Development of new synthetic methodologies on quinazolinones for the synthesis of quinazolinone alkaloids and total synthesis of actinophenanthroline A

A Thesis
Submitted for the Degree of
Doctor of Philosophy

By

SUMAN KR GHOSH

School of Chemistry
University of Hyderabad
Hyderabad-500046
INDIA

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STATEMENT

I hereby declare that the matter embodied in this thesis entitled "**Development of new synthetic methodologies on quinazolinones for the synthesis of quinazolinone alkaloids and total synthesis of actinophenanthroline A**" is the result of investigations carried out by me in the School of Chemistry, University of Hyderabad under the supervision of **Prof. R. NAGARAJAN.**

In keeping with the general practice of reporting scientific observations due acknowledgments have been made wherever the work described is based on the findings of other investigators.

Date:

Hyderabad **(SUMAN KR GHOSH)**

CERTIFICATE

This is to certify that the thesis entitled "**Development of new synthetic methodologies on quinazolinones for the synthesis of quinazolinone alkaloids and total synthesis of actinophenanthroline A**" submitted by **Suman Kr Ghosh** bearing registration number **11CHPH18** in partial fulfillment of the requirements for award of Doctor of Philosophy in the School of Chemistry is a bonafide work carried out by him under my supervision and guidance.

This thesis is free from plagiarism and has not been submitted previously in part or in full to this or any other University or Institution for award of any degree or diploma.

Parts of this thesis have been:

A. Published in the following publications:

1. **Ghosh, S. K.**; Nagarajan, R. *RSC Adv*. **2014**, *4*, 20136-20144. *ISSN Number: 2046-2069*. (**Chapter 1**)
2. **Ghosh, S. K.**; Nagarajan, R. *RSC Adv*. **2014**, *4*, 63147-63149. *ISSN Number: 2046-2069*. (**Chapter 2**)
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4. **"XII J-NOST Conference- 2016"** CDRI-CSIR, Lucknow, India, November 2016.

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2.	CY-805	Instrumental Methods A	3	Pass
3.	CY-802	Chemistry Pedagogy	3	Pass
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Prof. R. Nagarajan
(Thesis Supervisor)

Dean
School of Chemistry

List of Publications:

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1. **Ghosh, S. K.**; Nagarajan, R. "NIS-mediated regioselective amidation of indole with quinazolinone and pyrimidone" *RSC Adv.* **2014**, *4*, 20136-20144.
2. **Ghosh, S. K.**; Nagarajan, R. "Total synthesis of cruciferane via epoxidation/ tandem cyclization sequence" *RSC Adv.* **2014**, *4*, 63147-63149.
3. **Ghosh, S. K.**; Nagarajan, R. **"**Deep eutectic solvent mediated synthesis of quinazolinones and dihydroquinazolinones: synthesis of natural products and drugs" *RSC Adv.* **2016**, *6*, 27378-27387.
4. **Ghosh, S. K.**; Nagarajan, R. "Total synthesis of Actinophenanthroline A *via* double Doebner–Miller reaction" *Tetrahedron Lett.* **2016**, *57*, 4009–4011.
5. **Ghosh, S. K.**; Nagarajan, R. "Total synthesis of penipanoid C, 2-(4-hydroxybenzyl)quinazolin-4(3*H*)-one and NU1025" *Tetrahedron Lett.* **2016**, *57*, 4277–4279.
6. **Ghosh, S. K.**; Ali, T.; Nagarajan, R. "Total synthesis of antibacterial Terremide A, B, C and methyl 3,4,5-trimethoxy-2-(2-(nicotinamido)benzamido) benzoate" **2016** (***Manuscript under preparation***).

Other Publications:

7. Ramesh, S.; **Ghosh, S. K.**; Nagarajan, R. "Copper catalyzed synthesis of fused benzimidazolopyrazine derivatives via tandem benzimidazole formation/annulation of δ-alkynyl aldehyde" *Org. Biomol. Chem.* **2013**, *13*, 7712.
8. Viji, M.; **Ghosh, S. K.**; Nagarajan, R. "Palladium-Catalyzed Synthesis of Quino[2,3-*a*]carbazoles and Indolo[2,3-*a*]carbazoles *via* Intramolecular *ortho*-Arylation" *Synthesis* **2014**, *46*, 961.

Conference Presentations

- Participated and presented a poster on ***"NIS mediated regioselective amidation of indole with quinazolinone and pyrimidone"*** at the "**16th CRSI National Symposium in Chemistry (NSC-16)"** conducted by IIT-Bombay, Mumbai, India on February 7-9, 2014.
- Participated and gave an oral presentation on ***"Total synthesis of Actinophenanthroline A via double Doebner–Miller reaction"*** at the **"CHEMFEST 2016, 13th In-house symposium"** conducted by School of chemistry, University of Hyderabad, Hyderabad, India on March 18-19, 2016 and won the "***Best Oral Presentation***".
- Participated and presented a poster on ***"Total synthesis of Actinophenanthroline A via double Doebner–Miller reaction"*** at the International conference **"Nature Inspired Initiatives in Chemical Trends, NIICT-2016"** conducted by CSIR-IICT, Hyderabad, India on September 19-20, 2016 and won the "***Best Poster Award***".
- Participated and gave an oral presentation on ***"Total synthesis of various quinazolinone alkaloids via deep eutectic solvent mediated cyclization"*** at the **"XII J-NOST Conference- 2016"** conducted by CDRI-CSIR, Lucknow, India on November 24-27, 2016.

This thesis is dedicated to

My Maa & Baba

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Table of Contents

List of Abbreviations Used

Å	Angstrom
Ac	Acetyl/Acetic/Acetate
Anal. Calcd	Analytically calculated
aq.	Aqueous
Ar	Aryl
Ac_2O	Acetic Anhydride
Bn	Benzyl
br	Broad (spectral)
Bu	Butyl
t-Bu	tertiary-Butyl
Boc	*tert*-Butyloxycarbonyl
BBr_3	Boron tribromide
^oC	Degree Celsius
Calcd	Calculated
CAN	Cerium Ammonium Nitrate
cat.	Catalytic
Cbz	Carboxybenzyl
cm^{-1}	Wavenumber(s)
CDI	1,1′-Carbonyldiimidazole
m-CPBA	meta-Chloroperoxybenzoic acid

concd	Concentrated
δ	Chemical shift in parts per million
DABCO	1,4-diazabicyclo[2.2.2]octane
d	Doublet (spectral)
DCB	1,2-Dichlorobenzene
DCE	1,2-Dichloroethane
DCM	Dichloromethane
dd	Doublet of doublets (spectral)
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DES	Deep Eutectic Solvent
DIBAL	Diisobutylaluminium hydride
dil.	Dilute
DIPA	Diisopropylamine
DIPEA	*N*,*N*-Diisopropylethylamine
DMAP	4-Dimethylaminopyridine
DMF	*N*,*N*-Dimethylformamide
DIC	*N*,*N*′-Diisopropylcarbodiimide
DMM	Dimethoxymethane
DMDO	Dimethyldioxirane
DMSO	Dimethylsulfoxide
DMU	*N*,*N*′-Dimethylurea

DCC	Dicyclohexylcarbodiimide
dppf	1,1'-Bis(diphenylphosphino)ferrocene
dr	Diastereomeric ratio
dt	Doublet of triplets (spectral)
ee	Enantiomeric excess
EG	Ethylene glycol
Eqn.	Equation
equiv.	Equivalent(s)
EtOAc	Ethyl acetate
EtOH	Ethanol
EWG	Electron Withdrawing Group
ESI	Electronspray ionization
EDCI.HCl	*N*-(3-Dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride
g	Gram(s)
h	Hour(s)
HMPA	Hexamethylphosphoramide
HRMS	High Resolution Mass Spectrometry
Hz	Hertz
HATU	1-[Bis(dimethylamino)methylene]-*1H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxid hexafluorophosphate

HBTU	*N,N,N′,N′*-Tetramethyl-*O*-(1*H*-benzotriazol-1-yl) uronium hexafluorophosphate
IBX	2-Iodoxybenzoic acid
i-Pr	Isopropyl
IR	Infrared
J	Coupling constant (in NMR Spectroscopy)
K	Kelvin (Temperature)
Kbar	Kilobar (Pressure)
LDA	Lithium diisopropylamide
LiHMDS	Lithium hexamethyldisilazide
m	Meta
M	Molar (solution concentration)
m	multiplet (spectral)
Me	Methyl
MeCN	Acetonitrile
mg	Milligram(s)
MHz	Megahertz
min	minute(s)
mL	Millilitre(s)
mmol	Millimole(s)
MeOH	Methanol

MOM	Methoxymethyl
Mp	Melting point
MS	Molecular sieves
MW	Microwave
NBS	*N*-Bromosuccinimide
NMF	*N*-Methylformanilide
NMP	*N*-Methyl-2-pyrrolidone
NMR	Nuclear Magnetic Resonance
N	Normal (solution concentration)
NIS	*N*-iodosuccinimide
NBS	*N*-bromosuccinimide
ORTEP	Oak ridge thermal ellipsoid plot
o	Ortho
p	Para
PCC	Pyridinium chlorochromate
Ph	Phenyl
Phen	1,10-Phenanthroline
PG	Protecting group
ppm	Parts per millions
PTT	Phenyltrimethylammonium tribromide
p-TSA	para-Toluenesulfonic acid

py	Pyridine
q	Quartet (spectral)
rac	Racemic
R_f	Retention factor
rt	Room temperature
sec	Secondary
s	Singlet (spectral)
t	Triplet (spectral)
TBHP	*tert*-Butyl hydroperoxide
TFA	Trifluoroacetate/Trifluoroacetic acid
TFAA	Trifluoroacetic anhydride
Tf	Triflate(trifluoromethane sulfonate)
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMEDA	*N*,*N*,*N*′,*N*′-Tetramethylethane-1,2-diamine
TMP	Tetramethylpiperidine
TMS	Trimethylsilyl
TMSI	Trimethylsilyl iodide
Ts	Tosyl
TBTU	*O*-(Benzotriazol-1-yl)-*N,N,N′,N*′-tetramethyluronium tetrafluoroborate

Introduction

Heterocycles:

In 1600, chemistry started with the classification of inorganic and organic; and it was in accordance with the "vitalism theory". The theory rules unto the mid-nineteenth century then Wohler synthesized the first organic compound urea.[1] By 1900, a vast expansion of the subject forced scientists to classify chemistry into Organic, inorganic and physical chemistry. Throughout these years, a constant development was documented for heterocyclic chemistry and compounds.[2] After World War II an enormous number of researches have been done on this particular field of chemistry. This is the most classical and vast division of organic chemistry that enrich the modern synthetic chemistry, medicinal chemistry and biochemistry. The majority of the compounds used in pharmaceutical and agrochemical industries are heterocycles; apart from that there are innumerable heterocyclic modifier and additives which have been a constant part of our daily usage from food to cosmetic products, information storage to plastic but the major impact lies in the drug industry. The structural core with various substituent modification manifests different properties. They have a greater contribution to society not only from the biological and industrial point of view but also towards enhancing the quality of life.[3]

According to the IUPAC Gold Book,[4] heterocycles are: "Cyclic compounds having, as ring members, atoms of at least two different elements e.g. quinoline, 1,2-thiazole, bicyclo[3.3.1]tetrasiloxane."

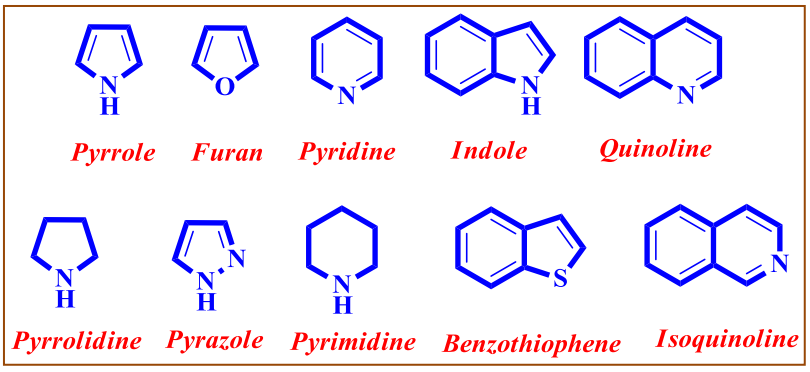


Figure 1. Representation of some important heterocyclic core

Another classical book, the Encyclopaedia Britannica,[5] represented a heterocyclic compound as a *heterocycle*, as: "Any of a class of organic compounds whose molecules contain one or more

rings of atoms with at least one atom (the heteroatom) being an element other than carbon, most frequently oxygen, nitrogen, or sulfur."

The incorporation of one heteroatom like oxygen, nitrogen, sulfur or any other element in an organic carbocycle in place of carbon will lead to a heterocycle. These structures can lead to either an aromatized ring or non-aromatized heteroatom containing carbocycle. Heterocycles which contain only one heteroatom are more stable and those which contain three or more heteroatoms are more unstable. Heterocycles are mostly privileged due to their presence in a huge number of naturally occurring alkaloids, flavones, proteins, nucleic acids. Many of these alkaloids and their scaffolds made by scientists are used as humanitarian drugs. A subsequent number of heterocyclic core has been reported in literature which directly or indirectly holds almost half of the organic compounds known in the literature.[6]

Quinazolinone:

Almost half of the compounds in organic chemistry are heterocyclic compounds. Among them the nitrogen containing ones are more abundant and an integral part of naturally occurring alkaloids, synthetic drugs, agrochemicals and pharmaceuticals. Due to their widespread properties a substantial effort has been made to develop their chemistry. Quinazolinones are an important nitrogen containing fused heterocyclic scaffold that displays a wide range of biological properties and around 200 naturally occurring alkaloids contain this motif.[7] Quinazolinone has two structural isomers, 2-quinazolinone and 4-quinazolinone, of which 4-quinazolinone is mostly known. Based on substitution pattern also 4(*3H*)-quinazolinones can be divided into three categories: i) 3-Substituted-4(*3H*)-quinazolinone, ii) 2-Substituted-4(*3H*)-quinazolinone and iii) 2, 3-Disubstituted-4(*3H*)-quinazolinone.[8]

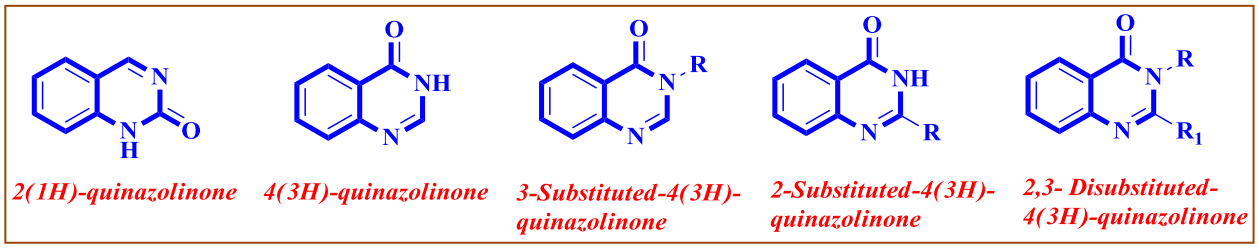


Figure 2. Differently substituted quinazolinone cores

The therapeutic and medicinal activities of quinazolinones made it an important target to chemists and biologists. It shows diverse pharmacological activities such as antimicrobial,[9]

antimalarial,[10] anti-inflammatory,[11] antihypertensive,[12] anti-diabetic,[13] anticancer,[14] cholinesterase inhibition,[15] dihydrofolate reductase inhibition,[16] and kinase inhibitory activity.[17]Apart from these properties it shows some biological functions like cellular phosphorylation inhibition,[18] ligands for benzodiazepine and GABA receptors in the central nervous system, [19] and some of them have acted as DNA binding agents.[20]

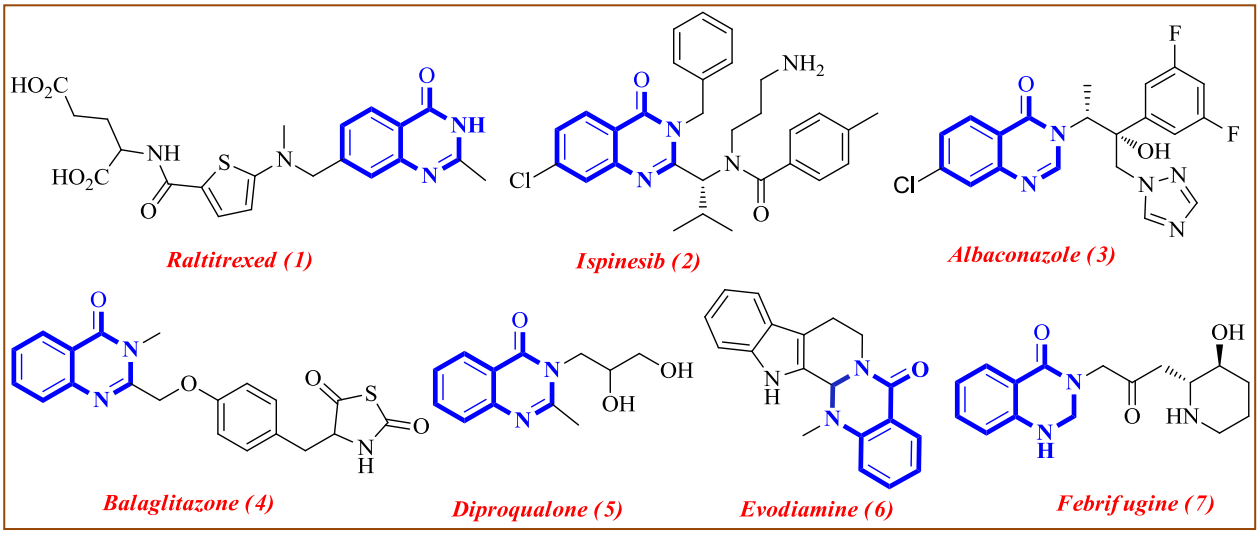


Figure 3. Representation of some important quinazolinone drugs

Among the quinazolinone based drugs in the market or in final clinical trials, **fig. 3** describes some of the essential drugs. Raltitrexed[21] **(1, fig. 3)** is an antimetabolite drug which is marketed with a brand name Tomudex. It has been used for the treatment of bowel (colorectal) cancer since 1998. Ispinesib[22] (**2**, **fig. 3**) is a small quinazolinone drug with antineoplastic properties that selectively inhibits the mitotic motor protein, kinesin spindle protein (KSP) that causes the cell death in tumor cells. Despite its important biological properties, it has still not been marketed. Ispinesib mesylate is more effective and thus study of the use of this salt in fighting cancer cells is still going on. Albaconazole[23] (**3, fig. 3**) is a novel triazole and quinazolinone fused drug. It has a broad-spectrum of antifungal property and a long half-life in dogs, monkeys, and human beings. Balaglitazone[24] (**4, fig. 3**) is a drug which is used for the treatment of type II diabetes. This drug is still in phase III clinical trials. Diproqualone[25] (**5, fig. 3**) is an analogue of methaqualone and had been developed in the late 1950s by a team at Nogentaise de Produits Chimique. It has sedative, anxiolytic, antihistamine and analgesic properties. These activities are due to its agonist activity at the β-subtype of the GABAa receptor and antagonist activity at

all histamine receptors. It also inhibits the cyclooxygenase-1 enzyme, and possibly shows agonist activity at both the sigma-1 receptor and sigma-2 receptor. Evodiamine[26] (**6, fig. 3**) is extracted from the Evodia sp. family of plants that has been known to reduce fat uptake in mouse studies and its method is believed to be like capsaicin. This chemical appeared in many body building supplements, but its fat-burning benefits or its potential risks and side effects were never proved scientifically or empirically. Evodiamine can increase the body temperature which kills certain cancer cells. It may also act like tianeptine by increasing the number of serotonin transporters in the brain that enhances the reuptake of serotonin. Febrifugine[27] (**7, fig. 3**) is a quinazolinone alkaloid first isolated almost 50 years ago from Chinese herb *Dichroa febrifuga*, and has been used as Chinese medicine almost for 2000 years. Its halogenated derivative halofuginone is found to be more active than febrifugine and is specifically shown to very effective in treating malaria, cancer, fibrosis and inflammatory diseases.

The utility of quinazolinone based drugs comes from a regular modification of the quinazolinone based alkaloids isolated from nature. There are almost 55 alkaloids which have been isolated from natural sources over the last decade. According to the classification made earlier, quinazolinone alkaloids also can be placed into those classes.

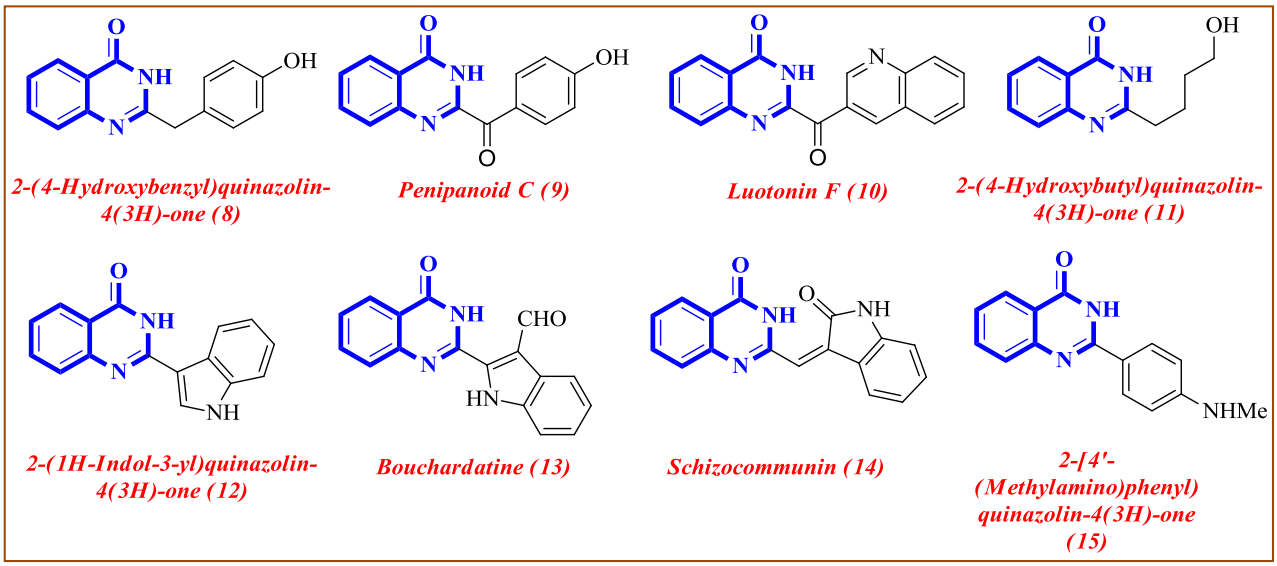


Figure 4. Representation of some important 2-substituted quinazolinone alkaloids

In 2011, Che et al. isolated this 2-(4-Hydroxybenzyl)quinazolin-4(3*H*)-one (**8**) along with other six alkaloids from the *Cordyceps*-colonizing fungus *Isaria farinose*. Wang group isolated

penipanoid C (**9**) from the marine sediment-derived fungus *Penicillium paneum* SD-44 in the same year along with compound **8** and other two alkaloids (**fig. 4**). In 2013, Penipanoid C and compound **8** was again isolated from another marine fungus *Penicillium oxalicum* $0312F_1$. Compound **8** was reported for its significant cytotoxic activity against the A-549 and BEL-7402 cell lines with IC_{50} values of 17.5 and 19.8 μM, and also exhibited strong inhibitory activity on the replication of tobacco mosaic virus (TMV).[28] In 1999, Nomura and co-workers from Japan with scientists from China have isolated six new alkaloids Luotonin A-F from the plant kingdom from the aerial parts of *Peganum nigellastrum* Bunge which have been found all over Asia and is more common in the northwestern region of China. All the luotonins are active towards selected human cancer cell lines, especially against leukemia P-388 cells. Luotonin F (**10, fig. 4**) has shown IC_{50} value of 2.3 μM against mouse leukemia P-388 cells.[29] 2-(4-Hydroxybutyl)quinazolin-4-one (**11, fig. 4**) was isolated in 2000 by Deng et al. from *Dichroa febrifuga* but its synthesis was reported prior to isolation.[30] In 2015, Thongpanchang et al. isolated 2-(*1H*-Indol-3-yl)quinazolin-4(*3H*)-one (**12, fig. 4**) from the crude extract of an actiomycete, *Streptomyces* sp. BCC 21795. It showed strong cytotoxic activity against vero cells with IC_{50} 3.30 mg/mL.[31] Bouchardatine (**13, fig. 4**) was isolated in 2003 by Waterman et al. from the aerial parts of *Bouchardatia neurococca* (Rutaceae) along with another four alkaloids. It is a β-indoloquinazoline alkaloid. Bouchardatine can potently reduce lipid accumulation in 3T3-L1 adipocytes that suggests it can be used in the prevention and treatment of obesity.[32] Schizocommunin (**14, fig. 4**, revised structure) was first isolated by Hosoe et al. in 1999 from the liquid culture medium of *Schizophyllum commune*. This structure was revised by Nishida et al. in 2013. The alkaloid shows strong cytotoxic activity against murine lymphoma cells.[33] 2-[4′-(Methylamino)phenyl]quinazolin-4(*3H*)-one (**15, fig. 4)** which was isolated from *Streptomyces sp.* A496, was reported to have potent firefly luciferase inhibitory activity with no effect on AMP-activated protein kinase (AMPK). This was the first report for a natural luciferase inhibitor.[34]

There are around seventeen 3-substituted quinazolinone alkaloids reported till last year. Among them, we featured some important alkaloids in fig.5. (-)-Chaetominine (**16, fig. 5**) was isolated from the solid-substrate culture of *Chaetomium sp.* IFB-E015, an endophytic fungus on apparently healthy *Adenophora axilliflora* leaves in 2006 by Tan et al. It has been reported that it

shows potent activity against human leukemia K562 (21 nM) and colon cancer SW1116 (28 nM) cell lines but the synthetic version of (-)-chaetominine failed to show inhibitory activity against many human cancer cell lines, even to human leukemia K562.[35] In 2013, Wang group isolated Aniquinazoline D (**17, fig. 5**), that was structurally related to (−)-chaetominine (**16, fig. 5**),

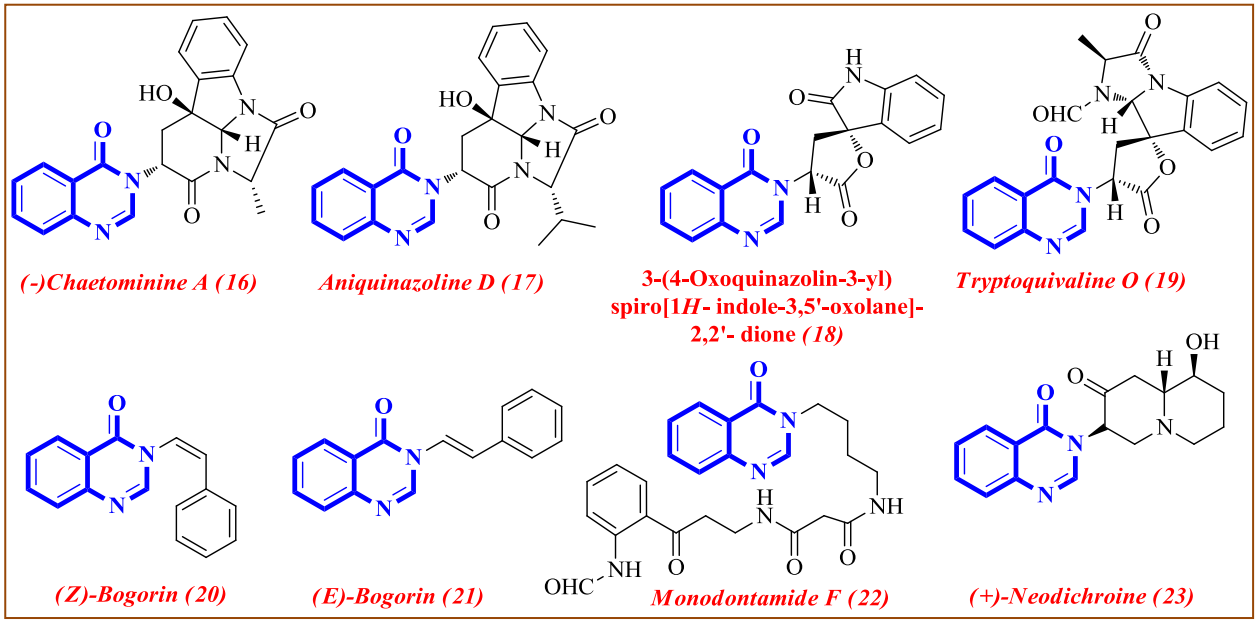


Figure 5. Representation of some important 3-substituted quinazolinone alkaloids

from the culture of the fungus *Aspergillus nidulans* MA-143 that was obtained from the leaves of a mangrove plant *Rhizophora stylosa*. This alkaloid showed potent brine shrimp toxicity with LD_{50} value of 3.42 µM.[36] In 2012, Kijjoa et al. isolated 3-(4-oxoquinazolin-3-yl)spiro[1*H*-indole 3,5-oxolane]-2,2-dione (**18, fig. 5**) and tryptoquivaline O (**19, fig. 5**) from the constituents of the fungus *Neosartorya siamensis* (KUFC 6349). Both the alkaloids are evaluated for their in vitro growth inhibitory activity on five human cancer cell lines but they did not show cytotoxic effects.[37] Z-Bogorin (**20, fig. 5**) was isolated by Seger group in 1998 from *Glycosmis cf. chlorosperma* Spreng (Rutaceae). It was isolated in lower quantity, thus they have synthesized it along with some of its analogues. E-Bogorin (**21, fig. 5**) is a synthetic version of this alkaloid. It shows antifungal activity in a bioautography assay against cladosporium herbarium with IC_{50} value 40 µg/mL. It also shows moderate cytotoxicity against *Artemia Selina*.[38] Monodontamide F (**22, fig. 5**) was isolated from the marine gastropod molhtsc *Motwdonra labio* (Linné) in 1994 by Yamada et al. along with five more monodontamide A-E. Monodontamides exhibit low

inhibitory activity against a serine proteas.[39] (+)-Neodichroine (**23, fig. 5**) was isolated from *Dichroa febrifuga* in 2000 by Deng et al. but there is still doubt about its absolute configuration as Wu group revised the structure to report it as (-)-Neodichroine.[40] Tryptanthrin (**24, fig. 6**), a well known indoloquinazolinone, was isolated from *Isatis tinctoria*. It has anti-inflammatory and anti cancer properties. It blocks leukotriene production in neutrophils and in whole blood assays and also inhibits P-glycoprotein and sensitizes resistant cancer cell lines. In 2008, Wu et al. isolated some new optically active indoloquinazolinones, phaitanthrins A–E (**fig. 6**) which was structurally related to tryptanthrin alkaloid. Phaitanthrin A (**25, fig. 6**) displayed moderate cytotoxicity against MCF-7, NCI-H460, and SF-268 cell lines with IC_{50} values of 33.8, 27.0 and 43.9 μM respectively. Another related alkaloid cephalanthrin-A (**28, fig. 6**) was isolated in 2015 from *Cephalantheropsis gracilis* but it has not showed any significant cytotoxicity against the cancer cell lines it was tested on.[41]

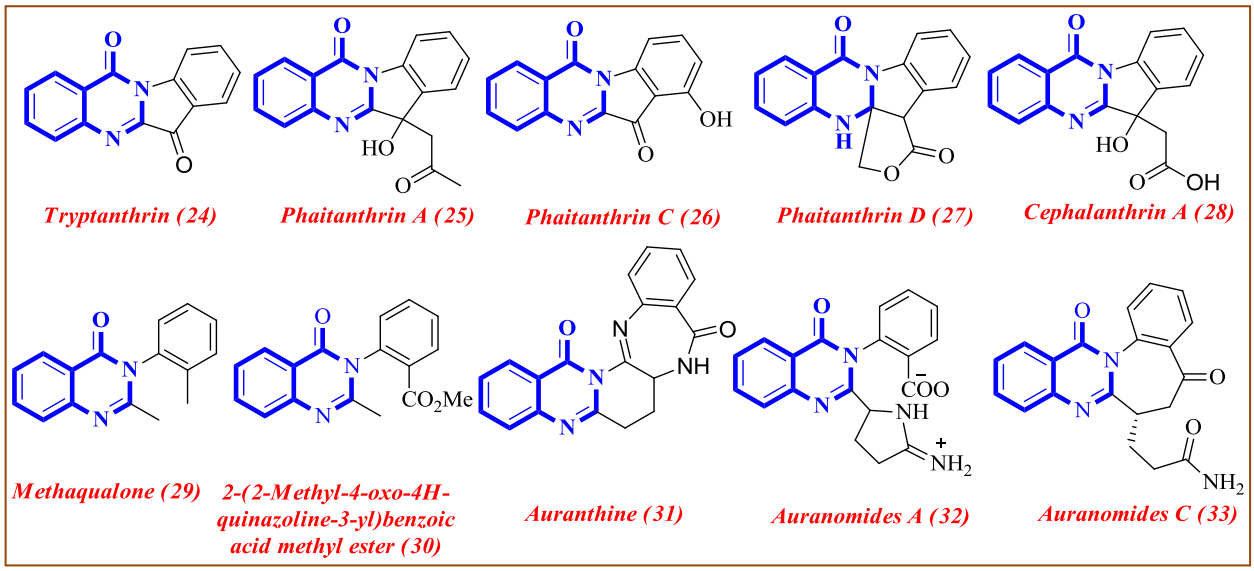


Figure 6. Representation of some important 2,3-disubstituted quinazolinone alkaloids

Methaqualone (**29, fig. 6**) is a synthetic quinazolinone drug which was first synthesized in 1951. It is known for its hypnotic and sedative properties.[42] 2-(2-Methyl-4-oxo-4*H*-quinazoline-3-yl) benzoic acid methyl ester (**30, fig. 6**) was isolated in 2006 by Kang et al. from the roots of at the *Aconitum pseudo-laeVe var. erectum* along with another two new norterpenoid quinazolinone alkaloids. Any biological property is not reported for this alkaloid till date.[43] Auranthine (**31, fig. 6**) was isolated in 1986 by Mantle group from *Penicillium aurantiogriseum* but the configuration

at the asymmetric center was not determined. It is reported as an antimicrobial.[44] Auranomides A and B (**fig. 6**) are quinazolin-4-one coupled with pyrrolidin-2-iminium alkaloids whereas auranomide C (**33, fig. 6**) is a fused alkaloid. They were isolated in 2012 from the marine-derived fungus *Penicillium aurantiogriseum*. These alkaloids show moderate cytotoxicity against some human tumor cells. Among them auranomide B is the most potent with an IC_{50} value of 0.097 μmol/mL against HEPG2 cells.[45] Circumdatins are quinazolinone core based marine natural product and they possess antitumor, antifungal, insecticide, and antibiotic activities.

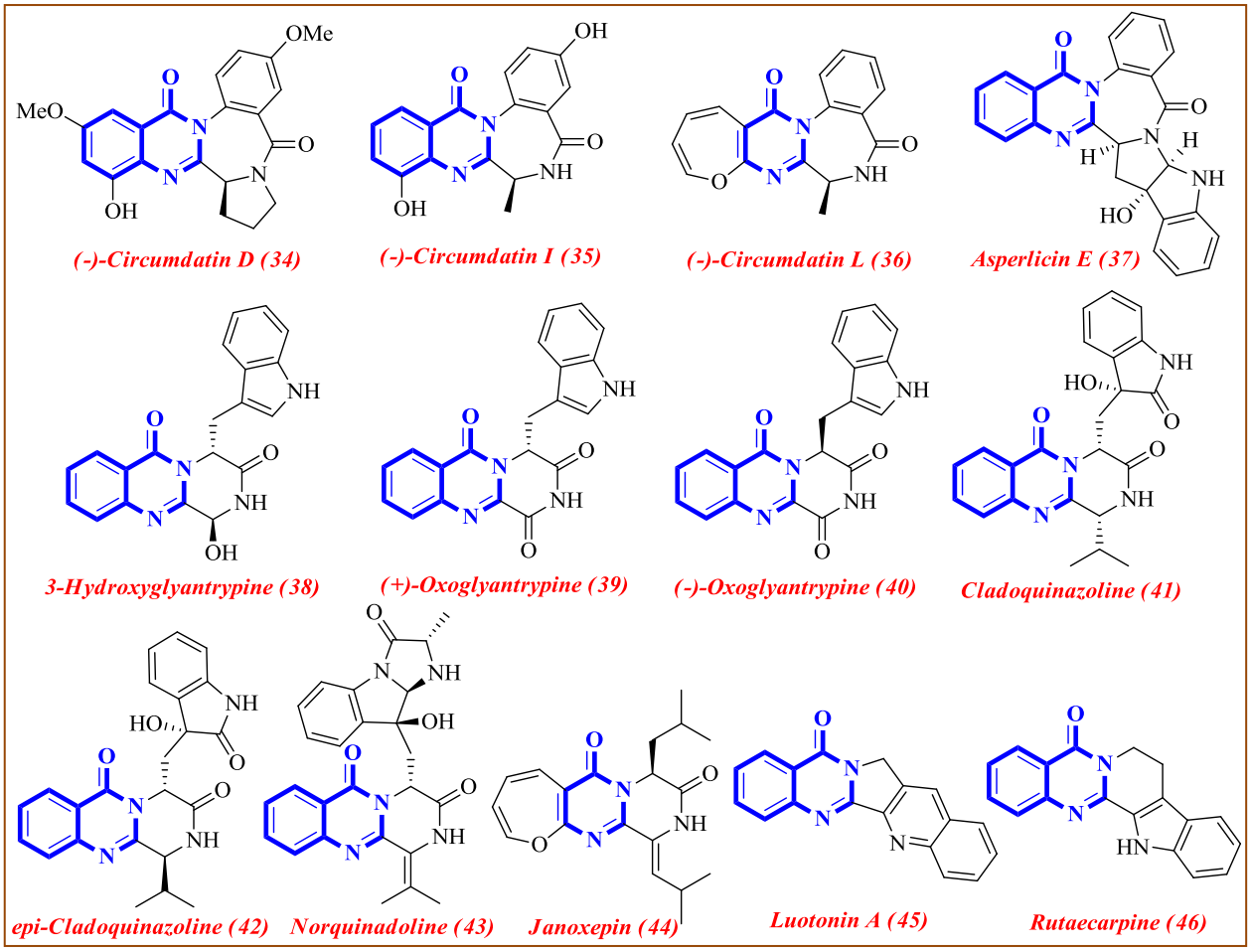


Figure 7. Biologically important 2,3-disubstituted quinazolinone alkaloids

Circumdatins A-G (**fig. 7**) was obtained from a terrestrial isolate of the fungus *Aspergillus ochraceus* and are suggested to be suitable chemotaxonomic markers for this species. (−)-Circumdatin I (**35, fig. 7**) was isolated from the mycelium of a marine derived fungus of the genus *Exophiala*. It shows an UV-A protecting activity (ED_{50} value 98 μM) that is more

effective than the currently used sunscreen agent, oxybenzone (ED_{50} value 350 μM). In 2013, Qi et al. isolated two more circumdatins (circumdatin K and L, **fig. 6**) from the deep sea-derived fungus *Aspergillus westerdijkiae* DFFSCS013. They were tested against human carcinoma A549, HL-60, K562, and MCF-7 cell lines but have not shown any cytotoxic activity.[46] Xin and Li et al. isolated some glyantrypine quinazolinone derivatives (**38- 42, fig. 7**) along with one new pyrazinoquinazoline derivative (**43, fig.7**). The six new alkaloids isolated, 3-hydroxyglyantrypine (**38**), oxoglyantrypine (**39, 40**), cladoquinazoline (**41**), epi-cladoquinazoline (**42**), and norquinadoline A (**43**) are depicted in **fig. 7**. A novel oxepin derivative janoxepin (**44**) was isolated in 2005 by Sprogøe et al. from the fungus *Aspergillus janus*. The alkaloid (**44**) is active against the malaria parasite Plasmodium falciparum 3D7 with IC_{50} values of 28 mg/ml.[47] Nomura et al. from Japan with collaboration of Chinese scientists have isolated six new alkaloids in 1999, and named as luotonin A–F (**45, fig. 7**) from the aerial parts of *P. nigellastrum*. Among them Luotonin A was found to be biologically more prominent and cytotoxic toward the murine leukemia P388 cell line, IC_{50} 1.8 mg/mL, naturally occurring human DNA topoisomerase I poison, IC_{50} 5.7–12.6 mmol/mL.[48] Rutaecarpine (**46, fig. 7**) is the first known representative of the quinazolinocarboline alkaloids. It was isolated from the dried fruits of *Evodia rutaecarpa* which has already been in use as a traditional Chinese medicine under the name Wu-Chu-ru. This alkaloid is well known for its pharmacological properties like strong analgesic, anti-emetic, astringent, anti-hypertensive, uterotonic, TCDD receptor, antinociceptive, anti-inflammatory, and cycloxygenase-2 (COX-2) inhibitory activities.[49] In 2011, Kijjoa et al. isolated a hexacyclic indole alkaloid sartorymensin (**47, fig. 8**), an indoloazepinone derivative from the culture of the fungus *Neosartoryasiamensis* (KUFC 6349) along with four new pyrazinoquinazolinone derivatives: epi-fiscalin C (**48, fig. 8**), epi-fiscalin A (**49**, **fig. 8**), neofiscalin A (**50**, **fig. 8**), epi-neofiscalin A (**51, fig. 8**). These isolated alkaloids are tested for their in vitro growth inhibitory activity on the human U373 and Hs683 glioblastoma, the A549 cell lung cancer, MCF-7 breast cancer and also SKMEL-28 melanoma cell lines. Among them sartorymensin (**47, fig. 8**) and

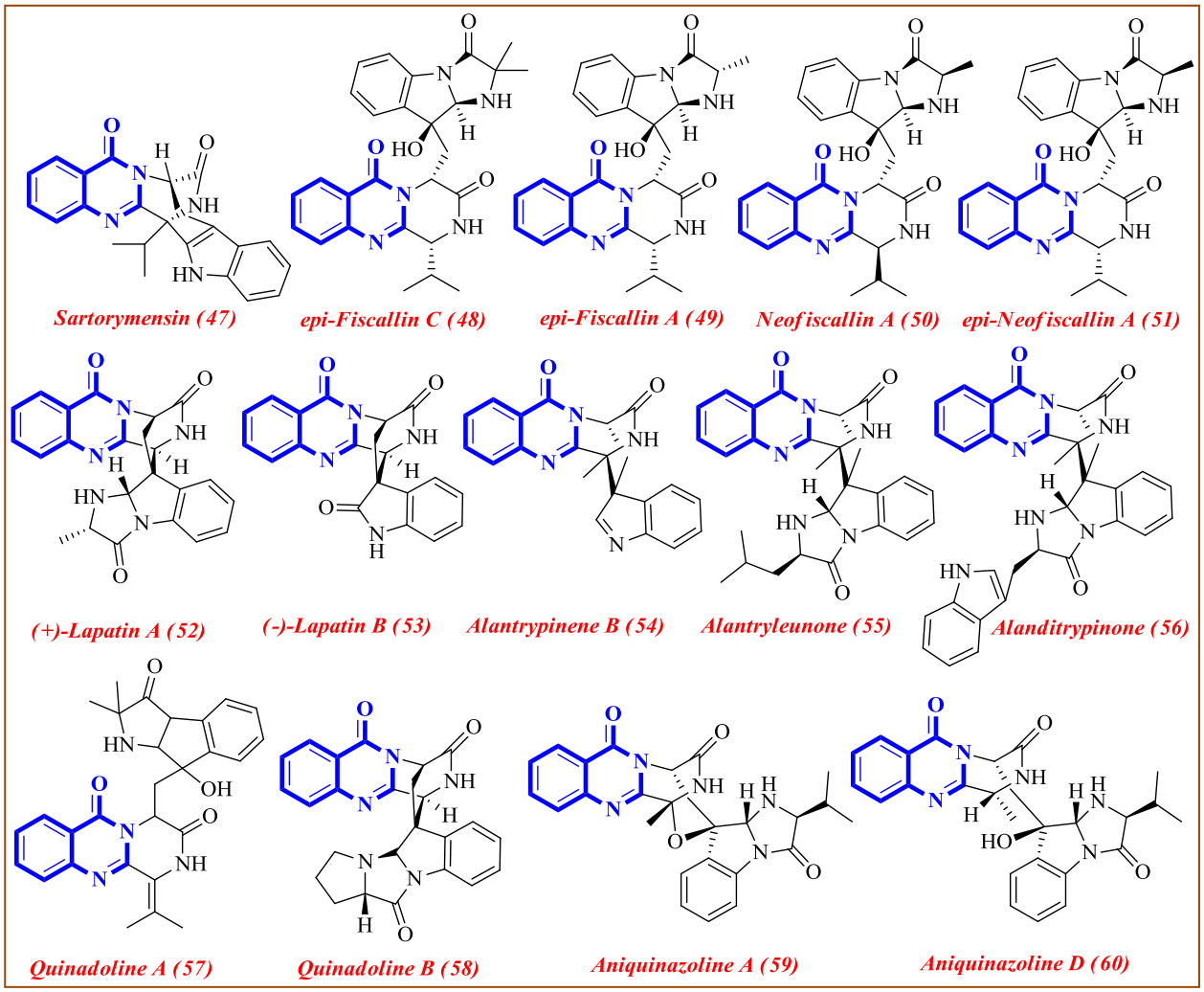


Figure 8. Representation of important 2, 3-disubstituted quinazolinone alkaloids

epi-fiscalin A (**49**, **fig. 8**) were found to show moderate activity.[50] In 2005, two novel spiro-quinazoline metabolites lapatin A (**52, fig. 8**) and lapatin B (**53, fig. 8**) were isolated via X-hitting, an algorithm for automated comparison of UV data. They were thought to be bioactive alkaloids due to their structural resemblance to known bioactive spiro-quinazoline metabolites from *Penicillium lapatayae*.[51] Similarly, some more new alkaloids alantrypinene B (**54, fig. 8**), alantryleunone (**55, fig. 8**) and alanditrypinone (**56, fig. 8**) were isolated from *A Eupenicillium sp.* derived from *Murraya paniculata* (Rutaceae). However any biological properties are still not reported for these alkaloids.[52] In 2008, Tomoda et al. isolated two alkaloids; quinadolines A and B (**57 and 58, fig. 8**) from culture broth of *Aspergillus sp.* FKI-1746 that can moderately inhibit lipid droplet synthesis in mouse macrophages.[53] Aniquinazolines A–D (**fig. 8**), were isolated

from the culture of endophytic fungus *Aspergillu snidulans* MA-143 which was found from the leaves of marine mangrove plant *Rhizophorastylosa*. These alkaloids were tested for antibacterial and cytotoxic activities along with brine shrimp (*Artemiasalina*) lethality. None of them were found to be active as antibacterial and cytotoxic but they showed potent lethality against brine shrimps with LD_{50} values of 1.27, 2.11 μM for alkaloids **59** and **6**0 respectively.[36]

Secondary metabolites Ardeemins (**61 and 62, fig. 9**) were isolated in 1993 from a soil sample collected from Brazil which was later identified as *Aspergillus fischeri var. brasiliensis* strain AB 1826M-35. The major and most active constituent isolated was 5-*N*-acetylardeemin which demonstrated the ability to restore vinblastine sensitivity to a tumor cell line. In 2010 two more alkaloids, 16*a*-hydroxy-5-*N*-acetylardeemin (**63, fig. 9**) and 15*b*-dehydro-5-*N*-acetylardeemin

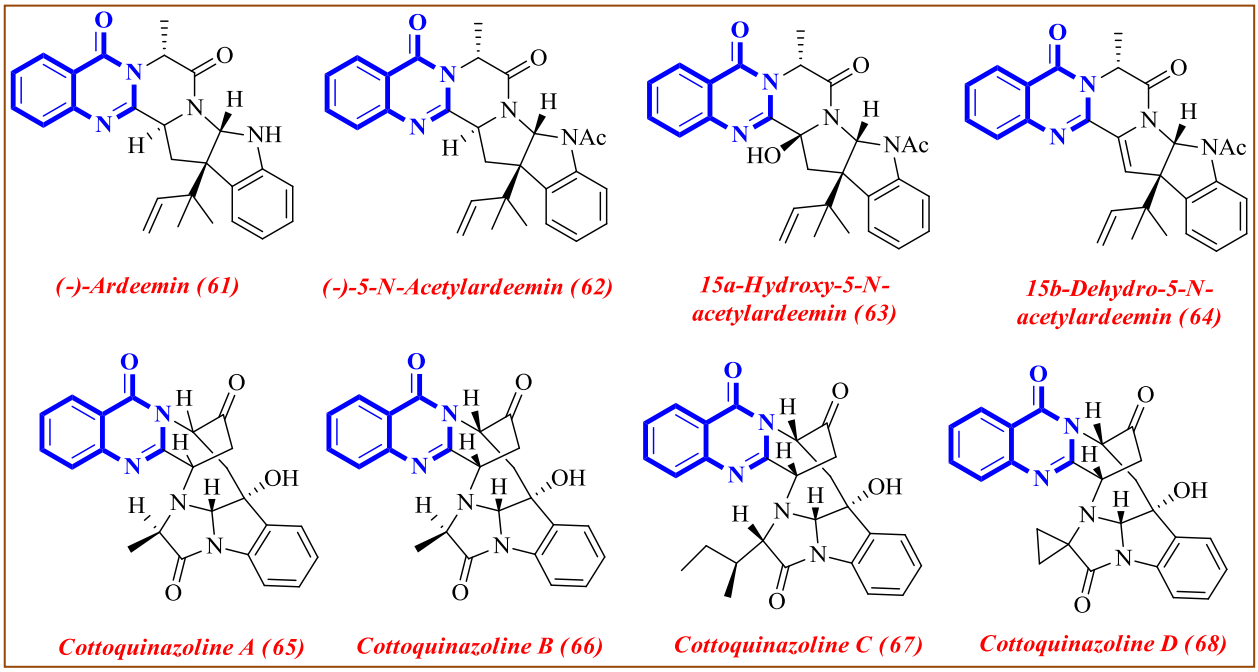


Figure 9. Various ardeemin and cottoquinazolinone alkaloids

(**64, fig. 9**), were isolated from endophytic fungi, *Aspergillus terreus* and *Aspergillus terreus* IFB-E030. Compound **63** displayed moderate cytotoxic activity against KB and HSC-T6 cell lines along with strong multidrug-resistant (MDR) reversing effect against K562/DOX & A549/DDP cancer cell lines. It also showed an inhibitory effect against acetyl cholinesterase as well, whereas compound **64** exhibits a MDR reversing effect against the SK-OV-S/DDP cell line. SAR study reveals the hydroxyl group plays an important role in the MDR reversing effect.[54]

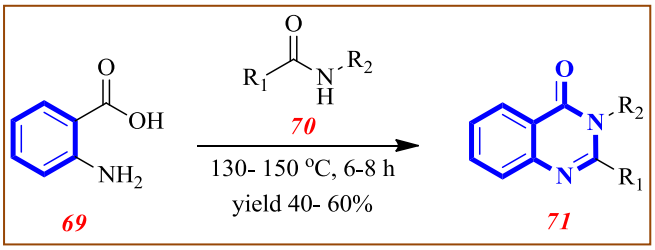
Cottoquinazoline A- D (**fig. 9**) was isolated over the years from 2008-2010 by Capon and Zhu et al. Cottoquinazoline A (**65, fig. 9**) was isolated from a marine derived isolate of *Aspergillus Versicolor* (MST-MF495) whereas Cottoquinazoline B-D (**66-68, fig. 9**) was isolated from coral-associated fungus *Aspergillus versicolor* LCJ-5-4. Cottoquinazoline D (**68, fig. 9**) is found to be an important alkaloid as it contained a rare 1-aminocyclopropane-1-carboxylic acid residue that was hardly found in nature. Cottoquinazolines B-D were tested for in vitro cytotoxicity against HeLa and P388 cells as well as antimicrobial activity against *E. coli*, *S. aureus*, *E. aerogenes*, *B. subtilis*, and *C. albicans* where only cottoquinazoline D (**68, fig.9**) displayed some moderate antifungal activity against *C. albicans* with MIC value of 22.6 μM.[55]

Quinazolinone Synthesis:

Over the years many synthetic methods were developed to synthesize quinazolinones, their analogues and their bioactive alkaloids due to the huge importance (*via infra*) of this heterocyclic moiety on biological and pharmaceutical fields. Among these numerous synthetic reports in literature till date one can summarize it on basis of reaction strategy that was used for synthesis of quinazolinone. i) **Condensation/Cyclization** ii) **Hetero Diels-Alder reaction** iii) **Microwave assisted reaction** iv) **Aza-Wittig reaction** v) **Radical Cascades** vi) **Transfer hydrogen reactions** vii) **Transition metal catalyzed cyclization** and viii) **Transition metal catalyzed cyclocarbonylation**.

i) Condensation/ Cyclization:

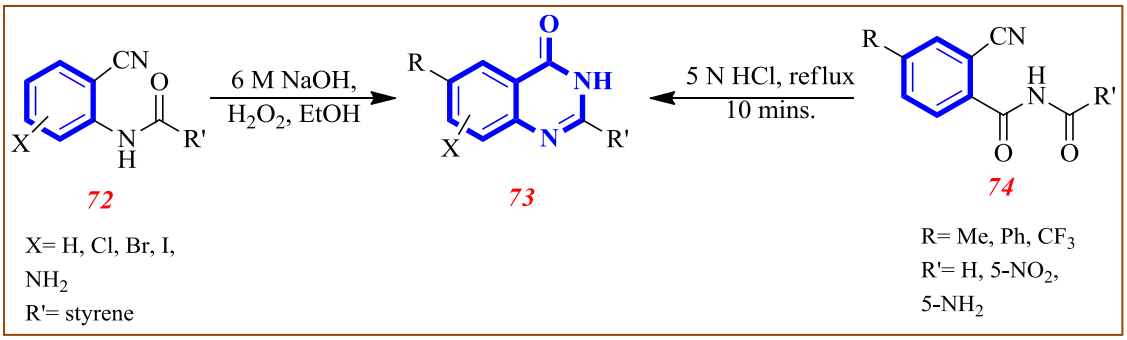
This is the best documented and old classical procedure for the synthesis of quinazolinones and the common precursor for this reaction is mostly 2-aminobenzoic acid, 2-aminobenzonitrile and 2-aminobenzamide.



Eqn. 1. Conventional Niementowski quinazoline synthesis

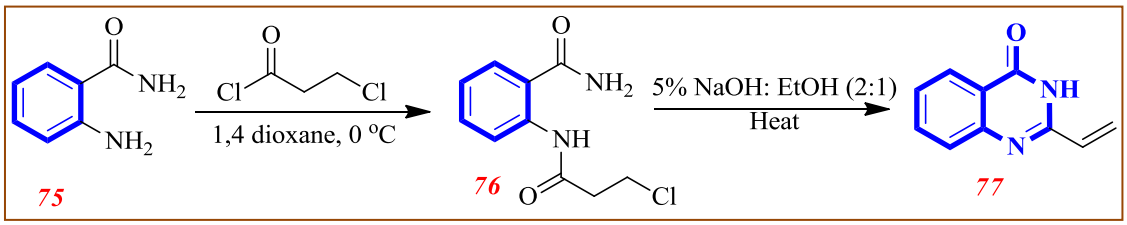
In 1895, Niementowski reported a condensation reaction between anthranilic acid (**69, Eqn. 1**) and amides (**70, Eqn. 1**) to form quinazolinones (**71, Eqn. 1**). The condition was quiet harsh as it

needed temperature around 140 °C and also yield was low.[56] After 5-6 years Bogert et al. described a reaction of various 2-aminobenzonitriles and acryloyl chlorides to give compound **72** (**Eqn. 2**) that undergoes an oxidative ring closure under basic conditions to produce quinazolinones (**73, Eqn. 2**). However due to the lower yield of quinazolinone, this method was modified by Bandgar et al. where a urea-hydrogen peroxide adduct has been used along with potassium carbonate that gave yield of almost 86-98%.



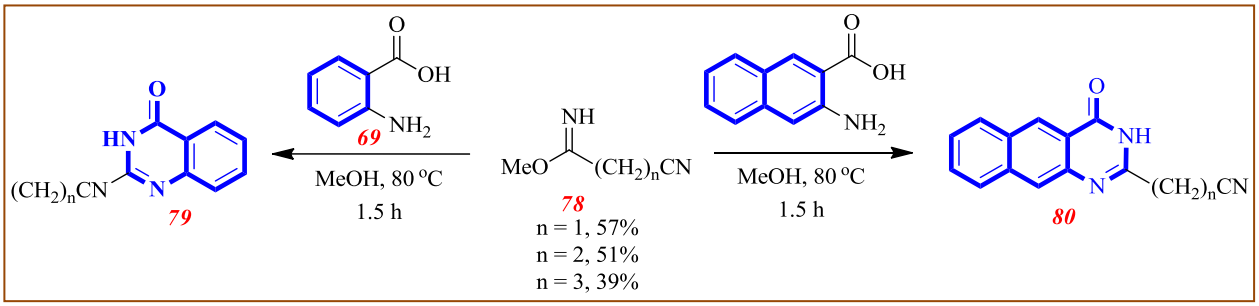
Eqn. 2. Quinazolinone synthesis via ring closure under basic and acidic conditions

In 1980, Showell group synthesized various 2-substituted quinazolinone (**73, Eqn. 2**) derivatives under acidic conditions from 2-cyanobenzamide derivatives (**74, Eqn. 2**). This methodology was proven to be advantageous due to its lower reaction time and high yield.[57]



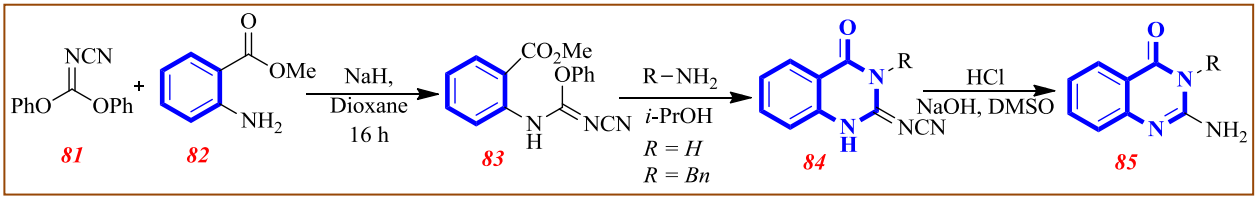
Eqn. 3. Modified Körner synthesis of quinazolinone by Bergman

The condensation between amides of anthranilamide was well reported with potassium hydroxide by Körner et al. in 1887. The strategy was modified by Bergman group to synthesize natural alkaloids like chrysogine and 2-vinylquinazolin-4(*3H*)-one (**77, Eqn. 3**).[58]



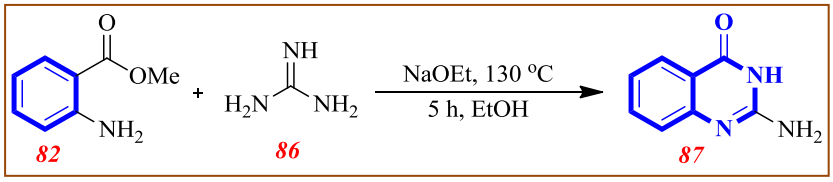
Eqn. 4. Condensation of 2-aminobenzoic acid with imidates

The condensation reaction between imidates (**78, Eqn. 4**) and anthranilic acid (**69, Eqn. 4**) was reported long back in 1960 by Reid et al. where these two components were heated at 80 °C in MeOH solvent. Later, almost similar approach was utilized by Hennequin et al. to synthesize various quinazoline antifolatethymidylate synthase inhibitors. Benzo-fused quinazolinones (**80, Eqn. 4**) were also synthesized using the same procedure with 3-amino-3-naphthalene-2-carboxylic acid and imidates (**78**). It was further extended for the synthesis of 2-aryl/alkyl substituted benzofused quinazolinones (**Eqn. 4**).[59] This method was extended by Guiry et al. for a series of 2-aryl- and 2-alkylquinazolinones. The necessary imidates were synthesized as their corresponding salts and on treatment with base it gave the corresponding imidates which has been condensed with anthranilic acids to give quinazolinones in good yields. Gaartt et al. synthesized 2-aminoquinazolin-4(*3H*)-ones using diphenylcyanocarbonimidate (**81, Eqn. 5**) and methyl anthranilate (**82, Eqn. 5**). Methyl anthranilate on treatment with sodium hydroxide in dioxane media for 16 h with cyanocarbonimidate generated the *o*-phenylisourea (**83, Eqn. 5**). This on treatment with amines in isopropanol solvent gave corresponding tetrahydroquinazoline (**84, Eqn. 5**). The cyano group was hydrolyzed using HCl and on treatment with NaOH/ DMSO it released the free base from hydrochloride salt to generate the 2-aminoquinazolin-4(*3H*)-ones (**85, Eqn. 5**).[60]



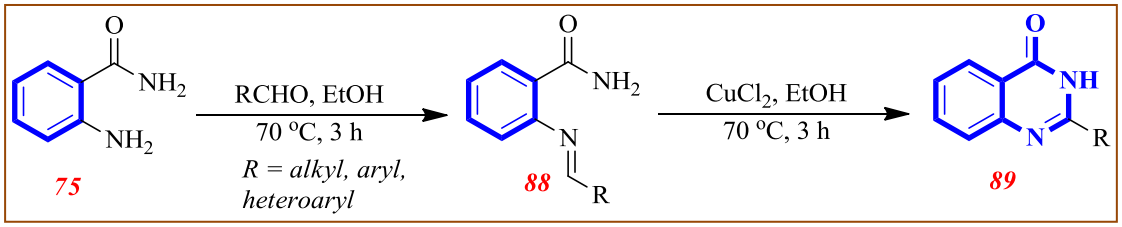
Eqn. 5. Condensation between methyl anthranilate with carbonimidates

In 1968, Hess et al. described the synthesis of 2-aminoquinazolin-4(*3H*)-one (**87, Eqn. 6**) from methyl anthranilate (**82, Eqn. 6**) and excess guanidine (**86**) in the presence of sodium ethoxide in EtOH solvent at 130 °C.[61]



Eqn. 6. Condensation reaction between anthranilate esters with guanidine

The condensation reaction of anthranilamide and aldehyde was well reported with sodium bisulfite and DDQ but with higher reaction temperature and harsh conditions. Hence, Abdel-Jalil et al. reported an alternative lower temperature and high yielding procedure for synthesis of quinazolinones via condensation between alkyl, aryl or heteroaryl aldehydes and anthranilamide.

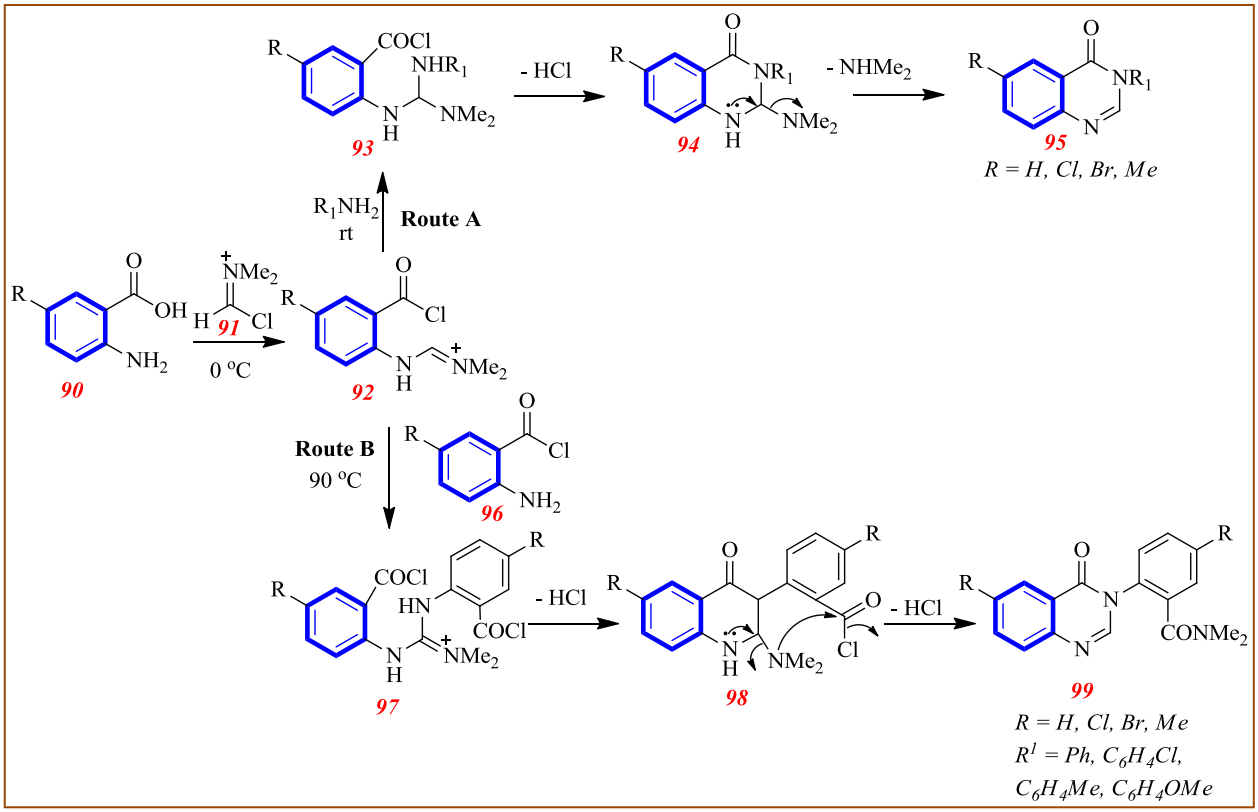


Eqn. 7. Condensation of aldehydes and anthranilamide and its derivatives

The Schiff base intermediate (**88, Eqn. 7**) was formed in EtOH solvent on refluxing condition by condensation of different aldehydes with anthranilamide (**75, Eqn. 7**) which on treatment with $CuCl_2$ in EtOH refluxing condition led to quinazolinones (**89, Eqn. 7**) in 3h.[62]

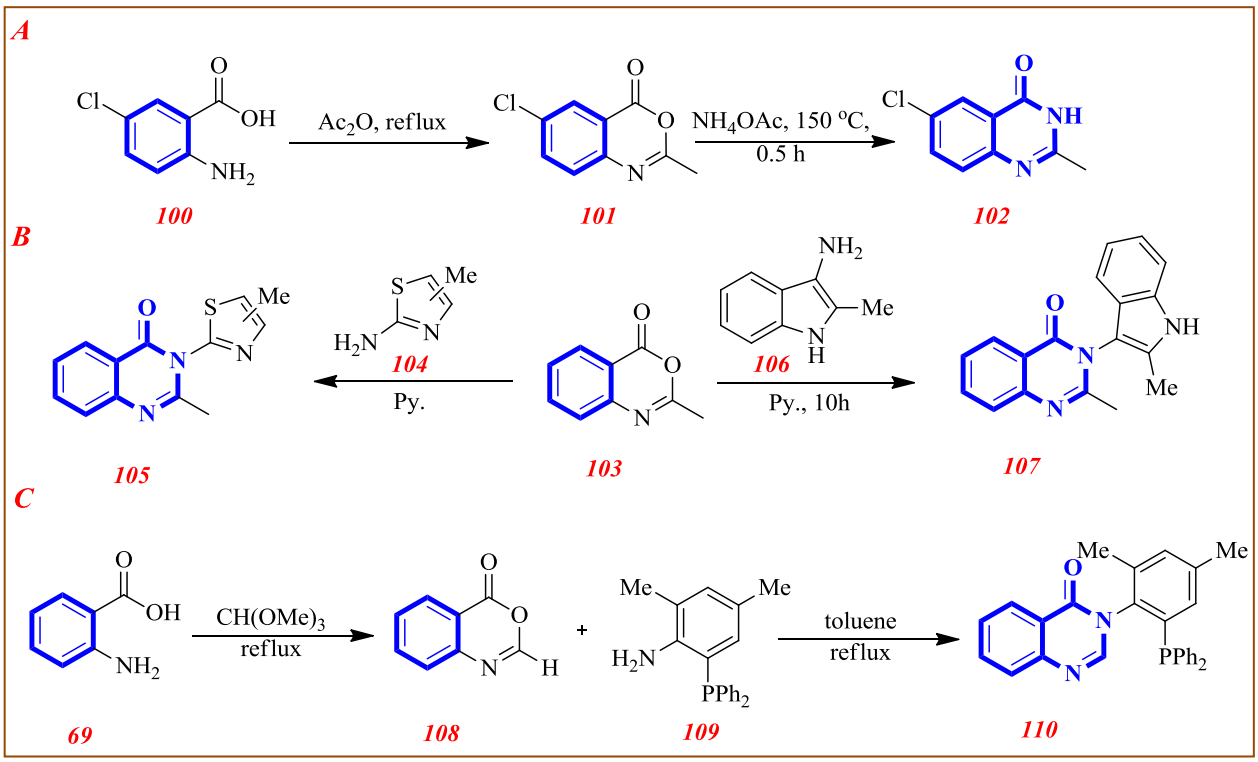
Perumal et al. developed the strategy for synthesis of 3-substituted quinazolinones starting from 5-substitued anthranilic acid derivatives (**90, Eqn. 8**) and Vilsmeier reagent (**91, Eqn. 8**). It was found that the reaction can work only on temperature 80-90 °C with differently substituted anthranilic acid derivatives without any dimerisation, however this reaction gave lower yield of the products when primary amines were used at room temperature. They proposed two routes for the progress of the reaction. In route B, the chloromethyleniminium salt (Vilsmeier reagent, **91, Eqn. 8**) that was formed from DMF and $POCl_3$ reacted with anthranilic acids to give the corresponding adduct (**92, Eqn. 8**) that reacts with the another acid chloride (**96, Eqn. 8**) to produce the diacid chloride adduct (**97, Eqn. 8**) that spontaneously undergo cyclization followed by aromatization to produce corresponding quinazolinone (**99, Eqn. 8**). In route A, the reaction

follows a different path where a low temperature has been subjected with an external primary amine. The amines react with the acid chloride (**92, Eqn. 8**) in rt and an expulsions of HCl followed by dimethylamine gave the corresponding substituted quinazolinone (**95, Eqn. 8**).[63]



Eqn. 8. 3-Substituted quinazolinones via Vilsmeier reagent

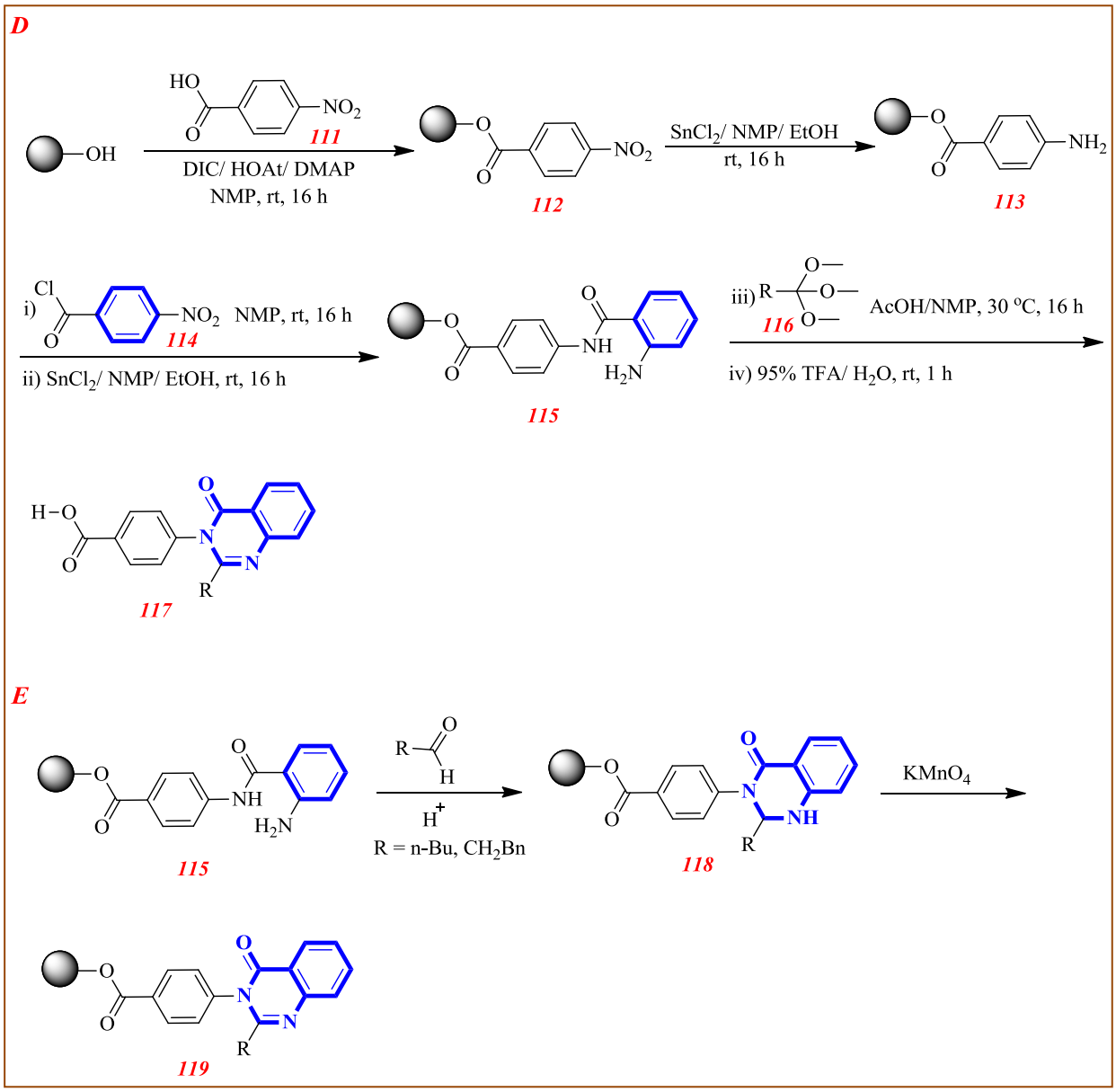
Jiang et al. developed a new method to synthesize 6-chloro-2-methylquinazolin-4(*3H*)-one (**102, Eqn. 9**) via corresponding benzoxazinone (**101, Eqn. 9**). Compound **101** was synthesized from 5-chloroanthranilic acid (**100, Eqn. 9**) on treatment with acetic anhydride under reflux condition. Corresponding quinazolinone **102** was obtained at 150 °C with ammonium acetate. (**A, Eqn. 9**). The same procedure being used for synthesis of 2-methyl-*4H*-benzo[*d*][1,3]oxazin-4-one **103** by Párkányi and Schmidt, it was then treated with substituted thiazoles (**104, Eqn. 9**) to produce some novel thiazole fused quinazolinones (**105, Eqn. 9**).



Eqn. 9. Synthesis of quinazolinones via benzoxazinones

A similar strategy was taken by Kumar group where they used compound **103** with 3-aminoindole (**106, Eqn. 9)** to synthesize 2, 3-disubstitued indoloquinazolinones (**107, Eqn. 9, B**). Virgil and Dai synthesized atropisomeric quinazolinone phosphine ligands (**110, Eqn. 9**) from (*4H*)-3,1-benzoxazin-4-one (**108, Eqn. 9**) on treatment with aminophosphine (**109, Eqn. 9**) in toluene under reflux condition for 6 h. Compound **108** was synthesized via condensation between anthranilic acid (**69, Eqn. 9, C**) and trimethylorthoester.[64] In 2000, Makino et al. developed a revised version for polymer bound quinazolinone synthesis (**Eqn. 10, D**). A series of quinazolinones (**117, Eqn. 10**) were synthesized via condensation of solid supported anthranilamides (**115, Eqn. 10**) and orthoformates (**116, Eqn. 10**) nphase™ Lanterns, with a long-chain hydroxymethylphenoxy linker was used as the surface of the polymer. Carboxylic acid precursors did not work well with polymer; hence they used different orthoesters for condensation in acetic acid and *N*-methyl-pyrrolidone (NMP). Due to mild acidic condition this strategy worked well with various alkyl and aryl substrates but the limited availability of othroformates remained the only drawback for this strategy. Still it was a much better process than Zhang's where aldehydes and compound **115** were used for condensation and one extra

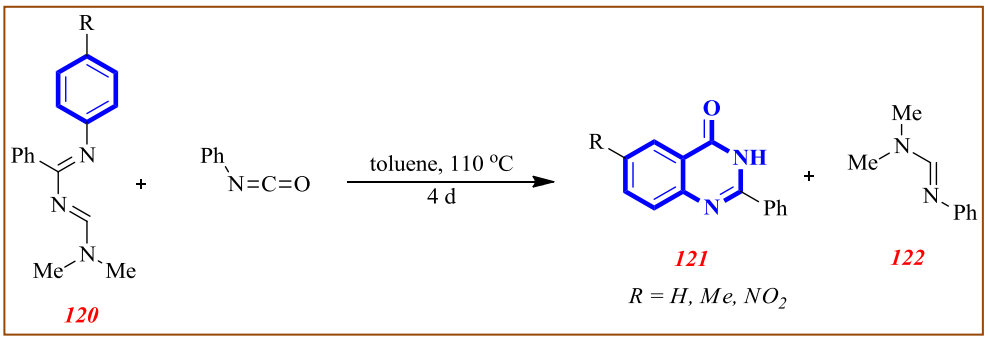
oxidation step has to be performed to get the quinazolinones (**119, Eqn. 10**). The major problem for Zhang procedure was purity that was solved by Makino.[65]



Eqn. 10. Synthesis of various quinazolinones via solid phase

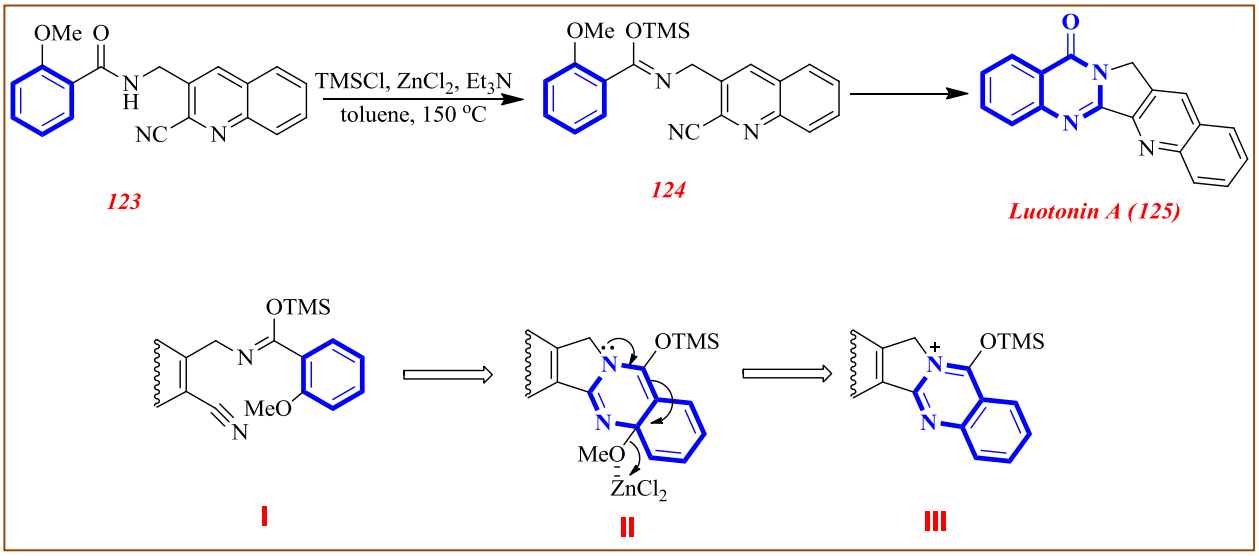
ii) Hetero Diels-Alder reaction:

Croce et al. reported the synthesis of 2-substituted-quinazolinones (**121, Eqn. 11**) via hetero Diels-Alder reaction between 1-aryl-4-dimethylamino-2-phenyl-1,3-diaza-1,3-butadienes (**120, Eqn. 11**) and phenyl isocyanate in toluene at reflux condition under nitrogen atmosphere.



Eqn. 11. Synthesis of 2-substituted-quinazolinones *via* hetero Diels-Alder reaction

The cycloaddition adduct was destabilized due to the presence of electron donating dimethylamino groups on the diene (**120, Eqn. 11**) that facilitate the elimination of the *N*,*N*-dimethyl-*N'*-phenylformamidine (**122, Eqn. 11**).[66]

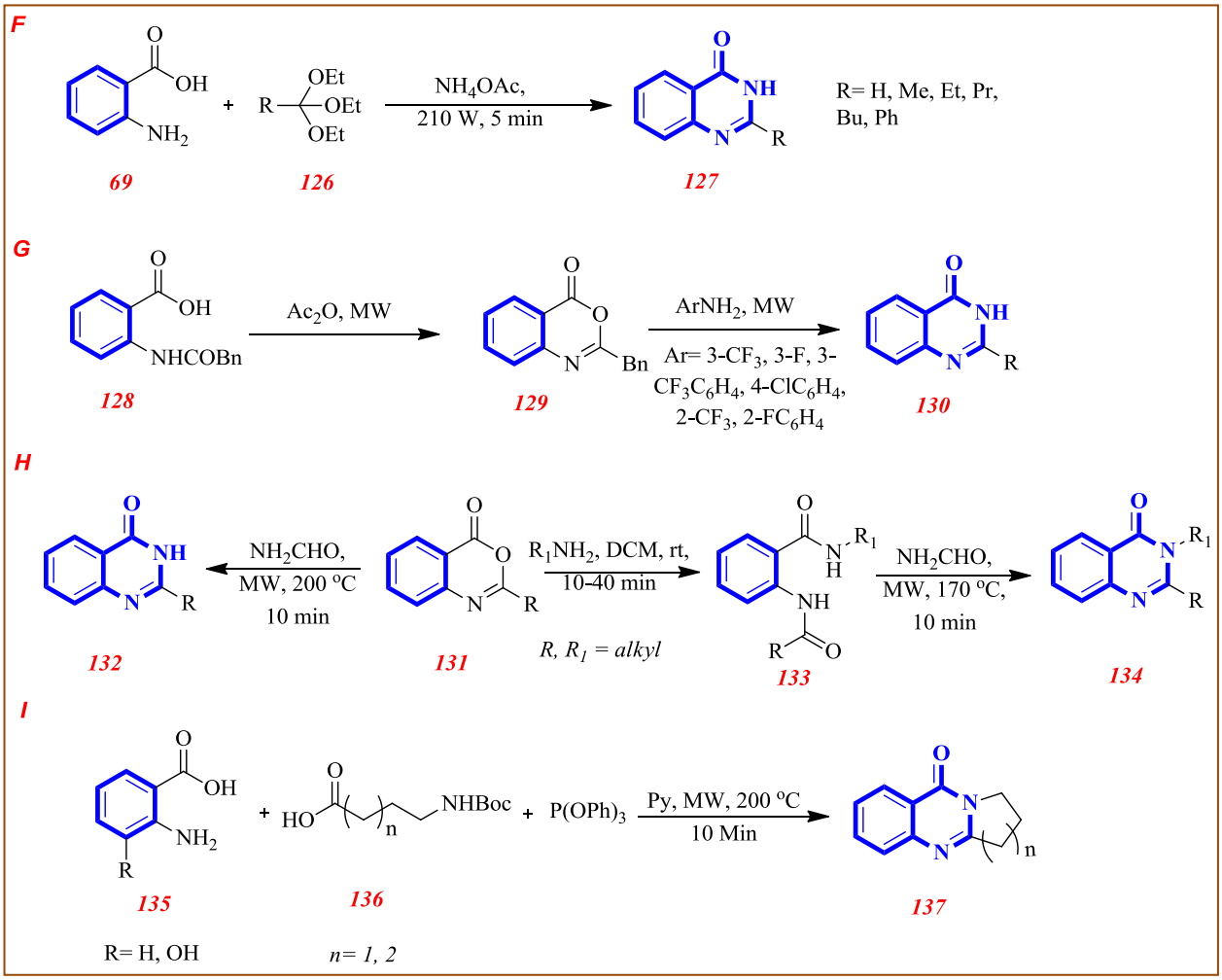


Eqn. 12. Synthesis of Luotonin A via hetero Diels-Alder reaction

The hetero Diels–Alder reaction was used by Toyota et al. in an intramolecular fashion with aryl imino ethers (diene) and aryl nitriles (dienophile) as the key reaction to develop an efficient synthetic route for pyrroloquinazolino-quinoline alkaloids. Luotonin A was synthesized by Toyota et al. using this intramolecular hetero Diels–Alder where they prepared the cyano-amide (**123, Eqn. 12**) as the key reaction intermediate. The presence of –OMe group was important to activate the diene. This compound **123** was then subjected to intramolecular hetero DA reaction using TMSCl and triethylamine with zinc chloride to form an intermediate **II** (**Eqn. 12**) that underwent in situ methoxy elimination as MeOH and later eradication of trimethylsilyl group to aromatize the intermediate **III** (**Eqn. 12**) to generate Luotonin A (**125, Eqn. 12**).[67]

iii) Microwave assisted reaction

Microwave assisted synthesis of quinazolinone was first reported by Rad-Moghadam and Mohseni et al. in 2003. The shorter reaction time and solvent free features make microwave techniques more useful. A simple condensation reaction of anthranilic acid (**69, Eqn. 13, F**) and orthoesters (**126, Eqn. 13, F**) in presence of ammonium acetate in neat condition was reported using microwave. The reaction took only 5 min to give the corresponding 2-substituted-4(*3H*)-quinazolinone (**127, Eqn. 3, F**) in good yield.[68]



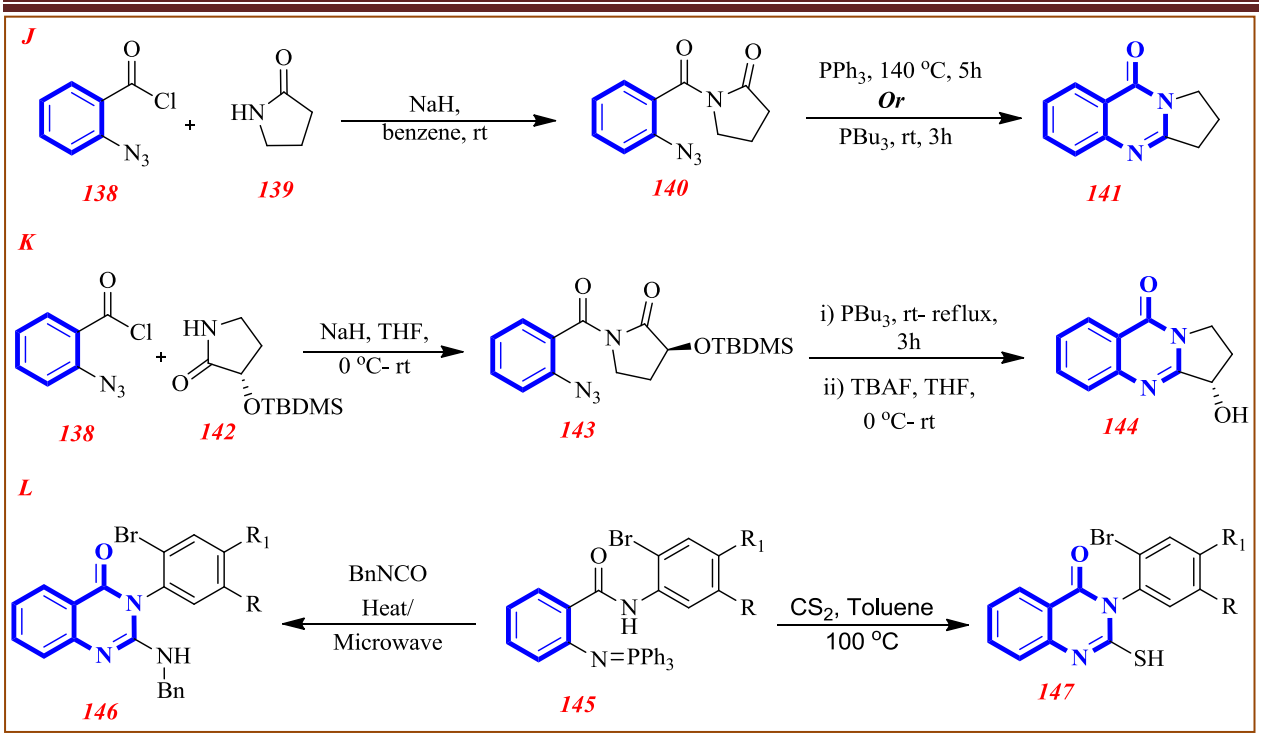
Eqn. 13. Synthesis of various quinazolinone via microwave

Fluorinated 2,3- disubstituted quinazoline-4(*3H*)ones (**130, Eqn. 13, G**) were synthesized by Dandia et al. using microwave condition. The benzoxazin-4-one (**129, Eqn. 13, G**) intermediate was generated in situ using microwave by condensation with anthranilic acid derivatives (**128,**

Eqn. 13, G) and acetic anhydride which reacted with *m* and *p*-aniline derivatives under microwave condition to give 2,3-disubstituted quinazolinones (**130, Eqn. 13, G**).[69] In 2007, Besson et al. reported the synthesis for 2,3-disubstituted quinazolinones (**134, Eqn. 13, H**) using dehydrative cyclization of a linear diamides (**133, Eqn. 13, H**) under microwave condition. Here formamide was used as solvent, however they also showed that formamide can be used as an ammonia source under controlled conditions of power, temperature and time with microwave to furnish 2-substituted quinazolinones (**132, Eqn. 13, H**) via rapid decomposition of formamide.[70] In 2005, Liu et al. reported total synthesis of some important quinazolinone alkaloids (**137, Eqn. 13, I**) using microwave technique. They reported a three component domino reaction for synthesis of alkaloids like deoxyvasicinone, mackinazolinone and 8-hydroxydeoxyvasicinone using anthranilic acid derivatives (**135, Eqn. 13, I**) with amino acids (**136, Eqn. 13, I**) along with triphenylphosphite under microwave at 150 °C for 10 minutes.[71]

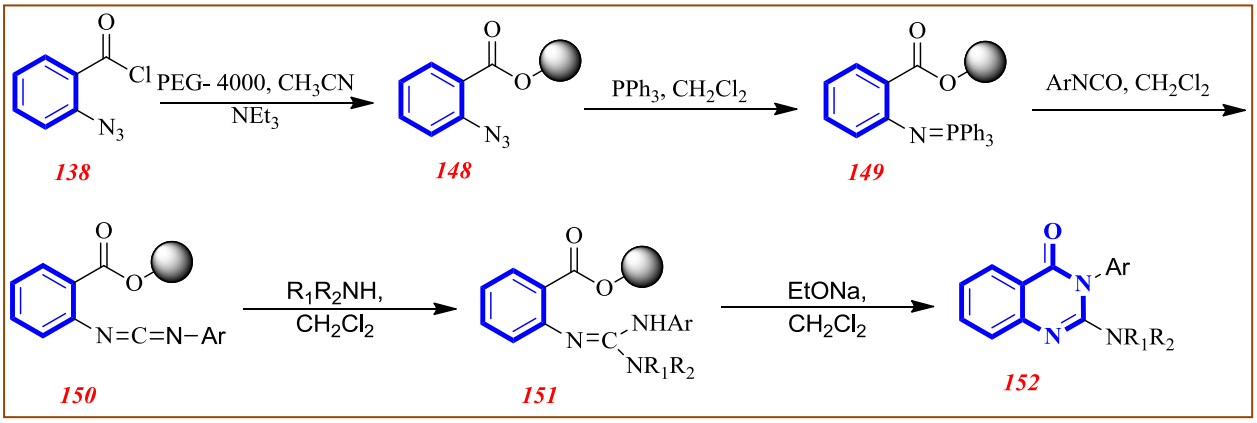
iv) Aza-Wittig reaction:

The aza-Wittig strategy which is famous as Eguchi's protocol is a very important constructing tool for quinazolinone alkaloids. The basic reaction was shown in **Eqn. 14** (**J**) where the pyrrolidone (**139, Eqn. 14, J**) was treated with compound **138** to obtain the azide (**140, Eqn. 14, J**). This azide **140** underwent cyclization in a shorter reaction time in presence of tributylphosphine whereas with triphenylphosphine it needed higher temperature and longer reaction time. In 1996, Eguchi et al. reported the total synthesis of optically active *l*-vasicinone (**144, Eqn. 14, K**) via intramolecular Aza-Wittig reaction. They have used this reaction as their key step to synthesize *l*-vasicinone. The synthesis was initiated by *tert*-butyldimethylsilyl chloride protection of the chiral synthon, (*3S*)-3-hydroxy-γ-lactam that underwent condensation with *o*-azidobenzoyl chloride in presence of sodium hydride and THF. The intermediate **143** underwent the tandem intramolecular Aza-Wittig reaction with tributylphosphine that furnished *o-tert*-butyldimethylsilyl vasicinone and finally they deprotected TBDMS group with tetra-*n*-butylammonium fluoride (TBAF) to achieve *l*-vasicinone (**144, Eqn. 14, K**) in 52% overall yield.[72]



Eqn. 14. Aza-Wittig method to synthesize quinazolinones

An efficient strategy was developed by Molina et al. to synthesize quinazolinone moieties with linear or angular tetracyclic ring systems that are not available readily (**Eqn. 14, L**).

