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

Received (in Cambridge, UK) 18th July 2003
First published as an Advance Article on the web 19th August 2003

Covering: July 2001 to June 2002. Previous review: *Nat. Prod. Rep.*, 2002, **19**, 742

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 2001 to June 2002 is reviewed, and 125 references are cited.

1 Quinoline alkaloids

1.1 Occurrence

The past year has brought to light an astonishing number of new quinoline alkaloids, some from unusual sources. By contrast, the number of known quinoline alkaloids isolated from previously unexplored sources was relatively small. The compounds of interest and their sources are listed in Table 1.[1–32]

1.2 Non-terpenoid quinoline and quinolinone alkaloids from rutaceous plants

While 2-arylquinoline alkaloids are not uncommon metabolites of plants belonging to the Rutaceae, it is unusual for them to bear substituents on the carbocyclic ring of the quinoline nucleus. However, no fewer than three 2-aryl-5,6-dimethoxyquinolin-4-one alkaloids, **1**–**3**, were isolated from the leaves of the medicinally useful central American plant *Casimiroa edulis*.[4] The alkaloids were also detected in the seed kernels by TLC. The structures were determined by a combination of spectroscopic methods, and the substitution patterns were inferred in part by comparing chemical shifts with those reported for related flavonoids.

A GC-MS method for detecting the constituents in the essential oils and extracts from the trunk bark of *Galipea officinalis*, another medicinally valuable plant from South America, has permitted the identification of a further five minor alkaloids, **4**–**8**.[7] The structures of the new alkaloids and a further ten known alkaloids were deduced on the basis of their mass spectral fragmentation patterns only. *G. officinalis* is the only species in this genus to contain tetrahydroquinoline alkaloids, and it is noteworthy that four of the five new alkaloids belong to this group. Some of the better-known *G. officinalis* tetrahydroquinolines, including cuspareine **9**, galipeine **10**, galipinine **11** and angustureine **12**, have been shown to possess antimalarial activity against both chloroquine-sensitive and chloroquine-resistant strains of the malaria parasite *Plasmodium falciparum*, with galipinine being the most active compound (IC_{50} 0.09–0.9 μg cm^{-3} for the resistant strain).[33] The same four alkaloids were cytotoxic towards human fibroblast cells, but in this case cuspareine was the most effective (IC_{50} 5.8–8.5 μg cm^{-3}). 2-Propylquinoline **13**, from the species *G. longiflora*, has proved to be clinically effective as a trypanocidal agent in mice chronically infected with *Trypanosoma cruzi*, an encouraging result for the treatment of conditions such as Chagas disease.[34]

Semecarpifoline **14** is an atypical metabolite from the root bark of the Taiwanese tree *Melicope semecarpifolia*, which is better known as a source of furoquinoline alkaloids.[16] The positions of the substituents in this new quinolin-2-one were ascertained by HMBC and nOe experiments. The isolation of **14** marks the first occurrence of a methoxymethyl substituent in a rutaceous quinoline alkaloid, although the authors seem not to have recognised that this is a precedent-setting feature.

^{1}H and ^{13}C NMR spectra have been reported in full for *N*-methyl-2-nonylquinolin-4-one **15**, *N*-methyl-2-phenylquinolin-4-one **16** and 2-nonylquinolin-4(1*H*)-one **17**, three well-known alkaloids recently isolated from the previously unexplored Brazilian shrub *Raulinoa echinata*.[23] Compounds **15** and **17** showed moderate antitrypanosomal activity against trypomastigote forms of *T. cruzi* (IC_{50} 134.9 and 100.9 μg cm^{-3}, respectively), and the latter was also weakly fungicidal towards *Leucoagaricus gongylophorus*, a symbiotic fungus of leaf-cutting ants.

The New Caledonian tree *Sarcomelicope megistophylla*, noteworthy for producing unusual quinoline alkaloids, has yielded perhaps its most astounding natural product to date.[24] The optically inactive cyclomegistine **18**, another in the series of putative oxidation products of an oxygenated precursor such as melicopicine **19** (*cf.* Ref. 35*a*), contains a cyclobuta[*b*]quinoline nucleus that is unprecedented both in nature and as a synthetic product. While spectroscopic methods pointed to the gross structure, the four-membered ring and the stereochemistry of its substituents could only be confirmed unambiguously by X-ray diffraction analysis. A plausible biosynthesis from melicopicine involves oxidative cleavage of ring A to give a butadiene intermediate **20**, photochemical electrocyclic ring closure of which leads to the observed product. Interestingly, when melicopicine was treated with hydrogen peroxide in acetic acid while being irradiated, cyclomegistine was isolated in low yield. The new alkaloid was moderately cytotoxic towards L1210 leukaemia cells (IC_{50} 80 μM).

 DOI: 10.1039/b208140g

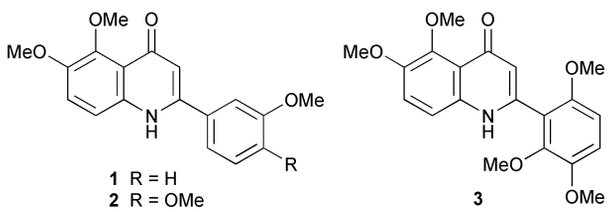
Table 1 Isolation and detection of quinoline alkaloids from plant, microbial and animal sources

Species	Alkaloid[a]	Ref.
Antidesma membranaceum	(+)-(17*RS*)-17-(β-D-Glucopyranosyloxy)antidesmone[b] **66**	1
	(+)-(17*RS*)-8-Deoxo-17-(β-D-glucopyranosyloxy)antidesmone[b] **67**	
Aplidium tabascum (tunicate)	(+)-Lepadin F[b] *rel*-**96**	2
	(+)-Lepadin G[b] *rel*-**98**	
	(+)-Lepadin H[b] *rel*-**99**	
Aquilegia ecalcarata	7-Hydroxy-4-[5-(hydroxymethyl)-2-furyl]quinolin-2(1*H*)-one[b] **68**	3
Casimiroa edulis	5,6-Dimethoxy-2-(3-methoxyphenyl)quinolin-4(1*H*)-one[b] **1**	4
	5,6-Dimethoxy-2-(3,4-dimethoxyphenyl)quinolin-4(1*H*)-one[b] **2**	
	5,6-Dimethoxy-2-(2,5,6-trimethoxyphenyl)quinolin-4(1*H*)-one[b] **3**	
Didemnum sp. (tunicate)	(+)-Lepadin D[b] *rel*-**94**	5
	(−)-Lepadin D, quaternary derivative[b]	
	(−)-Lepadin E[b] *rel*-**95**	
	(−)-Lepadin F[b] *rel*-**96**	
Esenbeckia conspecta	Flindersiamine **58**	6
	Maculosidine	
	8-Methoxy-*N*-methylflindersine (zanthobungeanine)	
Galipea officinalis	2-[2-(3,4-Dimethoxyphenyl)ethyl]quinoline	7
	2-[2-(3,4-Dimethoxyphenyl)ethyl]-1,2,3,4-tetrahydroquinoline[b] **4**	
	2-[2-(3-Hydroxy-4-methoxyphenyl)ethyl]-4-methoxyquinoline (or 3-methoxy-4-hydroxyphenyl isomer)[b] **5**	
	Maculosidine	
	2-[2-(3,4-Methylenedioxyphenyl)ethyl]-1,2,3,4-tetrahydroquinoline[b] **6**	
	1-Methyl-2-propyl-1,2,3,4-tetrahydroquinoline[b] **7**	
	2-Pentyl-1,2,3,4-tetrahydroquinoline[b] **8**	
Geocrinia laevis (frog)	Decahydroquinoline 195A **115**	8
Glycosmis parviflora (= *G. citrifolia*)	Flindersine **34**	9
	N-Methylflindersine **45**	
Halfordia kendack	(+)-*trans*-Deacetoxyerioaustralasine[b] **29**	10
	(+)-*trans*-Deacetoxyerioaustralasine hydrate[b] **30**	
	(+)-*trans*-1′-Epideacetoxyerioaustralasine hydrate[b] **32**	
	(+)-*trans*-Erioaustralasine **28**	
	(+)-*trans*-Erioaustralasine hydrate[b] **31**	
Haplophyllum acutifolium	Flindersine **34**	11
	Haplophytin-A[b] **33**	
	(+)-Haplophytin-B (= evoxine) **35**	
Haplophyllum patavinum	(−)-Edulinine	12
	Haplopine **55**	
	(+)-Isoplatydesmine	
	(−)-Ribalinine	
	Skimmianine **57**	
Hyrtios erecta (sponge)	6-Bromo-4-hydroxyquinolin-2(1*H*)-one[b] **102**	13
	6,7-Dibromo-4-hydroxyquinolin-2(1*H*)-one[b] **103**	
Ladenbergia oblongifolia	(−)-Cinchonidicinol **71**	14
	(−)-Epicinchonicinol **72**	
	Dihydrocinchonicinol/dihydrocinchonidicinol[b] **73** (mixture)	
Limonia crenulata	Integriquinolone	15
Melicope semecarpifolia (= *M. confusa*, *Evodia merrillii*)	2-Acetylevolitrine[b] **50**	16
	2-Acetylpteleine[b] **51**	
	Dictamnine **53**	
	(3*R*)-(−)-8,9-Dimethoxygeibalansine **36**	
	cis-(+)-7,8-Dimethoxymyrtopsine **37**	
	(2*S*)-(−)-7,8-Dimethoxyplatydesmine **38**	
	Evolitrine **54**	
	Semecarpifoline[b] **14**	
Micromonospora sp. IM 2670	7-(1-Methyl-2-oxopropyl)streptonigrin[b] **78**	17
	Streptonigrin **77**	
Nitraria sibirica	Dihydroschoberine[b] **75**	18
Oryza sativa cv. *Heugjinmi*	Methyl 6-hydroxy-2-oxo-1,2-dihydroquinoline-4-carboxylate[b] **69**	19
Oryza sativa cv. *Mihyangbyo*	Methyl 6-methoxy-2-oxo-1,2-dihydroquinoline-4-carboxylate[b] **70**	20
Penicillium citrinum 90648	Quinolactacin A1[b] **79**	21
	Quinolactacin A2[b] **80**	
Pseudomonas fluorescens G308	*N*-Mercapto-4-formylcarbostyril[b] **83**	22
Raulinoa echinata	Flindersiamine **58**	23
	Kokusaginine **56**	
	Maculine **59**	
	N-Methyl-2-nonylquinolin-4-one **15**	
	N-Methyl-2-phenylquinolin-4-one **16**	
	2-Nonylquinolin-4(1*H*)-one **17**	
	Skimmianine **57**	
Sarcomelicope megistophylla	Cyclomegistine[b] **18**	24
	Megistoquinone I[b] **60**	25
	Megistoquinone II[b] **62**	
Scolopendra subspinipes mutilans (centipede)	Scolopendrine[b] **104**	26
Severinia buxifolia	*N*-Methylswietinidine-B	27,28
Streptomyces SNA15896	(−)-SW-163C[b] **84**	29,30
	(−)-SW-163E[b] **85**	
Zanthoxylum dimorphophyllum	γ-Fagarine **64**	31

Table 1 (*Contd.*)

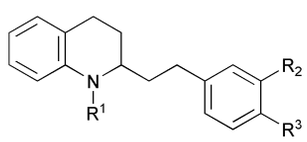
Species	Alkaloid[a]	Ref.
Zanthoxylum hyemale	(*R*)-(−)-Geibalansine[b] **39** Hyemaline[b] **63**	32

[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.

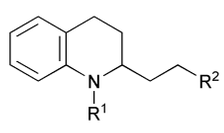


1 R = H
2 R = OMe

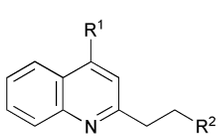
3



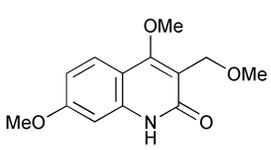
4 R^1 = H; R^2 = R^3 = OMe
6 R^1 = H; R^2R^3 = OCH_2O
9 Cuspareine R^1 = Me; R^2 = R^3 =OMe
10 Galipeine R^1 = Me; R^2 = OH; R^3 = OMe
11 Galipinine R^1 = Me; R^2R^3 = OCH_2O



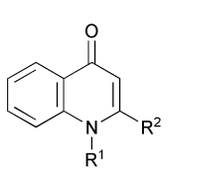
7 R^1 = R^2 = Me
8 R^1 = H; R^2 = *n*-Pr
12 Angustureine
R^1 = Me; R^2 = *n*-Pr



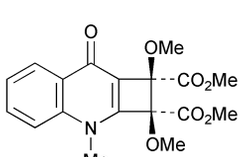
5 R^1 = OMe; R^2 = C_6H_3-3-OH-4-OMe
13 R^1 = H; R^2 = Me



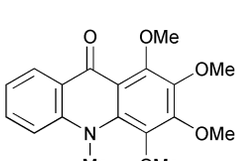
14 Semecarpifoline



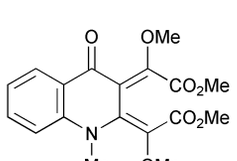
15 R^1 = Me; R^2 = *n*-C_9H_{19}
16 R^1 = Me; R^2 = Ph
17 R^1 = H; R^2 = *n*-C_9H_{19}



18 Cyclomegistine

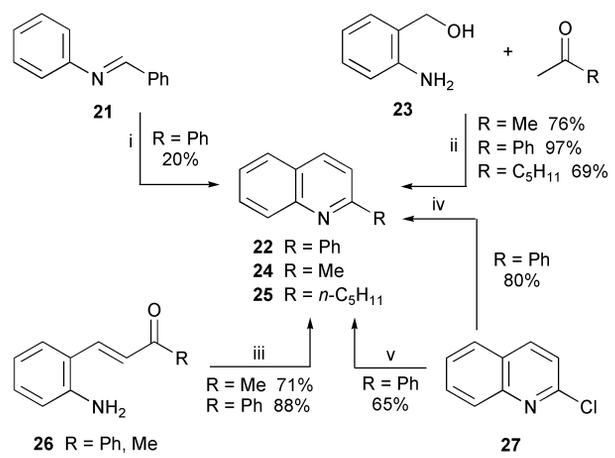


19 Melicopicine



20

A number of short synthetic approaches to simple naturally occurring 2-substituted quinolines merit brief mention (Scheme 1). Imino Diels–Alder reaction between the benzaldimine **21** and ethyl vinyl ether could be induced by samarium iodide to give the alkaloid 2-phenylquinoline **22** in modest yield.[36] Various ruthenium catalysts, and in particular the Grubbs catalyst $RuCl_2$(=CHPh)$(PCy_3)_2$, induced oxidative cyclisation of 2-aminobenzyl alcohol **23** with a range of enolisable ketones to give quinoline products, among them the alkaloids **22**, **24** and **25**, by a modified Friedländer reaction.[37] Irradiation of the *trans*-2-aminocinnamoyl derivatives **26** in acetonitrile induced *trans–cis* isomerisation and subsequent cyclisation to give the quinolines **22** and **24** in good yield.[38] Cross-coupling of



26 R = Ph, Me
27

Scheme 1 *Reagents*: i, $EtOCH=CH_2$, $SmI_2(THF)_2$ (0.1 equiv.), CH_2Cl_2, rt; ii, $RuCl_2$(=CHPh)$(PCy_3)_2$ (0.01 equiv.), KOH (1 equiv.), ketone (2 equiv.), dioxane, 80 °C; iii, *hv* (high pressure Hg lamp, Pyrex filter), MeCN, 15–25 min; iv, PhMgCl, $Pd(dba)_2$ (5 mol%), dppf (5 mol%), THF, −5 °C; v, PhMgBr, $Fe(acac)_3$ (10 mol%), THF, −30 °C.

2-chloroquinoline **27** with phenylmagnesium halides could be accomplished in the presence of a palladium catalyst to give 2-phenylquinoline **22** in 80% yield,[39] or somewhat less efficiently (65%) with iron(III) tris(acetylacetonate).[40]

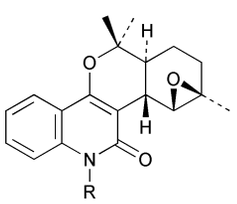
1.3 Terpenoid quinoline alkaloids and tricyclic derivatives

A group of structurally unprecedented polycyclic quinolinone alkaloids formally incorporating a 3-geranylquinoline motif was isolated from the Australian rutaceous plant *Eriostemon australasius* ssp. *banksii* (= *E. banksii*) in 1993[41] (*cf.* Ref. 35*b*). One of these compounds, *trans*-erioaustralasine **28**, has recently turned up in an apparently taxonomically remote source, *Halfordia kendack*, together with another four novel alkaloids of similar structure.[10] *trans*-Deacetoxyerioaustralasine **29** gave essentially the same NMR spectra as **28**, but the unusual *N*-acetoxymethyl substituent was replaced by *N*-methyl. The remaining three minor alkaloids, *trans*-deacetoxyerioaustralasine hydrate **30**, *trans*-erioaustralasine hydrate **31** and *trans*-1′-epideacetoxyerioaustralasine hydrate **32**, are 1,2-diols formally derived by hydrolysis of the epoxide rings of **28** and **29**. The relative stereochemistry of **30** was deduced by analysis of coupling constants and NOESY experiments, while minor differences in the spectra of **30** and the other two diols led to the assignment of structures **31** and **32**.

