Quinoline, quinazoline and acridone alkaloids

Joseph P. Michael

Molecular Sciences Institute, School of Chemistry, University of the Witwatersrand, Wits 2050, South Africa. E-mail: jmichael@aurum.chem.wits.ac.za

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This review covers the isolation, structure determination, synthesis and biological activity of quinoline, quinazoline and acridone alkaloids from plant, microbial and animal sources. The literature from July 2000 to June 2001 is reviewed, and 119 references are cited.

1 Quinoline alkaloids

1.1 Occurrence

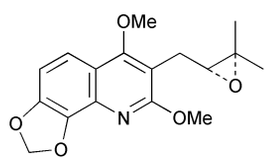
An impressively diverse range of novel quinoline alkaloids was reported during the period under review, and convincing spectroscopic evidence was presented for most of the new structures. These alkaloids and their sources are listed in Table 1, which also includes previously unreported sources of known alkaloids.[1–24]

Funayama *et al.* have largely been responsible for recent studies on the alkaloidal constituents of *Orixa japonica*, an oriental plant which has medicinal applications. Their findings have been summarised in a short review describing the 24 known and new alkaloids (mainly hemiterpenoid quinoline derivatives) that they have isolated from this source, as well as some of their studies on the biosynthesis and biological activity of selected alkaloids.[10] The review also recounts in some detail their investigations into the absolute stereochemistry of (−)-preorixine **1**, an important biosynthetic intermediate for several of the more complex *Orixa* alkaloids.

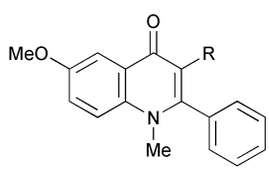
1.2 Non-terpenoid quinoline and quinolinone alkaloids from rutaceous plants

The ability of *Orixa japonica* extracts to act as relaxants of rat jejunum smooth muscle has been traced to two well-known alkaloids, eduline **2** and japonine **3**, the effects of which were comparable to that of the typical muscle relaxant papaverine.[9] The identity of eduline, isolated for the first time from this plant source, was confirmed by synthesis from 6-methoxy-1-methylisatoic anhydride and acetophenone.

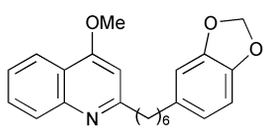
The novel alkaloids **4** and **5** isolated from root extracts of Saudi Arabian *Ruta chalepensis* are unique in possessing a 1,6-hexylene "spacer" between the ring moieties rather than the more common ethylene or butylene chains.[16] Long-range relationships in the NMR spectra proved particularly useful for the unambiguous siting of substituents. The alkaloids were correlated chemically by the conversion of **5** into **4** upon treatment with iodomethane and sodium carbonate in acetone.



1 (–)-Preorixine



2 Eduline R = H
3 Japonine R = OMe



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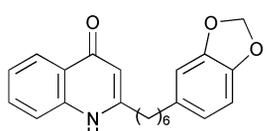

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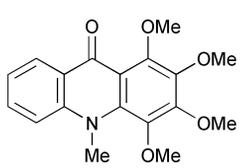
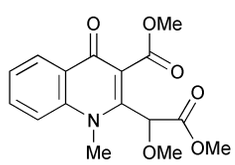
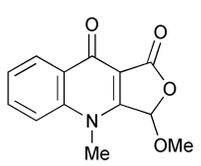


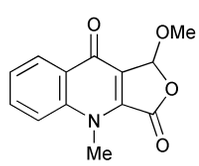
6 Melicopicine



7 Sarcomejine



8 Megistolactone



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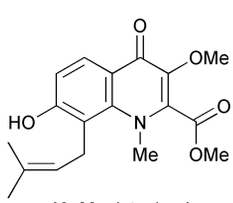
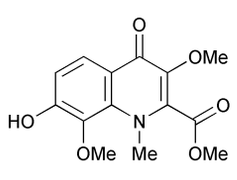


10 Megistonine I



11 Megistonine II

The bark of the New Caledonian tree *Sarcomelicope megistophylla* continues to yield an intriguing range of unprecedented quinoline alkaloids, all of which are conceivably

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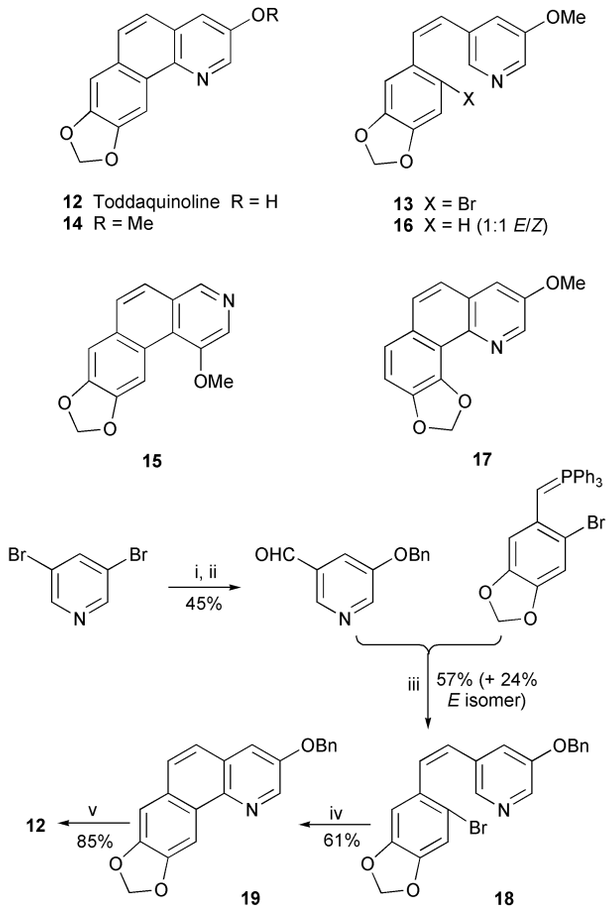
Table 1 Isolation and detection of quinoline alkaloids from plant, microbial and animal sources

Species	Alkaloid[a]	Ref.
Boronia pinnata	Dictamnine **77**	1
	Evolitrine **78**	
	Folimine	
	(−)-Pinolinone[b] **25**	
	Preskimmianine	
Castanea mollissima	(−)-Chestnutamide[b] **84**	2
Dictamnus dasycarpus	Dasycarine[b] **26**	3
Galipea officinalis	*N*-Methyl-4-hydroxy-3-(2,3-epoxy-3-methylbutyl)quinolin-2-one[b] **27**	4
Haplophyllum tuberculatum	(−)-Haplotubine[b] **71**	5
	rac-Haplotubinone[b] **33**	
Huperzia serrata	(+)-Huperzine J[b] **85**	6
	(−)-Huperzine K[b] **86**	
	(+)-Huperzine L[b] **87**	
Lycopodium chinense	(−)-Senepodine A[b] **88**	7
Oceanapia sp. (sponge)	Uranidine **125**	8
	Uranidine derivative[b] **127**	
Orixa japonica	Eduline **2**	9
	Isobalfourodine	10
	(−)-Isopteleflorine[b] **31**	11
	3′-*O*-Methylorixine[b] **29**	
	Orijanone (orixiarine) **30**	
Penicillium cf. *simplicissimum*	*rel*-(3*R*,4*R*)-(+)-3-Methoxy-4,5-dihydroxy-4-(4-methoxyphenyl)-3,4-dihydroquinolin-2-one **102**	12
	rel-(3*R*,4*R*)-(−)-3-Methoxy-4-hydroxy-4-(4-methoxyphenyl)-3,4-dihydroquinolin-2-one **103**	
	(+)-Penigequinolone A **104**	
	(+)-Penigequinolone B **105**	
	(−)-Peniprequinolone[b] **106**	
Penicillium sp. 386	(−)-Penicillazine[b] **107**	13
Penicillium sp. EPF-6	(+)-Quinolactacin A[b] **108**	14,15
	(−)-Quinolactacin B[b] **109**	
	(+)-Quinolactacin C[b] **110**	
Ruta chalepensis	Maculosidine	16
	4-Methoxy-1-methylquinolin-2-one	
	2-[6-(3,4-Methylenedioxyphenyl)hexyl]-4-methoxyquinoline[b] **4**	
	2-[6-(3,4-Methylenedioxyphenyl)hexyl]quinolin-4-one[b] **5**	
	Pteleine **79**	
Sarcomelicope megistophylla	Furomegistine I[b] **74**	17
	Furomegistine II[b] **75**	
	(−)-Megistolactone[b] **8**	18
	Megistonine I[b] **10**	19
	Megistonine II[b] **11**	
	(+)-Sarcomejine[b] **7**	20
Stauranthus perforatus	Skimmianine **82**	21
	Veprisine	
Strychnos cathayensis (Loganiaceae)	4-Methoxyquinolin-2-one	22
Zanthoxylum davyi	Skimmianine	23
Zanthoxylum schinifolium	γ-Fagarine **80**	24
	(+)-Platydesmine *ent*-**58**	
	Robustine **81**	

[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.

formed from highly oxygenated acridone alkaloids such as melicopicine **6** by oxidative cleavage of ring A. The structural similarity is clearly apparent in the new alkaloid (+)-sarcomejine **7** (absolute configuration unknown).[20] An unusual long-range ^{1}H–^{15}N heteronuclear shift correlation study at natural abundance showed a three-bond relationship between nitrogen and the side-chain methine proton, thereby excluding the alternative structure with the C-2 and C-3 substituents interchanged. Further degradation of the putative acridone ring A is apparent in the structure of the weakly cytotoxic alkaloid (−)-megistolactone, the absolute configuration of which could also not be determined.[18] Structure **8** rather than the alternative structure **9** was assigned on the basis of a strong NOE interaction between the *N*-methyl group and the methine proton. The biosynthetic origins of megistonine I **10** and megistonine II **11**, also unambiguously characterised by NMR spectroscopy, are less obviously ascribable to acridone oxidation.[19] These two compounds possess a methoxy group at C-3, which is unusual in rutaceous quinoline alkaloids (*cf.* japonine **3**), although less rare than the authors believe.

New approaches to the synthesis of toddaquinoline **12** by Harrowven *et al.*[25,26] have overcome the problems of regiochemical control apparent in their earlier synthesis, which involved intramolecular addition of an aryl radical to a pyridine[27] (*cf.* Ref. 28*a*). Whereas the azastilbene **13** (X = Br) yielded a mixture of the desired toddaquinoline methyl ether **14** (28%) and its regioisomer **15** (30%) on treatment with tributyltin hydride and AIBN in toluene at 80 °C, the use of a different radical initiator, sodium cobalt(I)salophen in THF at room temperature, yielded **14** (61%) and less than 5% of **15**. Cobalt appears to play a dual role in this reaction, first initiating homolysis of the carbon–bromine bond, and then acting as a Lewis acid to enhance the electrophilicity at C-6 in the pyridine ring towards attack by the nucleophilic radical. By contrast, photochemical cyclisation of the azastilbene **16** (X = H, 1 : 1 mixture of geometrical isomers) was less selective, giving a mixture of **14** (20%) and **15** (54%), while cyclisation initiated by lithium–halogen exchange of **13** (X = Br) with *n*-butyllithium at −78 °C gave **14** (11%) and yet another regioisomer, the unstable **17** (32%). Ironically, it proved impossible to demethylate the methyl ether **14**, necessitating a change of protecting group. The improved synthesis of toddaquinoline proceeded through



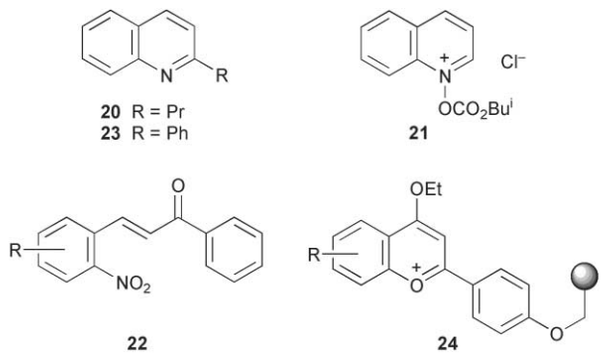
Scheme 1 *Reagents and conditions*: i, NaOBn, DMF, 65 °C; ii, *n*-BuLi, THF, −100 °C, 1 h, then DMF, −60 °C; iii, THF, 0 °C; iv, Na–Hg, Co(II)salophen, THF, rt, then add **18**, THF, −78 °C to rt; v, H_2 (1 atm), 5% Pd–C, HOAc, rt.

the benzyl ether **18**, prepared as shown in Scheme 1. Radical-mediated cyclisation with sodium cobalt(I) salophen gave toddaquinoline benzyl ether **19** in 61% yield, after which conventional hydrogenolytic debenzylation completed the synthesis of the target alkaloid **12**.

Several short syntheses of simple 2-substituted quinolines merit brief mention. A new route to 2-alkylquinolines, including the natural product 2-propylquinoline **20**, by addition of Grignard reagents to *N*-[(isobutoxycarbonyl)oxy]quinolinium chloride **21** holds promise for preparing other 2-substituted quinoline alkaloids.[29] Reduction of 1-aryl-3-(2-nitroaryl)prop-2-en-1-ones **22** with low-valent titanium, prepared from samarium powder and titanium tetrachloride in THF, also provided an efficient route to 2-arylquinolines, amongst them the alkaloid **23**.[30] Treatment of polymer-bound flavylium salts **24** with aqueous ammonia represents a versatile new route for the synthesis of analogues of the 2-phenylquinolin-4-one alkaloids.[31] Finally, the alkylation of 2-phenylquinolin-4-ones with haloalkanes in the presence of sodium hydride and THF yielded a range of 4-alkoxy-2-phenylquinoline alkaloid analogues, some of which showed potent antiplatelet activity.[32]

1.3 Terpenoid quinoline alkaloids and tricyclic derivatives

The 3,4-*trans*-diol structure of (−)-pinolinone **25**, extracted from roots of the Australian shrub *Boronia pinnata*,[1] is unique amongst rutaceous quinoline alkaloids. This novel alkaloid is effectively a 3-prenylquinolin-2-one that has been oxidised at C-3 and reduced at C-4. The location of substituents was fixed by HMBC correlations and NOE studies, and in particular the spatial relationship of the hydroxy groups was deduced from an NOE interaction between H-4 and 3-OH. The absolute configuration was not established.

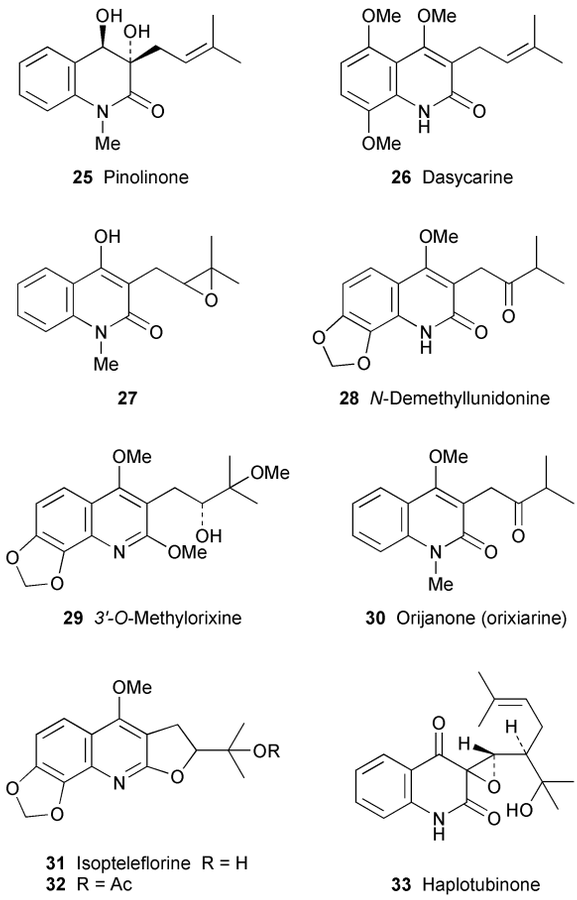


A more typical 3-prenylquinolin-2-one, dasycarine **26**, was isolated from the roots of Chinese *Dictamnus dasycarpus*.[3] Once again, long-range NMR spectroscopic methods were used to establish the location of the substituents.

