Quinoline, quinazoline and acridone alkaloids

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Received (in Cambridge, UK) 16th June 1999
Covering: July1997 to June 1998
Previous review: 1998, 15, 595

1 General reviews

A supplementary volume in the influential series *Rodd's Chemistry of Carbon Compounds* contains important updates on the quinoline[1] and acridone[2] alkaloids. The reviews, which cover the literature over the period 1985–1996, deal primarily with the isolation, characterisation and synthesis of new alkaloids from plant, microbial and animal sources. Information on recent biosynthetic advances is also included, and novel syntheses of previously known alkaloids are summarised in tabular form.

A significant review claiming to be the first general overview of the distribution of quinazoline alkaloids in the plant and animal kingdoms has been published in the Russian literature[3] and in an English translation.[4] Covering the primary literature to 1996, it is essentially a compilation of the families, genera and species from which quinazoline alkaloids have been obtained since their first isolation as natural products in 1888. It also contains a catalogue of all known quinazoline alkaloids together with a summary of spectroscopic data where available. The alkaloids surveyed include simple quinazolines and quinazolinones, pyrrolo[2,1-*b*]quinazolines of the vasicine class, quinazolino[3,2-*c*]carbolines related to rutaecarpine, miscellaneous microbial metabolites of mixed tryptophan/anthranilic acid origin, and (stretching the concept of quinazoline alkaloids beyond the customary limits) tetrodotoxins.

A comprehensive review on the phytochemistry of the genera *Boronia, Eriostemon* and *Phebalium* includes a list of the more than 270 secondary metabolites isolated to date from these members of the Australian Rutaceae (tribe Boronieae).[5] Amongst the metabolites are approximately thirty alkaloids, including quinolin-2-ones and quinolin-4-ones (some bearing the unusual *N*-acetoxymethyl substituent), furoquinolines and acridones. The article includes biogenetic speculation on the origin of the rare monoterpenoid quinoline alkaloids of *E. australasius* (*cf.* ref. 6*a*), and points out a possible error of interpretation in the original NOE data. A much shorter survey tabulates the acridone alkaloids isolated to date from the Australian genus *Bosistoa*.[7]

The quinolinone, furoquinoline and acridone alkaloids isolated from the nine known species belonging to the genus *Sarcomelicope*, which is endemic to New Caledonia and several Pacific islands, are listed in another short review.[8] Because pyranoacridones such as the antitumour alkaloid acronycine are characteristic of the genus, the review also describes some of the biological properties of natural and synthetic analogues of acronycine. The chemistry and biology of the acronycine-type alkaloids and their analogues have been described more fully in a comprehensive review that covers isolation, characterisation, synthesis and biological activity.[9] Another review in French deals mainly with new synthetic derivatives of acronycine and their antitumour activity.[10] A book chapter on the molecular genetics of plant alkaloid biosynthesis includes a section on acridone alkaloids.[11]

The bacterial degradation of quinoline and quinolinone derivatives is not normally dealt with in these annual reports. However, a substantial review on this topic[12] is worth highlighting because it provides a wealth of information on the pathways and biocatalysts by which microorganisms oxidise both natural and xenobiotic quinolines to products resulting from ring degradation *via* detectable intermediates such as quinolin-2-ones, quinolin-4-ones and various hydroxylated analogues. The article also presents intriguing speculations on potential industrial applications of molybdenum-containing hydroxylases.

2 Quinoline alkaloids

2.1 Occurrence

Several new quinoline alkaloids were reported in the period covered by this review. Table 1 lists these novel metabolites and their sources, as well as known alkaloids isolated from new sources.[13–33] In general, spectroscopic evidence for the proposed structures was ample, and details will be given in the ensuing discussion only when unusual circumstances warrant them.

2.2 Non-terpenoid quinoline and quinolinone alkaloids from higher plants

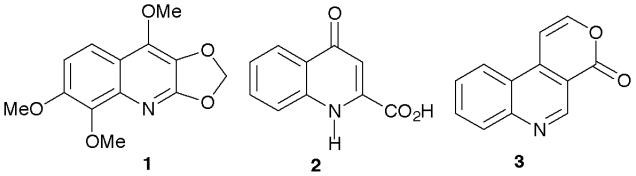
Although plant quinoline alkaloids are primarily metabolites of the Rutaceae, the new non-terpenoid quinolines in this year's crop were all isolated from non-rutaceous sources. Leaves of *Acanthosyris paulo-alvinii*, a Brazilian tree belonging to the Santalaceae, yielded the novel compound 2,3-methylenedioxy-4,7,8-trimethoxyquinoline **1**.[13] The substituents, including the unusually situated methylenedioxy ring, were located by HMBC, HMQC and NOE difference experiments. Compound **1** showed no activity towards a range of human cancer cell lines.

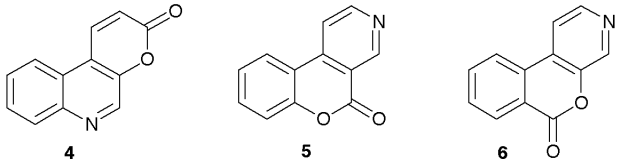
Transtorine **2**, an even simpler 'new' alkaloid isolated from the aerial parts of *Ephedra transitoria* (Ephedraceae), inhibited the growth of the common bacteria *Enterobacter cloacae*, *Pseudomonas aeruginosa* and *Staphylococcus aureus* (MIC 0.45, 0.5 and 0.38 mg cm^{-3} respectively), but was inactive towards several others.[18] The authors seem not to have realised

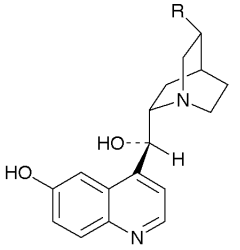
Table 1 Isolation and detection of quinoline alkaloids from microbial, plant and animal sources

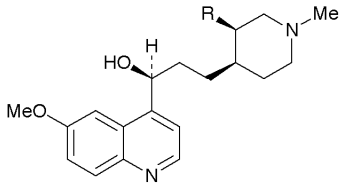
Species	Alkaloid[a]	Ref.
Acanthosyris paulo-alvinii	2,3-Methylenedioxy-4,7,8-trimethoxyquinoline[b] **1**	13
Almeidia coerulia	7-(*O*-Acetyl)haplophyllidine[b] **57** Dutadrupine **61** Isodutadrupine[b] **59** 7-Methoxy-8-(3,3-dimethylallyl)-dictamnine[b] **60**	14
Almeidia rubra	Evolitrine Folinine Kokusaginine Skimmianine	14
Annona cherimola	Cherimoline (see text)	15,16
Dictamnus dasycarpus	Haplopine **63**	17
Ephedra transitoria	Transtorine[b] **2**	18
Guettarda noumeana	Cupreine **7** Dihydrocupreine **8** *N*-Methyldihydroquinicinol **9** *N*-Methylquinicinol[b] **10**	19
Hortia colombiana	2,4-Dimethoxyquinoline Flindersine γ-Fagarine *N*-Methylflindersine Skimmianine	20
Isatis indigotica	(+)-Isaindigotidione[b] **11**	21
Lyngbya majuscula	4,8-Dimethyl-6-hydroxyquinoline[b] **65** 4,8-Dimethyl-6-*O*-(2,4-di-*O*-methyl-β-D-xylopyranosyl)hydroxy-quinoline[b] **66**	22
Micromonospora, strain L-13-ACM2-092	(−)-Thiocoraline[b] **75**	23
Micromonospora carbonacea var. *africana* (ATCC 39149)	(−)-Sch 40832[b] **76**	24
Oreophoetes peruana	Quinoline	25
Phellodendron amurense (callus tissue)	Dictamnine **62** γ-Fagarine Skimmianine	26
Pseudonocardia sp. CL38489	CJ-13,136[b] **67** CJ-13,217[b] **68** CJ-13,536[b] **69** CJ-13,564[b] **70** CJ-13,565[b] **71** CJ-13,566[b] **72** CJ-13,567[b] **73** CJ-13,568[b] **74**	27
Pseudomonas sp. KUH-001	2-Heptyl-4-hydroxyquinoline *N*-oxide	28
Skimmia laureola	(–)-Acetoxyedulinine[b] **35** (–)-Acetoxyptelefoliarine[b] **36** (–)-Evoxine Haplopine Kokusaginine Orixiarine[b] **37** (–)-Ptelefoliarine[b] **38**	29 30 29
Zanthoxylum lemairie	Skimmianine	31
Zanthoxylum schinifolium	4-Methoxy-*N*-methylquinolin-2-one	32
Zanthoxylum simulans	Benzosimuline[b] **42** Peroxysimulenoline[b] **41** Simulenoline[b] **40** (–)-Zanthodioline **43**	33

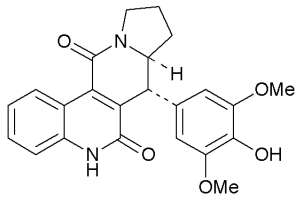
[a] Only new alkaloids and new records for a given species are listed in the Table. Structures of most known alkaloids may be found in previous reviews in this series. [b] New alkaloids.

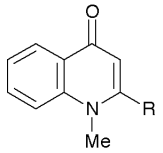












12 Evocarpine R = $(CH_2)_{12}Me$
13 R = (*Z*)-$(CH_2)_7CH{=}CH(CH_2)_3Me$
14 R = (4*Z*,7*Z*)-$(CH_2)_3CH{=}CHCH_2CH{=}CH(CH_2)_4Me$
15 R = (6*Z*,9*Z*)-$(CH_2)_5CH{=}CHCH_2CH{=}CH(CH_2)_4Me$

that compound **2** is, in fact, the keto tautomer of the well-studied compound kynurenic acid, which is a known metabolite of *Ephedra* species.

