Quinoline, quinazoline and acridone alkaloids

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1 Quinoline alkaloids

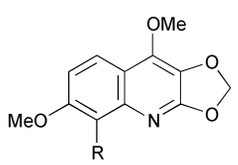
1.1 Occurrence

A bumper crop of new quinoline alkaloids was reported during the period covered by this review. Table 1 contains a list of these alkaloids and their sources, as well as several known alkaloids from new sources.[1–25] Characterisation of new compounds, invariably by spectroscopic methods, is described in the appropriate sections of the ensuing discussion if warranted.

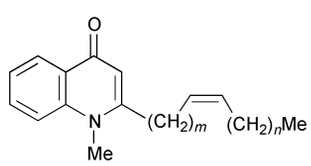
1.2 Non-terpenoid quinoline and quinolinone alkaloids from rutaceous plants

The new alkaloid 2,3-methylenedioxy-4,7-dimethoxyquinoline **1** was isolated from extracts of the root bark of *Acronychia laurifolia* (Rutaceae) after bioassay-guided fractionation.[2] The location of the methylenedioxy substituent is unique in a rutaceous quinoline alkaloid, although a very similar alkaloid, **2**, has been found in an unrelated plant, *Acanthosyris paulo-alvinii* (Santalaceae)[26] [*cf.* ref. 27(*a*)]. Compound **1** proved to be inactive when evaluated for cytotoxicity towards a panel of human cancer cell lines.

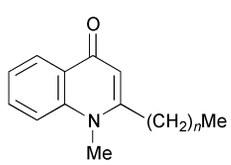
The quinolin-4-one alkaloids found in the fruits of *Evodia rutaecarpa* and *E. officinalis*, used in herbal remedies in the Far East, are characterised by long saturated or unsaturated hydrocarbon chains at C-2. A recent HPLC study of commercial samples of the fruits collected from Taiwanese markets has shown that the alkaloid profile depends less on the species than on the state of maturity of the fruits, the riper specimens accumulating compounds such as evocarpine **3**.[6] An apparently new positional isomer of evocarpine, 1-methyl-2-[(4*Z*)-tridec-4-enyl] quinolin-4-one **4**, was detected during this investigation, although the authors make no specific mention of this discovery. Also detected was the known but rare alkaloid 2-decyl-1-methylquinolin-4(1*H*)-one **5**, which is unusual in bearing a hydrocarbon substituent with an even number of carbon atoms. There is growing interest in the antibacterial activity of *E. rutaecarpa* extracts against *Helicobacter pylori* (HP), which is implicated in the pathogenesis of chronic gastritis, peptic ulcers and gastric cancers. Two recent articles on the bioactivity-guided fractionation of the extracts have shown that the antibacterial activity is due to several known alkaloids, including evocarpine **3**, the structural isomer **6**, and the saturated and unsaturated homologues **7**–**11**.[28,29] Minimum inhibitory concentrations against several HP strains were variously reported as less than 0.5 μg cm^{-3} for **3** and **6**,[28] and as being in the range 10–20 μg cm^{-3} for **3** and **7**–**11**.[29] Even at a concentration of 300 μg cm^{-3}, the compounds did not inhibit HP urease activity.[28] More significantly, they had virtually no antibacterial effect on other intestinal flora.[29]



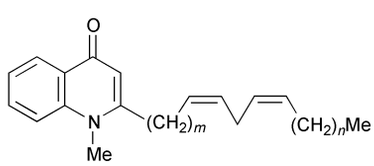
1 R = H
2 R = OMe



3 Evocarpine *m* = 7; *n* = 3
4 *m* = 3; *n* = 7
6 *m* = 6; *n* = 4



5 *n* = 9
7 *n* = 10
8 *n* = 12
9 *n* = 14



10 *m* = 3; *n* = 4
11 *m* = 5; *n* = 4

1,2,3,4-Tetrahydroquinoline alkaloids seem to be emerging as chemotaxonomic markers for *Galipea officinalis* (Rutaceae), the South American shrub whose bark is used in making Angostura bitters. Two members of this class of alkaloids, (−)-angustureine and (−)-galipeine, have been assigned the structures **12** and **13**, respectively.[7] The latter is a demethyl analogue of cuspareine **14**, which has been known for many years. The absolute configurations of the alkaloids were not ascertained.

Although 2-alkylquinolines and 2-alkylquinolin-4-ones are not uncommon metabolites of certain rutaceous plants, the four new quinoline alkaloids **15**–**18** isolated from leaf and fruit extracts of Moroccan *Ruta montana* are unusual in having functionality in the side chain.[21] Full NMR spectroscopic

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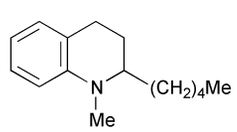
Table 1 Isolation and detection of quinoline alkaloids from plant, microbial and animal sources

Species	Alkaloid[a]	Ref.
Acalypha indica (Euphorbiaceae)	Flindersine	1
Acronychia laurifolia (= *A. pedunculata*)	Evolitrine **47**	2
	γ-Fagarine	
	Kokusaginine **48**	
	Maculosidine **49**	
	2,3-Methylenedioxy-4,7-dimethoxyquinoline[b] **1**	
	Skimmianine **50**	
Allium tuberosum (Alliaceae)	Tuberosine B[b] **54**	3
Antidesma membranaceum	(*S*)-(+)-Antidesmone[b] **57**	4,5
A. venosum	(*S*)-(+)-Antidesmone[b] **57**	5
Evodia rutaecarpa	2-Decyl-1-methylquinolin-4(1*H*)-one **5**	6
	1-Methyl-2-[(4*Z*)-tridec-4-enyl]quinolin-4-one[b] **4**	
Galipea officinalis	(−)-Angustureine[b] **12**	7
	(−)-Galipeine[b] **13**	
Glycosmis citrifolia	Glycocitlone-A[b] **33**	8
	Glycocitlone-B[b] **34**	
	Glycocitlone-C[b] **35**	
	Glycophylone	
	Glycosolone	
	Iso-γ-fagarine	
Haplophyllum bucharicum	4-Hydroxyquinolin-2(1*H*)-one	9
	4-Methoxyquinolin-2(1*H*)-one	
H. foliosum	Foliphorin[b] **36**	10
H. perforatum	Acetylhaplophyllidine **43**	11
	Dihydrohaplamine[b] **39**	10
H. suaveolens	*N*-Acetoxymethylflindersine **40**	12
	6-Methoxyflindersine (Haplamine) **38**	
H. tuberculatum	7-Prenyloxy-γ-fagarine	13
Melicope confusa	Evolitrine (*O*-Methylconfusameline) **47**	14
Peganum nigellastrum	3-(4-Hydroxyphenyl)quinoline[b] **64**	15
	3-(1*H*-Indol-3-yl)quinoline[b] **65**	15
	Luotonin F[b] **67** (see Section 2.1)	16
	3-Phenylquinoline[b] **66**	15
	Quinoline-3-carboxamide[b] **68**	16
Penicillium scabrosum	Penigequinolones A and B (1 : 1)	17
P. vulpinum	Viridicatin	18
Pseudomonas fluorescens ATCC 17400	Quinolobactin[b] **74**	19
Pseudomonas strain 1531-E7 (associated with sponge	2-Nonylquinolin-4-ol *N*-oxide **75**	20
Homophymia sp.)	2-Nonylquinolin-4(1*H*)-one **76**	
	2-[(1*E*)-Undec-1-enyl]quinoline-4(1*H*)-one[b] **78**	
	2-Undecylquinolin-4(1*H*)-one **77**	
Ruta montana	Evolitrine	21
	4-Methoxy-1-methylquinolin-2-one	
	4-Methoxy-2-(8-oxononyl)quinoline[b] **15**	
	1-Methyl-2-(9-oxodecyl)quinolin-4-one[b] **16**	
	1-Methyl-2-(8-oxononyl)quinolin-4-one[b] **17**	
	2-(8-Oxononyl)quinolin-4(1*H*)-one[b] **18**	
Sarcomelicope megistophylla	Dictamnine **52**	22
	(+)-Megistosarcimine[b] **45**	23
	(+)-Megistosarconine[b] **46**	
Zanthoxylum nitidum	Toddaquinoline	24
Z. rugosum (= *Z. chiloperone*, *Fagara chiloperone*)	Skimmianine	25

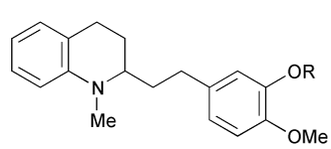
[a] Only new alkaloids and new records for a given species are listed in the table. Structures of known alkaloids, if not specifically numbered, may be found in previous reviews in this series. [b] New alkaloids.

characterisation, including HMQC and HMBC correlations, permitted the unambiguous assignment of structures **15** and **18**, which were shown to possess hitherto unprecedented terminal methyl ketone substituents. The structures of the less abundant metabolites **16** and **17**, on which only ^{1}H NMR spectra were recorded, were assigned by analogy with **18**.

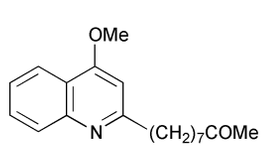
Several short syntheses of simple quinoline alkaloids merit attention. Inverse electron demand Diels–Alder reaction between the 1,2,3-benzotriazines **19** and the pyrrolidine enamines of suitably substituted acetophenones at 90–100 °C (sealed tube, in chloroform) in the presence of zinc bromide yielded 2-phenylquinoline **20** and dubamine **21** in yields of 45% and 42%, respectively.[30] Treatment of these and similar quinolines with methyl triflate followed by oxidation with potassium ferricyanide produced a number of 1-methyl-quinolin-4-one alkaloids, among them the compounds **22** (32% overall yield), graveoline **23** (40%), eduline **24** (19%) and the



12 Angustureine



13 Galipeine R = H
14 Cuspareine R = Me



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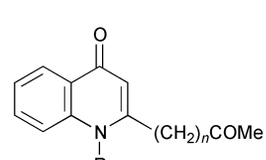
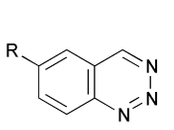


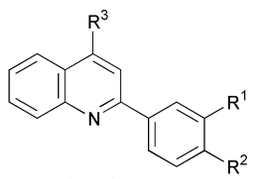
16 R = Me; *n* = 8
17 R = Me; *n* = 7
18 R = H; *n* = 7

unnatural analogue **25** (25%). *O*-Demethylation of **25** with boron tribromide completed a synthesis of reevesianine-A **26** (60%).

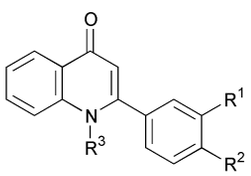
The reductive carbonylation of 2-nitrochalcones **27** and **28** in THF at 170 °C under pressure (30 atm of CO) in the presence of palladium(II) 2,4,6-trimethylbenzoate yielded the alkaloids 2-phenylquinolin-4(*1H*)-one **29** and norgraveoline **30** (61% and 45%, respectively), together with their isolable *N*-hydroxyquinolin-4-one analogues (39% and 55%).[31] With palladium(II) 2,4,6-triphenylbenzoate and toluene as solvent, the yield of norgraveoline was increased to 78%, and the corresponding *N*-hydroxyquinolin-4-one was not detected.

