STUDIES ON SYNTHESIS OF NATURALLY OCCURRING QUINAZOLINE AND QUINAZOLINONE ALKALOIDS

THESIS

SUBMITTED TO THE

UNIVERSITY OF PUNE

FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

IN CHEMISTRY

BY

UMESH A. KSHIRSAGAR

NARSHINHA P. ARGADE
(RESEARCH GUIDE)

DIVISION OF ORGANIC CHEMISTRY
NATIONAL CHEMICAL LABORATORY
PUNE-411 008
INDIA

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Dedicated to my Parents…

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CERTIFICATE

This is to certify that the work incorporated in the thesis entitled "***Studies on Synthesis of Naturally Occurring Quinazoline and Quinazolinone Alkaloids***" which is being submitted to the ***University of Pune*** for the award of ***Doctor of Philosophy*** in ***Chemistry*** by ***Mr. Umesh A. Kshirsagar*** 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.

October 2010
Pune

Dr. N. P. Argade
(Research Guide)

Candidate's Declaration

I hereby declare that the research work incorporated in the thesis entitled "***Studies on Synthesis of Naturally Occurring Quinazoline and Quinazolinone Alkaloids***" submitted for the degree of ***Doctor of Philosophy*** in ***Chemistry*** to the ***University of Pune***, has been carried out by me at the Division of Organic Chemistry, National Chemical Laboratory, Pune, India, from April 2005 to October 2010 under the supervision of Dr. Narshinha P. Argade. This work has not been submitted in part or full by me for a degree or diploma to this or any other University or Institution.

October 2010
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Let me take this opportunity to express my genuine gratitude to my research supervisor Dr. N. P. Argade who introduced me into this fascinating realm of chemistry. His discipline, principles, simplicity, caring attitude and provision of fearless work environment will be cherished in all walks of my life. I am very much grateful to him for his valuable guidance and everlasting encouragement throughout my course. I am certain that his ethics and moral values which I learnt from him will go a long way in making me a better human being.

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in the lab. I am very much thankful them for their constructive criticism, advices, support, true help, love and care that have helped me to give my best. My special thanks to lab-friends Ramesh, Prasad, Mandeeep, Prahsant, Pravat, Ramesh Jr. and Ravi for their helpful discussion, co-operation and maintaining amazing atmosphere with humour in the lab. The warm memories of my days in Lab-195 will haunt me forever. I also thank to Chavan mama for co-operation.

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No word would suffice to express my gratitude and love to my parents, uncle, aunt, brothers, sisters, brothers in-law and all family members for their continuous showering of boundless affection on me and supporting me in whatever I chose or did. It is my parent's prayer, constant struggle and relentless hard work to overcome the odds of life, which has inspired me to pursue life with a greater optimism. The warmth and moral value of my parents have stood me in good stead throughout my life and I would always look up to them for strength no matter what I have to go through. This Ph. D. thesis is a result of the extraordinary will, efforts and sacrifices of my parents. I would like to dedicate this moment of joy to my parents and family. My successes are dedicated to them now and always.

I wish to express my gratitude towards "god-almighty", who gave me the strength and courage to fulfil my dream and has showered upon me his choicest blessings.

Umesh

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General Remarks

- All the solvents used were purified using the known literature procedures.
- Petroleum ether used in the experiments was of 60-80 °C boiling range.
- Silica gel column chromatographic separations were carried out by gradient elution with light petroleum ether-ethyl acetate mixture, unless otherwise mentioned (silica gel, 60-120 mesh/100-200 mesh/230-400 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, *p*-anisaldehyde (in ethanol), bromocresol green (in ethanol) and ninhydrin (in ethanol).
- IR spectra were recorded on Shimadzu FTIR instrument, for solid either as nujol mull or in chloroform solution (concentration 0.05 to 10%) 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), ACF 400 (400 MHz for ^{1}H NMR and 100 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 taken on MS-TOF mass spectrometer.
- HRMS were taken using EI method on MSI-UK AUTOCONCEPT DIP-EI and ESI method on MS-TOF mass spectrometer.
- Microanalysis data were obtained using Flash EA 1112 series and Elementar Vario EL analyser.
- 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 IR and NMR spectra as well as melting point 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

Å	Angstrom
Aq.	Aqueous
AIBN	2,2'-Azobisisobutyronitrile
BINAP	2,2'-Bis(diphenylphosphino)1,1'-binaphthyl
CAN	Ceric ammonium nitrate
cat.	Catalytic
CCDC	Cambridge crystallographic data centre
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCM	Dichloromethane
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DEA	Diethylamine
DEAD	Diethyl azodicarboxylate
DEPT	Distortionless enhancement by polarization transfer
DIBAL-H	Diisobutylaluminium hydride
DIPEA	Diisopropyl ethyl amine
DMA	*N*,*N*-Dimethylacetamide
DMAP	4-(Dimethylamino)pyridine
DMDO	3,3-Dimethyldioxirane
DMF	Dimethylformamide
DMSO	Dimethyl sulphoxide
EDC	Ethylene dichloride
EDCI	*N*-Ethyl-*N*'-(3-dimethylaminopropyl)carbodimide hydrochloride
ee	Enantiomeric excess
ESI	Electro spray ionization
EI	Electron impact
eq.	Equation
equiv	Equivalent
h	Hour(s)
HATU	*o*-(7-Azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium
HOBt	1-Hydroxybenzotriazole
HRMS	High resolution mass spectra
HPLC	High performance liquid chromatography
Hz	Hertz
IC	Inhibitory concentration
IPA	Isopropyl alcohol
IR	Infra Red
Johnphos	(2-Biphenyl)di-*tert*-butylphosphine
HMDS	1,1,1,3,3,3-hexamethydisilazane
LAH	Lithium aluminum hydride
m-CPBA	*m*-Chloroperbenzoic acid
MHz	Megahertz
min.	Minute(s)
mL	Millilitre(s)
mmol	Millimole(s)
Mp	Melting point
MS	Mass Spectrum
MW	Microwave
NBS	*N*-Bromosuccinimide

NCS	*N*-Chlorosuccinimide
NMM	*N*-Methylmorpholine
NMO	4-Methylmorpholine *N*-oxide
NMR	Nuclear magnetic resonance
NPhth	Phthalimide
ORTEP	Orthogonal thermal ellipsoid plots
PCy_3	Tricyclohexylphosphine
$Pd_2(dba)_3$	Tris(dibenzylideneacetone)dipalladium
PE	Petroleum ether
PRPA	Propylphosphonic acid anhydride
p-TSOH	*p*-Toluenesulfonic acid
p-TsCl	*p*-Toluenesulfonyl chloride
Py	Pyridine
rt	Room temperature
TBTU	*o*-(Benzotriazol-1-yl)-*N,N,N′,N′*-tetramethyluronium tetrafluoroborate
TES	Triethylsilyl
TESOTf	Triethylsilyl trifluoromethanesulfonate
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMSOTf	Trimethylsilyl trifluoromethanesulfonate
UV	Ultraviolate
Xantphos	4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene

Abstract

The present dissertation entitled "***Studies on Synthesis of Naturally Occurring Quinazoline and Quinazolinone Alkaloids***" is divided into two chapters. The first chapter presents a brief literature account on the chemistry of recently isolated quinazoline and quinazolinone alkaloids. In second chapter, our concise and efficient approaches for the synthesis of various natural and unnatural quinazoline and quinazolinones (Figure 1) have been described implementing novel synthetic routes.

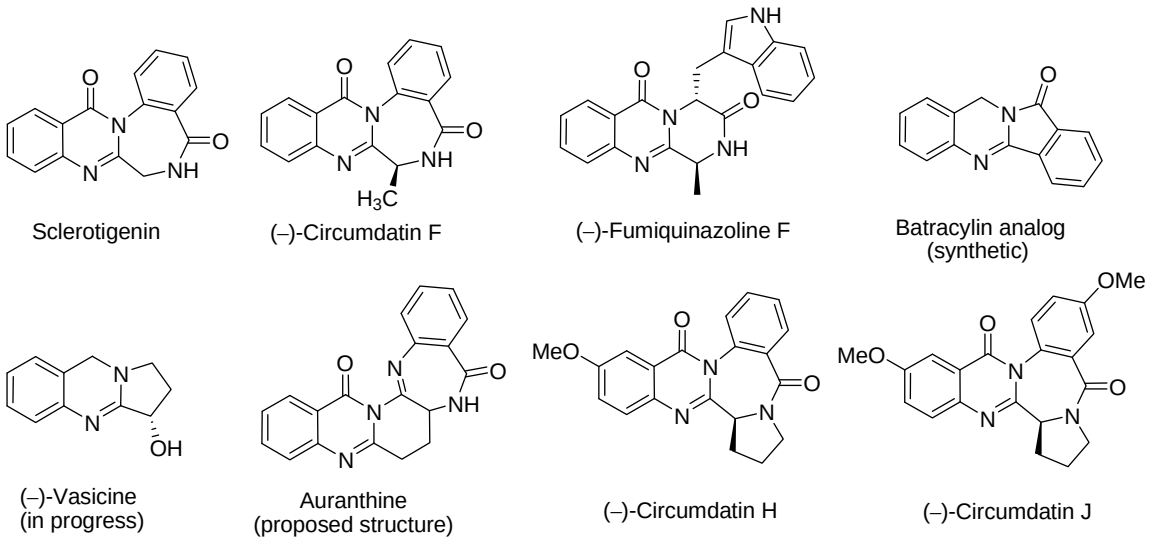


Figure1. Natural and unnatural bioactive quinazolinone alkaloids synthesized

Chapter 1: A Concise Account on the Chemistry of Naturally Occurring Quinazoline and Quinazolinone Alkaloids

Large number of quinazolinone alkaloids have been isolated from number of plants, animals and microorganisms and synthesized in view of their well-established pharmacological activities. Nearly 200 natural products with the quinazolinone nucleus are known in the literature and some are in clinical use. The literature on these quinazolinones has been well documented by Mhaske and Argade in 2006. This chapter portrays a concise account on isolation, bioactivity and synthesis of recently isolated quinazoline and quinazolinone natural products from the year 2005 to till date with an emphasis on new synthetic routes and strategies.

Chapter 2: Synthetic Studies on Quinazoline and Quinazolinone Alkaloids

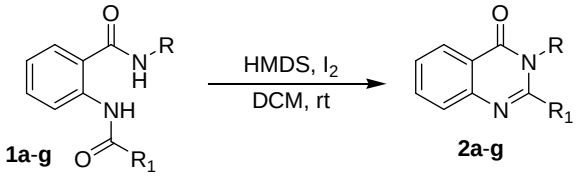
This chapter is divided into four sections. The first section presents synthesis of (**–**)-circumdatin F, sclerotigenin and (**–**)-fumiquinazoline F. The second section describes a facile synthesis of different analogs of anti-tumor agent batracylin. This section also presents our studies on the synthesis of (–)-vasicine. The third section describes first total synthesis of proposed auranthine. The fourth section presents an efficient total synthesis of (**–**)-circumdatin H and J.

Section A: Concise Synthesis of Quinazolinone Alkaloids Sclerotigenin, (–)-Circumdatin F and (–)-Fumiquinazoline F

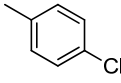
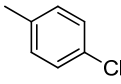
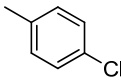
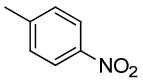
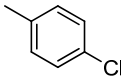
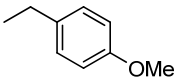
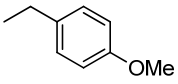
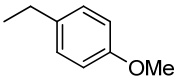
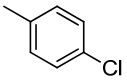
2A.1 Hexamethyldisilazane-Iodine Induced Intramolecular Dehydrative Cyclization of Diamides.

Quinazolinones are the important class of compounds and a large number of natural and unnatural quinazolinone skeletons with a variety of substituents have been designed using several synthetic strategies owing to the wide range of biological activities conferred on them. Retrosynthetically, the intramolecular dehydrative cyclization of suitably substituted *N*-benzoylanthranilamides constitutes a concise and biomimetic route to all types of quinazolinone alkaloids. However, such dehydrations demand harsh conditions and are suitable only for dehydrative cyclizations of unhindered 2,3-disubstituted-quinazoline-4-ones. Recently, a two-step approach for such a intramolecular dehydration of diamides has been developed using the $PPh_3/I_2/EtN(i\text{-}Pr)_2$ (Wipf's protocol) to form the benzoxazine intermediate, followed by the piperidine induced rearrangement to the target

Table 1. Intramolecular cyclization of diamides **1a**-**g** to quinazolinones **2a**-**g**



1a-g **2a-g**

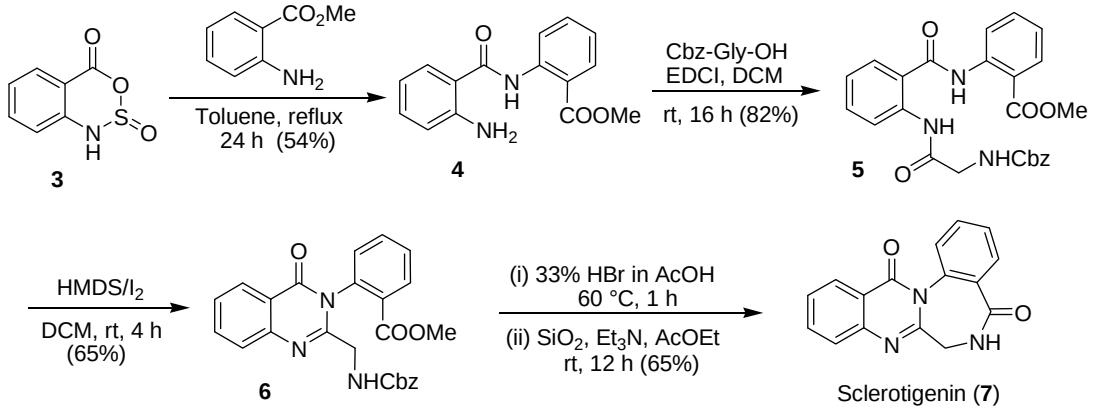
Entry	R	R_1	Condition	Product (% yield)
1		$-CH_2CH_3$	30 min	**2a** (93)
2			30 min	**2b** (95)
3			4 h	**2c** (86)
4			4 h	**2d** (70)
5		$-CH_2CH_3$	3 h	**2e** (97)
6			7 h	**2f** (96)
7			5 h	**2g** (90)

molecules. The development of a straightforward, simple and efficient approach to the natural and unnatural quinazolinones, more specifically for the peptidomimetic ones bearing a variety of protecting groups is a useful and challenging task of current interest. We have developed the facile and efficient one step approach to quinazolinones **2a**–**g** from linear diamides **1a**–**g** (Table 1), first

time by using the HMDS/I_2 for such a intramolecular dehydrative cyclization. Total synthesis of naturally occurring sclerotigenin, (–)-circumdatin F and (–)-fumiquinazolin F have been demonstrated by using our above mentioned protocol.

2A.2 Synthesis of Sclerotigenin

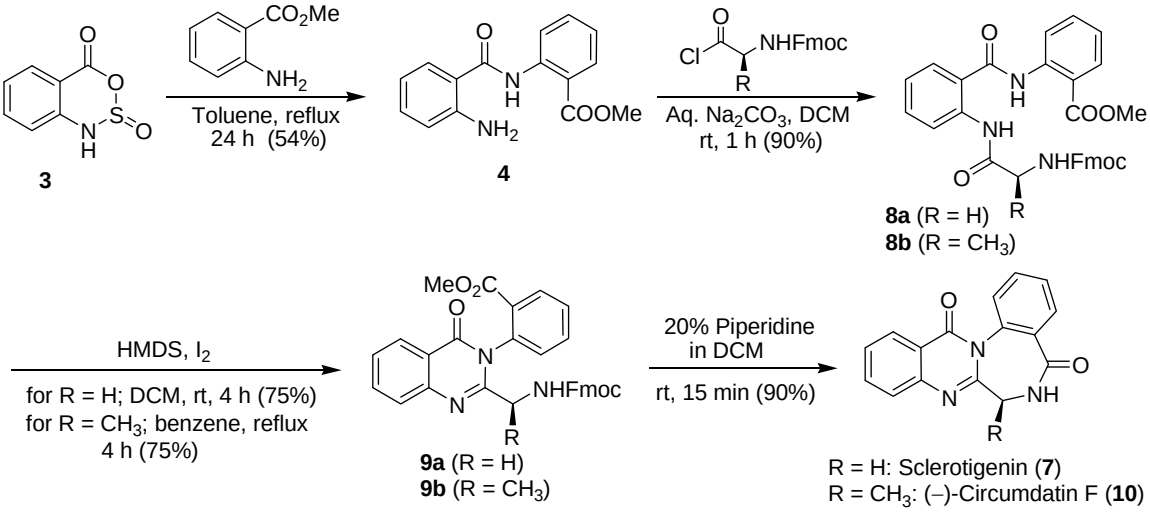
We started the synthesis of sclerotigen from sulfinamide anhydride (**3**) and methyl anthranilate (Scheme 1). Coupling of the obtained aminoester **4** with the Cbz-protected glycine using EDCI as a dehydrating agent gave the required linear diamide **5**. HMDS/Iodine induced intramolecular dehydrative cyclization of linear diamide **5** in DCM at room temperature gave the quinazolinone **6**. Deprotection of Cbz-group by treatment with 33% HBr in AcOH followed by Et_3N/SiO_2 induced cyclization furnished the desired sclerotigenin (**7**)



Scheme 1. Synthesis of sclerotigenin via intramolecular dehydrative cyclization

2A.3 Synthesis of (–)-Circumdatin F and Sclerotigenin

Our synthesis of (–)-circumdatin F and sclerotigenin started with coupling of aminoester **4** with Fmoc-protected glycine and L-alanine, which respectively gave the linear diamides **8a**/**b** in very good yields (Scheme 2). HMDS/Iodine induced dehydrative cyclization of diamide **8a** in DCM at room

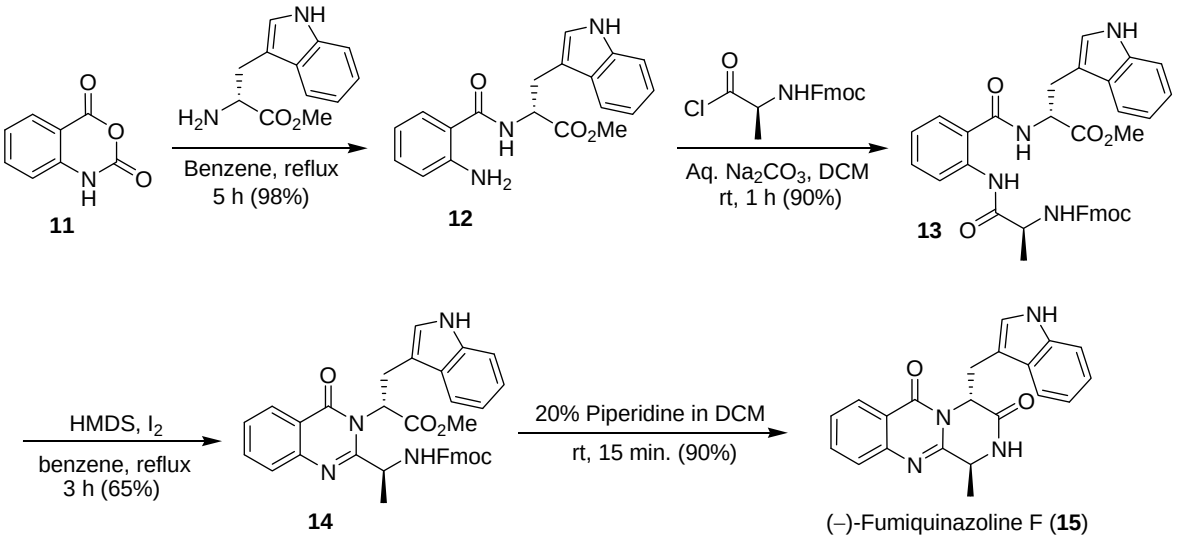


Scheme 2. Synthesis of sclerotigenin and (–)-circumdatin F via intramolecular dehydrative cyclization

temperature gave quinazolinone **9a**. The diamide **8b** did not react with HMDS/Iodine in DCM at room temperature. The same reaction in refluxing benzene gave desired quinazolinone **9b**. Piperidine induced Fmoc-deprotection of **9a**/**b** directly gave the sclerotigenin (7) and (–)-circumdatin F (10).

2A.4 Synthesis of (–)-Fumiquinazoline F

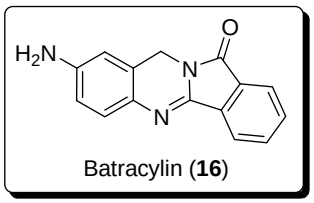
We started our synthesis of (–)-fumiquinazoline F (**15**) with the reaction of isatoic anhydride (**11**) and methyl ester of tryptophan, which gave the aminoester **12** (Scheme 3). The intermolecular dehydrative coupling of compound **12** with Fmoc-protected alanine gave required linear diamide **13**. HMDS/Iodine induced dehydrative cyclization of diamide **13** in refluxing benzene provided the desired quinazolinone **14**. Piperidine induced Fmoc-deprotection of **14** directly furnished the desired (–)-fumiquinazoline F (**15**).



Scheme 3. Synthesis of sclerotigenin (–)-fumiquinazoline F

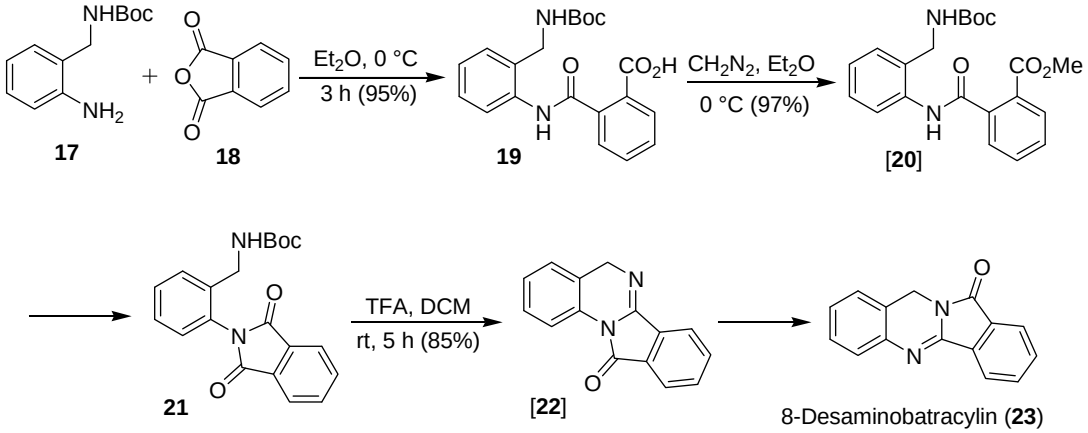
Section B: Studies on Synthesis of Analogs of Antitumoral Agent Batracylin and in Progress Synthesis of (–)-Vasicine

2B.1 Facile Approach to Diverse Range of Batracylin Analogs


Batracylin (**16**)

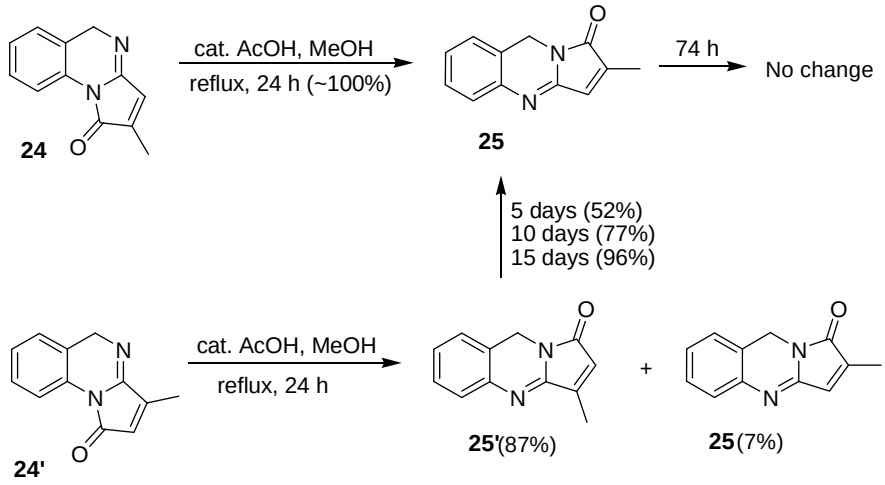
A large number of biological activities have been conferred to heterocycles and they play a pivotal role as both pharmaceutical and agrochemical products. Batracylin (**16**) displays antitumor activity in vivo against murine leukemia P-388 and colon adenocarcinoma 38 cell lines that are resistant to adriamycin, cisplatin, and methotrexate. However, because of the high toxicity of batracylin, it has never been approved for further clinical trials in human beings. In this context, new approaches to provide a variety of analogs of the antitumor agent batracylin have been reported in the literature by using intramolecular aza-Wittig reactions, Mitsunobu coupling reactions

and condensation of *o*-aminobenzylamine with *o*-cyanomethylbenzoic acid. We have studied the nucleophilic reaction of several cyclic anhydrides with *tert*-butyl 2-aminobenzylcarbamate and provided a new practical route to the 1,3-diazatricyclic/tetracyclic heterocycles in high yields (Scheme 4).



Scheme 4. Synthesis of 8-desaminobatracylin

Our present study clearly reveals that in all the cases, the anilic acid esters exclusively provide thermodynamically more stable linear 1,3-diazaheterocycles. In imides cases studied, the formed angular products rearranged to the corresponding more stable linear products, while only the methyl and dimethyl substituted maleimides exclusively provide the corresponding kinetically



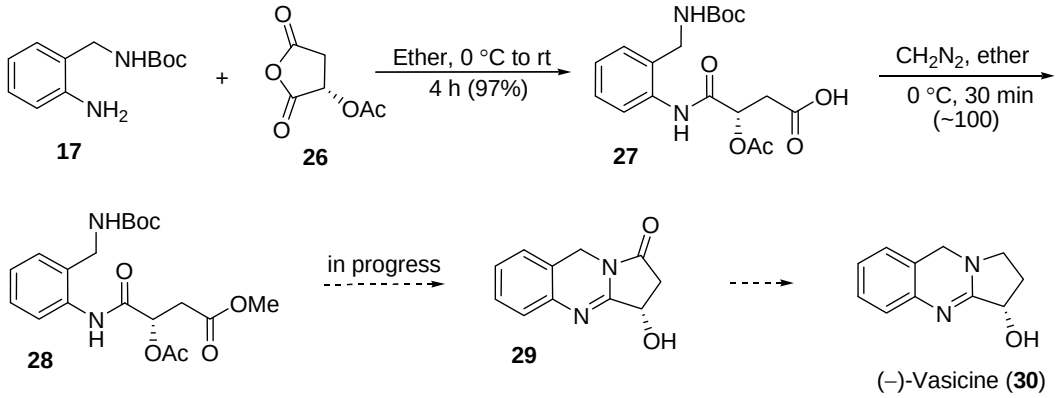
Scheme 5. Rearrangment of angular 1,3-diaza-heterocycles to linear 1,3-diaza-heterocycles

controlled angular 1,3-diaza-heterocycles. These kinetically controlled angular compounds were successfully rearranged to the corresponding thermodynamically controlled linear products by refluxing in methanol plus catalytic amount of acetic acid. In our study, when we tried to convert **24'** to **25'**, we also witnessed the serendipitous intramolecular shuffling of the methyl group (Scheme 5).

2B.2 Studies Towards the Synthesis of (–)-Vasicine

(–)-Vasicine has been isolatated from *Adhatoda Vasica Nees*. It has hypotensive and respiratory stimulant activities. We started the chiral pool synthesis of (–)-vasicine from (*S*)-acetoxysuccinic

anhydride (**26**) (Scheme 6). The reactions of *tert*-butyl 2-aminobenzylcarbamate (**17**) with anhydride **26** gave the acetoxysuccianilic acid **27**. Further esterification of the obtained acid using diazomethane provided the corresponding ester **28**. The deprotection of Boc-group in compound **28** to obtain the desired compound **29** and further transformation to (**–**)-vasicine is inprogress. In our preliminary studies on conversion of **28** to **29**, we have met with some difficulties such as decomposition and polymeric gum formation.

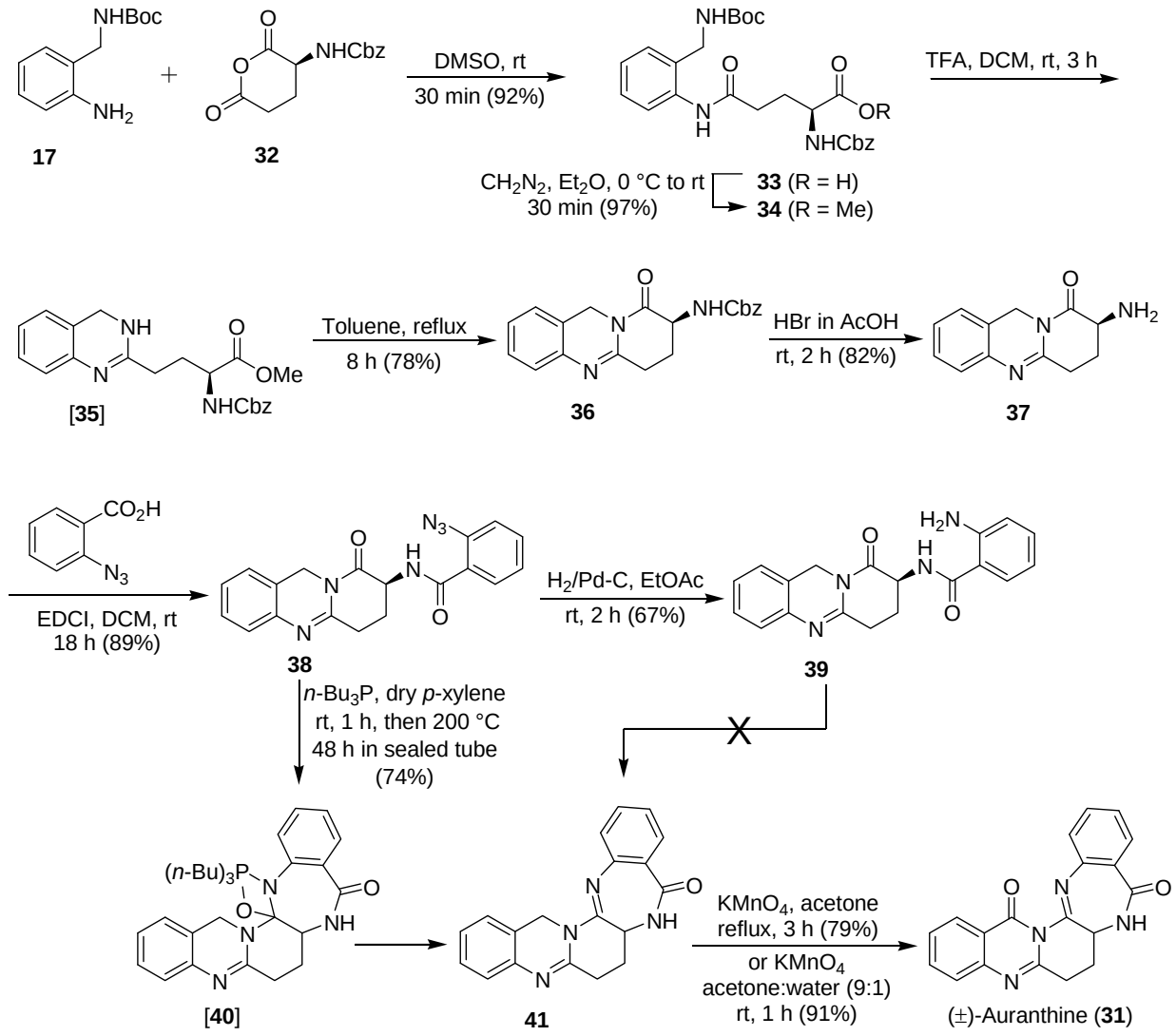


Scheme 6. Studies on synthesis of (**–**)-vasicine

In summary, we have systematically studied the nucleophilic reactions of several cyclic anhydrides with *tert*-butyl 2-aminobenzylcarbamate and provided a new practical route to the corresponding angular and linear 1,3-diazatricyclic/tetracyclic heterocycles in high yields.

Section C: First Total Synthesis of Proposed Auranthine

In the course of isolating nephrotoxins, a new fungal metabolite, (**–**)-auranthine (**31**) was isolated from *Penicillium aurantiogriseum.* Auranthine is a structurally unique quinazoline alkaloid which contains an unusually positioned diazepine moiety, a feature that has largely rendered its total synthesis a challenge till date. A look at the structure of auranthine reveals that (**–**)-glutamic acid and anthranilamide could be potential building blocks for constructing this structurally intriguing alkaloid. Based on our continuing interest in the chemistry of cyclic anhydrides and their applications in natural product synthesis, we have accomplished first total synthesis of the target compound (Scheme 7), starting from CBz-protected(*S*)-glutamic anhydride **32**. The nucleophilic regioselective ring opening of an anhydride **32** in DMSO with the *tert*-butyl 2-aminobenzylcarbamate (**17**), exclusively furnished the expected anilic acid **33**. Diazomethane esterification of anilic acid **33** provided the methyl ester **34**. Boc-deprotection of **34** using TFA followed by refluxing in toluene provided the lactam **36**. The compound **36** on treatment with hydrobromic acid gave the amine **37**. The EDCI driven dehydrative coupling between the amine **37** and *o*-azidobenzoic acid provided the azido compound **38**. The intramolecular tributylphosphine driven aza-Wittig reaction in a sealed tube at 200 ^{o}C in *p*-xylene for 48 h regioselectively furnished the desired auranthine precursor **41** in 74% yield, however, unfortunately with nearly complete racemization.



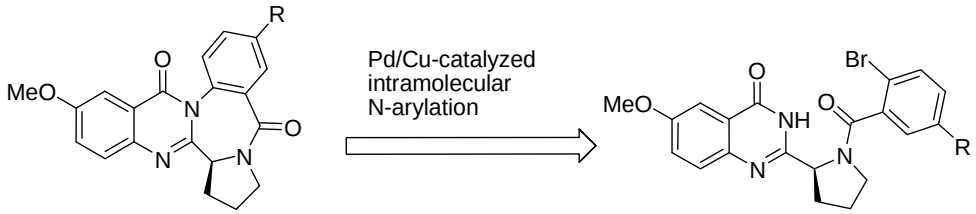
Scheme 7. Total synthesis of proposed structure of auranthine

Finally, the $KMnO_4$ induced chemoselective oxidation of benzylic methylene group of quinazolinopyridobenzodiazepine **41** to the corresponding carbonyl group, keeping the allylic methylene group intact, provided the auranthine (**31**). However the ^{1}H NMR spectrum of synthetic **31** in benzene-d_6 was not in agreement with the ^{1}H NMR spectrum of natural product. Finally, the structure of our synthetic auranthine was unequivocally confirmed on the basis of X-ray crystallographic data. Hence what we have accomplished is the first synthesis of proposed structure of auranthine.

Section D: Copper-Catalyzed Intramolecular N-Arylation of Quinazolinones: Facile Convergent Approach to (–)-Circumdatin H and J

Circumdatins are the marine natural products from fungi of the genus *Aspergillus* and they possess antitumor, antifungal, insecticide and antibiotic activities. (–)-Circumdatins H and J have been recently isolated from *Aspergillus ochraceus* and *Aspergillus ostianus* respectively and more

specifically, the (–)-circumdatin H is an inhibitor of the mammalian mitochondrial respiratory chain, with an IC_{50} value of 1.5 μM. Circumdatins are basically the quinazolinobenzodiazepines and the provision of new efficient synthetic routes to them is the pivotal task of current interest. We envisaged the metal catalyzed intramolecular *N*-arylation of quinazolinones implementing the advanced Goldberg-Buchwald protocol that would provide an efficient access to large number of desired naturally occurring quinazolinones and their analogues and congeners (Scheme 8).

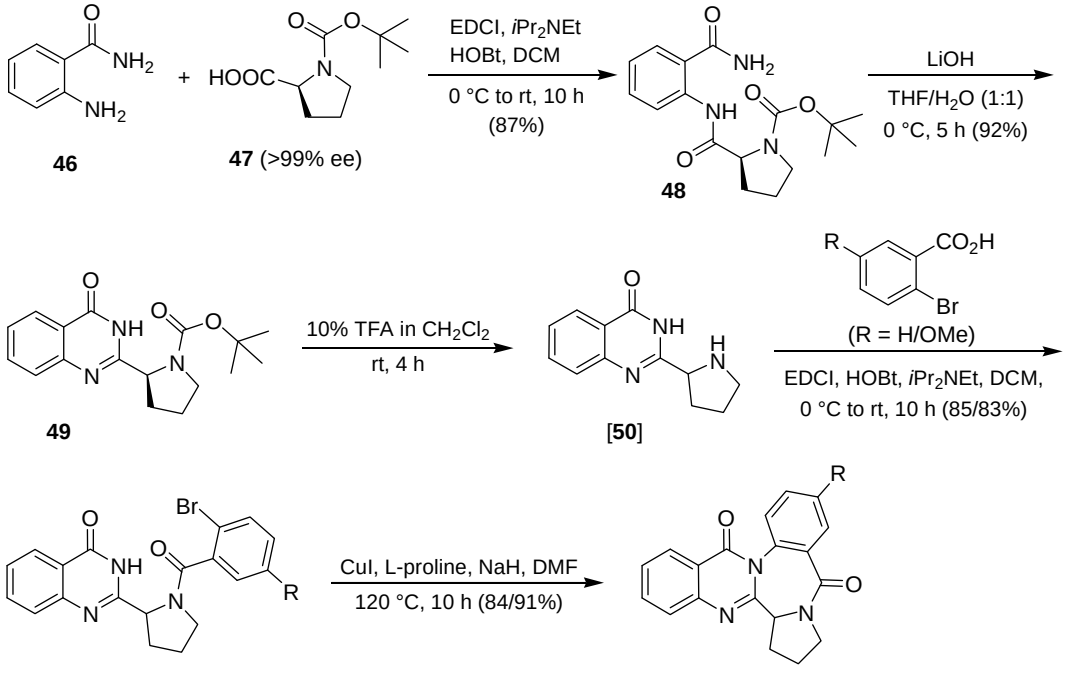


(–)-Circumdatin H (R = H, **42**)
(–)-Cicumdatin J (R = OMe, **43)**

44 (R = H)
45 (R = OMe)

Scheme 8. Retrosynthetic analysis of (–)-circumdatins H and J

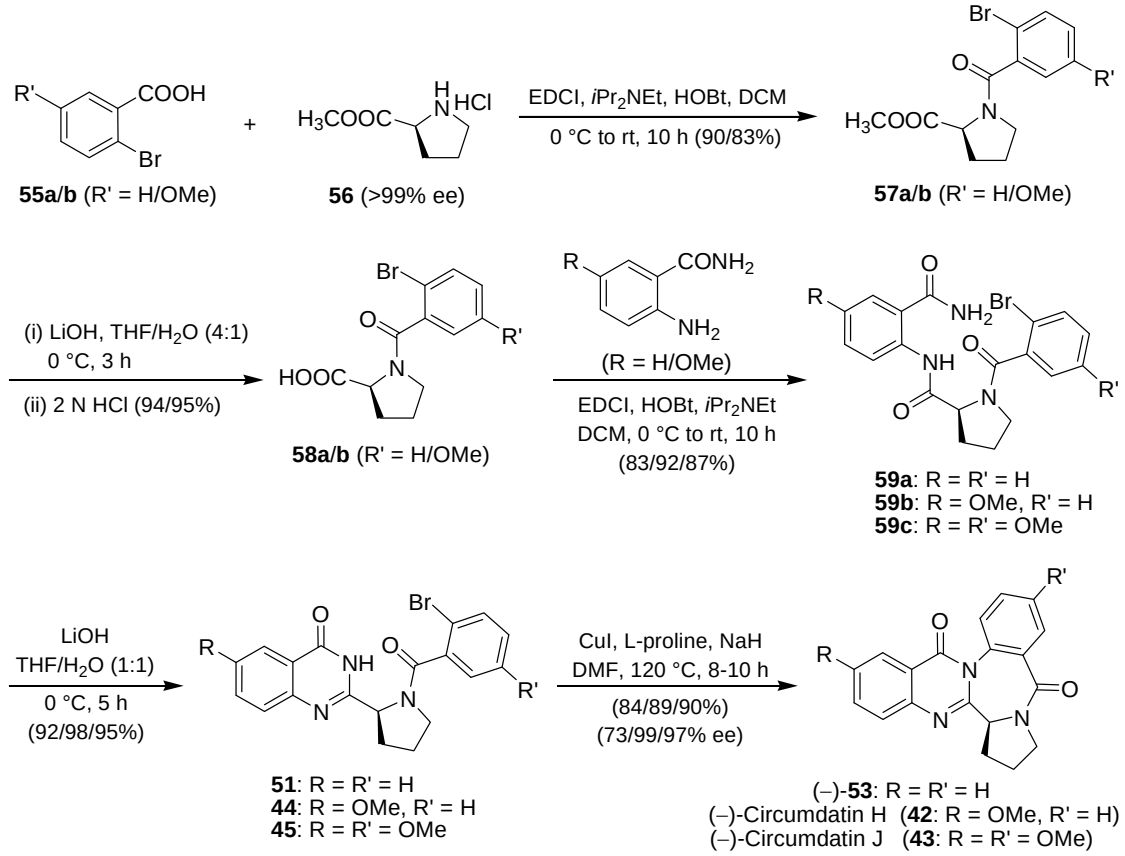
The EDCI-induced dehydrative coupling of the Boc-protected L-proline (**47**) with anthranilamide (**46**) furnished the diamide **48** (Scheme 9). The subsequent base-catalyzed intramolecular dehydrative cyclization of compound **48** provided the required quinazolinone **49**. The TFA-deprotection of Boc-group in compound **49**, followed by the dehydrative couplings of formed intermediate free amine **50** with 2-bromobenzoic acid and 2-bromo-5-methoxybenzoic acid furnished the desired precursors **51**/**52**, but unfortunately with the complete racemization in both the cases. We first studied the palladium-catalyzed intramolecular *N*-arylation of quinazolinone **51** to convert in **53** under variety of reaction conditions using the different promising ligands (xantphos, BINAP, johnphos), bases (Cs_2CO_3/$NaOBu^t$) and solvents (toluene/1,4-dioxane) at elevated temperature, but unfortunately all



46
47 (>99% ee)
48
49
[**50**]
(±)-**51**/**52** (R = H/OMe)
(±)-**53**/**54** (R = H/OMe)

Scheme 9. Synthesis of circumdatin frameworks via the intramolecular *N*-arylation

our attempts met with failure. We decided to screen the cheap and versatile copper catalysts for the intramolecular cyclization of compound **51** to form **53** using different ligands. We were delighted to learn that the copper-catalyzed regioselective intramolecular cross-coupling between quinazolinone nitrogen and an adjacent aryl bromide in compound **51** using L-proline as the ligand and sodium hydride as a base in the solvent DMF at 120 ^{o}C exclusively furnished the desired thermodynamically more stable linear product **53** in 84% yield. Similarly the reaction of compound **52** under above mentioned reaction conditions provided the desired product **54** in 91% yield. To circumvent the associated problem of racemization in our above described Scheme 9 and also to accomplish the synthesis of enantiomerically pure natural products the (–)-circumdatins **42** and **43**, we decided to



Scheme 10. Copper-catalysed intramolecular *N*-arylation of quinazolinones: synthesis of circumdatins H and J

suitably alter our synthetic sequence (Scheme 10). In our second approach, the EDCI-induced dehydrative couplings of the 2-bromobenzoic acid (**55a**) and 2-bromo-5-methoxybenzoic acid (**55b**) with methyl ester of L-proline (**56**) provided the corresponding products (–)-**57a**/**b**. The subsequent base-catalyzed ester hydrolysis of **57a**/**b** provided the corresponding *N*- benzoylprolines **58a**/**b** in high yields. Once again, the EDCI-induced dehydrative couplings of compound **58a** with both the anthranilamide and 5-methoxyanthranilamide and **58b** with 5-methoxyanthranilamide respectively provided the corresponding triamides **59a**/**b**/**c**. Triamides **50a**/**b**/**c** on base-catalyzed selective intramolecular dehydrative cyclization furnished the essential quinazolinones **51**/**44**/**45**.

Finally, the copper-catalyzed intramolecular *N*-arylation of compounds **51**/**44**/**45** using L-proline as the ligand and sodium hydride as the base in solvent DMF at 120 °C exclusively furnished the desired final products, the synthetic (–)-**53**, (–)-circumdatin H (**42**) and (–)-circumdatin J (**43**) with 73/99/97% ee respectively.

Note: Compound, scheme and figure numbers in the abstract are different from those in the thesis.

Chapter 1

A Concise Account on the Chemistry of Naturally Occurring Quinazoline and Quinazolinone Alkaloids

This chapter features the following topics:

1.1 Introduction

Quinazolinone is a building block for approximately 200 naturally occurring alkaloids isolated to date from a number of families of the plant kingdom, from animals and from microorganisms. The first quinazoline alkaloid to be isolated was vasicine (peganine **1**) in 1888, produced by Indian medicinal tree *Adhatoda vasica* and later isolated from other species along with the quinazolinone alkaloids, vasicinone (**2**) and deoxyvasicinone (**3**).[1] A variety of other quinazoline and quinazolinone natural products have been isolated, characterized and synthesized thereafter. The first quinazolinone was synthesized in the late 1860s from anthranilic acid and cyanogens to give 2-cyanoquinazolinone (**4**, Figure 1).[2] Interest in the medicinal chemistry of quinazolinone derivatives was stimulated in the early 1950 with the structural elucidation of a quinazolinone alkaloid, 3-[β-keto-γ-(3-hydroxy-2-piperidyl)-propyl]-4-quinazolone (febrifugine, **5**)[3] from an Asian plant *Dichroa febrifuga*, which is an ingredient of a traditional Chinese herbal remedy, effective against 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 **6**). Methaqualone (**6**) was synthesized[4] for the first time in 1951 and it is the most well-known synthetic quinazolinone drug, famous for its sedative–hypnotic effects.

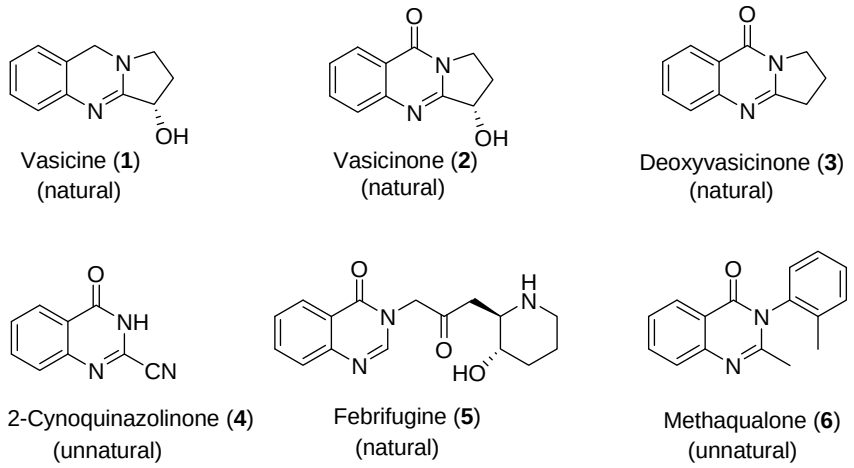


Figure 1. Natural and unnatural quinazolinones

The introduction of methaqualone and its discovery as a hypnotic triggered the research activities toward the isolation, synthesis and studies on the pharmacological properties of the quinazolinones and related compounds. Quinazoline and quinazolinone alkaloids are one of attractive natural products leading to drug developments. Bioassay-directed isolation followed by identification and characterization of bioactive compounds leads to a development of new medicinal drugs. The structural diversity of quinazolinones has been broadened with the discovery of asperlicin along with asperlicins B, C, D, and E (**7**–**11**) produced by *Aspergillus alliaceus*, which is a potent cholecystokinin (CCK) antagonist (Figure 2). A series of new quinazoline alkaloids fused with benzodiazepinone were

also isolated from a fungus culture of *Penicillium* sp., wherein benzomalvin A (**12**) is prototypical member. Quinazolinones and their derivatives are now known to have a wide range of useful biological properties, such as hypnotic, sedative, analgesic, anti-convulsant, anti-tussive, anti-bacterial, anti-diabetic, anti-inflammatory, anti-tumour, and several others.[5] Some of these compounds also have interesting biological properties such as anti-malarial activity, biofungicide, and diuretic properties.

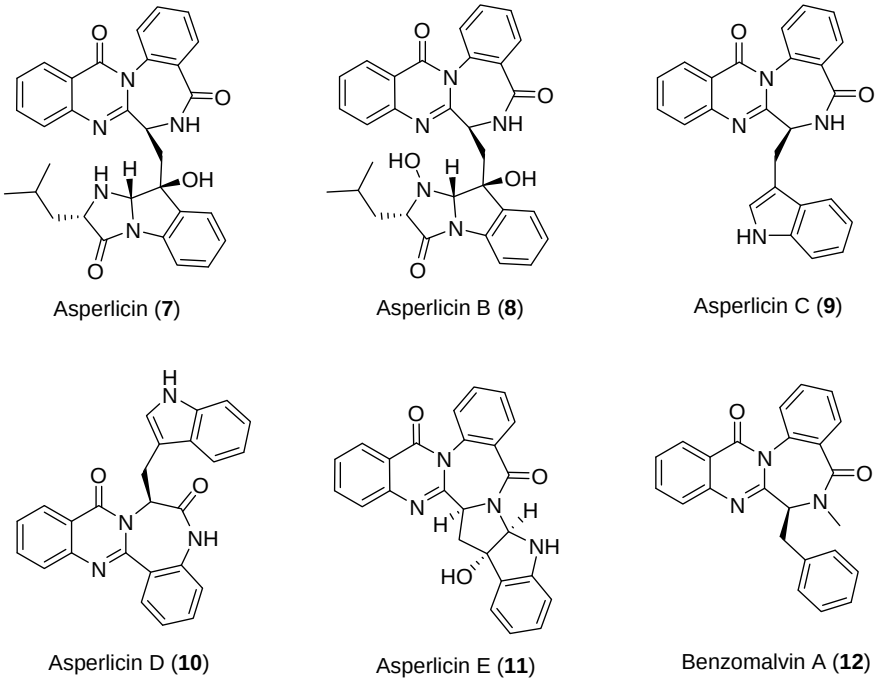


Figure 2. Naturally occurring quinazolinobenzodiazepinones

1.2 Background

The chemistry of the quinazolinone alkaloids is well documented in a number of comprehensive reviews and monographs and is continuously updated in Natural Product Reports.[1,5,6] Recently, from our research group Mhaske and Argade have published the review on the chemistry of quinazolinone alkaloids.[7] The review portrays a concise account of isolation, bioactivity, and synthesis of naturally occurring quinazolinone alkaloids isolated after the middle of 1983 up to 2005, and recent developments in the area of the complex quinazolinone natural products, with an emphasis on classical methods for their synthesis (Figure 3). The main synthetic routes to quinazolinone 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 as suitable precursors. In the solid-phase synthesis field, lithium reagents and transition metals have been used for the preparation of these compounds. Other important methods include coupling of *O*-methylbutyrolactam with anthranilic acid, cycloaddition of anthranilic acid iminoketene with methylbutyrolactam (via sulfonamide anhydride), reactions of anthranilic acid

derivatives with a wide range of substrates including imidates and imino halides, the reaction of anthranilic acid and the appropriately substituted imidate in a facile one-pot procedure, and microwave-promoted reaction of anthranilic acid with amines and formic acid (or its *ortho* ester) and isatoic anhydride. All these important methods for the synthesis of the quinazolinone alkaloids have been described in recent review from our group.[7]

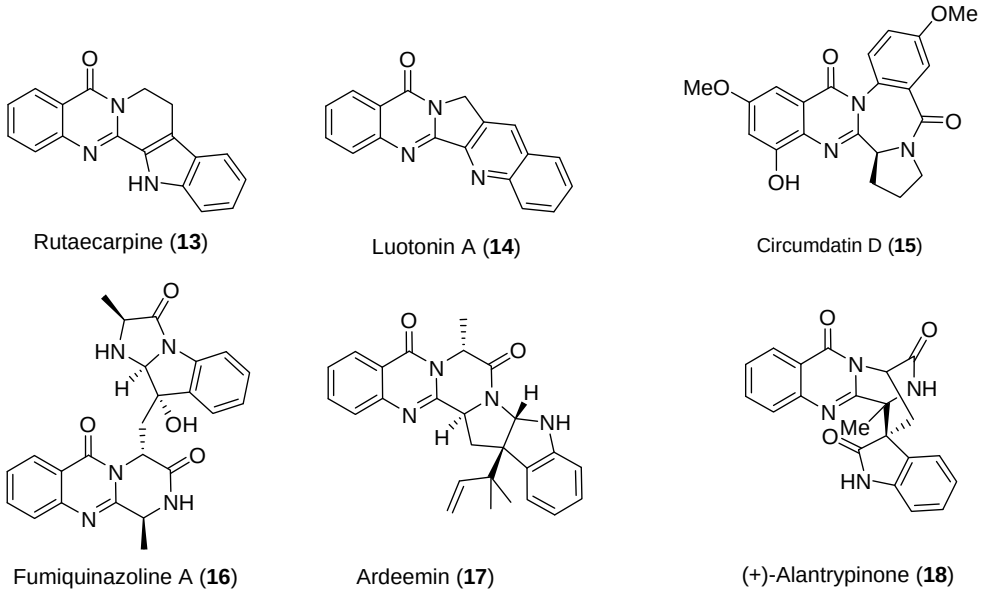
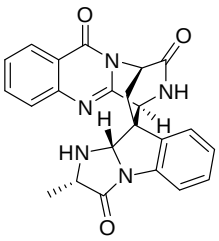


Figure 3. Selected quinazolinone alkaloids isolated up to the year 2005

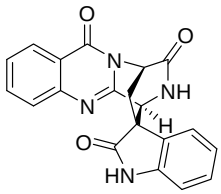
In the present chapter, we have described a concise account on isolation, bioactivity and synthesis of recently isolated, quinazolinone alkaloids and their derivatives with an emphasis on new synthetic routes and strategies published in the period of year 2005 to till date. Large amount of data is available in the literature, hence no pretension of completeness is claimed. To avoid repetition, the contents from our review have not been listed here.[7]

1.3 New quinazolinone alkaloids isolated after 2005

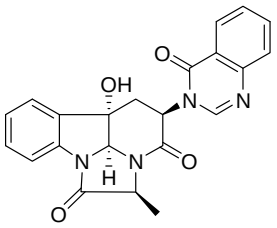
The 19 new natural quinazolin-4-ones have been isolated from various species during the period of 2005 to till date and are listed in figure 4 along with species from which it has been isolated with the details about their bioactivity and synthesis.



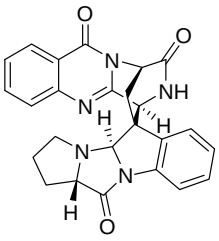
(+)-Lapatin A (**19**)
(*Penicillium lapatayae*)[8]
Activity: Not known
Synthesis: Not known



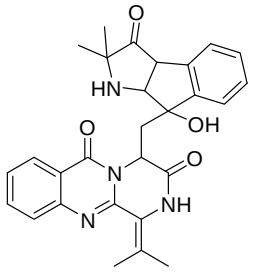
(–)-Lapatin B (**20**)
(*Penicillium lapatayae*)[8]
Activity: Not known
Synthesis: One[9]



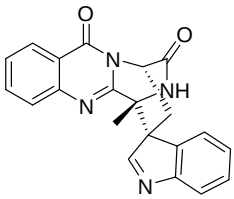
(–)-Chaetominine (**21**)
(*Chaetomium sp.* IFB-E015)[10]
Activity: Cytotoxic towards human leukemia K562 and colon cancer SW 1116 cell line
Synthesis: Three[11]



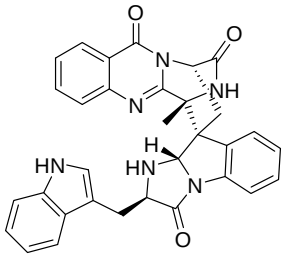
Quinadoline B (**22**)
(*Aspergillus sp.* FKI-1746)[12]
Activity: Lipid droplet synthesis inhibition
Synthesis: Not known



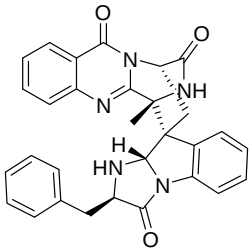
Quinadoline A (**23**)
(*Aspergillus sp.* FKI-1746)[12]
Activity: Lipid droplet synthesis inhibition
Synthesis: Not known



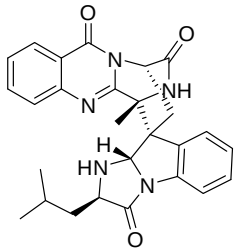
Alanditrypinene B (**24**)
(*Eupenicillium sp.*)[13]
Activity: Not known
Synthesis: Not known



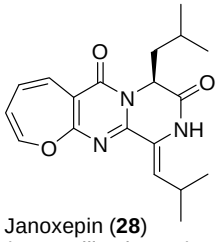
Alanditrypinone (**25**)
(*Eupenicillium sp.*)[13]
Activity: Not known
Synthesis: Not known



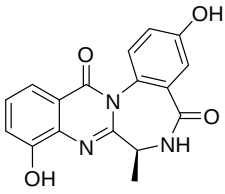
Alanditryphenone (**26**)
(*Eupenicillium sp.*)[13]
Activity: Not known
Synthesis: Not known



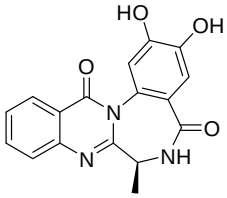
Alanditryleunone (**27**)
(*Eupenicillium sp.*)[13]
Activity: Not known
Synthesis: Not known



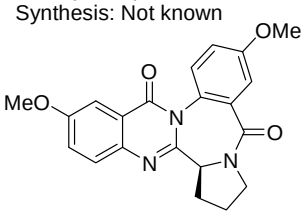
Janoxepin (**28**)
(*Aspergillus janus* (IBT 22274)[14]
Activity: Antiplasmodial
Synthesis: Not known



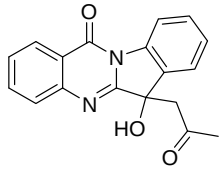
(–)-Circumdatine I (**29**)
(*Exophiala sp.*)[15]
Activity: UV-A protective
Synthesis: Not known



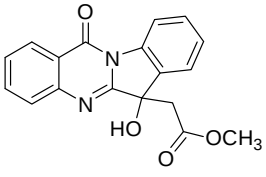
(–)-2-Hydroxycircumdatine C (**30**)
(*Aspergillus ochraceus*)[16]
Activity: DPPH radical-scavenging
Synthesis: Not known



(–)-Circumdatine J (**31**)
(*Aspergillus ostianus*)[17]
Activity: Not known
Synthesis: Two[18]



Phaitanthrin A (**32**)
(*Phaius mishmensis*)[19]
Activity: Weak cytotoxic
Synthesis: Not known



Phaitanthrin B (**33**)
(*Phaius mishmensis*)[19]
Activity: Weak cytotoxic
Synthesis: Not known

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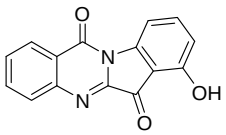
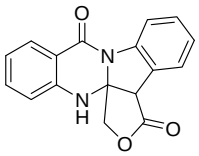
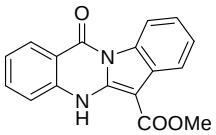


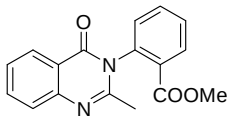
Phaitanthrin C (**34**)
(*Phaius mishmensis*)[19]
Activity: Weak cytotoxic
Synthesis: Not known



Phaitanthrin D (**35**)
(*Phaius mishmensis*)[19]
Activity: Weak cytotoxic
Synthesis: Not known



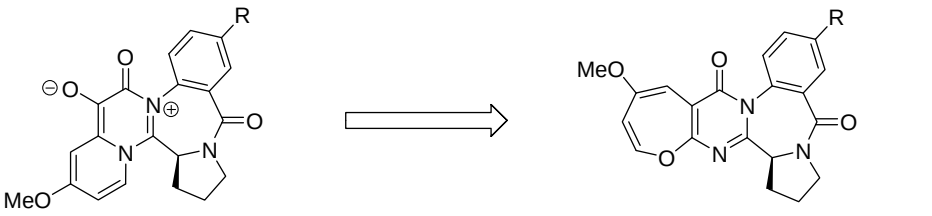
Phaitanthrin E (**36**)
(*Phaius mishmensis*)[19]
Activity: Weak cytotoxic
Synthesis: Not known



2-(2-Methyl-4-oxo-*4H*-quinazoline
-3-yl)benzoic acid methyl ester (**37**)
(*Pseudo-laeve var. erectum*)[20]
Activity: Not known
Synthesis: One (before isolation)[21]

Figure 4. Quinazolinone alkaloids isolated from the year 2005 onwards

Structure revision of (–)-Circumdatins A and B: The structures of circumdatins A and B (**38** and **39**), the pentacyclic alkaloids produced by *Aspergillus ostianus*, have been recently revised from the previously reported betaine structures to unique oxepine ones on the basis of X-ray crystallographic data (Figure 5).[17]



(–)-Circumdatin A (R = OMe)
(–)-Circumdatin B (R = H)
(Originally proposed structures)

(–)-Circumdatin A (R = OMe, **38)**
(–)-Circumdatin B (R = H, **39)**
(Revised structures)

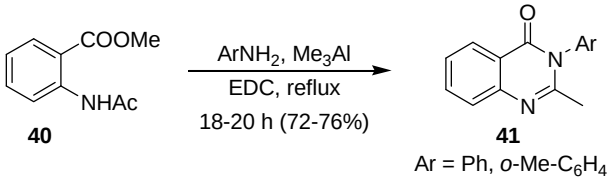
Figure 5. Revision in structural assignment of (**–**)-circumdatin A and B

To the best of our knowledge no quinazoline alkaloids have been isolated after 2005 to till date.

1.4 Recently developed synthetic methodologies towards the synthesis of quinazolinones (from the year 2005 to 2010)

During last five years remarkable progress on synthetic methodologies applicable to synthesis of quinazoline alkaloids and related molecules has been reported in the literature. Some of the important methodologies for the synthesis of quinazolinone have been described in this section.

Jeong and co-workers developed[22] a practical route to 2,3-disubstituted-quinazoline-4-one **41** (Scheme 1) involving the cyclization of benzodiamides derived from readily available benzoate **40**, with trimethylaluminium and various anilines in refluxing dichloroethane in moderate yields via the corresponding dimethylaluminium amide intermediates.



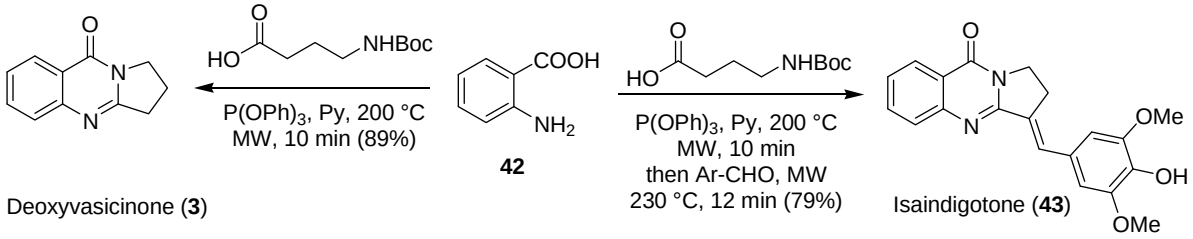
40

$ArNH_2$, Me_3Al
EDC, reflux
18-20 h (72-76%)

41
Ar = Ph, *o*-Me-C_6H_4

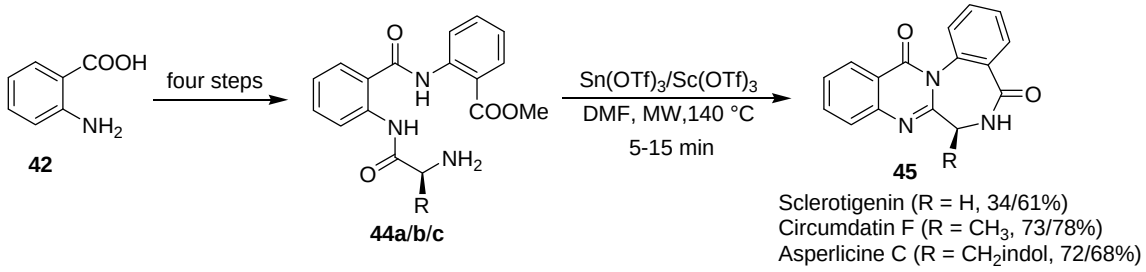
Scheme 1. Synthesis of 2,3-disubstituted-quinazoline-4-one from 2-acylamino-methylbenzoate

In last five years, microwave assisted syntheses of quinazolinones have been reported. Liu et al. reported highly efficient three-component one-pot reaction sequence promoted by microwave irradiation for the synthesis of 4-quinazoline-3,6-diones and have also devised one-pot total synthesis of isaindigotone, glyantrypine, fumiquinazoline F, fiscalin, asperlicine E, benzomalvin A. Liu et al. have also reported total synthesis of deoxyvasicinone, mackinazolinone, sclerotigenin, circumdatin F and asperlicine C via novel microwave-assisted domino reaction (Scheme 2).[23]



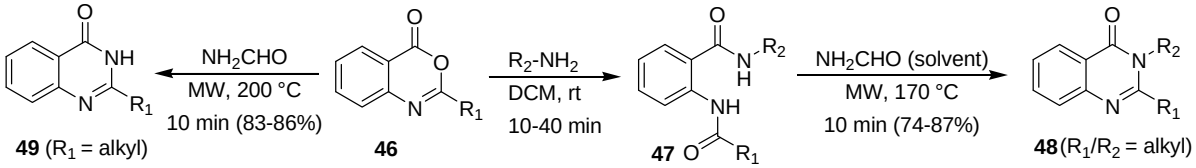
Scheme 2. Synthesis of deoxyvasicinone and isaindigotone via domino and three component one pot reactions

Chu and co-workers developed the microwave irradiated, tin triflate[24a] and scandium triflate[24b] catalyzed direct double cyclizations of bis(anthranilate)-containing tri-peptide **44a/b/c** precursors to afford the total synthesis of sclerotigenin, circumdatin F, asperlicine C and their derivatives (Scheme 3).



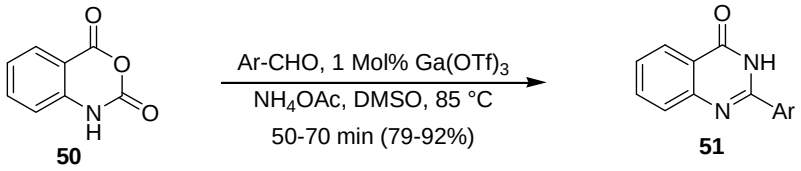
Scheme 3. Synthesis of quinazolinobenzodiazepinones from $Sn(OTf)_3/Sc(OTf)_3$-catalyzed cyclizations

Besson and co-workers reported an efficient methodology for the preparation of a series of 2,3-disubstituted-quinazolin-4(*3H*)-one **48** via microwave irradiation of linear diamide **47** using formamide as a solvent. Their results also revealed the microwave-assisted decomposition of formamide under controlled conditions of power, temperature and time were the important factors for the utilization of formamide as a very convenient source of ammonia for the synthesis of 2-substituted-quinazolin-4(*3H*)-one **49** (Scheme 4).[25]



Scheme 4. Microwave-assisted rapid synthesis of 2- and 2,3-disubstituted-quinazolin-4(*3H*)-one

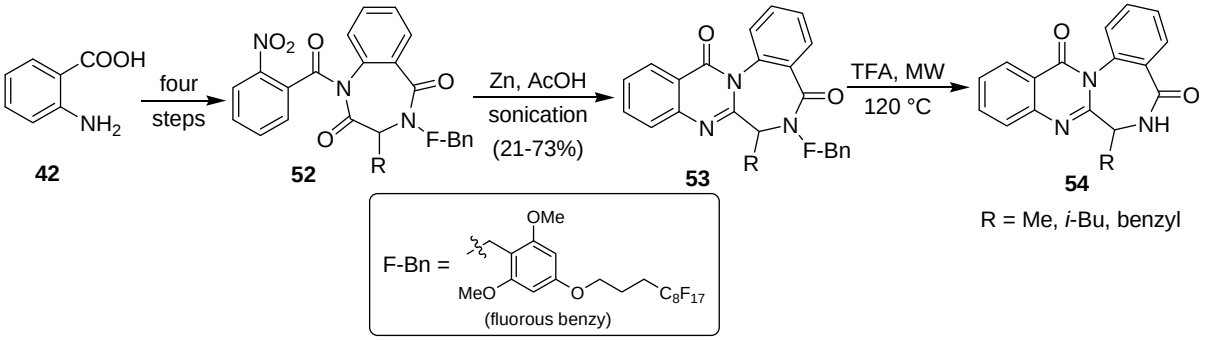
Su and co-workers developed $Ga(OTf)_3$ catalyzed simple and efficient protocol for the synthesis of 2-substituted-quinazoline-4(*3H*)-one **51** by one-pot reaction of isatoic anhydride **50**, ammonium acetate and aldehydes in DMSO under mild conditions (Scheme 5).[26] Mechanistically, the first step involves the reaction of isatoic anhydride **50** with ammonia to give anthranilamide. Then, condensation of anthranilamide with aldehydes promoted by $Ga(OTf)_3$ produce 2,3-dihydroquinazolin-4(*1H*)-ones and its oxidation using DMSO as the solvent provided them the corresponding 2-substituted-quinazoline-4(*3H*)-one **51**.



(Ar = Ph, *p*-Me-C_6H_4, *p*-NO_2-C_6H_4, *p*-Cl-C_6H_4, etc.)

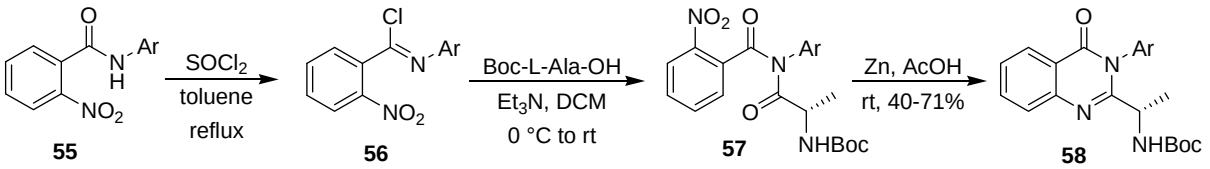
Scheme 5. Gallium triflate catalyzed one-pot synthesis of quinazolin-4(3*H*)-ones

Zhang and co-workers reported a new synthetic protocol for sclerotigenin-type benzodiazepine-quinazolinone library scaffold **54**.[27] A fluorous benzyl protecting group was used for the synthesis of 4-benzodiazepine-2,5-dione intermediate **53** and also as a phase tag for fluorous solid-phase extraction (Scheme 6).



