Studies on Total Synthesis of Bioactive Natural and Unnatural Quinazolinones

Thesis Submitted to AcSIR

For the Award of the Degree of

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In

CHEMICAL SCIENCES

BY

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April 2016

Dedicated to

My Parents and Teachers

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Thesis Certificate

This is to certify that the work incorporated in this Ph.D. thesis entitled **"Studies on Total Synthesis of Bioactive Natural and Unnatural Quinazolinones**" submitted by **Mr. Sagar Dilip Vaidya** to Academy of Scientific and Innovative Research (AcSIR) in fulfilment of the requirements for the award of the Degree of Doctor of Philosophy, embodies original research work under my supervision. I further certify that this work has not been submitted to any other University or Institution in part or full for the award of any degree or diploma. Research material obtained from other sources has been duly acknowledged in the thesis. Any text, illustration, table etc., used in the thesis from other sources, have been duly cited and acknowledged.

Sagar Dilip Vaidya
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(Research Supervisor)

CSIR-NATIONAL CHEMICAL LABORATORY

Declaration by the Candidate

I hereby declare that the original research work embodied in this thesis entitled, **"Studies on Total Synthesis of Bioactive Natural and Unnatural Quinazolinones''** submitted to Academy of Scientific and Innovative Research for the award of degree of Doctor of Philosophy (Ph.D.) is the outcome of experimental investigations carried out by me under the supervision of **Dr. N. P. Argade**, Senior Scientist, Organic Chemistry Division, CSIR-National Chemical Laboratory, Pune. I affirm that the work incorporated is original and has not been submitted to any other academy, university or institute for the award of any degree or diploma.

April 2016 **Sagar Dilip Vaidya**

CSIR-National Chemical Laboratory **(Research Student)**

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CONTENTS

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…Sagar

ABBREVATIONS

Ac	Acetyl
AIBN	Azobisisobutyronitrile
Ar	Aryl
Bn	Benzyl
Bz	Benzoyl
n-Bu	*n*-Butyl
n-BuLi	*n*-Butyl lithium
t-Bu	*tert*-Butyl
Cbz	Benzyloxy carbonyl
DEAD	Diethyl azodicarboxylate
DMP	Dess–Martin periodinane
DMF	Dimethyl formamide
DMDO	Dimethyldioxirane
DMSO	Dimethyl sulphoxide
DMAP	*N*,*N*-dimethyl-4-aminopyridine
dr	*Diastereomeric ratio*
ee	Enantiomeric excess
Et	Ethyl
EtOAc	Ethyl acetate
g	Grams
h	Hours
HPLC	High performance liquid chromatography
HRMS	High resolution mass spectroscopy
imid.	Imidazole
IR	Infra-red
LDA	Lithium diisopropylamide
LiHMDS	Lithium hexamethyldisilazide
M+	Molecular ion
Me	Methyl
min	Minute
mg	Miligram
mL	Milliliter
mp	Melting point
MS	Mass spectrum
Ms	Mesyl
NMR	Nuclear Magnetic Resonance
Pd/C	Palladium on activated charcoal
Ph	Phenyl
p-Ts	*p*-Tosyl
p-TSA	*p*-Toluene sulfonic acid
Py	Pyridine
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TBAF	Tetrabutylammonium fluoride
TFA	Trifluoroacetic acid

GENERAL REMARKS

1. All solvents were distilled and dried before use.
2. Petroleum ether refers to the fraction collected in the boiling range 60-80 °C.
3. Organic layers after every extraction were dried over anhydrous sodium sulfate.
4. Column Chromatography was performed over silica gel (60-120 & 230-400 mesh).
5. TLC analyses were performed over aluminum plates coated with silica gel (5-25 m) containing UV active G-254 additive.
6. IR spectra were recorded on a Perkin-Elmer model 683 B or 1605 FT-IR and absorptions were expressed in cm^{-1}.
7. ^{1}H and ^{13}C NMR spectra were recorded on Brucker FT AC-200 MHz, Brucker Avance 500 MHz and JEOL ECX 400 instruments using TMS as an internal standard. The following abbreviations were used: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br s = broad singlet, dd = doublet of doublet, dt = doublet of triplet and app = apparent.
8. Optical rotations were carried out on JASCO-181 digital polarimeter at 25 °C using sodium D light.
9. Enantiomeric excesses were determined on Agilent HPLC instrument equipped with a chiral column.
10. HRMS data were recorded on a Thermo Scientific Q-Exactive, Accela 1250 pump.
11. All melting points and boiling points are uncorrected and the temperatures are in centigrade scale.
12. Elemental analysis was done on Carlo ERBA EA 110B instrument.
13. The compounds, scheme and reference numbers given in each chapter refers to that particular chapter only.

Synopsis of the Thesis to be Submitted to the Academy of Scientific and Innovative Research for Award of the Degree of Doctor of Philosophy in Chemistry

Name of the Candidate	Mr. Sagar Dilip Vaidya
Degree Enrolment No. & Date	Ph. D. in Chemical Sciences (10CC11J26091); January 2011
Title of the Thesis	Studies on Total Synthesis of Bioactive Natural and Unnatural Quinazolinones
Research Supervisor	Dr. Narshinha P. Argade (AcSIR, CSIR-NCL, Pune)

Introduction

Quinazolinones are an important class of compounds and a building block for a large number of structurally diverse alkaloids with a wide range of biological activities.[1] Nearly 300 natural products with the quinazolinone nucleus are known in the literature and some are in clinical use.[2] The fused quinazoline alkaloids tryptanthrin, phaitanthrins A–E and (±)-cruciferane have been recently isolated from *Phaius mishmensis* and *Isatis tinctoria* (*Isatis indigotica* Fortune).[3] The interesting biological activities and fascinating molecular architectures of these compounds have attracted immediate attention and they became important synthetic targets as a result of their limited availability from natural sources.[4,5] Development of synthetic or biosynthetic routes for quinazolinone alkaloids is a challenging task for synthetic organic chemists.[6] Many elegant total syntheses of quinazoline-4-one alkaloids have been reported in recent past.[5] In the present dissertation work two major synthetic strategies have been described to access the core ring system, which have subsequently led to the concise and efficient total synthesis of several recently isolated bioactive natural products (Figure 1).[7-10]

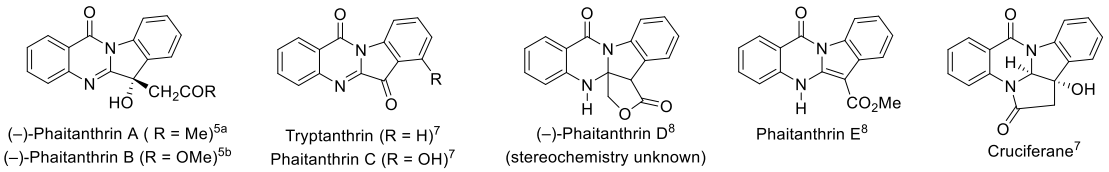


Figure 1. Recently isolated bioactive quinazolinone natural products.

Statement of Problem

The synthesis of bioactive natural products phaitanthrins A–E and cruciferane involving concise new routes from the commercially available starting materials is of current interest.

Methodology Used

1. The products were characterized by the advanced analytical and spectroscopic techniques such as high field ^{1}H & ^{13}C NMR, FT-IR, LC-MS and HRMS.

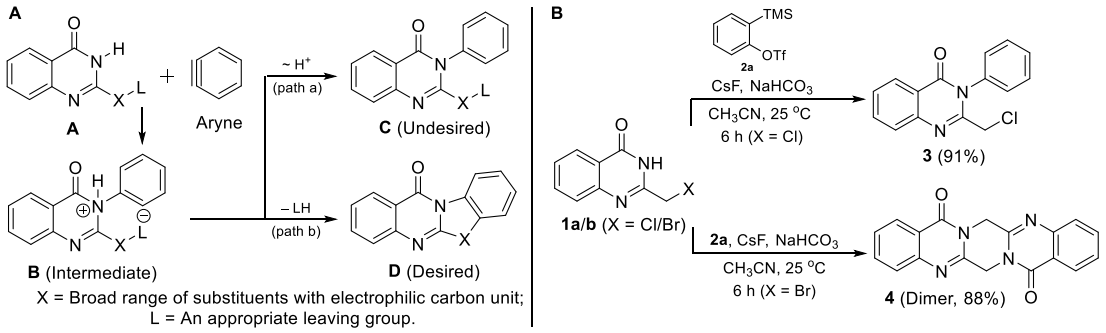
2. Single crystal X-ray crystallographic study has been carried out to determine the relative stereochemistry.

3. The optical purity of enantio enriched target compounds has been determined by using chiral HPLC analysis and comparing their specific rotation with those reported in the literature.

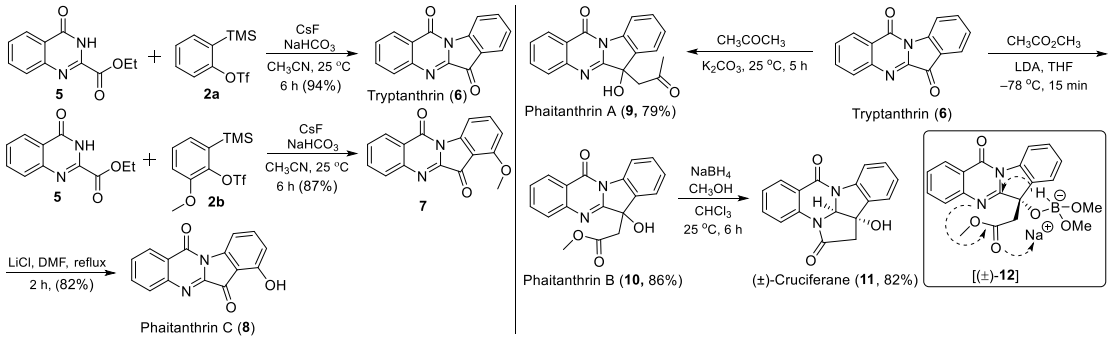
Sample Results

1. Insertion reactions of an in situ generated arynes to a variety of suitably substituted 1,3-quinazolin-4-ones have been demonstrated for a new efficient one-step approach to a diverse range of fused quinazolinone architectures. The present protocol has been effectively utilized to accomplish the concise total synthesis of recently isolated bioactive natural products tryptanthrin, phaitanthrins A–C and cruciferane.[7]

Scheme 1. Synthetic Proposal and Preliminary Studies on Aryne Insertion Reactions of 2-Halomethylquinazolinones



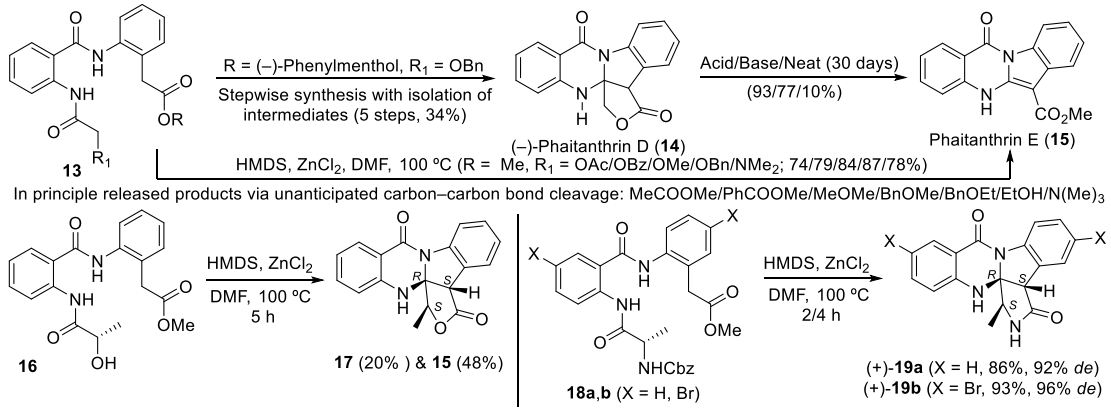
Scheme 2. Synthesis of Tryptanthrin, Phaitanthrins A–C and Cruciferane



The aryne insertion reaction of 2-chloromethylquinazolinone **1a** with aryne intermediate from the precursor **2a** exclusively furnished a *N*-arylated quinazolinone **3**. However, reaction of quinazolinone **1b** with aryne was not possible, as the starting material **1b** underwent dimerization to form the linear penta-cyclic dimer **4** (Scheme 1B)**.** The insertion reaction of aryne from precursor **2a** to quinazolinone **5** in acetonitrile at 25 °C

furnished the natural product tryptanthrin (**6**). Several appropriately designed starting quinazoliones were subjected for this aryne insertion reaction and they also delivered the corresponding tryptanthrin derivatives in good yields. Regioselective reaction of quinazolinone **5** with unsymmetrical aryne from precursor **2b** exclusively formed the desired product **7**. The demethylation was carried out by using LiCl in refluxing DMF to directly deliver phaitanthrin C (**8**) (Scheme 2). The K_2CO_3 induced chemoselective aldol condensation of acetone with natural product tryptanthrin (**6**) gave the phaitanthrin A (**9**). Chemoselective condensation of tryptanthrin (**6**) with methyl acetate using LDA as a base at −78 °C was successful and provided the phaitanthrin B (**10**). The $NaBH_4$ induced hydroxyl directed chemo- and diastereoselective reductive intramolecular cyclization of phaitanthrin B (**10**) furnished the (±)-cruciferane (**11**) via an intermediate (±)-**12** (Scheme 2).

2. A Biogenetic type total synthesis of alkaloids (±)/(–)-phaitanthrin D and phaitanthrin E have been described. The Csp3–Csp3 bond cleavage with the release of several heteroatom bearing unexpected leaving groups in intramolecular substitution reactions on an iminium double bond in the quinazolinones has been demonstrated using HMDS/$ZnCl_2$ or NaHMDS. The mechanistic aspects have been supported by isolation and characterization of appropriate intermediates.[8]



Scheme 3. Synthesis of Phaitanthrin E (**15**), (–)-Phaitanthrin D (**14**), (+)-Methylfuroindoloquinazolinone (**17**) and (+)-Dihydropyrroloindiloquinazolinones (**19**)

Starting from precursor **13** the one-pot synthesis of phaitanthrin E has been demonstrated from five different types of starting materials in very good yields with the release of unexpected carbon species. To the best of our knowledge, this is a unique example of spontaneous sp3 carbon–carbon bond cleavage in the absence of a metal catalyst and molecular oxygen. A stereoselective biogenetic type total synthesis of (**–**)-phaitanthrin D

in five steps with 34% overall yield has also been demonstrated. The rearrangements of phaitanthrin D to phaitanthrin E in presence of acid, base and in neat form was successfully carried out and confirmed an unusual carbon–carbon bond cleavage. The one pot synthesis of (+)-methylfuroindoloquinazolinone and (+)-dihydropyrroloindiloquinazolinone were also successfully carried out. All these results prove that under special circumstances the esters, ethers, alcohols and amines can also function as the good leaving groups via unexpected carbon–carbon bond cleavages and conceptually it will be useful to organic chemists to achieve what appears implausible.

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Chapter 1

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

1.1 Introduction

Quinazolinone is a building block of approximately 250 naturally occurring alkaloids isolated to date from a number of families of the plant kingdom, animals, marine sources and microorganisms. The first quinazoline alkaloid isolated was vasicine/ peganine (**1**) in 1888, produced by Indian medicinal plant *Adhatoda vasica* and later isolated from other species along with the quinazolinone alkaloids, vasicinone (**2**) and deoxyvasicinone (**3**).[1] A variety of other quinazolinone and quinazoline natural products have been isolated, characterized and synthesized thereafter. The first quinazolinone was synthesized in the late 1860s from anthranilic acid and cyanogens to give 2-cyanoquinazolinone (**4**) (Figure 1).[2] Interest in the medicinal chemistry of quinazolinone derivatives was stimulated in the early 1950 with the structural elucidation of a quinazolinone alkaloid. Febrifugine (**5**) was isolated from an Asian plant *Dichroa febrifuga*,[3] which is an ingredient of a traditional Chinese herbal remedy and it is effective against malaria. In a quest to find additional potential quinazolinone based drugs, various substituted quinazolinones have been synthesized,

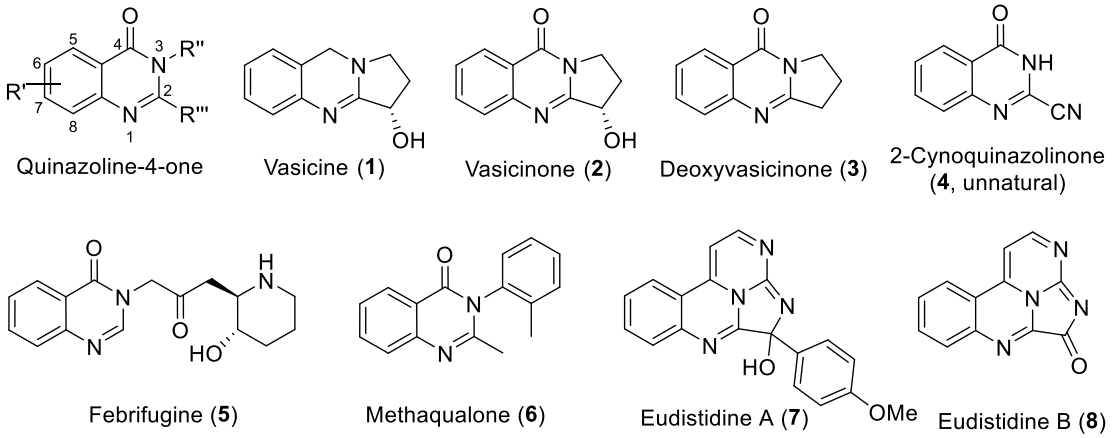


Figure 1. Natural and Unnatural Quinazolinones

which led to the synthesis of the derivative, methaqualone (**6**). Methaqualone (**6**) was synthesized[4] for the first time in 1951 and it is the most well-known synthetic quinazolinone drug, famous for its sedative–hypnotic effects. Very recently in 2015 pyrimidoquinazoline scaffold containing eudistidine A (**7**) and B (**8**)[5] were isolated from an extract of the marine ascidian *Eudistoma sp*. and identified as effective inhibitors of CH1/C-TAD binding, which is the key protein-protein interaction required to form the transcriptionally active p300/HIF-1α complex.

The introduction of methaqualone attracts the research community toward isolation, synthesis and studies on the pharmacological properties of the quinazolinone and

related compounds. Quinazolinone and quinazoline alkaloids are one of attractive natural products leading to drug developments. Bioassay-directed isolation followed by identification and characterization of bioactive compounds leads to a development of new medicinal drugs. The structural diversity of quinazolinones

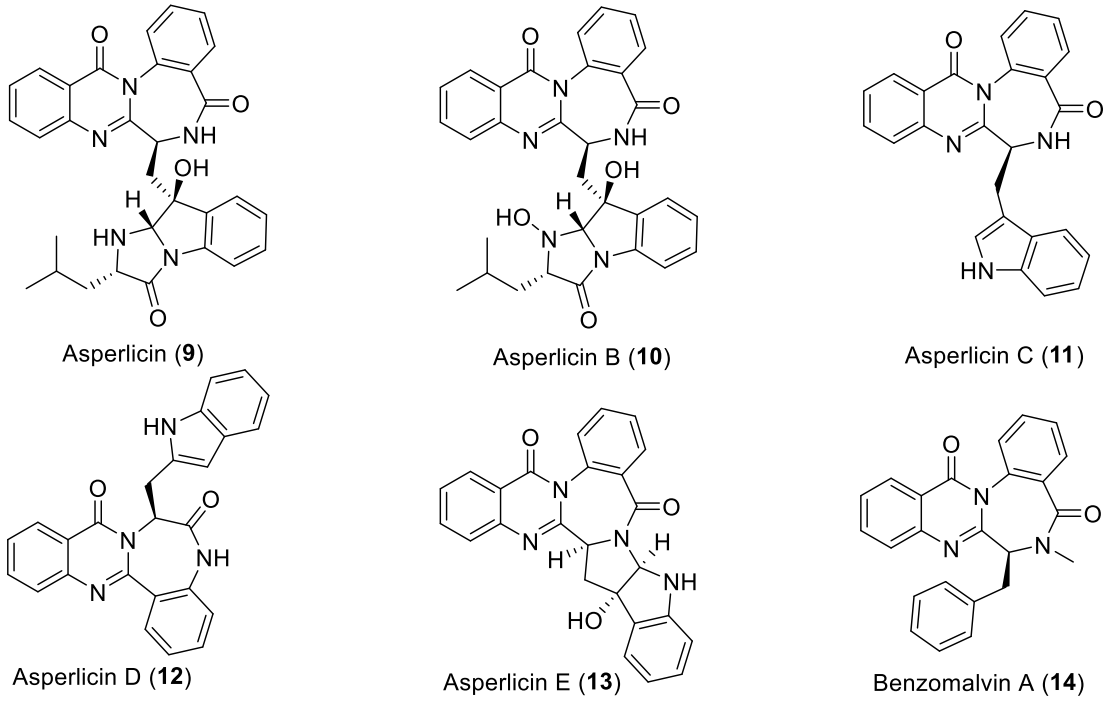


Figure 2. Naturally Occurring Quinazolinobenzodiazepinones

has been expanded with the discovery of asperlicin along with asperlicins B, C, D, and E (**9**−**13**) produced by *Aspergillus alliaceus*, which is a potent cholecystokinin (CCK) antagonist (Figure 2). A series of new quinazoline alkaloids fused with benzodiazepinone were also isolated from a fungus culture of *Penicillium sp*., wherein benzomalvin A (**14**) is prototypical member. Quinazolinones and their derivatives are now known to have a wide range of useful biological properties, such as hypnotic, sedative, analgesic, anticonvulsant, antitussive, antibacterial, anti-diabetic, anti-inflammatory, anti-tumour and several others.[6] Some of these compounds also have interesting biological properties such as anti-malarial activity, biofungicide and diuretic properties.

1.2 Background

The chemistry of the quinazolinone alkaloids is well documented in a number of comprehensive reviews and articles and is continuously updated in Natural Product Reports.[1,6,7] In 2006, from our research group Mhaske and Argade have published the comprehensive review on the chemistry of quinazolinone alkaloids.[8] The review represents a concise account of isolation, bioactivity and synthesis of naturally occurring

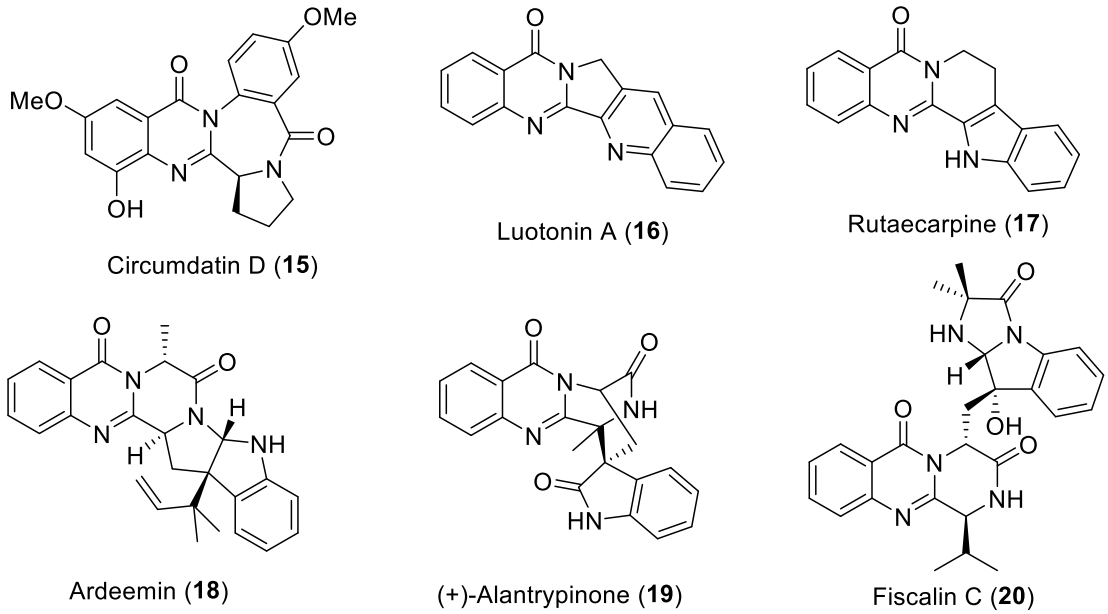
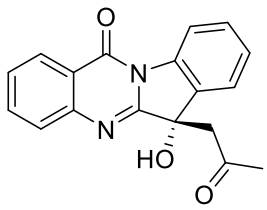


Figure 3. Selected Quinazolinone Alkaloids Isolated up to the Year 2005

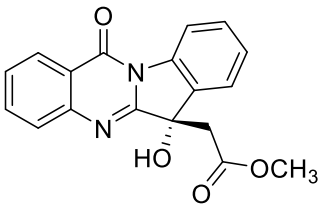
quinazolinone alkaloids isolated after the middle of 1983 up to 2005 and recent developments in the area of the complex quinazolinone natural products, with an emphasis on classical methods for their synthesis (Figure 3). The main synthetic routes to quinazolinone compounds utilize 2-aminobenzoic acid or its derivatives, 2-aminobenzamide, 2-aminobenzonitrile, isatoic anhydride, 2-carbomethoxyphenyl isocyanate, *N*-arylnitrilium salts and 4*H*-3,1-benzoxazinones as suitable precursors.

In the solid-phase synthesis field, lithium reagents and transition metals have been used for the preparation of these compounds. Other important methods include coupling of *o*-methylbutyrolactam with anthranilic acid, cycloaddition of anthranilic acid iminoketene with methylbutyrolactam (via sulfonamide anhydride), reactions of anthranilic acid derivatives with a wide range of substrates including imidates and imino halides, the reaction of anthranilic acid and the appropriately substituted imidate in a facile one-pot procedure and microwave-promoted reaction of anthranilic acid with amines and formic acid (or its *ortho* ester) and isatoic anhydride. All these important methods for the synthesis of the quinazolinone alkaloids have been neatly described in recent review from our group.[8]

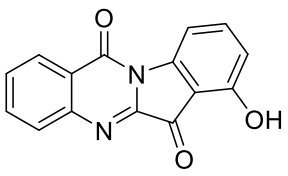
Very recently Kshirsagar published a review on naturally occurring bioactive quinazolinone alkaloids.[9] This review is focused on the chemistry of quinazolinone alkaloids in the last decade and it covers the newly isolated quinazolinone natural products with their biological activities and the recently reported total syntheses of quinazolinone alkaloids from 2006 to 2015. Phaitanthrin A–E have been isolated in 2008



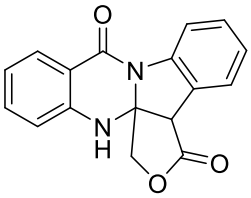
Phaitanthrin A (**21**)



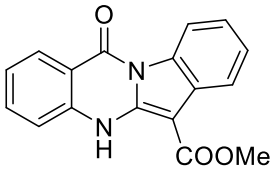
Phaitanthrin B (**22**)



Phaitanthrin C (**23**)



(–)-Phaitanthrin D (**24**)
(stereochemistry unknown)



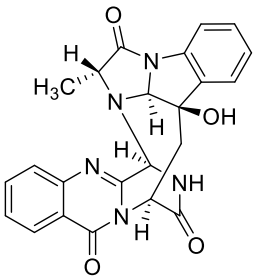
Phaitanthrin E (**25**)

Figure 4. Selected Quinazolinone Alkaloids Isolated in Year 2008

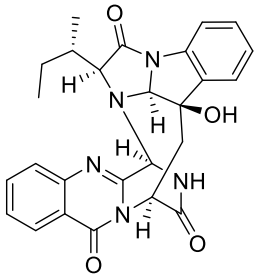
and which we eventually selected as target molecules for the synthesis (Figure 4).[10]

1.3 New Quinazolinone Alkaloids Isolated after 2010

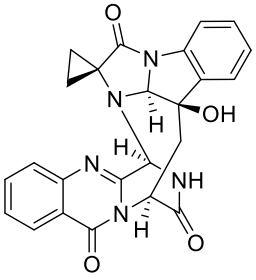
More than 55 new natural quinazolin-4-ones have been isolated from various species during the period of 2010 to till date and are listed in figure 5 along with species from which they have been isolated with the details about their bioactivity and synthesis.



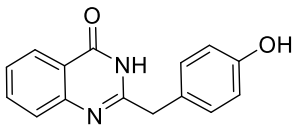
Cottoquinazoline B (**26**)
(*Aspergillus versicolor* LCJ-5-4)[11]
Activity: Weak cytotoxic
Synthesis: Not known



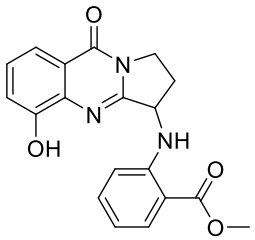
Cottoquinazoline C (**27**)
(*Aspergillus versicolor* LCJ-5-4)[11]
Activity: Weak cytotoxic
Synthesis: Not known



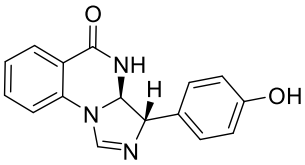
Cottoquinazoline D (**28**)
(*Aspergillus versicolor* LCJ-5-4)[11]
Activity: Antifungal activity
Synthesis: Not known



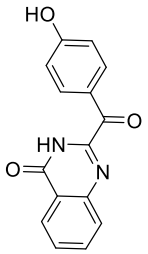
2-(4-Hydroxybenzyl) quinazolin-4(3*H*)-one (**29**)
(*Isaria farinosa*)[12]
Activity: Weak cytotoxic
Synthesis: Two



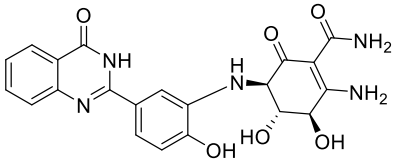
5-Hydroxyvasentine (**30**)
(*Anisotes trisulcus*)[13]
Activity: Not known
Synthesis: Not known



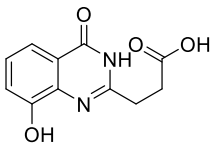
Penipanoids B (**31**)
(*Isaria farinosa*)[14]
Activity: Weak cytotoxic
Synthesis: Not known



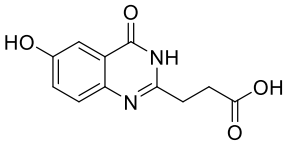
Penipanoids C (**32**)
(*Isaria farinosa*)[14]
Activity: Weak cytotoxic
Synthesis: Not known



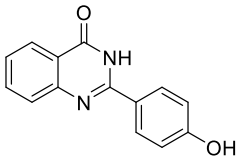
Farinamycin (**33**)
(*Streptomyces griseus*)[15]
Activity: Weak cytotoxic
Synthesis: Not known



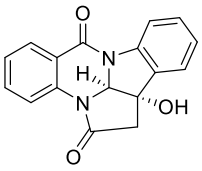
3-(8-Hydroxy-4-oxo-
3,4-dihydroquinazolin-2-yl)
propanoic acid (**34**)
(*Streptomyces*
michiganensis)[16]
Activity: Not known
Synthesis: Not known



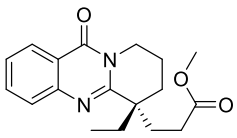
3-(6-Hydroxy-4-oxo-
3,4-dihydroquinazolin-2-yl)
propanoic acid (**35**)
(*Streptomyces*
michiganensis)[16]
Activity: Not known



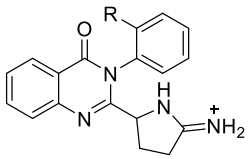
2-(4-Hydroxyphenyl)
quinazolin-4(3*H*)-one (**36**)
(*Streptomyces michiganensis*)[16]
Activity: Not known



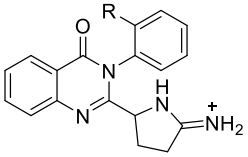
(±)-Cruciferane (**37**)
(*Isatis indigotica* Fort.)[17]
Activity: Antiviral activity
Synthesis: Three



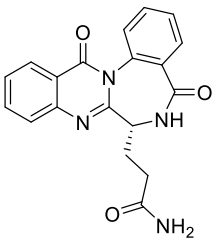
Leucomidine C (**38**)
(*Leuconotis griffithii*)[18]
Activity: Weak cytotoxic
Synthesis: Not known



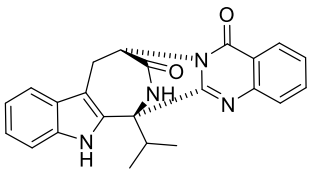
Auranomides A (R = COO^-, **39**)
(*Penicillium aurantiogriseum*)[19]
Activity: Weak cytotoxic
Synthesis: Not known



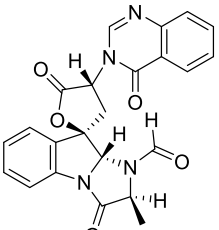
Auranomides B (R = COOMe, **40**)
(*Penicillium aurantiogriseum*)[19]
Activity: Weak cytotoxic
Synthesis: Not known



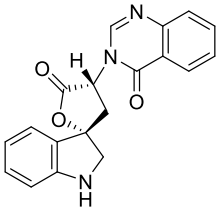
Auranomides C (**41**)
(*Penicillium aurantiogriseum*)[19]
Activity: Moderate cytotoxic
Synthesis: Not known



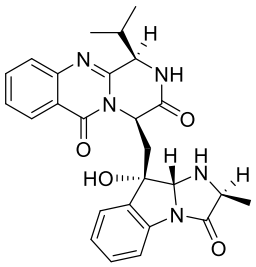
Sartorymensin (**42**)
Neosartorya siamensis
(KUFC 6349)[20]
Activity: Moderate cytotoxic
Synthesis: Not known



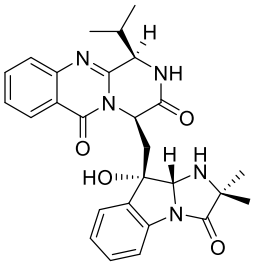
Tryptoquivaline O (**43**)
Neosartorya siamensis
(KUFC 6349)[20]
Activity: Weak cytotoxic
Synthesis: Not known



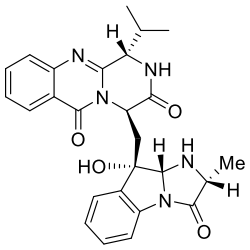
30-(4-Oxoquinazolin-3-yl)
spiro[1*H*-indole-3,50-oxolane]
-2,20-dione (**44**)
(*Neosartorya siamensis*)[20]
Activity: Weak cytotoxic
Synthesis: Not known



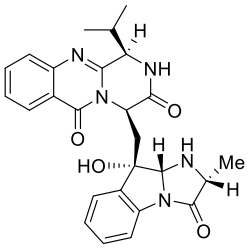
epi-Fiscalin A (**45**)
Neosartorya siamensis
(KUFC 6349)[20]
Activity: Weak cytotoxic
Synthesis: Not known



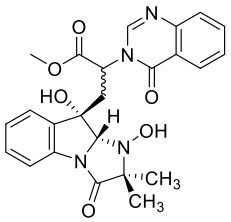
epi-Fiscalin C (**46**)
Neosartorya siamensis
(KUFC 6349)[20]
Activity: Weak cytotoxic
Synthesis: Not known



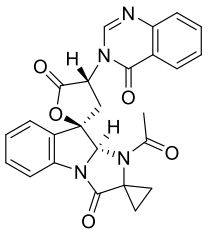
Neofiscalin A (**47**)
(*Neosartorya siamensis*)[20]
Activity: Weak cytotoxic
Synthesis: Not known



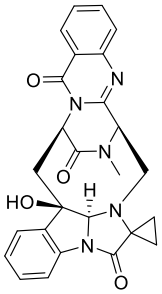
epi-Neofiscalin A (**48**)
Neosartorya siamensis
(KUFC 6349)[20]
Activity: Weak cytotoxic
Synthesis: Not known



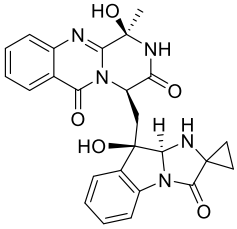
Tryptoquivaline R (**49**)
(*Neosartorya* sp.HN-M-3)[21]
Activity: Weak cytotoxic
Synthesis: Not known



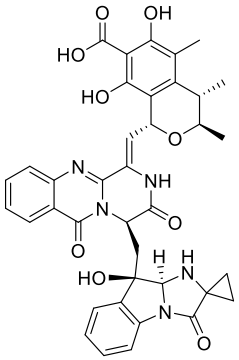
Tryptoquivaline K (**50**)
(*Tethya aurantium*)[22]
Activity: Weak cytotoxic
Synthesis: Not known



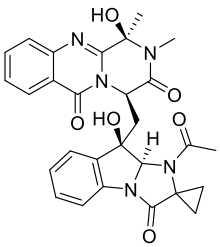
Fumiquinazoline K (**51**)
(*Tethya aurantium*)[22]
Activity: Weak cytotoxic
Synthesis: Not known



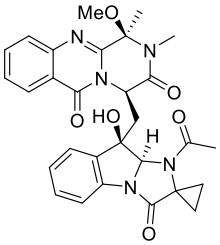
Fumiquinazoline L (**52**)
(*Tethya aurantium*)[22]
Activity: Weak cytotoxic
Synthesis: Not known



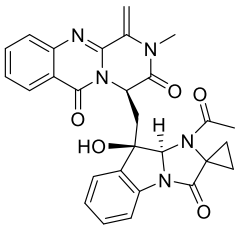
Fumiquinazoline M (**53**)
(*Tethya aurantium*)[22]
Activity: Weak cytotoxic
Synthesis: Not known



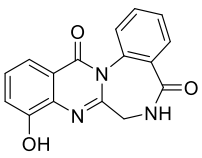
Fumiquinazoline N (**54**)
(*Tethya aurantium*)[22]
Activity: Weak cytotoxic
Synthesis: Not known



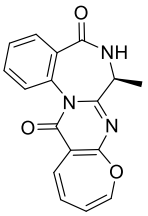
Fumiquinazoline O (**55**)
(*Tethya aurantium*)[22]
Activity: Weak cytotoxic
Synthesis: Not known



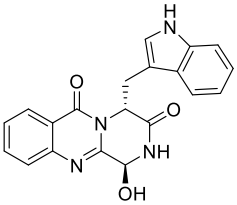
Fumiquinazoline P (**56**)
(*Tethya aurantium*)[22]
Activity: Weak cytotoxic
Synthesis: Not known



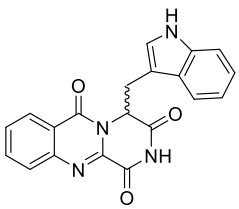
Circumdatin K (**57**)
(*Aspergillus westerdijkiae*)[23]
Activity: Weak cytotoxic
Synthesis: Not known



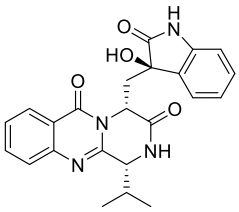
Circumdatin L (**58**)
(*Aspergillus westerdijkiae*)[23]
Activity: Weak cytotoxic
Synthesis: Not known



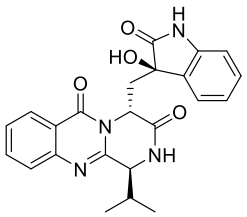
3-Hydroxyglyantrypine (**59**)
(*Cladosporium* sp.)[24]
Activity: Weak antiviral
Synthesis: Not known



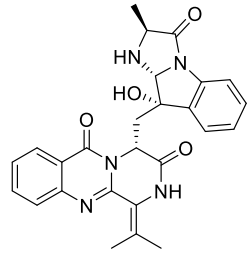
Oxoglyantrypine (**60**)
(*Cladosporium* sp.)[24]
Activity: Anti-H1N1 activity
Synthesis: Not known



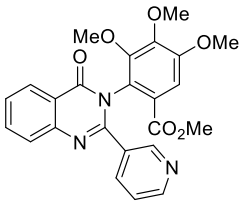
Cladoquinazoline (**61**)
(*Cladosporium* sp.)[24]
Activity: Weak anti-H1N1 activity
Synthesis: Not known



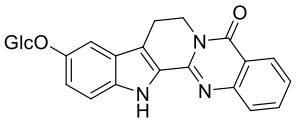
epi-Cladoquinazoline (**62**)
(*Cladosporium* sp.)[24]
Activity: Weak anti-H1N1 activity
Synthesis: Not known



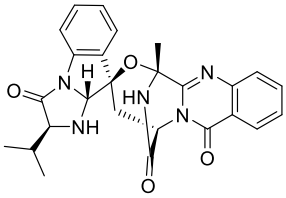
Norquinadoline A (**63**)
(*Cladosporium* sp.)[24]
Activity: Anti-H1N1 activity
Synthesis: Not known



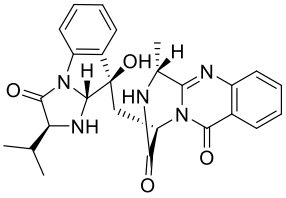
Terremide C (**64**)
(*Aspergillus terreus*)[25]
Activity: Cytotoxic
Synthesis: Not known



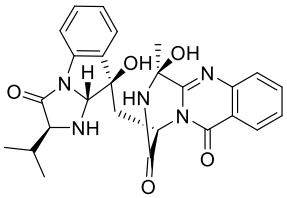
Rutaecarpine-10-*O*-ß-
D-glucopyranoside (**65**)
(*Evodia rutaecarpa*)[26]
Activity: Not known
Synthsis: Not known



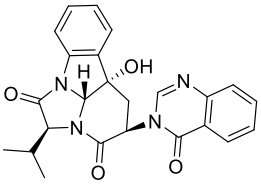
Aniquinazoline A (**66**)
(*Aspergillus nidulans* MA-143)[27]
Activity: Weak cytotoxic
Synthesis: Not known



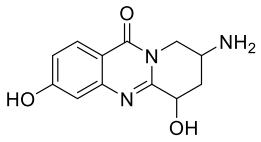
Aniquinazoline B (**67**)
(*Aspergillus nidulans* MA-143)[27]
Activity: Weak cytotoxic
Synthesis: Not known



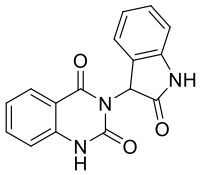
Aniquinazoline C (**68**)
(*Aspergillus nidulans* MA-143)[27]
Activity: Weak cytotoxic
Synthesis: Not known



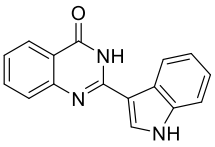
Aniquinazoline D (**69**)
(*Aspergillus nidulans* MA-143)[27]
Activity: Weak cytotoxic
Synthesis: Not known



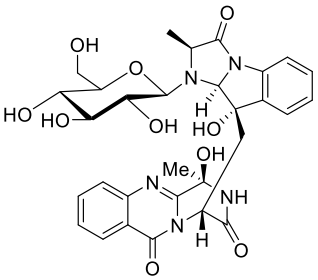
8-Amino-3,6-dihydroxy-6,7,8,9-
tetrahydro-11*H*-pyrido[2,1-*b*]
quinazolin-11-one (**70**)
(*Anisotes trisulcus*)[28]
Activity: Not known
Synthesis: Not known



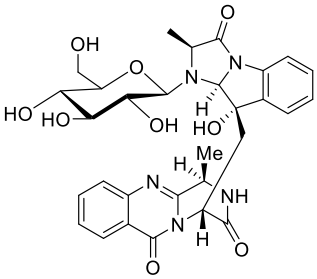
Shewanelline C (**71**)
(*Shewanella*
piezotolerans WP3)[29]
Activity: Cytotoxic
Synthesis: Not known



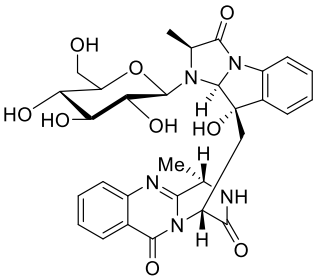
2-(1*H*-Indol-3-yl)quinazolin-4(3*H*)-one (**72**)
(*Streptomyces* sp. BCC 21795)[30]
Activity: Cytotoxic
Synthesis: Not known



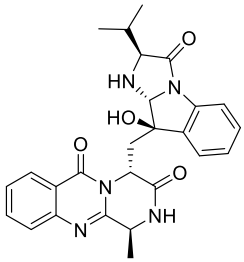
Fumigatoside B (**73**)
(*Aspergillus fumigatus*)[31]
Activity: Weak cytotoxic
Synthesis: Not known



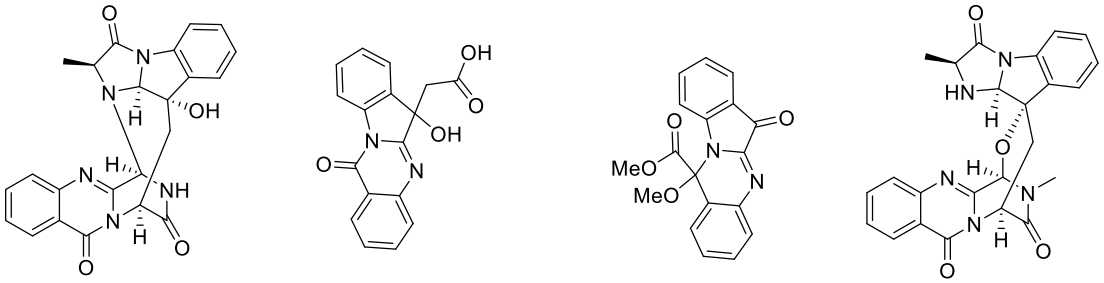
Fumigatoside C (**74**)
(*Aspergillus fumigatus*)[31]
Activity: Weak cytotoxic
Synthesis: Not known



Fumigatoside D (**75**)
(*Aspergillus fumigatus*)[31]
Activity: Weak cytotoxic
Synthesis: Not known



Fumiquinazoline S (**76**)
(*Aspergillus* sp.)[32]
Activity: Weak inhibition
against Na+/K+-ATPase
Synthesis: Not known



Cottoquinazoline E (**77**)
(*Neosartorya fischeri*)[33]
Activity: Not known
Synthesis: Not known

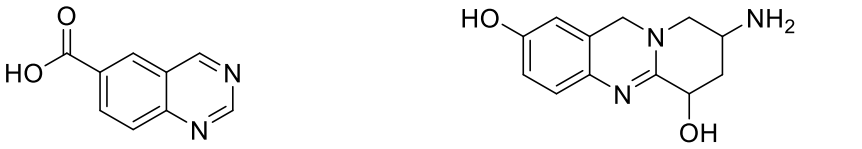
Cephalanthrin A (**78**)
(*Cephalantheropsis gracilis*)[34]
Activity: Weak cytotoxic
Synthesis: Not known

Cephalanthrin B (**79**)
(*Cephalantheropsis gracilis*)[34]
Activity: Weak cytotoxic
Synthesis: Not known

Cottoquinazoline F (**80**)
(*Neosartorya fischeri*)[33]
Activity: Not known
Synthesis: Not known

Figure 5. Quinazolinone Alkaloids Isolated from the Year 2010 Onwards

1.4 New Quinazoline Alkaloids Isolated after 2010



6-Quinazolinecarboxylic acid (**81**)
(*Zanthoxylum rhetsa*)[35]
Activity: Antialgal activities
Synthesis: Several

8-Amino-6,8,9,11-tetrahydro-7*H*-pyrido
[2,1-*b*]quinazoline-2,6-diol (**82**)
(*Anisotes trisulcus*)[28]
Activity: Not known
Synthesis: Several

Figure 6. Quinazoline Alkaloids Isolated from the Year 2010 Onwards

Two new natural quinazolines have been isolated namely 6-quinazolinecarboxylic acid (**81**) and 8-amino-6,8,9,11-tetrahydro-7*H*-pyrido[2,1-*b*]quinazoline-2,6-diol (**82**) from *Zanthoxylum rhetsa* and *Anisotes trisulcus* respectively (Figure 6).

