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Biologically Active Quinoline and Quinazoline Alkaloids Part II

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Abstract

To follow up on our prior Part I review, this Part II review summarizes and provides updated literature on novel quinoline and quinazoline alkaloids isolated during the period of 2009–2016, together with the biological activity and the mechanisms of action of these classes of natural products. Over 200 molecules with a broad range of biological activities, including antitumor, antiparasitic and insecticidal, antibacterial and antifungal, cardioprotective, antiviral, anti-inflammatory, hepatoprotective, antioxidant, anti-asthma, antitussive and other activities, are discussed. This survey should provide new clues or possibilities for the discovery of new and better drugs from the original naturally occurring quinoline and quinazoline alkaloids.

Keywords

quinoline alkaloids; quinazoline alkaloids; biological activities; camptothecin; natural products

1. INTRODUCTION

Quinoline and quinazoline alkaloids, two important classes of *N*-based heterocyclic aromatic compounds, have attracted tremendous attention from researchers worldwide, because of their wide-ranging biological activities and their varied applications over the past 200 years.[1] Since quinine was isolated in the 19th century,[2] increasing numbers of related natural products have been isolated and identified. Most of these compounds and their derivatives

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exhibit significant biological activities, such as antitumor, antimalarial, antiparasitic and insecticidal, antibacterial and antifungal, cardioprotective, antiviral, anti-inflammatory, anti-oxidant and other effects.[3,4] Many of the derivatives are used today as agricultural products and the pharmaceutical drugs. The prominent applications are antimalarial (Quinine, Quinidine, Chloroquine, Mefloquine, etc), antiviral (Saquinavir), antibacterial (fluoroquinolones such as Ciprofloxacin, Sparfloxacin, etc), antifungal-antiprozoal (Clioquinol), anthelmintic (Oxamniquine), local anesthetic (Dibucaine), antiasthmatic (Montelukast), anticancer (Camptothecin, Irinotecan, Topotecan, Gefitinib, etc), antipsychotic (Aripiprazole, Brexpiprazole, etc), antiglaucoma (Cartiolol) and cardiotonic (Vesnarinone).[5]

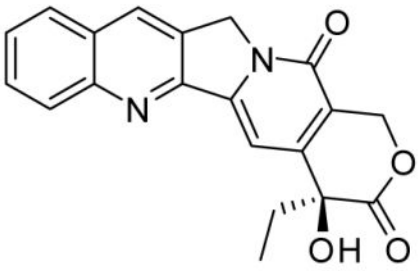
In view of the importance and significant biological activities of quinoline and quinazoline alkaloid natural products, we previously reviewed the developments in this field from the perspective of biological activities (covering the literature up to year 2008). Over the past decade, the marine environment has become an increasingly important resource in natural products research, and more new compounds have been isolated from marine microorganisms and identified as new leads in the discovery of useful chemotherapeutic agents. Meanwhile, research has been continually published on the new marked biological activities and mechanisms of action of quinoline and quinazoline alkaloids.

Consistent with our previous review, this review summarizes and provides updated literature on all novel quinoline and quinazoline alkaloids isolated during the period of 2009–2016 (Table 1), together with the biological activity and the mechanisms of action of these classes of natural products. The authors hope that the two reviews provide new clues or possibilities for the discovery of new and better drugs from naturally occurring quinoline and quinazoline alkaloids.

2. BIOLOGICAL ACTIVITIES OF QUINOLINE AND QUINAZOLINE ALKALOIDS

A. Antitumor Activity

1. Quinoline and quinazoline indole alkaloids—



Chemical structure of camptothecin

Since 1966, researchers have made significant attention to the important and famous quinoline indole alkaloid camptothecin (CPT), due to its specific and strong inhibitory

effects on the DNA-replicating enzyme topoisomerase I.[6,7] In the presence of CPT, cells either undergo cell cycle arrest in S-phase or continue progression with subsequent accumulation of DNA damage, ultimately resulting in cell death. Until now, more than 5000 related publications have been published; many focused on the derivatization of CPT. Because excessive harvesting has severely depleted the traditional plant sources. *Camptotheca acuminata* and *Nothapodytes nimmoniana,* of CPT over the past two decades, [8,9] alternate natural sources of CPT have been urgently sought, leading to the identification of *Apodytes dimidiata, Codiocarpus andamanicus, Gomphandra comosa, Gomphandra coriacea, Gomphandra polymorpha, Gomphandra tetrandra, Iodes cirrhosa, Iodes hookeriana, Miquelia dentata, Miquelia kleinii, Natsiatum herpeticum, Nothapodytes foetida, Ophiorrhiza mungos,* multiple shoot cultures of *Ophiorrhiza rugosa var. decumbens, Pyrenacantha volubilis* and *Sarcostigma kleinii*.[10,11,12,13] Meanwhile, methods to obtain CPT from microorganisms have been developed recently. In 2013, CPT, 9-MeO-CPT and 10-OH-CPT also were produced from three fungi, *Fomitopsis* sp. P. Karst (MTCC 10177), *Alternaria alternata* (Fr.) Keissl (MTCC 5477) and *Phomposis* sp. (Sacc.) in mycelial mats in shake flasks containing potato dextrose broth.[14]

Besides CPT, other cytotoxic quinoline and quinazoline indole alkaloids have been identified. In 2009 and 2014, Kam and coworkers identified three new quinoline bisindole alkaloids.[15,16] Leucophyllidine (**1**) (Fig. 1) from *Leuconotis griffithii* showed significant and comparable *in vitro* cytotoxicity toward drug-sensitive and vincristine-resistant (VJ300) human KB cells, with IC_{50} values of 2.95 and 2.92 μg/mL (5.16 and 5.10 μM), respectively. [15] Angustifonines A (**2**) and B (**3**) (Fig. 1) from *Bousigonia angustifolia* exhibited cytotoxicity against HL-60 (leukemia), SMMC-7721 (hepatoma), A549 (lung carcinoma), MCF-7 (breast cancer) and SW480 (colon cancer) (IC_{50} 2.71–16.2 μM).[17] Compared with the above compounds, meloyunine B (**4**) (Fig. 1), a 6/7-seco rearranged spiro-indolone alkaloid from *Melodinus yunnanensis*, showed weak cytoxicity against the same five human cancer cell lines with IC_{50} values of 13.3 to 40.0 μM.[18] Other new compounds, meloyunine A (**5**), a monoterpenoid quinoline alkaloid meloyunine C (**6**), the possible intermediate 14,15-dehydromelohenine B (**7**) and their precursor Δ^{14}-vincamenine (**8**) (Fig. 1), were inactive (IC_{50}>40 μM). In comparison, the paclitaxel control exhibited exceptional inhibitory activity (IC_{50}<0.008 μM), and cisplatin displayed IC_{50} values ranging from 1.05 to 21.9 μM.[18]

Rutaecarpine, an intriguing indoloquinazoline alkaloid from *Evodia rutaecarpa*, presents wide-ranging pharmacological activities, such as cardiovascular protective, antitumor, anti-inflammatory and other effects.[19] It presented weak cytotoxic effects against A375-S2 (human malignant melanoma), HeLa, MCF7, THP-1 and L929 with the IC_{50} values ranging from 150 to 239 μM.[19] During the last ten years, three new rutaecarpine derivatives, (7R, 8S)-7-hydroxy-8-methoxy-rutaecarpine (**9**), (7R,8S)-7-hydroxy-8-ethoxy-rutaecarpine (**10**) and 2-methoxy-7,8-dehydroruteacarpine (**11**) (Fig. 2) were isolated from two plants in the Rutaceae family along with other known alkaloids.[20,21] Compounds **9** and **10** displayed IC_{50} values of 7.82 and 8.31 μM against leukemia HL-60 cells, but only 22.3 and 27.9 μM against gastric carcinoma N-87 cells. Meanwhile, evodiamine presented the best cytotoxic activity among all isolated indolequinazoline alkaloids with significant IC_{50} values of 5.88 and 7.30

μM against the same two cell lines, respectively.[20] The presence of the two substituents at position-7 and -8 of the alkaloid led to decreased potency against N-87. Alkaloid **11** together with 2-hydroxyruteacarpine and 2-methoxyruteacarpine from *Zanthoxylum poggei* displayed a low level of cytotoxic activity against the prostate cancer PC-3 cell line with IC_{50} values of 22.1, 17.4 and 19.4 μM, respectively (IC_{50} value of the positive control doxorubicin was 0.9 μM).[21] They also strongly suppressed the phagocytosis response activated with serum opsonized zymosan in *in vitro* oxidative burst studies using whole blood; the IC_{50} values ranged from 21.6 to 25.9 μM.[21] Rutaecarpine exhibited weak cytotoxic activity against the human monocytic leukemia THP-1 cell line as well as protective effects toward murine liver cancer Hepa-1c1c7 cells against oxidative stress–induced DNA damage by reducing the condensation and fragmentation of nuclei and inhibiting DNA strand breaks and apoptosis.[22,23]

Our previous review reported that fumiquinazolines A–G were first isolated from the fungus *Aspergillus fumigatus* in 1992 and 1995.[24] Subsequently, fumiquinazolines J–P (**12**–**18**) and tryptoquivaline K (**19**) (Fig. 3) were identified from fungus of the same genus.[25,26] Fumiquinazoline J exhibited high cytotoxicity against murine lymphoma L5178Y cells with an IC_{50} value of 3.6 μM, but much lower activity against human ovarian A2780 and leukemia K562 cell lines with IC_{50} values of 18.5 and 15.0 μM, respectively. The remaining alkaloids were not cytotoxic against these cell lines.[25,26] Subsequently, some tryptoquivaline (**20**) analogues, tryptoquivalines F (**21**), H (**22**), L (**23**) and O (**24**), fiscalins A (**25**) and C (**26**), sartorymensin (**27**), a quinazolinone-containing indole, *epi*-fiscalins A (**28**) and C (**29**), neofiscalin A (**30**), *epi*-neofiscalin A (**31**) and 3′-(4-oxoquinazolin-3-yl)spiro[1*H*-indole-3,5′-oxolane]-2,2′-dione (**32**) (Fig. 3) were isolated from the fungus *Neosartorya siamensis* (KUFC 6349). Except for alkaloid **27** (IC_{50} 39–73 μM), all of the compounds showed no *in vitro* growth inhibitory activity (IC_{50} >100 μM) against U373 (glioblastoma), Hs683a (glioblastoma), A549, MCF-7 and SK-MEL-28 (melanoma) cell lines.[27] Meanwhile, 15β-hydroxy-5*N*-acetylardeemin (**33**) showed greater cytotoxic activity against human HeLa contaminant KB (IC_{50} 61.4 μM) and rat hepatic HSC-T6 (IC_{50} 88.2 μM) cell lines than its geometric hydroxylated and non-hydroxylated congeners, 16α-hydroxy-5*N*-acetylardeemin (**34**) and 5*N*-acetylardeemin (**35**) (Fig. 3), from *Aspergillus terreus*.[28]

During the past ten years, other new alkaloids without cytotoxic activity also were reported. Examples include three *N*-glycosylated fumiquinazoline-type alkaloids fumigatosides B–D (**36**–**38**) from *Aspergillus fumigatus*[29] and evollionines B and C (**39**, **40**)[30] (Fig. 4) from *Evodia rutaecarpa*.

2. Furoquinoline alkaloids—The furoquinoline alkaloids are biogenetically derived from 2-substituted oxygenated 4-quinolones after prenylation at C-3. Linear or angular dihydrofuroquinolines result from formation of a ring with the prenyl group at C-2 or C-4, respectively.[31,32] To date, more than 30 furoquinoline alkaloids, including some with marked antitumor activity, have been identified. Skimmianine and 5-methoxydictamnine (**41)** (Fig. 5) demonstrated weak cytotoxic activity *in vitro* against A549, BGC-823 (gastric cancer), HCT15 (colorectal cancer), HeLa (cervical cancer), HepG2 (liver cancer), MCF-7, SK-MEL-2 and SGC-7901 (gastric cancer) cells with IC_{50} values between 33.3 and 40.3

μg/mL.[33] The former compound also displayed weak cytotoxic activity against THP-1 and HCT116 (colon cancer) cell lines.[22,34] Other furoquinoline alkaloids, such as 5-methoxyrobustine (**42**), dictamnine, robustine, isopteleine (**43**) (Fig. 5) and γ-fagarine also presented weak cytotoxic activity against MCF-7 cells,[35,36] and two new furoquinoline alkaloids, aegelbines A (**44**) and B (**45**) (Fig. 5) from *Aegle marmelos* were weakly active against MCF-7 as well as HepG2 and PC-3 cell lines.[37]

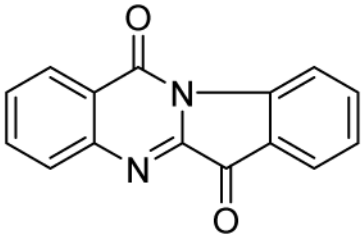
A new γ-fagarine derivative, 7-isopentenyloxy-γ-fagarine (**46**) (Fig. 6), exhibited significant cytotoxicity against Raji (lymphoma) and Jurkat (leukemia) cell lines with IC_{50} values of 1.5 and 3.6 μg/mL, respectively, compared with 14.5 and 9.3 μg/mL for atanine and 15.6 and 11.5 μg/mL for skimmianine.[38] Compound **46** was also more cytotoxic against the MCF-7 cell line (IC_{50} 15.5 μg/mL), than atanine, skimmianine and perfamine (**47**) (Fig. 6). Furthermore, all alkaloids displayed moderate to low cytotoxicity against KG-1a (leukemia) and HEp-2 (HeLa contaminant), and higher effects against the multidrug-resistant HL-60/MX1 cell line, compared with the control etoposide ($p<0.05$)., Flow cytometry analysis on treated Raji and Jurkat cells showed the arrest of cell cycle progression at the sub-G1 phase in a dose-dependent manner, and even at the lowest concentration used (40.9%) compound **46** caused the greatest increase in the number of these cells with sub-G1 DNA content. According to computational analyses, the cytotoxicity toward different cell lines correlated well with certain molecular descriptors. Based on the cytotoxicity relationships with the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO), charge transfer may be part of the interaction of these compounds with their target sites. The similar cytotoxic trends against various cell lines suggested that these compounds may act through parallel mechanisms.[38]

Anstifolines A (**48**) and B (**49**) (Fig. 6), two dimeric furoquinoline alkaloids from *Dictamnus angustifolius*, exhibited more significant cytotoxicity (IC_{50} 10.6–14.3 μM) against human lung cancers A549 and NCI-H460 than dictamnine and robustine.[39] Dictamine also demonstrated cytotoxicity toward HepG2 cells.[40]

3. 2-Substituted quinoline or quinazoline alkaloids—Evodiamine, a major 2-substituted quinoline alkaloid from *Evodia rutaecarpa,* displays various biological effects, including antitumor. More specifically, it inhibits cancer cell proliferation, invasion and metastasis, and induces apoptosis many tumor cell lines both *in vitro* and *in vivo*,[41] including breast cancer, prostate cancer, leukemic T-lymphocyte, melanoma, cervical cancers, colon cancer and lung cancer cells. Moreover, evodiamine shows insignificant toxicity against normal human peripheral blood cells. In addition, this alkaloid sensitizes chemoresistant breast cancer cells to adriamycin, Briefly, evodiamine induces apoptosis by caspase-dependent and caspase-independent pathways as well as the mitochondrial caspase-dependent apoptotic pathway, and could activate Cdc2/cyclin B to induce cell cycle arrest (G2/M phase). It directly inhibits human umbilical vein endothelial cell (HUVEC) tube formation and invasion as well as the release and expression of VEGF, which is related with endothelial cells angiogenesis. Structure-activity relationship studies showed that the functional groups at position 14 and the configuration of hydrogen at position 13b of evodiamine may affect its inhibitory effects on invasion and metastasis of Lewis lung carcinoma, lung metastasis of colon 26-L5 and B16-F10 cells.

In 2015, evodiamine, other known alkaloids and four new quinolone alkaloids, 1-methyl-2-[6-carbonyl-(E)-4-undecenyl]-4(1*H*)-quinolone (**50**), 1-methyl-2-[6-carbonyl-(E)-7-tridecenyl]-4(1*H*)-quinolone (**51**), 1-methyl-2-[15-hydroxypentadecenyl]-4(1*H*)-quinolone (**52**) and 1-methyl-2-[13-hydroxytridecenyl]-4(1*H*)-quinolone (**53**) (Fig. 7) were isolated from *E. rutaecarpa*.[42] Among these compounds, evodiamine exhibited the best cytotoxic activity against HL-60 and PC-3 cell lines with GI_{50} values of 0.51 μM and 14.4 μM, respectively, compared with 1.84 and >80 μM for the positive drug 5-Fu. Other active alkaloids were 1-hydroxyrutaecarpine, evocarpine, 1-methyl-2-undecyl-4(1*H*)-quinolone, 1-methyl-2-[13-hydroxytridecenyl]-4(1*H*)-quinolone and dihydroevocarpine with GI_{50} values between 8.34 and 16.0 μM against HL-60. The potencies of these quinolone alkaloids may relate to the length of the side-chain. An α,β-unsaturated carbonyl in the side-chain decreased the cytotoxicity. Indolopyridoquinazoline alkaloids with a phenolic hydroxyl on ring-E exhibited higher potency than those with an unsubstituted ring-E.[42]

4. Tryptanthrin—



Chemical structure of **tryptanthrin**

The quinazoline alkaloid tryptanthrin was first isolated from the traditional Chinese medicine (Qingdai) in 1985. Later studies reported its cytotoxic activity against melanoma B_{16},[43] U-937 and HL-60 cells,[44] as well as antitumor activity against azoxymethane-induced intestinal tumor.[45] At low concentrations (0.5 μg/mL), tryptanthrin induces differentiation of leukemia cells, but at higher concentrations (10 μg/mL), can kill cells through apoptosis, possibly through a caspase-3/Fas antigen pathway.[44] In addition, it strongly inhibited HGF production stimulated by various HGF inducers in human dermal fibroblasts, probably through events downstream of MAPK activation.[46] More recently, its significant cytotoxic effects against MCF-7, NCI-H460 and SF-268 (glioblastoma) cell lines (IC_{50} 9.4, 8.5 and 22.6 μM) have been reported.[47] Tryptanthrin significantly inhibits K562 cell proliferation in a time- and dose-dependent manner, and has proliferation-attenuating and apoptosis-inducing effects on K562 cells. This effect likely results from a reduction in mitochondria membrane potential, mito cyt-c release and pro-caspase-3 activation.[48] Flow cytometric analysis showed that tryptanthrin-treated WEHI-3B JCS cells underwent cell cycle arrest at the G0/G1 phase, and had down-regulated expression of cyclin D2, D3, Cdk 2, 4 and 6 genes. Meanwhile, tryptanthrin induced differentiation in the same cells by increasing vacuolation, cellular granularity and NBT-reducing activity. Thus, tryptanthrin exerts an antitumor effect on WEHI-3B JCS (myelomonocytic leukemia) cells by causing cell cycle arrest and triggering cell differentiation in a dose- and time-dependent manner.[49]

In 2013, studies were conducted to determine tryptanthrin's effects on the growth and differentiation of LA-N-1 cells, one of the most common extracranial solid cancers in young children.[50] Tryptanthrin inhibited the growth of the neuroblastoma cells in a dose- and time-dependent manner and induced cell cycle arrest at the G0/G1 phase. It also significantly reduced N-myc proto-oncogene protein expression. Thus, tryptanthrin suppresses the growth of and induces neuronal differentiation in neuroblastoma cells.[50] Subsequent studies showed that tryptanthrin inhibited the proliferation, migration and tube formation of human microvascular endothelial cells (HMEC-1) in a concentration-dependent manner and significantly suppressed angiogenesis in Matrigel plugs in mice *in vitro*. The *in vitro* and *in vivo* anti-angiogenic activities were realized by targeting the vascular endothelial growth factor2 (VEGFR2)-mediated extracellular-regulated kinase 1/2 (ERK1/2) signaling pathway.[51] In other studies, tryptanthrin exerted an anti-angiogenic effect by inhibiting cell cycle progression and Akt and FAK signaling in human vascular endothelial cells.[52]

Furthermore, in addition to the transporter pathway, tryptanthrin down regulated glutathione S-transferase (GST) π expression, reduced GST activity and reversed multi-drug-resistance (MDR) partly by modulating the GST π-related pathway in the MDR response in doxorubicin-resistant MCF-7 cells.[53,54] It was well absorbed across Caco-2 monolayers and inhibited P-glycoprotein (P-gp) and multidrug resistance-associated protein 2 (MRP2). These results indicated that tryptanthrin may act as a potential chemoadjuvant agent through multiple targets.

