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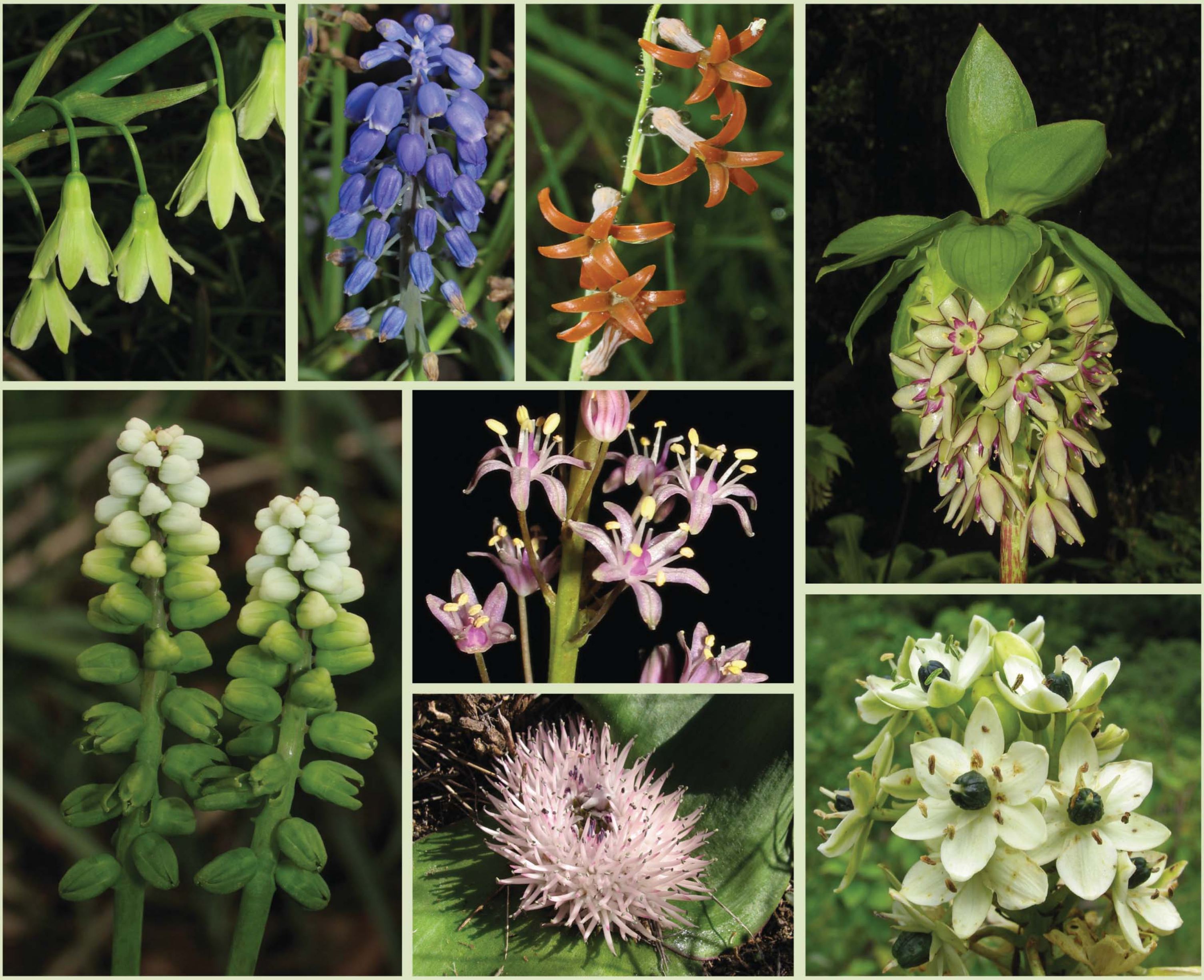

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The chemistry and biological activity of the Hyacinthaceae

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The Hyacinthaceae (*sensu* APGII), with approximately 900 species in about 70 genera, can be divided into three main subfamilies, the Hyacinthoideae, the Urgineoideae and the Ornithogaloideae, with a small fourth subfamily the Oziroëoideae, restricted to South America. The plants included in this family have long been used in traditional medicine for a wide range of medicinal applications. This, together with some significant toxicity to livestock has led to the chemical composition of many of the species being investigated. The compounds found are, for the most part, subfamily-restricted, with homoisoflavanones and spirocyclic nortriterpenoids characterising the Hyacinthoideae, bufadienolides characterising the Urgineoideae, and cardenolides and steroidal glycosides characterising the Ornithogaloideae. The phytochemical profiles of 38 genera of the Hyacinthaceae will be discussed as well as any biological activity associated with both crude extracts and compounds isolated. The Hyacinthaceae of southern Africa were last reviewed in 2000 (T. S. Pohl, N. R. Crouch and D. A. Mulholland, *Curr. Org. Chem.*, 2000, **4**, 1287–1324; ref. 1); the current contribution considers the family at a global level.

This review reflects a (bracketed)† family and subfamily taxonomic arrangement for the Hyacinthaceae *sensu* APGII.[2] A subsequent arrangement (APGIII)[3] based on further molecular analyses is not here adopted, where the Hyacinthaceae was hypothetically included in an expanded circumscription of the Asparagaceae. In that the group of plants here dealt with are monophyletic,[4] the systematic approach adopted for delimiting and naming family, subfamily or tribal level classifications ultimately has little bearing in relation to this review. We have adopted largely the phylogenies and generic concepts of Speta,[5] Pfosser and Speta,[4] and subsequent workers (Martínez-Azorín *et al.*)[6] who have considered molecular, morphological and biogeographic characters in their circumscriptions. Ali Syed *et al.*[7] have provided an excellent overview of alternative and often controversial systematic arrangements, of primary and secondary centres of geographic diversity, and the distribution of subfamilies and tribes at a global level. It should be noted that such is the state of flux of generic circumscription in the Hyacinthaceae that when providing a subfamilial classification for this unit (Asparagaceae subfamily Scilloideae *sensu* APGIII) Chase *et al.*[8] did not list genera names, which they otherwise offered with most other expanded Asparagalean families they treated. Given the past nomenclatural instability of the Hyacinthaceae, the names of plants under which the original phytochemical and pharmacological work was conducted often differs radically from the names accepted currently. For this reason we here provide both current and reported names, with species authors, to make clear this link. The literally reported (and sometimes incorrectly spelt) taxon names and species authors (if given) are provided in parentheses. The subfamilies are discussed in turn, starting with the Hyacinthoideae as most work has been conducted on this, the largest, subfamily. The Urgineoideae and finally the Ornithogaloideae follow. No reported investigations into the Oziroëoideae appear in the literature. Within each subfamily, those species receiving a substantial amount of attention will be discussed first, followed by the genera grouped by region (Europe and the Mediterranean, Middle and Far East and North Africa, southern Africa and finally, in the case of the Urgineoideae, India).

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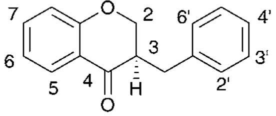
† 55 families under APGII came to be known as 'bracketed families'. These were optional segregates of families that could be circumscribed in a larger sense.

Plants have been considered on a regional basis as in many cases the secondary metabolites found reflect a strong geographic pattern. Any early work on a genus is discussed before later work.

1 The Hyacinthoideae

The subfamily Hyacinthoideae comprises more than 400 species in thirty-eight genera.[5,7] The Hyacinthoideae are distributed in sub-Saharan Africa, India, Madagascar, eastern Asia, the Mediterranean region and Eurasia. Sub-Saharan Africa appears to be the centre of origin for the subfamily, with a secondary centre of diversification and radiation being the Mediterranean region.[7] Twenty genera of the Hyacinthoideae have been investigated, with the bulbs receiving most attention. The exception is *Hyacinthus orientalis* L., the flowers of which have been extensively examined. Homoisoflavanones and spirocyclic nortriterpenoids are widespread throughout the subfamily with chalcones, xanthones, flavonoids, alkaloids, stilbenoids, chromones, norlignans and benzopyranones also being reported.