Structure revision

Schizocommunin (**83**) was isolated from the liquid culture medium of *Schizophyllum commune*, strain IFM 46788 (monokaryon) in 1999 which showed strong cytotoxic

Schizocommunin (**83**)
(Originally proposed structure)

Schizocommunin (**84**)
(**Revised structure**)

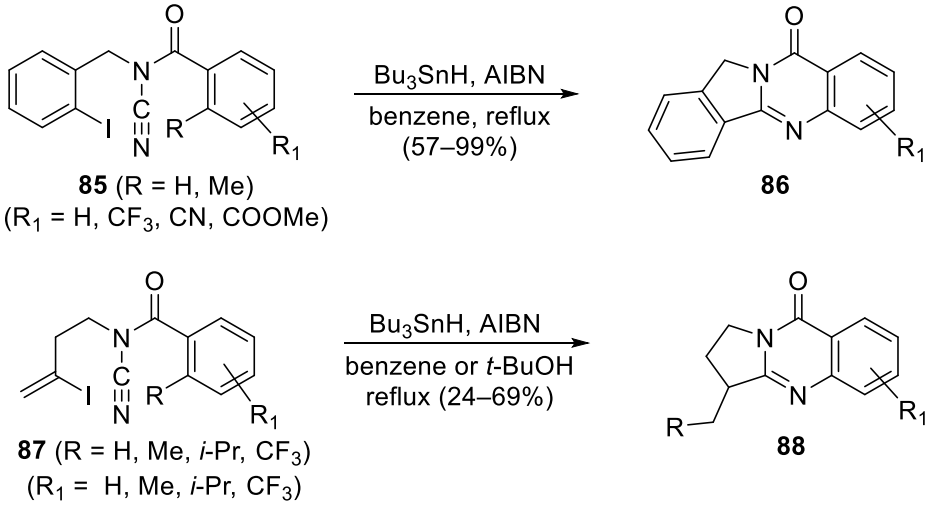
Figure 7. Revision in Structural Assignment of Schizocommunin

activity against murine lymphoma cells.[35a] Very recently, Nishida et al. during synthetic efforts on schizocommunin (**83**) revised its structure as **84**[35b] on the basis of total synthesis of the originally proposed structure of **83** and the revised structure **84**. The NMR and IR spectral data of synthetic schizocommunin (**84**) were matching entirely with naturally isolated schizocommunin. Synthetic schizocommunin (**84**) showed antiprolife-

rative activity against HeLa cells. (Figure 7).[28]

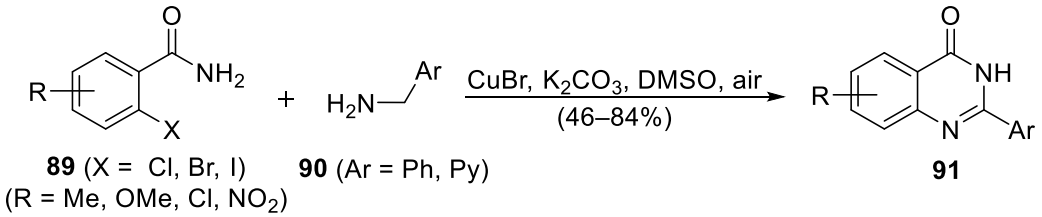
1.5 Recently Developed Synthetic Methodologies Towards the Synthesis of Quinazolinones (from the year 2010 to 2015)

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



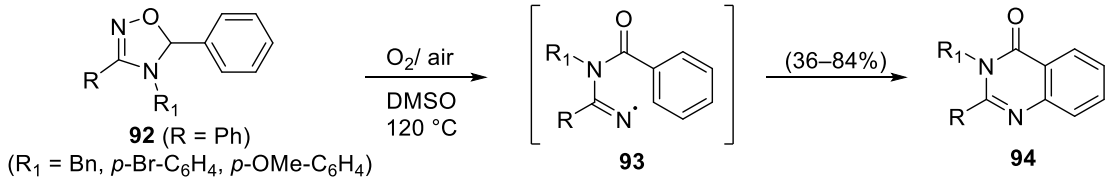
Scheme 1. Radical Cyclization Cascade of *N*-Acyl-*N*-(2-iodobenzyl)cyanamides

Malacria and co-workers developed cascade radical cyclization process of *N*-acylcyanamides **85**/**87** for the general access to pyrroloquinazoline-type polycyclic *N*-heterocycles **86**/**88** via a domino process that constructs new C−C & C−N bonds by radical migration of hydrogen atoms or carbon substituents on aromatic ring (Scheme 1).[36]



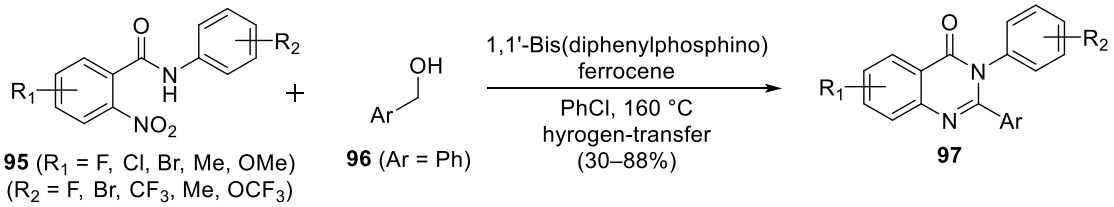
Scheme 2. Copper-Catalyzed Aerobic Oxidative Domino Synthesis of Quinazolinones

Fu and co-workers established copper-catalyzed Ullmann-type coupling approach to quinazolinone **91** derivatives using readily available substituted 2-halobenzamides **89** and (aryl)methanamines **90** as the starting materials. This domino reaction underwent sequential copper-catalyzed Ullmann-type coupling, aerobic oxidation and an intramolecular nucleophilic addition process in absence of any ligand and additive and the corresponding quinazolinone derivatives **91** were obtained in good yields (Scheme 2).[37]



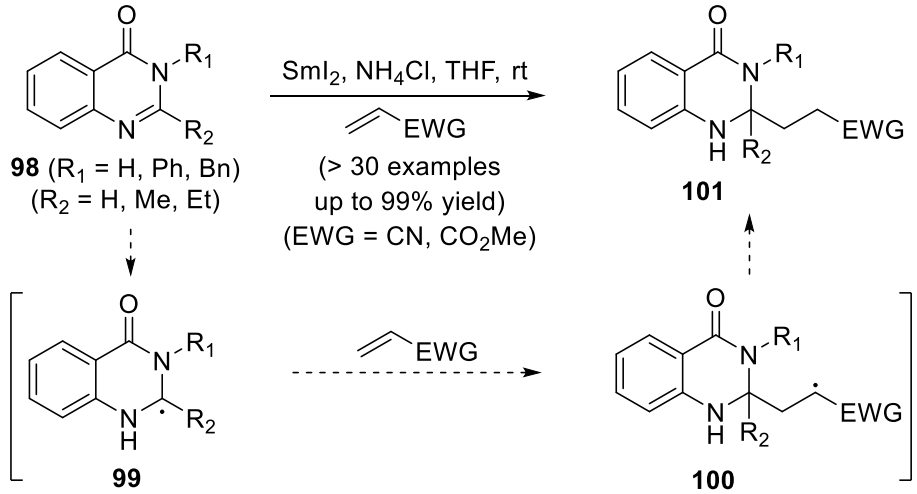
Scheme 3. Oxidative Radical Skeletal Rearrangement Induced by Molecular Oxygen: Synthesis of Quinazolinones

Chiba and co-workers advanced an unique oxidative radical skeletal rearrangement of 5-aryl-4,5-dihydro-1,2,4-oxadiazoles **92** induced by molecular oxygen in DMSO solvent at high temperature, that assists concise assembly of substituted quinazolinones **94** with the simple operation (Scheme 3).[38]



Scheme 4. Iron Catalysed One Pot Synthesis of Quinazolinones Using Redox Reaction

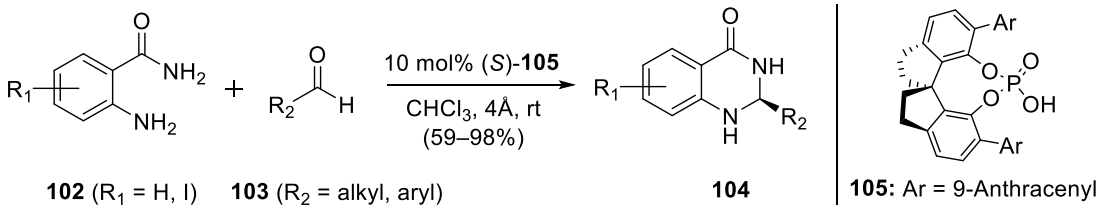
Deng and co-workers described a synthesis of 2,3-diarylquinazolinones **97** using 1,1'-bis(diphenylphosphino)ferrocene as catalyst via a hydrogen-transfer strategy from 2-nitrobenzamides **95** and alcohols **96** in chlorobenzene at higher temperature. The nitro group is reduced in situ by hydrogen generated from an alcohol oxidation process (Scheme 4).[39]



Scheme 5. Reductive Synthesis of Aminal Radicals for Carbon−Carbon Bond Formation

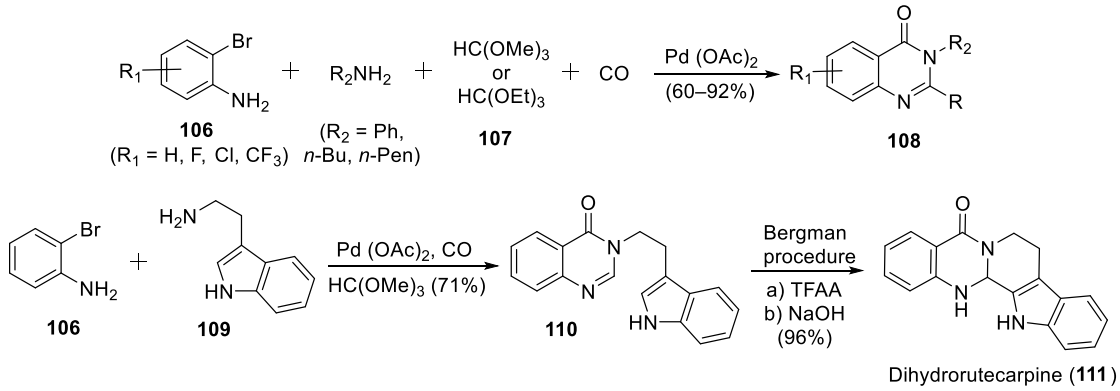
Beaudry and co-workers reported the reaction of quinazolinone **98** with *α,β*-unsaturated compounds using samarium iodide in THF at room temperature. In this reaction aminal radical **99** was generated by reduction of the corresponding amidine or amidinium ion. The intermediate radicals participate in C−C bond forming reactions to build fully

substituted aminal stereocenter as shown in compound **100**. More than 30 different substrate combinations have been reported and the chemical yields were as high as 99% (Scheme 5).[40]



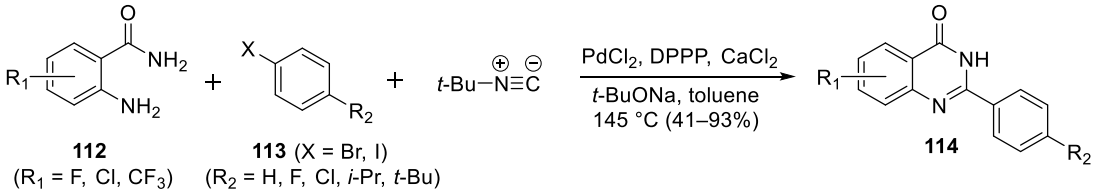
Scheme 6. Enantioselective Synthesis of Dihydroquinazolinones

Lin and co-workers established a method for the enantioselective synthesis of 2,3-dihydroquinazolinones **104** using an asymmetric condensation/amine addition cascade sequence of 2-aminobenzamides **102**, aldehydes **103** and chiral spirocyclic SPINOL-phosphoric acids **105** as a catalyst. SPINOL-phosphoric acid **105**, Ar = 9-anthracenyl was found to be a general, highly enantioselective organocatalyst for this cascade reactions at room temperature, affording 2,3-dihydroquinazolinones **104** up to 99% yield with good to excellent *ee* (up to 98%). The best level of stereocontrol was achieved for aromatic aldehydes with an *ortho*-substituent (Scheme 6).[41]



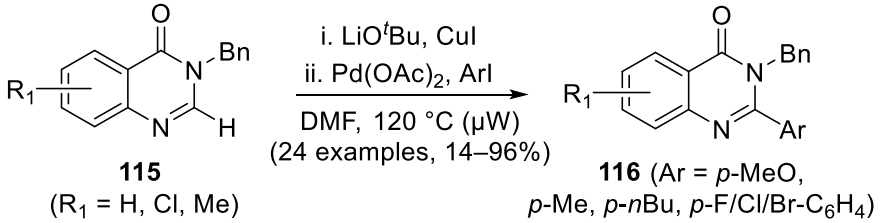
Scheme 7. Palladium-Catalyzed Carbonylative Four-Component Coupling Reactions for Synthesis of 4(3*H*)-Quinazolinones

Wu and co-workers described palladium-catalyzed four component carbonylative coupling reaction for the synthesis of various quinazolin-4(3*H*)-ones **108** in a convergent fashion. Starting from 2-bromoanilines **106**, trimethyl orthoformate and tryptamine **109**, under 10 bar of CO, the desired product **110** was isolated in good yields in the presence of $Pd(OAc)_2$, $BuPAd_2$ and *N*,*N*-diisopropylethylamine as a base in 1,4-dioxane at 100 ºC. From compound **110** the synthesis of dihydrorutaecarpine **111** is known by Bergman procedure (Scheme 7).[42]



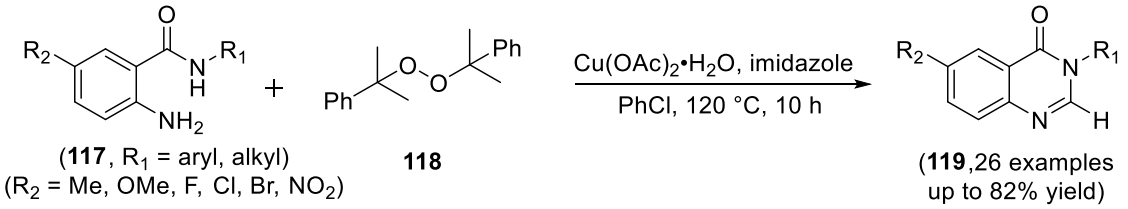
Scheme 8. Palladium-Catalyzed One Pot Synthesis of Quinazolinones via *tert*-Butyl Isocyanide Insertion

Ji and co-workers reported a palladium-catalyzed three-component reaction for the synthesis of quinazolin-4(3*H*)-ones **114** from readily available 2-aminobenzamides **112** and aryl halides **113** via a palladium-catalyzed isocyanide insertion/cyclization sequence. This methodology was efficiently utilized for the construction of quinazolin-4(3*H*)-ones **114** in moderate to excellent yields (Scheme 8).[43]



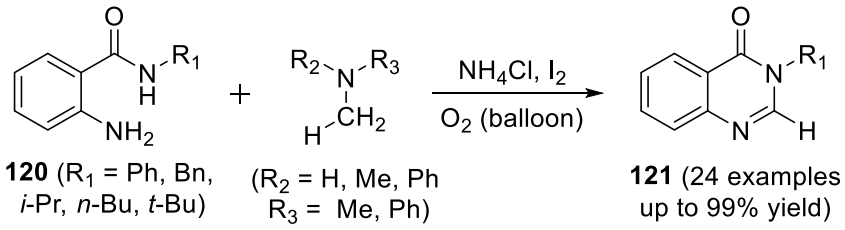
Scheme 9. Palladium/Copper-Catalyzed C−H Arylation of Quinazolinones with Aryl Iodides

Besson and co-workers designed a ligand free palladium catalyzed microwave-assisted method for the direct arylation of quinazolin-4-one **115** under copper assistance. In this reaction, to minimise the homocoupling of substrate **115** the copper source was first mixed with the base and the quinazolin-4-one substrate **115** for 10 min before adding the rest of the reactants. Microwave irradiation was also used to shorten the reaction time. This method was effectively applied for the preparation of 2-arylquinazolin-4*H*-ones **116** (Scheme 9).[44]



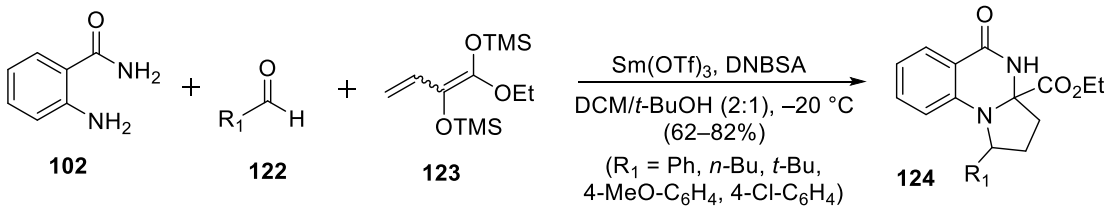
Scheme 10. Copper-Catalyzed Cascade for the Synthesis of Quinazolinones

Wang and co-workers reported a facile synthesis of quinazolinones **119** by using copper-catalyzed radical methylation/sp^3 C−H amination/oxidation reaction. In this cascade reaction, dicumyl peroxide **118** acting as a useful oxidant as well as an efficient methyl source. The generation of methyl radical from peroxide in the reaction was confirmed by electron paramagnetic resonance (Scheme 10).[45]



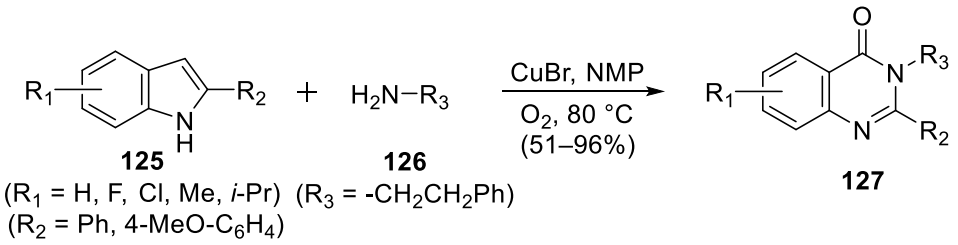
Scheme 11. I_2-Catalyzed Aerobic Oxidative C(sp^3)−H Amination/C−N Cleavage of Tertiary Amine in Synthesis of Quinazolinones

Liu and co-workers have established metal-free, peroxide-free route to quinazolinones **121** by using iodine-catalyzed oxidative C(sp^3)−H amination/C−N cleavage of tertiary amines under an oxygen atmosphere in good to excellent yields via ring annulation (Scheme 11).[46]



Scheme 12. [3 + 2]-Cycloannulation Towards Pyrroloquinazolinones

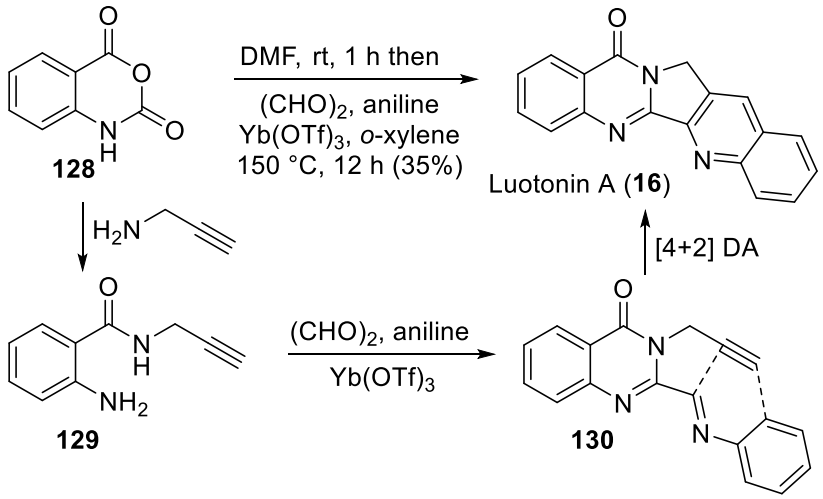
Schneider and co-workers developed a stereocontrolled [3 + 2]-cycloheteroannulation of bis-silyl dienediolate **123** with 2-aminobenzamide (**102**) derived imines to furnish highly substituted pyrrolo[1,2-*a*]quinazolinones **124** in good overall yields. This process rapidly generates pyrroloquinazolinone **124** and includes a Lewis acid catalyzed, vinylogous Mannich reaction of 2-aminobenzamide (**102**) and aldehyde **122** followed by an intramolecular *N*,*O*-acetal and *N*,*N*-aminal formation respectively, which proceeds with good to excellent stereocontrol (Scheme 12).[47]



Scheme 13. Copper-Catalyzed Synthesis of 2-Arylquinazolinones

Cui and co-workers described a copper-catalyzed expansion reaction of 2-arylindoles **125** with amines or ammoniums, affording both 2-substituted and 2,3-disubstituted quinazolinones **127** simultaneously via sequential Baeyer−Villiger oxidation expansion under O_2 together with continuous dehydrative cyclization. The corresponding products were obtained in good to excellent yields (Scheme 13).[48]

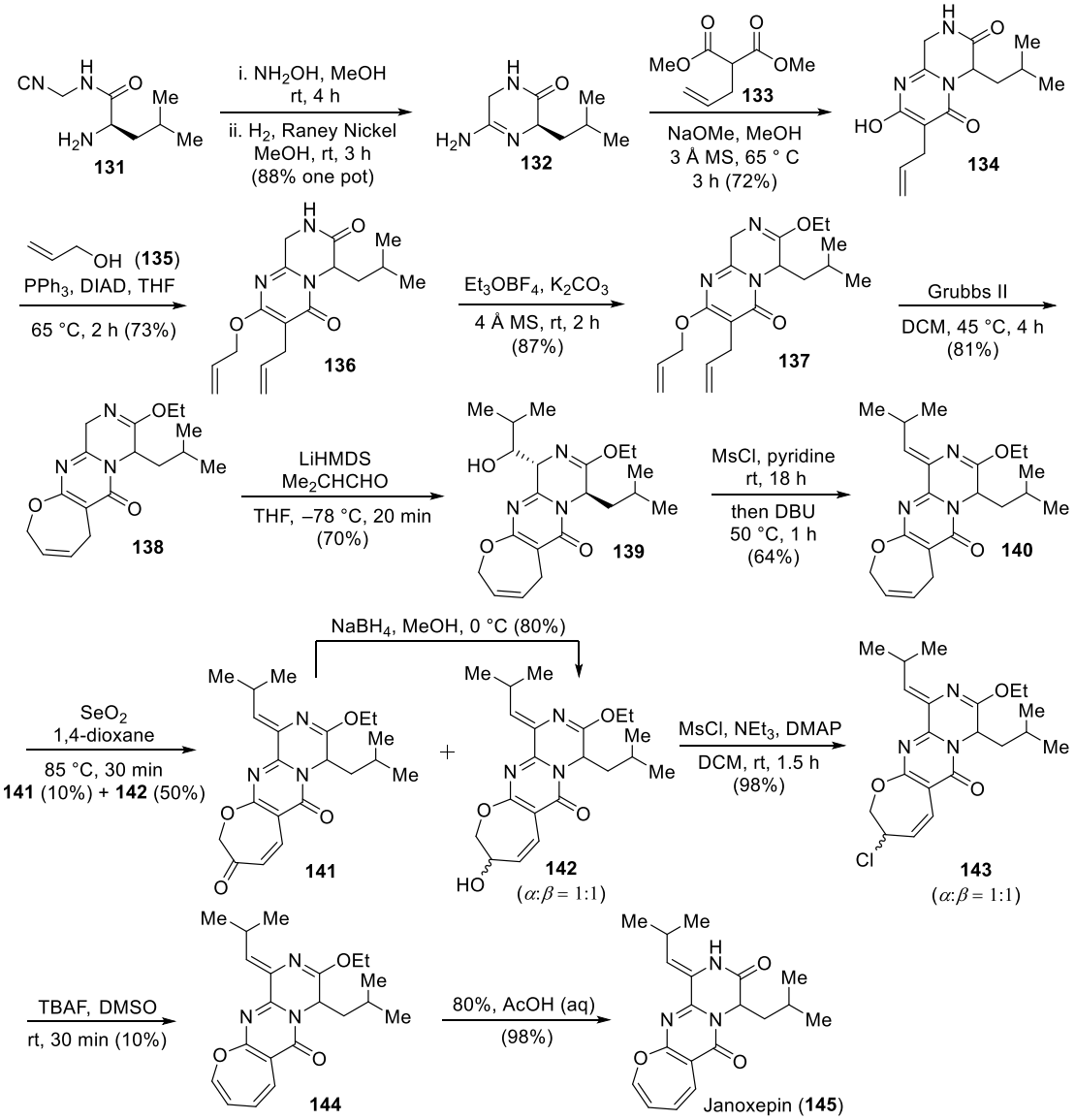
1.6 Total Synthesis of Quinazolinone Alkaloids



Scheme 14. $Yb(OTf)_3$ Catalyzed One Pot Synthesis of Luotonin A

One-pot synthesis of luotonin A (**16**) and its analogues was reported by Tseng et al. using Lewis acid catalysis. This approach presents the advantage of a one-pot route in moderate but acceptable isolated yield (Scheme 14).[49] This method not only avoids the need of harsh basic or acidic conditions but also avoids the isolation and purification of any intermediates and allows the concomitant construction of multiple ring system. Synthesis proceedes via the reaction of propargylamine with isatoic anhydride (**128**) to form an isolable amide intermediate **129** followed by the Lewis acid mediated formation of quinazolinone intermediate **130** via formation of the imine, ring-closing and consequent dehydrogenation. A $Yb(OTf)_3$ catalyzed inverse electron-demand aza-Diels–Alder cycloaddition reaction in the intramolecular fashion (IADA) between *N*-phenyliminium azadiene and an electron-rich alkyne dienophile followed by aromatization provided luotonin A (**16**) in 35% yield.

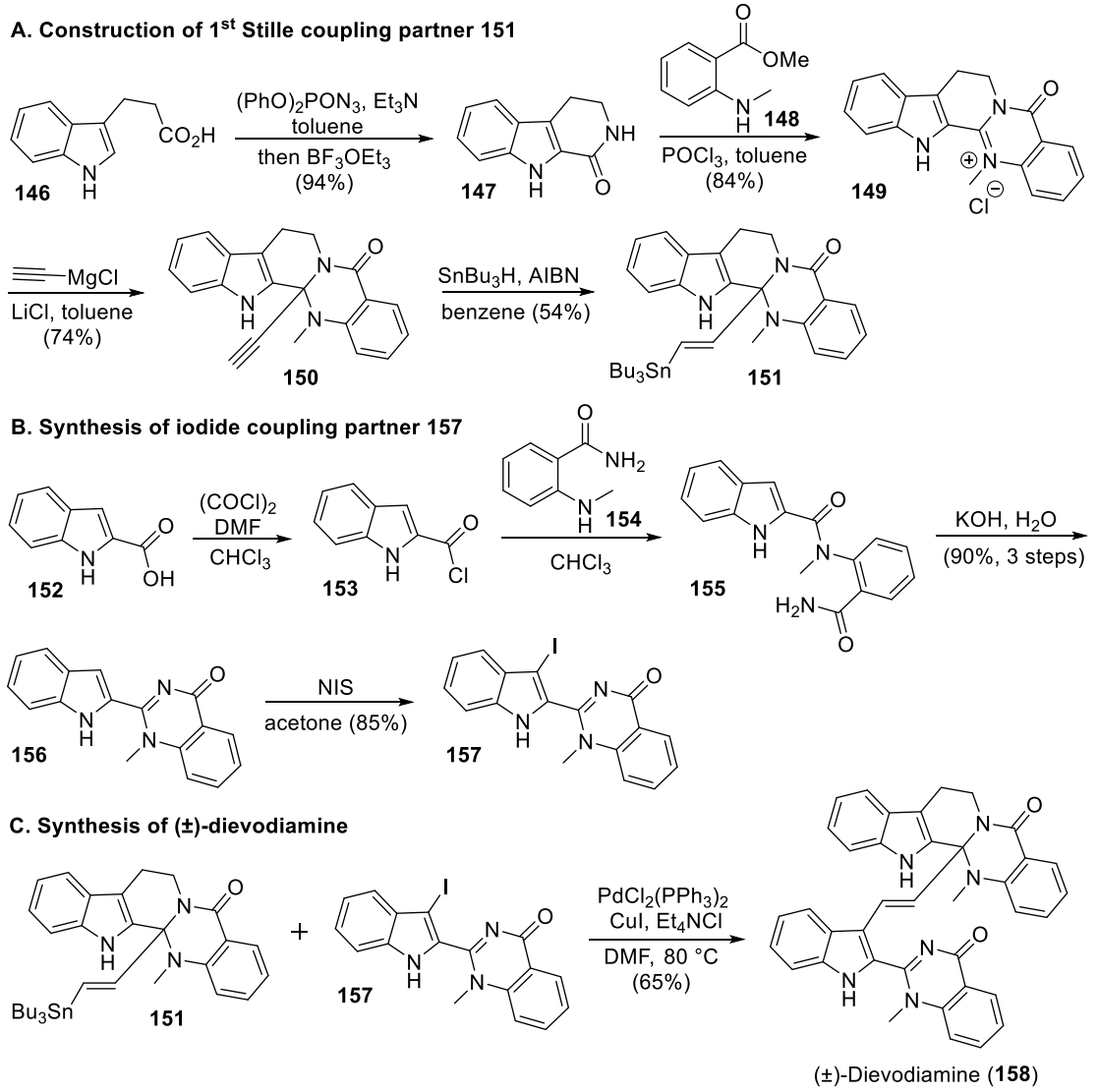
Janoxepin (**145**) was isolated in 2005 from the fungus *Aspergillus janus* by Sprogøe and co-workers (Scheme 15).[50] Janoxepin (**145**) exhibits an antiplasmodial activity against the malaria parasite *Plasmodium falciparum* 3D7 (IC_{50} 28 mg/mL). Structurally, janoxepin (**145**) is attractive, being based on an oxepinepyrimidinone-ketopiperazine tricyclic core derived from D-leucine. Taylor and co-workers developed a first synthetic route for janoxepin (**145**), comprising pyrimidinone preparation, ring-closing metathesis, aldol introduction of the enamide, and dihydro- oxepine elaboration were the key steps. Starting from known amine compound **131** synthesis was completed in 13 steps. Amine **131** was subjected to one-pot oximation–hydrogenation cyclization sequence to furnish the desired amidine **132** in 2 steps.



Scheme 15. Total Synthesis of an Oxepine Natural Product (±)-Janoxepin

Condensation of cyclic amidine **132** with the allylmalonate **133** using NaOMe as base furnished the required pyrimidinone **134** in 72% yield. In this reaction the racemiza- tion of the stereogenic center was observed. The *O*-allylation of compound **134** was carried out under Mitsunobu conditions (DIAD, PPh_3) using allyl alcohol (**135**) to furnish required diallylated pyrimidinone **136** in 73% yield. Meerwein's reagent mediated *O*-alkylation of lactam carbonyl of compound **136** delivered the compound **137**, subsequent treatment of compound **137** with the Grubbs second generation catalyst provided dihydro-oxepine **138** in good yield. Aldol expansion was achieved by deprotonation of imidate **138** with LiHMDS followed by addition of *iso*-butyraldehyde delivered aldol adduct **139** as a single diastereomer. A mesylation–elimination sequence was then employed to give enamine **140** as a single isomer. Treatment of dihydro-oxepine **140** with SeO_2 producing

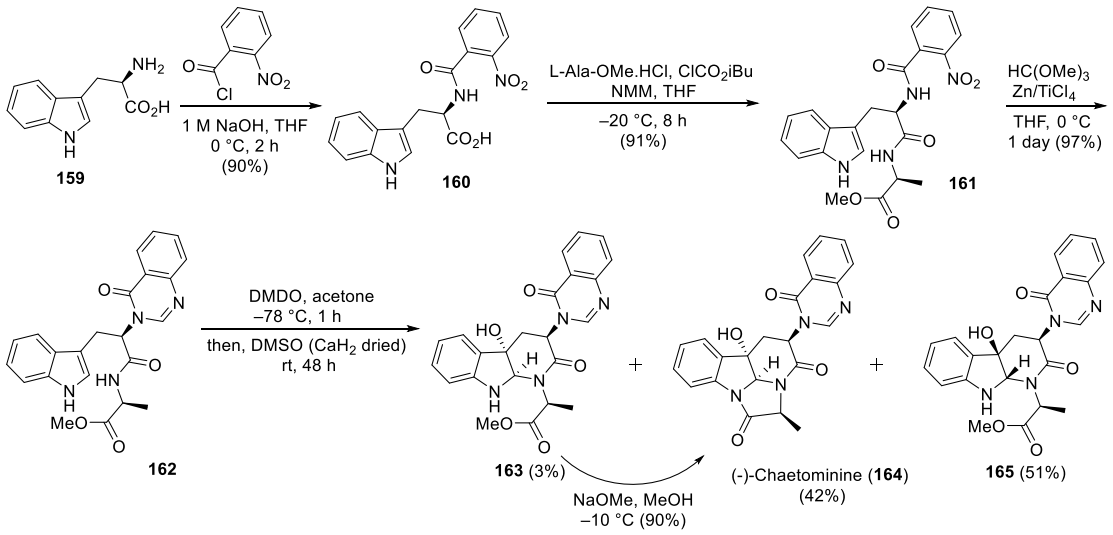
a mixture of allylic alcohol **142** (50%, α:β = 1:1) along with a small amount of the corresponding ketone **141** (10%), which could be converted into alcohol **142** (α:β = 1:1) using sodium borohydride. All attempt of dehydration of allylic alcohol **142** to generate oxepine **144** were unsuccessful by using various conditions (including sulfurane reagents, acid catalysis, Chugaev elimination, Shapiro/Bamford–Stevens chemistry, selenide oxidation, Tsuji–Trost elimination). Rewardingly, dehydration of compound **142** was carried out by using methanesulfonyl chloride in dichloromethane (98% yield) followed by TBAF-mediated dehydrohalogenation of **143** to produce oxepine **144** in low yield (10%). Finally, hydrolysis using aqueous acetic acid furnished janoxepin (**145**) in nearly quantitative yield (Scheme 15).



Scheme 16. Total Synthesis of (±)-Dievodiamine

Richard J. K. Taylor and co-workers described the first total synthesis of the natural product dievodiamine **158** derived *from Evodia rutaecarpa*. The convergent synthesis

was achieved without protecting groups, delivering a route that is short and high yielding. Key steps comprise organometallic addition into a dehydroevodiamine hydrochloride **149** adduct and the Stille coupling of two advanced intermediates (**151** and **157**) to complete the synthesis. Synthesis began with construction of 1st Stille coupling partner **151**, the conversion of indole **146** into known lactam **147** via a Curtius rearrangement and subsequent electrophilic aromatic substitution (Scheme 16). Using modified Deker's procedure dehydroevodiamine hydrochloride **149** was prepared by heating **147** with methyl anthranilate **148** and $POCl_3$. The reaction of commercially available ethynylmagnesium chloride with dehydroevodiamine hydro- chloride **149** gave the alkyne compound **150** in 74% yield. Finally, hydrostannylation with Bu_3SnH and AIBN in refluxing benzene completed the synthesis of stannane coupling partner **151**, which was isolated as a single regioisomer in reasonable yield. The synthesis of iodide coupling partner **157** was accomplished from commercially available indole-2-carboxylic acid **152**. Oxalyl chloride mediated acid chloride **153** formation was followed by reaction with 2-(methylamino)benzamide (**154**) to form amide **155**, which was then cyclized using aqueous KOH at higher temperature. The residue was then collected by filtration, affording quinazolinone **156** in good yield over the three-step sequence. The synthesis of indole **157** was completed by reaction with *N*-iodosuccinimide in acetone, affording the desired product **157** in 77% overall yield from **152** (Scheme 16). Finally, the coupling of stannane **151** with iodide **157** using $PdCl_2(PPh_3)_2$ and Et_4NCl led to a target compound (±)-dievodiamine (**158**) in 65% yield (Scheme 16).[51]



Scheme 17. Total Synthesis of (–)-Chaetominine

Pei-Qiang Huang and co-workers developed a route for total synthesis of the alkaloid (–)-chaetominine (**164**) in four steps with an overall yield of 33%. A one-pot cascade indole

epoxidation, epoxide ring opening cyclization, lactamization reaction sequence and the use of a nitro group as a latent serve of amino group for the one-pot construction of the quinazolinone ring were the key features. Prior to this, four syntheses for (–)-chaetominine (**164**) have been reported. Synthesis started with the aroylation of D-tryptophan (**159**) with *o*-nitrobenzoyl chloride furnished the aroylated product **160** in 90% yield (Scheme 17). Successive treatment of compound **160** with *i*-BuOCOCl/*N*-methylmorpholine and the L-alanine methyl ester hydrochloride salt produced the desired dipeptide derivative **161** in 91% yield. The quinazolinone ring system **162** was constructed by a modification of Shi's method.[19] The desired quinazolinone **162** was obtained in the reaction of compound **161** with trimethyl orthoformate and low valent titanium generated in situ from $TiCl_4$ and Zn powders in THF at 0–5 ˚C, in 97% yield. Finally, for the key epoxidation-initiated cascade reaction a dipeptide **162** was first treated with DMDO in acetone at –78 ˚C for 1 h and then DMSO was added and the mixture was stirred at 25 ˚C for 2 days to give the desired (–)-chaetominine (**164**) in 42% yield, along with a small portion of its lactamization precursor **163** (3% yield) and its epimer **165** in 51% yield. The structure of (–)-chaetominine (**164**) was confirmed by single crystal X-ray analysis (Scheme 17).[52]

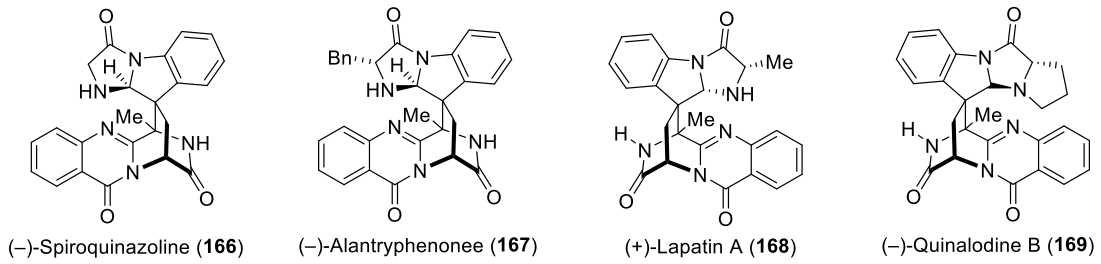
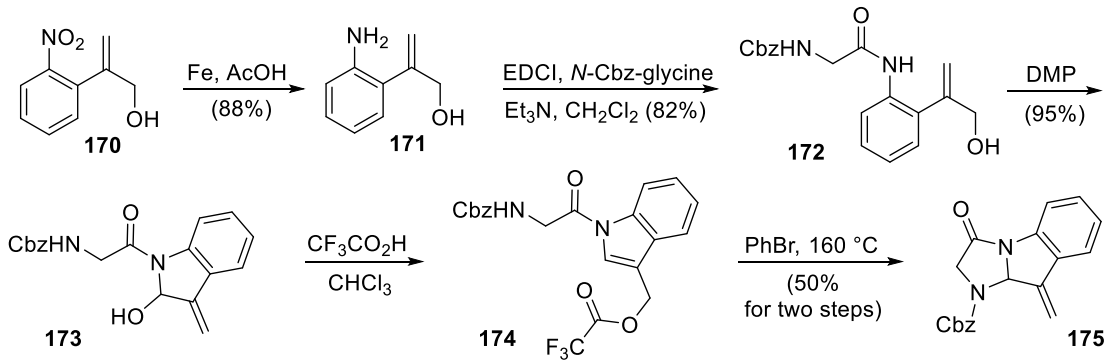


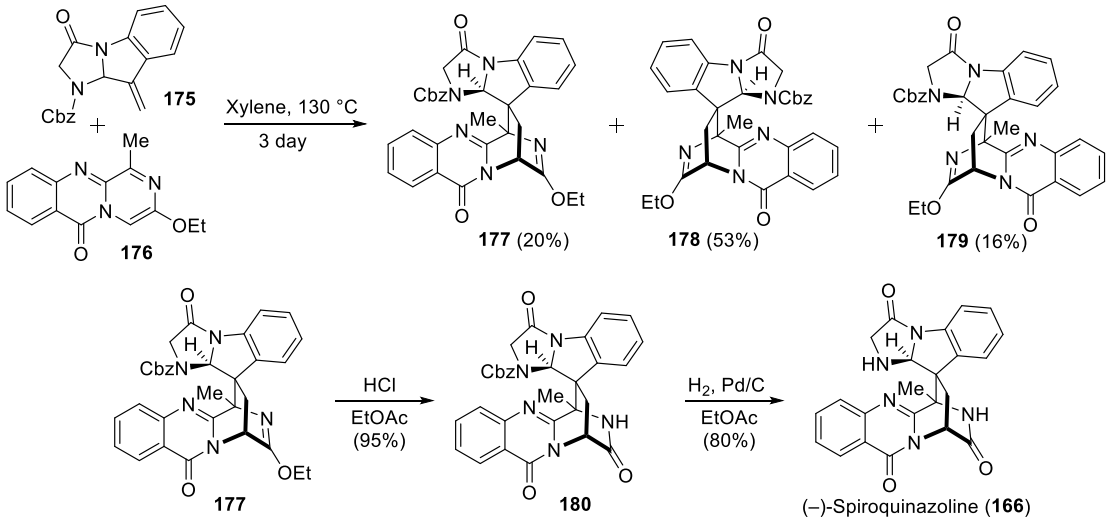
Figure 8. Representative Spiroquinazoline Alkaloids



Scheme 18. Synthesis of Aminal Embodied Olefin

Ma and co-workers accomplished the first total synthesis of (–)-spiroquinazoline (**166**) along with the first total synthesis of three indoline-containing spiroquinazoline alkaloids (Figure 8), namely (–)-alantryphenone (**167**), (+)-lapatin A (**168**) and (–)-quinadoline B

(**169**) using the aza-Diels–Alder reaction of aminal embodied olefins with azadienes in 11–12 steps. Aminal embodied olefin **175** was prepared from a known compound 2-(2-nitrophenyl)prop-2-en-1-ol in five steps. As depicted in Scheme 18, the preparation of the olefin **175** started with the Fe/HOAc reduction of **170** to resultant aniline **171** which was then condensed with *N*-Cbz-glycine to afford the amide **172**. Dess–Martin oxidation of **172** underwent concomitant intramolecular condensation provided the cyclic hemiaminal **173**. The hemiaminal **173** was then treated with one equivalent of TFA to afford indole **174**. At last the required olefin **175** was produced by heating **174** at 160 ˚C in bromobenzene and furnished desired olefin **175** in 50% over two steps.



Scheme 19. First Total Synthesis of (–)-Spiroquinazoline

The aza- Diels–Alder reaction of **175** with known azadiene **176** in xylene at 130 °C afforded the desired adduct **177** in 20% yield, together with its two isomers **178** (53%) and **179** (16%). Hydrolysis of **177** followed by hydrogenolysis of the formed lactam **180** furnished (–)-spiroquinazoline (**166**) in eight steps with 5.2% overall yield (Scheme 19). Using the same approach, total syntheses of (–)-alantryphenone (**167**), (+)-lapatin A (**168**) and (–)-quinadoline B (**169**) were achieved (Scheme 19).[53]

1.7 Summary

In summary, we have presented a concise account of the quinazolinone alkaloids isolated during the last six years, along with their bioactivity. Almost fifty five new quinazolinone alkaloids along with two quinazoline alkaloids have been isolated as natural products during last six years span. Several synthetic methodologies to the quinazolinone motif and related derivatives reported by different research groups have been presented. Emphasis has been placed on modern developments of synthetic methodologies of quinazolinone compounds, including microwave-assisted synthesis, multi-component one

pot reactions, samarium iodide mediated radical C–C bond formation, enantioselective synthesis using chiral phosphoric acid, palladium-catalyzed three component cyclocarbonylation, palladium-catalyzed three component t-butyl isocyanide insertion, Cu(I)-catalyzed coupling with aryl halides, copper-catalyzed radical methylation, I_2-catalyzed aerobic oxidative C−N cleavage, [3 + 2]-cycloannulation, copper-catalyzed C2-arylation. A variety of synthetic approaches to biologically active natural/synthetic quinazolinone and quinazoline alkaloids have been reported by number of research groups. All the information collected and presented here has been well supported by the provision of more than 66 contemporary references from various international journals.

Given the advances in synthetic methodology and technology in recent years and the continued interest in the quinazoline and quinazolinone skeleton in medicinal chemistry and drug development, the development of efficient and reliable methods for the building of these molecules will ensure that this is an active and important area of research in alkaloid chemistry. We strongly believe that the broad quinazolinone alkaloid field will be of continuing interest to both the synthetic and medicinal chemists and positively there will be interminable promising advancements in the knowledge. In this context, as part of this present dissertation, we have developed new methods for synthesis of quinazolinones and synthesized some related natural products. Our synthetic strategies towards the synthesis of these natural products and their synthetic analogues will be discussed in details in the second chapter of present dissertation.

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Chapter 2

Synthetic Studies on Quinazolinone Alkaloids

Section A

Aryne Insertion Reactions Leading to Bioactive Fused Quinazolinones: Diastereoselective Total Synthesis of Cruciferane

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

This chapter is divided into two sections. The first section presents synthesis of quinazolinone alkaloids tryptanthrin, phaitanthrins A−E and cruciferane using aryne insertion reaction approach (Figure 1). The second section describes a biomimetic synthesis of phaitanthrin E involving a fragmentation of sp^3 carbon–carbon bond, synthesis and rearrangement of (±)/(–)-phaitanthrin D to phaitanthrin E. This section also involves an independent two step approach for the synthesis of phaitanthrin E with the rearrangement of imine double bond in activated quinazolinones. The detailed experimental procedures, complete tabulated analytical and spectral data and some selected NMR spectra have been appropriately included at the end of each section.

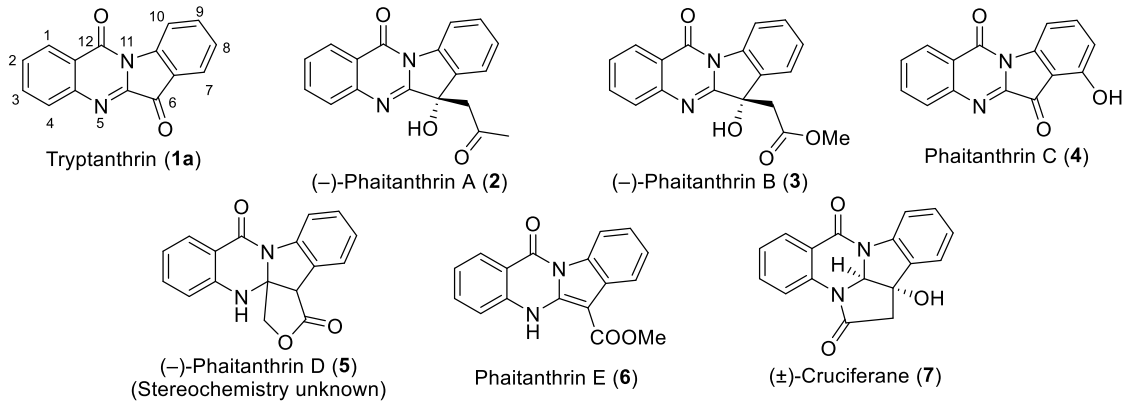


Figure 1. Bioactive quinazolinone alkaloids synthesized.

2A.1 Background

2,3-Disubstituted quinazolinones **8** represent one of the most interesting and useful group of heterocycles (Figure 2).[1] The fused quinazoline-4(3*H*)-one alkaloids such as

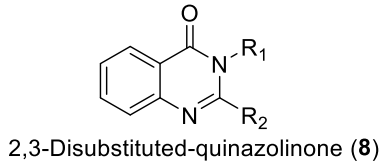


Figure 2. Quinazolinone basic structure.

asperlicins possessing cholecystokinin antagonist properties,[2] benzomalvins the neurokinin receptor antagonists,[3] cytotoxic fumiquinazolines[4] and other fused quinazolinones such as cytotoxic phaitanthrins and tryptanthrin have attracted significant attention of chemist's community (Figure 3).[5] The interesting biological activities and fascinating molecular architectures of these compounds have attracted immediate attention and became the synthetic targets as a result of their limited availability from natural sources. Many elegant total syntheses of chiral fused quinazoline-4(3*H*)-one alkaloids have been reported. In the total synthesis of these alkaloids, the formation of

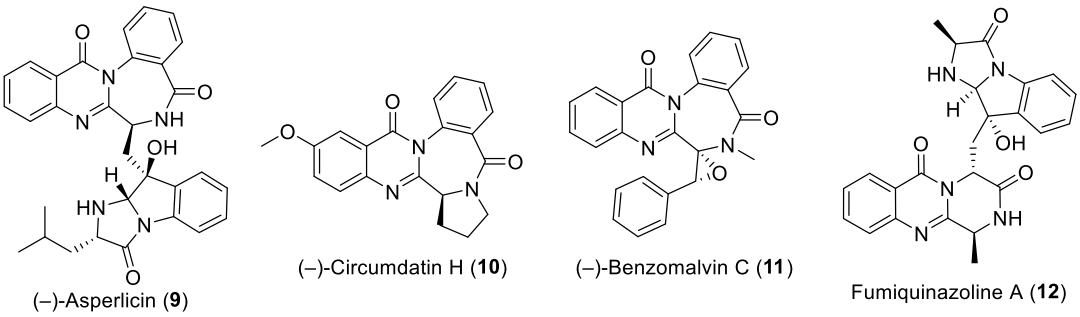


Figure 3. Bioactive fused quinazolinone alkaloids.[2-5]

quinazolinone scaffold and conservation of the chiral integrity of the substituents are the important steps.

2A.2 Concise Account of Tryptanthrin, Phaitanthrins A–E and Cruciferane Syntheses

Several syntheses of tryptanthrin (indolo[2,1-*b*]quinazoline-6,12-dione, **1a**), two syntheses of phaitanthrin A (**2**), one synthesis of phaitantrin B (**3**) and three syntheses of cruciferane (**7**) are known in the literature. The natural product tryptanthrin (**1a**) exhibits significant biological activities such as antibacterial,[6] antiparasitic[7] and antineoplastic.[8,9] Historically, tryptanthrin (**1a**)

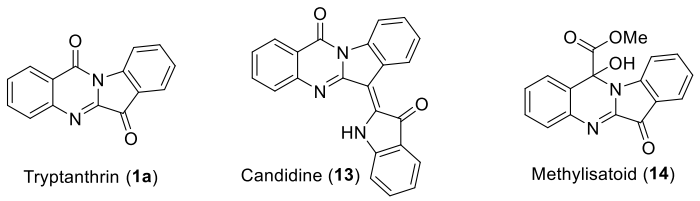


Figure 4. Two more bioactive fused quinazolinone alkaloids isolated along with trypatnthrin.

has been found as a component of herbal medicinal treatments. Extensive work has been put forth to elucidate the usefulness of tryptanthrin (**1a**) derivatives as dyes, pigments and as photoelectric materials.[10,11] Tryptanthrin (**1a**) is a weakly basic alkaloid. This bright yellow compound consists of a quinazolinone ring fused to an indole moiety with carbonyl groups in the 6 and 12-positions. The name *tryptanthrin* has been derived from the observation that this compound is produced by the yeast *Candida lipolytica* when grown in L-tryptophan containing medium (Figure 4).[12]

Very recently, the chemistry of tryptanthrin (**1a**) and its derivatives has been described in the concise review by Peter Grundt.[13] In 1892 O'Neil et al. described the formation of "silky golden-yellow crystals" which formed upon oxidation of indigo with potassium permanganate.[14,15] In 1915 Roschdestwensky and co-workers were able to elucidate the structure of tryptanthrin (**1a**)[16] which was further confirmed 60 years later by X-ray crystallography.[17]

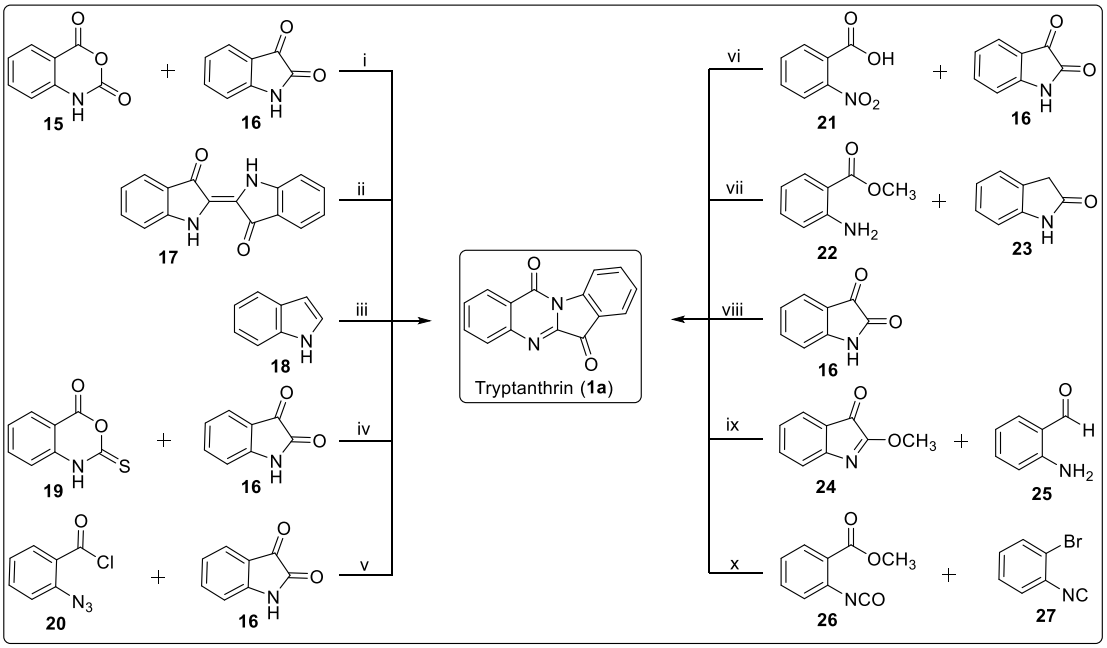
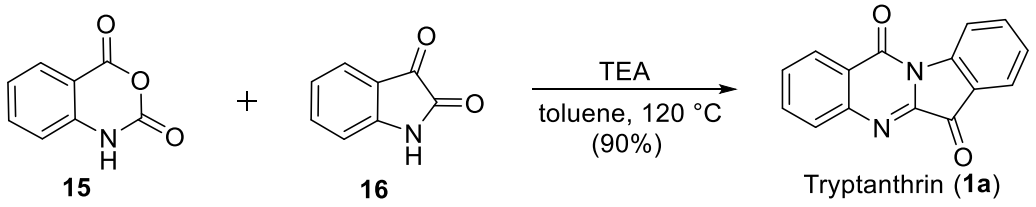


Figure 5. Schematic representation of tyrptanthrin syntheses.