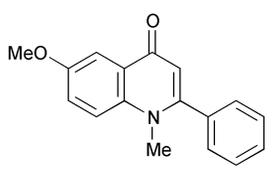


19 R = H, OMe



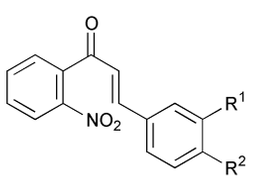
20 $R^1 = R^2 = R^3 = H$
21 Dubamine $R^1–R^2 = OCH_2O$; $R^3 = H$
32 $R^1 = R^2 = H$; $R^3 = OMe$

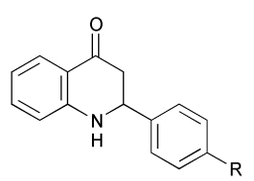




22 $R^1 = R^2 = H$; $R^3 = Me$
23 Graveoline $R^1–R^2 = OCH_2O$; $R^3 = Me$
25 $R^1 = H$; $R^2 = OMe$; $R^3 = Me$
26 Reevesianine A $R^1 = H$; $R^2 = OH$; $R^3 = Me$
29 $R^1 = R^2 = R^3 = H$
30 Norgraveoline $R^1–R^2 = OCH_2O$; $R^3 = H$

24 Eduline





27 $R^1 = R^2 = H$
28 $R^1–R^2 = OCH_2O$

31 R = H, F, Cl, Br, OMe, NO_2

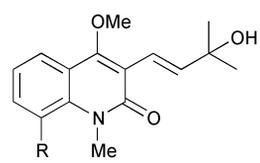
Treatment of 2-aryl-2,3-dihydroquinolin-4(1*H*)-ones **31** with iodine in methanol has been reported to yield 2-aryl-4-methoxyquinolines.[32] The products prepared in this way included the alkaloid **32** (73%) and several unnatural *p*-substituted analogues. A new synthesis of 3,3-dimethylquinoline-2,4-diones from isatoic anhydrides or 4*H*-benz-3,1-oxazin-4-ones and silyl ketene acetals holds potential for the synthesis of quinolinedione alkaloidal systems.[33]

1.3 Hemiterpenoid quinoline alkaloids and tricyclic derivatives

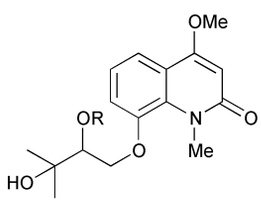
Glycocitlones A–C, **33**–**35**, isolated from the root and stem bark of *Glycosmis citrifolia*, are new representatives of the widespread 3-prenylated quinolin-2-one class of alkaloids.[8] In all three compounds, the prenyl side chain has been oxidatively modified to a 3-hydroxy-3-methylbut-1(*E*)-enyl substituent. Glycocitlone A **33** was formerly known as a synthetic product from the Heck reaction of the corresponding 3-iodoquinolin-2-one with 2-methylbut-3-en-2-ol.[34]

Investigation of the metabolites of the above-ground parts of *Haplophyllum foliosum* has resulted in the isolation of a minor new natural product, foliphorin **36**, which proved to be the monoacetate of foliosidine **37**, the chief alkaloidal constituent.[10] Extracts of the above-ground parts of *H. perforatum* yielded the well-known alkaloid haplamine **38** and a minor metabolite, dihydrohaplamine **39**.[11] The latter compound had previously been prepared from haplamine by hydrogenation, but this is the first time it has been found in nature. Haplamine and several other known alkaloids were also isolated from the aerial parts of *H. suaveolens* together with the unusual alkaloid *N*-acetoxymethylflindersine **40**.[12] The acetoxymethyl substituent is uncommon in rutaceous alkaloids, and this is its first reported occurrence in the genus *Haplophyllum*.

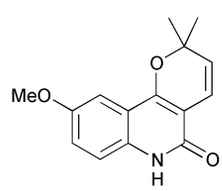
Silver carbonate on celite (Fetizon's reagent) has been found to promote the oxidative cycloaddition of alkenes or enol ethers to *N*-substituted 4-hydroxyquinolin-2-ones to form dihydrofuro[3,2-*c*]quinolinones of the general constitution shown in **41**.[35] The products from enol ethers (**41**, R^4 = alkoxy) underwent acid-catalysed elimination to give furo[3,2-*c*]quinolinones **42**. Although no natural products were made in this investigation, the methods described are potentially useful for the synthesis of angularly fused dihydrofuroquinoline and furoquinoline alkaloids.



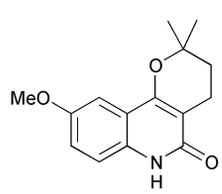
33 Glycocitlone-A R = H
34 Glycocitlone-B R = OH
35 Glycocitlone-C R = OMe



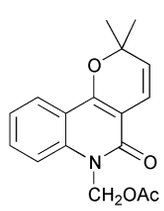
36 Foliphorin R = Ac
37 Foliosidine R = H



38 Haplamine



39 Dihydrohaplamine



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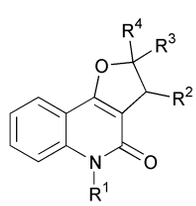

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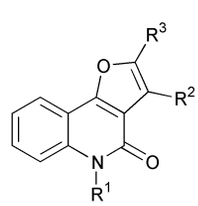


42

1.4 Furoquinoline alkaloids

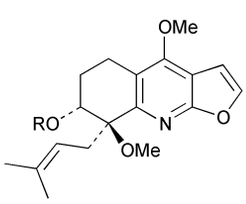
Acetylhaplophyllidine **43**, isolated together with haplophyllidine **44** and several known alkaloids from aerial parts of the central Asian plant *Haplophyllum perforatum*, has been claimed as a new natural product.[11] However, this compound was reported as a metabolite of the Brazilian plant *Almeidia coerulia* in 1998[36] [*cf.* ref. 27(*b*)]. In the present work, the compound was shown to be identical with a sample prepared by acetylating haplophyllidine. Thus, although the relative stereochemistry of the substituents at C-7 and C-8 was not specified, it is reasonable to assume that the known *trans* relationship between the oxygen substituents in haplophyllidine must also be present in **43**.

Further phytochemical studies on the chemical constituents of the New Caledonian tree *Sarcomelicope megistophylla* have brought to light two minor alkaloids with unprecedented

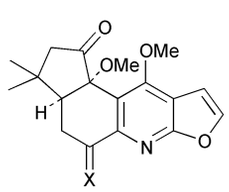
skeletons.[22] The structures of (+)-megistosarcimine **45** and (+)-megistosarconine **46**, elucidated on the basis of spectroscopic data and molecular modelling, incorporate a fused cyclopentanone ring that is clearly derived from a uniquely modified prenyl unit attached to C-5 of the furoquinoline nucleus. The *cis* ring junction was inferred from NOE interactions between the methoxy and hydrogen substituents at C-5 and C-6, respectively, as well as Monte Carlo conformational searches carried out to rationalise observed NMR spectroscopic correlations. However, the absolute configurations of the alkaloids could not be established. Megistosarcimine **45** could be acetylated on the imine nitrogen under mild conditions, but was otherwise unstable; it was readily transformed into megistosarconine **46** within a few hours on treatment with water. The reverse transformation failed when **46** was treated with aqueous ammonia solution, proving that the imine was not an artefact of the isolation procedure. Megistosarconine showed moderate cytotoxicity towards L 1210 leukaemia cells.

The furoquinoline alkaloids evolitrine **47**, kokusaginine **48**, maculosidine **49** and skimmianine **50**, isolated after bioassay-guided fractionation of a root extract of *Acronychia laurifolia*, demonstrated weak cytotoxic activity ($ED_{50} < 5$ μg cm^{-3}) against a range of human cancer cell lines.[2] Evolitrine, kokusaginine, skimmianine and confusameline **51**, all obtained from the leaves of *Melicope confusa* after bioactivity-guided fractionation, showed significant antiplatelet aggregation activity.[14] Evolitrine and dictamnine **52**, isolated from the stem wood of *Evodia lunu-ankenda*, demonstrated antifeedant activity against fourth instar larvae of the tobacco caterpillar *Spodoptera litura*.[37]

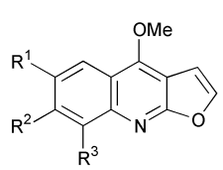
Acrophyllidine **53**, a constituent of the Chinese medicinal plant *Acronychia haplophylla* (not *halophylla*, as reported), was found to have considerable antiarrythmic potential.[38] Its electrophysiological properties have been thoroughly investigated in a comprehensive study that has provided useful insights into its mode of action.



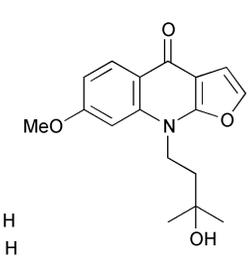
43 R = Ac
44 Haplophyllidine R = H



45 Megistosarcimine X = NH
46 Megistosarconine X = O



47 Evolitrine $R^1 = R^3 = H$; $R^2 = OMe$
48 Kokusaginine $R^1 = R^2 = OMe$; $R^3 = H$
49 Maculosidine $R^1 = R^3 = OMe$; $R^2 = H$
50 Skimmianine $R^1 = H$; $R^2 = R^3 = OMe$
51 Confusameline $R^1 = R^3 = H$; $R^2 = OH$
52 Dictamnine $R^1 = R^2 = R^3 = H$

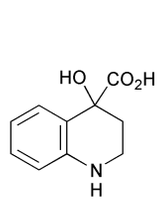


53 Acrophyllidine

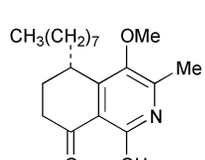
1.5 Miscellaneous quinoline alkaloids from higher plants

(+)-Tuberosine B **54**, an unprecedented tetrahydroquinoline alkaloid, has been reported in the inaccessible Chinese literature as a new metabolite of *Allium tuberosum* (Alliaceae).[3] The spectroscopic data for this unusual structure are comprehensive, and include HMBC correlations that pinpoint the location of the carboxylic acid substituent. The absolute configuration was not determined.

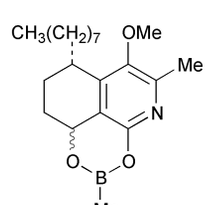
When the new antifungal alkaloid (+)-antidesmone, isolated from extracts of the tropical African plant *Antidesma membranaceum* (Euphorbiaceae), was first reported by Bringmann and co-workers in 1999, the authors believed that they had isolated a novel type of tetrahydroisoquinoline alkaloid. Structure **55** was assigned on the basis of a comprehensive suite of spectroscopic studies.[4] Chemical correlations included reduction with lithium aluminium hydride to give a mixture of alcohol diastereomers, and conversion of the alcohols into the putative methylboronate **56**, which was taken as proof of the position of the phenolic substituent on the heteroaromatic ring. The absolute configuration was inferred to be (5*S*) by comparison of the compound's CD spectrum with that calculated by quantum chemical methods. However, the subsequent isolation of larger amounts of (+)-antidesmone from *A. venosum*[5] permitted more sensitive NMR measurements to be undertaken. A crucial HMBC correlation between 5-H of the alicyclic ring and the 'phenolic' carbon site was revealed, thus disproving structure **55**. This feature, taken together with as yet unpublished biosynthetic feeding experiments, suggested that antidesmone was actually the tetrahydroquinolinedione **57**. Further support for the revised structure came from NOE and HMBC correlations observed for the *N*-methyl and *O*-methyl derivatives **58** and **59**, prepared in 22% and 61% yields respectively by treating **57** with diazomethane. The (5*S*) absolute configuration was again inferred by comparing calculated and actual CD spectra, this time on the derivative **59**. Structure **57** is not without precedent in nature; a reduced analogue, hyeronimone **60**, and its monoacetate **61** were previously reported from *Hyeronima alchorneoides*[39] – significantly, also a member of the Euphorbiaceae [*cf.* ref. 27(*c*)]. The authors pose an intriguing question: could hyeronine A **62** and hyeronine B **63**, two recently isolated tetrahydroisoquinoline alkaloids obtained from *H. oblonga*,[40] perhaps also be quinolin-4-ones analogous to **57**?



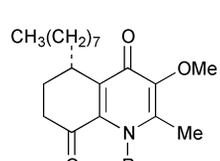
54 Tuberosine B



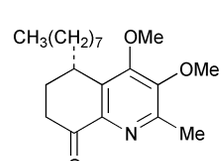
55



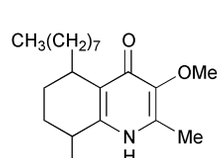
56



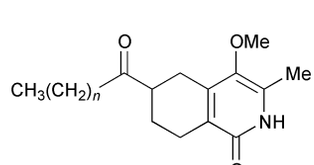
57 Antidesmone R = H
58 R = Me



59



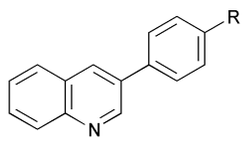
60 Hyeronimone R = H
61 R = Ac



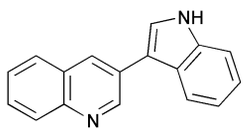
62 *n* = 6
63 *n* = 4

3-Arylquinolines, previously unknown as natural products, are surprising new metabolites of the Chinese medicinal plant *Peganum nigellastrum* (Zygophyllaceae).[15] Extracts of the dried aerial parts of the plant yielded 3-(4-hydroxyphenyl)quinoline **64**, 3-(1*H*-indol-3-yl)quinoline **65** and the simple 3-phenylquinoline **66**, the structures of which were corroborated by

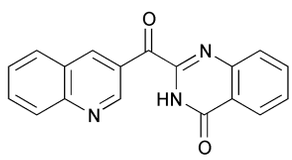
comparison of spectroscopic data and physical characteristics with those reported in the literature for purely synthetic materials. The same plant source also yielded luotonin F **67**, a mixed quinoline–quinazoline alkaloid (see Section 2.1), and quinoline-3-carboxamide **68**, another known compound never before obtained from a natural source.[16]



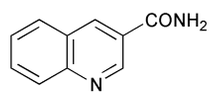
64 R = OH
66 R = H



65

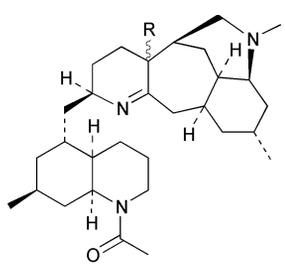


67 Luotonin F

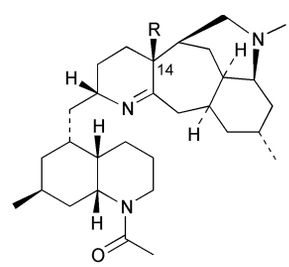


68

A highlight of last year's review in this series was the structural elucidation of two decahydroquinoline alkaloids, lucidine A **69** and oxolucidine A **70**, from the club-moss *Lycopodium lucidulum*[41] [*cf.* ref. 27(*d*)]. A full report on these studies has now been published, together with the structural elucidation of the related alkaloid lucidine B.[42] Reduction of lucidine B with lithium aluminium hydride gave a tetrahydrodeoxy derivative, the structure of which was fully analysed by means of one and two-dimensional NMR spectroscopic techniques. Long-range correlations and NOE effects clarified the relative configurations of the stereogenic centres, especially that at C-14, which had remained elusive for decades. The new information, taken in conjunction with a previously reported X-ray analysis of a tetrahydrodeoxy derivative of oxolucidine B,[43] revealed the structure **71** for lucidine B. Oxolucidine B, which can be formed from lucidine B by aerial oxidation, has the structure **72**.



