Quinoline, quinazoline and acridone alkaloids

Joseph P. Michael

Centre for Molecular Design, Department of Chemistry, University of the Witwatersrand, Wits 2050, South Africa

Covering: July 1995 to June 1996
Previous review: 1997, 14, 11

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1 Quinoline alkaloids

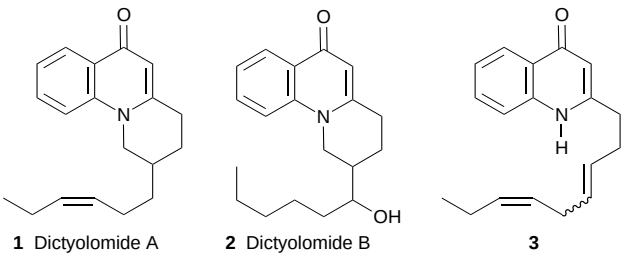
1.1 Occurrence

The overwhelming majority of quinoline alkaloids are found in the Rutaceae. In Table 1 are listed new rutaceous quinoline alkaloids described in the period from July 1995 to June 1996, as well as known alkaloids isolated from new sources belonging to this family.[1–15] Table 2 contains a list of quinoline alkaloids and antibiotics isolated from non-rutaceous plants, microbial sources and animals.[20–26] Unless otherwise stated, it may be assumed that all new compounds were comprehensively characterised with the aid of NMR and other spectroscopic techniques.

A substantial survey of the alkaloids isolated from medicinal plants of New Caledonia includes a large section on quinoline and acridone alkaloids from rutaceous plant sources unique to this South Pacific island.[27]

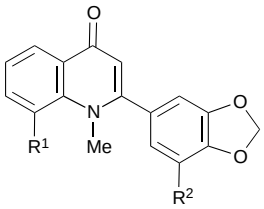
1.2 Non-terpenoid quinoline and quinolinone alkaloids from rutaceous sources

A surprising new twist on the 2-alkylquinolin-4-one alkaloids is provided by two new metabolites isolated from the Bolivian tree *Dictyoloma peruviana*.[1] Dictyolomides A and B, **1** and **2**, are unique optically active 1,2,3,4,6,11-hexahydropyrido-[1,2-*a*]quinolin-6-ones that can plausibly be derived by cyclisation of a simpler quinolinone bearing an unsaturated chain at C-2, for example, the known alkaloid 2-(nona-3,6-dienyl)-quinolin-4-one **3**. A more than usually comprehensive range of NMR experiments was used to deduce the gross structures of the two new alkaloids and the (*Z*)-geometry of the alkene substituent in **1**. However, neither the absolute stereochemistry of the alkaloids nor the relative stereochemistry of **2** were established. Both were found to have antileishmanial activity, and induced complete lysis of parasites at 100 μg ml^{-1}.

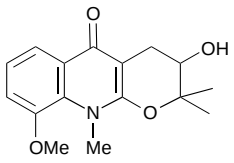


1 Dictyolomide A **2** Dictyolomide B **3**

Two 2-arylquinolin-4-one alkaloids from the roots of the Brazilian plant *Esenbeckia grandiflora* have proved to be more highly substituted derivatives of the well-known compound graveoline **4**. The new alkaloids are 3′-methoxygraveoline **5** and 3′,8-dimethoxygraveoline **6**.[2] The 8-methoxy substituent in the latter, uncommon in simple quinolin-4-ones [*cf*. ref. 28(*a*)], seems to be emerging as a chemotaxonomic marker for *Esenbeckia*. In support of this hypothesis is the recent isolation of (−)-lunacrinol **7** from *E. hieronimi*.[3]



4 Graveoline $R^1 = R^2 = H$
5 $R^1 = H$; $R^2 = OMe$
6 $R^1 = R^2 = OMe$



7 Lunacrinol

Glycocitridine **8**, a new quinolin-2-one alkaloid isolated from the leaves of *Glycosmis citrifolia*,[5] is unusual in bearing a formyl substituent at C-3. This group almost certainly arises from oxidation and cleavage of the furan ring in a furo-[2,3-*b*]quinoline alkaloid such as skimmianine **9**, which was also isolated in this investigation. The authors have apparently not realised that spontaneous aerial oxidation of methoxylated furoquinoline alkaloids to give 3-carbaldehydes akin to glycocitridine was demonstrated as recently as 1992.[29] Both *G. citrifolia*[5] and *Tetradium glabrifolium*[13] also produce the new alkaloid evomeliaefolin **10**, which can be envisaged as arising from glycocitridine by 'aldol' chain extension.

An even more unusual alkaloid, the diester-bearing quinolin-4-one **11**, was isolated from the leaves of *Sarcomelicope dogniensis*, a rutaceous tree from New Caledonia.[11] The authors postulate a novel biogenesis for this compound, which they suggest arises by oxidative cleavage of the electron-rich aromatic ring of an acridone alkaloid such as melicopidine **12**.

The ruthenium-catalysed reductive cyclisation of 2-nitrochalcones to give 2-arylquinolin-4-ones, described in the previous report in this series,[28a] has now been improved by using palladium(II) 2,4,6-trimethylbenzoate as catalyst, 3,4,7,8-tetramethyl-1,10-phenanthroline as ligand, and an atmosphere of carbon monoxide.[30] For example, the nitrochalcone **13** was easily converted into a mixture of norgraveoline **14** (78%) and its 2,3-dihydro analogue (16%). Oxidation of the crude reaction mixture with 2,3-dichloro-5,6-dicyanobenzoquinone

Table 1 Isolation and detection of quinoline alkaloids from rutaceous plants

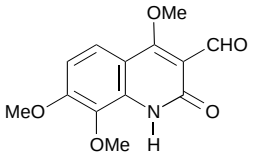
Species	Alkaloid[a]	Ref.
Dictyoloma peruviana	(+)-Dictyolomide A[b] **1**	1
	(+)-Dictyolomide B[b] **2**	
Esenbeckia almawillia	Flindersiamine	2
	Maculosidine	
Esenbeckia grandiflora	Flindersiamine	2
	Kokusaginine	
	Maculine	
	2-(3-Methoxy-4,5-methylenedioxyphenyl)-1-methylquinolin-4-one[b] **5**	
	8-Methoxy-2-(3-methoxy-4,5-methylenedioxyphenyl)-1-methylquinolin-4-one[b] **6**	
	4-Methoxy-1-methylquinolin-2-one	
Esenbeckia hieronimi	γ-Fagarine	3
	Flindersiamine	
	Kokusaginine	
	(−)-Lunacrinol **7**	
	Maculine	
	Skimmianine **9**	
Evodia roxburghiana	Buchapine **32**	4
	3-Prenyl-4-prenyloxyquinolin-2-one **33**	
	(+)-Roxiamine A[b] **34**	
	Roxiamine B[b] **35**	
	(+)-Roxiamine C[b] **36**	
Glycosmis citrifolia	1,2-Dimethylquinolin-4-one	5
	Evomeliaefolin[b] **10**	
	γ-Fagarine	
	Glycocitridine[b] **8**	
	(*E*)-Rhoifolinic acid methyl ester	
	(*Z*)-Rhoifolinic acid methyl ester	
	Skimmianine	
Haplophyllum perforatum	Haplosamine[b] **21**	6
Haplophyllum vulcanicum	Dictamnine **40**	7
	Haplopine	
Melicope semecarpifolia (= *M. confusa* = *Evodia merrillii*)	Evomerrine[b] **37**	8
	Haplopine	
	Platydesmine	
Metrodorea nigra	(*E*)-Rhoifolinic acid methyl ester	9
	(*Z*)-Rhoifolinic acid methyl ester	
Orixa japonica	(+)-3′-*O*-Acetylisopteleflorine[b] **23**	10
Sarcomelicope dogniensis	2,3-Dicarbomethoxy-1-methylquinolin-4-one[b] **11**	11
Skimmia caureola ssp. *multinervia*	Evoxine **39**	12
Tetradium glabrifolium (= *Evodia meliaefolia*)	(−)-Evomeliaefolin[b] **10**	13
	4-Methoxy-1-methylquinolin-2-one	
	Robustine	
Vepris bilocularis	Haplamine **25**	14
	7-Methoxyflindersine[b] **26**	
	N-Methyl-7-prenyloxyflindersine[b] **28**	
	7-Prenyloxyflindersine[b] **27**	
Zanthoxylum chalybeum	(+)-*N*-Methylplatydesmine	15
Zanthoxylum dissitum	Dictamnine	16
	γ-Fagarine	
	Haplopine	
	4-Methoxy-1-methylquinolin-2-one	
	Skimmianine	
Zanthoxylum nitidum (= *Fagara nitida*)	Edulitine	17
	γ-Fagarine	
	Isoplatydesmine	
	4-Methoxy-1-methylquinolin-2-one	
	Ribalinine	
Zanthoxylum regnellianum	Dictamnine	18
Zanthoxylum simulans	4-Methoxyquinolin-2-one	19
	Simulansine[b] **31**	
Zanthoxylum usambarense	(−)-Edulinine	15

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

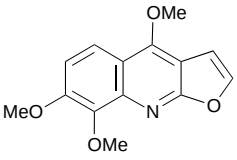
Table 2 Isolation and detection of quinoline alkaloids from non-rutaceous plants, microbial sources and animals