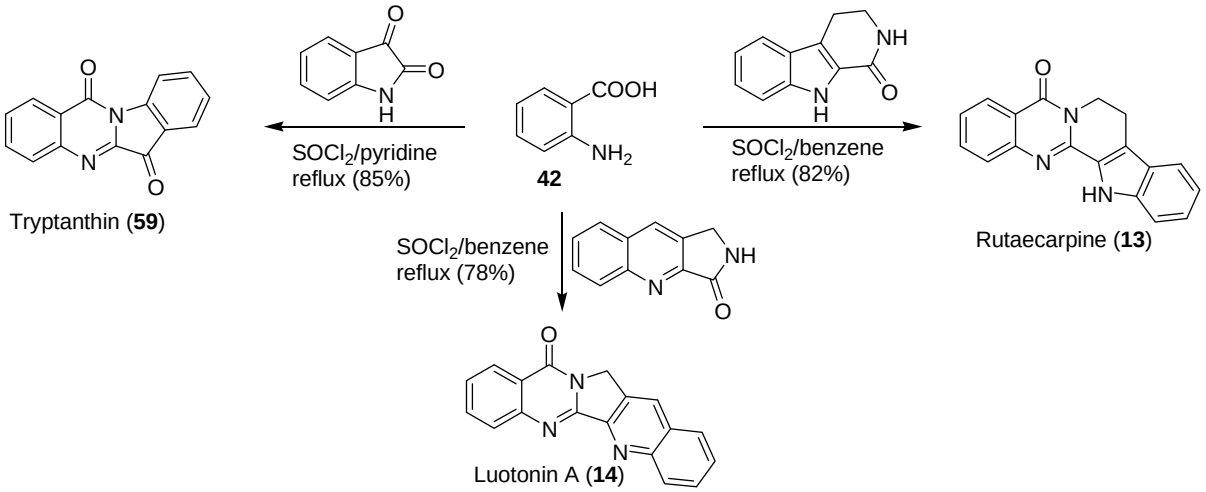
Scheme 6. Synthesis of quinazolinobenzodiazepinones

Zhichkin et al. reported an efficient three-step synthesis of chiral *3H*-quinazoline-4-one derivatives **58** from the commercial starting materials. Reaction of benzamide **55** with thionyl chloride gave the imidoyl chloride **56**.[28] The Mumm reaction of imidoyl chloride **56** with α-amino acids followed by reductive intramolecular cyclization using zinc metal in acetic acid at room temperature afforded enantiomerically pure (>93% ee) quinazoline-4-ones **58** in good overall yields (Scheme 7).



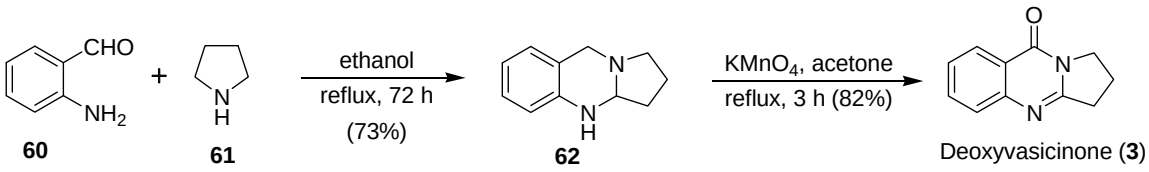
Scheme 7. Synthesis of 2,3-disubstituted-quinazolin-4(*3H*)-ones via the Mumm reaction

Jahng and co-workers developed the one pot synthesis of 2,3-disubstututed-4(3*H*)-quinazolinone by a reaction of anthranilic acid, corresponding lactam and thionyl chloride in refluxing benzene or pyridine. They have utilized this protocol for the one-pot synthesis of luotonin A (**14**), rutaecarpine (**13**) and tryptanthrin (**59**) (Scheme 8).[29] All the above mentioned condensation reactions proceed via the corresponding *N*-sulfinylanthraniloyl chloride intermediate.



Scheme 8. One-pot synthesis of quinazolinone alkaloids

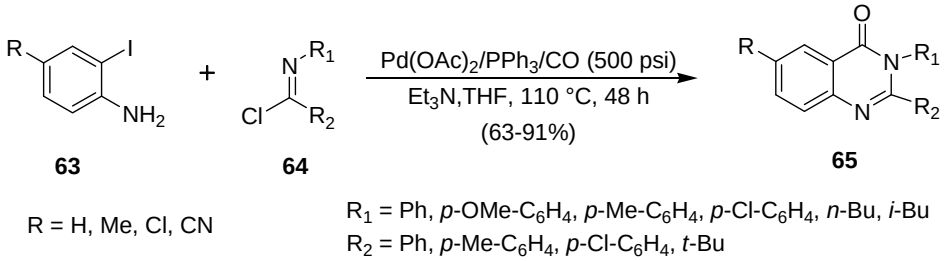
Seidel and co-workers reported a new α-functionalization reaction of cyclic amines that proceeds without the involvement of transition metal or other additives(Scheme 9).[30] In the redox-neutral condensation reaction, a C–H bond *α* to the ring nitrogen was replaced by a C–N bond with the concomitant formation of a new ring system. The thermally promoted reaction between an *o*-aminobenzaldehyde (**60**) and a pyrrolidine (**61**) resulted in the formation of a ring-fused aminal **62**. *o*-Aminobenzaldehydes were allowed to react with various cyclic amines in ethanol solution at reflux temperature. *o*-Aminobenzaldehydes with different substitution patterns and electronic properties also provided them the desired products in good yields. Selective oxidation of these ring-fused aminal provided rapid access to 2,3-disubstututed-quinazolin-4(3*H*)-ones.



Scheme 9. Synthesis of ring-fused aminals via *α*-functionalization of cyclic amines

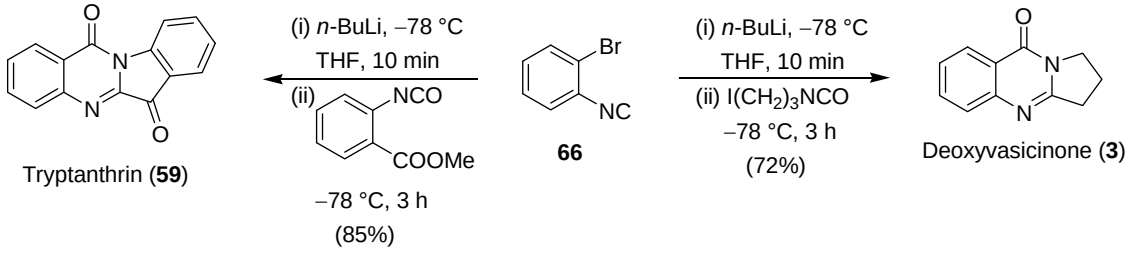
Alper and co-workers recently reported the palladium-catalyzed three component cyclocarbonylation reaction of *o*-iodoanilines **63** with imidoyl chlorides **64** and carbon monoxide via in situ formation of an amidine, followed by oxidative addition of palladium, CO insertion, and intramolecular cyclization, which furnished the substituted 2,3-disubstututed-quinazolin-4(*3H*)-ones

65. The method tolerates a range of functional groups, and substituted quinazoline-4(*3H*)-ones **65** were formed in 63-91% yields (Scheme 10).[31]



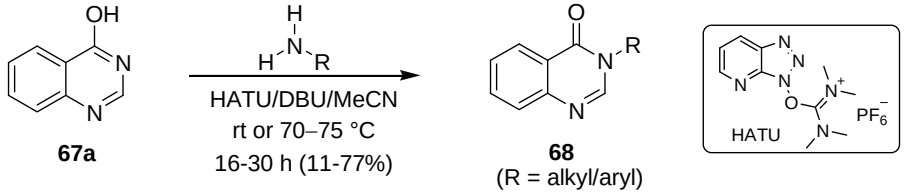
Scheme 10. Palladium-catalyzed cyclocarbonylation of *o*-iodoanilines

Meijiere and co-workers have generated *o*-lithiophenyl isocyanide by halogen-lithium exchange of *o*-bromophenyl isocyanide (**66**) and subsequently trapped the thus generated *o*-lithiophenyl isocyanide with electrophiles. This strategy has been effectively employed for the new three-step one-pot synthesis of substituted 3*H*-quinazolin-4-ones including the naturally occurring alkaloids deoxyvasicinone (**3**) and tryptanthrine (**59**) (Scheme 11).[32]



Scheme 11. Synthesis of 2,3-disubstituted-quinazolin-4(*3H*)-ones via *ortho*-lithiophenyl isocyanide

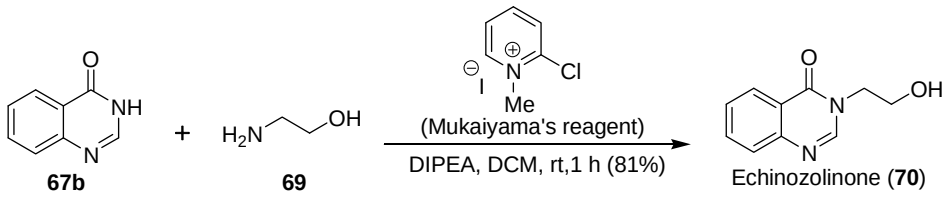
Very recently, Yang and co-workers developed a novel method for the synthesis of 3-substituted 4(3*H*)-quinazolinones from unsubstituted quinazolinones via a uronium-mediated coupling with amines.[33] In which primary alkyl amines were allowed to react with 4-hydroxyquinazolines (**67a**) in presence of uronium-based coupling reagent (HATU) and DBU in acetonitrile at room temperature to exclusively furnish the corresponding 3-substituted 4(3*H*)-quinazolinones (**68**). Whereas the aryl amines demand higher temperature (70−75 °C) for the same reaction (Scheme 12).



Scheme 12. HATU-mediated coupling of 4-hydroxyquinazolinones with amines

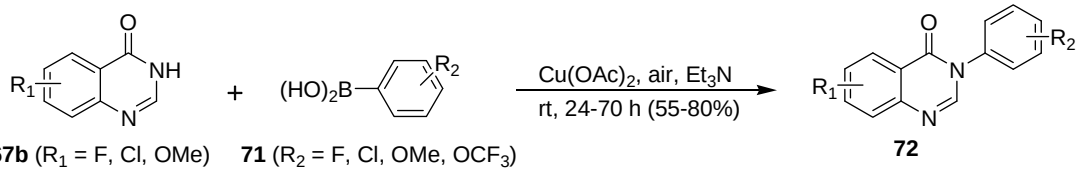
Wacharasindhu and co-workers also reported such type of reaction to obtain 3-substituted 4(3*H*)-quinazolinones from unsubstituted quinazolinones by using Mukaiyama's reagent-mediated coupling with amines.[34] In this reaction primary alkyl amines were allowed to react with 4-hydroxyquinazolines (**67b**) in presence of Mukaiyama's reagent and DIPEA in dichloromethane at

room temperature which provided 3-substituted 4(3*H*)-quinazolinones. Further they have also accomplished one step synthesis of echonozolinone **70** in 81% yield using the same methodology (Scheme 13). Mechanistically, they hypothesize that the Mukaiyama reagent first activates the nitrogen atom of the quinazolinone at the 3-position leading to the formation of a pyridinium-quinazolinone intermediate, attack of the primary amine on the amide moiety results in the ring opening product enamine and cyclization followed by elimination of an aminopyridinium generates the desired product.



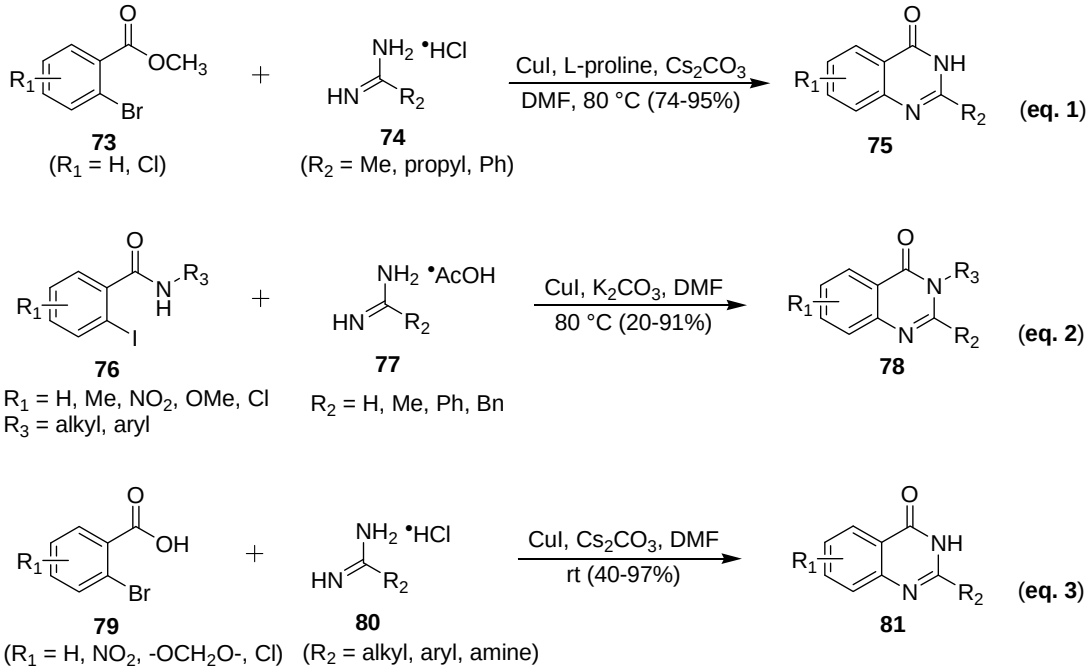
Scheme 13. Mukaiyama's reagent promoted coupling of 4-hydroxyquinazolinones with amines

Das and co-workers reported the copper-promoted *N*-arylation of quinazolin-4(3*H*)-one.[35] In which quinazolin-4(3*H*)-ones **67b** and arylboronic acids **71** in the presence of $Cu(OAc)_2$ at room temperature under atmospheric conditions gave the desired *N*-aryl quinazolinones **72** in good yields (Scheme 14).



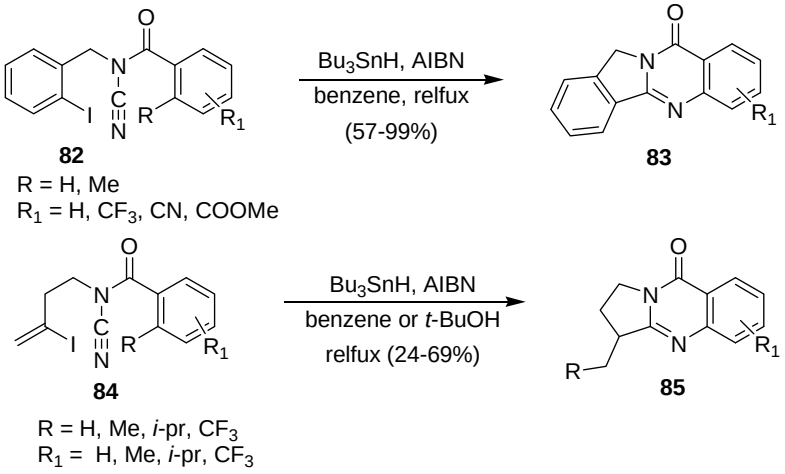
Scheme 14. Copper(II)-catalyzed coupling of quinazolinones with arylboronic acids

Zhao and co-workers developed a general and efficient copper-catalyzed method for 2-substitued-quinazoline-4(*3H*)-ones by cascade reaction of amidine hydrochlorides with 2-halomethylbenzoate (Scheme 15, eq. 1).[36a] Reaction of *ortho*-halomethylbenzoate **73** with amidine hydrochlorides **74** using copper iodide as catalyst, L-proline as ligand and cesium carbonate as the base in DMF as solvent at 110 °C exclusively provided 2-substitued-quinazoline-4(*3H*)-ones **75**. Ding and co-workers[36b] and latter Zhao and co-workers[36c] reported ligand-free copper-catalyzed reactions. In Ding and co-worker's approach, *o*-haloarylcarboxymide **76** were aminated with amidine acetate **77** under ligand-free copper iodide catalyzed coupling reaction and an in-situ intramolecular cyclization gave the corresponding 2-substituted, 3-substituted and 2,3-disubstututed-quinazolin-4(*3H*)-ones **78** (Scheme 15, eq. 2). Whereas in the Zhao and co-worker's strategy, *o*-haloarylcarboxylic acids **79** were coupled with amidine hydrochlorides **80** under ligand-free copper iodide catalyzed coupling reaction, then an in-situ dehydrative cyclization furnished the corresponding 2-substituted-quinazolin-4(*3H*)-ones **81** (Scheme 15, eq. 3). As expected, in the absence of ligands some of the desired quinazolinones were obtained in low yields.



Scheme 15. Copper(I)-catalyzed coupling of imidamides with *o*-haloaryl-carboxy derivatives

Malacria and co-workers developed cascade radical cyclization process of *N*-acylcyanamides **82**/**84** for the general access to pyrroloquinazoline-type polycyclic *N*-heterocycles **83**/**85** via a domino process that constructs new C–C and C–N bonds by radical migration of hydrogen atoms or carbon substituents on aromatic ring (Scheme 16).[37] This process was illustrated by a rapid synthesis of the naturally occurring alkaloid luotonin A.

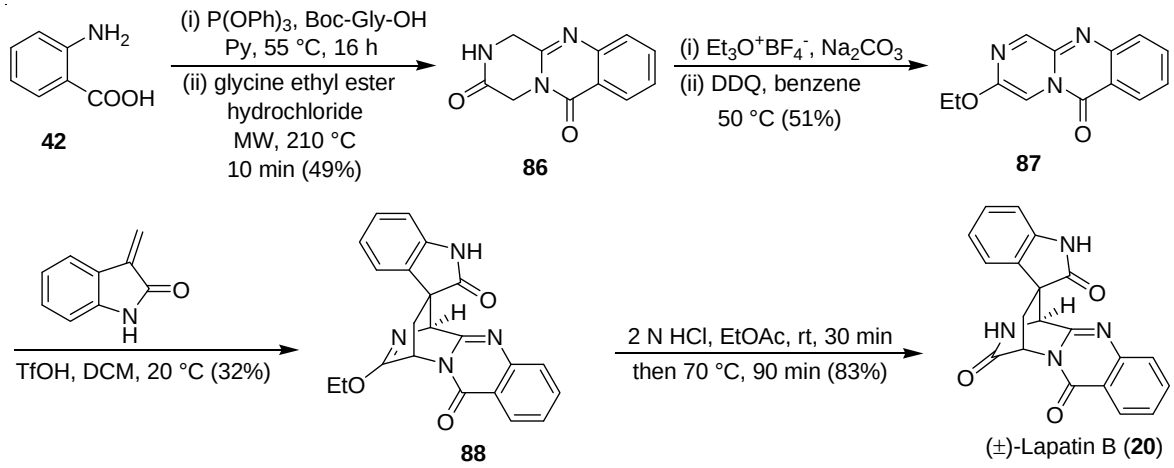


Scheme 16. Radical cyclization cascade of *N*-acyl-*N*-(2-iodobenzyl)cyanamides

1.5 Total synthesis of quinazolinone alkaloids

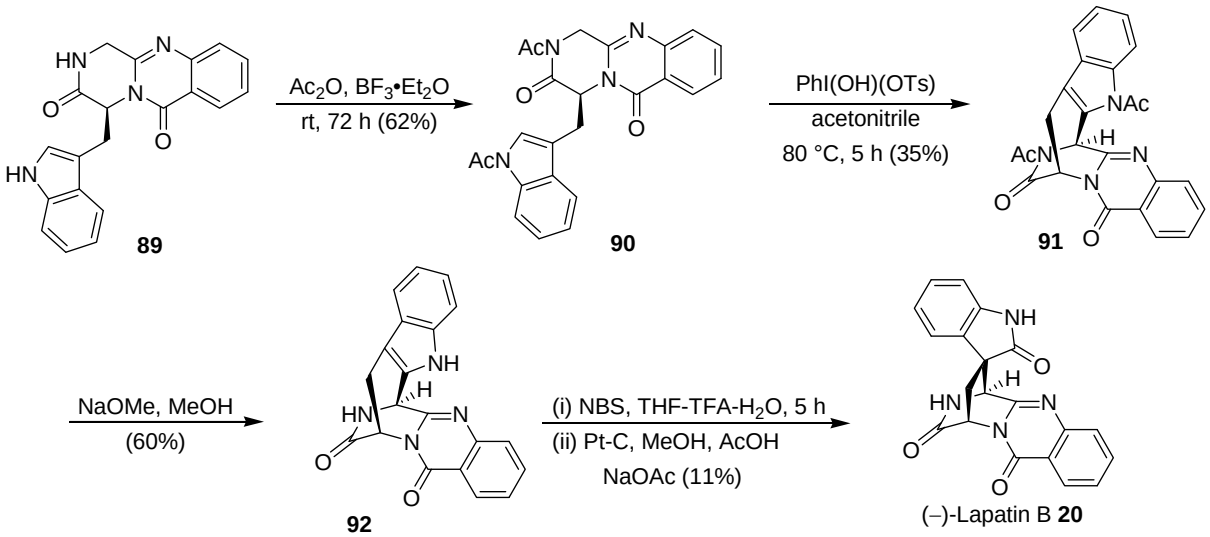
Houk and co-workers reported the first total synthesis of very recently isolated microfungal alkaloid (±)-lapatin B (**20**) in five steps with 8% overall yield via a aza-Diels-Alder reaction as the key step (Scheme 17).[9a] The pyrazino[2,1-*b*]quinazoline-3,6-diones (**86**) was prepared following Liu's

microwave mediated[23] procedure. Iminoether formation of **86**, followed by DDQ oxidation afforded the azadienes **87** in good yields. Aazadiene **87** was subjected to Bronsted acid catalyzed hetero-Diels-Alder reaction with metheleoxindol which gave the exo product **88** (32%) along with the endo product (30%) in 1:1 ratio. Hydrolysis of this exo product **88** with 2 N HCl in ethyl acetate afforded (±)-lapatin B (**20**) in 83% yield.



Scheme 17. First total synthesis of (±)-lapatin B via aza-Diels-Alder reaction

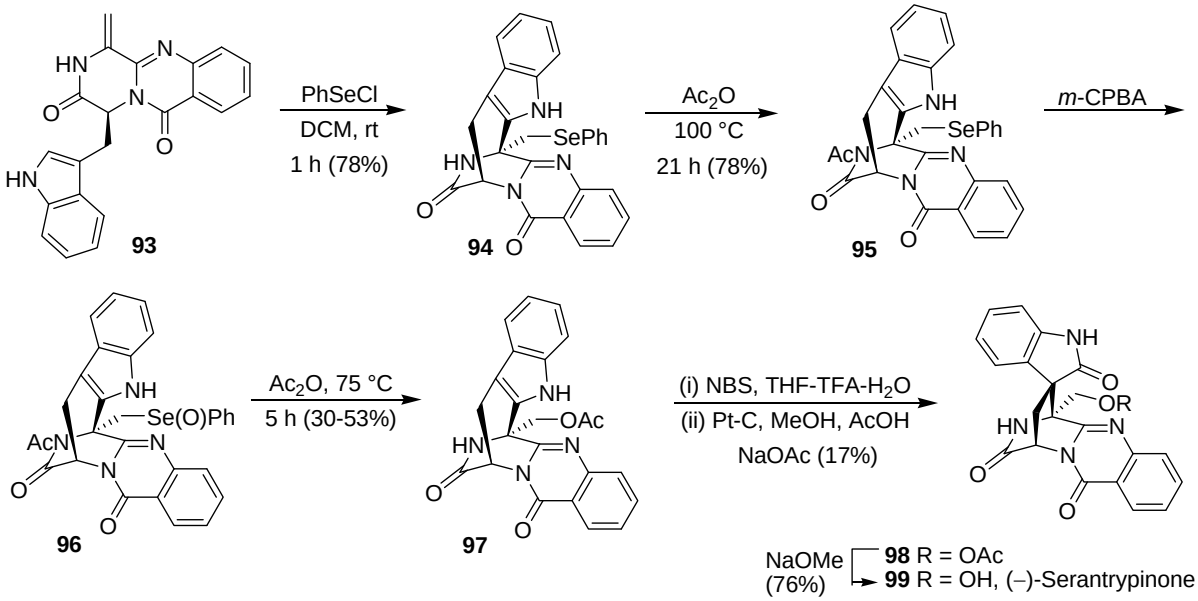
Hart and co-workers reported the first enatioselective synthesis of (–)-lapatin B (**20**) (Scheme 18).[9b] The natural product (+)-glyantrypine (**89**) was prepared using the literature procedure. Treatment of (+)-glyantrypine (**89**) with acetic anhydride and boron trifluoride etherate provided optically active **90** in 62% yield. Treatment of (+)-**90** with Koser's reagent [PhI(OH)(OTs)] gave bridged indole **91** in 35% yield via intramolecular cyclization. Upon treatment with a catalytic amount of sodium methoxide in methanol, the *N*-acetyl groups of **91** were removed to provide (+)-**92** in 60% yield. The synthesis was completed upon treatment of (+)-**92** with *N*-bromosuccinimide, followed by hydrogenolysis of the resulting brominated oxindoles over platinum on carbon in methanol and



Scheme 18. First enantioselective synthesis of (–)-lapatin B

acetic acid. Herein the NBS-catalyzed structural rearrangement of compound **92** to the spiro-system **20** is noteworthy. Finally, the preparative thin layer chromatographic purification provided (–)-lapatin B (**20**) and 13-*epi*-(+)-lapatin B in 11% yields.

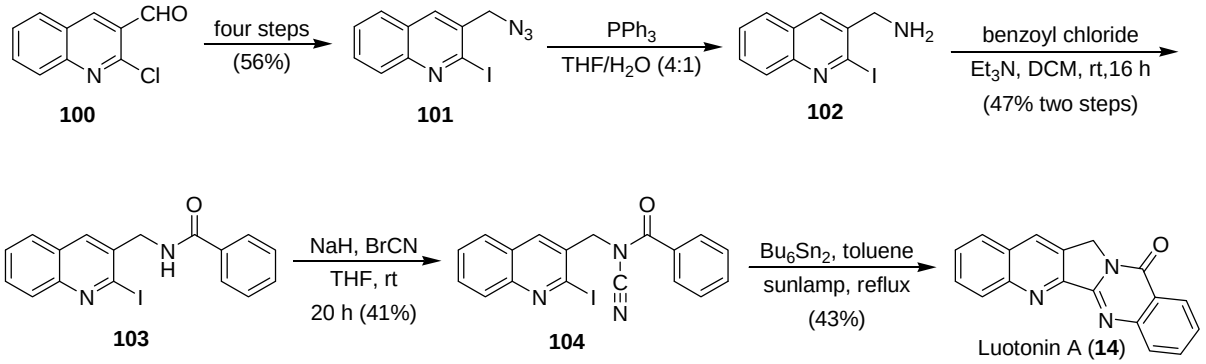
Hart and co-workers also accomplished the first total synthesis of (–)-serantrypinone (**99**) (Scheme 19).[38] The synthesis began with compound **93**, prepared from L-tryptophan ethyl ester in six steps, in their *ent*-(–)-alantrypinone synthesis.[39] Treatment of **93** with phenylselenenyl chloride in dichloromethane provided bridged indole **94** in 78% yield. Conversion of **94** to imide **95** was carried out by using acetic anhydride in 78% yield. Oxidation of **95** with *m*-CPBA followed by immediate reaction of the resulting mixture of selenoxides **96** with acetic anhydride gave **97** in 30–53% overall yield via an intramolecular acyl migration. Oxidative rearrangement of **97** was accomplished by treatment with *N*-bromosuccinimide, followed by hydrogenolysis of the resulting brominated oxindoles over platinum on carbon to provide spirooxindole **98**. Methanolysis of the ester **98** using sodium methoxide in DMSO provided (–)-serantrypinone (**99**) in 76% yield.



Scheme 19. First total synthesis of (–)-serantrypinone

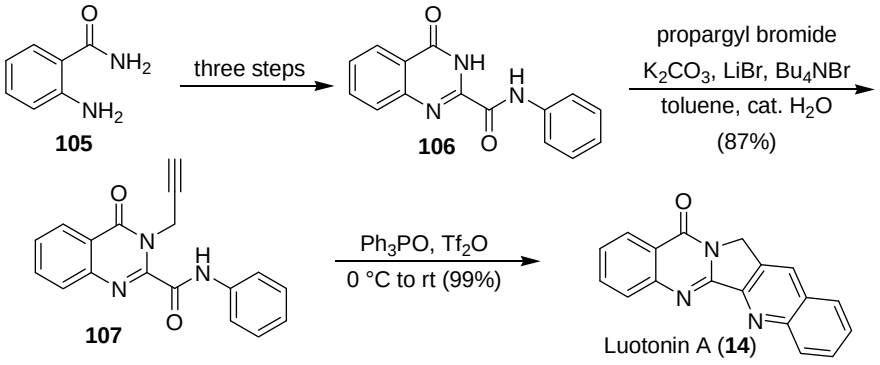
Malacria and co-workers have completed the total synthesis of luotonin A using their cascade radical cyclization methology (Scheme 20).[40] Azide **101** was prepared from commercially available quinoline chlorocarbaldehyde **100** in four steps (56% overall yield). Staudinger reduction of the azide **101** delivered an amine **102**, which was benzoylated to give amide **103** in 47% yield (two steps). Cyanation of amide **103** using cyanogen bromide yielded *N*-acylcyanamide **104** in 41% yield. Under radical cyclization conditions with tributyltin hydride, reaction of **104** did not afford the cyclized compound. The reaction proceeded with low conversion that turned into degradation, when the precursor was maintained under the same reaction conditions. Gratifyingly, atom-transfer

conditions using hexabutylditin in refluxing toluene under irradiation for 6 h successfully yielded luotonin A (**14**) in 43% yield.



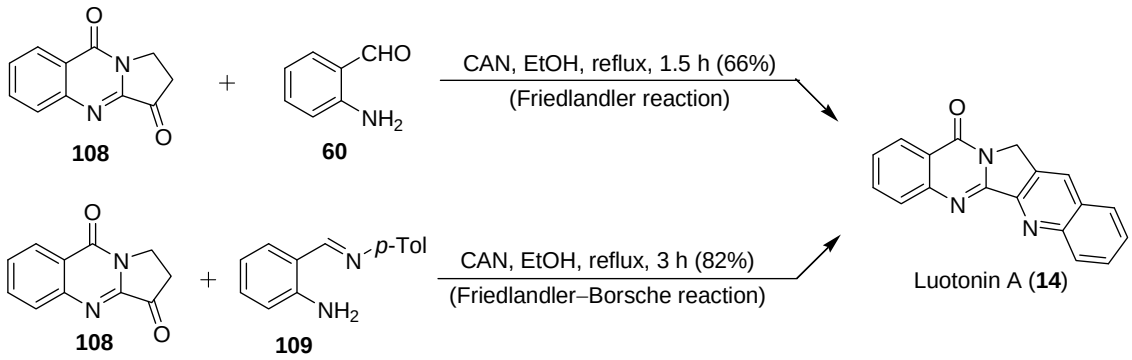
Scheme 20. Total synthesis of luotonin A via the cascade radical cyclization process

Yao and co-workers achieved the total synthesis of luotonin A (**14**) using key cascade annulations reaction in five steps with 47% overall yield (Scheme 21).[41] Starting from commercially available anthranilamide (**105**), they prepared amide **106** in three steps. *N*-Alkylation of amide **106** with propargyl bromide provided the precursor amide **107** in 87% yield. Finally, the cascade annulation was carried out by simple treatment of **107** with bis(triphenyl)-oxodiphosphonium trifluoromethanesulfonate at room temperature for 1 h, affording luotonin A (**14**) in 99% yield.



Scheme 21. Total synthesis of luotonin A via the cascade annulation strategy

Menendez and co-workers developed a mild, environmentally friendly, and very efficient protocol for the Friedlander and Friedlander-Borsche reactions under CAN catalysis, avoiding the need of

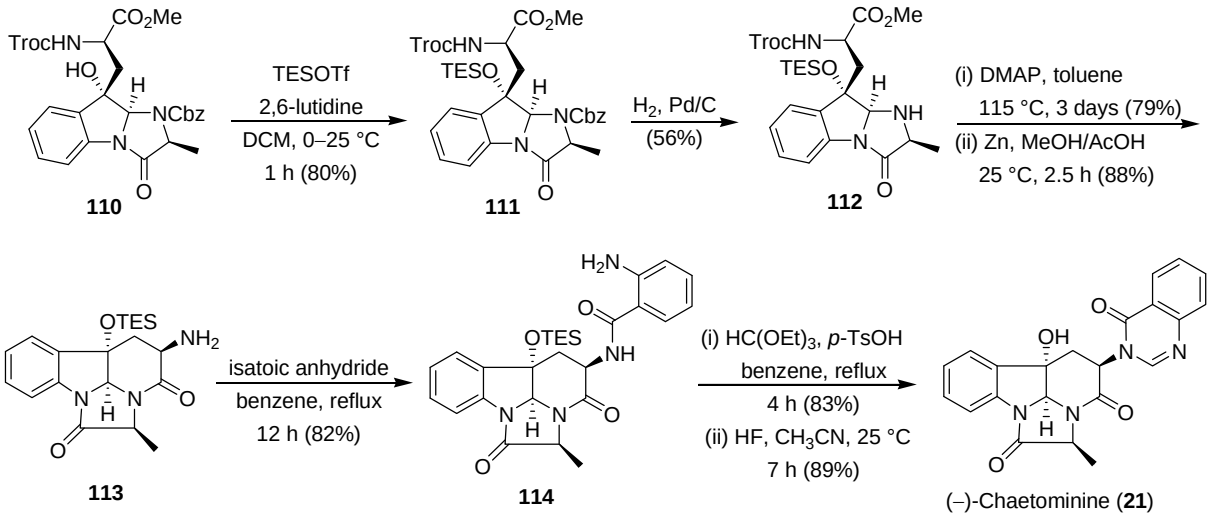


Scheme 22. Total synthesis of luotonin A via CAN-catalyzed Friedlander-Borsche reactions

harsh basic or acidic conditions.[42] This protocol has been applied for the synthesis of the naturally occurring cytotoxic alkaloid luotonin A (**14**) (Scheme 22). Cyclocondensation between **108** and 2-aminobenzaldehyde (**60**) was complete in 1.5 h under the CAN catalysis and gave 66% of luotonin A (**14**). Using *N*-(2-aminobenzylidene)-4-methylaniline (**109**) as a 2-aminobenzaldehyde equivalent (Borsche modification of the Friedlander reaction) under the CAN catalysis also afforded 82% of luotonin A (**14**).

(–)-Chaetominine (**21**) was isolated in 2006 by Tan and co-workers from the solid-substrate culture of *Chaetomium* sp. IFB-E015, an endophytic fungus on apparently healthy *Adenophora axilliflora* leaves.[10] (–)-Chaetominine (**21**) is very closely related to the fumiquinazoline alkaloids. It is a modified tripeptide alkaloid containing D-tryptophan, L-alanine, anthranilic acid, and formic acid. In vitro cytotoxic assays showed that (–)-Chaetominine (**21**) was highly potent against human leukemia K562 (IC_{50} 21 μM) and colon cancer SW1116 (IC_{50} 28 μM) cell lines with IC_{50} values smaller than the ones of 5-fluorouracil, which is one of the most frequently prescribed anticancer drugs. Due to its intriguing molecular architecture and its potential as a lead compound for anticancer drugs, (–)-chaetominine **21** has attracted immediate interest from the synthetic community. This culminated in three total syntheses of this exotic molecule.[11] Snider and Wu in a very short span of time (less than one year after its isolation) reported its first total synthesis[11a] using hydroxyimidazolidinone intermediate **110** from their (–)-fumiquinazoline[43] synthesis (Scheme 23).

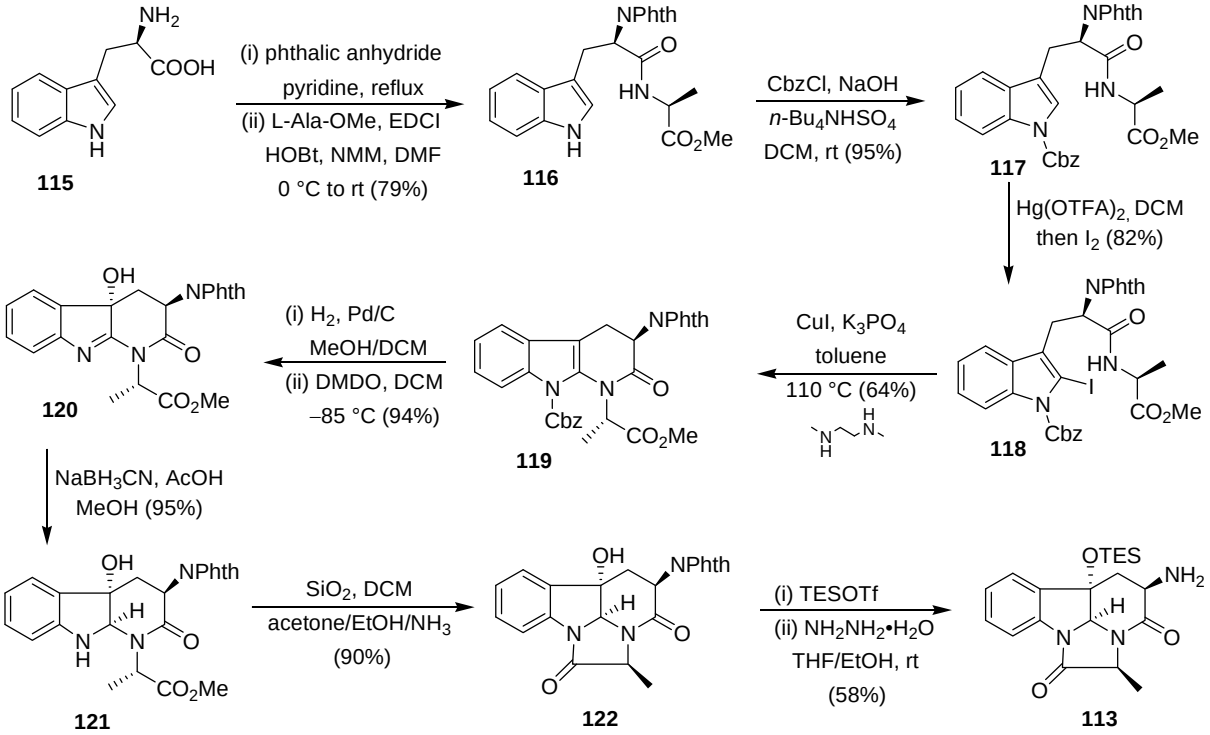
Reaction of hydroxyimidazolidinone **110** with TESOTf provided TES-ether **111** in 80% yield. Hydrogenolysis of **111** afforded the desired amino ester **112** in 56% yield. Lactamization of amino ester **112** by heating in toluene containing a catalytic amount of DMAP for 3 days at reflux in a sealed tube followed by deprotection of the Troc-group without cleavage of the TES-ether was accomplished with Zn in 1:1 MeOH/HOAc to provide the amine **113** in 88% yield. Reaction of amine **113** with isatoic anhydride in benzene at reflux condition afforded amino amide **114** in 82% yield.



Scheme 23. First total synthesis of (−)-chaetominine

Reaction of **114** with excess triethyl orthoformate and a catalytic amount of *p*-TsOH in benzene at reflux provided TES-protected chaetominine in 83% yield. Finally, simple cleavage of the TES-group provided (–)-chaetominine (**21**) in 89% yield. (−)-Chaetominine (**21**) was synthesized from (–)-fumiquinazoline intermediate the hydroxyimidazolidinone **110** in seven steps in 22% overall yield. They have also proved the nice way to the strained tetracyclic framework of this compact modified tripeptide.

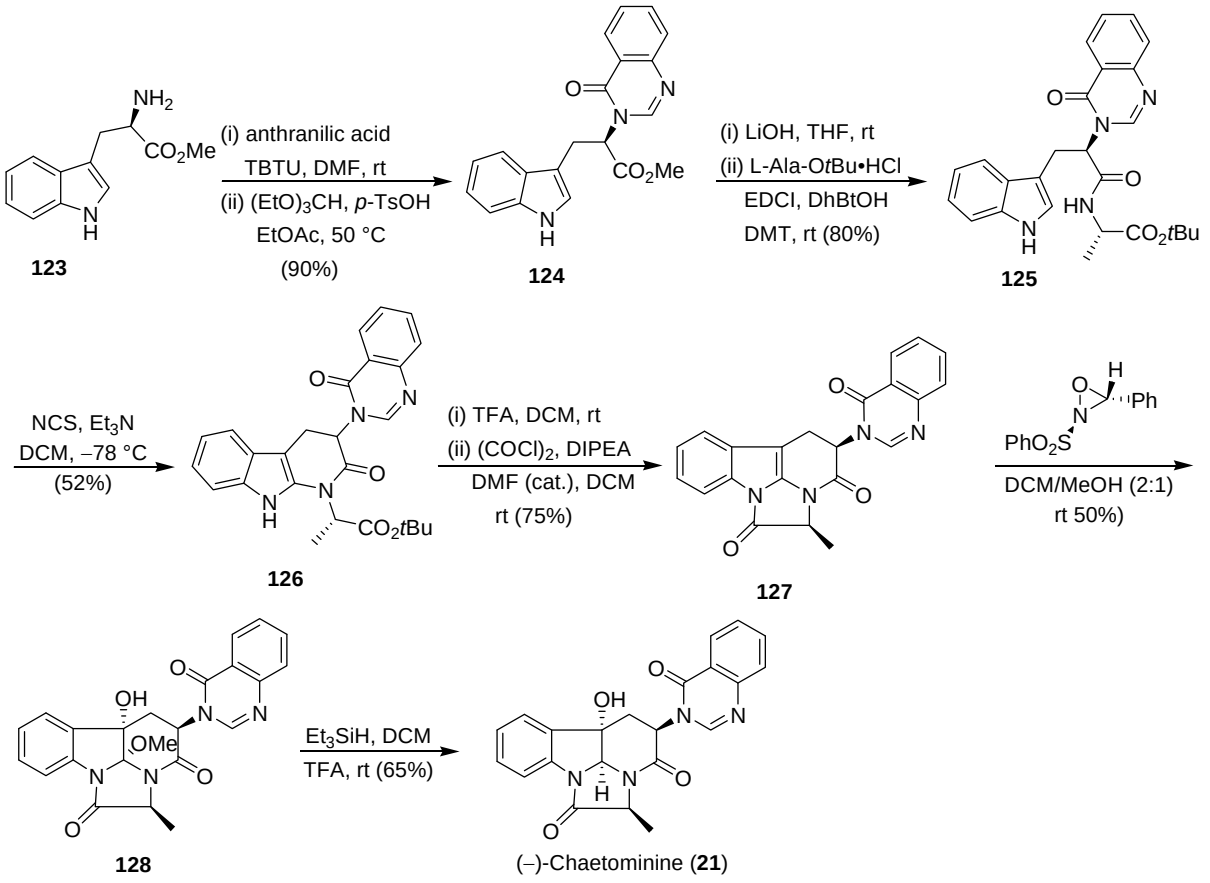
Evano and co-workers reported the second synthesis of (–)-chaetominine using copper(I)-mediated cyclization reaction as key step to install the ABC-tricyclic ring system in 14 steps with 10% overall yield (Scheme 24).[11b] Synthesis started with protection of D-tryptophan (**115**) by the reaction with phthalic anhydride followed by coupling with alanine methyl ester, which gave dipeptide **116**. The indole nitrogen was selectively protected as a carbamate using phase-transfer conditions to furnished fully protected dipeptide **117**. Mercuration with mercury trifluoroacetate followed by workup with potassium iodide and reaction with iodine allowed for a clean regioselective introduction of the iodide at C-2 position of the indole ring in **117** and set the stage for the key cyclization step. Intramolecular *N*-arylation of amide nitrogen of **118** was effected using a combination of copper iodide, *trans*-*N*,*N*'-dimethylcyclohexane-1,2-diamine and potassium phosphate at 110 °C in toluene to give tricyclic compound **119**. Carbamate protection in **119** was cleaved using hydrogenation reaction and diastereoselective oxidation with DMDO gave hydroxyl imine **120** and further reduction of imine functionality with sodium cyanoborohydride gave compound **121** as single diastereomer. Silica gel mediated γ–lactamization of **121** gave desired



Scheme 24. Evano's total synthesis of (–)-chaetominine via copper(I)-mediated cyclization reaction

tetracyclic compound **122**. Silyl protection of hydroxyl group followed by removal of phthalimide protection provided the Snider and Wu's advanced (–)-chaetominine intermediate free-amine **113**, which was coverted to (–)-chaetominine (**21**) using the known three-step sequence.

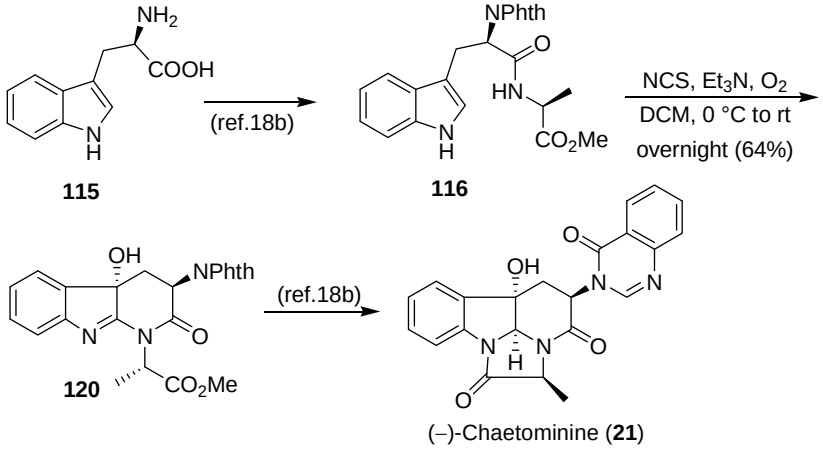
Papeo and co-workers reported a new total synthesis of (–)-chaetominine (**21**) in nine steps with 9% overall yield (Scheme 25).[11c] Quinazolinone moiety was introduced on D-tryptophan methyl ester (**123**) at early stage followed by hydrolysis of methyl ester and coupling with *tert*-butyl ester of L-alanine provided the compound **125**. Tricyclic tetrahydro-1*H*-pyrido[2,3-*b*]indole **126** was obtained by NCS mediated *N*-acyl cyclization on an indol ring of compound **125** in 9:1 diastereomeric ratio. TFA-mediated cleavage of *tert*-butyl ester **126** followed by intramolecular γ–lactamization via the corresponding acid chloride provided the tetracyclic intermediate **127** as a single diastereoisomer. Stereoselective manipulation of the indole double bond via an oxidation–reduction sequence using the classical Davis oxidant (±)-oxaziridine and Et_3SiH as reducing agent secured (–)-chaetominine (**21**). Early stage introduction of quinazolinone moiety and late stage introduction of hydroxyl group allowed this synthetic strategy with minimal use of protecting group.



Scheme 25. Papeo's straightforward synthesis of (–)-chaetominine

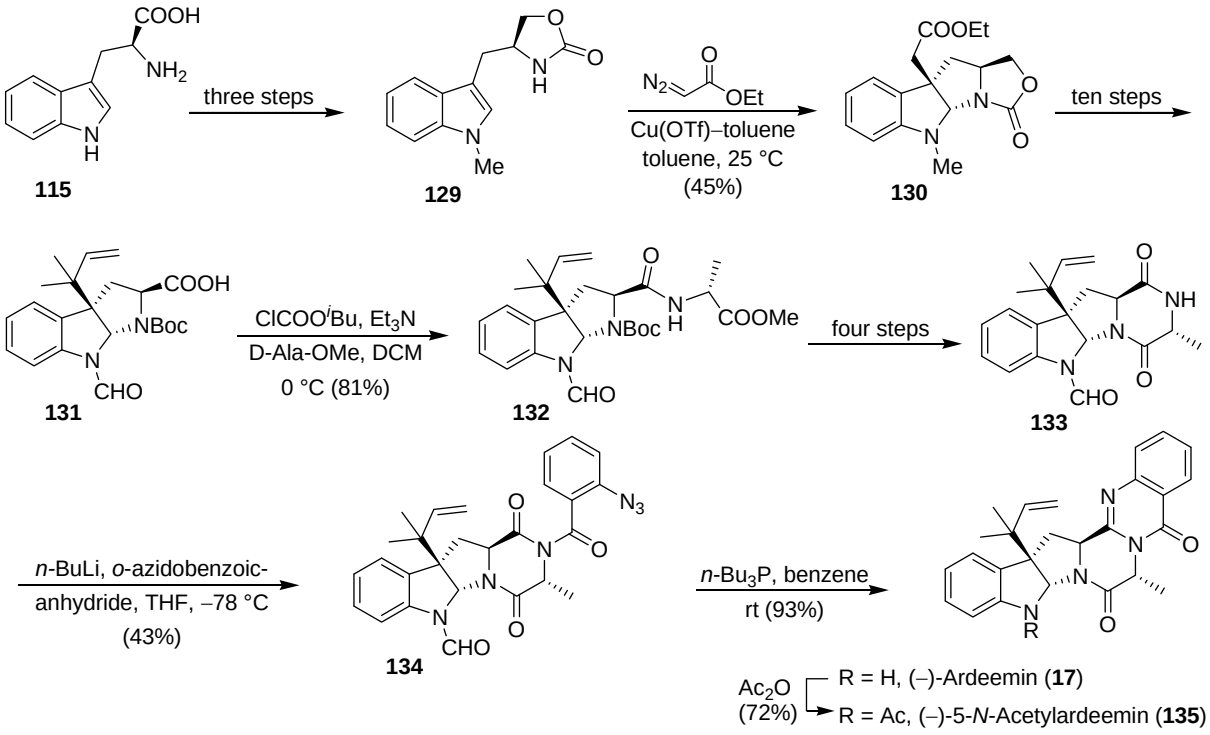
Recently, Evano and coworkers published their improved synthesis[11d] of (–)-chaetominine (**21**) using efficient domino process involving a diastereoselective oxidative cyclization followed by photo-

oxidation of a tryptophanyl-alanine dipeptide **116**, with *N*-chlorosuccinimide and triethylamine under an atmosphere of oxygen which gave compound **120**, which also provides a straightforward route to the (–)-chaetominine **21** in nine steps and 14% overall yield starting from D-tryptophan and L-alanine as the building blocks (Scheme 26).



Scheme 26. Evano's formal synthesis of (−)-chaetominine (**21**)

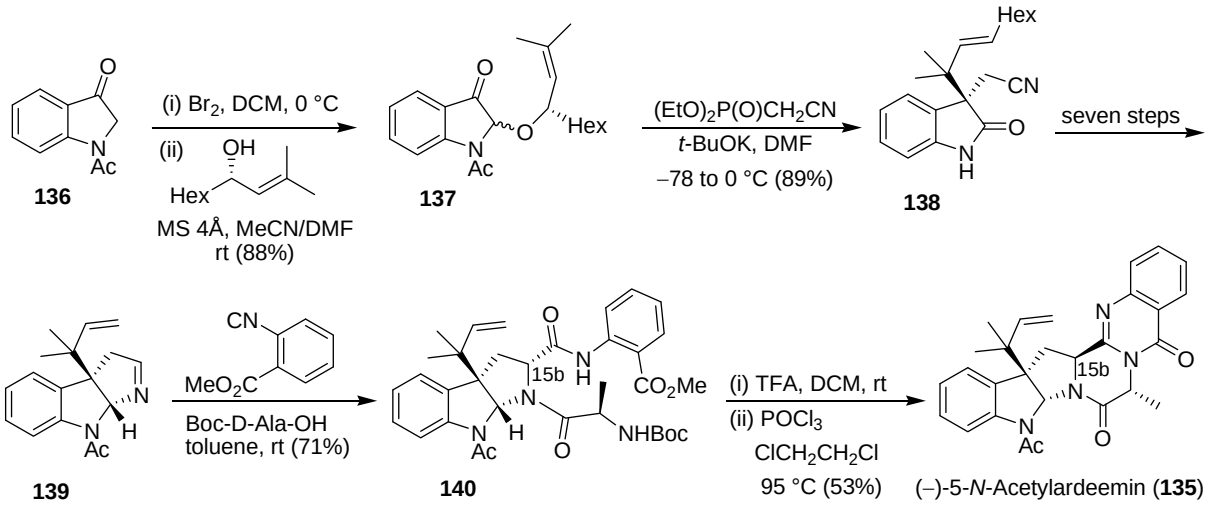
Qin and co-worker's have accomplished the total synthesis of (**–**)-ardeemin (**17**) and 5-*N*-acetylardeemin (**135**) from L-tryptophan with about 2% overall yield in 20 steps (Scheme 27).[44a] Oxazolidinone **129** was prepared form L-tryptophan in a three-step reaction sequence (methylation of L-tryptophan, reduction of acid and protection of amino alcohol). Three step one pot cascade reaction of this oxazolidinone **129** and diazoester in the presence of Cu(OTf)−toluene complex in toluene proceed smoothly through intermolecular cyclopropanation, ring opening and ring closer to



Scheme 27. Total synthesis of (−)-ardeemin and (−)-5-*N*-acetylardeemin

assemble the chiral 3-substituted hexahydropyrrolo[2,3-*b*]indole **130** with three stereocenters corresponding to natural products. The hexahydropyrrolo[2,3-*b*]indole **130** in ten routine steps gave them the rotameric mixture of acid **131**. Condensation of acid **131** with D-alanine methyl ester afforded rotamer **132** in 81% yield. Compound **132** after Boc-deprotection did not cyclized directly to diketopiperazine **133**, instead it was prepared through four-step sequence. Diketopiperazine **133** was converted to (–)-ardeemin (**17**) and (–)-5-*N*-acetylardeemin (**135**) by adopting a strategy similler to Danishefsky's[44b,c] ardeemin synthesis.

Kawasaki and co-workers reported the total synthesis of (–)-5-*N*-acetylardeemin (**135**) using highly enantioselective preparation of advanced imine intermediate **139** via domino olefination/isomerization/Claisen rearrangement (OIC) of **137** and a novel assembly of the pyrazino ring of this alkaloid via Ugi three-component reaction/cyclization of **139** with the corresponding amino acid and isonitrile (Scheme 28).[45] Bromination of 1-acetylindolin-3-one (**136**) at the C-2 site followed by substitution with (*S*)-2-methyl-2-decen-4-ol (99% ee) afforded ether **137** in 88% yield. Horner-Wadsworth-Emmons reaction of **137** with diethyl cyanomethylphosphonate in the presence of *t*-BuOK at -78 to 0 °C proceeded smoothly with domino olefination/isomerization/Claisen rearrangement (OIC) to produce an enantiomerically enriched oxindole **138** in 89% yield and 99% ee.

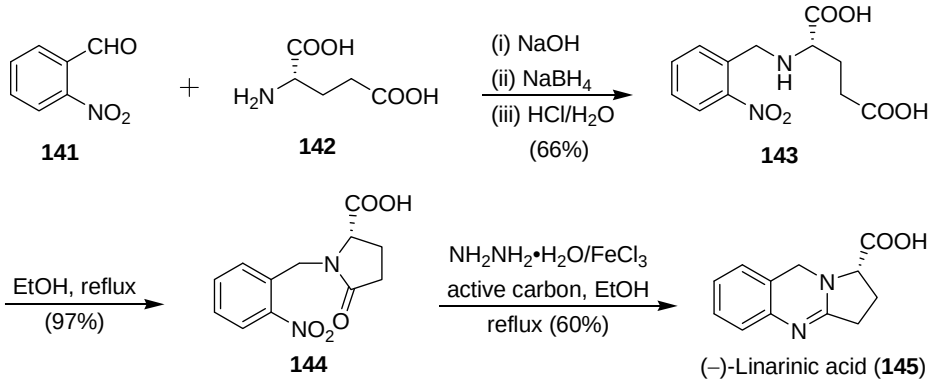


Scheme 28. Total synthesis of (−)-5-*N*-acetylardeemin

Oxindole **138** was converted to advanced imine intermediate **139** with seven-step reaction sequence. When this advanced imine intermediate **139** was treated with *N*-Boc-D-alanine and isonitrile at room temperature, the stereoselective three-component Ugi reaction proceeded smoothly to afford tripeptide **140** in 71% yield. After removal of the Boc-group of tripeptide **140** and successive heating with phosphorus oxychloride directly constructed the pyrazine and pyrimidine rings together with epimerizion at C-15b to give (**–**)-5-*N*-acetylardeemin (**135**) in 53% yield. Total synthesis of (−)-5-*N*-acetylardeemin (**135**) was achieved in 13 steps with 32% overall yield.

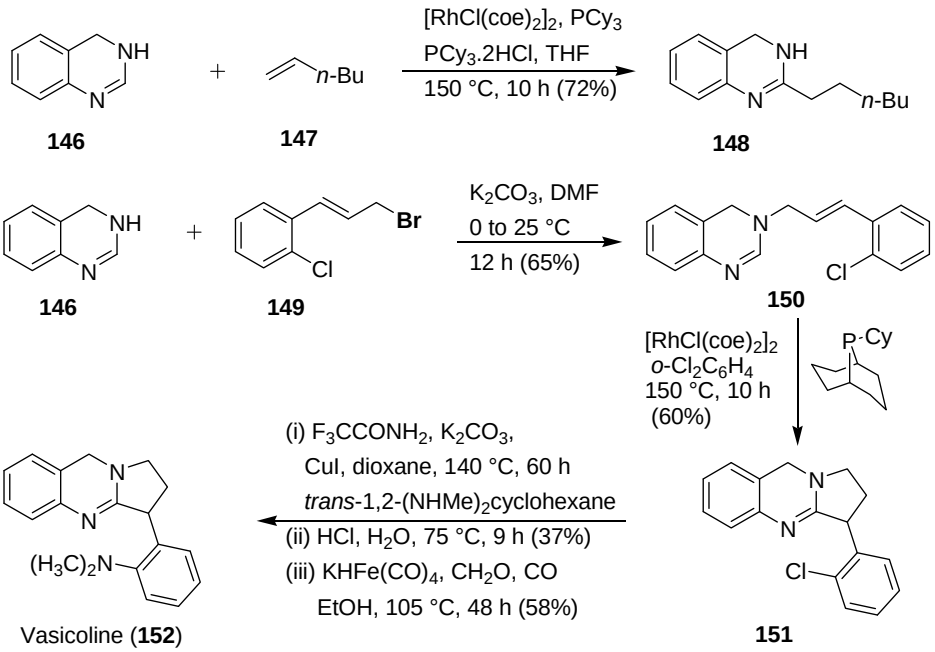
1.6 Total synthesis of quinazoline alkaloids

Cheng and co-workers achieved first total synthesis of quinazoline alkaloid (–)-linarinic acid[46a] (Scheme 29).[46b] Reductive amination of 2-nitrobenzaldehyde (**141**) with L-glutamic acid (**142**) afforded the product **143**, which underwent cyclization to the lactam **144** in boiling ethanol. Reduction of the nitro group with hydrazine and ferric chloride and subsequent intramolecular cyclization of thus formed amine with amide carbonyl produced the (–)-linarinic acid (**145**) in 38% overall yield.



Scheme 29. First total synthesis of (−)-linarinic acid

Bergman and co-workers reported the coupling of olefins **147** and 3,4-dihydroquinazoline (**146**) with a Rh(I) catalyst for the synthesis of 2-substituted quinazolines **148** (Scheme 30).[47] This method was applied for the total synthesis of vasicoline (**152**) in five steps with 10% overall yield. 3,4-Dihydroquinazoline (**146**) was regioselectively alkylated at *N*-3 position with 2-chlorocinnamyl bromide (**149**) to give **150** in 65% yield. An intramolecular coupling with a $[RhCl(cyclooctene)_2]_2$ in



Scheme 30. Rh(I) catalyzed total synthesis of vasicoline

the presence of the ligand Cy-[3.3.1]-Phoban in boiling 1,2-dichlorobenzene gave the tricyclic product **151** in 60% yield. The transformation of the chlorine substituent in **151** to the requisite amine using Goldberg-type amination was accomplished with trifluoroacetamide and copper(I) iodide in the presence of *trans*-1,2-methylaminocyclohexane as ligand to give the corresponding *ortho*-substituted aniline. The final reductive methylation of the primary amine with formaldehyde was achieved under very mild conditions with $KHFe(CO)_4$ under an atmosphere of carbon monoxide which gave vasicoline (**152**) in 58% yield. We feel that it is an excellent example of C-H activation on a quinazoline moiety.

1.7 Summary

In summary, we have presented a concise account of the quinazolinone alkaloids isolated during the last five years, along with their bioactivity. Twenty new quinazolinone alkaloids have been isolated as natural products during last five years span. Various synthetic methodologies to the quinazolinone motif and related derivatives reported by different research groups have been presented. Emphasis is placed on recent developments of synthetic methodologies of quinazolinone compounds, including microwave-assisted synthesis, domino and multi-component one pot reactions, Lewis acid catalyzed cyclizations, α-functionalization of cyclic amines, palladium-catalyzed three component cyclocarbonylation, Cu(I)-catalyzed coupling of o-haloaryl-carboxy derivative, cascade radical cyclization process, cascade annulation strategy, CAN-mediated Friedlander-Borsche reactions. Number of research groups have reported variety of synthetic approaches to biologically active natural/synthetic quinazoline and quinazolinone alkaloids. All the information collected and presented here has been well supported by the provision of more than 70 references from various monographs and international journals.

Given the advances in synthetic methodology and technology in recent years and the continued interest in the quinazoline and quinazolinone skeleton in medicinal chemistry and drug development, the development of efficient and reliable methods for the construction of these molecules will ensure that this is an active and important area of research in alkaloid chemistry.

We strongly believe that the broad quinazolinone field will be of continuing interest to both the synthetic and medicinal chemists and positively there will be interminable promising advancements in the knowledge. In this context, as part of this present dissertation, we have developed new methods for synthesis of quinazoline and quinazolinones and synthesized some related natural products. Our synthetic strategies towards the synthesis of these natural products and their synthetic analogs will be discussed in details in the second chapter of present dissertation.

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Chapter 2

Synthetic Studies on Quinazoline and Quinazolinone Alkaloids

This chapter features the following topics:

Note: An independent figure, table, scheme, structure and reference numbers have been used for the each section.

This chapter is divided into four sections. The first section presents synthesis of (–)-circumdatin F, sclerotigenin and (–)-fumiquinazoline F, first time implementing HMDS/I_2 as the reagent for the intramolecular dehydrative cyclization of amides to deliver the quinazolinones (Figure). The second section describes a facile synthesis of different analogs of anti-tumor agent batracylin via the intramolecular dehydrative cyclizations of suitably *ortho*-substituted anilic acid esters and imides along with novel an in situ methyl migration. This section also presents our studies on the synthesis of (–)-vasicine. The third section describes first total synthesis of proposed auranthine using an intramolecular aza-Wittig reaction involving a lactam carbonyl group that delivered the diazepine core unit. The fourth section presents an efficient total synthesis of (–)-circumdatin H and J using novel copper-catalyzed intramolecular *N*-arylation reaction as the key step. The detailed experimental procedures, complete tabulated analytical and spectral data and some selected NMR spectra have been appropriately included at the end of each section.

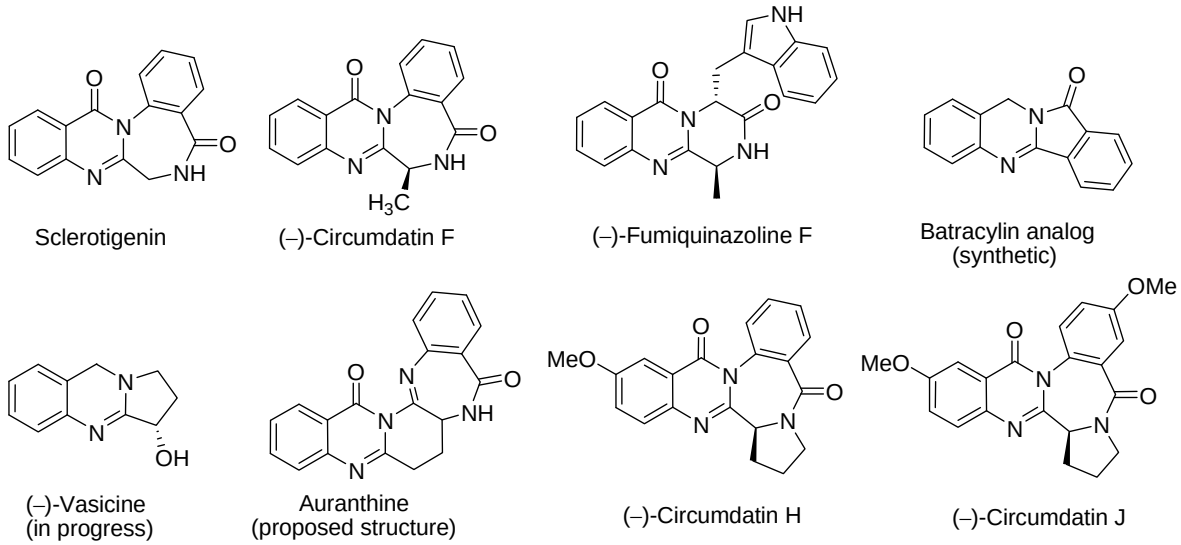


Figure. Natural and unnatural bioactive quinazolinone alkaloids synthesized

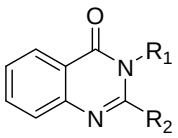
Chapter 2: Section A

Concise Synthesis of Quinazolinone Alkaloids Sclerotigenin, (–)-Circumdatin F and (–)-Fumiquinazoline F

This section A of chapter 2 features the following topics:

2A.1 Background

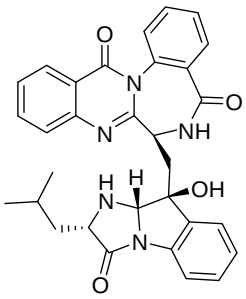
2,3-Disubstituted 3*H*-quinazoline-4-ones **1** represent one of the most interesting and useful group of heterocycles.[1]



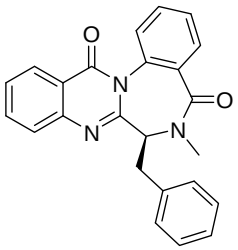
2,3-Disubstituted-quinazolin-4(3*H*)-one (**1**)

Figure 1. Quinazolinone basic structure

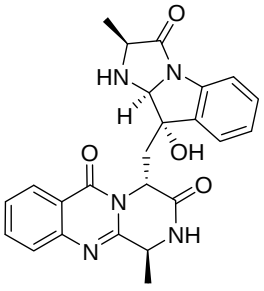
In particular, quinazoline-4-one alkaloids such as asperlicin possessing cholecystokinin antagonist properties[2] and benzomalvins which are neurokinin receptor antagonists,[3] cytotoxic fumiquinazolines[4] as well as other similar molecules such as chemotaxonomic markers circumdatins have attracted significant attention of chemist's community (Figure 1).[5] These alkaloids are often biosynthetically derived from anthranilic acid and chiral amino acids and as a result contain a chiral centre at the *α*-position of the 2-substituent.[6] The interesting biological activities and fascinating molecular architectures of these compounds have attracted immediate attention and became the attractive synthetic targets as a result of their limited availability from natural sources. Many elegant total synthesis of chiral quinazoline-4-one alkaloids have been reported. In the total synthesis of these alkaloids, the formation of quinazolinone ring and preservation of the chiral integrity of the substituents are the crucial steps. Two major synthetic strategies have been reported to access the core ring system, which have subsequently led to the total synthesis of several recently isolated bioactive natural products.



Asperlicin (**2**)



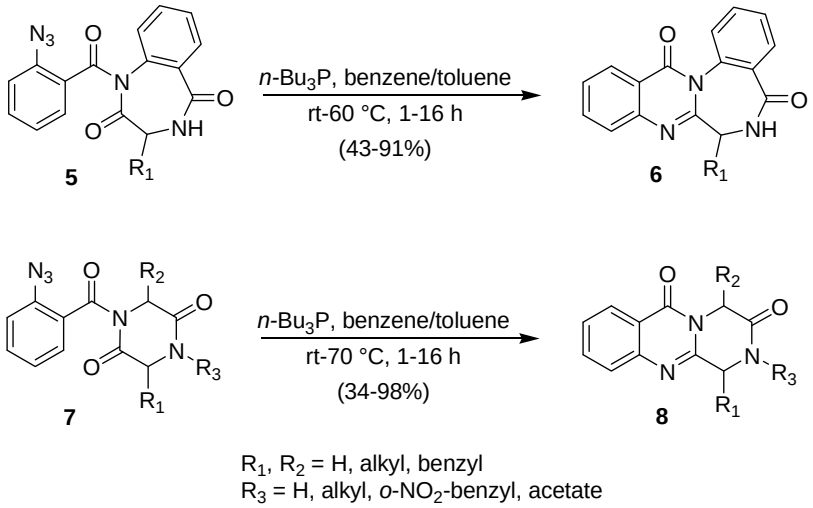
Benzomalvin A (**3**)



Fumiquinazoline A (**4**)

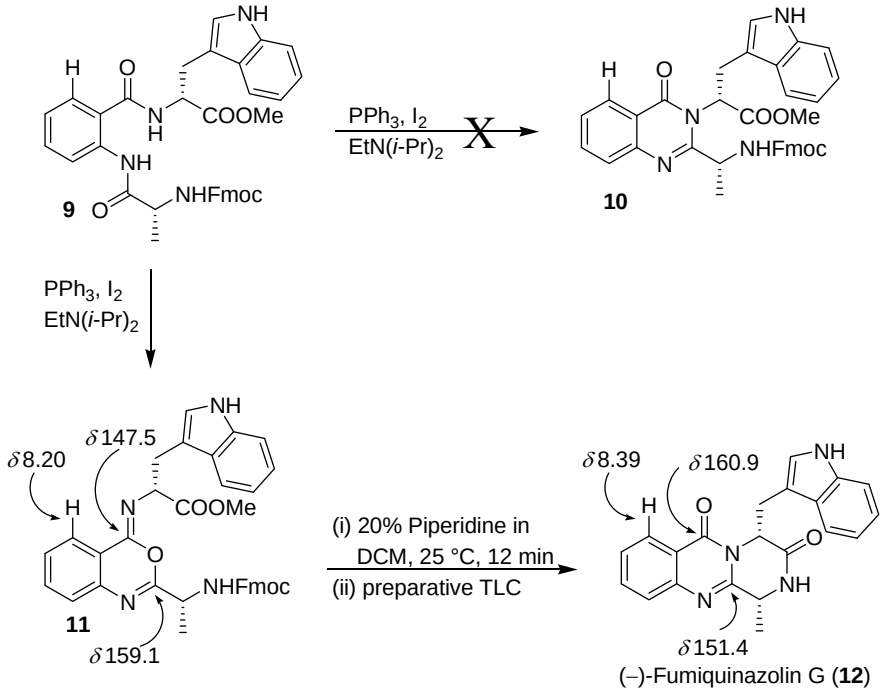
Figure 1. Bioactive quinazolinone alkaloids

The research groups of Danishefsky, Snider, Menendez and Sollhuber have used an aza-Wittig approach (Eguchi protocol, Scheme 1)[7] and successfully applied to the total syntheses of benzomalvin A[7c] ardeemin,[8] 5-*N*-acetylardeemin,[8] asperlicin,[2b] glyantrypine,[9] fumiquinazoline F,[9b] fumiquinazoline G,[9b,10] circumdatin F,[10b] sclerotigenin,[10b] fiscalin B,[9b] asperlicin C.[10b]



Scheme 1. Synthesis of 2,3-disubstituted 3*H*-quinazoline-4-ones using aza-Wittig approach

Retrosynthetically, intramolecular dehydrative cyclization of suitably substituted *N*-benzoylanthranilamides constitutes a concise and biomimetic route to the all types of desired quinazolinone alkaloids.[11a,12] In this concern, another approach was discovered by Mazurkiewicz[13] and later modified by Ganesan, as the two step sequence from linear diamides through isomerisation of 4-imino-4*H*-3,1-benzoxazines to the quinazoline-4-ones under acidic or basic conditions (Scheme 2).[11] Initially, Ganesan et al. reported[11a] a route to fumiquinazoline G (**12**) using protected tripeptide **9** as a key intermediate for the cyclization step. They have proposed the cyclization product to be a quinazolin-4-one **10**. Later on, Snider and co-workers re-examined Ganesan's fimiquinazoline G synthesis and proved it rather to be the 4-imino-4*H*-3,1-benzoxazine (**11**) on the basis of spectroscopic and chemical studies.[14] The downfield aromatic proton absorbs at

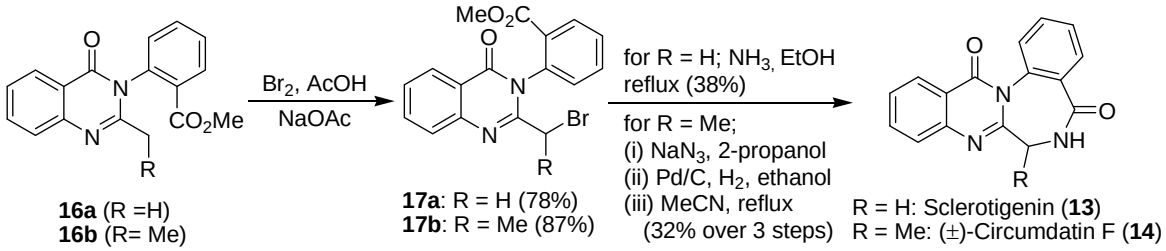


Scheme 2. Mazurkiewicz-Ganesan protocol for the Synthesis of 2,3-disubstituted 3*H*-quinazoline-4-ones

δ 8.20 rather than at δ 8.39 as in fumiquinazoline G (**12**). In ^{13}C NMR, C-2 absorbs at δ 159.1, as opposed to δ 151.4 in fumiquinazoline G, and C-4 absorbs at δ 147.5 as opposed to δ 160.9 in fumiquinazoline G. They have also indicated that, as expected the 4-imino-4*H*-3,1-benzoxazines are hydrolytically unstable. This transformation has been used in the total synthesis of fumiquinazolines A,[15b,e] B,[15b,e] C,[15d,e] E,[15d,e] F,[11b] G,[11,14] H,[15d,e] I,[15b,e] as well as fiscalin B,[11] alantrypinone,[15a,c] glyantrypine,[11b] circumdatins C,[12] F,[12] verrucines A,[15f] and B.[15f] These studies clearly indicate that the development of a straightforward, simple and efficient approach to natural and unnatural quinazolinones, more specifically for peptidomimetic examples bearing a variety of protecting groups, preserving the chiral integrity of the substituents is a challenging task of current interest. We decided to develop the method for direct conversion of linear diamides to quinazolin-4-ones and then extend it for the synthesis of quinazolinone alkaloids sclerotigenin (**13**), (–)-circumdatind F (**14**) and (–)-fumiquinazoline F (**15**).