The rise and fall of 'cherimoline', a putative new pyranoquinoline alkaloid isolated from the stem extract of *Annona cherimola* (Annonaceae),[15] has been rapid. Its discoverers conscientiously recorded its spectroscopic properties, the significant features of which are as follows. The high resolution mass spectrum indicated the molecular formula $C_{12}H_7NO_2$, while an IR absorption at 1760 cm^{-1} and a ^{13}C NMR signal at δ 162.8 suggested the presence of a lactone ring. The ^{13}C NMR and DEPT spectra also indicated seven methine and five quaternary carbons. When these data were considered together with HETCOR and NOESY correlations, the structure of cherimoline was apparently revealed as 4*H*-pyrano[3,4-*c*]quinolin-4-one **3**, which contains a previously unknown ring system. However, a simple synthesis of compound **3** by Joule and co-workers[16] yielded a product with similar, but clearly non-identical, spectroscopic properties to natural cherimoline, a sample of which was available for direct comparison. In particular, the IR carbonyl stretching frequency of the synthetic sample was at 1732 cm^{-1}, while the natural product's carbonyl frequency actually appeared at 1670 cm^{-1}, possibly implying a typographical transcription error in the original paper. This revised value suggested that the structure might possess a conjugated carbonyl group as shown in **4**. Accordingly, **4** was also synthesised, but it, too, gave spectra that did not agree with those of cherimoline. Published data for the alternative lactone structures **5** and **6** also did not fit those of the natural material. The correct structure of cherimoline thus remains a mystery, although the fact that isoquinoline, rather than quinoline, alkaloids are usual for annonaceous plants may point future workers in the right direction.

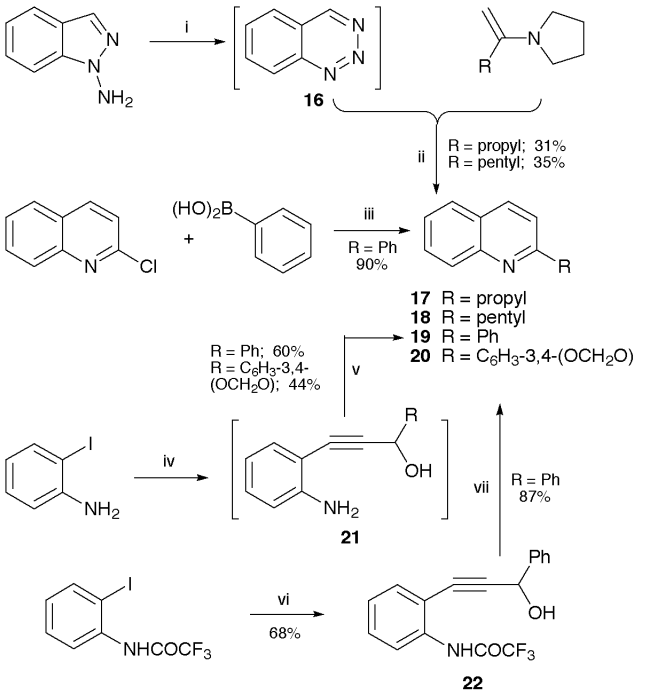
Alkaloids of the quinine group are typically found in the family Rubiaceae. The bark of *Guettarda noumeana*, a rubiaceous species that hails from New Caledonia, yielded the three known alkaloids cupreine **7**, dihydrocupreine **8** and *N*-methyldihydroquinicinol **9**, and a new compound, (−)-*N*-

methylquinicinol **10**.[19] In addition to standard spectroscopic evidence for the structure, catalytic hydrogenation of **10** over palladium on carbon afforded **9**, the absolute configuration of which is known.

A complex quinolin-2-one alkaloid, (+)-isaindigotidione, has been isolated from the roots of *Isatis indigotica* (Cruciferae), a plant used in traditional Chinese medicine for treatment of a wide range of ailments ranging from influenza to encephalitis. Extensive spectroscopic data complemented by an X-ray crystallographic study of the alkaloid's perchlorate salt revealed the structure shown in **11**.[21] This appears to be the first occurrence of an indolizino[7,6-*c*]quinoline in nature, as well as the first quinoline alkaloid from the genus *Isatis*, which is better known as a source of quinazoline alkaloids (*cf.* Section 3.1).

Evocarpine **12** and dihydroevocarpine **13**, two well-known alkaloids from the medicinally important fruits of *Evodia rutaecarpa*, showed toxicity in the brine shrimp test (LC_{50} 0.77 and 21.4 μg cm^{-3} respectively).[34] Biologically monitored fractionation of a methanolic extract of *E. rutaecarpa* fruits led to the isolation of evocarpine and the known alkaloids **14** and **15** as blockers of angiotensin II receptor binding (IC_{50} 43.4, 34.1 and 48.2 μM respectively).[35]

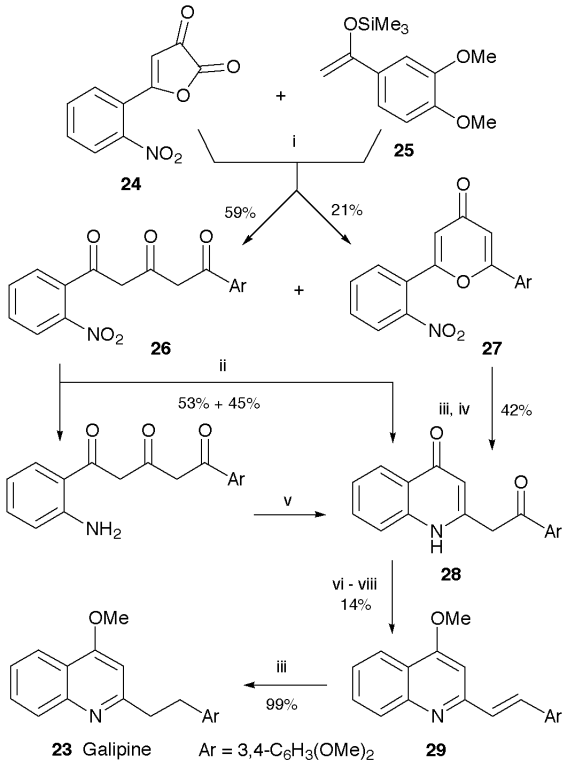
Scheme 1 summarises a number of new synthetic routes to 2-substituted quinoline alkaloids. The Diels–Alder reaction of the pyrrolidine enamines of pentan-2-one or heptan-2-one with



Scheme 1 *Reagents*: i, $Pb(OAc)_4$; ii, $ZnBr_2$, $CHCl_3$, sealed tube, 90–100 °C; iii, $(Ph_3P)_2NiCl_2$, Ph_3P, dioxane, 80 °C; iv, HC≡CCH(OH)R, $(Ph_3P)_2PdCl_2$, CuI, Et_3N, DMF, rt; v, $Pd(OAc)_2$, LiCl, K_2CO_3, DMF, 100 °C; vi, HC≡CCH(OH)Ph, $(Ph_3P)_2PdCl_2$, Et_3N, DMF, rt; vii, NaOEt, EtOH, reflux.

1,2,3-benzotriazine **16** (formed *in situ* by oxidation of 1-amino-1*H*-indazole with lead tetraacetate) gave the simple alkaloids 2-propylquinoline **17** and 2-pentylquinoline **18** respectively in low yield.[36] 2-Phenylquinoline **19** has been prepared in 90% yield by nickel(0)-catalysed cross-coupling of 2-chloroquinoline with phenylboronic acid.[37] Both **19** and the related compound dubamine **20** were produced in one-pot syntheses involving palladium-catalysed coupling of 2-iodoaniline with 1-arylpropargyl alcohols followed by palladium-induced cyclisation of the *o*-aminophenyl-substituted alkynol intermediates **21**.[38] A poorer yield of **19** resulted from base-induced cyclisation of the trifluoroacetanilide derivative **22**. It is also worth mentioning that acid-catalysed Meyer–Schuster rearrangement of acetanilides made from analogues of **21** opened up a short route to 2-aryl-2,3-dihydroquinolin-4(1*H*)-ones, which have frequently been used as intermediates in the synthesis of 4-oxygenated quinoline alkaloids. In this connection, two other recent syntheses of 2-substituted dihydroquinolin-4-ones (from 2′-aminochalcones under microwave irradiation,[39] and from cyclisation of enantiopure *N*-aryl β-aminoacids[40]) also merit citation.

A novel route to 2-aroylmethylenequinolin-4-ones has been applied to the simple quinoline alkaloid galipine **23** (Scheme 2).[41] The transient ketene generated by thermolysis of the furan-



Scheme 2 *Reagents*: i, toluene, 100 °C, then **25**; ii, H_2 (1 atm), 10% Pd/C, THF, rt; iii, H_2 (1 atm), 10% Pd/C, MeOH, rt; iv, $Ba(OH)_2$, MeOH–H_2O, reflux, then 10% HCl; v, 10% HCl, rt; vi, Bu_4NBH_4, CH_2Cl_2, rt; vii, AcOH, reflux; viii, CH_2N_2, Et_2O, rt.

2,3-dione **24** reacted with the silyl enol ether **25** to give a mixture of 1,3,5-trione **26** (59%) and pyrone **27** (21%). Catalytic hydrogenation of both products gave the corresponding amines, both of which could be converted into the 2-substituted quinolin-4-one **28**. The unexpectedly problematic deoxygenation of the aroylmethylene substituent was accomplished by reduction with tetrabutylammonium borohydride followed by dehydration of the resulting crude alcohol. Hydrogenation of the unsaturated intermediate **29** completed the synthesis of the target alkaloid **23**.