5. Simple quinoline or quinazoline alkaloids—While quinine is a well-known compound for treating malaria, it also exhibited a distinct antiproliferative and pro-apoptotic effect in HeLa and A549 tumor cell lines.[55] It inhibited the lipopolysaccharide (LPS)-induced activation of AKT by inhibiting its phosphorylation at Thr-308 and Ser-473. It also reversed LPS-induced proliferation and suppressed the anti-apoptotic protein B-cell lymphoma (BCL)-2, as well as the activation of the pro-apoptotic factor BCL-2-associated X protein. The inhibitory effect on the tumor cell proliferation was attributed to prevention of the tumor necrosis factor receptor-associated factor TRAF6 interaction.[55]

Quinoline-5,8-diones are also interesting potential anticancer agents. One new compound sannanine (**54**) (Fig. 8) from *Streptomyces sannanensis* showed cytotoxicity against four human tumor cell lines BGC823 (gastric cancer), PANC1 (pancreatic cancer), HepG2 and NCI-H460, with IC_{50} values of 6.6, 5.8, 3.1 and 1.8 μM, respectively.[56]

Two new quinazoline alkaloids (*S*)-vasicinone-1-O-β-D-glucopyranoside (**55**) and (*R*)-vasicinone-1-O-β-D-glucopyranoside (**56**), (Fig. 8) together with (*S*)-vasicinone, vasicine and deoxyvasicinone were isolated from the seeds of *Peganum harmala*.[57] Two (**55** and (*S*)-vasicinone) of the five compounds exhibited only weak inhibitory activity against human gastric cancer MCG-803 cells with IC_{50} values of 84.1 and 94.5 μM.

In contrast, 4-methyl-2-quinazolinamine (**57**) (Fig. 8) from *Streptomyces sp*. GS DV232 presented moderate activity against liver (HepG2), breast (MCF-7) and gastric (AGS, HMO2) cancer cell lines, and good antiproliferative effects on a lung (A549) cancer cell line

(IC_{50} 0.154 μM).[58] The IC_{50} values of the positive controls doxorubicin and melphalan were 0.045 and 3.4 μM, respectively.

Moreover, the benzoquinoline alkaloid marcanine A (**58**) (Fig. 8) from *Polyalthia plagioneura* displayed growth inhibitory activity against BEL-7402 (liver cancer), K562, SPC-A-1 (lung cancer) and SGC-7409 (gastric cancer) with IC_{50} values of 9.54, 11.8, 8.69 and 1.53 μM, respectively.[59] In contrast, saprosmines A (**59**) and B (**60**), with ketal groups rather than an oxo moiety at position-5, did not show cytotoxic activity against the same four cancer cell lines (all IC_{50} > 50 μM).[60] 4-Methoxycarbonyl-5,10-benzogquinolinequinone (**61**) exhibited IC_{50} values between 11.9 and 29.6 μM against SPCA-1, BEL-7402, SGC-7901 and K-562, while the 4-methylated cleistopholine (**62**) was inactive.[60] The quinazoline leucomidine C (**63**) (Fig. 8) from *Leuconotis griffithii* was also inactive against the HL-60 cell line.[61]

6. Flindersine derivaties—Flindersine, with a more unusual pyranoquinoline core, showed cytotoxicity against Raji cells with an IC_{50} value of 14.9 μg/mL.[38] 5-Methoxyflindersine or haplophytin-A (**64**) (Fig. 9) from *Haplophyllum acutifolium* induced the classical features of apoptosis and externalization of annexin-V-targeted phosphatidylserine residues in HL-60 cells at a concentration of 50 μM.[62] Treatment with compound **64** (50 μM) induced DNA fragmentation, DNA ladder formation and the externalization of annexin-V-targeted phosphatidylserine residues, and also resulted in the activations of caspase-8, -9 and -3, and the cleavage of poly (ADP-ribose) polymerase (PARP). Furthermore, loss of mitochondrial membrane potential ($\Delta\psi m$), release of cytochrome c and Smac/DIABLO to the cytosol, and formation of death-inducing signaling complex (DISC) also were found in the treated HL-60 cells. The alkaloid's potent apoptotic activity was exerted via both extrinsic and intrinsic pathways, suggesting a good potential to treat leukemia.

Because some alkaloids function as intercalative topoisomerase poisons, ten quinoline alkaloids were investigated for potential intercalation into DNA using a molecular docking approach.[63] Skimmianine, stauranthine (**65**), 3′,6′-dihydroxy-3′,6′-dihydrostauranthine (**66**) and *trans*-3′,4′-dihydroxy-3′,4′-dihydrostauranthine (**67**) (Fig. 9) were able to dock intercalatively and consistently into DNA, and the docked orientations were also electronically favorable.

7. Pyrrole-containing and other quinoline or quinazoline alkaloids—A growing class of natural products includes pyrrole-containing quinoline alkaloids. Most of them are isolated from marine sources,[64] and many exhibit antitumor activity. Ammosamides A and B (**68**, **69**) (Fig. 10) from marine-derived *Streptomyces variabilis* exhibited activity against colorectal cancer HCT-116 cells via covalent modification of myosin, which are involved in numerous cell processes, including cell cycle regulation, cytokinesis and cell migration.[65,66] In studies three years later, the oxidized ring-opened ammosamide D (**70**) (Fig. 10) exhibited good cytotoxicity (IC_{50} 3.2 μM) against pancreatic cancer MIA PaCa-2 cells, but did not inhibit mTOR up to 20 μM.[67] In contrast, the non-chlorinated pyrroloquinoline alkaloid lymphostin (**71**) (Fig. 10) from *Streptomyces* sp. KY11783 showed nanomolar inhibition of

mTOR and potent cytotoxicity against LNCap (prostate) and MDA-468 (breast) cancer cell lines.[64]

Meanwhile, the new 2-pyrrolyl-substituted 4-quinolinone alkaloid penicinoline E (**72**), together with three known derivatives, methyl-penicinoline (**73**), penicinoline (**74**) (Fig. 10) and quinolactacide, were isolated from *Penicillium sp.* ghq208.[68] Only **73** and **74** exhibited moderate cytotoxicity against the HepG2 cell line with IC_{50} values of 11.3 and 13.2 μM, respectively,[68] the latter compound also showed potent *in vitro* cytotoxicity toward 95-D cells with an IC_{50} value of 0.57 μg/mL.[69] The presence of a carboxyl group at C-3 appears to be essential for the cytotoxicity of this unusual pyrrolyl 4-quinolinone alkaloid type.

In 2015, novel heterocylic alkaloids eudistidines A (**75**) and B (**76**) (Fig. 11) were isolated from *Eudistoma sp.* in a screen for inhibitors of the binding interaction between HIF-1α and the transcriptional coactivator p300, which plays an important role in the survival of solid tumors in low oxygen environments and involves the C-terminal transactivation domain (C-TAD) and cysteine histidine-rich domain 1 (CH1), respectively, of the two proteins.[70] The former compound effectively inhibited CH1/C-TAD binding with an IC_{50} of 75 μM. The unique scaffold of this natural alkaloid could lead to novel molecular probes to study p300/HIF-1α interactions and the role these proteins play in tumor response to low oxygen conditions or new therapeutic anticancer lead compounds that could disrupt critical protein-protein binding events. During the same year, novel bisheterocyclic quinolineimidazole alkaloids (+)- and (−)-spiroreticulatine (**77**, **78**) (Fig. 11) from *Fascaplysinopsis reticulate* were inactive against K562, A549, Hela or Jurkat tumor cell lines, but inhibited IL-2 production in a dose-dependent manner.[71]

Eight compounds of the discorhabdin A- and B-type, including (+)-discorhabdin/prianosin A (**79**), (+)-discorhabdin B (**80**), (+)-discorhabdin G*/I (**81**), (−)-discorhabdin W (**82**), (+)-(*6R, 8S*)-1-thiomethyldiscorhabdin G*/I (**83**), both enantiomers of 16a,17a-dehydrodiscorhabdin W (**84**) and (+)-3-dihydrodiscorhabdin A [with reassignment of its configuration from (*3S, 5R,6S,8S*)-**85** to the C_3-epimeric (+)-(*3R,5R,6S,8S*)-**86**] (Fig. 12), were isolated from the marine genus *Latrunculia*.[72] In biological screening against the murine leukemia P388 cell line, **83** (IC_{50} 0.28 μM) and both enantiomers of **84** (IC_{50} 0.45 μM) exhibited potent antiproliferative activity comparable to the respective 'parent' compounds **81** (IC_{50} 0.6 μM) and discorhabdin W (IC_{50} 0.13 μM). However, **85** (IC_{50} 2.1 μM) and **86** (IC_{50} 1.8 μM) were less potent, reflective of the role played by the C-3 keto group in increasing the antiproliferative potency, as again observed with discorhabdin A (IC_{50} 0.11 μM).[72]

Meanwhile, nine new melodinus-type alkaloids, melohemsines A–I (**87**–**95**), meloscine (**96**), sandine (**97**), 10-hydroxyscandine (**98**), 10-hydroxy-14,15-β-epoxysandine (**99**), 14,15-β-epoxysandine (**100**), meloscine N_4-oxide (**101**), scandine N_4-oxide (**102**) and melodinine U (**103**) were isolated from *Melodinus hemsleyanus,*[73] and two rearranged quinuclidine alkaloids, cincholenines A (**104**) and B (**105**) (Fig. 13) were found in *Cinchona ledgeriana*.[74] None of the compounds showed IC_{50} values under 40 μM.

B. Anti-parasitic and Insecticidal Activities

1. Anti-malarial activity—Malaria is an infectious disease with ravaging effects in many parts of the world. Four protozoan species of the genus *Plasmodium* (*P. falciparum*, *P. malariae*, *P. ovale* and *P. vivax*) are responsible for this infection.[75] In 2013, this disease led to an estimated 198 million cases and resulted in 584,000 deaths.[76] Half of the world's population is at risk from malaria.[77] Isolated quinoline alkaloids have been investigated as possible antimalarial agents since quinine was found to inhibit the endocytosis of *P. falciparum*[78] and quinidine, an erythro diastereoisomer of quinine, was also found to exhibit significant antimalarial activity.[79]

Recently, increasing numbers of papers have focused on the mechanism of antimalarial drugs. Studies in 2014 showed that quinine significantly inhibited breast cancer resistance protein- (BCRP-) and P-gp-mediated transport at concentrations within the clinically relevant prophylactic and therapeutic range, and inhibited adenosine triphosphate (ATP) binding cassette transporter activity.[80] Quinidine and cinchonine, which have identical stereochemistry at carbons 8 and 9, exhibited stronger inhibition of human and *Drosophila melanogaster* serotonin receptor transporter (hSERT and dSERT) function than their enantiomers, quinine and cinchonidine.[81] Furthermore, quinine and cinchonidine bound to the central receptor binding site (S1), whereas quinidine and cinchonine bound to the S2 site in small molecule docking studies. These results indicated that distinct cinchona alkaloids bind to two different sites on SERT, with the most potent antimalarial inhibitors of SERT appearing to preferentially bind to the S2 site. This difference implies separate modes of transporter inhibition.[81]

Among quinoline alkaloids reported with antimalarial activity between 2009 to 2016, examples are 6-methoxy-7-hydroxydictamnine,[36] 4-methoxy-1-methylquinolin-2-one,[82] (2′R)-2′,3′-epoxy-*N*-methylatanine,[83] kokusaginine,[84] and maculosidine.[85] Nitidine (**106**) (Fig. 14) from *Toddalia asiatica* exhibited high antiplasmodial activity with an IC_{50} of 0.045 μg/mL against the K39 strain of *P. falciparum in vitro* and likely acts by a similar mechanism of that of chloroquine.[86] The furoquinoline evoxine (**107**) (Fig. 14) from *Teclea gerrardii* displayed the activity against the CQS (chloroquine susceptible) D10 strain of *P. falciparum* with an IC_{50} value of 24.5 μM.[87]

Aplidiopsamine A (**108**) (Fig. 15) from *Aplidiopsis condluata* has a tricyclic 3*H*-pyrrolo[2,3-*c*]quinoline substructure conjugated to adenine. It exhibited significant growth inhibition of *P. falciparum* chloroquine resistant (IC_{50} 1.65 μM for Dd2) and sensitive strains (IC_{50} 1.47 μM for 3D7) and minimal toxicity toward HEK-293 cells.[88] Ascidiathiazone A (**109**) (Fig. 15) was a moderately potent *in vitro* growth inhibitor of *P. falciparum* K1 strain (IC_{50} 3.3 μM) and *Trypanosoma brucei rhodesiense* (IC_{50} 3.1 μM). However, it was effectively inactive towards *T. cruzi* and *Leishmania donovani* and exhibited low cytotoxicity against a mammalian cell-line (L6, IC_{50} 167 μM).[89]

Several 4-hydroxyquinoline alkaloids, including six known [2-*n*-octyl-4-hydroxyquinoline (**110**), 2-*n*-nonyl-4-hydroxyquinoline (**111**), 2-*n*-undecyl-4-hydroxyquinoline (**112**), 2-(*E*)-non-1′-enyl-4-hydroxyquinoline (**113**), *n*-heptyl-4-hydroxyquinoline *N*-oxide (**116**), 2-*n*-nonyl-4-hydroxyquinoline *N*-oxide (**118**)] and four new [2-((*Z*)-undec-4′-enyl)-4-

hydroxyquinoline (**114**), 2-(3′-(2′-hexylcyclopropyl)propyl)-4-hydroxyquinoline (**115**), 2-*n*-octyl-4-hydroxyquinoline *N*-oxide (**117**) and 2-((*Z*)-undec-4′-enyl)-4-hydroxyquinoline *N*-oxide (**119**)] compounds as well as 3-*n*-heptyl-3-hydroxyquinoline-2,4(1*H*,3*H*)-dione (**120**) (Fig. 15), from *Pseudomonas aeruginosa* BCC76810 were evaluated for antimalarial effects. Most of the 11 compounds, including both 4-hydroxyquinolines (**110**–**114**) and 4-hydroxyquinoline-*N*-oxides (**116**–**119**), exhibited activity against *P. falciparum*, K1 strain (IC_{50} 0.25–2.07 μg/mL) with moderate to weak cytotoxicity against cancerous [KB, MCF-7, NCI-H187 (lung cancer)] and non-cancerous (Vero) cells.[90]

2. Antitrypanosomal and antileishmanial activities—American trypanosomiasis, known as Chagas disease, is a potentially life-threatening illness caused by the protozoan parasite *Trypanosoma cruzi*. To date, about 7 to 8 million people are estimated to be infected worldwide, mostly in Latin America.[91] To avoid the severe side effects induced by the current drugs benznidazole and nifurtimox as well as find enhanced clinical efficacy,[92,93] natural products, especially quinoline alkaloids, have been investigated as new antitrypanosomal medicines. Cretton and co-workers isolated waltheriones A (**121**), C (**122**) and E–L (**123**–**130**), together with antidesmone and 8-deoxoantidesmone (**131**) (Fig. 16) from *Waltheria indica* in the years 2014 and 2015.[94,95] Compounds **125**, **126** and **129** (Fig. 16) showed potent and selective growth inhibition toward *Trypanosoma cruzi* with IC_{50} values of 0.02 (**125**) and 0.04 (**126**, **129**) μM. The remaining compounds were less potent (IC_{50} 0.1–3.1 μM; >50 μM for **121**). All compounds exhibited weak activity against *T. brucei* and *T. brucei rhodesiense.* However, except for three compounds (**121**, **122** and antidesmone), the isolated alkaloids also showed significant cytotoxicity against murine skeletal L-6 cells, with **129** being the most cytotoxic (IC_{50} 0.07 μM *vs* podophyllotoxin 0.02 μM). Thus, the selectivity index (SI: IC_{50} cytotoxicity/IC_{50} anti-*T. cruzi* activity) values of most of the waltheriones ranged from 1.8 to 33.8, making them too toxic to be considered as antichagasic hits.[94,95] The sole exception was **122** with a cytotoxicity IC_{50} of 101 μM and better SI of 52.4.[95]

Leishmaniasis, a major health problem worldwide, is a neglected tropical parasitic disease resulting from the infection of macrophages by obligate intracellular parasites of the genus *Leishmania*.[96,97] Due to the prevalence of HIV/VL co-infections, leishmaniasis has recently become a more studied problem,[98] and alkaloids are prospective compounds to combat this disease.[99–101] Among five investigated furoquinoline alkaloids (dictamine, γ-fagarine, skimmianine, flindersiamine and masculine), γ-fagarine presented significant *in vitro* activity against *L. amazonensis*, *L. infantum* and *L. braziliensis* with IC_{50} values of 17.3, 26.5 and 22.2 μM, with comparable inhibition (97%) to that of the reference drug.[102] In *L. amazonensis* infected Balb/c mice treated orally with γ-fagarine at 10 mg/kg daily for 14 days, lesion weight decreased significantly by 90.5% and lesional parasites dropped drastically by 97.4%.[102] *N*-Methyl-8-methoxyflindersine (**132**) (Fig. 17) also exhibited selective leishmanicidal activity against intracellular promastigotes (EC_{50}: 14.3 μg/mL).[103]

3. Acaricidal and insecticidal activity—Luo and co-workers isolated *N*-methylswietenidine B (**133**), methyl 2-(3-hydroxy-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinolin-3-yl)-acetate (**134**) and 3-hydroxy-1-methyl-3-(2-

oxopropyl)quinoline-2,4(1*H*,3*H*)-dione (**135**), *N*-methylflindersine (**136**) and 4-hydroxy-3-methoxy-1-methyl-2(1*H*)-quinolinone (**137**) (Fig. 17) from *Micromelum falcatum*.[104] Only **136** showed strong toxicity toward brine shrimp with an LD_{50} value of 1.39 μg/mL; the LD_{50} values of the other four compounds were more than 50 μg/mL. Six new 4-phenyl-3,4-dihydroquinolones [6-deoxyaflaquinolone E (**138**), isoaflaquinolone E (**139**), 14-hydroxyaflaquinolone F (**140**), aniduquinolones A (**141**), B (**142**) and C (**143**)] were characterized from the endophytic fungus *Aspergillus nidulans*.[105] The two latter alkaloids as well as the known isolated aflaquinolone A (**144**) (Fig. 17) had reported LD_{50} values of 7.1, 4.5 and 5.5 μM, respectively, against brine shrimp (*Artemia salina*).[105] Moreover, two enantiomeric quinazolines, 2-[(*S*)-hydroxy(phenyl)methyl]-3-methylquinazolin-4(3*H*)-one (**145**) and 2-[(*R*)-hydroxy(phenyl)methyl]-3-methylquinazolin-4(3*H*)-one (**146**) (Fig. 17) from the alga-endophytic fungus *Talaromyces sp.* Cf 16 exhibited weak toxicity toward brine shrimp (LC_{50} 97.8 and 106 μg/mL).[106] The latter compound also showed weak inhibition against *Staphylococcus aureus*.