Naturally occurring 3-prenylquinolin-2-ones are commonly modified by oxidation of the prenyl side chain. A case in point is the epoxyprenylquinolin-2-one **27** (incorrectly named by the authors as an epoxyisobutyl-2-quinolone), a novel metabolite of the trunk bark (angostura) of Venezuelan *Galipea officinalis*, which is well known for its medicinal properties.[4] Several alkaloids isolated from leaves and stems of *Orixa japonica* and thoroughly characterised by spectroscopic techniques also show side-chain oxidation.[11] They include the known alkaloid *N*-demethyllunidonine **28**, the novel compound (+)-3′-*O*-methylorixine **29** and the apparently new compound orijanone **30**. The latter alkaloid had, in fact, been reported in 1998 as a metabolite of *Skimmia laureola*[33] (*cf.* Ref. 28*b*) and assigned the name orixiarine, which should thus take precedence.[34] The tricyclic derivative (−)-isopteleflorine **31** (absolute configuration unknown) is, however, a new natural product from *O. japonica*, although it had previously been prepared by hydrolysis of another *O. japonica* alkaloid, 3′-*O*-acetylisopteleflorine **32**.[35]

The growing family of 3-monoterpenoid quinoline alkaloids has been augmented by a most unusual member, haplotubinone.[5] When a comprehensive suite of NMR spectroscopic experiments on this optically inactive metabolite from Saudi Arabian *Haplophyllum tuberculatum* failed to yield an unambiguous structure, single crystal X-ray analysis was used to establish the complete structure and relative stereochemistry shown in **33**. Noteworthy features in the solid-state structure included hydrogen-bonding between the hydroxy group and the epoxide oxygen, the dimeric association of pairs of enantiomers by hydrogen bonds between the lactam N–H and C-2 carbonyl groups, and the folding back of the side chain to place the (*Z*)-methyl group of the prenyl unit over the benzene ring. The latter feature probably accounts for the unusual upfield shift (δ 0.85) for this methyl group in the ^{1}H NMR spectrum.

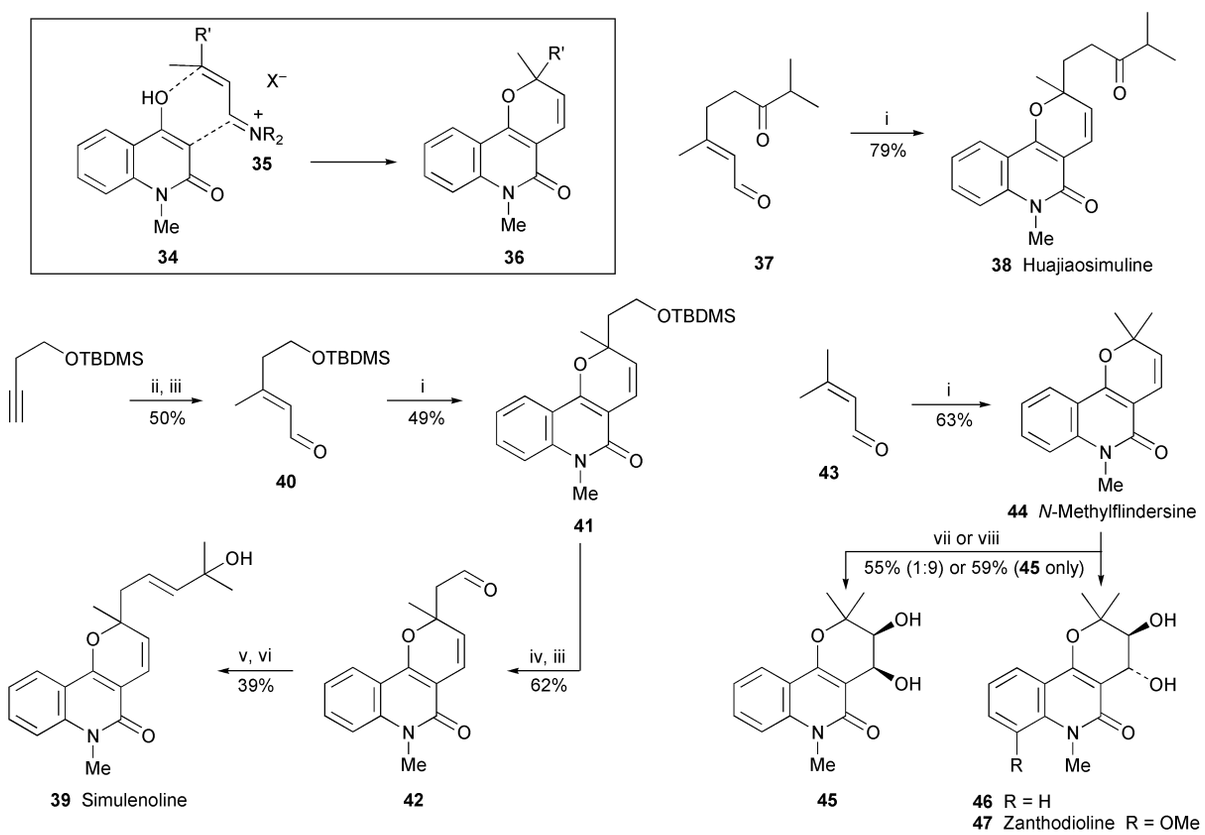
A formal [3 + 3] cycloaddition between 4-hydroxy-1-methylquinolin-2-one **34** and α,β-unsaturated iminium salts **35** in the sense shown in Scheme 2 (inset) underlies a conceptually simple route to ring C-substituted pyrano[3,2-*c*]quinolines **36** by McLaughlin and Hsung.[36] For example, the iminium species formed *in situ* from the geraniol-derived aldehyde **37**, piperidine and acetic anhydride, reacted with **34** in toluene at 85 °C to give (±)-huajiaosimuline **38** directly in 79% yield. The lengthier synthesis of (±)-simulenoline **39** from aldehyde **40** proceeded through the adduct **41**, which was then deprotected and oxidised to give the tricyclic product **42**. Wadsworth–Emmons homologation with diethyl 2-oxopropylphosphonate and subsequent addition of methyllithium completed the synthesis of **39**. Finally, prenal **43** was the precursor in a one-pot synthesis of *N*-methylflindersine **44** (63% yield). In this case, further transformation of the product **44** by dihydroxylation under appropriate conditions yielded the racemic *cis*- and *trans*-diols **45** and **46**, respectively. Although neither of these is a natural product, their spectroscopic data provided useful analogies for



confirming the tentatively assigned *trans*-configuration of a related natural product, zanthodioline **47**.

The significant contribution by Barr and Boyd on the enantioselective synthesis of various tricyclic hemiterpenoid alkaloids and the proof of their absolute configurations, communicated in 1994[37] (*cf.* Ref. 28*c*), has been published with full experimental details and several extensions.[38] The previous work described the conversion of the pyrano[2,3-*b*]quinoline **48**, prepared in two steps from atanine **49**, *via* bromohydrin ester **50** into several alkaloids, including (+)-(3*S*)-geibalansine **51**, (−)-(3*S*)-ribalinine **52**, (−)-(2′*S*)-edulinine **53**, (−)-(2*R*)-araliopsine **54**, as well as the alkaloid analogue (+)-(3*S*)-Ψ-ribalinine **55**. The results permitted the correction of incorrect absolute stereochemistries recorded in the literature for edulinine and araliopsine. The new extensions include conversion of atanine into chiral diols **56** and *ent*-**56** with AD-mix-α and AD-mix-β, respectively, and proof of absolute configuration by analysis of Mosher esters. Further transformation of **56** and its enantiomer into the bromoacetates **57** and *ent*-**57** with acetoxyisobutyryl bromide prefaced transformation into (−)-(2*R*)-platydesmine **58** and its (+)-(2*S*) enantiomer, respectively, upon treatment with base. The *N*-methylplatydesminium methiodides were readily prepared from the free bases by treatment with iodomethane in ethanol. The (+)-(2*S*) salt **59** proved to be identical to a natural sample isolated from *Skimmia japonica*, a result that conflicted with the literature assignment of the (2*R*)-configuration to (+)-platydesmine methiodide. To clinch matters, single-crystal X-ray crystallography of (+)-platydesminium perchlorate unequivocally supported the (2*S*) absolute configuration. Thus the (2*R*) absolute configurations previously assigned to both (+)-platydesmine and its (+)-methosalt are incorrect, and the structure of the former alkaloid is *ent*-**58**. Other transformations of relevance included mild alkaline hydrolysis of (+)-platydesminium methiodide **59** to complete an alternative synthesis of (−)-(2′*S*)-edulinine **53**; and treatment of *N*-methylatanine **60** with AD-mix-α to give the same (−)-alkaloid.

A short synthesis of racemic araliopsine (±)-**54** by Parsons and co-workers exploited the addition of 4-hydroxy-1-



Scheme 2 *Reagents and conditions*: i, piperidine, toluene, 0 °C, 5 min, then Ac_2O, 85 °C, 1 h, then **34**, 85 °C, 48 h; ii, Cp_2ZrCl_2, $AlMe_3$, *n*-BuLi, $(CH_2O)n$; iii, Dess–Martin periodinane, CH_2Cl_2, rt; iv, HF–pyridine, THF, rt; v, $(EtO)_2POCH_2COMe$, NaH, THF, rt; vi, MeLi, THF–Et_2O (1 : 1), −78 °C to rt; vii, magnesium monoperoxyphthalate, Pr^iOH–H_2O (2 : 1), rt; viii, OsO_4 (cat.), $K_3Fe(CN)_3$, K_2CO_3, Bu^tOH–H_2O (1 : 1), rt.

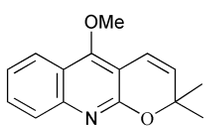
methylquinolin-2-one **34** (see Scheme 2) to 2-methylbut-3-en-2-ol upon sonication in acetic acid at 60 °C in the presence of manganese(III) acetate.[39,40] The target alkaloid was obtained directly in 40% yield. This radical-mediated process appears to be general for the addition of **34** to alkyl-substituted alkenes, and several analogues of general structure **61** could be prepared in yields of 31–65%. With styrenes, however, approximately equal amounts of the angularly fused dihydrofuro[3,2-*c*]-quinoline products **61** (R^1 = Ph) and the linearly fused isomers **62** were produced. The reaction of **34** with alkynes (phenylacetylene, 2-methylbut-1-en-3-yne) also yielded mixtures of isomeric tricyclic products, as did the reaction of quinoline-2,4-diol with alkenes.

An electrophysiological study of the ability of various linearly and angularly fused dihydrofuroquinolines and dihydropyranoquinolines to block the voltage-gated potassium channel Kv1.3 in mouse fibroblasts necessitated the preparation of a range of relevant alkaloids and alkaloid analogues from the 3-prenylquinolin-2-ones **63** and **64** by reported transformations.[41] The compounds in the study included, amongst others, the alkaloids dihydroflindersine **65**, *N*-methylhaplamine **66**, khaplofoline **67**, isoplatydesmine **68** and *O*-methylribaline **69**. The known based-induced skeletal rearrangements of **68** and **69** to give derivatives of araliopsine, ribalinine and Ψ-ribalinine (*vide supra*) were confirmed, and AM1 calculations on the heats of formation of the various isomers supported the experimental observation that angularly fused dihydropyranoquinolinones (*e.g.*, Ψ-ribalinine) are the most stable isomers and linear dihydrofuroquinolinones (*e.g.*, isoplatydesmine itself) the least. In the pharmacological studies themselves, angularly fused isomers were in general more potent channel blockers than their linear analogues, and furoquinolines more potent than dihydrofuroquinolines. The most active compounds, *N*-methylhaplamine **66** and **70**, might thus function as templates for the development of novel immunosuppressants.

1.4 Furoquinoline alkaloids

(−)-Haplotubine **71**, a new furoquinoline alkaloid isolated from the aerial parts of *Haplophyllum tuberculatum*, contains a 6,7-dihydroxygeranyloxy substituent at C-7.[5] This unusual substituent has only been encountered once before amongst the rutaceous quinoline alkaloids, namely, in the compound bucharaine **72**. The connectivity in the side chain was established from HMBC spectra.

The only secofuroquinoline alkaloids to have been reported in the past were the rhoifolinic esters **73**. Bark extracts of *Sarcomelicope megistophylla* have now yielded another two alkaloids of this class, furomegistine I **74** and furomegistine II **75**, both of which are conceivably derived by oxidative cleavage of a more conventional furoquinoline alkaloid such as acronycidine **76**.[17] The propensity of *S. megistophylla* to produce oxidatively modified alkaloids has already been commented upon (*vide supra*). The structures of the furomegistines were deduced on the basis of their spectroscopic characteristics, long-range NMR spectroscopic experiments and NOE effects once again playing a pivotal role in the structural elucidation. Furomegistine II was found to be racemic, possibly indicating its formation from furomegistine I by an unselective intramolecular conjugate addition. Both alkaloids showed moderate cytotoxicity towards human lung carcinoma A549 and human colon adenocarcinoma HT29 cells (IC_{50} 90 and 100 μM, respectively).