Species	Alkaloid[a]	Ref.
Archangium gephyra, strain Ar T205	4-Hydroxymethylquinoline **41** Quinoline-4-carbaldehyde[b] **42** Quinoline-4-carbaldoxime[b] **43** Quinoline-4-carboxylic acid[b] **44**	20
Cassia grandis	Kokusaginine	21
Clavelina lepadiformis (tunicate)	Lepadin A **63** (−)-Lepadin B[b] **64** (−)-Lepadin C[b] **65**	22
Eichhornia crassipes	1,4-Dimethylquinolinium iodide[b] Viridicatin	23
Myxococcus virescens, strain Mx v48	4-Hydroxymethylquinoline **41** Quinoline-4-carbaldoxime[b] **43**	20
Prostheceraeus villatus (marine flatworm)	Lepadin A **63** (−)-Lepadin B[b] **64** (−)-Lepadin C[b] **65**	22
Pseudomonas cepacia, strain PC-II	2-(Hept-2-enyl)-3-methylquinolin-4-one **45** 3-Methyl-2-(non-2-enyl)quinolin-4-one **46** 2-Heptyl-3-methylquinolin-4-one[b] **47** 3-Methyl-2-nonylquinolin-4-one[b] **48** 3-Methyl-4-pentylquinolin-4-one[b] **49**	24
Streptomyces nitrosporeus 30643	(−)-Benzastatin C[b] **53** (−)-Benzastatin D[b] **54**	25
Subcoccinella 24-punctata (Coccinellid beetle)	(+)-N_α-Quinaldyl-L-arginine hydrochloride[b] **62**	26

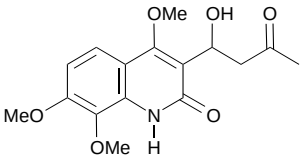
[a]Only new alkaloids and new records for a given species are listed. Structures of most known alkaloids may be found in previous reviews in this series. [b]New alkaloids.



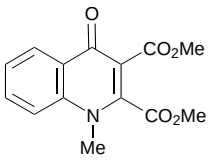
8 Glycocitridine



9 Skimmianine



10 Evomeliaefolin



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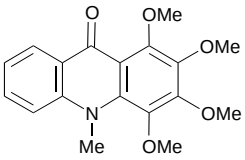
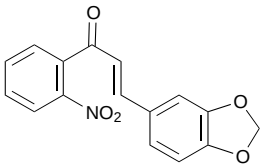


12 Melicopidine

(DDQ) gave a quantitative yield of **14**, which could easily be methylated with iodomethane in the presence of potassium carbonate to give graveoline **4** in 71% overall yield.

The crude alkaloidal extract isolated from the bark of *Galipea longiflora*, used as a traditional medicine in Bolivia for the treatment of recurrent fevers such as malaria, shows



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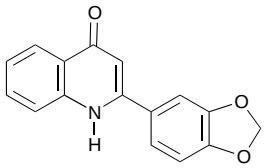

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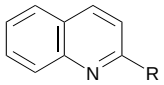
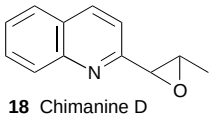
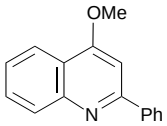


15 R = $(CH_2)_2Me$
16 R = $(CH_2)_4Me$
17 R = CH=CHMe



18 Chimanine D



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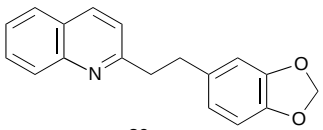

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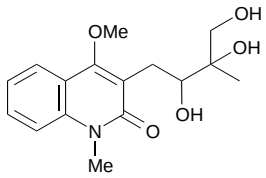
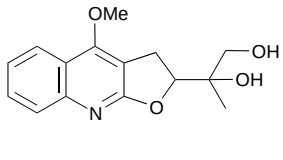
antiplasmodial activity in mice infected with the malaria-causing parasite *Plasmodium vinckei petteri*.[31] While all six alkaloids identified in this extract [2-propylquinoline **15**, 2-pentylquinoline **16**, chimanines B **17** and D **18**, 4-methoxy-2-phenylquinoline **19** and 2-(3,4-methylenedioxyphenylethyl)-quinoline **20**] proved effective when tested separately against the parasite, compound **16** was especially active, showing approximately the same level of activity as the well-known antimalarial compound chloroquine.

1.3 Terpenoid rutaceous quinoline alkaloids and tricyclic derivatives

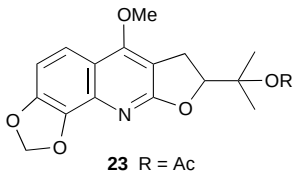
Epigeal parts of specimens of *Haplophyllum perforatum* collected in Kazakhstan have yielded haplosamine **21**, a new quinolin-2-one alkaloid bearing an unusually modified prenyl group at C-3.[6] This trihydroxylated chain seems to be unique amongst the quinoline alkaloids. Haplosamine proved to be identical with a compound previously obtained by hydrolysing the methiodide of dubinidine **22** with aqueous ammonia.[32]



21 Haplosamine



22 Dubinidine

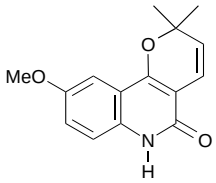


23 R = Ac
24 R = H

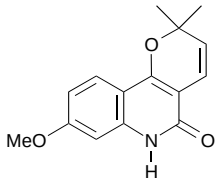
The stems of *Orixa japonica* have yielded a new dihydrofuro[2,3-*b*]quinoline alkaloid, (+)-3′-*O*-acetylisoptele-florine **23**.[110] The customary spectroscopic evidence for the structure was supplemented by hydrolysis of **23** with dilute alkali to give (−)-isopteleflorine **24** which, though not itself

a natural product, has previously been synthesised.[33] The absolute configuration of the alkaloid was not determined.

A suite of pyrano[3,2-*c*]quinolinones isolated from the leaf extract of *Vepris bilocularis*, a forest tree of south India, includes the known compound haplamine **25** and three



25 Haplamine



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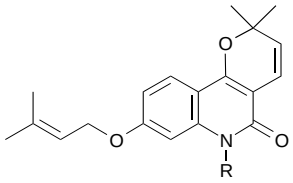
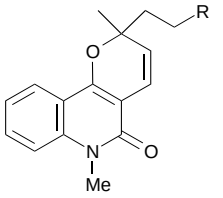


27 R = H
28 R = Me

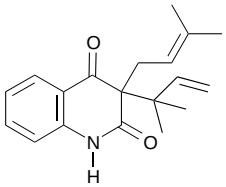
new flindersine derivatives bearing oxygen at C-7, namely 7-methoxyflindersine **26**, 7-prenyloxyflindersine **27** and *N*-methyl-7-prenyloxyflindersine **28**.[14] This exclusive oxygenation at C-7 has previously been observed only in the African genus *Oricia* which, like *Vepris*, belongs to the sub-family Toddalioideae.

So uncommon are the monoterpenoid quinoline alkaloids that the recent isolation of several new examples, including huajiaosimuline **29** and zanthosimuline **30** from *Zanthoxylum simulans* [*cf*. ref. 28(*b*)], was a noteworthy event. The root bark of this plant has now yielded a further new analogue, simulansine **31**.[19] Spectroscopic evidence for this structure was bolstered by transformation into huajiaosimuline **29** upon oxidation with chromium trioxide.

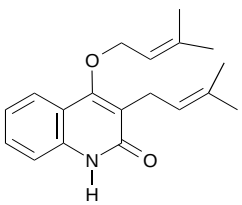


29 Huajiaosimuline R = C(=O)CHMe$_2$
30 Zanthosimuline R = CH=CMe$_2$
31 Simulansine R = CH(OH)CHMe$_2$

The anti-HIV activity of extracts of *Evodia roxburghiana* appears to be due to the presence of buchapine **32** and 3-prenyl-4-prenyloxyquinolin-2-one **33** rather than the roxiamines (see Section 1.4 below).[4] When isolated, both compounds were shown to be active against infectious HIV-1



32 Buchapine



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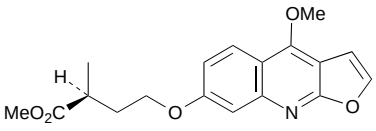
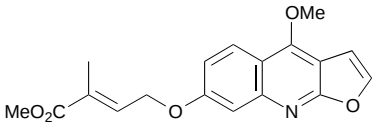
in human lymphoblastoid host cells (EC_{50} = 0.94 mM, IC_{50} = 29.0 mM, and EC_{50} = 1.64 mM, IC_{50} = 26.9 mM, respectively). They also showed inhibitory activity in an HIV-1 reverse transcriptase assay (IC_{50} = 12 and 8 mM, respectively).