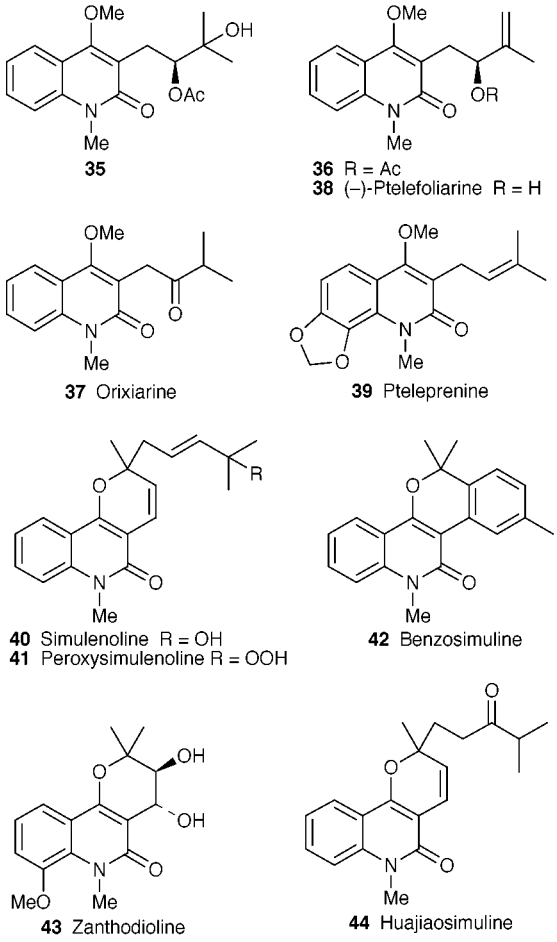
Several 3-substituted 4,8-dimethoxyquinolin-2(1*H*)-ones have been prepared by directed lithiation of precursors such as **30** (BuLi, TMEDA, THF, 50–60 °C) followed by electrophilic substitution.[42] For example, lithiation of **30** followed by

reaction with trimethyl borate and hydrolysis afforded the boronic acid **31** in 90% yield; oxidation with peracetic acid and subsequent methylation gave a low yield of the recently discovered alkaloid **32**. By contrast, lithiation of the trimethoxy-

quinolin-2-one **33** and treatment with dimethylformamide gave the aldehyde **34** in 54% yield. Structure **34** was recently assigned to the novel alkaloid glycocitridine.[43] However, the present work raises doubts about the correctness of the earlier assignment because some physical properties (melting point, IR and MS data) of **34** differed from those reported for glycocitridine although the ^{1}H NMR spectra were substantially the same. Since no ^{13}C or 2D NMR data were reported for glycocitridine in the original publication, the matter must remain unresolved for the present.

2.3 Terpenoid quinoline alkaloids and tricyclic derivatives

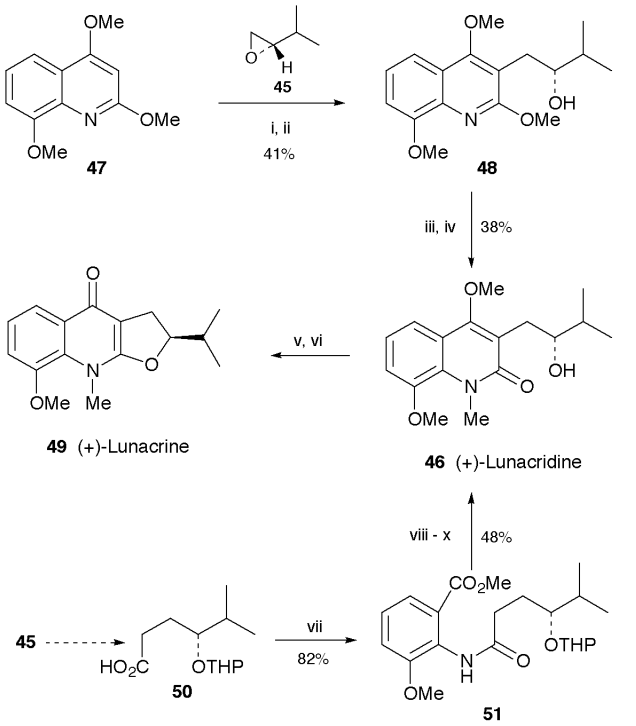
Four new alkaloids isolated from aerial parts of *Skimmia laureola*, an evergreen shrub found in the western Himalayas and Kashmir, are essentially 3-prenylquinolin-2-one alkaloids in which the side chain has undergone oxidation.[29] The gross structures of (−)-acetoxyedulinine **35**, (−)-acetoxyptelefoliarine **36**, orixiarine **37** and (−)-ptelefoliarine **38** were determined



with the aid of spectroscopic methods, and extensive NMR spectroscopic data were reported for all four compounds. The Horeau method (esterification of the alkaloid or its parent alcohol with racemic 2-phenylbutanoic anhydride followed by polarimetric analysis of recovered 2-phenylbutanoic acid) was used to establish the C2′-(*S*) absolute configuration of the optically active metabolites. Careful chromatographic comparisons established that the acetates **35** and **36** were genuine natural products, and not artifacts of the isolation procedure. A related alkaloid, pteleprenine **39**, has been shown to inhibit acetylcholine- and nicotine-induced contraction of guinea pig ileum significantly, which suggests that it might be a novel lead compound as an agonist of nicotinic acetylcholine receptors.[44]

Three new representatives of the exceedingly uncommon monoterpenoid quinoline alkaloids have been isolated from the stem bark of Taiwanese specimens of *Zanthoxylum simulans*.[33] The structural connectivities in simulenoline **40**, an alkaloid clearly derived by oxidation and cyclisation of a 3-geranylquinolin-2(1*H*)-one, were elucidated with the aid of NOESY and HETCOR experiments. Even more remarkable is the related metabolite peroxysimulenoline **41**, the hydroperoxide functional group of which is without precedent amongst the quinoline alkaloids. This unstable compound readily decomposed to simulenoline on exposure to air. Benzosimuline **42** is another ground-breaking metabolite in which the 3-monoterpenoid side chain has cyclised through both alkene bonds to give an isochromano[4,3-*c*]quinoline system, also unique in a natural product. A fourth alkaloid of interest, (−)-**43**, has previously been mentioned in a classic review on rutaceous quinoline alkaloids,[45] but has never been reported in the primary literature. The present article, which assigns the name zanthodioline to this compound, appears to contain the first authenticated description of the alkaloid's isolation and characterisation. The *trans* relative configuration of the hydroxy groups was inferred from the coupling constant between H-3 and H-4 (*J* 7.8 Hz), and further supported by NOESY studies. Bioactivity-guided fractionation of the chloroform extract from *Z. simulans* revealed that the metabolites responsible for strong anti-platelet aggregation activity included simulenoline **40** and benzosimuline **42**, the known quinoline alkaloids zanthobungeanine, skimmianine, γ-fagarine, robustine, edulitine and huajiaosimuline, and several benzo[*c*]phenanthridine alkaloids.[33] The new alkaloids were not cytotoxic towards several cultured human cancer cell lines, although the related monoterpenoid alkaloid huajiaosimuline **44** was.

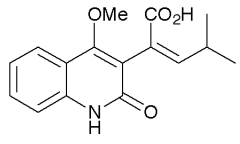
Enantiomerically pure epoxide **45**, prepared either from (*S*)-(+)-valine or D-(+)-mannitol, was the chiral starting material in two related syntheses of (*R*)-(+)-lunacridine **46** (Scheme 3).[46] In the first approach, lithiation of 2,4,8-trimethoxyquinoline **47** at



Scheme 3 *Reagents*: i, BuLi, THF, −78 °C; ii, epoxide **45**, THF, −78 °C to rt; iii, dry HCl in Et_2O; iv, CH_2N_2, Et_2O, MeOH, rt; v, *p*-TsCl, py; vi, aq. NaOH; vii, DCC, methyl 2-amino-3-methoxybenzoate, CH_2Cl_2, 5 °C to rt; viii, NaH (2 equiv.), toluene, 100 °C; ix, KOH, Me_2SO_4, DMF, 50–55 °C; x, *p*-TsOH, MeOH, rt.

C-3 followed by reaction with the epoxide **45** produced the alcohol **48**, which was transformed into the target alkaloid by acidic cleavage of the C-2 methoxy group followed by *N*-methylation. The optical purity of the product was confirmed by NMR spectroscopic analysis of its Mosher ester derivatives. Cyclisation of (+)-lunacridine under condition reported over 40 years ago also provided easy access to (*S*)-(+)-lunacrine **49**. In the second approach, epoxide **45** was converted in five steps into the THP-protected carboxylic acid **50**, reaction of which with methyl 2-amino-3-methoxybenzoate afforded amide **51**. Base-initiated cyclisation, *N*,*O*-dimethylation and removal of the protecting group completed the synthesis of (+)-lunacridine **46**.

Carboxylic acids such as **52** are readily prepared by condensing 2-oxoquinoline-3-acetic acids with isobutyraldehyde.[47] When heated with polyphosphoric acid, they undergo



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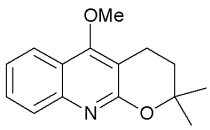

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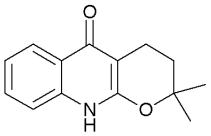
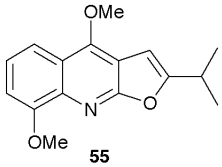


54 Khaplofoline



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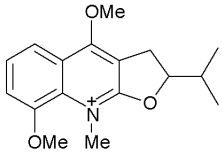


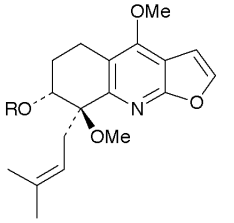
56 Lunasine

decarboxylation and cyclisation to form pyrano[2,3-*b*]quinolines such as the natural product **53** in about 60% yield. Alkaloid **53** itself could be hydrolysed with ethanolic hydrochloric acid to give khaplofoline **54** in 96% yield. A second group of syntheses described in the same article is based on a reported cyclisation of 4-methoxy-3-prenylquinolin-2-ones with Prévost reagent (I_2/HgO) to give furo[2,3-*b*]quinolines such as **55**. Catalytic hydrogenation of **55** followed by *N*-methylation yielded the quaternary alkaloid lunasine **56** (34% yield over two steps), and removal of the *O*-methyl group at C-4 with lithium bromide in boiling acetonitrile completed a synthesis of racemic lunacrine, *rac*-**49** (95%).