69 Lucidine A R = H
70 Oxolucidine A R = β-OH

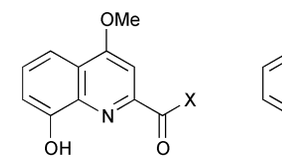


71 Lucidine B R = H
72 Oxolucidine B R = OH

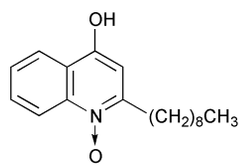
1.6 Quinoline alkaloids from fungal and microbial sources

It was reported in 1980 that iron-deprived cells of *Pseudomonas fluorescens* ATCC 17400 produced the readily hydrolysed thioquinaldic acid **73** as well as **74**, which was thought to be an artefact produced from **73** in the culture medium.[44] A new investigation of a mutant strain of *Pseudomonas fluorescens* ATCC 17400 has again shown the formation of **74** (now given the name quinolobactin), but casts no further light on its potentially artificial origin.[19] Quinolobactin is a siderophore, and its ^{59}Fe complex was readily taken up by cells of the iron-starved mutant organism, which is deficient in pyoverdine, the usual siderophore. However, the production of quinolobactin could be suppressed by adding pyoverdine to the culture medium. These studies resulted in the detection of an outer membrane protein responsible for the binding of quinolobactin.

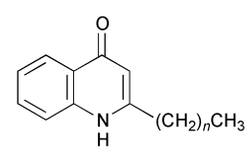
A new Gram-negative marine bacterial strain of *Pseudomonas* sp. collected from the surface of a sponge of the genus *Homophymia* harvested in the waters off New Caledonia yielded the known pseudans **75**, **76** and **77**, and the apparently new alkaloid **78**, for all of which full spectroscopic details were obtained.[20] Compounds **76**–**78** showed activity against the malaria parasite *Plasmodium falciparum* (ID_{50} 1–4.8 μg cm^{-3}). In addition, **77** was active against HIV-1 (ID_{50} 10^{-3} μg cm^{-3}), but only the *N*-oxide **75** showed antibacterial or cytotoxic properties.



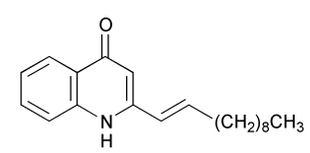
73 X = SH
74 Quinolobactin X = OH



75

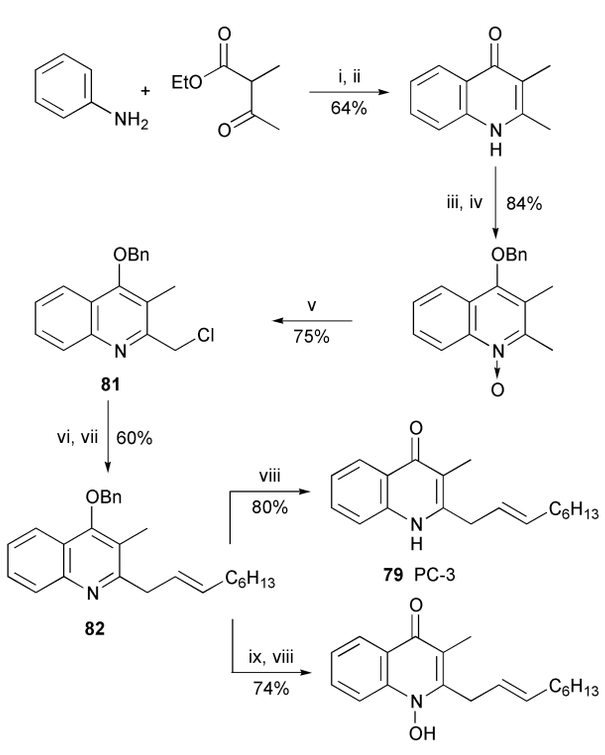


76 *n* = 8
77 *n* = 10



78

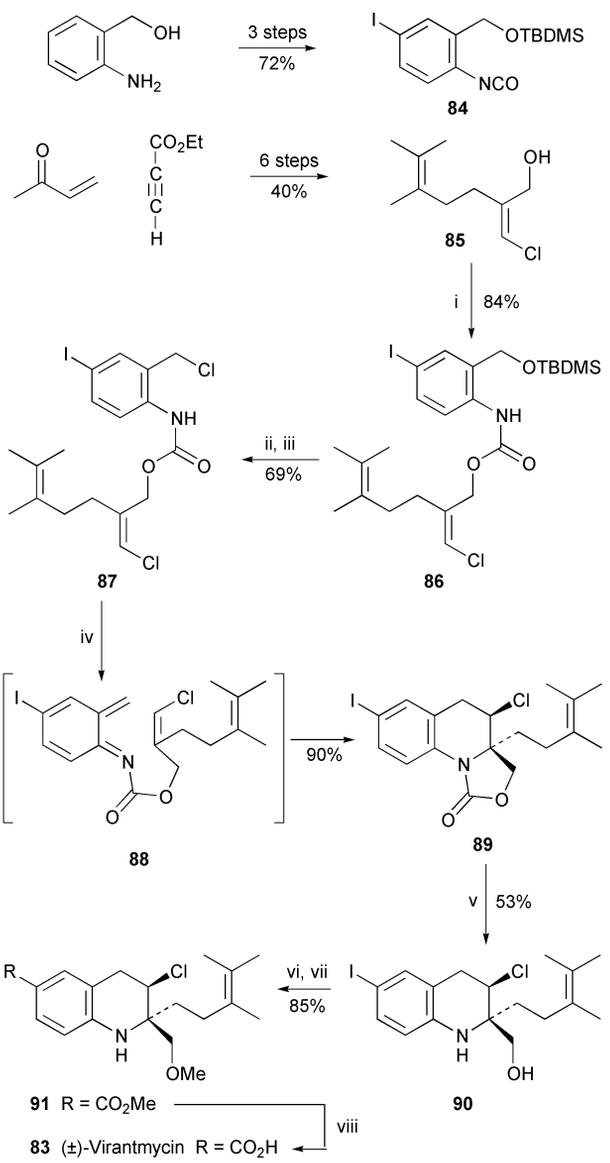
The structures of the antibacterial pseudans PC-3 **79** and YM-30059 **80** have been confirmed by the short syntheses illustrated in Scheme 1.[45] The key step was the palladium(0)-mediated coupling of the 2-chloromethylquinoline **81** with a vinylaluminium reagent (prepared *in situ* from oct-1-yne and DIBAL-H) to give the 2-substituted quinoline **82** in 60% yield.



79 PC-3
80 YM-30059

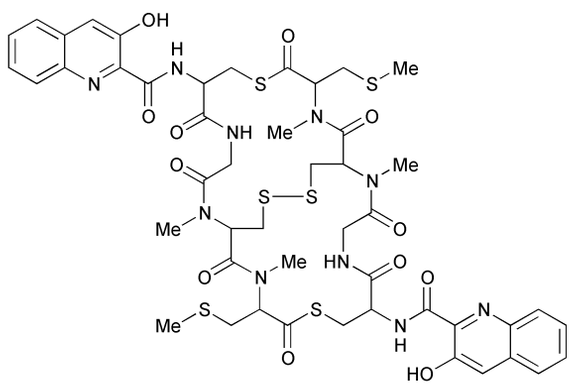
Scheme 1 *Reagents*: i, AcOH, C_6H_6, reflux; ii, Ph_2O, 250 °C; iii, $PhCH_2Cl$, K_2CO_3, DMF, 60 °C; iv, MCPBA, $CHCl_3$, rt; v, *p*-TsCl, K_2CO_3, MeCN, rt; vi, oct-1-yne, DIBAL-H, *n*-hexane, 60 °C; vii, $Pd(Ph_3P)_4$, THF, rt; viii, 10% Pd/C, cyclohexa-1,4-diene, rt; ix, MCPBA, $CHCl_3$, 0 °C.

Methodology applicable to the synthesis of analogues of the antiviral agent virantmycin **83** has been reported by Australian workers.[46] A convergent approach to the synthesis of virantmycin itself by Steinhagen and Corey (Scheme 2) made use of the building blocks **84** and **85**, which were coupled to give the carbamate **86** in 84% yield.[47] After conversion into the chloride **87**, treatment with base resulted in formation of the *o*-azaxylylene intermediate **88**, which underwent a completely stereoselective intramolecular [4 + 2] cycloaddition to give the tricyclic product **89** in 90% yield. A novel reductive cleavage of the cyclic urethane with DIBAL-H and *n*-butyllithium followed by an aqueous quench and methylation of the resulting alcohol produced the iodinated tetrahydroquinoline **90** (53%). Palladium-mediated methoxycarbonylation afforded virantmycin methyl ester **91** (85%), hydrolysis of which completed the synthesis of the racemic target compound (±)-**83**.

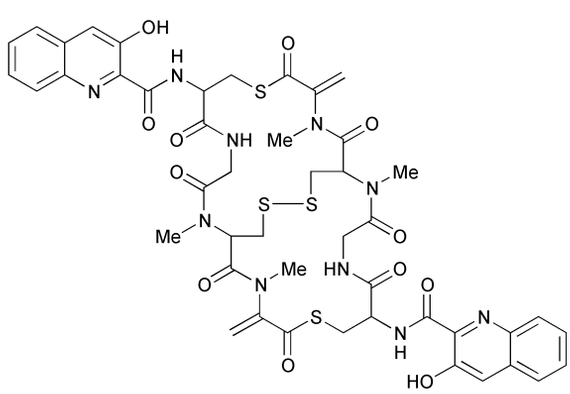


Scheme 2 *Reagents*: i, DMAP, CH_2Cl_2, 23 °C; ii, Bu_4NF, THF, 23 °C; iii, $SOCl_2$, Et_3N, CH_2Cl_2, 23 °C; iv, $CsCO_3$ (5 equiv.), CH_2Cl_2, 23 °C, 48 h; v, DIBAL-H/*n*-BuLi (1 : 1), THF, −78 °C, then H_3O^+; vi, KH, THF, then MeI; vii, CO (1 atm), $Pd(OAc)_2$ (0.2 equiv.), dppp (0.22 equiv.), Et_3N, MeOH–DMF, 75 °C, 6 h; viii, LiOH (3 equiv.), MeCN–H_2O (3 : 1).

Total syntheses of the potent antitumour antibiotic thiocoraline **92** and the related compound BE-22179 **93** by Boger and Ichikawa are primarily exercises in construction of the depsipeptide core, and will not be outlined here.[48] Acylation of the depsipeptide core with the chromophore, 3-hydroxyquinoline-2-carboxylic acid, was a trivial late step in the syntheses. The Boger group's total syntheses of luzopeptins A–C, **94**–**96**, communicated in 1999[49] [*cf.* ref. 27(*e*)], have been published with full experimental details.[50] The ability of the luzopeptins to bind to various oligonucleotide sequences has been evaluated in relation to that of similar decadepsipeptides, and similar comparisons have been drawn for their biological cytotoxicities towards mouse leukaemia and human carcinoma cells and their ability to inhibit HIV-1 reverse transcriptase.