1.4 Furoquinoline alkaloids from rutaceous sources

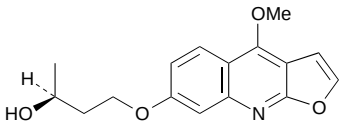
Three new 7-oxygenated furo[2,3-*b*]quinoline alkaloids, roxiamines A, B, and C, **34**–**36**, have been isolated from aerial



34 (+)-Roxiamine A

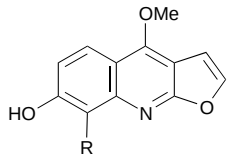


35 Roxiamine B

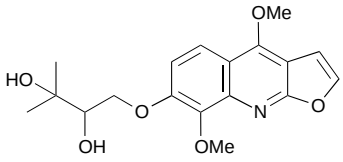


36 (+)-Roxiamine C

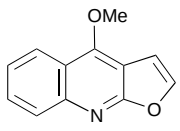
parts of the Thai plant *Evodia roxburghiana*.[4] These related compounds are different from most known 7-*O* 'prenylated' furoquinolines in having no methoxy substituent at C-8; furthermore, the prenyl group has been substantially modified in all three metabolites. The geometry of the double bond in roxiamine B **35**, in which the *E* methyl group of the prenyl unit has been oxidised and esterified, was established by NOE experiments. (+)-Roxiamine A **34** is a saturated analogue of **35**, and (+)-roxiamine C **36** is effectively the hydroxy–demethoxycarbonylated analogue of **34**. The *S* absolute configuration of **36** was determined from $\Delta\delta$ values in the ^{1}H NMR spectra of both the (*R*)- and (*S*)-Mosher's ester derivatives. Comparison of the ORD curves of **34** and **36**, and further correlations involving a suite of model compounds, provided good evidence that **34** also has the *S* configuration.



37 Evomerrine R = CHO
38 Confusameline R = H



39 Evoxine



40 Dictamnine

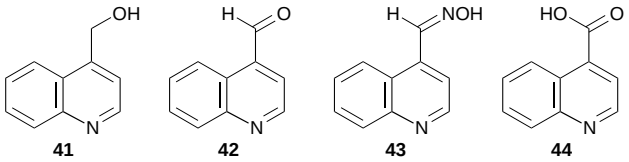
Evomerrine **37** was obtained as colourless needles from the leaves of *Melicope semecarpifolia* (= *M. confusa* = *Evodia merrillii*), a Rutaceous tree indigenous to Taiwan and the Philippines.[8] Like glycocitridine **8** (*cf*. Section 1.2), this new alkaloid bears a highly unusual formyl substituent, which in

this case is hydrogen-bonded to a phenolic OH group on an adjacent position. The location of these two substituents was substantiated by formylation of the related alkaloid confusameline **38** – also isolated in this study – under Reimer–Tiemann conditions with chloroform and sodium hydroxide.

The mass spectrometric fragmentation pattern of evoxine **39** has been elucidated with the aid of mass-analysed ion kinetic energy (MIKE) spectrometry.[12] Dictamnine **40** is one of the compounds responsible for the strong *in vitro* antiplatelet aggregation activity in the bark extract of Chinese *Zanthoxylum schinifolium*, coumarins constituting the remaining active constituents.[34]

1.5 Quinoline alkaloids from microbial sources

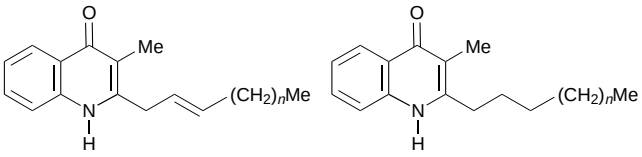
Alkaloids and antibiotics containing quinoline rings are cropping up with increasing frequency in non-rutaceous plants as well as in microbial sources and animals. A group of antifungal constituents isolated from cultures of the soil myxobacterium *Archangium gephyra* (strain Ar T205) included four simple quinoline alkaloids: 4-hydroxymethylquinoline **41**, quinoline-4-carbaldehyde **42**, quinoline-4-carbaldoxime **43** and



41 **42** **43** **44**

quinoline-4-carboxylic acid **44**.[20] Another gliding bacterium, *Myxococcus virescens* (strain Mx v48), also yielded small amounts of **41** and **43**. Although all these compounds are comparatively well known as synthetic materials, only 4-hydroxymethylquinoline **41** has previously been recorded as a natural product[35] [*cf*. ref. 28(*c*)]. Labelling studies with L-[1′-^{14}C]tryptophan, which was efficiently incorporated into both **41** and **43**, indicated that the quinoline ring must be derived by indole–quinoline rearrangement, a process that is well established in plant secondary metabolism.

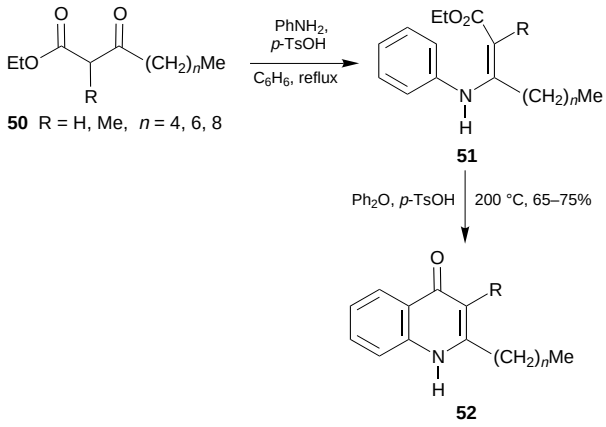
Many 2-alkylquinolin-4-one alkaloids bear the trivial names 'pseudans' because of their occurrence in bacteria of the genus *Pseudomonas*. In a search for natural antagonists of the soil-borne pathogen *Phytophthora capsici*, which is responsible for 'phytophthora blight' in red peppers (*Capsicum annuum*), the culture broth of *P. cepacia* strain PC-II was screened by bioactivity-guided fractionation.[24] Reverse-phase HPLC of the active fractions yielded two known 3-methylpseudans **45** and



45 *n* = 3
46 *n* = 5

47 *n* = 1
48 *n* = 3
49 *n* = 5

46 as well as the three new analogues **47**–**49** in the ratio 67:26:2:3:2. The *E* configuration of the unsaturated compounds was inferred from the large coupling constants (*J* 16.3 and 15.3 Hz, respectively) apparent in their ^{1}H NMR spectra. Of the five compounds isolated, 2-(hept-2-enyl)-3-methylquinolin-4-one **45** proved to be the most active against *P. capsici* and other fungal plant pathogens. Furthermore, when red pepper seeds were treated with this compound before planting, their growth was significantly enhanced. This is the first report of plant growth simulation by a quinolin-4-one alkaloid. The structures of compounds **47**, **48** and related 2-alkylquinolin-4-ones were confirmed by the simple Conrad–Limpach condensation shown as **50**→**51**→**52**.[36]

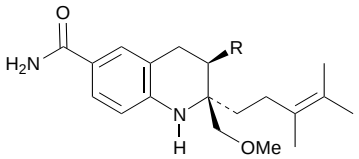


50 R = H, Me, *n* = 4, 6, 8

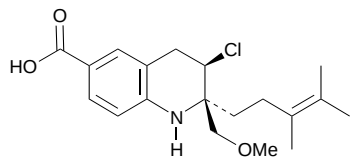
51

52

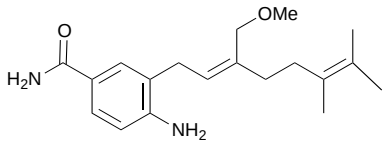
The culture broth of *Streptomyces nitrosporeus* 30643 has yielded two new tetrahydroquinoline antibiotics, (−)-benzastatins C and D, **53** and **54**, which are related in structure to the comparatively well-known microbial metabolite virantmycin **55**.[25] The gross structures of **53** and **54** were deduced



53 Benzastatin C R = Cl
54 Benzastatin D R = OH

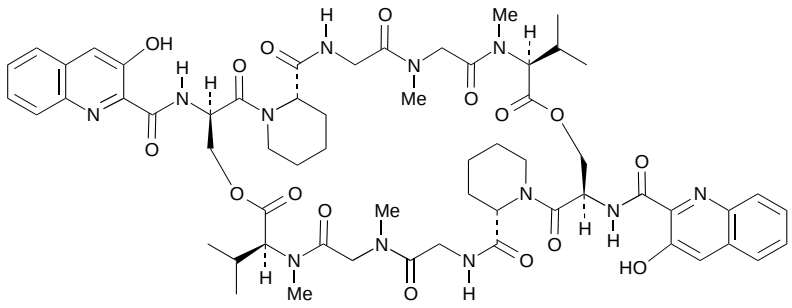


55 Virantmycin



56 Benzastatin A

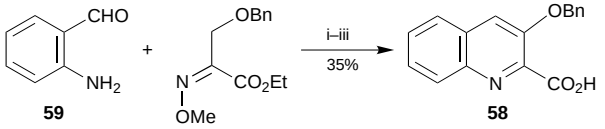
with the aid of standard spectroscopic techniques. However, nuclear Overhauser experiments gave ambiguous results for their relative stereochemistry because of the conformational flexibility of the piperidine ring. Nevertheless, the stereochemistry was assigned as shown because the 1H NMR chemical shifts and coupling constants matched those reported for virantmycin rather than its diastereomer. The (9*R*,10*R*) absolute configurations were apparent from comparisons of the circular dichroism spectra of the new compounds with that of virantmycin. Benzastatin D **54** appears to be biogenetically derived by oxidative cyclisation of another simpler new metabolite, benzastatin A **56**. All the benzastatins proved to be free-radical scavengers which inhibited lipid peroxidation in rat liver microsomes, albeit less effectively than vitamin E. However, benzastatins C and D were about as potent as



57 (–)-Sandramycin

vitamin E in inhibiting glutamate toxicity in N18-RE-105 hybrid cancer cells, although the former proved to be cytotoxic.

