or use of palladium or copper catalyzed Ullman type C-N bond forming cross-coupling reaction as a key step would provide an efficient and direct access to the quinazolinone natural products. Hence we planned for the synthesis of circumdatin C and circumdatin F by using two different routes.

4.2 Present Work: Results and Discussion

Reaction of anthranilic acid (**17**) and Boc-L-alanine (**18**) in presence of DCC at room temperature in dichoromethane furnished benzoxazinone **19** in quantitative yield, which was purified by silica gel column chromatography. Benzoxazinone **19** was found unstable and on keeping at room temperature for one day it transforms to the corresponding diamide **19a**. We feel that the presence of nitrogen lone pair on the side chain of benzoxazinone **19** is the cause for this instability and it may have an anchemeric assistance on the ring carbonyl. It is important to note that the benzoxazinone **11**, which



Scheme 4: (i) DCC, DCM, rt, 1 h (97%); (ii) DCC, heptane, reflux, 3 h (85%); (iii) in progress.

does not contain nitrogen in its side chain is quite stable and hence reacts smoothly with the aromatic nitrogen nucleophile. In our hands, several attempts using different reagents and reaction conditions for the condensation of benzoxazinone **19** with aromatic amines met with failure. To keep the unstable benzoxazinone ring intact, we performed the

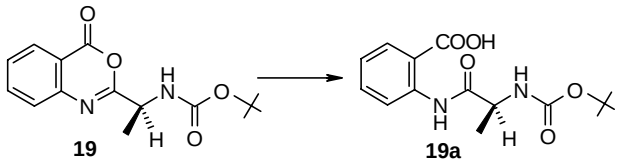
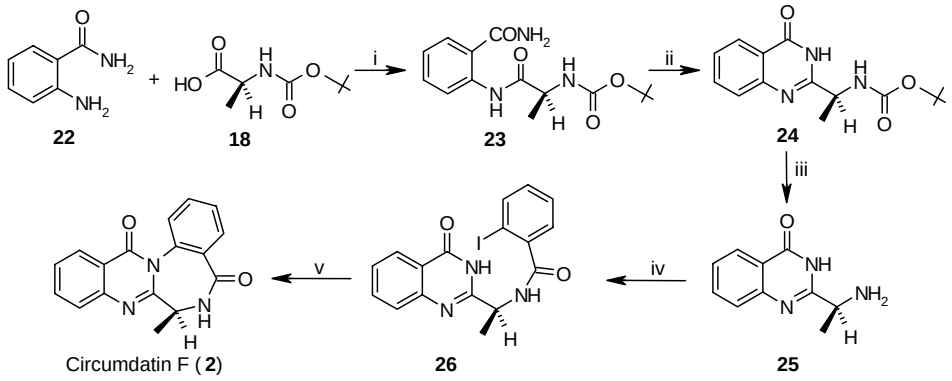


Figure 4: Unstable benzoxazinone **19** transforms to diamide **19a**

reaction of **19** and methyl ester of 5-hydroxyanthranilic acid in presence of DCC in heptane, but unfortunately the benzoxazinone ring was opened by phenolic -OH rather than the amino group to furnish compound **20** instead of quinazolinone **21**. Bergman et al also recently reported[15] that benzoxazinone of this type formed in situ in the reaction mixture does not react with the aromatic amine. Our efforts to find a suitable condition to make the aromatic amines react with benzoxazinone **19** for the efficient synthesis of circumdatin C (**1**) & F (**2**) are under progress (Scheme 4). The ^{1}H & ^{13}C NMR spectrum revealed that **19a** (Figure 4) exists in two rotameric forms. We have also proved by 2D, COSY, NOSY, ^{15}N-NMR, variable temperature NMR that this molecule exists in two different locked (please see ^{1}H NMR and ^{13}C NMR spectra) conformations. This conclusion is in agreement with the MOPAC calculations. In our second approach for the synthesis of circumdatin C (**1**) & F (**2**) we planned to use copper or palladium catalyzed intramolecular Ullman type coupling reaction as a key step (Scheme 5). Condensation of Boc-L-alanine (**18**) with anthranilamide (**22**) in presence of EDAC followed by aqueous work-up and silica gel column chromatographic purification of the crude product provided amide **23** in good yield. Use of DCC instead of EDAC provided the expected

compound **23** in a very poor yield and purification of the obtained product was very difficult due to dicyclohexyl urea formed in the reaction. Compound **23** was transformed to quinazolinone **24** in quantitative yields by using a base catalyzed dehydrative intramolecular cyclization[46] in refluxing mixture of ethanol and 5% aqueous KOH. Quinazolinone **24** was purified by silica gel column chromatography. Boc-deprotection



Scheme 5: (i) EDAC, THF, rt, 2 h (87%); (ii) aq. LiOH, THF (1:1), rt, 1 h (98%); (iii) $AlCl_3$, CH_2Cl_2, rt, 3 h (95%); (iv) 2-iodo benzoic acid, EDAC, THF, rt, 1 h (96%); (v) in progress.

of quinazolinone 24 using Lewis acid catalyzed[47] reaction in CH_2Cl_2 gave the crude product **25**, which was purified by silica gel column chromatography to obtain pure amine **25** in good yield. Same transformation using trifluroacetic acid furnished compound **25** in poor yield. Amine **25** was acylated with 2-iodobenzoic acid in presence of EDAC at room temperature to afford iodo-quinazolinone **26** in good yield. Quinazolinone **26** is a suitable compound for intramolecular C-N bond forming cross-coupling reaction to obtain natural product circumdatin F (**2**), but in our hands several attempts using palladium or copper catalyst to effect the cyclization met with failure. It is known that this type of coupling reactions are very much substrate, solvent and catalyst specific.[38,44] Buchwald et al also reported[34] that the formation of five and six membered

ring using palladium catalyzed Ullman type coupling is easy and feasible than the formation of seven membered ring, which always ends-up into a complex reaction mixture, with very poor yield of the expected product. To effect the cyclization of such larger size ring heterocycles a master screening of various catalysts is necessary.[35] Our efforts to find out a suitable catalyst and reaction condition for the conversion of **26** to circumdatin F (**2**) are under active progress and we feel that Ullman type coupling will surely provide an easy access to **2**.

In summary, in this chapter we have presented our studies on the attempted synthesis of circumdatin C and F using two different approaches. We feel that with proper control on reactivity and selectivity using appropriate catalyst and reaction condition should provide a way to these natural products by following our synthetic strategies. Same strategies would be applicable for the synthesis of circumdatin family of natural products, other quinazolinone natural products like sclerotigenin, benzomalvins and its logical extension for the synthesis of asperlicin C and asperlicin would be possible.

4.3 Experimental Section

Melting points are uncorrected. Column chromatographic separations were carried out on ACME silica gel (60-120 mesh). Commercially available anthranilic acid, Boc-L-alanine, DCC, 5-hydroxyanthranilic acid, anthranilamide, EDAC, $AlCl_3$ and 2-iodobenzoic acid were used.

[1-(4-Oxo-4*H*-benzo[*d*][1,3]oxazin-2-yl)-ethyl]-carbamic acid *tert*-butyl ester (19). To the solution of anthranilic acid (**17**, 2.00 g, 14.60 mmol) and Boc-L-alanine (**18**, 2.76 g, 14.60 mmol) in CH_2Cl_2 (50 mL) was added solution of DCC (6.32 g, 30.70 mmol) in

CH_2Cl_2 (20 mL) at 5-10 ^oC over a period of 10 min. The reaction mixture was allowed to reach rt and stirred further for 1 h. The dicyclohexyl urea formed in the reaction mixture was filtered off and the residue obtained after the concentration of the filtrate was purified by silica gel column chromatography using petroleum ether and ethyl acetate (80:20) to obtain pure compound **19**. **19**: 4.11 g (97% yield); thick oil; $[\alpha]^{20}_D = -30.0$ (*c* 1, $CHCl_3$).

2-Amino-5-hydroxybenzoic acid methyl ester. To the reaction mixture containing methanol (50 mL) and 5-hydroxyanthranilic acid (5.00 g, 32.70 mmol) was added $SOCl_2$ (4.70 mL, 65.36 mmol) at 0 ^oC. Reaction mixture was then allowed to reach rt and refluxed for 3 h. Reaction mixture was cooled to rt, methanol was evaporated under vacuo and ethyl acetate (50 mL) was added, followed by addition of aqueous $NaHCO_3$ solution. Organic layer was washed with aqueous $NaHCO_3$, water and brine and dried over Na_2SO_4. Concentration of the organic layer under vacuo followed by silica gel column chromatographic purification of the residue using petroleum ether and ethyl acetate (70:30), provided pure methyl 5-hydroxyanthranilate. Methyl 5-hydroxyanthranilate: 4.75 g (87% yield); mp 158-160 ^oC (ethyl acetate) [lit.[15] 152-153 ^oC, (dec.)].

2-(2-*tert*-Butoxycarbonylamino-propionylamino)-benzoic acid 4-amino-3-methoxycarbonyl-phenoxy ester (20). To the reaction mixture containing benzoxazinone **19** (1.00 g, 3.5 mmol) and DCC (1.42 g, 6.9 mmol) in heptane (30 mL) was added methyl 5-hydroxyanthranilate (576 mg, 3.5 mmol) and the reaction mixture was refluxed for 3 h. The reaction mixture was allowed to reach rt. The precipitate

formed was filtered, washed with petroleum ether (3 x 20 mL), dried under vacuo and purified by silica gel column chromatography using petroleum ether and ethyl acetate (70:30) to obtain pure compound **20**. **20**: 1.58 g (85% yield); mp 98-100 ^{o}C (benzene); $[\alpha]^{20}_{D} = -5.0$ (*c* 0.5, $CHCl_3$).

[1-(2-Carbamoyl-phenylcarbamoyl)-ethyl]-carbamic acid *tert*-butyl etster (23). To the reaction mixture containing anthranilamide (**22**, 5.00 g, 36.77 mmol) and EDAC (8.46 g, 44.11 mmol) in THF (70 mL) was added solution of Boc-L-alanine (**18**, 6.95 g, 36.77 mmol) in THF (30 mL) with stirring, over a period of 10 min. and further stirred for 2 h. THF was evaporated under vacuo and the reaction mixture was extracted with chloroform (150 mL). The organic layer was washed with water, aqueous $NaHCO_3$ solution, dil. HCl, water and brine and dried over Na_2SO_4. The residue obtained, after the concentration of the organic layer, was purified by the silica gel column chromatographic purification using petroleum ether and ethyl acetate (50:50) to obtain pure compound **23**. **23**: 9.82 g (87% yield); mp 117-119 ^{o}C (benzene); $[\alpha]^{20}_{D} = -35.5$ (*c* 0.5, $CHCl_3$).

[1-(4-Oxo-3,4-dihydro-quinazolin-2-yl)-ethyl-carbamic acid *tert*-butyl etster (24). To the solution of compound **23** (8.00 g, 26.06 mmol) in THF (50 mL) was added saturated aqueous solution of lithium hydroxide (50 mL) and the reaction mixture was stirred for 1 h. The reaction mixture was extracted in chloroform, washed with water and brine and dried over Na_2SO_4. Concentration of the organic layer under vacuo followed by the silica gel column chromatographic purification of the residue using petroleum ether and ethyl acetate (40:60) furnished quinazolinone **24**. **24**: 7.38 g (98% yield); mp 225-227 ^{o}C (benzene); $[\alpha]^{20}_{D} = -79.0$ (*c* 0.5, $CHCl_3$).

2-(1-Amino-ethyl)-3*H*-quinazolin-4-one (25). To the stirred solution of quinazolinone **24** (7.00 g, 24.22 mmol) in CH_2Cl_2 (60 mL) was added powdered $AlCl_3$ (3.87 g, 29.07 mmol) at 5-10 ^oC and the reaction mixture was further stirred for 3 h at rt. Reaction was quenched with aqueous $NaHCO_3$ and extracted using $CHCl_3$. The organic layer was washed with aqueous $NaHCO_3$, water and brine and dried over Na_2SO_4. Concentration of the organic layer under vacuo followed by the silica gel column chromatographic purification of the residue using ethyl acetate furnished amine **25**. **25**: 4.35 g (95% yield); mp 188-190 ^oC (ethyl acetate); $[\alpha]^{20}_D = -18.0$ (*c* 0.2, $CHCl_3$).

2-Iodo-*N*-[1-(4-oxo-3,4-dihydro-quinazolin-2-yl)-ethyl]-benzamide (26). To the stirred reaction mixture containing amine **25** (3.00 g, 15.87 mmol) and EDAC (3.65 g, 19.05 mmol) in THF (30 mL) was added a solution of 2-iodo benzoic acid (4.72 g, 19.05 mmol) in THF (20 mL) and the reaction mixture was further stirred for 1 h. THF was evaporated under vacuo and the reaction mixture was extracted with ethyl acetate (100 mL). The organic layer was washed with water, aqueous $NaHCO_3$ solution, dil. HCl, water and brine and dried over Na_2SO_4. The residue obtained, after the concentration of the organic layer, was purified by the silica gel column chromatographic purification using ethyl acetate to furnish pure compound **26**. **26**: 6.39 g (96% yield); mp 277-279 ^oC (MeOH); $[\alpha]^{20}_D = -5.0$ (*c* 0.4, THF).

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4.5 Summary

The present dissertation describes our studies on total synthesis of several naturally occurring bioactive quinazolinone alkaloids along with a concise account on the chemistry of the quinazolinone alkaloids isolated (approximately 73) under the present review period, describing their bioassay and various synthetic approaches. We have presented an efficient synthesis of bioactive quinazolinone natural products pegamine, deoxyvasicinone, (–)-vasicinone, 2-(4-hydroxybutyl)quinazolin-4(1*H*)-one, mackinazolinone and rutaecarpine by effectively using cyclic anhydrides as potential starting materials. Our present synthesis of (–)-vasicinone with chiral pool strategy directly confirms the stereochemistry of the natural product. The present zeolite induced Fischer-indole synthesis conditions used in the synthesis of rutaecarpine are mild and efficient compared to earlier known conditions and will be useful to design several indole skeletons. It is important to note that the natural products deoxyvasicinone, mackinazolinone and rutaecarpine have been synthesized via the natural products pegamine, 2-(4-hydroxybutyl)quinazolin-4(1*H*)-one and mackinazolinone respectively. The synthesis of natural product from another natural product is noteworthy because it reduces the total number of steps and also highlights their probable biological precursors. Attempted synthesis of 7,8-dehydrorutaecarpine is also presented here. We have also presented an efficient synthesis of quinazolinone natural products luotonin A, B & E, metabolite isovasicinone and luotonin F. A facile quinazolinone-directed regioselective ortho lithiation of quinazolinoylquinoline have been applied for the short, efficient and practical synthesis of naturally occurring promising anti-cancer agents luotonin A, B and E. We feel that our present approach is general in nature and such type of regioselective directed lithiation of aryl and heteroaryl substituted quinazolinone systems will be highly

useful for the synthesis of a large number of desired complex quinazolinone alkaloids, luotonin & camptothecin like analogs for structure activity relationship studies. Our biogenetic synthesis of luotonin F starting from natural product pegamine, via the metabolite isovasicinone is a good example of reproducing the nature's biosynthetic way of synthesizing the natural products, thus providing a direct proof of their genesis. We have presented our studies on the attempted synthesis of circumdatin C and F using two different approaches. Development of proper catalyst and reaction condition for this purpose is under progress. Same strategies would be applicable for the synthesis of circumdatin family of natural products, other quinazolinone natural products like sclerotigenin and benzomalvins. Logical extension of the approaches designed for circumdatin alkaloids will be possible for the synthesis of asperlicin C and asperlicin. We feel that our approaches to various quinazolinone natural products are general and have the potential to generate libraries of quinazolinone alkaloids for the search of a bioactive lead molecule.

The present studies on quinazolinone based natural product chemistry provides a clear impression that the combination of unique structural features, extensive functionalization and high biological activity found in quinazolinone alkaloids have presented an elegant challenge to the synthetic chemists world-wide. This has spurred the preparation and pharmacological evaluation of a great number of quinazolinone derivatives and intensive research in the quinazolinone area is still in active progress. In short, quinazolinone natural products and their derivatives have been centre of attraction from the past and continued and intensified to be the same in present time and increasing stream of publications in this field assures a bright future for quinazolinone chemistry.

Chapter Five

Spectral and Analytical Data of Compounds Synthesized and Spectra of Selected Compounds

This chapter is divided into two sections. Section A presents tabulated spectral and analytical data of the compounds synthesized, which includes compound number, its molecular formula, molecular weight, melting point, IR, ^{1}H NMR, ^{13}C NMR, mass spectral data, elemental analysis and optical rotation of chiral compounds. Section B presents ^{1}H NMR and ^{13}C NMR spectra of selected compounds.

5.1 Section A

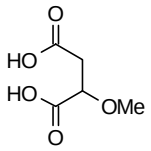
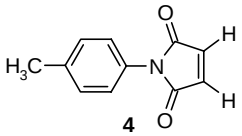
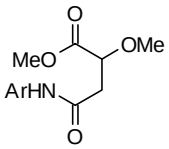
Tabulated Spectral and Analytical Data of Compounds Synthesized

Note: All the data obtained for known compounds is in agreement with the reported data.

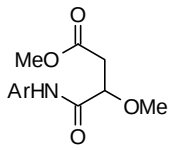
5.2 Section B

^{1}H and ^{13}C NMR Spectra of Selected Compounds

5.1.1 Spectral and Analytical Data for Compounds from Chapter Two

No.	Structure & Text No. Mol. Form. (Mol. Wt.)	Mp (^{o}C)/ IR (cm^{-1})/ ^{1}H NMR (δ)/ ^{13}C NMR (δ)/ mass spectral data/ elemental analysis/ α_D
1.	 (±)-Methoxysuccinic acid (**1a**) **$C_5H_8O_5$** (148.12)	**Mp**: 106-108 ^{o}C (ethyl acetate). **IR** (nujol): ν_{max} 2800-2500, 1715, 1710, 1456 cm^{-1}. **^{1}H NMR** (acetone-d_6, 200 MHz): δ 2.63 (dd, J = 16 and 10 Hz, 1H), 2.82 (dd, J = 16 and 6 Hz, 1H), 3.42 (s, 3H), 4.18 (dd, J = 8 and 4 Hz, 1H). **^{13}C NMR** (acetone-d_6, 50 MHz): δ 38.1, 58.7, 77.7, 171.7, 172.8. **MS** (*m/e*): 148, 131, 118, 103, 99, 89, 71, 61. **Anal. Calcd for $C_5H_8O_5$**: C, 40.55; H, 5.44. Found: C, 40.68; H, 5.69.
2.	 **4** **$C_{11}H_9NO_2$** (187.20)	**Mp**: 158-160 ^{o}C (ethanol). **IR** (nujol): ν_{max} 1709, 1678, 1153 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 200 MHz): δ 2.40 (s, 3H), 6.85 (s, 2H), 7.21 (d, J = 8 Hz, 2H), 7.29 (d, J = 8 Hz, 2H). **MS** (*m/e*): 187, 172, 158, 143, 130, 117, 104, 91, 82, 77, 65, 54. **Anal. Calcd for $C_{11}H_9NO_2$**: C, 70.58; H, 4.85; N, 7.48. Found: C, 70.39; H, 4.93; N, 7.42.
3.	 **6a** Ar = *p*-tolyl **$C_{13}H_{17}NO_4$** (251.28)	**Mp**: 126-128 ^{o}C (benzene). **IR** (nujol): ν_{max} 3285, 1751, 1649, 1595 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 200 MHz): δ 2.31 (s, 3H), 2.72 (dd, J = 10 and 6 Hz, 1H), 2.84 (dd, J = 10 and 4 Hz, 1H), 3.50 (s, 3H), 3.79 (s, 3H), 4.27 (dd, J = 6 and 2 Hz, 1H), 7.12 (d, J = 6 Hz, 2H), 7.39 (d, J = 6 Hz, 2H), 7.85 (bs, 1H). **^{13}C NMR** ($CDCl_3$, 50 MHz): δ 20.7, 40.4, 52.2, 58.7, 76.9, 120.0, 129.2, 133.8, 135.2, 167.4, 172.0. **MS** (*m/e*): 251, 192, 150, 133, 117, 107, 91, 75, 59. **Anal. Calcd for $C_{13}H_{17}NO_4$**: C, 62.14; H, 6.82; N, 5.58. Found: C, 62.21; H, 6.91; N, 5.69.

4.



7a

Ar = *p*-tolyl

$C_{13}H_{17}NO_4$ (251.28)

Mp: Thick oil.

IR (neat): ν_{max} 3329, 1740, 1678, 1595 cm^{-1}.

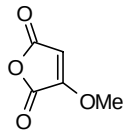
^{1}H NMR ($CDCl_3$, 200 MHz): δ 2.32 (s, 3H), 2.76 (dd, J = 10 and 6 Hz, 1H), 2.97 (dd, J = 10 and 2 Hz, 1H), 3.54 (s, 3H), 3.72 (s, 3H), 4.20 (dd, J = 6 and 2 Hz, 1H), 7.14 (d, J = 6 Hz, 2H), 7.46 (d, J = 6 Hz, 2H), 8.39 (bs, 1H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ 20.4, 37.0, 51.5, 58.6, 78.5, 119.6, 129.1, 133.7, 134.3, 168.7, 170.5.

MS (*m/e*): 251, 220, 188, 160, 150, 133, 118, 106, 91, 75, 58.

Anal. Calcd for $C_{13}H_{17}NO_4$: C, 62.14; H, 6.82; N, 5.58.
Found: C, 61.96; H, 6.73; N, 5.55.

5.



Methoxymaleic anhydride (**8a**)

$C_5H_4O_4$ (128.09)

Mp: 152-155 ^oC (benzene).

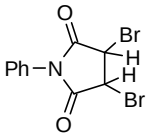
IR ($CHCl_3$): ν_{max} 1857, 1776, 1649, 1225 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz): δ 4.04 (s, 3H), 5.78 (s, 1H).

^{13}C NMR (acetone-d_6, 50 MHz): δ 61.0, 99.8, 161.9, 163.0, 164.4.

Anal. Calcd for $C_5H_4O_4$: C, 46.89; H, 3.15.
Found: C, 47.02; H, 3.18.

6.



10 (*trans*)

$C_{10}H_7Br_2NO_2$ (332.99)

Mp: 155-157 ^oC (CCl_4).

IR (nujol): ν_{max} 1798, 1728, 1591 cm^{-1}.

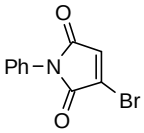
^{1}H NMR ($CDCl_3$, 200 MHz): δ 4.87 (s, 2H), 7.30-7.70 (m, 5H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ 41.9, 44.4, 126.0, 129.4, 130.8, 130.9, 169.2, 169.5.

MS (*m/e*): 335, 333, 331, 253, 251, 196, 173, 144, 128, 119, 104, 91, 77.

Anal. Calcd for $C_{10}H_7Br_2NO_2$: C, 36.07; H, 2.12; N, 4.21.
Found: C, 35.84; H, 2.19; N, 4.35.

7.



11

$C_{10}H_6BrNO_2$ (252.07)

Mp: 161-163 ^oC (CCl_4).

IR (nujol): ν_{max} 1782, 1716, 1713, 1595 cm^{-1}.

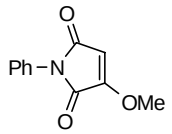
^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.03 (s, 1H), 7.30-7.60 (m, 5H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ 126.0, 128.2, 129.1, 131.0, 131.7, 131.8, 164.1, 167.3.

MS (*m/e*): 253, 251, 211, 196, 171, 144, 128, 119, 104, 91, 77, 71, 64.

Anal. Calcd for $C_{10}H_6BrNO_2$: C, 47.65; H, 2.40; N, 5.56.
Found: C, 47.71; H, 2.29; N, 5.50.

8.



12a

$C_{11}H_9NO_3$ (203.20)

Mp: 99-101 ^{o}C (benzene).

IR (nujol): ν_{max} 1778, 1730, 1715, 1643, 1599 cm^{-1}.

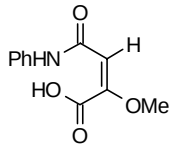
^{1}H NMR ($CDCl_3$, 200 MHz): δ 4.02 (s, 3H), 5.58 (s, 1H), 7.25-7.55 (m, 5H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ 58.9, 96.3, 125.9, 127.6, 128.9, 131.0, 160.6, 164.2, 168.8.

MS (*m/e*): 203, 174, 147, 119, 105, 88, 84, 77, 69, 64, 59.

Anal. Calcd for $C_{11}H_9NO_3$: C, 65.02; H, 4.46; N, 6.90.
Found: C, 65.19; H, 4.67; N, 6.76.

9.



13a

$C_{11}H_{11}NO_4$ (221.22)

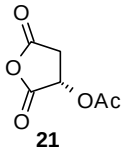
Mp: 184-185 ^{o}C (ethyl acetate).

IR (nujol): ν_{max} 3265, 1730, 1653, 1612, 1460, 1321 cm^{-1}.

^{1}H NMR (methanol-d_4, 200 MHz): δ 3.79 (s, 3H), 5.75 (s, 1H), 7.12 (t, J = 8 Hz, 1H), 7.33 (t, J = 8 Hz, 2H), 7.57 (d, J = 8 Hz, 2H).

Anal. Calcd for $C_{11}H_{11}NO_4$: C, 59.72; H, 5.01; N, 6.33.
Found: C, 59.61; H, 4.93; N, 6.19.

10.



21

$C_6H_6O_5$ (158.12)

Mp: 56 ^{o}C (hexane).

$[\alpha]^{20}_{D}$: –26.4 (*c* 5.0, $CHCl_3$).

IR (nujol): ν_{max} 1877, 1796, 1749, 1738 cm^{-1}.

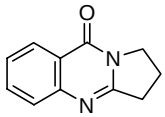
^{1}H NMR ($CDCl_3$, 200 MHz): δ 2.20 (s, 3H), 3.04 (dd, J = 18 and 8 Hz, 1H), 3.40 (dd, J = 20 and 8 Hz, 1H), 5.55 (dd, J = 8 and 6 Hz, 1H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ 20.0, 34.8, 67.7, 167.0, 168.3, 170.0.

MS (*m/e*): 158, 131, 116, 104, 99, 88, 70, 55.

Anal. Calcd for $C_6H_6O_5$: C, 45.58; H, 3.83.
Found: C, 45.69; H, 3.99.

11.



Deoxyvasicinone (**24**)

$C_{11}H_{10}N_2O$ (186.21)

Mp: 106-108 ^{o}C (benzene).

IR (nujol): ν_{max} 1674, 1620 cm^{-1}.

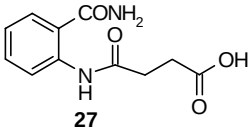
^{1}H NMR ($CDCl_3$, 200 MHz): δ 2.30 (quintet, J = 8 Hz, 2H), 3.19 (t, J = 8 Hz, 2H), 4.22 (t, J = 8 Hz, 2H), 7.46 (t, J = 8 Hz, 1H), 7.55-7.85 (m, 2H), 8.29 (d, J = 8 Hz, 1H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ 19.3, 32.3, 46.3, 120.3, 126.0, 126.2, 126.6, 133.9, 149.0, 159.3, 160.7.

MS (*m/e*): 185, 167, 160, 144, 130, 116, 102, 90, 76, 63.

Anal. Calcd for $C_{11}H_{10}N_2O$: C, 70.95; H, 5.41; N, 15.04. Found: C, 71.01; H, 5.45; N, 15.14.

12.



27

$C_{11}H_{12}N_2O_4$ (236.22)

Mp: 197-198 ^{o}C (methanol).

IR (nujol): ν_{max} 3414, 3346, 3242, 3217, 3165, 1709, 1680, 1659, 1616 cm^{-1}.

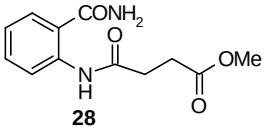
^{1}H NMR (methanol-d_4, 200 MHz): δ 2.68 (s, 4H), 7.13 (t, J = 8 Hz, 1H), 7.47 (t, J = 8 Hz, 1H), 7.73 (d, J = 8 Hz, 1H), 8.37 (d, J = 8 Hz, 1H).

^{13}C NMR (DMSO-d_6, 50 MHz): δ 28.9, 32.2, 119.7, 120.2, 122.3, 128.5, 132.1, 139.6, 169.9, 170.8, 173.5.

MS (*m/e*): 236, 218, 202, 174, 146, 136, 119, 107, 101, 90, 73, 65, 55.

Anal. Calcd for $C_{11}H_{12}N_2O_4$: C, 55.93; H, 5.12; N, 11.86. Found: C, 56.21; H, 5.29; N, 12.01.

13.



28

$C_{12}H_{14}N_2O_4$ (250.25)

Mp: 133-135 ^{o}C (benzene).

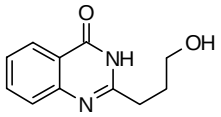
IR (nujol): ν_{max} 3358-3192, 1745, 1682, 1666 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz): δ 2.75 (s, 4H), 3.71 (s, 3H), 5.50-6.00 (bs, 1H), 6.00-6.50 (bs, 1H), 7.08 (t, J = 8 Hz, 1H), 7.40-7.60 (m, 2H), 8.61 (d, J = 10 Hz, 1H), 11.25 (bs, 1H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ 29.1, 32.6, 51.8, 118.8, 121.6, 122.6, 127.4, 133.1, 140.0, 170.2, 171.4, 173.1.

MS (*m/e*): 250, 219, 202, 174, 146, 136, 119, 100, 92, 72, 55.

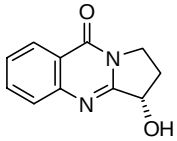
Anal. Calcd for $C_{12}H_{14}N_2O_4$: C, 57.59; H, 5.64; N, 11.19. Found: C, 57.49; H, 5.60; N, 11.32.

