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Biologically active quinoline and quinazoline alkaloids part I

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Abstract

Quinoline and quinazoline alkaloids, two important classes of *N*-based heterocyclic compounds, have attracted tremendous attention from researchers worldwide since the 19th century. Over the past 200 years, many compounds from these two classes were isolated from natural sources, and most of them and their modified analogs possess significant bioactivities. Quinine and camptothecin are two of the most famous and important quinoline alkaloids, and their discoveries opened new areas in antimalarial and anticancer drug development, respectively. In this review, we survey the literature on bioactive alkaloids from these two classes and highlight research achievements prior to the year 2008 (Part I). Over 200 molecules with a broad range of bioactivities, including antitumor, antimalarial, antibacterial and antifungal, antiparasitic and insecticidal, antiviral, antiplatelet, anti-inflammatory, herbicidal, antioxidant and other activities, were reviewed. 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

bioactivities; camptothecin; quinazoline alkaloids; quinine; quinoline alkaloids

1 | INTRODUCTION

Quinoline alkaloids are important *N*-based heterocyclic aromatic compounds with a broad range of bioactivities. They have attracted significant attention from researchers over the past 200 years.[1] After the quinoline alkaloid quinine (**1**) (Fig. 1) was isolated from the bark of the Cinchona tree in 1820, it replaced the crude bark in the treatment of malaria.[2,3]

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Although **1** has relatively low efficacy and tolerability, it played a historical role in the development of quinoline alkaloids, and still plays an important role in the treatment of multi-resistant malaria.[2,4] Camptothecin (CPT, **2**) (Fig. 1), isolated from the Chinese tree *Camptotheca acuminata* in the early 1960s, is the most important and famous quinoline alkaloid from an anticancer aspect.[5,6] Ever since mechanistic studies determined that CPT specifically targets DNA topoisomerase (topo) I, modified CPT analogs have been at the frontline of anticancer drug development. In addition, numerous quinoline alkaloids have been isolated and identified from natural sources, and many studies have documented their antitumor, antimalarial, antibacterial, antifungal, antiparasitic and insecticidal, antiviral, antiinflammatory, antiplatelet and other activities (Table 1).[1,7] Now, quinoline alkaloids and their derivatives have extensive medical and agricultural applications.

Quinazoline alkaloids are another class of *N*-based heterocyclic compounds. To date, approximately 150 naturally occurring quinazoline alkaloids have been isolated from several families of the plant kingdom, as well as from animals and microorganisms; many are derived biogenetically from anthranilic acid.[8,9] In 1888, the first quinazoline alkaloid, vasicine (**3**) (Fig. 1), was isolated from *Adhatoda vasica* and later from other species.[10,11] Our group optimized the extraction technology of this compound from *Peganum harmala* and recently reported its acaricidal activity.[12] In the 1950s, more comprehensive study of quinazoline alkaloids began after a new quinzolinone alkaloid, 3-[β-keto-γ-(3-hydroxy-2-piperidyl)-propyl]-4-quinazolone [febrifugine,[2] **4**] (Fig. 1), with antimalarial effects was isolated from the Asian plant *Dichroa febrifuga*.[13] Since then, many more quinazoline alkaloids and their derivatives were isolated, synthesized, and found to exhibit diverse pharmacological activities with broad agricultural and medical uses (Table 1).[14–21]

Several thousands of publications (journal articles, books, and patents) on quinoline and quinazoline alkaloids have been recorded through 2016. The topics include the extraction, synthesis, pharmacology, and other aspects of these compounds. The increasing numbers of publications reflect the importance and research intensity in this field, as well as the bright prospect for drug development of these compounds. Furthermore, some excellent reviews on quinoline and quinazoline alkaloids from a historical point of view are available.[1,6,8,9,12,22–57] These publications focused mainly on the chemical structures of isolated compounds, the synthetic methods and approaches to new derivatives, and the derivatives' biological properties. They have contributed significantly to the general scientific understanding of quinoline and quinazoline alkaloids. However, from 2008 to date, additional significant studies have been published, and a more comprehensive and up-to-date review is merited. Therefore, this review combines newer literature reports with the authors' research as well as presents the developments in this field more from the perspective of biological activities. It covers quinoline and quinazoline alkaloids related not only to anticancer and antimalarial effects, but also other biological activities. We hope that this review will provide new clues or possibilities for the development of these compounds. Due to the vast amount of literature, we will split the material into two review papers. This review will cover the literature up to 2008 (Part I, all active quinoline and quinazoline alkaloids isolated are listed in Table 1), and the forthcoming review (Part II) will summarize the literature from 2009 to 2016.

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2 | BIOACTIVITIES OF QUINOLINE AND QUINAZOLINE ALKALOIDS

2.1 | Antitumor activity

2.1.1 | Quinoline alkaloids—Cancer is known medically as a malignant neoplasm, which includes over 200 human diseases, all involving unregulated cell growth.[58] Many new natural products with anticancer activities have been isolated and could possibly The active quinoline and quinazoline alkaloids[a] be used in the treatment of cancer. Among such potential anticancer compounds or agents, some quinoline and quinazoline alkaloids fused with various heterocycles have displayed potent anticancer activity. CPT (**2**) is one of the most important and famous.[59] It is a specific and strong inhibitor of the DNA-replicating enzyme topo I.[59,60] 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.[61–63] Because of this distinct cytotoxic mechanism, CPT exhibits significant activity against established cell lines from leukemias and various solid cancers, such as colon, lung, breast, ovarian, and melanoma, in experimental systems. However, CPT is water insoluble and results in severe and unpredictable side effects. These shortcomings hampered the development of CPT in the 1970s. Meanwhile, these problems also stimulated interest in the synthesis of CPT analogs to find active and clinically useful anticancer drugs with the same mechanism of action.[6] More than 5000 publications on CPT were recorded between 1966 and 2012. This dramatic number of publications not only reflects the research intensity, but also the importance and bright prospect of CPT derivatives in cancer treatment.

To date, five non-water-soluble CPT analogs, rubitecan (**5**),[64,65] 9-aminocamptothecin (**6**),[66] gimatecan (**7**),[67] karenitecin (**8**),[68] DB-67 (**9**),[69] and three water-soluble analogs, exatecan (**10**)[70–72], lurtotecan (**11**),[73,74] and sinotecan (**12**)[75,76] (Fig. 2), are in preclinical and clinical studies. Newly emerging homocamptothecin (hCPT) derivatives, BN80915 (**13**) and BN-80927 (**14**)[77,78] (Fig. 2) with a stabilized seven membered hydroxylactone ring, the CPT prodrug afeletecan (**15**),[79,80] and different delivery systems (**16**–**18**)[81–84] (Fig. 3) are also currently undergoing clinical trials. More importantly, three CPT analogs, topotecan (**19**),[85] irinotecan (**20**),[86] and belotecan (approved only in South Korea) (**21**),[87] have received governmental approval for the clinical treatment of ovarian, small-cell lung, and refractory colorectal cancers.

In recent years, the authors' laboratories designed and synthesized several series of CPT derivatives. In 2008, a nitroxylradicalmoiety(1-oxyl-2,2,5,5-tetramethylpyrroline-3-carboxylicacid)waslinkedatthe20-hydroxylofCPTvia different hydrophilic amino acid spacers to generate a series of novel spin-labeled CPT derivatives (**23–27**) (Fig. 5).[88] The new compounds showed similar or better in vitro cytotoxic activity than the parent drug CPT and the clinically available drug **20** against human bladder cancer T-24. In 2012, a series of 7-acyl CPT derivatives showed significant inhibition of A-549, DU-145, KB, and KBvin cell growth with IC_{50} values ranging from 0.0154 to 13.3 μM.[89] In continued efforts, 20-sulfonylamidine CPT derivatives with potent antitumor activity were also synthesized.[90] Among them, compound **22** (Fig. 4) showed the best potency against the growth of A549, DU-145, KB, and KBvin with IC_{50} values of 0.031, 0.050, 0.14, and 0.026 μM, respectively. It induced significant DNA damage by selectively inhibiting topo I and activating the ATM/

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Chk-related DNA damage-response pathway. Furthermore, compound **22** at 300 mg/kg (i.p.) showed no overt acute toxicity in contrast to CPT in vivo (LD_{50} 56.2 mg/kg, i.p.). Thus, **22** is attractive as a potential candidate for anticancer chemotherapy, and the modification with sulfonylamidine-substituted side chains may overcome some limitations of CPT.

The antitumor activity of quinidine (**28**) (Fig. 6), another major quinoline alkaloid from the Cinchona tree, was observed in 1989.[91] This compound effectively modulates resistance, increasing the sensitivity of the multidrug resistant breast cancer cell line MCF-7 to adriamycin by eight-fold. In other studies, a combination of **28** and epirubicin was not more toxic than epirubicin alone and, at a dose of 250 mg b.d., levels of **28** equivalent to those active in vitro were achieved in patients.[92] Thus, the treatment of advanced breast cancer with a combination of **28** and epirubicin appears feasible. In addition, quinine (**1**) (Fig. 1) increased the cellular accumulation of anthracycline in resistant cells and enhanced the in vitro cytotoxic activity of epidoxorubicin in resistant DHD/K12 rat colon cancer cells, and also circumvented anthracycine resistance in clinical practice.[93]

Subsequently, more quinoline alkaloids were isolated and evaluated for cytotoxic activity. In 1994, Chen and coworkers isolated two pyranoquinoline alkaloids, zanthosimuline (**29**) and huajiaosimuline (**30**) (Fig. 6), from the root bark of *Zanthoxylum simulans*.[94] In cytotoxicity testing, **29** exhibited a general cytotoxic response to various cultured human cancer cell lines, especially P-388 cells (EC_{50} 5.20 μM). However, **30** produced a more selective cytotoxic activity profile and was especially effective against estrogen receptor-positive breast cancer ZR-75–1 (EC_{50} 11.1 μM) and P-388 (EC_{50} 9.80 μM) cells. The two compounds also induced the expression of cellular markers associated with cell differentiation in cultured HL-60 cells.[94] In later studies, the same authors again verified the cytotoxic activity of **30**.[95]

Two additional pyranoquinoline alkaloids, flindersine (**31**), and haplamine (**32**), as well as three furoquinoline alkaloids, γ-fagarine (**33**), skimmianine (**34**), and haplopine (**35**), (Fig. 6) from the genus *Haplophyllum*,[96,97] showed cytotoxic activity against the HeLa cell line ($IC_{50} < 50.0$ μM), while only **32** was active against the HCT 116 cell line (IC_{50} 64.5 μM). A structure–activity relationship (SAR) analysis showed that the aliphatic side chains at the $2'$-position of the pyrano group of the pyranoquinoline alkaloids may increase the cytotoxic activity against human cancer cell lines. However, colchicine (positive drug) was much more potent with IC_{50} values of 1.10 and 1.30 μM against HeLa and HCT 116 cell lines, respectively.[97]

As indicated above, furoquinoline alkaloids, which are derived biogenetically from 2-substituted oxygenated 4-quinolones after a prenylation at C-3, can exhibit cytotoxic activity. In 1999, several furoquinoline alkaloids, including γ-fagarine (**33**), skimmianine (**34**), evolitrine (**36**), kokusaginine (**37**), and maculosidine (**38**), along with 2,3-methylenedioxy-4,7-dimethoxyquinoline (**39**) (Fig. 6), were isolated from the root bark of *Acronychia laurifolia*.[98] Compounds **34** and **36–38** exhibited varying potencies of cytotoxic activity against specific human cancer cell lines, BC1 (EC_{50} 15.4, 25.3, >70, and >70 μM, respectively), KB-V1$^+$ (17.0, 12.7, 17.0, and 17.4 μM, respectively) and KB-V1$^-$ cell line

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(10.8, 16.6, 55.6, and 39.4 *μ*M, respectively), but were inactive against Lu1, Col2, KB, and LNCaP cells.[98]

The furoquinoline dictamnine (**40**) and the 2-phenylquinolinone graveoline (**41**) from *Ruta graveolens* demonstrated greater cytotoxic activity against HeLa (EC_{50} 12.6, 14 *μ*M) compared with KB (EC_{50} 103, 26.8 *μ*M) cancer cell lines.[99] In another study, **40**, **33**, and **34** were identified as moderate cytotoxic constituents from *Z. pistaciiflorum* against murine leukemia P-388, A549, and HT-29 cell lines.[100]

Five additional furoquinoline alkaloids, maculine (**42**); 5-methoxymaculine (**43**); 5,8-dimethoxymaculine (**44**); 4,5,6,7,8-pentamethoxyfuroquinoline (**45**); and flindersiamine (**46**) (Fig. 6), from *Vepris punctate*, showed modest cytotoxic activity toward the A2780 cell line ($IC_{50} < 20$ *μ*M).[101] In 2005 and 2006, 7-(2′-hydroxy-3′-chloroprenyloxy)4-methoxyfuroquinoline (**47**), 7-(2′,3′-epoxyprenyloxy)-4-methoxyfuroquinoline (**48**), pteleine (**49**), and (+)-7,8-dimethoxymyrtopsine (**50**) (Fig. 6) were isolated from two *Melicope* species, the former two compounds from *M. bonwickii* and the latter two from *M. semecarpifolia*.[102,103] Compounds **47** and **48** showed cytotoxic activity when tested against the HeLa cell line (IC_{50} 34 and 20.1 *μ*M, respectively).[102] Compound **49** showed similar potency toward the P-388 cell line (EC_{50} 39.0 *μ*M), but both **49** and **50** were less potent against the HT-29 cell line (EC_{50} 66.4 and 124 *μ*M, respectively).[103] The rare furanoquinoline alkaloid medicosmine (**51**) (Fig. 6) has a fused 2,2-dimethyl2*H*-pyran ring rather than the simple methoxy group found in **49**. It was isolated from the aerial parts of *Boronella koniambiensis* and was slightly cytotoxic against the murine L1210 leukemia cell line (IC_{50} 48.0 *μ*M).[104]

Jineol (**52**), a simple quinoline alkaloid from an animal rather than plant source, was isolated from the centipede *Scolopendra subspinipes mutilans* in 1996, together with 3,8-dimethoxyquinoline (**53**) and 3,8-diacetoxyquinoline (**54**) (Fig. 7).[105] Compared with **53** and **54**, compound **52** exhibited greater cytotoxic activity in vitro against five human tumor cell lines, A-549 (EC_{50} 36.0 *μ*M), SKOV-3 (EC_{50} 27.9 *μ*M), SK-Mel-2 (EC_{50} 34.7 *μ*M), XF-498 (EC_{50} 62.1 *μ*M) and HCT-15 (EC_{50} 11.8 *μ*M). It was less effective than cisplatin, but more effective than carboplatin.[105] Senepodine A (**55**) (Fig. 7), a novel $C_{22}N_2$ alkaloid isolated from *Lycopodium chinense*, was significantly cytotoxic toward murine lymphoma L1210 cells ($IC_{\mathbf{50}}$ 0.290 *μ*M).[106] 7-Hydroxy-4-[5′-hydroxymethylfuran-2′-yl]-2-quinolone (**56**) (Fig. 7) from *Aquilegia ecalcarata* was moderately cytotoxic toward GLC-82 and HCT cells (IC_{50} 8.80–10.1 *μ*M) in vitro.[107]

Other studies found cytotoxic activity with acetylcupreine[108] (**57**) (Fig. 7) from *Remijia peruviana* against mammalian CHO cells (ED_{50} 43.8 *μ*M) and with 3,3-diisopentenyl-*N*-methyl-2,4-quinoldione[109] (**58**) (Fig. 7) from *Esenbeckia almawillia* against HL-60, CEM, B-16, HCT-8, and MCF-7 cancer cells (IC_{50} 29.5– >80.3 *μ*M). The simple tetrahydroquinoline alkaloids cuspareine (**59**), galipeine (**60**), galipinine (**61**), and angustureine (**62**) (Fig. 7) were cytotoxic toward HeLa cells (IC_{50} 18.6–161 *μ*M), with **59** showing the highest potency (IC_{50} 18.6 *μ*M).[110]

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In 1992, the new 2-quinolone alkaloid asimicilone (**63**) (Fig. 7) was isolated from *Asimina parviflora*.[111] It showed cytotoxic activity against A-549, HT-29, and MCF-7 (IC_{50} 7.47, 11.4, and 25.3 *μ*M, respectively). The IC_{50} values of adriamycin (positive control) against the same three human tumor cell lines were 0.001, 0.008, and 0.425 *μ*M respectively.

Then, in 1995 and 2002, seven novel decahydroquinoline alkaloids, lepadins A–G (**64**–**70**) (Fig. 8), were isolated.[112,113] Compounds **65** and **66** showed significant in vitro cytotoxic activity toward various murine and human cancer cell lines, **69** and **70** showed mild activity, and **67** was inactive.[112,113] The biological activity was postulated to be dependent on the configuration at C-2 and the nature of the functionality at C-3 in the decahydroquinoline.

In 1996, two tetrahydroquinoline alkaloids, benzastatins C (**71**) and D (**72**) (Fig. 9) were isolated by Kim et al. from the bacterium *Streptomyces nitrosporeus* 30643.[114,115] The former chlorinated compound was cytotoxic against N18RE-105 cells with an IC_{50} value of 38.1 *μ*M, but its hydroxylated congener **72** was inactive even at 100 *μ*M.[114,115] In addition, two new quinoline-containing octadepsipeptides, (−)-SW-163C (**73**) and E (**74**) (Fig. 9) were isolated from culture broth of the *Streptomyces* strain SNA15896.[116,117] SW-163E (**74**) demonstrated better antitumor activity than SW-163C (**73**) in in vitro tests against various murine and human tumor cell lines (IC_{50} 0.200–1.60 vs. 17.0–140 nM, respectively). When in vivo activity was assessed in mice implanted with P388 leukemia, **74** prolonged life span at a dose of 0.010 mg/kg, but was acutely toxic at higher doses (LD_{50} 0.600 mg/kg for **74** vs. $>$100 mg/kg for **73**).

In 2006, two new diastereomeric alkaloids 3S*,4R*-dihydroxy-4-(4′- methoxyphenyl)-3,4-dihydro-2(1*H*)-quinolinone (**75**) and 3R*,4R*-dihydroxy-4-(4′- methoxyphenyl)-3,4-dihydro-2(1*H*)-quinolinone (**76**), together with the prenyl-substituted peniprequinolone (**77**) (Fig. 9), were isolated from cultures of the marine fungus *Penicillium janczewskii* strain H-TW5/869.[118] They showed moderate cytotoxic activity toward eight human tumor cell lines (MDA-MB 231, DU-145, SKOV-3, HT-29, A549, CAKI-1, SK-MEL 2, K562 cells). Among these compounds, **76** was markedly active against the SKOV-3 cell line. Furthermore, a novel cytotoxic alkaloid aspernigerin (**78**) (Fig. 9) from a culture of *Aspergillus niger* strain IFBE003 showed cytotoxic activity when tested against KB, HeLa, and SW1116 cell lines with IC_{50} values of 22.0, 46.0, and 35.0 *μ*M, respectively.[119] (+)-Quinocitrinine A (**79**) and (−)-quinocitrinine B (**80**) (Fig. 9) with a rare pyrrolo[3,4-*b*]quinoline ring system were isolated from cultures of *P. citrinum* Thom 1910 in 2003.[120] Both compounds showed antiproliferative activity toward L-929, K-562, and HeLa cells.

Two naturally occurring isoalkaloids, isodictamnine (**81**), and iso-*γ*-fagarine (**82**) (Fig. 9), as well as **γ**-fagarine (**33**), were found in *Glycosmis arborea*.[121] They showed inhibitory effects toward the tumor promoter 12-*O*-tetradecanoylphorbol 13-acetate induced Epstein-Barr virus early antigen.