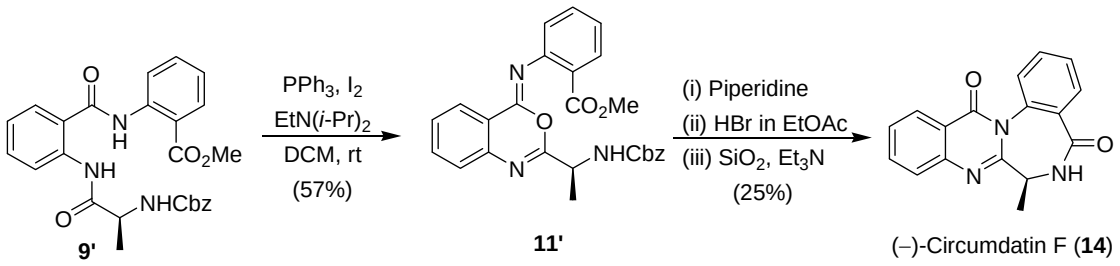
2A.2 Brief Account of Sclerotigenin, Circumdatind F and Fumiquinazoline F Syntheses

Total seven syntheses of sclerotigenin (**13**) and eight syntheses of circumdatin F (**14**) are known in the literature. Liu et al. synthesized both sclerotigenin and (±)-circumdatin F using highly efficient three-component one-pot reaction sequence promoted by microwave.[16] Chu and co-workers developed the microwave irradiated, tin triflate[17a] and scandium triflate[17b] catalyzed direct double cyclizations of bis(anthranilate)-containing tri-peptide precursors to afford the total synthesis of sclerotigenin, (–)-circumdatin F. Zhang and co-workers synthesized (±)-circumdatin F using fluorous benzyl protecting group and also as a phase tag for fluorous solid-phase extraction.[18] These syntheses have been reported after the year 2005 and are discussed in the chapter 1 of present dissertation. Four syntheses of sclerotigenin and circumdatin F were reported before the year 2005. One synthesis of sclerotigenin is well known before its isolation as natural product by Harrison et al. (Scheme 3).[19a] In which 2-bromomethyl-3-*o*-carbomethoxyphenyl-4(3*H*)quinazoline (**17a**) was used as the intermediate. Whereas the Bergman group reported the first synthesis of (±)-circumdatin F using quinazolinone intermediates **16b**/**17b** (Scheme 3).[19b]



Scheme 3. First synthesis of sclerotigenin and (±)-circumdatin F

Thomas and co-workers synthesized the sclerotigenin using a polymer-supported phosphine-mediated intramolecular aza-Wittig reaction as a key step.[20] Snider's group synthesized sclerotigenin as well as (–)-circumdatin F using aza-Wittig reaction as a key step as described in scheme 1.[10b] Bergman group reported an efficient synthesis of (–)-circumdatin F (**14**) using a tripeptide **9'** as a key intermediate and its dehydration to a benzoxazine **11'** by reaction with triphenylphosphine, iodine and a tertiary amine (Mazurkiewicz-Ganesan's protocol) as the key step (Scheme 4).[12]



Scheme 4. Synthesis of (–)-circumdatin F

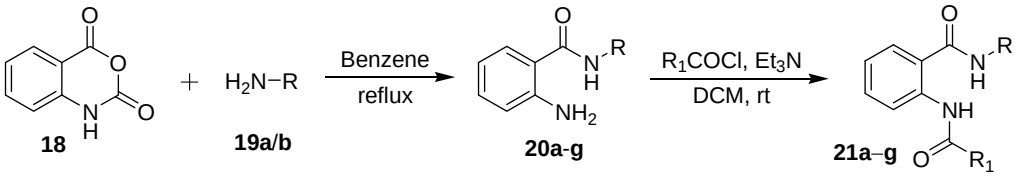
Four syntheses of fumiquinazoline F (**15**) are known in literature. Liu et al. synthesized (–)-fumiquinazoline F using highly efficient three-component one-pot reaction sequence promoted by microwave which has been discussed in chapter 1.[21] Ganesan and co-workers synthesized (–)-fumiquinazoline F using Mazurkiewicz-Ganesan's protocol as the key step (Scheme 2).[11b] Sollhuber and co-workers also synthesized (–)-fumiquinazoline F using aza-Wittig protocol (Scheme 1).[9b]

2A.3 Results and Discussion

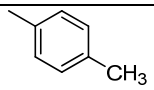
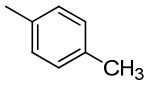
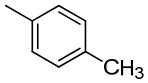
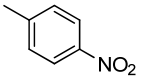
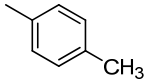
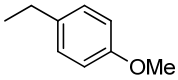
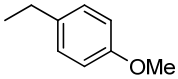
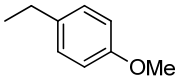
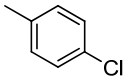
2A.3.1 Hexamethyldisilazane-Iodine Induced Intramolecular Dehydrative Cyclization of Diamides

Anthranilamides **20a**/**b** were prepared in very good yields from the reactions of isatoic anhydride with a *p*-toluedine (**19a**) and *p*-methoxybenzylamine (**19b**) using the known procedures.[12,15c] Intermediates **21a**-**g** were prepared by coupling the anthranilamides **20a**/**b** with appropriate acid chlorides in 82-98% yield (Table 1). Required linear diamide pecursors in hand, we started our studies to cyclize them to quinazolin-4-ones. As the net result of conversion of diamide **21a**-**g** to quinazolin-4-one is dehydrative cyclization, so we first decided to expose linear diamides to variety of dehydrating agents. Compounds **21a**,**b** in DCM did not undergo intramolecular cyclization reaction on treatment with cyanuric chloride/triethylamine, chlorotrimethylsilane/iodine and diethyl azodicarboxylate/triphenylphosphine. Hexamethyldisilazane (HMDS) has been earlier used for the acid catalyzed silylation of lactams, imides[22] and alcohols,[23a-d] for the preparation of cyclic imides[23e] and for the intramolecular dehydrative cyclization of 1-formyl and 1-acetyl semicarbazide to corresponding triazolinones.[23f] Hence we felt that the cheap and readily available hexamethyldisilazane (HMDS) would be a better reagent to induce the intramolecular dehydrative cyclizations of **21a**-**g** to obtain the corresponding quinazolinones **22a**-**g** via the highly regioselective

Table 1. Conversion of anthranilamides **20a**-**g** to diamides **21a**-**g**



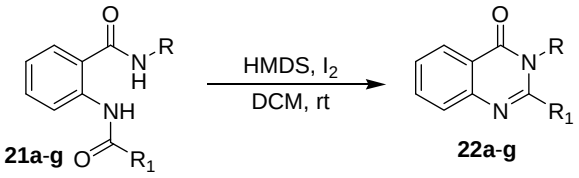
18 **19a/b** **20a-g** **21a–g**

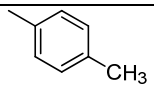
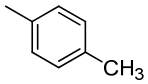
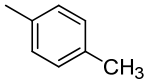
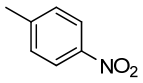
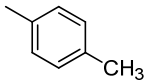
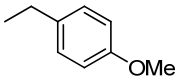
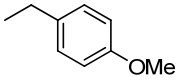
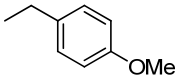
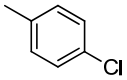
Entry	R	R_1	Time	Product (% yield)
1		$-CH_2CH_3$	8 h	**21a** (98)
2			10 h	**21b** (97)
3			12 h	**21c** (86)
4			16 h	**21d** (82)[a]
5		$-CH_2CH_3$	12 h	**21e** (96)
6			12 h	**21f** (90)
7			14 h	**21g** (85)

[a] *N*-Boc-L-Ala-OH was coupled with corresponding amine using EDCI, HOBt in DCM at rt

silylation of the more reactive anilide carbonyl oxygen, followed by deoxysilylation. To our delight, treatment of **21a**,**b** with HMDS/$ZnCl_2$ in benzene solution under reflux (Vorbruggen's protocol)[22] furnished the desired products **22a**,**b** in ~100% yields. However, in our hands, treatment of the peptidomimetic precursor **21d** with HMDS/$ZnCl_2$ resulted in the formation of a complex reaction mixture. We envisaged[23a] that the use of the soft Lewis acid, the iodine in place of the borderline Lewis acid the zinc chloride would result in efficient conversion of **21a**-**g** to **22a**-**g**. Rewardingly, the reactions of **21a**-**g** with HMDS (1.00 equiv.)/I_2 (0.50 equiv.) in DCM at room temperature furnished the desired quinazolinones **22a**-**g** in 65-97% yields (Table 2, entries 1-7). In the conversion of **21a**-**g** to **22a**-**g**, we noticed that an increase in the molar equivalents of HMDS and iodine reduced the reaction time with an improvement in the yields (Table 2). In the present reaction, the formation of **22a** was not observed even in trace amounts in the absence of either HMDS or iodine and the presence of a catalytic amount of iodine was necessary to induce the first silylation of the more reactive amide carbonyl group, which was followed by in situ ring closure with the deoxysilylation.

Table 2. Intramolecular cyclization of diamides **21a-g** to quinazolinones **22a-g**



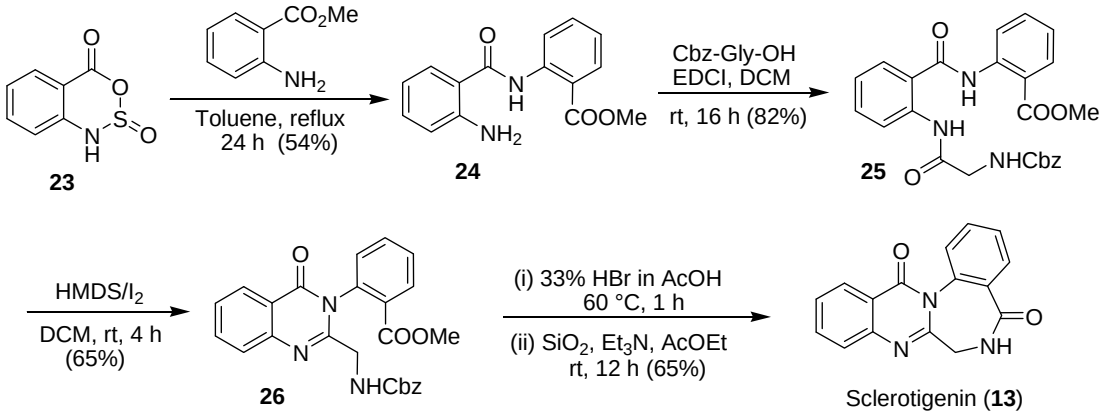
Entry	R	R_1	Condition	Product (% yield)
1		$-CH_2CH_3$	HMDS (1.50), I_2 (0.50), 30 min	**22a** (93)
2			HMDS (1.50), I_2 (0.50), 30 min	**22b** (95)
3			HMDS (2.00), I_2 (1.00), 4 h	**22c** (86)
4			HMDS (3.00), I_2 (0.70), 4 h	**22d** (70)
5		$-CH_2CH_3$	HMDS (1.50), I_2 (0.50), 3 h	**22e** (97)
6			HMDS (1.50), I_2 (0.50), 7 h	**22f** (96)
7			HMDS (2.00), I_2 (1.00), 5 h	**22g** (90)

Generalization of our protocol with different examples as well as feasibility with *N*-Boc-alanine side chain, these results encouraged us to demonstrate this protocol for the synthesis of quinazolinone alkaloids from the corresponding tripeptide intermediate bearing different amino protecting groups. We decided to synthesize quinazolinobenzodiazepinone alkaloids sclerotigenin (**13**) and (–)-circumdatind F (**14**) as well as pyrazino[2,1-*b*]quinazoline-3,6-dione family member, the (–)-fumiquinazoline F (**15**).

2A.3.2 Synthesis of Scleretogenin

Sclerotigenin is the simplest member of the quinazolinobenzodiazepinone family, which was isolated from the sclerotia of *Penicillium sclerotigenum* and has shown promising anti-insectan activity.[24] We started our synthesis of sclerotigenin from sulfinamide anhydride (**23**).[12,25] Reaction of sulfinamide anhydride (**23**) with methyl anthranilate in refluxing toluene gave the desired aminoester **24** in 54% yield (Scheme 5). Coupling of the obtained aminoester **24** with the Cbz-protected glycine using EDCI as a dehydrating agent in DCM as solvent gave the required Boc-protected linear diamide **25** in 82% yield. HMDS/Iodine induced intramolecular dehydrative cyclization of linear diamide **25** in DCM at room temperature gave the required quinazolinone **26** in 65% yield. Finally, deprotection of Cbz-

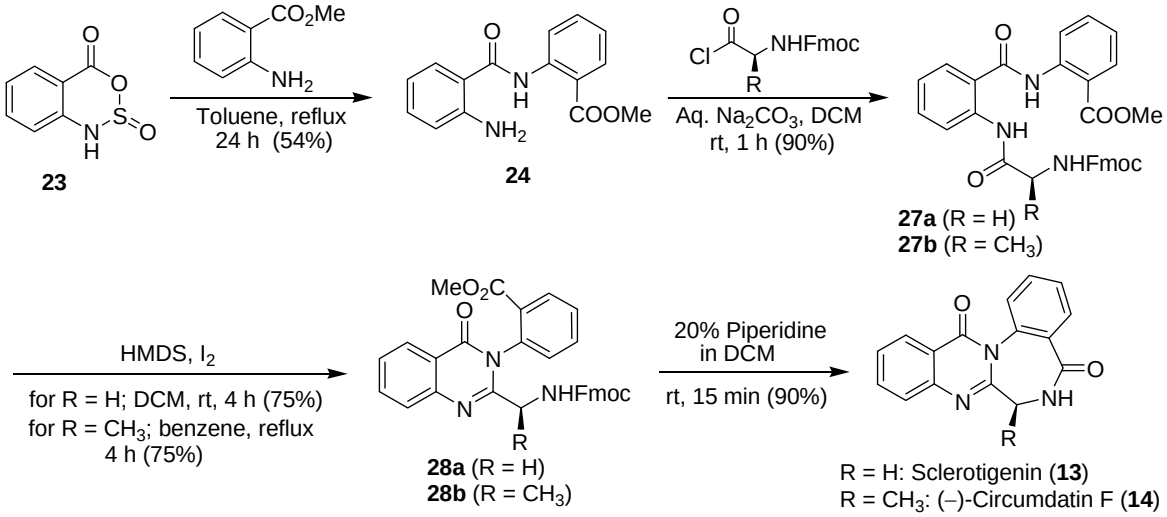
group by treatment with 33% HBr in AcOH followed by Et_3N/SiO_2 induced intramolecular cyclization furnished the desired sclerotigenin (**13**) in 65% yield.[12] The obtained analytical and spectral data for sclerotigenin (**13**) were in complete agreement with reported data.[10b,16]



Scheme 5. Synthesis of sclerotigenin via intramolecular dehydrative cyclization

2A.3.3 Synthesis of (–)-Circumdatin F

After sclerotigenin (**13**) synthesis using Cbz-protecting group, we planned to demonstrate the feasibility of Fmoc-protecting group in HMDS/Iodine induced intramolecular dehydrative cyclization reaction (Scheme 6). We started the synthesis of circumdatin F (**14**) and sclerotigenin (**13**) with the intermolecular dehydrative coupling of aminoester **24** with Fmoc-protected glycine and Fmoc-protected L-alanine chlorides[26] in DCM and aqueous sodium carbonate as base, which provided the Fmoc-protected linear dimides **27a**/**b** in 90% yields.[11b] HMDS/Iodine induced intramolecular dehydrative cyclization of linear diamide **27a** in DCM at room temperature gave the quinazolinone **28a** in 75% yield. The diamide **27b** did not react with HMDS/Iodine in DCM at room temperature, which may be due to the effect of α–methyl group.

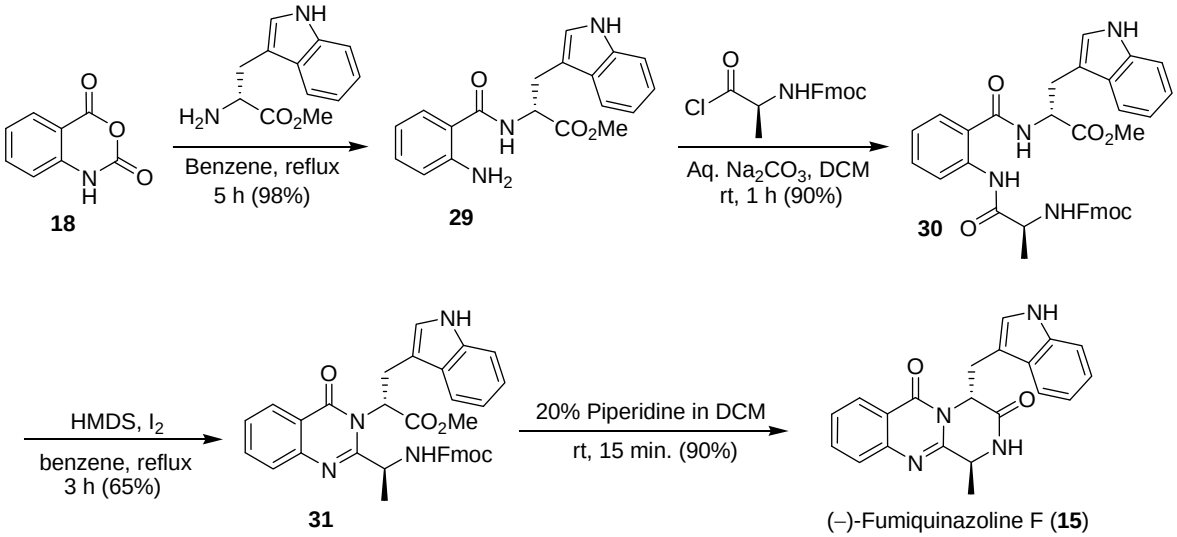


Scheme 6. Synthesis of sclerotigenin and (–)-circumdatin F via intramolecular dehydrative cyclization

However, the same reaction in refluxing benzene gave us the desired quinazolinone **28b** in 75% yield. Finally, piperidine induced Fmoc-deprotection of **28a**/**b** directly furnished the sclerotigenin (**13**) and (–)-circumdatin F (**14**) in 90% yields. The obtained analytical and spectral data for sclerotigenin (**13**) and (–)-circumdatin F (**14**) were in complete agreement with reported data.[10b,12,16]

2A.3.4 Synthesis of (–)-Fumiquinazoline F

We started our synthesis of (–)-fumiquinazoline F (**25**) with the reaction of isatoic anhydride (**18**) and methyl ester of D-tryptophan, which gave the aminoester **29**[15c] (Scheme 7). The intermolecular coupling of aminoester **29** with Fmoc-protected L-alanine chloride in DCM using aqueous sodium carbonate as base gave required tripeptide **30** in 90% yield.[11b] HMDS/Iodine induced dehydrative cyclization of tripeptide **30** in refluxing benzene provided the desired quinazolinone **31** in 65% yield.



Scheme 7. Synthesis of (–)-fumiquinazolin F via intramolecular dehydrative cyclization

Piperidine induced Fmoc-deprotection of **31** directly furnished the desired (–)-fumiquinazoline F (**15**) in 90% yield.[27] The obtained analytical and spectral data for (–)-fumiquinazoline F (**15**) were in complete agreement with reported data.[11b]

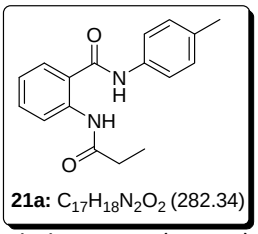
2A.4 Summary

In summary, we have demonstrated a simple, efficient and general approach to the various quinazolinone scaffolds for the first time by employing HMDS/I_2 for the intramolecular dehydrative cyclization of diamides. The protecting groups Boc-, Fmoc- and Cbz- were quite friendly with the present reaction conditions and also we did not observe any racemization. The present protocol has also been used as a key step for the efficient four-step syntheses of the naturally occurring quinazolinones, the sclerotigenin, (–)-circumdatin F and (–)-fumiquinazoline F. We feel that our present approach will be practically useful to design the focused libraries of broad range of quinazolinone congeners for structure-activity relationship studies as well as all other alkaloids discussed in introduction part of this section can also be prepared using this protocol.

2A.5 Experimental Section

Commercially available hexamethyldisilazane (HMDS), zinc chloride, iodine, protected amino acids, isatoic anhydride, HOBt, EDCI and were used. Dichloromethane was distilled from CaH_2 under argon.

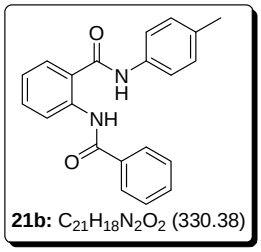
2-Propionamido-*N*-*p*-tolylbenzamide (21a). To a stirring solution of 2-amino-*N*-*p*-tolylbenzamide (450 mg, 2.00 mmol) and triethylamine (0.30 mL, 2.20 mmol) in DCM (20 mL) at room temperature was added propionyl chloride (0.19 mL, 2.20 mmol) in a dropwise fashion and the resulting reaction mixture was stirred for 8 h. The reaction mixture was concentrated in vacuo and the residue was diluted with ethyl acetate (25 mL) and the organic layer was washed with water, 5% $NaHCO_3$ solution, brine and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by the silica gel column chromatographic purification of the resulting residue with petroleum ether–ethyl acetate (75:25) as an eluent furnished **21a** (550 mg, 98% yield). Mp 161–163 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.24 (t, *J* = 8 Hz, 3H), 2.37 (s, 3H), 2.39 (q, *J* = 8 Hz, 2H), 7.01 (dt, *J* = 8 & 2 Hz, 1H), 7.21 (d, *J* = 8 Hz, 2H), 7.33 (dt, *J* = 8 & 2 Hz, 1H), 7.50 (dd, *J* = 8 & 2 Hz, 1H), 7.55 (d, *J* = 8 Hz, 2H), 8.39 (dd, *J* = 8 & 2 Hz, 1H), 8.57 (br s, 1H), 10.63 (br s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 9.5, 20.9, 31.2, 120.6, 121.7, 121.8, 122.5, 127.3, 129.5, 131.8, 134.4, 135.2, 138.5, 167.2, 173.1; IR (Nujol) ν_{max} 3290, 3250, 1668, 1651, 1607, 1601 cm^{-1}. Anal. Calcd for $C_{17}H_{18}N_2O_2$: C, 72.32; H, 6.42; N, 9.92. Found: C, 72.11; H, 6.54; N, 9.98.



21a: $C_{17}H_{18}N_2O_2$ (282.34)

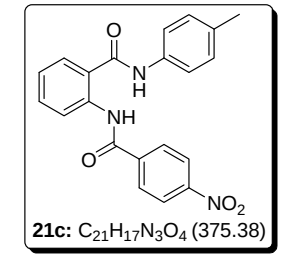
The diamides **21b**, **21c** and **21e**-**g** were prepared similarly. For the reaction time and yields obtained, see Table 1.

2-Benzamido-*N*-*p*-tolylbenzamide (21b). Mp 240–242 °C; ^{1}H NMR [$CDCl_3$+DMSO-d_6 (9:1), 200 MHz] δ 2.35 (s, 3H), 7.10–7.25 (m, 3H), 7.45–7.65 (m, 6H), 7.86 (dd, *J* = 8 & 2 Hz, 1H), 8.02 (dd, *J* = 6 & 2 Hz, 2H), 8.76 (dd, *J* = 8 & 2 Hz, 1H), 9.78 (br s, 1H), 12.02 (br s, 1H); ^{13}C NMR (DMSO-d_6, 50 MHz) δ 20.7, 121.3, 121.4, 121.5, 122.8, 123.5, 127.2, 129.2, 129.3, 132.3, 132.5, 133.6, 134.7, 136.1, 139.0, 164.8, 167.5; IR (Nujol) ν_{max} 3287, 3250, 1643, 1601 cm^{-1}. Anal. Calcd for $C_{21}H_{18}N_2O_2$: C, 76.35; H, 5.49; N, 8.47. Found: C, 76.44; H, 5.39; N, 8.56.



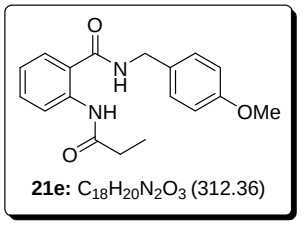
21b: $C_{21}H_{18}N_2O_2$ (330.38)

2-(4-Nitrobenzamido)-*N*-*p*-tolylbenzamide (21c). Mp 176–178 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.37 (s, 3H), 7.06 (dt, *J* = 8 & 2 Hz, 1H), 7.23 (d, *J* = 10 Hz, 2H), 7.48 (dt, *J* = 8 & 2 Hz, 1H), 7.54 (d, *J* = 10 Hz, 2H), 7.63 (dd, *J* = 8 & 2 Hz, 1H), 8.16 (d, *J* = 8 Hz, 2H), 8.34 (d, *J* = 8 Hz, 2H), 8.37 (br s, 1H), 8.67 (dd, *J* = 8 & 2 Hz, 1H), 12.13 (br s, 1H); ^{13}C NMR [$CDCl_3$+DMSO-d_6 (8:2), 125 MHz] δ 20.4, 120.7, 121.2, 122.7, 123.2, 127.8, 128.0, 128.3, 128.7, 132.0, 134.0, 134.8, 138.9, 139.9, 149.0, 162.6, 167.4; IR (Nujol) ν_{max} 3302, 3109, 1701, 1682, 1601 cm^{-1}. Anal. Calcd for $C_{21}H_{17}N_3O_4$: C, 67.19; H, 4.56; N, 11.19. Found: C, 67.30; H, 4.44; N, 11.37.



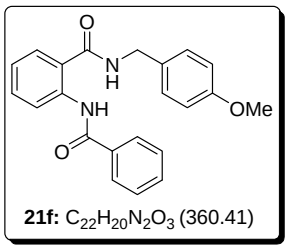
21c: $C_{21}H_{17}N_3O_4$ (375.38)

2-(4-Ethylbenzamido)-*N*-(4-methoxybenzyl)benzamide (21e). Mp 133–136 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.26 (t, *J* = 8 Hz, 3H), 2.45 (q, *J* = 8 Hz, 2H), 3.81 (s, 3H), 4.55 (d, *J* = 6 Hz, 2H), 6.56 (t, *J* = 6 Hz, 1H), 6.89 (d, *J* = 10 Hz, 2H), 7.02 (t, *J* = 8 Hz, 1H), 7.28 (d, *J* = 10 Hz, 2H), 7.35–7.50 (m, 2H), 8.60 (d, *J* = 8 Hz, 1H), 11.09 (br s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 9.5, 31.4, 43.3, 55.2, 114.1, 120.2, 121.3, 122.4, 126.6, 129.1, 129.6, 132.3, 139.4, 159.1, 168.8, 172.8; IR (Nujol) ν_{max} 3254, 3230, 1690, 1636, 1612 cm^{-1}. Anal. Calcd for $C_{18}H_{20}N_2O_3$: C, 69.21; H, 6.45; N, 8.97. Found: C, 69.30; H, 6.42; N, 9.02.



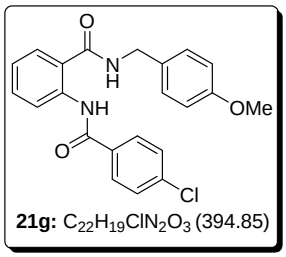
21e: $C_{18}H_{20}N_2O_3$ (312.36)

2-Benzamido-*N*-(4-methoxybenzyl)benzamide (21f). Mp 152–153 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.79 (s, 3H), 4.58 (d, *J* = 6 Hz, 2H), 6.68 (br s, 1H), 6.88 (d, *J* = 8 Hz, 2H), 7.04 (dt, *J* = 8 & 2 Hz, 1H), 7.28 (d, *J* = 8 Hz, 2H), 7.42–7.60 (m, 5H), 7.98–8.08 (m, 2H), 8.77 (d, *J* = 8 Hz, 1H), 12.13 (br s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 43.4, 55.2, 114.1, 120.4, 121.4, 122.7, 126.7, 127.3, 128.7, 129.1, 129.6, 131.8, 132.5, 134.7, 139.7, 159.1, 165.6, 169.0; IR (Nujol) ν_{max} 3333, 3209, 1653, 1647, 1603 cm^{-1}. Anal. Calcd for $C_{22}H_{20}N_2O_3$: C, 73.32; H, 5.59; N, 7.77. Found: C, 73.47; H, 5.72; N, 7.69.



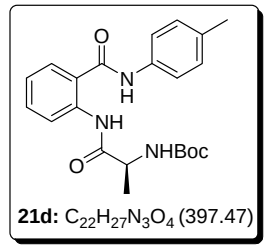
21f: $C_{22}H_{20}N_2O_3$ (360.41)

2-(4-Chlorobenzamido)-*N*-(4-methoxybenzyl)benzamide (21g). Mp 119–121 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.80 (s, 3H), 4.58 (d, *J* = 4 Hz, 2H), 6.61 (br s, 1H), 6.89 (d, *J* = 8 Hz, 2H), 7.07 (t, *J* = 8 Hz, 1H), 7.28 (d, *J* = 8 Hz, 2H), 7.40–7.55 (m, 4H), 7.98 (d, *J* = 8 Hz, 2H), 8.77 (d, *J* = 8 Hz, 1H), 12.23 (br s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 43.5, 55.3, 114.2, 120.2, 121.5, 122.9, 126.6, 128.8, 129.0, 129.2, 129.4, 132.7, 133.2, 138.1, 139.8, 159.2, 164.5, 169.0; IR (Nujol) ν_{max} 3344, 3177, 1657, 1651, 1643, 1597 cm^{-1}. Anal. Calcd for $C_{22}H_{19}ClN_2O_3$: C, 66.92; H, 4.85; N, 7.09. Found: C, 67.05; H, 4.88; N, 6.92.



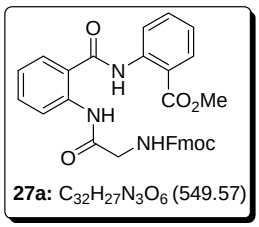
21g: $C_{22}H_{19}ClN_2O_3$ (394.85)

(*S*)-*tert*-Butyl 1-oxo-1-(2-(*p*-tolylcarmoyl)phenylamino)propan-2-ylcarbamate (21d). To a stirring solution of *N*-Boc-L-alanine (380 mg, 2.00 mmol), HOBt (340 mg, 2.20 mmol) and 2-amino-*N*-*p*-tolylbenzamide (455 mg, 2.00 mmol) in DCM (30 mL) at room temperature was slowly added a solution of EDCI (422 mg, 2.20 mmol) in DCM (10 mL) over a period of 10 minutes time and the reaction mixture was stirred for 16 h. The reaction mixture was diluted with DCM (60 mL) and the organic layer was washed with water, 5% $NaHCO_3$ solution, 2 N HCl, water, brine and dried over Na_2SO_4. The concentration of organic layer in vacuo followed by the silica gel column chromatographic purification of the obtained residue using 20% ethyl acetate in petroleum ether furnished the analytically pure **21d** (554 mg, 82% yield). Mp 174–176 °C; $[\alpha]^{29}_D$ = –32.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.42 (s, 9H), 1.46 (d, *J* = 6 Hz, 3H), 2.36 (s, 3H), 4.32 (quintet, *J* = 6 Hz, 1H), 5.13 (d, *J* = 8 Hz, 1H), 7.10 (t, *J* = 8 Hz, 1H), 7.19 (d, *J* = 8 Hz, 2H), 7.40 (t, *J* = 8 Hz, 1H), 7.52 (d, *J* = 8 Hz, 2H), 7.54 (d, *J* = 8 Hz, 1H), 8.24 (br s, 1H), 8.48 (d, *J* = 8 Hz, 1H), 11.24 (br s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 19.0, 20.9, 28.2, 51.4, 80.0, 120.8, 121.6, 121.7, 123.3, 126.9, 129.5, 132.3, 134.6, 135.0, 138.6, 155.1, 166.9, 172.0; IR (Nujol) ν_{max} 3358, 3341, 3333, 1688, 1670, 1655, 1597, 1587 cm^{-1}. Anal. Calcd for $C_{22}H_{27}N_3O_4$: C, 66.48; H, 6.85; N, 10.57. Found: C, 66.36; H, 6.80; N, 10.41.



21d: $C_{22}H_{27}N_3O_4$ (397.47)

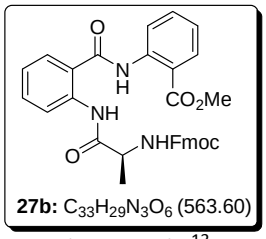
Methyl 2-(2-(2-(((9*H*-fluoren-9yl)methoxy)carbonylamino)acetamido)benzamido)benzoate (27a). To a stirring solution of 2-amino-*N*-*p*-tolylbenzamide (500 mg, 1.85 mmol) in dry DCM (30 mL) was added solution of Fmoc-Gly-Cl (758 mg, 2.40 mmol) in DCM (10 mL). The mixture was stirred for 4 min, followed by addition of aqueous Na_2CO_3 (1 M, 32 mL, 33.3 mmol). After being stirred for a total of 1 h, the reaction mixture was extracted with DCM (60 mL) and the organic layer was washed with water, 5% $NaHCO_3$ solution, 2 N HCl, water, brine and dried over Na_2SO_4. The concentration of organic layer in vacuo followed by the silica gel column chromatographic purification of the resultant residue using with petroleum ether-ethyl acetate (7:3) as an eluent furnished the analytically pure



27a: $C_{32}H_{27}N_3O_6$ (549.57)

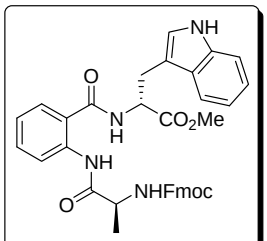
27a (800 mg, 96% yield). Mp 204–206 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.95 (s, 3H), 4.14 (d, *J* = 6 Hz, 2H), 4.28 (t, *J* = 8 Hz, 1H), 4.43 (d, *J* = 6 Hz, 2H), 5.64 (t, *J* = 6 Hz, 1H), 7.06 (t, *J* = 8 Hz, 1H), 7.15–7.45 (m, 6H), 7.55 (t, *J* = 8 Hz, 1H), 7.65 (d, *J* = 8 Hz, 2H), 7.77 (d, *J* = 8 Hz, 2H), 7.87 (d, *J* = 8 Hz, 1H), 8.04 (d, *J* = 8 Hz, 1H), 8.68 (d, *J* = 8 Hz, 2H), 11.75 (br s, 1H), 12.07 (br s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 45.6, 47.2, 52.6, 67.4, 115.6, 119.9, 120.5, 120.6, 121.5, 123.2, 123.6, 125.2, 127.0 (2 carbons), 127.6, 130.9, 133.1, 134.6, 139.7, 140.9, 141.2, 143.9, 156.4, 167.6, 167.7, 168.9; IR (Nujol) ν_{max} 3317, 3265, 3234, 1734, 1695, 1666, 1605, 1585 cm^{-1}. Anal. Calcd for $C_{32}H_{27}N_3O_6$: C, 69.94; H, 4.95; N, 7.65. Found: C, 70.02; H, 4.90; N, 7.76.

The diamides **27b** and **30** were prepared similarly. For the reaction time and yields obtained, see schemes 4 and 5.

(*S*)-Methyl 2-(2-(2-(((9*H*-fluoren-9-yl)methoxy)carbonylamino)propanmido)benzamido)benzoate (27b). 

27b: $C_{33}H_{29}N_3O_6$ (563.60)

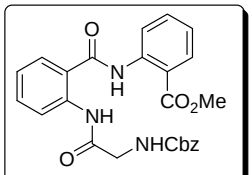
Mp 170–172 °C; $[\alpha]^{28}_D$ = −15.4 (*c* 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.57 (d, *J* = 8 Hz, 3H), 3.95 (s, 3H), 4.20–4.55 (m, 4H), 5.61 (d, *J* = 6 Hz, 1H), 7.07 (t, *J* = 8 Hz, 1H), 7.15–7.70 (m, 9H), 7.76 (d, *J* = 8 Hz, 2H), 7.89 (d, *J* = 8 Hz, 1H), 8.05 (d, *J* = 8 Hz, 1H), 8.70 (t, *J* = 8 Hz, 2H), 11.78 (br s, 1H), 12.08 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.2, 47.2, 52.0, 52.6, 67.2, 115.6, 119.9, 120.6, 121.6, 123.2, 123.6, 125.2, 127.0, 127.1, 127.6, 131.0, 133.1, 134.6, 140.0, 141.0, 141.2, 143.8, 144.1, 155.8, 167.6, 168.9, 171.1; IR (Nujol) ν_{max} 3279, 3268, 3196, 1728, 1717, 1695, 1684, 1661, 1607 cm^{-1}. Anal. Calcd for $C_{33}H_{29}N_3O_6$: C, 70.33; H, 5.19; N, 7.46. Found: C, 70.19; H, 5.08; N, 7.53.

(*R*)-Methyl 2-(2-((*S*)-2-(((9*H*-fluoren-9-yl)methoxy)carbonylamino)propanmido)benzamido)-3-(1*H*-indol-3-yl)propanoate (30). 

30: $C_{37}H_{34}N_4O_6$ (630.69)

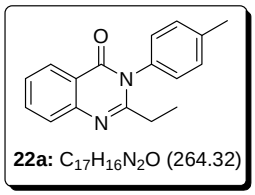
Mp 180–182 °C; $[\alpha]^{27}_D$ = −37.0 (*c* 0.3, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.49 (d, *J* = 6 Hz, 3H), 3.24 (dd, *J* = 14 & 8 Hz, 1H), 3.45 (dd, *J* = 14 & 6 Hz, 1H), 3.71 (s, 3H), 4.15–4.55 (m, 4H), 4.95–5.15 (m, 1H), 5.51 (d, *J* = 8 Hz, 1H), 6.70 (d, *J* = 8 Hz, 1H), 6.95–7.55 (m, 12H), 6.65 (t, *J* = 8 Hz, 2H), 7.77 (d, *J* = 8 Hz, 2H), 8.41 (br s, 1H), 8.55 (d, *J* = 8 Hz, 1H), 11.23 (br s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 18.9, 27.7, 47.1, 51.8, 52.5, 53.2, 67.1, 109.5, 111.3, 118.3, 119.6, 119.9, 121.3, 122.1, 122.9, 123.1, 125.1, 126.7, 127.0, 127.4, 127.6, 132.7, 136.1, 138.9, 141.2, 143.7, 144.0, 155.9, 168.2, 171.1, 172.0; IR (Nujol) ν_{max} 3430-3200, 1732, 1717, 1701, 1684, 1647, 1599, 1585 cm^{-1}. Anal. Calcd for $C_{37}H_{34}N_4O_6$: C, 70.46; H, 5.43; N, 8.88. Found: C, 70.23; H, 5.55; N, 8.72.

Methyl 2-2(-(2-(benzyloxycarbonylamino)acetamido)benzamido)benzoate (25). To a stirring solution of *N*-Cbz-Gly-OH (464 mg, 2.22 mmol), and 2-amino-*N*-*p*-tolylbenzamide (599 mg, 2.22 mmol) in DCM (30 mL) at room temperature was slowly added a solution of EDCI (566 mg, 2.88 mmol) in DCM (10 mL) over a period of 10 minutes time and the reaction mixture was stirred for 16 h. The reaction mixture was diluted with DCM (60 mL) and the organic layer was washed with water, 5% $NaHCO_3$ solution, 2 N HCl, water, brine and dried over Na_2SO_4. The concentration of organic layer in vacuo followed by the silica gel column chromatographic purification of the obtained residue using 20% ethyl acetate in petroleum ether furnished the analytically pure **25** (838 mg, 82% yield). Mp 148–150 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.96 (s, 3H), 4.09 (d, *J* = 4 Hz, 2H), 5.17 (s, 2H), 5.58 (t, *J* = 4 Hz, 1H), 7.14 (t, *J* = 8 Hz, 1H), 7.18–7.48 (m, 7H), 7.53 (dt, *J* = 8 & 2 Hz, 1H), 7.88 (dd, *J* = 8 & 2 Hz, 1H), 8.09 (dd, *J* = 8 & 2 Hz, 1H), 8.67 (d, *J* = 8 Hz, 1H), 8.75 (dd, *J* = 8 & 2 Hz, 1H), 11.74 (br s, 1H), 12.08 (br s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 45.5, 52.5, 67.1, 115.6, 120.5, 121.4, 123.1, 123.5, 127.0, 127.9, 128.0, 128.2, 128.4, 131.0, 133.1, 134.6, 136.2, 139.7, 141.0, 156.4, 167.5, 167.8, 168.9; IR (Nujol) ν_{max} 3308, 3223, 1693, 1682, 1660, 1609 cm^{-1}. Anal. Calcd for $C_{25}H_{23}N_3O_6$: C, 65.07; H, 5.02; N, 9.11. Found: C, 64.89; H, 4.91; N, 9.17.



25: $C_{25}H_{23}N_3O_6$ (461.47)

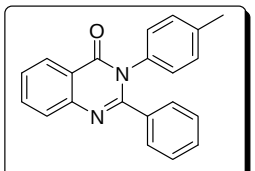
2-Ethyl-3-*p*-tolylquinazolin-4(3*H*)-one (22a). To a stirring solution of compound **21a** (287 mg, 1.00 mmol) and iodine (129 mg, 0.50 mmol) in DCM (15 mL) was slowly added HMDS (0.32 mL, 1.50 mmol) at room temperature and reaction mixture was stirred for 30 minutes. The reaction mixture was diluted with DCM (15 mL) and the organic layer was washed with 5% $Na_2S_2O_3$ solution, water and brine and dried over Na_2SO_4. The concentration of organic layer in vacuo followed by the silica gel column chromatographic purification of the obtained residue using 20% ethyl acetate in petroleum ether furnished the analytically pure **22a** (250 mg, 93% yield). Mp 167–169 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.22 (t, *J* = 8 Hz, 3H), 2.45 (s, 3H), 2.47 (q, *J* = 8 Hz, 2H), 7.13 (d, *J* = 8 Hz, 2H), 7.35 (d, *J* = 8 Hz, 2H), 7.40–7.50 (m, 1H), 7.67–7.82 (m, 2H), 8.27 (d, *J* = 8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 11.2, 21.2, 29.2, 120.7, 126.4, 126.9, 127.9, 130.4, 134.3, 134.6, 139.1, 147.5, 158.0, 162.5 (one carbon less because of the merging); IR (Nujol) ν_{max} 1684, 1605, 1589 cm^{-1}. Anal. Calcd for $C_{17}H_{16}N_2O$: C, 77.25; H, 6.10; N, 10.60. Found: C, 77.12; H, 5.99; N, 10.40.



22a: $C_{17}H_{16}N_2O$ (264.32)

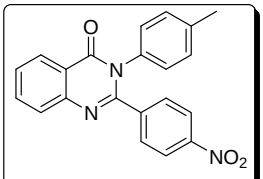
The compounds **22b**-**g**, **26** and **28a** were prepared similarly. The compounds **28b** and **31** were prepared in refluxing in benzene. For the equivalents of HMDS and iodine used and for the reaction time and yields, see Table 2.

2-Phenyl-3-*p*-tolylquinazolin-4(3*H*)-one (22b). Mp 186–188 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.31 (s, 3H), 7.02 (d, *J* = 8 Hz, 2H), 7.11 (d, *J* = 8 Hz, 2H), 7.16–7.38 (m, 5H), 7.45–7.60 (m, 1H), 7.75–7.86 (m, 2H), 8.36 (d, *J* = 8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 21.1, 121.0, 127.1, 127.2, 127.7, 127.9, 128.7, 129.0, 129.2, 129.6, 134.6, 135.0, 135.6, 138.3, 147.5, 155.3, 162.4; IR (Nujol) ν_{max} 1688, 1678, 1653, 1603 cm^{-1}. Anal. Calcd for $C_{21}H_{16}N_2O$: C, 80.75; H, 5.16; N, 8.97. Found: C, 80.67; H, 5.11; N, 8.88.



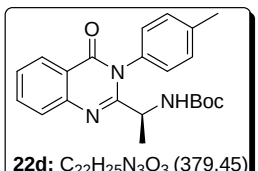
22b: $C_{21}H_{16}N_2O$ (312.36)

2-(4-Nitro-phenyl)-3-*p*-tolylquinazolin-4(3*H*)-one (22c). Mp 218–221 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.33 (s, 3H), 7.03 (d, *J* = 10 Hz, 2H), 7.15 (d, *J* = 10 Hz, 2H), 7.50–7.63 (m, 3H), 7.77–7.90 (m, 2H), 8.09 (d, *J* = 8 Hz, 2H), 8.37 (d, *J* = 8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 21.1, 121.1, 123.1, 127.3, 127.8, 127.9, 128.6, 130.0, 130.1, 134.3, 134.9, 139.1, 141.5, 147.1, 147.7, 153.0, 161.9; IR (Nujol) ν_{max} 1682, 1601 cm^{-1}. Anal. Calcd for $C_{21}H_{15}N_3O_3$: C, 70.58; H, 4.23; N, 11.76. Found: C, 70.49; H, 4.15; N, 11.83.



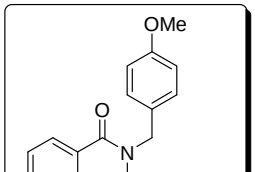
22c: $C_{21}H_{15}N_3O_3$ (357.36)

(*S*)-*tert*-Butyl 1-(4-oxo-3-*p*-tolyl-3,4-dihydroquinazolin-2-yl)ethylcarbamate (22d). Mp 188–190 °C; $[\alpha]^{29}_D$ = –21.8 (*c* 0.6, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.27 (d, *J* = 6 Hz, 3H), 1.42 (s, 9H), 2.44 (s, 3H), 4.57 (quintet, *J* = 8 Hz, 1H), 5.73 (d, *J* = 6 Hz, 1H), 7.16 (dd, *J* = 8 & 2 Hz, 1H), 7.25 (dd, *J* = 8 & 2 Hz, 1H), 7.37 (t, *J* = 8 Hz, 2H), 7.43–7.53 (m, 1H), 7.68–7.83 (m, 2H), 8.27 (d, *J* = 8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 20.8, 21.2, 28.3, 47.6, 79.5, 120.9, 126.8, 127.0, 127.1, 128.0, 128.4, 130.2, 130.9, 133.2, 134.4, 139.5, 147.0, 154.7, 158.0, 162.2 (in *p*-tolyl moiety all six carbons displayed six separate signals); IR (Nujol) ν_{max} 3356, 1720, 1693, 1651 cm^{-1}. Anal. Calcd for $C_{22}H_{25}N_3O_3$: C, 69.64; H, 6.64; N, 11.07. Found: C, 69.79; H, 6.52; N, 11.00.



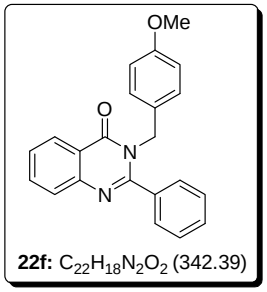
22d: $C_{22}H_{25}N_3O_3$ (379.45)

2-Ethyl-3-(4-methoxybenzyl)quinazolin-4(3*H*)-one (22e). Mp 121–123 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.32 (t, *J* = 8 Hz, 3H), 2.80 (q, *J* = 8 Hz, 2H), 3.77 (s, 3H), 5.35 (s, 2H), 6.84 (d, *J* = 8 Hz, 2H), 7.14 (d, *J* = 8 Hz, 2H), 7.40–7.50 (m, 1H), 7.62-7.80 (m, 2H), 8.31 (d, *J* = 8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 11.2, 28.3, 45.7, 55.2, 114.2, 120.4, 126.3, 126.9, 127.0, 127.8, 128.2, 134.2, 147.3, 158.0, 159.0, 162.6; IR (Nujol) ν_{max} 1682, 1655, 1601 cm^{-1}. Anal. Calcd for $C_{18}H_{18}N_2O_2$: C, 73.45; H, 6.16; N, 9.52. Found: C, 73.59; H, 6.07; N, 9.42.



22e: $C_{18}H_{18}N_2O_2$ (294.35)

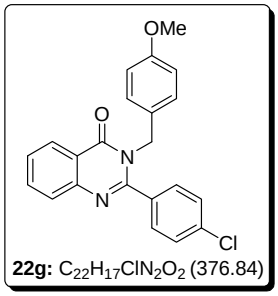
3-(4-Methoxybenzyl)-2-phenylquinazolin-4(3*H*)-one (22f). Mp 187–189 °C; ^{1}H NMR ($CDCl_3$ 200 MHz)



22f: $C_{22}H_{18}N_2O_2$ (342.39)

δ 3.75 (s, 3H), 5.22 (s, 2H), 6.72 (d, *J* = 8 Hz, 2H), 6.86 (d, *J* = 8 Hz, 2H), 7.32–7.58 (m, 6H), 7.72–7.84 (m, 2H), 8.37 (d, *J* = 8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 48.1, 55.1, 113.8, 120.9, 127.0 (2 carbons), 127.5, 128.1, 128.5, 128.6, 128.7, 129.8, 134.4, 135.3, 147.2, 156.3, 158.9, 162.4; IR (Nujol) ν_{max} 1676, 1605, 1585 cm^{-1}. Anal. Calcd for $C_{22}H_{18}N_2O_2$: C, 77.18; H, 5.30; N, 8.18. Found: C, 77.29; H, 5.22; N, 8.31.

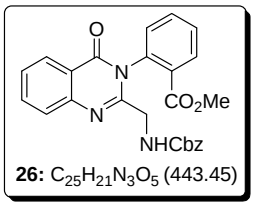
2-(4-Chlorophenyl)-3-(4-methoxybenzyl)quinazolin-4(3*H*)-one (22g). Mp 168–170 °C; ^{1}H NMR



22g: $C_{22}H_{17}ClN_2O_2$ (376.84)

($CDCl_3$, 200 MHz) δ 3.75 (s, 3H), 5.19 (s, 2H), 6.74 (d, *J* = 8 Hz, 2H), 6.86 (d, *J* = 8 Hz, 2H), 7.29 (d, *J* = 8 Hz, 2H), 7.40 (d, *J* = 8 Hz, 2H), 7.48–7.59 (m, 1H), 7.68–7.84 (m, 2H), 8.37 (d, *J* = 8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 48.1, 55.2, 113.9, 120.8, 127.1, 127.3, 127.5, 128.3, 128.4, 128.7, 129.5, 133.7, 134.5, 136.0, 147.0, 155.2, 158.9, 162.3; IR (Nujol) ν_{max} 1682, 1614, 1601 cm^{-1}. Anal. Calcd for $C_{22}H_{17}ClN_2O_2$: C, 70.12; H, 4.55; N, 7.43. Found: C, 69.97; H, 4.42; N, 7.51.

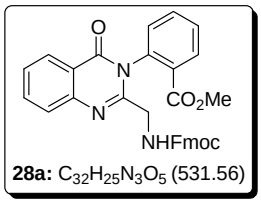
Methyl 2-(2-((benzyloxycarbonylamino)methyl)-4-oxoquinazolin-3(4*H*)-yl)benzoate (26). Mp 78–80



26: $C_{25}H_{21}N_3O_5$ (443.45)

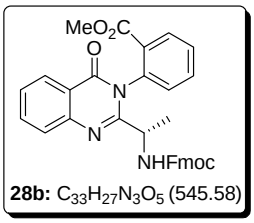
°C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.70 (s, 3H), 3.86 (dd, *J* = 18 & 4 Hz, 1H), 4.09 (dd, *J* = 18 & 6 Hz, 1H), 5.10 (s, 2H), 6.34 (t, *J* = 4 Hz, 1H), 7.27–7.84 (m, 11H), 8.24 (dt, *J* = 8 & 2 Hz, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 43.4, 52.4, 66.9, 120.9, 127.0, 127.1, 127.2, 127.3, 128.0, 128.1, 128.5, 130.0, 130.2, 132.5, 134.3, 134.6, 135.8, 136.4, 146.7, 151.5, 156.0, 162.0, 164.6; IR ($CHCl_3$) ν_{max} 3402, 1728, 1724, 1715, 1693, 1682, 1614, 1599 cm^{-1}. Anal. Calcd for $C_{25}H_{21}N_3O_5$: C, 67.71; H, 4.77; N, 9.48. Found: C, 67.54; H, 4.89; N, 9.48.

Methyl 2-(2-((((9*H*-fluoren-9-yl)methoxy)carbonylamino)methyl)-4-oxoquinazolin-3(4*H*)-yl)benzoate (28a). Mp 90–93 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.72 (s, 3H), 3.80–4.50 (m, 5H), 6.31 (t, *J* = 4 Hz, 1H), 7.25–7.85 (m, 14H), 8.25 (t, *J* = 8 Hz, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 43.5, 47.2, 52.6, 67.3, 120.0, 121.0, 125.1, 125.2, 127.1, 127.2, 127.4, 127.8, 128.1, 130.1, 130.4, 132.5, 134.4, 134.8, 135.8, 141.3, 143.9, 146.5, 152.1, 156.2, 162.0, 164.7; IR (Nujol) ν_{max} 3350, 1726, 1722, 1715, 1682, 1612, 1599 cm^{-1}. Anal. Calcd for $C_{32}H_{25}N_3O_5$: C, 72.30; H, 4.74; N, 7.90. Found: C, 72.15; H, 4.79; N, 7.77.



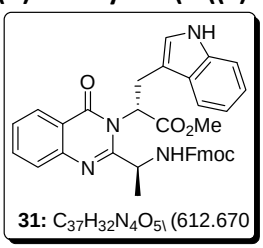
28a: $C_{32}H_{25}N_3O_5$ (531.56)

(*S*)-Methyl 2-(2-(1-(((9*H*-fluoren-9-yl)methoxy)carbonylamino)ethyl)-4-oxoquinazolin-3(4*H*)-yl)benzoate (28b). Mp 88–92 °C; $[\alpha]^{27}_{D}$ = –52.0 (*c* 1.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.29 (d, *J* = 6 Hz, 3H), 3.60 (s, 0.15H), 3.72 (s, 2.85H), 4.05–4.30 (m, 1H), 4.30–4.50 (m, 2H), 4.59 (quintet, *J* = 6 Hz, 1H), 5.88 (d, *J* = 8 Hz, 1H), 7.20–7.70 (m, 9H), 7.70–7.85 (m, 5H), 8.25 (t, *J* = 8 Hz, 2H); IR (Nujol) ν_{max} 3180, 1697, 1690, 1672, 1661, 1614, 1597 cm^{-1}. Anal. Calcd for $C_{33}H_{27}N_3O_5$: C, 72.65; H, 4.98; N, 7.70. Found: C, 72.57; H, 5.04; N 7.77. [Exists as mixture of two rotamers in 95:5 ratio].



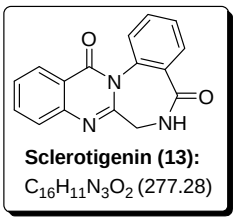
28b: $C_{33}H_{27}N_3O_5$ (545.58)

(*R*)-Methyl 2-(2-((*S*)-1-(((9*H*-fluoren-9yl)methoxy)carbonylamino)ethyl)-4-oxoquinazolin-3(4*H*)-yl)-3-(1*H*-indol-3-yl)propanoate (31). Mp 108–110 °C; $[\alpha]^{28}_{D}$ = +176.0 (*c* 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.33 (d, *J* = 8 Hz, 3H), 3.77 (t, *J* = 8 Hz, 2H), 3.83 (s, 3H), 4.05–4.45 (m, 4H), 4.78 (br s, 1H), 5.92 (d, *J* = 8 Hz, 1H), 6.70 (t, *J* = 8 Hz, 1H), 6.83–7.02 (m, 3H), 7.11 (d, *J* = 8 Hz, 1H), 7.30–7.86 (m, 12H), 8.33 (d, *J* = 6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 21.1, 24.1, 47.3, 47.5, 52.8, 60.3, 66.5, 110.5, 111.0, 117.7, 119.6, 120.0, 120.7, 122.1, 123.0, 125.1, 125.2, 126.8, 126.9, 127.0, 127.1, 127.8, 134.6, 135.9, 141.3, 143.9, 144.0, 146.3, 154.5, 161.7, 168.9; IR (Nujol) ν_{max} 3346, 1746, 1715, 1682, 1672, 1666, 1651 cm^{-1}. Anal. Calcd for $C_{37}H_{32}N_4O_5$: C, 72.53; H, 5.26; N, 9.14. Found: C, 72.39; H, 5.11; N, 9.02.



31: $C_{37}H_{32}N_4O_5$\ (612.670

6,7-Dihydro-6,8,13*a*-triaza-benzo[3,4]cyclohepta[1,2-*b*]naphthalene-5,13-dione (Sclerotigenin, 13). To a stirring solution of compound **28a** (100 mg, 0.19 mmol) in DCM (8 mL) was slowly added piperidine (2.00 mL) at room temperature and the reaction mixture was stirred for 15 minutes. The reaction mixture was concentrated in vacuo and the obtained residue was purified by silica gel column chromatography using ethyl acetate to furnish the analytically pure **13** (47 mg, 90% yield). Mp 272–275 °C {lit.[10b] mp 277–280 °C}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 4.28 (s, 2H), 7.11 (br s, 1H), 7.50–7.87 (m, 6H), 7.98 (d, *J* = 6 Hz, 1H), 8.33 (dd, *J* = 8 & 2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 47.1, 121.6, 127.3, 127.6, 127.8, 128.1, 129.1, 129.8, 130.4, 131.5, 133.8, 135.1, 146.3, 153.6, 161.4, 168.1; IR (Nujol) ν_{max} 3310, 1672, 1666, 1660, 1651, 1614, 1597 cm^{-1}. Anal. Calcd for $C_{16}H_{11}N_3O_2$: C, 69.31; H, 4.00; N, 15.15. Found: C, 69.47; H, 4.12; N, 15.03.

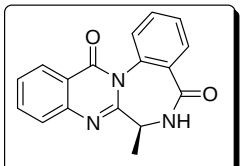


Sclerotigenin (13): $C_{16}H_{11}N_3O_2$ (277.28)

The compounds **14** and **15** were prepared similarly.

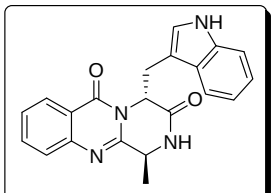
The compound **26** on Cbz-deprotection[12] also furnished the desired product **13** in 65% yield.

7-Methyl-6,7-dihydro-6,8,13*a*-triaza-benzo[3,4]cyclohepta[1,2-*b*]naphthalene 5,13-dione [(–)-Circumdatin-F, 14]. Mp 233–235 °C {lit.[10b] mp 249–250 °C}; $[\alpha]^{29}_{D}$ = –152.4 (*c* 0.4, $CHCl_3$) {lit.[12] $[\alpha]^{20}_{D}$ = –55(*c* 0.94, $CHCl_3$)}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.72 (d, *J* = 8 Hz, 3H), 4.39 (quintet, *J* = 6 Hz, 1H), 6.65 (d, *J* = 6 Hz, 1H), 7.45–7.65 (m, 4H), 7.65–7.85 (m, 2H), 7.97 (d, *J* = 8 Hz, 1H), 8.29 (d, *J* = 8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 15.3, 49.9, 121.3, 127.3, 127.5, 127.7, 128.3, 128.9, 129.8, 130.5, 131.3, 133.5, 134.7, 146.0, 154.9, 161.6, 168.0; IR (Nujol) ν_{max} 3348, 1724, 1686, 1682, 1607, 1597 cm^{-1}. Anal. Calcd for $C_{17}H_{13}N_3O_2$: C, 70.09; H, 4.50; N, 14.42. Found: C, 70.14; H, 4.39; N, 14.55.



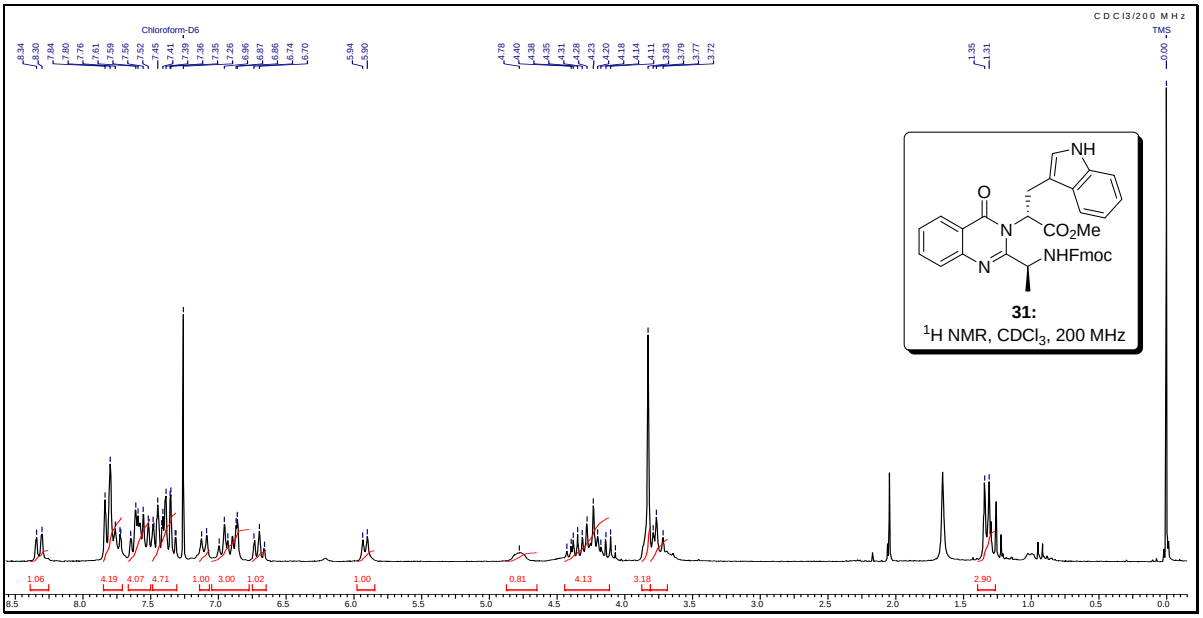
(–)-Circumdatin F (14): $C_{17}H_{13}N_3O_2$ (291.30)

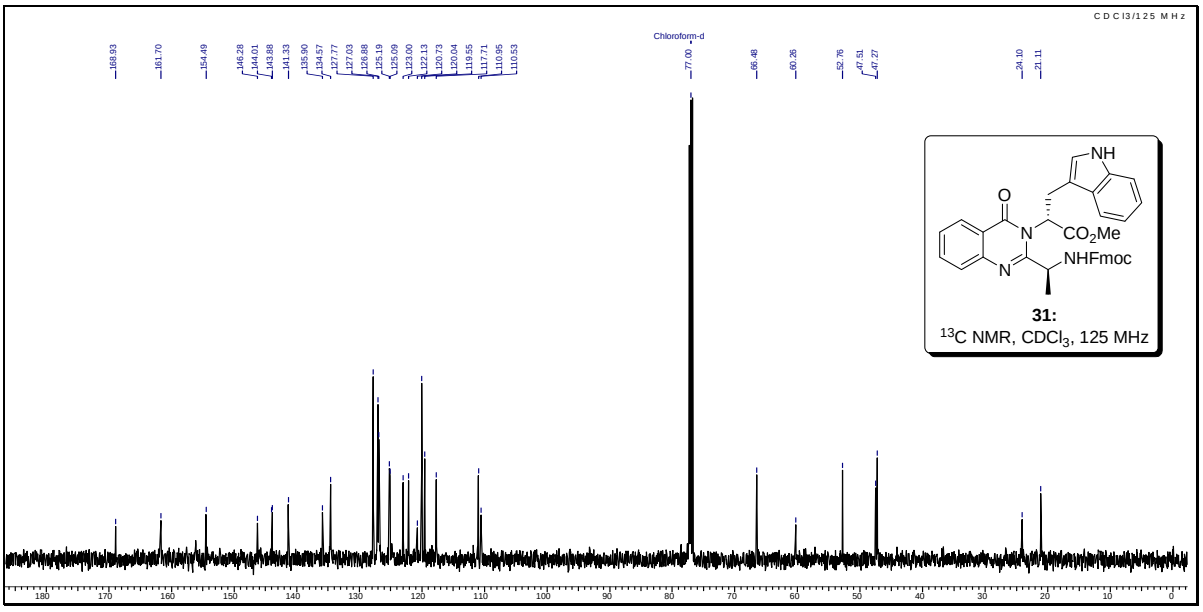
(1*S*,4*R*)-4-((1*H*-Indol-3yl)methyl)-1-methyl-1,2-dihydro-4*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione [(–)-Fumiquinazoline-F, 15]. Mp 170–172 °C {lit.[11b] mp 137 °C (foam)}; $[\alpha]^{28}_{D}$ = –472.0 (*c* 1.0, $CHCl_3$) {lit.[11b] $[\alpha]^{30}_{D}$ = –516 (*c* 0.74, $CHCl_3$)}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.36 (d, *J* = 10 Hz, 3H), 3.11 (q, *J* = 10 Hz, 1H), 3.65 (dd, *J* = 15 & 5 Hz, 1H), 3.71 (dd, *J* = 15 & 2 Hz, 1H), 5.68 (t, *J* = 5 Hz, 1H), 6.26 (br s, 1H), 6.71 (s, 1H), 6.92 (t, *J* = 10 Hz, 1H), 7.13 (t, *J* = 10 Hz, 1H), 7.30 (d, *J* = 10 Hz, 1H), 7.40 (d, *J* = 10 Hz, 1H), 7.53 (t, *J* = 10 Hz, 1H), 7.59 (d, *J* =10 Hz, 1H), 7.77 (dt, *J* = 10 & 5 Hz, 1H), 8.17 (br s, 1H), 8.37 (d, *J* = 10 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 18.9, 27.0, 49.1, 57.5, 109.3, 111.2, 118.4, 119.9, 120.2, 122.5, 123.6, 126.8, 127.1, 127.2, 127.3, 134.7, 136.0, 147.1, 151.6, 160.8, 169.4; IR (Nujol) ν_{max} 3248, 1688, 1682, 1666, 1651, 1597 cm^{-1}. Anal. Calcd for $C_{21}H_{18}N_4O_2$: C, 70.38; H, 5.06; N, 15.63. Found: C, 70.42; H, 5.13; N, 15.57.