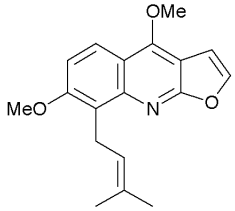
A short review describing applications of sigmatropic rearrangements in the synthesis of coumarins and quinolones amongst other heterocycles includes mention of the regioselective synthesis of the pyrano[3,2-*b*]quinolinone core found in many rutaceous alkaloids.[48]

2.4 Furoquinoline alkaloids

The rare 7,8-dihydro- and 5,6,7,8-tetrahydro-furo[2,3-*b*]quinoline alkaloids have hitherto been found only in the rutaceous genera *Haplophyllum* and *Sarcomelicope*. The relatively unexplored genus *Almeidia* has now yielded a further example of this unusual group of alkaloids.[14] The structure of 7-(*O*-acetyl)haplophyllidine **57**, isolated from the leaves of the Brazilian species *A. coerulia*, was elucidated with the aid of standard spectroscopic techniques, and by hydrolysis to the known alkaloid haplophyllidine **58**. Since spectroscopic data for both haplophyllidine and its C7 epimer have been reported in the literature, the *cis* relationship between the acetoxy and



57 R = Ac
58 Haplophyllidine R = H



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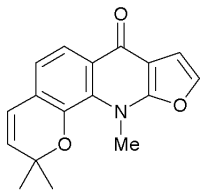
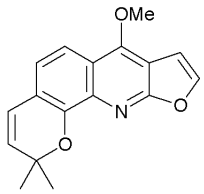
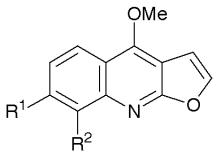


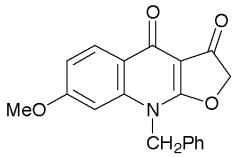
59 Isodutadrupine



61 Dutadrupine



62 Dictamnine $R^1 = R^2 = H$
63 Haplopine $R^1 = OH$; $R^2 = OMe$



64

prenyl substituents in the new alkaloid seems secure. Other new alkaloids isolated in this study were isodutadrupine **59** and 7-methoxy-8-(3,3-dimethylallyl)dictamnine **60**. The former has in fact been known for many years as a rearrangement product of dutadrupine **61**, but this is apparently the first time it has been obtained from a natural source.

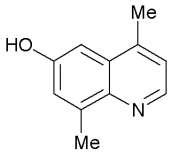
An alkaloidal fraction from *Helietta apiculata* containing an unspecified mixture of furoquinoline alkaloids has been found to inhibit cytochrome P450-dependent monooxygenases, an effect which markedly potentiates the hypnotic action of pentobarbital.[49] Dictamnine **62** has been reported to be a powerful inhibitor of the pathogenic fungus *Cladosporium cucumerinum* (MIC 25 μg ml^{-1}), while haplopine **63** exhibited relatively low activity in the same assay.[17] The structures of alkaloids such as these have provided the inspiration for the design of the synthetic furoquinoline **64**, which shows promising activity as an antiarrhythmic agent.[50]

2.5 Quinoline alkaloids from microbial sources

A marine bacterial symbiont isolated from specimens of the sponge *Suberia creba* collected along the eastern coast of New Caledonia, and identified as a pseudomonad, yielded several typical *Pseudomonas* metabolites, including 2-heptylquinolin-4-one, 2-nonylquinolin-4-one, 2-[(*E*)-1-nonenyl]quinolin-4-one, 3-heptyl-3-hydroxyquinoline-2,4-dione and an *N*-oxide derivative of 2-heptylquinoline.[51] The feature of interest in this publication is that none of these compounds could be detected in the host organism, which produced metabolites of tryptophan instead.

The biologically inactive lipophilic extract of the Caribbean marine cyanobacterium *Lyngbya majuscula* has yielded two relatively simple new quinoline alkaloids, **65** and the glycoside (−)-**66**.[22] Comprehensive spectroscopic evidence was obtained for the proposed structures, and both the positions of the substituents and the stereochemistry within the sugar moiety were confirmed by means of appropriate NMR spectroscopic experiments. The absolute configuration of the sugar, 2,4-di-*O*-methyl-β-D-xylopyranoside, was suggested on the basis of

optical rotation comparisons with related monosaccharides. It is not certain whether the aglycone **65** is an artifact of the isolation process.



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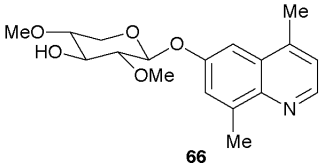

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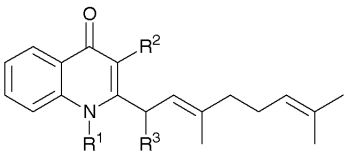
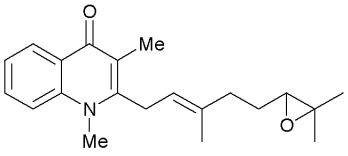
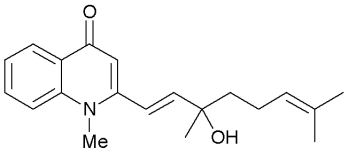


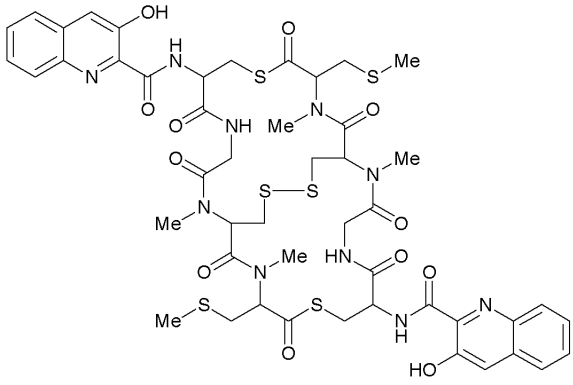
67 CJ-13,136 $R^1 = R^3 = H$; $R^2 = Me$
68 CJ-13,217 $R^1 = R^2 = Me$; $R^3 = H$
69 CJ-13,536 $R^1 = CH_2SMe$; $R^2 = Me$; $R^3 = H$
71 CJ-13,565 $R^1 = R^2 = R^3 = H$
72 CJ-13,566 $R^1 = Me$; $R^2 = R^3 = H$
73 CJ-13,567 $R^1 = Me$; $R^2 = H$; $R^3 = OH$



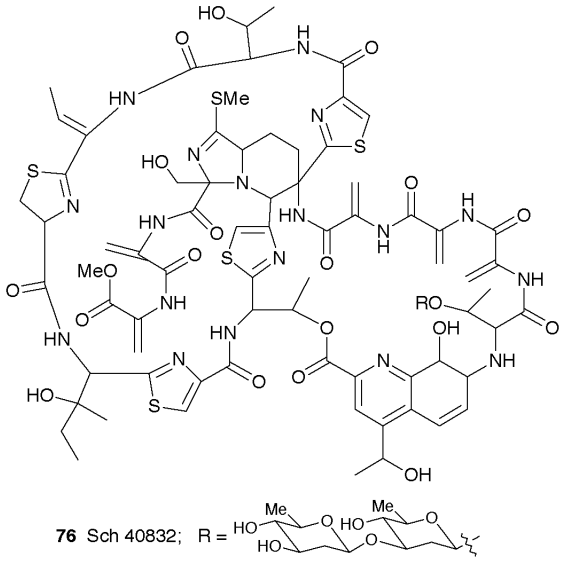
70 CJ-13,564



74 CJ-13,568



75 Thiocoraline

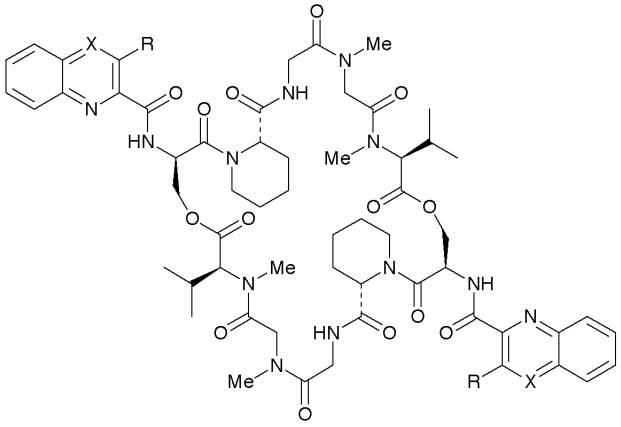


76 Sch 40832; R =

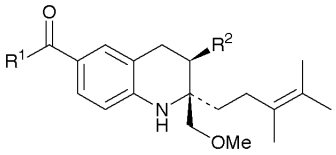
A screening programme for novel metabolites possessing activity against the Gram-negative bacterium *Helicobacter pylori* (implicated in the formation of gastric and duodenal ulcers) has revealed no fewer than eight new quinolin-4-ones from the fermentation broth of the actinomycete *Pseudonocardia* sp. CL38489.[27] These related compounds have been given the code names CJ-13,136 **67**, CJ-13,217 **68**, CJ-13,536 **69**, (–)-CJ-13,564 **70**, CJ-13,565 **71**, CJ-13,566 **72**, (+)-CJ-13,567 **73** and (–)-CJ-13,568 **74**. Full spectroscopic details supported the assigned structures, but absolute configurations were not determined for the three optically active metabolites. The unusual feature of all these compounds is the incorporation of a geranyl or oxidised geranyl side chain at C-2 in place of the customary fatty acid-derived side chain normally found at this position in microbial quinolones; the few known terpenoid quinolones from microbial sources carry the substituent chains at C-3 or C-4. While all the new compounds proved to be individually active in inhibiting the growth of *H. pylori*, the most potent compound was the epoxide CJ-13,564 **70**, which had a significant bacteriocidal effect (MBC 10 ng ml^{-1}) and an even more pronounced bacteriostatic effect (MIC 0.1 ng ml^{-1}). However, the most striking aspect of the activity of the new compounds was their specificity; their inactivity towards microorganisms other than *H. pylori* offers prospects for therapeutic use as antiulcer agents because they are less likely to disturb the normal gastro-intestinal microbial flora.

Two complex depsipeptides in which quinoline-2-carboxylic acid building blocks are embedded have been obtained from microorganisms belonging to the genus *Micromonospora*. (−)-Thiocoraline **75** was isolated from the mycelial cake of a marine *Micromonospora* species during the course of anti-tumour screening.[23] It was found to have potent antibiotic activity against Gram-positive bacteria (MIC *ca.* 0.05 μg ml^{-1}), and showed cytotoxic effects against various tumour cell lines (IC_{50} 0.002–0.01 μg ml^{-1}). It also inhibited RNA synthesis more specifically than DNA synthesis, bound to supercoiled DNA, but did not inhibit topoisomerases I and II. A less conventional depsipeptide, (−)-Sch 40832 **76**, was a minor metabolite in the suite of antibiotics isolated from the fermentation broth of *M. carbonacea* var. *africana*, a soil microorganism.[24] This disaccharide-containing sulfur-rich compound is related to the thiostreptons, and is unique amongst the microbial metabolites in its inclusion of a 7,8-dihydroquinoline segment. It showed potent activity in the range 0.1–1.0 μg ml^{-1} against Gram-positive bacteria.