14. 

Pegamine (**30**)

$C_{11}H_{12}N_2O_2$ (204.22)

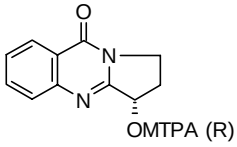
Mp: 163-165 ^{o}C (ethyl acetate).
IR (nujol): ν_{max} 3395, 3319, 3173, 3123, 3038, 1695, 1682 cm^{-1}.
^{1}H NMR (methanol-d_4, 200 MHz): δ 2.00 (quintet, J = 6 Hz, 2H), 2.77 (t, J = 8 Hz, 2H), 3.66 (t, J = 6 Hz, 2H), 7.48 (t, J = 8 Hz, 1H), 7.63 (d, J = 8 Hz, 1H), 7.79 (t, J = 8 Hz, 1H), 8.17 (d, J = 8 Hz, 1H).
^{13}C NMR (methanol-d_4, 50 MHz): δ 31.3, 33.0, 62.1, 121.8, 127.1, 127.3, 127.4, 127.6, 135.9, 150.0, 159.3.
MS (*m/e*): 204, 187, 173, 160, 132, 119, 90, 77, 63.
Anal. Calcd for $C_{11}H_{12}N_2O_2$: C, 64.70; H, 5.92; N, 13.72. Found: C, 64.93; H, 6.11; N, 14.00.

15. 

(-)-Vasicinone (**31**) (98% ee)

$C_{11}H_{10}N_2O_2$ (202.21)

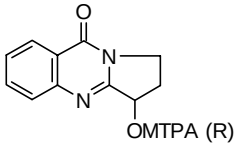
Mp: 205-207 ^{o}C (ethanol).
$[\alpha]^{20}_{D}$: −105.6 (c 1.0, $CHCl_3$).
IR (nujol): ν_{max} 3169, 1683, 1635, 1463 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz): δ 2.20-2.45 (m, 1H), 2.60-2.80 (m, 1H), 3.90-4.15 (m, 1H), 4.30-4.50 (m, 1H), 5.27 (t, J = 6 Hz, 1H), 7.40-7.60 (m, 1H), 7.65-7.85 (m, 2H), 8.31 (d, J = 6 Hz, 1H).
^{13}C NMR ($CDCl_3$, 75 MHz): δ 29.4, 43.5, 72.0, 121.1, 126.7, 126.8, 126.9, 134.4, 148.6, 160.1, 160.6.
MS (*m/e*): 202, 185, 174, 146, 130, 119, 102, 90, 76, 63, 55.
Anal. Calcd for $C_{11}H_{10}N_2O_2$: C, 65.34; H, 4.99; N, 13.85. Found: C, 65.24; H, 5.07; N, 13.87.

16. 

OMTPA (R)

$C_{21}H_{17}F_3N_2O_4$ (418.37)

Mp: 172-174 ^{o}C.
^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.43 (m, 1H), 2.75 (m, 1H), 3.57 (s, 2.955H), 3.65 (s, 0.045H), 4.22 (m, 1H), 4.30 (m, 1H), 6.37 (m, 0.985H), 6.43 (m, 0.015H), 7.35-7.80 (m, 8H), 8.30 (d, J = 10 Hz, 1H).
MS (*m/e*): 418, 388, 359, 201, 189, 184, 119, 105, 91, 77.
Anal. Calcd for $C_{21}H_{17}F_3N_2O_4$: C, 60.29; H, 4.09; N, 6.70. Found: C, 60.12; H, 4.17; N, 6.77.

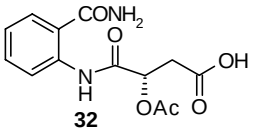
17. 

OMTPA (R)

$C_{21}H_{17}F_3N_2O_4$ (418.37)

Mp: Thick oil.
^{1}H NMR ($CDCl_3$, 200 MHz): δ 2.15-2.55 (m, 2H), 2.60-2.90 (m, 2H), 3.57 (s, 3H), 3.66 (s, 3H), 4.00-4.50 (m, 4H), 6.30-6.55 (m, 2H), 7.20-7.90 (m, 16H), 8.31 (d, J = 8 Hz, 2H).
MS (*m/e*): 418, 388, 359, 201, 189, 184, 119, 105, 91, 77.
Anal. Calcd for $C_{21}H_{17}F_3N_2O_4$: C, 60.29; H, 4.09; N, 6.70. Found: C, 60.33; H, 3.97; N, 6.91.

18.



32

$C_{13}H_{14}N_2O_6$ (294.26)

Mp: 152-153 ^{o}C (ethyl acetate).

[α]$^{20}_{D}$: –88.7 (*c* 0.6, acetone).

IR (nujol): ν_{max} 3445, 3396, 3336, 3188, 1747, 1693, 1666, 1660 cm^{-1}.

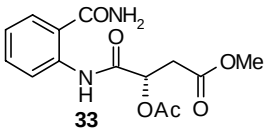
^{1}H NMR (methanol-d_4, 200 MHz): δ 2.26 (s, 3H), 2.92 (d, *J* = 6 Hz, 1H), 2.95 (d, *J* = 2 Hz, 1H), 5.53 (dd, *J* = 8 and 4 Hz, 1H), 7.16 (t, *J* = 8 Hz, 1H), 7.49 (t, *J* = 8 Hz, 1H), 7.76 (d, *J* = 8 Hz, 1H), 8.51 (d, *J* = 8 Hz, 1H).

^{13}C NMR (methanol-d_4, 75 MHz): δ 20.9, 37.5, 71.8, 121.7, 122.0, 124.7, 129.5, 133.6, 139.8, 169.8, 171.6, 173.0, 173.3.

MS (*m/e*): 294, 277, 259, 235, 216, 198, 163, 146, 136, 119, 92, 71, 65.

Anal. Calcd for $C_{13}H_{14}N_2O_6$: C, 53.06; H, 4.80; N, 9.52. Found: C, 53.13; H, 4.71; N, 9.74.

19.



33

$C_{14}H_{16}N_2O_6$ (308.29)

Mp: 80-82 ^{o}C (benzene).

[α]$^{20}_{D}$: –65.7 (*c* 1.2, $CHCl_3$).

IR (nujol): ν_{max} 3448, 3340, 1740, 1737, 1662 cm^{-1}.

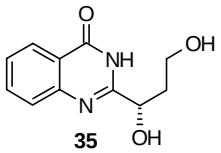
^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.30 (s, 3H), 2.90-3.10 (m, 2H), 3.71 (s, 3H), 5.68 (dd, *J* = 9 and 6 Hz, 1H), 5.57-6.00 (bs, 1H), 6.00-6.50 (bs, 1H), 7.11 (t, *J* = 6 Hz, 1H), 7.50 (t, *J* = 9 Hz, 1H) 7.55 (d, *J* = 9 Hz, 1H), 8.64 (d, *J* = 9 Hz, 1H), 11.94 (s, 1H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ 20.7, 36.4, 51.9, 70.0, 119.0, 121.0, 123.2, 127.5, 133.0, 138.9, 167.6, 169.9, 170.1, 171.1.

MS (*m/e*) 277, 180, 147, 131, 107, 93, 81, 59.

Anal. Calcd for $C_{14}H_{16}N_2O_6$: C, 54.54; H, 5.23; N, 9.09. Found: C, 54.33; H, 5.09; N, 9.14.

20.



35

$C_{11}H_{12}N_2O_3$ (220.22)

Mp: 134-136 ^{o}C (ethyl acetate).

[α]$^{20}_{D}$: –22.6 (*c* 1.0, methanol).

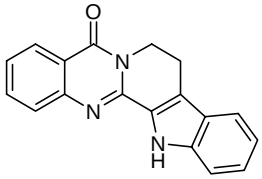
IR (nujol): ν_{max} 3373, 3276, 3119, 1683, 1613 cm^{-1}.

^{1}H NMR (methanol-d_4, 200 MHz): δ 1.85-2.25 (m, 2H), 3.78 (t, *J* = 6 Hz, 2H), 4.65-4.85 (m, 1H), 7.49 (t, *J* = 8 Hz, 1H), 7.66 (d, *J* = 8 Hz, 1H), 7.79 (t, *J* = 8 Hz, 1H), 8.18 (d, *J* = 8 Hz, 1H).

^{13}C NMR (methanol-d_4, 75 MHz): δ 39.5, 59.4, 70.1, 122.2, 127.2, 127.4, 127.8, 135.9, 149.5, 160.9, 164.3.

MS (*m/e*): 220, 198, 170, 158, 132, 107, 81, 57.

Anal. Calcd for $C_{11}H_{12}N_2O_3$: C, 60.00; H, 5.49; N, 12.72. Found: C, 59.78; H, 5.29; N, 12.83.

21. 

Rutaecarpine (**36a**)

$C_{18}H_{13}N_3O$ (287.32)

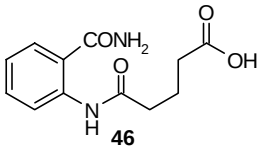
Mp: 257-259 ^{o}C (ethyl acetate).

IR ($CHCl_3$): ν_{max} 3416, 1670, 1651, 1630, 1599 cm^{-1}.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.15 (t, J = 10 Hz, 2H), 4.51 (t, J = 10 Hz, 2H), 7.09 (t, J = 10 Hz, 1H), 7.17-7.28 (m, 2H), 7.34 (t, J = 10 Hz, 1H), 7.52-7.64 (m, 3H), 8.25 (d, J = 10 Hz, 1H), 9.62 (bs, 1H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 19.7, 41.2, 112.1, 118.5, 120.1, 120.6, 121.2, 125.6 (2-carbons), 126.2, 126.5, 127.1, 127.3, 134.3, 138.4, 145.1, 147.4, 161.5.

Anal. Calcd for $C_{18}H_{13}N_3O$: C, 75.25; H, 4.56; N, 14.63. Found: C, 75.31; H, 4.67; N, 14.72.

22. 

46

$C_{12}H_{14}N_2O_4$ (250.25)

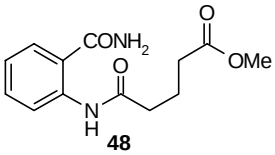
Mp: 131-133 ^{o}C (ethyl acetate).

IR (nujol): ν_{max} 3449, 3317, 3260, 2700-2500, 1688, 1680, 1634 cm^{-1}.

^{1}H NMR (methanol-d_4, 300 MHz): δ 2.01 (quintet, J = 9 Hz, 2H), 2.42 (t, J = 9 Hz, 2H), 2.49 (t, J = 9 Hz, 2H), 7.16 (t, J = 9 Hz, 1H), 7.50 (t, J = 9 Hz, 1H), 7.75 (d, J = 9 Hz, 1H), 8.41 (d, J = 9 Hz, 1H).

^{13}C NMR (methanol-d_4, 75 MHz): δ 21.9, 34.1, 37.9, 122.2, 122.6, 124.4, 129.4, 133.4, 140.2, 173.5, 173.6, 176.7.

Anal. Calcd for $C_{12}H_{14}N_2O_4$: C, 57.59; H, 5.64; N, 11.19. Found: C, 57.72; H, 5.81; N, 11.03.

23. 

48

$C_{13}H_{16}N_2O_4$ (264.28)

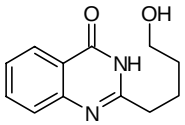
Mp: 98-100 ^{o}C (benzene).

IR (nujol): ν_{max} 3337, 3273, 3179, 1740, 1680, 1678, 1616 cm^{-1}.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.06 (quintet, J = 10 Hz, 2H), 2.43 (t, J = 10 Hz, 2H), 2.47 (t, J = 10 Hz, 2H), 3.68 (s, 3H), 6.15 (bs, 1H), 6.48 (bs, 1H), 7.06 (t, J = 10 Hz, 1H), 7.48 (t, J = 10 Hz, 1H), 7.55 (d, J = 10 Hz, 1H), 8.61 (d, J = 10 Hz, 1H), 11.24 (s, 1H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 20.5, 33.0, 37.1, 51.5, 118.7, 121.3, 122.5, 127.4, 133.0, 139.9, 171.0, 171.6, 173.5.

Anal. Calcd for $C_{13}H_{16}N_2O_4$: C, 59.08; H, 6.10; N, 10.60. Found: C, 58.97; H, 6.18; N, 10.69.

24. 

2-(4-Hydroxybutyl)-quinazolin-4(1*H*)-one (**50**)

$C_{12}H_{14}N_2O_2$ (218.25)

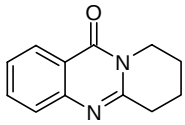
Mp: 175-177 ^{o}C (ethyl acetate).

IR (nujol): ν_{max} 3398, 3173, 1686, 1614, 1468 cm^{-1}.

^{1}H NMR (methanol-d_4, 500 MHz): δ 1.66 (quintet, J = 10 Hz, 2H), 1.90 (quintet, J = 10 Hz, 2H), 2.73 (t, J = 10 Hz, 2H), 3.63 (t, J = 10 Hz, 2H), 7.50 (t, J = 10 Hz, 1H), 7.65 (d, J = 10 Hz, 1H), 7.80 (t, J = 10 Hz, 1H), 8.19 (d, J = 10 Hz, 1H).

^{13}C NMR (methanol-d_4, 125 MHz): δ 25.3, 33.0, 35.9, 62.4, 121.9, 127.2, 127.3, 127.6, 135.9, 150.1, 159.6, 164.5.

Anal. Calcd for $C_{12}H_{14}N_2O_2$: C, 66.04; H, 6.47; N, 12.83. Found: C, 66.11; H, 6.54; N, 12.98.

25. 

Mackinazolinone (**51**)

$C_{12}H_{12}N_2O$ (200.23)

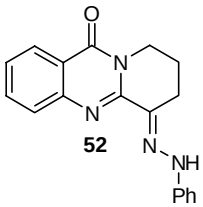
Mp: 99-101 ^{o}C (hexane).

IR (nujol): ν_{max} 1657, 1612, 1587, 1566, 1462 cm^{-1}.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.96 (quintet, J = 10 Hz, 2H), 2.02 (quintet, J = 10 Hz, 2H), 3.00 (t, J = 10 Hz, 2H), 4.08 (t, J = 10 Hz, 2H), 7.42 (t, J = 10 Hz, 1H), 7.60 (d, J = 10 Hz, 1H), 7.71 (t, J = 10 Hz, 1H), 8.26 (d, J = 10 Hz, 1H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 19.2, 22.0, 31.7, 42.2, 120.3, 125.9, 126.2, 126.5, 134.0, 147.2, 154.8, 162.0.

Anal. Calcd for $C_{12}H_{12}N_2O$: C, 71.98; H, 6.04; N, 13.99. Found: C, 72.08; H, 6.19; N, 14.12.

26. 

52

$C_{18}H_{16}N_4O$ (304.36)

Mp: 184-186 ^{o}C (*n*-propanol).

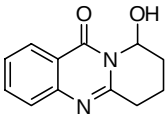
IR ($CHCl_3$): ν_{max} 3018, 1670, 1607 cm^{-1}.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.06 (quintet, J = 10 Hz, 2H), 2.79 (t, J = 10 Hz, 2H), 4.02 (t, J = 5 Hz, 2H), 6.89 (t, J = 10 Hz, 1H), 7.20 (d, J = 10 Hz, 2H), 7.25 (t, J = 10 Hz, 2H), 7.39 (t, J = 10 Hz, 1H), 7.57 (d, J = 10 Hz, 1H), 7.68 (t, J = 10 Hz, 1H), 8.20 (d, J = 10 Hz, 1H), 14.56 (s, 1H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 21.3, 31.0, 43.0, 113.5, 120.2, 121.6, 124.0, 126.3, 126.6, 126.9, 129.2, 134.1, 143.7, 145.5, 147.3, 161.3.

Anal. Calcd for $C_{18}H_{16}N_4O$: C, 71.03; H, 5.30; N, 18.41. Found: C, 70.89; H, 5.41; N, 18.66.

27.



53

$C_{12}H_{12}N_2O_2$ (216.23)

Mp: 139-141 ^{o}C (benzene).

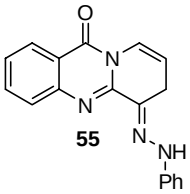
IR ($CHCl_3$): ν_{max} 3418, 1665, 1611 cm^{-1}.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.84-1.93 (m, 1H), 1.98-2.07 (m, 1H), 2.11-2.22 (m, 1H), 2.24-2.31 (m, 1H), 2.89-2.98 (m, 1H), 3.09-3.17 (m, 1H) 4.96 (s, 1H), 6.16 (t, J = 5 Hz, 1H), 7.44 (t, J = 10 Hz, 1H), 7.63 (d, J = 10 Hz, 1H), 7.74 (t, J = 10 Hz, 1H), 8.23 (d, J = 10 Hz, 1H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 15.2, 29.4, 32.1, 76.2, 120.4, 126.3, 126.39, 126.42, 134.7, 147.3, 153.9, 163.5.

Anal. Calcd for $C_{12}H_{12}N_2O_2$: C, 66.66; H, 5.59; N, 12.95. Found: C, 66.83; H, 5.69; N, 13.06.

28.



55

$C_{18}H_{14}N_4O$ (302.34)

Mp: 186-188 ^{o}C (ethyl acetate).

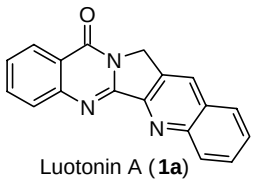
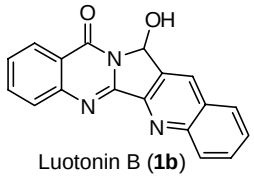
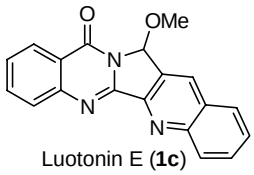
IR ($CHCl_3$) ν_{max} 3435, 1680, 1594 cm^{-1}.

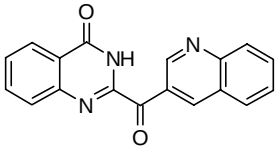
^{1}H NMR ($CDCl_3$, 200 MHz): δ 3.48 (dd, J = 4 and 2 Hz, 2H), 5.11-5.22 (m, 1H), 6.75 (d, J = 8 Hz, 1H), 7.09-7.20 (m, 1H), 7.34-7.55 (m, 5H), 7.76 (d, J = 4 Hz, 2H), 8.30 (d, J = 8 Hz, 1H), 10.09 (bs, 1H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 20.0, 101.4, 116.3, 122.3, 123.9, 125.9, 126.7, 127.1, 128.0, 129.3, 133.8, 134.4, 143.8, 148.3, 149.0, 161.1.

Anal. Calcd for $C_{18}H_{14}N_4O$: C, 71.51; H, 4.67; N, 18.53. Found: C, 71.32; H, 4.78; N, 18.42.

5.1.2 Spectral and Analytical Data for Compounds from Chapter Three

No.	Structure & Text No. Mol. Form. (Mol. Wt.)	Mp (^{o}C)/ IR (cm^{-1})/ ^{1}H NMR (δ)/ ^{13}C NMR (δ)/ mass spectral data/ elemental analysis/ α_D
29.	 Luotonin A (**1a**) **$C_{18}H_{11}N_3O$** (285.31)	**Mp**: 284-285 ^{o}C (ethyl acetate). **IR** (nujol): ν_{max} 1672, 1628, 1607, 1466 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 500 MHz): δ 5.34 (s, 2H), 7.58 (t, *J* = 10 Hz, 1H), 7.68 (t, *J* = 10 Hz, 1H), 7.84 (t, *J* = 10 Hz, 1H), 7.86 (t, *J* = 10 Hz, 1H), 7.94 (d, *J* = 10 Hz, 1H), 8.12 (d, *J* = 10 Hz, 1H), 8.43 (d, *J* = 10 Hz, 1H), 8.44 (s, 1H), 8.47 (d, *J* = 10 Hz, 1H). **^{13}C NMR** ($CDCl_3$, 125 MHz): δ 47.3, 121.3, 126.4, 127.4, 127.9, 128.5, 128.8 (2-carbons), 129.4, 130.68, 130.71, 131.5, 134.6, 149.35, 149.42, 151.2, 152.5, 160.7. **Anal. Calcd for $C_{18}H_{11}N_3O$**: C, 75.78; H, 3.89; N, 14.73. Found: C, 75.89; H, 3.98; N, 14.61.
30.	 Luotonin B (**1b**) **$C_{18}H_{11}N_3O_2$** (301.31)	**Mp**: 274-276 ^{o}C (ethyl acetate). **IR** ($CHCl_3$): ν_{max} 3238, 1686, 1636, 1609 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 500 MHz): δ 5.08 (bs, 1H), 7.14 (s, 1H), 7.61 (t, *J* = 10 Hz, 1H), 7.73 (t, *J* = 10 Hz, 1H), 7.88 (t, *J* = 10 Hz, 1H), 7.90 (d, *J* = 10 Hz, 1H), 8.02 (d, *J* = 10 Hz, 1H), 8.11 (d, *J* = 10 Hz, 1H), 8.41 (d, *J* = 10 Hz, 1H), 8.49 (d, *J* = 10 Hz, 1H), 8.59 (s, 1H). **^{13}C NMR** ($CDCl_3$, 125 MHz): δ 80.9, 121.9, 126.5, 127.9, 128.6, 128.8, 128.9, 129.2, 130.9, 131.0, 131.4, 133.3, 135.1, 149.5, 150.3, 150.4, 150.9, 161.6. **Anal. Calcd for $C_{18}H_{11}N_3O_2$**: C, 71.75; H, 3.68; N, 13.95. Found: C, 71.66; H, 3.51; N, 14.01.
31.	 Luotonin E (**1c**) **$C_{19}H_{13}N_3O_2$** (315.33)	**Mp**: 225-227 ^{o}C (benzene). **IR** ($CHCl_3$): ν_{max} 1686, 1638, 1607 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 500 MHz): δ 3.60 (s, 3H), 6.94 (s, 1H), 7.59 (t, *J* = 10 Hz, 1H), 7.71 (t, *J* = 10 Hz, 1H), 7.85 (t, *J* = 10 Hz, 1H), 7.88 (t, *J* = 10 Hz, 1H), 7.99 (d, *J* = 10 Hz, 1H), 8.09 (d, *J* = 10 Hz, 1H), 8.43 (d, *J* = 10 Hz, 1H), 8.48 (d, *J* = 10 Hz, 1H), 8.52 (s, 1H). **^{13}C NMR** ($CDCl_3$, 125 MHz): δ 56.3, 87.0, 122.3, 126.9, 127.9, 128.5, 128.7, 128.88, 128.94, 130.1, 130.8, 131.4, 133.2, 134.9, 149.0, 150.37, 150.43, 151.4, 160.8. **Anal. Calcd for $C_{19}H_{13}N_3O_2$**: C, 72.37; H, 4.15; N, 13.33. Found: C, 72.43; H, 4.19; N, 13.51.

32. 

Luotonin F (**1d**)

$C_{18}H_{11}N_3O_2$ (301.31)

Mp: 241-242 ^{o}C ($CHCl_3$).

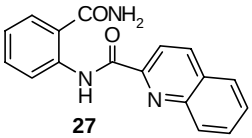
IR (nujol): ν_{max} 3431, 1659, 1614, 1599, 1466 cm^{-1}.

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.70 (t, J = 6 Hz, 2H), 7.91 (t, J = 6 Hz 1H), 7.93 (t, J = 6 Hz, 1H), 7.99 (d, J = 6 Hz, 1H), 8.06 (d, J = 6 Hz, 1H), 8.23 (d, J = 6 Hz, 1H), 8.44 (d, J = 6 Hz, 1H), 9.52 (s, 1H), 9.92 (s, 1H), 10.34 (bs, 1H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 123.5, 126.7, 127.1 (2-carbons), 127.7, 129.5 (2-carbons), 129.86, 129.89, 132.9, 135.0, 141.9, 145.9, 147.5, 149.8, 150.9, 160.6, 184.2.

MS (*m/e*): 301, 273, 245, 156, 128, 119, 101, 90, 83, 71, 57.

Anal. Calcd for $C_{18}H_{11}N_3O_2$: C, 71.75; H, 3.68; N, 13.95. Found: C, 71.63; H, 3.71; N, 14.01.

33. 

27

$C_{17}H_{13}N_3O_2$ (291.31)

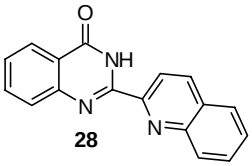
Mp: 269-271 ^{o}C (methanol).

IR (nujol): ν_{max} 3360, 3290, 3192, 1688, 1649, 1616 cm^{-1}.

^{1}H NMR (DMSO-d_6, 200 MHz): δ 7.21 (t, J = 8 Hz, 1H), 7.60 (t, J = 8 Hz, 1H), 7.75 (t, J = 8 Hz, 1H), 7.82-7.95 (m, 3H), 8.12 (d, J = 8 Hz, 2H), 8.28 (d, J = 8 Hz, 1H), 8.33 (bs, 1H), 8.64 (d, J = 8 Hz, 1H), 8.82 (d, J = 8 Hz, 1H), 13.55 (s, 1H).

^{13}C NMR (DMSO-d_6, 75 MHz): δ 118.7, 120.3, 121.4, 123.0, 128.2, 128.5, 128.8, 129.1, 129.4, 130.7, 132.1, 138.3, 138.9, 146.0, 150.0, 162.9, 170.6.

Anal. Calcd for $C_{17}H_{13}N_3O_2$: C, 70.09; H, 4.50; N, 14.43. Found: C, 69.89; H, 4.62; N, 14.39.

34. 

28

$C_{17}H_{11}N_3O$ (273.30)

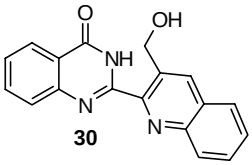
Mp: 229-231 ^{o}C (ethyl acetate).

IR (nujol): ν_{max} 3319, 1682, 1605 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.45-7.65 (m, 2H), 7.65-7.90 (m, 4H), 8.12 (d, J = 8 Hz, 1H), 8.34 (t, J = 8 Hz, 2H), 8.61 (d, J = 8 Hz, 1H), 11.19 (bs, 1H).

^{13}C NMR ($CDCl_3$, 75 MHz) : δ 118.4, 122.6, 126.7, 127.4, 127.6, 128.2 (2-carbons), 129.2, 129.6, 130.4, 134.4, 137.5, 146.7, 148.0, 148.9, 149.1, 161.3.

Anal. Calcd for $C_{17}H_{11}N_3O$: C, 74.71; H, 4.06; N, 15.38. Found: C, 74.83; H, 4.17; N, 15.42.

35. 

30

$C_{18}H_{13}N_3O_2$ (303.32)

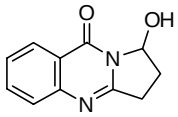
Mp: 212-214 ^{o}C (benzene).

IR ($CHCl_3$): ν_{max} 3747, 3304, 1682, 1638, 1605 cm^{-1}.

^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.07 (d, J = 6 Hz, 2H), 6.33 (t, J = 6 Hz, 1H), 7.54-7.70 (m, 2H), 7.75-7.79 (m, 4H), 8.15 (d, J = 6 Hz, 1H), 8.28 (s, 1H), 8.39 (d, J = 6 Hz, 1H), 11.45 (bs, 1H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 63.9, 122.5, 126.9, 127.5, 127.7, 128.2, 128.9, 129.0, 129.4, 130.7, 134.1, 134.8, 139.1, 145.9, 146.5, 147.9, 150.1, 160.9.

Anal. Calcd for $C_{18}H_{13}N_3O_2$: C, 71.28; H, 4.32; N, 13.85. Found: C, 71.17; H, 4.43; N, 13.96.

36. 

Isovasicinone (**41**)

$C_{11}H_{10}N_2O_2$ (202.21)

Mp: 176-178 ^{o}C (benzene).

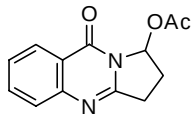
IR (nujol): ν_{max} 3111, 1680, 1640, 1609, 1466 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz): δ 2.15-2.38 (m, 1H), 2.38-2.65 (m, 1H), 2.95-3.25 (m, 1H), 3.25-3.55 (m, 1H), 5.20 (bs, 1H), 6.34 (d, J = 4 Hz, 1H), 7.45 (t, J = 8 Hz, 1H), 7.55-7.90 (m, 2H), 8.25 (d, J = 6 Hz, 1H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ 27.7, 29.8, 82.8, 120.5, 126.3 (2-carbons), 126.8, 134.6, 149.3, 158.5, 161.5.

MS (*m/e*): 202, 185, 173, 146, 130, 119, 102, 90, 76, 63, 55.

Anal. Calcd for $C_{11}H_{10}N_2O_2$: C, 65.34; H, 4.99; N, 15.83. Found: C, 65.21; H, 5.07; N, 15.92.

37. 

42

$C_{13}H_{12}N_2O_3$ (244.24)

Mp: 89-91 ^{o}C (benzene + pet. ether).

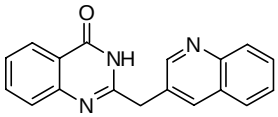
IR (nujol): ν_{max} 1751, 1682, 1634, 1610, 1468 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz): δ 2.11(s, 3H), 2.20-2.40 (m, 1H), 2.40-2.65 (m, 1H), 3.00-3.20 (m, 1H), 3.25-3.50 (m, 1H), 7.17 (d, J = 6 Hz, 1H), 7.48 (t, J = 8 Hz, 1H), 7.60-7.85 (m, 2H), 8.28 (d, J = 8 Hz, 1H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ 20.8, 27.3, 29.7, 81.9, 120.6, 126.7, 126.8, 127.0, 134.8, 148.8, 158.9, 159.7, 169.3.

MS (*m/e*): 244, 201, 184, 173, 146, 130, 119, 102, 90, 77, 63.