Since the recently published[37] total synthesis of the antitumour antibiotic (−)-sandramycin **57** is essentially an exercise in the construction of a cyclic decadepsipeptide, it will not be outlined here. Of greater interest is the synthesis of the pendent 3-hydroxyquinoline-2-carboxylic acid group, the benzyl ether **58** of which was prepared from 2-aminobenzaldehyde **59** and the pyruvic ester derivative **60** by a modified Friedlander synthesis (Scheme 1).[38] Attaching this



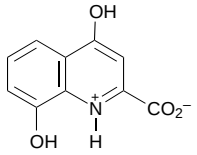
59 **60** **58**

Scheme 1 *Reagents*: i, KOH, EtOH, reflux; ii, MeI, Bu_4NI, $NaHCO_3$, CH_2Cl_2, 25 °C; iii, $LiOH·H_2O$, THF–MeOH–H_2O (3:1:1), 25 °C

heteroaromatic chromophore to the cyclic depsipeptide at a comparatively late stage of the synthesis permitted access to a number of analogues, which proved useful in probing the antibiotic's preferential binding to DNA in regions containing alternating A and T residues. Studies of the 1:1 complex of sandramycin and $d(GCATGC)_2$ revealed that the antibiotic maintains a twofold axis of symmetry when intercalating between the central two AT base pairs, but that it folds such that the distance between the chromophores is 10.1 Å. This is significantly different from the single rigid conformation adopted in solvents other than DMSO (determined from NMR studies), the estimated distance between the chromophores being 17–19 Å, enough to span three DNA base pairs. Studies of the binding between calf thymus DNA and **57** or analogues bearing zero or one heteroaromatic chromophore revealed that the cyclic decadepsipeptide backbone is responsible for the largest share of the minor-groove binding ($\Delta G° = -6$ kcal mol^{-1}), with increments of 3.2 and 1.0 kcal mol^{-1}, respectively, as each chromophore is added. Sandramycin thus ends up being about 10^3 times as potent a binder as an analogue with only one chromophore, and 10^5 times as potent as the cyclic depsipeptide parent itself.

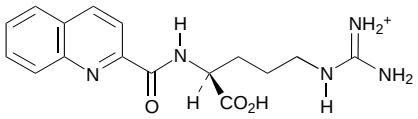
1.6 Quinoline alkaloids from animals

The crystal structure of the monohydrate of xanthurenic acid, a well-known metabolic product of kynurenin induced as a result of vitamin B_6 deficiency, has been determined.[39] The authors interpret the results in favour of the zwitterionic structure **61**, with an intramolecular hydrogen bond between the protonated nitrogen atom and the carboxylate group, and a molecule of water acting as an intermolecular hydrogen-bonding bridge between several different sites in the molecule.



61

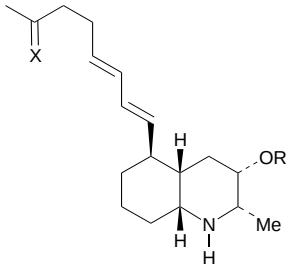
When under threat, ladybirds and other insects of the Coccinellidae exude hemolymph droplets from their leg joints in a process known as 'reflex bleeding'. Defensive alkaloids contained in this fluid are responsible for its powerful repellency towards predators. Quinoline alkaloids have not hitherto been detected in these exudates, but the ladybird *Subcoccinella 24-punctata* has now been found to secrete (+)-N_α-quinaldyl-L-arginine **62**, which was isolated as the hydrochloride salt



62

(8 mg from 328 adult insects).[26] Spectroscopic evidence for this structure was complemented by a simple synthesis from quinoline-2-carbonyl chloride and L-arginine. The new alkaloid proved to be a highly effective feeding deterrent to the ant species *Myrmica rubra*; the concentration at which 50% of ants were repelled (RD50) was 10^{-4} M, making it a more powerful antifeedant than other Coccinellid alkaloids for which deterrence has been evaluated.

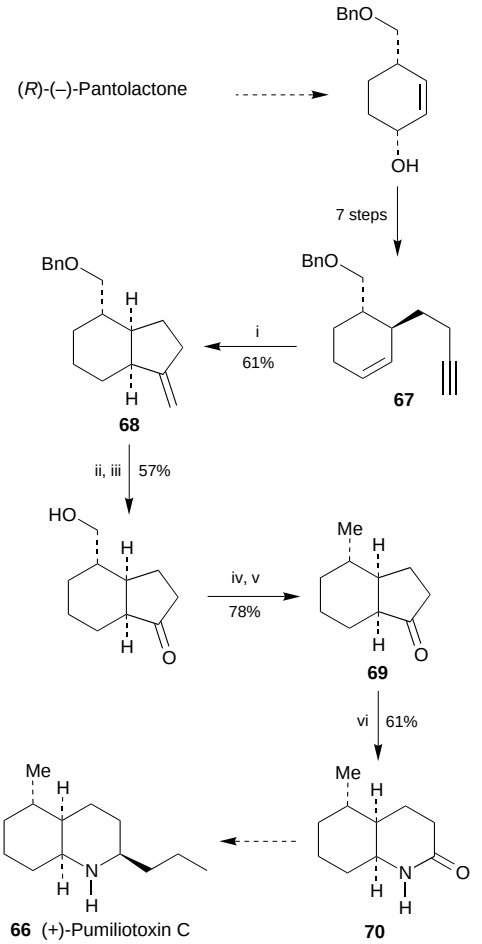
The carnivorous marine flatworm *Prostheceraeus villatus* has been found[22] to sequester defensive alkaloids from its prey, the tunicate (sea-squirt) *Clavelina lepadiformis*, which has previously been shown to produce the decahydroquinoline alkaloid lepadin A **63**.[40] Specimens of both animals were collected by SCUBA off the coast of Norway at Bergen. The



63 Lepadin A R = $COCH_2OH$; X = 2H
64 Lepadin B R = H; X = 2H
65 Lepadin C R = $COCH_2OH$; X = O

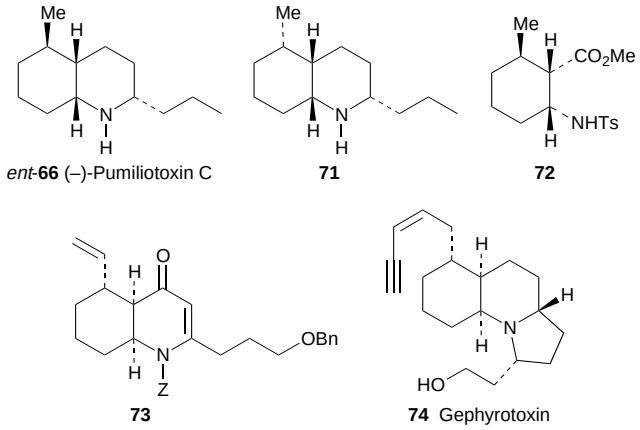
chloroform-soluble extract from 200 flatworms was purified by fractionation on Sephadex followed by reverse-phase HPLC to give, as the trifluoroacetate salts, lepadin A (0.2 mg per worm) and the new alkaloids (−)-lepadin B **64** (0.04 mg per worm) and (−)-lepadin C **65** (0.02 mg per worm), as well as two new pyrrolidine alkaloids, all of which were thoroughly characterised by spectroscopic methods. The alkaloidal extract from the tunicate had essentially the same composition. This appears to be the first known case of alkaloid transfer from a prey organism to a flatworm predator. Lepadins A and B showed significant *in vitro* cytotoxic activity towards a variety of murine and human cancer cell lines, but lepadin C was inactive.

The frog skin alkaloid pumiliotoxin C, also known as decahydroquinoline *cis*-195A, remains a popular target for synthesis. (+)-Pumiliotoxin C **66**, the unnatural enantiomer, has been formally prepared by Fukumoto and co-workers by a route in which a pivotal palladium-induced reductive cyclisation of enyne **67** to **68** was later followed by the regio- and stereo-specific Beckmann rearrangement of **69** to **70** in order to introduce the nitrogen atom (Scheme 2).[41] The conversion of