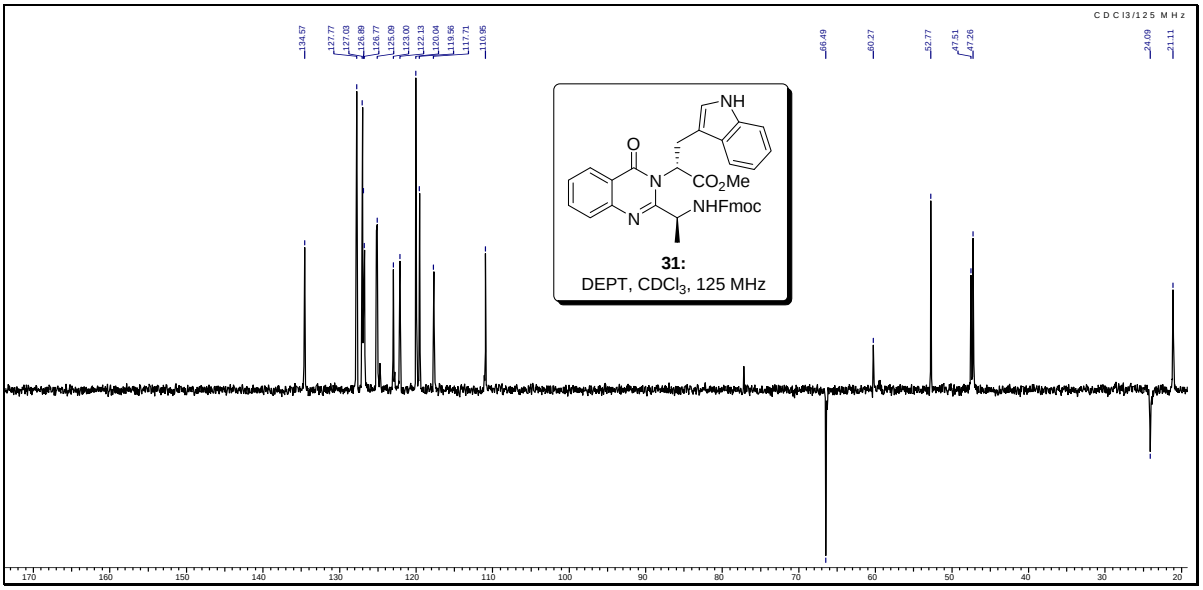


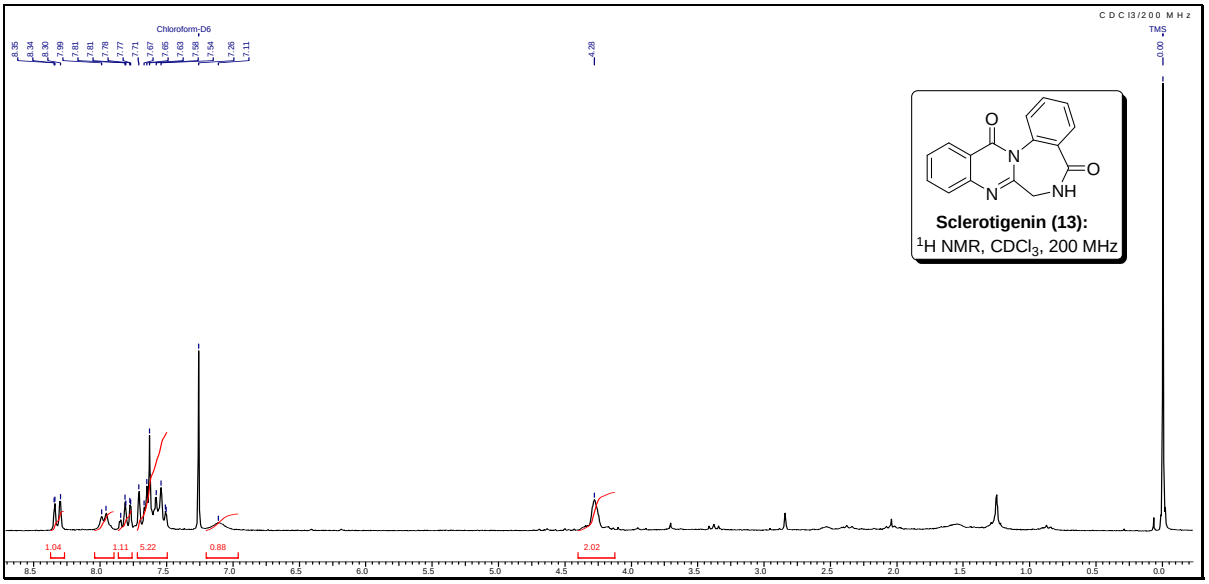
(–)-Fumiquinazoline F (15): $C_{21}H_{18}N_4O_2$ (358.39)

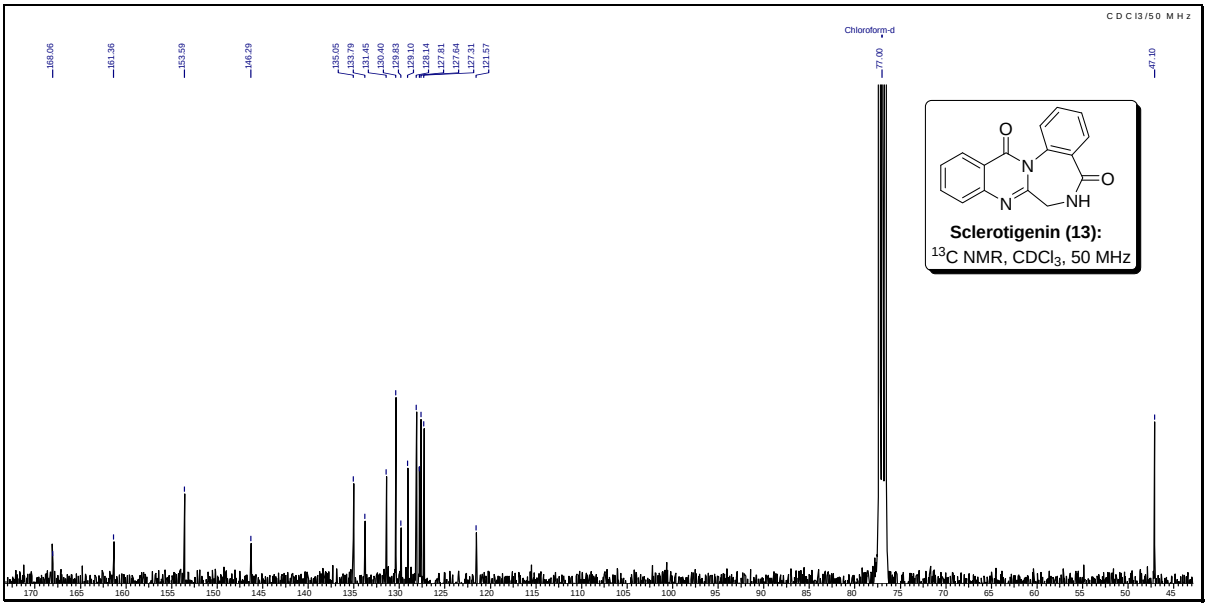
2A.6 Selected Spectra

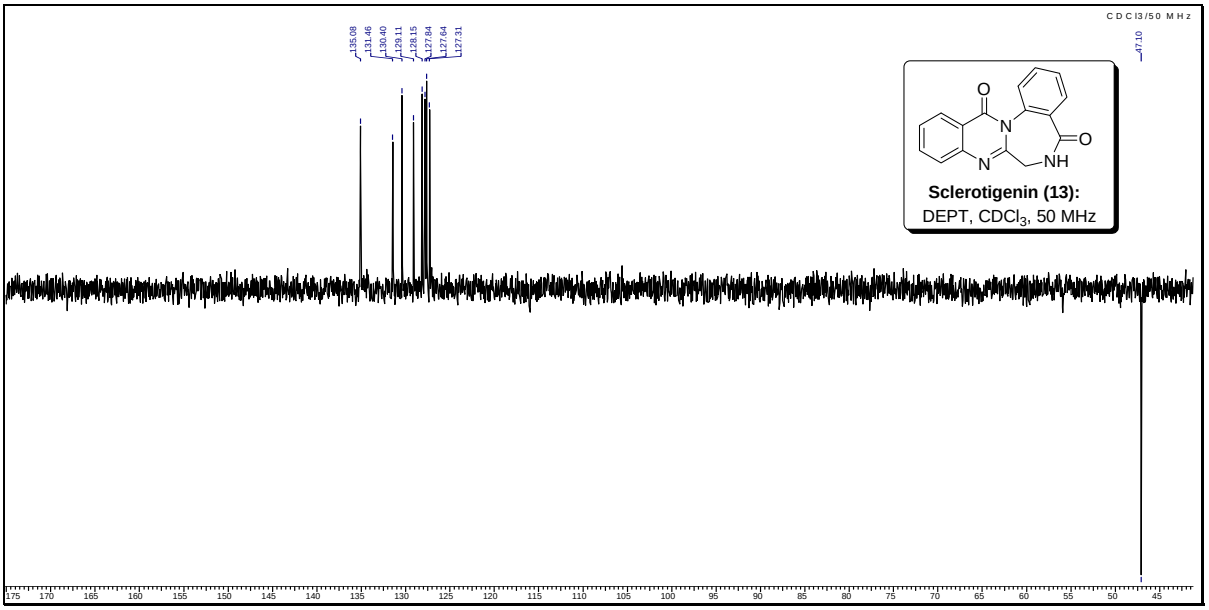

CDCl3/200 MHz
Chloroform-D6
TMS
NH
O
N
CO2Me
N
NHFmoc
31:
1H NMR, CDCl3, 200 MHz

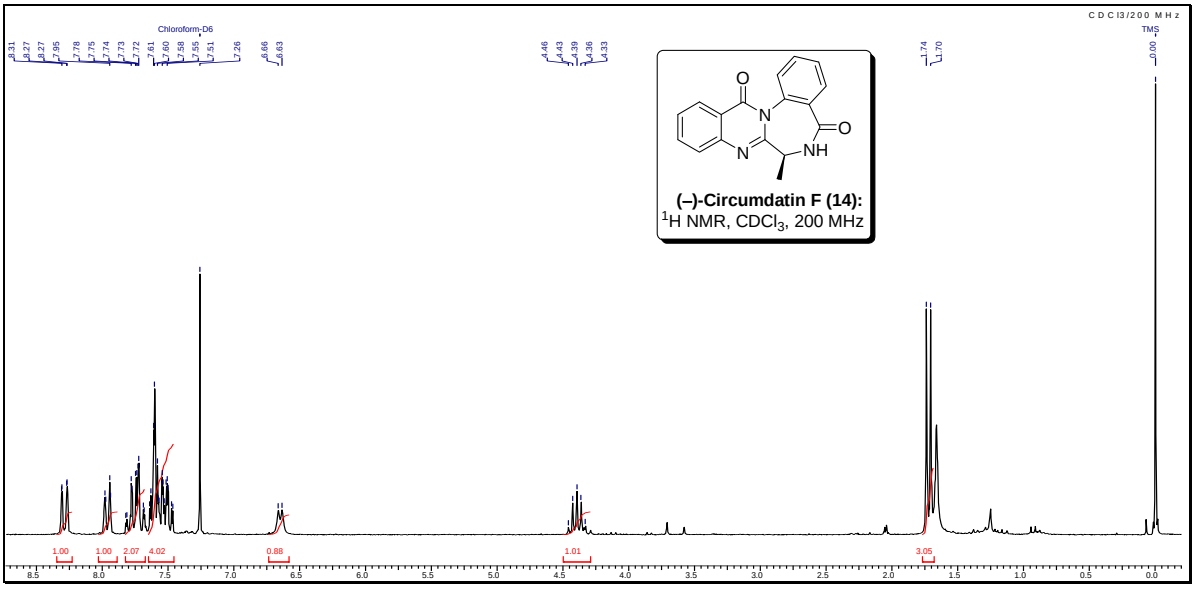

CDCl3/125 MHz
Chloroform-d
NH
O
N
CO2Me
N
NHFmoc
31:
13C NMR, CDCl3, 125 MHz

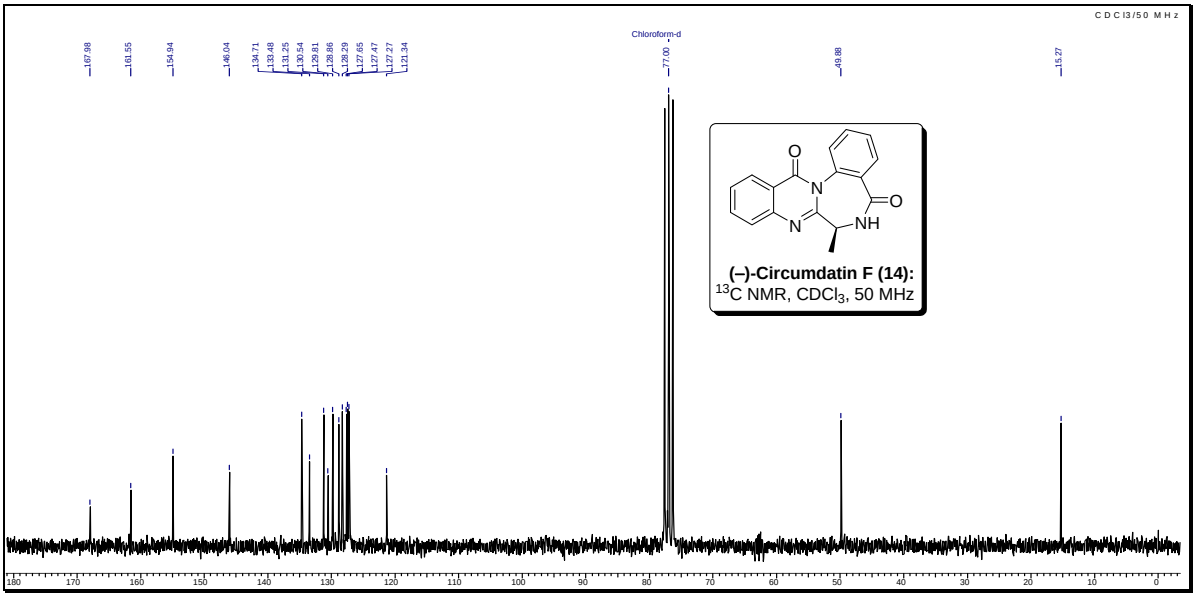

CDCl3/125 MHz
NH
O
N
CO2Me
N
NHFmoc
31:
DEPT, CDCl3, 125 MHz

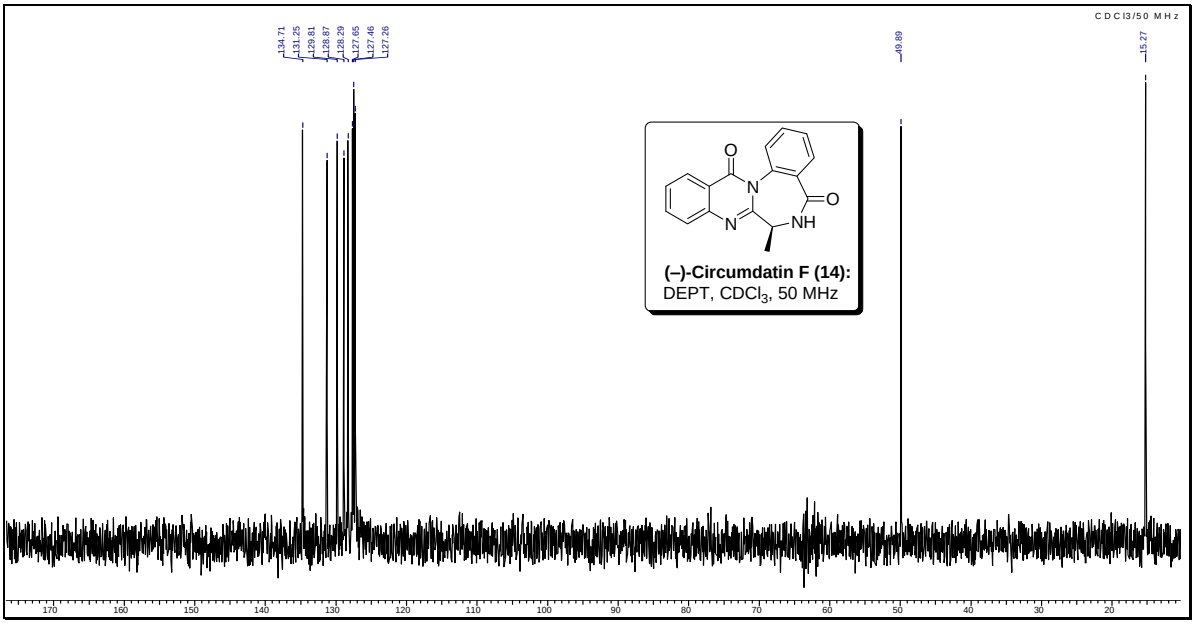

Chloroform-D6
TMS
Sclerotigenin (13):
^{1}H NMR, $CDCl_3$, 200 MHz

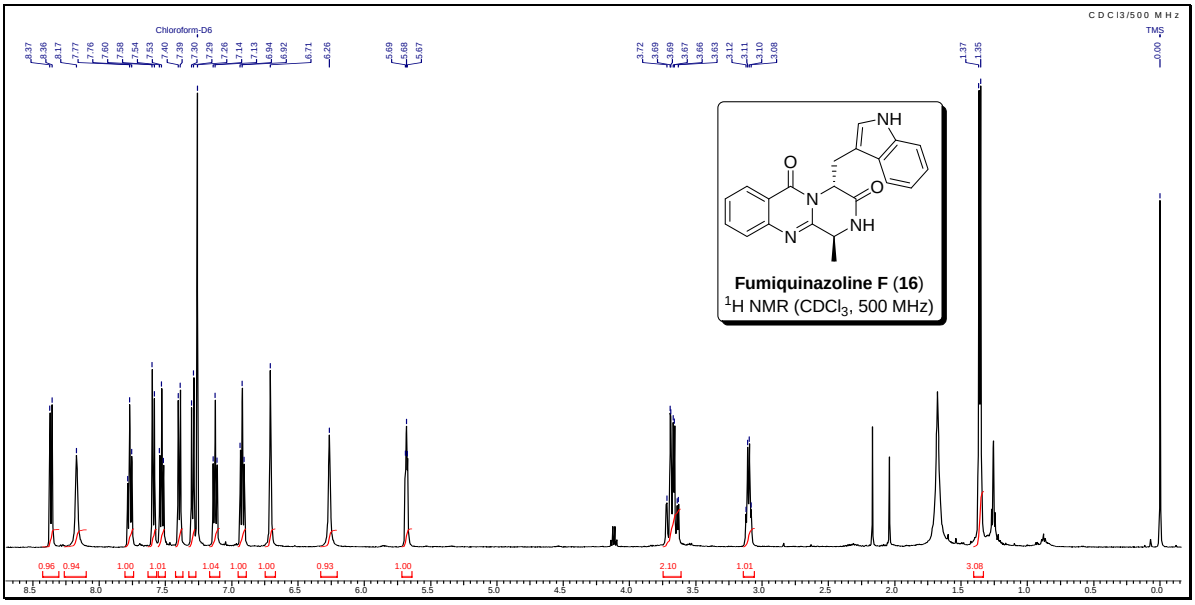

Chloroform-d
Sclerotigenin (13):
^{13}C NMR, $CDCl_3$, 50 MHz

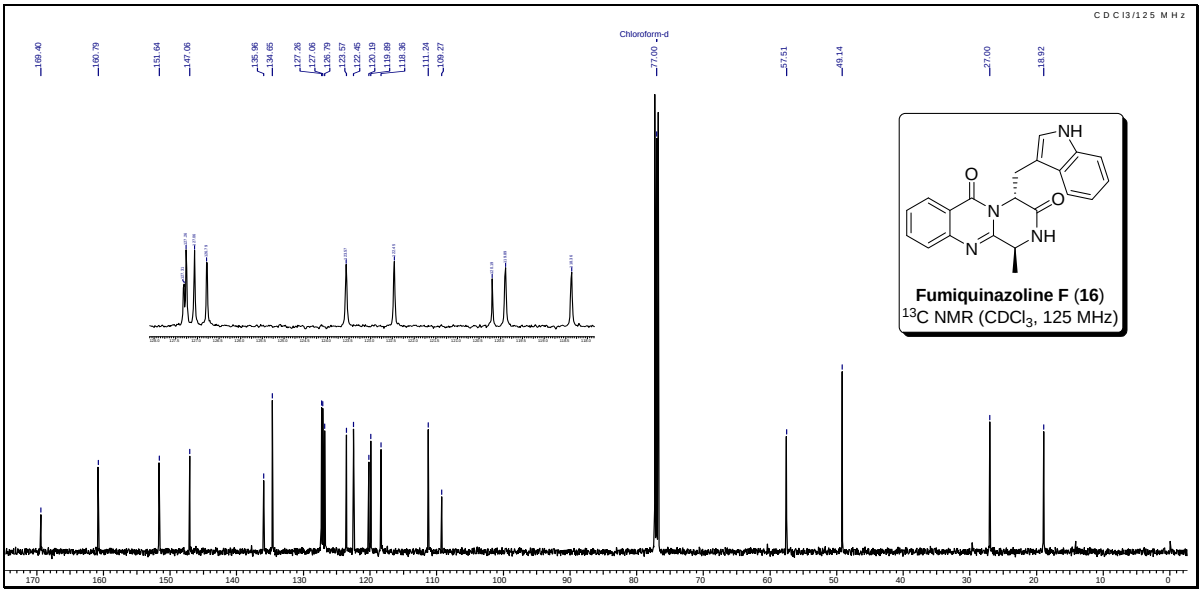

Sclerotigenin (13):
DEPT, $CDCl_3$, 50 MHz

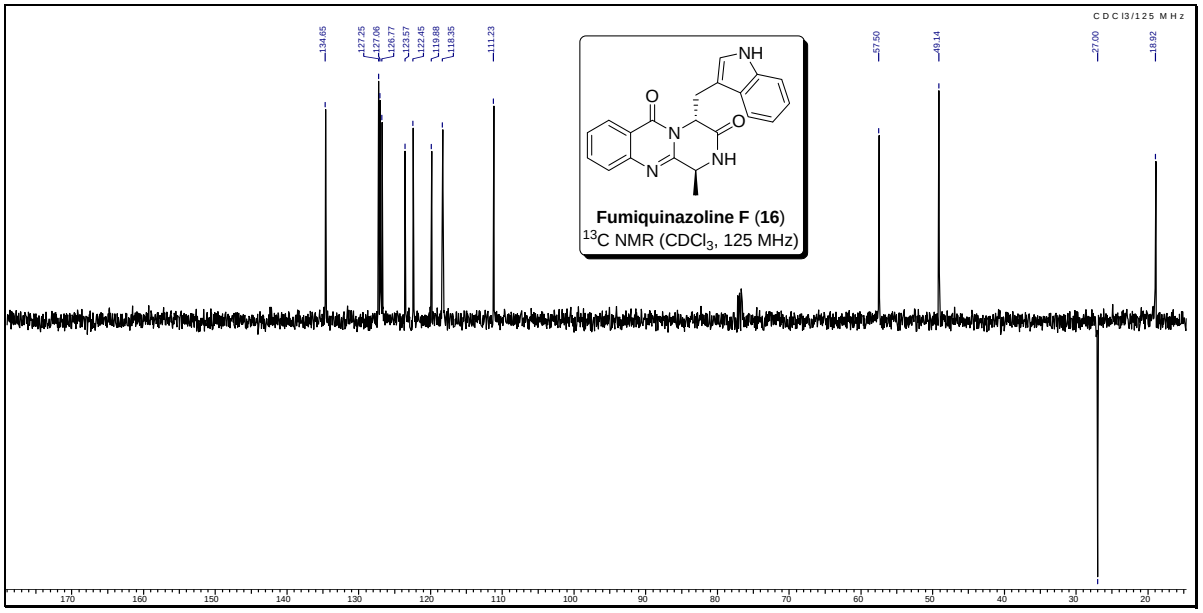

CDCl3/200 MHz
Chloroform-D6
TMS
(–)-Circumdatin F (14):
1H NMR, CDCl3, 200 MHz


CDCl3/50 MHz
Chloroform-d
(–)-Circumdatin F (14):
13C NMR, CDCl3, 50 MHz


CDCl3/50 MHz
(–)-Circumdatin F (14):
DEPT, CDCl3, 50 MHz


CDCl3/500 MHz
Chloroform-D6
TMS
Fumiquinazoline F (16)
1H NMR (CDCl3, 500 MHz)


CDCl3/125 MHz
Chloroform-d
Fumiquinazoline F (16)
13C NMR (CDCl3, 125 MHz)


CDCl3/125 MHz
Fumiquinazoline F (16)
13C NMR (CDCl3, 125 MHz)

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Chapter 2: Section B

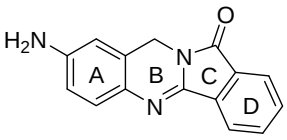
Studies on Synthesis of Analogs of Antitumoral Agent Batracylin and in Progress Synthesis of (–)-Vasicine

This section B of chapter 2 features the following topics:

2B.1 Facile Approach to Diverse Range of Batracylin Analogs

2B.1.1 Background

Batracylin, 8-aminoisoindolo-[1,2-*b*]quinazolin-1,2-(10*H*)-one [NSC 320846, **1** (Figure 1)] is a water insoluble, solid tumor active compound discovered by the Development Therapeutics Program of the National Cancer Institute (NCI).[1]

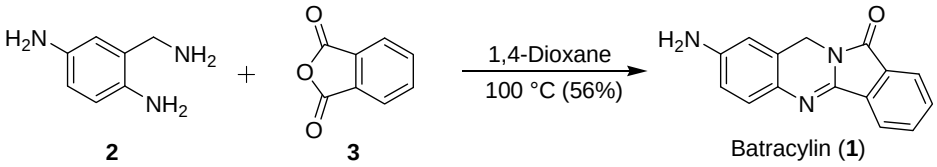


Batracylin (**1**)

Figure 1. Structure of batracylin (NSC 320846, **1**)

Compound **1** had entered large animal toxicology trials at NCI, anticipating phase I clinical evaluation.[2] Batracylin displays antitumor activity in vivo against murine leukemia P-388 and colon adenocarcinoma 38 in mice sublines with acquired resistance to adriamycin, cisplatin, and methotrexate.[3,4] Oral administration of batracylin is effective against other murine solid tumors including pancreatic ductal adenocarcinoma, colon adenocarcinoma no. 51, and hepatoma 129. Batracylin (**1**) also acts as a topoisomerase II inhibitor.[2]

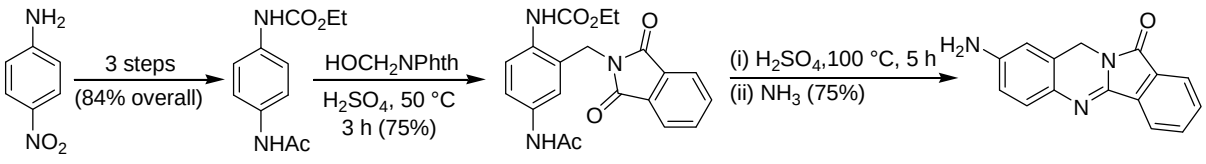
Kabbe[5] synthesized batracylin (**1**) first time by the condensation of 2,5-diaminobenzylamine (**2**) with phthalic anhydride (**3**) (Scheme 1). The reaction involves heating of substrates in 1,4-dioxane for 4 h under relatively mild conditions to obtain batracylin (**1**) in 56% yield.



2 **3** Batracylin (**1**)

Scheme 1. Kebbe's synthesis of batracylin

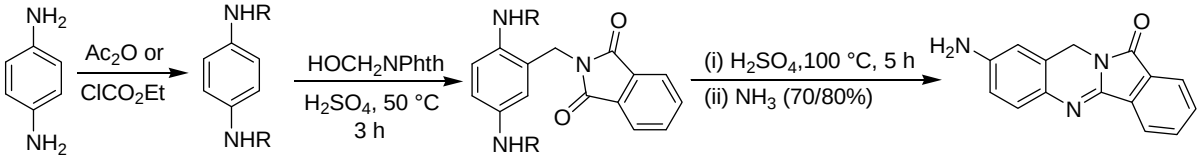
Roservear and Wilshere[6] described the synthesis of batracylin (**1**) using ethyl *N*-(4-acetamidophenyl) carbamate (**5**) (Scheme 2). In which the reaction with *N*-(hydroxymethyl)phthalimide, according to the Czerniak-Einhorn reaction provides the ethyl [4-acetamido)-2-(phthalimidomethyl)phenyl]carbamate (**6**) (Scheme 2). The Czerniak-Einhorn reaction is an electrophilic substitution, where the proton donor *N*-(hydroxymethyl)phthalimide is the electrophilic reagent. Compound **6** was hydrolysed with concentrated sulfuric acid as the hydrolyzing agent in 5 h at 100 °C followed by alkalinisation with ammonia provided batracylin (**1**).



4 **5** **6** Batracylin (**1**)

Scheme 2. Roservear and Wilshere's synthesis of batracylin

The improved approach to Roservear and Wilshere's batracylin synthesis was reported by Dzierzbicka et al. (Scheme 3).[7] In which the *N,N*'-diacetyl-1,4-phenylenediamine (**8a**) or *N,N*'-diethoxycarbonyl-1,4-phenylenediamine (**8b**) were reacted with *N*-(hydroxymethyl)phthalimide under standard conditions of the Czerniak-Einhorn reaction to obtain the intermediates **9a**/**b**. Compounds **9a**/**b** were hydrolysed with concentrated sulfuric acid as the hydrolyzing agent in 5 h at 100 °C followed by alkalinisation with ammonia provided batracylin (**1**) in 70 and 80% yields from the **9a** and **9b** respectively. The advantage of the method consists of elimination of two steps carried out in previously explored methods and avoiding of the reduction of the aromatic nitro group to the amino group.



7

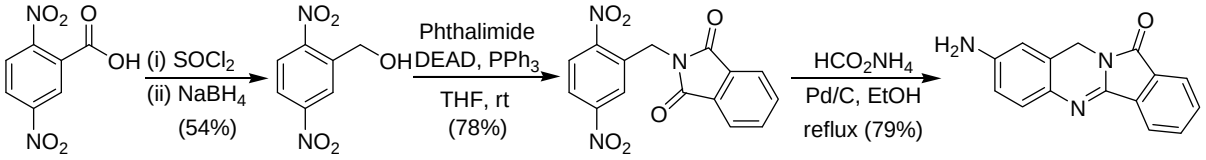
8a: R = Ac (92%)
8b: R = CO_2Et (89%)

9a: R = Ac (64%)
9b: R = CO_2Et (54%)

Batracylin (**1**)

Scheme 3. Dzierzbicka's modified synthesis of batracylin

Dominguez et al. synthesized batracylin starting from 2,5-dinitrobenzoic acid (**10**) (Scheme 4).[8] One-pot reduction of this substrate by conversion to the acid chloride, followed by a treatment with sodium borohydride, gave 54% yield of alcohol **11**. Treatment of **11** with phthalimide in the presence of DEAD and triphenylphosphine gave the phthalimido derivative **12** in a 78% yield. Reduction of **12** with ammonium formate and catalytic amounts of Pd/C gave a diamine that underwent spontaneous cyclodehydration, affording batracylin (**1**) in a 79% yield (33% for the three steps).



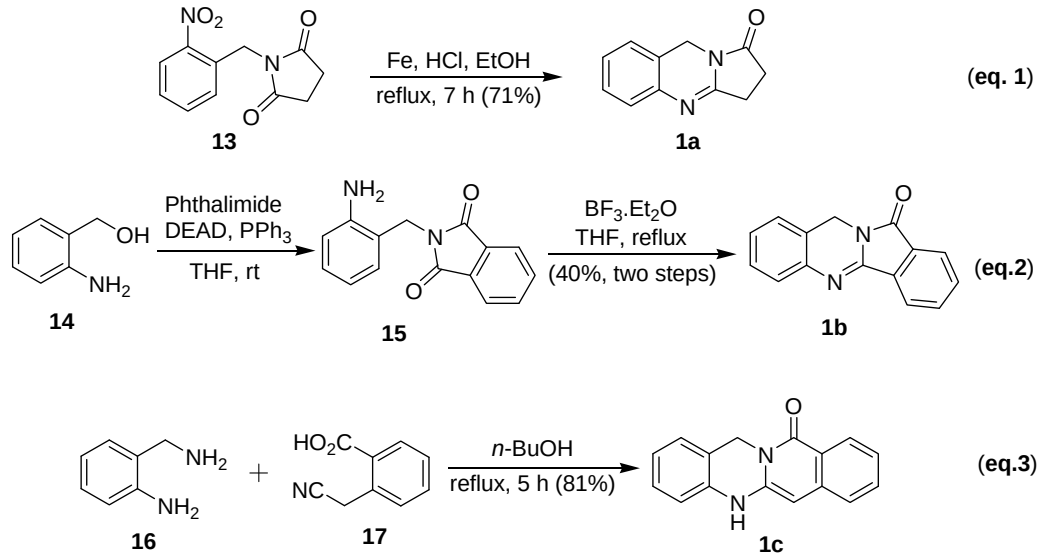
10 **11** **12**

Batracylin (**1**)

Scheme 4. Dominguez's synthesis of batracylin

The major limitations associated with the chemotherapeutic potential of batracylin (**1**) were the high dose levels required for antineoplastic activity and its systemic toxicity, especially in rats. However, it also induces unscheduled DNA synthesis in nonreplicating cells,[9] the low water solubility of batracylin, which limited its oral administration and its high toxicity, which reduced the maximal dose possible to use in vivo, are the causes that it failed to reach the further level clinical trial in human beings despite of promising anticancer activity.[5-9]

In this context, new approaches to provide a variety of analogs of the antitumor agent batracylin have been reported in the literature by using intramolecular reductive cyclizations (Scheme 5, eq. 1),[10] Mitsunobu coupling reactions (Scheme 5, eq. 2)[8,11] and condensation of *o*-aminobenzylamine with *o*-cyanomethylbenzoic acid (Scheme 5, eq. 3).[12]



Scheme 5. Synthesis of batracylin analogs

Accordingly, numerous studies have sought analogues with more favourable characteristics. Structural modifications effected in the hope of retaining ability to inhibit topoisomerase II while reducing toxicity and increasing water solubility include the introduction of diverse substituents on the isoindoloquinazolinone core **1b'** (R = H, Cl, Br, NO_2, Me, CO_2Me, OMe, acids, dipeptides and sugar moieties),[6,9,13] the inclusion of a nitrogen atom in ring A[9] or ring D (**18** and **19**),[13b] an increase in the size of the polycyclic system (**20**)[13b] and contraction of the ring B from six to a five-membered to obtain benzimidazole (**21**)[9] or indole (**22**)[14] analogues (Figure 2).

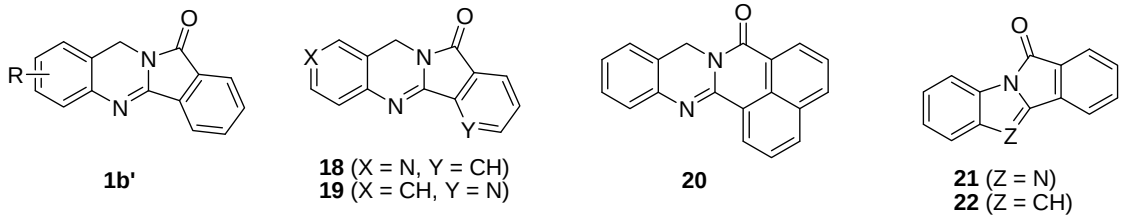
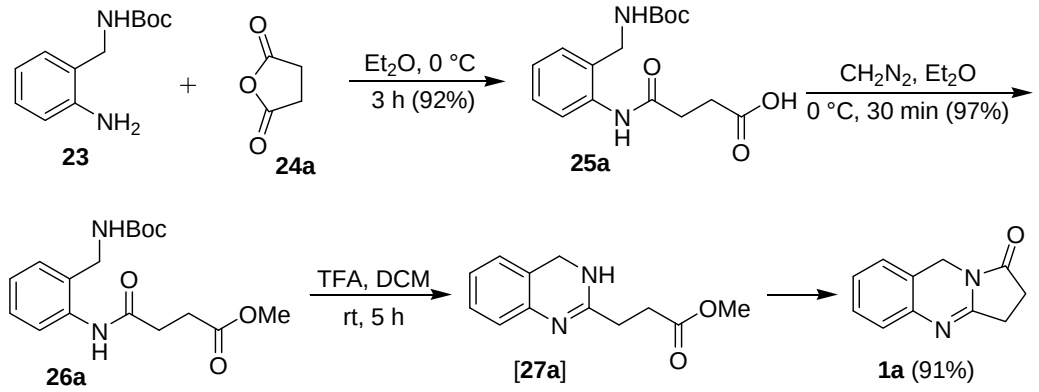


Figure 2. Structural modifications of batracylin

In continuation of our studies on the cyclic anhydrides chemistry to design the bioactive natural and unnatural heterocyclic compounds,[15] we reasoned and planned to study the nucleophilic reactions of several cyclic anhydrides with *tert*-butyl 2-aminobenzylcarbamate (**23**)[16] to provide an avenue to both angular and linear 1,3-diaza-heterocycles in line with their selective formation with respect to the thermodynamic stability. Starting from imides/anilic acid esters, we have developed a simple and efficient synthetic approach to angular/linear 1,3-diazatricyclic/tetracyclic heterocycles that seems capable of providing access to a wide range of analogues of batracylin (**1**) along with a very interesting case of intramolecular methyl group migration.

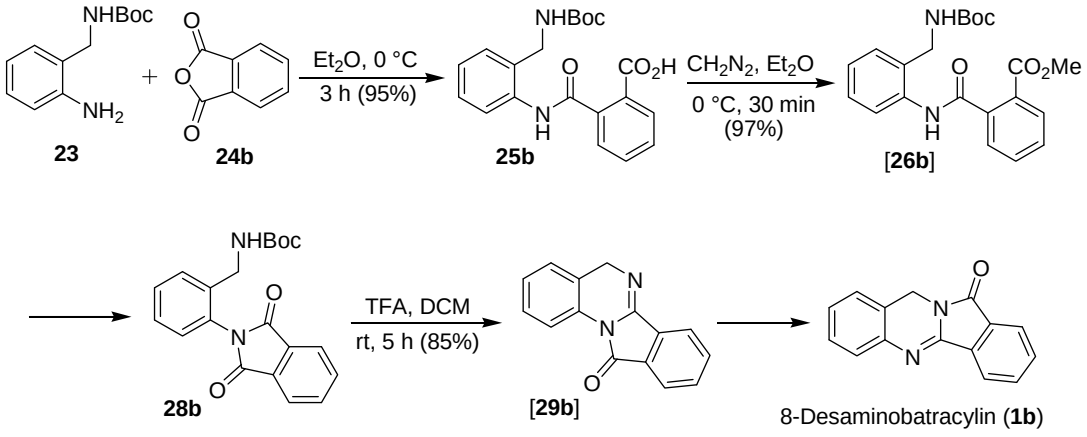
2B.1.2 Results and Discussion

The reactions of *tert*-butyl 2-aminobenzylcarbamate (**23**) with succinic anhydride (**24a**) in diethyl ether at room temperature furnished the required anilic acid **25a** in very good yield (Scheme 6). Compound **25a** on treatment with requisite amount of diazomethane in diethyl ether at 0 °C in 30 min furnished the corresponding methyl ester **26a** in high yield. The trifluoroacetic acid induced Boc-deprotection of succinanilic ester **26a** in CH_2Cl_2 at room temperature directly furnished the pyrrolidinoquinazoline **1a** in 91% yield via dehydrative cyclization to form unisolable intermediate **27a** followed by an intramolecular lactamization route.



Scheme 6. Synthesis of pyrrolidinoquinaziline

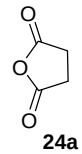
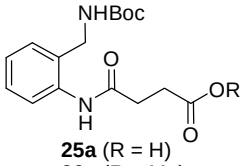
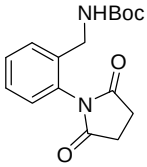
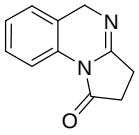
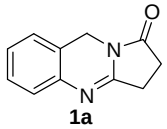
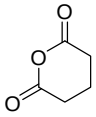
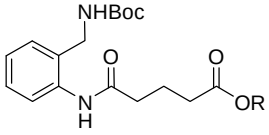
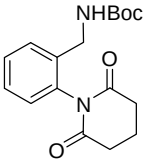
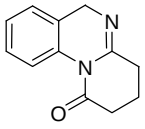
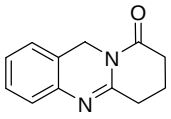
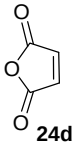
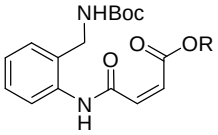
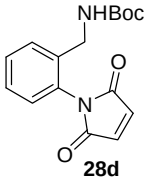
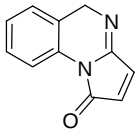
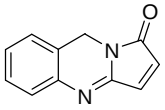
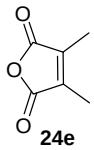
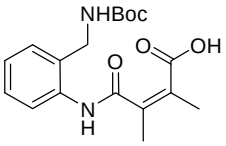
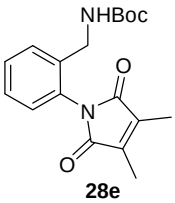
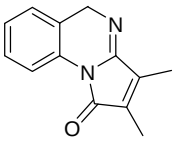
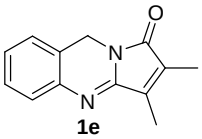
The reactions of *tert*-butyl 2-aminobenzylcarbamate (**23**) with phthalic anhydride (**24b**) in diethyl ether at room temperature furnished the required anilic acid **25b** in 95% yield (Scheme 7). The reaction of phthalanilic acid **25b** with diazomethane directly provided the more stable ring closed product, the imide **28b** in 97% yield and the conditions to obtain the phthalanilic ester **26b** are still elusive. To our surprise the trifluoroacetic acid induced Boc-deprotection of phthalimide **28b** in CH_2Cl_2 at room temperature directly furnished the linear product 8-desaminobatracylin (**1b**) in 85% yield instead of expected angular product **29b**. We feel that, the imide **28b** exclusively provides thermodynamically more stable product **1b** in quantitative yield via the ring opening and ring closing

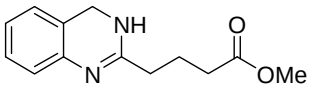


Scheme 7. Synthesis of 8-desaminobatracylin

sequence of ring "C" of the proposed unisolable angular product **29b**. These results encouraged us to study the nucleophilic reaction of *tert*-butyl 2-aminobenzylcarbamate (**23**) with different cyclic anhydrides. The reactions of *tert*-butyl 2-aminobenzylcarbamate (**23**) with glutaric anhydride (**24c**) and maleic anhydride (**24d**) in diethyl ether at room temperature furnished the required anilic acids **25c** and **25d** respectively, in 93% and 98% yields (Table 1). The reaction of *tert*-butyl 2-aminobenzylcarbamate (**23**) with dimethylmaleic anhydride (**24e**) directly furnished the expected imide **28e** in quantitative yield via the unisolable intermediate anilic acid **25e**. The anilic acids **25c** and **25d** on treatment with requisite amount of diazomethane in diethyl ether at 0 °C in 30-40 min furnished the corresponding methyl esters **26c** and **26d** in high yields. In our hands, the dehydrative cyclizations of **25a**/**c** and the intramolecular cyclizations of **26a**/**c** to obtain the corresponding succinimide/glutarimide **28a**/**c** under the several known standard reaction conditions met with failure and we always ended up with corresponding starting materials. Our studies revealed that the formed imides **28a**/**c** (by TLC) are unstable and they undergo an in situ facile ring opening with the anchimeric assistance of the nitrogen lone pair from the suitably *ortho*-substituted -CH_2NHBoc moiety. The base catalyzed intramolecular cyclization of ester **26d** furnished the corresponding imide **28d** in 75% yield. Having prepared imides **28d**/**e** and esters **26c**/**d** we planned to systematically study the Boc-deprotection and intramolecular double cyclizations of these advanced starting materials to obtain the corresponding desired angular/linear 1,3-diaza-heterocycles respectively (Table 1). The Boc-deprotection of glutaranilic ester **26c** in CH_2Cl_2 at room temperature furnished the intermediate quinazoline **27c** (Figure 3) in quantitative yield via intramolecular monocyclization route, which in refluxing methanol furnished intramolecularly ring closed final product piperidinoquinazoline **1c** in 87% yield. These observations also revealed that **26a** passes through an unisolable intermediate **27a** (Scheme 6) to directly furnish the product **1a**. We failed to obtain the corresponding imide intermediates **28a**/**b**, hence we could not prepare the angular products **29a**/**c**. The Boc-deprotection of maleanilic ester **26d** in CH_2Cl_2 at room temperature directly furnished the linear product **1d** via the double intramolecular cyclization pathway. The Boc-deprotection of maleimide **28d** under the similar reaction conditions also furnished only linear product **1d** in quantitative yield via the ring opening and ring closing sequence of ring "C" of the proposed unisolable angular product **29d**. The Boc-deprotection of the 2,3-dimethyl substituted imide **28e** on intramolecular condensation exclusively formed the angular product **29e** in 94% yield. It could be an effect of the methyl groups conferring more stability to the imide functionality. To convert the kinetically controlled angular product **29e** to thermodynamically stable linear product **1e**, first we refluxed the **29e** in methanol, which remained completely unreacted for the span of 5 days. However, the same reaction in the presence of a catalytic amount of acetic acid furnished thermodynamically more stable linear product **1e** with ~100% yield in 48 h via the expected ring opening and closing mechanism.

Table 1. Nucleophilic reactions of cyclic anhydrides with *tert*-butyl 2-aminobenzylcarbamate: synthesis of angular/linear 1,3-diaza-heterocycles

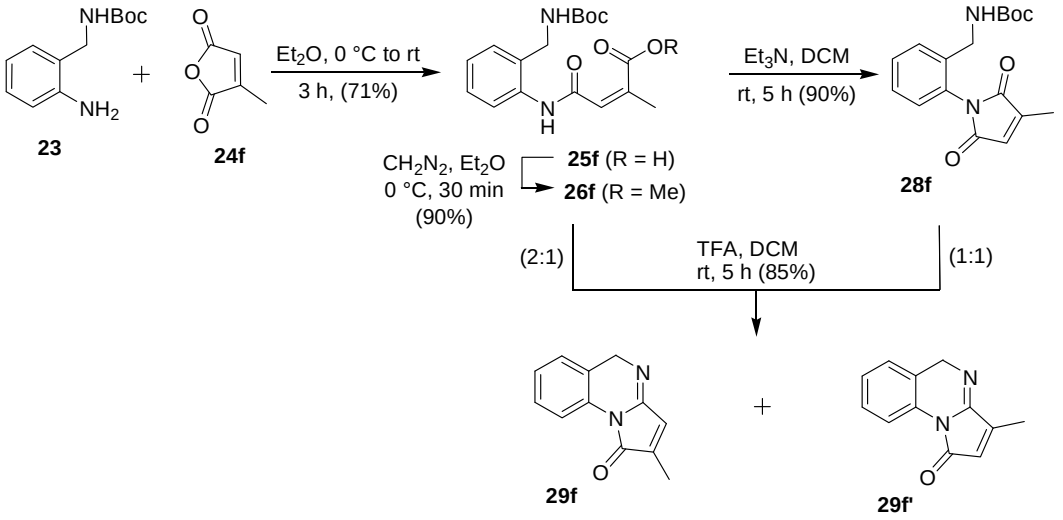
Anhydride	Anilic acid/ester	Imide	Angular product	Linear product
 **24a**	 **25a** (R = H) **26a** (R = Me)	 **28a** (Unstable)	 **29a** (Not obtained)	 **1a**
 **24c**	 **25c** (R = H) **26c** (R = Me)	 **28c** (Unstable)	 **29c** (Not obtained)	 **1c**
 **24d**	 **25d** (R = H) **26d** (R = Me)	 **28d**	 **29d** (Unisolable)	 **1d**
 **24e**	 **25e** (Unisolable)	 **28e**	 **29e**	 **1e**



27c

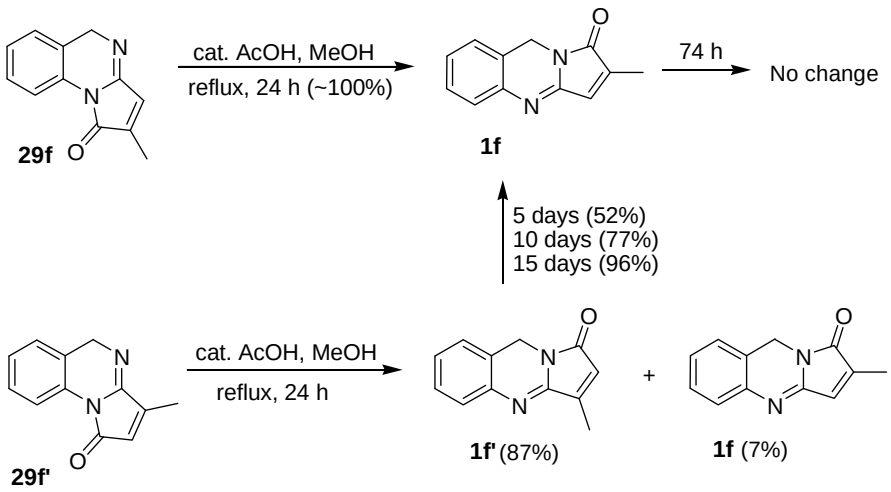
Figure 3. Isolable monocyclized product

The reaction of *tert*-butyl 2-aminobenzylcarbamate (**23**) with methylmaleic anhydride (**24f**) was not completely regioselective (Scheme 8) and as expected, the mixture of two regioisomers [major (attack at unhindered carbonyl) : minor (attack at hindered carbonyl) = 85:15] was obtained in quantitative yield. One recrystalization of the above mixture from ethyl acetate provided the major isomer **25f** in 71% yield. The anilic acid **25f** on treatment with requisite amount of diazomethane in diethyl ether at 0 °C in 30 min furnished the corresponding methyl ester **26f** in 90% yield. The base catalyzed intramolecular cyclization of ester **26f** furnished the corresponding imide **28f** in 90% yields. The imide **26f** on Boc-deprotection provided the column separable mixture of ring closed angular products **29f/f'** in 85% yield with a 1:1 ratio. The Boc-deprotection of maleanilic ester **26f** also



Scheme 8. Synthesis of angular 1,3-diaza-heterocycles

exclusively furnished the column separable mixture of the ring closed angular products **29f/f'** in 85% yield with 2:1 ratio and it could be an effect of the methyl group conferring more stability to the possible imide intermediate. The column purified product **29f** on refluxing in methanol for 75 h gave corresponding thermodynamically more stable linear product **1f** in high yield via the "C" ring opening and closing pathway (Scheme 9). However, the corresponding unhindered regioisomer **29f'** under the same set of reaction conditions was transformed into **1f'** but only to the extent of 11% in 75 h.



Scheme 9. Rearrangment of angular 1,3-diaza-heterocycles to linear 1,3-diaza-heterocycles

As expected, in ^{1}H NMR spectra, the β-vinylic proton signal in **29f** (δ 6.69) was more deshielded (Figure 4) than the α-vinylic proton in the corresponding **29f'** (δ 6.33). The β-vinylic proton signal in **1f** (δ 6.83) was more deshielded than the α-vinylic proton in the corresponding **1f'** (δ 6.27). The relatively slow conversion of unhindered **29f'** to **1f'** can be attributed to the hyperconjugative influence of the β-methyl group in **29f'** on the reactivity of the lactam carbonyl group. The angular

product **29f**, on treatment with methanol plus acetic acid at reflux temperature exclusively gave the desired linear product **1f** in 24 h in quantitative yield. The pure **29f'** under the same conditions gave the desired **1f'** with 87% yield in 24 h. We presume that both of the mentioned conversions take place via "C" ring opening and closing. Surprisingly, during these studies on conversion of pure **29f'** to **1f'** we also noticed the formation of a small amount of compound **1f** (detection by TLC, 7% by ^{1}H NMR). We were very curious about the formation of **1f** in conversion of **29f'** to **1f'** and therefore we refluxed the pure **1f'** in methanol plus acetic acid for 5/10/15 days and obtained the rearranged product **1f** in 52/77/96% yields respectively, with the change in methyl group position.

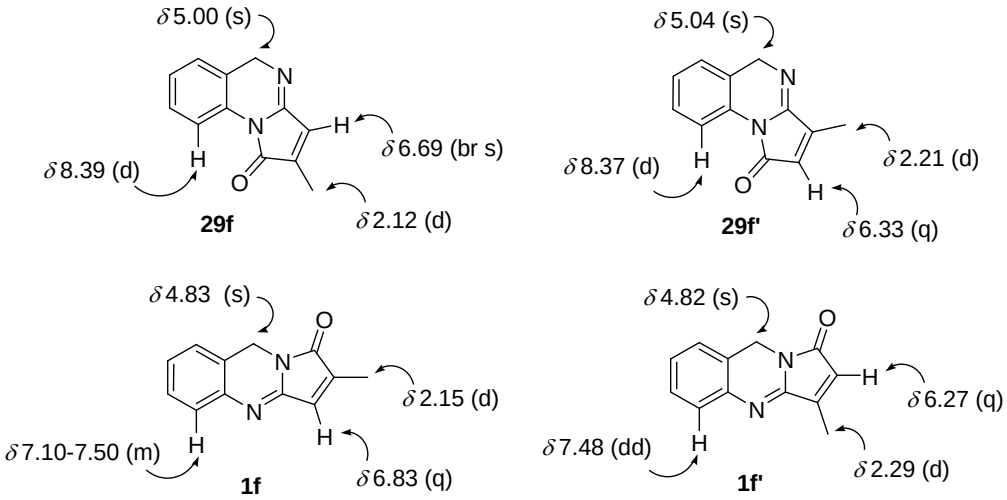
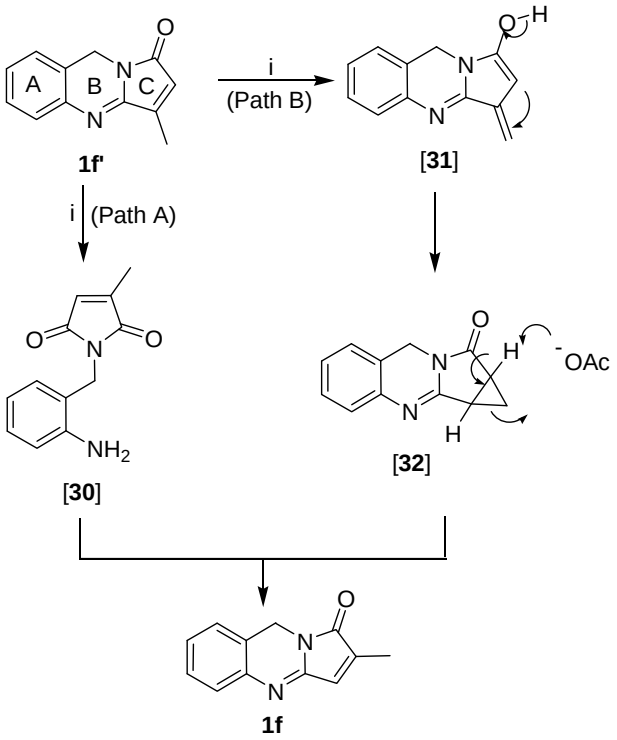


Figure 4. NMR spectroscopic analysis of angular/linear compounds

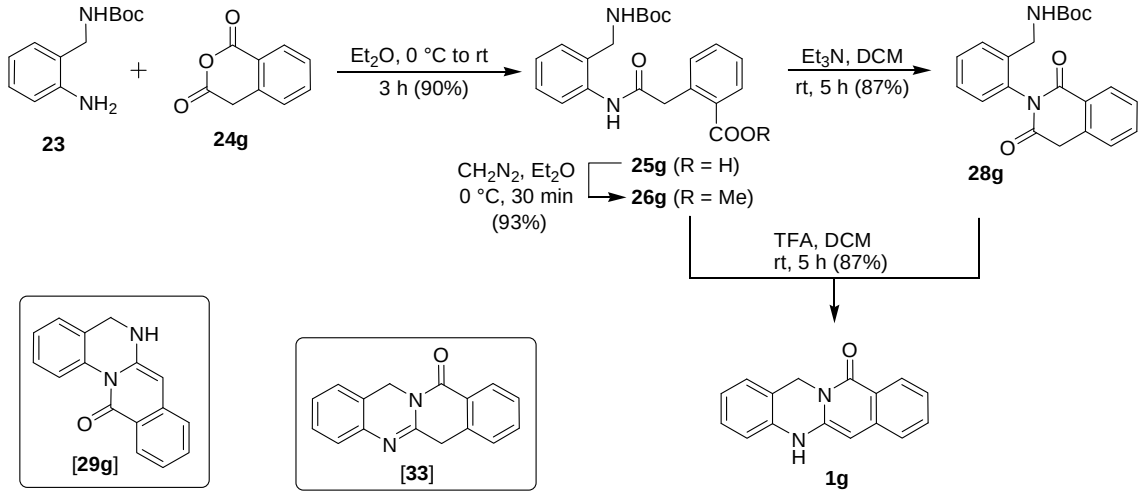
To explain the observed methyl shift in the conversion of **1f'** to **1f**, two plausible mechanisms are depicted in scheme 10 (path A/B). The path A with the cleavage of ring "B" by imine hydrolysis to form the unisolable imide intermediate **30** and an in situ intramolecular ring closing with the other carbonyl group appears simpler and straightforward. We strongly believe that the formation of the free imide intermediate **30** should lead to a mixture of **1f** and **1f'**, as the methyl group on the imide moiety is not expected to control the complete regioselectivity. The slow rate of conversion of **29f'** to **1f'** in refluxing methanol due to the hyperconjugative effect of the methyl group and the exclusive transformation of **29f** to **1f** in refluxing methanol plus acetic acid in 24 h support the mechanistic path B which does not demand the cleavage of ring "B". As depicted in path B, the proton shift from the methyl group to the carbonyl group followed by cyclopropane ring formation is possible. Its cleavage with the abstraction of the more acidic α-proton can also lead to the net methyl shift from the β-carbon to the α-carbon for thermodynamic reasons. In a control experiment, the pure linear product **1f** remained completely unreacted in refluxing methanol plus acetic acid mixture for 72 h and we did not observe any methyl group shuffling, which also supports the mechanistic path B. Such a example of methyl migration through cyclopropane ring formation is known in literature.[17]

We feel that the proposed 1,2-methyl shift via the cyclopropane ring formation is important from a mechanistic point of view and appears to be very amenable to isotopic labeling.



Scheme 10. Proposed mechanisms for the observed 1,2-methyl shift

Regioselective opening of homophthalic anhydride (**24g**) at more reactive carbonyl group with *tert*-butyl 2-aminobenzylcarbamate (**23**) in diethyl ether at room temperature followed by esterification with requisite amount of diazomethane in diethyl ether at 0 °C in 30 min furnished the corresponding methyl esters **26g** in 93% yields (Scheme 11). The base catalyzed intramolecular cyclization of ester **26g** furnished the corresponding imide **28g** in 87% yield. The Boc-deprotection of homophthalanilic ester **26g** in CH_2Cl_2 at room temperature directly provided the isoquinolinodihydroquinazoline **1g** in 87% yield. Herein, both the intramolecular cyclizations to form



Scheme 11. Synthesis of isoquinolinodihydroquinazoline

isoquinolinodihydroquinazoline **1g** in 87% yield. Herein, both the intramolecular cyclizations to form the unisolable isoquinolinone intermediate **33** and the prototopic shift to confer the quasi-aromatic character on ring "C" took place in one pot for thermodynamic reasons. Such prototopic shift for thermodynamic stability reasons has also been observed for the phaitanthrin E (Chapter 1, Figure 4, structure **34**). This observation also concurs the structural determination of **1g** done by Potikha et al.[12b] The corresponding imide **28g** on Boc-deprotection also formed only the linear product **1g** in high yield via the ring opening and closing of unisolable intermediate **29g**.

In all of the studied examples,[18] as expected the linear products had higher melting points than the corresponding angular products. The analytical and spectral data for all the compounds synthesized were in complete agreement with the assigned structures/reported data.[8,10,12] The angular and linear products were also clearly distinguished from each other on the basis of ^{1}H NMR data. In all of the angular products **29e/29f/29f'**, one of the aromatic proton signals was more deshielded (ca δ 8.38) due to the close proximity with the lactam carbonyl group. We feel that the proposed 1,2-methyl shift via the cyclopropane ring formation is important from a mechanistic point of view and appears to be very amenable to isotopic labeling.

2B.2 Studies Towards the Synthesis of (–)-Vasicine

2B.2.1 Background

A number of plants belonging to the families acanthaceae, cruciferae, malvaceae, and rutaceae are known to contain quinazoline alkaloids.[19] The leaves, roots, and the young plants of *Adhatoda vasica* Nees (Family: Acanthaceae; Sanskrit: vasaca) is an evergreen bush and extract of leaves are used in the *The Indian Ayurvedic System of Medicine* as a remedy for cold, cough, bronchitis and asthama.[20] The leaves, roots and the young plants of *Adhatoda vasica* Nees have been extensively investigated and lead to the isolation of the quinazoline alkaloids (–)-vasicine (34a) and (+)-vasicine (34b), the major alkaloid of the plant[21,22] along with deoxyvasicine (35),[23a] (+)-vasicinol (36),[23b] 5-methoxyvasicine (37),[24] (–)-vasicol (38)[25] vasicoline (39)[26] and adhatodine (40)[26] along with quinazolinone alkaloids (–)-vasicinone (41),[27] deoxyvasicinone (42),[27b] vasicolinone (43),[26] and anisotine (44)[26] (Figure 5).

Vasicine (peganine, **34**), the alkaloid of *Adhatoda vasica Nees,* is the first member of quinazoline and quinazolinone alkaloid family isolated in 1888.[21] It has been found to be biologically active and is the subject of many chemical and pharmacological studies.[28] It is of special interest in connection with its marked hypotensive, bronchodilator and respiratory stimulant activity. Around 1977 it was discovered that vasicine possesses uterine stimulating activity with similar effect as oxytocin.[29] After this discovery and due to the fact that there is a great need for new drugs for fertility regulation, a lot of efforts have been put into research to develop vasicine as a new abortifacient agent. In the

1980's the WHO also included *A. vasica* in *The Special Programme of Research in Human Reproduction* as a plant worthy of study for fertility regulation.[28]

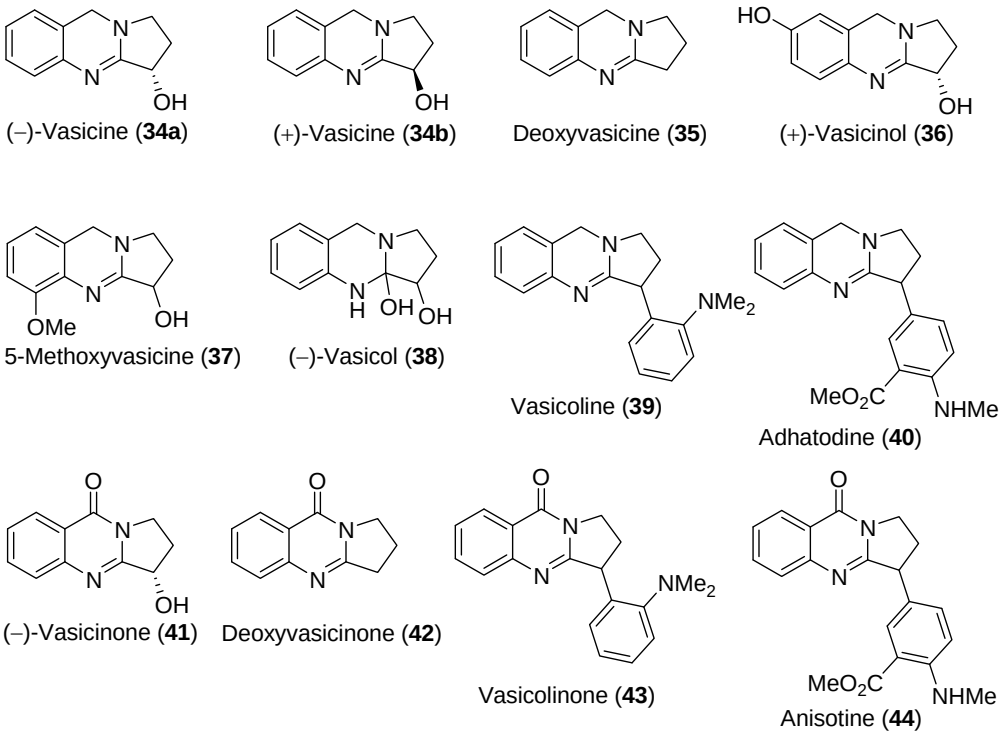
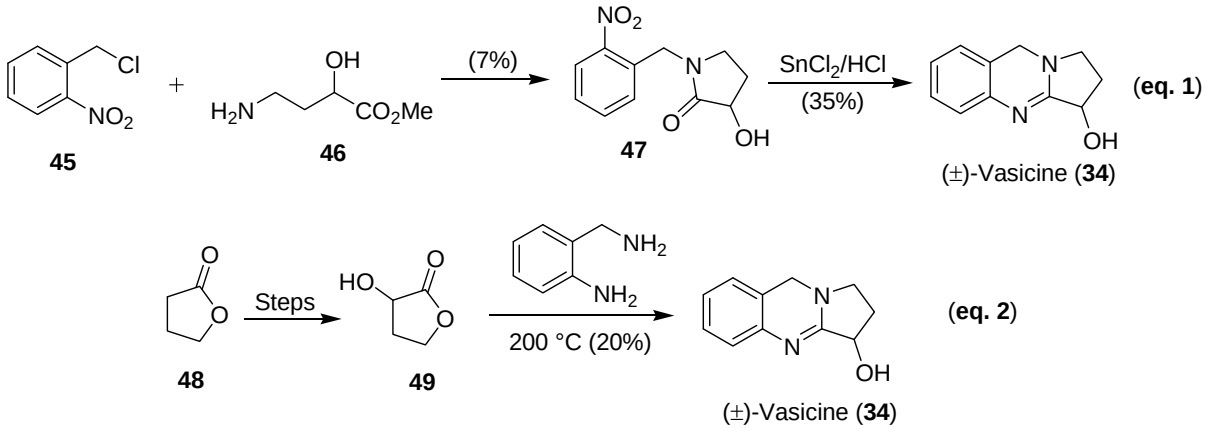


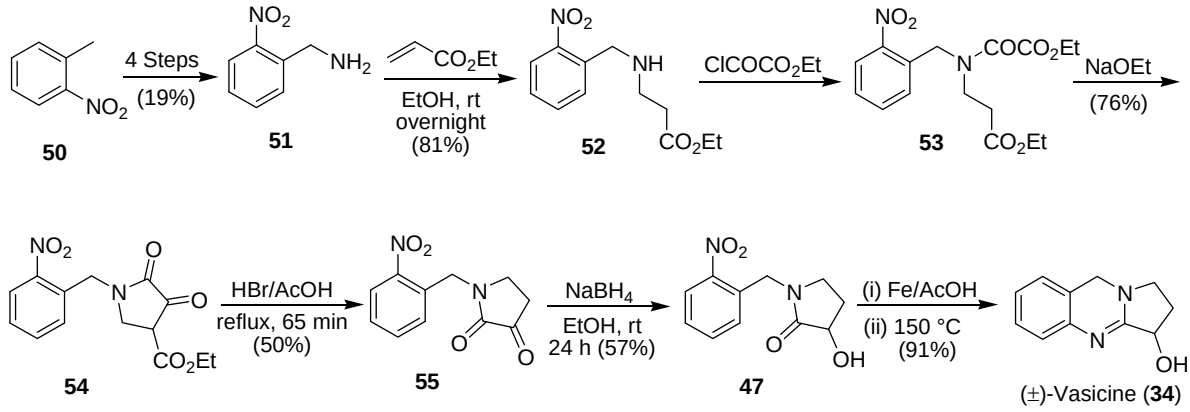
Figure 5. Vasicine and related alkaloids from the plant *Adhatoda vasica Nees*

Till date six synthesis of (±)-vasicine (**34**) are known in literature. The first synthesis by Spath et al.[30] depended on the preparation of methyl α-hydroxy-γ-aminobutyrate (**46**), which was treated with *o*-nitrobenzyl chloride (**45**) and provided 1-(*o*-nitrobenzyl)-3-hydroxy-2-oxopyrrolidine (**47**) in very low yield (Scheme 12, eq. 1). Compound **47** when treated with stannous chloride in hydrochloric acid, underwent spontaneously reductive intramolecular dehydrative cyclization to give a 35% yield of (±)-vasicine (**34**). Later Spath and Platzefl[31] described a more convenient procedure (Scheme 12, eq. 2) for the synthesis of (±)-vasicine (**34**). Where α-hydroxybutyrolactone was prepared from butyrolactone and heated at high temperature with *o*-aminobenzylamine (**16**) to give (±)-vasicine (**34**) with only 20% yield.



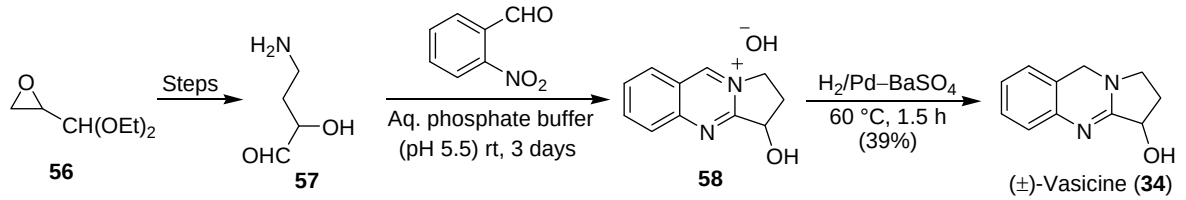
Scheme 12. Spath's synthesis of (±)-vasicine

Southwickand and Casanova[32] synthesized (±)-vasicine (**34**) starting from *o*-nitrotoluene (Scheme 13). Addition of *o*-nitrobenzylamine (prepared from *o*-nitrotoluene in four steps with 19% overall yield) to ethyl acrylate produced ethyl *β*-(*o*-nitrobenzylamino)-propionate (**52**) in 81% yield. Treatment of aminopropionate **52** with ethoxalyl chloride to form the *N*-ethoxalyl derivative **53**, which then underwent the desired Dieckmann cyclization, on treatment with sodium ethoxide to give the 4-carbethoxy-2,3-dioxopyrrolidine (**54**) in 76% yield. The compound 1-(*o*-nitrobenzyl)-2,3-dioxopyrrolidine (**55**) was obtained by acid hydrolysis and decarboxylation of the 4-carbethoxy compound **54**. The more reactive ketone carbonyl group was reduced with sodium borohydride to provide 1-(*o*-nitrobenzyl)-3-hydroxy-2-oxopyrrolidone (**47**). Reduction of nitro group was performed with iron in aqueous acetic acid followed by sublimation of the intermediate at 150 °C provided the (±)-vasicine (**34**) in 91% yield.



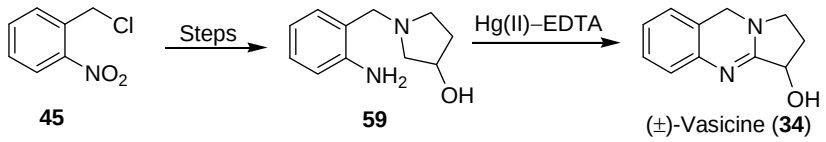
Scheme 13. Southwickand's synthesis of (±)-vasicine

Leonard and Martell[33] also synthesized (±)-vasicine (**34**) (Scheme 14), in which *γ*-amino-*α*-hydroxybutyraldehyde (**57**) was prepared from glycidaldehyde diethyl acetal (**56**). Condensation of *γ*-amino-*α*-hydroxybutyraldehyde (**57**) with *o*-nitrobenzaldehyde in the presence of aq. phosphate buffer (pH 5.5) at room temperature in 3 days provided an orange solution of **58**, which on catalytic hydrogenation with palladium on barium sulphate at 60 °C provided (±)-vasicine (**34**) in 39% overall yield.



Scheme 14. Leonard and Martell's synthesis of (±)-vasicine

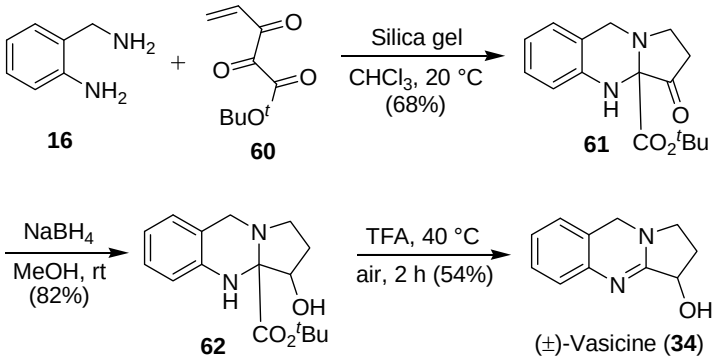
Mohrle and Gundlach's[34] synthesized (±)-vasicine (**34**) using mercuric ion-promoted intramolecular dehydrative cyclization as a key step (Scheme 15). Hydroxyl-diamine **59** was prepared from *o*-nitrobenzylchloride (**45**). Mercuric ion-promoted intramolecular oxidative cyclization of hydroxyl-diamine **59** provided (±)-vasicine (**34**) in very good yield.



45 **59** (±)-Vasicine (**34**)

Scheme 15. Mohrle and Gundlach's synthesis of (±)-vasicine

Wasserman and Kuo[35] synthesized (±)-vasicine (**34**) in which vinyl vicinal tricarbonyl (VTC, **60**) was used as trielectrophile (Scheme 16). Treatment of *o*-aminobenzylamine with the vinyl vicinal tricarbonyl (VTC, **60**) in chloroform at 20 °C for 2 h, in the presence of silica gel directly furnished the tricyclic compound **61** in 68% yield. Compound **61** was reduced with sodium borohydride in methanol to a diastereomeric mixture of alcohols **62** (3:I, 82%). In the final step of the synthesis, treatment of **62** with trifluoroacetic acid at 40 °C for 2 h in the presence of air led directly to the (±)-vasicine (**34**) in 45% yield with the possible role of air oxidation in the transformation.



16 **60** **61** **62** (±)-Vasicine (**34**)

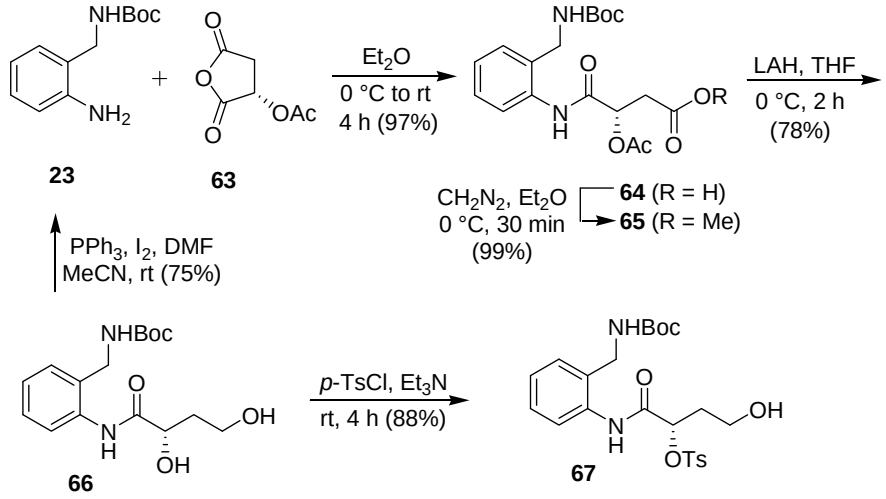
Scheme 16. Wasserman and Kuo's synthesis of (±)-vasicine

The total synthesis of (–)-vasicinone (**41**) has been reported from our group from (*S*)- acetoxysuccinic anhydride utilizing chiral pool strategy.[36a] Till date, the synthesis of (–)-vasicine (**34a**) and (+)-vasicine (**34b**) is not reported. In continuation of our studies[36] on the use of enantiomerically pure cyclic anhydrides as building blocks for the total synthesis of bioactive natural and unnatural products, we planned to undertake the synthesis of (–)-vasicine (**34a**) from (*S*)-acetoxysuccinic anhydride as chiral building block.