Anal. Calcd for $C_{13}H_{12}N_2O_3$: C, 63.93; H, 4.95; N, 11.47. Found: C, 64.02; H, 5.09; N, 11.33.

38. 

Deoxoluotonin F (**43**)

$C_{18}H_{13}N_3O$ (287.32)

Mp: 263-265 ^{o}C ($CHCl_3$ + acetone).

IR (nujol): ν_{max} 3445, 1678, 1609, 1464 cm^{-1}.

^{1}H NMR ($CDCl_3$, 300 MHz): δ 4.31 (s, 2H), 7.51 (t, J = 6 Hz, 1H), 7.54 (t, J = 6 Hz, 1H), 7.70 (t, J = 6 Hz 1H), 7.75 (d, J = 9 Hz, 1H), 7.78 (d, J = 9 Hz, 1H), 7.81 (t, J = 6 Hz, 1H), 8.11 (d, J = 9 Hz 1H), 8.28 (d, J = 9 Hz, 1H), 8.29 (s, 1H), 9.07 (s, 1H), 11.51 (bs, 1H).

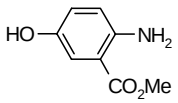
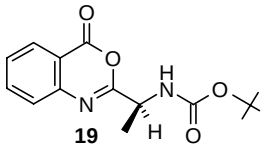
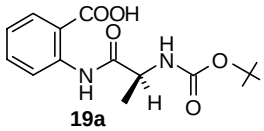
^{1}H NMR (methanol-d_4, 300 MHz): δ 4.26 (s, 2H), 7.51 (t, J = 9 Hz, 1H), 7.61 (t, J = 9 Hz, 1H), 7.66 (d, J = 9 Hz, 1H), 7.72-7.83 (m, 2H), 7.93 (d, J = 9 Hz, 1H), 8.02 (d, J = 9 Hz, 1H), 8.19 (d, J = 9 Hz, 1H), 8.32 (s, 1H), 8.90 (s, 1H).

^{13}C NMR ($CDCl_3$ + DMSO-d_6, 75 MHz): δ 38.6, 120.9, 125.7, 125.9, 126.4, 126.8, 127.3, 127.5, 128.6, 128.9, 133.8, 135.3, 146.7, 148.8, 151.4, 154.4, 162.6, 169.1.

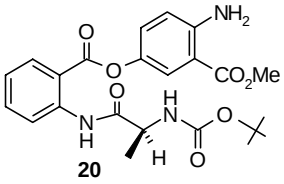
MS (*m/e*): 287, 286, 258, 231, 140, 115, 90, 77, 69, 63.

Anal. Calcd for $C_{18}H_{13}N_3O$: C, 75.25; H, 4.56; N, 14.63. Found: C, 75.30; H, 4.44; N, 14.69.

5.1.3 Spectral and Analytical Data for Compounds from Chapter Four

No.	Structure & Text No. Mol. Form. (Mol. Wt.)	Mp (^{o}C)/ IR (cm^{-1})/ ^{1}H NMR (δ)/ ^{13}C NMR (δ)/ mass spectral data/ elemental analysis/ α_D
39.	 2-Amino-5-hydroxybenzoic acid methyl ester **$C_8H_9NO_3$** (167.17)	**Mp**: 158-160 ^{o}C (ethyl acetate). **IR** (nujol): ν_{max} 3379, 3299, 1708, 1591, 1510, 1456 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 200 MHz): δ 3.87 (s, 3H), 5.29 (bs, 3H), 6.61 (d, J = 8 Hz, 1H), 6.88-6.92 (dd, J = 8 and 4 Hz, 1H), 7.33-7.35 (m, 1H). **Anal. Calcd for $C_8H_9NO_3$**: C, 57.48; H, 5.43; N, 8.38. Found: C, 57.36; H, 5.51; N, 8.54.
40.	 **19** **$C_{15}H_{18}N_2O_4$** (290.32)	**Mp**: Thick oil. **$[\alpha]^{20}_D$**: –30.0 (c 1, $CHCl_3$). **IR** (neat) ν_{max} 3350, 1768, 1714, 1651, 1606, 1506, 1456 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 200 MHz): δ 1.46 (s, 9H), 1.57 (d, J = 6 Hz, 3H), 4.67-4.77 (m, 1H), 5.34 (bs, 1H), 7.49-7.62 (m, 2H), 7.82 (t, J = 8 Hz, 1H), 8.20 (d, J = 8 Hz, 1H). **^{1}H NMR** (acetone-d_6, 200 MHz): δ 1.43 (s, 9H), 1.57 (d, J = 8 Hz, 3H), 4.56-4.72 (m, 1H), 6.53 (bs, 1H), 7.57-7.67 (m, 2H), 7.93 (t, J = 8 Hz, 1H), 8.15 (d, J = 8 Hz, 1H). **^{13}C NMR** (acetone-d_6, 75 MHz): δ 20.0, 30.2, 51.1, 80.0, 118.0, 128.2, 130.1, 131.3, 139.3, 147.0, 156.4, 161.1, 165.2. **MS** (m/e): 234, 216, 190, 175, 162, 146, 133, 119, 103, 90, 70, 63, 57. **Anal. Calcd for $C_{15}H_{18}N_2O_4$**: C, 62.06; H, 6.25; N, 9.65. Found: C, 61.82; H, 6.33; N, 9.87.
41.	 **19a** **$C_{15}H_{20}N_2O_5$** (308.34)	**Mp**: 159-162 ^{o}C (pet. ether + diethyl ether). **$[\alpha]^{20}_D$**: –113.7 (c 1, CH_2Cl_2). **IR** (nujol): ν_{max} 3280, 1710, 1681, 1660, 1602, 1587, 1519, 1454 cm^{-1}. **^{1}H & ^{13}C NMR**: Please see spectra in Section B. **MS** (m/e): 308, 252, 235, 217, 193, 175, 164, 146, 144, 137, 119, 88, 77, 65, 57. **Anal. Calcd for $C_{15}H_{20}N_2O_5$**: C, 58.43; H, 6.54; N, 9.08. Found: C, 58.65; H, 6.69; N, 9.21.

42.



20

$C_{23}H_{27}N_3O_7$ (457.48)

Mp: 98-100 °C (benzene).

[α]$^{20}_{D}$: –5.0 (*c* 0.5, $CHCl_3$).

IR (nujol): ν_{max} 3469, 3359, 3292, 1697, 1625, 1587, 1506, 1450 cm^{-1}.

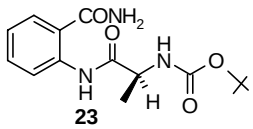
^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.36 (s, 9H), 1.44 (d, *J* = 8 Hz, 3H), 3.85 (s, 3H), 4.21-4.33 (m, 1H), 5.14 (d, *J* = 6 Hz, 1H), 5.80 (bs, 2H), 6.70 (d, *J* = 8 Hz, 1H), 7.05-7.19 (m, 2H), 7.55-7.65 (m, 2H), 8.24 (d, *J* = 8 Hz, 1H), 8.76 (d, *J* = 10 Hz, 1H), 11.40 (bs, 1H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ 18.6, 28.2, 51.5, 51.8, 80.0, 110.4, 114.6, 117.3, 120.5, 122.8, 123.4, 127.9, 131.1, 135.2, 139.9, 141.7, 148.8, 155.0, 167.2, 167.6, 171.9.

MS (*m/e*): 384, 352, 291, 281, 253, 235, 224, 217, 209, 191, 167, 146, 135, 128, 119, 107, 92, 71, 57.

Anal. Calcd for $C_{23}H_{27}N_3O_7$: C, 60.39; H, 5.95; N, 9.19. Found: C, 60.27; H, 5.79; N, 9.12.

43.



23

$C_{15}H_{21}N_3O_4$ (307.36)

Mp: 117-119 °C (benzene).

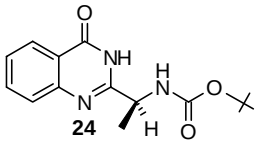
[α]$^{20}_{D}$: –35.5 (*c* 0.5, $CHCl_3$).

IR ($CHCl_3$): ν_{max} 3433, 3315, 1697, 1683, 1664, 1610, 1583, 1521 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.45 (s, 9H), 1.47 (d, *J* = 6 Hz, 3H), 4.23-4.34 (m, 1H), 5.32 (bd, *J* = 8 Hz, 1H), 6.29 (bs, 1H), 6.57 (bs, 1H), 7.07 (t, *J* = 8 Hz, 1H), 7.43-7.58 (m, 2H), 8.59 (d, *J* = 8 Hz, 1H), 11.66 (s, 1H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ 18.5, 28.2, 51.6, 79.9, 119.1, 121.0, 122.8, 127.7, 132.8, 139.4, 155.4, 171.6, 172.0.

Anal. Calcd for $C_{15}H_{21}N_3O_4$: C, 58.62; H, 6.89; N, 13.67. Found: C, 58.73; H, 7.04; N, 13.57.

44. 

24

$C_{15}H_{19}N_3O_3$ (289.34)

Mp: 225-227 °C (benzene).

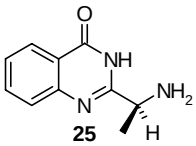
[α]$^{20}_{D}$: −79.0 (*c* 0.5, $CHCl_3$).

IR (nujol): ν_{max} 3332, 1689, 1622, 1608, 1515, 1461 cm^{-1}.

^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.41 (s, 9H), 1.62 (d, *J* = 6 Hz, 3H), 4.80-4.90 (m, 1H), 5.74 (bd, *J* = 6 Hz, 1H), 7.47 (t, *J* = 9 Hz, 1H), 7.70-7.79 (m, 2H), 8.31 (d, *J* = 9 Hz, 1H), 11.87 (s, 1H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 19.8, 28.3, 29.7, 49.7, 80.6, 120.9, 126.5, 127.0, 134.9, 155.6, 157.2, 163.1.

Anal. Calcd for $C_{15}H_{19}N_3O_3$: C, 62.27; H, 6.62; N, 14.52. Found: C, 62.36; H, 6.78; N, 14.64.

45. 

25

$C_{10}H_{11}N_3O$ (189.22)

Mp: 188-190 °C (ethyl acetate).

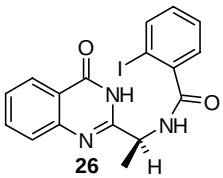
[α]$^{20}_{D}$: −18.0 (*c* 0.2, $CHCl_3$).

IR (nujol): ν_{max} 3365, 3313, 3292, 1677, 1606, 1564, 1494, 1467 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.54 (d, *J* = 6 Hz, 3H), 4.12-4.28 (m, 1H), 7.41-7.48 (m, 1H), 7.64-7.78 (m, 2H), 8.27 (d, *J* = 8 Hz, 1H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ 22.9, 49.9, 121.1, 126.3, 127.0, 134.1, 134.5, 149.1, 159.6, 162.6.

Anal. Calcd for $C_{10}H_{11}N_3O$: C, 63.48; H, 5.86; N, 22.21. Found: C, 63.34; H, 6.04; N, 22.10.

46. 

26

$C_{17}H_{14}N_3O_2I$ (419.22)

Mp: 277-279 °C (methanol).

[α]$^{20}_{D}$: −5.0 (*c* 0.4, THF).

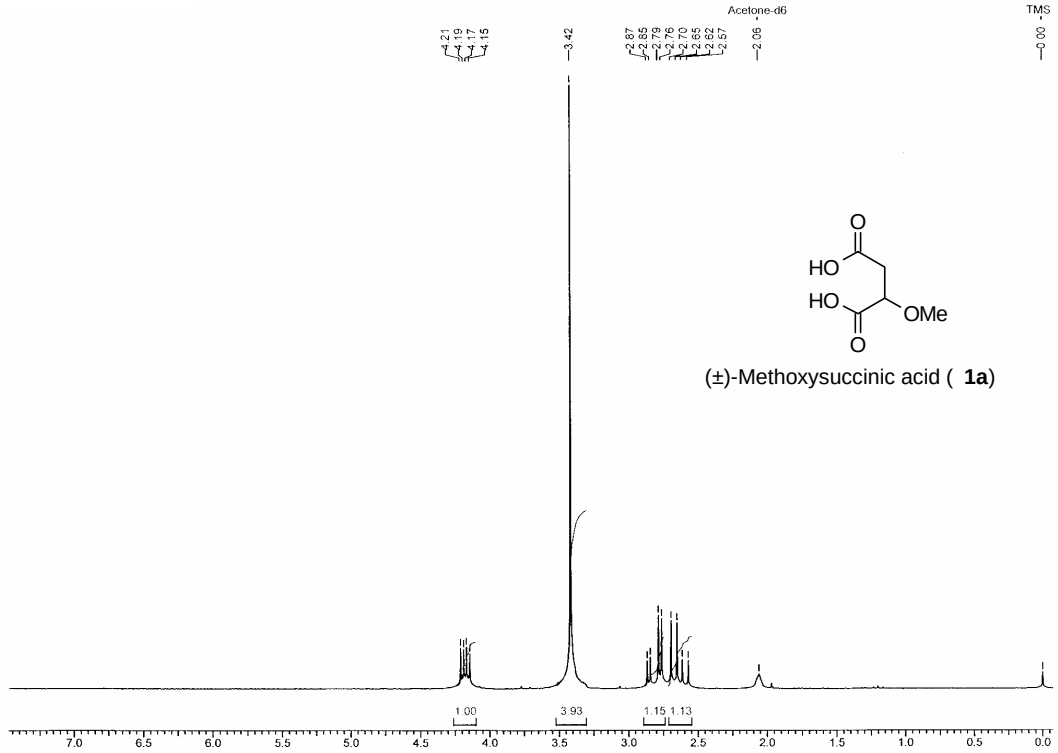
IR (nujol) ν_{max} 3315, 3232, 1679, 1650, 1608, 1519, 1461 cm^{-1}.

^{1}H NMR (pyridine-d_5, 500 MHz): δ 1.88 (d, *J* = 10 Hz, 3H), 5.70-5.76 (m, 1H), 6.99 (t, *J* = 10 Hz, 1H), 7.27 (t, *J* = 10 Hz, 1H), 7.40 (t, *J* = 10 Hz, 1H), 7.65-7.70 (m, 2H), 7.81 (d, *J* = 10 Hz, 1H), 8.46 (d, *J* = 10 Hz, 1H), 10.00 (d, *J* = 10 Hz, 1H).

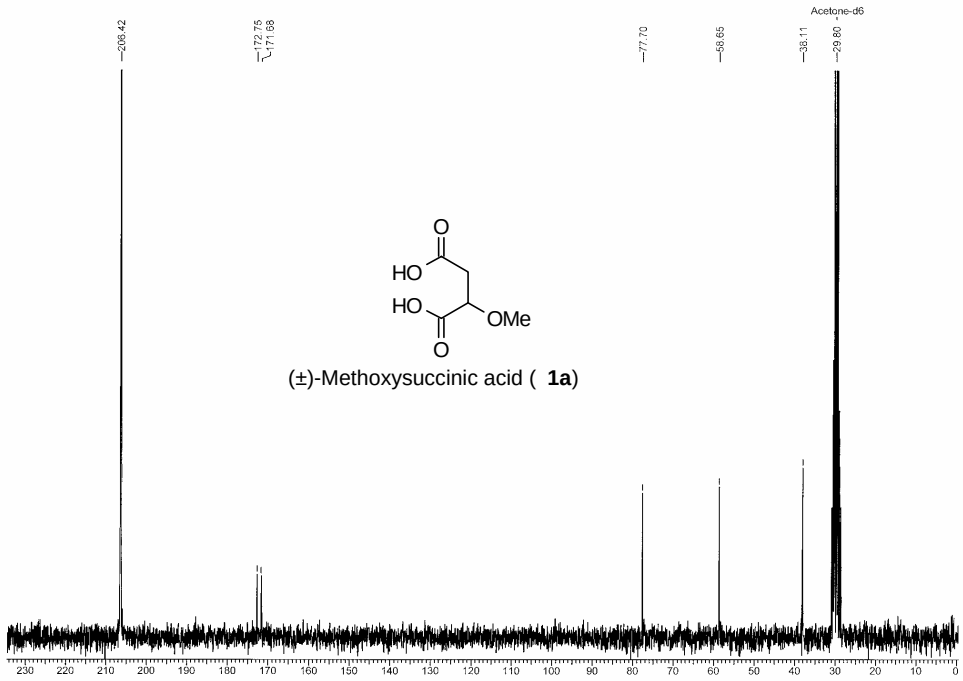
^{13}C NMR (pyridine-d_5, 125 MHz): δ 19.4, 49.0, 122.3, 123.7, 126.5, 127.5, 128.1, 128.6, 130.9, 134.4, 135.9, 139.6, 143.1, 149.8, 158.0, 162.8, 170.1.

Anal. Calcd for $C_{17}H_{14}N_3O_2I$: C, 48.71; H, 3.37; N, 10.02. Found: C, 48.67; H, 3.48; N, 9.94.