Abegaz *et al.*[9] and du Toit *et al.*[10] have reviewed the phytochemistry, biological activity, biosynthesis and synthesis of the homoisoflavanones. The homoisoflavanones can be divided into five categories, the 3-benzyl-4-chromanones **1**, the 3-hydroxy-3-benzyl-4-chromanones **2**, the 3-benzylidene-4-chromanones (*E* or *Z*) **3**, the 3-benzyl-chrom-2-en-4-ones **4** and the scillascillins **5**. The spirocyclic nortriterpenoids are generally of the lanosterol-type, showing a wide range of substitution patterns. The genera receiving the most attention, *Eucomis* L'Hér., *Muscari* Mill. and *Ledebouria* Roth. will be discussed first, followed by the lesser-studied Eurasian and Mediterranean genera *Leopoldia* Parl., *Scilla* L., *Barnardia* Lindl., *Othocallis* Salisb., *Oncostema* Raf., *Hyacinthus* L., *Bellevalia* Lapeyr., *Autonoe* (Webb & Berthel.) Speta and *Hyacinthoides* Medik. Lastly, the southern African genera *Drimiopsis* Lindl. & Paxton, *Resnova* van der Merwe, *Veltheimia* Gled., *Merwilla* Speta, *Lachenalia* J.Jacq. ex Murray,



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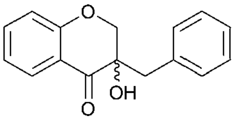

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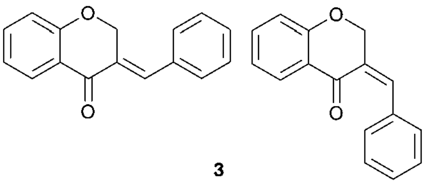

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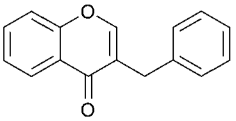

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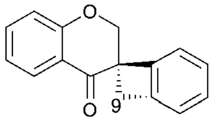

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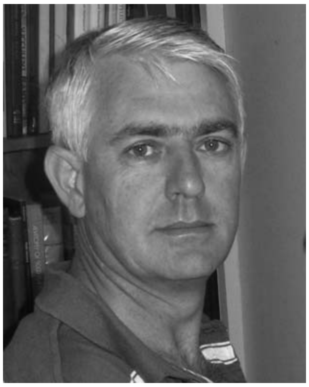
Dulcie Mulholland leads the Natural Products Research Group and is Head of the Department of Chemistry at the University of Surrey. She undertook her PhD at the University of Natal, Durban, South Africa, under the supervision of David Taylor on the Chemistry of the Meliaceae. For the last 20 years she has collaborated with Neil Crouch investigating the phytochemistry of the Hyacinthaceae of southern Africa.

Sianne Schwikkard obtained her PhD from the University of Kwazulu-Natal, South Africa in 1998 (under the supervision of Professor Dulcie Mulholland). This was followed by post-doctoral studies at Virginia Tech with Professor David Kingston and further post-doctoral studies at the Rand Academic University with Professor Fanie van Heerden. After spending 18 months working for Sasol Ltd, Sianne relocated to the United Kingdom and following a post-doctoral position, under Professor Keith Jones at Kingston University, has continued to teach in a part-time capacity at Kingston University in addition to her position as a part-time research associate at the University of Surrey.

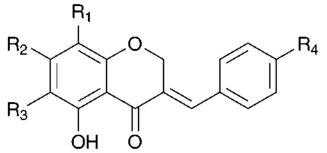


Neil Crouch PhD (Natal) has worked as an ethnobotanist for the South African National Biodiversity Institute (SANBI) for nearly 20 years, largely on Zulu traditional medicine. He networks SANBI in natural products, pharmacological, horticultural, conservation, and Indigenous Knowledge Systems cataloguing programmes and is accordingly involved in state-sponsored bioprospecting consortia that develop new drugs for malaria and tuberculosis. As an Honorary Professor in the School of Chemistry and Physics at the University of KwaZulu-Natal, he explores his strong interest in the chemistry, traditional use and biosystematics of the Hyacinthaceae, a plant family with a major centre of diversity in southern Africa.

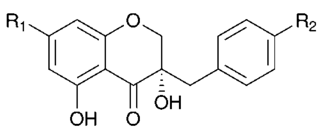
Pseudoprospero Speta, *Schizocarphus* van der Merwe and *Spetaea* Wetchnig & Pfosser are dealt with.

The genus *Eucomis* is widespread throughout eastern and southern Africa. It is used by traditional healers to treat a wide range of complaints, including rheumatism, as an anti-inflammatory and as a treatment for mental disease. Homoisoflavanones and triterpenoid glycosides have been isolated from the bulbs of many of the species investigated, with the homoisoflavanones usually accumulating in the waxy layer between the storage leaves of the bulb and the terpenoids in the bulb tissue.[11] Early work on *Eucomis bicolor* Baker resulted in the isolation of the yellow crystalline needles of eucomin **6** and the colourless hexagonal plates of eucomol **7**.[12] The configuration at C-3 of eucomol **7** was determined by CD experiments and confirmed by X-ray analysis of the *p*-bromophenacyl derivative.[13] Four additional homoisoflavonoids have been isolated from the bulbs of *E. bicolor*, (**8–11**)[14,15] followed a number of years later by the identification of seven triterpenoid oligosaccharides (**12–18**).[16,17] Scillasaponin A **12** has a modified spirocyclic side chain at C-17 and C-23 and has been found to inhibit cyclic AMP phosphodiesterase ($IC_{50} = 11.5 \times 10^{-5}$ M).[16] Compounds **13, 14** and **16** were found to be toxic to HeLa cells at concentrations of both 50 μg ml^{-1} and 5 μg ml^{-1}.[17] A later investigation of *E. bicolor* resulted in the isolation of twelve compounds from the dichloromethane extract and ten from the methanol extract. The dichloromethane extract yielded the seven known compounds (**7, 10, 19, 20, 21, 22** and **23**) and five novel triterpenoids (**24** [the aglycone of **25**], **26**, **27**, **28** and **29**). The methanol extract was found to contain the known homoisoflavonoid **30** as well as nine novel lanosterol glycosides (**31–39**).[18]

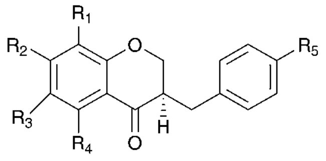
Eucomis autumnalis (Mill.) Chitt. (*syn. Eucomis undulata* Aiton) bulbs are used in the Eastern Cape of South Africa to treat cancer,[19] and are used by Zulu traditional healers as an emetic and enema to treat fevers, as well as for the treatment of skin infections, biliousness, and urinary and respiratory infections. It is also used as a charm against witchcraft.[20] Phytochemical investigations of the bulbs of *E. autumnalis* have resulted in the isolation of three homoisoflavanones (**40–42**),[14,21,22] two dibenzo-α-pyrones (**43–44**),[23] two spirocyclic nortriterpenoids (**20** and **45**) and an acid, compound **46**.[24] The structures assigned to compounds **43** and **44** were subsequently revised and reported to be the corresponding xanthones.[25] The proposed structure for eucosterol **20** was confirmed by the X-ray structure of the *p*-bromobenzenesulphonate derivative.[26] The extensive use of *E. autumnalis* by traditional healers for fever and the treatment of skin conditions, in particular wounds, boils and open sores, has led to extensive investigations into the anti-inflammatory and antibacterial effects of extracts of the leaves, bulbs and roots. The inhibition of prostaglandin synthesis was assessed in terms of the inhibition of the cyclooxygenase enzymes COX-1 and COX-2. COX-1 is found in normal cells and serves to produce substances that protect the stomach and kidneys (prostanoids). While both enzymes are involved in the inflammatory process, inhibition of COX-1 is associated with gastro-intestinal and kidney related side effects. As such, a higher selectivity for COX-2 inhibition is preferred.[27] Initial testing of the leaves, bulbs and roots of *E. autumnalis* against COX-1 showed good activity from all extracts (leaf extract IC_{50} = 15 μg ml^{-1}, root extract 27 μg ml^{-1} and bulb extract 72 μg ml^{-1}).[28,29] A comparison of the COX-1 and COX-2



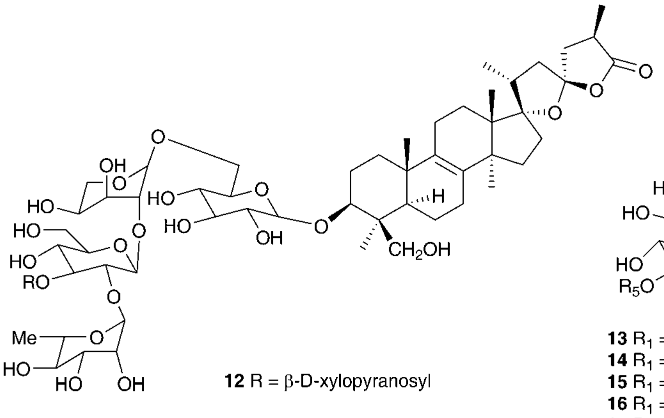
6 $R_1 = H, R_2 = OH, R_3 = H, R_4 = OMe$
8 $R_1 = H, R_2 = OMe, R_3 = H, R_4 = OMe$
40 $R_1 = OMe, R_2 = OH, R_3 = H, R_4 = OMe$
41 $R_1 = H, R_2 = OH, R_3 = OMe, R_4 = OH$
47 $R_1 = OMe, R_2 = OH, R_3 = H, R_4 = OH$
49 $R_1 = H, R_2 = OH, R_3 = H, R_4 = OH$
53 $R_1 = OMe, R_2 = OH, R_3 = OH, R_4 = OH$