92 Thiocoraline

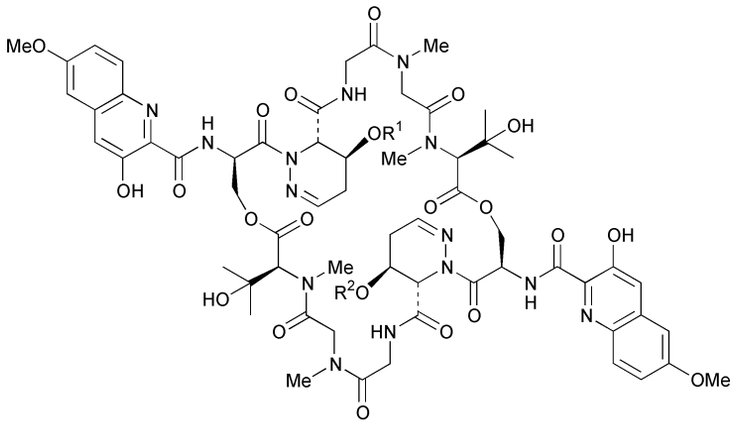


93 BE-22179

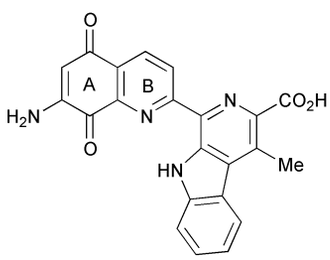
Analogues of the cytotoxic and antibacterial antibiotic lavendamycin **97** have been prepared by a modified Pictet–Spengler cyclisation between various monohaloquinoline-2-carbaldehydes **98** and substituted tryptophans.[51] The reactants **98** were in turn prepared in 84–99% yields by oxidising 2-methylquinolines with freshly prepared selenium dioxide in boiling dioxane. ABC analogues **99** and **100** of the related antitumour antibiotic streptonigrin **101** were prepared by palladium-mediated Stille coupling between various 2-iodoquinolines and 2-methyl-6-(trimethylstannyl)pyridine, followed by oxidation of the pyridylmethyl group and quinone formation.[52]

1.7 Decahydroquinoline alkaloids from ants and amphibians

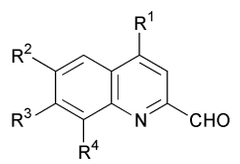
The hypothesis that many of the skin alkaloids isolated from neotropical frogs are actually sequestered from dietary sources has gained credibility in recent years. The isolation of the first decahydroquinoline alkaloids from myrmicine ants,[53] given prominence in last year's review [*cf.* ref. 27(*f*)], provided strong circumstantial evidence in favour of the hypothesis. It has now been shown that wild-caught specimens of the Panamanian poison frog *Dendrobates auratus* shared two pyrrolizidine alkaloids and the well-known decahydroquinoline alkaloid (−)-*cis*-195A **102** (pumiliotoxin C) with alate queens, but not



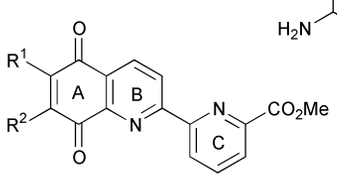
94 Luzopeptin A $R^1 = R^2 = Ac$
95 Luzopeptin B $R^1 = H$; $R^2 = Ac$
96 Luzopeptin C $R^1 = R^2 = H$



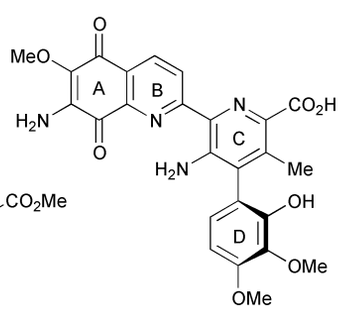
97 Lavendamycin



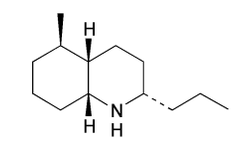
98 R^1, R^2, R^3, R^4 = H, Cl, F



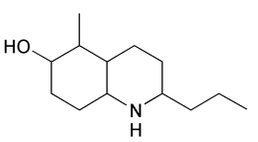
99 $R^1 = R^2 = H$,
100 $R^1 = OMe$; R^2 = H, Br, N_3, NH_2



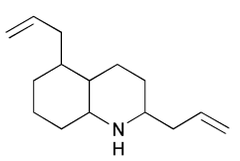
101 Streptonigrin



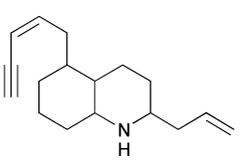
102
Decahydroquinoline *cis*-195A



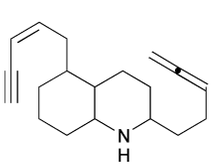
103
Decahydroquinoline 211A



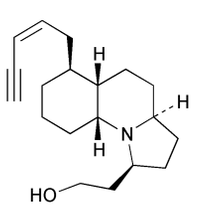
104
Decahydroquinoline 219A



105
Decahydroquinoline 243A



106
Decahydroquinoline 269AB



107 Gephyrotoxin 287C

workers, of a *Solenopsis* (*Diplorhoptrum*) sp. of myrmicine ant from the same microhabitat.[54] The frog skin extracts also contained several other decahydroquinoline alkaloids of unspecified stereochemistry, including those coded as 211A **103**, 219A **104**, 243A **105** and 269AB **106**, as well as gephyrotoxin 287C **107**. Interestingly enough, captive specimens of the frog provided with leaf litter from their natural habitat accumulated rather few alkaloids, and no decahydroquinolines at all.

In 1997 Padwa and Kuethe communicated a synthesis of the decahydroquinolin-2-one **108** by means of a tandem Pummerer rearrangement–isomünchnone dipolar cycloaddition[55] [*cf.* ref. 27(*g*)]. Their route constituted a formal synthesis of racemic *cis*-decahydroquinoline 195A, (±)-**102**. A full paper giving experimental details pertaining to this route has now been published.[56] Another formal synthesis of the same alkaloid involved the base induced cyclisation of the iron–diene complex **109** in the presence of carbon monoxide to give the *cis*-decahydroindanone **110** (54%).[57] A further four steps led to the ketal **111**, an intermediate that featured in the prior synthesis of (±)-**102** by Mehta and Praveen[58] [*cf.* ref. 27(*h*)]. Finally, formal [3 + 3] cycloaddition between chiral vinylogous amide **112** and the conjugated iminium species **113** at 150 °C afforded the tetrahydroquinolin-5-one **114** (67%), which was converted in two standard steps into the hexahydroquinolin-5-one **115** (75%).[59] This new approach to partly saturated quinoline systems proved to be fairly general, and the specific example cited here provides a clear pointer to a future enantioselective synthesis of decahydroquinoline 195A.

The enantioselective total synthesis of the ascidian alkaloid (2*S*,3*S*,4a*S*,5*S*,8a*R*)-lepadin B **116** by Toyooka and co-workers, communicated in 1999[60] [*cf.* ref. 27(*i*)], has recently been published as a full paper with comprehensive experimental details.[61]

2 Quinazoline alkaloids

A recent supplementary volume in the series *Rodd's Chemistry of Carbon Compounds* contains a review by Johne of the literature of quinazoline alkaloids covering the period from August 1993 to December 1998.[62] The emphasis is on the isolation and characterisation of alkaloids; the coverage of synthesis is more selective.

2.1 Occurrence, characterisation and biological activity

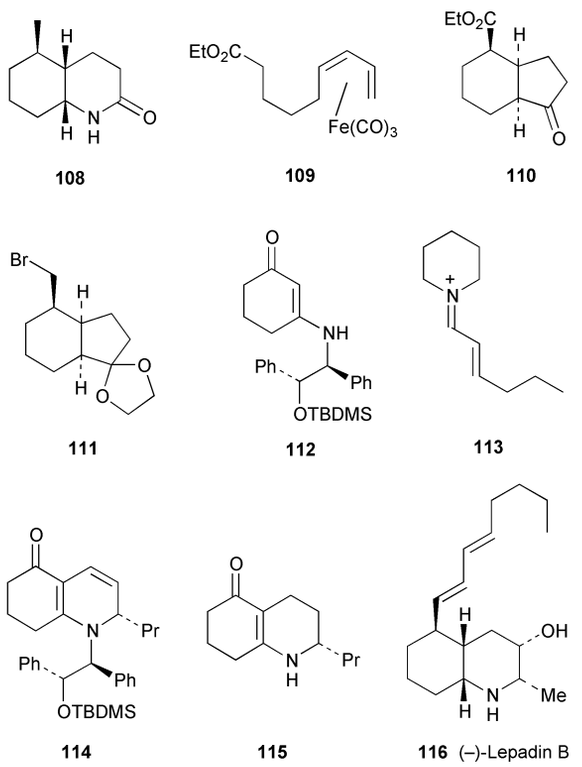
New quinazoline alkaloids isolated during the period under review are listed in Table 2 together with known alkaloids isolated from new sources.[16,63–67] Structures of new compounds were inferred from spectroscopic data in all cases.

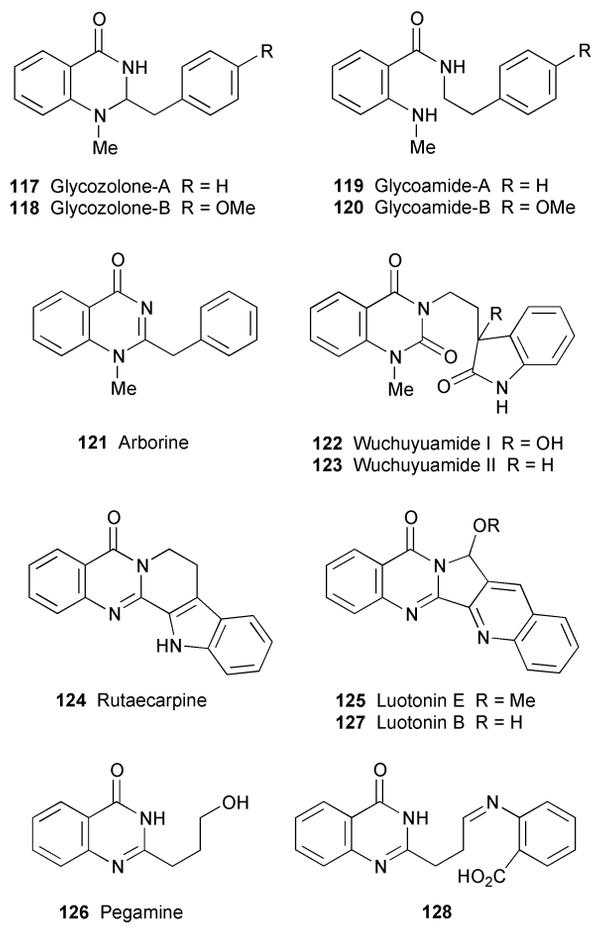
The simple 2-benzylated dihydroquinazolin-4-one alkaloids glycozolone-A **117** and glycozolone-B **118** were obtained as racemates from leaf extracts of Thai specimens of *Glycosmis*

Table 2 Isolation and detection of quinazoline alkaloids

Species	Alkaloid[a]	Ref.
Acremonium sp.	(−)-Fumiquinazoline H[b] **129** (−)-Fumiquinazoline I[b] **130**	63
Evodia rutaecarpa	Wuchuyuamide I[b] **122** Wuchuyuamide II[b] **123**	64
Glycosmis cochinchinensis	Arborine **121** Glycozolone-A[b] **117** Glycozolone-B[b] **118**	65
Peganum nigellastrum	Luotonin E[b] **125** Luotonin F[b] **67** (see Section 1.5) Pegamine **126**	16
Penicillium verrucosum	(+)-Verrucine A[b] **131** (+)-Verrucine B[b] **132**	66
Schizophyllum commune (basidiomycetous fungus)	Tryptanthrin **138**	67

[a] Only new alkaloids and new records for a given species are listed in the table. [b] New alkaloids.



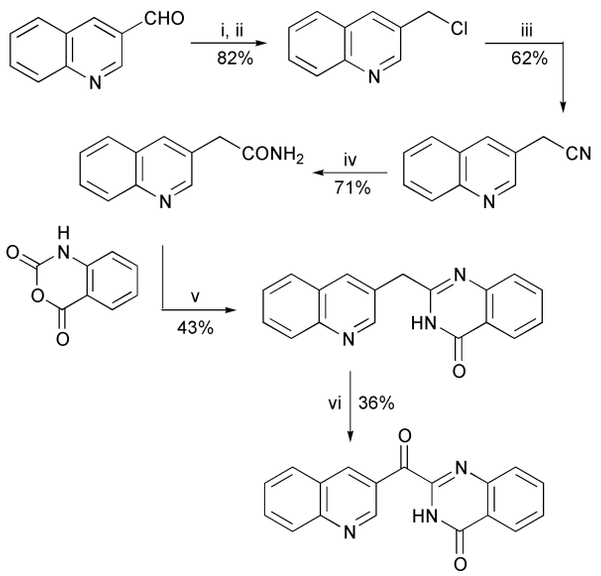


cochinchinensis.[65] Also isolated in the same investigation were two plausible biogenetic precursors, glycoamide-A **119** and glycoamide-B **120**. Glycozolone-A, the 2,3-dihydro analogue of the more familiar alkaloid arborine **121** (also isolated in this study), was in fact first reported almost fifty years ago as a product formed by catalytic hydrogenation of **121**.[68]

That prolific source of quinoline and quinazoline alkaloids, the medicinally valuable plant *Evodia rutaecarpa*, has yielded two new quinazolinediones, named wuchuyuamide I and wuchuyuamide II after the Chinese name for the plant, Wu-Chu-Yu.[64] These optically inactive alkaloids, to which the structures **122** and **123**, respectively, were assigned, are seco variants of a well-known group of alkaloids exemplified by rutaecarpine **124**. However, the unusual oxindole moiety in the new alkaloids is apparently unique amongst *Evodia* metabolites.