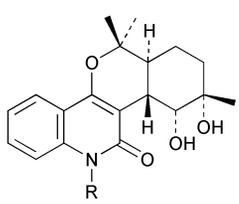
The novel tricyclic hemiterpenoid alkaloid haplophytin-A **33**, isolated from a methanol extract of *Haplophyllum acutifolium*, is a simple methoxy derivative of the common alkaloid flindersine **34**, which was also found in the extract.[11] However, the structure reported for haplophytin-B, another apparently new metabolite from the same source, is actually identical to that of the well-known alkaloid evoxine **35**—confusingly, also known as haploperine. The name haplophytin-B should thus be abandoned in favour of the long-established name evoxine.[42] Neither **33** nor **35** showed activity when tested against various bacteria and fungi.

Neither optical rotations nor absolute configurations were reported for the three linearly fused tricyclic quinoline alkaloids 8,9-dimethoxygeibalansine **36**, 7,8-dimethoxymyrtopsine **37**

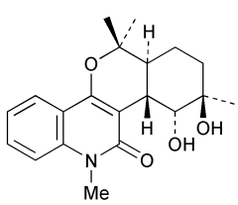
and 7,8-dimethoxyplatydesmine **38** when they were first described in 1992 as metabolites of the New Caledonian plant *Dutaillyea baudouinii*[43] (*cf.* Ref. 35*c*), or in a later isolation of **37** and **38** from *Dictamnus dasycarpus*[44] (*cf.* Ref. 35*d*). The recent isolation of the same three alkaloids from a methanol extract of the root bark of *Melicope semecarpifolia* has now permitted some stereochemical inferences to be drawn.[16] Analogy with the known (3*S*)-(+)-9-methoxygeibalansine, for instance, suggested that the laevorotatory pyrano[2,3-*b*]quinoline **36** ($[\alpha]_D$ −18.6, *c* 0.065, $CHCl_3$) should have the (3*R*) configuration as illustrated. A similar comparison drawn between (2*R*)-(+)-8-methoxyplatydesmine and **38** ($[\alpha]_D$ −10.3, *c* 0.16, $CHCl_3$) led to assignment of the (2*S*) configuration for the latter. Although the absolute configuration of (+)-7,8-dimethoxymyrtopsine **37** ($[\alpha]_D$ +16.2, *c* 0.165, $CHCl_3$) was not deduced, the NOESY spectrum indicated that the hydrogen substituents at C-2 and C-3 were *cis* to each other. Interestingly enough, the parent (3*R*)-(−)-geibalansine **39** was recently isolated as a new natural product from the stem bark of *Zanthoxylum hyemale*, and its absolute configuration was established by the Horeau method.[32] The absolute configuration of the (3*S*)-(+)-enantiomer, a metabolite of *Geijera balansae*, was established as recently as 2000 by total synthesis[45] (*cf.* Ref. 35*e*).



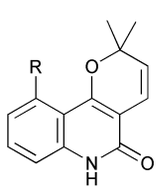
28 R = CH_2OAc
29 R = Me

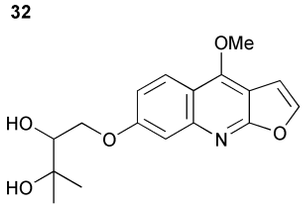


30 R = Me
31 R = CH_2OAc



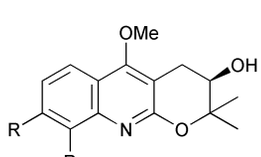
32

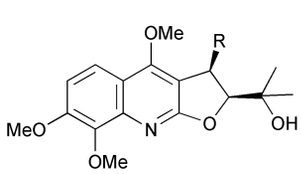




33 Haplophytin-A R = OMe
34 Flindersine R = H

35 Evoxine (Haplophytin-B)

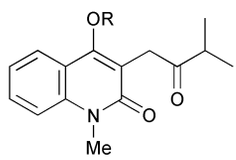




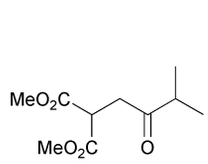
36 R = OMe
39 (*R*)-(−)-Geibalansine R = H

rel-**37** R = OH
38 R = H

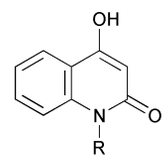
Several short syntheses of terpenoid quinoline alkaloids and related model systems were published during the review period. The first reported synthesis of the simple hemiterpenoid alkaloid orixiarine **40** has as its central feature the formation of the 3-substituted quinolin-2-one **41** by condensation of the malonate derivative **42** with *N*-methylaniline at 200 °C, after which sequential treatment with phosphorus oxychloride and sodium methoxide yielded the target alkaloid.[46] A new one-pot synthesis of pyrano[3,2-*c*]quinolin-5-ones by reaction of 4-hydroxyquinolin-2-ones **43** or **44** with α,β-unsaturated aldehydes in the presence of ytterbium(III) trifluoromethanesulfonate in acetonitrile at reflux yielded, among other products, flindersine **34** (50%) from **43** and prenal, *N*-methylflindersine **45** (57%) from **44** and prenal, and zanthosimuline **46** (55%) from **44** and citral.[47] Another potentially useful route to pyrano[3,2-*c*]-quinolin-5-one alkaloids, applied so far only to model systems, involved the *in situ* formation of the 3-methylenequinoline-2,4-dione **47** from **44** and paraformaldehyde in boiling dioxane, followed by Diels–Alder trapping with various alkenes to give products of general structure **48**.[48] Also worth noting is the finding that the manganese(III) acetate-mediated radical-reaction of **44** with alkenes to give furoquinolinones, *e.g.*, **49**, could be improved when carried out in the ionic liquid 1-butyl-3-methylimidazolium tetrafluoroborate.[49]



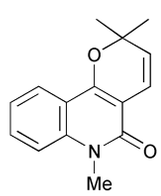
40 Orixiarine R = Me
41 R = H



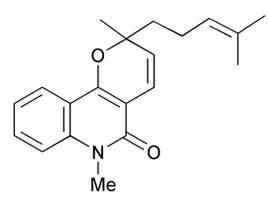
42



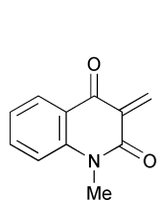
43 R = H
44 R = Me



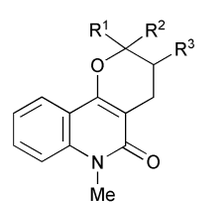
45



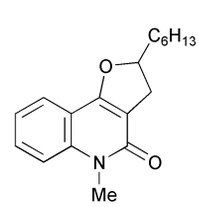
46 Zanthosimuline



47



48



49

1.4 Furoquinoline alkaloids

While hemiterpenoid 2,3-dihydrofuro[2,3-*b*]quinoline alkaloids (*cf.* Section 1.3 above) invariably betray their 3-prenylquinoline origins by bearing a three-carbon substituent at C-2, the substituent is lost in their biosynthetically more advanced furo[2,3-*b*]quinoline cousins. It is thus intriguing that two unprecedented 2-acetylfuro[2,3-*b*]quinoline alkaloids have been isolated from the root bark of *Melicope semecarpifolia*.[16] The structures of the two compounds, 2-acetylevolitrine **50** and 2-acetylpteleine **51**, were elucidated spectroscopically, with one- and two-dimensional NMR spectroscopic methods providing unambiguous support for the structures and the location of the substituents. Once again, however, the authors seem not to have recognised the novelty of their discovery. It is worth noting that the antiplatelet aggregation activity of the plant extract was traced to a suite of more conventional furoquinoline alkaloids, among them confusameline **52**, dictamnine **53**, evolitrine **54**, haplopine **55**, kokusaginine **56** and skimmianine **57**.

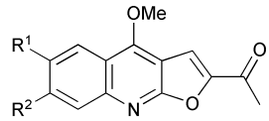
The X-ray crystal structure of the known alkaloid flindersiamine **58**, isolated for the first time from *Raulinoa echinata*, has been reported.[23] This alkaloid and its congeners kokusaginine, skimmianine and maculine **59** showed antifungal activity against *Leucoagaricus gongylophorus*, but were ineffective towards *Trypanosoma cruzi* (*cf.* Section 1.2).

A further hitherto unprecedented variation in the oxidation pattern found in the astonishing suite of quinoline alkaloids

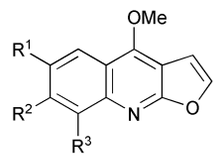
from *Sarcomelicope megistophylla* (*cf.* Section 1.2) involves the oxidation of the aromatic ring up to the quinone level.[25] Megistoquinone I **60**, fully characterised by spectroscopic techniques, is probably derived biogenetically by oxidation of a precursor such as acronycidine **61**, a major alkaloid from the same source. Indeed, treatment of **61** with nitric acid yielded **60**, an experiment first reported in 1950 during the structural elucidation of **61** by degradation experiments.[50] A second metabolite, megistoquinone II **62**, is apparently derived from **60** by hydrolysis of the furan ring followed by methylation of the resulting enol. While a number of quinoline-5,8-quinones have been found in sponges, this is the first report of their occurrence in terrestrial plants. Both new alkaloids showed antibacterial properties, with minimum inhibitory concentrations ranging from 2.35 to 5.25 mg cm^{-3} for **60** and 0.73 to 1.23 mg cm^{-3} for **62**. Acronycidine itself was inactive in the same battery of tests.

The first example of a naturally occurring furo[3,2-*g*]quinoline alkaloid has been reported as a constituent of the stem bark of *Zanthoxylum hyemale*, a South American plant with a history of use in folk medicine.[32] The structure of this unique compound, hyemaline **63**, was established by spectroscopic methods, and the positioning of substituents was based on HMBC experiments.

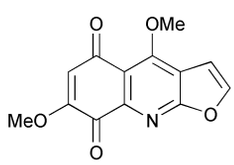
Haplopine **55**, skimmianine **57**, γ-fagarine **64** and other furoquinoline alkaloids that occur in the genus *Haplophyllum* have been found to show more pronounced estrogenic activity than dihydrofuroquinoline, quinolin-2-one and quinolin-4-one alkaloids from the same genus.[51] The related alkaloid dictamnine **53** has proved to be a feeding deterrent against two insect pests (*Sitophilus zeamays* and *Trilobium castaneum*) responsible for spoilage of stored products.[52]



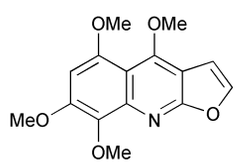
50 2-Acetylevolitrine R^1 = H; R^2 = OMe
51 2-Acetylpteleine R^1 = OMe; R^2 = H



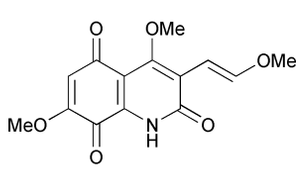
52 Confusameline R^1 = R^3 = H; R^2 = OH
53 Dictamnine R^1 = R^2 = R^3 = H
54 Evolitrine R^1 = R^3 = H; R^2 = OMe
55 Haplopine R^1 = H; R^2 = OH; R^3 = OMe
56 Kokusaginine R^1 = R^2 = OMe; R^3 = H
57 Skimmianine R^1 = H; R^2 = R^3 = OMe
58 Flindersiamine R^1R^2 = OCH_2O; R^3 = OMe
59 Maculine R^1R^2 = OCH_2O; R^3 = H
64 γ-Fagarine R^1 = R^2 = H; R^3 = OMe



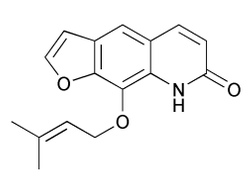
60 Megistoquinone I



61 Acronycidine



62 Megistoquinone II



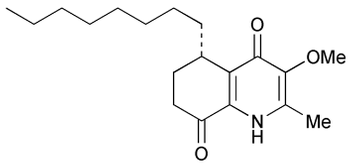
63 Hyemaline

1.5 Miscellaneous quinoline alkaloids from higher plants

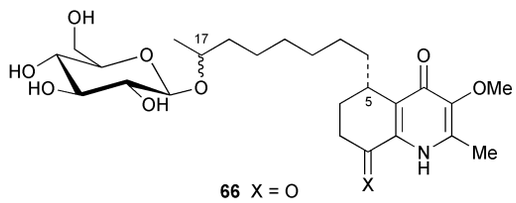
Two new glucoside derivatives of antidesmone **65**, a recently discovered alkaloid from the African tree *Antidesma membranaceum* (Euphorbiaceae) (*cf.* Ref. 35*f*), have been detected in leaf extracts of the same plant.[1] The salient structural features of the novel metabolites, (+)-(17*RS*)-17-(β-D-glucopyranosyloxy)antidesmone **66** and (+)-(17*RS*)-8-deoxo-17-(β-D-glucopyranosyloxy)antidesmone **67**, were revealed by thorough NMR and mass spectrometric analysis. Although both compounds were mixtures of diastereomers at C-17 in the side chain, comparison with reported ^{1}H NMR spectroscopic data for alk-2-yl β-D-glucopyranosides allowed unambiguous differentiation of the (17*R*) and (17*S*) forms, and integration of the methyl signals indicated the (*R*)/(*S*) ratio in **66** and **67** to be 3 : 1 and 1.3 : 1, respectively. Analysis of coupling constants showed that the proton at C-5 was in an equatorial or pseudoequatorial position in both alkaloids, while the maxima in the CD spectrum of compound **66** were the same as in antidesmone itself, from which the (*S*) absolute configuration at C-5 was inferred. The presence of the new alkaloids is thought to imply a biological function for antidesmone as a vehicle for the storage or transport of glucosides. In the meantime, antidesmone has been found to display potent and selective antitrypanosomal activity against *Trypanosoma cruzi*, the pathogenic agent of Chagas disease (IC_{50} 0.02 μg ml^{-1}), but little or no activity against *T. brucei rhodesiense*, an extracellular protozoan parasite responsible for African sleeping sickness, or against *Leishmania donovani*, the cause of visceral leishmaniasis.[53]

Three new carbostyril derivatives have been reported from atypical plant sources and characterised by spectroscopic methods. Bioactivity-guided fractionation of an ethyl acetate extract of the Chinese medicinal plant *Aquilegia ecalcarata* (Ranunculaceae) led to the isolation of 7-hydroxy-4-[5-(hydroxymethyl)-2-furyl]quinolin-2(1*H*)-one **68**, the furyl substituent of which is unprecedented in a quinoline alkaloid.[3] The purified alkaloid was moderately cytotoxic towards two human cancer cell lines (IC_{50} 8.8–10.1 μM) in *in vitro* tests. The less exotic alkaloid methyl 6-hydroxy-2-oxo-1,2-dihydroquinoline-4-carboxylate **69** was isolated from the aleurone (protein-containing) layer of the dark purple anthocyanin-pigmented rice cultivar *Oryza sativa* cv. *Heugjinmi* (Gramineae).[19] Structural characterisation of the new alkaloid and its readily prepared acetate derivative by spectroscopic methods was straightforward. This is the first report of the compound from a natural source, although it has previously been synthesised.[54] Compound **69** may well act as an anti-oxidant in the plant, since it was found to exhibit moderate anti-oxidative activity in a radical-scavenging assay (IC_{50} 36.4 μg ml^{-1}). A different rice cultivar, *Oryza sativa* cv. *Mihyangbyo*, yielded the corresponding 6-methoxy compound **70**, which exhibited moderate antineoplastic activity towards the human leukemia cell line U937 (IC_{50} 118.1 μg ml^{-1}).[20]

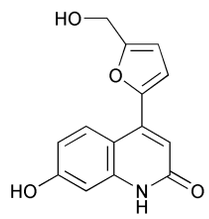
A brief note describing the constituents of the bark of Peruvian *Ladenbergia oblongifolia*, a previously unexplored plant of the Rubiaceae with no apparent history of medicinal use, reported the isolation and full spectroscopic characterisation of the known alkaloids cinchonidicinol **71** and epicinchonicinol **72**, as well as a mixture of the epimeric alkaloids dihydrocinchinicinol and dihydrocinchonidicinol **73**.[14] The latter may well be new alkaloids, since no previous reference to them in *Chemical Abstracts* could be traced. None of these compounds showed antimalarial activity towards a chloroquine-sensitive strain of *Plasmodium falciparum*. In this regard, several synthetic analogues of known antimalarial alkaloids such as quinine and cinchonidine having the general



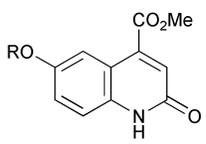
65 Antidesmone



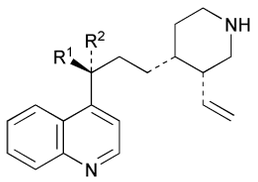
66 X = O
67 X = 2H



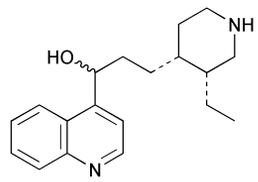
68



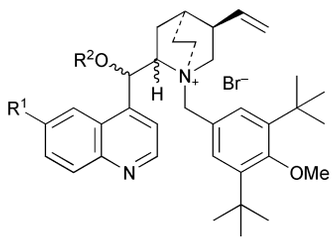
69 R = H
70 R = Me



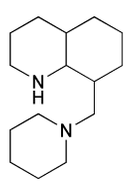
71 R^1 = OH; R^2 = H
72 R^1 = H; R^2 = OH



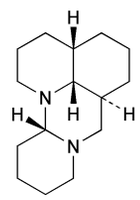
73



74 R^1 = H, OMe; R^2 = H, allyl, Bn



75 Dihydroschoberine



76 Schoberine

structure **74** showed potent activity against a chloroquine resistant strain of *P. falciparum*, and may be promising alternatives for currently used drugs in antimalarial chemotherapy.[55]

Dihydroschoberine **75** is a novel decahydroquinoline alkaloid isolated from a chloroform extract of the aerial parts of *Nitraria sibirica* (Nitrareaceae, Zygophyllaceae).[18] The natural product, an optically inactive oil, proved to be identical to the product obtained by catalytic hydrogenation of schoberine **76**, a well-known metabolite of the genus *Nitraria*, in acetic acid. The stereochemistry of the ring junction in the new alkaloid was not reported, but is presumably unchanged from that in schoberine itself.