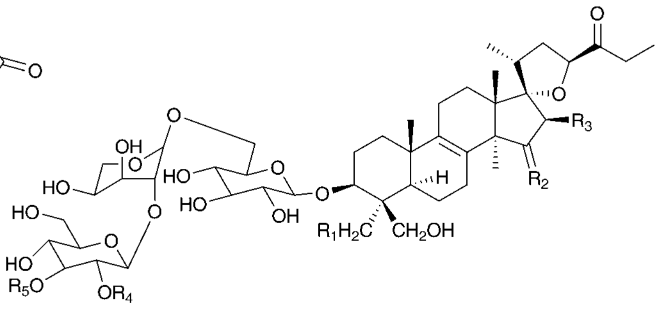
7 $R_1 = OH, R_2 = OMe$
9 $R_1 = OMe, R_2 = OMe$
57 $R_1 = OH, R_2 = OH$



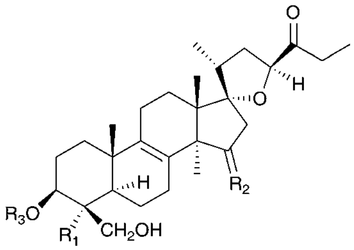
10 $R_1 = H, R_2 = OH, R_3 = H, R_4 = OH, R_5 = OMe$
11 $R_1 = H, R_2 = OMe, R_3 = H, R_4 = OH, R_5 = OMe$
19 $R_1 = OMe, R_2 = OH, R_3 = H, R_4 = OH, R_5 = OMe$
30 $R_1 = H, R_2 = OH, R_3 = H, R_4 = OH, R_5 = OH$
42 $R_1 = H, R_2 = OH, R_3 = OMe, R_4 = OH, R_5 = OH$
48 $R_1 = OMe, R_2 = OH, R_3 = H, R_4 = OH, R_5 = OH$



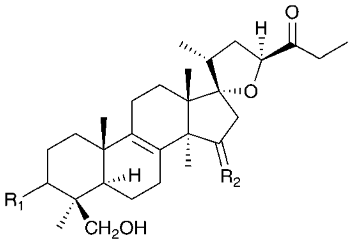
12 R = β-D-xylopyranosyl



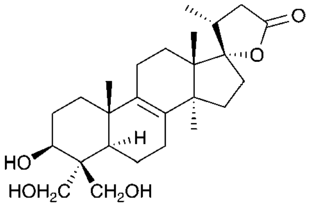
13 $R_1 = H, R_2 = 2H, R_3 = H, R_4$ = α-L-rhamnopyranosyl, $R_5 = H$
14 $R_1 = OH, R_2 = 2H, R_3 = H, R_4$ = β-apiofuranosyl, $R_5 = H$
15 $R_1 = H, R_2 = O, R_3 = OH, R_4$ = α-L-rhamnopyranosyl, $R_5 = H$
16 $R_1 = OH, R_2 = 2H, R_3 = H, R_4$ = α-L-rhamnopyranosyl, R_5 = α-D-xylopyranosyl
17 $R_1 = H, R_2 = O, R_3 = H, R_4$ = α-L-rhamnopyranosyl, R_5 = α-D-xylopyranosyl
18 $R_1 = H, R_2 = O, R_3 = OH, R_4$ = α-L-rhamnopyranosyl, R_5 = α-D-xylopyranosyl



20 $R_1 = CH_3$, $R_2 = O$, $R_3 = H$
21 $R_1 = CH_2OH$, $R_2 = 2H$, $R_3 = H$
22 $R_1 = CH_3$, $R_2 = 2H$, $R_3 = H$
31 $R_1 = CH_3$ $R_2 = O$, R_3 = β-D-glucopyranoside
54 $R_1 = CH_2OH$, $R_2 = O$, $R_3 = H$



23 R_1 = =O, R_2 =2 H
32 R_1 = β-O-β-D-glucopyranoside, R_2 = 2H
35 R_1 = β-O-β-D-arabinopyranosyl-β-D-glucopyranoside, R_2 = O
36 R_1 = β-O-β-D-arabinopyranosyl-β-D-glucopyranoside, R_2 = 2H
39 R_1 = β-D-arabinopyranosyl-(1''→6')-[β-D-xylopyranosyl-(1'''→3')]-β-D-glucopyranoside, R_2 = O
63 R_1 = β-OH, R_2 = β-OH



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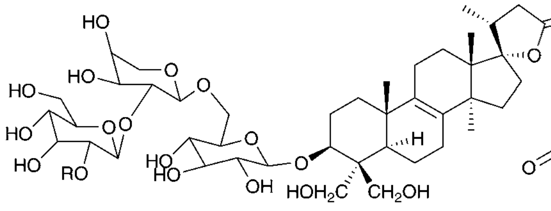
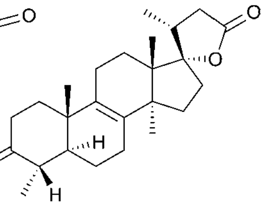


25 R = β-apiofuranosyl



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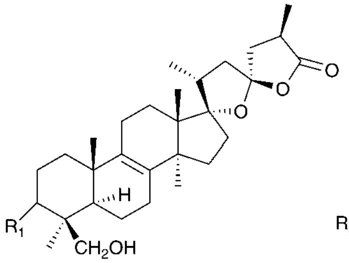
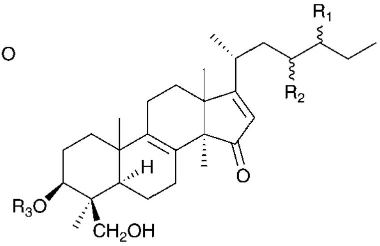


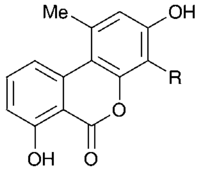
27 R_1 = =O
33 R_1 = β-O-β-D-glucopyranoside
38 R_1 = β-O-β-D-arabinopyranosyl-β-D-glucopyranoside



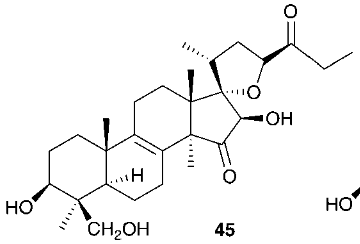
28 $R_1 = OH$, $R_2 = OH$, $R_3 = H$
29 R_1 = =O, $R_2 = OH$, $R_3 = H$
34 R_1 = =O, $R_2 = OH$, R_3 = β-D-glucopyranoside
37 R_1 = =O, $R_2 = OH$, R_3 = β-D-arabinopyranosyl-β-D-glucopyranoside

inhibitory activity of the leaf, root and bulb extracts, showed that the leaf extract inhibited COX-1 to a greater extent while the root and bulb extract showed greater inhibition of COX-2 (COX-2/COX-1 of 0.7 and 0.8 respectively for the root and bulb extracts).[27,30] There has been some interest in the biological effects of plant lectins obtained from the bulbs of *E. autumnalis*. These non-enzymatic proteins can bind, with high specificity and reversibility, mono- and oligosaccharides. Cyclooxygenase is a membrane-bound glycoprotein and as such could be affected by plant lectins. The partially purified lectin-like protein extract of *E. autumnalis* was found to have very good cyclooxygenase inhibitory activity (COX-1 inhibition of 88%)[31] as well as good activity against the Gram-positive bacterium *Bacillus subtilis* (MIC of 0.2 mg ml^{-1}).[32] Due to the widespread use of the bulbs of *E. autumnalis* by South African traditional healers, extensive work has been carried out on the factors possibly affecting the effectiveness of the bulb extracts. Environmental factors such as sunlight intensity, temperature and watering as well as age of the bulbs and the effect of cold storage have all been examined.[33] Bulbs lifted and stored at a low temperature (8–10 °C) showed greater COX-1 inhibitory activity.[34] The leaves of young plants showed greater COX-1 inhibitory activity than those of older plants, where the greatest activity was associated with bulbs and roots.[35]

Six homoisoflavanones (**19**, **40**, **47–50**)[14,36] and the optically active 2-hydroxy-2-[(4-hydroxyphenyl)methyl]butanedioic acid **51** have been isolated from the bulbs of *Eucomis comosa* (Houtt.) H. R. Wehrh. (as *Eucomis punctata* L'Herit).[37] The bulb wax of *Eucomis comosa* yielded the chroman-4-one **52**[38] while an examination of the methanol extract of the fresh, air-dried bulbs gave five homoisoflavanones (**47**, **48**, **50** and both the *E* and *Z* form of **6**).[39] The same study included



43 R = H
44 R = OMe



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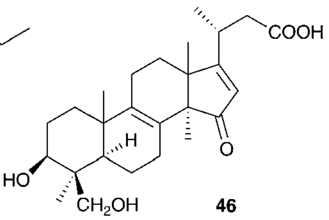