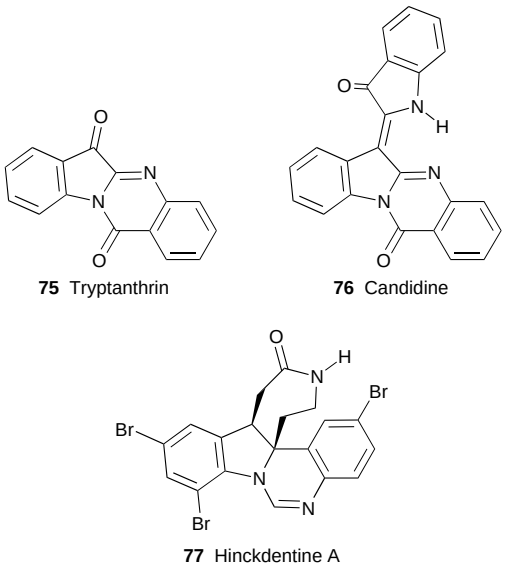
Scheme 2 *Reagents*: i, $(dba)_3Pd_2{\cdot}CHCl_3$ (2.5 mol%), *N*,*N*′-bis(benzylidene)ethylenediamine, (5 mol%), polymethylhydrosiloxane, HOAc, $ClCH_2CH_2Cl$; ii, Na, NH_3, THF, −78 °C, then NH_4Cl; iii, O_3, MeOH, −78 °C, then Me_2S; iv, 1,1′-thiocarbonyldiimidazole, DMAP, CH_2Cl_2, reflux; v, Bu_3SnH, AIBN, C_6H_6, reflux; vi, $NH_2OH{\cdot}HCl$, NaOAc, MeOH, then *p*-TsCl, NaOH, H_2O–THF

ent-**70** into the (−)-alkaloid *ent*-**66** has been described by Murahashi *et al.*,[42] while a similar conversion in the racemic series was recently described by Mehta and Praveen[43] [*cf.* ref. 28(*d*)]. Kibayashi's acylnitroso Diels–Alder route to (−)-pumiliotoxin C, *ent*-**66**, previously revealed in a communication[44] [*cf.* ref. 28(*d*)], has now been published in full together with related studies on the epimer **71**.[45] This research has also been summarised in a more wide-ranging review.[46] The synthesis of compound (−)-**72** by Davies and Bhalay[47] in several steps from (*R*)-(+)-pulegone represents a formal synthesis of the (−)-alkaloid, since *ent*-**72** has previously been transformed into the unnatural (+)-pumiliotoxin C **66**.[48] Finally, the work of Comins *et al.* in preparing alkaloids of the pumiliotoxin C class has been outlined in a comprehensive review on the use of 1-acylpyridinium salts as intermediates in alkaloid synthesis.[49] In this regard, Comins has also prepared the octahydroquinolinone **73** as part of a planned synthesis of the tricyclic amphibian alkaloid gephyrotoxin **74**.[50]



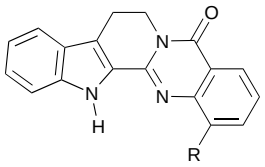
2 Quinazoline alkaloids

A review describing a century of progress in the chemistry of indoloquinazolines includes brief mention of the isolation and synthesis of the quinazoline alkaloids tryptanthrin **75**, candidine **76** and hinckdentine A **77**.[51]

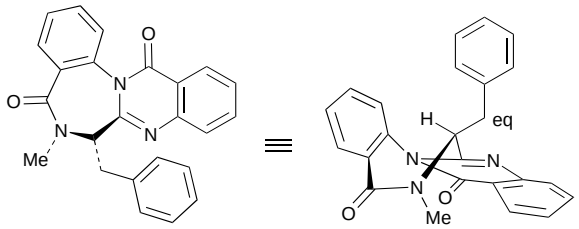


2.1 Isolation

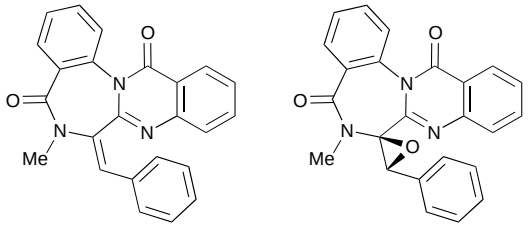
Bioassay-guided fractionation of the extracts of *Zanthoxylum integrifolium* fruits yielded three alkaloids that showed antiplatelet aggregation activity.[52] These proved to be the known compounds rutaecarpine **78** and 1-hydroxyrutaecarpine **79**, and a new natural product, 1-methoxyrutaecarpine **80**. The structure of **80** was established by comparison with a



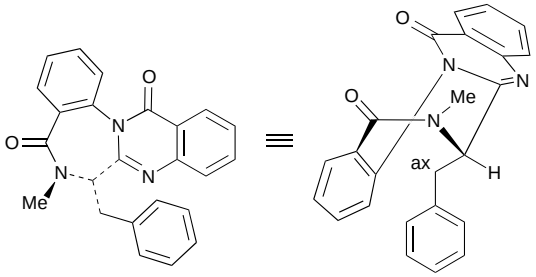
78 Rutaecarpine R = H
79 1-Hydroxyrutaecarpine R = OH
80 1-Methoxyrutaecarpine R = OMe



81 Benzomalvin A **86**



82 Benzomalvin B **83** Benzomalvin C

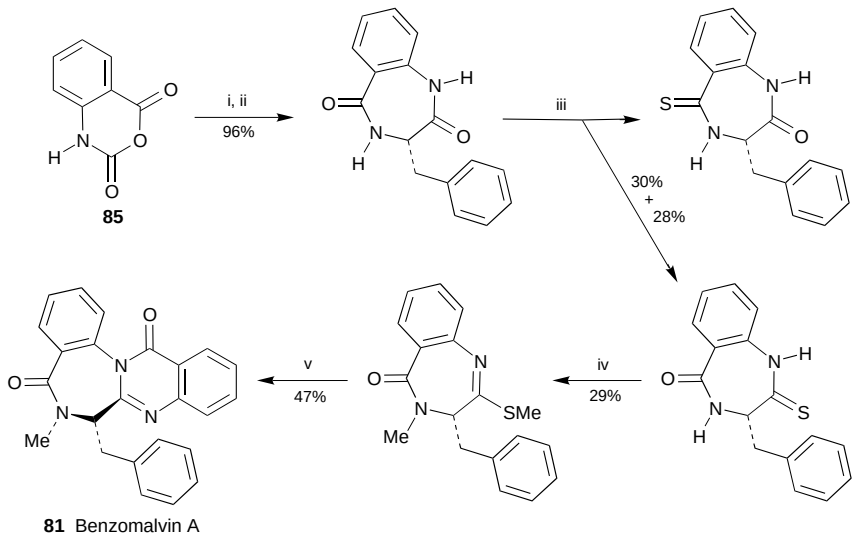


84 Benzomalvin D **87**

sample prepared by methylating **79** with diazomethane, and further confirmed by an NOE difference experiment. In *in vitro* tests, 1-hydroxyrutaecarpine was the strongest inhibitor of platelet aggregation induced by arachidonic acid, and showed an IC_{50} value of 1–2 mg ml^{-1}. Rutaecarpine has also been isolated from the leaves of *Tetradium glabrifolium*.[53] The vasodilatory effects of rutaecarpine and two related carbazoloquinazoline alkaloids have been demonstrated in smooth muscle from rat thoracic aortas containing intact endothelium cells.[54]

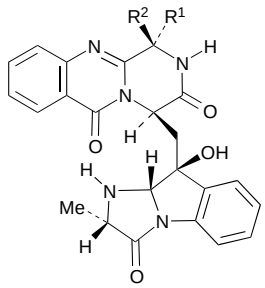
Benzomalvins A–C, **81**–**83**, reported in 1994 as metabolites of a *Penicillium* culture,[55] have previously been mentioned in this series of reviews.[28e] A further unstable new metabolite, (+)-benzomalvin D, has now been extracted from the same culture.[56] On standing overnight in solution at room temperature, benzomalvin D was converted into benzomalvin A **81**; similarly, benzomalvin A interconverted with benzomalvin D. The equilibrated mixtures contained a 4:1 mixture of **81** and the new metabolite **84**. Separation of these compounds was possible by HPLC, and storage of the solid compounds at − 40 °C retarded their equilibration. When thorough spectroscopic analysis failed to give a clear picture of the structural differences between the two compounds, a total synthesis of benzomalvin A from isatoic anhydride **85**, L-phenylalanine and methyl anthranilate was undertaken (Scheme 3). The enantiomerically pure synthetic benzomalvin A (3.7% overall yield based on isatoic anhydride) equilibrated in the same way as the natural product. Eventually, variable temperature NMR revealed that the two compounds are conformational isomers – in fact, atropisomers. Molecular dynamics calculations suggested the conformers **86** and **87**, possessing equatorial and axial benzyl groups, for the structures of benzomalvins A and D respectively; and these structures correlated well with the observed NMR spectra. Furthermore, atropisomerism now provides a feasible rationalisation for the observed optical activity of benzomalvin B **82**, which possesses no stereogenic carbon centres.

The structures of fumiquinazolines A–C, **88**–**90**, metabolites of the fungus *Aspergillus fumigatus* separated from the gastrointestinal tract of the marine fish *Pseudolabrus japonicus*, were revealed in a communication in 1992,[57] and described in this series of reviews shortly afterwards.[28f] Full details on the structural elucidation have now been published in a paper in which the structures of four new fumiquinazolines D–G,

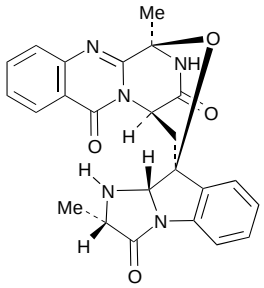


85 **81** Benzomalvin A

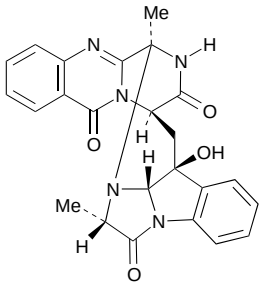
Scheme 3 *Reagents*: i, L-phenylalanine, NEt_3, H_2O, rt; ii, HOAc, reflux; iii, Lawesson's reagent, THF, rt, then flash chromatography on SiO_2; iv, NaOH (40% aq.), MeI, Bu_4NHSO_4, toluene, rt; v, methyl anthranilate, 135 °C



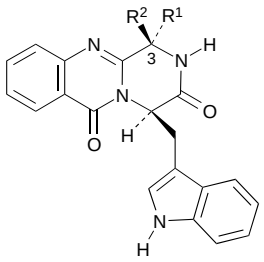
88 Fumiquinazoline A R^1 = Me; R^2 = H
89 Fumiquinazoline B R^1 = H; R^2 = Me
92 Fumiquinazoline E R^1 = Me; R^2 = OMe



90 Fumiquinazoline C



91 Fumiquinazoline D

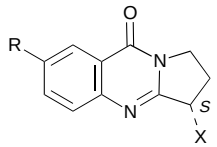


93 Fumiquinazoline F R^1 = Me; R^2 = H
94 Fumiquinazoline G R^1 = H; R^2 = Me

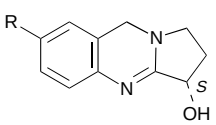
91–**94**, are also reported.[58] X-Ray crystallography established the structures and relative stereochemistry of fumiquinazolines C and D, while the absolute configurations of these two compounds were established by the formation of L-(+)-alanine upon acidic hydrolysis. In addition, the expected plethora of NMR studies and a range of chemical interconversions and degradations served to establish the relative and absolute stereostructures of the remaining metabolites, as well as several interesting conformational effects. Fumiquinazolines F **93** and G **94** proved to be epimeric at C-3; basic equilibration of either yielded a 3:2 mixture of the isomers, with F predominating. All the fumiquinazolines were moderately cytotoxic in the P388 lymphocytic leukaemia test system.

