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The chemistry of recently isolated naturally occurring quinazolinone alkaloids☆

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Abstract—The present review portrays a concise account of the isolation, bioactivity, and synthesis of bioactive quinazolinone-based natural products for the period 1983–2005 and the recent developments in the area of complex quinazolinone natural products with a special emphasis on new synthetic routes and strategies.

Contents

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Keywords: Natural quinazolinones; Isolation; Bioactivity; Synthesis; Concise account; 1983–2005.

Abbreviations: AIBN, 2,2′-azobisisobutyronitrile; Bn, benzyl; Boc, *tert*-butoxycarbonyl; BOP, benzotriazol-1-yloxytris(dimethylamino)-phosphoniumhexafluorophosphate; CAN, ceric ammonium nitrate; Cbz, carbobenzyloxy; CCK, cholecystokinin; COX-2, cyclooxygenase-2; CyH, cyclohexane; DBP, dibenzoyl peroxide; DBU, 1,8-diazabicyclo[5.4.0]undec-7-ene; DCC, 1,3-dicyclohexylcarbodiimide; DCM, dichloromethane; DDQ, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone; DEAD, diethyl azodicarboxylate; DMA, dimethyl acetamide; DMAP, 4-(dimethylamino)pyridine; DMF, dimethylformamide; DMSO, dimethyl sulfoxide; DPPF, diphenylphosphinoferrocene; $Dy(OTf)_3$, dysprosium trifluoromethanesulfonate; EDAC, *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride; EDC, *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide; Fmoc, 9-fluorenylmethoxycarbonyl; IC, inhibitory concentration; KHMDS, potassium hexamethyldisilazide; LAH, lithium aluminum hydride; LDA, lithium diisopropylamide; Lipase PS, lipase from *Burkholderia cepacia*; *m*-CPBA, *meta*-chloroperbenzoic acid; MDR, multiple drug resistance; MF, molecular formula; MS, molecular sieves; MW, microwave; NBS, *N*-bromosuccinimide; NMP, *N*-methylpyrrolidinone; PCC, pyridinium chlorochromate; PCy_3, tricyclohexylphosphine; $Pd_2(dba)_3$, tris(dibenzylideneacetone)dipalladium; PPA, polyphosphoric acid; PPTS, pyridinium *p*-toluenesulfonate; *p*-TsCl, *p*-toluenesulfonyl chloride; *p*-TsOH, *p*-toluenesulfonic acid; Py, pyridine; TBAF, tetrabutylammonium fluoride; TBDMS, *tert*-butyldimethylsilyl; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; TEA, triethylamine; TFA, trifluoroacetic acid; TFAA, trifluroacetic anhydride; THF, tetrahydrofuran; TMSCl, trimethylchlorosilane; TMSI, trimethyliodosilane.

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1. Introduction

Quinazolinone (Fig. 1) is a building block for approximately 150 naturally occurring alkaloids isolated to date from a number of families of the plant kingdom, from animals and from microorganisms. The first quinazolinone was synthesized[1] in the late 1860s from anthranilic acid and cyanogen to give 2-cyanoquinazolinone (**1**, Fig. 2). Interest in the medicinal chemistry of quinazolinone derivatives was stimulated in the early 1950s with the elucidation of a quinazolinone alkaloid, 3-[β-keto-γ-(3-hydroxy-2-piperidyl)-propyl]-4-quinazolone [febrifugine[2] (**2**), Fig. 2], from an Asian plant *Dichroa febrifuga*, which is an ingredient of a traditional Chinese herbal remedy, effective against malaria.

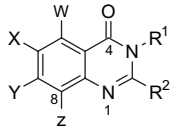


Figure 1. Quinazolinone basic structure.

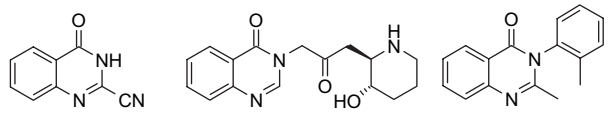


Figure 2. Synthetic and natural quinazolinones.

In a quest to find additional potential quinazolinone-based drugs, various substituted quinazolinones have been synthesized, which led to the synthesis of the derivative, 2-methyl-3-*o*-tolyl-4-(3*H*)-quinazolinone [methaqualone (**3**), Fig. 2]. Methaqualone (**3**) was synthesized[3] for the first time in 1951 and it is the most well-known synthetic quinazolinone drug, famous for its sedative–hypnotic effects.[4] The introduction of methaqualone and its discovery as a hypnotic triggered the research activities toward the isolation, synthesis, and studies on the pharmacological properties of the quinazolinones and related compounds. Quinazolinones and their derivatives are now known to have a wide range of useful biological properties, such as hypnotic, sedative, analgesic, anti-convulsant, anti-tussive, anti-bacterial, anti-diabetic, anti-inflammatory, anti-tumor, and several others.[5,6] The chemistry of the quinazolinone alkaloids is well documented[5,6] in a number of comprehensive reviews and monographs and is continuously updated in *Natural Product Reports*.[7]

The review by Johne[6b] has covered the literature of all the quinazolinone natural products isolated up to the middle of 1983. After 1983, relatively few reviews have appeared on quinazolinones, which were very specific to either selected natural products[5,6i] or to general quinazolinone synthetic methods.[6g,h] Quinazolinone is an important pharmacophore and several new natural products have been isolated and synthesized during the past two decades. We, therefore feel that a complete literature review of all the quinazolinone natural products isolated after 1983 is necessary at this point in time. Accordingly, the present review portrays a concise account of the isolation, bioactivity, and synthesis of naturally occurring quinazolinone alkaloids isolated after the middle of 1983 up to 2005, pertaining strictly to the basic structure shown in Figure 1 and recent developments in the area of the complex quinazolinone natural products, with an emphasis on new synthetic routes and strategies. The chemistry of quinazolinone alkaloids is published in a broad range of scientific journals. We have tried, to the best of our ability, to assemble and present the information on natural quinazolinones in this report, but no pretension of completeness is claimed. In order to simplify and understand the chemistry of the naturally occurring quinazolinone alkaloids, these compounds have been divided into subclasses according to their structures. Each group contains information about the natural products in tabular form, incorporating their structure, name, molecular formula, species from which they were isolated, bioactivity, and references pertaining to synthesis. A table is followed by a discussion and illustration of the synthesis of the representative quinazolinone alkaloids from the list. In the last part, the biological activity of quinazolinones and their applications in clinical treatments have been discussed and this is followed by a final summary.

Quinazolinone derivatives are of interest because of their pharmacological properties,[6g,8] e.g., protein tyrosine kinase inhibitory, cholecystokinin inhibitory, anti-microbial, anti-convulsant, sedative, hypotensive, anti-depressant, anti-inflammatory, and anti-allergy properties. Some of these compounds also have interesting biological properties[8] such as anti-malarial activity, biofungicide, and diuretic properties. A literature survey has revealed that there are about 75 new quinazolinone-based natural products isolated under the present review period, and these were characterized by UV, IR, ^{1}H NMR, ^{13}C NMR, 2D NMR, and mass spectroscopic methods, together with X-ray crystallographic analysis data. In view of the importance of quinazolinones and their derivatives, many classical methods for their synthesis have been reported in the literature.[5,6g,h,8,9] 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.[5] Other important methods include coupling of *O*-methylbutyrolactam with anthranilic acid, cycloaddition of anthranilic acid iminoketene to 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.[9]

All the important methods for the synthesis of the quinazolinone alkaloids are described in the following sections in detail. These alkaloids have been divided into six major categories according to their structural features and further subdivided depending on their substitution pattern.

2. Quinazolinones substituted at 2- and/or 3-positions

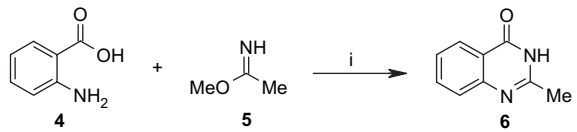
These compounds are simple quinazolinones substituted at 2- and/or 3-positions. They are further divided into subclasses depending on the position of the substituents.

2.1. Simple 2-substituted quinazolin-4-ones

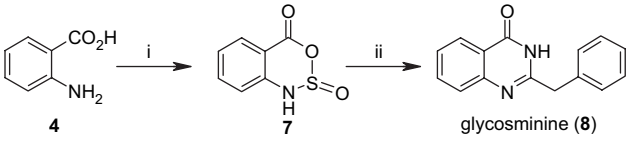
Three simple 2-substituted quinazolin-4-ones isolated from various species under the review period are listed in Table 1.

2-Methyl-4(3*H*)-quinazolinone (**6**) was isolated from culture of the microorganism *Bacillus cereus*[10a] and has been prepared synthetically before its isolation.[10a] Recently, it was synthesized by Connolly and Guiry.[11] In their general approach to the synthesis of this type of alkaloids (Scheme 1), in which a straightforward condensation between anthranilic acid (**4**) and various imidates of general formula RC(=NH)OMe in boiling methanol produced a range of 2-substituted quinazolin-4(3*H*)-ones, e.g., condensation with the imidate **5** produced the alkaloid **6** (Table 1, entry 1) in 42% overall yield. A more efficient one-pot approach to this type of moiety was provided by Kametani et al.,[16] in which a natural product, glycosminine (**8**), has been synthesized starting from anthranilic acid via a sulfonamide anhydride **7** in 40% overall yield (Scheme 2).

The natural product, 2-(4-hydroxybutyl)-quinazolin-4-one (Table 1, entry 2), is a one-carbon homologue of the cytotoxic alkaloid, pegamine, i.e., 2-(3-hydroxypropyl)-quinazolin-4-one, a natural product isolated from *Peganum harmala*.[17] We have synthesized both these natural products in our research group and have further transformed them into the natural products, mackinazolinone[14] and deoxyvasicinone,[18] respectively. To date, no synthetic approach to bouchardatine (Table 1, entry 3) is known in the literature. The natural product, luotonin F, also comes under this structural



Scheme 1. Reagents and conditions: (i) MeOH, 25 °C, 30 min, then 80 °C, 6 h (42%).



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

class of alkaloids and, for better representation, it will be discussed under the luotonin class of alkaloids in Section 4.

2.2. 3-Substituted quinazolin-4-ones

Nine natural 3-substituted quinazolin-4-ones have been isolated from various species (Table 2, entries 1–9) during the present review period.

(+)-Hydrachine A was reported to be a new natural product isolated from *Hydrangea chinensis*,[26a] but the discoverers with the help of additional NMR have now conceded that (+)-hydrachine A and the alkaloid, (+)-neodichroine, isolated from *D. febrifuga*[12] are identical, although there is still doubt about the absolute stereostructure.[26b]

A general route to this structural type can be exemplified by two recent approaches. In a search to speed up an aspect of drug-discovery processes, Besson et al.[27] have

Table 1. Simple 2-substituted quinazolin-4-ones

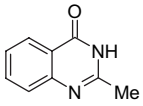
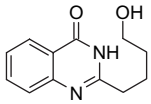
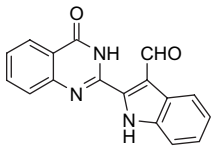
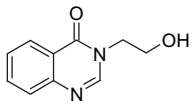
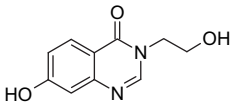
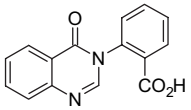
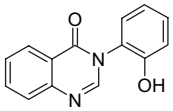
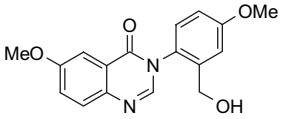
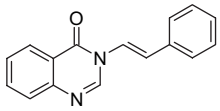
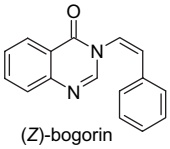
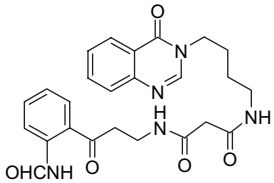
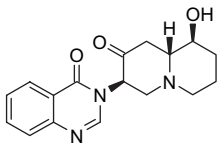
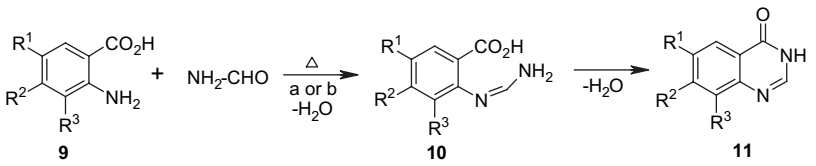
Entry	Quinazolinone alkaloid (MF)	Source[Ref.] (activity)	Synthesis[Ref.]
1	 2-methyl-4(3*H*)-quinazolinone ($C_9H_8N_2O$)	*Bacillus cereus*[10a] BMH225-mF1, *Streptomyces sp.*[10b] GW23/1540 (low acute toxicity in mice)	Synthesis known before isolation[10a] Connolly and Guiry[11]
2	 2-(4-hydroxybutyl)quinazolin-4-one ($C_{12}H_{14}N_2O_2$)	*Dichroa febrifuga*[12]	Synthesis known before isolation[13] Mhaske and Argade[14]
3	 bouchardatine ($C_{17}H_{11}N_3O_2$)	*Bouchardatia neurococca*[15]	Not known

Table 2. 3-Substituted quinazolin-4-ones

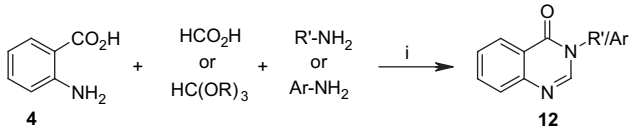
Entry	Quinazolinone alkaloid (MF)	Source[Ref.] (activity)	Synthesis[Ref.]
1	 echinozolinone ($C_{10}H_{10}N_2O_2$)	*Echinops echinatus*[19]	Synthesis known before isolation[19]
2	 7-hydroxyechinozolinone ($C_{10}H_{10}N_2O_3$)	*Echinops echinatus*[20]	Not known
3	 3-(2-carboxyphenyl)-4(3*H*)-quinazolinone ($C_{15}H_{10}N_2O_3$)	*Isatis indigotica*[21] (anti-endotoxic)	Synthesis known before isolation[21]
4	 3-(2-hydroxyphenyl)-4(3*H*)-quinazolinone ($C_{14}H_{10}N_2O_2$)	*Isatis indigotica*[22]	Synthesis known before isolation[22]
5	 dictyoquinazol A ($C_{17}H_{15}N_2O_4$)	*Dictyophora indusiata*[23]	Not known
6	 (*E*)-bogorin ($C_{16}H_{12}N_2O$)	*Glycosmis cf. chlorosperma*[24] (cytotoxic, anti-fungal)	Seger et al.[24]
7	 (*Z*)-bogorin ($C_{16}H_{12}N_2O$)	*Glycosmis cf. chlorosperma*[24] (cytotoxic, anti-fungal)	Seger et al.[24]
8	 monodontamide F ($C_{25}H_{27}N_5O_5$)	*Monadonta labio*[25]	Niwa et al.[25]
9	 (+)-neodichroine ($C_{17}H_{19}N_3O_3$)	*Dichroa febrifuga*[12]	Deng et al.[12]



Scheme 3. Niementowski reaction: (a) conventional conditions: 130–150 °C, average time 6 h (40–60%); (b) microwave conditions: MW (60 W), 150 °C, average time 20 min (70–90%).

re-investigated the Niementowski synthesis of the 3*H*-quinazolin-4-one core using microwave irradiation and have improved the yields and reduced the reaction time (Scheme 3). The product **11** can be further transformed into the structural type shown in Table 2 by reaction with the corresponding alkyl/aryl halides or epoxides.

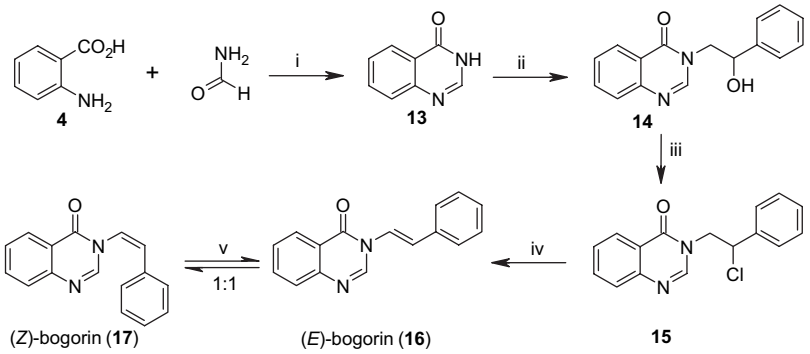
The other approach describes an efficient one-pot synthesis of an array of quinazolin-4-(3*H*)-ones from anthranilic acid, *ortho* esters (or formic acid), and amines using $Yb(OTf)_3$ as a catalyst under solvent-free conditions.[9a] Compared with the classical reaction conditions, this new synthetic method has the advantage of high to excellent yields (75–99%), shorter reaction times (few minutes), and re-usability of the catalyst (Scheme 4).



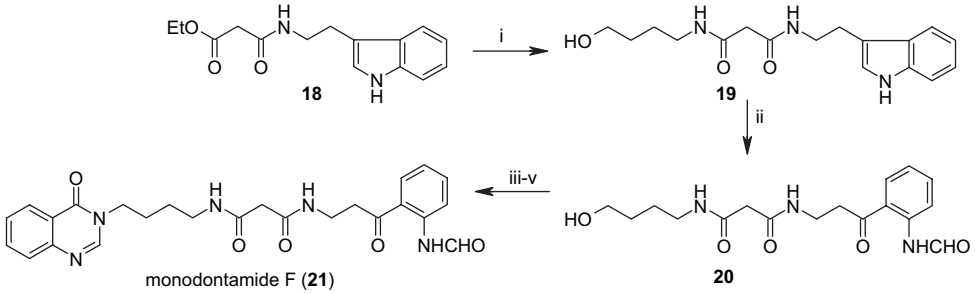
Scheme 4. Reagents and conditions: (i) $Yb(OTf)_3$, heat under solvent-free conditions (75–99%).

(*Z*)-Bogorin (**17**, entry 7), a new quinazolone alkaloid isolated from Javanese *Glycosmis cf. chlorosperma*, was obtained in quantities too small for confirmation of its structure by 2D NMR spectroscopic experiments.[24] The putative structure was therefore substantiated by the short synthesis[24] depicted in Scheme 5. Base-induced elimination of hydrogen chloride from **15** produced exclusively (*E*)-bogorin (**16**, entry 6), which proved to be identical to another trace alkaloid in the plant extract. Photochemical isomerization of **16** yielded a separable 1:1 mixture of (*E*)- and (*Z*)-bogorins, the latter of which gave ^1H and ^{13}C NMR spectroscopic signals identical to those of natural **17**. (*Z*)-Bogorin showed anti-fungal activity toward *Cladosporium herbarium* (IC_{50} 40 μg cm^{-3}) and was moderately cytotoxic toward *Artemia salina* (brine shrimp). The corresponding (*E*)-isomer and the synthetic precursors were found to be significantly less active.

Monodontamide F (**21**, entry 8) was isolated[25] from *Monodonta labio*. The structure **21** was determined spectroscopically, and confirmed by a synthesis (Scheme 6).[25] Ozonolysis of alcohol **19**, followed by reductive workup, provided formamide **20**, which was converted into the corresponding iodo compound using NaI. Finally, N-3 alkylation



Scheme 5. Reagents and conditions: (i) 130 °C, 2.5 h (83%); (ii) styrene oxide, Py (cat.), Pr^{i}OH, reflux (43%); (iii) $SOCl_2$, benzene, reflux (93%); (iv) DBU, benzene, reflux (65%); (v) hν (Hg lamp), CyH, rt (50%).