The new luotonins E and F, **125** and **67** (see Section 1.5), were isolated from the aerial parts of *Peganum nigellastrum* together with the known quinazoline alkaloid pegamine **126**.[16] Luotonin E, obtained as optically inactive yellow crystals, is the methyl ether of luotonin B **127**, from which it could be prepared in 70% yield by treatment with boron trifluoride etherate in methanol. Luotonin F is an unusual mixed quinoline–quinazoline alkaloid, the biogenesis of which is plausibly suggested to be from pegamine. Oxidation of the latter to the corresponding aldehyde followed by imine formation with anthranilic acid is thought to produce an intermediate imine **128**, cyclisation and further elaboration of which leads to the new natural product. The structure of luotonin F was verified by the short synthesis shown in Scheme 3

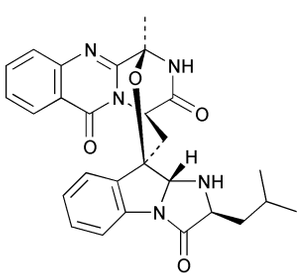
A further two fumiquinazolines have been isolated from organic extracts of the culture broth and mycelia of an *Acremonium* sp., a fungus found growing on the surface of a Caribbean tunicate (sea squirt) *Ecteinascidia turbinata*.[63] Extensive NMR spectrosopic data for the laevorotatory fumiquinazolines H and I, supported by spectroscopic comparisons with previously identified fumiquinazolines as well as chemical correlations, revealed the absolute structures shown in **129** and **130**, respectively. In particular, acidic hydrolysis and analysis of derivatised amino acid fragments by chiral capillary GC proved



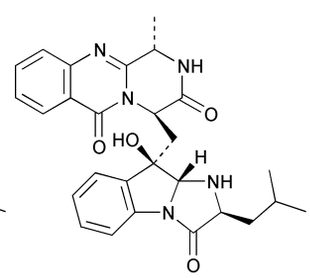
67 Luotonin F

Scheme 3 *Reagents*: i, $NaBH_4$, MeOH, rt; ii, $SOCl_2$, C_6H_6, reflux; iii, KCN, KI, EtOH–H_2O (4 : 1), reflux; iv, conc. H_2SO_4, heat (*ca.* 100 °C); v, 200–210 °C, 2 h; vi, MnO_2, $CHCl_3$, sunlight.

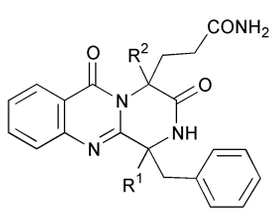
that the leucine residue belonged to the L (or *S*) series. Furthermore, reaction of fumiquinazoline H with sodium borohydride resulted in an approximately 50% conversion into fumiquinazoline I, indicating that the two compounds exist in the same configurations. The new alkaloids showed weak antifungal activity towards *Candida albicans*, but no activity in antimicrobial assays or towards various cancer cell lines.



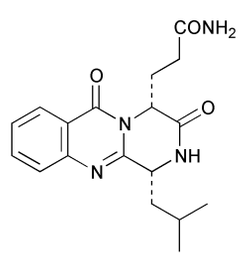
129 Fumiquinazoline H



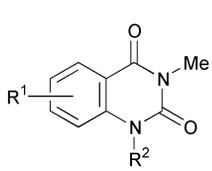
130 Fumiquinazoline I



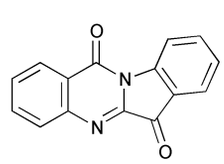
131 Verrucine A R^1, R^2 = α-H, α-H
132 Verrucine B R^1, R^2 = α-H, β-H or β-H, α-H



133 Anacine



134 R^1 = H; R^2 = Me
135 R^1 = R^2 = H
136 R^1 = OH; R^2 = Me
137 R^1 = OH; R^2 = H



138 Tryptanthrin

Structurally related to the simpler fumiquinazolines are two new metabolites isolated from cultures of the fungus *Penicillium verrucosum*.[66] (+)-Verrucines A and B, the major and minor metabolites, respectively, were assigned the epimeric structures **131** and **132** in the light of exhaustive spectroscopic studies and acid hydrolysis of the former to the constituent amino acids. Although some racemisation occurred during the hydrolysis experiments, it appeared indisputable that **131** was derived from L-phenylalanine and L-glutamine. The absolute configuration of **132** could not be determined with certainty, however, because of the racemisation problem. It nevertheless appears that both verrucines must be genuine natural products, because analysis of the extract from a different isolate of *P. verrucosum* gave verrucine B as the major product. The current study led the authors to propose that the benzodiazepine structure previously assigned to anacine, a metabolite of *P. aurantiogriseum*,[69] should be revised to **133** in view of the striking similarity of its spectra to those of the verrucines.

The simple alkaloid 1,3-dimethylquinazoline-2,4-dione **134** is a sex pheromone of the pale-brown chafer beetle, *Phyllopertha diversa*. Its catabolism by the insect's antennal enzymes has been traced to a cytochrome P450 system that is highly specific to males of this species; twelve related scarab beetles were incapable of metabolising the alkaloid.[70] HPLC and GC-MS were used to separate and characterise the major metabolic product, 3-methylquinazoline-2,4-dione **135**, and two minor degradation products resulting from oxygenation of the aromatic ring, tentatively identified as **136** and **137**.

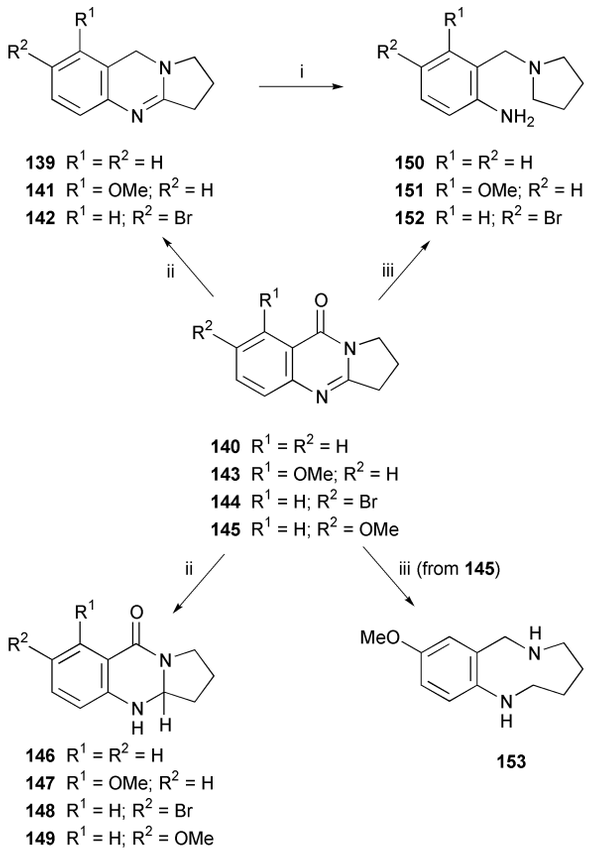
Previous work on the activity of tryptanthrin **138** and analogues as agonists of the aryl hydrocarbon receptor, a binding site implicated in the mode of action of environmental pollutants such as dioxins, has been revisited in a review paper.[71]

2.2 Synthesis and other chemical studies

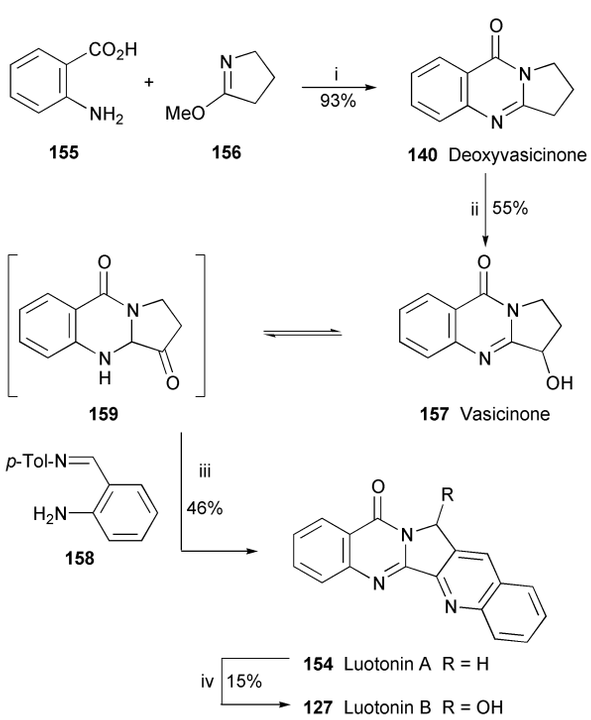
The outcome of the reduction of deoxyvasicine (deoxypeganine) **139**, deoxyvasicinone **140** and related compounds such as **141**–**145** is known to depend on the nature of the reducing agent and the substituents on the aromatic ring. Bruskov *et al.* have collated the published results, some of which are summarised in Scheme 4, and provided additional examples involving the use of sodium borohydride with and without added boron trifluoride etherate.[72] Quantum chemical calculations on the course of the reaction were performed to rationalise the observed products, which included dihydro derivatives **146**–**149**, *N*-(2-aminobenzyl)pyrrolidines **150**–**152** and, in one case, a macrocyclic diamine **153**.

A biogenetically-patterned synthesis of the cytotoxic alkaloid luotonin A **154** from anthranilic acid **155** has been reported by Nomura and co-workers.[73] The route involved condensation of **155** with 2-methoxy-Δ^1-pyrroline **156** by reported methods to give vasicinone **157** *via* deoxyvasicinone **140** (Scheme 5). When vasicinone was heated under reflux with imine **158** and toluene-*p*-sulfonic acid in xylene, the target alkaloid **154** was obtained in 30% yield. This unusual condensation is thought to proceed by isomerisation of vasicinone to the dione **159**, imine formation with the free amino group of **158**, cyclisation *via* the enamine tautomer, and a late-stage dehydrogenation. Indeed, repeating the final step in the presence of *p*-benzoquinone as a hydrogen acceptor resulted in an improved yield of 46%. Luotonin A could be oxidised to luotonin B **127** in 15% yield (50% conversion) by treatment with ceric ammonium nitrate (CAN) in boiling acetonitrile.

The remarkable resurgence of interest in the antimalarial alkaloids febrifugine and isofebrifugine, pointed out in last year's review in this series, has continued. The most important development of the previous review period, Kobayashi's

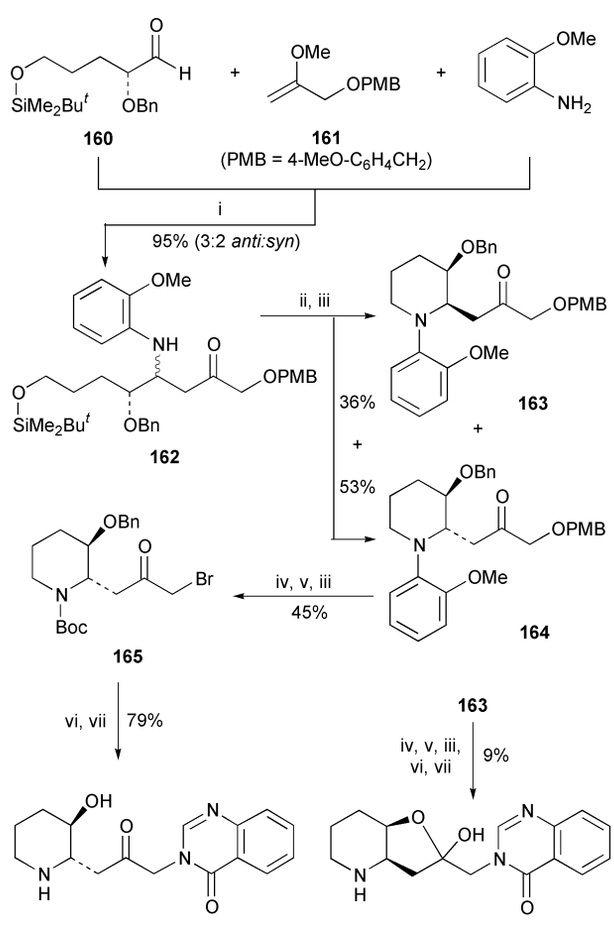


Scheme 4 *Reagents*: i, $NaBH_4$, EtOH, heat; ii, Zn, H^+; iii, $NaBH_4$, $BF_3{\cdot}Et_2O$, THF, heat.