2B.2.2 Results and Discussion

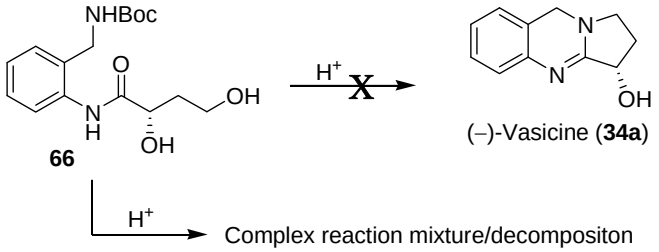
A highly regioselective ring opening of (*S*)-acetoxysuccinic anhydride (**63**)[36a] at the more reactive electron-deficient carbonyl carbon, with *tert*-butyl 2-aminobenzylcarbamate (**23**) in diethyl ether at 0 °C to room temperature in 4 h furnished the required (*S*)-acetoxysuccinanilic acid **64** in 97% yield (Scheme 17). (*S*)-Acetoxysuccinanilic acid **64** on treatment with requisite amount of diazomethane in diethyl ether at 0 °C in 30 min furnished the corresponding methyl esters **65** in 99% yield. Chemoselective reduction of methyl esters **65** with lithium aluminium hydride in tetrahydrofuran at 0 °C provided the corresponding diol **66** in 78% yield. First we tried to convert primary alcohol in diol **66** to corresponding iodo compound by the standard reagent triphenylphosphine/iodine. To our surprise, instead of alcohol to iodo conversion in this reaction we got back our first starting material

i. e. *tert*-butyl 2-aminobenzylcarbamate (**23**) in 75% yield, which may be due to the amide hydrolysis of diol **66** by in situ formation of imidoyl iodide of the amide functionality. In the literature we found that similar type of reagent combination has been used for amide cleavage under mild conditions.[37] Prati et al. used the $(PhO)_3P.Cl_2$ reagent, prepared in situ by titrating a solution of triphenyl phosphite with chlorine, for conversion of *N*-monosubstituted amides into their corresponding amines at –30 °C to rt.[37a] Whereas Koenig et al. used the propylene glycol for the hydrolysis of in situ imidoyl chloride generated from acetamides and oxalyl chloride.[37b] We tried to convert primary alcohol to tosylate by the treatment of diol **66** with *p*-toluenesulfonyl chloride in presence of triethyl amine as base, but



Scheme 17. Synthesis of desired diol intermediate

surprisingly we exclusively obtained the secondary tosylated product **67**. We also tried the deprotection of Boc-group of diol **66** with acid (Scheme 18) for intramolecular dehydrative cyclization of formed primary benzyl amine with amide carbonyl followed by in situ displacement of primary alcohol with second dehydrative cyclization to directly get the (–)-vasicine (**34a**). We tried

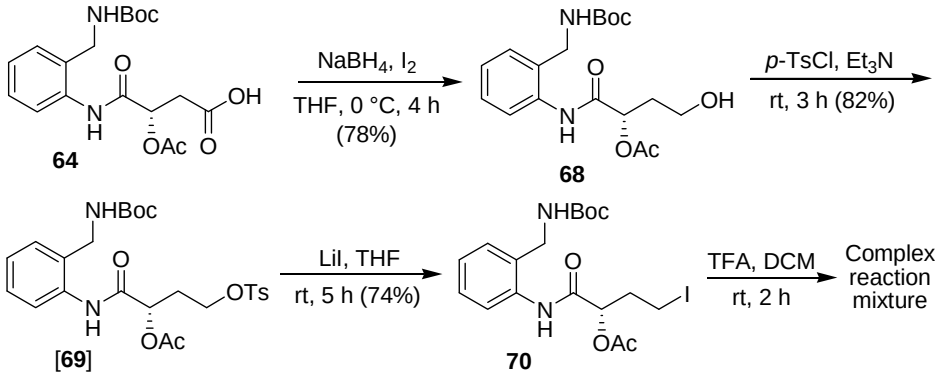


Scheme 18. Attempts for double cyclization of diol

variety of reagents like trifluoroacetic acid, aluminium chloride, $SnCl_4$, hydrochloric acid, polyphosphoric acid, but in all the cases we got either complex reaction mixture, polymeric gums or decomposed material only.

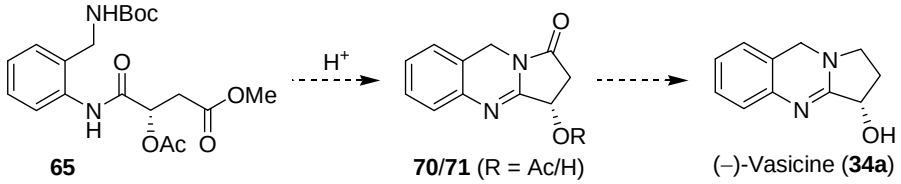
Here we felt that the problem might be arising due to the free secondary alcohol and hence we planned to keep secondary alcohol as acetate and conversion of primary alcohol to good leaving group to assist the double cyclization to provide the (–)-vasicine (**34a**) (Scheme 19). Chemoselective

reduction of (*S*)-acetoxysuccinanilic acid **64** with sodium borohydride in presence of iodine provided the alcohol **68** in 78% yield. Conversion of primary alcohol to tosylate was achieved by treatment of **68** with *p*-toluenesulfonyl chloride in presence of triethyl amine as base. Compound **69** was converted to iodo compound **70** in 74% yield using lithium iodide. Again all our attempts to convert the compound **70** in to corresponding (–)-acetoxyvasicine or (–)-vasicine (**34a**) met with failure.



Scheme 19. Our second approach for (–)-vasicine

Now, we plan to prepare acetoxy and hydroxyl quinazolinones **70**/**71** from the acetoxy ester **65** using our developed[18] Boc-deprotection and intramolecular double cyclizations sequence to provide the quinazolinones (Scheme 20). Chemoselective reduction of amide carbonyl group of quinazolinones **70**/**71** will provide (–)-vasicine (**34a**).



Scheme 20. Proposed approach for (–)-vasicine

Our experience on the synthesis of (–)-vasicine (**34a**) lead us to understand that an intellectual soft trick is required to handle the multifunctional compound **65** and its derivatives. This work is under progress in our group.

2B.3 Summary

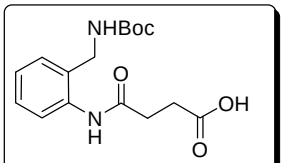
In summary, we have systematically studied the nucleophilic reactions of several cyclic anhydrides with tert-butyl 2-aminobenzylcarbamate and provided a simple, efficient and new practical route to the synthesis of diverse range of kinetically controlled angular and thermodynamically controlled linear tricyclic and tetracyclic 1,3-diaza-heterocycles in high yields. Our present study clearly reveals that in all the cases, the anilic acid esters exclusively provide thermodynamically more stable linear 1,3-diaza-heterocycles, while only the methyl and dimethyl substituted maleimides exclusively provide the corresponding kinetically controlled angular 1,3-diaza-heterocycles. In all the imides studied, formed kinetically controlled angular products were successfully transformed to the corresponding thermodynamically controlled linear products by refluxing in methanol or methanol plus catalytical amount of acetic acid mixture. The serendipitously witnessed intramolecular shuffling of the methyl group is also noteworthy and important from the basic chemistry points of view, but the two different mechanistic aspects discussed on observed methyl migration are only the proposals. We feel that our present simple and efficient general approach to these 1,3-diaza-heterocycles will be useful to design the focused libraries of analogs and congeners of batracylin for SAR-studies. Our studies on synthesis of (–)-vasicine have been also described and it clearly indicates that for the synthesis of (–)-vasicine, we need an intellectual solution to handle the multifunctional starting materials. Further work on this synthesis is in progress in our group and we are hopeful that we will be in position to identify and address the root cause in our problem and complete the synthesis.

2B.4 Experimental Section

Commercially available cyclic anhydrides and trifluoroacetic acid were used. *tert*-Butyl 2-aminobenzylcarbamate (**23**) was prepared from commercially available *o*-aminobenzylamine using the known procedure.[16]

General procedure for the preparation of anilic acids (25a-d, 25f, 25g). To a stirred solution of anhydride (2.00 mmol) in diethyl ether (15 mL) at 0 °C was added a solution of *tert*-butyl 2-aminobenzylcarbamate (**23**, 2.00 mmol) in diethyl ether (10 mL) in a dropwise fashion over a period of 10 minutes and the reaction mixture was further stirred at room temperature for 3 h. The precipitated product was filtered, washed with ether (25 mL) and dried under vacuum to obtain the corresponding anilic acid in quantitative yield.

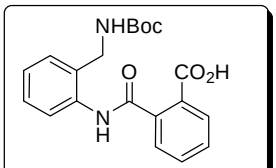
4-(2-((*tert*-Butoxycarbonylamino)methyl)phenylamino)-5-oxobutanoic acid (25a): Mp 134–136 °C;



25a: $C_{16}H_{22}N_2O_5$ (322.36)

^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.43 (s, 9H), 2.70–2.90 (m, 4H), 4.25 (d, *J* = 6 Hz, 2H), 5.16 (br s, 1H), 7.07 (t, *J* = 8 Hz, 1H), 7.14 (t, *J* = 8 Hz, 1H), 7.32 (dd, *J* = 8 & 2 Hz, 1H), 8.12 (d, *J* = 8 Hz, 1H), 9.74 (br s, 1H); ^{13}C NMR (CD_3OD, 50 MHz) δ 28.7, 30.1, 32.0, 41.5, 80.6, 126.1, 126.9, 128.9, 130.4, 134.3, 136.5, 158.9, 173.6, 176.4; IR (Nujol) ν_{max} 3360, 2700-2500, 1711, 1697, 1661 cm^{-1}. Anal. Calcd for $C_{16}H_{22}N_2O_5$: C, 59.62; H, 6.88; N, 8.69. Found: C, 59.55; H, 6.96; N, 8.71.

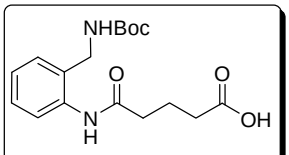
2-(2-((*tert*-Butoxycarbonylamino)methyl)phenylcarbamoyl)benzoic acid (25b): Mp 155–157 °C; ^{1}H



25b: $C_{20}H_{22}N_2O_5$ (370.40)

NMR (DMSO-d_6, 200 MHz) δ 1.35 (s, 9H), 4.21 (d, *J* = 6 Hz, 2H), 7.12–7.40 (m, 4H), 7.45–7.75 (m, 4H), 7.88 (d, *J* = 8 Hz, 1H), 9.94 (br s, 1H); ^{13}C NMR (DMSO-d_6, 50 MHz) δ 28.5, 40.1, 78.4, 125.8 (2 carbons), 127.3, 128.2 (2 carbons), 129.7, 129.8, 130.3, 132.0, 134.4, 135.7, 139.2, 156.5, 168.0, 168.2; IR (Nujol) ν_{max} 3350, 3288, 2700-2500, 1707, 1690, 1657 cm^{-1}. Anal. Calcd for $C_{20}H_{22}N_2O_5$: C, 64.85; H, 5.99; N, 7.56. Found: C, 64.98; H, 5.87; N, 7.60.

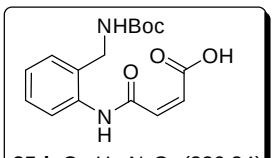
5-(2-((*tert*-Butoxycarbonylamino)methyl)phenylamino)-5-oxopentanoic acid (25c): Mp 113–115 °C;



25c: $C_{17}H_{24}N_2O_5$ (336.38)

^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.43 (s, 9H), 2.08 (quintet, *J* = 8 Hz, 2H), 2.50 (t, *J* = 8 Hz, 2H), 2.56 (t, *J* = 8 Hz, 2H), 4.25 (d, *J* = 6 Hz, 2H), 5.16 (br s, 1H), 7.05 (t, *J* = 8 Hz, 1H), 7.15 (d, *J* = 6 Hz, 1H), 7.30 (dt, *J* = 8 & 2 Hz, 1H), 8.16 (d, *J* = 8 Hz, 1H), 9.56 (br s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 20.6, 28.3, 33.2, 36.0, 41.6, 80.7, 122.8, 124.3, 128.8 (two carbons), 130.2, 136.5, 157.3, 171.8, 178.0; IR (Neat) ν_{max} 3329, 2974, 2700-2500, 1713, 1682, 1659 cm^{-1}. Anal. Calcd for $C_{17}H_{24}N_2O_5$: C, 60.70; H, 7.19; N, 8.33. Found: C, 60.51; H, 7.04; N, 8.29.

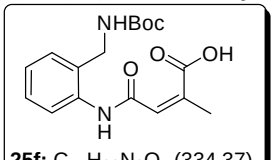
(*Z*)-4-(2-((*tert*-Butoxycarbonylamino)methyl)phenylamino)-4-oxobut-2-enoic acid (25d): Mp 140–



25d: $C_{16}H_{20}N_2O_5$ (320.34)

142 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.45 (s, 9H), 4.28 (d, *J* = 8 Hz, 2H), 5.45 (br t, *J* = 8 Hz, 1H), 6.48 (d, *J* = 14 Hz, 1H), 6.72 (d, *J* = 12 Hz, 1H), 7.15–7.29 (m, 2H), 7.34–7.44 (m, 1H), 8.18 (d, *J* = 8 Hz, 1H), 11.19 (bs, 1H); ^{13}C NMR (DMSO-d_6, 50 MHz) δ 28.5, 40.1, 78.6, 125.0, 125.9, 127.5, 128.4, 130.3, 132.9, 133.8, 134.8, 156.5, 164.2, 167.0; IR (Nujol) ν_{max} 3487, 3057, 2700-2500, 1707, 1636 cm^{-1}. Anal. Calcd for $C_{16}H_{20}N_2O_5$: C, 59.99; H, 6.29; N, 8.74. Found: C, 60.08; H, 6.13; N, 8.65.

(*Z*)-4-(2-((*tert*-Butoxycarbonylamino)methyl)phenylamino)-2-methyl-4-oxobut-2-enoic acid (25f):

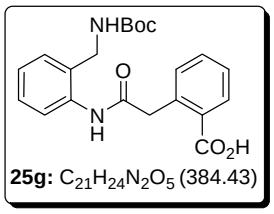


25f: $C_{17}H_{22}N_2O_5$ (334.37)

Mp 111–113 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.46 (s, 9H), 2.24 (s, 3H), 4.29 (d, *J* = 8 Hz, 2H), 5.37 (br t, *J* = 6 Hz, 1H), 6.76 (s, 1H), 7.02–7.26 (m, 2H), 7.32–7.44 (m, 1H), 8.17 (d, *J* = 8 Hz, 1H), 10.86 (br s, 1H); ^{13}C NMR ($CDCl_3$,

50 MHz) δ 24.1, 28.3, 41.5, 81.3, 123.3, 126.2, 127.9, 129.0, 129.9, 130.8, 135.0, 146.4, 158.0, 165.2, 165.9; IR ($CHCl_3$) ν_{max} 3389, 1720, 1715, 1697, 1645 cm^{-1}. Anal. Calcd for $C_{17}H_{22}N_2O_5$: C, 61.07; H, 6.63; N, 8.38. Found: C, 60.92; H, 6.54; N, 8.27.

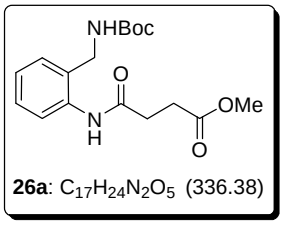
2-(2-(2-((*tert*-Butoxycarbonylamino)methyl)phenylamino)-2-oxoethyl)benzoic acid (25g): Mp 148–150 °C; ^{1}H NMR (DMSO-d_6, 200 MHz) δ 1.39 (s, 9H), 4.10 (s, 2H), 4.12 (d, J = 8 Hz, 2H), 7.05–7.28 (m, 2H), 7.30–7.60 (m, 5H), 7.89 (dd, J = 8 & 2 Hz, 1H), 9.61 (br s, 1H); ^{13}C NMR (DMSO-d_6, 50 MHz) δ 28.5, 40.1, 41.9, 78.5, 124.7, 125.0, 127.2, 127.3, 128.3, 130.7, 131.2, 132.1, 132.7, 133.1, 136.0, 137.3, 156.6, 168.9, 169.7; IR (Nujol) ν_{max} 3346, 3300, 1700, 1693, 1670 cm^{-1}. Anal. Calcd for $C_{21}H_{24}N_2O_5$: C, 65.61; H, 6.29; N, 7.29. Found: C, 65.55; H, 6.40; N, 7.16.



25g: $C_{21}H_{24}N_2O_5$ (384.43)

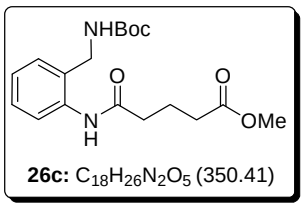
General procedure for the preparation of anilic esters (26a, 26c, 26d, 26f, 26g). An ether solution of diazomethane was added dropwise to a suspension of acid (2.00 mmol) in diethyl ether (15 mL) at 0 °C until the acid dissolved with persistence of light yellow color. The reaction mixture was stirred further 30 min at 0 °C. The solvent was removed under reduced pressure and silica gel column chromatographic purification of the resulting residue using ethyl acetate-petroleum ether as an eluent afforded the corresponding pure ester product. The reaction of **25b** with diazomethane directly furnished the corresponding imide **28b** in 97% yield.

Methyl 4-(2-((*tert*-butoxycarbonylamino)methyl)phenylamino)-4-oxobutanoate (26a): Thick oil; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.44 (s, 9H), 2.65–3.85 (m, 4H), 3.69 (s, 3H), 4.25 (d, J = 8 Hz, 2H), 5.17 (br t, J = 6 Hz, 1H), 7.02 (dt, J = 8 & 2 Hz, 1H), 7.13 (dd, J = 8 & 2 Hz, 1H), 7.28 (dt, J = 8 & 2 Hz, 1H), 8.16 (d, J = 8 Hz, 1H), 9.51 (br s, 1H); ^{13}C NMR [$CDCl_3$: CCl_4 (4:1), 50 MHz] δ 28.3, 29.1, 31.5, 41.5, 51.6, 80.3, 122.7, 124.1, 128.6, 128.8, 130.2, 136.6, 157.2, 170.4, 173.1; IR ($CHCl_3$) ν_{max} 3447, 3327, 1738, 1688, 1682 cm^{-1}. Anal. Calcd for $C_{17}H_{24}N_2O_5$: C, 60.70; H, 7.19; N, 8.33. Found: C, 60.57; H, 7.03; N, 8.24.



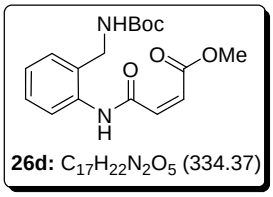
26a: $C_{17}H_{24}N_2O_5$ (336.38)

Methyl 5-(2-((*tert*-butoxycarbonylamino)methyl)phenylamino)-5-oxopentanoate (26c): Mp 73–75 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.44 (s, 9H), 2.08 (quintet, J = 8 Hz, 2H), 2.46 (t, J = 8 Hz, 2H), 2.52 (t, J = 8 Hz, 2H), 3.67 (s, 3H), 4.24 (d, J = 8 Hz, 2H), 5.25 (br s, 1H), 7.04 (t, J = 8 Hz, 1H), 7.14 (d, J = 8 Hz, 1H), 7.29 (t, J = 8 Hz, 1H), 8.17 (d, J = 8 Hz, 1H), 9.50 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.8, 28.3, 33.3, 36.2, 41.6, 51.5, 80.6, 122.5, 124.0, 128.5, 128.8, 130.3, 136.7, 157.2, 171.4, 173.6; IR ($CHCl_3$) ν_{max} 3323, 3277, 1734, 1686, 1676 cm^{-1}. Anal. Calcd for $C_{18}H_{26}N_2O_5$: C, 61.70; H, 7.48; N, 7.99. Found: C, 61.77; H, 7.39; N, 8.04.



26c: $C_{18}H_{26}N_2O_5$ (350.41)

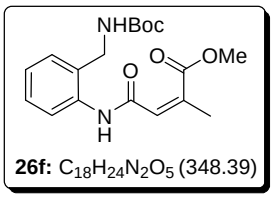
(*Z*)-Methyl 4-(2-((*tert*-butoxycarbonylamino)methyl)phenylamino)-4-oxobut-2-enoate (26d): Mp



26d: $C_{17}H_{22}N_2O_5$ (334.37)

93–95 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.42 (s, 9H), 3.82 (s, 3H), 4.28 (d, *J* = 6 Hz, 2H), 5.18 (br t, *J* = 6 Hz, 1H), 6.25 (d, *J* = 12 Hz, 1H), 6.54 (d, *J* = 12 Hz, 1H), 7.09 (dt, *J* = 8 & 2 Hz, 1H), 7.21 (dd, *J* = 8 & 2 Hz, 1H), 7.32 (dt, *J* = 8 & 2 Hz, 1H), 8.17 (d, *J* = 8 Hz, 1H), 10.05 (br s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 28.3, 41.5, 52.2, 80.5, 123.1, 124.8, 127.8, 128.8, 129.4, 130.2, 133.9, 136.0, 157.1, 162.9, 166.9; IR (Nujol) ν_{max} 3342, 3234, 1732, 1690, 1641 cm^{-1}. Anal. Calcd for $C_{17}H_{22}N_2O_5$: C, 61.07; H, 6.63; N, 8.38. Found: C, 61.23; H, 6.54; N, 8.41.

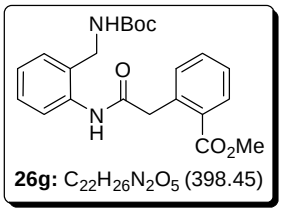
(*Z*)-Methyl 4-(2-((*tert*-butoxycarbonylamino)methyl)phenylamino)-2-methyl-4-oxobut-2-enoate



26f: $C_{18}H_{24}N_2O_5$ (348.39)

(26f): Mp 105–107 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.45 (s, 9H), 2.10 (s, 3H), 3.86 (s, 3H), 4.27 (d, *J* = 8 Hz, 2H), 5.13 (br t, *J* = 6 Hz, 1H), 6.18 (q, *J* = 2 Hz, 1H), 7.04 (t, *J* = 8 Hz, 1H), 7.14 (dd, *J* = 8 & 2 Hz, 1H), 7.30 (dt, *J* = 8 & 2 Hz, 1H), 8.28 (d, *J* = 8 Hz, 1H), 9.61 (br s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 20.5, 28.3, 41.6, 52.3, 80.7, 122.5, 124.2 (two carbons), 128.5, 128.9, 130.2, 136.5, 142.6, 157.3, 162.9, 170.5; IR (Nujol) ν_{max} 3369, 3346, 1736, 1678, 1663 cm^{-1}. Anal. Calcd for $C_{18}H_{24}N_2O_5$: C, 62.05; H, 6.94; N, 8.04. Found: C, 62.10; H, 7.00; N, 8.21.

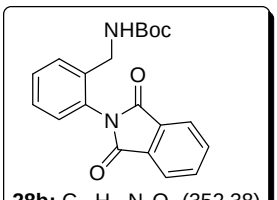
Methyl 2-(2-(2-((*tert*-butoxycarbonylamino)methyl)phenylamino)-2-oxoethyl)benzoate (26g): Mp



26g: $C_{22}H_{26}N_2O_5$ (398.45)

117–119 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.43 (s, 9H), 3.92, (s, 3H), 4.12 (s, 2H), 4.21 (d, *J* = 6 Hz, 2H), 5.15 (br t, *J* = 6 Hz, 1H), 7.06 (dt, *J* = 8 & 2 Hz, 1H), 7.23 (d, *J* = 8 Hz, 2H), 7.27–7.41 (m, 1H), 7.43–7.57 (m, 2H), 7.89–8.03 (m, 2H), 9.26 (br s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 28.3, 41.4, 42.9, 52.3, 79.9, 123.2, 124.5, 127.2, 128.4, 129.5, 129.6, 130.1, 130.9, 132.2, 132.6, 136.3, 136.8, 156.6, 168.3, 169.8; IR (Nujol) ν_{max} 3341, 3246, 1719, 1674, 1605 cm^{-1}. Anal. Calcd for $C_{22}H_{26}N_2O_5$: C, 66.32; H, 6.58; N, 7.03. Found: C, 66.29; H, 6.56; N, 6.88.

***tert*-Butyl 2-(1,3-dioxoisoindolin-2-yl)benzylcarbamate (28b):** Mp 98–100 °C; ^{1}H NMR ($CDCl_3$, 200



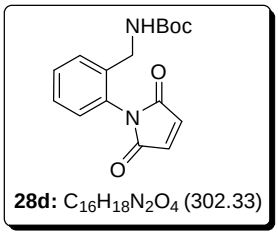
28b: $C_{20}H_{20}N_2O_4$ (352.38)

MHz) δ 1.34 (s, 9H), 4.23 (d, *J* = 4 Hz, 2H), 4.95 (br s, 1H), 7.18–7.26 (m, 1H), 7.37–7.48 (m, 2H), 7.49–7.58 (m, 1H), 7.74–7.85 (m, 2H), 7.90–8.01 (m, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 28.2, 40.9, 79.3, 123.8, 128.6, 129.1, 129.8, 130.0, 130.3, 131.9, 134.3, 137.3, 155.6, 167.6; IR (Nujol) ν_{max} 3327, 1744, 1713, 1684 cm^{-1}. Anal. Calcd for $C_{20}H_{20}N_2O_4$: C, 68.17; H, 5.72; N, 7.95. Found: C, 67.99; H, 5.64; N, 8.05.

General procedure for the preparation of imides (28d, 28f, 28g). To a stirred solution of ester (1.00 mmol) in dry DCM (10 mL) was added triethylamine (1.00 mmol) at room temperature and the

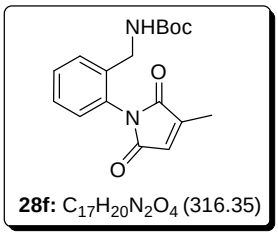
reaction mixture was stirred for 5 h. Then the solvent was removed under reduced pressure and silica gel column chromatographic purification of the resulting residue using ethyl acetate-petroleum ether as an eluent afforded the corresponding pure imide product. The reaction of *tert*-butyl 2-aminobenzylcarbamate (**23**) with dimethylmaleic anhydride (**24e**) in ethanol under reflux for 1 hour time provided the corresponding imide **28e** in 95% yield.

***tert*-Butyl 2-(2,5-dioxo-2*H*-pyrrol-1(5*H*)-yl)benzylcarbamate (28d):** Mp 104–106 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.41 (s, 9H), 4.18 (d, *J* = 6 Hz, 2H), 4.85 (br s, 1H), 6.86 (s, 2H), 7.08–7.18 (m, 1H), 7.34–7.52 (m, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 28.3, 41.0, 79.5, 128.7, 129.1, 129.6, 129.7, 130.2, 134.4, 137.4, 155.5, 169.8; IR ($CHCl_3$) ν_{max} 3445, 1776, 1715 cm^{-1}. Anal. Calcd for $C_{16}H_{18}N_2O_4$: C, 63.57; H, 6.00; N, 9.27. Found: C, 63.42; H, 6.11; N, 9.39.



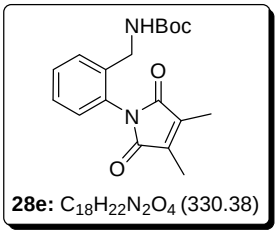
28d: $C_{16}H_{18}N_2O_4$ (302.33)

***tert*-Butyl 2-(3-methyl-2,5-dioxo-2*H*-pyrrol-1(5*H*)-yl)benzylcarbamate (28f):** Thick oil; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.42 (s, 9H), 2.19 (d, *J* = 2 Hz, 3H), 4.19 (d, *J* = 6 Hz, 2H), 4.91 (br t, *J* = 6 Hz, 1H), 6.50 (q, *J* = 2 Hz, 1H), 7.08–7.17 (m, 1H), 7.33–7.53 (m, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 11.2, 28.3, 40.9, 79.4, 127.6, 128.6, 129.0, 129.6, 129.9, 130.2, 137.3, 146.2, 155.6, 170.0, 170.9; IR (Nujol) ν_{max} 3389, 3368, 1715 cm^{-1}. Anal. Calcd for $C_{17}H_{20}N_2O_4$: C, 64.54; H, 6.37; N, 8.85. Found: C, 64.55; H, 6.49; N, 8.72.



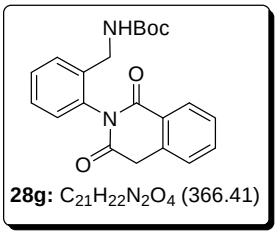
28f: $C_{17}H_{20}N_2O_4$ (316.35)

***tert*-Butyl 2-(3,4-dimethyl-2,5-dioxo-2*H*-pyrrol-1(5*H*)-yl)benzylcarbamate (28e):** Thick oil; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.42 (s, 9H), 2.06 (s, 6H), 4.16 (d, *J* = 6 Hz, 2H), 4.93 (br t, *J* = 4 Hz, 1H), 7.05–7.15 (m, 1H), 7.31-7.54 (m, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 8.9, 28.3, 40.9, 79.3, 128.5, 128.9 (two carbons), 129.4, 130.2, 137.3, 137.8, 155.7, 171.3; IR ($CHCl_3$) ν_{max} 3443, 1765, 1713 cm^{-1}. Anal. Calcd for $C_{18}H_{22}N_2O_4$: C, 65.44; H, 6.71; N, 8.48. Found: C, 65.55; H, 6.82; N, 8.53.



28e: $C_{18}H_{22}N_2O_4$ (330.38)

***tert*-Butyl 2-(1,3-dioxo-3,4-dihydroisoquinolin-2(1*H*)-yl)benzylcarbamate (28g):** Mp 290–292 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.26 (s, 9H), 3.99–4.45 (m, 4H), 4.78 (br t, *J* = 4 Hz, 1H), 7.08–7.18 (m, 1H), 7.35 (d, *J* = 8 Hz, 1H), 7.39–7.52 (m, 4H), 7.64 (dt, *J* = 8 & 2 Hz, 1H), 8.23 (dd, *J* = 8 & 2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 28.1, 36.9, 41.4, 79.2, 125.2, 127.3, 127.6, 128.9, 129.3, 129.4 (2 carbons), 130.4, 134.0, 134.2, 134.7, 136.2, 155.5, 165.2, 170.2; IR (Nujol) ν_{max} 3368, 1701, 1663, 1609 cm^{-1}. Anal. Calcd for $C_{21}H_{22}N_2O_4$: C, 68.84; H, 6.05; N, 7.65. Found: C, 68.68; H, 6.17; N, 7.53.

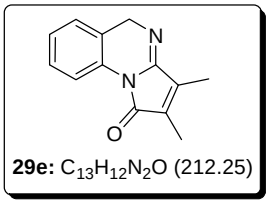


28g: $C_{21}H_{22}N_2O_4$ (366.41)

General procedure for the preparation of quinazolin-1-one (29e, 29f/f', 1a-d, 1g, 27c). To a srirred solution of imide/ester (2.00 mmol) in dry DCM (15 mL) was added trifluoroacetic acid (10 mmol)

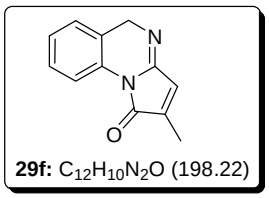
and the reaction mixture was stirred at room temperature for 5 h. The reaction mixture was basified slowly with saturated solution of $NaHCO_3$ (10 mL) and extracted with DCM (25 mL x 3). The combined organic layer was washed with brine (20 mL) and dried over Na_2SO_4. The concentration of organic layer in vacuo followed by silica gel column chromatographic purification of the resulting residue using ethyl acetate-petroleum ether as an eluent afforded the corresponding pure quinazolinone product. The compound **27c** on refluxing in methanol for 5 h time furnished the desired ring closed product **1c** in 87% yield.

2,3-Dimethylpyrrolo[1,2-*a*]quinazolin-1(5*H*)-one (29e): Mp 117–119 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.01 (s, 3H), 2.09 (s, 3H), 4.98 (s, 2H), 7.09 (d, *J* = 4 Hz, 2H), 7.26 (dt, *J* = 8 & 2 Hz, 1H), 8.37 (d, *J* = 8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 8.7, 9.0, 50.3, 115.1, 119.7, 124.4, 125.6, 127.9, 132.5, 135.4, 137.9, 152.7, 168.7; IR (Nujol) ν_{max} 1726, 1715, 1682, 1665 cm^{-1}. Anal. Calcd for $C_{13}H_{12}N_2O$: C, 73.57; H, 5.70; N, 13.20. Found: C, 73.77; H, 5.82; N, 13.07.



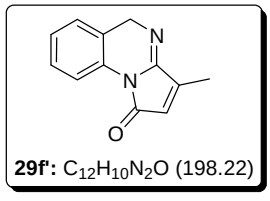
29e: $C_{13}H_{12}N_2O$ (212.25)

2-Methylpyrrolo[1,2-*a*]quinazolin-1(5*H*)-one (29f): Mp 93–96 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.12 (d, *J* = 2 Hz, 3H), 5.00 (s, 2H), 6.69 (br s, 1H), 7.04–7.18 (m, 2H), 7.27 (dt, *J* = 6 & 2 Hz, 1H), 8.39 (d, *J* = 8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 11.1, 50.5, 115.3, 120.1, 124.8, 125.6, 127.9, 128.7, 132.3, 142.4, 151.5, 168.5; IR ($CHCl_3$) ν_{max} 1720, 1678, 1640 cm^{-1}. Anal. Calcd for $C_{12}H_{10}N_2O$: C, 72.71; H, 5.09; N, 14.13. Found: C, 72.48; H, 5.01; N, 14.22.



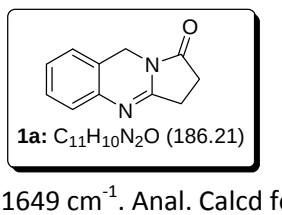
29f: $C_{12}H_{10}N_2O$ (198.22)

3-Methylpyrrolo[1,2-*a*]quinazolin-1(5*H*)-one (29f'): Mp 155–158 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.21 (d, *J* = 2 Hz, 3H), 5.04 (s, 2H), 6.33 (q, *J* = 2 Hz, 1H), 7.06–7.19 (m, 2H), 7.20–7.33 (m, 1H), 8.37 (d, *J* = 8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 11.2, 50.6, 115.3, 119.4, 124.8, 125.6, 126.9, 128.0, 132.6, 145.9, 153.2, 167.7; IR ($CHCl_3$) ν_{max} 1722, 1676, 1630 cm^{-1}. Anal. Calcd for $C_{12}H_{10}N_2O$: C, 72.71; H, 5.09; N, 14.13. Found: C, 72.79; H, 5.03; N, 14.02.



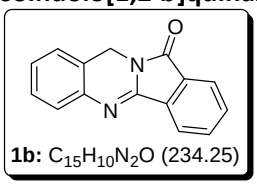
29f': $C_{12}H_{10}N_2O$ (198.22)

2,3-Dihydropyrrolo[2,1-*b*]quinazolin-1(9*H*)-one (1a): Mp 185–187 °C (lit.[10] 189-191 °C); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.55–2.80 (m, 2H), 2.85–3.00 (m, 2H), 4.80 (s, 2H), 6.95–7.30 (m, 4H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 26.1, 27.4, 41.5, 119.2, 126.0, 126.4 (2 carbons), 128.8, 140.1, 157.0, 175.8; IR ($CHCl_3$) ν_{max} 1736, 1665, 1655, 1649 cm^{-1}. Anal. Calcd for $C_{11}H_{10}N_2O$: C, 70.95; H, 5.41; N, 15.04. Found: C, 71.11; H, 5.44; N, 15.15.



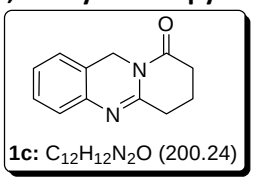
1a: $C_{11}H_{10}N_2O$ (186.21)

Isoindolo[1,2-*b*]quinazolin-12(10*H*)-one (1b): Mp 175–177 °C (lit.[8] 175-177 °C); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 5.00 (s, 2H), 7.13–7.40 (m, 3H), 7.50 (dd, *J* = 8 & 2 Hz, 1H), 7.61–7.77 (m, 2H), 7.85–7.96 (m, 1H), 8.01–8.12 (m, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 40.6, 121.3, 122.2, 123.2, 126.9, 127.7, 128.1, 128.8, 130.4, 132.1, 132.9, 134.4, 140.3, 148.9, 166.9; IR (Nujol) ν_{max} 1726, 1651, 1597 cm^{-1}. Anal. Calcd for $C_{15}H_{10}N_2O$: C, 76.91; H, 4.30; N, 11.96. Found: C, 77.08; H, 4.41; N, 12.13.



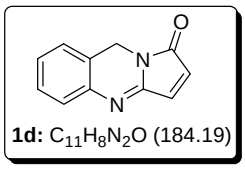
1b: $C_{15}H_{10}N_2O$ (234.25)

7,8-Dihydro-6*H*-pyrido[2,1-*b*]quinazolin-9(11*H*)-one (1c): Mp 101–103 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.99 (quintet, *J* = 6 Hz, 2H), 2.72 (t, *J* = 6 Hz, 2H), 2.83 (t, *J* = 6 Hz, 2H), 4.90 (s, 2H), 7.00–7.30 (m, 4H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 17.7, 31.7, 33.1, 42.2, 122.1, 125.0, 125.7, 126.7, 128.5, 138.7, 152.4, 170.2; IR ($CHCl_3$) ν_{max} 1692, 1682, 1620, 1601 cm^{-1}. Anal. Calcd for $C_{12}H_{12}N_2O$: C, 71.98; H, 6.04; N, 13.99. Found: C, 72.06; H, 6.00; N, 14.05.



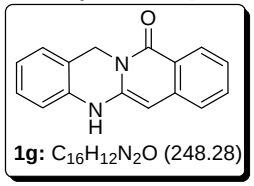
1c: $C_{12}H_{12}N_2O$ (200.24)

Pyrrolo[2,1-*b*]quinazolin-1(9*H*)-one (1d): Mp 128–130 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 4.85 (s, 2H), 6.61 (d, *J* = 6 Hz, 1H), 7.05–7.47 (m, 4H), 7.48 (dd, *J* = 8 & 2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 40.4, 121.9, 127.0, 128.5, 128.8, 128.9, 129.8, 136.3, 140.3, 152.4, 169.5; IR ($CHCl_3$) ν_{max} 1720, 1647, 1641 cm^{-1}. Anal. Calcd for $C_{11}H_8N_2O$: C, 71.73; H, 4.38; N, 15.21. Found: C, 71.82; H, 4.44; N, 15.13.



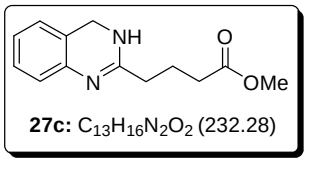
1d: $C_{11}H_8N_2O$ (184.19)

5*H*-Isoquinolino[3,2-*b*]quinazolin-11(13*H*)-one (1g): Mp 290–292 °C (lit.[12a] 308–310 °C); ^{1}H NMR (DMSO-d_6, 200 MHz) δ 5.07 (s, 2H), 5.86 (s, 1H), 6.88 (d, *J* = 8 Hz, 1H), 6.90 (t, *J* = 8 Hz, 1H), 7.12 (t, *J* = 8 Hz, 1H), 7.20 (t, *J* = 8 Hz, 1H), 7.27 (d, *J* = 8 Hz, 1H), 7.37 (d, *J* = 8 Hz, 1H), 7.50 (dt, *J* = 8 & 2 Hz, 1H), 8.03 (d, *J* = 8 Hz, 1H), 9.72 (br s, 1H); ^{13}C NMR (DMSO-d_6, 50 MHz) δ 42.1, 83.3, 113.3, 117.1, 120.0, 121.0, 122.5, 124.3, 126.9, 127.5, 128.8, 132.8, 136.9, 139.0, 140.8, 161.5; IR (Nujol) ν_{max} 1657, 1624, 1607 cm^{-1}. Anal. Calcd for $C_{16}H_{12}N_2O$: C, 77.40; H, 4.87; N, 11.28. Found: C, 77.43; H, 4.92; N, 11.35.



1g: $C_{16}H_{12}N_2O$ (248.28)

Methyl 4-(3,4-dihydroquinazolin-2-yl)butanoate (27c): Mp 96–98 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.10 (quintet, *J* = 8 Hz, 2H), 2.44 (t, *J* = 8 Hz, 2H), 2.76 (t, *J* = 8 Hz, 2H), 3.59 (s, 3H), 4.78 (s, 2H), 6.98 (d, *J* = 8 Hz, 1H), 7.11–7.17 (m, 1H), 7.21 (d, *J* = 4 Hz, 2H), 9.88 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 22.4, 31.2, 32.7, 42.5, 51.7, 116.8, 117.5, 126.2, 127.0, 129.0, 131.6, 162.5, 172.8; IR (Nujol) ν_{max} 3194, 1735, 1641 cm^{-1}. Anal. Calcd for $C_{13}H_{16}N_2O_2$: C, 67.22; H, 6.94; N, 12.06. Found: C, 67.09; H, 6.82; N, 12.17.

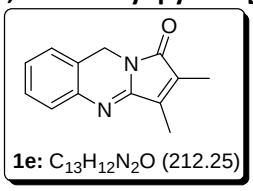


27c: $C_{13}H_{16}N_2O_2$ (232.28)

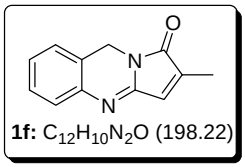
General procedure for the conversion of angular quinazolin-1-ones (29e, 29f, 29f') to linear quinazolin-1-ones (1e, 1f, 1f'). To a stirred solution of angular quinazolin-1-one (1.00 mmol) in methanol (10 mL) was added acetic acid (0.10 mL) and the resulting reaction mixture was refluxed

for 24/48 h. Then the reaction mixture was allowed to attain room temperature and the solvent was evaporated under reduced pressure. The silica gel column chromatographic purification of the resulting residue using ethyl acetate-petroleum ether as an eluent afforded the corresponding pure quinazolinone product. The transformation of **1f'** to **1f** was completed in 15 days time with 96% yield.

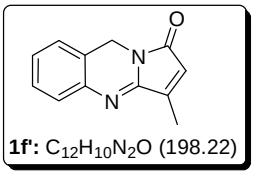
2,3-Dimethyllpyrrolo[2,1-*b*]quinazolin-1(9*H*)-one (1e): Mp 170–172 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.02 (d, *J* = 2 Hz, 3H), 2.17 (d, *J* = 2 Hz, 3H), 4.79 (s, 2H), 7.11-7.37 (m, 3H), 7.47 (dd, *J* = 8 & 2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 8.7, 9.0, 40.4, 122.1, 126.8, 127.6, 128.4, 128.6, 133.7, 139.5, 140.7, 153.1, 170.7; IR (Nujol) ν_{max} 1712, 1638, 1599, 1459 cm^{-1}. Anal. Calcd for $C_{13}H_{12}N_2O$: C, 73.57; H, 5.70; N, 13.20. Found: C, 73.44; H, 5.61; N, 13.35.


1e: $C_{13}H_{12}N_2O$ (212.25)

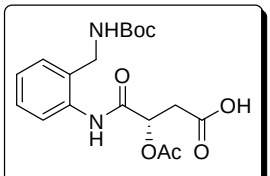
2-Methylpyrrolo[2,1-*b*]quinazolin-1(9*H*)-one (1f): Mp 150–152 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.15 (d, *J* = 2 Hz, 3H), 4.82 (s, 2H), 6.83 (q, *J* = 2 Hz, 1H), 7.10–7.50 (m, 4H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 11.1, 40.4, 121.8, 126.9, 127.9, 128.5, 128.7, 129.8, 140.5, 140.7, 151.9, 170.3; IR (Nujol) ν_{max} 1721, 1650, 1634, 1460 cm^{-1}. Anal. Calcd for $C_{12}H_{10}N_2O$: C, 72.71; H, 5.09; N, 14.13. Found: C, 72.66; H, 4.83; N, 14.02.


1f: $C_{12}H_{10}N_2O$ (198.22)

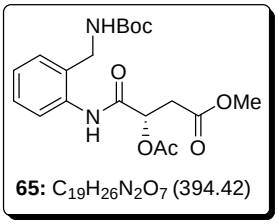
3-Methylpyrrolo[2,1-*b*]quinazolin-1(9*H*)-one (1f'): Mp 165–168 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.29 (d, *J* = 2 Hz, 3H), 4.82 (s, 2H), 6.27 (q, *J* = 2 Hz, 1H), 7.13–7.38 (m, 3H), 7.48 (dd, *J* = 8 & 2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 11.4, 40.5, 122.1, 124.7, 126.9, 128.2, 128.7, 128.8, 140.5, 147.8, 153.2, 169.7; IR (Nujol) ν_{max} 1718, 1648, 1634, 1461 cm^{-1}. Anal. Calcd for $C_{12}H_{10}N_2O$: C, 72.71; H, 5.09; N, 14.13. Found: C, 72.85; H, 5.11; N, 14.04.


1f': $C_{12}H_{10}N_2O$ (198.22)

(*S*)-3-Acetoxy-4-(2-((*tert*-butoxycarbonylamino)methyl)phenylamino)-4-oxobutanoic acid (64): Compound **64** was prepared using the general procedure for the preparation of anilic acids (**25a**-**d**, **25f**, **25g**) and silica gel column chromatographic purification of the crude product using ethyl acetate-petroleum ether as an eluent afforded the acid **64**. Thick oil; $[\alpha]^{28}_D$ = –18.2 (*c* 0.66, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.41 (s, 9H), 2.24 (s, 3H), 3.08 (d, *J* = 6 Hz, 2H), 4.00–4.15 (m, 1H), 4.15–4.33 (m, 1H), 5.23 (br s, 1H), 5.56 (bs, 1H), 5.67 (t, *J* = 6 Hz, 1H), 7.10–7.35 (m, 3H), 7.79 (d, *J* = 8 Hz, 1H), 9.93 (br s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 20.9, 28.2, 36.3, 40.7, 69.9, 80.3, 125.0, 125.9, 128.4, 130.2, 131.1, 134.7, 157.1, 168.2, 170.3, 174.1; IR ($CHCl_3$) ν_{max} 3452, 3277, 1744, 1717, 1690, 1689 cm^{-1}. Anal. Calcd for $C_{18}H_{24}N_2O_7$: C, 56.83; H, 6.36; N, 7.36. Found: C, 56.92; H, 6.47; N, 7.25.

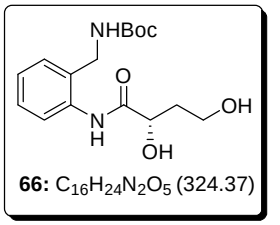

64: $C_{18}H_{24}N_2O_7$ (380.39)

(*S*)-Methyl 3-acetoxy-4-(2-((*tert*-butoxycarbonylamino)methyl)phenylamino)-4-oxobutanoate (65): Compound **65** was prepared using the general procedure for the preparation of anilic esters (**26a**, **26c**, **26d**, **26f**, **26g**) and silica gel column chromatographic purification of the crude product using ethyl acetate-petroleum ether as an eluent afforded the ester **65**. Thick oil; $[\alpha]^{28}_{D}$ = −16.0 (*c* 0.50, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.41 (s, 9H), 2.25 (s, 3H), 3.05 (d, *J* = 8 Hz, 2H), 3.72 (s, 3H), 4.12 (dd, *J* = 14 & 6 Hz, 1H), 4.26 (dd, *J* = 14 & 6 Hz, 1H), 5.22 (br t, *J* = 6 Hz, 1H), 5.69 (t, *J* = 6 Hz, 1H), 7.08–7.25 (m, 2H), 7.32 (dt, *J* = 6 & 2 Hz, 1H), 7.86 (d, *J* = 8 Hz, 1H), 9.89 (br s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 20.9, 28.2, 36.4, 40.8, 51.9, 70.2, 80.2, 124.6, 125.5, 128.4, 130.3, 130.7, 135.1, 157.0, 167.8, 170.1 (two carbons); IR ($CHCl_3$) ν_{max} 3452, 3277, 1746, 1692, 1682 cm^{-1}. Anal. Calcd for $C_{19}H_{26}N_2O_7$: C, 57.86; H, 6.65; N, 7.10. Found: C, 57.88; H, 6.69; N, 6.95.



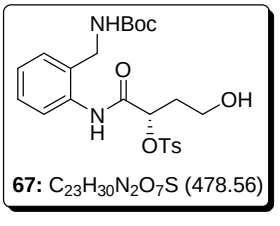
65: $C_{19}H_{26}N_2O_7$ (394.42)

(*S*)-*tert*-Butyl 2-(2,4-dihydroxybutanamido)benzylcarbamate (66): To the suspention of lithium aliminium hydride (48 mg, 1.27 mmol) in tetrahydrofuran (20 mL) at 0 °C was added anilic ester **65** (500 mg, 1.27 mmol) in tetrahydrofuran (10 mL) over apreriod of 10 min. Reaction mixture was stirred at 0 °C for 2 h. Reaction was quench using water (2 mL) and filtered through celite and washed with ethyl acetate. The combined organic layer was dried over Na_2SO_4. The concentration of organic layer in vacuo followed by silica gel column chromatographic purification of the resulting residue using ethyl acetate-petroleum ether as an eluent afforded the diol **66** (321 mg, 78%). Mp 110–112 °C; $[\alpha]^{28}_{D}$ = −27.4 (*c* 1.24, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.43 (s, 9H), 1.95–2.15 (m, 1H), 2.15–2.35 (m, 1H), 3.13 (br s, 1H), 3.94 (t, *J* = 6 Hz, 2H), 4.27 (dd, *J* = 8 & 4 Hz, 2H), 4.49 (br s, 2H), 5.12 (br t, *J* = 6 Hz, 1H), 7.14 (t, *J* = 8 Hz, 1H), 7.24 (d, *J* = 8 Hz, 1H), 7.34 (dt, *J* = 8 & 2 Hz, 1H), 7.92 (d, *J* = 8 Hz, 1H), 9.43 (br s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 28.3, 36.0, 41.4, 60.1, 71.4, 80.4, 124.1, 125.6, 128.6, 129.8, 130.3, 135.0, 156.6, 173.5; IR (Nujol) ν_{max} 3375, 3339, 3250, 1682, 1665 cm^{-1}. Anal. Calcd for $C_{16}H_{24}N_2O_5$: C, 59.25; H, 7.46; N, 8.63. Found: C, 59.13; H, 7.39; N, 8.52.



66: $C_{16}H_{24}N_2O_5$ (324.37)

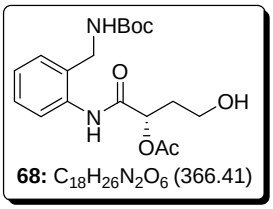
(*S*)-1-(2-((*tert*-Butoxycarbonylamino)methyl)phenylamino)-4-hydroxy-1-oxobutan-2-yl 4-methylbenzenesulfonate (67): To a stirred solution of diol **66** (200 mg, 0.62 mmol) and triethyl amine (0.1 mL, 0.72 mmol) in DCM (10 mL) at 0 °C was added slowly *p*-toluenesulfonyl chloride (117 mg, 0.62 mmol) in DCM (5 mL). Reaction mixture was stirred at room temperature for 4 h. Reaction mixture was diluted with DCM (25 mL) and washed with water, sat. solution of $NaHCO_3$, brine and dried over Na_2SO_4. The concentration of organic layer in vacuo followed by silica gel column chromatographic purification of the resulting residue using ethyl acetate-petroleum ether as an eluent afforded the alcohol **67** (260 mg, 88%). Thick oil; $[\alpha]^{28}_{D}$ = −24.2 (*c* 0.34, $CHCl_3$); ^{1}H NMR ($CDCl_3$,



67: $C_{23}H_{30}N_2O_7S$ (478.56)

200 MHz) δ 1.45 (s, 9H), 2.18 (dq, *J* = 6 & 2 Hz, 2H), 2.42 (s, 3H), 3.70–3.85 (m, 2H), 4.10 (dd, *J* = 6 & 2 Hz, 2H), 5.16 (t, *J* = 8 Hz, 1H), 5.18–5.30 (m, 1H), 7.06–7.28 (m, 3H), 7.32 (d, *J* = 8 Hz, 2H), 7.54 (d, *J* = 8 Hz, 1H), 7.89 (d, *J* = 8 Hz, 2H), 9.66 (br s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 21.6, 28.3, 35.5, 41.0, 57.7, 77.5, 80.5, 124.5, 125.9, 128.2, 128.4, 129.9, 130.2, 131.1, 132.7, 134.7, 145.4, 156.9, 167.6; IR (Nujol) ν_{max} 3368, 3315, 1688, 1668, 1531 cm^{-1}. Anal. Calcd for $C_{23}H_{30}N_2O_7S$: C, 57.72; H, 6.32; N, 5.85. Found: C, 57.43; H, 6.10; N, 5.63.

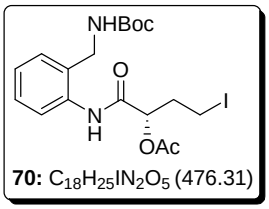
(*S*)-1-(2-((*tert*-Butoxycarbonylamino)methyl)phenylamino)-4-hydroxy-1-oxobutan-2-yl acetate



68: $C_{18}H_{26}N_2O_6$ (366.41)

(68): To a suspention of sodium borohydride (60 mg, 1.58 mmol) in tetrahydrofuran (10 mL) at 0 °C was added slowly the solution of iodine (167 mg, 0.66 mmol) in DCM (10 mL) over a period of 10 min. Acid **66** (500 mg, 1.3 mmol) in tetrahydrofuran (10 mL) was added slowly to the above reaction mixture and stirred at 0 °C for 4 h. Reaction mixture was diluted with ethyl acetate (30 mL) and organic layer was washed with water, aq. $Na_2S_2O_3$, brine and dried over Na_2SO_4. The concentration of organic layer in vacuo followed by silica gel column chromatographic purification of the resulting residue using ethyl acetate-petroleum ether as an eluent afforded the alcohol **68** (376 mg, 78%). Thick oil; $[\alpha]^{28}_D$ = −34.2 (*c* 0.50, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.42 (s, 9H), 2.10–2.35 (m, 2H), 2.25 (s, 3H), 3.70–3.95 (m, 2H), 4.20 (d, *J* = 6 Hz, 2H), 5.23 (t, *J* = 6 Hz, 1H), 5.44 (t, *J* = 8 Hz, 1H), 7.08–7.45 (m, 3H), 7.92 (d, *J* = 10 Hz, 1H), 9.88 (br s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 21.0, 28.3, 34.9, 41.1, 58.6, 71.9, 80.6, 124.5, 125.4, 128.6, 130.2, 130.3, 135.2, 157.1, 169.4, 170.5; IR ($CHCl_3$) ν_{max} 3386, 3367, 1720, 1682, 1560 cm^{-1}. Anal. Calcd for $C_{18}H_{26}N_2O_6$: C, 59.00; H, 7.15; N, 7.65. Found: C, 59.13; H, 6.88; N, 7.32.

(*S*)-1-(2-((*tert*-butoxycarbonylamino)methyl)phenylamino)-4-iodo-1-oxobutan-2-yl acetate (70): To

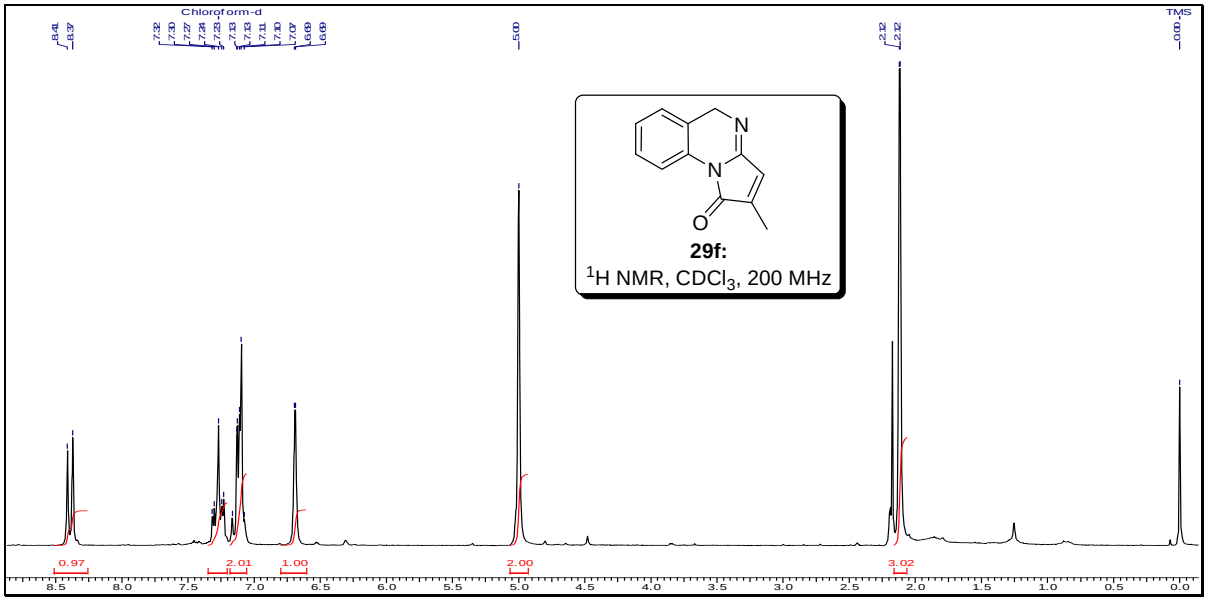


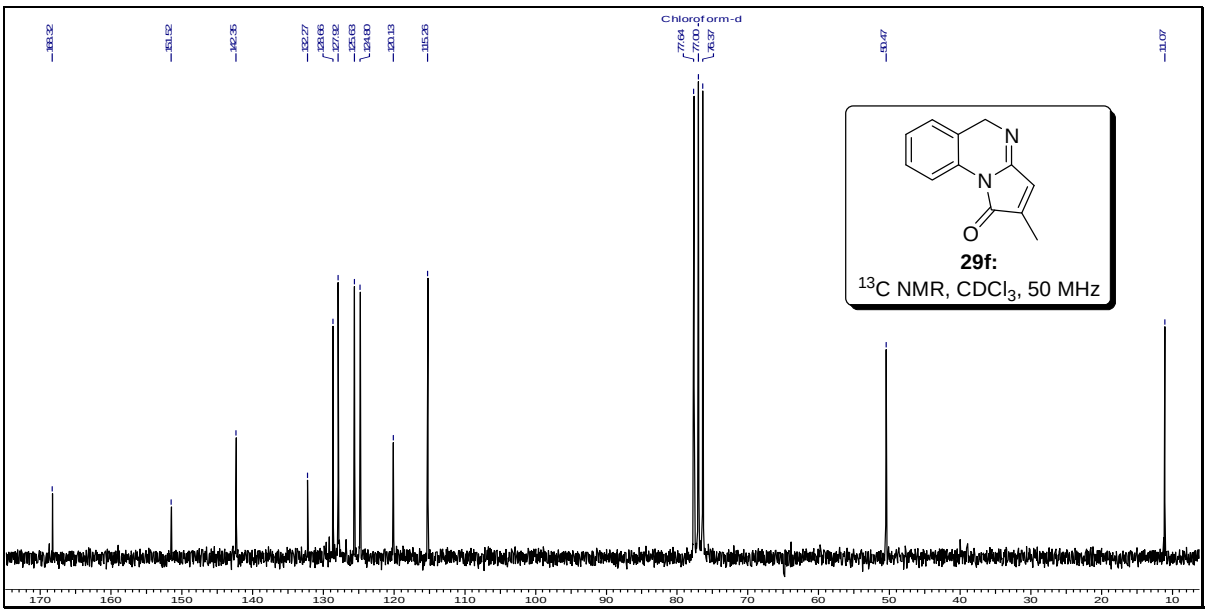
70: $C_{18}H_{25}IN_2O_5$ (476.31)

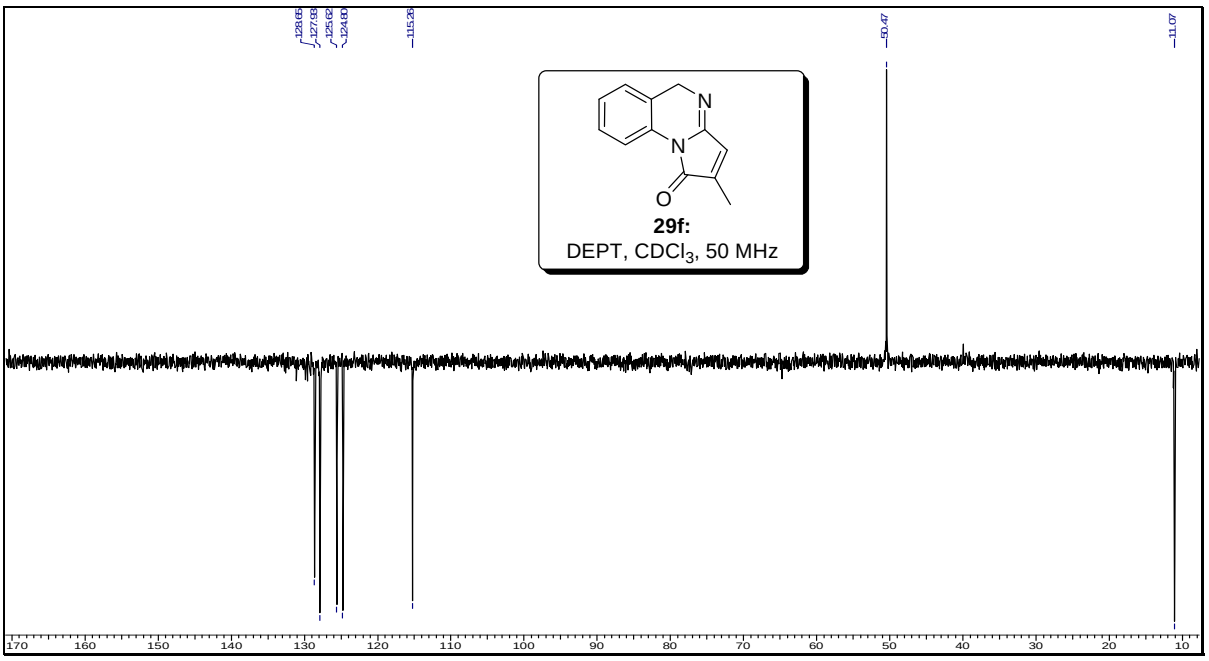
a stirred solution of alcohol **68** (300 mg, 0.82 mmol) and triethyl amine (0.14 mL, 0.98 mmol) in DCM (10 mL) at 0 °C was added slowly *p*-toluenesulfonyl chloride (156 mg, 0.82 mmol) in DCM (5 mL). Reaction mixture was stirred at room temperature for 3 h. Reaction mixture was diluted with DCM (20 mL) and washed with water, saturated solution of $NaHCO_3$, brine and dried over Na_2SO_4. The concentration of organic layer in vacuo provided the compound **69** which was used for the next reaction without any further purification. To a suspention of lithium iodide (220 mg) in tetrahydrofuran (5 mL) at room temperature was added the solution of compound **69** in tetrahydrofuran (5 mL) and resultant reaction mixture was stirred at room temperature for 5 h. Reaction mixture was diluted with ethyl acetate and organic layer was washed with water, aq. $Na_2S_2O_3$, brine and dried over Na_2SO_4. The concentration of organic layer in vacuo followed by silica gel column chromatographic purification of the resulting residue using ethyl acetate-petroleum ether as an eluent afforded the compound **70** (290 mg, 74%). Thick oil; $[\alpha]^{28}_D$ = −13.5 (*c* 0.32, $CHCl_3$);

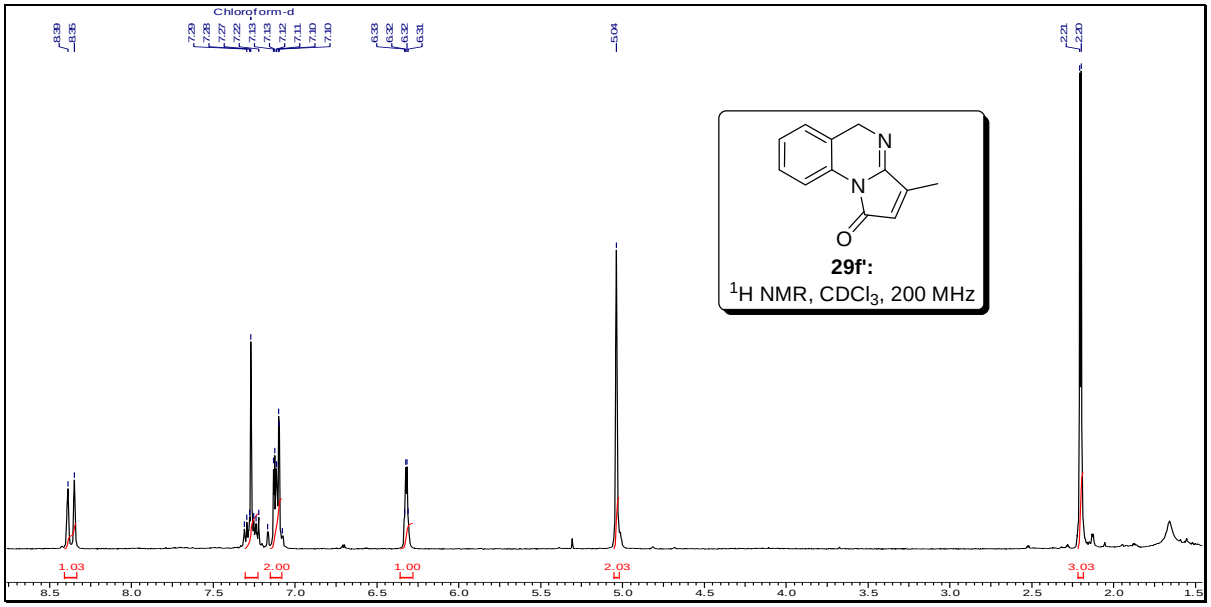
^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.42 (s, 9H), 2.24 (s, 3H), 2.43-2.65 (m, 2H), 3.29 (t, *J* = 8 Hz, 2H), 4.04–4.30 (m, 2H), 5.18 (t, *J* = 8 Hz, 1H), 5.30 (dd, *J* = 8 & 6 Hz, 1H), 7.06–7.37 (m, 3H), 7.92 (d, *J* = 8 Hz, 1H), 10.02 (br s, 1H); IR (Nujol) ν_{max} 3329, 1713, 1682, 1657, 1587 cm^{-1}. Anal. Calcd for $C_{18}H_{25}IN_2O_5$: C, 45.39; H, 5.29; N, 5.88. Found: C, 45.71; H, 5.53; N, 6.19.

