Recent Developments in the Chemistry of Quinazolinone Alkaloids

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Recent Developments in the Chemistry of Quinazolinone Alkloids

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Quinazolinone, an important class of fused heterocyclic alkaloids has attracted high attention in organic and medicinal chemistry due to their significant and wide range of biological activities. There are approximately 150 naturally occurring quinazolinone alkaloids are known to till 2005. Several new quinazolinone alkaloids (~55) have been isolated in the last decade. Natural quinazolinones with exotic structural features and remarkable biological activities have incited a lot of activity in the synthetic community towards the development of new synthetic strateies and approaches for the total synthesis of quinazolinone alkaloids. This review is focused on these advances in the chemistry of quinazolinone alkalids in the last decade. Article covers the account of newly isolated quinazolinone natural products with their biological activities and recently reported total syntheses of quinazolinone alkaloids from 2006 to 2015.

1. Introduction

Quinazolinone is an important class of fused heterocyclic scaffold due to their significant range of biological activities and their occurrence in approximately 200 naturally occurring alkaloids (Figure 1).[1] Natural and unnatural quinazolinones has attracted high attention in organic and medicinal chemistry because of their therapeutic prospective such as anticancer, antibacterial, antidiabetic hypnotic, sedative, analgesic, anticonvulsant, antitussive, antiinflammatory and several others.[1] This was evidenced by a structure search of quinazoline as a substructure yielding hits >300000 compounds in SciFinder. Among them, ~40000 compounds were known to be biologically active.[1] Some synthetic quinazolinones, such as Raltitrexed, Ispinesib and Tempostatin are already in the market/clinical trials for cancer treatment.[1]

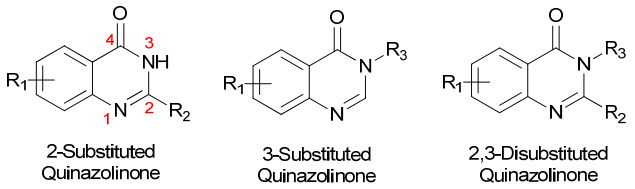

Figure 1. Quinazolinone core structures.

Several new quinazolinone alkaloids have been isolated in the last decade with different pharmacological activities. Various research groups achieved the total synthesis of quinazolinone alkaloids with novel synthetic routes and strategies. Present review portrays these recent advances in this field with an emphasis on newly isolated natural products, their biological activities, new methods to construct the core structure, new synthetic routes and strategies for complex natural products with emphasis on key reactions published in the period from 2005 to till date. For simplicity quinazolinones are mainly subdivided in three major classes 2-substitutes, 3-substituted and 2,3-disubstituted-quinazolineone (Figure 1).

2. Newly isolated quinazolinone alkaloids

Quinazolinone alkaloids are one of the 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 quinazolinone alkaloids has been broadened with the discovery of number of naturally occurring alkaloids with varying and complex structural skeleton. Approximately 55 new natural quinazolinones have been isolated from various natural species during the last decade.

2.1 2-Substituted-quinazolinone alkaloids

Four new 2-substituted quinazolinone alkaloids have been reported (Figure 2). 2-(4-Hydroxybenzyl)quinazolinon-4(*3H*)-one (**1**) was isolated from an entomopathogenic fungus *Isaria farinosa* (formerly known as *Paecilomyces farinosus*).[2a] Penipanoid C (**2**) was isolated from marine fungus *Penicillium oxalicum* 0312F1[2b] and later on from *Penicillium paneum* SD-44 along with the compound **1**.[3b] Compound **1** exhibits strong inhibitory activity of the replication of tobacco mosaic virus (TMV) whereas Penipanoid C (**2**) showed moderate inhibitory activity of the replication of TMV.[2,3] Compound **1** also displayed significant cytotoxic activity against the Du145, A-549, HeLa cell and BEL-7402 cell lines. [2,3] First natural firefly

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luciferase inhitor 2-[4′-(Methylamino)phenyl]quinazolin-4(3*H*)-one (**3**) was isolated from *Streptomyces sp.* A496.[4a] Very recently, 2-(1*H*-Indol-3-yl)quinazolin-4(3*H*)-one (**4**) has been isolated from an actinomycete, *Streptomyces* sp. BCC 21795 and exhibit cytotoxic activity against Vero cells.[4b]

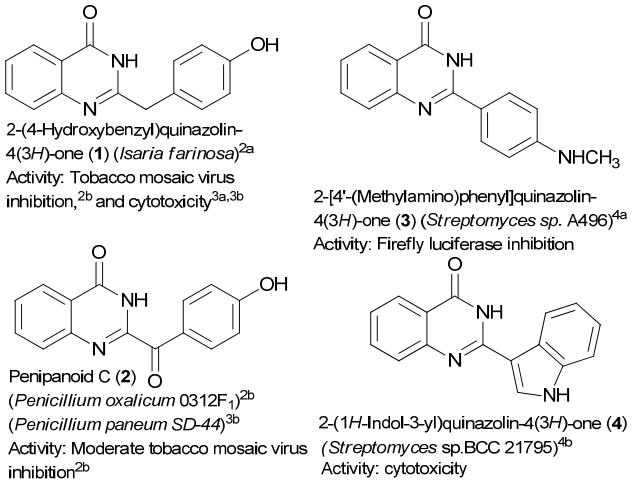

Figure 2. Naturally occurring 2-substituted quinazolinones.

2.2 3-Substituted-quinazolinone alkaloids

Eight new alkaloids have been isolated during this period in this class (Figure 3). Tan and co-workers in 2006 isolated (–)-Chaetominine (**5**), a compact tripeptide with strained tetracyclic framework from the solid-substrate culture of *Chaetomium* sp. IFB-E015, an endophytic fungus on apparently healthy *Adenophora axilliflora* leaves.[5a] It is a modified tripeptide alkaloid containing D-tryptophan, L-alanine, anthranilic acid, and formic acid. In vitro cytotoxic assays showed that (–)-Chaetominine (**5**) was highly potent against human leukemia K562 (IC_{50} 21 μM) and colon cancer SW1116 (IC_{50} 28 μM) cell lines with IC_{50} values smaller than the most frequently prescribed anticancer drugs 5-fluorouracil.[5a] However, synthetic (–)-Chaetominine (**5**) did not showed inhibitory activity against number of cancer cell line including human leukemia K562.[5b] Very recently, closely similar compounds Isochaetominines A–C (**6-8**) and 14-*epi*-Isochaetominine C (**9**) were isolated from *aspergillus sp*. which all exhibited weak inhibitory activity against Na+/K+-ATPase.[6] Aniquinazolines D (**10**), structurally related to the (–)-Chaetominine (**5**) was isolated from the culture of an endophytic fungus *Aspergillus nidulans* MA-143 obtained from the leaves of marine mangrove plant *Rhizophora stylosa*.[7] Aniquinazolines D (**10**) exhibits the potent lethality against brine shrimp (LD_{50} value 3.42 μM). 3′-(4-Oxoquinazolin-3-yl)spiro[1*H*-indole-3,5′-oxolane]-2,2′-dione (**11**) and Tryptoquivaline O (**12**) were isolated from the culture of the fungus *Neosartorya siamensis* (KUFC 6349) along with new 2,3-disubstituted quinazolinone alkaloids.[8] Compounds **11** and **12** were evaluated for cytotoxic activity but did not show cytotoxic effect.

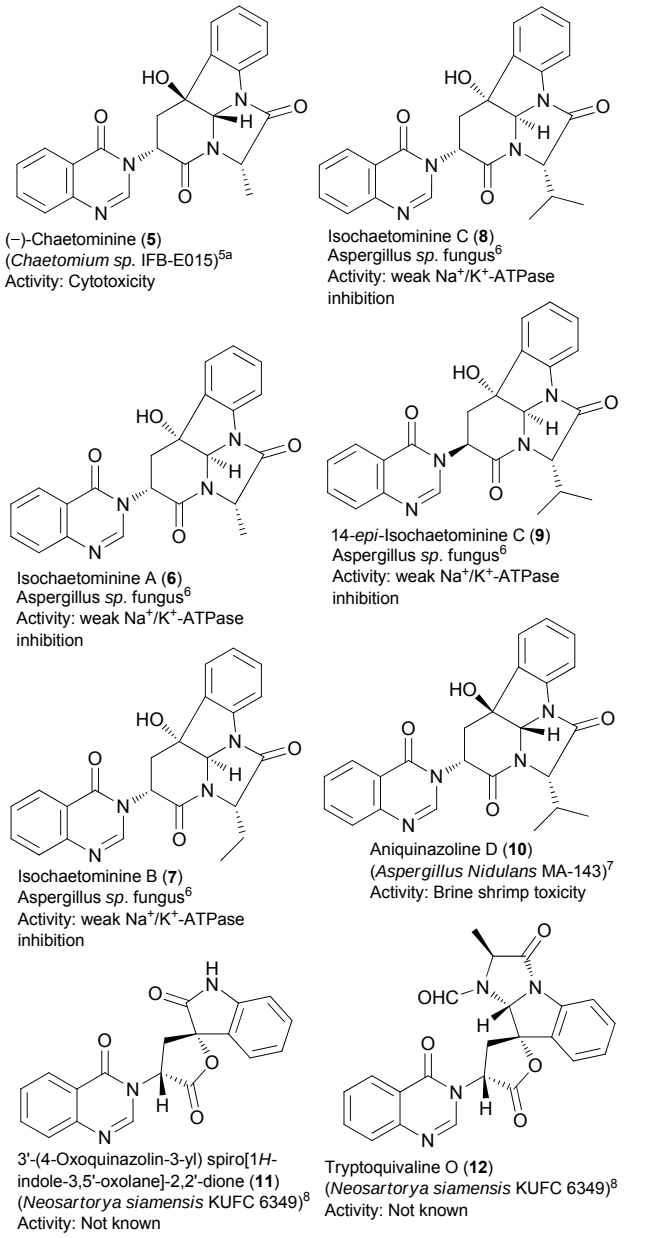

Figure 3. Naturally occurring 3-substituted-quinazolinones.

2.3 2,3-Disubstituted-quinazolinone alkaloids

Approximately 43 new 2,3-disubstituted quinazolinone alkaloids have been reported during this period (Figure 4-13). Tryptanthrin related optically active new indoloquinazolinones, Phaitanthrins A-E (**13-17**) have been isolated from *Phaius mishmensis* (Orchidaceae), which is a native orchid of Taiwan Phaius mishmensis (Figure 4).[9a] Attempts were made to determine absolute configuration by acylation with MTPA chloride and by using chiral shift reagent with no success. Only Phaitanthrin A (**13**) showed moderate cytotoxicity against MCF-7, NCI-H460, and SF-268 cell lines with IC_{50} values of 33.8, 27.0, and 43.9 μM respectively, which is just lower than known natural product Tryptanthrin (IC_{50}

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values of 11.1, 9.0, and 24.4 μM). Recently, related compound Cephalanthrin A **18** has been isolated *Cephalantheropsis gracilis*.[9b]

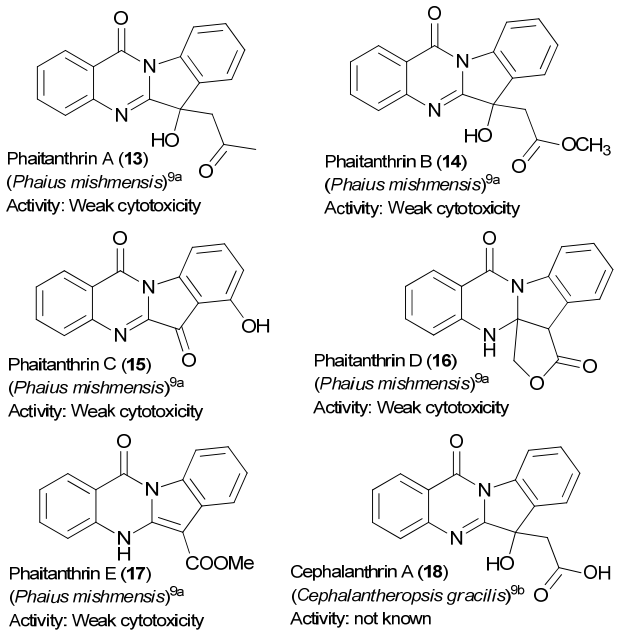

Figure 4. Tryptanthrin related natural 2,3-disubstituted quinazolinones.