Reaction conditions: (i) TEA, toluene 120 ˚C; (ii) O_3, 0 ˚C, MeOH; (iii) CuI, O_2, DMSO; (iv) Benzene, reflux ; (v) TEA, DMAP, dioxane, then Bu_3P; (vi) $SOCl_2$, then $SnCl_2$, HCl, ethanol, reflux; (vii) $POCl_3$, THF; (viii) $KMnO_4$; (ix) a) Benzene, reflux, b) CrO_3, AcOH:H_2O, reflux; (x) *n*-BuLi, THF.

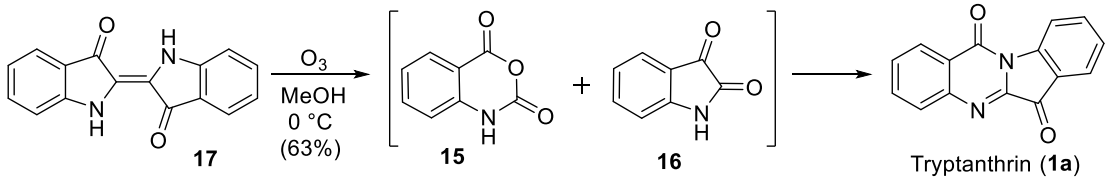
Tryptanthrin (**1a**) has been isolated from numerous natural sources. In particular, tryptanthrin (**1a**) is found in plant materials and traditionally used as colorants including Chinese woad (*Isatis tinctoria*),[18,19] Japanese indigo (*Polygonum tinctorium*),[18,20] Assam indigo *(Strobilanthes cusia*),[21] *Indigo naturalis* (*Strobilanthes formosanus*),[22] and dyer's oleander (*Wrightia tinctoria*).[23] Additionally tryptanthrin (**1a**) has also been isolated from the fruits of the cannonball tree (*Couroupita guaianensis*),[24,25] the orchids *Phaius mishmensis,*[26a] *Calanthe discolor,*[27] the fungi *Schizophyllum commune, Leucopaxillus cerealis*[28,29] and a strain of the bacterial *Cytophaga* genus.[30] Tryptanthrin (**1a**) has also been found in mammals, specifically in the urine of the Asian elephants (*Elephas maximus*)[31] and the wing sac liquids of the bat *Saccopteryx bilineata*.[32] Numerous reaction conditions have been developed to accomplish synthesis of tryptanthrin (**1a**).



Scheme 1. Synthesis of Tryptanthrin

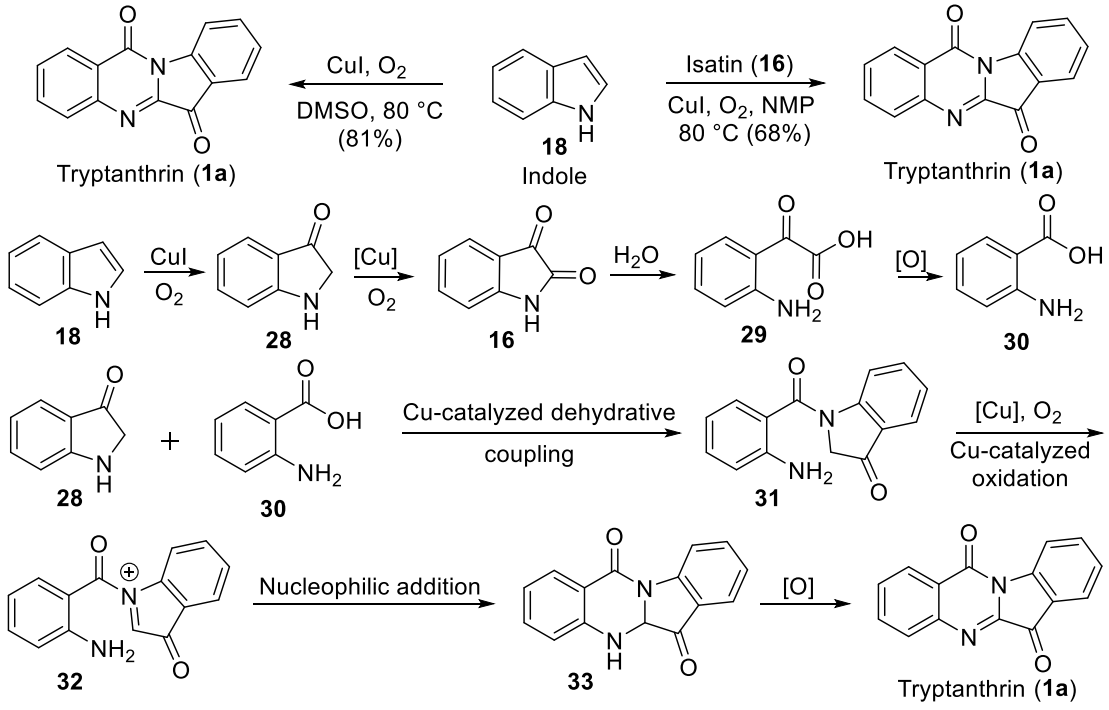
Around ten synthesis of tryptanthrin (**1a**) are represented in figure 5. One common approach for the synthesis of tryptanthrin (**1a**) and its analogues involves construction of the quinazoline system using derivatives of isatoic anhydride (**15**), which react with isatin (**16**) or oxindole **23** as a key step.

Experimentally the simplest method involves heating isatoic anhydride (**15**) and isatin (**16**) in toluene in the presence of triethylamine (Scheme 1).[9,25] Alternative reaction conditions involve DBU/DMAP or an inorganic base such as a sodium hydride/DMF[33-36] or sodium hydroxide/dioxane.[37]



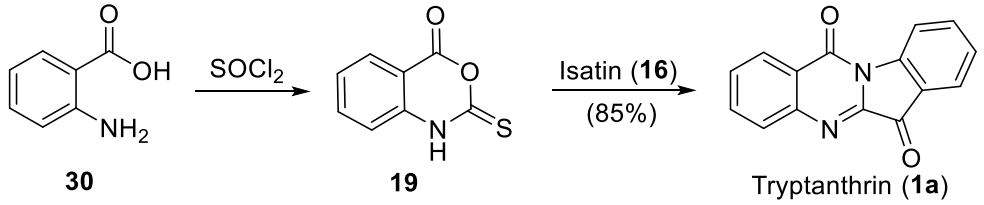
Scheme 2. Synthesis of Tryptanthrin from Indigo

Formation of tryptanthrin (**1a**) also takes place during the oxidation of indigo (**17**) using ozone, which can be explained by the formation of isatoic anhydride (**15**) and isatin (**16**) in the reaction mixture. Under the prescribed reaction conditions the central double bond of indigo (**17**) is cleaved to form isatin (**16**) as a primary oxidation product. Some amount of isatin (**16**) then in situ undergoes oxidation resulting in isatoic anhydride (**15**). Finally, condensation of these two oxidation products yields tryptanthrin (**1a**) in 63% yield (Scheme 2).[38]



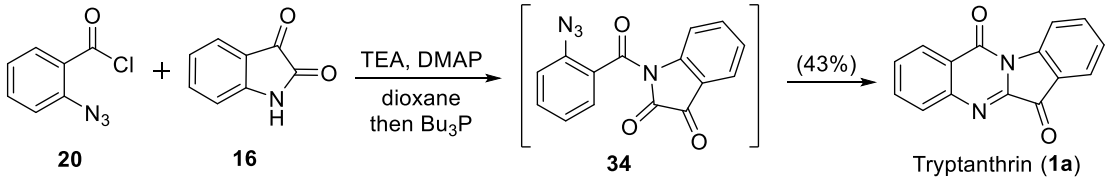
Scheme 3. Synthesis of Tryptanthrin Using Cu-catalyzed Oxidation of Indole

Wang and co-workers reported a concise method for the preparation of tryptanthrin (**1a**) from indole (**18**) via the copper-catalyzed aerobic oxidation. This cascade process includes an oxidation of indole (**18**) to indolinone **28** and isatin (**16**), hydrolysis of isatin (**16**) to 2-(2-aminophenyl)-2-oxoacetic acid (**29**) which undergoes further oxidation to anthranilic acid (**30**), then copper-catalyzed dehydrative coupling of indolinone **28** with in situ formed anthranilic acid (**30**) offered compound **31**. The compound **31** was further oxidized to amine **32** and finally intramolecular nucleophilic addition in amine **32** followed by an oxidative aromatization of **33** produced tryptanthrin (**1a**, Scheme 3).[39]



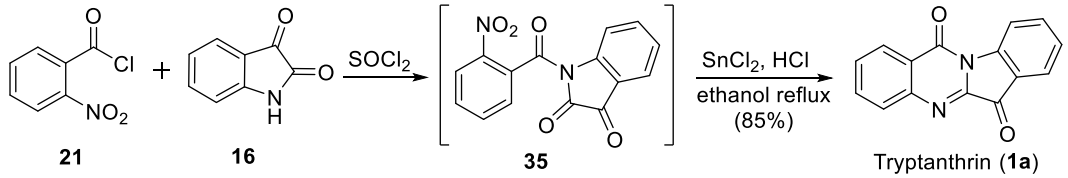
Scheme 4. Synthesis of Tryptanthrin Using Sulfinamide Anhydride

Recently, Jahng et al. described a synthesis of tryptanthrin (**1a**) using anthranilic acid (**30**) as starting material. In this reaction anthranilic acid (**30**) reacts with thionyl chloride to form a thio-analogue of isatoic anhydride (sulfinamide anhydride, **19**) which then condenses with isatin (**16**) to form tryptanthrin (**1a**) in 85% yield (Scheme 4).[40]



Scheme 5. Synthesis of Tryptanthrin Using *aza*-Wittig Reaction

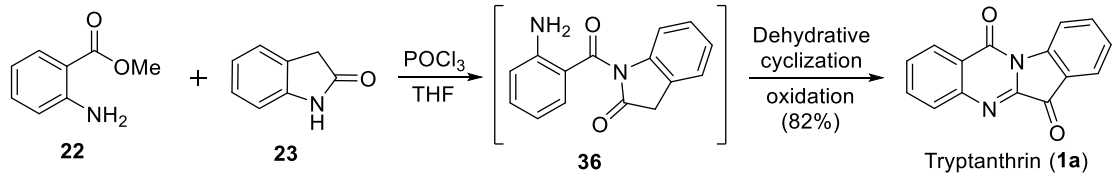
Eguchi et al. reported the preparation of tryptanthrin (**1a**) from 2-azidobenzoyl chloride (**20**) with an intramolecular *aza*-Wittig reaction as the key step (Scheme 5).[41]



Scheme 6. Synthesis of Tryptanthrin Using Reductive Cyclization

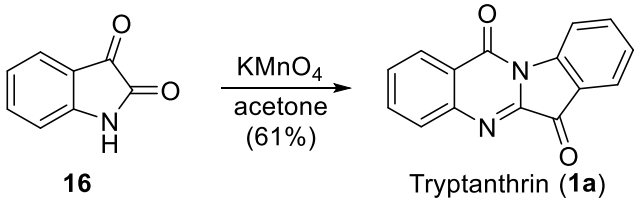
Kikumoto and Kobayashi prepared tryptanthrin (**1a**) by reductive *N*-heterocyclization. In this procedure 2-nitrobenzoyl chloride (**21**) was reacted with isatin (**16**) to form the intermediate 1-(2-nitrobenzoyl)indoline-2,3-dione (**35**). The intermediate **35** further on tin(II) chloride induced reductive intramolecular cyclization offered tryptanthrin (**1a**) in 85% yield (Scheme 6).[42]

An alternative procedure for the synthesis of tryptanthrin (**1a**) was developed by Jahng et al. In this process the methyl anthranilate (**22**) was reacted with oxindole **23** in presence



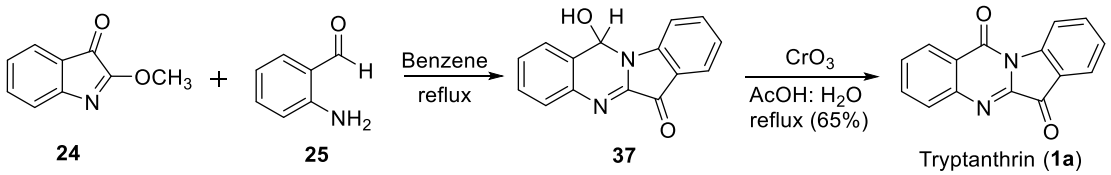
Scheme 7. Synthesis of Tryptanthrin Using Oxidative Cyclization

of phosphorus oxychloride in THF. In this reaction in situ formed corresponding quinazolinone intermediate **36** underwent intramolecular dehydrative cyclization and auto-oxidized to tryptanthrin (**1a**) in 82% yield (Scheme 7).[43]



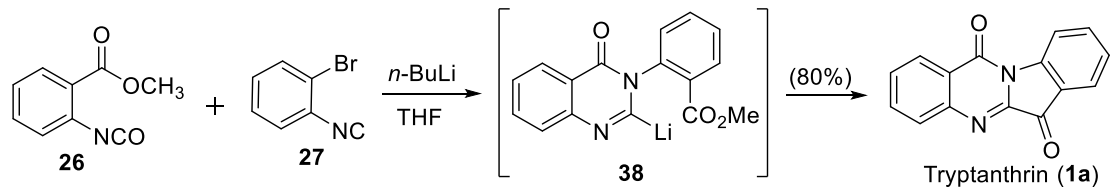
Scheme 8. Synthesis of Tryptanthrin

Tabada and co-workes have described the formation of thryptanthrin (**1a**) by oxidation of isatin (**16**) using $KMnO_4$ in acetone as solvent (Scheme 8).[44]



Scheme 9. Synthesis of Tryptanthrin Using 2-Aminobenzaldehyde

In a different approach by Brid et al. tryptanthrin (**1a**) was prepared from the reaction of *O*-methylisatin (**24**) with 2-aminobenzaldehyde (**25**) first resulting in the product **37**. Oxidation of **37** with CrO_3 at room temperature furnished tryptanthrin (**1a**) in 65% yield (Scheme 9).[45]

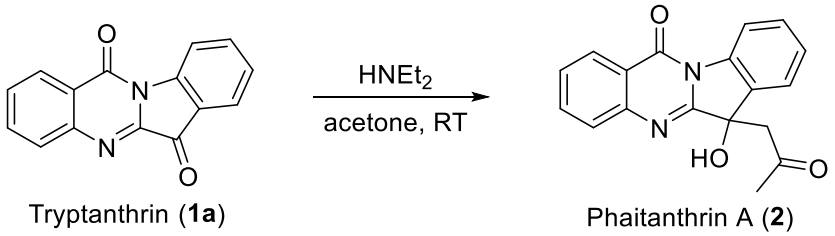


Scheme 10. Synthesis of Tryptanthrin Using *o*-Lithiation Approach

Lygin and de Meijere have offered a one-pot approach to tryptanthrin (**1a**) involving isocyanate **26** and isocyanide **27** as the starting materials. Lithiation of **27** was carried out by using *n*-butyllithium in THF and the addition of isocyanate **26** gave lithiated quinazoline anion intermediate **38** which on an in situ cyclization provided tryptanthrin

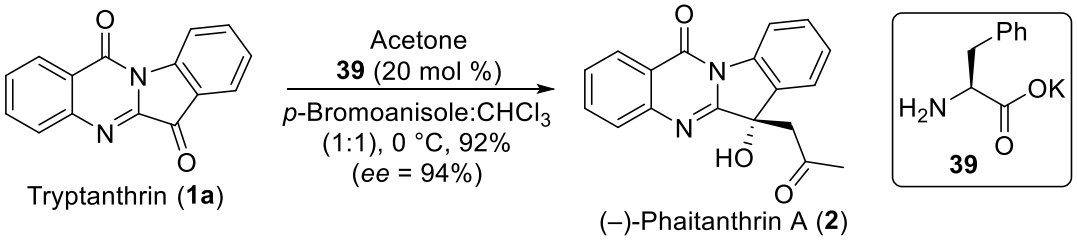
(**1a**) in 80% yield (Scheme 10).[46]

Phaitanthrins A−E, a new type of indoloquinazoline alkaloids have been isolated from *Phaius mishmensis* (Figures 1 & 4).[26a] Phaitanthrin A shows promising cytotoxicity against MCF-7 and SF-268 cell lines. Two syntheses of phaitanthrin A (**2**) are known in literature.



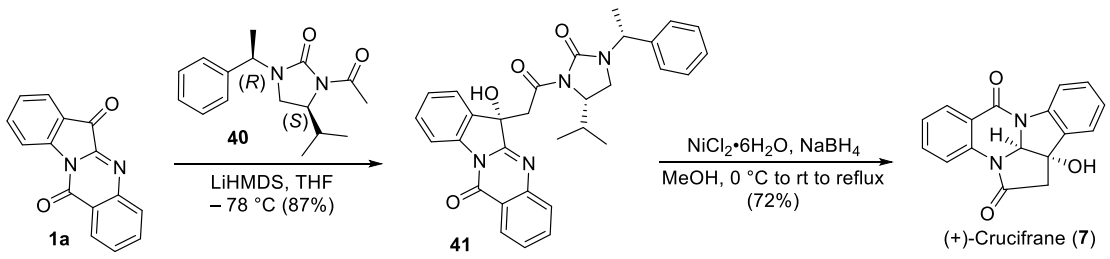
Scheme 11. Synthesis of (±)-Phaitanthrin A

Wu and co-workers described the first synthesis of (±)-phaitanthrin A (**2**) from tryptanthrin (**1a**) by treatment with acetone in the presence of diethylamine. In this reaction acetone serves both as solvent and as a reactant (Scheme 11).[26a]



Scheme 12. Enantioselective Synthesis of (–)-Phaitanthrin A

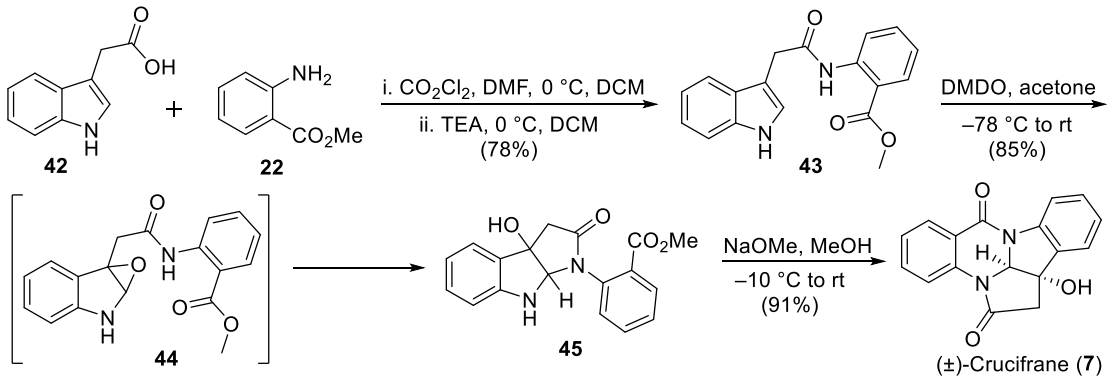
Kang et al. reported the first asymmetric synthesis of (*S*)-Phaitanthrin A (**2**) and its derivatives via a catalytic aldol reaction of tryptanthrin (**1a**) by using easily prepared potassium salt of phenylalanine (**39**). The potassium salt **39** exhibited unique catalytic ability and produced the phaitanthrin A (**2**) and its derivatives in good yield with high amount of enantiomeric excess. This methodology allows synthesis of wide range of substrates with different substitution patterns (Scheme 12).[47]



Scheme 13. Enantioselective Synthesis of (+)-Cruciferane

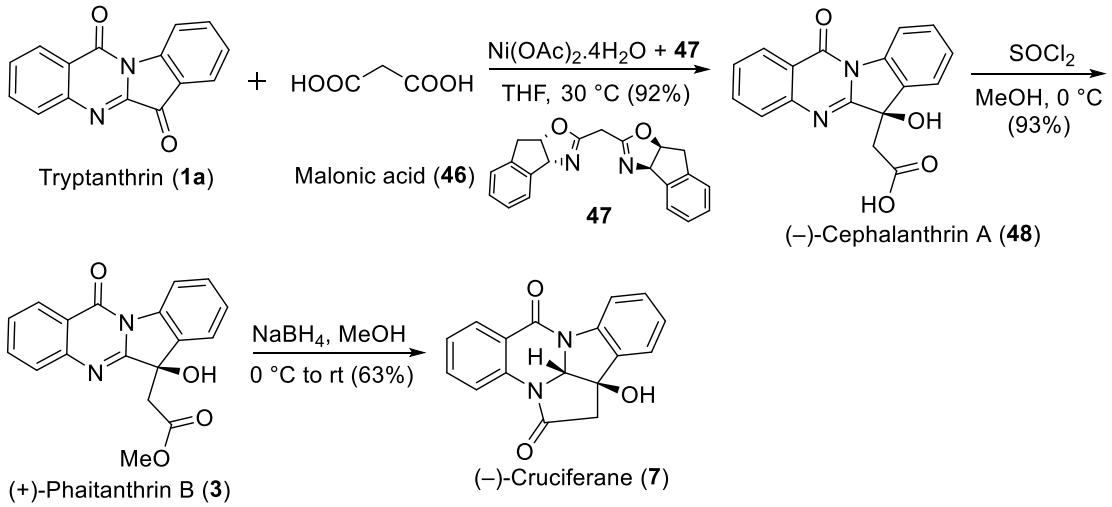
The fused quinazoline alkaloid (±)-cruciferane (**7**) was recently isolated from *Isatis tinctoria* (*Isatis indigotica* Fortune) and it possesses antiviral activity.[48a] The alkaloids

tryptanthrin and phaitanthrins A–E have been also isolated from the same species.[26a,48] Three syntheses of cruciferane (**7**) are known in literature. Nair and co-workers reported the enantioselective synthesis of (+)-cruciferane (**7**) [(+)-pyrrolo[2,3-*b*]indolo[5,5a,6-*b*,*a*]quinazoline] involving the following key steps (i) an asymmetric acetate aldol reaction of chiral auxiliary **40** on keto carbonyl of tryptanthrin (**1a**) by using LiHMDS as a base and (ii) a reductive cyclization/ transamidation of **41** using $NiCl_2.6H_2O/NaBH_4$ in methanol (Scheme 13).[49]



Scheme 14. Racemic Synthesis of Cruciferane

Nagarajan and co-workers reported total synthesis of (±)-cruciferane (**7**) *via* epoxidation/tandem cyclization sequence. The required starting indole amide **43** was prepared by coupling of acid **42** with methyl anthranilate (**22**) using oxalyl chloride. Compound **43** on reaction with DMDO in acetone underwent subsequent regioselective epoxidation to form an intermediate **44** which was followed by tandem cyclization leading to product **45**. The lactamization was carried out using sodium methoxide in methanol to furnish (±)-crucifrane (**7**). This total synthesis of (±)-cruciferane (**7**) was accomplished in three steps with 60% overall yield (Scheme 14).[50]

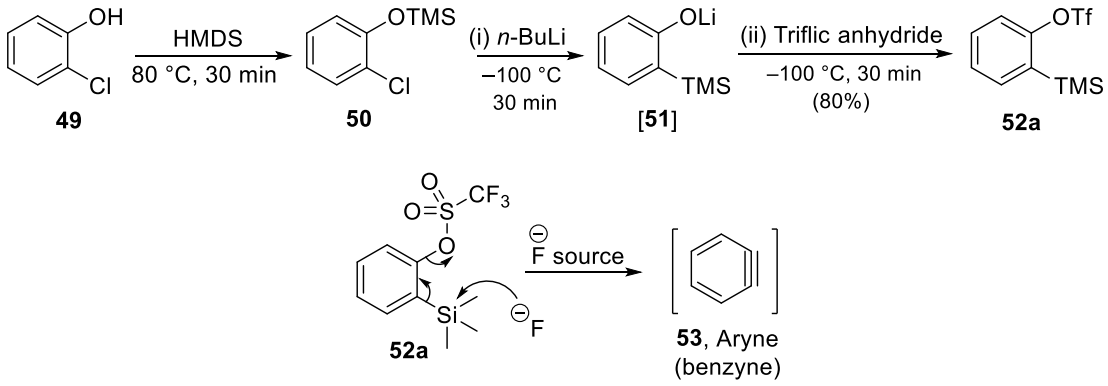


Scheme 15. Asymmetric Synthesis of (–)-Cruciferane

Very recently Jiang and co-workers reported asymmetric synthesis of (–)-cruciferane (**7**) via (**3**) (–)-cephalanthrin A (**48**) and (+)-phaitanthrin B as intermediates by using a nickel (II) catalyzed asymmetric reaction of malonic acid (**46**) and tryptanthrin (**1a**) in 51% overall yield. The condensation of tryptanthrin (**1a**) with malonic acid (**46**) using nickel catalyst in presence of chiral ligand **47** gave (–)-cephalanthrin A (**48**) in 89% yield. Treatment of (–)-cephalanthrin A (**48**) with thionyl chloride in methanol delivered (+)-phaitanthrin B (**3**) in 93% yield with 91% enantiomeric excess. Finally, sodium borohydride induced reduction of (+)-phaitanthrin B (**3**) in methanol furnished (–)-cruciferane (**7**) in 62% yield (Scheme 15).[51]

2A.3 Brief Introduction of Aryne Chemistry

Aryne was first proposed by Georg Wittig in 1940[52] while studying the formation of biphenyl via reaction of fluorobenzene and phenyllithium and experimentally confirmed by John Roberts in 1953 with the help of classic ^{14}C labelling experiment,[53] which provided strong support for benzyne. Three decades later Kobayashi in 1983 discovered a very mild way of generating highly reactive aryne intermediates by using *o*-silyl aryl triflates as aryne precursors which allowed generation of the reactive intermediate under almost neutral conditions (Scheme 16).[54] About two decades after Kobayashi's discovery the synthetic organic chemists recognized the potential to explore this highly reactive intermediate in the total synthesis of natural products.[55a] To date, in literature ~100 individual natural products have been prepared by using



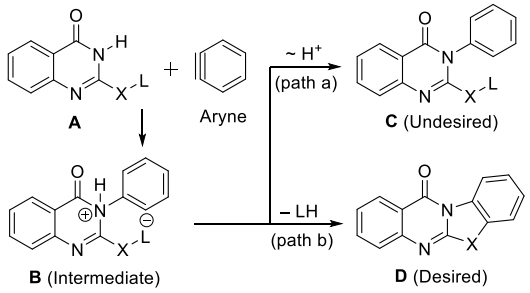
Scheme 16. Generation of Aryne Intermediate

arynes to generate the key synthetic intermediates.[55b] Particularly syntheses of natural products are divided into subgroups on the basis of the type of aryne transformation: (i) *σ*-bond insertion reactions,[56] (ii) nucleophilic additions or multicomponent reactions,[57] (iii) [4 + 2],[58] [2 + 2],[59] and [2 + 2 +2][60] cycloaddition strategies and (iv) metal-catalyzed aryne reactions.[61]

2A.4 Results and Discussion

2A.4.1 Aryne Insertion Reactions Leading to Bioactive Fused Quinazolinones: Diastereoselective Total Synthesis of Cruciferane

Quinazolinones are an important class of compounds and a building block for a large number of structurally diverse alkaloids with a wide range of biological activities. [62,63] More specifically, the fused quinazolinones such as asperlicins, benzomalvins, circumdatins, phaitanthrins and their synthetic congeners have been imperative targets due to their structural architectures and promising bioactivities (please see figure 3).[2-5] Several well designed synthetic routes involving intramolecular cyclization strategies have been known for these significant targets.[2-5] After Kobayashi's discovery of a very mild way of generating highly reactive aryne intermediates,[54] chemistry of arynes has become a subject of contemporary interest.[64] Since then, plenty of meticulous new applications of aryne reactions have been continuously reported by synthetic chemists.[65] On the basis of our continuing interest in the synthesis of quinazolinone alkaloids[66] and their retrosynthetic disconnections, we reasoned that the selective insertion of aryne between the 3-position nitrogen atom and suitable 2-position substituent of 1,3-quinazolin-4-ones would constitute an appropriate one step new synthetic approach to the desired fused quinazolinone systems. We herein describe our detailed studies on aryne insertion reactions of quinazolinones and their applications in the synthesis of several natural and unnatural quinazolinone systems (Schemes 17–21 and Table 1).[67] As depicted in scheme 17, our synthetic proposal



X = Broad range of substituents with electrophilic carbon unit;

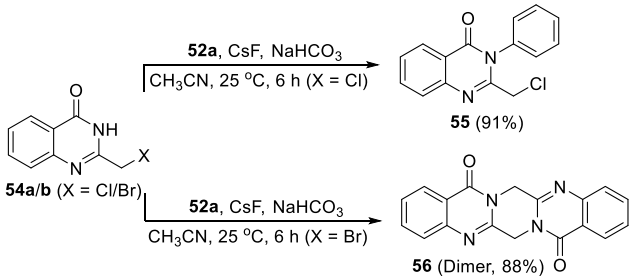
L = An appropriate leaving group.

Scheme 17. Synthetic Proposal for Aryne Insertion Reactions of 1,3-Quinazolin-4-ones

for aryne insertion reactions of 1,3-quinazolin-4-ones was mainly based on the following fundamental concepts, namely: (i) the lone pair of electrons on the 3-position nitrogen atom in quinazolinone **A** would be sufficiently nucleophilic to regioselectively attack an in situ generated reactive arynes to afford a zwitterionic intermediate **B**, (ii) the

intermediate **B** upon intramolecular prototropic shift would provide the undesired *N*-arylated product **C** via a strained four membered transition state (path a), (iii) however, the intermediate **B** upon intramolecular cyclization with a displacement of suitable leaving group from 2-position of quinazolinone would lead to the desired aryl insertion product **D** via five/six/seven-membered transition states (path b) and (iv) tailoring the compatibility of carbanion nucleophilicity with electrophilicity of 2-position carbon unit in an intermediate **B** for intramolecular cyclization would be feasible to make the reaction furnish desired aryne insertion product **D**.

The bioactive tryptanthrin (**1a**) has been isolated from numerous natural sources and several synthesis of **1a** have been known.[26a,48a] The fused quinazoline alkaloids tryptanthrin, phaitanthrins A–E and (±)-cruciferane have been recently isolated from *Phaiusmishmensis* and *Isatis tinctoria* (*Isatis indigotica* Fortune), and are potential antiviral and anticancer agents.[26,48] We surmise that the tryptanthrin could be a biogenetic precursor of (±)-cruciferane (**7**). Exotic (±)-cruciferane (**7**) is the first natural product with pyrroloindoloquinazoline skeleton and also encompasses an angular oxygen function alike antitumor antibiotics mitomycins.[68] On the basis of their structural features, we selected these as synthetic targets and instigated our studies on aryne insertion reactions of 1,3-quinazolin-4-ones. Initial aryne insertion reaction of 2-chloromethylquinazolinone **54a** with an in situ generated aryne intermediate exclusively furnished the corresponding *N*-arylated quinazolinone **55** in 91% yield (Scheme 18). Above experiment clearly indicated that the lone pair of electrons on 3-position nitrogen atom of quinazolinone is sufficiently nucleophilic to



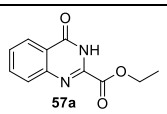
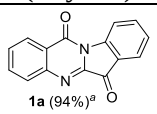
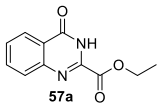
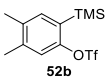
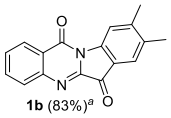
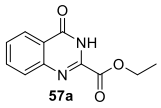
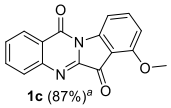
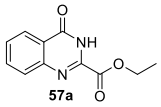
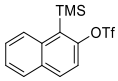
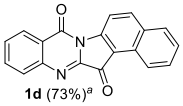
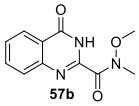
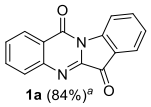
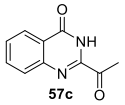
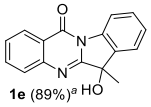
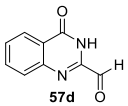
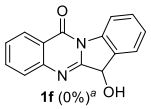
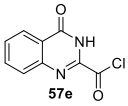
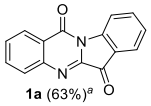
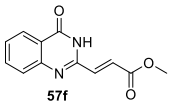
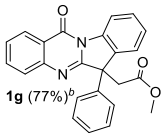
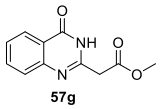
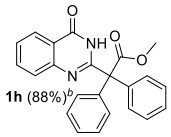
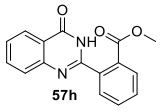
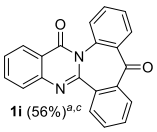
Scheme 18. Preliminary Studies on Aryne Insertion Reactions of 2-Halomethylquinazolinones

attack arynes under the present reaction conditions. However, reaction of 2-bromomethylquinazolinone **54b** with aryne was not possible, as the starting material **54b** underwent a self-coupling reaction to form the linear penta-cyclic dimer **56**[69] in 88% yield via conjugative intermolecular-intramolecular nucleophilic substitution pathway.

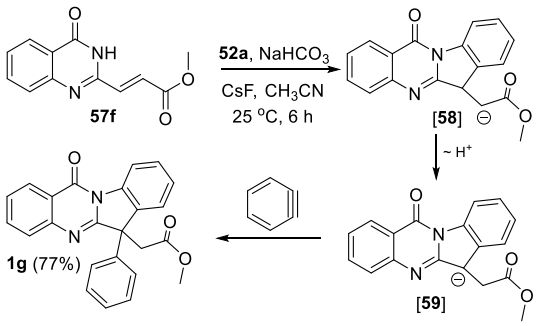
Rewardingly, the insertion reaction of an in situ generated aryne from precursor **52a** to

quinazolinone **57a** in acetonitrile at 25 °C was very clean and furnished the desired natural product tryptanthrin (**1a**) in 94% yield via *N*-arylation followed by a concomitant intramolecular cyclization route (Table 1, entry 1). As anticipated, the intermediate carbanion attacked on the proximal carboethoxy moiety to generate a new carbon–carbon bond prior to prototropic shift and exclusively delivered product **1a**. As described in table 1, several requisite starting quinazolinones **57a**–**h** bearing suitable carbonyl units were prepared to study the generality of present approach.[70] Similarly, insertion reaction of symmetrical aryne from precursor **52b** to quinazolinone **57a** provided the desired product **1b** in 83% yield (Table 1, entry 2). Reaction of quinazolinone **57a** with unsymmetrical aryne from precursor **52c** was highly regioselective and exclusively formed the desired product **1c** in 87% yield (Table 1, entry 3). The lone pair of electrons on nitrogen atom in compound **57a** selectively attacked an electron deficient *meta*-position of aryne[71] to form the product **1c**. Reaction of quinazolinone **57a** with yet another unsymmetrical aryne from precursor **52d** was also highly regioselective and exclusively delivered the desired product **1d** in 73% yield (Table 1, entry 4). The lone pair of electrons on nitrogen atom in compound **57a** selectively attacked a relatively electron deficient *β*-position carbon atom of *α*-naphthalyne to form the product **1d**. This observation is in accordance with literature precedence.[72] Reaction of quinazolinone **57b** with the Weinreb amide unit at 2-position and symmetrical aryne from precursor **52a** also gave the desired product **1a** in 84% yield (Table 1, entry 5). Reaction of quinazolinone **57c** bearing an acyl unit at 2-position and symmetrical aryne from precursor **52a** yielded the desired cycloadduct **1e**[73] in 89% yield (Table 1, entry 6). Reaction of quinazolinone **57d** bearing a formyl unit at 2-position with symmetrical aryne from precursor **52a** underwent excessive decomposition and failed to provide the desired product **1f** (Table 1, entry 7). Reaction of quinazolinone **57e** with an acid chloride unit at 2-position and symmetrical aryne from precursor **52a** also afforded the desired product **1a** but only in 63% yield (Table 1, entry 8). The decline in yield could be due to relatively less stability of an acid chloride under the present reaction conditions. Reaction of quinazolinone **57f** bearing the *α*,*β*-unsaturated unit at 2-position with symmetrical aryne from precursor **52a** (1.20/2.40 mmol) exclusively furnished the double aryne inclusion product **1g** in 35/77% yield (Table 1, entry 9). As depicted in scheme 19, product **1g** was formed via *N*-arylation followed by a Michael addition to form the intermediate **58**, which on an in situ prototropic shift formed the more stable doubly conjugated carbanionic intermediate **59**. Intermediate **59** bearing net negative charge

Table 1. Aryne Insertion Reactions of Quinazolinones[a/b]

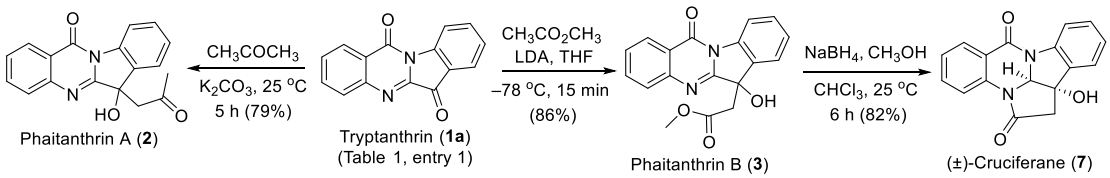
Entry	Quinazolinone	Aryl TMS triflate	Product (% yield)
1	 **57a**	 **52a**	 **1a** (94%)[a]
2	 **57a**	 **52b**	 **1b** (83%)[a]
3	 **57a**	 **52c**	 **1c** (87%)[a]
4	 **57a**	 **52d**	 **1d** (73%)[a]
5	 **57b**	 **52a**	 **1a** (84%)[a]
6	 **57c**	 **52a**	 **1e** (89%)[a]
7	 **57d**	 **52a**	 **1f** (0%)[a] (Not obtained)
8	 **57e**	 **52a**	 **1a** (63%)[a]
9	 **57f**	 **52a**	 **1g** (77%)[b]
10	 **57g**	 **52a**	 **1h** (88%)[b]
11	 **57h**	 **52a**	 **1i** (56%)[a,c]

[a]Reaction condition: Quinazolinone (1.00 mmol), aryl triflate (1.20 mmol), CsF (2.40 mmol), $NaHCO_3$ (1.20 mmol), CH_3CN (10 mL), 25 ^oC, 6 h. [b]Reaction condition: Quinazolinone (1.00 mmol), aryl triflate (2.40 mmol), CsF (4.80 mmol), $NaHCO_3$ (2.40 mmol), CH_3CN (15 mL), 25 ^oC, 6 h.[c] The corresponding simple *N*-arylated product **1j** (please see experimental section) was also formed in 41% yield.



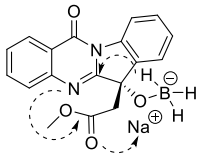
Scheme 19. Proposed Mechanism for Aryl Insertion and *C*-Arylation

being relatively more reactive than the starting material **57f** itself undergoes second arylation process at a faster rate and forms product **1g** with a generation of new quaternary center (Scheme 19). Reaction of quinazolinone **57g** with an active methylene unit ($–CH_2CO_2Me$) at 2-position and symmetrical aryne from precursor **52a** (1.20/2.40 mmol) underwent stepwise double *C*-arylation process and exclusively provided a new quaternary carbon bearing product **1h** in 39/88% yield (Table 1, entry 10). The mono-arylated intermediate product exhibits higher enol character than the starting material **57g** and hence enhances the formation of diarylated product **1h**. Present observation is in accordance with a recent literature report by Mhaske and co-workers.[74] Finally, reaction of quinazolinone **57h** with symmetrical aryne from precursor **52a** afforded the desired seven membered product **1i** in 56% yield (Table 1, entry 11). The corresponding simple *N*-arylated product **1j** was also formed in 41% yield and it could be attributed to a slower rate of generation of seven membered ring systems utilizing the relatively less reactive aromatic ester unit.



Scheme 20. Synthesis of Phaitanthrin A, Phaitanthrin B and Cruciferane

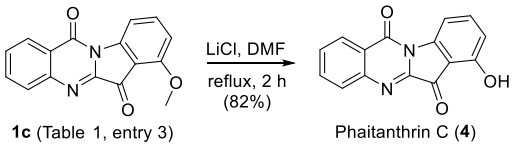
In the next part of our study, the fused quinazolinone systems were used for the synthesis of recently isolated bioactive natural products (Scheme 20). K_2CO_3 induced chemoselective aldol condensation of acetone with natural product tryptanthrin (**1a**) gave the (**2**) in 79% yield. Several attempts to perform the Reformatsky reaction on tryptanthrin (**1a**) were unsuccessful. However, chemoselective condensation of tryptanthrin (**1a**) with methyl acetate using LDA as the base at –78 °C was successful and provided the desired natural product phaitanthrin B (**2**) in 86% yield. The sodium borohydride induced hydroxyl directed[73] highly chemo and diastereoselective reductive



[(±)-**60**]

Figure 6. Proposed TS for reductive intramolecular cyclization.

intramolecular cyclization of phaitanthrin B (**2**) furnished yet another natural product (±)-cruciferane (**7**) in 82% yield. As indicated in the transition state **60** from figure 6, initially the boron atom forms a complex with an adjacent oxygen atom and delivers a hydride from the same phase to imine moiety to generate nitrogen anion in the opposite phase, which undergoes concomitant intramolecular cyclization to form a γ-lactam unit. We feel that the present selective intramolecular cyclization follows a concerted pathway and it is both enthalpically (formation of amide bond) and entropically (formation of five membered ring) favoured process. The demethylation of quinazolinone **1c** using BBr_3/BCl_3 was not very efficient and product **4** was obtained only in 15% yield.



1c (Table 1, entry 3) Phaitanthrin C (**4**)

Scheme 21. Synthesis of Phaitanthrin C

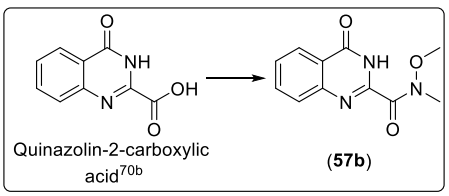
Finally, LiCl induced demethylation of quinazolinone **1c** in refluxing DMF afforded the desired natural product phaitanthrin C (**4**) in 82% yield (Scheme 21). The analytical and spectral data obtained for natural products tryptanthrin, phaitanthrins A–C and cruciferane were in agreement with the reported data.[26a,48a,75]

2A.5 Summary

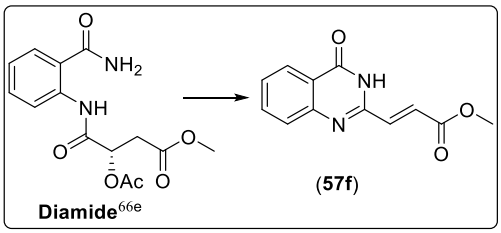
In summary, we have demonstrated a new simple and efficient one-step aryne-based synthetic protocol for a diverse range of fused quinazolinones. It has also been successfully utilized to accomplish a concise total synthesis of five recently isolated different bioactive quinazolinone based natural products. More specifically, the first total synthesis of (±)-cruciferane has been accomplished in three steps with 66% overall yield via two natural products as the intermediates. In the synthesis of cruciferane, selective reduction of an imine moiety in the quinazolinone unit in the presence of an aliphatic ester moiety is noteworthy from a basic chemistry point of view. The present transition metal free convergent approach to fused quinazolinones is general in nature and will be useful to design several focused mini-libraries of natural and unnatural quinazolinone systems for structure-activity relationship studies.

2A.6 Experimental Section

***N*-Methoxy-*N*-methyl-4-oxo-3,4-dihydroquinazoline-2-carboxamide (57b).** To a stirred solution of quinazoline-2-carboxylic acid [70b] (500 mg, 2.63 mmol) in CH_2Cl_2 (10 mL) was added $(COCl)_2$ (0.45 mL, 5.26 mmol) and catalytic amount of DMF at 0 °C under argon atmosphere. The reaction mixture was stirred for 2 h. After the ceasing of gas evolution, it was concentrated and vacuum dried. The residue was again dissolved in CH_2Cl_2 (10 mL) and it was added to a suspension of *N*,*O*-dimethylhydroxylamine hydrochloride (300 mg, 3.15 mmol) and $NaHCO_3$ (660 mg, 7.89 mmol) in CH_2Cl_2 (10 mL). The reaction mixture was stirred for 1 h at 25 °C and the reaction was quenched with water (10 mL). The reaction mixture was extracted with CH_2Cl_2 (15 mL × 3) and the combined organic layer was washed with brine and dried over Na_2SO_4. Concentration of the dried organic layer in vacuo followed by rapid silica gel (60–120 mesh) column chromatographic purification of the obtained residue using ethyl acetate–petroleum ether (7:3) as an eluent gave **57b** as a thick oil (430 mg, 71%). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.54 (s, 3H), 3.83 (s, 3H), 7.48 (dt, J = 8 and 2 Hz, 1H), 7.76 (dt, J = 8 and 2 Hz, 1H), 7.90 (d, J = 8 Hz, 1H), 8.51 (d, J = 8 Hz, 1H), 8.72 (s, 1H); IR ($CHCl_3$) ν_{max} 3385, 1688, 1610 cm^{-1}. The Weinreb amide **57b** was unstable and it was immediately used for the next step.



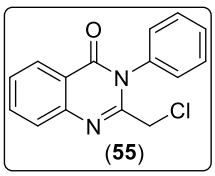
Methyl (*E*)-3-(4-Oxo-3,4-dihydroquinazolin-2-yl)acrylate (57f). To a stirred solution of diamide[66e] (500 mg, 1.62 mmol) in MeOH (20 mL) was added anhydrous K_2CO_3 (448 mg, 3.24 mmol) at 25 °C. The reaction mixture was stirred for 1 h and it was concentrated in vacuo. The obtained residue was directly purified by silica gel (60–120 mesh) column chromatography using ethyl acetate–petroleum ether (3:7) as an eluent to afford **57f** as a white solid (276 mg, 74%). Mp 208–210 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 3.81 (s, 3H), 7.15 (d, J = 16 Hz, 1H), 7.36 (d, J = 16 Hz, 1H), 7.58 (t, J = 8 Hz, 1H), 7.74 (d, J = 8 Hz, 1H), 7.87 (t, J = 8 Hz, 1H), 8.16 (d, J = 8 Hz, 1H), 12.59 (s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 52.1, 121.7, 125.9, 126.9, 127.5, 127.8, 134.7, 136.8, 148.2, 149.1, 161.4, 165.4; ESIMS (m/z) 231 $[M+H]^+$; HRMS (ESI) calcd for $C_{12}H_{11}N_2O_3$ 231.0764, found 231.0766; IR ($CHCl_3$) ν_{max} 3364, 1720, 1678, 1607 cm^{-1}.



General Procedure for Aryne Insertion Reactions of Quinazolinones. A flame-dried

screw-capped Schlenk tube was charged with CsF (2.40 mmol), $NaHCO_3$ (1.20 mmol), quinazolinone (1.00 mmol) and dry CH_3CN (10 mL). The above stirred reaction mixture was purged with argon and then aryne precursor (1.20 mmol) was added at 25 °C. The reaction mixture was stirred for 6 h and filtered through a plug of silica gel. The residue was washed with ethyl acetate (10 mL × 2) and the filtrate was concentrated in vacuo. The obtained residue was purified by silica gel (60–120 mesh) column chromatography using ethyl acetate–petroleum ether as the eluent system to obtain the desired product. For the preparation of compounds **1g** and **1h**, CsF (4.80 mmol), $NaHCO_3$ (2.40 mmol), quinazolinone (1.00 mmol), aryne precursor (2.40 mmol) and CH_3CN (15 mL) were used.

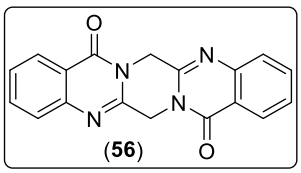
2-(Chloromethyl)-3-phenylquinazolin-4(3*H*)-one (55): White solid (245 mg, 91%); mp



(**55**)

152–154 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.27 (s, 2H), 7.35–7.39 (m, 2H), 7.53–7.61 (m, 4H), 7.79 (dt, J = 10 and 2 Hz, 1H), 7.82 (dt, J = 10 and 2 Hz, 1H), 8.30 (dd, J = 10 and 2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 43.5, 121.3, 127.2, 127.7, 128.0, 128.7, 129.8 (2C), 134.8, 136.0, 147.0, 151.5, 162.1; ESIMS (m/z) 271 $[M+H]^+$; IR ($CHCl_3$) ν_{max} 1688, 1600 cm^{-1}.

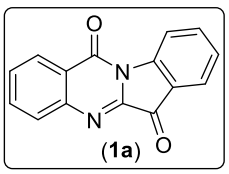
Pyrazino[2,1-*b*:5,4-*b'*]diquinazoline-8,16(6*H*,14*H*)-dione (56): White solid (278 mg,



(**56**)

88%); mp >300 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 5.33 (s, 4H), 7.59 (t, J = 8 Hz, 2H), 7.73 (d, J = 8 Hz, 2H), 7.88 (dt, J = 8 and 2 Hz, 2H), 8.20 (dd, J = 8 and 2 Hz, 2H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 44.5, 120.2, 126.4, 127.1, 127.2, 134.8, 147.1, 149.5, 159.5; ESIMS (m/z) 317 $[M+H]^+$; IR ($CHCl_3$) ν_{max} 1661, 1625 cm^{-1}.

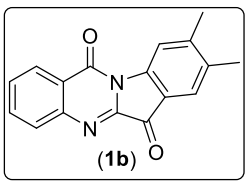
Indolo[2,1-*b*]quinazoline-6,12-dione (Tryptanthrin, 1a): Yellow solid (233 mg, 94%);



(**1a**)

mp 258–260 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.43 (t, J = 8 Hz, 1H), 7.68 (dt, J = 8 and 2 Hz, 1H), 7.79 (dt, J = 8 and 2 Hz, 1H), 7.86 (dt, J = 8 and 2 Hz, 1H), 7.92 (dd, J = 8 and 2 Hz, 1H), 8.03 (dd, J = 8 and 2 Hz, 1H), 8.44 (dd, J = 8 and 2 Hz, 1H), 8.63 (d, J = 8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 118.0, 121.9, 123.7, 125.4, 127.2, 127.6, 130.3, 130.7, 135.2, 138.3, 144.3, 146.3, 146.6, 158.1, 182.6; ESIMS (m/z) 249 $[M+H]^+$; IR ($CHCl_3$) ν_{max} 1741, 1654 cm^{-1}.

8,9-Dimethylindolo[2,1-*b*]quinazoline-6,12-dione (1b): Yellow solid (229 mg, 83%);

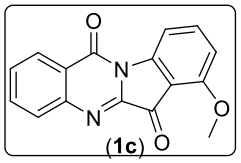


(**1b**)

mp 248–249 °C; ^{1}H NMR (Acetone-d_6, 400 MHz) δ 2.38 (s, 3H), 2.48 (s, 3H), 7.64 (s, 1H), 7.74 (br s, 1H), 7.92 (s, 2H), 8.36 (s, 1H), 8.38 (s, 1H); ^{13}C NMR (Acetone-d_6, 100 MHz) δ 19.6, 21.6, 119.2, 121.4, 124.9, 126.0, 128.0, 130.6, 131.1, 135.7, 136.8, 146.2,

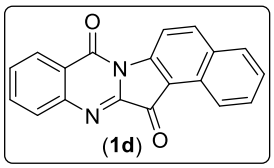
146.4, 148.0, 149.5, 158.7, 182.9; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.35 (s, 3H), 2.45 (s, 3H), 7.67 (s, 1H), 7.67 (t, J = 8 Hz, 1H), 7.85 (dt, J = 8 and 2 Hz, 1H), 8.03 (d, J = 8 Hz, 1H), 8.42 (s, 1H), 8.44 (d, J = 8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.8, 21.6, 118.8, 120.0, 123.7, 125.9, 127.4, 130.0, 130.6, 135.0, 136.2, 145.0, 146.7, 149.4, 158.0, 182.2; ESIMS (*m*/*z*) 277 $[M+H]^+$; HRMS (ESI) calcd for $C_{17}H_{13}N_2O_2$ 277.0972, found 277.0974; IR ($CHCl_3$) ν_{max} 1728, 1693 cm^{-1}.