The antibiotic sandramycin **77**, a relative of thiocoraline, was recently synthesised by Boger and co-workers[52] (*cf.* ref. 6*b*) by a route in which the 3-hydroxyquinoline-2-carboxylic acid chromophore was introduced in the final stages. Boger's group has now prepared over twenty analogues of sandramycin by attaching a range of aroyl substituents (including various substituted quinoline-2-carboxylates, naphthalene-2-carboxylates, pyridine-2-carboxylates, quinoxaline-2-carboxylates and isoquinoline-1-carboxylates) to the depsipeptide core of sandramycin.[53] Fluorescence quenching studies were then used to determine binding constants with calf thymus DNA and within the high-affinity bis-intercalation binding site 5′-d$(GCATGC)_2$, and to establish the preference for sandramycin binding to 5′-d$(GCXXGC)_2$ (X = AT, TA, CG, GC). Amongst many noteworthy results is that, while analogue **78** was less potent than sandramycin itself against leukaemia cell lines, it was up to 10^5 more potent against melanomas, carcinomas and adenocarcinomas (IC_{50} in the range 1 pM–10 nM). These results place it amongst the most potent anticancer agents identified to date.



77 Sandramycin R = OH; X = CH
78 R = H; X = CH
79 R = OMe; X = CH
80 R = H; X = N

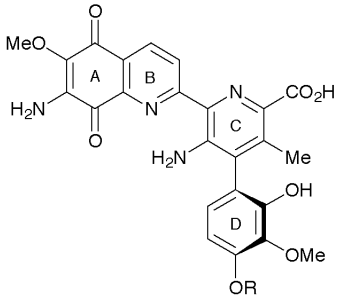


81 Virantmycin R^1 = OH; R^2 = Cl
82 Benzastatin C R^1 = NH_2; R^2 = Cl
83 Benzastatin D R^1 = NH_2; R^2 = OH

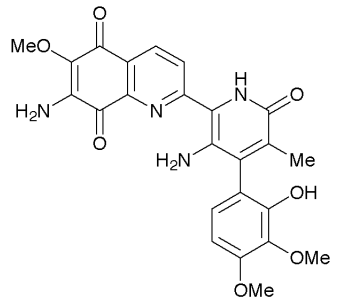
Also demonstrated for the first time was sandramycin's exceptional ability to inhibit HIV-1 reverse transcriptase (IC_{50} 0.13 μM). The analogues **79** and **80**, though slightly less potent than sandramycin itself in the reverse transcriptase assay, were two to three orders of magnitude less cytotoxic, which makes them exciting candidates for further examination in HIV-1 chemotherapy.

The formerly contentious question of the relative and absolute stereostructure of virantmycin **81** has recently been resolved (*cf.* ref. 6*c*), but the probable effects of the flexible conformation on the ^{1}H NMR and NOE spectra remain uncertain. PM3 semi-empirical molecular orbital calculations have now been used to evaluate the conformational behaviour of virantmycin, the related antibiotics benzastatin C **82** and benzastatin D **83**, and several synthetic analogues.[54] When the geometries of the two possible half-chair conformers were optimised, the thermodynamic distributions that emerged were consistent with the coupling constants observed in NMR experiments. The energy barriers for ring inversion were calculated to be in the range 4.86–11.13 kcal mol^{-1}, which supports the expected rapid interconversion of the two conformers at ambient temperature.

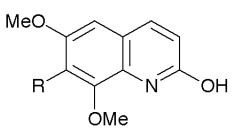
The broad-spectrum antibiotic and antitumour compound streptonigrin was first isolated in 1959, and has been synthesised several times since then. However, the absolute configuration of this axially chiral compound has not been determined to date, even though its CD spectrum has been reported and X-ray crystallographic studies have been performed. Tennant and Rickards have now used exciton coupled circular dichroism to determine the *R* absolute configuration about the C/D biaryl axis, as shown in **84**.[55] The AB and C rings appear to be coplanar. The related compound 10′-*O*-demethylstreptonigrin **85** gave very similar CD spectra, and indubitably has the same absolute configuration as streptonigrin itself. However, the CD spectrum of streptonigrone **86** indicated that it was not optically active; the compound is thus either inherently achiral, or exists as an atropisomeric racemate. Recent synthetic studies aimed at streptonigrin have concentrated on methods for making a range of 2-hydroxyquinoline models **87** for the AB ring system,[56] and on condensation routes for making pyridine models **88** of ring C.[57]



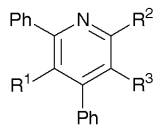
84 Streptonigrin R = Me
85 R = H



86 Streptonigrone



87 R = H, NH_2



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2.6 Quinoline alkaloids from animals

The strikingly coloured phasmid insect *Oreophoetes peruana* (the Peruvian fire stick insect) exudes a malodorous white fluid from a pair of thoracic glands when disturbed. The secretion proved to be an aqueous emulsion containing quinoline as the inner phase.[25] This heterocyclic compound, rare enough as a natural product, has never before been isolated from an animal source. That quinoline is indeed the insects' active defence component was proved in bioassays with ants, spiders, cockroaches and frogs, all of which displayed marked aversion on contact or near-contact with the alkaloid. It is most interesting that the insect does not shed the cuticular lining of its thoracic glands during moulting, thereby retaining its chemical defences at an otherwise vulnerable stage of its development.

3 Quinazoline alkaloids

3.1 Occurrence, characterisation and biological activity

Table 2 lists the new quinazoline alkaloids isolated during the period under review as well as known alkaloids isolated from new sources.[21,26,58–62]

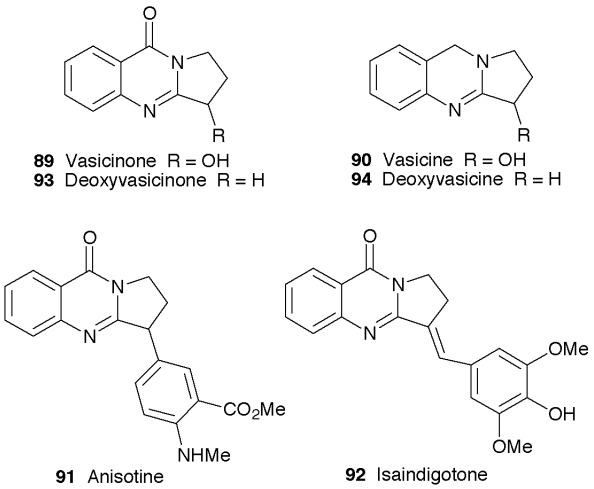
X-Ray diffraction studies have been performed on vasicinone **89**, a bronchodilating and hypotensive principle of *Adhatoda vasica*.[58] A methanolic extract from the aerial parts of the Saudi Arabian shrub *Anisotes trisulcus* has yielded the known alkaloids (−)-vasicinone **89**, (−)-peganine (vasicine) **90** and (+)-anisotine **91**.[59] This article also contains the first reported ^{13}C NMR spectroscopic data for anisotine, as well as some revisions to reported assignments of ^{1}H NMR signals for anisotine and peganine.

The structure of (−)-isaindigotone **92** from *Isatis indigotica*, revealed in a communication in 1997[63] (*cf.* ref. 6*d*), has been described in detail in a full paper published in a more accessible journal.[21] The present article also describes the X-ray crystal structure of isaindigotone, and mentions the isolation of deoxyvasicinone **93** from the same plant source.

Table 2 Isolation and detection of quinazoline alkaloids

Species	Alkaloid[a]	Ref.
Adhatoda vasica	Peganidine	58
Anisotes trisulcus	(+)-Anisotine **91**	59
	(−)-Vasicinone **89**	
	(−)-Peganine (vasicine) **90**	
Isatis indigotica	Deoxyvasicinone **93**	21
Peganum multisectum	Deoxyvasicinone	60,61
	Deoxyvasicine	
	Vasicinone	
	Vasicine	
Peganum nigellastrum	Deoxyvasicine **94**	62
	Luotonin A[b] **95**	
	Luotonin B[b] **96**	
Phellodendron amurense	7,8-Dehydrorutaecarpine[b] **99**	26
	Rutaecarpine **98**	

[a] Only new alkaloids and new records for a given species are listed in the Table. Structures of most known alkaloids may be found in previous reviews in this series. [b] New alkaloids.

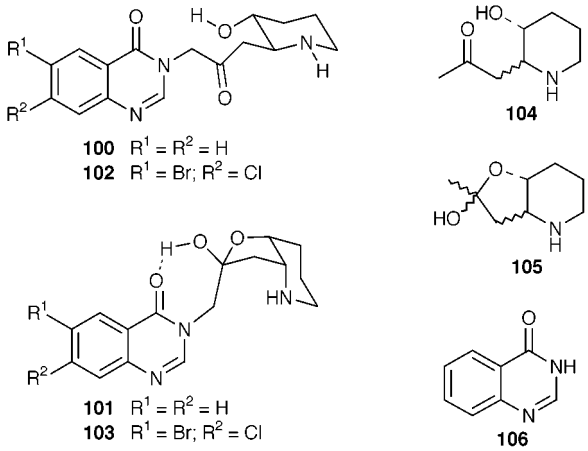


Deoxyvasicine **94** has been isolated for the first time from *Peganum nigellastrum* (the traditional Chinese medicine "Luo-Tuo-Hao") together with several congeners previously known from this plant source as well as two new metabolites, luotonin A **95** and luotonin B **96**.[62] These interesting compounds possess a quino[2′,3′:3,4]pyrrolo[2,1-*b*]quinazoline skeleton, which has not previously been found in a natural product. The alternative quino[3′,2′:4,5]pyrrolo[2,1-*b*]quinazoline structure **97** for luotonin A was ruled out on the basis of the chemical shifts of the methylene protons and carbon (δ_H 5.40 and δ_C 47.3 respectively). Luotonin A underwent slow conversion into luotonin B when a solution of the compound in chloroform was exposed to sunlight for two weeks. The alkaloid exhibited good cytotoxicity towards mouse leukaemia P-388 cells (IC_{50} 1.8 μg ml^{-1}).