Luzopeptins A–C (**83**–**85**) (Fig. 10), quinoline-substituted cyclic decadepsipeptides from *Actinomadura luzonensis,* showed potent cytotoxic and antitumor activity.[122–126] Compound **83**, with two acetylated sites in its peptide ring, was active against several experimental animal tumor systems. Compound **84** (one acetylated site) was less active, and compound **85**

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(no acetylation) was inactive. However, compound **85** was slightly more effective than **83** and **84** in assays to evaluate bifunctional DNA intercalation and drug-induced DNA-DNA intermolecular cross-linking. The peptidic cyclic structure of luzopeptins is essential for the bifunctional intercalation of the twin chromophores, probably by providing proper conformational orientations of the chromophores.[122–126]

In 2002, streptonigrin (**86**) and its *N*-(1-methyl-2-oxopropyl) derivative, 7-(1-methyl-2-oxopropyl)-streptonigrin (**87**) (Fig. 10), were isolated from the fermentation broth of the actinomycete strain *Micromonospora* sp. IM 2670.[127] They induced apoptosis through a p53-dependent pathway in human neuroblastoma SH-SY5Y cells. Compound **86** also caused nuclear accumulation of p53 and induced DNA ladders in SH-SY5Y cells as well as mediated p53-dependent apoptosis. Compound **86** was more cytotoxic than **87** (IC_{50} 0.050 vs. 0.900 μM) toward SH-SY5Y cells.[127]

Furthermore, two quinoline-containing octadepsipeptides, BE-22179 (**88**) and thiocoraline (**89**) (Fig. 10), were isolated from the culture broths of *Streptomyces* strain A22179[128,129] and *Micromonospora* sp. L-13-ACM2–092,[130,131] respectively. BE-22179 (**88**) exhibited potent inhibition of topo Π and significant in vitro cytotoxic activity against various murine leukemia and human stomach adenocarcinoma cell lines, as well as in vivo activity in mice transplanted with L1210 leukemic cells.[128,129] More specifically, it inhibited the DNA-relaxing activity of L1210 topo Π and prevented both DNA and RNA synthesis as well as the growth of L1210 mouse leukemic cells.[128,129] Compound **89** also displayed significant cytotoxic effects against P-388, A-549, and MEL-28 cell lines (IC_{50} 0.002 μM). It also inhibited RNA synthesis more specifically than DNA synthesis, bound to supercoiled DNA, but, unlike **88**, did not inhibit topo II.[130,131] Boger and co-workers reported the first total syntheses of both macrocyclic compounds and noted the exceptional IC_{50} values of **88** and **89** (200 and 400 pM, respectively) against the L1210 cell line.[132,133]

Of course, some isolated natural alkaloids exhibit weak or no cytotoxic activity in various studies against specific tumor cell lines. Confusadine (**90**) (Fig. 11) from the plant *Melicope semecarpifolia* showed poor cytotoxic activity toward P-388, A549, and HT-29 human cancer cell lines, and was substantially less potent than the related confusameline with a simple hydroxyl group and dutadrupine with a fused 2,2-dimethyl-2*H*-pyran ring rather than the 2-hydroxy-3-methylbut-3-enyloxy side chain.[134] Furomegistines I (**91**) and II (**92**) (Fig. 11) were isolated from bark extracts of *Sarcomelicope megistophylla*;[135] both alkaloids showed weak to no cytotoxic activity toward A549 and HT29 cells (IC_{50} 90 and 100 μM, respectively). Megistosarconine (**93**, IC_{50} 70 μM)[136] and cyclomegistine (**94**, IC_{50} 80 μM)[137] (Fig. 11) from *S. megistophylla* also exhibited poor cytotoxic activity towards L1210 leukemia cells. 4-Carbomethoxy-6-hydroxy2-quinolone (**95**) (Fig. 11), a new alkaloid isolated from *Oryza sativa* cv. *Mihyangbyo*, did not exhibit antiproliferative activity toward the U937 cell line (IC_{50} 539 μM).[138]

The fungal metabolites viridicatin (**96**) and viridicatol (**97**) (Fig. 11) were isolated from cultures of *P. crustosum* and *P. discolor,* respectively, grown on cheese agar.[139] The compounds exhibited weak to no cytotoxic activity in an MTT assay; the IC_{50} values of **97**

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toward KB, KBv200, A549, HepG2, MCF7, K562, SMMC7221, and SGC 7901 tumor cell lines were 98.8, 65.2, 237, 336, 178, 98.8, 317, and 316 μM, respectively.[140]

2.1.2 | Quinazoline alkaloids

In 1992 and 1995, fumiquinazolines A–C (**98**–**100**) and D–G (**101**–**104**) (Fig. 12) were isolated from the fungus *A. fumigatus*.[141,142] All seven fumiquinazolines were moderately cytotoxic in a P388 lymphocytic leukemia test system. Meanwhile, (−)-spiroquinazoline (**105**) (Fig. 12) from cultures of the fungus *A. flavipe* inhibited the binding of substance P to human astrocytoma cells.[143]

Four important quinazoline alkaloids, luotonins A, B, E, and F (**106**–**109**) (Fig. 12), from the aerial parts of *P. nigellastrum* have two major skeleton types, pyrroloquinazolinoquinoline (**106**–**108**) and 4(3*H*)-quinazolinone (**109**).[144,145] All four compounds exhibited promising cytotoxic activity toward P388 murine leukemia as well as potent topo II inhibition, but **106** was the most cytotoxic (IC$_{50}$ 6.32 μM)[146] with the added ability to stimulate topo I-mediated cleavage of DNA.[147] It stabilized the covalent binary complex formed between DNA and human topo I during DNA relaxation and mediated topo I-dependent activity in yeast *Saccharomyces cerevisiae* lacking the yeast topo but containing a plasmid with the human topo I gene. Due to its outstanding cytotoxic activity toward murine leukemia P-388 cells at low concentrations and the ability to inhibit topos I and II, **106** has been studied extensively.[148] Alkaloid **106** and its derivatives were cytotoxic against a human lung large cell carcinoma cell line H460, but were less potent than a CPT-related control.[149] To improve the biological as well as pharmacokinetic properties of **106** as an anticancer drug lead compound, systematic syntheses of derivatives have been performed.[149–151] Another metabolite of this plant, deoxyvasicine (**110**) (Fig. 12), exhibited good cytotoxic activity toward mouse leukemia P-388 cells.[148]

Tryptanthrin (**111**, indolo[2,1-*b*]quinazolin-6,12-dione) and qingdainone (**112**) (Fig. 13) were first isolated from the traditional Chinese medicine Qingdai in 1985, and both compounds showed cytotoxic activity against melanoma B$_{16}$ cells in vitro.[152] Compound **111** also affected cell differentiation and apoptosis of U-937 and HL-60 leukemia cells.[153] Low concentrations of **111** induced differentiation of leukemia cells but higher concentrations killed leukemia cells through apoptosis, possibly through a caspase-3/Fas antigen pathway. Meanwhile, **111** suppressed the growth of azoxymethane-induced intestinal tumors in F344 rats,[154] and strongly inhibited the induction of hepatocyte growth factor in human dermal fibroblasts.[155] 3-(2-Carboxyphenyl)-4(3*H*)-quinazolinone (**113**) (Fig. 13) from *Isatis indigotica*, an open-ring analog of **111**, showed endotoxic activity in vitro in the limulus amoebocyte lysate test.[156]

In 2005, Chen and co-workers isolated three new quinazoline alkaloids, 1-methoxy-7,8-dehydrorutaecarpine (**114**), rutaecarpine (**115**), and 1-hydroxyrutaecarpine (**116**) (Fig. 13), from the root bark of *Z. integrifoliolum*.[157] In in vitro tests, all three alkaloids were cytotoxic toward murine P-388 (EC$_{50}$ 12.3, 36.8, and 12.4 μM, respectively) and human HT-29 (EC$_{50}$ 27.1, 118, and 24.7 μM, respectively) cells. Samoquasine A (**117**) (Fig. 13) with a benzo[*h*]quinazoline ring system was isolated from seeds of the custard apple *Annona squamosa*.[158–161] It showed significant cytotoxic activity against murine lymphoma L1210 cells (IC$_{50}$ 1.94 μM).[158] However, the original published structure was reinvestigated and

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revised.[159–161] The simple quinazoline alkaloid 2-acetyl-4(*3H*)-quinazolinone (**118**) (Fig. 13) showed cytotoxic activity only at high concentrations.[162,163]

2.2 | Antimalarial activity

2.2.1 | Quinoline alkaloids—

Malaria is the most lethal human parasitic infection. According to the WHO World Malaria Report 2015, an estimated 292,000 African children under five died from malaria, and the disease caused an estimated 306,000 deaths worldwide in the same age group.[164] Malaria is caused by five species of protozoan parasites of the genus *Plasmodium*, including *P. falciparum, P. vivax, P. ovale, P. malariae*, and *P. knowlesi*. Of these, *P. falciparum* and *P. vivax* account for more than 95% of malaria cases in the world.[165] The bark of the Cinchona tree was utilized in early clinical history to treat human malaria. With the development of natural product technology, quinine (**1**), a quinoline alkaloid, was isolated from the bark of the Cinchona tree in 1820. Due to its low price, parenteral administration, and high efficacy against *P. falciparum*, it was widely used to treat malaria worldwide.[166,167] To meet the needs of this compound in southeast Asia during World War II, the synthesis of **1** was promoted and completed, and some derivatives were developed with better potency and lower toxicity.[168–171] In 2006, WHO stopped recommending **1** as a first-line treatment for malaria, because of its high toxicity and the developing resistance of *Plasmodium* sp. However, it has still been used when artemisinins are not available.[171] To date, **1** and its analogs have saved thousands of people's lives worldwide and made an enormous contribution to human health.

In 1996, Gantier and co-workers isolated six quinoline alkaloids, 2-*n*-propylquinoline (**119**), 2-pentylquinoline (**120**), chimanines B (**121**) and D (**122**), 4-methoxy-2-phenylquinoline (**123**), and 2-(3,4-methylenedioxyphenylethyl)quinoline (**124**) (Fig. 14) from the bark of *Galipea longiflora*, which is used to treat recurrent fevers, such as malaria, in Bolivia.[172] All six compounds showed the same approximate level of activity as the well-known antimalarial compound chloroquine against *P. vinckei* petteri infected mice. Four *G. officinalis* tetrahydroquinolines, cuspareine (**59**), galipeine (**60**), galipinine (**61**), and angustureine (**62**) (Fig. 7) exhibited antimalarial activity against one chloroquine-sensitive and two chloroquine-resistant strains of the malaria parasite *P. falciparum*; **61** was the most active compound (IC_{50} 0.276–2.76 μM for the resistant strains at 24 and 72 h).[110] Three novel decahydroquinoline alkaloids lepadins D–F (**67**–**69**) (Fig. 8) from the genus *Didemnum* also showed significant antiplasmodial activity; the most potent compound was **69**.112,113

Certain furoquinoline alkaloids also demonstrated antimalarial activity. In in vitro tests, kokusaginine (**37**), skim-mianine (**34**), haplopine (**35**) (Fig. 6), acronycidine (**125**), and acronydine (**126**) (Fig. 14) were active against HB3 (chloroquine-sensitive) and W2 (chloroquine-resistant) clones of *P. falciparum*.[173] The most active compound, **126**, was at least fourfold more potent against the resistant clone (IC_{50} 22.6 and 4.63 μM, respectively), although it was less potent than chloroquine (IC_{50} 0.032 and 0.466 μM, respectively). The pyranoquinolone veprisine (**127**) and its prenylated congener *N*-methylpreskimmianine (**128**) (Fig. 14) also exhibited antimalarial activity against *P. falciparum* D6 (IC_{50} 6.65 and > 14.8 μM, respectively) and W2 (IC_{50} 6.98 and 5.68 μM, respectively) clones.[174]

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In 1999, three quinolone alkaloids were isolated from a new gram-negative marine bacterial strain of *Pseudomonas* sp.[175] Compounds **129–131** (Fig. 14) showed activity against the malaria parasite *P. falciparum* (ID_{50} 3.51–16.8 μM).

2.2.2 | Quinazoline alkaloids

—Febrifugine (**4**) (Fig. 1) and isofebrifugine (**132**) (Fig. 15) were first isolated as active components of the traditional Chinese medicine *Chan Shan* (roots of *D. febrifuga* Lour.), which has marked antimalarial effects. Both compounds were named by Koepfli and co-workers in the 1940s.[176–178] They found that **4** was 100 times more active against *P. lophurae* in ducks than quinine (**1**), while **132** possessed only modest activity against the same malaria strain.[176–178]

Additional antimalarial testing showed that **4** (EC_{50} 0.910 nM) was almost 100 times more potent toward *P. falciparum* compared with chloroquine (EC_{50} 18.0 nM), twice as potent as its hydrochloride salt (EC_{50} 1.8 nM) and about ten times as potent as **132** (EC_{50} 9.00 nM).[179] Takaya and co-workers verified that compounds **4** and **132** exert powerful antimalarial activity in vitro, with similar potencies against chloroquine-sensitive *P. falciparum* FCR-3 (EC_{50} 0.700 and 3.40 nM, respectively), as well as against chloroquine-resistant *P. falciparum* K1 (EC_{50} 1.20 and 1.80 nM, respectively).[180] In in vivo assays, the acetone adduct of **4** displayed better activity than the acetone adduct of **132** against mouse malaria *P. berghei*. In 2003, Murata et al. investigated the mechanisms of **4**, **132**, and quinazolin-4(3*H*)-one (**133**) (Fig. 15).[181] The results indicated that **4** may act differently from other antimalarial drugs, and could be used as a novel lead compound for antiplasmodial chemotherapy. The basicity of both the 1- and the 1′′-nitrogen atoms of **4** is crucial in conferring powerful antimalarial activity.

To possibly decrease unacceptable emetic properties and other side effects, a combination of **4** and **132** was studied against a blood-induced infection with chloroquine-resistant *P. berghei* NK65 in ICR mice.[180,182] A four-day dosage of 1 mg/kg of the **4**/**132** mixture alone showed slight antimalarial activity, but all mice died during days 19 to 27 with increasing parasitemia. However, mice treated with chloroquine (20 mg/kg) plus the two alkaloids survived the entire experiment. In addition, malaria parasites in the mice given chloroquine plus alkaloids decreased on day 6 and then were undetectable by microscopic examination during the remaining observation period. Several analogs, including halofuginone, a chloro-bromo substituted derivative of **4**, were also synthesized to produce better efficacy and lower toxicity.[183–186]

Three new quinazoline alkaloids, 2-methoxyrutaecarpine (**134**), 2-methoxy-13-methylrutaecarpine (**135**), and the cationic variant 5,8,13,14-tetrahydro-2-methoxy-14-methyl-5-oxo-7*H*-indolo[2′,3′:3,4]pyrido[2,1-*b*]quinazolin-6-ium chloride (**136**) (Fig. 15), were isolated from stem bark of *Araliopsis tabouensis*.[174] The two latter compounds showed promising antimalarial activity against *P. falciparum* D6 (IC_{50} 5.44 and 5.99 μM, respectively) and W2 ($IC_{50} > 14.2$ μM) clones, but were less potent than the positive drug artemisinin ($IC_{50} < 0.92$ μM against both clones).

Furthermore, the indoloquinazolinedione tryptanthrin (**111**) (Fig. 13) showed significant in vitro antimalarial activity against *P. falciparum*, both sensitive and multidrug-resistant

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strains,[187,188] and exhibited remarkable in vitro activity (below 100 ng/mL) against sensitive and multidrug-resistant *P. falciparum* malaria. The pharmacophore containing two hydrogen bond acceptors (lipid) and two hydrophobic (aromatic) features mapped well onto many well-known antimalarial drug classes, including quinolines, chalcones, rhodamine dyes, Pfmrk cyclin dependent kinase inhibitors, malarial FabH inhibitors, and plasmepsin inhibitors. Compound **111** and its analogs are also highly potent against strains of *P. falciparum* that are up to 5000-fold resistant to atovoquone, 50-fold resistant to chloroquine, and 20-fold resistant to mefloquine. This novel class of compounds has opened a new chapter for study in the chemotherapy of malaria (−)-Janoxepin (**137**) (Fig. 15), an interesting oxepine-pyrimidinone natural product, was isolated from a culture of the fungus *A. janus*.[189] However, it did not·show antiplasmodial activity against *P. falciparum*.

2.3 | Antiparasitic and insecticidal activities

2.3.1 | Quinoline alkaloids—Leishmaniasis (kala-azar) is a major public health problem in Africa, Asia, and Latin America,[190] causing significant morbidity and mortality. To date, more than 70 isolated natural alkaloids have been used to treat this disease. Some of these alkaloids are quinoline or quinazoline type.[191] In the 1990s, Fournet et al. studied the antiprotozoal activity of several 2-substituted quinoline alkaloids isolated from *G. longiflora*.[192–195] After administrating chimanine D (**122**) subcutaneously and 2-*n*-propylquinoline (**119**) orally (0.540 mmol/kg per day) to mice for 10 days, the liver parasites were suppressed by 86.6% and 99.9%, respectively. The reference drug resulted in 97.4% parasite suppression in the liver. The alkaloids did not cause any apparent toxicity during the experiment. Additional studies indicated that chimanine B (**121**) reduced lesion weight and parasite loads substantially after oral administration or intralesion injection, and showed improved performance compared with the positive drug glucantime in BALB/c mice infected with *Leishmania amazonensis* and *L. venezuelensis*. Compound 121 may be chosen as a lead molecule in the development of oral therapy against leishmaniasis. Compounds **119** and **122** were also more potent than glucantime against *L. amazonensis* PH8. After a single treatment with proximate injection, **119** reduced the lesion severity; however, it was less active than glucantime.

2-Propyl- and 2-pentyl-quinoline (**119** and **120**) were again investigated by Belliard and co-workers in 2003.[196] The compounds exhibited significant activity against the virulent strain *L. venezuelensis*, and **119** decreased intestinal P-glycoprotein activity in mice infected with *L. donovani*. Based on the P-gp inhibition, **119** could be valuable as an oral drug to restrict leishmanial multi-drug-resistance in humans with kala-azar.

Besides its antiprotozoal activity, **119** was as clinically effective as the known trypanocidal agent benznidazole in mice chronically infected with *Trypanosoma cruzi*, the pathogenic parasite of Chagas disease.[197] Benznidazole and **119** were administered orally at 25 mg/kg for 30 days starting at 60 days post-infection. At day 35 post-treatment, the **119**-treated mice had a significantly different serological value from those of the control and the benznidazole-treated mice; however, at day 85 post-treatment, the difference was not statistically different. These results indicate that **119** and its analogs should be further investigated for potent trypanocidal activity and control of chronic Chagas' disease. In

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addition, compounds **119** and **120**, as well as 2-(3,4-methylenedioxyphenylethyl)quinoline (**124**), exhibited molluscicidal activity against the freshwater snail *Biomphalaria glabrata*.[198]

Four quinoline alkaloids **121**, **124**, cusparine (**138**) (Fig. 16), and 2-(3,4-dimethoxyphenylethyl)quinoline (**139**) (Fig. 16) as well as the furanoquinoline alkaloid skimmianine (**34**) were as effective as the positive control drug against the *Leishmania* parasite.[199] In addition, **34** inhibited the parasite enzyme adenine phosphoribosyltransferase. Other furoquinoline alkaloids also exhibit antiparasitic and insecticidal activities. Kokusaginine (**37**) (IC_{50} 0.560 mM), **34** (IC_{50} 1.46 mM), and *rel*-(7*R*,8*R*)-8-[(*E*)-3-hydroxy-3-methyl-1-butenyl]-4,8-dimethoxy-5,6,7,8-tetrahydrofuro [2,3-*b*]quinolin-7-yl acetate (**140**) (Fig. 16) (IC_{50} 0.977 mM) from *Almeidea rubra* exhibited moderate in vitro trypanocidal activity against the trypomastigote forms of *T. cruzi*.[200] Dictamnine (**40**) and evolitrine (**36**, 8-methoxydictamnine) exhibited antifeedant activity against fourth instar larvae of the tobacco caterpillar *Spodoptera litura*.[201] Compound **40** was also deterrent against two insect pests [*Sitophilus zeamays* (maize weevil) and *Trilobium castaneum* (red flour beetle)] responsible for spoilage of stored products.[202] However, the furoquinoline alkaloid **37** (LC_{50} 1420 μM) was extremely less potent than the quinolinone alkaloids evocarpine **(141**) and dihydroevocarpine (**142**) (Fig. 16) in a brine shrimp toxicity assay (LC_{50} 2.27 and 62.6 μM, respectively).[203,204]

The Cinchona alkaloid quinine (**1**)[108] and lepadins D–F (**67**–**69**) showed significant antitrypanosomal activity; the most potent compound was **69**.[112,113] Antidesmone (**143**) (Fig. 16), a tetrahydroquinolinedione alkaloid from *Antidesma membranaceum*, also displayed potent and selective antitrypanosomal activity (IC_{50} 0.066 μM) against *T. cruzi*, but only weak antimalarial activity against *P. falciparum* K1 and NF254 and anti-leishmanial activity against *L. donovani*.[205] In contrast, 2-nonylquinolin-4(1*H*)-one (**129**), *N*-methyl-2-nonylquinolin-4-one (**144**), and *N*-methyl-2-phenylquinolin-4-one (**145**) (Fig. 16) from *Raulinoa echinata* did not show activity against the trypomastigote forms of *T. cruzi* ($IC_{50} >$ 300 μM), but compound **129** was weakly fungicidal toward *Leucoagaricus gongylophorus*.[206]

In 1995, Perrett and Whitfield reported that atanine (**146**) (Fig. 16), a quinolin-2-one alkaloid from *Evodia rutaecarpa*, showed antiparasitic and anthelmintic activity against larvae of the human parasite *Schistosoma mansoni* and the soil nematode *Caenorhabditis elegans*.[207] The novel tetracyclic quinolin-4-one quinolactacide (**147**) (Fig. 16) from the fermentation broth of *P. citrinum* Thom F 1539 also showed excellent insecticidal activity against green peach aphids (*Myzus persicae*) (88% and 100% mortality at 250 and 500 ppm, respectively) and diamondback moth (*Plutella xylostella*) (42% at 500 ppm).[208,209]

Subsequently, peniprequinolone (**77**), penigequinolones A (**148**) and B (**149**), 3-methoxy-4-hydroxy-4-(4′-methoxyphenyl)quinolinone (**150**), and 3-methoxy-4,6-dihydroxy-4-(4′-methoxyphenyl)quinolinone (**151**) (Fig. 16) were isolated from *Penicillium* cf. *simplicissimum* in 2000.[210] Compounds **148** and **149** showed potent nematicidal activity (LD_{50} 100 mg/L) toward *Pratylenchus penetrans*. Thus, the penigequinolones may be useful for controlling parasitic nematodes.