In addition, penicinoline showed strong insecticidal activity against *A. gossypii*,[65] and quinolactacide showed excellent activity against *Myzus persicae*.[107] 8-Hydroxyquinoline was very effective against the growth of *Toxoplasma*; its IC_{50} value was 0.213 μM.[108] The LD_{50} values of quinoline-4-carbaldehyde from *Ruta chalepensis* were 0.084 mg/cm^2 and 0.065 mg/cm^2 against *Sitophilus oryzae* by the fumigant and the contact methods, respectively.[109] Changing the position of the aldehyde groups in the quinoline skeleton increased the insecticidal activity.

Our group reported that the quinazoline alkaloid vasicine from *Peganum harmala* presented weak acaricidal activity against *Psoroptes cuniculi*.[110] Its LT_{50} values were 12.2 h and 9.79 h at 1.25 and 2.5 mg/mL, respectively.

C. Antibacterial and Antifungal Activities

Several antibacterial drugs have been developed from alkaloids. Quinolone antibiotics arose out of the synthesis of quinine, metronidazole resulted from the structural alteration of azomycin, and bedaquiline was produced from studies on the quinoline scaffold.[111] Quinolone antibiotics target the bacterial type IIA topoisomerase/gyrase.[112,113] The compounds stabilize the enzyme-DNA cleavage complex; two quinolone molecules bind with the enzyme and intercalate into the cleaved DNA. This action stops the free 3′ hydroxyl of the DNA from attacking the phosphotyrosine link in the enzyme-DNA complex and thereby prevents religation of the DNA.[114] The decreased level of religation eventually leads to bacterial cell death.

Flindersine alkaloids are a novel class of quinoline alkaloids. Flindersine exhibits both antibacterial and antifungal activities. Its MIC values against bacteria *Bacillus subtilis*, *Staphylococcus aureus*, *S. epidermidis*, *Enterococcus faecalis*, *Pseudomonas aeruginosa*, *Acinetobacter baumannii* and fungi *Trichophyton rubrum* 57, *T. mentagrophytes*, *T. simii*, *Epidermophyton floccosum*, *Magnaporthe grisea* and *Candida albicans* were 31.25, 62.5, 62.5, 31.25, 250, 125, 62.5, 62.5, 62.5, 62.5, 250 and 250 μg/mL.[115] The analog 8-methoxyflindersine exhibited similar inhibitory activity against the *C. albicans*-sensitive

mutant strain DSY2621, but was inactive against a wild strain of this yeast.[116] Meanwhile, the structurally related veprisine showed moderate activity against *S. aureus*.[117]

Furoquinoline alkaloids also exhibit antibacterial and antifungal activities. Skimmianine showed weak antimicrobial and antifungal activities against two Gram-positive bacteria (*S. aureus* and *S. epidermidis*), five Gram-negative bacteria (*Escherichia coli, Enterobacter cloacae, Pseudomonas aeruginosa, Klebsiella pneumoniae* and *Shigella dysenteriae*), three pathogen fungi (*C. albicans, C. tropicalis* and *C. glabrata*) and the oral pathogens *S. mutans* and *S. viridans*.[33] Skimmianine also exhibited antimycobacterial activity against *Mycobacterium tuberculosis* H37Ra ATCC 25177 and *M. tuberculosis* H37Rv ATCC 27294.[22] Kokusaginine exhibited moderate antibacterial activity against methicillin-resistant *S. aureus* SK1with an MIC value of 16 μg/mL.[118]

Our prior review summarized the antibacterial effects of four sesquiterpenoid quinoline antibiotics, aurachins A–D. Since then, aurachins C and D together with two new related compounds, aurachins Q (**147**) and R (**148**) (Fig. 18), were isolated from *Rhodococcus sp.* Acta 2259.[119] Aurachins C and R exhibited moderate antibacterial activity against *Staphylococcus epidermidis* DSM 20044, *Bacillus subtilis* DSM 347 and *Propionibacterium acnes* DSM 1897, and weak inhibitory activity against glycogen synthase kinase 3β. The two other aurachins were inactive at concentrations below 100 μM, and all four compounds were inactive against Gram-negative bacteria.[119] Meanwhile, 4-oxo-1,4-dihydroquinoline-3-carboxamide (**149**) (Fig. 18) from *Nocardiopsis terrae* YIM 90022 showed antimicrobial activity against *S. aureus, B. subtilis* and *E. coli* with MICs of 64, 64 and 128 μg/mL and antifungal activity against *P. oryzae* with an MIC of 256 μg/mL.[120] 4-Hydroxyquinoline *N*-oxides also displayed anti-*Bacillus cereus* activity,[90] and 5-hydroxy-4-(chloromethyl)-5,6,7,8-tetrahydroquinoline (**150**) (Fig. 18) from a Belize extract inhibited the growth of pathogenic, saprophytic marine fungi and marine bacteria.[121]

Eight novel 5-alkyl-1,2,3,4-tetrahydroquinolines (5aTHQs, **151**–**158**) (Fig. 19) bearing different side chains were isolated from a combined culture of *Streptomyces nigrescens* HEK616 and *Tsukamurella pulmonis* TP-B0596.[122] All eight compounds inhibited the growth of yeast cells, most likely by targeting the membrane lipids. 5aTHQ-7n (**151**) exhibited the most potent growth inhibition with an MIC value of 6.3 μM compared with 0.25 μM for amphotericin B. The length and methylation pattern of the side chain at C-5 had a critical effect on the potency and selectivity toward the growth of yeast cells.[122] Among several quinoline alkaloids [waltherions E–L and M–Q (**159**–**163**, respectively), 5(*R*)-vanessine (**164**) (Fig. 19), 8-deoxoantidesmone and antidesmone] isolated from *Waltheria indica*, waltheriones E–I, N and Q, 5(*R*)-vanessine, 8-deoxoantidesmone and antidesmone showed growth inhibitory activity against *Candida albicans* on both planktonic cells and biofilms (MIC ≤32 μg/mL).[123] However, the selectivities were much weaker (SI, 0.3–5) compared with those of fluconazole and caspofungin (>100). All compounds also exhibited *in vitro* toxicity against HeLa cells with IC_{50} values ranging between 9.5 and 50 μg/mL.

Various new and known pentacyclic alkaloids were isolated from different chromotypes of the western Mediterranean ascidian *Cystodytes dellechiajei*.[124] The purple morph collected in Catalonia contained shermilamine B (**165**) (known) and *N*-deacetylshermilamine B (**166**)

(new) (Fig. 20). The green morph collected in the Balearic Islands contained 11-hydroxyascididemin (**167**) (known) as well as cystodimines A (**168**) and (**169**) (new) (Fig. 20). The blue morph collected in Catalonia yielded ascididemin (**170**) (known) (Fig. 20). Among the tested compounds, **170** exhibited the best activity with MIC values of 0.2 and 0.3 μM against *E. coli* and *E. luteus,* respectively, while **167** and **169** showed the weakest activity with MIC values of 2.6 μM against *E. coli* and 10.5 μM against *E. luteus*.[124] The benzo[*g*]quinoline-5,10-dione cleistopholine (**171**) (Fig. 20) from the fruiting tree *Annona salzmannii* showed significant antibacterial activity (MIC 250 μg/mL) against *S. epidermidis*, *Enterococcus faecalis* and *Candida dubliniensis*.[125]

The important quinazoline alkaloid tryptanthrin has a wide range of biological effects, including promising antibacterial activity toward methicillin-resistant *S. aureus*[126] and anti-tubercular activity against *Mycobacterium tuberculosis*.[127] Tryptanthrin could bind the site of InhA with free binding energy of −7.94 kcal/mol and inhibition constant (Ki) of 1.50 microm. Active site residues of InhA interacting with tryptanthrin were Ser13, Thr39, Phe41, Leu63, Asp64, Val65, Ile95, Phe97 and Ile122. So, tryptanthrin has good affinity at the binding site of the enoyl-acyl carrier protein reductase of *M. tuberculosis* and compounds of this type could be developed as anti-tubercular drugs against this therapeutic target, particularly for combating MDR strains.[127] While the quinazoline alkaloid vasicine[128] and its acetate[129] showed moderate antibacterial activity, vasicine acetate also significantly inhibited *M. tuberculosis* at 200 and 50 μg/mL for one multi-drug-resistant (MDR) strain and one sensitive strain, respectively. Besides vasicine, additional quinazoline alkaloids vasicoline, vasicolinone, vasicinone, adhatodine (**172**) and anisotine (**173**) (Fig. 21) also exhibited anti-tubercular activity.[130]

Among the four new cottoquinazolines A–D (**174**–**177**) (Fig. 21) from *Aspergillus versicolor* and *A. versicolor* LCJ-5-4, only compound **177** showed moderate antifungal activity against *Candida albicans.*[131,132] Rutaecarpine and 7β-hydroxyrutaecarpine also showed antimycobacterial effects.[22,133]

D. Cardioprotective Activity

As mentioned previously, rutaecarpine exhibits multiple biological effects;[134] however, its cardiovascular pharmacological properties, such as inotropic and chronotropic, vasorelaxant, anti-platelet aggregation and anti-inflammatory effects, are undoubtedly among the most important and have attracted much research interest.[135,136] It significantly prolonged the latent period of inducing platelet plug formation in mesenteric venules when it was intravenously injected, and prolonged occlusion time by approximately 1.5-fold. Intravenous injection of rutaecarpine prolonged the bleeding time in the severed mesenteric arteries of rats.[134] In 2015 studies on endothelial dysfunction related to atherosclerosis, Peng et al. found that pretreatment with rutaecarpine effectively inhibited Cx43 expression, but recovered the expression of Cx37 and Cx40. The alkaloid effectively improved gap junction communication and significantly prevented endothelial dysfunction induced in HUVEC-12 cells by exposure to oxidized low-density lipoprotein (ox-LDL) *in vitro*, which is related to regulation of connexin expression patterns via TRPV1 activation.[137] Rutaecarpine decreased monocyte adhesion by reversing the altered connexin (Cx) expression also induced by ox-

LDL.[138] In subsequent studies, the same group found that, more specifically, rutaecarpine pretreatment led to recovered Cx37 (artheroprotective) expression and inhibited Cx43 (artherogenic) upregulation, thus, improving adenosine triphosphate-dependent hemichannel activity.[138] In earlier studies, Xu et al. found that rutaecarpine promoted reverse cholesterol transport (RCT) *in vivo* and suppressed atherosclerosis in ApoE/mice by promoting ABCA1 and SR-B1 activities within RCT.[139] It triggered promoters of ABCA1 and CLA-1 genes, and increased ABCA1 and SR-BI/CLA-1 expression *in vitro* related to liver X receptor alpha and liver X receptor beta. In RAW264.7 cells, rutaecarpine could induce cholesterol efflux. Meanwhile, it attenuated macrophages and cholesterol accumulations in atherosclerotic lesions *in vivo*. The anti-atherosclerotic activity of rutaecarpine, as well as evodiamine, has also been linked to other targets or pathways, such as LIGHT, cAMP-related pathways, etc.[140–142] The inhibitory effects of evodiamine and rutaecarpine on LIGHT-induced migration and the activation of CCR1, CCR2, ICAM-1, ERK, and p38 MAPK occur via decreased ROS production and NADPH oxidase activation.[140]

Moreover, rutaecarpine displays cardioprotective effects against ischaemia-reperfusion injury. Treatment with rutaecarpine led to a hypotensive effect in spontaneously hypertensive rats (SHR) and reversed cardiac susceptibility to reperfusion injury by increasing plasma calcitonin gene-related peptide (CGRP).[143] Both cardiac function and vasodilator responses were significantly improved. Stimulation of CGRP release by rutaecarpine also led to reduced hypoxia-induced right ventricular remodeling in rats, and the effects involve the eIF3a/p27 pathway.[144] Rutaecarpine down-regulated NOX4 expression and collagen accumulation in rats with pulmonary hypertension induced by monocrotaline.[145] In addition, rutaecarpine protected against hypoxia-reoxygenation-induced myocardial cell injury and apoptosis in myocardial H9c2 cells partly due to the inhibition of the NADPH oxidase-ROS pathway,[146] increased prolylcarboxypeptidase expression and decreased angiotensin II levels in 2K1C hypertensive rats,[147] and inhibited vasoconstriction induced by anaphylaxis in guinea pigs.[148]

Several studies have reported evodiamine and rutaecarpine alkaloids to be putative selective agonists both *in vitro* and *in vivo* for transient receptor potential vanilloid 1 (TRPV1), a nonselective cation channel expressed on either sensory neuronal systems or nonneuronal sites.[149–154] In 2016, Wang et al. investigated the inhibitory effects of evodiamine and rutaecarpine against TRPV1 channels, and against capsaicin- or proton-activated TRPV1 activities.[155] The results indicated that, compared with capsaicin, the two alkaloids had lower maximum responses for activating TRP1, suggestive of partial agonism. Thus, evodiamine and rutaecarpine may share the capsaicin binding site and act as partial TRPV1agonists (antagonists). In addition, evodiamine desensitized or competitively inhibited the activity of TRPV1. Rutaecarpine could be used as a potential anti-hypertensive lead compound with a novel mechanism.[155]

Both cardiovascular and cerebrovascular diseases are forms of ischemic vascular disease. Accordingly, Yan and co-workers reported on the neuroprotective effects of rutaecarpine on cerebral ischemia reperfusion injury in 2013.[156] The compound enhanced learning and memory ability, ameliorated neurological symptoms, and reduced infarction volume and cerebral water content in mice with cerebral ischemia reperfusion injury.[156] Administration

of rutaecarpine attenuated hyperglycemia and enhanced insulin sensitivity, significantly decreased obesity, visceral fat accumulation, water consumption, and serum TC, TG and LDL-cholesterol levels in fat-fed, streptozotocin-treated rats. In addition, it increased PI3K p85 subunit levels and Akt/PKB phosphorylation, and decreased IRS-1 phosphorylation in liver tissues. In skeletal muscle cells, it promoted the phosphorylation of AMPK and ACC2, and increased glucose uptake. Results indicated that rutaecarpine improved hyperlipidemia and hyperglycemia in fat-fed, streptozotocin-treated rats by regulating the hepatic IRS-1/PI3K/Akt signaling pathway and skeletal muscular AMPK/ACC2 signaling pathway.[157]

The diastereoisomeric quinoline akaloids quinidine and quinine, which are used to treat arrhythmia and malaria, respectively, block the hERG (human ether-a-go-go-related gene) potassium channel, which is essential for myocardium repolarization.[158] Quinine was 14-fold less potent than quinidine. In addition, they distinctly impacted the channel dynamics. The results also indicate stereospecific block effect on the hERG channel, but F656C-hERG reversed this stereoselectivity. The mutation decreased affinity of the two drugs with hERG, and quinine was more potent than quinidine in F656C-hERG blockage.[158] Quinine also stimulated adipogenesis through ERK/S6 signaling, acting at least partly via the bitter taste receptor T2R106.[159]

A new quinoline alkaloid, 8-hydroxy-9-methyl-furo[2,3-*b*]quinolin-4(9H)-one (**178**) (Fig. 22) together with isopteleine, robustine, γ-fagarine, isodictamnine and skimmianine were isolated from *Dictamnus angustifolius*.[160] All of the compounds showed significant inhibitory effects on platelet aggregation induced by adenosine diphosphate (ADP) at 250 μM. Meanwhile, 8-hydroxy-4-quinolone (**179**) (Fig. 22), from *Scolopendra subspinipes multilans*, the Chinese red-headed centipede, exhibited antiplatelet effects.[161] It prolonged activated partial thromboplastin and prothrombin times and inhibited the activity and production of thrombin and activated factor X. Furthermore, it inhibited thrombin-catalyzed fibrin polymerization and platelet aggregation, and enhanced antithrombotic effects in an *in vivo* pulmonary embolism and arterial thrombosis model.

E. Anti-viral Activity

Fumiquinazolines are quinazoline-containing indole alkaloids that possess pyrimido[2,1-*b*]quinazoline and imidazo[1,2-*a*]indole moieties linked by a methylene (and in some cases further linked via additional spiro-bridges). The first compounds of this type were isolated from *Aspergillus fumigates* in 1992.[162] During the following decades, about 40 fumiquinazoline analogues were reported from various fungal genera. In 2016, two new fumiquinazoline analogues, neosartoryadins A (**180**) and B (**181**) (Fig. 23), were isolated from the endophytic fungus *Neosartorya udagawae* HDN13-313.[163] They displayed anti-influenza virus A (H1N1) effects with IC_{50} values of 66 and 58 μM, respectively, compared with 94 μM for the positive control ribavirin. Six new indole alkaloids, including five new glyantrypine derivatives and a new pyrazinoquinazoline derivative, together with eight known alkaloids were isolated from a culture of the mangrove-derived fungus *Cladosporium sp*. PJX-41.[164] Oxoglyantrypine (**182**), norquinadoline A (**183**), deoxynortryptoquivaline (**184**) and quinadoline B (**185**) (Fig. 23) exhibited significant activity against H1N1 virus (IC_{50} 82–89 μM). Trytoquivaline, quinadoline A (**186**), 3-hydroglyantrypine (**187**),

cladoquinazoline (**188**), *epi*-cladoquinazoline (**189**), glyantrypine (**190**), deoxytrytoquivaline (**191**) and CS-C (**192**) were weakly active (IC_{50} 100–150 μM), and prelapatin B **(193)** (Fig. 23) was inactive (IC_{50} >200 μM).[164]

Anti-HIV activity is another important biological activity of quinoline and quinazoline alkaloids. In 2010, buchapine and 3-(3-methylbut-2-enyl)-4-(3-methylbut-2-enyloxy)quinolin-2-ol **(194)** were evaluated for their anti-HIV potential in the human $CD4^+$ T cell line CEM-GFP infected with HIV-$1_{NL4.3}$ virus.[165,166] The IC_{50} and CC_{50} values of the former compound were 2.99 and 55.9 μM, respectively, and those of the latter compound were 3.80 and 71.2 μM, respectively, giving them identical therapeutic indices (TIs). In comparison, the IC_{50} and CC_{50} values of AZT were 1.04 and 24.0 μM, respectively. From a synthetic study on alkylated quinoline-2,4-diols, an unsubstituted ring B and free 2-OH group are essential for anti-HIV activity, and a prenyl group is best for HIV-1 inhibitory activity.[165,166] Furthmore, trigonoine B **(195)** (Fig. 24) showed weak anti-HIV activity, preventing the cytopathic effects of HIV-1_{IIIB} in C8166 cells with an EC_{50} value of 17.6 μg/mL and TI value of 4.48, but no anti-HBV activity.[167] Meanwhile, waltheriones A (**121**) and C (**122**) (Fig. 16) showed significant effects in an *in vitro* anti-HIV cytoprotection assay at concentrations of 56.2 and 0.84 μM and inhibition of HIV P24 formation of more than 50% at 1.7 and 0.95 μM, respectively, while waltheriones B **(196)** and D **(197)** (Fig. 24) were only weakly active or inactive.[168]

Hepatitis C virus (HCV) infection is highly prevalent among global populations. The 4-quinolone alkaloid pseudane IX **(198)** (Fig. 25) isolated from *Ruta angustifolia* possessed strong anti-HCV activity (IC_{50} 1.4 μg/mL) and was more potent than ribavirin (IC_{50} 2.8 μg/mL).[169] Also, the furoquinolines γ-fagarine and kokusaginine showed weaker but significant anti-HCV activity (IC_{50} 20.4 and 6.4 μg/mL, respectively).