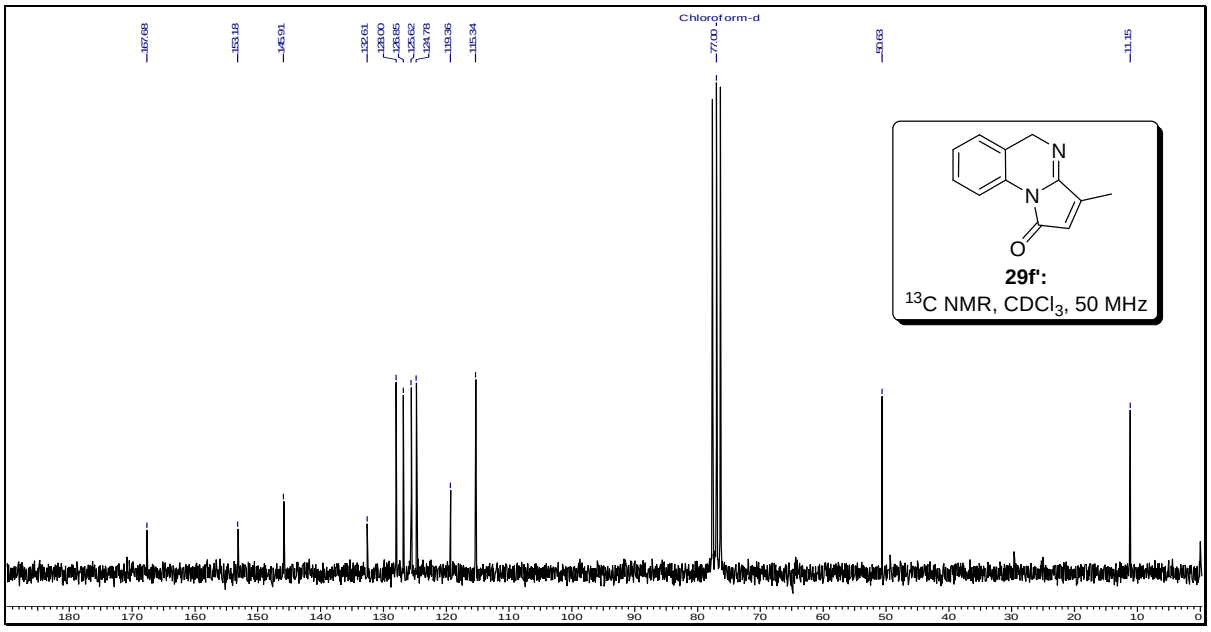
2B. 5 Selected Spectra:

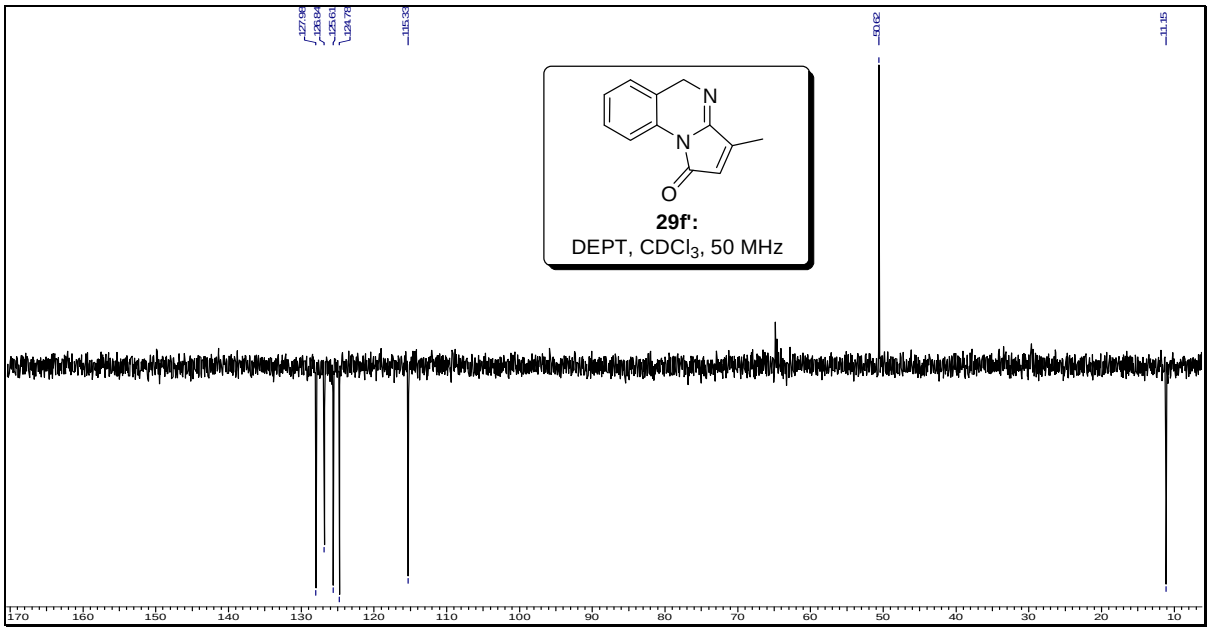

Chloroform-d
TMS
0.97
2.01
1.00
2.00
3.02
29f:
^{1}H NMR, $CDCl_3$, 200 MHz

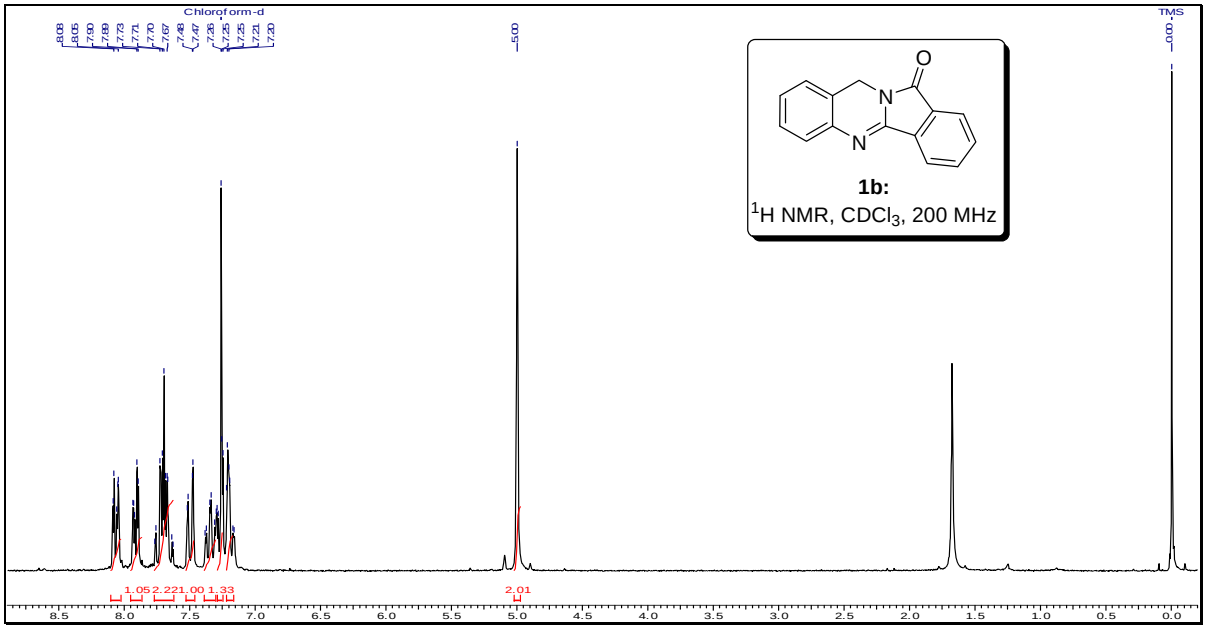

Chloroform-d
29f:
^{13}C NMR, $CDCl_3$, 50 MHz

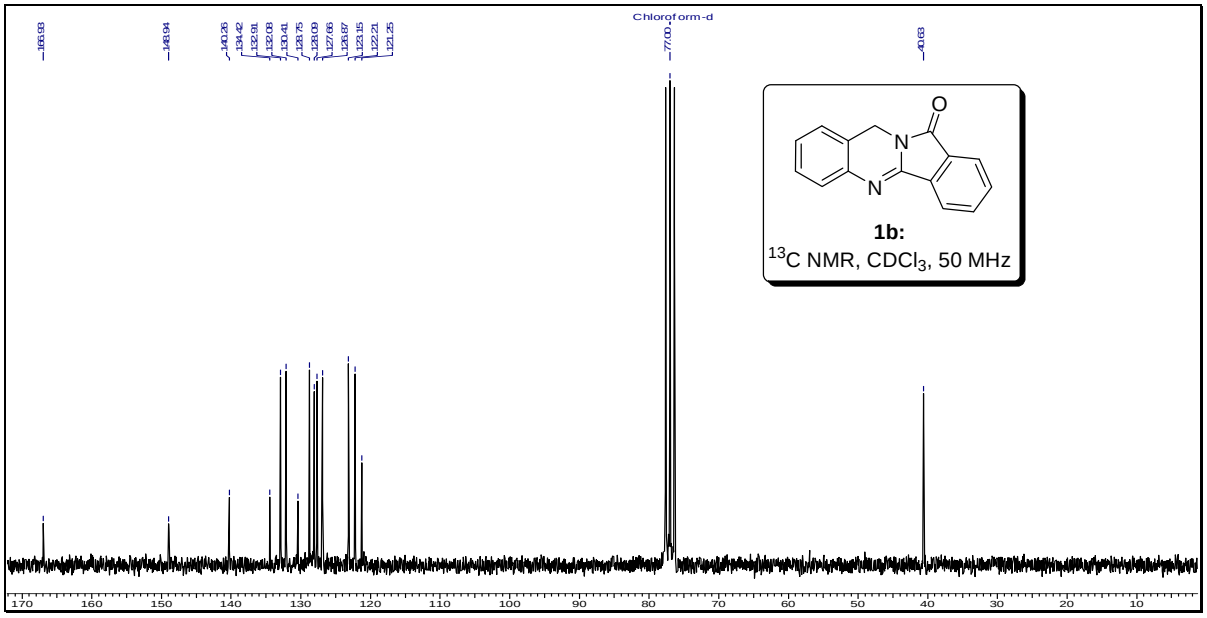

29f:
DEPT, $CDCl_3$, 50 MHz

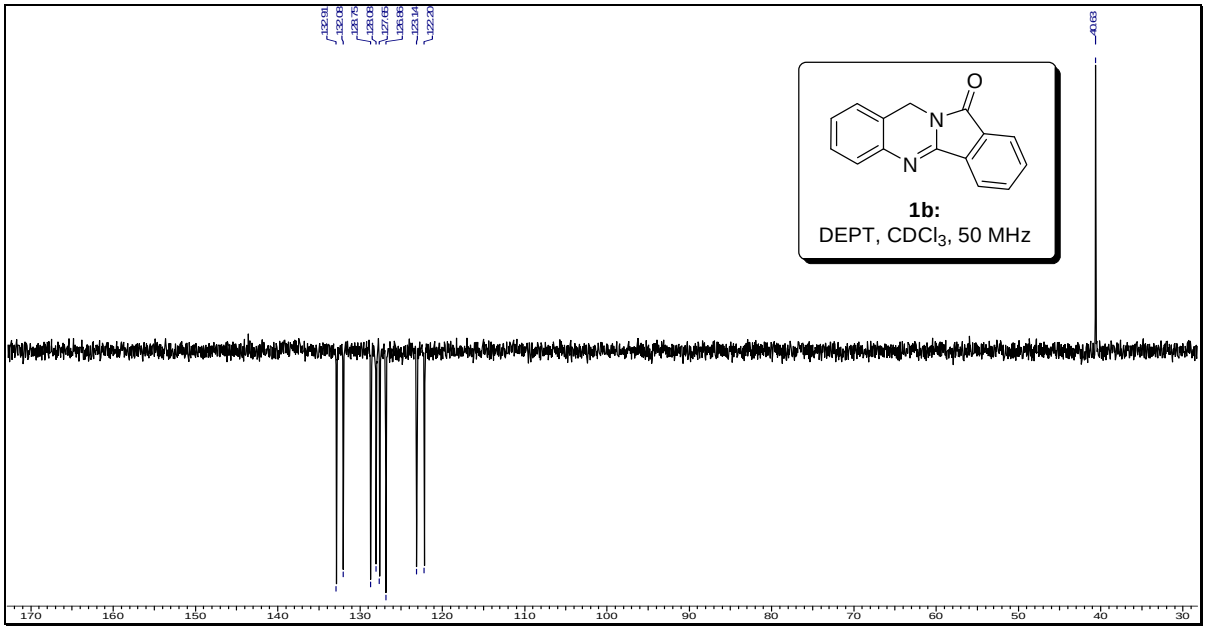

Chloroform-d
8.39
8.35
7.99
7.98
7.27
7.22
7.13
7.12
7.11
7.10
7.10
6.33
6.32
6.32
6.31
5.04
2.21
2.20
1.03
2.00
1.00
2.03
3.03
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
N
N
O
29f':
1H NMR, CDCl3, 200 MHz

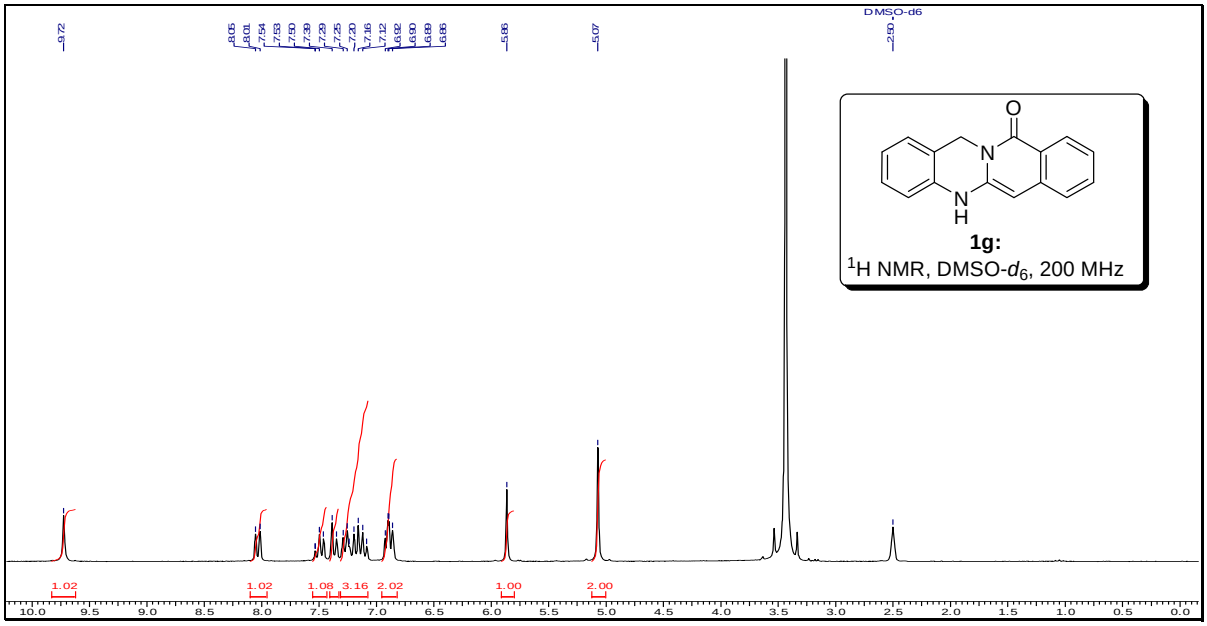

Chloroform-d
167.68
153.18
145.91
132.61
128.00
126.85
125.62
124.78
119.36
115.34
77.00
50.63
11.15
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
N
N
O
29f':
13C NMR, CDCl3, 50 MHz

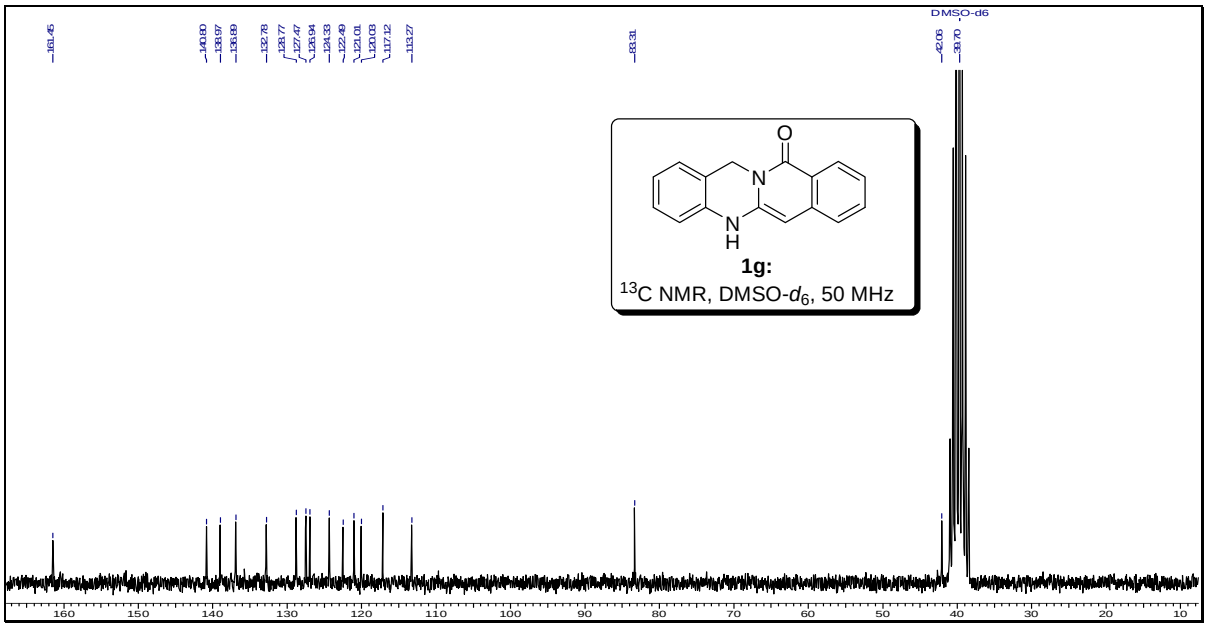

127.96
126.84
125.61
124.78
115.33
50.62
11.15
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
N
N
O
29f':
DEPT, CDCl3, 50 MHz

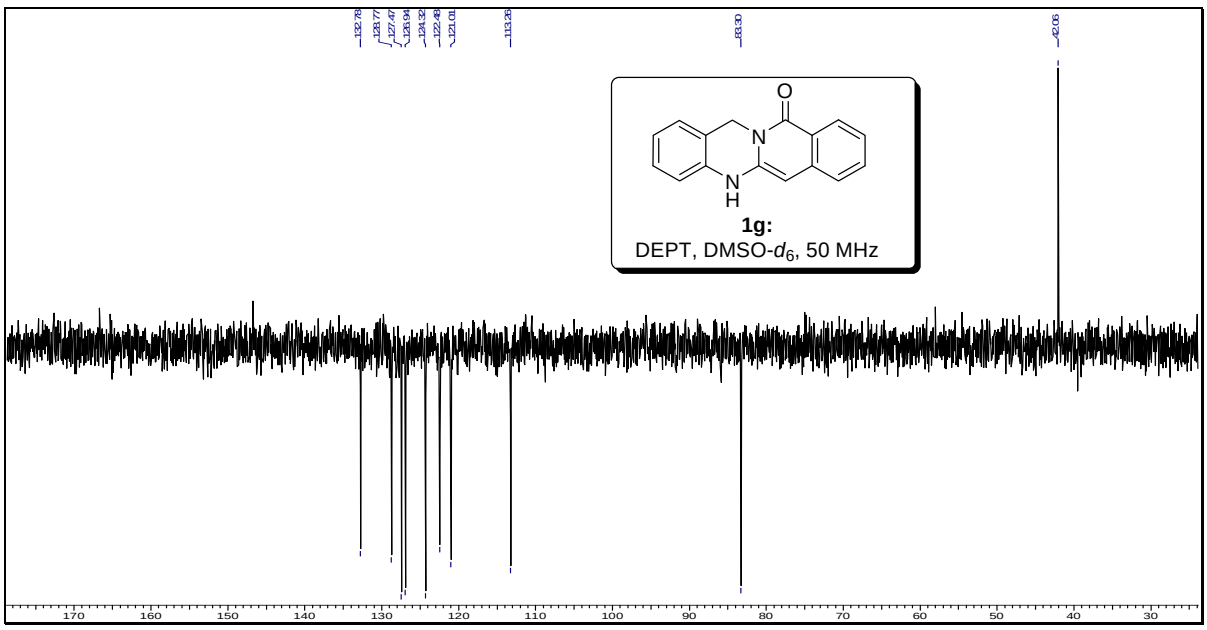

Chloroform-d
TMS
1.05 2.22 1.00 1.33
2.01
1b:
^{1}H NMR, $CDCl_3$, 200 MHz

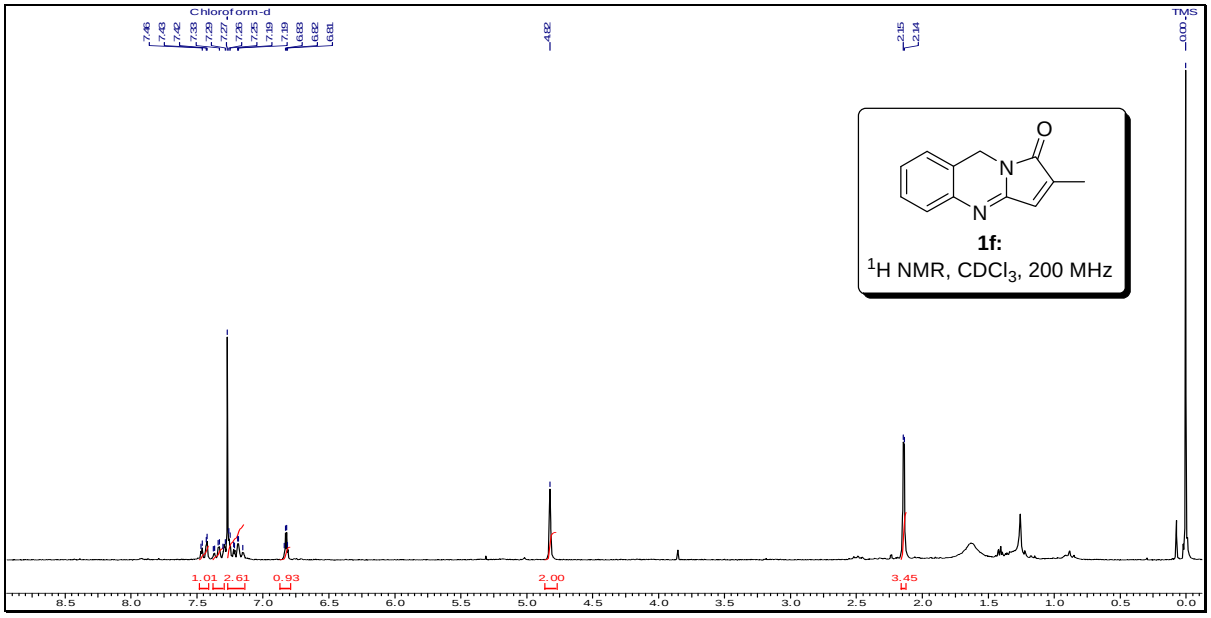

Chloroform-d
77.00
40.63
1b:
^{13}C NMR, $CDCl_3$, 50 MHz

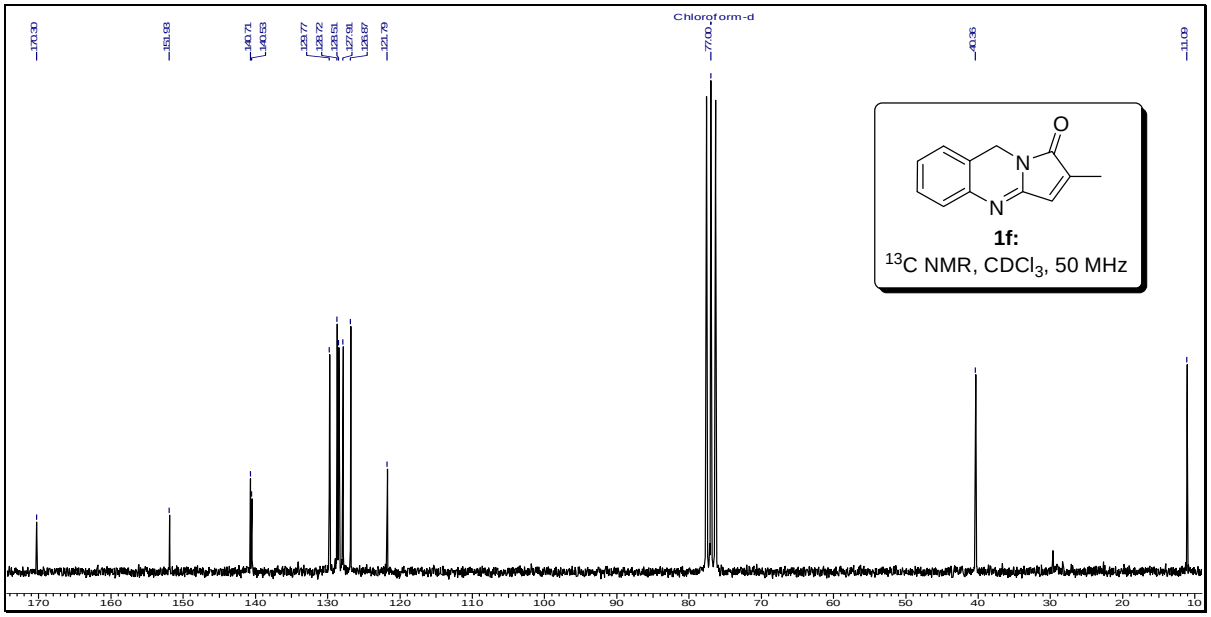

40.63
1b:
DEPT, $CDCl_3$, 50 MHz

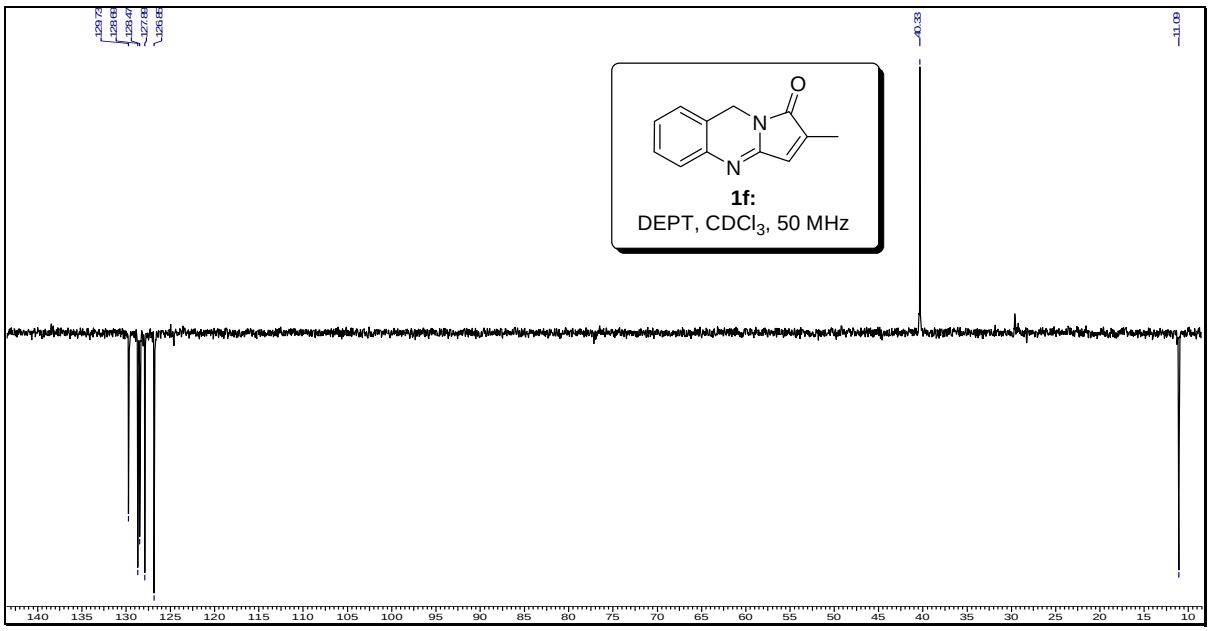

DMSO-d6
1.02
1.02
1.08
3.16
2.02
1.00
2.00
1g:
^{1}H NMR, DMSO-d_6, 200 MHz

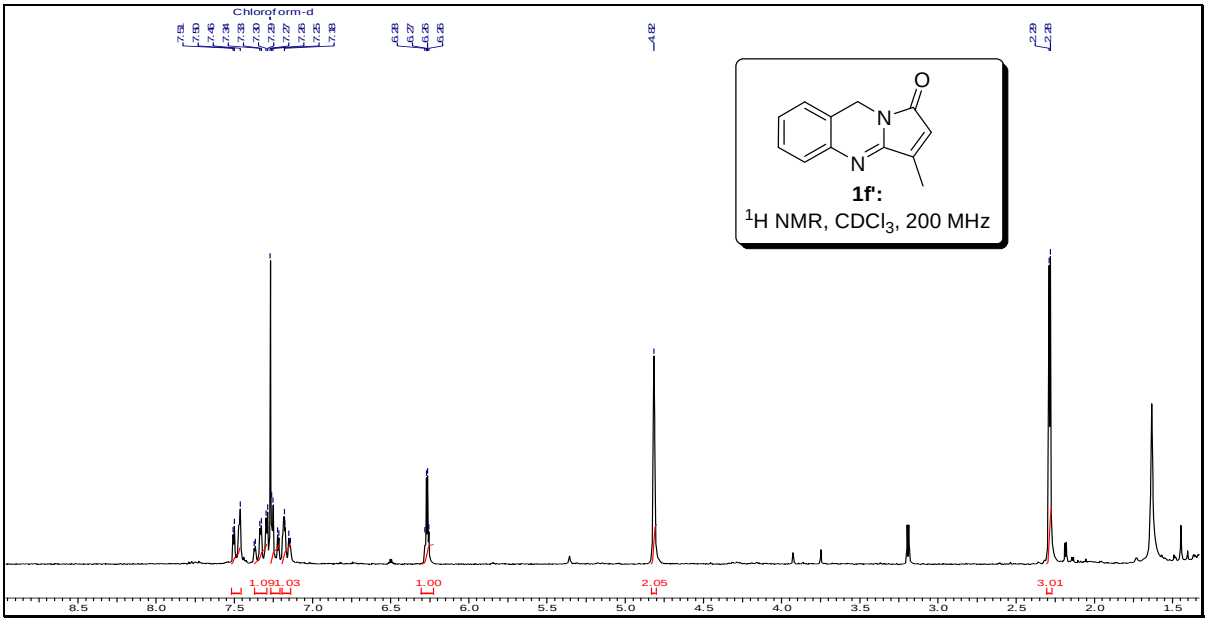

DMSO-d6
1g:
^{13}C NMR, DMSO-d_6, 50 MHz

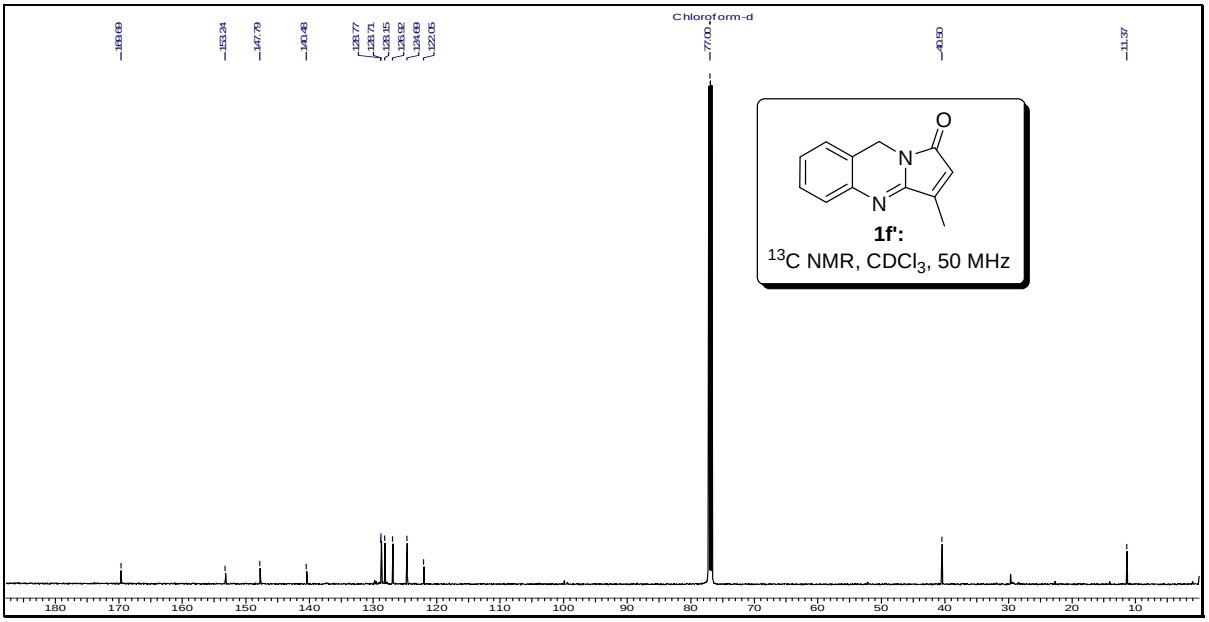

1g:
DEPT, DMSO-d_6, 50 MHz

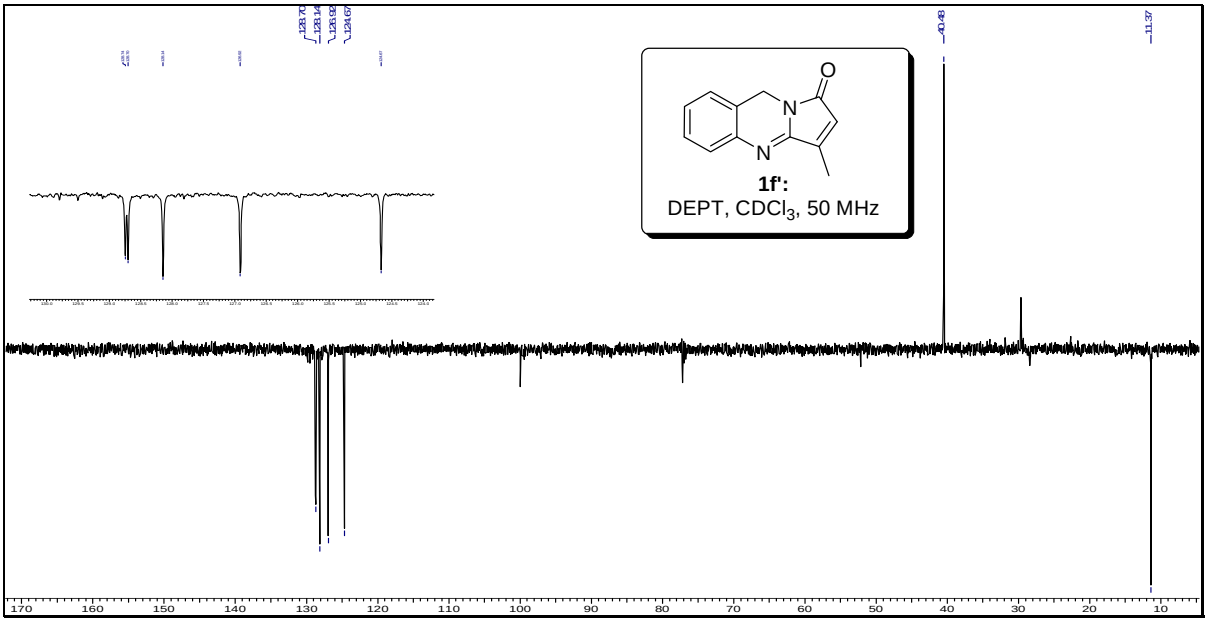

Chloroform-d
TMS
1.01 2.61 0.93
2.00
3.45
1f:
^{1}H NMR, $CDCl_3$, 200 MHz

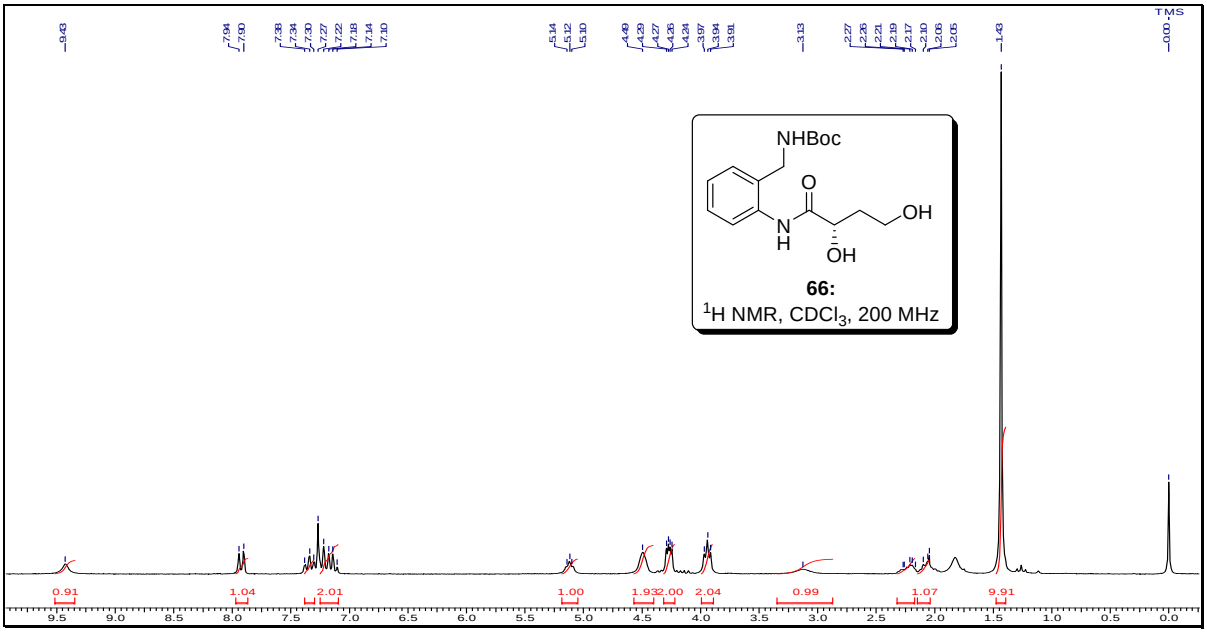

Chloroform-d
1f:
^{13}C NMR, $CDCl_3$, 50 MHz

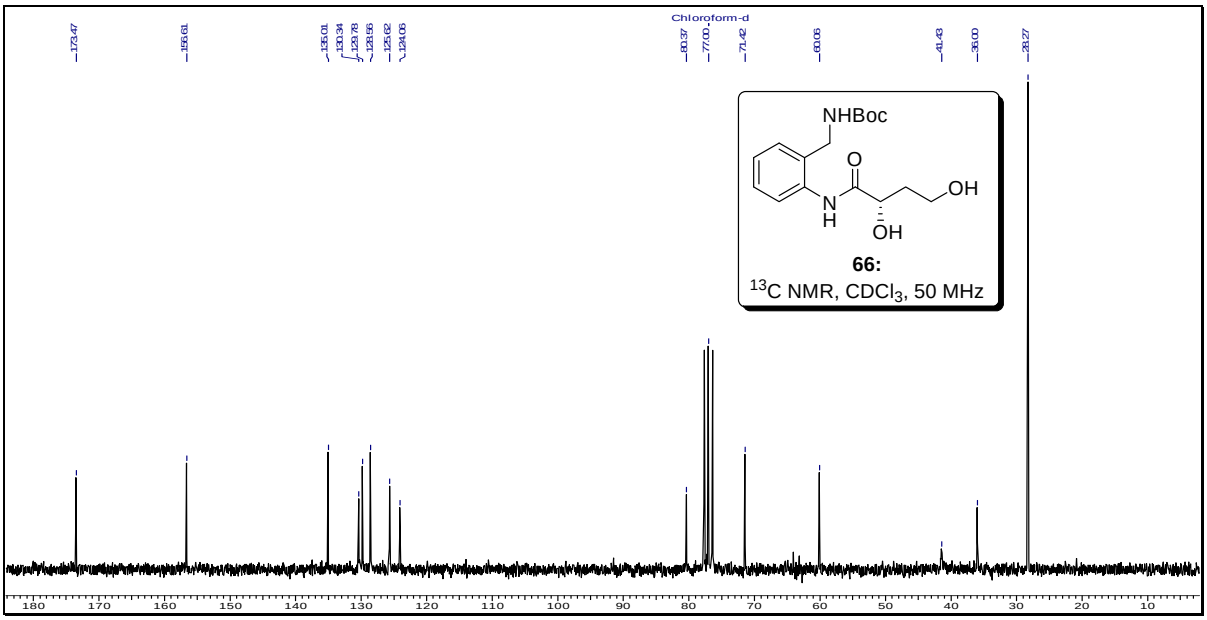

1f:
DEPT, $CDCl_3$, 50 MHz

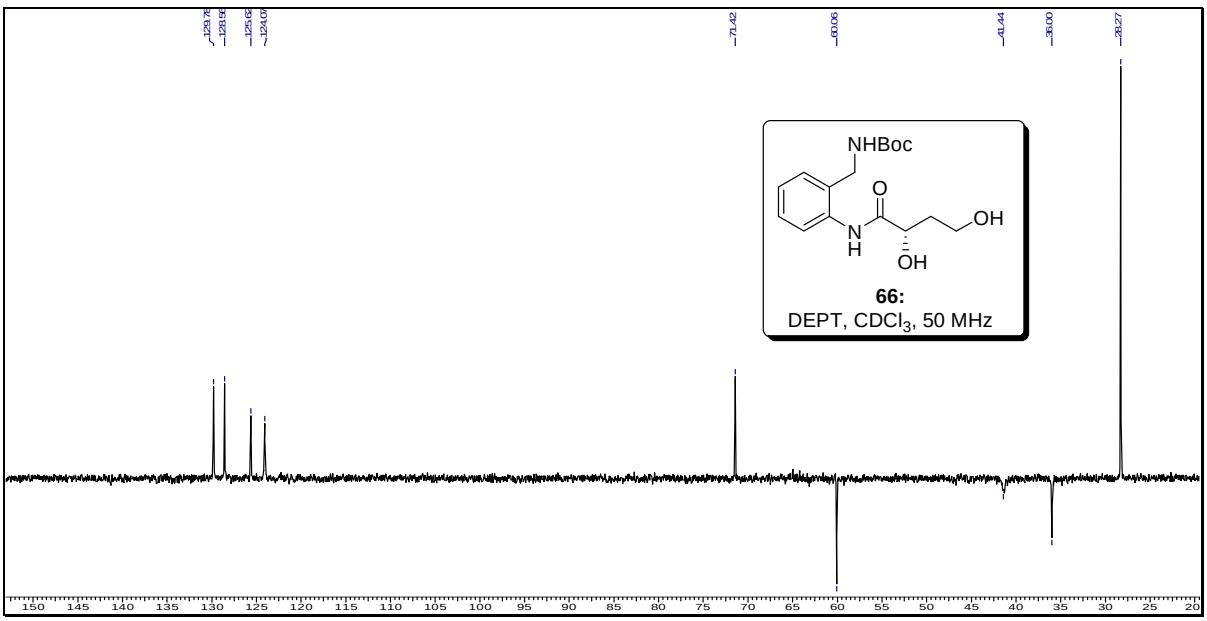

Chloroform-d
1.09 1.03
1.00
2.05
3.01
1f':
^{1}H NMR, $CDCl_3$, 200 MHz


Chloroform-d
1f':
^{13}C NMR, $CDCl_3$, 50 MHz


1f':
DEPT, $CDCl_3$, 50 MHz


NHBoc
O
N
H
OH
OH
66:
1H NMR, CDCl3, 200 MHz
TMS


NHBoc
O
N
H
OH
OH
66:
13C NMR, CDCl3, 50 MHz
Chloroform-d


NHBoc
O
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OH
OH
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Chapter 2: Section C

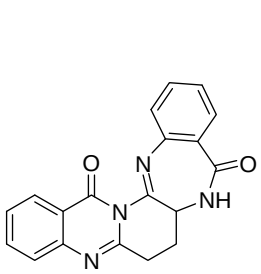
First Total Synthesis of Proposed Auranthine

This section C of chapter 2 features the following topics:

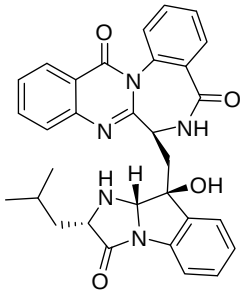
2C.1 Background

2C.1.1 Auranthine Literature

In the course of isolation and characterization of nephrotoxins, a new fungal metabolite, (–)-auranthine (**1**) was isolated from *Penicillium aurantiogriseum*[1a] and recently from *P. aurantiogriseum* VKM F-1298.[1b] This alkaloid formation was also confirmed by UV-guided screening of benzodiazepine producing species in *Penicillium*.[1c] The structure of (–)-auranthine (**1**) was deduced with spectroscopic methods as well as with biosynthetic studies.[1a] (–)-Auranthine (**1**) was an amorphous white solid, insoluble in water but soluble in organic solvents, in which it had a negative specific rotation, but the configuration at the asymmetric center is still not known.[1a]



Auranthine (**1**)



(–)-Asperlicin (**2**)

Figure 1. Quinazolinone alkaloids with diazepine core

Structurally, auranthine bears a close resemblance to the novel microbial metabolite (–)-asperlicin produced by *Aspergillus alliaceus*, a potent neuropeptide antagonist[2] (Figure 1). (–)-Auranthine is a structurally unique quinazolinone alkaloid which contains an unusually positioned diazepine moiety, a feature that largely rendered its total synthesis a challenge.[3] A look at the structure of auranthine reveals that (–)-glutamic acid and anthranilamide could be potential building blocks for constructing this structurally intriguing alkaloid. Bergman and co-workers reported their studies on the different approaches towards the synthesis of auranthine (**1**).[3a]

Bargman's retrosynthetic analysis revealed the three possible synthetic routes towards the auranthine (**1**) (Figure 2). Intramolecular dehydrative cyclization of the precursor **3** provides a straightforward route to auranthine (**1**). Other approaches involve the aza-Wittig methodology,[4–12] in which coupling of the compounds **4** and **5** with o-azidobezoic acid or chloride followed by intramolecular aza-Wittig reaction with imide carbonyl represent an alternative routes to the auranthine (**1**). In Berman's first approach the benzodiazepine **7** was prepared from the isatoic anhydride (**6**) and glutamic acid in 45% yield (Scheme 1). Cyclization to the pyrrolobenzodiazepine **8** was achieved by heating compound **7** in acetic anhydride for 5 minutes. When the pyrrolobenzodiazepine **8** was heated with anthranilamide in diphenyl ether for 48 h, the auranthine precursor **3** was isolated in 94% yield. Several attempts for the straightforward dehydrative intramolecular cyclization of precursor **3** to give auranthine (**1**) failed with standard reagents such as

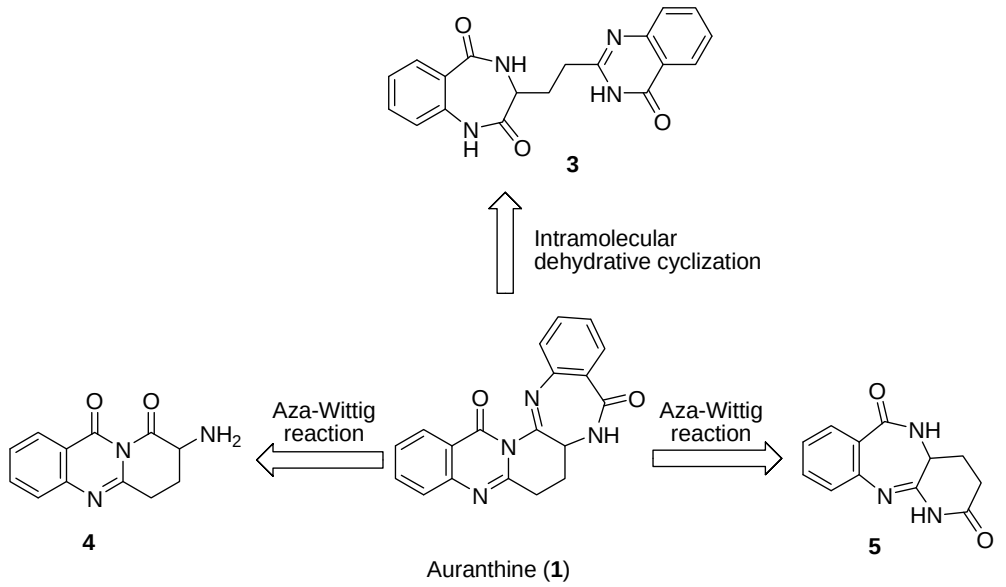
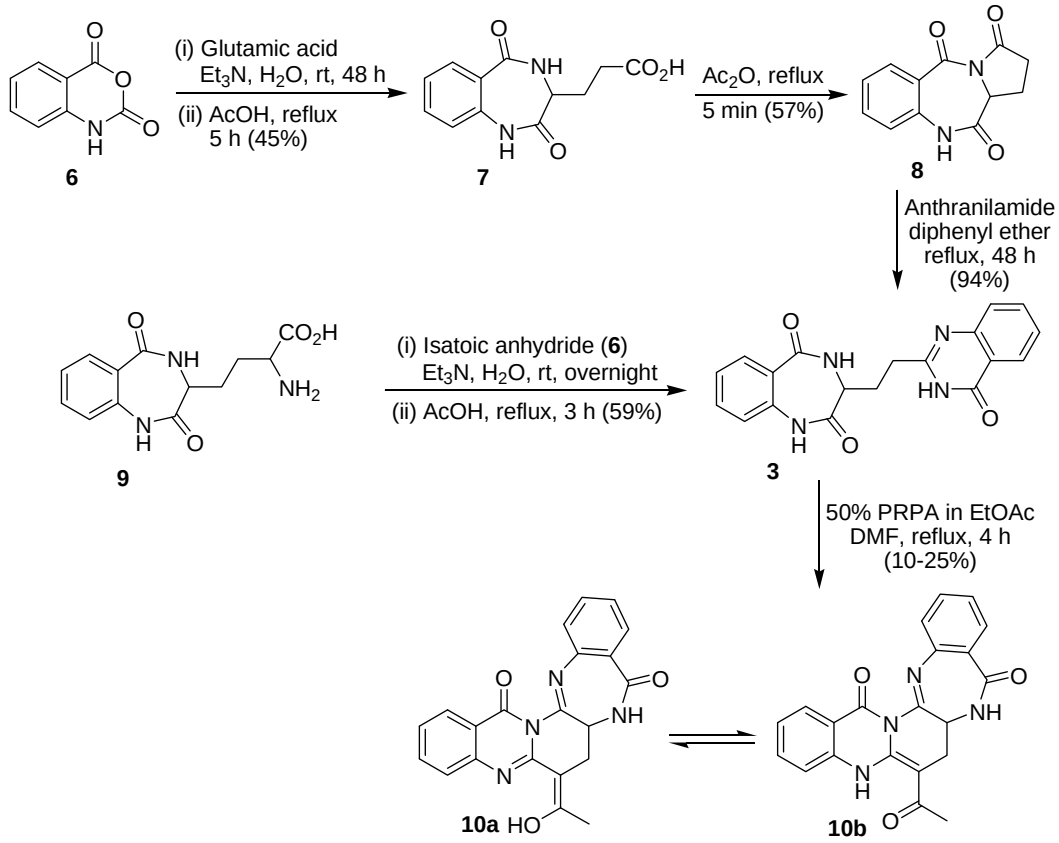


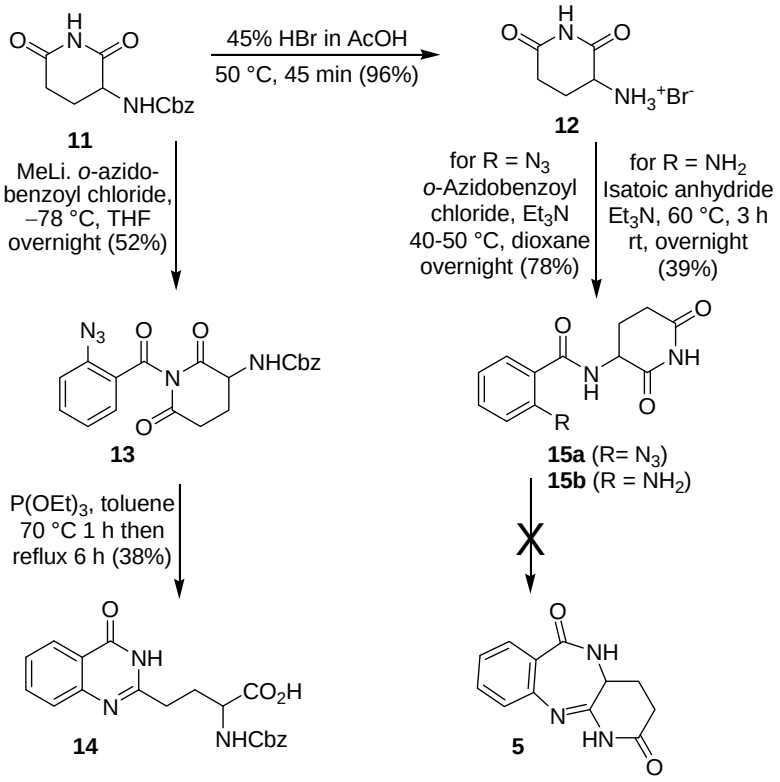
Figure 2. Bergman's retrosynthetic analysis of auranthine

dicyclohexylcarbodiimide, phosphoryl chloride and phosphorus trichloride. When a mixture of the auranthine precursor **3**, 50% propylphosphonic acid anhydride (PRPA) solution in ethyl acetate and dimethyl acetamide (DMA) was heated at reflux for 4h, it gave an equilibrium mixture of product products **10a**/**b**. Structure of which was proposed on the basis of the spectral data as **10a** or its tautomer **10b**, i.e. a C-acetyl derivative of auranthine (**1**). Using *N*,*N*-dimethylformamide, dimethyl sulfoxide or *N*-methylpyrrolidone as the solvents, no such cyclization occurred.



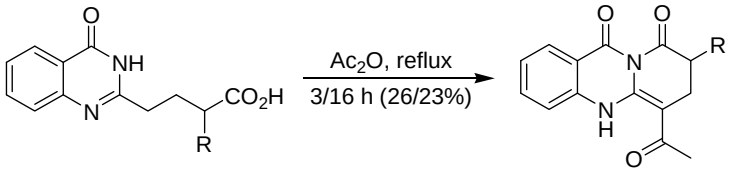
Scheme 1. Bergman's first approach to the auranthine

In their second approach (Scheme 2), treatment of Cbz-protected glutarimide **11** with *o*-azidobenzoyl chloride in the presence of methyllithium as a base provided the imide **13** in 52% yield. Attempts to cyclize imide **13** to a protected analog of compound **4** using aza-Wittig conditions such as triphenylphospine or triethylphosphite in boiling toluene or xylene resulted in the open chain compound **14**.



Scheme 2. Bergman's second and third approaches to the auranthine

In the third approach (Scheme 2), Cbz-protected glutarimide **11** was deprotected with 45% HBr in acetic acid to the hydrobromide salt **12** in 96% yield. The hydrobromide salt **12** on coupling with o-azidobenzoyl chloride in the presence triethylamine as a base afforded the azide **15a** in 78% yield. The corresponding amine **15b** was obtained from the hydrobromide salt **12** and isatoic anhydride in the presence of triethylamine as a base in 39% yield. Attempts were made to cyclize the azide **15a** using aza-Wittig conditions, or the amine **15b**, using acetic acid or various dehydrating agents such as phosphorus pentoxide to the compound **5** with no success. They have also studied the cyclization reaction of the protected acid **14a** and compound **14b** which can be considered as precursors to the



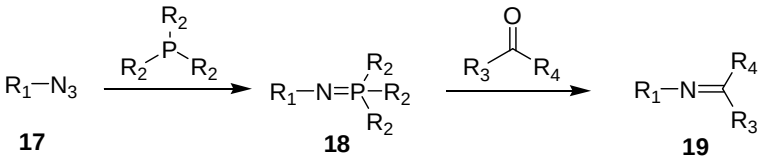
Scheme 3. Intramolecular dehydrative cyclization study

fused quinazolinone **4** (Scheme 3). When **14a** and **14b** were heated with acetic anhydride at reflux, it provided C-acetyl derivatives **16a** and **16b** in 26% and 23% yield.

All these studies on the synthesis of auranthine (**1**) by Bergman and co-workers indicate that the instability of the potential intermediate **4** and the presence of an active methylene group in the product were the major impediments in accessing it.[3a]

2C.1.2 Brief Account of Aza-Wittig Reaction

Iminophosphoranes **18** were first prepared at the beginning of the last century by Staudinger, using the reaction of azide **17** with phosphines (Scheme 4).[5] Iminophosphoranes have become a powerful tool in organic synthetic strategies directed towards the construction of nitrogen containing heterocycles.[4] Iminophosphoranes undergo reactions with carbonyl compounds in a similar way to phosphonium ylids, leading to an excellent method for the construction of carbon-nitrogen double bond containing compounds **19** through intramolecular and intermolecular process and this process is known as aza-Wittig reaction (Scheme 4). In other words, the aza-Wittig reaction is the nitrogen analog of the Wittig olefination process and involves the reaction of an iminophosphorane with a carbonyl group. This method provides one of the best procedures for the formation of carbon-nitrogen double bonds under mild and neutral reaction conditions.[4,6–12]



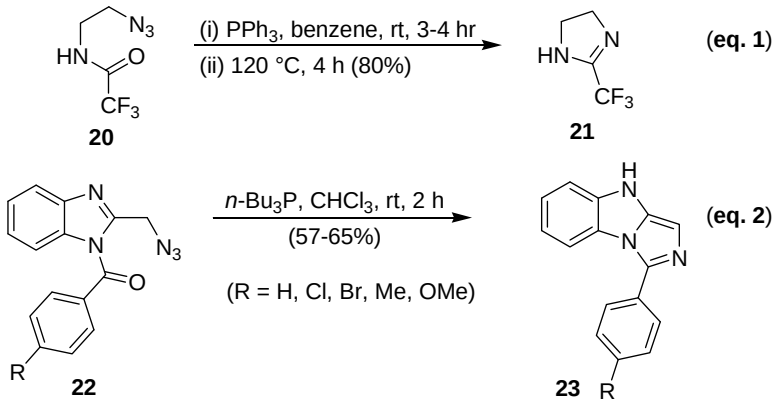
Scheme 4. Principle of aza-Wittig reaction

The intramolecular version of the aza-Wittig reaction has attracted considerable attention recently because of its high potential for the synthesis of nitrogen containing heterocycles. Aza-Wittig reactions with a variety of carbonyl compounds such as aldehydes,[6] ketones,[7] esters,[8] acyl chlorides,[9] carboxylic acid anhydrides,[10] imides[11] and amides[12] provide a valuable method for the regiospecific formation of cyclic imines. Reactivity of aza-Wittig reaction is mainly determined by the substituents at the nitrogen atom, phosphorous atom and nature of carbonyl group. General reactivity trends of substituents at the nitrogen atom, phosphorous atom and nature of carbonyl group are summarized in figure 3.[4–12]

R_1: -alkyl > -aryl > -COR_1
R_2: -alkyl > -aryl > -*O*-alkyl > -*O*-aryl
R_3COR_4: aldehyde, ketone > acid chloride > imide, ester, acid > amide or lactam

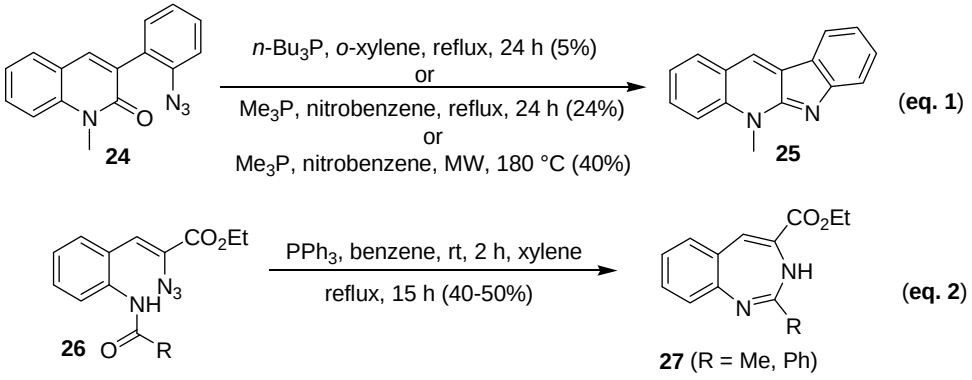
Figure 3. Reactivity trends of substituents in aza-Wittig reaction

In the intramolecular version of aza-Wittig reaction, ring size of the product formed also plays important role (five, six > seven > four member ring).[4] Aza-Wittig reactions involving amide or lactam carbonyl are very rare. First example of intramolecular aza-Wittig reaction involving amide carbonyl was reported by Gololobov in 1985 (Scheme 5, eq. 1),[12a] in which *N*-acyl-*p*-azidoamine **20** undergoes an intramolecular aza-Wittig reaction at 120 °C to give the five member ring system, imidazoline **21** in 80% yield. Molina and co-workers reported the second example in which benzoyl derivatives of 2-azidomethylbenzimidazole **22** was treated with tributylphosphine at room temperature, which lead directly to imidazo[1,5-*a*]benzimidazoles **23** in 57-65% yields (Scheme 5, eq. 2).[12b]



Scheme 5. Intramolecular aza-Wittig reaction involving amide carbonyl

Molina and co-workers accomplished the total synthesis of cryptotackiene (**25**) using the intramolecular aza-Wittig reaction with lactam carbonyl group to assemble five member ring systems (Scheme 6, eq. 1).[12c] Treatment of 1-methyl-(*o*-azidophenyl)quinoline-2-one (**24**) with *n*-tributylphosphine in *o*-xylene at room temperature followed by heating at reflux temperature for 24 h gave the cryptotackiene (**25**) in only 5% yield; whereas the use of trimethylphosphine afforded the **25** in 24% yield. Further improvement up to 40% yield was achieved by microwave irradiation with trimethylphosphine in nitrobenzene as a solvent at 180 °C. To the best of our knowledge only one example of aza-Wittig reaction with an amide carbonyl group is reported to design the seven-member diazepine nucleus **27** (Scheme 6, eq. 2),[12d] wherein in the starting material **26** the lone pair on an amide nitrogen atom is in cross conjugation with an *ortho*-substituted ester unit.



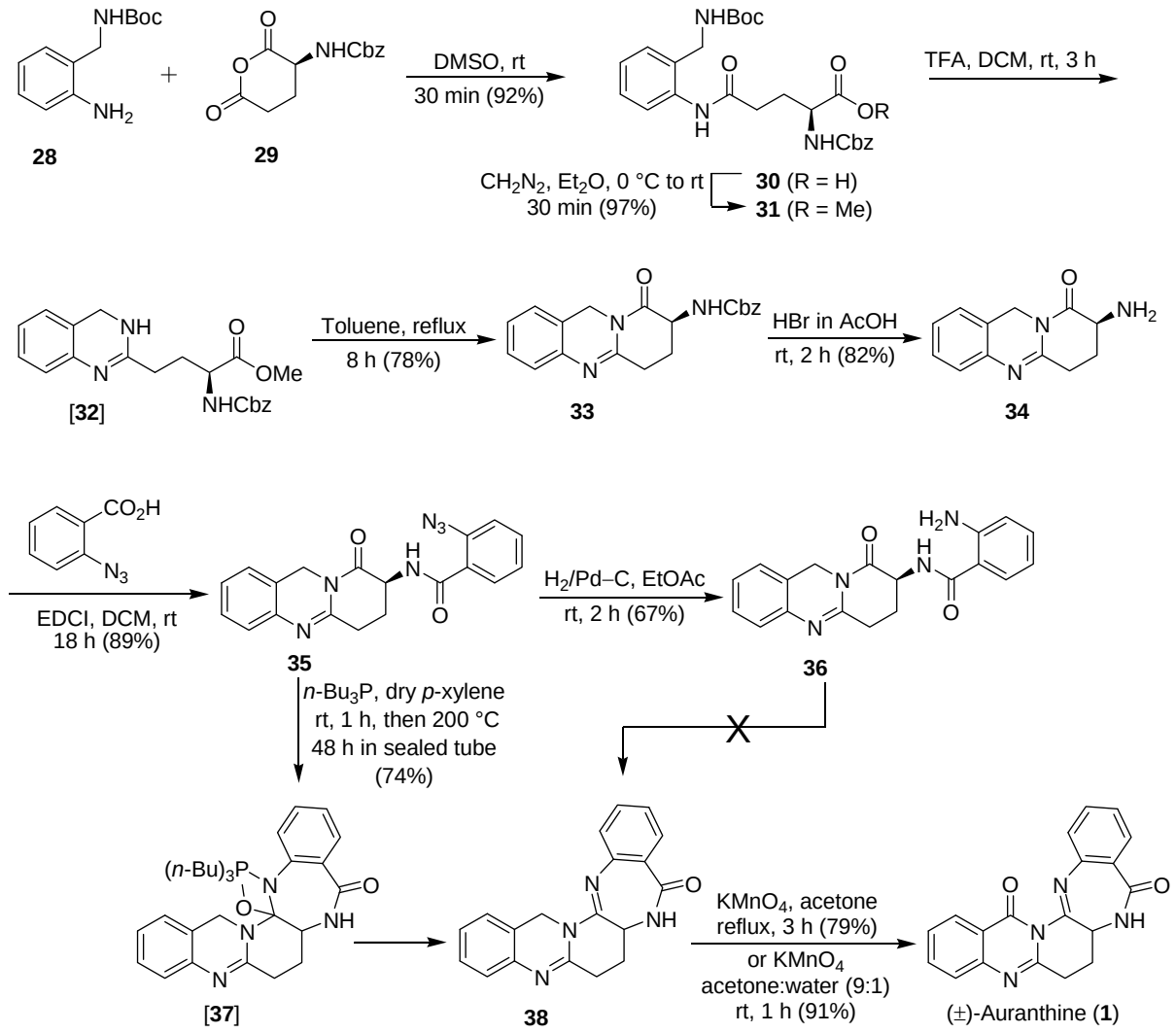
Scheme 6. Intramolecular aza-Wittig reaction involving amide/lactam carbonyl

On the basis of our continuing interest in the application of cyclic anhydrides in natural product synthesis[13] and our studies on synthesis of batracylin alnalogs,[14] we planned to synthesize the enantiomerically pure auranthine (**1**) using late-stage chemoselective oxidation strategy and intramolecular aza-Wittig reaction with the lactam carbonyl group for the construction of unusually positioned benzodiazepine core unit as a key reaction. We selected *tert*-butyl 2-aminobenzylcarbamate[15a] and Cbz-protected (*S*)-glutamic anhydride[15b] as potential starting materials. Postulation behind the late-stage chemoselective oxidation strategy was to reduce the reactivity of an active methylene group for better stability of the intermediates up to the penultimate stage. Quinazolinone carbonyl group can be introduced in the final step of synthesis by simple benzylic oxidation.

2C.2 Results and Discussion

Starting the synthesis of auranthine (**1**) from Cbz-protected (*S*)-glutamic anhydride (**29**), we could foresee that our major challenges would lie in the following: (i) regioselective nucleophilic ring opening of the unsymmetrical anhydride **29** with an aromatic amine **28**, (ii) intramolecular cyclization reaction involving the lactam carbonyl using an aromatic amine/azide in **35**/**36** that would deliver the diazepine ring system and (iii) the smooth pool of enantiomeric purity throughout the synthesis.

As per the literature reports,[16] the nucleophilic regioselective ring opening of an anhydride **29** in DMSO with the *tert*-butyl 2-aminobenzylcarbamate (**28**), exclusively furnished the expected anilic acid **30** in 92% yield (Scheme 7). Carrying out the reaction in a polar solvent such as DMSO brings about intermolecular hydrogen bonding of the hydrogen atom on amide nitrogen with the solvent, rather than the five member intramolecular hydrogen bonding with an adjacent carbonyl group of anhydride **29**. The incoming nucleophile, the primary aromatic amine, thus exclusively attacks on an unhindered carbonyl group of anhydride **29** to form the product **30**. Diazomethane esterification of anilic acid **30** provided the methyl ester **31** in 97% yield. Cleaving the Boc-protection in **31** resulted in instantaneous intramolcular dehydrative cyclization to **32**, which upon an immediate refluxing in toluene effected another intramolecular cyclization to afford the lactam **33** in 78% yield.[15a] The compound **33** on treatment with hydrobromic acid gave the desired amine **34**. The EDCI driven dehydrative coupling between the amine **34** and *o*-azidobenzoic acid provided the azido compound **35** in 89% yield. At this stage we decided to study the intramolecular dehydrative cyclization of corresponding amine **36** of azido compound **35** to obtain the auranthine precursor **38**. We reduced the azide group in compound **35** to the corresponding amine **36** using catalytic hydrogenation and attempted an intramolecular dehydrative cyclization under a variety of reaction conditions including



Scheme 7. Total synthesis of proposed auranthine

microwave irradiation, but all our attempts met with failure. We moved towards our pre-planned intramolecular aza-Wittig reaction for the transformation of azide **35** to the potential auranthine precursor **38**.[4–12] The intramolecular aza-Wittig reaction using triphenylphosphine in refluxing *p*-xylene, however, was not successful. Instead, using tributylphosphine driven aza-Wittig reaction in refluxing *p*-xylene gave the required product **38**, but in only 4 to 5% yield, after 48 h. We were delighted to find that the same reaction in a sealed tube at 200 ^{o}C for 48 h regioselectively furnished the desired auranthine precursor **38** in 74% yield, however, unfortunately, with the nearly complete racemization (by specific rotation). The structure of aza-Wittig product **38** was unequivocally confirmed on the basis of single X-ray crystallographic data (Figures 4 and 5).[17,18] The higher reaction temperature and the longer reaction time were essential for the formation of compound **38** in an acceptable yield for two reasons, viz (i) the stabilized nitrogen ylide formed is in conjugation with a suitably *ortho*-substituted amide carbonyl group and (ii) the nitrogen ylide has to react with the less

reactive lactam carbonyl group to form the seven member cyclized product. Herein, in the conversion of **35** to **38**, the formation of a corresponding four-membered betaine type intermediate **37** must be a high energy process. Hence, during the course of the reaction, the starting material and/or product suffered from a thermal racemization process.[19]

Finally, the $KMnO_4$ induced[20] chemoselective oxidation of benzylic methylene group of quinazolinopyridobenzodiazepine **38** to the corresponding carbonyl group, keeping the allylic methylene group intact in refluxing acetone, provided the (±)-auranthine (**1**), in 79% yield.[18] We were also delighted to know that the same reaction in acetone plus water mixture (9:1) falicitate the benzylic oxidation at room temperature providing the (±)-auranthine (**1**) in 91% yield. Starting from anhydride **29**, the overall yield of auranthine (**1**) in seven steps was 30%.

The analytical and spectral data obtained for tetrahydroquinazolinopyridobenzodiazepindione (auranthine, **1**) were in complete agreement with those of the assigned structure.[1] Finally, the structure of synthetic auranthine was unequivocally confirmed on the basis of X-ray crystallographic data (Figures 6 and 7).[17,18] However, the ^{1}H NMR spectrum of synthetic **1** in benzene-d_6 was not in agreement with the ^{1}H NMR spectrum of natural product.[1,18] We were unable to obtain a ^{13}C NMR spectrum of the synthetic auranthine in benzene-d_6 for comparison since the solubility of synthetic auranthine **1** in benzene-d_6 was very weak (<1 mg/mL), hence we were unable to record the ^{13}C NMR spectrum of synthetic **1** even after overnight scanning. Hence what we have accomplished is the synthesis of the proposed structure of auranthine.

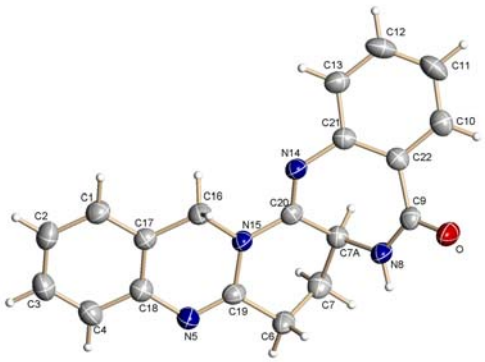


Figure 4. *ORTEP* diagram of compound **38**

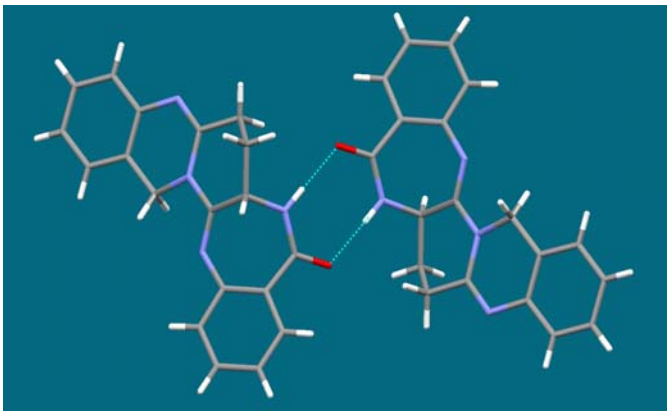


Figure 5. Hydrogen bonded dimer of **38** via N–H….O interaction

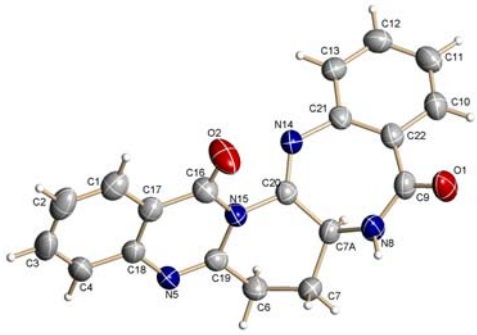


Figure 6. *ORTEP* diagram of compound **1**

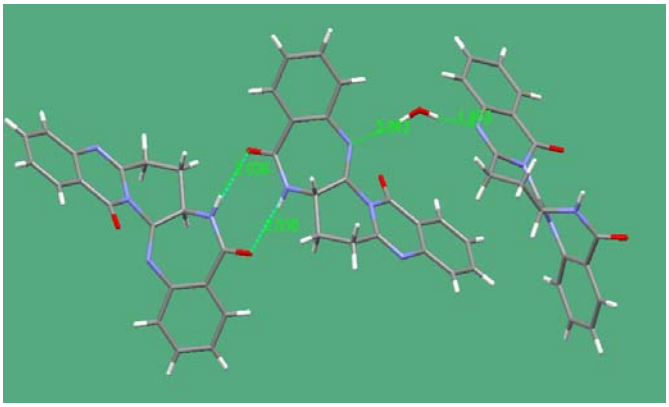


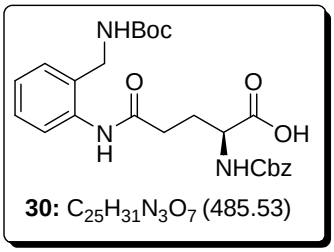
Figure 7. Hydrogen bonded dimer of **1** via N–H….O interaction

2C.3 Summary

Starting from Cbz-protected glutamic anhydride and Boc-protected o-aminobenzyl amine, we have accomplished the first total synthesis of proposed structure of auranthine using late-stage chemoselective oxidation strategy. An intramolecular aza-Wittig reaction involving a lactam carbonyl group that delivered the diazepine core unit was the key step in the synthesis. The reported spectral data for aurathine did not match that of our synthetic auranthine. The structure of synthetic auranthine was unambiguously confirmed by using single X-ray crystallographic analysis. These results clearly demonstrate that a revision of the structure of natural auranthine is necessary. We strongly believe that the present approach will be useful to design several desired bioactive natural and unnatural diazepine analogs and congeners.

2C. 4 Experimental Sections

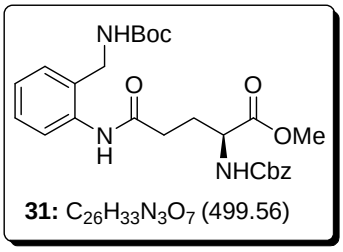
(*S*)-2-(Benzyloxycarbonylamino)-5-(2-((*tert*-butoxycarbonylamino)methyl)phenylamino)-5-



30: $C_{25}H_{31}N_3O_7$ (485.53)

oxopentanoic acid (30). To a stirred solution of anhydride **29** (5.00 g, 19.01 mmol) in DMSO (25 mL) was added solution of *tert*-butyl 2-aminobenzylcarbamate (**28**, 4.60 g, 22.91 mmol) in DMSO (10 mL) in a dropwise fashion over a period of five min and the resulting reaction mixture was further stirred at room temperature for 25 min. The reaction mixture was diluted with ethyl acetate (200 mL) and washed with brine, 1 N HCl, water and again with brine and the organic layer was dried over Na_2SO_4. Concentration of organic layer in vacuo followed by silica gel column chromatographic purification of residue with petroleum ether-ethyl acetate (3:7) as an eluent afforded the acid **30** as a white solid (8.49 g, 92%). Mp 93−95 °C; $[\alpha]^{25}_D$ +14.6 (*c* 0.90 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.39 (s, 9H), 2.19 (br s, 2H), 2.61 (br s, 2H), 4.20 (br d, *J* = 4 Hz, 2H), 4.39 (br d, *J* = 2 Hz, 1H), 4.68 (br s, 1H), 5.06 (s, 2H), 5.27 (br quintet, *J* = 4 Hz, 1H), 6.10 (br d, *J* = 4 Hz, 1H), 6.95−7.45 (m, 8H), 7.95 (br d, *J* = 6 Hz, 1H), 9.70 (br s, 1H); ^{1}H NMR (CD_3OD, 200 MHz) δ 1.41 (s, 9H), 2.03 (sextet, *J* = 8 Hz, 1H), 2.32 (sextet, *J* = 8 Hz, 1H), 2.58 (t, *J* = 8 Hz, 2H), 4.17 (s, 2H), 4.24 (dd, *J* = 8 and 4 Hz, 1H), 5.08 (s, 2H), 7.07−7.40 (m, 8H), 7.58 (d, *J* = 8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 28.3, 29.7, 33.1, 41.4, 53.9, 66.9, 80.7, 123.6, 124.9, 127.8, 128.0, 128.4, 128.7, 129.7, 130.2, 135.9, 136.3, 156.4, 157.3, 172.4, 174.9; ESIMS (*m*/*z*) 486 $[M+H]^+$, 508 $[M+Na]^+$, 524 $[M+K]^+$; IR (Nujol) ν_{max} 3330, 1691, 1660 cm^{-1}. Anal. Calcd for $C_{25}H_{31}N_3O_7$: C, 61.84; H, 6.44; N, 8.65. Found: C, 61.96; H, 6.44; N, 8.97.