Callus tissue cultured from the stem of *Phellodendron amurense* has been shown to produce a variety of alkaloids, amongst them the well-known indolopyridoquinazoline alkaloid rutaecarpine **98** (isolated for the first time from this genus) and its 7,8-dehydro analogue **99**.[26] The latter has not been obtained from a natural source before, although is has been made from rutaecarpine. A further two unidentified alkaloids were detected when the cultures were grown over a 40-day period. The roots and aerial parts of the intact plant did not produce any of these alkaloids, although rutaecarpine could be isolated from the ripe fruits.

trans-Febrifugine **100** is an important anticoccidial agent that has been isolated from a variety of sources including *Hydrangea macrophylla* (Saxifragaceae), which also produces the inactive *cis* isomer isofebrifugine **101**. Synthetic halogenated versions of both isomers (halofuginones), **102** and **103**, have been patented. Since conformational effects are thought to contribute to the difference in biological activity of the two febrifugines, Uesato and co-workers have analysed their stereostructures and those of the halofuginones by means of NMR spectroscopy.[64] In deuteriated chloroform solution, ^{13}C NMR and NOE experiments revealed that the *cis* isomers have a stable hemiketal ring whose hydroxy group is probably hydrogen-bonded to the carbonyl group of the quinazolinone ring, as shown in **101**. By contrast, the ketone group in the *trans* isomers is unambiguously "free". In deuteriated dimethyl sulfoxide and in acetate buffer, the *cis*-halofuginone exists as a mixture of the keto form and both epimeric hemiketals, whereas the *trans* isomer is once again present only in the keto form. AM1 molecular orbital calculations on the simpler model compounds **104** and **105** lend support to the conclusions. It is known that the febrifugines can be interconverted on heating, probably through a mechanism involving cleavage and re-formation of the piperidine ring by retro-Michael/Michael reactions; the halofuginones have now been shown to undergo the same kind of isomerisation.

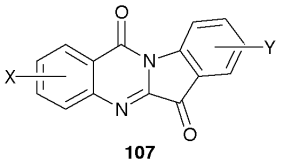
Febrifugine **100** and isofebrifugine **101** were originally isolated over fifty years ago from *Dichroa febrifuga*, traditionally used in China as an antimalarial drug. Since there is



evidence that the efficacy of antimalarial agents can be enhanced by potentiating the production of the highly topical compound nitric oxide (NO), the effects of the *D. febrifuga* alkaloids on NO production were studied with activated mouse peritoneal macrophages, which contain an isoform of nitric oxide synthase capable of producing large amounts of the gas over a long period when stimulated with lipopolysaccharide (LPS).[65] A methanolic extract of the plant enhanced NO production in the macrophages by 97% when fed to mice at a dose of 20 mg kg^{-1} per day for three days before the assay was performed. When the alkaloids were tested individually at doses of 1 mg kg^{-1} per day, febrifugine potentiated the LPS-mediated production of NO by 91%, while isofebrifugine and the minor alkaloid quinazolin-4(3*H*)-one **106** enhanced NO formation by 22% and 29% respectively. The enhancement was dose-dependent, but cell viability was compromised and toxic effects

were apparent at higher dosages. The mode of action of febrifugine appears to be different from that of other antimalarial drugs such as quinine, chloroquine and artemisinin, and it holds promise as a novel lead compound for antiplasmodial chemotherapy.

Tryptanthrin **107** (X, Y = H), known since 1915, has recently shown exciting potential as an antimycobacterial agent.[66] Not only did its activity prove to be comparable to that of established



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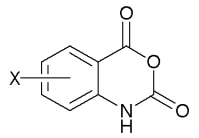

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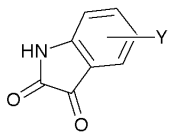

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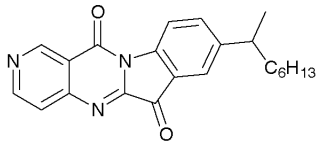

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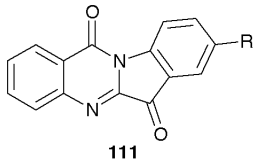

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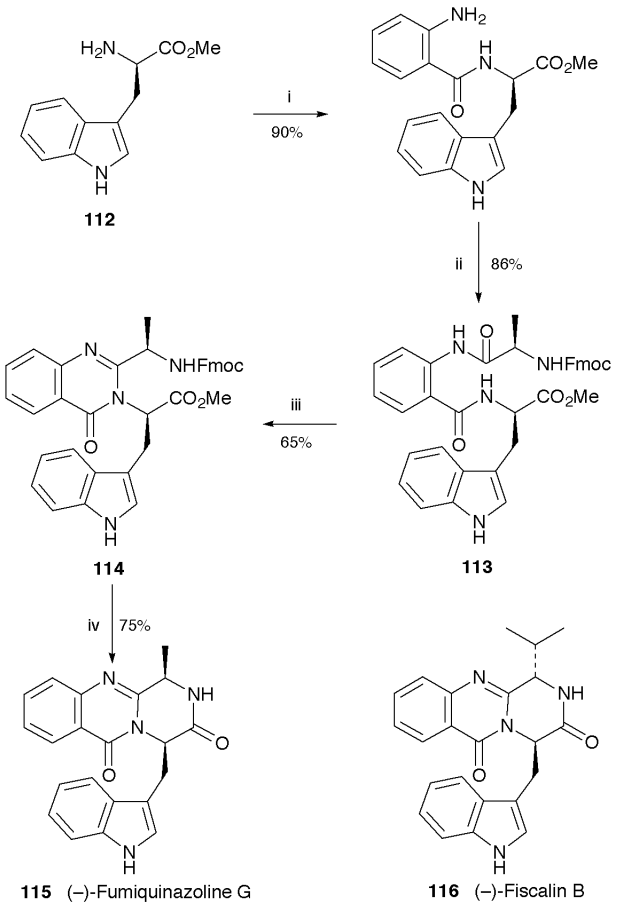
antitubercular agents, but it was also effective against a multiply drug-resistant strain of *Mycobacterium tuberculosis*. These findings prompted the synthesis of a large range of analogues by the condensation of isatoic anhydrides **108** with isatins **109**. The C-6 carbonyl group turned out to be essential for activity; cyclic voltammetry established that it was capable of entering into a redox cycle, and that the oxidised state was the bioactive form. Substituents in both the A and the D rings were compatible with powerful antitubercular activity, and several analogues were up to 100 times as potent *in vitro* as tryptanthrin itself. Singled out for *in vivo* studies was the azatryptanthrin PA-505 **110**, but unfortunately it failed to cure infected test animals, perhaps because of unfavourable pharmacokinetic features.

Tryptanthrin and several substituted analogues show activity as agonists of the aryl hydrocarbon receptor (AHR), a binding site implicated in the mode of action of environmental pollutants such as polyhalogenated aromatics and dioxins.[67] The test compounds were prepared biosynthetically by incubating the yeast *Candida lipolytica* with tryptophan and substituted anthranilic acids. The most potent agonists proved to be the 8-substituted derivatives **111** (R = Me, Cl, Br), the EC_{50} induction values for which were higher by about three orders of magnitude than that of the potent carcinogen and teratogen 2,3,7,8-tetrachlorodibenzo-*p*-dioxin. The tryptanthrins induced cytochrome P4501A1 mRNA and protein in rat hepatocytes, and were shown by gel retardation studies to transform the AHR into a double-stranded oligonucleotide possessing a xenobiotic-responsive element (XRE). It is suggested that the AHR may be part of a defence system that protects higher organisms from microbial secondary metabolites such as tryptanthrins, or those formed by microorganisms found in the gastro-intestinal tract. Other synthetic analogues of tryptanthrin have also been prepared, but were reported to show little or no antimicrobial activity.[68]

3.2 Structural and synthetic studies

The IR spectra of the complexes formed between with zinc(II) chloride, cobalt(II) chloride and manganese(II) chloride and the hydrochloride salts of deoxypeganine (deoxyvasicine) **94** and its synthetic cyclohexa and cyclohepta analogues, as well as peganine (vasicine) and peganol, have been reported.[69] New absorption bands in the region 3100–3300 cm^{-1} were ascribed to the formation of hydrogen bonds between the protonated quinazolinium cations and the tetrachlorometallate counterions.

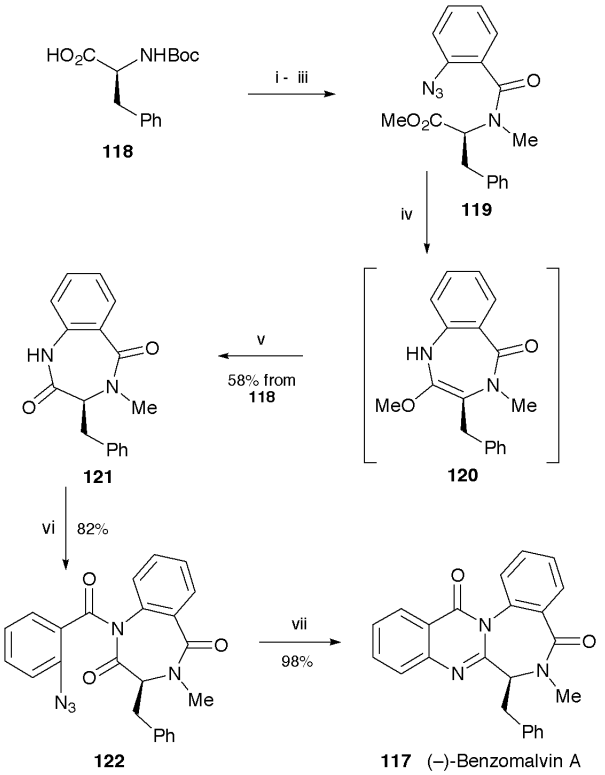
Several recently discovered quinazoline-containing fungal metabolites are essentially peptide derivatives, and synthetic approaches to them are frequently biomimetic. Scheme 4 shows



Scheme 4 *Reagents*: i, EDAC, anthranilic acid, MeCN, rt; ii, Fmoc-D-Ala-Cl, CH_2Cl_2, aq. $NaHCO_3$, rt; iii, Ph_3P, I_2, Pr^i_2NEt, CH_2Cl_2, rt; iv, 20% piperidine in CH_2Cl_2, rt, then SiO_2.

part of a short biomimetic route to one such metabolite.[70] D-Tryptophan methyl ester **112** was converted into tripeptide **113** by means of standard coupling reactions, after which dehydration with triphenylphosphine and iodine brought about cyclisation to the quinazolinone **114** in 65% yield. When the Fmoc protecting group was removed and the liberated primary amine purified by chromatography on silica gel, a second cyclisation occurred spontaneously to complete a synthesis of (−)-fumiquinazoline G **115** in a total of four steps and 38% overall yield from **112**. The synthesis of the related compound (−)-fiscalin B **116** proceeded analogously, but the final cyclisation had to be driven by refluxing in acetonitrile; the overall yield of this five-step sequence was 48% based on D-tryptophan methyl ester **112**.