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Nakatsu and co-workers studied the anti-feedant activity of two unusual quinolin-4-ones, leiokinines A (**152**) and B (**153**) (Fig. 16), from *E. leiocarpa*.[211] The compounds showed weak effects against the pink bollworm *Pectinophora gossypiella.* 3,4-Dihydroxyquinoline-2-carboxylic acid (**154**) (Fig. 16) from the sponge *Aplysina cavernicola* acted as a powerful feeding deterrent of the fish species *Blennius sphynx*,[212] and acetylcupreine (**57**) affected the feeding behavior of the potato beetle *Leptinotarsa decemlineata*.[108]

(−)-Yaequinolone J1 (**155**) and (+)-yaequinolone J2 (**156**) (Fig. 16), two new alkaloids related to the abovementioned penigequinolones, were isolated from a Japanese soil sample of *Penicillium* sp. FKI-2140 in 2005.[213] Both compounds showed activity in a brine shrimp assay with a minimum inhibitory concentration (MIC) of 13.9 μM. 3-Methoxy-4,5-dihydroxy-4-(4′-methoxyphenyl)-quinolinone (**157**) (Fig. 16), without the side chain at C-6, was also toxic to brine shrimp with an IC_{50} value of 63.5 μM.[214]

2.3.2 | Quinazoline alkaloids—Among vasicine alkaloids found in *A. vasica,* vasicine (**3**), vasicinone (**158**), and vasicinol (**159**) (Fig. 16) showed feeding deterrence at concentrations of 0.05 and 0.1% against two beetle species *Aulacophora foveicollis* and *Epilachna vigintioctopunctata*.[215] The latter compound blocked oocytes in the oviduct and exhibited severe antifertility effects against *T. castaneum* and the cotton pest *Dysdercus koenigii*.

The well-known alkaloid tryptanthrin (**111**) showed insecticidal activity against larvae of the house longhorn beetle *Hylotrupes bajulus* and the termite *Reticulitermis santonensis*. Moreover, the compound also displayed antifeedant activity, as termites avoided the treated pine samples.[216] In addition, compound **111** showed antitrypanosomal activity against *T. brucei* with an EC_{50} value of 23.0 μM.[217] Furthermore, (+)-N_α-quinaldyl-L-arginine (**160**) (Fig. 16) found in the exudates of the ladybird beetle *Subcoccinella 24-punctata* proved to be a highly effective feeding deterrent to the ant species *Myrmica rubra*.[218]

A mixture of the *cis* and *trans* isomers of febrifugine (**4**) was isolated from *Hydrangea macrophylla*.[219] *Trans*-**4** showed anticoccidial activity against *Eimeria* parasites in chickens, whereas *cis*-**4** was inactive even at much higher dosages.

1,3-Dimethylquinazoline-2,4-dione **(161)** (Fig. 16) was identified as a sex pheromone of *Phyllopertha diversa* or chafer beetle.[220] Female beetles release the compound in only picogram quantities. As many as 153 male beetles per trap per hour were successfully lured to field traps baited with **161**, while the control captures were extremely low (0.4). The compound was catabolized by an antennal cytochrome P450 system, which was highly specific to male insects.[221]

2.4 | Antibacterial and antifungal activities

2.4.1 | Quinoline alkaloids—*E. rutaecarpa* extracts display antibacterial activity against *Helicobacter pylori*, which is implicated in the pathogenesis of chronic gastritis, peptic ulcers, and gastric cancers. Consequently, many compounds have been isolated and identified from this plant. In 1999, Rho and co-workers isolated six quinolone alkaloids,

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evocarpine (**141**), dihydroevocarpine (**142**), 1-methyl-2-pentadecyl-4(1*H*)-quinolone (**162**), 1-methyl-2-[(4*Z*,7*Z*)-4,7-tridecadienyl]-4(1*H*)-quinolone (**163**), 1-methyl-2-[(6*Z*,9*Z*)-6,9-pentadecadienyl]-4(1*H*)-quinolone (**164**), and 1-methyl-2-undecyl-4(1*H*)-quinolone (**165**), (Fig. 17), which showed potent anti-*H. pylori* activity with MIC values of 10–20 μg/mL.[222]

The following year, Hamasaki et al. explored the in vitro anti-*H. pylori* activity of an extract from the fruits of *E. rutae-carpa* (Gosyuyu), one part of the Chinese herbal medicine Gosyuyu-to (Wu-Chu-Yu).[223] Two 1-methyl-2-tridecenyl-4(1*H*)-quinolones [**141** (8*Z*) and **166** (7*Z*)] (Fig. 17) were identified as the strongest antibacterial principles. Their MIC values were less than 0.147 μM against clinically isolated and reference *H. pylori* strains and similar to the values of the antibiotics amoxicillin and clarithromycin.[223] Additional studies indicated that these alkaloids were highly selective against *H. pylori* and almost inactive against other intestinal pathogens. They inhibited the bacterial respiration and reduced the bacterial growth in vivo, but not DNA synthesis.[224] In addition, these compounds significantly decreased the number of viable *H. pylori* in the stomachs of infected Mongolian gerbils and reduced neutrophil infiltration without causing harmful adverse effects, including animal mortality.[224] The above results indicated that these alkyl methyl quinolone alkaloids have a unique antimicrobial mechanism(s) different from those of other antibiotics such as amoxicillin and clarithromycin. They may be beneficial in the treatment of *H. pylori*-associated gastroduodenal diseases, whether used alone or together with the above-mentioned antibiotics or proton pump inhibitors.[223]

Five quinolone alkaloids, **141**, **163–165**, and 1-methyl-2-(6Z)-6-undecenyl-quinolone (**167**) (Fig. 17), from *E. rutaecarpa* also displayed promising antimycobacterial activities in in vitro tests with *Mycobacterium fortuitum*, *M. smegmatis*, and *M. phlei* (MICs 12.5–200 μM).[225] Among these compounds, **141** was the most active (MIC 12.5 μM). Quinolone alkaloid **129**, its *N*-methyl congener (**144**), and 2,3-dimethyl-4-quinolone (**168**) (Fig. 17) from *Boronia bowmanii* exhibited moderate antibacterial activity against *Bacillus subtilis*, *Staphylocccus aureus*, *Sarcina lutea*, exeterotoxigenic *E. coli*, *Salmonella typhi*, and *Klebsiella* sp.[226]

The furoquinoline alkaloid flindersiamine (**46**) from *E. yaaxhokob* exhibited moderate antimicrobial activity against *S. aureus* and *S. faecalis*.[227] In other studies, the furoquinolines kokusaginine (**37**), skimmianine (**34**) and haplopine (**35**), as well as the pyranoquinoline flindersine (**31**), exhibited photo-activated antimicrobial activity against *S. aureus*.[228] Compounds **37**, **34**, and **35** displayed photo-activated DNA binding activity in the presence of several restriction enzymes and likely target DNA. However, the pyranoquinoline alkaloid **31** did not show photo-activated DNA binding activity and must act on other cellular target components to exert its photo-toxic activity.[228] The furoquinoline pteleine (**49**) showed moderate antimicrobial activity against *M. smegmatis*, *B. subtilis*, *S. aureus*, and *Candida albicans* (MIC 4.39– 87.8 μM), while **34** and dictamnine (**40**) were less potent against the two former microbes and inactive against the latter two microbes.[229]

Megistoquinones I (**169**) and II (**170**) (Fig. 17), probable oxidation products of a furo[2,3-*b*]quinoline precursor, were isolated from the bark of *S. megistophylla*.[230] Both alkaloids showed antibacterial properties against two gram-positive, *S. aureus* (MIC 9.073, 2.577 mM) and *S. epidermidis* (MIC 10.7, 2.51 mM), and four gram-negative, *Pseudomonas aeruginosa*

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(MIC 12.5, 3.33 mM), *E. coli* (MIC 18.3, 3.51 mM), *Enterobacter cloacae* (MIC, 12.0, 3.06 mM), and *Klebsiella pneumoniae* (MIC 20.3, 4.23 mM), bacteria.

Two new functionalized 3-prenylquinolinones, *N*-methyl-4-hydroxy-7-methoxy-3-(2,3-epoxy-3-methylbutyl)-1*H*quinolin-2-one (**171**) and 3-(2,3-dihydroxy-3-methylbutyl)-4,7-dimethoxy-1-methyl-1*H*-quinolin-2-one (**172**) (Fig. 17) were isolated from *Toddalia aculeata*.[231] Both compounds strongly inhibited the growth of the bacteria *E. coli*, *B. cereus*, and *Lactobacillus lactis* at millimolar concentrations.

A special carbaldehyde substituted compound, quinoline-4-carbaldehyde (**173**) (Fig. 17), was isolated from the herb *R. chalepensis*.[232,233] It significantly inhibited the growth of *Clostridium perfringens*. This result may verify the phytoprotective effects of the herbal remedy. However, the compound's effect on *E. coli* was weak, and effects on the beneficial gastrointestinal bacteria *Bifidobacterium bifidum*, *B. longum*, and *L. acidophilus* were slight or absent.

During a research escalation on the antibacterial activity of microorganism metabolites, two 2-alkyl-4(1*H*)-quinolinone alkaloids (**174**, **175**) (Fig. 17) were isolated from *P. cepacia* strain RB425 collected from lettuce root[234] and strain LT4–12-W,[235] respectively. Both alkaloids exhibited antibiotic activity against fungal and bacterial plant pathogens. Meanwhile, YM-30059 (a structurally related *N*-hydroxyquinolin-4-one) (**176**) (Fig. 17) was isolated from *Arthrobacter* sp. YL-02729S as an antibacterial and cytotoxic compound.[236] It displayed moderate activity against gram-positive bacteria, including *B. subtilis* and multiple-drug resistant *S. aureus* and *S. epidermidis.*

Four sesquiterpenoid quinoline antibiotics, aurachins A–D (**177**–**180**) (Fig. 18) from the myxobacterium, *Stigmatella aurantiaca*, were active against gram-positive bacteria and weakly active against some fungi.[237] Against *B. subtilis, S. aureus*, *Arthrobacter aurescens, Brevibacterium ammoniagenes*, and *Corynebacterium fascians*, the four compounds showed the following MIC values, **177**: 12.658, 6.329, 0.481, 0.987, 3.949; **178**: 6.849, 3.425, 2.137, 3.425, 4.273; **179**: 0.396, 1.029, 0.501, 0.132, 2.058; **180**: 0.413, 1.074, 0.523, 0.138, 2.149 μM, respectively. Meanwhile, one of the simplest quinolines, helquinoline (**181**) (Fig. 18), from the fermentation broth of *Janibacter limosus* strain Hel-1, showed moderate activity toward *B. subtilis*, *S. viridochromogenes* Tü57, and *S. aureus*.[238]

In 1998, Dekker and co-workers isolated eight new quinolin-4-ones from the fermentation broth of the actinomycete *Pseudonocardia* sp. CL38489.[239] These compounds were given the code numbers CJ-13136 (**182**), CJ-13217 (**183**), CJ-13536 (**184**), (–)-CJ-13564 (**185**), CJ-13565 (**186**), CJ-13566 (**187**), (+)-CJ-13567 (**188**), and (–)-CJ-13568 (**189**) (Fig. 18). All eight compounds inhibited the growth of *H. pylori*; the most potent compound was the epoxide CJ13564 (**185**) with minimum bacterial concentration (MBC) 30.769 nM and MIC 0.308 nM. Moreover, the antibacterial activity of these compounds was highly selective and specific. Thus, because they are less likely to disturb the normal gastro-intestinal microbial flora, they could be used as antiulcer agents.

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In addition to promising antitumor activity with potential clinical value,[240] the octadepsipeptide (−)-thiocoraline (**89**) exhibited potent antibiotic activity against *S. aureus* (MIC 0.05 μg/mL), *B. subtilis* (MIC 0.05 μg/mL), and *Micrococcus luteus* (MIC 0.03 μg/mL).[130,131] Sch 40832 (**190**) (Fig. 19), a minor metabolite from the fermentation broth of *M. carbonacea* var. *africana*, also exhibited potent activity less than 0.504 μM against gram-positive bacteria.[241]

Two bacterial alkaloids 2-heptylquinolin-4-ol (**191**) and 2-pentylquinolin-4-ol (**192**) (Fig. 19) were isolated from *Alteromonas* sp.[242] The latter compound inhibited respiration in other bacteria at a low concentration (75.0 nM) and DNA and protein synthesis, as well as bacterial motility, at micromolar concentrations. It also inhibited the growth of phytoplankton and diatoms, and altered the composition of bacterial communities growing on particles suspended in sea water.

Quinoline-related animal metabolites also show antibacterial activity. *trans*-Decahydroquinoline 243A (**193**) (Fig. 19) was isolated from amphibian (frog) skin in 2005.[243] It inhibited the growth of the gram-positive bacterium *B. subtilis*, gram-negative bacterium *E. coli*, and the fungus *C. albicans.* The two novel pyrrolo[3,4-*b*]quinoline alkaloids quinocitrinine A (**79**) and (−)-quinocitrinine B (**80**) showed moderate antimicrobial activity toward a range of bacteria and fungi.[120]

As indicated above, quinoline alkaloids have also been investigated for antifungal activities. Decahydroquinoline alkaloids lepadins D–F (**67**–**69**) showed weak antifungal effects.[112,113] The decahydroquinolone alkaloid anhydroevoxine (**194**) (Fig. 19), as well as two pyranoquinolone alkaloids flindersine (**31**), and haplamine (**32**) from *Haplophyllum sieversii* showed growth-inhibitory antifungal activity against *Colletotrichum fragariae, C. gloeosporioides, C. acutatum, Botrytis cinerea, Fusarium oxysporum*, and *Phomopsis obscurans* in a dose-response manner at 100, 50, and 150 μM.[244] Among these compounds, **31** presented the highest antifungal activity. In addition, **32** was selectively more toxic toward freshwater phytoplanktons such as *Pseudanabaena* sp. LW397 and the odor-producing cyanobacterium *Oscillatoria perornata*. The furoquinoline alkaloid flindersiamine (**46**) and its congeners kokusaginine (**37**), skimmianine (**34**), dictamnine (**40**), maculine (**42**), and platydesmine (**195**) (Fig. 19) inhibited the growth of the fungus *L. gongylophorus*, a symbiotic fungus of the insect pest *Atta sexdens rubropilosa*.[245] Dictamnine (**40**) also was a weak inhibitor of the pathogenic fungus *Cladosporium cucumerinum* (MIC 125.628 μM), while haplopine (**35**) exhibited relatively low activity.[246]

1-Methyl-2-[6′-(3′′,4′′-methylenedioxyphenyl)hexyl]-4-quinolone (**196**) (Fig. 20) from *R. graveolens* was highly active against the necrotrophic fungus *B. cinerea*.[247] Distomadine B (**197**) and its analog (+)-distomadine A (**198**) (Fig. 20) with furo[3′,4′:5,6]pyrano[2,3,4-*de*]quinoline skeletons were isolated from *Pseudodistoma aureum.*[248] Compound **198** showed moderate antifungal activity toward *C. albicans*, but was inactive in various antitumor, antiviral, anti-inflammatory, and antimycobacterial assays.

One quinolone [2-(hept-2-enyl)-3-methylquinolin-4-one (**175**)] and four quinoline [quinoline-4-carbaldehyde (**173**), 4-hydroxymethylquinoline (**199**), quinoline-4-

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carbaldoxime **(200)**, and quinoline-4-carboxylic acid (**201**) (Fig. 20)] alkaloids were isolated from cultures of the soil myxobacterium *Archangium gephyra* (strain Ar T205) in 1996.[249] Among these five alkaloids, compound **176** proved to be the most active against *Phytophthora capsici* and other fungal plant pathogens. In 2001, the simple antibiotic *N*-mercapto-4-formylcarbostyril (**202**) (Fig. 20) from *P. fluorescens* (strain G308) showed good activity against a range of plant pathogenic fungi, including *F. oxysporum*, *F. culmorum*, *C. cucumerinum,* and *C. lagenarium*.[250] Moreover, a new antiviral antibiotic, virantmycin (**203**) (Fig. 20), was isolated from the culture broth of strain AM-2722 in 1980.[251,252] It exhibited weak antifungal activity with MICs from 12.5 to 50 μg/mL against *S. sake, Piricularia oryzae, Trichophyton interdigitale, A. niger*, *Alternaria kikuchiana, Mucor racemosus,* and *C. albicans*.

2.4.2 | Quinazoline alkaloids—

The quinazoline alkaloid tryptanthrin (**111**) showed exciting potential as an antimycobacterial agent against a multiple drug-resistant strain of *M. tuberculosis*.[253] It also exhibited good antibacterial activity against *H. pylori* in both in vitro and in vivo studies.[254]

Fumiquinazolines H and I (**204**, **205**) (Fig. 19) were isolated from the culture broth and mycelia of an *Acremonium* sp. in 2000.[255] Both compounds showed weak antifungal activity toward *C. albicans* in a broth microdilution assay, but no activity in antimicrobial assays or toward various cancer cell lines.