2-(2-Methyl-4-oxo-4*H*quinazoline-3-yl)benzoic acid methyl ester (**19**) was isolated from the roots of *Aconitum pseudo-laeVe var. erectum* (Figure 5).[10a] OSMAC approach (one strain-many compound approach) was successfully applied by Zhang and co-workers for the isolation of quinazolinone alkaloids Auranomide A-C (**20-22**) in which Auranomide A (**20**) and Auranomide B (**21**) contains the pyrrolidin-2-iminium moiety.[10b] Auranomide A-C (**20-22**) were isolated from *Penicillium aurantiogriseum* which showed moderated cytotoxicity towards human tumor cells (Figure 5). Possible biosynthetic pathway was proposed for them which began with two molecules of anthranilic acid and involve one molecule glutamine.

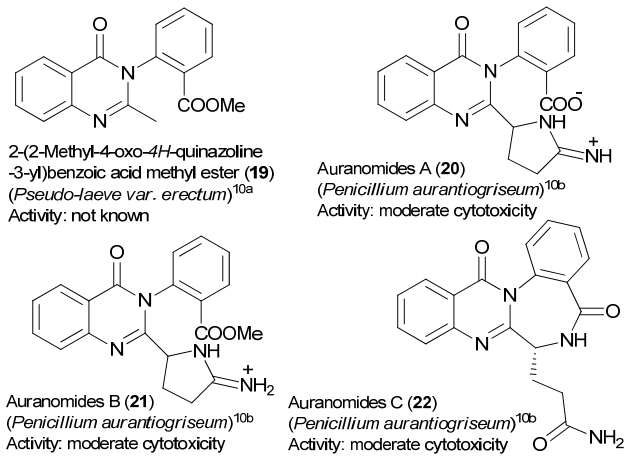

Figure 5. 2,3-Disubstituted quinazolinones containing the pyrrolidin-2-iminium moiety.

Three new benzodiazepine fused quinazolinone alkaloids (**23-25**) have been reported (Figure 6). (–)-Circumdatin I (**23**) was isolated from the mycelium of a marine derived fungus of the genus *Exophiala*. Structure and absolute stereochemistry was assigned on the basis of physicochemical evidence and by comparison of optical rotation and CD experiments with related known compounds.[11] (–)-Circumdatin I (**23**) exhibited an UV-A protecting activity (ED_{50} value 98 μM) which is more potent than currently used sunscreen agent, oxybenzone (ED_{50} value 350 μM). (–)-Circumdatin J (**24**) was isolated from the marine-derived fungus *Aspergillus ostianus*[12] and (–)-2-Hydroxycircumdatin C (**25**) was isolated from an endophytic fungus *Aspergillus ochraceus* derived from the marine brown alga *Sargassum kjellmanianum*.[13] Compound **25** displayed significant DPPH radical-scavenging activity (IC_{50} value 9.9 μM) which is 8.9-fold more potent than that of butylated hydroxytoluene (BHT).[13]

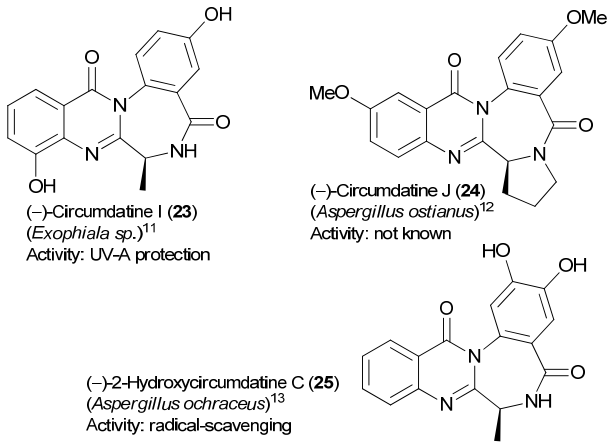

Figure 6. Naturally occurring quinazolinones fused with benzodiazepinones.

Fumiquinazoline S (**26**), a new member of fumiquinazoline alkaloid was recently isolated from *aspergillus sp*. which showed weak inhibitory activity against Na+/K+-ATPase (Figure 7).[6] Janoxepin (**27**), a novel oxepin derivative incorporated with rare D-leucine was isolated from the fungus *Aspergillus janus* (Figure 6). It exhibits antiplasmodial activity (IC_{50} value 28 mg/mL) against the malaria parasite Plasmodium falciparum 3D7 in the radio isotope assay.[14]

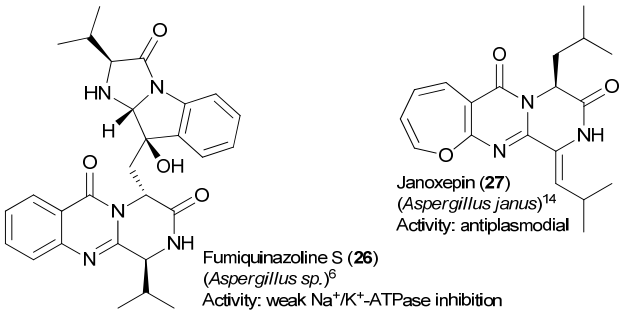

Figure 7. Fumiquinazoline S and Janoxepine.

Five glyantrypine derivatives 3-Hydroxyglyantrypine (**28**), (–)-Oxoglyantrypine (**29**), (+)-Oxoglyantrypine (**30**), Cladoquinazoline (**31**), *epi*-Cladoquinazoline (**32**) and a pyrazinoquinazoline derivative, Norquinadoline A (**33**) were isolated from the culture of the mangrove-derived fungus *Cladosporium* sp. PJX-41 (Figure 8). Structure and absolute configuration were elucidated on the basis of spectroscopic date and CD, NOESY and single crystal X-ray data. (–)-Oxoglyantrypine (**31**) and Norquinadoline A (**33**) exhibits significant activity against influenza virus A (H1N1), whereas the others were found weekly active. This study revealed new type of carbon skeleton as leads for investigating antiviral mechanisms and for developing antiviral agents against influenza virus A (H1N1).[15]

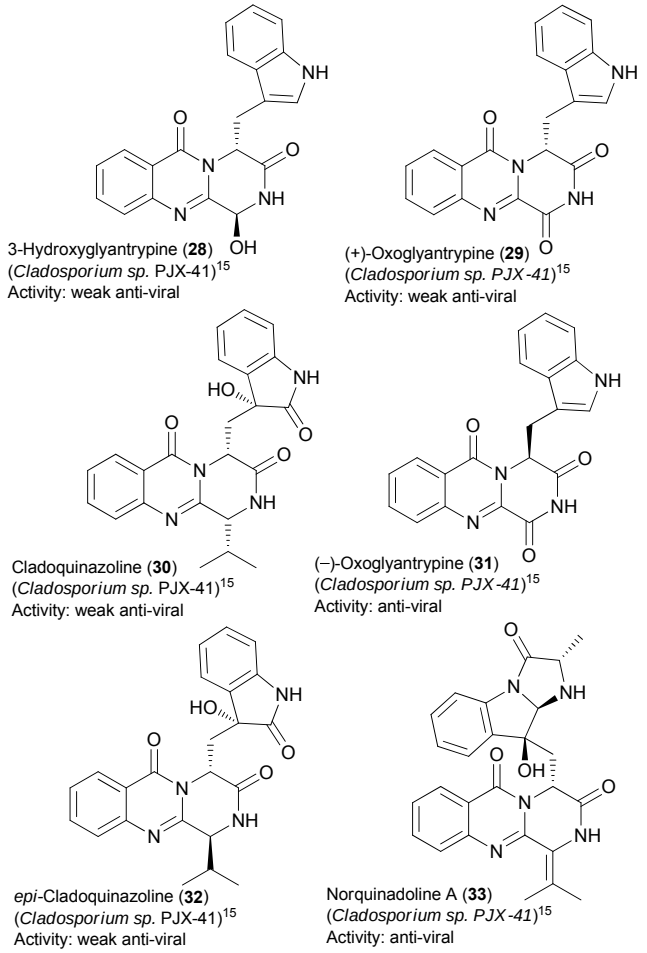

Figure 8. Glyantrypine related quinazolinone alkaloids.

Indoloazepinone derivative Sartorymensin (**34**), a hexacyclicindole alkaloid that exhibits a structural feature not observed among other indole alkaloids was isolated from the culture of the fungus *Neosartorya siamensis* (KUFC 6349) along with four new pyrazinoquinazolinone derivatives, *epi*-Fiscalin C (**35**), *epi*-Fiscalin A (**36**), Neofiscalin A (**37**) and *epi*-Neofiscalin A (**38**) (Figure 9). Compounds were tasted for anticancer activity against several cancer cell lines but only Sartorymensin (**34**) displayed a moderate in vitro growth inhibitory activity.[8]

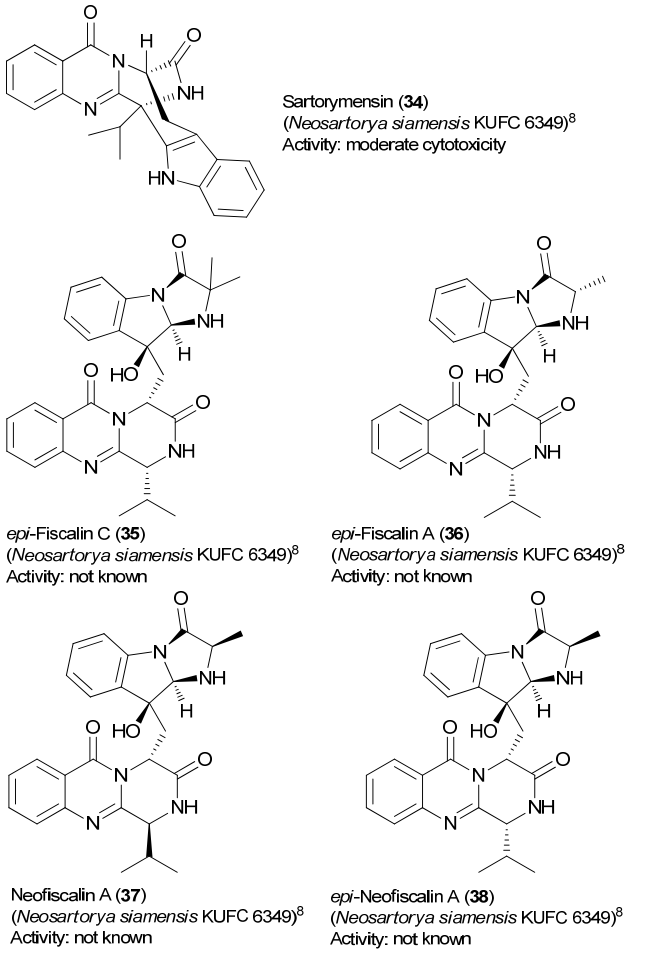

Figure 9. New pyrazinoquinazolinones and indoloazepinone alkaloids.