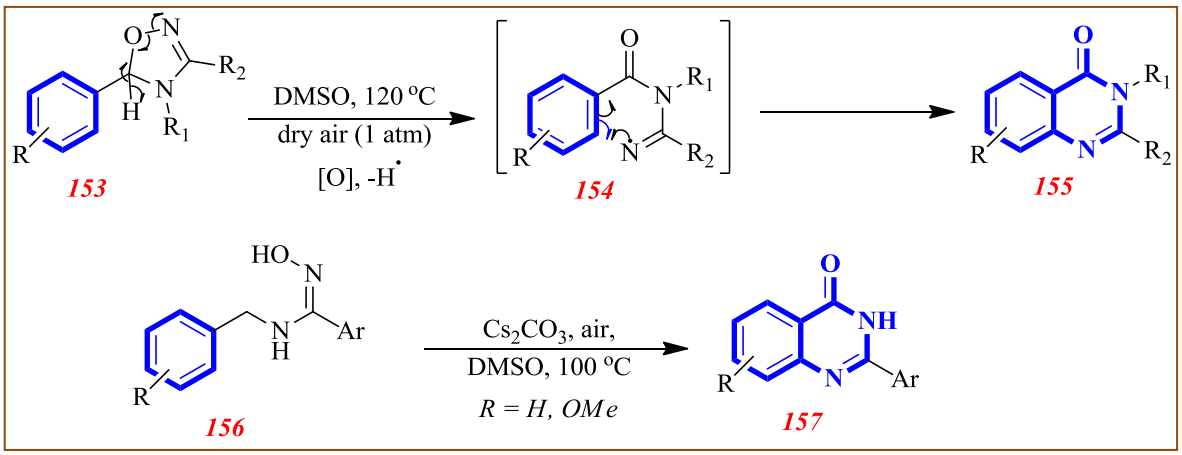


Eqn. 15. Solid phase supported Aza-Wittig synthesis for quinazolinones

They have used an (arylimino)phosphoranes (**145, Eqn. 14, L**) whose *ortho*-position was substituted with *N*-(*o*-substituted-aryl) carboxamide substituents to synthesize the quinazolinone (**146, Eqn. 14, L**), this nitrogen functionality promotes heterocyclization after the aza-Wittig reaction. Aryl isothiocyanates (**147, Eqn. 14, L**) was also synthesized via aza-Wittig reaction using carbon disulfide with iminophosphoranes (**145, Eqn. 14, L**).[73]

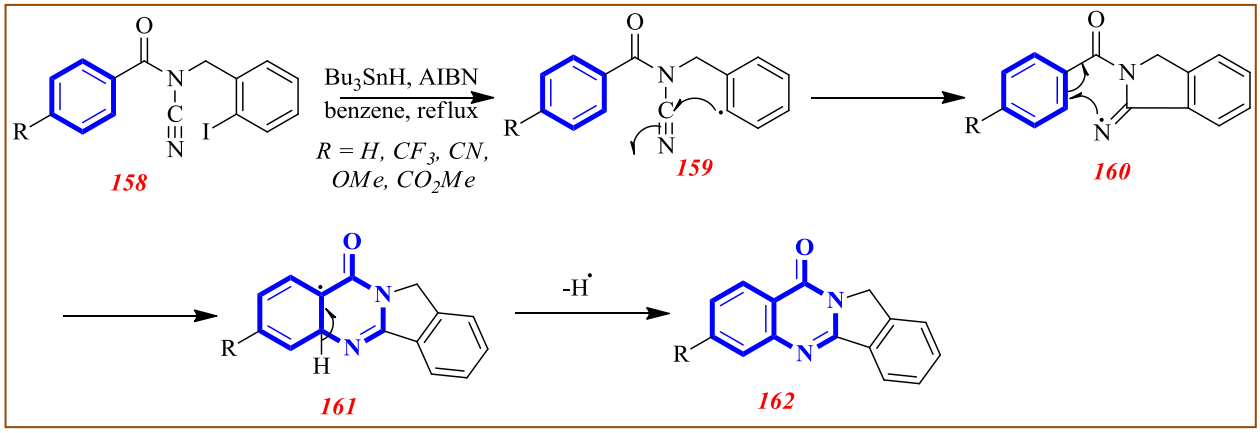
In 2008, Ding et al. reported a polymer supported aza-Wittig reaction for synthesis of 4(*3H*)-quinazolinones. They have used cheap difunctional poly(ethylene glycol) PEG-4000 as a soluble polymer support. A large number of quinazolinone were synthesized with good yields using different secondary amines and isocyanate (**Eqn. 15**).[74]

v) Radical cascade:



Eqn. 16. Synthesis of quinazolinone via radical cascade reaction

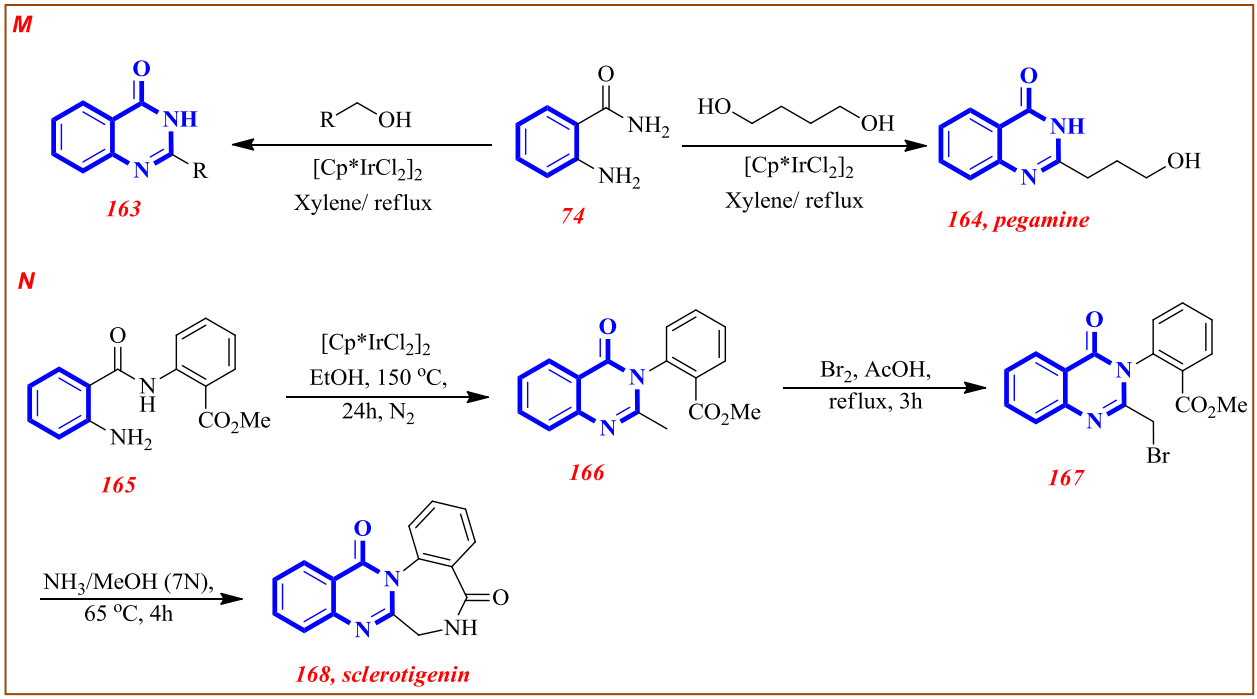
An atom- and step-economical radical cascade rearrangement of 5-aryl-4,5-dihydro-1,2,4-oxadiazoles was reported by Chiba and co-workers to synthesize various 2,3-disubstituted quinazolinones. They proposed a single-electron oxidation or hydrogen radical abstraction by an external radical source that cleaved the N-O bond homolytically to form iminyl radical (**154)**. This iminyl radical (**154)** underwent intramolecular radical cascade with the various aryl substituent that followed by aromatization to generate 2,3-disubstituted quinazolinones (**155)**. This strategy was further extended with *N*-benzyl amidoximes (**156)** to synthesize 2-subsitituted quinazolinones (**157**, **Eqn. 16**).[75] Another cascade radical cyclization process was developed by Malacria and co-workers from *N*-acylcyanamides (**158)** to access pyrroloquinazoline-type polycyclic *N*-heterocycles (**162)**. Due to the homolytic cleavage of hydrogen atom or carbon bond of aromatic ring it creates a radical that migrates to generate new C-N and C-C bonds. A various number of pyrimidones fused with alkyl, aryl, or heteroaryl moieties were synthesized using this protocol and has also been extended for synthesis of the biologically important alkaloid luotonin A (**Eqn. 17**).[76]



Eqn. 17. Cascade cyclization of *N*-acyl-*N*-(2-iodobenzyl)cyanamides

vi)Transfer hydrogen:

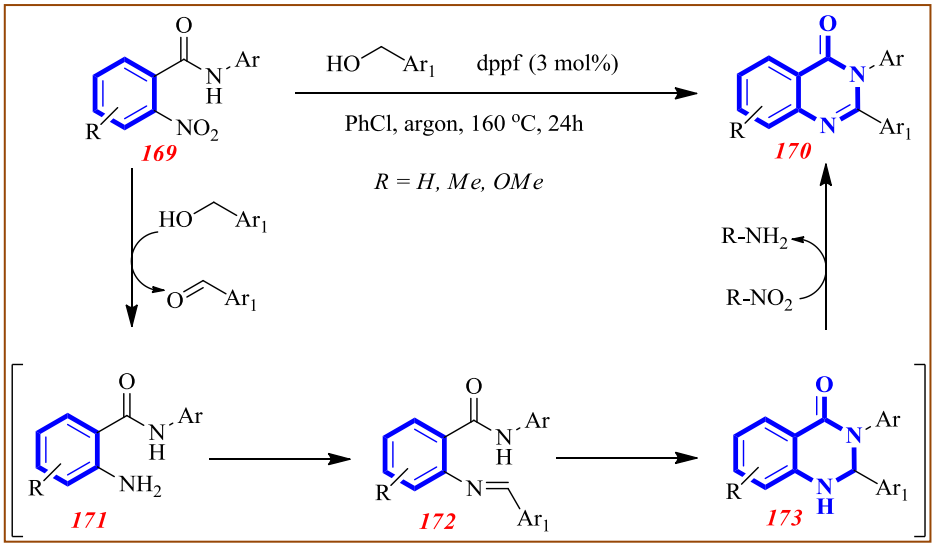
Recently, hydrogen transfer strategy became a useful tool for C-N bond formation, especially N-alkylation of amines with alcohols. This protocol based on the in situ dehydrogenation of the alcohol to corresponding aldehyde or ketone which reacted with amine to generate the imine that reduced to corresponding amine with the previously liberated hydrogen.



Eqn. 18. Iridium catalyzed synthesis of quinazolinones

Using this strategy Zhou et al. synthesized various quinazolinone in a one pot method from primary alcohol and anthranilamide. The reaction was carried out under base free condition using

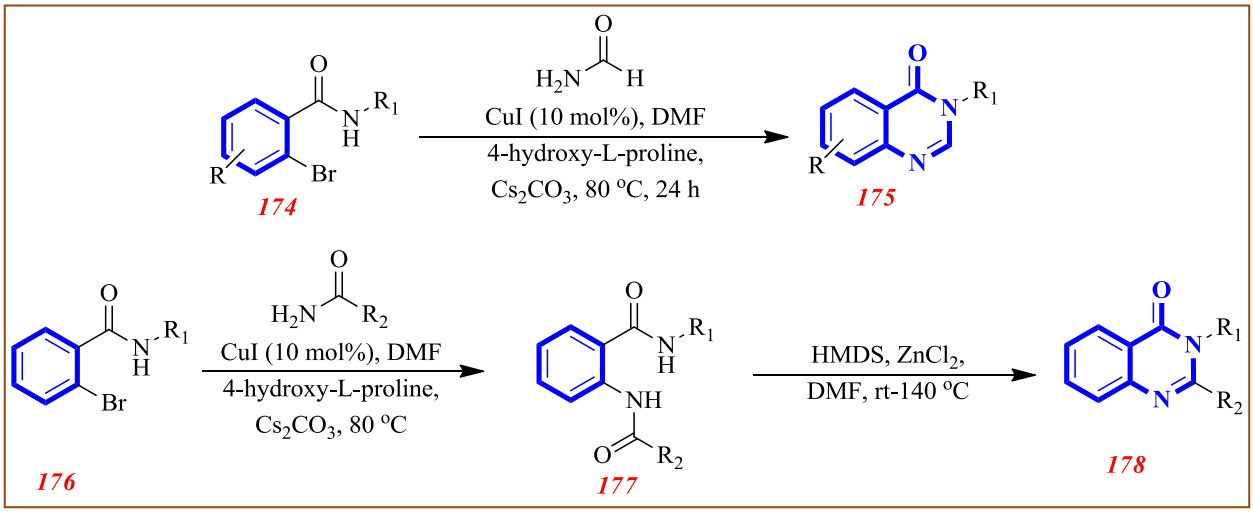
Ir catalyzed dehydrogenation. It was further extended for the synthesis of two biologically active alkaloids pegamine and sclerotigenin (**Eqn. 18**).[77] Deng et al. also used hydrogen transfer protocol to synthesize 2,3-diarylquinazolinones from *o*-nitrobenzamides and aryl alcohols. They have used iron catalyzed method for hydrogen transfer (**Eqn. 19**).[78]



Eqn. 19. Fe catalyzed hydrogen transfer to synthesize quinazolinones

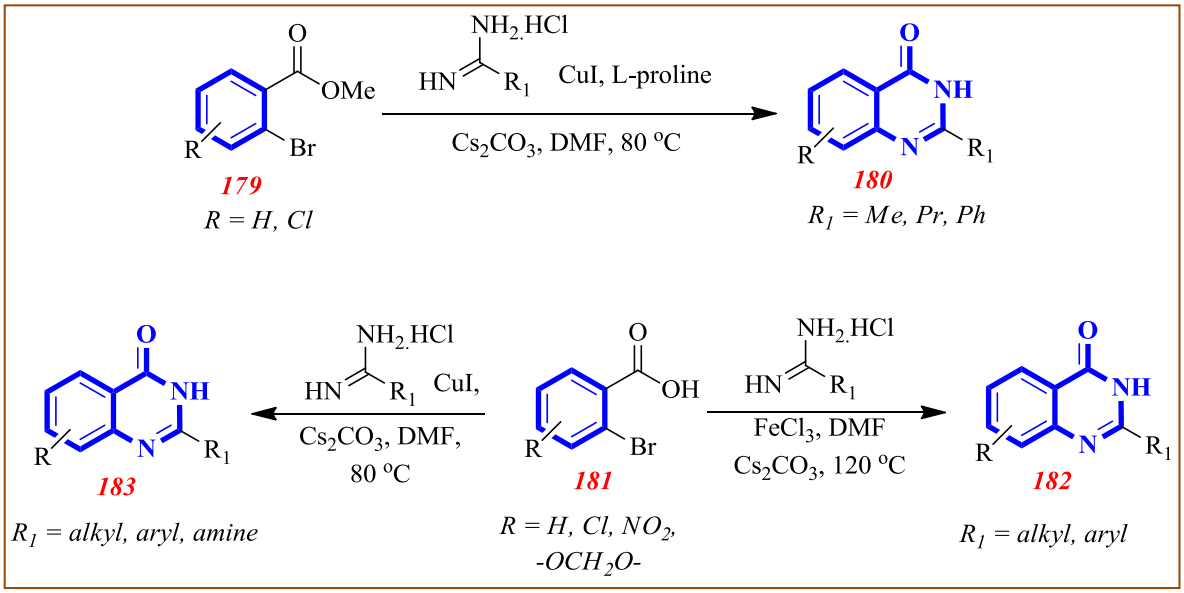
vii) Transition metal catalyzed cyclization:

Ma et al. reported the Cu catalyzed aryl amidation reaction between *O*-bromobenzamides (**174, Eqn. 20**) and formamide which directly furnish the 3-substituted quinazolinones (**175, Eqn. 20**); whereas, in case of aryl/ alkyl amides only coupled product (**177, Eqn. 20**) was formed on using the same condition. To afford 2,3-disubstituted quinazolinones from compound **177,** Ma and co workers used HMDS/$ZnCl_2$ mediated cyclization (**Eqn. 20**). This protocol was further applied for the formal synthesis of dictyoquinazol A and methaqualone. Ullmann *N*-arylation was found to be one of the important strategies to synthesize quinazolinone by using transition metals.[79] Very recently, Zhao and co-workers developed a copper-catalyzed cascade for synthesis of 2-substituted quinazolin-4(*3H*)-ones (**180, Eqn. 21)** using amidine hydrochlorides and methyl 2-bromobenzoates (**179, Eqn. 21)**.



Eqn. 20. Diamide cyclization via HMDS to synthesize quinazolinone

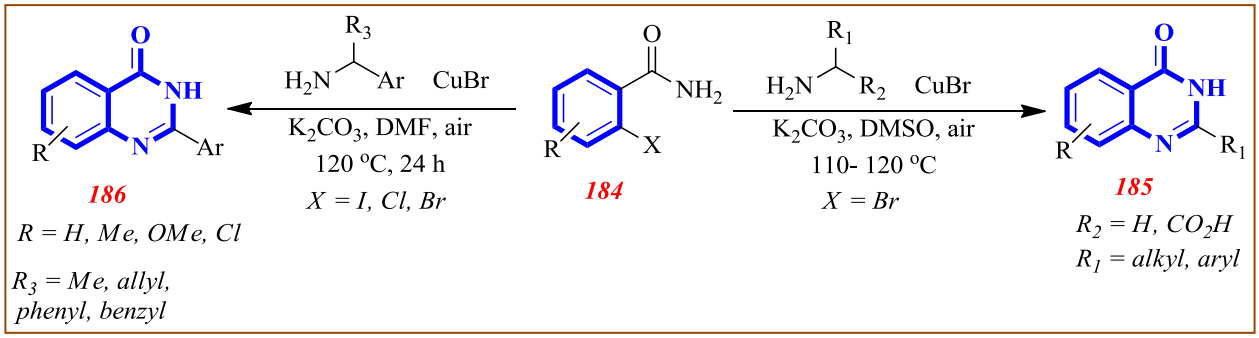
They have used CuI as a catalyst and L-proline as a ligand to form the C-N bond with amidine hydrochloride to get substituted quinazolinones with excellent yields. Later, the same group reported a ligand free synthesis of 2-substituted quinazolin-4(*3H*)-ones (**183, Eqn. 21)** using Cu salts as catalyst with amidine hydrochlorides via C-N bond formation followed by intramolecular cyclization; however they used 2-bromoarylcarboxylic acids (**181, Eqn. 21)** instead of ester.[80]



Eqn. 21. Quinazolinone synthesis via amidine cyclization

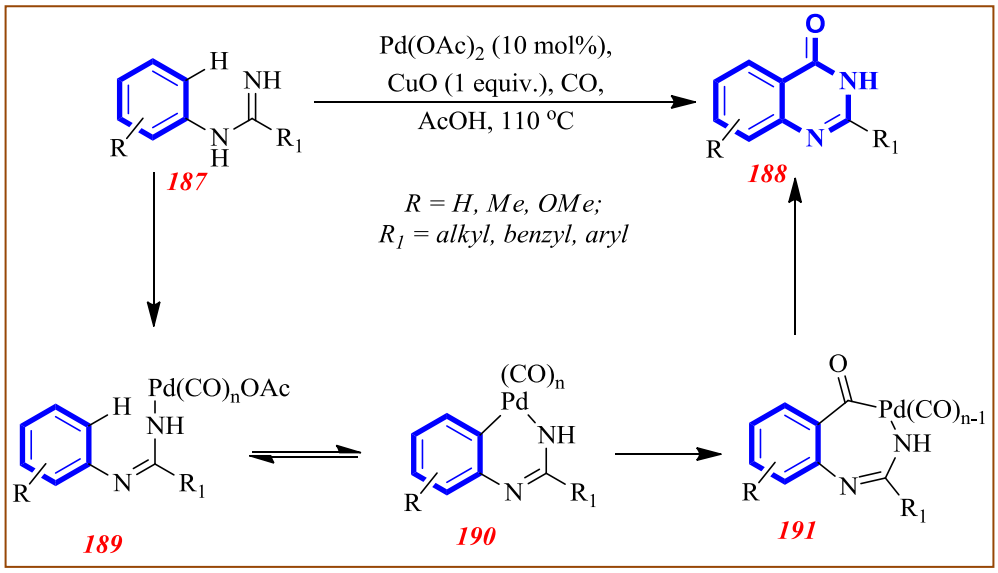
An inexpensive and environmentally friendly Fe catalyzed protocol was further developed by Fu and co-workers to synthesize 2-substituted quinazolin-4(*3H*)-ones from 2-bromoarylcarboxylic acids (**181, Eqn. 21)** and amidine hydrochlorides.[81] Fu and coworkers also reported a Cu catalyzed Ullmann type *N*-arylation and cyclization with o-bromobenzamide and amines/ amino

acids (**Eqn. 22**). An initially formed C-N coupled intermediate underwent aerobic oxidation to form an imine which cyclized via intramolecular amidation and oxidized to 2-substituted quinazolinones (**185, Eqn. 22**). Tang and co-workers also reported a similar protocol to synthesize compound **186** that included C-N bond formation via C-C bond cleavage. This protocol was more efficient in order to substrate scopes.[82]



Eqn. 22. Cu catalyzed benzylamine cyclization

viii) Transition metal catalyzed cyclocarbonylation:

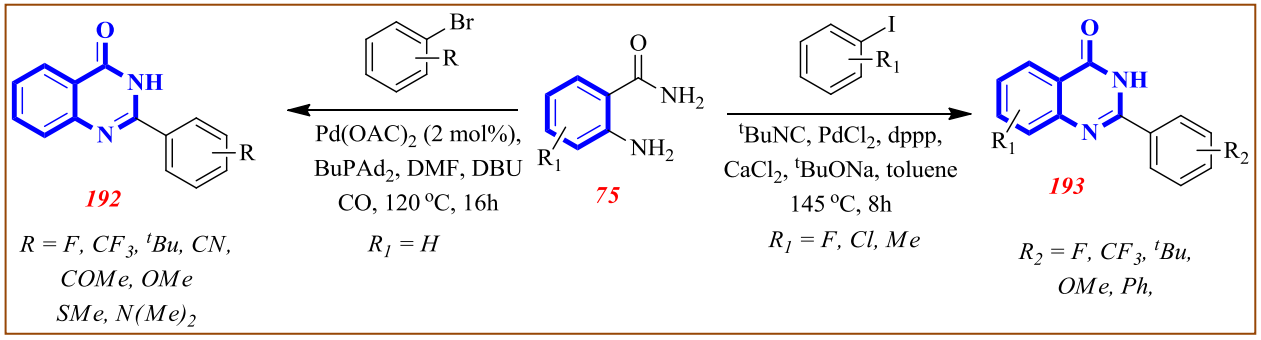


Eqn. 23. Palladium-catalyzed C(sp^2)–H carboxamidation of *N*-arylamidines

In 2011, Zhu and coworkers reported a Pd catalyzed intramolecular C(sp^2)-H activation of *N*-arylamidines (**187, Eqn. 23**) to produce the quinazolin-4(*3H*)-ones (**188, Eqn. 23**). This carboxamidation was developed by using $Pd(OAc)_2$ as catalyst, CuO as oxidant under Carbon monoxide atmosphere to synthesize various alkyl and aryl substituted quinazolinones. The

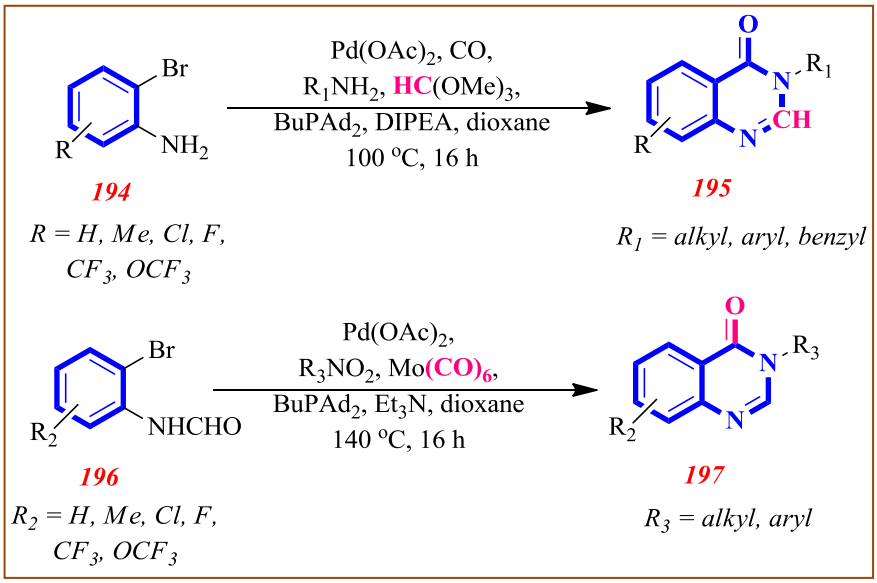
mechanistic path described an chelation with amidine nitrogen and Pd(II) gave the intermediate that underwent reversible cyclopalladation. Next, the insertions of CO into the C-Pd bond generated the seven member carbopalladacycle that underwent reductive elimination and released Pd(0) to generate **188**, whereas Pd(0) was again reoxidized by CuO (**Eqn. 23**).[83]

Another carbonyaltive process was developed by Beller et al. to synthesize 2-substituted quinazolinone (**194, Eqn. 24**) from 2-amino benzamides and aryl bromides via Pd salt. The reaction proceed through with initial addition of Pd(0) to the aryl bromide, followed by CO insertion to generate acylpalladium complex which underwent nucleophilic attack by amine. Finally reductive elimination followed by intramolecular condensation gave compound (**192, Eqn. 24**).[84] Another Pd catalyzed multicomponent synthesis was reported for 2-substituted quinazolinones by Ji et al. with 2-aminobenzamides and aryl bromides. Here they used isocyanide which inserted with aryl bromide that reacted with benzamide and later expelled to give the cyclized product (**193, Eqn. 24**).[85]



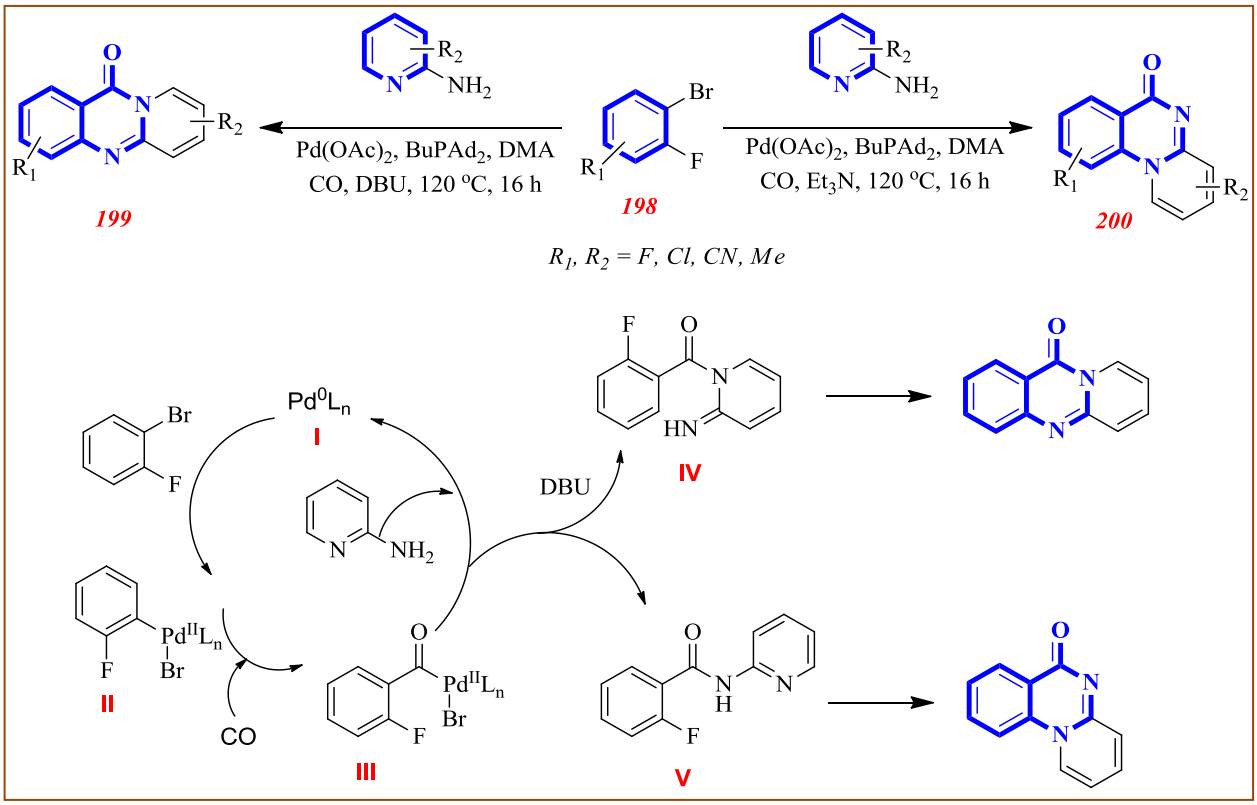
Eqn. 24. Palladium-catalyzed diamidation reaction

Beller and Wu et al. reported two consecutive processes to synthesize 3-substituted quinazolinone using Pd catalyzed multicomponent carbonylation reaction. A four component reaction was reported for synthesis of **195** with 2-bromoaniline and aryl/alkyl amines using Pd salt as catalyst under CO atmosphere. The main advantages of this protocol were selectivity high substrate scopes and easy work up. Subsequently, the same group reported another protocol to synthesize 3-substituted quinazolinone from 2′-bromoformanilides (**196)** with nitroaryl/ alkyl compounds where $Mo(CO)_6$ worked as multiple promoter. This protocol was also applied for a large range of substrates (**Eqn. 25**).[86]

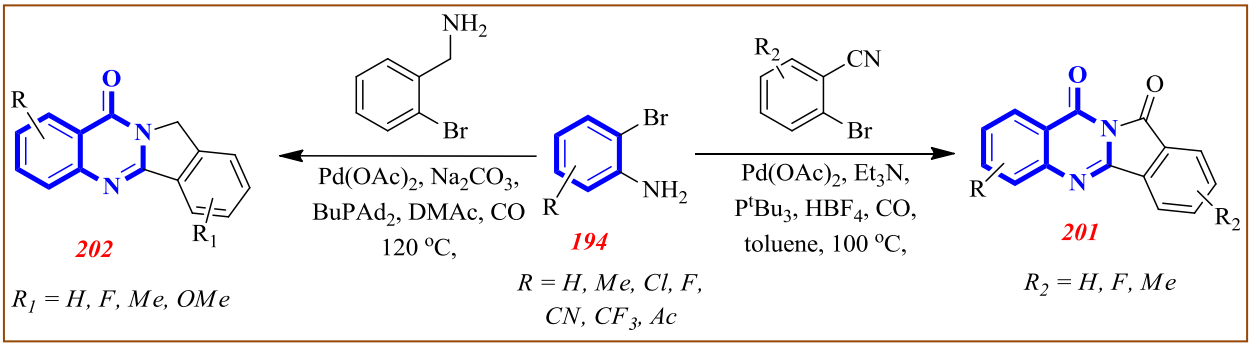


Eqn. 25. Palladium-catalyzed carbonylation

Beller and Wu et al. again reported a Pd-catalyzed carbonylation followed by intramolecular nucleophilic substitution reaction to synthesized linear or angular pyridoquinazolinones **199** or **200** (**Eqn. 26**). The formations of either isomer were entirely based on selection of the base. On use of Et_3N the angular derivatives were formed in 40–78% yield; whereas, with DBU linear products **199** were obtained. The proposed mechanism involves an initial insertion of Pd followed by carbonylation which gives complex III which undergo amine attack to generate complexes IV and V. These complexes underwent intramolecular nucleophilic substitution to generate compound **199** and **200** (**Eqn. 26**).[87] The same group later reported same Pd-catalyzed double carbonylation protocol for synthesis of isoindolo[1,2-*b*]quinazoline-10,12-diones **201.** They have used bromoanilines **194** and bromobenzonitriles as a starting material and reaction proceeds with minimum five C-C/ C-N bond formations. Later, Wu and co-workers used (2-bromobenzyl)amines instead of bromobenzonitrile to synthesize isoindolo[1,2-*b*]quinazolin-10(*12H*)-ones **202** with bromoanilines via double carbonylation (**Eqn. 27**).[88]



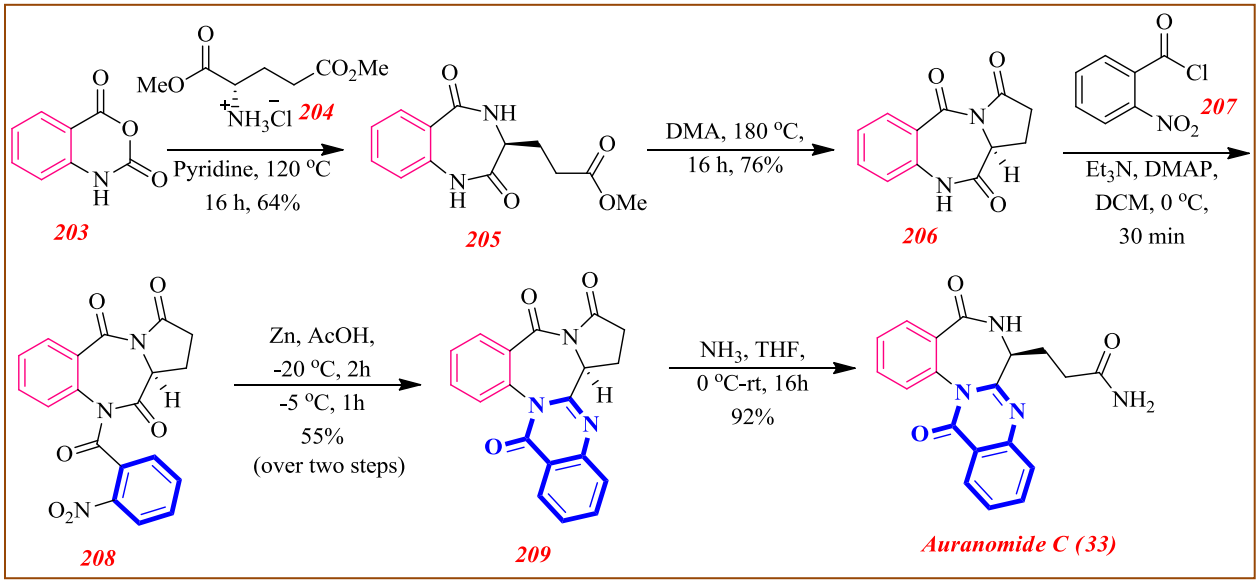
Eqn. 26. Palladium-catalyzed carbonylation of *N*-aryl-2-aminopyridines



Eqn. 27. Palladium-catalyzed double carbonylation

Total synthesis of some important quinazolinone alkaloids:

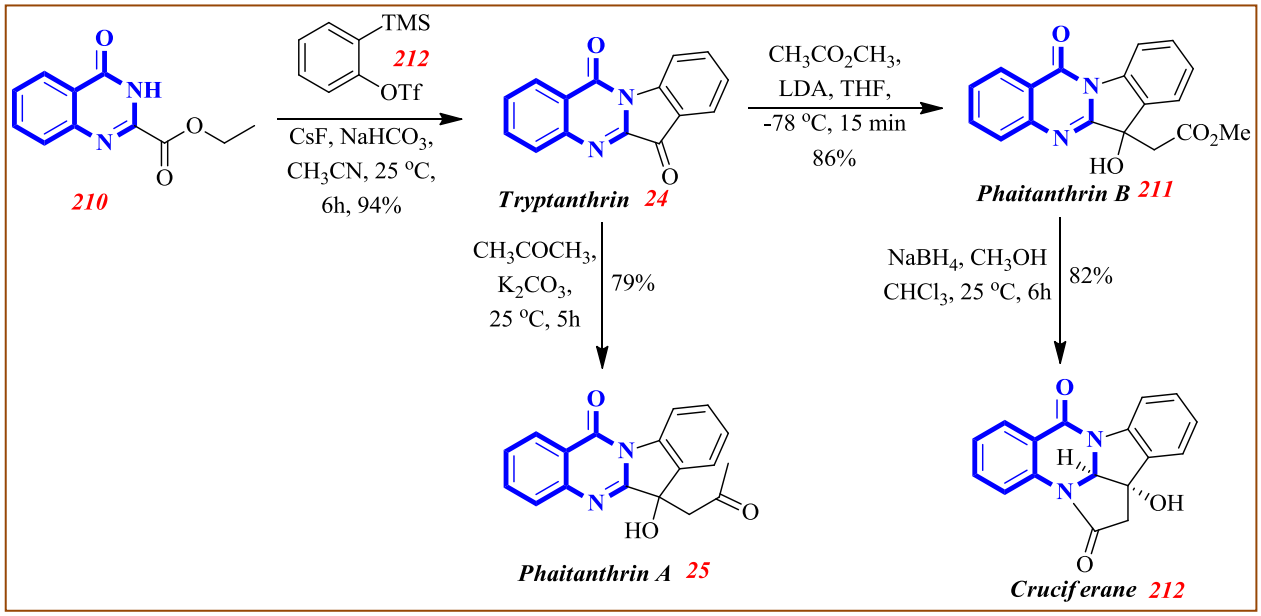
The importance and different methodologies for synthesizing quinazolinone was discussed so far; with respect to that some recent synthesis of important biologically active quinazolinone alkaloids is also necessary. In 2014, Sorra et al. reported the first total synthesis of (-)-auranomide C (**33, Eqn. 28**).They prepared a dilactam intermediate (**205, Eqn. 28**) from isatoic anhydride (**203**) and glutamate (**204**).



Eqn. 28. Synthesis of (-)-auranomide C

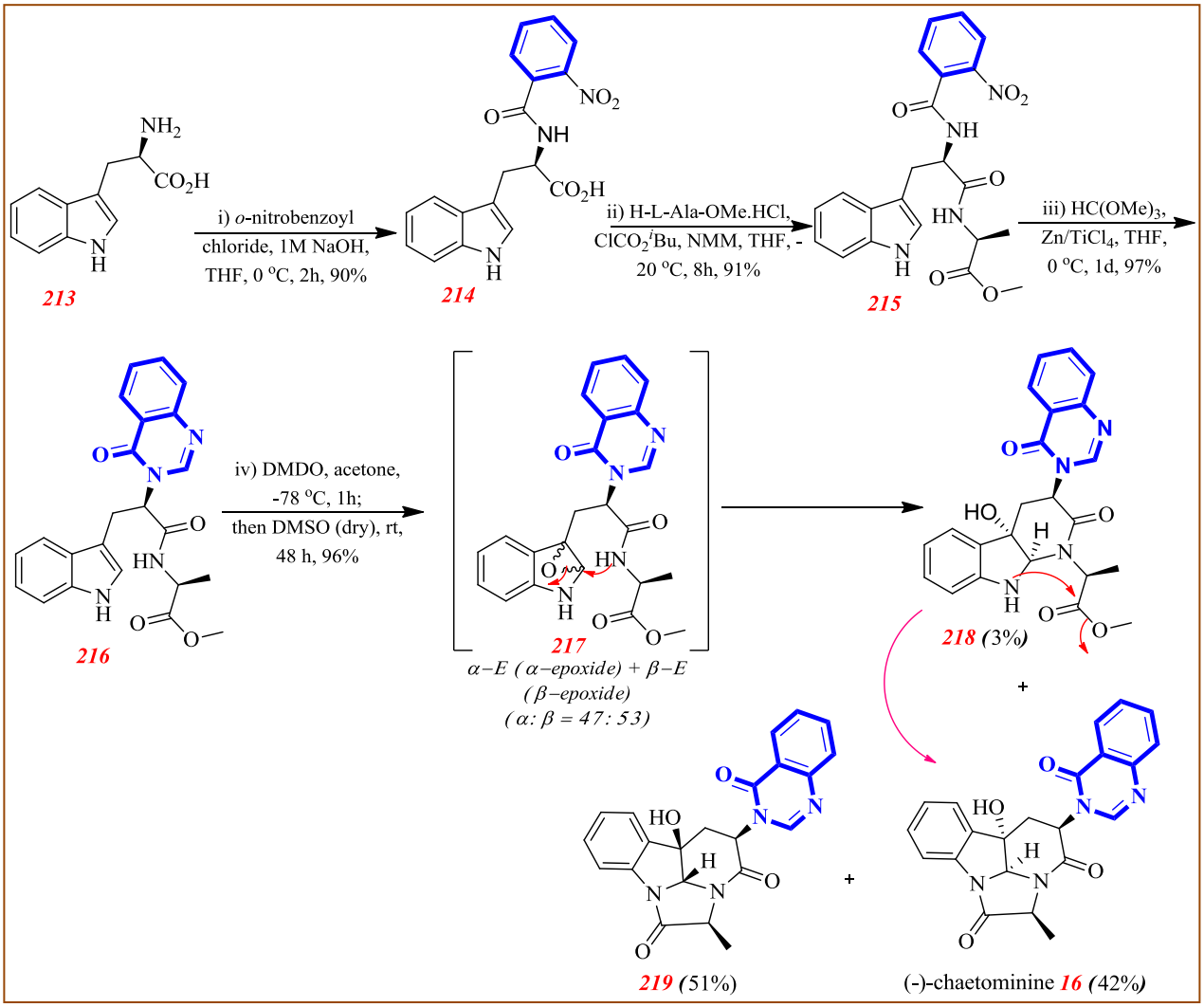
The dilactam then underwent an intramolecular cyclization with DMA at high temperature to furnish a tricyclic compound (**206**). This tricyclic intermediate reacted very smoothly to give the amidation product (**208**) with 2-nitrobenzoyl chloride. This compound **208** later underwent a reductive cyclization to produce compound **209** in high enantiomeric excess. Later an ammonia mediated ring opening of this fused lactam **209** gave (-)-auranomide C (**33**) in high enantiomeric purity.[89]

Argade et al. developed an aryne insertion reaction with quinazolinone to synthesis biologically active alkaloids like tryptanthrin, phaitanthrin A and B, along with cruciferane. A concerted aryene insertion to quinazolinone (**210, Eqn. 29**) gave tryptanthrin (**24**), it underwent aldol condensation with acetone and K_2CO_3 to furnish phaitanthrin A (**25**) in 79% yield.



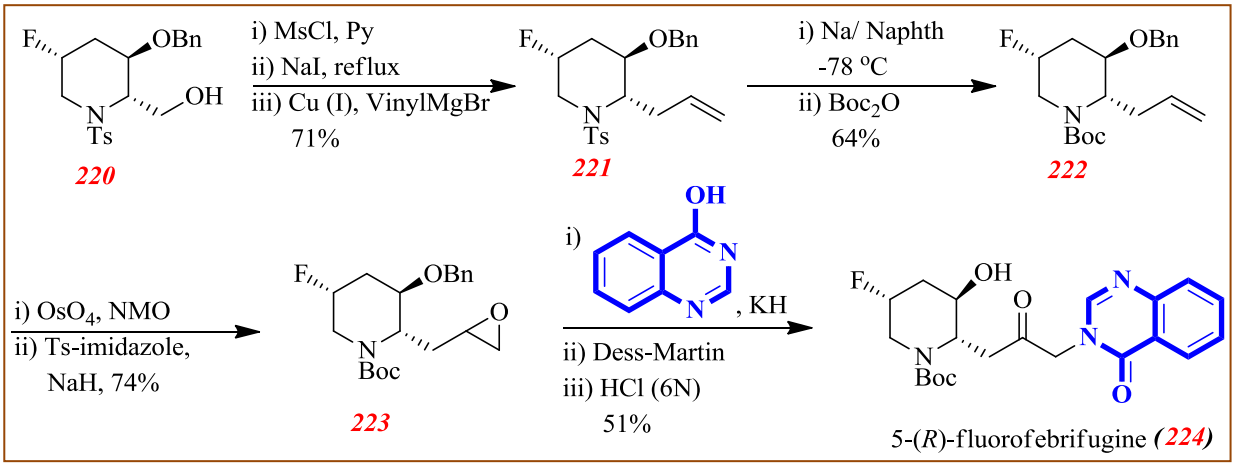
Eqn. 29. Synthesis of phaitanthrin A, B and cruciferane

On the other side to get a chemoselective condensation for synthesis of phaitanthrin B (**211**) they treated tryptanthrin (**24**) with methyl acetate using LDA as base at -78 °C. This phaitanthrin B (**211**) underwent a chemo and diastereoselective reductive intramolecular cyclization by sodium borohydride to generate cruciferane (**212, Eqn. 29**) in 82% yield.[90] In 2014, Huang group reported a total synthesis for (-)-chaetominine (**Eqn. 30**), which showed potent activity against human colon cancer SW1116 (28 nM) and leukemia K562 (21 nM) cell lines. Their protocol was very effective as they used a one pot cascade; epoxidation-ring opening and cyclization-lactmization. They started their reaction with D-tryptophan (**213, Eqn. 30**) followed by two amidation one with *o*-nitrobenzoyl chloride and then with L-alanine methyl ester hydrochloride salt to acquire the dipeptide intermediate (**215, Eqn. 30**). Next, they have used modified Shi protocol to form the quinazolinone ring (**216, Eqn. 30**). Then, on treatment with an optimized basic condition with DMDO and dry calcium hydride they were able to furnish (-)-chaetominine (**16, Eqn. 30**) along with its lactamized precursor **218** with very lower yield and the epimer of (-)-chaetominine (**219, Eqn. 30**).[91]



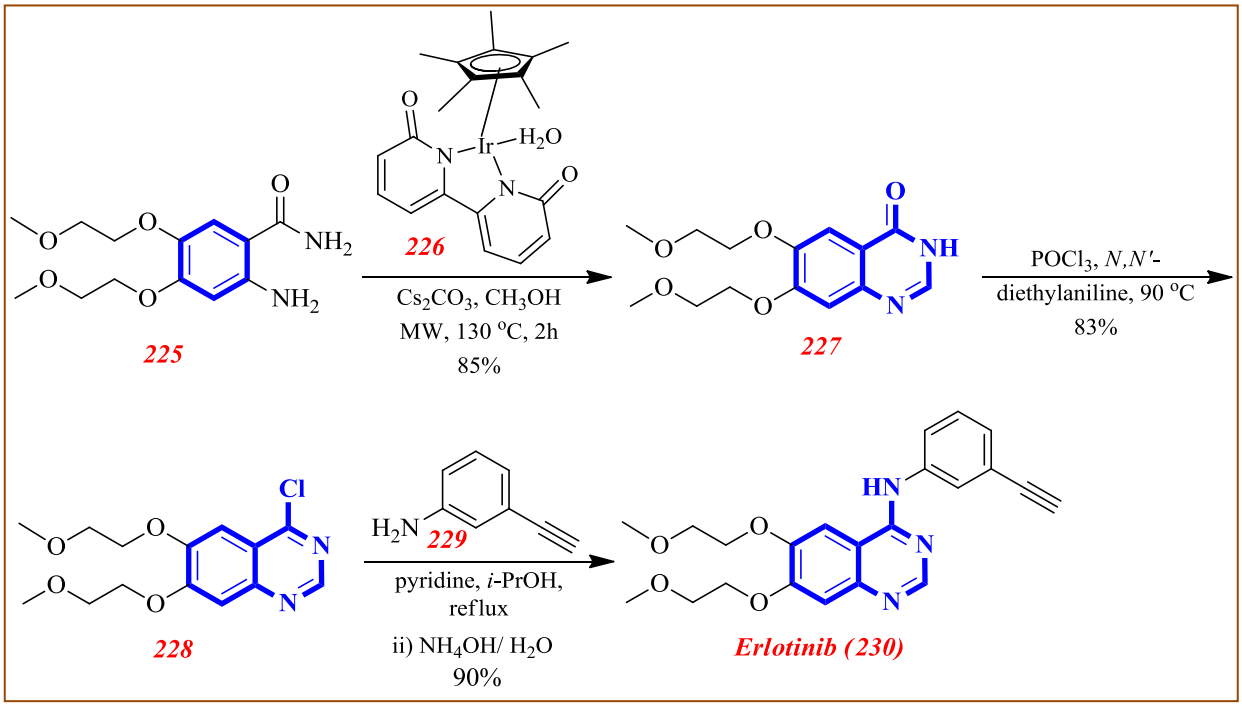
Eqn. 30. Synthesis of (-)-chaetominine

Recently, Liu and Chen et al. reported the synthesis of another quinazolinone alkaloid 5-(*R*)-fluorofebrifugine (**224, Eqn. 31**). They started with a fluoro intermediate **220** which underwent a total three step interconversion from alcohol to an alkene intermediate **221**. Intermediate **226** then underwent a protecting group exchange to furnish compound **222**. This intermediate was further subjected to the upjohn conditions to form the epoxide (**223, Eqn. 31**) on the terminal double bond via two steps. The nucleophilic attack with 4-hydroxy quinazolinone gave the skeleton of fluorofebrifugine which underwent DMP oxidation to give 5-(*R*)-fluorofebrifugine (**224, Eqn. 31**).[92]



Eqn. 31. Synthesis of 5-(*R*)-fluorofebrifugine

Li et al. also described a novel methodology to synthesize quinazolinone via a metal−ligand bifunctional iridium catalyst [Cp*Ir(2,2′-bpyO)(H_2O)] (**226, Eqn. 32**). They extended this protocol to synthesize a tyrosine kinase inhibitor alkaloid erlotinib (**230, Eqn. 32**). On treatment with methanol under microwave condition via Ir-catlyst (**226**), 2-amino-4,5-bis(3-methoxypropyl)-benzamide (**225, Eqn. 32)** gave corresponding quinazolinone in 85% yield (**227, Eqn. 32**). Next, compound **227** underwent chlorination with $POCl_3$ to furnish the



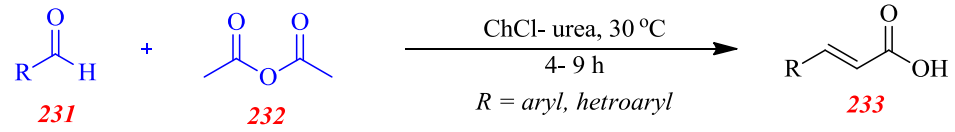
Eqn. 32. Synthesis of Erlotinib

intermediate **228** that on amidation with 3-ethynylaniline (**229, Eqn. 32**) produce the target alkaloid erlotinib (**230, Eqn. 32**).[93]

Deep Eutectic Solvent (DES):

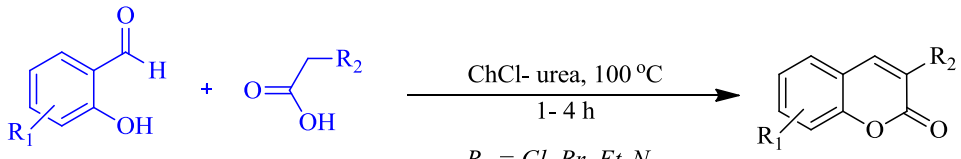
Development of environment friendly and sustainable chemistry is one of the challenges in modern science. There are different ways to develop a greener method; like reducing risk, hazard, wastage, energy, material, and cost.[94] One of the most effective methods to generate a sustainable protocol is replacement of hazardous volatile organic solvent by more eco-friendly solvents like water, glycerol, perfluorinated solvents, supercritical liquids, ionic liquids (ILs) and bio-based solvents. However, these solvents are associated with problems like poor solubility of organic compounds, sophisticated instrumentation, cost and also sometimes toxicity. ILs were one of the effective green solvent in last decade but as study progressed, it showed that ILs cannot be generalised as either green or toxic because their environmental impact is strongly dependent on the kind of cation and anion used to produce the IL. Recently, deep eutectic solvents (DES) emerged as the most effective eco-friendly solvent, due to its polarity, low toxicity, non-volatility, biodegradability, low-cost, thermal stability, and ready availability from bulk renewable resources without any further modification. There are categories in which it has been divided; like low-melting mixtures (LMMs), low-transition temperature mixtures (LTTMs), natural deep eutectic solvents (NADESs) and deep eutectic ionic liquids (DEILs). In 2003, Abbott etal. discovered the first DES with choline chloride (m.p 302 °C) and (urea m.p 134 °C) where both are solid at room temperature but when they were mixed at molar ratio urea: ChCl 2:1, a sharp drop was observed in melting point and it gave a liquid at rt. It was hypothesised that this is due to the charge delocalisation caused by hydrogen bonding between anion and hydrogen bond donor. [95] DES has been used as solvents for many typical organic transformations like, Perkin reaction, Knoevenagel reaction, Diels-Alder reaction, Heck reaction, Bieginili reaction etc. (**Eqn. 33**) to reduce the hazard. [96]

Perkin reaction:



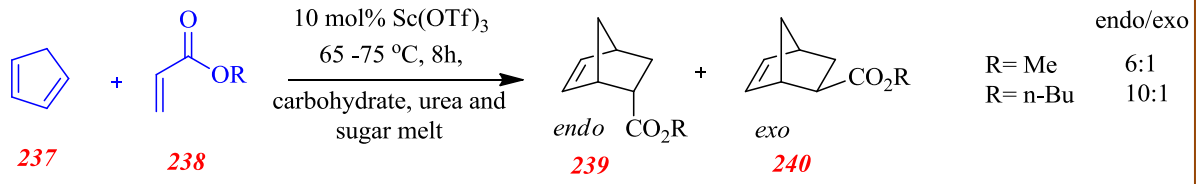
231 232 233

Knoevenagel reaction:



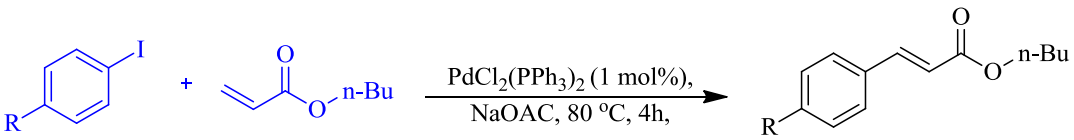
234 235 236

Diels- Alder reaction



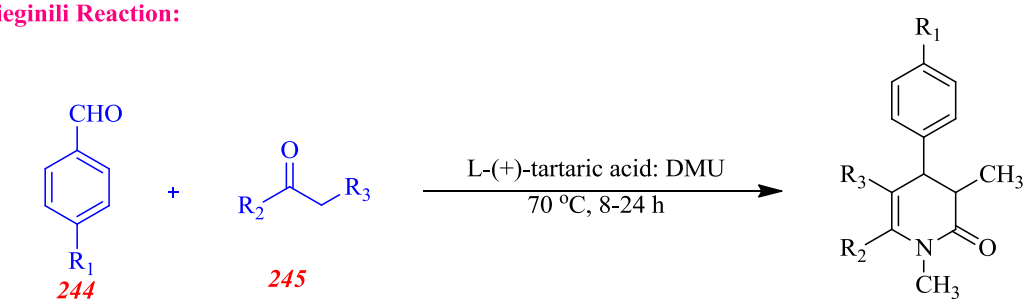
237 238 239 240

Heck Reaction:



241 242 243

Bieginili Reaction:



244 245 246

R1= NO2, Cl, Br, CN, OMe, Me

R2= Me, Ph

R3= CO2Et, CO2Me, COPh

Eqn. 33. Applications of DES on different organic synthesis

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Chapter 1

SYNTHESIS OF NOVEL INDOLYLQUINAZOLINONES AND PYRROLYLQUINAZOLINONES VIA REGIOSELECTIVE C2 AMIDATION OF INDOLE AND PYRROLE

1.1 Introduction

Quinazolinone[1] and pyrimidones[2] represent two very important classes of heterocyclic compounds. They shows diverse range of pharmacological properties like anti-inflammatory, diuretic, anticonvulsant, anticancer and antihypertensive. Study shows, functionalization of quinazolinone's, particularly of amide N-H with aryl or alkyl groups increases the biological properties of quinazolinone motif.[3] In 2003, Kumar et al. reported various trisubstituted indolylquinazolinones, those were found to be very potent analgesic, anti-inflammatory and COX-II inhibitors (**Fig. 10**).[4] In spite of these fascinating results, heterocycles like indole,[5] pyrrole[6] and other cyclic amides which always remained a 'privileged' skeleton for many synthetic or naturally occurring alkaloids and drugs, have never been fused with quinazolinones to synthesize novel indolyl/ pyrrolylquinazolinones that might possess unexplored biological properties.

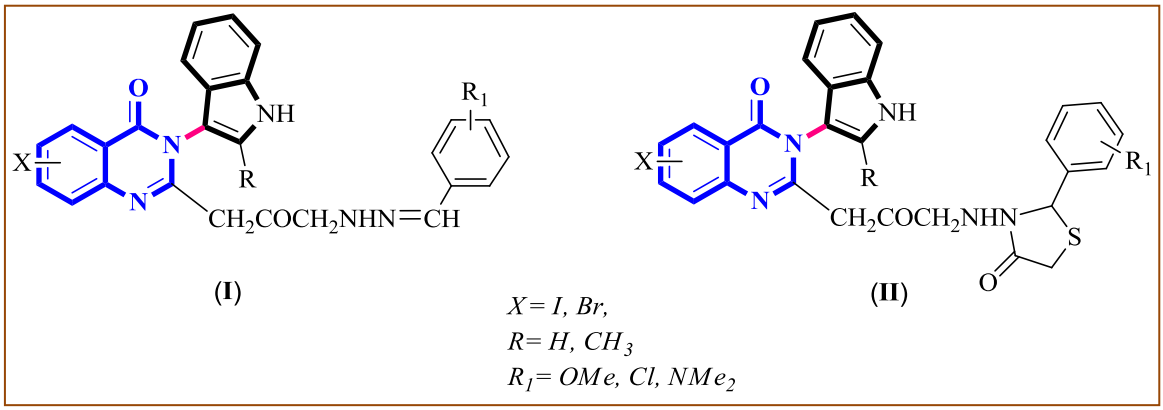


Figure 10. Indolylquinazolinone as anti-inflammatory, analgesic and COX-II Inhibitors

As shown in **fig. 11** biologically active natural products such as asperazine, chetomin contains C-N amide linkage at C2 position of indole. Among these natural products, cyclic amide linkage, are more prominent but with cyclic amide direct amidation at the C2 position of indole till

remain unexplored. Thus, some important properties might appear with fused heterocycles while fusing with nitrogen of quinazolinone or other cyclic amides in C2 position of indole or pyrrole. There are numerous synthetic strategy documented for functionalization at indole C2 position; whereas, the most effective one is direct regioselective functionalization.[7] Many synthetic groups have displayed regioselective C-C bond formation at C2 position of indoles[8] and pyrroles;[9] however only few reports were available for C-N bond formation at the same. In maximum cases, research groups used metals or other harsh conditions for regioselective amination in indole.[10] On the other hand, reports of a metal free mild condition for C2 amination are scarce. Recently, Huang group displayed C-N bond formation at C2 of indole with azole with iodine.[11]

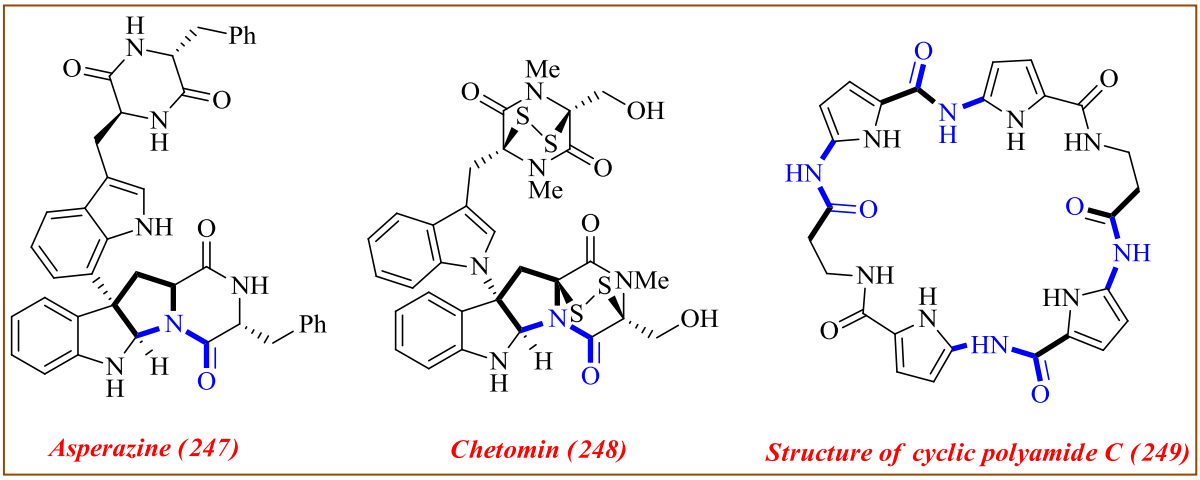
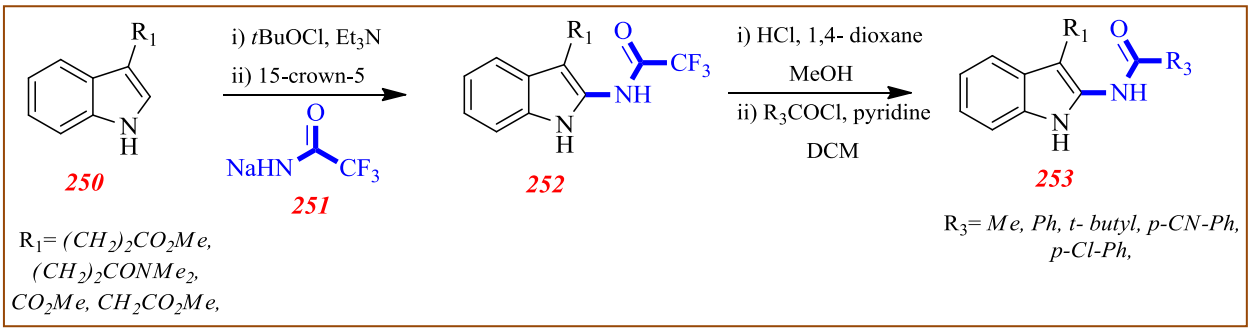


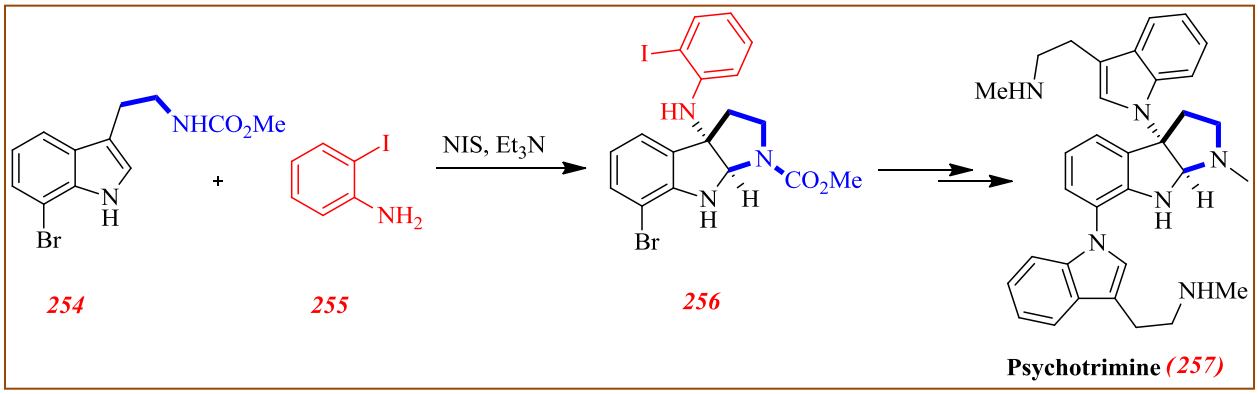
Figure 11. Indole and pyrrole alkaloids contain C-N aminde linkages at C2

However, regioselective C2 amidation of indoles and pyrroles always remained as a challenge to synthetic community. Till date, only few reports were displayed regarding amidation at C2 of indoles[12] and pyrroles.[13] Roth et al. developed a protocol for synthesis of 2-acyl indoles (**253, Eqn. 34**) from indoles via 2-trifluoroacetyl aminoindoles (**252, Eqn. 34**).[12b]



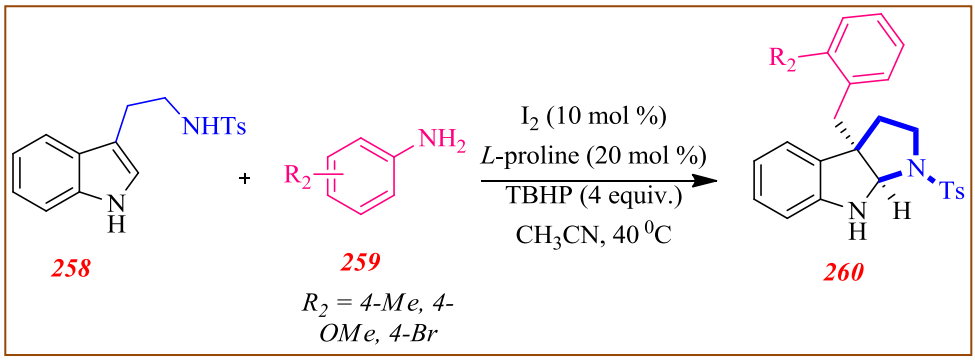
Eqn. 34. 2-Tirifluoroacetyl aminoindoles via amidation of indole

However the conditions were harsh and multistep (**Eqn. 34**). Very recently, Li group presented a Cu catalyzed direct amidation on indoles using CDC process.[14] Although till now, reports for metal free direct amidation at indole C2 are limited. In 2008, Baran's group reported a intramolecular C2 amidation of indole to synthesize psychotrimine (**Eqn. 35**).[15]



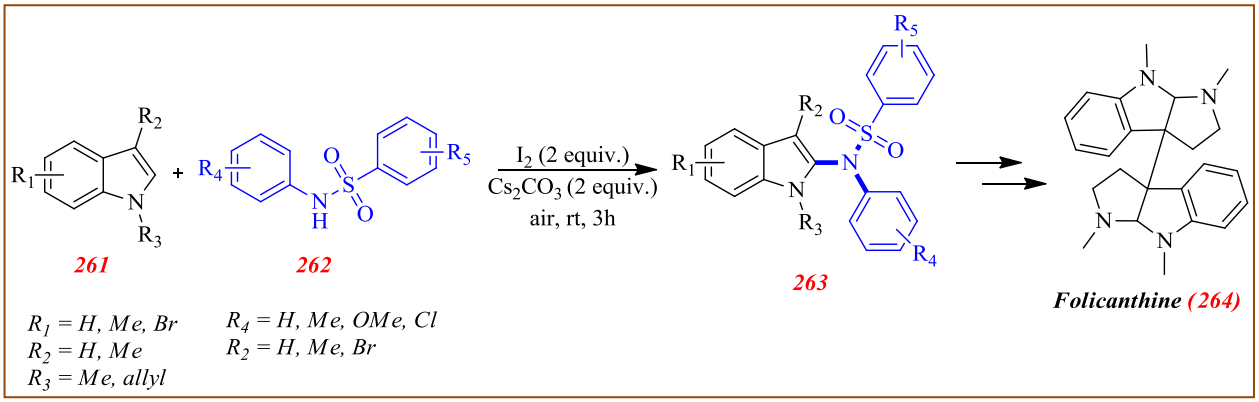
Eqn. 35. Indole amidation as a key step to synthesize of psychotrimine

Very recently, Ji and Wang co-workers also reported an iodine and TBHP mediated intramolecular amidation at indole C2 with sulphonamides which gave a single diastereoisomer **260** with good yields. Later they used this protocol for a formal synthesis of cruciferane (**Eqn. 36**).[16]



Eqn. 36. I_2/TBHP-catalyzed chemoselective amination of indoles

Liang group also reported iodine mediated intermolecular C2 amidation of *N*-protected indoles with tosylbenzenamine. This methodology was further applied for a concise synthesis of racemic folicanthine alkaloid (**Eqn. 37**).[17]



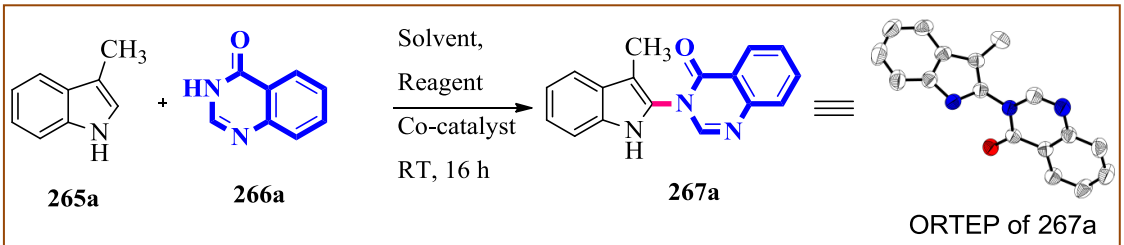
Eqn. 37. Iodine-mediated regioselective C2-amination of indoles for synthesis of folicanthine

A keen survey of literature showed, reports for direct metal free intermolecular C2 amidation of indoles with cyclic amide are none. Thus, we developed a novel metal free mild protocol for direct intermolecular C2 amidation between indole/ pyrrole with cyclic amides like pyrimidone /quinazolinone derivatives.

1.2 Results and discussion:

To optimize the metal free selective amidation on indole moiety with quinazolinone, we started our study with reaction between 3-methylindole (**265a**, 1.1 equiv.) and quinazolinone (**266a**, 1.0 equiv.) in presence of *N*-iodosuccinimide (NIS) 1.2 equiv. as iodinating agent in CH_3CN solvent at rt for 16h and we obtained our desired product 3-(3-methyl-1*H*-indol-2-yl)-3*H*-quinazolin-4-one (**267a**) in 30% yield. The structure of compound **267a** was confirmed by spectroscopic studies as well as X-ray crystallographic study (**Table 1**). Next, we screened different polar and nonpolar solvents to improve the yield of the desired product (**267a, entries 1-12**). Compound **267a** was obtained in moderate yields when polar solvents like CH_3CN, THF, DMSO, EtOAc (entries 1-4) were used. On the other hand, $CHCl_3$ which is comparatively a nonpolar solvent, gave **267a** in 70% yield (entry 5). Next, we have tried some of the nonpolar solvents such as toluene, benzene, p-xylene but they proved to be inferior in comparision with $CHCl_3$ with respect to yields (entries 6-8). We presumed that other chlorinated solvent can increase the yield of **267a** compare to $CHCl_3$; hence, we have used chlorinated solvents like DCM, DCE and 1,2-dichlorobenzene (entries 9-11). Out of these only DCE gave a maximum yield of 64% of compound **267a**.

Table 1. Screening of reaction parameters[a]



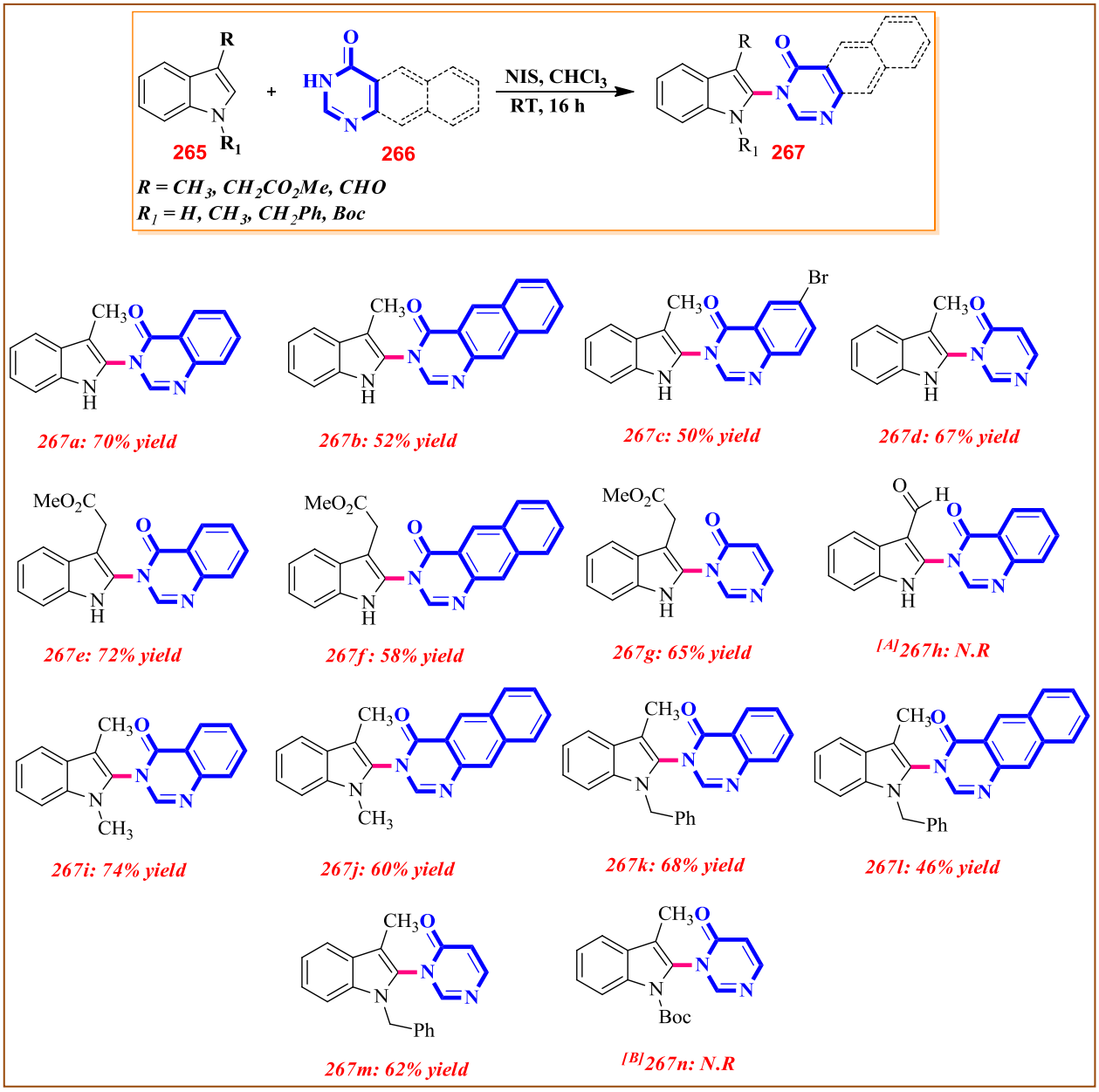
Entry	Solvent	Reagent/ Catalyst	Co-catalyst [b]	Yields [c] **3** [%]
1	CH_3CN	NIS	-	30
2	THF	NIS	-	10
3	DMSO	NIS	-	40
4	EtOAc	NIS	-	58
5	**$CHCl_3$**	**NIS**	-	**70**
6	Toluene	NIS	-	15
7	Benzene	NIS	-	34
8	p- xylene	NIS	-	20
9	DCM	NIS	-	53
10	DCE	NIS	-	64
11	1,2 DCB	NIS	-	42
12	H_2O	NIS	-	40
13	neat	NIS	-	33
14	$CHCl_3$	NBS	-	62
15	$CHCl_3$	I_2	-	67
16	$CHCl_3$	NIS	CuI	62
17	$CHCl_3$	NIS	CuBr	56
18	$CHCl_3$	NIS	DIB	20
19	$CHCl_3$	NIS	KI	30
20[d]	$CHCl_3$	NIS	-	70
21[e]	$CHCl_3$	NIS	-	50

[a] Unless otherwise specified, reaction was performed on 0.34 mmol scale with **265a** (1.1 equiv.), **266a** (1.0 equiv.), reagent (1.2 equiv.) and solvent 5 mL. The reaction time was 16 h. [b] co-catalyst used 10 mol%. [c] Isolated yields. [d] NIS used 2 equiv. [e] NIS used 30 mol%.

Yield of this reaction was not improved under neat condition and on water conditions also (entries 12- 13). Thus, we took $CHCl_3$ as the optimized solvent and was varied other parameters.

On using *N*-bromosuccinimide (entry 14) in place of NIS, the yield has been lowered; whereas with iodine (entry 15) yield of compound **267a** remained unaffected. Next, the use of co-catalysts such as, CuI, CuBr, DIB, KI in 10 mol% along with catalyst failed to improve the yield of the product. To find out the role of NIS, whether its cataytic or stoichiometric, we used NIS 2 equiv. (entry 20) and 30 mol% (entry 21) in two consecutive reactions. It was observed that use of catalytic NIS decreased the yield of the product; whereas, higher lodaing of NIS cannot increase the yield of the product more than 70%. As we summarized the results from table 1, reaction of 1.0 equiv. quinazolinones (**266a**) and 1.1 equiv. indole (**265a**) in presence of 1.2 equiv. NIS in $CHCl_3$ solvent at rt for 16h was found to provide the best condition (entry 5). Next, with these optimum conditions, we tested the generality and scope of this reaction for a range of 3-substituted/ 1,3-disubstituted indoles along with various quinazolinone and pyrimidone derivatives (**Scheme 1**). Indoles substituted with moderate electron withdrawing and donating groups were well adjusted to give well to excellent yields of corresponding indolylquinazolinone and indolylpyrimidones products (**267a-n**). When an indole (substituted with electron donating group at C3) was reacted with quinazolinone and pyrimidone in these optimized conditions, a good yield of respectivly coupled products was obtained (**267a, 267d**). However, quinazolinones which are electron deficient such as, 6-bromoquinazolinone, benzoquinazolinone gave lower yields of coupled products (**267b-c**). In case of substituent like CH_2CO_2Me at indole C3 which is a moderate electron withdrawing group did not affect much in the yield of the corresponding product (**267f-g**). Surprisingly, in case of aldehyde substituted indole the reaction did not proceed even after 3 days (**267h**). After testing indoles with C3 substituted electron withdrawing and donating groups, we examined reaction feasibility for 1,3-disubstituted indoles. We have found that *N*-substituted indoles with methyl, benzyl groups were well tolerated (**267i-m**). In comparision with 3-methylindole; 1,3-dimethylindole gave much better yield of corresponding indolylquinazolinone products. In case of Boc protected indole, this reaction did not proceed after 48h also (**267n**). This may be because of Boc group which reduces the nucleophilicity of indole that is essential for iodination. Next, we expanded the scope of our optimized conditions for C3 unsubstituted indoles and quinazolinones.

Scheme 1: Synthesis of indolylquinazolinone derivatives [a]

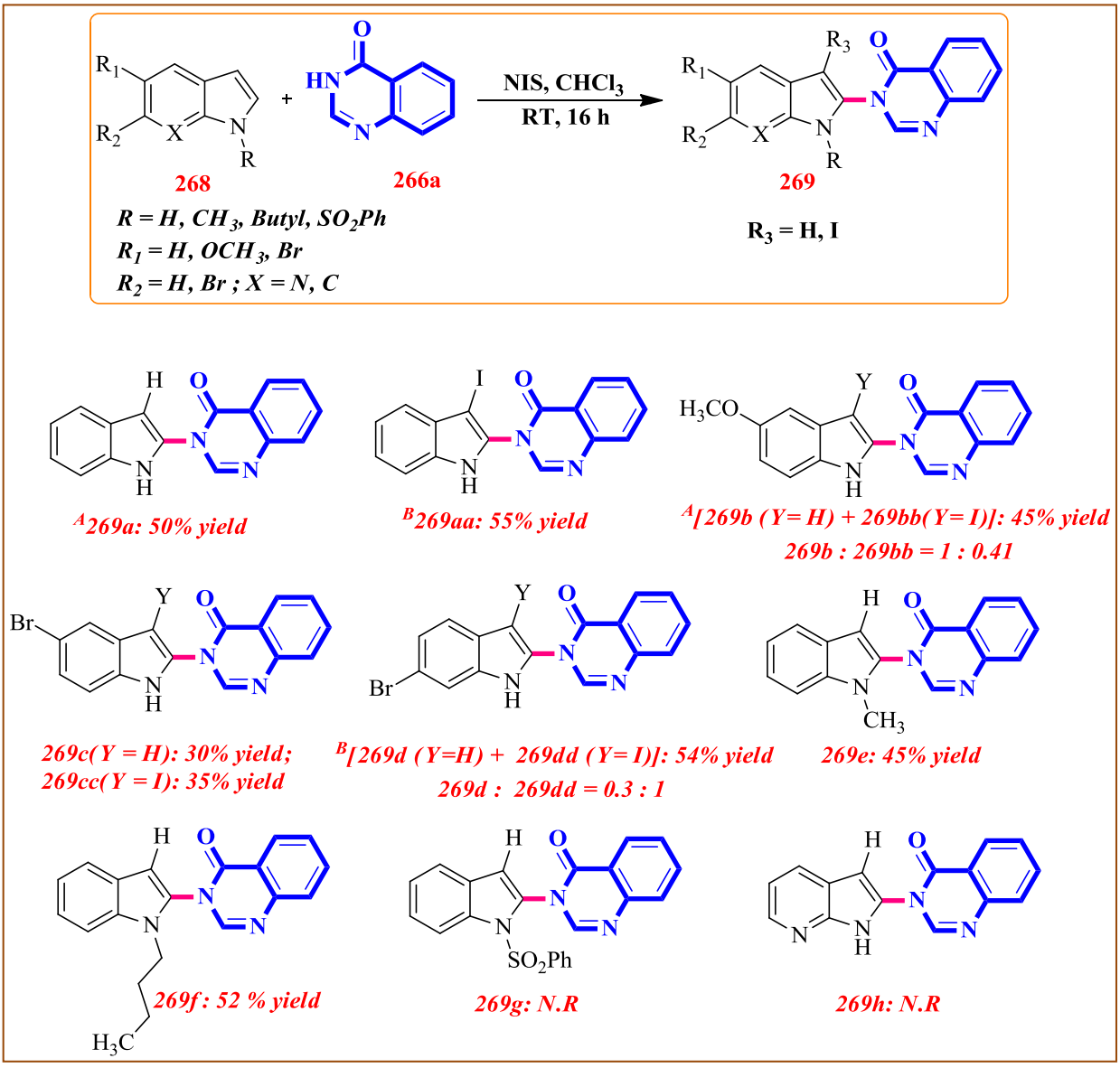


[a]unless otherwise specified, reaction was performed on 0.68 mmol scale with **265** (1.1 equiv.), **266** (1 equiv.), NIS (1.2 equiv.) in solvent 7 mL at rt. [A] Reaction time was 72 h. [B] Reaction time was 48 h. N.R = No Reaction.

Thus, we carried out the reaction with simple indole. Though the outcome of this reaction is not very surprising, as we obtained the expected compound **269a**; but we also obtained a lower percentage of 3-iodoindolylquinazolinone (**269aa**). We assumed that with variation of NIS amount this may give only one product specifically. Hence, we have chosen indole and

quinazolinone as coupling partners and used 1.05 equiv. of NIS in place of 1.2 equiv. keeping other optimized conditions intact. We found 3-(1*H*-indol-2-yl)-3*H*-quinazolin-4-one (**269a**) specifically as the solo product after 16h. However, on use of 1.7 equiv. NIS, 3-(3-iodo-1*H*-indol-2-yl)-3*H*-quinazolin-4-one (**269aa**) product was obtained specifically.

Scheme 2: Synthesis of 3-unsubstitued indolylquinazolinone derivatives [a]



[a] Synthesis of 3-unsubstituted indolylquinazolinone derivatives. Unless otherwise specified, the reaction was performed on 0.68 mmol scale with **268** (1.1 equiv.), **269aa** (1 equiv.), NIS (1.2 equiv.) in solvent (7 mL) at RT. [A] 1.05 equiv. of NIS was used, and reaction time 16 h. [B] 1.7 equiv. of NIS was used, and reaction time was 24 h. N.R.= no reaction.

Futhermore, 5 and 6-bromoindoles and 5-methoxyindole was also tolerated under these conditions and gave their corresponding indolylquinazolinone compound along with the undesired iodo-substituted products. The amount of NIS and reaction time varied the yield of the products. The variation of yields between the desired products and unwanted 3-iodoindolylquinazolinone products can be obtained from ^{1}H NMR (see experimental section). Astonishingly, 1-methylindole and 1-butylindoles gave only the desired indolylquinazolinones (**269f-g**); whereas 1-sulfonylindole and 7-azaindole have not reacted at all. This observation can be justified by electron withdrawing/ releasing group of indole nitrogen which triggered the nucleophilicity of the moiety (**scheme 2**).

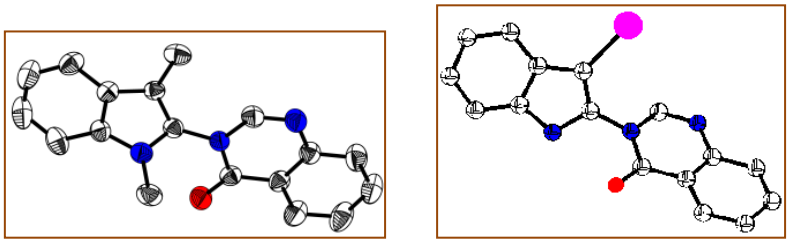
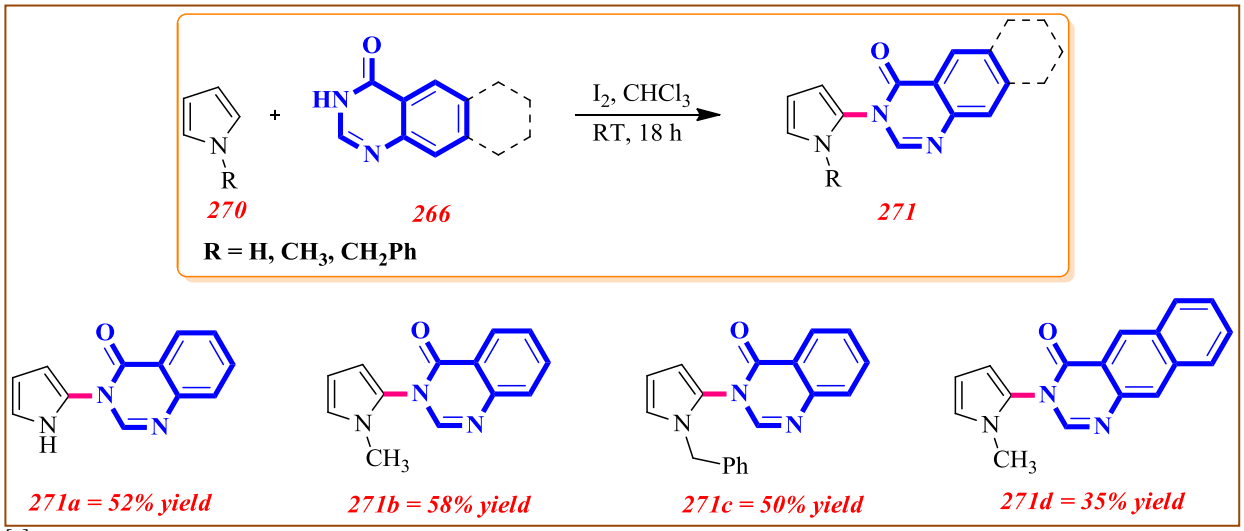


Figure 12. ORTEP of Compound **267i**, **269aa** (Hydrogens are removed for clarity)

After a successful exploration with indoles, we extended our scope for pyrrole heterocycle. As the reports for C-N bond formation in a regioselective manner at pyrrole C2 were limited, we carried out our optimized conditions on pyrrole and quinazolinone moiety (**scheme 3**).

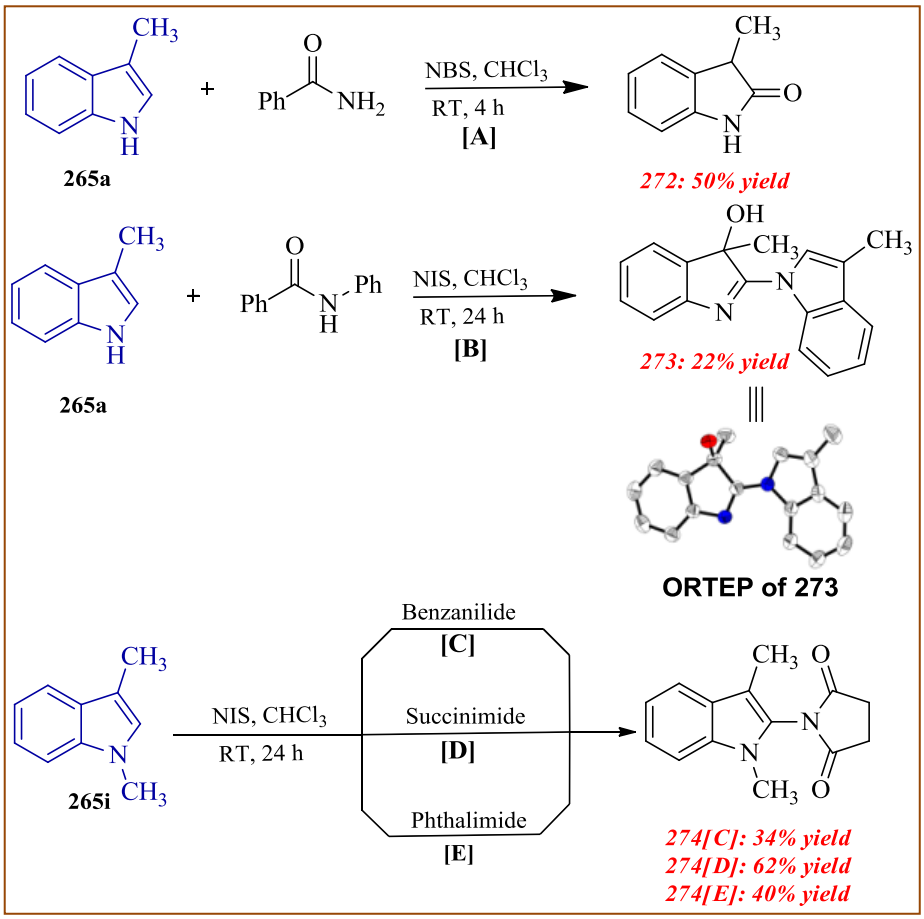
Scheme 3: Synthesis of pyrrolylquinazolinone derivatives [a]



[a] unless otherwise specified reaction was performed on 0.68 mmol scale with **270** (1.1 equiv.), **266** (1 equiv.), I_2 (1.3 equiv.) in solvent 7 mL at RT.

Unfortunately, after 48 h of stirring at rt in our optimized condition we failed to obtain any trace of our desired pyrrolylquinazolinone product (**271, scheme 3**) but when we added a pinch of iodine in the same pot and stirred for another 12 h, we obtained desired pyrrolylquinazolinone product in 30% yields. Hence, we again optimized the reaction to synthesize pyrrolylquinazolinones. We had screened different solvents, catalysts (iodine, NIS) and found that iodine is essential to obtain the desired couple product. The optimum conditions (1.1 equiv. of **270**, 1.3 equiv of I_2, $CHCl_3$, RT, 18 h) were tolerable over a various *N*-substituted/ unsubstituted pyrroles and quinazolinones derivatives (**scheme 3**) to give moderate yield of corresponding pyrroloquinazolinone products (**271a-d**). To generalise the methodology on a larger perspective, we tested this method with aliphatic amides/imides in place of quinazolinones and reacted them with 3-methylindole (**265a**). Thus, we reacted 3-methylindole (1.1 equiv) with benzamide (1.0 equiv.) in presence of NBS (1.1 equiv.) at rt for 4 h. Instead of getting our expected indolylquinazolinone, we obtained unexpected 3-methyl-1,3-dihydro-indol-2-one (**272**) in 50% yield (**scheme 4**, [A]). Next, on treatment of 3-methylindole (1.1 equiv.) with benzanilide (1.0 equiv.) in presence of NIS (1.1 equiv.) in $CHCl_3$, we again obtained an undesired compound 3, 3'-dimethyl-3'*H*-[1, 2']biindolyl-3'-ol product (**273**). It was obtained in very low yield after 24 h of stirring. This undesired compound was fully characterized using NMR techniques and X-ray crystallographic study. The lower nucleophilicity of benzanilide nitrogen compare to the indole, might be the reason for formation of this unexpected compound (**273, scheme 4**, [B]). Although this kind of dimer is already reported in literature using Co-Salen complex under oxygen atmosphere.[18] With this observations, we presumed that a *N*-protected indole can able to furnish our desired couple product. Thus, we carried out the same reaction with 1,3-dimethylindole; however, we got a couple prodcuct but it was succinimide that coupled with the 1,3-dimethylindole instead of benzanilide (**Scheme 4**, [C]). The lower yield of 1-(1, 3-dimethyl-1*H*-indol-2-yl)-pyrrolidine-2, 5-dione (**274)** might be justified as the formation of succinimide is in situ. Next, we used succinimide as a reagent and the yield of coupled compound **274** has increased to 62% (**Scheme 4**, [D]). When phthalimide was used as a starting material, that also gave succinimide-coupled product (**274**) (**Scheme 4**, [E]).

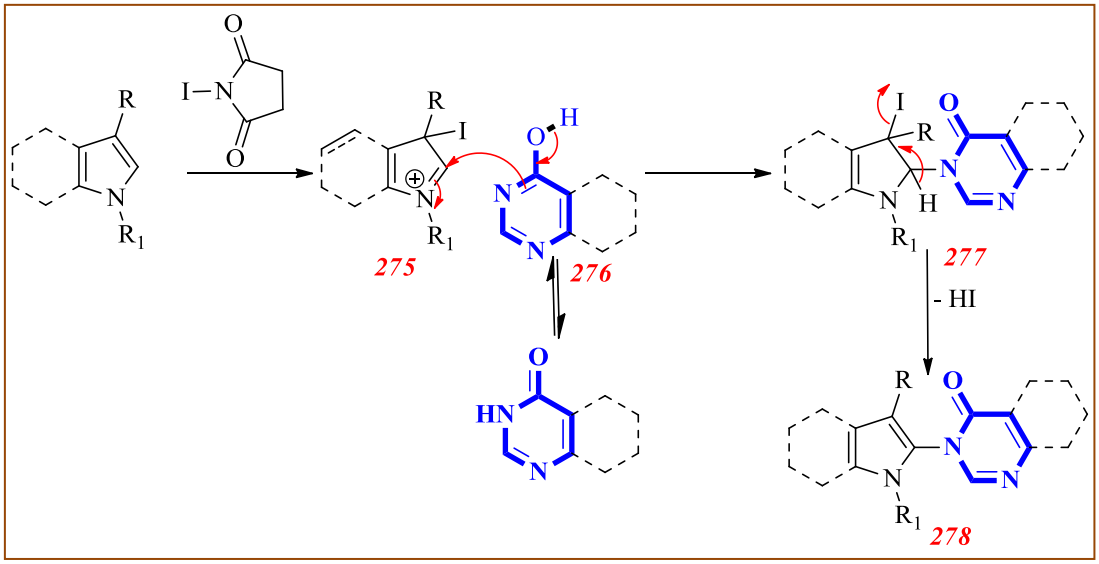
Scheme 4: Reaction between indole and aliphatic amide/imide



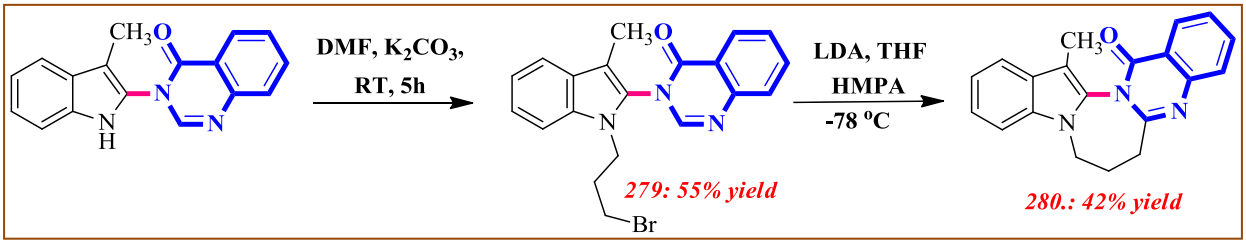
[A] **265a** (0.98 mmol), benzamide (0.82 mmol) and NBS (0.98 mmol) in solvent at RT for 4 h. [B] **265a** (0.51 mmol), benzanilide (0.51 mmol), NIS (0.61 mmol) in solvent at RT for 24 h. [C] **265i** (0.35 mmol), benzanilide (0.35 mmol), NIS (0.35 mmol) in solvent at RT for 24 h. [D] **265i** (1 mmol), succinimide (1 mmol), NIS (1 mmol) in solvent at RT for 24 h.[E] **267i** (0.68 mmol), pthalimide (0.68 mmol), NIS (0.82 mmol) in solvent at RT for 24 h.

From all these extensive experiments with various substrates we proposed a possible mechanism of this methodology in **Scheme 5**. The intermediate **275** was generated by iodination at indole C3 that underwent successive nucleophilic substitution with the proposed iminol (**276**) and furnish another intermediate **277**. Next, subsequent HI elimination gave the expected product (**278**).

Scheme 5. Possible mechanism



Scheme 6: Synthesis of the indolo-[1,3]-diazepine skeleton



In the last portion of our study, we have synthesised a novel indolo-[1,3]-diazepine skeleton amalgamated with quinazolinone. Diazepines are pharmacologically active heterocyclic class of compounds as they shows wide spectrum of biological properties. 1,4-diazepine are most common in terms of biological properties compare to 1,3-diazepine. Literature shows, 1,3-diazepine fused with heterocycles exhibits anticancer, anti-AIDS activity and inhibits HIV protease.[19] Hence, we have synthesized a novel indolylquinazolinone compound fused with 1,3-diazepine that might possess exciting pharmacological properties. Thus, we started with compound **267a** and reacted it with 1,3-dibromopropane in presence of base K_2CO_3 at rt for 5h to generate 3-[1-(3-bromo-propyl)-3-methyl-1*H*-indol-2-yl]-3*H*-quinazolin-4-one (**279**). Next, it was treated with LDA along with HMPA at -78 ^oC that furnished our expected macrocycle **280** in 42% yield (**scheme 6**).

1.3 Conclusion:

In conclusion, an efficient metal free regioselective amidation methodology for indole/ pyrrole C2 centre with various quinazolinones and pyrimidones was developed. A series of indoles and pyrroles were subjected to this methodology with quinazolinones to synthesize indolylquniazolinone/ pyrimidone and pyrrolylquinazolinone. Further, this protocol was applied to synthesize a highly functionalized indolo-[1,3]-diazepine compound that might possess useful pharmacological properties.

1.4 Experimental Section:

Melting Points: The melting point of the products was recorded on a Superfit (India) capillary melting point apparatus and is uncorrected.

IR: Infrared spectra were recorded on a JASCO FT/IR-5300 spectrophotometer. All the spectra were calibrated against polystyrene absorption at 1601 cm^{-1}. Solid samples were recorded as KBr wafers and liquid samples as thin film between NaCl plates or solution spectra in DCM.

NMR Spectra: ^{1}H NMR and ^{13}C NMR spectrums were recorded on BRUKER-AVANCE-400/ 500 spectrometers. ^{1}H NMR (400 or 500 MHz) spectra for all the samples were measured in chloroform-*d*, unless otherwise mentioned (δ = 2.50 ppm for ^{1}H NMR in the case of DMSO-d_6), with TMS (δ = 0 ppm) as an internal standard. ^{13}C NMR (100 or 125MHz) spectra for all the samples were measured in chloroform-*d*, unless otherwise mentioned (in the case of DMSO-d_6, δ = 39.70 ppm its middle peak of the septet), with its middle peak of the triplet (δ = 77.10 ppm) as an internal standard.

Mass Spectral Analysis: Shimadzu LCMS 2010A mass spectrometer. All the cases DCM or MeOH were used to dissolve the compounds. The TOF and quadrupole mass analyzer types are used for the HRMS measurements. Mass spectral data were obtained from HRMS (ESI).

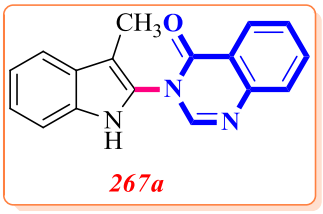
Elemental Analysis: Elemental analyses were performed on a Thermo Finnigan Flash EA 1112-CHN analyzer.

X-ray Crystallography: The X-ray diffraction measurements were carried out at 293 K on a Bruker SMART APEX CCD area detector system equipped with a graphite monochromator and a Mo-K_α fine-focus sealed tube (λ = 0.71073 Å) operated at 1500 W power (50 kV, 30 mA). The detector was placed at a distance of 4.995 cm from the crystal. The frames were integrated with the Bruker SAINT Software package using a narrow-frame algorithm. Data were corrected for absorption effects using the multi-scan technique (SADABS). The structure was solved and refined using the Bruker SHELXTL (Version 6.1) software package.

General procedure A:

An oven dried Schlenk tube was charged with indole or its derivative (**265,** 0.74 mmol), quinazolinone derivatives (**266**, 0.68 mmol), NIS (0.81 mmol) and distilled $CHCl_3$ (7 mL). The Schlenk tube was then flushed with nitrogen. The reaction mixture was stirred at rt for 16h. The reaction mixture was diluted with water, and aqueous phase was extracted with DCM (30 mL).The combined organic layer was dried over Na_2SO_4 and concentrated using a rotary evaporator under reduced pressure. The resulting residue was purified by column chromatography on silica gel (ethyl acetate/ hexanes = 3:7) to afford the desired product.