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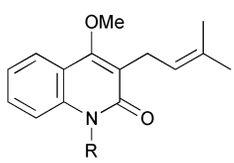
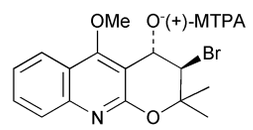


49 Atanine R = H
60 R = Me



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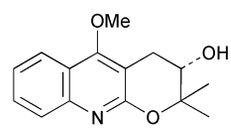
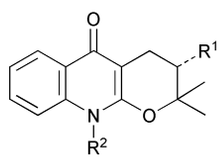
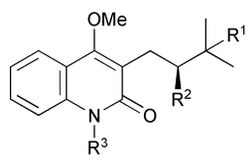


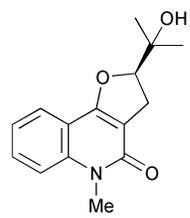
51 (+)-(3*S*)-Geibalansine



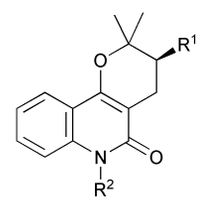
52 (–)-(3*S*)-Ribalinine
R^1 = OH; R^2 = Me
67 Khaplofoline R^1 = R^2 = H



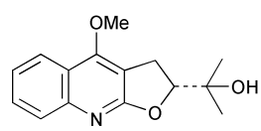
53 (–)-(2'*S*)-Edulinine
R^1 = R^2 = OH; R^3 = Me
56 R^1 = R^2 = OH; R^3 = H
57 R^1 = Br; R^2 = OAc; R^3 = H



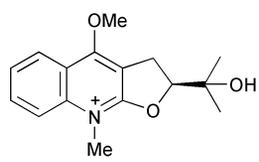
54 (–)-(2*R*)-Araliopsine



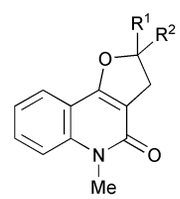
55 (+)-(3*S*)-Ψ-Ribalinine
R^1 = OH; R^2 = Me
65 Dihydroflindersine
R^1 = R^2 = H



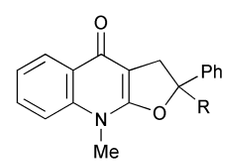
58 (–)-(2*R*)-Platydesmine



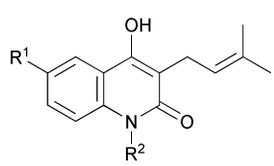
59 (+)-(2*S*)-Platydesminium



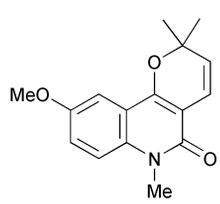
61 R^1, R^2 = alkyl, Ph



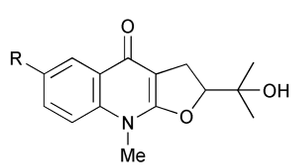
62 R = H, Me, Ph



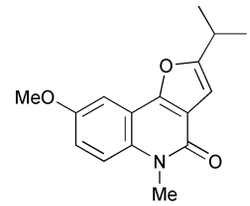
63 R^1 = H; R^2 = H or Me
64 R^1 = OMe; R^2 = Me



66 *N*-Methylhaplamine

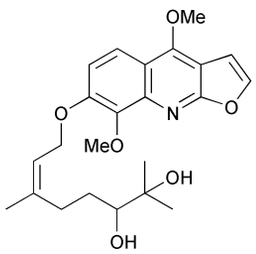


68 Isoplatydesmine R = H
69 *O*-Methylribaline R = OMe

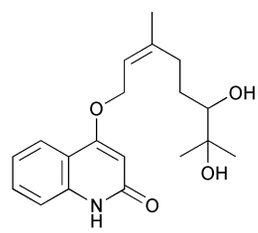


70

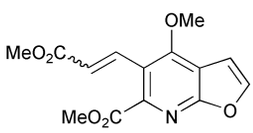
That many furoquinoline alkaloids are biologically active is well known. Dictamnine **77** and evolitrine **78**, amongst other compounds, have recently been shown to inhibit activation of Epstein–Barr virus early antigen (EBV–EA) in Raji cells.[1] Pteleine **79** showed moderate antimicrobial activity against *Mycobacterium smegmatis*, *Bacillus subtilis*, *Staphylococcus aureus* and *Candida albicans* (minimum inhibitory concentration 5–100 μg cm^{-3}),[16] while antiplatelet aggregation activity has been demonstrated for (+)-platydesmine *ent*-**58**, dictamnine, γ-fagarine **80**, robustine **81** and skimmianine **82**.[24] Dictamnine, skimmianine and especially kokusaginine **83** were able to block potassium channel Kv1.3 currents in mouse fibroblasts.[41] Dictamnine and evolitrine showed antifeedant activity against fourth instar larvae of the tobacco caterpillar, *Spodoptera litura*.[42]



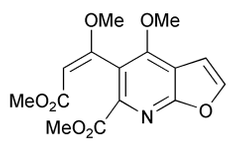
71 Haplotubine



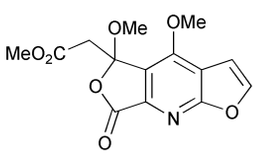
72 Bucharaine



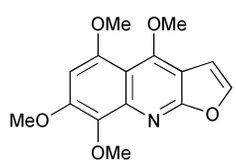
73 Dimethyl rhoifolinate



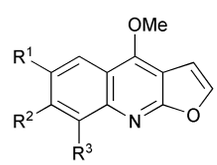
74 Furomegistine I



75 Furomegistine II



76 Acronycidine

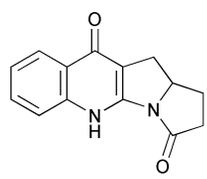


77 Dictamnine $R^1 = R^2 = R^3 = H$
78 Evolitrine $R^1 = R^3 = H$; $R^2 = OMe$
79 Pteleine $R^1 = OMe$; $R^2 = R^3 = H$
80 γ-Fagarine $R^1 = R^2 = H$; $R^3 = OMe$
81 Robustine $R^1 = R^2 = H$; $R^3 = OH$
82 Skimmianine $R^1 = H$; $R^2 = R^3 = OMe$
83 Kokusaginine $R^1 = R^2 = OMe$; $R^3 = H$

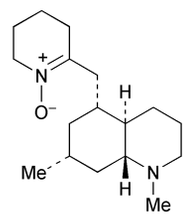
1.5 Miscellaneous quinoline alkaloids from higher plants

The flowers of *Castanea mollissima* (Fagaceae), an economically important variety of chestnut tree that is widely distributed in China, are the source of an unusual new alkaloid, chestnutamide **84**.[2] Convincing spectroscopic evidence was presented for the unprecedented pyrrolizino[3,2-*b*]quinoline skeleton in this compound. In particular, comprehensive HMBC and NOESY correlations established the full connectivity in the assigned structure. The natural product was very slightly laevorotatory ($[\alpha]_D$ −0.016, *c* 0.25, $CHCl_3$), but its absolute configuration was not determined.

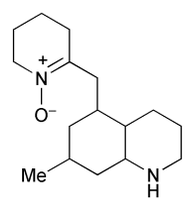
The club mosses of the Lycopodiaceae have yielded several novel decahydroquinoline alkaloids in recent years. The latest additions to this growing group of compounds are huperzines J **85**, K **86** and L **87**, which were isolated from *Huperzia serrata*, a Chinese herbal plant used in the treatment of contusions, strains and swellings.[6] The relative configurations in **85** and **87** were deduced from NOESY correlations, and that in **86**, although not specifically elucidated, is expected to be the same. However, the CD spectra of J and L showed negative Cotton effects, while that in K was positive. These three alkaloids, the first examples of naturally occurring *N*-oxides in the genus *Huperzia*, belong to the well-known phlegmarane ($C_{16}N_2$) group of *Lycopodium* alkaloids.



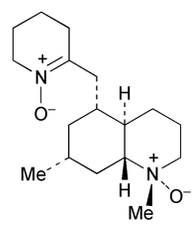
84 Chestnutamide



85 Huperzine J

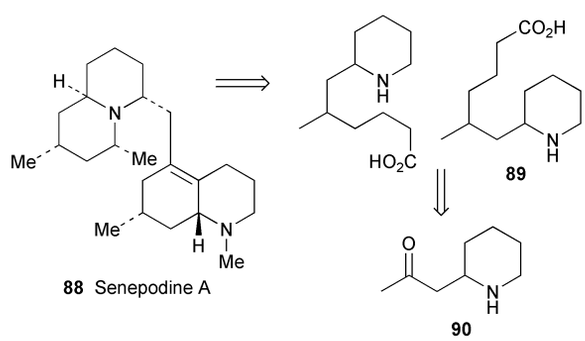


86 Huperzine K



87 Huperzine L

The first member of a new class of $C_{22}N_2$ *Lycopodium* alkaloids, (−)-senepodine A **88**, has recently been isolated from Japanese specimens of *L. chinense*.[7] The structure of this unique octahydroquinoline–quinolizidine dimer was amply supported by one- and two-dimensional NMR spectroscopy. Analysis of proton–proton coupling constants and NOESY data revealed the complex relative stereochemistry shown in **88**; moreover, the latter also indicated that the quinolizidine system had a *cis*-fused ring junction between two piperidine chair conformations. The authors suggest that senepodine A is biogenetically derived from two identical precursors such as **89**, themselves conceivably originating in pelletierine **90** (Scheme 3). The new alkaloid was cytotoxic towards murine lymphoma L1210 cells (IC_{50} 0.1 mg cm^{-3}), but not towards human epidermoid carcinoma KB cells.



88 Senepodine A

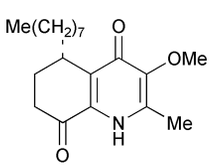
89

90

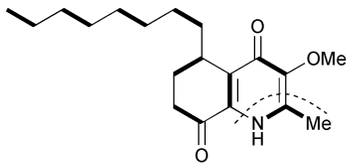
Scheme 3

The revised structure of antidesmone **91**,[43] a metabolite of *Antidesma membranaceum* (Euphorbiaceae) and probably identical to hyeronine A from *Hyeronima oblonga*, was described in last year's review in this series (*cf.* Ref. 28*d*). The revision resulted in part from biosynthetic feeding experiments in cell cultures of *A. membranaceum* with ^{13}C- and ^{15}N-labelled precursors (sodium acetate, glucose, ammonium nitrate, glycine, alanine, aspartic acid), which Bringmann and co-workers have now published in full.[44] The results showed that antidesmone is

built up in a biosynthetically novel manner from a linear C_{16} polyketide and a C_2 unit derived directly from glycine. Acetate and, unexpectedly, alanine and glycine were efficient sources of the polyketide chain (**92**, above the dashed line), which indicated conversion of both amino acids into acetyl-CoA. The transformation of glycine into acetyl-CoA apparently represents a new biosynthetic pathway. Glycine also served as the precursor of the methoxy group. Very significantly, [U-$^{13}C_2$,^{15}N]glycine appeared as an *intact* C_2N fragment in the pyridone ring (**92**, below the dashed line), its CO_2H group obviously undergoing an unusual change in oxidation state to form the 2-CH_3 substituent. Alanine, on the face of it a more plausible source of the C_2N unit, was not incorporated at these positions at all. A final noteworthy feature of the feeding experiments was the specific incorporation of [U-$^{13}C_4$]aspartic acid into the 2-CH_3 substituent and, less prominently, into the acetate-derived positions, which suggests novel conversion of this amino acid into both acetyl-CoA and glycine.

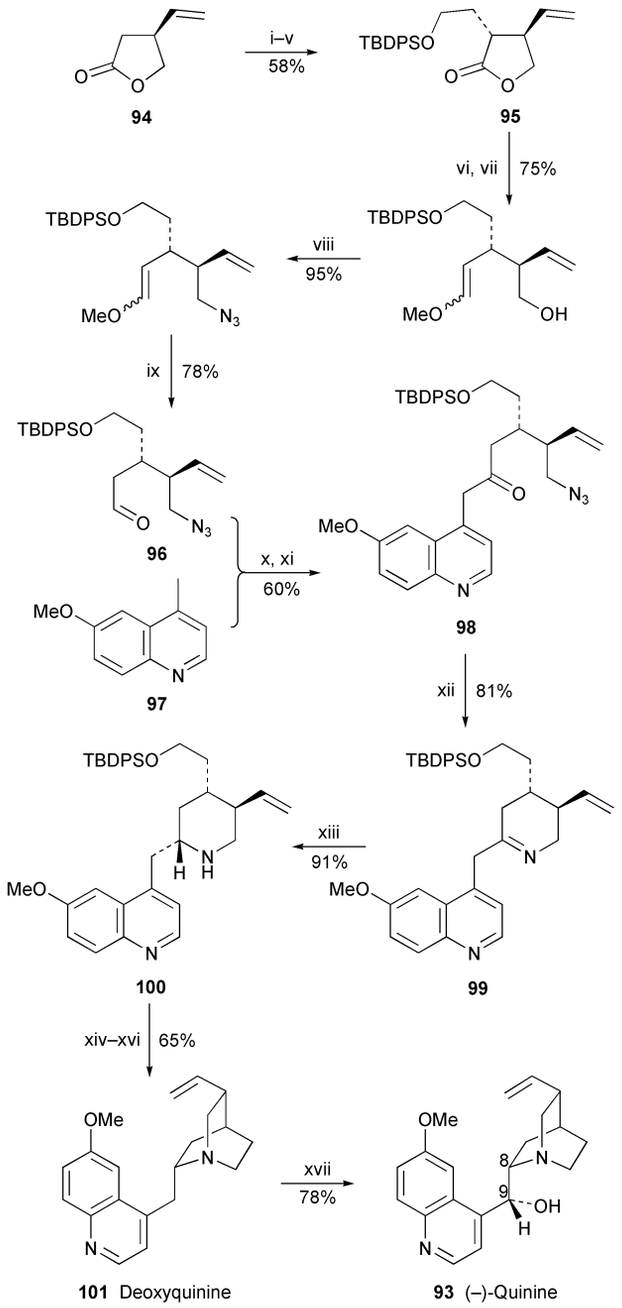


91 Antidesmone



92

The cinchona alkaloids have normally been surveyed with indole alkaloids and related tryptophan-derived metabolites in this *Journal*[45] rather than with the quinoline alkaloids. However, an exception must be made this year for a publication of uncommon significance: the first stereoselective total synthesis of (−)-quinine **93**, by Stork and co-workers.[46] Previous attempts to synthesise this historically and medicinally important alkaloid, succinctly summarised in the prolegomenon to the article, go back almost 150 years, but up to now there has never been a satisfactory solution to the problem of controlling the relative stereochemistry at C-8 and C-9. Stork's approach (Scheme 4) commenced with the (*S*)-4-vinylbutyrolactone **94** and introduced a second stereogenic centre to give *trans*-disubstituted **95** (>20 : 1) by a circuitous but efficient route (58% overall yield). After one-carbon homologation and functional group interconversions, the key azido aldehyde **96** was treated with the lithium salt of 6-methoxy-4-methylquinoline **97**. The diastereomeric mixture of alcohols thus produced was oxidised to the azido ketone **98**, Staudinger reaction of which yielded tetrahydropiperidine **99**. A crucial reduction of this compound with sodium borohydride proceeded with axial delivery of hydride to give the trisubstituted piperidine **100** as a single diastereomer in 91% yield, thereby ensuring the correct absolute stereochemistry at the future C-8 position. The formation of the quinuclidine ring system from **100** was easily achieved by removing the silyl protecting group and mesylating the liberated primary alcohol. The ensuing cyclisation afforded deoxyquinine **101** in 65% yield based on **100**. The final phase of the synthesis exploited a stereoselective benzylic hydroxylation first reported by Gutzwiller and Uskoković in 1978.[47] This entailed treating deoxyquinine with sodium hydride and oxygen in dry DMSO to give (−)-quinine **93** in 78% yield. The C-9 epimeric compound, epiquinine, was only a minor component of the final product (*ca.* 14 : 1).



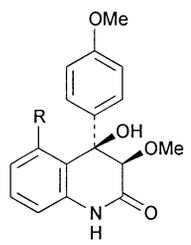
Scheme 4 *Reagents and conditions*: i, Et_2NH, Me_3Al; ii, TBDMS–Cl, imidazole, DMF; iii, LDA, −78 °C, then $ICH_2CH_2OTBDPS$; iv, PPTS (0.3 equiv.), EtOH; v, xylenes, reflux; vi, DIBAL-H, −78 °C; vii, Ph_3P=CHOMe; viii, Ph_3P, DEAD, $(PhO)_2P(O)N_3$; ix, HCl (5 M), THF–CH_2Cl_2, rt; x, **97** + LDA, THF, −78 °C, then add **96**, THF, −78 °C; xi, Swern oxidation; xii, Ph_3P, THF, reflux; xiii, $NaBH_4$, MeOH–THF (1 : 1); xiv, HF, MeCN; xv, $MeSO_2Cl$, pyridine, CH_2Cl_2; xvi, MeCN, reflux; xvii, NaH, DMSO, then O_2.