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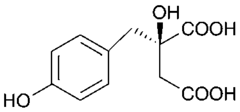
Eucomis pallidiflora Baker subsp. *pole-evansii* (N.E.Br.) Reyneke ex J.C.Manning and *Eucomis schijffii* Reyneke. The bulbs of *Eucomis pallidiflora* subsp. *pole-evansii* contained the homoisoflavanone **53** and the spirocyclic nortriterpenoid **20** while *Eucomis schijffii* yielded two compounds, the spirocyclic nortriterpenoid **54** and scillascillin **55**.[39] *Eucomis montana* Compton was investigated and the bulbs were found to contain eleven homoisoflavanones (**6**, **7**, **9**, **10**, **30**, **50**, **56**, **57**, **58**, **59** and **60**).[40] No inhibitory activity against cyclooxygenase enzymes (COX-1 and COX-2) was found for compounds **48**, **53** and **55** isolated from *E. comosa*, *E. pallidiflora* and *E. schijffii* respectively.[39] Some antibacterial activity has been observed for homoisoflavanones isolated from *E. comosa* (MIC of 0.52 mM for compound **6** (*E* isomer) and 0.24 mM for compound **47**) and *E. schijffii* (MIC of 0.50 mM for compound **55**).[41] The dichloromethane and methanol extracts of the whole plant of *Eucomis vandermerwei* I.Verd. yielded four known homoisoflavanones (**6**, **7**, **10** and **56**).[42] Similarly, the whole plant of *Eucomis zambesiaca* Baker was investigated and this resulted in the isolation and identification of five homoisoflavanones (**6**, **19**, **40**, **61** and **62**) and three nortriterpenoids (**20**, **21** and **63**).[42]

The bulbs of *Muscari racemosum* Mill. were found to contain homoisoflavanones of the 3-benzylidene-4-chromanone-type (**64–66**).[43] Long-range coupling between C-2 and C-9, was indicative of *Z* geometry. These homoisoflavanones have been investigated with respect to their effect on lipid peroxidation *in vitro*.[44,45] Strong anti-oxidant activity was noted ($IC_{50} = 0.94–7.98$ μM) and this led to an investigation into their antimutagenic/anticarcinogenic activity. It has been suggested that polyphenolics may be cancer preventative due to their antioxidant properties[44] and a mixture of these three homoisoflavanones was found to contain significant antimutagenic activity.[44] Estrogenic activity was found in an ether extract of the bulbs. The extract induced proliferation of MCF7 cells in a dose dependent manner at concentrations up to 5 μg ml^{-1}. This concentration produced the greatest effect of 181% of the control.[46]



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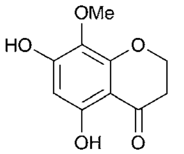

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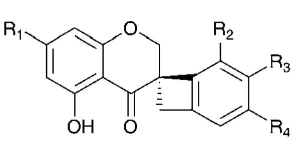
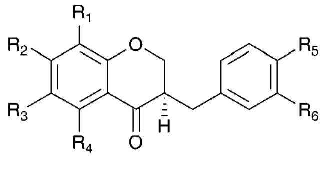
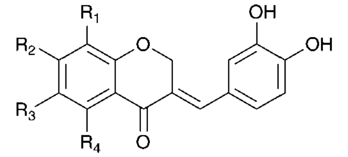


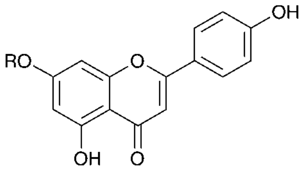
55 R_1 = OH, R_2 = H, R_3-R_4 = O-CH₂-O
60 R_1 = OMe, R_2 = H, R_3 = OMe, R_4 = OH
77 R_1 = OMe, R_2 = H, R_3 = OH, R_4 = OH
79 R_1 = OH, R_2 = H, R_3 = OH, R_4 = OMe
98 R_1 = OH, R_2 = H, R_3 = OMe, R_4 = OH
104 R_1 = OH, R_2 = H, R_3 = OH, R_4 = OMe
105 R_1 = OMe, R_2 = H, R_3 = OH, R_4 = OH
106 R_1 = OMe, R_2 = H, R_3 = OMe, R_4 = OH
107 R_1 = OMe, R_2 = OH, R_3 = OMe, R_4 = H



50 R_1 = H, R_2 = OH, R_3 = H, R_4 = OMe, R_5 = OH, R_6 = H
56 R_1 = H, R_2 = OH, R_3 = OMe, R_4 = OMe, R_5 = OH, R_6 = H
58 R_1 = OH, R_2 =OMe, R_3 = H, R_4 = OH, R_5 = OH, R_6 = H
59 R_1 = OMe, R_2 = OMe, R_3 = H, R_4 = OH, R_5 = OH, R_6 = H
61 R_1 = OMe, R_2 = OH, R_3 = H, R_4 = OH, R_5 = OH, R_6 = H
62 R_1 = H, R_2 = OH, R_3 = OMe, R_4 = OH, R_5 = OH, R_6 = H
70 R_1 = H, R_2 = OH, R_3 = OMe, R_4 = OH, R_5 = OH, R_6 = OH
71 R_1 = H, R_2 = OH, R_3 = OMe, R_4 = OH, R_5 = OH, R_6 = OMe
72 R_1 = H, R_2 = OH, R_3 = OMe, R_4 = OH, R_5 = OMe, R_6 = OH
73 R_1 = OH, R_2 = OMe, R_3 = H, R_4 = OH, R_5 = OH, R_6 = OH
74 R_1 = H, R_2 = OH, R_3 = H, R_4 = OH, R_5 = OH, R_6 = OH
75 R_1 = H, R_2 = OH, R_3 = H, R_4 = OMe, R_5 = OH, R_6 = OH
76 R_1 = H, R_2 = OH, R_3 = H, R_4 = OMe, R_5 = OMe, R_6 = OH
78 R_1 = H, R_2 = OMe, R_3 = H, R_4 = OH, R_5 = OH, R_6 = OH
80 R_1 = H, R_2 = OH, R_3 = H, R_4 = OH, R_5 = OMe, R_6 = OH
97 R_1 = OH, R_2 = OMe, R_3 = OMe, R_4 = OH, R_5 = OH, R_6 = H,



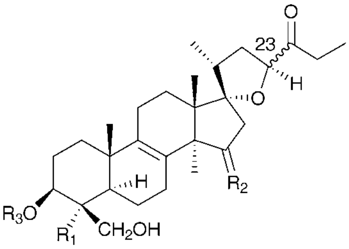
64 R_1 = H, R_2 = OH, R_3 = OMe, R_4 = OH,
65 R_1 = H, R_2 = OH, R_3 = H, R_4 = OMe,
66 R_1 = OH, R_2 = OMe, R_3 = H, R_4 = OH,



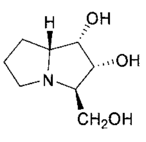
67 R = β-D-arabinopyranoside
68 R = β-D-xylospyranoside
69 R = β-D-glucopyranoside

A wide range of compounds has been isolated from the bulbs of *Muscari armeniacum* Leichtlin ex Baker. These include flavonoids (**67–69**),[47] homoisoflavanones, with an unusual 3′,4′ substitution pattern in the B ring (**30**, **62**, **70–80**),[48,49] spirocyclic nortriterpenoid glycosides (**81–87**)[50] and polyhydroxylated pyrrolizidine alkaloids (**88–92**).[51] The alkaloids were assessed for their action against glycosidases. Compound **88** was found to be a potent inhibitor of rat intestine lactase ($IC_{50} = 4.4$ μM) as well as a moderate inhibitor of α-L-fucosidase ($IC_{50} = 46$ μM) and amyloglucosidase ($IC_{50} = 25$ μM). Inverting the hydroxyl group at C-1 to give compound **89**, enhanced the amyloglucosidase inhibition ($IC_{50} = 8.6$ μM) but resulted in the loss of the α-L-fucosidase inhibition. Compounds **90** and **91** were less active.[51] Three ribosome-inactivating proteins have been isolated from the bulbs of *M. armeniacum*. It has been proposed that this type of activity is linked to an anti-viral response.[52] The petals of *M. armeniacum* have yielded four anthocyanins, the new muscarinin A **93** and the known 3-*O*-β-D-glucopyranoside of delphinidin, petunidin and malvidin (**94–96**).[53–55] The principle water soluble polysaccharide in the bulbs of *M. armeniacum* (as *Muscari szovitsianum* Baker) was found to be a neutral glucofructan, with glucose and fructose residues in the ratio 26 : 1.[56,57]