(3-Methyl-1*H*-indol-2-yl)-4a,8a-dihydro-3*H*-quinazolin-4-one (267a):



267a

Yield: 70 %

Mp: 222 °C

IR (KBr) ν_{max} cm^{-1}: 3274, 2921, 2853, 1708, 1662, 1600, 1257, 1014, 738

^{1}H NMR (400 MHz) δ: 11.48 (1H, s), 8.40 (1H, s), 8.24 (1H, d, *J* = 7.6 Hz), 7.93 (1H, t, *J* = 7.2 Hz), 7.79 (1H, d, *J* = 8.0 Hz), 7.64 (1H, t, *J* = 7.2 Hz), 7.59 (1H, d, *J* = 7.6 Hz), 7.38 (1H, d, *J* = 8.0 Hz), 7.20 (1H, t, *J* = 7.2 Hz), 7.09 (1H, t, *J* = 7.2 Hz), 2.14 (3H, s)

^{13}C NMR (100 MHz) δ: 160.5, 147.9, 135.6, 134.3, 128.3, 128.0, 127.5, 127.0, 122.9, 122.1, 119.5, 119.5, 111.8, 106.4 (aromatic C), 8.1 (aliphatic C)

HRMS (ESI-MS)

Calcd for: $C_{17}H_{13}N_3O$: 276.1137 (M+H)

Found: 276.1139

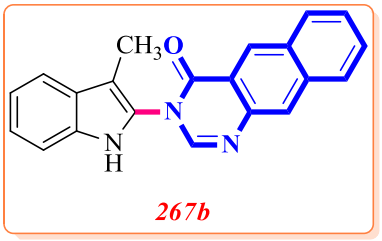
3-(3-Methyl-1*H*-indol-2-yl)-4a,10a-dihydro-3*H*-benzo[g]quinazolin-4-one (267b):

Yield: 52 %

Mp: 228 ^oC

IR (KBr) ν_{max} cm^{-1}: 3271, 2920, 1671, 1605, 1265, 739, 706

^{1}H NMR (500 MHz) δ: 11.51 (1H, s), 9.00 (1H, s), 8.39 (1H, s), 8.38 (1H, s), 8.30 (1H, d, *J* = 8.0 Hz), 8.20 (1H, d, *J* = 8.5 Hz), 7.76-7.73 (1H, m), 7.68-7.65 (1H, m), 7.61 (1H, d, *J* = 7.5 Hz), 7.40 (1H, d, *J* = 8.5 Hz), 7.24-7.20 (1H, m), 7.13-7.10 (1H, m), 2.18 (3H, s)



267b

^{13}C NMR (125 MHz) δ: 160.9, 146.9, 143.3, 136.7, 134.3, 131.9, 129.9, 129.5, 128.8, 128.5, 128.2, 127.5, 127.4, 125.8, 122.9, 120.9, 119.5, 119.4, 111.8, 106.4 (aromatic C), 8.1 (aliphatic C)

HRMS (ESI-MS)

Calcd for: $C_{21}H_{15}N_3O$: 326.1293 (M+H)

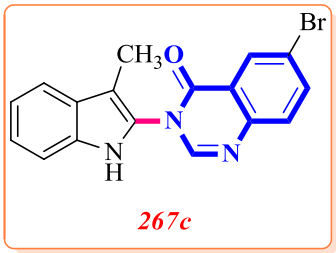
Found: 326.1294

6-Bromo-3-(3-methyl-1*H*-indol-2-yl)-4a,8a-dihydro-3*H*-quinazolin-4-one (267c):

Yield: 50 %

Mp: 220 ^{o}C

IR (KBr) ν_{max} cm^{-1}: 3276, 2958, 1665, 1600, 1265, 832, 739



267c

^{1}H NMR (500 MHz) δ: 11.48 (1H, s), 8.47 (1H, s), 8.33 (1H, d, *J* = 2.5 Hz), 8.10 (1H, dd, *J* = 8.5 Hz, *J* = 2.5 Hz), 7.76 (1H, d, *J* = 8.5 Hz), 7.60 (1H, d, *J* = 8.0 Hz), 7.40 (1H, d, *J* = 7.8 Hz), 7.23-7.20 (1H, m), 7.12-7.09 (1H, m) (aromatic C), 2.15 (3H, s) (aliphatic C)

^{13}C NMR (125 MHz) δ: 159.4, 148.6, 147.0, 138.4, 134.3, 130.5, 129.0, 127.7, 127.4, 123.7, 123.1, 120.8, 119.6, 119.5, 111.9, 106.6 (aromatic C), 8.1 (aliphatic C)

HRMS (ESI-MS)

Calcd for: $C_{17}H_{12}Br^{81}N_3O$: 356.0222 (M+H)

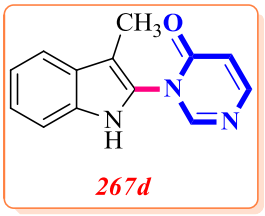
Found: 356.0219

Calcd for: $C_{17}H_{12}Br^{79}N_3O$: 354.0242 (M+H)

Found: 354.0240

3-(3-Methyl-1*H*-indol-2-yl)-3*H*-pyrimidin-4-one (267d):

Yield: 67 %



267d

Mp: 138 °C

IR (KBr) ν_{max} cm^{-1}: 3336, 3063, 1671, 1589, 1221, 991, 750

^{1}H NMR (400 MHz) δ: 11.50 (1H, s), 8.52 (1H, s), 8.04 (1H, dd, *J* = 6.4 Hz, *J* = 2.0 Hz), 7.58 (1H, d, *J* = 8.0 Hz), 7.38 (1H, dd, *J* = 8.0 Hz, *J* = 0.8 Hz), 7.22-7.18 (1H, m), 7.11-7.07 (1H, m), 6.60 (1H, dd, *J* = 6.0 Hz, *J* = 0.8 Hz), 2.11 (3H, s)

^{13}C NMR (100 MHz) δ: 160.3, 154.3, 153.3, 134.3, 127.6, 127.4, 123.1, 119.6, 119.5, 116.2, 111.9, 106.2 (aromatic C), 8.0; (aliphatic C)

HRMS (ESI-MS)

Calcd for: $C_{13}H_{11}N_3O$: 226.0980 (M+H)

Found: 226.0980

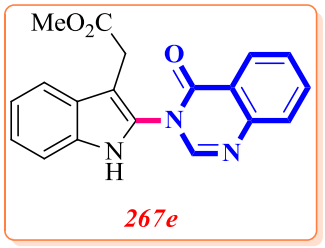
[2-(4-Oxo-4a,8a-dihydro-4*H*-quinazolin-3-yl)-1*H*-indol-3-yl]-acetic acid methyl ester (267e):

Yield: 72 %

Mp: 102 ^oC

IR (KBr) ν_{max} cm^{-1}: 3260, 2926, 1731, 1676, 1605, 1276, 739

^{1}H NMR (500 MHz) δ: 11.76 (1H, s), 8.35 (1H, s), 8.25 (1H, dd, *J* = 8.0 Hz, *J* = 1.0 Hz), 7.96-7.92 (1H, m), 7.80 (1H, d, *J* = 8.0 Hz), 7.67-7.64 (1H, m), 7.62 (1H, d, *J* = 8.0 Hz), 7.43 (1H, d, *J* = 8.5 Hz), 7.26-7.22 (1H, m), 7.14-7.11 (1H, m) (aromatic C), 3.72 (2H, s), 3.50 (3H, s) (aliphatic C)



267e

^{13}C NMR (125 MHz) δ: 171.6, 160.4, 147.9, 147.6, 135.6, 134.1, 129.2, 128.3, 128.0, 127.0, 126.8, 123.2, 122.1, 120.0, 119.6, 112.1, 104.2, (aromatic C), 52.1, 29.3 (aliphatic C)

HRMS (ESI-MS)

Calcd for: $C_{19}H_{15}N_3O_3$: 334.1192 (M+H)

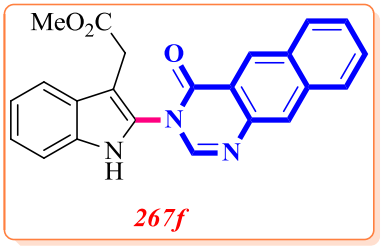
Found: 334.1187

[2-(4-Oxo-4a,10a-dihydro-4*H*-benzo[g]quinazolin-3-yl)-1*H*-indol-3-yl]-acetic acid methyl ester (267f):

Yield: 58 %

Mp: 106 ^{o}C

IR (KBr) ν_{max} cm^{-1}: 3441, 3046, 1731, 1676, 1276, 745



267f

^{1}H NMR (500 MHz) δ: 11.79 (1H, s), 9.00 (1H, s), 8.38 (1H, s), 8.32 (1H, s), 8.30 (1H, d, *J* = 8.0 Hz), 8.20 (1H, d, *J* = 8.5 Hz), 7.76-7.73 (1H, m), 7.68-7.62 (2H, m), 7.44 (1H, d, *J* = 8.0 Hz), 7.26-7.23 (1H, m), 7.15-7.12 (1H, m) (aromatic C), 3.75 (2H, s), 3.50 (3H, s) (aliphatic C)

^{13}C NMR (125 MHz) δ: 171.6, 160.9, 146.6, 143.2, 136.7, 134.1, 131.9, 129.9, 129.5, 129.4, 128.8, 128.5, 127.4, 126.9, 125.8, 123.1, 120.90, 119.99, 119.6, 112.1, 104.2 (aromatic C), 52.1, 29.4 (aliphatic C)

HRMS (ESI-MS)

Calcd for: $C_{23}H_{17}N_3O_3$: 384.1348 (M+H)

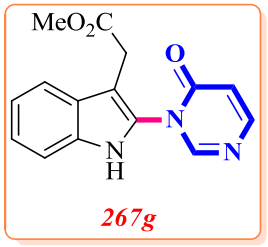
Found: 384.1349

[2-(6-Oxo-6*H*-pyrimidin-1-yl)-1*H*-indol-3-yl]-acetic acid methyl ester (267g):

Yield: 65 %

Mp: 92 ^oC

IR (KBr) ν_{max} cm^{-1}: 3221, 2947, 1736, 1698, 1600, 1238, 827, 761



267g

^1H NMR (400 MHz) δ: 11.78 (1H, s), 8.46 (1H, s), 8.03 (1H, dd, *J* = 8.8 Hz, *J* = 2.0 Hz), 7.60 (1H, d, *J* = 7.6 Hz), 7.40 (1H, d, *J* = 8.0 Hz), 7.22 (1H, t, *J* = 8.0 Hz), 7.11 (1H, t, *J* = 8.0 Hz), 6.58 (1H, d, *J* = 6.8 Hz) (aromatic C), 3.65 (2H, s), 3.52 (3H, s) (aliphatic C)

^{13}C NMR (100 MHz) δ: 171.5, 160.1, 154.2, 152.9, 134.1, 128.7, 126.7, 123.3, 120.0, 119.6, 116.2, 112.1, 103.9 (aromatic C), 52.2, 29.3 (aliphatic C)

HRMS (ESI-MS)

Calcd for: $C_{15}H_{13}N_3O_3$: 284.1035 (M+H)

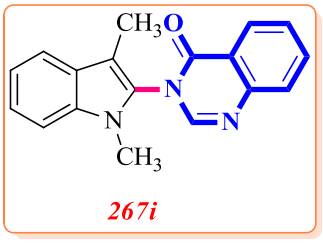
Found: 284.1031

3-(1,3-Dimethyl-1*H*-indol-2-yl)-4a,8a-dihydro-3*H*-quinazolin-4-one (267i):

Yield: 74 %

Mp: 156 ^oC

IR (KBr) ν_{max} cm^{-1}: 3221, 2947, 1736, 1698, 1600, 1238, 827, 761



267i

^1H NMR (500 MHz) δ: 8.37 (1H, s), 8.26 (1H, dd, *J* = 8.0 Hz, *J* = 1.0 Hz), 7.98-7.94 (1H, m), 7.82 (1H, d, *J* = 8.0 Hz), 7.68-7.65 (1H, m), 7.64 (1H, d, *J* =

8.0 Hz), 7.52 (1H, d, *J* = 8.5 Hz), 7.31-7.28 (1H, m), 7.15 (1H, t, *J* = 8.0 Hz) (aromatic C), 3.54 (3H, s), 2.14 (3H, s) (aliphatic C)

^{13}C NMR (125 MHz) δ: 160.8, 148.1, 147.9, 135.8, 135.3, 129.4, 128.4, 128.1, 127.1, 126.5, 123.2, 122.0, 119.8, 119.6, 110.4, 106.7 (aromatic C), 29.6, 8.1(aliphatic C)

HRMS (ESI-MS)

Calcd for: $C_{18}H_{15}N_3O$: 290.1293 (M+H)

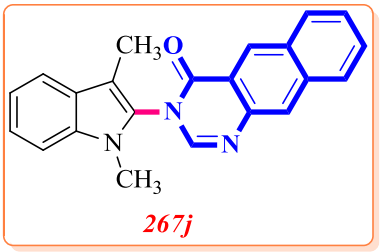
Found: 290.1291

3-(1, 3-Dimethyl-1*H*-indol-2-yl)-4a,10a-dihydro-3*H*-benzo[g]quinazolin-4-one (267j):

Yield: 60 %

Mp: 164 ^{o}C

IR (KBr) ν_{max} cm^{-1}: 3310, 2894, 1682, 1249, 942, 756



267j

^{1}H NMR (400 MHz) δ: 8.99 (1H, s), 8.39 (1H, s), 8.31 (1H, s), 8.27 (1H, d, *J* = 8.4 Hz), 8.18 (1H, d, *J* = 8.4 Hz), 7.73 (1H, t, *J* = 7.6 Hz), 7.66-7.62 (2H, m), 7.51 (1H, d, *J* = 8.4 Hz), 7.28 (1H, t, *J* = 7.6 Hz), 7.14 (1H, t, *J* = 7.2 Hz) (aromatic C), 3.56 (3H, s), 2.16 (3H, s) (aliphatic C)

^{13}C NMR (100 MHz) δ: 161.4, 146.9, 143.4, 136.8, 135.3, 131.9, 129.9, 129.6, 128.9, 128.5, 127.4, 126.5, 125.9, 123.1, 120.8, 119.8, 119.6, 110.4, 106.7 (aromatic C), 29.6, 8.2 (aliphatic C)

HRMS (ESI-MS)

Calcd for: $C_{22}H_{17}N_3O$: 340.1450 (M+H)

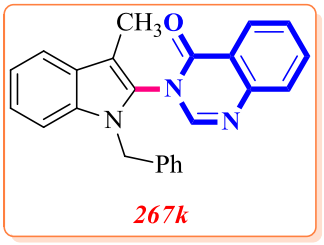
Found: 340.1450

3-(1-Benzyl-3-methyl-1*H*-indol-2-yl)-4a,8a-dihydro-3*H*-quinazolin-4-one (267k):

Yield: 68 %

Mp: 106 ^{o}C

IR (KBr) ν_{max} cm^{-1}: 3364, 3024, 2909, 1687, 1610, 1249, 920, 739



267k

^{1}H NMR (500 MHz) δ: 8.23 (1H, d, *J* = 8.0 Hz), 8.14 (1H, s), 7.92 (1H, t, *J* = 7.5 Hz), 7.74 (1H, d, *J* = 8.0 Hz), 7.68 (1H, d, *J* = 8.0 Hz), 7.64 (1H, t, *J* = 7.5 Hz), 7.45 (1H, d, *J* = 8.0 Hz), 7.24 (1H, t, *J* = 7.5 Hz), 7.18-7.14 (4H, m), 6.96-6.94 (2H, m), (aromatic C), 5.43 (1H, d, *J* = 17 Hz), 5.05 (1H, d, *J* = 17 Hz), 2.15 (3H, m) (aliphatic C)

^{13}C NMR (125 MHz) δ: 160.8, 147.9, 147.7, 137.9, 135.7, 135.1, 129.2, 128.9, 128.4, 128.0, 127.7, 127.1, 126.9, 126.7, 123.5, 121.9, 120.1, 119.9, 110.9, 107.9 (aromatic C), 46.6, 8.2 (aliphatic C)

HRMS (ESI-MS)

Calcd for: $C_{24}H_{19}N_3O$: 366.1606 (M+H)

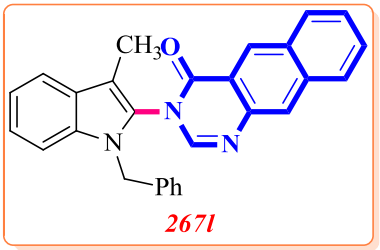
Found: 366.1606

3-(1-Benzyl-3-methyl-1*H*-indol-2-yl)-4a,10a-dihydro-3*H*-benzo[g]quinazolin-4-one (267l):

Yield: 46 %

Mp: 130 ^{o}C

IR (KBr) ν_{max} cm^{-1}: 3052, 2920, 1687, 1600, 1265, 898, 750



267l

^{1}H NMR (500 MHz) δ: 8.96 (1H, s), 8.31 (1H, s), 8.27 (1H, d, *J* = 8.4 Hz), 8.16 (1H, d, *J* = 8.4 Hz), 8.08 (1H, s), 7.72 (1H, t, *J* = 7.2 Hz), 7.68- 7.62 (2H, m), 7.45 (1H, d, *J* = 8.0 Hz), 7.30 (1H, d, *J* = 6.4 Hz), 7.24 (1H, t, *J* = 7.6 Hz), 7.17-7.14 (3H, m), 6.99-6.96 (2H, m) (aromatic C), 5.45 (1H, d, *J* = 16.8 Hz), 5.09 (1H, d, *J* = 16.8 Hz), 2.17 (3H, s) (aliphatic C)

^{13}C NMR (125 MHz) δ: 161.3, 146.6, 143.2, 138.1, 136.7, 135.1, 131.9, 129.9, 129.5, 129.3, 129.1, 128.9, 128.4, 127.7, 127.6, 127.4, 126.9, 126.8, 125.8, 123.4, 120.7, 120.0, 119.8, 110.9, 107.9 (aromatic C), 46.61, 8.2 (aliphatic C)

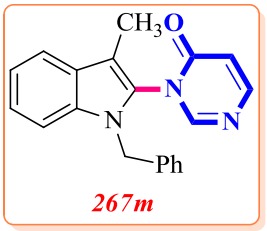
HRMS (ESI-MS)

Calcd for: $C_{28}H_{21}N_3O$: 416.1763 (M+H)

Found: 416.1764

3-(1-Benzyl-3-methyl-1*H*-indol-2-yl)-3*H*-pyrimidin-4-one (267m):

Yield: 62 %



267m

Mp: 102 ^{o}C

IR (KBr) ν_{max} cm^{-1}: 3079, 2915, 1731, 1698, 1282, 843, 739

^{1}H NMR (400 MHz) δ: 8. 22 (1H, s), 7.99 (1H, d, *J* = 6.8 Hz), 7.66 (1H, d, *J* = 7.6 Hz), 7.48 (1H, d, *J* = 8.0 Hz), 7.26-7.13 (5H, m), 6.97-6.95 (2H, m), 6.59 (1H, dd, *J* = 6.8 Hz, *J* = 0.8 Hz) (aromatic C), 5.43 (1H, d, *J* = 16.4 Hz), 4.94 (1H, d, *J* = 16.8 Hz), 2.11 (3H, s) (aliphatic C)

^{13}C NMR (100 MHz) δ: 160.5, 154.4, 153.3, 137.8, 135.2, 129.0, 128.8, 127.8, 126.9, 126.6, 123.6, 120.1, 119.9, 116.3, 110.8, 107.7 (aromatic C), 46.6, 8.1 (aliphatic C)

HRMS (ESI-MS)

Calcd for: $C_{20}H_{17}N_3O$: 316.1450 (M+H)

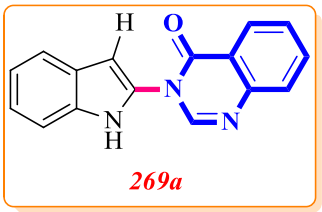
Found: 316.1451

3-(1*H*-Indol-2-yl)-3*H*-quinazolin-4-one (269a):

Yield: 50 %

Mp: 140 ^{o}C

IR (KBr) ν_{max} cm^{-1}: 3276, 2920, 1660, 1600, 1265, 1008, 734



269a

^{1}H NMR (400 MHz) δ: 11.81 (1H, s), 8.49 (1H, s), 8.23 (1H, d, *J* = 8.0 Hz), 7.92-7.88 (1H, m), 7.77 (1H, d, *J* = 8.0 Hz), 7.63 (2H, t, *J* = 8.0 Hz), 7.46 (1H, d, *J* = 8.0 Hz), 7.20 (1H, t, *J* = 8.0 Hz), 7.09 (1H, t, *J* = 8.0 Hz), 6.69 (1H, s) (aromatic C)

^{13}C NMR (100 MHz) δ: 160.3, 147.7, 147.4, 135.6, 134.9, 131.9, 128.3, 127.9, 126.9, 122.7, 121.9, 120.9, 120.2, 112.1, 98.1 (aromatic C)

HRMS (ESI-MS)

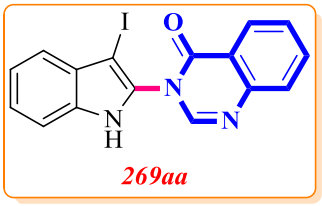
Calcd for: $C_{16}H_{11}N_3O$: 262.0980 (M+H)

Found: 262.0981

3-(3-Iodo-1*H*-indol-2-yl)-3*H*-quinazolin-4-one (269aa):

Yield: 55 %

Mp: 205 ^{o}C



269aa

IR (KBr) ν_{max} cm^{-1}: 3342, 3063, 1682, 1254, 904, 767

^{1}H NMR (400 MHz) δ: 12.34 (1H, s), 8.42 (1H, s), 8.26 (1H, d, *J* = 8.0 Hz), 7.96 (1H, t, *J* = 8.0 Hz), 7.81 (1H, d, *J* = 8.0 Hz), 7.67 (1H, t, *J* = 7.2 Hz), 7.48 (1H, d, *J* = 8.0 Hz), 7.39 (1H, d, *J* = 7.6 Hz), 7.30 (1H, t, *J* = 7.2 Hz), 7.21 (1H, t, *J* = 7.6 Hz); (aromatic C)

^{13}C NMR (100 MHz) δ: 160.2, 147.9, 147.8, 136.0, 135.3, 133.2, 129.3, 128.6, 128.2, 127.1, 124.2, 121.8, 121.2, 121.1, 112.8, 58.8 (aromatic C)

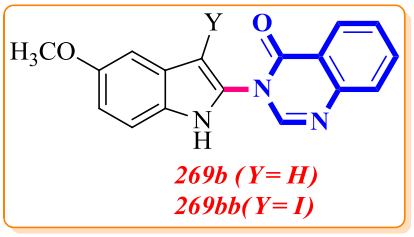
HRMS (ESI-MS)

Calcd for: $C_{16}H_{10}IN_3O$: 387.9947 (M+H)

Found: 387.9946

3-(5-Methoxy-1*H*-indol-2-yl)-3*H*-quinazolin-4-one (269b)

3-(3-Iodo-5-methoxy-1*H*-indol-2-yl)-3*H*-quinazolin-4-one (269bb)



269b (Y= H)
269bb(Y= I)

Yield: 45 % (**269b**:**269bb** = 1:0.41);

Mp: 205 ^{o}C

IR (KBr) ν_{max} cm^{-1}: 3358, 3260, 2991, 2926, 1682, 1654, 1254, 1210, 767, 690

^{1}H NMR (400 MHz) δ: 12.20 (0.396H, s), 11.62 (1.00H, s), 8.46 (1.040H, s), 8.38 (0.443H, s), 8.25-8.23 (1.428H, m), 7.97-7.89 (1.433H, m), 7.82- 7.76 (1.390H, m), 7.68-7.61 (1.392H, m), 7.39-7.32 (1.459H, m), 7.102 (1.063H, s), 6.94-6.92 (0.446H, m), 6.84- 6.82 (1.387H, m), 6.59 (0.978H, s) (aromatic C), 3.81 (1.184H, s), 3.76 (2.961H, s) (aliphatic C)

^{13}C NMR (100 MHz) δ: 160.3, 155.0, 154.2, 147.7, 147.4, 135.6, 132.1, 129.9, 128.4, 127.9, 127.4, 126.9, 121.9, 113.0, 112.9, 102.5, 97.9 (aromatic C), 55.8 (aliphatic C)

HRMS (ESI-MS)

Calcd for:

$C_{17}H_{13}N_3O_2$ **269b**: 292.1086 (M+H)

Found: 292.1079

$C_{17}H_{12}IN_3O_2$ **269bb**: 418.0052 (M+H)

Found: 418.0051

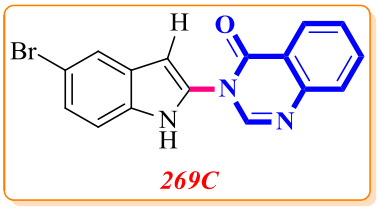
3-(5-Bromo-1*H*-indol-2-yl)-3*H*-quinazolin-4-one (269c):

Yield: 30 %

Mp: 188 ^{o}C

IR (KBr) ν_{max} cm^{-1}: 3221, 2926, 1682, 1654, 904, 772

^{1}H NMR (400 MHz) δ: 12.03 (1H, s), 8.48 (1H, s), 8.25 (1H, d, *J* = 8.0 Hz), 7.92 (1H, t, *J* = 7.6 Hz), 7.81 (1H, s), 7.77 (1H, d, *J* = 8.0 Hz), 7.64 (1H, t, *J* = 7.6 Hz), 7.42 (1H, d, *J* = 8.8 Hz), 7.30 (1H, d, *J* = 8.8 Hz), 6.69 (1H, s) (aromatic C)



269C

^{13}C NMR (100 MHz) δ: 160.2, 147.7, 147.2, 135.7, 133.5, 133.2, 128.8, 128.4, 128.0, 126.9, 125.3, 123.2, 121.8, 114.2, 112.6, 97.7 (aromatic C)

HRMS (ESI-MS)

Calcd for: $C_{16}H_{10}Br^{79}N_3O$: 340.0085 (M+H)

Found: 340.0082

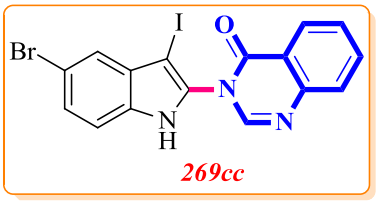
Calcd for: $C_{16}H_{10}Br^{81}N_3O$: 342.0065 (M+H)

Found: 342.0085

3-(5-Bromo-3-iodo-1*H*-indol-2-yl)-3*H*-quinazolin-4-one (269cc):

Yield: 35 %

Mp: 218 °C



269cc

IR (KBr) ν_{max} cm^{-1}: 3407, 2932, 1675, 1601, 1455, 1008, 938

^{1}H NMR (500 MHz) δ: 12.59 (1H, s), 8.43 (1H, s), 8.26 (1H, dd, *J* = 8.0 Hz, *J* = 1.0 Hz), 7.99-7.95 (1H, m), 7.82 (1H, d, *J* = 8.0 Hz), 7.68 (1H, t, *J* = 8.0 Hz), 7.55 (1H, d, *J* = 1.5 Hz), 7.49 (1H, d, *J* = 9.0 Hz), 7.43 (1H, dd, *J* = 8.5 Hz, *J* = 2.0 Hz) (aromatic C)

^{13}C NMR (125 MHz) δ: 160.1, 147.8, 147.5, 136.1, 134.5, 134.1, 131.1, 128.7, 128.2, 127.1, 126.9, 123.2, 121.7, 115.0, 113.6, 58.1 (aromatic C)

HRMS (ESI-MS)

Calcd for: $C_{16}H_9Br^{79}IN_3O$: 465.9052 (M+H)

Found: 465.9049

Calcd for: $C_{16}H_9Br^{81}IN_3O$: 467.9031 (M+H)

Found: 467.9028

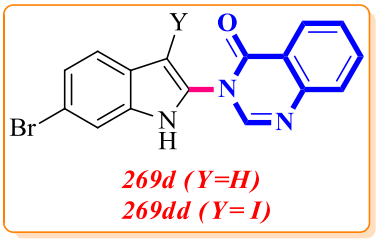
3-(6-Bromo-1*H*-indol-2-yl)-3*H*-quinazolin-4-one (269d) and

3-(6-Bromo-3-iodo-1*H*-indol-2-yl)-3*H*-quinazolin-4-one (269dd):

Yield: 54 % (**269d**: **269dd** = 0.3:1);

IR (KBr) ν_{max} cm^{-1}: 3342, 2915, 1676, 1610, 1413, 1260, 772, 701

^1H NMR (400 MHz) δ: 12.48 (1H,s), 11.96 (0.304H, s), 8.49 (0.326H, s), 8.41 (0.994H, s), 8.26-8.24 (1.35H, m), 7.98-7.90 (1.48H, m), 7.82-7.76 (1.356H, m), 7.72 (1.048H, s), 7.68-7.62 (1.672H, m), 7.59-7.57 (0.334H, m), 7.35 (2.14H, s), 7.22-7.20 (0.346H, m), 6.73 (0.298H, s)



269d (Y=H)
269dd (Y= I)

^{13}C NMR (100 MHz) δ: 160.1, 147.9, 147.5, 147.2, 136.0, 135.9, 135.7, 134.0, 128.6, 128.4, 128.2, 127.9, 127.0, 125.9, 124.2, 123.0, 121.8, 116.8, 115.3, 114.6, 98.2, 59.1(aromatic C)

HRMS (ESI-MS)

Calcd for:

$C_{16}H_{10}Br^{79}N_3O$ **269d**: 340.0085 (M+H)

Found: 340.0075

$C_{16}H_{10}Br^{81}N_3O$ **269d**: 342.0065 (M+H)

Found: 342.0056

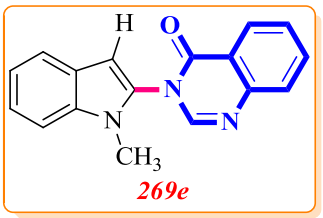
$C_{16}H_9Br^{79}IN_3O$ **269dd**: 465.9052 (M+H)

Found: 465.9049

$C_{16}H_9Br^{81}IN_3O$ **269dd**: 467.9031 (M+H)

Found: 467.9029

3-(1-Methyl-1*H*-indol-2-yl)-3*H*-quinazolin-4-one (269e):



269e

Yield: 45 %

Mp: 178 ^oC

IR (KBr) ν_{max} cm^{-1}: 3106, 2920, 1676, 1600, 1238, 810, 772

^1H NMR (500 MHz) δ: 8.37 (1H, s), 8.24 (1H, d, *J* = 7.6 Hz), 7.93 (1H, t, *J* = 8.0 Hz), 7.79 (1H, d, *J* = 8.0 Hz), 7.66-7.63 (2H, m), 7.54 (1H, d, *J* = 8.4 Hz), 7.28 (1H, t, *J* = 7.6 Hz), 7.14 (1H, t, *J* = 7.6 Hz), 6.72 (1H, s), (aromatic C), 3.56 (3H, s) (aliphatic C)

^{13}C NMR (125 MHz) δ: 160.9, 148.1, 147.9, 135.9, 135.7, 133.0, 128.4, 128.0, 127.1, 126.1, 122.9, 121.9, 121.3, 120.4, 110.7, 99.6 (aromatic C), 29.8 (aliphatic C)

HRMS (ESI-MS)

Calcd for: $C_{17}H_{13}N_3O$: 298.0956 (M+Na)

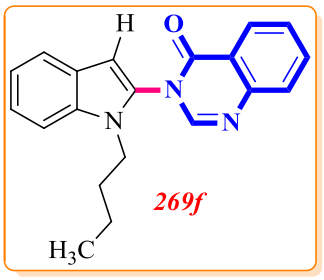
Found: 298.0960

3-(1-Butyl-1*H*-indol-2-yl)-3*H*-quinazolin-4-one (269f):

Yield: 52 %

Mp: 170 ^oC

IR (KBr) ν_{max} cm^{-1}: 3025, 2920, 1670, 1600, 1310, 926, 701



269f

^{1}H NMR (400 MHz) δ: 8.42 (1H, s), 8.24 (1H, d, *J* = 7.6 Hz), 7.96-7.92 (1H, m), 7.80 (1H, d, *J* = 8.0 Hz), 7.67-7.63 (2H, m), 7.56 (1H, d, *J* = 8.0 Hz), 7.27 (1H, t, *J* = 7.2 Hz), 7.13 (1H, t, *J* = 7.6 Hz), 6.71 (1H, s),) (aromatic C), 4.06 (1H, s), 3.86 (1H, s), 1.57 (2H, s), 1.13 (2H, s), 0.71 (3H, t, *J* = 7.6 Hz (aliphatic C)

^{13}C NMR (100 MHz) δ: 160.9, 147.9, 135.8, 135.3, 132.4, 128.5, 128.1, 127.1, 126.3, 123.0, 121.9, 121.4, 120.4, 110.9, 100.2, (aromatic C), 42.8, 31.9, 19.8, 13.9 (aliphatic C)

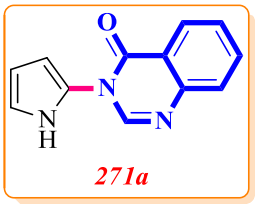
HRMS (ESI-MS)

Calcd for: $C_{20}H_{19}N_3O$ 318.1606 (M+H)

Found: 318.1606

3-(1*H*-Pyrrol-2-yl)-3*H*-quinazolin-4-one (271a):

Yield: 52 %



271a

IR (KBr) ν_{max} cm^{-1}: 3043, 2934, 1675, 1420, 863

^{1}H NMR (400 MHz) δ: 10.01 (1H, s), 8.34 (1H, s), 8.29 (1H, d, *J* = 8.0 Hz), 7.80-7.72 (2H, m), 7.54-7.50 (1H, m), 6.84- 6.82 (1H, m), 6.29-6.27 (1H, m), 6.26-6.25 (1H, m) (aromatic C)

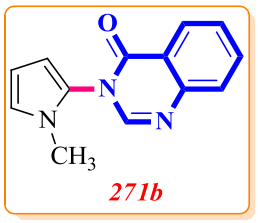
^{13}C NMR (100 MHz) δ: 160.8, 147.0, 144.6, 134.7, 127.9, 127.7, 126.9, 126.4, 121.8, 116.8, 108.1, 100.4 (aromatic C)

HRMS (ESI-MS)

Calcd for: $C_{12}H_9N_3O$: 212.0824 (M+H)

Found: 212.0830

3-(1-Methyl-1*H*-pyrrol-2-yl)-3*H*-quinazolin-4-one (271b):



271b

Yield: 58 %

Mp: 112 ^{o}C

IR (KBr) ν_{max} cm^{-1}: 3117, 3073, 1687, 1600, 1320, 772

^{1}H NMR (400 MHz) δ: 8.38 (1H, d, *J* = 7.6 Hz), 8.10 (1H, s), 7.84-7.78 (2H, m), 7.58 (1H, t, *J* = 7.6 Hz), 6.74 (1H, s), 6.232-6.226 (2H, m) (aromatic C), 3.50 (3H, s) (aliphatic C)

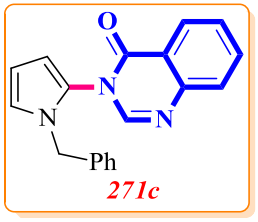
^{13}C NMR (100 MHz) δ: 161.2, 147.7, 147.2, 134.9, 127.9, 127.6, 127.3, 125.3, 122.2, 121.9, 107.4, 106.3 (aromatic C), 33.5 (aliphatic C)

HRMS (ESI-MS)

Calcd for: $C_{13}H_{11}N_3O$: 226.0980 (M+H)

Found: 226.0979

3-(1-Benzyl-1*H*-pyrrol-2-yl)-3*H*-quinazolin-4-one (271c):



271c

Yield: 50 %

Mp: 178 ^{o}C

IR (KBr) ν_{max} cm^{-1}: 3603, 2920, 1693, 1610, 1276, 723

^{1}H NMR (400 MHz) δ: 8.36 (1H, d, *J* = 8.0 Hz), 7.79 (1H, t, *J* = 7.2 Hz), 7.69 (1H, d, *J* = 8.0 Hz), 7.65 (1H, s), 7.56 (1H, t, *J* = 8.0 Hz), 7.22-7.21 (3H, m), 7.00-6.96 (2H, m), 6.82 (1H, s), 6.30-6.28 (1H, m), 6.25-6.24 (1H, m) (aromatic C), 5.00-4.92 (2H, m) (aliphatic C)

^{13}C NMR (100 MHz) δ: 161.4, 147.7, 147.1, 136.8, 134.8, 128.8, 128.0, 127.7, 127.6, 127.2, 127.0, 125.2, 122.0, 121.9, 107.7, 107.1 (aromatic C), 50.9 (aliphatic C)

HRMS (ESI-MS)

Calcd for: $C_{19}H_{15}N_3O$: 302.1293 (M+H)

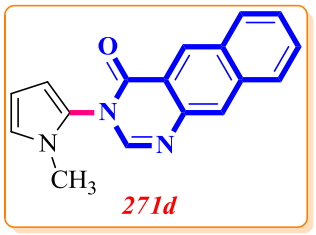
Found: 302.1293

3-(1-Methyl-1*H*-pyrrol-2-yl)-3*H*-benzo[g]quinazolin-4-one (271d):

Yield: 35 %

Mp: 152 ^{o}C

IR (KBr) ν_{max} cm^{-1}: 2958, 2926, 1682, 1605, 1265, 756



271d

^{1}H NMR (400 MHz) δ: 8.98 (1H, s), 8.26 (1H, s), 8.10-8.02 (3H, m), 7.67 (1H, t, *J* = 6.8 Hz), 7.60 (1H, t, *J* = 7.2 Hz), 6.76-6.75 (1H, m), 6.26-6.24 (2H, m) (aromatic C), 3.53 (3H, s) (aliphatic C)

^{13}C NMR (100 MHz) δ: 161.4, 147.7, 147.1, 136.8, 134.8, 128.8, 128.0, 127.7, 127.6, 127.2, 127.0, 125.2, 122.0, 121.9, 107.7, 107.1 (aromatic C), 50.9 (aliphatic C)

HRMS (ESI-MS)

Calcd for: $C_{17}H_{13}N_3O$: 276.1137 (M+H)

Found: 276.1138

3-Methyl-1,3-dihydro-indol-2-one (272) [20]:

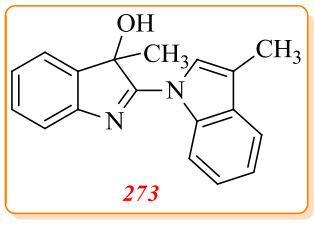
This compound was verified by the literature values.

3, 3'-Dimethyl-3'*H*-[1, 2'] biindolyl-3'-ol (273):

Yield: 22 %

Mp: 174 ^{o}C

IR (KBr) ν_{max} cm^{-1}: 3347, 3052, 1791, 1561, 1205, 942, 745



273

^{1}H NMR (400 MHz) δ: 8.78 (1H, d, *J* = 8.0 Hz), 8.06 (1H, s), 7.60 (1H, d, *J* = 7.6 Hz), 7.44-7.28 (5H, m), 7.16 (1H, t, *J* = 7.6 Hz), 6.68 (1H, s) (aromatic C), 2.31 (3H, s), 1.65 (3H, s) (aliphatic C)

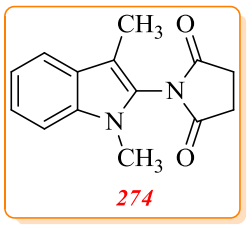
^{13}C NMR (100 MHz) δ: 170.9, 151.9, 140.9, 135.9, 130.9, 129.7, 124.9, 124.6, 123.2, 122.1, 119.3, 117.1, 116.6, 81.9 (aromatic C), 26.3, 9.9 (aliphatic C)

HRMS (ESI-MS)

Calcd for: $C_{18}H_{16}N_2O$: 277.1341 (M+H)

Found: 277.1344

1-(1, 3-Dimethyl-1*H*-indol-2-yl)-pyrrolidine-2, 5-dione (274):



274

Yield: 34 %, 62 %, 40 % ([C], [D], [E])

Mp: 178 ^{o}C

IR (KBr) ν_{max} cm^{-1}: 3347, 3052, 1791, 1561, 1205, 942, 745

^{1}H NMR (400 MHz) δ: 7.54 (1H, d, *J* = 8.0 Hz), 7.41 (1H, d, *J* = 8.0 Hz), 7.22 (1H, t, *J* = 7.2 Hz), 7.08 (1H, t, *J* = 7.2 Hz) (aromatic C), 3.48 (3H, s), 2.94 (4H, s), 2.05 (3H, s) (aliphatic C)

^{13}C NMR (100 MHz) δ: 177.4, 135.4, 126.6, 124.5, 122.7, 119.5, 119.3, 110.2, 107.2 (aromatic C), 29.5, 29.2, 8.4 (aliphatic C)

HRMS (ESI-MS)

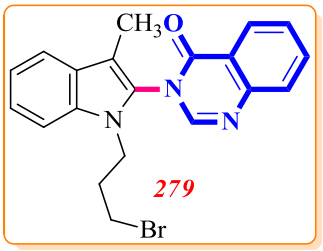
Calcd for: $C_{14}H_{14}N_2O_2$: 243.1134 (M+H)

Found: 243.1133

3-[1-(3-Bromo-propyl)-3-methyl-1*H*-indol-2-yl]-3*H*-quinazolin-4-one (279):

To a solution of 3-(3-methyl-1*H*-indol-2-yl)-4a,8a-dihydro-3*H*-quinazolin-4-one (**267a**) (0.100 g, 0.36 mmol) in dry DMF (5 mL), K_2CO_3 (0.100 g, 0.72 mmol) was added and stirred at RT for 1h. Then 1, 3 dibromopropane (0.109 g, 0.54 mmol) was added to the reaction mixture drop wise and stirred at rt for another 5 h. Then the reaction mixture was extracted with EtOAc,

dried over Na_2SO_4 and evaporated in vacuum. The residue was purified by column chromatography on silica gel (EtOAc: hexanes = 1:9). This compound was obtained as yellow sticky semisolid with little inseparable impurities.



279

Yield: 55 %

IR (KBr) ν_{max} cm^{-1}: 3052, 2920, 1693, 1610, 1276, 920

^1H NMR (400 MHz) δ: 8.42 (1H, d, *J* = 7.5 Hz), 8.025 (1H, s), 7.89-7.84 (2H, m), 7.67 (1H, d, *J* = 8.0 Hz), 7.63 (1H, t, *J* = 7.5 Hz), 7.46 (1H, d, *J* = 8.0 Hz), 7.38-7.35 (1H, m), 7.24 (1H, t, *J* = 7.5 Hz), (aromatic C), 4.24-4.10 (2H, m), 3.39-3.29 (2H, m), 2.33-2.23 (2H, m), 2.24 (3H, s) (aliphatic C)

^{13}C NMR (100 MHz) δ: 161.1, 147.9, 146.6, 135.1, 133.2, 128.1, 127.9, 127.4, 126.9, 123.5, 122.2, 120.0, 119.8, 117.0, 109.8, 108.5 (aromatic C), 41.4, 32.4, 30.5, 8.1 (aliphatic C)

HRMS (ESI-MS)

Calcd for: $C_{20}H_{18}Br^{79}N_3O$: 396.0711 (M+H)

Found: 396.0711

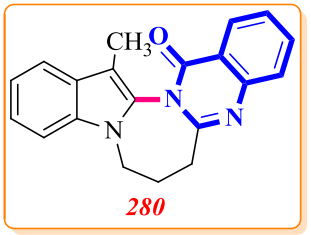
Calcd for: $C_{20}H_{18}Br^{81}N_3O$: 398.0691 (M+H)

Found: 398.0693

14-Methyl-7,8-dihydroindolo[2',1':2,3][1,3]diazepino[7,1-*b*]quinazolin-16(6*H*)-one (280):

To a freshly prepared solution of LDA (0.054 g, 0.50 mmol) in anhydrous THF (8 mL) at -78 ^{0}C under nitrogen atmosphere, a solution of 3-[1-(3-bromo-propyl)-3-methyl-1*H*-indol-2-yl]-3*H*-quinazolin-4-one (**279**) (0.100 g, 0.25 mmol) in THF and HMPA (0.180g, 1.00 mmol) was added dropwise. The reaction mixture was stirred for another 3 h at -78 ^{0}C, followed by additional 2 h at rt. Then the reaction mixture was quenched with saturated solution of NH_4Cl

and extracted with EtOAc. The solvent was dried over Na_2SO_4 and evaporated in vacuum. The residue was purified by column chromatography on silica gel (EtOAc: hexanes = 3:7).



280

Yield:	42%
Mp:	158 ^{o}C
IR (KBr) ν_{max} cm^{-1}:	3046, 2958, 2920, 1693, 1605, 1457, 1260, 739
^{1}H NMR (400 MHz,) δ:	8.22 (1H, d, *J*= 8.0 Hz), 7.89 (1H, t, *J* = 7.2 Hz), 7.72 (1H, d, *J* = 8.0 Hz), 7.63-7.56 (3H, m), 7.23 (1H, t, *J* = 7.6 Hz), 7.11 (1H, t, *J* = 7.2 Hz), (aromatic C), 4.62-4.57 (1H, m), 4.02-3.95 (1H, m), 2.78-2.74 (1H, m), 2.25-2.17 (3H, m), 2.11 (3H, s) (aliphatic C)
^{13}C NMR (100 MHz) δ:	159.6, 156.1, 147.4, 135.4, 133.5, 127.9, 127.6, 127.6, 127.3, 127.0, 122.7, 121.0, 119.8, 119.4, 110.0, 106.2, (aromatic C), 39.0, 32.9, 27.6, 9.4 (aliphatic C)
HRMS (ESI-MS)	
Calcd for: $C_{20}H_{17}N_3O$:	316.1450 (M+H)
Found:	316.1448

Table 2. Crystal data and structure refinement for 267a

Empirical formula	: $C_{17}H_{13}IN_3O$	
Formula weight	: 275.30	
Temperature	: 298(2) K	
Wavelength	: 0.71073 Å	
Crystal system	: Monoclinic	
Space group	: P -1	
Unit cell dimensions	: a = 10.830(3) Å	α= 102.67 (4)°.
	: b = 12.205(3) Å	β= 106.686 (4)°.
	: c = 12.209(3) Å	γ = 110.923(4)°.
Volume	: 1347.2(6) $Å^3$	
Z	: 4	
Density (calculated)	: 1.357 Mg/m^3	
Absorption coefficient	: 2.318 mm^{-1}	
F(000)	: 576	
Theta range for data collection	: 3.170 to 28.893°.	
Index ranges	: -16<=h<=12, -5<=k<=14, -10<=l<=14	
Completeness to theta = 25.242°	: 99 %	
Absorption correction	: Semi-empirical from equivalents	
Max. and min. transmission	: 0.987 and 0.974	
Refinement method	: Full-matrix least-squares on F^2	
Goodness-of-fit on F^2	: 1.071	
Final R indices [I>2sigma(I)]	: R1 = 0.0494, wR2 = 0.1366	
Extinction coefficient	: n/a	
CCDC Number	: 956412	

Table 3. Crystal data and structure refinement for 269aa

Empirical formula	: $C_{16}H_9IN_3O$	
Formula weight	: 386.16	
Temperature	: 298(2) K	
Wavelength	: 0.71073 Å	
Crystal system	: Monoclinic	
Space group	: P 21/n	
Unit cell dimensions	: a = 13.0741(18) Å	α= 90°.
	: b = 4.2988(4) Å	β= 100.040(11)°.
	: c = 24.974(3) Å	γ = 90°.
Volume	: 1382.1(3) $Å^3$	
Z	: 4	
Density (calculated)	: 1.856 Mg/m^3	
Absorption coefficient	: 2.318 mm^{-1}	
F(000)	: 748	
Crystal size	: 0.180 x 0.160 x 0.120 mm^3	
Theta range for data collection	: 3.170 to 28.893°.	
Index ranges	: -16<=h<=14, -3<=k<=5, -33<=l<=17	
Reflections collected	: 3832	
Independent reflections	: 2763 [R(int) = 0.0428]	
Completeness to theta = 25.242°	: 89.1 %	
Absorption correction	: Semi-empirical from equivalents	
Max. and min. transmission	: 1.00000 and 0.49096	
Refinement method	: Full-matrix least-squares on F^2	
Data / restraints / parameters	: 2763 / 0 / 192	
Goodness-of-fit on F^2	: 1.071	
Final R indices [I>2sigma(I)]	: R1 = 0.0559, wR2 = 0.1556	
R indices (all data)	: R1 = 0.0722, wR2 = 0.1842	
Extinction coefficient	: n/a	
Largest diff. peak and hole	: 1.305 and -1.938 $e.Å^{-3}$	
CCDC Number	: 956409	

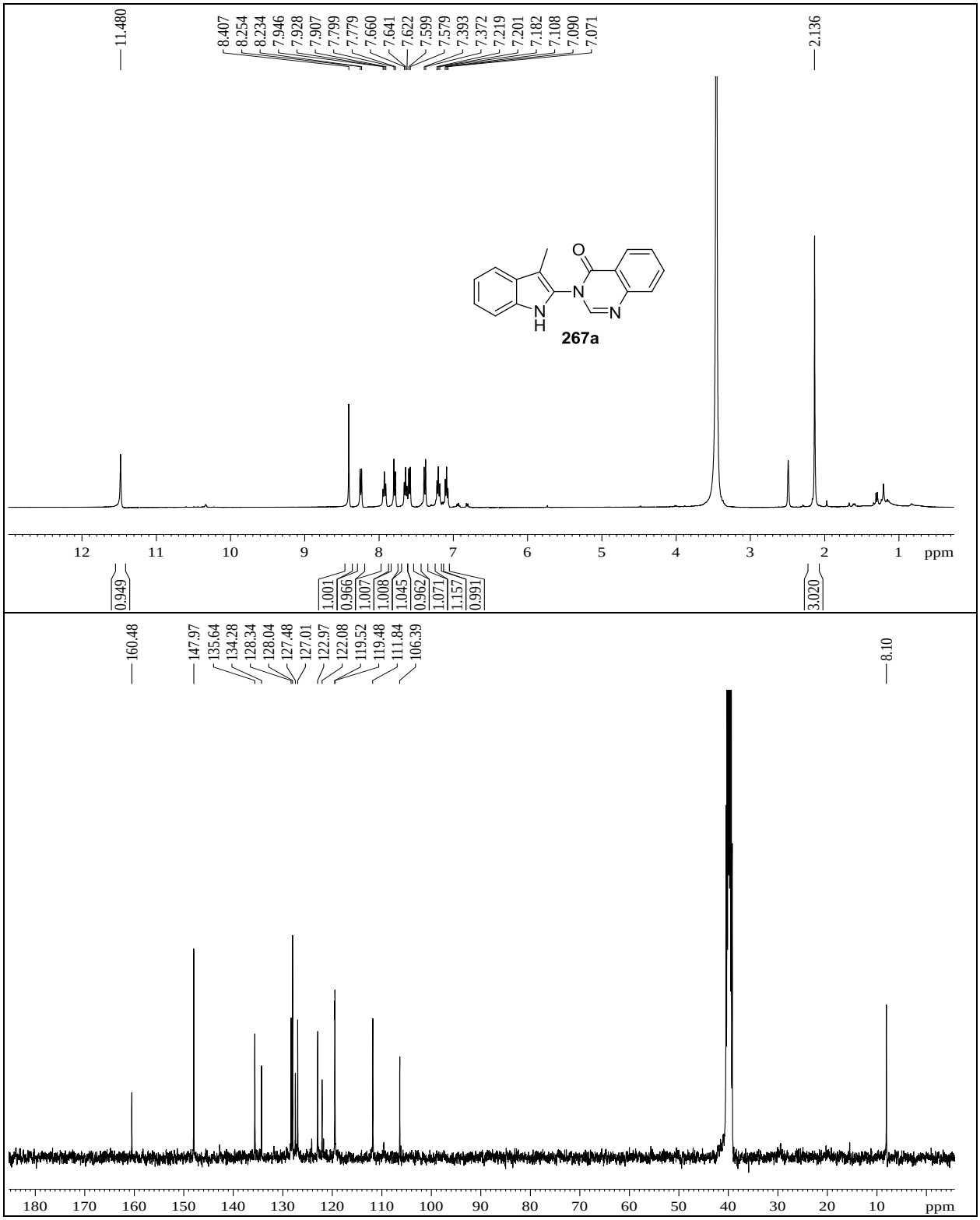
Table 4. Crystal data and structure refinement for 267i

Empirical formula	: $C_{18}H_{15}N_3O$	
Formula weight	: 289.33	
Temperature	: 298(2) K	
Wavelength	: 0.71073 Å	
Crystal system	: Monoclinic	
Space group	: P 21/n	
Unit cell dimensions	: a = 8.3989(18) Å	α= 90°.
	: b = 12.9656(14) Å	β= 101.702(16)°.
	: c = 13.6993(18) Å	γ = 90°.
Volume	: 1460.8(4) $Å^3$	
Z	: 4	
Density (calculated)	: 1.316 Mg/m^3	
Absorption coefficient	: 0.084 mm^{-1}	
F(000)	: 608	
Crystal size	: 0.800 x 0.200 x 0.100 mm^3	
Theta range for data collection	: 2.933 to 26.364°.	
Index ranges	: -10<=h<=7, -10<=k<=16, -16<=l<=17	
Reflections collected	: 5857	
Independent reflections	: 2989 [R(int) = 0.0269]	
Completeness to theta = 25.242°	: 99.9 %	
Absorption correction	: Semi-empirical from equivalents	
Max. and min. transmission	: 0.9916 and 0.9357	
Refinement method	: Full-matrix least-squares on F^2	
Data / restraints / parameters	: 2989 / 0 / 201	
Goodness-of-fit on F^2	: 1.191	
Final R indices [I>2sigma(I)]	: R1 = 0.0669, wR2 = 0.1994	
R indices (all data)	: R1 = 0.0859, wR2 = 0.2100	
Extinction coefficient	: n/a	
Largest diff. peak and hole	: 0.225 and -0.263 $e.Å^{-3}$	
CCDC Number	: 956410	

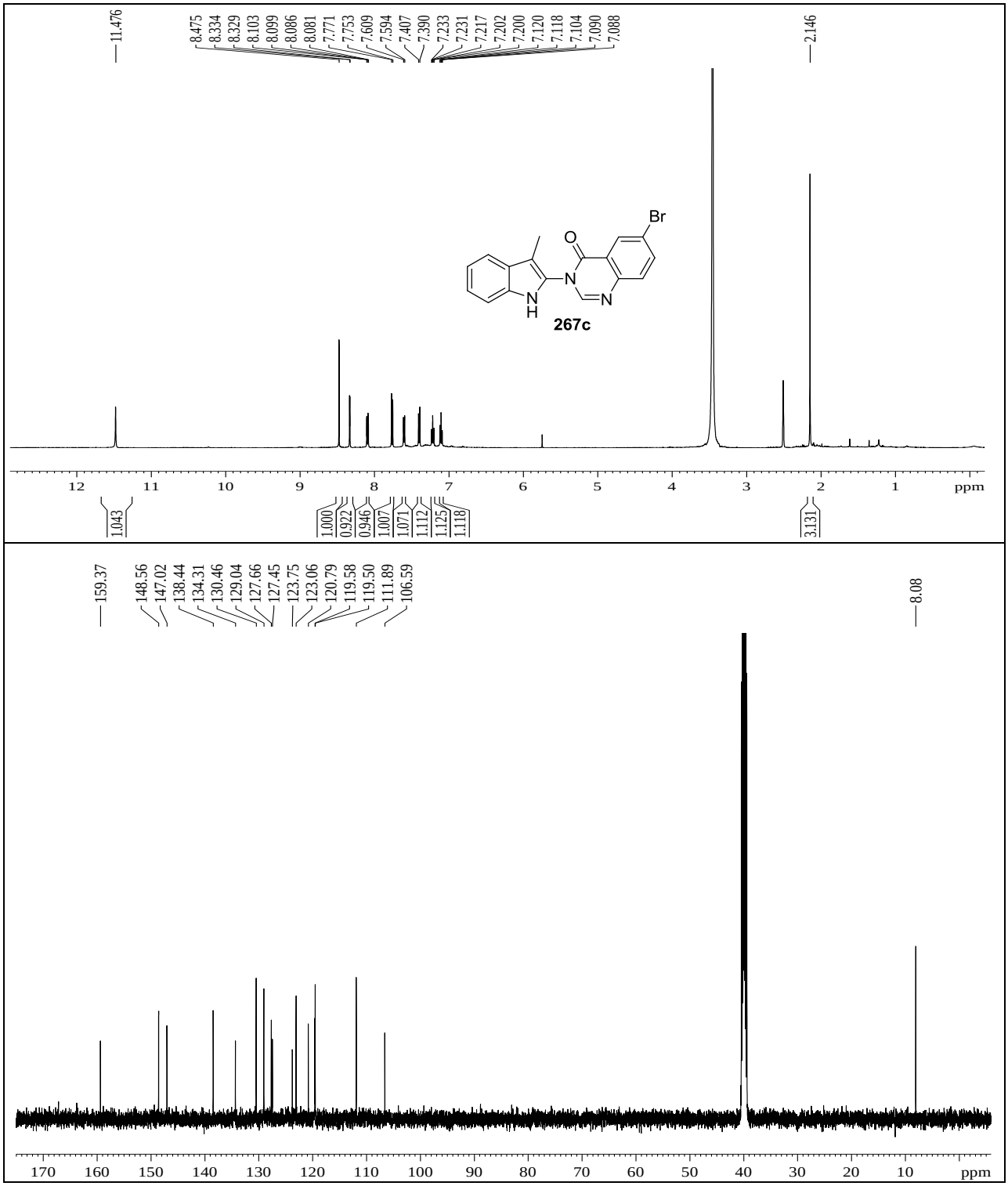
Table 5. Crystal data and structure refinement for 273

Empirical formula	: $C_{18}H_{16}N_2O$
Formula weight	: 276.33
Temperature	: 298 K
Wavelength	: 0.71073 Å
Crystal system, space group	: Triclinic, P -1
Unit cell dimensions	: a = 10.8278(7) Å α = 100.716(5)°.
	: b = 11.3669(8) Å β= 106.227(5)°.
	: c = 13.0687(6) Å γ = 104.477(6)°.
Volume	: 1437.64(15) A^3
Z	: 4, 1.277 Mg/m^3
Absorption coefficient	: 0.080 mm^{-1}
F(000)	: 584
Crystal size	: 0.80 x 0.25 x 0.20 mm^3
Theta range for data collection	: 2.77 to 26.37°
Limiting indices	: -13<=h<=13, -14<=k<=9, -15<=l<=16
Reflections collected / unique	: 10424 / 5875 [R(int) = 0.0270]
Completeness to theta = 26.37	: 99.8 %
Absorption correction	: Semi-empirical from equivalents
Max. and min. transmission	: 0.9841 and 0.9385
Refinement method	: Full-matrix least-squares on F^2
Data / restraints / parameters	: 5875 / 0 / 385
Goodness-of-fit on F^2	: 0.955
Final R indices [I>2sigma(I)]	: R1 = 0.0472, wR2 = 0.1128
R indices (all data)	: R1 = 0.0722, wR2 = 0.1322
Largest diff. peak and hole	: 0.144 and -0.191 $e.A^{-3}$
CCDC Number	: 956411

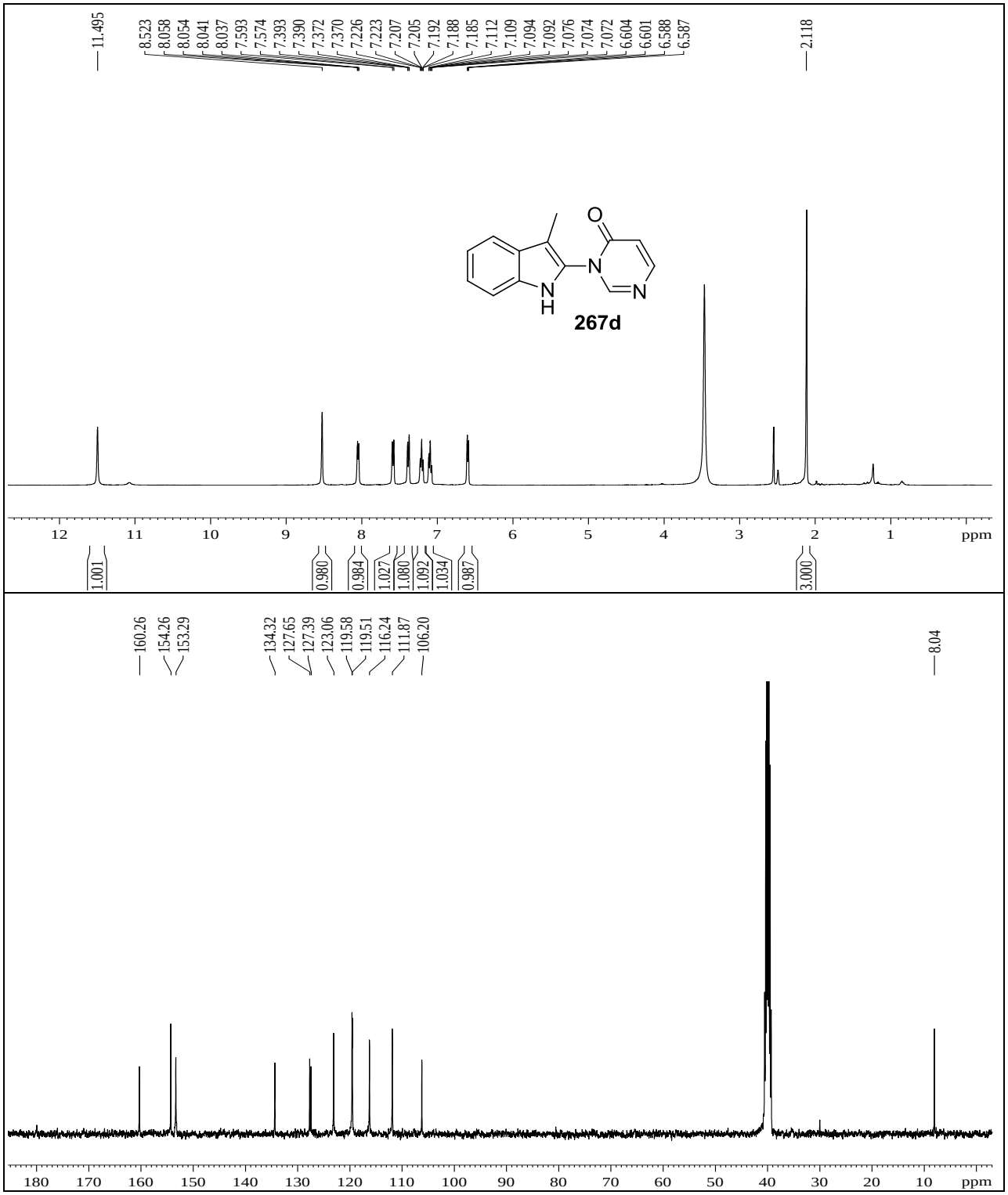
^{1}H, ^{13}C NMR of compound 267a



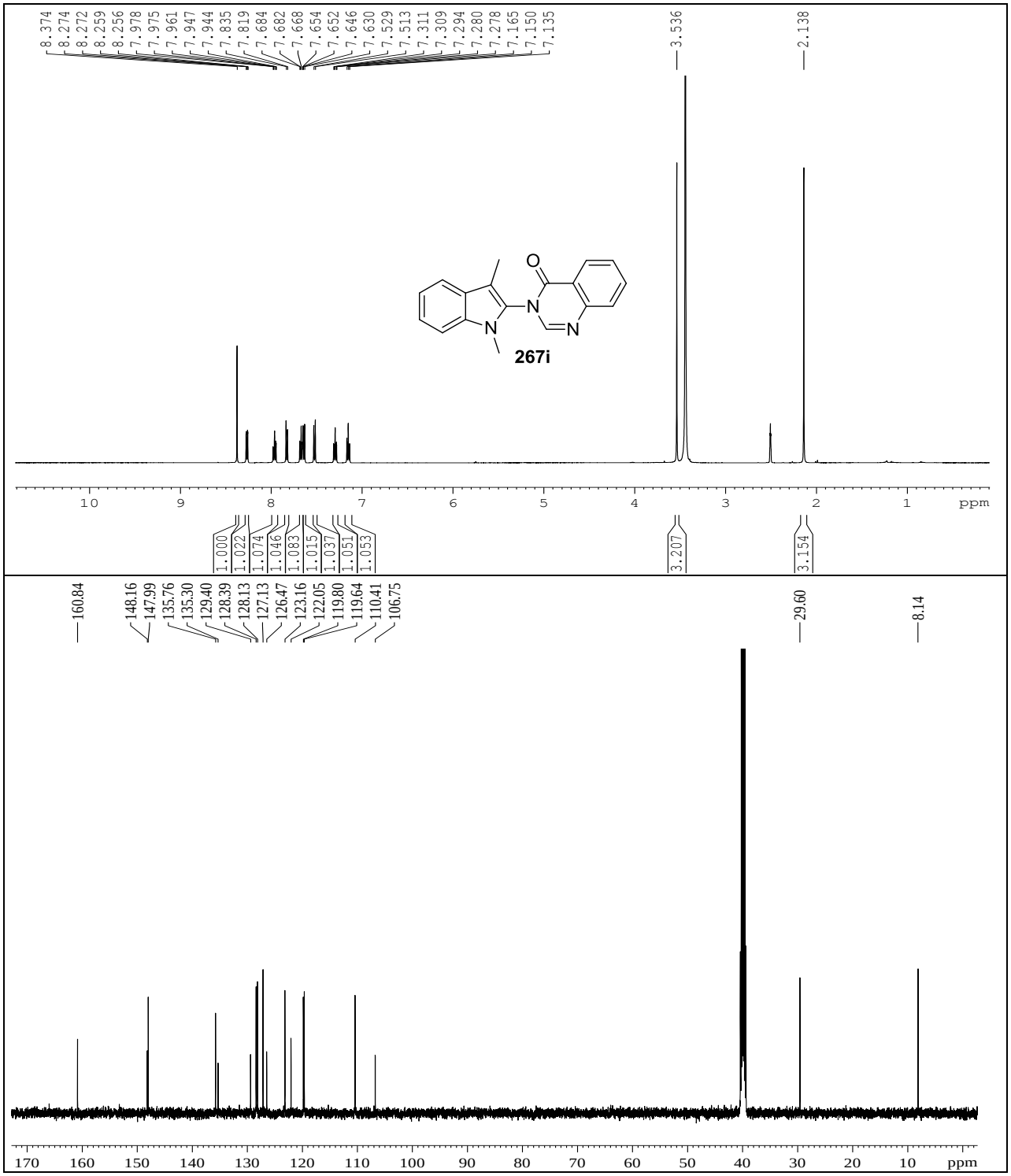
^{1}H, ^{13}C NMR of compound 267c



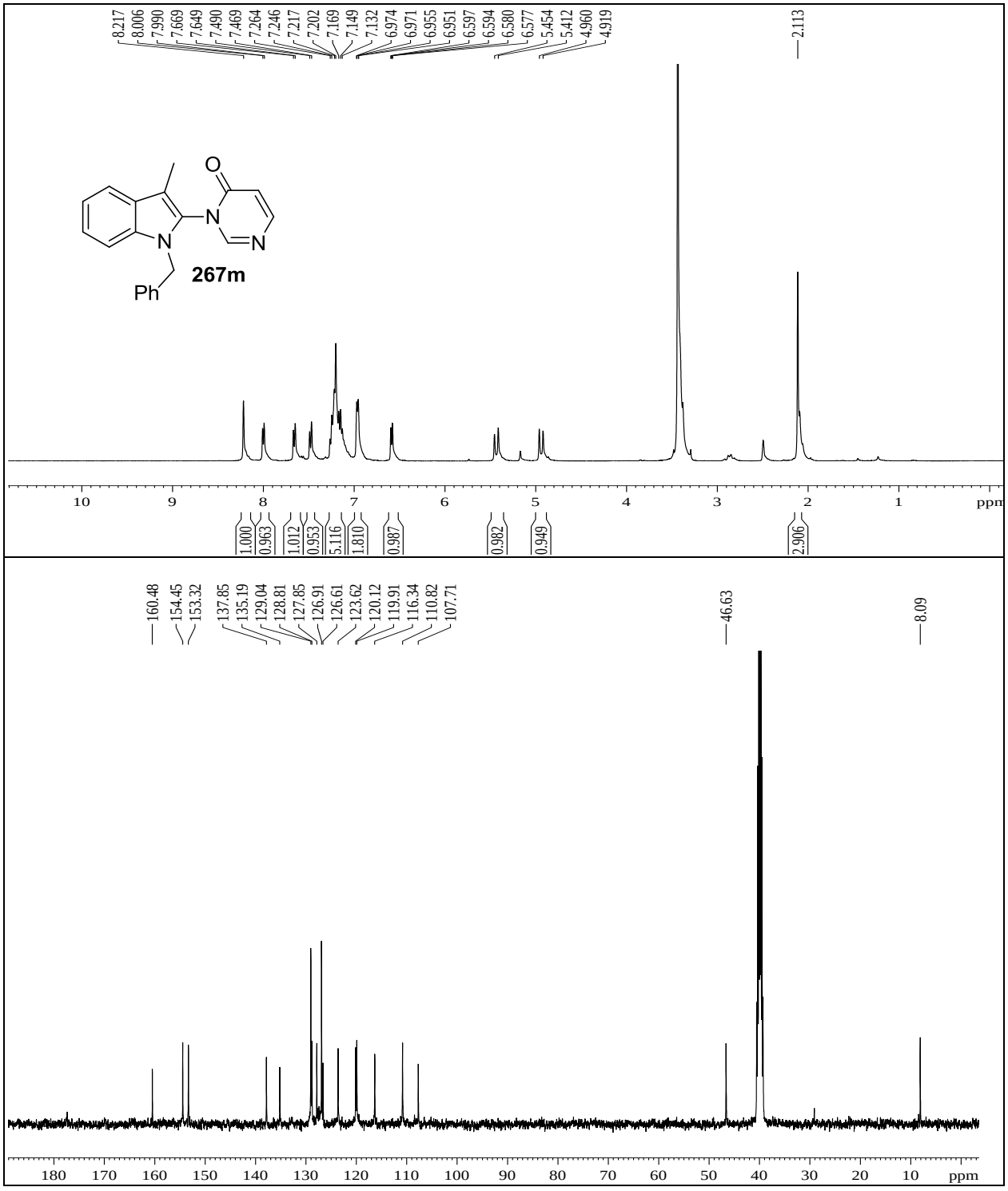
^{1}H, ^{13}C NMR of compound 267d



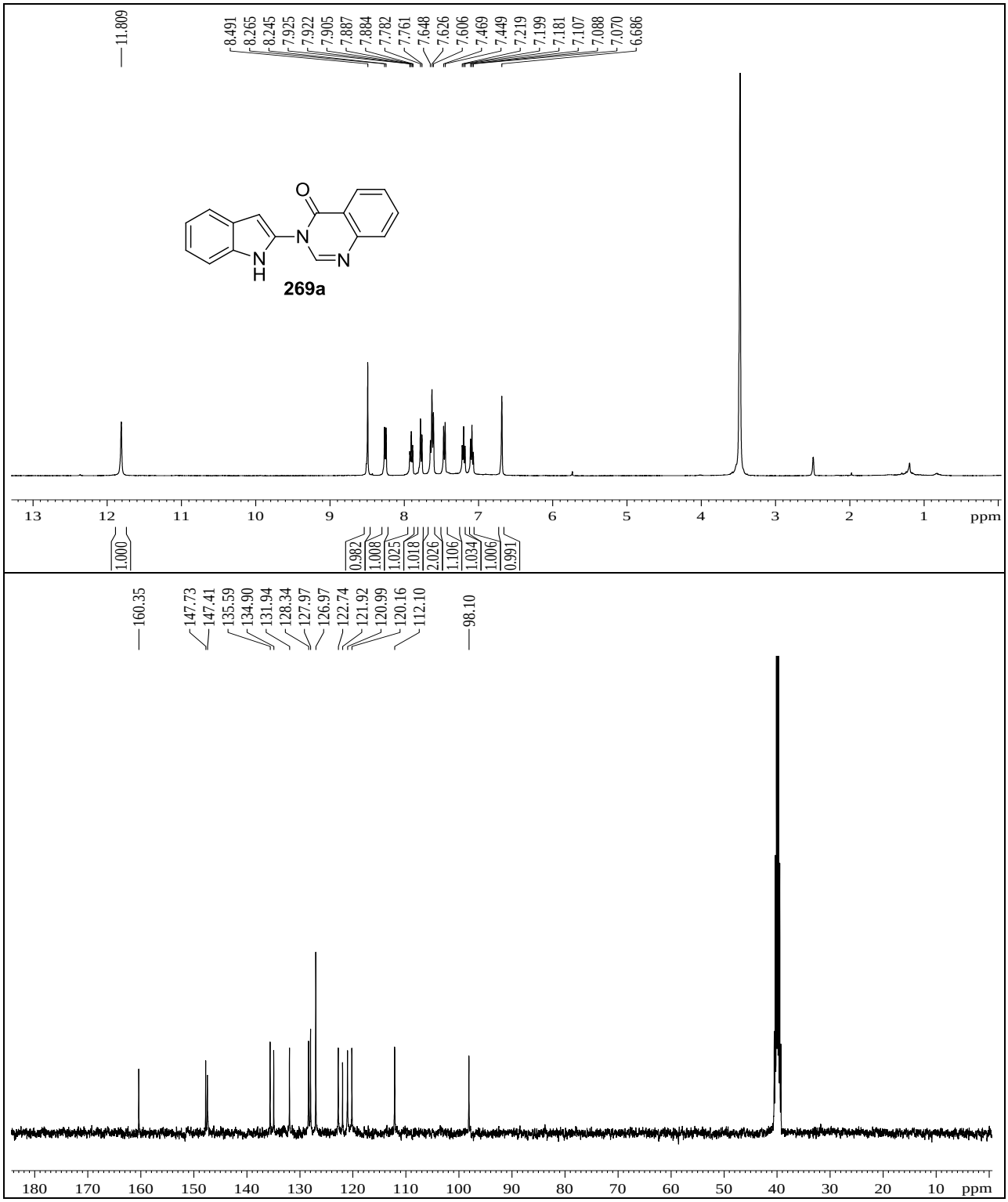
^{1}H, ^{13}C NMR of compound 267i



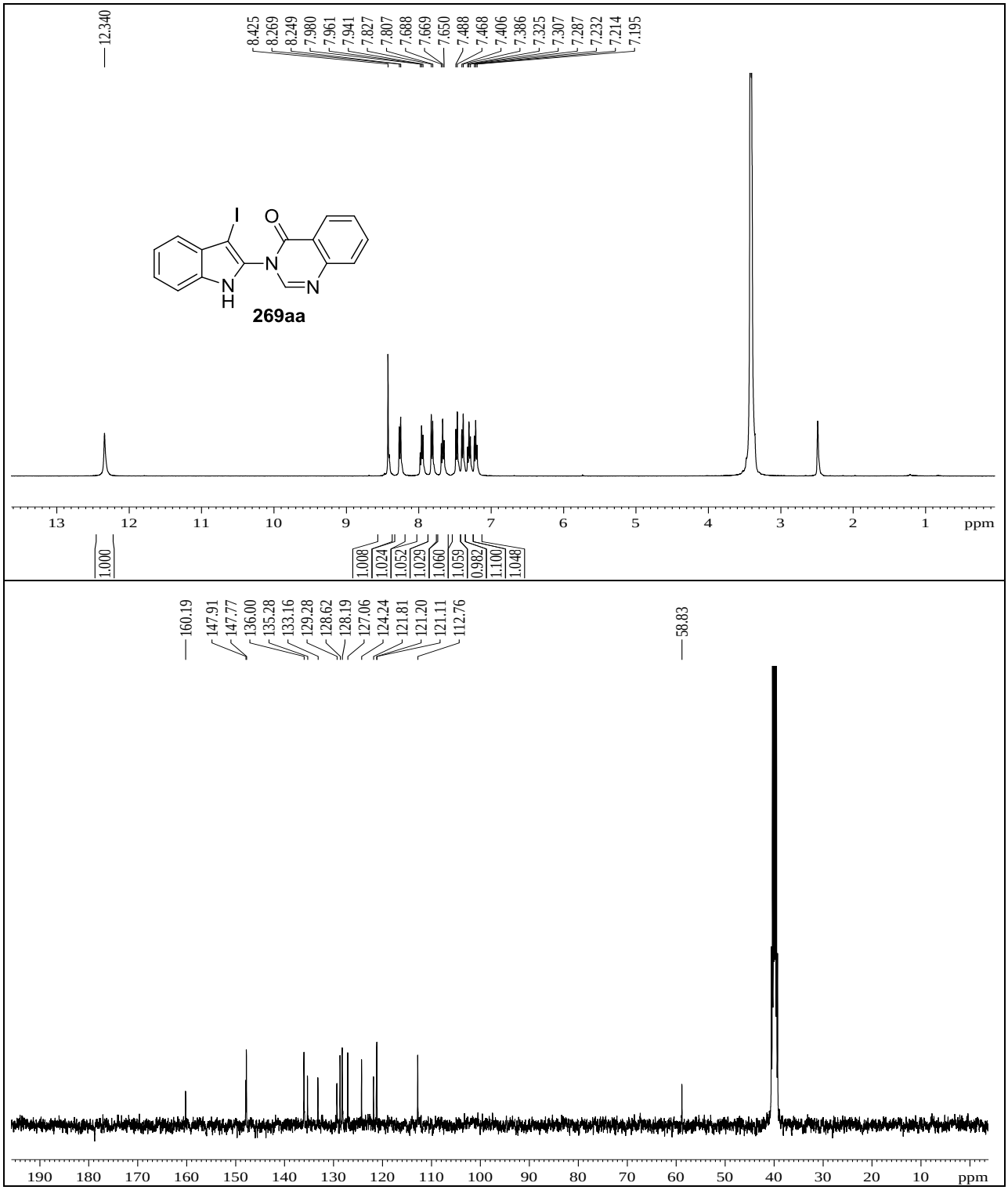
^{1}H, ^{13}C NMR of compound 267m



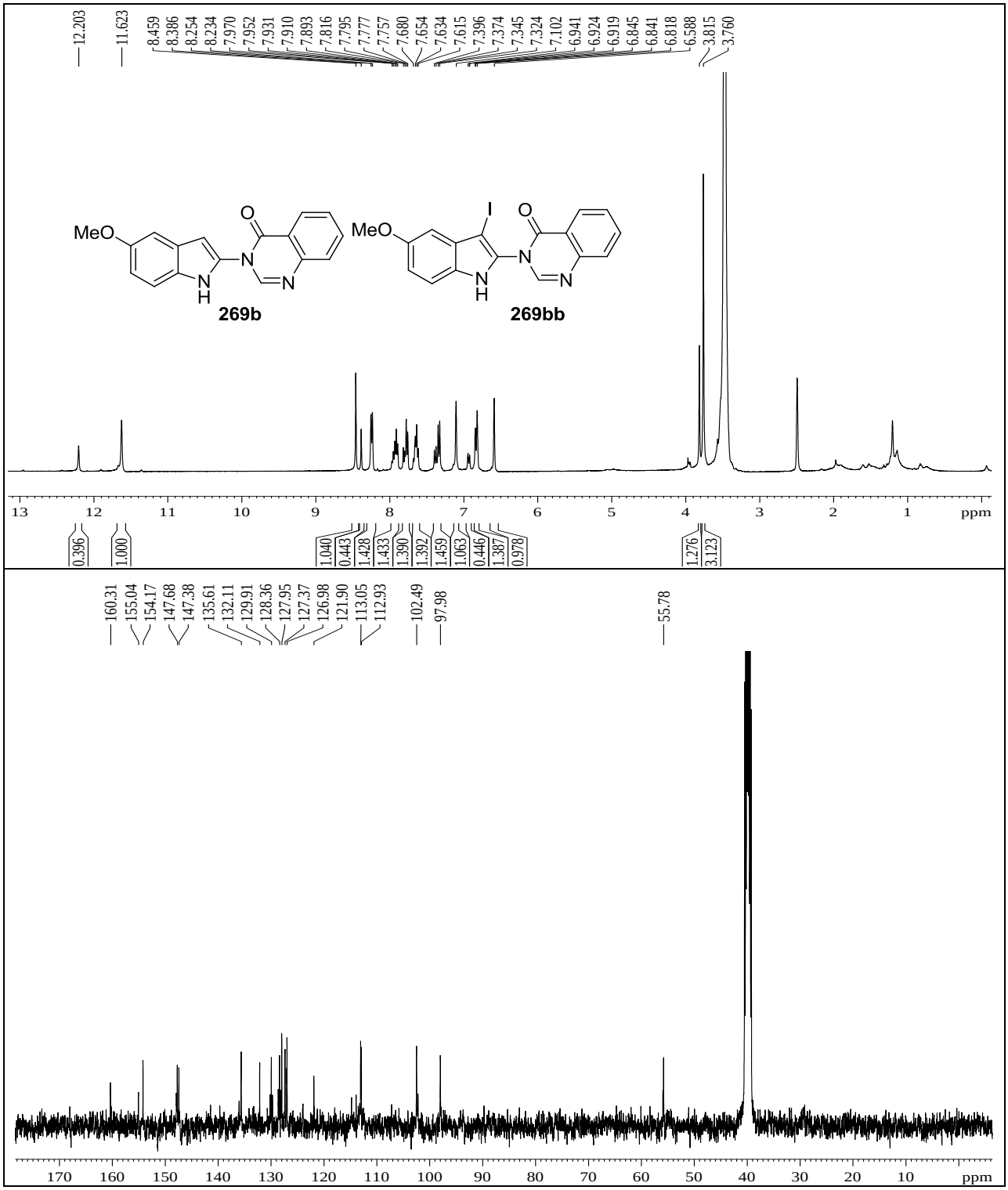
^{1}H, ^{13}C NMR of compound 269a



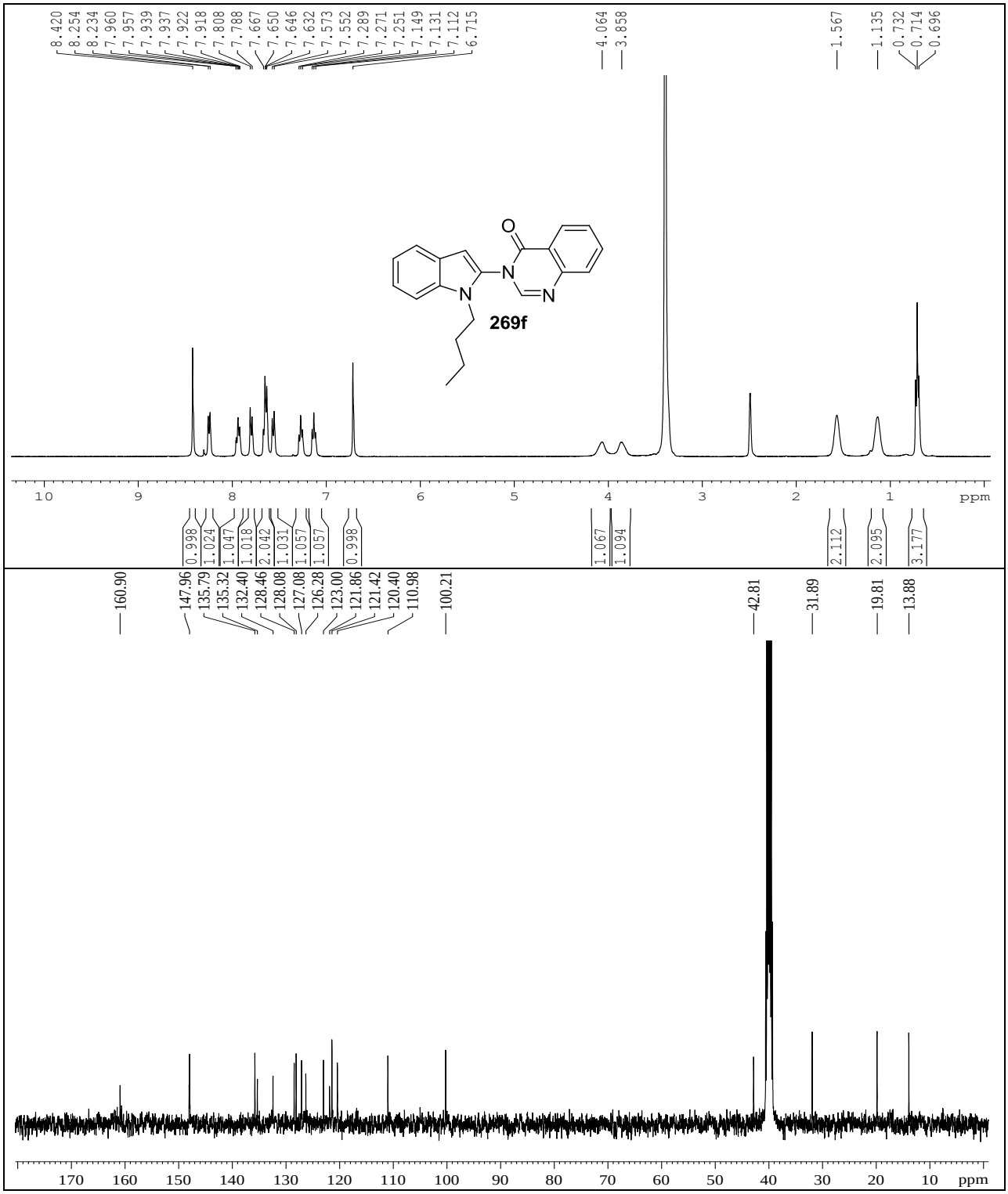
^{1}H, ^{13}C NMR of compound 269aa



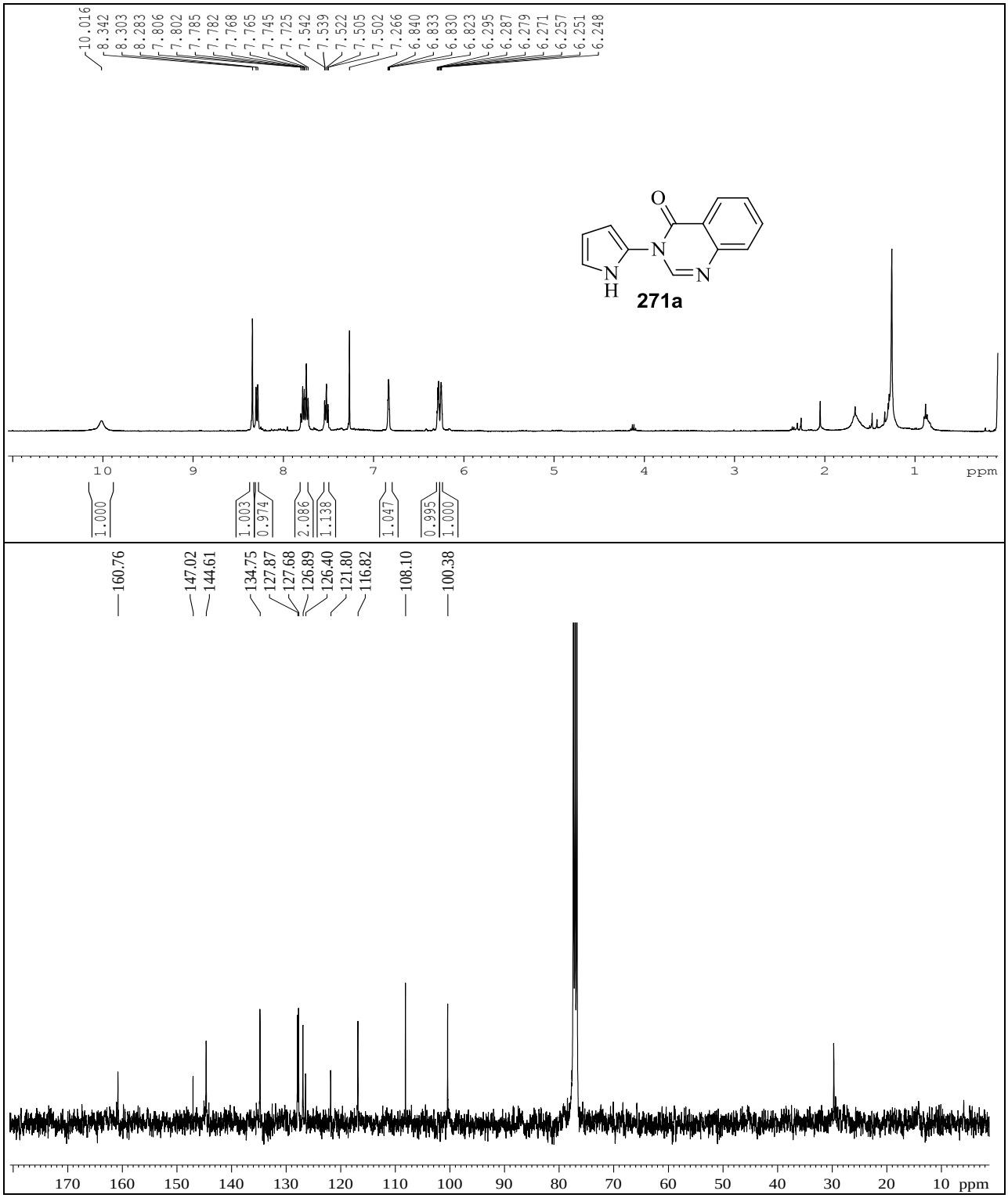
[1]H, [13]C NMR of compound 269b, 269bb



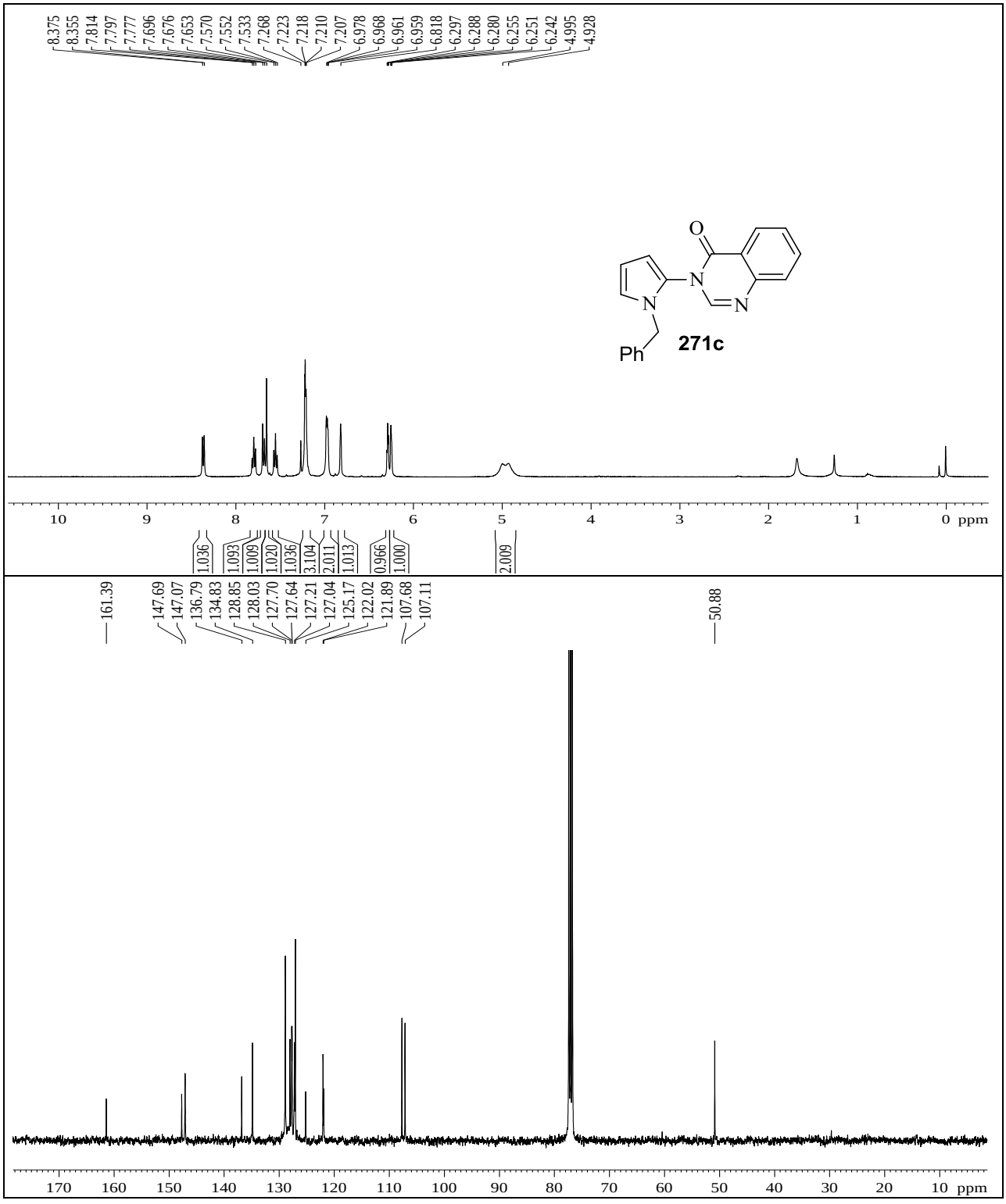
^{1}H, ^{13}C NMR of compound 269f



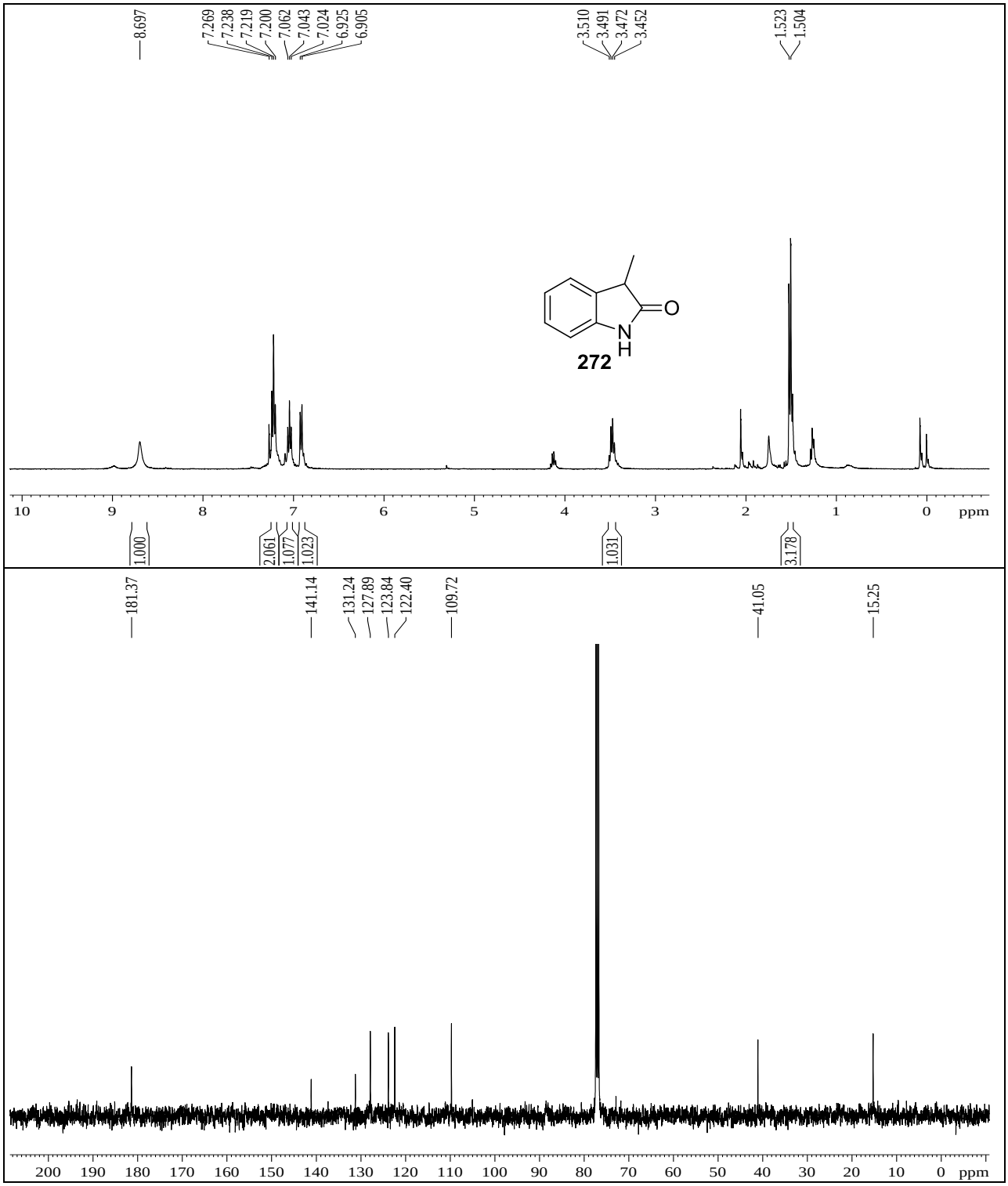
^{1}H, ^{13}C NMR of compound 271a



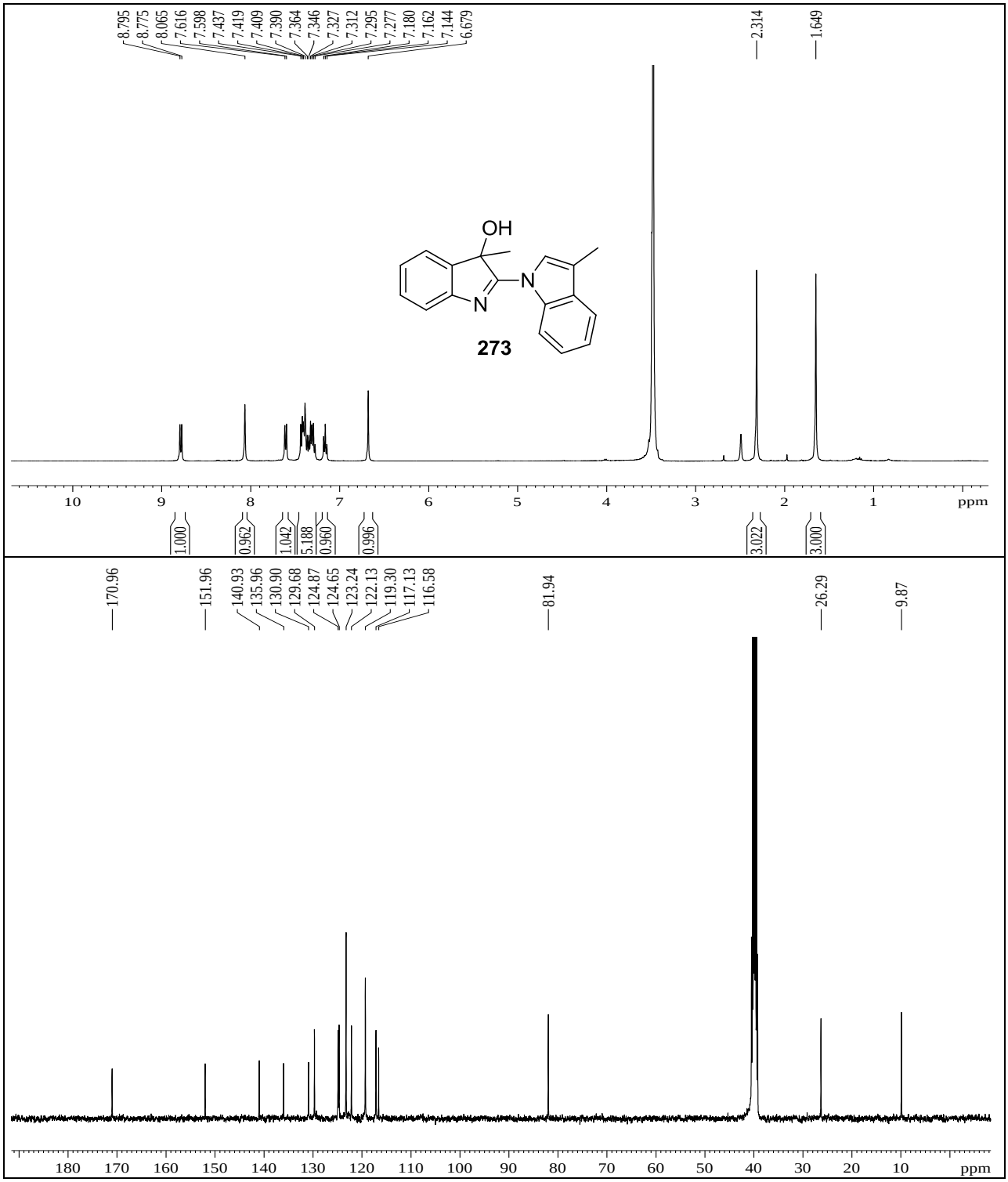
^{1}H, ^{13}C NMR of compound 271c



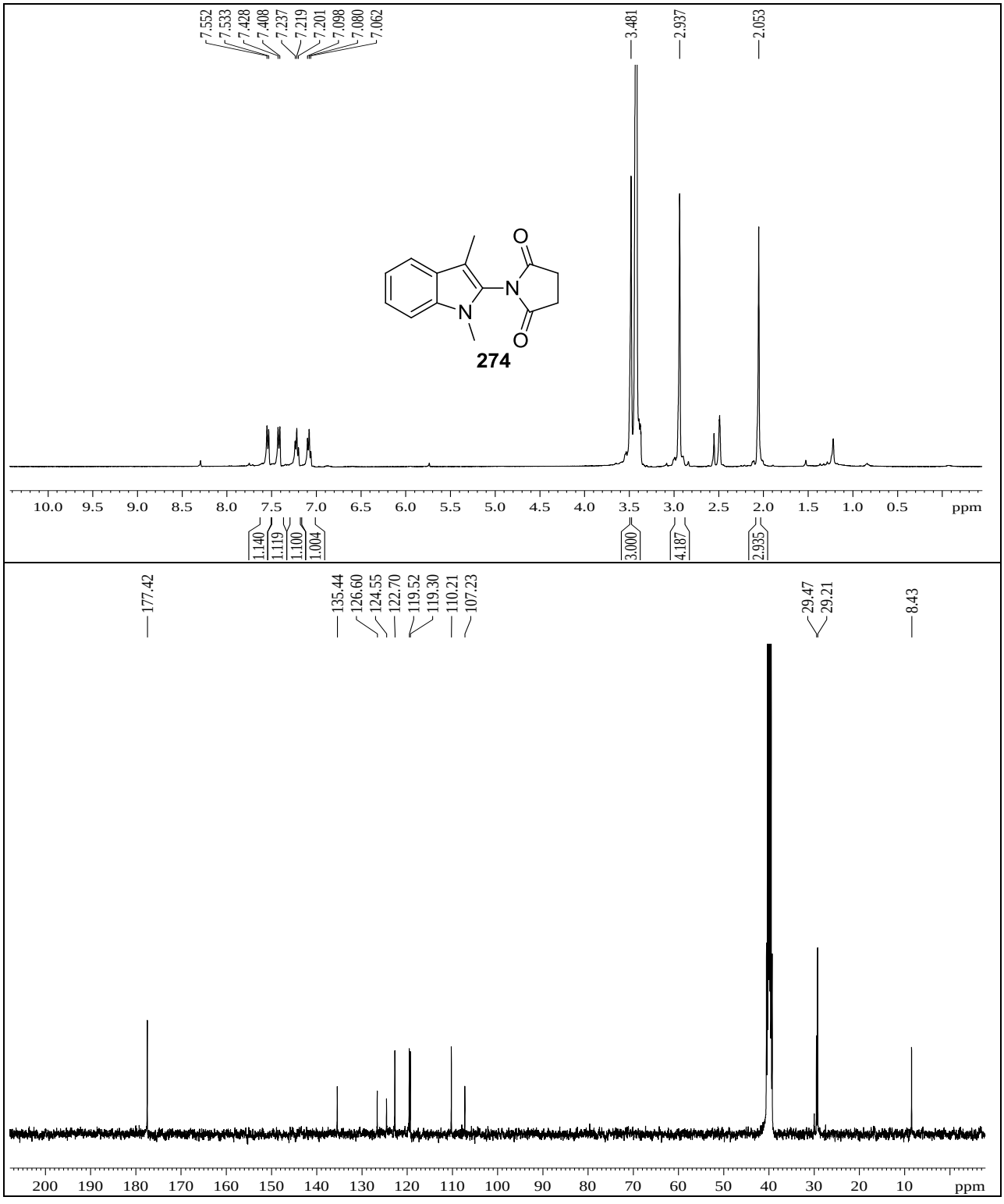
^{1}H, ^{13}C NMR of compound 272



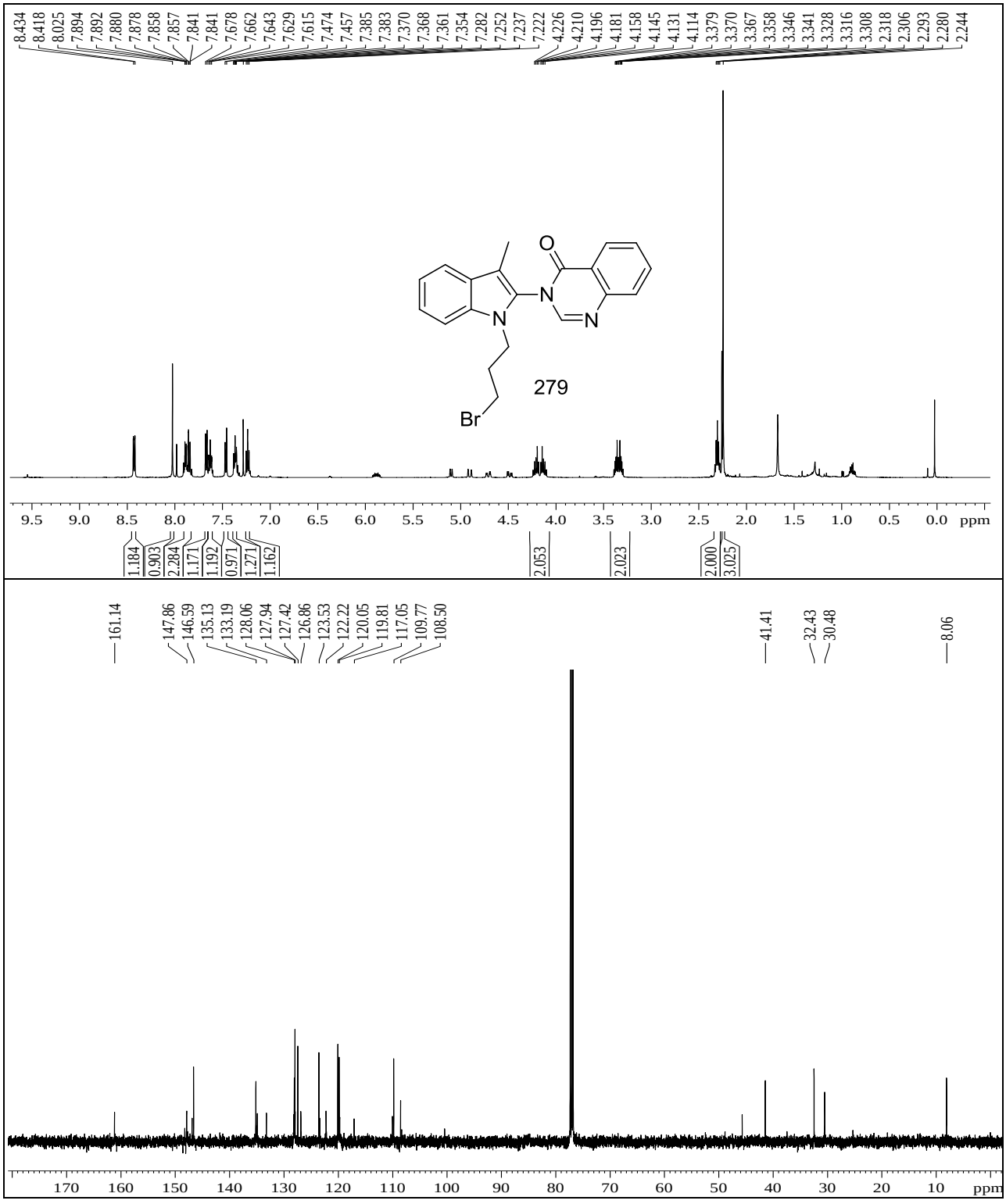
^{1}H, ^{13}C NMR of compound 273



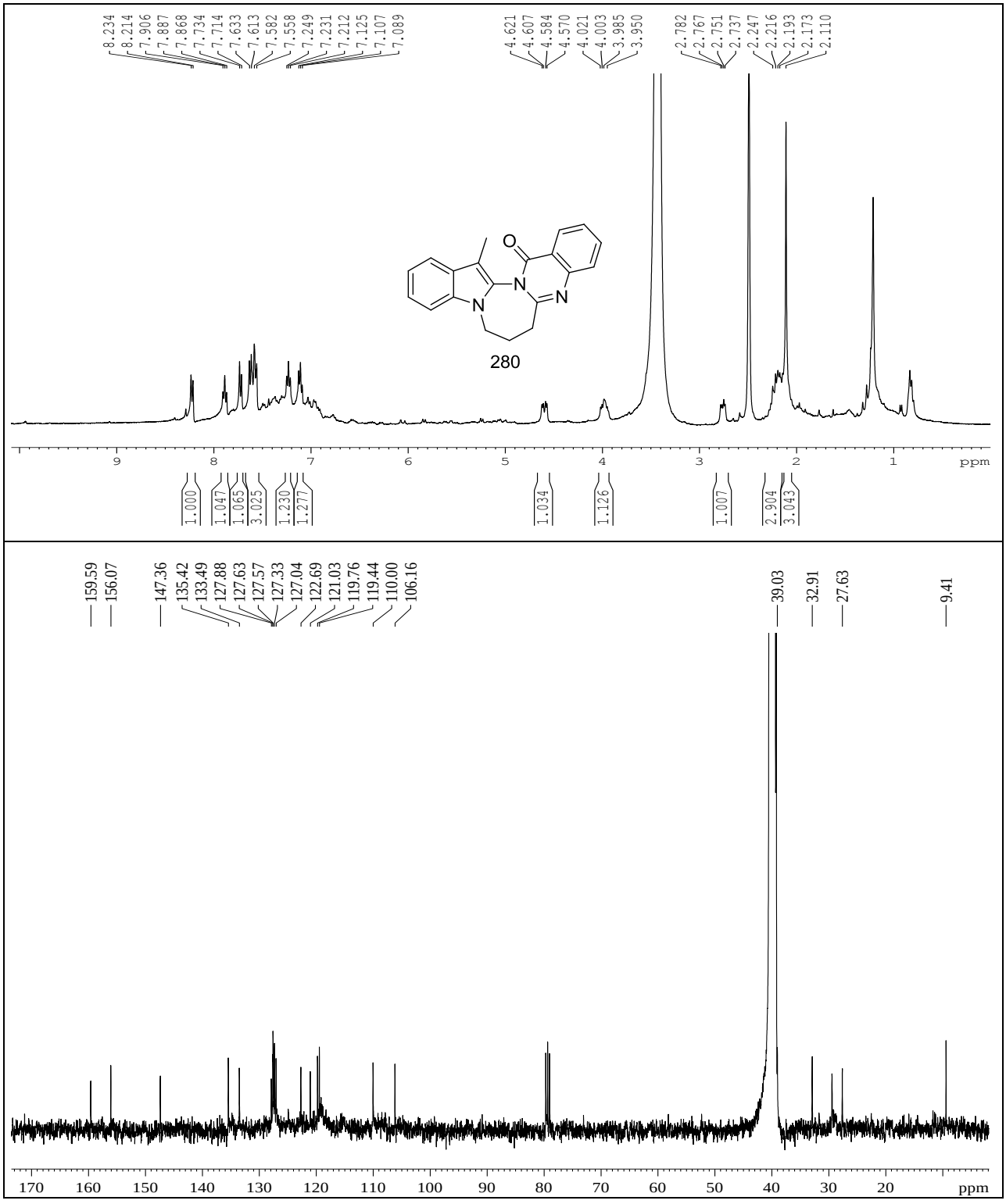
^{1}H, ^{13}C NMR of compound 274



^{1}H, ^{13}C NMR of compound 279



^{1}H, ^{13}C NMR of compound 280



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Chapter 2

TOTAL SYNTHESIS OF CRUCIFERANE VIA EPOXIDATION/TANDEM CYCLIZATION SEQUENCE

2.1 Introduction

Nitrogen containing alkaloids always remained as one of the major constituent for nature.[1] Among them, indole based alkaloids particularly are known to display a diverse range of biological properties.[2] Thus, indole oriented natural products always fascinate synthetic chemists as a challenging target.[3] Most of these indole natural products contains a broad skeleton diversity that might be the reason for their vast bioactivity spectrum.[2,3] Another class of heterocycle is quinazolinone that displays pharmacological properties like, anticancer, anti-inflammatory, anticonvulsant, diuretic, and anti-hypertensive.[4] Indoloquinazolinone is a fused heterocycle class and natural products which contain this skeleton are rare.[5] In 2012, Shi et al. isolated around 17 new alkaloids from the dried roots of *Isatis indigotica* plant. Among this 17 alkaloids, they have isolated the first alkaloid that contains pyrrolo[2,3-*b*]indolo[5,5*a*,6-*b*,*a*]quinazoline skeleton which later named as cruciferane (Figure 13).[6] *Isatis indigotica* Fortune, a biennial plant belongs to Cruciferae family which also known as "Chinese woad".