1.6 Quinoline alkaloids from fungal and microbial sources

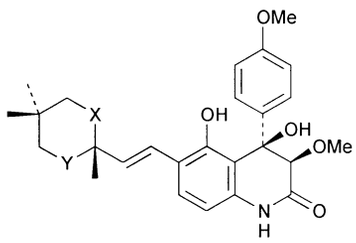
The nematicidal activity of the culture metabolites of *Penicillium* cf. *simplicissimum* was traced by bioassay to several structurally related compounds, among them the known natural products **102** and **103**, penigequinolones A and B, **104** and **105**, and the novel compound (−)-peniprequinolone **106**.[12] Comprehensive ^1H and ^{13}C NMR spectra were recorded for all these products, and similar Cotton effects in their CD spectra indicated that they all possess the same relative stereochemistry at C-3 and C-4. All but **103** showed nematicidal activity (at concentrations of greater than 100 mg dm^{-3}) towards *Pratylenchus penetrans*, a parasitic nematode that causes root lesions in various economically important crops. The penigequinolones in particular may prove to be useful for controlling parasitic nematodes, since they were found to be non-toxic to a free-living nematode, and to lettuce and rice seedlings; in fact, both peniprequinolone and the penigequinolones actually accelerated root growth in rice seedlings.

A strain of the fungus *Penicillium* sp. (strain 386) collected from sand in a marine habitat in the South China Sea has yielded (−)-penicillazine **107**, a novel quinolin-2-one that

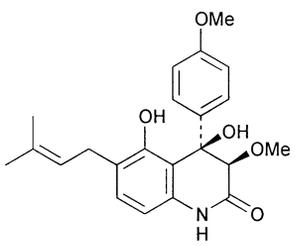
incorporates an unprecedented 5,6-dihydro-4*H*-1,2-oxazine substituent.[13] Various spectroscopic techniques were used to establish the gross structure of this unique natural product, and the stereochemical relationships of the hydrogen atoms in ring D were deduced from analysis of coupling constants and ROESY correlations. Unusual changes in chemical shifts revealed by variable temperature ^{1}H NMR spectroscopy were ascribed to intermolecular hydrogen bonding effects. However, it required single crystal X-ray diffraction on penicillazine monohydrate to reveal the complete structure shown in **107**, with *cis*-fusion of the dihydrooxazine and cyclohexene rings. The absolute stereochemistry was not determined.



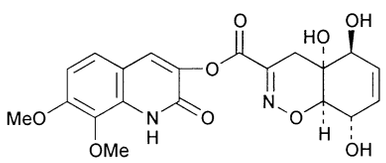
102 R = OH
103 R = H



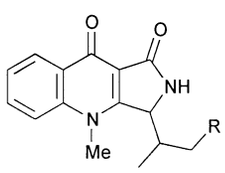
104 Penigequinolone A X = O; Y = CH_2
105 Penigequinolone B X = CH_2; Y = O



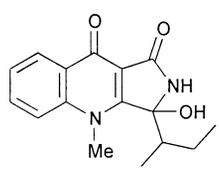
106 Peniprequinolone



107 Penicillazine

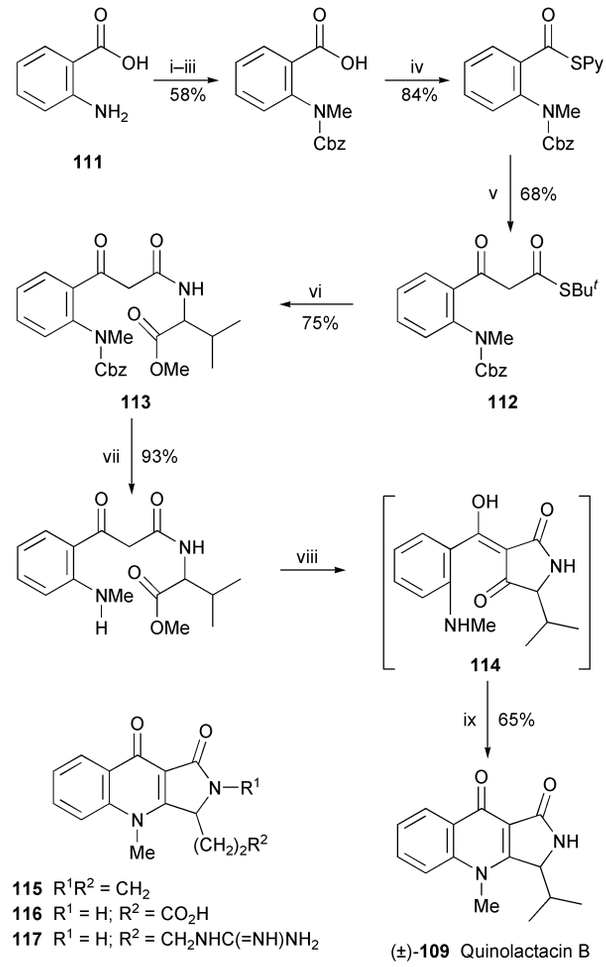


108 Quinolactacin A R = Me
109 Quinolactacin B R = H



110 Quinolactacin C

Cultured broth of the entomopathogenic fungus *Penicillium* sp. EPF-6, isolated from larvae of the mulberry pyralid moth, yielded three new quinolone antibiotics, (+)-quinolactacin A **108**, (−)-quinolactacin B **109** and (+)-quinolactacin C **110**.[14,15] The novel 2,3-dihydro-1*H*-pyrrolo[3,4-*b*]quinoline-1,9(4*H*)-dione structures were established uneventfully with the aid of spectroscopic techniques. Disappointingly, the quinolactacins were inactive towards a wide range of bacteria, fungi and yeasts; very weak activity was apparent only against *Aspergillus niger*. However, quinolactacin A inhibited the production of tumour necrosis factor (TNF) induced by lipopolysaccharide in murine peritoneal macrophages (IC_{50} 12.2 μg cm^{-3}) and in macrophage-like J774.1 cells. This interesting biological effect prompted Tatsuta and co-workers to devise a short biomimetic approach to the synthesis of members of this group of compounds (Scheme 5).[48] Anthranilic acid **111** was converted in five



111
112
113
114
115 $R^1R^2 = CH_2$
116 R^1 = H; $R^2 = CO_2H$
117 R^1 = H; $R^2 = CH_2NHC(=NH)NH_2$
(±)-**109** Quinolactacin B

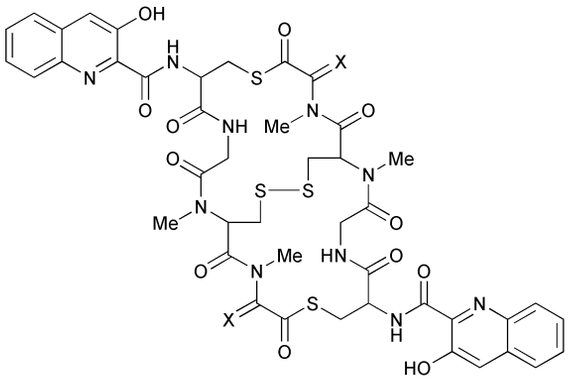
Scheme 5 *Reagents and conditions*: i, $ClCO_2Bn$, Na_2CO_3, THF–H_2O, rt; ii, MeI, NaH, DMF, rt; iii, KOH, MeOH–H_2O, 65 °C; iv, 2,2′-dipyridyl disulfide, Ph_3P, THF, rt; v, MeCOSBu^t, LiHMDS, THF, −78 °C to rt; vi, Et_3N, CuI, THF, rt; vii, H_2 Pd–C, EtOH, rt; viii, NaOMe, MeOH, reflux; ix, SiO_2.

steps into the β-keto thiolester **112**, reaction of which with L-valine methyl ester yielded the β-keto amide **113**. Hydrogenolysis of the benzyloxycarbonyl protecting group was followed by Dieckmann-like condensation to give the intermediate tetramic acid **114**, which on exposure to silica gel afforded racemic quinolactacin B, (±)-**109**. Analogues **115**–**117** were similarly prepared by replacing valine with suitable derivatives of proline, glutamic acid and arginine, respectively. Quinolactacin A could presumably be made in the same way with isoleucine as precursor.

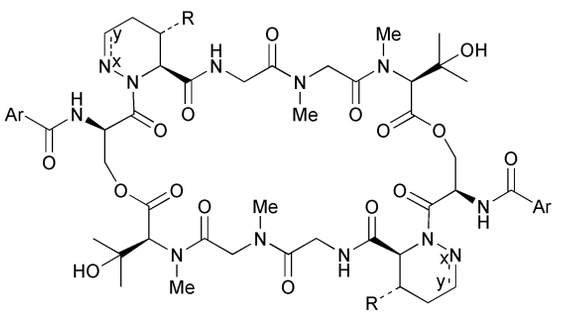
Boger and Ichikawa communicated syntheses of the antitumour antibiotic thiocoraline **118** and the related octadepsipeptide BE-22179 **119** in 2000[49] (*cf*. Ref. 28*h*). Full details of the syntheses have since appeared in a publication that also included an evaluation of their ability to bind to duplex DNA by bisintercalation, and their exceptionally potent cytoxicity towards the L1210 cell line at subnanomolar concentrations.[50] Syntheses of two larger cyclic decadepsipeptides, luzopeptin C **120**[51] and luzopeptin E2 **121**[52] by Ciufolini and coworkers involved macrocyclodimerisation of the key pentapeptides **122** and **123**, respectively. Deprotection of the *N*-Boc group and acylation with 3-hydroxy-6-methoxyquinaldic acid **124** was a late and comparatively trivial step in the synthesis of the target antibiotics.

1.7 Quinoline alkaloids from animals

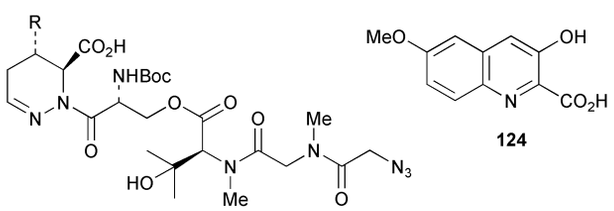
When the Australian sponge *Oceanapia* sp. was screened for activity against mycothiol *S*-conjugate amidase (MCA), a recently discovered mycobacterial enzyme, bioactivity-guided



118 Thiocoraline X = H, CH_2SMe
119 BE-22179 X = CH_2

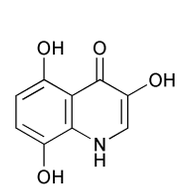


120 Luzopeptin C R = OH; xy = double bond;
Ar = 3-OH-6-OMe-quinolin-2-yl
121 Luzopeptin E2 R = H; xy = single bond;
Ar = 3-OH-6-OMe-quinolin-2-yl

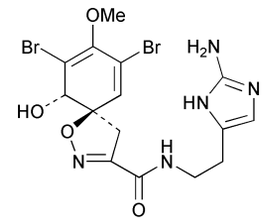


122 R = OTBDMS
123 R = H

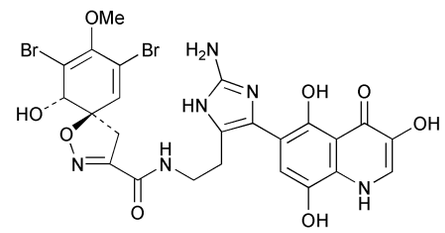
124



125 Uranidine



126 Pseudoceratine



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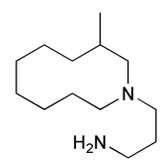

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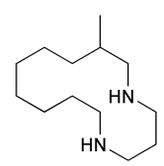

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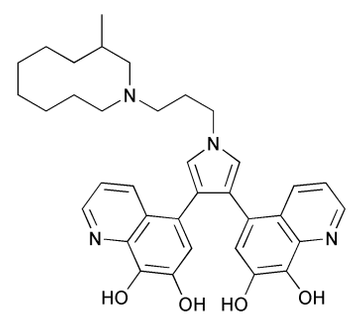
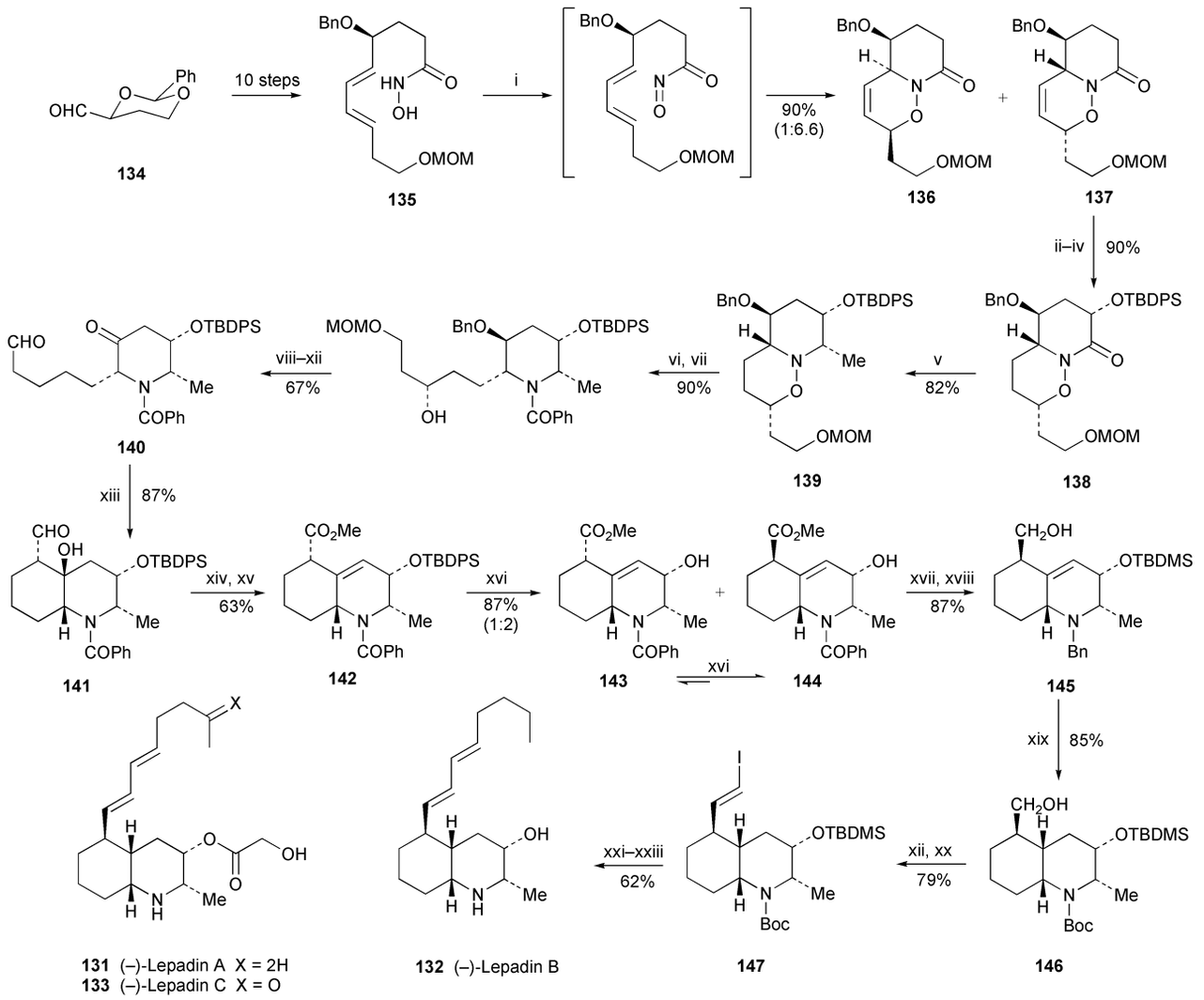


129 Halitulin?

fractionation led to the isolation of the known sponge metabolite uranidine **125**, several bromotyrosine alkaloids, *e.g.* (−)-pseudoceratine **126**, and the interesting uranidine–bromotyrosine hybrid (−)-**127**.[8] The elucidation of the structure was facilitated by obvious spectroscopic similarities between the three alkaloids, as well as various long-range NMR spectroscopic correlations. The (1*S*,6*R*) absolute stereochemistry of (−)-**127** was ascertained by comparing its CD spectra with those of (1*S*,6*R*)-(−)-**126** and its enantiomer.