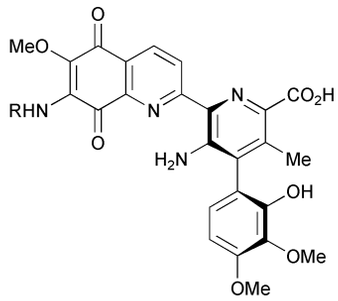
1.6 Quinoline alkaloids from fungal and microbial sources

Bioassay-guided HPLC fractionation of the fermentation broth of the actinomycete strain *Micromonospora* sp. IM 2670 yielded the well-known quinolinequinone antibiotic streptonigrin **77** and its novel *N*-(1-methyl-2-oxopropyl) derivative **78**.[17] The structure of **78** was deduced largely on the basis of NMR spectra and chemical shift comparisons with streptonigrin and a model *N*-(1-methyl-2-oxopropyl)aniline. Both compounds induced apoptosis in human neuroblastoma SH-SY5Y cells containing wild-type p53 (a tumour-suppressing protein functioning as a key component of the cellular emergency response mechanism), although streptonigrin was more active (IC_{50} 0.05 μM, *vs.* 0.9 μM).

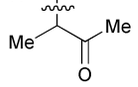
The isolation of quinolactacin A from the entomopathogenic fungus *Penicillium* sp. EPF-6 was reported in last year's review[56,57] (*cf.* Ref. 35*g*). Although a novel 3-(*sec*-butyl)-2,3-dihydro-1*H*-pyrrolo[3,4-*b*]quinoline-1,9(4*H*)-dione structure was proposed for the alkaloid, the stereochemistry at the two stereogenic centres was not elucidated. However, two diastereomeric metabolites having the same gross structure, isolated more recently from *Penicillium citrinum* 90648 and thoroughly characterised by a range of spectroscopic techniques, cast light on this stereochemical ambiguity.[21] On the basis of significant nOe differences involving the NH, NCH_3 and 3-H protons on the one hand, and the protons on the conformationally restricted *sec*-butyl group on the other, the authors proposed relative (*S**,*R**) and (*S**,*S**) stereochemistries for quinolactacins A1 and A2, respectively, as shown in **79** and **80**. H-3 and the methyl group of the *sec*-butyl chain appear to be *anti* in the former compound, while H-3 and the methylene group are *anti* in the latter. The chemical shifts of quinolactacin A2 were very similar to those previously reported for quinolactacin A, to which structure **80** should now also be assigned. Quinolactacin A2 was found to be a more pronounced inhibitor of acetylcholinesterase than quinolactacin A1 (IC_{50} 19.8 *vs.* 280 μM); its selectivity for acetylcholinesterase rather than butyrylcholinesterase (IC_{50} 650 μM) may offer opportunities for exploration in the treatment of Alzheimer-type dementia.

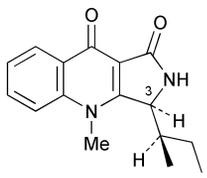
2-Alkyl-4-hydroxyquinolines (or their quinolin-4-one tautomers) have long been known as metabolites of *Pseudomonas* organisms, from which source their alternative name of 'pseudans' is derived. While the recent isolation of the 2-heptyl and 2-nonyl homologues **81** and **82** (pseudans VII and IX) from *Pseudomonas aeruginosa* ATCC 15692 was not in itself novel, the point of interest is that these compounds turned out to be novel membrane-associated iron chelators (MAIC) in the cytoplasmic membrane of iron-rich bacterial cells.[58] The structure of **82** was confirmed by spectroscopic comparison with a sample prepared by alkylating the dianion of 2-methylquinolin-4-ol with octyl bromide. Although *in vitro* complexation of synthetic pseudan IX with iron(III) chloride could not be verified spectroscopically, pink micelles similar to those found in the ethanol extract of cell membranes were formed on mixing the precursors. Also, after growth of the cells in the presence of $^{55}FeCl_3$, the radioactivity co-eluted with pseudan IX from an LH-20 Sephadex gel filtration column.

The simple antibiotic *N*-mercapto-4-formylcarbostyril **83** is a novel metabolite of *Pseudomonas fluorescens* (strain G308), a microorganism originally found growing on barley leaves.[22] The structure was deduced from its relatively simple spectra and those of its easily prepared *S*-acetyl derivative. Although no mention was made of the fact, this is the first occurrence of the *N*-mercapto substituent—effectively, part of the rare *N*-mercaptoamide functional group—in a quinolinone alkaloid. The purified antibiotic exhibited good activity against a range of plant pathogenic fungi, including *Fusarium oxy-*

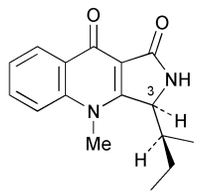


77 Streptonigrin R = H
78 R =

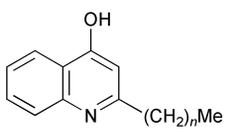




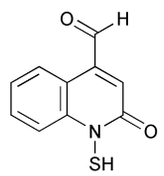
rel-**79** Quinolactacin A1



rel-**80** Quinolactacin A2



81 *n* = 6
82 *n* = 8

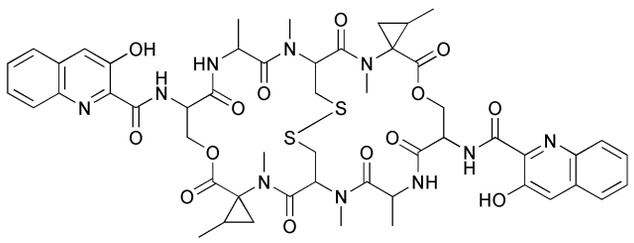


83

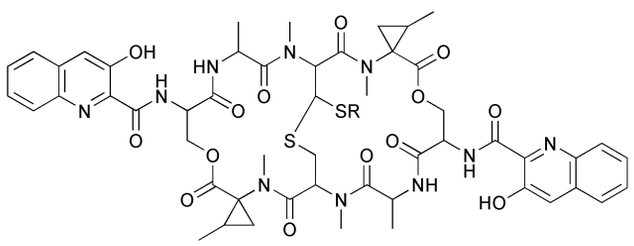
sporum, *F. culmorum*, *Cladosporium cucumerinum* and *Colletotrichum lagenarium*.

Two new octadepsipeptides bearing pendent 3-hydroxyquinaldic acid chromophores have been isolated from the culture broth of the *Streptomyces* strain SNA15896, collected from a Japanese soil sample.[29,30] The symmetrical dimer (−)-SW-163C **84** incorporates a central disulfide bridge, while the related compound (−)-SW-163E **85** possesses the same periphery as **84** but differs only in its inclusion of an internal dithioacetal linkage. Compound SW-163E is, in fact, the *S*-ethyl analogue of three antibiotics reported in 1989, and coded as UK-63,052 **86**, UK-65,662 **87** and UK-63,598 **88**.[59] The stereochemistry of all these natural products has not been elucidated, although it could no doubt be inferred from the nature of the amino acid constituents. Both SW-163C and SW-163E displayed good antibacterial activity, especially against Gram-positive bacteria. More importantly, potent antitumour activity was demonstrated in *in vitro* tests against various murine and human tumour cell lines, with **85** being about a hundredfold more active than **84** (IC_{50} 0.2–1.6 *vs.* 17–140 nM, respectively). When *in vivo* activity was assessed in mice implanted with P388 leukaemia, SW-163E was remarkable in prolonging life span at a dose of 0.01 mg kg^{-1}, but proved to be acutely toxic at higher doses (LD_{50} 0.6 mg kg^{-1}; *cf.* > 100 mg kg^{-1} for **84**).

Several model studies aimed at the synthesis of quinoline-containing natural products require brief mention. Evolving approaches to the synthesis of lavendamycin **89** by Holzapfel *et al.* have involved optimising the palladium-catalysed aminocarbonylation of 2-chloroquinolines with amines in the presence of carbon monoxide to give intermediates such as **90**, Bischler–Napieralski cyclisation of which produces the antibiotic's pentacyclic core.[60] Nicolaou and co-workers have reported a stereocontrolled synthesis of the macrocycle **91**, envisaged as a key intermediate in the synthesis of the complex thiopeptide antibiotic thiostrepton.[61,62] The dihydroquinoline building block **92** employed in this route was prepared in a multi-step procedure from quinaldic acid. Coincidentally, Hashimoto and co-workers almost simultaneously reported a similar multi-step synthesis of the dihydroquinoline **93** starting

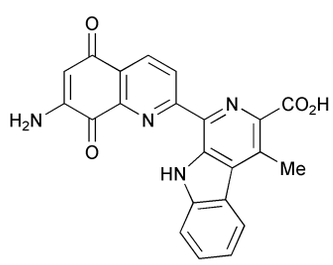


84 SW-163C

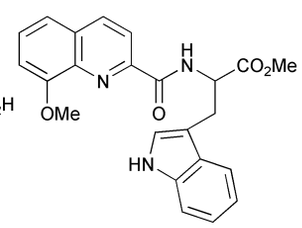


85 SW-163E R = Et
86 UK-63,052 R = *sec*-butyl
87 UK-65,662 R = isopropyl
88 UK-63,598 R = Me

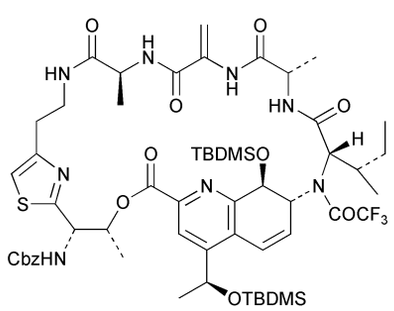
from 5,6,7,8-tetrahydroquinoline.[63] Compound **93** is proposed as an intermediate *en route* to siomycin D_1, another member of the thiostrepton group of peptide antibiotics.



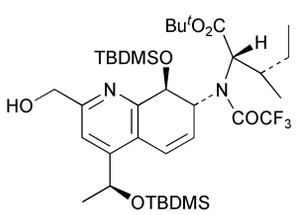
89 Lavendamycin



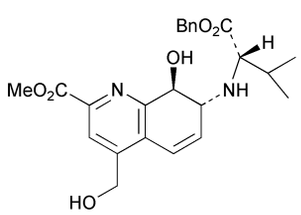
90



91



92



93

1.7 Quinoline alkaloids from animals

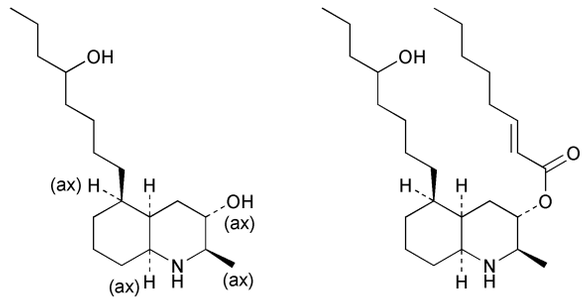
Several new lepadins, a group of decahydroquinoline alkaloids isolated from ascidians (tunicates or sea squirts) collected on the Great Barrier Reef, have been described in two independent

publications that appeared almost simultaneously. A new species of the animal belonging to the genus *Didemnum* yielded four novel lepadins, the structures of which were elucidated with the aid of a comprehensive suite of spectroscopic techniques.[5] In the case of (+)-lepadin D *rel*-**94**, for example, analysis of coupling constants in combination with nOe experiments indicated *cis*-fusion of the decahydroquinoline nucleus, chair conformations of both rings, a *trans*-diaxial arrangement of the C-2 and C-3 methyl and hydroxy substituents, and a 1,3-diaxial relationship between 5-H and 8a-H. This analysis established the relative stereochemistry of the stereogenic centres on the ring system, but both the configuration of the hydroxy group on the side chain and the molecule's absolute configuration remain unknown despite attempts to form a *p*-bromobenzoyl derivative for crystallographic analysis. Similar considerations led to the elucidation of the relative structures **95** and **96** for (−)-lepadins E and F, respectively, the last-named differing from the others in having an equatorial methyl substituent at C-2. The fourth alkaloid was simply the protonated form of lepadin D, probably with chloride as counter-ion. All the new alkaloids displayed biological activity: lepadins D–F were weakly antifungal, while the mildly cytotoxic **95** and **96** were also moderate inhibitors of tyrosine kinase p56. Most importantly, all four natural products showed significant antitrypanosomal and antiplasmodial activity, the most potent compound being lepadin F. The isolates may thus serve as novel lead compounds for the development of new antimalarial drugs.

The three new lepadins described in the second publication were isolated from the ascidian *Aplidium tabascum*.[2] Apart from its optical rotation (+5.5 rather than −1.5), lepadin F proved to be identical to the compound described above; slight differences in the reported ^{1}H NMR spectra were a consequence of measurement in different solvents (C_6D_6 *vs.* $CDCl_3$). It is unlikely that the two isolates are mirror images; it is more probable that minor impurities have distorted the small specific rotations recorded. The structure drawn for lepadin F in this publication was actually *ent*-**96**, but the relative stereochemistry in the two representations is the same. [In this regard, it is pertinent to note that a recent enantioselective total synthesis of three lepadins, *e.g.*, (−)-lepadin A **97**, by Kibayashi's group[64] (*cf.* Ref. 35*h*) has established a correlation between absolute configuration and optical rotation that may be valid for other members of the lepadin family.] (+)-Lepadin G *rel*-**98** is a dienoate analogue of lepadin F, while (+)-lepadin H *rel*-**99** is the octa-2,4-dienoate ester of lepadin D. In this study, molecular modelling was also used for ascertaining the minimum energy conformations of the alkaloids, and substantiated the conformational deductions based on NMR data. Interestingly, the preferred *cis*-fused twin-chair decahydroquinoline ring system for lepadins G and H places the ring nitrogen equatorial, as shown in **100**, whereas it is known that the nitrogen is axial in lepadin A, as depicted in **101**.

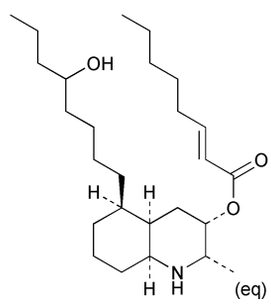
The Okinawan sponge *Hyrtios erecta* was the source of the two simple brominated carbostyrils **102** and **103**.[13] Both are novel natural products, although the former was previously reported as a synthetic compound.[65] The compounds were good but unselective inhibitors of the neural and inducible isozymes of nitric oxide synthase. Another new alkaloid, represented as the 2-hydroxyquinoline **104** but more probably the tautomeric carbostyril, was isolated from whole body extracts of the centipede *Scolopendra subspinipes mutilans*, which is used in traditional Chinese and Korean medicines.[26] Treatment of **104**, which has been named scolopendrine, with diazomethane gave **105**, HMBC correlations on which assisted in the location of the substituents. Scolopendrine's benzyl group at C-7 and sulfate group at C-8 are unprecedented substituents among the quinoline alkaloids.