Isatis indigotica plant

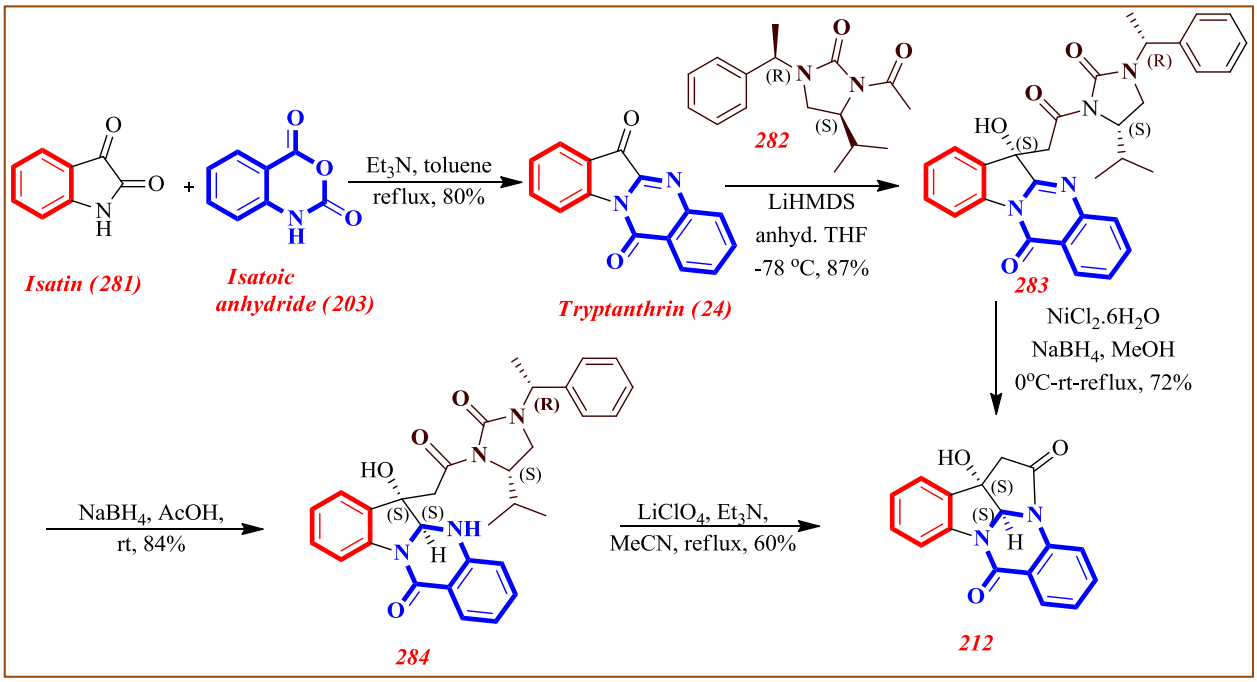
Picture courtesy: Google image

Cruciferane (212)

Figure 13. Isolation of pyrrolo[2,3-*b*]indolo[5,5*a*,6-*b*,*a*]quinazoline from the roots of *Isatis indigotica* plant

Medicinally active portions for *Isatis indigotica* is its dried roots and leaves (also known as "Ban Lan Gen"). From a long time, this dried roots been used as a medicine in Chinese herb and it was also recorded as drug in Chinese pharmacopeia from 1985. Apart from this alkaloid a number of other compounds have also been isolated from *Isatis indigotica* like isaindigotidione, indigotin, indrubin, trytanthrin, purin, isatin, isatan A, isatan B, organic acids and many amino acids.[7] This dried roots of *Isatis indigotica* are used ethnomedically for treatment of epidermic hepatitis, erysipelas, carbuncles, encephalitis B and influenza. It is also known as an antipyretic. Studies revealed that Ban-Lan-Gen has properties like antibacterial and antiinflammatory.[7c] Still now, only two reports demonstrates the synthesis of Cruciferane.[8, 9]

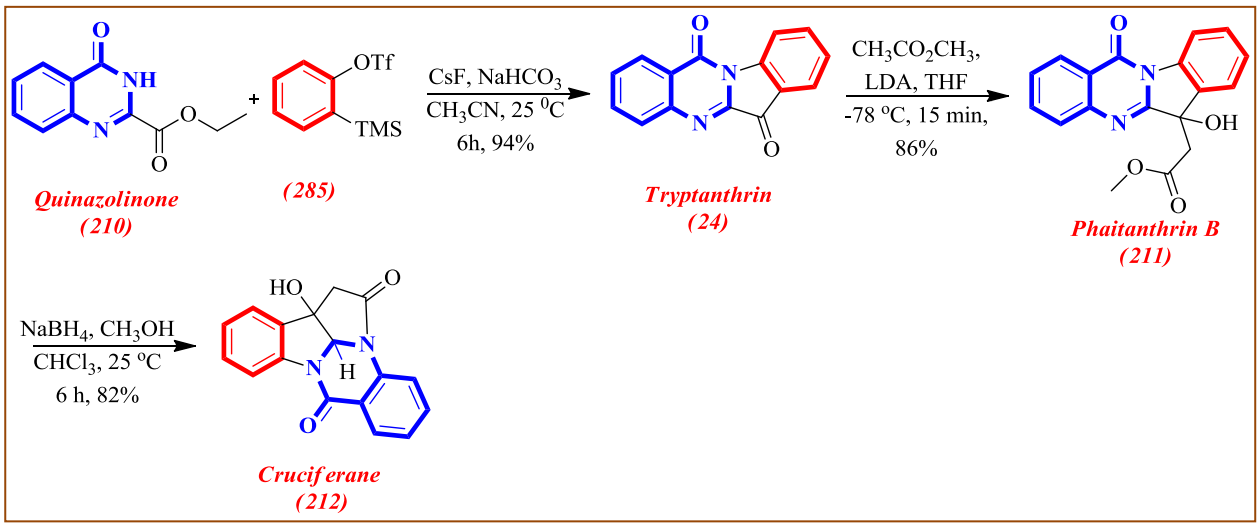
Nair et al. reported the first stereoselcetive synthesis of (+)-cruciferane (**212**) using a stereospecific chiral auxiliary (**282, Eqn. 44**). Tryptanthrin (**24**) was prepared using literature procedure from istain and isatoic anhydride. Next this tryptanthrin was subjected to an steroselective aldol reaction with acetylated auxiliary, *N*-acetyl-(*S*)-4-isopropyl-1-[(*R*)-1-phenylethyl]imidazolidin-2-one (**282**) and it gave a highly *syn*-selective aldol adduct **283**. They used two different pathways to achieve enantioselective **212** where adduct **283** was reduced with sodium borohydride in AcOH followed by removal of chiral auxiliary with lithium perchlorate to get the (+)-cruciferane.



Eqn. 44. Nair's protocol to synthesize cruciferane

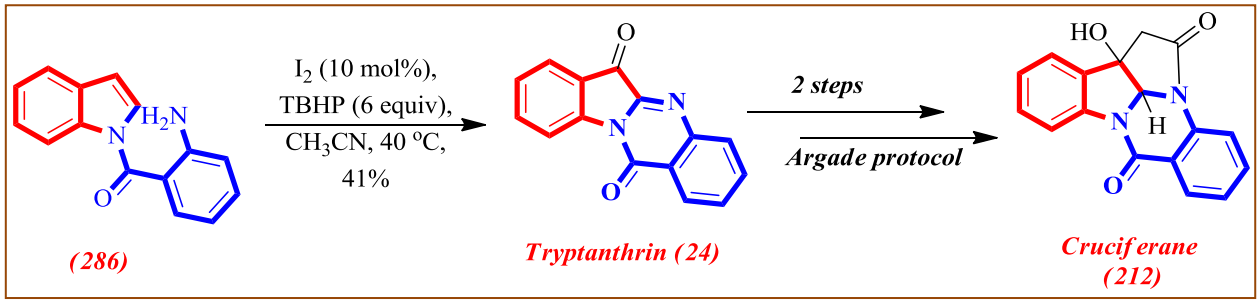
In another path they have improved the process and yield in a one pot manner by using $NiCl_2.6H_2O/NaBH_4$ in methanol.[8]

In the same year, Argade et al. also reported total synthesis of racemic cruciferane via tryptanthrin intermediate (**24**). They have used an insitu generated aryene insertion methodology with 1, 3-quinazolin-4-ones to generate tryptanthrin which has been further converted to phaitanthrin B (**211**) via chemoselective condensation. Next, compound **211** was subjected to a reductive cyclization using sodium borohydride in MeOH to generate the racemic cruciferane.[9]



Eqn. 45: Argade's methodology to synthesize cruciferane

In 2013, Ji et al. reported a formal total synthesis of cruciferane following Argade's method from tryptanthrin (**24**). They have developed an intramolecular amination of indole to synthesize the tryptanthrin (**24**) using iodine and tertrabutyl hydrogen peroxide (TBHP) (**Eqn. 46**).[10]



Eqn. 46: Formal synthesis of cruciferane

2.1.1 Strategy to synthesize cruciferane

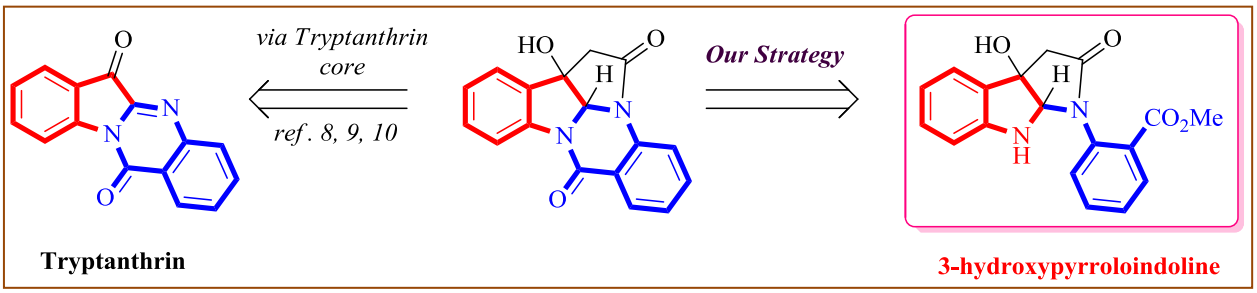
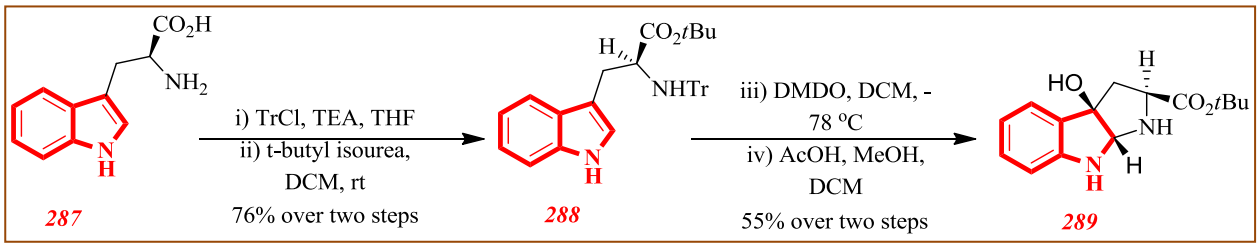


Figure 14. Comparison of strategies to synthesize cruciferane

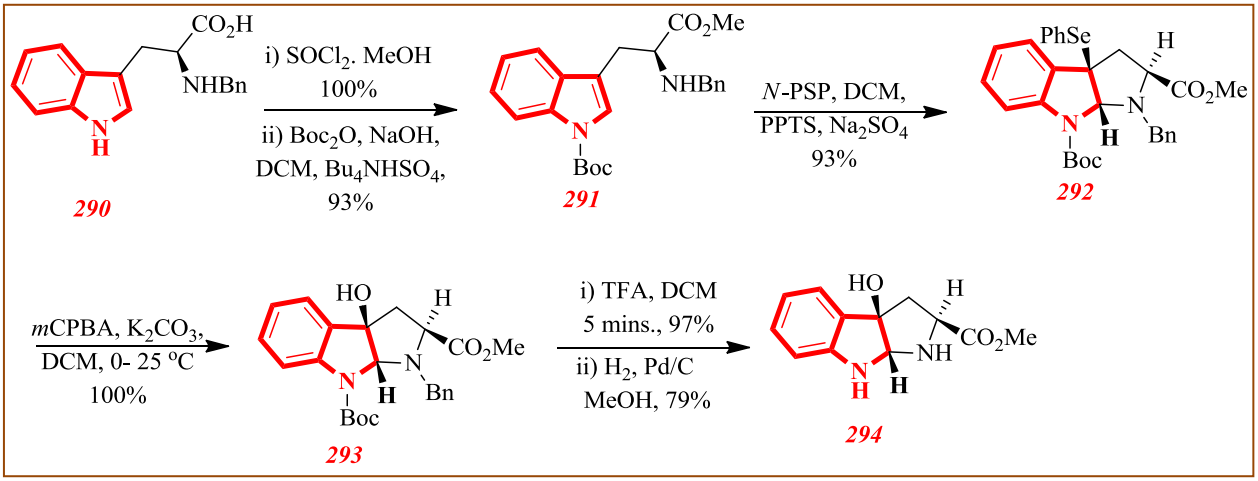
The two reports for synthesis of cruciferane were demonstrated via a common intermediate tryptanthrin and both the synthesis is non-economical. Thus, we have designed a different pathway to synthesize a protecting group free economical pathway to synthesize this particular alkaloid. As, shown in **fig. 12** we designed our synthesis via an intermediate 3-hydroxypyrroloindoline. There are several reports in literature to synthesize 3-hydroxypyrroloindoline core. One of the finest report was by Danishefsky in 2001 where they used l-tryptophan and derivatized it with trityl group and *tert*-butyl ester (**288, Eqn. 47**). It was further treated with dimethyldioxirane (DMDO) for epoxidation on indole C2-C3 bond which on intramolecular cyclization gave 3-hydroxypyrroloindoline core. It was further treated with acetic acid to deprotect trityl group to get compound **289** (**Eqn. 47**).[11]

Eqn. 47: Danishefsky's synthesis of 3*a*-hydroxy-pyrroloindole



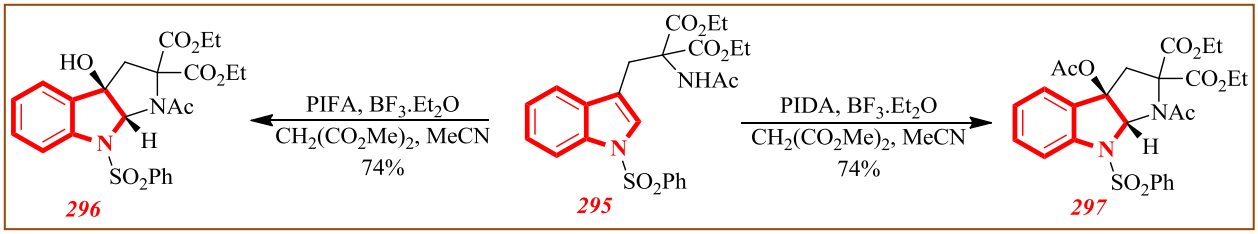
In 2003, Ley et al. modified the strategy with selenocyclisation–oxidative deselenation strategy where they reduced the number of steps from four to two (**Eqn. 48**). They have prepared the exact l-tryptophan derivative **291** from **290**; compound **291** was subjected to selenocyclisation using N-Phenylselenophthalimide (N-PSP) in presence of PPTS. Compound **292** was obtained in 11:1 diasteromeric ratio with a favor of *exo* isomer. It has been reported that the stereocontrol was dependent on the N-protecting group. On treatment with excess wet *m*CPBA, 3*a*-hydroxy-

pyrroloindole Skelton (**293**) was achieved via oxidative deselenation. Next, the use of appropriate reagent to deprotect the N-protecting group led to the compound **294**.[12]



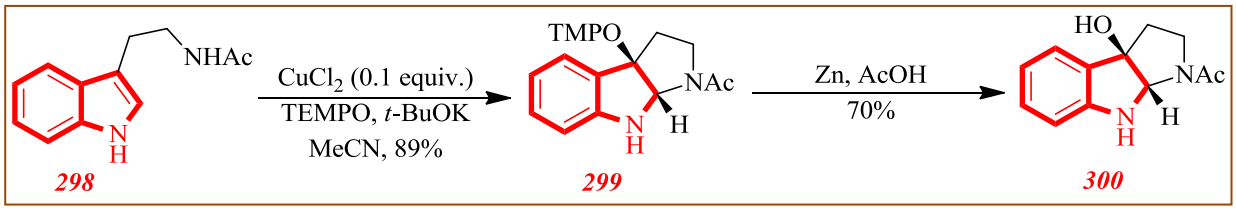
Eqn. 48: Stereocontrolled synthesis of 3*a*-hydroxy-pyrroloindole

In 2013, Xia et al. developed an intramolecular annulation protocol to synthesize different pyrroloindoles from indoles using iodine (III) as a reagent (**Eqn. 49**). They have synthesized a various 3-halosubstituted-pyrroloindoles along with 3-hydroxy/acetoxy-pyrroloindoles. Compound **295**, on treatment with phenyliodonium bis(trifluoroacetate) (PIFA) generate the trifluoroacetate anion intermediate which while workup led to the 3-hydroxypyrroloindole (**296**). Similarly when compound **295** was treated with (Diacetoxyiodo)benzene (PIDA) it generated the 3-acetoxypyrroloindole (**297**).[13]



Eqn. 49: Iodine (III) mediated synthesis of pyrroloindoles

The same group had developed one more protocol to synthesize 3-hydroxypyrroloindolines via radical cyclization with Cu catalyst (**Eqn. 50**). The appropriately substituted indole was treated with 2,2,6,6-Tetramethyl-1-piperidinyloxy (TEMPO) in presence of $CuCl_2$ (which found to be the appropriate catalyst) gave the TEMPO substituted pyrroloindoline (**299**) in excellent yields. The tetramethylpiperidine (TMP) was later removed with Zinc and acetic acid to generate the 3-hydroxypyrroloindoline (**300**).[14]



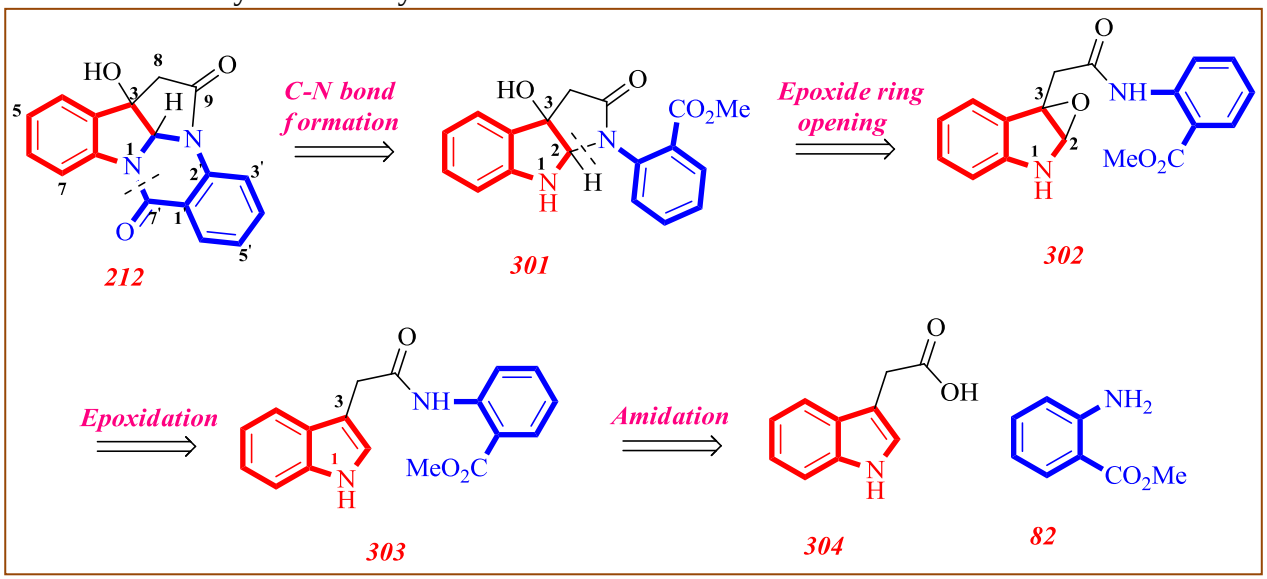
Eqn. 50: Synthesis of 3-hydroxypyrroloindolines via radical cyclization

2.2 Results and discussion:

2.2.1 Our Strategy to synthesize cruciferane

In **Scheme 7**, we have shown the retrosynthesis of cruciferane (**212**). We envisioned cruciferane can be obtained via an end stage C-N bond generation of 3-hydroxypyrroloindoline skeleton (**301**). This 3-hydroxypyrroloindoline core (**301**) can be elaborated from the C2-C3 epoxide containing intermediate of indole core (transition structure **302**). The epoxidation on C2-C3 of this indole intermediate (**303**) can furnish the transition intermediate **302**. This indole intermediate **303** can be stem from corresponding indole-3-acetic acid (**304**) in a one pot manner by treating it with methyl anthranilate (**82**).

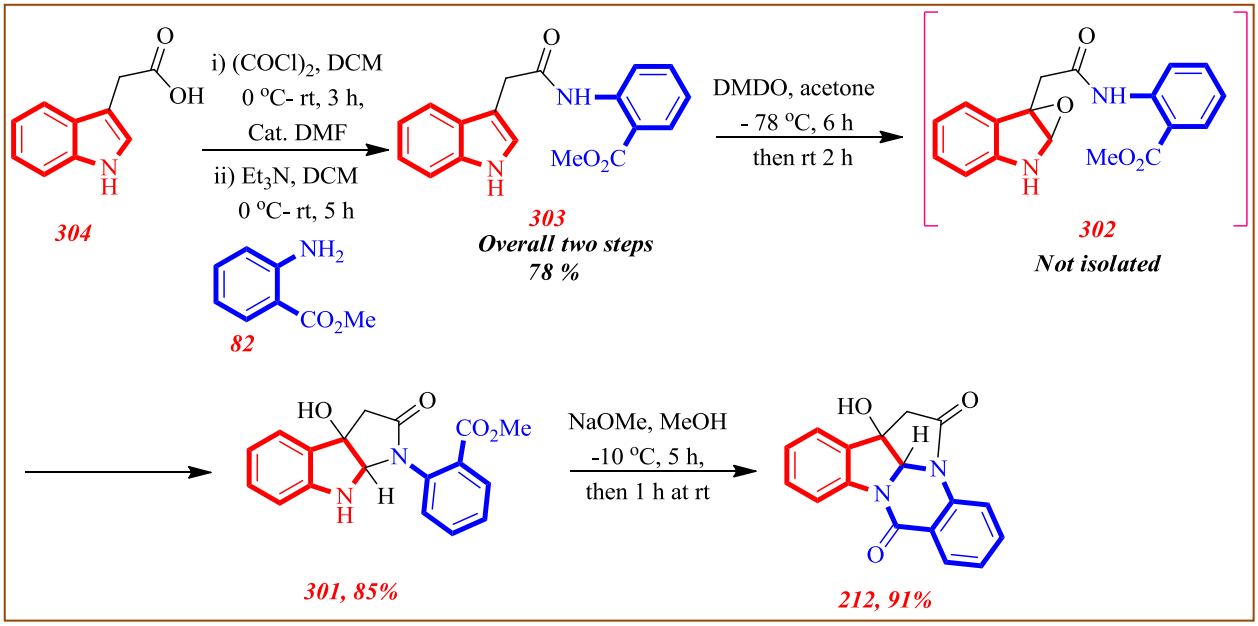
Scheme 7: Retrosynthetic analysis of cruciferane



As we envisaged the retrosynthesis, we started our journey with synthesis of respective starting materials. We have synthesized methyl anthranilate (**82**) following literature process from anthranilic acid[15] and the other starting compound indole-3-acetic acid (**304**) was obtained

commercially. We have taken the most classical and conventional path to synthesize compound **303** via C-N bond formation between methyl anthranilate and indole 3-acetic acid (**304**). We have treated the acid (**304**) with oxalyl chloride in DCM at rt for 3h using DMF (catalytic amount) to generate the intermediate acid chloride. Next the excess oxalyl chloride was removed under vacuum and the acid chloride was further used for subsequent amidation without purification. Next, to obtain the target amidation product (**303**), we have added the intermediate acid chloride solution to a mixture of methyl anthranilate and triethylamine (base) solution of dry DCM and stirred it at rt for 5h. It gave the amidation product **303** in 78% yields over two steps. We next opted for the epoxidation reaction on compound **303** that supposed to be key step of this total synthesis.

Scheme 8: Forward synthesis of cruciferane



We envisioned that DMDO (dimethyldioxirane) might be the right reagent for the epoxidation on indole C2-C3 to get our targeted 3-hydroxypyrroloindoline core due to its chemoselectivity. Maximum example of DMDO in literature was demonstrated over trypophan derivatives (*vide supra*). Although the Intermediate **303** looks like a tryptophan derivative but due to the presence of an aromatic ester substitution and carbonyl group at C9 adjacent to the nucleophilic nitrogen, the inherent chemical properties will differ. Next, we followed the Taber process[16] to prepare the DMDO in acetone solution and these freshly prepared DMDO was added dropwise to the solution of compound **303** in dry acetone at -78 °C. This reaction mixture was stirred at same

temperature for another 6 h and then it was brought to rt where it was stirred another 2 h. A formation of complex mixture was observed while checking TLC after one hour but on completion of this reaction a polar intense spot was observed in TLC. The insitu expoide formation followed by ready cyclization gave the step economy for this cruriferane synthesis. Next, we looked for the condition that can generate C-N bond N1-C7' for compound **301**. We optimized that a freshly prepared NaOMe in MeOH solvent on addition to a MeOH solution of compound **301** at -10 °C initially for 5 h and followed by 1 h at rt stirring can generate the cyclized product in 91% yields. The generation of this C-N bond finally gave our target molecule cruciferane (**212**). Thus, we accomplished the total synthesis of cruciferane (212) in three graceful steps with an overall yield 60.31%. The NMR data and HRMS data of synthetic crcuiferane is consistent accord to the data of isolated natural product.

2.3 Conclusion

In conclusion, we have completed the synthesis of cruciferane via step economical and protecting group pathway. The main highlights of this total synthesis were easily accessable starting materials, void of any protecting groups, mild conditions and excellent overall yield.

2.4 Experimental Section

Melting Points: The melting point of the products was recorded on a Superfit (India) capillary melting point apparatus and is uncorrected.

IR: Infrared spectra were recorded on a JASCO FT/IR-5300 spectrophotometer. All the spectra were calibrated against polystyrene absorption at 1601 cm^{-1}. Solid samples were recorded as KBr wafers and liquid samples as thin film between NaCl plates or solution spectra in DCM.

NMR Spectra: ^{1}H NMR and ^{13}C NMR spectrums were recorded on BRUKER-AVANCE-400/ 500 spectrometers. ^{1}H NMR (400 or 500 MHz) spectra for all the samples were measured in chloroform-*d*, unless otherwise mentioned (δ = 2.50 ppm for ^{1}H NMR in the case of DMSO-d_6), with TMS (δ = 0 ppm) as an internal standard. ^{13}C NMR (100 or 125MHz) spectra for all the samples were measured in chloroform-*d*, unless otherwise mentioned (in the case of DMSO-d_6, δ = 39.70 ppm its middle peak of the septet), with its middle peak of the triplet (δ = 77.10 ppm) as an internal standard.

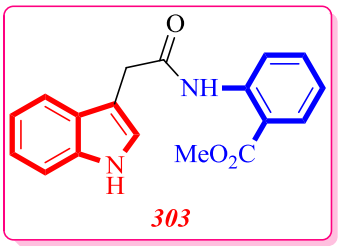
Mass Spectral Analysis: Shimadzu LCMS 2010A mass spectrometer. All the cases DCM or MeOH were used to dissolve the compounds. The TOF and quadrupole mass analyzer types are used for the HRMS measurements. Mass spectral data were obtained from HRMS (ESI).

Elemental Analysis: Elemental analyses were performed on a Thermo Finnigan Flash EA 1112-CHN analyzer.

X-ray Crystallography: The X-ray diffraction measurements were carried out at 293 K on a Bruker SMART APEX CCD area detector system equipped with a graphite monochromator and a Mo-K_α fine-focus sealed tube (λ = 0.71073 Å) operated at 1500 W power (50 kV, 30 mA). The detector was placed at a distance of 4.995 cm from the crystal. The frames were integrated with the Bruker SAINT Software package using a narrow-frame algorithm. Data were corrected for absorption effects using the multi-scan technique (SADABS). The structure was solved and refined using the Bruker SHELXTL (Version 6.1) software package.

2-(2-1*H*-Indol-3-yl-acetylamino)-benzoic acid methyl ester (303):

To a suspension of **304** (200 mg, 1.0 mmol) in 10 mL of dry dichloromethane at 0 °C were added oxalyl chloride (0.48 mL, 5.7 mmol, 5.0 equiv) dropwise and DMF (3 drops) successively. The mixture was stirred at 0 °C for 3 h and concentrated under vacuum to give **287** mg of crude 1*H*-indole-3-acetyl chloride, which was utilized for the synthesis of **303** without further purification. Then, to the solution of methyl anthranilate **82** prepared via literature procedure[17] (224 mg, 1.3 mmol) and Et_3N (0.80 mL, 5.0 mmol) in 10 mL of DCM at 0 °C was added a solution of crude **303** (287 mg from (200mg of **304**)) in 4 mL of DCM. The reaction mixture was stirred at room temperature for 5 h and concentrated under vacuum. To the residue was added 15 mL of saturated water. The mixture was extracted with EtOAc (30 mL). The combined organic layers were dried over Na_2SO_4 and concentrated. Flash chromatography of the residue on silica gel (7:3 hexanes/ EtOAc) gave 272 mg of compound **303** as light brownish solid.

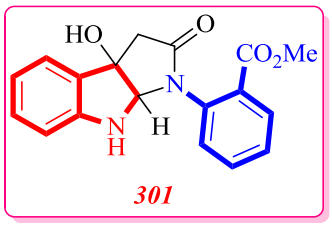


303

Yield:	78 %
Mp:	136-140 °C
IR (KBr) ν_{max} cm^{-1}:	3205, 2947, 1698, 1654, 756
^1H NMR (400 MHz) δ:	10.96 (1H, s), 8.74 (1H, d, *J* = 8.0 Hz), 8.33 (1H, s, br), 7.92 (1H, dd, *J* = 1.2 Hz, *J* = 8.0 Hz), 7.66 (1H, d, *J* = 8.0 Hz), 7.51 (1H, t, *J* = 8.0 Hz), 7.39 (1H, d, *J* = 8.0 Hz), 7.29 (1H, s), 7.21 (1H, t, *J* = 7.2 Hz), 7.13 (1H, t, *J* = 7.2 Hz), 7.04 (1H, t, *J* = 8.0 Hz), 3.94 (2H, s), 3.70 (3H, s)
^{13}C NMR (100 MHz) δ:	170.8, 168.1, 141.1, 136.5, 134.4, 130.7, 127.4, 123.9, 122.5, 122.4, 120.5, 119.9, 118.9, 115.5, 111.2, 108.7 (aromatic C), 52.1, 35.6 (aliphatic C)
HRMS (ESI-MS)	
Calcd for: $C_{18}H_{16}N_2O_3$:	331.1059 (M+Na)
Found:	331.1061

2-(3a-hydroxy-2-oxo-3,3a,8,8a-tetrahydro-2*H*-pyrrolo[2,3-*b*]indol-1-yl)-benzoic acid methyl ester (301):

To a solution of compound **303** (50 mg, 0.16 mmol) in anhydrous acetone (4 mL) was added dropwise a solution of DMDO (prepared by Taber's method)[16] in acetone (0.021 M, 7.7 ml, 0.64 mmol) at –78 °C. Reaction mixture was stirred at the same temperature for 6 h, then temperature was increased to rt and stirred for additional 2 h at rt. Then to the reaction mixture 20 ml water was added and resulting mixture was extracted from EtOAc (30 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (hexanes: EtOAc = 2:8) to give compound **301** as white solid.



301

Yield: 85 %

Mp: 72-76 °C

IR (KBr) ν_{max} cm^{-1}: 3313, 2921, 1710, 1676, 1604, 745

^{1}H NMR (400 MHz, DMSO- d_6) δ: δ 7.81 (1H, d, *J* = 8.0 Hz), 7.66 (1H, t, *J* = 8.0 Hz), 7.45 (1H, t, *J* = 7.2 Hz), 7.32 (2H, t, *J* = 7.2 Hz), 7.11 (1H, t, *J* = 7.6 Hz), 6.73 (1H, t, *J* = 7.2 Hz), 6.64 (1H, s), 6.58 (1H, d, *J* = 7.6 Hz), 6.04 (1H, s), 5.40 (1H, d, *J* = 4.0 Hz), 3.38 (3H, s), 2.96 (1H, d, *J* = 16.8 Hz), 2.90 (1H, d, *J* = 17.6 Hz)

^{13}C NMR (100 MHz, $CDCl_3$) δ: 171.9, 166.1, 148.2, 136.1, 132.2, 131.8, 131.4, 130.9, 130.0, 129.3, 128.5, 124.3, 120.8, 111.4 (aromatic C), 85.4, 81.9, 52.3, 43.6 (aliphatic C)

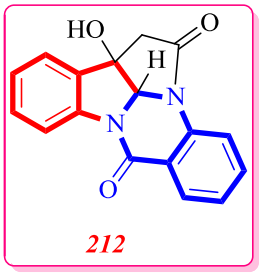
HRMS (ESI-MS)

Calcd for: $C_{18}H_{16}N_2O_4$: 347.1008 (M+Na)

Found: 347.1008

Cruciferane (212):

To a solution of compound **301** (30 mg, 0.09 mmol) in MeOH (3 mL) was added a solution of freshly prepared CH_3ONa (19 mg, 0.36 mmol) in CH_3OH (3 mL) at -10 °C. The reaction mixture was stirred for 5 h at the same temperature; afterwards mixture was kept at rt stirring for additional 1 hr. After completion of reaction (checked by TLC), 10 ml of water was added to the reaction and the residue was extracted with EtOAc (20 mL). The combined organic layers was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (hexanes:EtOAc = 7:3) to give compound **212** as white solid.



212

Yield:	91 %
Mp:	208-210 ^oC
IR (KBr) ν_{max} cm^{-1}:	3328, 2920, 1721, 1644, 1602, 824
^1H NMR (400 MHz, DMSO- d_6) δ:	δ 8.02 (1H, d, *J* = 8.0 Hz), 7.91 (1H, d, *J* = 8.0 Hz), 7.75-7.70 (2H, m), 7.53 (1H, d, *J* = 7.04 Hz), 7.47-7.38 (2H, m), 7.21 (1H, t, *J* = 7.2 Hz), 6.70 (1H, s), 5.79 (1H, s), 3.15 (1H, d, *J* = 18.4 Hz), 3.04 (1H, d, *J* = 18.4 Hz)
^{13}C NMR (100 MHz, DMSO- d_6) δ:	170.3, 158.5, 140.2, 136.3, 135.3, 133.5, 129.8, 128.3, 126.0, 124.8, 124.5, 123.3, 121.9, 114.7 (aromatic C), 82.4, 77.4, 45.7 (aliphatic C)
HRMS (ESI-MS)	
Calcd for: $C_{17}H_{12}N_2O_3$:	293.0926 (M+H)
Found:	293.0924

^{1}H, ^{13}C NMR of compound 303

HRMS of compound 303

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University of Hyderabad

Analysis Info

Analysis Name	D:\Data\2014\NAGARAJAN\JUNE\SKG-416.d	Acquisition Date	6/24/2014 3:08:05 PM
Method	tune_low_Pos-R2.m	Operator	Ramu Sridhar
Sample Name	SKG-416-DCM-MEOH	Instrument	maXis 10138
Comment			

Acquisition Parameter

Source Type	ESI	Ion Polarity	Positive	Set Nebulizer	4.4 psi
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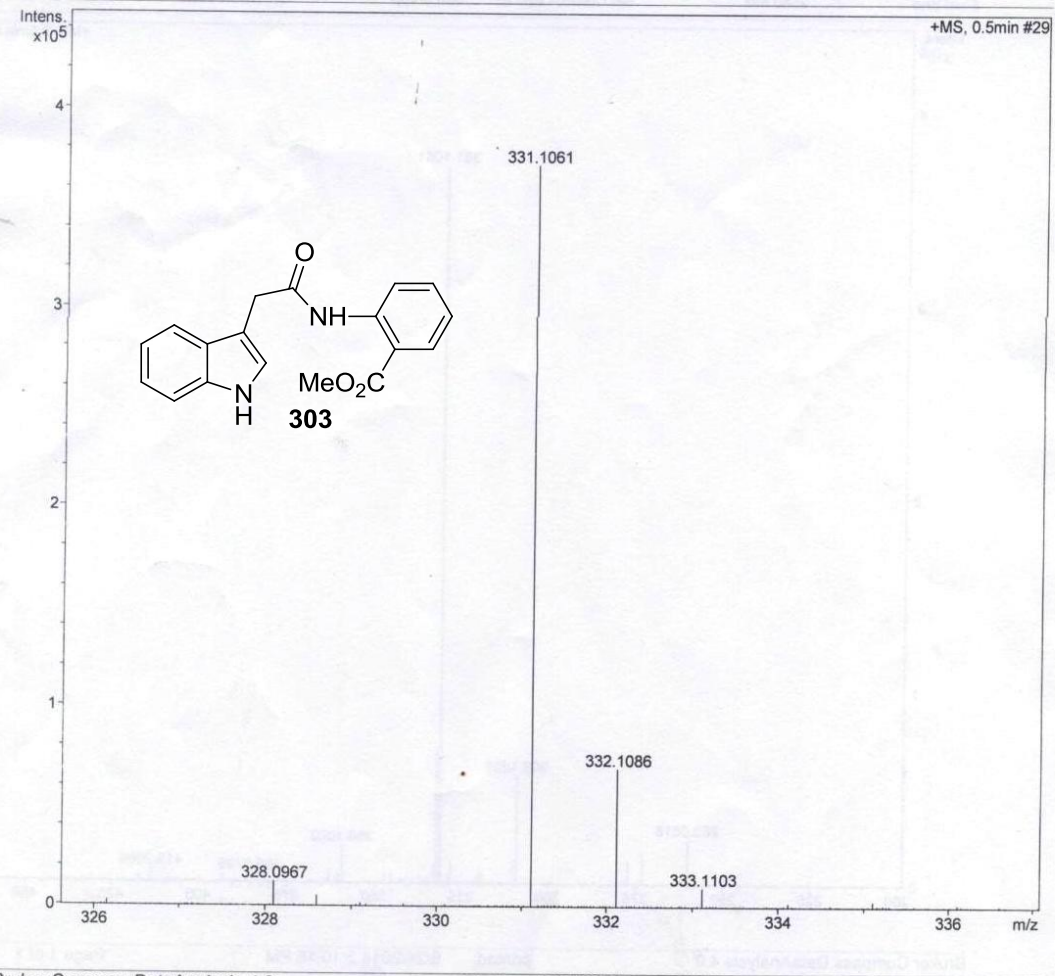

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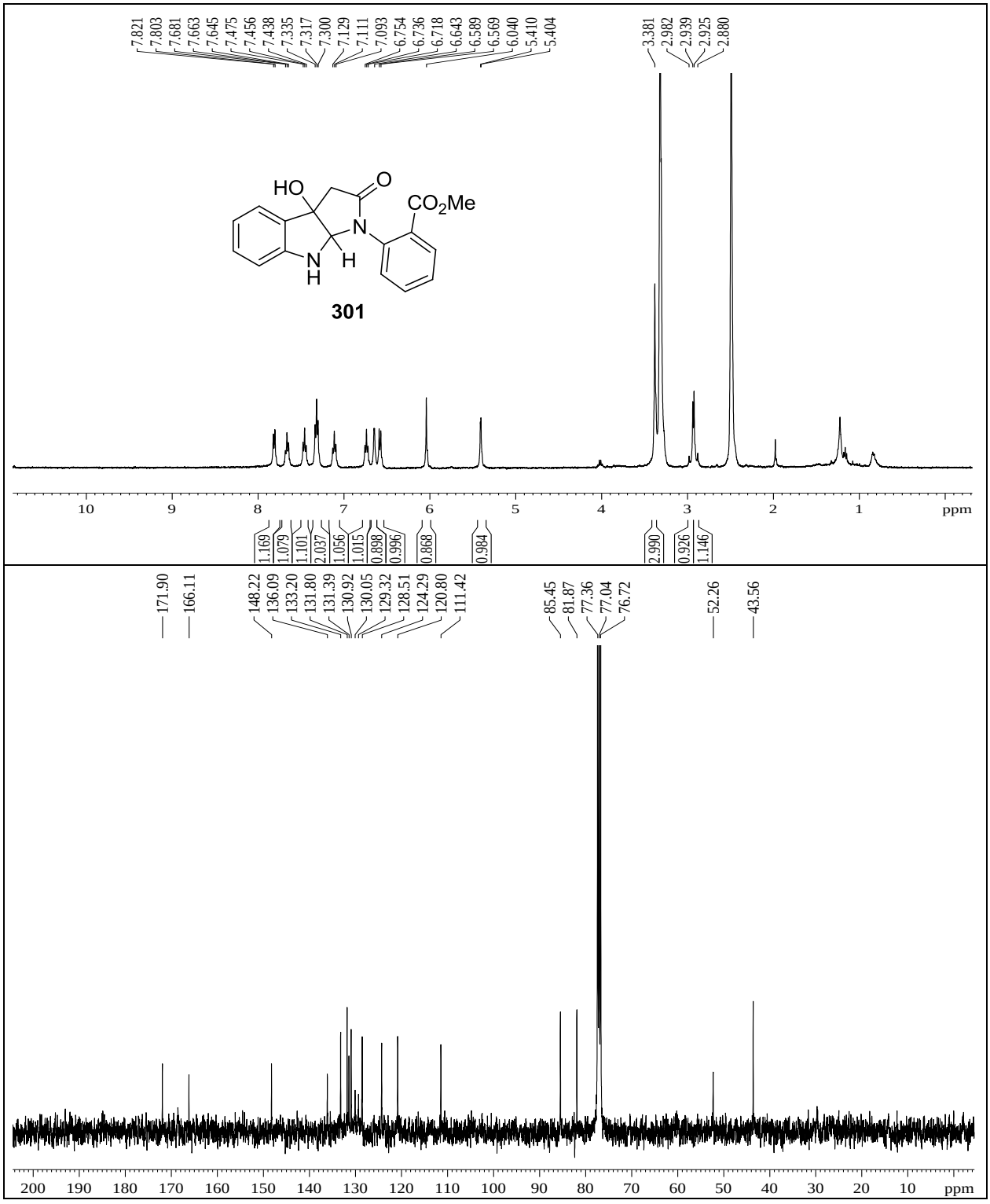
^{1}H, ^{13}C NMR of compound 301



HRMS of compound 301

BRUKER MAXIS HRMS REPORT

School of Chemistry
University of Hyderabad

Analysis Info

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Sample Name	SKG-417-DCM-MEOH	Instrument	maXis 10138
Comment			

Acquisition Parameter

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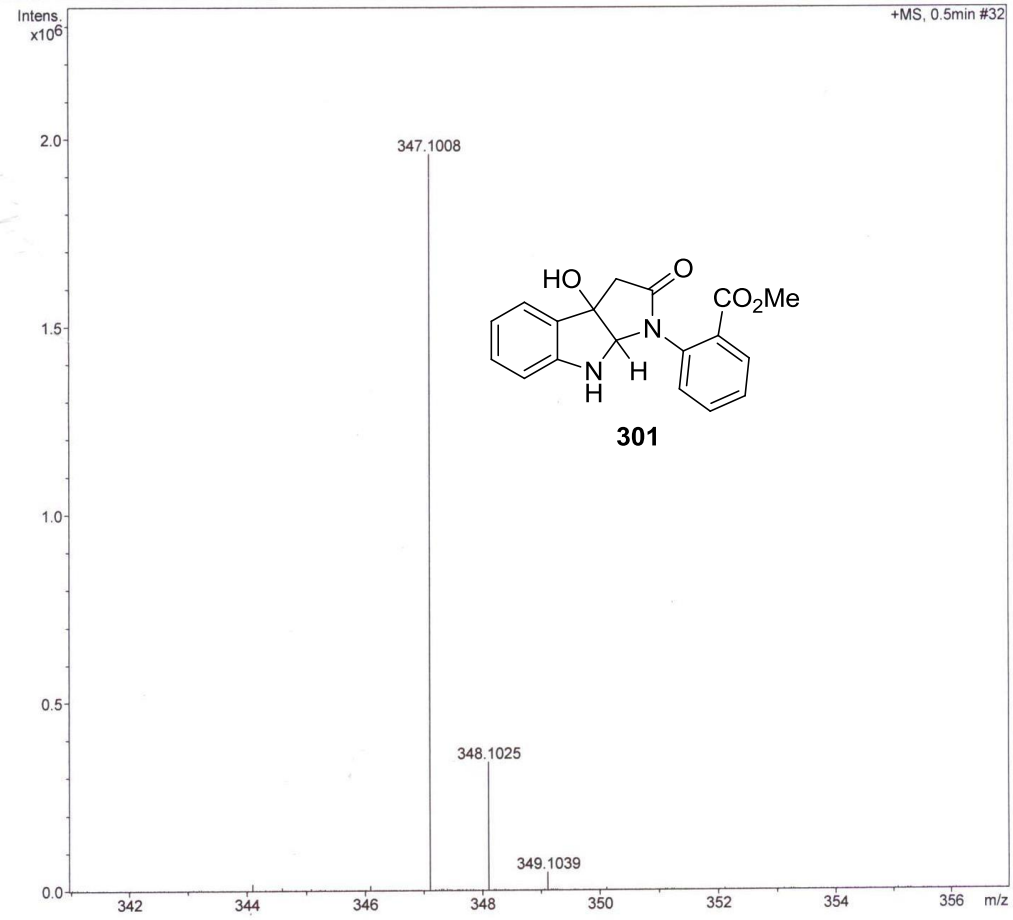
Scan End	2580 m/z	Set Collision Cell RF	350.0 Vpp	Set Divert Valve	Waste



301

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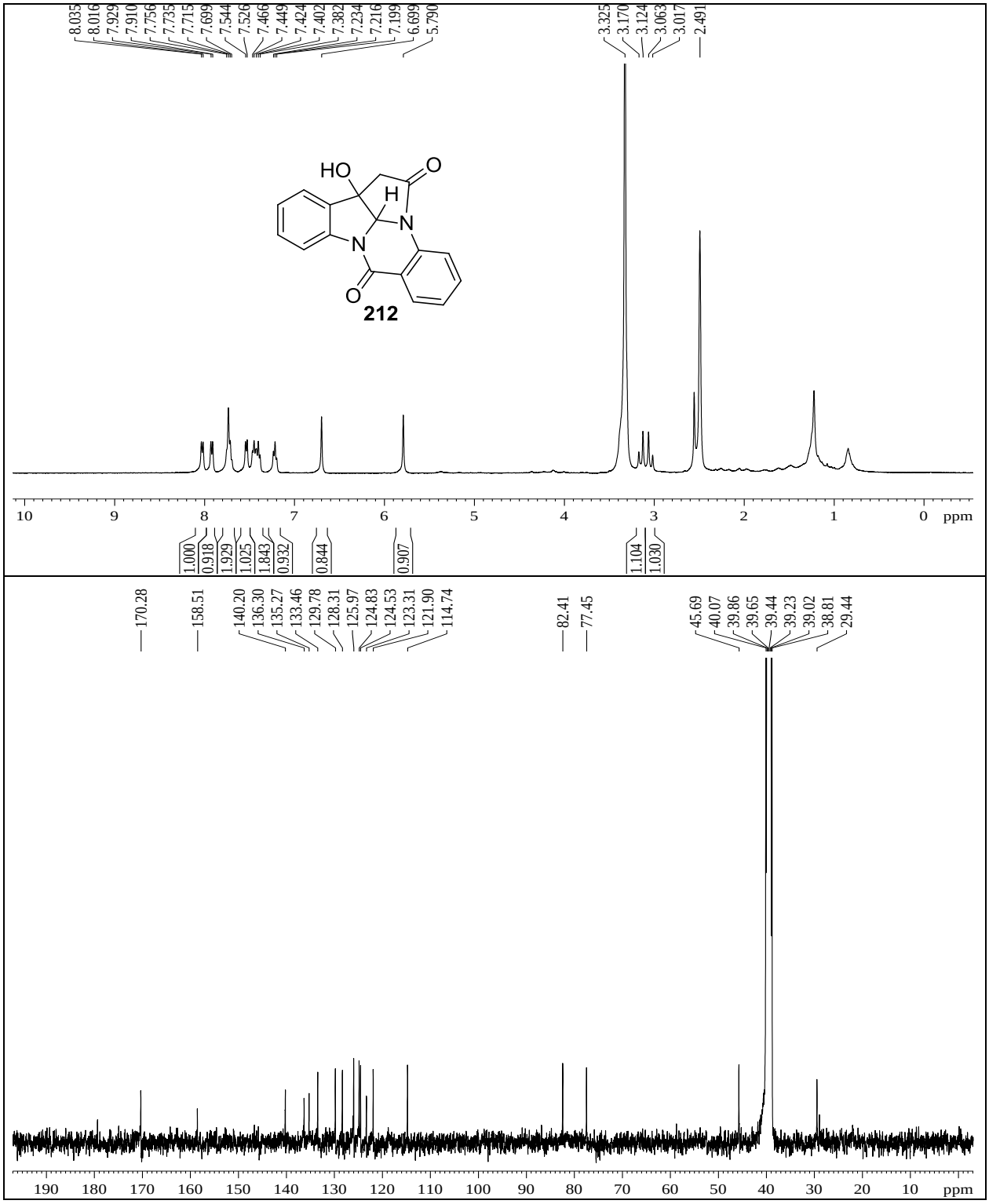
^{1}H, ^{13}C NMR of compound 212



HRMS of compound 212

BRUKER MAXIS HRMS REPORT

School of Chemistry
University of Hyderabad

Analysis Info

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Comment			

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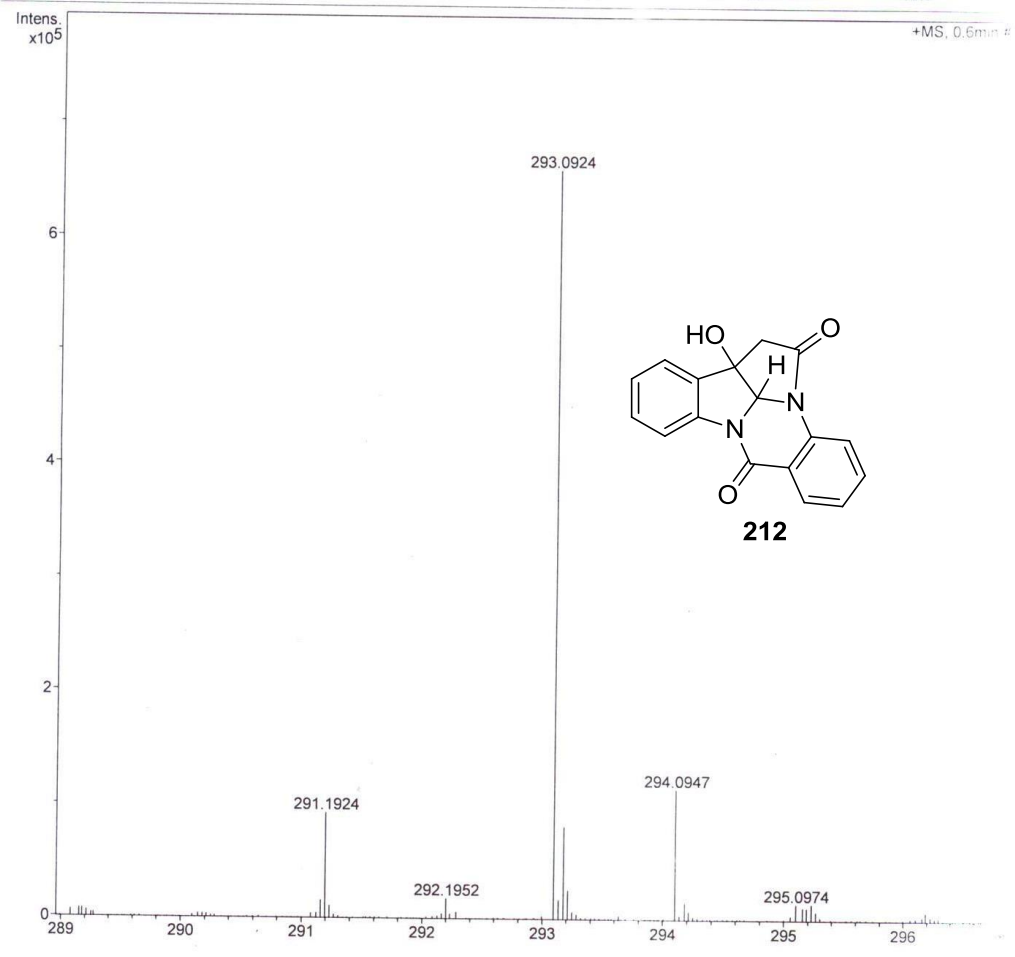
Scan End	1500 m/z	Set Collision Cell RF	350.0 Vpp	Set Divert Valve	Waste



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Chapter 3

SYNTHESIS OF SUBSTITUTED QUINAZOLINONES VIA DEEP EUTECTIC SOLVENT (DES) MEDIATED CYCLIZATION: TOTAL SYNTHESIS OF NATURAL PRODUCTS AND DRUGS

3.1 Introduction

Minimization of waste and maximization of reusability in organic chemistry could be a forward step that will favour the human race in socio and economical way.[1] The success rate of applications of sustainable chemistry in human society are still limited but it is a new era in beginning. It is very challenging for a chemist to mimic the nature in accord with solvents, chemical reagents and ambient conditions to develop an environment friendly chemical reaction. Since, from last decade extensive efforts were dedicated towards designing of environmentally benign solvents which could be biodegradable or reusable without difficulty.[2] In recent years green solvents like water,[3] supercritical liquids,[4] Polyethylene glycol (PEG)[5], Ionic liquids (ILs),[6] emerged to replace typical organic solvents in many chemical reactions; however the application of these solvents are constrained because of poor solubility and lower stability of organic compounds. Extensive uses of ILs as green solvent were well accepted for various organic transformations over a decade; however depending on the counterparts, ILs could be toxic and non biodegradable. Thus in present day, the use of ILs as a green solvent was reduced.[7] The rise of deep eutectic solvents (DES) as a green solvent is majorly due to their properties such as polarity, biodegradability, low toxicity, thermal stability, non-volatility, low-cost, and ready availability from bulk renewable sources without further modification.[8] Literature shows that in reactions such as, Perkin,[9] Diels-Alder,[10] Biginelli,[11] Heck,[12] Suzuki,[13] DES was used as a reusable solvent in place of common organic solvents. Hence, the main focus should be on the improvisation of the applications of DES in chemical transformations.

Quinazolinone is one of the significant nitrogen accessorized heterocyclic cores that was present in various naturally occurring alkaloids and market drugs. Substituted and unsubstituted quinazolinones show wide biological and pharmacological properties like hypotensive, anti-microbial, anticonvulsant, sedative, inhibition of protein tyrosine kinase and cholecystokinin, anti-depressant, antiinflammatory, and anti-allergy.[14] The marketed quinazolinone drugs, such as

methqualone (marketed as quaalude), mebroqualone, mecloqulaone (marketed as Casfen) have sedative, hypnotic as well as anxiolytic properties and also used for insomnia (**Fig. 15**).[15]

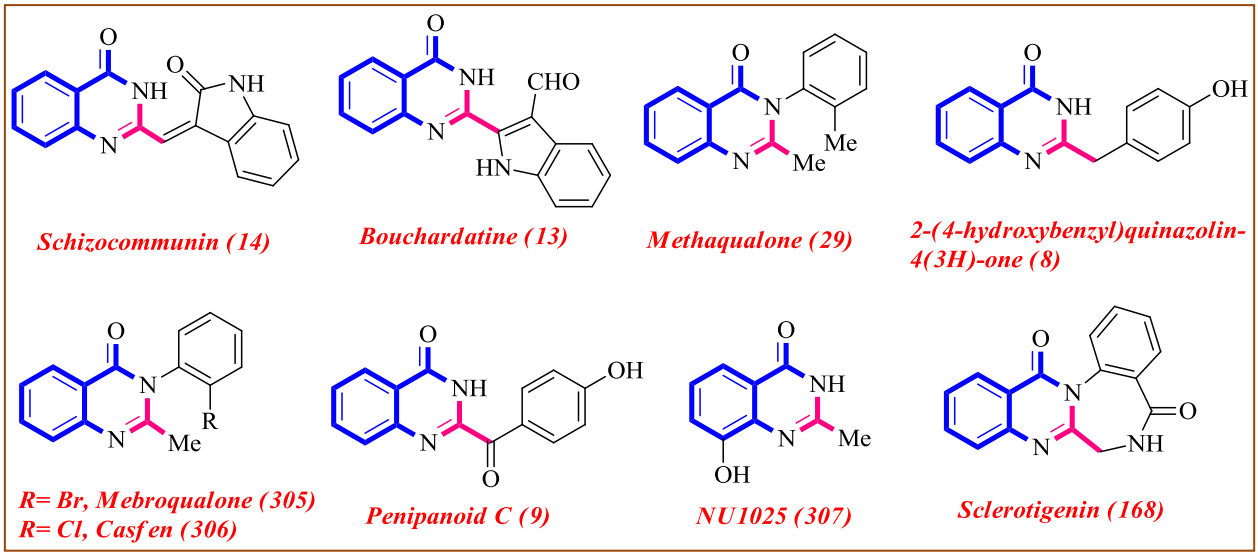
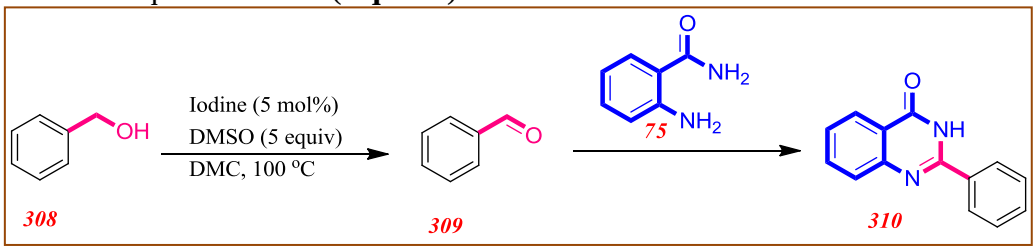


Figure 15. Examples of biologically and pharmaceutically important quinazolinone

3.1.1. Synthetic reports for dihydroquinazolinones and quinazolinones

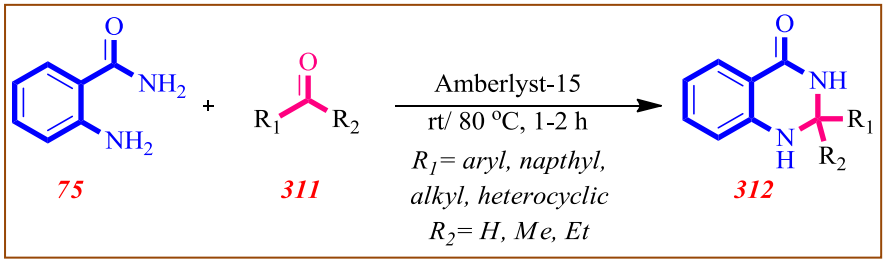
These aformentioned unavoidable pharmacological and biological properties of quinazolione alkaloids have always been the trigger for the chemist to develop new synthetic methods for synthesis of various quinazolinone cores. Over the years, many protocols were reported by different scientific groups using Sp^3 carbon oxidation,[16] microwave condition,[17] metal (Cu, Pd, Ir),[18] multi component reaction,[19] Cu-CNTs,[20] montmorillonite K-10,[21] [Zn-$(PFO)_2$], $Al(H_2PO_4)_3$,[22,23] $KAl(SO_4)_2{\cdot}12H_2O$,[24] gallium(III) triflate,[25] and MNP-PSA (*N*-propylsulfamic acid supported onto Fe_3O_4 nanoparticles)[26] as catalysts.

Wei et al. reported an iodine catalyzed reaction using DMSO as oxidant which demonstrate the metal free synthesis of quinazolinones from primary alcohols (**308**) and anthranilamides (**75**) in excellent yields. It is the in situ oxidation of primary alcohol to aldehyde followed by cyclization that led to quinazolinone (**Eqn. 53**).[27]



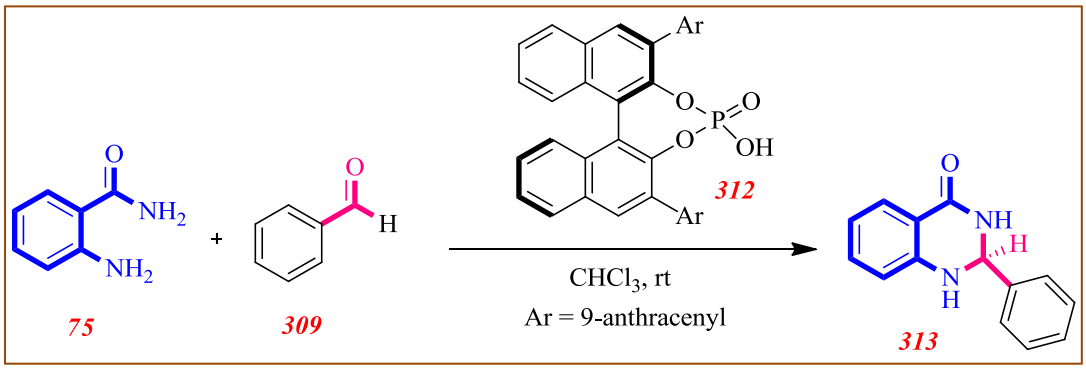
Eqn. 53. Iodine catalyzed synthesis of quinazolinones

Vishwakarma etal. reported a heterogenous solid acid catalyzed reaction for formation of various dihydroquinazolinones where they used Amberlyst-15 and silica-$HClO_4$ as catalyst. The condensation between anthranilamides (**75**) and aldehydes/ ketones (**311**) gave good yield of the product. The reaction gave 2,2'-disubstituted dihydroquinazolinones when pyrans are used in place of aldehydes. These catalysts are reusable (**Eqn. 54**).[28]

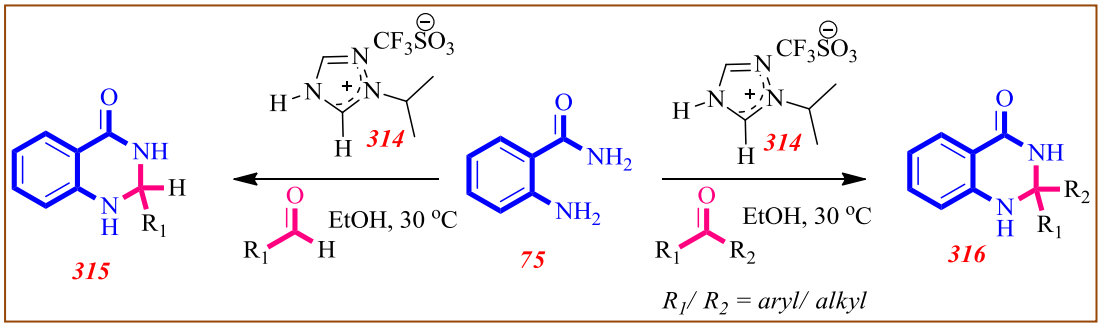


Eqn. 54. Synthesis of quinazolinones via heterogenous solid acid catalyst

An asymmetric synthesis of dihydroquinazolinone (**313**) was developed by Rueping et al. using bronsted acid as catalyst (**312**). The enantiopure compound was obtained using commercially available starting materials and phosphorus bronsted acid as catalyst (**Eqn. 55**).[29]



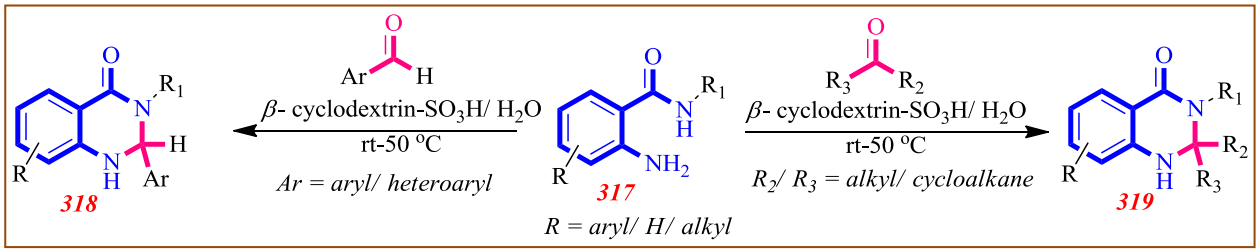
Eqn. 55. Synthesis of quinazolinones via asymmetric bronsted acid catalyst



Eqn. 56. Synthesis of quinazolinones via ionic liquid catalyst

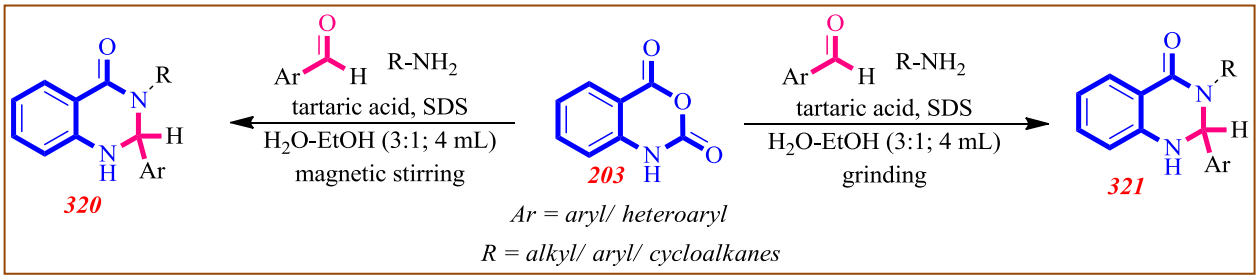
A mild and less time consuming methodology was developed by Kandasamy group using ILs as catalyst. This methodology demonstrated ILs (**314**) as catalyst and they used EtOH as solvent to synthesize dihydroquinazolinones (**315/ 316**). This catalyst (**314**) can be reusable without any loss of activity (**Eqn. 56**).[30]

In 2014, Wu group demonstrated another efficient metal free protocol with *β*-cyclodextrin-SO_3H catalyst to synthesize dihydroquinazolinones (**318/ 319**). Substituted anthranilamide was treated with aldehyde in water media using this cyclodextrin catalyst (10 mol%). The major advantages of these protocols are short reaction time, practicality and reusability of the catalyst (**Eqn. 57**).[31]



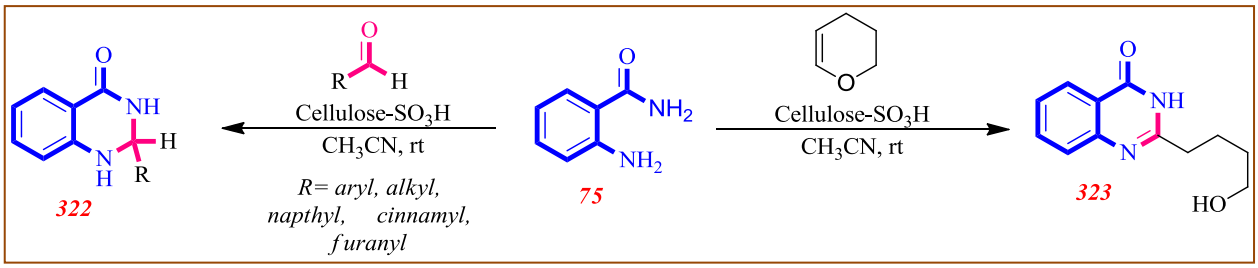
Eqn. 57. Synthesis of quinazolinones via *β*-cyclodextrin-SO_3H

A three component condensation was reported by Chauhan et al. to synthesize dihydroquinazolinones. This reaction was catalyzed by a reusable catalyst tartaric acid–SDS (sodium dodecadyl sulfate) catalyst. They have demonstrated two methods, one is magnetic stirring (mechanochemical activation) and other is simple grinding; where the grinding method showed very shorter reaction time (**Eqn. 58**).[32]



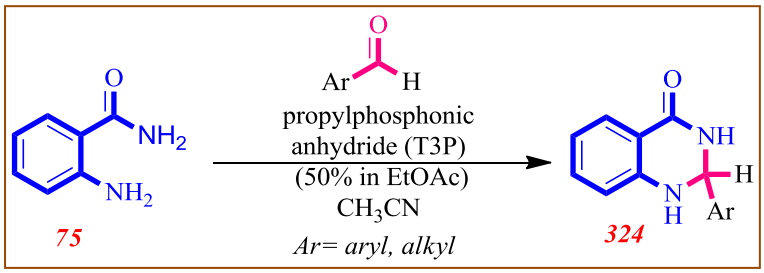
Eqn. 58. Synthesis of quinazolinones via natural acid/ SDS catalysis

Reddy et al. used cellulosulfonic acid as catalyst to synthesis dihydroquinazolinone (**322**) from anthranilamides and aldehydes. This catalyst is biodegradable which makes it more practical and convenient for use. The reaction gave good yield of the product with high selectivity. This protocol was further used for synthesis of hydroxyalkylquinazolin-4-ones (**323**) from different cyclic enol ethers (**Eqn. 59**).[33]



Eqn. 59. Synthesis of quinazolinones via cellulose-SO_3H

Propylphosphonic anhydride (T3P) was used as a synthetic reagent to synthesize dihydroquinazolinones (**324**) from anthranilamides (**75**) and aldehydes. The main advantages of this protocol were short reaction time, easy isolation and practicality (**Eqn. 60**).[34]



Eqn. 60. Synthesis of quinazolinones via T3P

Deep eutectic solvents (DES) is environment-friendly due to their natural properties (*vide supra*). It has now become the choice of solvent for many organic transformations. A keen survey of literature shows there was limited report[35] for synthesis of quinazolinone via deep eutectic solvents till now despite of the aforementioned impact on the environment. Furthermore, this DES mediated protocol can be used as a key reaction to synthesize different quinazolinone alkaloids and drugs. In environmental perspective, use of this methodology as a key step for alkaloid synthesis will open new directions to the scientific community. With this outlook on continuing our ongoing research on quinazolinones, we developed a DES mediated cyclization strategy for synthesis of various substituted/ unsubstituted quinazolinones. We have further used this protocol to achieve some biologically active quinazolinone alkaloids which have not been synthesized before.

3.1.2. Quinazolinone alkaloids, their isolations and biological properties

Wang et al. isolated three new quinazolinone alkaloids along with one triazole alkaloid from the fungus derived from marine sediment of *penicillium paneum* SD-44 in 2011. The

triazole alkaloid named as penipanoid A (**325**) and the respective quinazolinones were named as penipanoid B (**326**) and C (**307**) (**Figure 16**).[36] The other isolated quinazolinone derivative 2-(4-Hydroxybenzyl)quinazolin-4(*3H*)-one (**8**), was already known. In 2011, Che group isolated alkaloid **8** from *Isaria farinose* (*Cordyceps*-colonizing fungus) along with another six alkaloids.[37] Penipanoid C (**9**) and compound **8** was also isolated from a marine derived fungus *Penicillium oxalicum* 0312F$_1$.[38] Cytotoxic activity of compound **8** was tested against two cell lines A-549 and BEL-7402 that shows IC_{50} values of 17.5 and 19.8 μM respectively. It also shows strong inhibition over replication of tobacco mosaic virus (TMV).[36,38]

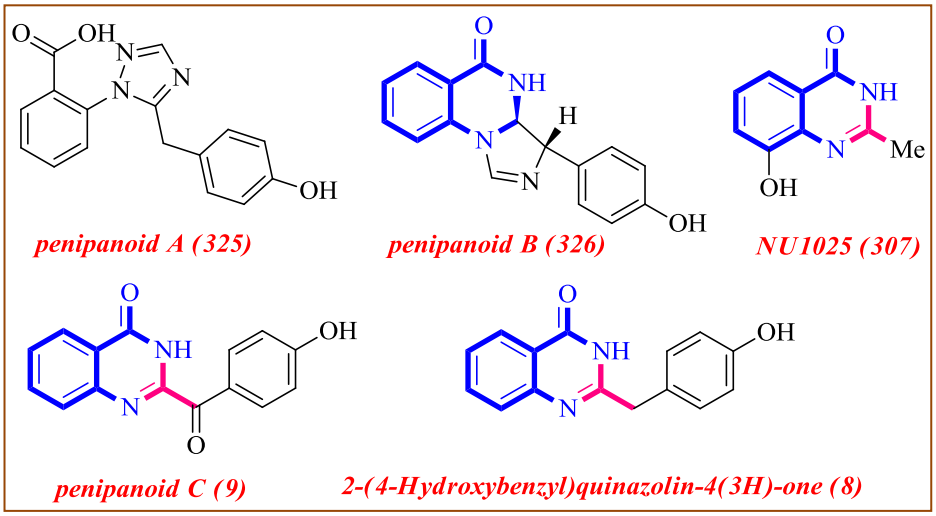


Figure 16. Structures of penipanoids and NU1025

Penipanoid C also exhibits moderate inhibition against TMV and human gastric-cancer cell line SGC-7901. [36, 37, 38] Penipanoid C was only trialed against two bacterias and five plant-pathogenic fungis for antimicrobial activity as it was extratcted in very few miligrams from nature. Hence, the chemical synthesis of these alkaloids were necessary as they are low abundant and displays potent biological activities.[36]

NU1025 [8-hydroxyl-2-methyl-4(3*H*)-quinazoline, **307**] (**Figure 16**) is reported as a drug which inhibits poly(ADP ribose) polymerase. NU1025 potentiate the cytotoxic activity of a panel for mechanistically diverse anti-cancer agents those were evaluated in L1210 cells.[39]

In 2011, Zhu et al. isolated some bioactive natural products from the fermentation broth of *A. terreus* PT06-2 at 10% salinity. Among these natural products only three compounds were new

and others were already reported (**fig. 17**). Out of them two were alkaloids and named as Terremide A (**327**) and B (**328**).[40]

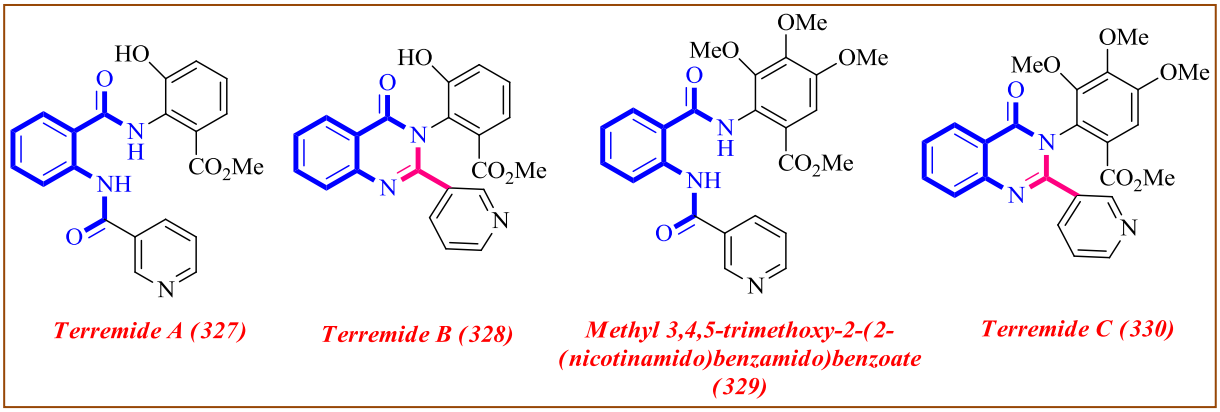


Figure 17. Structure of Terremide A, B, C and Methyl 3,4,5-trimethoxy-2-(2-(nicotinamido)benzamido)benzoate

In 2013, Qi et al. isolated another terremide like alkaloids from the fermentation broth of the marine-derived fungus *Aspergillus terreus* SCSGAF0162 and named as terremide C (**330**).[41] Methyl 3,4,5-trimethoxy-2-(2-(nicotinamido)benzamido)benzoate (**329**) was first isolated by Yamamoto in 1981 though it was again isolated by Zhu and Qi et al. also from the aforementioned sources.[42] Zhu group also tested Terremide A and B for their antibacterial activities against *Pseudomonas aeruginosa* and *Enterobacter aerogenes* that displayed MIC values 63.9 and 33.5 μM, respectively. Any synthesis has not been reported for these alkaloids till date and terremides were isolated in very low quantity to study further their biological properties. Thus, looking onto the significant antibacterial properties reported by Zhu et al. it is important to synthesize these natural alkaloids in laboratory (**fig. 17**). Thus, we used our DES cyclization protocol for first total synthesis of penipanoid C, 2-(4-hydroxybenzyl)quinazolin-4(3*H*)-one, NU1025, terremide A, B, C and methyl 3,4,5-trimethoxy-2-(2-(nicotinamido)benzamido)benzoate.

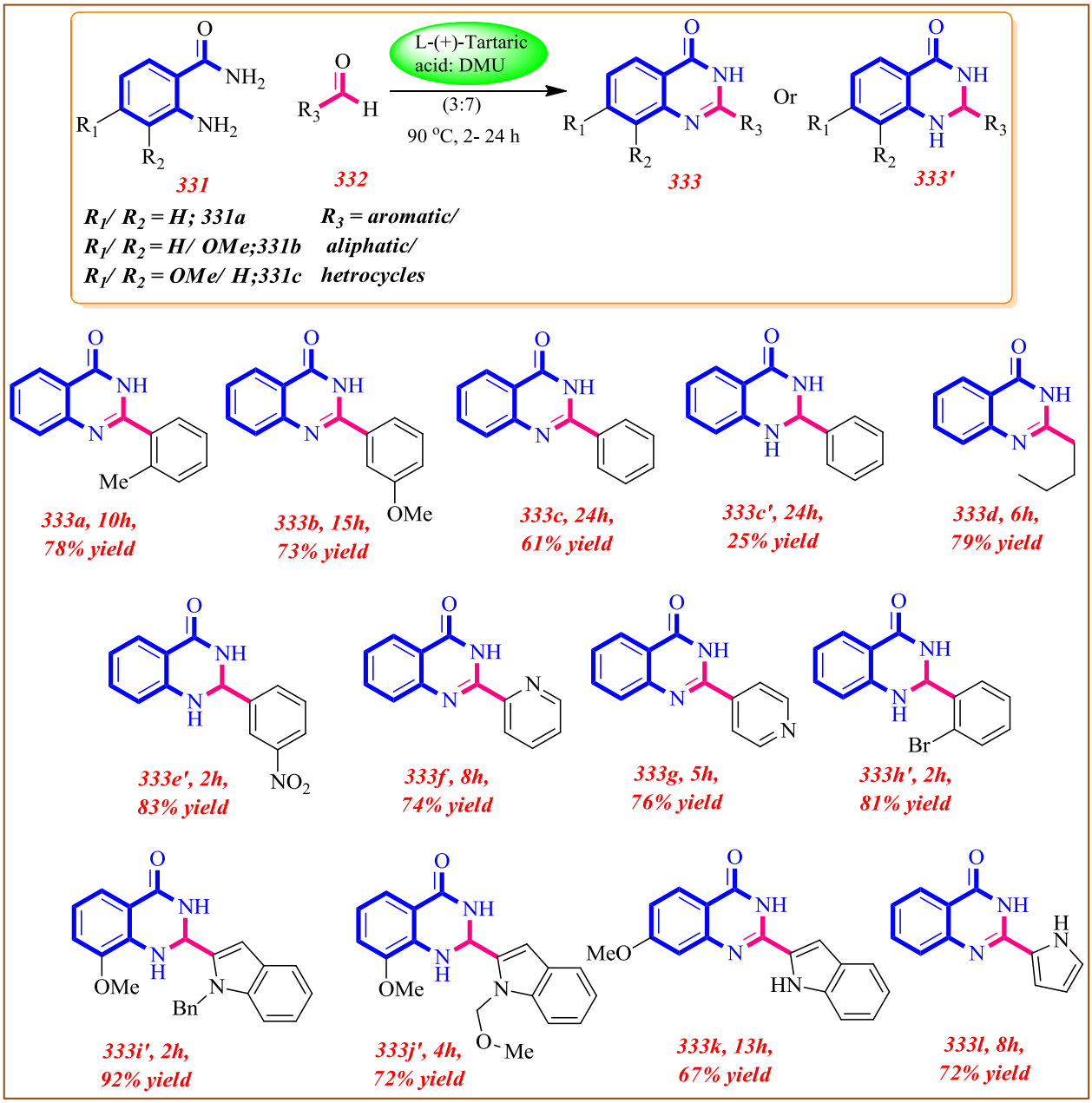
3.2 Results and discussion:

3.2.1. Development of DES cyclization methodology:

We started our endeavor with optimization of few literature reported deep eutectic mixture like, citric acid–N, N'-Dimethylurea (DMU), L-(+)-tartaric acid–DMU, mannose–DMU–NH_4Cl and D-(−)-fructose–DMU with model substrates; anthranilamide (**331a**) (1.0 equiv.) and *o*-

tolualdehyde (**332a**) (1.2 equiv) to obtain 2-(*o*-tolyl)quinazolin-4(3*H*)-one (**333a**, **scheme 9**). Among these eutectic mixtures, L-(+)-tartaric acid–DMU (3:7) mixture-melt at 90 °C was found to be the best that gives the maximum yield of compound **333a**. The reaction was performed in open air atmosphere; hence it aromatizes the primarily formed dihydroquinazolinone to the quinazolinone product through aerobic oxidation.

Scheme 9. Synthesis of 2-substituted quinazolinone[a]

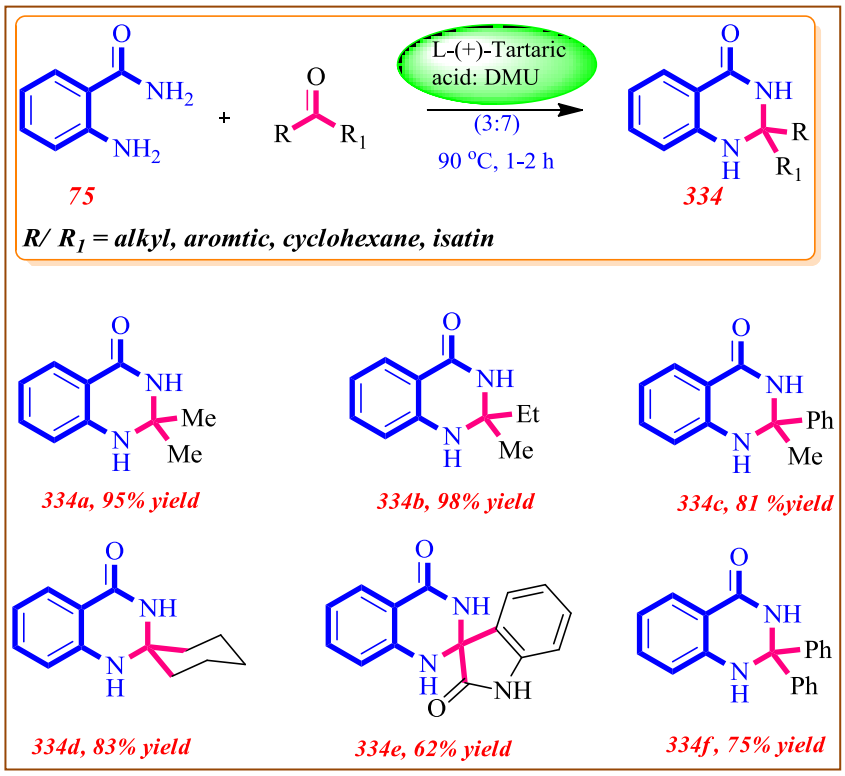


[a]Reaction was performed in a scale with **331** (1.0 equiv.), **332** (1.2 equiv.), in L-(+)-Tartaric acid : DMU (3:7) mixture at 90 °C in an open mouth round bottomed flask.