Recent refutations of structure **128** for the sponge metabolite haliclorensin have cast a cloud over the proposed structure **129** for the more complex alkaloid halitulin, which was found in the same organism (*Haliclona tulearensis*).[53] Heinrich and Steglich synthesised both enantiomers of the putative alkaloid **128**, but found that the optical rotation and ^{13}C chemical shifts differed considerably from those reported for the natural product.[54] Similarly, a synthesis of (±)-**128** by Banwell and co-workers showed that its properties were different from those of the natural product.[55] The revised structure **130** for haliclorensin has been proposed very recently and confirmed by synthesis, and indications from chiroptical properties are that the natural product is a 3 : 1 mixture of the (*S*)- and (*R*)-enantiomers.[56] This unusual diazacyclotetradecane system can obviously not be a component of the halitulin structure, and structure **129** for halitulin may well still turn out to be correct.

Kibayashi and co-workers have synthesised (−)-lepadins A, B and C, **131**–**133**, three complex decahydroquinoline alkaloids isolated from the tunicate (sea squirt) *Clavelina lepadiformis* and a predatory flatworm that feeds on it, by a route that includes their hallmark reaction, a stereocontrolled intramolecular acylnitroso Diels–Alder reaction.[57,58] Several key steps in the lengthy synthesis are shown in Scheme 6. Enantiocontrol originated from benzylidene-protected (2*S*)-2,4-dihydroxybutanal **134**, a readily prepared derivative of (*S*)-malic acid. The key cycloaddition was initiated by oxidation of the hydroxamic acid **135** with tetrapropylammonium periodate in water–DMF (50 : 1), which gave the two oxazino lactams **136** and **137** (90%) in a ratio of 1 : 6.6. The aqueous conditions proved crucial for maximising the formation of the desired diastereomer. After hydrogenation of **137**, the next important step was the stereoselective α-hydroxylation of the lactam, which was optimally achieved by treating the lithium enolate with (+)-[(8,8-dichlorocamphoryl)sulfonyl]oxaziridine. After silylation, compound **138** was obtained in a ratio of 17 : 1 with its β-silyloxy epimer. Treatment of lactam **138** with methylmagnesium bromide followed by sodium cyanoborohydride afforded the methylated product **139** as the sole diastereomer because of the approach of hydride from the less hindered face of the iminium ion intermediate. Construction of the quinoline framework was most satisfactorily achieved by intramolecular aldol reaction of **140** with catalytic amounts of piperidine and acetic acid to give **141** (87%). However, dehydration of the 3-hydroxycarbonyl product was accomplished only after the aldehyde had been converted into the corresponding methyl ester. The product **142** yielded a 1 : 2 mixture of the labile alcohol **143** and the C-5 epimer **144** in 87% yield upon desilylation with tetrabutylammonium fluoride in THF over 5 days. The yield of the desired 5β-isomer **144** could be increased to 75% by equilibrating **143** under the same conditions. The final stereogenic centre was introduced by catalytic hydrogenation of the amino alcohol **145** over palladium on carbon, which gave



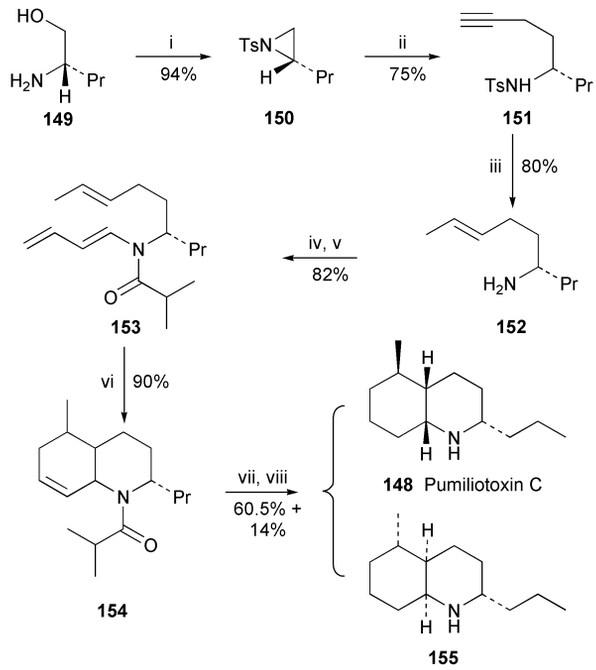
Scheme 6 *Reagents and conditions*: i, Pr_4NIO_4, H_2O–DMF (50 : 1), 0 °C; ii, H_2, Pd–C, THF; iii, LiHMDS, THF, −78 °C, then (+)-[(8,8-dichlorocamphoryl)sulfonyl]oxaziridine; iv, TBDPSCl, imidazole, DMF, rt; v, MeMgBr, THF, 0 °C, then $NaBH_3CN$, AcOH, THF, 0 °C; vi, Zn, 90% AcOH, 60 °C; vii, PhCOCl, then 5% aq. KOH; viii, CS_2, NaH, imidazole, then MeI, THF; ix, Bu_3SnH, AIBN, C_6H_6, reflux; x, PPTS, Bu^{t}OH, reflux; xi, H_2, $Pd(OH)_2$, MeOH; xii, $(COCl)_2$, DMSO, Et_3N, −78 °C to 0 °C; xiii, piperidine (0.2 equiv.), AcOH (0.2 equiv.), C_6H_6, reflux; xiv, PDC, DMF, then CH_2N_2, Et_2O; xv, $SOCl_2$, Et_3N; xvi, Bu_4NF, THF, rt, 5 d; xvii, TBDMSCl, imidazole, DMF; xviii, $LiAlH_4$, THF, reflux; xix, H_2 (5 atm), 10% Pd–C, THF, then $(Boc)_2O$, CH_2Cl_2, 0 °C to rt; xx, CHI_3, $CrCl_2$, THF, rt; xxi, (*E*)-$C_4H_9CH{=}CHB(OH)_2$, $Pd(Ph_3P)_4$ (5 mol%), aq. KOH (2 M), THF, 50 °C; xxii, Bu_4NF, THF; xxiii, TFA, CH_2Cl_2, then K_2CO_3.

exclusively the *cis*-fused decahydroquinoline **146** (85%) after *N*-Boc protection. Oxidation to the aldehyde and Takai methylenation with iodoform and chromium(II) chloride yielded the (*E*)-vinyl iodide **147**, which proved to be the pivotal intermediate in the synthesis of all three lepadins. Completion of the synthesis of (−)-lepadins A **131** and B **132**, for example, entailed Suzuki coupling of **147** with (*E*)-hex-1-enylboronic acid followed by appropriate manipulations at the alcohol and amine groups. For (−)-lepadin C **133**, the Suzuki cross-coupling was performed with (*E*)-5-hydroxyhex-1-enylboronic acid, and oxidation of the side chain preceded the functional group manipulations in the bicyclic nucleus. While (−)-lepadin B has previously been synthesised, this is the first reported synthesis of (−)-lepadins A and C. The spectra of the trifluoroacetate salts of the synthetic compounds proved identical to those obtained on the natural products, but the optical rotations were larger.

Oppolzer and Flaskamp reported a short synthesis of the frog skin alkaloid (−)-*cis*-decahydroquinoline 195A **148**, commonly referred to as pumiliotoxin C, in 1977.[59] Methodological refinements[60] (Scheme 7) have now resulted in an improved overall yield of **148** to 25% – approximately 20 times that of the original procedure – based on the chiral amino alcohol **149**. The improvements entailed ring opening of the aziridine **150** with propargylmagnesium bromide† followed by a one-pot conversion of product **151** into the (*E*)-amine **152**, and an optimised imine formation and *N*-acylation to give dienamide **153**. The subsequent intramolecular Diels–Alder cycloaddition afforded the octahydroquinoline **154** as a mixture of diastereomers. After catalytic hydrogenation and removal of the *N*-acyl group, the decahydroquinoline **148**, diastereomer **155** and an unidentified isomer were obtained in a ratio of 62 : 37 : 1. The target alkaloid **148** could be crystallised from the mixture as the hydrochloride salt (57%). Chromatography of the mother liquors yielded a further quantity of **148** (3.5%) and the more polar diastereomer **155**, also isolated as the hydrochloride salt (14%).

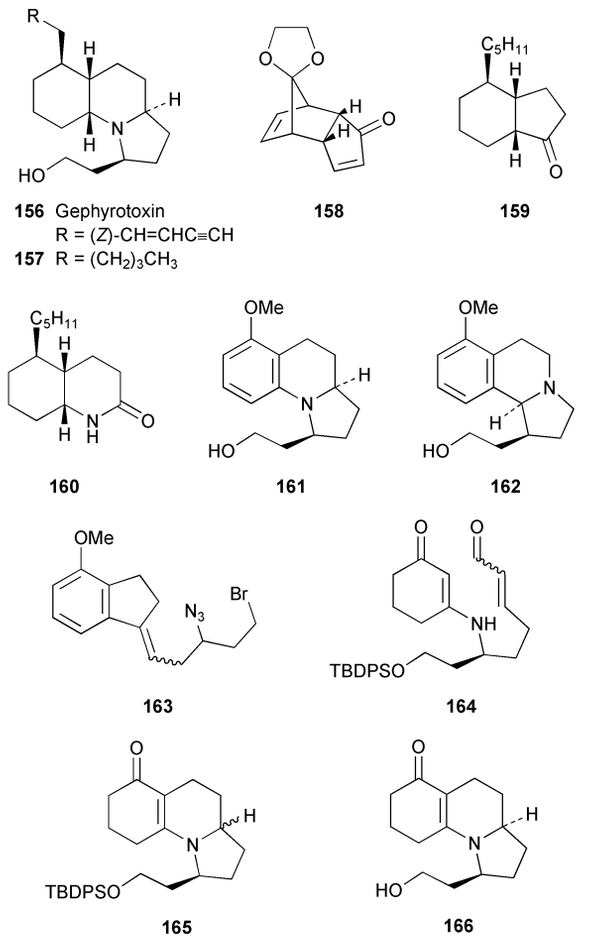
The tricyclic frog skin alkaloid gephyrotoxin **156** and its perhydro analogue **157** have been popular synthetic targets for over 20 years. Three formal syntheses of these compounds have appeared recently. The approach to **157** by Mehta and Reddy,[61] employing ideas they had developed in a prior route to pumiliotoxin C, involved the conversion of the protected cyclopentadienone dimer **158** via the *cis*-hydrindanone **159** into the decahydroquinolinone **160**, which had previously featured

† The IUPAC name for propargyl is prop-2-ynyl.



Scheme 7 *Reagents and conditions*: i, NaH, *p*-TsCl, THF, 0 °C to rt; ii, $HC{\equiv}CCH_2MgBr$, Et_2O, 0 °C to rt; iii, BuLi, NH_3, −78 °C to −30 °C, then MeI, −30 °C, then Na; iv, MeCH=CHCHO, 4 Å molecular sieves, Et_2O, 0 °C to rt; v, $Me_2CHCOCl$, Et_3N, CH_2Cl_2, −78 °C to 5 °C; vi, toluene, sealed tube, 230–240 °C; vii, H_2, 10% Pd–C, MeOH, rt; viii, BuLi, THF, −78 °C to rt, then recrystallisation as HCl salt.

in a synthesis of perhydrogephyrotoxin **157** by Ibuka and Chu.[62] Pearson's continuing explorations of the intramolecular Schmidt reaction of azides with carbocations has recently been extended to include the preparation of an impressive range of benzo-fused 1-azabicycloalkanes.[63] Extensive model studies aimed at the synthesis of gephyrotoxin itself culminated in the synthesis of **161** (45%) and the regioisomer **162** (10%) by treatment of azido alkene **163** with trifluoromethanesulfonic acid followed by reduction of iminium ion intermediates with L-Selectride™ and replacement of bromide by hydroxy. Compound **161** had previously featured as an intermediate in a prior route to gephyrotoxin **156** by Ito *et al.*,[64] which itself converged with a pioneering synthesis of the racemic alkaloid by the Kishi group.[65] The route to (+)-**156** by Hsung and co-workers[66] exploited a formal [3 + 3] cycloaddition similar to that already depicted in Scheme 2 (Section 1.3, *vide supra*). In this case, intramolecular cycloaddition resulting from treatment of precursor **164** with piperidinium acetate yielded a mixture of isomers of the tricyclic vinylogous amide **165**. If the alcohol was not protected, only the unwanted β-H isomer was obtained. Removal of the silyl protecting group from **165** and chromatographic separation afforded the α-H tricyclic compound **166**, a central intermediate in the 1981 synthesis of (+)-**156** by Fujimoto and Kishi.[67]



2 Quinazoline alkaloids

2.1 Occurrence, characterisation and biological activity

A list of new quinazoline alkaloids, and known quinazolines isolated from new sources, is presented in Table 2.[68–76] The simple alkaloid samoquasine A **167**, isolated from seeds of the custard apple *Annona squamosa* (Annonaceae), is especially interesting in being the first naturally occurring compound to possess the benzo[*h*]quinazoline ring system.[68] The structure was established by spectroscopic methods and corroborated by preparation of the *O*-methyl derivative by treatment with trimethylsilyldiazomethane. The authors were apparently unaware that this compound was first prepared almost 40 years ago by reaction between 1-naphthylamine and ethoxymethyleneurethane, although no spectroscopic details are given in this earlier work.[77,78] Samoquasine A showed significant cytotoxicity against murine lymphoma L1210 cells (IC_{50} 0.38 μg cm^{-3}).

A resurgence of interest in the potent antimalarial alkaloids (+)-isofebrifugine **168** and (+)-febrifugine **169** (see Section 2.2) has resulted in reinvestigations of their main plant sources, the genera *Dichroa* and *Hydrangea* (Saxifragaceae). Chinese workers re-isolated these two alkaloids (to which they appended the old-fashioned names α-dichroine and β-dichroine, respectively) as principal components from extracts of the leaves of *Dichroa febrifuga*, and in addition obtained much smaller amounts of quinazolin-4-one **170** (3*H* tautomer shown), 2-(4-hydroxybutyl)quinazolin-4-one **171** and the interesting new quinazolinone–quinolizidine dimer (+)-neodichroine **172**, which was isolated as a crystalline solid.[71] While the authors made no specific comments about compound **171**, it also appears to be a new natural product, although it has previously been synthesised.[79] Evidence for the structure of neodichroine **172** came from ^1H and ^{13}C NMR spectra, recorded in deuterated pyridine, together with COSY and NOE data. The *trans*-diaxial disposition of 9′-H and 9a′-H in the quinolizidine ring was apparent from the large coupling constant (*J* 10.1 Hz), and another large coupling constant for 3′-H (*J* 11.3 Hz) indicated that the quinazolinyl substituent was equatorial. Neodichroine also formed an acetate that gave a well-resolved ^1H spectrum. However, definitive evidence for the structure came from a semi-synthesis by Mannich reaction between febrifugine and formaldehyde at pH 4. Although this direct correlation with putative (2′*S*,3′*R*)-(+)-febrifugine led the authors to propose the (9′*R*,9a′*S*) absolute configuration for **172**, it seems that they were unaware that the absolute configuration of (+)-febrifugine was recently revised to (2′*R*,3′*S*) as a result of Kobayashi's unambiguous total synthesis[80] (*cf.* Ref. 28*f*,*g*). (+)-Neodichroine is thus more likely to be the (3′*R*,9′*S*,9a′*R*) enantiomer, as shown in **172**.