Scheme 6. Reagents and conditions: (i) 4-aminobutan-l-ol, 70 °C (90%); (ii) O_3, $NaHCO_3$, MeOH, −78 °C, then Me_2S, −78 °C to rt (62%); (iii) *p*-TsC1, Py, 0 °C; (iv) NaI, $CaCO_3$, acetone, 50 °C; (v) 4-hydroxyquinazoline, KOH, EtOH, rt to reflux (43% over iii–v).

of quinazoline with the iodo compound was effected using KOH, yielding **21** (43% from **20**).

A group of researchers from China have isolated the interesting new quinazolinone–quinolizidine dimer, (+)-neodichroine (entry 9), which was isolated as a crystalline solid[12] as the principal component from extracts of the leaves of *D. febrifuga*. Evidence for the structure of neodichroine came from ^{1}H and ^{13}C NMR spectra, recorded in deuterated pyridine, together with COSY and NOE data. Neodichroine also formed an acetate that gave a well-resolved ^{1}H spectrum. A short synthesis[12] of neodichroine by a Mannich reaction between the natural product, febrifugine (**2**), and formaldehyde at pH 4 provided a definitive evidence for the structure of the isolated natural product.

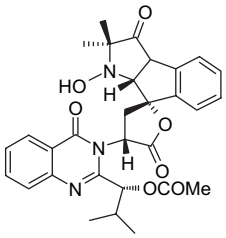
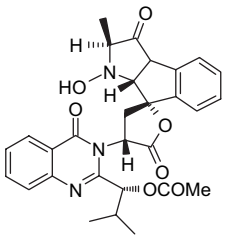
There is no synthetic method reported to date for 7-hydroxyechinozolinone (entry 2) and dictyoquinazol A (entry 5), but their synthesis should be possible by using strategies used for the synthesis of other members of this class.

2.3. 2,3-Disubstituted quinazolin-4-ones

There are only two quinazolinone natural products (Table 3, entries 1 and 2) isolated under the review period, substituted both at the 2- and the 3-positions, and they are tryptoquivaline analogs. 27-*epi*-Tryptoquivaline (entry 1) and 27-*epi*-nortryptoquivaline (entry 2) are the epimers of the previously known quinazolinone alkaloids, tryptoquivaline and nortryptoquivaline, respectively, which were isolated from *Aspergillus clavatus*.[28]

The first total synthesis of tryptoquivaline was achieved by Nakagawa et al.[30] and this can be extended to the synthesis of the new tryptoquivalines by using an amino acid with the appropriate stereochemistry. Several efficient methods for the synthesis of a variety of 2,3-disubstituted quinazolinones are available in the literature.[9g,31]

Table 3. 2,3-Disubstituted quinazolin-4-ones (tryptoquivaline analogs)

Entry	Quinazolinone alkaloid (MF)	Source[Ref.] (activity)	Synthesis[Ref.]
1	 27-epi-tryptoquivaline ($C_{29}H_{30}N_4O_7$)	*Corynascus setous*[29] (tremorgenic)	Not known
2	 27-epi-nortryptoquivaline ($C_{28}H_{28}N_4O_7$)	*Corynascus setous*[29] (tremorgenic)	Not known

In conclusion, the quinazolinones substituted at positions 2 and/or 3 (Tables 1–3) are structurally quite simple alkaloids with a wide range of bioactivity and most have been synthesized using various simple synthetic strategies. We feel that the synthesis of bouchardatine (Table 1, entry 3) should be possible by using an *ortho*-directed lithiation strategy, which was developed by us[32] in the synthesis of the quinazolinone alkaloids, luotonins A, B, and E. The synthesis of (*Z*)-bogorin (Scheme 5) can probably be improved by performing a chemoselective Wittig reaction on the *N*-formyl derivative of compound **13** (similar imides) or by using a better trans–cis isomerization catalyst for converting **16** into **17**. The lower yields for the last two steps in the synthesis of monodontamide F (Scheme 6) may be possibly due to a feasible intramolecular cyclization in compound **20**, under the reaction conditions. Besson et al.[27] made the 3-substitued quinazolinones more readily accessible by improving the classical and famous Niementowski reaction in terms of reaction conditions and yield. We feel that 1,3-benzoxazinones will be potential precursors for the synthesis of 3-substitued quinazolinones (Table 2, entries 1–9) and tryptoquivaline analogs (Table 3).

3. Quinazolinones fused with a pyrrole ring system

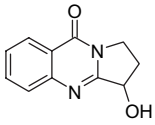
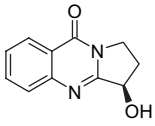
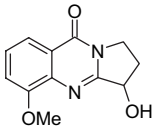
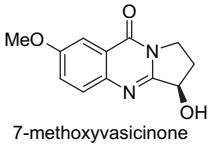
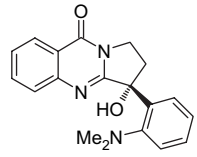
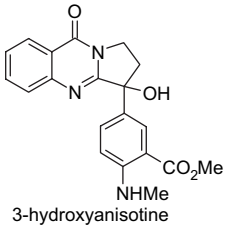
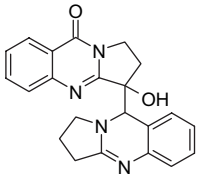
There are nine naturally occurring quinazolinone alkaloids having quinazolinone ring fused with a pyrrole ring system. They all are analogs or derivatives of deoxyvasicinone or vasicinone isolated from various species and are listed in Table 4 (entries 1–9). The synthetic methods for this structural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

Deoxyvasicinone (**22**) has been isolated from *Adhatoda vasica*[44] and possesses anti-microbial, anti-inflammatory and anti-depressant acitivities.[45] Several synthetic routes to deoxyvasicinone (**22**) are known in the literature.[16,43b,46] Two efficient and easy approaches are discussed in detail below and the selected methods have been summarized in Table 5.

Kametani et al.[46e] synthesized deoxyvasicinone (**22**) in good yields from the reaction of the unstable sulfonamide anhydride **7** with *O*-methylpyrrolidone (Scheme 7), affording deoxyvasicinone in 65% overall yield. Later, they improved[16] these conditions by using simple 2-pyrrolidone to obtain **22** in 93% overall yield.

The azide **24** obtained from pyrrolidone (**23**) was treated with triphenylphosphine, but the cyclization required heating at a higher temperature for a longer time. When tributylphosphine was used, the reaction was complete in a shorter time at room temperature with a good yield (Scheme 8).[46i] This aza-Wittig reaction protocol is now famous as Eguchi's protocol. Gil et al.[46p] synthesized deoxyvasicinone in quantitative yields by using polystyrene-supported triphenylphosphine in the aza-Wittig reaction, which facilitates easy

Table 4. Pyrroloquinazolinones (deoxyvasicinone/vasicinone and derivatives)

Entry	Quinazolinone alkaloid (MF)	Source[Ref.] (activity)	Synthesis[Ref.]
1	 (±)-vasicinone ($C_{11}H_{10}N_2O_2$)	*Galium aparine*,[33a] *Peganum multisectum*,[33b,c] *Nitraria schoberi*[33d]	Eguchi et al.,[34] Kamal et al.[35]
2	 (+)-vasicinone ($C_{11}H_{10}N_2O_2$)	*Adhatoda vasica*[36]	Eguchi et al.,[34] Kamal et al.[35]
3	 adhavasinone ($C_{12}H_{12}N_2O_3$)	*Adhatoda vasica*[37]	Chowdhury and Bhattacharyya[37]
4	 7-methoxyvasicinone ($C_{12}H_{12}N_2O_3$)	*Adhatoda vasica*[38]	Not known
5	 desmethoxyaniflorine ($C_{19}H_{19}N_3O_2$)	*Adhatoda vasica*[38]	Not known
6	 3-hydroxyanisotine ($C_{20}H_{19}N_3O_4$)	*Adhatoda vasica*[39]	Synthesis known before isolation[40]
7	 dipeginol ($C_{22}H_{20}N_4O_2$)	*Peganum harmala*[41]	Not known

(*continued*)

Table 4. (*continued*)

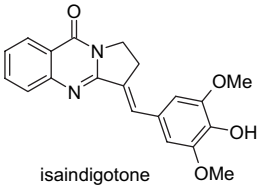
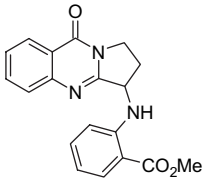
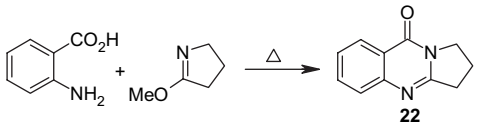
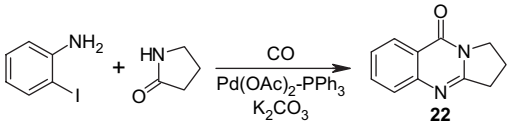
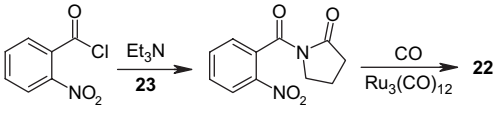
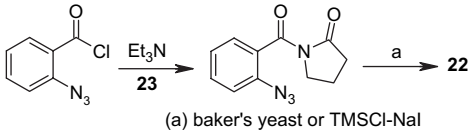
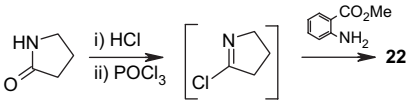
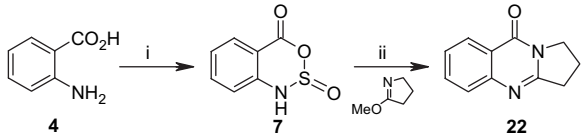
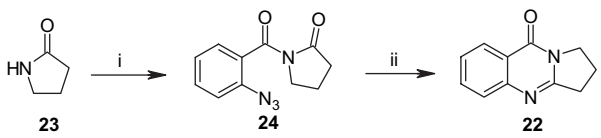
Entry	Quinazolinone alkaloid (MF)	Source[Ref.] (activity)	Synthesis[Ref.]
8	 isaindigotone ($C_{20}H_{18}N_2O_4$)	*Isatis indigotica*,[22,42a] *Isatis tinctoria*[42b] scavenger of superoxide (anti-oxidant)	Molina et al.,[43a] Liu et al.[43b]
9	 vasnetine ($C_{19}H_{17}N_3O_3$)	*Adhatoda vasica*[39]	Not known

Table 5. Various approaches to deoxyvasicinone (**22**)

Entry	Brief scheme	Overall yield (%) (steps)	Ref.
1		82% (one step)	Onaka[46c]
2		52% (one step)	Mori et al.[46g]
3		55% (two steps)	Watanabe et al.[46k]
4	 (a) baker's yeast or TMSCl-NaI	~82% (two steps)	Kamal and Ramana[35]
5		88% (two steps)	Lee et al.[46n]



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



Scheme 8. Reagents and conditions: (i) NaH, benzene, *o*-azidobenzoyl chloride, rt (75%); (ii) PPh_3, 140 °C, 5 h or PBu_3, rt, 3 h (99%).

removal of the byproduct, triphenylphosphine oxide from the reaction mixture.

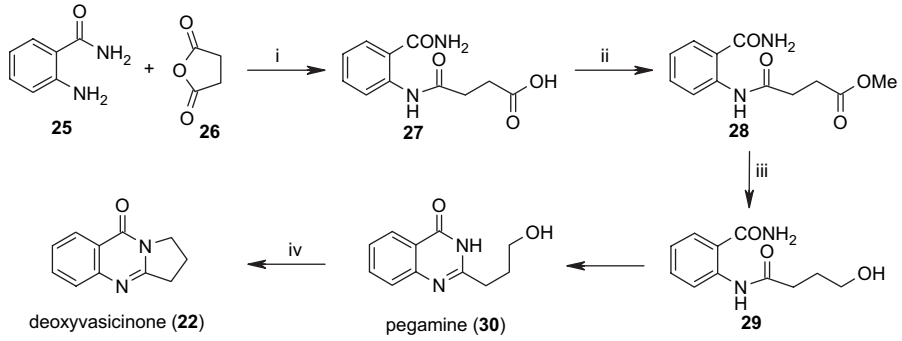
We have developed[18] a new route to deoxyvasicinone (**22**) with 85% overall yield via the acylation of anthranilamide (**25**) with succinic anhydride (**26**), followed by diazomethane esterification of the formed succinanilic acid **27**, chemoselective LAH-reduction of ester **28**, in situ LiOH-catalyzed dehydrative cyclization and an intramolecular Mitsunobu ring-closure reaction pathway (Scheme 9).

Morris et al.[46a] completed a partial synthesis of deoxyvasicinone (**22**) by oxidation of deoxyvasicine, which is also a natural product. Kamal et al.[46l] recently developed a route for the synthesis of deoxyvasicinone (Table 5, entry 4), in which they have used $FeCl_3$–NaI as a reagent for the last reductive cyclization step. Nishiyama et al.[46m] used selenium as a catalyst for the reductive cyclization step and could synthesize deoxyvasicinone in good yield by following the same strategy as used by Watanabe et al.[46k] (Table 5, entry 3). A new method for the preparation of deoxyvasicinone has been reported,[46o] in which 2-nitrobenzoic acid on reaction with 2-pyrrolidinone followed by 10% Pd/C reduction afforded **22** in good yields. A novel one-pot microwave-assisted domino reaction, between anthranilic acid and 4(*tert*-butoxycarbonylamino)butyric acid in the presence of $P(OPh)_3$ in pyridine, developed by Liu et al.,[43b] furnished deoxyvasicinone in 89% yield. This is a very efficient and general method for the synthesis of quinazolinones.

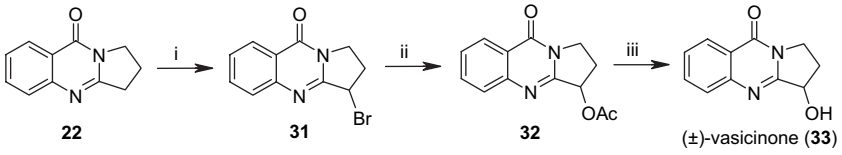
(−)-Vasicinone (**33**) has been isolated[44] from the aerial parts of an evergreen subherbaceous bush *A. vasica* and exhibits anti-tumor, bronchodilating, hypotensive, anthelmintic, and anti-anaphylactic activities.[33b,47] It is used in the Indian ayurvedic system of medicine as a remedy for cold, cough, bronchitis, rheumatism, phthisis, and asthma.[44,48] Recently, Joshi and co-workers[39,49] reversed the previously assigned[50] 3(*R*)-configuration of (−)-**33** on the basis of X-ray crystallographic analysis[49a] and by using the Mosher ester analysis method.[49b] Three synthetic routes to vasicinone are known in the literature.[34,35,46c,g]

Onaka[46c] completed the synthesis of (±)-vasicinone (**33**) from deoxyvasicinone (**22**) (Scheme 10). Deoxyvasicinone (**22**), obtained by following his own scheme as shown in Table 5 (entry 1), was brominated using NBS and the monobromo product **31** was converted into acetylvasicinone **32** by treatment with AcONa–AcOH. Acetylvasicinone **32** was then hydrolyzed under basic conditions to obtain (±)-vasicinone (**33**) in 17% overall yield starting from anthranilic acid. A similar approach was used by Ziaee et al.[46o] Mori et al.[46g] synthesized (±)-vasicinone by a modification of Onaka's method,[46c] employing the expensive AcOAg instead of AcONa.

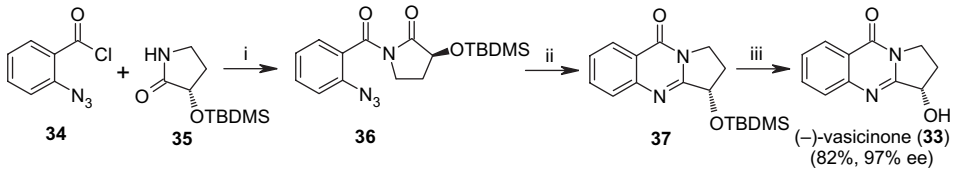
Eguchi et al.[34] completed the synthesis of (±)-vasicinone (**33**), (−)-vasicinone (**33**), and (+)-vasicinone (**33**) via an aza-Wittig reaction as the key step (Scheme 11). The sequence of the reactions shown in Scheme 11 was first carried



Scheme 9. Reagents and conditions: (i) Et_2O/benzene/1,4-dioxane (2:2:1), rt, 2 h (98%); (ii) CH_2N_2, Et_2O, rt, 1 h (98%); (iii) LAH, THF, 90 min, aqueous workup (93%); (iv) PPh_3, DEAD, THF, rt, 1 h (95%).



Scheme 10. Reagents and conditions: (i) NBS, benzoyl peroxide, CCl_4, reflux (57%); (ii) AcONa–AcOH, reflux (33%); (iii) aq KOH, rt (17% overall yield from anthranilic acid).



Scheme 11. Reagents and conditions: (i) NaH, THF, 0 °C to rt, 3 h (83% from *o*-azidobenzoic acid); (ii) *n*-Bu_3P, toluene, rt, 1 h, then reflux, 2 h (76%); (iii) TBAF, THF, 0 °C to rt, 15 h (97%).

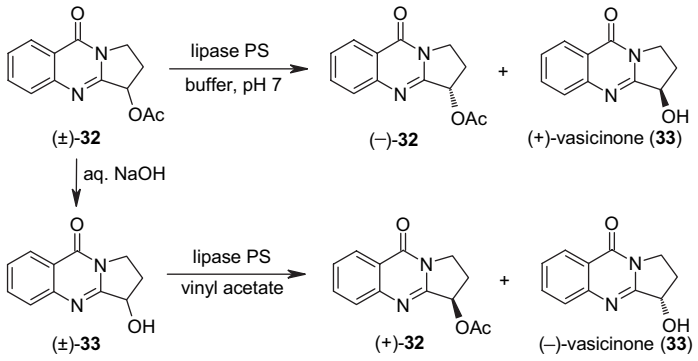
out by using racemic 3-hydroxy-γ-lactam to obtain (±)-vasicinone (**33**). Both optical isomers of the quinazolinone alkaloid, vasicinone, were synthesized by two different methods. The first method used 3(*S*)-3-hydroxy-γ-lactam (derived from L-aspartic acid in six steps)[51] as a chiral synthon, which was, after *O*-TBDMS protection, *o*-azidobenzoylated followed by sequential treatment with tri-*n*-butylphosphine and TBAF to afford (*S*)-(−)-vasicinone via the tandem Staudinger/intramolecular aza-Wittig reaction (Scheme 11). The second method utilized asymmetric oxygenation of deoxyvasicinone (**22**) with (1*S*)-(+)- or (1*R*)-(−)-(10-camphorsulfonyl)oxaziridine (Davis reagent). The aza-enolate anion of deoxyvasicinone was treated with the (*S*)-(+)-reagent to afford (*R*)-(+)-vasicinone in 71% ee, while the reaction with the (*R*)-(−)-reagent gave (*S*)-(−)-vasicinone in 62% ee. These results provided a good method to prepare both the enantiomers of vasicinone and confirmed the recently reversed[39,49] stereochemistry of natural (−)-vasicinone.