2.5 | Cardiovascular protective and antiplatelet activities

2.5.1 | Quinoline alkaloids—

Although Pasteur first isolated quinidine (**28**) from the bark of the Cinchona tree in 1853, the compound's possible use in arrhythmias was not noted until 1912 after patient observed that quinine, another Cinchona alkaloid and a stereoisomer of quinindine, had a beneficial effect on his own heart arrhythmia. Compound **28** was later noted to be the most effective Cinchona alkaloid on the heart. In 1920, Lewis proposed that **28** restores normal cardiac rhythm by closing the gap between the crest and wake of the circus wave generated in arrhythmia.[256] Since then, alkaloid **28** has been widely investigated for its antiarrhythmic activity and was acknowledged as the most potent of the antiarrhythmic compounds in the early 20th century.[257] In studies on the effect of reserpine pretreatment on the action of **28** in isolated cat hearts with complete heart blocks, exogenous catecholamines were demonstrated to antagonize the cardiac actions of **28**, and cardiac catecholamines to antagonize the depressant action of **28**.[258–261] Alkaloid **28** slows amphibian heart rate with its foremost effects attributed to a rise in the threshold for electrical stimuli and its consequences.[262] Further studies indicated that **28** interferes selectively with vasoconstrictor stimuli, which activate *alpha* adrenergic receptors, and this mechanism as well as a direct vasodilator effect may contribute to vasodilatation and hypotension.[263] Therapeutic doses (10–20 μM) of **28** strongly inhibit fast inward current I_{Na} in isolated ventricular cells,[264] affect the spontaneous contractions of rabbit atria,[265] and depress the active transport of serotonin by platelets.[266]

Other quinoline and quinazoline alkaloids also have cardiovascular effects. At a concentration of 100 μg/mL, the furoquinoline alkaloid dictamnine (**40**), isolated from

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Zanthoxylum species in 1994,[267,268] completely inhibited the platelet aggregation induced by arachidonic acid, and was also markedly effective in inhibiting platelet aggregation induced by collagen and PAF. Pyranoquinolone [huajiaosimuline (**30**), simulenoline (**206**), benzosimuline (**207**), zanthobungeanine (**208**)], furoquinoline [*γ*-fagarine (**33**), skimmianine (**34**), haplopine (**35**), robustine (**209**)], and quinolone [edulitine (**210**)] alkaloids (Fig. 21) also inhibited the aggregation induced by thrombin, arachidonic acid, collagen, and PAF in washed rabbit platelets.[95] Likewise, 4-methoxy-1-methylquinolin-2-one (**211**) (Fig. 21) completely inhibited arachidonic acid-induced platelet aggregation in vitro at a concentration of 100 *μ*g/mL.[268]

In other related studies on furoquinoline alkaloids from *Zanthoxylum* and *Melicope* species, confusameline (**212**) (Fig. 21), skimmianine (**34**), evolitrine (**36**), kokusaginine (**37**), dictamnine (**40**), and pteleine (**49**) showed significant antiplatelet aggregation activity.[269–272] Compound **34** affected the cardiovascular function and vasopressor responses in rats,[273] and confusadine (**90**) inhibited the platelet aggregation triggered by various inducers.[274]

Moreover, furoquinoline alkaloids also show cardiovascular protective activity. Robustine (**209**) and confusameline (**212**) (Fig. 21), as well as γ-fagarine (**33**), skimmianine (**34**), haplopine (**35**), evolitrine (**36**), kokusaginine (**37**), dictamnine (**40**), inhibited human phosphodiesterase 5, which regulates the intracellular levels of cGMP and influences vascular smooth muscle tone.[275] Three quinolone alkaloids, evocarpine (**141**), 1-methyl-2-[(4*Z*,7*Z*)-4,7-tridecadienyl]-4(1*H*)-quinolone (**163**), and 1-methyl-2-[(6*Z*,9*Z*)-6,9-pentadecadienyl]-4(1*H*)-quinolone (**164**) from *E. rutaecarpa* blocked the angiotensin II receptor and inhibited angiotensin II binding to rat liver receptor (IC_{50} 43.4, 34.1, and 48.2 *μ*M, respectively).[276]

2.5.2 | Quinazoline alkaloids—The antiplatelet activity of the quinazoline alkaloids rutaecarpine (**115**), 1-hydroxyrutaecarpine (**116**), and 1-methoxyrutaecarpine (**213**) (Fig. 21) from *Z. integrifolium* was investigated.[277] In in vitro tests, **116** was the strongest inhibitor of arachidonic acid-induced platelet aggregation, with an IC_{50} values of 3.32–6.65 *μ*M.

In 2000, studies showed that acrophyllidine (**214**) (Fig. 21) from *A. haplophylla* has antiarrhythmic activity.[278] It suppressed ischemia/reperfusion-induced polymorphic ventricular tachyarrhythmias with an EC_{50} value of 4.40 *μ*M in isolated rat heart, increased the atrioventricular and His-Purkinje system conduction intervals, ventricular repolarization time, and basic cycle length, and prolonged the refractory periods of the AV node, His-Purkinje system, and ventricle in a perfused whole-heart model. Moreover, this furoquinoline alkaloid prolonged the action potential duration and decreased both the maximal upstroke velocity of depolarization and action potential amplitude in a concentration-dependent manner in isolated rat ventricular myocytes.[278] These changes alter the electrophysiological properties of the conduction system and may be responsible for the compound's termination of ischaemia/reperfusion induced ventricular arrhythmias.

The quinazoline alkaloids rutaecarpine (**115**), evodiamine (**215**), and dehydroevodiamine (**216**) (Fig. 21) produced a vasodilatory effect on endothelium-intact rat aorta with equal potency in smooth muscle from rat thoracic aortas.[279] Compound **115** produced a full nitric

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oxide (NO)-dependent vasodilation, whereas **216** and **217** exhibited partial endothelium-dependent effects, 50% and 10%, respectively. Another quinazoline alkaloid vasicine (**3**) also showed hypotensive and cardiac depressant properties.[280,281]

2.6 | Antiviral activity

Uranidine (**217**) (Fig. 22), a quinolone alkaloid and well-known yellow pigment, inhibits the RNA-directed DNA synthesis of the reverse transcriptases (RTs) of human immunodeficiency viruses HIV-1 and HIV-2, with the 3-hydroxy-4-oxo system likely being a key structural element for the inhibitory activity.[282] Furthermore, 2-undecyl-4(1*H*)-quinolone (**130**) from the gram-negative marine bacterial strain of *Pseudomonas* sp. showed activity against HIV-1.[175]

Buchapine [**218**, 3-(1,1-dimethylallyl)-3-(3-methylbut-2-enyl)-1*H*-quinoline-2,4-dione] and 3-prenyl-4-prenyloxy1*H*-quinolin-2-one (**219**) (Fig. 22) from *E. roxburghiana* also showed anti-HIV-1 activity.[283] Both compounds were active against infectious HIV-1 (EC_{50} 0.940 and 1.64 μM, respectively) in human lymphoblastoid host cells (cell growth IC_{50} 29 and 26.9 μM, respectively). They also showed inhibitory activity in an HIV-1 RT assay (IC_{50} 12 and 8 μM, respectively).

Three furoquinoline alkaloids, γ-fagarine (**33**), haplopine (**35**), and (+)-platydesmine (**196**), as well as 4-methoxy1-methylquinolin-2-one (**212**) also inhibited HIV-1 replication in H9 lymphocyte cells at low concentrations ($EC_{50} < 5.85$ μM) without significantly affecting the growth of uninfected H9 cells.[284] Compound **33** showed the best therapeutic index, while **35**, **196**, and **212** were less effective. 2-Acetyl-4(*3H*)-quinazolinone (**118**) also inhibited HIV replication.[162,163]

Moreover, quinoline-containing decadepsipeptides can significantly inhibit HIV-1 RT, but also display notable cytotoxicity against tumor cell lines. Various modified derivatives of sandramycin (**220**) (Fig. 22) (HIV RT IC_{50} 0.13 nM) retained its HIV potency, but exhibited 150- to 1000-fold less cytotoxic activity.[285] Thus, promising candidates could be further developed as HIV-1 chemotherapeutic agents. Three other decadepsipeptides luzopeptins A–C (**83–85**) were identified as potent inhibitors of the HIV RT responsible for the emerging clinical resistance to recently introduced RT inhibitors.[286] Moreover, the rank orders of cytotoxic potency ($A > B >> C$) and antiviral potency/HIV RT inhibition ($C > B > A$) were reversed, and **85** suppressed HIV replication in infected MT-4 cells at noncytotoxic concentrations.[123–126,287]

At very low concentrations, virantmycin (**203**) inhibited various RNA and DNA viruses, including the Indiana strain of vesicular stomatitis virus, Egypt Ar 339 strain of Sindbis virus, M_CM_{ILLAN} strain of Western equine encephalitis virus, MIYADERA strain of Newcastle disease virus, DIE strain of vaccinia virus, IHD strain of vaccinia virus, HF strain of herpes simplex virus type 1, and UW strain of herpes simplex virus type 2.[251,252] The compound affected the cell membranes, including specific virus receptor sites, and suppressed viral replication at a very early stage. In addition, compound **203** showed excellent growth inhibition of influenza virus.[288]

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2-(3,4-Methylenedioxyphenethyl)quinoline (**124**), chimanine D (**122**), 2-pentylquinoline (**120**), and 2-*n*-proplyquinoline (**119**) from *G. longiflora* inhibited the growth of cells infected with human T-lymphotropic virus type 1 (HLTV-1).[289–291] Certain quinolines also showed antiproliferative activity against HTLV-1 infected HUT-102 cells. Evolitrine (**36**) and dictamnine (**40**) inhibited activation of Epstein-Barr virus early antigen in Raji cells.[292]

2.7 | Anti-inflammatory and immunomodulatory activities

2.7.1 | Quinoline alkaloids—

In 2005, Lal and co-workers studied the anti-inflammatory activity of the furoquinoline alkaloid evolitrine (**36**) and its analogs.[293] The results showed that **36** effectively inhibited the formation of edema resulting from sub-plantar injection of carrageena in rats (57% inhibition at a dosage of 20 mg/kg), but did not produce toxic symptoms, cardiovascular effects, or weight loss.[293] Also, the quinolone alkaloid orixalone A (**221**) (Fig. 23) from *Orixa japonica* strongly inhibited NO production in murine macrophage RAW 264.7 cells stimulated with interferon-γ and LPS at micromolar concentrations and, thus, might be used as an anti-inflammatory or cancer-preventive agent to suppress excessive synthesis of NO.[294]

Quinolactacins A1 and A2 (**222**, **223**), B (**224**), and C (**225**) (Fig. 23) were isolated from culture broth of the entomopathogenic fungus *Penicillium* sp. EPF-6.[295,296] This rare compound class contains an *N*-methyl quinolone fused to a lactam ring. Only compound **223** inhibited the production of tumor necrosis factor (TNF) induced by LPS in murine peritoneal macrophages (IC_{50} 12.2 μg/mL) and in macrophage-like J774.1 cells.

In 2003, nine 2-alkyl-4(1*H*)-quinolone alkaloids, **129**, **130**, **141**, **142**, **144**, and **162**–**165** from the fruits of *E. rutaecarpa* were evaluated for immunomodulatory effects.[297] With IC_{50} values between 0.910 and 15.9 μM, these alkaloids inhibited the activity of nuclear factor of activated T cells (NFAT), without affecting cell viability. Among the *N*-methylated quinolones, compounds with longer aliphatic side chains on the quinolone ring showed stronger inhibition of NFAT activity and comparable inhibitory effects against NF-κB activity. These results indicated that these quinolones could be used as lead compounds for treating diseases of the immune system.[297]

2.7.2 | Quinazoline alkaloids—

In 2000, the anti-inflammatory activity of tryptanthrin (**111**) was first reported.[298] This alkaloid significantly inhibited the production of both NO and prostaglandin E_2 (PGE_2) in murine macrophage RAW 264.7 cells activated by interferon-γ and LPS inadose-dependent manner.This potential new anti-inflammatory agent was subsequently investigated for other anti-inflammatory effects and its mechanism of action. In pharmacological studies, **111** ameliorated artificially induced colitis in mice, as well as suppressed weight loss, tissue damage, and subsequent mortality.[299] Meanwhile, it showed 100-fold greater selectivity toward COX-2 than COX-1 in the biosynthesis of eicosanoids, as well as inhibition of 5-lipoxygenase.[300] Moreover, it inhibited the production of interferon-γ and interleukin-2 by lymphocytes in response to staphylococcal enterotoxin B.[301] These results indicated that **111** not only has potent dual effects on prostaglandin and leukotriene synthesis for the treatment of inflammatory diseases, but also can potentially be used to control food-borne intestinal diseases. Finally, Oberthür et al.[302] and Heinemann et

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al.[303] postulated that **111** could be more easily absorbed through the skin than other alkaloids, because of its lower bioavailability resulting from ready crystallization from solution.

Subsequently, the natural vasicinone analog isaindigotone (**226**) (Fig. 23), isolated from *I. tinctoria*, was found to be a superior scavenger of superoxide generated in the hypoxanthine/xanthine oxidase system (IC_{50} 42.2 nM).[304] The compound inhibited PGE_2 and NO generation in RAW 264.7 macrophages stimulated by LPS. Its free phenolic group wasimportanttotheanti-inflammatoryactivity.Thesimplealkaloidquinazoline-2,4-dione(**227**) (Fig. 23)alsoexhibited anti-inflammatory and antihypertensive properties.[305]

In 2006, two indolopyridoquinazolinone alkaloids rutaecarpine (**115**) and evodiamine (**215**), as well as the structurally related quinazoline-2,4-dione goshuyuamide II (**228**) (Fig. 23) were evaluated for anti-inflammatory activity.[306] Compounds **115** and **215** strongly inhibited PGE_2 synthesis in LPS-treated RAW 264.7 cells at 1 to 10 μM, and **215** also inhibited COX-2 induction and NF-κB activation. Compound **228** inhibited 5-lipoxygenase from RBL-1 cells (IC_{50}, 6.60 μM), resulting in reduced synthesis of leukotrienes. However, these three compounds did not inhibit inducible NO synthase-mediated NO production.[306]

2.8 | Anti-Alzheimer's disease and other neurological disorders

2.8.1 | Quinoline alkaloids—The furoquinoline alkaloids skimmianine (**34**), kokusaginine (**37**), and confusameline (**212**) inhibited 5-HT-induced contraction mediated by 5-HT_2 receptors in the presence of methiothepin in rat isolated aorta.[307] These three compounds may act on 5-HT receptors in animals, more selectively to the 5-HT_2 subtype, in the rank order of **34** > **37** > **212**. The quinoline alkaloids benzastatins C (**71**) and D (**72**) inhibited glutamate toxicity in N18-RE-105 cells with EC_{50} values of 2 and 5.40 μM, respectively.[114,115]

The quinolone alkaloid pteleprenine (**229**) (Fig. 24) from *O. japonica* significantly inhibited acetylcholine- and nicotine-induced contraction of guinea pig ileum.[308] Thus, this natural product might be a novel lead compound as an agonist of nicotinic acetylcholine receptors.

2.8.2 | Quinazoline alkaloids—In 1996, the anticholinergic natural product deoxyvasicine (**110**) was identified in a search for a new compound for the treatment of Alzheimer's disease, and a 3-chloro derivative of the parent hexahydroazepino[2,1-*b*]quinazoline structure was found to be about eight-fold more potent as an acetylcholinesterase (AChE) inhibitor than the unsubstituted compound.[309] In addition, both quinolactacin A2 (**223**) and quinolactacin A1 (**222**) inhibited AChE, but **223** was more potent (IC_{50} 19.8 vs 280 μM).[310] 1-Methyl-2-undecylquinolin-4(1*H*)-one (**165**), an *Evodia* alkaloid, acted as an irreversible and selective inhibitor of type B monoamine oxidase.[311]

Dictyoquinazols A–C (**230**–**232**) (Fig. 24), from the mushroom *Dictyophora indusiata,* showed protective effects in primary cultured mouse cortical neurons against the excitotoxicity induced by glutamate and *N*-methyl-D-aspartate in a dose-dependent manner.[312] These results indicated that the above compounds have potential value in the treatment of neurological disorders or neurodegenerative diseases of the brain, such as Parkinson's and

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Alzheimer's diseases and Huntington's chorea. Fiscalins A (**233**), B (**234**), and C (**235**) (Fig. 24), from a fungal culture of *Neosartorya fischeri*, inhibited the binding of substance P, an undecapeptide neurotransmitter, to human neurokinin-I receptors with *Ki* values of 57, 174, and 68 μM, respectively.[313]

2.9 | Herbicidal activity

In 2004, Hale and co-workers found that the 2-phenylquinolinone alkaloid graveoline (**41**) has marked herbicidal activity and may be useful as a biodegradable, environmentally friendly herbicide. It inhibited the germination of representative monocot and dicot seeds, impeded the growth of aquatic duckweed, and reduced cell division in onion.[314] A mixture of two highly substituted 4-phenyl 2-quinolone alkaloids penigequinolones A (**148**) and B (**149**) inhibited the growth of tea pollen tubes by 40% at 10 mg/L and 100% at 100 mg/L.[315] Compared with other natural pollen inhibitors, the mixture's effects were stronger than those of emeniveol, but weaker than those of hericerin and isofunicone.[315]

2.10 | Effects on CYP450 family and cytochromes

In 1990, Oettmeier et al. reported that aurachins A–D (**177**–**180**) inhibit photosynthetic electron transport.[316] Aurachin C (**179**) was an extremely potent inhibitor of the quinol oxidation sites of two different cytochrome enzymes and competed for the binding sites normally occupied by quinones of the electron transport chain. Aurchin D (**180**) was a highly effective inhibitor of cytochrome bd. Both **179** and **180** were active on the cytochrome b_6/f-complex, the latter showing the most pronounced inhibition to date.[317]

In 2003, Don et al. studied the indolopyridoquinazolinone alkaloid rutaecarpine (**115**) and its analogs for their effects on CYP450.[318] 2-Methoxyrutaecarpine **(134)** and **115** inhibited all three cytochromes (CYP1A1, CYP1A2, and CYP1B1) of the human cytochrome P450 family without particular selectivity. Alkaloid **115** also modulated the effects of CYP1A1 and 1A2 in human or mouse liver and kidney and CYP2B in rat liver.[319–322] and the Cinchona alkaloid quinidine (**28**) also modified CYP3A4 activity.[323]

Finally, the quinazoline-benzodiazepine alkaloids, (−)-circumdatins H (**236**) and E (**237**) (Fig. 25), isolated from fungal sources, inhibited the mitochondrial respiratory chain in submitochondrial particles from beef heart.[324] Their effects were presumably due to interference with NADH oxidase activity (IC_{50} 1.50 and 2.50 μM, respectively).

2.11 | Hypolipidemic and anti-hyperglycemic activities

FR225659 (**238**) and four related compounds (**239**–**242**) (Fig. 25) were isolated from the culture broth of *Helicomyces* sp. No. 19353 as novel gluconeogenesis inhibitors in 2003.[325,326] Despite high hypoglycemic activity in vitro, **241** and **242** exhibited weak or no activity in vivo, while **240** showed weak activity in vitro and in vivo. Compounds **238** and **239** showed significant activity, and furthermore, orally administered **238** suppressed glucagon-induced hyperglycemia in mice. The peripheral blood glucose levels of db/db mice, an animal model of spontaneous type 2 diabetes, were significantly decreased in a dose-dependent manner by the administration of **238**. Thus, this compound could be used as a novel lead to develop new hypoglycemic agents.[325–327]

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Activity-guided fractionation based on inhibition of diacylglycerol acyltransferase led to the isolation of evocarpine (**141**), dihydroevocarpine (**142**), 1-methyl-2-[(4*Z*,7*Z*)-4,7-decadienyl]-4(1*H*)-quinolone (**163**), and 1-methyl-2-[(6*Z*,9*Z*)-6,9-pentadecadienyl]-4(1*H*)-quinolone **(164)** from the fruits of *E. rutaecarpa*.[328] The four compounds displayed moderate activity (IC_{50} 23.8, 69.5, 20.1, and 13.5 μM, respectively) suggesting they could be used in the design of hypolipidemic and antiobesity agents.