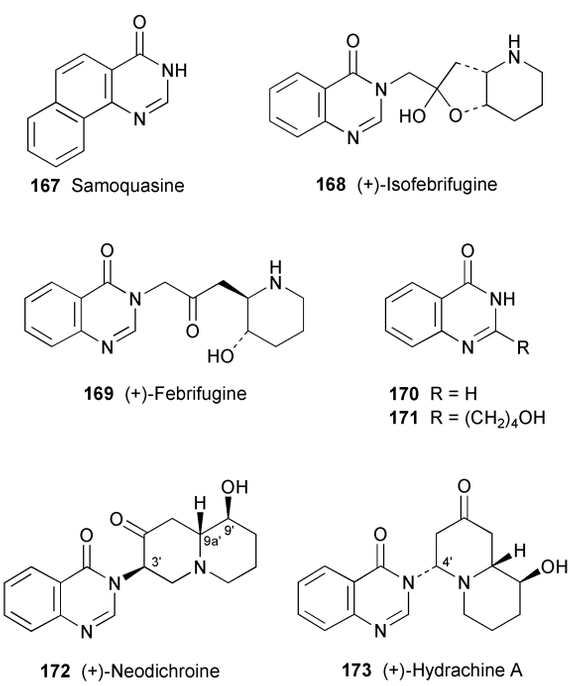
Table 2 Isolation and detection of quinazoline alkaloids

Species	Alkaloid[a]	Ref.
Annona squamosa	Samoquasine A[b] **167**	68
Aspergillus ochraceus	(−)-Circumdatin G[b] **179**	69
Calanthe liukiuensis	Tryptanthrin **183**	70
Dichroa febrifuga	2-(4-Hydroxybutyl)quinazolin-4-one[b] **171** (+)-Neodichroine[b] **172**	71
Hydrangea chinensis	(+)-Hydrachine A[b] **173** Quinazolin-4-one **170**	72
Isatis indigotica	Tryptanthrin	73
Nitraria komarovii	Peganol *N*-oxide[b] **174**	74
Nitraria schoberi	Deoxypeganine (deoxyvasicine) **176** Deoxyvasicinone **186** (±)-Vasicinone **187**	75
Peganum harmala	Dipegine **177** Dipeginol[b] **178**	76

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

Another more recently reported quinazolinone–quinolizidine dimer, (+)-hydrachine A **173**, was isolated as a semi-solid by Taiwanese workers from the roots of *Hydrangea chinensis*, where it occurred together with quinazolin-4(3*H*)-one **170**.[72] ^{1}H and ^{13}C NMR spectra, recorded in deuterated chloroform, were supplemented by COSY and HMBC correlations to establish the atomic connectivity. Central to the structural assignment were HMBC correlations between 4′-H and both carbonyl groups, C-2 on the quinazolinone, and signals ascribed to C-3′ (mistakenly listed as C-5′), C-6′ and C-9a′; these were taken as evidence for siting the quinazolinyl substituent at C-4′ on the quinolizidine ring. The stereochemistry was determined from NOESY correlations and analysis of coupling constants; in particular, 4′-H, 9′-H and 9a′-H all showed large couplings consistent with axial orientations. Bohlmann bands in the IR spectrum indicated *trans*-fusion of the quinolizidine ring. While the evidence presented for the structure of **173** seems irreproachable, one cannot but be intrigued by the tantalising similarity between the structures proposed for neodichroine and hydrachine A and their relationship to febrifugine. The ^{1}H NMR spectroscopic data for the two compounds are not directly comparable, since they were recorded in different solvents, and other reported spectroscopic and physical properties (IR, UV, MS, optical rotation) show similarities and differences that may or may not be significant. However, the ^{13}C NMR spectroscopic data are in remarkable agreement (±1.3 ppm in the quinolizidine ring) despite the difference in solvents; the only discrepancy in interpretation is that the authors interchange the assignments of the doublet signals for the bridgehead position C-9a′ and the carbon bearing the quinazoline substituent. Is it conceivable that the two alkaloids, both originating in genera known for their production of febrifugine, are in fact the same? If so, the conversion of febrifugine into neodichroine must be regarded as deciding the issue.

The identity of the new alkaloid peganol *N*-oxide **174**, isolated from aerial parts of *Nitraria komarovii*, was established spectroscopically, and by reduction with zinc in hydrochloric acid to give a mixture of peganol **175** and deoxypeganine (deoxyvasicine) **176**.[74] More interesting are the two dimeric peganine derivatives dipegine **177** and dipeginol **178**, which were obtained from *Peganum harmala*.[76] Although dipegine was originally reported as long ago as 1974, comprehensive NMR data in the present publication permitted unambiguous location of the bridge between C-4 and C-9′, rather than C-11′ as had previously been proposed. However, the relative configurations at these stereogenic sites could not be ascertained directly. Molecular mechanics calculations on the most stable conformers of both possible diastereomers led the authors to predict average vicinal coupling constants between 4-H and 9′-H. While the predicted ^3J value of 2.7 Hz for the diastereomer shown in **177** was reasonably close to the experimentally determined coupling constant (J 2.1 Hz), this stereochemical assignment for dipegine should still be regarded as tentative. The gross structure of the novel alkaloid dipeginol **178** was also revealed by analysis of its NMR spectra and those of its mono-acetate derivative, but no attempts were made to assign the relative configuration. Since both dimeric alkaloids are high-melting solids, the structural ambiguities could probably be resolved by X-ray crystallography.

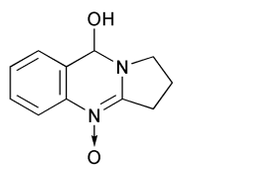


The only new quinazoline alkaloid reported from a fungal source during the review period was (−)-circumdatin G **179**, extracted together with (−)-circumdatin F **180** from the culture broth of *Aspergillus ochraceus*.[69] Circumdatin F had previously been isolated in such small quantities that its optical rotation and absolute configuration could not be determined.[81] The present work permitted the measurement of optical rotations for both **180** ($[\alpha]_D$ −18.9, *c* 0.11, MeOH) and **179** ($[\alpha]_D$ −21.7, *c* 0.19, MeOH), as well as the acquisition of comprehensive spectroscopic data. Their (*S*)-absolute configurations were assigned by analogy with (*S*)-(−)-circumdatin C **181**, the stereochemistry of which had previously been determined by degradation to L-alanine.[82]

A critical review of the ethnopharmacology and toxicology of the Indian medicinal plant *Adhatoda vasica* (Acanthaceae), the principal alkaloid of which is vasicine **182**, has called into question several reports on potentially adverse effects both of the plant extract and of vasicine itself.[83] While traditional

applications in the treatment of various disorders, especially ailments of the respiratory tract, appear to be well documented, claims of oxytocic and abortifacient effects and of acute and general toxicity seem to be based on inappropriate testing methods and unreliable data. In the meantime, medicinal uses of the vasicine alkaloids continue to be documented, and patent applications have been filed for the use of deoxypeganine **176** in the treatment of nicotine dependence,[84] drug dependence,[85] alcoholism[86] and Alzheimer's dementia,[87] and in the treatment of poisoning by an organophosphorus cholinesterase inhibitor.[88]

Tryptanthrin **183** has been found to inhibit the production of both nitric oxide and prostaglandin E_2 in murine macrophage RAW 264.7 cells activated by interferon-γ and lipopolysaccharide.[89] In the former case, the mechanism appears to involve suppression of inducible NO synthase expression, and in the latter case the alkaloid inhibits cyclooxygenase activity. The results suggest that tryptanthrin may be a useful anti-inflammatory agent. The alkaloid has also shown good antibacterial activity against *Helicobacter pylori* both *in vitro* and during *in vivo* studies with Mongolian gerbils infected with the ulcer-causing pathogen.[90]



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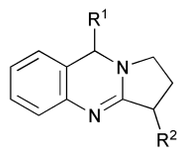
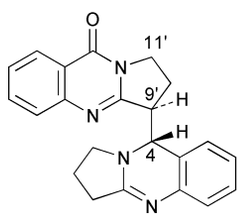
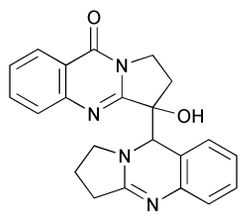


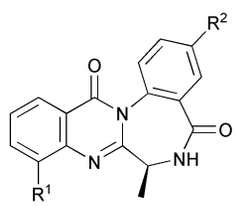
175 Peganol R^1 = OH; R^2 = H
176 Deoxypeganine R^1 = R^2 = H
182 Vasicine R^1 = H; R^2 = OH

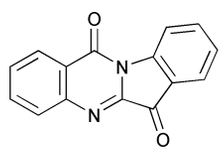


177 Dipegine



178 Dipeginol





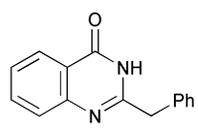
179 (–)-Circumdatin G R^1 = OH; R^2 = H
180 (–)-Circumdatin F R^1 = R^2 = H
181 (–)-Circumdatin C R^1 = H; R^2 = OH

183 Tryptanthrin

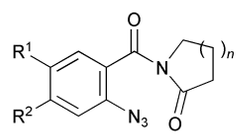
2.2 Synthesis and other chemical studies

Samarium(II) iodide in THF has been shown to mediate the reaction between *N,N*-diethyl-*o*-nitrobenzamide and various benzonitriles or phenylacetonitrile to yield 2-substituted quinazolin-4(3*H*)-ones in yields of 55–75%.[91] Among the products formed was the alkaloid glycosminine (glycophymine) **184**. The reaction failed with acetonitrile.

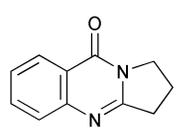
Kamal *et al.* found that the intramolecular aza-Wittig reaction of *N*-(2-azidobenzoyl)lactams **185** gave deoxyvasicinone **186** and analogues in quantitative yield within 10–15 minutes when the precursors were treated with chlorotrimethylsilane and sodium iodide in acetonitrile at room temperature.[92] This mild transformation provides a useful alternative to the standard cyclisation conditions, which entail treatment of the azide precursors with triphenylphosphine or tributylphosphine in boiling toluene for several hours. Even more interestingly, the reductive cyclisation of **185** proceeded in yields of 25–50% when catalysed by bakers' yeast in a water–ethanol mixture at 37.5 °C. With convenient access to deoxyvasicinone, the authors embarked on a lipase-mediated resolution of vasicinone **187** itself. The 3-bromo derivative **188** was prepared by free radical bromination of **186** with NBS (57%), and this product was converted into (±)-acetylvasicinone **189** by treatment with potassium acetate and 18-crown-6 in acetonitrile (100%). Enzymatic hydrolysis of the ester with lipase PS 'Amano' in a mixture of acetonitrile and phosphate buffer (pH 7) was highly enantioselective, yielding (*R*)-(+)-vasicinone and the (*S*)-(−)-acetate in 98% enantiomeric excess (ee). Alternatively, chemical hydrolysis of **189** yielded racemic vasicinone, which could then be resolved by enzymatic transesterification with vinyl acetate in THF in the presence of lipase PS in THF to yield (*S*)-(−)-vasicinone, as well as the (*R*)-(+)-acetate in better than 99% ee.



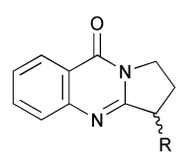
184 Glycosminine



185 R^1, R^2 = H, Me Cl; *n* = 1–3

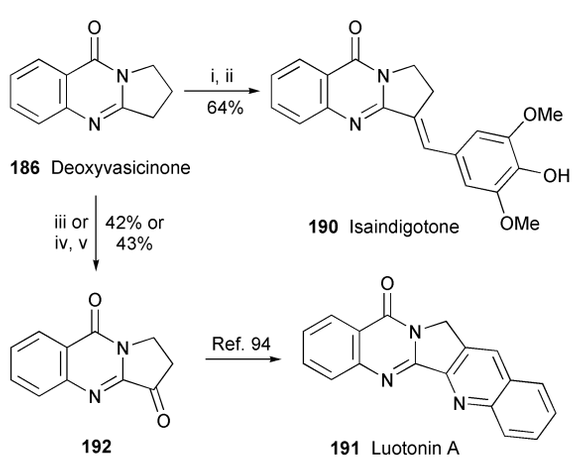


186 Deoxyvasicinone



187 Vasicinone R = OH
188 R = Br
189 R = OAc

Deoxyvasicinone **186** was the common precursor in the short divergent syntheses of isaindigotone **190** and luotonin A **191** by Molina *et al.* (Scheme 8).[93] Straightforward condensation of **186**

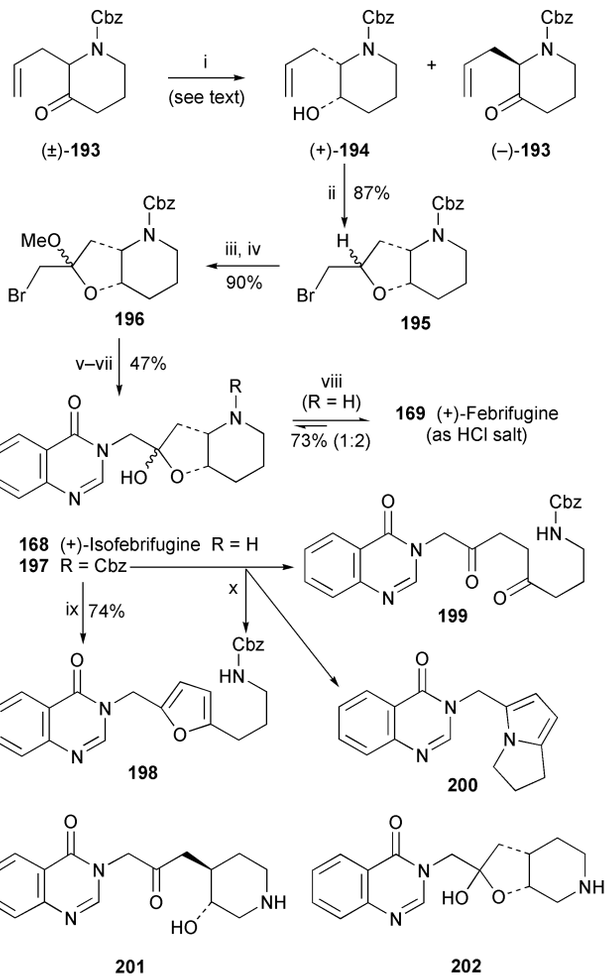


186 Deoxyvasicinone
190 Isaindigotone
192
191 Luotonin A

Scheme 8 *Reagents and conditions*: i, 4-Acetoxy-3,5-dimethoxybenzaldehyde, Ac_2O, reflux; ii, NaOH, EtOH, reflux; iii, SeO_2, H_2O, dioxane, reflux; iv, PhCHO, Ac_2O, reflux; v, O_3, CH_2Cl_2, 3 min, then Me_2S.

with 4-acetoxy-3,5-dimethoxybenzaldehyde in acetic anhydride followed by hydrolysis of the ester completed the first reported synthesis of **190** in 64% overall yield. The formal synthesis of **191** simply entailed the oxidation of **186** with selenium dioxide to give the dione **192** (42%). Alternatively, a two-step reaction sequence commencing with condensation of **186** with benzaldehyde followed by ozonolysis afforded **192** in similar yield (43%). The synthesis is formal because Kelly and co-workers recently converted **192** into luotonin A **191** by base-catalysed reaction with 2-aminobenzaldehyde[94] (*cf.* Ref. 28*h*).