With these optimum conditions, we further explored the scope and generality of this reaction using DES. The initially generated dihydroquinazolinone can be easily identified with thin layer chromatography (TLC) in which compound shows bright blue long UV active spot. This dihydroquinazolinone was next aromatized to its corresponding quinazolinone via air oxidation. A series of aldehydes (heterocyclic, aromatic and aliphatic) (**332a-l**) was reacted with substituted/ unsubstituted anthranilamides (**331a- c**) under optimized conditions. To our delight, all the transformations underwent effortlessly to give the respective dihydroquinazolinones or quinazolinones depending upon the time of the reaction. The electron donating aldehydes (aromatic/ aliphatic) with anthranilamides can be transferred smoothly to the corresponding quinazolinone products in 6-15 h with good yields (**333a, 333b, 333d**). However, with benzaldehyde the reaction did not went upto completion after 24 h and we have obtained both quinazolinone (**333c**) and its corresponding dihydroquinazolinone (**333c'**) product. The electron-withdrawing aromatic aldehydes gave their corresponding dihydroquinazolinones (**333e', 333h'**) within 2h but they were never converted to their quinazolinone derivatives even after 24 h. A similar outcome was obtained when substituted anthranilamides (**331b, 331c**) were treated with heterocyclic aldehydes like pyridine, indole and pyrrole. This observation made us conclude that by varying the time, one can obtained both quinazolinone and dihydroquinazolinone product.

Next, we extended this methodology to synthesize 2,2'-disubstituted quinazolinones. Occurrences of disubstituted quinazolinones are scare in natural products but many reports are available for their synthetic version and many of them showed good pharmacological activities. Literature shows that on incorporating cyclohexane, aliphatic group and heterocycles at C2 of quinazolinones may give rise to antileishmanial, anti-inflammatory and analgesic properties. Few spiroquinazolinones were also tested as a depressants for central nervous system as they exhibits anti-amoebic activity.[43] Hence, we were eager to test DES cyclization protocol for synthesis of various 2,2'–disubstituted quinazolinones. Various ketones (aliphatic–aliphatic, aliphatic–aromatic, aromatic–aromatic, cyclic ketones and isatin) were well tolerated with anthranilamides (**75**) over the melt at our optimized conditions and gave excellent yield of the disubstituted quinazolinones (**334a- f, scheme 9**).

Scheme 10. Synthesis of 2,2'-disubstituted quinazolinone[a]

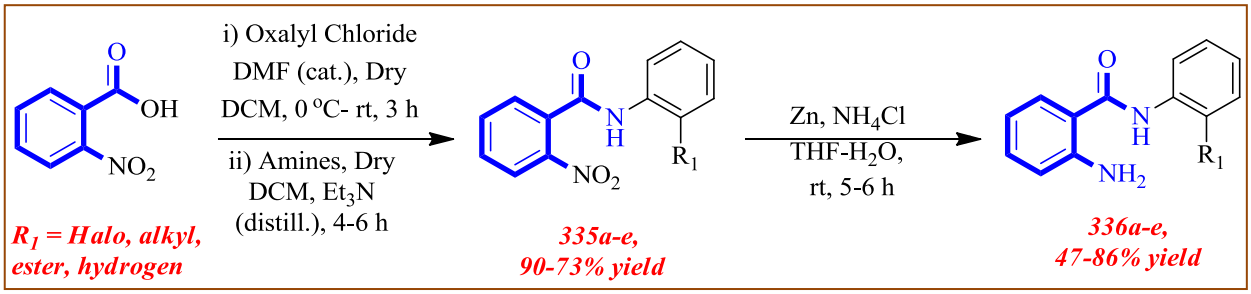


[a]Reaction was performed in a scale with **75** (1.0 equiv.), ketone (1.0 equiv.), in L-(+)-Tartaric acid : DMU (3:7) mixture at 90 ^{0}C in an open mouth round bottomed flask.

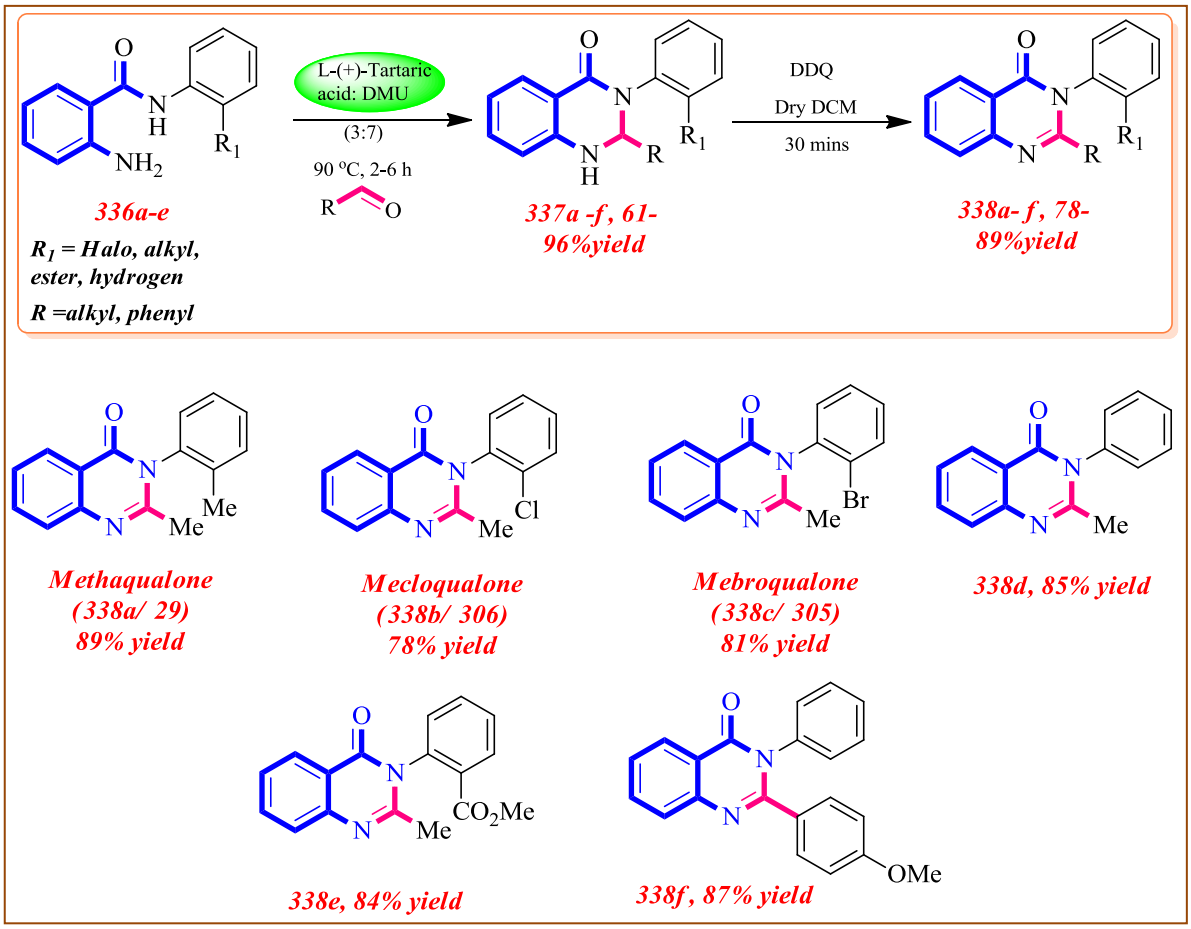
After a successful demonstration of DES cyclization protocol on 2-substituted/ 2, 2'-disubstituted quinazolinones, we wanted to investigate the generality of the protocol for 2, 3-disubstitued quinazolinones. With respect to pharmacological properties, 2, 3-disubstituted quinazolinones are more prominent (*vide supra*, **fig.15**). Hence, we wanted to synthesize various 2, 3-disubstitued quinazolinones along with some already reported natural alkaloids or drugs (methaqualone, mecloqualone, mebroqualone) via our DES cyclization protocol. As our synthesis began, we prepared the respective starting material to synthesize exact target molecules. 2-Amino-*N*-(substituted) benzamide (**336a- e**) was prepared in two steps from 2-nitrobenzoic acid. In first step acid chloride was prepared from 2-nitrobenzoic acid; the acid was dissolved in dry DCM and was stirred at rt for 3h with excess oxalyl chloride. Later, this excess oxalyl chloride was removed under pressure to get the acid chloride.

Scheme 11: Synthesis of 2, 3 substituted quinazolinones (Drugs and Natural products)

Part A: Preparation of starting materials



Part B: General method for synthesis of 2, 3 substituted quinazolinone drugs and alkaloids



Next, this acid chloride was dissolved in solvent and added slowly to a mixture of substituted benzamides and triethylamine. It was further stirred for another 4-6 h at rt that furnished respective 2-nitro-*N*-(substituted)benzamides (**335a-e**).[44] On treatment with Zn/ NH_4Cl in H_2O-THF mixture, the nitro group of compound **335a- e** were reduced to amines and gave 2-amino-*N*-(substituted)benzamides (**336a-e**) in excellent yields. Pleasingly, all 2-amino-*N*-

(substituted)benzamides (**336a-e**) underwent cyclization smoothly with respective aldehydes on the DES melt at 90 °C to furnish the corresponding dihydroquinazoliones (**337a-f**) in good yields. Then, these dihydroquinazolinones (**337a-f**) were oxidized to corresponding quinazolinones in excellent yields via DDQ oxidation. Various substituents like halo, ester and alkyl on aniline were tested under this protocol to synthesize the targeted drugs and alkaloids.

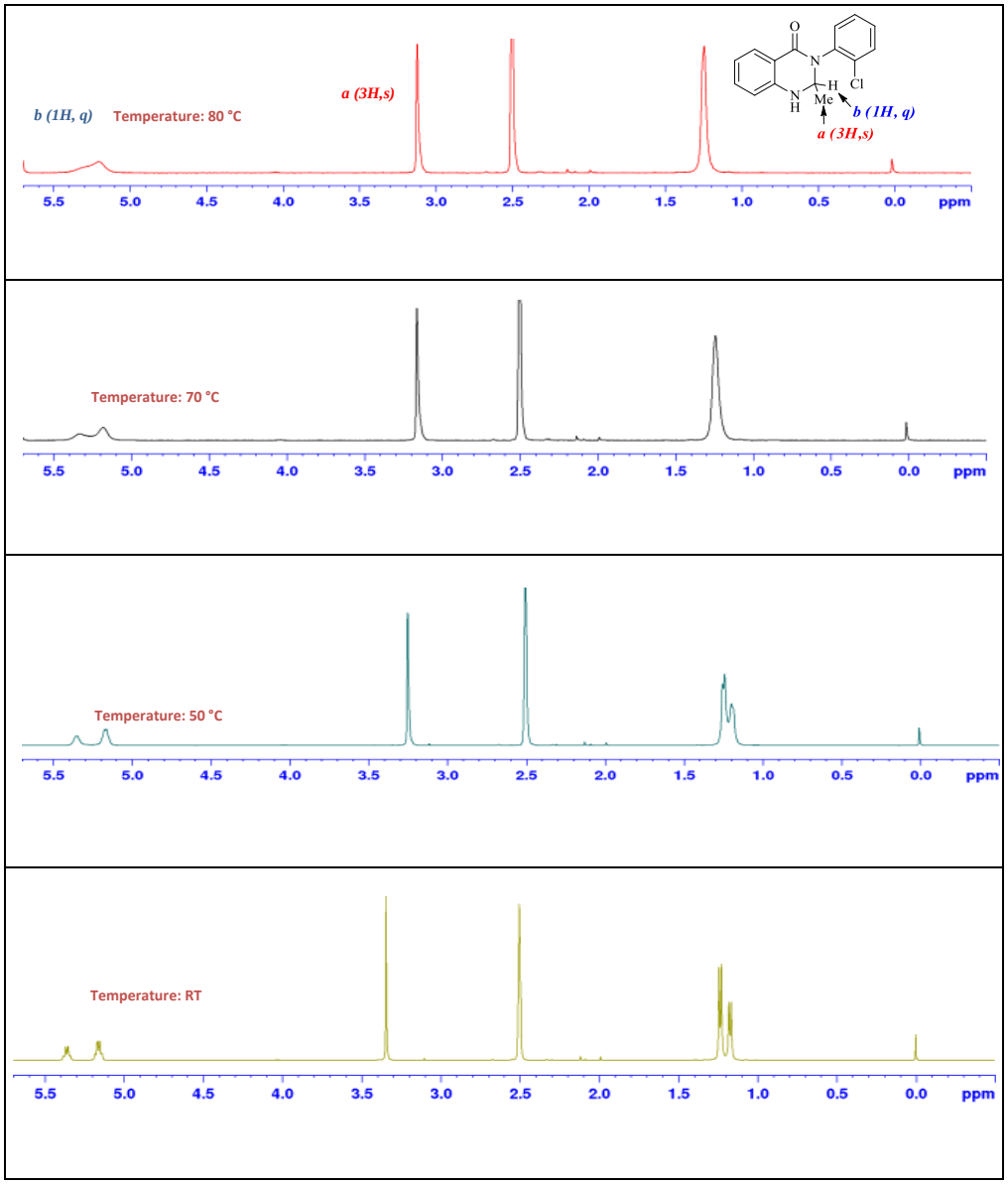


Figure 18: Temperature effect on conformational isomerism

To our delight, all the reactions went well and gave excellent yields along with 2-(4-methoxyphenyl)-3-phenylquinazolin-4(*3H*)-one (**338f**). Methaqualone (**338a**), mecloqualone

(**338b**), mebroqualone (**338c**) drugs and the alkaloid methyl 2-(2-methyl-4-oxoquinazolin-3(*4H*)-yl) benzoate (**338e**) were synthesized with good overall yields (**Scheme 11**).

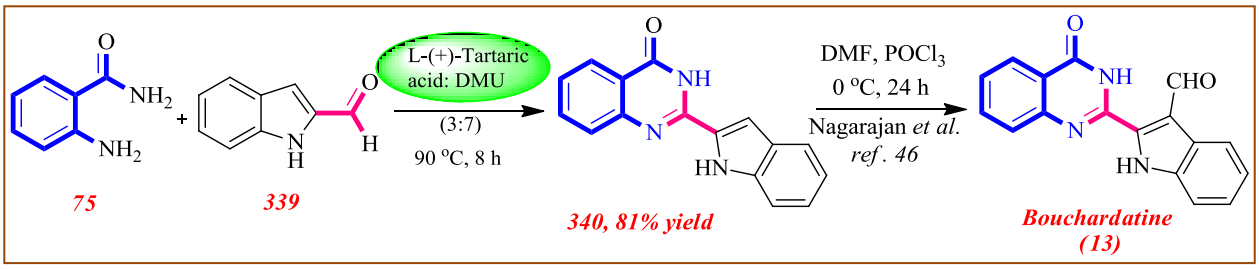
An interesting observation was noticed for compounds **337a, 337b, 337c** and **337e** in their NMR spectra (see experimental). They showed a firm existence of two conformational isomers but with different ratios. We assume that it was due to the R_1 group in compound **337** that restrict the C-C bond rotation. To certify our assumption we performed a temperature variant NMR experiment. We have measured the spectral changes between temperature range rt-80 °C using DMSO-d_6 as NMR solvent. As **fig. 18** shows for compound **337b**, with the temperature increased the signal spread (Dd) between the signals of peaks a (3H, s) and b (1H, q) decreases. At 50 °C the signals of a and b start to coalesce on the NMR time scale. The measurement at 70 °C shows that the peaks of both a and b merged as both the conformers lost their identity and exhibited as one rapidly equilibrating species.

After establishing this DES mediated cyclization protocol in a broader scope, specifically for synthesis of various 2-substituted; 2,2'-disubstituted and 2,3-disubstituted dihydroquinazolinones/ quinazolinones, the next step was application of this methodology. As we work on total synthesis of various alkaloids we wanted to apply this protocol to synthesize some of the recently reported bioactive quinazolinone alkaloids like penipanoids, terremides etc. which have not been synthesized earlier (*vide supra*) along with some formal synthesis.

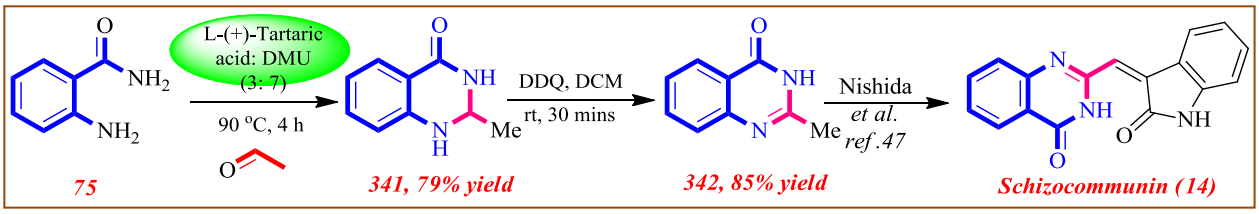
3.2.2. Formal synthesis of Bouchardatine and Schizocommunin:

A very famous β-indoloquinazoline alkaloid is Bouchardatine[45] (**Fig. 15**) which has been isolated from *B. neurococca* (Rutaecae). This alkaloid exhibits like anti-cancer, anti-inflammatory and anti-tuberculosis activities. Lately, it has also been reported for showing inhibitory activity against adipogenesis/ lipogenesis in 3T3-L1 adipocytes. Due to these important properties it drawn our attention immediately and we were keen to apply our methodology for synthesis of this alkaloid. Thus, we treated indole-2-carboxaldehyde (**339**) that was obtained following two steps from indole-2-carboxylic acid, with anthranilamide (**75**) in DES melt at 90 °C. After 8h of stirring at same temperature we obtained 2-(1*H*-indol-2-yl)quinazolin-4(3*H*)-one (**340)** in 81% yield. On treatment with DMF/$POCl_3$, aldehyde group can be introduced at C3 of compound **340** which will furnish the alkaloid bouchardatine (**13**). This reaction has already been documented by our group (**Scheme 12**).[46]

Scheme 12. Formal Synthesis of Bouchardatine



Scheme 13. Formal Synthesis of Schizocommunin



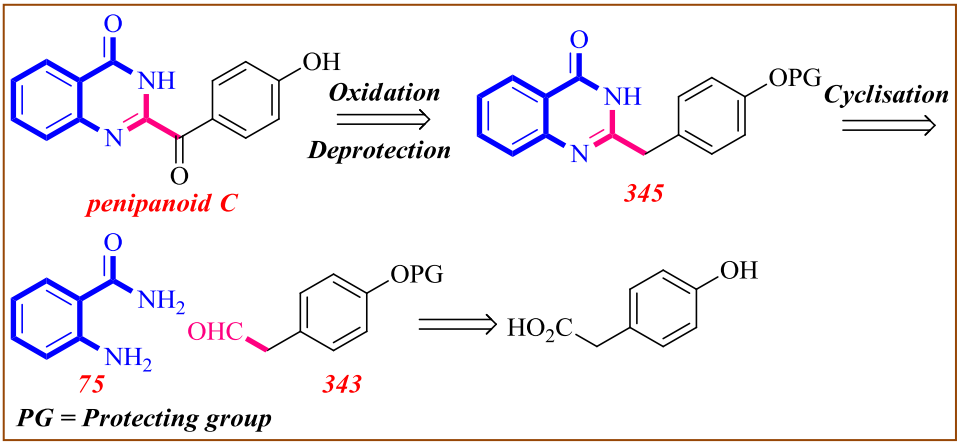
In **Scheme 13**, the formal synthesis of schizocommunin (**14**) was reported by using the DES cyclization method. In 1999, Hosoe et al. isolated this alkaloid from liquid culture medium of *Schizophyllum commune*. Schizocommunin exhibits strong cytotoxicity against murine lymphoma cells. Due to its scarcity in nature further biological studies were not done on this alkaloids and there was no chemical synthesis reported till 2013 when Nishida et al. revised its structure.[47] Their synthesis of schizocommunin was demonstrated from 2-methyl-4(3*H*)-quinazolinone on refluxing in acetic acid media with istain. Thus, the scarcity of schizocommunin in nature, and high cost of the commercially available 2-methyl-4(3*H*)-quinazolinone attracted us. Our DES cyclization protocol gave an easy access to synthesize 2-methyl-4(3*H*)-quinazolinone from anthranilamide (**75**). Anthranilamide (1.0 equiv.) was reacted with acetaldehyde (3.0 equiv.) on the melt at 90 °C to furnish the dihydroquinazolinone (**341**) in 2h which was further oxidized with DDQ to obtain 2-methyl-4(3*H*)-quinazolinone (**342**) in 85% yield; from this Schizocommunin can be obtained by Nishida's procedure in one step (**scheme 13**).

3.2.3. Total synthesis of penipanoid c, 2-(4-hydroxybenzyl) quinazolin-4(3*H*)-one and NU1025:

The biological properties and natural scarcity of penipanoid C have drawn our attention (*vide supra*); also no chemical synthesis was reported till date for this important alkaloid. The retrosynthetic analysis was given in the **scheme 14**. We assumed a late stage benzylic-oxidation

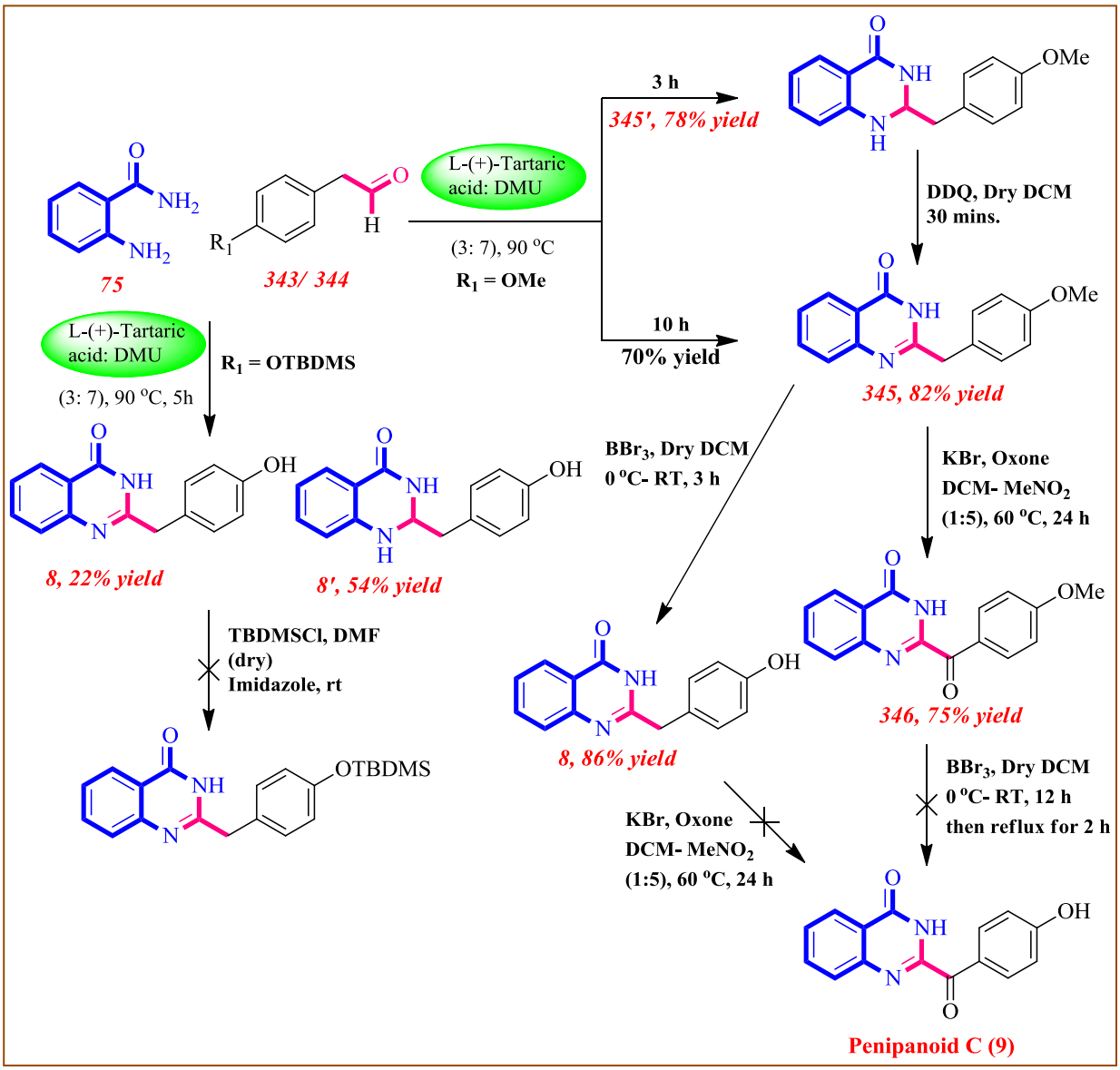
of compound **345** followed by phenolic –OH deprotection may generate penipanoid C. Compound **345** can be obtained via cyclization of anthranilamide (**75**) and suitably protected phenylacetaldehyde (**343**) followed by aromatization. The protected aldehyde could be obtained from 4-hydroxyphenylacetic acid by three consecutive steps (**scheme 14**).

Scheme 14: Retrosynthesis of penipanoid C



We started our venture with preparation of 4-methoxyphenylacetaldehyde (**343**); it was prepared from 4-hydroxyphenylacetic acid via three consecutive steps. Then this aldehyde (**343**) was subjected to DES cyclization with anthranilamide (**75**) at 90 °C to obtain 2-(4-methoxybenzyl)-2,3-dihydroquinazolin-4(1*H*)-one (**345'**) in 78% yield that was further oxidized to 2-(4-methoxybenzyl)quinazolin-4(3*H*)-one (**345**) by DDQ at rt. Compound **345** can be obtain directly from compound **343**, if the cyclization reaction was continued for 10 h. The deprotection of methoxy group with BBr_3 in DCM furnished the alkaloid 2-(4-hydroxybenzyl) quinazolin-4(3*H*)-one (**8**) with good yields. We assumed that penipanoid C can be obtained easily via benzylic oxidation of compound **8** but unfortunately the reaction was a failure. It might be the free phenolic –OH that caused the failure for this reaction. Hence, we have performed the benzylic oxidation on compound **345** with KBr/Oxone in DCM-$MeNO_2$ solvents and obtained compound **346** in 75% yields.[48] Then we carried out the methoxy deprotection with BBr_3 in compound **346** but it was a failure again.

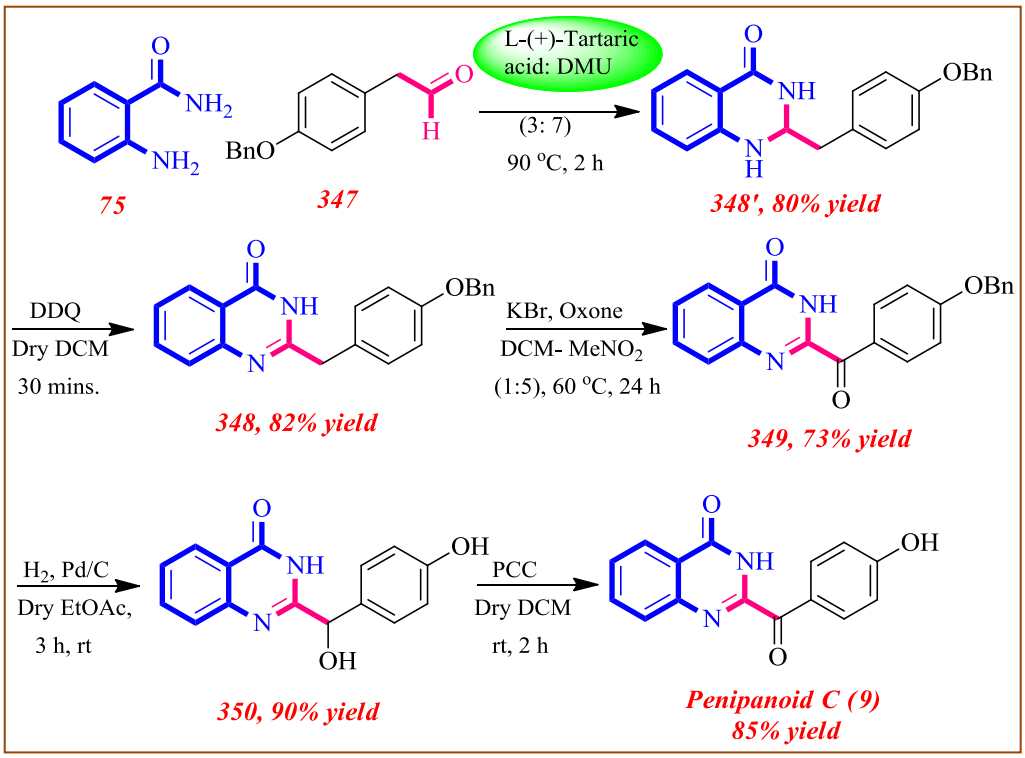
Scheme 15: Synthesis of penipanoid C

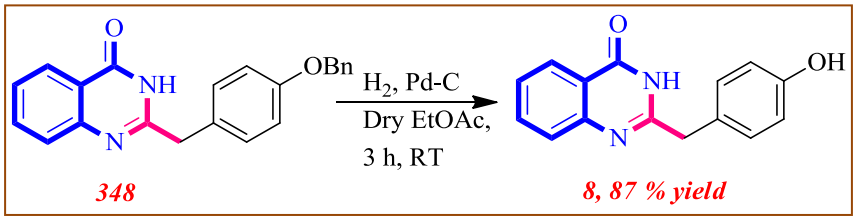


We presumed, due to the coordination between boron tribromide with carbonyl oxygen caused the failure. Thus, we have modified the protecting group from methoxy to *tert*-butyldimethylsilyl ether (-OTBDMS) and prepared *tert*-butyldimethylsilyl ether protected phenylacetaldehyde (**344**). Next we have reacted compound **344** with anthrnilamide (**75**) in the optimum condition but unfortunately we obtained TBDMS deprotected dihydro product (**8'**) as well as quinazolinone (**8**). The acidic media of this cyclization reaction might have deprotected the TBDMS group. We have tried the protection again with TBDMS for compound **8** using TBDMSCl with imidazole in dry DMF but reaction did not work out. After two times of

disappointment we changed the protecting group to benzyl which is a neutral and easy leaving group. 2-(4-(Benzyloxy)phenyl)acetaldehyde (**347**) was prepared from 4-hydroxyphenylacetic acid in three consecutive steps. Next, it was treated with anthranilamide (**75**) in L-(+) tartaric acid-DMU mixture (3:7) for 2h at 90 °C to generate the dihydroquinazolinone product (**348'**) in 80% yield.

Scheme 16: Revised synthesis of 2-(4-hydroxybenzyl)quinazolin-4(3*H*)-one and penipanoid C



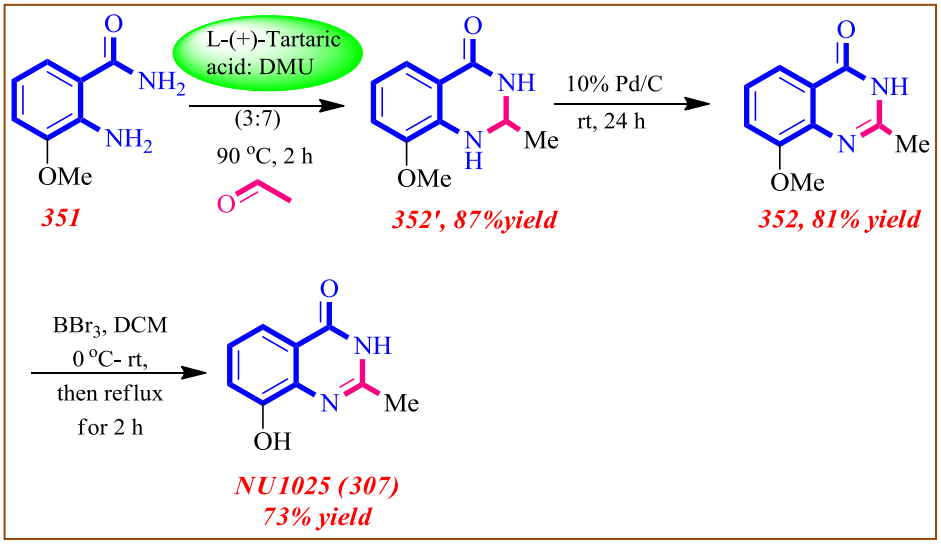


Compound **348'** was further oxidized with DDQ in dry DCM to its aromatized version 2-(4-(benzyloxy)benzyl)quinazolin-4(3*H*)-one (**348**) in 82% yield. Next the benzylic oxidation was carried out on compound **348** with KBr/Oxone in DCM-$MeNO_2$ solvent that gave compound **349** in 73% yields. Then, we carried out the hydrogenation reaction on compound **349** with H_2 on Pd/C to deprotect the benzyl group which unfortunately reduced the carbonyl group also to a

secondary alcohol group (**350, scheme 16**). Hence, the secondary alcohol of compound **350** was again oxidized to the carbonyl group with Pyridinium chlorochromate (PCC) in DCM to obtain penipanoid C (**9**) in 85% yield. Debenzylation of compound **348** with H_2 in Pd/C gave the alkaloid 2-(4-hydroxybenzyl)quinazolin-4(3*H*)-one (**8**) in 87% yield. Thus, we have achieved first total synthesis of penipanoid C and 2-(4-hydroxybenzyl)quinazolin-4(3*H*)-one with good overall yields 36.6% and 57% respectively.

NU1025 is another drug and its pharmacological importance has already been discussed in introduction portion was our next target. The starting material 2-amino-3-methoxybenzamide (**351**) was synthesized in two steps from 3-methoxy-2-nitrobenzoic acid. Next, compound **351** was reacted with acetaldehyde on DES melt at 90 °C for 2h which furnished 8-methoxy-2-methyl-2,3-dihydroquinazolin-4(1*H*)-one (**352'**) in 87% yield. On treatment with 10% Pd/C compound **352'** was oxidized to its quinazolinone product (**352**). Deprotection of methoxy group of compound **352** led to **NU1025** (**307**) which was achieved using BBr_3 in dry DCM under reflux condition. Thus, we have accomplished the synthesis of **NU1025** with an excellent overall yield 51.4%.

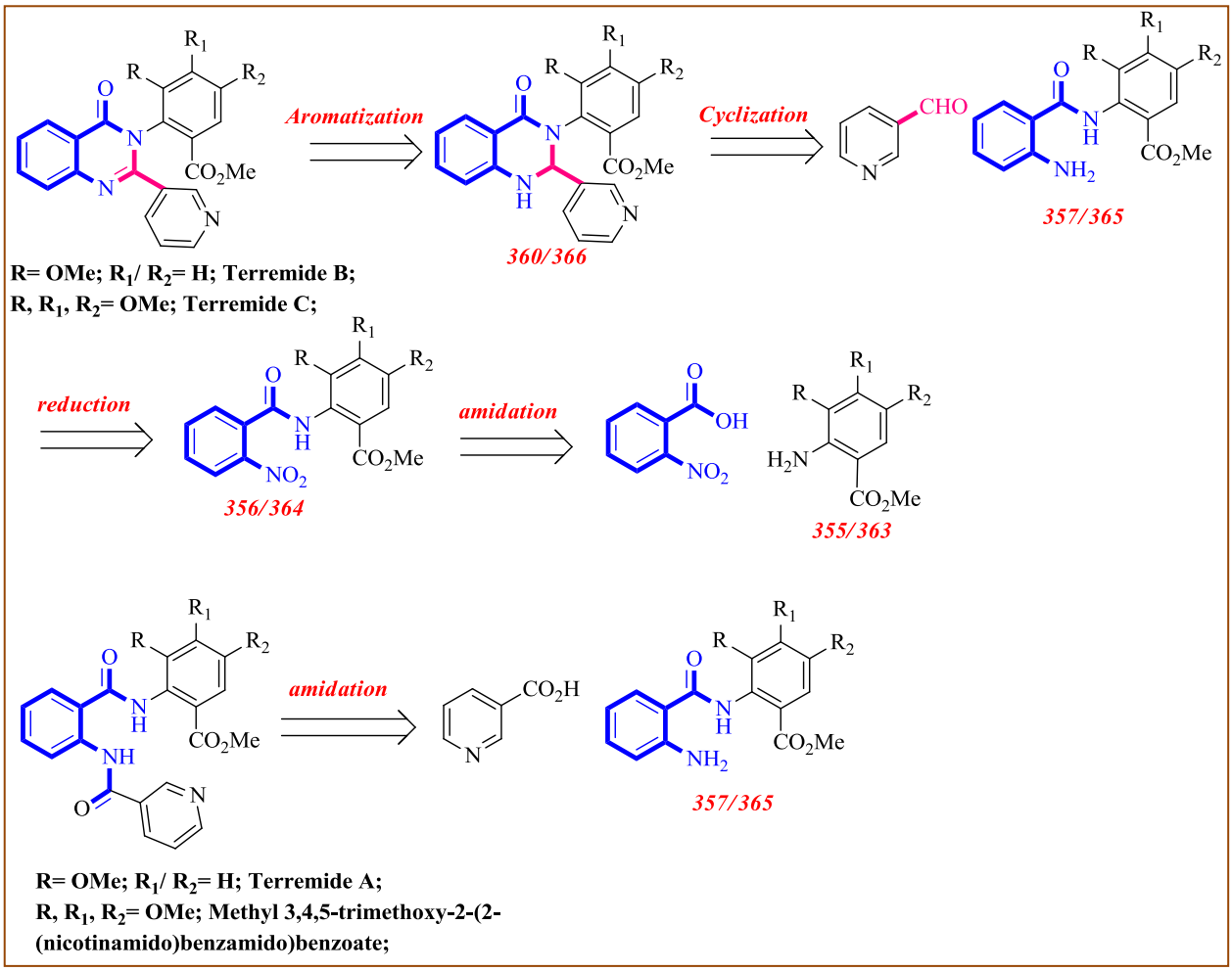
Scheme 17: Synthesis of 8-hydroxy-2-methylquinazolin-4(3*H*)-one (**NU1025**)



3.2.4. Total synthesis of Terremide A, B, C and Methyl 3,4,5-trimethoxy-2-(2-(nicotinamido)benzamido)benzoate:

A retrosynthethic approach was discussed in **scheme 18** for terremide A, B, C and Methyl 3,4,5-trimethoxy-2-(2- (nicotinamido)benzamido)benzoate.

Scheme 18: Retrosynthesis of Terremide A, B, C and Methyl 3,4,5-trimethoxy-2-(2-(nicotinamido)benzamido)benzoate

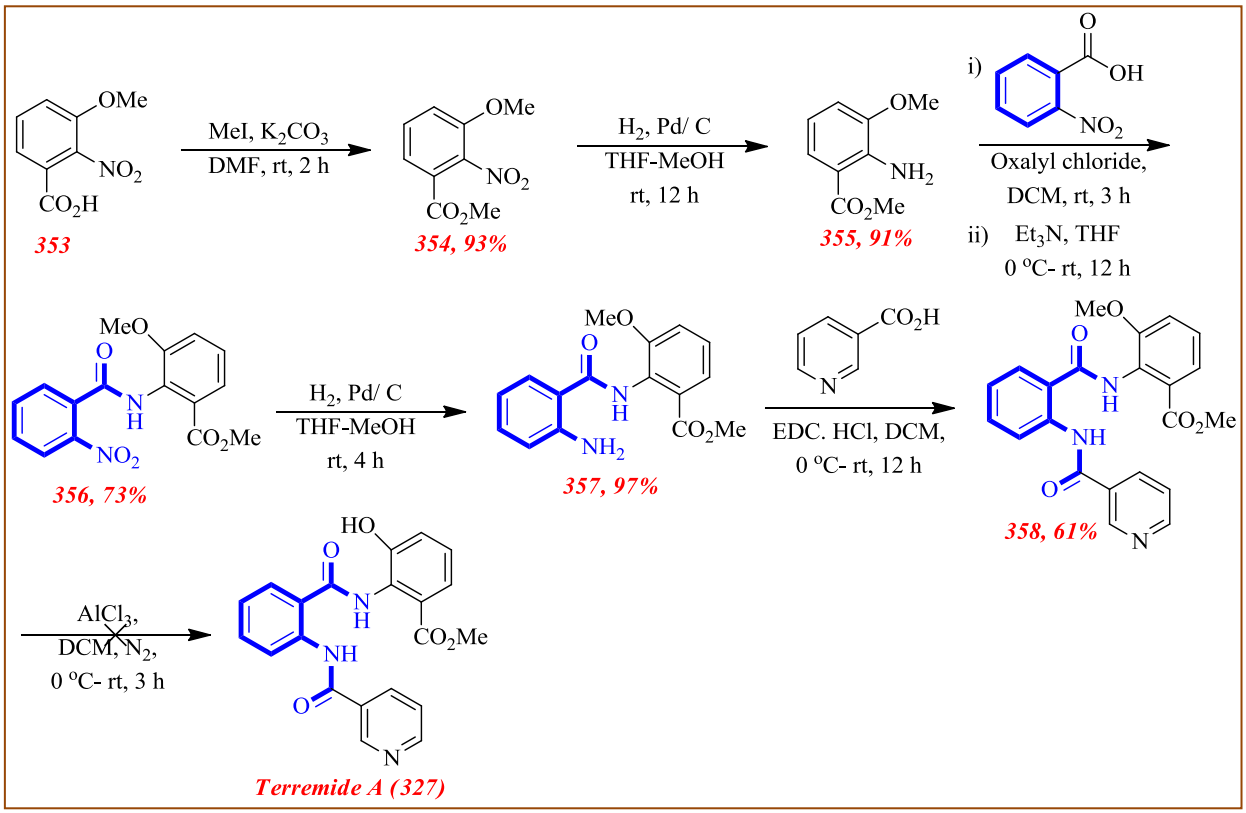


We envisioned terremide B and C can be obtained by a late stage aromatization reaction from compound **360** and compound **366** respectively. These compound **360** and **366** can be obtained via a cyclization reaction between pyridine-3-carboxaldehyde and appropriately substituted anthranilamide derivatives (**357** and **365**). These amides could be achieved from their corresponding nitro derivatives through reduction. These 2-nitrobenzamide derivatives could be stemmed from 2-nitrobenzoic acid and appropriate amines (**353** and **363**) via amide formation

reaction. Terremide A and Methyl 3,4,5-trimethoxy-2-(2-(nicotinamido)benzamido)benzoate both can also obtained using a similar strategy. These alkaloids can be generated via coupling reaction to form an amide bond between nicotinic acid and respective amines (**357** and **365**).

We stared our venture from synthesizing terremide A (**scheme 19**), from synthesizing the starting amine compound **355** in two consecutive steps from 3-methoxy-2-nitrobenzoic acid (**353**). Next, compound **355** was further subjected to an amidation reaction with 2-nitrobenzoic acid; where 2-nitrobenzoic acid was treated with oxalyl chloride in dry DCM at rt to generate the intermediate acid chloride. This acid chloride was further reacted with methyl 2-amino-3-methoxybenzoate (**355**) in presence of triethylamine base at rt to obtain the amide product **356** in 73% yield. The nitro group of compound **356** was further reduced to the corresponding amine compound **357** in 97% yield via hydrogenation reaction in Pd/C at rt in THF-MeOH (1:1) by 18 h. Once we obtained methyl 2-(2-aminobenzamido)-3-methoxybenzoate (**357**), it was reacted to nicotinic acid with coupling agent EDCI.HCl in dry DCM at 0 °C-rt under nitrogen atmosphere for 12 h. The reaction went smoothly to give the respective coupled product (**358**) in 61% yield.

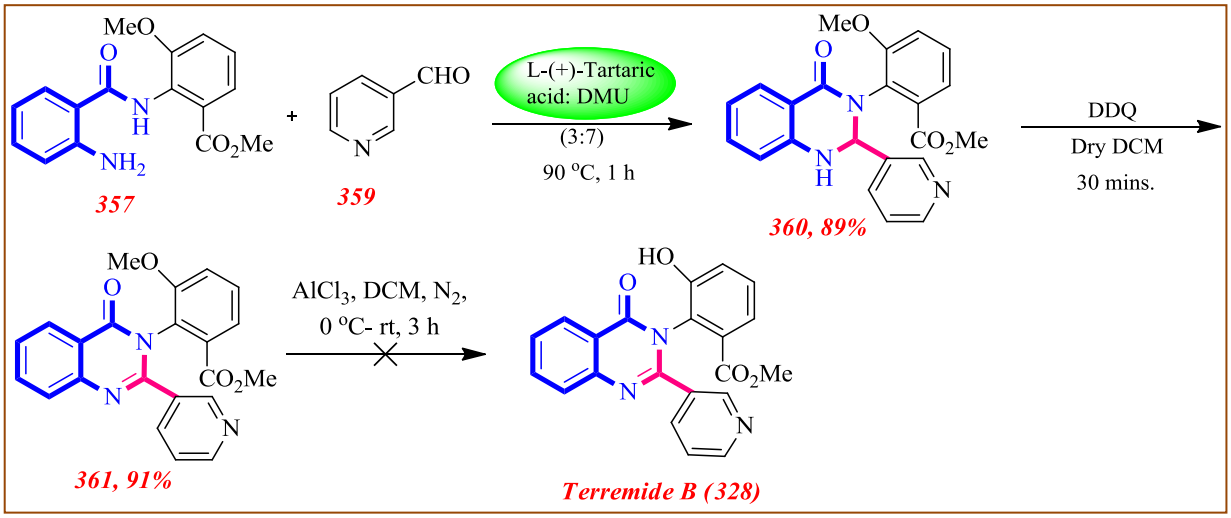
Scheme 19: Synthesis of Terremide A



After obtaining the core of the terremide A; we have to deprotect the methoxy group to get the exact alkaloid. Thus we treated compound **358** with anhydrous $AlCl_3$ in dry DCM under nitrogen atmosphere for 3 h at rt but unfortunately that did not furnished our final target alkaloid terremide A (**327**). Hence, we are trying some new conditions and further investigations are going on in our laboratory.

Next, we shifted our focus to synthesize terremide B (**Scheme 20**). As we envisaged, this alkaloid can be synthesized from compound **357** which can be obtained in two steps from compound **355** as shown in **Scheme 19**. Next, compound **355** was treated with 3-pyridinecarboxaldehyde (**359**) in L-(+)-tartaric acid-DMU mixture (3:7) for 1h at 90 °C to generate the cyclized dihydroquinazolinone compound (**360**) in 89% yield. This dihydroquinazolinone (**360**) was futher aromatized with DDQ to its respective quinazolinone (**361**) in dry DCM with 91% yield. Next, $AlCl_3$ condition again could not able to deprotect the methoxy group to furnish terremide B.

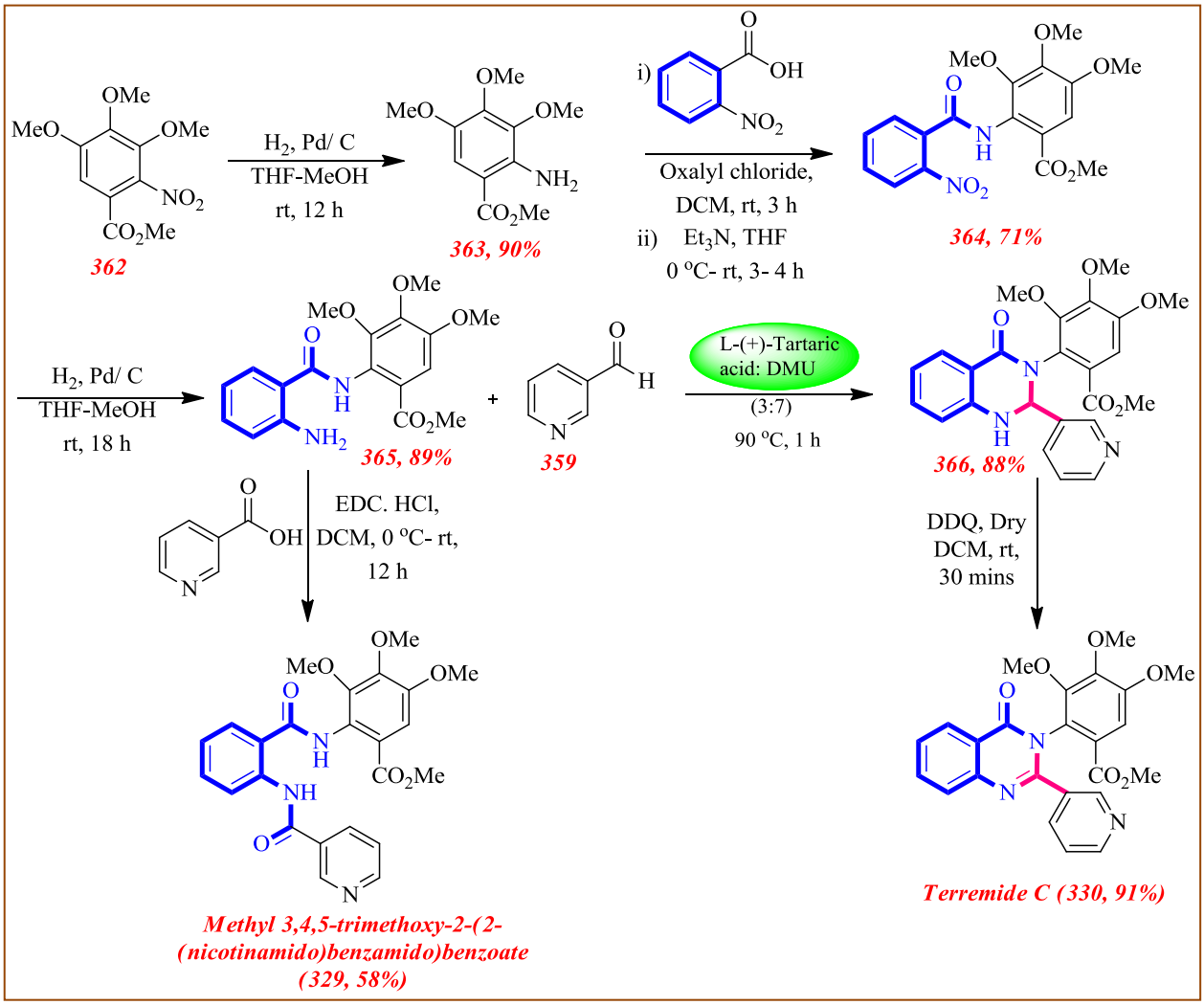
Scheme 20: Synthesis of Terremide B



The other two terremide alkaloids also can be synthesized using similar methodology. In **Scheme 21**, we described the forward synthesis for terremide C and Methyl 3,4,5-trimethoxy-2-(2-(nicotinamido)benzamido)benzoate. In the beginning, commercially available methyl 3,4,5-trimethoxy-2-nitrobenzoate (**362**) was reduced to its corresponding amine compound **363** in 90% yield by hydrogenation reaction with 10% Pd/C in THF:MeOH (1:1) solvent in 12 h. Once we obtained the amine **363**, it was subjected to the amidation reaction with 2-nitrobenzoic acid via two consecutive steps. Firstly, 2-nitrobenzoic acid was converted to its acid chloride using

excess oxalyl chloride in dry DCM. After removing the excess oxalyl chloride under vacuum, the acid chloride was reacted with methyl 2-amino-3,4,5-trimethoxybenzoate (**363**) in presence of triethylamine base to generate methyl 3,4,5-trimethoxy-2-(2-nitrobenzamido)benzoate (**364**) in 71% yield. Compound **364** was then reduced to its amine **365** with hydrogenation reaction in 18 h with an excellent yield. With the desired methyl 2-(2-aminobenzamido)-3,4,5-trimethoxybenzoate (**365**) we carried out the coupling reaction with nicotinic acid in presence of the coupling reagent EDCI.HCl in dry DCM at 0 °C-rt under nitrogen atmosphere to obtain methyl 3,4,5-trimethoxy-2-(2-(nicotinamido)benzamido)benzoate alkaloid (**329**) with 58% yield.

Scheme 21: Synthesis of Terremide C and Methyl 3,4,5-trimethoxy-2-(2-(nicotinamido)benzamido)benzoate



Next we focused on another alkaloid terremide C; Compound **365** was reacted with 3-pyridinecarboxaldehyde (**359**) in DES melt at 90 °C for 1 h to obtain its corresponding dihydroquinazolinone product (**366**) in 88% yield. Compound **366** was further aromatized to terremide C (**330**) using DDQ in dry DCM with 91% yield. Thus, we have completed first total synthesis of two biologically active alkaloids terremide C and Methyl 3,4,5-trimethoxy-2-(2-(nicotinamido)benzamido)benzoate with an overall yield of 45.5%, 33%.

3.3 Conclusion:

In conclusion, a greener and economical protocol was developed to synthesize various substituted and unsubstituted dihydroquinazolinones along with different quinazolinones in good to excellent yields. Different aldehydes/ketones along with substituted anthranilamides were well tolerated in our standard optimized conditions. This strategy was further utilized to carry out the formal synthesis of few biologically active alkaloids as well as drugs. In particular, we have utilized this economical strategy for first chemical synthesis of alkaloids, such as, penipanoid C, 2-(4-hydroxybenzyl) quinazolin-4(3*H*)-one, terremide C, Methyl 3,4,5-trimethoxy-2-(2-(nicotinamido)benzamido)benzoate and **NU1025** drug. All these alkaloids have obtained with good to excellent overall yields. Although we could not able to obtain the final step for terremide A and B but further optimization is still going.

3.4 Experimental section:

Melting Points: The melting point of the products was recorded on a Superfit (India) capillary melting point apparatus and is uncorrected.

IR: Infrared spectra were recorded on a JASCO FT/IR-5300 spectrophotometer. All the spectra were calibrated against polystyrene absorption at 1601 cm^{-1}. Solid samples were recorded as KBr wafers and liquid samples as thin film between NaCl plates or solution spectra in DCM.

NMR Spectra: ^{1}H NMR and ^{13}C NMR spectrums were recorded on BRUKER-AVANCE-400/ 500 spectrometers. ^{1}H NMR (400 or 500 MHz) spectra for all the samples were measured in chloroform-*d*, unless otherwise mentioned (δ = 2.50 ppm for ^{1}H NMR in the case of DMSO-d_6), with TMS (δ = 0 ppm) as an internal standard. ^{13}C NMR (100 or 125MHz) spectra for all the samples were measured in chloroform-*d*, unless otherwise mentioned (in the case of DMSO-d_6, δ = 39.70 ppm its middle peak of the septet), with its middle peak of the triplet (δ = 77.10 ppm) as an internal standard.

Mass Spectral Analysis: Shimadzu LCMS 2010A mass spectrometer. All the cases DCM or MeOH were used to dissolve the compounds. The TOF and quadrupole mass analyzer types are used for the HRMS measurements. Mass spectral data were obtained from HRMS (ESI).

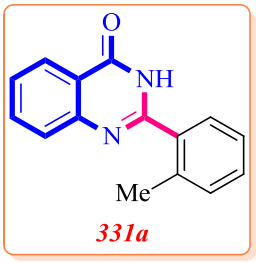
Elemental Analysis: Elemental analyses were performed on a Thermo Finnigan Flash EA 1112-CHN analyzer.

X-ray Crystallography: The X-ray diffraction measurements were carried out at 293 K on a Bruker SMART APEX CCD area detector system equipped with a graphite monochromator and a Mo-K_α fine-focus sealed tube (λ = 0.71073 Å) operated at 1500 W power (50 kV, 30 mA). The detector was placed at a distance of 4.995 cm from the crystal. The frames were integrated with the Bruker SAINT Software package using a narrow-frame algorithm. Data were corrected for absorption effects using the multi-scan technique (SADABS). The structure was solved and refined using the Bruker SHELXTL (Version 6.1) software package.

General experimental procedure to synthesis dihydroquinazolinone/ quinazolinone:

For 0.100 g starting amide, a total 2g mixture of L-(+)-Tartaric acid and N, N'-Dimethylurea (DMU) in a ratio of 3:7 was taken in an oven dried open mouth round bottomed flask and heated to its eutectic point 70 ^{0}C, where the mixture melted to give a clear solution. Next, aldehyde (1.2/ 1.5 equiv.) and substituted anthraniliamide (1.0 equiv.) was added to this melt and heated at 90 ^{0}C for 2-24h, depending on the desired product. On Completion of the reaction water was (checked by thin layer chromatography technique) added to it. The mixture was extracted with EtOAc, dried over Na_2SO_4 and evaporated in vacuum. The residue was purified by column chromatography on silica gel using ethyl acetate/hexanes mixture to afford the desired dihydroquinazolinone/ quinazolinone.

2-(o-Tolyl)quinazolin-4(3*H*)-one (333a):



331a

Yield: 78 %

Mp: 232-234 ^{o}C

IR (KBr) ν_{max} cm^{-1}: 3057, 1670, 1601, 1469, 1286, 1264, 765

^{1}H NMR (400 MHz) δ: 11.49 (1H, s, br), 8.34 (1H, d, *J* = 7.6 Hz), 8.15 (2H, d, *J* = 8.0 Hz), 7.82 (2H, t, *J* = 8.0 Hz), 7.50 (1H, t, *J* = 8.0 Hz), 7.38 (2H, d, *J* = 2.0 Hz), 2.47 (3H, s)

^{13}C NMR (100 MHz) δ: 164.1, 151.9, 149.6, 142.1, 134.8, 130.0, 129.7, 127.9, 127.4, 127.3, 126.5, 126.3, 120.8 (aromatic C), 21.5 (aliphatic C)

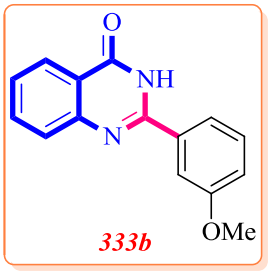
LCMS (m/z): 237$(M+H)^+$

Anal. calcd. for $C_{15}H_{12}N_2O$: C, 76.25; H, 5.12; N, 11.86%

Found: C, 76.12; H, 5.18; N, 11.96%

2-(3-Methoxyphenyl)quinazolin-4(3*H*)-one (333b):

Yield: 73 %



333b

Mp: 216 ^{o}C

IR (KBr) ν_{max} cm^{-1}: 1678, 1602, 1484, 1264, 834

^{1}H NMR (500 MHz, DMSO-d_6) δ: 12.39 (1H, s, br), 8.19 (2H, d, *J* = 8.5 Hz), 8.13 (1H, d, *J* = 7.0 Hz), 7.81 (1H, t, *J* = 6.5 Hz), 7.70 (1H, d, *J* = 8.0 Hz), 7.48 (1H, t, *J* = 7.0 Hz), 7.09 (2H, d, *J* = 9.0 Hz), 3.85 (3H, s)

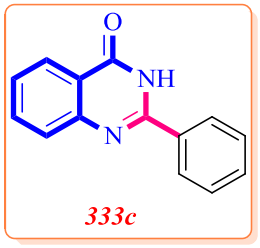
^{13}C NMR (125 MHz, DMSO-d_6) δ: 162.7, 162.4, 152.3, 149.4, 134.9, 129.9, 127.7, 126.5, 126.3, 125.3, 121.2, 114.5 (aromatic C), 55.9 (aliphatic C)

LCMS (m/z): 253(M+H)$^{+}$

Anal. calcd. for $C_{15}H_{12}N_2O_2$: C, 71.42; H, 4.79; N, 11.10%.

Found: C, 71.57; H, 4.71; N, 11.26%.

2-Phenylquinazolin-4(3*H*)-one (333c):



333c

Yield: 61 %

Mp: 236 ^{o}C

IR (KBr) ν_{max} cm^{-1}: 2918, 1666, 1601, 1291, 1265, 768

^{1}H NMR (400 MHz, $CDCl_3$+ DMSO-d_6) δ: 11.94 (1H, s), 8.05 (1H, d, *J* = 7.2 Hz), 7.99-7.98 (2H, m), 7.57-7.55 (2H, m), 7.32-7.29 (3H, m), 7.27-7.21 (1H, m)

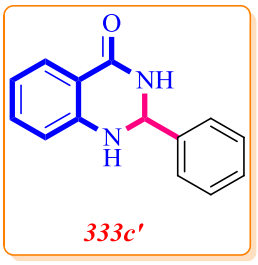
^{13}C NMR (100 MHz, $CDCl_3$+ DMSO-d_6) δ: 163.2, 152.3, 149.2, 134.3, 132.9, 131.2, 129.5, 128.6, 128.1, 127.6, 126.3, 126.0, 121.1 (aromatic C)

LCMS (m/z): 223(M+H)$^{+}$

Anal. calcd. for $C_{14}H_{10}N_2O$: C, 75.66; H, 4.54; N, 12.60%

Found: C, 75.81; H, 4.51; N, 12.53%

2-Phenyl-2,3-dihydroquinazolin-4(1*H*)-one (333c'):



333c'

Yield: 25 %

Mp: 216 ^{o}C

IR (KBr) ν_{max} cm^{-1}: 3299, 2925, 1651, 1608, 1264

^{1}H NMR (400 MHz, DMSO-d_6) δ: δ 8.29 (1H, s), 7.63 (1H, d, *J* = 7.6 Hz), 7.51 (2H, d, *J* = 7.6 Hz), 7.42- 7.34 (3H, m), 7.26 (1H, t, *J* = 7.2 Hz), 7.12 (1H, s), 6.77 (1H, d, *J* = 8.4 Hz), 6.69 (1H, t, *J* = 7.2 Hz), 5.77 (1H, s)

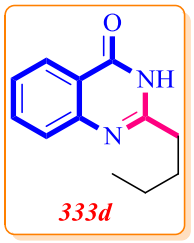
^{13}C NMR (100 MHz, DMSO-d_6) δ: 164.1, 148.3, 142.1, 133.8, 128.9, 128.8, 127.8, 127.3, 117.6, 115.4, 114.9 (aromatic C), 67.0 (aliphatic C)

LCMS (m/z): 225$(M+H)^{+}$

Anal. calcd. for $C_{14}H_{12}N_2O$: C, 74.98; H, 5.39; N, 12.49%.

Found: C, 74.82; H, 5.45; N, 12.56%.

2-Butylquinazolin-4(3*H*)-one (333d):



333d

Yield: 79 %

Mp: 110 ^{o}C

IR (KBr) ν_{max} cm^{-1}: 2919, 1682, 1616, 1467, 1261, 1130

^{1}H NMR (400 MHz, DMSO-d_6) δ: 12.02 (1H, s), 8.29 (1H, d, *J* = 8.0 Hz), 7.77 (1H, t, *J* = 8.0 Hz), 7.71 (1H, d, *J* = 8.0 Hz), 7.47 (1H, t, *J* = 8.0 Hz), 2.81 (2H, t, *J* = 8.0 Hz), 1.92-1.82 (2H, m), 1.51 (2H, q, *J* = 7.4 Hz), 1.00 (3H, t, *J* = 8.0 Hz)

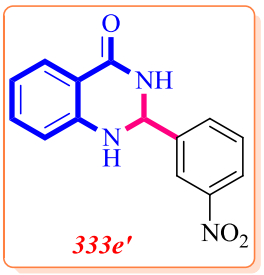
^{13}C NMR (100 MHz DMSO-d_6) δ: 164.4, 157.0, 149.5, 134.8, 127.2, 126.3, 126.2, 120.5, (aromatic C), 35.7, 29.7, 22.4, 13.8 (aliphatic C)

HRMS (ESI-MS)

Calcd for: $C_{12}H_{14}N_2O$: 203.1184 (M+H)

Found: 203.1187

2-(3-Nitrophenyl)-2,3-dihydroquinazolin-4(1*H*)-one (333e'):



Yield: 83 %

Mp: 216 ^{o}C

IR (KBr) ν_{max} cm^{-1}: 2920, 1731, 1682, 1616, 1468, 1200, 1145

^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.53 (1H, s), 8.35 (1H, s), 8.19 (1H, d, *J* = 8.0 Hz), 7.93 (1H, d, *J* = 7.2 Hz), 7.68 (1H, t, *J* = 8.0 Hz), 7.61 (1H, d, *J* = 7.2 Hz), 7.34 (1H, s), 7.26 (1H, t, *J* = 7.2 Hz), 6.78 (1H, d, *J* = 8.0 Hz), 6.68 (1H, t, *J* = 7.2 Hz), 5.94 (1H, s)

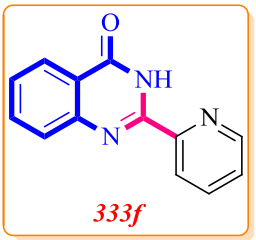
^{13}C NMR (100 MHz DMSO-d_6) δ: 163.8, 148.2, 147.8, 144.7, 134.1, 133.8, 130.5, 127.9, 123.7, 122.0, 118.0, 115.4, 115.1 (aromatic C), 65.6 (aliphatic C)

HRMS (ESI-MS)

Calcd for: $C_{14}H_{11}N_3O_3$: 270.0878 (M+H)

Found: 270.0874

2-(Pyridin-2-yl)quinazolin-4(3*H*)-one (333f):



Yield: 74 %

Mp: 166 ^{o}C

IR (KBr) ν_{max} cm^{-1}: 1684, 1607, 1472, 1331, 769

^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.82 (1H, s, br), 8.74 (1H, d, *J* = 4.4 Hz), 8.43 (1H, d, *J* = 8.0 Hz), 8.17 (1H, d, *J* = 8.0 Hz), 8.06 (1H, t, *J* = 8.0 Hz), 7.86 (1H, t, *J* = 8.0 Hz), 7.79 (1H, d, *J* = 8.0 Hz), 7.65-7.62 (1H, m), 7.56 (1H, t, *J* = 7.6 Hz)

^{13}C NMR (100 MHz DMSO-d_6) δ: 161.3, 150.3, 149.5, 149.0, 148.8, 138.5, 135.2, 128.1, 127.8, 127.0, 126.5, 122.6, 122.4 (aromatic C)

LCMS (m/z): 224$(M+H)^+$

Anal. calcd. for $C_{13}H_9N_3O$: C, 69.95; H, 4.06; N, 18.82%

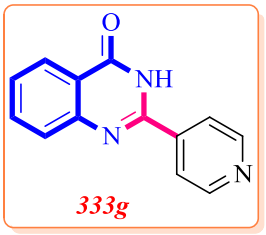
Found: C, 69.86; H, 4.15; N, 18.75%

2-(Pyridin-4-yl)quinazolin-4(3*H*)-one (333g):

Yield: 76 %

Mp: >240 ^{o}C

IR (KBr) ν_{max} cm^{-1}: 3358, 2964, 1682, 1561, 1468, 1260, 1030



333g

^{1}H NMR (500 MHz, DMSO-d_6) δ: 12.77 (1H, s), 8.79 (2H, d, *J* = 4.0 Hz), 8.18 (1H, d, *J* = 7.6 Hz), 8.12 (2H, d, *J* = 4.5 Hz), 7.88 (1H, t, *J* = 7.5 Hz), 7.79 (1H, d, *J* = 7.9 Hz), 7.58 (1H, t, *J* = 7.2Hz)

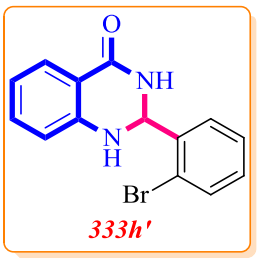
^{13}C NMR (125 MHz DMSO-d_6) δ: 162.5, 151.0, 150.7, 140.4, 135.3, 128.2, 127.9, 126.4, 122.0, 121.9 (aromatic C)

HRMS (ESI-MS)

Calcd for: $C_{13}H_9N_3O$: 224.0824 (M+H)

Found: 224.0820

2-(2-Bromophenyl)-2,3-dihydroquinazolin-4(1*H*)-one (333h'):



333h'

Yield: 81 %

Mp: 188 °C

IR (KBr) ν_{max} cm^{-1}: 3220, 1656, 1612, 1486, 1249

^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.21 (1H, s), 7.69-7.65 (3H, m), 7.44 (1H, t, *J* = 7.2 Hz), 7.32 (1H, t, *J* = 7.6 Hz), 7.27 (1H, t, *J* = 7.6 Hz), 7.00 (1H, s), 6.78 (1H, d, *J* = 8.4 Hz), 6.74 (1H, t, *J* = 7.6 Hz), 6.11 (1H, s)

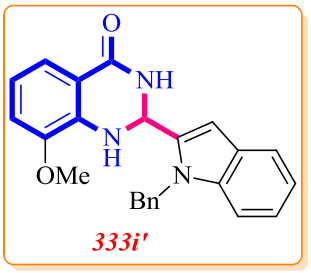
^{13}C NMR (100 MHz DMSO-d_6) δ: 164.2, 148.1, 139.6, 133.9, 133.3, 131.2, 129.5, 128.5, 127.9, 122.6, 118.0, 115.1, 115.0 (aromatic C), 66.8 (aliphatic C)

HRMS (ESI-MS)

Calcd for: $C_{14}H_{11}BrN_2O$: 324.9952 (M+Na)

Found: 324.9959

2-(1-Benzyl-1*H*-indol-2-yl)-8-methoxy-2,3-dihydroquinazolin-4(1*H*)-one (333i'):



333i'

Yield: 92 %

Mp: 198-200 °C

IR (KBr) ν_{max} cm^{-1}: 2920, 1671, 1610, 1457, 1249

^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.48 (1H, s), 7.52 (1H, d, *J* = 7.6 Hz), 7.33-7.28 (5H, m), 7.09-6.94 (5H, m), 6.69 (1H, t, *J* = 7.6 Hz), 6.43 (1H, s, br), 6.39 (1H, s), 6.05 (1H, s), 5.65 (2H, s), 3.72 (3H, s)

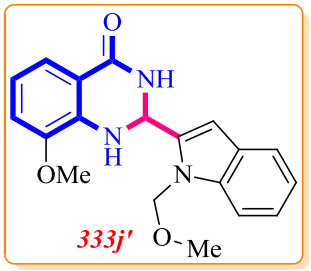
^{13}C NMR (100 MHz DMSO-d_6) δ: 164.0, 146.9, 140.5, 138.6, 137.8, 136.5, 129.0, 127.6, 127.0, 126.8, 122.2, 120.9, 120.0, 119.3, 117.4, 116.0, 114.0, 110.8, 101.9 (aromatic C), 66.8 (aliphatic C)

HRMS (ESI-MS)

Calcd for: $C_{24}H_{21}N_3O_2$: 384.1712 (M+H)

Found: 384.1712

8-Methoxy-2-(1-(methoxymethyl)-1*H*-indol-2-yl)-2,3-dihydroquinazolin-4(1*H*)-one (333j'):



Yield: 72 %

Mp: >184 °C

IR (KBr) ν_{max} cm^{-1}: 3419, 1687, 1605, 1468, 1276, 761

^{1}H NMR (400 MHz, $CDCl_3$+ DMSO-d_6) δ: 7.57 (1H, s, br), 7.52-7.43 (3H, m), 7.22 (1H, t, *J* = 8.0 Hz), 7.09 (1H, t, *J* = 8.0 Hz), 6.85 (1H, dd, *J* = 1.2 Hz, *J* = 8.0 Hz), 6,74 (1H, t, *J* = 8.0 Hz), 6.63 (1H, s), 6.16 (1H, d, *J* = 2.0 Hz), 5.70 (1H, s, br), 5.66 (1H, d, *J* = 11.2 Hz), 5.55 (1H, d, *J* = 11.6 Hz), 3.79 (3H, s), 3.31 (3H, s)

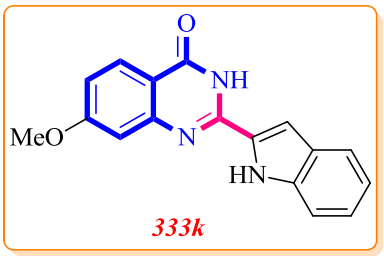
^{13}C NMR (100 MHz, $CDCl_3$+ DMSO-d_6) δ: 169.5, 151.2, 143.3, 142.7, 141.8, 131.7, 127.8, 125.9, 125.4, 124.2, 122.8, 120.2, 118.3, 114.2, 108.9 (aromatic C), 78.9, 66.3, 60.8, 60.4 (aliphatic C)

LCMS (m/z): 338$(M+H)^+$

Anal. calcd. for $C_{19}H_{19}N_3O_3$: C, 67.64; H, 5.68; N, 12.46%

Found: C, 67.49; H, 5.73; N, 12.38%

2-(1*H*-Indol-2-yl)-7-methoxyquinazolin-4(3*H*)-one (333k):



333k

Yield: 67 %

Mp: 244-246 ^{o}C

IR (KBr) ν_{max} cm^{-1}: 3484, 2898, 1654, 1600, 1315, 1145

^{1}H NMR (400 MHz, DMSO-d_6) δ: 12.48 (1H, s), 11.77 (1H, s), 8.06 (1H, t, *J* = 9.2 Hz), 7.63 (2H, d, *J* = 11.2 Hz), 7.51 (1H, d, *J* = 8.4 Hz), 7.21 (1H, t, *J* = 8.4 Hz), 7.12 (1H, s), 7.09-7.03 (2H, m), 3.91 (3H, s)

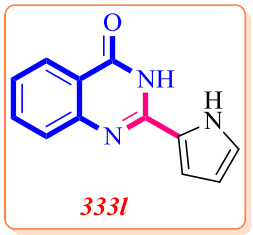
^{13}C NMR (100 MHz DMSO-d_6) δ: 164.6, 161.8, 151.4, 147.6, 138.1, 130.5, 128.2, 127.9, 124.5, 122.0, 120.4, 116.1, 115.0, 112.9, 108.6, 105.4 (aromatic C), 56.1 (aliphatic C)

HRMS (ESI-MS)

Calcd for: $C_{17}H_{13}N_3O_2$: 292.1086 (M+H)

Found: 292.1086

2-(1*H*-Pyrrol-2-yl)quinazolin-4(3*H*)-one (333l):



333l

Yield: 72 %

Mp: >240 ^{o}C

IR (KBr) ν_{max} cm^{-1}: 2919, 1672, 1596, 1496, 1261, 765

^{1}H NMR (400 MHz, DMSO-d_6) δ: 12.18 (1H, s), 11.70 (1H, s), 8.08 (1H, d, *J* = 7.6 Hz), 7.77 (1H, t, *J* = 7.6 Hz), 7.62 (1H, d, *J* = 8.0 Hz), 7.41 (1H, t, *J* = 7.2 Hz), 7.29 (1H, s), 7.05 (1H, s), 6.21 (1H, s)

^{13}C NMR (100 MHz DMSO-d_6) δ: 162.4, 149.7, 146.8, 135.0, 126.9, 126.4, 125.7, 124.7, 124.3, 120.9, 112.9, 110.2 (aromatic C)

LCMS (m/z): 212$(M+H)^+$

Anal. calcd. for $C_{12}H_9N_3O$: C, 68.24; H, 4.29; N, 19.89%

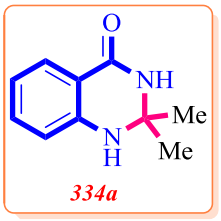
Found: C, 68.15; H, 4.36; N, 19.78%

2,2-Dimethyl-2,3-dihydroquinazolin-4(1*H*)-one (334a):

Yield: 95 %

Mp: 176- 178 ^oC

IR (KBr) ν_{max} cm^{-1}: 3255, 1632, 1485, 1270, 1175, 750



334a

^{1}H NMR (400 MHz) δ: 7.89 (1H, d, *J* = 7.2 Hz), 7.31 (1H, t, *J* = 8.0 Hz), 7.05 (1H, s, br), 6.83 (1H, t, *J* = 7.2 Hz), 6.64 (1H, d, *J* = 7.6 Hz), 4.25 (1H, s, br), 1.58 (6H, s)

^{13}C NMR (100 MHz) δ: 164.7, 146.0, 133.9, 128.3, 118.7, 114.7, 114.6 (aromatic C), 67.6, 29.6 (aliphatic C)

LCMS (m/z): 177$(M+H)^+$

Anal. calcd. for $C_{10}H_{12}N_2O$: C, 68.16; H, 6.86; N, 15.90%

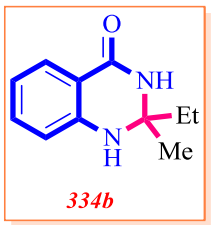
Found: C, 68.26; H, 6.81; N, 15.82%

2-Ethyl-2-methyl-2,3-dihydroquinazolin-4(1*H*)-one (334b):

Yield: 98 %

Mp: 164- 166 ^oC

IR (KBr) ν_{max} cm^{-1}: 3270, 1638, 1612, 1266, 754



334b

^{1}H NMR (500 MHz) δ: 7.88 (1H, d, *J* = 7.5 Hz), 7.31 (1H, d, *J* = 8.5 Hz), 6.82 (1H, t, *J* = 7.0 Hz), 6.62 (1H, d, *J* = 8.0 Hz), 6.17 (1H, s, br), 4.13 (1H, s, br), 1.82 (2H, q, *J* = 7.4 Hz), 1.51 (3H, s), 1.01 (3H, t, *J* = 7.4 Hz)

^{13}C NMR (100 MHz) δ: 165.1, 146.1, 134.1, 128.3, 118.4, 114.5, 114.2 (aromatic C), 70.1, 34.8, 27.5, 8.2 (aliphatic C)

LCMS (m/z): 191$(M+H)^+$

Anal. calcd. for $C_{11}H_{14}N_2O$: C, 69.45; H, 7.42; N, 14.73%

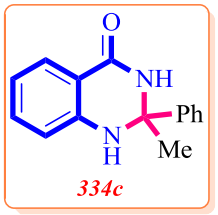
Found: C, 69.56; H, 7.35; N, 14.62%

2-Methyl-2-phenyl-2,3-dihydroquinazolin-4(1*H*)-one (334c):

Yield: 81 %

Mp: 220 ^oC

IR (KBr) ν_{max} cm^{-1}: 3402, 1665, 1610, 1501, 1380, 1265



334c

^{1}H NMR (500 MHz, $CDCl_3$+ DMSO-d_6) δ: 7.64 (1H, d, *J* = 8.0 Hz), 7.60 (1H, s, br), 7.43 (2H, d, *J* = 8.0 Hz), 7.17 (2H, t, *J* = 8.0 Hz), 7.14-7.08 (2H, m), 6.64 (1H, d, *J* = 8.0 Hz), 6.59 (1H, t, *J* = 8.0 Hz), 5.98 (1H, s, br), 1.72 (3H, s)

^{13}C NMR (100 MHz $CDCl_3$+ DMSO-d_6) δ: 164.8, 146.4, 146.0, 133.7, 128.2, 128.0, 127.6, 125.2, 118.1, 115.2, 114.7 (aromatic C), 70.7, 30.3 (aliphatic C)

HRMS (ESI-MS)

Calcd for: $C_{15}H_{14}N_2O$: 261.1004 (M+Na)

Found: 261.1003

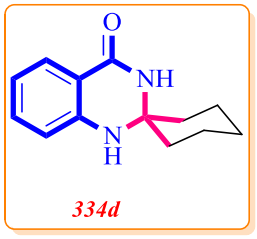
1'*H*-Spiro[cyclohexane-1,2'-quinazolin]-4'(3'*H*)-one (334d):

Yield: 83 %

Mp: 212- 214 ^oC

IR (KBr) ν_{max} cm^{-1}: 3169, 2922, 2852, 1642, 1606, 1479, 1267

^{1}H NMR (400 MHz, $CDCl_3$+ DMSO-d_6) δ: 7.62-7.58 (1H, m), 7.06 (1H, d, *J* = 6.8 Hz), 6.89 (1H, s), 6.55-6.52 (2H, m), 5.21 (1H, s, br), 1.63 (4H, s), 1.41 (4H, s), 1.26 (2H, s)



334d

^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6) δ: 164.3, 146.2, 133.5, 127.8, 117.7, 114.7 (aromatic C), 68.2, 37.4, 24.6, 21.6 (aliphatic C)

LCMS (m/z): $217(M+H)^+$

Anal. calcd. for $C_{13}H_{16}N_2O$: C, 72.19; H, 7.46; N, 12.95%

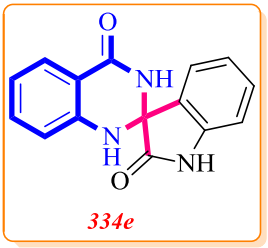
Found: C, 72.25; H, 7.41; N, 13.07%

1'*H*-Spiro[indoline-3,2'-quinazoline]-2,4'(3'*H*)-dione (334e):

Yield: 62 %

Mp: 214 ^{o}C

IR (KBr) ν_{max} cm^{-1}: 1726, 1659, 1609, 1585, 1264



334e

^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.31 (1H, s), 8.36 (1H, s), 7.61 (1H, d, *J* = 7.2 Hz), 7.48 (1H, d, *J* = 7.2 Hz), 7.34 (1H, t, *J* = 7.6 Hz), 7.28 (1H, s), 7.24 (1H, t, *J* = 8.0 Hz), 7.07 (1H, t , *J* = 7.6 Hz), 6.87 (1H, d, *J* = 7.6 Hz), 6.69 (1H, t, *J* = 7.6 Hz), 6.62 (1H, d, *J* = 7.6 Hz)

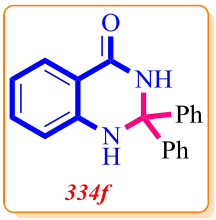
^{13}C NMR (100 MHz DMSO-d_6) δ: 176.5, 164.5, 147.3, 142.5, 133.8, 131.3, 129.8, 127.3, 125.8, 122.8, 117.7, 114.7, 114.3, 110.6 (aromatic C), 71.4 (aliphatic C)

LCMS (m/z): $266(M+H)^+$

Anal. calcd. for $C_{15}H_{11}N_3O_2$: C, 67.92; H, 4.18; N, 15.84%

Found: C, 67.85; H, 4.12; N, 15.76%

2, 2-Diphenyl-2,3-dihydroquinazolin-4(1*H*)-one (334f):



334f

Yield: 75 %

Mp: 140 ^{o}C

IR (KBr) ν_{max} cm^{-1}: 3375, 3243, 1649, 1610, 1484, 1375, 1210, 750

^{1}H NMR (500 MHz) δ: 7.81 (1H, d, *J* = 7.6 Hz), 7.43-7.40 (4H, m), 7.34-7.27 (7H, m), 6.78 (1H, t, *J* = 7.6 Hz), 6.73 (2H, d, *J* = 8.0 Hz), 5.36 (1H, s, br)

^{13}C NMR (100 MHz) δ: 164.3, 145.6, 143.7, 134.2, 128.6, 128.5, 127.3, 119.2, 115.4, 114.9 (aromatic C), 76.0 (aliphatic C)

HRMS (ESI-MS)

Calcd for: $C_{20}H_{16}N_2O$: 323.1160 (M+Na)

Found: 323.1163

Compound 335a- 335e:

These compounds were prepared via adopting method from *reference* 44.The same procedure was later used for synthesis of compound **356** and **364.**

General procedure for synthesis of compound 336a- 336e:

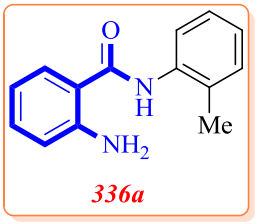
Compound **335a** (0.500, 2.2 mmol) was dissolved in THF-H_2O solution (5:1, 20 mL). To this solution NH_4Cl (0.353 g, 6.6 mmol) and Zn dust (1.15 g, 17.6 mmol) was added. The reaction was stirred at rt for 5-6 h. After the completion of the reaction, reaction mixture was filtered and extracted with ethyl acetate and evaporated to dryness. The residue was purified by column chromatography on silica gel to give compound **336a**. We followed the same procedure for preparation of compound **336b- 336e**.

2-Amino-*N*-(o-tolyl)benzamide (336a):

Yield: 86 %

Mp: 104 ^{o}C

^{1}H NMR (400 MHz) δ: 7.84 (1H, d, *J* = 8.0 Hz), 7.66 (1H, s, br), 7.53 (1H, d, *J* = 8.0 Hz), 7.31-7.26 (3H, m), 7.15 (1H, t, *J* = 7.2 Hz), 6.76 (2H, d, *J* = 8.0 Hz), 5.56 (2H, s, br), 2.35 (3H, s)



336a

^{13}C NMR (100 MHz) δ: 167.6, 149.2, 135.7, 132.8, 130.6, 130.0, 127.2, 126.8, 125.5, 123.7, 117.6, 116.8, 116.1 (aromatic C), 17.9 (aliphatic C)

HRMS (ESI-MS)

Calcd for: $C_{14}H_{14}N_2O$: 249.1004 (M+Na)

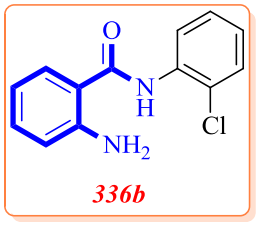
Found: 249.1008

2-Amino-*N*-(2-chlorophenyl)benzamide (336b):

Yield: 77 %

Mp: 108 ^{o}C

^{1}H NMR (400 MHz) δ: 8.48 (1H, d, *J* = 8.4 Hz), 8.37 (1H, s, br), 7.57 (1H, d, *J* = 7.6 Hz), 7.44 (1H, d, *J* = 8.0 Hz), 7.37-7.29 (2H, m), 7.10 (1H, t, *J* = 8.0 Hz), 6.77 (2H, t, *J* = 7.6 Hz), 5.63 (2H, s, br)



336b

^{13}C NMR (100 MHz) δ: 167.3, 149.4, 134.8, 133.1, 129.1, 127.7, 127.2, 124.6, 123.4, 121.7, 117.7, 116.9, 115.6 (aromatic C)

HRMS (ESI-MS)

Calcd for: $C_{13}H_{11}ClN_2O$: 247.0638 (M+H)

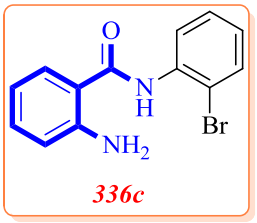
Found: 247.0636

2-Amino-*N*-(2-bromophenyl)benzamide (336c):

Yield: 82 %

Mp: 102 ^{o}C

^{1}H NMR (400 MHz) δ: 8.47 (1H, dd, *J* = 1.6 Hz, *J* = 8.4 Hz), 8.37 (1H, s, br), 7.60 (2H, t, *J* = 7.6 Hz), 7.39 (1H, t, *J* = 7.6 Hz), 7.33-7.29 (1H, m), 7.03 (1H, dt, *J* = 1.2 Hz, *J* = 7.6 Hz), 6.77 (2H, t, *J* = 8.0 Hz), 5.65 (2H, s, br)



336c

^{13}C NMR (100 MHz) δ: 169.3, 149.5, 135.9, 133.1, 132.3, 128.4, 127.2, 125.1, 122.0, 117.7, 117.0, 115.5, 114.1 (aromatic C)

HRMS (ESI-MS)

Calcd for: $C_{13}H_{11}BrN_2O$: 291.0133 (M+H)

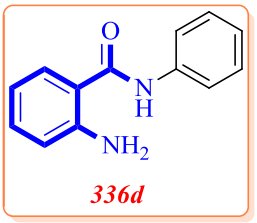
Found: 291.0139

2-Amino-*N*-phenylbenzamide (336d):

Yield: 84 %

Mp: 118 ^{o}C

^{1}H NMR (400 MHz) δ: 7.82 (1H, s, br), 7.59 (2H, d, *J* = 8.0 Hz), 7.50 (1H, d, *J* = 8.0 Hz), 7.39 (2H, t, *J* = 7.6 Hz), 7.28 (1H, t, *J* = 7.6 Hz), 7.17 (1H, t, *J* = 7.2 Hz), 6.74 (2H, d, *J* = 7.6 Hz), 5.51 (2H, s, br)



336d

^{13}C NMR (100 MHz) δ: 167.6, 148.9, 137.8, 132.7, 129.1, 127.2, 124.5, 120.6, 117.6, 116.8, 116.3 (aromatic C)

HRMS (ESI-MS)

Calcd for: $C_{13}H_{12}N_2O$: 213.1028 (M+H)

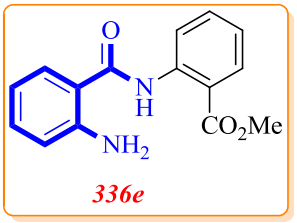
Found: 213.1026

Methyl 2-(2-aminobenzamido)benzoate (336e):

Yield: 47 %

Mp: 112 ^{o}C

^{1}H NMR (400 MHz) δ: 11.84 (1H, s, br), 8.85 (1H, dd, *J* = 0.8 Hz, *J* = 8.8 Hz), 8.10 (1H, dd, *J* = 1.6 Hz, *J* = 8.0 Hz), 7.76 (1H, dd, *J* = 1.2 Hz, *J* = 8.0 Hz), 7.61 (1H, t, *J* = 7.2 Hz), 7.29 (1H, t, *J* = 8.4 Hz), 7.13 (1H, t, *J* = 8.0 Hz), 6.80 (1H, t, *J* = 8.0 Hz), 6.74 (1H, dd, *J* = 0.8 Hz, *J* = 8.4 Hz), 5.80 (2H, s, br), 4.00 (3H, s)



336e

^{13}C NMR (100 MHz) δ: 169.0, 168.2, 149.8, 141.9, 134.6, 132.9, 131.0, 127.7, 122.3, 120.5, 117.5, 116.9, 115.7, 115.3 (aromatic C), 52.5 (aliphatic C)

HRMS (ESI-MS)

Calcd for: $C_{15}H_{14}N_2O_3$: 293.0902 (M+Na)

Found: 293.0907

Compound 337a- 337f:

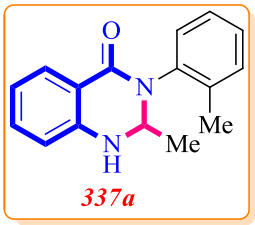
It is probably the steric reason for that these compounds exists as rotamers, the ratio of both isomer is variable depending on the substitution (**337a, 337b, 337c, 337e, 360, 366**).

2-Methyl-3-(o-tolyl)-2,3-dihydroquinazolin-4(1*H*)-one (337a):

Yield: 87 %

Mp: 176-178 ^{o}C

IR (KBr) ν_{max} cm^{-1}: 3296, 1632, 1612, 1506, 1326, 1263, 758



337a

^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.68 (2H, t, *J* = 6.4 Hz), 7.33 (4H, t, *J* = 6.8 Hz), 7.28-7.24 (5H, m), 7.19 (1H, d, *J* = 6.8 Hz), 6.93 (2H, d, *J* = 8.8 Hz), 6.80 (2H, d, *J* = 8.0 Hz), 6.75 (2H, t, *J* = 7.6 Hz), 5.33 (1H, q, *J* = 5.6 Hz), 4.97 (1H, q, *J* = 5.6 Hz), 2.22 (3H, s), 2.17 (3H, s), 1.28 (3H, d, *J* = 5.6 Hz), 1.13 (3H, d, *J* = 5.6 Hz)

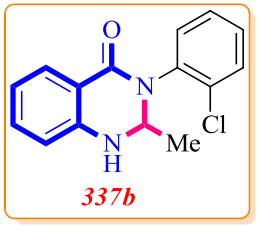
^{13}C NMR (100 MHz, DMSO-d_6) δ: 162.5, 162.2, 148.5, 147.9, 139.43, 139.38, 137.3, 136.0, 133.91, 133.86, 131.3, 130.8, 130.6, 128.5, 128.4, 128.3, 128.2, 127.9, 127.3, 126.8, 118.0, 117.9, 115.9, 115.5, 115.3, 114.9 (aromatic C), 67.9, 67.1, 20.5, 18.6, 17.9 (aliphatic C)

LCMS (m/z): 253$(M+H)^+$

Anal. calcd. for $C_{16}H_{16}N_2O$: C, 76.16; H, 6.39; N, 11.10%

Found: C, 76.31; H, 6.31; N, 11.18%

3-(2-Chlorophenyl)-2-methyl-2,3-dihydroquinazolin-4(1*H*)-one (337b):



337b

Yield: 91 %

Mp: 162 ^{o}C

IR (KBr) ν_{max} cm^{-1}: 3057, 2915, 1687, 1605, 1468, 1282, 1068

^{1}H NMR (400 MHz) δ: 8.00 (1H, d, *J* = 8.0 Hz), 7.54-7.51 (1H, m), 7.41-7.31 (4H, m), 6.92 (1H, t, *J* = 7.6 Hz), 6.74 (1H, d, *J* = 8.0 Hz), 5.31 (1H, q, *J* = 5.2 Hz), 4.59-4.54 (1H, m), 1.38-1.34 (3H, m)

^{13}C NMR (100 MHz) δ: 163.2, 162.7, 146.6, 146.5, 136.8, 134.5, 133.7, 132.9, 132.3, 130.4, 130.3, 129.9, 129.3, 129.2, 127.9, 127.5, 119.6, 116.6, 115.3, 115.1 (aromatic C), 68.4, 66.6, 20.5 (aliphatic C)

LCMS (m/z): 272 $(M+H)^+$

Anal. calcd. for $C_{15}H_{13}ClN_2O$: C, 66.06; H, 4.80; N, 10.27%

Found: C, 66.15; H, 4.73; N, 10.36%

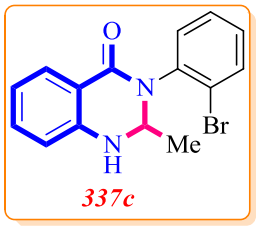
3-(2-Bromophenyl)-2-methyl-2,3-dihydroquinazolin-4(1*H*)-one (337c):

Yield: 93 %

Mp: 120 ^{o}C

IR (KBr) ν_{max} cm^{-1}: 3088, 2349, 1679, 1601, 1567, 1469, 1275, 757

^{1}H NMR (400 MHz) δ: 8.00 (1.2H, dd, *J* = 0.8 Hz, *J* = 7.6 Hz), 7.73-7.69 (1.2H, m), 7.43-7.31 (3.6H, m), 7.27- 7.22 (1.2H, m), 6.94-6.90 (1.33H, m), 6.75- 6.72 (1.29H, m), 5.32 (1.4H, q, *J* = 6.0 Hz), 4.62-4.57 (1.36H, m), 1.37-1.35 (3.6H, m)



337c

^{13}C NMR (100 MHz) δ: 163.0, 162.9, 146.8, 146.5, 139.1, 138.5, 133.75, 133.69, 133.6, 132.4, 129.9, 129.5, 129.3, 129.27, 129.2, 128.6, 128.2, 125.1, 123.2, 119.6, 116.9, 116.6, 115.4, 115.1 (aromatic C), 68.2, 66.7, 20.45, 20.42 (aliphatic C)

HRMS (ESI-MS)

Calcd for: $C_{15}H_{13}{}^{79}BrN_2O$: 339.0109 (M+Na)

Found: 339.0114

Calcd for: $C_{15}H_{13}{}^{81}BrN_2O$: 341.0088 (M+Na)

Found: 341.0099

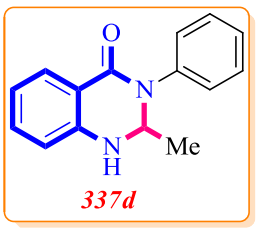
2-Methyl-3-phenyl-2,3-dihydroquinazolin-4(1*H*)-one (337d):

Yield: 96 %

Mp: 168 ^{o}C

IR (KBr) ν_{max} cm^{-1}: 3299, 1634, 1612, 1495, 1263

^{1}H NMR (400 MHz) δ: 8.00 (1H, d, *J* = 8.0 Hz), 7.44 (2H, t, *J* = 8.0 Hz), 7.36-7.29 (4H, m), 6,90 (1H, t, *J* = 7.6 Hz), 6.70 (1H, d, *J* = 8.0 Hz), 5.23 (1H, q, *J* = 6.0 Hz), 4.61 (1H, s, br), 1.42 (3H, d, *J* = 6.0 Hz)



337d

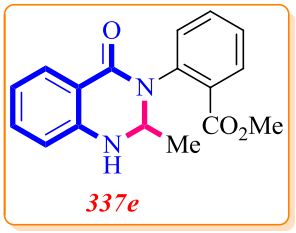
^{13}C NMR (100 MHz, $CDCl_3$ + DMSO- d_6) δ: 162.9, 145.9, 140.2, 133.7, 129.3, 129.1, 127.8, 127.3, 119.4, 116.7, 115.1 (aromatic C), 68.5, 20.9 (aliphatic C)

LCMS (m/z): 239$(M+H)^+$

Anal. calcd. for $C_{15}H_{14}N_2O$: C, 75.61; H, 5.92; N, 11.76%

Found: C, 75.52; H, 6.07; N, 11.65%

Methyl 2-(2-methyl-4-oxo-1,2-dihydroquinazolin-3(4*H*)-yl)benzoate (337e):



337e

Yield: 61 %

Mp: 158 °C

IR (KBr) ν_{max} cm^{-1}: 3304, 2958, 2920, 1726, 1649, 1523, 1260

^{1}H NMR (400 MHz) δ: 8.04 (1H, s, br), 7.98 (1H, d, *J* = 7.6 Hz), 7.61 (1H, t, *J* = 7.6 Hz), 7.45 (1H, t, *J* = 6.8 Hz), 7.36 (2H, d, *J* = 6.8 Hz), 6.93 (1H, t, *J* = 7.6 Hz), 6.76 (1H, d, *J* = 8.0 Hz), 5.41 (1H, d, *J* = 5.2 Hz), 4.51 (1H, s, br), 3.83 (3H, s), 1.3 (3H, s)

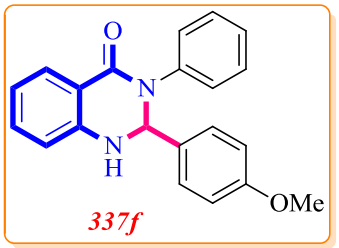
^{13}C NMR (125 MHz) δ: 166.0, 163.8, 146.5, 139.2, 134.6, 133.5, 132.9, 132.3, 132.1, 131.5, 131.0, 129.1, 128.0, 127.7, 122.4, 120.5, 119.8, 117.5, 115.7 (aromatic C), 67.7, 52.3, 20.6 (aliphatic C)

HRMS (ESI-MS)

Calcd for: $C_{17}H_{16}N_2O_3$: 319.1059 (M+Na)

Found: 319.1065

2-(4-Methoxyphenyl)-3-phenyl-2,3-dihydroquinazolin-4(1*H*)-one (337f):



337f

Yield: 84 %

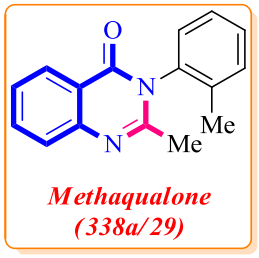
Mp: 194- 196 °C

IR (KBr) ν_{max} cm^{-1}: 3294, 1631, 1610, 1507, 1249, 747

^{1}H NMR (400 MHz) δ:	8.05 (1H, t, *J* = 7.2 Hz), 7.33-7.29 (5H, m), 7.22-7.19 (3H, m), 6.91 (1H, t, *J* = 7.2 Hz), 6.79 (2H, d, *J* = 7.6 Hz), 6.65 (1H, d, *J* = 8.0 Hz), 6.09 (1H, s), 4.77 (1H, s), 3.77 (3H, s)
^{13}C NMR (100 MHz) δ:	163.2, 159.9, 145.5, 140.6, 133.8, 131.9, 129.1, 128.9, 128.2, 127.1, 126.8, 119.5, 116.9, 114.8, 113.9 (aromatic C), 74.3, 55.2 (aliphatic C)
LCMS (m/z):	331$(M+H)^{+}$
Anal. calcd. for $C_{21}H_{18}N_2O_2$:	C, 76.34; H, 5.49; N, 8.48%
Found:	C, 76.25; H, 5.41; N, 8.56%

Methaqualone (338a):

Compound **337a** (0.050g, 1.0 equiv.) was taken in to an oven dried round bottom flask, dry DCM (5mL), DDQ (5.0 equiv.) was added and stirred at rt for 30 mins. After completion of the (checked by TLC) reaction, reaction mixture was extracted with DCM, dried over Na_2SO_4 and evaporated in vacuum. The residue was purified by column chromatography on silica gel (EtOAc: hexanes) to afford a desired product (**338a**). We followed the same procedure for compound **338b- 338**f. later it was also used for compound **342, 345, 361, 330**.