F. Anti-inflammatory Activity

Lipopolysaccharide (LPS) stimulation in cells causes inducible nitric oxide synthase (iNOS) overexpression and subsequently NO synthesis. Such stimulation occurs in response to exposure to inflammatory and immunologic stimuli, and has been implicated in the pathogenesis of numerous diseases, including septic shock, asthma, inflammatory bowel disease, osteoarthritis, and rheumatoid arthritis.[170]

In 2012, Yoon et al. evaluated the anti-inflammatory activity of alkaloids from *Dictamnus dasycarpus* by determining NO production in BV2 cells.[171] The compounds included the new glycosidic quinoline alkaloid 3-[1β-hydroxy-2-(β-D-glucopyranosyloxy)-ethyl)-4-methoxy-2(1*H*)-quinolinone (**199**), preskimmianine, seven known furoquinolines [skimmianine, dictamine, γ-fagarine, iso-γ-fagarine, halopine, dictangustine-A (**200**), and isomaculosidine (**201**) (Fig. 26)], and the known pyranoquinolone 8-methoxy-*N*-methylflindersine. 8-Methoxy-*N*-methylflindersine and skimmianine showed the most potent inhibition of LPS-induced NO production with IC_{50} values of 0.4 and 7.0 μM, respectively. The corresponding value for the positive drug N_G-nitro-L-arginine was 53.5 μM.[171] Other studies showed that, when injected into mice (5.0 mg/kg), skimmianine alleviated carrageenan-induced acute inflammation, decreased the mRNA levels of TNF-α

and IL-6, and reduced PGE_2 and NO amounts, cyclooxygenase-2 (COX-2) and 5-lipoxygenase (5-LOX) activities, neutrophil infiltration, lipid peroxidation, and associated oxidative stress in the paw tissue.[172] In addition, a new compound, 2-[(6*Z*,9*Z*)-pentadeca-6,9-dienyl]quinolin-4(1*H*)-one (**202**) from *Tetradium ruticarpum* and evodol inhibited fMLP/CB-induced elastase release with IC_{50} values lower than 14.4 μM, while rutaecarpine, evodiamine, and skimmianine inhibited O^{-2} generation (IC_{50} ≤20.9 μM) by human neutrophils in response to *N*-formyl-L-methionyl-L-leucyl-L-phenylalanine/cytochalasin B (fMLP/CB).[173] However, skimmianine, haplopine, and glycohaplopine from *Zanthoxylum schinifolium* did not inhibit NF-κB.[174]

Four new alkaloid glycosides clausenasides D–F (**203**–**205**) and 4-methoxy-8-O-β-D-glucopyranosyloxy-2(1*H*)-quinolinone (**206**), along with two new quinoline alkaloids, clausenasides G–H (**207**, **208**), as well as other known quinoline alkaloids, including integriquinolone (**209**), 4-methoxy-2(1*H*)-quinolone, 4-methoxy-1-methyl-2-quinolone, and ribalinine (**210**) (Fig. 27), were obtained from *Clausena lansium*.[175] Compounds **203**, **205**, **206**, and **210** showed moderate inhibitory effects on LPS-induced NO production in BV2 cells (IC_{50} <10 μM), the remaining compounds had IC_{50} values of over 10 μM. Leucophyllidine and eucophylline (**211**) (Fig. 27), a new tetracyclic vinylquinoline alkaloid, were isolated from *Leuconotis eugenifolius*.[176] Leucophyllidine caused dose dependent inhibition of NO production stimulated by LPS (IC_{50} 7.1 μM), showed iNOS inhibitory activity, and decreased iNOS protein expression, while eucophylline was inactive. Both compounds showed high cell J774.1 viability at the above concentration.[176] In addition, the novel alkaloid scholarisine II (**212**) selectively inhibited COX-2 and markedly inhibited 5-LOX, while scholarisine I (**213**) (Fig. 27) with a vinyl rather than hydroxyethyl group did not.[177]

The anti-inflammatory activity of tryptanthrin, a well-known indolo[2,1-*b*]quinazoline alkaloid, has been widely studied and was reported in our previous review. The compound potently inhibited COX-2 and 5-LOX-catalyzed leukotriene synthesis *in vitro* and *in vivo*,[178–180] as well as iNOS-catalyzed NO production and prostaglandin E_2 production by activated macrophages.[181] In view of these proven pharmacological effects, in 2016, the pharmacokinetic properties of tryptanthrin and its ability to cross blood-brain barrier (BBB) were evaluated *in vivo* and *in vitro*.[182] A high BBB permeation potential was found *in vivo* that correlated well with an immortalized human monoculture BBB model (hBMEC cell line) and corroborated with the in silico prediction of BBB penetration. In addition, tryptanthrin was not subject to active efflux.[182]

G. Effect on AChE and BChE

The newest drugs to treat Alzheimer's disease are acetylcholinesterase inhibitors (AChEIs). As a newly discovered AChEI, the furoquinoline alkaloid skimmianine from *Zanthoxylum nitidum* inhibited 50% of AChE activity at a concentration of 8.6 μg/mL, while the IC_{50} value of the standard physostigmine was 0.013 μg/mL.[183] In the same study, other quinoline alkaloids, inclucing dictamnine, γ-fagarine, (−)-(*S*)-edulinine, zanthodioline, edulitine and haplopine, were weakly active or inactive. TLC bioautographic assay also supported skimmianine's inhibitory activity, which was enhanced by the presence of a methoxy group

at C-7.[183] In other studies, skimmianine, another furoquinoline kokusaginine, and the quinolin-4-one leiokinine A, inhibited AChE inhibition with IC_{50} values of 1.4 mM, 46 μM, and 0.21 mM, respectively.[184] However, leptomerine (**214**) (Fig. 28), a natural quinolin-4-one from *Esenbeckia leiocarpa*, showed the highest activity (IC_{50} 2.5 μM), similar to that of the reference compound galanthamine (IC_{50} 1.7 μM). In 2014, Sichaem and co-workers reported that, among three new furoquinoline alkaloids, leptanoines A–C (**215**–**217**) (Fig. 28), together with known related alkaloids, including melineurine, skimmianine and 7-hydroxydictamnine, isolated from *Evodia lepta*,[185] melineurine showed the highest inhibitory activity towards butyrylcholinesterase (BChE) with an IC_{50} value of 47.9 μM, and skimmianine showed the highest inhibitory activity towards AChE with an IC_{50} value of 69.1 μM.[186] Lineweaver-Burk plots indicated that both compounds were mixed mode inhibitors of both ChE enzymes. Meanwhile, the new alkaloid **217** did not inhibit either enzyme (IC_{50} >200 μM).[186] Another known furoquinoline alkaloid evolitrine significantly promoted nerve growth factor-mediated neurite outgrowth in PC12 cells (EC_{50} 3.8 μg/mL), and potentially prevent neuronal degeneration and be useful for the medical treatment of Alzheimer's disease.[187]

16α-Hydroxy-5*N*-acetylardeemin (**34**) (Fig. 3) displayed good inhibitory effect against AChE (IC_{50}, 58.3 μM).[28] Waltheriones A (**121**) (Fig. 16) and B (**196**) (Fig. 24) also inhibited AChE activity with IC_{50} values of 134 and 123 μg/mL, respectively, in a dose-dependent manner.[188]

Deoxyvasicine and vasicine from *Peganum harmala* showed potent AChE (IC_{50} 2.37 and 0.04 μM, respectively) and BChE (IC_{50} 3.38 and 0.1 μM, respectively) inhibitory activity, but deoxyvasicinone, vasicinone and 2-carboxyl-3,4-dihydroquinazoline were inactive.[189] Vasicine undergoes metabolic inactivation *in vivo* in respect to cholinesterase inhibitory activity, as most of its main metabolites were weaker inhibitors of AChE and BChE.[190] In studies on the seeds of *P. nigellastrum*, two new alkaloids nigellastrine I (**218**) and nigellastrine II (**219**) (Fig. 29), along with, vasicinone, vasicine, deoxyvasicinone, deoxyvasicine, showed good inhibitory effects against AChE.[191] In 2016, ten new alkaloids were isolated from *P. harmala*.[192] Among the compounds, peganumine D (**220**), *S*-peganumine E (**221**) and *R*-peganumine E (**222**) have quinazolone skeletons, and peganumine F (**223**) and peganumine G (**224**) (Fig. 29) have both β-carboline and quinazolone skeletons. Compound **220** selectively inhibited AChE (IC_{50} 5.71 μM), while the other compounds were inactive against both AChE and BChE. In addition, compound **224** showed cytotoxicity against a ZR-75-1 (breast cancer) cell line (IC_{50} 6.20 μM).[192]

H. Anti-oxidant Activity

The furoquinoline alkaloid haplopine-3,3′-dimethylallyl ether, isolated from *Vepris glomerata*,, has strong antioxidant effects, similar to and, in some instances, better than those of ascorbic acid.[193] This alkaloid together with two additional furoquinoline alkaloids dictamnine and robustine inhibited superoxide anion generation (IC_{50}: 13.0, 17.4, 32.8, 26.1 μM, respectively) and elastase release (IC_{50}: 19.6, 12.1, 29.3, 32.2 μM, respectively).[193] In addition, various 4-hydroxyquinoline *N*-oxides also displayed antioxidant activities, with 2-*n*-nonyl-4-hydroxyquinoline *N*-oxide showing the best antagonist activity.[90] The nitrogen

oxide group was essential for the activity, as well as the length of the alkyl chain. The oxygen radical absorbance capacity (ORAC) value of cleistopholine, a quinoline alkaloid found in *Annona salzmannii*, was 0.25 relative trolox equivalents.[125]

In 2015, Popv et al investigated the antioxidant and membranotropic activities of the quinazoline alkaloid tryptantrin (triptantrin from orginal paper) in different model systems.[194,195] Tryptanthrin exhibited very weak antioxidant activity, 1000 times lower than that of trolox, a vitamin E water-soluble analog commonly used an anti-oxidative benchmark, and 3000 times lower than that of the bioflavonoid dihydroquercetin. Meanwhile, vasicine, a quinazoline alkaloid isolated from *Adhatoda vasica*, inhibited the activities of ACh and trypsin by 38.4% and 37.4%, respectively, as well as 2-diphenyl-1-picrylhydrazyl (DPPH) by 70.4% (IC_{50} 212.3 μM).[128] Dose-dependent behavior was also seen in a ferric reducing ability of plasma (FRAP) assay.

I. Hepatoprotective Effect

Seventeen new alkaloids and their analogues were isolated from *Isatis indigotica* in 2012.[196] One quinolin-4-one [methyl l2-(4-oxo-1,4-dihydroquinoline-3-carboxamido)benzoate (**225**)] and two quinolin-2-ones [6-hydroxy-4-(5-hydroxymethylfuran-2-yl)-quinolin-2(1*H*)-one (**226**), (+)-(*R*)-2-oxo-1,2,3,4-tetrahydroquinoline-4-carboxamide (**227**)] were included. Chiral HPCL was used to separate two enantiomers [(−)- and (+)-3-hydroxy-2*H*-pyrrolo[2,3-*b*]indolo[5,5*a*,6-*b*,*a*]quinazoline-9(8*H*),7′-dione (**228**, **229**)] with a unprecedented pyrrolo[2,3-*b*]indolo[5,5*a*,6-*b*,*a*]quinazoline skeleton (Fig. 30). Compounds **227**–**229** reduced DL-galactosamine-induced hepatocyte (WB-F344 cell) damage with 44–55% inhibition at 10 μM, while the positive reference bicyclol resulted in 42% inhibition. However, the isolated alkaloids were inactive at 10 μM against HIV-1, HSV-1, and several human cancer cell lines.[196]

In 2014, Moon and co-workers proved that tryptanthrin protected hepatocytes against oxidative stress induced by *tert*-butyl hydroperoxide (tBHP) by activating the ERK/Nrf2 (nuclear factor erythroid 2-related factor) pathway in HepG2 cells.[197] The compound blocked tBHP-induced reactive oxygen species (ROS) production, mitochondrial dysfunction, and cell death, as well as reversed tBHP-induced glutathione (GSH) reduction. Meanwhile, tryptanthrin also brought about nuclear translocation and transactivation of Nrf2, as well as phosphorylation of ERK, a potential upstream kinase of Nrf2. However, rutaecarpine, a related quinazoline alkaloid, decreased the primary rat hepatocyte viability, increased lactate dehydrogenase and reactive oxygen species, reduced JC-1 and caused cell stress and membrane damage. It inhibited the activities of cytochrome P450 enzymes (CYPs) in human liver microsomes, especially CYP1A2, CYP2C9, CYP2C19, CYP2E1 and CYP3A4, which could lead to herb-drug interactions or result in hepatotoxicity.[198]

Members of the asperlicin family of metabolites, including the major metabolite asperlicin (**230**) and asperlicins B–E (**231**–**234**) (Fig. 31), which are produced by several strains of *Aspergillus alliaceus*, were discovered in the 1980s as selective antagonists of the cholecystokinin receptor CCK_A. Compound **230** was a lead scaffold for subsequent high affinity, selective CCK_A ligands. In 2012, Haynes et al. reported the identification of the

asperlicin gene cluster and characterization of short, efficient two enzymatic pathways to **234**.[199]

J. Anti-asthma, Antitussive, Expectorant and Bronchodilating Activities

Quinoline from *Ruta chalepensis* displayed a stronger relaxant effect (IC_{50}, 0.42 mM) on the contractile activity of guinea pig trachea than five other compounds, including quinoline-3-carboxaldehyde (>0.64 mM), quinoline-4-carboxaldehyde (>0.64 mM), 8-hydroxyquinoline (0.54 mM), quinazoline (0.48 mM) and quinoxaline (0.46 mM).[200] The results indicated that quinoline derivatives have anti-asthma activity.

Because of the traditional clinical uses of *Peganum harmala*, in 2015 Liu and co-worker studied the antitussive, expectorant, and bronchodilating activity of two active quinazoline alkaloids (±)-vasicine and deoxyvasicine, found in this plant.[201] In the antitussive studies in animals, the two compounds significantly inhibited coughing frequency and prolonged the cough latency period. The alkaloids also significantly increased phenol red secretion in expectorant testing done in mice. Compared with pretreatment in bronchodilation tests, vasicine and deoxyvasicine prolonged the pre-convulsive time by 28.6% and 29.7% at a dose of 45 mg/kg in guinea pigs, whereas aminophylline prolonged the pre-convulsive time by 47.0%. These results suggested that (±)-vasicine and deoxyvasicine have significant antitussive, expectorant, and bronchodilating properties.[201]

K. Anti-allergic Activity

Allergic diseases are initiated by the development of allergen-specific T helper type 2 (Th2) cells and amplified by the degranulation of and cytokine release from basophils and mast cells during an effector phase. In 2011, tryptanthrin was studied for its effects on the initiation and effector phase responses of Type I allergy *in vitro*.[202] It suppressed c-Maf mRNA expression in Th2 clone cells, inhibited IgE-mediated degranulation and IL-4 production in RBL-2H3 cells, and reduced differentiation toward the Th2 phenotype, which is a key step in allergic initiation. Thus, tryptanthrin effectively inhibited the effector and exacerbation responses, as well as the initiator responses, of Type I allergy.[202] Then in 2016, tryptanthrin was investigated regarding its regulating effects on thymic stromal lymphopoietin (TSLP)-induced mast cell proliferation and proinflammatory cytokine, tumor necrosis factor (TNF)-α production from mast cells.[203] It significantly inhibited HMC-1 cell proliferation and suppressed mRNA expression and production of TNF-α induced by TSLP, and inhibited Ki67 mRNA expression, mRNA expression and production of IL-13, as well as the mRNA expression of IL-7 receptor a chain and TSLP receptor in TSLP-promoted HMC-1 cells.[203] Moreover, tryptanthrin significantly suppressed the levels of intracellular calcium, IL-4, IFN-α, IL-6, TNF-α, and TARC/CCL17 (thymus and activation-regulated chemokine) as well as the production and mRNA expression of TSLP in activated HMC-1 cells.[204] It also inhibited IgE and IL-4 synthesis and promoted the secretion of IFN-γ.[205] Cumulatively, these results indicate that tryptanthrin has potential anti-allergic activity and could be used to treat mast cell-mediated allergic diseases or atopic dermatitis-like skin lesions.

The uncommon U-shaped pyranoquinoline alkaloid euodenine A (**235**) (Fig. 32) from *Euodia asteridula* induced cytokine response via agonism of the human Toll-like receptor 4 (TLR4).[206] Thus, it can likely modulate the Th2 immune response without causing lung damage. Structure-activity relationship studies on the cyclobutane ring led to 10-fold more potent analogs. In cytotoxicity testing toward peripheral blood mononuclear cells (PBMCs), **235** showed a small effect at 33 μM and clear evidence of toxicity at 100 μM.

L. Effect on Thioredoxin Reductase

Thioredoxin reductase (TrxR) is a potential target for new treatments for human diseases, such as cancer, AIDS, and autoimmune diseases.[207] Since fumiquinazolines A–C were first reported in 1992,[24a] their structural novelty and potent pharmaceutical effects have attracted much attention from chemists and pharmacologists. In 2016, nine fumiquinazoline-type alkaloids, versiquinazolines A–I (**236**–**244**) (Fig. 33), along with cottoquinazolines B–D, were isolated from the gorgonian-derived fungus *Aspergillus versicolor* LZD-14-1.[208] Compounds **236**, **237**, and **241**, bearing a methanediamine or an aminomethanol unit, represent unique fumiquinazoline subtypes found for the first time. Compounds **236**, **237**, and **242** exhibited inhibitory activity against TrxR (IC_{50} 12–20 μM). All compounds exhibited weak growth inhibitory activity against A549 and A2780 tumor cell lines (IC_{50} >50 μM).[208]

M. Antidiabetic Activity

In 2016, Selvaraj and co-workers isolated glycosin (**245**) (Fig. 34) from *Rhizophora apiculata* by bioassay guided fractionation and studied its antidiabetic effects and possible mechanism of action.[209] In diabetic rats (induced by streptozotocin and nicotinamide) treated with **245**, blood-glucose levels were significantly reduced and hepatic enzyme activities, as well as levels of urea and creatinine, were decreased. However, increases were seen in body weight, hemoglobin, high-density lipoprotein and insulin levels, and hexokinase activity when compared to untreated rats. Compound **245** interacted with dipeptidyl peptidase-IV, insulin receptor, protein tyrosine phosphatase 1B and PPARγ with good affinity and binding energy in a docking simulation. These results indicated that **245** could act as antihyperglycemic agent, associated with antihyperlipidemia, and possibility function as a ligand for proteins that are targets for antidiabetic drugs.[209]

Rutaecarpine also enhanced the blood lipid profile, mitigated inflammation, and improved kidney, liver, and pancreas pathology status of T2DM rats.[210] When incubating 24 hours with this alkaloid (20–180 μmol/L), production of IL-1, IL-6 and TNF-α in cultured IR-PSMC cells induced by palmitic acid significant decreased dose-dependently. However, the alkaloid did not show cytotoxic effect towards the cultured primary skeletal muscle cells at concentrations up to 180 μmol/L. It also promoted glucose consumption and improved insulin resistance, possibly by suppressing inflammatory cytokines in insulin-resistant primary skeletal muscle cells.