Continuing uncertainty over the proposed structure **106** for the sponge metabolite halitulin has prompted Banwell and coworkers to undertake the short convergent synthesis shown in

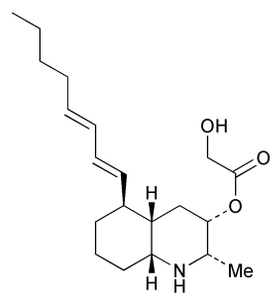


rel-**94** Lepadin D

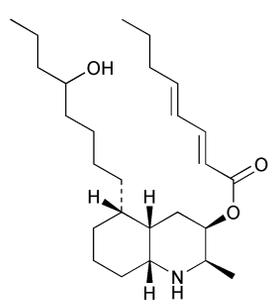
rel-**95** Lepadin E



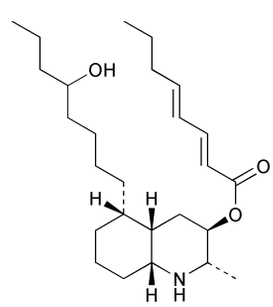
rel-**96** Lepadin F



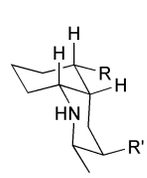
97 (–)-Lepadin A



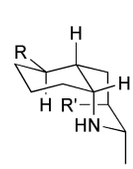
rel-**98** Lepadin G



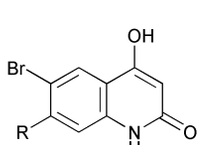
rel-**99** Lepadin H



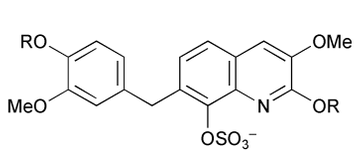
100



101

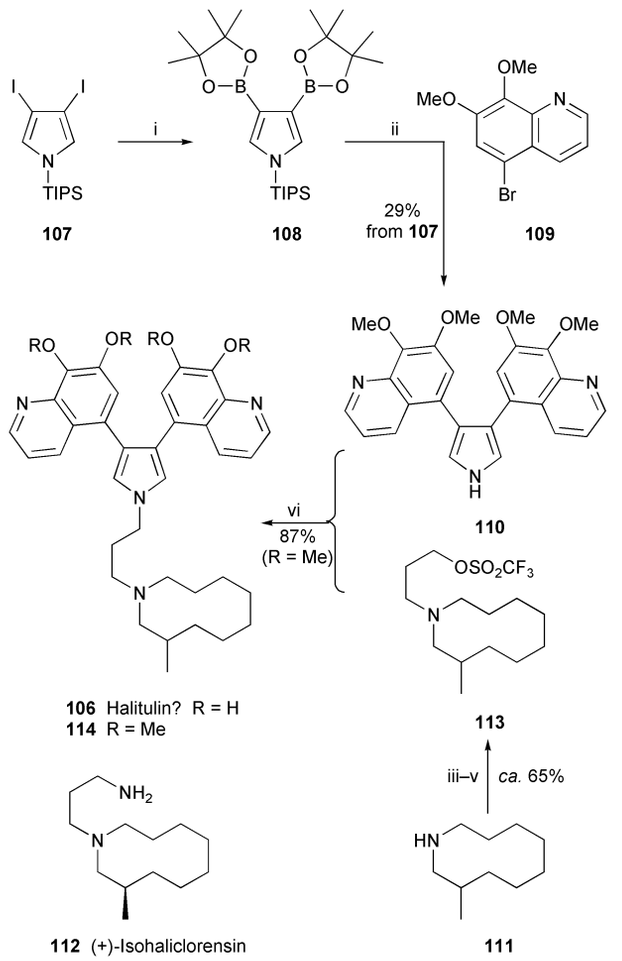


102 R = H
103 R = Br



104 Scolopendrine R = H
105 R = Me

Scheme 2.[66] Palladium(0)-mediated coupling of the 3,4-diiodopyrrole **107** with pinacolborane followed by Suzuki–Miyaura cross-coupling of the resulting bis(boronic ester) **108** with the bromoquinoline **109** produced the desilylated pyrrole **110** in an overall yield of 29% based on **107**. The structure of compound **110** was confirmed by single-crystal X-ray crystallography. The 3-methylazecane **111**, previously prepared by Banwell's group[67] during a synthesis of the putative alkaloid haliclorensin (originally thought to be **112**, but now known to be a diazacyclotetradecane[68]), was converted in three steps into the unstable trifluoromethanesulfonate **113**, which readily alkylated the potassium salt of pyrrole **110** to give halitulin tetramethyl ether **114** in 87% yield. Unfortunately, all attempts to cleave the

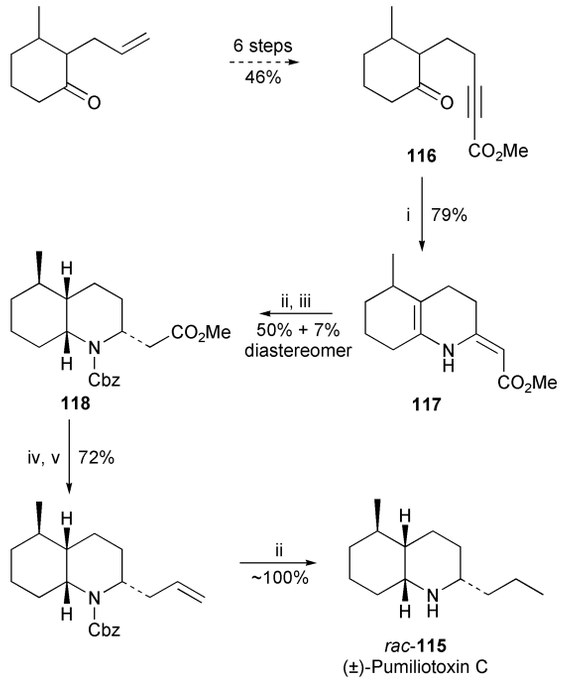


Scheme 2 *Reagents*: i, pinacolborane (6 equiv.), $PdCl_2(dppf)$ (14 mol%), Et_3N (10 equiv.), dioxane, 85 °C, 24 h; ii, **109** (1.4 equiv.), $Pd(PPh_3)_4$ (10 mol%), Na_2CO_3 (2 M, 10 equiv.), PhMe–MeOH (6 : 5), 65 °C, 24 h; iii, $H_2C{=}CHCO_2Me$, AcOH, reflux; iv, $LiAlH_4$, THF, 18 °C; v, Tf_2O, 2,6-di-*tert*-butyl-4-methylpyridine, CH_2Cl_2, 0 °C; vi, KHMDS + **110**, THF, 0 °C, then add **113**, 0 °C.

methyl ethers failed. However, detailed comparison of the spectroscopic data reported for halitulin with those obtained on **110** and **114** showed disturbing discrepancies in both the cyclic amine and the 3,4-bis(quinolin-5-yl)pyrrole portions of structure **106**. In the interim, Usuki *et al.* have reported an enantioselective synthesis of (*R*)-(+)-**112**[69] (renamed isohaliclorensin), the ^{13}C NMR data for which were claimed to be comparable with those for the corresponding substructure of halitulin. Final resolution of the disputed structure of halitulin must thus await complete total synthesis or re-collection and further spectroscopic investigation.

The fascinating aspect of the synthesis of decahydroquinoline 195A **115** (commonly known as pumiliotoxin C) by Mori and co-workers is the use of a nitrogen fixation process to introduce the nitrogen atom as an N-1 synthon (Scheme 3).[70] Nitrogen, bound in a "Ti–N complex" prepared from titanium(IV) tetrakis(isopropoxide), lithium metal and trimethylsilyl chloride in the presence of molecular nitrogen gas, was efficiently incorporated into the keto-alkyne precursor **116** to give the azabicyclic product **117** in 79% yield. Catalytic hydrogenation over palladium on carbon followed by protection of the basic nitrogen site yielded the *cis*-fused decahydroquinoline **118** as the major diastereomer (50%), probably because of the easier approach of the reagent from the precursor's convex face. The synthesis of the racemic target compound *rac*-**115**, characterised as the hydrochloride salt, was completed by standard methods as illustrated.

The use of tetra-*O*-pivaloyl-β-D-galactopyranosylamine **119** as a chiral auxiliary in enantioselective and stereochemically



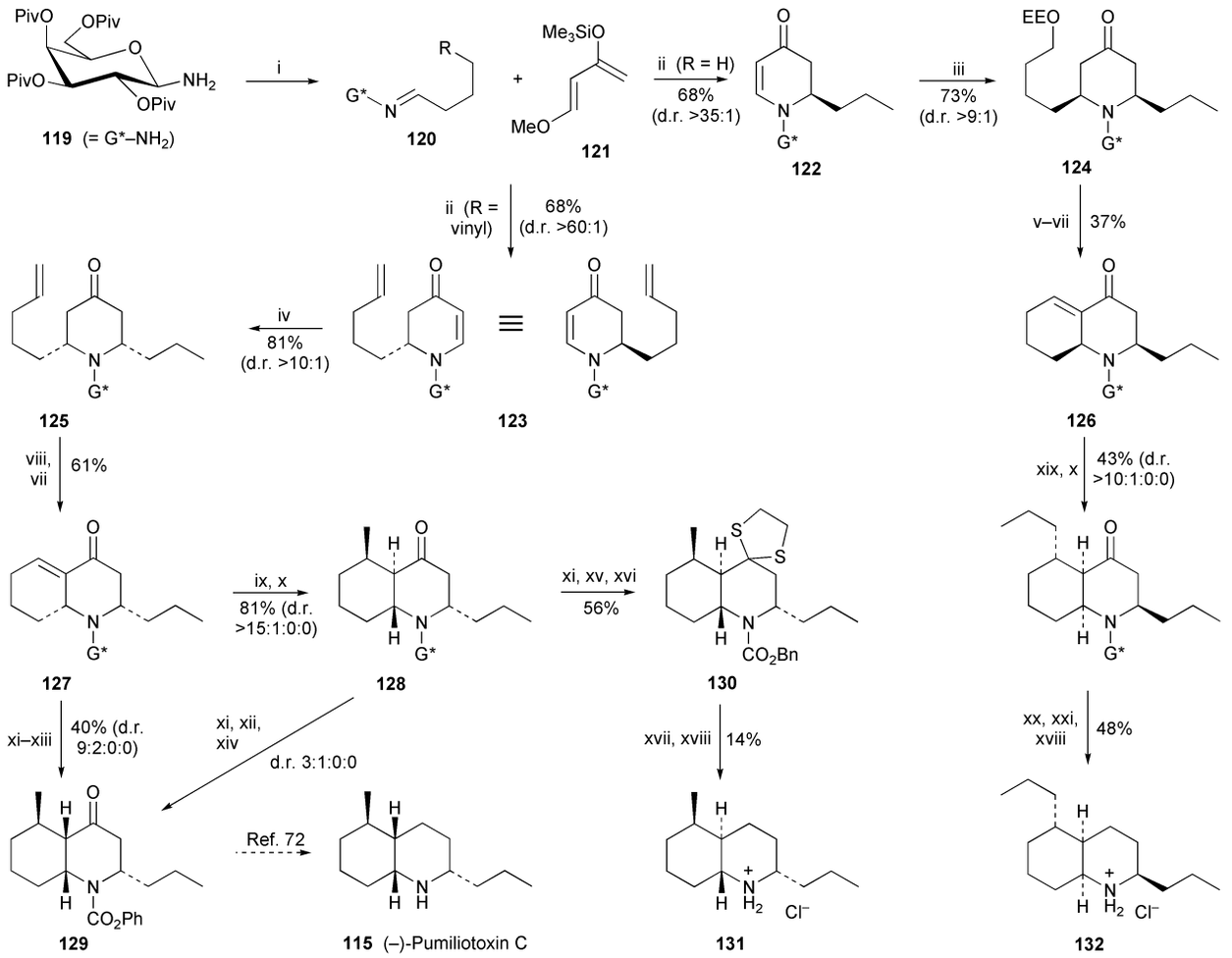
Scheme 3 *Reagents*: i, "Ti–N" complex [from $Li–Ti(OPr^i)_4–Me_3SiCl$ (10 : 1 : 15) + N_2], CsF, THF, −78 °C, then rt, 20 h; ii, H_2 (1 atm), 5% Pd/C, MeOH; iii, $ClCO_2Bn$, K_2CO_3, CH_2Cl_2, 0 °C to rt; iv, DIBAL-H, $PhCH_3$, −78 °C, 15 min, then MeOH, aq. NH_4Cl, rt; v, $Ph_3P{=}CH_2$, THF, rt.

complementary syntheses of several stereoisomers of pumiliotoxin C has been investigated by Kunz and co-workers.[71] Imines **120** formed from this precursor underwent highly diastereoselective annulation with the diene **121** in the presence of zinc(II) chloride to give the dihydropyridones **122** and **123** in 68% yield (Scheme 4). Diastereoselective conjugate addition of appropriate cuprates then yielded the 2,6-*cis*-disubstituted piperidinones **124** and **125** which, with suitable manipulation of the functionalised side chains, afforded octahydroquinolinones **126** and **127** possessing opposite absolute configurations at the C-2 and C-8a sites. Treating isomer **127** with lithium dimethylcuprate in the presence of trimethylsilyl chloride proceeded with excellent diastereoselectivity to give the expected (5*R*)-methyl product, but resulted in the unanticipated formation of a *trans*-fused decahydroquinoline **128**, apparently because the chiral auxiliary steered protonation of the intermediate enolate. To substantiate the involvement of the chiral auxiliary in **127**, exchange with a phenoxycarbonyl protecting group prior to conjugate addition yielded the expected *cis*-fused decahydroquinoline **129**, a compound previously prepared by Comins and Dehghani in their 1993 synthesis of (−)-pumiliotoxin C.[72] Epimerisation of the *N*-phenoxycarbonyl analogue of **128** to give **129** could also be rapidly effected upon treatment with triethylamine. Alternatively, replacing the auxiliary in **128** with a benzyloxycarbonyl protecting group before defunctionalising the ketone *via* the dithiolane intermediate **130** eventually completed the total synthesis of *trans*-4a-*epi*-pumiliotoxin C **131**, which was characterised by spectroscopy and X-ray crystallography as the laevorotatory hydrochloride salt. Finally, similar transformations performed on the octahydroquinolinone **126** as shown in the Scheme resulted in the synthesis of *cis*-4a-*epi*-perhydrodecahydroquinoline 219A hydrochloride **132**, which gave NMR spectroscopic data that agreed with those reported in the literature.

2 Quinazoline alkaloids

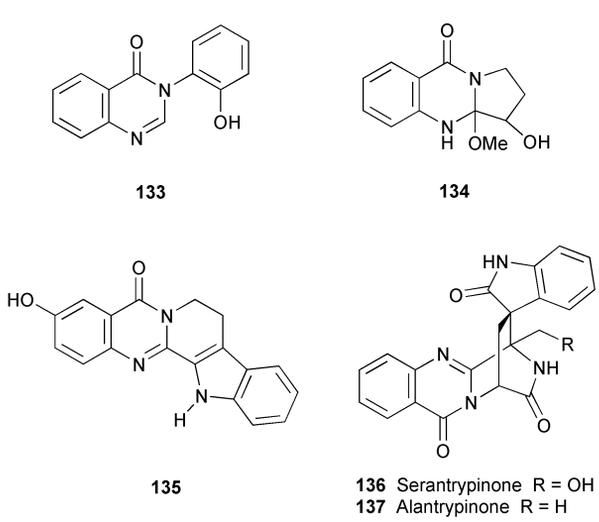
2.1 Occurrence, characterisation and biological activity

Few new quinazoline alkaloids were reported during the period under review. 3-(2-Hydroxyphenyl)quinazolin-4(3*H*)-one **133**



Scheme 4 *Reagents*: i, $R(CH_2)_3CHO$ (R = H, vinyl), 4 Å molecular sieves, pentane; ii, $ZnCl_2{\cdot}Et_2O$, THF, −20 °C; iii, $EtOCH(Me)O(CH_2)_4MgCl$, $CuBr{\cdot}SMe_2$, Me_3SiCl; iv, *n*-PrMgCl, CuCl, $BF_3{\cdot}Et_2O$, THF, −78 °C; v, PPTS, CH_2Cl_2; vi, TPAP, *N*-methylmorpholine-*N*-oxide, 4 Å molecular sieves, CH_2Cl_2, rt; vii, NaOH, dibenzo-18-crown-6, C_6H_6, reflux; viii, $K_2OsO_4{\cdot}2H_2O$ (cat.), $NaIO_4$, dioxane–H_2O; ix, Me_2CuLi, THF, −78 °C, then Me_3SiCl; x, Bu_4NF, THF, −20 °C; xi, aq. HCl, MeOH, rt; xii, $ClCO_2Ph$, aq. $NaHCO_3$; xiii, Me_2CuLi, $BF_3{\cdot}Et_2O$, THF, −78 °C; xiv, Et_3N, THF, 2 min; xv, $ClCO_2Bn$, aq. $NaHCO_3$; xvi, $HSCH_2CH_2SH$, $BF_3{\cdot}Et_2O$, CH_2Cl_2, 0 °C to rt; xvii, H_2, Raney Ni, Pr^iOH, rt; xviii, aq. HCl; xix, *n*-PrMgCl, $CuBr{\cdot}SMe_2$, THF, −78 °C, then **126**, Me_3SiCl; xx, NaHMDS, THF, −78 °C, then 2-$N(SO_2CF_3)_2$-5-Cl-pyridine, −78 °C to −20 °C; xxi, H_2, 5% Pd/C, Li_2CO_3, MeOH, rt.

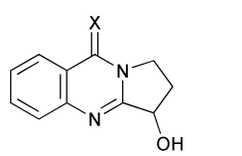
has been claimed as a new alkaloid from the roots of *Isatis indigotica*,[73] but in fact it was reported from the same source in 1997—by the same research group![74] The 3a-methoxy-substituted vasicinone analogue **134** (incorrectly named as 3-methoxyvasicinone) was isolated from leaves of *Eranthemum nervosum*, and its structure was established by electrospray mass spectrometry in combination with IR and NMR spectroscopy.[75] An unusual feature in the structural assignment of 3-hydroxy-rutaecarpine **135**, a new natural product isolated from leaves and twigs of *Leptothyrsa sprucei* (Rutaceae), was the use of gradient ^1H–^{15}N HMBC NMR spectroscopy at natural nitrogen abundance for establishing some of the skeletal connectivities.[76] The more complex peptide-derived alkaloid (−)-serantrypinone **136**, obtained from mycelial extracts of the fungus *Penicillium thymicola* IBT 5891, is a hydroxylated congener of the known spiroquinazoline alantrypinone **137**, and effectively arises by replacing an alanine residue with serine.[77] The similarity in the CD spectra of the two metabolites suggested that serantrypinone and alantrypinone share the same (3*R*,14*R*, 17*S*) absolute configuration.