7-Methoxyindolo[2,1-*b*]quinazoline-6,12-dione (1c): Yellow solid (241 mg, 87%); mp



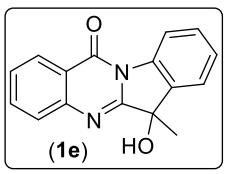
278–280 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.08 (s, 3H), 6.91 (d, J = 10 Hz, 1H), 7.66 (t, J = 10 Hz, 1H), 7.73 (t, J = 10 Hz, 1H), 7.85 (t, J = 10 Hz, 1H), 8.05 (d, J = 10 Hz, 1H), 8.23 (d, J = 10 Hz, 1H), 8.43 (d, J = 10 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 56.5, 110.0, 110.3, 110.4, 123.4, 127.5, 129.9, 130.5, 135.1, 140.2, 144.5, 146.7, 146.9, 158.2, 159.1, 179.5; ESIMS (*m*/*z*) 279 $[M+H]^+$; HRMS (ESI) calcd for $C_{16}H_{11}N_2O_3$ 279.0764, found 279.0760; IR ($CHCl_3$) ν_{max} 1727, 1691 cm^{-1}.

Benzo[4,5]indolo[2,1-*b*]quinazoline-8,14-dione (1d): Yellow solid (277 mg, 73%); mp



240–242 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.57 (t, J = 8 Hz, 1H), 7.67 (t, J = 8 Hz, 1H), 7.75 (t, J = 8 Hz, 1H), 7.85 (t, J = 8 Hz, 1H), 7.91 (d, J = 8 Hz, 1H), 8.05 (d, J = 8 Hz, 1H), 8.28 (d, J = 8 Hz, 1H), 8.44 (d, J = 8 Hz, 1H), 8.81 (d, J = 8 Hz, 1H), 8.97 (d, J = 8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 115.1, 116.0, 123.9, 124.3, 127.2, 127.7, 128.9, 129.0, 130.2, 130.8, 131.2, 132.0, 135.1, 140.0, 144.8, 146.8, 148.9, 158.0, 182.3; ESIMS (*m*/*z*) 299 $[M+H]^+$; HRMS (ESI) calcd for $C_{19}H_{11}N_2O_2$ 299.0815, found 299.0819; IR ($CHCl_3$) ν_{max} 1745, 1661 cm^{-1}.

6-Hydroxy-6-methylindolo[2,1-*b*]quinazolin-12(6*H*)-one (1e): Thick oil (234 mg,

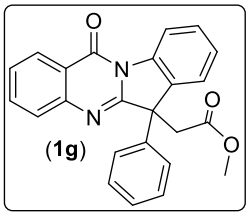


89%); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.70 (s, 3H), 6.42 (br s, 1H), 7.44 (t, J = 8 Hz, 1H), 7.59 (t, J = 8 Hz, 1H), 7.67 (t, J = 8 Hz, 1H), 7.74 (d, J = 8 Hz, 1H), 7.99 (dt, J = 8 and 2 Hz, 1H), 8.26 (d, J = 8 Hz, 1H), 8.27 (d, J = 8 Hz, 1H), 8.53 (d, J = 8 Hz, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 25.7, 74.8, 114.4,116.2, 119.1, 124.5, 126.1, 126.5, 128.5, 130.0,

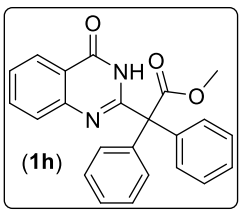
134.8, 136.4, 137.6, 139.3, 168.5, 169.8; ESIMS (*m*/*z*) 265 $[M+H]^+$; IR ($CHCl_3$) ν_{max} 3294, 1667, 1604 cm^{-1}.

Methyl 2-(12-Oxo-6-phenyl-6,12-dihydroindolo[2,1-*b*]quinazolin-6-yl)acetate (1g): White solid (294 mg, 77%); mp 204–206 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.43 (s, 3H),

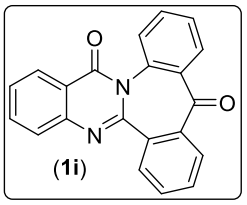
3.52 (d, *J* = 20 Hz, 1H), 4.14 (d, *J* = 15 Hz, 1H), 7.26–7.34 (m, 3H), 7.40–7.46 (m, 3H), 7.52 (d, *J* = 10 Hz, 1H), 7.56 (t, *J* = 10 Hz, 1H), 7.59 (t, *J* = 10 Hz, 1H), 7.85 (dt, *J* = 10 and 2 Hz, 1H), 8.05 (d, *J* = 10 Hz, 1H), 8.26 (d, *J* = 10 Hz, 1H), 8.48 (dd, *J* = 10 and 2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 42.6, 51.8, 54.2, 113.7, 115.0, 119.5, 125.1, 125.7, 126.3, 126.9, 128.2, 128.9, 129.2, 129.7, 133.8, 134.8, 137.9, 138.9, 141.8, 169.0, 169.9, 170.4; ESIMS (*m*/*z*) 383 $[M+H]^+$; HRMS (ESI) calcd for $C_{24}H_{19}N_2O_3$ 383.1390, found 383.1392; IR ($CHCl_3$) ν_{max} 1740, 1659, 1620 cm^{-1}.



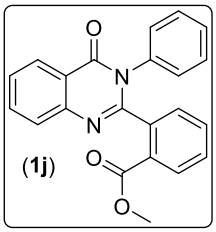
Methyl 2-(4-Oxo-3,4-dihydroquinazolin-2-yl)-2,2-diphenylacetate (1h): White solid (325 mg, 88%); mp 186–188 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.85 (s, 3H), 7.20–7.28 (m, 4H), 7.32–7.40 (m, 6H), 7.48 (t, *J* = 8 Hz, 1H), 7.62 (d, *J* = 8 Hz, 1H), 7.72 (t, *J* = 8 Hz, 1H), 8.25 (d, *J* = 8 Hz, 1H), 10.02 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 53.6, 67.7, 121.0, 126.3, 127.3, 128.1, 128.28, 128.32, 129.8, 134.5, 138.7, 148.2, 154.6, 161.6, 172.6; ESIMS (*m*/*z*) 371 $[M+H]^+$; HRMS (ESI) calcd for $C_{23}H_{19}N_2O_3$ 371.1390, found 371.1390; IR ($CHCl_3$) ν_{max} 1743, 1668, 1610 cm^{-1}.



Dibenzo[3,4:6,7]azepino[2,1-*b*]quinazoline-10,16-dione (1i): White solid (193 mg, 56%); mp >300 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 6.93 (dd, *J* = 10 and 2 Hz, 1H), 7.30–7.42 (m, 1H), 7.45–7.77 (m, 8H), 8.30–8.40 (m, 1H), 8.65–8.75 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 118.4, 121.3, 127.0, 127.1, 127.7, 127.8, 128.3, 129.7, 130.8, 132.0, 132.8, 133.1, 133.3 (2C), 134.7, 140.8, 142.6, 143.0, 156.9, 168.4, 194.2; ESIMS (*m*/*z*) 347 $[M+H]^+$; HRMS (ESI) calcd for $C_{21}H_{13}N_2O_2$ 325.0972, found 325.0970; IR ($CHCl_3$) ν_{max} 1687, 1658 cm^{-1}.

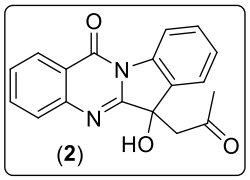


Methyl 2-(4-Oxo-3-phenyl-3,4-dihydroquinazolin-2-yl)benzoate (1j): White solid (145 mg, 41%); mp 110–112 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.66 (s, 3H), 7.28–7.37 (m, 3H), 7.39–7.55 (m, 4H), 7.57–7.70 (m, 2H), 7.85–7.98 (m, 2H), 7.99 (t, *J* = 10 Hz, 1H), 8.40 (d, *J* = 10 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 52.1, 114.9, 121.9, 123.7, 125.6, 127.3, 128.1, 128.7, 129.4, 130.4, 130.5, 133.2, 134.1, 137.7, 152.2, 152.5, 160.3, 166.3, 170.0; ESIMS (*m*/*z*) 357 $[M+H]^+$; HRMS (ESI) calcd for $C_{22}H_{17}N_2O_3$ 357.1234, found 357.1235; IR ($CHCl_3$) ν_{max} 1731, 1620 cm^{-1}.



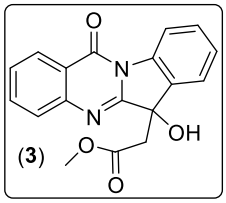
6-Hydroxy-6-(2-oxopropyl)indolo[2,1-*b*]quinazolin-12(6*H*)-one (Phaitanthrin A, 2).

To a stirred solution of tryptanthrin (**1a**, 50 mg, 0.20 mmol) in dry acetone (5 mL) was added anhydrous K_2CO_3 (42 mg, 0.30 mmol) at 25 °C. The reaction mixture was stirred for 5 h and concentrated in vacuo. The obtained residue was directly purified by silica gel (60–120 mesh) column chromatography using ethyl acetate–petroleum ether (1:1) as an eluent to afford product **2** as a white solid (48 mg, 79%). Mp 170–172 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.12 (s, 3H), 3.44 (d, J = 20 Hz, 1H), 3.55 (d, J = 20 Hz, 1H), 5.00 (s, 1H), 7.11 (dt, J = 10 and 2 Hz, 1H), 7.18 (dt, J = 10 and 2 Hz, 1H), 7.44–7.48 (m, 1H), 7.47 (t, J = 10 Hz, 1H), 7.69–7.74 (m, 2H), 8.19 (d, J = 10 Hz, 1H), 8.28 (d, J = 10 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 30.9, 51.0, 75.6, 116.8, 121.7, 123.3, 126.9, 127.0, 127.3, 127.7, 130.3, 132.1, 134.4, 138.9, 147.1, 159.6, 159.7, 206.4; ESIMS (*m*/*z*) 329 $[M+Na]^+$; IR ($CHCl_3$) ν_{max} 3325, 1713, 1668, 1643, 1600 cm^{-1}.



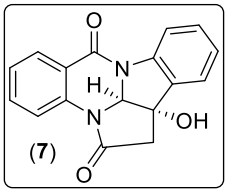
(**2**)

Methyl 2-(6-Hydroxy-12-oxo-6,12-dihydroindolo[2,1-*b*]quinazolin-6-yl)acetate (Phaitanthrin B, 3). To a stirred solution of methyl acetate (95 µL, 1.20 mmol) in THF (2 mL) was added freshly prepared LDA (1 M in THF, 1.26 mL, 1.26 mmol) at −78 °C under argon atmosphere. The reaction mixture was further stirred for 30 min at same temperature and then it was added dropwise to a stirred solution of tryptanthrin (**1a**, 150 mg, 0.60 mmol) in THF (7 mL) at −78 °C. The reaction was quenched after 15 min with saturated aq NH_4Cl solution. The reaction mixture was concentrated in vacuo and the obtained residue was directly purified by silica gel (60–120 mesh) column chromatography using ethyl acetate–petroleum ether (6:4) as an eluent to afford product **3** as a white solid (167 mg, 86%). Mp 210–212 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.30 (d, J = 15 Hz, 1H), 3.43 (d, J = 15 Hz, 1H), 3.49 (s, 3H), 5.15 (s, 1H), 7.08 (dt, J = 10 and 2 Hz, 1H), 7.12 (dt, J = 10 and 2 Hz, 1H), 7.42–7.47 (m, 1H), 7.51 (dd, J = 10 and 2 Hz, 1H), 7.68–7.74 (m, 2H), 8.14 (d, J = 10 Hz, 1H), 8.21 (d, J = 10 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 42.7, 51.9, 75.2, 116.6, 121.5, 123.4, 127.0 (2C), 127.3, 127.7, 130.4, 131.6, 134.4, 138.8, 147.1, 159.5, 159.8, 170.1; ESIMS (*m*/*z*) 345 $[M+Na]^+$; IR ($CHCl_3$) ν_{max} 3349, 1740, 1662, 1645, 1603 cm^{-1}.



(**3**)

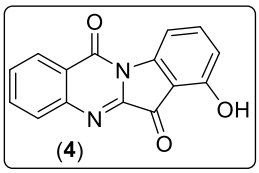
11b-Hydroxy-2a1,11b-dihydro-7*H*-2a,7a-diazabenzo[*b*]cyclopenta[*lm*]fluorene-2,7(1*H*)-dione (Cruciferane, 7). To a stirred solution of phaitanthrin B (**3**, 100 mg, 0.31 mmol) in MeOH:$CHCl_3$ (1:1, 6 mL) was added $NaBH_4$ (23 mg, 0.62 mmol) in small portions at 25 °C. The reaction mixture was further stirred for 6 h at 25 °C and quenched



(**7**)

with 2 N HCl. The reaction mixture was concentrated in vacuo and the obtained residue was dissolved in ethyl acetate (20 mL). The organic phase was washed with brine and dried over Na_2SO_4. Concentration of the dried organic layer in vacuo followed by the silica gel (60–120 mesh) column chromatographic purification of the resulting residue using ethyl acetate–petroleum ether (6:4) as an eluent provided the (±)-cruciferane (**7**) as a white solid (74 mg, 82%). Mp 208–210 °C; ^{1}H NMR (DMSO-d_6, 200 MHz) δ 3.06 (d, J = 18 Hz, 1H), 3.19 (d, J = 20 Hz, 1H), 5.82 (s, 1H), 6.72 (s, 1H), 7.24 (t, J = 8 Hz, 1H), 7.37–7.53 (m, 2H), 7.57 (d, J = 8 Hz, 1H), 7.68–7.82 (m, 2H), 7.95 (d, J = 8 Hz, 1H), 8.06 (d, J = 8 Hz, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 45.8, 77.5, 82.5, 114.8, 122.0, 123.4, 124.6, 124.9, 126.1, 128.4, 129.9, 133.6, 135.4, 136.4, 140.3, 158.6, 170.4; ESIMS (m/z) 293 $[M+H]^+$; IR ($CHCl_3$) ν_{max} 3346, 1723, 1667, 1603 cm^{-1}.

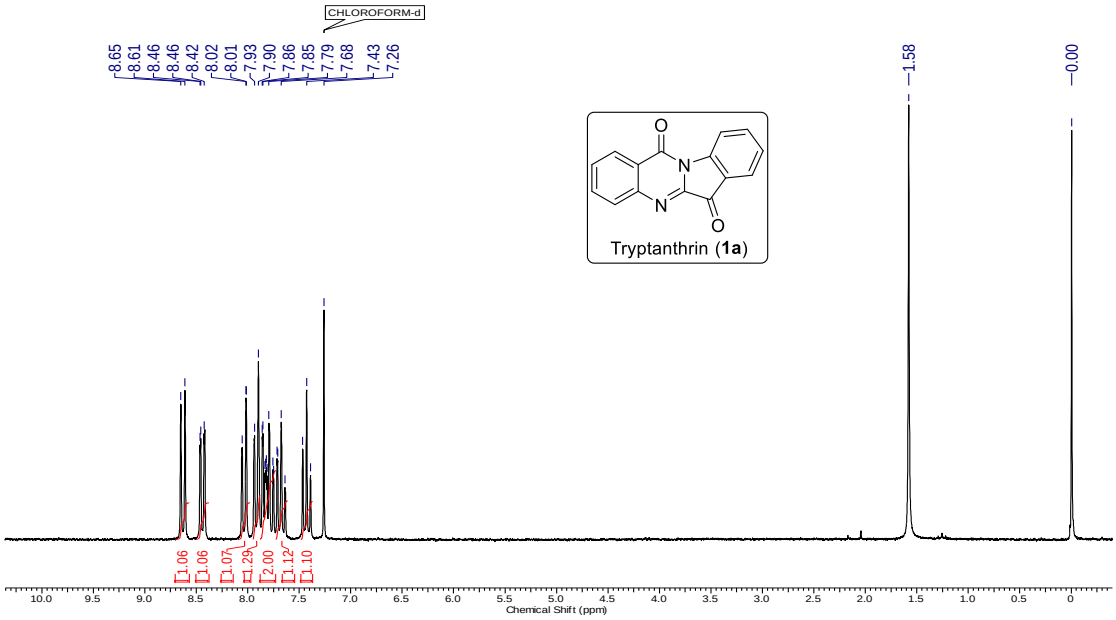
7-Hydroxyindolo[2,1-*b*]quinazoline-6,12-dione (Phaitanthrin C, 4). To a mixture of

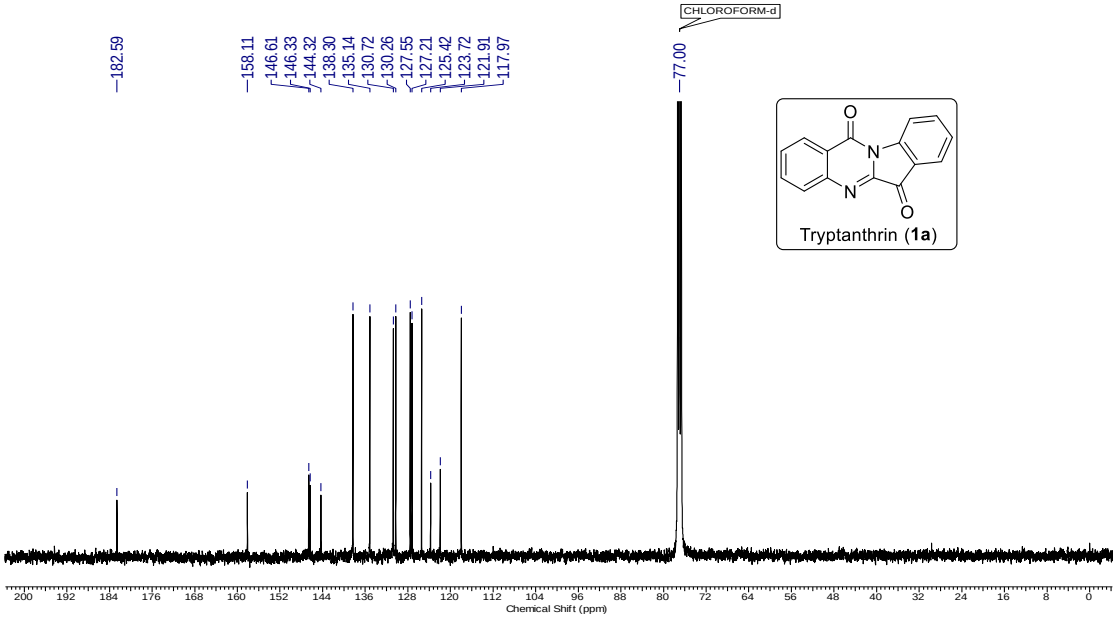


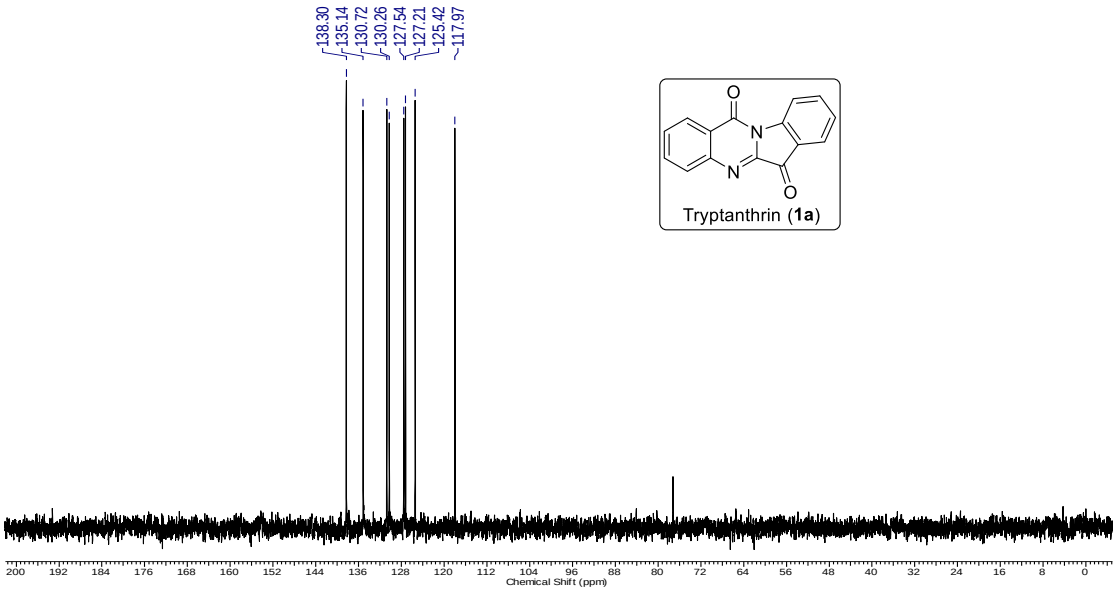
(**4**)

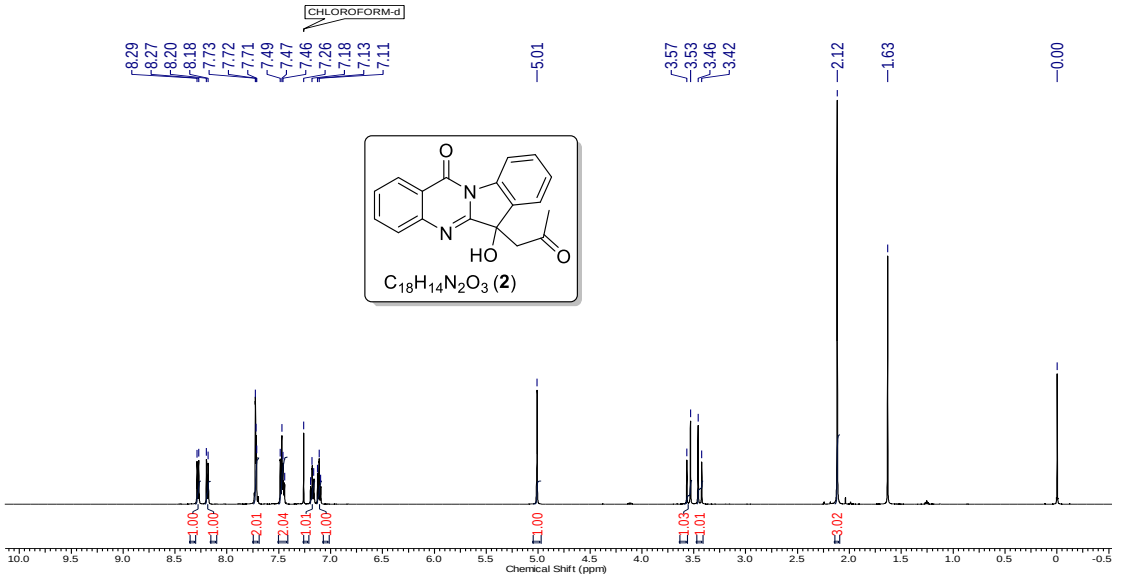
quinazolinone **1c** (100 mg, 0.36 mmol) and LiCl (46 mg, 1.08 mmol) was added DMF (5 mL) under argon atmosphere. The reaction mixture was refluxed for 2 h and it was allowed to reach 25 °C temperature. The reaction mixture was acidified with 2 N HCl and diluted with ethyl acetate (15 mL). The separated organic layer was washed with water, brine and dried over Na2SO4. The concentration of dried organic layer in vacuo followed by silica gel (60–120 mesh) column chromatographic purification of the resulting residue using ethyl acetate as an eluent furnished phaitanthrin C (**4**) as an orange solid (77 mg, 82%). Mp >300 °C; 1H NMR (CDCl3, 500 MHz) δ 6.87 (d, J = 10 Hz, 1H), 7.66 (t, J = 10 Hz, 1H), 7.68 (t, J = 10 Hz, 1H), 7.86 (dt, J = 10 and 2 Hz, 1H), 8.02 (d, J = 10 Hz, 1H), 8.03 (d, J = 10 Hz, 1H), 8.23 (br s, 1H), 8.44 (d, J = 10 Hz, 1H); 13C NMR (CDCl3, 125 MHz) δ 108.9, 109.6, 115.6, 123.5, 127.6, 130.4, 130.7, 135.2, 141.2, 144.2, 144.8, 146.5, 157.9, 158.1, 183.7; ESIMS (m/z) 265 [M+H]+; IR (CHCl3) νmax 3366, 1722, 1697 cm^{-1}.

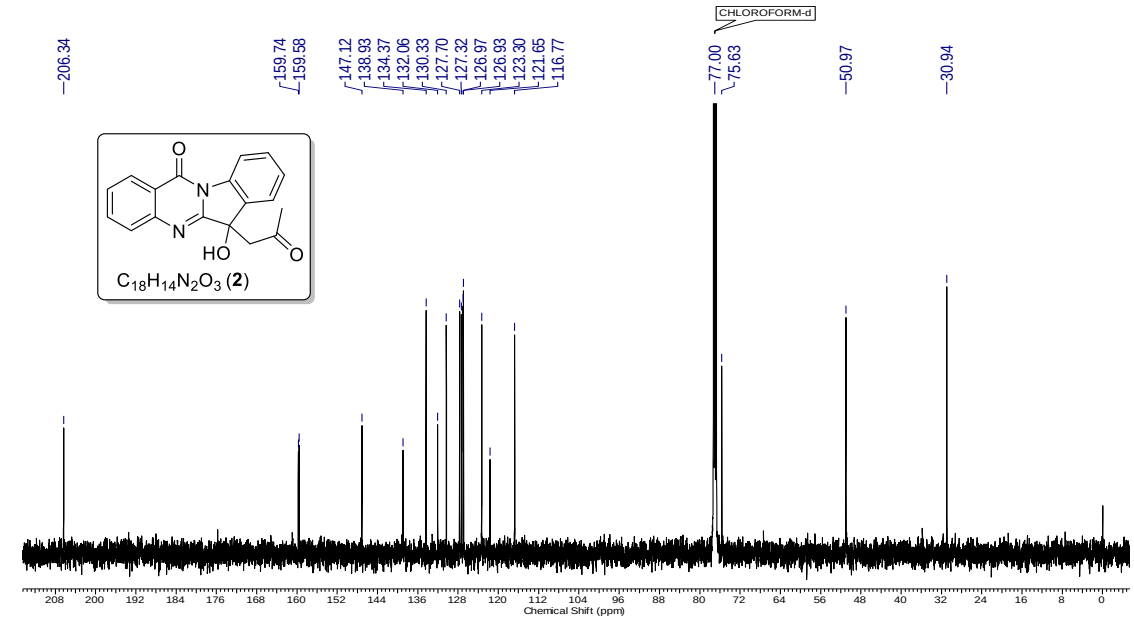
2A.7 Selected Spectra:

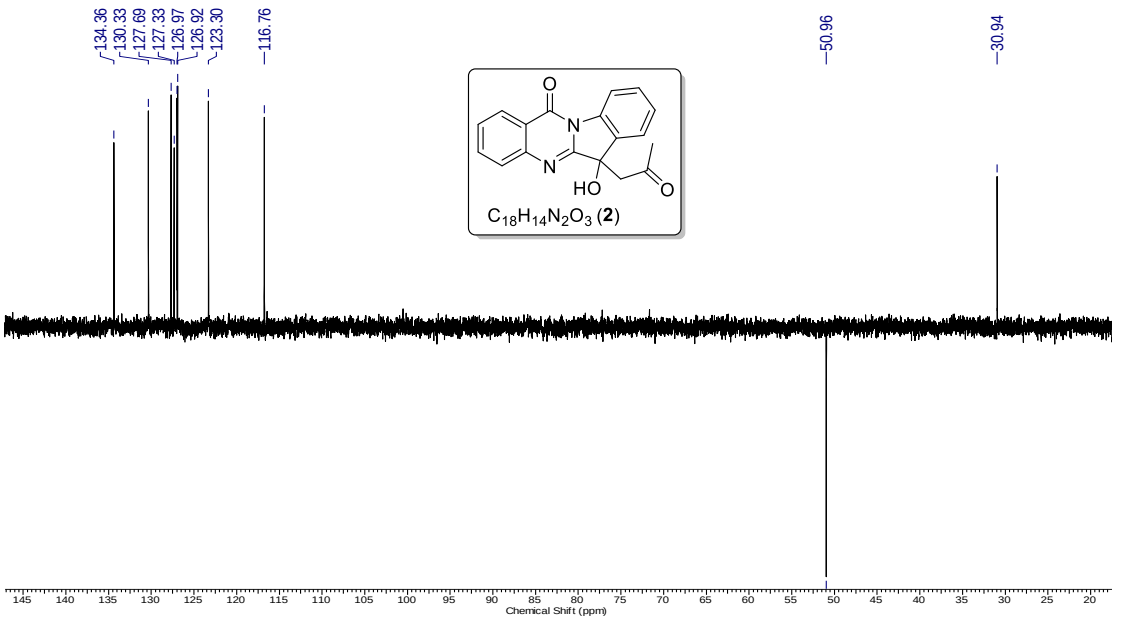

CHLOROFORM-d
8.65
8.61
8.46
8.46
8.42
8.02
8.01
7.93
7.90
7.86
7.85
7.79
7.68
7.43
7.26
1.58
0.00
Tryptanthrin (1a)
1.06
1.06
1.07
1.29
2.00
1.12
1.10
Chemical Shift (ppm)

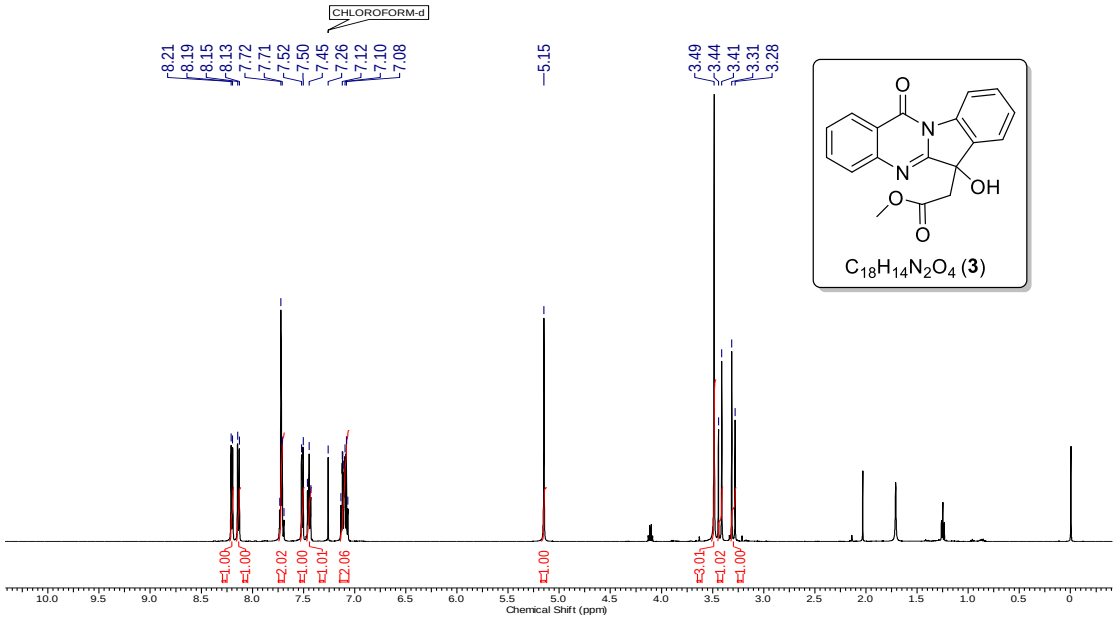

182.59
158.11
146.61
146.33
144.32
138.30
135.14
130.72
130.26
127.55
127.21
125.42
123.72
121.91
117.97
CHLOROFORM-d
77.00
Tryptanthrin (1a)
Chemical Shift (ppm)

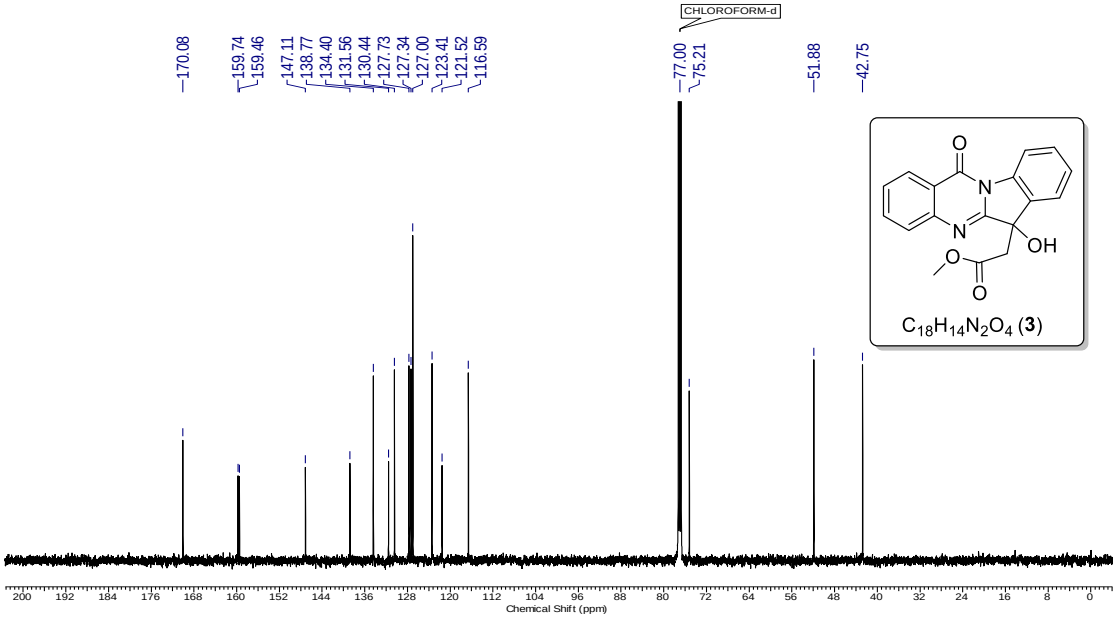

138.30
135.14
130.72
130.26
127.54
127.21
125.42
117.97
Tryptanthrin (1a)
Chemical Shift (ppm)

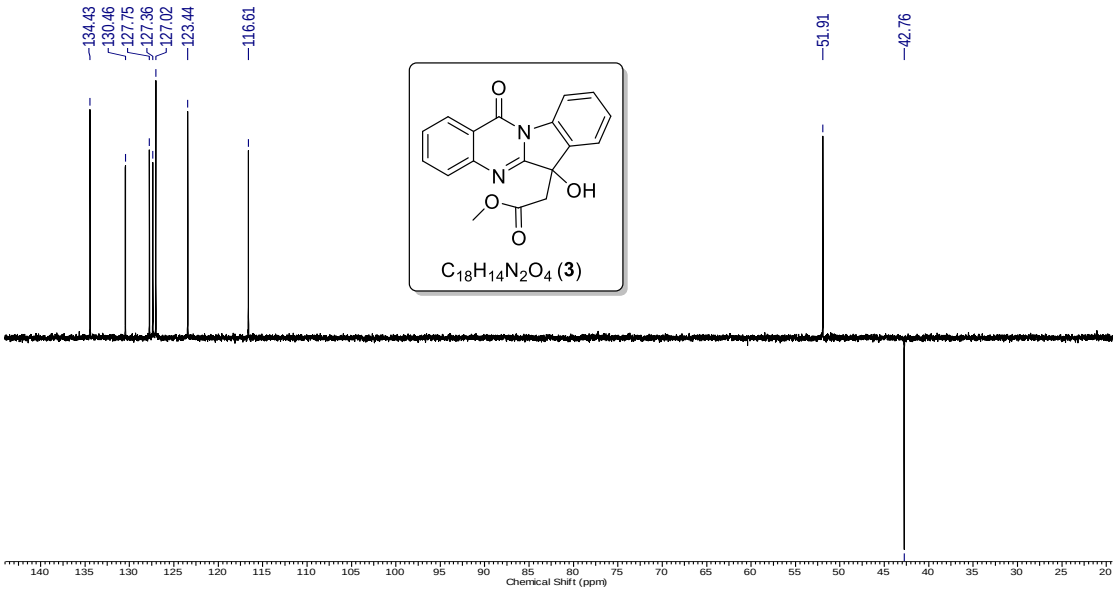

CHLOROFORM-d
8.29
8.27
8.20
8.18
7.73
7.72
7.71
7.49
7.47
7.46
7.26
7.18
7.13
7.11
5.01
3.57
3.53
3.46
3.42
2.12
1.63
0.00
O
N
N
HO
O
$C_{18}H_{14}N_2O_3$ (**2**)
1.00
1.00
2.01
2.04
1.01
1.00
1.00
1.03
1.01
3.02
Chemical Shift (ppm)

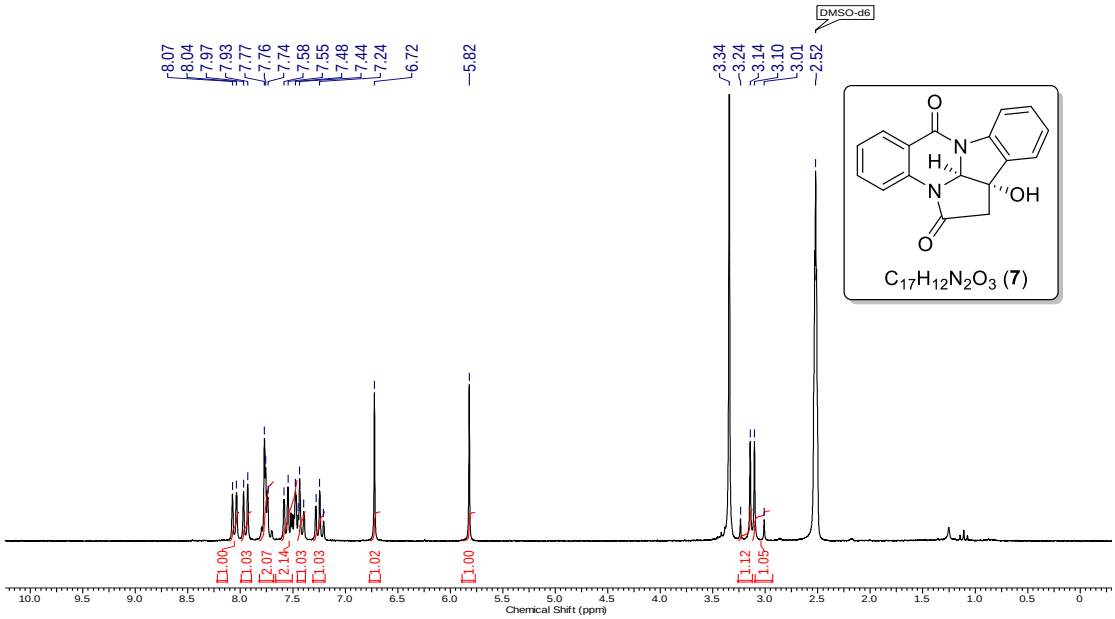

CHLOROFORM-d
206.34
159.74
159.58
147.12
138.93
134.37
132.06
130.33
127.70
127.32
126.97
126.93
123.30
121.65
116.77
77.00
75.63
50.97
30.94
O
N
N
HO
O
$C_{18}H_{14}N_2O_3$ (**2**)
Chemical Shift (ppm)

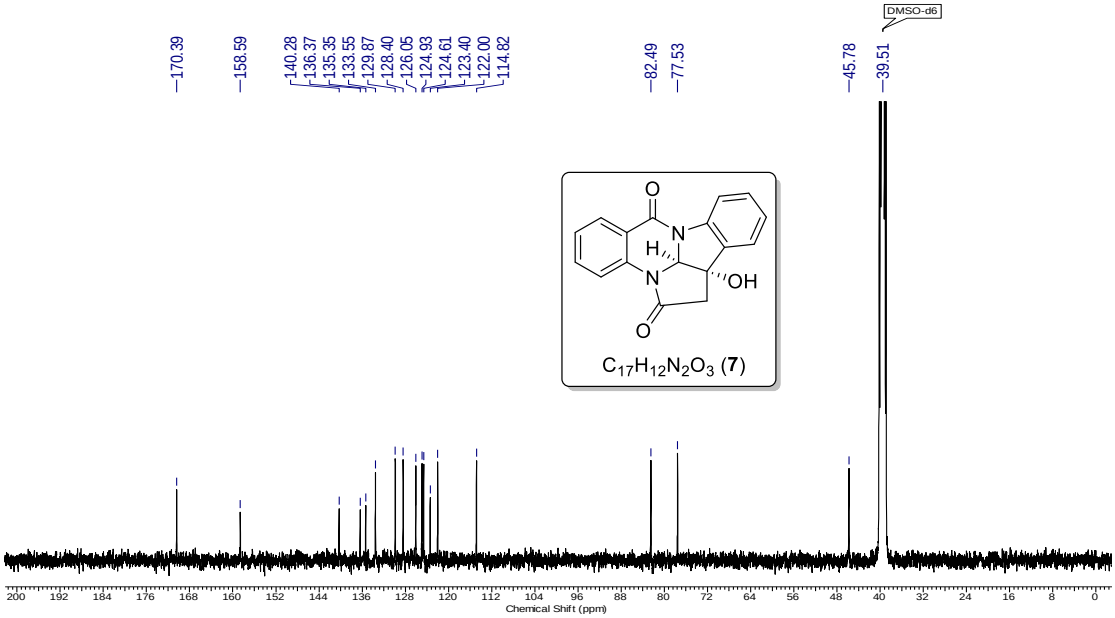

134.36
130.33
127.69
127.33
126.97
126.92
123.30
116.76
50.96
30.94
O
N
N
HO
O
$C_{18}H_{14}N_2O_3$ (**2**)
Chemical Shift (ppm)

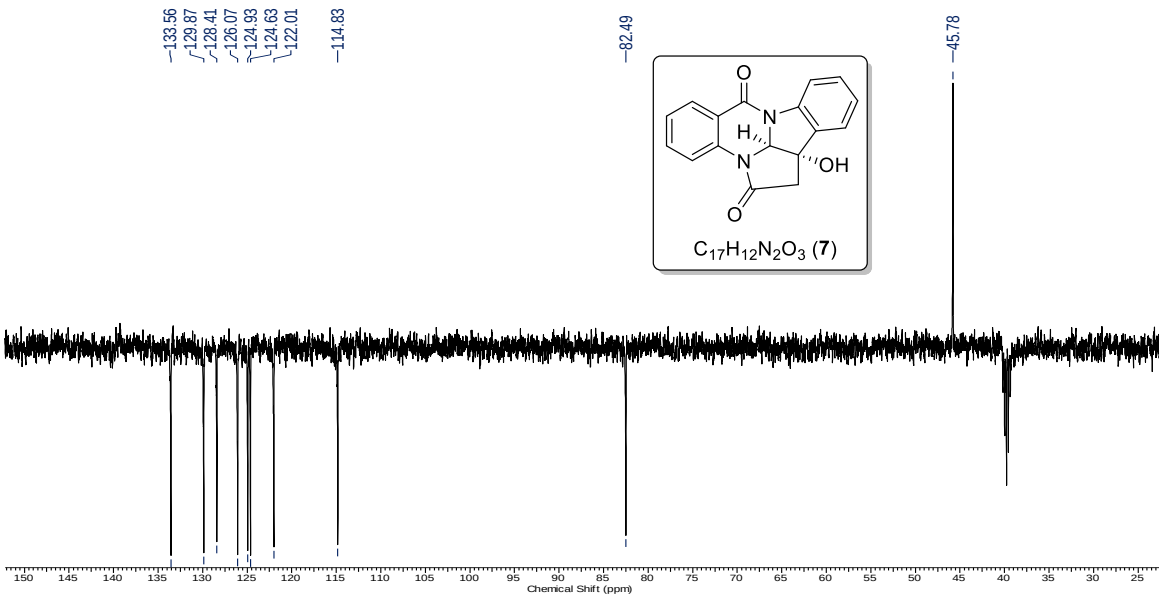

CHLOROFORM-d
8.21
8.19
8.15
8.13
7.72
7.71
7.52
7.50
7.45
7.26
7.12
7.10
7.08
5.15
3.49
3.44
3.41
3.31
3.28
C18H14N2O4 (3)
Chemical Shift (ppm)

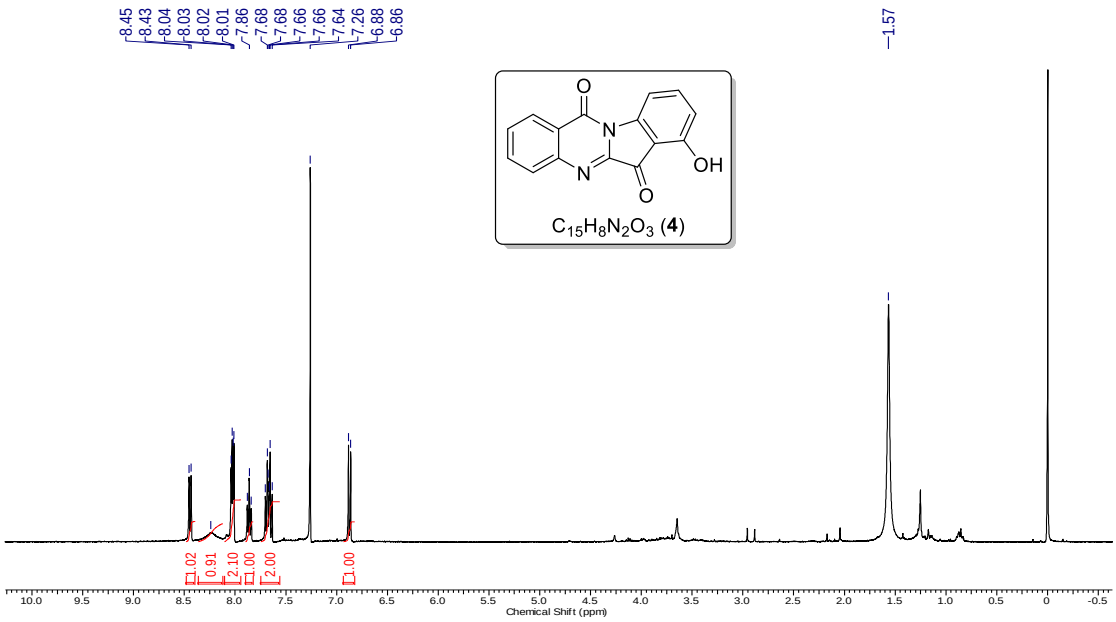

CHLOROFORM-d
170.08
159.74
159.46
147.11
138.77
134.40
131.56
130.44
127.73
127.34
127.00
123.41
121.52
116.59
77.00
75.21
51.88
42.75
C18H14N2O4 (3)
Chemical Shift (ppm)

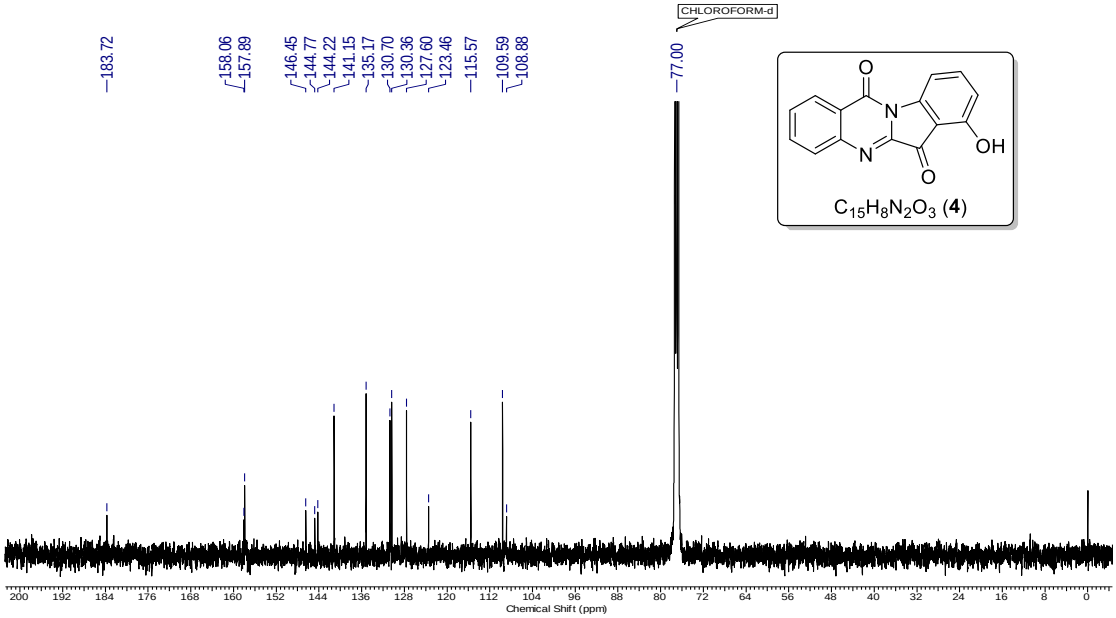

134.43
130.46
127.75
127.36
127.02
123.44
116.61
51.91
42.76
C18H14N2O4 (3)
Chemical Shift (ppm)

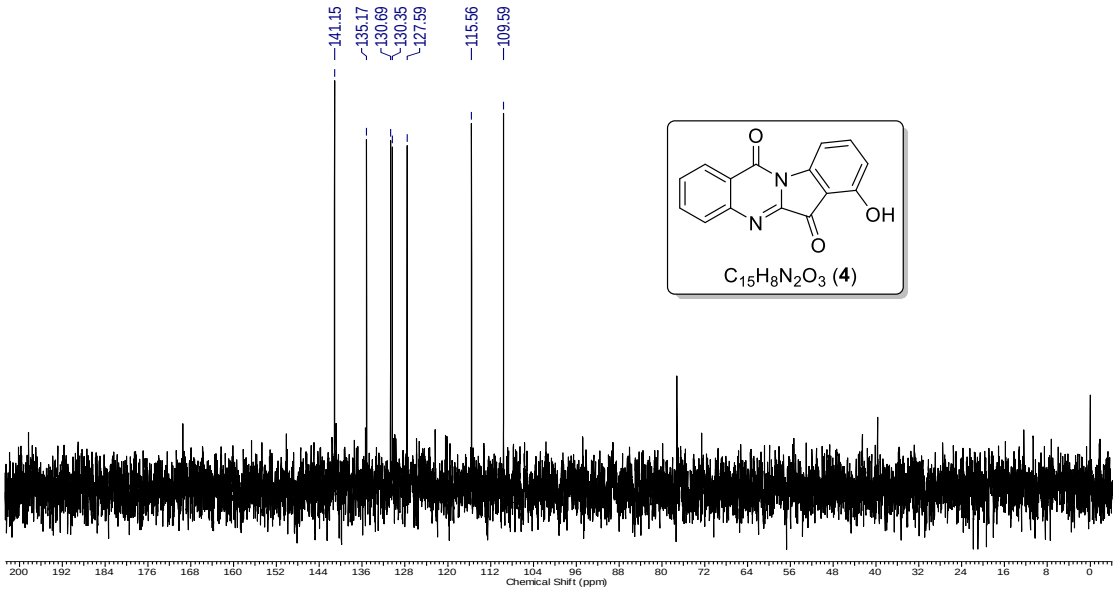

DMSO-d6
8.07
8.04
7.97
7.93
7.77
7.76
7.74
7.58
7.55
7.48
7.44
7.24
6.72
5.82
3.34
3.24
3.14
3.10
3.01
2.52
O
N
H
N
OH
O
$C_{17}H_{12}N_2O_3$ (**7**)
1.00
1.03
1.03
2.07
2.14
1.03
1.02
1.00
1.12
1.05
Chemical Shift (ppm)


DMSO-d6
170.39
158.59
140.28
136.37
135.35
133.55
129.87
128.40
126.05
124.93
124.61
123.40
122.00
114.82
82.49
77.53
45.78
39.51
O
N
H
N
OH
O
$C_{17}H_{12}N_2O_3$ (**7**)
Chemical Shift (ppm)


133.56
129.87
128.41
126.07
124.93
124.63
122.01
114.83
82.49
45.78
O
N
H
N
OH
O
$C_{17}H_{12}N_2O_3$ (**7**)
Chemical Shift (ppm)


8.45
8.43
8.04
8.03
8.02
8.01
7.86
7.68
7.68
7.66
7.66
7.64
7.26
6.88
6.86
1.57
O
N
N
OH
O
C15H8N2O3 (4)
1.02
0.91
2.10
1.00
2.00
1.00
Chemical Shift (ppm)


CHLOROFORM-d
183.72
158.06
157.89
146.45
144.77
144.22
141.15
135.17
130.70
130.36
127.60
123.46
115.57
109.59
108.88
77.00
O
N
N
OH
O
C15H8N2O3 (4)
Chemical Shift (ppm)


141.15
135.17
130.69
130.35
127.59
115.56
109.59
O
N
N
OH
O
C15H8N2O3 (4)
Chemical Shift (ppm)

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Chapter 2

Section B

A Biomimetic Synthesis of Phaitanthrin E Involving a Fragmentation of sp^3 Carbon–Carbon Bond: Synthesis and Rearrangement of (±)/(–)-Phaitanthrin D to Phaitanthrin E

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

2B. 1 Background

Carbon–carbon and carbon–hydrogen bonds are the defining motifs of organic compounds. Selective C–C and C–H bond cleavages have always been a dynamic area of research in organic chemistry, but they are mainly dependent on precious metal complexes.[1,2] The C–C bond cleavage is more challenging than a C–H bond cleavage, in view of thermodynamic stability and uncontrollable selectivity.[3] Over the years, several approaches have been developed for the cleavage of a carbon–carbon single bond, including the employment of strained carbon skeletons (three and four membered rings)[3] or the use of chelation assistance strategies,[4] both of which are representative methods to promote a desired C–C bond cleavage.