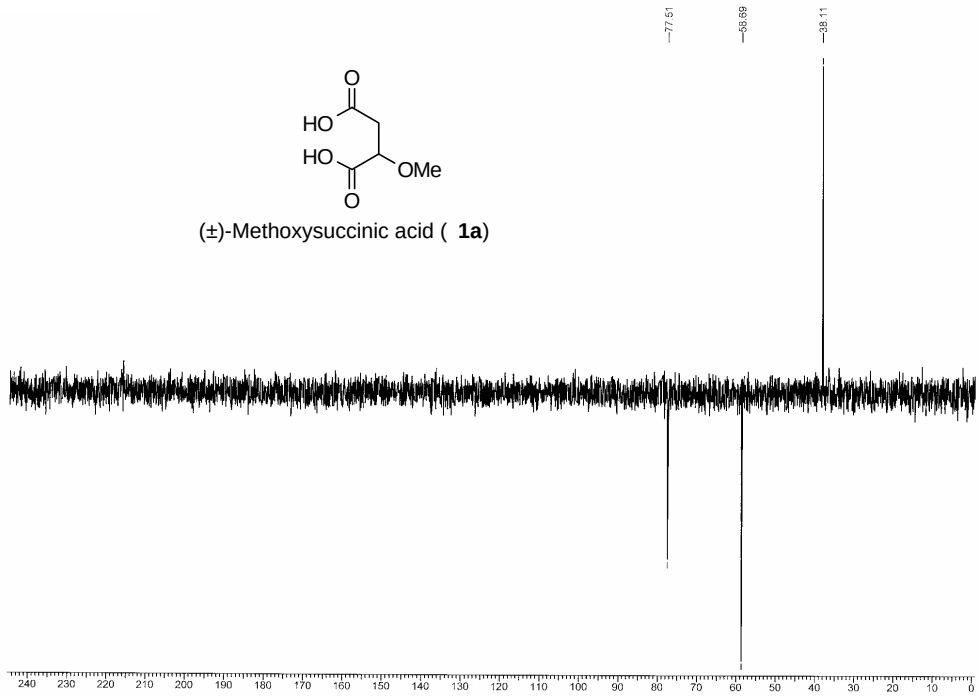
Acetone-d_6, 200 MHz



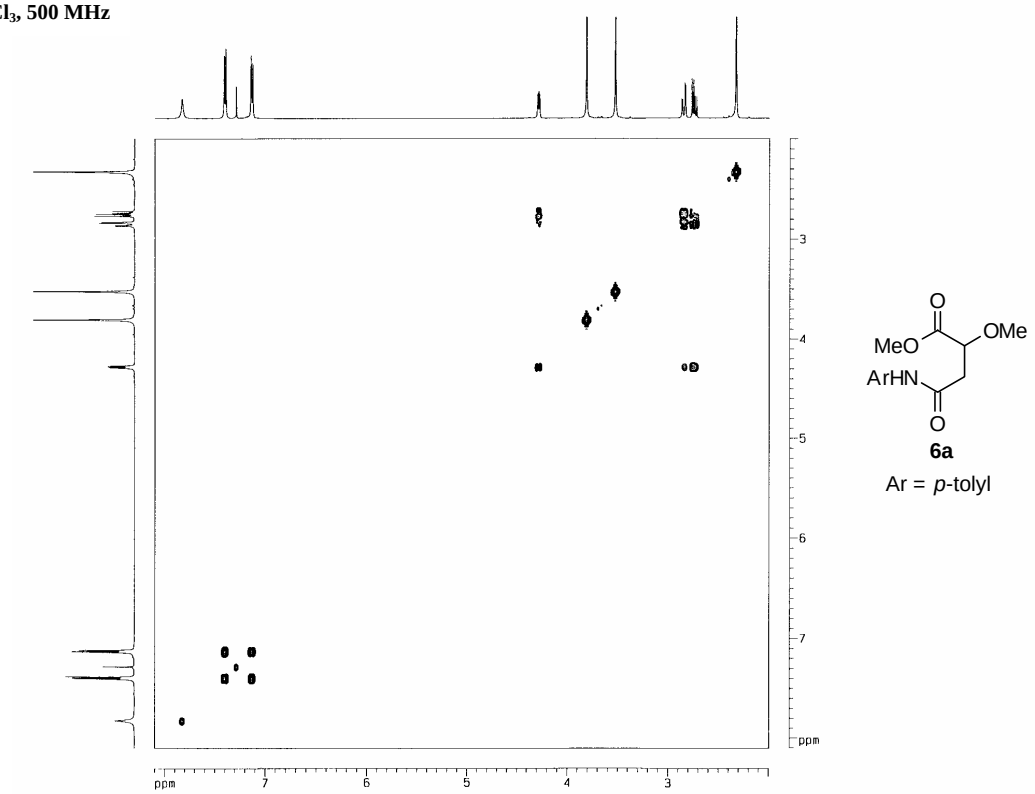
Acetone-d_6, 50 MHz

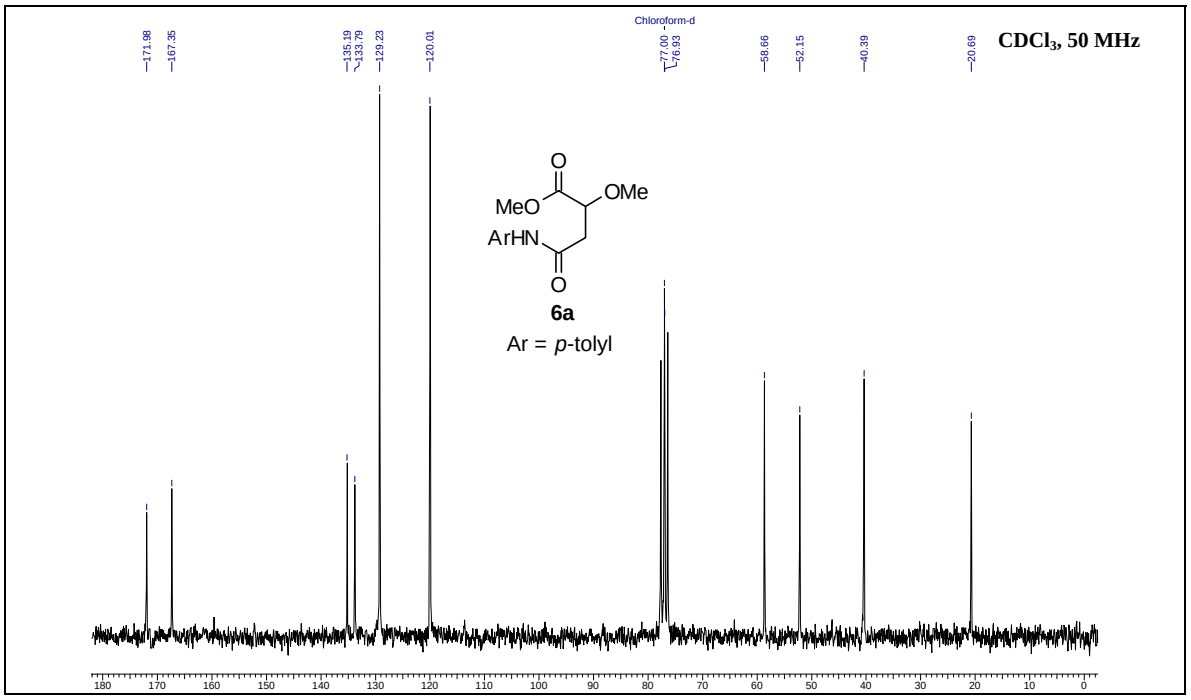


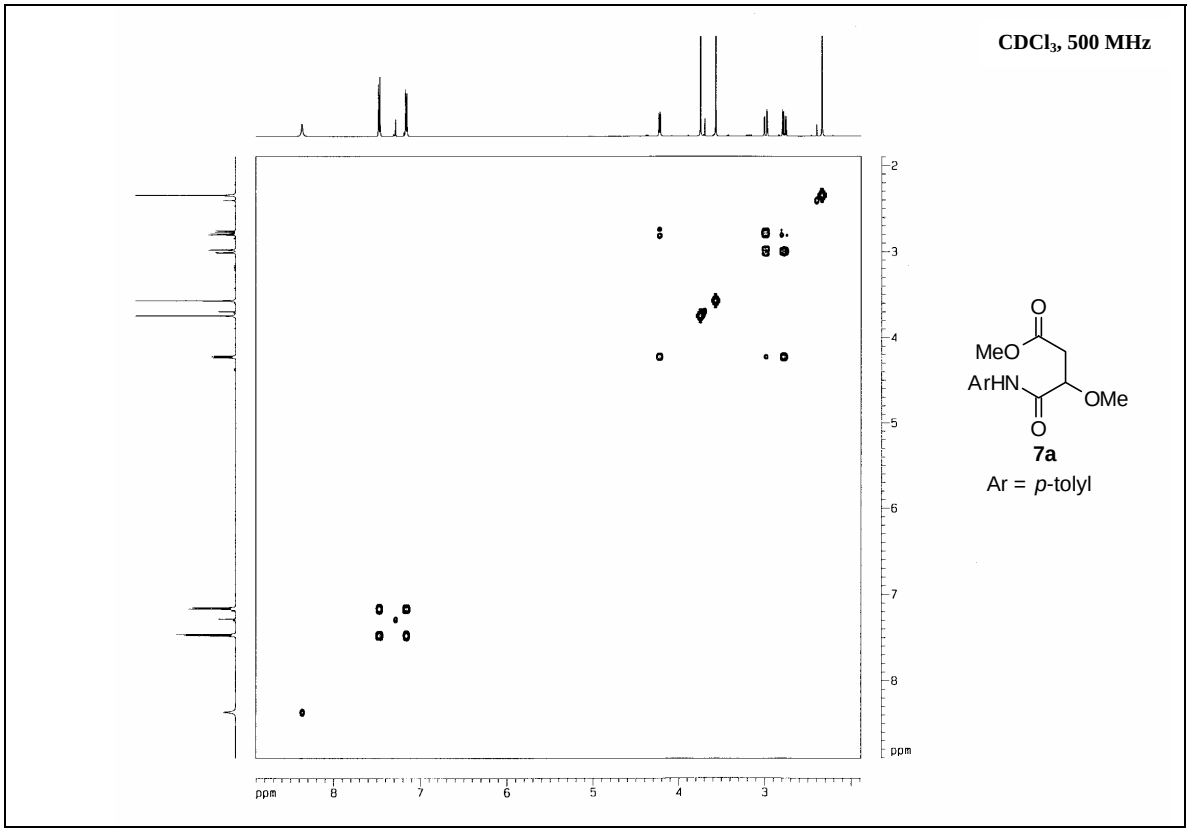
Acetone-d_6, 50 MHz

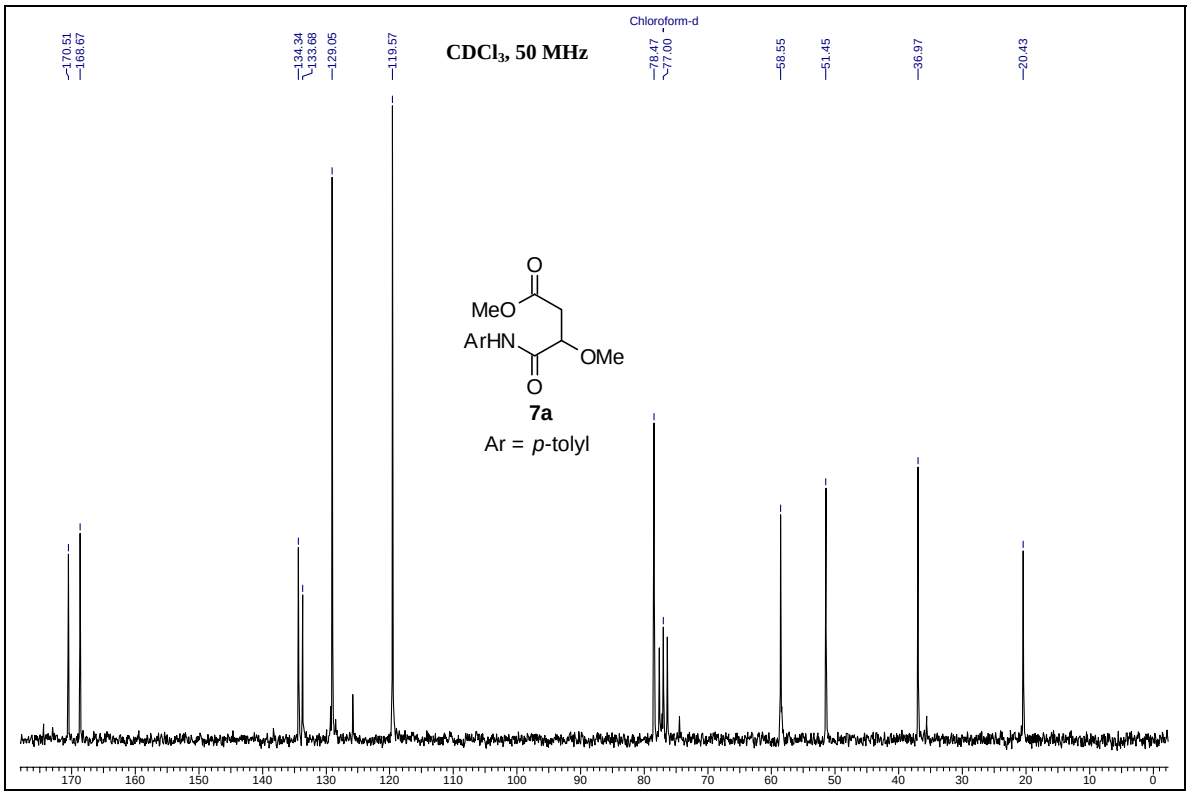


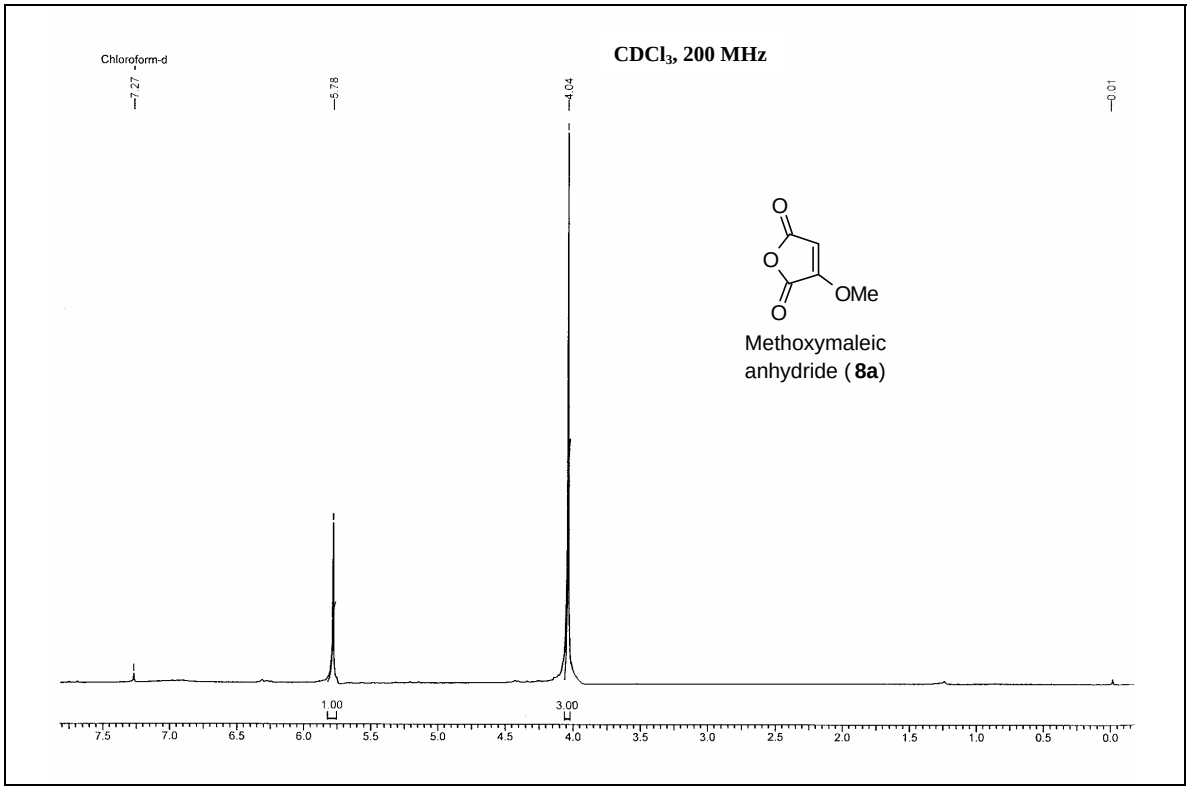
$CDCl_3$, 500 MHz

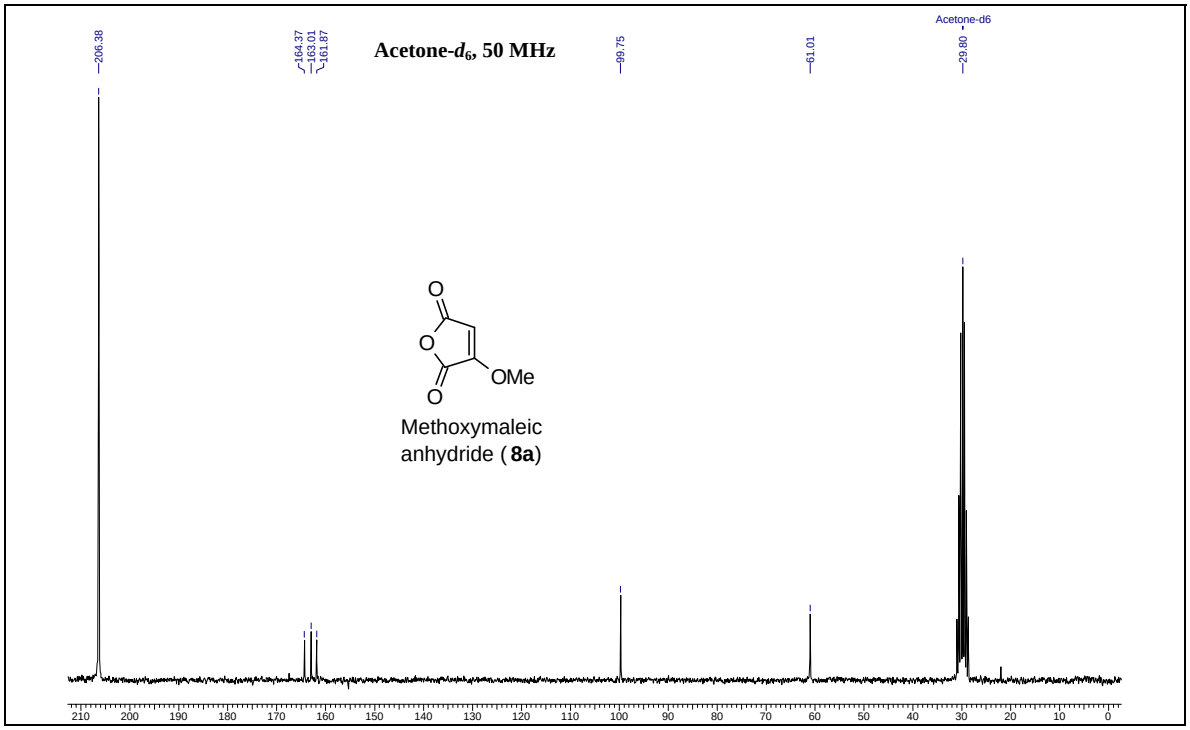


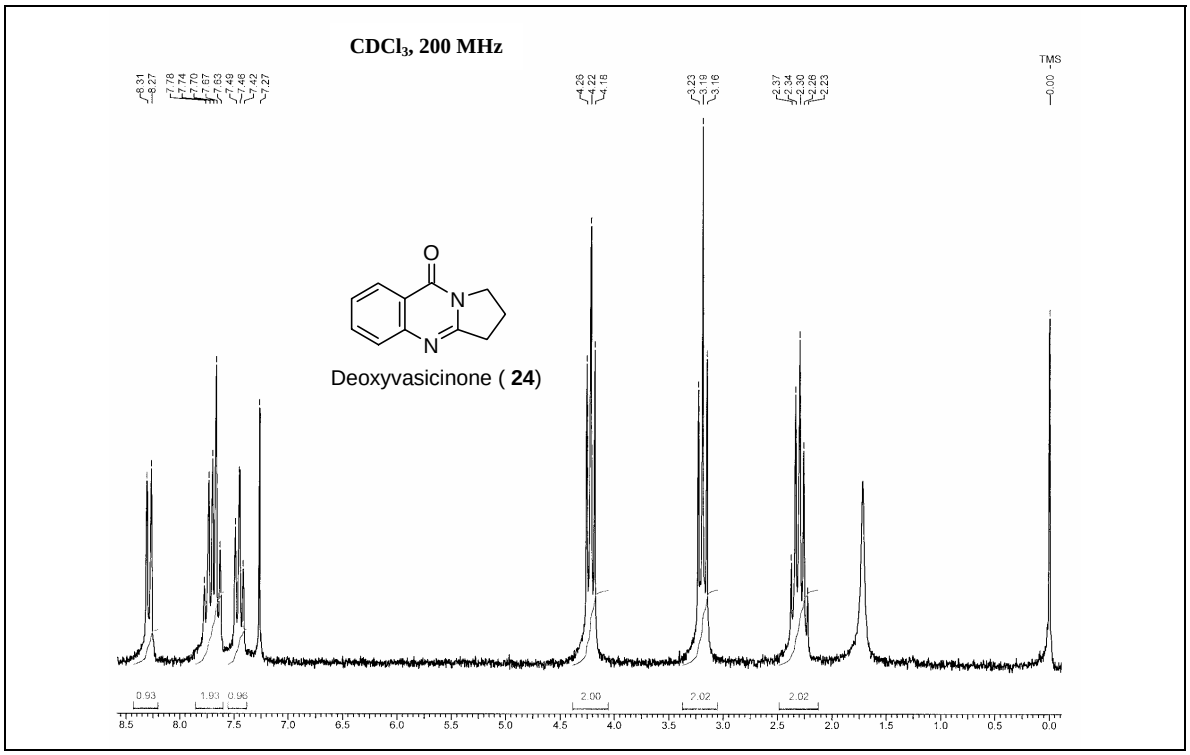

CDCl3, 50 MHz
Chloroform-d
171.98
167.35
135.19
133.79
129.23
120.01
77.00
76.93
58.66
52.15
40.39
20.69
MeO
OMe
ArHN
6a
Ar = p-tolyl

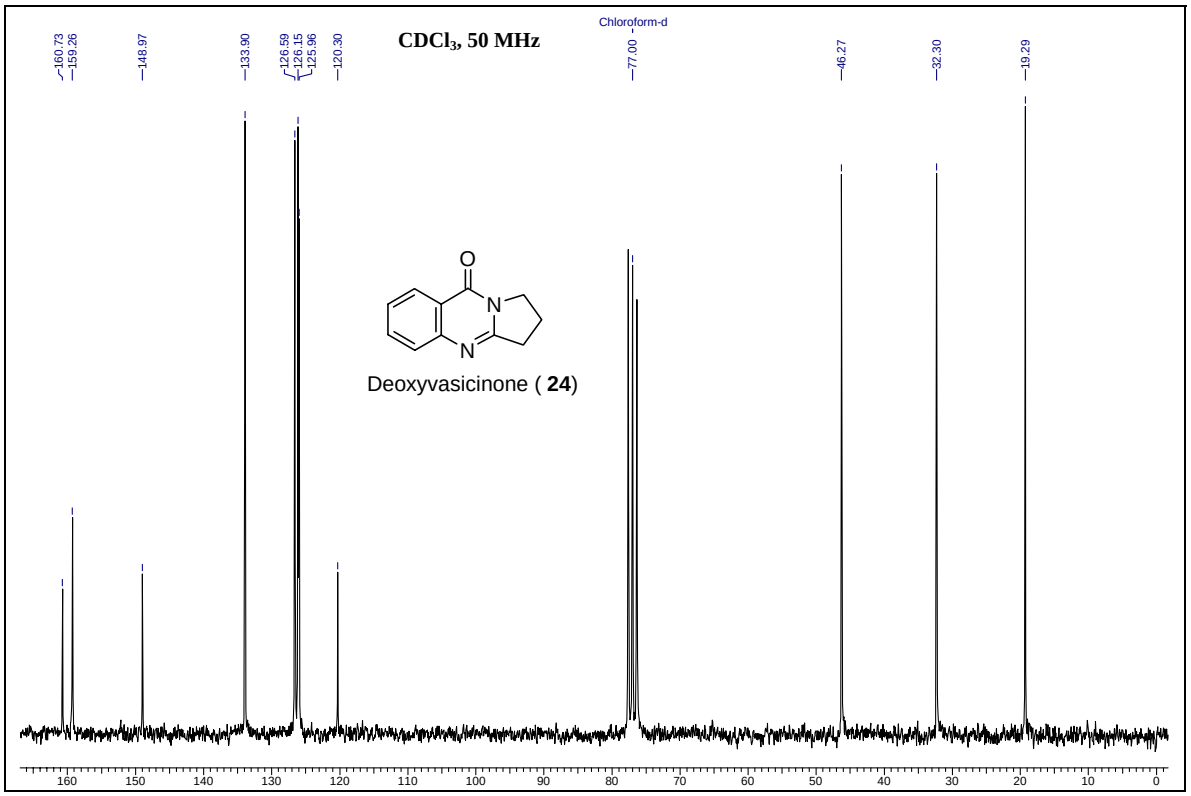

CDCl3, 500 MHz
MeO
ArHN
OMe
7a
Ar = p-tolyl
ppm

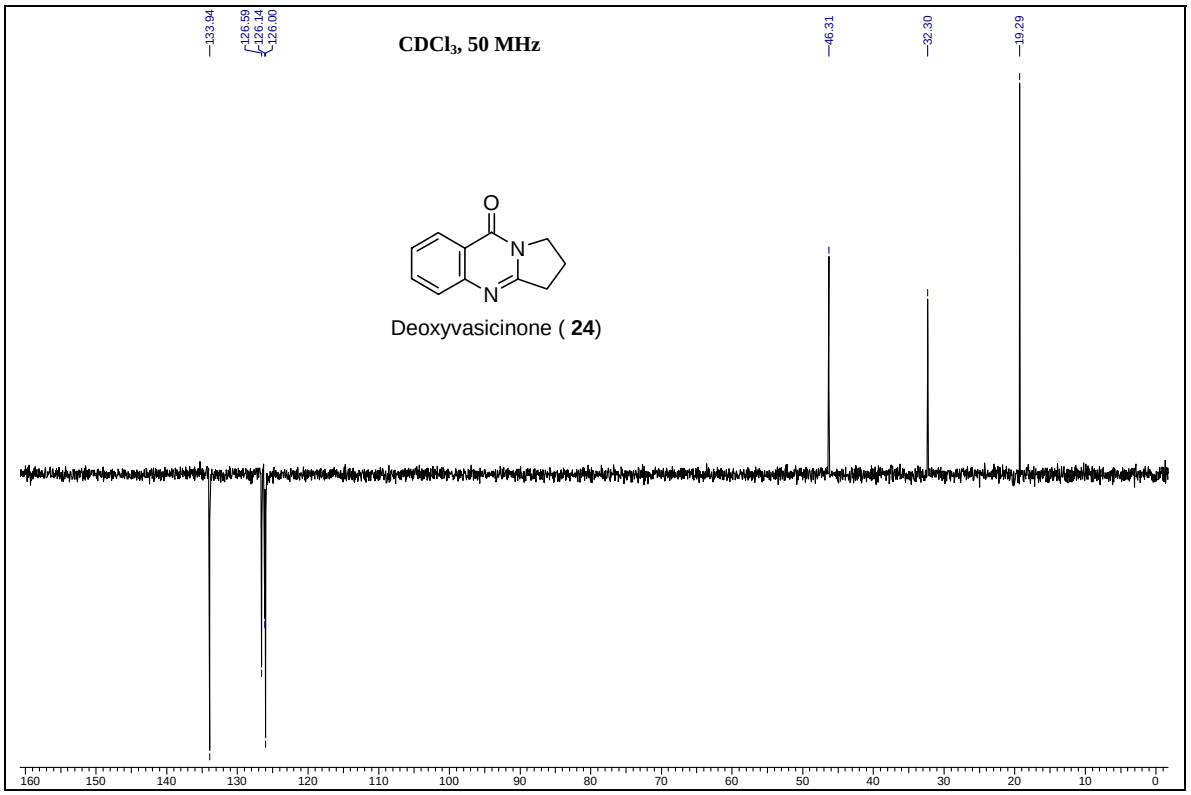

CDCl3, 50 MHz
Chloroform-d
170.51
168.67
134.34
133.68
129.05
119.57
78.47
77.00
58.55
51.45
36.97
20.43
MeO
ArHN
OMe
7a
Ar = p-tolyl

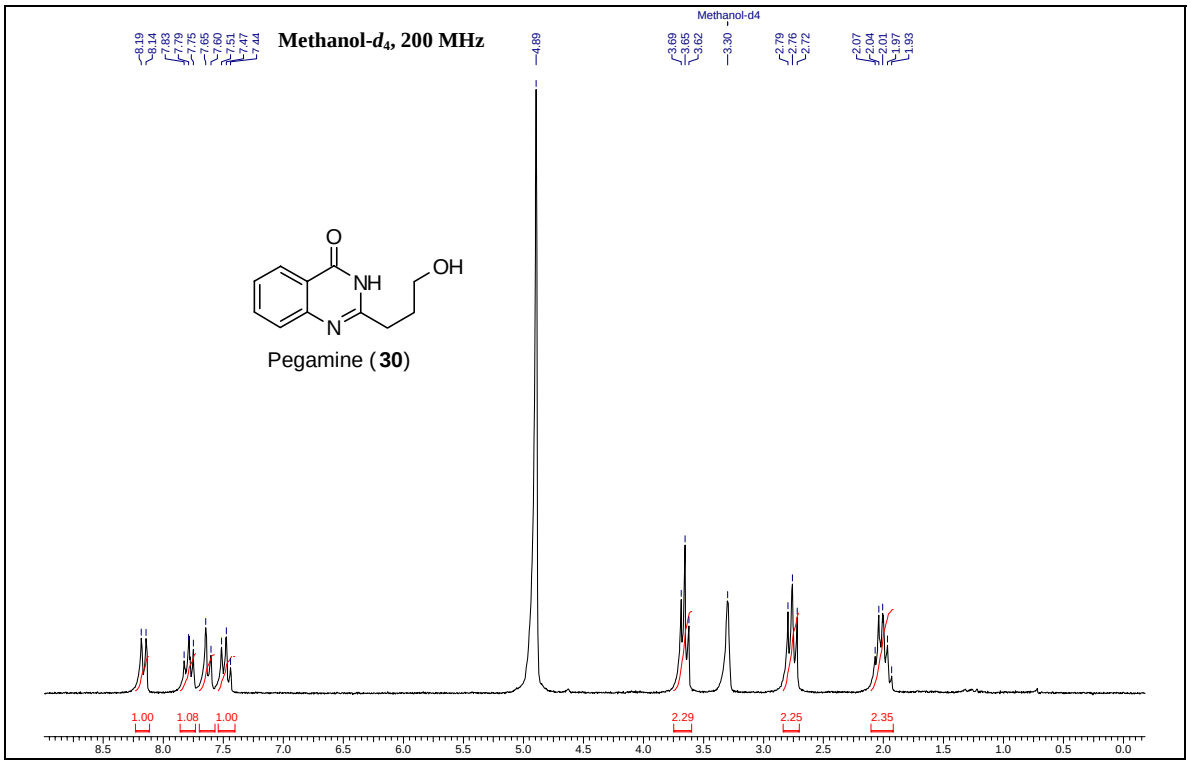

CDCl3, 200 MHz
Chloroform-d
7.27
5.78
4.04
0.01
OMe
Methoxymaleic
anhydride (8a)
1.00
3.00

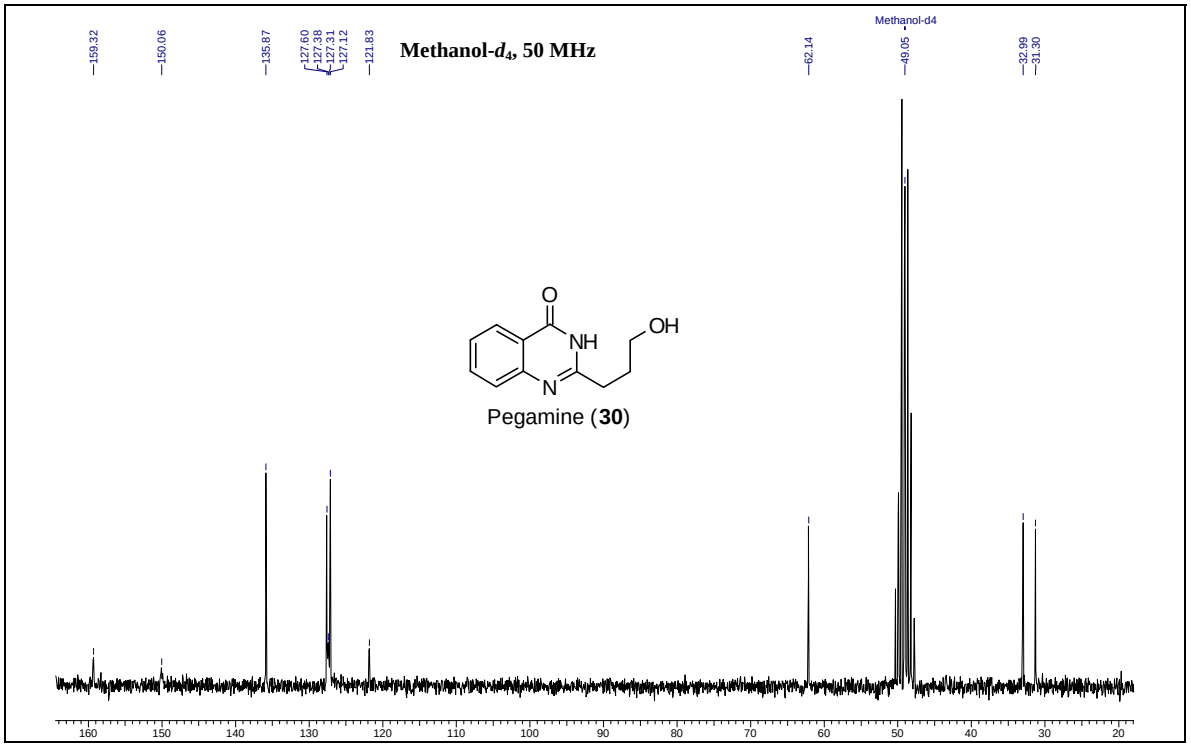

Acetone-d_6, 50 MHz
206.38
164.37
163.01
161.87
99.75
61.01
Acetone-d6
29.80
O
O
O
OMe
Methoxymaleic anhydride (**8a**)

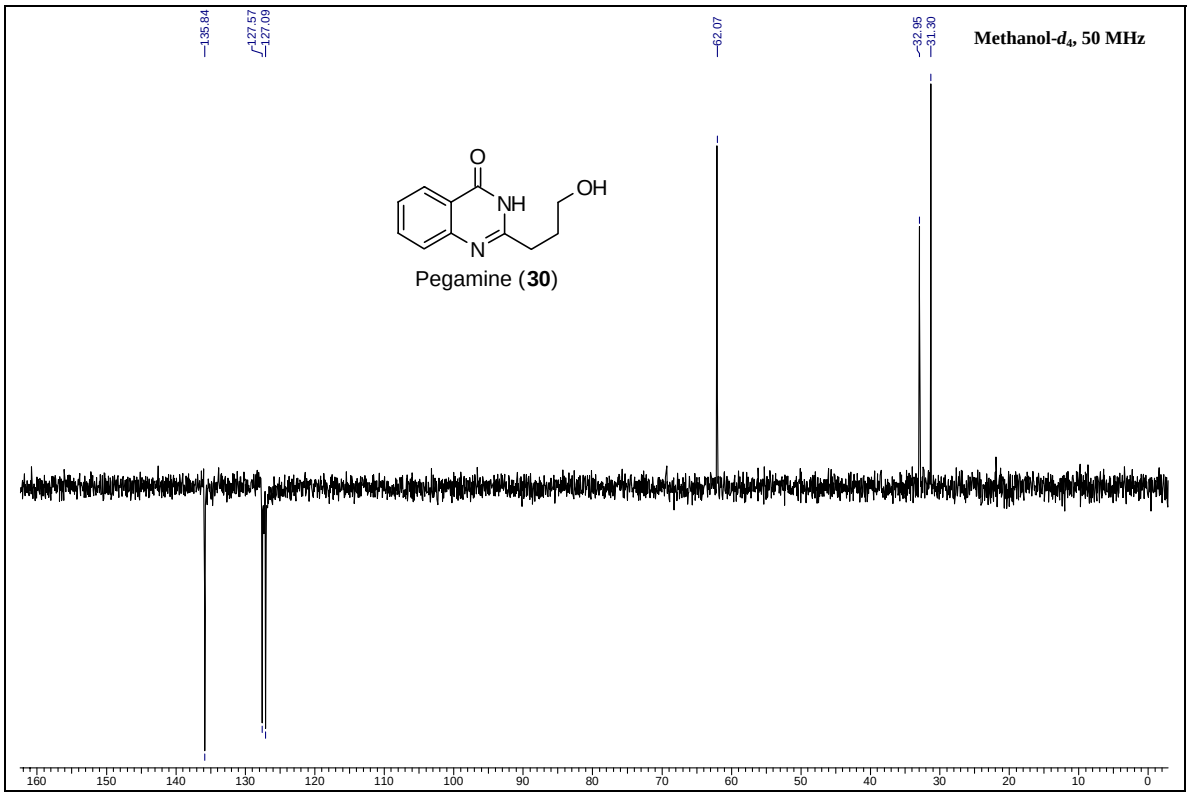

$CDCl_3$, 200 MHz
8.31
8.27
7.78
7.74
7.70
7.67
7.63
7.49
7.46
7.42
7.27
4.26
4.22
4.18
3.23
3.19
3.16
2.37
2.34
2.30
2.26
2.23
TMS
0.00
O
N
N
Deoxyvasicinone (**24**)
0.93
1.93
0.96
2.00
2.02
2.02

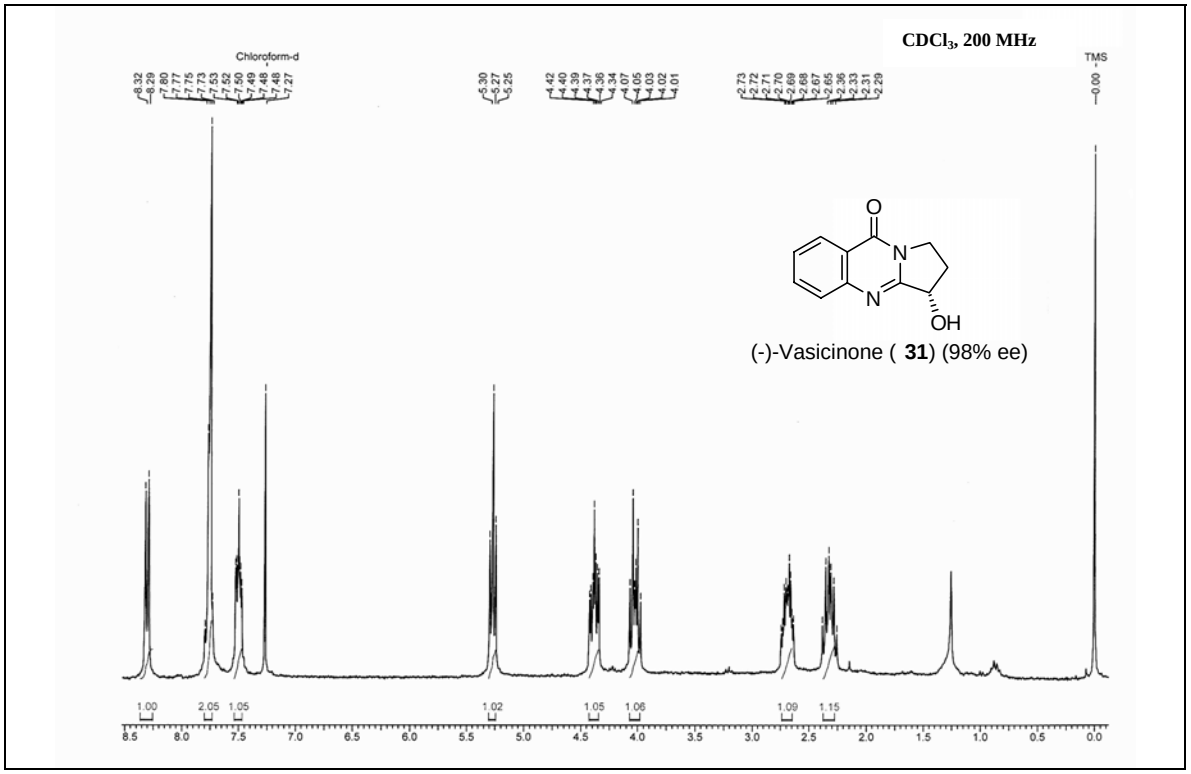

CDCl3, 50 MHz
Chloroform-d
160.73
159.26
148.97
133.90
126.59
126.15
125.96
120.30
77.00
46.27
32.30
19.29
O
N
N
Deoxyvasicinone (24)
160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