Kamal et al.[35] have reported an efficient enzymatic resolution of (±)-acetylvasicinone **32** and (±)-vasicinone (**33**) to obtain both enantiomers of vasicinone (Scheme 12). Deoxyvasicinone (**22**) was synthesized using their own scheme (Table 5, entry 4) and it was converted in good yields into (±)-acetylvasicinone **32** and (±)-vasicinone (**33**) by bromination followed by displacement with acetate and hydrolysis reaction sequence.

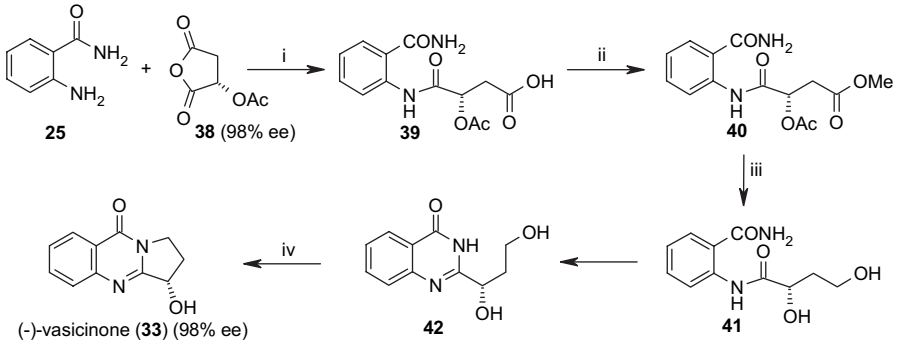
Acetylvasicinone thus obtained has been enzymatically hydrolyzed employing lipase PS Amano into its (*R*)-alcohol and (*S*)-acetate in 98% ee with nearly 50% conversion. Alternatively, racemic vasicinone has been resolved by transesterification with different lipases. It was observed that THF, followed by toluene and di-isopropyl ether, provides good selectivity with good conversions and, interestingly, the (*R*)-acetate is obtained in >99% ee employing lipase PS in THF.

Recently, we have demonstrated[18] a concise, efficient, and practical chiral pool synthesis of (−)-vasicinone (**33**) starting from the readily available (*S*)-malic acid as a chiral synthon. A total synthesis of (−)-vasicinone (**33**) with 80% overall yield (97–98% ee) has been accomplished via a highly regioselective ring opening of 2(*S*)-acetoxysuccinic anhydride (**38**) at the more reactive electron-deficient carbonyl carbon, followed by repetition of the same reaction sequence, as depicted in Scheme 9, without using any protection–deprotection chemistry. The present synthesis of (−)-vasicinone with a chiral pool strategy directly confirmed the stereochemistry of the natural product (Scheme 13).

Adhavasicinone (Table 4, entry 3) has been synthesized by Chowdhury and Bhattacharya[37] starting from 2-amino-3-methoxybenzaldehyde. 7-Methoxyvasicinone (entry 4) can be very easily synthesized by using the various methods available for the synthesis of vasicinone. Desmethoxyanisoflorine (entry 5), 3-hydroxyanisotine (entry 6), the semisynthesis[40] of which by oxidation of the natural product anisotine is known, and dipeginol (entry 7) can be synthesized using Kokosi's[52] synthetic route. This route was



Scheme 12. Enzymatic resolution of (±)-acetylvasicinone (**32**) and (±)-vasicinone (**33**).



Scheme 13. Reagents and conditions: (i) Et_2O/benzene/1,4-dioxane (2:2:1), rt, 2 h (98%); (ii) CH_2N_2, Et_2O, rt, 1 h (98%); (iii) LAH, THF, 90 min, aqueous workup (92%); (iv) PPh_3, DEAD, THF, rt, 1 h (90%).

originally developed for the synthesis of the quinazolinone natural product, vasicolinone, the structure of which is similar to that of the alkaloids listed in entries 5–7. A straightforward condensation of deoxyvasicinone (**22**) with 4-acetoxy-3,5-dimethoxybenzaldehyde in acetic anhydride followed by hydrolysis of the ester completed the first synthesis[43a] of isaindigotone (entry 8) in 64% overall yield. A novel microwave-assisted, three-component, one-pot approach, developed by Liu et al.,[43b] provided isaindigotone in 79% yield. Vasnetine (entry 9), having a similar structure to that of the natural alkaloid, anisessine (the only difference being the alkoxycarbonyl moiety), was synthesized by Onaka[46c] by nucleophilic displacement of the bromine atom in bromovasicinone **31** with ethyl anthranilate. Synthesis of vasnetine will also be easily possible following Onaka's procedure for anisessine.

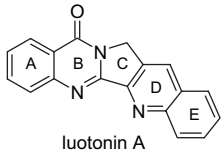
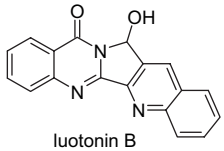
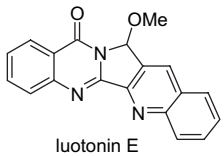
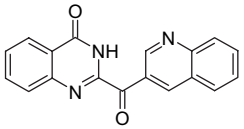
In conclusion, the new pyrroloquinazolinone alkaloids presented in Table 4 (entries 1–9) are deoxyvasicinone/vasicinone analogs and the synthesis of some of them is known. The synthesis of these alkaloids should be possible by employing various synthetic strategies available for the synthesis of deoxyvasicinone/vasicinone (Schemes 7–13 and Table 5) and by their transformations including oxidation, substitution or condensation. The reductive cyclization using various catalysts developed for this class of compounds provided an easy access to these alkaloids and the use of baker's yeast for this purpose is novel and interesting. To the best of our knowledge, the enzymatic resolution of (±)-vasicinone is the first example of a quinazolinone resolution using lipases and it seems possible to apply it to the resolution of other quinazolinone alkaloids, e.g., isovasicinone, luotonin B, and 7-hydroxyrutaecarpine. A microwave-assisted domino reaction sequence, developed by Liu et al., for the construction of quinazolinone alkaloids is very efficient, general, and useful for the synthesis of a large number of combinatorial libraries.

4. Quinazolinones fused with a pyrroloquinoline ring system

The species from the plant kingdom *Peganum nigellastrum* Bunge (Zygophyllaceae) is found all over Asia and is more common in the northwestern region of China. The same plant with the Chinese name Luo-Tuo-Hao[53] has been used in Chinese traditional medicine as a remedy for rheumatism, abscesses, and inflammation.[53] Recently, Nomura and co-workers from Japan in their collaborative work with scientists from China have isolated six new alkaloids,[17b,54] luotonin A–F (Table 6 and Fig. 3), from the aerial parts of *P. nigellastrum*.

Luotonins C and D are unusual canthin-6-one derivatives. The structural assignments of luotonins A–F have been achieved on the basis of analytical and spectral data,[17b,54] and these bioactive natural products exhibit anti-tumor activity.[54a,58] Ma et al.[59a] have reported an interesting bioactivity study of luotonins A and F analogues. Hecht et al.[59b,c] and Dallavalle et al.[59d] reported the synthesis and biochemical

Table 6. Pyrroloquinalinoquinazolinones (luotonin alkaloids)

Entry	Quinazolinone alkaloid (MF)	Source[Ref.] (activity)	Synthesis[Ref.]
1	 luotonin A ($C_{18}H_{12}N_3O$)	*Peganum nigellastrum*[54a] (cytotoxic toward the murine leukemia P388 cell line, IC_{50} 1.8 μg/mL) (naturally occurring human DNA topoisomerase I poison, IC_{50} 5.7–12.6 μmol/mL)[55]	Thirteen syntheses[43a,46n,54b,56] Mhaske and Argade[32]
2	 luotonin B ($C_{18}H_{12}N_3O_2$)	*Peganum nigellastrum*[54a] (cytotoxic toward leukemia P388 cells)	Four syntheses[54a,b,56c,h,j,k] Mhaske and Argade[32]
3	 luotonin E ($C_{19}H_{13}N_3O_2$)	*Peganum nigellastrum*[17b]	Three syntheses[17b,54b,56j] Mhaske and Argade[32]
4[a]	 luotonin F ($C_{18}H_{11}N_3O_2$)	*Peganum nigellastrum*[17b] (anti-tumor)	Ma et al.,[17b,54b] Mhaske and Argade[57]

[a] Described here, along with other luotonin alkaloids, although it comes under different class.

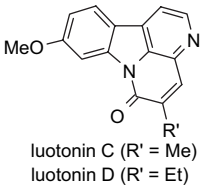


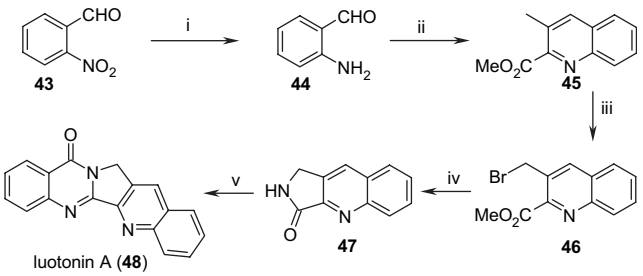
Figure 3. Luotonins C and D.

properties of luotonin A derivatives. Ma et al.[6i] have recently published a review on the isolation, structural determination, synthesis, and biological activity of luotonin A and related derivatives.

Luotonin A (**48**, Table 6, entry 1) is cytotoxic toward the murine leukemia P388 cell line (IC_{50} 1.8 μg/mL).[17b,54] Recently, Hecht et al.[55] have demonstrated that, despite the lack of lactone ring functionality, luotonin A stabilizes the human DNA topoisomerase I-DNA covalent binary complex and mediates topoisomerase I-dependent cytotoxicity in intact cells (IC_{50} 5.7–12.6 μmol/mL), like camptothecin and its analogs[60] (Fig. 4). In a very short time span (6 years), 13 syntheses (Schemes 14–17, Table 7) of luotonin A have been reported from different laboratories using a variety of elegant synthetic strategies.[43a,46n,54b,56] A few approaches are illustrated below and the remaining syntheses have been summarized in Table 7.

The structure of luotonin A (**48**) was unambiguously confirmed by Ganesan's total synthesis[56a] (Scheme 14). 3-Oxo-1*H*-pyrrolo[3,4-*b*]quinoline (**47**) was synthesized starting from *o*-nitrobenzaldehyde (**43**) via quinoline **46** in five steps. Deprotonation of quinoline **47** gave an anion, which was coupled with 2-sulfinylaminobenzoyl chloride (prepared from the reaction of anthranilic acid with thionyl chloride) to afford the natural product, luotonin A (**48**), in 7% overall yield starting from *o*-nitrobenzaldehyde (**43**) in five steps (Scheme 14).

In Toyota's approach,[56d,i] the intramolecular hetero Diels–Alder reaction of an aryl imino ether (diene) with an aryl nitrile (dienophile) has been used as the key reaction for an efficient approach to the pyrroloquinazolino-quinoline alkaloid, luotonin A (**48**) (Scheme 15). Activation of the diene moiety by the incorporation of a methoxy group played an important role for the hetero Diels–Alder reaction. Acylation of amine **50** with acid **49** provided the bromo-amide **51**, which was converted into the cyano-amide **52** by using a palladium-catalyzed coupling reaction with CuCN.

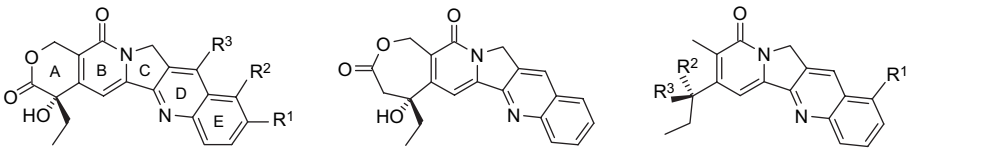


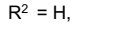
Scheme 14. Reagents and conditions: (i) $FeSO_4$, NH_4OH (57%); (ii) (a) $EtCOCO_2H$, NaOEt, MeOH, reflux, 16.5 h; (b) H_2SO_4, MeOH, reflux, 24.5 h (60%); (iii) NBS, AIBN, CCl_4, reflux, 7 h (34%); (iv) NH_3, MeOH (74%); (v) $LiN(TMS)_2$, 2-sulfinylaminobenzoyl chloride (85%).

Cyano-quinoline **52** was next subjected to an intramolecular hetero Diels–Alder reaction by heating with TMSCl and Et_3N in the presence of $ZnCl_2$, which was followed by an in situ elimination of methoxy group as methanol to regain the aromaticity, to obtain luotonin A (**48**) in 35% overall yield in three steps (Scheme 15).

Most of the multistep syntheses of linear pentacyclic luotonin A have been completed using two suitable building blocks with the construction of ring B or D. Harayama et al.[56h,k] completed the synthesis of luotonin A (**48**) with the construction of middle ring C using a Pd-assisted biaryl coupling reaction, in which quinazolinone **55** was synthesized by coupling of quinazolinone **13** and bromo-quinoline **54**. A total synthesis of luotonin A (**48**) was completed by using a Pd-assisted biaryl coupling reaction of compound **55** in an overall 79% yield over two steps (Scheme 16). Both of such couplings have been used earlier by Comins et al.[60b] in their total synthesis of camptothecin.

A regioselective quinazolinone-directed *ortho*-lithiation on an adjacent quinoline moiety has been used by us as a key step for a short, efficient, and practical synthesis[32a] of luotonins A, B, and E. The qinazolinoylquinoline **58**, prepared starting from anthranilamide (**25**) and quinoline-2-carboxylic acid chloride (**56**), on treatment with in situ-generated non-nucleophilic mesityllithium,[32b] furnished the desired dilithiated intermediate **59**, which, on treatment with formaldehyde followed by a Mitsunobu ring-closure reaction, gave luotonin A (**48**) in very good yield. The reaction of the dilithiated intermediate **59** with DMF directly furnished luotonin B (**62**) in 81% yield. Luotonin B (**62**), on methylation with *p*-TsOH/methanol, gave luotonin E (**63**) in 82% yield (Scheme 17).

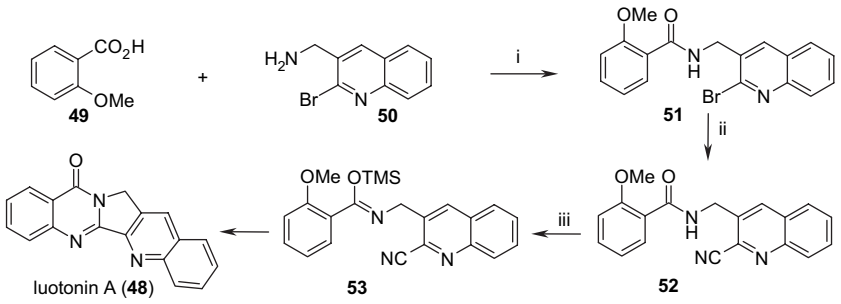


camptothecin: R^1, R^2, R^3 = H
topotecan : R^1 = OH, R^2 = -CH_2-N(Me)$_2$, R^3 = H
DB-67 : R^1 = OH, R^2 = H, R^3 = TBS
irinotecan : R^1 =  , R^2 = H, R^3 = Et

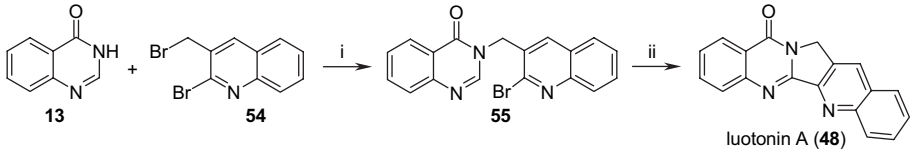
homocamptothecin

nothapodytine A: R^1 = OMe, R^2R^3 = O
nothapodytine B: R^1 = H, R^2R^3 = O
mappicine : R^1 = H, R^2 = OH, R^3 = H

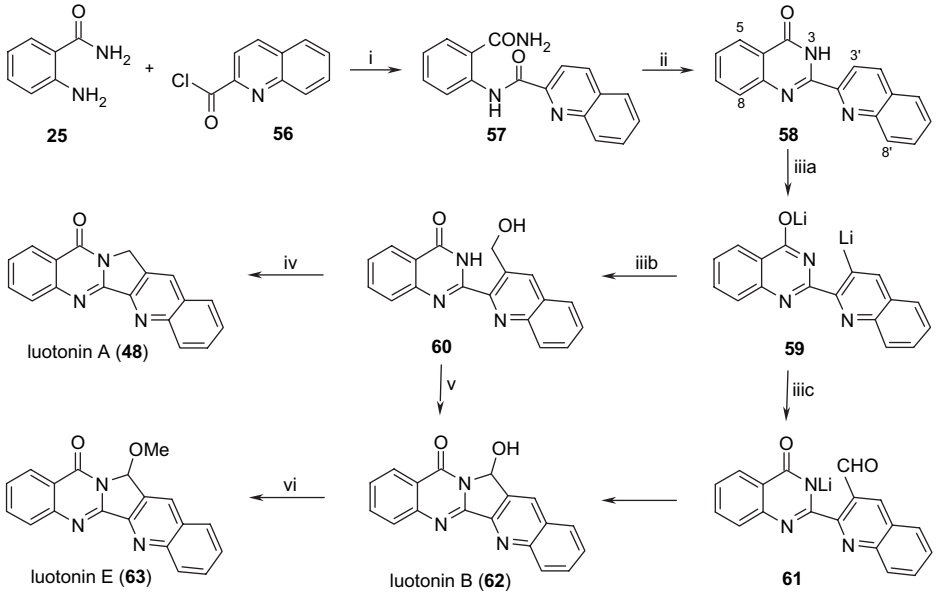
Figure 4. Camptothecin and its analogs.



Scheme 15. Reagents and conditions: (i) BOP, Et_3N, DCM (91%); (ii) $Pd_2(dba)_3$, DPPF, CuCN, Et_4NCN, 1,4-dioxane, reflux (84%); (iii) TMSCl, $ZnCl_2$, Et_3N, toluene, 150 °C in a sealed tube (46%).



Scheme 16. Reagents and conditions: (i) *t*-BuOK, DMF, rt, 1.5 h (92%); (ii) $Pd(OAc)_2$, Cy_3P, KOAc, DMF, reflux, 30 min (86%).