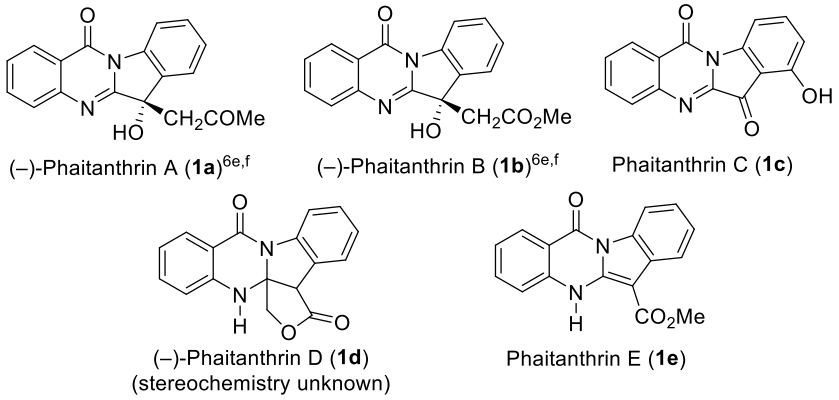
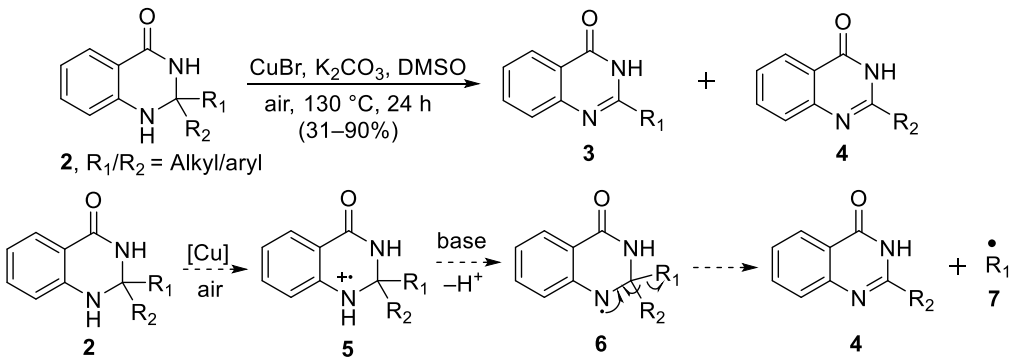


Figure 1. Recently isolated bioactive quinazolinone and dihydroquinazolinone alkaloids.

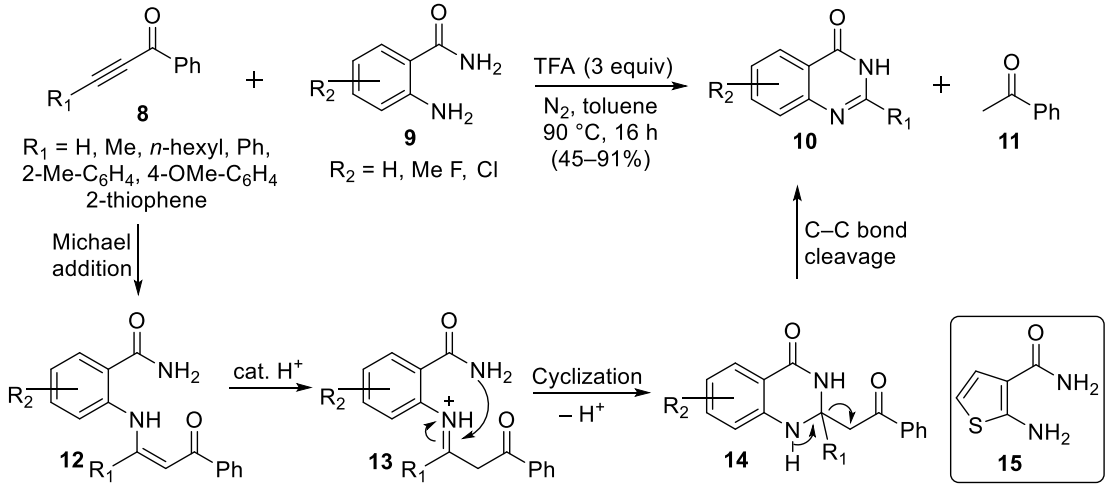
N-Heterocyclic compounds are the most abundant and integral frameworks that occur universally in a large number of bioactive natural products, synthetic drugs, pharmaceuticals and agrochemicals.[5] Among the various *N*-heterocycles quinazolinones are important class of compounds with a diverse range of biological activities (Figure 1).[6a-d]



Scheme 1. Copper-catalyzed C–C Bond Cleavage to Construct 2-Substituted Quinazolinones

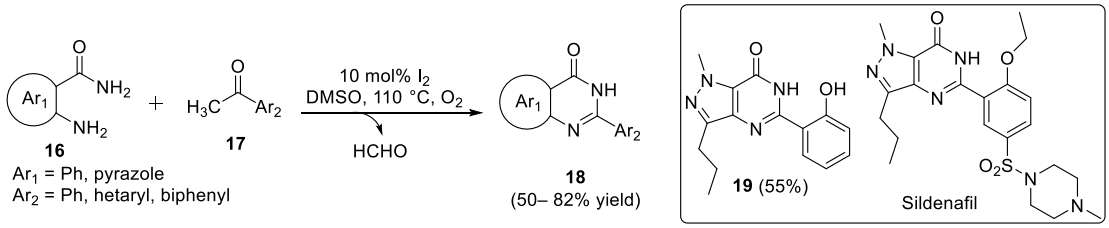
In the construction of quinazolinone skeleton metal/Lewis acid induced C–C bond cleavages are reported by few groups. Tang and co-workers reported an efficient method

for a copper-catalyzed intramolecular C–C bond cleavage to construct 2-substituted quinazolinones **3** and **4** through C–C bond cleavage with air as the oxidant under basic conditions. The C–C bond at the 2-position of 2,2-disubstituted-1,2,3,4-tetrahydroquinazolinone **2** was selectively cleaved by a Cu/air involving radical mechanism. In this reaction the generation of radical was confirmed with help of TEMPO and GC-MS (Scheme 1).[7]



Scheme 2. Cleavage of the C–C Triple Bond of Ketoalkynes in Synthesis of 4(3*H*)-Quinazolinones

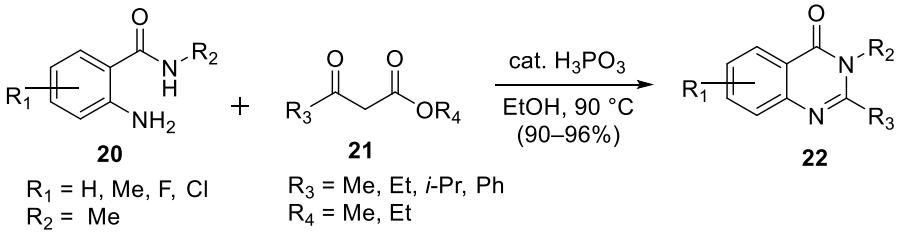
Cui et al. described protocol for the synthesis of 4(3*H*)-quinazolinones **10** via selective cleavage of the triple bond of ketoalkynes **8** under oxidant, metal and ligand-free condition. Various 4(3*H*)-quinazolinones **10** were obtained through fragmentation of the C–C triple bond and formation of two C–N bonds. This reaction proceeded efficiently with TFA, affording 2-aryl(alkyl)-quinazolin-4(3*H*)-ones **10** in moderate to excellent yields. In addition, the scope of this reaction was successfully expanded to heteroaryl ketoalkyne **8** and 2-aminothiophene-3-carboxamide (**15**) (Scheme 2).[8]



Scheme 3. Iodine Catalyzed Oxidative Synthesis of Quinazolin-4(3*H*)-ones

Bharate and co-workers developed a molecular iodine catalyzed oxidative coupling of 2-aminobenzamides **16** with aryl methyl ketones **17** in the absence of metal or ligand to produce 2-aryl quinazolin-4(3*H*)-ones **18**. The quantity of iodine played a very crucial role in this transformation in order to selectively get the 2-aryl quinazolin-4(3*H*)-ones **18**.

By using this protocol the pyrazolo[4,3-*d*]pyrimidin-7(6*H*)-ones **19**, which is a key intermediate involved in synthesis of sildenafil has also been obtained in 55% yield (Scheme 3).[9]



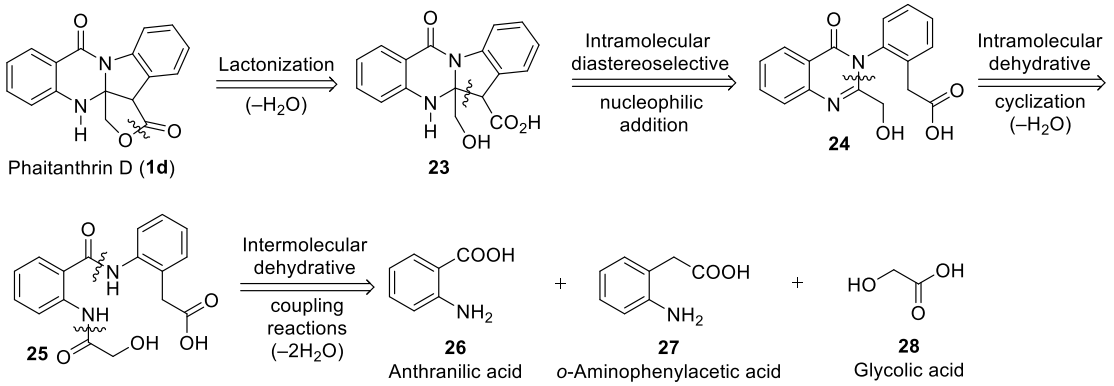
Scheme 4. Synthesis of Quinazolinones from *β*-Ketoesters with *o*-Aminobenzamides Involving Selective C−C Bond Cleavage

Yin and co-workers reported a general and efficient phosphorous acid-catalyzed cyclocondensation of *β*-ketoesters **21** with *o*-aminobenzamides **20** via selective C−C bond cleavage to produce quinazolinones **22**. This reaction proceeds smoothly under metal and oxidant-free conditions, giving both 2-alkyl- and 2-aryl-substituted quinazolinones **22** in excellent yields (Scheme 4).[10]

2B. 2 Results and Discussion

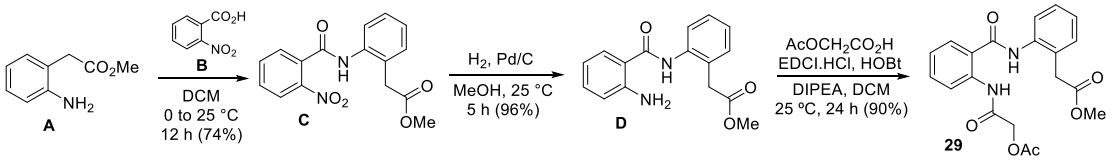
2B. 2. 1 A Biomimetic Synthesis of Phaitanthrin E Involving a Fragmentation of sp3 Carbon–Carbon Bond: Synthesis and Rearrangement of (±)/(–)-Phaitanthrin D to Phaitanthrin E

Quinazolinones are an important class of clinically useful compounds and building blocks for a large number of structurally diverse alkaloids with a wide range of promising biological activities.[6] Wu and co-workers isolated five different quinazolinone based cytotoxic natural products phaitanthrins A–E from Phaius mishmensis orchid (Figure 1).[11] The nucleophilic substitution reactions play a very important role in biogenesis and chemical synthesis.[12] The nucleophilic substitution reactions involving both carbon as a nucleophile and leaving groups are limited, wherein actually the stable nitrile/carbon anions are the departing units.[7-10,13] Conversely, the carbon–carbon bond forming substitution reactions with release of unstable carbanions/carbon free radicals/carbenes remain as the most crucial strategic challenge. In continuation of our studies on total synthesis of quinazolinone alkaloids,[14] we could achieve substitution of unexpected leaving groups by a stable carbanion in intramolecular reactions on an iminium double bond in quinazolinones via an exceptional Csp^3–Csp^3 bond cleavage[15] due to relatively higher stability of the formed product. In this context, we herein report the investigation results accomplishing first total synthesis of phaitanthrin E and synthesis and structural



Scheme 5. Proposed Retrobiogenetic Pathway and Retrosynthetic Analysis of Phaitanthrin D

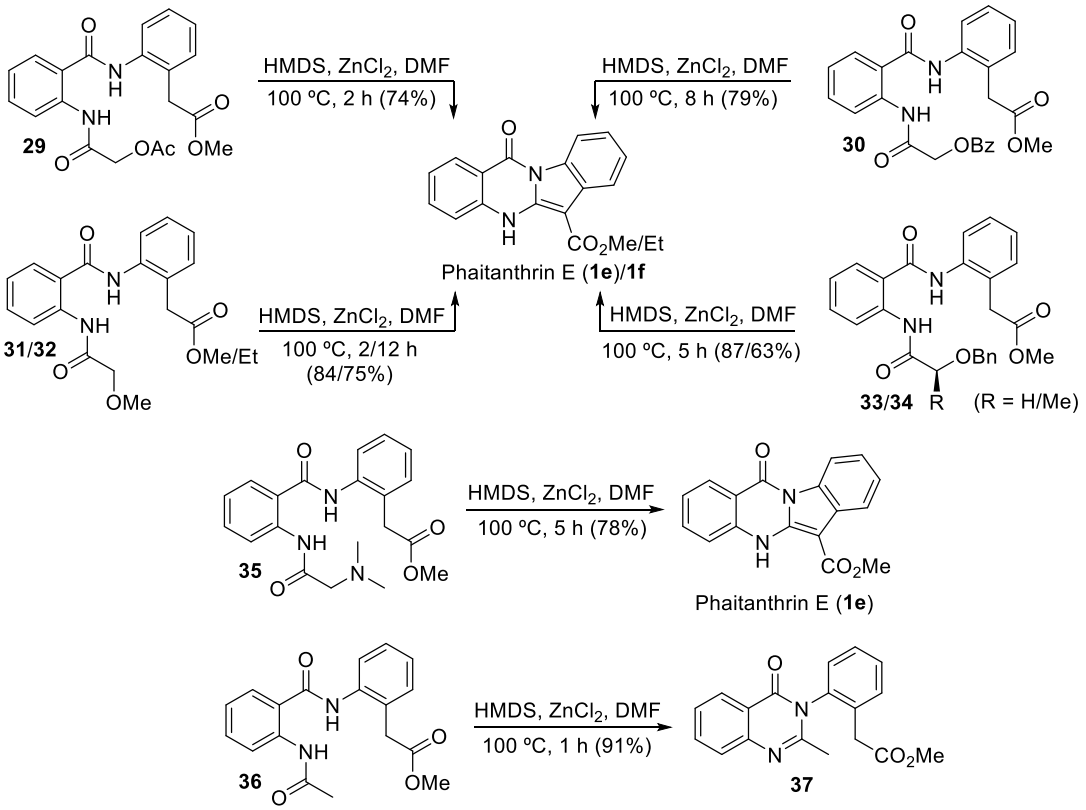
rearrangement of (±)/(–)-phaitanthrin D to phaitanthrin E (Schemes 5–10).[16] An anticipated retrobiogenetic pathway and the proposed retrosynthetic analysis of unprecedented indolofuroquinazolinone phaitanthrin D (**1d**) has been depicted in scheme 5. Nature creates the phaitanthrin D (**1d**) starting from anthranilic acid, *o*-aminophenylacetic acid and glycolic acid via an appropriate sequence of dehydrative coupling reactions and intramolecular cyclization pathways with complete carbon economy involving overall loss of four water molecules.



Scheme 6. Preparation of Required Building Block

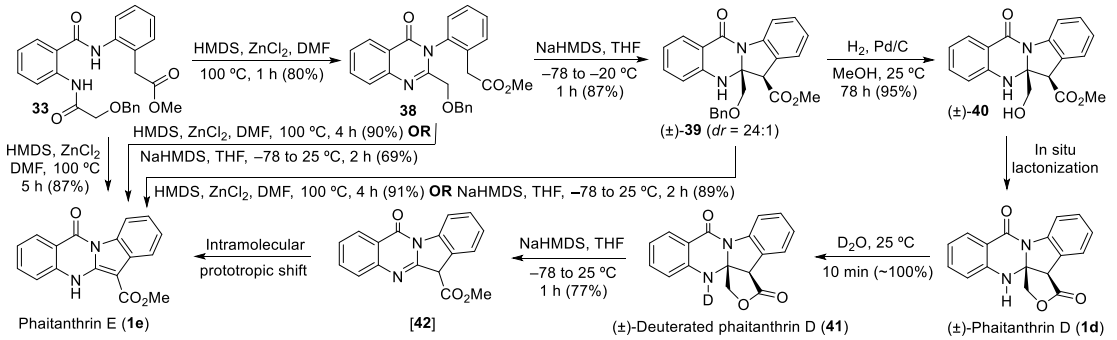
Accordingly the building block **29** was synthesized via appropriate stepwise intermolecular dehydrative coupling reactions (Scheme 6). As per the recently developed protocol, compound **29** was subjected for intramolecular dehydrative cyclization using hexamethyldisilazane/zinc chloride (HMDS/$ZnCl_2$) in DMF at 100 °C to obtain the corresponding quinazolinone.[17] A careful examination of the analytical and spectral data of formed purified product revealed that the above specified reaction has directly delivered a phaitanthrin E (**1e**, 74% yield) (Scheme 7). The present one-pot transformation of compound **29** to phaitanthrin E (**1e**) was unusual from basic chemistry point of view and it was suggestive of some interesting chemical transformation taking place. In principle there was an overall loss of water and methyl acetate from the parent system **29** in formation of phaitanthrin E (**1e**). The reactions of similarly designed compounds **30**–**34** with HMDS/$ZnCl_2$ in DMF at 100 °C again directly furnished the phaitanthrin E (**1e**) and its ethyl ester analogue **1f** in very good yields. The another type of an additional nitrogen atom containing building block **35** on reaction with HMDS/$ZnCl_2$

also followed the similar pathway and delivered phaitanthirn E (**1e**) in 78% yield. However the formally designed building block **36**, without a hetero atom in departing unit on reaction with HMDS/$ZnCl_2$ only formed the corresponding quinazolinone **37** in 91% yield.



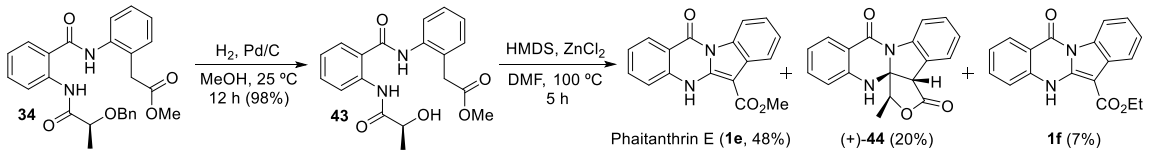
Scheme 7. Unexpected Leaving Groups in One Pot Synthesis of Phaitanthrin E and its Ethyl Analogue

The search for suitable precursor which allowed isolating the intermediate products was successful with benzyl ether **33**. As depicted in scheme 8, the reaction of compound **33** with HMDS/$ZnCl_2$ in DMF at 100 °C was arrested after one hour to obtain the anticipated intermediate quinazolinone **38** in 80% yield along with ~2% of phaitanthrin E (**1e**). The compound **38** on treatment with NaHMDS in THF at –78 to –20 °C underwent an intramolecular diastereoselective nucleophilic addition of the formed *α*-stablized benzylic carbanion to the proximal iminium double bond in a quinazolinone moiety to deliver yet another intermediate product dihydroquinazolinone **39** in 87% yield (92% *de* by ^{1}H NMR). The quinazolinone **38** and dihydroquinazolinone **39** on reaction with either HMDS/$ZnCl_2$ in DMF at 100 °C or NaHMDS in THF at –78 to 25 °C again furnished the target product phaitanthrin E (**1e**) in very good yields. The deprotection of benzyl group in dihydroquinazolinone **39** produced alcohol **40**, which on concomitant lactonization provided the expected (±)-phaitanthrin D (**1d**) in 95% yield in 78 hours.



Scheme 8. Diastereoselective Total Synthesis of (±)-Phaitanthrin D and its Methyl Analogue and their Structural Rearrangement to Phaitanthrin E and its Ethyl Analogue

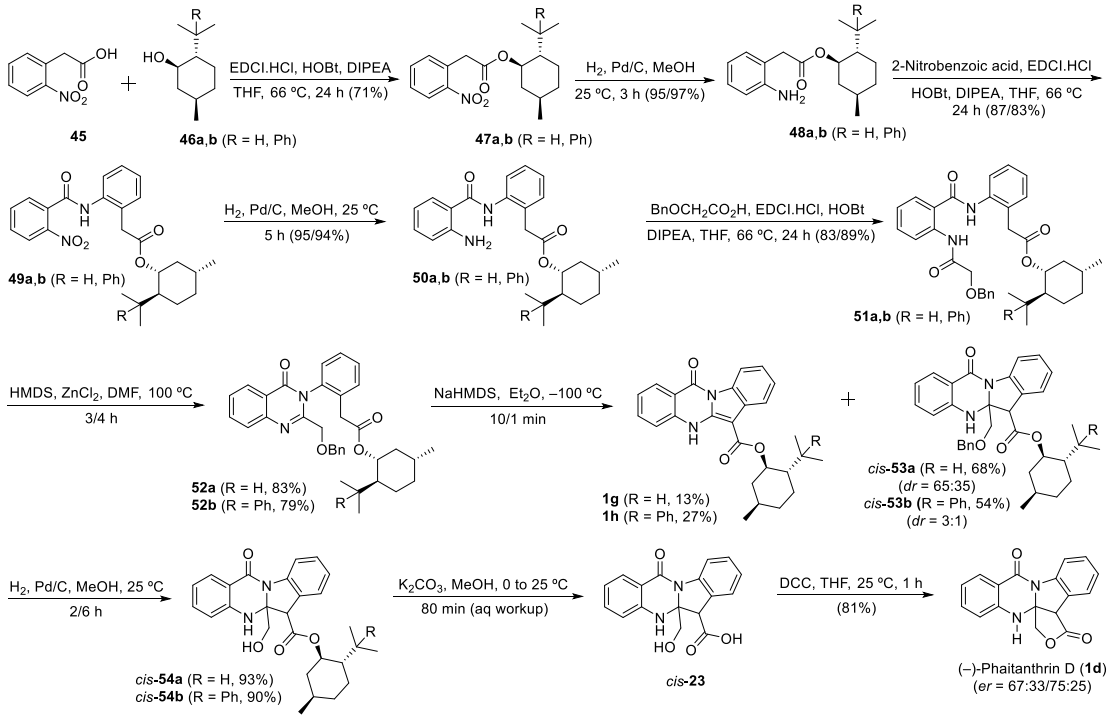
The alcohol **40** was unstable; however its immediate characterization by ^{1}H NMR was feasible. The phaitanthrin D (**1d**) on treatment with 2 N HCl in chloroform at 25 °C underwent structural rearrangement to phaitanthrin E (**1e**) in 93% yield via an unusual carbon–carbon bond cleavage. Phaitanthrin D (**1d**) on treatment with D_2O formed the *N*-deuterated phaitanthrin D (**41**) in quantitative yield (by ^{1}H NMR). The compound **41** on reaction with NaHMDS transformed to phaitanthrin E (**1e**) in 77% yield with complete loss of label proving that the deuterium atom on nitrogen is relatively more acidic than the active methine proton. Accordingly in the transformation of phaitanthrin D to phaitanthrin E, the methyl group originates from the methylene unit in a lactone moiety.



Scheme 9. Diastereoselective Total Synthesis of (+)-Dihydrofuroindoloquinazolinone

The specifically designed compound **34** on debenzylation provided requisite alcohol **43** in quantitative yield. As expected the compound **43** on treatment with HMDS/$ZnCl_2$ delivered the mixture of phaitanthrin E (**1e**, 48%), in situ formed lactone **44** (20%, 98% *de* by ^{1}H NMR) and the rearranged product **1f** (7%). As anticipated the in situ formed carbanion approached the iminium double bond form the less hindered α-side to form product **44**. The purified lactone **44** on treatment with HMDS/$ZnCl_2$ slowly got transformed into the rearranged product **1f** with good yield (Scheme 9). These transformations of **1d** to **1e** and **44** to **1f** provide the compelling evidence for the proposed carbon–carbon bond cleavage and affirm that phaitanthrin D (**1d**) is the biogenetic precursor of phaitanthrin E (**1e**).

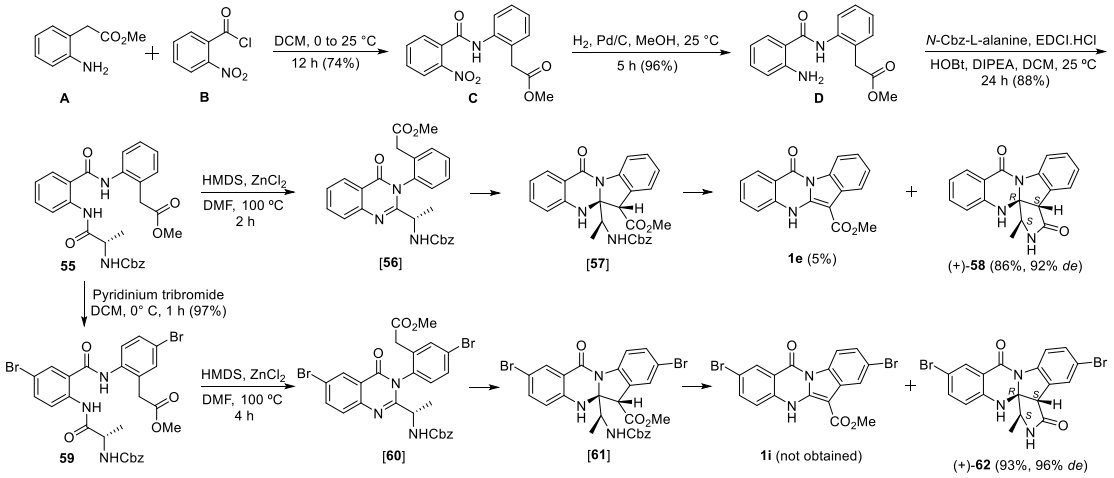
In next part the essential chiral building blocks **51a**,**b** were designed in five steps starting from *o*-nitrophenylacetic acid and (–)-menthol/(–)-phenylmenthol as the enantioenriched



Scheme 10. Stereoselective Total Synthesis of (–)-Phaitanthrin D

auxiliaries (Scheme 10). The reactions of compounds **51a**,**b** with HMDS/$ZnCl_2$ respectively delivered the expected quinazolinones **52a**,**b** in 83/79% yield. The reaction of quinazolinone **52a** with NaHMDS (2 equiv) in diethyl ether at –100 °C furnished the desired product **53a** in 68% yield as an inseparable 65:35 mixture of diastereomers (by ^{1}H NMR) along with the formation of a minor product **1g** in 13% yield in ten minutes time. Unfortunately, the reaction of quinazolinone **52b** with NaHMDS (2 equiv) in diethyl ether at –100 °C resulted in the ultimate product **1h** in more than 75% yield in five minutes reaction time. However, the same reaction using four equivalents of NaHMDS in one minute time delivered the desired major product **53b** in 54% yield as an inseparable 3:1 mixture of diastereomers (by ^{1}H NMR) along with the formation of a minor product **1h** in 27% yield. The compounds **53a**,**b** on catalytic hydrogenation formed the corresponding alcohols **54a**,**b** in >90% yield. The product **54b** was used for the next transformation without any purification and characterization for stability issues. The alcohols **54a**,**b** were also continuously getting transformed into the expected corresponding products **1g** and **1h**. The compounds **54a**,**b** on reaction with catalytic amount of K_2CO_3 in anhydrous methanol underwent trans esterification to produce the common intermediate methyl ester **40** (by TLC comparison), which on an in situ lactonization quantitatively transformed into the desired (–)-phaitanthrin D (**1d**). In both cases the isolated yield of (–)-phaitanthrin D (**1d**) was only ~20% along with the

formation of corresponding carboxylic acid (–)-**23** as a major product. The hydroxyacid **23** was also not stable; however the isolation of very small amount of acid **23** and its immediate characterization by ^{1}H NMR was feasible. Thus the obtained two different samples of acid **23** from **54a**,**b** were immediately subjected for DCC-induced dehydrative lactonization to obtain the (–)-phaitanthrin D (**1d**) in 81% yield. As expected the enantiomeric purity of obtained (–)-phaitanthrin D (**1d**) using (–)-menthol/(–)-phenylmenthol as a enantioenriched auxiliary was only moderate (30/50% *ee*, by HPLC). The stereochemical assignment of (–)-phaitanthrin D was not possible due to its amorphous nature and intrinsic instability reason.



Scheme 11. Stereoselective Synthesis of (+)-Dihydropyrroloindoloquinazolinone

The appropriately designed yet another building block **55** starting from corresponding *o*-nitrobenzoic acid, *o*-aminophenylacetic acid and Cbz-protected L-alanine on reaction with HMDS/$ZnCl_2$ again furnished the target product phaitanthrin E (**1e**) but in 5% yield. The intramolecular cyclization of intermediate **56** to **57** was also highly diastereoselective and an in situ deprotection of –Cbz group in intermediate **57** took place to directly deliver the (+)-dihydropyrroloindoloquinazolinone **58** in 86% yield via lactamization (92% *de*, by ^{1}H NMR, Scheme 11). Direct bromination of **55** in DCM formed the corresponding dibromo precursor **59** in 97% yield. The compound **59** on reaction with HMDS/$ZnCl_2$ exclusively furnished the nice crystalline solid product **62** in 93% yield (96% *de*, by ^{1}H NMR). The stereochemistry of products **58** was established on the basis of X-ray crystallographic data obtained for compound **62** (Scheme 11).

In principle the one-pot formation of phaitanthrin E can take place via host of alternative reaction pathways, namely: (i) redox, (ii) carbenoid, (iii) radical, (iv) unstabilized carbanions serving as a leaving group and (v) alternative internal structural rearrangement accounting for carbon–carbon bond cleavage. The consistent formation of phaitanthrin E

(**1e**) and analogues both at 100 °C and –100 °C in absence of metal and/or molecular oxygen in very good yields ruled out the possibility of redox mechanism. All attempts to isolate primary and/or secondary products derived from the released carbon species in above specified reactions met with failure. The slow transformation of phaitanthrin D (**1d**) in its solid form to phaitanthrin E (**1e**) was noticed and confirmed by ^{1}H NMR (~10% in four week time). This important observation substantiated that it would be possible to isolate the formed product from the corresponding released species under neutral conditions. Accordingly scanned ^{1}H and ^{13}C NMR spectra of ten days preserved compound **39** indicated its complete transformation into phaitanthrin E (**1e**) along with an appropriate presence of all requisite signals for the expected released benzyl methyl ether. The presence of released benzyl methyl ether was further confirmed by HPLC and HRMS data. Similarly the release of benzyl methyl ether in the respective transformations of **53a** and **53b** to **1g** and **1h** was also confirmed by ^{1}H NMR and HRMS data. Finally small amount of benzyl methyl ether released in the transformation of compound **39** to phaitanthrin E (**1e**) was isolated by using preparative thin layer chromatography and confirmed by comparison with authentic sample using analytical and spectral data. The isolation of benzyl methyl ether rules out the carbenoid mechanistic pathways. The reactions reported in schemes 7 to 11 clearly indicate that in the last step they follow radical pathway releasing the corresponding reactive radical species such as $^{\bullet}CH_2OCOCH_3$, $^{\bullet}CH_2OCOPh$, $^{\bullet}CH_2OCH_3$, $^{\bullet}CH_2OCH_2Ph$, $^{\bullet}CH(Me)OCH_2Ph$, $^{\bullet}CH(Me)OH$ and $^{\bullet}CH_2N(CH_3)_2$. Such type of radical formation on quinazolinone nucleus is known under copper catalysis in the presence of oxygen.[7] In the specifically formed/designed quinazolinones the Csp^3–Csp^3 bond appears to be quite delicate and undergoes an aromaticity driven facile homolytic fission leading to the corresponding radicals. However an alternative ionic pathway releasing the corresponding high energy carbanionic species such as $^{-}CH_2OCOCH_3$, $^{-}CH_2OCOPh$, $^{-}CH_2OCH_3$, $^{-}CH_2OCH_2Ph$, $^{-}CH(Me)OCH_2Ph$, $^{-}CH(Me)OH$ and $^{-}CH_2N(CH_3)_2$ appears almost impossible. Accordingly the compound **37** from scheme 7 on further treatment with NaHMDS in THF remained completely unreacted and did not deliver the phaitanthrin E (**1e**). This proved that the presence of an adjacent heteroatom on all methanide leaving groups was essential for the natural Csp^3–Csp^3 bond cleavage. The observation that CH_2O leaves well, CH_2N leaves slow and CH_3 does not leave at all suggests that the oxygen better stabilizes an adjacent radical thermodynamically and more important kinetically. Finally

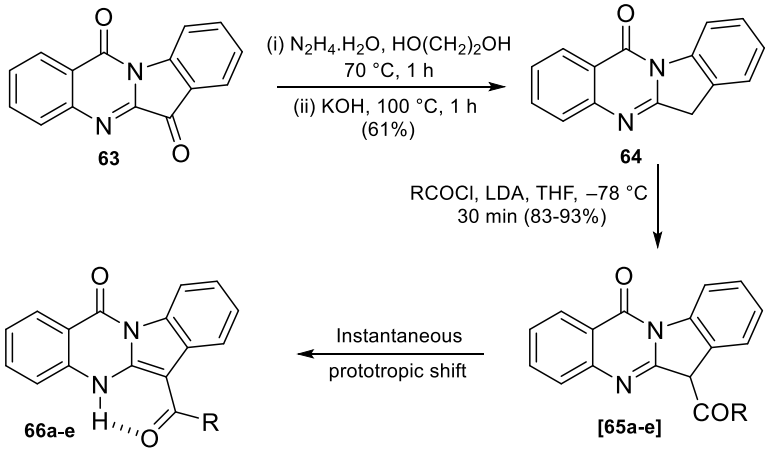
to conclude, all above mentioned novel reactions became feasible due to the formation of very stable quasi-aromatic products with an overall negative Gibbs free energy.

2B. 2. 2 Rearrangement of Imine Double Bond in Activated Quinazolinones: Synthesis of Phaitanthrin E

The chemistry of tryptanthrin (**63**) has been recently reviewed by Tucker and Grundt.[18] We synthesized our precursor tryptanthrin in 94% yield by employing the aryne insertion approach.[14a] Several syntheses of indoloquinazolinone **64** have been well-known in the literature.[19–22] Generally indoloquinazolinone **64** is prepared from tryptanthrin by using a two-step protocol involving sodium borohydride reduction of both ketone and imine followed by the dehydration sequence.[22] Alternatively the Wolff-Kishner reduction of tryptanthrin would form the desired indoloquinazolinone in one-step. Providentially, treatment of tryptanthrin (**63**) with hydrazine hydrate/potassium hydroxide furnished the indoloquinazolinone **64** in 61% yield. The analytical and spectral data obtained for the desired product **64** was in complete agreement with the reported data.[19] Indoloquinazolinone is highly prone for air oxidation and gets back transformed to the tryptanthrin under normal atmospheric conditions. Thus the obtained product was either preserved under argon atmosphere in a refrigerator or immediately used for the next synthetic steps for stability reasons. The base-induced intermolecular acylation reaction of indoloquinazolinone **64** using different acyl chlorides were planned to study the product specificity and their relative stability (**65a**–**e** and /or **66a**–**e**).

Reaction of lithium diisorpropylamide (LDA, 1.20 equiv) with indoloquinazolinone **64** formed the corresponding stable allylic-benzylic carbanionic species which on treatment with methyl chloroformate directly delivered the desired natural product phaitanthrin E (**66a**) in 91% yield (Table 1, entry 1). It is noteworthy that the electron rich carbon atom in the five membered ring in product **66a** appeared only at 86.6 ppm; possibly due to the electron donating effect of the neighboring nitrogen atom. Similarly, the LDA-stimulated reactions of indoloquinazolinone **64** with benzyl chloroformate, acetyl chloride, ethyl chlorooxaloacetate and chloroacetyl chloride were also selective and exclusively provided the corresponding double bond rearranged products **66b**–**e** in 83–93% yields (Table 1, entries 2–5). Unfortunately, the same reaction with bromoacetyl bromide resulted in decomposition, plausibly due to its higher reactivity (Table 1, entry 6). Mechanistically, LDA abstracts an acidic proton from the activated methylene carbon in indoloquinazolinone **64** and the formed carbanion reacts with acyl chlorides to form the

Table 1. Synthesis and Base Induced Acylations of Indoloquinazolinone



Entry	Acyl chloride	Product	% Yield
1	$ClCO_2Me$	**66a** (R = OMe)	91
2	$ClCO_2Bn$	**66b** (R = OBn)	89
3	MeCOCl	**66c** (R = Me)	87
4	$ClCOCO_2Et$	**66d** (R = CO_2Et)	83
5	$ClCOCH_2Cl$	**66e** (R = CH_2Cl)	93
6	$BrCOCH_2Br$	decomposition	0

corresponding unisolable intermediates **65a**–**e**. The methine proton in intermediates **65a**–**e** is highly acidic due to its allylic and benzylic character coupled with the *α*-position to carbonyl groups. Thus the stability driven instantaneous carbon to nitrogen prototropic shifts[23,24] take place to form the products **66a**–**e** in excellent yields. Accordingly the formed products are thermodynamically more stable due to (i) formation of new *α,β*-unsaturated carbonyl systems with extended conjugation with the lone of nitrogen atoms at *γ/γ'*-positions, (ii) the formation of intramolecular six-membered hydrogen bonding and moreover (iii) gain of quasi-aromatic characters with the involvement of lone pairs on both the nitrogen atoms in a *π*-cloud system. In the transformation of indoloquinazolinone **64** to provide **66a**–**e** , we did not notice the formation of any *gem*-diacylated products due to the above described concomitant structural rearrangement.

2B. 3 Summary

In summary, one-pot synthesis of phaitanthrin E has been demonstrated from different type of starting materials in very good yields with a release of unexpected carbon species. To the best of our knowledge, this is a unique example of spontaneous sp^3 *carbon–carbon bond cleavage in the absence of a metal catalysis and molecular oxygen. The first*

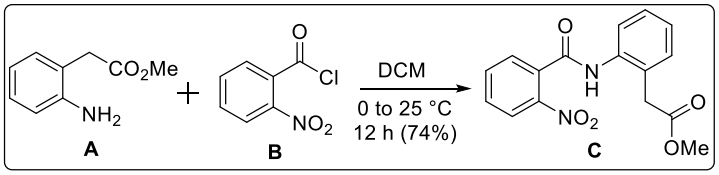
diastereoselective and an enantioselective biogenetic type total synthesis of (±)/(–)-phaitanthrin D with very good overall yields and stereoselectivity has also been demonstrated. We could successfully mimic nature to perform the rearrangements of phaitanthrin D to phaitanthrin E and confirmed an unusual carbon–carbon bond cleavage. There is a fair chance of (+)-methylfuroindoloquinazolinone and (+)-dihydropyrroloindiloquinazolinone being isolated as bioactive natural products in the near future. The present concept of designing an appropriate type of structural unit bearing precisely situated heteroatoms to release such type of carbon leaving groups at the cost of relatively higher formed product stability has a broad scope. These results prove that under special circumstances the esters, ethers, alcohols and amines can also function as the good leaving groups via unexpected carbon–carbon bond cleavages and conceptually it will be useful to organic chemists to achieve what appears implausible.

We have also described an independent two steps synthesis of phaitanthrin E starting from tryptanthrin via an acylation of indoloquinazolinone. The witnessed spontaneous rearrangement of β-imino esters/ketones to the corresponding γ-amino α,β-unsaturated carbonyl systems is noteworthy from basic chemistry point of view. The present protocol is general in nature and will be useful for the synthesis of analogues and congeners of phaitanthrins. We also feel that these compounds will serve as potential building blocks for the synthesis of novel heterocyclic architectures.

2B. 4 Experimental Section

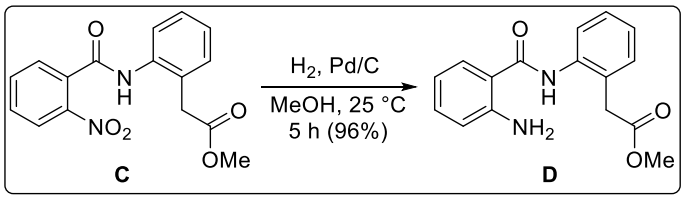
Commercially available *o*-nitrobenzoic acid, thionyl chloride, glycolic acid, acetic anhydride, benzoyl chloride, metoxyacetic acid, (–)-ethyl L-lactate, (–)-menthol, (–)-phenylmenthol, L-alanine, *N*,*N*-dimethyl glycine, DCC, DIPEA, EDCI.HCl, HMDS, HOBt, NaHMDS, Pd/C, pyridinium perbromide, $ZnCl_2$ and D_2O were used.

Methyl 2-(2-(2-Nitrobenzamido)phenyl)acetate (C). To a stirred solution of 2-nitrobenzoyl chloride **B** (5.00 g, 27.17 mmol) in DCM (20 mL) was added solution of methyl 2-(2-aminophenyl)acetate **A** (5.38 g, 32.6 mmol) in DCM (20 mL) at 0 ^oC. The reaction mixture was allowed to reach 25 ^oC and further stirred for 12 h. The reaction was quenched by adding saturated aq. $KHCO_3$ solution. The organic layer was separated and the aqueous layer was extracted with DCM (3 × 50 mL). The combined organic layer was washed with brine and dried over Na_2SO_4. Concentration of the dried organic layer in

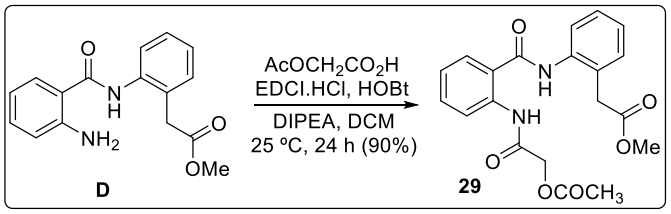


vacuo followed by the silica gel (60–120 mesh) column chromatographic purification of the resulting residue with ethyl acetate–petroleum ether (7:3) as an eluent furnished nitro compound **C** as a white solid (6.30 g, 74%). Mp 117 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.65 (s, 3H), 3.71 (s, 2H), 7.10–7.28 (m, 2H), 7.36 (dt, J = 8 & 2 Hz, 1H), 7.55–7.75 (m, 3H), 7.93 (d, J = 8 Hz, 1H), 8.07 (d, J = 8 Hz, 1H), 9.20 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 38.6, 52.6, 115.0, 116.6, 117.4, 125.3, 125.4, 126.4, 127.4, 128.2, 130.8, 132.7, 136.7, 149.6, 167.8, 173.2; HRMS (ESI) calcd for $C_{16}H_{14}N_2O_5Na$ 337.0795, found 337.0784; IR ($CHCl_3$) ν_{max} 3288, 1728, 1673, 1529, 1446, 1348 cm^{-1}.

Methyl 2-(2-(2-Aminobenzamido)phenyl)acetate (D). To a stirred solution of nitro compound **C** (6.00 g, 19.10 mmol) in methanol (50 mL) was added activated Pd/C (600 mg, 10 wt %) and the reaction mixture was stirred under balloon pressure hydrogen atmosphere at 25 °C for 5 h. The reaction mixture was filtered to remove Pd/C and concentrated in vacuo. The silica gel (60–120 mesh) column chromatographic purification of the obtained residue using ethyl acetate–petroleum ether (3:7) as an eluent provided the pure product amine **D** as a white solid (5.20 g, 96% yield). Mp 115 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.67 (s, 2H), 3.73 (s, 3H), 5.74 (br s, 2H), 6.70 (d, J = 8 Hz, 1H), 6.72 (dt, J = 8 & 2 Hz, 1H), 7.08–7.30 (m, 3H), 7.36 (dt, J = 8 & 2 Hz, 1H), 7.66 (d, J = 8 Hz, 1H), 7.87 (d, J = 8 Hz, 1H), 9.42 (br s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 38.4, 52.5, 124.6, 125.4, 126.1, 126.7, 128.5, 128.6, 130.6, 130.8, 132.9, 133.8, 135.8, 146.5, 164.8, 173.3; HRMS (ESI) calcd for $C_{16}H_{17}N_2O_3$ 285.1234, found 285.1230; IR (Nujol) ν_{max} 3447, 3367, 1722, 1648, 1599 cm^{-1}.

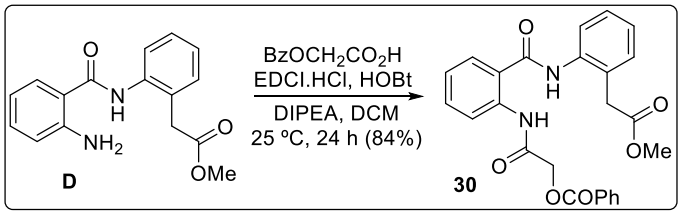


Methyl 2-(2-(2-(2-Acetoxyacetamido)benzamido)phenyl)acetate (29). A solution of EDCI.HCl (160 mg, 0.84 mmol), HOBt (113 mg, 0.84 mmol) and 2-acetoxyacetic acid (99 mg, 0.84 mmol) in DCM (10 mL) was added dropwise to a stirred suspension of amine **D** (200 mg, 0.70 mmol) and DIPEA (0.244 mL, 1.40 mmol) in DCM (10 mL) at 25 °C. The reaction mixture was stirred at 25 °C for 24 h and then the reaction was quenched with water. The organic layer was separated and the aqueous layer was extracted with DCM (3 × 10 mL). The combined organic layer was



washed with brine and dried over Na_2SO_4. Concentration of the dried organic layer in vacuo followed by the silica gel (60–120 mesh) column chromatographic purification of the resulting residue with ethyl acetate–petroleum ether (3:7) as an eluent furnished compound **29** as a white solid (243 mg, 90%). Mp 125 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.25 (s, 3H), 3.70 (s, 2H), 3.76 (s, 3H), 4.72 (s, 2H), 7.19 (t, J = 8 Hz, 1H), 7.23 (t, J = 8 Hz, 1H), 7.27 (d, J = 8 Hz, 1H), 7.37 (t, J = 8 Hz, 1H), 7.55 (t, J = 8 Hz, 1H), 7.86 (d, J = 8 Hz, 1H), 7.91 (d, J = 8 Hz, 1H), 8.70 (d, J = 8 Hz, 1H), 9.83 (s, 1H), 11.93 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.7, 38.8, 52.9, 63.0, 120.4, 121.6, 123.6, 125.2, 125.9, 126.3, 126.9, 128.4, 131.0, 133.1, 136.3, 139.4, 166.2, 167.3, 170.0, 173.6; HRMS (ESI) calcd for $C_{20}H_{20}N_2O_6Na$ 407.1214, found 407.1203; IR ($CHCl_3$) ν_{max} 3439, 1737, 1685, 1605 cm^{-1}.

2-((2-((2-(2-Methoxy-2-oxoethyl)phenyl)carbamoyl)phenyl)amino)-2-oxoethyl



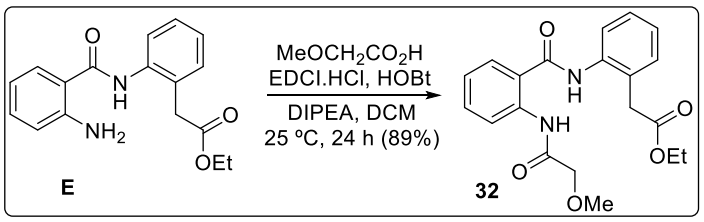
Benzoate (30). A solution of EDCI.HCl (160 mg, 0.84 mmol), HOBt (113 mg, 0.84 mmol) and 2-(benzoyloxy)acetic acid (152 mg, 0.84 mmol) in DCM (10 mL) was added dropwise to a stirred suspension of amine **D** (200 mg, 0.70 mmol) and DIPEA (0.244 mL, 1.40 mmol) in DCM (10 mL) at 25 ^{o}C. The reaction mixture was stirred at 25 ^{o}C for 24 h and then the reaction was quenched with water. The organic layer was separated and the aqueous layer was extracted with DCM (3 × 10 mL). The combined organic layer was washed with brine and dried over Na_2SO_4. Concentration of the dried organic layer in vacuo followed by the silica gel (60–120 mesh) column chromatographic purification of the resulting residue with ethyl acetate–petroleum ether (3:7) as an eluent furnished compound **30** as a white solid (263 mg, 84%). Mp 138 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.68 (s, 2H), 3.75 (s, 3H), 4.94 (s, 2H), 7.19 (t, J = 8 Hz, 1H), 7.23 (t, J = 8 Hz, 1H), 7.26 (d, J = 8 Hz, 1H), 7.31 (t, J = 8 Hz, 1H), 7.37 (t, J = 8 Hz, 1H), 7.38 (d, J = 8 Hz, 1H), 7.57 (t, J = 8 Hz, 2H), 7.84 (d, J = 8 Hz, 1H), 7.87 (d, J = 8 Hz, 1H), 8.34 (d, J = 8 Hz, 2H), 8.80 (d, J = 8 Hz, 1H), 9.88 (br s, 1H), 12.22 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 38.8, 52.8, 63.9, 120.3, 121.7, 123.6, 125.1, 125.7, 126.1, 126.9, 128.2, 128.3, 129.0, 130.3, 131.0, 133.1, 133.3, 136.3, 139.5, 165.5, 166.0, 167.2, 173.6; HRMS (ESI) calcd for $C_{25}H_{22}N_2O_6Na$ 469.1370, found 469.1361; IR ($CHCl_3$) ν_{max} 3326, 1722, 1677, 1593 cm^{-1}.