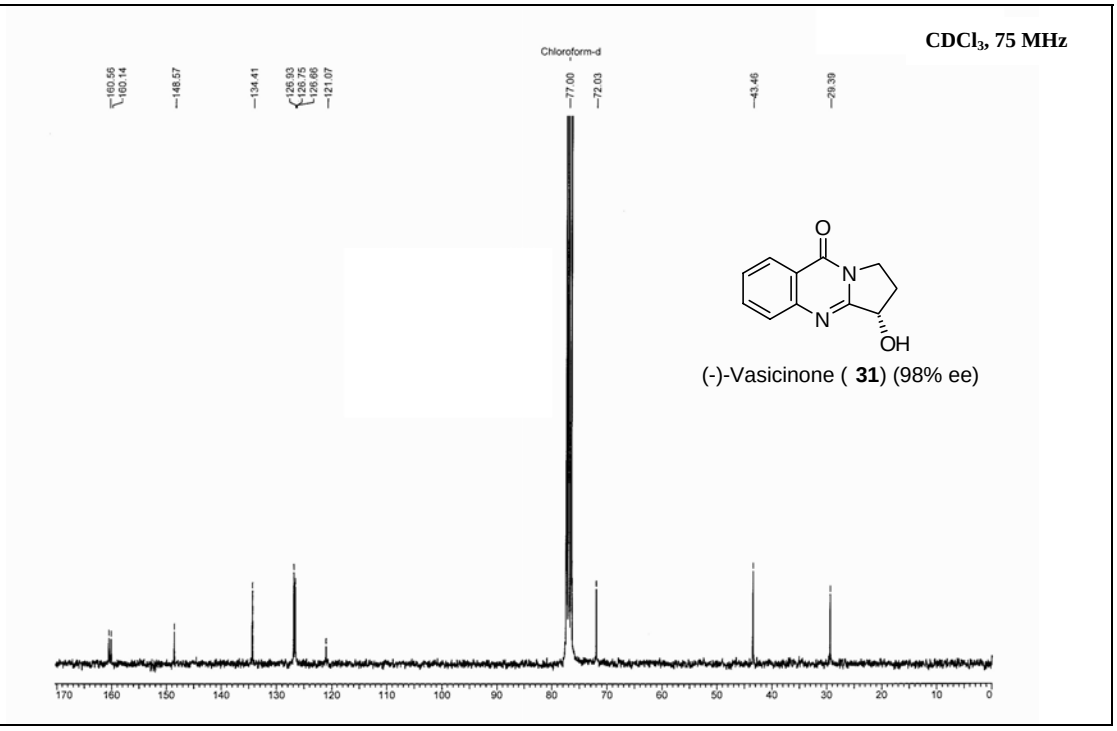

CDCl3, 50 MHz
133.94
126.59
126.14
126.00
46.31
32.30
19.29
O
N
N
Deoxyvasicinone (24)
160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

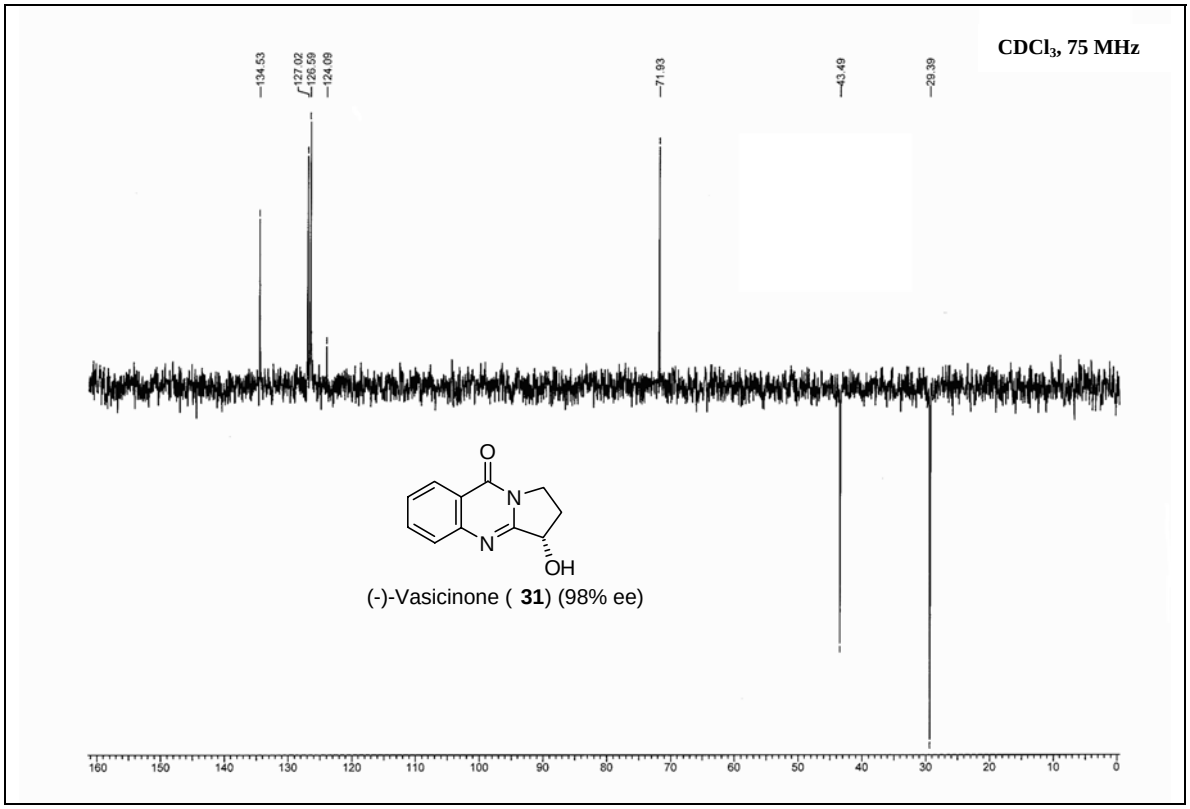

Methanol-d_4, 200 MHz
Methanol-d4
8.19
8.14
7.83
7.79
7.75
7.65
7.60
7.51
7.47
7.44
4.89
3.69
3.65
3.62
3.30
2.79
2.76
2.72
2.07
2.04
2.01
1.97
1.93
O
NH
OH
N
Pegamine (**30**)
1.00
1.08
1.00
2.29
2.25
2.35
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

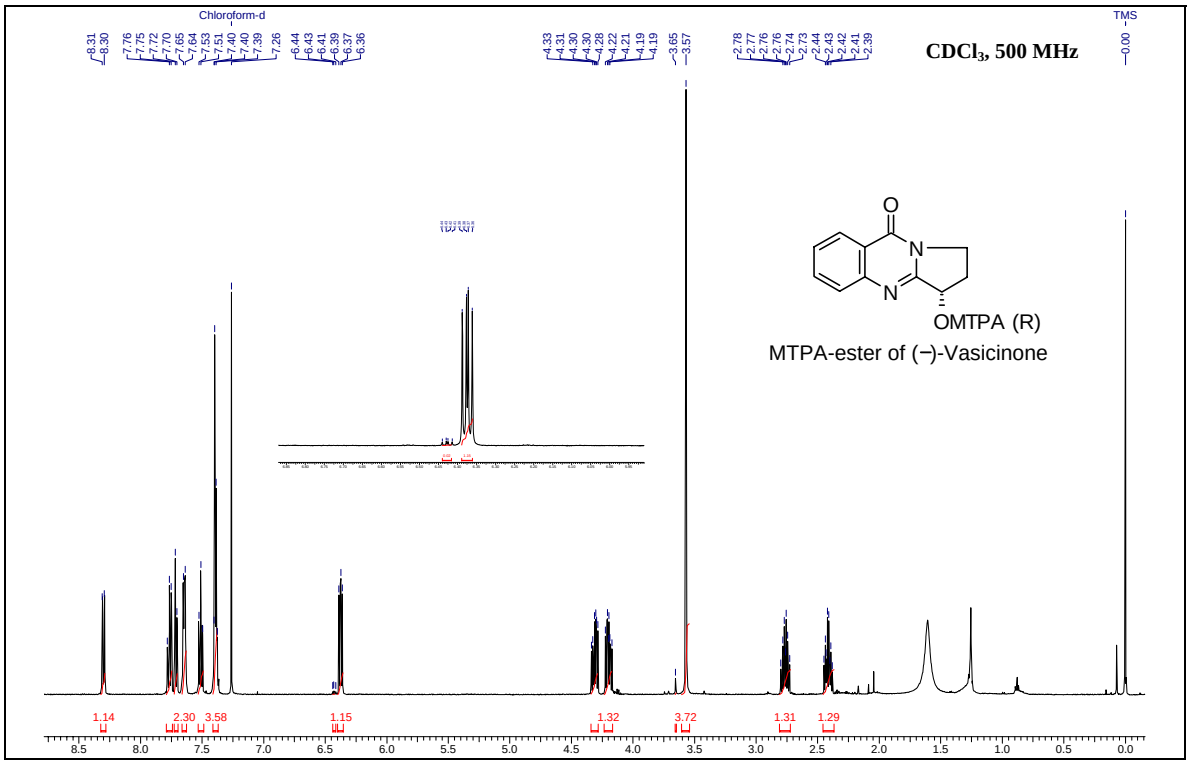

Methanol-d_4, 50 MHz
Methanol-d4
159.32
150.06
135.87
127.60
127.38
127.31
127.12
121.83
62.14
49.05
32.99
31.30
O
NH
OH
N
Pegamine (**30**)
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20

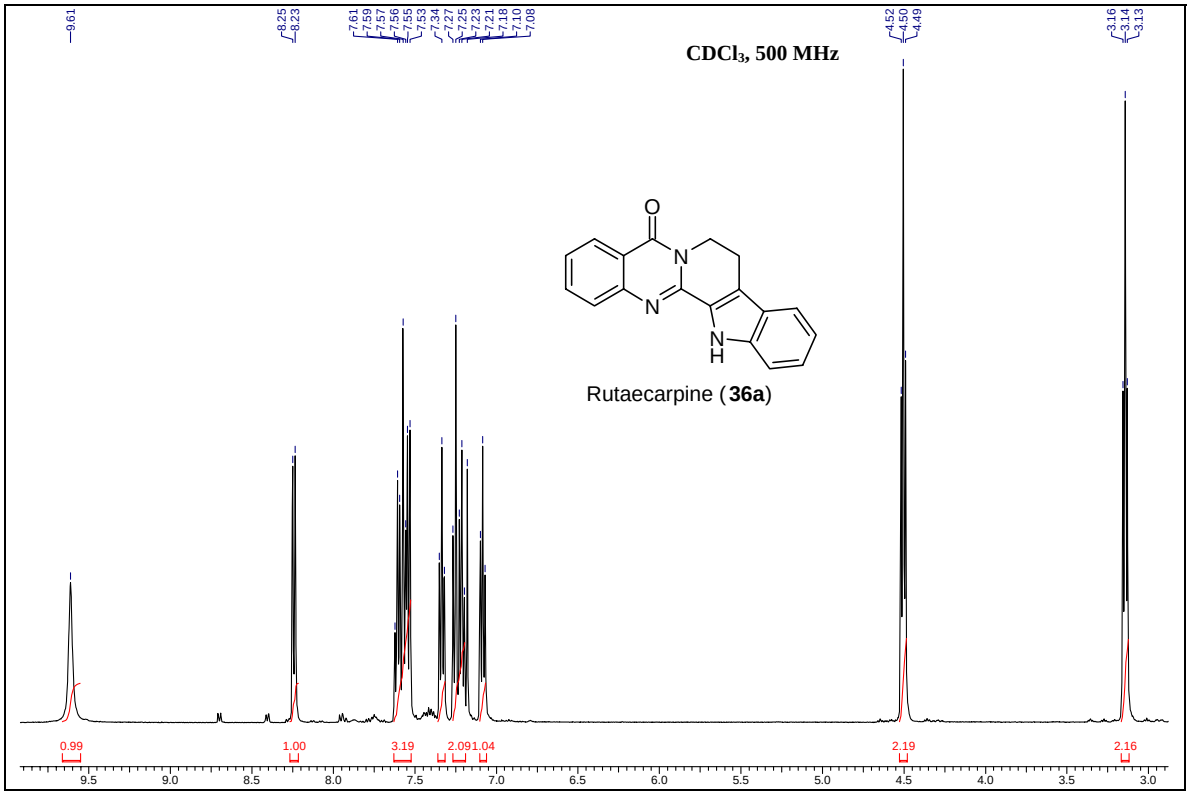

Methanol-d_4, 50 MHz
135.84
127.57
127.09
62.07
32.95
31.30
O
NH
OH
N
Pegamine (**30**)
160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

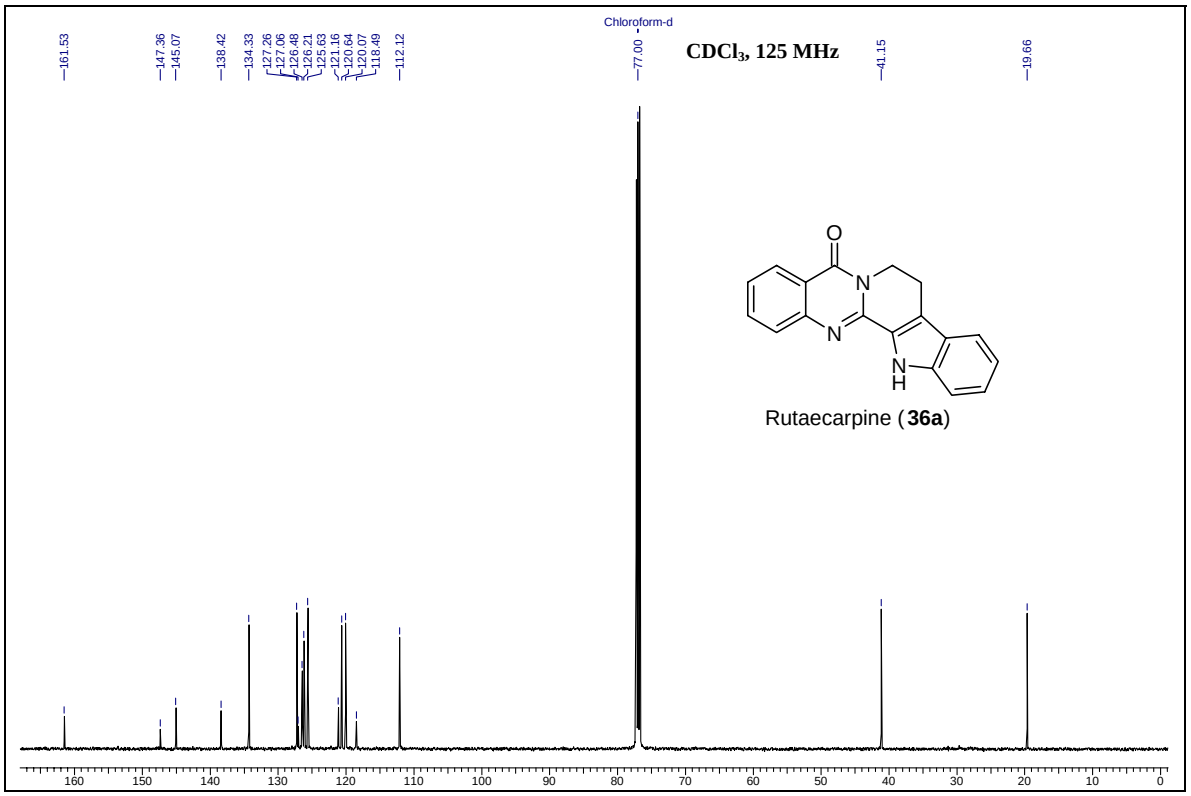

$CDCl_3$, 200 MHz
Chloroform-d
TMS
O
N
N
OH
(-)-Vasicinone (**31**) (98% ee)
1.00 2.05 1.05 1.02 1.05 1.06 1.09 1.15
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0

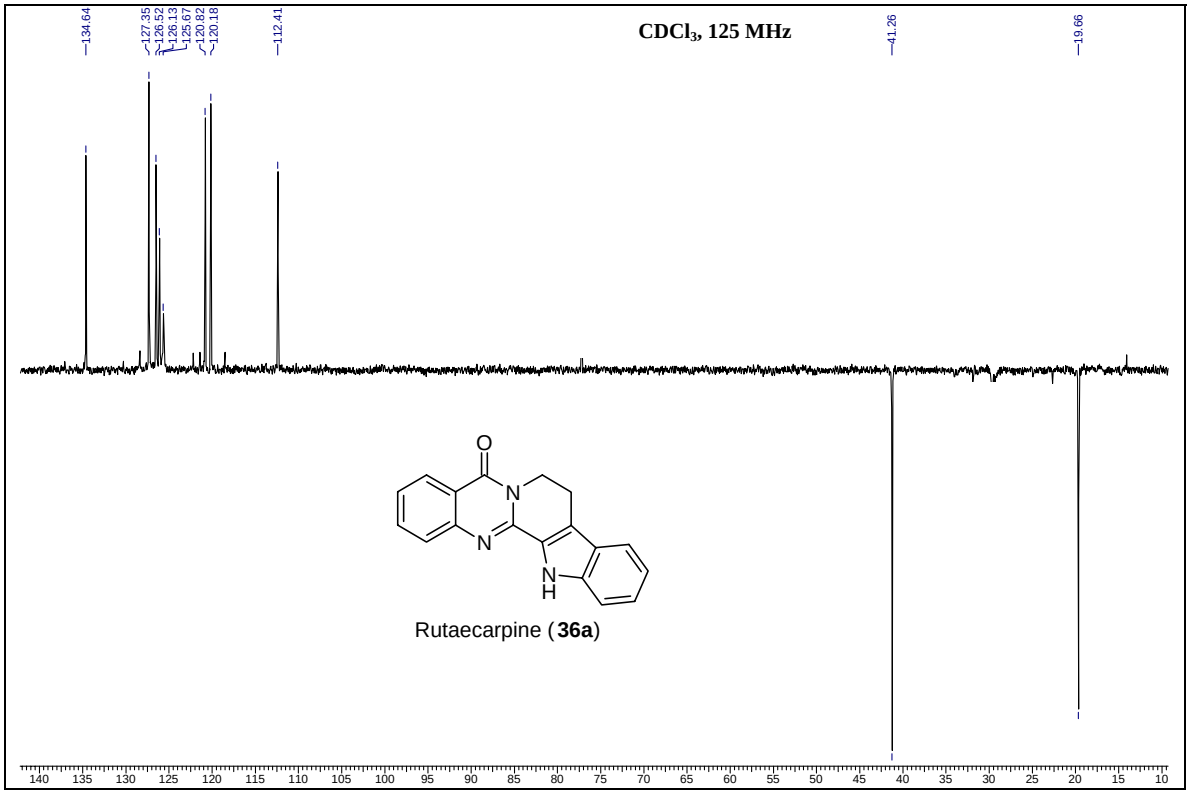

CDCl3, 75 MHz
Chloroform-d
160.56
160.14
148.57
134.41
126.93
126.75
126.66
121.07
77.00
72.03
43.46
29.39
O
N
N
OH
(-)-Vasicinone (31) (98% ee)

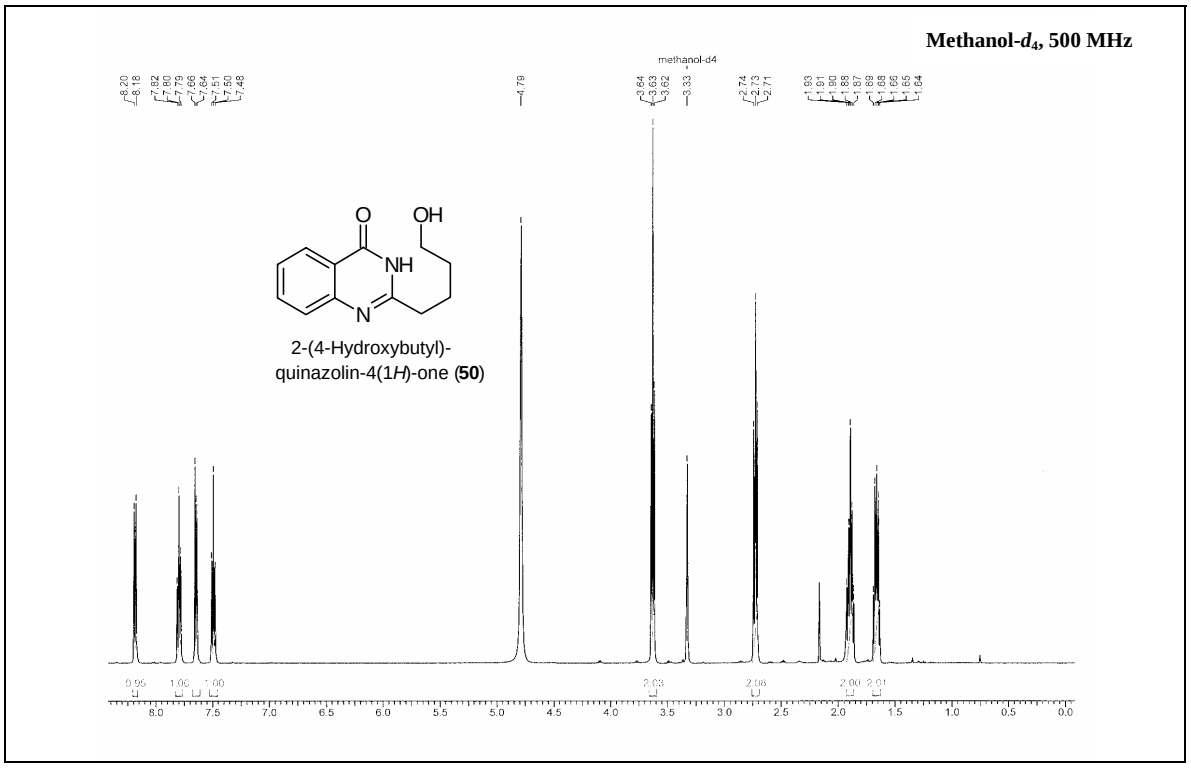

CDCl3, 75 MHz
134.53
127.02
126.59
124.09
71.93
43.49
29.39
O
N
N
OH
(-)-Vasicinone (31) (98% ee)

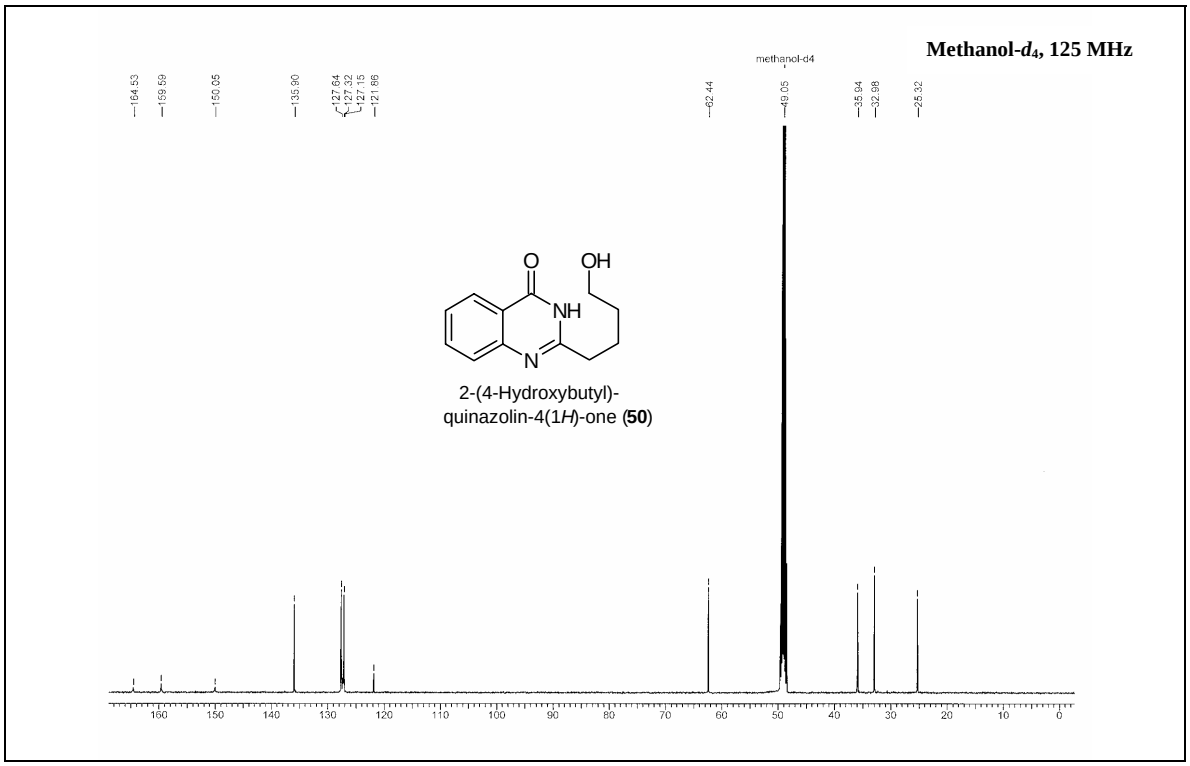

Chloroform-d
TMS
CDCl3, 500 MHz
OMTPA (R)
MTPA-ester of (−)-Vasicinone

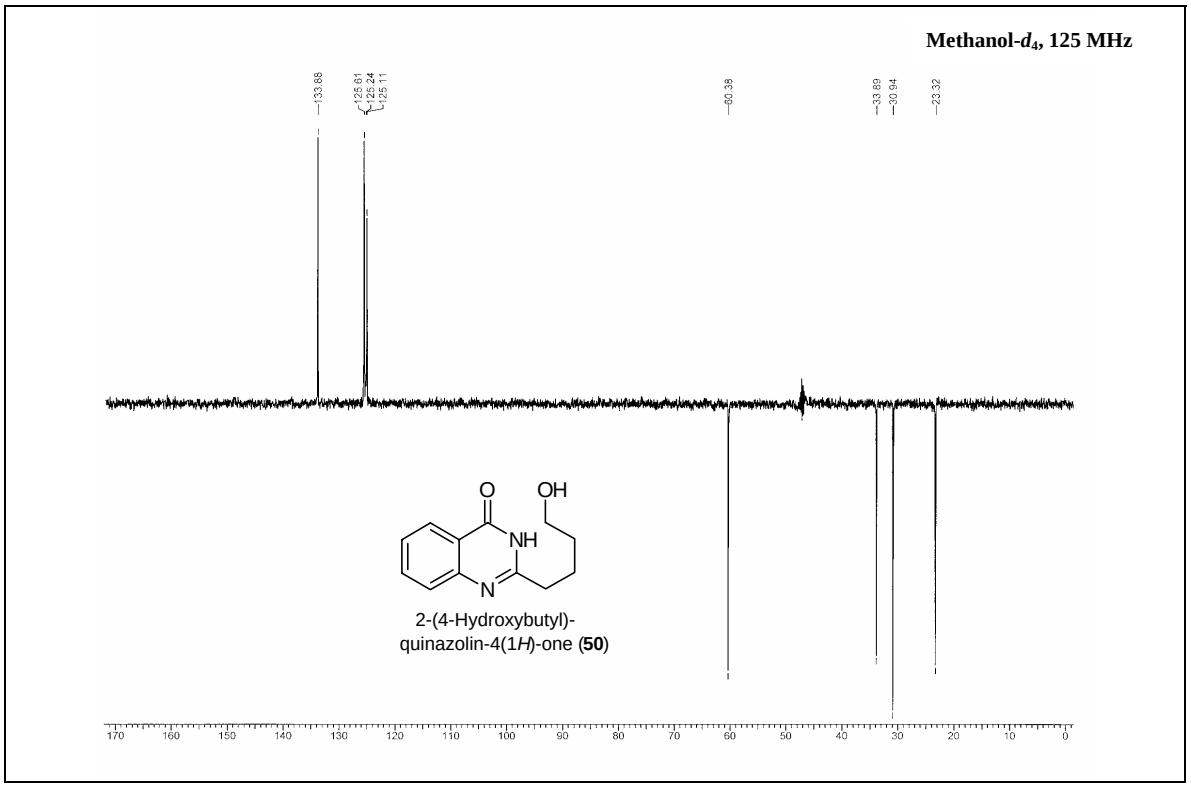

CDCl3, 500 MHz
Rutaecarpine (36a)

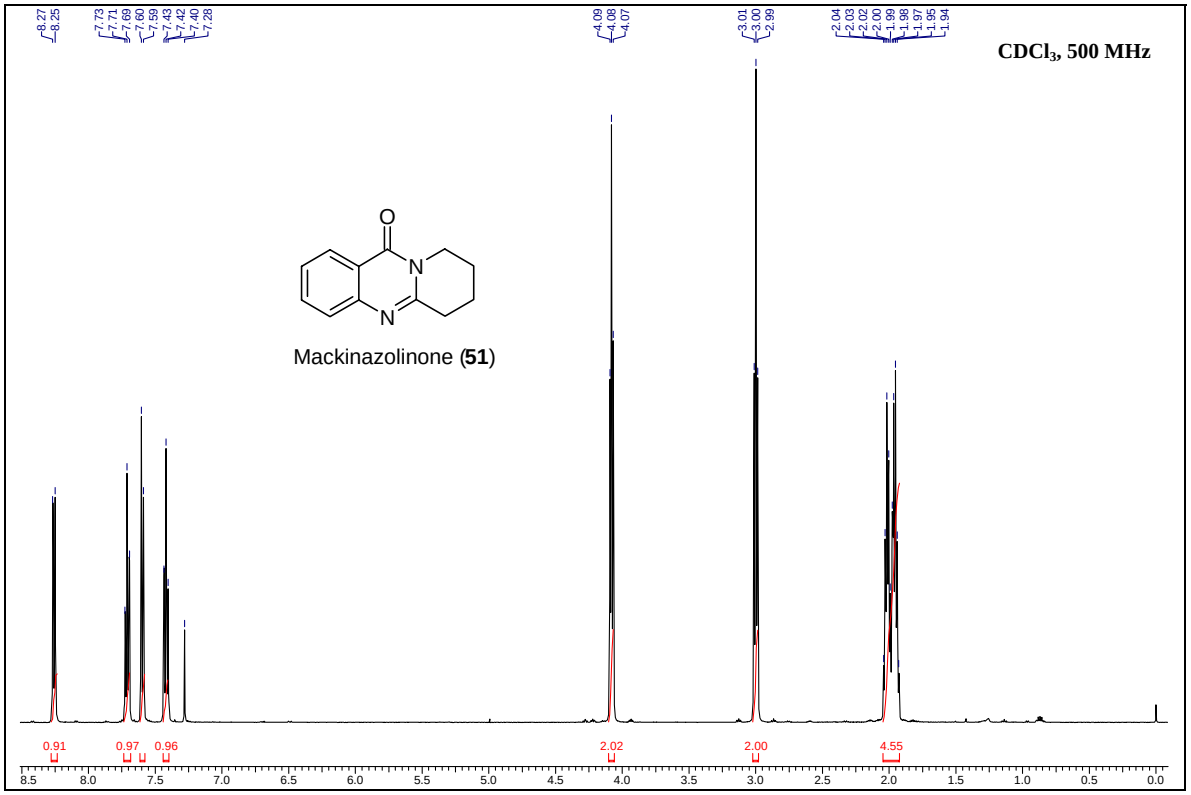

Chloroform-d
161.53
147.36
145.07
138.42
134.33
127.26
127.06
126.48
126.21
125.63
121.16
120.64
120.07
118.49
112.12
77.00
41.15
19.66
CDCl3, 125 MHz
O
N
N
N
H
Rutaecarpine (36a)