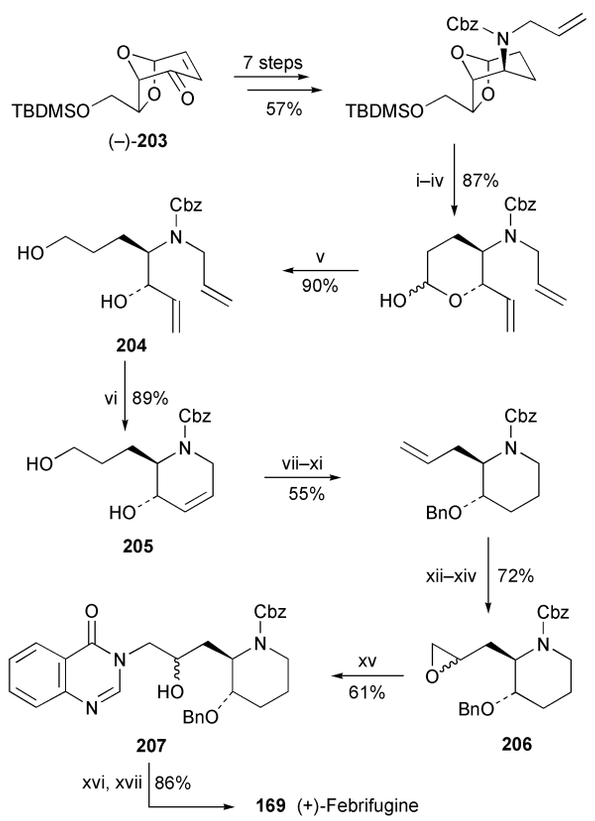
The recent upsurge of activity in the synthesis of febrifugine **169** and related antimalarial compounds shows no signs of abating, as evidenced by a review in the Japanese literature by Takeuchi and Harayama.[95] Following hard on the heels of their stereoselective synthesis of racemic febrifugine[96] (*cf.* Ref. 28*g*), Takeuchi and co-workers have devised the enantioselective modification shown in Scheme 9.[97,98] The central feature was the



Scheme 9 *Reagents and conditions*: i, Bakers' yeast, sucrose, EtOH–H_2O (1 : 10), K_2CO_3, 15 °C, 90 h; ii, NBS, MeCN, rt; iii, KOBu^t, THF, rt; iv, NBS, MeOH, rt; v, 10% aq. HCl, MeCN, rt; vi, quinazolin-4(3*H*)-one, K_2CO_3, DMF, rt; vii, H_2, 20% $Pd(OH)_2$–C, MeOH, rt; viii, H_2O, 80 °C, then 10% aq. HCl; ix, $BF_3{\cdot}Et_2O$, MeCN, reflux, 0.5 h; x, aq. HCl (5 M), MeCN, reflux, 0.5–2 h.

use of bakers' yeast and sucrose in an ethanol–water solvent for the enantioselective reduction of the 2-allylpiperidin-3-one (±)-**193** to give a separable mixture of unreduced (*R*)-(−)-**193** (31%, 93% ee) and the (+)-alcohol **194** (41%, 97% ee). However, since racemisation of (−)-**193** was readily accomplished with potassium carbonate, a reductive dynamic optical resolution could be achieved by adding this base to the fermentation mixture. In this way the yield of (+)-**194** was boosted to 62% (97% ee), while (−)-**193** was recovered with diminished optical activity (14% yield, 14% ee). Intramolecular bromoetherification of (+)-**194** with NBS in acetonitrile afforded **195** as a 3 : 1 mixture of diastereomers. Elimination of hydrogen bromide from this product followed by methoxybromination with NBS in methanol yielded the ketal **196**, this time as a 4 : 1 mixture of diastereomers. Hydrolysis of the ketal, reaction with the anion of quinazoline-4(3*H*)-one and removal of the benzyloxycarbonyl protecting group from nitrogen completed this "green" synthesis of (+)-isofebrifugine **168**. Furthermore, since isomerisation of isofebrifugine to febrifugine has been well documented, the authors were able to form a 1 : 2 equilibrium mixture of **168** and (+)-febrifugine **169** simply by heating the former in water at 80 °C for 15 minutes. Isomerisation did not occur under acidic conditions. Oddly enough, when the deprotection of racemic Cbz-isofebrifugine **197** with aqueous hydrochloric acid was investigated, mixtures of the piperidine-cleavage products **198**, **199** and **200** were obtained.[99] The reaction of **197** with boron trifluoride–diethyl ether yielded **198** as the sole product (74%). Further antimalarial tests on the products confirmed that (+)-febrifugine was almost 100 times as active towards *Plasmodium falciparum* as chloroquine, and also showed that it was twice as potent as its hydrochloride salt and about ten times as potent as (+)-isofebrifugine.[98] In an interesting corollary to this work, Takeuchi's team synthesised the racemic regioisomers **201** and **202** from the 4-allylpiperidin-3-one analogue of **193**, and proved that they have negligible antimalarial activity.[100]

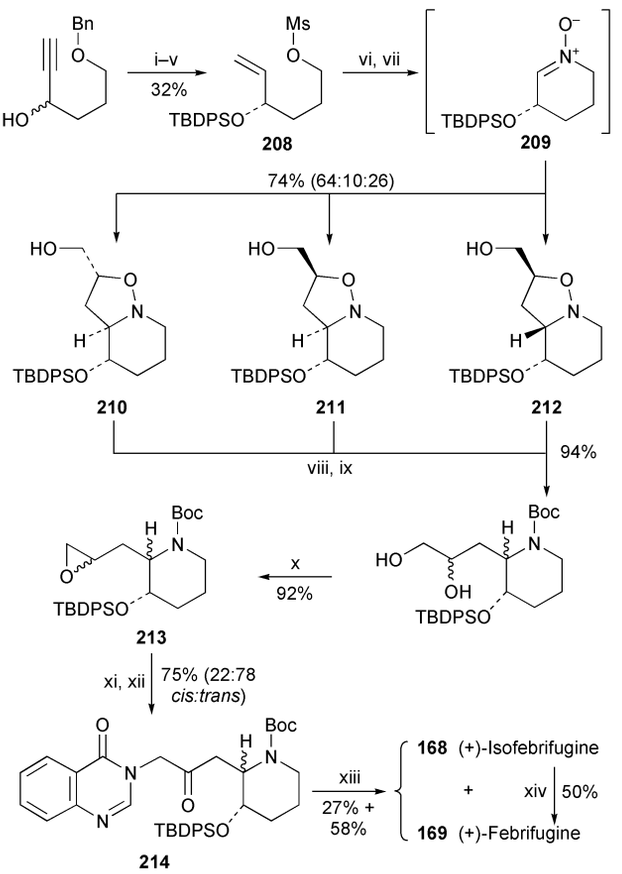
A stereocontrolled synthesis of (+)-febrifugine by Taniguchi and Ogasawara[101] (Scheme 10) commenced with the chiral



Scheme 10 *Reagents and conditions*: i, Bu_4NF, THF; ii, $MeSO_2Cl$, Et_3N; iii, LiI, THF; iv, Zn, EtOH–HOAc (10 : 1); v, $NaBH_4$, EtOH; vi, $(Cy_3P)_2Cl_2Ru$=CHPh (5 mol%); vii, H_2, PtO_2; viii, $(PhS)_2$, Bu_3P, pyridine; ix, BnBr, NaH; x, 30% H_2O_2; xi, $CaCO_3$, Ph_2O, reflux; xii, OsO_4 (cat.), NMO, aq. THF; xiii, *p*-TsCl, pyridine; xiv, K_2CO_3, MeOH; xv, quinazolin-4(3*H*)-one, KOH, MeOH; xvi, Dess–Martin periodinane; xvii, HCl (6 M), reflux.

building block (−)-**203**, which was prepared from furfural by reported methods. A key step in this route was the ring-closing metathesis of **204** with Grubbs catalyst to give the dehydropiperidine **205** in 89% yield. The quinazoline substituent was introduced at a late stage by treating the epoxide **206** with the anion of quinazolin-4(3*H*)-one to give the alcohol **207** as a mixture of diastereomers. Oxidation with Dess–Martin periodinane and removal of the protecting groups under acidic conditions completed the synthesis of (+)-febrifugine **169** in 24 steps and 11% overall yield from (−)-**203**.

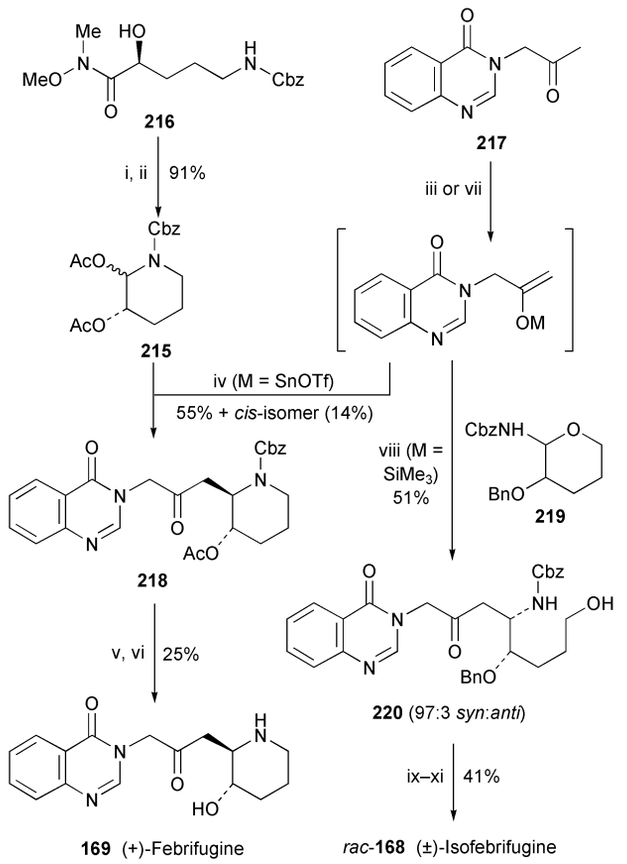
In the synthesis of the febrifugine alkaloids by Hatakeyama and co-workers,[102] the key sequence of steps involved ozonolysis of the chiral alkene **208** followed by condensation of the resulting aldehyde with hydroxylamine hydrochloride in allyl



Scheme 11 *Reagents and conditions*: i, $H_2C{=}CHOAc$, Novozym 435, Pr^i_2O; ii, H_2, Lindlar catalyst, MeOH, then K_2CO_3; iii, TBDPSCl. imidazole, DMF; iv, Li naphthalenide, THF, −25 °C; v, $MeSO_2Cl$, Et_3N, CH_2Cl_2; vi, O_3, then Me_2S, $NaHCO_3$, CH_2Cl_2. −78 °C; vii, $HONH_2{\cdot}HCl$, Et_3N, $H_2C{=}CHCH_2OH$; viii, H_2, $PdCl_2$, MeOH; ix, $(Boc)_2O$, Et_3N, CH_2Cl_2; x, *N*-Ts-imidazole, NaH, THF; xi, quinazolin-4(3*H*)-one, KH, DMF; xii, Dess–Martin periodinane, CH_2Cl_2; xiii, HCl (6 M), reflux; xiv, MeOH, reflux.

alcohol as solvent (Scheme 11). The unsaturated alcohol trapped the intermediate nitrone **209** to give the three cycloadducts **210**–**212** in a ratio of 64 : 10 : 26 and an overall combined yield of 74%. Although these adducts could be separated, it was more convenient to take the mixture through the subsequent hydrogenolysis, protection and epoxidation to give the epoxide diastereomers **213**, treatment of which with the anion of quinazolin-4(3*H*)-one followed by Dess–Martin oxidation gave the *cis*-and *trans*-2,3-disubstituted piperidines **214** in a ratio of 22 : 78, respectively. Acid-induced deprotection with boiling 6 M hydrochloric acid yielded a mixture of (+)-isofebrifugine **168** (27%) and (+)-febrifugine **169** (58%), the 33 : 67 ratio of which indicated that partial epimerisation had taken place. In a result that casts light on this epimerisation process (presumably a reversible Michael reaction) and reinforces Takeuchi's observations[97] (*vide supra*), a purified sample of *cis*-**214** afforded only (+)-isofebrifugine when heated with hydrochloric acid, whereas *trans*-**214** yielded an 84 : 16 mixture of (+)-febrifugine and (+)-isofebrifugine. However, isofebrifugine could be isomerised to febrifugine under neutral conditions in boiling methanol.

The important enantioselective synthesis of febrifugine and isofebrifugine by Kobayashi and co-workers[80] (*cf.* Ref. 28*f*,*g*) has already been mentioned. Patent applications based on the original route[80a] have recently been filed.[103] However, these workers subsequently devised alternative syntheses of both alkaloids based on the Lewis acid-catalysed reaction of silyl enol ethers and related nucleophiles with acyliminium ions prepared *in situ* from *N*,*O*-acetals. After an extensive series of model studies with *N*-Cbz-protected 2-methoxypiperidines and 2-acyloxypiperidines, scandium(III) triflate‡ was found to give the best yields of 2-acylmethylpiperidine products, and also resulted in high 2,3-*trans*/*cis* selectivity with 2,3-diacyloxypiperidine substrates.[104,105] The synthesis of febrifugine itself (Scheme 12) employed the (3*S*)-substrate **215**, which was

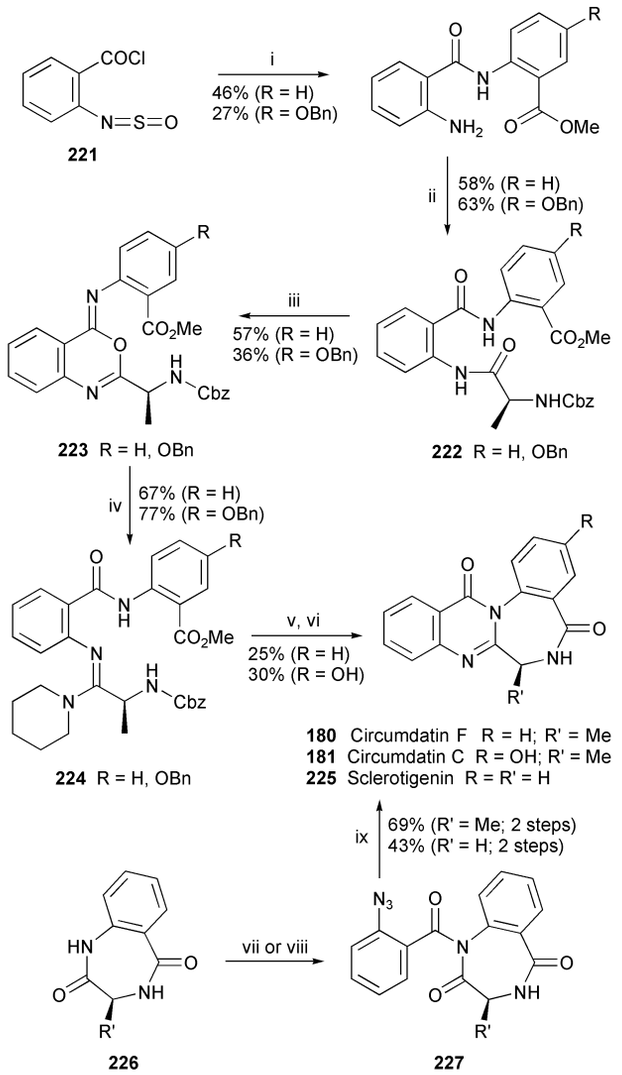


Scheme 12 *Reagents and conditions*: i, $LiAlH_4$, Et_2O, 0 °C; ii, Ac_2O, Et_3N, DMAP (cat.), rt; iii, $Sn(OTf)_2$ (2 equiv.), Pr^i_2NEt (2 equiv.), CH_2Cl_2, 0 °C to reflux; iv, add **217** (0.5 equiv.), $Sc(OTf)_3$ (0.1 equiv.), CH_2Cl_2, reflux; v, 25% HBr in HOAc, 0 °C, then piperidine; vi, NaOMe, MeOH, rt; vii, Me_3SiOTf (2 equiv.), Pr^i_2NEt (2 equiv.), CH_2Cl_2, 0 °C to rt; viii, Me_3SiOTf (2.5 equiv.), MeCN, rt; ix, SO_3·pyridine, DMSO, Et_3N; x, Et_3SiH, $BF_3{\cdot}OEt_2$; xi, aq. HCl (6 M), reflux.

prepared *via* the Weinreb amide **216** either from L-ornithine or by a route involving an asymmetric aldol reaction.[105] In this case the tin(II) enolate of the quinazolinone-substituted ketone **217** was required in order to maximise the formation of the 2,3-*trans*-disubstituted product **218** (55%) in relation to its *cis*-isomer (14%). A disappointing two-step deprotection of **218** (25% yield) completed the synthesis of (+)-febrifugine **169**. For isofebrifugine, reaction between the trimethylsilyl enol ether of **217** and the racemic semicyclic *N*,*O*-acetal **219** (a 74 : 26 mixture of isomers) was catalysed by trimethylsilyl triflate, and yielded the ring-opened product **220**, almost exclusively as the *syn* diastereomer (93 : 7), in 51% yield.[106] The piperidine ring was formed by oxidation of the terminal alcohol to the aldehyde and reduction of the ensuing cyclic acyliminium ion, after which removal of the protecting groups completed the synthesis of racemic isofebrifugine (±)-**168**.