Methyl 2-(2-(2-(2-Methoxyacetamido)benzamido)phenyl)acetate (31). A solution of

EDCI.HCl (160 mg, 0.84 mmol), HOBt (113 mg, 0.84 mmol) and 2-methoxyacetic acid

(76 mg, 0.84 mmol) in DCM (10 mL) was added dropwise to a stirred suspension of amine **D** (200 mg, 0.70 mmol) and DIPEA (0.244 mL, 1.40 mmol) in DCM (10 mL) at 25 ^{o}C. The reaction mixture was stirred at 25 ^{o}C for 24 h and then the reaction was quenched with water. The organic layer was separated and the aqueous layer was extracted with DCM (3 × 10 mL). The combined organic layer was washed with brine and dried over Na_2SO_4. Concentration of the dried organic layer in vacuo followed by the silica gel (60–120 mesh) column chromatographic purification of the resulting residue with ethyl acetate–petroleum ether (3:7) as an eluent furnished compound **31** as a white solid (216 mg, 86%). Mp 156 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.50 (s, 3H), 3.68 (s, 2H), 3.73 (s, 3H), 4.03 (s, 2H), 7.17 (t, J = 8 Hz, 1H), 7.20 (t, J = 8 Hz, 1H), 7.25 (d, J = 8 Hz, 1H), 7.37 (t, J = 8 Hz, 1H), 7.53 (t, J = 8 Hz, 1H), 7.84 (d, J = 8 Hz, 1H), 7.93 (d, J = 8 Hz, 1H), 8.71 (d, J = 8 Hz, 1H), 9.70 (s, 1H), 11.71 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 38.7, 52.7, 59.6, 72.6, 121.2, 121.7, 123.4, 125.3, 125.7, 126.3, 127.0, 128.4, 130.9, 132.8, 136.4, 139.2, 167.1, 168.9, 173.4; HRMS (ESI) calcd for $C_{19}H_{20}N_2O_5Na$ 379.1264, found 379.1262; IR ($CHCl_3$) ν_{max} 3313, 1695, 1673, 1589 cm^{-1}.

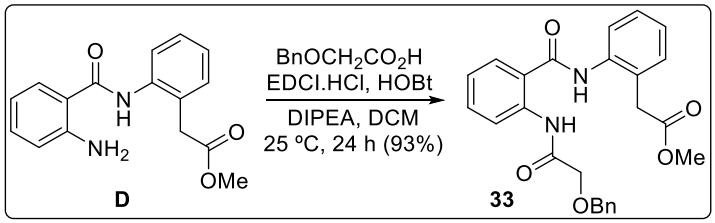
Ethyl 2-(2-(2-(2-Methoxyacetamido)benzamido)phenyl)acetate (32). A solution of



EDCI.HCl (152 mg, 0.80 mmol), HOBt (108 mg, 0.80 mmol) and 2-methoxyacetic acid (72 mg, 0.80 mmol) in DCM (10 mL) was added dropwise to a stirred suspension of amine **E** (200 mg, 0.67 mmol) and DIPEA (0.233 mL, 1.34 mmol) in DCM (10 mL) at 25 ^{o}C. The reaction mixture was stirred at 25 ^{o}C for 24 h and then the reaction was quenched with water. The organic layer was separated and the aqueous layer was extracted with DCM (3 × 10 mL). The combined organic layer was washed with brine and dried over Na_2SO_4. Concentration of the dried organic layer in vacuo followed by the silica gel (60–120 mesh) column chromatographic purification of the resulting residue with ethyl acetate–petroleum ether (3:7) as an eluent furnished compound **32** as a gummy solid (223 mg, 89%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.27 (t, J = 8 Hz, 3H), 3.51 (s, 3H), 3.67 (s, 2H), 4.04 (s, 2H), 4.18 (q, J = 8 Hz, 2H), 7.17

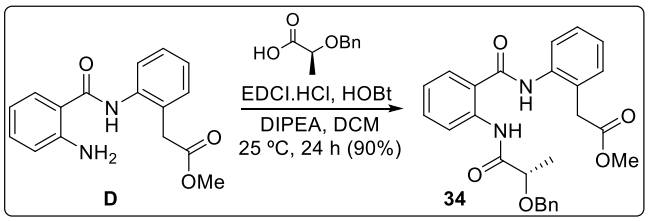
(t, *J* = 8 Hz, 1H), 7.20 (t, *J* = 8 Hz, 1H), 7.26 (d, *J* = 8 Hz, 1H), 7.37 (t, *J* = 8 Hz, 1H), 7.53 (t, *J* = 8 Hz, 1H), 7.84 (d, *J* = 8 Hz, 1H), 7.94 (d, *J* = 8 Hz, 1H), 8.71 (d, *J* = 8 Hz, 1H), 9.76 (br s, 1H), 11.72 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.0, 39.0, 59.6, 61.9, 72.7, 121.2, 121.7, 123.4, 125.3, 125.7, 126.4, 127.1, 128.4, 130.9, 132.8, 136.4, 139.2, 167.1, 169.0, 173.0; HRMS (ESI) calcd for $C_{20}H_{22}N_2O_5Na$ 393.1421, found 393.1418; IR ($CHCl_3$) ν_{max} 3262, 1724, 1642, 1592 cm^{-1}.

Methyl 2-(2-(2-(2-(Benzyloxy)acetamido)benzamido)phenyl)acetate (33). A solution



of EDCI.HCl (160 mg, 0.84 mmol), HOBt (113 mg, 0.84 mmol) and 2-(benzyloxy)acetic acid (139 mg, 0.84 mmol) in DCM (10 mL) was added dropwise to a stirred suspension of amine **D** (200 mg, 0.70 mmol) and DIPEA (0.244 mL, 1.40 mmol) in DCM (10 mL) at 25 ^{o}C. The reaction mixture was stirred at 25 ^{o}C for 24 h and then the reaction was quenched with water. The organic layer was separated and the aqueous layer was extracted with DCM (3 × 10 mL). The combined organic layer was washed with brine and dried over Na_2SO_4. Concentration of the dried organic layer in vacuo followed by the silica gel (60–120 mesh) column chromatographic purification of the resulting residue with ethyl acetate–petroleum ether (3:7) as an eluent furnished compound **33** as a gummy solid (283 mg, 93%). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.68 (s, 2H), 3.73 (s, 3H), 4.14 (s, 2H), 4.69 (s, 2H), 7.11–7.31 (m, 6H), 7.37 (dt, *J* = 8 & 2 Hz, 1H), 7.41–7.67 (m, 3H), 7.85 (dd, *J* = 8 & 2 Hz, 1H), 7.97 (d, *J* = 8 Hz, 1H), 8.73 (dd, *J* = 8 & 2 Hz, 1H), 9.75 (br s, 1H), 11.95 (br s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 38.8, 52.7, 70.2, 73.6, 121.2, 121.7, 123.4, 125.2, 125.6, 126.1, 126.9, 127.8 (2C), 128.3, 128.4, 130.9, 132.8, 136.5, 137.0, 139.3, 167.0, 168.0, 173.4; HRMS (ESI) calcd for $C_{25}H_{24}N_2O_5Na$ 455.1577, found 455.1574; IR ($CHCl_3$) ν_{max} 3274, 1736, 1661 cm^{-1}.

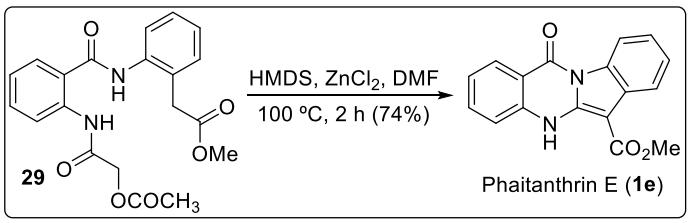
Methyl (*S*)-2-(2-(2-(2-(Benzyloxy)propanamido)benzamido)phenyl)acetate (34). A



solution of EDCI.HCl (243 mg, 1.27 mmol), HOBt (194 mg, 1.27 mmol) and (*S*)-2-(benzyloxy)propanoic acid (228 mg, 1.27 mmol) in DCM (10 mL) was added dropwise to a stirred suspension of amine **D** (300 mg, 1.06 mmol) and DIPEA (0.244 mL, 1.40 mmol) in DCM (10 mL) at 25 ^{o}C. The reaction mixture was

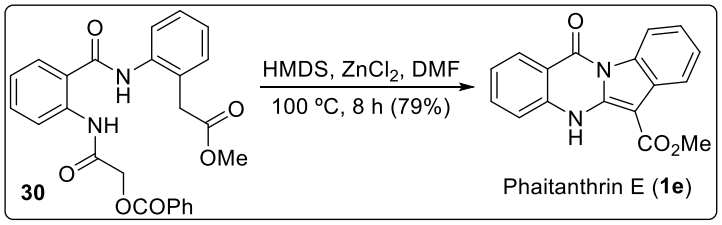
stirred at 25 ^{o}C for 24 h and then the reaction was quenched with water. The organic layer was separated and the aqueous layer was extracted with DCM (3 × 10 mL). The combined organic layer was washed with brine and dried over Na_2SO_4. Concentration of the dried organic layer in vacuo followed by the silica gel (60–120 mesh) column chromatographic purification of the resulting residue with ethyl acetate–petroleum ether (3:7) as an eluent furnished compound **34** as gummy solid (427 mg, 90%). $[\alpha]^{25}_{D}$ –1.13 (*c* 0.50 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.53 (d, *J* = 8 Hz, 3H), 3.68 (s, 2H), 3.72 (s, 3H), 4.08 (q, *J* = 8 Hz, 1H), 4.58 (d, *J* = 12 Hz, 1H), 4.79 (d, *J* = 12 Hz, 1H), 7.12–7.32 (m, 6H), 7.35 (t, *J* = 8 Hz, 1H), 7.47 (br s, 2H), 7.54 (t, *J* = 8 Hz, 1H), 7.87 (d, *J* = 8 Hz, 1H), 7.94 (d, *J* = 8 Hz, 1H), 8.79 (d, *J* = 8 Hz, 1H), 9.77 (s, 1H), 12.03 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 18.7, 38.6, 52.6, 72.0, 76.6, 121.0, 121.4, 123.2, 125.1, 125.5, 126.0, 126.9, 127.6, 127.8, 128.1, 128.3, 130.8, 132.7, 136.3, 137.2, 139.4, 166.9, 172.5, 173.3; HRMS (ESI) calcd for $C_{26}H_{26}N_2O_5Na$ 469.1734, found 469.1724; IR ($CHCl_3$) ν_{max} 3300, 1719, 1659, 1590 cm^{-1}.

Methyl 12-Oxo-5,12-dihydroindolo[2,1-*b*]quinazoline-6-carboxylate (Phaitanthrin E, 1e). To a stirred solution of compound **29** (150 mg, 0.39 mmol) and $ZnCl_2$ (53 mg, 0.39 mmol) in DMF (5 mL) was added hexamethyldisilazane (163 µL, 0.78 mmol) at 25 ^{o}C under argon atmosphere. The reaction mixture was heated at 100 ^{o}C for 2 h and allowed to reach 25 ^{o}C. The reaction was quenched by adding saturated NH_4Cl and the reaction mixture was extracted with EtOAc (3 × 10 mL). The organic layer was washed with water, brine and dried over Na_2SO_4. After concentration in vacuo, the obtained residue was purified by silica gel (60–120 mesh) column chromatography using ethyl acetate–petroleum ether (1:9) as an eluent to provide phaitanthrin E (**1e**) as white amorphous solid (84 mg, 74%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.00 (s, 3H), 7.25–7.35 (m, 3H), 7.41 (t, *J* = 8 Hz, 1H), 7.70 (t, *J* = 8 Hz, 1H), 7.92 (d, *J* = 8 Hz, 1H), 8.37 (d, *J* = 8 Hz, 1H), 8.68 (d, *J* = 8 Hz, 1H), 10.25 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 51.3, 86.6, 114.2, 115.6, 116.1, 119.3, 122.3, 123.0, 125.6, 126.2, 128.6, 130.2, 135.2, 138.1, 143.9, 158.4, 167.2; ESIMS (*m*/*z*) 331 $[M+K]^+$; IR ($CHCl_3$) ν_{max} 3057, 1820, 1730, 1653 cm^{-1}.

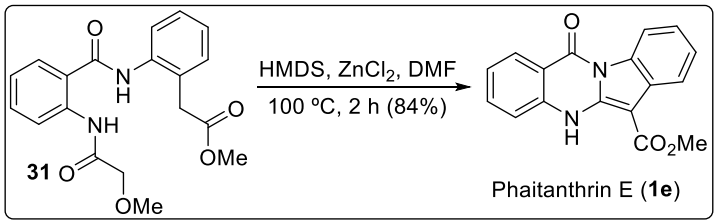


Methyl 12-Oxo-5,12-dihydroindolo[2,1-*b*]quinazoline-6-carboxylate (Phaitanthrin E, 1e). To a stirred solution of compound **30** (150 mg, 0.33 mmol) and $ZnCl_2$ (45 mg, 0.33

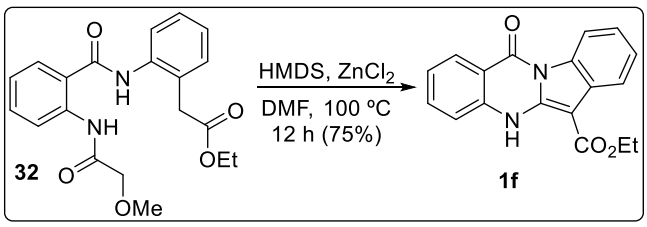
mmol) in DMF (5 mL) was added hexamethyldisilazane (138 μL, 0.66 mmol) at 25 °C under argon atmosphere. The reaction mixture was heated at 100 °C for 8 h and allowed to reach 25 °C. The reaction was quenched by adding saturated NH_4Cl and the reaction mixture was extracted with EtOAc (3 × 10 mL). The organic layer was washed with water, brine and dried over Na_2SO_4. After concentration in vacuo, the obtained residue was purified by silica gel (60–120 mesh) column chromatography using ethyl acetate–petroleum ether (1:9) as an eluent to provide phaitanthrin E (**1e**) as white amorphous solid (77 mg, 79%).



Methyl 12-Oxo-5,12-dihydroindolo[2,1-*b*]quinazoline-6-carboxylate (Phaitanthrin E, 1e). To a stirred solution of compound **31** (150 mg, 0.42 mmol) and $ZnCl_2$ (57 mg, 0.42 mmol) in DMF (5 mL) was added hexamethyldisilazane (171 μL, 0.82 mmol) at 25 °C under argon atmosphere. The reaction mixture was heated at 100 °C for 2 h and allowed to reach 25 °C. The reaction was quenched by adding saturated NH_4Cl and the reaction mixture was extracted with EtOAc (3 × 10 mL). The organic layer was washed with water, brine and dried over Na_2SO_4. After concentration in vacuo, the obtained residue was purified by silica gel (60–120 mesh) column chromatography using ethyl acetate–petroleum ether (1:9) as an eluent to provide phaitanthrin E (**1e**) as white amorphous solid (103 mg, 84%).

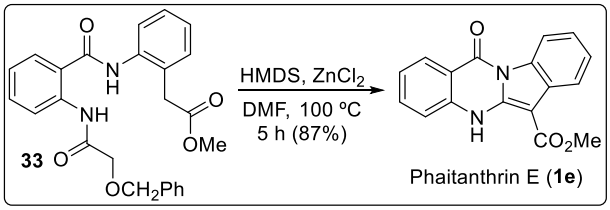


Ethyl 12-Oxo-5,12-dihydroindolo[2,1-*b*]quinazoline-6-carboxylate (1f). To a stirred solution of compound **32 (**150 mg, 0.40 mmol) and $ZnCl_2$ (55 mg, 0.40 mmol) in DMF (5 mL) was added hexamethyldisilazane (169 μL, 0.81 mmol) at 25 °C under argon atmosphere. The reaction mixture was heated at 100 °C for 12 h and allowed to reach 25 °C. The reaction was quenched by adding saturated NH_4Cl and the reaction mixture was extracted with EtOAc (3 × 10 mL). The organic layer was washed with water, brine and dried over Na_2SO_4. After concentration in vacuo, the obtained residue was purified by silica gel (60–120 mesh) column chromatography using ethyl acetate–petroleum ether (1:9) as an eluent to provide desired product **1f** as white

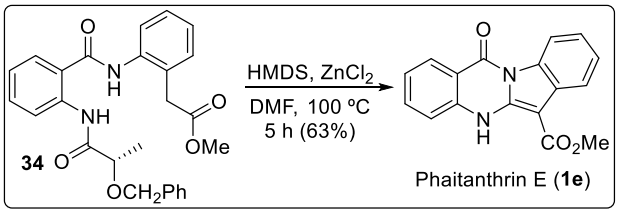


amorphous solid (93 mg, 75%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.50 (t, J = 10 Hz, 3H), 4.45 (q, J = 10 Hz, 2H), 7.24 (d, J = 10 Hz, 1H), 7.29 (t, J = 10 Hz, 2H), 7.40 (t, J = 10 Hz, 1H), 7.68 (t, J = 10 Hz, 1H), 7.91 (d, J = 10 Hz, 1H), 8.36 (d, J = 10 Hz, 1H), 8.67 (d, J = 10 Hz, 1H), 10.24 (br s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.6, 60.2, 86.7, 114.2, 115.5, 116.1, 119.3, 122.2, 122.9, 125.5, 126.3, 128.5, 130.2, 135.1, 138.1, 143.9, 158.4, 166.9; HRMS (ESI) calcd for $C_{18}H_{15}N_2O_3$ 307.1077, found 307.1075; IR ($CHCl_3$) ν_{max} 3313, 1699, 1661, 1621 cm^{-1}.

Methyl 12-Oxo-5,12-dihydroindolo[2,1-*b*]quinazoline-6-carboxylate (Phaitanthrin E, 1e). To a stirred solution of compound **33** (150 mg, 0.34 mmol) and $ZnCl_2$ (47 mg, 0.34 mmol) in DMF (5 mL) was added hexamethyldisilazane (145 µL, 0.69 mmol) at 25 °C under argon atmosphere. The reaction mixture was heated at 100 °C for 5 h and allowed to reach 25 °C. The reaction was quenched by adding saturated NH_4Cl and the reaction mixture was extracted with EtOAc (3 × 10 mL). The organic layer was washed with water, brine and dried over Na_2SO_4. After concentration in vacuo, the obtained residue was purified by silica gel (60–120 mesh) column chromatography using ethyl acetate–petroleum ether (1:9) as an eluent to provide phaitanthrin E (**1e**) as white amorphous solid (88 mg, 87%).

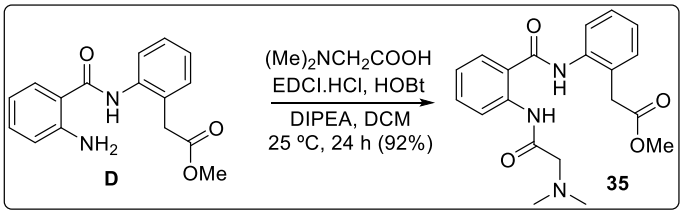


Methyl 12-Oxo-5,12-dihydroindolo[2,1-*b*]quinazoline-6-carboxylate (Phaitanthrin E, 1e). To a stirred solution of compound **34** (150 mg, 0.34 mmol) and $ZnCl_2$ (47 mg, 0.34 mmol) in DMF (5 mL) was added hexamethyldisilazane (150 µL, 0.69 mmol) at 25 °C under argon atmosphere. The reaction mixture was heated at 100 °C for 5 h and allowed to reach 25 °C. The reaction was quenched by adding saturated NH_4Cl and the reaction mixture was extracted with EtOAc (3 × 10 mL). The organic layer was washed with water, brine and dried over Na_2SO_4. After concentration in vacuo, the obtained residue was purified by silica gel (60–120 mesh) column chromatography using ethyl acetate–petroleum ether (1:9) as an eluent to provide phaitanthrin E (**1e**) as white amorphous solid (61 mg, 63%).



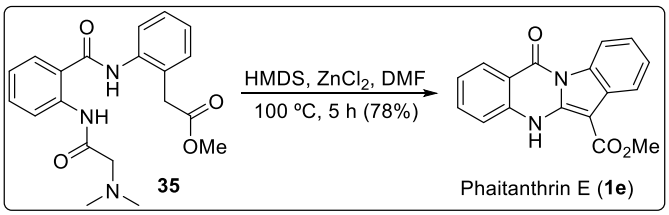
Methyl 2-(2-(2-(2-(Dimethylamino)acetamido)benzamido)phenyl)acetate (35). A solution of EDCI.HCl (160 mg, 0.84 mmol), HOBt (113 mg, 0.84 mmol) dimethyl

glycine (87 mg, 0.84 mmol) in DCM (10 mL) was added dropwise to a stirred suspension

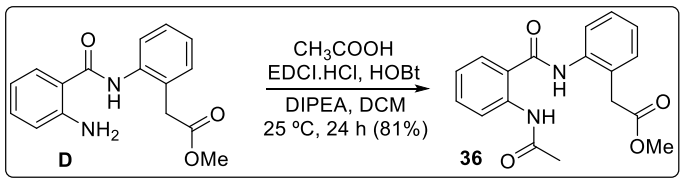


of amine **D** (200 mg, 0.70 mmol) and DIPEA (0.244 mL, 1.40 mmol) in DCM (10 mL) at 25 °C. The reaction mixture was stirred at 25 °C for 24 h and the reaction was quenched with water. The organic layer was separated and the aqueous layer was extracted with DCM (3 × 10 mL). The combined organic layer was washed with brine and dried over Na_2SO_4. Concentration of the dried organic layer in vacuo followed by the silica gel (60–120 mesh) column chromatographic purification of the resulting residue with ethyl acetate–petroleum ether (3:7) as an eluent furnished compound **35** as gummy solid (240 mg, 92%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.37 (s, 6H), 3.11 (s, 2H), 3.69 (s, 2H), 3.72 (s, 3H), 7.18 (t, J = 10 Hz, 2H), 7.26 (d, J = 10 Hz, 1H), 7.37 (t, J = 10 Hz, 1H), 7.51 (t, J = 10 Hz, 1H), 7.79 (d, J = 10 Hz, 1H), 7.92 (d, J = 10 Hz, 1H), 8.64 (d, J = 10 Hz, 1H), 9.54 (s, 1H), 11.65 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 38.6, 45.9, 52.6, 64.2, 121.9, 122.1, 123.2, 125.2, 125.7, 126.4, 127.0, 128.4, 130.9, 132.4, 136.4, 138.9, 166.9, 170.2, 173.2; HRMS (ESI) calcd for $C_{20}H_{24}N_3O_4$ 370.1761, found 370.1761; IR ($CHCl_3$) ν_{max} 3260, 1737, 1716, 1662 cm^{-1}.

Methyl 12-Oxo-5,12-dihydroindolo[2,1-*b*]quinazoline-6-carboxylate (Phaitanthrin E, 1e). To a stirred solution of compound **35 (**150 mg, 0.40 mmol) and $ZnCl_2$ (55 mg, 0.40 mmol) in DMF (5 mL) was added hexamethyldisilazane (169 μL, 0.81 mmol) at 25 °C under argon atmosphere. The reaction mixture was heated at 100 °C for 5 h and allowed to reach 25 °C. The reaction was quenched by adding saturated NH_4Cl and extracted with EtOAc (3 × 10 mL). The organic layer was washed with water, brine and dried over Na_2SO_4. After concentration in vacuo, the obtained residue was purified by silica gel (60–120 mesh) column chromatography using ethyl acetate–petroleum ether (1:9) as an eluent to provide phaitanthrin E (**1e**) as white amorphous solid (92 mg, 78%).

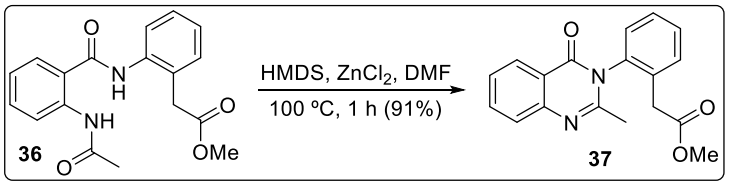


Methyl 2-(2-(2-Acetamidobenzamido)phenyl)acetate (36). A solution of EDCI.HCl (160 mg, 0.84 mmol), HOBt (113 mg, 0.84 mmol), acetic acid (50 mg, 0.84 mmol) in DCM (10 mL)

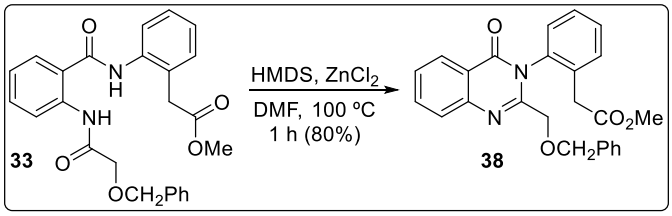


was added dropwise to a stirred suspension of amine **D** (200 mg, 0.70 mmol) and DIPEA (0.244 mL, 1.40 mmol) in DCM (10 mL) at 25 ^{o}C. The reaction mixture was stirred at 25 ^{o}C for 24 h and the reaction was quenched with water. The organic layer was separated and the aqueous layer was extracted with DCM (3 × 10 mL). The combined organic layer was washed with brine and dried over Na_2SO_4. Concentration of the dried organic layer in vacuo followed by the silica gel (60–120 mesh) column chromatographic purification of the resulting residue with ethyl acetate–petroleum ether (3:7) as an eluent furnished compound **36** as a white solid (185 mg, 81%). Mp 138 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.19 (s, 3H), 3.69 (s, 2H), 3.75 (s, 3H), 7.18 (t, *J* = 8 Hz, 1H), 7.20 (t, *J* = 8 Hz, 1H), 7.28 (d, *J* = 8 Hz, 1H), 7.40 (t, *J* = 8 Hz, 1H), 7.53 (t, *J* = 8 Hz, 1H), 7.82 (d, *J* = 8 Hz, 1H), 7.85 (d, *J* = 8 Hz, 1H), 8.66 (d, *J* = 8 Hz, 1H), 9.79 (s, 1H), 11.20 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 25.3, 38.7, 52.8, 119.9, 121.6, 122.9, 125.4, 126.1, 126.7, 126.9, 128.5, 131.1, 133.1, 136.1, 140.4, 167.7, 169.1, 173.5; HRMS (ESI) calcd for $C_{18}H_{18}N_2O_4Na$ 349.1159, found 349.1148; IR ($CHCl_3$) ν_{max} 3297, 1731, 1688, 1654 cm^{-1}.

Methyl 2-(2-(2-Methyl-4-oxoquinazolin-3(4*H*)-yl)phenyl)acetate (37). To a stirred solution of compound **36** (150 mg, 0.46 mmol) and $ZnCl_2$ (62 mg, 0.46 mmol) in DMF (5 mL) was added hexamethyldisilazane (192 μL, 0.92 mmol) at 25 ^{o}C under argon atmosphere. The reaction mixture was heated at 100 ^{o}C for 1 h and allowed to reach 25 ^{o}C. The reaction was quenched by adding saturated NH_4Cl and the reaction mixture was extracted with EtOAc (3 × 10 mL). The organic layer was washed with water, brine and dried over Na_2SO_4. After concentration in vacuo, the obtained residue was purified by silica gel (60–120 mesh) column chromatography using ethyl acetate–petroleum ether (2:8) as an eluent to provide compound **37** as gummy solid (128 mg, 91%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.24 (s, 3H), 3.47 (d, *J* = 16 Hz, 1H), 3.52 (d, *J* = 16 Hz, 1H), 3.55 (s, 3H), 7.24 (d, *J* = 8 Hz, 1H), 7.40–7.57 (m, 4H), 7.70 (d, *J* = 8 Hz, 1H), 7.79 (t, *J* = 8 Hz, 1H), 8.28 (d, *J* = 8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 24.1, 37.0, 52.0, 120.5, 126.7, 126.8, 127.1, 128.6, 129.0, 129.9, 131.9, 132.2, 134.7, 136.7, 147.6, 154.6, 161.7, 170.8; HRMS (ESI) calcd for $C_{18}H_{17}N_2O_3$ 309.1234, found 309.1227; IR ($CHCl_3$) ν_{max} 1675, 1623 cm^{-1}.

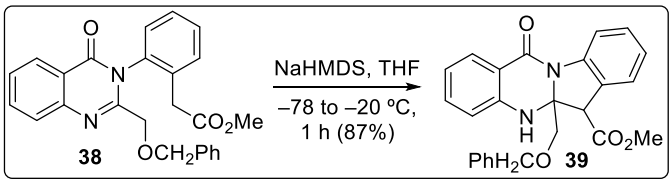


Methyl 2-(2-(2-((Benzyloxy)methyl)-4-oxoquinazolin-3(4*H*)-yl)phenyl)acetate (38). To a stirred solution of compound **33** (300 mg, 0.69 mmol) and $ZnCl_2$ (64 mg, 0.69



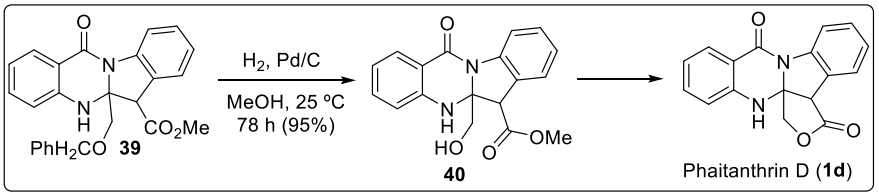
mmol) in DMF (10 mL) was added hexamethyldisilazane (288 μL, 1.38 mmol) at 25 °C under argon atmosphere. The reaction mixture was heated at 100 °C for 1 h and allowed to reach 25 °C. The reaction was quenched by adding saturated NH_4Cl and the reaction mixture was extracted with EtOAc (3 × 10 mL). The organic layer was washed with water, brine and dried over Na_2SO_4. After concentration in vacuo, the obtained residue was purified by silica gel (60–120 mesh) column chromatography using ethyl acetate–petroleum ether (2:8) as an eluent to provide compound **38** as gummy solid (230 mg, 80%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.46 (q, J = 16 Hz, 2H), 3.51 (s, 3H), 4.18 (d, J = 12 Hz, 1H), 4.22 (d, J = 12 Hz, 1H), 4.38 (d, J = 12 Hz, 1H), 4.47 (d, J = 12 Hz, 1H), 7.20–7.34 (m, 6H), 7.38–7.45 (m, 1H), 7.45–7.57 (m, 3H), 7.78–7.87 (m, 2H), 8.30 (d, J = 8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 37.0, 52.0, 70.2, 73.3, 121.1, 127.1, 127.5, 127.8, 127.9, 128.0, 128.3, 128.5, 129.1, 129.9, 131.6, 132.7, 134.7, 135.3, 137.1, 147.3, 152.7, 161.6, 170.8; HRMS (ESI) calcd for $C_{25}H_{23}N_2O_4$ 415.1652, found 415.1642; IR ($CHCl_3$) ν_{max} 1738, 1687, 1609 cm^{-1}.

Methyl 5a-((Benzyloxy)methyl)-12-oxo-5,5a,6,12-tetrahydroindolo[2,1-*b*]quinazoline-6-carboxylate (39). To a stirred solution of compound **38** (220 mg, 0.53



mmol) in THF at –78 °C was added solution of NaHMDS (1 M in THF, 0.58 mL, 0.58 mmol) under argon atmosphere and allowed to reach –20 °C over 1 h. The reaction was quenched at –20 °C with saturated NH_4Cl solution. The reaction mixture was concentrated in vacuo and the obtained residue was directly purified by silica gel (60–120 mesh) column chromatography using ethyl acetate–petroleum ether (2:8) as an eluent to afford product **39** as gummy solid (191 mg, 87%, *dr* 93:7). Major isomer: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.26 (d, J = 10 Hz, 1H), 3.70 (s, 3H), 3.74 (d, J = 10 Hz, 1H), 4.45 (d, J = 10 Hz, 1H), 4.47 (s, 1H), 4.49 (d, J = 10 Hz, 1H), 5.24 (s, 1H), 6.74 (d, J = 10 Hz, 1H), 6.94 (t, J = 10 Hz, 1H), 7.13 (t, J = 10 Hz, 1H), 7.16–7.21 (m, 2H), 7.23–7.31 (m, 4H), 7.33–7.38 (m, 2H), 7.97 (d, J = 10 Hz, 1H), 8.29 (d, J = 10 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 52.6, 54.4, 69.0, 73.4, 80.1, 115.8, 116.4, 116.8, 120.3, 124.4, 125.8, 126.0, 127.5, 128.0, 128.45, 128.49, 129.4, 134.0, 137.1, 142.1, 144.5, 159.8, 169.8; HRMS (ESI) calcd for $C_{25}H_{23}N_2O_4$ 415.1652, found 415.1642; IR ($CHCl_3$) ν_{max} 3335, 1763, 1664, 1614 cm^{-1}.

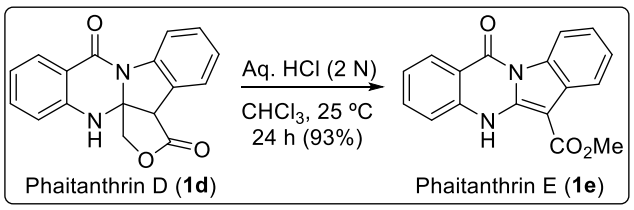
1*H*-Furo[3',4':2,3]indolo[2,1-*b*]quinazoline-3,9(3a*H*,14*H*)-dione (Phaitanthrin D, 1d).



To a stirred solution of compound **39** (150 mg, 0.36 mmol) in methanol (4 mL) was added activated Pd–C (15 mg, 10 wt %) and the reaction mixture was stirred under balloon pressure hydrogen atmosphere at 25 ^{o}C for 78 h. The reaction mixture was filtered to remove Pd–C and concentrated in vacuo. The silica gel (230–400 mesh) column chromatographic purification of the obtained residue using ethyl acetate–petroleum ether (2:8) as an eluent provided the pure product phaitanthrin D (**1d**) as yellow amorphous solid (100 mg, 95% yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.35 (d, J = 12 Hz, 1H), 4.36 (s, 1H), 4.66 (d, J = 12 Hz, 1H), 5.22 (s, 1H), 6.93 (d, J = 8 Hz, 1H), 7.10 (t, J = 8 Hz, 1H), 7.24 (t, J = 8 Hz, 1H), 7.47 (t, J = 8 Hz, 2H), 7.57 (d, J = 8 Hz, 1H), 8.09 (d, J = 8 Hz, 1H), 8.33 (d, J = 8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 53.4, 78.6, 82.7, 116.8, 117.0, 117.8, 121.7, 121.9, 125.0, 125.4, 129.1, 130.5, 134.4, 140.6, 143.2, 159.3, 172.7; HRMS (ESI) calcd for $C_{17}H_{13}N_2O_3$ 293.0921, found 293.0911; IR ($CHCl_3$) ν_{max} 3326, 1781, 1659, 1608 cm^{-1}.

Methyl 5a-(Hydroxymethyl)-12-oxo-5,5a,6,12-tetrahydroindolo[2,1-*b*]quinazoline-6-carboxylate (40). It was possible to isolate a small amount of pure product **40** (7 mg) by arresting the above specified reaction after 48 hours and silica gel column chromatography. The obtained product was not very stable and we could only collect the ^{1}H NMR data. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.10–2.40 (br s, 1H), 3.41 (d, J = 10 Hz, 1H), 3.72 (s, 3H), 3.89 (d, J = 10 Hz, 1H), 4.49 (s, 1H), 5.46 (br s, 1H), 6.82 (d, J = 8 Hz, 1H), 6.97 (t, J = 8 Hz, 1H), 7.14 (t, J = 8 Hz, 1H), 7.31 (d, J = 8 Hz, 1H), 7.37 (t, J = 8 Hz, 2H), 8.00 (d, J = 8 Hz, 1H), 8.29 (d, J = 8 Hz, 1H); HRMS (ESI) calcd for $C_{18}H_{17}N_2O_4$ 325.1183, found 325.1175.

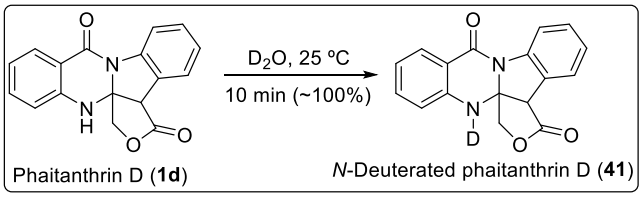
Methyl 12-Oxo-5,12-dihydroindolo[2,1-*b*]quinazoline-6-carboxylate (Phaitanthrin E, 1e).



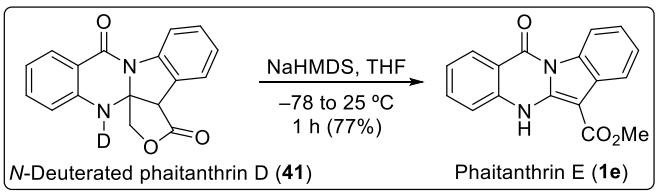
To a stirred solution of phaitanthrin D (**1d**, 40 mg, 0.136 mmol) in chloroform (5 mL) was added 2 N HCl (0.20 mL) and the reaction mixture was stirred at 25 ^{o}C for 24 h. The reaction was quenched by using saturated K_2CO_3 solution. The organic layer was separated and the aqueous layer was

extracted with chloroform (3 × 10 mL). The combined organic layer was washed with brine and dried over Na_2SO_4. Concentration of the dried organic layer in vacuo followed by the silica gel (60–120 mesh) column chromatographic purification of the resulting residue with ethyl acetate–petroleum ether (1:9) as an eluent furnished the product phaitanthrin E (**1e**) as white amorphous solid (37 mg, 93%).

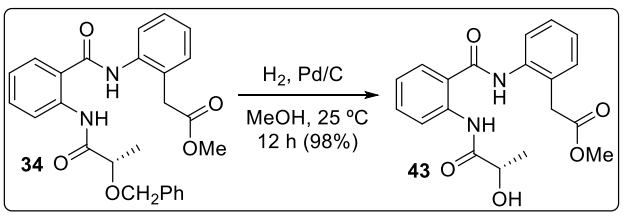
1*H*-Furo[3',4':2,3]indolo[2,1-*b*]quinazoline-3,9(3a*H*,14*H*)-dione-14-*d* (41). To a stirred solution of phaitanthrin D (**1d**, 40 mg, 0.136 mmol) in $CHCl_3$ was added a drop of D_2O and the reaction mixture was stirred at 25 °C for 10 min. The reaction mixture was dried over Na_2SO_4 and concentrated in vacuo to offer the desired compound **41** as white amorphous solid (40 mg, ~100%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.34 (d, J = 12 Hz, 1H), 4.37 (s, 1H), 4.65 (d, J = 12 Hz, 1H), 6.92 (d, J = 8 Hz, 1H), 7.10 (t, J = 8 Hz, 1H), 7.24 (t, J = 8 Hz, 1H), 7.47 (t, J = 8 Hz, 2H), 7.58 (d, J = 8 Hz, 1H), 8.09 (d, J = 8 Hz, 1H), 8.33 (d, J = 8 Hz, 1H).



Methyl 12-Oxo-5,12-dihydroindolo[2,1-*b*]quinazoline-6-carboxylate (Phaitanthrin E, 1e). To a stirred solution of compound **41** (30 mg, 0.102 mmol) in THF at –78 °C was added solution of NaHMDS (1 M in THF, 0.10 mL, 0.102 mmol) under argon atmosphere and it was allowed to reach 25 °C over 1 h. The reaction was quenched with saturated NH_4Cl solution at 25 °C. The reaction mixture was concentrated in vacuo and the obtained residue was directly purified by silica gel (60–120 mesh) column chromatography using ethyl acetate–petroleum ether (1:9) as an eluent to afford the desired product phaitanthrin E (**1e**) as a white amorphous solid (23 mg, 77%).

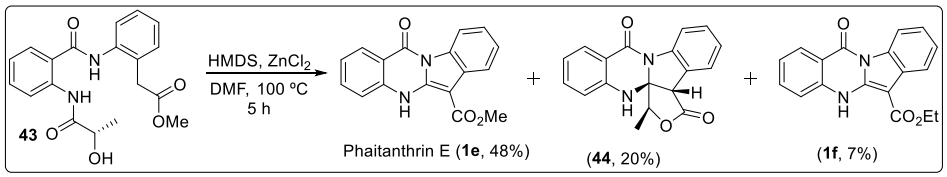


Methyl (*S*)-2-(2-(2-(2-Hydroxypropanamido)benzamido)phenyl)acetate (43). To a stirred solution of compound **34** (150 mg, 0.22 mmol) in methanol (10 mL) was added activated Pd–C (10 mg, 10 wt %) and reaction mixture was stirred under balloon pressure hydrogen atmosphere 25 °C for 12 h. The reaction mixture was filtered to remove Pd–C and concentrated in vacuo. The silica gel (230–400 mesh) column chromatographic purification of the obtained residue using ethyl



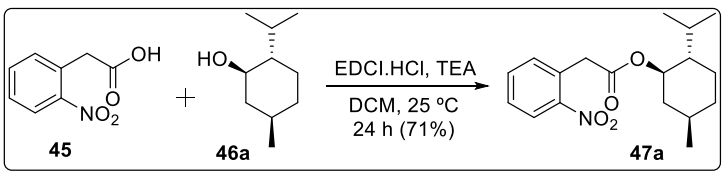
acetate–petroleum ether (8:2) as an eluent provided the pure product compound **43** as thick oil (117 mg, 98% yield). $[\alpha]^{25}_{D}$ –0.61 (*c* 0.50 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.43 (d, *J* = 8 Hz, 3H), 3.66 (s, 2H), 3.70–3.90 (br s, 1H), 3.72 (s, 3H), 4.22 (q, *J* = 8 Hz, 1H), 7.17 (t, *J* = 8 Hz, 1H), 7.18 (d, *J* = 8 Hz, 1H), 7.25 (d, *J* = 8 Hz, 1H), 7.32 (t, *J* = 8 Hz, 1H), 7.51 (t, *J* = 8 Hz, 1H), 7.80 (t, *J* = 8 Hz, 1H), 7.81 (d, *J* = 8 Hz, 1H), 8.66 (d, *J* = 8 Hz, 1H), 9.73 (s, 1H), 11.74 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.0, 30.5, 44.7, 60.6, 112.6, 113.4, 115.3, 117.5, 118.1, 118.8, 119.1, 120.4, 123.0, 124.9, 128.0, 131.4, 159.4, 165.5, 165.9; HRMS (ESI) calcd for $C_{19}H_{20}N_2O_5Na$ 379.1264, found 379.1255; IR (CHCl3) ν_{max} 3302, 1722, 1661, 1591 cm^{-1}.

(1*S*,3a*S*,14a*R*)-1-Methyl-1*H*-furo[3',4':2,3]indolo[2,1-*b*]quinazoline-3,9(3a*H*,14*H*)-dione (44). To a stirred solution of compound **43** (100 mg, 0.28 mmol) and $ZnCl_2$ (38 mg, 0.28 mmol) in DMF (5 mL) was added hexamethyldisilazane (125 µL, 0.56 mmol) at 25 °C under argon atmosphere. The reaction mixture was heated at 100 °C for 5 h and allowed to reach 25 °C. The reaction was quenched by adding saturated NH_4Cl and the reaction mixture was extracted with EtOAc (3 × 10 mL). The organic layer was washed with water, brine and dried over Na_2SO_4. After concentration in vacuo, the obtained residue was purified by silica gel (60–120 mesh) column chromatography using ethyl acetate–petroleum ether (2:8) as a eluent to provide compound **1f** as amorphous solid (6 mg, 7%), compound **1e** as amorphous solid (39 mg, 48% yield) and compound **44** as gummy solid (17 mg, 20%).



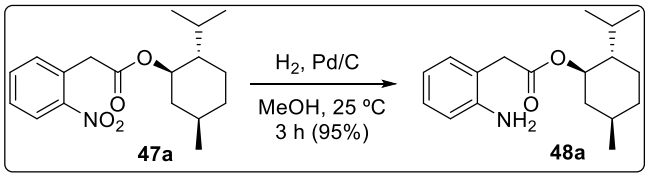
44: $[\alpha]^{25}_{D}$ +2.29 (*c* 0.50 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.30 (d, *J* = 8 Hz, 3H), 4.40 (s, 1H), 4.58 (q, *J* = 8 Hz, 1H), 5.55 (s, 1H), 6.87 (d, *J* = 8 Hz, 1H), 7.00 (t, *J* = 8 Hz, 1H), 7.24 (t, *J* = 8 Hz, 1H), 7.43 (t, *J* = 8 Hz, 1H), 7.46 (t, *J* = 8 Hz, 1H), 7.55 (d, *J* = 8 Hz, 1H), 8.04 (d, *J* = 8 Hz, 1H), 8.36 (d, *J* = 8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 15.3, 56.0, 84.4, 85.3, 114.9, 116.1, 117.5, 120.6, 121.9, 124.8, 125.4, 128.8, 130.4, 134.7, 140.9, 144.4, 159.4, 172.4; HRMS (ESI) calcd for $C_{18}H_{15}N_2O_3$ 307.1077, found 307.1075; IR ($CHCl_3$) ν_{max} 3326, 1773, 1650, 1610 cm^{-1}.

(1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl 2-(2-Nitrophenyl)acetate (47a). A solution of EDCI.HCl (527 mg, 2.76 mmol), HOBt (372 mg, 2.76 mmol), 2-(2-



nitrophenyl)acetic acid (**45**, 500 mg, 2.76 mmol) in THF (10 mL) was added dropwise to a stirred suspension of (–)-menthol (**46a**, 430 mg, 2.76 mmol) and DIPEA (0.481 mL, 2.76 mmol) in THF (10 mL) at 25 °C. The reaction mixture was stirred at 25 °C for 24 h and reaction was quenched with water (10 mL). The organic layer was separated and aqueous layer was extracted with EtOAc (3 × 30 mL). The combined organic layer was washed with brine (25 mL) and dried over Na_2SO_4. Concentration of the dried organic layer in vacuo followed by silica gel (60–120 mesh) column chromatographic purification of the resulting residue with ethyl acetate–petroleum ether (2:8) as an eluent furnished compound **47a**. White solid (625 mg, 71%). Mp 80°C; $[\alpha]^{25}_{D}$ –62.0 (*c* 0.56 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.74 (d, *J* = 10 Hz, 3H), 0.81–0.89 (m, 1H), 0.86 (d, *J* = 10 Hz, 3H), 0.89 (d, *J* = 10 Hz, 3H), 0.94–1.09 (m, 2H), 1.35 (tt, *J* = 10 & 2 Hz, 1H), 1.40–1.52 (m, 1H), 1.61–1.70 (m, 2H), 1.84 (doublet of quintet, *J* = 10 & 2 Hz, 1H), 2.02 (td, *J* = 10 & 2 Hz, 1H), 4.00 (q, *J* = 20 Hz, 2H), 4.71 (dt, *J* = 10 & 5 Hz, 1H), 7.36 (d, *J* = 10 Hz, 1H), 7.47 (t, *J* = 10 Hz, 1H), 7.59 (t, *J* = 10 Hz, 1H), 8.10 (d, *J* = 10 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 16.2, 20.7, 22.0, 23.4, 26.2, 31.3, 34.2, 40.0, 40.6, 46.9, 75.4, 125.2, 128.4, 130.0, 133.3, 133.4, 148.9, 169.5; HRMS (ESI) calcd for $C_{18}H_{26}NO_4$ 320.1856, found 320.1854; IR ($CHCl_3$) ν_{max} 1743, 1646, 1529, 1457, 1376 cm^{-1}.

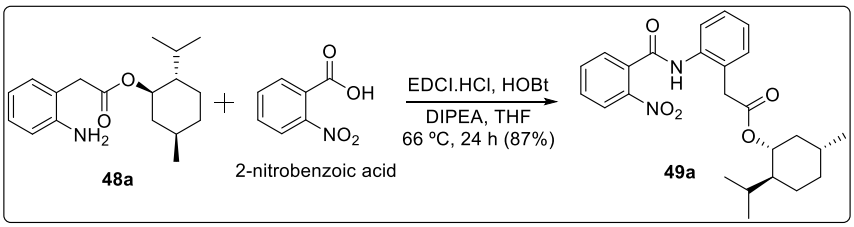
(1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl 2-(2-Aminophenyl)acetate (48a).



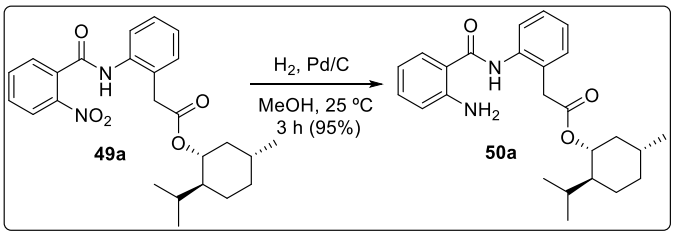
To a stirred solution of compound **47a** (600 mg, 1.51 mmol) in methanol (20 mL) was added activated Pd–C (60 mg, 10 wt %) and the reaction mixture was stirred under balloon pressure hydrogen atmosphere at 25 °C for 3 h. The reaction mixture was filtered to remove Pd–C and concentrated in vacuo. Silica gel (230–400 mesh) column chromatographic purification of the obtained residue using ethyl acetate–petroleum ether (2:8) as an eluent provided pure product **48a**. Thick oil (516 mg, 95% yield). $[\alpha]^{25}_{D}$ –54.84 (*c* 0.50 CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.69 (d, *J* = 8 Hz, 3H), 0.85 (d, *J* = 8 Hz, 3H), 0.90 (d, *J* = 8 Hz, 3H), 0.87–1.10 (m, 3H), 1.38 (tt, *J* = 12 & 4 Hz, 1H), 1.42–1.54 (m, 1H), 1.62–1.80 (m, 3H), 1.97 (td, *J* = 12 & 4 Hz, 1H), 3.55 (s, 2H), 4.08 (br s, 2H), 4.68 (dt, *J* = 16 & 4 Hz, 1H), 6.71 (d, *J* = 8 Hz, 1H), 6.76 (t, *J* = 8 Hz, 1H), 7.05–7.15 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 16.2, 20.6, 21.9, 23.4, 26.1, 31.3, 34.2, 38.8, 40.7, 47.1, 74.9, 116.4, 118.8, 119.8, 128.3, 131.0, 145.4, 171.5; HRMS (ESI) calcd for $C_{18}H_{28}NO_2$ 290.2115, found 290.2111; IR ($CHCl_3$) ν_{max} 3445,

3372, 1718, 1632, 1500, 1457, 1373 cm^{-1}.