A newly developed method *X-hitting*, a algorithm for systematic and automated computer-assisted comparison of UV data in a large number of data files has been used to track the spiro-quinazoline metabolites, Lapatin A (**39**) and B (**40**) which are isolated from *Penicillium lapatayae* (Figure 10).[16] Four new spiroquinazoline alkaloids Alanditrypinone (**41**), Alantrypinene B (**42**), Alantryleunone (**43**) and Alantryphenone (**44**) were isolated from A *Eupenicillium* spp. derived from *Murraya paniculata* (Rutaceae) (Figure 9). However, bioactivities of these compounds have not been studies.[17]

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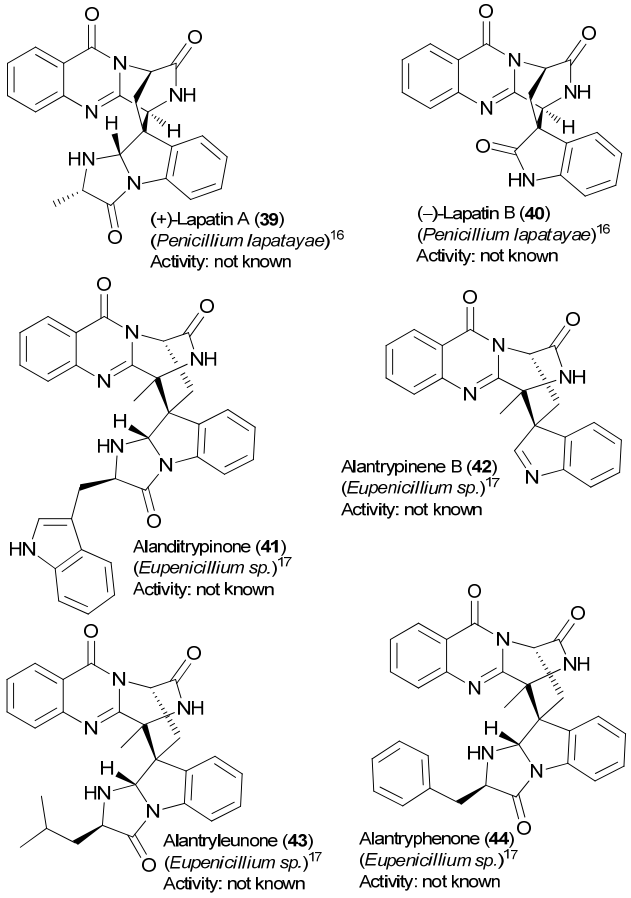

Figure 10. Lapatin and related spiroquinazoline alkaloids.

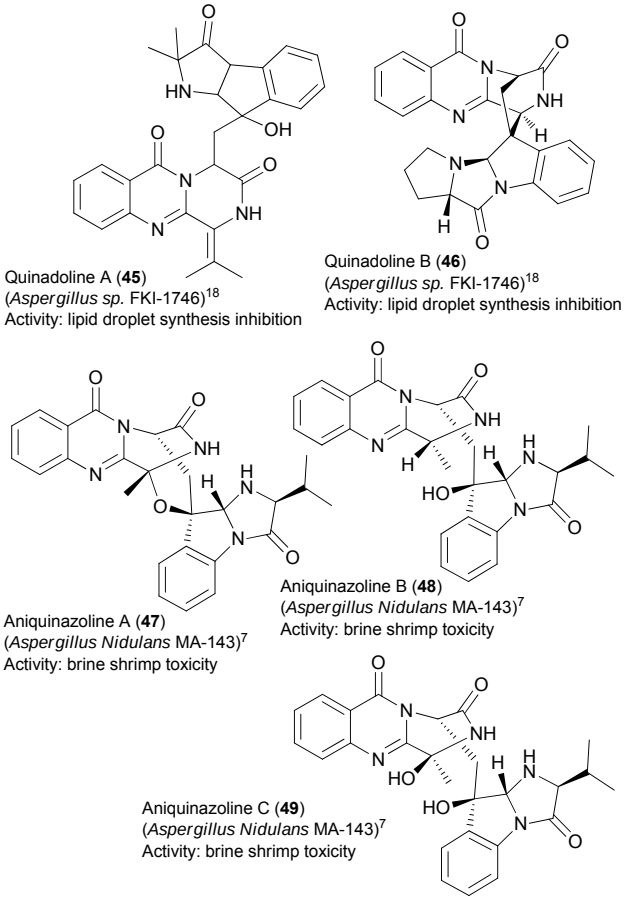

Figure 11. Quinadoline and Aniquinazoline alkaloids.

Quinadolines A (**45**) and B (**46**), the fungal metabolites were isolated from culture broth of *Aspergillus* sp. FKI-1746 which shows moderate inhibitory activity towards lipid droplet synthesis in mouse macrophages (Figure 11).[18] Aniquinazoline A–C (**47-49**) along with Aniquinazoline D (**10**) were isolated from the culture of *Aspergillus nidulans* MA-143 (Figure 10).[7] The structure for **47** was confirmed by single-crystal X-ray diffraction analysis. All these compounds were examined for antibacterial and cytotoxic as well as brine shrimp (*Artemia salina*) lethality. Although, none of them displayed antibacterial and cytotoxic activity, all these showed potent lethality against brine shrimp with LD_{50} values of 1.27, 2.11, 4.95 and 3.42 μM, respectively, which were stronger than that of the positive control colchicine (LD_{50} value of 88.4 μM).[7]

Cottoquinazoline A (**50**) has been isolated from terrestrial fungus *Aspergillus Versicolor* (MST-MF495) recovered from beach sandat Cottesloe, Western Australia.[19a] Whereas cottoquinazoline D (**53**), a new alkaloid with a 1-aminocyclopropane-1-carboxylic acid residue which rarely discovered in nature, was isolated together with two new quinazolinone alkaloids, Cottoquinazolines B (**51**) and C (**52**) from coral-associated fungus *Aspergillus versicolor* LCJ-5-4 obtained from the soft coral *Cladiella* sp. collected from the South China Sea (Figure 12).[19b] Amino acid biogenetic pathway as possible biosynthetic way for these alkaloids was proposed. Compounds **51-53** were evaluated in vitro for cytotoxicity (against Hela and P388 cells using an MTT assay) and for antimicrobial activity (against *Escherichia coli, Staphylococcus aureus, Enterobacteraerogenes, Bacillus subtilis*, and *Candida albicans*). Only Cottoquinazolines D (**53**) showed moderate antifungal activity (MIC value of 22.6 μM) against *Candida albicans* and none of them showed cytotoxicity.[19b]

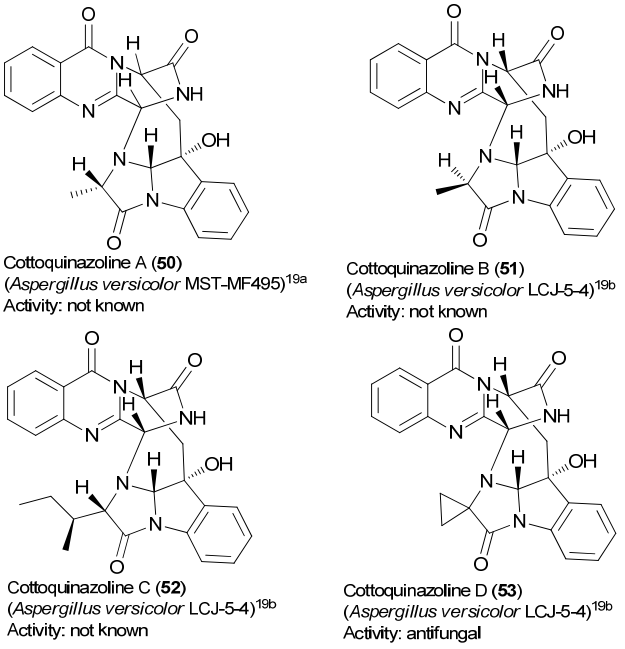

Figure 12. Cottoquinazoline alkaloids.

Recently, Ardeemin related alkaloids, 16*α*-Hydroxy-5 *N*-Acetylardeemin (**54**) and 15*b*-Dehydro-5-*N*-acetylardeemin (**55**) were isolated from an endophytic fungus, *Aspergillus terreus*[20a] and *Aspergillus terreus* IFB-E030 (Figure 13).[20b] Later both were obtained together from *Aspergillus fumigatus* SPS-02.[20c] Compound **54** showed inhibitory effect against acetylcholinesterase as well as moderate cytotoxic activity against KB and HSC-T6 cell lines.[20a] Compound **54** also exhibit strong multidrug-resistant (MDR) reversing effect against K562/DOX & A549/DDP cancer cell lines and compound **55** exhibit MDR reversing effect against SK-OV-S/DDP cell line.[20c] Structure activity relationship (SAR) revealed that hydroxyl group plays important role in MDR reversing effect.

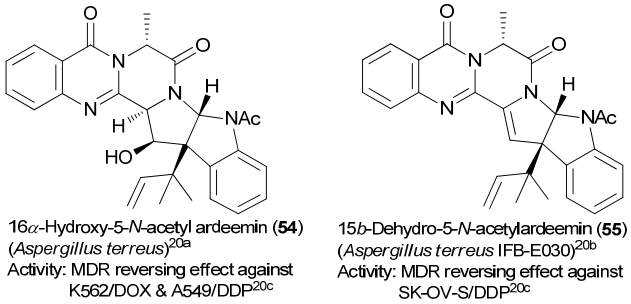

Figure 13. Ardeemin related new quinazolinone alkaloids.

2.4 Structural reassignment

(–)-Circumdatins A and B: (–)-Circumdatin A (**56a**) and B (**57a**) were isolated in 1999 from *Aspergillus ochraceus* and structures were deduce as **56a** and **57a** using INEPT2- and HMBC-INADEQUATE spectroscopy and analysis of hydrolytic products of **56a** (Figure 14).[12b] Kusumi and co-workers recently isolated these two alkaloids from marine-derived fungus *Aspergillus ostianus*.[12a] While studying the spectroscopic data of these isolated compounds, Kusumi and co-workers noticed some unusual observation. The UV spectra of (–)-Circumdatins A and B were similar to (–)-Circumdatins J (**24**), except that the bands at 340 nm were absent in the spectra of (–)-Circumdatins A and B. In the HMBC spectra of (–)-Circumdatins A and B, it showed unusual long range H-C couplings between H-13/C-10 and H-16/C-11 that is $^4J_{CH}$ with very intense cross peaks between these protons and carbons. Hence, structural reassignment was subjected for single X-ray crystal analysis which revealed the oxepin framework structures **56b** and **57b**, for which observed H-C couplings is more reasonable between H-12/C-10 and H-15/C-17 ($^3J_{CH}$).[12a]

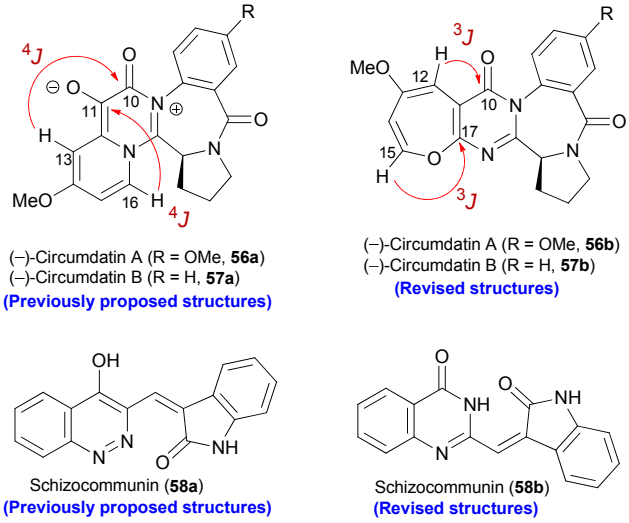

Figure 14. Structure revision of Circumdatin A/B and Schizocommunin.