2.2 Structural and synthetic studies

Important new crystallographic investigations[59] on two well-known alkaloids from the Indian medicinal plant *Adhatoda vasica* have been used to refute a 20 year old claim[60] that (−)-vasicine has the 3*R* absolute configuration. The discovery came about because X-ray analysis of the hydrobromide salt of (−)-vasicinone **95** revealed an incontrovertible 3*S* absolute



95 (–)-Vasicinone R = H; X = OH
98 Vasicinolone R = X = OH
100 Deoxyvasicinone R = X = H

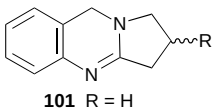


96 (–)-Vasicine R = H
97 (+)-Vasicinol R = OH
99 R = OMe

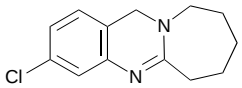
configuration based on analysis of the Flack parameter α and a consistent set of anomalous dispersion results. The authors' suspicions concerning the correctness of the earlier work were aroused in view of the well-established fact that (−)-vasicinone can be obtained from (−)-vasicine by autoxidation or oxidation with hydrogen peroxide. They therefore analysed (−)-vasicine and its dextrorotatory hydrobromide salt by X-ray crystallography, and their anomalous dispersion studies strongly suggested that the earlier assignment of absolute configuration for (−)-vasicine should be revised to 3*S*, as shown in **96**. The absolute structures of two other alkaloids which have previously been correlated with (−)-vasicine, (+)-vasicinol **97** and vasicinolone **98**, must now also be revised to 3*S*. A fascinating corollary to the above study was provided by analysis of the (+)- and (−)-Mosher's esters of (−)-vasicinone by NMR spectroscopy. These results did *not* support the revised 3*S* absolute configuration, but this aberration was ascribed to the profound change in molecular conformation imparted by the heteroatoms close to the stereogenic centre, which invalidates the correlation upon which the Mosher method is based.

The structure of the monohydrate of 7-methoxyvasicinone **99**, another alkaloid from *Adhatoda vasica*, has been determined by X-ray crystallography, but no assignment of absolute configuration was made.[61] Other recent crystallographic studies include those on deoxyvasicinone **100**, its hydrochloride salt and a tetrachlorocobaltate salt.[62] Vasicine **96** (commonly named peganine in the Russian literature) can conveniently be separated from mixtures containing related *Peganum harmala* quinazoline alkaloids by formation of tetrachlorozincate salts followed by sequential precipitation and recrystallisation of the perchlorate and nitrate salts.[63]

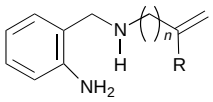
In a search for new therapeutic agents for the treatment of Alzheimer's disease, deoxyvasicine **101** and eleven synthetic analogues have been assayed for anticholinesterase activity in the rat brain and in human red blood cells.[64] The most potent inhibitor in the series, **102**, provides a useful new lead for further investigations.



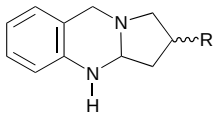
101 R = H
107 R = Me



102



103 *n* = 1; R = H
105 *n* = 1; R = Me
108 *n* = 2; R = H
109 *n* = 2; R = Me

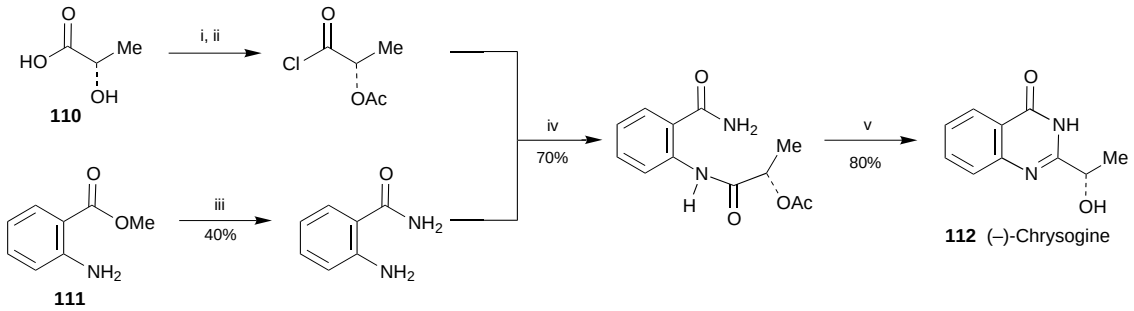


104 R = H
106 R = Me

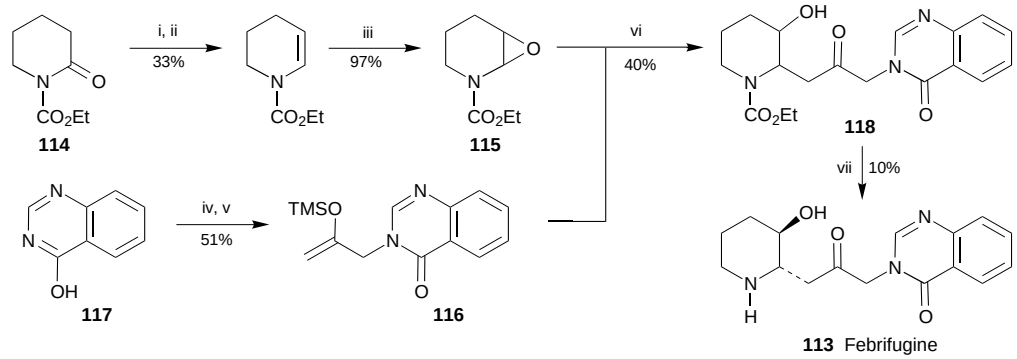
Reductive carbonylation of *N*-allyl-2-aminobenzylamine **103** with carbon monoxide and hydrogen over a rhodium catalyst yielded dihydrodeoxyvasicine **104** in 96% yield.[65] The methylallyl analogue **105** yielded mixtures of the hexahydropyrroloquinazoline **106** and the tetrahydro derivative **107**, while the homologues **108** and **109** afforded even more complex mixtures of fused quinazoline products.

The fungal metabolite chrysogine has been mentioned frequently in these reviews,[28e, g] and the assignment of its absolute configuration has been discussed on several occasions. The first asymmetric synthesis of this alkaloid (incorrectly called chrysogenine) from (*S*)-(−)-lactic acid **110** and anthranilamide **111** (Scheme 4) has now been published.[66] The synthesis supports the assignment of *S* absolute stereochemistry for the (−)-alkaloid **112**.

Febrifugine **113** is a *Hydrangea* alkaloid that possesses antimalarial and anticoccidial properties. A new synthetic route to *trans*-2-alkylpiperidin-3-ols has now paved the way for a stereoselective synthesis of the racemic alkaloid (Scheme 5).[67] In this route, partial reduction of 1-ethoxycarbonylpiperidin-2-one **114** followed by elimination and oxidation with dimethyldioxirane yielded the epoxide **115**.

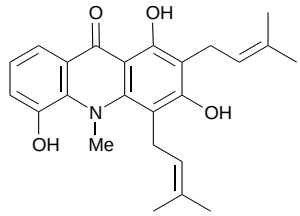


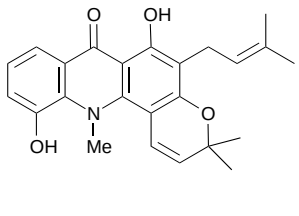
Scheme 4 *Reagents*: i, AcCl; ii, $SOCl_2$, 0–10 °C; iii, NH_4OH, 0–90 °C; iv, py, rt; v, 1% aq. NaOH, MeOH, rt

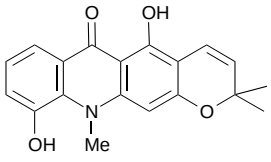


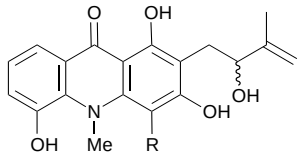
Scheme 5 *Reagents*: i, $LiBHEt_3$, THF, −78 °C, then HCl, EtOH; ii, $MgSO_4$, toluene, reflux; iii, dimethyldioxirane, acetone, 0 °C to rt; iv, NaH, DMF, 0 °C, then chloroacetone, 0 °C to rt; v, TMSOTf, Pr^i_2NEt, CH_2Cl_2, rt; vi, $TiCl_4$, CH_2Cl_2, 0 °C; vii, flash chromatography, then KOH, diethylene glycol, H_2O, heat

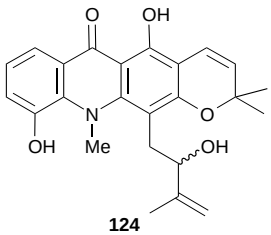
This disguised *N*-acyliminium ion precursor reacted with the trimethylsilyl enol ether **116**, made in two steps from 4-hydroxyquinazoline **117** (probably co-existing with its keto tautomer), in the presence of titanium tetrachloride, giving a 1:1 mixture of *cis* and *trans* isomers of *N*-ethoxycarbonylfebrifugine **118**. The isomers were separated by flash chromatography, after which the desired alkaloid *trans*-**113** was formed by basic hydrolysis of the ethoxycarbonyl substituent.