(1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl 2-(2-(2-Nitrobenzamido)phenyl)acetate (49a). A solution of EDCI.HCl (395 mg, 2.07 mmol), HOBt (279 mg, 2.07 mmol), 2-nitrobenzoic acid (345 mg, 2.07 mmol) in THF (20 mL) was added dropwise to a stirred suspension of amine **48a** (500 mg, 1.73 mmol) and DIPEA (0.603 mL, 3.46 mmol) in THF (20 mL) at 25 °C. The reaction mixture was refluxed for 24 h and reaction was quenched with water. The organic layer was separated and aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic layer was washed with brine and dried over Na_2SO_4. Concentration of the dried organic layer in vacuo followed by silica gel (60–120 mesh) column chromatographic purification of the resulting residue with ethyl acetate–petroleum ether (3:7) as an eluent furnished compound **49a**. Thick oil (659 mg, 87%). $[\alpha]^{25}_D$ –31.07 (*c* 0.50 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.70 (d, *J* = 8 Hz, 3H), 0.90 (d, *J* = 8 Hz, 3H), 0.95 (d, *J* = 8 Hz, 3H), 0.90–1.15 (m, 3H), 1.41 (tt, *J* = 12 & 4 Hz, 1H), 1.45–1.55 (m, 1H), 1.68–1.85 (m, 3H), 1.95 (d, *J* = 12 Hz, 1H), 3.80 (s, 2H), 4.70 (dt, *J* = 12 & 4 Hz, 1H), 7.30 (d, *J* = 8 Hz, 1H), 7.36 (d, *J* = 8 Hz, 1H), 7.48 (t, *J* = 8 Hz, 1H), 7.68–7.78 (m, 1H), 7.80–7.90 (m, 2H), 8.09 (d, *J* = 8 Hz, 1H), 8.20 (d, *J* = 8 Hz, 1H), 9.37 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 16.1, 20.5, 21.8, 23.3, 26.2, 31.3, 34.0, 39.2, 40.5, 46.9, 75.8, 124.6, 125.2, 126.0, 126.6, 128.4, 128.6, 130.6, 130.8, 133.1, 133.8, 135.9, 146.6, 164.7, 172.5; HRMS (ESI) calcd for $C_{25}H_{31}N_2O_5$ 439.2227, found 439.2224; IR ($CHCl_3$) ν_{max} 3288, 1687, 1592, 1529, 1453, 1351 cm^{-1}.



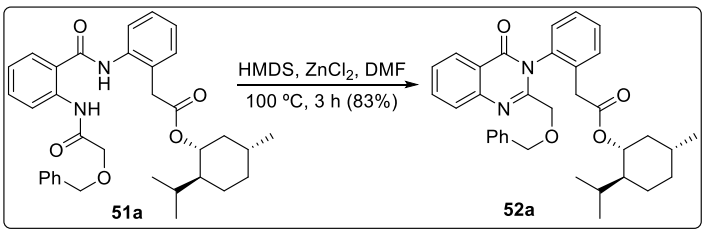
(1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl 2-(2-(2-Aminobenzamido)phenyl)acetate (50a). To a stirred solution of compound **49a** (500 mg, 1.14 mmol) in methanol (20 mL) was added activated Pd–C (50 mg, 10 wt %) and the reaction mixture was stirred under balloon pressure hydrogen atmosphere at 25 °C for 3 h. The reaction mixture was filtered to remove Pd–C and concentrated in vacuo. Silica gel (230–400 mesh) column chromatographic purification of the obtained residue using ethyl acetate–petroleum ether (2:8) as an eluent provided the pure product **50a**. Thick oil (442 mg, 95% yield). $[\alpha]^{25}_D$ –9.07 (*c* 0.50 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500



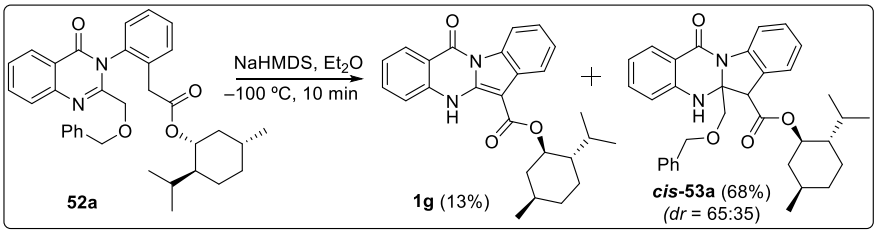
MHz) δ 0.66 (d, J = 5 Hz, 3H), 0.83 (d, J = 5 Hz, 3H), 0.85–0.90 (m, 1H), 0.89 (d, J = 5 Hz, 3H), 0.93–1.08 (m, 2H), 1.40 (tt, J = 10 & 2 Hz, 1H), 1.43–1.53 (m, 1H), 1.63–1.75 (m, 3H), 1.94 (d, J = 15 Hz, 1H), 3.66 (dd, J = 15 & 10 Hz, 2H), 4.73 (dt, J = 10 & 5 Hz, 1H), 5.76 (br s, 2H), 6.69–6.75 (m, 2H), 7.14 (t, J = 10 Hz, 1H), 7.22–7.28 (m, 2H), 7.35 (t, J = 10 Hz, 1H), 7.67 (d, J = 10 Hz, 1H), 7.91 (d, J = 10 Hz, 1H), 9.44 (br s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 16.2, 20.6, 21.9, 23.3, 26.2, 31.3, 34.1, 39.3, 40.6, 47.0, 75.7, 115.1, 116.6, 117.4, 125.2, 125.3, 126.6, 127.5, 128.2, 130.7, 132.7, 136.7, 149.7, 167.8, 172.4; HRMS (ESI) calcd for $C_{25}H_{33}N_2O_3$ 409.2486, found 409.2482; IR ($CHCl_3$) ν_{max} 3467, 3354, 1708, 1657, 1583, 1519, 1457 cm^{-1}.

(1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl 2-(2-(2-(2-(Benzyloxy)acetamido)benzamido)phenyl)acetate (51a). A solution of EDCI.HCl (110 mg, 0.58 mmol), HOBt (79 mg, 0.84 mmol), 2-(benzyloxy)acetic acid (96 mg, 0.58 mmol) in THF (10 mL) was added dropwise to a stirred suspension of amine **50a** (200 mg, 0.49 mmol) and DIPEA (0.170 mL, 0.98 mmol) in THF (10 mL) at 25 °C. The reaction mixture was refluxed for 24 h and reaction was quenched with water. The organic layer was separated and aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layer was washed with brine and dried over Na_2SO_4. Concentration of the dried organic layer in vacuo followed by silica gel (60–120 mesh) column chromatographic purification of the resulting residue with ethyl acetate–petroleum ether (3:7) as an eluent furnished compound **51a**. Gummy solid (226 mg, 83%). $[\alpha]^{25}_D$ –26.23 (*c* 0.50 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.67 (d, J = 8 Hz, 3H), 0.85 (d, J = 8 Hz, 3H), 0.85–1.10 (m, 4H), 0.90 (d, J = 8 Hz, 3H), 1.40 (tt, J = 12 & 4 Hz, 1H), 1.45–1.55 (m, 1H), 1.65–1.80 (m, 3H), 1.94 (d, J = 12 Hz, 1H), 3.68 (s, 2H), 4.16 (s, 2H), 4.71 (s, 2H), 4.74 (dt, J = 12 & 4 Hz, 1H), 7.20 (t, J = 8 Hz, 1H), 7.22 (t, J = 8 Hz, 1H), 7.26–7.35 (m, 4H), 7.38 (t, J = 8 Hz, 1H), 7.48–7.53 (m, 2H), 7.55 (t, J = 8 Hz, 1H), 7.87 (d, J = 8 Hz, 1H), 8.01 (d, J = 8 Hz, 1H), 8.77 (d, J = 8 Hz, 1H), 9.82 (br s, 1H), 12.02 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 16.2, 20.6, 21.9, 23.3, 26.2, 31.3, 34.0, 39.4, 40.6, 47.0, 70.1, 73.5, 75.9, 121.1, 121.6, 123.3, 125.0, 125.5, 126.3, 126.9, 127.7, 127.8, 128.2, 128.3, 130.7, 132.8, 136.4, 137.0, 139.3, 166.9, 168.8, 172.6; HRMS (ESI) calcd for $C_{34}H_{41}N_2O_5$ 557.3010, found 557.3009; IR ($CHCl_3$) ν_{max} 3294, 1695, 1682, 1589 cm^{-1}.

(1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl 2-(2-(2-((Benzyloxy)methyl)-4-oxoquinazolin-3(4H)-yl)phenyl)acetate (52a). To a stirred solution of compound **51a** (400 mg, 0.71 mmol) and $ZnCl_2$ (96 mg, 0.71 mmol) in DMF (10 mL) was added hexamethyldisilazane (296 μL, 1.26 mmol) at 25 ^oC under argon atmosphere. The reaction mixture was heated at 100 ^oC for 3 h and allowed to reach 25 ^oC. Reaction was quenched by adding saturated NH_4Cl (10 mL) and the reaction mixture was extracted with EtOAc (3 × 20 mL). The organic layer was washed with water, brine and dried over Na_2SO_4. After concentration in vacuo, the obtained residue was purified by silica gel (60–120 mesh) column chromatography using ethyl acetate–petroleum ether (15:85) as an eluent to provide compound **52a**. Thick oil (321 mg, 79%). $[\alpha]^{25}_D$ +24.27 (*c* 0.50 $CHCl_3$); rotameric mixture; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.55–1.02 (m, 12H), 1.15–1.95 (m, 6H), 3.43–3.53 (m, 2H), 4.20–4.32 (m, 2H), 4.37 (d, *J* = 10 Hz, 1H), 4.52 (d, *J* = 10 Hz, 1H), 4.54–4.62 (m, 1H), 7.25–7.34 (m, 6H), 7.39–7.44 (m, 1H), 7.47–7.56 (m, 3H), 7.78–7.86 (m, 2H), 8.32 (d, *J* = 10 Hz 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.1, 16.1, 16.2, 20.4, 20.7, 21.91, 21.94, 22.6, 23.2, 23.3, 26.07, 26.1, 31.2, 31.3, 31.5, 34.0, 34.1, 37.2, 37.3, 40.3, 40.7, 46.7, 48.8, 70.4, 70.5, 73.3, 74.89, 74.93, 120.99, 121.05, 127.1, 127.3, 127.79, 127.84, 128.0, 128.3, 129.1, 129.2, 129.7, 131.3, 131.4, 132.7, 132.8, 134.6, 135.36, 135.42, 137.2, 147.3, 152.9, 153.0, 161.4, 161.5, 170.0, 170.1; HRMS (ESI) calcd for $C_{34}H_{38}N_2O_4$ 539.2904, found 539.2905; IR ($CHCl_3$) ν_{max} 1728, 1684, 1602 cm^{-1}.



(1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl 12-Oxo-5,12-dihydroindolo[2,1-*b*]quinazoline-6-carboxylate (1g) and (1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl 5a-((Benzyloxy)methyl)-12-oxo-5,5a,6,12-tetrahydroindolo[2,1-*b*]quinazoline-6-carboxylate (53a). To a stirred solution of compound **52a** (300 mg, 0.55 mmol) in THF (15 mL) at –100 ^oC was added solution of NaHMDS (1 M in THF, 1.1 mL, 1.1 mmol) under argon atmosphere. After ten minute the reaction mixture was diluted by adding diethyl ether (20 mL) at –100 ^oC and allowed it to reach 25 ^oC. The organic layer was washed with water, brine and dried over Na_2SO_4. After concentration in vacuo, the

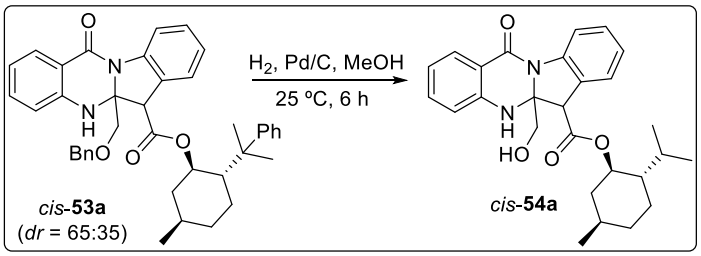


obtained residue was purified by silica gel (60–120 mesh) column chromatography using ethyl acetate–petroleum ether (1:9) as an eluent to provide compound **1g** as gummy solid (30 mg, 13%) and compound **53a** as thick oil (204 mg, 68%).

Compound 1g: $[\alpha]^{25}_{D}$ –80.82 (*c* 0.50 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.84 (d, *J* = 10 Hz, 3H), 0.95–1.05 (m, 2H), 0.98 (d, *J* = 10 Hz, 6H), 1.15–1.30 (m, 2H), 1.70 (t, *J* = 10 Hz, 1H), 1.79 (t, *J* = 10 Hz, 2H), 2.12 (quintet, *J* = 10 Hz, 1H), 2.22 (d, *J* = 15 Hz, 1H), 5.05 (dt, *J* = 10 & 2 Hz, 1H), 7.29 (d, *J* = 10 Hz, 1H), 7.34 (t, *J* = 10 Hz, 2H), 7.46 (t, *J* = 10 Hz, 1H), 7.73 (t, *J* = 10 Hz, 1H), 7.98 (d, *J* = 10 Hz, 1H), 8.42 (d, *J* = 10 Hz, 1H), 8.75 (d, *J* = 10 Hz, 1H), 10.44 (br s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 16.5, 20.9, 22.1, 23.6, 26.5, 31.6, 34.3, 41.6, 47.4, 74.2, 87.0, 114.2, 115.6, 116.2, 119.5, 122.2, 123.0, 125.6, 126.5, 128.6, 130.3, 135.2, 138.2, 144.0, 158.5, 166.9; HRMS (ESI) calcd for $C_{26}H_{28}N_2O_3Na$ 439.1992, found 439.1995; IR ($CHCl_3$) ν_{max} 3288, 1687, 1592 cm^{-1}.

Compound 53a (*dr* 65:35)**:** $[\alpha]^{25}_{D}$ –62.85 (*c* 0.50 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.45–1.65 (m, 16H), 1.65–1.80 (m, 1H), 1.95–2.03 (m, 1H), 3.28–3.35 (m, 1H), 3.75–3.80 (m, 1H), 4.40–4.58 (m, 3H), 4.60–4.72 (m, 1H), 5.29 (s, 1H), 6.72 (d, *J* = 10 Hz, 1H), 6.92–7.00 (m, 1H), 7.10–7.42 (m, 9H), 8.01 (d, *J* = 10 Hz, 1H), 8.31 (d, *J* = 10 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.1, 15.5, 16.0, 20.3, 20.6, 21.8, 21.9, 22.6, 23.0, 23.1, 25.6, 26.0, 31.2, 31.3, 31.6, 33.95, 33.99, 40.2, 40.5, 46.51, 56.54, 55.1, 55.3, 69.3, 73.3, 75.7, 76.0, 80.1, 115.5, 115.9, 116.2, 116.8, 120.0, 124.2, 124.4, 125.3, 125.4, 126.4, 126.6, 127.4, 127.5, 127.9, 128.39, 128.42, 128.5, 129.2, 133.9, 134.0, 137.2, 142.2, 144.4, 144.6, 159.7, 159.9, 168.87, 168.92; HRMS (ESI) calcd for $C_{34}H_{38}N_2O_4$ 539.2904, found 539.2902; IR ($CHCl_3$) ν_{max} 3354, 1708, 1657 cm^{-1}.

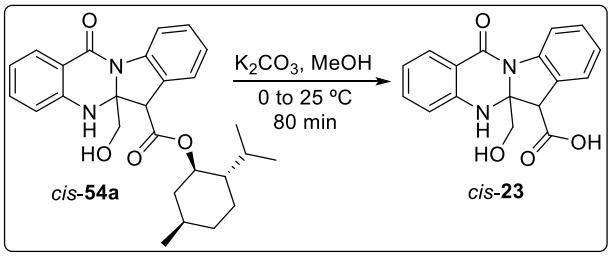
(1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl 5a-(Hydroxymethyl)-12-oxo-5,5a,6,12-tetrahydroindolo[2,1-*b*]quinazoline-6-carboxylate (54a). To a stirred solution of

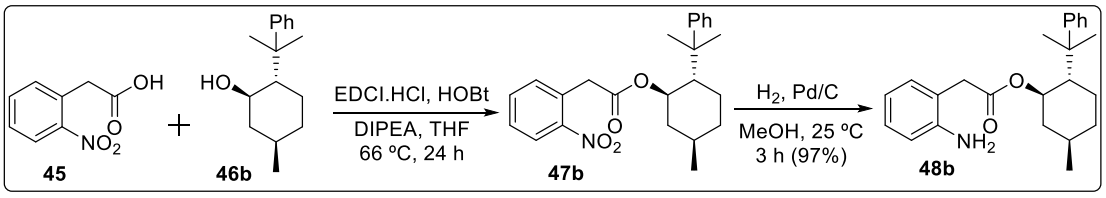


compound **53a** (150 mg, 0.27 mmol) in methanol (5 mL) was added activated Pd–C (15 mg, 10 wt %) and the reaction mixture was stirred under balloon pressure hydrogen atmosphere at 25 °C for 2 h. Reaction mixture was filtered to remove Pd–C and concentrated in vacuo. Silica gel (230–400 mesh) column chromatographic purification of the obtained residue using ethyl acetate–petroleum ether (2:8) as an eluent provided product **54a** (*dr* 65:35). Gummy solid (116 mg, 93% yield). $[\alpha]^{25}_{D}$ –40.68 (*c*

0.50 $CHCl_3$); (*dr* 65:35); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.40–2.00 (m, 18H), 2.85–3.10 (br s, 1H), 3.45 (d, *J* = 10 Hz, 1H), 3.89 (d, *J* = 10 Hz, 1H), 4.47 (d, *J* = 5 Hz, 1H), 4.67 (t, *J* = 10 Hz, 1H), 5.61 (s, 1H), 6.75–6.83 (m, 1H), 6.90–6.98 (m, 1H), 7.10–7.18 (m, 1H), 7.25–7.40 (m, 3H), 7.98 (d, *J* = 10 Hz, 1H), 8.27 (d, *J* = 10 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.1, 15.4, 16.0, 20.3, 20.6, 21.8, 21.9, 22.6, 22.9, 23.1, 25.6, 26.0, 31.2, 31.3, 31.6, 33.87, 33.90, 40.2, 40.4, 46.5, 53.9, 54.4, 62.5, 62.6, 76.0, 76.2, 80.6, 80.8, 115.9, 116.1, 116.2, 116.5, 116.80, 116.84, 120.1, 120.3, 124.3, 124.5, 125.4, 125.5, 126.2, 126.3, 128.35, 128.39, 129.3, 134.0, 134.1, 142.0, 142.1, 144.27, 144.33, 160.0, 160.1, 169.5; HRMS (ESI) calcd for $C_{27}H_{32}N_2O_4Na$ 471.2254, found 471.2252; IR ($CHCl_3$) ν_{max} 3348, 1728, 1684, 1602 cm^{-1}.

5a-(Hydroxymethyl)-12-oxo-5,5a,6,12-tetrahydroindolo[2,1-*b*]quinazoline-6-carboxylicacid (23). To a stirred solution of compound **54a** (120 mg, 0.22 mmol) in methanol (10 mL) was added catalytic amount of K_2CO_3 (5 mg) at 0 ^{o}C and the reaction mixture was allowed it to reach 25 ^{o}C over 80 minute. Reaction mixture was concentrated in vacuo and the obtained residue was three times rinsed with EtOAc (10 mL). The rinsed residue was dried under vacuum to provide crude hydroxyl acid compound **23**. The obtained product was not very stable and we could only collect the ^{1}H NMR data. ^{1}H NMR (MeOH-d_4, 500 MHz) δ 3.74 (q, *J* = 10 Hz, 2H), 4.40 (s, 1H), 6.83 (t, *J* = 10 Hz, 1H), 6.87 (d, *J* = 10 Hz, 1H), 7.12 (t, *J* = 10 Hz, 1H), 7.25 (t, *J* = 10 Hz, 1H), 7.35 (t, *J* = 10 Hz, 1H), 7.43 (d, *J* = 10 Hz, 1H), 7.84 (d, *J* = 10 Hz, 1H), 8.16 (d, *J* = 10 Hz, 1H).

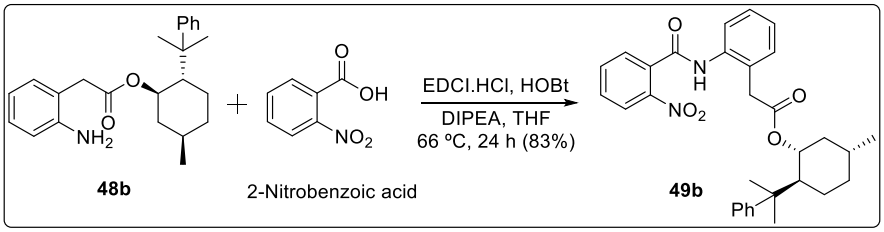




(1*R*,2*S*,5*R*)-5-Methyl-2-(2-phenylpropan-2-yl)cyclohexyl 2-(2-Aminophenyl)acetate (48b). A solution of EDCI.HCl (527 mg, 2.76 mmol), HOBt (372 mg, 2.76 mmol), 2-(2-nitrophenyl)acetic acid **45** (500 mg, 2.76 mmol) in THF (10 mL) was added dropwise to a stirred suspension of (−)-8-phenylmenthol (**46b**, 640 mg, 2.76 mmol) and DIPEA (0.481 mL, 2.76 mmol) in THF (10 mL) at 25 ^{o}C. The reaction mixture was refluxed for 24 h and reaction was quenched with water. The organic layer was separated and aqueous

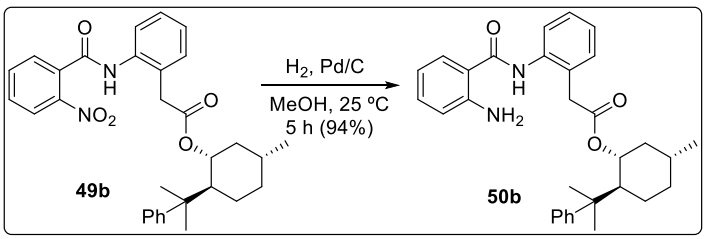
layer was extracted with EtOAc (3 × 10 mL). The combined organic layer was washed with brine and dried over Na_2SO_4. Concentration of the dried organic layer in vacuo followed by silica gel (60–120 mesh) column chromatographic purification of the resulting residue with ethyl acetate–petroleum ether (2:8) as an eluent furnished compound **47b** as thick oil. Compound **47b** was used as such for the next step due to purification issues. To a stirred solution of compound **47b** (600 mg, 1.51 mmol) in methanol (20 mL) was added activated Pd–C (60 mg, 10 wt %) and the reaction mixture was stirred under balloon pressure hydrogen atmosphere at 25°C for 3 h. The reaction mixture was filtered to remove Pd–C and concentrated in vacuo. The obtained residue purified by silica gel (230–400 mesh) column chromatography using ethyl acetate–petroleum ether (2:8) as an eluent provided pure product compound **48b**. Thick oil (537 mg, 97% yield). $[\alpha]^{25}_{D}$ –7.72 (*c* 0.50 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.85 (d, *J* = 10 Hz, 3H), 0.85–0.95 (m, 2H), 1.14 (dq, *J* = 15 & 5 Hz, 1H), 1.23 (s, 3H), 1.32 (s, 3H), 1.38–1.50 (m, 1H), 1.66 (td, *J* = 10 & 5 Hz, 1H), 1.78 (dd, *J* = 15 & 5 Hz, 2H), 2.07 (dt, *J* = 10 & 5 Hz, 1H), 2.86 (d, *J* = 15 Hz, 1H), 3.08 (d, *J* = 15 Hz, 1H), 3.92 (br s, 2H), 4.80 (dt, *J* = 10 & 5 Hz, 1H), 6.67 (d, *J* = 10 Hz, 1H), 6.70 (t, *J* = 10 Hz, 1H), 6.91 (d, *J* = 10 Hz, 1H), 7.06 (t, *J* = 10 Hz, 1H), 7.17–7.23 (m, 1H), 7.31–7.37 (m, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 21.7, 24.4, 26.4, 28.4, 31.2, 34.5, 38.4, 39.6, 41.3, 50.3, 74.9, 116.2, 118.6, 119.4, 125.2, 125.4, 128.0, 128.2, 131.0, 145.4, 151.6, 171.0; HRMS (ESI) calcd for $C_{24}H_{32}NO_2$ 366.2428, found 366.2424; IR ($CHCl_3$) ν_{max} 3442, 3373, 1715, 1630 cm^{-1}.

(1*R*,2*S*,5*R*)-5-Methyl-2-(2-phenylpropan-2-yl)cyclohexyl 2-(2-(2-Nitrobenzamido)phenyl)acetate (49b). A solution of EDCI.HCl (313 mg, 1.64 mmol), HOBt (221 mg, 1.64 mmol), 2-nitrobenzoic acid (273 mg, 1.64 mmol) in THF (20 mL) was added dropwise to a stirred suspension of amine **48b** (500 mg, 1.37 mmol) and DIPEA (0.477 mL, 2.73 mmol) in THF (20 mL) at 25 °C. The reaction mixture was refluxed for 24 h and reaction was quenched with water. The organic layer was separated and aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic layer was washed with brine and dried over Na_2SO_4. Concentration of the dried organic layer in vacuo followed by silica gel (60–120 mesh)



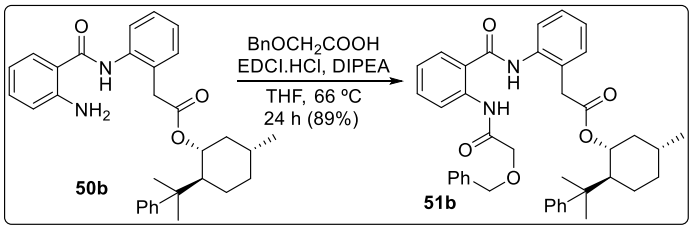
column chromatographic purification of the resulting residue with ethyl acetate–petroleum ether (3:7) as an eluent furnished compound **49b**. Thick oil (584 mg, 83%). $[\alpha]^{25}_{D}$ –7.10 (*c* 0.50 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.83 (d, *J* = 8 Hz, 3H), 0.84–0.93 (m, 2H), 1.10 (dq, *J* = 12 & 4 Hz, 1H), 1.19 (s, 3H), 1.24 (s, 3H), 1.26–1.31 (m, 1H), 1.31–1.43 (m, 1H), 1.66–1.71 (m, 1H), 1.77 (dd, *J* = 12 & 4 Hz, 1H), 2.20 (dt, *J* = 12 & 4 Hz, 1H), 2.96 (d, *J* = 16 Hz, 1H), 3.21 (d, *J* = 16 Hz, 1H), 4.69 (dt, *J* = 12 & 4 Hz, 1H), 7.05 (d, *J* = 8 Hz, 1H), 7.12–7.20 (m, 2H), 7.20–7.26 (m, 2H), 7.26–7.33 (m, 2H), 7.37 (t, *J* = 8 Hz, 1H), 7.68 (t, *J* = 8 Hz, 1H), 7.72–7.83 (m, 2H), 8.00 (d, *J* = 8 Hz, 1H), 8.16 (d, *J* = 8 Hz, 1H), 9.22 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.7, 24.4, 26.4, 28.5, 31.2, 34.4, 38.8, 39.5, 41.2, 50.2, 75.8, 124.7, 125.0, 125.29, 125.33, 125.8, 126.2, 128.0, 128.4, 128.8, 130.7, 130.9, 133.8, 136.0, 151.2, 164.6, 172.3; HRMS (ESI) calcd for $C_{31}H_{34}N_2O_5Na$ 537.2360, found 537.2369; IR ($CHCl_3$) ν_{max} 3294, 1715, 1681, 1591, 1531, 1352 cm^{-1}.

(1*R*,2*S*,5*R*)-5-Methyl-2-(2-phenylpropan-2-yl)cyclohexyl 2-(2-(2-Aminobenzamido)phenyl)acetate (50b). To a stirred solution of compound **49b** (500 mg, 0.97 mmol) in methanol (20 mL) was added activated Pd–C (50 mg, 10 wt %) and the reaction mixture was stirred under balloon pressure hydrogen atmosphere at 25 ^{o}C for 5 h. The reaction mixture was filtered to remove Pd–C and concentrated in vacuo. Silica gel (230–400 mesh) column chromatographic purification of the obtained residue using ethyl acetate–petroleum ether (2:8) as an eluent provided pure product compound **50b**. Thick oil (442 mg, 94% yield). $[\alpha]^{25}_{D}$ –51.16 (*c* 0.50 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.90 (d, *J* = 8 Hz, 3H), 0.90–1.05 (m, 2H), 1.19 (dt, *J* = 12 & 4 Hz, 1H), 1.23 (s, 3H), 1.32 (s, 3H), 1.43–1.58 (m, 1H), 1.73 (d, *J* = 12 Hz, 1H), 1.81 (d, *J* = 12 Hz, 1H), 1.88 (dd, *J* = 12 & 4 Hz, 1H), 2.13 (dt, *J* = 12 & 4 Hz, 1H), 2.90 (d, *J* = 16 Hz, 1H), 3.07 (d, *J* = 16 Hz, 1H), 4.89 (dt, *J* = 12 & 4 Hz, 1H), 6.79 (d, *J* = 8 Hz, 1H), 6.83 (t, *J* = 8 Hz, 1H), 7.06–7.20 (m, 3H), 7.23–7.32 (m, 4H), 7.34 (t, *J* = 8 Hz, 1H), 7.36 (t, *J* = 8 Hz, 1H), 7.70 (d, *J* = 8 Hz, 1H), 7.89 (d, *J* = 8 Hz, 3H), 9.31 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.7, 23.7, 26.3, 29.1, 31.2, 34.4, 38.7, 39.5, 41.4, 50.1, 75.4, 115.4, 116.6, 117.4, 125.1, 125.2, 125.3, 126.4, 127.6, 128.0, 130.8, 132.7, 136.7, 149.6, 151.3, 167.8, 172.0; HRMS (ESI) calcd for $C_{31}H_{37}N_2O_3$ 485.2799, found 485.2801; IR



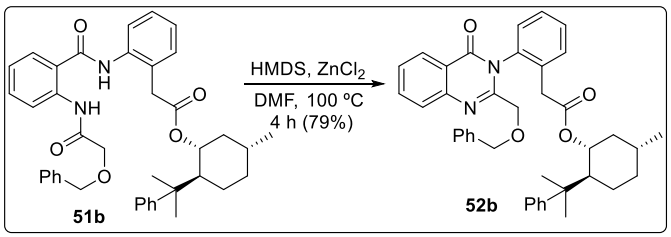
($CHCl_3$) ν_{max} 3477, 3356, 1703, 1658, 1613 cm^{-1}.

(1*R*,2*S*,5*R*)-5-Methyl-2-(2-phenylpropan-2-yl)cyclohexyl 2-(2-(2-(2-(Benzyloxy)acetamido)benzamido)phenyl)acetate (51b). A solution of EDCI.HCl (202



mg, 1.06 mmol), 2-(benzyloxy)acetic acid (175 mg, 1.06 mmol) in THF (15 mL) was added dropwise to a stirred suspension of amine **50b** (430 mg, 0.88 mmol) and DIPEA (0.309 mL, 1.77 mmol) in THF (15 mL) at 25 °C. The reaction mixture was refluxed for 24 h and reaction was quenched with water. The organic layer was separated and aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic layer was washed with brine and dried over Na_2SO_4. Concentration of the dried organic layer in vacuo followed by silica gel (60–120 mesh) column chromatographic purification of the resulting residue with ethyl acetate–petroleum ether (3:7) as an eluent furnished compound **51b**. Thick oil (499 mg, 89%). $[\alpha]^{25}_D$ –31.34 (*c* 0.50 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.89 (d, *J* = 10 Hz, 3H), 0.90–1.03 (m, 2H), 1.20 (dd, *J* = 10 & 2 Hz, 1H), 1.24 (s, 3H), 1.32 (s, 3H), 1.43–1.55 (m, 1H), 1.72 (d, *J* = 10 Hz, 1H), 1.78 (d, *J* = 10 Hz, 1H), 1.87 (dd, *J* = 15 & 5 Hz, 1H), 2.12 (dt, *J* = 10 & 2 Hz, 1H), 2.91 (d, *J* = 15 Hz, 1H), 3.12 (d, *J* = 15 Hz, 1H), 4.20 (s, 2H), 4.75 (s, 2H), 4.86 (dt, *J* = 10 & 5 Hz, 1H), 7.08 (d, *J* = 10 Hz, 1H), 7.13–7.20 (m, 2H), 7.25–7.35 (m, 8H), 7.37 (t, *J* = 10 Hz, 1H), 7.50–7.80 (m, 2H), 7.62 (t, *J* = 10 Hz, 1H), 7.87 (d, *J* = 10 Hz, 1H), 7.99 (d, *J* = 10 Hz, 1H), 8.82 (d, *J* = 10 Hz, 1H), 9.69 (br s, 1H), 12.04 (br s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 21.7, 23.9, 26.3, 29.0, 31.2, 34.4, 38.9, 39.6, 41.4, 50.2, 70.2, 73.6, 75.7, 121.2, 121.7, 123.3, 124.9, 125.27, 125.33, 125.4, 126.0, 127.1, 127.79, 127.84, 128.0, 128.1, 128.4, 130.9, 132.8, 137.0, 139.3, 151.3, 166.9, 168.9, 172.3; HRMS (ESI) calcd for $C_{40}H_{45}N_2O_5$ 633.3323, found 633.3321; IR ($CHCl_3$) ν_{max} 3290, 1688, 1587 cm^{-1}.

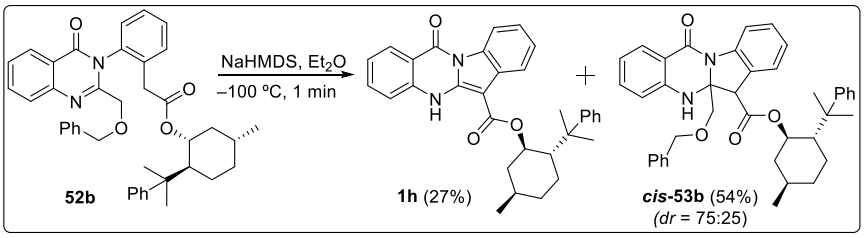
(1*R*,2*S*,5*R*)-5-Methyl-2-(2-phenylpropan-2-yl)cyclohexyl 2-(2-(2-((Benzyloxy)methyl)-4-oxoquinazolin-3(4*H*)-yl)phenyl)acetate (52b). To a stirred



solution of compound **51b** (400 mg, 0.63 mmol) and $ZnCl_2$ (85 mg, 0.63 mmol) in DMF (10 mL) was added hexamethyldisilazane (264 μL, 1.26 mmol) at 25 °C under argon

atmosphere. The reaction mixture was heated at 100 °C for 4 h and allowed to reach 25 °C. Reaction was quenched by adding saturated NH_4Cl (20 mL) and the reaction mixture was extracted with EtOAc (3 × 20 mL). The organic layer was washed with water, brine and dried over Na_2SO_4. After concentration in vacuo, the obtained residue was purified by silica gel (60–120 mesh) column chromatography using ethyl acetate–petroleum ether (15:85) as an eluent to provide compound **52b**. Thick oil (307 mg, 79%). $[\alpha]^{25}_D$ +10.61 (*c* 0.50 $CHCl_3$) ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.45–1.50 (m, 12H), 1.55–2.00 (m, 5H), 2.74 (dd, *J* = 28 & 16 Hz, 1H), 2.83 (dd, *J* = 40 & 16 Hz, 1H), 4.10–4.76 (m, 5H), 6.80–7.60 (m, 15H), 7.80–7.95 (m, 2H), 8.30–8.40 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.7, 21.8, 23.4, 23.9, 26.1, 26.3, 28.1, 29.1, 31.1, 31.2, 34.3, 34.4, 36.6, 36.7, 39.3, 39.4, 41.1, 41.3, 49.9, 50.0, 65.3, 70.4, 70.5, 73.20, 73.24, 74.4, 75.0, 121.1, 121.2, 124.9, 125.0, 125.2, 126.95, 127.0, 127.3, 127.4, 127.6, 127.8, 127.9, 127.98, 128.03, 128.2, 128.25, 128.33, 128.5, 129.0, 129.1, 129.7, 131.3, 131.4, 132.6, 134.6, 134.7, 135.3, 135.4, 137.29, 137.33, 147.3, 147.4, 151.57, 151.63, 152.9, 153.1, 161.3, 161.5, 169.8; HRMS (ESI) calcd for $C_{40}H_{43}N_2O_4$ 615.3217, found 615.3212; IR ($CHCl_3$) ν_{max} 1727, 1687, 1608 cm^{-1}.

(1*R*,2*S*,5*R*)-5-Methyl-2-(2-phenylpropan-2-yl)cyclohexyl 12-Oxo-5,12-dihydroindolo[2,1-*b*]quinazoline-6-carboxylate (1h) and (1*R*,2*S*,5*R*)-5-Methyl-2-(2-phenylpropan-2-yl)cyclohexyl 5a-((Benzyloxy)methyl)-12-oxo-5,5a,6,12-tetrahydroindolo[2,1-*b*]quinazoline-6-carboxylate (53b). To a stirred solution of



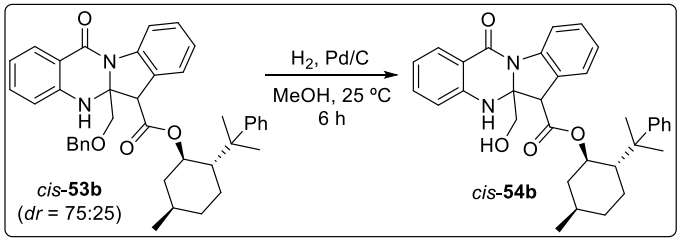
compound **52b** (300 mg, 0.48 mmol) in THF (15 mL) at –100 °C was added solution of NaHMDS (1 M in THF, 1.95 mL, 1.95 mmol) under argon atmosphere. After one minute the reaction mixture was diluted by adding diethyl ether (20 mL) at –100 °C and allowed it to reach 25 °C. The organic layer was washed with water, brine and dried over Na_2SO_4. After concentration in vacuo, the obtained residue was purified by silica gel (60–120 mesh) column chromatography using ethyl acetate–petroleum ether (1:9) as an eluent to provide compound **1h** as gummy solid (64 mg, 27%) and compound **53b** as thick oil (162 mg, 54%).

Compound 1h: $[\alpha]^{25}_D$ –62.32 (*c* 0.50 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.87–0.98 (m, 1H), 0.92 (d, *J* = 10 Hz, 3H), 1.07–1.20 (m, 1H), 1.20–1.40 (m, 5H), 1.43 (s, 3H),

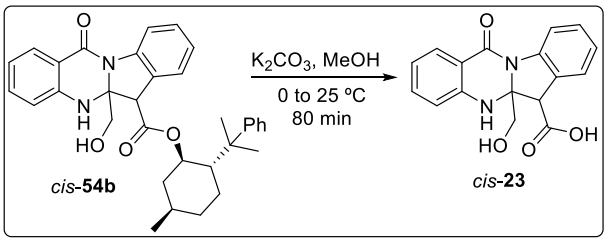
1.50–1.70 (m, 2H), 2.03–2.09 (m, 1H), 2.22 (dt, *J* = 10 & 2Hz, 1H), 5.31 (br s, 1H), 6.95 (br s, 1H), 7.14 (br s, 2H), 7.25–7.37 (m, 5H), 7.41 (t, *J* = 5 Hz, 1H), 7.74 (t, *J* = 10 Hz, 2H), 8.42 (d, *J* = 10 Hz, 1H), 8.72 (d, *J* = 10 Hz, 1H), 10.51 (br s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 21.8, 25.2, 27.2, 28.6, 31.6, 34.6, 40.3, 42.8, 51.1, 74.1, 87.4, 114.3, 115.7, 116.0, 119.8, 122.1, 122.9, 125.2, 125.5, 126.2, 127.9 (2C), 128.6, 130.2, 135.2, 138.2, 144.1, 150.7, 158.5, 166.6; HRMS (ESI) calcd for $C_{32}H_{33}N_2O_3$ 493.2486, found 493.2429; IR ($CHCl_3$) ν_{max} 3327, 1718, 1658, 1610 cm^{-1}.

Compound 53b (*dr* 75:25)**:** $[\alpha]^{25}_D$ –24.27 (*c* 0.50 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.55–1.65 (m, 15H), 1.85–2.10 (m, 2H), 3.18 (d, *J* = 10 Hz, 0.80H), 3.30 (d, *J* = 10 Hz, 0.20H), 3.65 (d, *J* = 10 Hz, 0.80H), 3.73 (d, *J* = 10 Hz, 0.20H), 3.77 (s, 0.80H), 3.80 (s, 0.20H), 4.24–4.52 (m, 2H), 4.82 (dt, *J* = 10 & 5Hz, 0.25H), 4.91 (dt, *J* = 10 & 5Hz, 0.75H), 5.12 (s, 0.80H), 5.32 (s, 0.20H), 6.63 (d, *J* = 10 Hz, 0.75H), 6.71 (d, *J* = 10 Hz, 0.25H), 6.87–6.97 (m, 1H), 7.03–7.40 (m, 14H), 7.93 (d, *J* = 10 Hz, 0.75H), 8.00 (d, *J* = 10 Hz, 0.25H), 8.26 (d, *J* = 10 Hz, 0.75H), 8.30 (d, *J* = 10 Hz, 0.25H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.1, 21.8, 22.7, 25.7, 26.7, 26.8, 29.7, 31.3, 31.9, 34.0, 34.4, 39.8, 41.3, 42.0, 50.0, 50.3, 53.9, 54.8, 69.7, 73.3, 76.1, 79.9, 115.0, 116.2, 116.7, 120.0, 124.3, 125.0, 125.5, 125.9, 127.3, 127.8, 127.9, 128.4, 128.5, 129.2, 134.0, 137.4, 142.2, 144.3, 151.2, 159.8, 168.5; HRMS (ESI) calcd for $C_{40}H_{43}N_2O_4$ 615.3217, found 615.3226; IR ($CHCl_3$) ν_{max} 3299, 1696, 1622 cm^{-1}.

(1*R*,2*S*,5*R*)-5-Methyl-2-(2-phenylpropan-2-yl)cyclohexyl 5a-(Hydroxymethyl)-12-oxo-5,5a,6,12-tetrahydroindolo[2,1-*b*]quinazoline-6-carboxylate (54b). To a stirred solution of compound **53b** (150 mg, 0.24 mmol) in methanol (5 mL) was added activated Pd–C (15 mg, 10 wt %) and the reaction mixture was stirred under balloon pressure hydrogen atmosphere at 25 ^{o}C for 6 h. The reaction mixture was filtered to remove Pd–C and concentrated in vacuo to provide crude hydroxy ester compound **54b** as gummy solid (127 mg). It was immediately used for the next step without any purification.



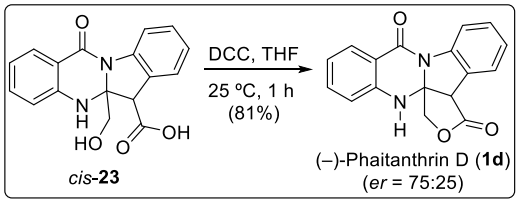
5a-(Hydroxymethyl)-12-oxo-5,5a,6,12-tetrahydroindolo[2,1-*b*]quinazoline-6-carboxylicacid (23). To a stirred solution of compound **54b** (120 mg, 0.22 mmol) in methanol (10 mL) was added catalytic amount of K_2CO_3 (5 mg) at 0 ^{o}C and the reaction



mixture was allowed it to reach 25 ^{o}C over 80 minute. Reaction mixture was concentrated in vacuo and the obtained residue was three times rinsed with EtOAc (10 mL). The rinsed residue was dried under vacuum to provide crude hydroxyl acid compound **23**.

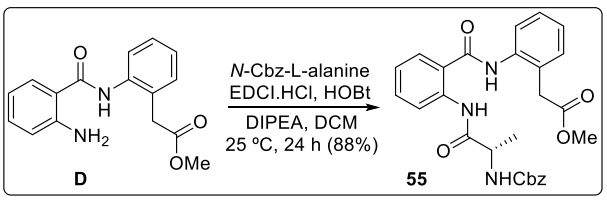
White gummy solid; (65 mg). The obtained product was not very stable and we could only collect the ^{1}H NMR data.

1*H*-Furo[3',4':2,3]indolo[2,1-*b*]quinazoline-3,9(3a*H*,14*H*)-dione (Phaitanthrin D, 1d).



To a stirred solution of crude hydroxyl acid compound **23** (60 mg, 0.19 mmol) in THF (5 mL) was added DCC (39 mg, 0.19 mmol) under argon atmosphere. The reaction mixture was stirred at 25 ^{o}C for 1 h and reaction was quenched with water; The organic layer was separated and aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic layer was washed with brine and dried over Na_2SO_4. Concentration of the dried organic layer in vacuo followed by silica gel (60–120 mesh) column chromatographic purification of the resulting residue with ethyl acetate–petroleum ether (2:8) as an eluent provided pure product (–)-phaitanthrin D (**1d**).

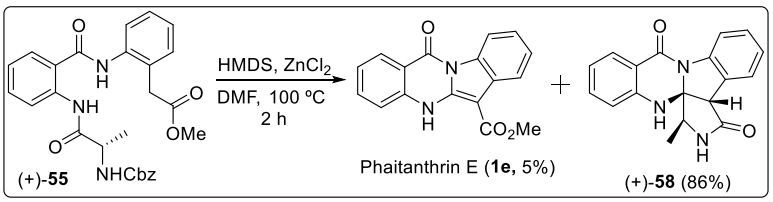
Methyl (*S*)-2-(2-(2-(2-(((Benzyloxy)carbonyl)amino)propanamido) benzamido) phenyl)acetate (55). A solution of EDCI.HCl (320 mg, 1.69 mmol), HOBt (226 mg, 1.69 mmol) *N*-Cbz-L-alanine (376 mg, 1.69 mmol) in DCM (10 mL)



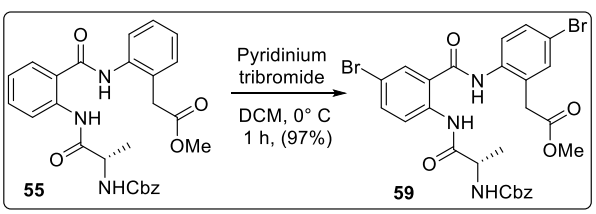
was added dropwise to a stirred suspension of amine **D** (400 mg, 1.40 mmol) and DIPEA (0.488 mL, 2.81 mmol) in DCM (10 mL) at 25 ^{o}C. The reaction mixture was stirred at 25 ^{o}C for 24 h and reaction was quenched with water. The organic layer was separated and aqueous layer was extracted with DCM (3 × 10 mL). The combined organic layer was washed with brine and dried over Na_2SO_4. Concentration of the dried organic layer in vacuo followed by silica gel (60–120 mesh) column chromatographic purification of the resulting residue with ethyl acetate–petroleum ether (3:7) as an eluent furnished compound **55**. Gummy solid (606 mg, 88%). $[\alpha]^{25}_{D}$ –2.38 (*c* 0.50 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.49 (d, *J* = 8 Hz, 3H), 3.69 (s, 2H), 3.74 (s, 3H), 4.40 (quintet, *J* = 8

Hz, 1H), 5.00 (d, *J* = 12 Hz, 1H), 5.11 (d, *J* = 12 Hz, 1H), 5.57 (d, *J* = 8 Hz, 1H), 7.18 (t, *J* = 8 Hz, 1H), 7.20 (t, *J* = 8 Hz, 1H), 7.26 (d, *J* = 8 Hz, 1H), 7.26–7.37 (m, 6H), 7.53 (t, *J* = 8 Hz, 1H), 7.85 (d, *J* = 8 Hz, 2H), 8.66 (d, *J* = 8 Hz, 1H), 9.78 (s, 1H), 11.74 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.0, 38.7, 51.9, 52.7, 66.9, 120.3, 121.5, 123.3, 125.5, 126.0, 126.6, 126.9, 128.0, 128.37 (2C), 128.43, 131.0, 133.0, 136.1, 136.3, 139.9, 155.7, 167.5, 171.2, 173.5; HRMS (ESI) calcd for $C_{27}H_{27}N_3O_6Na$ 512.1792, found 512.1791; IR ($CHCl_3$) ν_{max} 3299, 1734, 1697, 1636 cm^{-1}.

(1*S*,3a*S*,14a*R*)-1-Methyl-1,2-dihydropyrrolo[3',4':2,3]indolo[2,1-*b*]quinazoline-3,9(3a*H*,14*H*)-dione (58). To a stirred solution of compound (+)-**55** (150 mg, 0.30 mmol) and $ZnCl_2$ (44 mg, 0.30 mmol) in DMF (5 mL) was added hexamethyldisilazane (127 µL, 0.61 mmol) at 25 °C under argon atmosphere. The reaction mixture was heated at 100 °C for 2 h and allowed to reach 25 °C. Reaction was quenched by adding saturated NH_4Cl (10 mL) and extracted with EtOAc (3 × 10 mL). The organic layer was washed with water, brine and dried over Na_2SO_4. After concentration in vacuo, the obtained residue was purified by silica gel (60–120 mesh) column chromatography using ethyl acetate–petroleum ether (9:1) as an eluent to provide phaitanthrin E (**1e**) as white amorphous solid (4 mg, 5%) and then compound **58** as gummy solid (80 mg, 86%, *dr* 96:4). Major isomer: $[\alpha]^{25}_D$ +88.84 (*c* 0.50 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.13 (d, *J* = 5 Hz, 3H), 3.92 (q, *J* = 5 Hz, 1H), 4.13 (s, 1H), 5.70 (s, 1H), 5.88 (s, 1H), 6.84 (d, *J* = 10 Hz, 1H), 6.95 (t, *J* = 10 Hz, 1H), 7.16 (t, *J* = 10 Hz, 1H), 7.39 (t, *J* = 10 Hz, 2H), 7.52 (d, *J* = 10 Hz, 1H), 8.02 (d, *J* = 10 Hz, 1H), 8.31 (d, *J* = 10 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 16.3, 57.4, 61.4, 84.2, 114.7, 116.3, 117.2, 120.1, 124.1, 124.6, 125.1, 128.7, 129.7, 134.5, 141.2, 145.0, 159.7, 172.4; HRMS (ESI) calcd for $C_{18}H_{16}N_3O_2$ 306.1237, found 306.1235; IR (Nujol) ν_{max} 3286, 1707, 1646 cm^{-1}.