Schizocommunin (**58a**) was isolated in 1999 from the liquid culture medium of *Schizophyllum commune*, strain IFM 46788 (monokaryon) which showed strong cytotoxic activity against murine lymphoma cells.[21a] Very recently, Nishida and co-workers during synthetic efforts on Schizocommunin (**58a**), revised its structure as **58b** on the basis of total synthesis of originally proposed structure **58a** and revised structure **58b**.[21b] Nishida and co-workers synthesized of originally proposed structure **58a** whose NMR spectral data was not identical with those of naturally isolated compound. Reinvestigation of NMR and IR spectral data of naturally isolated compound, they proposed revised structure as **58b**. Revised structure **58b** was synthesized from 2-methyl-4(3*H*)-quinazolinone and isatin in one step. Spectral data of synthetic Schizocommunin (**58b**) were entirely matching with naturally isolated Schizocommunin. Synthetic Schizocommunin (**58b**) showed antiproliferative activity against HeLa cells (Figure 14).[21b]

3. Total synthesis of quinazolinone alkaloids

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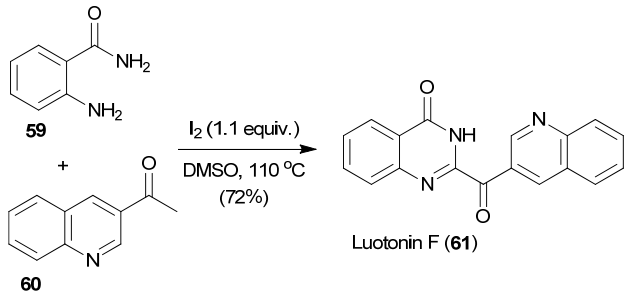
Quinazolinone alkaloids have the fascinating structures and their remarkable bioactivity has attracted synthetic community towards their synthesis. Number of research groups has reported variety of synthetic approaches to biologically active and complex quinazolinone alkaloids using various synthetic strategies and novel methods.

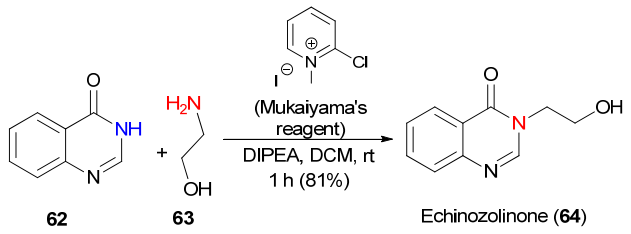
3.1 2-Substituted and 3-substituted quinazolinone alkaloid

Wu and co-workers demonstrated their developed Iodine catalyzed simple procedure for the one pot synthesis of luotonin F (**61**) from 2-aminobenzamides **59** and aryl methyl ketone **60** (Scheme 1).[22] One pot multiple reaction involved the iodination of methylketone followed by DMSO catalyzed Kornblum oxidation forms the corresponding aldehyde which on oxidative condensation procured the Luotonin F (**61**).



Scheme 1. I_2-catalyzed one-pot synthesis of Luotonin F from acetophenone.

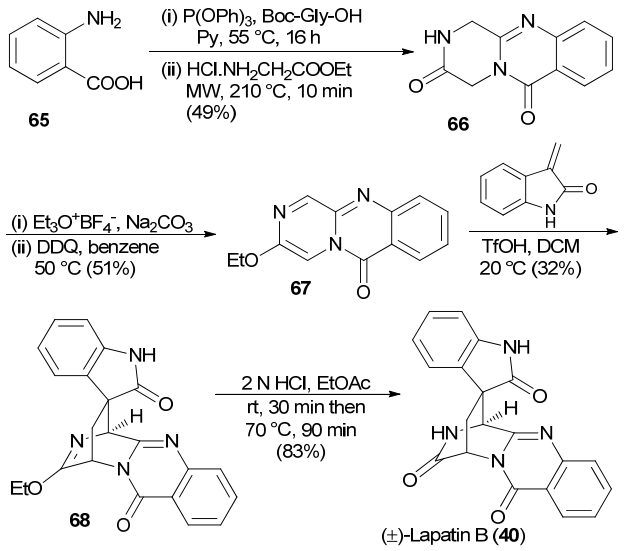
Wacharasindhu and co-workers synthesized Echiozolinone by demonstrating the Mukaiyama's reagent mediated coupling of unsubstituted quinazolinones **62** and simple amine **63** in 81% yield (Scheme 2).[23]



Scheme 2. Synthesis of Echiozolinone via Mukaiyama's reagent mediated coupling.

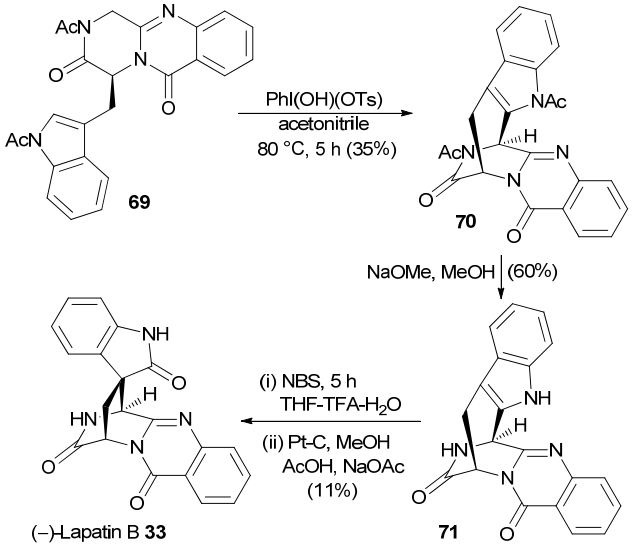
3.2 Lapatin and related spiroquinazolinones

Houk and co-workers reported the first total synthesis of microfungal alkaloid (±)-Lapatin B (**40**) in five steps with 8% overall yield via aza-Diels-Alder reaction as the key step (Scheme 3).[24a] Synthetic sequence presented in this synthesis was mimicked from Kende's versatile racemic synthesis of Alantrypinone.[24b,c] The pyrazino[2,1-*b*]quinazoline-3,6-diones (**66**) was prepared following the microwave mediated[24d,e,f] procedure from anthranilic acid **65**. Iminoether formation followed by DDQ oxidation afforded the azadienes **67** in good yields. Aazadiene **67** was subjected to Bronsted acid catalyzed hetero-Diels-Alder reaction with methelenoxindol which gave 32% exo product **68** along with the 30% endo product in 1:1 ratio. Hydrolysis of exo product **68** with 2 N HCl in ethyl acetate afforded (±)-Lapatin B (**40**) in 83% yield.



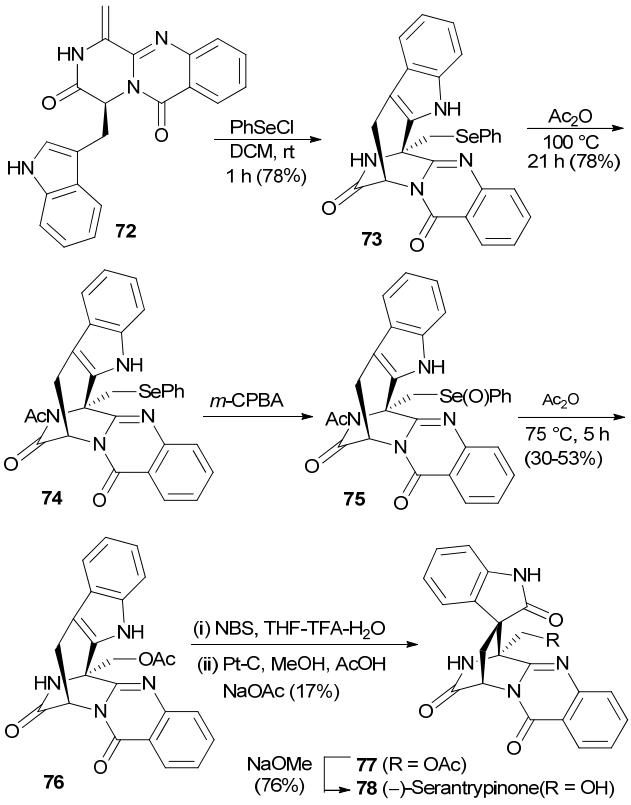
Scheme 3. First total synthesis of (±)-Lapatin B.

Enatioselective synthesis of (–)-Lapatin B (**40**) was achieved by Hart and co-workers in 10 steps with 0.26% overall yield from isatoic anhydride (Scheme 4)[25]. Required compound **69** was prepared from the (+)-Glyantrypine. Treatment of **69** with Koser's reagent [PhI(OH)(OTs)] gave bridged indole **70** in 35% yield via intramolecular cyclization. Upon treatment with a catalytic amount of sodium methoxide in methanol, the *N*-acetyl groups were removed to provide **71**. The synthesis was completed upon treatment of **71** with *N*-bromosuccinimide, followed by hydrogenolysis of the resulting brominated oxindoles over Pt-C. Herein the NBS-catalyzed structural rearrangement of compound **71** to the spiro-system **40** was noteworthy.



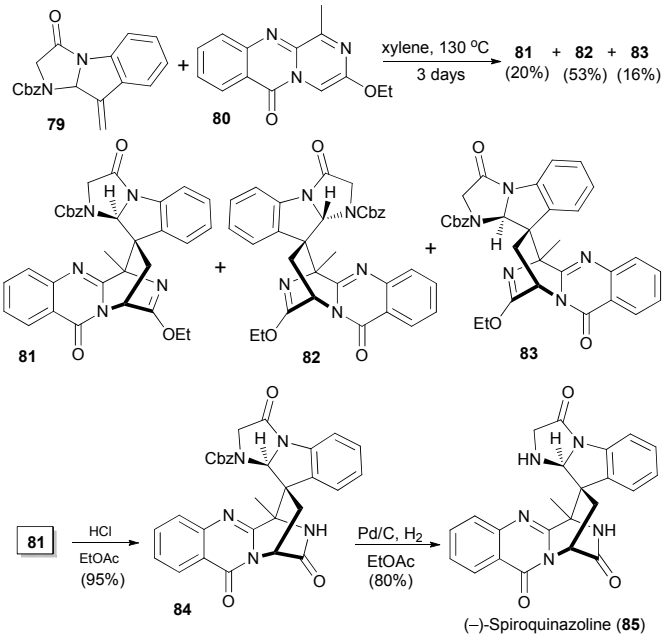
Scheme 4. First enantioselective synthesis of (–)-Lapatin B.

Hart and co-workers also accomplished the first total synthesis of (–)-Serantrypinone (**78**) (Scheme 5) in 12 steps from L-tryptophan methyl eater with 1.8% overall yield.[26a] Transformation of a selenoxide **75** to an acetate **76** via trapping of a presumed intermediate in a seleno-Pummerer reaction was the key feature of this synthesis. Compound **72** was prepared from L-tryptophan methyl ester in six steps.[26b] Treatment of compound **72** with phenylselenenyl chloride provided bridged indole **73** which was converted to selenoxides **75** via acylation and oxidation. Immediate reaction of selenoxides **75** with Ac_2O gave **76** in 30–53% yield via an intramolecular acyl migration. Mechanism of intramolecular acyl migration involves the activation of selenium by acylation of selenoxide of compound **75** followed by its nucleophilic displacement by NGP of *N*-acetyl group of imide which was followed by hydrolysis and imide N-C bond cleavage to afford the product **76**. Oxidative rearrangement of **76** by treatment with *N*-bromosuccinimide, followed by hydrogenolysis of the resulting brominated oxindoles on Pt-C provided spiro-oxindole **77**. Methanolysis of the ester **77** using sodium methoxide in DMSO provided (–)-Serantrypinone (**78**) in 76% yield.



Scheme 5. First total synthesis of (–)-Serantrypinone.

Several efforts for the synthesis of Spiroquinazoline (**85**) have been reported with no success.[27a-d] Ma and co-workers achieved the first total synthesis of (–)-Spiroquinazoline (**85**) along with first total synthesis of other indoline-containing spiroquinazoline alkaloids, namely (+)-Lapatin A (**39**), (–)-Alantryphenone (**44**) and (–)-Quinadoline B (**46**) using the aza-Diels-Alder reaction of aminal embodied olefines with azadienes in 11-12 steps (Scheme 6).[27e] Although similar aza-Diels-Alder reaction has been used earlier for the synthesis of alantrypinone and lapatin B by Kende,[24b,c] Houck[24a] and in the synthetic studies for Spiroquinazoline (**85**) by Hart,[27a-d] installation of aminal moiety remained unsuccessful. Ma and co-workers first time developed the aza-Diels-Alder reaction of aminal embodied olefines **79** with azadienes **80**. Aminal embodied olefin **79** was prepared from known compound 2-(2-nitrophenyl)prop-2-en-1-ol in five steps. Aza-Diels Alder reaction of **79** with the azadiene **80** in xylene at 130 °C afforded the desired adduct **81** in 20% yield, together with its two isomers **82** (53%) and **83** (16%). Hydrolysis of **81** followed by hydrogenolysis of formed lactam **84** furnished the (–)-Spiroquinazoline (**85**) in 8 steps from known compound 2-(2-nitrophenyl)prop-2-en-1-ol in 5.2% overall yield. Using same strategy, total synthesis of (+)-Lapatin A (**39**), (–)-Alantryphenone (**44**) and (–)-Quinadoline B (**46**) were acheived.[27e]



Scheme 6. First total synthesis of indoline-containing Spiroquinazolines.