(*S*)-Methyl 2-(benzyloxycarbonylamino)-5-(2-((*tert*-butoxycarbonylamino)methyl)phenylamino)-5-

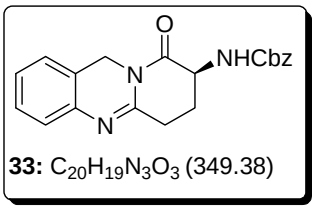


31: $C_{26}H_{33}N_3O_7$ (499.56)

oxopentanoate (31). Ether solution of diazomethane was added dropwise to a suspension of acid **30** (5.00 g, 10.30 mmol) in diethyl ether (50 mL) at 0 °C until the acid dissolved with persistence of light yellow color and the reaction mixture was stirred at room temperature for 30 min. The solvent was removed under reduced pressure and silica gel column chromatographic purification of the resulting residue using petroleum ether-ethyl acetate (6:4) as an eluent afforded the pure ester **31** as a white solid (4.99 g, 97%). Mp 71−73 °C; $[\alpha]^{25}_D$ +13.2 (*c* 1.64 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.41 (s, 9H), 2.00−2.40 (m, 2H), 2.58 (t, *J* = 8 Hz, 2H), 3.73 (s, 3H), 4.24 (br s, 2H), 4.44 (br q, *J* = 6 Hz, 1H), 5.09 (s, 2H), 5.15 (m, 1H), 5.85 (br d, *J* = 8 Hz, 1H), 7.04 (t, *J* = 8 Hz, 1H), 7.13 (dt, *J* = 8 & 2 Hz, 1H), 7.17−7.42 (m, 6H), 8.15 (d, *J* = 8 Hz, 1H), 9.54 (br s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 27.8, 28.2, 33.1, 41.5, 52.4, 53.7, 66.9, 80.6, 122.6, 124.2, 128.0, 128.4, 128.70, 128.73, 128.8, 130.3, 136.2, 136.5, 156.2, 157.3, 171.0, 172.5;

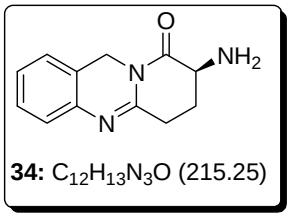
ESIMS (*m*/*z*) 500 $[M+H]^+$, 522 $[M+Na]^+$, 538 $[M+K]^+$; IR ($CHCl_3$) ν_{max} 3330, 1715, 1683 cm^{-1}. Anal. Calcd for $C_{26}H_{33}N_3O_7$: C, 62.51; H, 6.66; N, 8.41. Found: C, 62.20; H, 6.96; N, 8.36.

(*S*)-Benzyl 9-oxo-7,8,9,11-tetrahydro-6*H*-pyrido[2,1-*b*]quinazolin-8-ylcarbamate (33). To a stirred solution of ester **31** (4.00 g, 8.02 mmol) in dry DCM (50 mL) was added trifluoroacetic acid (5.95 mL, 10.00 mmol) and the reaction mixture was stirred at room temperature for 8 h. The reaction mixture was basified slowly with saturated solution of $NaHCO_3$ and extracted with DCM (3 x 100 mL). The combined organic layer was washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure and resulting crude product was immediately dissolved in dry toluene (50 mL) and the reaction mixture was refluxed for 8 h under argon atmosphere. The reaction mixture was allowed to cool to room temperature and the solvent was removed in vacuo. Silica gel column chromatographic purification of the resulting residue using petroleum ether-ethyl acetate (1:1) as an eluent afforded the pure **33** as an off-white solid (2.18 g, 78%). Mp 145−147 °C; $[\alpha]^{25}_D$ −38.7 (*c* 0.82 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.83 (dq, *J* = 8 & 4 Hz, 1H), 2.45−2.62 (br m, 1H), 2.87 (dt, *J* = 8 & 2 Hz, 1H), 2.97−3.05 (m, 1H), 4.25−4.40 (br m, 1H), 4.73 (d, *J* = 16 Hz, 1H), 5.05 (d, *J* = 16 Hz, 1H), 5.14 (s, 2H), 5.75 (br s, 1H), 7.05 (d, *J* = 8 Hz, 1H), 7.10−7.40 (m, 8H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 25.0, 30.1, 42.9, 53.0, 67.1, 121.6, 125.5, 125.7, 126.9, 128.1, 128.2, 128.5, 128.7, 136.1, 139.0, 150.0, 156.0, 169.2; ESIMS (*m*/*z*) 350 $[M+H]^+$, 372 $[M+Na]^+$; HRMS (EI) Calcd for $C_{20}H_{19}N_3O_3$ 349.1426, found 349.1420; IR (Nujol) ν_{max} 3265, 1726, 1679 cm^{-1}. Anal. Calcd for $C_{20}H_{19}N_3O_3$: C, 68.75; H, 5.48; N, 12.03. Found: C, 68.46; H, 5.44; N, 11.70.



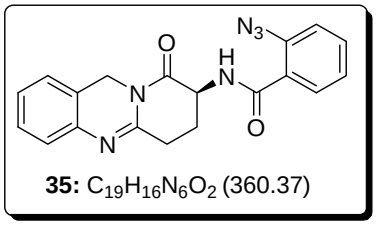
33: $C_{20}H_{19}N_3O_3$ (349.38)

(*S*)-8-Amino-7,8-dihydro-6*H*-pyrido[2,1-*b*]quinazolin-9(11*H*)-one (34). Compound **33** (1.00 g, 2.87 mmol) was stirred in 30% HBr in AcOH (10 mL) at room temperature for 2 h. The reaction mixture was concentrated under reduced pressure and the resulting hydrobromide salt was neutralized with saturated solution of $NaHCO_3$. The reaction mixture was extracted with DCM (3 x 100 mL) and the organic layer was washed with brine and dried over Na_2SO_4. Concentration of organic layer in vacuo afforded the amine **34** as an off-white solid (0.51 g, 82%). The amine **34** was immediately used for the next step without any purification. Mp 115−118 °C; $[\alpha]^{25}_D$ −27.1 (*c* 0.42 MeOH); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.70−1.95 (m, 3H), 2.20−2.37 (m, 1H), 2.68−3.08 (m, 2H), 3.58 (dd, *J* = 12 & 4 Hz, 1H), 4.92 (q, *J* = 16 Hz, 2H), 7.00−7.32 (m, 4H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 26.7, 30.5, 42.7, 52.9, 121.8, 125.4, 125.7, 126.7, 128.6, 139.0, 151.2, 173.3; ESIMS (*m*/*z*) 216 $[M+H]^+$; HRMS (EI) Calcd for $C_{12}H_{13}N_3O$ 215.1059, found 215.1073; IR (Neat) ν_{max} 3447, 3358, 1690, 1665, 1620 cm^{-1}.



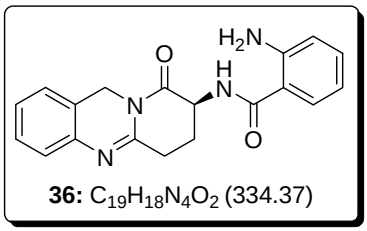
34: $C_{12}H_{13}N_3O$ (215.25)

(*S*)-2-Azido-*N*-(9-oxo-7,8,9,11-tetrahydro-6*H*-pyrido[2,1-*b*]quinazolin-8-yl)benzamide (35). To the stirred mixture of *o*-azidobenzoic acid (0.38 g, 2.32 mmol) and EDCI (0.54 g, 2.79 mmol) in DCM (20 mL) was added amine **34** (0.50 g, 2.32 mmol) in DCM (15 mL) and the reaction mixture was further stirred at room temperature for 18 h. The reaction mixture was diluted with DCM (100 mL) and washed with water, saturated solution of $NaHCO_3$, brine and dried over Na_2SO_4. The solvent was removed under reduced pressure and silica gel column chromatographic purification of the resulting residue using petroleum ether-ethyl acetate (3:7) as an eluent furnished the pure azide **35** as an off-white solid (0.76 g, 89%). Mp 177−178 °C; $[\alpha]^{25}_{D}$ +55.6 (*c* 0.50 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.70−2.10 (m, 1H), 2.65−2.80 (m, 1H), 2.85−3.18 (m, 2H), 4.76 (dd, *J* = 18 & 6 Hz, 1H), 4.80 (d, *J* = 16 Hz, 1H), 5.12 (d, *J* = 16 Hz, 1H), 7.04−7.34 (m, 6H), 7.55 (dt, *J* = 8 & 2 Hz, 1H), 8.20 (dd, *J* = 8 & 2 Hz, 1H), 8.53 (br d, *J* = 4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 24.7, 30.2, 42.9, 52.6, 118.5, 121.6, 124.0, 125.2, 125.5, 125.7, 126.9, 128.7, 132.3, 132.8, 137.5, 139.0, 150.3, 164.5, 169.6; ESIMS (*m*/*z*) 383 $[M+Na]^+$; HRMS (EI) Calcd for $C_{19}H_{16}N_6O_2$ 360.1335, found 360.1338; IR (Nujol) ν_{max} 3298, 2127, 1697, 1657, 1620 cm^{-1}.



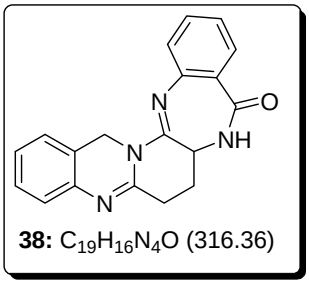
35: $C_{19}H_{16}N_6O_2$ (360.37)

(*S*)-2-Amino-*N*-(9-oxo-7,8,9,11-tetrahydro-6*H*-pyrido[2,1-*b*]quinazolin-8-yl)benzamide (36): Palladium on carbon (10 wt%) was added to the stirred solution of azide **35** (0.20 g, 0.55 mmol) in ethyl acetate (10 mL) at room temperature. The reaction mixture was stirred under an atmosphere of hydrogen (2 psi, balloon pressure) for 2 h and filtered through a pad of Celite. The filtrate was concentrated under reduced pressure and silica gel column chromatographic purification of the resulting residue using petroleum ether-ethyl acetate (2:8) as an eluent furnished the pure amine **36** as an pale-yellow solid (0.12 g, 67%). Mp 132−134 °C; $[\alpha]^{25}_{D}$ +15.3 (*c* 0.53 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.75−1.95 (m, 1H), 2.63−2.73 (m, 1H), 2.92−3.15 (m, 2H), 4.64−4.72 (m, 1H), 4.76 (d, *J* = 15 Hz, 1H), 5.11 (d, *J* = 15 Hz, 1H), 6.68 (t, *J* = 10 Hz, 1H), 6.69 (d, *J* = 10 Hz, 1H), 7.05 (d, *J* = 5 Hz, 1H), 7.08 (d, *J* = 10 Hz, 1H), 7.17 (t, *J* = 10 Hz, 1H), 7.20−7.30 (m, 3H), 7.45 (d, *J* = 10 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 24.9, 30.2, 43.0, 52.0, 115.0, 116.8, 117.4, 121.6, 125.5, 125.7, 127.0, 127.6, 128.7, 132.8, 139.0, 149.0, 150.3, 169.4, 169.9; ESIMS (*m*/*z*) 357 $[M+Na]^+$; IR (Nujol) ν_{max} 3439, 3339, 1686, 1647, 1618 cm^{-1}. Anal. Calcd for $C_{19}H_{18}N_4O_2$: C, 68.25; H, 5.43; N, 16.76. Found: C, 67.81; H, 5.19; N, 18.15.



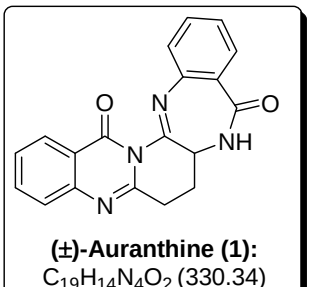
36: $C_{19}H_{18}N_4O_2$ (334.37)

6,7,7a,8-Tetrahydro-16*H*-quinazolino[3',2':1,6]pyrido[2,3-*b*][1,4]benzodiazepin-9-one (38). To a stirred mixture of compound **35** (0.40 g, 1.11 mmol) in dry *p*-xylene (5 mL) was added *n*-Bu_3P (0.33 mL, 1.33 mmol) at room temperature under argon atmosphere in a sealed tube and the stirring was continued for 1 h. The reaction mixture was heated at 200 °C in a sealed tube for 48 h and it was allowed to cool to room temperature. Precipitated product was filtered off and washed with *n*-hexane and then recrystalization from DCM afforded **38** as an off-white solid (0.26 g, 74%). Mp 273−275 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.75−2.14 (m, 1H), 2.15−2.43 (m, 1H), 2.70−2.90 (m, 1H), 3.00−3.20 (m, 1H), 4.07 (q, *J* = 4 Hz, 1H), 4.88 (d, *J* = 18 Hz, 1H), 5.33 (d, *J* = 16 Hz, 1H), 7.08−7.33 (m, 6H), 7.55 (dt, *J* = 8 & 2 Hz, 1H), 7.99 (dd, *J* = 8 & 2 Hz, 1H), 8.70 (br d, *J* = 4 Hz, 1H); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.95−2.05 (m, 1H), 2.14−2.26 (m, 1H), 2.58 (ddd, *J* = 16, 4 & 4 Hz, 1H), 2.90 (ddd, *J* = 12, 12 & 4 Hz, 1H), 4.03 (q, *J* = 4 Hz, 1H), 4.83 (d, *J* = 16 Hz, 1H), 5.19 (d, *J* = 16 Hz, 1H), 7.10 (d, *J* = 8 Hz, 1H), 7.13 (t, *J* = 8 Hz, 1H), 7.20−7.27 (m, 4H), 7.55 (dt, *J* = 8 & 2 Hz, 1H), 7.81 (d, *J* = 8 Hz, 1H), 8.68 (br d, *J* = 4 Hz, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 21.8, 28.0, 44.1, 45.6, 122.7, 124.2, 124.7, 126.0, 126.2, 126.6, 126.9, 128.3, 130.0, 131.9, 139.8, 145.5, 151.8, 156.0, 168.4; ESIMS (*m*/*z*) 317 $[M+H]^+$, 339 $[M+Na]^+$; HRMS (EI) Calcd for $C_{19}H_{16}N_4O$ 316.1324, found 316.1315; IR (Nujol) ν_{max} 3435, 1661, 1636, 1612 cm^{-1}.



38: $C_{19}H_{16}N_4O$ (316.36)

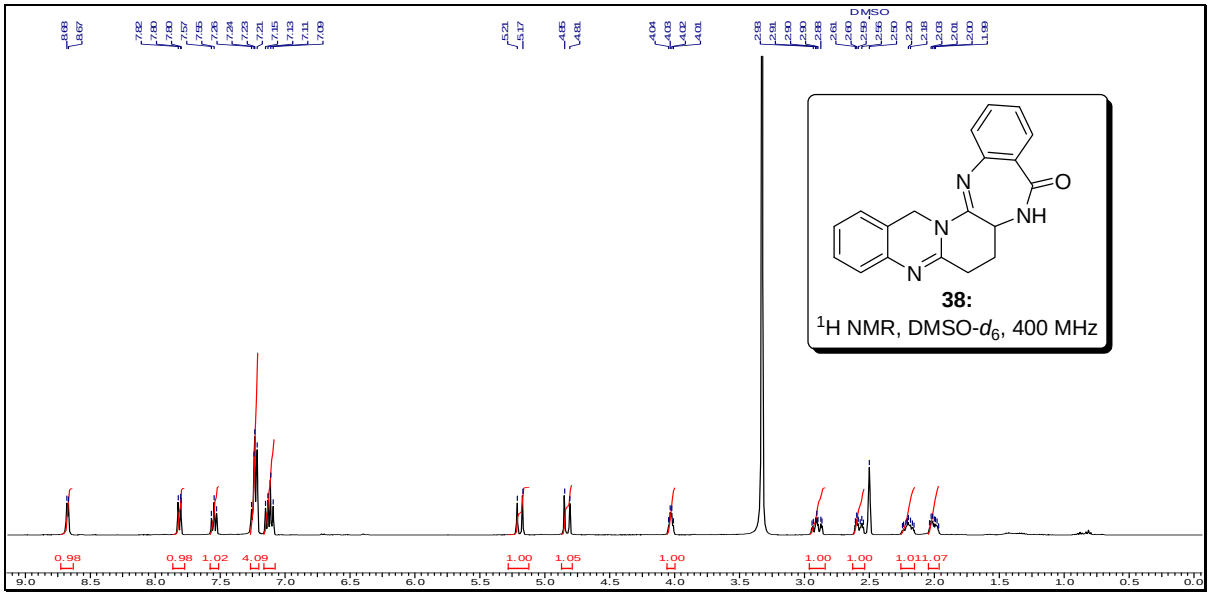
6,7,7a,8-Tetrahydroquinazolino[3',2':1,6]pyrido[2,3-*b*][1,4]benzodiazepin-9,16-dione (Auranthine, 1). Method A: To a stirred solution of compound **38** (64 mg, 0.20 mmol) in dry acetone (5 mL) was added $KMnO_4$ (64 mg, 0.40 mmol) and the reaction mixture was refluxed for 3 h under argon atmosphere. The reaction mixture was allowed to cool to room temperature and filtered off and the residue was washed with acetone. Concentration of filtrate in vacuo followed by silica gel column chromatographic purification of residue with dichloromethane-methanol (9:1) as an eluent furnished the final product auranthine (**1)** (52 mg, 79%). **Method B:** To a stirred solution of compound **38** (64 mg, 0.20 mmol) in acetone:water (9:1, 5 mL) was added $KMnO_4$ (64 mg, 0.40 mmol) and the reaction mixture was strirred for 1 h. Solvent was removed under reduced pressure and diluted with ethyl acetate (25 mL). The organic layer was washed with brine and dried over Na_2SO_4. Concentration of organic layer in vacuo followed by silica gel column chromatographic purification of residue with ethyl acetate as an eluent furnished the final product aurnthine (**1)** (60 mg, 91%). Mp 188−189 °C (ethyl acetate); ^{1}H NMR (benzene-d_6, 500 MHz) δ 1.40−1.43 (m, 1H), 1.50−1.58 (m, 2H), 2.33−2.39 (m, 1H), 2.98−3.04 (m, 1H), 6.01 (br s, 1H), 6.95 (t, *J* = 10 Hz, 2H), 7.07−7.25 (m, 2H), 7.34 (d, *J* = 10 Hz, 1H), 7.61 (d, *J* = 10 Hz,

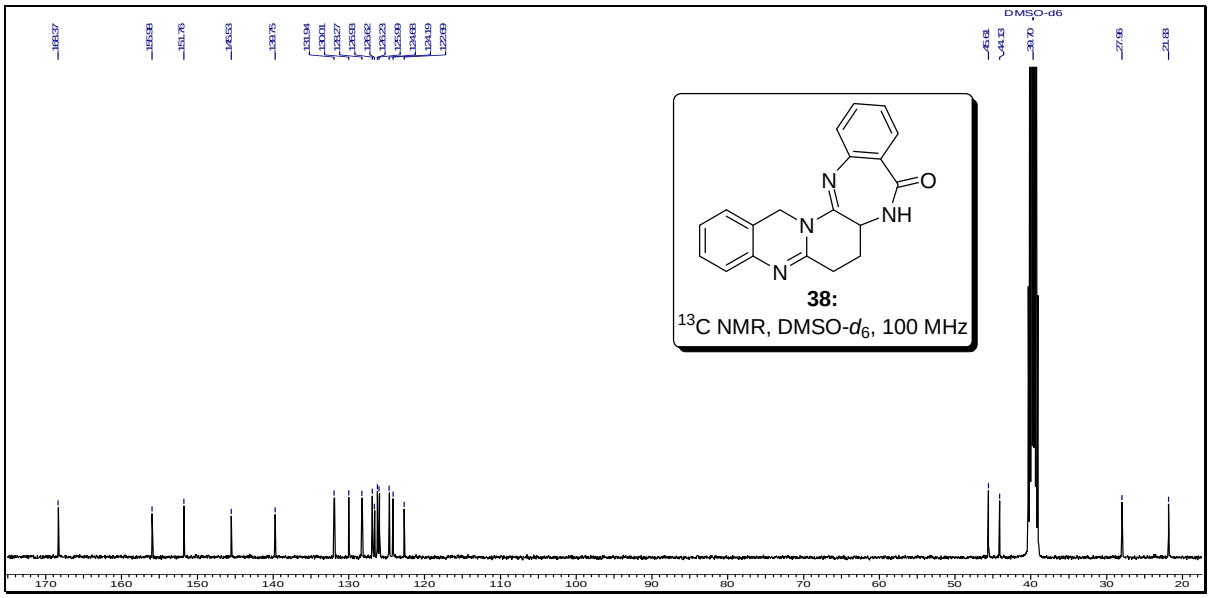


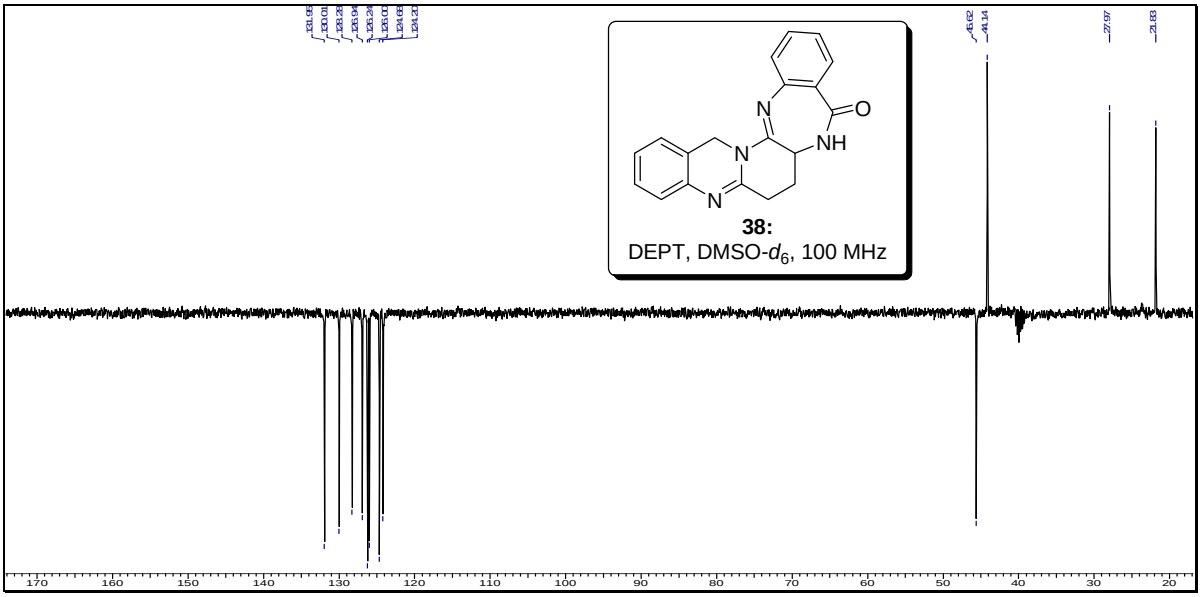
(±)-Auranthine (1):
$C_{19}H_{14}N_4O_2$ (330.34)

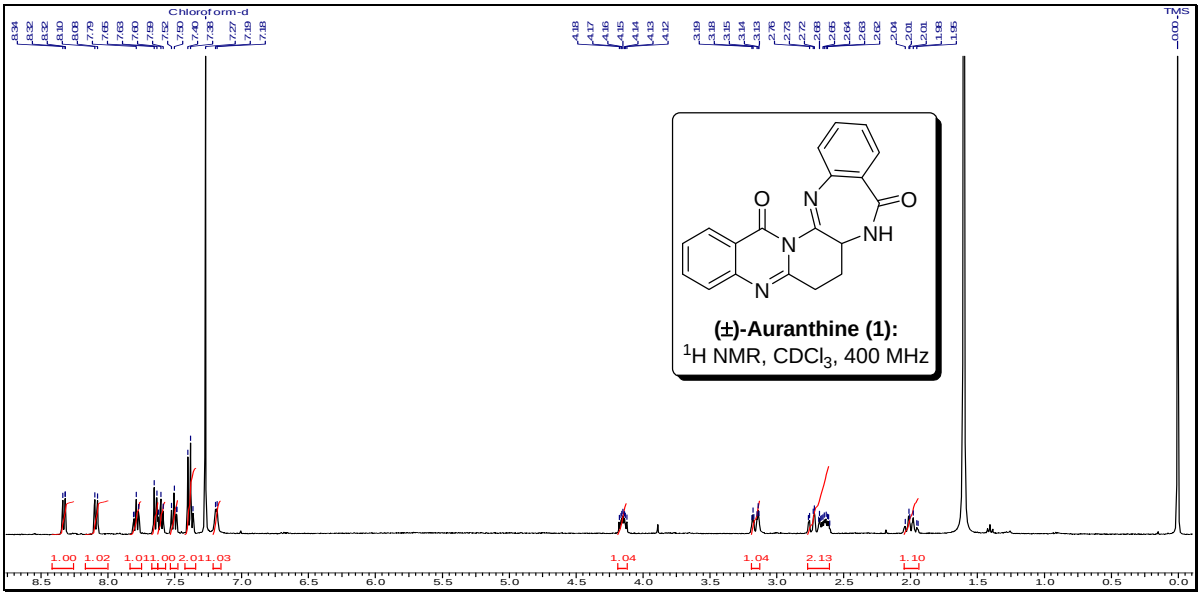
1H), 8.34 (d, *J* = 10 Hz, 1H), 8.39 (d, *J* = 10 Hz, 1H); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.00 (dq, *J* = 12 & 4 Hz, 1H), 2.59−2.68 (m, 1H), 2.73 (dt, *J* = 12 & 4 Hz, 1H), 3.16 (ddd, *J* = 16, 4 & 4 Hz, 1H), 4.11−4.19 (m, 1H), 7.19 (br d, *J* = 4 Hz, 1H), 7.38 (t, *J* = 8 Hz, 1H), 7.39 (d, *J* = 8 Hz, 1H), 7.50 (t, *J* = 8 Hz, 1H), 7.60 (dt, *J* = 8 & 4 Hz, 1H), 7.64 (d, *J* = 8 Hz, 1H), 7.79 (t, *J* = 8 Hz, 1H), 8.09 (d, *J* = 8 Hz, 1H), 8.33 (d, *J* = 8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 24.3, 30.2, 48.8, 122.0, 126.0, 126.89, 126.94, 127.46, 127.54, 128.2, 130.7, 132.5, 135.2, 143.4, 145.6, 151.2, 152.9, 159.6, 168.6; ESIMS (*m*/*z*) 331 $[M+H]^+$, 353 $[M+Na]^+$, 369 $[M+K]^+$; IR (Nujol) ν_{max} 3400, 1716, 1664, 1601 cm^{-1}. Anal. Calcd for $C_{19}H_{14}N_4O_2$: C, 69.08; H, 4.27; N, 16.96. Found: C, 69.02; H, 4.27; N, 16.87.

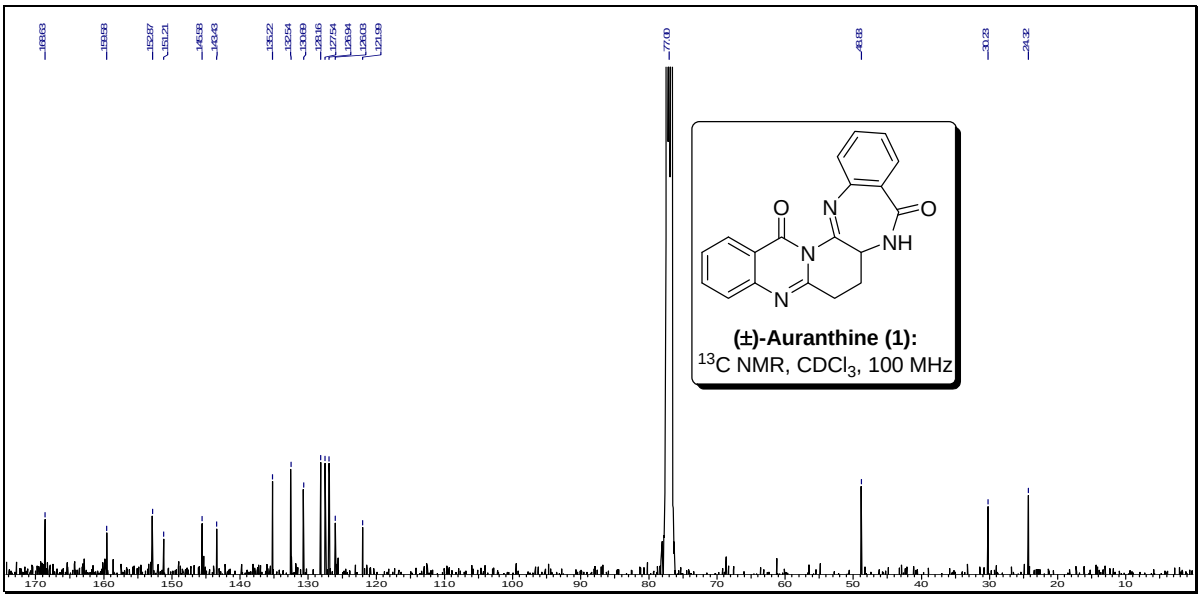
2C.5 Selected Spectra

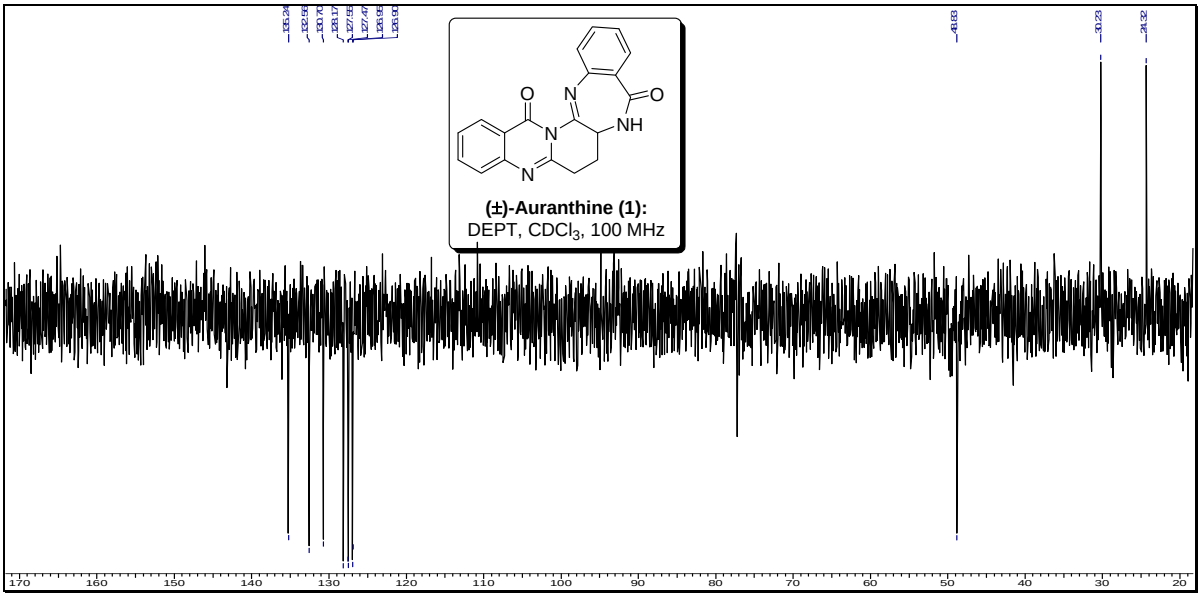

DMSO
N
O
NH
N
N
38:
1H NMR, DMSO-d6, 400 MHz

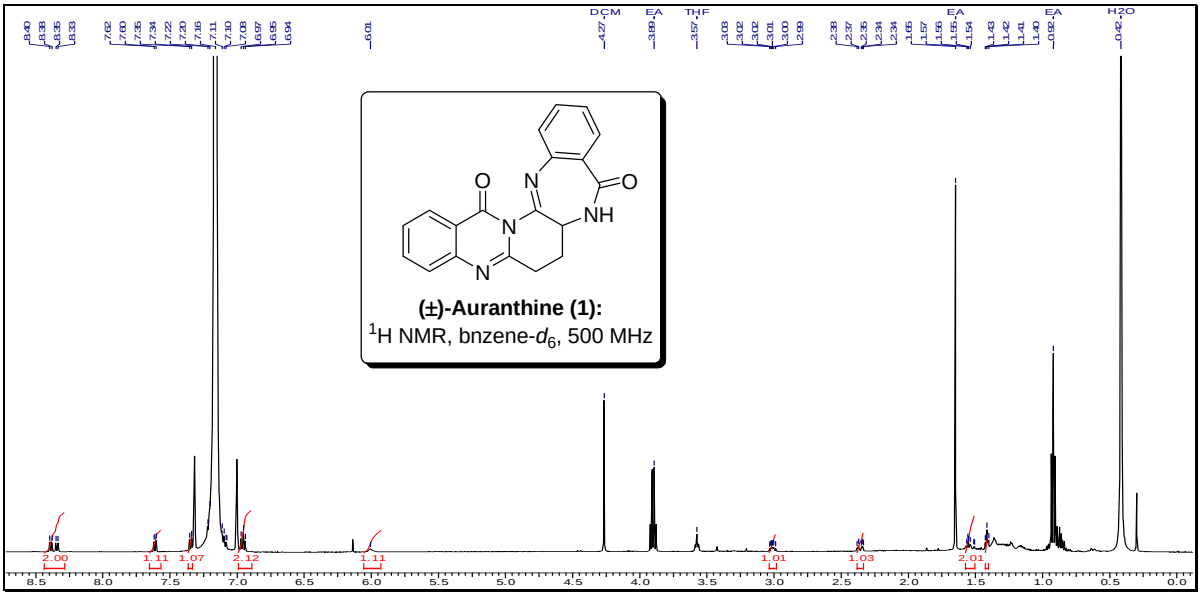

DMSO-d6
N
O
NH
N
N
38:
13C NMR, DMSO-d6, 100 MHz

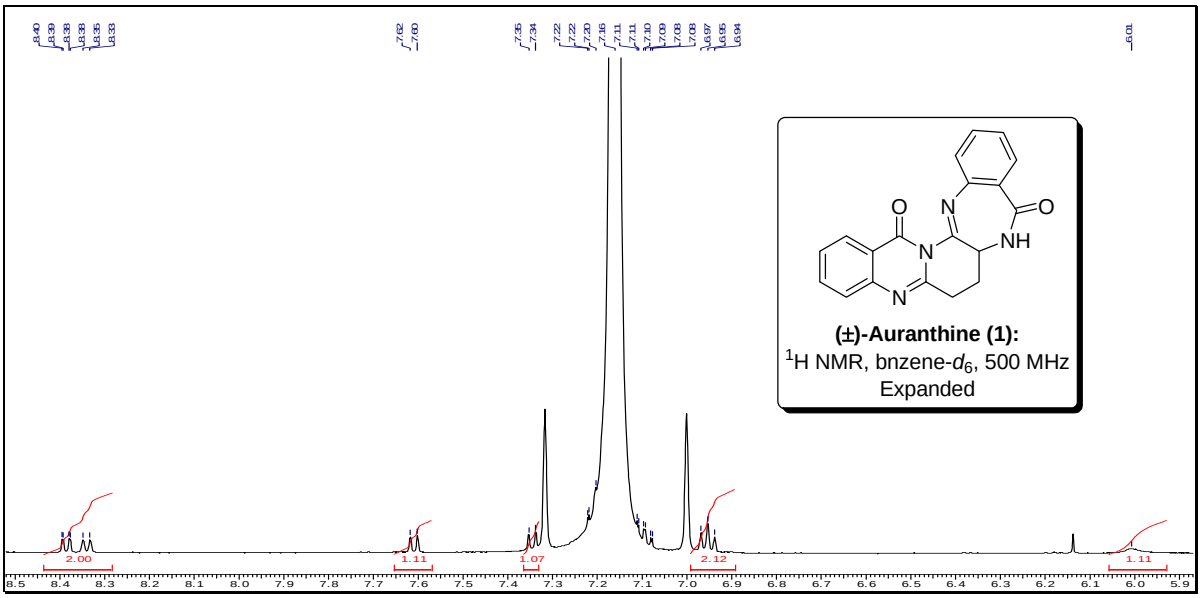

N
O
NH
N
N
38:
DEPT, DMSO-d6, 100 MHz

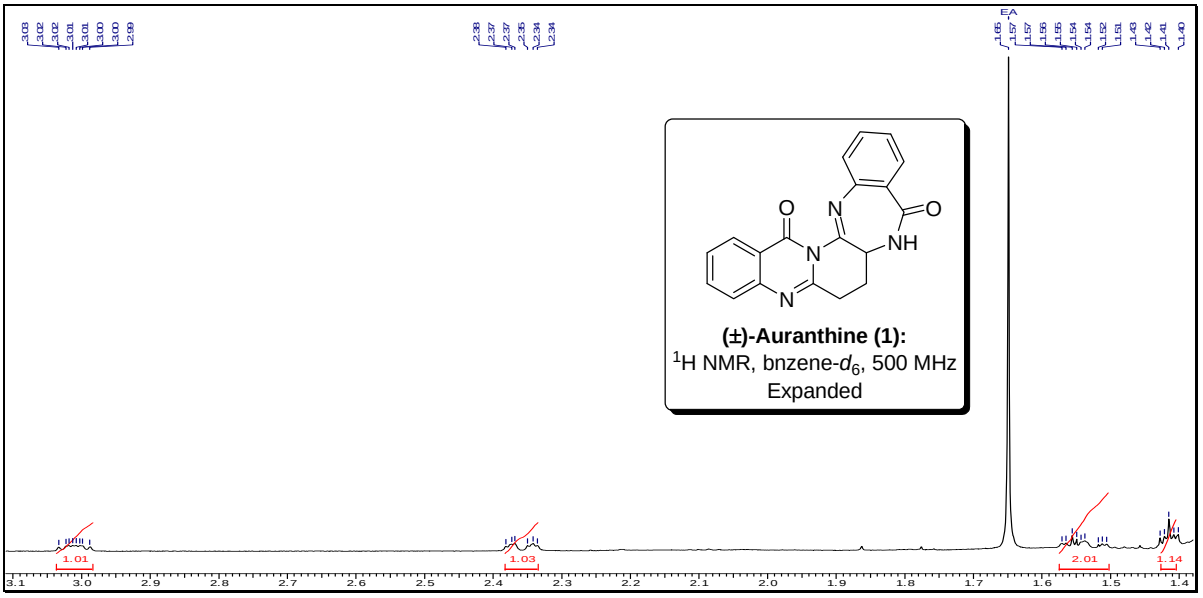

Chloroform-d
TMS
(±)-Auranthine (1):
1H NMR, CDCl3, 400 MHz


(±)-Auranthine (1):
13C NMR, CDCl3, 100 MHz


(±)-Auranthine (1):
DEPT, CDCl3, 100 MHz


(±)-Auranthine (1):
^{1}H NMR, bnzene-d_6, 500 MHz


(±)-Auranthine (1):
^{1}H NMR, bnzene-d_6, 500 MHz
Expanded


(±)-Auranthine (1):
^{1}H NMR, bnzene-d_6, 500 MHz
Expanded

2C.6 References

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17. Crystallographic data for the structures **38** and **1** have been deposited with the cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 768233 and 768232 respectively and can be access free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (e-mail: deposit@ccdc.cam.ac.uk).
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Chapter 2: Section D

Copper-Catalyzed Intramolecular *N*-Arylation of Quinazolinones: Facile Convergent Approach to (–)-Circumdatin H and J

This section D of chapter 2 features the following topics:

2D.1 Background

Nitrogen-containong compounds are one of the most important class of pharmacologically active medicinal compounds and many bioactive natural products. This has accelerated the quest for new methods in heterocyclic chemistry. Quinazolinobenzodiazepinone is a particular class of quinazolinone alkaloids such as asperlicins, benzomavins or sclerotigenin that incorporated the benzodiazepinone chromophore fused with quinazolinone core (Figure 1).[1]

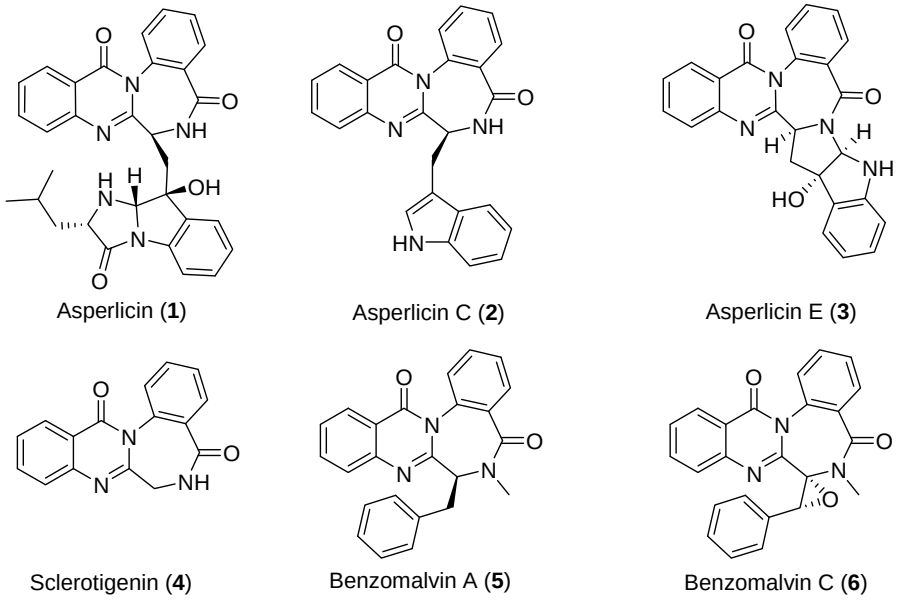
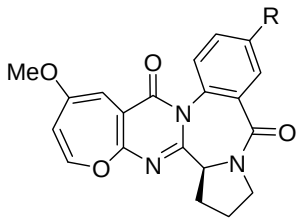
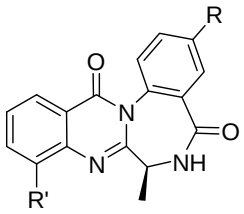


Figure 1. Quinazolinone alkaloids fused with benzodiazepinone chromophore

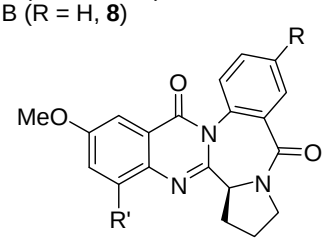
Quinazolinobenzodiazepinone family also includes the circumdatins A-J (Figure 2), the marine natural products that are isolated from fungi of the genus *Aspergillus*, they possess antitumor, antifungal, insecticide and antibiotic activities.[2] (–)-Circumdatins H and J have been recently isolated



Circumdatin A (R = OMe, **7**)
Circumdatin B (R = H, **8**)



Circumdatin C (R = OH, R' = H, **9**)
Circumdatin F (R = R' = H, **10**)
Circumdatin G (R = H, R' = OH, **11**)
Circumdatin I (R = R' = OH, **12**)

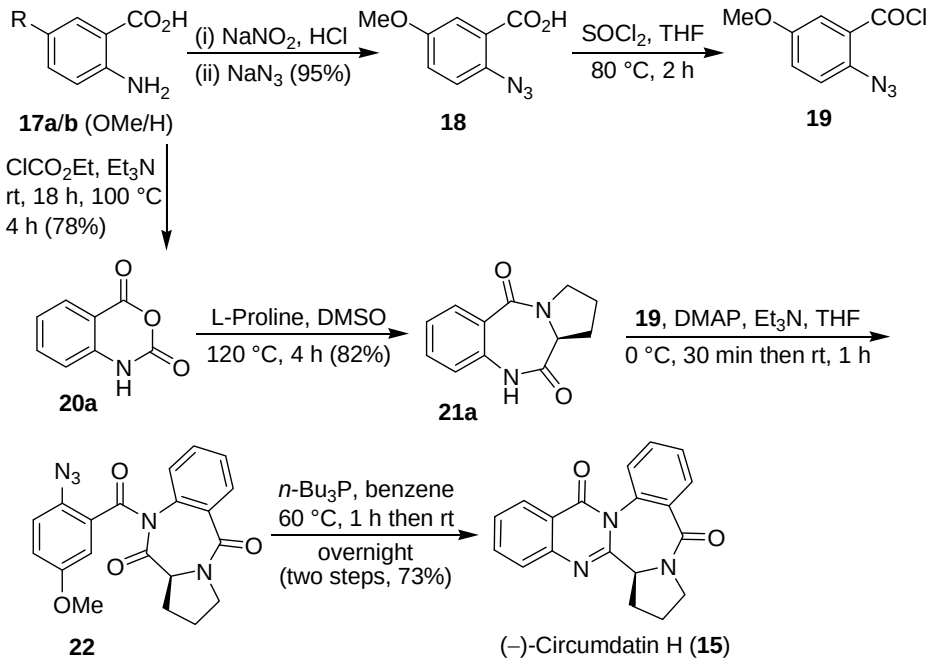


Circumdatin D (R = OMe, R' = OH, **13**)
Circumdatin E (R = H, R' = OH, **14**)
Circumdatin H (R = OMe, R' = H, **15**)
Circumdatin J (R = R' = OMe, **16**)

Figure 2. Naturally occurring bioactive circumdatins A-J

from *Aspergillus ochraceus* and *Aspergillus ostianus* respectively and more specifically, the (–)-circumdatin H is an inhibitor of the mammalian mitochondrial respiratory chain, with an IC_{50} value of 1.5 μM.[3] In the literature, quinazolinobenzodiazepinone alkaloids have been synthesized using different strategies like aza-Wittig protocol,[1b,4] Mazurkiewicz-Ganesan's protocol,[5] microwave irradiated three-component one-pot reaction sequence,[6] microwave irradiated, tin triflate[7a] and scandium triflate[7b] catalyzed double cyclization methodologies.

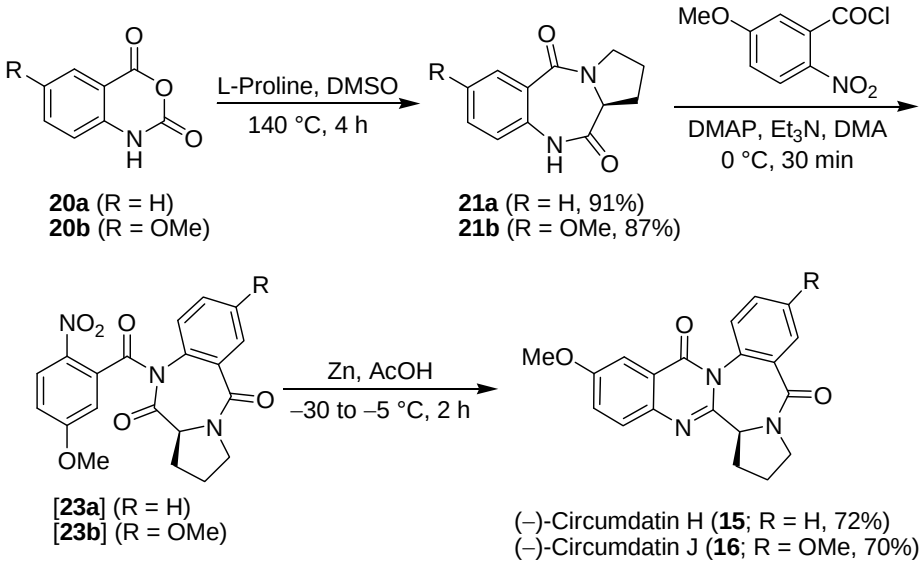
Very recently, Bose et al.[8] reported the first total synthesis of (–)-circumdatin H using the intramolecular aza-Wittig reaction (Scheme 1). The required 2-azido-5-methoxybenzoyl chloride (**19**) was prepared from 2-amino-5-methoxybenzoic acid via a sequence which involved diazotization of amino group followed by nucleophilic substitution by sodium azide to give compound **18** and then treatment with thionyl chloride. Treatment of isatoic anhydride (**20a**) with L-proline in dimethyl sulfoxide at 120 °C afforded the benzodiazepinone **21a**. Acylation of dilactam **21a** with 2-azido-5-methoxybenzoyl chloride (**19**) in the presence of triethylamine and 4-dimethytlaminopyridine in tetrahydrofuran gave the imide **22**. Intramolecular aza-Wittig reaction[1b,4] of azide with imide carbonyl of imide **22** was achieved using tributylphosphine, which provided the (–)-circumdatin H(**15**) in 73% yield over two steps.



Scheme 1. First synthesis of circumdatin H

Very recently Zichkin et al.[9] reported the first total synthesis of (–)- circumdatin J (**16**) as well as the second synthesis of (–)-circumdatin H (**15**) using intramolecular reductive cyclization strategy (Scheme 2). Benzodiazepinones **21a** and **21b** were obtained by the treatment of isatoic anhydride **20a/b** with L-proline in dimethyl sulfoxide at 140 °C. Acylation of compound **21a** and **21b** with 2-nitro-5-methoxybenzoylchloride in the presence of triethylamine and 4-dimethytlaminopyridine in

dimethyl acetamide as the solvent provided the imide **23a**/**b**. Intramolecular reductive cyclization reaction[10] was performed without isolating **23a**/**b**, by treating with excess acetic acid and zinc, which smoothly afforded (–)-circumdatin H/J (**15**/**16**) in 72/70% yields.



20a (R = H)
20b (R = OMe)

21a (R = H, 91%)
21b (R = OMe, 87%)

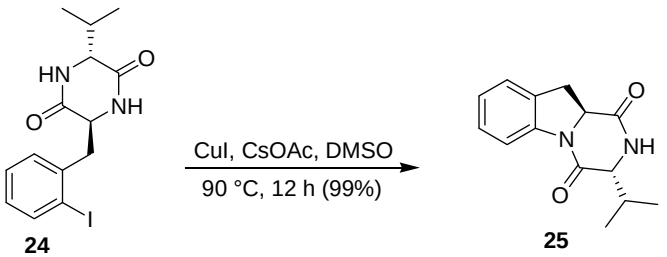
[**23a**] (R = H)
[**23b**] (R = OMe)

(–)-Circumdatin H (**15**; R = H, 72%)
(–)-Circumdatin J (**16**; R = OMe, 70%)

Scheme 2. First synthesis of circumdatin J and second synthesis of circumdatin H

Metal-catalyzed C(aryl)–N bond forming reactions under mild catalytic conditions utilizing amines, amides, and nitrogen heterocycles are imperative from a synthetic point of view to design the exotic natural products and synthetic compounds.[11-14] In the past few years, these reactions have been successfully utilized for the smart constructions of nitrogen-containing heterocyclic scaffolds, which represents a conceptually different approach for heterocyclic synthesis. Besides intermolecular *N*-arylation under copper catalysis, these reactions have been further extended for the synthesis of an array of nitrogen heterocycles involving intramolecular *N*-arylation process.

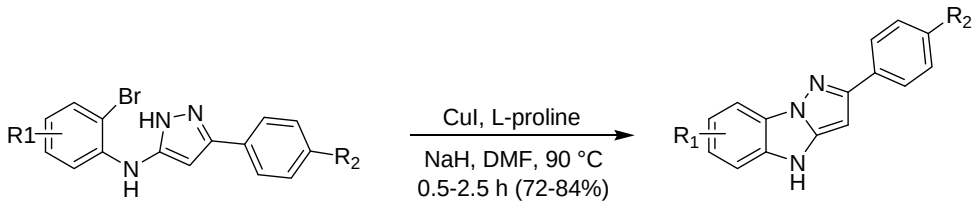
Rajanbabu et al. reported (Scheme 3)[12e] the copper-catalyzed intrmolecular *N*-arylation of diketopiperazine **24** using the Fukuyama modification of the Ullmann-Goldberg reaction to obtain enantiopure polycyclic diketopiperazines **25**.



24 **25**

Scheme 3. Copper-catalyzed annulations of diketopiperazine

Kumar et al. have reported[12m] synthetic route to pyrazolo[1,5-*a*]benzimidazoles **27** from 3-substituted-5-(2-bromoanilino)pyrazoles **26** using intramolecular copper-catalyzed *N*-arylation reaction (Scheme 4).

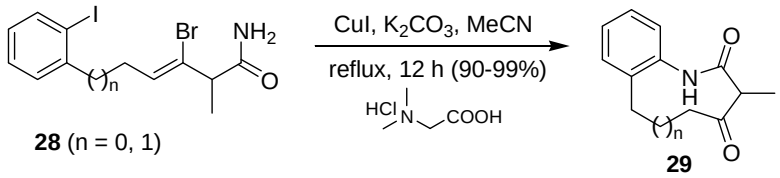


26 **27**

R_1 = H, Me, *i*-Pr, OMe, F; R_2 = H, OMe, Cl, F, CF_3

Scheme 4. Copper-catalyzed synthesis of pyrazolo-[1,5-*a*]benzimidazoles

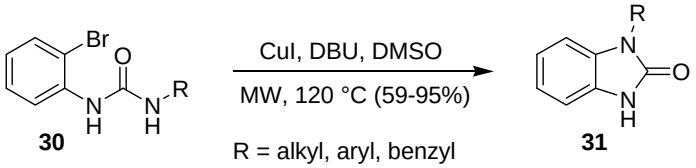
Zhao and Li reported the copper-catalyzed tandem C-N bond formation for the convenient generation of medium-size lactams **29** (Scheme 5).[12s]



28 (n = 0, 1) **29**

Scheme 5. Copper-catalyzed tandem C-N bond formation: synthesis of medium-size lactams

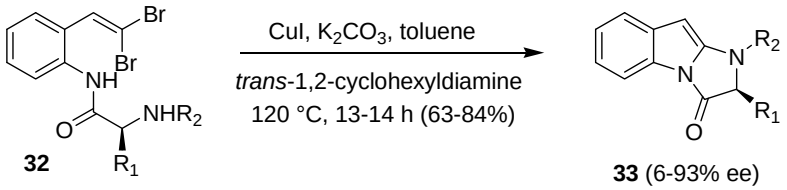
Li et al. developed[12t] the method for preparation of *N*-substituted 1,3-dihydrobenzimidazol-2-ones **31** from *N*'-substituted *N*-(2-halophenyl)ureas **30** via a copper-catalyzed intramolecular cyclization in DMSO under microwave heating (Scheme 6).



30 **31**

Scheme 6. Synthesis of *N*-substituted 1,3-dihydrobenzimidazol-2-ones

The first example of a copper-catalyzed tendem intramolecular amidation forming substituted imidazoindolones **33** from readily accessible *ortho gem*-dibromovinylanilines **32** has been reported by Lautens et al. (Scheme 7).[13c]

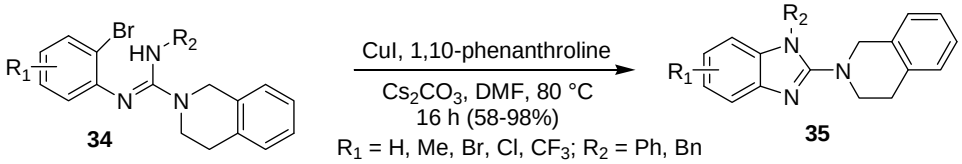


32 **33** (6-93% ee)

R_1 = H, Me, *i*-Pr, Bn, -$(CH_2)_2CO_2$Bn, -$(CH_2)_4$NHBoc; R_2 = Cbz, Boc

Scheme 7. Copper-catalyzed tendem intramolecular amidation forming substituted imidazoindolones

Evinder and Batey have reported[13g] efficient method for the synthesis of 2-aminobenzimidazoles **35**

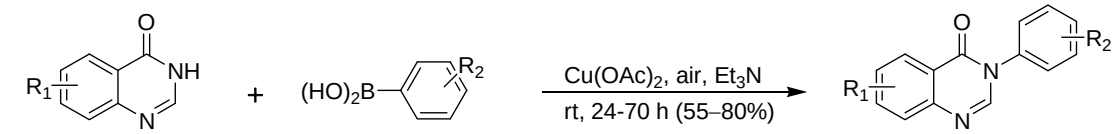


34 **35**

Scheme 8. Synthesis of 2-aminobenzimidazoles via copper-catalyzed intramolecular C-N bond formation

via copper-catalyzed intramolecular C-N bond formation between an aryl halide and a guanidine moiety (Scheme 8).

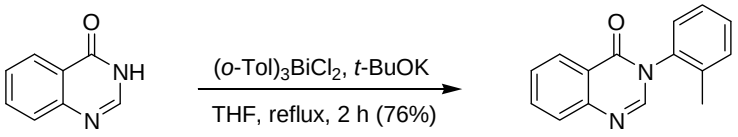
In the quinazolinone chemistry, Das et al. and Mukaiyama et al. have contributed for the intermolecular *N*-arylation of quinazolin-4(3*H*)-ones (Scheme 9 and 10).[14] Das et al. reported the copper-promoted *N*-arylation of quinazolin-4(3*H*)-one. In which quinazolin-4(3*H*)-ones **36a** and arylboronic acids **37** in the presence of $Cu(OAc)_2$ at room temperature under atmospheric conditions gave the desired *N*-aryl quinazolinones **38a** in good yields (Scheme 9).



36a (R_1 = F, Cl, OMe) **37** (R_2 = F, Cl, OMe, OCF_3) **38a**

Scheme 9. Copper(II)-catalyzed coupling of quinazolinones with arylboronic acids

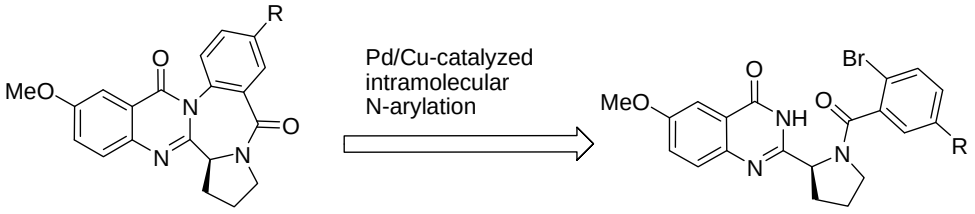
While, Mukaiyama et al. reported the copper free method for the *N*-arylation of pyridin-2(1*H*)-ones and the related heteroaromatic lactams via ligand-coupling reactions using triarylbismuth dichlorides in which quinazolin-4(3*H*)-one was arylated using tri-*o*-tolylbismuth dichloride in 76% yield in the presence of potassium *t*-butoxide (Scheme 10).



36b **38b**

Scheme 10. *N*-*o*-Tolylation of quinazolin-4(3*H*)-one

However, metal-catalyzed intramolecular *N*-arylation of quinazolinones has not been studied, to the best of our knowledge.[15,16] In continuation of our studies on quinazolinone chemistry,[17] we envisaged the metal-catalyzed intramolecular *N*-arylation of quinazolinones implementing the advanced Goldberg-Buchwald protocol[12,13] that would provide an efficient convergent access to a large number of desired naturally occurring quinazolinones and their analogues and congeners (Scheme 11).



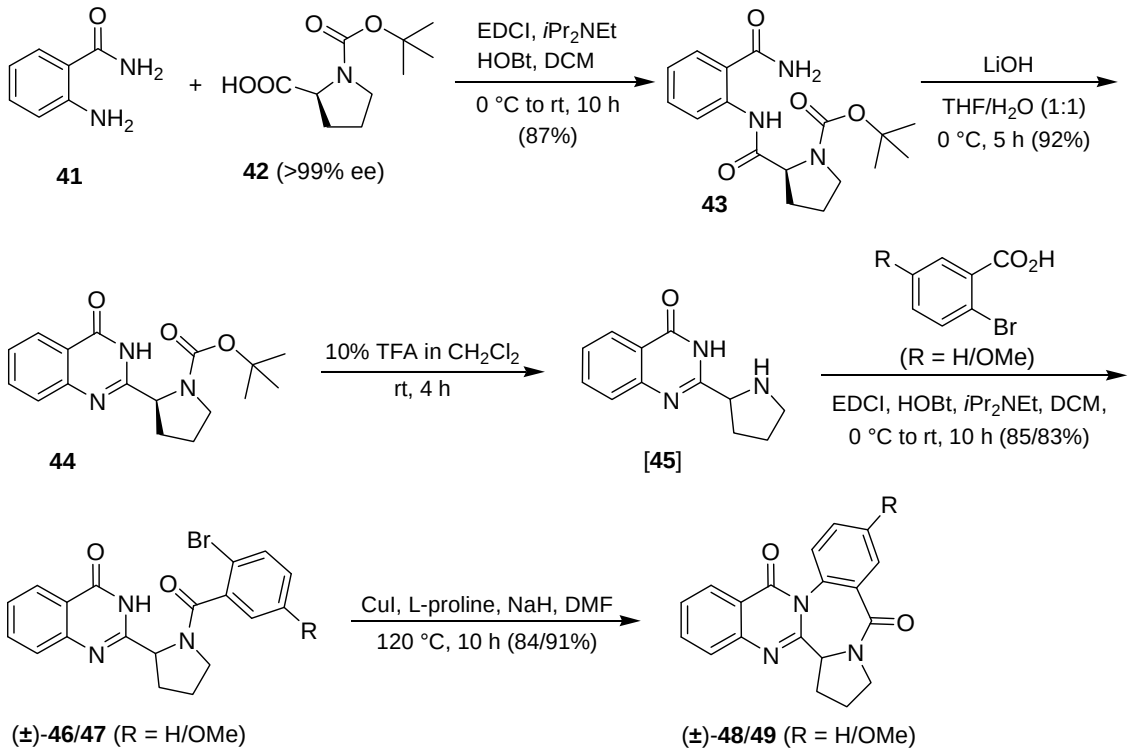
(–)-Circumdatin H (R = H, **15**)
(–)-Cicumdatin J (R = OMe, **16)**

39 (R = H)
40 (R = OMe)

Scheme 11. Retrosynthetic analysis of (**–**)-circumdatins H and J

2D.2 Results and Discussion

Careful scrutiny of circumdatin skeletons revealed that nature most likely utilizes two appropriate anthranilic acid units and L-proline/L-alanine to create them. We planned our biogenetic-type synthesis of circumdatin framework starting from anthranilamide and L-proline via the corresponding potential quinazolinone intermediate **46**/**47** (Scheme 12). We could foresee that our major challenges would be in the metal-catalyzed intramolecular *N*-arylation of quinazolinones to form the intricate seven-membered diazepine cores and the complete conservation of enantiomeric purity throughout the synthesis. The EDCI-induced dehydrative coupling of the Boc-protected L-proline (**42**) with anthranilamide (**41**) at room temperature furnished the diamide **43** in 87% yield. The subsequent base-catalyzed intramolecular dehydrative cyclization of compound **43** provided the required quinazolinone **44** in 92% yield. The TFA deprotection of the Boc group in compound **44**, followed by the dehydrative couplings of thus formed intermediate free amine **45** with 2-bromobenzoic acid and 2-bromo-5-methoxybenzoic acid, furnished the desired precursors **46**/**47** in 85/83% yields but, unfortunately, with complete racemization in both the cases. Herein, the acid-catalyzed racemization of our substrate **45** took place during the TFA-induced Boc-deprotection step,



Scheme 12. Synthesis of circumdatin frameworks via the intramolecular *N*-arylation

plausibly because of the presence of adjacent imine functionality from the quinazolinone moiety. We first studied the palladium-catalyzed intramolecular *N*-arylation of quinazolinone **46** under a variety of reaction conditions using different promising ligands (xantphos, BINAP, johnphos), bases (Cs_2CO_3/$NaOBu^t$), and solvents (toluene/1,4-dioxane) at elevated temperature, but unfortunately, all

our attempts met with failure and we always recovered starting material, the compound **46** (Table 1, entries 1-4). The palladium-catalyzed *N*-arylations are known to have some limitations,[12h] and hence, we decided to screen cheap and versatile copper catalysts for the intramolecular cyclization of compound **46** to form **48** using different ligands.[12,13] We noticed that the copper iodide catalyzed

Table 1. Optimization of reaction conditions for the metal-catalyzed intramolecular *N*-arylation of quinazolinones

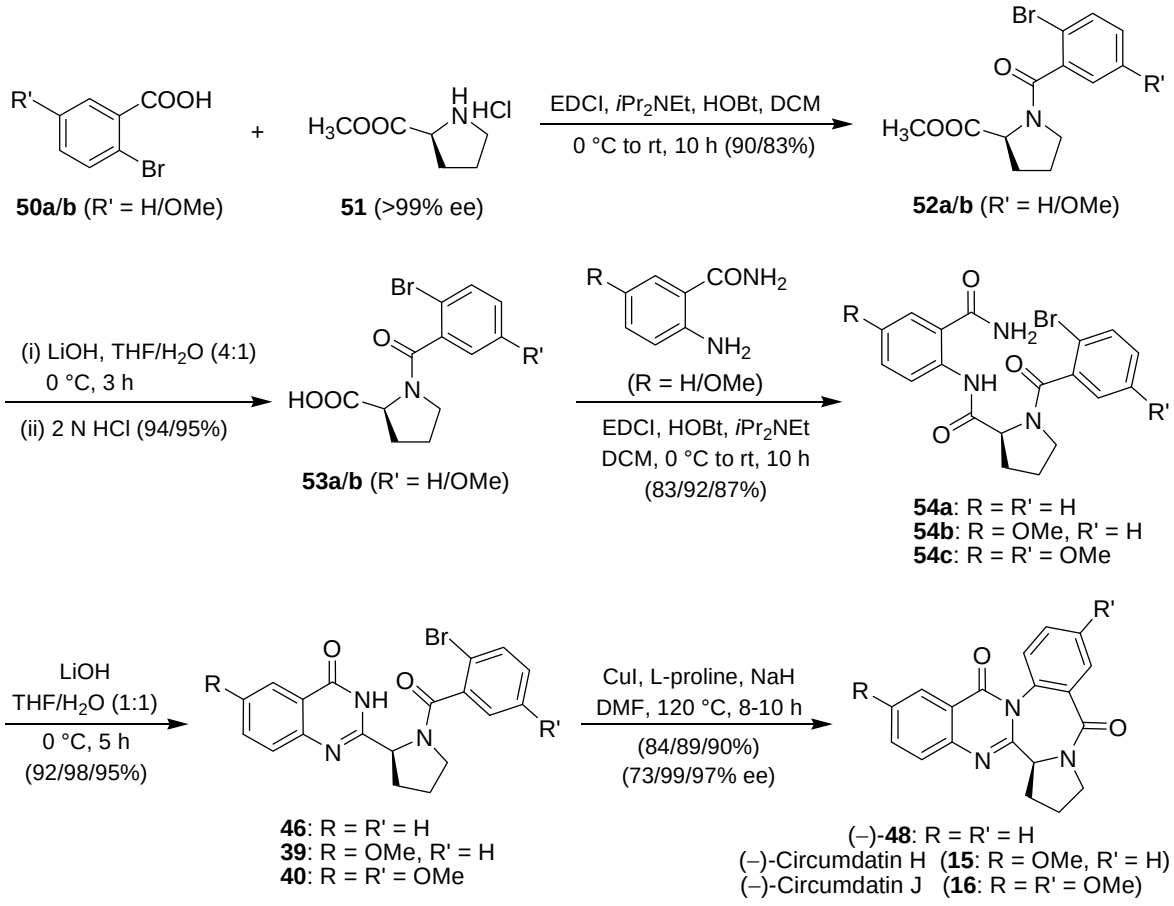
Entry	Reaction conditions[a]	**48**/**49** (% yield)
1	$Pd(OAc)_2$, xantphos, Cs_2CO_3, dioxane, 100 °C, 24 h	**48** (NR)[b]
2	$Pd(OAc)_2$, BINAP, Cs_2CO_3, toluene, 100 °C, 24 h	**48** (NR)
3	$Pd_2(dba)_3$, xantphos, Cs_2CO_3, dioxane, 100 °C, 24 h	**48** (NR)
4	$Pd_2(dba)_3$, johnphos, *t*-BuONa, toluene, 100 °C, 24 h	**48** (NR)
5	CuI, 8-hydroxyquinoline, K_2CO_3, DMSO, 120 °C, 24 h	**48** (11)
6	CuI, 2-oxazolidinone, MeONa, DMSO, 120 °C, 24 h	**48** (30)
7	CuI, L-proline, NaH, DMF, 120 °C, 10 h	**48** (84)
8	CuI, L-proline, NaH, DMF, 120 °C, 10 h	**49** (91)

[a] 20 mol % catalyst; 30 mol % ligand and 2 equiv of base were used in all the entries. [b] NR: No reaction.

intramolecular *N*-arylation of compound **46** using 8-hydroxyquinoline/2-oxazolidinone ligands was feasible, and we could obtain the desired product **48**, but in low yields (Table 1, entries 5 and 6). All our attempts to further improve the yield by changing the molar ratios and reaction conditions were unsuccesful. Finally, we were delighted to learn that the copper-catalyzed regioselective intramolecular cross-coupling between the 3-position nitrogen atom in the polar quinazolinone **46** and an adjacent aryl bromide using L-proline as the ligand and sodium hydride as the base in the solvent DMF at 120 °C exclusively furnished the desired thermodynamically more stable linear product **48** in 84% yield (Table 1, entry 7). The circumdatin J has the methoxy group in the nonquinazolinone aromatic ring, and hence, at this stage we also studied the intramolecular *N*-arylation of compound **47**. Similarly, the reaction of compound **47** under the above-mentioned reaction conditions provided the desired product **49** in 91% yield (Table 1, entry 8). Herein, mechanistically the bond formation between ligand-coordinated copper iodide and quinazolinone nitrogen atom followed by the copper-catalyzed intramolecular cross-coupling with an aryl bromide which generates the new carbon-nitrogen bond to deliver the middle diazepine ring is significant from a synthetic point of view. Thus, the racemic circumdatin frame works **48**/**49** were obtained in

five steps with 57/61% overall yields, and the obtained analytical and spectral data for the compound **48** were in complete agreement with the reported data.[7a]

To circumvent the associated problem of racemization in our above-described Scheme 12 and also to accomplish the synthesis of enantiomerically pure natural products, the (–)-circumdatins **15** and **16**, we reasoned and decided to suitably alter our synthetic sequence. In our second approach, we planned to avoid the use of Boc-protected proline and its subsequent TFA-catalyzed deprotection for the conservation of enantiomeric excess. Hence, we first performed the EDCI induced dehydrative couplings of the 2-bromobenzoic acid (**50a**) and 2-bromo-5-methoxybenzoic acid (**50b**) with the methyl ester of L-proline (**51**) and respectively obtained the corresponding products (–)-**52a**[18]**/b** in 90/83% yields (Scheme 13). The subsequent base-catalyzed ester hydrolysis of (–)-**52a**/**b** followed by the careful acidification with dilute hydrochloric acid provided the corresponding *N*-benzoylprolines (–)-**53a/b** in high yields. Once again, the EDCI induced dehydrative couplings of compound (–)-**53a** with both the anthranilamide and 5-methoxyanthranilamide and that of (–)-**53b** with 5-methoxyanthranilamide, respectively, provided the corresponding triamides (–)-**54a/b/c** in 83-92% yields. The triamides (–)-**54a**/**b**/**c** on base-catalyzed selective intramolecular dehydrative cyclization furnished the essential quinazolinones (–)-**46**/(+)-**39**/(+)-**40** in 92-98% yields. Thus, by altering the reaction sequence we were successful in avoiding the problem of racemization in the preparation of



Scheme 13. Copper-catalysed intramolecular *N*-arylation of quinazolinones: synthesis of circumdatins H and J

our potential precursors **46**/**39**/**40**, required for the synthesis of compounds (–)-**48**/**15**/**16**. Finally, we decided to expose the requisite quinazolinones **46**/**39**/**40** to our previously established efficient copper-catalyzed intramolecular *N*-arylation conditions as described in entries 7 and 8 of Table 1. The copper-catalyzed intramolecular *N*-arylation of compounds **46**/**39**/**40** using L-proline as the ligand and sodium hydride as the base in solvent DMF at 120 °C exclusively furnished the desired final products, the synthetic and natural quinazolinones (–)-**48**/**15**/**16** in 84-90% yields. Thus, the desired products (–)-**48**/**15**/**16** were obtained in five steps with 54/68/59% overall yields,[19] and the obtained analytical and spectral data for the natural products (–)-circumdatins H and J (**15** and **16**) were in complete agreement with the reported data.[3,8.9]

Starting from the (±)-methyl ester of proline (**51**), we similarly synthesized the racemic products **15** and **16** required for the comparison and then checked the enantiomeric purity of our final products (–)-**48**/**15**/**16** by chiral HPLC. The chiral HPLC results revealed that we obtained the circumdatin framework product (–)-**48** with 73% ee and the (–)-circumdatins H/J (**15**/**16**) with 99/97% ee. These results on the conserved enantiomeric purity of (–)-**48**/**15**/**16** clearly indicate that the compounds (–)-**46** and/or (–)-**48** experience ~13% racemization under basic conditions, while the (–)-circumdatins H/J (**15**/**16**) with the suitably placed methoxy group in ring A were not prone for such type of racemization under the set of our reaction conditions as depicted in Scheme 4. We believe the π-conjugation of methoxy group with an imine moiety from the quinazolinone ring is responsible for the preclusion of racemization at an adjacent allylic asymmetric center in the compounds (–)-**15**/**16**. The enantiomerically pure circumdatins H and J are also the likely biosynthetic precursors of circumdatins B and A, respectively.[3b]

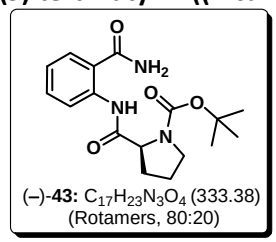
2D.3 Summary

In summary, we have accomplished the concise, highly efficient and convergent total synthesis of (–)-circumdatins H and J. The first copper-catalyzed intramolecular N-arylation of quinazolinone nucleus with the noteworthy generation of a central benzodiazepine unit was the key step in the synthesis of enantiomerically pure (–)-circumdatins H and J. We believe that, our copper-catalyzed intramolecular N-arylation of quinazolinone nucleus strategy will be helpful to synthesize all type of circumdatins, asperlicins, benzomalvins and unnatural quinazolinones fused with benzodiazepine chromophore as well as with five and six membered ring systems.