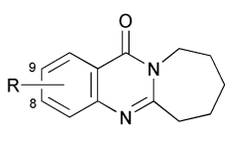
The alkaloids of *Adhatoda vasica*, an important plant in Ayurvedic medicine, are principally derivatives of vasicine **138** and vasicinone **139**. Recent tests on the unseparated alkaloid fraction showed anti-inflammatory activity in the HET-CAM assay approximately equal to that of hydrocortisone.[78] Several synthetic tricyclic vasicinone analogues of general structure **140** proved to be effective bronchodilators in *in vitro* tests with guinea pig tracheal chain pre-contracted with acetylcholine, the most active compound being the 8,9-dimethoxy derivative.[79] Isaindigotone **141**, a naturally occurring vasicinone analogue isolated from *Isatis tinctoria*, and seven synthetic derivatives displayed a range of biological effects related to anti-inflammatory activity, including inhibition of superoxide, nitric oxide and prostaglandin-E_2 production.[80] Isaindigotone itself was a superior scavenger of superoxide generated in the

hypoxanthine/xanthine oxidase system (IC_{50} 42.2 nM), no doubt because of its free phenolic group, whereas derivatives **142** and **143** were, respectively, the most effective inhibitors of PGE_2 (IC_{50} 80 nM) and nitrite (1.8 μM) accumulation in mouse macrophages.

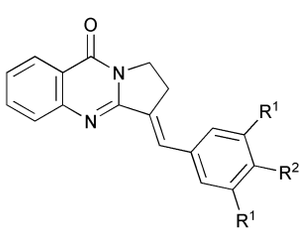
The efficient extraction and quantitative analysis of tryptanthrin **144**, the anti-inflammatory principle of *Isatis tinctoria* (woad), have been reproducibly achieved by accelerated solvent extraction (ASE) in a commercial instrument followed by HPLC with electrospray-MS detection.[81] Analysis of over 70 woad samples from different sources indicated a highly variable tryptanthrin content of $0.56–16.74 \times 10^{-3}$ % by mass. In further pharmacological developments, tryptanthrin has been found to ameliorate artificially induced colitis in mice, at the same time suppressing weight loss, tissue damage and subsequent mortality;[82] this relatively non-toxic alkaloid thus has potential for treating inflammatory bowel disease. It also effected cell differentiation and apoptosis of both monocytic (U-937) and promyelocytic (HL-60) leukaemia cells,[83] and suppressed the growth of azoxymethane-induced intestinal tumours in F344 rats.[84] Tryptanthrin has shown activity as an antitrypanosomal agent against *Trypanosoma brucei*; furthermore 11 synthetic analogues were also active, the most potent compounds, **145** (EC_{50} 0.82 μM) and **146** (EC_{50} 0.4 μM), being substantially more effective than the parent alkaloid (EC_{50} 23.0 μM).[85] Another protozoan parasite, *Leishmania donovani*, was sensitive to no fewer than 27 synthetic analogues of tryptanthrin, 13 of the compounds displaying IC_{50} values of less than 100 ng ml^{-1} as well as being more toxic to the parasite than to mammalian cell lines; the most active compounds were **147** and **148** (IC_{50} 16 ng ml^{-1}).[86] (For comparison, the clinically prescribed antileishmanial agent amphotericin has an IC_{50} value of 416 ng ml^{-1}). Structure–activity relationships revealed a reasonable correlation between activity and some calculated and measured molecular properties such as molecular density, LUMO energies and redox potentials (determined by cyclic voltammetry), the implication of the latter two being that electron transfer involving the carbonyl groups might be a crucial factor in the mechanism of action of the compounds.



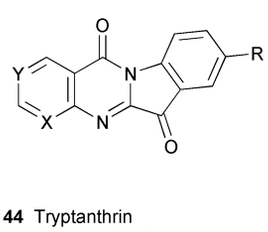
138 Vasicine X = 2H
139 Vasicinone X = O



140

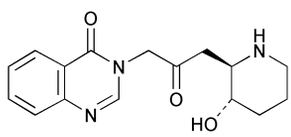


141 Isaindigotone
R^1 = OMe; R^2 = OH
142 R^1 = H; R^2 = F
143 R^1 = H; R^2 = OAc

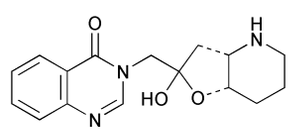


144 Tryptanthrin
X = Y = CH; R = H
145 X = Y = CH; R = NO_2
146 X = N; Y = CH; R = Br
147 X = CH; Y = N; R = $CH(OMe)_2$
148 X = N; Y = CH; R = I

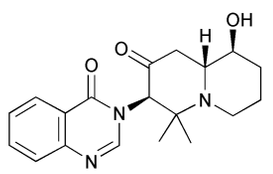
The revival of interest in the antimalarial alkaloid febrifugine **149** seems set to continue. A brief review by Takeuchi and Harayama includes useful information on the history, structure determination, synthesis, biological activity and structure–activity relationships of the alkaloid and its isomer isofebrifugine **150**.[87] However, the unacceptable emetic effects of these two compounds have prevented their clinical use as antimalarial agents. In attempts to find analogues with improved properties, Oshima and co-workers investigated the biological activity of **151** and **152**, products of condensation of the parent alkaloids with acetone, as well as eleven other synthetic derivatives of **149** and **150** and a further fifteen analogues of **151** and **152**.[88] All compounds exhibited good *in vitro* antimalarial activity against *P. falciparum*, though none were as potent as febrifugine itself (EC_{50} 7.0×10^{-10} M). Additionally, all compounds were cytotoxic to FM3A mouse mammary cells, but only four of them, *viz*. **153**–**156**, were significantly more selective (> 500 : 1) towards the parasite than towards the mammary cells, **156** being a staggering 3100 times as selective. These findings prompted *in vivo* studies of the antimalarial efficacy of the more accessible racemates of **153**–**155** in mice infected with *P. berghei*. The first two proved to be more potent (ED_{50} 1.3 and 2.9 μmol kg^{-1}) than chloroquine or artemisinin (ED_{50} 4.7 and 17.7 μmol kg^{-1}), and only slightly less effective than febrifugine (ED_{50} 1 μmol kg^{-1}). When injected intraperitoneally, they also prolonged the survival rate of infected mice. Thus this study appears to have revealed exciting new lead compounds for the development of novel antiplasmodial drugs.



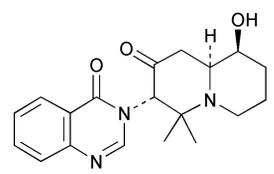
149 (+)-Febrifugine



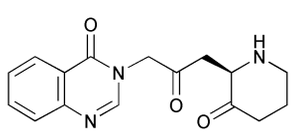
150 (+)-Isofebrifugine



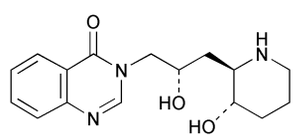
151



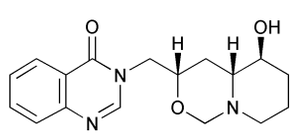
152



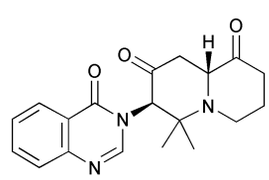
153



154



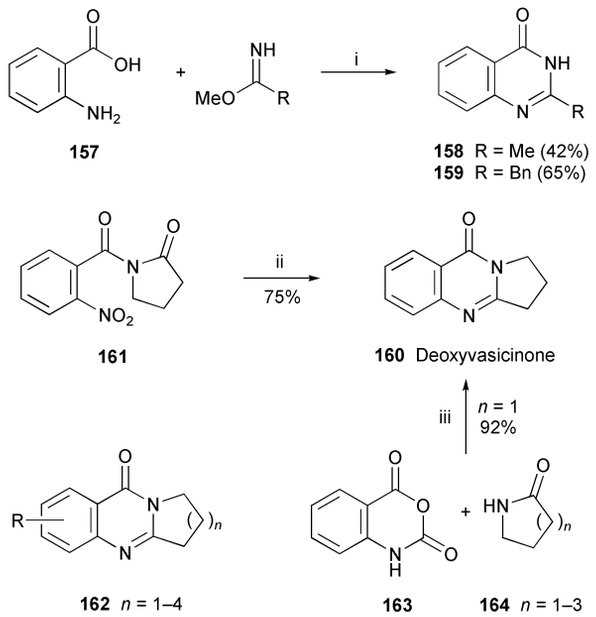
155



156

2.2 Synthesis and other chemical studies

Three simple syntheses of quinazoline alkaloids are illustrated in Scheme 5. A straightforward condensation between anthranilic acid **157** and various imidates of general formula RC(=NH)OMe in boiling methanol produced a range of 2-substituted quinazolin-4(3*H*)-ones, among them the alkaloids 2-methylquinazolin-4(3*H*)-one **158** (42%) and glycosminine **159** (65%).[89] A short synthesis of deoxyvasicinone **160** showcasing the reductive cyclisation of *N*-(2-nitrobenzoyl)-pyrrolidin-2-one **161** with carbon monoxide in DMF in the presence of triethylamine and a catalytic amount of selenium was also applied to the synthesis of substituted and six- to eight-membered ring C analogues **162** in yields that were generally above 75%.[90] The shortest synthesis of all, entailing reaction of isatoic anhydride **163** with lactams **164** (n = 1–3) under solvent-free conditions in a microwave oven, gave deoxyvasicinone in 92% yield within 6 minutes, and was also used for preparing the six- and seven-membered ring C congeners **162** (R = H; n = 2, 3) in 90% and 89% yields, respectively.[91]

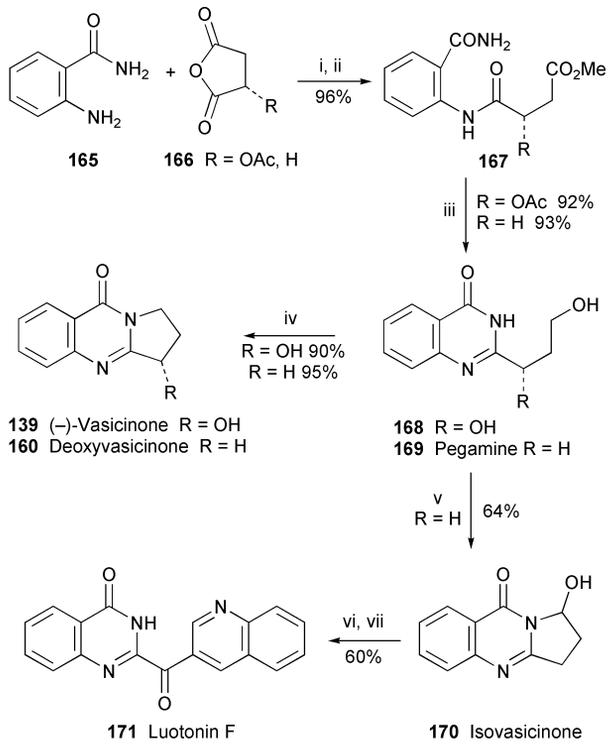


Scheme 5 *Reagents*: i, MeOH, 25 °C, 30 min, then 80 °C, 6 h; ii, CO (5 atm), Se (5 mol%), NEt_3 (1 equiv.), DMF, 100 °C, 10–20 h; iii, microwave irradiation (450 W), 6 min.

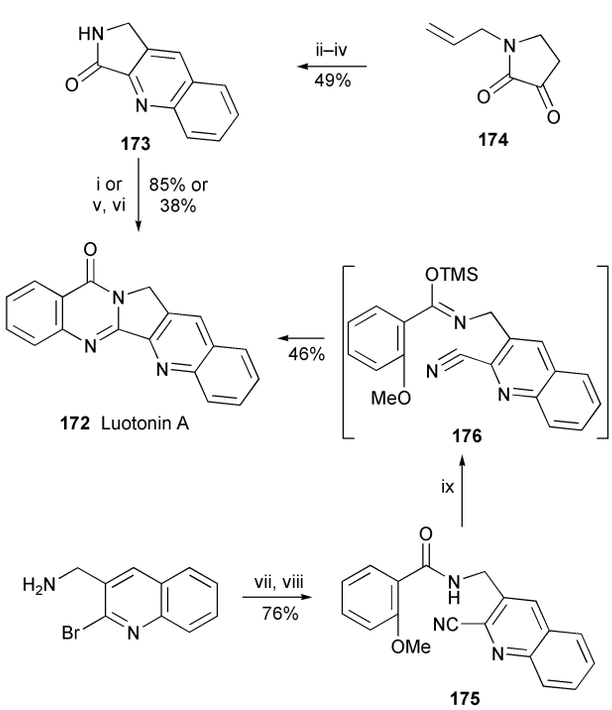
Treatment of anthranilamide **165** with the succinic anhydrides **166** and esterification of the intermediate succinanilic acids produced esters **167**, chemoselective reduction of which with lithium aluminium hydride followed by aqueous work-up smoothly yielded the quinazolinones **168** and **169** (Scheme 6).[92] The latter is a natural product, pegamine, and this is the first report of its synthesis (in 89% overall yield from **165**). Both **168** and **169** underwent further ring closure under Mitsunobu conditions to give (−)-vasicinone **139** and deoxyvasicinone **160**. The (*S*) absolute configuration of (−)-vasicinone was established by NMR spectroscopic analysis of its Mosher esters, a technique that also indicated its enantiomeric excess to be 97–98%. In an extension of this work, pegamine **169** was oxidised with pyridinium chlorochromate to give the masked aldehyde isovasicinone **170** (64%), Friedländer condensation of which with 2-aminobenzaldehyde followed by benzylic oxidation of the resulting quinoline completed a synthesis of luotonin F **171**, an anti-tumour alkaloid originally obtained from *Peganum nigellastrum*.[93]

The current popularity of luotonin A **172** as a synthetic target is a consequence of its cytotoxicity towards murine leukemia P-388 cells. A further three syntheses of this alkaloid were published during the review period. The key steps are shown in Scheme 7. Adaptation of the microwave synthesis described above entailed heating isatoic anhydride with the known pyrroloquinoline **173** under solvent-free conditions in a microwave oven to give luotonin A in 85% yield within seven minutes.[91] Alternatively, the same pyrroloquinoline **173**, prepared in a novel manner by Friedländer synthesis from 1-allylpyrrolidine-2,3-dione **174** and 2-aminobenzaldehyde followed by removal of the *N*-allyl protecting group, was acylated with 2-nitrobenzoyl chloride, after which reductive cyclisation completed the synthesis of **172**.[94] In the third route, *in situ* conversion of the amide **175** into the *O*-silylimidate **176** in a sealed tube at 150 °C preceded spontaneous intramolecular hetero Diels–Alder reaction to give luotonin A in 46% yield.[95]

Much of the recent synthetic activity aimed at the synthesis of febrifugine analogues has centred on the stereoselective construction of the piperidinol moiety, as, for instance, in the asymmetric synthesis of model 2-substituted piperidin-3-ols such as **177** by Enders *et al*.[96] The ongoing researches of Kobayashi have concentrated on the ring opening of racemic[97] and enantiomerically pure[98] semicyclic *N*,*O*-acetals with nucleophiles in the presence of Lewis acid catalysts. The systematic



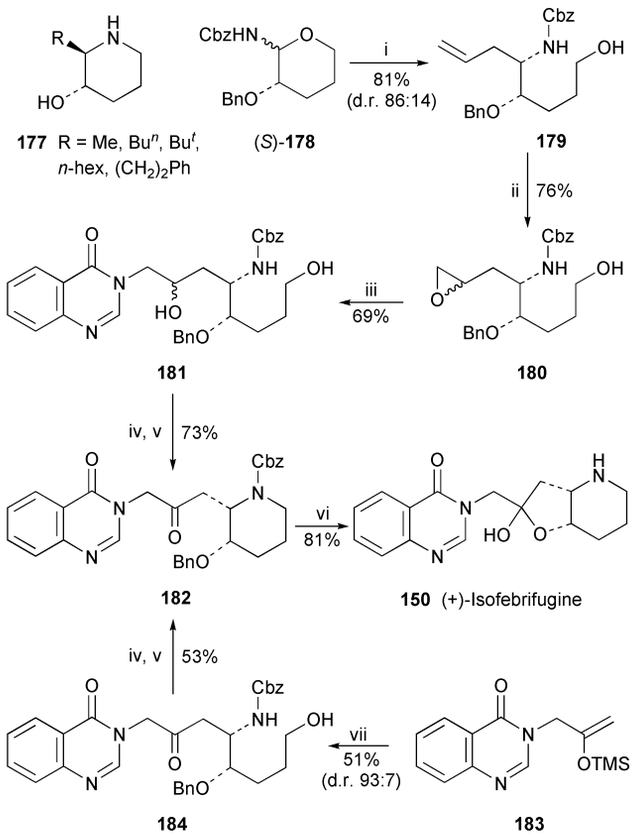
Scheme 6 *Reagents*: i, Et_2O–C_6H_6–dioxane (2 : 2 : 1), rt, 2 h; ii, CH_2N_2, Et_2O, 0 °C to rt; iii, $LiAlH_4$, THF, 0 °C to rt, then aq. NH_4Cl, evaporation *in vacuo*; iv, PPh_3, $EtO_2CN{=}NCO_2Et$, THF, rt; v, PCC, 4 Å molecular sieves, CH_2Cl_2, rt; vi, 2-aminobenzaldehyde, KOH, EtOH, reflux; vii, CrO_3, H_5IO_6, DMF, rt.