3.3 Luotonin A

Human DNA topoisomerase I inhibitor, Luotonin A (**88**) which also exhibits potent cytotoxicity against P-388 cells is of intense interest of synthetic community. Malacria et al. have constructed Luotonin A (**88**) in eight steps with 4.7% overall yield (Scheme 7).[28a] Required *N*-acylcyanamide **87** was prepared from commercially available quinoline chlorocarbaldehyde **86** in seven steps. Cascade radical cyclization conditions with tributyltin hydride[28b,c] on *N*-acylcyanamide **87** did not afford the cyclized compound. The reaction proceeded with low conversion that turned into degradation when the precursor was maintained under the same reaction conditions. Gratifyingly, modified atom-transfer condition using hexabutylditin in refluxing toluene under

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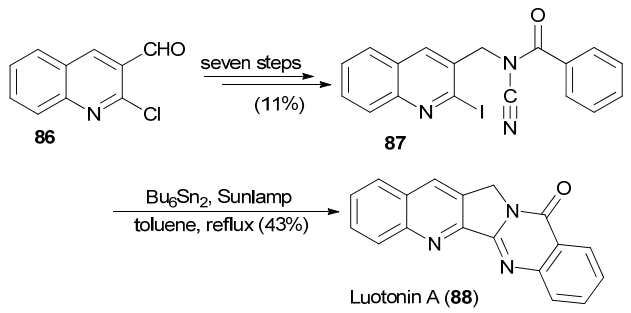
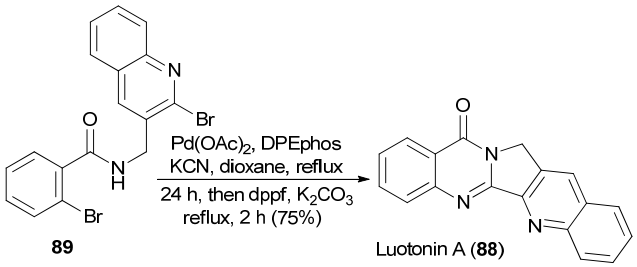
irradiation of sunlamp for 6 h successfully yielded Luotonin A (**88**) in 43% yield.



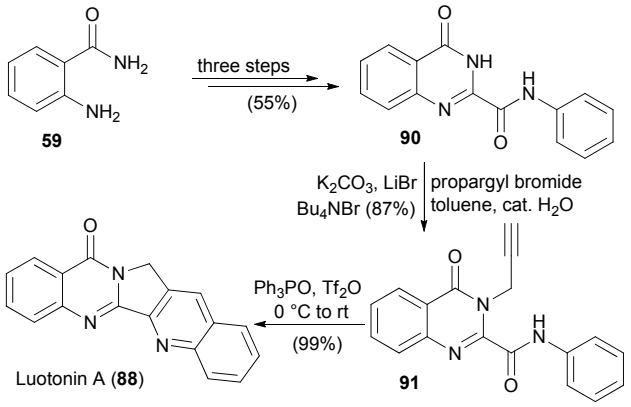
Scheme 7. Synthesis of Luotonin A via cascade radical cyclization.

Li and co-workers developed the straightforward, one pot procedure for the synthesis of pyrroloquinazolinones from *N*-(2-halobenzyl)-2-bromobenzamides via palladium catalyzed sequential cyanation/intramolecuar *N*-addition/intramolecular *N*-arylation.[29] Synthesis of Luotoine A (**88**) was achieved using this one pot method. *N*-(2-bromobenzyl)-2-bromobenzamide **89** was refluxed with $Pd(OAc)_2$ and KCN in presence of DPEphos as ligand for 24 hr followed by addition of dppf and K_2CO_3 and refluxed for additional 2 hr gave the Luotonin A (**88**) in 75% yield (Scheme 8).



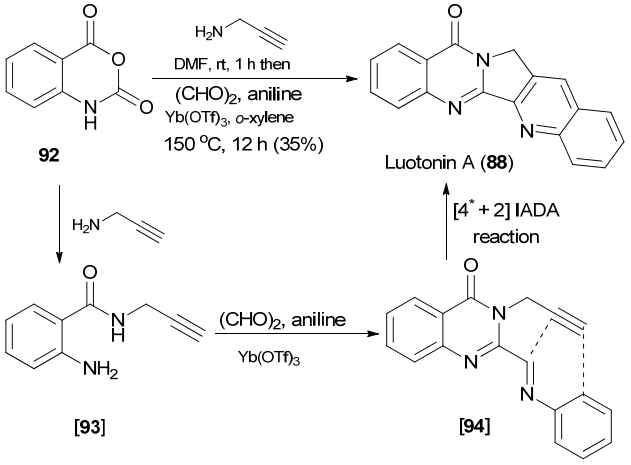
Scheme 8. Sequential cyanation/intramolecuar *N*-addition/intramolecular *N*-arylation.

Yao and co-workers synthesized the Luotonin A (**88**) using cascade annulations reaction as a key step in five steps with 47% overall yield (Scheme 9).[30] Starting from commercially available anthranilamide (**59**), amide **90** was prepared in three simple steps which was followed by *N*-alkylation with propargyl bromide provided the precursor amide **91** in 87% yield. Finally, the cascade annulation reaction was carried out by simple treatment of **91** with bis(triphenyl)-oxodiphosphonium trifluoromethanesulfonate at room temperature for 1 h affording Luotonin A (**88**) in 99% yield.



Scheme 9. Synthesis of Luotonin A via the cascade annulation strategy.

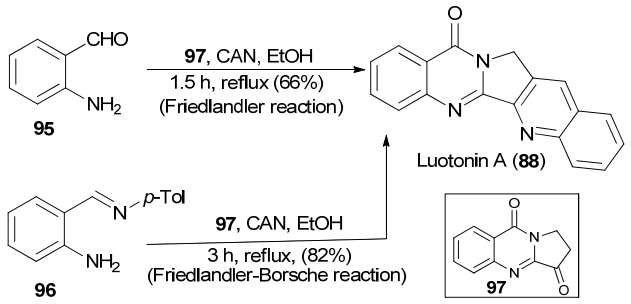
One-pot synthesis of Luotonin A (**88**) and its analogues was disclosed by Chu and et al. under Lewis acid catalysis. This approach presents the advantages of a one-pot route in moderate but acceptable isolated yield (Scheme 10).[31] This approach not only avoids the need of harsh basic or acidic conditions but also avoids the isolation and purification of any intermediates and allows concomitant construction of multiple rings. Synthesis proceed via the reaction of propargylamine with isatoic anhydride **92** to form an isolable intermediate **93** followed by the Lewis acid mediated formation of quinazolinone intermediate **94** via formation of the imine, ring-closing and subsequent dehydrogenation. $Yb(OTf)_3$ catalyzed, inverse electron-demand aza-Diels-Alder cycloaddition reaction in the intramolecular fashion (IADA) between *N*-phenyliminium azadiene and the electron-rich alkyne dienophile followed by aromatisation provided the Luotonin A (**88**) in 35% yield.



Scheme 10. $Yb(OTf)_3$-catalysed one pot synthesis of Luotonin A.

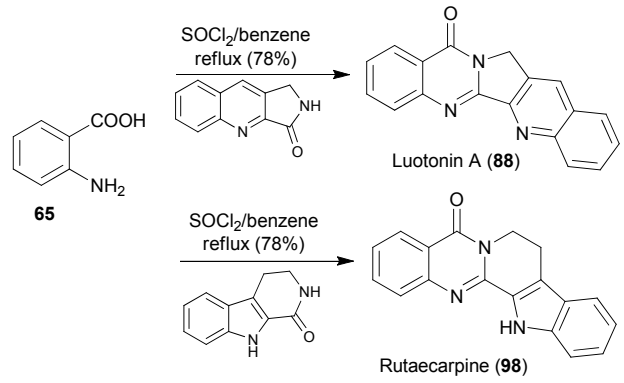
Menendez and co-workers developed a mild, environmentally friendly protocol of Friedlander and Friedlander-Borsche reactions under CAN catalysis, avoiding the need for harsh conditions.[32] This protocol has been used as key reaction for the one step synthesis of the Luotonin A (**88**) (Scheme 11). Cyclo-condensation between quinazolinone **97** and 2-aminobenzaldehyde (**95**) gave 66% of Luotonin A (**88**). Starting

from *N*-(2-aminobenzylidene)-4-methylaniline (**96**) as a 2-aminobenzaldehyde equivalent (Borsche modification of the Friedlander reaction) afforded 82% of Luotonin A (**88**).



Scheme 11. Luotonin A via CAN-catalyzed Friedlander-Borsche reactions.

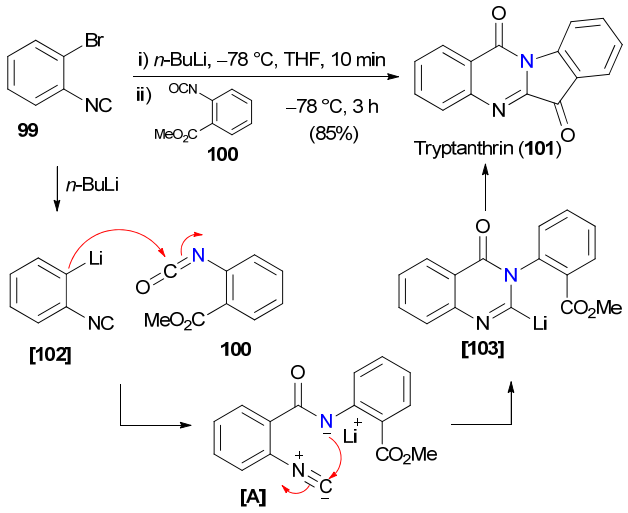
Jahng and co-workers reported the one pot synthesis of Luotonin A (**88**) and rutaecarpine (**98**) (Scheme 12). Reaction of anthranilic acid **65** with corresponding lactams in the presence of thionyl chloride provided corresponding quinazolinones in one pot.[33] Condensation reactions were proceed via the corresponding *N*-sulfinylanthraniloyl chloride intermediate.



Scheme 12. One-pot synthesis of Luotonin A and Rutaecarpine.

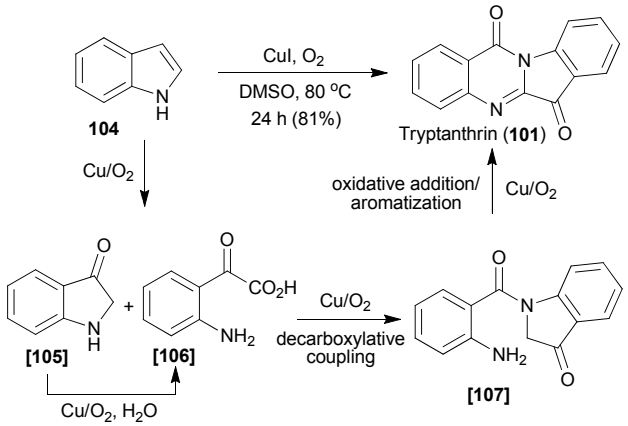
3.4 Tryptanthrin and Phaitanthrin alkaloids

Meijere group reported the one pot synthesis of Tryptanthrin (101) from *o*-bromophenylisocyanide **99** and isocyanate **100**. *In-situ* formation *o*-lithiophenylisocyanide **102** by treatment of *o*-bromophenylisocyanide **99** with *n*-BuLi by halogen-lithium exchange and subsequent trapping of *o*-lithiophenylisocyanide **102** with isocyanates **100** gave the lithium amide intermediate **A**. Intermediate **A** on intramolecular cyclization provided the intermediate **103** which on further intramolecular cyclization provided Tryptanthrin (**101**) in one step from **99** with 85% yield (Scheme 13).[34] Deoxyvasicinone, another quinazolinone natural product was also synthesized using same strategy.