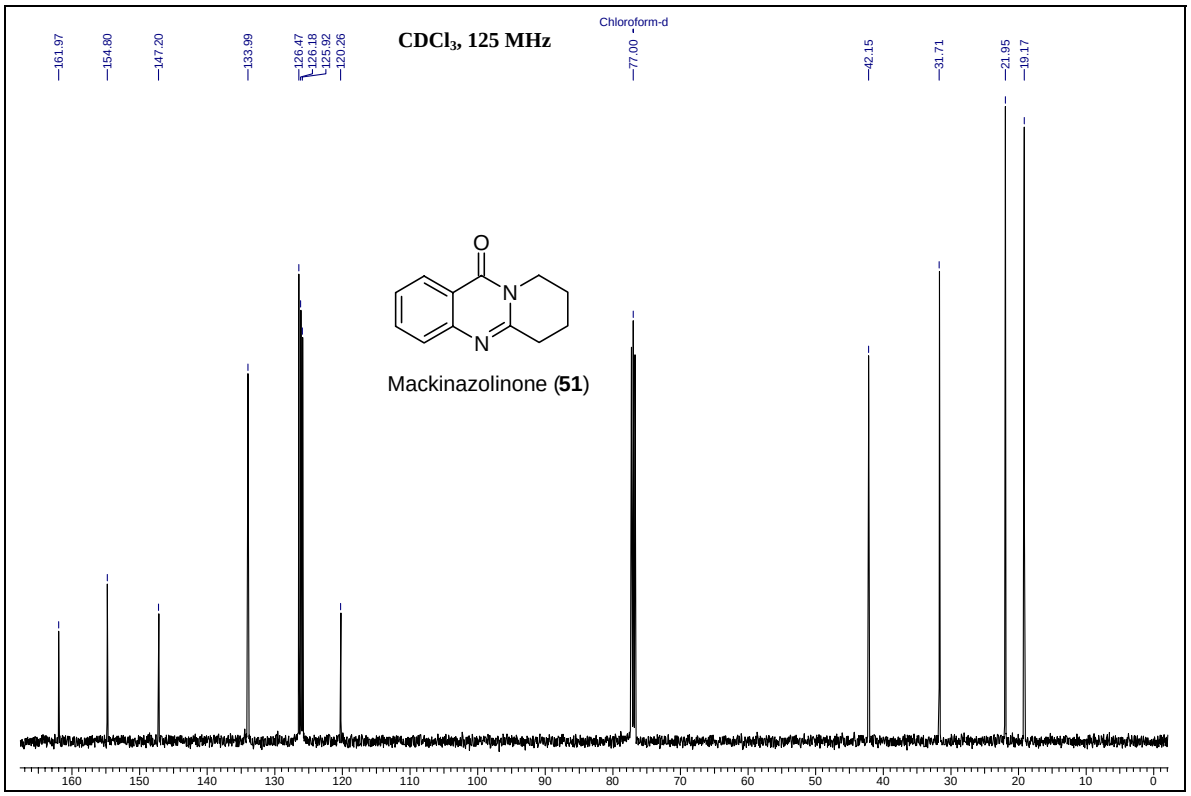

134.64
127.35
126.52
126.13
125.67
120.82
120.18
112.41
41.26
19.66
CDCl3, 125 MHz
O
N
N
N
H
Rutaecarpine (36a)

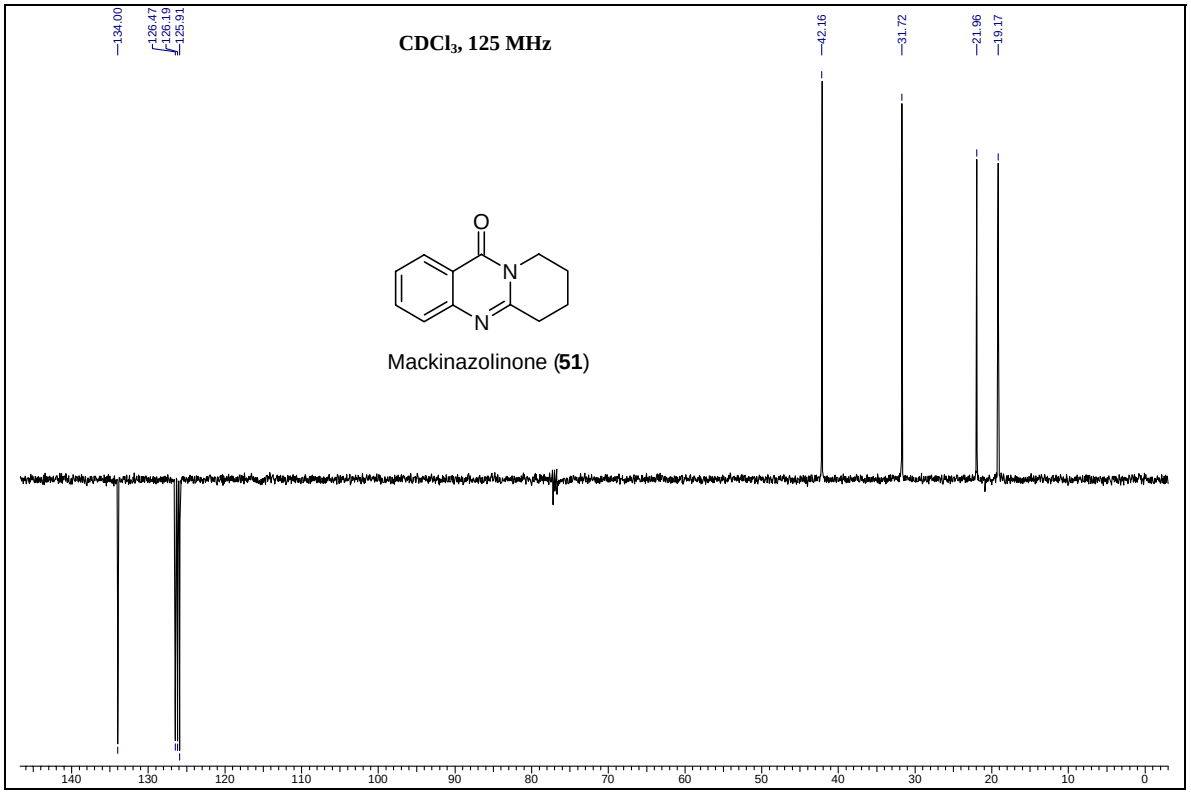

Methanol-d_4, 500 MHz
methanol-d4
8.20
8.18
7.82
7.80
7.79
7.66
7.64
7.51
7.50
7.48
4.78
3.64
3.63
3.62
3.33
2.74
2.73
2.71
1.93
1.91
1.90
1.88
1.87
1.68
1.66
1.65
1.64
O
OH
NH
N
2-(4-Hydroxybutyl)-
quinazolin-4(1*H*)-one (**50**)
0.99
1.00
1.00
2.03
2.08
2.00
2.01
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

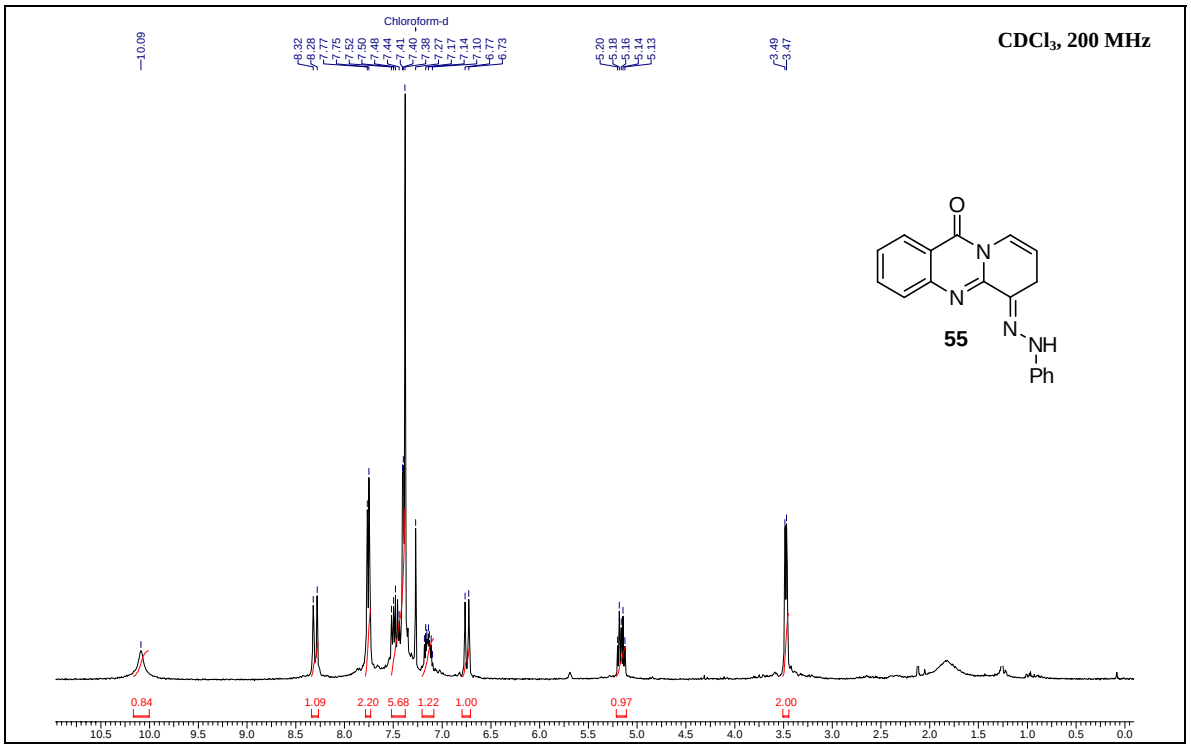

Methanol-d_4, 125 MHz
methanol-d4
164.53
159.59
150.05
135.90
127.64
127.32
127.15
121.86
62.44
49.05
35.94
32.98
25.32
O
OH
NH
N
2-(4-Hydroxybutyl)-
quinazolin-4(1*H*)-one (**50**)
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

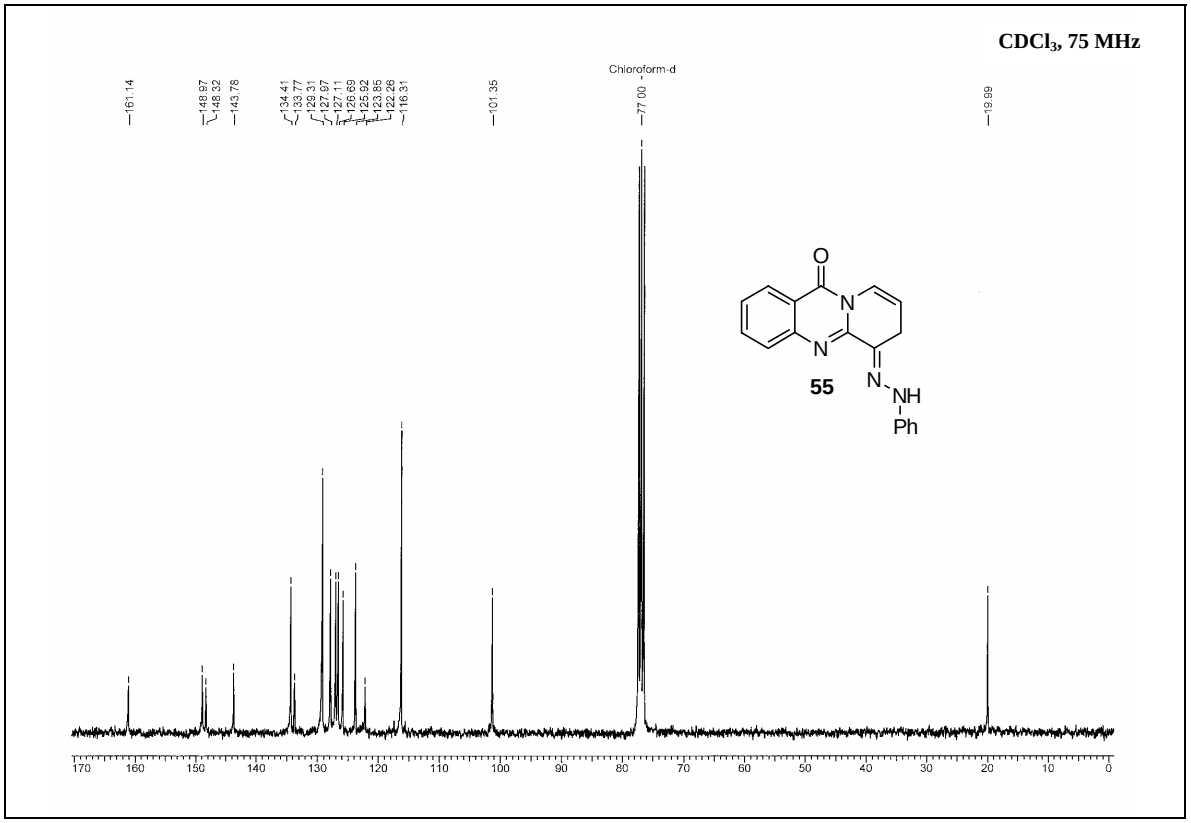

Methanol-d_4, 125 MHz
133.88
125.61
125.24
125.11
60.38
33.89
30.94
23.32
O
OH
NH
N
2-(4-Hydroxybutyl)-
quinazolin-4(1*H*)-one (**50**)

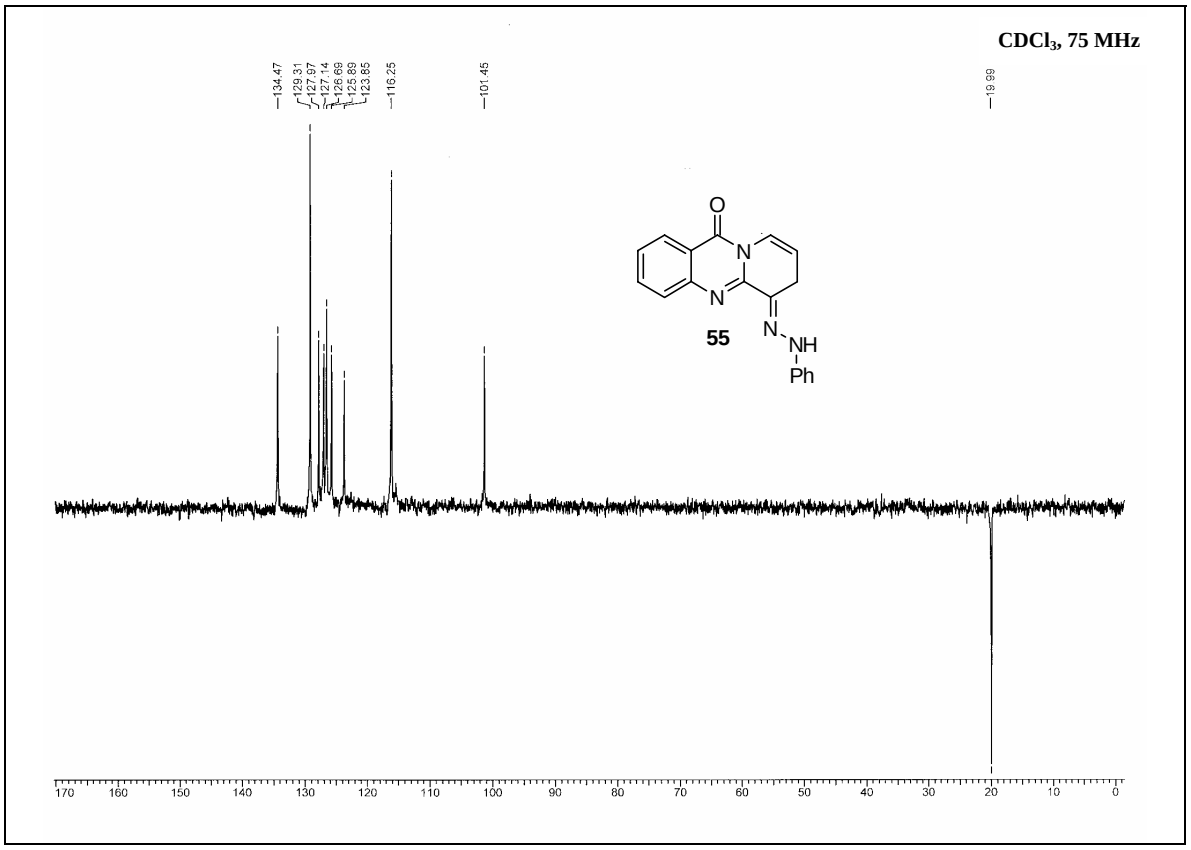

CDCl$_3$, 500 MHz
8.27
8.25
7.73
7.71
7.69
7.60
7.59
7.43
7.42
7.40
7.28
4.09
4.08
4.07
3.01
3.00
2.99
2.04
2.03
2.02
2.00
1.99
1.98
1.97
1.95
1.94
O
N
N
Mackinazolinone (**51**)
0.91
0.97
0.96
2.02
2.00
4.55

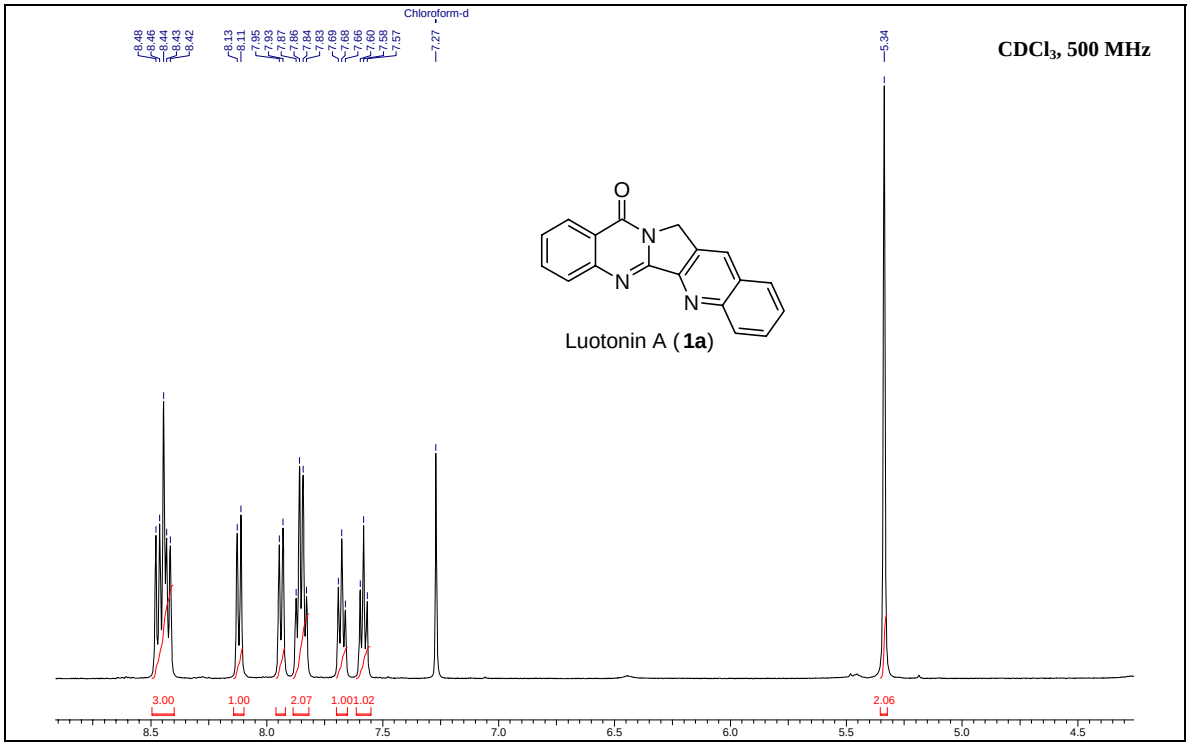

CDCl3, 125 MHz
Chloroform-d
161.97
154.80
147.20
133.99
126.47
126.18
125.92
120.26
77.00
42.15
31.71
21.95
19.17
O
N
N
Mackinazolinone (51)

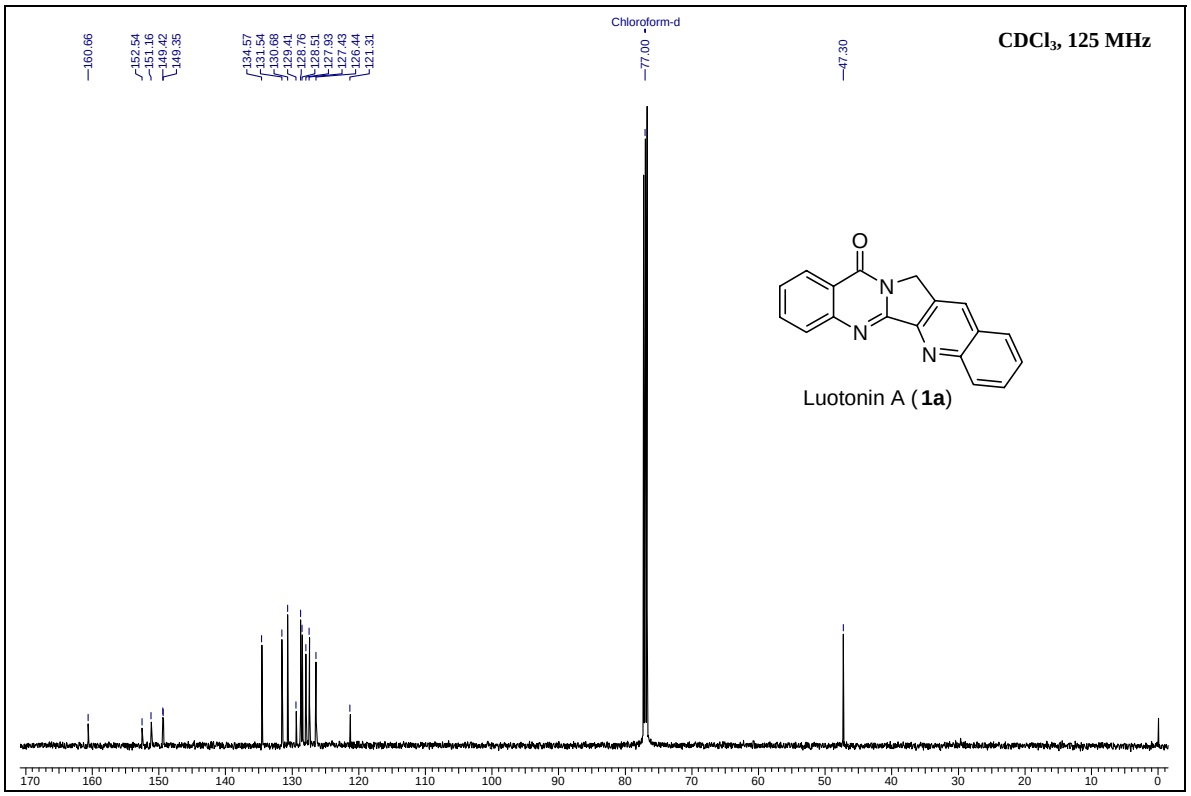

CDCl3, 125 MHz
134.00
126.47
126.19
125.91
42.16
31.72
21.96
19.17
O
N
N
Mackinazolinone (51)

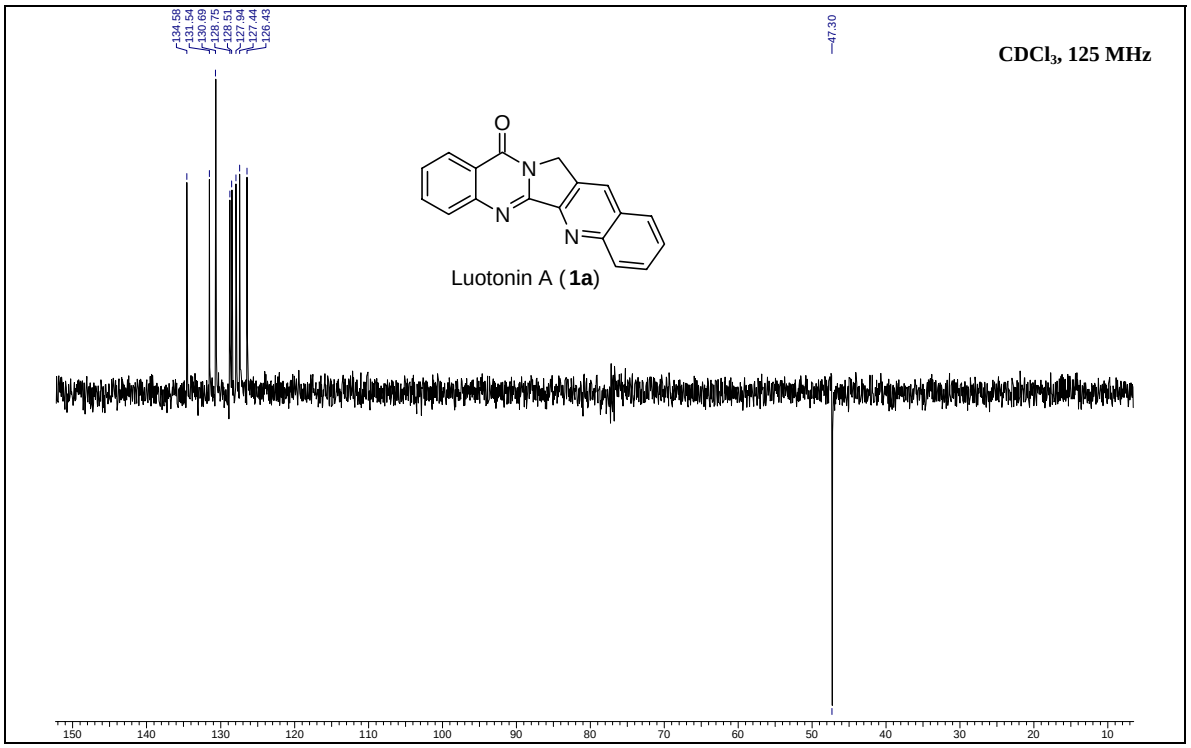

CDCl3, 200 MHz
Chloroform-d
10.09
8.32
8.28
7.77
7.75
7.52
7.50
7.48
7.44
7.41
7.40
7.38
7.27
7.17
7.14
7.10
6.77
6.73
5.20
5.18
5.16
5.14
5.13
3.49
3.47
0.84
1.09
2.20
5.68
1.22
1.00
0.97
2.00
55
O
N
N
N
NH
Ph

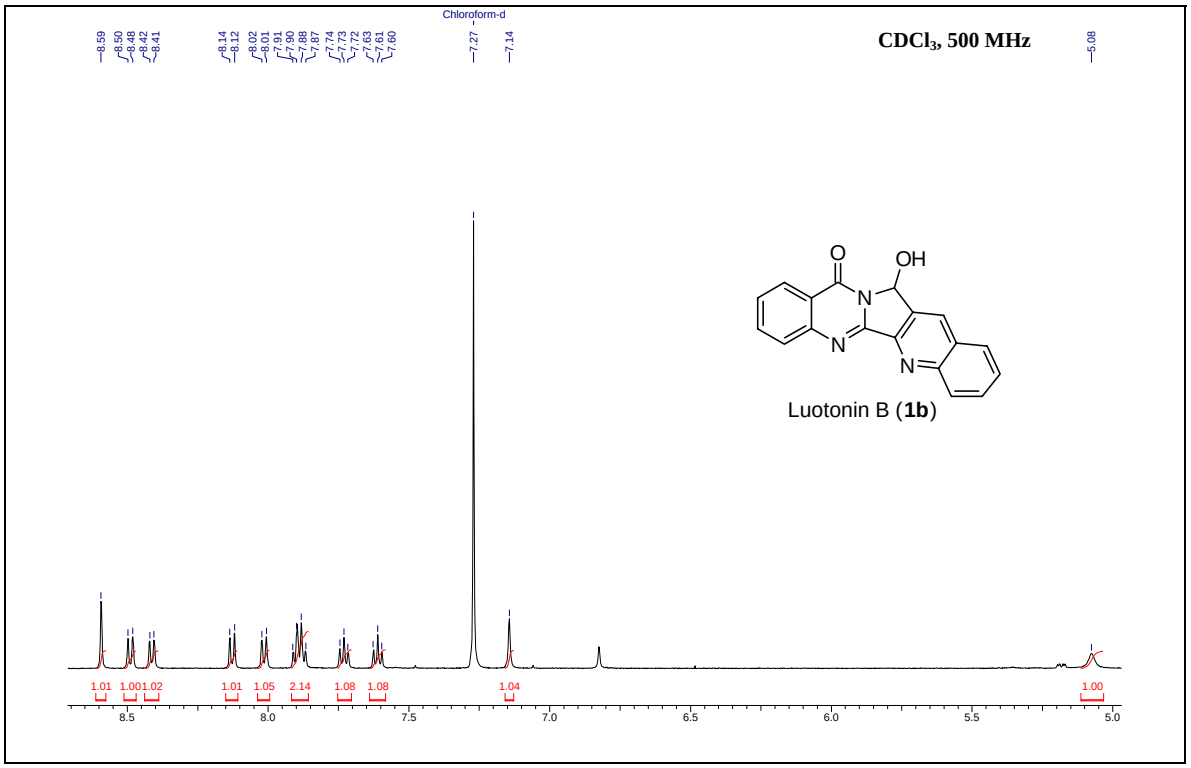

CDCl3, 75 MHz
Chloroform-d
161.14
148.97
148.32
143.76
134.41
133.77
129.31
127.97
127.11
126.69
125.92
123.85
122.26
116.31
101.35
77.00
19.99
55
O
N
N
N
NH
Ph