Scheme 7 *Reagents*: i, isatoic anhydride **163**, microwave irradiation (450 W), 7 min; ii, 2-aminobenzaldehyde, *p*-TsOH (cat.), PhMe, reflux (Dean–Stark apparatus); iii, $PdCl_2$ (5 mol%), PPh_3 (20 mol%), DMF–H_2O (4 : 1), reflux; iv, HCl (6 M), reflux; v, NaH, THF, 60 °C, then 2-nitrobenzoyl chloride, 0 °C to 50 °C; vi, Fe, AcOH–EtOH (1 : 1), reflux; vii, *o*-anisic acid, bis(2-oxo-3-oxazolidinyl)phosphinic chloride, Et_3N, CH_2Cl_2; viii, $Pd_2(dba)_3$, dppf, CuCN, Et_4N^+ CN^-, dioxane, reflux; ix, TMSCl, $ZnCl_2$, Et_3N, PhMe, 150 °C (sealed tube).

model studies performed by these workers culminated in the diastereoselective transformation of (*S*)-**178** into **179**, which proceeded in 81% yield and a diastereomeric ratio of 86 : 14 (Scheme 8). This compound was converted *via* the 1 : 1 diastereo-

meric mixture of epoxides **180** into the 3-substituted quinazolin-4-one **181**, oxidation and intramolecular reductive amination of which yielded the protected isofebrifugine analogue **182**. The same workers had previously converted racemic **182** into (±)-isofebrifugine[99] (*cf.* Ref. 35*i*); similar hydrolysis of the enantiomer (+)-**182** with boiling hydrochloric acid completed the synthesis of (+)-isofebrifugine **150**. The less efficient alternative reaction of (3*S*)-**178** with the silyl enol ether **183** was mediated by trimethylsilyl triflate to yield **184** (51%, *syn* : *anti* ratio 93 : 7), which was also converted into the isofebrifugine precursor **182** as illustrated.



Scheme 8 *Reagents*: i, $H_2C{=}CHCH_2SiMe_3$ (2 equiv.), TMSOTf (0.2 equiv.), MeCN, −20 °C; ii, MCPBA, CH_2Cl_2, rt; iii, quinazolin-4-ol, KOH (0.2 equiv.), MeOH, reflux; iv, Dess–Martin reagent, CH_2Cl_2, rt; v, Et_3SiH, TMSOTf, MeCN, 0 °C; vi, HCl (6 M), reflux, 2 h; vii, (3*S*)-**178**, **183** (2 equiv.), TMSOTf (2.5 equiv.), MeCN, rt.

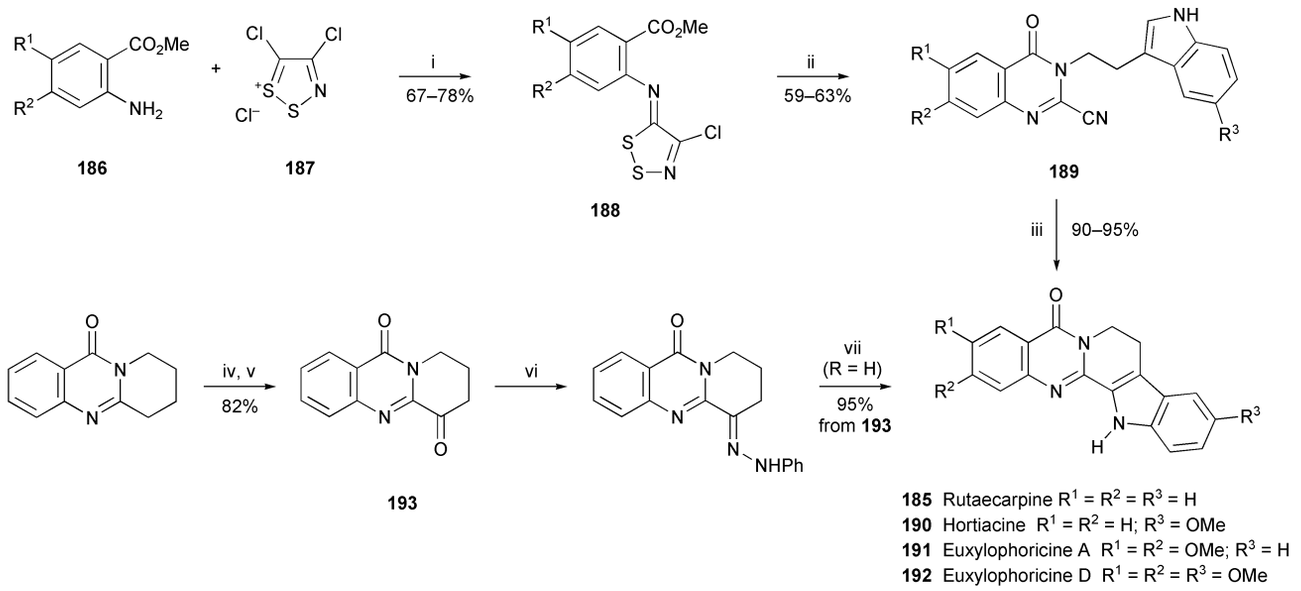
The short synthesis of rutaecarpine **185** and related alkaloids shown in Scheme 9 commenced with reaction of anthranilate esters **186** with 4,5-dichloro-1,2,3-dithiazolium chloride (Appel's salt) **187** to produce the imines **188**, which reacted with substituted tryptamines to yield the 2-cyanoquinazolin-4-ones **189**.[100] Simply heating these intermediates with trifluoroacetic anhydride and hydrogen chloride gas completed syntheses of rutaecarpine **185**, hortiacine **190**, euxylophoricine A **191** and euxylophoricine D **192** in 90–95% yields. Also shown in the Scheme is another short synthesis of rutaecarpine, the key step of which was a Fischer indole synthesis using the readily prepared quinazolinedione **193**.[101]

The reaction of benzoxazine **194** with methyl anthranilate followed by thermal recyclisation, although rapidly giving the quinazolin-4-one **195** in a poor overall yield of 4.7%, was featured in a short new synthesis of circumdatin F **196** (Scheme 10).[102] Electrophilic bromination of **195** yielded **197** as a mixture of two diastereomers, probably arising from restricted rotation around the N–aryl bond. Conversion of **197** into the amine **198** followed by thermally-induced lactam formation completed the synthesis of the target alkaloid **196**. Similarly, acid-induced conversion of the bromoacetamide **199** into the corresponding quinazolinone followed by treatment with ammonia yielded sclerotigenin **200** (16% overall yield), while heating **199** and the methyl homologue **201** in DMF at reflux produced the oxygen analogues of sclerotigenin and circumdatin, **202** and **203**, respectively, in 20% yield.

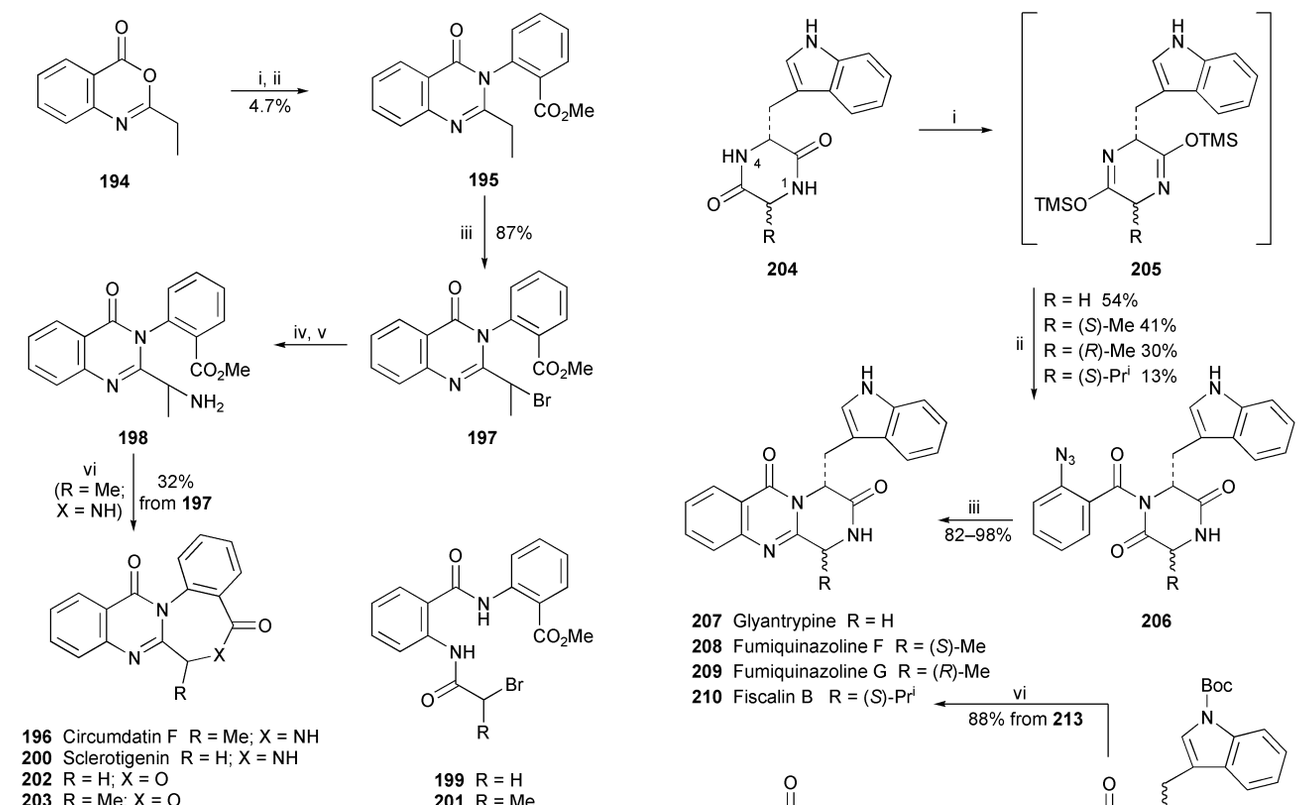
Avendaño and co-workers have investigated the acylation of a range of diketopiperazines **204**, prepared by standard methods from the respective *N*-Boc dipeptides, with 2-azidobenzoyl chloride *via* the silyl imidates **205** (Scheme 11).[103] With the glycine derivative of **204** (*i.e.*, R = H), selective monoacylation on *N*(4) to give **206** was ascribed to a boat-like conformation of the silylated intermediate, with the indolyl substituent folding in such a way that *N*(1) was blocked. Selectivity was also good with the (*S*)-alanine derivative of **204** [R = (*S*)-Me], but less impressive with the (*R*)-alanine and (*S*)-valine analogues [R = (*R*)-Me and (*S*)-Pr^i], which gave almost equal amounts of the *N*(1)-acylated products. All of the acylated products **206** could be cyclised by an intramolecular Staudinger reaction upon treatment with tributylphosphine to complete syntheses of (−)-glyantrypine **207**, (−)-fumiquinazoline F **208**, fumiquinazoline G **209** and fiscalin B **210**, respectively. In an alternative synthesis of fiscalin B, treatment of the quinazolinedione **211** with lithium hexamethyldisilazide and *N*-Boc-3-indolylmethyl bromide gave a mixture of the 1,4-*syn*- and *anti*-disubstituted products **212** (46%) and **213** (31%). Deprotection of the minor isomer was accomplished with boron tribromide to give fiscalin B in 88% yield.[104] The *syn* preference in this example was somewhat surprising, since alkylation of the methyl analogue of **211** gave mainly 1,4-*anti*-disubstituted products,[104,105] a feature that was also borne out by SCF-MO calculations.[106] This research group has also reported a variety of model studies on the formation of the pyrazino[2,1-*b*]-quinazoline-3,6-dione ring system *via* *N*-acyliminium ion intermediates.[107,108]

The first reported syntheses of three related pyrazino[2,1-*b*]-quinazoline-3,6-dione alkaloids, verrucine A **214**, verrucine B **215** and anacine **216**, have been accomplished by exploiting peptide assembly on Sasrin resin (Scheme 12).[109] For example, the resin-bound L-glutamine derivative **217** was sequentially condensed with anthranilic acid and Fmoc-protected L-phenylalanine chloride to give the resin-bound tripeptide **218**. Intramolecular dehydration followed by treatment with piperidine, a general procedure developed by Wang and Ganesan[110] and optimised by He and Snider[111] (*cf*. Ref. 35*j*), afforded amidine **219**. Cyclisation with concomitant detachment from the resin was effected by overnight heating in a mixture of acetonitrile and 1,2-dichloroethane to give *N*-tritylverrucine A **220** in 17% overall yield from **217**; only 0.8% of the corresponding 1,4-*anti*-disubstituted isomer was isolated. The removal of the trityl group was achieved reductively with triethylsilane in trifluoroacetic acid to give (+)-verrucine A **214**, the specific rotation of which was much greater than for the natural product isolated from its fungal source. Similar reaction sequences employing D-phenylalanine and L-leucine afforded (+)-verrucine B **215** and (+)-anacine **216**, respectively, in overall yields of 14.5% and 9.3% based on **217**. The absolute configuration of the former, not assigned when it was originally isolated, has thus been established unambiguously. The originally proposed benzodiazepine structure **221** for anacine, revised to **216** after the isolation of the verrucines, has also been unequivocally refuted. It is worth noting that verrucine B and anacine underwent aerial oxidation in solution, the former yielding the hydroxy product **222**. This type of reaction may explain the origin of the hydroxy group in related pyrazinoquinazoline alkaloids.

The advanced intermediate **223**, previously used by Snider and Zeng in a synthesis of the *Aspergillus* metabolite fumiquinazoline A[112] (*cf.* Ref. 35*k*), has been transformed into another two complex fumiquinazolines by the same workers (Scheme 13).[113] Condensation of **223** with a selenocysteine



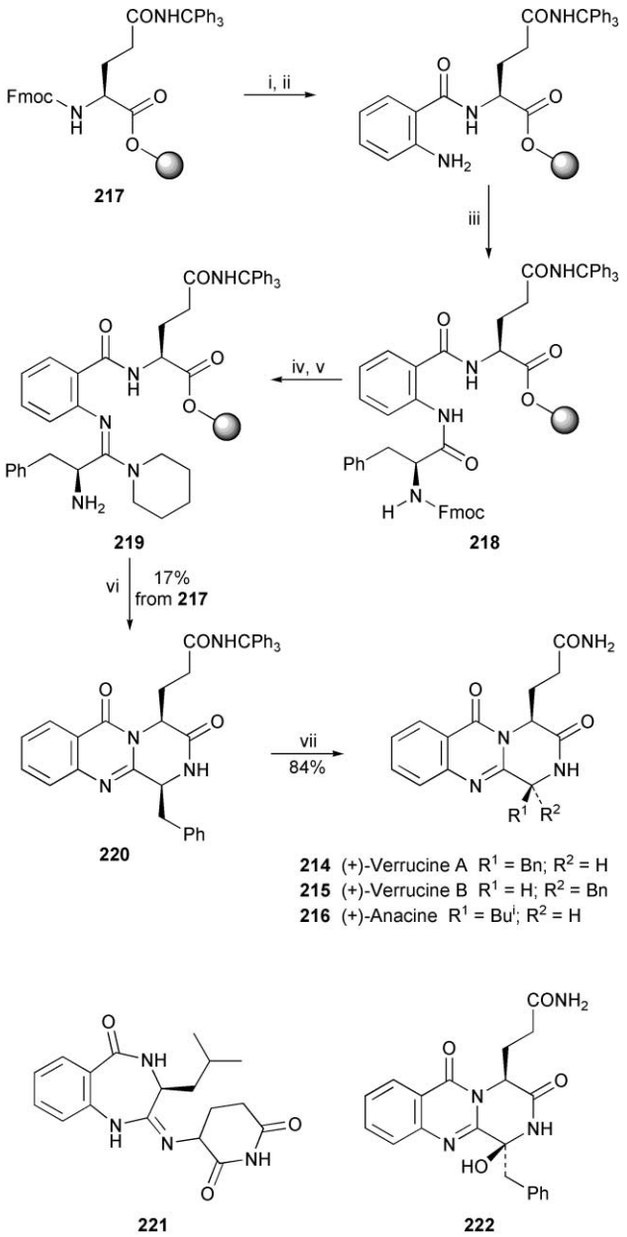
Scheme 9 *Reagents*: i, pyridine, CH_2Cl_2, rt, 2–3 h; ii, CH_2Cl_2, rt, 24–31 h; iii, TFAA, HCl(g), 120–130 °C; iv, PhCHO, Ac_2O, reflux; v, O_3, CH_2Cl_2, −78 °C, then Me_2S; vi, $PhNHNH_2$, EtOH; vii, PPA, 180 °C.