Scheme 13. Synthesis of Tryptanthrin via *ortho*-lithiophenyl isocyanide.

In 2013, four reports on synthesis of Tryptanthrin and Phaitanthrin related natural products have been reported simultaneously from different research groups. Two approaches of them have been extended for the synthesis of Cruciferane (**109**). Wang and Lu group achieved the copper catalyzed cascade one pot synthesis of Tryptanthrin (**101**) starting from indole (**104**) (Scheme 14).[35] Transformation is believed to proceed via Cu-catalyzed aerobic oxidation of indol (**104**) to indolin-3-one **105** and α-oxoacetic acid **106** via isatin. Cu-catalyzed decarboxylative coupling of **105** and **106** followed by oxidation/intramolecular addition and aromatization gave the Tryptanthrin (**101**) in 81% yield.



Scheme 14. Synthesis of Tryptanthrin via Cu-catalyzed aerobic oxidation.

Nair and co-workers reported highly concise synthesis of (+)-Cruciferane (**109**) (Scheme 15).[36] Tryptanthrin (**101**) was prepared from isatoic anhydride **92** using known procedure. A chiral auxiliary mediated asymmetric acetate aldol reaction on tryptanthrin was carried out using LiHMDS as base to give **108** with 96% *ee* in 87% yield. Stereo- and Chemo-selective reductive transamidation of **108** by substrate controlled asymmetric induction provided the (+)-Cruciferane (**109**) in 50% overall yield.

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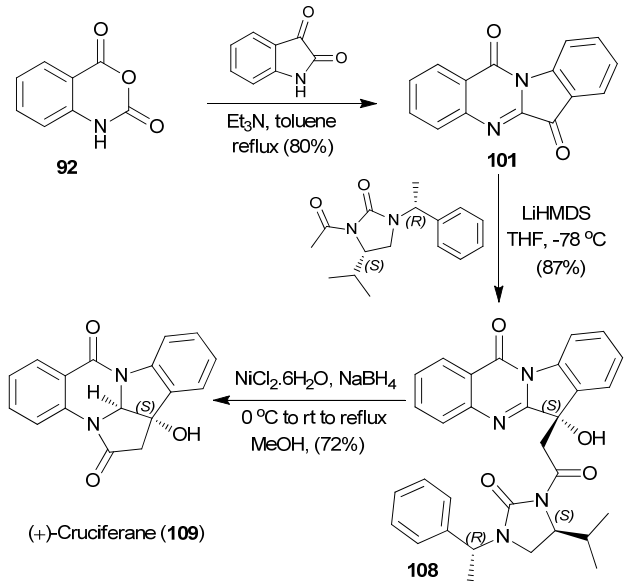
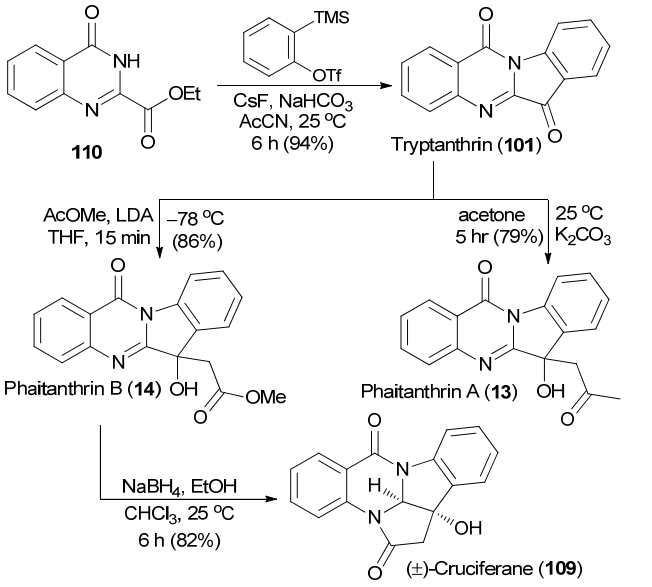


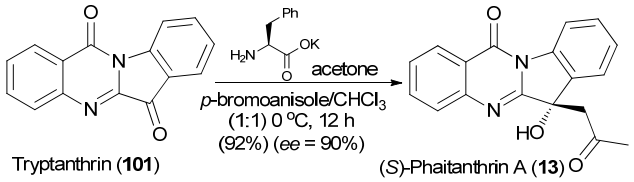
Scheme 15. Synthesis of (+)-Cruciferane chiral auxiliary mediated asymmetric acetate aldol reaction.



Scheme 16. Synthesis of Phaitanthrin A, B and Cruciferane.

Subsequently, Argade et al. disclosed the transition metal free, one step synthetic protocol for the Phaitanthrin and related fused quinazolinones (Scheme 16).[37] Synthesis of (±)-Cruciferane (**109**) was also acheived with 66% overall yield. Synthetic sequence involves the synthesis of Tryptanthrin (**101**), first synthesis of Phaitanthrin A (**13**) and B (**14**). Key step involved the trapping of *in-situ* generated aryne intermediate with quinazolinone **110** via *N*-arylation followed by concomitant intramolecular cyclization which provided Tryptanthrin (**101**) in 94% yield. Chemo-selective aldol condensation of Tryptanthrin (**101**) with acetone using K_2CO_3 as a base gave the Phaitanthrin A (**13**) in 79% whereas condensation of Tryptanthrin with methyl acetate using LDA as a base furnished Phaitanthrin B (**14**) in 86% yield. Hydroxyl group directed chemo and diastereo-selective reductive cyclization of Phaitanthrin B (**14**) using $NaBH_4$ furnished (±)-Cruciferane (**109**) in 82% yield.

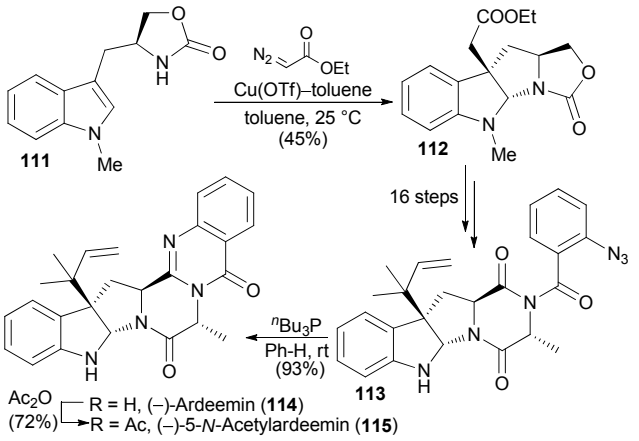
Asymmetric synthesis of (*S*)-phaitanthrin A (**13**) and its derivatives was disclosed by Jiang and co-workers via a cheap, easily prepared potassium salt of natural amino acid catalyzed asymmetric aldol reaction of Tryptanthrin (**101**) with ketones (Scheme 17).[38] Synthetic utility of this strategy was further illustrated by a gram-scale synthesis of (*S*)-Phaitanthrin A (**13**).



Scheme 17. Asymmetric synthesis of (*S*)-Phaitanthrin A.

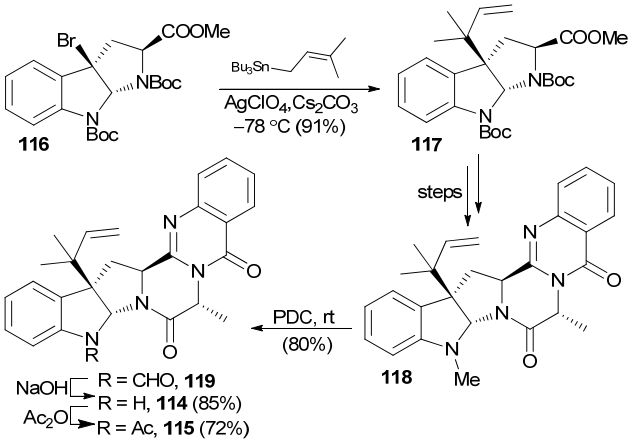
3.5 Ardeemin and related alkaloid

Qin and co-workers have accomplished the total synthesis of (–)-Ardeemin (**114**) from L-tryptophan in 20 steps with 2% overall yield and (–)-5-*N*-Acetylardeemin (**115**) (Scheme 18).[39] Key step was the copper catalyzed one pot three step cascade reaction (intermolecular cyclopropanation, ring opening and ring closer) of the oxazolidinone **111** with diazoester which smoothly assembled the hexahydropyrrolo[2,3-*b*]indole **112** with three stereocenters corresponding to natural products. Compound **112** was converted in to *o*-azidobenzoylated diketopiperazine **113** in 16 routine steps. Compound **113** was converted in to (–)-Ardeemin (**114**) and (–)-5-*N*-Acetylardeemin (**115**) via intramolecular aza-Wittig reaction.



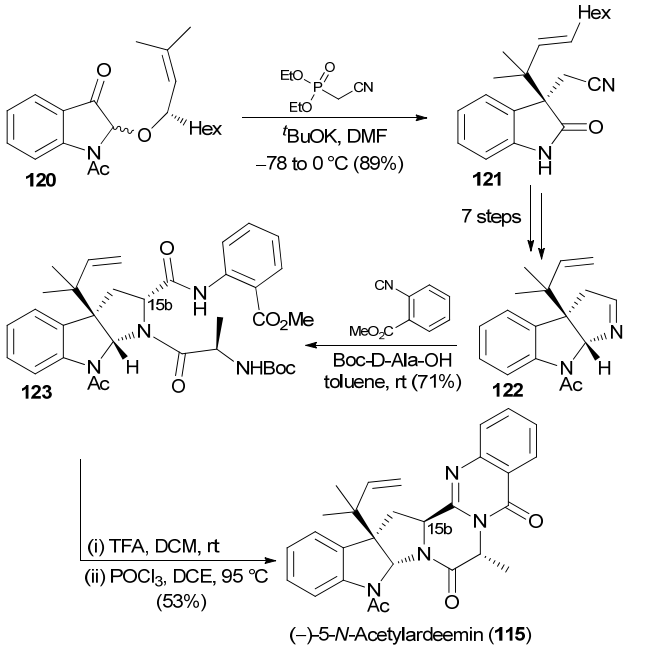
Scheme 18. Synthesis of (−)-Ardeemin and (−)-5-*N*-Acetylardeemin.

Qin group recently accomplished new syntheses of (−)-Ardeemin (**144**) and (−)-5-*N*-Acetylardeemin (**115**) in 10 and 11 steps with 26 and 19% overall yield from L-tryptophan derivative (Scheme 19).[40a] Silver-promoted asymmetric Friedel–Crafts isoprenylation of bromopyrroloindoline **116** was the key reaction of synthesis which was developed by Qin group by inspiring form Danishefsky's[40b,c] direct prenylation strategy.



Scheme 19. Synthesis of (−)-Ardeemin and (−)-5-*N*-Acetylardeemin.