Scheme 5 *Reagents*: i, C_6H_6, 5 °C to reflux; ii, NaHMDS, (*S*)-(10-camphorsulfonyl)oxaziridine (Davis reagent), THF, −78 °C; iii, *p*-benzoquinone, *p*-TsOH (cat.), molecular sieves 4 Å, xylene, reflux; iv, CAN, MeCN, reflux.

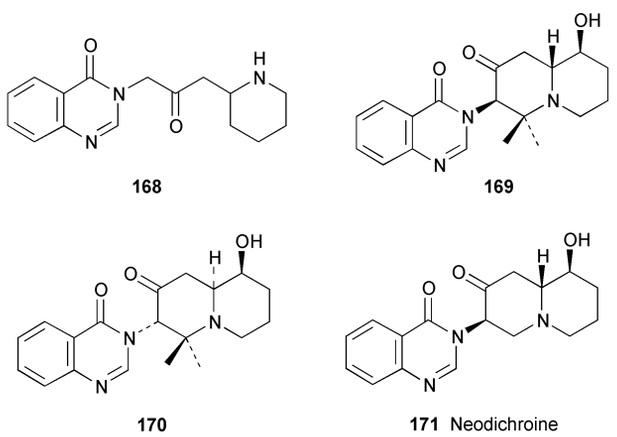
synthesis of both enantiomers of the two alkaloids and the revision of the absolute configurations of the natural products[74] [*cf.* ref. 27(*j*)], has now been published with full experimental details and one substantial improvement to the synthetic route.[75] The improved route involves the three-component coupling of (*R*)-aldehyde **160**, the enol ether **161** and *o*-methoxyaniline in the presence of ytterbium(III) dodecylsulfate [$(Yb(DS)_3$] to give the Mannich-type product **162** as a 2 : 3 mixture of *syn* and *anti* diastereomers in 95% yield (Scheme 6). Desilylation and cyclisation *via* an intermediate bromide produced the separable 2,3-*cis*- and 2,3-*trans*-disubstituted *N*-arylpiperidines **163** and **164** in a combined yield of 89%. Removal of both methoxyaryl substituents with ceric ammonium nitrate from the *trans*-compound **164** followed by conversion of the resulting α-hydroxyketone into α-bromoketone **165** proceeded in a yield of 45%. The overall yield of **165** from the (*R*)-aldehyde **160** was 23% – unimpressive, perhaps, but noticeably better than the overall yield of 8% reported in their previous route. The synthesis of unnatural (2′*S*,3′*R*)-(−)-febrifugine **166** was completed by treating bromide **165** with the anion of 4-hydroxyquinazoline, followed by removal of the Boc protecting group. A similar sequence of reactions transformed the *cis*-piperidine **163** into unnatural (2′*R*,3′*R*)-(−)-isofebrifugine **167**. The entire reaction sequence, when repeated with the (*S*)-enantiomer of aldehyde **160**, yielded (+)-febrifugine *ent*-**166** and (+)-isofebrifugine *ent*-**167**, the optical rotations of which were consistent with those reported for the natural products. When both sets of enantiomers were tested for antimalarial activity against *Plasmodium falciparum*, the EC_{50} values of (+)-febrifugine and (+)-isofebrifugine were 7.6×10^{-11} M and 2.9×10^{-10} M, respectively, while those of the (−)-enantiomers were approximately 3×10^{-7} M. The (+)-enantiomers were also about two orders of magnitude more cytotoxic towards mouse mammary tumour FM3A cells.



Scheme 6 *Reagents*: i, $Yb(DS)_3$ (see text; 10 mol%), H_2O, 0 °C, 18 h; ii, aq. HF (48%), THF; iii, CBr_4, Ph_3P, CH_2Cl_2, rt; iv, CAN, MeCN–H_2O (4 : 1), 0 °C; v, $(Boc)_2O$, CH_2Cl_2, 0 °C; vi, 4-hydroxyquinazoline, KOH, EtOH, rt; vii, HCl (6 M), reflux, then aq. Na_2CO_3.

The synthesis of racemic febrifugine and isofebrifugine previously communicated by Takeuchi *et al.*[76] [*cf.* ref. 27(*j*)] has been reprised with minor extensions and the addition of experimental details.[77] The Takeuchi group has also published a synthesis of an analogue, (±)-deoxyfebrifugine **168**, which proved to be about as active as quinine towards *P. falciparum*, but about 150 times less effective than febrifugine itself.[78]

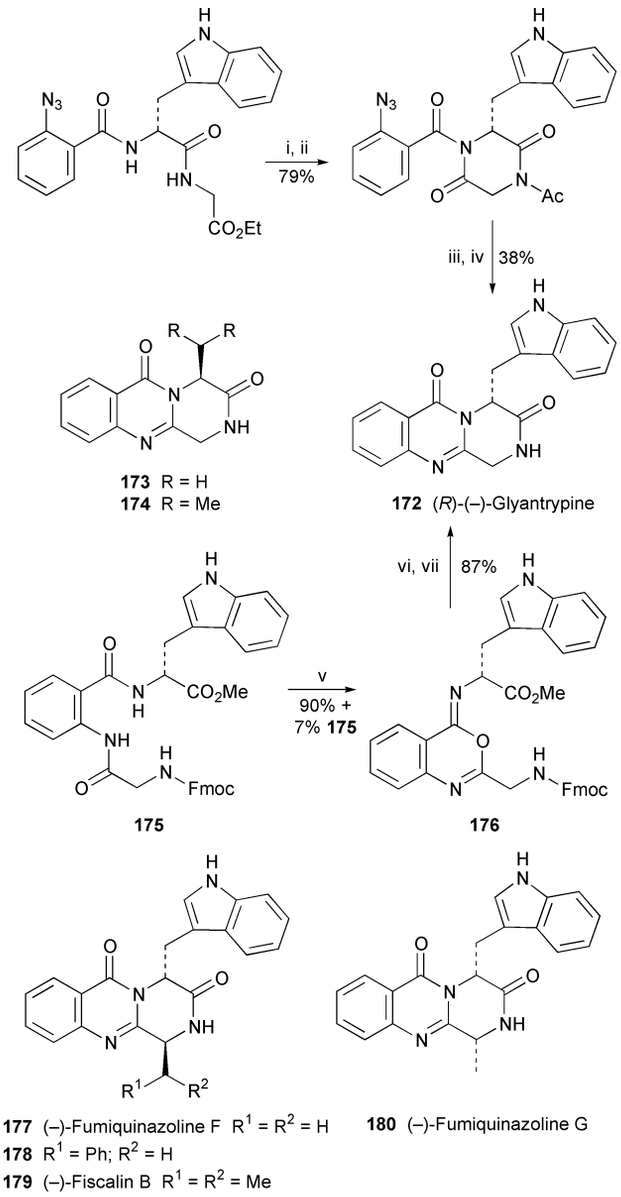
Other workers have synthesised the quinolizidine analogues (−)-**169** and (+)-**170** by a Mannich reaction between acetone and natural febrifugine or isofebrifugine, respectively, in the presence of silica gel.[79] These compounds proved to be highly potent antimalarial agents; their *in vitro* activities towards chloroquine-sensitive and -resistant strains of *P. falciparum* were of the same order of magnitude as those of natural febrifugine and isofebrifugine, and better than that of chloroquine. Compound **169** was somewhat less effective against *P. berghei* than febrifugine *in vivo*, but 24 times as potent as **170**, which appears to be metabolised by liver enzymes at a much faster rate. Both compounds were also effective in the cytotoxicity assay against FM3A mouse mammary cells. Some analogous results from this research group have also been patented.[80] Intriguingly, the first quinazoline–quinolizidine natural product, neodichroine **171**, has very recently been isolated from *Dichroa febrifuga*, the major source of the febrifugines.[81] This compound will be discussed fully in next year's review.



168 **169**

170 **171** Neodichroine

Total syntheses of the tripeptide-derived quinazoline alkaloids are essentially exercises in marshalling the amino acid constituents prior to assembling the 2*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione core that is common to so many of them. One of the simplest of these alkaloids, glyantrypine, has been prepared by Cledera *et al.*, who employed the sequential cyclisations shown in Scheme 7.[82] The route proved suitable not only for the synthesis of (*R*)-(−)-glyantrypine **172**, but also of the (*S*)-(+)-enantiomer *ent*-**172**, the (*R*)-(−)- and (*S*)-(+)-methyl analogues **173** and *ent*-**173**, and the (*S*)-(+)-isopropyl analogue **174**. Oddly enough, neither the absolute configuration nor the optical rotation of natural glyantrypine were determined when it was originally isolated. The route to (*R*)-(−)-glyantrypine devised by Wang and Ganesan, also shown in Scheme 7, assembled the amino acid constituents in a different order.[83] The tripeptide precursor **175** was dehydrated with triphenylphosphine, iodine and a tertiary amine to give the intermediate oxazine **176**, which underwent deprotection with piperidine and thermal cyclisation *via* a putative piperidine amidine to give the target. This route was also applied to the synthesis of (−)-fumiquinazoline F **177** and the unnatural analogue (−)-**178**, and, as described in a prior communication[84] [*cf.* ref. 27(*k*)], to the synthesis of (−)-fiscalin B **179** and (−)-fumiquinazoline G **180**. Wang and Ganesan have also devised a variant of this route in which linear tripeptides containing a central anthranilate unit were assembled on Wang resin to



173 R = H
174 R = Me

172 (*R*)-(–)-Glyantrypine

175 **176**

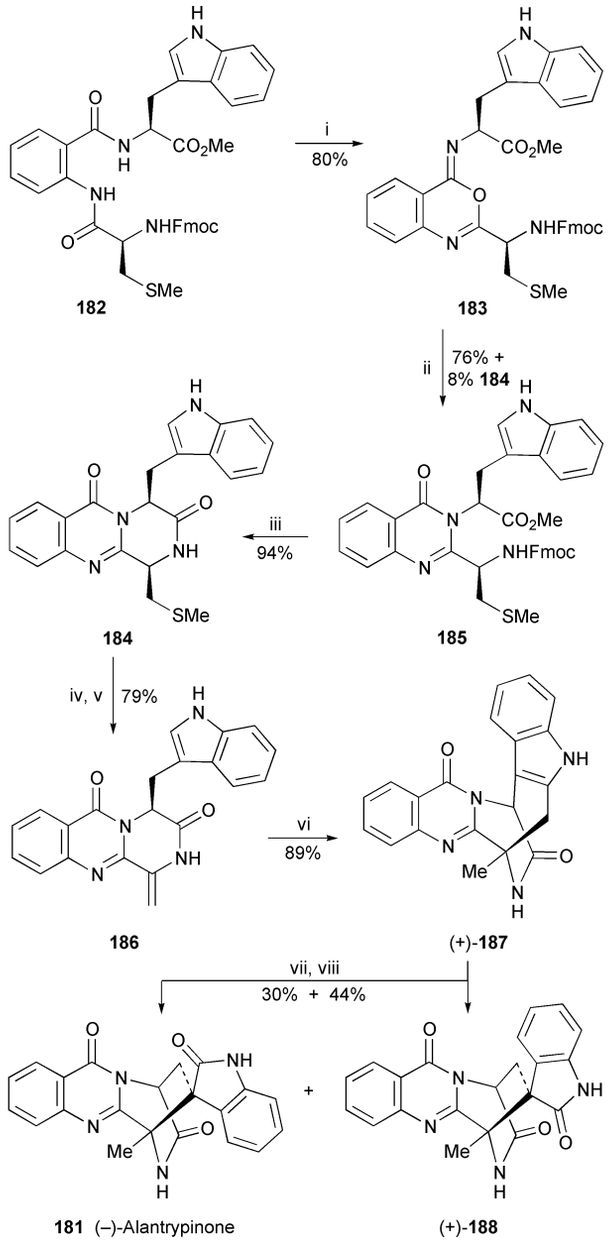
177 (–)-Fumiquinazoline F $R^1 = R^2 = H$
178 R^1 = Ph; R^2 = H
179 (–)-Fiscalin B $R^1 = R^2$ = Me

180 (–)-Fumiquinazoline G

Scheme 7 *Reagents*: i, aq. NaOH (0.5 M), MeOH, 50 °C; ii, Ac_2O, 80 °C; iii, Bu_3P, PhMe, rt; iv, $H_2NNH_2{\cdot}H_2O$ (80%), DMF, rt; v, Ph_3P, I_2, $EtNPr^i_2$, CH_2Cl_2, rt; vi, 20% piperidine in CH_2Cl_2, rt; vii, MeCN, reflux.

give intermediates related to **175**, but with the methyl ester replaced by a polymer-bound benzyl ester.[85] Application of the dehydration and piperidine-deprotection reactions was followed by thermal cyclisation and concomitant release of the target products. The scope of this procedure was demonstrated by the synthesis of (*S*)-(+)-glyantrypine *ent*-**172**, and the parallel synthesis of a library of 20 unnatural fumiquinazoline analogues.