The intramolecular aza-Wittig reaction features twice in a short synthesis of (–)-benzomalvin A **117** from *N*-Boc-L-phenylalanine **118** by Eguchi and co-workers (Scheme 5).[71] The first application involved Staudinger reaction of azide **119** with tributylphosphine followed by an unusual aza-Wittig reaction with an ester to give an intermediate iminoether **120**. This was hydrolysed to the benzodiazepinedione **121** in an overall yield of 58% from **118**. The ensuing construction of the target's quinazolino[3,2-*a*][1,4]benzodiazepinedione nucleus was by means of a reaction sequence that has become known[72] as the "Eguchi protocol". This involves acylation of the more acidic

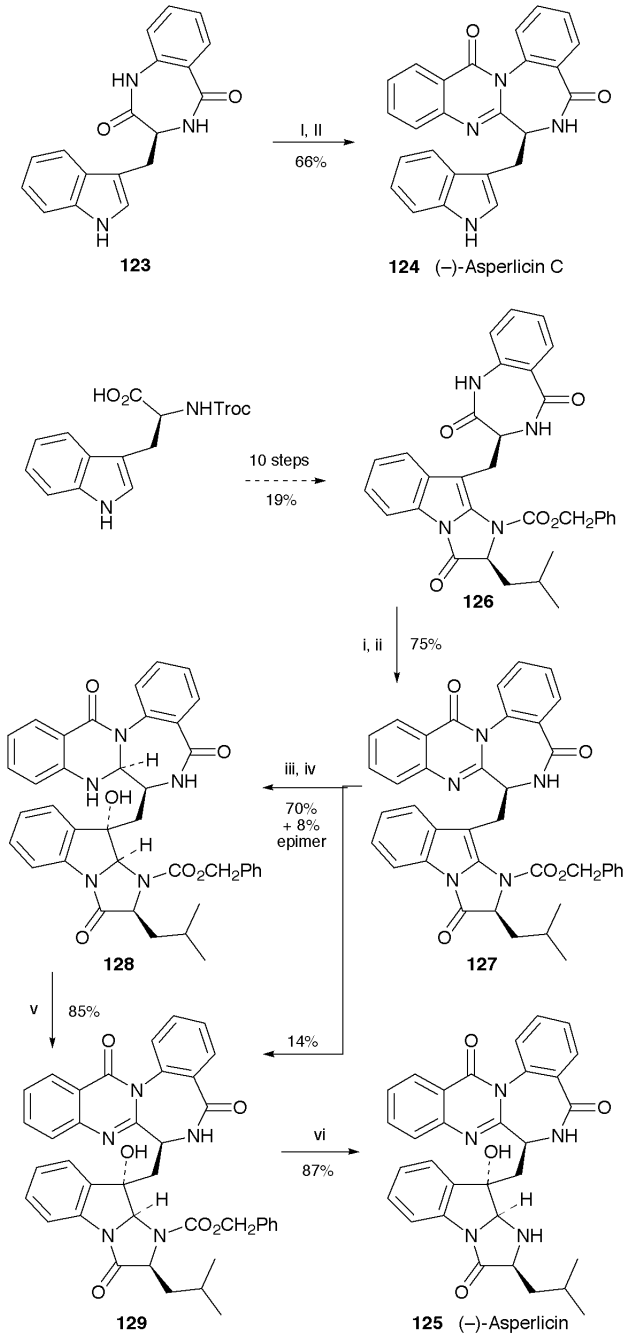


Scheme 5 *Reagents*: i, NaH (2.1 equiv.), MeI (16 equiv.), THF–DMF (10:1), reflux; ii, 15% HCl in MeOH, 50 °C; iii, *o*-$N_3C_6H_4COCl$, Et_3N, THF, 0 °C to rt; iv, Bu_3P, toluene, rt to reflux; v, THF, HCl (40:1), 50 °C; vi, KHMDS, THF, −78 °C, then *o*-$N_3C_6H_4COCl$, THF, −78 °C to rt; vii, Ph_3P, toluene, rt to reflux.

anilide nitrogen site with *o*-azidobenzoyl chloride, followed by heating the resulting azide **122** with tributylphosphine to effect the second aza-Wittig transformation. The target alkaloid **117** was obtained from **121** in 80% overall yield. The ee of the product was only 85%, however, and it is suspected that some racemisation took place during the early methylation steps.

The "Eguchi protocol" was also used for constructing the quinazolino[3,2-*a*][1,4]benzodiazepinedione nucleus of two alkaloidal antibiotics related to benzomalvin A (Scheme 6).[72] When the reaction sequence was applied to the tryptophan-derived benzazepinedione **123**, (−)-asperlicin C **124** was obtained in 66% overall yield. The most challenging aspect of the synthesis of the more complex antibiotic (−)-asperlicin **125** was the construction (not illustrated) of the tryptophan-derived 1*H*-imidazo[1,2-*a*]indol-3-one substituent of intermediate **126**, following which the Eguchi protocol yielded the fused quinazolinone **127** (75%). Hydroxylation of the indole ring with an oxaziridine followed by reductive work-up with sodium borohydride competitively reduced the quinazolinone to the dihydroquinazolinone **128**, but reoxidation with DDQ restored the unsaturated linkage to give **129**. Removal of the benzyloxycarbonyl protecting group completed a stereospecific synthesis of (−)-asperlicin **125** in fifteen steps and 8% overall yield from Troc-protected tryptophan.

Several other syntheses of quinazoline-containing systems are worth mentioning because of their potential applicability to the synthesis of natural products. In probing the chemoselectivity of the intramolecular aza-Wittig reaction with substrates **130**, Eguchi's group has shown that the distribution of pyrrolo[2,1-*c*][1,4]benzodiazepinediones **131** and the vasicinone-like products **132** depends both on the nature of the phosphine used (PR_3, R = Ph, Bu, OEt) and on substituent X; amides (X = NEt_2) gave quinazolinones almost exclusively.[73] French workers found that pyrrolobenzodiazepinones **133** could be rearranged to pyrrolo[2,1-*b*]quinazolinones **134** in 70–80% yields merely on treatment with concentrated hydrochloric acid



Scheme 6 *Reagents*: i, *o*-$N_3C_6H_4COCl$, Et_3N, DMAP, CH_2Cl_2, rt; ii, Bu_3P, C_6H_6, 60 °C; iii, 3-butyl-2,3-epoxy-1,2-benzisothiazole-1,1-dione, MeOH–CH_2Cl_2 (4:1), 25 °C; iv, $NaBH_4$, HOAc, 25 °C; v, DDQ, $CHCl_3$, rt; vi, H_2 (1 atm), 5% Pd/C, MeOH, rt.

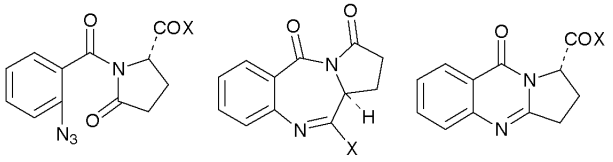
at 60 °C.[74] Biomimetic syntheses of the pyrazinoquinazolines **135**, analogues of the multidrug resistance reversal agent 5-*N*-acetylardeemin **136**, have been reported.[75]

4 Acridone alkaloids

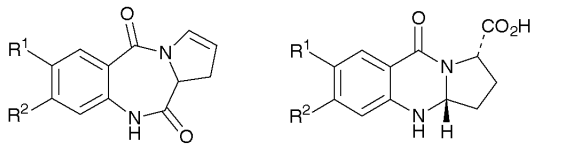
4.1 Occurrence

There has been little activity in the isolation of acridone alkaloids during the period under review, and only three new alkaloids were reported. The few phytochemical investigations are summarised in Table 3.[14,33,76,77]

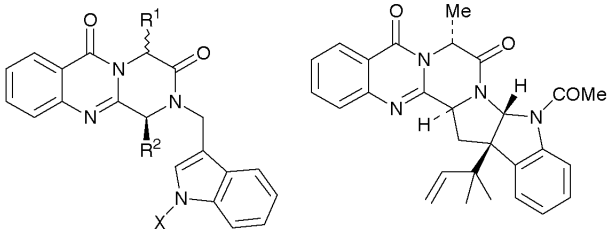
Two new acridone–coumarin dimers of the neoacrimarine class have been isolated from the roots of *Citrus* varieties.[76] "Yalaha", a hybrid of the Duncan grapefruit (*C. paradisi*) and Dancy tangerine (*C. tangerina*), was the source of (+)-neoacri-