Phytochemical investigations into the bulbs of *Muscari botryoides* (L.) Mill. confirmed a close taxonomic relationship with *Muscari armeniacum*. Similar homoisoflavanones (**19**, **30**, **58**, **60**, **77**, **79**, **97**, **98**)[48] were isolated as well as similar spirocyclic nortripertenoid glycosides (**86**, **87**, **99**, **100**, **101**, **102**, **103**).[50] *Muscari neglectum* Guss. ex Ten. was found to contain a similar spread of homoisoflavanones in the bulbs (**30**, **62**, **80**, **104–107**) as well as an interesting scillascillin-type homoisoflavanone with an unusual oxygenation pattern in the B ring (**55**).[58] Ethanol extracts of the bulbs and leaves of *Muscari neglectum* have been tested for antifungal activity against the wood rots *Postia placenta* and *Trametes versicolor*. Significant reduction in wood weight loss was observed for Turkish oriental beech and Scots pine (weight loss dropped from 35–42% in the untreated wood to 5.4–18.3% in the treated wood).[59]



81 (23*R*) $R_1 = CH_3$ R_2 = O, R_3 = β-D-glucopyranoside
82 (23*R*) $R_1 = CH_3$ R_2 = O, R_3 = α-L-arabinopyranosyl-(1→3)-α-L-rhamnopyranosyl-(1→2)-β-D-glucopyranoyl-(1→2)-α-L-arabinopyranosyl-(1→6)-β-D-glucopyranoside
83 (23*R*) $R_1 = CH_3$ R_2 = O, R_3 = β-D-glucopyranosyl-(1→2)-α-L-arabinopyranosyl-(1→3)-α-L-rhamnopyranosyl-(1→2)-β-D-glucopyranoyl-(1→2)-α-L-arabinopyranosyl-(1→6)-β-D-glucopyranoside
84 (23*S*) $R_1 = CH_2OH$, R_2 = 2H, R_3 = β-D-glucopyranoyl-(1→2)-α-L-arabinopyranosyl-(1→6)-β-D-glucopyranoside
85 (23*S*) $R_1 = CH_2OH$, R_2 = 2H, R_3 = α-L-rhamnopyranosyl-(1→2)-β-D-glucopyranoyl-(1→2)-α-L-arabinopyranosyl-(1→6)-β-D-glucopyranoside
86 (23*R*) $R_1 = CH_3$, R_2 = O, R_3 = α-L-rhamnopyranosyl(1→2)-β-D-glucopyranosyl(1→2)-α-L-arabinopyranosyl-(1→6)-β-D-glucopyranoside
87 (23*R*) $R_1 = CH_3$, R_2 = O, R_3 = α-L-arabinofuranosyl(1→2)-α-L-arabinopyranosyl(1→3)[rhamnopyranosyl(1→2)]-β-D-glucopyranosyl(1→2)-α-L-arabinopyranosyl-(1→6)-β-D-glucopyranoside
99 (23*R*) $R_1 = CH_3$ R_2 = O, R_3 = β-D-glucopyranoyl-(1→2)-α-L-arabinopyranosyl-(1→6)-β-D-glucopyranoside
100 (23*S*) $R_1 = CH_2OH$, R_2 = 2H, R_3 = α-L-arabinopyranosyl-(1→2)-β-D-galactopyranosyl-(1→3)-[β-D-apiofuranosyl-(1→2)-β-D-glucopyranoyl-(1→2)-α-L-arabinopyranosyl-(1→6)-β-D-glucopyranoside
101 (23*S*) $R_1 = CH_2OH$, R_2 = 2H, R_3 = β-D-glucopyranoside
102 (23*R*) $R_1 = CH_2OH$, R_2 = 2H, R_3 = α-L-arabinopyranosyl(1→3)[β-D-apio-D-furanosyl-(1→2)]]-β-D-glucopyranosyl(1→2)-α-L-arabinopyranosyl-(1→6)-β-D-glucopyranoside
103 (23*R*) $R_1 = CH_2OH$, R_2 = 2H, R_3 = β-D-apio-D-furanosyl-(1→2)]-β-D-glucopyranosyl(1→2)-α-L-arabinopyranosyl-(1→6)-β-D-glucopyranoside



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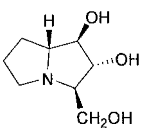

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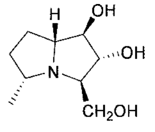

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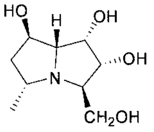

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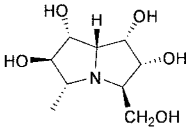

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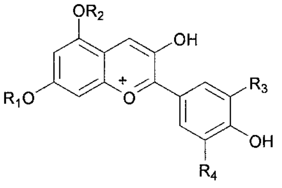
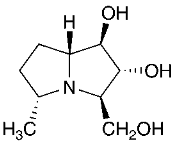


93 R_1 = 6-O-(*E*)-*p*-coumaroyl-β-D-glucopyranoside, R_2 = 6-O-malonyl-4-O-(α-L-rhamnopyranosyl)-β-D-glucoside, R_3 = OH, R_4 = OH
94 R_1 = β-D-glucopyranoside, R_2 = H, R_3 = OH, R_4 = OH
95 R_1 = β-D-glucopyranoside, R_2 = H, R_3 = OH, R_4 = OMe
96 R_1 = β-D-glucopyranoside, R_2 = H, R_3 = OMe, R_4 = OMe

An aqueous ethanol extract of the bulbs of *Ledebouria socialis* (Baker) Jessop (as *Scilla socialis* Baker) was found to contain eleven hyacinthacines (**108–118**) as well as two pyrrolidines (**119–120**) and three piperidines (**121–123**).[60] Hyacinthacines appear to be restricted to the Hyacinthoideae. These compounds have been found in *Othocallis siberica* (Haw.) Speta (as *Scilla sibirica*), *Oncostema peruviana* (L.) Speta (as *Scilla peruviana*), *Hyacinthoides non-scripta* (L.) Chouard ex Rothm., *Hyacinthoides hispanica* (Mill.) Rothm. (as *Scilla campanulata*), and *Muscari armeniacum.* The hyacinthacines are characterised as 7α-*R*-hydro-1,2-dihydroxy-3-hydroxymethylpyrrolizidines and in general appear to be weak to moderate inhibitors of glycosidases.[60] The dichloromethane and methanol extracts of the bulbs of *Ledebouria socialis* have yielded five compounds, the scillascillin-type homoisoflavanones **124** and **125**, phytol, stigmasterol and the polyhydroxylated difuran derivative, polybotrin **126**.[61] The different types of compounds isolated reflect the different solvents used for extraction, with the more polar extracts yielding the more polar polyhydroxy alkaloids and the less polar extracts the homoisoflavanones and sterols.

Early work by Gunn *et al.*[62] on some southern African *Ledebouria* species, examined the cardiac effect of *Ledebouria cooperi* (Hook.f.) Jessop (as *Scilla cooperi* Hook and as *Scilla rogersii* Baker) and *Ledebouria ovatifolia* (Baker) Jessop (as *Scilla lanceaefolia* Baker). Both species produced a similar action to digitalis when applied to isolated frog and cat hearts as well as *in situ* frog, cat and dog hearts. The extracts obtained were, however, insufficient in quantity to determine minimum lethal doses and the active components were not identified.

The chemical constituents of a further six southern African *Ledebouria* species have been investigated. Two samples of the bulbs of *Ledebouria zebrina* (Baker) S.Venter (as *Scilla zebrina* Baker), collected from two different regions in South Africa (Durban and Blyde River, Mpumalanga) have been investigated and the chemical differences noted. Both contained homoisoflavanones (Durban bulbs compounds **127** and **128** and the Blyde River bulbs compounds **127**, **129**, **130**). In addition to the homisoflavanones, the Blyde River bulbs also contained spirocyclic nortriterpenoids (**131**, **21**), while the Durban bulbs produced a chalcone **132**.[63] The bulbs of *Ledebouria cooperi*



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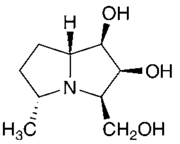

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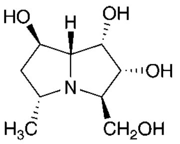

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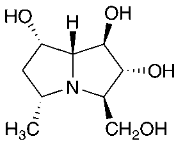

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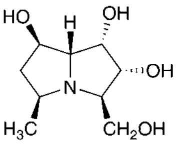

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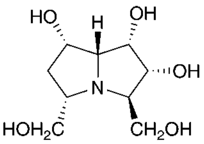

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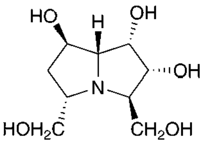

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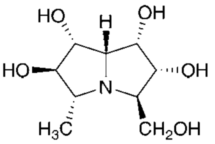

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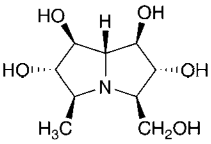

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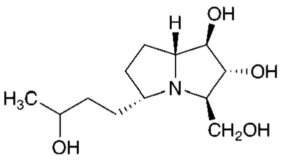