N-Sulfinylanthraniloyl chloride **221** was the preferred starting material for Witt and Bergman's assembly of the tripeptides **222** (R = H, OBn), key intermediates *en route* to the fungal metabolites (−)-circumdatin F **180** and (−)-circumdatin C **181** (Scheme 13).[107] Cyclisation of **222** with triphenylphosphine and iodine in the presence of Hunig's base gave the 4-imino-4*H*-3,1-benzoxazines **223** (R = H, OBn), aminolysis of which with

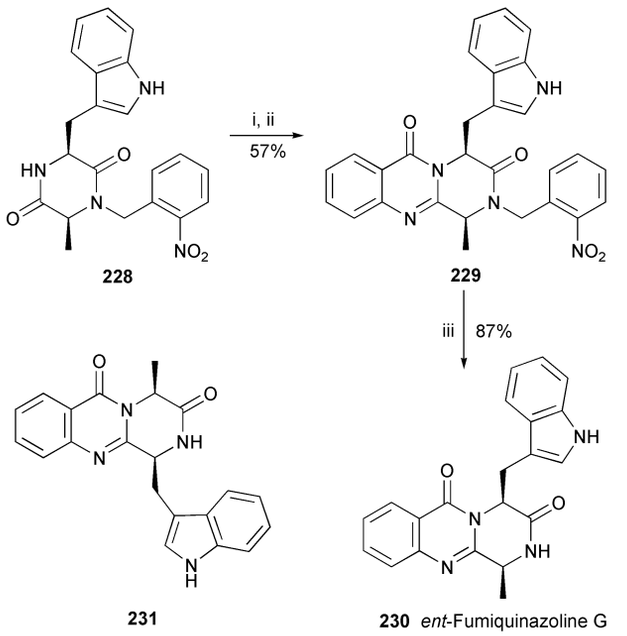
‡ The IUPAC name for triflate is trifluoromethanesulfonate.



Scheme 13 *Reagents and conditions*: i, Methyl anthranilate (R = H) or methyl 5-benzyloxyanthranilate (R = OBn), toluene, rt; 48 h; ii, *N*-Cbz-L-Ala, DCC, CH_2Cl_2, 0 °C to rt; iii, Ph_3P, I_2, Pr^i_2NEt, CH_2Cl_2, rt; iv, 20% piperidine in EtOAc, rt; v, 45% HBr in HOAc, 60 °C; vi, Et_3N (for R = H) or Pr^i_2NEt (for R = OH), EtOAc, rt; vii, Et_3N, DMAP, THF, then 2-$N_3C_6H_4COCl$, THF, 20 °C (for R′ = Me); viii, Et_3N, DMAP, DMSO–CH_2Cl_2, then 2-$N_3C_6H_4COCl$, CH_2Cl_2, 20 °C (for R′ = H); ix, Bu_3P, C_6H_6, rt to 60 °C.

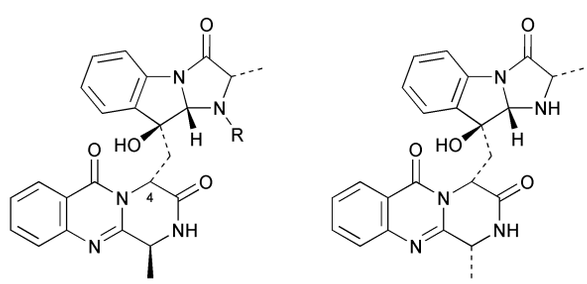
piperidine produced the amidines **224**. The target alkaloids **180** ($[a]_D$ −55, *c* 0.94, $CHCl_3$) and **181** ($[a]_D$ −91, *c* 0.17, MeOH) were obtained after deprotection of **224** with hydrobromic acid in acetic acid followed by treatment with a tertiary amine and silica gel. It should be noted that the optical rotation of synthetic (−)-circumdatin F is considerably larger than that recently recorded on a natural sample (*cf.* Section 2.1). A different synthesis of circumdatin F and the related alkaloid sclerotigenin **225** by Snider and Busuyek,[108] also shown in Scheme 13, entailed the selective acylation of the benzodiazepinediones **226**, without the need for protecting groups, at the more acidic anilide position with 2-azidobenzoyl chloride, followed by aza-Wittig cyclisation of the resulting imides **227** with tributylphosphine. The optical rotation for circumdatin F, incorrectly reported in this publication, has subsequently been corrected ($[a]_D$ −52.9, *c* 0.5, $CHCl_3$).[109] It is also intriguing that the ^1H NMR spectrum of this alkaloid showed the presence of two conformers in the ratio 99 : 1, arising from flipping of the seven-membered ring.

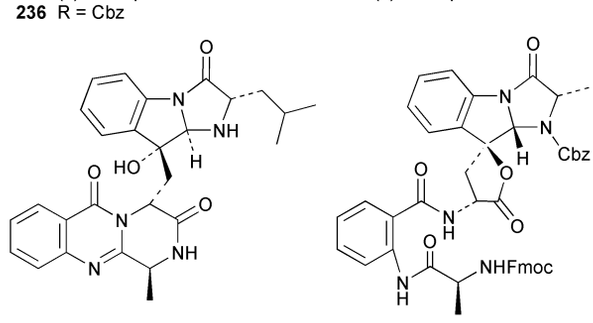
A synthesis of (+)-fumiquinazoline G reported some years ago by Snider and He[110] (*cf.* Ref. 28*i*) suffered from poor yields during the removal of a 2,4-dimethoxybenzyl protecting group. The difficulty has now been overcome by using the photolabile



Scheme 14 *Reagents and conditions*: i, NaH, THF, −5 °C, then 2-$N_3C_6H_4COCl$, THF, rt; ii, Bu_3P, C_6H_6, rt to 75 °C; iii, MeOH, Pyrex, *hv* (254 nm).

2-nitrobenzyl protecting group.[108] Thus the final steps, shown in Scheme 14, entailed acylation of the protected diketopiperazine **228** with 2-azidobenzoyl chloride and aza-Wittig cyclisation of the product to give **229**. Photolytic removal of the 2-nitrobenzyl group from a dilute solution of **229** in methanol at 254 nm afforded an 87% yield of *ent*-fumiquinazoline G **230**. It is of interest that Avendaño and co-workers recently experienced problems in the removal of a 2,4-dimethoxybenzyl protecting group at the end of a synthesis of the fumiquinazoline regioisomer **231** by a similar aza-Wittig protocol.[111]

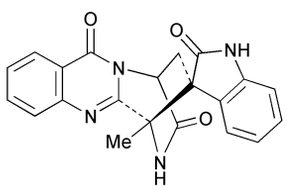




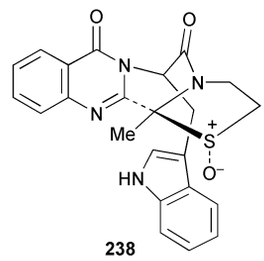
The more complex (−)-fumiquinazolines A, B and I, **232**–**234**, have also been synthesised by Snider's group by routes in which most of the effort was, understandably, devoted to constructing the 3-oxotetrahydro-1*H*-imidazo[1,2-*a*]indol-9-yl substituents.[112] Formation of the 2*H*-pyrazino[2,1-*b*]quinazoline-3,6(1*H*,4*H*)-dione moieties was left to the final stages of the synthesis, and involved methodology similar to that shown in Scheme 13 (*cf.* steps **222** ⟶ **224** ⟶ **181**). In the case of

fumiquinazoline A, for example, treatment of the precursor **235** with triphenylphosphine and bromine in the presence of triethylamine followed by aminolysis of the resulting 3,1-benzoxazine with piperidine and final cyclisation gave a mixture of the Cbz-protected product **236** and its C-4 epimer in overall yields of 49% and 14%, respectively. Removal of the Cbz protecting group from the former by hydrogenolysis over palladium completed the synthesis of (−)-fumiquinazoline A **232** in 90% yield. The overall yields for (−)-fumiquinazolines B and I from the appropriate precursors analogous to **235** were 42% and 52%, respectively.

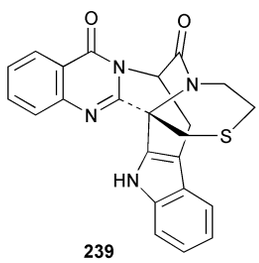
The synthesis of *ent*-alantrypinone **237** communicated by Hart and Magomedov in 1999[113] and summarised in last year's review in this series (*cf.* Ref. 28*j*) has been published as a full paper with experimental details and additional observations on aspects of the chemistry.[114] A related article by these authors on the Morin rearrangement of sulfoxides such as **238** with trifluoroacetic acid described the isolation of bridged products such as **239** (21–35%) and **240** (22–25%), amongst others, as well as the putative mechanism of the process.[115]



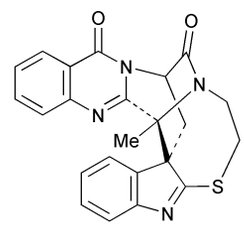
237 *ent*-Alantrypinone



238



239



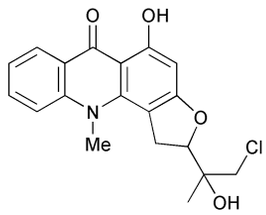
240

3 Acridone alkaloids

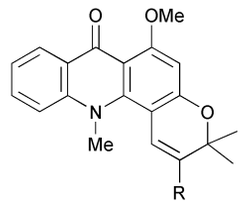
The known alkaloid isogravacridonechlorine **241** has been isolated from root extracts of *Ruta chalepensis*.[16]

Oxidation of the potentially valuable antitumour alkaloid acronycine **242** and its nitro derivative **243** with *meta*-chloroperoxybenzoic acid in toluene has yielded the Baeyer–Villiger ring-expansion products **244** (20% and 30% yields respectively), as well as the hydroxylated compounds **245** (10%).[116] The pyran ring remained unaffected. However, similar oxidation of the *cis*-diol **246** yielded only the triol **247** (29%), whereas oxidation of **246** with lead tetraacetate followed by treatment with sodium borohydride afforded the ring-D expanded hemiacetal **248** (30%), which could in turn be oxidised to the lactone **249** with pyridinium chlorochromate (25%). The products showed varying degrees of *in vitro* cytotoxicity towards L-1210 leukemia cells, with **248** and **249** being approximately as active as acronycine itself. In related studies, the acronycine-inspired benzo[*b*]-xanthenone derivative **250** was found to be more active than the parent alkaloid in inhibiting the proliferation of the same cell line.[117] Cognate work on benzo[*b*]-fused acridones and pyranoacridones, some of which has previously been discussed in this series of reviews, has since been patented.[118]

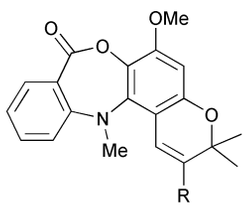
In efforts to improve the bioavailability of the potent antitumour agent glyfoline **251**, several water-soluble derivatives **252**–**255** were prepared by derivatising the parent alkaloid.[119] *In vitro* tests proved that all the derivatives were less cytotoxic than glyfoline towards nasopharyngeal carcinoma (NPC) cells. However, only **253** (n = 3) showed significant *in vivo* activity in mice bearing NPC xenografts. Although the effective dose was about half that of glyfoline itself, this compound might still prove to be a useful prodrug in combination chemotherapies.



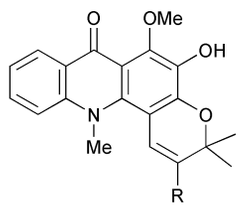
241 Isogravacridonechlorine



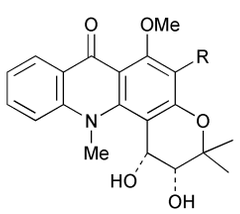
242 Acronycine R = H
243 R = NO_2



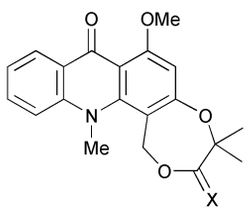
244 R = H, NO_2



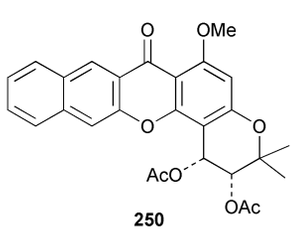
245 R = H, NO_2



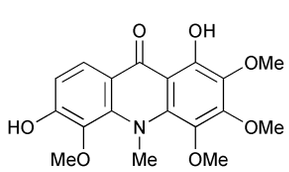
246 R = H
247 R = OH



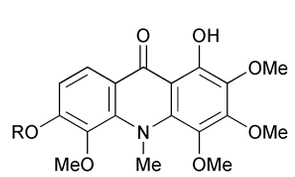
248 X = H, OH
249 X = O



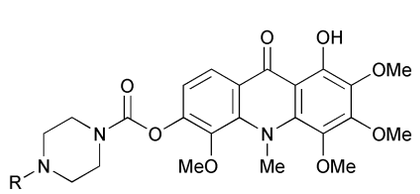
250



251 Glyfoline



252 R = $(CH_2)_nNMe_2{\cdot}HCl$; n = 1, 2
253 R = $(CH_2)_nCO_2^-$ $(HOCH_2CH_2)_3NH^+$; n = 1, 3
254 R = $CH(Me)CO_2^-$ $(HOCH_2CH_2)_3NH^+$



255 R = $PhCH_2$, $Me_2CHNHCOCH_2$

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