2.12 | Anti-oxidant activity

In 2006, jineol (**52**) and 2,8-dihydroxy-3,4-dimethoxyquinoline (**243**) (Fig. 25) were isolated from the centipede *S. subspinipes*.[329] Both compounds exhibited antioxidant activities on copper-mediated (IC_{50} 2.60 and 63.0 μM), AAPHmediated oxidation (IC_{50} 3.90 and 71.8 μM), and SIN-1-mediated oxidation (70% and 29% at 5 μM) in thiobarbituric acid reactive substances (TBARS) assay. Both compounds also showed 1,1-diphenyl-2-picrylhydrasyl radical scavenging activity and **52** exhibited metal chelating activity.[329]

Moreover, 4-carbomethoxy-6-hydroxy-2-quinolone (**95**), from the aleuronic layer of the dark purple anthocyaninpigmented rice cultivar *O. sativa* cv. *Heugjinmi*, exhibited moderate anti-oxidative activity in a radical-scavenging assay (IC_{50} 166 μM).[330] The quinoline alkaloids benzastatins C (**71**) and D (**72**) were also identified as free-radical scavengers, inhibiting lipid peroxidation in rat liver microsomes with EC_{50} values of 3.30 and 4.20 μM, but they were less effective than vitamin E (0.400 μM).[114,115]

2.13 | Bronchodilator activity

In 1959, Amin and Merta identified the effect of quinazolin-4(3*H*)-one (**133**) and vasicinone (**158**) on bronchial musculature.[331] In in vitro tests on guinea pig tracheal rings, these two compounds produced relaxation at 495 μM, about 1/2000 the activity of adrenaline, whereas vasicine (**3**) caused slight relaxation at 53.2 μM, but contraction at higher concentrations.[332]

In 1996, Kamikawa et al. reported that three pyranoquinolone alkaloids flindersine (**31**), veprisine (**127**), and *N*-methylflindersine **(244)** (Fig. 25) from *Fagara chalybea* showed good bronchodilator activity on both perfused guinea pig lungs and isolated tracheal preparations.[333] Compounds **31** and **244** were slightly less potent than **127**. Compound **127** also exhibited moderate positive inotropic activity on guinea pig left atria, which was inhibited by propranolol, indicating the presence of a β_2-agonist action. In addition, all three compounds were antagonists of slow reacting substance-A (SRS-A), with **127** active at a concentration as low as 1 μg/mL without showing antihistaminic and anti-serotonin properties.[333]

2.14 | Mutagenicity

In 1987, the mutagenic activity of extracts of *R. graveolens* was attributed in part to well-known furoquinoline alkaloids.[334] Schimmer and co-workers reported further study results in 1988 and 1989.[335,336] γ-Fagarine (**33**), skimmianine (**34**), and dictamnine (**40**) exhibited strong mutagenicity in *S. typhimurium* strains TA98 and TA100, but had comparatively little or no activity in the corresponding non-R-factor strains TA1538 and TA1535.[335] The metabolic capacity of the corresponding liver microsome preparations was increased by pretreatment of rats with phenobarbital (Pb) and to a lesser amount with 3-

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methylkholanthrene. The results suggested that furoquinolines are activated to mutagenic metabolites by cytochrome P450 and cytochrome P448, and feasibly the flavin-containing monooxygenase.[335] Alkaloid **33** induced sister chromatid exchange in human lymphocyte culture.[336] Akaloid **40** showed photo-induced genotoxicity toward an *E.* coli lysogen, as determined by prophage induction.[337]

2.15 | Other activities

2-Methyl-4(*3H*)-quinazolinone (**245**) (Fig. 25) from the culture broth of the micro-organism *B. cereus* BMH225-mF1 strongly inhibited poly(ADP-ribose) synthetase (IC_{50} 1.10 μM) and was competitive with the substrate.[338] It also had low acute toxicity, and the mice tolerated i.p. treatment with 250 mg/kg of compound.

Eduline (**246**) and japonine (**247**) (Fig. 25), two well-known 2-phenyl 4-quinolone alkaloids from *O. japonica*, showed strong relaxant activity on small intestine muscle, with equal potency (relaxative tension 0.17 ± 0.05 g at 10 μM for **245**, 0.12 ± 0.03 g at 5 μM for **246**) to that of papaverine (10 μM, 0.16 ± 0.03 g).[339] The quinazoline alkaloid vasicine (**3**) potentiated the effect of oxytocin on rat mammary gland and stimulated muscular contraction in guinea pig ileum and uterus.[340]

The furoquinoline alkaloids μ-fagarine (**33**), skimmianine (**34**), and haplopine (**35**) showed pronounced estrogenic activity.[341] When these three compounds (10 mg/kg) were administered to immature rats, the uterine mass increased by 193.9%, 22.6%, and 74.4% without liquid. The compounds differed structurally only in the C-7 substituent (H, OMe, OH, respectively). Results with other compounds also showed that the basicity/electronic state of the N atom influences the level of estrogenic activity.[341]

3 | CONCLUSIONS AND OUTLOOK

Since the first quinoline alkaloid (quinine) and quinazoline alkaloid (vasicine) were identified in 1820 and 1888, respectively, quinoline and quinazoline alkaloids have attracted significant attention from researchers worldwide, and represent a promising and expanding platform for active natural compounds.

Among these compounds, CPT is the most famous and important as a DNA topo I inhibitor. Its discovery opened a new area for anticancer drug development. Subsequently, many alkaloids containing a quinoline ring, such as luzopeptin C, streptonigrin, BE-22179 and thiocoraline, with significant inhibitory effects on DNA and RNA synthesis and the topo II enzyme have been identified. The molecular structures have provided valuable clues for antitumor drug design. Besides quinine, the discoveries of febrifugine, tryptanthrin, and their analogs with significant antimalarial activity and different mechanism of action have provided additional modalities for treating malarial disease. These novel classes of compounds have opened a new chapter for study in the chemotherapy of malaria. Alkyl methyl quinolone alkaloids have a highly selective and unique antimicrobial mechanism different from that of other antibiotics, and thus, may be beneficial in the treatment of *H. pylori*-associated gastroduodenal diseases. In addition to the aforementioned activities, quinoline and quinazoline alkaloids exhibit other important bioactivities, such as antifungal,

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antiparasitic, insecticidal, anti-inflammatory, antiplatelet, and other effects. We hope that such compounds will provide more avenues for the development of new drugs in the future, particularly as improved methods of isolation and identification of quinoline and quinazoline alkaloids open the way to targeted pharmacological modeling and resulting synthetic modification.

Undoubtedly, these two alkaloid classes will attract tremendous continued attention and long-lasting interest from boththeacademiccommunityandthepharmaceuticalindustrytoadvancethediscoveryofnewandbetterdrugsbased on the original effects of the naturally occurring quinoline and quinazoline alkaloids.

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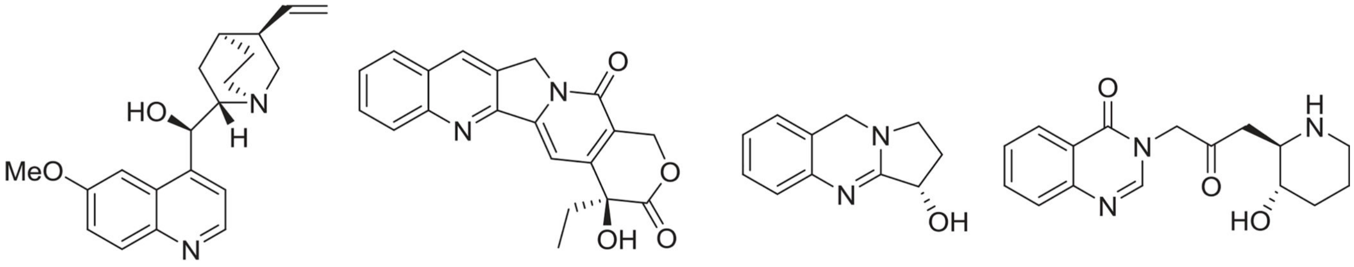

1 Quinine **2** Camptothecin (CPT) **3** Vasicine **4** Febrifugine

FIGURE 1:

Chemical structures of historically important quinoline and quinazoline alkaloids **1–4**

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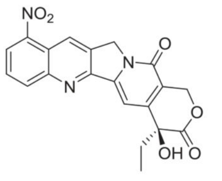

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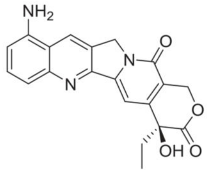
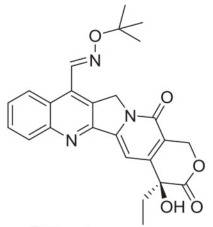


6 9-Aminocamptothecin



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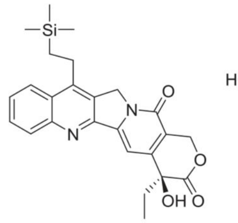

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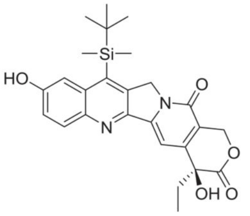
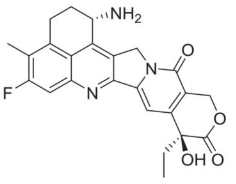


9 DB-67



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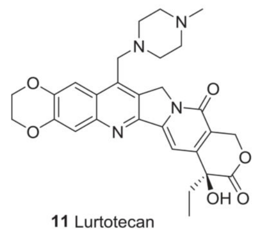

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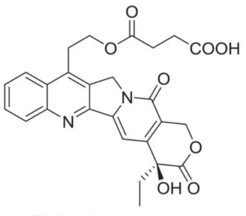

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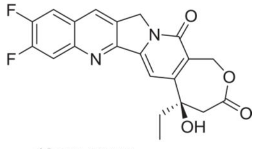

13 BN-80915

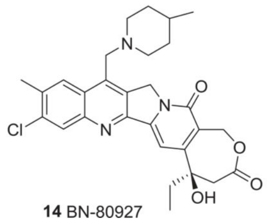

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FIGURE 2:

The chemical structures of camptothecin analogs **5–14**

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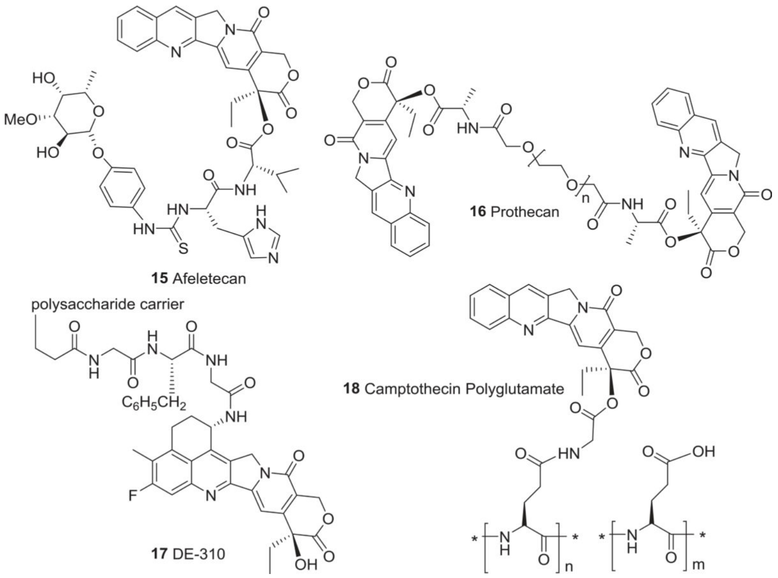

15 Afeletecan

16 Prothecan

17 DE-310

18 Camptothecin Polyglutamate

FIGURE 3:

The chemical structures of camptothecin analogs **15–18**

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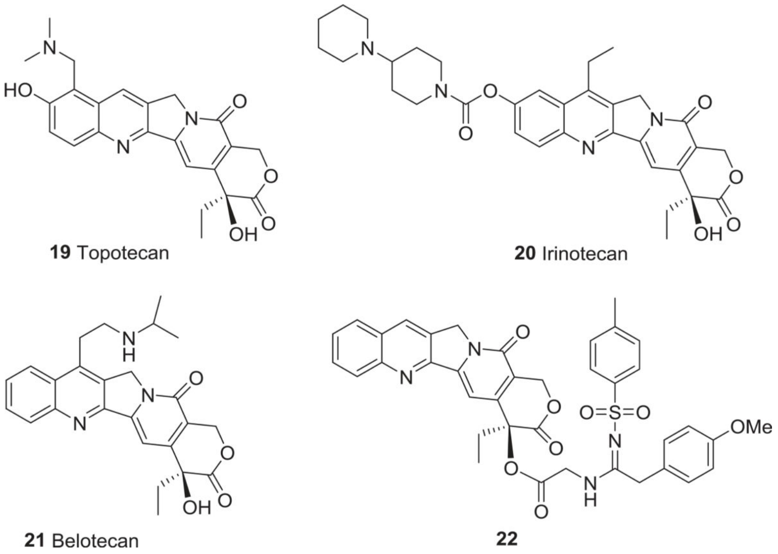

19 Topotecan

20 Irinotecan

21 Belotecan

22

FIGURE 4:

The chemical structures of camptothecin analogs **19–22**

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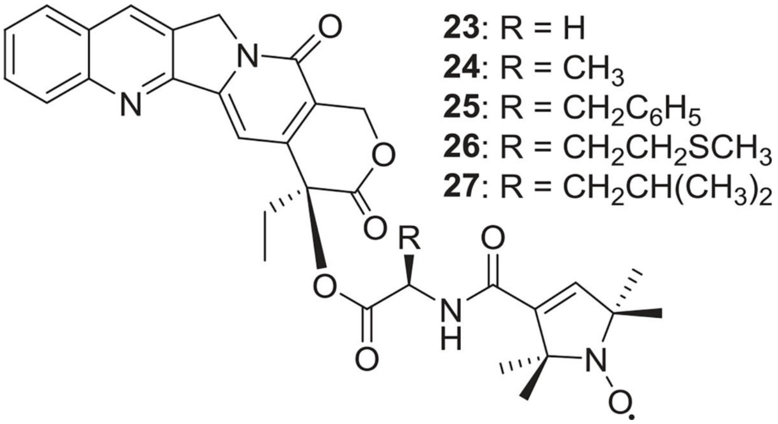

FIGURE 5:

The chemical structures of camptothecin analogs **23–27**

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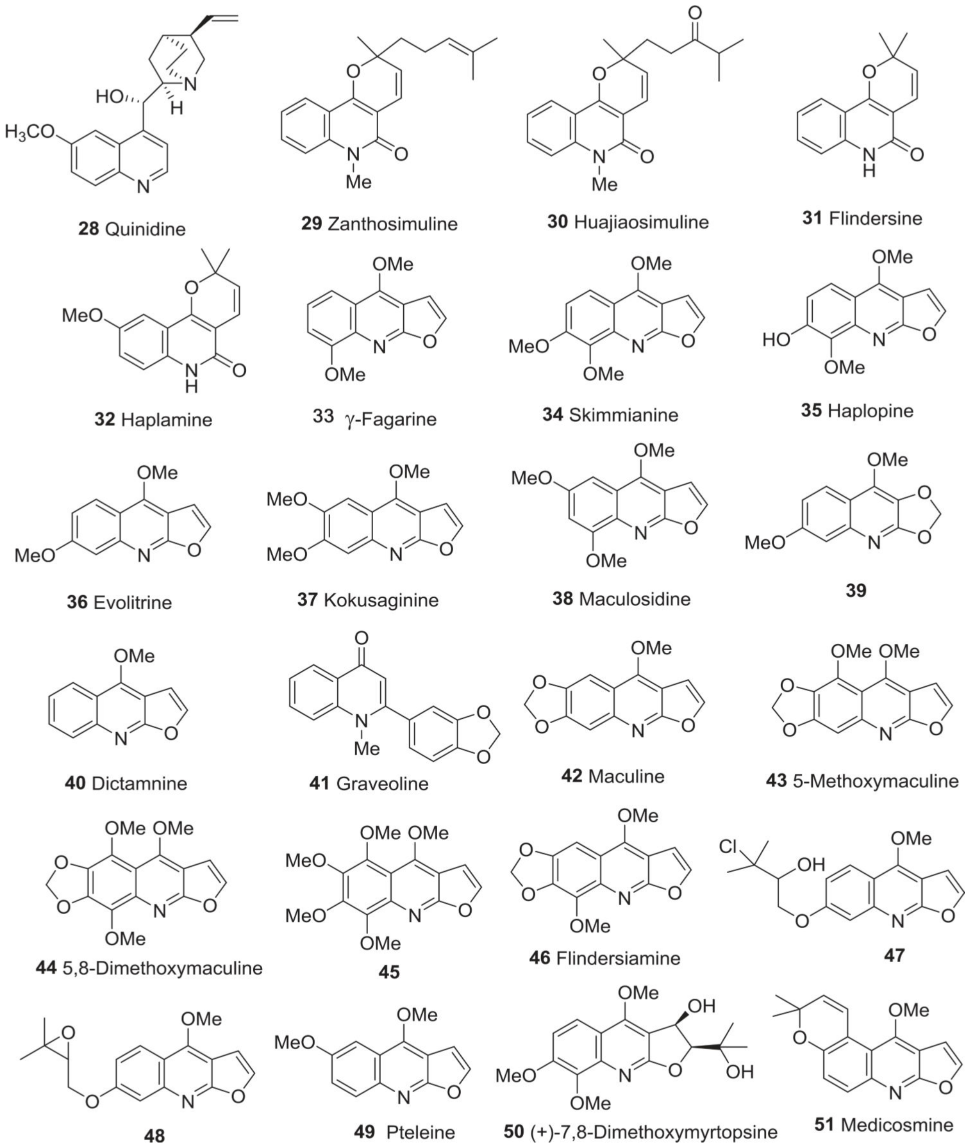

28 Quinidine
29 Zanthosimuline
30 Huajiaosimuline
31 Flindersine
32 Haplamine
33 γ-Fagarine
34 Skimmianine
35 Haplopine
36 Evolitrine
37 Kokusaginine
38 Maculosidine
39
40 Dictamnine
41 Graveoline
42 Maculine
43 5-Methoxymaculine
44 5,8-Dimethoxymaculine
45
46 Flindersiamine
47
48
49 Pteleine
50 (+)-7,8-Dimethoxymyrtopsine
51 Medicosmine

FIGURE 6:

Chemical structures of compounds **28–51**

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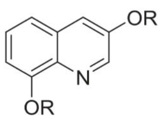
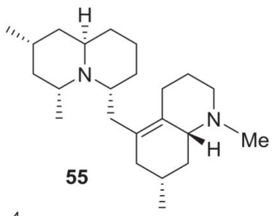


52 Jineol, R=H
53 R=Me
54 R=Ac



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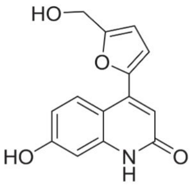

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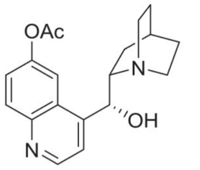
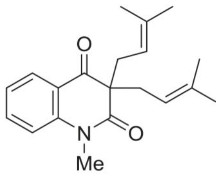


57 Acetylcupreine



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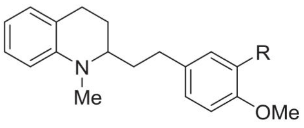
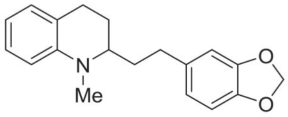
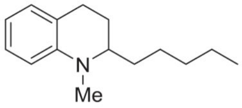


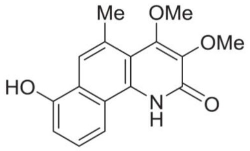
59 Cuspareine, R = OMe
60 Galipeine, R = OH



61 Galipinine



62 Angustureine



63 Asimicilone

FIGURE 7:

Chemical structures of compounds **52–63**

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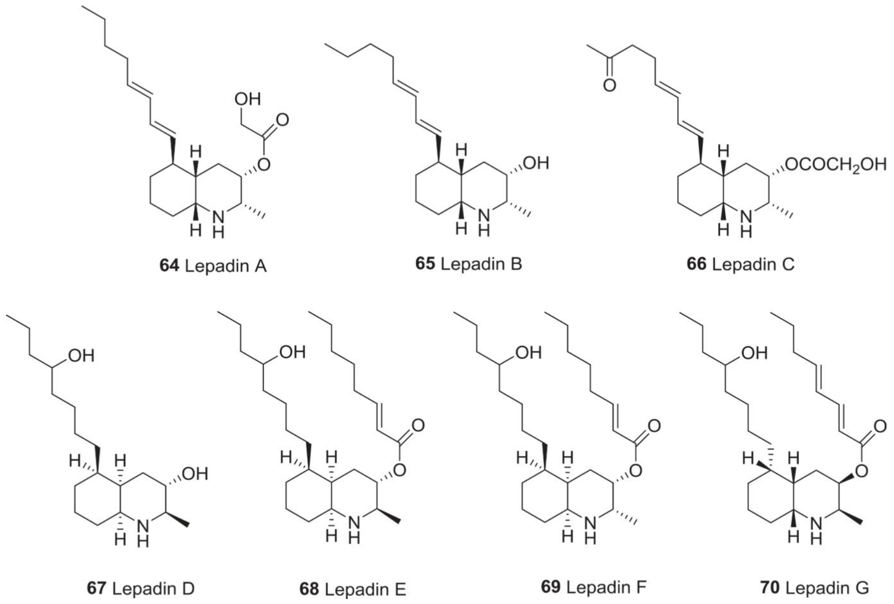