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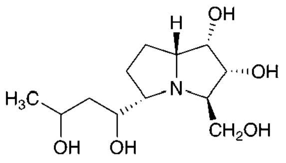

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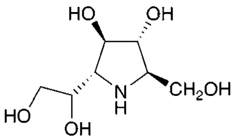

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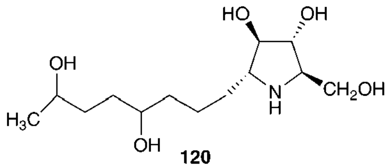

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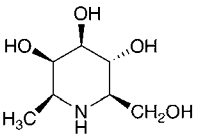

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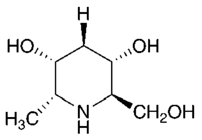

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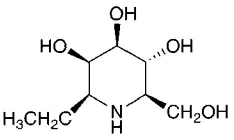

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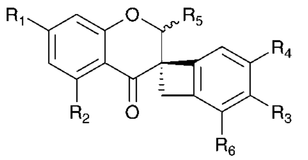
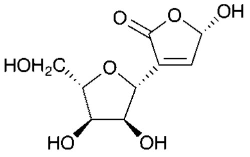


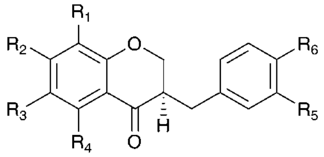
124 R_1 = OMe, R_2 = OH, R_3 = OMe, R_4 = OMe, R_5 = H, R_6 = OMe
125 R_1 = OMe, R_2 = OH, R_3 = OMe, R_4 = OMe, R_5 = H, R_6 = OH
139 R_1 = OMe, R_2 = OAc, R_3-R_4 = O-CH_2-O, R_5 = β-OAc, R_6 = H
140 R_1 = OMe, R_2 = OAc, R_3-R_4 = O-CH_2-O, R_5 = α-OAc, R_6 = H
142 R_1 = OMe, R_2 = OH, R_3-R_4 = O-CH_2-O, R_5 = H, R_6 = H
143 R_1 = OH, R_2 = OH, R_3 = OMe, R_4 = OH, R_5 = H, R_6 = H
144 R_1 = OH, R_2 = OH, R_3 = OH, R_4 = OMe, R_5 = H, R_6 = H
160 R_1 = OH, R_2 = OH, R_3 = OMe, R_4 = OMe, R_5 = H, R_6 = H
161 R_1 = OMe, R_2 = OH, R_3 = OMe, R_4 = OMe, R_5 = H, R_6 = H



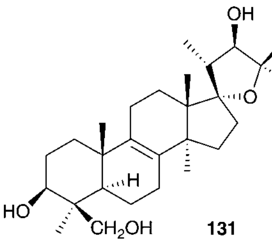
126

yielded the homoisoflavanones **59** and **62** as well as the eucosterol-type spirocyclic nortriterpenoid **133** and malic acid. *Ledebouria ovatifolia* bulbs were found to contain the chalcones **132** and **134** as well as the homoisoflavanone **30**.[64,65] *L. ovatifolia* is used by the Zulu to treat gastro-enteritis, influenza and backache. In addition, it has been found to be toxic to sheep.[66] Extracts of the bulbs were found to have good antibacterial activity against Gram-positive bacteria (MIC of 0.8–12.5 mg ml^{-1}), but poor anti-inflammatory and poor antihelmintic activity.[66,67] A later investigation of the dichloromethane, ethyl acetate and methanol extracts of the bulbs led to the isolation of twenty-nine compounds, including xanthones (**135–138**), homoisoflavanones (**7**, **10**, **30**, **50**, **74**, **75**, **139–148**), triterpenoids (**133**, **149–150**), chalcones (**132**, **151**) and simple aromatic compounds (**152–154**), including polybotrin **126**.[61,68] Sixteen of the above compounds isolated from *L. ovatifolia* were assessed for anti-inflammatory activity, in particular the selective inhibition of the COX-2 enzyme. Compounds **75**, **137** and **146** were found to significantly inhibit COX-1 and COX-2 (percentage activity relative to the non-inhibitor control of 54–56% for COX-1 and 0% for COX-2), while compound **145** showed good selectivity for the inhibition of COX-2 over COX-1 (IC_{50} for COX-2 of 2.87 μM, with no statistically significant inhibition for COX-1 up to a concentration of 20 μM).[61,68] During the same study, the norlignan hinokiresinol **155**, previously isolated from *Drimiopsis burkei* Baker,[69] was synthesised and tested for selective COX-2 inhibitory activity. Significant selective inhibition against COX-2 was observed (percentage activity relative to the non-inhibitor control of 93.8% for COX-1 and 0% for COX-2).[61,68] *Ledebouria leptophylla* (Baker) S.Venter (as *Ledebouria graminifolia* (Baker) Jessop), sourced in Botswana, is used traditionally to treat gastro-enteritis, backache and coughs as well as a treatment for skin irritations and for dressing wounds. A phytochemical investigation of the bulbs found seven 3-benzyl-4-chromanones (**30**, **62**, **128**, **156–159**), two 3-benzyl-3-hydroxy-4-chromanones (**7**, **57**), two scillascillin-type homisoflavanones (**160–161**) and two xanthones (**136** and **162**). Cultivated and wild-sourced bulbs contained the same compounds.[70,71] There was initial concern about the presence of the xanthones and speculation as to whether they may have come from a fungal or lichen contamination of the wild bulbs. The fact that the cultured bulbs contained the same xanthones confirmed that they were secondary metabolites of *L. leptophylla*.[72]

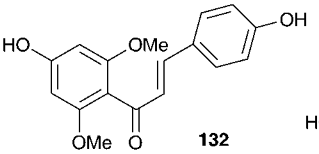
Within South Africa *Ledebouria revoluta* (L.f.) Jessop is extremely widespread. It is used by the Sotho to drive away lightening and with the exception of pregnant women, to treat lumbago. The Kwena and Tswana use it to treat wounds and skin conditions. The bulbs were found to contain homoisoflavanones (**30**, **59**, **61** and **157**).[73] *Ledebouria floribunda* (Baker) Jessop is used by traditional healers in the Eastern Cape of South Africa to treat skin disorders, tuberculosis, urinary tract infections and gastro-enteritis. Three homoisoflavanones, with unusual substituents at C-6, -7 and -8 (**163–165**) have been isolated from the bulbs as well as two 7-*O*-diglycosides (**166–167**) and five additional homoisoflavanones (**10**, **30**, **50**, **62**, **168**). These latter seven homoisoflavanones have shown good antioxidant activity against the DPPH radical (IC_{50} of 31–273 μg ml^{-1}) and in the β-carotene/



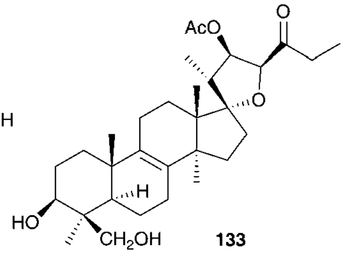
127 R_1 = H, R_2 = OMe, R_3 = OH, R_4 = OMe, R_5 = OMe, R_6 = OH
128 R_1 = H, R_2 = OMe, R_3 = OH, R_4 = OMe, R_5 = H, R_6 = OH
129 R_1 = H, R_2 = OMe, R_3 = OH, R_4 = OH, R_5 = OMe, R_6 = OH
130 R_1 = H, R_2 = OH, R_3 = H, R_4 = OH, R_5 = OMe, R_6 = OH
141 R_1 = OMe, R_2 = OH, R_3 = H, R_4 = OMe, R_5 =H, R_6 = OH
148 R_1 = H, R_2 = OH, R_3 = H, R_4 = OMe, R_5 =OMe, R_6 = OAc
156 R_1 = H, R_2 = OMe, R_3 = H, R_4 = OH, R_5 = H, R_6 = OH
157 R_1 = H, R_2 = OH, R_3 = H, R_4 = OH, R_5 = H, R_6 = OMe
158 R_1 = H, R_2 = OMe, R_3 = OMe, R_4 = OH, R_5 = H, R_6 = OH
159 R_1 = H, R_2 = OH, R_3 = H, R_4 = OH, R_5 =OH, R_6 = OH
166 R_1 = H, R_2 = O-[α-L-rhamnopyranosyl-(1→6)-β-D-glucopyranoside], R_3 = H, R_4 = OH, R_5 = H, R_6 = OMe
167 R_1 = H, R_2 = O-[α-L-rhamnopyranosyl-(1→6)-β-D-glucopyranoside], R_3 = H, R_4 = OH, R_5 = H, R_6 = OH
168 R_1 = H, R_2 = OH, R_3 = OMe, R_4 = OH, R_5 =H, R_6 = OH