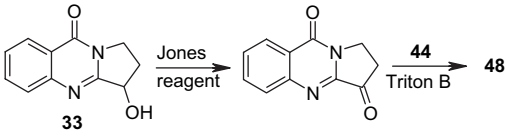
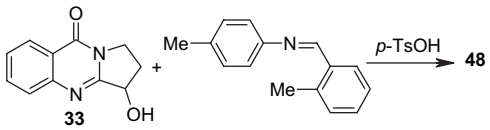
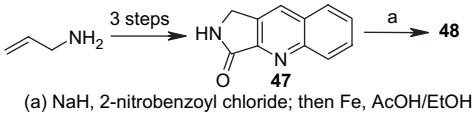
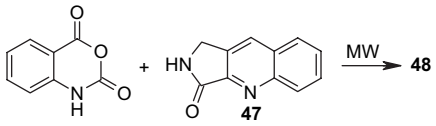
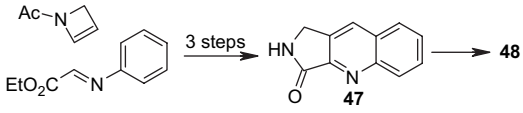
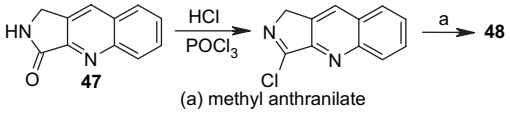
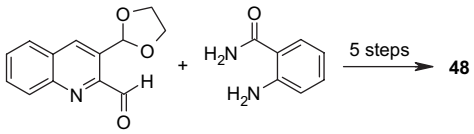
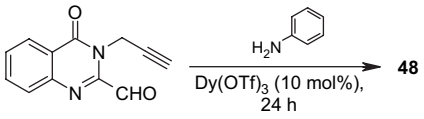
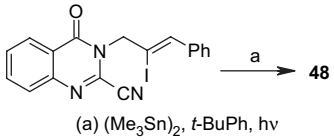
Scheme 17. Reagents and conditions: (i) Et_3N (2 equiv), THF, rt, 3 h (96%); (ii) 5% aq KOH, EtOH, reflux, 5 min (98%); (iii) (a) mesityllithium (2.2 equiv), −78 °C, 30 min to −20 °C (gradually), (b) THF solution of HCHO (5 equiv), −30 °C, 20 min, satd aq solution of NH_4Cl (86%), (c) DMF (5 equiv), −20 °C, 30 min, satd aq solution of NH_4Cl (81%); (iv) PPh_3 (1.3 equiv), DEAD (1.2 equiv), THF, rt, 1 h (95%); (v) PCC (1.2 equiv), powdered 4 Å MS, CH_2Cl_2, rt, 1 h (61%); (vi) *p*-TsOH (5 equiv), MeOH, reflux, 3 h (82%).

Molina et al.,[43a] in their formal synthesis of luotonin A (**48**), directly oxidized deoxyvasicinone to the corresponding precursor dione (Table 7, entry 1), the transformation of which into luotonin A (**48**) by a Friedländer condensation with 2-aminobenzaldehyde using Kelly's procedure[56b] is known.

To date, four syntheses of luotonin B,[54a,b,56c,h,j] three of luotonin E,[17b,54b,56j] and two of luotonin F[17b,54b] are known. Ma et al.[54a] exposed a chloroform solution of luotonin A (**48**) to sunlight for two weeks to obtain luotonin B (Table 6, entry 2), whereas the reaction of luotonin A (**48**) with ceric ammonium nitrate (CAN) also gave luotonin B in 15% yield.[56c] Harayama et al.[56h] brominated luotonin A with NBS under irradiation from a tungsten lamp, followed by solvolysis with silver nitrate in aqueous acetone to obtain luotonin B in 59% yield. Ma et al.[17b] confirmed the structure of luotonin E (Table 6, entry 3) by a synthesis from luotonin B, in which luotonin B was treated with BF_3-etherate in a methanol solution to obtain luotonin E in 70% yield.

Ma et al.[17b] completed the first total synthesis of luotonin F (Table 6, entry 4), starting from 3-formylquinoline with 5.6% overall yield in six steps (Scheme 18). This molecule comes under a different class, but has been described here along with other members of the luotonins. Quinoline **68**, obtained in four steps from formylquinoline **64** via alcohol **65**, chloride **66**, and cyano-quinoline **67**, was reacted with isatoic anhydride to obtain the bioactive precursor, deoxoluotonin F (**69**). Ma et al.[59a] recently reported that the synthetic compound, deoxoluotonin F, has cytotoxic activity (IC_{50} 2.3 μg/mL) and shows DNA topoisomerase II

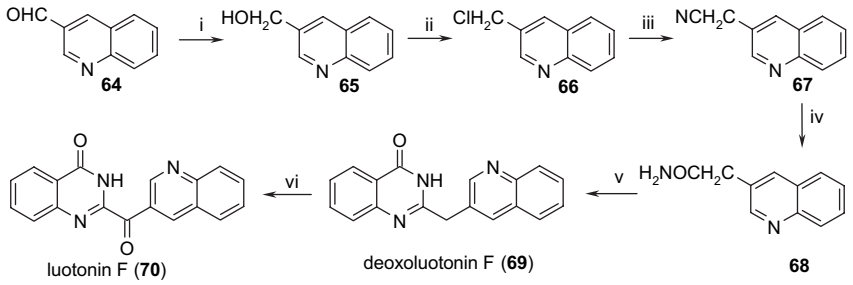
Table 7. Various approaches to luotonin A (**48**)

Entry	Brief scheme	Overall yield (%) (steps)	Ref.
1		5% (seven steps)	Kelly et al.[56b]
2		24% (three steps)	Ma et al.[56c]
3	 (a) NaH, 2-nitrobenzoyl chloride; then Fe, AcOH/EtOH	8% (six steps)	Dallavalle et al.[56e]
4		85% (one step)	Yadav et al.[56f]
5		Formal synthesis	Osborne et al.[56g]
6	 (a) methyl anthranilate	88% (two steps)	Lee et al.[46n]
7		51% (five steps)	Chavan and Sivappa[56j]
8		51% (last step)	Twin and Batey[56l]
9	 (a) $(Me_3Sn)_2$, *t*-BuPh, hν	21% (last step)	Bowman et al.[56m]

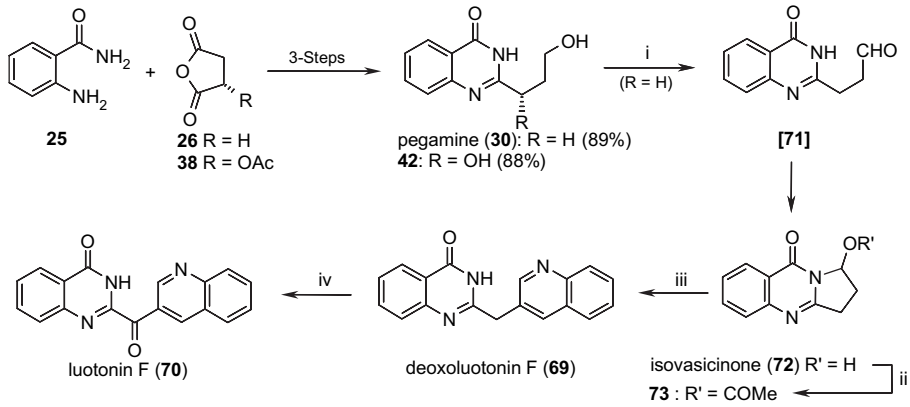
inhibition at a concentration of 25 μM. Deoxoluotonin F was oxidized with MnO_2 in the presence of sunlight to obtain luotonin F **70** (Scheme 18).

We have demonstrated[57] an efficient biogenetic-type synthesis of the alkaloid, luotonin F (**70**), starting from succinic anhydride (**26**) via PCC oxidation of the natural product, pegamine[18] (**30**), Friedländer condensation, and Yamazaki's CrO_3–H_5IO_6 oxidation reaction sequence. The overall yield of **70** starting from **30** was 38% and, starting from succinic anhydride (**26**), luotonin F (**70**) was obtained in six steps with 34% overall yield. In our hands, all attempts to oxidize hydroxypegamine **42** to the corresponding desired keto-aldehyde or its ring-closed form, e.g., **72**, using a variety of oxidizing agents, failed and, hence, we were unable to complete the short two-step synthesis of **70** starting from **42** (Scheme 19).

In conclusion, the pyrroloquinazolino-quinoline alkaloids, luotonins A, B, and E, and the 2-substituted quinazolino-quinoline alkaloid, luotoin F (Table 6, entries 1–4), isolated by Nomura and co-workers, are important alkaloids having anti-tumor activity. Various elegant synthetic methods for all these alkaloids are known. Several syntheses of the



Scheme 18. Reagents and conditions: (i) $NaBH_4$, MeOH (85%); (ii) $SOCl_2$, benzene (96%); (iii) KCN, KI, 80% EtOH (62%); (iv) concd H_2SO_4 (71%); (v) isatoic anhydride, 200–210 °C (43%); (vi) MnO_2, $CHCl_3$, sunlight (36%).



Scheme 19. Reagents and conditions: (i) PCC, CH_2Cl_2, rt, 3 h (64%); (ii) Ac_2O, Py, rt, 8 h (98%); (iii) *o*-aminobenzaldehyde, KOH, EtOH, reflux, 15 h (62%); (iv) CrO_3, H_5IO_6, DMF, rt, 1 h (96%).

alkaloid, luotonin A, in a short time period and its correlation with camptothecin prove the importance of the luotonin class of alkaloids as promising candidates for clinical purposes.

5. Quinazolinones fused with a piperidine ring system

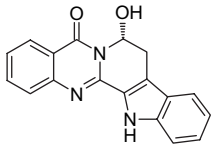
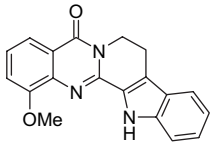
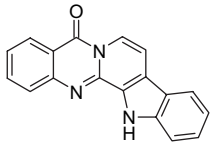
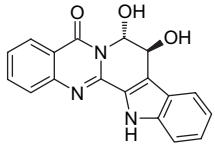
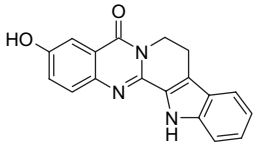
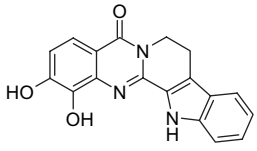
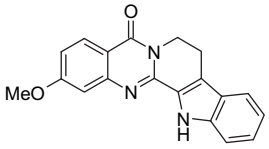
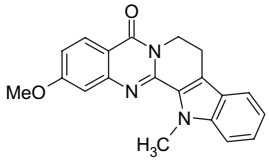
Ten new quinazolinones fused with a piperidine ring system have been isolated from various species in the review period and these are listed in Table 8 (entries 1–10). Actually, nine of them possess the indolopiperidine moiety.

Rutaecarpine (**74**), its analogs and auranthine (Fig. 5 and Table 8, entries 1–10) are derivatives of mackinazolinone (**76**), the simplest quinazolinone alkaloid having a quinazolinone ring fused with a piperidine ring system, which was isolated[64] from *Mackinalaya* species, for which several syntheses[16,43b,46l,m,p,64,65] are known. Mackinazolinone was also synthesized[35,46k,n] by repeating the same reactions as shown in Table 5 (entries 3–5) using 2-piperidone instead of 2-pyrrolidone. Spath and Ruffner[66] synthesized compound **76** by the reduction of pyridoquinazoline **75** (Scheme 20). The first known representatives of the quinazolinocarboline alkaloids were rutaecarpine and evodiamine. The dried fruits of *Evodia rutaecarpa* have been used[67] in traditional Chinese medicine under the name Wu-Chu-ru[67b] and Shih-Hu[67c] as a remedy for headache, dysentery, cholera, worm infections, and postpartum.[67a,d] The drug extract contains the quinazolinocarboline alkaloids, rutaecarpine (**74**) and evodiamine.[68] Recently, callus tissue cultured from the stem of *Phellodendron amurense* has been shown to produce **74**, along with a variety of other alkaloids[7b(ix),61c,69] (Fig. 5). In the recent literature, **74** and its derivatives have been reported to possess strong analgesic, anti-emetic, astringent, anti-hypertensive, uterotonic, TCDD-receptor, antinociceptive, anti-inflammatory, and cyclooxygenase-2 (COX-2) inhibitory activities.[70] Rutaecarpine (**74**) was also found to suppress platelet plug formation in mesenteric venules and increase intracellular Ca^{2+} in endothelial cells.[71] Recently, Don et al.[63a] reported their studies on the effect of structural modification on the inhibitory selectivity of rutaecarpine derivatives on human CYP1A1, CYP1A2, and CYP2B1 and found a few of them to be highly selective inhibitors.

The rutaecarpines shown in Table 8 (entries 1–9) are new quinazolinocarboline alkaloids isolated form various species.[61] 1-Methoxyrutaecarpine (Table 8, entry 2) was prepared[61b] by methylating 1-hydroxyrutaecarpine with diazomethane and 7,8-dehydrorutaecarpine (Table 8, entry 3) was synthesized by Bergman and Bergman[62] from rutaecarpine by oxidation with DDQ. 2-Methoxyrutaecarpine (Table 8, entry 7) has been synthesized[63a] in good yields by condensing anthranilic acid with 1,2,3,4-tetrahydro-β-carboline. A synthetic route could be designed for other natural products of this class of alkaloids by utilizing various approaches available for the synthesis of rutaecarpine.

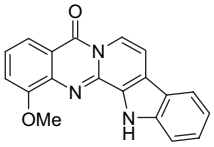
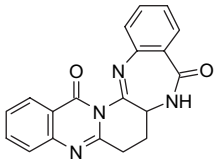
The first total synthesis of the important bioactive natural product, rutaecarpine (**74**), was reported[72] by Robinson et al. in 1927 and, since then, several routes to **74** and its derivatives have been developed.[5,16,46e,g,n,52,56k,62,65,73] A few syntheses are described below in detail and the remaining preparations are listed in Table 9.

Table 8. Quinazolinones fused with a piperidine ring system (rutaecarpines and auranthine)

Entry	Quinazolinone alkaloid (MF)	Source[Ref.] (activity)	Synthesis[Ref.]
1	 (+)-7-hydroxyrutaecarpine ($C_{18}H_{13}N_3O_2$)	*Tetradium glabrifolium*[61a] [*Evodia meliaefolia*], *Tetradium ruticarpum*[61a], *Phellodendron amurense*[61c]	Not known
2	 1-methoxyrutaecarpine ($C_{19}H_{15}N_3O_2$)	*Zanthoxylum integrifolium*[61b] (anti-platelet aggregation activity)	Sheen et al.[61b]
3	 7,8-dehydrorutaecarpine ($C_{18}H_{11}N_3O$)	*Phellodendron amurense*[61d]	Synthesis known before isolation[62]
4	 (–)-7,8-dihydroxyrutaecarpine ($C_{18}H_{13}N_3O_3$)	*Phellodendron amurense*[61c]	Not known
5	 3-hydroxyrutaecarpine ($C_{18}H_{13}N_3O_2$)	*Leptothyrsa sprucei*[61e] [Rutaceae]	Not known
6	 1,2-dihydroxyrutaecarpine ($C_{18}H_{13}N_3O_3$)	*Bouchardatia neurococca*[15]	Not known
7	 2-methoxyrutaecarpine ($C_{19}H_{15}N_3O_2$)	*Araliopsis tabouensis*[61f] (anti-malarial)	Don et al.[63a]
8	 2-methoxy-13-methyl-rutaecarpine ($C_{20}H_{17}N_3O_2$)	*Araliopsis tabouensis*[61f] (anti-malarial)	Not known

(*continued*)

Table 8. (*continued*)

Entry	Quinazolinone alkaloid (MF)	Source[Ref.] (activity)	Synthesis[Ref.]
9	 1-methoxy-7,8-dehydrorutaecarpine ($C_{19}H_{13}N_3O_2$)	*Zanthoxylum integrifolium*[61g] (cytotoxic against P-388 or HT-29 cell lines in vitro)	Not known
10	 auranthine ($C_{19}H_{14}N_4O_2$)	*Penicillium aurantiogriseum*[63b]	Not known

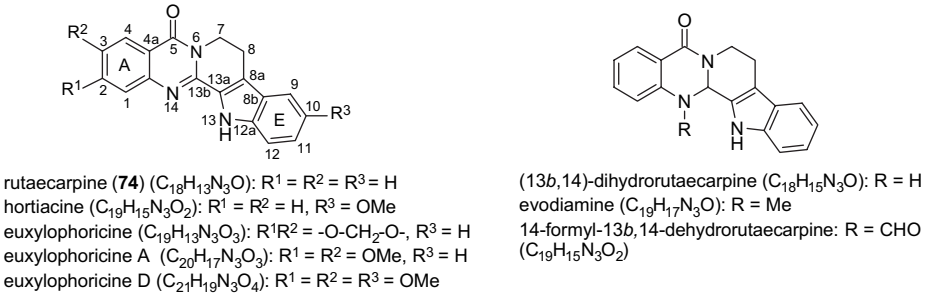
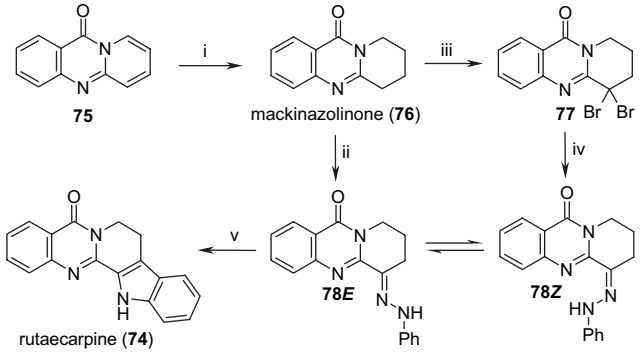


Figure 5. Naturally occurring bioactive rutaecarpines and analogs.



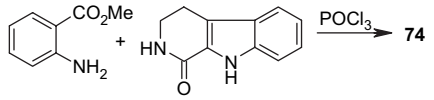
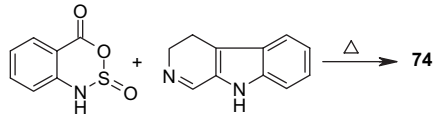
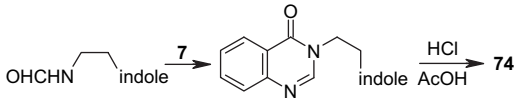
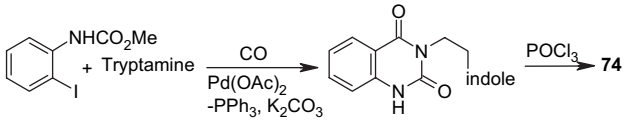
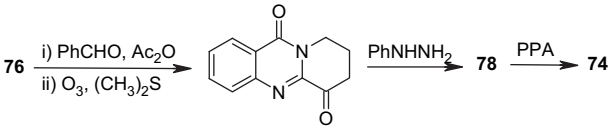
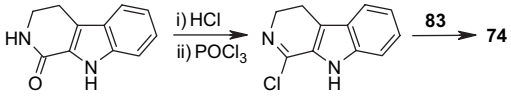
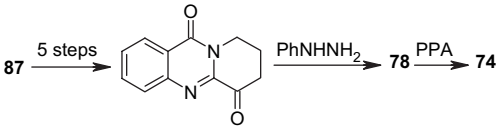
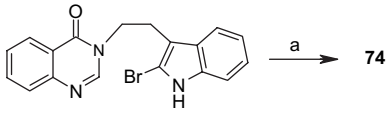
Scheme 20. Reagents and conditions: (i) H_2, cat. (92%); (ii) $PhN_2^+Cl^-$, AcOH, pH 4, −5 to 10 °C, 12 h (98%); (iii) Br_2, AcOH–AcONa, 50 °C, 1 h (98%); (iv) phenylhydrazine, EtOH, reflux, 4 h (81%); (v) polyphosphoric acid, 180 °C, (92%).