Methaqualone (338a/29)

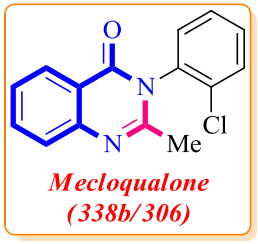
Yield:	89 %
Mp:	112 ^{o}C
IR (KBr) ν_{max} cm^{-1}:	2920, 1678, 1608, 1270, 771
^{1}H NMR (400 MHz) δ:	8.18 (1H, d, *J* = 8.0 Hz), 7.66 (1H, t, *J* = 8.0 Hz), 7.59 (1H, d, *J* = 8.0 Hz), 7.36 (1H, t, *J* = 7.6 Hz), 7.30-7.23 (3H, m), 7.05 (1H, d, *J* = 7.2 Hz), 2.08 (3H, s), 2.02 (3H, s)
^{13}C NMR (100 MHz) δ:	161.0, 153.7, 147.0, 136.2, 134.7, 134.0, 130.9, 128.9, 127.3, 127.0, 126.5, 126.2, 126.0, 120.1 (aromatic C), 23.3, 16.8 (aliphatic C)

HRMS (ESI-MS)

Calcd for: $C_{16}H_{14}N_2O$: 251.1184 (M+Na)

Found: 251.1181

Mecloqualone (338b):



Mecloqualone (338b/306)

Yield: 78 %

Mp: 98-100 ^oC

IR (KBr) ν_{max} cm^{-1}: 2917, 1686, 1607, 1472, 1280

^1H NMR (400 MHz) δ: δ 8.31 (1H, dd, *J* = 1.2 Hz, *J* = 8.0 Hz), 7.83-7.79 (1H, m), 7.72 (1H, d, *J* = 8.0 Hz), 7.66-7.62 (1H, m), 7.52-7.47 (3H, m), 7.38-7.35 (1H, m), 2.25 (3H, s)

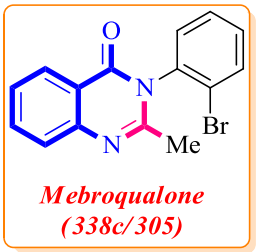
^{13}C NMR (100 MHz) δ: 161.5, 153.7, 147.5, 135.5, 134.8, 132.6, 130.85, 130.81, 129.9, 128.4, 127.2, 126.9, 126.8, 120.6 (aromatic C), 23.6 (aliphatic C)

LCMS (m/z): 271$(M+H)^+$

Anal. calcd. for $C_{15}H_{11}ClN_2O$: C, 66.45; H, 4.10; N, 10.35%

Found: C, 66.42; H, 4.18; N, 10.26%

Mebroqualone (338c):



Mebroqualone (338c/305)

Yield: 81 %

Mp: 144 ^oC

IR (KBr) ν_{max} cm^{-1}: 1685, 1605, 1341, 1282, 774

^1H NMR (400 MHz) δ: 8.31 (2H, d, *J* = 7.6 Hz), 7.81 (1H, t, *J* = 8.0 Hz), 7.72 (1H, d, *J* = 7.6 Hz), 7.57-7.49 (2H, m), 7.42 (1H, t, *J* = 8.0 Hz), 7.38 (1H, d, *J* = 8.0 Hz), 2.25 (3H, s)

^{13}C NMR (100 MHz) δ: 161.4, 153.6, 147.6, 137.2, 134.8, 134.0, 130.9, 129.9, 129.1, 127.2, 126.9, 126.7, 122.9, 120.6 (aromatic C), 23.7 (aliphatic C)

HRMS (ESI-MS)

Calcd for: $C_{15}H_{11}{}^{79}BrN_2O$: 315.0133 (M+H)

Found: 315.0128

Calcd for: $C_{15}H_{11}{}^{81}BrN_2O$: 317.0113 (M+H)

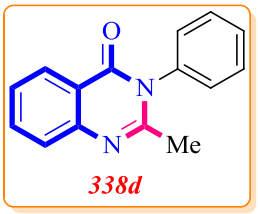
Found: 317.0109

2-Methyl-3-phenylquinazolin-4(3*H*)-one (338d):

Yield: 85 %

Mp: 130-132 ^{o}C

IR (KBr) ν_{max} cm^{-1}: 1682, 1607, 1342, 1274, 769



338d

^{1}H NMR (500 MHz) δ: 8.28 (1H, dd, *J* = 1.0 Hz, *J* = 7.5 Hz), 7.79-7.76 (1H, m), 7.70 (1H, d, *J* = 8.0 Hz), 7.59-7.51 (3H, m), 7.49-7.46 (1H, m), 7.29-7.27 (2H, m), 2.26 (3H, s)

^{13}C NMR (125 MHz) δ: 162.3, 154.3, 147.4, 137.8, 134.6, 130.0, 129.3, 128.0, 127.1, 126.75, 126.7, 120.8 (aromatic C), 24.4 (aliphatic C)

HRMS (ESI-MS)

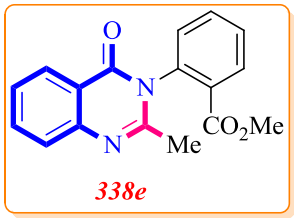
Calcd for: $C_{15}H_{12}N_2O$: 259.0848 (M+Na)

2-Methyl-3-phenylquinazolin-4(3*H*)-one (338e):

Yield: 84 %

Mp: 136 ^{o}C

IR (KBr) ν_{max} cm^{-1}: 1682,1607, 1342, 1274, 769



338e

^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.20 (1H, d, *J* = 8.0 Hz), 8.12 (1H, d, *J* = 7.6 Hz), 7.91 (2H, t, *J* = 8.0 Hz), 7.78-7.73 (2H, m), 7.68 (1H, d, *J* = 7.6 Hz), 7.57 (1H, t, *J* = 8.0 Hz), 3.70 (3H, s), 2.15 (3H, s)

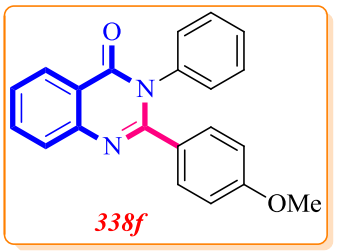
^{13}C NMR (100 MHz, DMSO-d_6) δ: 164.4, 161.3, 154.1, 147.3, 137.7, 134.6, 134.3, 131.3, 130.4, 129.7, 127.3, 126.6, 126.3, 126.2, 120.2 (aromatic C), 52.3, 23.6 (aliphatic C)

HRMS (ESI-MS)

Calcd for: $C_{17}H_{14}N_2O_3$: 317.0902 (M+Na)

Found: 317.0899

2-(4-Methoxyphenyl)-3-phenylquinazolin-4(3*H*)-one (338f):



338f

Yield: 87 %

Mp: 146 °C

IR (KBr) ν_{max} cm^{-1}: 1682, 1606, 1512, 1252, 774

^{1}H NMR (400 MHz) δ: 8.37 (1H, d, *J* = 7.6 Hz), 7.84 (2H, s), 7.56- 7.54 (1H, m), 7.39-7.29 (5H, m), 7.19 (2H, d, *J* = 7.2 Hz), 6.74 (2H, d, *J* = 8.4 Hz), 3.78 (3H, s)

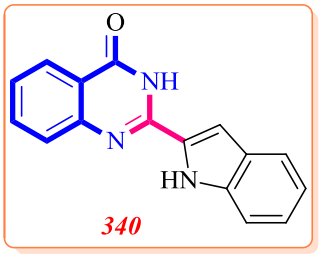
^{13}C NMR (100 MHz) δ: 162.5, 160.3, 154.9, 147.6, 137.9, 134.7, 130.8, 129.1, 129.0, 128.3, 127.8, 127.6, 127.2, 127.0, 120.8, 113.4 (aromatic C), 55.2; (aliphatic C)

LCMS (m/z): 329(M+H)$^+$

Anal. calcd. for $C_{21}H_{16}N_2O_2$: C, 76.81; H, 4.91; N, 8.53%

Found: C, 76.95; H, 5.07; N, 8.45%

2-(1*H*-Indol-2-yl)quinazolin-4(3*H*)-one (340):



340

Yield: 81 %

Mp: 268 °C

IR (KBr) ν_{max} cm^{-1}: 3413, 1665, 1589, 1468, 1260, 772

^{1}H NMR (400 MHz,

DMSO-d_6) δ: 12.62 (1H, s), 11.81 (1H, s), 8.17 (1H, d, *J* = 8.0 Hz); 7.88-7.85 (1H, m), 7.75 (1H, d, *J* = 8.0 Hz), 7.68 (1H, s), 7.65 (1H, d, *J* = 8.0 Hz), 7.54 (2H, t, *J* = 7.2 Hz), 7.24 (1H, t, *J* = 8.4 Hz), 7.07 (1H, t, *J* = 7.2 Hz)

^{13}C NMR (125 MHz,

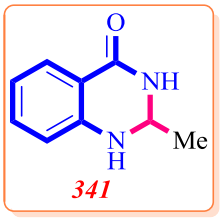
DMSO-d_6) δ: 162.3, 149.2, 147.0, 138.1, 135.2, 130.5, 127.9, 127.4, 126.7, 126.5, 124.5, 122.0, 121.6, 120.4, 112.9, 105.5 (aromatic C)

HRMS (ESI-MS)

Calcd for: $C_{16}H_{11}N_3O$: 262.0980 (M+H)

Found: 262.0980

2-Methyl-2,3-dihydroquinazolin-4(1*H*)-one (341):



341

Yield: 79 %

Mp: 136 ^{o}C

IR (KBr) ν_{max} cm^{-1}: 3266, 1668, 1615, 1257, 753

^{1}H NMR (400 MHz,

DMSO-d_6) δ: 7.90 (1H, s), 7.59 (1H, d, *J* = 8.0 Hz), 7.23 (1H, t, *J* = 8.0 Hz), 6.68 (2H, d, *J* = 8.0 Hz), 6.60 (1H, s), 4.82 (1H, q, *J* = 5.6 Hz), 1.31 (3H, d, *J* = 5.6 Hz)

^{13}C NMR (100 MHz,

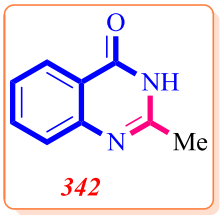
DMSO-d_6) δ: 164.6, 149.2, 133.6, 127.9, 117.6, 115.6, 114.8 (aromatic C), 61.3, 21.7 (aliphatic C)

HRMS (ESI-MS)

Calcd for: $C_9H_{10}N_2O$: 163.0871 (M+H)

Found: 163.0870

2-Methylquinazolin-4(3*H*)-one (342):



342

Yield: 85 %

Mp: 228 °C

IR (KBr) ν_{max} cm^{-1}: 2915, 1693, 1665, 1610, 1468, 1254

^{1}H NMR (400 MHz) δ: 11.81 (1H, s, br), 8.29 (1H, d, *J* = 8.0 Hz), 7.78 (1H, t, *J* = 8.0 Hz), 7.69 (1H, d, *J* = 8.0 Hz), 7.48 (1H, t, *J* = 8.0 Hz), 2.60 (3H, s)

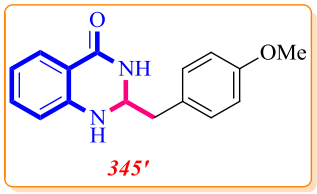
^{13}C NMR (100 MHz) δ: 164.2, 153.2, 149.4, 134.9, 127.0, 126.4, 126.2, 120.3 (aromatic C), 22.1 (aliphatic C)

HRMS (ESI-MS)

Calcd for: $C_9H_8N_2O$: 161.0715 (M+H)

Found: 161.0710

2-(4-Methoxybenzyl)-2,3-dihydroquinazolin-4(1*H*)-one (345'):



345'

Yield: 78 %

Mp: 102 °C

IR (KBr) ν_{max} cm^{-1}: 3380, 2926, 1665, 1605, 1298,1035, 750

^{1}H NMR (500 MHz, DMSO-d_6) δ: 7.79 (1H, s), 7.56 (1H, d, *J* = 7.0 Hz), 7.22 (1H, t, *J* = 7.5 Hz), 7.17 (2H, t, *J* = 8.5 Hz), 6.86 (2H, d, *J* = 8.5 Hz), 6.71 (1H, d, *J* = 6.5 Hz), 6.63 (1H, t, *J* = 7.5 Hz), 6.51 (1H, s, br), 4.91 (1H, t, *J* = 5.5 Hz), 3.72 (3H, s), 2.86 (2H, d, *J* = 4.5 Hz)

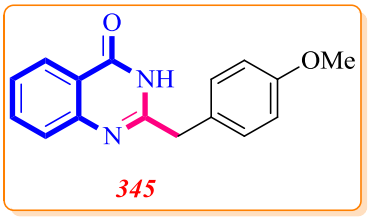
^{13}C NMR (100 MHz, DMSO-d_6) δ: 164.1, 158.4, 148.4, 133.6, 131.5, 128.3, 127.8, 117.3, 115.2, 114.9, 114.1 (aromatic C), 65.8, 55.4, 40.6 (aliphatic C)

HRMS (ESI-MS)

Calcd for: $C_{16}H_{16}N_2O_2$: 269.1290 (M+H)

Found: 269.1293

2-(4-Methoxybenzyl)quinazolin-4(3*H*)-one (345):



345

Yield: 70 % (10h) and 82 % (DDQ)

Mp: 216 ^{o}C

IR (KBr) ν_{max} cm^{-1}: 1679, 1619, 1252, 783

^{1}H NMR (400 MHz,

DMSO-d_6) δ: 12.36 (1H, s), 8.06 (1H, d, *J* = 8.0 Hz), 7.76 (1H, t, *J* = 8.0 Hz), 7.60 (1H, d, *J* = 8.0 Hz), 7.45 (1H, t, *J* = 8.0 Hz), 7.30 (2H, d, *J* = 8.0 Hz), 6.87 (2H, d, *J* = 8.0 Hz), 3.85 (2H, s), 3.70 (3H, s)

^{13}C NMR (100 MHz,

DMSO-d_6) δ: 162.4, 158.6, 156.8, 149.4, 134.9, 130.4, 128.8, 127.3, 126.6, 126.1, 121.1, 114.4 (aromatic C), 55.5, 40.6 (aliphatic C)

HRMS (ESI-MS)

Calcd for: $C_{16}H_{14}N_2O_2$: 267.1134 (M+H)

Found: 267.1136

2-(4-Hydroxybenzyl)quinazolin-4(3*H*)-one (8):

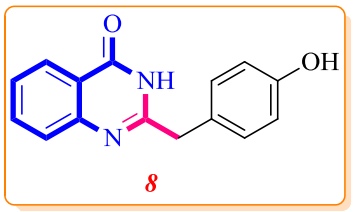
Compound **345** (0.040g, 0.15 mmol) was dissolved in dry dichloromethane (5 mL) and stirred at 0 ^{o}C. Then 0.60 mL of BBr_3 (1.0M in DCM, 0.6mmol) was added dropwise to the mixture maintaining the temperature at 0 ^{o}C. After addition the reaction mixture was brought to rt and kept at same temperature for 3h. The progress of the reaction was monitored with TLC. Upon completion of the reaction water was added slowly to the mixture and stirred for additional 10 mins. Reaction mixture was extracted with DCM, dried over Na_2SO_4 and evaporated in vacuum. The residue was purified by column chromatography on silica gel (EtOAc: hexanes) to afford a desired product (**8**).

Yield: 86 %

Mp: 218 ^{o}C

IR (KBr) ν_{max} cm^{-1}: 3210, 2922, 1679, 1610, 1588, 1434, 1158, 772

^{1}H NMR (500 MHz, DMSO-d_6) δ: 12.35 (1H, s), 9.38 (1H, s), 8.07 (1H, dd, *J* = 1.5 Hz, *J* = 9.0 Hz), 7.77 (1H, t, *J* = 8.5 Hz), 7.61 (1H, d, *J* = 8.0 Hz), 7.46 (1H, t, *J* = 8.0 Hz), 7.18 (2H, d, *J* = 8.5 Hz), 6.70 (2H, d, *J* = 8.5 Hz), 3.80 (2H, s)



8

^{13}C NMR (100 MHz, DMSO-d_6) δ: 161.9, 156.5, 156.2, 148.9, 134.4, 129.9, 126.9, 126.6, 126.2, 125.7, 120.6, 115.3 (aromatic C), 39.9 (aliphatic C)

HRMS (ESI-MS)

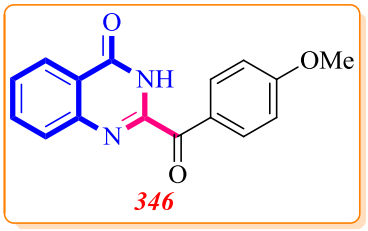
Calcd for: $C_{15}H_{12}N_2O_2$: 253.0977 (M+H)

Found: 253.0975

2-(4-Methoxybenzoyl)quinazolin-4(3*H*)-one (346): To the solution of **345** (0.080g, 0.18 mmol) in nitromethane and dichloromethane (5:1, 6mL), Oxone® (0.165g, 0.54 mmol) and KBr (0.278g, 0.93 mmol) was added at room temperature, and stirred at 50 °C for 24 h. Upon completion of the reaction saturated Na_2SO_3 aqueous solution was added to the reaction mixture, and the product was extracted with ethyl acetate, washed by brine and dried over Na_2SO_4. The organic phase was concentrated under reduced pressure and the crude product purified by column chromatography on silica gel (EtOAc: hexanes) to afford a desired product (**346**) and also we obtained 17 mg un-reacted starting material (**9**). We followed the same procedure for compound **349**.

Yield: 75 %

Mp: 176 ^{o}C



346

IR (KBr) ν_{max} cm^{-1}: 2921, 1691, 1586, 1273, 919, 770

^{1}H NMR (400 MHz) δ: 10.34 (1H, s), 8.66 (2H, d, *J* = 8.0 Hz), 8.41 (1H, d, *J* = 7.2 Hz), 7.95 (1H, d, *J* = 7.2 Hz), 7.87 (1H, t, *J* = 8.0 Hz), 7.66 (1H, t, *J* = 6.8 Hz), 7.05 (2H, d, *J* = 8.0 Hz), 3.95 (3H, s)

^{13}C NMR (100 MHz) δ: 183.3, 164.8, 161.0, 147.6, 146.4, 134.8, 134.6, 129.29, 129.26, 126.8, 123.2, 113.9 (aromatic C), 55.6 (aliphatic C)

HRMS (ESI-MS)

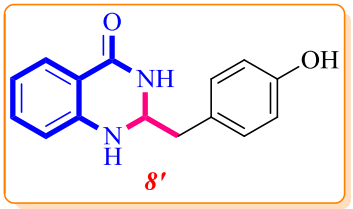
Calcd for: $C_{16}H_{12}N_2O_3$: 281.0926 (M+H)

Found: 281.0928

2-(4-Hydroxybenzyl)-2,3-dihydroquinazolin-4(1*H*)-one (8'):

Yield: 54 %

Mp: 172-174 ^{o}C



8'

IR (KBr) ν_{max} cm^{-1}: 3309, 1638, 1610, 1517, 1227, 843

^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.29 (1H, s), 7.78 (1H,s), 7.55 (1H, d, *J* = 7.6 Hz), 7.22 (1H, t, *J* = 7.6 Hz), 7.03 (2H, d, *J* = 8.0 Hz), 6.73-6.62 (4H, m), 6.49 (1H, s), 4.86 (1H, s), 2.81 (2H, s)

^{13}C NMR (100 MHz, DMSO-d_6) δ: 164.1, 156.4, 148.4, 133.7, 131.3, 127.8, 126.5, 117.3, 115.5, 115.2, 114.9 (aromatic C), 65.8, 40.8 (aliphatic C)

LCMS (m/z): 329(M+H)$^{+}$

Anal. calcd. for $C_{15}H_{14}N_2O_2$: C, 70.85; H, 5.55; N, 11.02%

Found: C, 70.68; H, 5.63; N, 11.21%

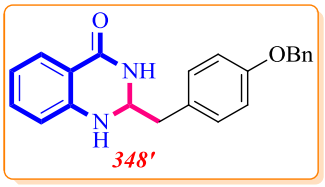
2-(4-(Benzyloxy)benzyl)-2,3-dihydroquinazolin-4(1*H*)-one (348'):

Yield: 80 %

Mp: 124-126 ^{o}C

IR (KBr) ν_{max} cm^{-1}: 2958, 2920, 2849, 1682, 1600, 1506, 1254, 1013

^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.80 (1H, s), 7.54 (1H, d, *J* = 7.6 Hz), 7.41 (2H, t, *J* = 6.8 Hz), 7.36 (2H, d, *J* = 7.6 Hz), 7.31 (1H, d, *J* = 6.8 Hz), 7.21 (1H, d, *J* = 8.0 Hz), 7.16 (2H, d, *J* = 8.4 Hz), 6.92 (2H, d, *J* = 8.4 Hz), 6.70 (1H, d, *J* = 8.0 Hz), 6.62 (1H, t, *J* = 7.6 Hz), 6.52 (1H, s), 5.05 (2H, s), 4.91-4.88 (1H, m), 2.85 (2H, d, *J* = 4.8 Hz)



348'

^{13}C NMR (100 MHz, DMSO-d_6) δ: 164.1, 157.5, 148.4, 137.7, 133.6, 131.5, 128.9, 128.6, 128.2, 128.1, 127.7, 117.3, 115.2, 114.9 (aromatic C), 69.6, 65.7, 40.6 (aliphatic C)

DEPT- 135 (100 MHz, DMSO-d_6) δ: 133.6, 131.5, 128.9, 128.2, 128.1, 127.7, 117.3, 114.9, 69.6, 65.7, 40.6

HRMS (ESI-MS)

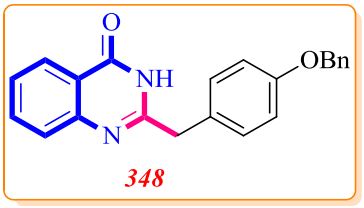
Calcd for: $C_{22}H_{20}N_2O_2$: 345.1603 (M+H)

Found: 345.1601

2-(4-(Benzyloxy)benzyl)quinazolin-4(3*H*)-one (348):

Compound **348'** (0.050g, 1.0 equiv.) was taken in to an oven dried round bottom flask, dry DCM (5mL), DDQ (5.0 equiv.) was added and stirred at rt for 30 mins. After completion of the reaction (checked by TLC), the reaction mixture was extracted with DCM, dried over Na_2SO_4

and evaporated in vacuum. The residue was purified by column chromatography on silica gel (EtOAc: hexanes) to afford a desired product (**348**).



348

Yield: 82 %

Mp: 170-172 ^{o}C

IR (KBr) ν_{max} cm^{-1}: 2886, 1682, 1610, 1264, 1014

^{1}H NMR (400 MHz, DMSO-d_6) δ: 12.35 (1H, s), 8.05 (1H, d, *J* = 8.0 Hz), 7.75 (1H, t, *J* = 8.0 Hz), 7.59 (1H, d, *J* = 8.0 Hz), 7.47-7.34 (5H, m), 7.31-7.28 (3H, m), 6.95 (2H, d, *J* = 8.4 Hz), 5.05 (2H, s), 3.84 (2H, s)

^{13}C NMR (100 MHz, DMSO-d_6) δ: 162.2, 157.8, 151.3, 137.5, 135.0, 130.4, 129.6, 128.9, 128.8, 128.30, 128.26, 128.1, 126.9, 126.7, 126.2, 121.0, 115.3, 114.2, 102.0 (aromatic C), 69.6, 40.1 (aliphatic C)

HRMS (ESI-MS)

Calcd for: $C_{22}H_{18}N_2O_2$: 343.1446 (M+H)

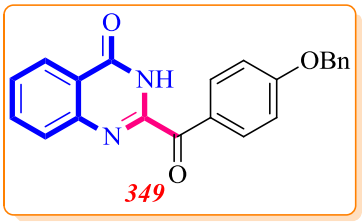
Found: 343.1446

2-(4-(Benzyloxy)benzoyl)quinazolin-4(3*H*)-one (349):

Yield: 73 %

Mp: 174-176 ^{o}C

IR (KBr) ν_{max} cm^{-1}: 3169, 1681, 1656, 1507, 1246, 1164, 736



349

^{1}H NMR (400 MHz) δ: 10.20 (1H, s), 8.66 (2H, d, *J* = 8.0 Hz), 8.41 (1H, d, *J* = 8.0 Hz), 7.95 (1H, d, *J* = 8.0 Hz), 7.88 (1H, t, *J* = 7.6 Hz), 7.66 (1H, t, *J* = 7.6 Hz), 7.49 - 7.38 (5H, m), 7.12 (2H, d, *J* = 8.0 Hz), 5.22 (2H, s)

^{13}C NMR (100 MHz) δ: 183.3, 163.9, 160.8, 147.6, 146.3, 135.9, 134.8, 134.6, 129.32, 129.30, 128.8, 128.4, 127.5, 127.0, 126.8, 123.2, 114.7 (aromatic C), 70.3 (aliphatic C)

HRMS (ESI-MS)

Calcd for: $C_{22}H_{16}N_2O_3$: 357.1239 (M+H)

Found: 357.1239

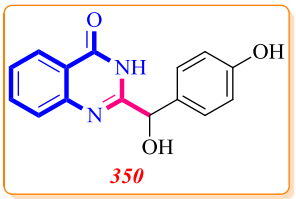
2-(Hydroxy(4-hydroxyphenyl)methyl)quinazolin-4(3*H*)-one (350):

Compound **349** (0.030g, 0.084 mmol) was dissolved in dry ethyl acetate (5 mL) to an oven dried round bottom flask. Next, 10% Pd/C (0.0019 mg, 0.018 mmol) was stirred under an atmosphere of hydrogen gas for 3h. The progress of the reaction was monitored *via* TLC. Upon completion of the reaction the Pd/C was filtered off on celite and the solvent was removed by rotary evaporation. The compound was used further for consecutive steps without column purification.

Yield: 90 %

Mp: 202 ^{o}C

IR (KBr) ν_{max} cm^{-1}: 3234, 2962, 1680, 1648, 1582, 1440, 1009, 787



350

^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.90 (1H, s), 9.41 (1H, s), 8.07 (1H, d, *J* = 6.8 Hz), 7.77 (1H, t, *J* = 7.6 Hz), 7.62 (1H, d, *J* = 7.6 Hz), 7.46 (1H, t, *J* = 8.4 Hz), 7.33 (2H, d, *J* = 6.4 Hz), 6.71 (2H, d, *J* = 6.8 Hz), 6.21 (1H, s), 5.47 (1H, s)

^{13}C NMR (100 MHz, DMSO-d_6) δ: 161.9, 159.2, 157.5, 149.1, 134.9, 131.8, 128.4, 127.5, 126.8, 126.3, 121.6, 115.4 (aromatic C), 73.4 (aliphatic C)

HRMS (ESI-MS)

Calcd for: $C_{15}H_{12}N_2O_3$: 269.0926 (M+H)

Found: 269.0925

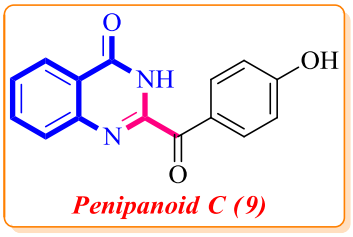
Penipanoid C (351):

To the solution of **350** (0.015g, 0.056 mmol) in dry dichloromethane (3 mL), PCC (0.018g, 0.083 mmol) was added at room temperature, under nitrogen atmosphere and stirred at same temperature for 2h. Upon completion of the reaction, solvent was removed under vacuum and the product was extracted with ethyl acetate, washed by brine and dried over Na_2SO_4. The organic phase was concentrated under reduced pressure and the crude product was purified by silica gel column chromatography.

Yield: 85 %

IR (KBr) ν_{max} cm^{-1}: 3413, 2920, 1693, 1600, 1457, 1282, 1161

^1H NMR (400 MHz, DMSO-d_6) δ: 12.61 (1H, s, br), 10.76 (1H, s, br), 8.21 (1H, d, *J* = 8.0 Hz), 8.08 (2H, d, *J* = 8.5 Hz), 7.89 (1H, t, *J* = 7.0 Hz), 7.78 (1H, d, *J* = 7.5 Hz), 7.64 (1H, t, *J* = 8.0 Hz), 6.93 (2H, d, *J* = 9.0 Hz)



Penipanoid C (9)

^{13}C NMR (100 MHz, DMSO-d_6) δ: 185.1, 163.5, 161.0, 149.9, 147.3, 134.7, 133.7, 133.7, 128.2, 128.2, 126.0, 125.2, 122.6, 115.5, 115.5 (aromatic C)

HRMS (ESI-MS)

Calcd for: $C_{15}H_{10}N_2O_3$: 289.0589 (M+H)

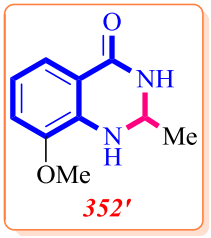
Found: 289.0602

8-Methoxy-2-methyl-2,3-dihydroquinazolin-4(1*H*)-one (352'):

Yield: 87 %

Mp: 154- 156 °C

IR (KBr) ν_{max} cm^{-1}: 3233, 1660, 1616, 1507, 1249, 749



352'

^{1}H NMR (400 MHz) δ: 7.49 (1H, d, *J* = 8.0 Hz), 7.18 (1H, s, br), 6.87 (1H, d, *J* = 8.0 Hz), 6.77 (1H, t, *J* = 8.0 Hz), 5.04 (1H, q, *J* = 5.6 Hz), 4.70 (1H, s, br), 3.84 (3H, s), 1.53 (3H, d, *J* = 5.6 Hz)

^{13}C NMR (100 MHz) δ: 165.8, 146.2, 138.3, 119.9, 118.1, 115.8, 113.4 (aromatic C), 61.6, 55.7, 21.8 (aliphatic C)

HRMS (ESI-MS)

Calcd for: $C_{10}H_{12}N_2O_2$: 215.0796 (M+Na)

Found: 215.0793

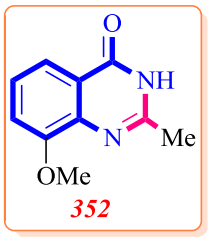
8-Methoxy-2-methylquinazolin-4(3*H*)-one (352):

Compound **352'** (0.050g, 0.260 mmol) was dissolved in dry ethyl acetate (5 mL) to an oven dried round bottom flask. Next, 10% Pd/C (0.041 mg, 0.390 mmol) was added to this solution and stirred at rt for 24 h. The progress of the reaction is slow which has been monitored *via* TLC. Upon completion of the reaction the Pd/C was filtered off on celite and the solvent was removed by rotary evaporation. The compound was used further for consecutive steps without column purification.

Yield: 81 %

Mp: 258 ^{o}C

IR (KBr) ν_{max} cm^{-1}: 1666, 1621, 1482, 1264, 896



352

^{1}H NMR (400 MHz, DMSO-d_6) δ: 12.20 (1H, s), 7.60 (1H, d, *J* = 8.0 Hz), 7.35 (1H, t, *J* = 8.0 Hz), 7.29 (1H, d, *J* = 8.0 Hz), 3.85 (3H, s), 2.32 (3H, s)

^{13}C NMR (100 MHz, DMSO-d_6) δ: 162.1, 154.5, 153.4, 139.9, 126.5, 122.0, 117.1, 115.2 (aromatic C), 56.2, 21.9 (aliphatic C)

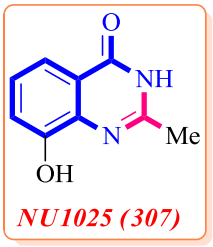
LCMS (m/z): 191(M+H)$^{+}$

Anal. calcd. for $C_{10}H_{10}N_2O_2$: C, 63.15; H, 5.30; N, 14.73%.

Found: C, 63.36; H, 5.35; N, 14.65%

8-Hydroxy-2-methylquinazolin-4(3*H*)-one (NU1025, 307):

Compound **352** (0.030g, 0.157 mmol) was dissolved in dry dichloromethane (3mL) and stirred at 0 ^{o}C. Then 0.63 mL of BBr_3 (1.0M in DCM, 0.628 mmol) was added dropwise to the mixture maintaining the temperature at 0 ^{o}C. After addition the reaction mixture was brought to rt and kept at reflux for 2h. The progress of the reaction was monitored with TLC. Upon completion of the reaction it was cooled to rt and water was added slowly to the mixture and stirred for addition 10 mins. Reaction mixture was extracted with DCM, dried over Na_2SO_4 and evaporated in vacuum. The residue was purified by column chromatography on silica gel (EtOAc: hexanes) to afford a desired product (**307**).



NU1025 (307)

Yield: 73 %

Mp: 246 ^{o}C

IR (KBr) ν_{max} cm^{-1}: 2958, 1669, 1643, 1476, 1264, 702

^{1}H NMR (400 MHz, DMSO-d_6) δ: 12.11 (1H, s, br), 9.43 (1H, s, br), 7.46 (1H, dd, *J* = 1.6 Hz, *J* = 8.0 Hz), 7.22 (1H, t, *J* = 8.0 Hz), 7.11 (1H, dd, *J* = 1.6 Hz, *J* = 8.0 Hz), 2.34 (3H, s)

^{13}C NMR (100 MHz, DMSO-d_6) δ: 161.6, 152.4, 152.0, 137.8, 126.1, 121.2, 118.0, 115.3 (aromatic C), 21.2 (aliphatic C)

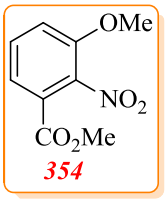
HRMS (ESI-MS)

Calcd for: $C_9H_8N_2O_2$: 177.0664 (M+Na)

Found: 177.0658

Methyl 3-methoxy-2-nitrobenzoate (354):

To a mixture of 3-methoxy-2-nitrobenzoic acid (1.0 g, 5 mmol) and K_2CO_3 (1.4 g, 10 mmol) in DMF (10 mL) was added with MeI (1.0 mL, 15 mmol) at room temperature. The mixture was stirred at room temperature for another 2 hours. Upon completion water was added to the mixture and product was extracted with ethyl acetate, washed by brine and dried over Na_2SO_4. The organic phase was concentrated under reduced pressure and the crude product was used for consecutive reaction without further purification.



354

Yield: 93 %

Mp: 138 ^oC

IR (KBr) ν_{max} cm^{-1}: 1732, 1577, 1535, 1458, 1277, 1055, 874, 745

^1H NMR (500 MHz) δ: 7.64 (1H, d, *J* = 8.0 Hz), 7.54 (1H, t, *J* = 8.0 Hz), 7.31(1H, d, *J* = 8.5 Hz), 3.97 (3H, s), 3.94 (3H, s)

^{13}C NMR (125 MHz) δ: 163.5, 151.0, 140.9, 130.8, 123.7, 122.2, 117.0 (aromatic C), 56.8, 53.0 (aliphatic C)

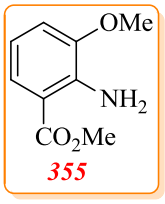
HRMS (ESI-MS)

Calcd for: $C_9H_9NO_5$: 234.0378 (M+Na)

Found: 234.0383

Methyl 3-methoxy-2-nitrobenzoate (355):

Compound **354** (0.900g, 4.2 mmol) was dissolved in dry THF and MeOH mixture (15 mL, 2:1 ratio) to an oven dried round bottom flask. Next, 10% Pd/C (0.151 mg, 1.4 mmol) was stirred under an atmosphere of hydrogen gas for 12h. The progress of the reaction was monitored via TLC. Upon completion of the reaction the Pd/C was filtered off on celite and the solvent was removed by rotary evaporation. The compound was used further for consecutive steps without column purification.



355

Yield: 92 %

Mp: 138 ^oC

IR (KBr) ν_{max} cm^{-1}: 3493, 3375, 1618, 1587, 1474, 1303, 1086, 746

^{1}H NMR (500 MHz) δ: 7.49 (1H, dd, *J* = 1.5 Hz, *J* = 8.5 Hz), 6.86 (1H, dd, *J* = 1.0 Hz, *J* = 7.5 Hz), 6.59 (1H, t, *J* = 8.0 Hz), 3.88 (3H, s), 3.87 (3H, s)

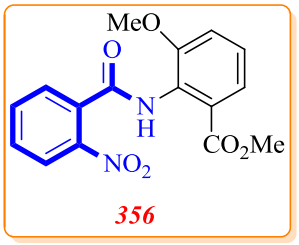
^{13}C NMR (125 MHz) δ: 168.7, 147.1, 141.7, 122.5, 114.6, 112.9, 110.1 (aromatic C), 55.7, 51.4 (aliphatic C)

HRMS (ESI-MS)

Calcd for: $C_9H_{11}NO_3$: 182.0817 (M+H)

Found: 182.0814

Methyl 3-methoxy-2-(2-nitrobenzamido)benzoate (356)



356

Yield: 73 %

Mp: 138- 140 °C

IR (KBr) ν_{max} cm^{-1}: 3313, 2946, 1722, 1680, 1582, 1061, 916

^{1}H NMR (500 MHz) δ: 8.66 (1H, s), 8.06 (1H, d, *J* = 8.0 Hz), 7.79 (1H, d, *J* = 7.5 Hz), 7.72 (1H, t, *J* = 7.5 Hz), 7.61 (1H, t, *J* = 7.5 Hz), 7.51 (1H, d, *J* = 7.5 Hz), 7.28 (1H, t, *J* = 8.0 Hz), 7.16 (1H, d, *J* = 8.0 Hz), 3.94 (3H, s), 3.92 (3H, s)

^{13}C NMR (125 MHz) δ: 167.5, 164.2, 153.5, 146.9, 133.6, 132.8, 130.7, 129.0, 126.5, 125.9, 125.7, 124.5, 122.1, 115.7 (aromatic C), 56.4, 52.5 (aliphatic C)

HRMS (ESI-MS)

Calcd for: $C_{16}H_{14}N_2O_6$: 353.0750 (M+Na)

Found: 353.0752

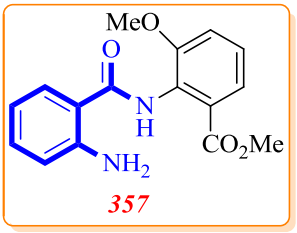
Methyl 2-(2-aminobenzamido)-3-methoxybenzoate (357)

Yield: 97 %

Mp: 132 °C

IR (KBr) ν_{max} cm^{-1}: 3457, 3349, 1717, 1660, 1613, 1505, 921, 751

^{1}H NMR (500 MHz) δ: 8.85 (1H, s, br), 7.68 (1H, d, *J* = 8.0 Hz), 7.50 (1H, d, *J* = 7.5 Hz), 7.26 (1H, d, *J* = 8.0 Hz), 7.22 (1H, t, *J* = 8.0 Hz), 7.13 (1H, d, *J* = 8.5 Hz), 6.74 (1H, t, *J* = 8.0 Hz), 6.70 (1H, d, *J* = 8.5 Hz), 5.60 (2H, s, br), 3.90 (3H, s), 3.85 (3H, s)



357

^{13}C NMR (125 MHz) δ: 167.9, 167.7, 152.7, 149.4, 132.9, 128.3, 126.8, 125.5, 122.0, 117.2, 116.7, 115.6, 114.9 (aromatic C), 56.2, 52.3 (aliphatic C)

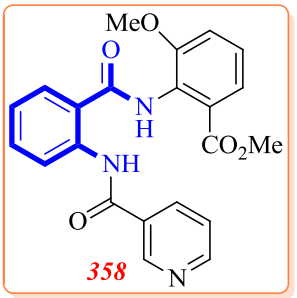
HRMS (ESI-MS)

Calcd for: $C_{16}H_{16}N_2O_4$: 323.1008 (M+Na)

Found: 323.1010

Methyl 3-methoxy-2-(2-(nicotinamido)benzamido)benzoate (358):

To a stirred solution of dry dichloromethane (5-6 mL), compound **357** (0.100 g, 0.27 mmol) and nicotinic acid (0.034 g, 1.0 equiv.) was added under nitrogen atmosphere and stirred at 0 °C for 20 mins. To this mixture, EDCI.HCl (0.159g, 3.0 equiv.) was added maintaining the same temperature and continued for another 2 h, followed by additional 12 h. The reaction mixture was then extracted with DCM. The organic layer was dried over anhydrous Na_2SO_4 and evaporated in vacuum. The residue was purified by column chromatography on silica gel using ethyl acetate/ hexanes mixture to afford the desired compound. We have followed the same procedure for compound **329**.



358

Yield: 61 %

Mp: 166 °C

IR (KBr) ν_{max} cm^{-1}: 3328, 2925, 1721, 1675, 1308, 1065, 750.

^{1}H NMR (500 MHz) δ: 12.16 (1H, s), 9.26 (1H, s, br), 9.21 (1H, s), 8.84 (1H, d, *J* = 8.5 Hz), 8.75 (1H, s, br), 8.28 (1H, d, *J* = 8.0 Hz), 7.93 (1H, d, *J* = 8.0

Hz), 7.62 (1H, t, *J* = 8.0 Hz), 7.57 (1H, d, *J* = 7.5 Hz), 7.42-7.40 (1H, m), 7.33-7.24 (2H, m), 7.20 (1H, d, *J* = 8.5 Hz), 3.91 (3H, s), 3.86 (3H, s)

^{13}C NMR (100 MHz) δ: 167.54, 167.51, 163.7, 153.4, 152.3, 149.0, 139.9, 135.0, 133.3, 127.7, 126.4, 126.2, 125.3, 123.6, 123.4, 122.2, 121.6, 120.5, 115.7 (aromatic C), 56.2, 52.4 (aliphatic C)

HRMS (ESI-MS)

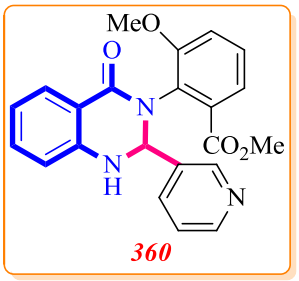
Calcd for: $C_{22}H_{19}N_3O_5$: 428.1222 (M+Na)

Found: 428.1225

Methyl 3-methoxy-2-(4-oxo-2-(pyridin-3-yl)-1,2-dihydroquinazolin-3(4*H*)-yl)benzoate (360)

Yield: 89 %

Mp: 166 ^{o}C



360

IR (KBr) ν_{max} cm^{-1}: 3281, 2935, 1721, 1639, 1613, 1055, 750

^{1}H NMR (400 MHz) δ: 8.58 (1.74H, s), 8.45 (1.93H, s), 8.06 (1.07H, d, *J* = 8.0 Hz), 7.99 (2.19H, d, *J* = 7.6 Hz), 7.81 (1.16H, d, *J* = 7.6 Hz), 7.48 (1.05H, d, *J* = 7.6 Hz), 7.40-7.33 (3.5H, m), 7.24-7.10 (4.55H, m), 6.98-6.84 (4.65H, m), 6.76 (2.29H, t, *J* = 8.0 Hz), 6.50 (1.06H, s), 6.43 (0.97H, s), 4.71 (0.98H, s), 4.58 (1H, s), 3.88 (3H, s), 3.83 (3H, s), 3.77 (3H, s), 3.54 (3H, s)

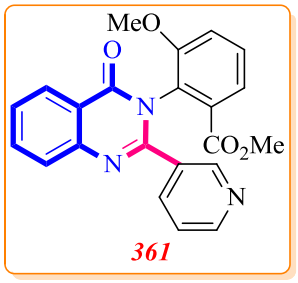
^{13}C NMR (100 MHz) δ: 166.1, 166.0, 163.5, 162.9, 156.2, 155.4, 147.3, 147.0, 136.3, 135.7, 133.6, 133.5, 131.4, 130.4, 129.4, 129.3, 129.1, 129.0, 128.5, 127.8, 127.1, 122.8, 122.78, 122.74, 122.4, 120.1, 119.9, 119.7, 116.8, 116.7, 115.5, 115.0, 114.84, 114.81 (aromatic C), 72.8, 72.0, 55.8, 55.5, 52.5, 52.2 (aliphatic C)

HRMS (ESI-MS)

Calcd for: $C_{22}H_{19}N_3O_4$: 390.1454 (M+H)

Found: 390.1454

Methyl 3-methoxy-2-(4-oxo-2-(pyridin-3-yl)quinazolin-3(4*H*)-yl)benzoate (361)



361

Yield: 91 %

Mp: 130 °C

IR (KBr) ν_{max} cm^{-1}: 2946, 2920, 1716, 1680, 1468, 1349, 946

^{1}H NMR (400 MHz) δ: 8.70 (1H, s, br), 8.49 (1H, s, br), 8.34 (1H, d, *J* = 7.6 Hz), 7.84-7.82 (2H, m), 7.75 (1H, d, *J* = 7.6 Hz), 7.58-7.52 (2H, m), 7.37 (1H, t, *J* = 8.0 Hz), 7.15-7.12 (1H, m), 7.04 (1H, d, *J* = 8.4 Hz), 3.76 (3H, s), 3.75 (3H, s)

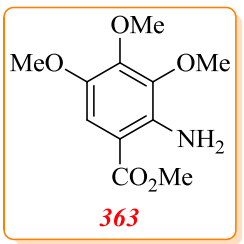
^{13}C NMR (100 MHz) δ: 162.2, 161.6, 154.7, 153.3, 150.2, 148.7, 147.6, 135.4, 134.7, 130.4, 129.5, 127.7, 127.3, 126.2, 122.9, 121.1, 115.8 (aromatic C), 56.0, 52.6 (aliphatic C)

HRMS (ESI-MS)

Calcd for: $C_{22}H_{17}N_3O_4$: 388.1297 (M+H)

Found: 388.1297

Methyl 6-amino-2,3,4-trimethoxybenzoate (363)



363

Yield: 90 %

IR (KBr) ν_{max} cm^{-1}: 3483, 3369, 1691, 1624, 1587, 1226, 1071

^{1}H NMR (500 MHz) δ: 7.14 (1H, s), 5.71 (2H, s, br), 3.95 (3H, s), 3.86 (6H, s), 3.81 (3H, s).

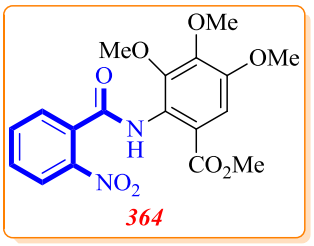
^{13}C NMR (125 MHz) δ: 168.0, 147.4, 143.5, 140.9, 140.3, 108.4, 104.8 (aromatic C), 60.8, 60.3, 56.4, 51.4 (aliphatic C)

HRMS (ESI-MS)

Calcd for: $C_{11}H_{15}NO_5$: 242.1028 (M+H)

Found: 242.1030

Methyl 3,4,5-trimethoxy-2-(2-nitrobenzamido)benzoate (364)



364

Yield: 72 %

Mp: 132 ^{o}C

IR (KBr) ν_{max} cm^{-1}: 3323, 2997, 1722, 1680, 1593, 1298, 787

^{1}H NMR (500 MHz) δ: 8.56 (1H, s), 8.08 (1H, d, *J* = 7.5 Hz), 7.80 (1H, d, *J* = 6.5 Hz), 7.73 (1H, t, *J* = 7.0 Hz), 7.61 (1H, t, *J* = 7.0 Hz), 7.26 (1H, s), 4.02 (3H, s), 3.96 (3H, s), 3.90 (6H, s)

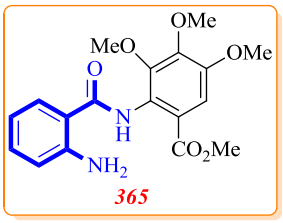
^{13}C NMR (125 MHz) δ: 166.9, 164.9, 151.3, 148.8, 146.7, 146.5, 133.7, 133.0, 130.6, 128.9, 124.7, 124.6, 119.9, 108.6 (aromatic C), 61.2, 61.0, 56.3, 52.5 (aliphatic C)

HRMS (ESI-MS)

Calcd for: $C_{18}H_{18}N_2O_8$: 391.1141 (M+H)

Found: 391.1141

Methyl 2-(2-aminobenzamido)-3,4,5-trimethoxybenzoate (365)



365

Yield: 89 %

Mp: 132 ^{o}C

IR (KBr) ν_{max} cm^{-1}: 3467, 2940, 1711, 1618, 1029, 750

^{1}H NMR (400 MHz) δ: 8.93 (1H, s), 7.68 (1H, dd, *J* = 1.2 Hz, *J* = 8.0 Hz), 7.26 (2H, s), 6.74-6.69 (2H, m), 5.60 (2H, s, br), 3.97 (3H, s), 3.91 (3H, s), 3.90 (3H, s), 3.84 (3H, s)

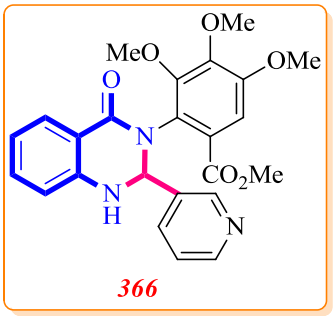
^{13}C NMR (100 MHz) δ: 168.0, 167.3, 150.6, 149.5, 148.2, 146.4, 132.8, 128.2, 126.3, 119.1, 117.3, 116.7, 115.4, 108.5 (aromatic C), 61.0, 60.9, 56.3, 52.3 (aliphatic C)

HRMS (ESI-MS)

Calcd for: $C_{18}H_{20}N_2O_6$: 383.1219 (M+Na)

Found: 383.1215

Methyl 3,4,5-trimethoxy-2-(4-oxo-2-(pyridin-3-yl)-1,2-dihydroquinazolin-3(*4H*)-yl)benzoate (366)



366

Yield: 88 %

Mp: 144-146 ^oC

IR (KBr) ν_{max} cm^{-1}: 3276, 1717, 1644, 1463, 1112, 766

^1H NMR (400 MHz) δ: 8.62 (1H, s), 8.46 (1H, s), 8.42 (2.35H, d, *J* = 4.0 Hz), 7.96 (3.38H, d, *J* = 8.0 Hz), 7.92 (1.14H, d, *J* = 8.0 Hz), 7.38-7.33 (2.33H, m), 7.20 (1.24H, s), 7.15-7.08 (3.42H, m), 6.93 (2.34H, t, *J* = 7.2 Hz), 6.75- 6.73 (2.27H, m), 6.41 (2.19H, d, *J* = 2.4 Hz), 6.75-6.73 (2.27H, m), 6.41 (2.19H, d, *J* = 2.4 Hz), 4.81 (2H, s), 3.86- 3.85 (6H, m), 3.82 (3H, s), 3.80 (3H, s), 3.76 (3H, s), 3.70 (3H, s), 3.68 (3H, s), 3.64 (3H, s)

^{13}C NMR (100 MHz) δ: 165.4, 165.2, 164.0, 163.7, 152.4, 152.1, 151.1, 150.6, 150.5, 150.3, 149.8, 147.4, 147.3, 146.2, 145.8, 136.2, 133.7, 133.6, 133.2, 132.9, 129.3, 129.2, 127.1, 126.7, 124.9, 124.1, 123.0, 119.8, 116.8, 116.5, 114.8, 109.4, 109.3 (aromatic C), 72.9, 72.3, 61.4, 61.1, 60.9, 56.03, 56.00, 52.5, 52.2 (aliphatic C)

HRMS (ESI-MS)

Calcd for: $C_{24}H_{23}N_3O_6$: 450.1665 (M+H)

Found: 450.1668

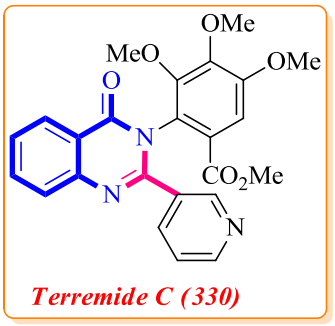
Methyl 3,4,5-trimethoxy-2-(4-oxo-2-(pyridin-3-yl)quinazolin-3(*4H*)-yl)benzoate (330)

Yield: 91 %

Mp: 124-126 ^{o}C

IR (KBr) ν_{max} cm^{-1}: 2987,1722, 1680, 1334, 1097, 911, 787

^{1}H NMR (400 MHz) δ: 8.67 (1H, s, br), 8.48 (1H, d, *J* = 4.0 Hz), 8.34 (1H, d, *J* = 8.0 Hz), 7.82 (2H, d, *J* = 3.6 Hz), 7.78-7.76 (1H, m), 7.55- 7.51 (1H, m), 7.26 (1H, s), 7.15-7.12 (1H, m), 3.86 (3H, s), 3.81 (3H, s), 3.78 (3H, s), 3.71 (3H, s)



Terremide C (330)

^{13}C NMR (100 MHz) δ: 165.0, 162.5, 154.0, 153.9, 150.6, 150.1, 149.2, 148.0, 146.6, 135.9, 135.2, 132.1, 128.2, 127.6, 125.7, 123.4, 122.8, 121.3, 109.8 (aromatic C), 61.8, 61.3, 56.5, 52.9 (aliphatic C)

HRMS (ESI-MS)

Calcd for: $C_{24}H_{21}N_3O_6$: 448.1509 (M+H)

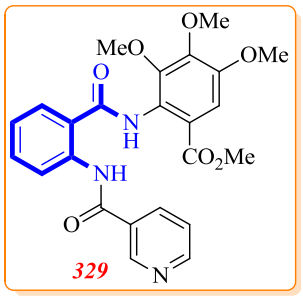
Found: 448.1510

Methyl 3,4,5-trimethoxy-2-(2-(nicotinamido)benzamido)benzoate (329)

Yield: 58 %

Mp: 126 ^{o}C

IR (KBr) ν_{max} cm^{-1}: 3318, 2946, 1717, 1680, 1443, 1236, 921



329

^{1}H NMR (400 MHz) δ: 12.27 (1H, s, br), 9.27 (1H, s), 9.25 (1H, s, br), 8.87 (1H, d, *J* = 8.5 Hz), 8.73 (1H, s, br), 8.28 (1H, d, *J* = 8.0 Hz), 7.93 (1H, dd, *J* = 1.5 Hz, *J* = 8.0 Hz),7.62 (1H, t, *J* = 8.5 Hz), 7.41-7.38 (1H, m), 7.30 (1H, s), 7.25 (1H, t, *J* = 8.5 Hz), 4.00 (3H, s), 3.934 (3H, s), 3.930 (3H, s), 3.85 (3H, s)

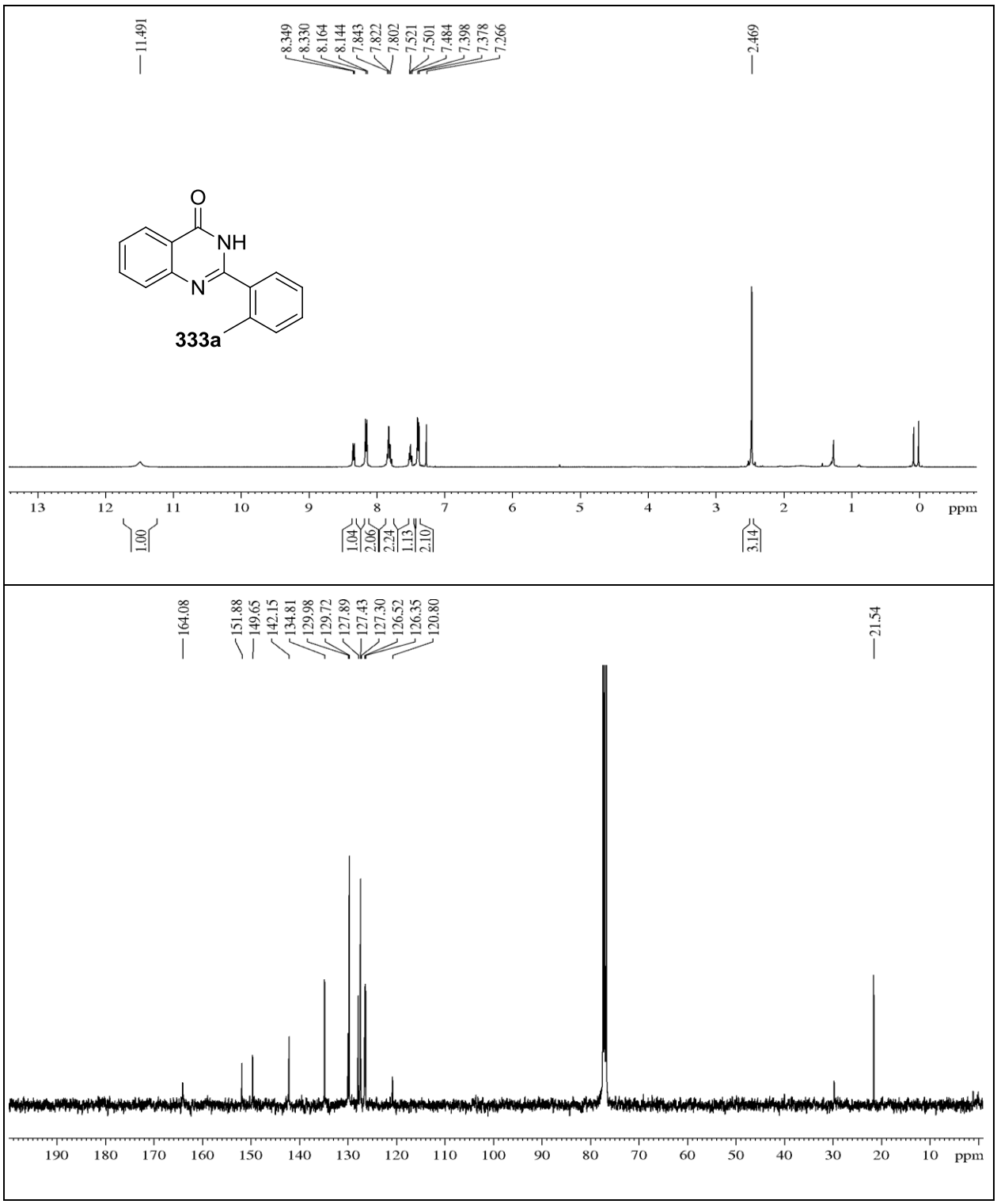
^{13}C NMR (100 MHz) δ: 168.0, 166.9, 163.8, 152.3, 151.3, 149.0, 148.7, 146.7, 140.2, 135.0, 133.4, 130.5, 127.7, 125.5, 123.6, 123.4, 121.6, 120.2, 118.9, 108.6 (aromatic C), 61.1, 56.3, 52.4 (aliphatic C)

HRMS (ESI-MS)

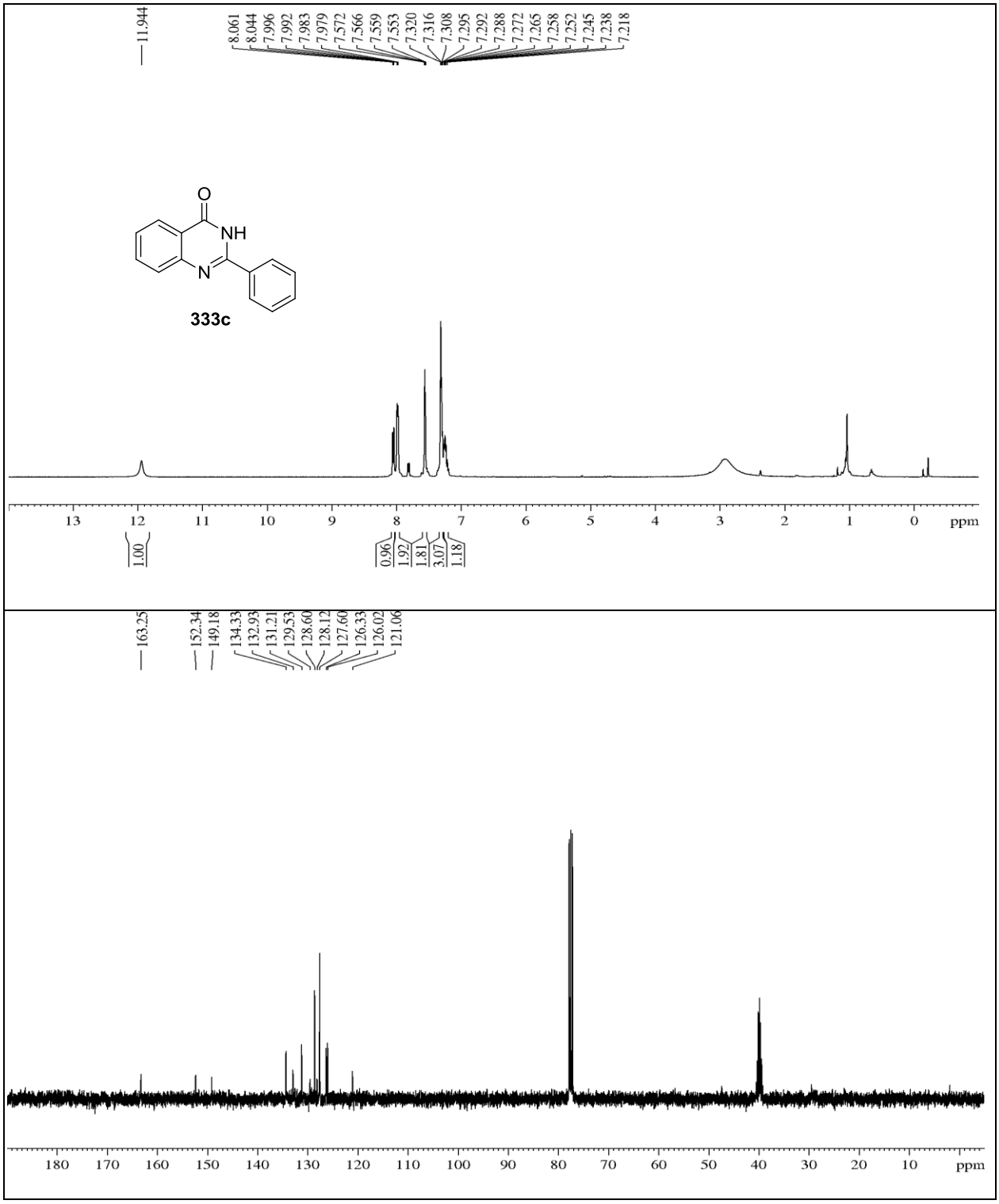
Calcd for: $C_{24}H_{23}N_3O_7$: 488.1434 (M+Na)

Found: 488.1434

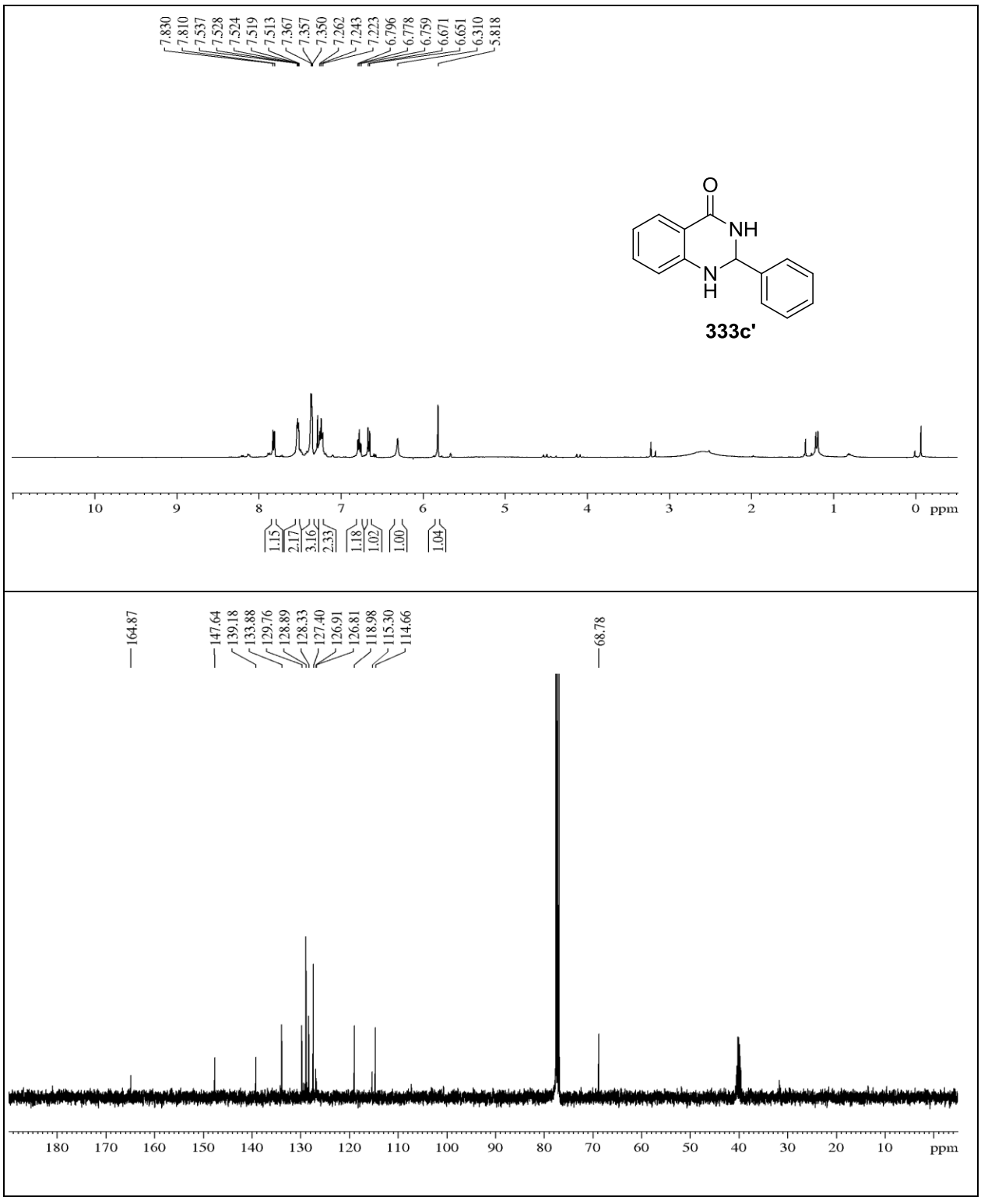
^{1}H, ^{13}C NMR of compound 333a



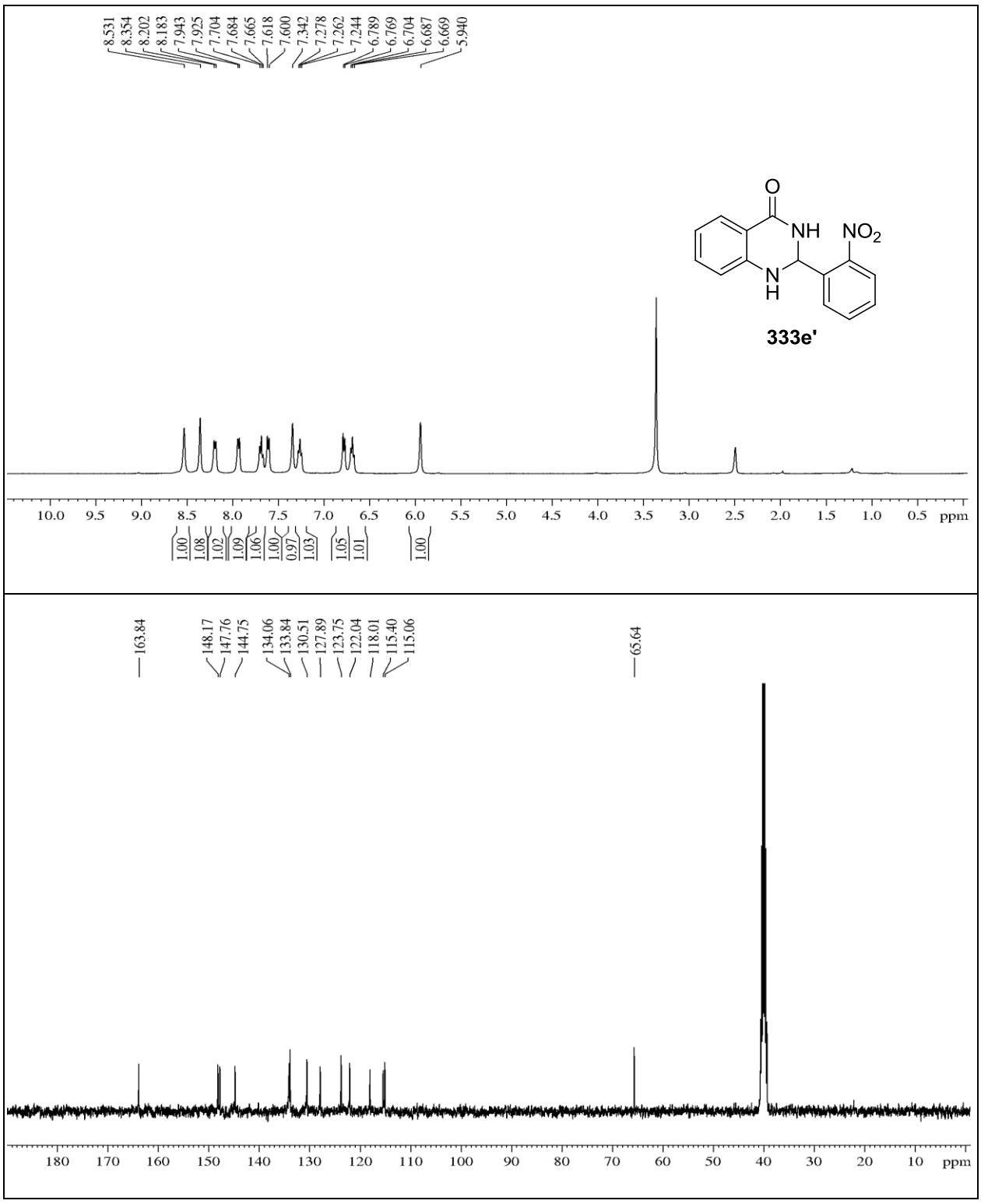
^{1}H, ^{13}C NMR of compound 333c



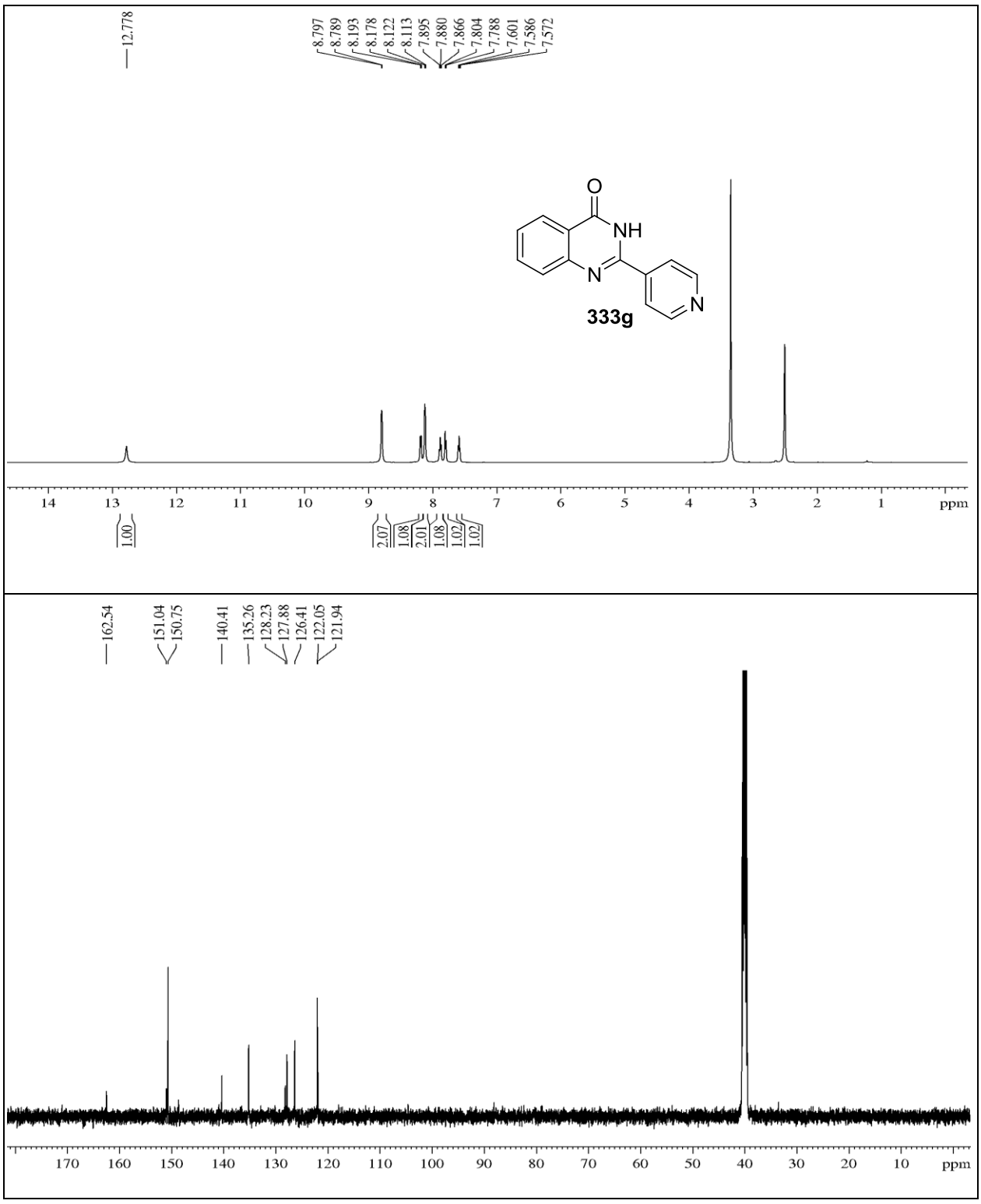
^{1}H, ^{13}C NMR of compound 333c'



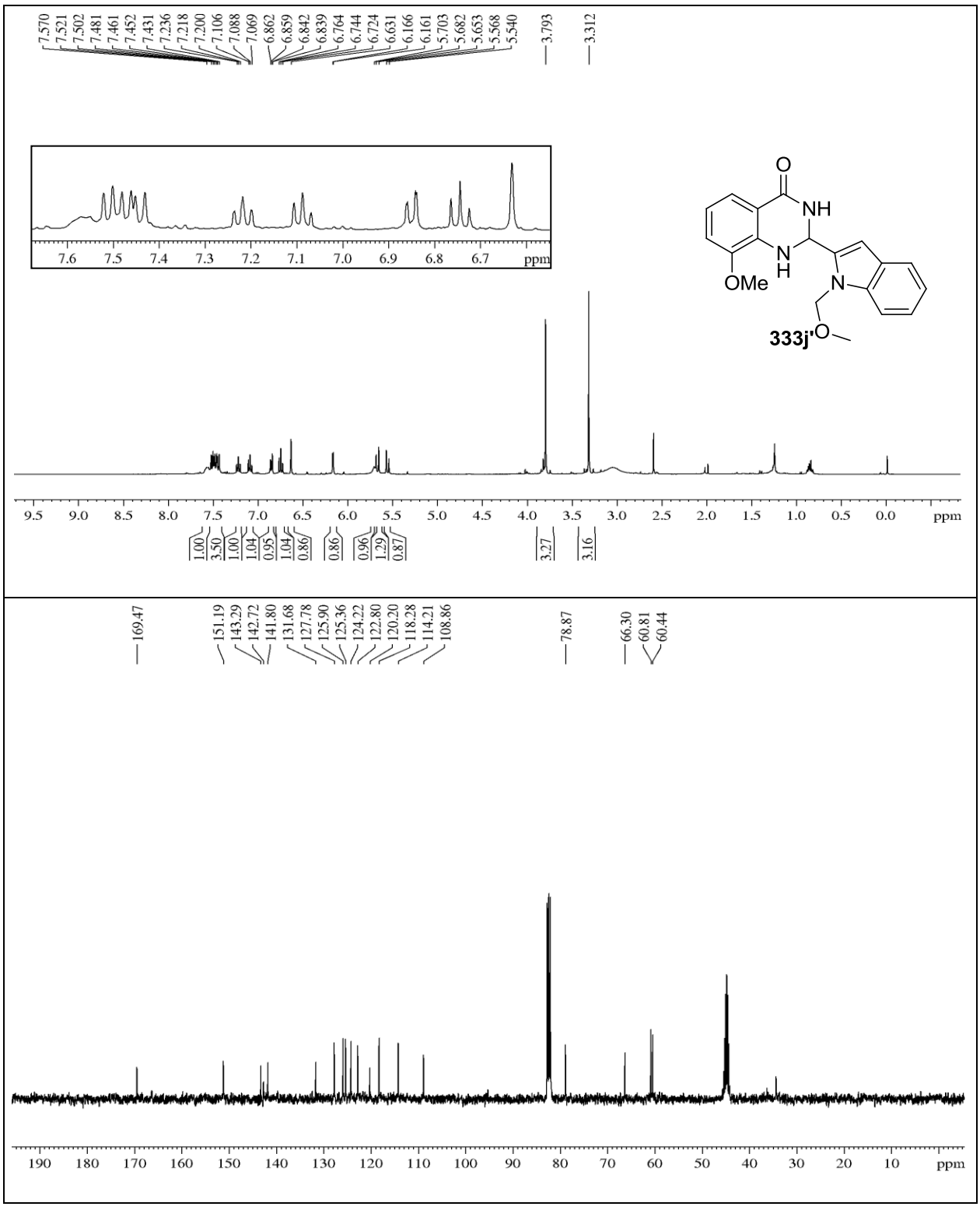
^{1}H, ^{13}C NMR of compound 333e'



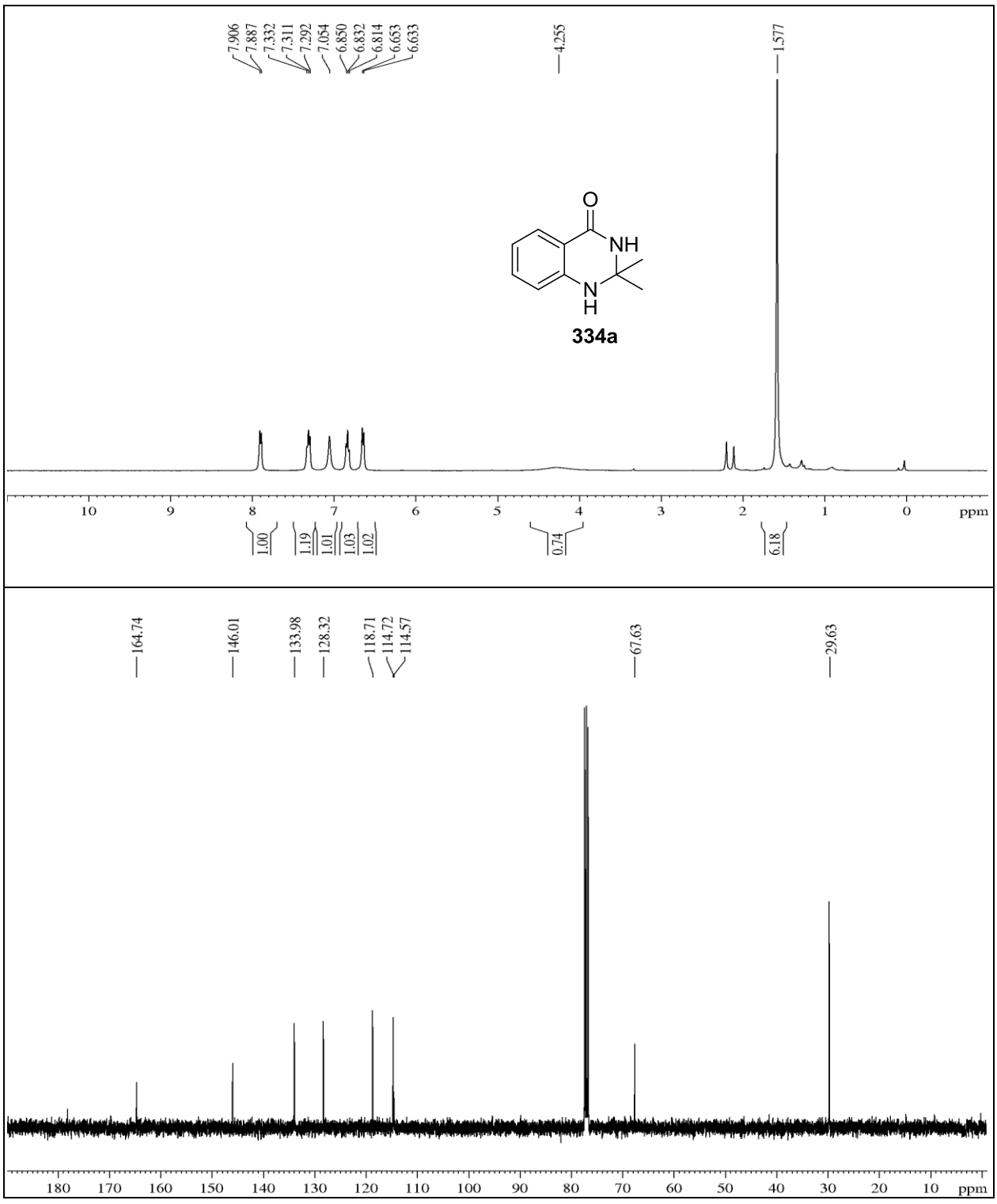
^{1}H, ^{13}C NMR of compound 333g



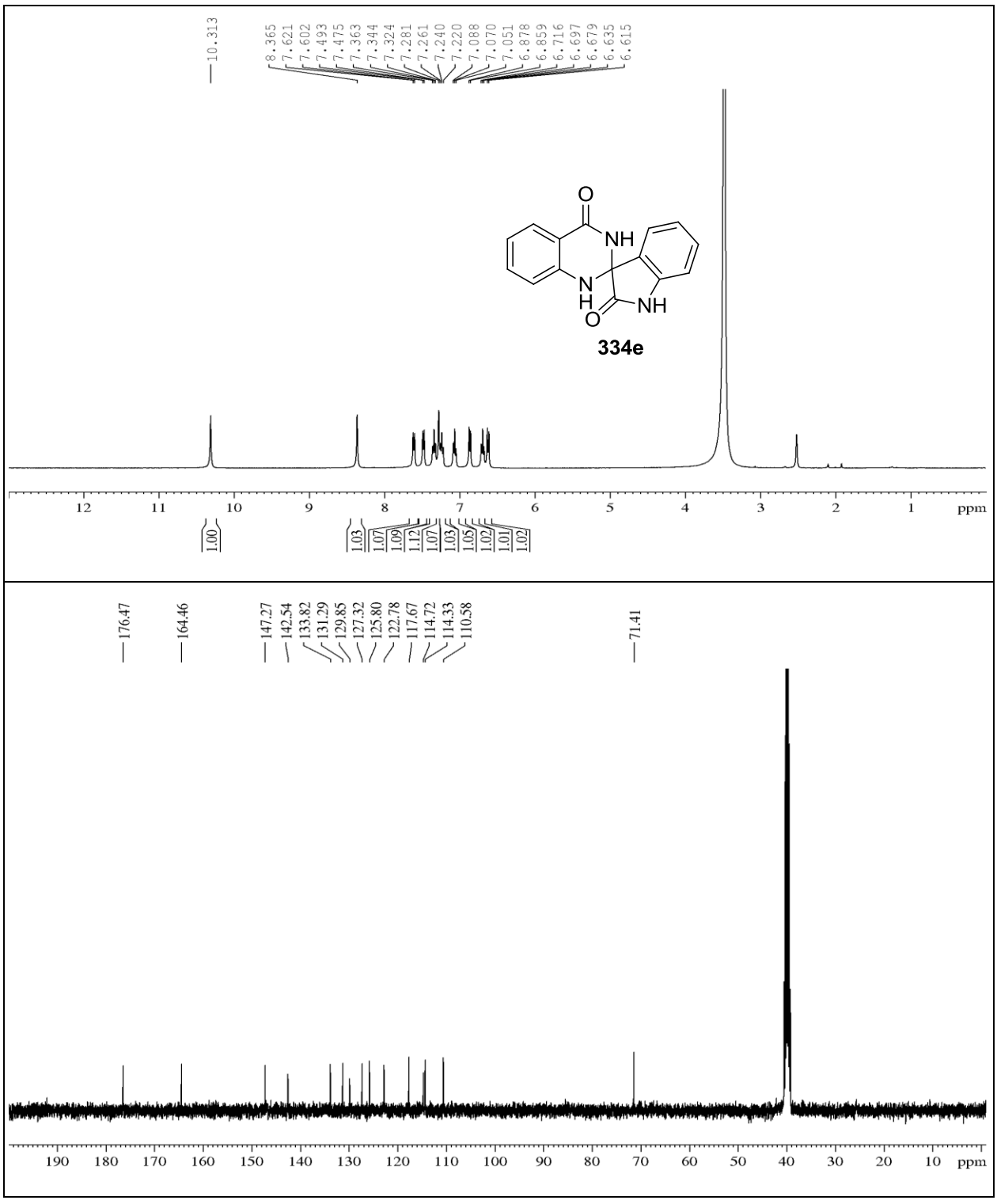
^{1}H, ^{13}C NMR of compound 333j'