119 *N*-Methylatalaphylline


120 *N*-Methylatalaphyllinine


121 Yukocitrine


122 Bosistidine R = H
123 Bosistine R = prenyl


124

3 Acridone alkaloids

3.1 Occurrence and structural studies

The thirteen new acridone alkaloids reported during the review period, all from plants belonging to the Rutaceae, are listed in Table 3 along with known alkaloids from new plant sources.[11, 14, 68–73]

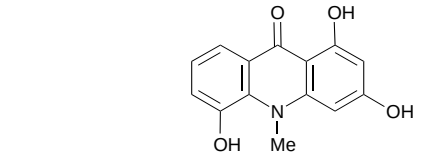
1,3,5-Trihydroxy-2,4-diprenylacridone alkaloids, hitherto found almost exclusively in the genera *Atalantia* and *Citrus*, have now been isolated from the taxonomically distant plant *Bosistoa transversa*.[68] Leaf and bark material of this previously unexplored Australian tree yielded several known acridone alkaloids of the type under discussion, including *N*-methylatalaphylline **119**, *N*-methylatalaphyllinine **120** and yukocitrine **121**, as well as the three new compounds bosistidine **122**, bosistine **123** and the yukocitrine derivative **124**. The structures were determined with the aid of standard spectroscopic techniques, but insufficient quantities were isolated to permit the absolute configuration to be established.

Over the past few years, this series of reviews has kept track of the phenomenal number of new acridone alkaloids isolated from *Citrus* plants and hybrids by the research groups of Ju-ichi and Furukawa. Much of the work on the hybrid 'Yalaha' has now been collected into a single paper that not only gives full details of the isolation of no fewer than seventy alkaloids, coumarins and other compounds, but also introduces another new alkaloid, 1,3,5-trihydroxy-*N*-methylacridone **125** – ironically, one of the simplest acridones that these workers have yet reported.[72] Furukawa and co-workers have also isolated two new acridones, acrifoline **126** and glycofolinine **127**, from *Glycosmis citrifolia*.[73] The structure of **126** was confirmed by conversion into the known alkaloid citracridone-II **128** upon treatment with iodomethane and anhydrous potassium carbonate in acetone. The structure

Table 3 Isolation and detection of acridone alkaloids

Species	Alkaloid[a]	Ref.
Bosistoa transversa	(−)-Bosistidine[b] **122**	68
	(−)-Bosistine[b] **123**	
	Citrusamine	
	(+)-4-(2-Hydroxy-3-methylbut-3-enyl)yukocitrine[b] **124**	
	Junosine	
	N-Methylatalaphylline **119**	
	N-Methylatalaphyllinine **120**	
	Yukocitrine **121**	
Citrus grandis	Citbismine-A **132**	69
	Citbismine-B[b] **133**	
	Citbismine-C[b] **134**	
	Citbismine-E[b] **136**	70
Citrus grandis f. *buntan*	Buntanbismine[b] **137**	71
Citrus hybrid '*Yalaha*' (*C. paradisi* × *C. tangerina*)	Acrignine-A	72
	Acrimarine-B, -C, -D, -E, -F and -H	
	Citpressine-I and -II	
	Citracridone-I, -II and -III	
	Citramine	
	Citropone-C	
	Citrusamine	
	Citrusinine-I and -II	
	1,3-Dihydroxy-10-methylacridone	
	Glycocitrine-I	
	Grandisinine	
	5-Hydroxynoracronycine	
	Marshmine	
	Natsucitrine-I and -II	
	Neoacrimarine-C	
	Pummeline	
	1,3,5-Trihydroxy-10-methylacridone[b] **125**	
Citrus paradisi	Citbismine-B[b] **133**	69
	Citbismine-C[b] **134**	
	Citbismine-D[b] **135**	70
	Citbismine-E[b] **136**	
Glycosmis citrifolia	Acrifoline[b] **126**	73
	Glycofolinine[b] **127**	
Sarcomelicope dogniensis	1-Oxo-1,2-dihydro-12-demethyl-12-hydroxyacronycine[b] **130**	11
Vepris bilocularis	Vebilocine[b] **129**	14

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



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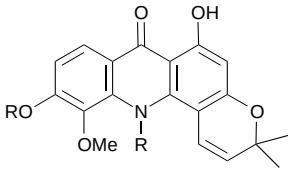
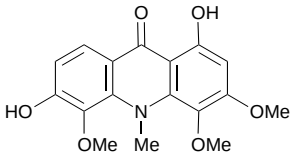
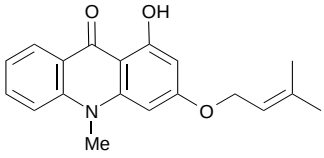


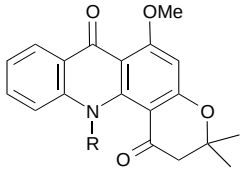
126 Acrifoline R = H
128 Citracridone-II R = Me



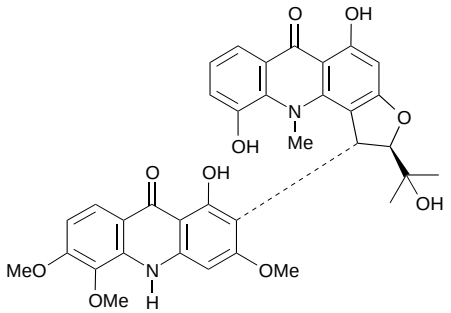
127 Glycofolinine



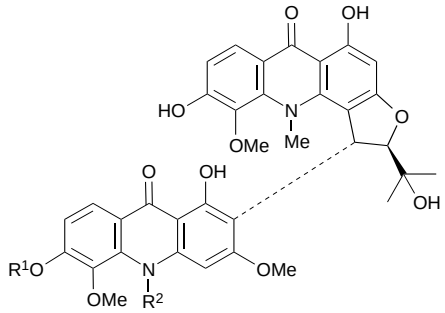
129 Vebilocine



130 R = OH
131 R = H



132 Citbismine-A

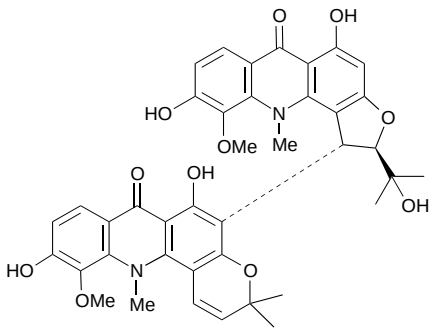


133 Citbismine-B R^1 = Me; R^2 = H
134 Citbismine-C R^1 = Me; R^2 = Me
136 Citbismine-E R^1 = H; R^2 = Me

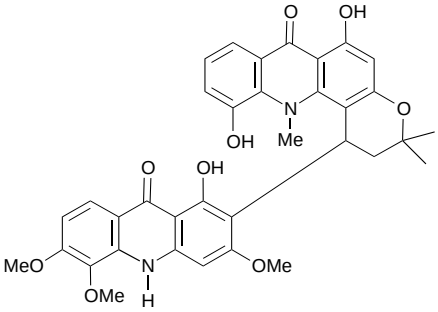
of vebilocine **129**, isolated from leaves of *Vepris bilocularis*, was determined by standard spectroscopic methods.[14]

The acronycine derivative **130**, isolated from the leaves of *Sarcomelicope dogniensis*,[11] is unusual on two counts. Firstly, modifications to the pyran moiety of pyrano[3,2-*c*]acridone alkaloids are extremely rare; oxidation to a pyran-4-one has been found only once before, in the alkaloid **131** – also a metabolite from *S. dogniensis*.[74] More striking, however, is the *N*-hydroxy substituent, which is unprecedented amongst the acridone alkaloids. It should be borne in mind, of course, that even though the compound has been represented as an *N*-hydroxy-9-acridone, this structure probably exists in equilibrium with the 9-hydroxy-*N*-oxide tautomer.