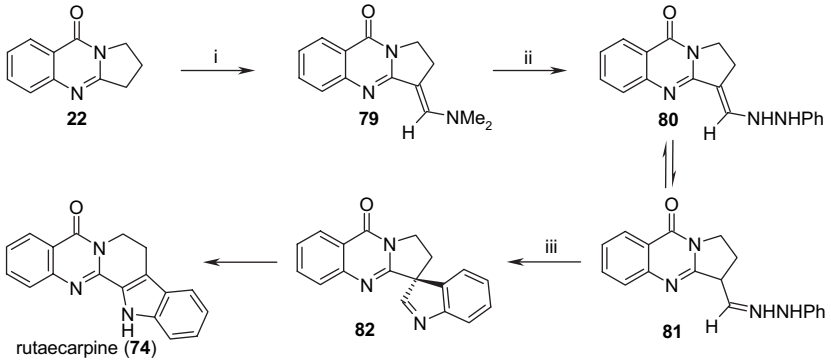
Hermecz et al.[65] completed an efficient synthesis of rutaecarpine via the natural product mackinazolinone (**76**). Mackinazolinone (**76**) was synthesized either from 2-piperidone and anthranilic acid[46e] or by the reduction[66] of compound **75**. Compound **76** was converted into hydrazone **78** by two different methods. In one of the methods, **76** was brominated to the dibromo compound **77**, which was then treated with phenylhydrazine to obtain the hydrazone **78** in good yield. In the other method, which was later generalized by the authors,[74] the compound **76** was treated with phenyldiazonium chloride to obtain directly the hydrazone **78** in quantitative yield. Interestingly, the hydrazone **78** shows solvent-dependent geometric isomerism. Hydrazone **78**, under PPA-catalyzed Fischer indolization, gave rutaecarpine (**74**) in good yield, completing its total synthesis in three steps and 83% overall yield (Scheme 20).

Kokosi's[52] rutaecarpine synthesis started with deoxyvasicinone (**22**). Treatment of the active methylene group of deoxyvasicinone (**22**) with the Vilsmeier–Haack reagent afforded the amino derivative **79**, which, on treatment with phenylhydrazine, gave the hydrazone **81** via the intermediate **80**. Heating the hydrazone **81** in Dowtherm A gave rutaecarpine (**74**) via **82** in 49% yield and in 40% overall yield from deoxyvasicinone (**22**) (Scheme 21).

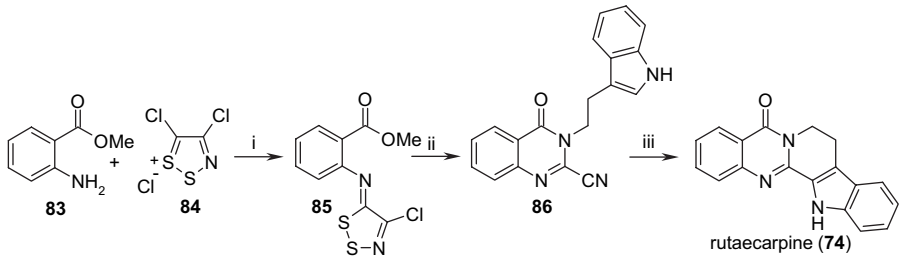
Mohanta and Kim[73d] developed an efficient general approach for the synthesis of rutaecarpine (**74**) and its analogs (Scheme 22), starting from the reaction of methyl anthranilate (**83**) with 4,5-dichloro-1,2,3-dithiazolium chloride (Appel's salt, **84**)[75] to obtain the derivative **85**. The anthranilate derivative **85** was then treated with tryptamine to obtain the cyanoquinazolinone **86**. Quinazolinone **86** was then converted into rutaecarpine (**74**) by treatment with trifluroacetic anhydride and HCl gas, completing the total synthesis of rutaecarpine (**74**) in two steps with 59% overall yield from **85**.

Table 9. Various approaches to rutaecarpine

Entry	Brief scheme	Overall yield (%) (steps)	Ref.
1		24% (one step)	Robinson et al.[72]
2		80% (one step)	Kametani et al.[46e]
3		27% (two steps)	Kametani et al.[16]
4		31% (two steps)	Mori et al.[46g]
5		78% (four steps)	Lee et al.[73c]
6		92% (two steps)	Lee et al.[46n]
7		45% (seven steps)	Chavan and Sivappa[73f]
8	 (a) $Pd(OAc)_2$, PCy_3, KOAc, DMF, reflux	89% (last step)	Harayma et al.[56k]

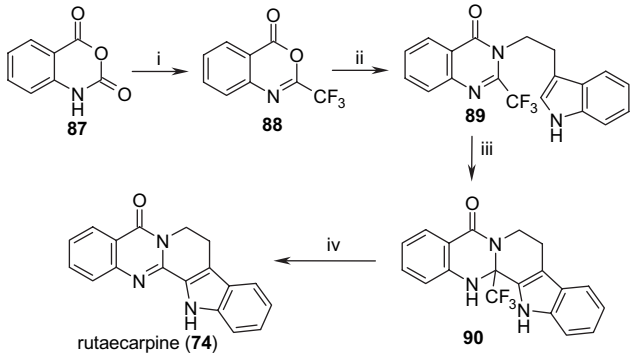


Scheme 21. Reagents and conditions: (i) $POCl_3$, DMF, rt, 1 h; (ii) $PhNHNH_2$, EtOH, Δ, 3 h; (iii) Dowtherm A, 160–190 °C, 0.5 h (49%).



Scheme 22. Reagents and conditions: (i) CH_2Cl_2, Py, rt, 3 h; (ii) tryptamine, CH_2Cl_2, rt, 31 h (62%); (iii) TFAA, HCl (g), 120–130 °C, 4 h (95%).

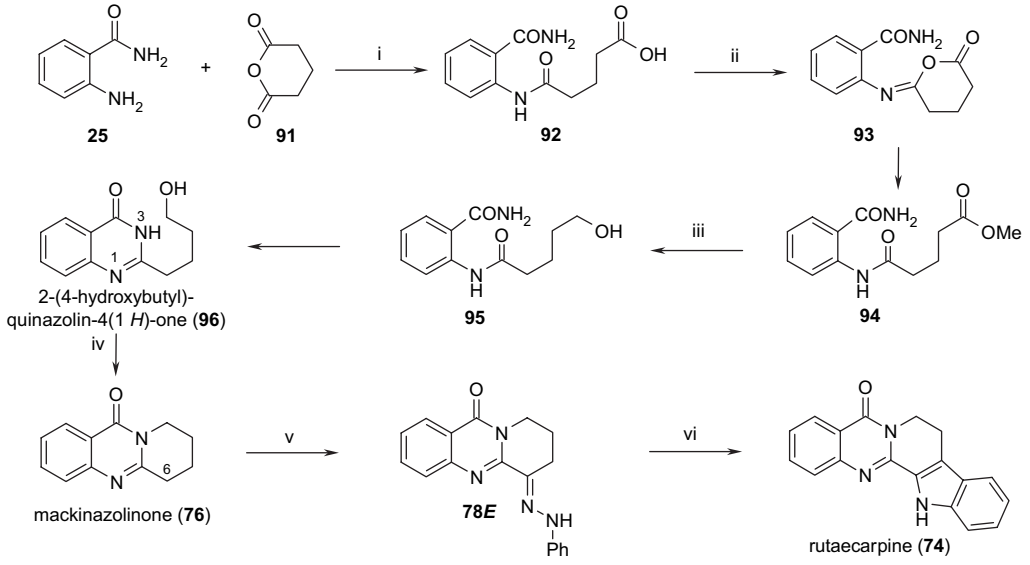
Bergman and Bergman[62] provided the most efficient approach for the synthesis of rutaecarpine (**74**). Isatoic anhydride (**87**) was converted into 2-fluoromethyl-benzoxazinone **88** and then treated with tryptamine under mild conditions to obtain **89**. Quinazolinone **89** was cyclized under acidic conditions to compound **90**, which, on refluxing in aqueous EtOH, gave rutaecarpine (**74**), completing the total synthesis in 93% overall yield from benzoxazinone **88** (Scheme 23).



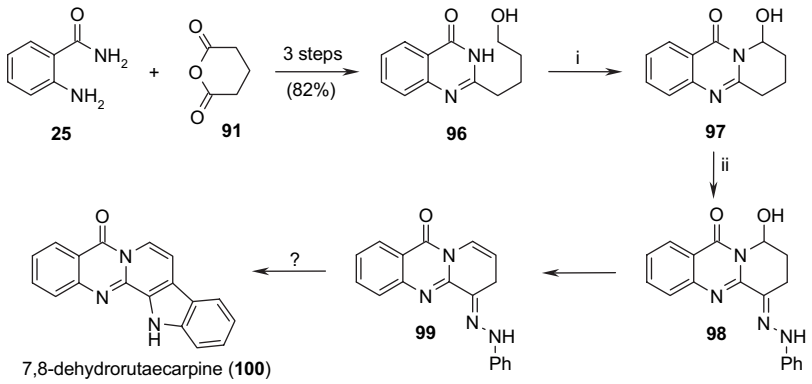
Scheme 23. Reagents and conditions: (i) TFAA, Py, 25 °C/15 min+115 °C/5 min; (ii) tryptamine, 30 min (98%); (iii) HCl, AcOH (95%); (iv) H_2O, EtOH (100%).

In continuation of our work on the synthesis of quinazolinone natural products, we have completed[14] a total synthesis of rutaecarpine (**74**) via the natural products, 2-(4-hydroxybutyl)quinazolin-4-one (Table 1, entry 2) and mackinazolinone (**76**), by using a zeolite-induced Fischer-indole reaction as a key step. We envisaged that it would be possible to design the five-carbon, six-membered ring C in **74** from glutaric anhydride (**91**) and a facile six-step synthesis of **74** has been completed, starting from glutaric anhydride (**91**), via *o*-amidoglutaranilic acid (**92**) formation, esterification, chemoselective ester reduction, intramolecular dehydrative cyclizations, hydrazone formation, and zeolite-induced Fischer-indole synthesis with 53% overall yield. The conditions employed in the present synthesis are mild, efficient, and general (Scheme 24).

Kaneko et al.[73b] completed the synthesis of rutaecarpine (**74**) by following almost the same strategy as described by Bergman and Bergman[62] (Scheme 23). They replaced the CF_3 group by Cl in order to study the mechanism of the reaction and obtained rutaecarpine in better yields. Their studies also provided evidence for the participation of the spiro intermediate in the cyclization step of Bergman's[62] rutaecarpine synthesis. Chang et al.[73e] extended this approach for the synthesis of rutaecarpine analogs for COX-2 inhibitory activity studies developed by their own group.[73c]



Scheme 24. Reagents and conditions: (i) Benzene/1,4-dioxane (2:1), rt, 2 h (98%); (ii) MeOH, H_2SO_4 (cat.), rt, 8 h (96%); (iii) $NaBH_4$, THF, reflux, 3 h, aqueous workup (86%); (iv) NaH, *p*-TsCl, THF, rt, 30 min (81%); (v) aniline, 30% HCl, $NaNO_2$, AcOH, −5 to 5 °C, 8 h (98%); (vi) Zeolite (H-Mordenite), AcOH, reflux, 5 h (82%).



Scheme 25. Reagents and conditions: (i) PCC, CH_2Cl_2, rt, 1 h (72%); (ii) aniline, 30% HCl, $NaNO_2$, AcOH, −5 to 5 °C, 8 h (98%).

Rutaecarpine (**74**) on DDQ oxidation is known to provide 7,8-dehydrorutaecarpine (**100**) in 77% yield.[62] We also planned to synthesize **100** starting from the natural product **96**, obtained in our rutaecarpine synthesis.[14] The alcohol **96** was converted into the quinazolinone **97**, by PCC oxidation. The compound **97** in a diazonium-coupling reaction directly furnished the hydrazone **99** in quantitative yield, plausibly via dehydration of the intermediate **98**. We tried several reagents/reaction conditions such as PPA, $ZnCl_2$, BF_3-ether, neat heating, heating in high-boiling solvents, and zeolite and acidic resins for conversion of **99** into 7,8-dehydrorutaecarpine (**100**), but all of them met with failure (Scheme 25).[76] Protection of the secondary alcohol in **100**, followed by hydrazone formation, Fischer-indolization, and deprotection, may provide a way to the natural product, (±)-7-hydroxyrutaecarpine (Table 8, entry 1), and further dehydration under acidic conditions would provide 7,8-dehydrorutaecarpine (**100**). We feel that the alkaloid, 7,8-dehydrorutaecarpine (**100**), would be a potential precursor for the enantioselective synthesis of (+)-7-hydroxyrutaecarpine and (−)-7,8-dihydroxyrutaecarpine (Table 8, entries 1 and 4).

Auranthine (Table 8, entry 10), a derivative of mackinazolinone (**76**), is a structurally quite different quinazolinone alkaloid in this class and, to date, no synthetic method is known for this compound. Recently, Bergman et al.[77] reported studies toward the synthesis of the alkaloid, auranthine, in which different approaches have been discussed. The auranthine precursor (Fig. 6) synthesized was treated with 50% polyphosphonic acid anhydride in ethyl acetate and DMA for the dehydration to occur, but, unfortunately, instead of auranthine, a *C*-acetyl derivative of auranthine was obtained.

In conclusion, rutaecarpine analogs (Table 8, entries 1–9) isolated from various species have moderate to good bioactivity and their synthesis should be possible by extending the several approaches available for rutaecarpine (Schemes 20–24 and Table 9). Some approaches to rutaecarpine used tryptamine as a starting material, in which the indole moiety was carried forward from the beginning, whereas, in many approaches, the indole moiety was built up in the last step by using a Fischer-indole reaction. Several publications on the synthesis and bioactivity of rutaecarpine and its analogs reveal that they are molecules of pharmaceutical importance. We feel that the synthesis of auranthine (Table 8, entry 10) should be possible by further functionalization of the natural product mackinazolinone.

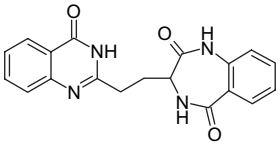


Figure 6. Auranthine precursor.

6. Quinazolinones fused with a piperazine ring system

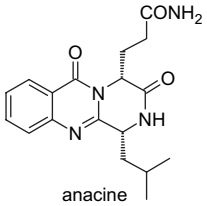
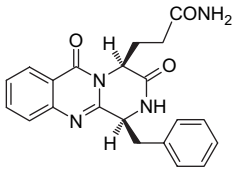
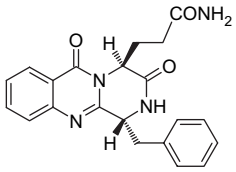
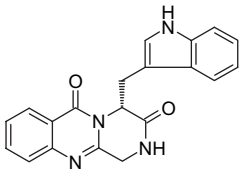
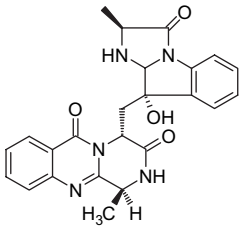
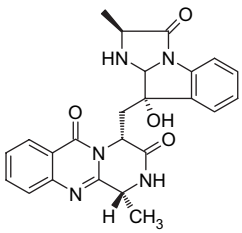
The quinazolinones fused with a piperazine ring system are subdivided into three classes: (a) quinazolinones fused with a simple piperazine ring, (b) quinazolinones fused with a piperazine ring, along with a spiro-ring functionality, and (c) quinazolinones fused with a piperazine ring, along with a prenyl-substituted indole moiety, i.e., the alkaloids, ardeemins.

6.1. Quinazolinones fused with a simple piperazine ring system

During the review period, 14 (Table 10, entries 1–14) quinazolinones having a quinazolinone ring fused with a simple piperazine ring system have been isolated from various species. Some representative syntheses are discussed in this section.

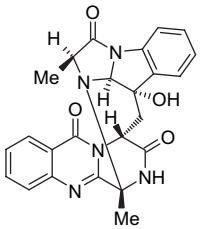
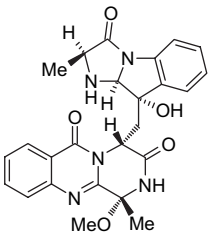
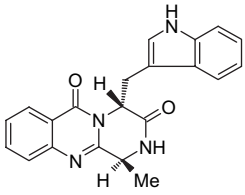
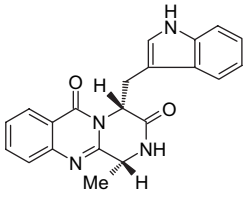
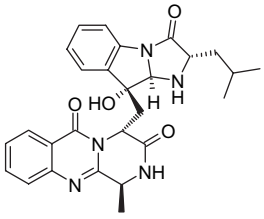
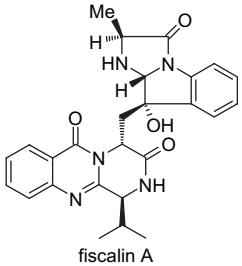
The first synthesis of the three related pyrazino[2,1-*b*]quinazoline-3,6-dione alkaloids, anacine, verrucine A, and verrucine B (entries 1–3) has been accomplished by exploring the peptide assembly on Sasrin resin (Scheme 26),[80] e.g., the resin-bound L-glutamine derivative **101** was sequentially condensed with anthranilic acid and Fmoc-protected L-phenylalanine chloride to give via **102** the resin-bound tripeptide **103**. Intramolecular dehydration followed by treatment with piperidine, a general procedure developed by Wang and Ganesan,[83] the scope, limitations, and mechanism of which was proposed by Snider et al.,[9b,94] afforded the amidine **104**. Cyclization with concomitant detachment from the resin was effected by overnight heating in a mixture of acetonitrile and 1,2-dichloroethane to give *N*-tritylverrucine A (**105**) in 17% overall yield from **101**, with only 0.8% of the corresponding 1,4-*anti*-disubstituted isomer being isolated. Removal of the trityl group was achieved

Table 10. Quinazolinones fused with a simple piperazine ring system

Entry	Quinazolinone alkaloid (MF)	Source[Ref.] (activity)	Synthesis[Ref.]
1	 anacine ($C_{18}H_{22}N_4O_3$)	*Penicillium verrucosum*,[78] *Penicillium aurantiogriseum*[79]	Wang and Sim[80]
2	 (+)-verrucine A ($C_{21}H_{20}N_4O_3$)	*Penicillium verrucosum*[78]	Wang and Sim[80]
3	 (+)-verrucine B ($C_{21}H_{20}N_4O_3$)	*Penicillium verrucosum*[78]	Wang and Sim[80]
4	 (–)-glyantrypine ($C_{20}H_{16}N_4O_2$)	*Aspergillus clavatus*[81]	Six syntheses[82–87]
5	 fumiquinazoline A ($C_{24}H_{23}N_5O_4$)	*Aspergillus fumigatus*[88,89] (cytotoxic)	Snider and Zeng[90]
6	 fumiquinazoline B ($C_{24}H_{23}N_5O_4$)	*Aspergillus fumigatus*[88,89] (cytotoxic)	Snider and Zeng[90]

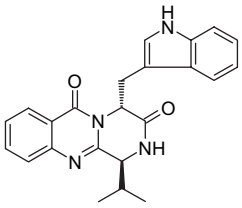
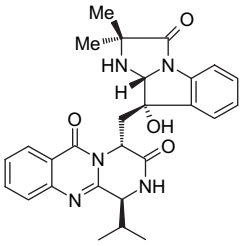
(*continued*)