2D.4 Experimental Section

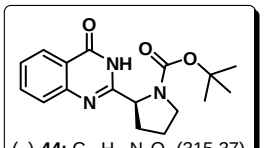
Commercially available EDCI, HOBt, 2-bromobenzoic acid, 2-bromo-5-methoxybenzoic acid, anthranilamide, Boc-L-proline, (*S*)-proline methyl ester hydrochloride, $Pd(OAc)_2$, $Pd_2(dba)_3$, CuI, xantphos, BINAP, johnphos, 8-hydroxyquinoline, 2-oxazolidinone and L-proline were used. 5-Methoxyanthranilamide was prepared from 2-amino-5-methoxybenzoic using known procedure.[20]

(*S*)-*tert*-Butyl 2-((2-carbamoylphenyl)carbamoyl)pyrrolidine-1-carboxylate (43). A solution of EDCI (2.32 g, 12.09 mmol) and HOBt (1.52 g, 11.16 mmol) in CH_2Cl_2 (30 mL) was added dropwise to a stirred suspension of Boc-L-proline (2.00 g, 9.30 mmol), anthranilamide (1.27 g, 9.30 mmol), and DIPEA (2.38 mL, 13.95 mmol) in CH_2Cl_2 (25 mL) at 0 °C. The reaction mixture was stirred at room temperature for 10 h and then quenched with water (25 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 X 50 mL). The combined organic layer was washed with brine and dried over Na_2SO_4. Concentration of the dried organic layer in vacuo followed by the silica gel column chromatographic purification of the resulting residue with petroleum ether–ethyl acetate (3:2) as an eluent gave **43** as a thick liquid (2.69 g, 87%). $[\alpha]^{25}_{D}$ –91.7 (*c* 2.50 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.30 (s, 7H), 1.49 (s, 2H), 1.85–2.07 (m, 2H), 2.07–2.45 (m, 2H), 3.40–3.64 (m, 1H), 3.64–3.80 (m, 1H), 4.29 (dd, *J* = 8 & 4 Hz, 0.80H), 4.34–4.45 (m, 0.20H), 6.81 (br s, 1H), 7.12 (t, *J* = 8 Hz, 1H), 7.49 (br s, 1H), 7.52 (t, *J* = 8 Hz, 1H), 7.68 (d, *J* = 6 Hz, 1H), 8.69 (d, *J* = 6 Hz, 0.20H), 8.79 (d, *J* = 8 Hz, 0.80H), 11.63 (br s, 0.20H), 12.17 (br s, 0.80H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 23.7, 24.3, 28.2, 28.4, 30.5, 31.5, 46.7, 47.1, 62.0, 62.8, 80.1, 80.4, 118.1, 119.0, 120.5, 121.3, 122.7, 127.4, 127.7, 133.1, 133.3, 139.8, 140.2, 154.5, 154.9, 171.2, 172.0, 172.2; ESIMS (*m*/*z*) 334 $[M+H]^+$, 356 $[M+Na]^+$; HRMS (ESI) calcd for $C_{17}H_{24}N_3O_4$ 334.1767, found 334.1758; IR (Nujol) ν_{max} 3348, 3214, 1682, 1667, 1616 cm^{-1}.



(–)-**43:** $C_{17}H_{23}N_3O_4$ (333.38)
(Rotamers, 80:20)

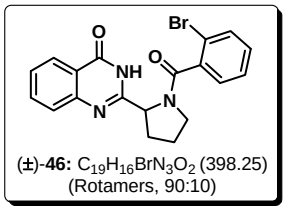
(*S*)-*tert*-Butyl 2-(4-oxo-3,4-dihydroquinazolin-2-yl)pyrrolidine-1-carboxylate (44). A solution of $LiOH.H_2O$ (1.26 g, 30.00 mmol) in H_2O (10 mL) was added to a stirred solution of **43** (2.00 g, 6.00 mmol) in THF (10 mL) at 0 °C. The reaction mixture was further stirred at the same temperature for 5 h and then it was extracted with ethyl acetate (3 X 25 mL). The combined organic layer was washed with brine and dried over Na_2SO_4. Concentration of the dried organic layer in vacuo followed by the silica gel column chromatographic purification of the resulting residue with petroleum ether–ethyl acetate (1:1) as an eluent yielded **44** as a white solid (1.74 g, 92%). Mp 173–175 °C; $[\alpha]^{25}_{D}$ –134.0 (*c* 0.62 $CHCl_3$); ^{1}H NMR (CD_3OD, 200 MHz) δ 1.18 (s, 6H), 1.45 (s, 3H), 1.85–2.20 (m, 3H), 2.25–2.55 (m, 1H), 3.45–3.63 (m, 1H), 3.63–3.78 (m, 1H), 4.55–4.75 (m, 1H), 7.51 (t, *J* = 8 Hz, 1H),



(–)-**44:** $C_{17}H_{21}N_3O_3$ (315.37)
(Rotamers, 67:33)

7.66 (d, *J* = 8 Hz, 1H), 7.82 (dt, *J* = 8 & 2 Hz, 1H), 8.20 (d, *J* = 8 Hz, 1H); ^{13}C NMR (CD_3OD, 50 MHz) δ 24.7, 25.2, 28.4, 28.7, 32.7, 33.9, 48.1, 48.5, 61.4, 61.8, 81.4, 81.5, 122.0, 127.2, 127.8, 135.9, 136.1, 150.1, 155.7, 156.6, 159.3, 160.1, 164.3; ESIMS (*m*/*z*) 316 $[M+H]^+$, 338 $[M+Na]^+$; HRMS (ESI) calcd for $C_{17}H_{22}N_3O_3$ 316.1661, found 316.1665; IR (Nujol) ν_{max} 3173, 3130, 1705, 1669, 1615 cm^{-1}.

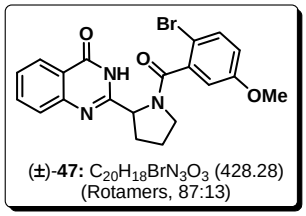
2-(1-(2-Bromobenzoyl)pyrrolidin-2-yl)quinazolin-4(3*H*)-one (46). To a stirred solution of **44** (1.50 g, 4.76 mmol) in CH_2Cl_2 (18 mL) at room temperature was added trifluoroacetic acid (2 mL) and after 4 h time the reaction mixture was neutralized slowly with a saturated solution of $NaHCO_3$. The reaction mixture was extracted with CH_2Cl_2 (3 X 50 mL) and the combined organic layer was washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure and the residue was dried using the vacuum pump. The obtained crude product was re-dissolved in CH_2Cl_2 (25 mL) along with 2-bromobenzoic acid (935 mg, 4.65 mmol) and DIPEA (1.19 mL, 6.98 mmol) and the resultant solution was cooled to 0 °C. A solution of EDCI (1.16 g, 6.05 mmol) and HOBt (753 mg, 5.58 mmol) in CH_2Cl_2 (30 mL) was added dropwise to the above stirred reaction mixture. The reaction mixture was further stirred at room temperature for 10 h and then quenched with water (25 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 X 50 mL). The combined organic layer was washed with brine and dried over Na_2SO_4. Concentration of the dried organic layer in vacuo followed by the silica gel column chromatographic purification of the resulting residue with petroleum ether–ethyl acetate (1:1) as an eluent provided **46** as a white solid (1.61 g, 85%). Mp 125–127 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.90–2.40 (m, 3H), 2.40–2.67 (m, 0.10H), 2.75–2.95 (m, 0.90H), 3.25–3.57 (m, 1.80H), 3.95–4.20 (m, 0.20H), 4.70 (dd, *J* = 7 & 4 Hz, 0.10H), 5.36 (dd, *J* = 7 & 4 Hz, 0.90H), 7.20–7.40 (m, 3H), 7.48 (dt, *J* = 8 & 2 Hz, 1H), 7.61 (d, *J* = 8 Hz, 1H), 7.65–7.80 (m, 2H), 8.16 (d, *J* = 8 Hz, 0.10H), 8.27 (d, *J* = 8 Hz, 0.90H), 10.75–11.40 (br s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 24.8, 28.8, 49.2, 59.7, 118.7, 121.7, 126.5, 126.8, 127.56, 127.57, 127.8, 130.7, 132.8, 134.5, 138.1, 148.6, 154.7, 162.6, 169.8; ESIMS (*m*/*z*) 420 $[M+Na, ^{79}Br]^+$, 422 $[M+Na, ^{81}Br]^+$; HRMS (ESI) calcd for $C_{19}H_{17}BrN_3O_2$ 398.0504, found 398.0490; IR (Nujol) ν_{max} 3169, 3124, 1659, 1631, 1610 cm^{-1}.



(±)-**46:** $C_{19}H_{16}BrN_3O_2$ (398.25)
(Rotamers, 90:10)

Similarly, the compound **47** was obtained using above procedure.

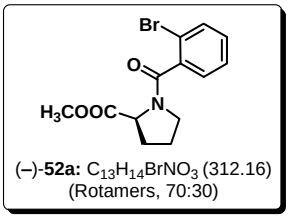
2-(1-(2-Bromo-5-methoxybenzoyl)pyrrolidin-2-yl)quinazolin-4(3*H*)-one (47). White solid (1.69 g, 83%); mp 175–177 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.90–2.40 (m, 3H), 2.43–2.65 (m, 0.13H), 2.72–2.93 (m, 0.87H), 3.14 (br s, 0.39H), 3.30–3.60 (m, 1.74H), 3.76 (s, 2.61H), 3.95–4.15 (m, 0.26H), 4.70 (dd, *J* = 8 & 4 Hz,



(±)-**47:** $C_{20}H_{18}BrN_3O_3$ (428.28)
(Rotamers, 87:13)

0.13H), 5.33 (dd, *J* = 8 & 4 Hz, 0.87H), 6.52 (dd, *J* = 8 & 4 Hz, 0.13H), 6.78–6.92 (m, 1.74H), 7.16 (dd, *J* = 8 & 4 Hz, 0.13H), 7.41–7.54 (m, 2H), 7.56–7.83 (m, 2H), 8.18 (dd, *J* = 8 & 2 Hz, 0.13H), 8.28 (dd, *J* = 8 & 2 Hz, 0.87H), 11.06 (br s, 0.87H), 11.33 (br s, 0.13H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 23.1, 24.8, 29.4, 33.3, 47.1, 49.1, 54.7, 55.5, 59.9, 108.7, 112.8, 116.89, 116.92, 120.5, 121.4, 126.2, 126.4, 126.7, 126.8, 127.5, 133.3, 133.6, 134.5, 134.8, 138.7, 138.9, 148.7, 148.8, 154.9, 158.4, 159.0, 163.0, 163.6, 168.0, 169.2; ESIMS (*m*/*z*) 450 [M+Na, ^{79}Br]$^+$, 452 [M+Na, ^{81}Br]$^+$; IR (Nujol) ν_{max} 3176, 1667, 1643, 1609 cm^{-1}. Anal. Calcd for $C_{20}H_{18}BrN_3O_3$: C, 56.09; H, 4.24; N, 9.81. Found: C, 56.18; H, 3.89; N, 9.77.

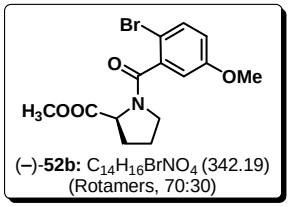
(*S*)-Methyl 1-(2-bromobenzoyl)pyrrolidine-2-carboxylate (52a). A solution of EDCI (2.86 g, 14.92 mmol) and HOBt (1.88 g, 13.93 mmol) in CH_2Cl_2 (30 mL) was added dropwise to a stirred suspension of carboxylic acid **50a** (2.00 g, 9.95 mmol), (*S*)-proline methyl ester hydrochloride (1.97 g, 11.94 mmol) and DIPEA (2.55 mL, 14.92 mmol) in CH_2Cl_2 (25 mL) at room temperature. The reaction mixture was cooled to 0 °C and DIPEA (2.00 mL, 11.94 mmol) was added dropwise. The reaction mixture was stirred at room temperature for 10 h and then quenched with water (25 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 X 50 mL). The combined organic layer was washed with brine and dried over Na_2SO_4. Concentration of the dried organic layer in vacuo followed by the silica gel column chromatographic purification of the resulting residue with petroleum ether–ethyl acetate (3:1) as an eluent furnished compound **52a** as a white solid (2.79 g, 90%). Mp 75–78 °C; $[\alpha]^{25}_D$ –80.4 (*c* 1.60 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.82–2.44 (m, 4H), 3.23–3.47 (m, 1.40H), 3.55 (s, 0.90H), 3.80 (s, 2.10H), 3.75–3.87 (m, 0.60H), 4.17 (dd, *J* = 9 & 4 Hz, 0.30H), 4.71 (dd, *J* = 10 & 4 Hz, 0.70H), 7.15–7.45 (m, 3H), 7.52–7.62 (m, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 22.8, 24.6, 29.5, 31.1, 46.0, 48.3, 52.1, 52.2, 58.3, 60.4, 118.5, 127.3, 127.6, 127.7, 128.2, 130.3, 130.4, 132.6, 132.7, 138.6, 167.4, 167.6, 172.2; ESIMS (*m*/*z*) 312 [M+H, ^{79}Br]$^+$, 314 [M+H, ^{81}Br]$^+$, 334 [M+Na, ^{79}Br]$^+$, 336 [M+Na, ^{81}Br]$^+$; IR (Nujol) ν_{max} 1747, 1645 cm^{-1}.



(–)-**52a:** $C_{13}H_{14}BrNO_3$ (312.16)
(Rotamers, 70:30)

Similarly, the compound **52b** was obtained using above procedure.

(*S*)-Methyl 1-(2-bromo-5-methoxybenzoyl)pyrrolidine-2-carboxylate (52b). Thick liquid (2.83 g, 83%); $[\alpha]^{25}_D$ –61.1 (*c* 1.20 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.85–2.43 (m, 4H), 3.25–3.50 (m, 1.40H), 3.57 (s, 0.90H), 3.76 (s, 0.90H), 3.80 (s, 4.20H), 3.75–3.85 (m, 0.60H), 4.18 (dd, *J* = 8 & 4 Hz, 0.30H), 4.69 (dd, *J* = 10 & 4 Hz, 0.70H), 6.74–6.88 (m, 2H), 7.41 (d, *J* = 8 Hz, 0.30H), 7.44 (d, *J* = 8 Hz, 0.70H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 22.9, 24.7, 29.5, 31.2, 46.1, 48.3, 52.2, 52.3, 55.5, 55.6, 58.3, 60.4, 108.7, 112.7, 113.2, 116.9, 117.0, 133.4, 133.6, 139.0, 139.3, 158.8, 159.0, 167.3, 167.4, 172.3;



(–)-**52b:** $C_{14}H_{16}BrNO_4$ (342.19)
(Rotamers, 70:30)

ESIMS (*m*/*z*) 364 [M+Na, ^{79}Br]$^+$, 366 [M+Na, ^{81}Br]$^+$; HRMS (ESI) calcd for $C_{14}H_{17}BrNO_4$ 342.0341, found 342.0335; IR (Nujol) ν_{max} 1747, 1645 cm^{-1}.

(*S*)-1-(2-Bromobenzoyl)pyrrolidine-2-carboxylic acid (53a). To a solution of **52a** (1.00 g, 3.20 mmol) in THF and water mixture (10 mL, 4:1) was added LiOH.H_2O (673 mg, 16 mmol) at 0 °C and the mixture was stirred for 3 h. The reaction mixture was acidified with 2 N HCl and extracted with Et_2O (3 X 25 mL). The combined organic layer was washed with brine and dried over Na_2SO_4. Concentration of the dried organic layer in vacuo followed by the silica gel column chromatographic purification of the resulting residue with petroleum ether–ethyl acetate (2:3) as an eluent gave acid **53a** as a white solid (898 mg, 94%). Mp 132–134 °C; $[\alpha]^{25}_D$ –80.6 (*c* 0.30 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.85–2.50 (m, 4H), 3.34 (t, *J* = 8 Hz, 1.70H), 3.81 (t, *J* = 8 Hz, 0.30H), 4.17 (dd, *J* = 8 & 4 Hz, 0.15H), 4.79 (dd, *J* = 8 & 4 Hz, 0.85H), 7.15–7.45 (m, 3H), 7.55 (d, *J* = 8 Hz, 0.15H), 7.61 (d, *J* = 8 Hz, 0.85H), 8.19 (br s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 22.8, 24.6, 28.7, 31.1, 46.1, 48.9, 59.1, 60.5, 118.5, 127.7, 127.8, 128.5, 130.6, 130.8, 132.5, 132.8, 137.8, 138.0, 168.0, 169.2, 174.2, 175.9; ESIMS (*m*/*z*) 320 [M+Na, ^{79}Br]$^+$, 322 [M+Na, ^{81}Br]$^+$; IR (Nujol) ν_{max} 2700-2500, 1731 cm^{-1}. Anal. Calcd for $C_{12}H_{12}BrNO_3$: C, 48.34; H, 4.06; N, 4.70. Found: C, 48.61; H, 3.85; N, 4.56.

(–)-**53a:** $C_{12}H_{12}BrNO_3$ (298.13) (Rotamers, 85:15)

Similarly, the compound **53b** was obtained using above procedure.

(*S*)-1-(2-Bromo-5-methoxybenzoyl)pyrrolidine-2-carboxylic acid (53b). White solid (997 mg, 95%); mp 135–137 °C; $[\alpha]^{25}_D$ –90.9 (*c* 0.56 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.82–2.48 (m, 4H), 3.36 (t, *J* = 6 Hz, 1.70H), 3.74 (s, 0.45H), 3.81 (s, 2.55H), 3.81 (t, *J* = 6 Hz, 0.30H), 4.20 (dd, *J* = 8 & 2 Hz, 0.15H), 4.76 (dd, *J* = 8 & 4 Hz, 0.85H), 6.75–6.90 (m, 2H), 7.41 (d, *J* = 10 Hz, 0.15H), 7.46 (d, *J* = 8 Hz, 0.85H), 7.74 (br s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 22.7, 24.6, 28.9, 31.1, 46.0, 48.7, 55.55, 55.64, 58.9, 60.5, 108.6, 112.7, 113.2, 117.1, 117.5, 133.3, 133.6, 138.47, 138.53, 158.9, 159.1, 167.8, 168.6, 174.5, 175.6; ESIMS (*m*/*z*) 350 [M+Na, ^{79}Br]$^+$, 352 [M+Na, ^{81}Br]$^+$; HRMS (ESI) calcd for $C_{13}H_{15}BrNO_4$ 328.0184, found 328.0179; IR (Nujol) ν_{max} 2700-2500, 1732, 1613, 1603 cm^{-1}.

(–)-**53b:** $C_{13}H_{14}BrNO_4$ (328.16) (Rotamers, 85:15)

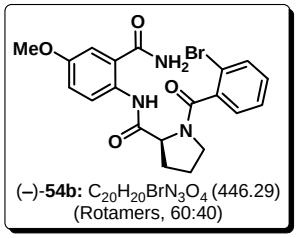
(*S*)-1-(2-Bromobenzoyl)-*N*-(2-carbamoylphenyl)pyrrolidine-2-carboxamide (54a). A solution of EDCI (335 mg, 1.75 mmol) and HOBt (216 mg, 1.61 mmol) in CH_2Cl_2 (12 mL) was added dropwise to a stirred suspension of acid **53a** (400 mg, 1.34 mmol), anthranilamide (183 mg, 1.34 mmol) and DIPEA (0.34 mL, 2.01 mmol) in CH_2Cl_2 (10 mL) at 0 °C. The reaction mixture was stirred at room temperature for 10 h and then quenched with water (25 mL). The organic

(–)-**54a:** $C_{19}H_{18}BrN_3O_3$ (416.27) (Rotamers,55:45)

layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 X 20 mL). The combined organic layer was washed with brine and dried over Na_2SO_4. Concentration of the dried organic layer in vacuo followed by the silica gel column chromatographic purification of the resulting residue with petroleum ether–ethyl acetate (3:7) as an eluent yielded product **54a** as a white solid (463 mg, 83%). Mp 123–125 °C; $[\alpha]^{25}_D$ –134.9 (*c* 0.68 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.80–2.48 (m, 4H), 3.27–3.58 (m, 1.10H), 3.80–4.05 (m, 0.90H), 4.22 (dd, *J* = 8 & 4 Hz, 0.45H), 4.80 (dd, *J* = 7 & 6 Hz, 0.55H), 5.87 (br s, 0.45H), 6.65–6.95 (br s, 0.55H), 6.95–7.85 (m, 8H), 8.60 (d, *J* = 8 Hz, 1H), 11.73 (s, 0.55H), 12.43 (s, 0.45H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 22.8, 24.7, 30.2, 31.9, 46.5, 49.0, 61.8, 64.1, 118.0, 118.4, 118.5, 119.0, 120.4, 121.2, 123.0, 123.3, 127.6, 127.8, 127.9, 128.3, 130.5, 130.6, 132.5, 132.6, 132.9, 133.4, 138.2, 138.5, 139.4, 139.7, 168.8, 168.9, 170.2, 170.3, 171.3, 172.2; ESIMS (*m*/*z*) 438 [M+Na, ^{79}Br]$^+$, 440 [M+Na, ^{81}Br]$^+$; HRMS (ESI) calcd for $C_{19}H_{19}BrN_3O_3$ 416.0610, found 416.0604; IR (Nujol) ν_{max} 3341, 3217, 1660, 1631 cm^{-1}.

Similarly, the compounds **54b** and **54c** were obtained using above procedure.

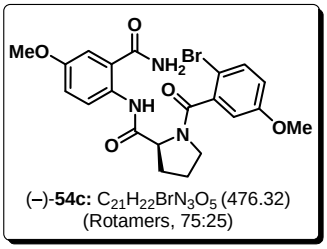
(*S*)-1-(2-Bromobenzoyl)-*N*-(2-carbamoyl-4-methoxyphenyl)pyrrolidine-2-carboxamide (54b). White



(–)-**54b:** $C_{20}H_{20}BrN_3O_4$ (446.29)
(Rotamers, 60:40)

solid (551 mg, 92%); mp 82–85 °C; $[\alpha]^{25}_D$ –136.8 (*c* 0.64 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.85–2.45 (m, 4H), 3.25–3.55 (m, 1.20H), 3.74 (s, 1.80H), 3.78 (s, 1.20H), 3.83–3.92 (m, 0.80H), 4.20 (dd, *J* = 6 & 4 Hz, 0.40H), 4.76 (dd, *J* = 8 & 6 Hz, 0.60H), 5.88 (br s, 0.40H), 6.66–7.75 (m, 7.60H), 8.45 (d, *J* = 8 Hz, 0.60H), 8.50 (d, *J* = 8 Hz, 0.40H), 11.39 (s, 0.60H), 11.99 (s, 0.40H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 22.8, 24.7, 30.1, 31.8, 46.5, 49.0, 55.5, 55.7, 61.7, 64.0, 112.6, 113.0, 118.4, 118.5, 119.6, 120.7, 121.9, 122.8, 127.6, 127.8, 127.9, 128.2, 130.5, 130.6, 132.4, 132.5, 132.6, 132.9, 138.2, 138.4, 154.9, 155.0, 168.88, 168.90, 169.6, 169.8, 171.0, 171.7; ESIMS (*m*/*z*) 446 [M+H, ^{79}Br]$^+$, 468 [M+Na, ^{79}Br]$^+$, 470 [M+Na, ^{81}Br]$^+$; IR (Nujol) ν_{max} 3346, 3207, 1662, 1625, 1592 cm^{-1}. Anal. Calcd for $C_{20}H_{20}BrN_3O_4$: C, 53.82; H, 4.52; N, 9.42. Found: C, 53.96; H, 4.04; N, 9.12.

(*S*)-1-(2-Bromo-5-methoxybenzoyl)-*N*-(2-carbamoyl-4-methoxyphenyl)pyrrolidine-2-carboxamide

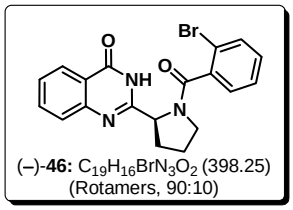


(–)-**54c:** $C_{21}H_{22}BrN_3O_5$ (476.32)
(Rotamers, 75:25)

(54c). White solid (557 mg, 87%); mp 123–125 °C; $[\alpha]^{25}_D$ –92.5 (*c* 0.46 MeOH); ^{1}H NMR (DMSO-d_6, 200 MHz) δ 1.75–2.40 (m, 4H), 3.13–3.50 (m, 2H), 3.76 (s, 0.75H), 3.78 (s, 3H), 3.80 (s, 2.25H), 3.92–4.04 (m, 0.25H), 4.44 (dd, *J* = 8 & 4 Hz, 0.75H), 6.66–8.50 (m, 6+2H), 11.77 (s, 0.25H), 11.86 (s, 0.75H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 22.6, 24.4, 30.0, 31.5, 46.3, 48.7, 55.2, 55.3, 55.6, 55.8, 61.5, 63.1, 108.0, 112.7, 112.8, 113.2, 113.5, 113.6, 117.2, 117.3, 117.9, 118.1, 119.8, 120.8, 121.1, 121.5, 132.2, 132.8, 133.4, 133.5, 139.2, 139.4, 154.4, 154.6, 158.5, 158.9, 166.7, 167.4, 169.4, 169.6, 170.5, 170.6; ESIMS (*m*/*z*) 476 [M+H, ^{79}Br]$^+$,

478 [M+H, $^{81}Br]^+$, 498 [M+Na, $^{79}Br]^+$, 500 [M+Na, $^{81}Br]^+$; HRMS (ESI) calcd for $C_{21}H_{23}BrN_3O_5$ 476.0821, found 476.0814; IR (Nujol) ν_{max} 3359, 3196, 1652, 1626 cm^{-1}.

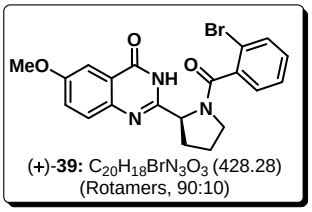
(*S*)-2-(1-(2-Bromobenzoyl)pyrrolidin-2-yl)quinazolin-4(3*H*)-one (46). A solution of $LiOH.H_2O$ (100 g, 2.40 mmol) in H_2O (2 mL) was added to a stirred solution of **54a** (200 mg, 0.48 mmol) in THF (3 mL) at 0 °C. The reaction mixture was further stirred at the same temperature for 5 h and then it was extracted with ethyl acetate (3 X 20 mL). The combined organic layer was washed with brine and dried over Na_2SO_4. Concentration of the dried organic layer in vacuo followed by the silica gel column chromatographic purification of the resulting residue with petroleum ether–ethyl acetate (4:6) as an eluent provided acid **46** as a white solid (176 mg, 92%). Mp 126 °C; $[\alpha]^{25}_D$ –33.9 (*c* 0.60 $CHCl_3$).



(–)-**46:** $C_{19}H_{16}BrN_3O_2$ (398.25)
(Rotamers, 90:10)

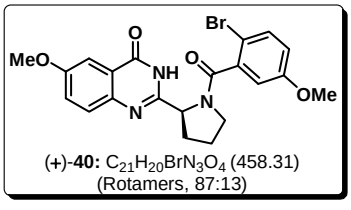
Similarly, the compounds **39** and **40** were obtained using above procedure.

(*S*)-2-(1-(2-Bromobenzoyl)pyrrolidin-2-yl)-6-methoxyquinazolin-4(3*H*)-one (39). White solid (201 mg, 98%); mp 206–208 °C; $[\alpha]^{25}_D$ + 9.41 (*c* 0.80 $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz) δ 1.90–2.40 (m, 3H), 2.40–2.65 (m, 0.10H), 2.75–2.95 (m , 0.90H), 3.25–3.55 (m, 1.80H), 3.91 (s, 3H), 3.95–4.09 (m, 0.20H), 4.67 (dd, *J* = 8 & 2 Hz, 0.10H), 5.35 (dd, *J* = 8 & 4 Hz, 0.90H), 6.87–7.70 (m, 7H), 11.07 (br s, 0.90H), 11.32 (br s, 0.10H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 23.0, 24.7, 28.7, 33.5, 47.0, 49.1, 55.71, 55.74, 59.3, 59.4, 105.8, 105.9, 118.7, 121.3, 122.4, 124.5, 124.9, 127.1, 127.6, 127.7, 127.8, 129.1, 130.1, 130.6, 132.5, 132.8, 138.1, 138.3, 143.2, 143.4, 152.4, 158.3, 162.4, 163.3, 168.2, 169.6; ESIMS (*m*/*z*) 450 [M+Na, $^{79}Br]^+$, 452 [M+Na, $^{81}Br]^+$; HRMS (ESI) calcd for $C_{20}H_{19}BrN_3O_3$ 428.0610, found 428.0604; IR (Nujol) ν_{max} 3176, 1665, 1645, 1621 cm^{-1}.



(+)-**39:** $C_{20}H_{18}BrN_3O_3$ (428.28)
(Rotamers, 90:10)

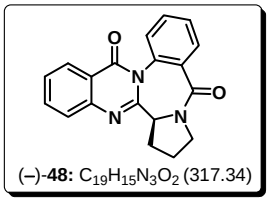
(*S*)-2-(1-(2-Bromo-5-methoxybenzoyl)pyrrolidin-2-yl)-6-methoxyquinazolin-4(3*H*)-one (40). White solid (209 mg, 95%); mp 115–118 °C; $[\alpha]^{25}_D$ +27.0 (*c* 0.40 $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz) δ 1.90–2.38 (m, 3H), 2.40–2.63 (m, 0.13H), 2.75–2.95 (m, 0.87H), 3.17 (br s, 0.39H), 3.27–3.55 (m, 1.74H), 3.77 (s, 2.61H), 3.89 (s, 0.39H), 3.91 (s, 2.61H), 3.92–4.08 (m, 0.26H), 4.67 (dd, *J* = 8 & 4 Hz, 0.13H), 5.33 (dd, *J* = 8 & 4 Hz, 0.87H), 6.50 (dd, *J* = 9 & 4 Hz, 0.13H), 6.79–6.91 (m, 1.74H), 7.10 (d, *J* = 10 Hz, 0.13H), 7.30–7.40 (m, 1H), 7.42–7.68 (m, 3H), 11.05 (br s, 0.87H), 11.37 (br s, 0.13H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 23.1, 24.7, 29.0, 33.4, 46.9, 49.0, 54.8, 55.6, 55.7, 59.5, 61.2, 105.6, 105.8, 108.6, 108.7, 112.0, 112.7, 117.0, 117.3, 121.3, 122.3, 124.6, 124.9, 129.0, 133.3, 133.6, 138.8, 138.9, 143.2, 143.5, 152.3, 152.4, 158.3, 158.4, 159.1, 162.5, 163.3, 167.9, 169.3;



(+)-**40:** $C_{21}H_{20}BrN_3O_4$ (458.31)
(Rotamers, 87:13)

ESIMS (*m*/*z*) 480 [M+Na, $^{79}Br]^+$, 482 [M+Na, $^{81}Br]^+$; IR (Nujol) ν_{max} 3176, 1660, 1652, 1622 cm^{-1}. Anal. Calcd for $C_{21}H_{20}BrN_3O_4$: C, 55.03; H, 4.40; N, 9.17. Found: C, 55.11; H, 4.06; N, 9.12.

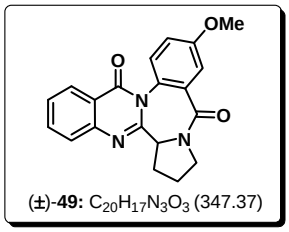
(*S*)-5b,6,7,8-Tetrahydrobenzo[6,7]pyrrolo[2',1':3,4][1,4]diazepino[2,1-*b*]quinazoline-10,16-dione


(–)-**48:** $C_{19}H_{15}N_3O_2$ (317.34)

(48). Pre-dried a screwcapped test tube was charged with CuI (4.70 mg, 0.20 mmol), L-proline (4.30 mg, 0.30 mmol), (–)-**46** (50 mg, 1.00 mmol), NaH (6.00 mg, 2.00 mmol) and DMF (2 mL). The reaction mixture was blanketed with argon atmosphere and the tube was sealed with a Teflon valve. The reaction vessel was immersed in the preheated oil bath and stirred at 120 °C for 10 h. The reaction vessel was removed from the oil bath and allowed to reach room temperature. The reaction mixture was diluted with ethyl acetate and washed with H_2O (2 X 10 mL), brine and dried over Na_2SO_4. The solvent was removed under reduced pressure and the silica gel column chromatographic purification of the resulting residue with petroleum ether–ethyl acetate (4:6) as an eluent furnished corresponding desired product (–)-**48** as a white solid (33 mg, 84%). Mp 232–234 °C; $[\alpha]^{25}_D$ –77.2 (*c* 0.30 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.00–2.50 (m, 3H), 3.08–3.27 (m, 1H), 3.52–3.70 (m, 1H), 3.73–3.88 (m, 1H), 4.57 (d, *J* = 6 Hz, 1H), 7.46–7.63 (m, 4H), 7.68–7.86 (m, 2H), 8.01 (dd, *J* = 8 & 2 Hz, 1H), 8.32 (dd, *J* = 8 & 2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 23.7, 27.0, 46.5, 58.9, 121.5, 127.4, 127.55, 127.59, 128.3, 128.7, 129.9, 130.7, 132.4, 133.2, 134.8, 146.1, 153.6, 161.7, 164.5; ESIMS (*m*/*z*) 318 $[M+H]^+$, 340 $[M+Na]^+$; IR (Nujol) ν_{max} 1690, 1644, 1616 cm^{-1}.

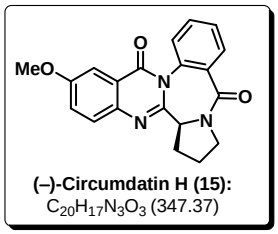
Similarly, from (±)-**46** and (±)-**47**, the compounds (±)-**48** and (±)-**49** were obtained using above procedure respectively. The compounds (–)-**15** and (–)-**16** were also obtained using above procedure but in 8 h reaction time.

12-Methoxy-5b,6,7,8-tetrahydrobenzo[6,7]pyrrolo[2',1':3,4][1,4]diazepino[2,1-*b*]quinazoline-


(±)-**49:** $C_{20}H_{17}N_3O_3$ (347.37)

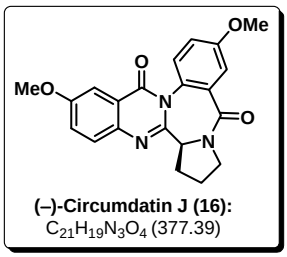
10,16-dione (49). White solid (40 mg, 91%); mp 258–260 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.00–2.50 (m, 3H), 3.09–3.26 (m, 1H), 3.52–3.70 (m, 1H), 3.72–3.87 (m, 1H), 3.91 (s, 3H), 4.59 (dd, *J* = 8 & 2 Hz, 1H), 7.12 (dd, *J* = 6 & 4 Hz, 1H), 7.43–7.58 (m, 3H), 7.67–7.85 (m, 2H), 8.32 (dd, *J* = 8 & 2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 23.6, 27.0, 46.6, 55.8, 58.9, 112.9, 117.9, 121.5, 126.0, 127.4, 127.5, 127.6, 129.6, 133.4, 134.6, 146.1, 153.8, 159.2, 161.9, 164.4; ESIMS (*m*/*z*) 348 $[M+H]^+$, 370 $[M+Na]^+$; IR (Nujol) ν_{max} 1683, 1634, 1607 cm^{-1}. Anal. Calcd for $C_{20}H_{18}N_3O_3$: C, 69.15; H, 4.93; N, 12.10. Found: C, 69.07; H, 4.62; N, 11.89.

(*S*)-2-Methoxy-5b,6,7,8-tetrahydrobenzo[6,7]pyrrolo[2',1':3,4][1,4]diazepino[2,1-*b*]quinazoline-10,16-dione (15). White solid (39 mg, 89%); mp 204–206 °C; $[\alpha]^{25}_{D}$ –57.2 (*c* 0.36 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.97–2.47 (m, 3H), 3.07–3.25 (m, 1H), 3.52–3.70 (m, 1H), 3.70–3.88 (m, 1H), 3.93 (s, 3H), 4.55 (dd, *J* = 8 & 2 Hz, 1H), 7.38 (dd, *J* = 9 & 4 Hz, 1H), 7.47–7.72 (m, 5H), 7.95–8.04 (m, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 23.7, 27.0, 46.5, 55.9, 58.8, 106.9, 122.3, 124.9, 128.4, 128.6, 129.2, 129.9, 130.7, 132.4, 133.4, 140.6, 151.5, 159.0, 161.7, 164.5; ESIMS (*m*/*z*) 348 $[M+H]^+$, 370 $[M+Na]^+$; IR (Nujol) ν_{max} 1688, 1646, 1618 cm^{-1}.



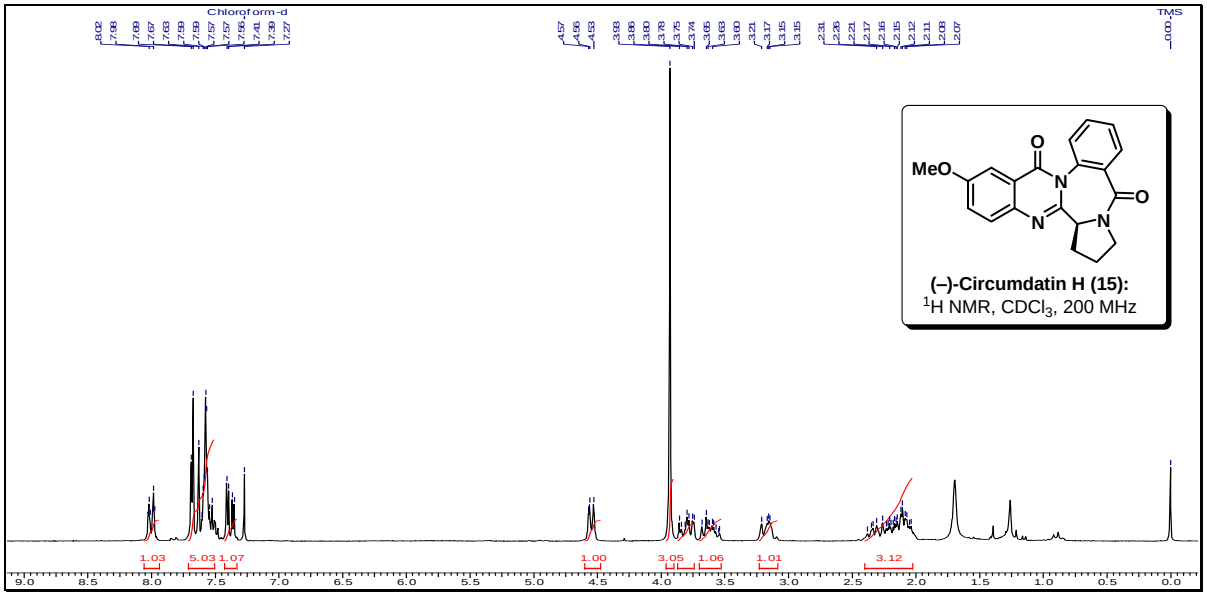
(–)-Circumdatin H (15):
$C_{20}H_{17}N_3O_3$ (347.37)

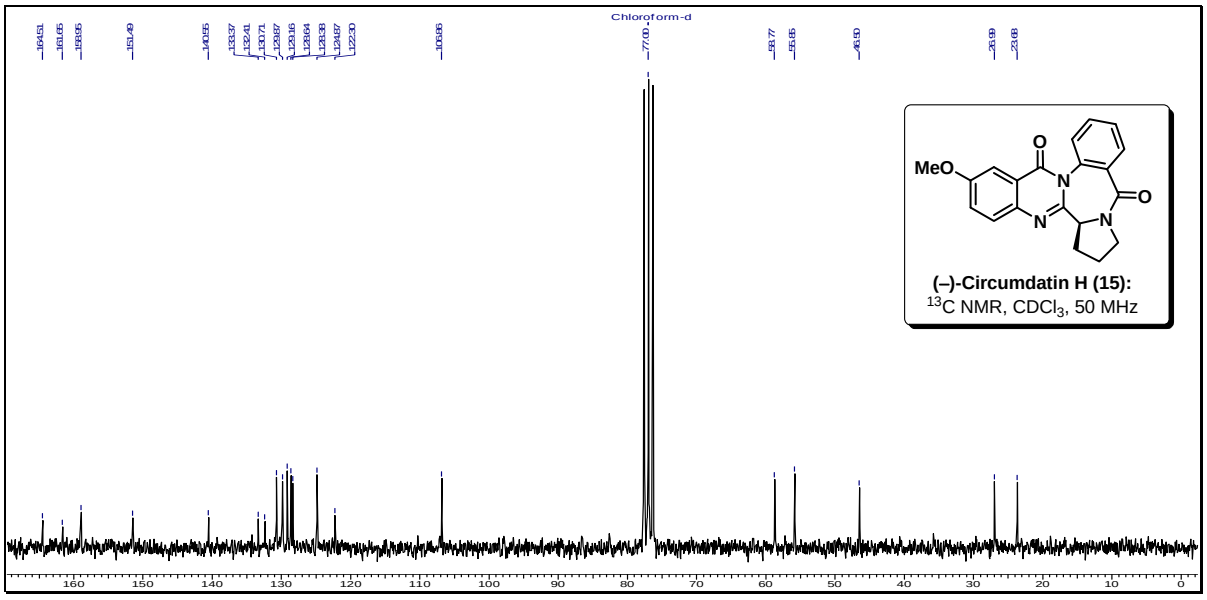
(*S*)-2,12-Dimethoxy-5b,6,7,8-tetrahydrobenzo[6,7]pyrrolo[2',1':3,4][1,4]diazepino[2,1-*b*]quinazoline-10,16-dione (16). White solid (43 mg, 90%); mp 208–210 °C; $[\alpha]^{25}_{D}$ –50.0 (*c* 0.80 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.00–2.20 (m, 2H), 2.20–2.38 (m, 1H), 3.17 (dd, *J* = 12 & 8 Hz, 1H), 3.55–3.66 (m, 1H), 3.73–3.82 (m, 1H), 3.91 (s, 3H), 3.92 (s, 3H), 4.56 (d, *J* = 8 Hz, 1H), 7.11 (dd, *J* = 8 & 4 Hz, 1H), 7.37 (dd, *J* = 6 & 4 Hz, 1H), 7.46 (d, *J* = 4 Hz, 1H), 7.48 (d, *J* = 12 Hz, 1H), 7.64 (d, *J* = 8 Hz, 1H), 7.67 (d, *J* = 4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 23.7, 27.0, 46.6, 55.8, 55.9, 58.8, 106.8, 112.8, 117.9, 122.3, 124.8, 126.2, 129.1, 129.7, 133.5, 140.6, 151.6, 158.9, 159.1, 161.8, 164.4; ESIMS (*m*/*z*) 378 $[M+H]^+$, 400 $[M+Na]^+$; IR (Nujol) ν_{max} 1683, 1646, 1616 cm^{-1}.

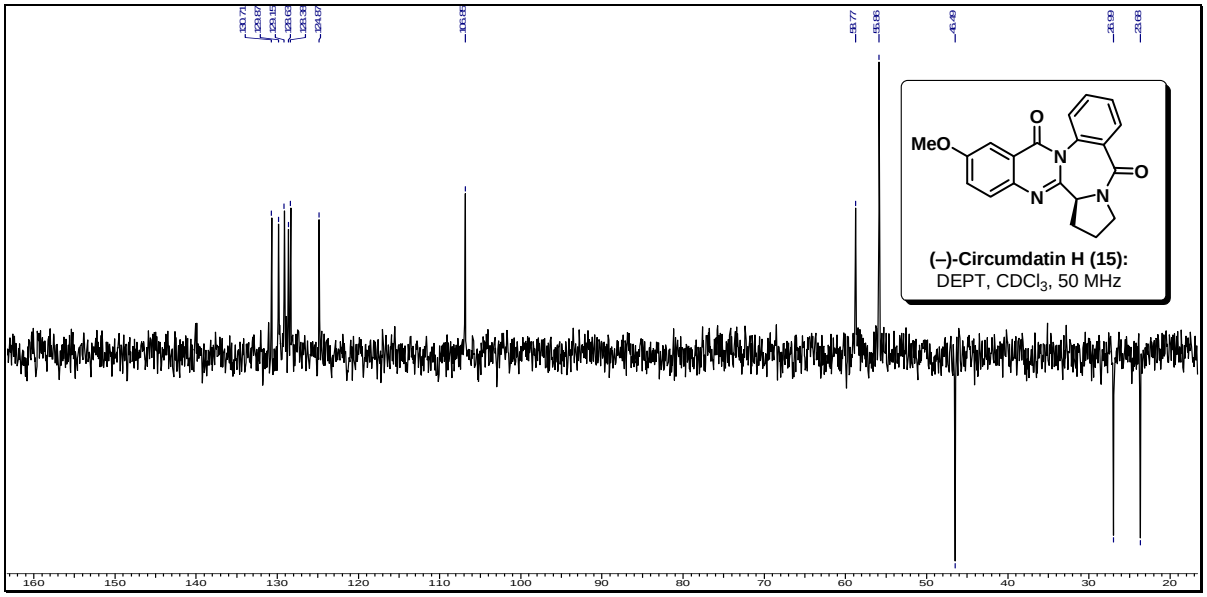


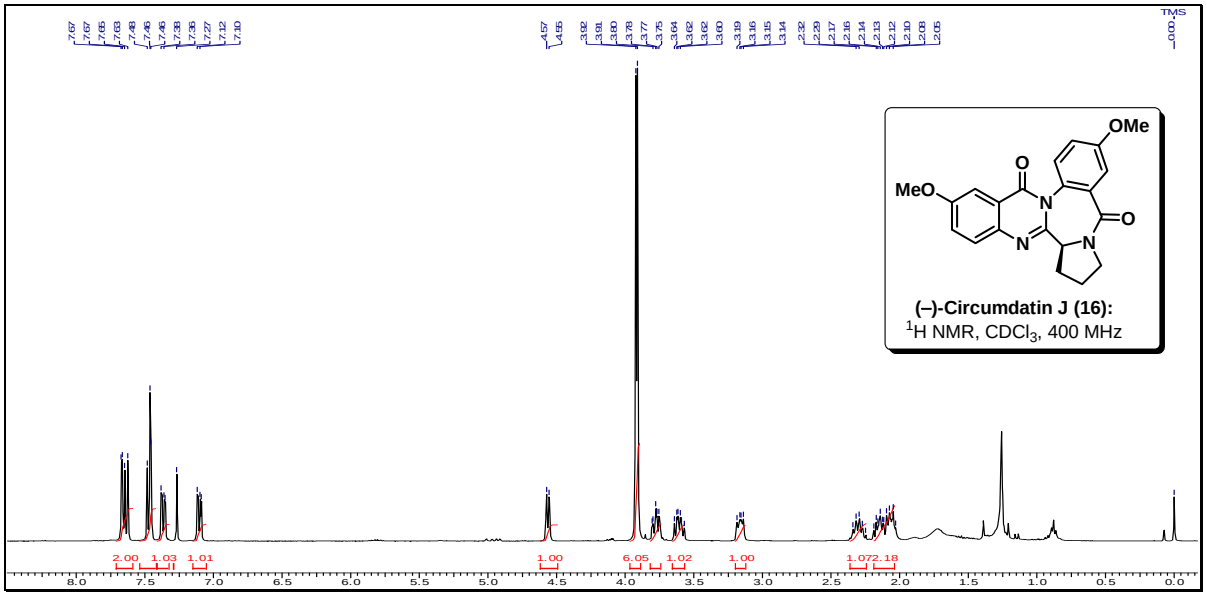
(–)-Circumdatin J (16):
$C_{21}H_{19}N_3O_4$ (377.39)

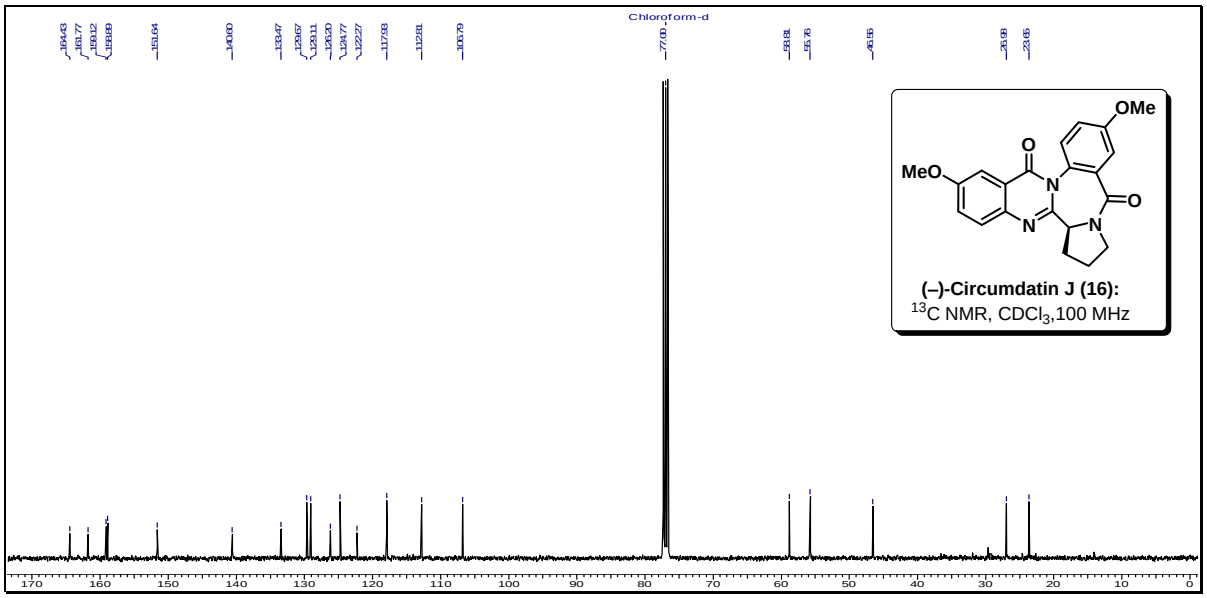
2D.5 Selected Spectra

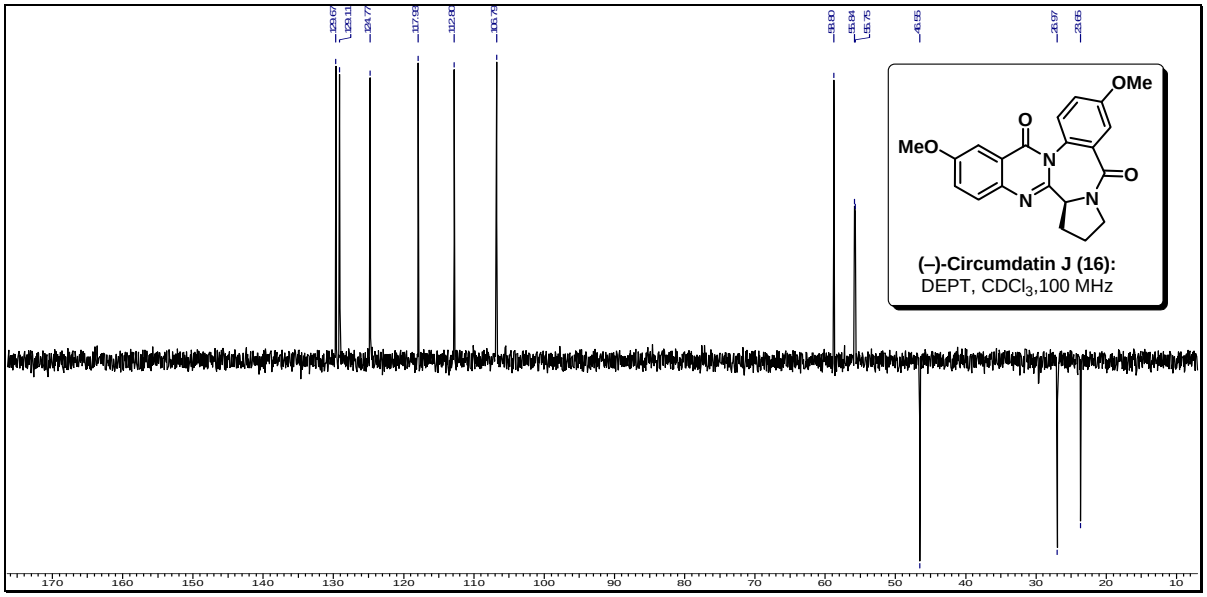

Chloroform-d
TMS
MeO
O
N
O
N
N
(–)-Circumdatin H (15):
^{1}H NMR, CDCl$_3$, 200 MHz


Chloroform-d
MeO
O
N
O
N
N
(–)-Circumdatin H (15):
^{13}C NMR, CDCl$_3$, 50 MHz

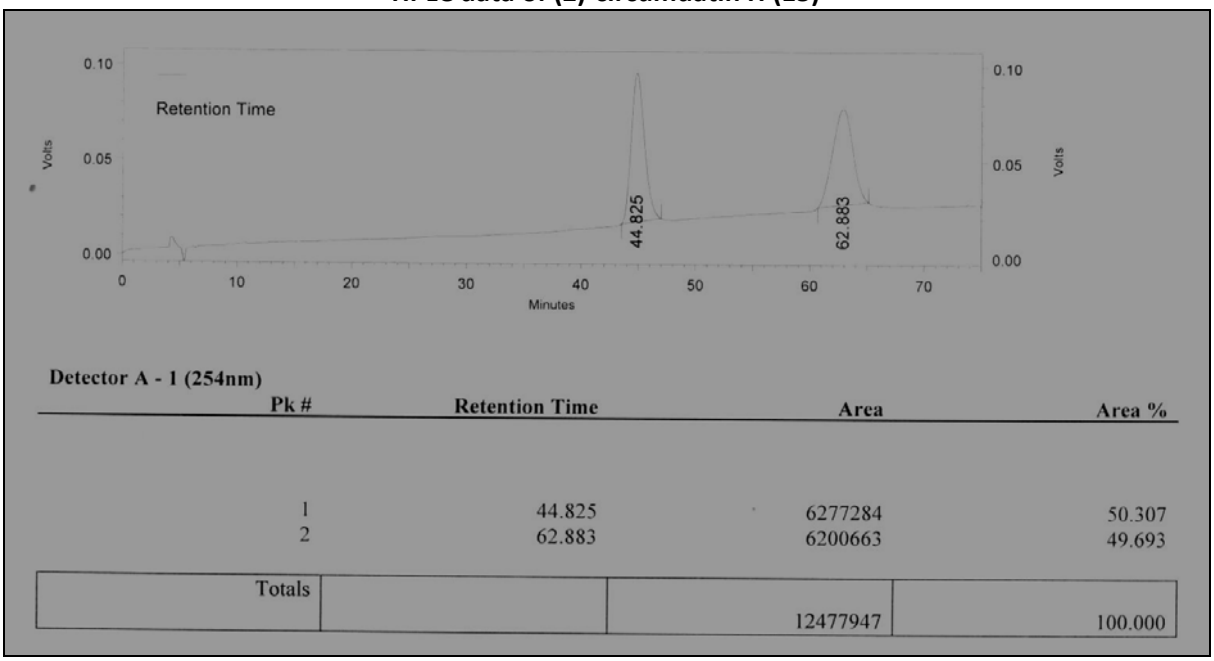

MeO
O
N
O
N
N
(–)-Circumdatin H (15):
DEPT, CDCl$_3$, 50 MHz


TMS
OMe
MeO
O
N
O
N
N
(–)-Circumdatin J (16):
1H NMR, CDCl3, 400 MHz


Chloroform-d
OMe
MeO
O
N
O
N
N
(–)-Circumdatin J (16):
13C NMR, CDCl3,100 MHz


OMe
MeO
O
N
O
N
N
(–)-Circumdatin J (16):
DEPT, CDCl3,100 MHz

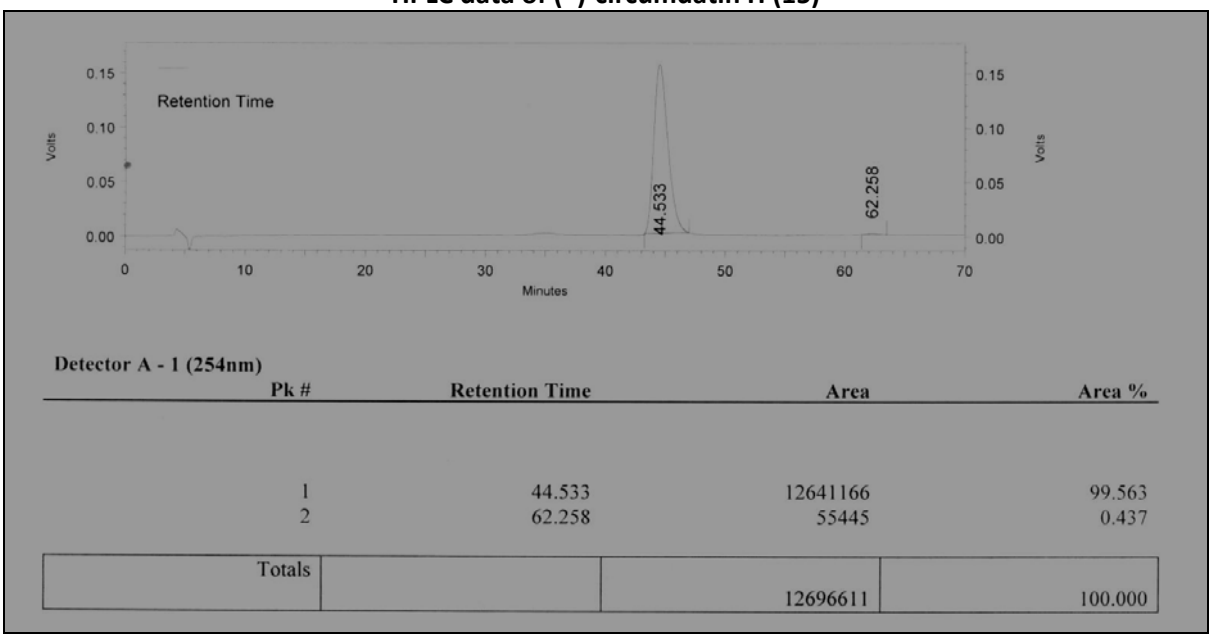
HPLC data of (±)-circumdatin H (15)



Detector A - 1 (254nm)

Pk #	Retention Time	Area	Area %
1	44.825	6277284	50.307
2	62.883	6200663	49.693
Totals		12477947	100.000

HPLC data of (–)-circumdatin H (15)

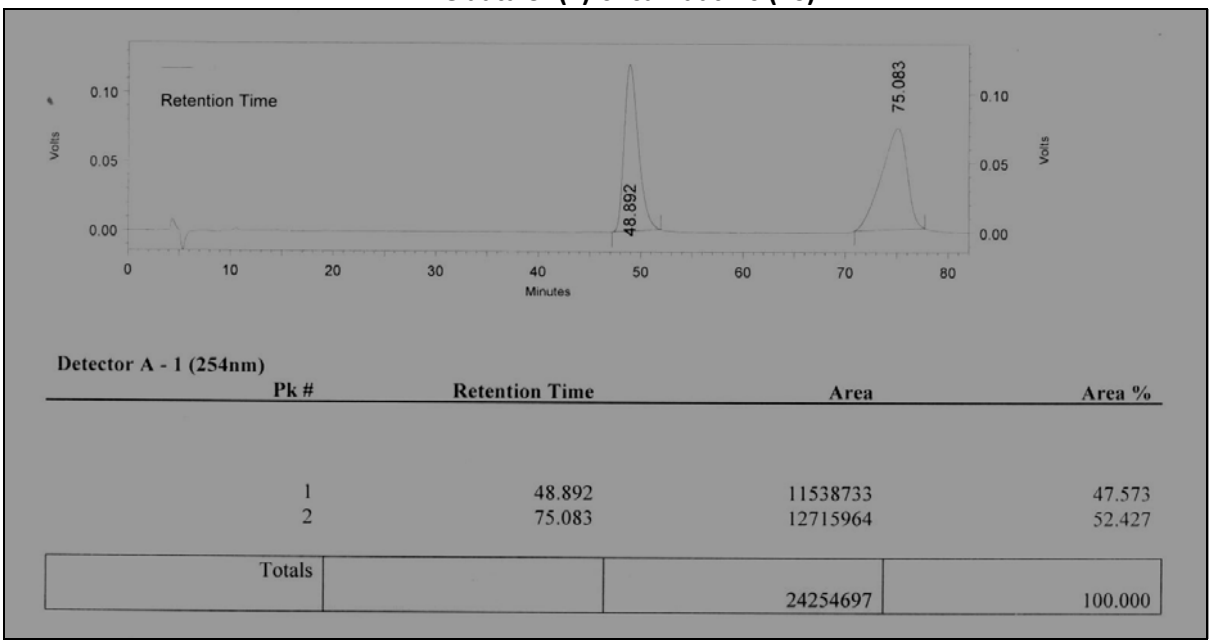


Detector A - 1 (254nm)

Pk #	Retention Time	Area	Area %
1	44.533	12641166	99.563
2	62.258	55445	0.437
Totals		12696611	100.000

Column: Kromasil 5-AmyCoat (250 x 4.6 mm)
Mobile Phase: IPA:PE:DEA (15:85:0.25)
Wavelength: 254 nm
Flow Rate: 0.7 mL/min (39 kgf)
Sample Conc.: 1 mg/2 mL

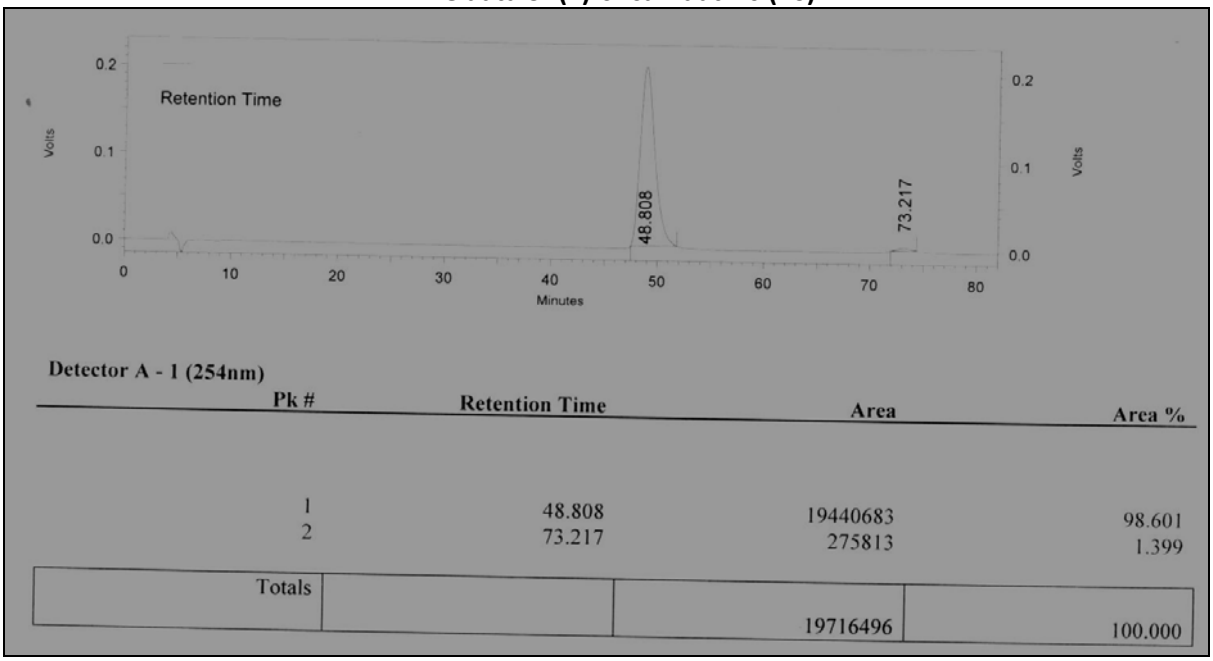
HPLC data of (±)-circumdatin J (16)



Detector A - 1 (254nm)

Pk #	Retention Time	Area	Area %
1	48.892	11538733	47.573
2	75.083	12715964	52.427
Totals		24254697	100.000

HPLC data of (–)-circumdatin J (16)



Detector A - 1 (254nm)

Pk #	Retention Time	Area	Area %
1	48.808	19440683	98.601
2	73.217	275813	1.399
Totals		19716496	100.000

Column: Kromasil 5-AmyCoat (250 x 4.6 mm)
Mobile Phase: IPA:PE:DEA (15:85:0.25)
Wavelength: 254 nm
Flow Rate: 0.7 mL/min (39 kgf)
Sample Conc.: 1 mg/2 mL

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Overall Conclusion and Perspective

Present dissertation describes our concise and efficient approaches for the synthesis of various natural and unnatural quinazolines and quinazolinones, implementing novel synthetic routes along with the concise account of the quinazolinone literature during the last five years with some newly isolated alkaloids. Various synthetic methodologies to the quinazolinone motif and related derivatives reported by different research groups have been presented. Different synthetic approaches to biologically active natural/synthetic quinazoline and quinazolinone alkaloids reported by various research groups have also been described. Quinazolines and quinazolinones are the fascinating structure and their remarkable bioactivity has incited a lot of activity in the synthetic community towards their total synthesis. Some synthetic quinazolinones, such as raltitrexed, ispinesib and tempostatin have been on the market or are currently in clinical trials for cancer treatment.

We have demonstrated a simple, efficient and general approach to the various quinazolinone scaffolds in one step for the first time by employing HMDS/I_2 for the intramolecular dehydrative cyclization of diamides. Synthesis of the naturally occurring quinazolinones, the sclerotigenin, (–)-circumdatin F and (–)-fumiquinazolin F using the HMDS/I_2 protocol developed by us as a key step has been described.

Batracylin is promising anticancer agent and it also acts as a topoisomerase II inhibitor but because of low water solubility and some toxic effect it could not reach further clinical trials. We have demonstrated the simple, efficient new approach which provides a variety of analogs of the batracylin. In this we have systematically studied the nucleophilic reactions of several cyclic anhydrides with tert-butyl 2-aminobenzylcarbamate and provided a simple, efficient and new practical route to the synthesis of diverse range of kinetically controlled angular and thermodynamically controlled linear tricyclic and tetracyclic 1,3-diaza-heterocycles in high yields. The serendipitously witnessed intramolecular shuffling of the methyl group is also noteworthy and important from the basic chemistry points of view. We feel that our present simple and efficient general approach to these 1,3-diaza-heterocycles will be useful to design the focused libraries of analogs and congeners of batracylin for SAR-studies. Our studies on synthesis of (–)-vasicine have been also described and it clearly indicates that for the synthesis of (–)-vasicine, we need an intellectual solution to handle the multifunctional starting materials.

We have also presented a first total synthesis of proposed structure of auranthine starting from Cbz-protected glutamic anhydride and Boc-protected o-aminobenzyl amine. An intramolecular aza-Wittig reaction involving a lactam carbonyl group that delivered the diazepine core unit and the late-stage chemoselective oxidation strategy were the key points in accessing this intriguing structure of

auranthine. Though the reported spectral data for aurathine did not match that of our synthetic auranthine, the structure of synthetic auranthine was unambiguously confirmed by using single X-ray crystallographic analysis. These results clearly indicate that a revision of the structure of natural auranthine is necessary.

Another significant contribution in the synthesis of quinazolinone alkaloids resulted from copper-catalyzed intramolecular N-arylation of quinazolinone. We have accomplished a highly efficient and convergent total synthesis of (–)-circumdatins H and J by demonstrating the first copper-catalyzed intramolecular N-arylation of quinazolinone nucleus with a noteworthy generation of a central benzodiazepine unit. We believed that, our copper-catalyzed intramolecular N-arylation of quinazolinone nucleus strategy will be helpful to synthesize all types of circumdatins, asperlicins, benzomalvins and unnatural quinazolinones fused with benzodiazepine chromophore as well as with five and six membered ring systems.

In short, we have accomplished a concise and efficient total synthesis of quinazolinone alkaloids sclerotigenin, (-)-circumdatin F, (-)-fumiquinazolin F, auranthine and circumdatins H & J during using different routes and strategies.

All these studies provided us a nice opportunity for learning a lot of new basic and applied chemistry not just from our work but also from the vast literature in this field. We also feel that the approaches which we have developed are quite general and biogenetic in nature and would be useful in designing several important complex natural products and natural product hybrids for structure activity relationship studies. A look at the recent literature also revealed that the histogram of the quinazolinone chemistry is in escalating slope and increasing medicinal and pharmaceutical demands for natural and designed quinazolines and quinazolinones would maintain the high positive slope in the present day world of medicinal and synthetic chemistry. In our opinion, a combination of natural and hybrid quinazolinones would serve as a launching pad to fight against new generation diseases. Finally, on the basis of exposure to the literature of quinazolinone chemistry and our contribution to the same, it can be said with assurance that this interesting discipline will spread the wings still wider in the field of organic and pharmaceutical chemistry in future.

List of Publications

1. Hexamethyldisilazane-Iodine Induced Intramolecular Dehydrative Cyclization of Diamides: A General Access to Natural and Unnatural Quinazolinones
   U. A. Kshirsagar, S. B. Mhaske and N. P. Argade*
   Tetrahedron Lett. **2007**, *48*, 3243.

2. Facile Approach to Diverse Range of 1,3-Diaza-heterocycles: Angular/Linear Selectivity Paradigm and a Remarkable Intramolecular Methyl Migration
   U. A. Kshirsagar and N. P. Argade*
   Tetrahedron **2009**, *65*, 5244.

3. Total Synthesis of Proposed Auranthine
   U. A. Kshirsagar, V. G. Puranik and N. P. Argade* *J. Org. Chem.* **2010**, *75*, 2702.

4. Copper-Catalyzed Intramolecular N-Arylation of Quinazolinones: Facile Convergent Approach to (–)-Circumdatins H and J
   U. A. Kshirsagar and N. P. Argade*
   Org. Lett. **2010**, *12*, 3716.

Erratum