Citbismine A **132**,[75] the first naturally-occurring bis-acridone dimer from the genus *Citrus*, was described in last year's review.[28h] Full spectroscopic and crystallographic characterisation of this compound, which possesses a novel skeleton containing a C–C linkage between aromatic and dihydrofuran rings of two monomeric acridone alkaloids, has now been published.[69] In addition, the roots of *C. paradisi* have been shown to contain four new analogues of citbismine A, to which the names citbismines B **133**,[69] C **134**,[69] D **135**[70] and E **136**[70] have been given. With the exception of citbismine D, the alkaloids were also isolated from the roots of *C. grandis*.[69, 70] The structures of the new alkaloids were elucidated with the aid of exhaustive spectroscopic methods, and NOE experiments played a major role in ascertaining the location of substituents. It should be noted that all five dimers were isolated in optically inactive form; the authors suggest



135 Citbismine-D



137 Buntanbismine

that they may either be artifacts, or formed in the plant cells by non-enzymatic processes.

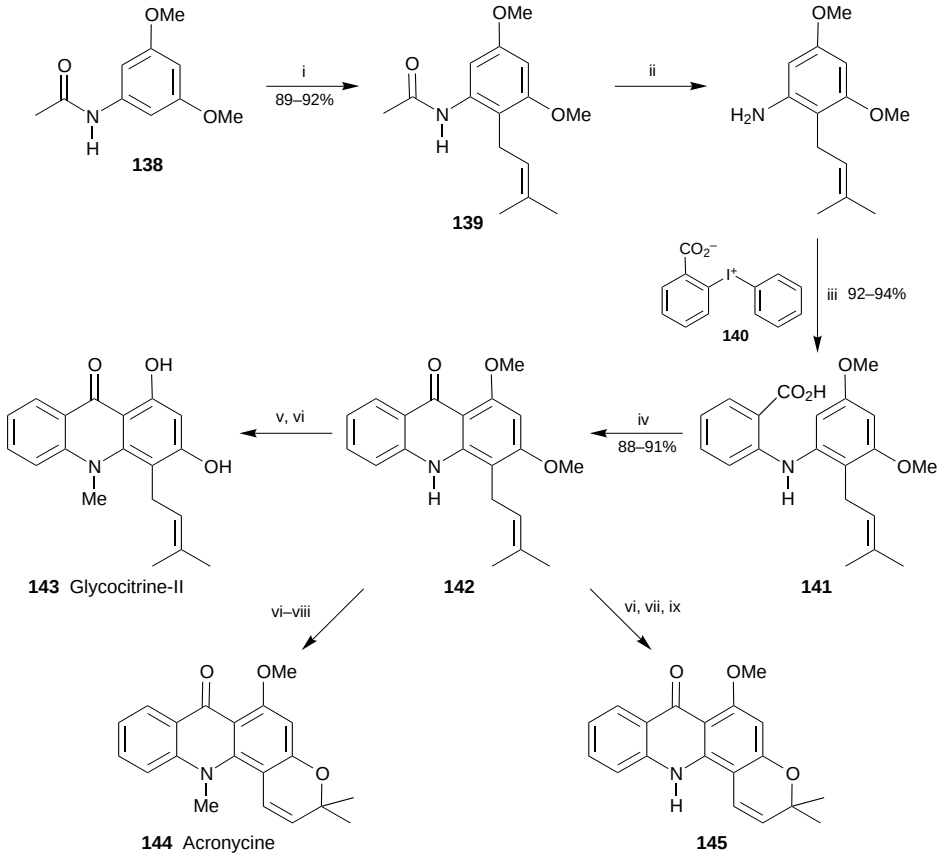
Yet another novel skeleton is found in buntanbismine **137**, a bis-acridone alkaloid isolated from the stem bark of *C. grandis* f. *buntan*.[71] In this case, the two moieties (both of them known alkaloids) are linked by a C–C bond between an aromatic and a dihydropyran ring. The structure was elucidated by spectroscopic analysis of the native alkaloid and its 1-acetyl and 1,5-diacetyl derivatives.

3.2 Synthesis and biological studies

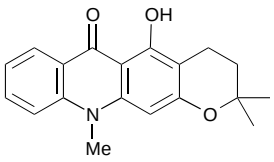
A high-yielding, highly regioselective 2-prenylation of 3,5-dimethoxyacetanilide **138** with 3-methylbut-1-en-3-ol in the presence of boron trifluoride has facilitated a simple synthesis of important acridone alkaloids possessing antitumour activity (Scheme 6).[76] After hydrolysis of the amide group of product **139**, an interesting copper-catalysed *N*-arylation with iodonium salt **140** yielded the diarylamine **141** in 92–94% yield. Cyclisation to the acridone **142** was induced with polyphosphoric ester under strictly anhydrous conditions, following which this intermediate was converted into glycocitrine-II **143**, acronycine **144** and des-*N*-methylacronycine **145** as illustrated.

Heating the hydrochloride salt of acronycine **144** at 250 °C for 2.5 h has yielded dihydronorisoacronycine **146** as the major product (7.2%) together with no fewer than seven identifiable minor products, all in minuscule yield.[77] Heating norisoacronycine **147** under reflux with hydrochloric acid in methanol afforded, in 15% yield, a new type of dimer **148** possessing a C–C linkage between the prenyl-derived moieties.[78]

In last year's review, the synthesis of *o*-quinomethanes from the reaction between acridone alkaloids and organolithium compounds was described.[28*i*] Similar intermediates **149** have now been obtained by treating 1-hydroxy-3-methoxy-*N*-methylacridone **150** with *o*-lithiated *N*-(*tert*-butoxycarbonyl)anilines.[79] Upon further treatment with hydrochloric acid, cyclisation of the blue intermediates occurred to give red quino[4,3,2-*kl*]acridines **151** (25–42% overall yields), which contain fused ring systems reminiscent of those found in



Scheme 6 *Reagents*: i, 3-methylbut-1-en-3-ol, $BF_3{\cdot}Et_2O$ (cat.), dioxane, reflux; ii, alkaline hydrolysis; iii, **140**, $Cu(OAc)_2$, Pr^iOH; iv, PPE, anhydrous conditions; v, MeI; vi, EtSNa, DMF; vii, DDQ, *o*-$Cl_2C_6H_4$, reflux; viii, excess MeI; ix, CH_2N_2, $BF_3{\cdot}Et_2O$



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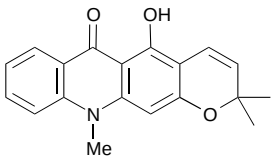

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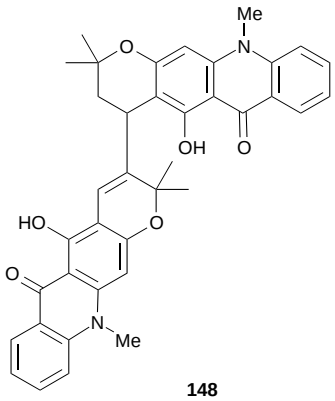

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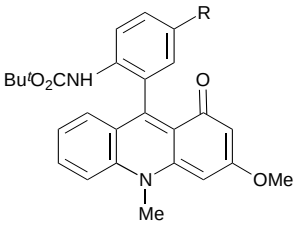
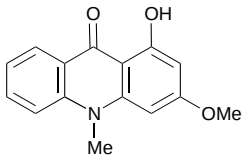


149 R = H or OMe



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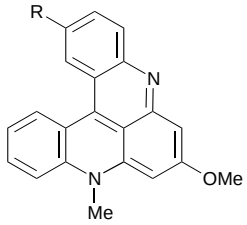
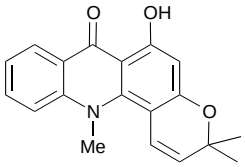
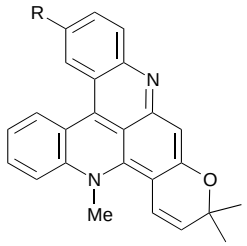


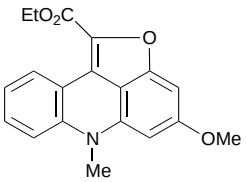
151 R = H or OMe



152 Noracronycine



153 R = H or OMe



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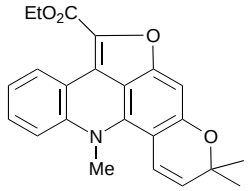

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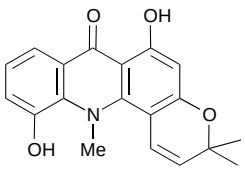
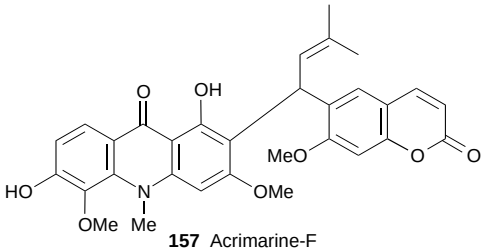
several marine alkaloids. Noracronycine **152** underwent similar reactions to yield products **153**. *O*-Alkylation of the same two precursors **150** and **152** with diethyl bromomalonate followed by base-induced cyclisation has yielded furo[2,3,4-*kl*]acridines **154** and **155** (17–18%).[80] All compounds prepared in the latter study were weakly cytotoxic towards L1210 murine lymphocytic leukaemia cells.



156



157 Acrimarine-F

Twenty-five acridone alkaloids from *Citrus* plants have been assayed for their inhibitory effects on the activation of Epstein–Barr virus in Raji cells incubated with butyric acid as inducer and then stained with a serum containing a human cancer cell line carrying the EBV genome.[81] All test samples showed weak cytotoxicity, with 5-hydroxynoracronycine **156** and acrimarine-F **157** holding the greatest potential as antitumour promotors.

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