64 Lepadin A **65** Lepadin B **66** Lepadin C

67 Lepadin D **68** Lepadin E **69** Lepadin F **70** Lepadin G

FIGURE 8:

Chemical structures of compounds **64–70**

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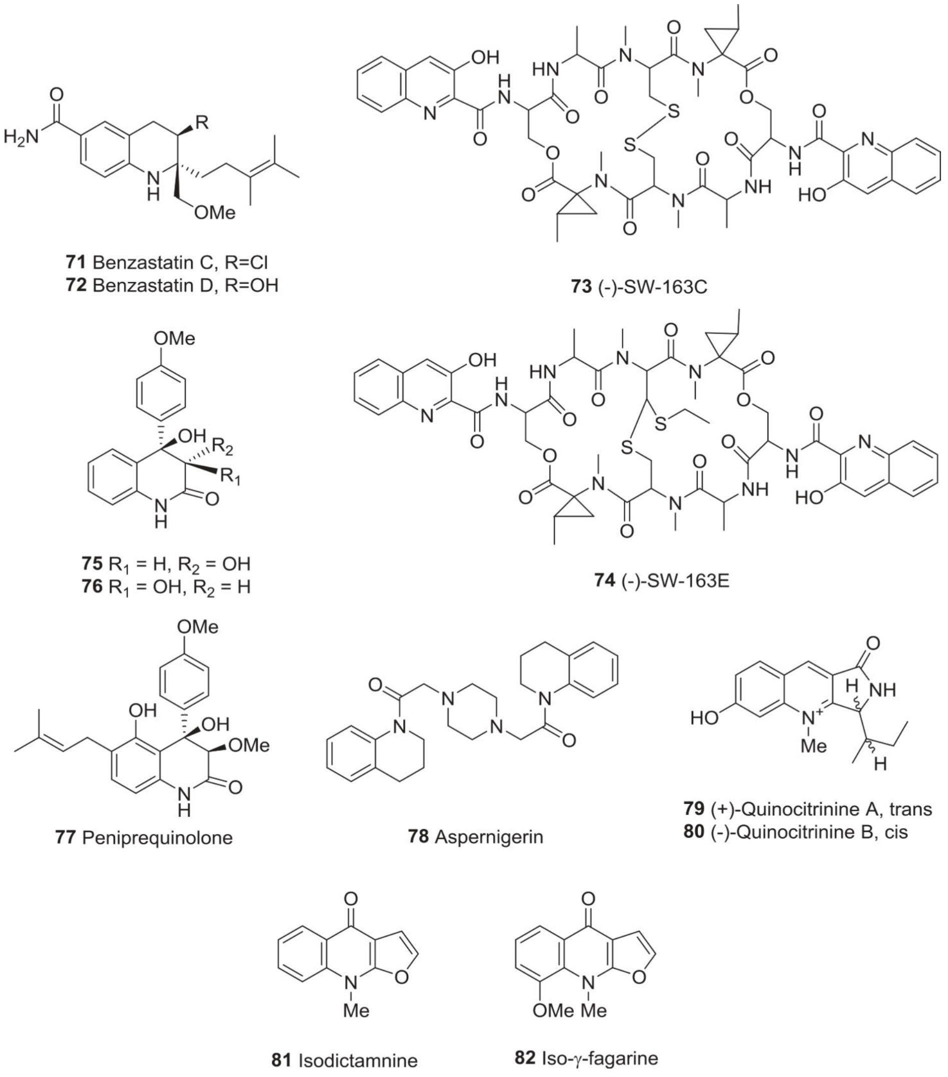

FIGURE 9 :

Chemical structures of compounds **71–82**

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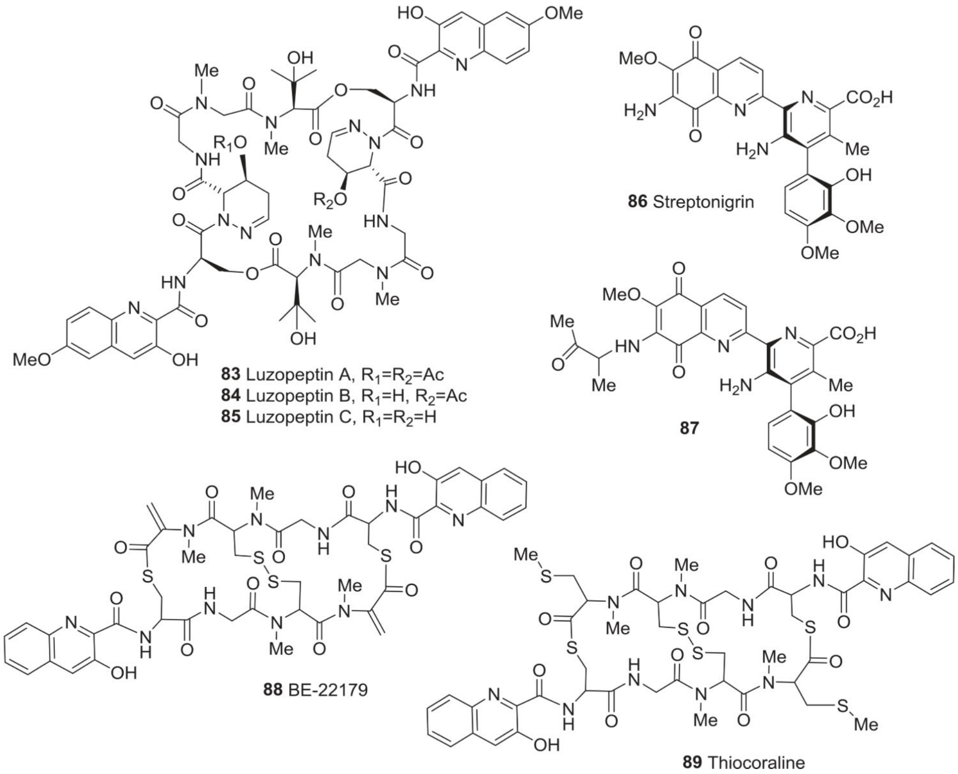

83 Luzopeptin A, R_1=R_2=Ac

84 Luzopeptin B, R_1=H, R_2=Ac

85 Luzopeptin C, R_1=R_2=H

86 Streptonigrin

87

88 BE-22179

89 Thiocoraline

FIGURE 10:

Chemical structures of compounds **83–89**

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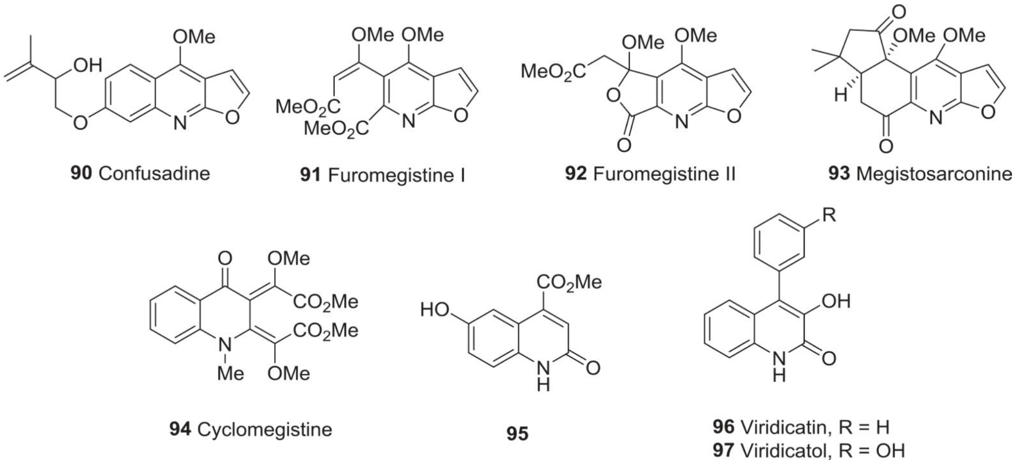

FIGURE 11:
Chemical structures of compounds **90–97**

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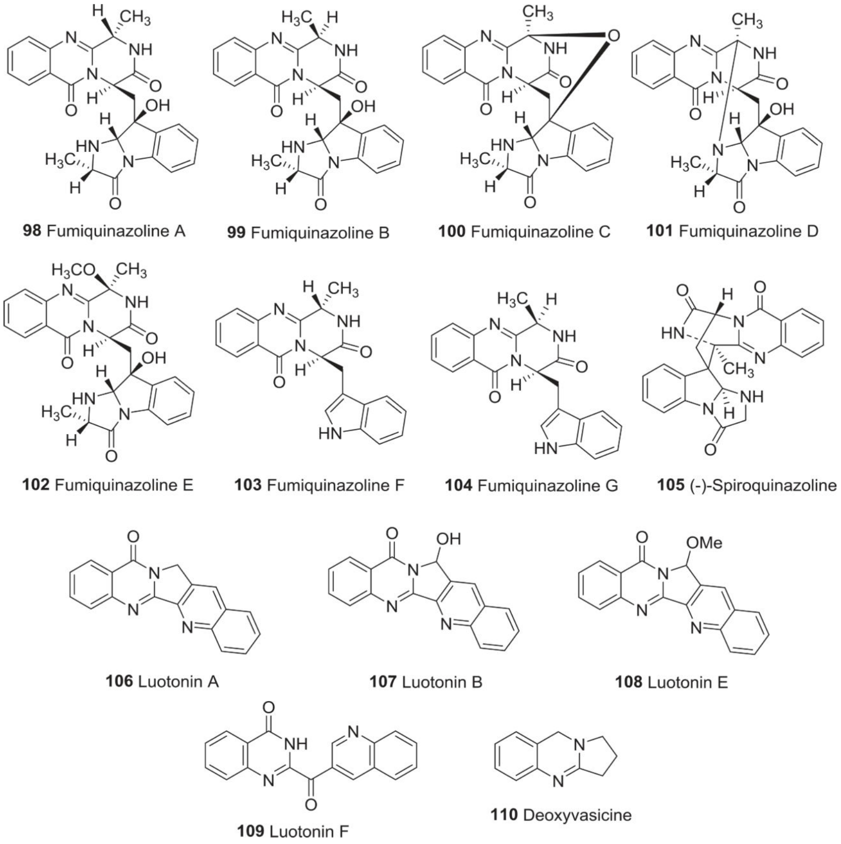

98 Fumiquinazoline A **99** Fumiquinazoline B **100** Fumiquinazoline C **101** Fumiquinazoline D

102 Fumiquinazoline E **103** Fumiquinazoline F **104** Fumiquinazoline G **105** (-)-Spiroquinazoline

106 Luotonin A **107** Luotonin B **108** Luotonin E

109 Luotonin F **110** Deoxyvasicine

FIGURE 12:

Chemical structures of compounds **98–110**

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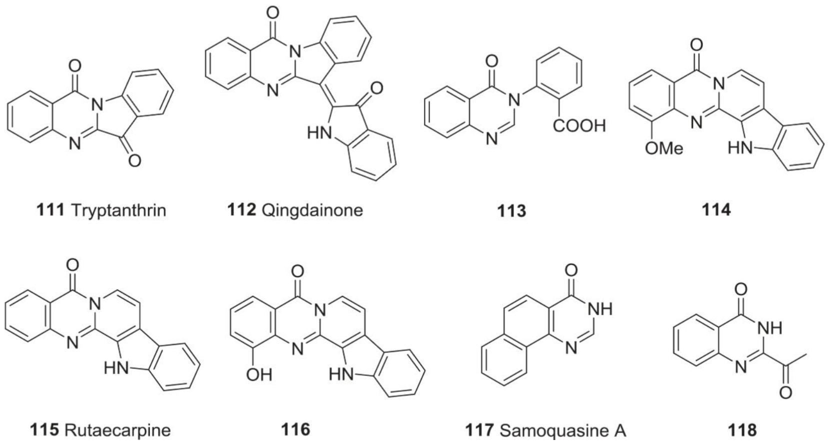

FIGURE 13:
Chemical structures of compounds **111–118**

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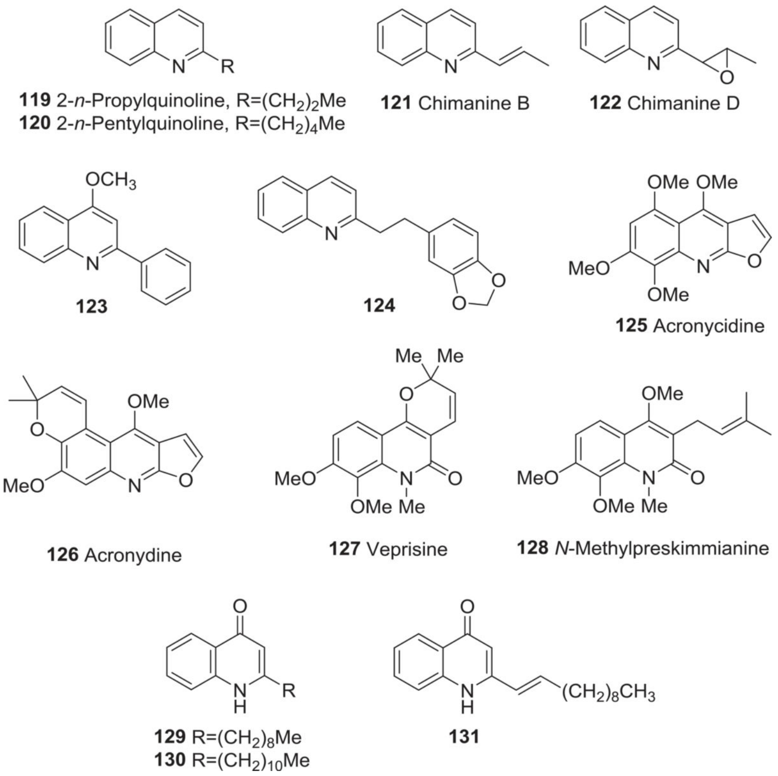

FIGURE 14:

Chemical structures of compounds **119–131**

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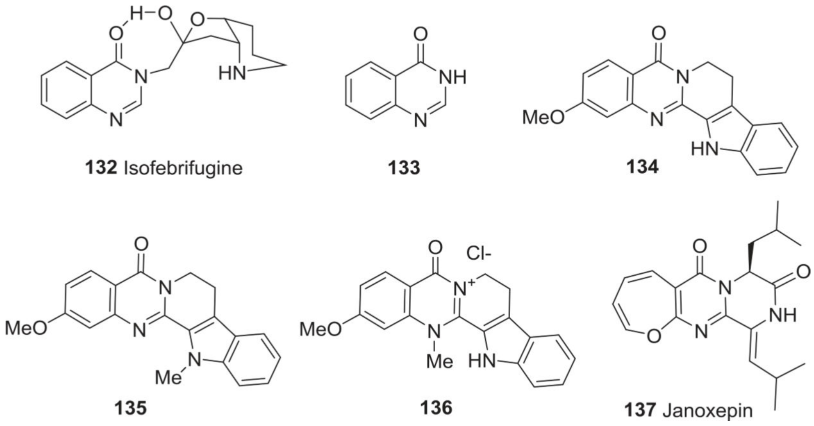

132 Isofebrifugine

133

134

135

136

137 Janoxepin

FIGURE 15:

Chemical structures of compounds **132–137**

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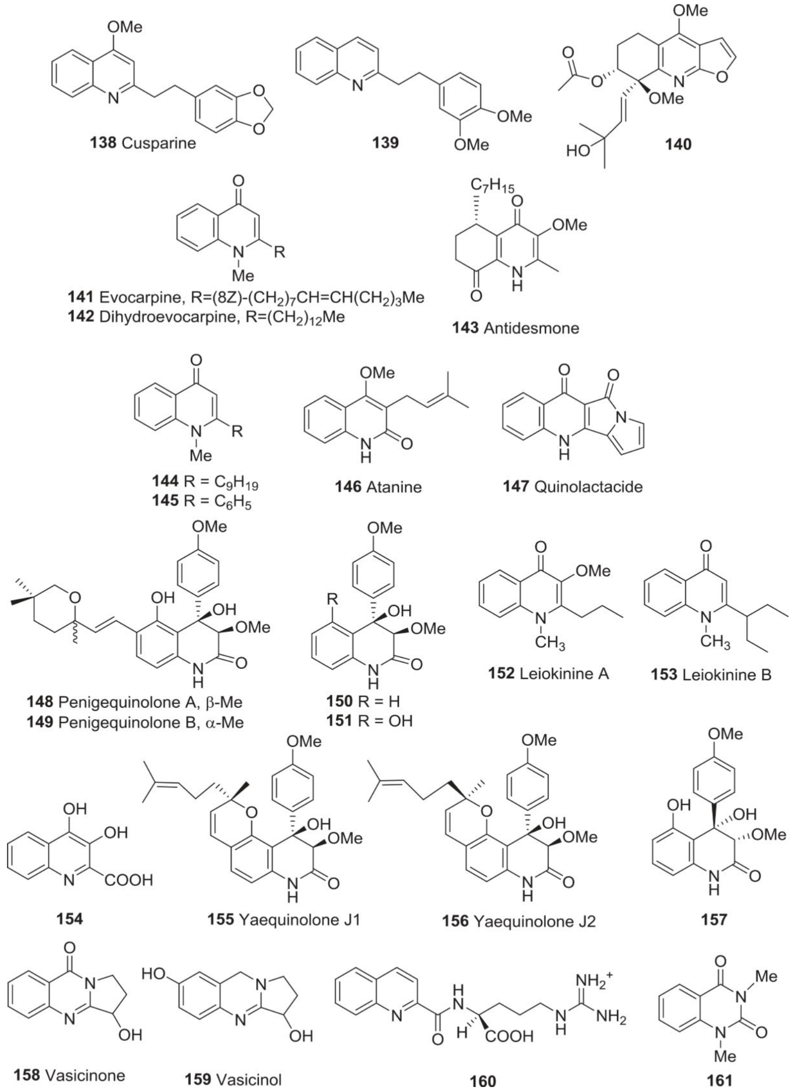

FIGURE 16:

Chemical structures of compounds **138–161**

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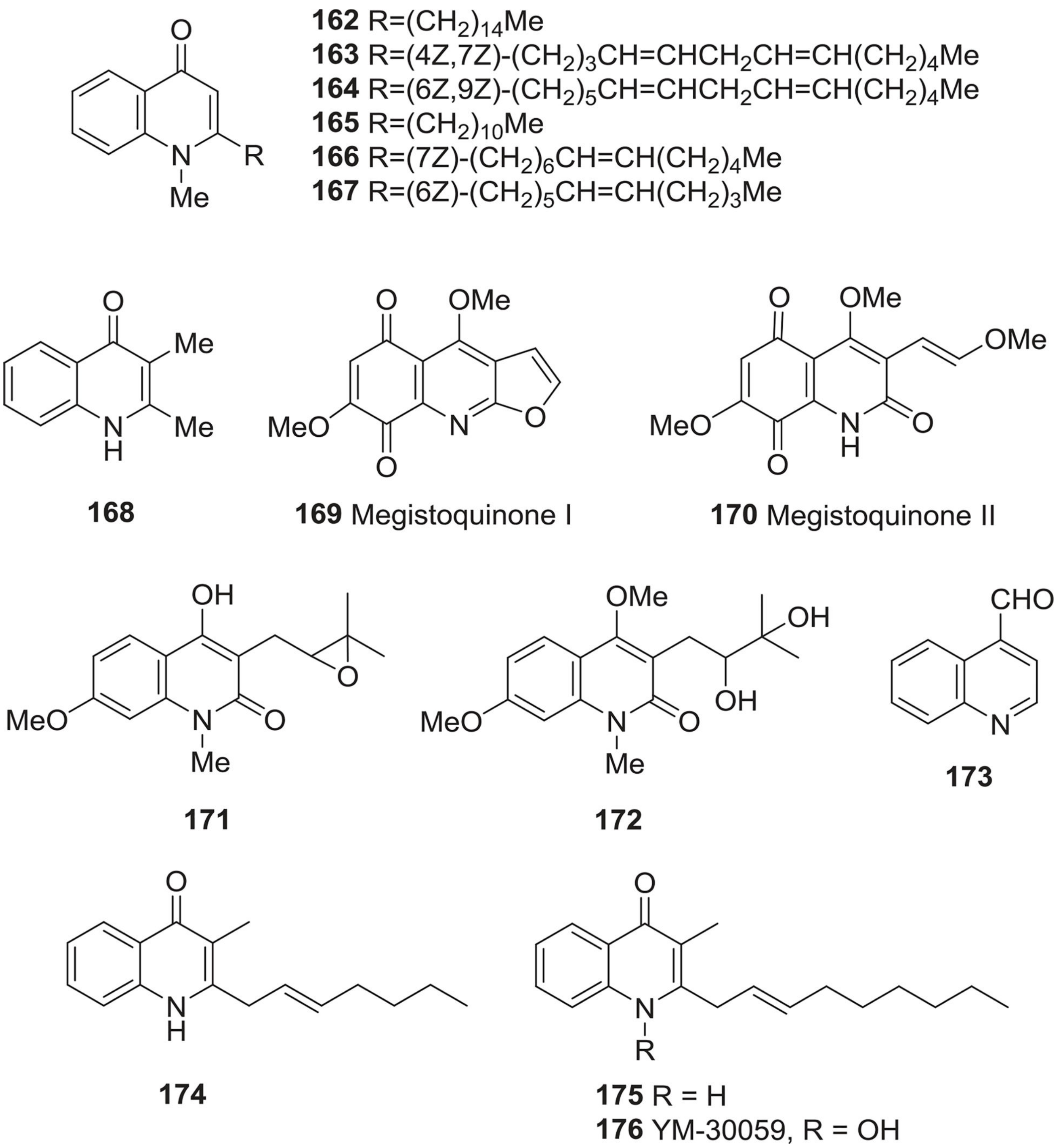