131



132



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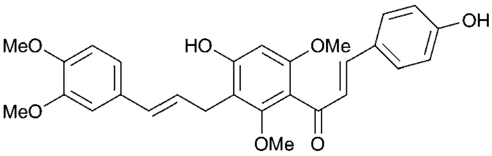
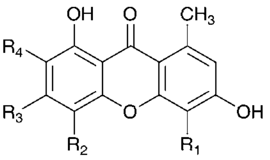
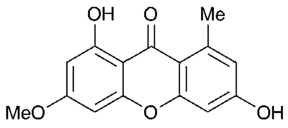


134



135 R_1 = OMe, R_2 = H, R_3 = OMe, R_4 = OMe
137 R_1 = H, R_2 = H, R_3 = OH, R_4 = OMe
138 R_1 = H, R_2 = H, R_3 = OH, R_4 = H
162 R_1 = H, R_2 = OMe, R_3 = OH, R_4 = OMe



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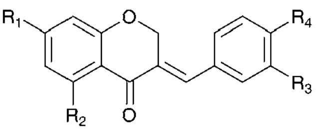
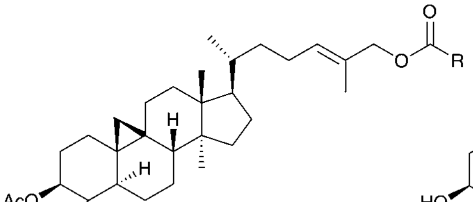
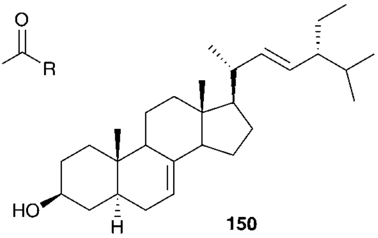


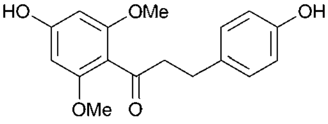
145 R_1 = OH, R_2 = OMe, R_3 = OH, R_4 = OH
146 R_1 = OH, R_2 = OH, R_3 = OH, R_4 = OH
147 R_1 = OAc, R_2 = OMe, R_3 = H, R_4 = OAc



149 R = $C_{22}H_{41}$



150



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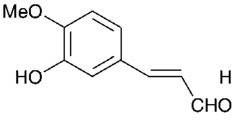

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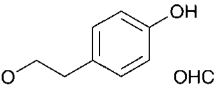
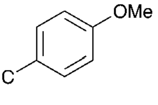
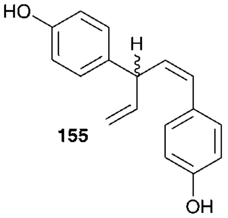


153



154



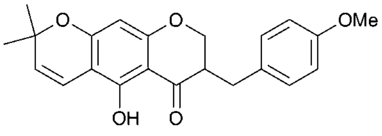
155

linoleic acid system (antioxidant activity of up to 79% after 120 min) as did **164** and **165** against the DPPH radical (IC_{50} of 23.2 and 28.7 $\mu g\ ml^{-1}$ respectively).[74,75]

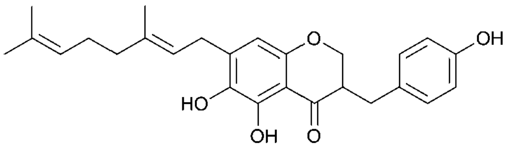
Leopoldia comosa (L.) Parl. is found largely in the Mediterranean region and the bulbs have been used as a food source for generations.[76] Evidence for the ancient use of this plant includes the discovery of traces of this species in a Neanderthal grave in Iraq.[77] The bulbs (as *Muscari comosum* Mill.) were examined for antioxidant activity as part of a study on non-cultivated vegetables commonly consumed by Albanians living in southern Italy. Twenty-seven plant species were investigated, with two showing high activity, one of which was *L. comosa* (inhibitory activity on a DPPH assay of 85%).[78] A further study also found good antioxidant activity as well as hypoglycemic activity *via* the inhibition of carbohydrate digestive enzymes.[79] Extracts of *L. comosa* (as *Muscari comosum* Mill.) have been found to be effective in combatting the wood rot fungus *Postia placenta* in samples of *Pinus sylvestris* L. and *Fagus orientalis*.[80] Phytochemical studies on *L. comosa* (as *Muscari comosum* Mill.) have resulted in the isolation of nineteen nortriterpenoids of the lanosterol-type as well as homoisoflavanones.

Initial work on the bulbs was complicated by the presence of complex glycosides. Acid catalysed methanolysis of the glycoside mixture resulted in the identification of the aglycones. Eucosterol **20** was found to be the major component, with compounds **21**, **54**, **169**, **170** and **171** present in smaller amounts.[76,81–84] Extensive work on the bulbs by Adinolfi *et al.* resulted in the isolation of the free aglycones present in the bulbs (**20**, **21**, **22**, **54**, **169–175**)[85–89] as well as the full structural elucidation of the glycosides (**86**, **87**, **102**, **103** and **176**).[90–94] All the nortriterpenes isolated from *Leopoldia comosa* mentioned so far have *S* configuration at C-23, three compounds with *R* configuration have also been identified, **177**,[91] **178** (23*R* **20**) and **179** (23*R* **170**).[89]

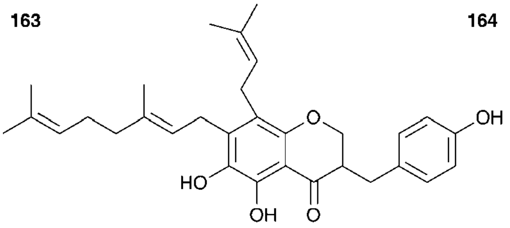
Two classes of homoisoflavanones have been isolated from the bulbs of *L. comosa*, the 3-benzyl-4-chromones (**30**, **58**, **59**, **61**, **62**, **80**, **97**, **180–181**)[95,96] and the scillascillin type (**55**, **104–107** and **182**).[97,98] The absolute configuration at C-3 of these



163



164



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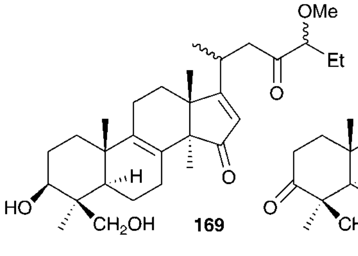

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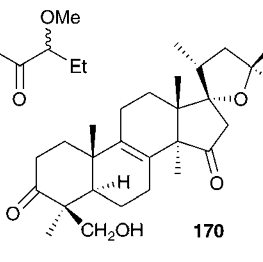

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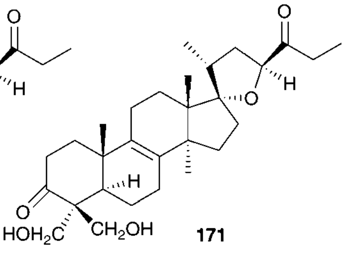

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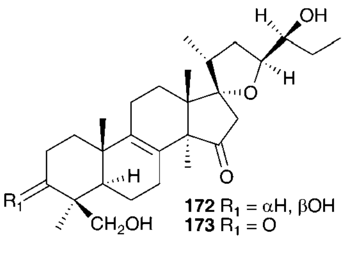
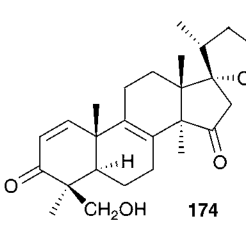


172 $R_1 = \alpha H, \beta OH$
173 $R_1 = O$



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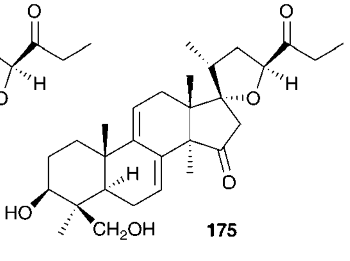

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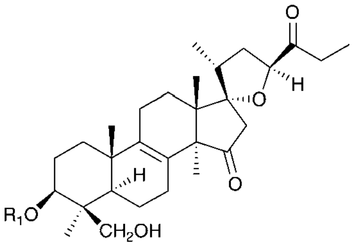
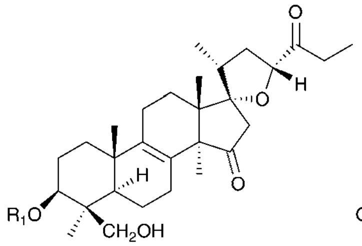
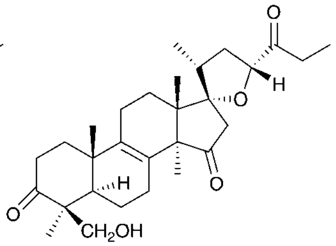