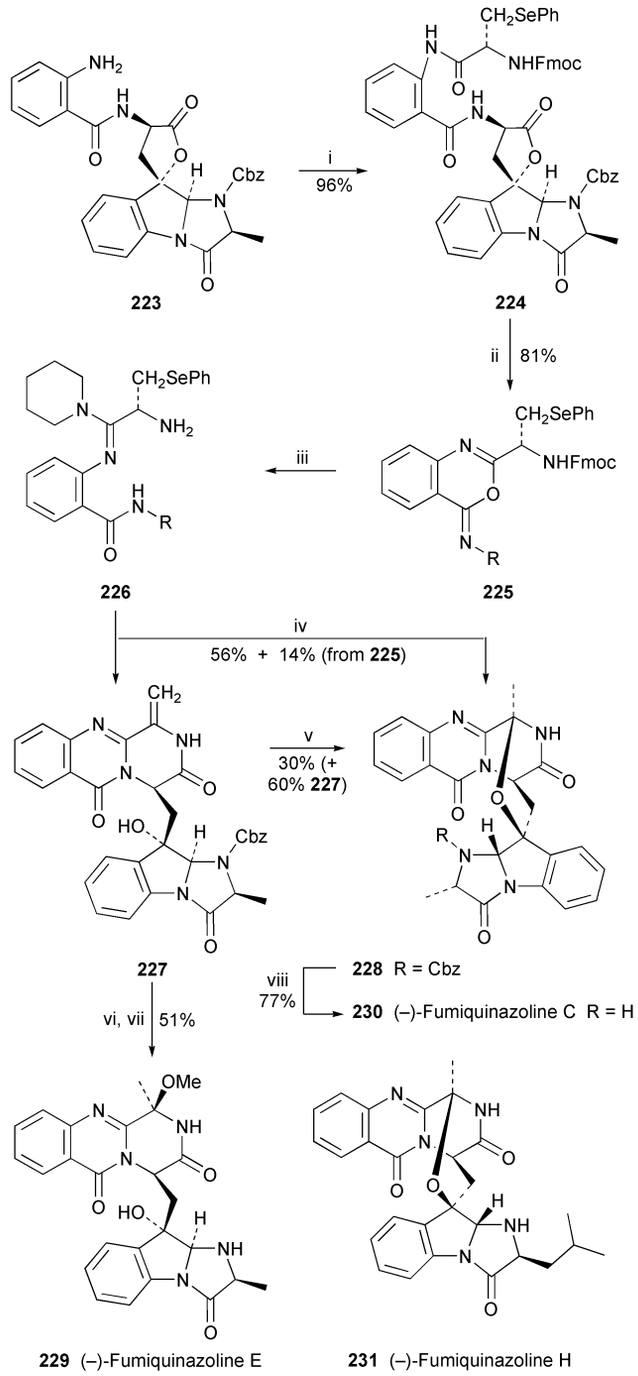
Scheme 10 *Reagents*: i, methyl anthranilate, AcOH, reflux; ii, DMF, reflux; iii, Br_2, NaOAc, HOAc, 60 °C; iv, NaN_3, H_2O–Pr^iOH (1 : 5), reflux; v, H_2 (220 psi), 5% Pd/C, EtOH, rt; vi, MeCN, reflux.

Scheme 11 *Reagents*: i, TMSCl (2 equiv.), Et_3N (2 equiv.), CH_2Cl_2, rt; ii, 2-$N_3C_6H_4COCl$ (1.1 equiv.), CH_2Cl_2, rt; iii, Bu_3P, PhMe, rt; iv, LiHMDS (10 equiv.), THF, −78 °C, 10 min; v, *N*-Boc-3-indolylmethyl bromide (2 equiv.), THF, −78 °C; vi, BBr_3, CH_2Cl_2, −78 °C.

derivative, (*R*)-FmocNHCH(CH_2SePh)CO_2H, yielded the quinazoline precursor **224**, subjection of which to the Ganesan cyclisation procedure (*cf*. Scheme 12) sequentially afforded the benzoxazine and amidine intermediates **225** and **226**. Simply heating crude **226** in acetonitrile–acetic acid (25 : 1) at reflux set off a cascade of reactions that culminated in the formation of a mixture of **227** and its oxygen-bridged isomer **228** in yields of 56% and 14%, respectively, based on **225**. Compound **227** could be partially converted into **228** by further heating, and recovered **227** could be recycled. Finally, standard transformations on both products completed the first reported total syntheses of (−)-fumiquinazolines E **229** and C **230**, respectively. A similar set of reactions on the appropriate analogue of **224**, designed to produce (−)-fumiquinazoline H **231**, was less easily accomplished, and required replacement of the Cbz protecting group by Fmoc in the benzoxazine equivalent of **225** before satisfactory cyclisation could be effected.



Scheme 12 *Reagents*: i, 20% piperidine in DMF, 15 min, then repeat; ii, EDC (13.4 equiv.), anthranilic acid (12.1 equiv.), DMF or NMP, rt, 19 h; iii, Fmoc-L-Phe-Cl (5.1 equiv.), pyridine (29 equiv.), CH_2Cl_2, rt, 13 h, then workup, then repeat in DMF; iv, PPh_3 (12 equiv.), I_2 (11.1 equiv.), $EtNPr^i_2$ (25 equiv.), CH_2Cl_2, rt, 15 h; v, 20% piperidine in CH_2Cl_2, rt, 30 min; vi, MeCN–$(CH_2Cl)_2$ (1 : 1), reflux overnight; vii, TFA–Et_3SiH–CH_2Cl_2 (2 : 2 : 1), rt, 15 min.



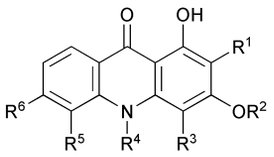
Scheme 13 *Reagents*: i, (*R*)-FmocNHCH(CH_2SePh)CO_2H, EDAC, MeCN; ii, PPh_3, Br_2, $EtNPr^i_2$; iii, piperidine (10 equiv.), EtOAc, rt, 10 min; iv, MeCN–HOAc (25 : 1), reflux, 2 h; v, MeCN–HOAc (100 : 1), reflux, 2 h; vi, HCl (0.2 M), MeOH, 25 °C; vii, H_2 (1 atm), Pd/C, 30 min; viii, H_2 (4 atm), Pd/C, 30 h.

3 Acridone alkaloids

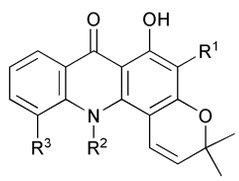
Known acridone alkaloids isolated from new sources during the period covered by this review include 1-hydroxy-3-methoxy-*N*-methylacridone **232** from *Feronia limonia* (= *F. elephantum*),[114] 5-hydroxynoracronycine **233** from *Swinglea citrumelo*,[115] and citrusinine-II **234**, glycocitrine-IV **235** and 5-hydroxynoracronycine from *S. glutinosa*.[116] The last-named species was also the source of a novel alkaloid, 1,3,5-trihydroxy-2,8-diprenyl-*N*-methylacridone **236**, which is one of the very few acridone alkaloids to bear a substituent at C-8, and the only one to have a prenyl substituent at this position.

The biological activities of acridone alkaloids continue to attract interest. Citrusinine-II **234**, citrusinine-I **237**, severifoline **238** and buxifoliadine-H **239**, isolated from the root bark of *Severinia buxifolia*, were cytotoxic towards nasopharyngeal carcinoma KB cells (ED_{50} 0.09–0.82 μg ml^{-1}); **237** and **239** were also marginally active against hepatoma 3B cells (ED_{50} 6.6 and 5.2 μg ml^{-1}), whereas **237**, buxifoliadine-B **240** and buxifoliadine-D **241** were cytotoxic towards colon carcinoma colo-205 cells (ED_{50} 0.58–6.3 μg ml^{-1}).[28] The four alkaloids from *S. glutinosa* mentioned in the previous paragraph, and glycocitrine-IV in particular, were cytotoxic towards human fibroblast (HeLa) cells, and also showed antiplasmodial activity against both chloroquine-sensitive and -resistant strains of *Plasmodium falciparum*.[116] Three acridones from the African medicinal plant *Fagara macrophylla*, *viz.* 1-hydroxy-3-methoxy-*N*-methylacridone **232**, arborinine **242** and xanthoxoline **243**, showed potent antifeedant activity against final stage larvae of the lepidopteran pest *Spodoptera frugiperda*, but only xanthoxoline was effective against *S. littoralis*.[117]

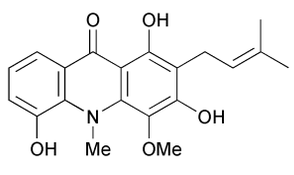
Acronycine **244** is a promising lead compound for the development of novel antitumour agents. Recent progress in



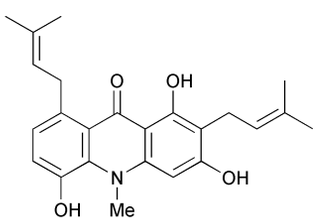
232 $R^1 = R^3 = R^5 = R^6 = H$; $R^2 = R^4 = Me$
234 Citrusinine-II $R^1 = R^2 = R^6 = H$; $R^3 = OMe$; $R^4 = Me$; $R^5 = OH$
237 Citrusinine-I $R^1 = R^6 = H$; $R^2 = R^4 = Me$; $R^3 = OMe$; $R^5 = OH$
239 Buxifoliadine-H $R^1 = R^2 = H$; $R^3 = R^5 = OMe$; $R^4 = Me$; $R^6 = OH$
240 Buxifoliadine-B $R^1 = R^3 =$ prenyl; $R^2 = Me$; $R^4 = R^6 = H$; $R^5 = OH$
242 Arborinine $R^1 = OMe$; $R^2 = R^4 = Me$; $R^3 = R^5 = R^6 = H$
243 Xanthoxoline $R^1 = OMe$; $R^2 = Me$; $R^3 = R^4 = R^5 = R^6 = H$



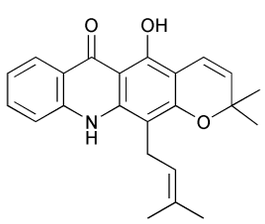
233 $R^1 = H$; $R^2 = Me$; $R^3 = OH$
238 Severifoline $R^1 =$ prenyl; $R^2 = R^3 = H$



235 Glycocitrine-IV



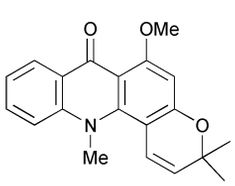
236



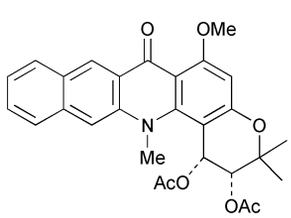
241 Buxifoliadine-D

the synthesis and evaluation of novel acronycine analogues has been summarised in two timely reviews, both of which highlight the unique pharmacological profile of the derivative S23906-1 **245** when tested on aggressive human lung, ovarian and colon cancer xenografts in nude mice.[118,119] Details of the experimental testing of this potent new anticancer agent and its probable mode of action were described in two full publications.[120,121]

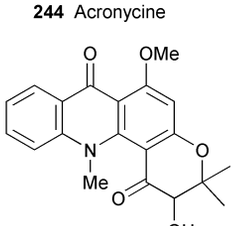
1-Oxo-2-hydroxy-1,2-dihydroacronycine **246**, easily prepared by permanganate oxidation of acronycine, has proved to be a useful precursor for preparing biologically active nitrogen-containing derivatives both by replacement of the methoxy group and by further manipulation of the pyran ring; it has also been transformed into the cytotoxic furanone derivative **247** by treatment with sodium hydroxide in methanol.[122] Isoacronycine **248**, synthesised from 1,3-dihydroxy-*N*-methylacridone and prenal, has itself been transformed into various derivatives by functionalisation of the double bond in the pyran ring, but only



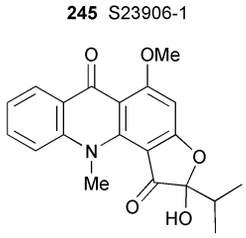
244 Acronycine



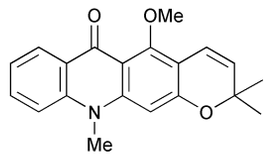
245 S23906-1



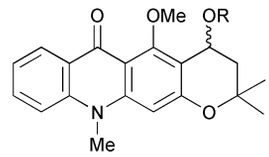
246



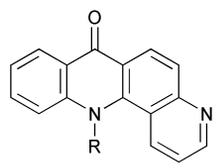
247



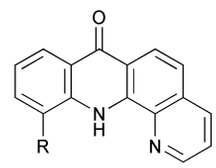
248 Isoacronycine



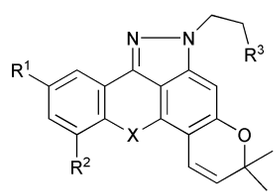
249 R = H
250 R = Ac



251 R = H, Me



252 R = NO_2, NH_2



253 X = O, S, NMe; R^1, R^2 = H, OMe; R^3 = OH, OSO_2Me, NMe_2, NEt_2, pyrrolidino, piperidino

249 and **250** were appreciably cytotoxic towards L-1210 leukaemia cells.[123] Further synthetic analogues of acronycine to exhibit promising cytotoxicity included benzophenanthroline derivatives such as **251** and **252**,[124] while some more exotic pyrazole-fused systems of general structure **253** were substantially more active towards L-1210 cells than the parent alkaloid, and even inhibited the proliferation of several human solid tumour cells.[125]

4 Acknowledgements

This material is based upon work supported by the National Research Foundation under grant number 2053652. Financial support from the University of the Witwatersrand is also gratefully acknowledged.

5 References

1 A. Buske, J. Schmidt, A. Porzel and G. Adam, *Eur. J. Org. Chem.*, 2001, 3537.
2 R. A. Davis, A. R. Carroll and R. J. Quinn, *J. Nat. Prod.*, 2002, **65**, 454.
3 S.-B. Chen, G.-Y. Gao, Y.-S. Li, S.-C. Yu and P.-G. Xiao, *Planta Med.*, 2002, **68**, 554.
4 A. E. M. Khaleel, *Monatsh. Chem.*, 2002, **133**, 183.
5 A. D. Wright, E. Goclik, G. M. König and R. Kaminsky, *J. Med. Chem.*, 2002, **45**, 3067.
6 M. Y. Rios, E. Rosas-Alonso and A. B. Aguilar-Guadarrama, *Biochem. Syst. Ecol.*, 2002, **30**, 367.
7 I. Jacquemond-Collet, J.-M. Bessière, S. Hannedouche, C. Bertrand, I. Fourasté and C. Moulis, *Phytochem. Anal.*, 2001, **12**, 312.
8 B. P. Smith, M. J. Tyler, T. Kaneko, H. M. Garraffo, T. F. Spande and J. W. Daly, *J. Nat. Prod.*, 2002, **65**, 439.
9 T. Pacher, M. Bacher, O. Hofer and H. Greger, *Phytochemistry*, 2001, **58**, 129.
10 N. Sultana and P. G. Waterman, *Phytochemistry*, 2001, **58**, 329.
11 M. S. Ali, M. K. Pervez, M. Saleem and R. B. Tareen, *Phytochemistry*, 2001, **57**, 1277.
12 L. Puricelli, G. Innocenti, L. Delle Monache, R. Caniato, R. Filippini and E. M. Cappelletti, *Nat. Prod. Lett.*, 2002, **16**, 95.
13 S. Aoki, Y. Ye, K. Higuchi, A. Takashima, Y. Tanaka, I. Kitagawa and M. Kobayashi, *Chem. Pharm. Bull.*, 2001, **49**, 1372.
14 A. L. Okunade, W. H. Lewis, M. P. Elvin-Lewis, S. J. Casper and D. E. Goldberg, *Fitoterapia*, 2001, **72**, 717.
15 X.-M. Niu, S.-H. Li, L.-Y. Peng, Z.-W. Lin, G.-X. Rao and H.-D. Sun, *J. Asian Nat. Prod. Res.*, 2001, **3**, 299; (*Chem. Abstr.*, 2002, **136**, 259980).
16 I.-S. Chen, H.-F. Chen, M.-J. Cheng, Y.-L. Chang, C.-M. Teng, I. Tsutomu, J.-J. Chen and I.-L. Tsai, *J. Nat. Prod.*, 2001, **64**, 1143.