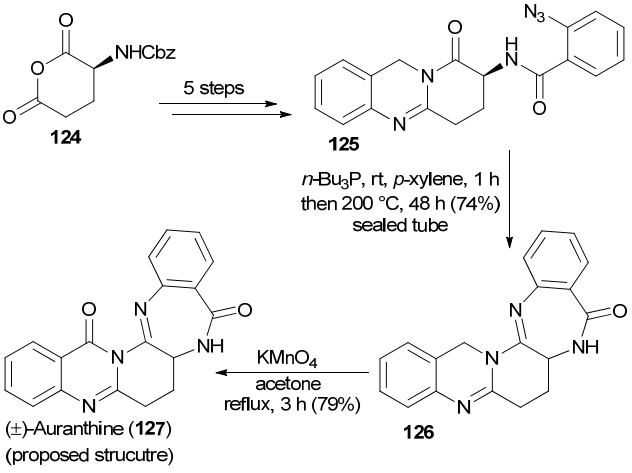
Kawasaki group approach synthesized (–)-5-*N*-Acetylardeemin (**115**) was in 13 steps with 32% overall yield (Scheme 20).[41] Compound **120** on domino olefination/isomerization/Claisen rearrangement (OIC) provided oxindole **121**. Enantioselective preparation of advanced imine intermediate **122** was carried out in seven-step reaction sequence including reductive cyclization and regioselective oxidation on oxindole **121**. (–)-5-*N*-Acetylardeemin (**115**) was assembled via stereoselective three-component Ugi reaction on **122** with the Boc- protected alanine and isonitrile to give **123** followed by removal of the Boc-group and successive heating with $POCl_3$ with epimerizion at C-15b in 53% yield.



Scheme 20. Synthesis (–)-5-*N*-Acetylardeemin.

3.5 Quinazolinobenzodiazepine alkaloids

First total synthesis of proposed structure of Auranthine (**127**) was accomplished by Argade group. Synthesis was achieve in seven steps with 30% overall yield starting from Cbz-protected glutamic anhydride **124** using late-stage chemoselective oxidation strategy (Scheme 21).[42] An intramolecular aza-Wittig reaction involving a lactam carbonyl group that delivered the diazepine core unit was the key step in the synthesis. An intramolecular aza-Wittig reaction of compound **125** gave the compund **126**. The $KMnO_4$ induced chemoselective oxidation on **126** provided the proposed structure of (±)-Auranthine (**127**). However the ^{1}H NMR spectrum of synthetic compound **127** was not in agreement with the ^{1}H NMR spectrum of naturally isolated compound. Finally, the structure of synthetic Auranthine (**127**) was confirmed on the basis of X-ray crystallographic data. These results clearly revealed that a revision of the structure of natural Auranthine is necessary.



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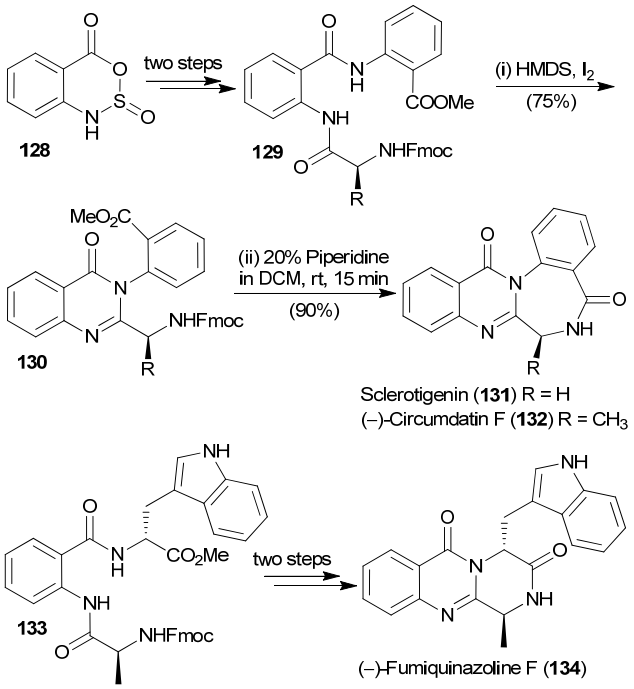
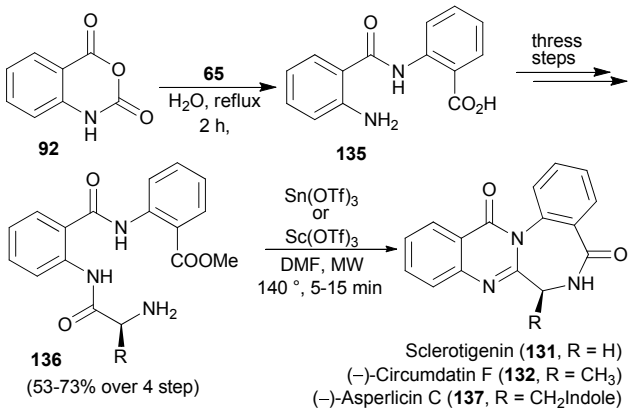
Scheme 21. Synthesis of proposed structure of Auranthine.

Argade and co-workers reported the concise synthesis of Sclerotigenin (**131**), (–)-Circumdatin F (**132**) and (–)-Fumiquinazoline F (**134**) by demonstrating direct intramolecular dehydrative cyclization approach of **129** to **130** by employing HMDS/I_2 as the key step (Scheme 22).[43] Required diamides **129** were prepared in two steps from sulfinamide **128**. HMDS/I_2 catalyzed intramolecular dehydrative cyclization of diamides **129** provided cyclised compounds **130** in 75% yields which on removal of protecting group directly furnished the Sclerotigenin (**131**) and (–)-Circumdatin F (**132**) in 35% overall yields in four steps. Using similar approach, (–)-Fumiquinazoline F (**134**) was prepared starting from isatoic anhydride **92** with 75% overall yield in four steps.



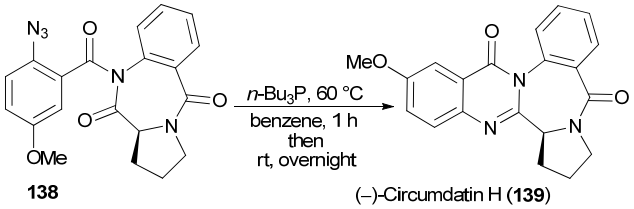
Scheme 22. HMDS/I_2-catalyzed intramolecular cyclization of diamides.

Chu and co-workers reported the syntheses of Sclerotigenin (**131**), Circumdatin F (**132**) and Asperlicin C (**137**) (Scheme 23).[44] Required tripeptides **136** were prepared from isatoic anhydride (**92**) and anthranilic acid (**65**) in four step sequence. Microwave irradiated, Tin triflate[44a] and Scandium triflate[44b] catalyzed double cyclization of bis(anthranilate)-containing tri-peptide **136** afforded directly the quinazolinones **131/132/137** which was the key step of synthesis. Quinazolinones **131/132/137** were synthesized in five steps with 23-65% and 23-43% overall Yields. Conventional heating instead of microwave irradiation results in some racemization.



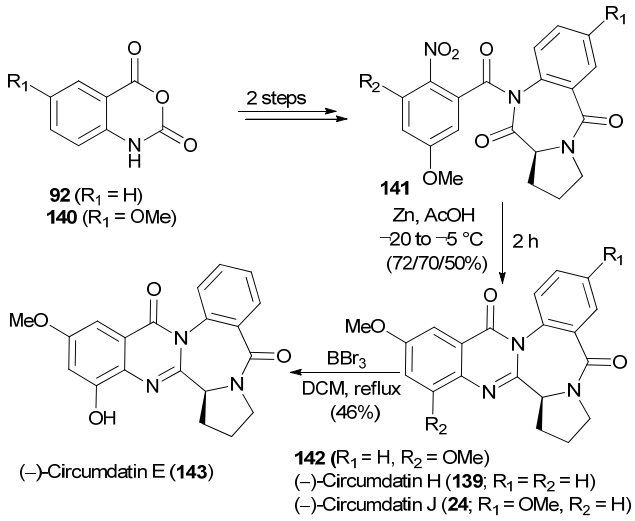
Scheme 23. $Sn(OTf)_3$/$Sc(OTf)_3$-catalyzed double cyclizations.

Bose et al. reported the first total synthesis of (–)-Circumdatin H (**139**), a novel mitochondrial NADH oxidase Inhibitor (Scheme 24).[45] Intermediate **138** was prepared from anthranilic acid derivatives in convergent manner which on intramolecular aza-Wittig reaction of azide with imide carbonyl provided the (–)-Circumdatin H (**139**) in 4 step with 48% overall yield. Intramolecular aza-Wittig reaction was the key step of synthesis.



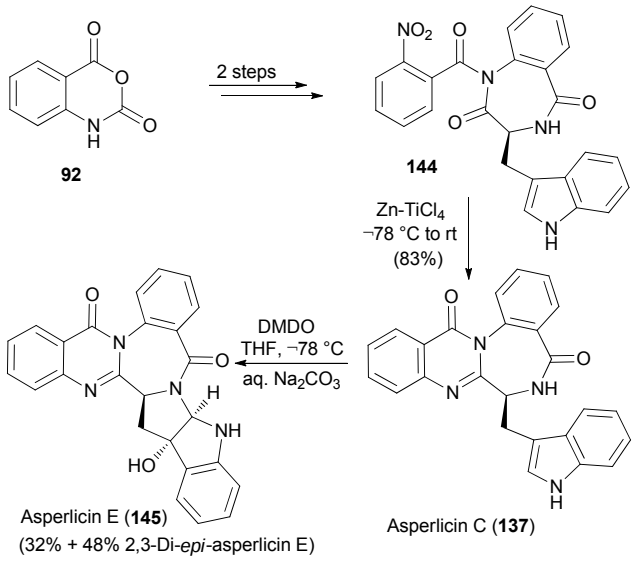
Scheme 24. First total synthesis of (–)-Circumdatin H.

The first total synthesis of (–)-Circumdatin J (**24**) and E (**143**) and synthesis of (–)-Circumdatin H (**139**) was reported from Zichkin group, where the key step was intramolecular reductive cyclization of intermediates **141** (Scheme 25).[46] Intermediates **141** were prepared from isatoic anhydride in two steps which were used for further reaction without isolation. Intramolecular reductive cyclization reaction was performed using Zinc in acetic acid which smoothly afforded (–)-Circumdatin H (**139**) and J (**24**) in 65 and 61% overall yield in 3 steps and compound **142**. Regioselective methoxy group deprotection of compound **142** was carried out with careful treatment on BBr_3 which afforded (–)-Circumdatin E (**143**) in 21% overall yield in 4 steps.



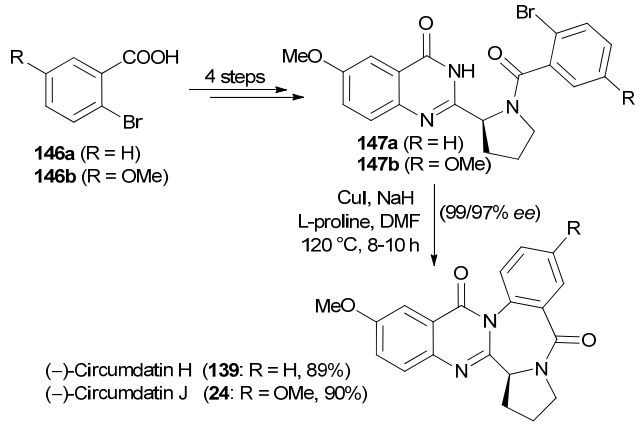
Scheme 25. Synthesis of quinazolinobenzodiazepine alkaloids via reductive cyclization.

Recently, Huang and co-workers reported the synthesis of Asperlicin C (**137**) and E (**145**) (Scheme 26) demonstrating similar type of reductive cyclization approach using low-valent titanium catalyst system ($Zn/TiCl_4$) as the catalyst.[47a] Intermediate **144** was prepared from isatoic anhydride **92** in two steps. Reductive cyclization of compound **144** using $Zn/TiCl_4$ afforded Asperlicin C (**137**) in 83% yield. Demonstrating same approach, Circumdatin F (**132**) and H (**139**) were also prepared.[47b] Oxidative cyclization of Asperlicin C (**137**) with the treatment of dimethyldioxirane (DMDO) gave another natural product Asprlicin E (**145**) in 32% with 48% of its diastereomer 2,3-Di-*epi*-asprlicin E.