N. Antinociceptive Activity

Anhydroevoxine and choisyine (**246**) (Fig. 35) from *Choisya* Aztec-Pearl, a hybrid of *C. ternata* and *C. dumosa*, were investigated for antinociceptive activity.[211] At the doses of 3

and 10 mg/kg, these two furoquinoline alkaloids were two-fold more potent than morphine in treated animals using the hot plate model. Furthermore, mechanistic studies indicated that the opiate and nitric oxide (NO) system may play an important role in the antinociceptive activity. The cholinergic system may also be involved.[211]

O. Other Activities

The prescription of quinine is severely restricted in some countries, although serious adverse effects and fatality are rare. However, in many other countries, quinine is used to treat cramps from all causes. The Grading of Recommendations Assessment, Development and Evaluation system was applied to articles published during the period of 2010–2014 to assess the efficacy and safety of quinine-based treatment of muscle cramps.[212] The study found low quality evidence that quinine (200 mg to 500 mg/daily) significantly reduced the total number of cramps and days experiencing cramps, and moderate quality evidence that quinine reduced the intensity of cramps. Moderate quality evidence showed that the use of quinine for up to 60 days did not lead to a significantly greater incidence of serious adverse events than use of placebo in the identified trials. Based on these results, quinine likely can be used safely to treat muscle cramps, but certainly, more evidence should be collected as further proof of safety.[212]

In 2014, Dhingra and Valecha reported that punaravine (**247**) (Fig. 36), a quinolin-4-one alkaloid isolated from *Boerhaavia diffusa*, showed significant antidepressant activity in unstressed and stressed mice in different models.[213,214] When compound **247** was administered orally for 14 successive days, immobility periods and sucrose preference were significantly decreased in both stressed and unstressed mice. In addition, the alkaloid also significantly decreased monoamine oxidase activity and malondialdehyde levels, and significantly reversed the stress-induced decreases in reduced glutathione and catalase activity. The stress-induced increases in plasma nitrite and corticosterone levels also were significantly diminished. Evodiamine, a quinazoline alkaloid, also exerted antidepressant effects in rats as determined by reversal of various stress-associated behavior measures (decreased sucrose preference, numbers of crossing in an open-field test, increased immobility time in a forced swimming test) as well as biological measures (decreased 5-HT and Na^+ levels).[215]

In 2015, known fumiquinazolines F and L (**14**, Fig. 3) as well as new fumiquinazoline S (**248**), isochaetominines A–C (**249**–**251**), and 14-*epi*-isochaetominine C (**252**) (Fig. 36) were isolated from a culture of a marine-derived *Aspergillus sp*. fungus; they exhibited weak inhibition against Na^+/K^+-ATPase (IC_{50} 17, 20, 34, 78, 20, 38, and 57 μM, respectively).[216] *Aspergillus fumigatus* Af293 is also a known source of fumiquinazoline alkaloids.[217]

Indoleamine 2,3-dioxygenase (IDO) is overexpressed in various diseases, including cancer,[218] Alzheimer's disease,[219] age-related cataracts,[220] and HIV encephalitis.[221] Recent studies have suggested that IDO inhibition might enhance the efficacy of cancer treatment and concomitant administration of an IDO inhibitor might improve the efficacy of therapeutic vaccination or chemotherapy, thus, IDO has been highlighted as an attractive chemotherapeutic target.[218,222–224] In 2012, three benzodiazepine alkaloids, benzomalvins B (**253**), C (**254**), and E (**255**), (Fig. 37) were isolated from *Penicillium sp.* FN070315.[225]

Compound **255** inhibited IDO activity in a dose-dependent manner. While **255** was less potent (IC_{50} 21.4 μM) than mendione, the positive control IDO inhibitor (IC_{50} 3.7 μM), it was more potent than **253** and **254** (IC_{50} 126 and 130 μM, respectively).[225]

3. CONCLUSION

Quinoline and quinazoline alkaloids present a promising and expanding platform of active natural compounds and their potential has only been partially developed by both the academic community and the pharmaceutical industry to date. Although the discovery of quinine and camptothecin opened a new area for antimalarial and anticancer drug development, respectively, the identification of additional new compounds or significant biological activities will undoubtedly contribute continually to the development of future new drugs. During the period of 2009 to 2016, more than 200 compounds from these classes were newly found and most of them exhibited marked biological properties. The continued attention and long-lasting research on the isolation and identification of naturally occurring quinoline and quinazoline alkaloids will open the way to targeted pharmacological modelling and synthetic modifications, resulting in new and better drugs based on the original effects of these alkaloids.

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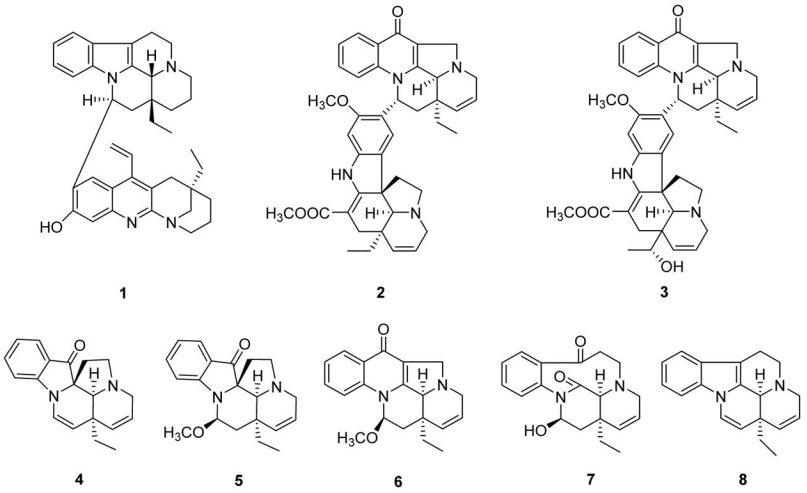


Figure 1.
Chemical structures of compounds **1–8**

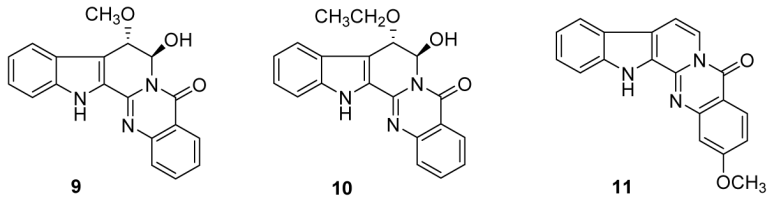


Figure 2.
Chemical structures of compounds **9–11**

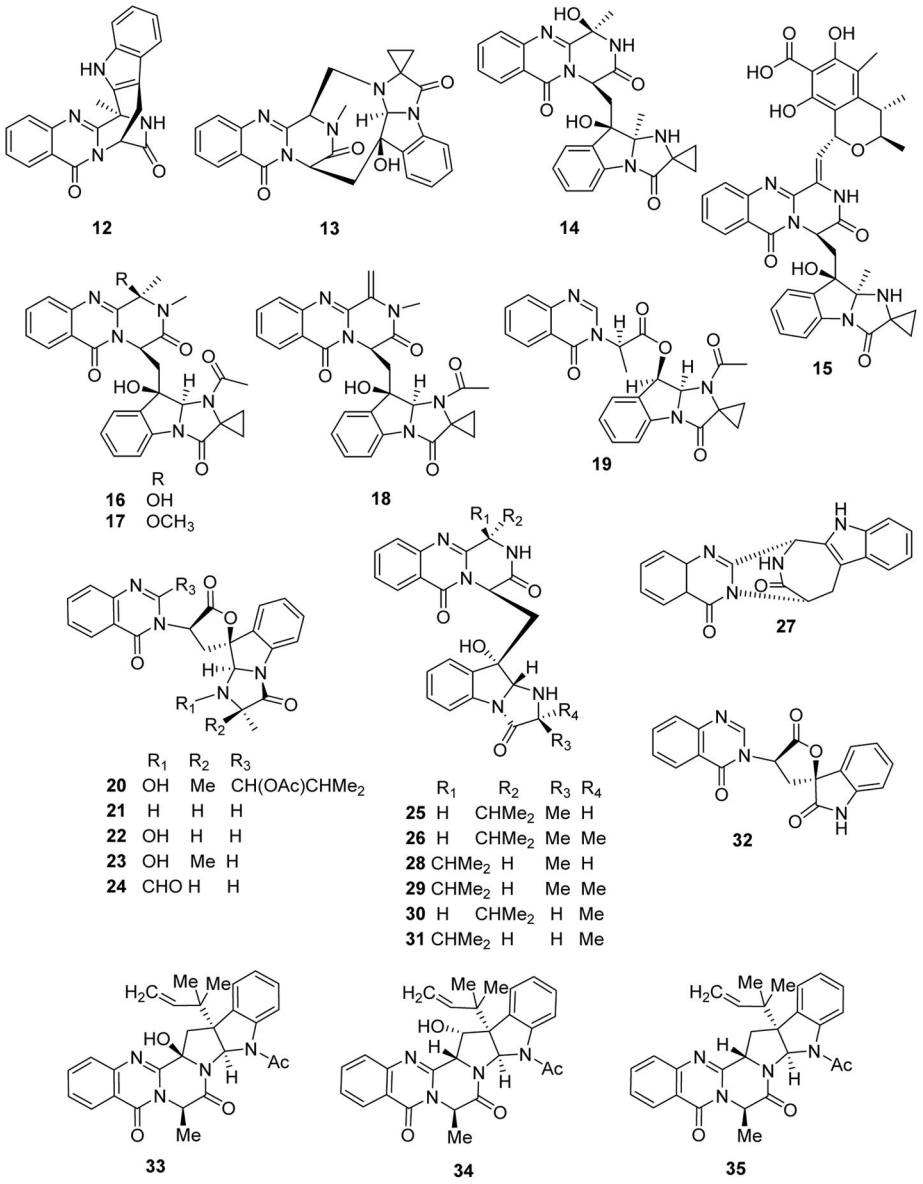
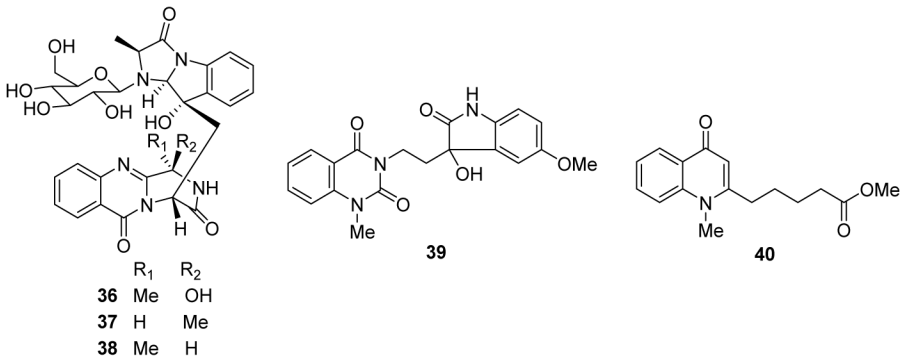