130 X = OMe, NEt_2 **131** X = OMe, NEt_2 **132** X = OMe, NEt_2

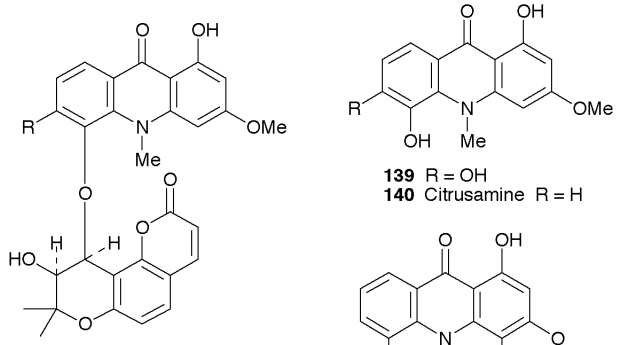


133 R^1, R^2 = H, Cl, Me **134** R^1, R^2 = H, Cl, Me



135 X = H, Ac; R^1 = H, Me, Pr^i; R^2 = H, Me

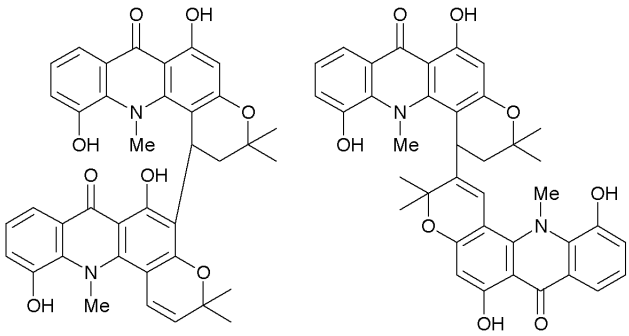
136 *N*-Acetylardeemin



137 Neoacrimarine F R = OH
138 Neoacrimarine G R = H

139 R = OH
140 Citrusamine R = H

142 5-Hydroxynoracronycine



141 Bis-5-hydroxynoracronycine **143**

Table 3 Isolation and detection of acridone alkaloids

Species	Alkaloid[a]	Ref.
Almeidia coerulia	Arborinine	14
Almeidia rubra	Arborinine	14
	Methylarborinine	
Citrus hybrid 'Yalaha' (*C. paradisi* × *C. tangerina*)	(+)-Neoacrimarine-F[b] **137**	76
Citrus paradisi	Bis-5-hydroxynoracronycine[b] **141**	77
	Citpressine-I	
	Citpressine-II	
	Citracridone-I	
	Glycocitrine-I	
	Grandisinine	
	Natsucitrine-II	
	(+)-Neoacrimarine-G[b] **138**	76
Zanthoxylum simulans	Arborinine	33

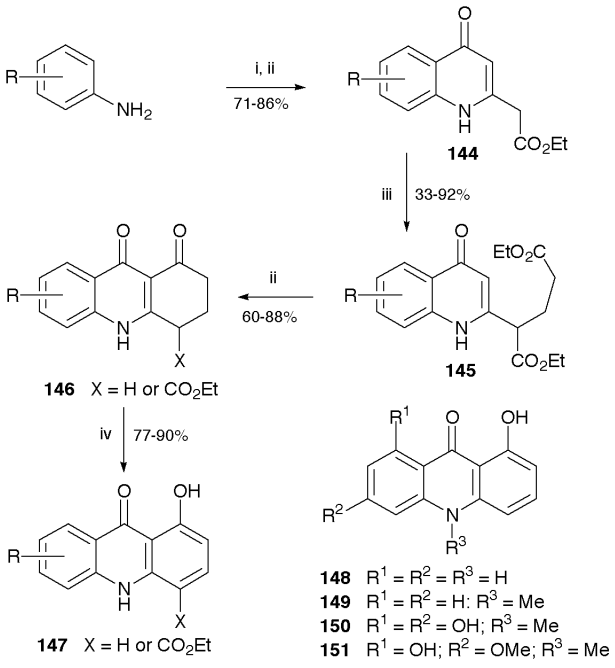
[a] Only new alkaloids and new records for a given species are listed in the Table. Structures of most known alkaloids may be found in previous reviews in this series. [b] New alkaloids.

marine F **137**, while its-6-deoxy analogue, (+)-neoacrimarine G **138**, was isolated from *C. paradisi*. Thorough NMR spectroscopic studies were used to elucidate the structures and relative stereochemistries of the new metabolites, but the absolute stereostructures remain unknown. As a matter of interest, the acridone moiety in neoacrimarine F, **139**, has not yet been found as a natural product, but the corresponding acridone unit **140** in neoacrimarine G is the familiar alkaloid citrusamine.

The roots of *C. paradisi* have also yielded a new bisacridone dimer, bis-5-hydroxynoracronycine **141**, which was obtained as a racemate.[77] This is the first dimeric acridone alkaloid to contain two identical moieties. Although its structure was largely apparent from its spectroscopic properties, the small quantity isolated (0.5 mg from 1.1 kg of plant material) made full characterisation difficult. A synthetic sample was thus prepared in 30% yield by treating the monomer, 5-hydroxynoracronycine **142**, with concentrated sulfuric acid in methanol. The synthesis also yielded the novel compound **143** in which the monomeric units are unusually linked through the pyran rings (12%).

4.2 Synthesis and biological studies

General routes to oxygenated acridones are uncommon enough to make a new approach to these systems[78] worthy of attention (Scheme 7). The condensation of anilines with diethyl 3-oxo-



144 **145** **146** X = H or CO_2Et **147** X = H or CO_2Et

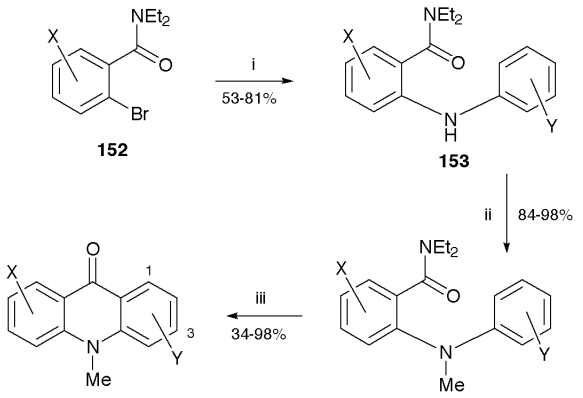
148 R^1 = R^2 = R^3 = H
149 R^1 = R^2 = H: R^3 = Me
150 R^1 = R^2 = OH; R^3 = Me
151 R^1 = OH; R^2 = OMe; R^3 = Me

Scheme 7 *Reagents:* i, $(EtO_2CCH_2)_2CO$, $CHCl_3$, cat. HCl; ii, PPA, 110–120 °C; iii, NaOEt, EtOH, then $H_2C{=}CHCO_2Et$, DMSO; iv, 10% Pd/C, Ph_2O, reflux, 30 min (retention of ester) or 3 h (loss of ester).

glutarate provided easy access to quinolin-4-ones **144**, which then underwent conjugate addition with ethyl acrylate to give adducts **145** in variable yield. Cyclisation in hot polyphosphoric acid afforded tetrahydroacridine-1,9-diones **146** in which the ester group at C-4 could be retained or lost depending on the severity of the reaction conditions. Although aromatisation of

146 to the target 1-hydroxyacridone systems **147** could be achieved by treatment with bromine followed by basic elimination of hydrobromic acid, a more satisfactory method involved heating the dione with one-third of its weight of 10% palladium on carbon in diphenyl ether. One of the eight reported compounds, **148**, is a natural product. *N*-Methylation or *O*-demethylation of appropriate 1-hydroxyacridones **147** extended the range of accessible products to include a further three alkaloids, **149**, **150** and oligophylidine **151**.

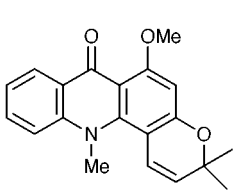
Snieckus and co-workers have shown that palladium(II)-induced coupling of anilines with *N*,*N*-dialkyl-2-halobenzamides **152** provides an excellent route to diarylamines **153** (Scheme 8).[79] Furthermore, after *N*-methylation of the products,



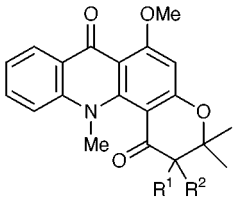
Scheme 8 *Reagents*: i, Y-$C_6H_4NH_2$, NaOBu^t, $Pd_2(dba)_3$, BINAP, toluene, 90–100 °C; ii, BuLi, THF, 0 °C, MeI, then dioxane, 60 °C; iii, LDA, THF, 0 °C to rt.

the amide group on ring A directs lithiation to the "remote" *ortho* site on ring B, thereby facilitating an anionic cyclisation that completes a new synthesis of acridones. Amongst the compounds prepared were the natural products **154** and **155**, and several other methoxyacridones akin to known alkaloids.

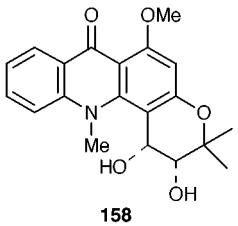
Continuing their extensive exploration of the chemistry and biological activity of the antitumour alkaloid acronycine **156** and its synthetic derivatives, Skaltsounis, Tillequin and their co-



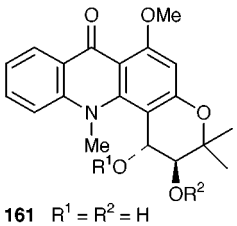
156 Acronycine



157 R^1 = H; R^2 = OH
159 R^1 = OH; R^2 = CH_2COMe
160 R^1 = R^2 = H



158



161 R^1 = R^2 = H
162 R^1 = H; R^2 = Ac
163 R^1 = H; R^2 = $COCH_2Cl$
164 R^1 = R^2 = Ac

workers have prepared several oxygenated analogues by oxidising the alkaloid with potassium permanganate in acetone.[80] The three products were the hydroxyketone **157**, the *cis*-diol **158** and the unusual condensation product **159**. This result corrects an earlier report[81] in which the regiochemistry of products **157** and **159** was transposed (*cf.* ref. 6*e*). A number of transformations of the hydroxyketone **157** were reported, including dehydroxylation to **160** *via* the thiocarbonylimidazolide, and reduction with sodium borohydride to give the *trans*-diol **161** (a known natural product) in 50% yield. Mono- and di-esters **162**–**164** of the latter compound were also prepared, and proved to be several times more cytotoxic than acronycine itself in inhibiting the proliferation of L-1210 leukaemia cells. Indeed, the diacetate **164** was sixteen times more active than acronycine when evaluated *in vivo* against murine P-388 leukaemia. However, the recently described[82] diacetate of *cis*-diol **158** is still the most active antitumour agent in the series prepared by this research group to date (*cf.* ref. 6*f*).

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Review 8/09408J