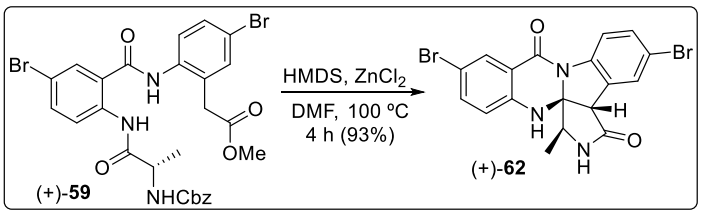


Methyl (*S*)-2-(2-(2-(2-(((Benzyloxy)carbonyl)amino)propanamido)-5-bromobenzamido)-5-bromophenyl)acetate (59). To a stirred solution of compound **55** (200 mg, 0.30 mmol) in DCM was added pyridinium tribromide (90%, 304 mg, 0.85 mmol) at 0 °C. The reaction mixture was stirred for 1 h

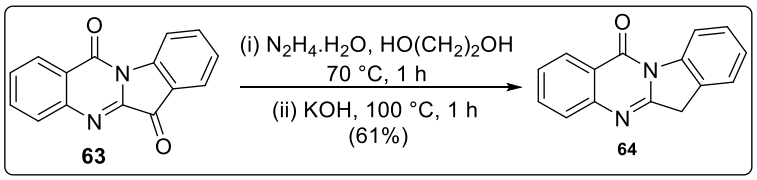


and reaction was quenched by adding saturated solution of $Na_2S_2O_3 \cdot 5H_2O$ (15 mL). The organic layer was separated and aqueous layer was extracted with DCM (3 × 20 mL). The combined organic layer was washed with water, brine and dried over Na_2SO_4. After concentration in vacuo, the obtained residue was purified by silica gel (60–120 mesh) column chromatography using ethyl acetate–petroleum ether (3:7) as an eluent to provide the desired compound **59**. Gummy solid (256 mg, 97%). $[\alpha]^{25}_D$ –0.77 (*c* 0.50 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.50 (d, *J* = 5 Hz, 3H), 3.67 (s, 2H), 3.81 (s, 3H), 4.39 (quintet, *J* = 5 Hz, 1H), 5.01 (d, *J* = 15 Hz, 1H), 5.11 (d, *J* = 15 Hz, 1H), 5.44 (d, *J* = 5 Hz, 1H), 7.28–7.37 (m, 5H), 7.40 (d, *J* = 10 Hz, 1H), 7.42 (d, *J* = 5 Hz, 1H), 7.64 (dd, *J* = 10 & 5 Hz, 1H), 7.73 (d, *J* = 10 Hz, 1H), 7.94 (d, *J* = 5 Hz, 1H), 8.59 (d, *J* = 10 Hz, 1H), 9.78 (s, 1H), 11.60 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 18.8, 38.5, 51.9, 53.1, 67.1, 115.8, 119.0, 121.7, 123.2, 126.7, 128.0, 128.1, 128.5 (2C), 129.8, 131.5, 133.8, 135.0, 135.9, 136.1, 138.9, 155.8, 166.1, 171.3, 172.9; HRMS (ESI) calcd for $C_{27}H_{25}N_3O_6Br_2$ 648.0162, found 648.0158; IR ($CHCl_3$) ν_{max} 3411, 1707, 1657, 1611, 670 cm^{-1}.

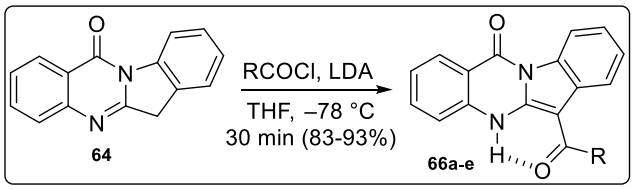
(1*S*,3a*S*,14a*R*)-5,11-Dibromo-1-methyl-1,2-dihydropyrrolo[3',4':2,3]indolo[2,1-*b*]quinazoline-3,9(3a*H*,14*H*)-dione (62). To a stirred solution of compound **59** (150 mg, 0.23 mmol) and $ZnCl_2$ (31 mg, 0.23 mmol) in DMF (5 mL) was added hexamethyldisilazane (96 µL, 0.46 mmol) at 25 °C under argon atmosphere. The reaction mixture was heated at 100 °C for 4 h and allowed to reach 25 °C. Reaction was quenched by adding saturated NH_4Cl (15 mL) and extracted with EtOAc (3 × 10 mL). The organic layer was washed with water, brine and dried over Na_2SO_4. After concentration in vacuo, the obtained residue was purified by silica gel (60–120 mesh) column chromatography using ethyl acetate–petroleum ether (9:1) as an eluent to provide compound **62**. White solid (99 mg, 93%, *dr* 98:2). Major isomer: Mp 200 °C (decomposition); $[\alpha]^{25}_D$ +58.19 (*c* 0.50 $CHCl_3$); ^{1}H NMR (Acetone-d_6, 500 MHz) δ 1.16 (d, *J* = 10 Hz, 3H), 3.98 (q, *J* = 10 Hz, 1H), 4.13 (s, 1H), 6.99 (d, *J* = 10 Hz, 1H), 7.12 (br s, 1H), 7.56 (dd, *J* = 10 & 5 Hz, 1H), 7.57 (dd, *J* = 10 & 5 Hz, 1H), 7.59 (d, *J* = 5 Hz, 1H), 7.65 (br s, 1H), 7.97 (d, *J* = 5 Hz, 1H), 8.16 (d, *J* = 10 Hz, 1H); ^{13}C NMR (Acetone-d_6, 125 MHz) δ 17.5, 57.8, 63.0, 85.9, 111.5, 117.8, 118.4, 118.6, 119.4, 128.9, 129.8, 131.7, 133.3, 138.4, 142.0, 147.0, 159.0, 171.7; HRMS (ESI) calcd for $C_{18}H_{14}N_3O_2Br_2$ 463.9427, found 463.9425; IR ($CHCl_3$) ν_{max} 3377, 1711, 1597, 670 cm^{-1}.



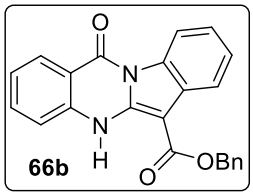
Indolo[2,1-b]quinazolin-12(6H)-one (64). To a stirred solution of tryptanthrin (**63**, 1.20 g, 4.83 mmol) in ethylene glycol (10 mL) was added hydrazine hydrate (1.20 mL, 4.83 mmol) and the reaction mixture was heated at 70 °C for 1 h. To the reaction mixture was added KOH (539 mg, 9.62 mmol) and then it was heated at 100 °C for 1 h. The reaction mixture was allowed to cool to room temperature and diluted with water. The total reaction mixture was extracted with ethyl acetate (3 × 20 mL) and the organic layer was washed with water, brine and dried over Na_2SO_4. Concentration of the dried organic layer in vacuo followed by rapid silica gel (60−120 mesh) column chromatographic purification of the obtained residue using ethyl acetate:petroleum ether (7:3) as an eluent gave product **64**. White solid; 690 mg (61%); Mp 214–216 °C; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 4.25 (s, 2H), 7.27–7.60 (m, 4H), 7.65–7.85 (m, 2H), 8.43 (d, J = 8 Hz, 1H), 8.61 (d, J = 8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 35.9, 117.4, 121.1, 124.5, 126.4 (2 C), 126.8, 126.88, 126.94, 128.5, 134.4, 141.0, 147.2, 157.4, 160.1; MS (ESI): m/z = 257 $[M+Na]^+$; IR ($CHCl_3$ νmax): 1728, 1686 cm^{-1}.



General Procedure for Acylation of Indoloquinazolinone 64. To a stirred solution of indoloquinazolinone **64** (0.50 mmol) in THF (2 mL) was added freshly prepared solution of LDA in THF (1 M, 0.60 mL, 0.60 mmol) at −78 °C under argon atmosphere. The reaction mixture was further stirred for 30 min at same temperature and acyl chloride (0.60 mmol) was added in a drop wise fashion. The reaction was quenched after 30 min with saturated aq NH_4Cl solution (1 mL). The reaction mixture was concentrated in vacuo and the obtained residue was directly purified by silica gel (60−120 mesh) column chromatography using ethyl acetate:petroleum ether (6:4) as an eluent to obtain the desired product **66**.



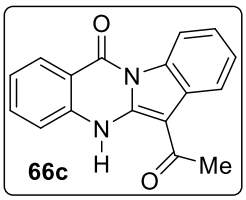
Benzyl 12-Oxo-5,12-dihydroindolo[2,1-*b*]quinazoline-6-carboxylate (66b):



Gummy white solid; 163 mg (89%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.49 (s, 2H), 7.22–7.46 (m, 7H), 7.53 (d, J = 10 Hz, 2H), 7.71 (t, J = 10 Hz, 1H), 7.98 (d, J = 10 Hz, 1H), 8.40 (d, J = 10 Hz, 1H), 8.72 (d, J = 10 Hz, 1H), 10.34 (br s, 1H); ^{13}C NMR ($CDCl_3$,125 MHz) δ

65.9, 86.6, 114.3, 115.6, 116.2, 119.5, 122.4, 123.1, 125.7, 126.3, 127.9, 128.2, 128.6, 128.7, 130.3, 135.2, 136.5, 138.1, 144.3, 158.4, 166.6; HRMS (ESI): calcd for $C_{23}H_{17}N_2O_3$ 369.1234; found: 369.1227; IR ($CHCl_3$ νmax): 3021, 1740, 1684, 1627 cm^{-1}.

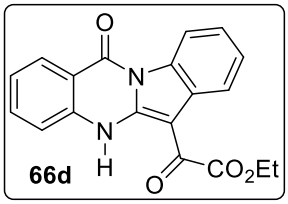
6-Acetylindolo[2,1-b]quinazolin-12(5H)-one (66c): Gummy white solid; 120 mg (87%).



66c

^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.74 (s, 3H), 7.36 (t, *J* = 8 Hz, 1H), 7.37 (d, *J* = 8 Hz, 1H), 7.39 (t, *J* = 8 Hz, 1H), 7.48 (t, J = 8 Hz, 1H), 7.76 (t, *J* = 8 Hz, 1H), 7.80 (d, *J* = 8 Hz, 1H), 8.43 (d, *J* = 8 Hz, 1H), 8.80 (d, *J* = 8 Hz, 1H), 11.80 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 30.0, 97.5, 115.2, 116.3, 116.8, 118.4, 122.5, 123.6, 125.8, 126.4, 128.6, 130.9, 135.3, 138.0, 144.6, 158.4, 194.2; HRMS (ESI): calcd for $C_{17}H_{13}N_2O_2$ 277.0972; found: 277.0968; IR ($CHCl_3$ νmax): 3022, 1687, 1630 cm^{-1}.

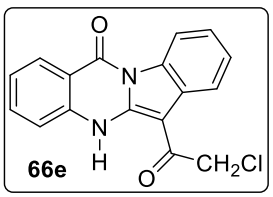
Ethyl 2-Oxo-2-(12-oxo-5,12-dihydroindolo[2,1-b]quinazolin-6-yl)acetate (66d):



66d

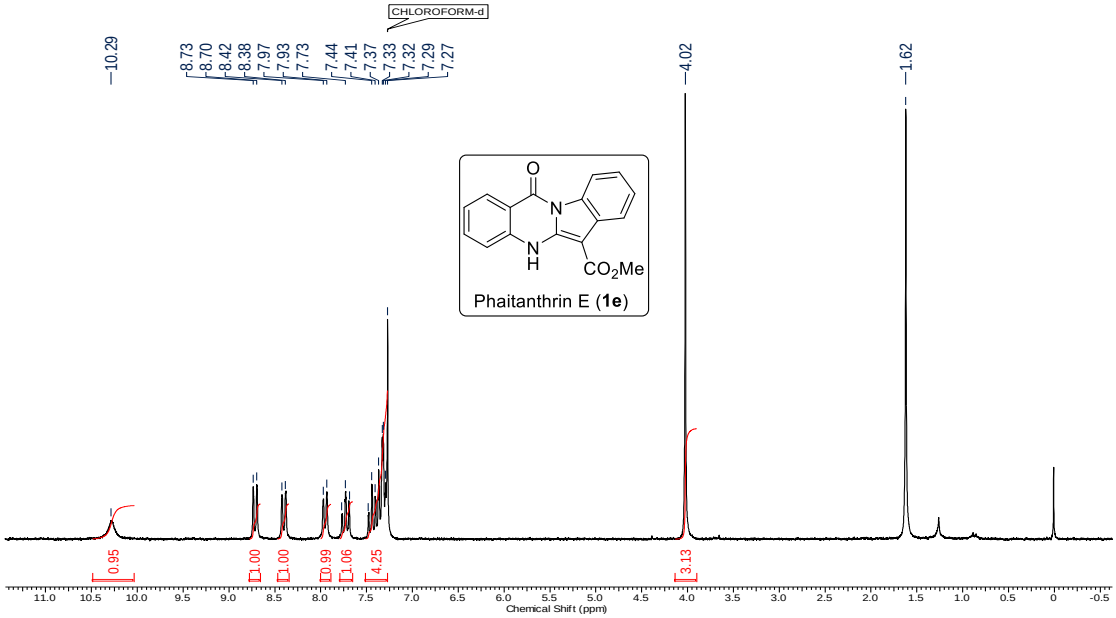
Yellow solid; 138 mg (83%). Mp 198 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.48 (t, *J* = 8 Hz, 3H), 4.53 (q, *J* = 8 Hz, 2H), 7.30–7.50 (m, 4H), 7.70–7.90 (m, 2H), 8.44 (d, *J* = 8 Hz, 1H), 8.74 (d, *J* = 8 Hz, 1H), 11.86 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.1, 62.3, 95.4, 115.9, 116.5, 116.7, 119.1, 123.7, 124.7 (2C), 126.2, 128.6, 131.4, 135.6, 137.4, 147.7, 157.8, 164.6, 179.2; HRMS (ESI): calcd for $C_{19}H_{15}N_2O_4$ 335.1026; found: 335.1018; IR ($CHCl_3$ νmax): 3021, 1734, 1698, 1631 cm^{-1}.

6-(2-Chloroacetyl)indolo[2,1-b]quinazolin-12(5H)-one (66e): Brown solid; 144 mg (93%). Mp 245 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 4.74 (s, 2H), 7.30–7.47 (m, 3H), 7.49 (t, *J* = 8 Hz, 1H), 7.65 (d, *J* = 8 Hz, 1H), 7.78 (t, *J* = 8 Hz, 1H), 8.42 (d, *J* = 8 Hz, 1H), 8.78 (d, *J* = 8 Hz, 1H), 11.72 (br s, 1H); ^{13}C NMR ($CDCl_3$,100 MHz) δ 47.7, 95.5, 115.5, 116.4, 116.9, 118.6, 123.1, 124.2, 124.9, 126.2, 128.6, 131.1, 135.6, 137.7, 146.0, 158.1, 186.6; HRMS (ESI): calcd for $C_{17}H_{12}ClN_2O_2$ 311.0582; found: 311.0576; IR ($CHCl_3$ νmax): 3021, 1695, 1632 cm^{-1}.



66e

2B. 5 Selected Spectra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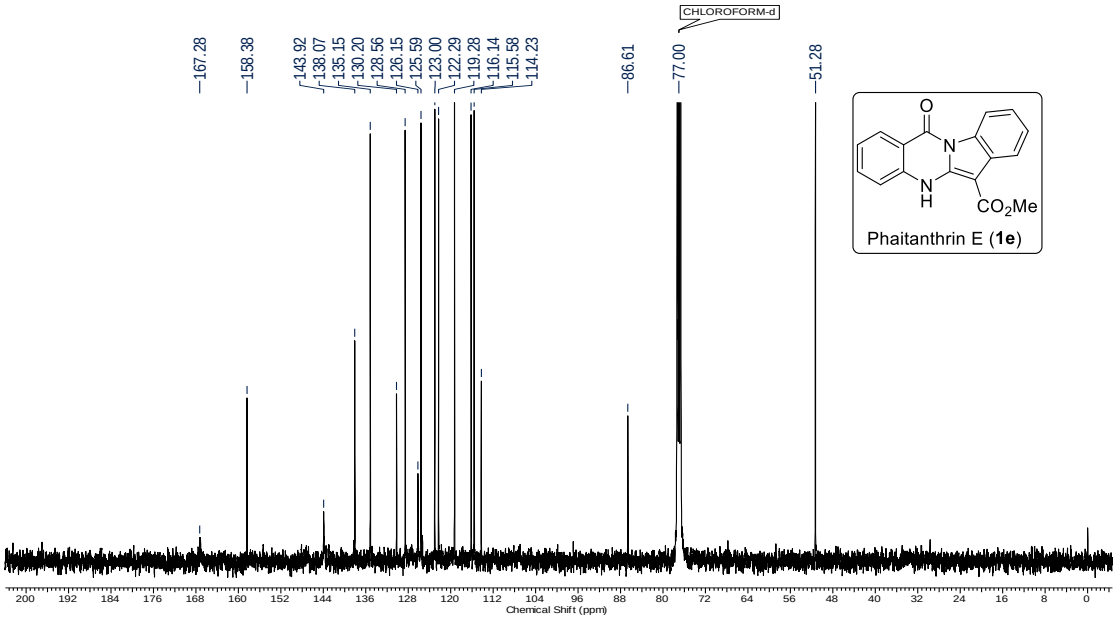
8.73
8.70
8.42
8.38
7.97
7.93
7.73
7.44
7.41
7.37
7.33
7.32
7.29
7.27
4.02
1.62
0.95
1.00
1.00
0.99
1.06
4.25
3.13
Chemical Shift (ppm)
Phaitanthrin E (1e)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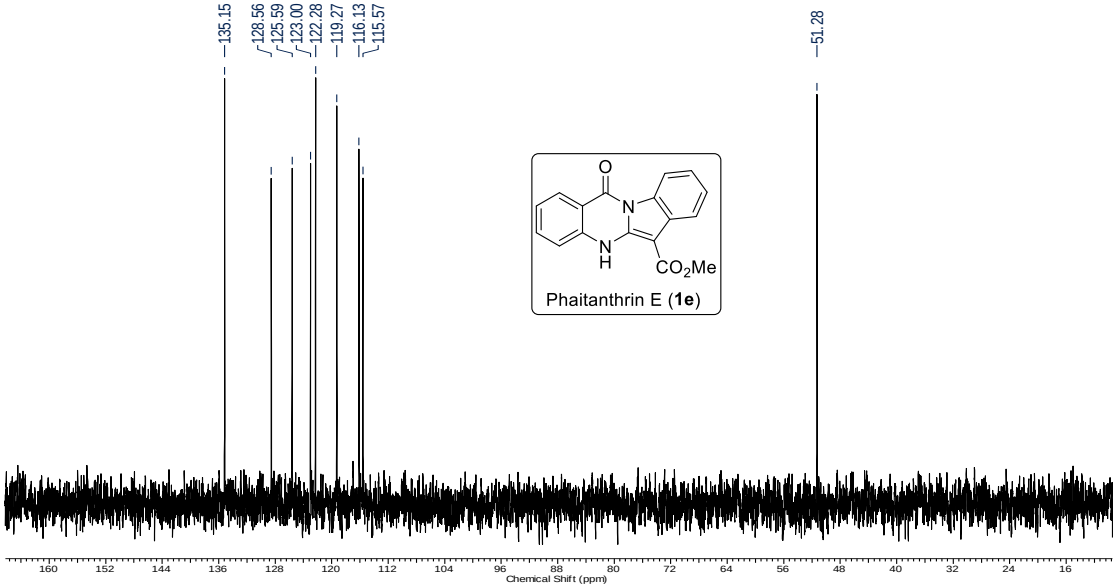
135.15
130.20
128.56
126.15
125.59
123.00
122.29
119.28
116.14
115.58
114.23
86.61
77.00
51.28
Chemical Shift (ppm)
Phaitanthrin E (1e)


135.15
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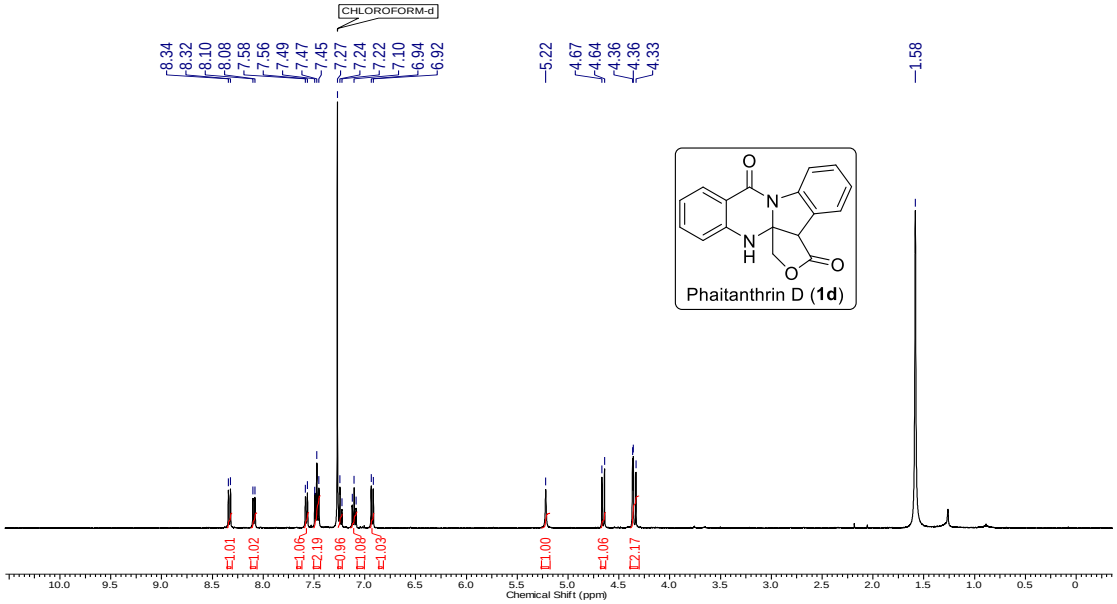
123.00
122.28
119.27
116.13
115.57
51.28
Chemical Shift (ppm)
Phaitanthrin E (1e)


CHLOROFORM-d
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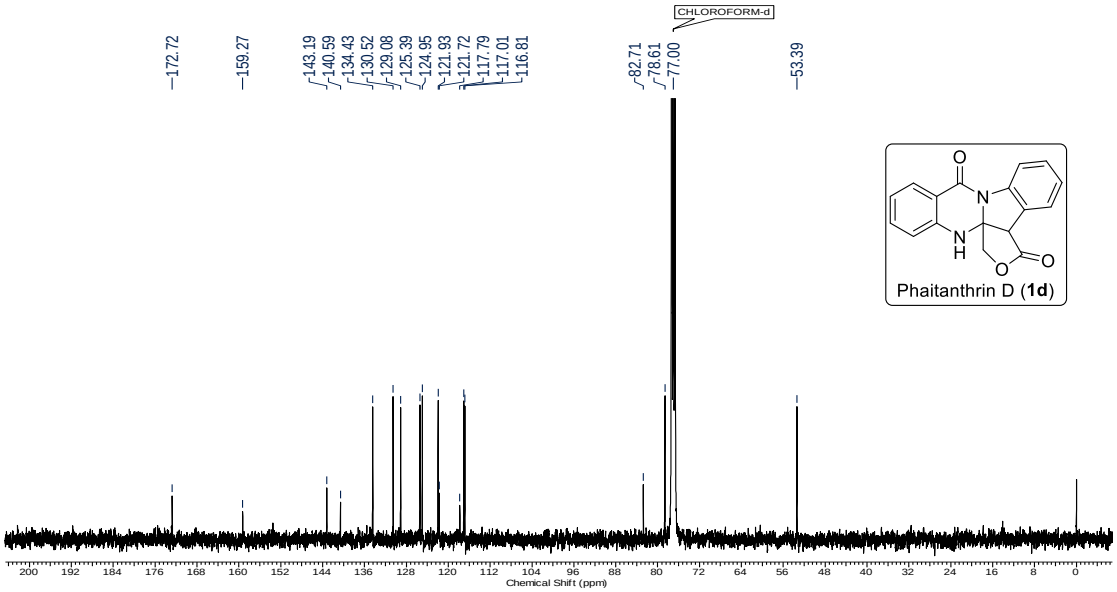
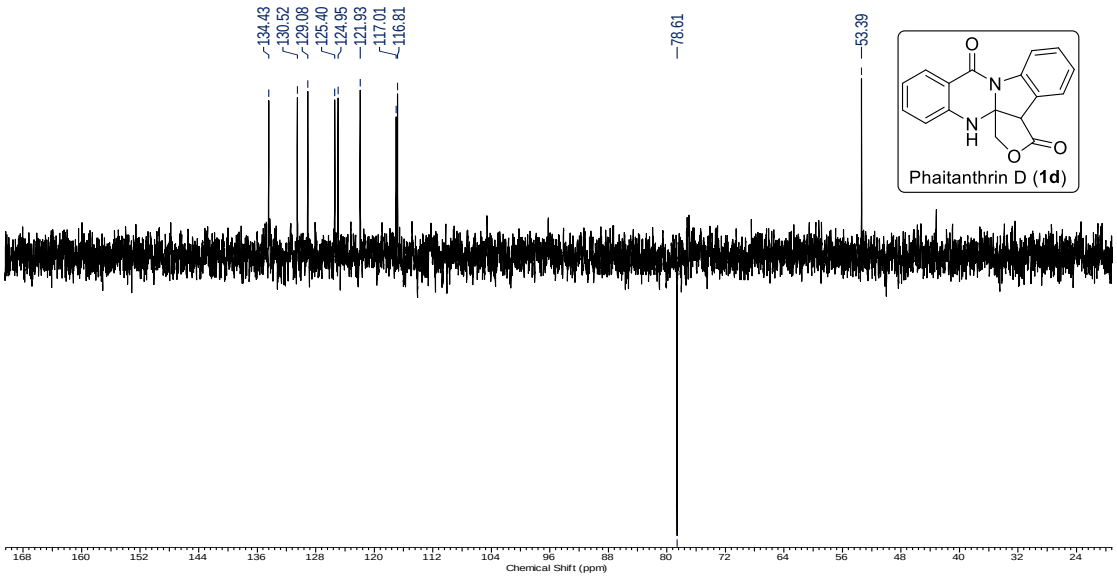
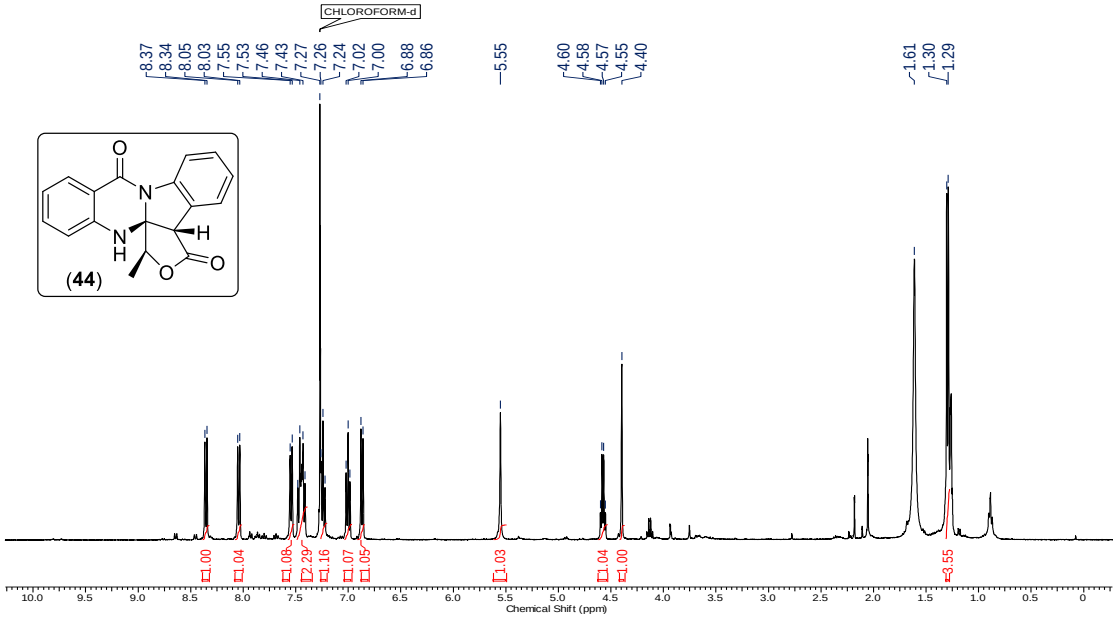
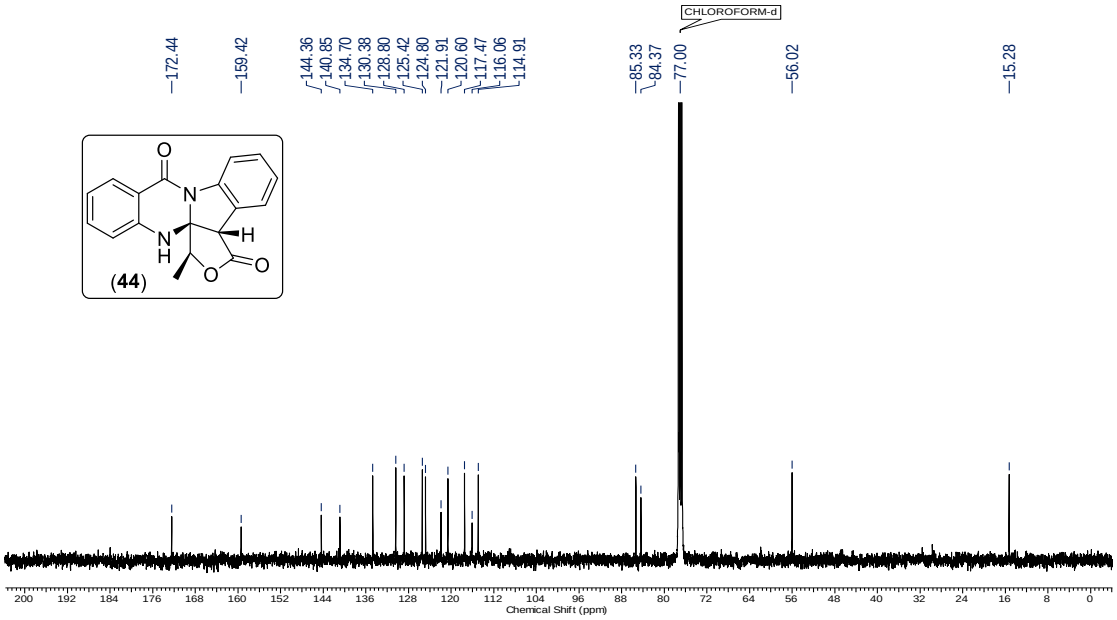
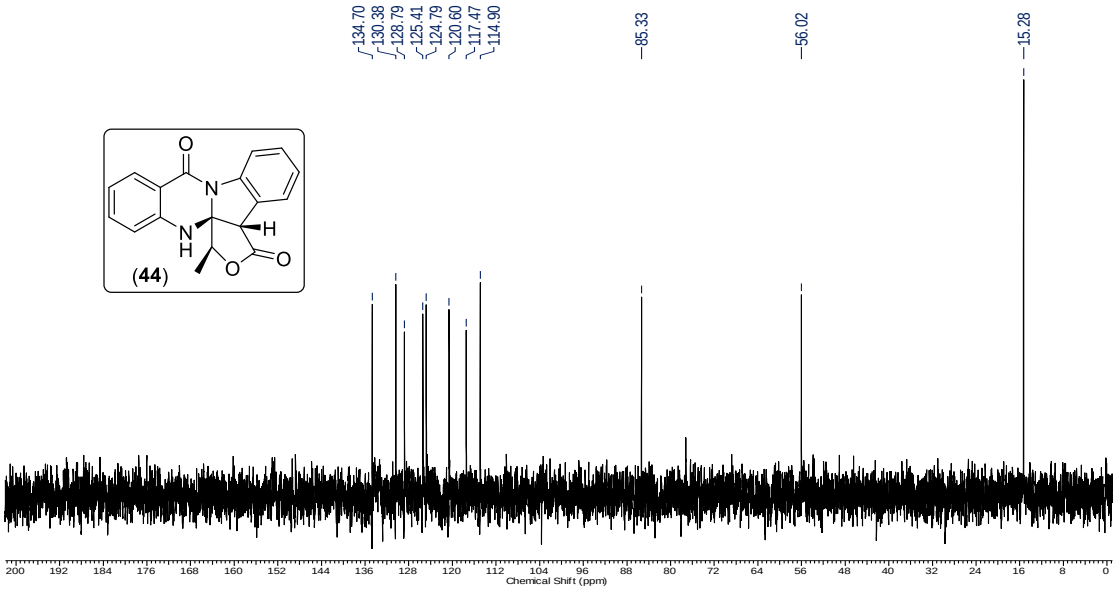
8.32
8.10
8.08
7.58
7.56
7.49
7.47
7.45
7.27
7.24
7.22
7.10
6.94
6.92
5.22
4.67
4.64
4.36
4.36
4.33
1.58
1.01
1.02
1.06
2.19
0.96
1.08
1.03
1.00
1.06
2.17
Chemical Shift (ppm)
Phaitanthrin D (1d)

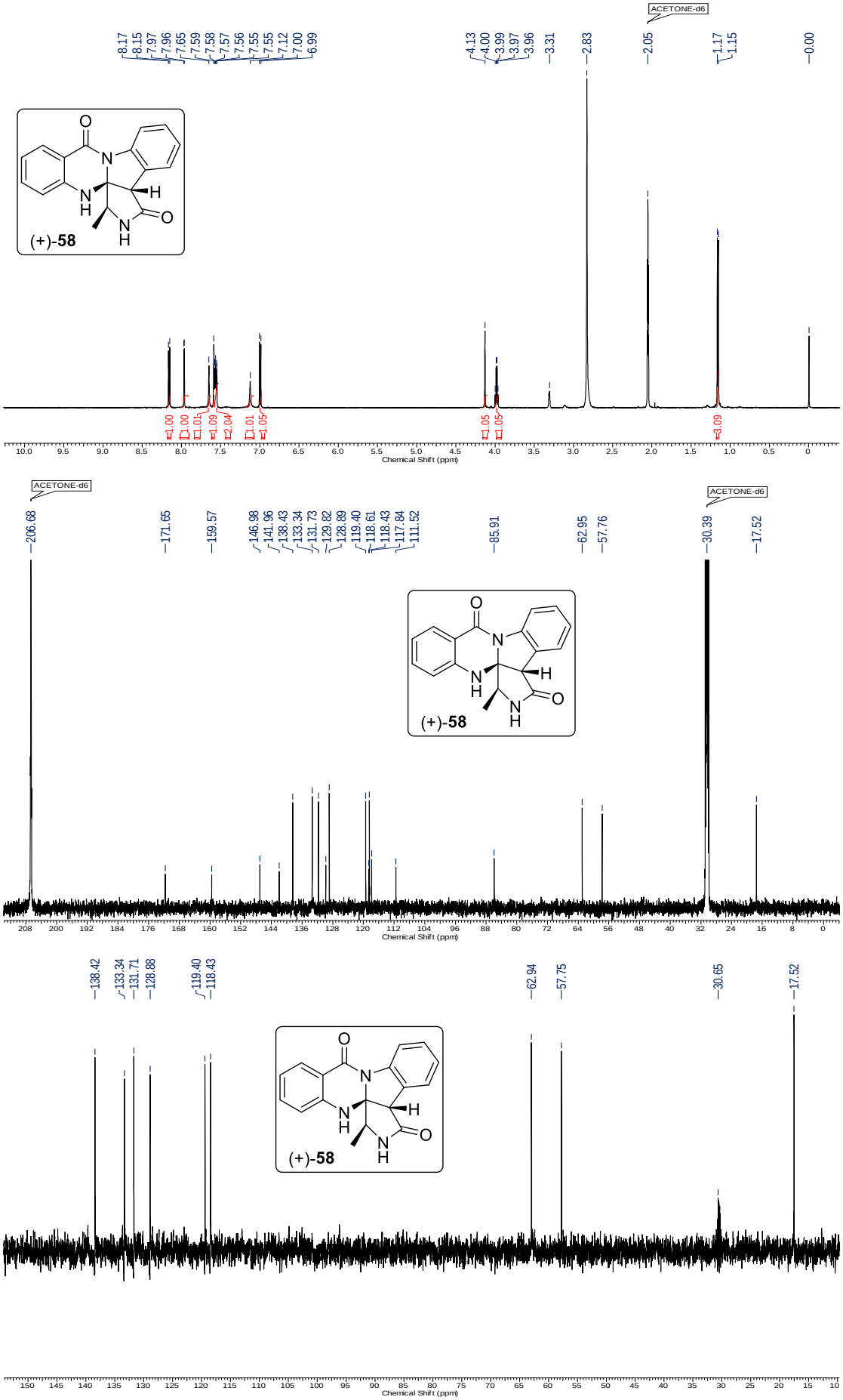

CHLOROFORM-d
172.72
159.27
143.19
140.59
134.43
130.52
129.08
125.39
124.95
121.93
121.72
117.79
117.01
116.81
82.71
78.61
77.00
53.39
Chemical Shift (ppm)
Phaitanthrin D (1d)


134.43
130.52
129.08
125.40
124.95
121.93
117.01
116.81
78.61
53.39
Chemical Shift (ppm)
Phaitanthrin D (1d)


CHLOROFORM-d
8.37
8.34
8.05
8.03
7.55
7.53
7.46
7.43
7.27
7.26
7.24
7.02
7.00
6.88
6.86
5.55
4.60
4.58
4.57
4.55
4.40
1.61
1.30
1.29
(44)
1.00
1.04
1.08
2.29
1.16
1.07
1.05
1.03
1.04
1.00
3.55
Chemical Shift (ppm)


CHLOROFORM-d
172.44
159.42
144.36
140.85
134.70
130.38
128.80
125.42
124.80
121.91
120.60
117.47
116.06
114.91
85.33
84.37
77.00
56.02
15.28
(44)
Chemical Shift (ppm)


134.70
130.38
128.79
125.41
124.79
120.60
117.47
114.90
85.33
56.02
15.28
(44)
Chemical Shift (ppm)


ACETONE-d6
8.17
8.15
7.97
7.96
7.65
7.59
7.58
7.57
7.56
7.55
7.55
7.12
7.00
6.99
4.13
4.00
3.99
3.97
3.96
3.31
2.83
2.05
1.17
1.15
0.00
(+)-58
Chemical Shift (ppm)
ACETONE-d6
206.68
171.65
159.57
146.98
141.96
138.43
133.34
131.73
129.82
128.89
119.40
118.61
118.43
117.84
111.52
85.91
62.95
57.76
30.39
17.52
(+)-58
Chemical Shift (ppm)
138.42
133.34
131.71
128.88
119.40
118.43
62.94
57.75
30.65
17.52
(+)-58
Chemical Shift (ppm)

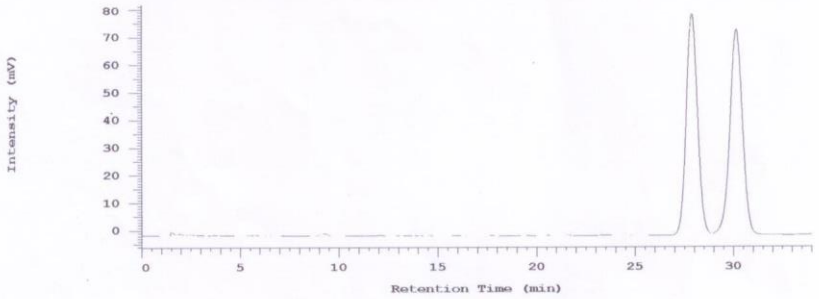
2B.6 HPLC Chromatogram of Compound 1d

D-7000 HPLC System Manager Report

Analyzed: 02/02/15 05:05 PM
Reported: 02/02/15 06:37 PM
Processed: 02/02/15 06:37 PM

Data Path: C:\WIN32APP\HSM\HPLC\DATA\7675\
Processing Method: SANTOSHH
System(acquisition): Sys 1
Series:7675
Application: HPLC
Volume: 10.0 ul
Sample Name: PD=R
Injection from this vial: 1 of 1
Sample Description: ACN:H2O (40:60)

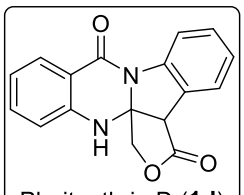
Chrom Type: HPLC Channel : 1



No.	RT	Height	Area	Area %
1	27.89	78786	3104266	50.055
2	30.15	72269	3097406	49.945
		151055	6201672	100.000

Peak rejection level: 0

Group Leader :- DR.N.P.Argade
COLUMN :-Chiralcel OD-RH(150 X 4.6mm)
MOBILE PHASE :- ACN:H20 (40:60)
WAVELENGTH :- 254nm
FLOW RATE :- 0.5ml/min (940psi)
SAMPLE CONC :- 1mg/2ml Injection vol:2ul



Phaitanthrin D (**1d**)
Racemic

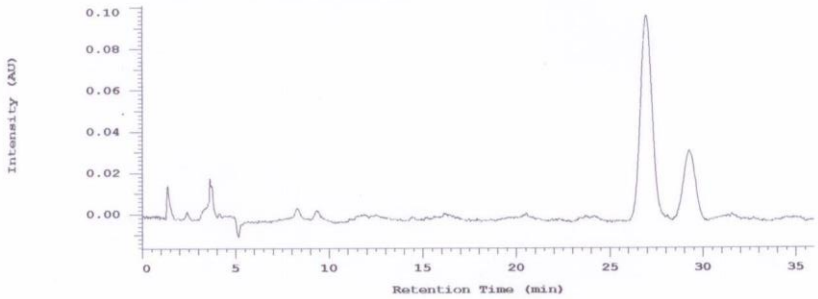
D-7000 HPLC System Manager Report

Analyzed: 04/27/15 10:33 AM
Reported: 04/27/15 11:18 AM
Processed: 04/27/15 11:18 AM

Data Path: C:\WIN32APP\HSM\HPLC\DATA\7914\
Processing Method: SANTOSHH

System(acquisition): Sys 1
Series:7914
Application: HPLC
Volume: 10.0 ul
Sample Name: PD Chiral
Injection from this vial: 1 of 1
Sample Description: ACN:H2O(40:60)

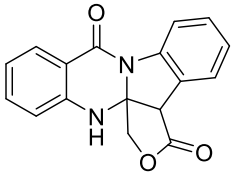
Chrom Type: HPLC Channel : 1



No.	RT	Height	Area	Area %
1	26.95	49503	2173687	74.781
2	29.26	16560	733055	25.219
		66063	2906742	100.000

Peak rejection level: 0

```
Group Leader   :- DR.N.P.Argade
COLUMN         :-Chiralcel OD-RH (150 X 4.6mm)
MOBILE PHASE   :-ACN:H20(40:60)
WAVELENGTH     :- 254nm
FLOW RATE      :- 0.5 ml/min (515psi)
SAMPLE CONC    :- x mg/1ml Injection vol:10ul
```



(–)-Phaitanthrin D (**1d**)
Chiral

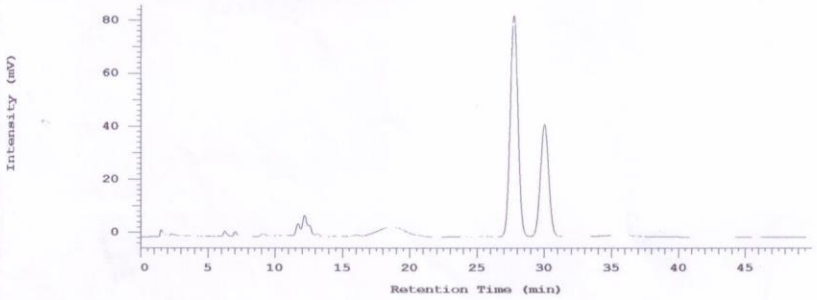
D-7000 HPLC System Manager Report

Analyzed: 02/02/15 06:30 PM
Reported: 02/03/15 12:33 PM
Processed: 02/03/15 12:33 PM

Data Path: C:\WIN32APP\HSM\HPLC\DATA\7676\
Processing Method: SANTOSHH

System(acquisition): Sys 1
Series:7676
Application: HPLC
Volume: 10.0 ul
Sample Name: PD=C
Injection from this vial: 1 of 1
Sample Description: ACN:H20 (40:60)

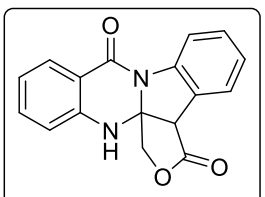
Chrom Type: HPLC Channel : 1



No.	RT	Height	Area	Area %
1	27.74	82033	3171548	65.408
2	30.01	40908	1677334	34.592
		122941	4848882	100.000

Peak rejection level: 0

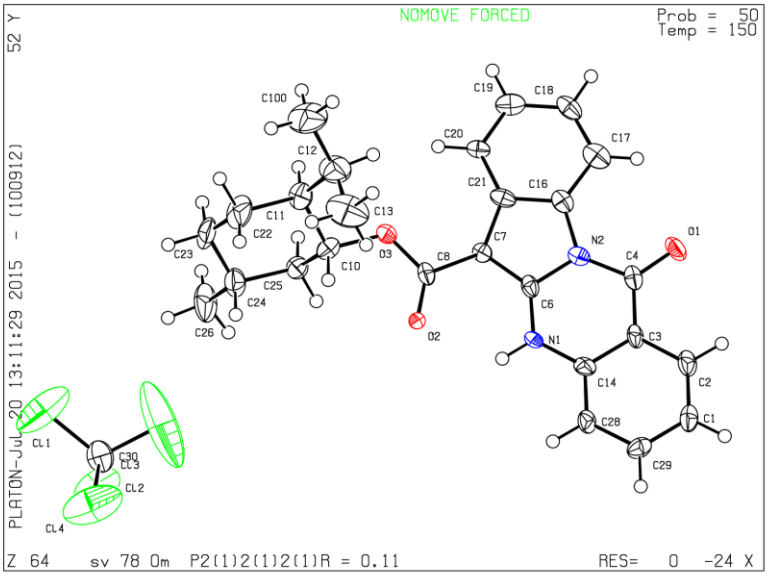
```
Group Leader   :- DR.N.P.Argade
COLUMN         :-Chiralcel OD-RH(150 X 4.6mm)
MOBILE PHASE   :- ACN:H20 (40:60)
WAVELENGTH     :- 254nm
FLOW RATE      :- 0.5ml/min (940psi)
SAMPLE CONC    :- 1mg/2ml Injection vol:2ul
```

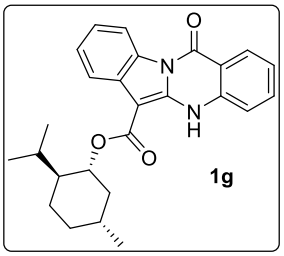


(–)-Phaitanthrin D (**1d**)
Chiral

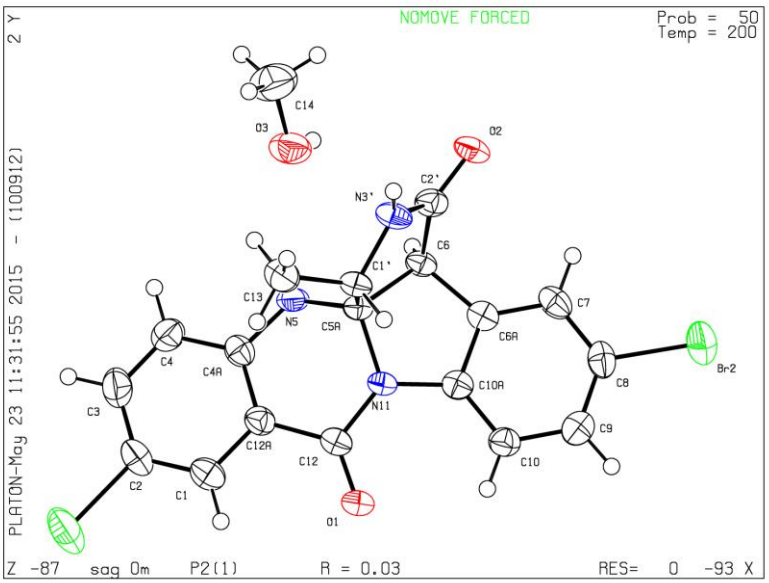
2 B. 7. X-ray

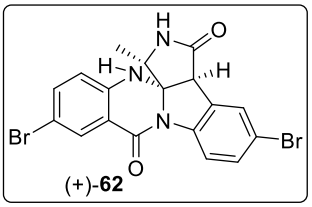
1) Compound 1g.





2) Compound 62.





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

We have presented a brief literature account on the isolation, bioactivity and synthesis of tryptanthrin, phaitanthrins A–C and cruciferane. We have demonstrated a new simple and efficient one-step aryne-based synthetic protocol for a diverse range of fused quinazolinones. It has also been successfully utilized to accomplish a concise total synthesis of five recently isolated different bioactive quinazolinone based natural products. More specifically, the first total synthesis of (±)-cruciferane has been accomplished in three steps with 66% overall yield via two natural products as the intermediates. In the synthesis of cruciferane, selective reduction of an imine moiety in the quinazolinone unit in the presence of an aliphatic ester moiety is noteworthy from a basic chemistry point of view.

We have also presented a concise literature account on the isolation, bioactivity and synthesis of quinazolinone alkaloids phaitanthrins D and E. We have demonstrated one-pot synthesis of phaitanthrin E from different type of starting materials in very good yields with a release of unexpected carbon species. To the best of our knowledge, this is a unique example of spontaneous sp3 carbon–carbon bond cleavage in the absence of a metal catalysis and molecular oxygen. We have also demonstrated the first diastereoselective and an enantioselective biogenetic type total synthesis of (±)/(–)-phaitanthrin D with very good overall yields and stereoselectivity. We could successfully mimic nature to perform the rearrangements of phaitanthrin D to phaitanthrin E and confirmed an unusual carbon–carbon bond cleavage. The present concept of designing an appropriate type of structural unit bearing precisely situated heteroatoms to release such type of carbon leaving groups at the cost of relatively higher formed product

stability has a broad scope. These results prove that under special circumstances the esters, ethers, alcohols and amines can also function as the good leaving groups via unexpected carbon–carbon bond cleavages and conceptually it will be useful to organic chemists to achieve what appears implausible.

We have also described an independent two steps synthesis of phaitanthrin E starting from tryptanthrin via an acylation of indoloquinazolinone. The witnessed spontaneous rearrangement of β-imino esters/ketones to the corresponding γ-amino α,β-unsaturated carbonyl systems is noteworthy from basic chemistry point of view. The present protocol is general in nature and will be useful for the synthesis of analogues and congeners of phaitanthrins. We also feel that these compounds will serve as potential building blocks for the synthesis of novel heterocyclic architectures. In short, we have accomplished a concise and efficient synthesis of tryptanthrin, Phaitanthrin A–C and (±)*-cruciferane using aryne insertion reaction approach and synthesis of phaitanthrins D and E using* Csp^3 *carbon–carbon bond fragmentation approach.*

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

List of Publications

1. Aryne Insertion Reactions Leading to Bioactive Fused Quinazolinones: Diastereoselective Total Synthesis of Cruciferane.
   Vaidya, S. D; Argade, N. P. *Org. lett.* **2013**, *15*, 4006.

2. A Biomimetic Synthesis of Phaitanthrin E Involving Fragmentation of sp3 Carbon–Carbon Bond: Synthesis and Rearrangement of (±)-Phaitanthrin D to Phaitanthrin E
   Vaidya, S. D; Argade, N. P. *Org. lett.* **2015**, *17*, 6218.

3. Synthesis of (–)-Phaitanthrin D and (+)-Dihydropyrroloindoloquinazolinone
   Vaidya, S. D; Argade, N. P. *Synthesis* **2016**, *48*, *e-first.*

4. Rearrangement of Iminie Double Bond in Quinazolinones with Unusual Carbon to Nitrogen Prototropic Shifts: Synthesis of Phaitanthrin E
   Vaidya, S. D; Argade, N. P. *Ind. J. Chem.*, **2016**, *Communicated.*