The principles implicit in the Wang and Ganesan route to fumiquinazolines have been applied by Hart and Magomedov to a synthesis of the structurally more complex alkaloid alantrypinone **181** (Scheme 8).[86] In this case, dehydration of the tripeptide **182** gave the oxazine intermediate **183** in 80% yield. Treatment with ten equivalents of $(Me_3AlSPh)Li$ in THF at low temperature gave the expected pyrazino[2,1-*b*]quinazoline-3,6-dione **184** in a disappointing yield of 46%. However, with five equivalents of the reagent, the intermediate quinazolinone **185** was isolated in 76% yield, along with 8% of **184**. Compound **185** was efficiently cyclised to **184** (94% yield) when treated with piperidine in THF at 0 °C. Oxidative elimination of the methylthio group then yielded the *exo*-methylene product **186** (79%), which cyclised in trifluoroacetic acid to the bridged hexacyclic compound (+)-**187** (89%). Oxidative rearrangement of this



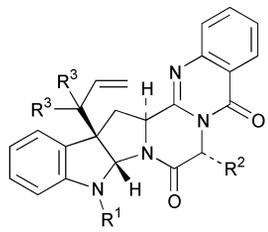
Scheme 8 *Reagents*: i, Ph_3P, I_2, $EtNPr^i_2$, CH_2Cl_2; ii, $(Me_3AlSPh)Li$ (5 equiv.), THF, −78 to −10 °C; iii, piperidine, THF, 0 °C; iv, MCPBA, CH_2Cl_2. −78 °C; v, Ph_3P, C_6H_6, reflux; vi, TFA, 70 °C; vii, NBS, TFA–THF–H_2O; viii, H_2, Pt/C, MeOH.

indole to an oxindole produced a mixture of (−)-alantrypinone **181** (the unnatural enantiomer) and its C-17 epimer (+)-**188** in yields of 30% and 44%, respectively. The synthesis confirmed the absolute configuration of natural alantrypinone, previously determined by the anomalous dispersion technique.

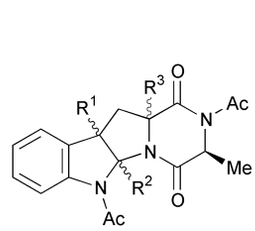
In 1994, Danishefsky and co-workers communicated a synthesis of ardeemin **189** and 5-*N*-acetylardeemin **190**, two members of a group of alkaloids notable for their ability to reverse multidrug resistance (MDR) in various cell lines[87] [*cf.* ref. 27(*l*)]. Further information on the syntheses has now been provided in a full paper that also includes syntheses of analogues such as **191**–**194**, and preliminary accounts of biological studies.[88] Spanish workers have reported the synthesis and bromination of tetracyclic and hexacyclic analogues **195**–**197** and **198** of *N*-acetylardeemin,[89] and the synthesis of didehydro analogues **199** and **200**.[90]

3 Acridone alkaloids

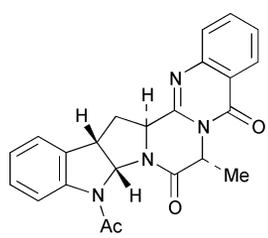
A major new survey of the acridone alkaloids, by Skaltsounis,



189 Ardeemin R^1 = H; R^2 = R^3 = Me
190 R^1 = Ac; R^2 = R^3 = Me
191 R^1 = Ac; R^2 = H; R^3 = Me
192 R^1 = $COCF_3$; R^2 = H; R^3 = Me
193 R^1 = Ac; R^2 = Me; R^3 = H
194 R^1 = Ac; R^2 = Bn; R^3 = Me



195 R^1 = R^2 = R^3 = β-H
196 R^1 = R^2 = β-H; R^3 = α-H
197 R^1 = R^2 = α-H; R^3 = β-H



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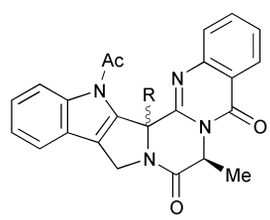


199 R = α-H
200 R = β-H

Mitaku and Tillequin, has appeared in Volume 54 of the important monograph series *The Alkaloids*.[91] The review includes biosynthetic considerations, aspects of structural elucidation, a comprehensive survey of the occurrence of the alkaloids (organised according to structural features), a wide-ranging analysis of published syntheses, and a short account of biological properties.

3.1 Occurrence and characterisation

A list of new acridone alkaloids, and known acridones isolated from new sources, is presented in Table 3.[8,22,92–94]

The four new acridone alkaloids **201**–**204**, designated as glycocitrines III–VI, respectively, were isolated from root and stem bark of Taiwanese *Glycosmis citrifolia*, and characterised with the help of the full range of spectroscopic techniques.[8] Three of these alkaloids have novel structural features. Glycocitrine-III **201**, also obtained from stem extracts of *G. pentaphylla* from Papua New Guinea,[92] is the first natural acridone with an unmodified geranyl substituent directly attached to the acridone nucleus. Glycocitrine-V **203**, isolated as an optically inactive oil, is a unique dihydrofuroacridone in which the oxygen-containing ring is fused to ring A rather than the customary ring C. This ring is clearly derived from a 7-prenylacridone precursor – in itself remarkable, since only one natural 7-prenylacridone alkaloid has ever been reported. The *trans* orientation of the two substituents on the dihydrofuran ring was inferred from the coupling constant (*J* 4.4 Hz) between the vicinal protons on C-1′ and C-2′. The eye-catching feature in glycocitrine-VI **204** is the oxidised C ring with the geminal prenyl substituents at C-4. It is surely more than coincidental that the only natural acridine-3,9-dione alkaloids to have been identified previously, the dimeric diastereomers glycobismines B and C **205**, were also metabolites of *G. citrifolia*.[95] The current investigation also turned up two new optically inactive bisacridones **206** and **207**, which were named glycobismine-D and -E, respectively.[8] These, too, have a novel structural feature: the 1,4-dioxane ring fused at C-5 and C-6 on ring A of the 'upper' acridone moieties, which are derived from known naturally-occurring 5,6-dihydroxyacridone alkaloids (*e.g.*, citracridone-III for **207**). The 4-prenylated acridone precursor of the 'lower half of glycobismine-E is glycocitrine-I **208**. It

Table 3 Isolation and detection of acridone alkaloids

Species	Alkaloid[a]	Ref.
Glycosmis citrifolia	Glycobismine-D[b] **206**	8
	Glycobismine-E[b] **207**	
	Glycocitrine-III[b] **201**	
	Glycocitrine-IV[b] **202**	
	Glycocitrine-V[b] **203**	
	Glycocitrine-VI[b] **204**	
G. pentaphylla	Acrifoline	92
	Arborinine **277**	
	Citracridone-I	
	Glycocitrine-III[b] **201**	
	5-Hydroxyarborinine	
Sarcomelicope megistophylla	Acronycine **225**	22
	N-Desmethylacronycine	
	Fareanine **211**	
	(+)-Megistophylline I[b] **209**	
	(+)-Megistophylline II[b] **210**	
	Melicopicine **222**	
	Melicopine	
	Noracronycine	
	Normelicopidine	
	Normelicopine	
Severinia buxifolia	Atalaphyllidine	93
	Buxifoliadine-A[b] **212**	
	Buxifoliadine-B[b] **213**	
	Buxifoliadine-C[b] **214**	
	Buxifoliadine-D[b] **215**	
	Buxifoliadine-E[b] **216**	
	Buxifoliadine-F[b] **217**	
	Buxifoliadine-G[b] **218**	
	Buxifoliadine-H[b] **219**	
	Citrusinine-I	
	Citrusinine-II	
	Glycocitrine-I **208**	
	1,2,3-Trihydroxyacridone[b] **220**	
Vepris sclerophylla	Evoxanthine **221**	94
	Melicopicine **222**	
	6-Methoxytecleanthine **223**	
	Tecleanthine **224**	

[a] Only new alkaloids and new records for a given species are listed in the table. Structures of known alkaloids, if not specifically numbered, may be found in previous reviews in this series. [b] New alkaloids.

should be noted that the only previously characterised dimeric acridone alkaloids with a 1,4-dioxane linkage are the mixed acridone–lignan dimer acrignine-A and the acridone–coumarin dimer dioxinoacrimarine-A.

Shortly after the above new alkaloids were reported, a publication by Skaltsounis and co-workers revealed the unusual structures of (+)-megistophyllines I and II, **209** and **210**, which were extracted from the bark of the New Guinean tree *Sarcomelicope megistophylla*.[22] These compounds, highly oxygenated in ring C, also proved to be acridine-3,9-diones; but, unlike glycocitrine-VI, they have the terpenoid unit at C-4 twinned with a methoxy group. The authors, understandably unaware of the precedent-setting glycocitrine-III, claimed megistophylline II as the first example of a *C*-geranyl acridone. It is interesting that the highly oxidised acridone-derived alkaloid fareanine **211**, previously isolated only from *Medicosma fareana*, was also detected in the present study. The absolute configurations of the new alkaloids were not determined.

Extracts of the root bark of *Severinia buxifolia*, used as a folk remedy in China for a variety of ailments, yielded a suite of seventeen acridone alkaloids, among them the new metabolites **212**–**219**, to which the names buxifoliadines-A–H, respectively, were assigned.[93] The most unusual of these metabolites are the optically inactive buxifoliadine-E **216** and buxifoliadine-G **218**, which contain the linearly-fused furo[3,2-*b*]acridone skeleton, hitherto unknown in nature. Also isolated for the first time from a natural source was 1,2,3-trihydroxyacridone **220**. The authors contrasted the outcome of this study, which was on plant material collected in Hainan province, China, with a previous study on *S. buxifolia* from Taiwan; in the latter case, simple acridones and furoacridones were not detected. This seems to bear out the observation that the pharmacological activity of traditional Chinese medicines depends very much on the area in which they are collected.

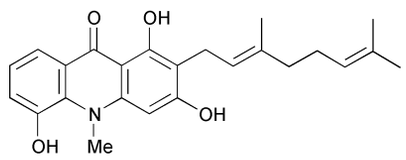
^{13}C NMR spectroscopic data have been reported, apparently for the first time, for the alkaloids evoxanthine **221**, melicopicine **222**, 6-methoxytecleanthine **223** and tecleanthine **224**, isolated from Madagascan *Vepris sclerophylla*.[94]

The important investigations of Tillequin and co-workers into the synthesis, characterisation and biological activity of derivatives of the anticancer alkaloid acronycine **225** continue to yield interesting results. Since the pyran D ring appears to play a crucial role in the biological activity of this group of compounds, NMR spectroscopic studies were undertaken to probe the stereochemistry and conformation of this ring in the natural and synthetic compounds **226**–**242**.[96] The publication gives comprehensive tabulations of ^{1}H and ^{13}C NMR data, as well as full details of the NOESY and coupling constant analyses on which the conformational analysis was based. Conformational analysis by molecular mechanics was also used to corroborate the spectroscopic results. For free hydroxy compounds, intermolecular hydrogen bonding was detected in solution, as evinced by temperature, concentration and solvent effects. Electrospray mass spectrometry revealed similar intermolecular associations in the gas phase. A useful correlation between the ^{13}C chemical shifts of the methyl groups on ring D and the *cis*- or *trans*-relative stereochemistry of the other substituents on this ring was established in this study.