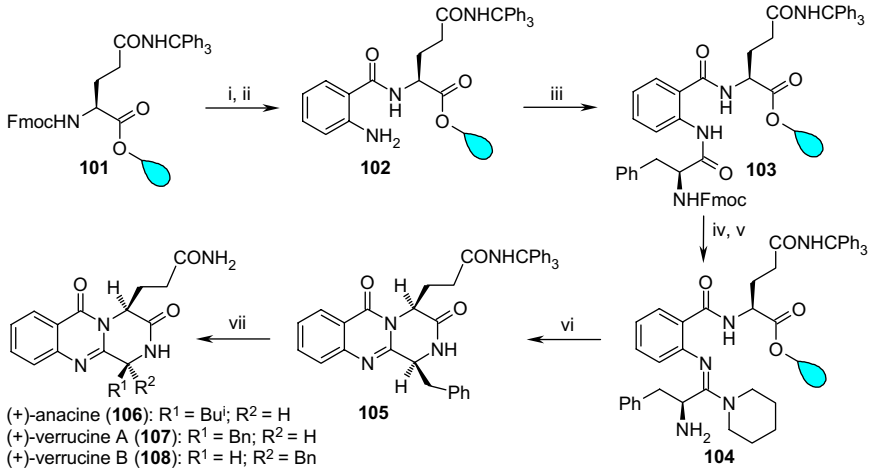
Table 10. (*continued*)

Entry	Quinazolinone alkaloid (MF)	Source[Ref.] (activity)	Synthesis[Ref.]
7	 fumiquinazoline D ($C_{23}H_{21}N_5O_4$)	*Aspergillus fumigatus*[89] (cytotoxic in P388 lymphocytic leukemia test system)	Not known
8	 fumiquinazoline E ($C_{29}H_{25}N_5O_5$)	*Aspergillus fumigatus*[89] (cytotoxic in P388 lymphocytic leukemia test system)	Snider and Zeng[90,91]
9	 fumiquinazoline F ($C_{21}H_{18}N_4O_2$)	*Aspergillus fumigatus*,[89] *Penicillium thymicola*[92] (cytotoxic in P388 lymphocytic leukemia test system)	Wang and Ganesan,[83,84] Hernández et al.,[86] Liu et al.[87]
10	 fumiquinazoline G ($C_{21}H_{18}N_4O_2$)	*Aspergillus fumigatus*[89] (cytotoxic in P388 lymphocytic leukemia test system)	Six syntheses[83,84,86,93–95]
11	 (–)-fumiquinazoline I ($C_{27}H_{29}N_5O_4$)	*Acremonium sp.*[96] (anti-fungal)	Snider and Zeng[90]
12	 fiscalin A ($C_{26}H_{27}N_5O_4$)	*Neosartorya fischeri*[97]	Not known

(*continued*)

Table 10. (*continued*)

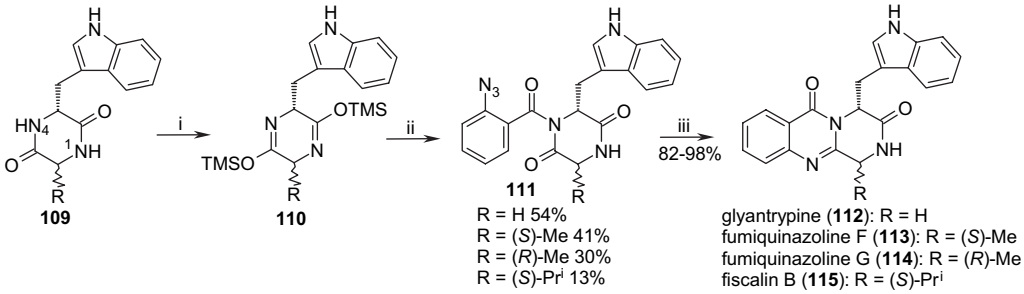
Entry	Quinazolinone alkaloid (MF)	Source[Ref.] (activity)	Synthesis[Ref.]
13	 fiscalin B ($C_{23}H_{22}N_4O_2$)	*Neosartorya fischeri*,[97] *Corynascus setous*[29]	Five syntheses[83,84,86,87,98]
14	 fiscalin C ($C_{27}H_{29}N_5O_4$)	*Neosartorya fischeri*[97]	Not known



Scheme 26. Reagents and conditions: (i) 20% piperidine in DMF, 15 min; (ii) EDC, anthranilic acid, DMF or NMP, rt, 19 h; (iii) Fmoc-L-Phe-Cl, Py, CH_2Cl_2, rt, 13 h, workup, repeat condition (i); (iv) PPh_3, I_2, EtN^iPr_2, CH_2Cl_2, rt, 15 h; (v) 20% piperidine in CH_2Cl_2, rt, 30 min; (vi) MeCN/$(CH_2Cl)_2$ (1:1), reflux overnight (17% over six steps); (vii) TFA/Et_3SiH/CH_2Cl_2 (2:2:1), rt, 15 min (84%).

reductively with triethylsilane in trifluoroacetic acid to give (+)-verrucine A (**107**). Similar reaction sequences employing D-phenylalanine and L-leucine afforded (+)-verrucine B (**108**) and (+)-anacine (**106**), respectively, in 14.5 and 9.3% overall yields, based on **101** (Scheme 26). The absolute configuration of the former, not assigned when it was first isolated, has thus been established unambiguously.

The other members of this family, e.g., glyantrypine, fumiquinazolines F and G, and fiscalin B (entries 4, 9, 10, and 13), have been synthesized[86] as shown in Scheme 27. Avendaño and co-workers[86] have investigated the acylation of a range of diketopiperazines **109**, prepared by standard methods from the respective *N*-Boc dipeptides, with 2-azidobenzoyl chloride via the silyl imidates **110** (Scheme 27).[86] The selective monoacylation on the *N*(4) nitrogen atom of the glycine derivative **109** (R=H) to give **111** was ascribed to a boat-like conformation of the silylated intermediate, with the indolyl substituent folding in such a way that *N*(1) becomes blocked. The selectivity was also good with the (*S*)-alanine derivative of **109** [R=(*S*)-Me], but less impressive with the (*R*)-alanine and (*S*)-valine analogues [R=(*R*)-Me and (*S*)-Pr^i], which gave almost equal amounts of the *N*(1)-acylated products. All of these acylated products **111** could be cyclized by an intramolecular Staudinger reaction upon treatment with tributylphosphine to complete the syntheses of (−)-glyantrypine (**112**), (−)-fumiquinazoline F (**113**), fumiquinazoline G (**114**), and fiscalin B (**115**), respectively. Very recently, Liu et al.[87] developed a microwave-promoted, three-component, one-pot reaction for



Scheme 27. Reagents and conditions: (i) TMSCl, Et_3N, CH_2Cl_2, rt; (ii) 2-$N_3C_6H_4COCl$, CH_2Cl_2, rt; (iii) Bu_3P, toluene, rt.

a highly efficient and concise total synthesis of glyantrypine (**112**), fumiquinazoline F (**113**), and fiscalin B (**115**), achieving overall yields of 55, 39 and 20%, respectively.

The more complex (−)-fumiquinazolines A, B, and I (entries 5, 6, and 11) have been synthesized by Snider's group[90] using routes in which most of the effort was, understandably, devoted to constructing the 3-oxotetrahydro-1*H*-imidazo[1,2-*a*]indol-9-yl substituents. Formation of the 2*H*-pyrazino[2,1-*b*]quinazoline-3,6(1*H*,4*H*)-dione moieties was left to the final stages of the synthesis, and involved a methodology similar to that shown in Scheme 26 (see steps from **102** to **105**). In the case of fumiquinazoline A, e.g., treatment of the precursor **117** (prepared from the advanced intermediate **116**) with triphenylphosphine and bromine in the presence of triethylamine followed by aminolysis of the resulting benzoxazine with piperidine and final cyclization gave a mixture of the Cbz-protected quinazolinone and its C-4 epimer in overall yields of 49 and 14%, respectively (Scheme 28). Removal of the Cbz protecting group from the former by hydrogenolysis over palladium completed the synthesis of (−)-fumiquinazoline A (**118**) in 90% yield. The overall yields for (−)-fumiquinazolines B (**119**) and I from the appropriate precursors similar to **117** were 42 and 52%, respectively (Scheme 28).

6.2. Quinazolinopiperazines with a spiro-ring system

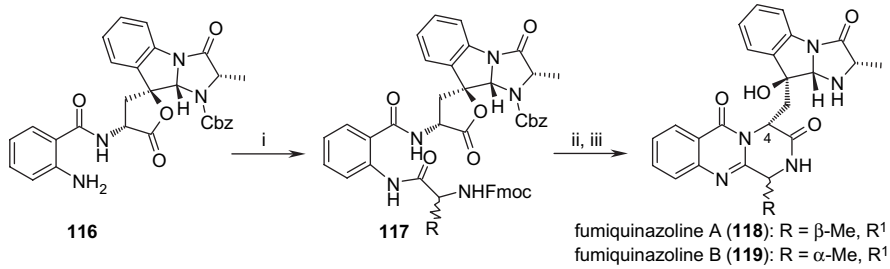
There are five alkaloids (Table 11, entries 1–5), having a quinazolinone ring fused with a piperazine ring, along with a spiro-ring system, which have been isolated from various species.

The advanced intermediate **116** (Scheme 28), previously used by Snider and Zeng[90] in a synthesis of the *Aspergillus* metabolite, fumiquinazoline A (**118**), has been elegantly transformed into two other complex fumiquinazolines by the same group (Scheme 29).[91]

Condensation of **116** with a selenocysteine derivative, (*R*)-FmocNHCH(CH_2SePh)CO_2H, yielded the quinazoline precursor of the type **117** (Scheme 28), which was subjected to Ganesan's cyclization conditions to sequentially afford the benzoxazine and amidine (of the type **104**, Scheme 26) intermediates. Heating the crude amidine in acetonitrile/acetic acid (25:1) at reflux set off a cascade of reactions that culminated in the formation of a mixture of **121** and its oxygen-bridged isomer **122** in yields of 56 and 14%, respectively, based on the benzoxazine. Compound **121** could be partially converted into **122** by further heating, and recovered **121** was recycled. Finally, standard transformations on both products completed the first total syntheses of (−)-fumiquinazolines C (**123**) and E (**120**), respectively. A similar set of reactions on the appropriate analogue of **116**, designed to produce (−)-fumiquinazoline H (Table 11, entry 2), was accomplished, and required replacement of the Cbz protecting group by Fmoc in the benzoxazine intermediate before a satisfactory cyclization could be effected.

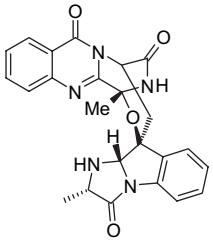
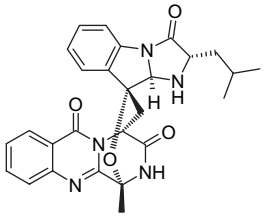
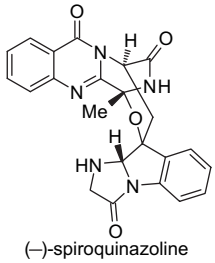
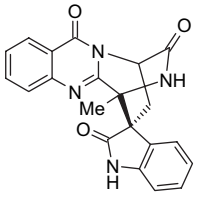
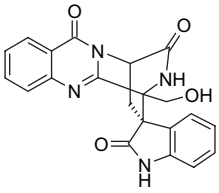
The principles implicit in the Wang and Ganesan[83,84] route to fumiquinazolines have been applied by Hart and Magomedov[100,101] to a synthesis of the structurally complex alkaloid, alantrypinone (**129**) (Scheme 30).

In this case, dehydration of the precursor tripeptide of the type **117** (Scheme 28) gave the benzoxazine intermediate **124** in 80% yield. Treatment with 10 equiv of (Me_3AlSPh)Li in THF at low temperature gave the expected pyrazino[2,1-*b*]quinazoline-3,6-dione **125** in 46% yield. With 5 equiv of the reagent, however, the intermediate quinazolinone was isolated and efficiently cyclized to **125** (94% yield) when treated with piperidine in THF at 0 °C. Oxidative elimination of the methylthio group then yielded the *exo*-methylene product **126** (79%), which cyclized in trifluoroacetic acid to the bridged hexacyclic compound (−)-**127** (89%). Oxidative rearrangement of this indole to an oxindole produced



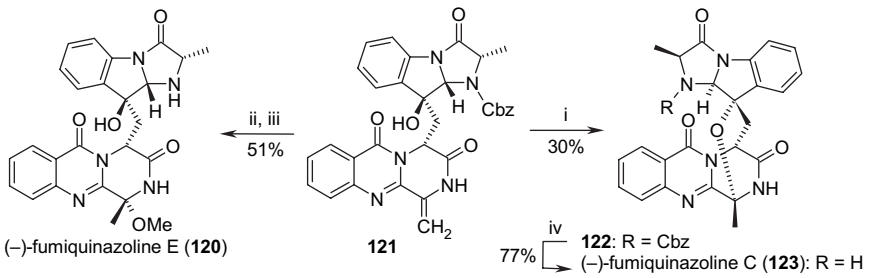
Scheme 28. Reagents and conditions: (i) Fmoc-L-Ala/D-Ala, EDAC, MeCN; (ii) (a) PPh_3, Br_2, Et_3N, (b) piperidine, EtOAc, (c) MeCN, reflux; (iii) H_2, Pd/C.

Table 11. Quinazolinones fused with a piperazine ring along with a spiro-ring system

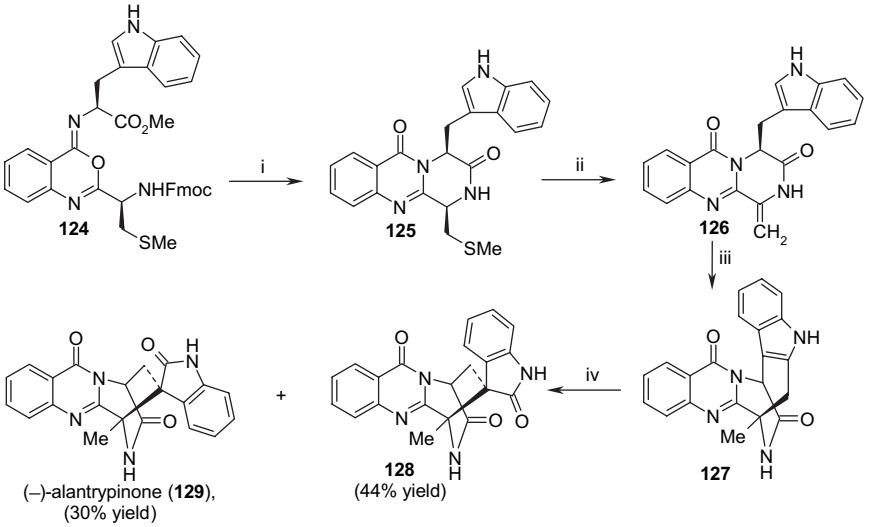
Entry	Quinazolinone alkaloid (MF)	Source[Ref.] (activity)	Synthesis[Ref.]
1	 fumiquinazoline C ($C_{24}H_{21}N_5O_4$)	*Aspergillus fumigatus*[88,89] (cytotoxic)	Snider and Zeng[90,91]
2	 (–)-fumiquinazoline H ($C_{27}H_{27}N_5O_4$)	*Acremonium* sp.[96] (anti-fungal)	Snider and Zeng[90,91]
3	 (–)-spiroquinazoline ($C_{23}H_{19}N_5O_4$)	*Aspergillus flavipes*[99] (inhibits binding of substance P to human astrocytoma cells)	Not known
4	 (+)-alantrypinone ($C_{21}H_{16}N_4O_3$)	*Penicillium thymicola*,[92a] *Aspergillus terreus*[92b]	Hart and Magomedov,[100,101] Kende et al.[102]
5	 (–)-serantrypinone ($C_{21}H_{16}N_4O_4$)	*Penicillium thymicola*[103] [IBT 5891], *Aspergillus terreus*[92b]	Not known

a mixture of (−)-alantrypinone **129** (the unnatural enantiomer) and its C-17 epimer (−)-**128** in 30 and 44% yields, respectively. The synthesis confirmed the absolute configuration of natural alantrypinone, previously determined by the anomalous dispersion technique.

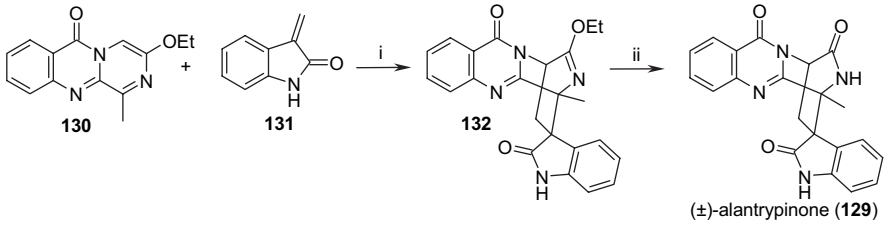
Recently, Kende et al.[102] accomplished an efficient synthesis of (±)-alantrypinone and its 17-*epi*-isomer by employing a novel aza-Diels–Alder reaction between compounds **130** and **131** as the key step. The reaction sequence comprises eight steps starting from anthranilic acid and proceeds via



Scheme 29. Reagents and conditions: (i) MeCN/AcOH (100:1), reflux, 2 h; (ii) HCl (0.2 M), MeOH, 25 °C; (iii) H_2 (1 atm), Pd/C, 30 min; (iv) H_2, Pd/C, 30 h.



Scheme 30. Reagents and conditions: (i) (a) $(Me_3AlSPh)Li$, THF, −78 to −10 °C, (b) piperidine, THF, 0 °C (71%); (ii) (a) *m*-CPBA, CH_2Cl_2, −78 °C, (b) Ph_3P, benzene, reflux (79%); (iii) TFA, 70 °C (89%); (iv) (a) NBS, TFA/THF/H_2O, (b) H_2, Pt/C, MeOH.



Scheme 31. Reagents and conditions: (i) $CHCl_3$, rt, 24 h (55%); (ii) EtOAc, 1.0 N HCl, rt, 5 h (85%).

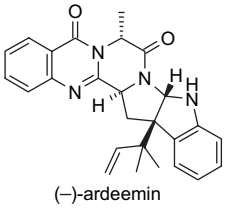
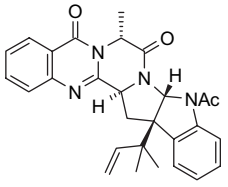
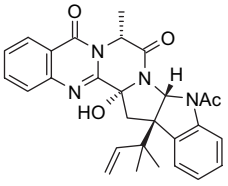
132 in 13.5% overall yield (Scheme 31). The present hetero Diels–Alder reaction provides an efficient method for the synthesis of (±)-alantrypinone and its analogues.