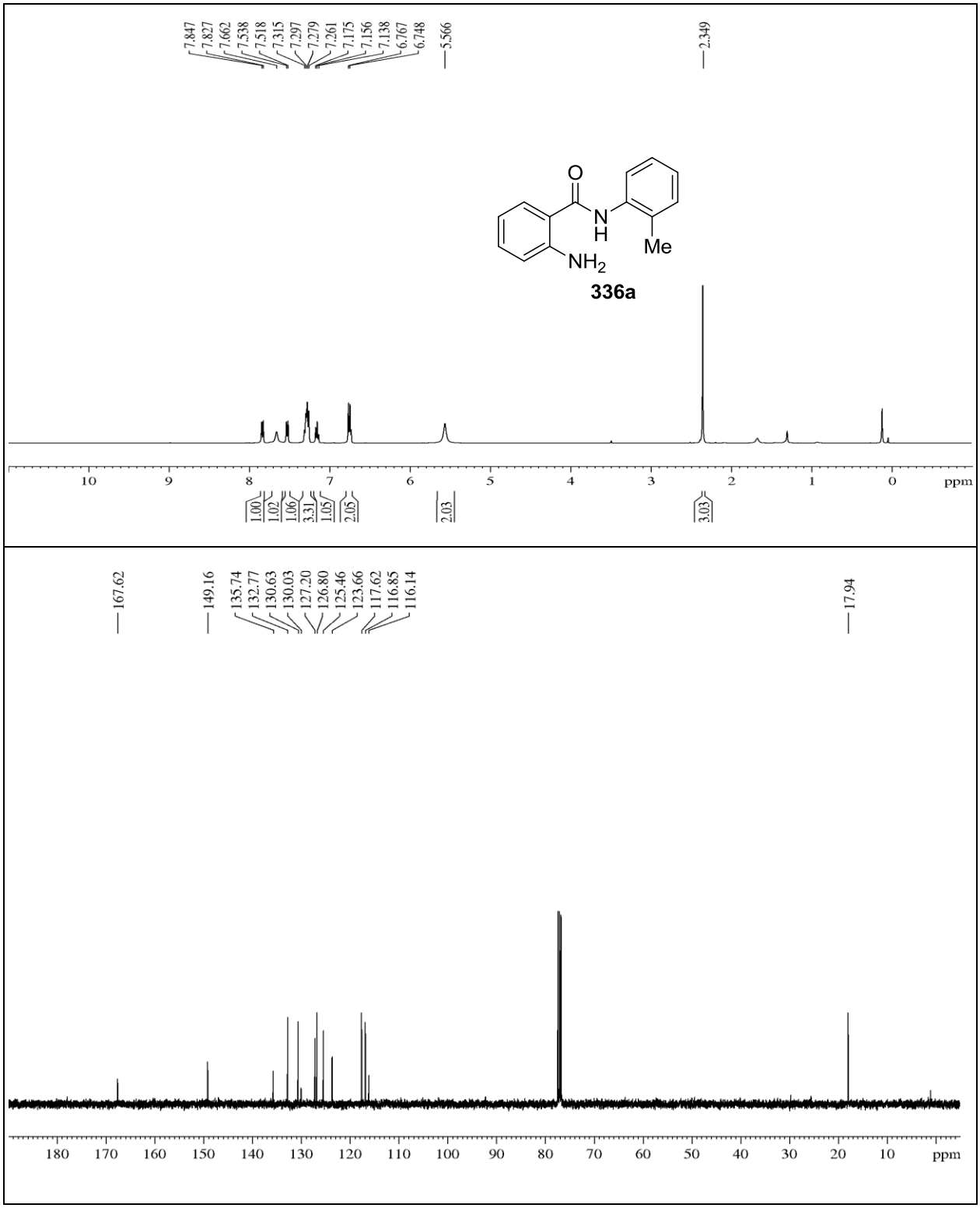
^{1}H, ^{13}C NMR of compound 334a



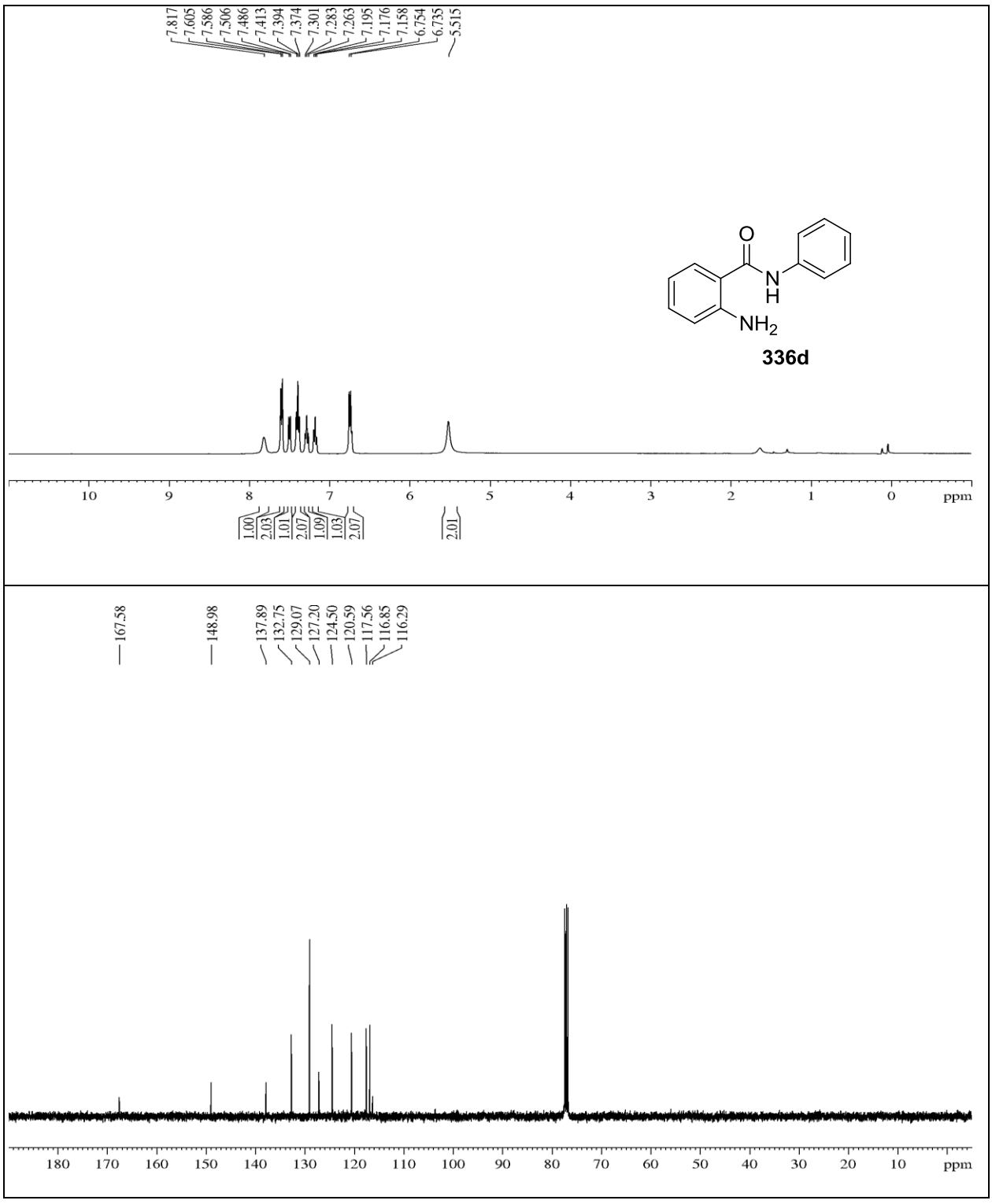
^{1}H, ^{13}C NMR of compound 334e



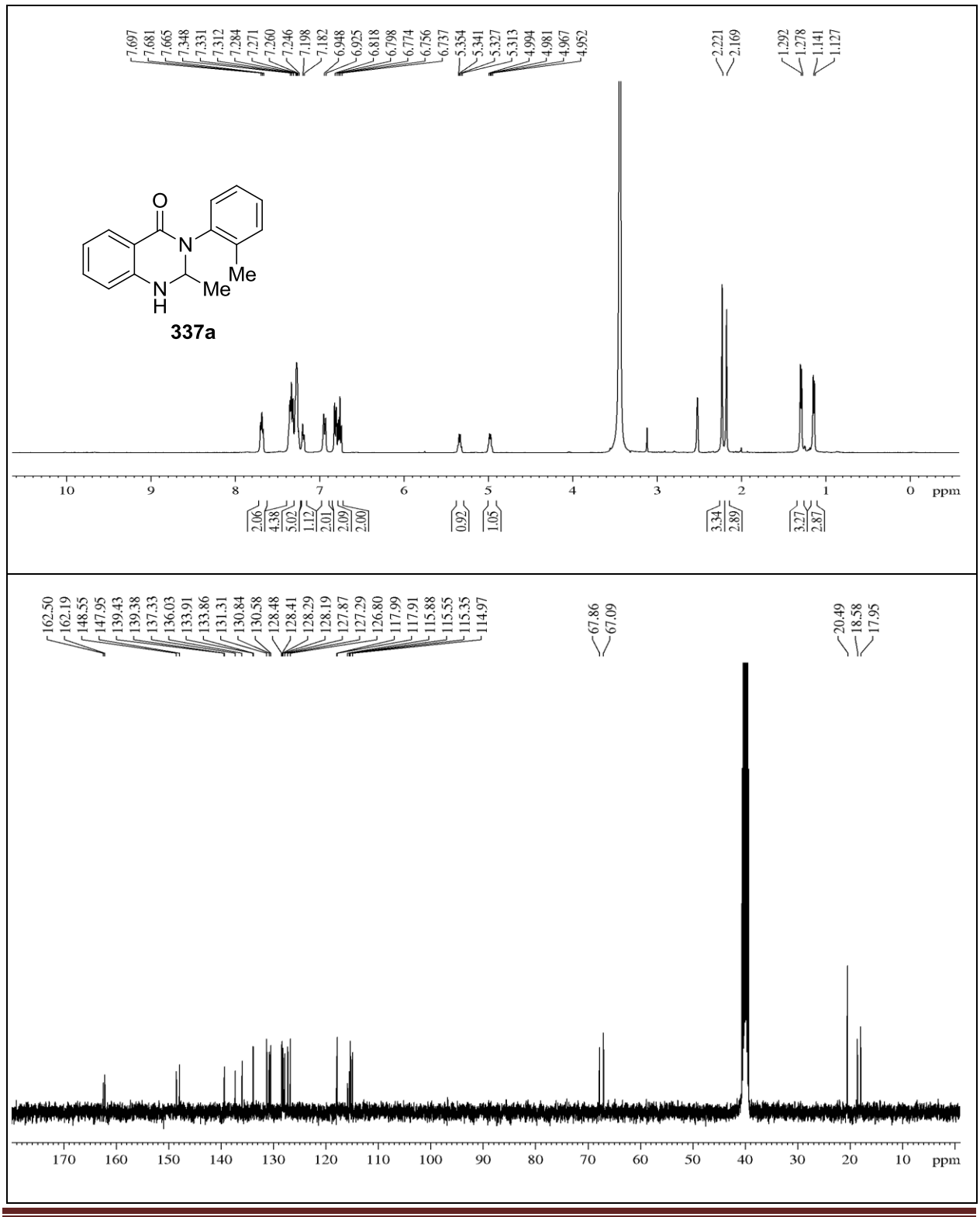
^{1}H, ^{13}C NMR of compound 336a



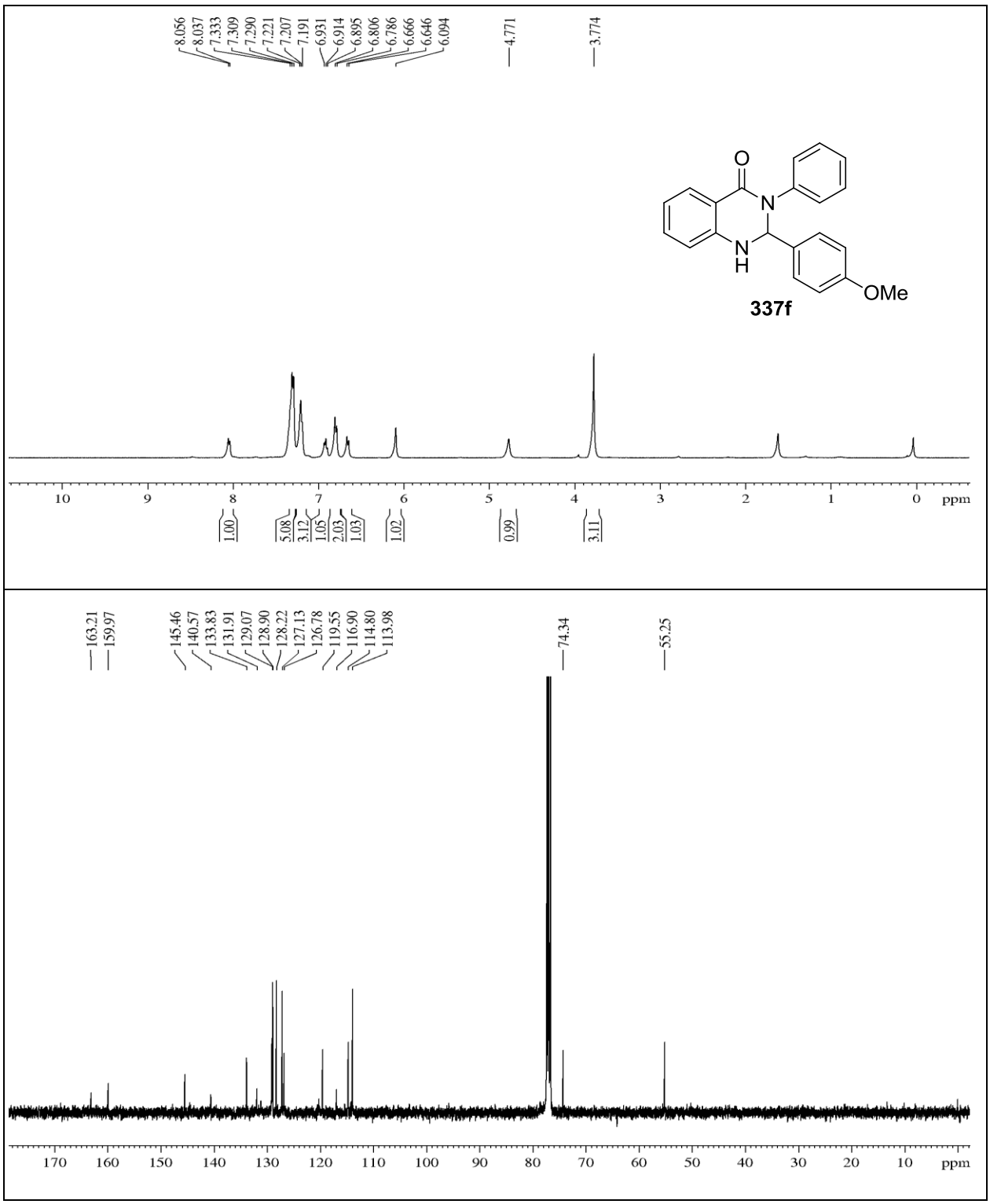
^{1}H, ^{13}C NMR of compound 336d



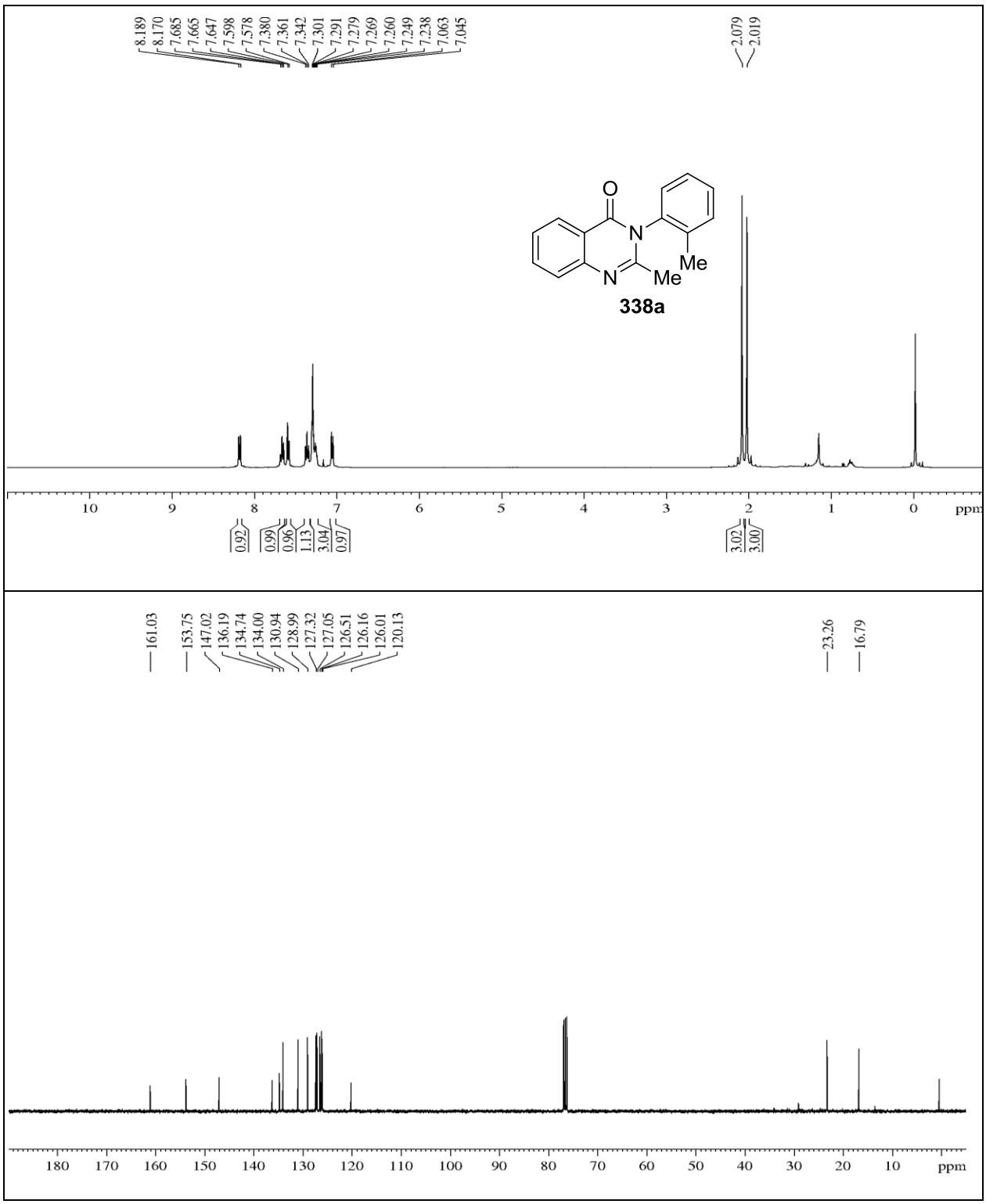
^{1}H, ^{13}C NMR of compound 337a



^{1}H, ^{13}C NMR of compound 337f



^{1}H, ^{13}C NMR of compound 338a



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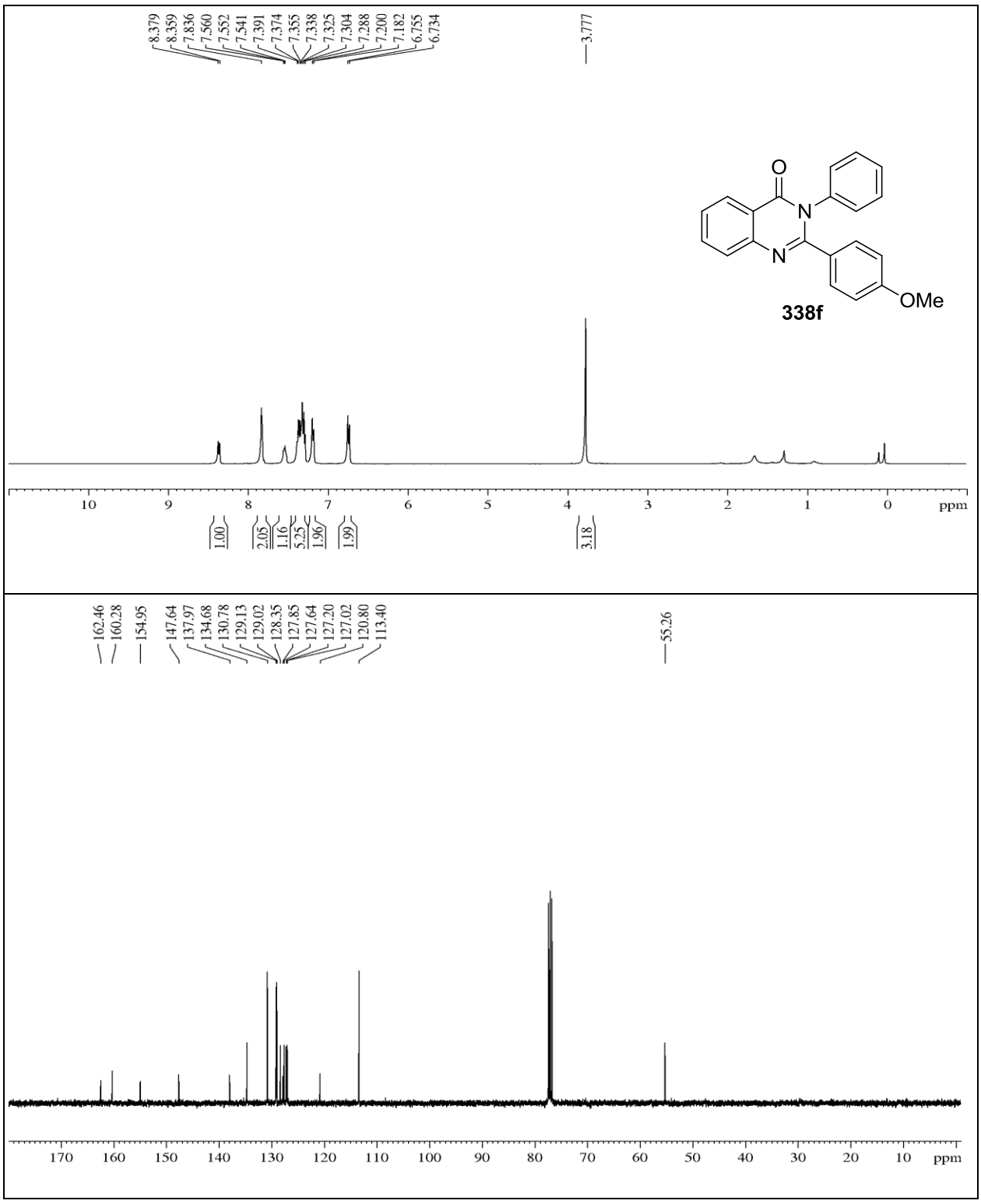
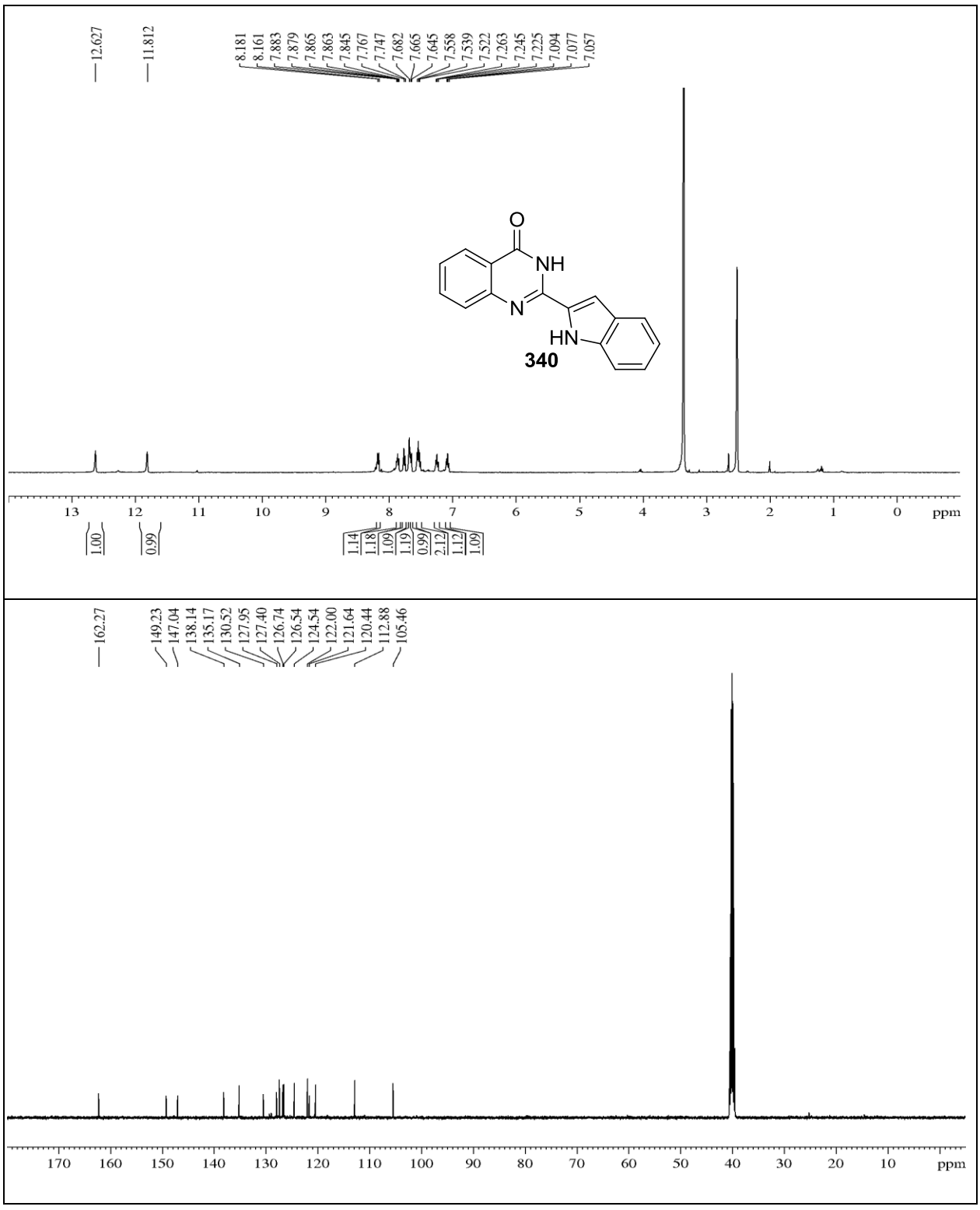
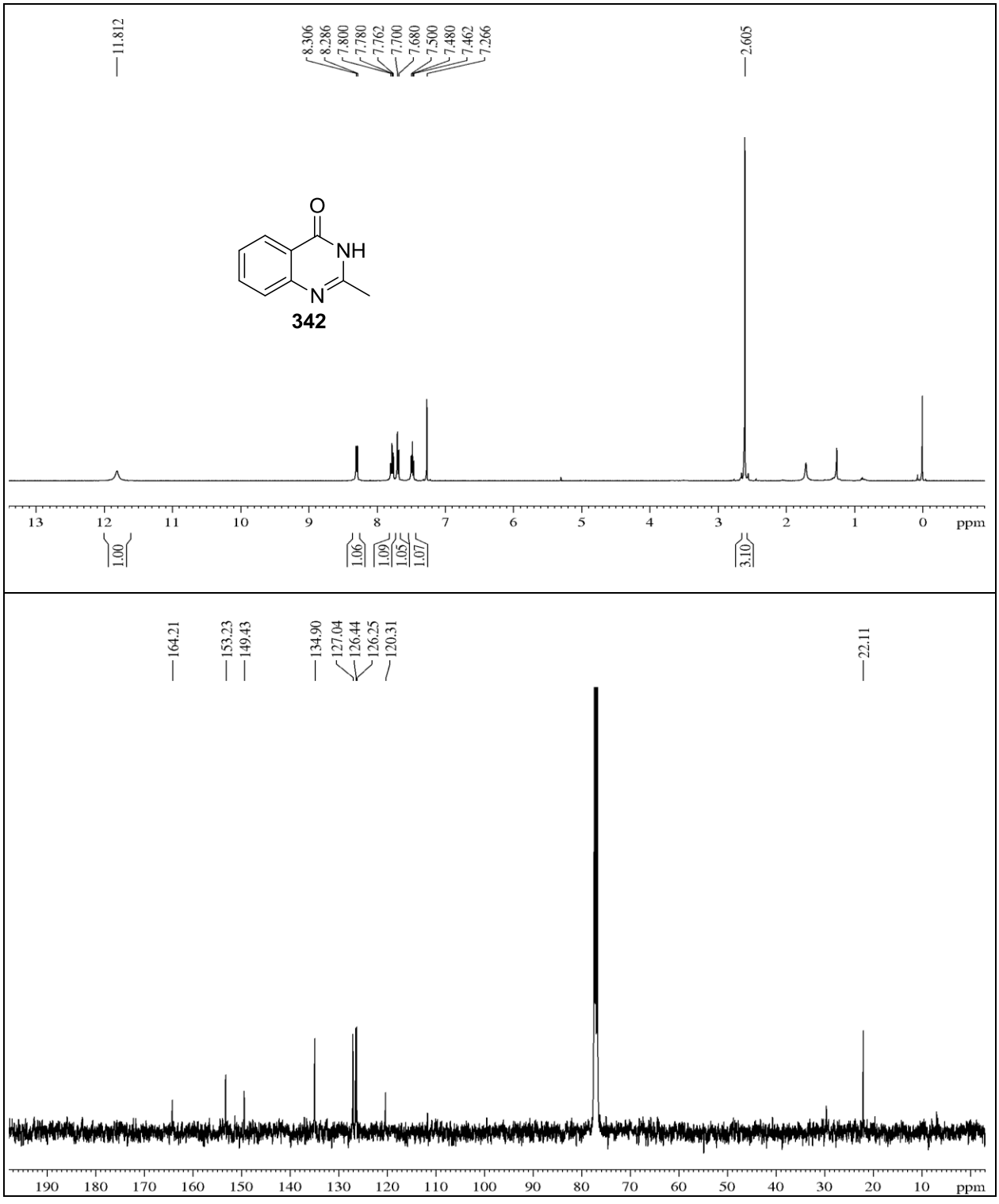


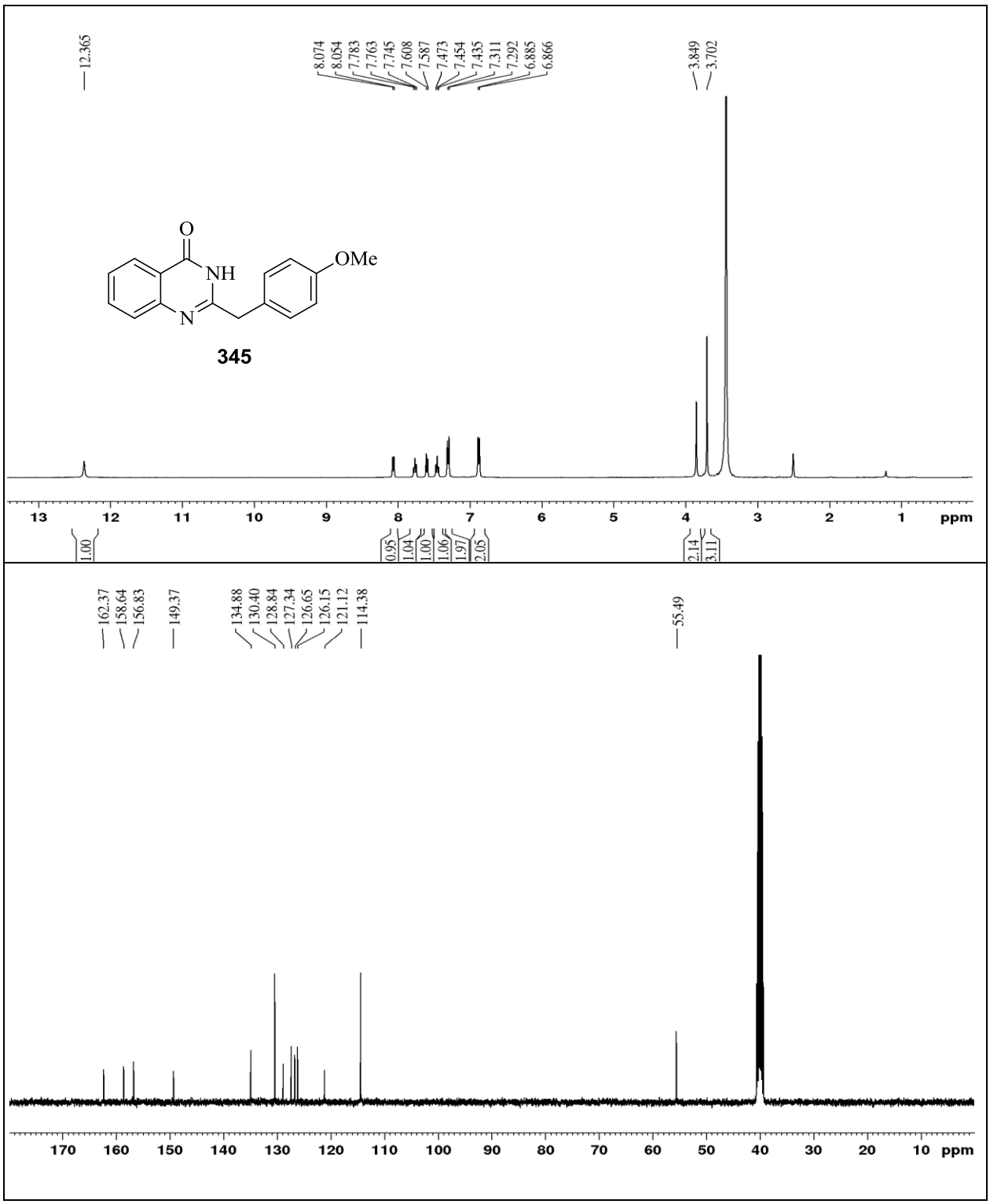
^{1}H, ^{13}C NMR of compound 340



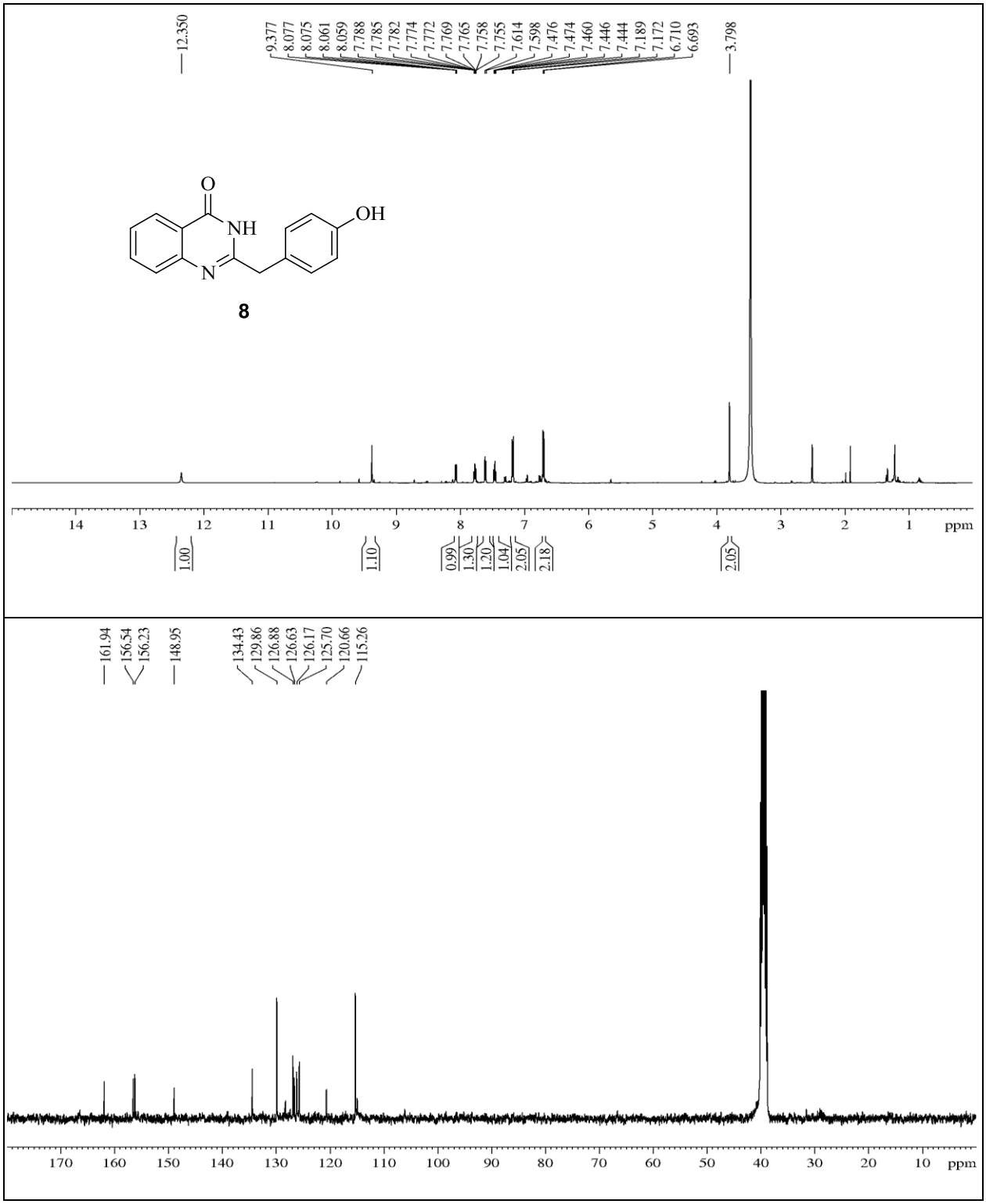
^{1}H, ^{13}C NMR of compound 342



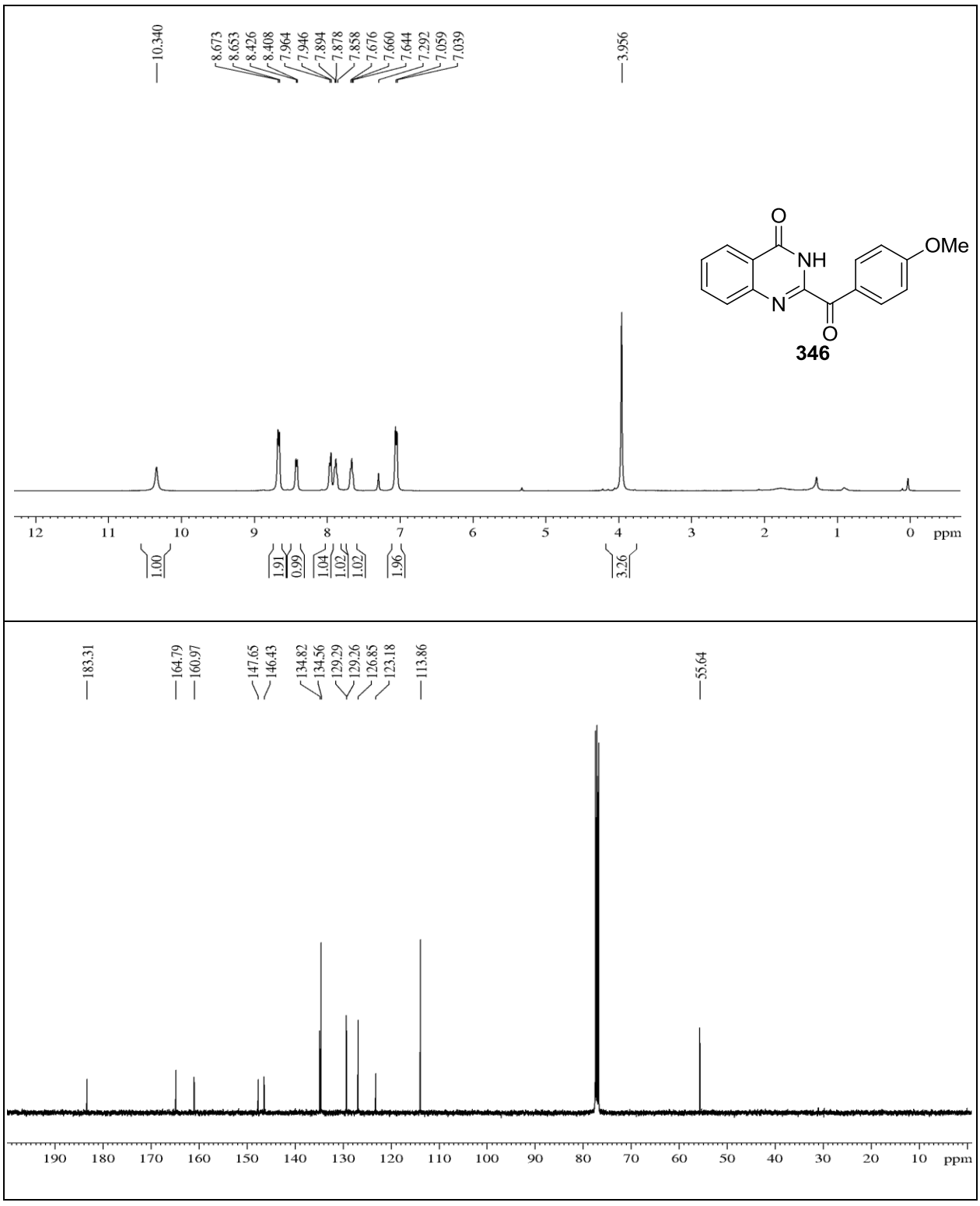
^{1}H, ^{13}C NMR of compound 345



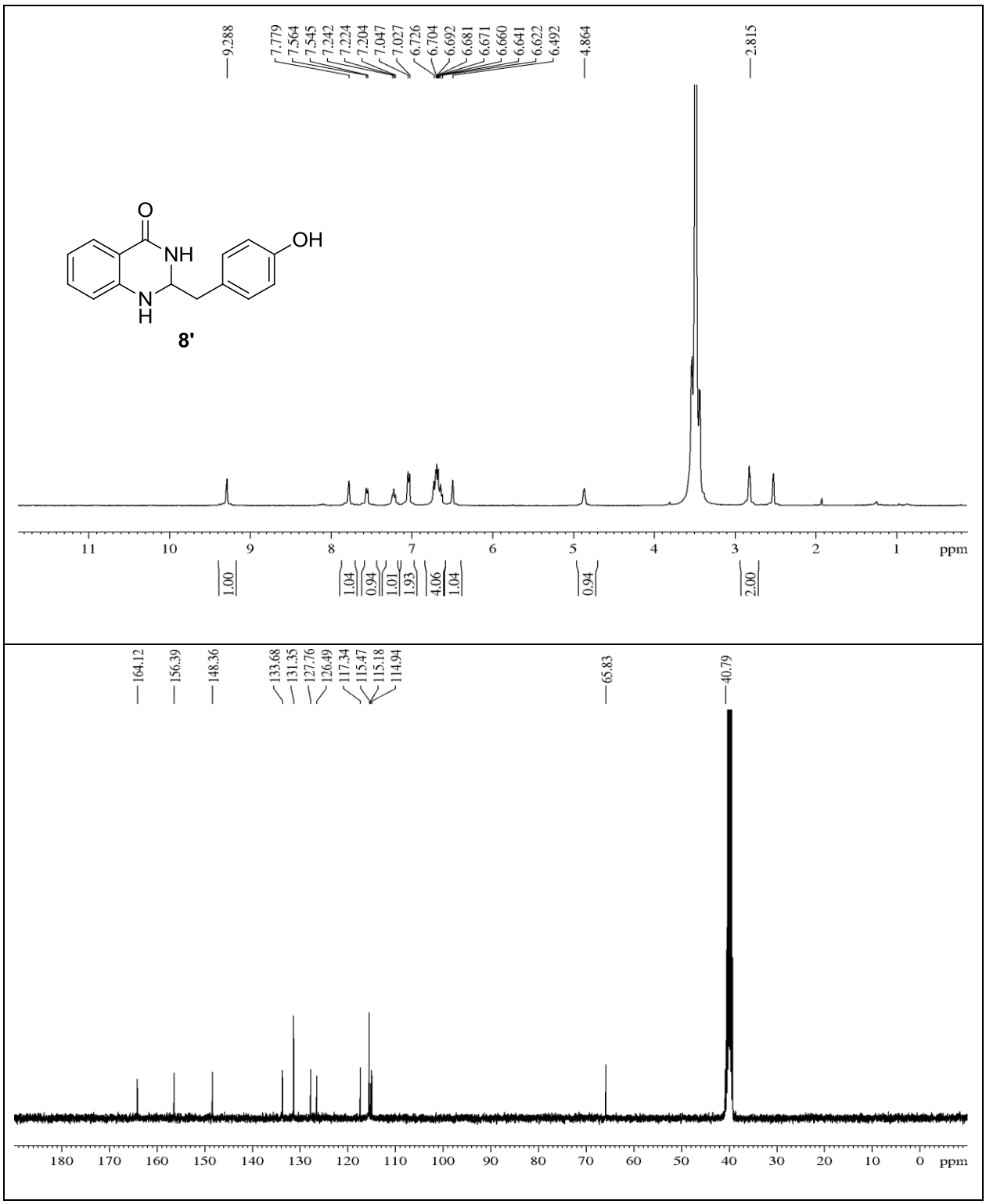
^{1}H, ^{13}C NMR of compound 5



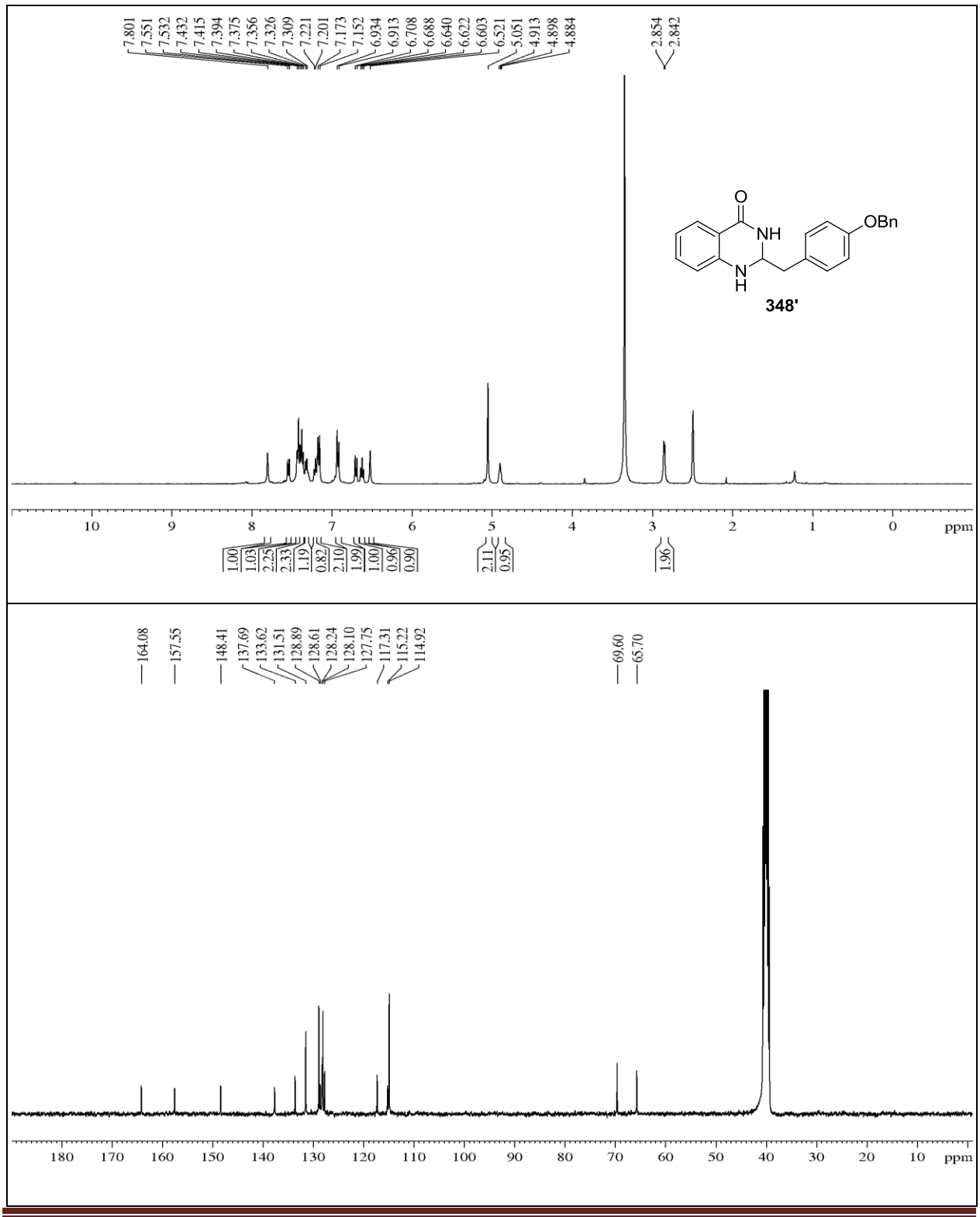
^{1}H, ^{13}C NMR of compound 346



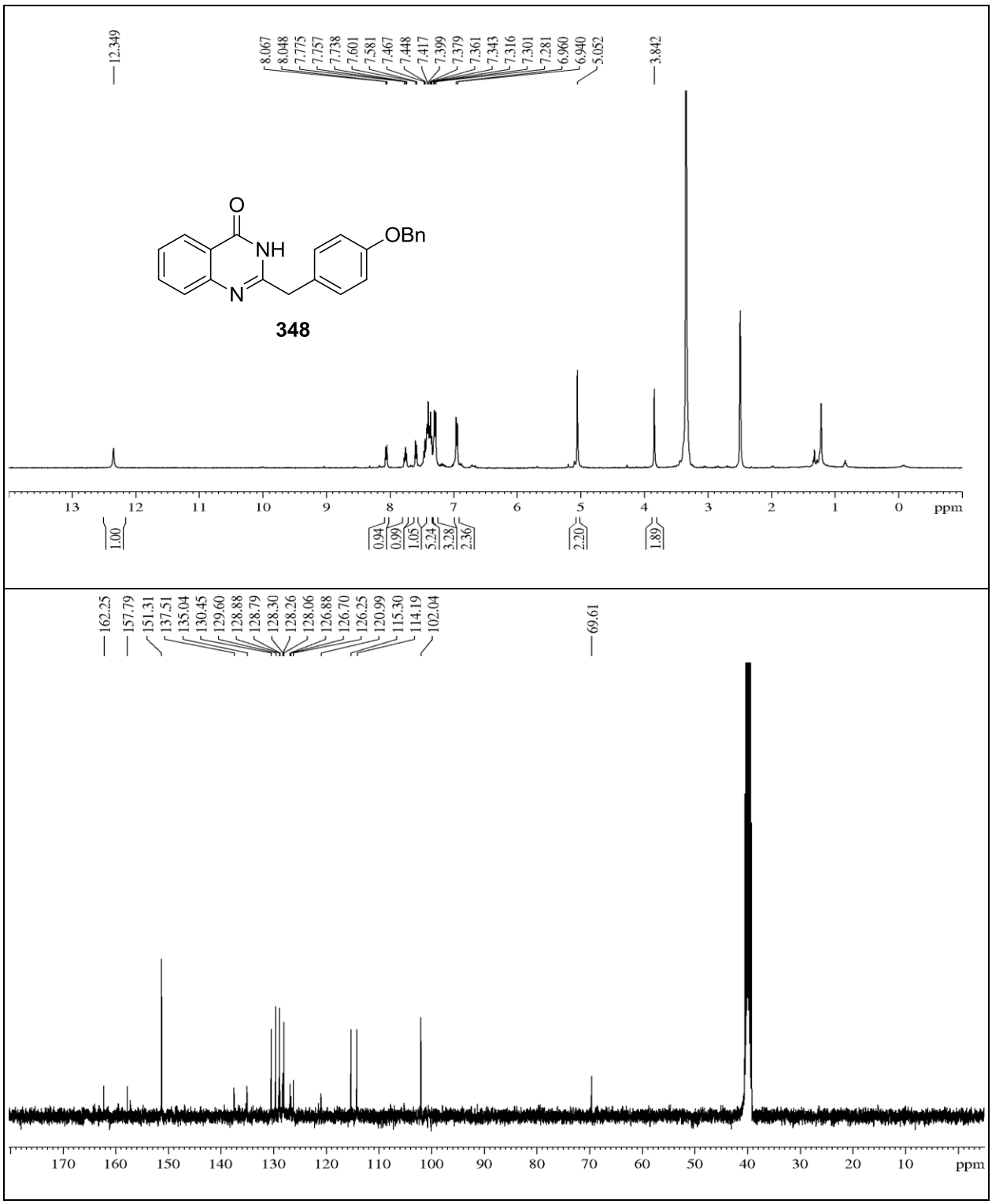
^{1}H, ^{13}C NMR of compound 8'



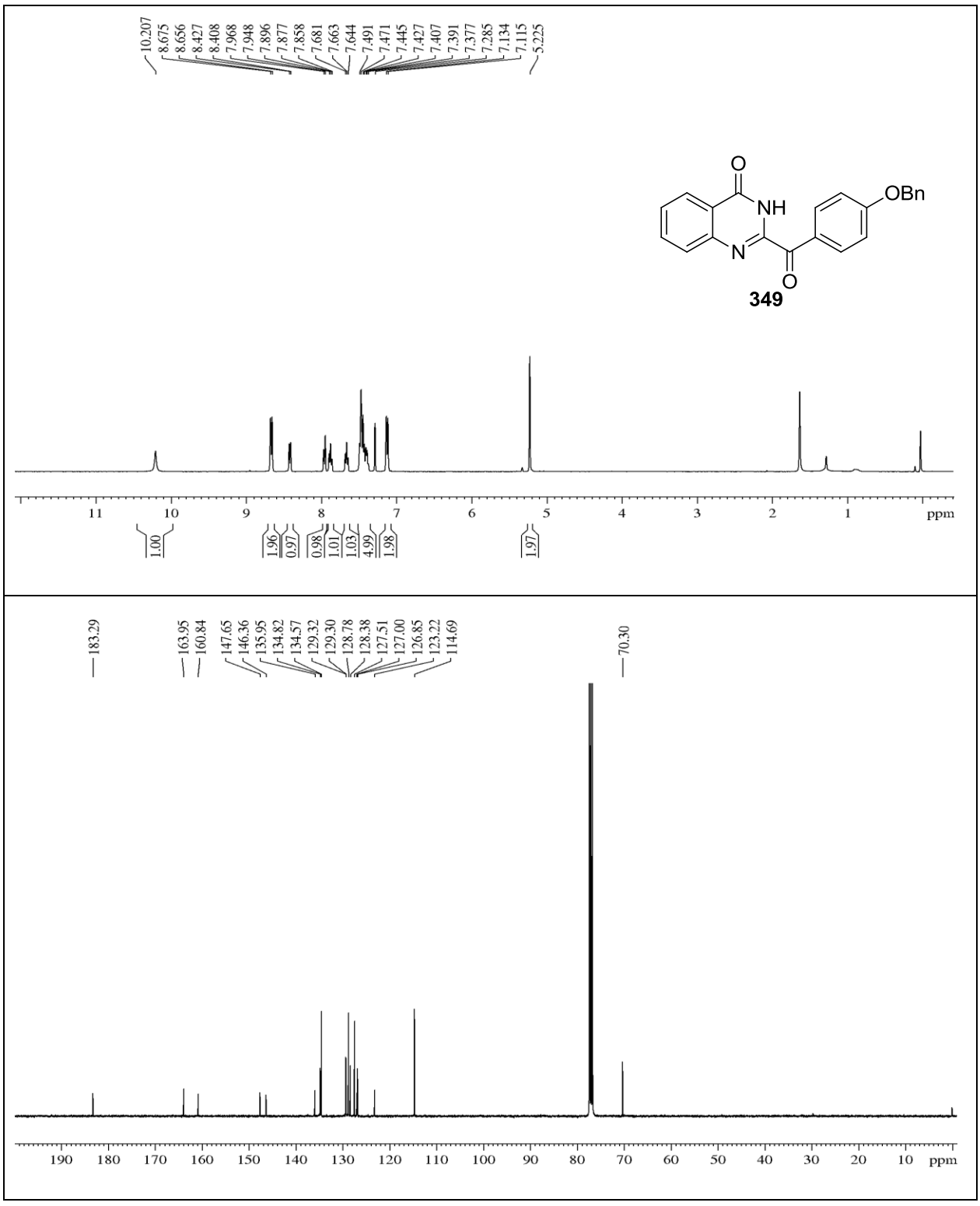
^{1}H, ^{13}C NMR of compound 348'



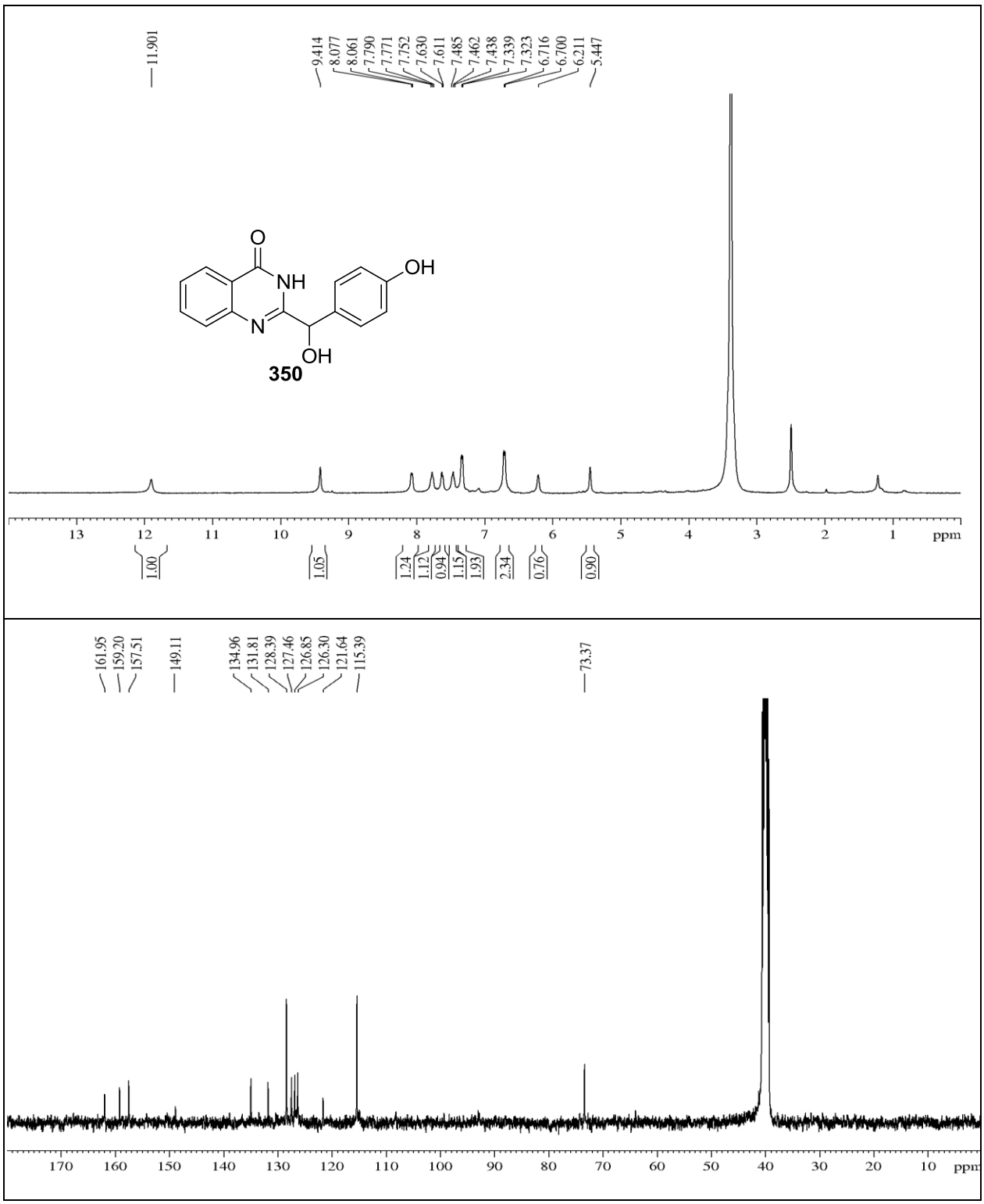
^{1}H, ^{13}C NMR of compound 348



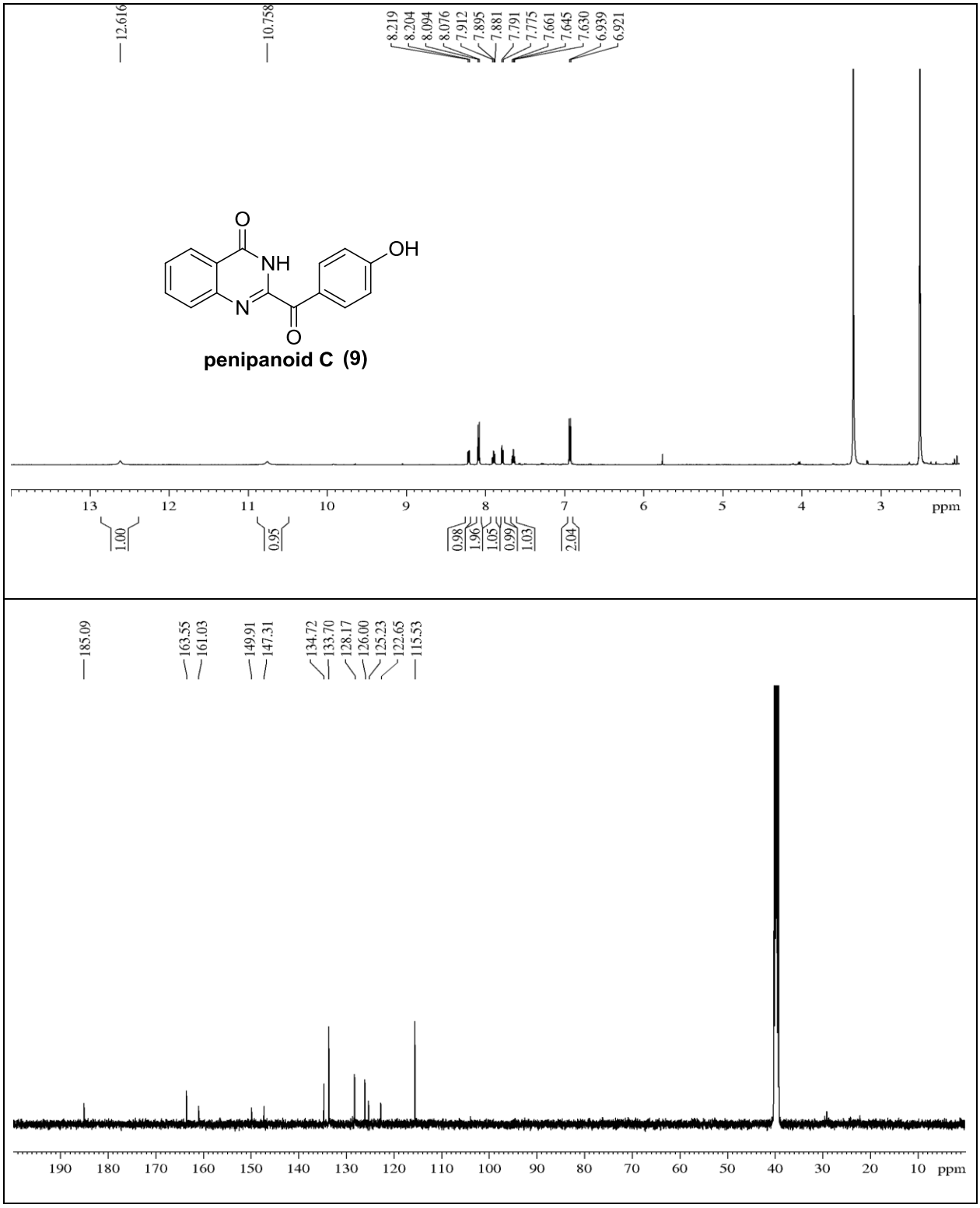
[1]H, [13]C NMR of compound 349



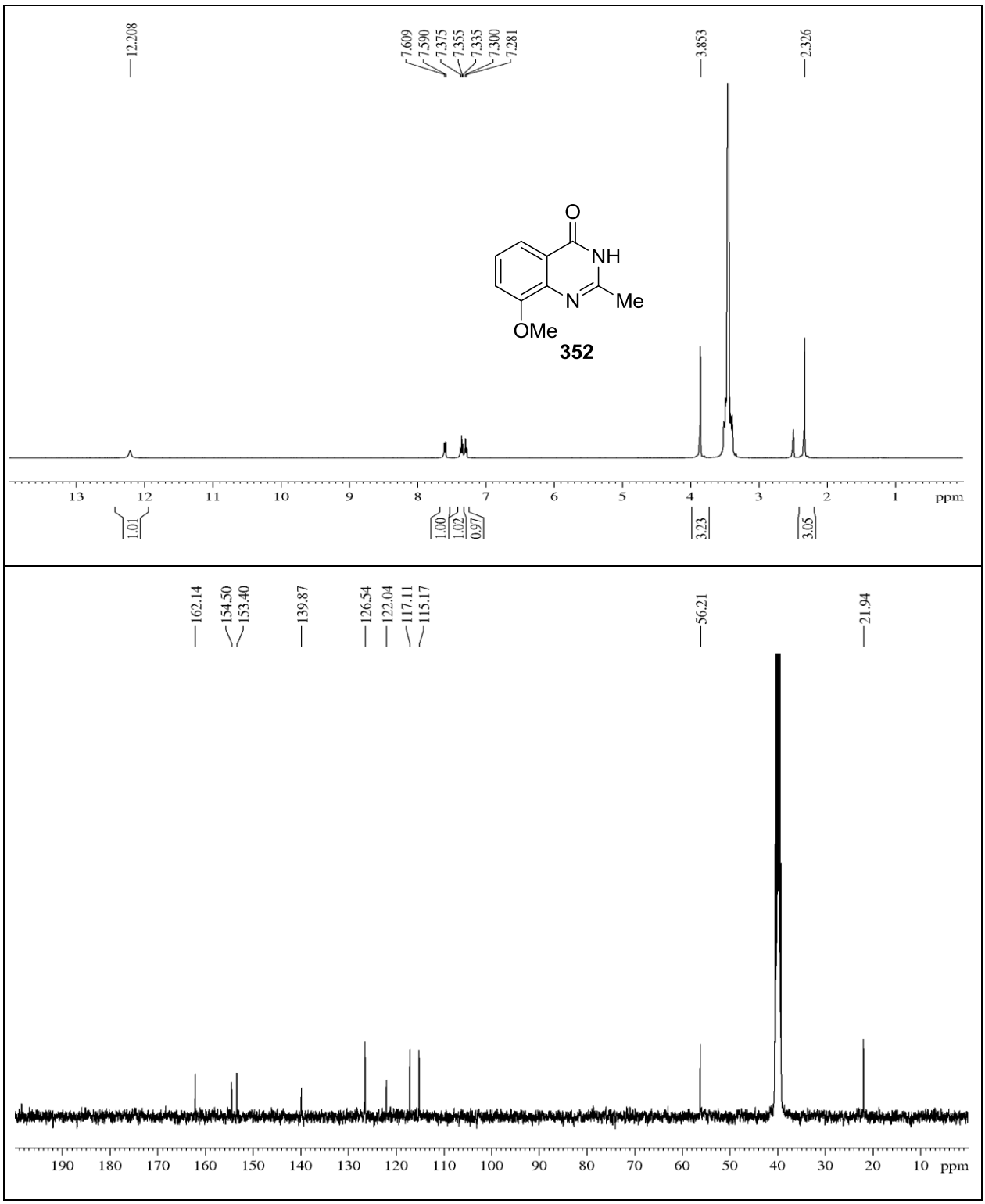
^{1}H, ^{13}C NMR of compound 350



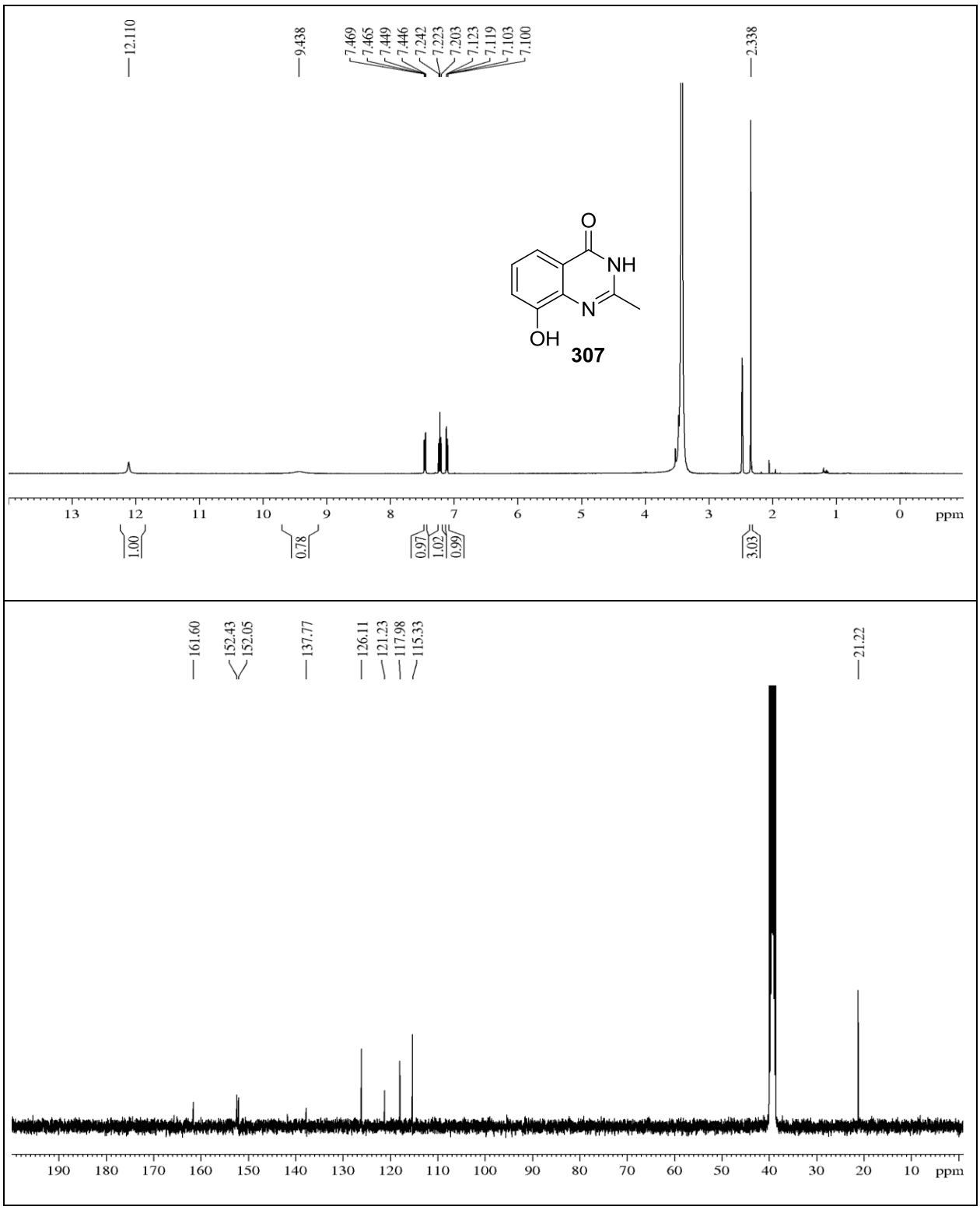
^{1}H, ^{13}C NMR of compound 9



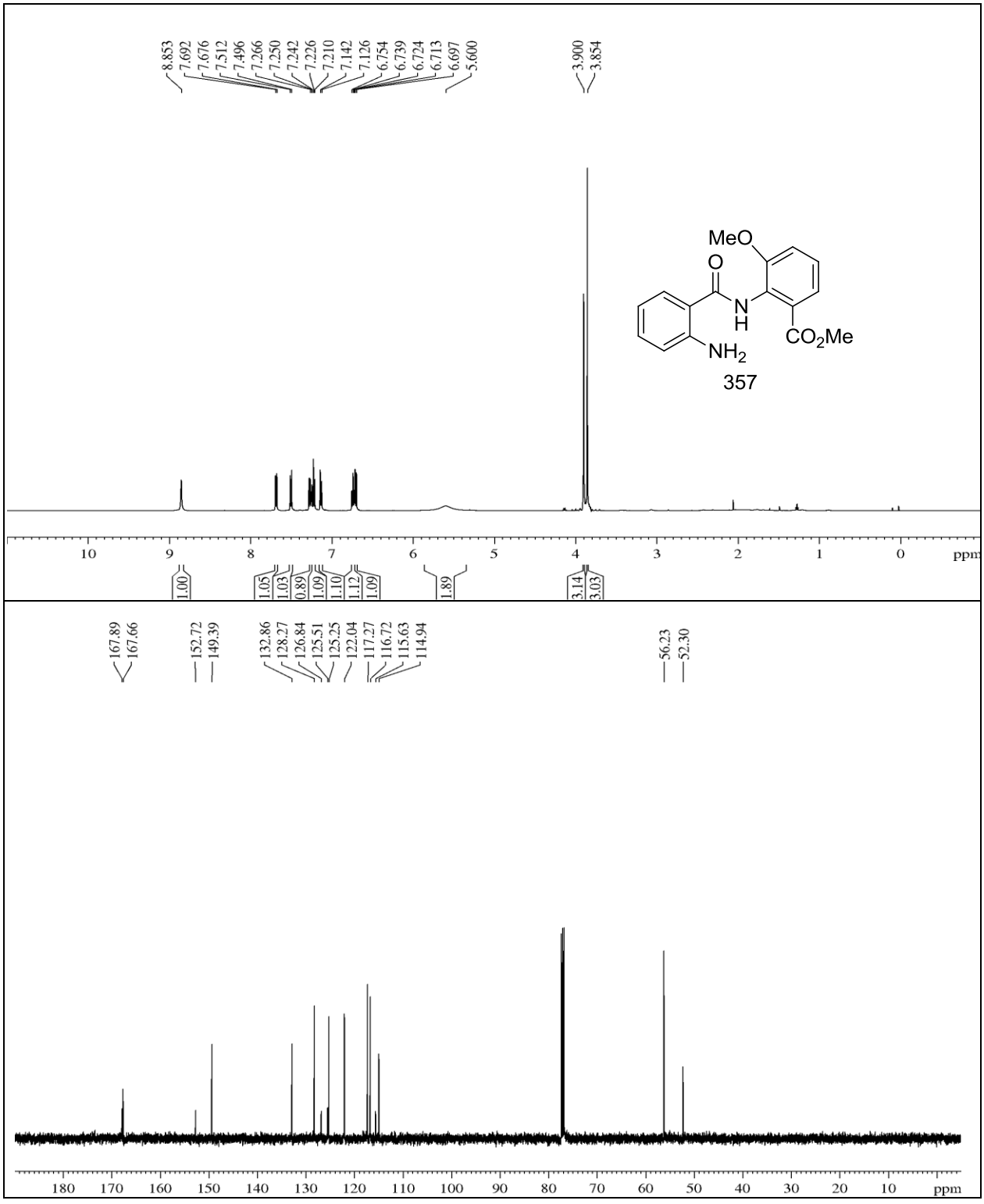
^{1}H, ^{13}C NMR of compound 352



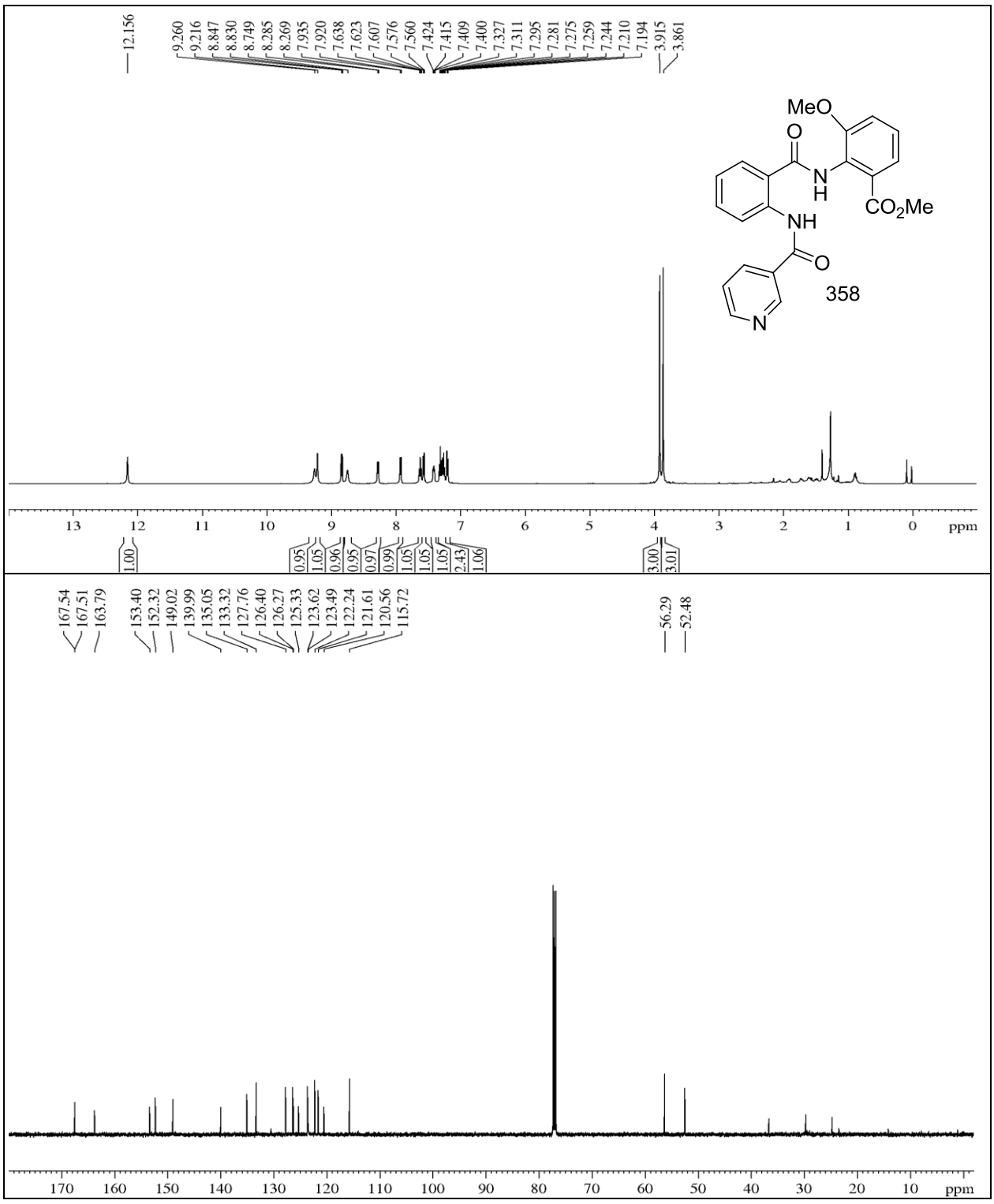
^{1}H, ^{13}C NMR of compound 307



^{1}H, ^{13}C NMR of compound 357



^{1}H, ^{13}C NMR of compound 358



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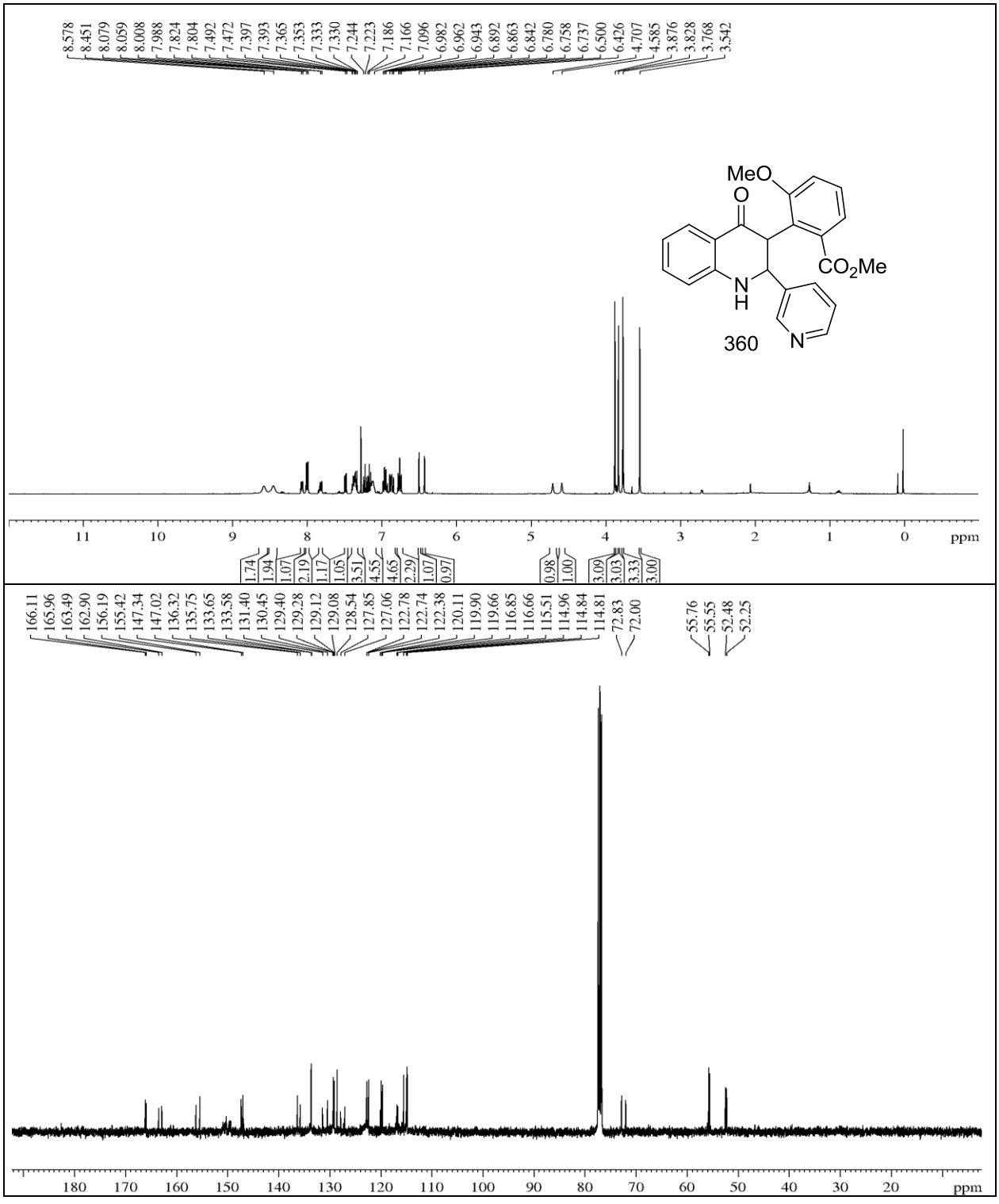

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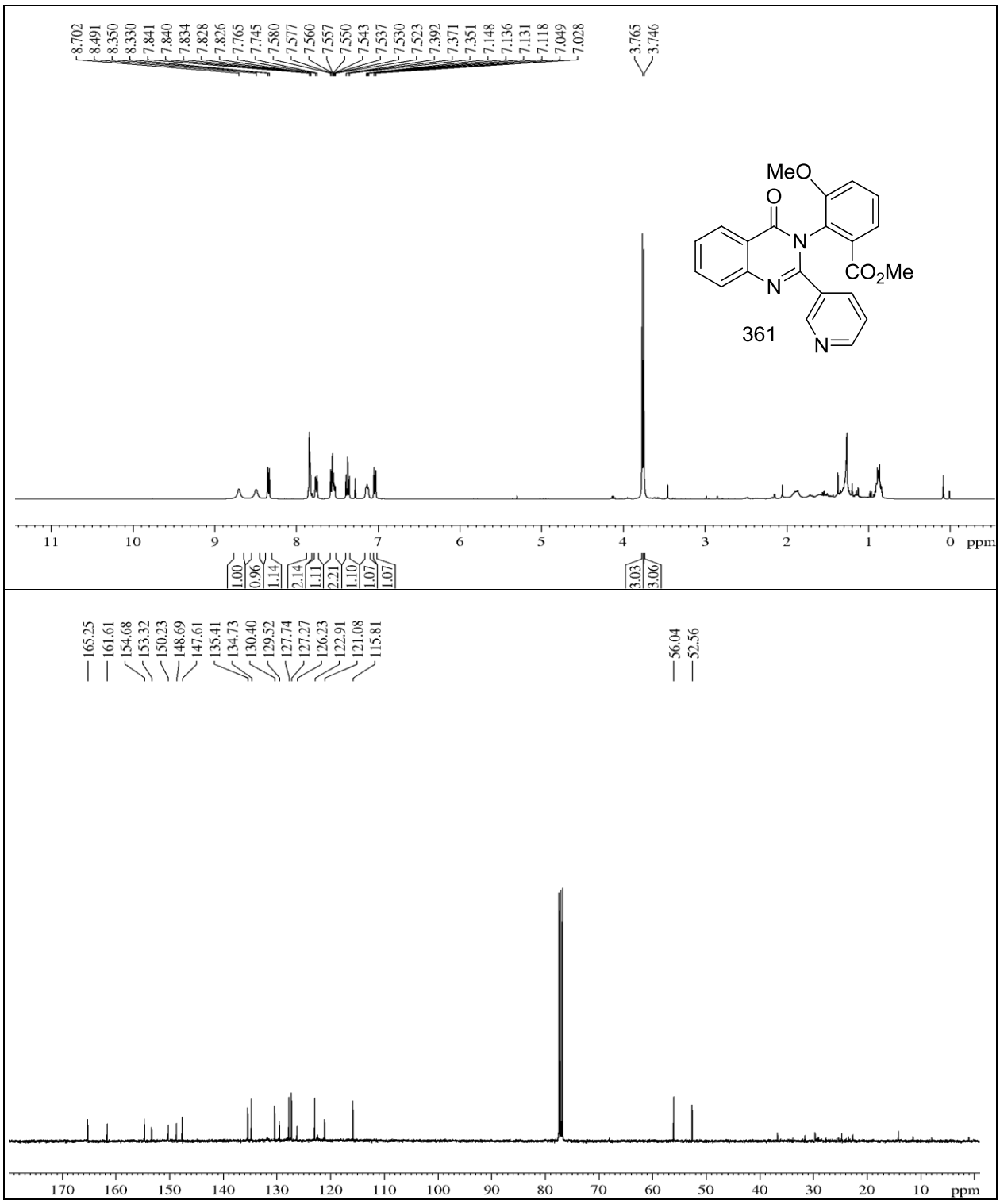
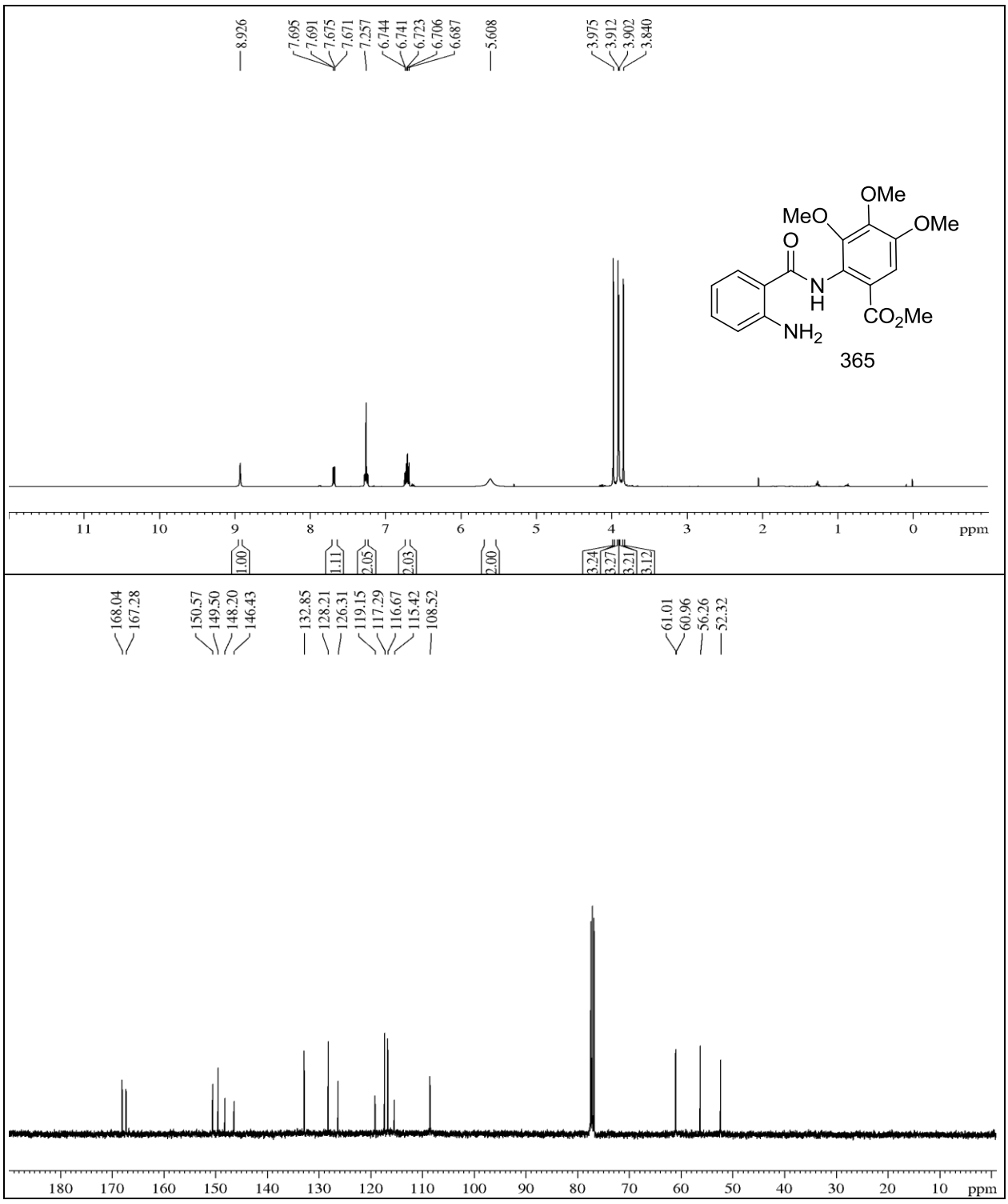
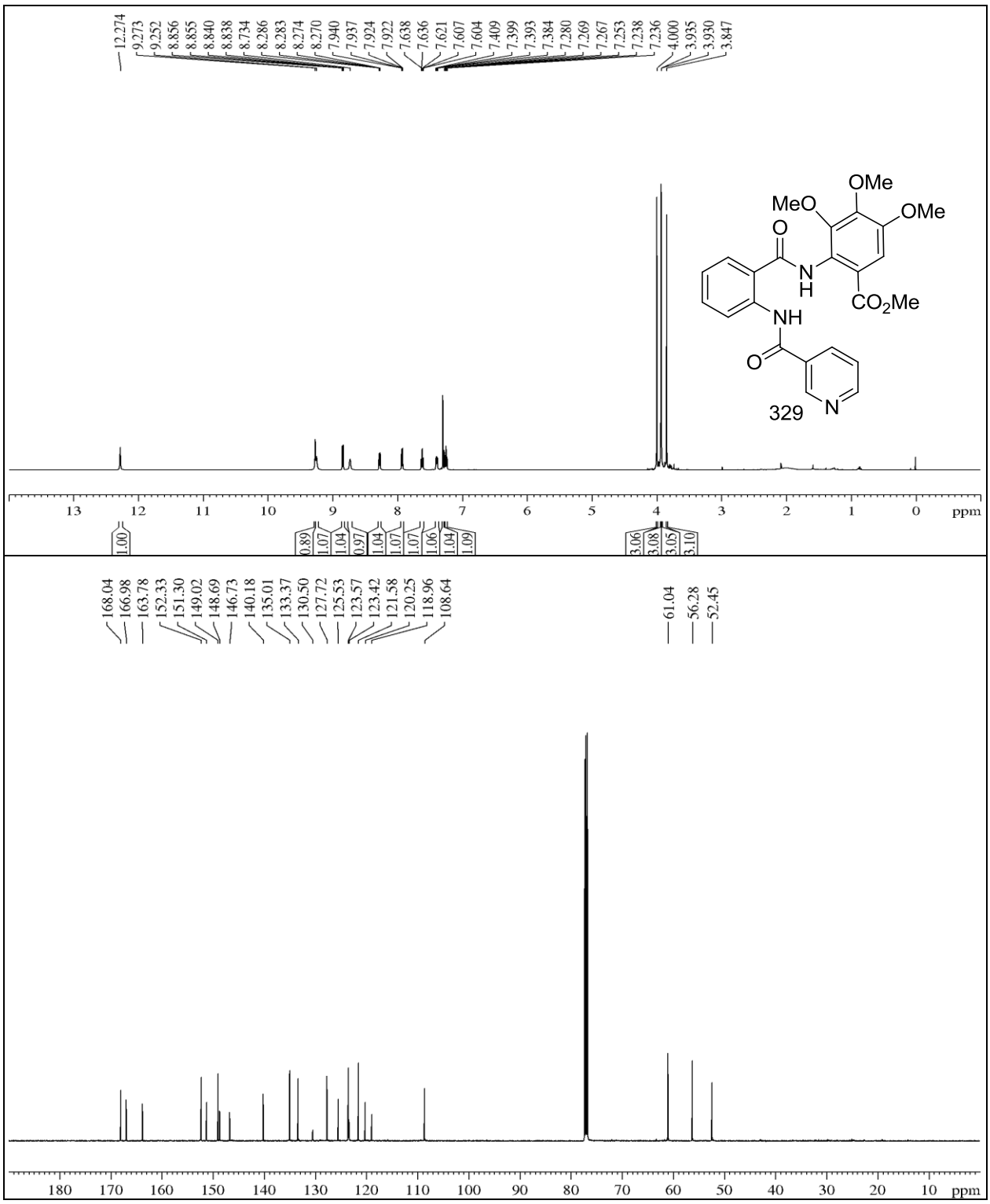


^{1}H, ^{13}C NMR of compound 365



^{1}H, ^{13}C NMR of compound 329



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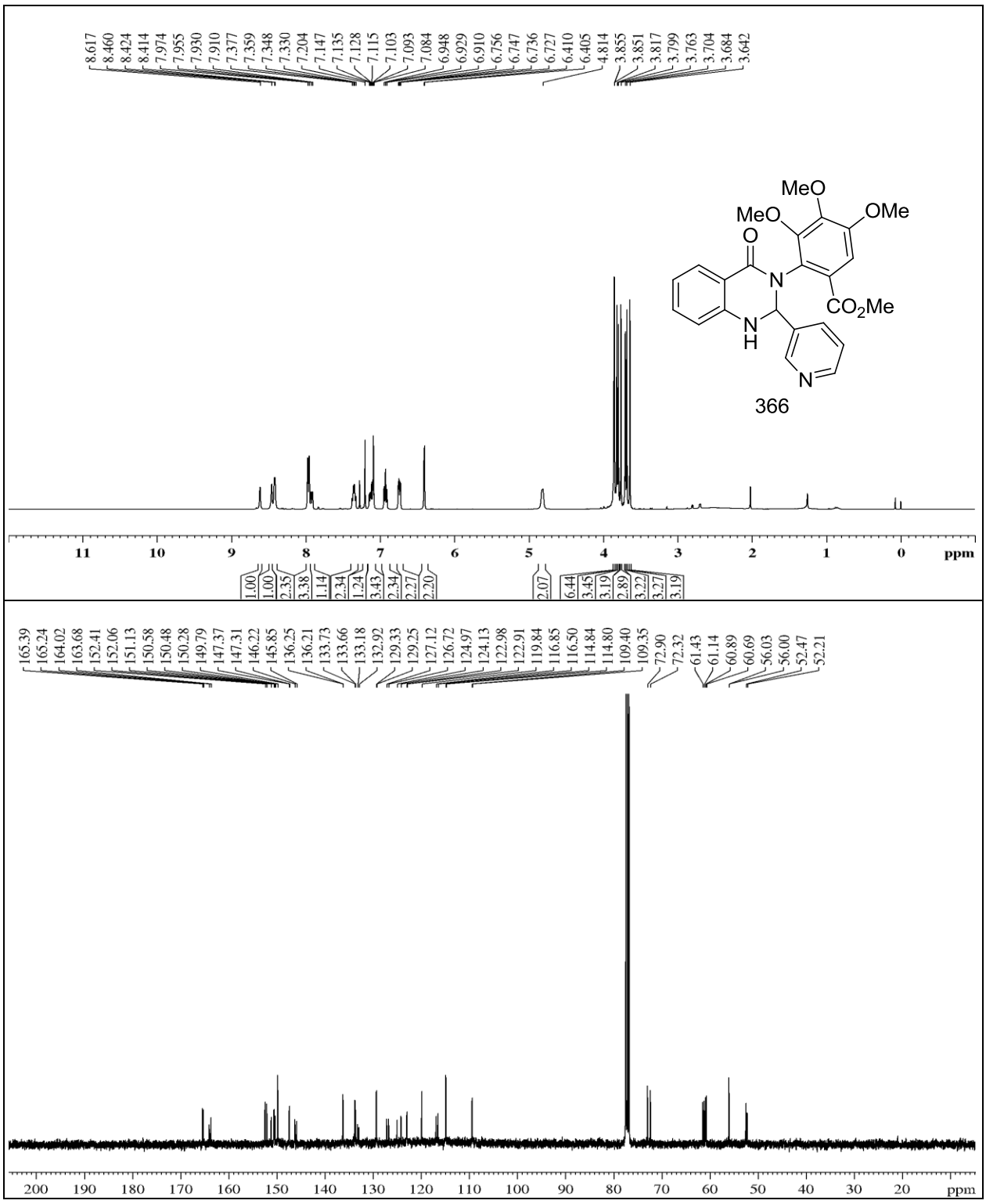

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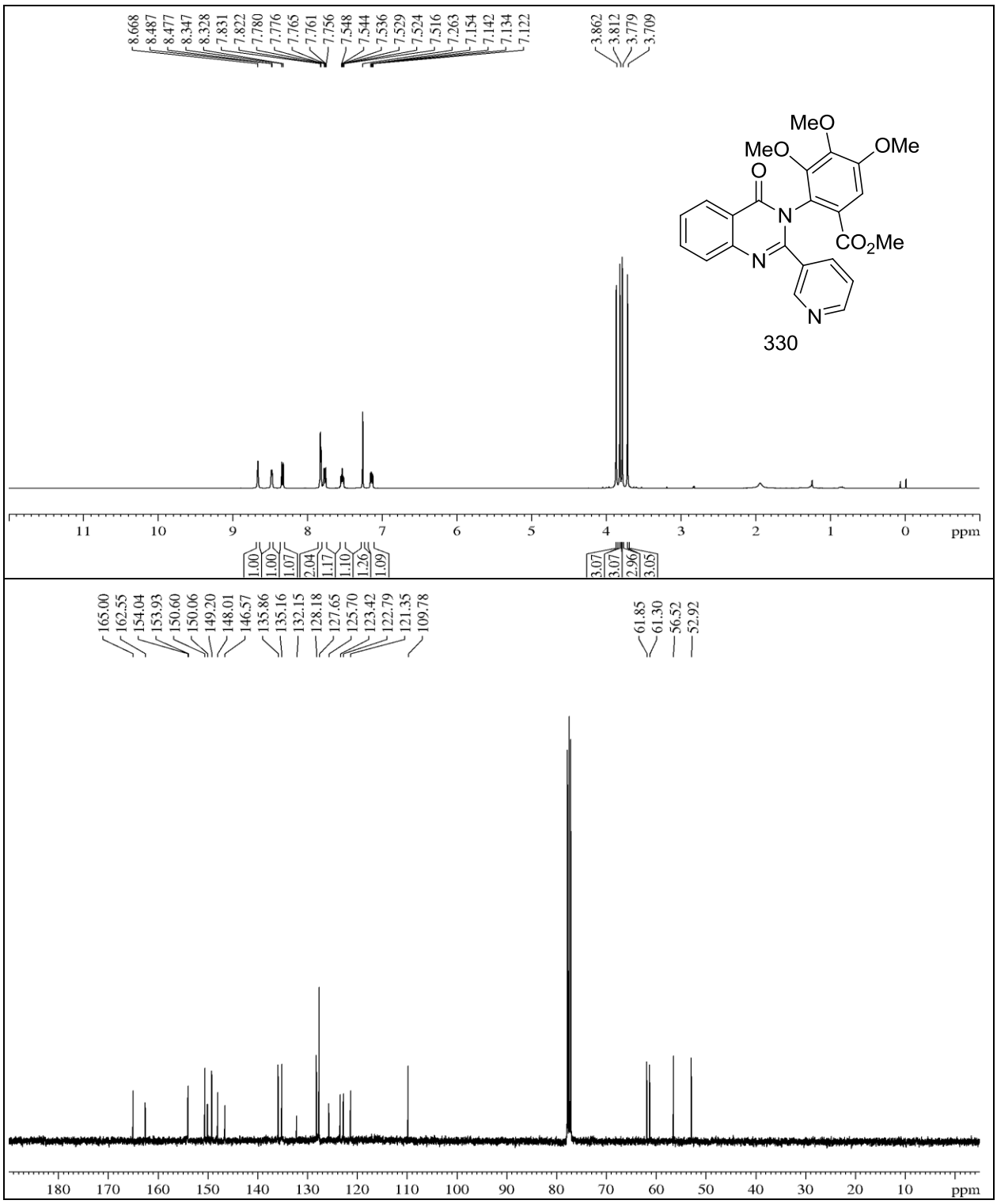

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Chapter 4

SYNTHESIS OF ACTINOPHENANTHROLINE A VIA DOUBLE DOEBNER–MILLER REACTION

4.1 Introduction:

Fenical group isolated some new alkaloids actinobenzoquinoline and actinophenanthroline A-C (**Figure 19**) in 2015 from a marine actinomycete belongs to the family of streptomycetaceae (strain CNQ-149).[1] The basic skeleton of these alkaloids were previously not known in the literature and these alkaloids actinophenanthrolines A−C are the first examples of naturally occurring alkaloids that contains 1,7-phenanthroline core.

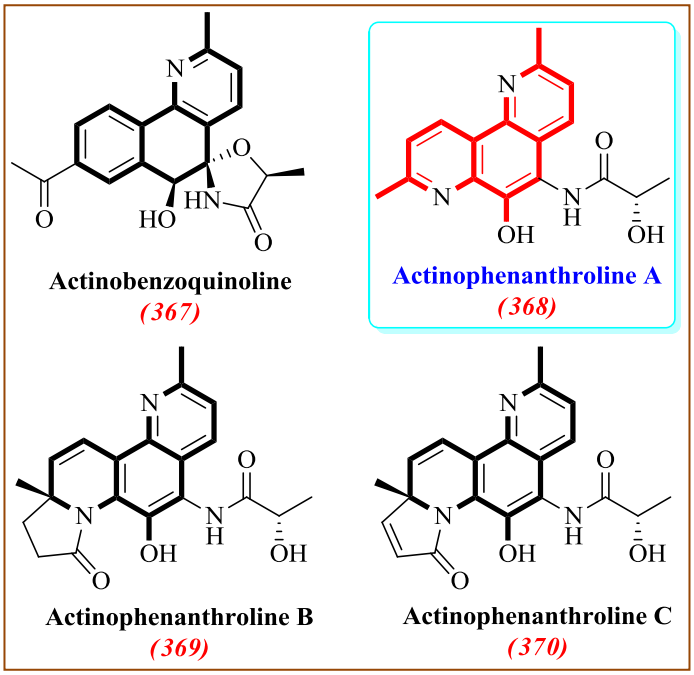
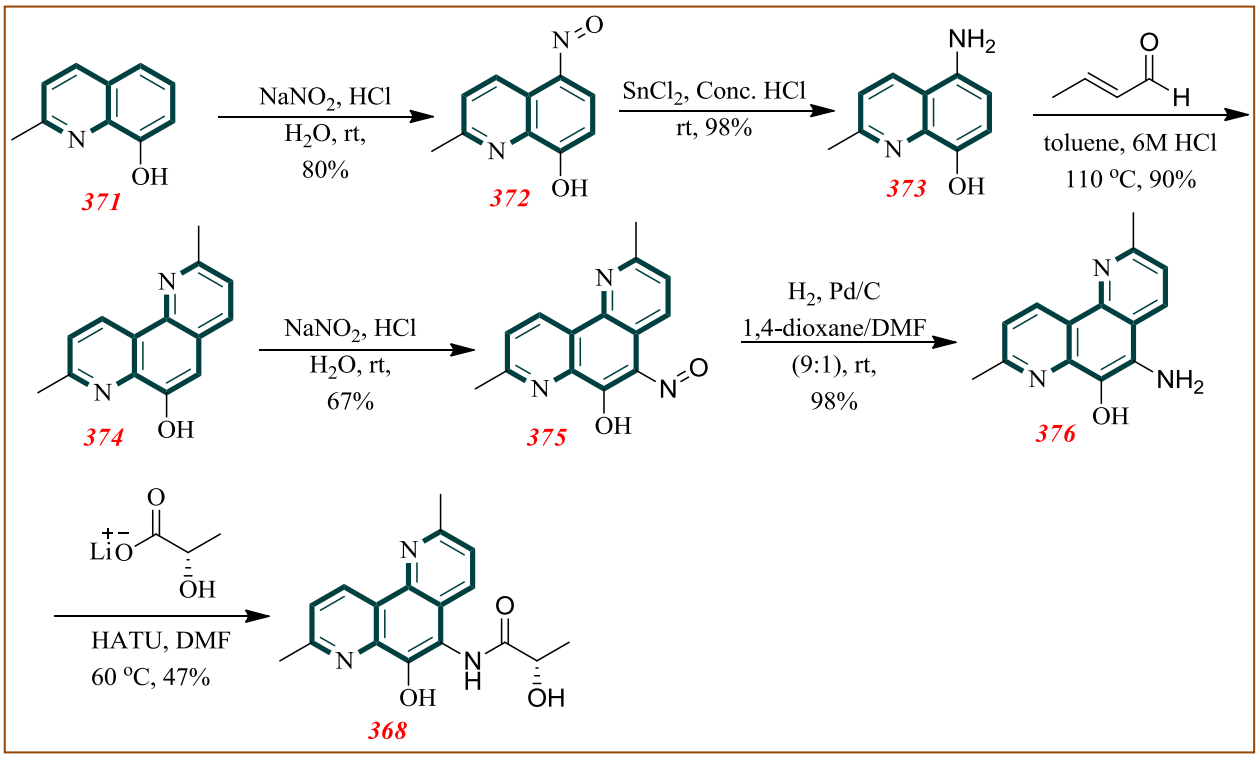


Figure 19. Unprecedented alkaloids from marine actinomycete streptomycetaceae (strain CNQ-149).

Synthetic phenanthrolines were already well known in literature and 1, 7-, 1,10-, 4,7- are mostly common among them. In 1882, Skarup et al. reported the first synthesis of 1, 7-phenanthrolines and it was also the first phenanthroline that was synthesized.[2] Later, it was reported that these

can induce the biosynthesis of drug-metabolizing enzymes via binding to the metals.[3] In spite of that it is the 1, 10-phenanthrolines that were studied mostly among them and it shows a wide spectrum of pharmacological properties like, inhibitions of zinc metallopeptidases,[4] antimalarial activities[5] as well as metal binding capacity.[6] Hence, the importance of the chemical synthesis for the first alkaloid that contains 1, 7-phenanthroline core is immensely important and studies might open up many important pharmacological and biological properties for these alkaloids. As we are working on chemical synthesis of different alkaloids with different cores, this alkaloid actinophenanthroline A immediately drew our attentions and we were eager to perform the chemical synthesis. There are plenty of reports available for the synthesis of 1, 7-phenanthroline core[7] in literature but we opted for a methodology that will be economically favored. Thus, we planned the synthetic route with the classic and economic Doebner-Miller reaction.[8]



Eqn. 61. Lindsley's synthesis of actinophenanthroline A

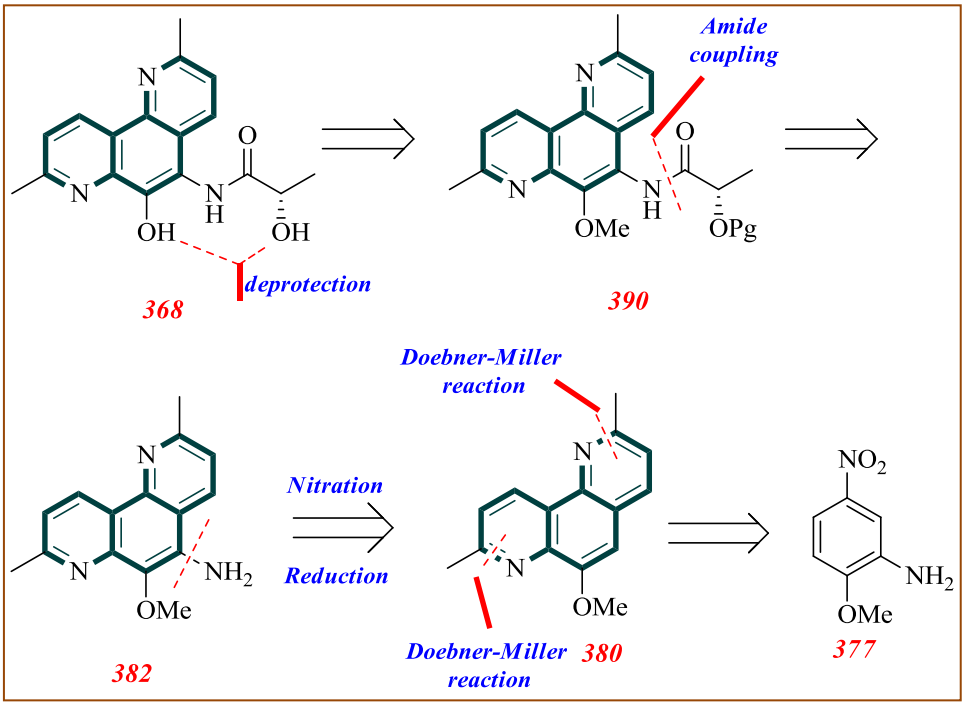
Very recently, Lindsley group described the first chemical synthesis for this alkaloid following six linear steps. Their reaction commenced with 8-hydroxy-2-methylquinoline (**371**) and they have also utilized the Doebner-Miller reaction to form the 1, 7-phenanthroline core (**374**). Later functional group transformation followed by HATU coupling with lithium salt of (S)-2-

hydroxypropanoic acid gave them the actinophenanthroline A (**368**, **Eqn.61**). Although the synthetic route gave a good overall yield but it consists of isolation and purification problems in every step as the author mentioned in their manuscript.[9]

Hence, we demonstrated an easier and economically favored total synthesis of actinophenanthroline A using double Doebner-Miller reaction.