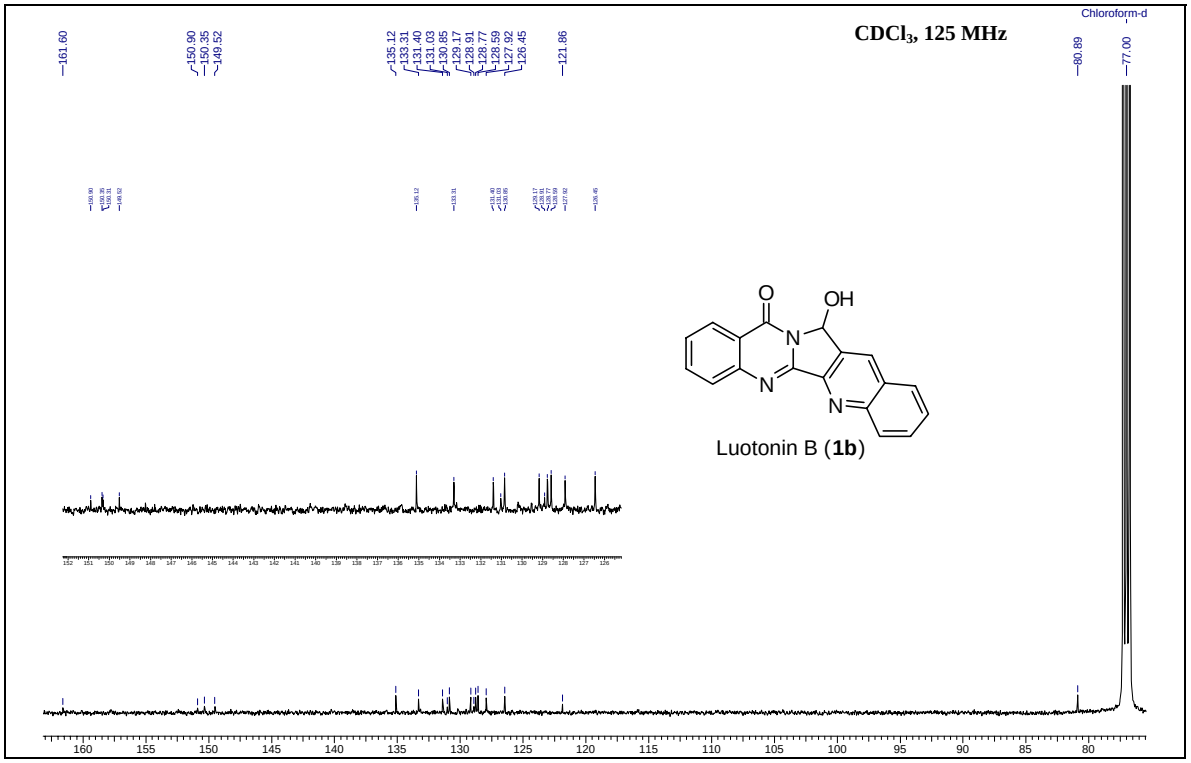

CDCl3, 75 MHz
134.47
129.31
127.97
127.14
126.69
125.89
123.85
116.25
101.45
19.99
55
O
N
N
N
NH
Ph
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

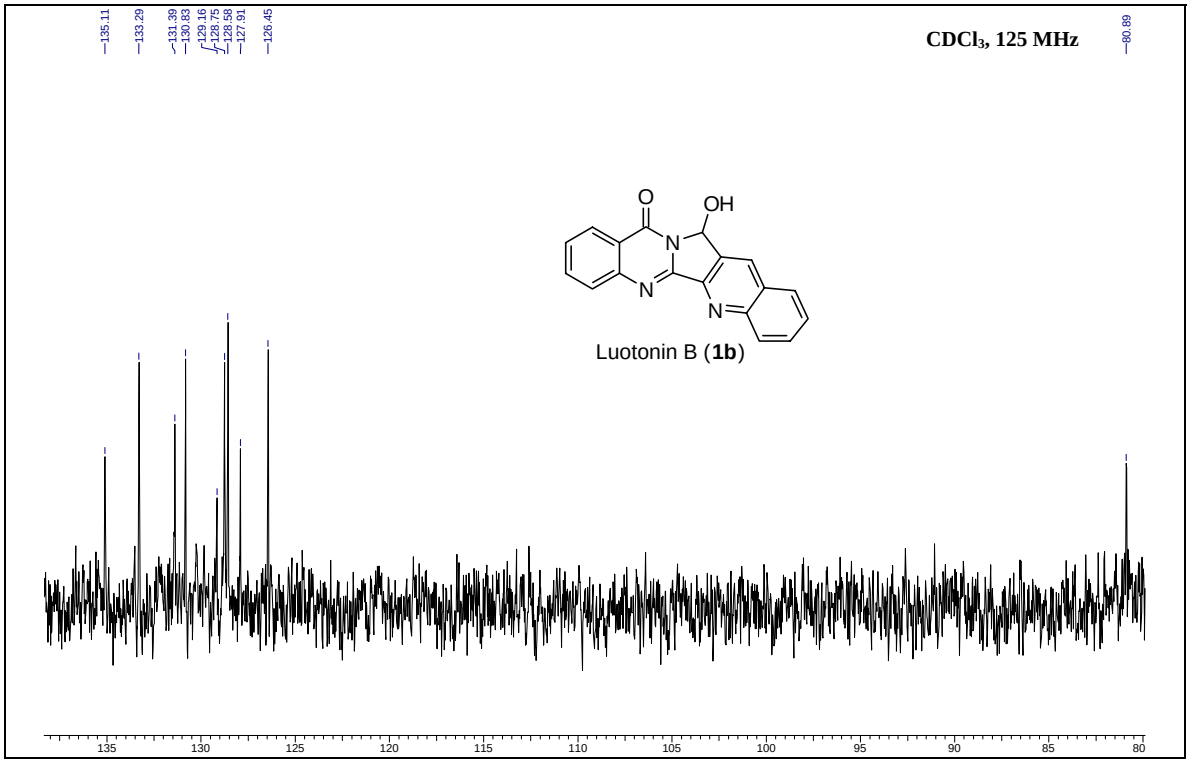

CDCl3, 500 MHz
Chloroform-d
8.48
8.46
8.44
8.43
8.42
8.13
8.11
7.95
7.93
7.87
7.86
7.84
7.83
7.69
7.68
7.66
7.60
7.58
7.57
7.27
5.34
O
N
N
N
Luotonin A (1a)
3.00
1.00
2.07
1.00
1.02
2.06
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5

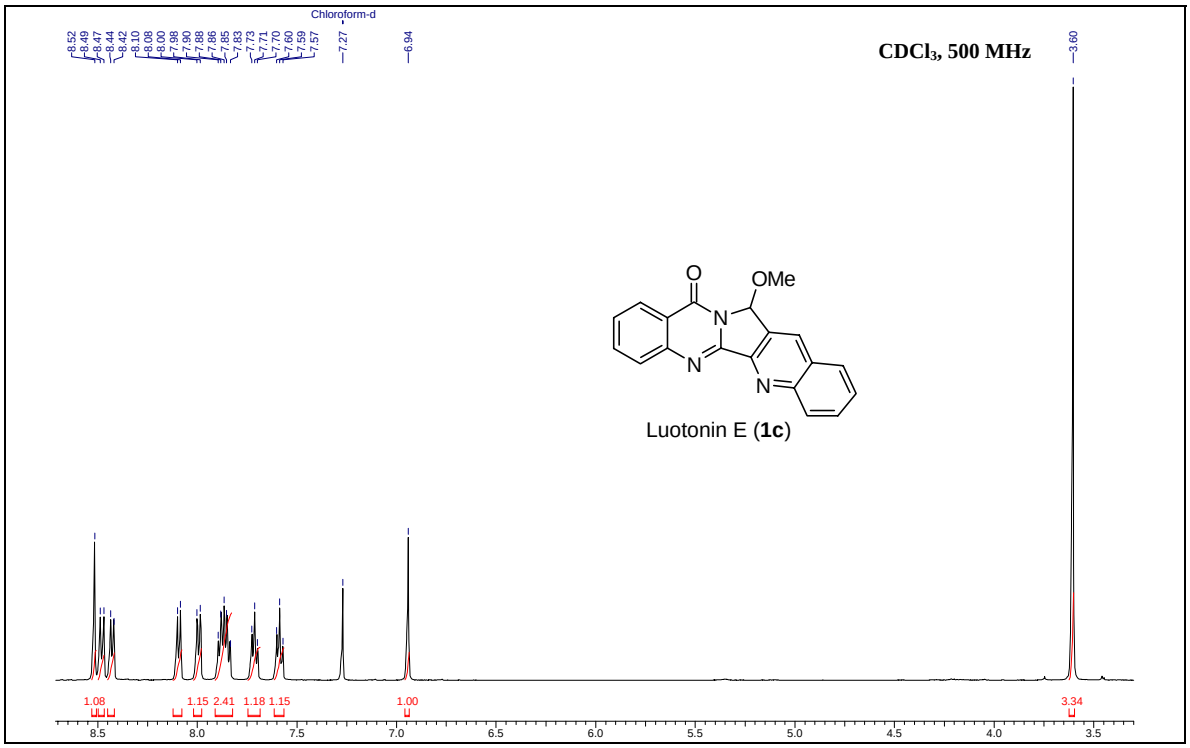

CDCl3, 125 MHz
Chloroform-d
160.66
152.54
151.16
149.42
149.35
134.57
131.54
130.68
129.41
128.76
128.51
127.93
127.43
126.44
121.31
77.00
47.30
Luotonin A (1a)

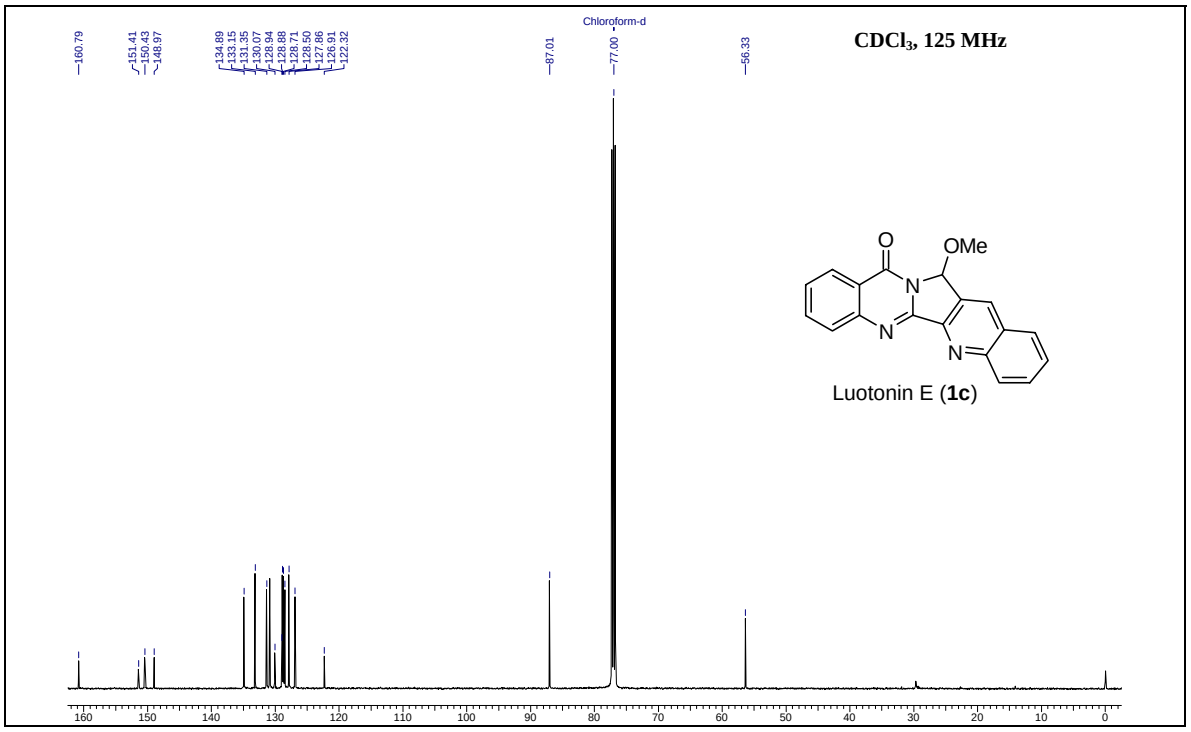

CDCl3, 125 MHz
134.58
131.54
130.69
128.75
128.51
127.94
127.44
126.43
47.30
Luotonin A (1a)

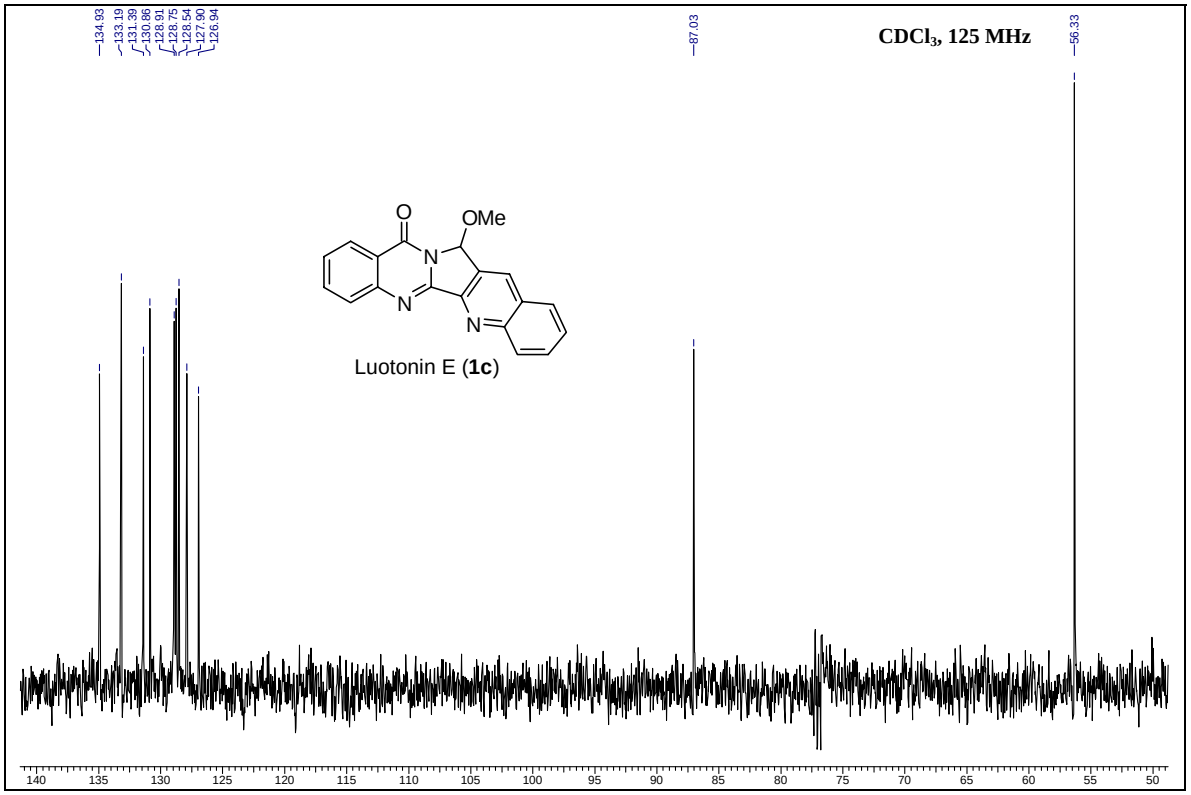

CDCl3, 500 MHz
Chloroform-d
8.59
8.50
8.48
8.42
8.41
8.14
8.12
8.02
8.01
7.91
7.90
7.88
7.87
7.74
7.73
7.72
7.63
7.61
7.60
7.27
7.14
5.08
1.01
1.00
1.02
1.01
1.05
2.14
1.08
1.08
1.04
1.00
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
O
OH
N
N
N
Luotonin B (1b)


CDCl3, 125 MHz
Chloroform-d
161.60
150.90
150.35
149.52
135.12
133.31
131.40
131.03
130.85
129.17
128.91
128.77
128.59
127.92
126.45
121.86
80.89
77.00
160
155
150
145
140
135
130
125
120
115
110
105
100
95
90
85
80
O
OH
N
N
N
Luotonin B (1b)

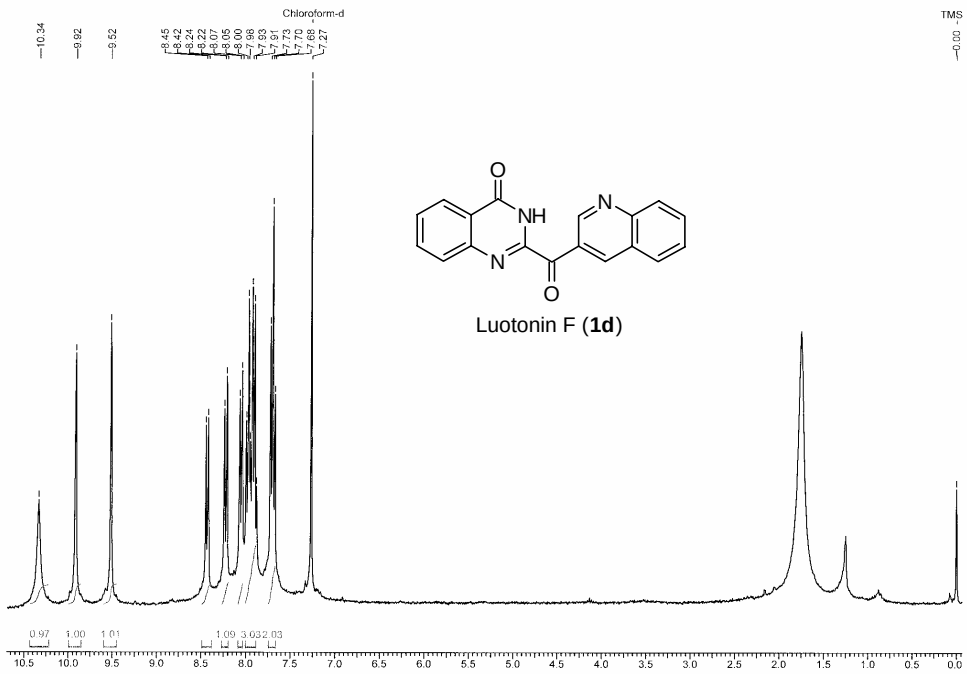

CDCl3, 125 MHz
135.11
133.29
131.39
130.83
129.16
128.75
128.58
127.91
126.45
80.89
O
OH
N
N
N
Luotonin B (1b)
135
130
125
120
115
110
105
100
95
90
85
80


CDCl3, 500 MHz
Chloroform-d
8.52
8.49
8.47
8.44
8.42
8.10
8.08
8.00
7.98
7.90
7.88
7.86
7.85
7.83
7.73
7.71
7.70
7.60
7.59
7.57
7.27
6.94
3.60
O
OMe
N
N
N
Luotonin E (1c)
1.08
1.15
2.41
1.18
1.15
1.00
3.34
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5


CDCl3, 125 MHz
Chloroform-d
160.79
151.41
150.43
148.97
134.89
133.15
131.35
130.07
129.84
129.89
128.71
128.50
127.86
126.91
122.32
87.01
77.00
56.33
O
OMe
N
N
N
Luotonin E (1c)

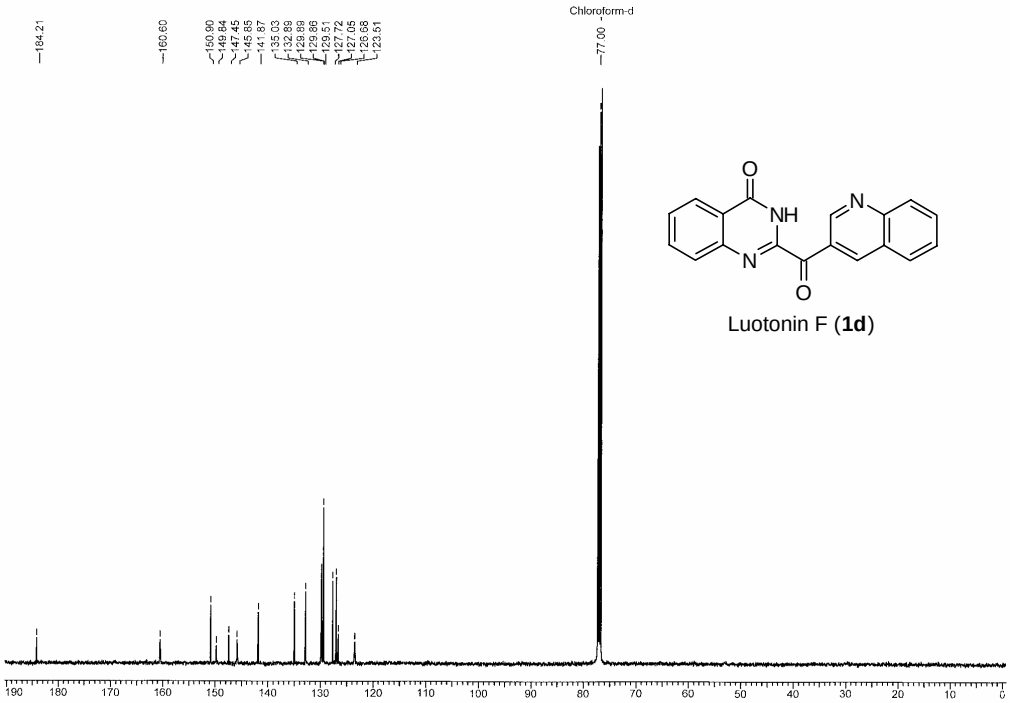

CDCl3, 125 MHz
134.93
133.19
131.39
130.86
128.91
128.75
128.54
127.90
126.94
87.03
56.33
O
OMe
N
N
N
Luotonin E (1c)

$CDCl_3$, 300 MHz



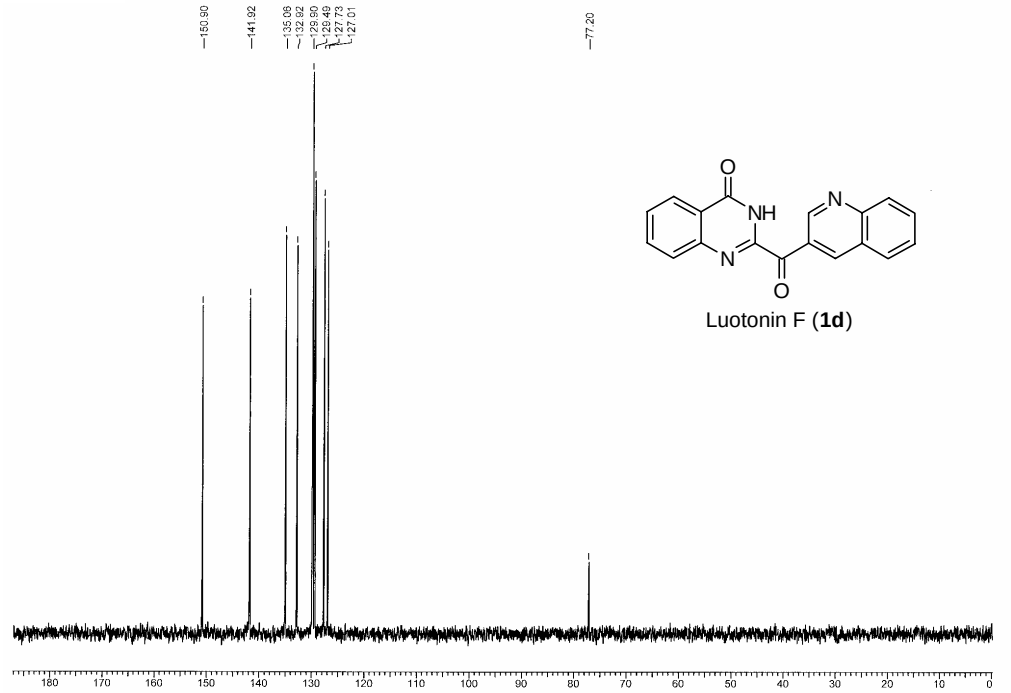
Luotonin F (**1d**)

$CDCl_3$, 125 MHz

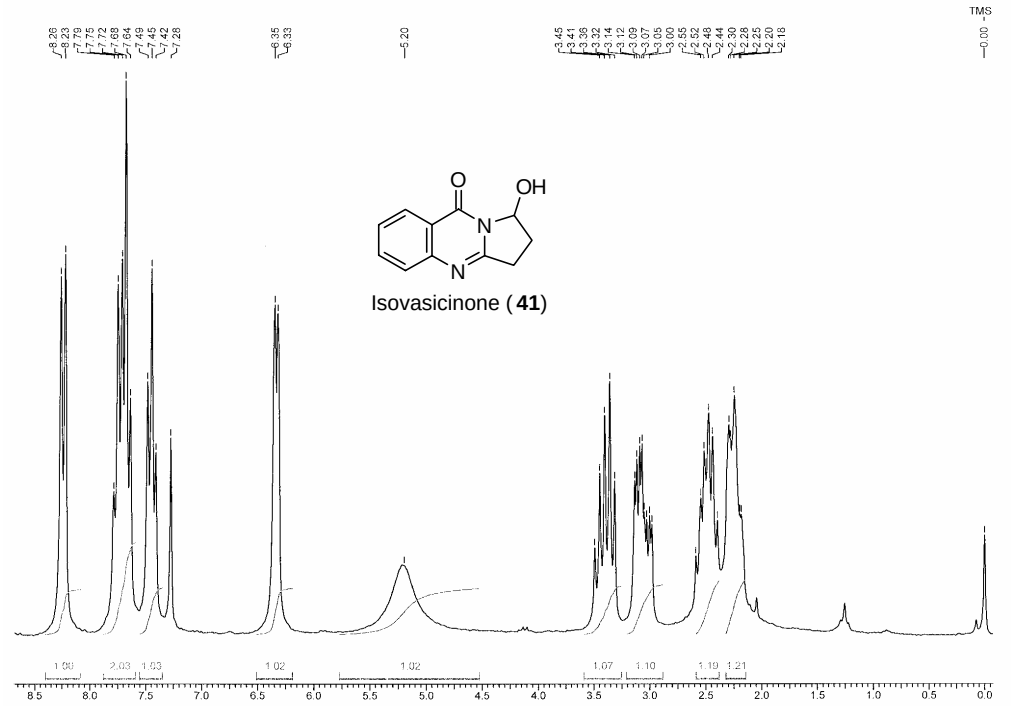


Luotonin F (**1d**)