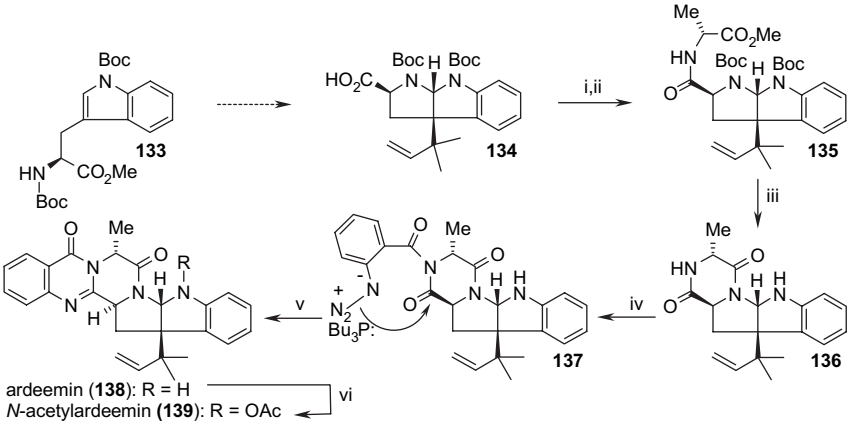
6.3. Quinazolinopiperazines with a prenylated indole moiety

As part of a screening program for bioactive metabolites, McAlpine et al.[104,105] found that extracts of the fungus *Aspergillus fischeri* (var. brasiliensis) demonstrated the ability to restore vinblastine sensitivity to a tumor cell line that was otherwise insensitive. Isolation of the active components from the fermentation mixture led to the characterization of three structurally related agents, which were called ardeemins for their ability to reverse drug insensitivity (vide infra). The major and most active constituent was named 5-*N*-acetylardeemin and two other constituents isolated from the product mixture were termed ardeemin and 15*b*-β-hydroxy-5-*N*-acetylardeemin (Table 12, entries 1–3).

Structurally, the ardeemins belong to an interesting class of natural products, which are termed reverse prenyl hexahydropyrrolo[2,3-*b*]indole alkaloids. Danishefsky et al.[106,107] completed the first total synthesis of these structurally complex quinazolinones. The starting material was bis(Boc)-tryptophan methyl ester **133** (Scheme 32), which was transformed to the diketopiperazine **136** via the prenyl-acid **134** and prenyl-ester **135** by using standard transformations. The diketopiperazine **136** was obtained in 76% yield upon deprotection of **135** and ammonia–DMAP-induced intramolecular cyclization. An intramolecular variant of the aza-Wittig reaction was used for the efficient fusion of the

Table 12. Quinazolinopiperazines with a prenylated indole moiety (ardeemin alkaloids)

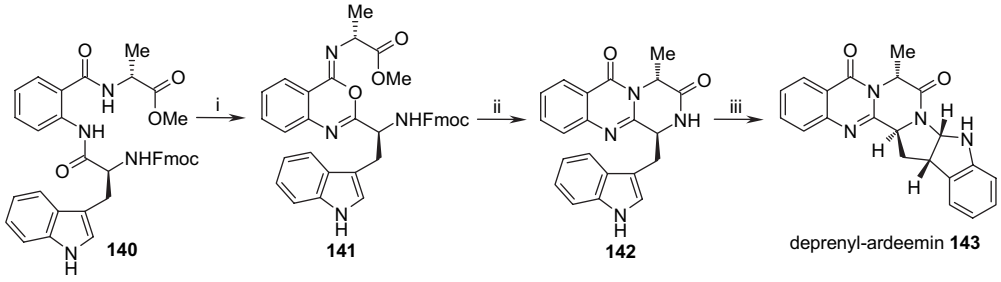
Entry	Quinazolinone alkaloid (MF)	Source[Ref.] (activity)	Synthesis[Ref.]
1	 (−)-ardeemin ($C_{26}H_{26}N_4O_2$)	*Aspergillus fischeri*[104,105] [var. brasiliensis]	Danishefsky et al.[106,107]
2	 (−)-5-*N*-acetylardeemin ($C_{28}H_{28}N_4O_3$)	*Aspergillus fischeri*[104,105] [var. brasiliensis] (reversed multiple drug resistance (MDR) in human tumor cell lines and sensitized cells to anti-cancer vinblastine)	Danishefsky et al.[106,107]
3	 (−)-15b-β-hydroxy-5-*N*-acetylardeemin ($C_{28}H_{28}N_4O_4$)	*Aspergillus fischeri*[104,105] [var. brasiliensis]	Not known



Scheme 32. Reagents and conditions: (i) FCN, Py, CH_2Cl_2, −15 °C; (ii) D-Ala-OMe·HCl, $NaHCO_3$, H_2O, CH_2Cl_2 (71%); (iii) TMSI, MeCN, 0 °C, then NH_3, DMAP, MeOH (76%); (iv) KHMDS, *o*-$N_3C_6H_4COCl$, THF, −78 °C (80%); (v) Bu_3P, benzene (72%); (vi) LDA, THF, −78 °C to rt, then AcCl, reflux (82%).

(3*H*)-quinazolin-4-one sector. Acylation of **136** with *o*-azidobenzoyl chloride furnished **137**, which reacted with tributylphosphine in benzene to afford ardeemin (**138**) in 56% yield starting from **136**. Finally, acylation of **138** provided 5-*N*-acetylardeemin (**139**) in 11% overall yield. In summary, the core structure of the three reverse prenylated hexahydropyrroloindole alkaloids was assembled rapidly and stereoselectively (through thermodynamic control) from a suitably protected tryptophan in two steps. Synthesis of (−)-15*b*-β-hydroxy-*N*-acetylardeemin appears possible following the same strategy.

Recently, Sollhuber et al.[108a] have developed a new method for the synthesis of the framework of ardeemin without the prenyl group (Scheme 33). Deprenyl-ardeemin **143** was synthesized[108a] in four steps via **141** with 45% overall yield, starting from *N*-2-aminobenzoyl-α-amino ester **140** using standard transformations (Scheme 33). In the last step, the acid-promoted cyclization of the dione **142** occurs in an irreversible and stereocontrolled fashion. Cledera et al.[108b] synthesized deprenyl-ardeemin by the reaction of the appropriate lactim ether with anthranilic acid, under microwave irradiation, in the absence of solvent, with 48% yield.



Scheme 33. Reagents and conditions: (i) PPh_3, I_2, EtN^iPr_2, 3 h; (ii) (a) 20% piperidine/CH_2Cl_2, rt, 3 h, (b) CH_3CN, reflux, 2 h; (iii) TFA, rt (45% overall yield).

In conclusion, it appears that the two important protocols, Eguchi's protocol and Ganesan's protocol, have been used extensively for the synthesis of this class of alkaloids (Tables 10–12). We feel that the most difficult and challenging task in the synthesis of the complex alkaloids, fumiquinazolines A, B, C, E, H and I, was further functionalization of the indole moiety. Snider et al., in their elegant approaches to various fumiquinazolines, have developed an easy and straightforward access to these structurally complex and strained moieties.

7. Quinazolinones fused with a diazepine ring system

This class of quinazolinones is subdivided into simple benzodiazepines like sclerotigenin, circumdatins, and benzomalvins and the more complex asperlicins.

7.1. Sclerotigenin, circumdatins, and benzomalvins

The 11 quinazolinones isolated from various species and listed in Table 13 (entries 1–11) have a diazepine ring fused with a quinazolinone system.

Sclerotigenin (**148**) was known as a synthetic compound before its isolation.[110] After its isolation, many syntheses have been reported.[110–112] Snider and Busuyek[95] provided an efficient general synthetic method for the synthesis of sclerotigenin and other members of the benzodiazepine class (Scheme 34). The benzodiazepinedione **144** was selectively acylated at the more acidic anilide nitrogen, followed by aza-Wittig cyclization of the resulting imide **146** with Bu_3P, affording 43% of sclerotigenin (**148**) from dione **144** in two steps, without using protection–deprotection chemistry. This strategy is general and can be applied for the synthesis of other quinazolinones (Table 13, entries 2, 5, and 6) of this class. Liu et al.[112b] completed an efficient one-pot total synthesis of sclerotigenin (**148**) in 55% yield, via a novel microwave-assisted domino reaction of anthranilic acid, *N*-Boc-glycine, and methyl anthranilate in the presence of triphenyl phosphite. This important methodology was further generalized for the synthesis of more complex quinazolinone natural products.

Circumdatins are fused benzodiazepine alkaloids isolated from terrestrial isolates of the fungus *Aspergillus ochraceus*.[113,115] Circumdatins C, F, and G are prototypical members, while others, such as circumdatins D, E, and H, contain an additional tetrahydropyrrole ring (Table 13, entries 2–7). Benzodiazepines constitute a widely prescribed class of psychoactive drugs.[113] The first total synthesis of circumdatins C (**158**) and F (**149**) was reported by Witt and Bergman[114] (Scheme 35).

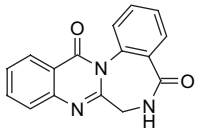
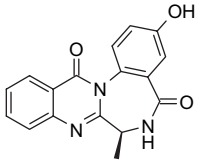
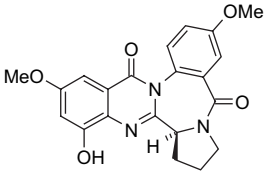
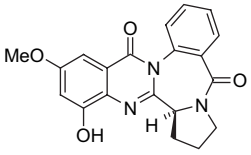
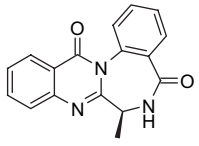
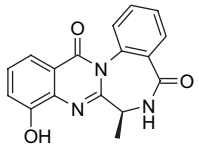
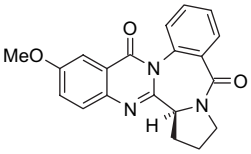
N-Sulfinylanthraniloyl chloride was the preferred starting material for Witt and Bergman's assembly of the tripeptides **152** and **153**, key intermediates in a route to the fungal metabolites, circumdatins F (**149**) and C (**158**) (Scheme 35), respectively.[114] Cyclization of **152** and **153** with triphenylphosphine and iodine in the presence of Hunig's base gave the benzoxazines **154** and **155**, respectively. Aminolysis of the benzoxazines with piperidine produced the respective amidines **156** and **157**. The target alkaloids **149** and **158** were obtained after deprotection with HBr in acetic acid followed by treatment with a tertiary amine and silica gel.

An efficient total synthesis of circumdatin F (**149**) was reported by Snider and Busuyek[95] in 69% yield from the dione **145**, following a selective acylation and aza-Wittig cyclization reaction sequence via **147** (Scheme 34). A new synthesis of circumdatin F arose from the work of Witt and Bergman,[111] where a suitable benzoxazinone was used as a potential intermediate.

Grieder and Thomas[112] developed a concise building-block approach to a diverse multi-array library of the circumdatin family of natural products using a polymer-supported, phosphine-mediated intramolecular aza-Wittig reaction as a key step of the reaction sequence, e.g., an analogue of the type shown in Figure 7 has been prepared using a novel modified Eguchi protocol. The multi-array library-generation strategy commenced from readily accessible benzodiazepinedione derivatives. Liu et al.[112b] extended their one-pot, microwave-assisted, domino-reaction strategy to the synthesis of circumdatin F (32% yield) and, additionally, analogues of circumdatin E were synthesized via the three-component, one-pot, sequential reactions promoted by microwave irradiation.

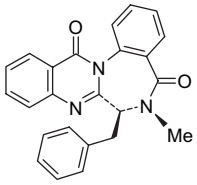
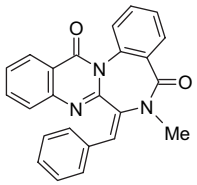
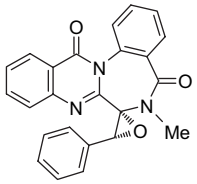
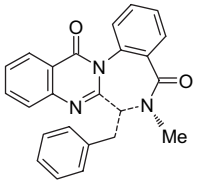
We planned the synthesis of circumdatin F using Ullman-type coupling (Goldberg reaction) as a key step.[76] Condensation of Boc-L-alanine (**159**) with anthranilamide (**25**) in the presence of EDAC gave amide **160**, which was transformed into quinazolinone **161** by using a base-catalyzed dehydrative cyclization. Boc deprotection of quinazolinone **161** furnished the amine **162**, which was condensed with 2-iodobenzoic acid to obtain compound **163**. We tried several reagents and reaction conditions to cyclize compound **163**, but all of them met with failure. We feel that Ullman-type coupling (Goldberg reaction) will provide an access

Table 13. Quinazolinobenzodiazepines (sclerotigenin, circumdatins and benzomalvins)

Entry	Quinazolinone alkaloid (MF)	Source[Ref.] (activity)	Synthesis[Ref.]
1	 sclerotigenin ($C_{16}H_{11}N_3O_2$)	*Penicillium sclerotigenum*[109] (anti-insect)	Synthesis known before isolation[110] four syntheses[95,111,112]
2	 (–)-circumdatin C ($C_{17}H_{13}N_3O_3$)	*Aspergillus ochraceus*[113]	Witt et al.[114]
3	 (–)-circumdatin D ($C_{21}H_{19}N_3O_5$)	*Aspergillus ochraceus*[113]	Not known
4	 (–)-circumdatin E ($C_{20}H_{17}N_3O_4$)	*Aspergillus ochraceus*[113]	Not known
5	 (–)-circumdatin F ($C_{17}H_{13}N_3O_2$)	*Aspergillus ochraceus*[113]	Witt and Bergman,[111,114] Snider and Busuyek,[95] Liu et al.[112b]
6	 (–)-circumdatin G ($C_{17}H_{13}N_3O_3$)	*Aspergillus ochraceus*[115a]	Not known
7	 (–)-circumdatin H ($C_{20}H_{17}N_3O_3$)	*Aspergillus ochraceus*[115b] (inhibitor of mitochondrial NADH oxidase)	Not known

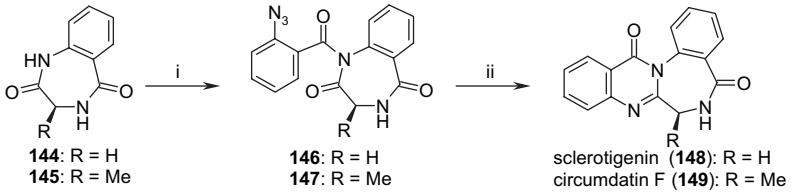
(*continued*)

Table 13. (*continued*)

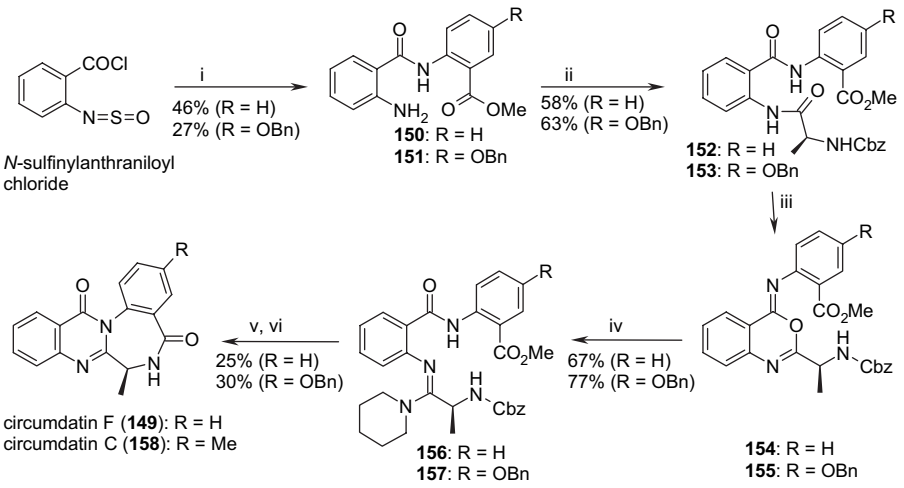
Entry	Quinazolinone alkaloid (MF)	Source[Ref.] (activity)	Synthesis[Ref.]
8	 benzomalvin A ($C_{24}H_{19}N_3O_2$)	*Penicillium culture*[116] (inhibitor of substance P, the endogenous ligand for neurokinin-1 receptor)	Sun et al.,[117] Eguchi et al.,[118,119] Liu et al.[112b]
9	 benzomalvin B ($C_{24}H_{17}N_3O_2$)	*Penicillium culture*[116]	Sugimori et al.[119]
10	 benzomalvin C ($C_{24}H_{17}N_3O_3$)	*Penicillium culture*[116]	Not known
11	 benzomalvin D ($C_{24}H_{19}N_3O_2$)	*Penicillium culture*[117]	Sun et al.[117]

to **149** (Scheme 36). The same strategy would be applicable to the synthesis of the circumdatin family of natural products and other quinazolinone natural products like sclerotigenin and benzomalvins and its logical extension to the synthesis of asperlicin C and asperlicin would be also possible.

Benzomalvins (Table 13, entries 8–10) are another class of benzodiazepine-fused quinazolinones isolated from the fungus *Penicillium culture*.[116] A further unstable new metabolite, (+)-benzomalvin D (entry 11), has now been extracted from the same culture.[117] On standing overnight in a chloroform solution at room temperature, benzomalvin D was converted into benzomalvin A and, similarly, benzomalvin A interconverted with benzomalvin D. Storage of the solid compounds at −40 °C retarded their equilibration. The structural differences between the two compounds were confirmed by the first total synthesis[117] of benzomalvin A from isatoic anhydride, L-phenylalanine, and methyl anthranilate, following a similar reaction sequence to that used by Bock et al.[120] in their synthesis of asperlicins C and E (see Scheme 38). The enantiomerically pure synthetic benzomalvin A (3.7% overall yield) equilibrated in the same



Scheme 34. Reagents and conditions: (i) (a) Et_3N, DMAP, DMSO–CH_2Cl_2, then 2-$N_3C_6H_4COCl$, CH_2Cl_2, 20 °C (for R=H), (b) Et_3N, DMAP, THF, then 2-$N_3C_6H_4COCl$, THF, 20 °C (for R=Me); (ii) Bu_3P, benzene, rt to 60 °C.



Scheme 35. Reagents and conditions: (i) Methyl anthranilate (R=H) or methyl 5-benzyloxyanthranilate (R=OBn), toluene, rt, 48 h; (ii) *N*-Cbz-L-Ala, DCC, CH_2Cl_2, 0 °C to rt; (iii) Ph_3P, I_2, Pr^i_2NEt, CH_2Cl_2, rt [57% (R=H), 36% (R=OBn)]; (iv) 20% piperidine in EtOAc, rt; (v) 45% HBr in HOAc, 60 °C; (vi) Et_3N (for R=H) or Pr^i_2NEt (for R=OH), EtOAc, rt.