Figure 3.
Chemical structures of compounds **12–35**



	R_1	R_2
36	Me	OH
37	H	Me
38	Me	H

Figure 4.
Chemical structures of compounds **36–40**

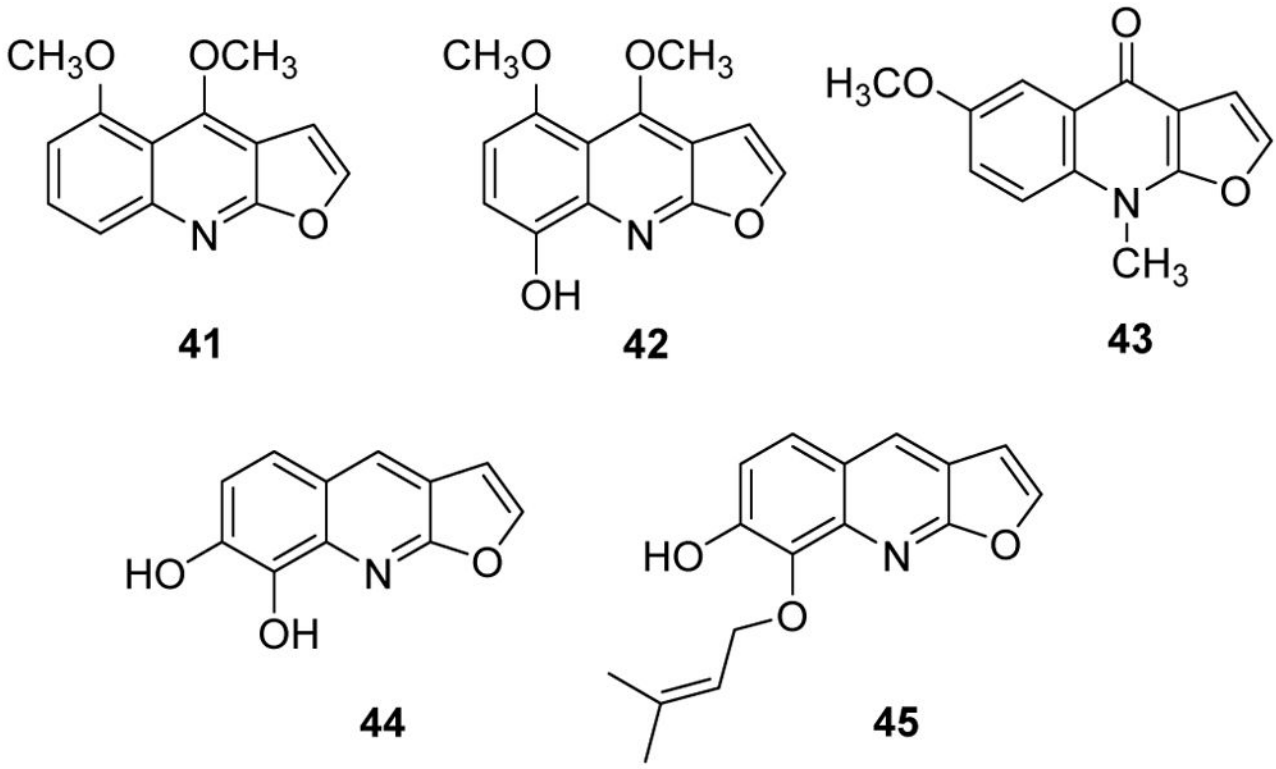


Figure 5.
Chemical structures of compounds **41–45**

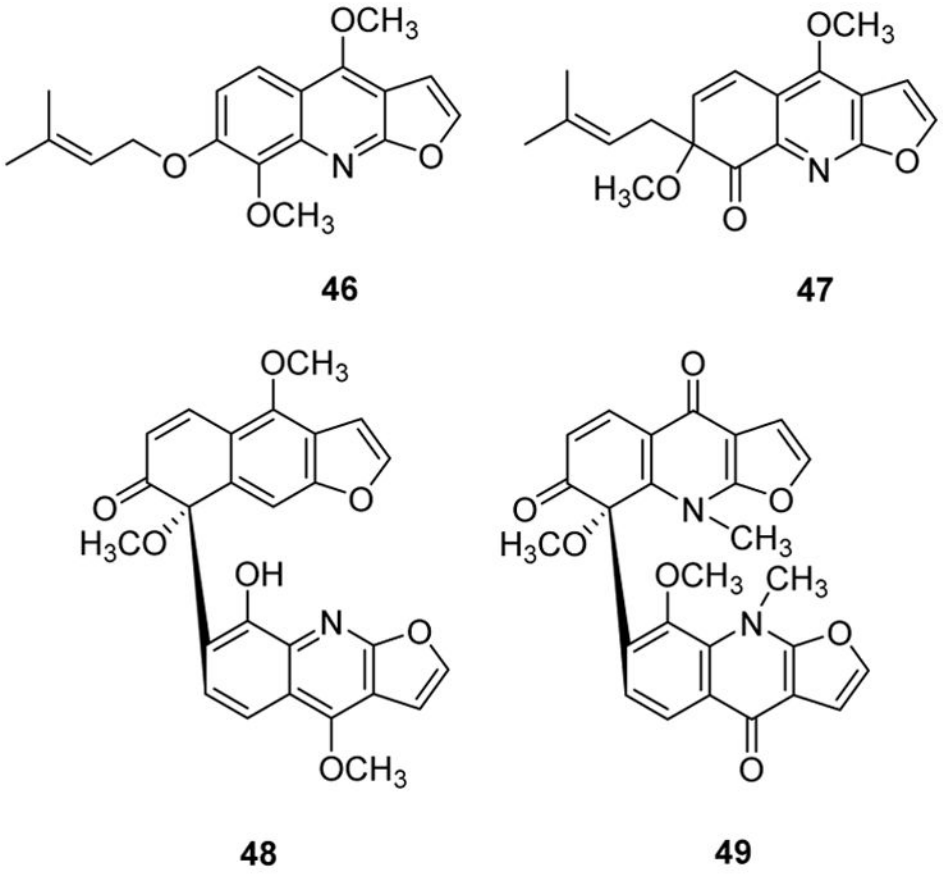


Figure 6.
Chemical structures of compounds **46–49**

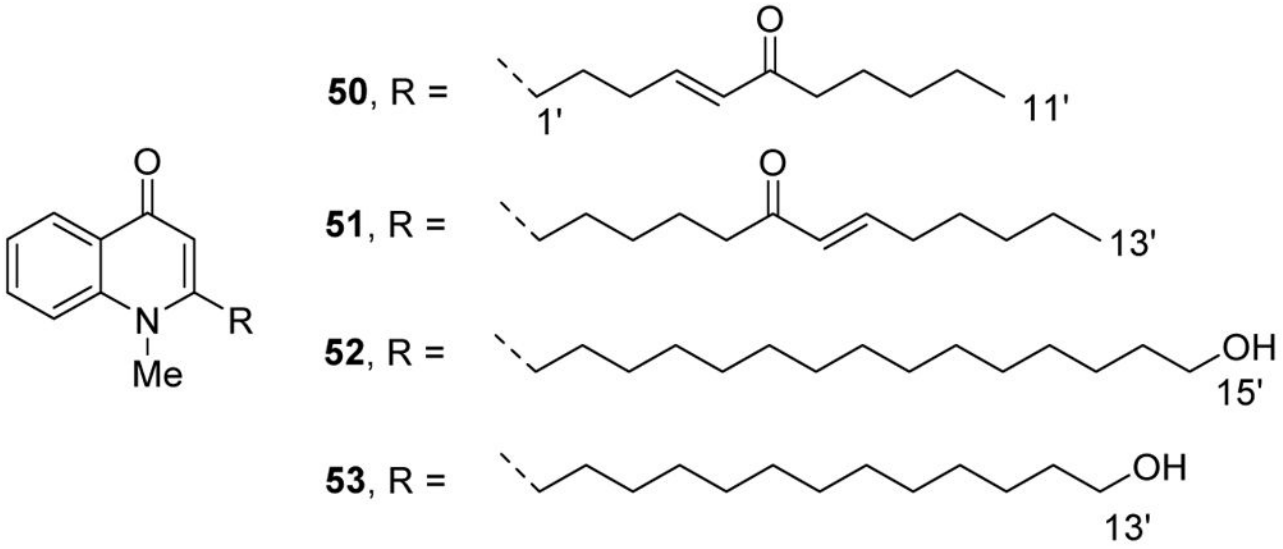


Figure 7.
Chemical structures of compounds **50–53**

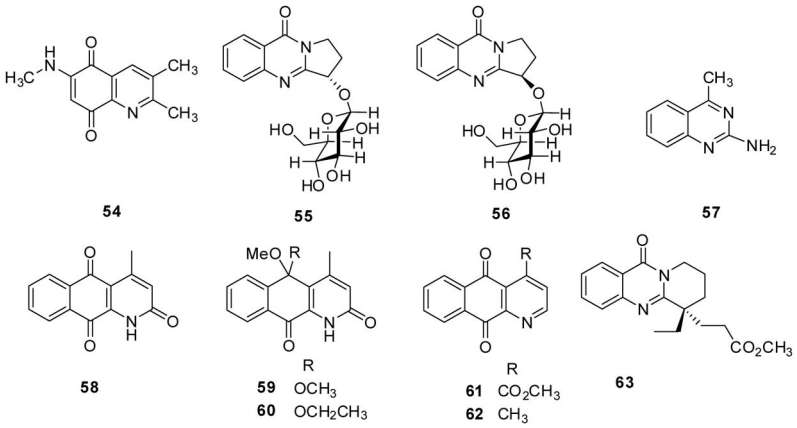


Figure 8.
Chemical structures of compounds **54–63**

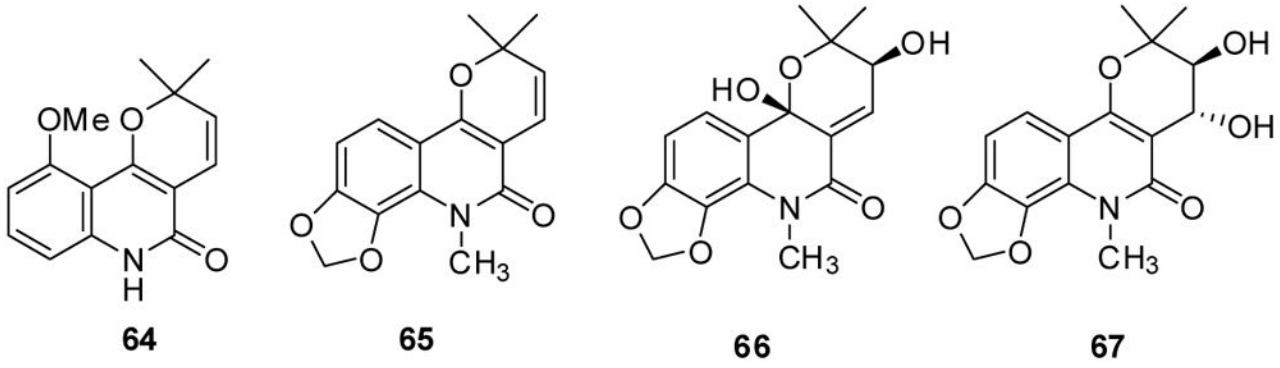


Figure 9.
Chemical structures of compounds **64–67**

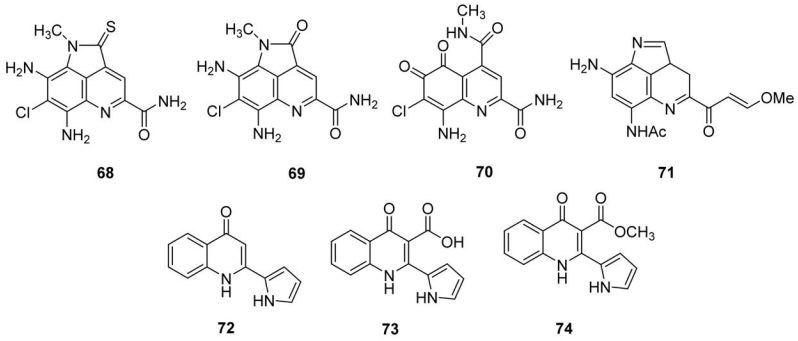


Figure 10.
Chemical structures of compounds **68–74**

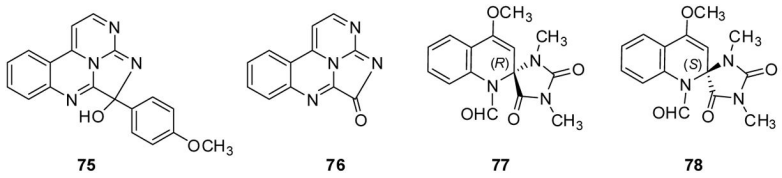


Figure 11.
Chemical structures of compounds **75–78**

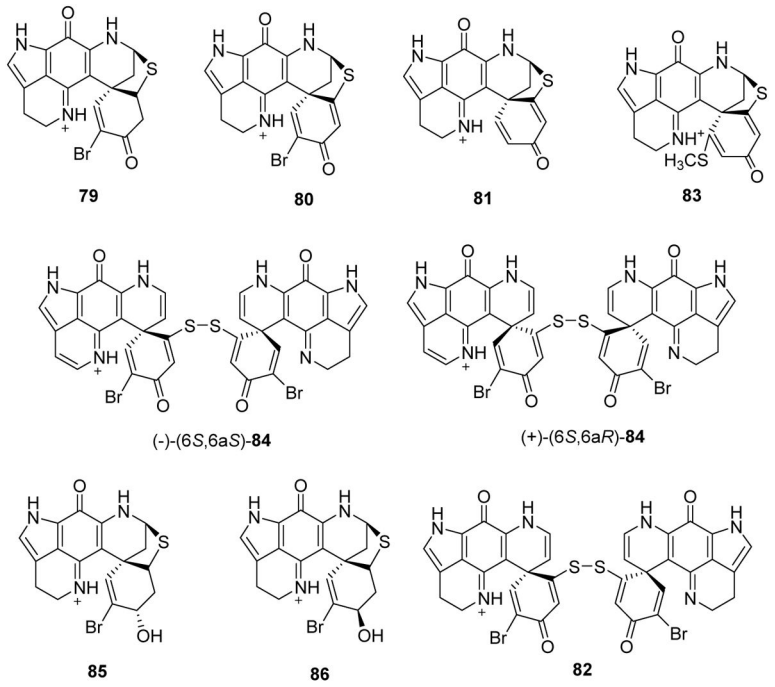


Figure 12.
Chemical structures of compounds **79–86**

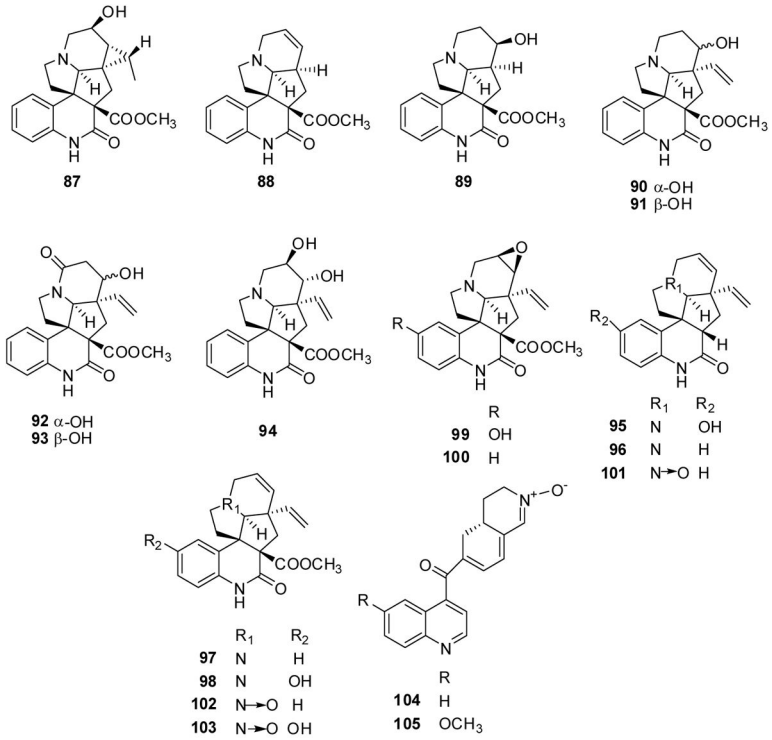


Figure 13.
Chemical structures of compounds **87–105**

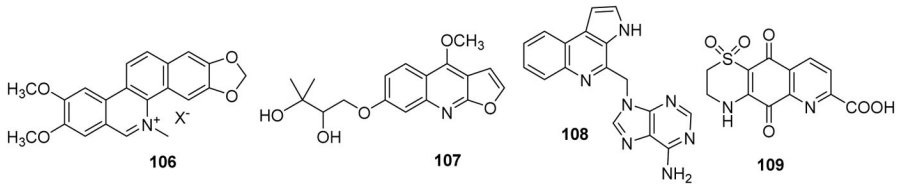


Figure 14.
Chemical structures of compounds **106–109**

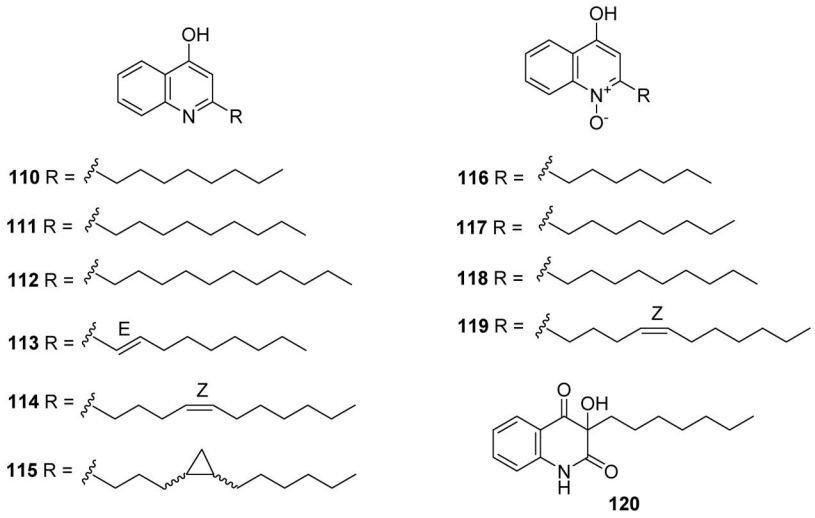


Figure 15.
Chemical structures of compounds **110–120**

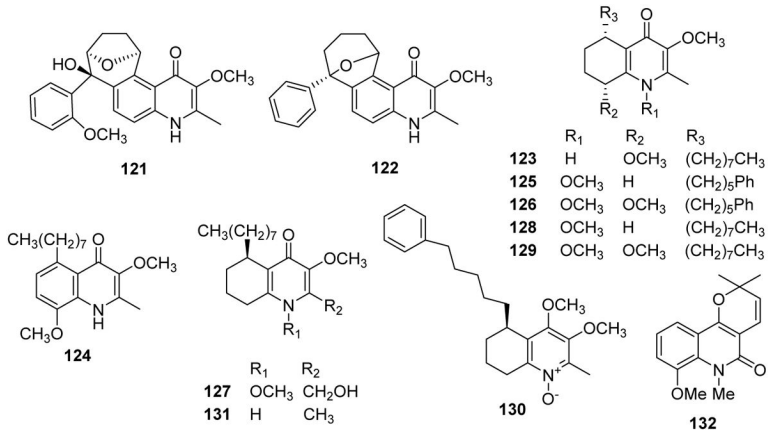


Figure 16.
Chemical structures of compounds **121–132**

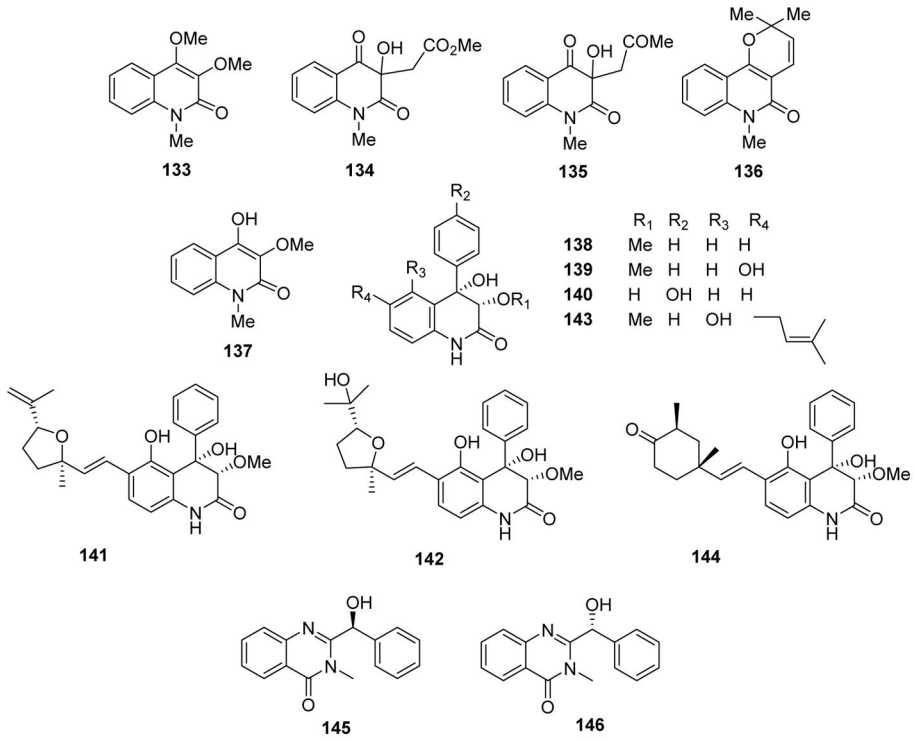


Figure 17.
Chemical structures of compounds **133–146**

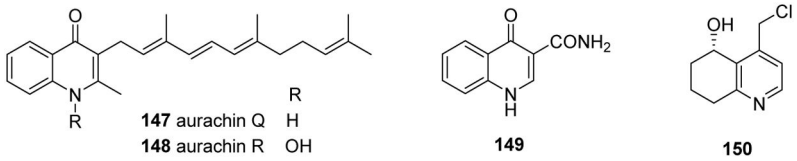


Figure 18.
Chemical structures of compounds **147–150**

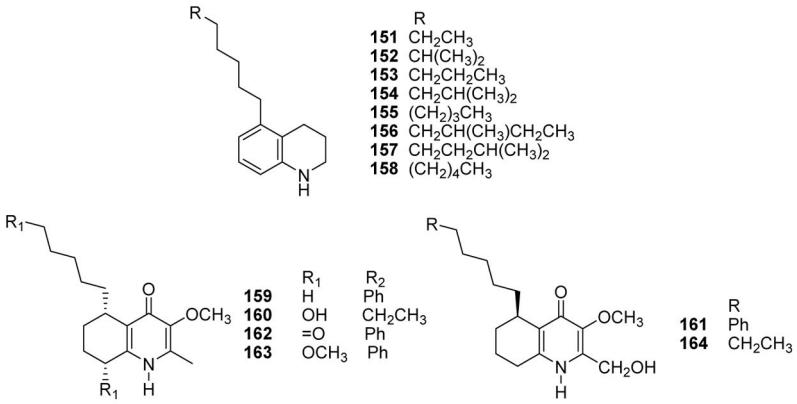


Figure 19.
Chemical structures of compounds **151–158**

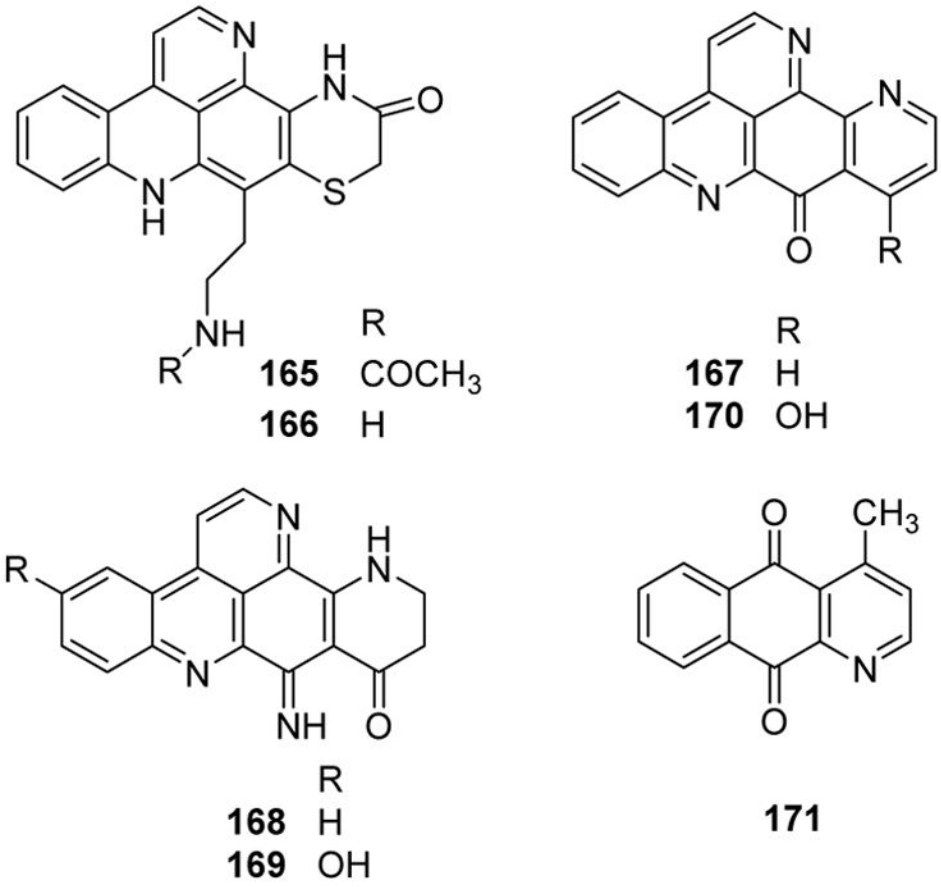


Figure 20.
Chemical structures of compounds **165–171**

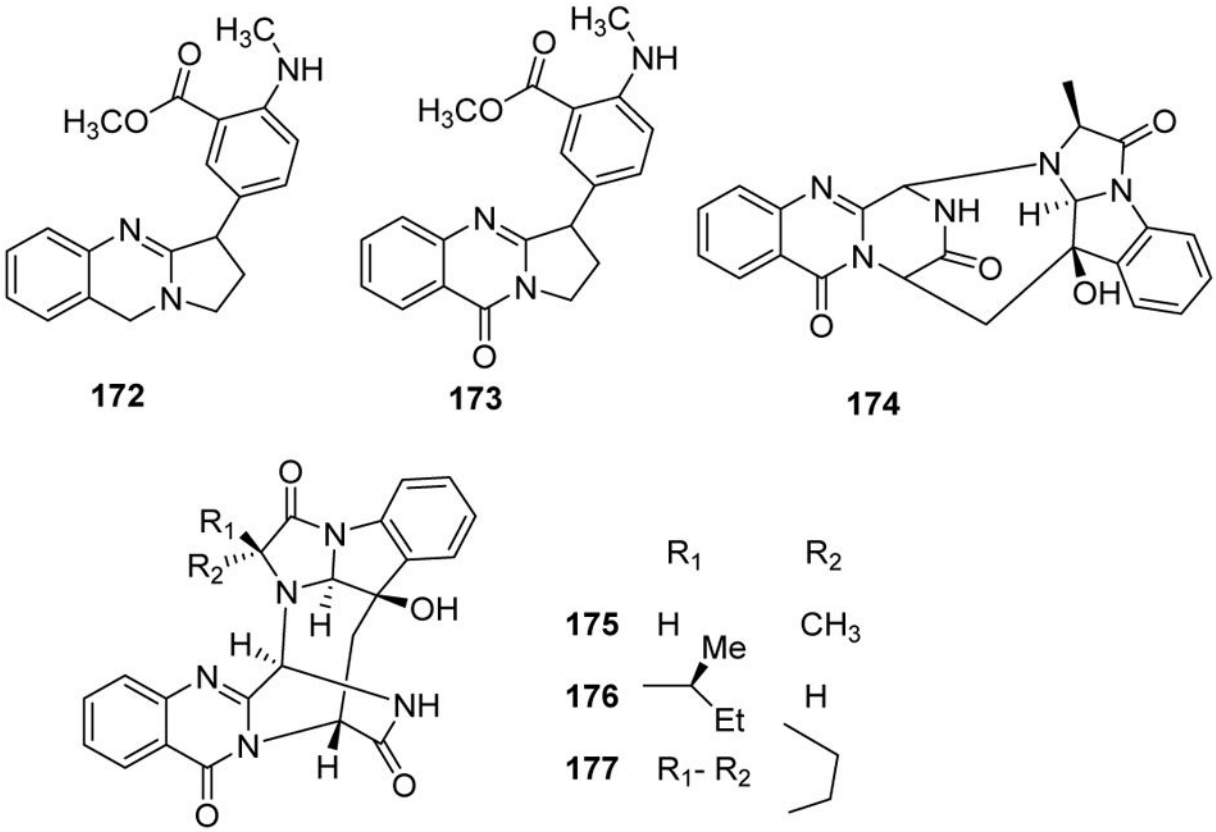
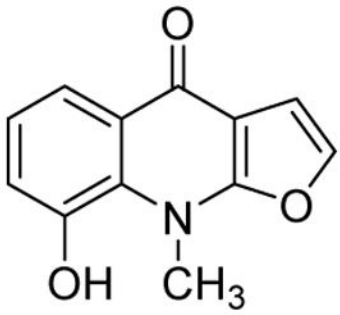
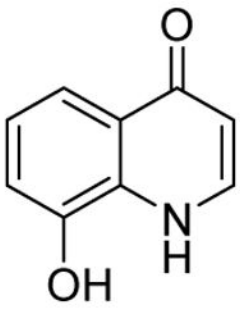