17 H. Wang, S. L. Yeo, J. Xu, X. Xu, H. He, F. Ronca, A. E. Ting, Y. Wang, V. C. Yu and M. M. Sim, *J. Nat. Prod.*, 2002, **65**, 721.
18 T. S. Tulyaganov and F. K. Allaberdiev, *Chem. Nat. Compd.*, 2001, **37**, 556; (*Engl. transl. of Khim. Prir. Soedin.*, 2001, 476).
19 H. S. Chung and W. S. Woo, *J. Nat. Prod.*, 2001, **64**, 1579.
20 H. S. Chung, *Nutraceuticals Food*, 2002, **7**, 119; (*Chem. Abstr.*, 2003, **138**, 163102).
21 W.-G. Kim, N.-K. Song and I.-D. Yoo, *J. Antibiot.*, 2001, **54**, 831.
22 W. Fakhouri, F. Walker, B. Vogler, W. Armbruster and H. Buchenauer, *Phytochemistry*, 2001, **58**, 1297.
23 M. W. Biavatti, P. C. Vieira, M. F. das G. F. da Silva, J. B. Fernandes, S. R. Victor, F. C. Pagnocca, S. Albuquerque, I. Caracelli and J. Zukerman-Schpector, *J. Braz. Chem. Soc.*, 2002, **13**, 66; (*Chem. Abstr.*, 2002, **136**, 263287).
24 N. Fokialakis, P. Magiatis, A. Terzis, F. Tillequin and A.-L. Skaltsounis, *Tetrahedron Lett.*, 2001, **42**, 5323.
25 N. Fokialakis, P. Magiatis, I. Chinou, S. Mitaku and F. Tillequin, *Chem. Pharm. Bull.*, 2002, **50**, 413.
26 N. Noda, Y. Yashiki, T. Nakatani, K. Miyahara and X.-M. Du, *Chem. Pharm. Bull.*, 2001, **49**, 930.
27 C.-M. Chen, F.-W. Lin, P.-C. Kuo, L.-S. Shi, J.-J. Wang and T.-S. Wu, *J. Chin. Chem. Soc.*, 2001, **48**, 933.
28 T.-S. Wu, C.-M. Chen and F.-W. Lin, *J. Nat. Prod.*, 2001, **64**, 1040.
29 K. Kurosawa, K. Takahashi and E. Tsuda, *J. Antibiot.*, 2001, **54**, 615.
30 K. Takahashi, H. Koshino, Y. Esumi, E. Tsuda and K. Kurosawa, *J. Antibiot.*, 2001, **54**, 622.
31 H. D. T. Mai, H. T. Van-Dufat, S. Michel, F. Tillequin, D. Bastien and T. Sévenet, *Z. Naturforsch., Teil C*, 2001, **56**, 492.
32 N. F. de Moura, A. F. Morel, E. C. Dessoy, N. Zanatta, M. M. Bürger, N. Ahlert, G. P. Porto and B. Baldisserotto, *Planta Med.*, 2002, **68**, 534.
33 I. Jacquemond-Collet, F. Benoit-Vical, Mustofa, A. Valentin, E. Stanislas, M. Mallié and I. Fourasté, *Planta Med.*, 2002, **68**, 68.
34 H. Nakayama, M. E. Ferreira, A. R. de Arias, N. V. de Bilbao, S. Torres, A. Schinini and A. Fournet, *Phytother. Res.*, 2001, **15**, 630.
35 (*a*) J. P. Michael, *Nat. Prod. Rep.*, 2002, **19**, 742; (*b*) J. P. Michael, *Nat. Prod. Rep.*, 1995, **12**, 469; (*c*) J. P. Michael, *Nat. Prod. Rep.*, 1994, **11**, 165; (*d*) J. P. Michael, *Nat. Prod. Rep.*, 1997, **14**, 11; (*e*) J. P. Michael, *Nat. Prod. Rep.*, 2002, **19**, 745; (*f*) J. P. Michael, *Nat. Prod. Rep.*, 2001, **18**, 546; (*g*) J. P. Michael, *Nat. Prod. Rep.*, 2002, **19**, 749; (*h*) J. P. Michael, *Nat. Prod. Rep.*, 2002, **19**, 750; (*i*) J. P. Michael, *Nat. Prod. Rep.*, 2002, **19**, 756; (*j*) J. P. Michael, *Nat. Prod. Rep.*, 2000, **17**, 617; (*k*) J. P. Michael, *Nat. Prod. Rep.*, 2002, **19**, 757.
36 J. Collin, N. Jaber and M. I. Lannou, *Tetrahedron Lett.*, 2001, **42**, 7405.
37 C. S. Cho, B. T. Kim, T.-J. Kim and S. C. Shim, *Chem. Commun.*, 2001, 2576.
38 T. Horaguchi, N. Hosokawa, K. Tanemura and T. Suzuki, *J. Heterocycl. Chem.*, 2002, **39**, 61.
39 V. Bonnet, F. Mongin, F. Trécourt, G. Quéguiner and P. Knochel, *Tetrahedron*, 2002, **58**, 4429.
40 J. Quintin, X. Franck, R. Hocquemiller and B. Figadère, *Tetrahedron Lett.*, 2002, **43**, 3547.
41 E. V. L. da Cunha, J. A. Armstrong, A. I. Gray, D. C. R. Hockless, P. G. Waterman and A. H. White, *Aust. J. Chem.*, 1993, **46**, 1507.
42 I am grateful to Professor M. S. Ali, University of Karachi, for confirming that the name evoxine should be used in preference to haplophytin-B.
43 F. Muyard, F. Bevalot, B. Laude and J. Vaquette, *Phytochemistry*, 1992, **31**, 1087.
44 T.-S. Wu, M.-L. Wang, H.-J. Shyur, Y-L. Liu, Y.-Y. Chan, C.-M. Teng and S.-C. Kuo, *Chin. Pharm. J.*, 1994, **46**, 447.
45 D. R. Boyd, N. D. Sharma, S. A. Barr, J. G. Carroll, D. Mackerracher and J. F. Malone, *J. Chem. Soc., Perkin Trans. 1*, 2000, 3397.
46 R. N. Kumar, S. T. Selvi, T. Suresh and P. S. Mohan, *Heterocycles*, 2002, **57**, 357.
47 Y. R. Lee, H. I. Kweon, W. S. Koh, K. R. Min, Y. Kim and S. H. Lee, *Synthesis*, 2001, 1851.
48 V. Nair, P. M. Treesa, C. N. Jayan, N. P. Rath, M. Vairamani and S. Prabhakar, *Tetrahedron*, 2001, **57**, 7711.
49 G. Bar, A. F. Parsons and C. B. Thomas, *Chem. Commun.*, 2001, 1350.
50 F. N. Lahey, J. A. Lamberton and J. R. Price, *Aust. J. Sci. Res.*, 1950, **3**, 155; cited in ref. 25.
51 S. S. Nazrullaev, I. A. Bessonova and K. S. Akhmedkhodzhaeva, *Chem. Nat. Compd.*, 2001, **37**, 551; (*Engl. transl. of Khim. Prir. Soedin.*, 2001, 472).
52 Z. L. Liu, Y. J. Xu, J. Wu, S. H. Goh and S. H. Ho, *J. Agr. Food Chem.*, 2002, **50**, 1447.
53 G. Bringmann, S. Schlauer, H. Rischer, M. Wohlfahrt, R. Haller, S. Bär and R. Brun, *Pharm. Pharmacol. Lett.*, 2001, **2**, 47.
54 N. A. Cortese, C. B. Ziegler, Jr., B. J. Hrnjez and R. F. Heck, *J. Org. Chem.*, 1978, **43**, 2952.
55 B.-S. Park, D.-Y. Kim, P. J. Rosenthal, S.-C. Huh, B. J. Lee, E.-J. Park, S.-M. Kim, J.-E. Kim, M.-H. Kim, T.-L. Huh, Y.-J. Choi, K.-H. Suh, W.-S. Choi and S.-E. Lee, *Bioorg. Med. Chem. Lett.*, 2002, **12**, 1351.
56 N. Kakinuma, H. Iwai, S. Takahashi, K. Hamano, T. Yanagisawa, K. Nagai, K. Tanaka, K. Suzuki, F. Kirikae, T. Kirikae and A. Nakagawa, *J. Antibiot.*, 2000, **53**, 1247.
57 S. Takahashi, N. Kakinuma, H. Iwai, T. Yanagisawa, K. Nagai, K. Suzuki, T. Tokunaga and A. Nakagawa, *J. Antibiot.*, 2000, **53**, 1252.
58 P. W. Royt, R. V. Honeychuck, V. Ravich, P. Ponnaluri, L. K. Pannell, J. S. Buyer, V. Chandhoke, W. M. Stalick, L. C. DeSesso, S. Donohue, R. Ghei, J. D. Relyea and R. Ruiz, *Bioorg. Chem.*, 2001, **29**, 387.
59 M. J. Rance, J. C. Ruddock, M. S. Pacey, W. P. Cullen, L. H. Huang, M. T. Jefferson, E. B. Whipple, H. Maeda and J. Tone, *J. Antibiot.*, 1989, **42**, 206.
60 C. W. Holzapfel and W. Marais, *J. Chem. Res. (S)*, 2002, 22.
61 K. C. Nicolaou, B. S. Safina, C. Funke, M. Zak and F. J. Zécri, *Angew. Chem., Int. Ed.*, 2002, **41**, 1937.
62 K. C. Nicolaou, M. Nevalainen, B. S. Safina, M. Zak and S. Bulat, *Angew. Chem., Int. Ed.*, 2002, **41**, 1941.
63 S. Higashibayashi, T. Mori, K. Shinko, K. Hashimoto and M. Nakata, *Heterocycles*, 2002, **57**, 111.
64 T. Ozawa, S. Aoyagi and C. Kibayashi, *J. Org. Chem.*, 2001, **66**, 3338.
65 D. R. Buckle, B. C. C. Cantello, H. Smith and B. A. Spicer, *J. Med. Chem.*, 1975, **18**, 726.
66 M. G. Banwell, A. M. Bray, A. J. Edwards and D. J. Wong, *J. Chem. Soc., Perkin Trans. 1*, 2002, 1340.
67 M. G. Banwell, A. M. Bray, A. J. Edwards and D. J. Wong, *New J. Chem.*, 2001, **25**, 1347.
68 M. R. Heinrich, Y. Kashman, P. Spiteller and W. Steglich, *Tetrahedron*, 2001, **57**, 9973.
69 Y. Usuki, H. Hirakawa, K. Goto and H. Iio, *Tetrahedron: Asymmetry*, 2001, **12**, 3293.
70 M. Akashi, Y. Sato and M. Mori, *J. Org. Chem.*, 2001, **66**, 7873.
71 M. Weymann, M. Schulz-Kukula, S. Knauer and H. Kunz, *Monatsh. Chem.*, 2002, **133**, 571.
72 D. L. Comins and A. Dehghani, *J. Chem. Soc., Chem. Commun.*, 1993, 1838.
73 Y. Liu, G. Qin, S. Ding and X. Wu, *Chin. Trad. Herbal Drugs (= Zhongcaoyao)*, 2002, **33**, 97; (*Chem. Abstr.*, 2002, **137**, 152323).
74 K. Deng, X. Wu, G. Yang and G. Qin, *Chin. Chem. Lett.*, 1997, **8**, 237.
75 L. D. Ismail, *Al-Azhar J. Pharm. Sci.*, 2001, **27**, 293; (*Chem. Abstr.*, 2002, **136**, 2958).
76 X.-C. Li, D. C. Dunbar, H. N. ElSohly, L. A. Walker and A. M. Clark, *Phytochemistry*, 2001, **58**, 627.
77 M. R. Ariza, T. O. Larsen, B. O. Petersen, J. Ø. Duus, C. Christophersen and A. F. Barrero, *J. Nat. Prod.*, 2001, **64**, 1590.
78 A. Chakraborty and A. H. Brantner, *Phytother. Res.*, 2001, **15**, 532.
79 D. P. Jindal, R. S. Bhatti, S. Ahlawat and R. Gupta, *Eur. J. Med. Chem.*, 2002, **37**, 419.
80 P. Molina, A. Tárraga, A. Gonzalez-Tejero, I. Rioja, A. Ubeda, M. C. Terencio and M. J. Alcaraz, *J. Nat. Prod.*, 2001, **64**, 1297.
81 H. Danz, D. Baumann and M. Hamburger, *Planta Med.*, 2002, **68**, 152.
82 M. J. Micallef, K. Iwaki, T. Ishihara, S. Ushio, M. Aga, T. Kunikata, S. Koya-Miyata, T. Kimoto, M. Ikeda and M. Kurimoto, *Int. Immunopharmacol.*, 2002, **2**, 565.
83 T. Kimoto, K. Hino, S. Koya-Miyata, Y. Yamamoto, M. Takeuchi, Y. Nishizaki, M. J. Micallef, S. Ushio, K. Iwaki, M. Ikeda and M. Kurimoto, *Pathol. Int.*, 2001, **51**, 315; (*Chem. Abstr.*, 2002, **136**, 256816).
84 S. Koya-Miyata, T. Kimoto, M. J. Micallef, K. Hino, M. Taniguchi, S. Ushio, K. Iwaki, M. Ikeda and M. Kurimoto, *Anticancer Res.*, 2001, **21**, 3295; (*Chem. Abstr.*, 2002, **137**, 210516).
85 J. Scovill, E. Blank, M. Konnick, E. Nenortas and T. Shapiro, *Antimicrobial Agents Chemother.*, 2002, **46**, 882.
86 A. K. Bhattacharjee, D. J. Skanchy, B. Jennings, T. H. Hudson, J. J. Brendle and K. A. Werbovetz, *Bioorg. Med. Chem.*, 2002, **10**, 1979.
87 Y. Takeuchi and T. Harayama, *Trends Heterocycl. Chem.*, 2001, **7**, 65.
88 H. Kikuchi, H. Tasaka, S. Hirai, Y. Takaya, Y. Iwabuchi, H. Ooi, S. Hatakeyama, H.-S. Kim, Y. Wataya and Y. Oshima, *J. Med. Chem.*, 2002, **45**, 2563.
89 D. J. Connolly and P. J. Guiry, *Synlett*, 2001, 1707.

90 Y. Nishiyama, M. Hirose, W. Kitagaito and N. Sonoda, *Tetrahedron Lett.*, 2002, **43**, 1855.
91 J. S. Yadav and B. V. S. Reddy, *Tetrahedron Lett.*, 2002, **43**, 1905.
92 S. B. Mhaske and N. P. Argade, *J. Org. Chem.*, 2001, **66**, 9038.
93 S. B. Mhaske and N. P. Argade, *Synthesis*, 2002, 323.
94 S. Dallavalle and L. Merlini, *Tetrahedron Lett.*, 2002, **43**, 1835.
95 M. Toyota, C. Komori and M. Ihara, *Heterocycles*, 2002, **56**, 101.
96 D. Enders, B. Nolte and J. Runsink, *Tetrahedron: Asymmetry*, 2002, **13**, 587.
97 M. Sugiura, H. Hagio, R. Hirabayashi and S. Kobayashi, *Synlett*, 2001, 1225.
98 M. Sugiura, H. Hagio, R. Hirabayashi and S. Kobayashi, *J. Am. Chem. Soc.*, 2001, **123**, 12510.
99 M. Sugiura and S. Kobayashi, *Org. Lett.*, 2001, **3**, 477.
100 P. K. Mohanta and K. Kim, *Tetrahedron Lett.*, 2002, **43**, 3993.
101 S. H. Lee, S. I. Kim, J. G. Park, E. S. Lee and Y. Jahng, *Heterocycles*, 2001, **55**, 1555.
102 A. Witt and J. Bergmann, *J. Heterocycl. Chem.*, 2002, **39**, 351.
103 F. Hernández, A. Lumetzberger, C. Avendaño and M. Söllhuber, *Synlett*, 2001, 1387.
104 F. Hernández, F. L. Buenadicha, C. Avendaño and M. Söllhuber, *Tetrahedron: Asymmetry*, 2001, **12**, 3387.
105 F. L. Buenadicha, C. Avendaño and M. Söllhuber, *Tetrahedron: Asymmetry*, 2001, **12**, 3019.
106 S. Martín-Santamaria, R. Corzo-Suárez, C. Avendaño, M. Espada, F. Gago, S. García-Granda and H. S. Rzepa, *J. Org. Chem.*, 2002, **67**, 2013.
107 M. L. Heredia, E. de la Cuesta and C. Avendaño, *Tetrahedron: Asymmetry*, 2001, **12**, 2883.
108 J. D. Sánchez, M. T. Ramos and C. Avendaño, *J. Org. Chem.*, 2001, **66**, 5731.
109 H. Wang and M. M. Sim, *J. Nat. Prod.*, 2001, **64**, 1497.
110 H. Wang and A. Ganesan, *J. Org. Chem.*, 1998, **63**, 2432.
111 F. He and B. B. Snider, *J. Org. Chem.*, 1999, **64**, 1397.
112 B. B. Snider and H. Zeng, *Org. Lett.*, 2000, **2**, 4103.
113 B. B. Snider and H. Zeng, *Org. Lett.*, 2002, **4**, 1087.
114 M. M. Rahman and A. I. Gray, *Phytochemistry*, 2002, **59**, 73.
115 A. M. El-Shamy, A. H. Shehata and H. M. M. Eid, *Egypt. J. Biomed. Sci.*, 2001, **8**, 145; (*Chem. Abstr.*, 2002, **137**, 60272).
116 B. Weniger, B.-H. Um, A. Valentin, A. Estrada, A. Lobstein, R. Anton, M. Maillé and M. Sauvain, *J. Nat. Prod.*, 2001, **64**, 1221.
117 C. Tringali, C. Spatafora, V. Cali and M. S. J. Simmonds, *Fitoterapia*, 2001, **72**, 538.
118 F. Tillequin, *Ann. Pharm. Fr.*, 2002, **60**, 246.
119 N. Guilbaud, S. Léonce, F. Tillequin, M. Koch, J. A. Hickman and A. Pierré, *Anti-Cancer Drugs*, 2002, **13**, 445.
120 N. Guilbaud, L. Kraus-Berthier, F. Meyer-Losic, V. Malivet, C. Chacun, M. Jan, F. Tillequin, S. Michel, M. Koch, B. Pfeiffer, G. Atassi, J. A. Hickman and A. Pierré, *Clin. Cancer Res.*, 2001, **7**, 2573.
121 J. Kluza, A. Lansiaux, N. Wattez, M.-P. Hildebrand, S. Léonce, A. Pierré, J. A. Hickman and C. Bailly, *Biochem. Pharmacol.*, 2002, **63**, 1443.
122 P. Magiatis, S. Mitaku, A.-L. Skaltsounis and F. Tillequin, *Chem. Pharm. Bull.*, 2001, **49**, 1304.
123 P. Magiatis, S. Mitaku, A. Pierré and G. Atassi, *Heterocycles*, 2002, **57**, 341.
124 J.-P. Bongui, A. Elomri, E. Seguin, F. Tillequin, B. Pfeiffer, P. Renard, A. Pierré and G. Atassi, *Chem. Pharm. Bull.*, 2001, **49**, 1077.
125 I. K. Kostakis, P. Magiatis, N. Pouli, P. Marakos, A.-L. Skaltsounis, H. Pratsinis, S. Léonce and A. Pierré, *J. Med. Chem.*, 2002, **45**, 2599.