FIGURE 17:
Chemical structures of compounds **162–176**

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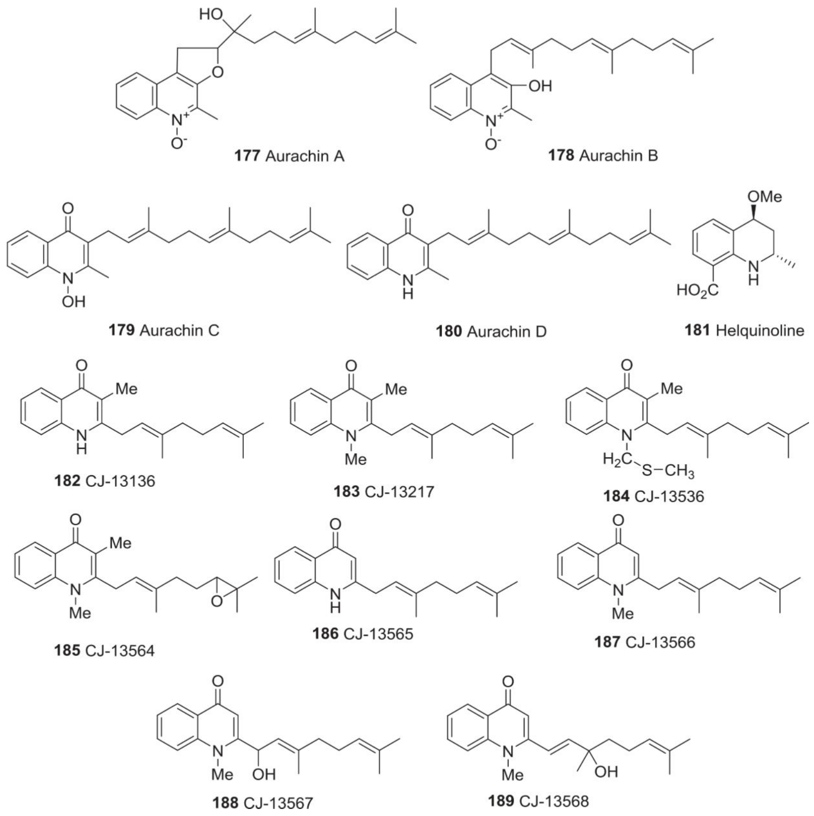

FIGURE 18:

Chemical structures of compounds **177–189**

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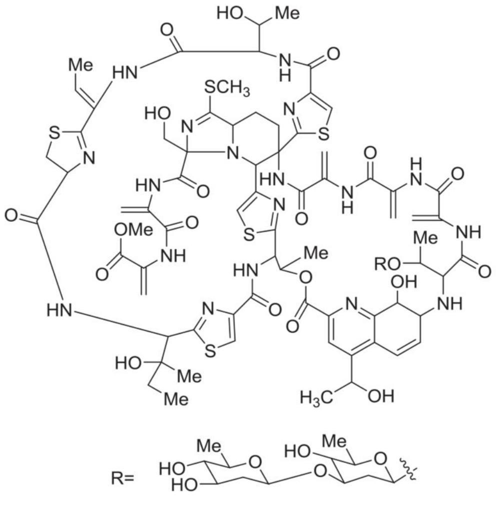
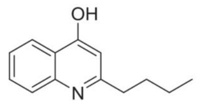
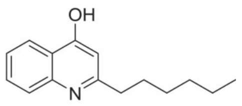
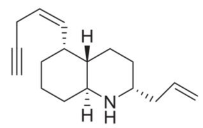
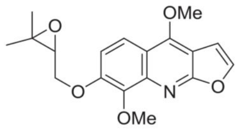

190 Sch 40832


191 2-Pentylquinolin-4-ol


192 2-Heptylquinolin-4-ol


193


194 Anhydroevoxine

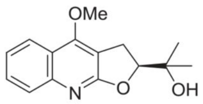

195 Platydesmine

FIGURE 19:

Chemical structures of compounds **190–195**

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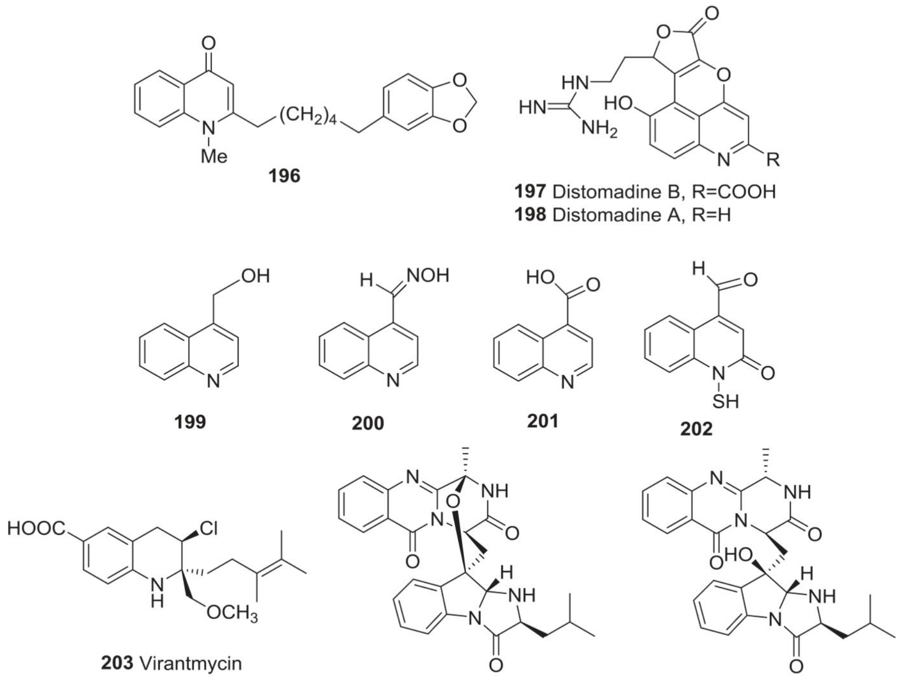

196

197 Distomadine B, R=COOH
198 Distomadine A, R=H

199

200

201

202

203 Virantmycin

204 Fumiquinazoline H

205 Fumiquinazoline I

FIGURE 20:

Chemical structures of compounds **196–205**

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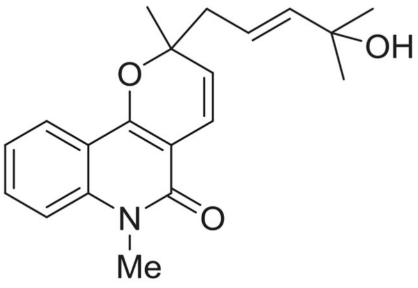
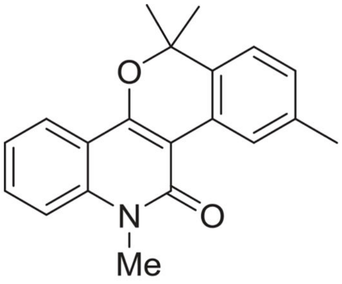
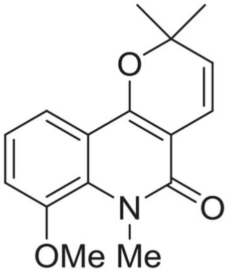


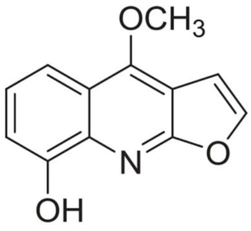
206 Simulenoline



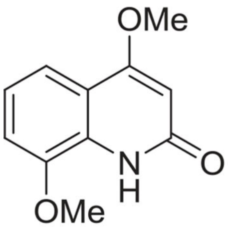
207 Benzosimuline



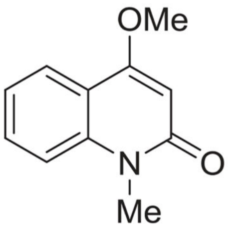
208



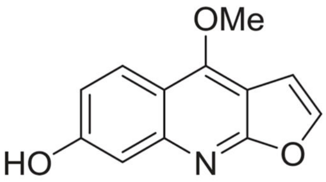
209 Robustine



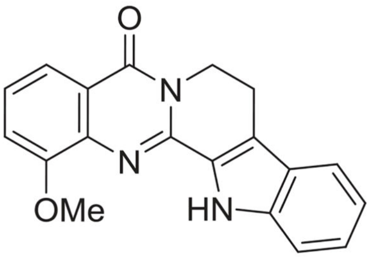
210 Edulitine



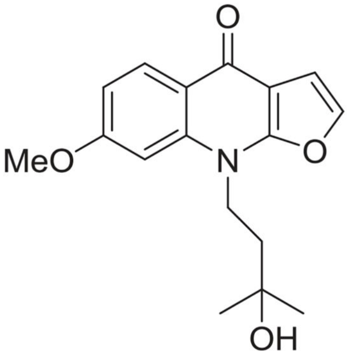
211



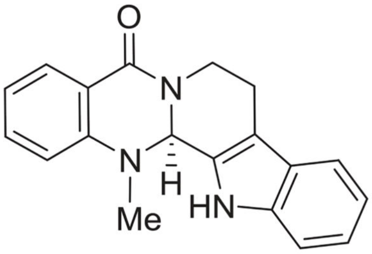
212 Confusameline



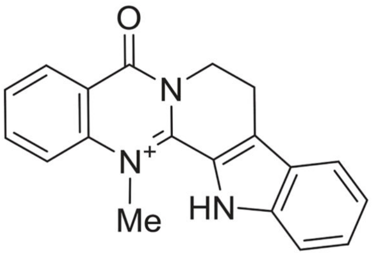
213



214 Acrophyllidine



215 Evodiamine



216 Dehydroevodiamine

FIGURE 21:
Chemical structures of compounds **206–216**

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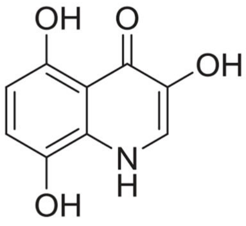
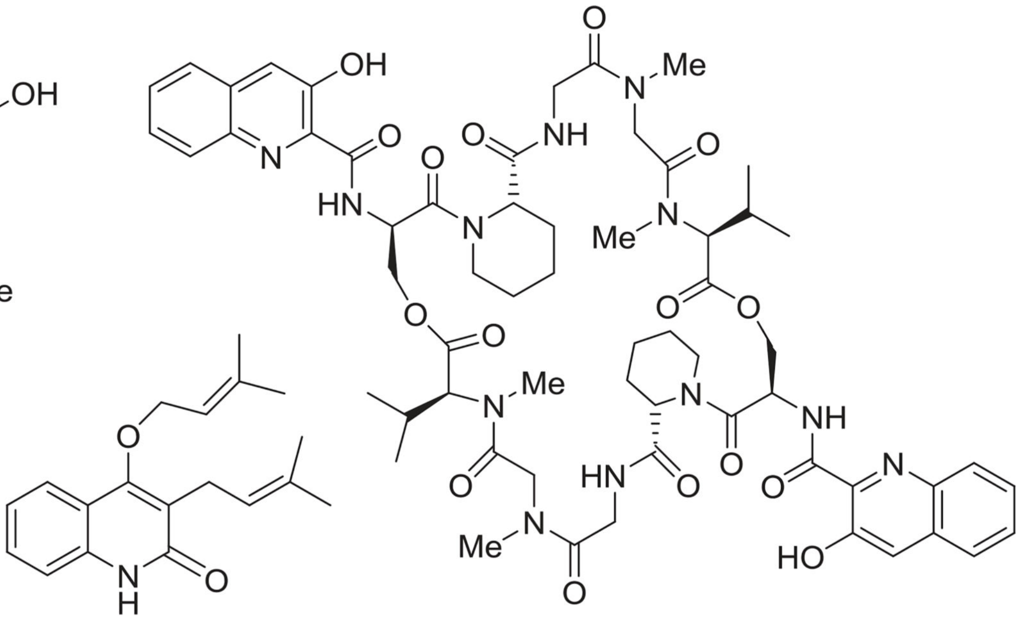
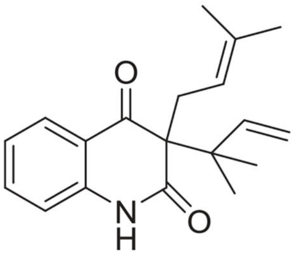


217 Uranidine





218 Buchapine

219

220 Sandramycin

FIGURE 22:

Chemical structures of compounds **217–220**

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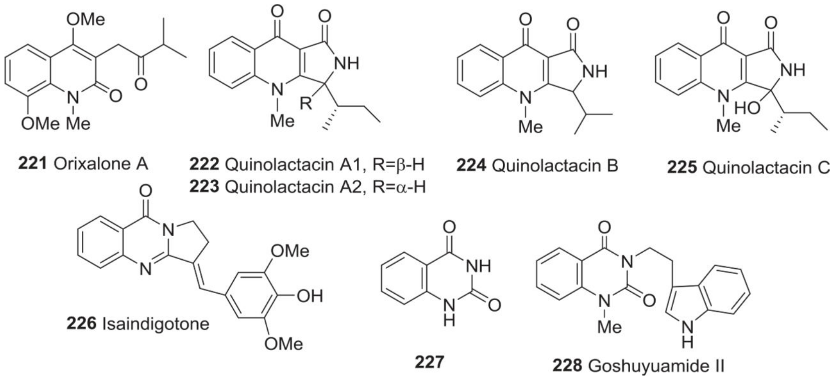

FIGURE 23:

Chemical structures of compounds **221–228**

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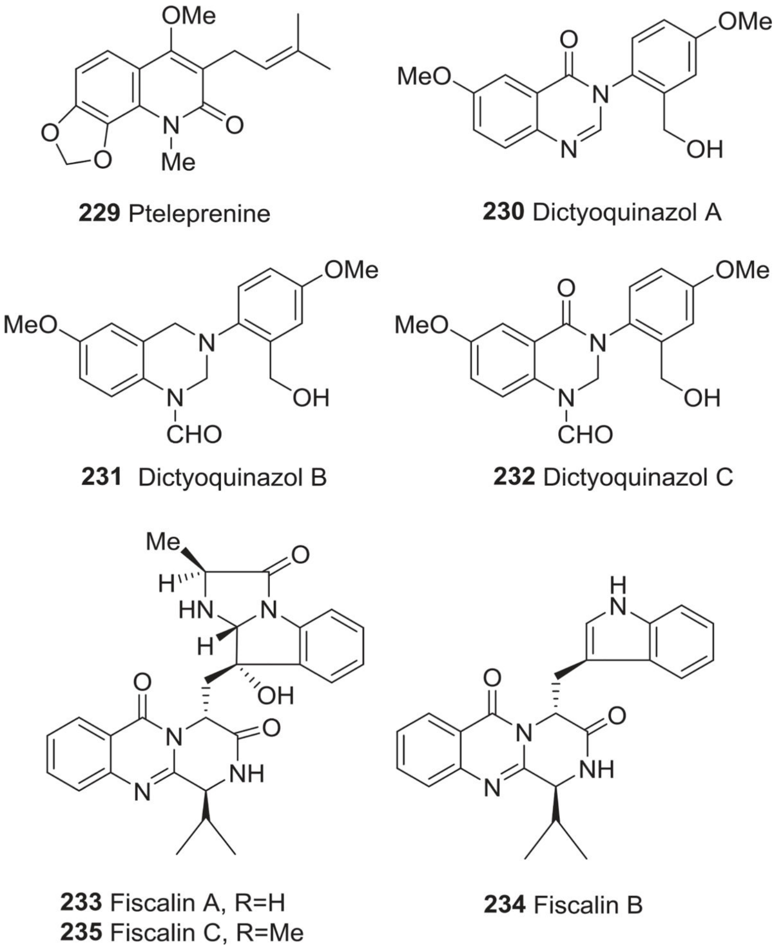

229 Pteleprenine

230 Dictyoquinazol A

231 Dictyoquinazol B

232 Dictyoquinazol C

233 Fiscalin A, R=H

235 Fiscalin C, R=Me

234 Fiscalin B

FIGURE 24:

Chemical structures of compounds **229–235**

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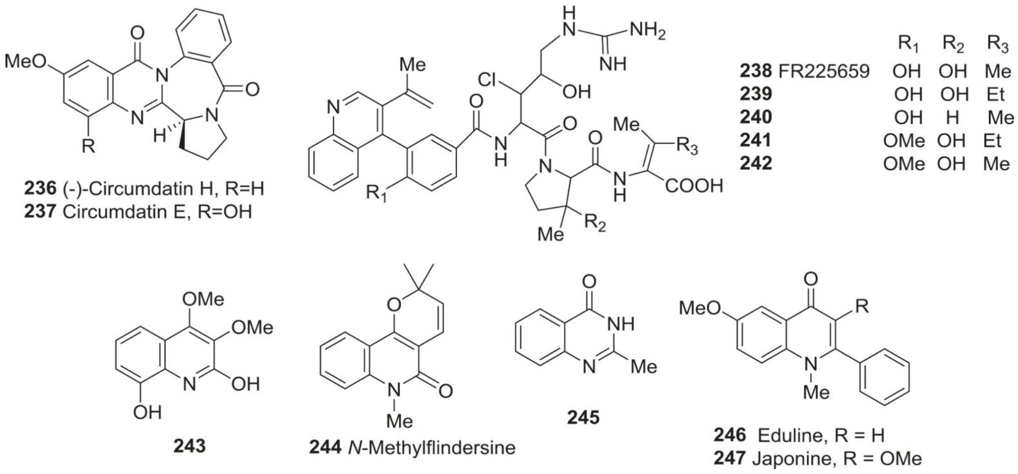

	R$_1$	R$_2$	R$_3$
238 FR225659	OH	OH	Me
239	OH	OH	Et
240	OH	H	Me
241	OMe	OH	Et
242	OMe	OH	Me

FIGURE 25:
Chemical structures of compounds **236–247**

Table 1

The active quinolone and quinazoline alkaloids[a]