Figure 21.
Chemical structures of compounds **172–177**



178



179

Figure 22.
Chemical structures of compounds **178** and **179**

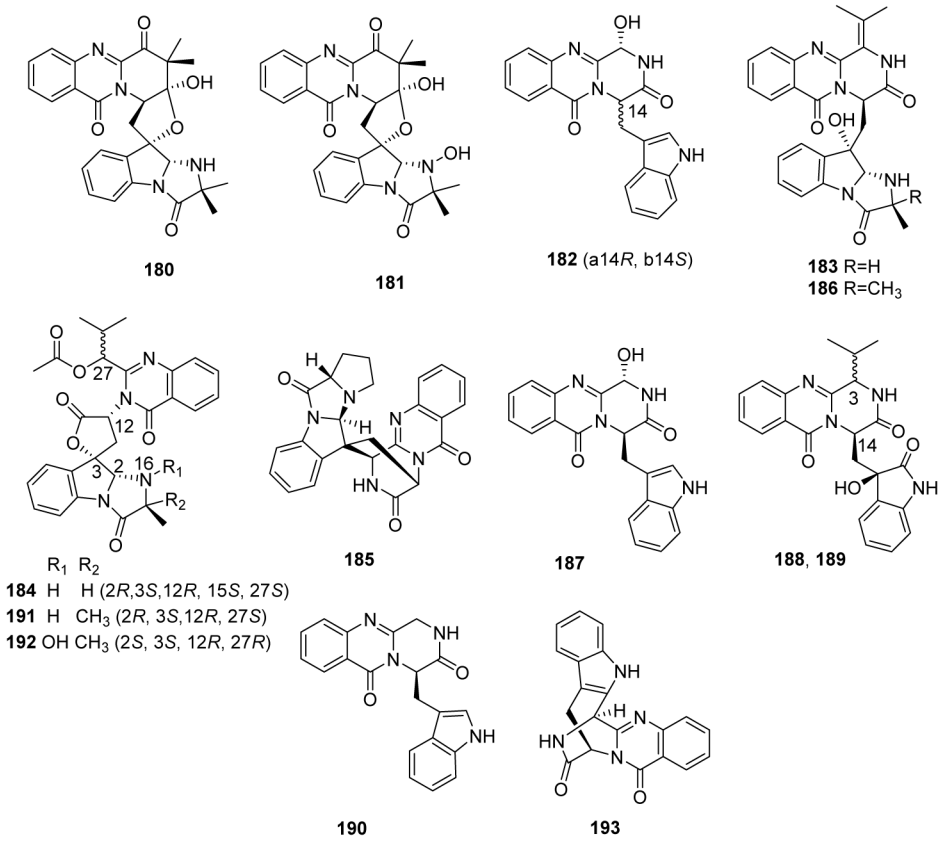


Figure 23.
Chemical structures of compounds **180–193**

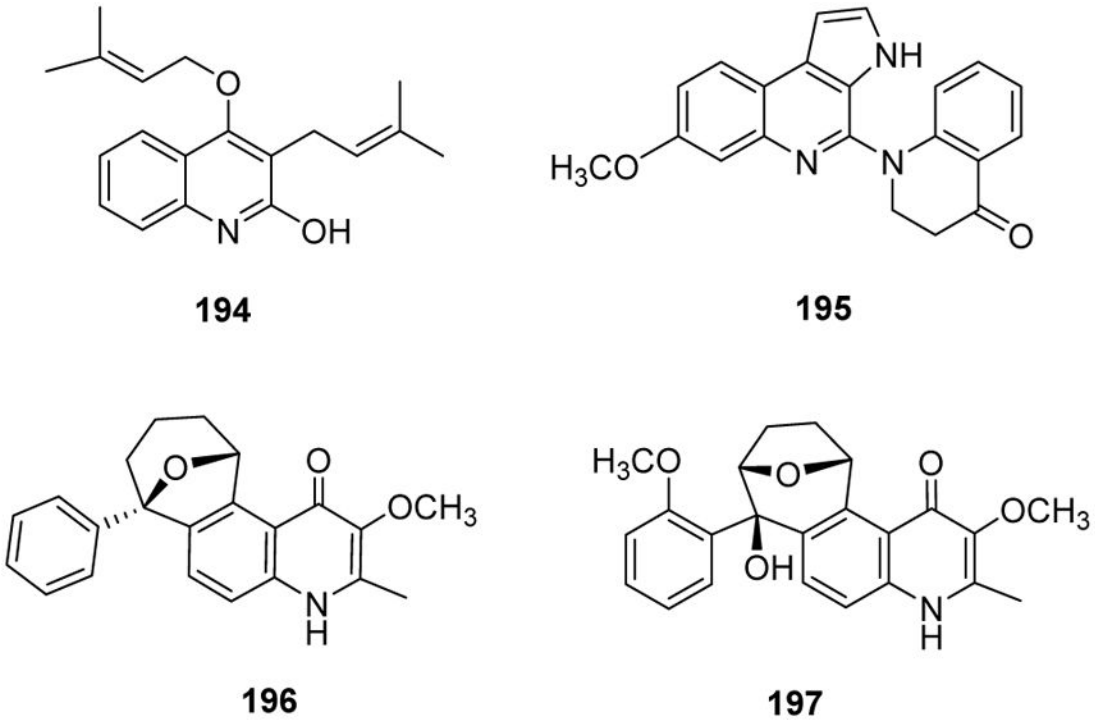
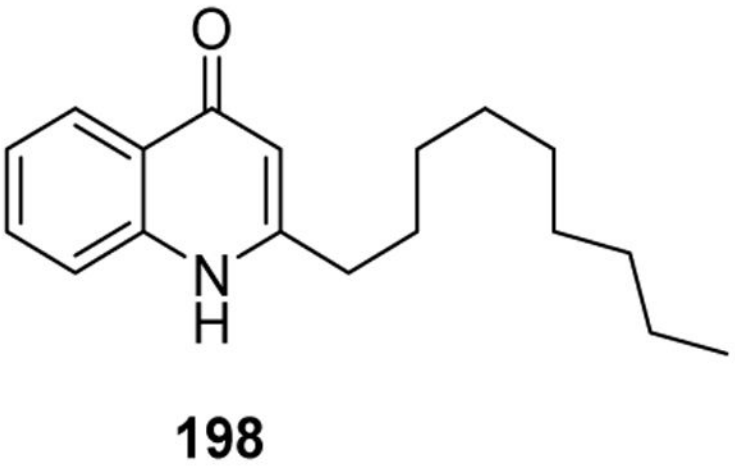


Figure 24.
Chemical structures of compounds **194–197**



198

Figure 25.
Chemical structures of compounds **198**

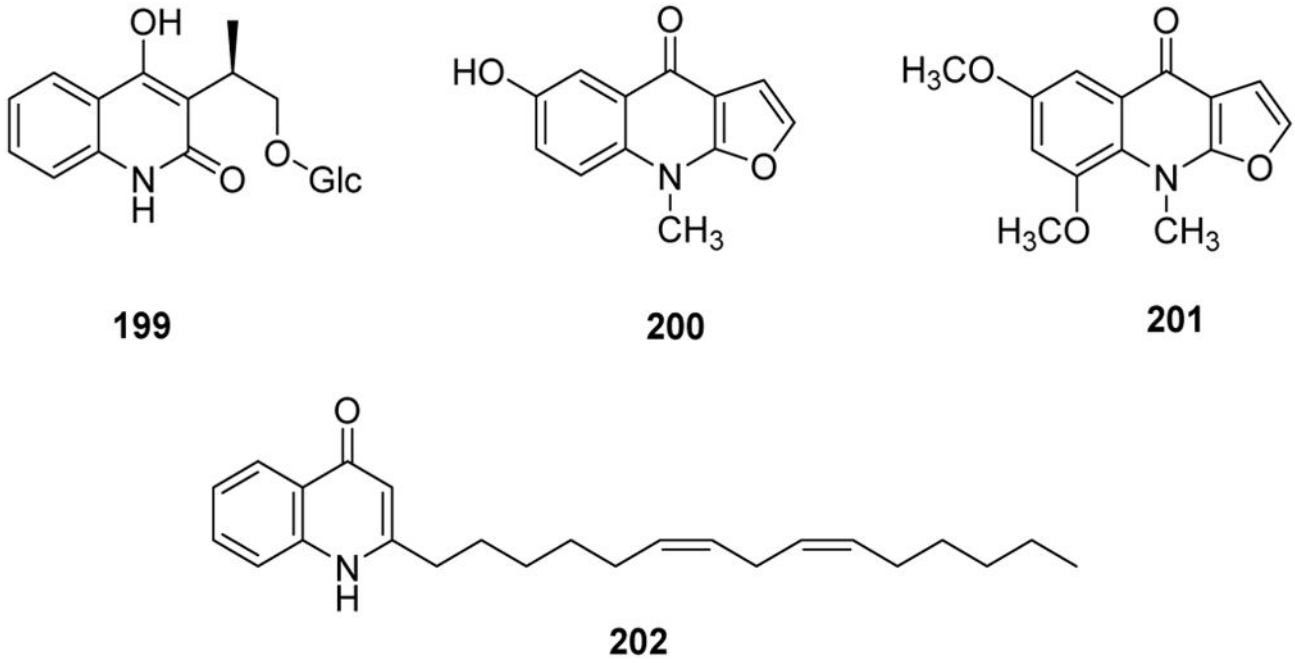


Figure 26.
Chemical structures of compounds **199–202**

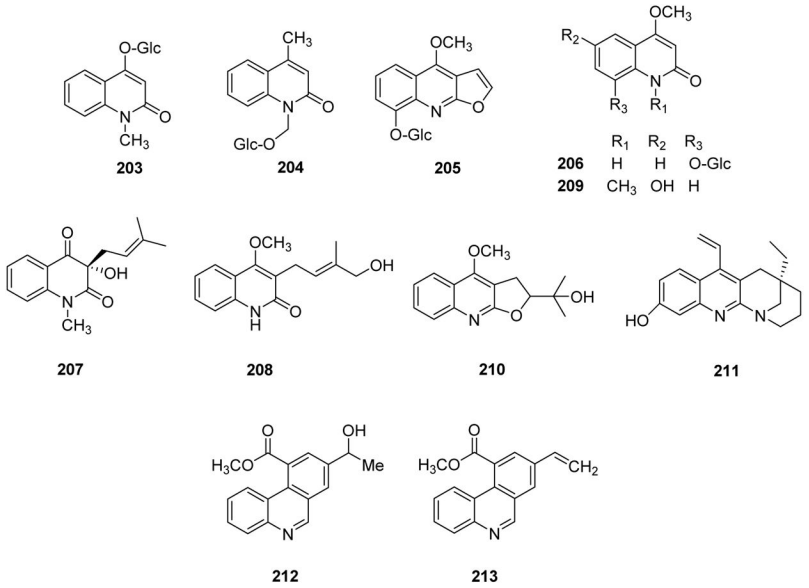


Figure 27.
Chemical structures of compounds **203–213**

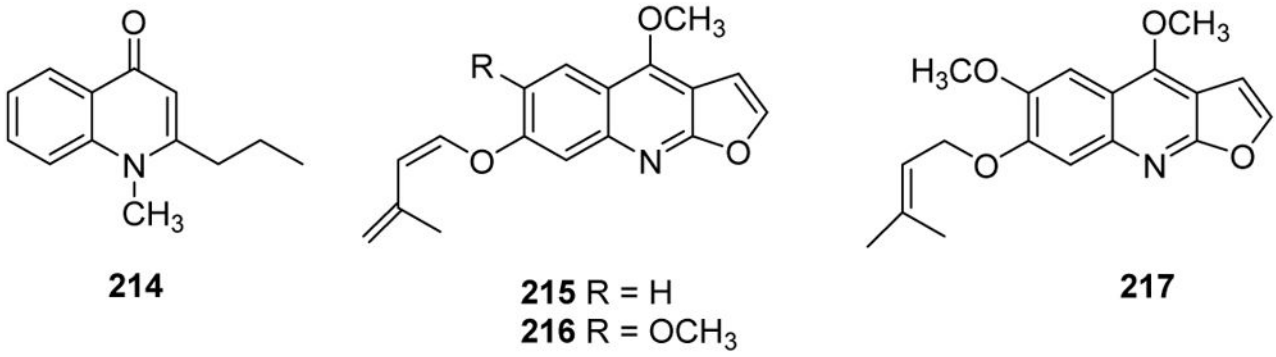


Figure 28.
Chemical structures of compounds **214–217**

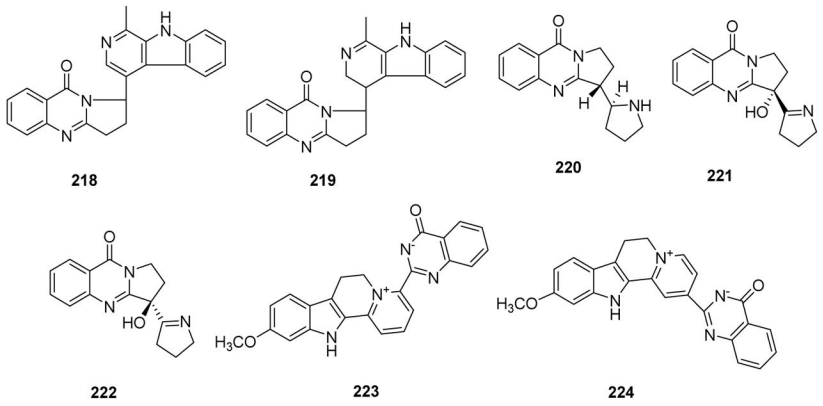


Figure 29.
Chemical structures of compounds **218–224**

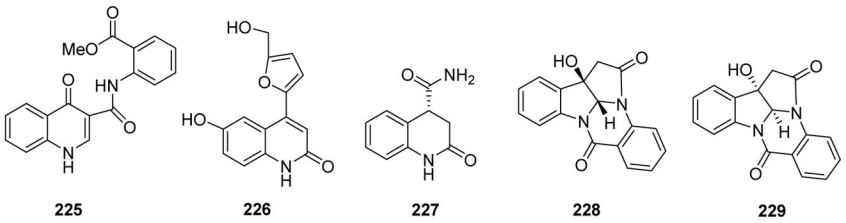


Figure 30.
Chemical structures of compounds **225–229**

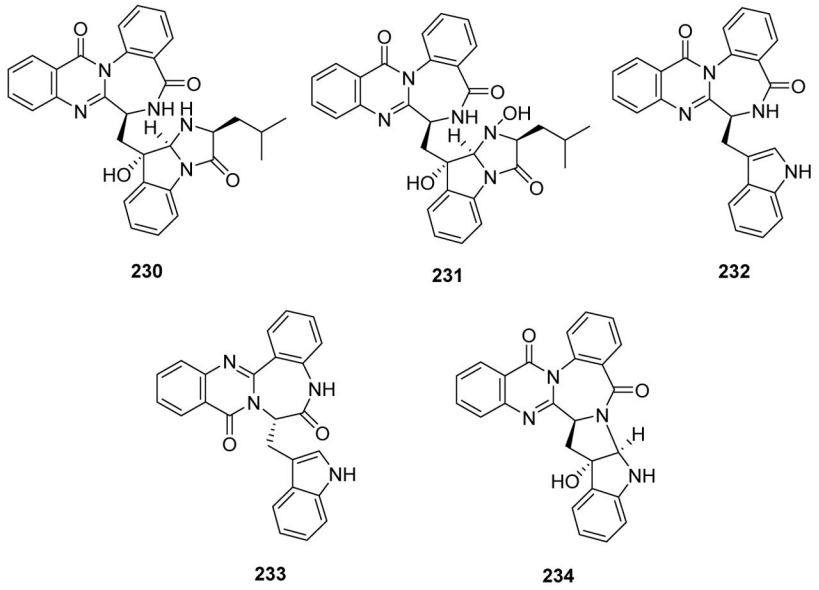
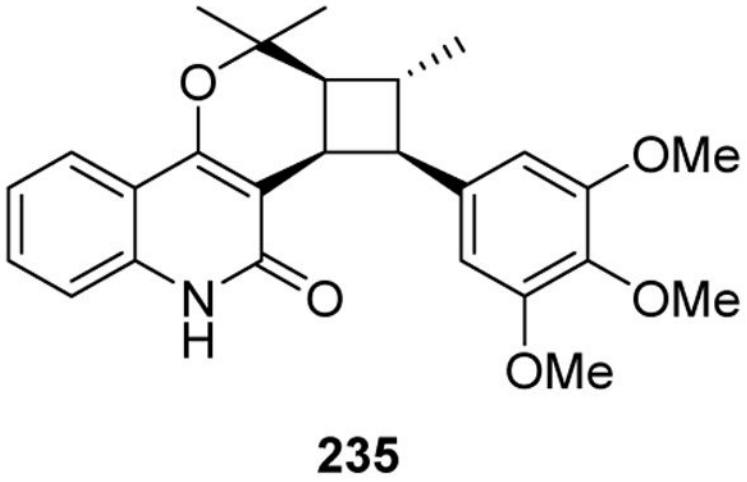