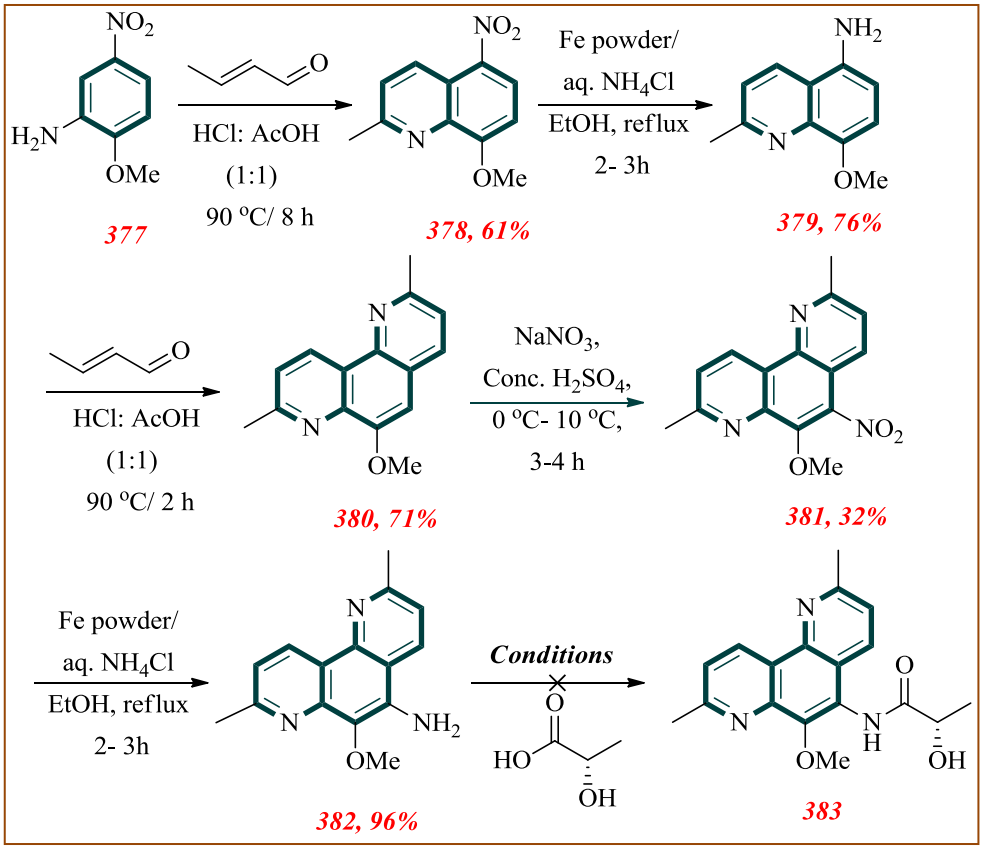
4.2 Results and discussion:

Scheme 22. Retrosynthetic analysis



We have demonstrated the retrosyntheis for actinophenanthroline A in **Scheme 22**. We envisioned that compound **368** can be hinged from compound **390** via deprotection of two hydroxyl groups (aliphatic and aromatic) in two consecutive steps. Next, compound **390** could be stemmed through the coupling reaction between compound **382** and protected L-lactic acid. This amine (**382**) could be furnished from compound **380** through nitration followed by reduction. The 1, 7-phenanthroline core (**380**) can be obtained via repeated Doebner-Miller reaction of 2-methoxy-5-nitroaniline and this could be the best path to achieve this core.

Scheme 23. Forward Synthesis



We started our venture with Doebner-Miller reaction, where 2-methoxy-5-nitroaniline (**377**) and crotonaldehyde was treated with mixed acid (AcOH and HCl) at 90 °C to furnish nitro substituted 2-methylquinoline (**378**) in 61% yield. This nitro group of compound **378** was next reduced to the amine (**379**) with Fe powder/NH_4Cl under the reflux condition. Next, compound **379** was again reacted with crotonaldehyde in same above mentioned condition for 2h at 90 °C to carry out the second Doebner-Miller reaction that gave our desired 1, 7- phenanthroline core (**380**) in 71% yield. Introduction of nitro group at C5 of compound **380** was the next step and it can be obtained preferably with an electron donating group at C6 and we got an upper-hand due to the presence of methoxy group at C6. Then, we have carried out nitration on compound **380** with HNO_3-H_2SO_4 at 0 °C but unfortunately we got a poor yielded nitro compound (**381**). We tried various nitrating agents like NO_2BF_4, $AcONO_2$ and $NaNO_3$-H_2SO_4 to increase the yield of compound **381** and we found that $NaNO_3$-H_2SO_4 at 0-10 °C was the best condition to get moderate yield of compound **381**. Next, we carried out the reduction of nitro group of compound

381 with Fe powder at refluxing condition to get 5-amino-1, 7-phenanthroline (**382**) in almost quantitative yields.

Table 6. Conditions for Amidation

Entry No.	Coupling Reagent	Base	Temperature	Additives	Time/ Solvent	Yield of 383
1	EDCI.HCl	—	rt	—	48 h/ DCM	Not obtained
2	EDCI.HCl	—	50 °C	—	72 h/ DCM	Not obtained
3	EDCI.HCl	Et_3N	50 °C	—	48 h/ DCM	Not obtained
4	EDCI.HCl	Et_3N	50 °C	DMAP	48 h/ DCM	Not obtained
5	TBTU	Ethylene diisopropylamine	rt	—	24 h/ DCM	Not obtained
6	HBTU	Et_3N	rt	—	24 h/ DCM	Not obtained
7	DCC	—	rt	DMAP	48 h/ DCM	Not obtained
8	DCC	Et_3N	40 °C	DMAP	72 h/ DCM	Not obtained
9	DIC	—	rt	DMAP	24 h/ DCM	Not obtained
10	Thionyl Chloride	Et_3N	rt		24 h/ DCM	decomposed
11	Oxalyl chloride	Et_3N	rt		24 h/ DCM	decomposed
12	CDI	—	40 °C	—	24 h/THF	Not obtained

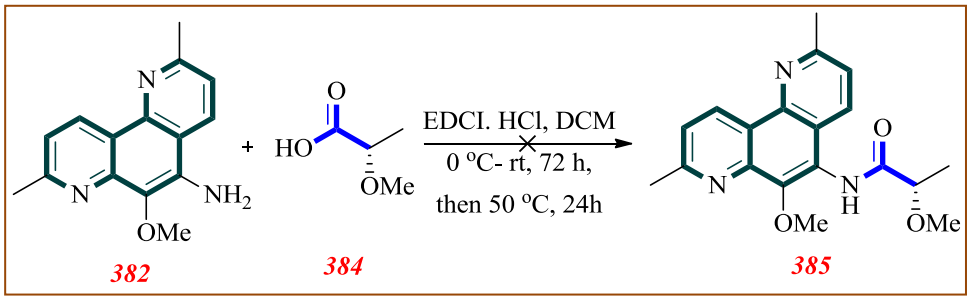
Once we have obtained compound **382** we were eager to perform the key coupling reaction with between amine (**382**) and L-lactic acid using EDCI.HCl as coupling agent; that was reported for benzene moiety already[10] but unfortunately the coupling did not work out for 1, 7-phenanthroline core. Hence, we tried various conditions using different coupling agents (EDCI.HCl, HBTU, HATU, TBTU, DCC, DIC, CDI) in presence of activating agents (DMAP, HOBt) at different

temperatures even then we were not able to obtain our desired coupled product **383** (***see Table 6***).

Figure 21. X-ray structure of 6-methoxy-2, 8-dimethyl-1,7-phenanthrolin-5-amine (**382**)

We presumed that the free hydroxyl group of lactic acid might be the reason for these consecutive failures. Hence, we protected the free hydroxyl group of L-lactic acid with methoxy group. We have prepared the (S)-2-methoxypropanoic acid (**384**) following three steps starting from L-lactic acid using literature procedure.[11] We have treated compound **382** with (S)-2-methoxypropanoic acid (**384**) in presence of coupling agent EDCI.HCl in dry DCM at 0 °C- rt for 72 h but unfortunately we failed to obtain coupled product **385;** on heating at 50 °C for another 24 h also did not change the scenario.

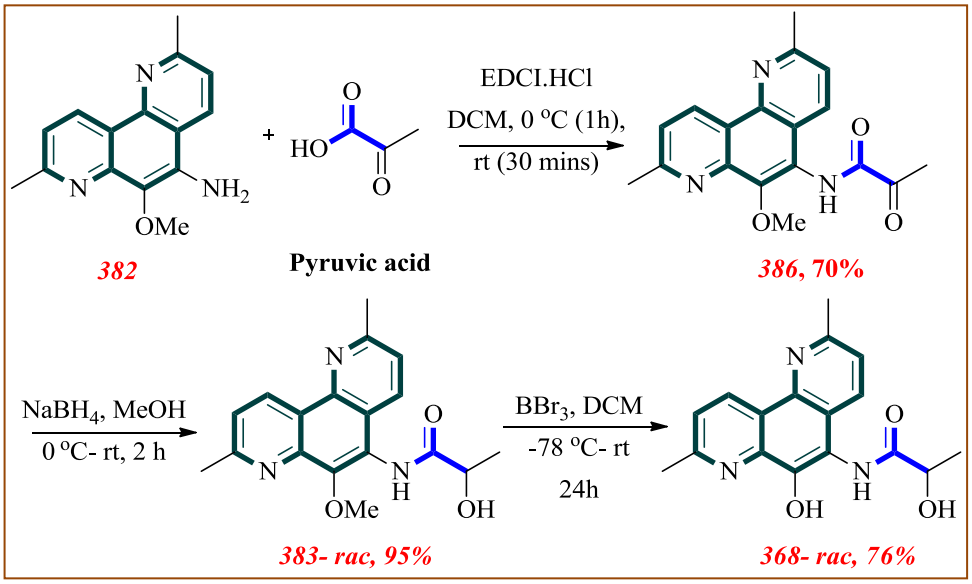
Scheme 24. Synthesis of enantiospecific Actinophenanthroline A



We assumed that it is not the hydroxyl group alone but there might be additional electronic and steric factors that play a vital role for this failure of reaction. It is probably that C5 amine on this phenanthroline core which is lesser nucleophilic (in comparison with simple benzene core) due to the presence of two other electron withdrawing pyridine rings. Hence, the nucleophlicity of amine might not be enough to dislocate the *o*-acyl lactic acid intermediate (that forms in situ with

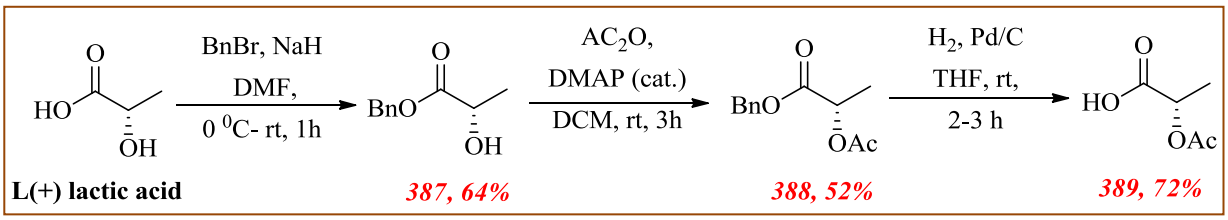
EDCI and lactic acid) to form the desired amide (**383/385**). We envisioned that the eletrophilicity of the lactic acid intermediate could be increased by keeping an electron withdrawing group at the α-/β position of the L-lactic acid and that might be enough to form our desired coupled product (**383/ 385**). With this perspective, we primarily began the venture of synthesizing racemic actinophenanthroline A. Thus, we have carried out reaction between compound **382** and pyruvic acid using the coupling agent EDCI.HCl in dry DCM at 0 °C for 1 h; then at rt for 30 mins to obtain our desired coupled product **386** with an excellent yield. Next the keto group was reduced to secondary alcohol using sodium borohydride in methanol at 0 °C that led to the racemic compound **383**. Compound **383-rac** was then reacted to BBr_3 in DCM at -78 °C to rt in a highly diluted DCM medium to deprotect the methoxy group; after 24 h racemic actinophenanthroline A (**368**) was obtained in good yields (**Scheme 25**). The NMR spectrum of synthetic racemic actinophenanthroline A (**368**) accurately matches with the reported actinophenanthroline A.

Scheme 25. Synthesis of racemic Actinophenanthroline A



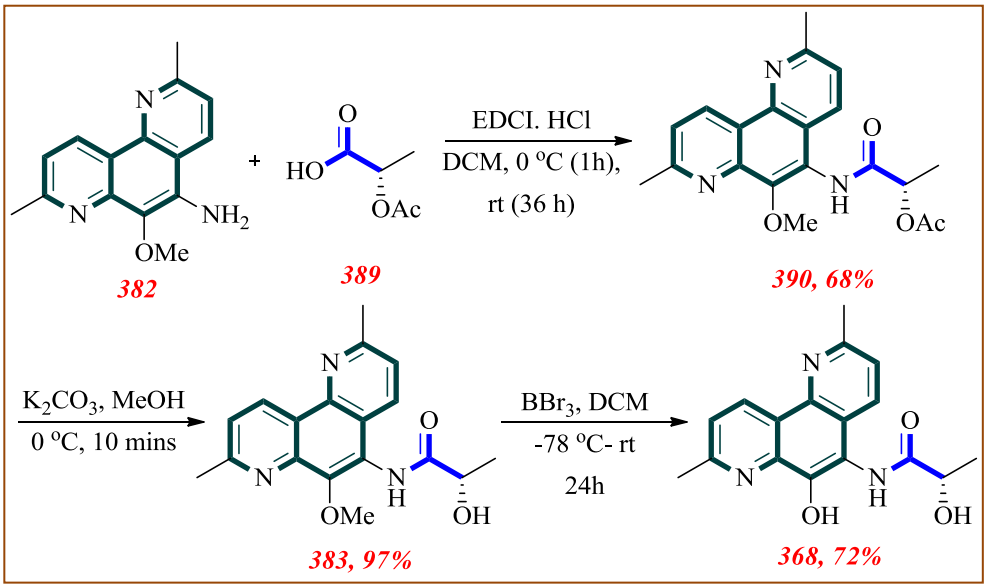
After completing the chemical synthesis of racemic actinophenanthroline A; our next target was to synthesize the enantiopure actinophenanthroline A. Hence, we converted the hydroxyl group of L-lactic acid to acetoxy group that indeed became the electron withdrawing group as we needed just α to the acid group.

Scheme 26. Synthesis of (S)-2-acetoxypropanoic acid



(S)-2-Acetoxypropanoic acid was prepared following three steps from L-lactic acid. L-lactic acid was first protected with benzyl group using benzyl bromide with sodium hydride. Then we carried out the acetoxylation reaction using acetic anhydride in presence of DMAP (*catalyst*); the benzyl group was next deprotected using hydrogenation reaction that led to the (S)-2-acetoxypropanoic acid. (**Scheme 26**).

Scheme 27. Synthesis of enantiospecific Actinophenanthroline A



Once we obtained the acid (**389**) we performed the coupling reaction with the amine (**382**) in presence of EDCI.HCl in DCM; this reaction found out to be very sluggish, it did not go till completion after 72 h also. Thus, we stopped the reaction and the coupled product **390** was isolated along with the unreacted starting amine (**382**). Next, compound **390** was treated with K_2CO_3 in MeOH solvent at 0 °C to selectively cleave of *O*-acetate group; the reaction completed within 10 mins to generate compound **383** in quantitative yields. Next, compound **383** was treated with BBr_3 in DCM that deprotects the methoxy group and it furnished the enantiopure actinophenanthroline A (**368**) in 72% yield.

We accomplished the chemical synthesis of racemic and enantiopure actinophenanthroline A (**368**) with overall 5.11% and 4.8% yields respectively. The spectral data and HRMS data of the synthetic product are consistent with the data of isolated natural product (***see experimental section***).

4.3 Conclusion:

In conclusion, we have accomplished an easier and economical synthesis of both racemic and enantiopure actinophenanthroline A. The easier, classical and economical strategies were utilized to synthesize this alkaloid. These synthetic strategies administer a much easier route to synthesize the other analogue of this alkaloid.

4.4 Experimental Section

Melting Points: The melting point of the products was recorded on a Superfit (India) capillary melting point apparatus and is uncorrected.

IR: Infrared spectra were recorded on a JASCO FT/IR-5300 spectrophotometer. All the spectra were calibrated against polystyrene absorption at 1601 cm^{-1}. Solid samples were recorded as KBr wafers and liquid samples as thin film between NaCl plates or solution spectra in DCM.

NMR Spectra: ^{1}H NMR and ^{13}C NMR spectrums were recorded on BRUKER-AVANCE-400/ 500 spectrometers. ^{1}H NMR (400 or 500 MHz) spectra for all the samples were measured in chloroform-*d*, unless otherwise mentioned (δ = 2.50 ppm for ^{1}H NMR in the case of DMSO-d_6), with TMS (δ = 0 ppm) as an internal standard. ^{13}C NMR (100 or 125MHz) spectra for all the samples were measured in chloroform-*d*, unless otherwise mentioned (in the case of DMSO-d_6, δ = 39.70 ppm its middle peak of the septet), with its middle peak of the triplet (δ = 77.10 ppm) as an internal standard.

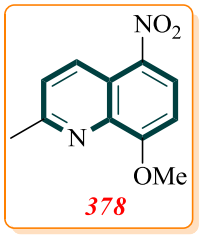
Mass Spectral Analysis: Shimadzu LCMS 2010A mass spectrometer. All the cases DCM or MeOH were used to dissolve the compounds. The TOF and quadrupole mass analyzer types are used for the HRMS measurements. Mass spectral data were obtained from HRMS (ESI).

Elemental Analysis: Elemental analyses were performed on a Thermo Finnigan Flash EA 1112-CHN analyzer.

X-ray Crystallography: The X-ray diffraction measurements were carried out at 293 K on a Bruker SMART APEX CCD area detector system equipped with a graphite monochromator and a Mo-K_α fine-focus sealed tube (λ = 0.71073 Å) operated at 1500 W power (50 kV, 30 mA). The detector was placed at a distance of 4.995 cm from the crystal. The frames were integrated with the Bruker SAINT Software package using a narrow-frame algorithm. Data were corrected for absorption effects using the multi-scan technique (SADABS). The structure was solved and refined using the Bruker SHELXTL (Version 6.1) software package.

8-Methoxy-2-methyl-5-nitroquinoline (378):

5-Nitro-*o*-anisidine (**377**, 7.0 g) was taken in a 250 mL RB and a mixed solution of HCl (60 mL) and AcOH (60 mL) was added to it. Next, 7 mL (2.0 equiv.) of crotonaldehyde was added to the mixture and stirred for 5 mins, till a clear solution being obtained. The mixture was then heated to 90 °C for 12 h. After cooling to room temperature, it was extracted with dichloromethane. Dark DCM layer was discarded and aqueous layer was made to just basic using 10% NaOH solution. This basic solution was then extracted with ethyl acetate and washed with brine. The organic layer was dried over anhydrous Na_2SO_4 and evaporated in vacuum. The residue was purified by column chromatography on silica gel using ethyl acetate/ hexanes mixture to afford the desired quinoline.



378

Yield: 61 %

Mp: 122 ^{o}C

IR (KBr) ν_{max} cm^{-1}: 1611, 1563, 1503, 1314, 1260, 1109, 817

^{1}H NMR (400 MHz) δ: 9.10 (1H, d, *J* = 8.8 Hz), 8.46 (1H, d, *J* = 8.8 Hz), 7.57 (1H, d, *J* = 8.8 Hz), 7.06 (1H, d, *J* = 8.8 Hz), 4.20 (3H, s), 2.84 (3H, s)

^{13}C NMR (100 MHz) δ: 160.2, 159.5, 139.0, 137.9, 132.6, 126.5, 125.6, 121.2, 105.4, (aromatic C), 56.9, 25.5 (aliphatic C)

HRMS (ESI-MS)

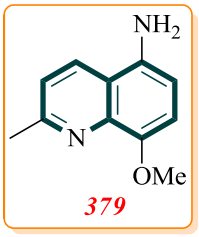
Calcd for: $C_{11}H_{10}N_2O_3$: 219.0770 (M+H)

Found: 219.0768

8-Methoxy-2-methylquinolin-5-amine (379):

Compound **378** (4.0 g) was dissolved in EtOH (60 mL) by warming. Next saturated aqueous solution of NH_4Cl was added to it followed by Fe powder (5.11g, 5.0 equiv.). The mixture was heated to reflux at 80 °C for 3-4 h. The reaction mixture was then cooled to room temperature and was filtered through celite using ethyl acetate as eluent. The filtrate was then evaporated to dryness and again extracted using ethyl acetate and water. The organic layer was dried over anhydrous Na_2SO_4 and evaporated in vacuum. The residue was purified by column

chromatography on silica gel using ethyl acetate/hexanes mixture to afford the desired compound.



379

Yield: 76 %

Mp: 138 °C

IR (KBr) ν_{max} cm^{-1}: 3373, 3189, 2946, 1600, 1568, 1476, 1276, 828

^{1}H NMR (400 MHz) δ: 8.08 (1H, d, *J* = 8.8 Hz), 7.29 (1H, d, *J* = 8.4 Hz), 6.87 (1H, d, *J* = 8.4 Hz), 6.71 (1H, d, *J* = 8.4 Hz), 4.01 (3H, s), 3.78 (2H, s, br), 2.79 (3H, s)

^{13}C NMR (100 MHz) δ: 157.9, 148.5, 140.0, 134.9, 130.1, 121.3, 118.7, 109.5, 108.0, (aromatic C), 56.0, 25.6 (aliphatic C)

HRMS (ESI-MS)

Calcd for: $C_{11}H_{12}N_2O$: 189.1028 (M+H)

Found: 189.1027

6-Methoxy-2,8-dimethyl-1,7-phenanthroline (380):

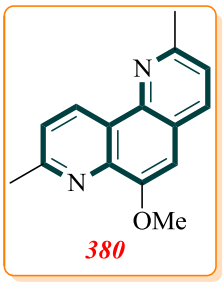
Compound **379** (1.0 g) was taken in a 100 mL RB and a mixed solution of HCl (10 mL) and AcOH (10 mL) was added to it. Next, 0.9 mL (2.0 equiv.) of crotonaldehyde was added to the mixture and stirred for 5 mins, till a clear solution being obtained. The mixture was then heated to 90 °C for 2h (till the starting material was consumed). After cooling to room temperature, it was extracted with dichloromethane. Dark DCM layer was discarded and aqueous layer was made to just basic using 10% NaOH solution. This basic solution was then extracted with ethyl acetate and washed with brine. The organic layer was dried over anhydrous Na_2SO_4 and evaporated in vacuum. The residue was purified by column chromatography on silica gel using ethyl acetate/hexanes mixture to afford the desired phenanthroline.

Yield: 71 %

Mp: 130- 134 °C

IR (KBr) ν_{max} cm^{-1}: 3265, 1600, 1487, 1433, 1314, 1201, 860

^{1}H NMR (400 MHz) δ: 9.47 (1H, d, *J* = 8.4 Hz), 7.98 (1H, d, *J* = 8.0 Hz), 7.55 (1H, d, *J* = 8.4 Hz), 7.36 (1H, d, *J* = 8.4 Hz), 7.09 (1H, s), 4.17 (3H, s), 2.88 (3H, s), 2.79 (3H, s)



380

^{13}C NMR (100 MHz) δ: 159.7, 155.8, 152.9, 142.6, 141.4, 134.6, 133.2, 125.5, 124.2, 122.9, 122.7, 103.7, (aromatic C), 56.1, 25.6, 25.1(aliphatic C)

HRMS (ESI-MS)

Calcd for: $C_{15}H_{14}N_2O$: 239.1184 (M+H)

Found: 239.1178

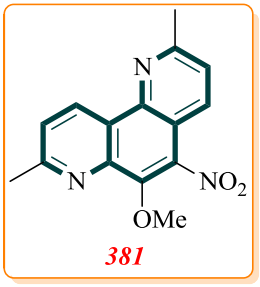
6-Methoxy-2,8-dimethyl-5-nitro-1,7-phenanthroline (381):

Compound **380** (0.800 g) was mixed with conc. H_2SO_4 and stirred at 0 °C for 10 mins till it dissolves to give a dark brown clear solution. To this mixture $NaNO_3$ (0.571g, 2.0 equiv.) in conc. H_2SO_4 (5 mL) was added maintaining 0 °C and it was continued at same temperature for another 1 hr. Then it was brought to 10-15 °C and continued the reaction for another 3 h. After 3 h, it was added to ice and basified using 10% NaOH solution. The reaction mixture was then extracted using ethyl acetate and washed with brine. The organic layer was dried over anhydrous Na_2SO_4 and evaporated in vacuum. The residue was purified by column chromatography on silica gel using ethyl acetate/hexanes mixture to afford the desired phenanthroline.

Yield: 32%

Mp: 156- 158 ^{o}C

IR (KBr) ν_{max} cm^{-1}: 1600, 1530, 1417, 1368, 1238, 995, 801



381

^{1}H NMR (400 MHz) δ: 9.49 (1H, d, *J* = 8.4 Hz), 7.97 (1H, d, *J* = 8.4 Hz), 7.61 (1H, d, *J* = 8.4 Hz), 7.50 (1H, d, *J* = 8.4 Hz), 4.41 (3H, s), 2.88 (3H, s), 2.84 (3H, s)

^{13}C NMR (100 MHz) δ: 160.9, 158.8, 146.1, 143.1, 141.8, 140.3, 133.6, 130.0, 126.8, 124.2, 123.8, 116.3 (aromatic C), 64.1, 25.5, 25.2 (aliphatic C)

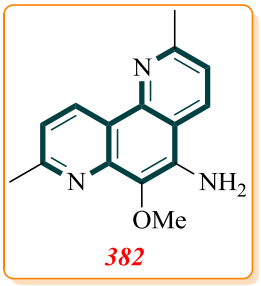
HRMS (ESI-MS)

Calcd for: $C_{15}H_{13}N_3O_3$: 284.1035 (M+H)

Found: 284.1033

6-Methoxy-2,8-dimethyl-1,7-phenanthrolin-5-amine (382):

Compound **381** (0.240 g) was dissolved in EtOH (20 mL) by warming. Next saturated aqueous solution of NH_4Cl was added to it followed by Fe powder (0.236 g, 5.0 equiv.). The mixture was heated to reflux at 80 °C for 3-4h. The reaction mixture was then cooled to room temperature and was filtered through celite using ethyl acetate as eluent. The filtrate was then evaporated to dryness and again extracted using ethyl acetate and water. The organic layer was dried over anhydrous Na_2SO_4 and evaporated in vacuum. The residue was purified by column chromatography on silica gel using ethyl acetate/hexanes mixture to afford the desired compound.



382

Yield: 96 %

Mp: 108- 110 °C

IR (KBr) ν_{max} cm^{-1}: 3357, 2930, 1627, 1492, 1406, 828, 790

^1H NMR (400 MHz) δ: 9.30 (1H, d, *J* = 8.4 Hz); 8.04 (1H, d, *J* = 8.4 Hz), 7.34 (1H, d, *J* = 8.4 Hz), 7.27 (1H, d, *J* = 8.4 Hz), 4.53 (2H, s, br), 4.15 (3H, s), 2.80 (3H, s), 2.79 (3H, s)

^{13}C NMR (100 MHz) δ: 159.7, 157.0, 144.9, 143.0, 136.1, 133.6, 132.9, 129.4, 121.6, 120.3, 119.1, 117.5 (aromatic C), 60.8, 25.6, 25.1 (aliphatic C)

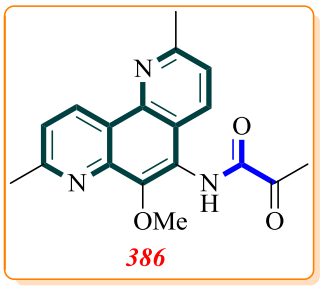
HRMS (ESI-MS)

Calcd for: $C_{15}H_{15}N_3O$: 254.1293 (M+H)

Found: 254.1287

N-(6-Methoxy-2,8-dimethyl-1,7-phenanthrolin-5-yl)-2-oxopropanamide (386):

To a stirred solution of dry dichloromethane (4-5 mL), compound **382** (0.070 g) and pyruvic acid (0.037 g, 1.5 equiv.) was added under nitrogen atmosphere and stirred at 0 °C for 20 mins. To this mixture, EDCI.HCl (0.158g, 3.0 equiv.) was added maintaining the same temperature and continued for another 2 h, followed by additional 1 h at rt until the starting material was fully consumed. The reaction mixture was then extracted with DCM. The organic layer was dried over anhydrous Na_2SO_4 and evaporated in vacuum. The residue was purified by column chromatography on silica gel using ethyl acetate/ hexanes mixture to afford the desired compound.



386

Yield: 96%

Mp: 196-198 °C

IR (KBr) ν_{max} cm^{-1}: 1693, 1594, 1561, 1353, 1260, 800

^{1}H NMR (400 MHz) δ: 9.48 (1H, d, *J* = 8.4 Hz), 8.97 (1H, s, br), 7.96 (1H, d, *J* = 8.4 Hz), 7.53 (1H, d, *J* = 8.4 Hz), 7.41 (1H, d, *J* = 8.4 Hz), 4.25 (3H, s), 2.85 (3H, s), 2.82 (3H, s), 2.68 (3H, s)

^{13}C NMR (100 MHz) δ: 196.6, 159.9, 159.3, 157.6, 148.4, 143.8, 142.6, 133.4, 132.1, 125.6, 122.7, 122.4, 120.5 (aromatic C), 62.5, 25.5, 25.1, 24.5 (aliphatic C)

HRMS (ESI-MS)

Calcd for: $C_{18}H_{17}N_3O_3$: 324.1348 (M+H)

Found: 324.1345

2-Hydroxy-*N*-(6-methoxy-2,8-dimethyl-1,7-phenanthrolin-5-yl)propanamide (383-rac):

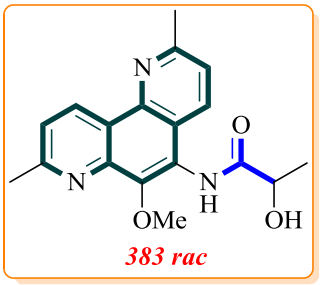
Compound **383** (0.060 g) was dissolved in methanol (5 mL, GR grade) by warming and stirred at 0 °C for 5-10 mins. Next, $NaBH_4$ (0.014 g, 2.0 equiv.) was added to the reaction and stirred it at same temperature for another 40 mins. After completion of the reaction 2 mL of saturated aqueous NH_4Cl solution was added to the reaction mixture and methanol was evaporated from the reaction mixture. Then the reaction mixture was extracted with ethyl

acetate. The organic layer was dried over anhydrous Na_2SO_4 and evaporated in vacuum. The residue was purified by column chromatography on silica gel using ethyl acetate/ hexanes mixture to afford the desired compound.

Yield: 95 %

Mp: 206-208°C

IR (KBr) ν_{max} cm^{-1}: 2843, 1660, 1600, 1567, 1336, 1265, 1068



383 rac

^{1}H NMR (500 MHz) δ: 9.38 (1H, d, *J* = 8.5 Hz), 8.94 (1H, s, br), 7.49 (2H, d, *J* = 8.5 Hz), 7.14 (1H, d, *J* = 8.5 Hz) 4.93 (1H, s, br), 4.47 (1H, q, *J* = 6.5 Hz), 4.11 (3H, s), 2.87 (3H, s), 2.70 (3H, s), 1.59 (3H, d, *J* = 5.2 Hz)

^{13}C NMR (100 MHz) δ: 174.9, 159.8, 157.4, 147.1, 143.6, 142.3, 133.8, 132.2, 125.3, 124.8, 122.5, 122.1, 120.7(aromatic C), 68.9, 62.2, 25.3, 25.1, 21.2(aliphatic C)

HRMS (ESI-MS)

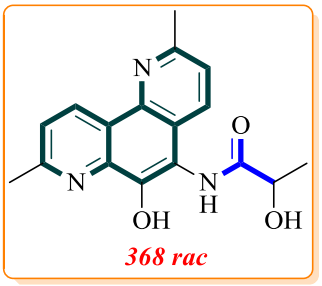
Calcd for: $C_{18}H_{19}N_3O_3$: 326.1505 (M+H)

Found: 326.1504

(2-Hydroxy-*N*-(6-hydroxy-2,8-dimethyl-1,7-phenanthrolin-5-yl)propanamide (368-rac):

Compound **383-rac** (0.050 g) was taken in a 50 mL RB, dissolved in dry DCM (25 mL, high dilution), and stirred at -78 °C. Next, 1 mL of BBr_3 in DCM solution (1.0M in DCM, 6.0 equiv.) was added to this mixture at the same temperature and stirred for another 1h. Then, slowly the reaction mixture was brought to 0 °C and stirred at 0 °C for additional 2-3 h. The reaction mixture was then allowed to come to rt and stirred for 10-12 h. On completion water was added to it and was neutralized with saturated $NaHCO_3$ solution. It was then extracted with DCM; the organic layer was dried over anhydrous Na_2SO_4 and evaporated in vacuum. The residue was purified by column chromatography on silica gel using ethyl acetate/hexanes mixture to afford the desired compound.

Yield: 76 %



368 rac

Mp: 232-234°C

IR (KBr) ν_{max} cm^{-1}: 3355, 2976, 1720, 1642, 1605, 1487, 796

^{1}H NMR (500 MHz, DMSO- d_6) δ: 9.43 (1H, s, br), 9.30 (1H, d, *J* = 8.5 Hz), 7.99 (1H, d, *J* = 8.5 Hz), 7.68 (1H, d, *J* = 8.5 Hz), 7.51 (1H, d, *J* = 8.5 Hz), 5.82-5.81 (1H, m), 4.34-4.29 (1H, m), 2.79 (3H, s), 2.71 (3H, s), 1.43 (3H, d, *J* = 7.0 Hz)

^{13}C NMR (125 MHz, DMSO- d_6) δ: 174.5, 158.8, 154.9, 145.0, 140.6, 139.1, 132.9, 131.4, 123.1, 123.1, 122.9, 122.5, 114.4 (aromatic C), 67.7, 24.5, 24.5, 21.2 (aliphatic C)

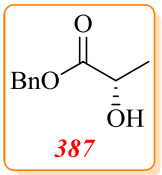
HRMS (ESI-MS)

Calcd for: $C_{17}H_{17}N_3O_3$: 312.1348 (M+H)

Found: 312.1354

(S)-Benzyl 2-hydroxypropanoate (387):

To a well stirred solution of L-lactic acid (1g, 11.1 mmol) in dry DMF (20 mL), K_2CO_3 (0.534g, 22.2 mmol) was added under nitrogen atmosphere at 0 °C. After 10-15 mins, benzyl bromide (1.4 mL, 12.2 mmol) was added and the reaction was allowed to proceed for 1 h at rt. The reaction mixture was then poured into the ice-water (30 mL) and extracted with ethyl acetate. Organic fraction was dried over anhydrous sodium sulphate and subjected to column chromatography to separate excess benzyl bromide. This compound was obtained as colourless liquid.



387

Yield: 61 %

^{1}H NMR (400 MHz) δ: 7.40-7.37 (5H, m), 5.22 (2H, s), 4.35 (1H, q, *J* = 4.8 Hz), 3.30 (1H, s, br), 1.46 (3H, d, *J* = 6.8 Hz)

^{13}C NMR (100 MHz) δ: 175.5, 135.3, 128.7, 128.2 (aromatic C), 67.2, 66.9, 20.3 (aliphatic C)

HRMS (ESI-MS)

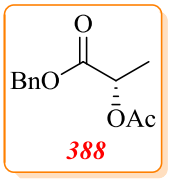
Calcd for: $C_{10}H_{12}O_3$: 203.0684 (M+Na)

Found: 203.0681

(S)-Benzyl 2-acetoxypropanoate (388)[12]:

Compound **387** (0.200 g, 1.1 mmol) were acylated with acetic anhydride (0.2 mL, 2.2 mmol) and a catalytic amount of DMAP in dry DCM (6.0 mL) at rt for 3 h. The reaction mixture was then poured into the water (20 mL) and extracted with ethyl acetate. Organic fraction was dried over anhydrous sodium sulphate and subjected to column chromatography. This compound was obtained as light yellowish liquid.

Yield: 54 %



388

^{1}H NMR (400 MHz) δ: 7.39- 7.35 (5H, m), 5.21 (2H, d, *J* = 4.0 Hz), 5.18- 5.12 (1H, m), 2.15 (3H, s), 1.52 (3H, d, *J* = 6.8 Hz)

^{13}C NMR (100 MHz) δ: 170.7, 170.4, 135.4, 128.6, 128.1 (aromatic C), 68.6, 67.0, 20.7, 16.9 (aliphatic C)

HRMS (ESI-MS)

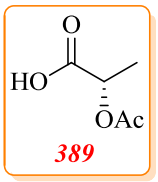
Calcd for: $C_{12}H_{14}O_4$: 245.0790 (M+Na)

Found: 245.0794

(S)-2-Acetoxypropanoic acid (389):

To a solution of compound **388** (0.100g, 0.45 mmol) in THF (10 mL) a catalytic amount of 10% Pd/C was stirred under H_2 atmosphere at rt. After 2- 3 h, the mixture was diluted with ethyl acetate and filtered through celite to remove Pd/C. Removal of the solvent from the filtrate under reduced pressure gave debenzylated compound **389**. This compound was obtained brown liquid.

Yield: 95 %



389

^{1}H NMR (400 MHz) δ: 9.62 (1H, s, br), 5.10 (1H, q, *J* = 7.2 Hz), 2.14 (3H, s), 1.54 (3H, d, *J* = 7.2 Hz)

^{13}C NMR (100 MHz) δ: 176.3, 170.7, 68.3, 20.6, 16.8

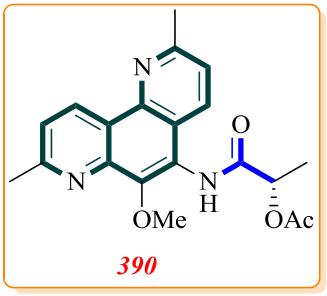
HRMS (ESI-MS)

Calcd for: $C_5H_8O_4$: 155.0320 (M+Na)

Found: 155.0317

(S)-1-((6-Methoxy-2,8-dimethyl-1,7-phenanthrolin-5-yl)amino)-1-oxopropan-2-yl acetate (390):

To a stirred solution of dry dichloromethane (4-5 mL), compound **382** (0.150 g) and compound **389** (0.117 g, 1.5 equiv.) was added under nitrogen atmosphere and stirred at 0 °C for 20 mins. To this mixture, EDCI.HCl (0.340 g, 3.0 equiv.) was added maintaining the same temperature and continued for another 1 h, followed by additional 72 h at rt but still the starting material was not consumed fully. Then the reaction mixture was then extracted with DCM. The organic layer was dried over anhydrous Na_2SO_4 and evaporated in vacuum. The residue was purified by column chromatography on silica gel using ethyl acetate/ hexanes mixture to afford the desired compound. 0.050 g of compound **382** was recovered after column.



390

Yield: 68 %

Mp: 212-214°C

IR (KBr) ν_{max} cm^{-1}: 3249, 1742, 1671, 1545, 1484, 805

^{1}H NMR (400 MHz) δ: 9.42 (1H, d, *J* = 8.4 Hz), 8.09 (1H, s, br), 7.96 (1H, d, *J* = 8.0 Hz), 7.48 (1H, d, *J* = 8.4 Hz), 7.37 (1H, d, *J* = 8.4 Hz), 5.47 (1H, q, *J* = 6.4 Hz), 4.17 (3H, s), 2.83 (3H, s), 2.79 (3H, s), 2.29 (3H, s), 1.73 (3H, d, *J* = 6.8 Hz)

^{13}C NMR (100 MHz) δ: 170.8, 170.0, 159.8, 157.5, 148.0, 143.8, 142.5, 133.3, 132.4, 125.4, 123.9, 122.5, 121.2 (aromatic C), 71.1, 62.4, 25.5, 25.2, 21.1, 18.0 (aliphatic C)

HRMS (ESI-MS)

Calcd for: $C_{20}H_{21}N_3O_4$: 368.1610 (M+H)

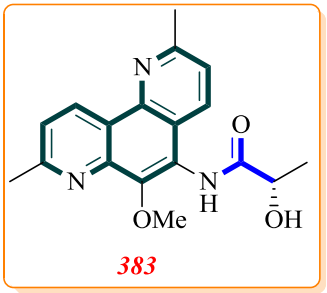
Found: 368.1610

(S)-2-Hydroxy-*N*-(6-methoxy-2,8-dimethyl-1,7-phenanthrolin-5-yl)propanamide (383):

To a stirred solution of compound **390** (0.080 g) in methanol (GR grade, 7-8 mL) at 0 °C, anhydrous K_2CO_3 (0.090 g, 3.0 equiv.) was added and it was stirred for 10-15 mins in the same temperature. After completion of the reaction, methanol was evaporated under vacuum. Next, it was extracted with ethyl acetate; the organic layer was dried over anhydrous Na_2SO_4 and evaporated in vacuum. The residue was purified by column chromatography on silica gel using ethyl acetate/hexanes mixture to afford the desired compound.

Yield: 97 %

Mp: 212-214^{o}C



383

IR (KBr) ν_{max} cm^{-1}: 3353, 1649, 1621, 1512, 1331, 1227, 805

^{1}H NMR (500 MHz, $CDCl_3$ + DMSO- d_6) δ: 9.33 (1H, d, *J* = 8.5 Hz), 8.92 (1H, s, br), 7.84 (1H, d, *J* = 8.0 Hz), 7.40 (1H, d, *J* = 8.5 Hz), 7.23 (1H, d, *J* = 8.5 Hz), 5.41 (1H, s, br), 4.45-4.40 (1H, m), 4.10 (3H, s), 2.75 (3H, s), 2.68 (3H, s), 1.54 (3H, d, *J* = 7.0 Hz)

^{13}C NMR (100 MHz, $CDCl_3$ + DMSO- d_6) δ: 175.3, 159.7, 157.2, 148.0, 144.0, 142.4, 133.3, 132.4, 125.2, 124.5, 122.3, 122.2, 121.3 (aromatic C), 68.7, 62.0, 25.4, 25.1, 21.3 (aliphatic C)

HRMS (ESI-MS)

Calcd for: $C_{18}H_{19}N_3O_3$: 326.1505 (M+H)

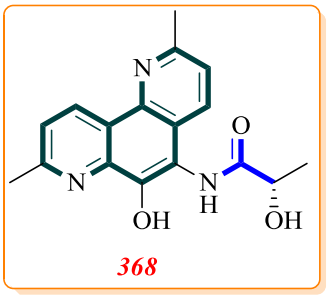
Found: 326.1500

(S)-2-Hydroxy-*N*-(6-methoxy-2,8-dimethyl-1,7-phenanthrolin-5-yl)propanamide (368):

Compound **383** (0.030 g) was taken in a 50 mL RB, dissolved in dry DCM (25 mL, high dilution), and stirred at -78 °C. Next, 0.56 mL BBr_3 in DCM solution (1.0M in DCM, 6.0 equiv.) was added to this mixture at the same temperature and stirred for another 1h. Then, slowly bring the reaction mixture to 0 °C and stirred at 0 °C for additional 2-3 h. The reaction mixture was then allowed to come to rt and stirred for 10-12 h. On completion water was added to it and was neutralized with saturated $NaHCO_3$ solution. It was then extracted with DCM; the organic layer was dried over anhydrous Na_2SO_4 and evaporated in vacuum. The residue was purified by column chromatography on silica gel using ethyl acetate/hexanes mixture to afford the desired compound. This compound was obtained as a white solid.

Yield: 72 %

Mp: 204-208°C



368

IR (KBr) ν_{max} cm^{-1}: 3255, 2933, 1733, 1690,1455, 1112, 796

^{1}H NMR (500 MHz, DMSO- d_6) δ: 9.43 (1H, s, br), 9.30 (1H, d, *J* = 8.5 Hz), 7.99 (1H, d, *J* = 8.0 Hz), 7.68 (1H, d, *J* = 8.0 Hz), 7.51 (1H, d, *J* = 8.5 Hz), 5.82-5.81 (1H, m), 4.34- 4.29 (1H, m), 2.79 (3H, s), 2.71 (3H, s), 1.43 (3H, d, *J* = 6.5 Hz)

^{13}C NMR (100 MHz, DMSO- d_6) δ: 174.5, 158.9, 154.9, 145.2, 140.8, 139.1, 132.7, 131.4, 123.1, 123.1, 122.9, 122.5, 114.3 (aromatic C), 67.7, 24.6, 24.6, 21.3 (aliphatic C)

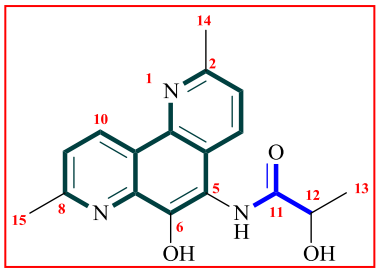
HRMS (ESI-MS)

Calcd for: $C_{17}H_{17}N_3O_3$: 312.1348 (M+H)

Found: 312.1352

$[\alpha]_D^{28}$: 9 (*c* 0.33, MeOH);

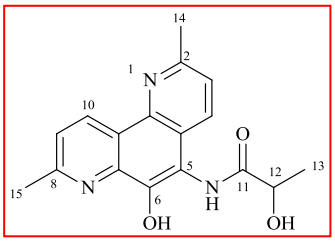
Important NOTE:



The value reported in the isolation for 6-OH is δ5.90 ppm which is incorrect. The value δ 5.90 ppm they received in NMR spectrum is for 12-OH and not for 6-OH. In the process of doing the stepwise synthesis of Actinophenanthroline A we found that δ 5.90 belongs to 12-OH and not to the 6-OH (***see NMR of compound 368-rac and 368***). Thus, we corrected the value of synthetic Actinophenanthroline A.

Comparison values of isolated and synthetic racemic Actinophenanthroline A

No.	δ_H (*J* in Hz) isolated	δ_H (*J* in Hz) synthesized	δ_C (*J* in Hz) isolated	δ_C (*J* in Hz) synthesized
1	-	-	-	-
1a	-	-	138.9	139.1
2	-	-	154.5	154.9
3	7.49 (d, 8.5)	7.51 (d, 8.5)	123.0	122.5
4	7.99 (d, 8.5)	7.99 (d, 8.5)	131.2	131.2
4a	-	-	123.1	123.1
5	-	-	114.2	114.4
6	-	-	145.8	145.0
6a	-	-	141.1	140.6
7	-	-	-	-
8	-	-	158.8	158.8
9	7.66 (d, 8.5)	7.68 (d, 8.5)	123.1	122.9
10	9.30 (d, 8.5)	9.30 (d, 8.5)	132.7	132.9
10a	-	-	123.2	123.1
11	-	-	174.5	174.5
12	4.32 (q, 6.8)	4.34- 4.29 (1H, m)	67.7	67.7
13	1.44 (d, 6.8)	1.43 (d, 7.0)	21.3	21.2
14	2.71 s	2.71 s	24.6	24.5
15	2.79 s	2.79 s	24.6	24.5
5-NH	9.50	9.43		
6-OH	5.90	-		
12-OH		5.82- 5.81 (1H, m)		



Comparison values of isolated and synthetic Actinophenanthroline A

No.	δ_H (*J* in Hz) isolated	δ_H (*J* in Hz) synthesized	δ_C (*J* in Hz) isolated	δ_C (*J* in Hz) synthesized
1	-	-	-	-
1a	-	-	138.9	139.1
2	-	-	154.5	154.9
3	7.49 (d, 8.5)	7.51 (d, 8.5)	123.0	122.5
4	7.99 (d, 8.5)	7.99 (d, 8.0)	131.2	131.4
4a	-	-	123.1	123.1
5	-	-	114.2	114.3
6	-	-	145.8	145.2
6a	-	-	141.1	140.8
7	-	-	-	
8	-	-	158.8	158.9
9	7.66 (d, 8.5)	7.68 (d, 8.0)	123.1	122.9
10	9.30 (d, 8.5)	9.30 (d, 8.5)	132.7	132.7
10a	-	-	123.2	123.1
11	-	-	174.5	174.5
12	4.32 (q, 6.8)	4.34- 4.29 (1H, m)	67.7	67.7
13	1.44 (d, 6.8)	1.43 (d, 6.5)	21.3	21.3
14	2.71 s	2.71 s	24.6	24.6
15	2.79 s	2.79 s	24.6	24.6
5-NH	9.50	9.43		
6-OH	5.90	-		
12-OH		5.82- 5.81 (1H, m)		

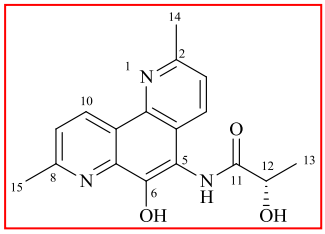
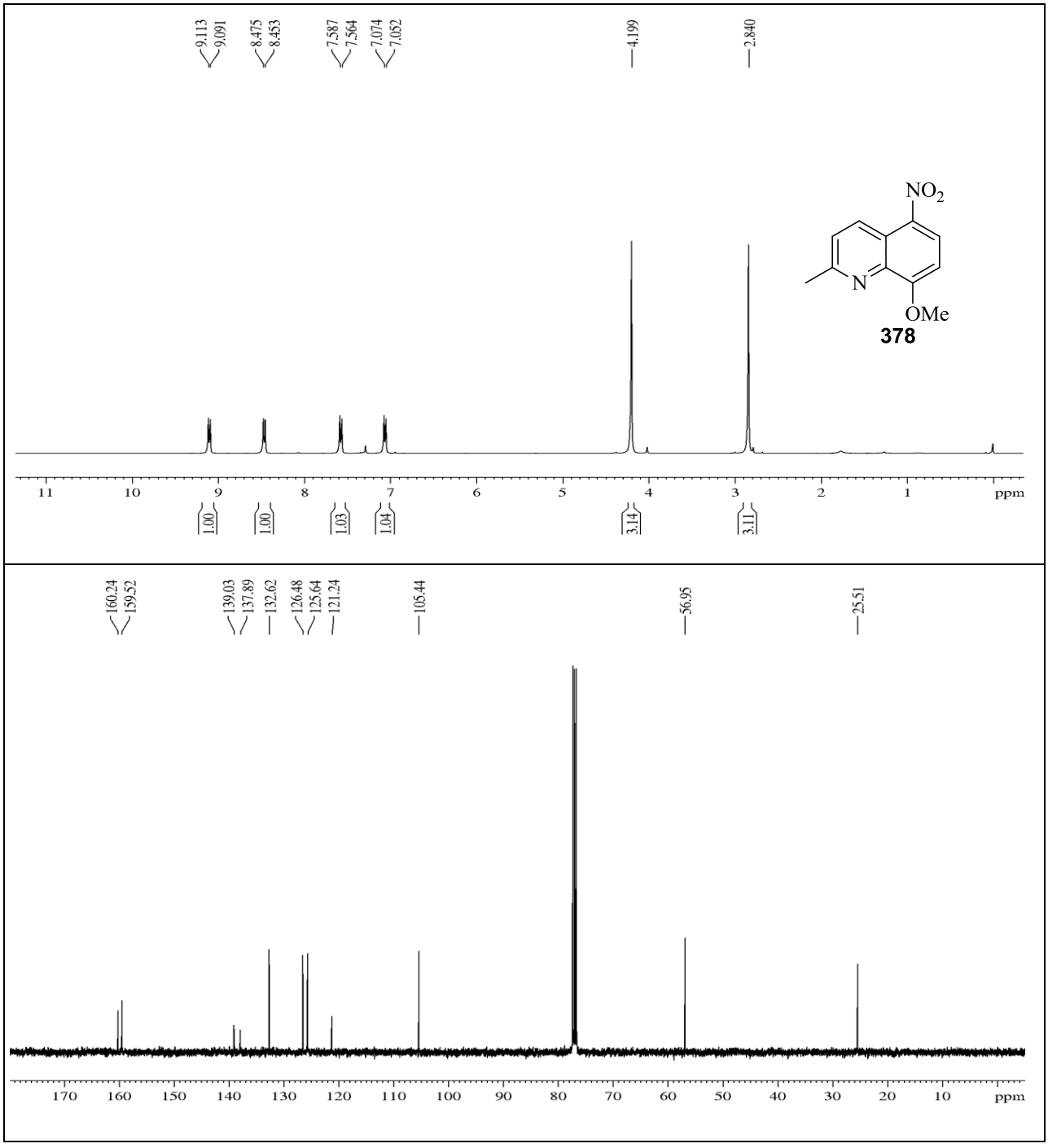


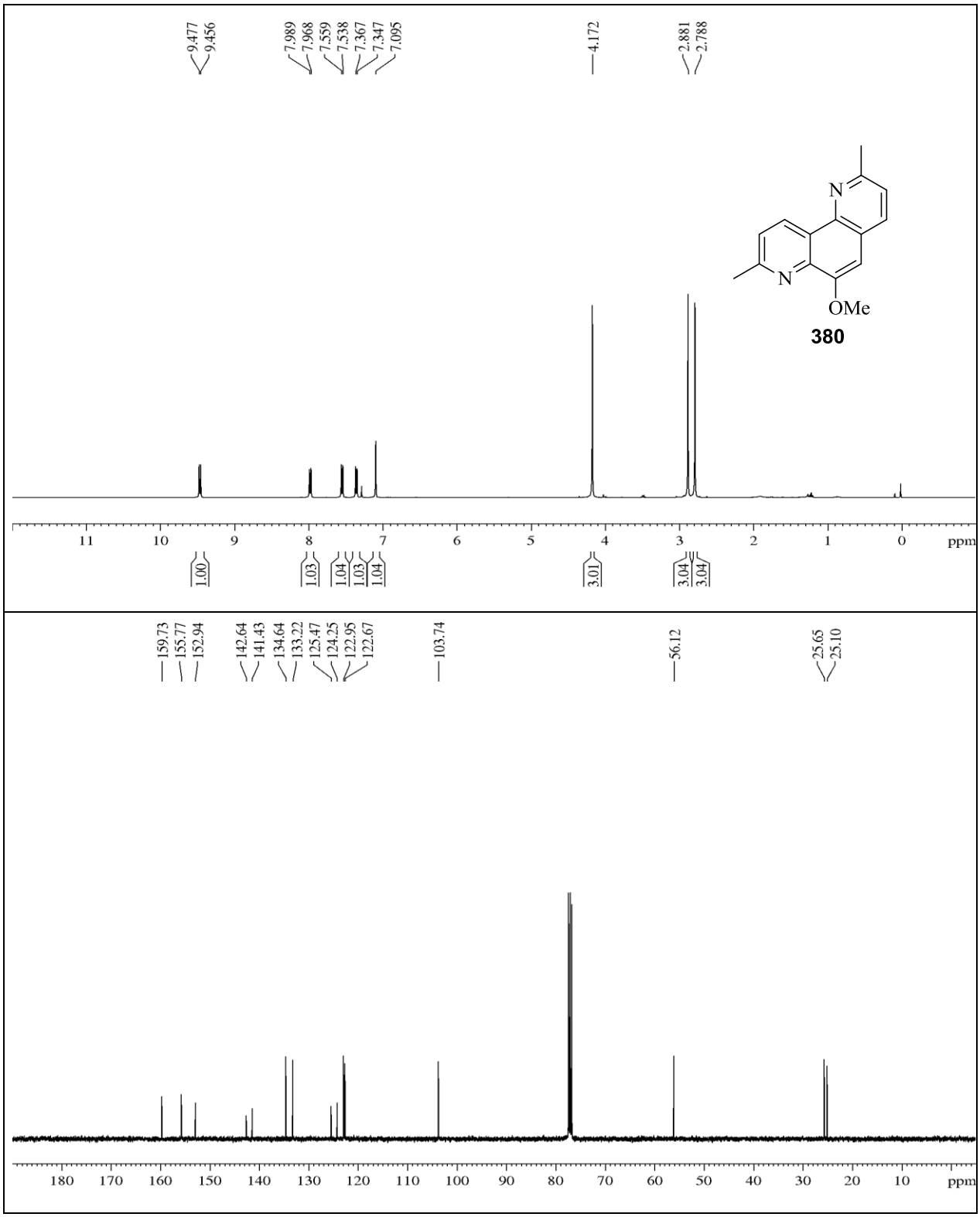
Table 7. Crystal data and structure refinement for 382

Empirical formula	:$C_{15}H_{15}N_3O$	
Formula weight	:253.29	
Temperature	:298(2) K	
Wavelength	:0.71073 Å	
Crystal system	:Hexagonal	
Space group	:P b c a	
Unit cell dimensions	:a = 12.2068(11) Å	α= 90°.
	:b = 12.9661(9) Å	β= 90°.
	:c = 16.6958(14) Å	γ = 90°.
Volume	:2642.5(4) $Å^3$	
Z	:8	
Density (calculated)	:1.268 Mg/m^3	
Absorption coefficient	:0.080 mm^{-1}	
F(000)	:1072	
Crystal size	:0.18 x 0.16 x 0.14 mm^3	
Theta range for data collection	:3.14 to 25.06°.	
Index ranges	:-14<=h<=14, -15<=k<=14, -19<=l<=19	
Reflections collected	:22311	
Independent reflections	:2321 [R(int) = 0.3118]	
Completeness to theta = 25.06°	:99.2 %	
Absorption correction	:Semi-empirical from equivalents	
Max. and min. transmission	:0.9888 and 0.9857	
Refinement method	:Full-matrix least-squares on F2	
Data / restraints / parameters	:2321 / 0 / 176	
Goodness-of-fit on F2	:1.596	
Final R indices [I>2sigma(I)]	:R1 = 0.1430, wR2 = 0.3643	
R indices (all data)	:R1 = 0.1563, wR2 = 0.3913	
Largest diff. peak and hole	:0.632 and -0.714 $e.Å^{-3}$	
CCDC Number	:1445332	

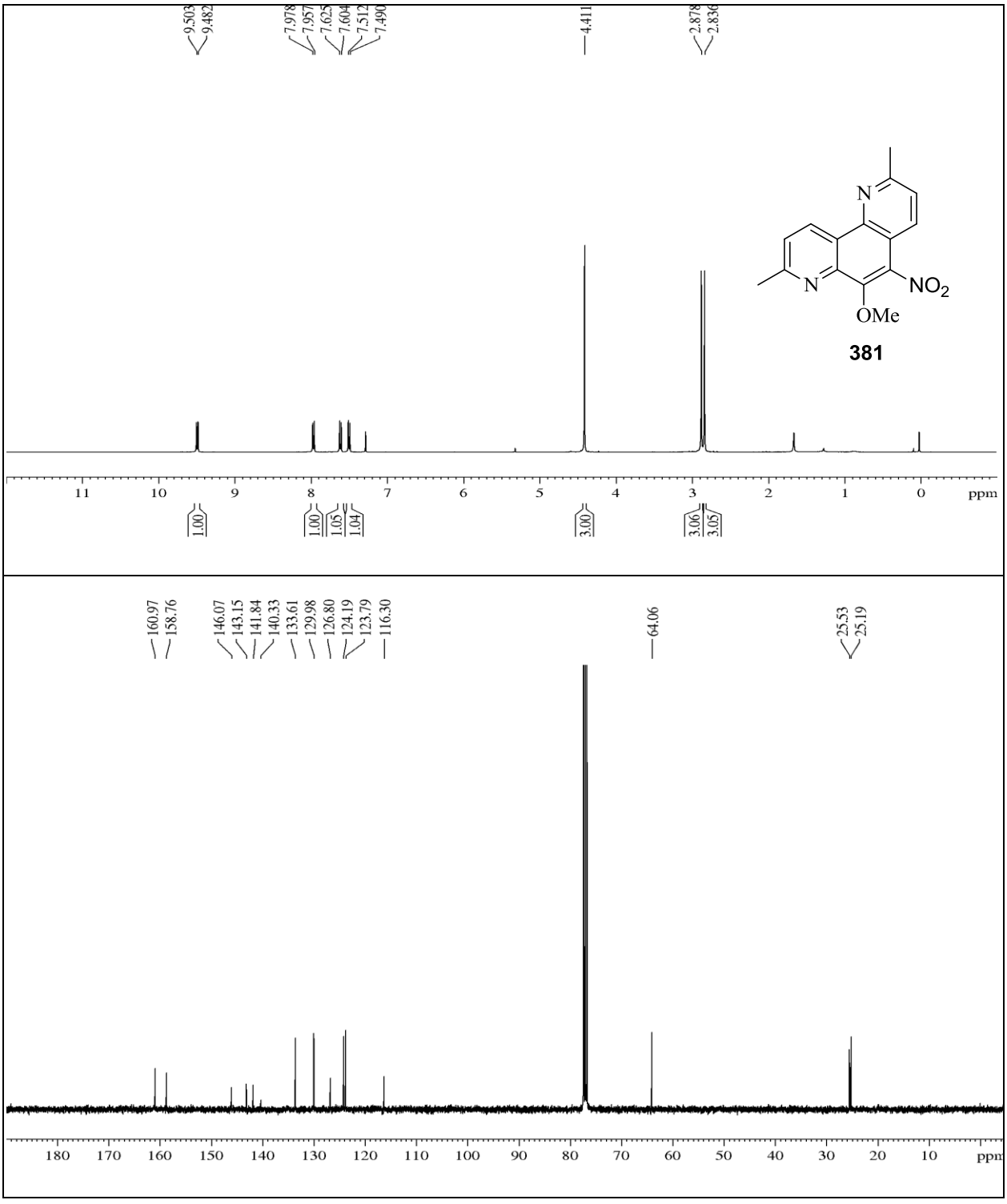
^{1}H, ^{13}C NMR of compound 378



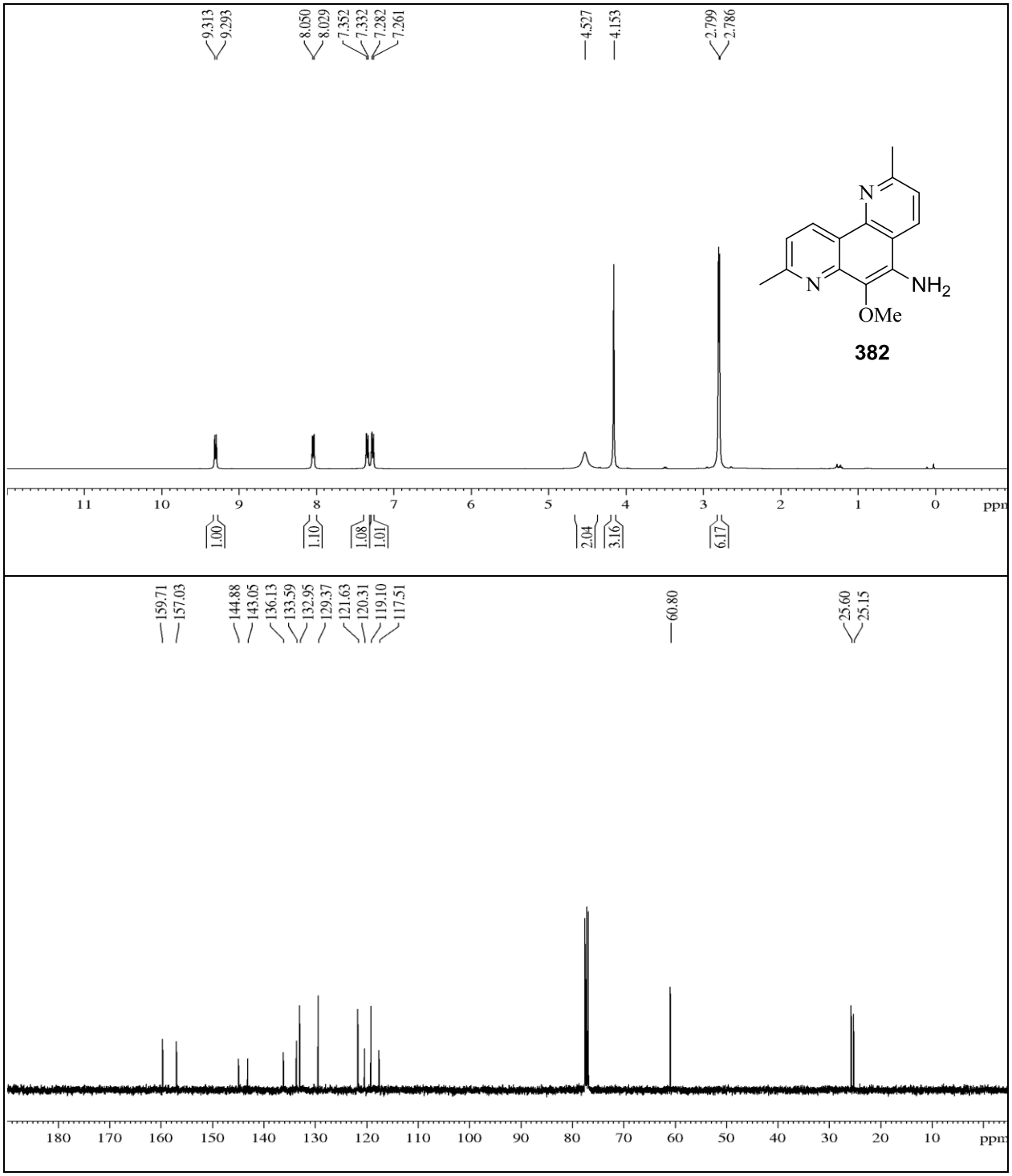
^{1}H, ^{13}C NMR of compound 380



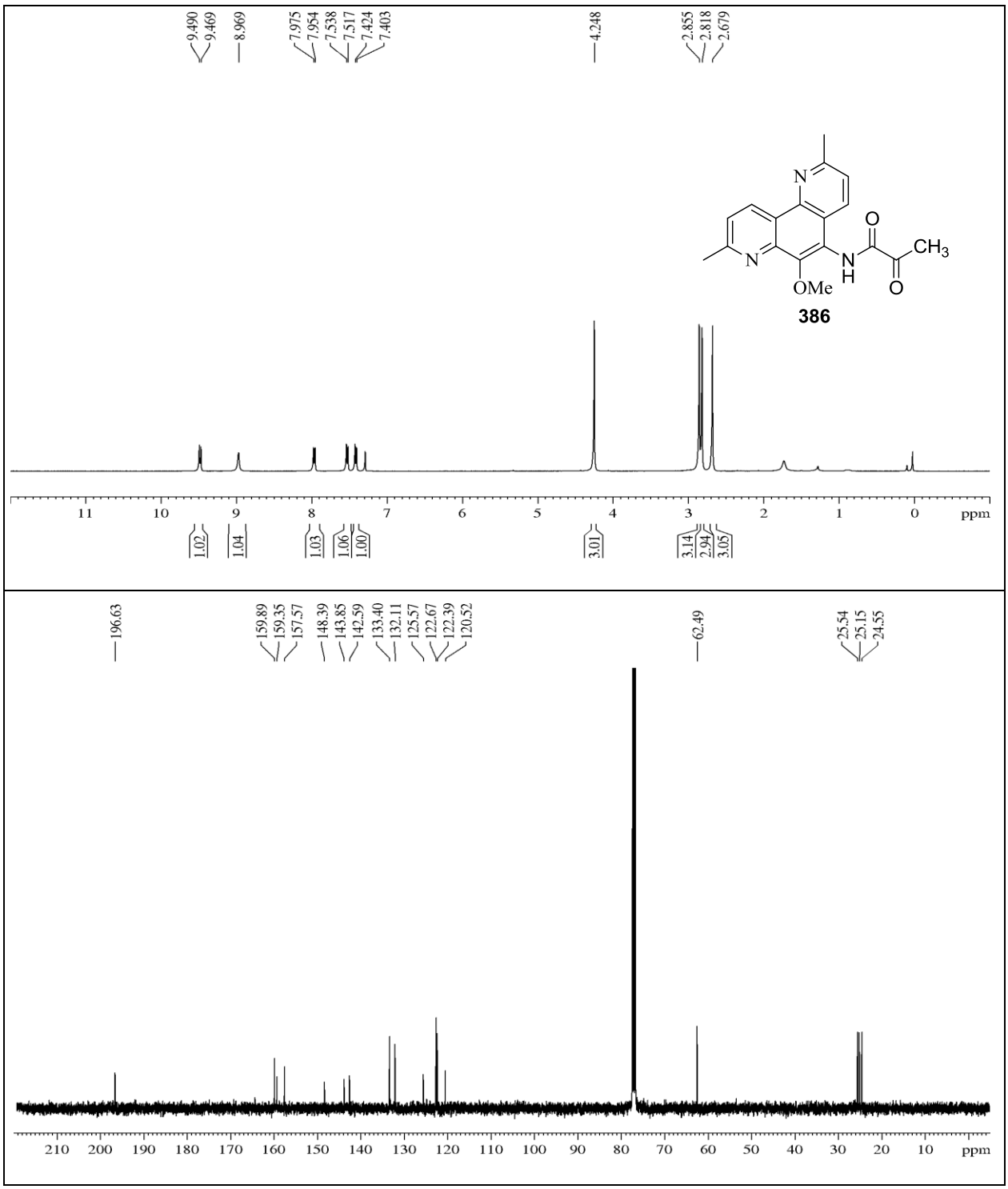
^{1}H, ^{13}C NMR of compound 381



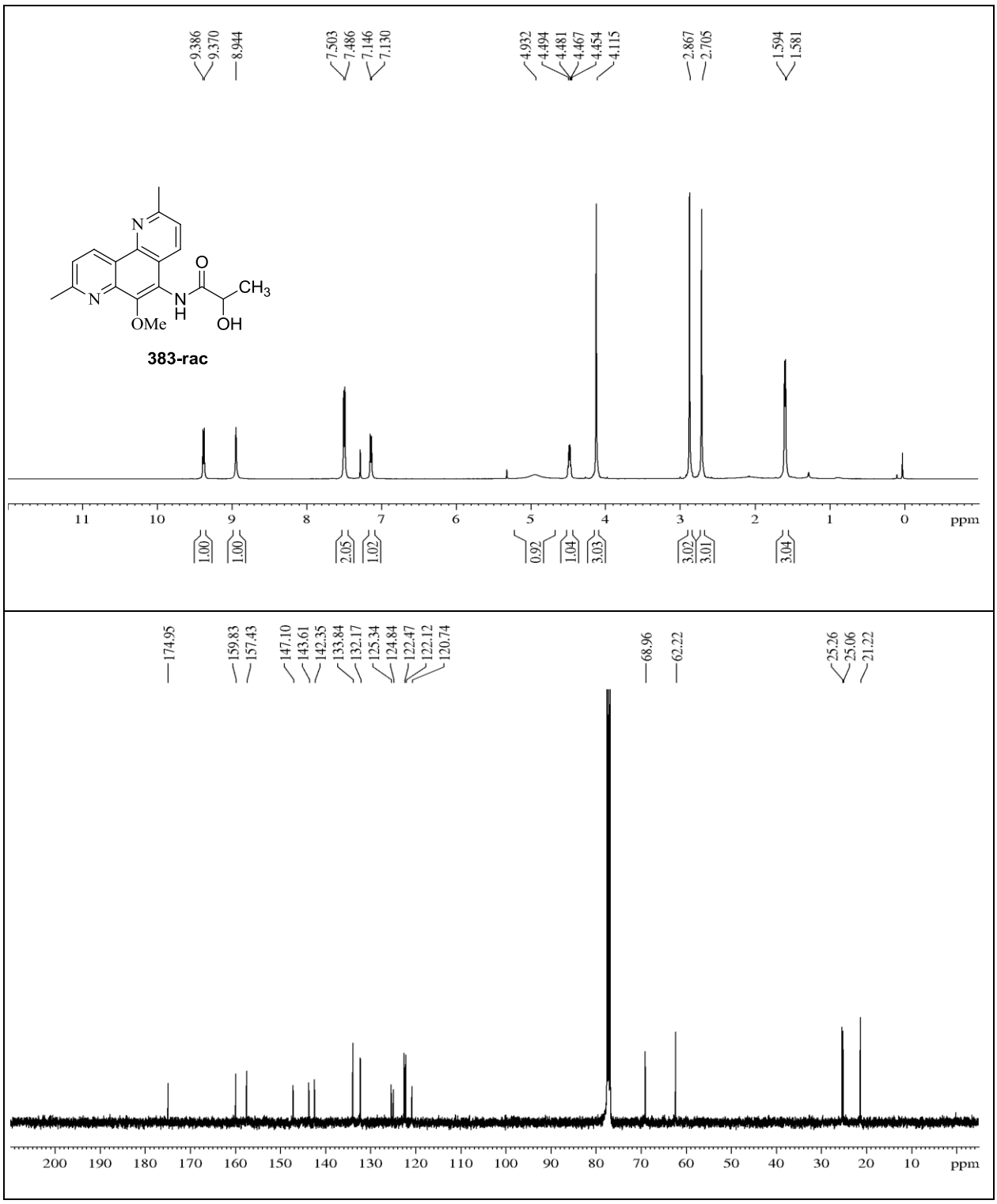
^{1}H, ^{13}C NMR of compound 382



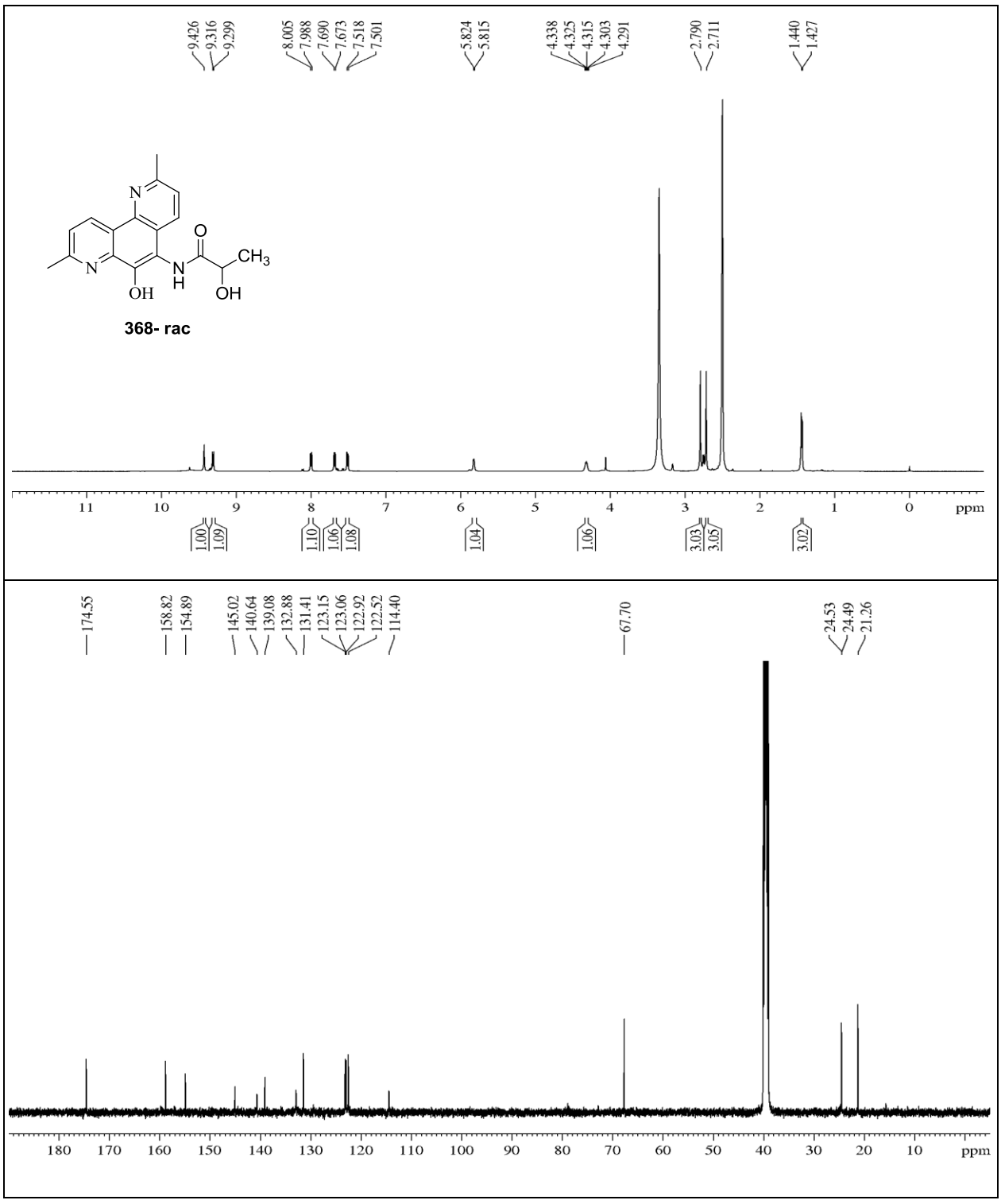
^{1}H, ^{13}C NMR of compound 386



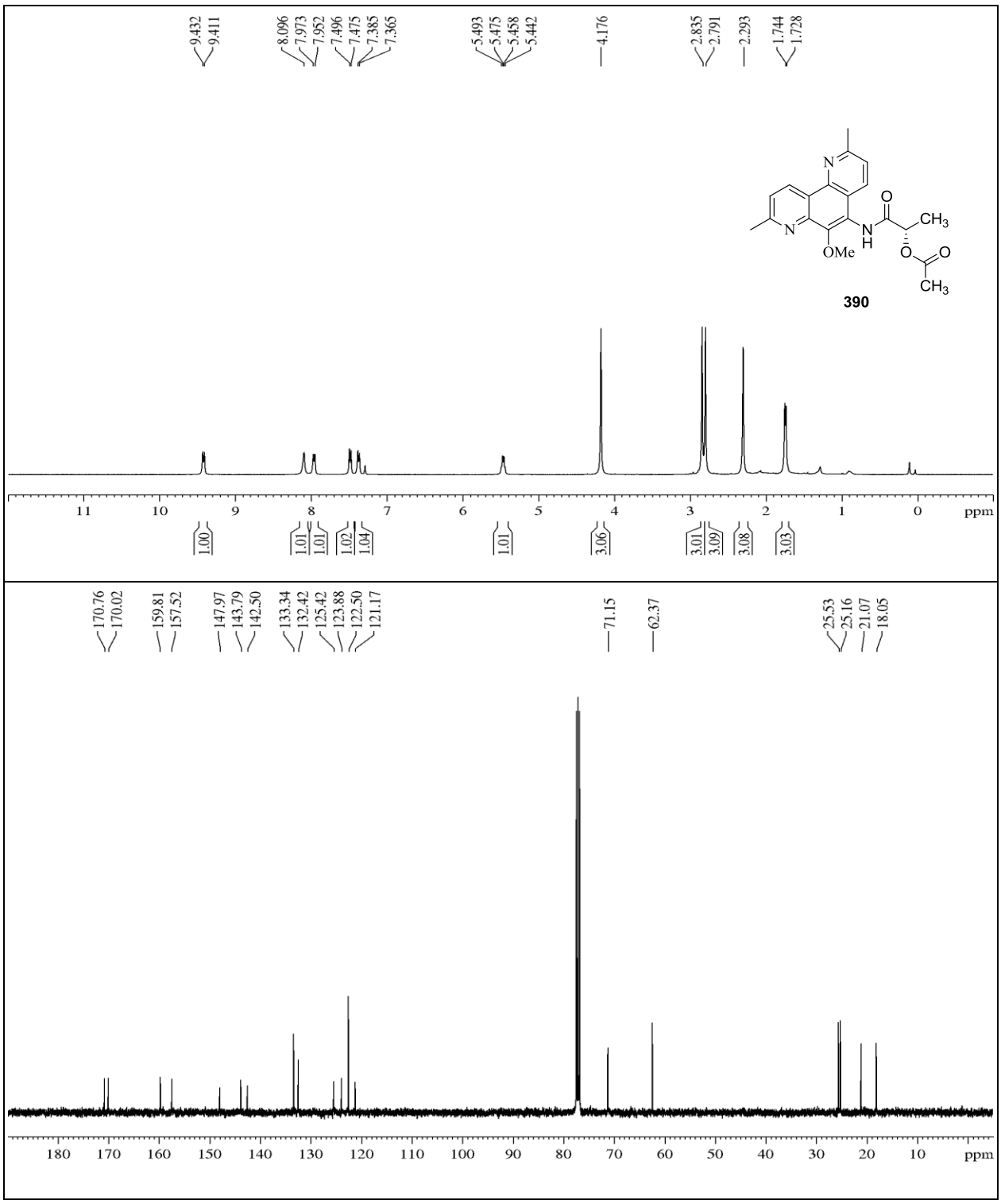
^{1}H, ^{13}C NMR of compound 383-rac



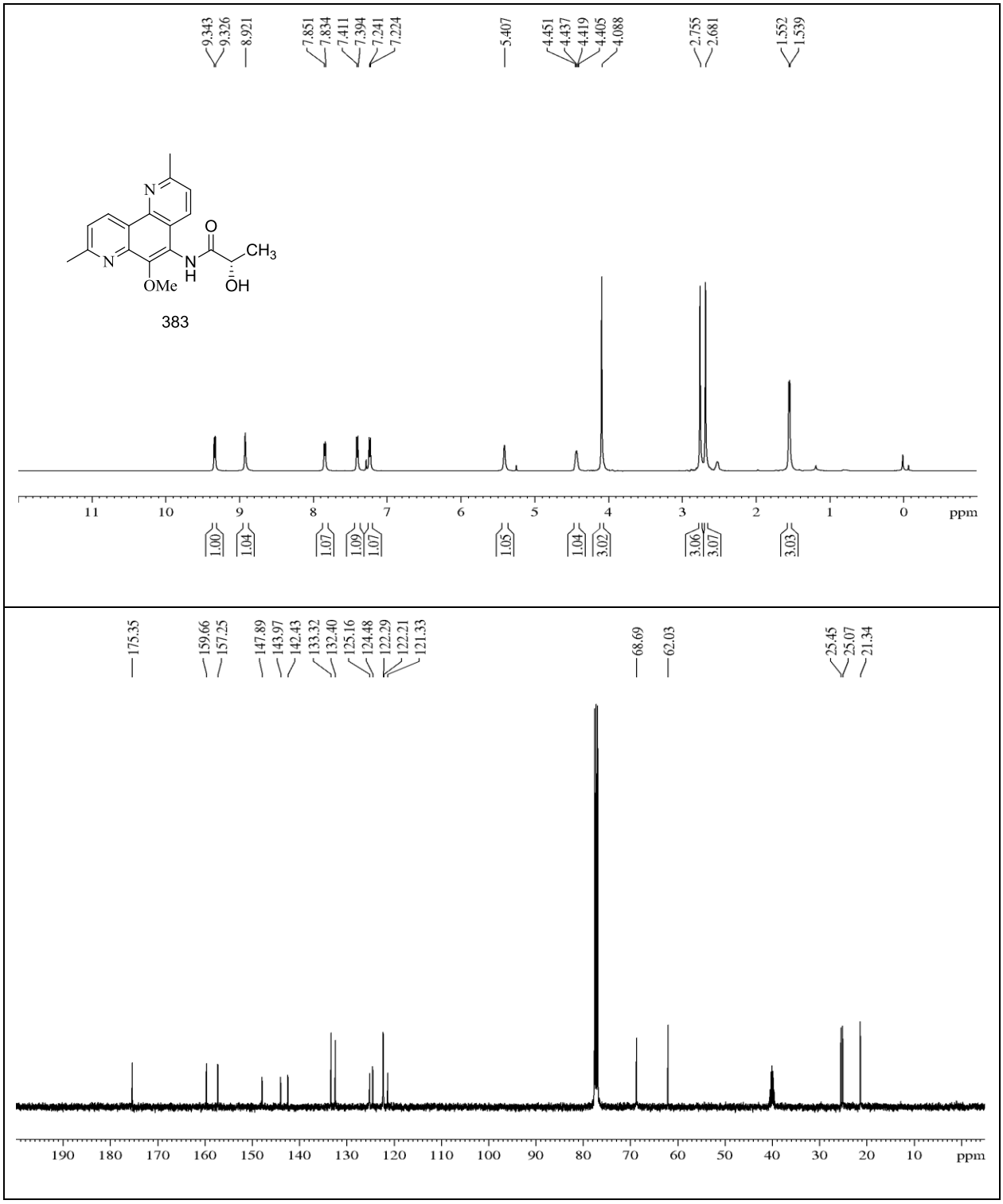
^{1}H, ^{13}C NMR of compound 368-rac



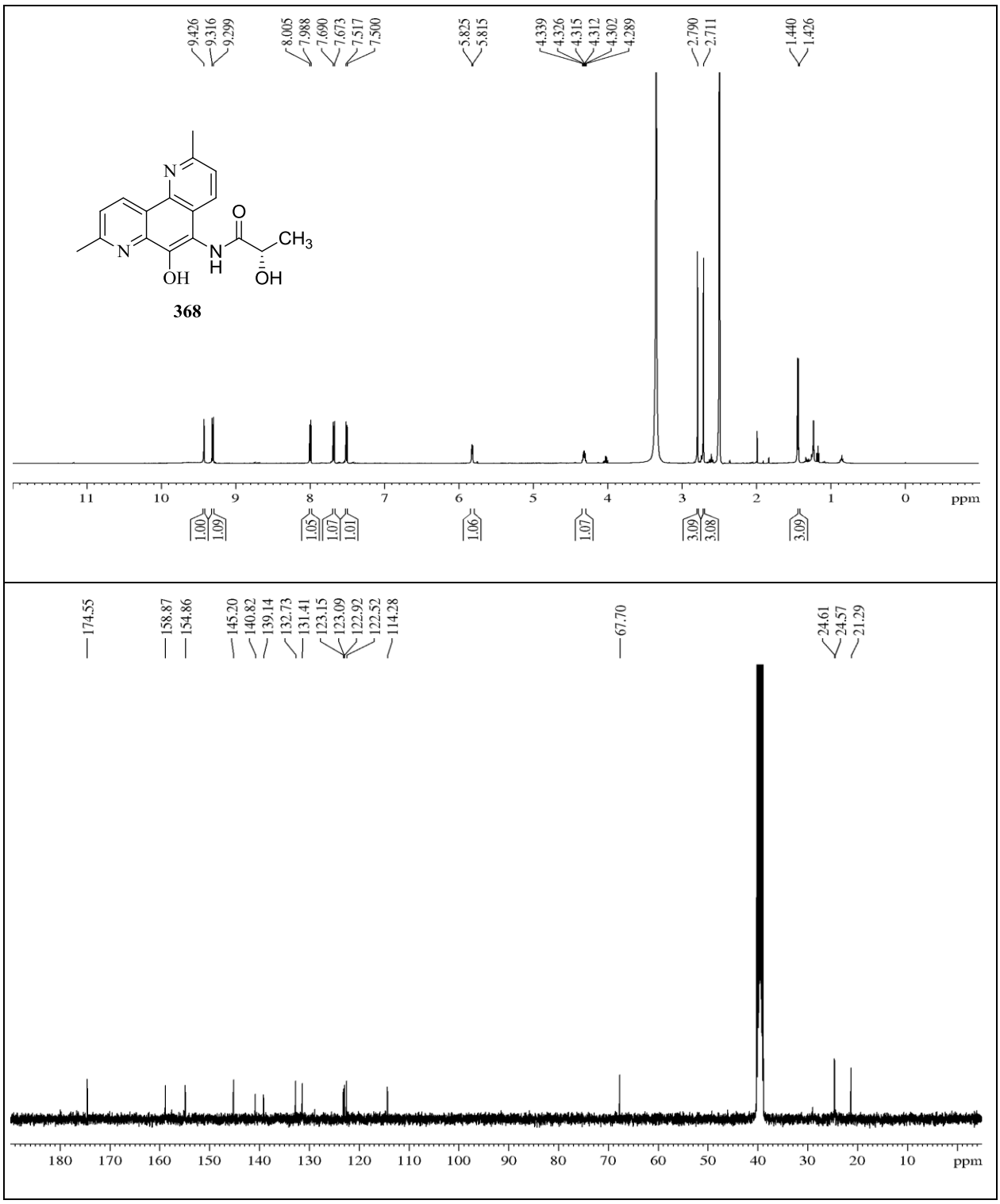
^{1}H, ^{13}C NMR of compound 390



^{1}H, ^{13}C NMR of compound 383



^{1}H, ^{13}C NMR of compound 368



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Conclusions

We have made noticeable progress and accomplished considerable success in our objectives on the development of new methodologies on quinazolinone heterocycle and applied them for the synthesis of various quinazolinone based natural products. We have also accomplished the total synthesis of a phenanthroline alkaloid actinophenanthroline A.

- We have developed an efficient metal free regioselective C2 amidation methodology with indole/ pyrrole and quinazolinones/pyrimidones to synthesize indolylquniazolinone/ pyrimidone and pyrrolylquinazolinone. Further, highly functionalized indolo-[1,3]-diazepine compound was also prepared using this strategy.

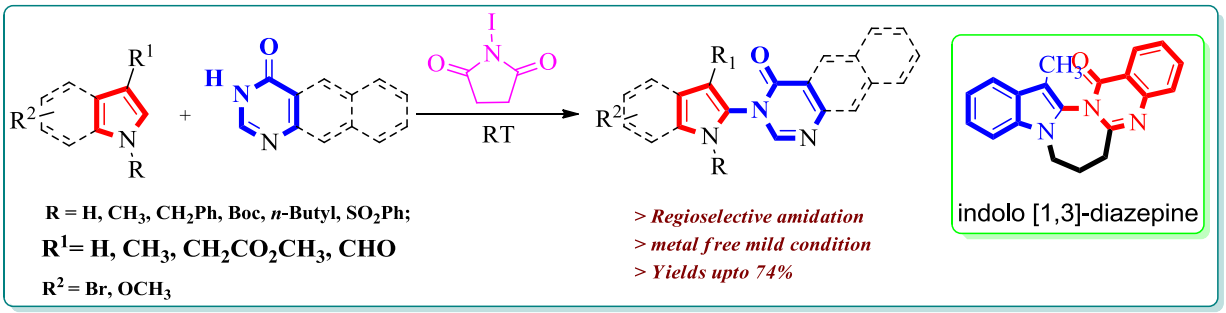
- We have completed a step economical and protecting group free total synthesis of cruciferane via easily accessible starting materials and mild conditions with excellent overall yield.

- We have developed a greener and economical protocol to synthesize various substituted and unsubstituted dihydroquinazolinones along with different quinazolinones in good to excellent yields. This strategy was further utilized to carry out the formal synthesis of few biologically active alkaloids as well as drugs. In particular, we have utilized this economical strategy for first chemical synthesis of alkaloids, such as, penipanoid C, 2-(4-hydroxybenzyl) quinazolin-4(3*H*)-one, terremide C, Methyl 3,4,5-trimethoxy-2-(2- (nicotinamido)benzamido)benzoate and NU1025 drug.

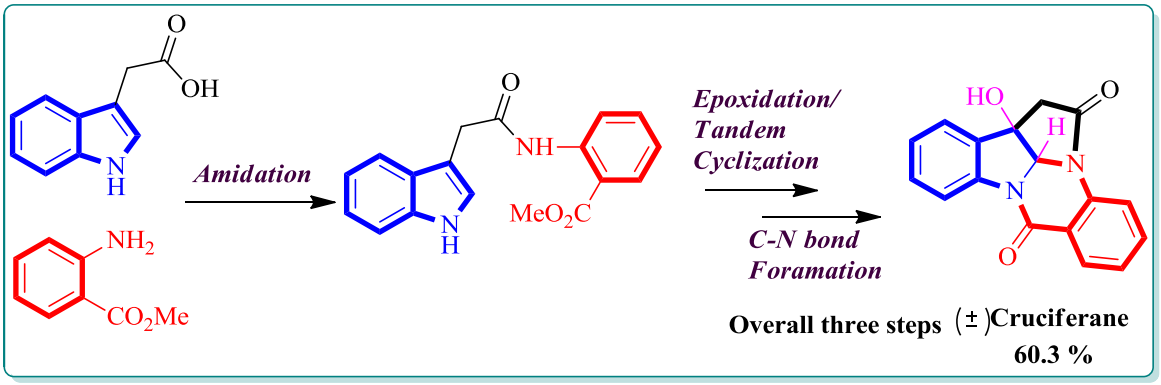
- We have accomplished the synthesis of both racemic and enantiopure actinophenanthroline A using easier, classical and economical strategies. These synthetic strategies administer a much easier route to synthesize the other analogue of this alkaloid.

Graphical Abstracts

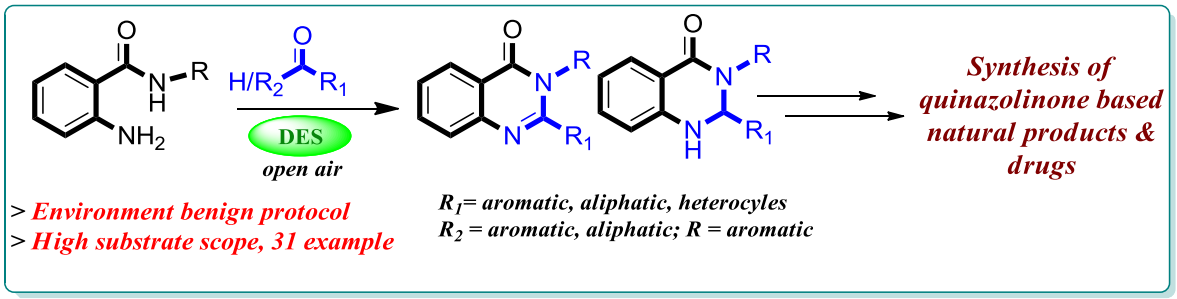
CHAPTER 1: Synthesis of Novel Indolylquinazolinones and Pyrrolylquinazolinones via regioselective C2 amidation of Indole and Pyrrole

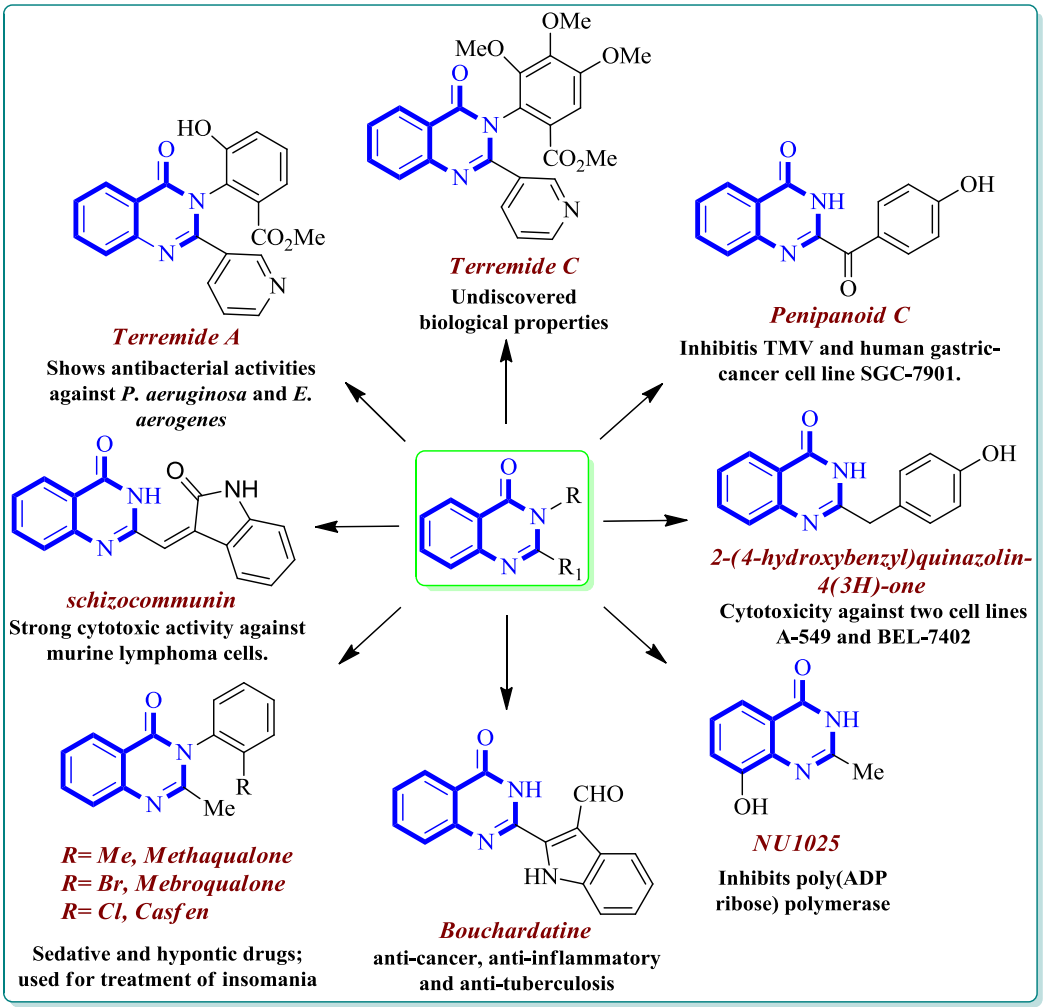


Chapter 2: Total Synthesis of Cruciferane via Epoxidation/Tandem Cyclization Sequence



Chapter 3: Synthesis of substituted quinazolinones via Deep Eutectic Solvent (DES) mediated cyclization: Total synthesis of natural products and drugs





Chapter 4: Synthesis of Actinophenanthroline A via double Doebner–Miller reaction