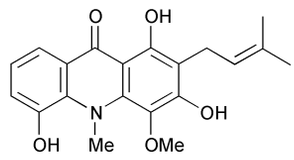
3.2 Synthesis and biological studies

A new synthetic route to the pyrano[3,2-*b*]acridones **243** and **244** is potentially applicable to acridone alkaloids such as honyumine **245** and yukocitrine **246**.[97] A short route to the model furo[2,3-*c*]acridone system **247** has potential for the synthesis of alkaloids such as furacridone **248**.[98]

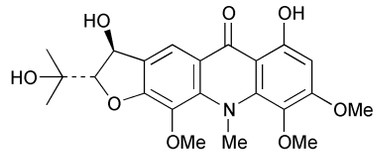
Tillequin's group recently undertook a *de novo* synthesis of the six unnatural acronycine analogues **249**–**254** from 2-chloro-3-nitrobenzoic acid and the chromenes **255**.[99] The amines **251** and **254** were particularly sought after as potential anticancer drugs in view of the expected water-solubility of their salts. These two compounds proved to be two to three times more active than acronycine **225** or demethoxyacronycine **256** in inhibiting the proliferation of L1210 murine leukaemia cells (IC_{50} 18.8 and 9.4 μM, respectively); the nitro derivatives were substantially less active. The hypothesis that a step involving DNA intercalation is implicated in acronycines mode of action provided the rationale for the synthesis of a suite of benzo[*b*]acridones **257**–**264**, all of which were prepared *via* the diol **265**, itself obtained by condensing phloroglucinol with 2-aminonaphthalene-2-carboxylic acid.[100] Catalytic dihydroxylation of **257** with osmium tetroxide in turn provided the racemic diol **266**, and thence the additional mono- and di-ester derivatives **267**–**274**. Fascinatingly, all the new compounds except **266** were more potent inhibitors of L1210 cells *in vitro* than acronycine; the esters **267**–**273**, in particular, were up to two orders of magnitude more effective, and **274** (IC_{50} 0.02 μM) was about a thousand times more cytotoxic. However, their mode of action appears to be different from that of acronycine, since cell development was arrested at a different phase. In *in vivo* tests with mice inoculated intraperitoneally with P288 murine leukaemia, compounds **267** and **274** were significantly more active than acronycine in prolonging the survival rate of animals, although they were not curative. They also proved to be very efficient



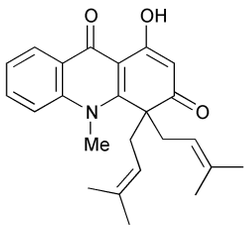
201 Glycocitrine-III



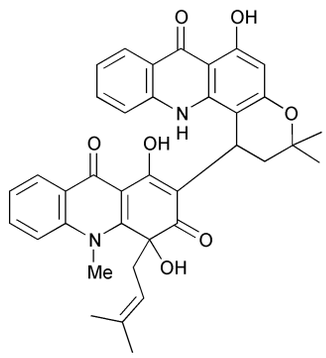
202 Glycocitrine-IV



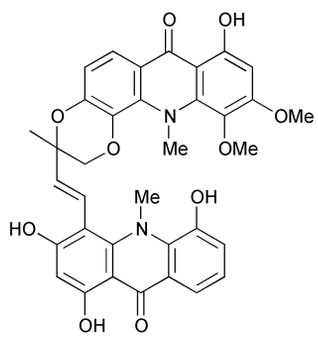
203 Glycocitrine-V



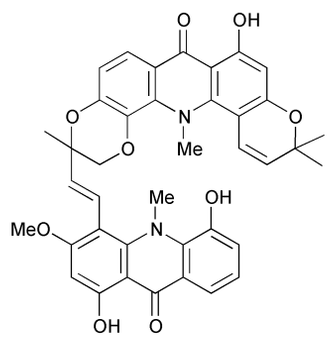
204 Glycocitrine-VI



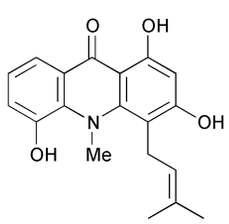
205 Glycobismine-B and -C



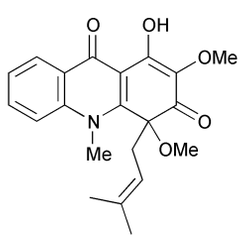
206 Glycobismine-D



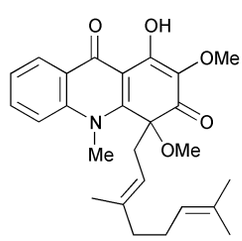
207 Glycobismine-E



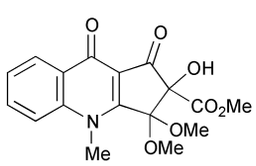
208 Glycocitrine-I



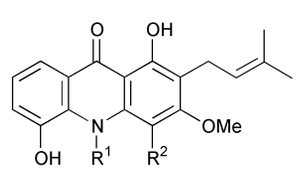
209 Megistophylline I



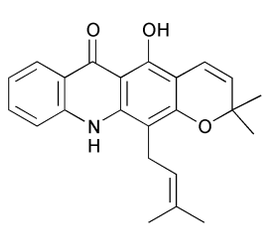
210 Megistophylline II



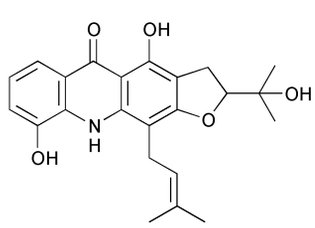
211 Fareanine



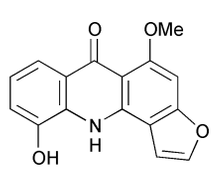
212 Buxifoliadine-A R^1 = Me; R^2 = prenyl
213 Buxifoliadine-B R^1 = R^2 = prenyl
214 Buxifoliadine-C R^1 = R^2 = H



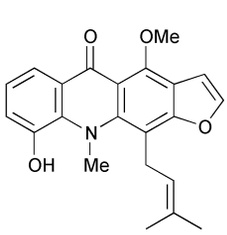
215 Buxifoliadine-D



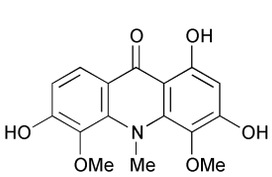
216 Buxifoliadine-E



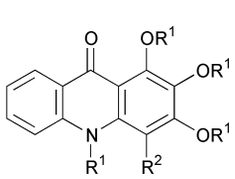
217 Buxifoliadine-F



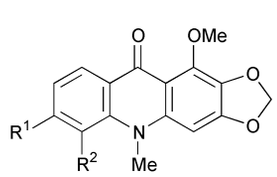
218 Buxifoliadine-G



219 Buxifoliadine-H



220 R^1 = R^2 = H
222 R^1 = Me; R^2 = OMe

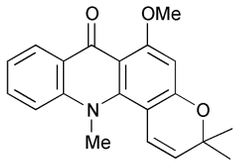


221 Evoxanthine R^1 = R^2 = H
223 R^1 = R^2 = OMe
224 Tecleanthine R^1 = H; R^2 = OMe

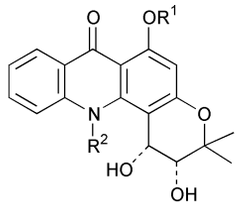
inhibitors of colon 38 adenocarcinoma in mice, compound **267** in particular inhibiting tumour growth by 96% at a dosage of 6.25 mg kg^{-1}, and even promoting the disappearance of tumours in some test animals.

Glyfoline **275** is another well-known acridone alkaloid with impressive antineoplastic activity. However, its mode of action appears to be quite different from that of other clinically used antitumour drugs. To probe the mechanism of action, Su *et al.* prepared the biotinylated derivative **276**, the idea being to use electron microscopy to visualise the changes in nasopharyngeal carcinoma cells once **276** was delivered to the glyfoline binding sites.[101] The study showed that the inner membrane of the mitochondria is the favoured site for glyfoline localisation.

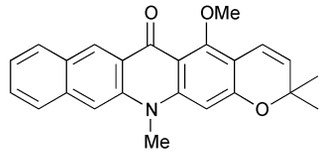
The common alkaloid arborinine **277**, found in *Glycosmis pentaphylla*, amongst other sources, has been found to inhibit the growth of crown gall tumours in an *in vitro* assay.[102] Certain acridone derivatives, and in particular 1-hydroxy-*N*-methylacridone **278**, have proved to be selective inhibitors of HIV-1 replication in chronically infected cells.[103]



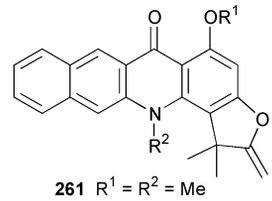
225 Acronycine



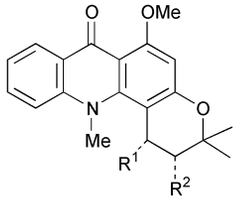
226 R^1 = Me; R^2 = H
227 R^1 = H; R^2 = Me



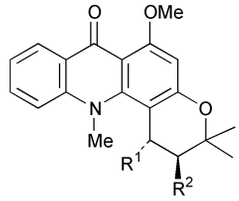
260



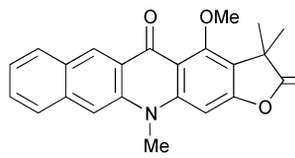
261 R^1 = R^2 = Me
262 R^1 = R^2 = H
263 R^1 = Me; R^2 = H



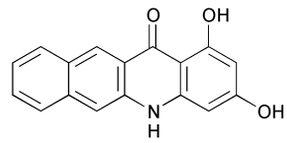
228 R^1 = R^2 = OH
229 R^1 = R^2 = OAc
230 R^1 = R^2 = OCOPh
231 R^1 = OH; R^2 = OCOPh
232 R^1 = OAc; R^2 = OCOPh
233 R^1–R^2 = OC(S)O
234 R^1 = H; R^2 = OH
235 R^1 = OH; R^2 = H



236 R^1 = R^2 = OH
237 R^1 = R^2 = OAc
238 R^1 = R^2 = OCOPh
239 R^1 = OH; R^2 = OAc
240 R^1 = OH; R^2 = Cl
241 R^1 = OH; R^2 = Br
242 R^1 = OH; R^2 = I



264



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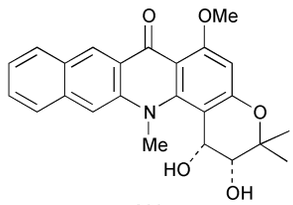
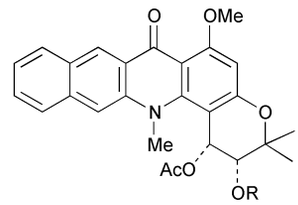
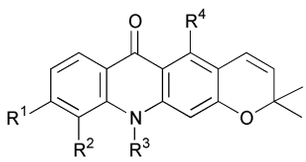


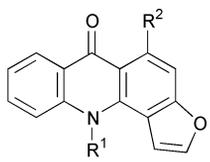
rac-**266**



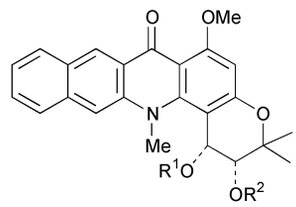
267 R = Ac
268 R = COBu^i
269 R = COPh



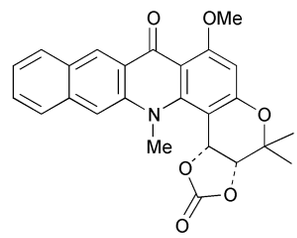
243 R^1 = R^2 = R^3 = R^4 = H
244 R^1 = R^2 = R^4 = H; R^3 = Me
245 R^1 = R^4 = OH; R^2 = OMe; R^3 = Me
246 R^1 = H; R^2 = R^4 = OH; R^3 = Me



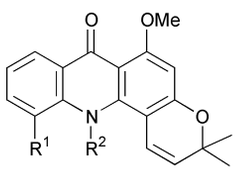
247 R^1 = R^2 = H
248 R^1 = Me; R^2 = OH



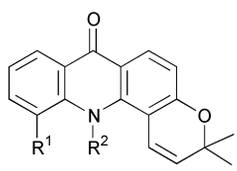
270 R^1 = R^2 = COEt
271 R^1 = R^2 = COBu^i
272 R^1 = H; R^2 = COBu^i
273 R^1 = H; R^2 = COPh



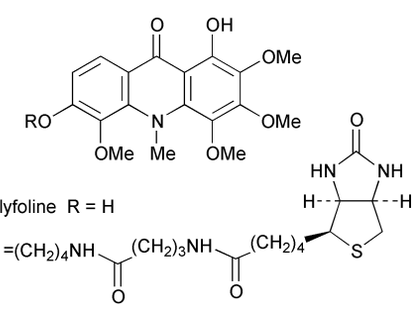
274



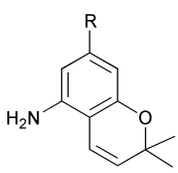
249 R^1 = NO_2; R^2 = H
250 R^1 = NO_2; R^2 = Me
251 R^1 = NH_2; R^2 = Me



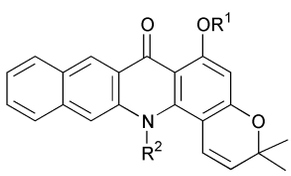
252 R^1 = NO_2; R^2 = H
253 R^1 = NO_2; R^2 = Me
254 R^1 = NH_2; R^2 = Me
256 R^1 = H; R^2 = Me



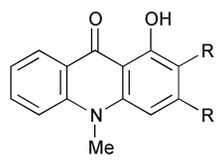
275 Glyfoline R = H
276 R = $(CH_2)_4NH$–$(CH_2)_3NH$–$(CH_2)_4$



255 R = OMe or H



257 R^1 = R^2 = Me
258 R^1 = R^2 = H
259 R^1 = H; R^2 = Me



277 Arborinine R = OMe
278 R = H

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