Figure 31.
Chemical structures of compounds **230–234**



235

Figure 32.
Chemical structures of compounds **235**

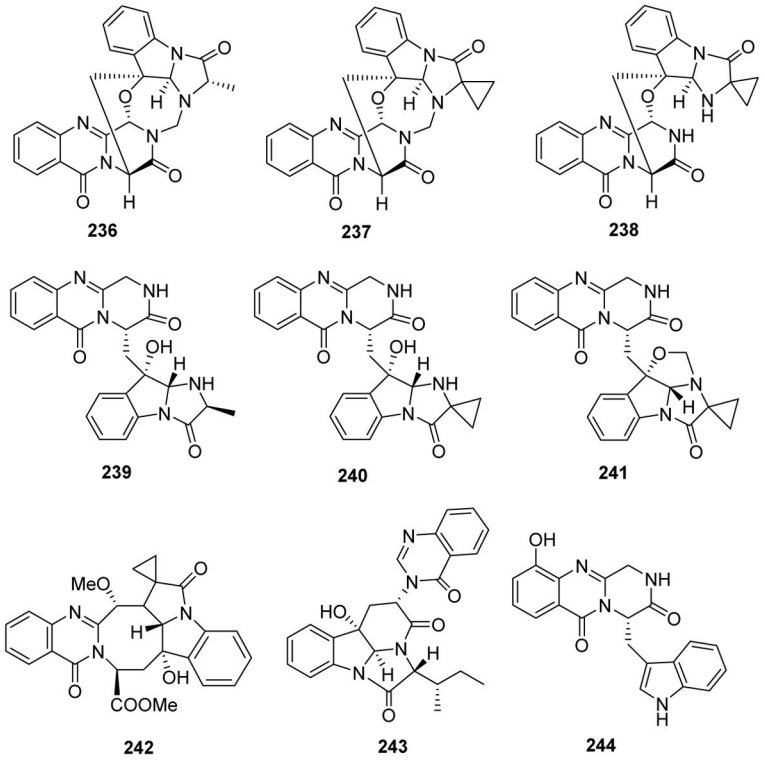
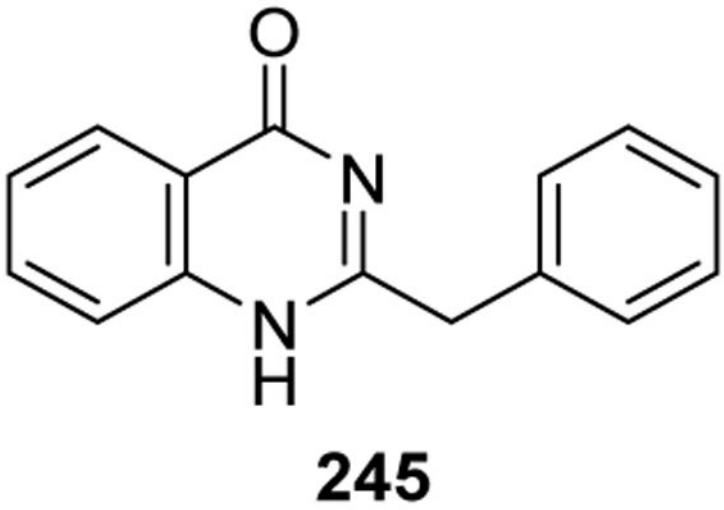
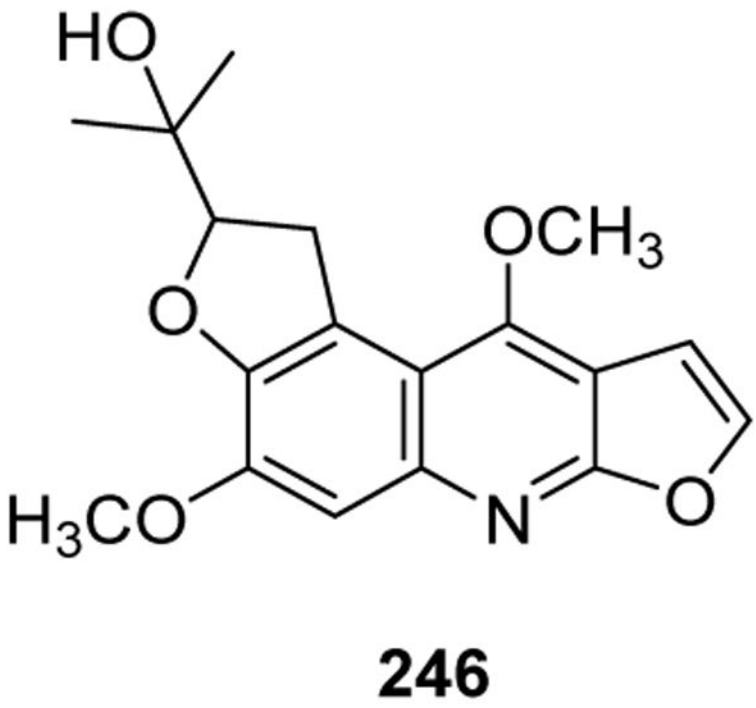


Figure 33.
Chemical structures of compounds **236–244**



245

Figure 34.
Chemical structures of compounds **245**



246

Figure 35.
Chemical structures of compounds **246**

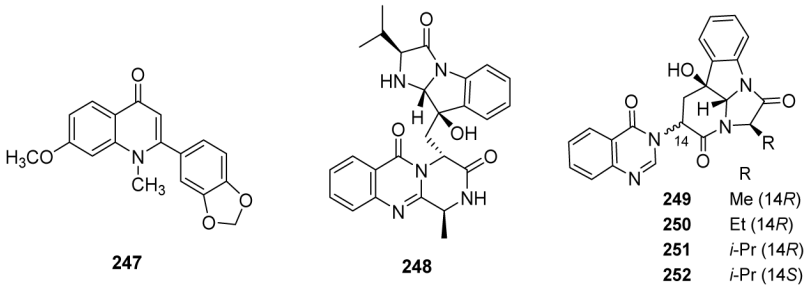


Figure 36.
Chemical structures of compounds **247–252**

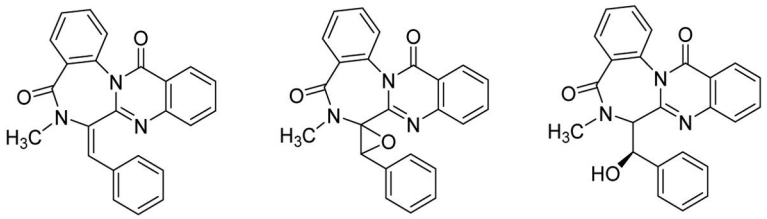


Figure 37.
Chemical structures of compounds **253–255**

Table 1

Quinoline and quinazoline alkaloids isolated during 2009–2016

No.	Compound	Species	Ref.
1	Leucophyllidine	*Leuconotis griffithii*	15,16
2	Angustifonine A	*Bousigonia angustifolia*	17
3	Angustifonine B		
4	Meloyunine B	*Melodinus yunnanensis*	18
5	Meloyunine A		
6	Meloyunine C		
7	14,15-Dehydromelohenine B		
8	Δ^{14}-Vincamenine		
9	(*7R,8S*)-7-Hydroxy-8-methoxyrutaecarpine	*Evodia rutaecarpa*	20,21
10	(*7R,8S*)-7-Hydroxy-8-ethoxyrutaecarpine		
11	2-Methoxy-7,8-dehydroruteacarpine	*Zanthoxylum poggei*	20,21
12	Fumiquinazoline J	*Aspergillus sp.*	25,26
13	Fumiquinazoline K		
14	Fumiquinazoline L		
15	Fumiquinazoline M		
16	Fumiquinazoline N		
17	Fumiquinazoline O		
18	Fumiquinazoline P		
19	Tryptoquivaline K	*Neosartorya siamensis*	27
20	Tryptoquivaline		
21	Tryptoquivaline F		
22	Tryptoquivaline H		
23	Tryptoquivaline L		
24	Tryptoquivaline O		
25	Fiscalin A		

No.	Compound	Species	Ref.
26	Fiscalin C		
27	Sartorymensin		
28	*Epi*-fiscalin A		
29	*Epi*-fiscalin C		
30	Neofiscalin A		
31	*Epi*-neofiscalin A		
32	3′-(4-Oxoquinazolin-3-yl)spiro[1*H*-indole-3,5′-oxolane]-2,2′-dione		
33	15b-β-Hydroxy-5*N*-acetylardeemin	*Aspergillus terreus*	28
34	16α-Hydroxy-5*N*-acetylardeemin		
35	5*N*-Acetylardeemin		
36	Fumigatoside B	*Aspergillus fumigatus*	29
37	Fumigatoside C		
38	Fumigatoside D		
39	Evollionine B	*Evodia rutaecarpa*	30
40	Evollionine C		
41	5-Methoxydictamnine	*Toddalia asiatica*	33
42	5-Methoxyrobustine	*Dictamnus angustifolius*	35
43	Isopteleine		
44	Aegelbine A	*Aegle marmelos*	37
45	Aegelbine B		
46	7-Isopentenyloxy-γ-fagarine	*Haplophyllum canaliculatum*	38
47	Perfamine		
48	Anstifoline A	*Dictamnus angustifolius*	39
49	Anstifoline B		
50	1-Methyl-2-[6-carbonyl-(*E*)-4-undecenyl]-4(1*H*)-quinolone	*Evodia rutaecarpa*	42
51	1-Methyl-2-[6-carbonyl-(*E*)-7-tridecenyl]-4(1*H*)-quinolone		
52	1-Methyl-2-[15-hydroxyl-pentadecenyl]-4(1*H*)-quinolone		

No.	Compound	Species	Ref.
53	1-Methyl-2-[13-hydroxyl-tridecenyl]-4(1*H*)-quinolone		
54	Sannanine	*Streptomyces sannanensis*	56
55	(*S*)-Vasicinone-1-*O*-β-D-glucopyranoside	*Peganum harmala*	57
56	(*R*)-Vasicinone-1-*O*-β-D-glucopyranoside		
57	4-Methyl-2-quinazolinamine	*Streptomyces sp.* GS DV232	58
58	Marcanine A	*Polyalthia plagioneura*	59
59	Saprosmine A	*Saprosma hainanense*	60
60	Saprosmine B		
61	4-Methoxycarbonyl-5,10-benzoquinolinequinone		
62	Cleistopholine		
63	Leucomidine C	*Leuconotis griffithii*	61
64	Haplophytin A	*Haplophyllum acutifolium*	62
65	Stauranthine	*Stauranthus perforatus*	63
66	3′,6′-Dihydroxy-3′,6′-dihydrostauranthine		
67	*trans*-3′,4′-Dihydroxy-3′,4′-dihydrostauranthine		
68	Ammosamide A	*Streptomyces variabilis*	65
69	Ammosamide B		
70	Ammosamide D	*Streptomyces variabilis*	67
71	Lymphostin	*Streptomyces sp.*	64
72	Penicinoline E	*Penicillium sp.* ghq208	68,69
73	Methyl-penicinoline		
74	Penicinoline		
75	Eudistidine A	*Eudistoma sp.*	70

No.	Compound	Species	Ref.
76	Eudistidine B		
77	(+)-Spiroreticulatine	*Fascaplysinopsis reticulate*	71
78	(−)-Spiroreticulatine		
79	(+)-Discorhabdin/prianosin A	*Latrunculia sp.*	72
80	(+)-Discorhabdin B		
81	(+)-Discorhabdin G*/I		
82	(-)-Discorhabdin W		
83	(+)-(*6R,8S*)-1-Thiomethyldiscorhabdin G*/I		
84	16a,17a-Dehydrodiscorhabdin W		
85	(+)-(*3S,5R,6S,8S*)-3-Dihydrodiscorhabdin A		
86	(+)-(*3R,5R,6S,8S*)-3-Dihydrodiscorhabdin A		
87	Melohemsine A	*Melodinus hemsleyanus*	73
88	Melohemsine B		
89	Melohemsine C		
90	Melohemsine D		
91	Melohemsine E		
92	Melohemsine F		
93	Melohemsine G		
94	Melohemsine H		
95	Melohemsine I		
96	Meloscine		
97	Sandine		
98	10-Hydroxyscandine		
99	10-Hydroxy-14,15-β-epoxysandine		
100	14,15-β-Epoxysandine		
101	Meloscine N_4-oxide		
102	Scandine N_4-oxide		
103	Melodinine U		
104	Cincholenine A	*Cinchona ledgeriana*	74

No.	Compound	Species	Ref.
105	Cincholenine B		
106	Nitidine	*Toddalia asiatica*	86
107	Evoxine	*Teclea gerrardii*	87
108	Aplidiopsamine A	*Aplidiopsis condluata*	88
109	Ascidiathiazone A	*Aplidium sp.*	89
110	2-*n*-Octyl-4-hydroxyquinoline-4-hydroxyquinoline	*Pseudomonas aeruginosa* BCC7601	90
111	2-*n*-Nonyl-4-hydroxyquinoline		
112	2-*n*-Undecyl-4-hydroxyquinoline		
113	2-(*E*)-Non-1′-enyl-4-hydroxyquinoline		
114	2-((*Z*)-Undec-4′-enyl)-4-hydroxyquinoline		
115	2-(3′-(2′-Hexylcyclopropyl)propyl)-4-hydroxyquinoline		
116	*n*-Heptyl-4-hydroxyquinoline		
117	2-*n*-Octyl-4-hydroxyquinoline *N*-oxide		
118	2-*n*-Nonyl-4-hydroxyquinoline *N*-oxide		
119	2-((*Z*)-Undec-4′-enyl)-4-hydroxyquinoline *N*-oxide		
120	2-*n*-Heptyl-3-hydroxyquinoline-2,4(1*H*,3*H*)-dione		
121	Waltherione A	*Waltheria indica*	94,95
122	Waltherione C		
123	Waltherione E		
124	Waltherione F		
125	Waltherione G		
126	Waltherione H		
127	Waltherione I		
128	Waltherione J		
129	Waltherione K		
130	Waltherione L		
131	8-Deoxoantidesmone		
132	*N*-Methyl-8-methoxyflindersine	*Raputia heptaphylla*	103

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No.	Compound	Species	Ref.
133	*N*-Methylswietenidine B	*Micromelum falcatum*	104
134	Methyl 2-(3-hydroxy-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinolin-3-yl)-acetate		
135	3-Hydroxy-1-methyl-3-(2-oxopropyl)-quinoline-2,4(1*H*,3*H*)-dione		
136	*N*-Methylflindersine		
137	4-Hydroxy-3-methoxy-1-methyl-2(1*H*)-quinolinone		
138	6-Deoxyaflaquinolone E	*Aspergillus nidulans* MA-143	105
139	Isoaflaquinolone E		
140	14-Hydroxyaflaquinolone F		
141	Aniduquinolone A		
142	Aniduquinolone B		
143	Aniduquinolone C		
144	Aflaquinolone A		
145	2-[(*S*)-Hydroxy(phenyl)methyl]-3-methyl-quinazolin-4(3*H*)-one	*Talaromyces sp.* Cf 16	106
146	2-[(*R*)-Hydroxy(phenyl)methyl]-3-methyl-quinazolin-4(3*H*)-one		
147	Aurachin Q	*Rhodococcus sp.* Acta 2259	119
148	Aurachin R		
149	4-Oxo-1,4-dihydroquinoline-3-carboxamide	*Nocardiopsis terrae* YIM 90022	120
150	5-Hydroxy-4-(chloromethyl)-5,6,7,8-tetrahydroquinoline	Belize extract	121
151	5aTHQ-7n	Combined culture of *Streptomyces nigrescens* HEK616 & *Tsukamurella pulmonis* TP-B0596	122
152	5aTHQ-8i		
153	5aTHQ-8n		
154	5aTHQ-9i		
155	5aTHQ-9n		
156	5aTHQ-10a		
157	5aTHQ-10i		
158	5aTHQ-10n		

No.	Compound	Species	Ref.
159	Waltherion M	*Waltheria indica*	123
160	Waltherion N		
161	Waltherion O		
162	Waltherion P		
163	Waltherion Q		
164	5(*R*)-Vanessine		
165	Shermilamine B	*Cystodytes dellechiajei*	124
166	*N*-Deacetylshermilamine B		
167	11-Hydroxyascididemin		
168	Cystodimine A		
169	Cystodimine B		
170	Ascididemin		
171	Cleistopholine	*Annona salzmannii*	125
172	Adhatodine	*Justicia adhatoda*	130
173	Anisotine		
174	Cottoquinazoline A	*Aspergillus versicolor*	131
175	Cottoquinazoline B		
176	Cottoquinazoline C		
177	Cottoquinazoline D		
178	8-Hydroxy-9-methyl-furo[2,3-*b*]quinolin-4(9*H*)-one	*Dictamnus angustifolius*	160
179	8-Hydroxy-4-quinolone	*Scolopendra subspinipes mutilans*	161
180	Neosartoryadin A	*Neosartorya udagawae* HDN13-313	163
181	Neosartoryadin B		
182	Oxoglyantrypine	*Cladosporium sp.* PJX-41	164
183	Norquinadoline A		
184	Deoxynortryptoquivaline		
185	Quinadoline B		

No.	Compound	Species	Ref.
186	Quinadoline A		
187	3-Hydroglyantrypine		
188	Cladoquinazoline		
189	*epi*-Cladoquinazoline		
190	Glyantrypine		
191	Deoxytrytoquivaline		
192	CS-C		
193	Prelapatin B		
194	3-(3-Methylbut-2-enyl)-4-(3-methylbut-2-enyloxy)-quinolin-2-ol	*Evodia roxburghiana*	165
195	Trigonoine B	*Trigonostemon lii*	167
196	Waltherione B	*Melochia odorata*	168
197	Waltherione D		
198	Pseudane IX	*Ruta angustifolia*	169
199	3-[1β-Hydroxy-2-(β-D-glucopyranosyloxy)-ethyl)-4-methoxy-2(1*H*)-quinolinone	*Dictamnus dasycarpus*	171
200	Dictangustine A		
201	Isomaculosidine		
202	2-[(6*Z*,9*Z*)-Pentadeca-6,9-dienyl]quinolin-4(1*H*)-one	*Tetradium ruticarpum*	173
203	Clausenaside D	*Clausena lansium*	175
204	Clausenaside E		
205	Clausenaside F		
206	4-Methoxy-8-*O*-β-D-glucopyranosyloxy-2(1*H*)-quinolinone		
207	Clausenaside G		
208	Clausenaside H		
209	Integriquinolone		
210	Ribalinine		
211	Eucophylline	*Leuconotis eugenifolius*	176
212	Scholarisine II	*Alstonia scholaris*	177

No.	Compound	Species	Ref.
213	Scholarisine I		
214	Leptomerine	*Esenbeckia leiocarpa*	184
215	Leptanoine A	*Evodia lepta*	185,186
216	Leptanoine B		
217	Leptanoine C		
218	Nigellastrine I	*Peganum nigellastrum*	191
219	Nigellastrine II		
220	Peganumine D	*Peganum harmala*	192
221	*S*-Peganumine E		
222	*R*-Peganumine E		
223	Peganumine F		
224	Peganumine G		
225	Methyl 2-(4-oxo-1,4-dihydroquinoline-3-carboxamido)benzoate	*Isatis indigotica*	196
226	6-Hydroxy-4-(5-hydroxymethylfuran-2-yl)-quinolin-2(1*H*)-one		
227	(+)-(*R*)-2-Oxo-1,2,3,4-tetrahydroquinoline-4-carboxamide		
228	(+)-3-Hydroxy-2*H*-pyrrolo[2,3-*b*]indolo[5,5a,6-*b,a*]-quinazoline-9-(8*H*),7′-dione		
229	(−)-3-Hydroxy-2*H*-pyrrolo[2,3-*b*]indolo[5,5a,6-*b,a*]-quinazoline-9-(8*H*),7′-dione		
230	Asperlicin	*Aspergillus alliaceus*	199
231	Asperlicin B		
232	Asperlicin C		
233	Asperlicin D		
234	Asperlicin E		
235	Euodenine A	*Evodia asteridula*	206
236	Versiquinazoline A	*Aspergillus versicolor* LZD-14-1	208
237	Versiquinazoline B		
238	Versiquinazoline C		
239	Versiquinazoline D		

No.	Compound	Species	Ref.
240	Versiquinazoline E		
241	Versiquinazoline F		
242	Versiquinazoline G		
243	Versiquinazoline H		
244	Versiquinazoline I		
245	Glycosin	*Rhizophora apiculata*	209
246	Choisyine	*Choisya* Aztec-Pearl	211
247	Punaravine	*Boerhaavia diffusa*	213,214
248	Fumiquinazoline S	*Aspergillus sp.*	216
249	Isochaetominine A		
250	Isochaetominine B		
251	Isochaetominine C		
252	14-*Epi*-isochaetominine C		
253	Benzomalvin E	*Penicillium sp.* FN070315	225
254	Benzomalvin B		
255	Benzomalvin C		