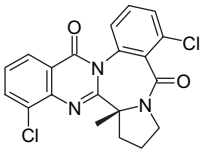
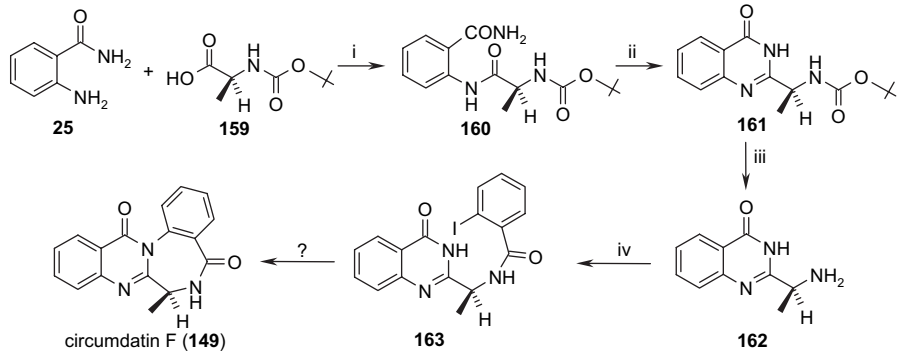
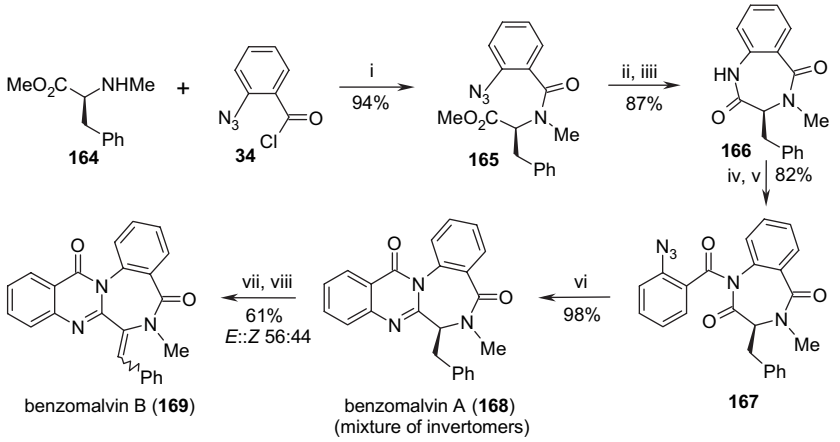


Figure 7. Circumdatin analogue.

manner as the natural product. Eventually, variable-temperature NMR revealed that the two compounds are conformational isomers and, in fact, atropisomers. The syntheses of (−)-benzomalvin A (**168**) and benzomalvin B (**169**) by Eguchi and co-workers[118,119] utilized their own Eguchi protocol [acylation of suitable precursors with 2-azidobenzoyl chloride (**34**) followed by an intramolecular aza-Wittig reaction] to construct both heterocyclic rings (Scheme 37).[119] In brief,

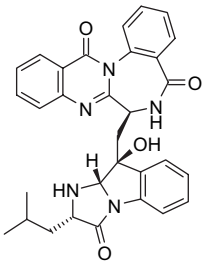
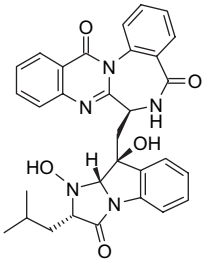
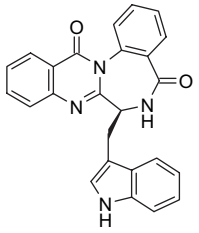
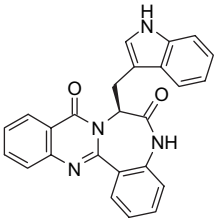
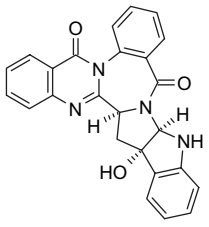


Scheme 36. Reagents and conditions: (i) EDAC, THF, rt, 2 h (87%); (ii) aq LiOH/THF (1:1), rt, 1 h (98%); (iii) $AlCl_3$, CH_2Cl_2, rt, 3 h (95%); (iv) 2-iodobenzoic acid, EDAC, THF, rt, 1 h (96%).



Scheme 37. Reagents and conditions: (i) Et_3N, THF, 0 °C to rt; (ii) Bu_3P, toluene, rt to reflux; (iii) TFA/H_2O/THF (1:1:12.5), rt; (iv) $KN(SiMe_3)_2$, THF, −78 °C; (v) **28**, THF, −78 °C to rt; (vi) Ph_3P, toluene, rt to reflux; (vii) NBS, AIBN, CCl_4, reflux; (viii) DBU, toluene, reflux.

Table 14. Quinazolinobenzodiazepines (asperlicin alkaloids)

Entry	Quinazolinone alkaloid (MF)	Source[Ref.] (activity)	Synthesis[Ref.]
1	 (–)-asperlicin ($C_{31}H_{29}N_5O_4$)	*Aspergillus alliaceus*[121] (antagonist of the peptide hormone CCK)	Snider et al.[124]
2	 asperlicin B ($C_{31}H_{29}N_5O_5$)	*Aspergillus alliaceus*[122] (agonist of CCK, selectivity affecting peripheral CCK receptors)	Not known
3	 asperlicin C ($C_{25}H_{17}N_4O_2$)	*Aspergillus alliaceus*[123] (agonist of the peptide hormone CCK)	Bock et al.,[120] Snider et al.,[95,124] Liu et al.[112b]
4	 asperlicin D ($C_{25}H_{18}N_4O_2$)	*Aspergillus alliaceus*[123]	Not known
5	 asperlicin E ($C_{25}H_{18}N_4O_3$)	*Aspergillus alliaceus*[123]	Bock et al.[120]

the reaction of **34** with *N*-methyl-L-phenylalanine methyl ester **164** yielded the intermediate azide **165** (ee 99.7%), which, after treatment with tributylphosphine in boiling toluene followed by acidic workup, yielded the (−)-benzodiazepinedione **166** in 87% yield and high optical purity. A second application of the Eguchi protocol completed the synthesis of (−)-benzomalvin A (**168**). Benzomalvin B (**169**) was prepared from benzomalvin A (**168**) as a mixture

of (*E*)- and (*Z*)-isomers by a benzylic bromination–dehydrobromination sequence. An efficient one-pot total synthesis of (±)-benzomalvin A in 16% yield was completed by Liu et al.,[112b] using a microwave-assisted domino reaction.

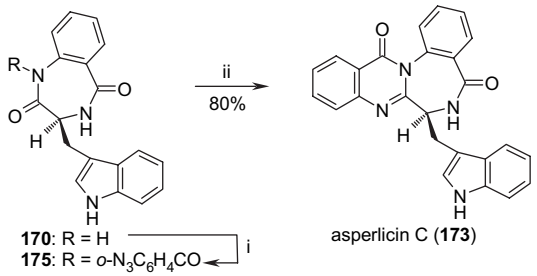
7.2. Asperlicin alkaloids

Asperlicins A–E (Table 14, entries 1–5) are competitive non-peptide cholecystokinin (CCK) antagonists isolated from the fungus *Aspergillus alliaceus*.[121–123]

Asperlicin has 300- to 400-fold more affinity for pancreatic, gastrointestinal, and gallbladder CCK receptors than proglumide, a standard agent of this class. Moreover, asperlicin is highly selective for peripheral CCK receptors relative to brain CCK and gastrin receptors. Bock and co-workers[120] reported the first total synthesis of the potentially important asperlicins C and E (Scheme 38). Compound **170** was synthesized starting from isatoic anhydride (**87**) and L-tryptophan and was then reacted with Lawesson's reagent to give a 1:1 mixture of monothioamides, which were separated. The desired thioamide **171** was elaborated to asperlicin C (**173**) in two steps via **172** and further transformed into asperlicin E (**174**) by rose Bengal-sensitized photooxygenation and in situ reduction with dimethyl sulfide (Scheme 38).

Liu et al.[112b] developed a novel one-pot, microwave-assisted domino reaction for the synthesis of (±)-asperlicin C (20% yield) and also completed a formal synthesis of (±)-asperlicin E using the same strategy.

Snider et al.,[124] in their communication, reported an efficient synthesis of asperlicin C (**173**) (Scheme 39) and further successfully extended this to the first total synthesis of (−)-asperlicin (Scheme 40). The most challenging aspect of the synthesis of the more complex antibiotic, (−)-asperlicin (**181**), was the construction of the tryptophan-derived 1*H*-imidazo[1,2-*a*]indol-3-one moiety in the intermediate **177**, following which the Eguchi protocol yielded the fused quinazolinone **178** (75%). Hydroxylation of the indole ring with an oxaziridine followed by reductive workup with sodium borohydride, competitively reduced the quinazolinone



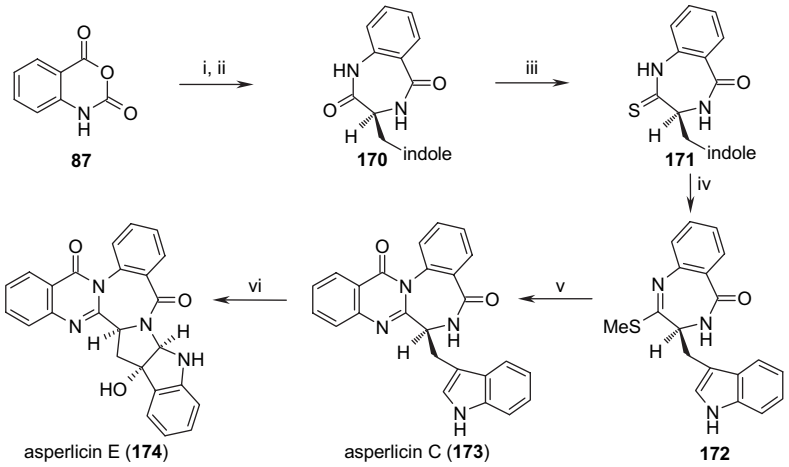
Scheme 39. Reagents and conditions: (i) *o*-$N_3C_6H_4COCl$, Et_3N, DMAP (83%); (ii) Bu_3P, benzene, 60 °C (80%).

to the dihydroquinazolinone **179**, but re-oxidation with DDQ restored the unsaturated linkage to give **180**. Removal of the benzyloxycarbonyl protecting group completed a stereospecific synthesis of (−)-asperlicin (**181**) in 15 steps and 8% overall yield from the Troc-protected tryptophan (**176**). The authors have elegantly shortened and improved the synthesis of asperlicin C (**173**). They have developed a general route to the hydroxyimidazoindolone ring system, and applied it for the first synthesis of (−)-asperlicin (**181**), which proceeds stereospecifically and efficiently.

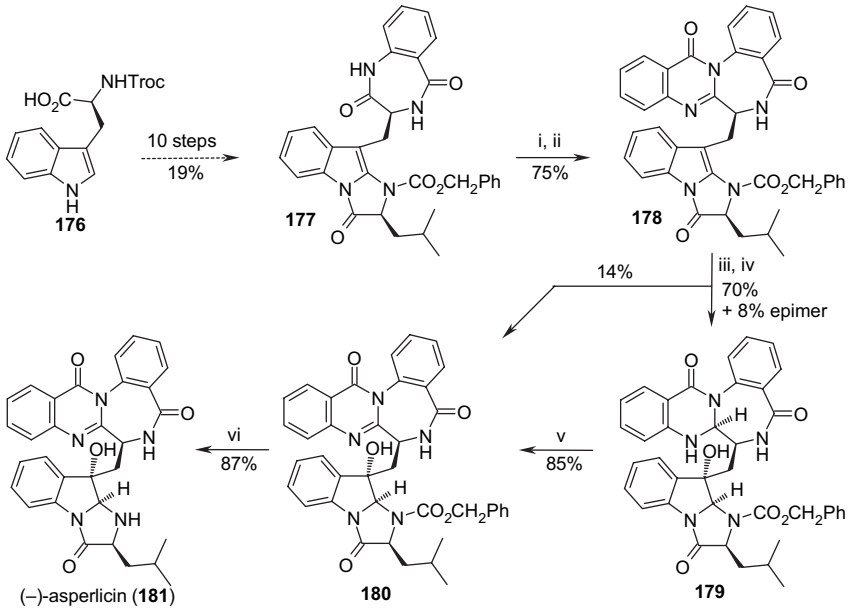
In conclusion, structurally interesting new benzodiazepine alkaloids isolated from various species, tabulated in Tables 13 and 14, have good bioactivity and various research groups have synthesized important alkaloids from this class. The synthesis of sclerotigenin, circumdatin F and, asperlicin by Snider et al. and an efficient synthesis of asperlicin E by Bock et al. provided an easy access to these bioactive natural products and also generated a significant amount of new chemistry. A novel microwave-assisted, domino-reaction strategy, developed by Liu et al. for this class of alkaloids, made these natural products easily accessible in a high yielding, one-pot reaction sequence.

8. Quinazolinones in clinical treatments

Several quinazolinone alkaloids are known to elicit a wide variety of biological responses. This has stimulated the



Scheme 38. Reagents and conditions: (i) L-Trp, NEt_3, H_2O, 23 °C, 5 h; (ii) HOAc, 118 °C, 5 h (90% from **66**); (iii) $(MeOC_6H_4)_2P_2S_4$, THF, 23 °C, 2 h (33%); (iv) MeI, $(n\text{-}Bu)_4NHSO_4$, NaOH (40%), toluene, 23 °C, 20 min (74%); (v) methyl anthranilate, 135 °C, 1 h (83%); (vi) (a) O_2, rose Bengal, MeOH/Py (5%), 0 °C, 5 h, (b) dimethyl sulfide (32%).

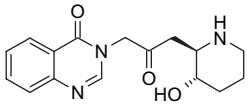
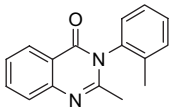
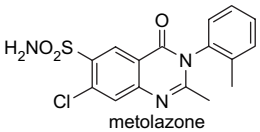
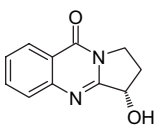


Scheme 40. Reagents and conditions: (i) *o*-$N_3C_6H_4COCl$, Et_3N, DMAP, CH_2Cl_2, rt; (ii) Bu_3P, C_6H_6, 60 °C; (iii) 3-butyl-2,3-epoxy-1,2-benzisothiazole-1,1-dione, MeOH/CH_2Cl_2 (4:1), 25 °C; (iv) $NaBH_4$, HOAc, 25 °C; (v) DDQ, $CHCl_3$, rt; (vi) H_2 (1 atm), 5% Pd/C, MeOH, rt.

preparation and pharmacological evaluation of a great number of quinazolinone derivatives and intensive research in the quinazolinone area is still in active progress. This topic has been very well reviewed in the literature[4,6b,g,125,126] and only a few quinazolinone natural products and derivatives of pharmaceutical importance are provided in Table 15.

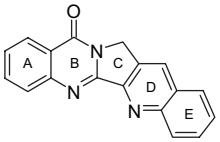
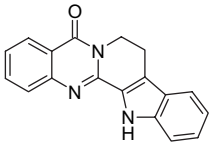
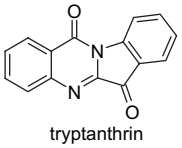
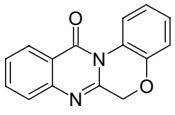
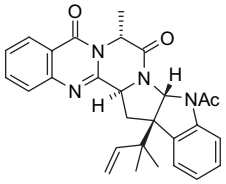
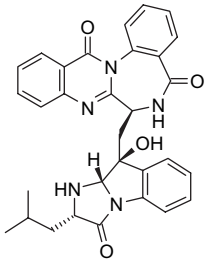
The quinazolinone alkaloid, luotonin A, has attracted the attention of chemists and pharmacists worldwide, because it is strikingly reminiscent of the cytotoxic alkaloid, camptothecin, the derivatives of which are clinically useful anti-cancer agents. Cagir et al.[55] recently increased the importance of these findings by demonstrating that, despite the lack of

Table 15. Natural/synthetic quinazolinones of therapeutic importance[4,6b,g,7,125,126]

Entry	Natural/synthetic quinazolinones	Activity
1	 febrifugine	Anti-malarial ingredient in a traditional Chinese herbal remedy effective against malaria
2	 methaqualone	Sedative-hypnotic
3	 metolazone	Diuretic
4	 (–)-vasicinone	Anti-tumor, bronchodilating, hypotensive, anthelmintic, anti-anaphylactic used in the Indian ayurvedic system of medicine as a remedy for cold, cough, bronchitis, rheumatism, phthisis, and asthma

(*continued*)

Table 15. (*continued*)

Entry	Natural/synthetic quinazolinones	Activity
5	 luotonin A	Anti-tumor cytotoxic toward the murine leukemia P-388 cell line (IC_{50} 1.8 μg/mL) naturally occurring human DNA topoisomerase I poison (IC_{50} 5.7–12.6 μmol/mL), activity like camptothecin
6	 rutaecarpine	Strong analgesic, anti-emetic, astringent, anti-hypertensive, uterotonic, TCDD-receptor, antinociceptive, anti-inflammatory, and cycloxygenase-2 (COX-2) inhibitory activities
7	 tryptanthrin	Antibiotic
8		Anti-fertility
9	 (–)-5-*N*-acetylardeemin	Reversed multiple drug resistance (MDR) in human tumor cell lines and sensitized cells to the anti-cancer agent, vinblastine
10	 (–)-asperlicin	300- to 400-fold more affinity for pancreatic, gastrointestinal, and gallbladder CCK receptors than proglumide, a standard agent of this class; highly selective for peripheral CCK receptors relative to brain CCK and gastrin receptors

A-ring functionality, luotonin A stabilizes human DNA topoisomerase I-dependent cytotoxicity in intact cells. It is important to note that the quinazolinone alkaloids are a class of natural compounds with very diverse structures and, hence, at the present time, approximately 50 quinazolinone derivatives with a wide variety of biological activities are available for clinical use.[6b,g,125,126]

9. Summary

In the present review, we have presented a concise account of the natural quinazolinone alkaloids isolated during the review period, along with their bioactivity and various synthetic approaches. All the information collected and presented here has been well supported by the provision of more than 230 references from various monographs and international journals. The combination of unique structural features, extensive functionalization, and very high biological activity found in the quinazolinone alkaloids have presented an elegant challenge to the synthetic chemists to design these molecules in a shorter and smarter fashion. During the last 20 years, a number of research groups have reported a variety of synthetic approaches to biologically active natural/synthetic quinazolinone alkaloids.

There have been approximately 75 new quinazolinone alkaloids isolated as natural products during the review period. Various synthetic approaches to these quinazolinone alkaloids and their analogs have been illustrated and are discussed in detail. The importance of natural and synthetic quinazolinones for clinical purposes has also been reviewed. From the synthetic chemistry point of view, the Eguchi protocol and the Ganesan protocol are two important protocols developed during the synthesis of quinazolinones. To date, the Ganesan protocol provides the best conditions for the dehydration of diamides to form a quinazolinone moiety, but it proceeds through the intermediate benzoxazine–amidine and, hence, efficient reagent and reaction conditions to effect the direct transformation to the quinazolinone are presently in need of discovery. We feel that a variety of benzoxazinones are potential intermediates for the synthesis of quinazolinones. A more detailed investigation is needed for the development of reaction conditions that would facilitate the condensation of benzoxazinones with aliphatic/aromatic amines, which is otherwise difficult or low yielding. (−)-Vasicinone, luotonin A, rutaecarpine, ardeemin, and (−)-asperlicin are the important quinazolinone natural products from a structural and therapeutic point of view. We strongly feel that luotonin A or its derivatives will be lead molecules for the treatment of cancer and may replace the clinically useful complex anti-cancer agents, the camptothecin derivatives.

It should be obvious that investigations over the last few years have revealed that the natural quinazolinone alkaloids and their synthetic derivatives exhibit a wide variety of pharmacological activities. The continually increasing stream of publications on this subject permits the hope that, even in the foreseeable future, an answer must be found to the general philosophical question of the place and role of alkaloids in nature in general and of the quinazolinone alkaloids in particular. In the continuing search for the compounds producing interesting biological activities, the quinazolinone alkaloids should provide an excellent starting point for further investigation. The use of several other natural and unnatural α-amino acids in combination for the design of natural, pseudo-natural, and hybrid quinazolinones with tailored properties is the most challenging task. The applications of β-amino acids in the synthesis of quinazolinones will provide an elegant entry to new quinazolinone entities. In conclusion, quinazolinone chemistry has a very rich past to its credit and a very bright present, coupled with a highly promising future from both the basic and application point of view.

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