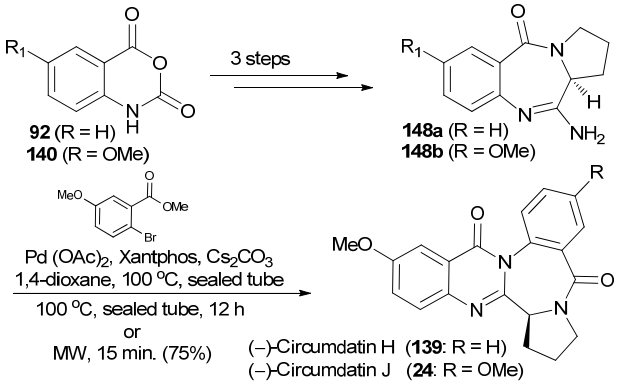
Scheme 26. Synthesis of quinazolinobenzodiazepine alkaloids via reductive cyclization.

The first copper-catalyzed intramolecular *N*-arylation reaction of quinazolinone nucleus with the noteworthy generation of a central benzodiazepine unit was the key step in the Argade et al.'s synthesis of (–)-Circumdatins H (**139**) and J (**24**) (Scheme 27).[48] Essential intermediate compounds **147a/b** were prepared from bromobenzoic acids **146a/b** in four simple and routine steps. The copper-catalyzed intramolecular *N*-arylation of compounds **147a/b** using L-proline as the ligand exclusively furnished the desired products (–)-Circumdatin H (**139**) and (–)-Circumdatin J (**24**) with 68 and 59% overall yields in five steps with 99 and 97% *ee* respectively.



Scheme 27. Cu-catalyzed intramolecular *N*-arylation of quinazolinones.

Sorra and co-workers used the Pd-catalyzed annulations strategy as the key step in the synthesis of (–)-Circumdatins H (**139**) and J (**24**) (Scheme 28).[49] Amidine intermediates **148a/b** were prepared from isatoic anhydrides **92/140** in three steps. Pd-catalysed *N*-arylation of these amidine derivatives with 5-methoxy-2-bromobenzoate followed by intramolecular cyclization provided Circumdatin H (**139**) and J (**24**) in 4 steps with 49/53% overall yield.



Scheme 28. Circumdatin H/J via Pd-catalyzed annulations strategy.

Liu et al. reported highly efficient, microwave assisted domino reaction of anthranilic acid (**65**) with amino acids catalyzed by $P(OPh)_3$ for the synthesis of Sclerotigenin (**131**), Circumdatin F (**132**) and Asperlicine C (**137**), Deoxyvacisicinone (**149**) and Mackinazolinone (**150**) in one step. Isaindigotone (**151**) was synthesized by the treatment of Deoxyvacisicinone (**149**) with 4-hydroxy-3,5-dimethoxybenzaldehyde (Scheme 29).[50]

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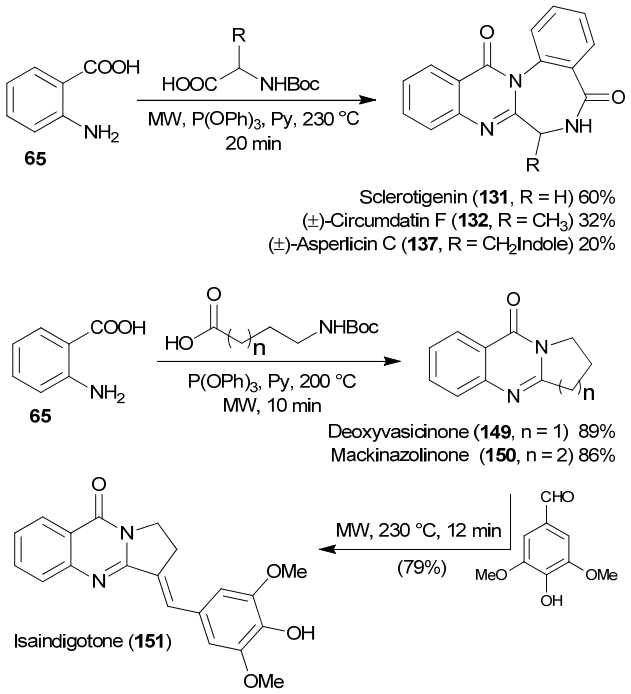


Scheme 29. $P(OPh)_3$ catalyzed microwave assisted domino reaction.

3.6 Chaetominine

Due to the intriguing molecular architecture and potential as a lead compound for anticancer drugs, (–)-Chaetominine (**5**) has attracted immediate interest from the synthetic community after its isolation which culminated in various synthetic approaches for this molecule which are summarized briefly in Figure 14.[5b,51a,52,53] Snider and Wu, in a very short span of time from isolation, reported first total synthesis of (–)-Chaetominine (**5**)[51a] using the potential intermediate from their (–)-Fumiquinazoline synthesis[51b]. From D-tryptophan methyl ester (**152**), (–)-Chaetominine (**5**) was synthesized in 13 steps in 4.6% overall yield. Second synthesis of (–)-Chaetominine (**5**) was reported by Evano and co-workers where the Cu catalyzed cyclization reaction was the key step to install the ABC-tricyclic ring system and total synthesis was achieved in 14 steps with 10% overall yield from D-tryptophan (**153**).[52a] Subsequently, Evano and co-workers also reported improved and short synthesis[52b] of (–)-Chaetominine (**5**) in which the efficient domino process involving a diastereoselective oxidative cyclization with NCS under O_2 atmosphere was the key step. This provides a straightforward route to the (–)-Chaetominine (**5**) in nine steps with 14% overall yield. Third synthesis was accomplished by Papeo and co-workers in nine steps with 9% overall yield from D-tryptophan methyl ester (**152**).[5b] Stereoselective manipulation of the indole double bond via an oxidation–reduction sequence and early stage introduction of quinazolinone moiety and late stage introduction of hydroxyl group to secure the (–)-Chaetominine (**5**) were the key features of synthesis.

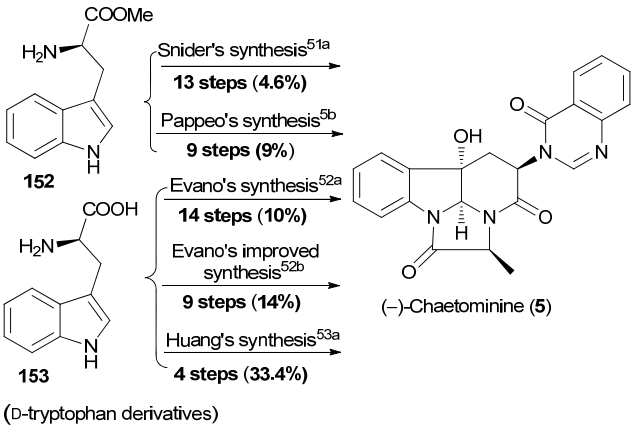
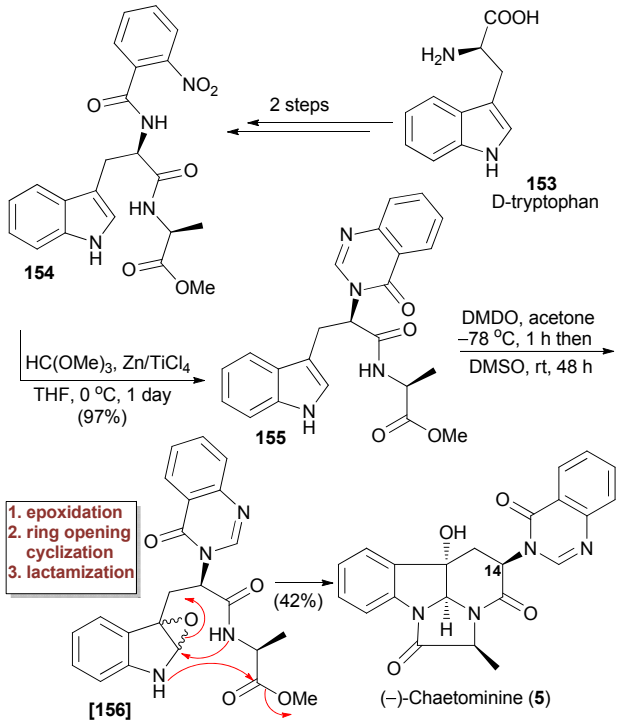


Figure 15. Various synthetic reports for (–)-Chaetominine.

Very recently Huang and co-workers reported the very concise and efficient, step and redox economical and protecting group free total synthesis of (–)-Chaetominine (**5**) in only 4 steps with an 33.4% overall yield from D-tryptophan (**153**) (Scheme 30).[53a] The key feature of this approach is one-pot formation of (–)-Chaetominine (**5**) from the intermediate **155** via a one-pot cascade indole epoxidation, epoxide ring opening, cyclization and lactamization reaction sequence. This synthesis is the shortest synthesis with the highest overall yield so far.



Scheme 30. Huangs's step and redox economical and protecting group free synthesis of (–)-Chaetominine.

Huang group also showed that (–)-Chaetominine (**5**) can also synthesize starting from natural amino acid L-tryptophan (**157**) using same strategy (Scheme 31).[53b] Starting from L-tryptophan (–)-Chaetominine (**5**) was synthesized in five steps

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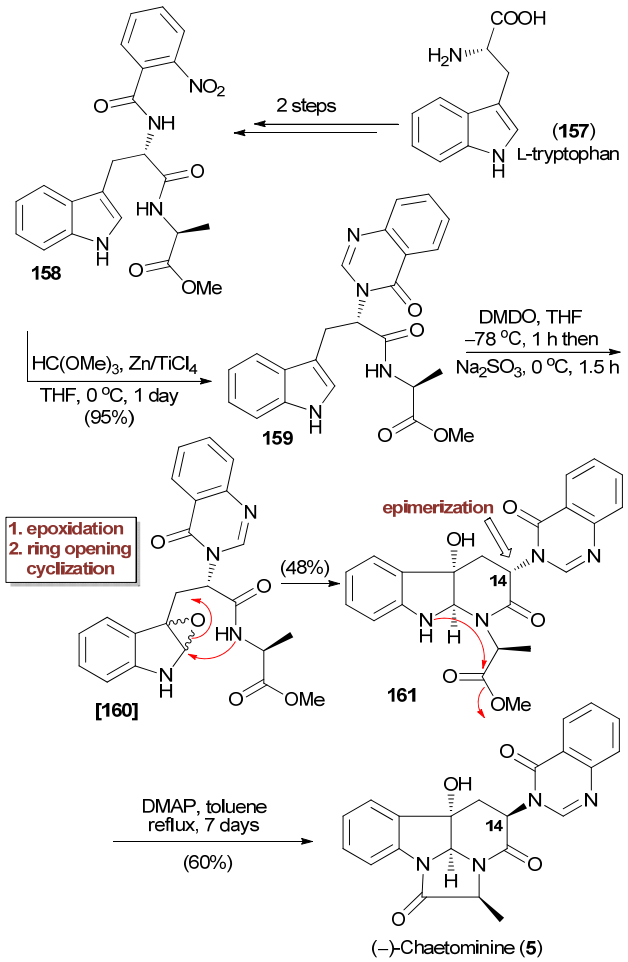
with 23.2% overall yield by base catalyzed regioselective epimerization at C14.[53b]



Scheme 31. Huangs's synthesis of (–)-Chaetominine from L-tryptophan via C14 epimerization.

Conclusions

A concise account of the recent developments in the chemistry of quinazolinone has been presented. Isolation and biological activities of about 55 quinazolinone alkaloids which have been isolated during this period are discussed. Synthetic efforts for complex quinazolinone alkaloids by different research groups have been covered. Emphasis is placed on key reaction of the synthesis. Given the advances in synthetic methodology and technology in recent years and the continued interest in the quinazolinone skeleton in medicinal chemistry and drug development, the development of efficient and reliable methods for the construction of these molecules ensure that this is an active and important area of research in chemistry. Quinazolinone field will be of continuing interest to both the synthetic and medicinal chemists and positively there will be interminable promising advancements in the knowledge. A look at the recent literature also revealed that the histogram of the quinazolinone chemistry is in escalating slope and increasing medicinal and pharmaceutical demanding natural and designed quinazolinones would maintain the high positive slope in the present day world of medicinal and synthetic chemistry.

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