No.	Compound	Activity	Reference
1	Quinine	Anti-tumor activity	93
		Antimalarial activity	2,3,166,167
		Trypanocidal activity	108
2	Camptothecin	Anti-tumor activity	6,60–64
3	Vasicine	Antifeedant activity	215
		Cardiovascular protective activity	281
		Bronchodilator activity	332
		Oxytocic activity	340
4	Febrifugine	Antimalarial activity	176–186
		Trypanocidal activity	219
28	Quinidine	Anti-tumor activity	91,92
		Antiarrhythmic activity	256–266
		Effect on CYP3A4	323
29	Zanthosimuline	Anti-tumor activity	94
30	Huajiaosimuline	Anti-tumor activity	94,95
		Antiplatelet activity	95
31	Flindersine	Anti-tumor activity	96,97
		Anti-bacterial activity	228
		Anti-fungal activity	244
		SRS-A antagonist	333
32	Haplamine	Anti-tumor activity	97
		Anti-fungal activity	244
33	γ-Fagarine	Anti-tumor activity	100,121
		Antiplatelet activity	95
		Cardiovascular protective activity	275
		Anti-HIV activity	284
		Mutagenicity	336
		Estrogenic activity	341
34	Skimmianine	Anti-tumor activity	98,100
		Antimalarial activity	173
		Anti-leishmania activity	199
		Trypanocidal activity	200
		Anti-bacterial activity	228
		Anti-fungal activity	245
		Antiplatelet activity	95,269–272
		Cardiovascular protective activity	273,275
		Antagonists at the 5-HT$_2$ receptor site	307
		Mutagenicity	335
		Estrogenic activity	341

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No.	**Compound**	**Activity**	**Reference**
35	Haplopine	Anti-tumor activity	97
		Antimalarial activity	173
		Anti-bacterial activity	228
		Antiplatelet activity	95
		Cardiovascular protective activity	275
		Anti-HIV activity	284
		Estrogenic activity	341
36	Evolitrine	Anti-tumor activity	98
		Antifeedant activity	201
		Antiplatelet activity	269–272
		Cardiovascular protective activity	275
		Antiviral activity	292
		Anti-inflammatory activity	293
37	Kokusaginine	Anti-tumor activity	98
		Antimalarial activity	173
		Trypanocidal activity	200
		Insecticidal activity	203,204
		Anti-bacterial activity	228
		Anti-fungal activity	245
		Antiplatelet activity	269–272
		Cardiovascular protective activity	275
		Antagonists at the 5-HT$_2$ receptor site	307
38	Maculosidine	Anti-tumor activity	98
39	2,3-Methylenedioxy-4,7-dimethoxyquinoline	Anti-tumor activity	98
40	Dictamnine	Anti-tumor activity	99,100
		Antifeedant activity	201,202
		Anti-fungal activity	245,246
		Antiplatelet activity	267,269–272
		Cardiovascular protective activity	275
		Antiviral activity	292
		Mutagenicity	335
41	Graveoline	Anti-tumor activity	99
		Herbicidal activity	314
42	Maculine	Anti-tumor activity	101
		Anti-fungal activity	245
43	5-Methoxymaculine	Anti-tumor activity	101
44	5,8-Dimethoxymaculine	Anti-tumor activity	101
45	4,5,6,7,8-Pentamethoxyfuroquinoline	Anti-tumor activity	101
46	Flindersiamine	Anti-tumor activity	101
		Anti-bacterial activity	227
		Anti-fungal activity	245
47	7-(2′-Hydroxy-3′chloroprenyloxy)-4-methoxy-furoquinoline	Anti-tumor activity	102

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No.	Compound	Activity	Reference
48	7-(2′,3′-Epoxyprenyloxy)-4-methoxyfuroquinoline	Anti-tumor activity	102
49	Pteleine	Anti-tumor activity	103
		Antiplatelet activity	269–272
50	(+)-7,8-Dimethoxymyrtopsine	Anti-tumor activity	102,103
51	Medicosmine	Anti-tumor activity	104
52	Jineol	Anti-tumor activity	105
		Anti-oxidant activity	329
53	3,8-Dimethoxyquinoline	Anti-tumor activity	105
54	3,8-Diacetoxyquinoline	Anti-tumor activity	105
55	Senepodine A	Anti-tumor activity	106
56	7-Hydroxy-4-[5′-hydroxymethylfuran-2′-yl]-2-quinolone	Anti-tumor activity	107
57	Acetylcupreine	Anti-tumor activity	108
		Insecticidal activity	108
58	3,3-Diisopentenyl-*N*-methyl2,4-quinoldione	Anti-tumor activity	109
59	Cuspareine	Anti-tumor activity	110
		Antimalarial activity	110
60	Galipeine	Anti-tumor activity	110
		Antimalarial activity	110
61	Galipinine	Anti-tumor activity	110
		Antimalarial activity	110
62	Angustureine	Anti-tumor activity	110
		Antimalarial activity	110
63	Asimicilone	Anti-tumor activity	111
64	Lepadin A	Anti-tumor activity	112,113
65	Lepadin B	Anti-tumor activity	112,113
66	Lepadin C	Anti-tumor activity	112,113
67	Lepadin D	Antimalarial activity	112,113
		Trypanocidal activity	112,113
		Anti-fungal activity	112,113
68	Lepadin E	Anti-tumor activity	112,113
		Antimalarial activity	112,113
		Trypanocidal activity	112,113
		Anti-fungal activity	112,113
69	Lepadin F	Anti-tumor activity	112,113
		Antimalarial activity	112,113
		Trypanocidal activity	112,113
		Anti-fungal activity	112,113
70	Lepadin G	Anti-tumor activity	112,113
71	Benzastatin C	Neuroprotective activity	114,115
		Anti-oxidant activity	114,115
72	Benzastatin D	Neuroprotective activity	114,115
		Anti-oxidant activity	114,115

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No.	Compound	Activity	Reference
73	(−)-SW-163C	Anti-tumor activity	116,117
74	(−)-SW-163E	Anti-tumor activity	116,117
75	3S*,4R*-Dihydroxy-4-(4′methoxyphenyl)-3,4-dihydro-2(1H)-quinolinone	Anti-tumor activity	118
76	3R*,4R*-Dihydroxy-4-(4′methoxyphenyl)-3,4-dihydro-2(1*H*)-quinolinone	Anti-tumor activity	118
77	Peniprequinolone	Anti-tumor activity	118
		Nematicidal activity	210
78	Aspernigerin	Anti-tumor activity	119
79	(+)-Quinocitrinine A	Anti-tumor activity	120
		Anti-bacterial activity	120
80	(−)-Quinocitrinine B	Anti-tumor activity	120
		Anti-bacterial activity	120
81	Isodictamnine	Anti-tumor activity	121
82	Iso-γ-fagarine	Anti-tumor activity	121
83	Luzopeptin A	Anti-tumor activity	121–126
		Anti-HIV activity	286
84	Luzopeptin B	Anti-tumor activity	121–126
		Anti-HIV activity	286
85	Luzopeptin C	Anti-tumor activity	121–126
		Anti-HIV activity	286
86	Streptonigrin	Anti-tumor activity	127
87	7-(1-Methyl-2-oxopropyl)streptonigrin	Anti-tumor activity	127
88	BE-22179	Anti-tumor activity	128,129,132,133
89	Thiocoraline	Anti-tumor activity	130–133
		Anti-bacterial activity	240
90	Confusadine	Anti-tumor activity	134
		Antiplatelet activity	274
91	Furomegistine I	Anti-tumor activity	135
92	Furomegistine II	Anti-tumor activity	135
93	Megistosarconine	Anti-tumor activity	136
94	Cyclomegistine	Anti-tumor activity	137
95	4-Carbomethoxy-6-hydroxy2-quinolone	Anti-tumor activity	138
		Anti-oxidant activity	330
96	Viridicatin	Anti-tumor activity	139
97	Viridicatol	Anti-tumor activity	139,140
98	Fumiquinazoline A	Anti-tumor activity	141,142
99	Fumiquinazoline B	Anti-tumor activity	141,142
100	Fumiquinazoline C	Anti-tumor activity	141,142
101	Fumiquinazoline D	Anti-tumor activity	141,142
102	Fumiquinazoline E	Anti-tumor activity	141,142
103	Fumiquinazoline F	Anti-tumor activity	141,142
104	Fumiquinazoline G	Anti-tumor activity	141,142
105	(−)-Spiroquinazoline	Anti-tumor activity	143

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No.	Compound	Activity	Reference
106	Luotonin A	Anti-tumor activity	144–146
107	Luotonin B	Anti-tumor activity	144–146
108	Luotonin E	Anti-tumor activity	144–146
109	Luotonin F	Anti-tumor activity	144–146
110	Deoxyvasicine	Anti-tumor activity	148
		Anticholinesterase activity	309
111	Tryptanthrin	Anti-tumor activity	152–155
		Antimalarial activity	187,188
		Trypanocidal activity	217
		Antifeedant activity	216
		Anti-bacterial activity	253,254
		Anti-inflammatory activity	298,299
112	Qingdainone	Anti-tumor activity	152
113	3-(2-Carboxyphenyl)-4(3*H*)-quinazolinone	Anti-tumor activity	156
114	1-Methoxy-7,8-dehydrorutaecarpine	Anti-tumor activity	157
115	Rutaecarpine	Anti-tumor activity	157
		Antiplatelet activity	277
		Anti-inflammatory activity	306
		Effect on CYP1A1, CYP1A2 and CYP1B1	318–322
116	1-Hydroxyrutaecarpine	Anti-tumor activity	157
		Antiplatelet activity	277
117	Samoquasine A	Anti-tumor activity	158–161
118	2-Acetyl-4(*3H*)-quinazolinone	Anti-tumor activity	162,163
		Anti-HIV activity	162,163
119	2-n-Propylquinoline	Antimalarial activity	172
		Anti-leishmania activity	192–196
		Trypanocidal activity	197
		Molluscicidal activity	198
		Antiviral activity	289–291
120	2-Pentylquinoline	Antimalarial activity	172
		Anti-leishmania activity	192–196
		Trypanocidal activity	197
		Molluscicidal activity	198
		Antiviral activity	289–291
121	Chimanine B	Antimalarial activity	172
		Anti-leishmania activity	192–195
122	Chimanine D	Antimalarial activity	172
		Anti-leishmania activity	192–195
		Antiviral activity	289–291
123	4-Methoxy-2phenylquinoline	Antimalarial activity	172
124	2-(3,4- Methylenedioxyphenylethyl)quinoline	Antimalarial activity	172
		Anti-leishmania activity	192–195

No.	Compound	Activity	Reference
		Molluscicidal activity	198
		Antiviral activity	289–291
125	Acronycidine	Antimalarial activity	173
126	Acronydine	Antimalarial activity	173
127	Veprisine	Antimalarial activity	174
		SRS-A antagonists	333
128	*N*-Methylpreskimmianine	Antimalarial activity	174
129	2-Nonyl-4-(1*H*)-quinolone	Antimalarial activity	175
		Immunomodulatory activity	297
130	2-Undecyl-4-(1*H*)-quinolone	Antimalarial activity	175
		Immunomodulatory activity	297
131	2-(Undec-1-enyl)quinolin4-(1*H*)-one	Antimalarial activity	175
132	Isofebrifugine	Antimalarial activity	176–186
133	Quinazolin-4-(3*H*)-one	Antimalarial activity	181
		Bronchodilator activity	331,332
134	2-Methoxyrutaecarpine	Effect on CYP1A1, CYP1A2 and CYP1B1	318
136	5,8,13,14-Tetrahydro-2methoxy-14-methyl-5oxo-7*H*-indolo[2′,3′:3,4]pyrido[2,1-*b*]quinazolin-6-ium chloride	Antimalarial activity	174
137	(−)-Janoxepin	Antimalarial activity	189
138	Cusparine	Anti-leishmania activity	199
140	*rel*-(7R,8R)-8-[(E)-3-hydroxy3-methyl-1-butenyl]-4,8-dimethoxy-5,6,7,8-tetrahydrofuro[2,3-*b*]quinoline-7-ol acetate	Trypanocidal activity	200
141	Evocarpine	Insecticidal activity	204
		Anti-bacterial activity	222,223,225
		Cardiovascular protective activity	276
		Immunomodulatory activity	297
		Hypolipidaemic activity	328
142	Dihydroevocarpine	Insecticidal activity	204
		Anti-bacterial activity	222
		Immunomodulatory activity	297
		Hypolipidaemic activity	328
143	Antidesmone	Trypanocidal activity	205
144	*N*-Methyl-2-nonylquinolin-4(1*H*)-one	Trypanocidal activity	206
145	*N*-Methyl-2-hexylquinolin-4(1*H*)-on	Trypanocidal activity	206
146	Atanine	Antiparasitic and anthelmintic activity	207
147	Quinolactacide	Insecticidal activity	208,209
148	Penigequinolone A	Nematicidal activity	210
		Herbicidal activity	315
149	Penigequinolone B	Nematicidal activity	210
		Herbicidal activity	315
150	3-Methoxy-4-hydroxy-4-(4′-methoxyphenyl)quinolinone	Nematicidal activity	210
151	3-Methoxy-4,6-dihydroxy-4- (4′-methoxyphenyl)quinolinone	Nematicidal activity	210
152	Leiokinine A	Antifeedant activity	211

No.	Compound	Activity	Reference
153	Leiokinine A	Antifeedant activity	211
154	3,4-Dihydroxyquinoline-2-carboxylic acid	Antifeedant activity	212
155	(−)-Yaequinolone J1	Insecticidal activity	213
156	(−)-Yaequinolone J2	Insecticidal activity	213
157	3-Methoxy-4,5-dihydroxy-4- (4′-methoxyphenyl)quinolinone	Insecticidal activity	214
158	Vasicinone	Antifeedant activity	215
		Bronchodilator activity	331
159	Vasicinol	Antifeedant activity	215
160	(+)-N_a-Quinaldyl-L-arginine	Antifeedant activity	218
161	1,3-Dimethylquinazoline2,4-dione	Insecticidal activity	220,221
162	1-Methyl-2-pentadecyl4(1*H*)-quinolone	Anti-bacterial activity	222
		Immunomodulatory activity	297
163	1-Methyl-2-[(4Z,7Z)-4,7-tridecadienyl]-4(1*H*)-quinolone	Anti-bacterial activity	222,225
		Cardiovascular protective activity	276
		Immunomodulatory activity	297
		Hypolipidaemic activity	328
164	1-Methyl-2-[(6Z,9Z)-6,9-pentadecadienyl]-4(1*H*)-quinolone	Anti-bacterial activity	222,225
		Cardiovascular protective activity	276
		Immunomodulatory activity	297
		Hypolipidaemic activity	328
165	1-Methyl-2-undecyl-4(1*H*)-quinoline	Anti-bacterial activity	222,225
		Immunomodulatory activity	297
166	1-Methyl-2-[(Z)-7tridecadienyl]-4(1*H*)-quinolone	Anti-bacterial activity	223
167	1-Methyl-2-(6Z)-6undecenyl-quinolone	Anti-bacterial activity	225
168	2,3-Dimethyl-4-quinolone	Anti-bacterial activity	226
169	Megistoquinone I	Anti-bacterial activity	230
170	Megistoquinone II	Anti-bacterial activity	230
172	3-(2,3-Dihydroxy-3-methylbutyl)-4,7-dimethoxy-1-methyl-1*H*-quinolin-2-one	Anti-bacterial activity	231
173	Quinoline-4-carbaldehyde	Anti-bacterial activity	232,233
		Anti-fungal activity	249
174	3-Methyl-2-(non-2enyl)quinolin-4(1*H*)-one	Anti-bacterial activity	234,235
175	2-(2-Heptenyl)-3-methyl-4(l*H*)-quinolone	Anti-bacterial activity	234,235
		Anti-fungal activity	249
176	YM-30059	Anti-bacterial activity	236
177	Aurachin A	Anti-bacterial activity	237
		Effect on cytochrome	316,317
178	Aurachin B	Anti-bacterial activity	237
		Effect on cytochrome	316,317
179	Aurachin C	Anti-bacterial activity	237
		Effect on cytochrome	316,317
180	Aurachin D	Anti-bacterial activity	237
		Effect on cytochrome	316,317

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No.	Compound	Activity	Reference
181	Helquinoline	Anti-bacterial activity	238
182	CJ-13136	Anti-bacterial activity	239
183	CJ-13217	Anti-bacterial activity	239
184	CJ-13536	Anti-bacterial activity	239
185	(−)-CJ-13564	Anti-bacterial activity	239
186	CJ-13565	Anti-bacterial activity	239
187	CJ-13566	Anti-bacterial activity	239
188	(+)-CJ-13567	Anti-bacterial activity	239
189	(−)-CJ-13568	Anti-bacterial activity	239
190	Sch 40832	Anti-bacterial activity	241
191	2-Heptylquinolin-4-ol	Anti-bacterial activity	242
192	2-Pentylquinolin-4-ol	Anti-bacterial activity	242
193	*trans*-Decahydroquinoline 243A	Anti-bacterial activity	243
194	Anhydroevoxine	Anti-fungal activity	244
195	Platydesmine	Anti-fungal activity	245
		Anti-HIV activity	284
196	1-Methyl-2-[6′-(3′′,4′′-methylenedioxyphenyl)hexyl]-4-quinolone	Anti-fungal activity	247
197	Distomadine B	Anti-fungal activity	248
198	Distomadine A	Anti-fungal activity	248
199	4-Hydroxymethylquinoline	Anti-fungal activity	249
200	Quinoline-4-carbaldoxime	Anti-fungal activity	249
201	Quinoline-4-carboxylic acid	Anti-fungal activity	249
202	*N*-Mercapto-4-formylcarbostyril	Anti-fungal activity	250
203	Virantmycin	Anti-fungal activity	251,252
		Antiviral activity	251,252
204	Fumiquinazoline H	Anti-bacterial activity	255
205	Fumiquinazoline I	Anti-bacterial activity	255
206	Simulenoline	Antiplatelet activity	95
207	Benzosimuline	Antiplatelet activity	95
208	Zanthobungeanine	Antiplatelet activity	95
209	Robustine	Antiplatelet activity	95
		Cardiovascular protective activity	275
210	Edulitine	Antiplatelet activity	95
211	4-Methoxy-1-methylquinolin-2-one	Antiplatelet activity	268
		Anti-HIV activity	284
212	Confusameline	Antiplatelet activity	269–272
		Cardiovascular protective activity	275
		Antagonists at the 5-HT$_2$ receptor site	307
213	1-Methoxyrutaecarpine	Antiplatelet activity	277
214	Acrophyllidine	Cardiovascular protective activity	278
215	Evodiamine	Anti-inflammatory activity	297
		Vasodilatory effect	279

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No.	Compound	Activity	Reference
216	Dehydroevodiamine	Vasodilatory effect	279
217	Uranidine	Anti-HIV activity	282
218	Buchapine	Anti-HIV activity	283
219	3-Prenyl-4-prenyloxyquinolin-2-one	Anti-HIV activity	283
220	Sandramycin	Anti-HIV activity	285
221	Orixalone A	Anti-inflammatory activity	294
222	Quinolactacin A1	Anti-inflammatory activity	295,296
		Anticholinesterase activity	310
223	Quinolactacin A1	Anti-inflammatory activity	295,296
		Anticholinesterase activity	310
224	Quinolactacin B	Anti-inflammatory activity	295,296
225	Quinolactacin C	Anti-inflammatory activity	295,296
226	Isaindigotone	Anti-inflammatory activity	304
227	Quinazoline-2,4-dione	Anti-inflammatory activity	305
		Antihypertensive activity	305
228	Goshuyuamide II	Anti-inflammatory activity	306
229	Pteleprenine	Agonist of nicotinic acetylcholine receptors	308
230	Dictyoquinazol A	Cortical neurons protective activity	312
231	Dictyoquinazol B	Cortical neurons protective activity	312
232	Dictyoquinazol C	Cortical neurons protective activity	312
233	Fiscalin A	Inhibition of the binding of substance P	313
234	Fiscalin B	Inhibition of the binding of substance P	313
235	Fiscalin C	Inhibition of the binding of substance P	313
236	Circumdatin H	Effect on the respiratory chain	324
237	Circumdatin E	Effect on the respiratory chain	324
238	FR225659	Hypoglycemic activity	325–327
239	239	Hypoglycemic activity	325–327
240	240	Hypoglycemic activity	325–327
241	241	Hypoglycemic activity	325–327
242	242	Hypoglycemic activity	325–327
243	2,8-Dihydroxy-3,4-dimethoxyquinoline	Anti-oxidant activity	329
244	*N*-Methylflindersine	SRS-A antagonists	333
245	2-Methyl-4(*3H*)-quinazolinone	Inhibitor of poly(ADP-ribose) synthetase	338
246	Eduline	Effect on muscle	339
247	Japonine	Effect on muscle	339

[a] Compounds **5**–**27** are CPT analogs and are not specifically listed in this table.