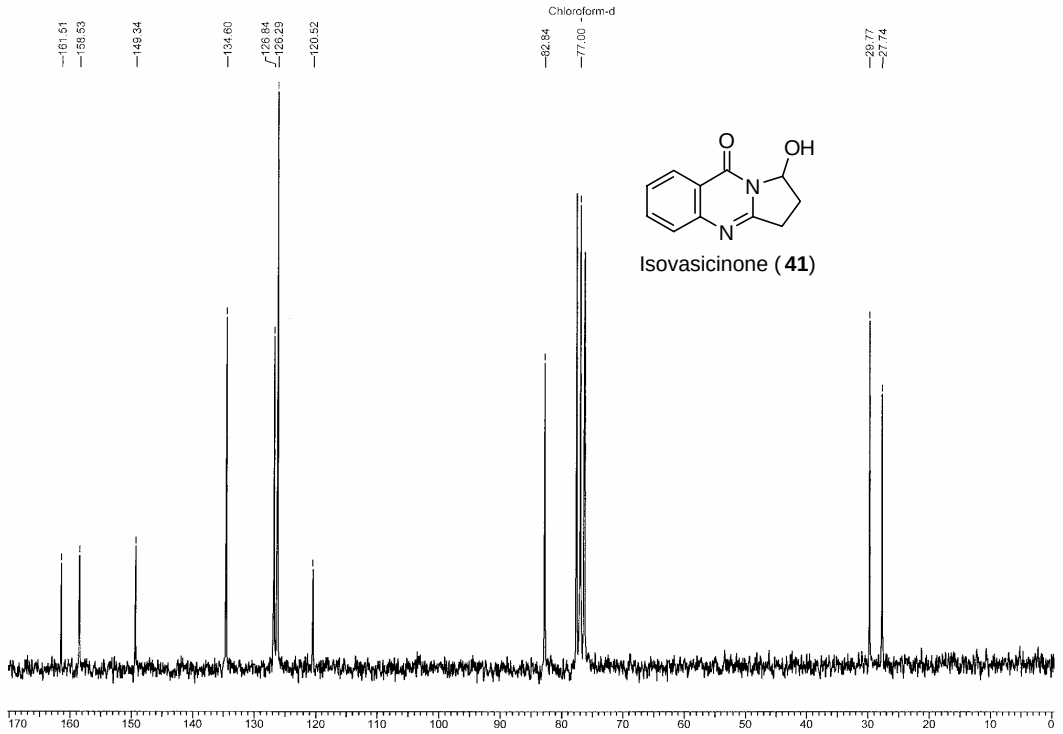
$CDCl_3$, 125 MHz



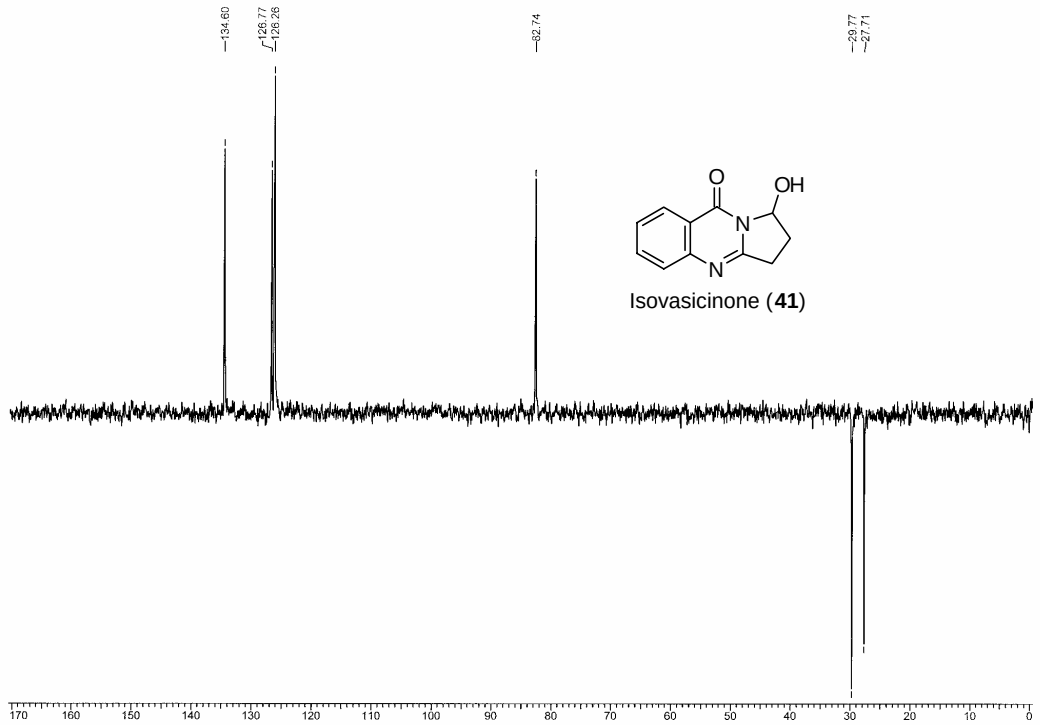
$CDCl_3$, 200 MHz

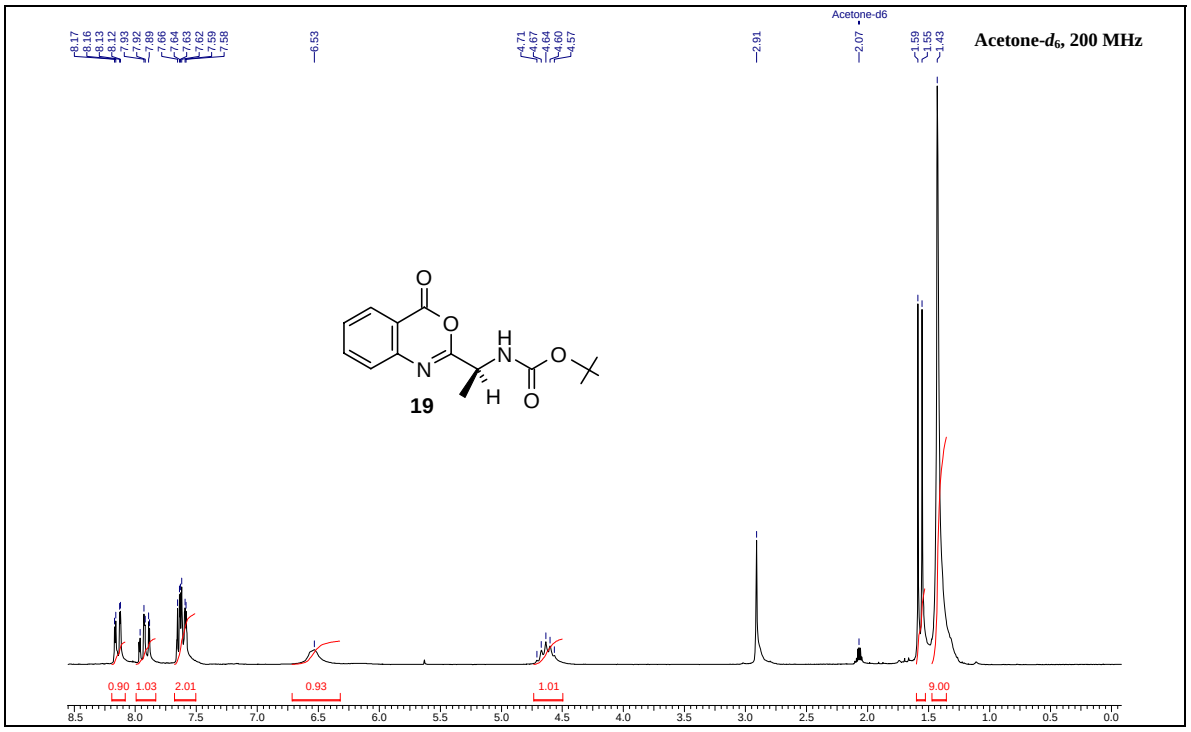


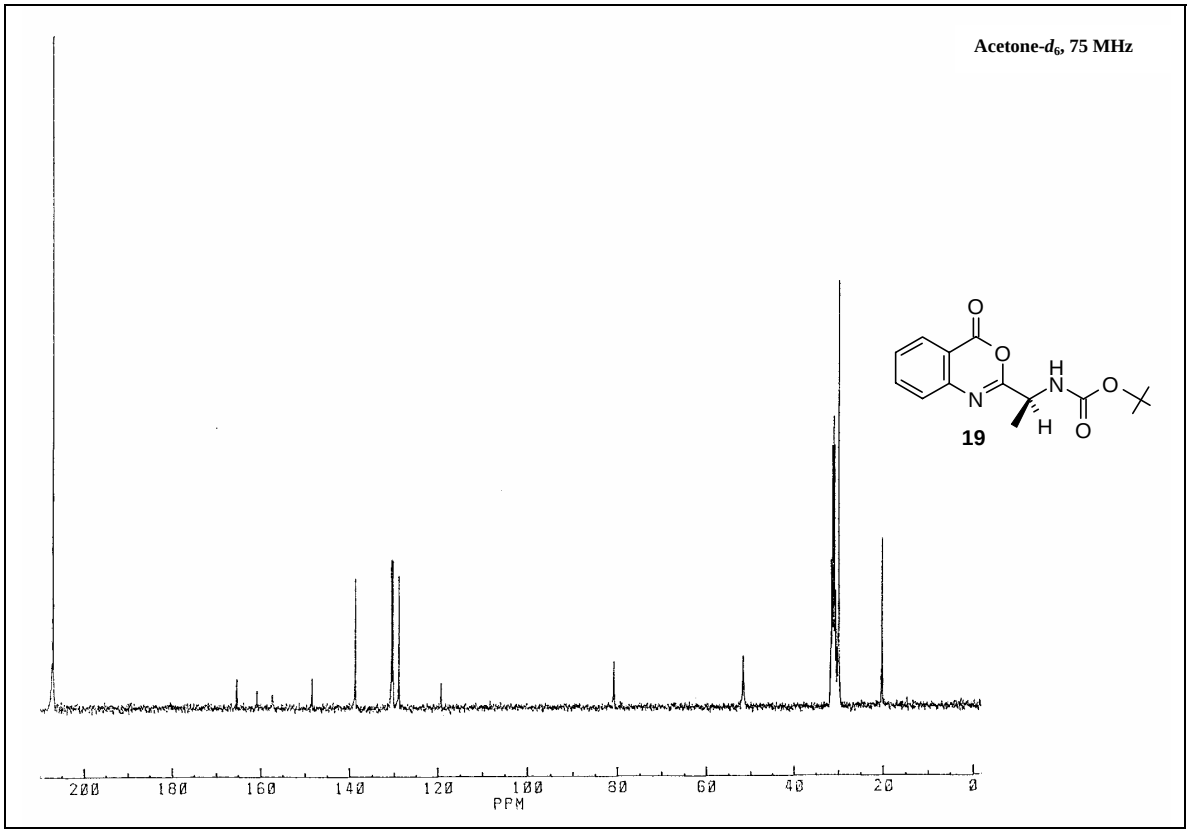
$CDCl_3$, 50 MHz

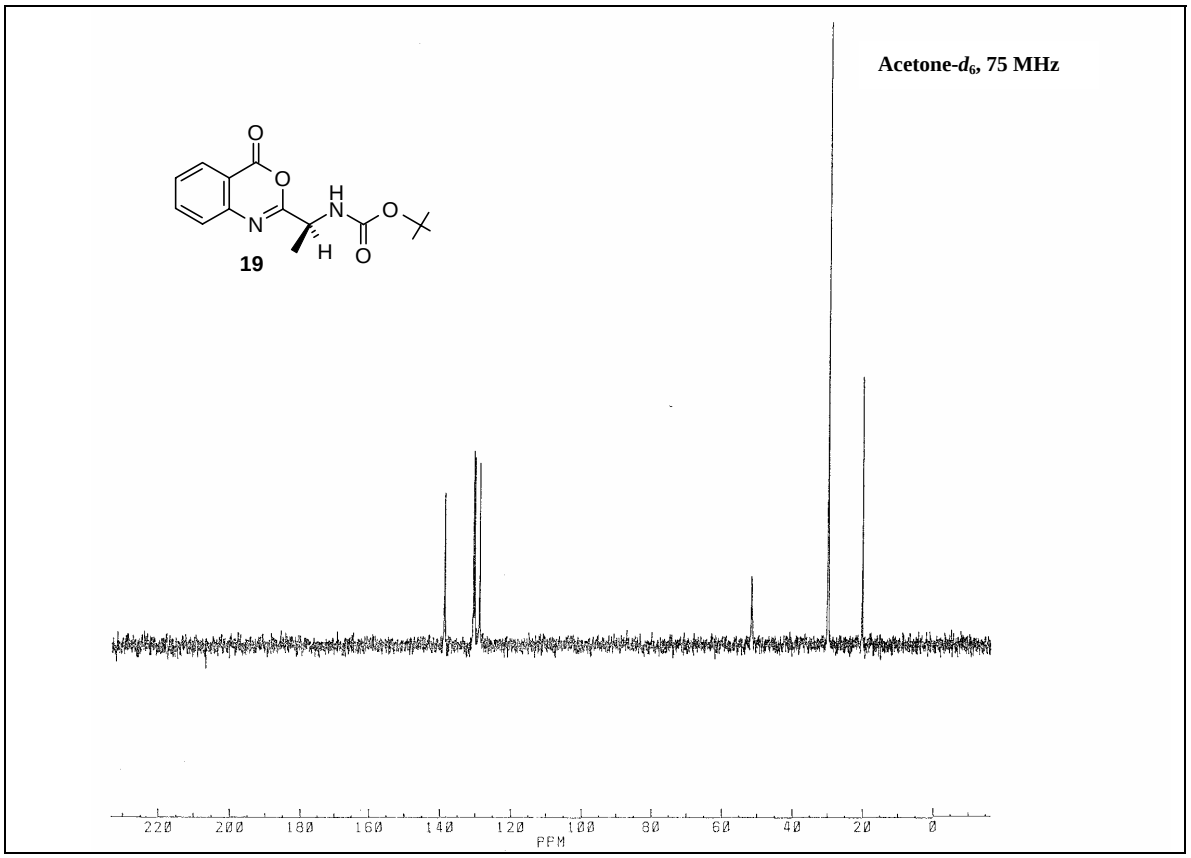


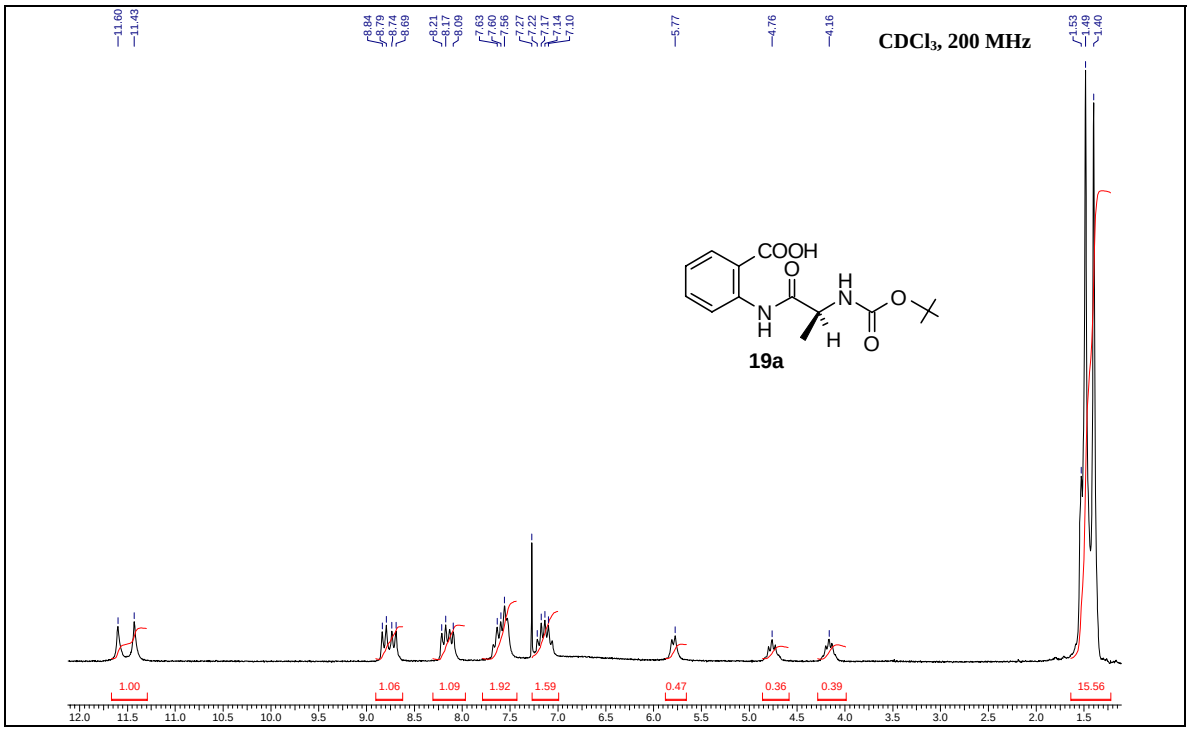
$CDCl_3$, 50 MHz

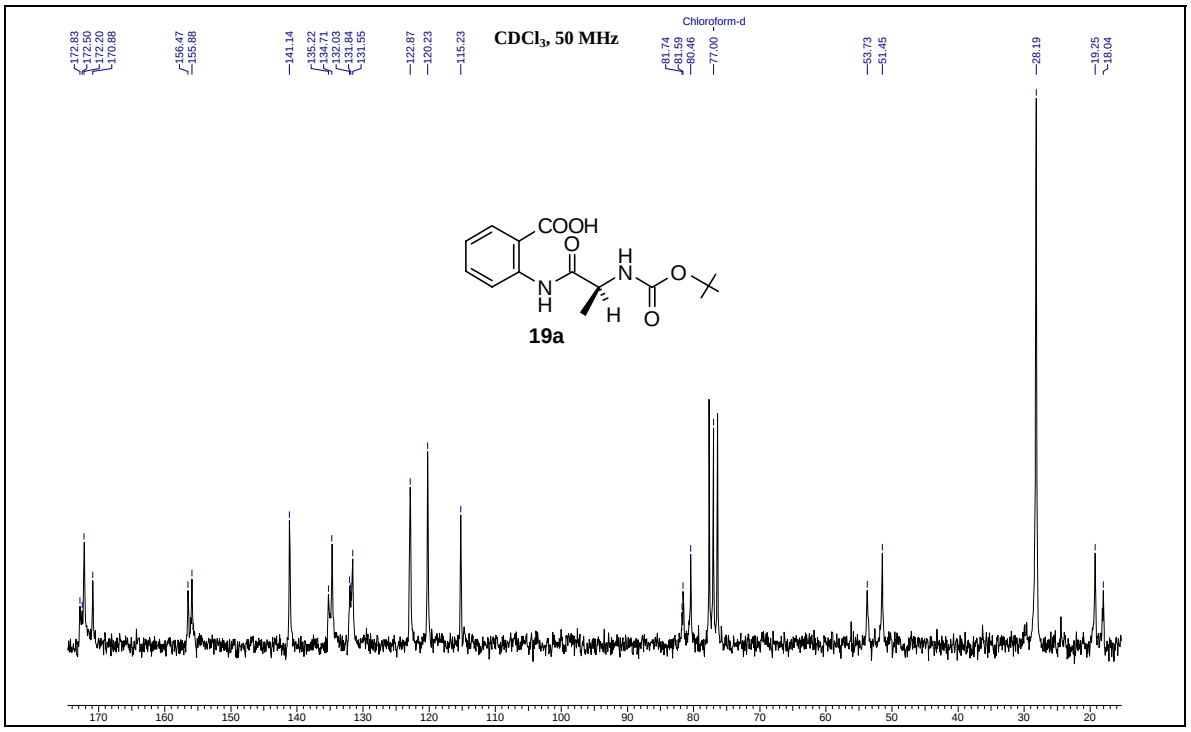


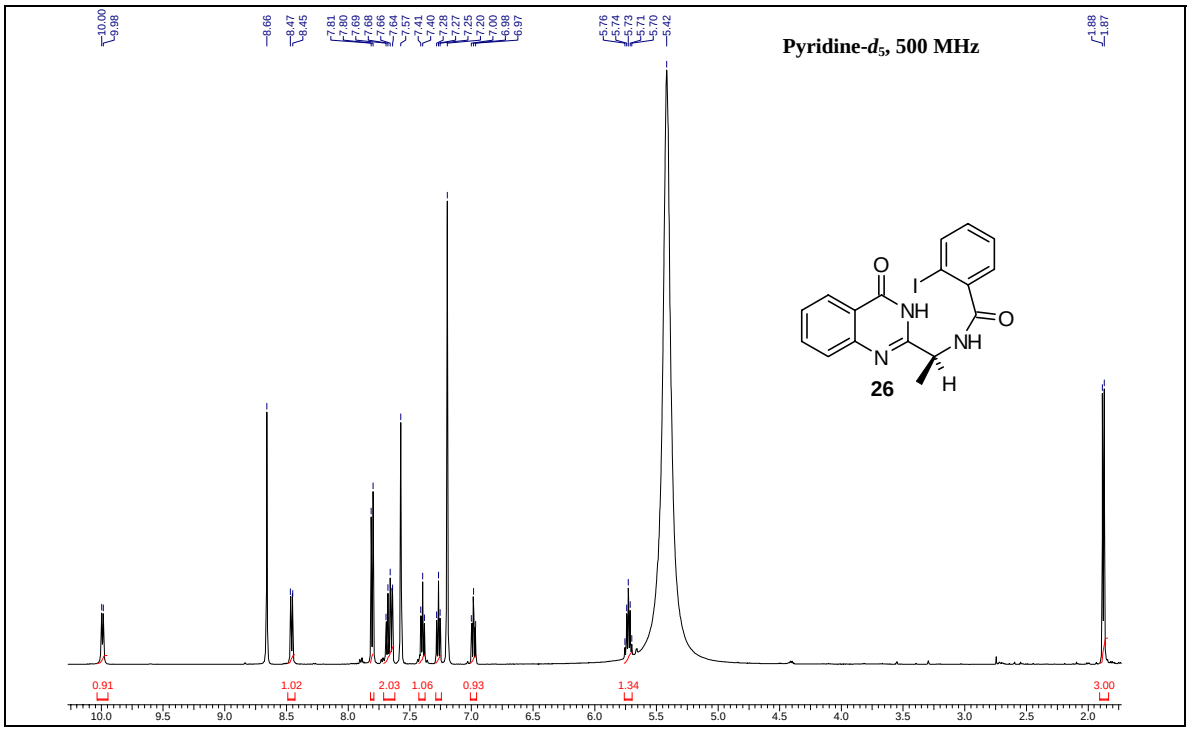

Acetone-d_6, 200 MHz
Acetone-d6
8.17
8.15
8.13
8.12
7.93
7.92
7.89
7.66
7.64
7.63
7.62
7.59
7.58
6.53
4.71
4.67
4.64
4.60
4.57
2.91
2.07
1.59
1.55
1.43
0.90
1.03
2.01
0.93
1.01
9.00
19

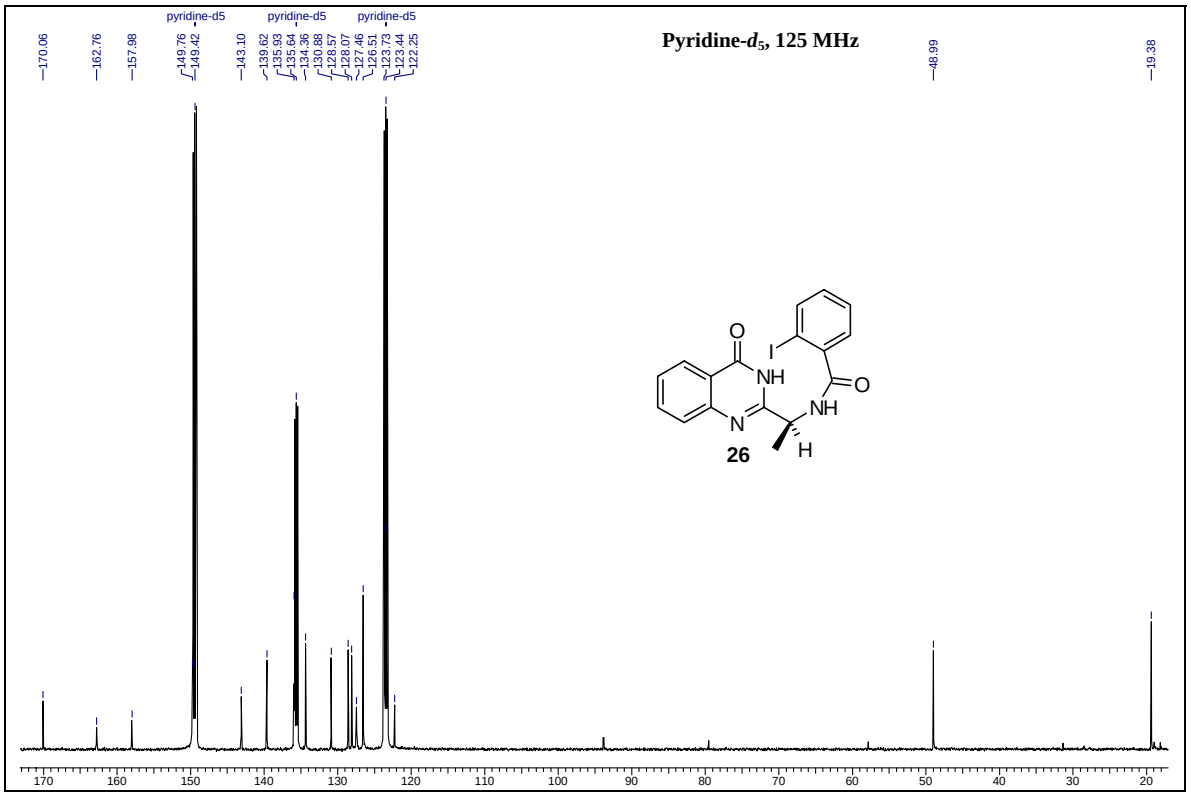

Acetone-d_6, 75 MHz
19
PPM

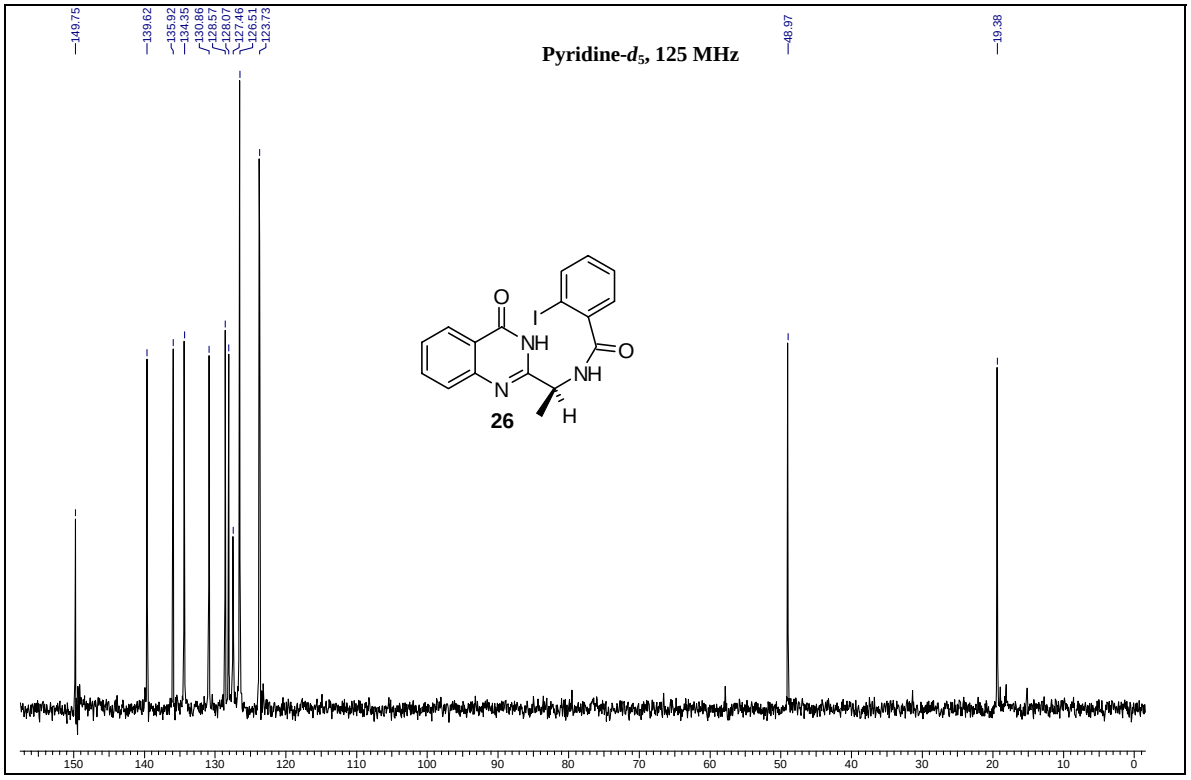

Acetone-d_6, 75 MHz
19
220 200 180 160 140 120 100 80 60 40 20 0
PPM


CDCl$_3$, 200 MHz
19a
11.60 11.43 8.84 8.79 8.74 8.69 8.21 8.17 8.09 7.63 7.60 7.56 7.27 7.22 7.17 7.14 7.10 5.77 4.76 4.16 1.53 1.49 1.40
1.00 1.06 1.09 1.92 1.59 0.47 0.36 0.39 15.56
12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5


CDCl3, 50 MHz
Chloroform-d
172.83
172.50
172.20
170.88
156.47
155.88
141.14
135.22
134.71
132.03
131.84
131.55
122.87
120.23
115.23
81.74
81.59
80.46
77.00
53.73
51.45
28.19
19.25
18.04
COOH
O
H
N
O
N
H
H
O
19a
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20


Pyridine-d5, 500 MHz
10.00
9.98
8.66
8.47
8.45
7.81
7.80
7.69
7.68
7.66
7.64
7.57
7.41
7.40
7.28
7.27
7.25
7.20
7.00
6.98
6.97
5.76
5.74
5.73
5.71
5.70
5.42
1.88
1.87
O
I
NH
O
NH
N
H
26
0.91
1.02
2.03
1.06
0.93
1.34
3.00
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0


Pyridine-d_5, 125 MHz
pyridine-d5
pyridine-d5
pyridine-d5
170.06
162.76
157.98
149.76
149.42
143.10
139.62
135.93
135.64
134.36
130.88
128.57
128.07
127.46
126.51
123.73
123.44
122.25
48.99
19.38
26


Pyridine-d_5, 125 MHz
149.75
139.62
135.92
134.35
130.86
128.57
128.07
127.46
126.51
123.73
48.97
19.38
26

List of Publications

1. Regioselective quinazolinone-directed ortho Lithiation of quinazolinoylquinoline: Practical synthesis of naturally occurring human DNA topoisomerase I poison luotonin A and luotonins B and E
   S. B. Mhaske and N. P. Argade*
   J. Org. Chem. **2004**, *69*, 4563.

2. Facile zeolite induced Fischer-indole Synthesis: A new approach to bioactive natural product rutaecarpine
   S. B. Mhaske and N. P. Argade*
   Tetrahedron **2004**, *60*, 3417.

3. Base-induced alcoholysis of *N*-arylmaleimides: facile in situ oxa-Michael addition to alkyl maleanilates: Two-step one-pot rapid access to alkoxysuccinic acids
   S. B. Mhaske and N. P. Argade*
   Synthesis **2003**, 863.

4. Facile routes to alkoxymaleimides/maleic anhydrides
   M. K. Sahoo, **S. B. Mhaske** and N. P. Argade*
   Synthesis **2003**, 346.

5. Biogenetic synthesis of luotonin F
   S. B. Mhaske and N. P. Argade*
   Synthesis **2002**, 323.

6. Concise and efficient synthesis of bioactive natural products pegamine, deoxyvasicinone and (–)-vasicinone
   S. B. Mhaske and N. P. Argade*
   J. Org. Chem. **2001**, *66*, 9038.

7. Synthesis and characterization of end-capped polyimides and their Gas permeability properties
   S. B. Mhaske, R. V. Bhingarkar, M. B. Sabne, R. Mercier and S. P. Vernekar*
   J. Appl. Polym. Sci. **2000**, *77*, 627.

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8. A concise account on the chemistry of the recently isolated naturally occurring quinazolinone alkaloids
   S. B. Mhaske and N. P. Argade*
   A review, communicated.

Erratum