176 R_1 = β-D-apio-D-furanosyl-(1→2)]-β-D-glucopyranosyl(1→2)-α-L-arabinopyranosyl-(1→6)-β-D-glucopyranoside



177 R_1 = α-L-arabinofuranosyl(1→2)-α-L-arabinopyranosyl(1→3)[α-L-rhamnopyranosyl(1→2)]-β-D-glucopyranosyl(1→2)-α-L-arabinopyranosyl(1→6)-β-D-glucopyranoside
178 R_1 = H



179

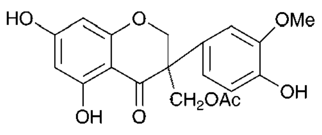
homoisoflavanones was determined using circular dichroism and found to be *R* in all cases.[99] For the scillascillin type, this was further confirmed by X-ray analysis.[98] The crude extract of the bulbs has been subjected to anti-inflammatory bioassay-directed fractionation using a croton oil-induced mouse ear dermatitis test. The homoisoflavanone rich fraction was found to have high activity and further fractionation resulted in the isolation of **30**, **59**, **61**, **80** and **97**, all of which showed activity, with compound **30** being the most active at 41% inhibition (100 μg ear^{-1}).[100] Two flavonoids have been isolated from the flowers of *L. comosa*, 3-glucoarabinosyl- and 3-rhamnoarabinosyl-3,4,5-trihydroxy-7-alkoxyl flavone.[101]

Leopoldia comosa is used in the Basilicata region of southern Italy to treat toothache and headache.[102] One third of the plants used for medicinal purposes in southern Italy are used to treat skin and soft tissue infections. As *Staphylococcus aureus* is a common cause of such infections, the effect of a number of Italian plants, including the bulbs of *Leopoldia comosa*, on the inhibition of the *S. aureus* biofilms has been studied. Significant dose-dependent biofilm inhibition (IC_{50} = 16 μg ml^{-1}) was noted for *L. comosa*.[103]

Investigations into the chemistry of the bulbs of *Scilla luciliae* (Boiss.) Speta (as *Chionodoxa gigantea* Whittall and as *Choinodoxa luciliae* Boiss.) has yielded a large number of lanosterol-type spirocyclic nortriterpenoids, many of which have been tested for biological activity. Compounds **183–186**[16,104] and compounds **13** and **187–188**[17] have been isolated from the bulbs of *Scilla luciliae* (as *Chionodoxa gigantea*). In separate investigations, compounds **13**, **184** and **187–190**[17] as well as compounds **189** and **190–197** and eucosterol **20**,[105] compounds **198–204**,[106] **205–207**[107] and **208–209**[108] have been found in the bulbs of this species (as *C. luciliae*). Compounds **183–186** all showed some inhibitory activity on cyclic AMP phosphodiesterase, with compound **183** giving the best results (IC_{50} = 11.2 × 10^{-5} M).[104] Cytotoxicity against HeLa cells was assessed for **13**, **184**, **187**, **188**, **189**, and **190** with the 15-deoxoeucosterol oligosaccharides (**13**, **187** and **190**) showing good activity down to 5 μg ml^{-1}.[17] Compounds **198–204** as well as **183** and **185** were tested for activity against HSC-2 human oral squamous carcinoma cells. Compounds **183**, **185**, **200**, **201** and **204** all gave good results with LD_{50} values in the range 10–23 μg ml^{-1} (etoposide LD_{50} = 24 μg ml^{-1}, for etoposide resistant HSC cells). It was noted that the 23*R* isomer of **185**, compound **186** did not show any activity.[106] Compounds **208** and **209** showed only weak activity in the same assay (LD_{50} of 254 and 238 μg ml^{-1} respectively).[108] In addition to the spirocyclic nortriterpenoids, the bulbs of *Scilla luciliae* (as *Chionodoxa luciliae*) have been found to contain the homoisoflavanones **210–222**.[109]

The bulbs and aerial parts of *Scilla bifolia* L. have been studied using HPLC and mass spectrometry. Eighteen polyphenols were identified from extracts of the bulbs and aerial parts (caftaric acid, isoquercitin, routine, myricetol, fistein, quercetol, patuletin, gentisic acid, caffeic acid, chlorogenic acid, *p*-coumaric acid, ferulic acid, hyperoside, quercitrin, luteolin, kaempferol, apigenin and sinapic acid).[110]

The methanol and aqueous ethanol extracts of the bulbs of *Autonoe madeirensis* (Menezes) Speta (as *Scilla maderensis* Menezes), a species endemic to the Portuguese archipelago of Madeira, was found to produce cardiac action on a frog heart and although TLC showed compounds with R_f values and colours very similar to the bufadienolides proscillaridin A **223** and scillaren A **224**, typical of the Urgineoideae, the presence of these compounds was not conclusively established.[111]



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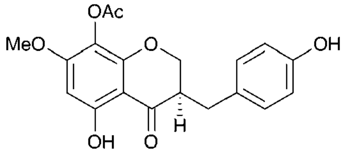

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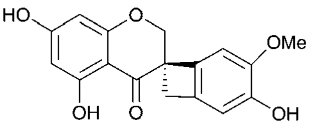

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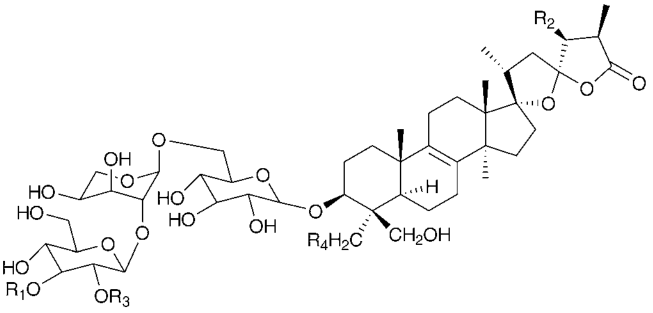
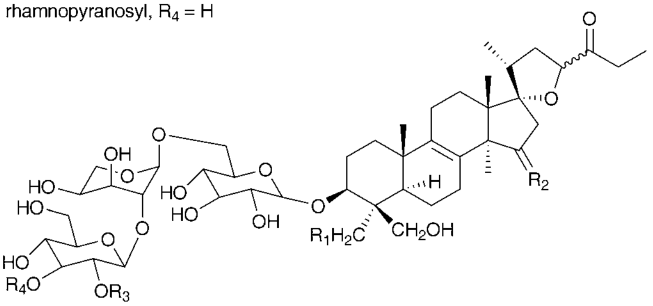
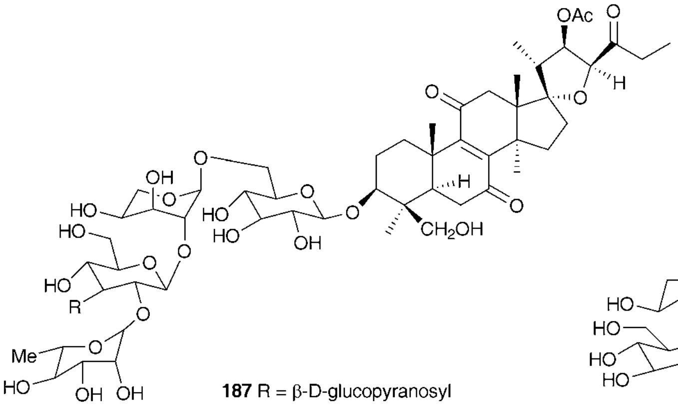


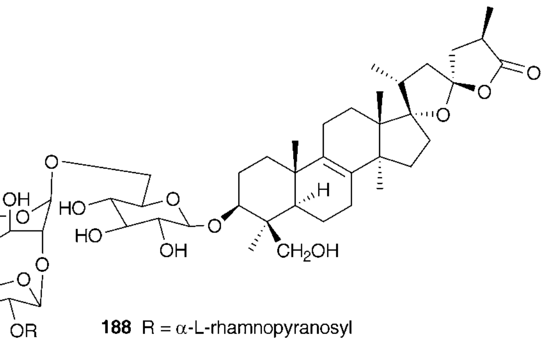
183 R_1 = β-D-glucopyranosyl(1→2)-β-D-glucopyranosyl, R_2 = H, R_3 = α-L-rhamnopyranosyl, R_4 = H
184 R_1 = H, R_2 = OH, R_3 = α-L-rhamnopyranosyl, R_4 = H
203 R_1 = H, R_2 = H, R_3 = β-D-apiofuranosyl, R_4 = OH
204 R_1 = β-D-glucopyranosyl, R_2 = H, R_3 = α-L-rhamnopyranosyl, R_4 = H
205 R_1 = H, R_2 = H, R_3 = α-L-rhamnopyranosyl, R_4 = H
206 R_1 =(1→3)-β-D-galactopyranosyl, R_2 = H, R_3 = α-L-rhamnopyranosyl, R_4 = H
207 R_1 = β-D-glucopyranosyl(1→2)-β-D-galactopyranosyl, R_2 =OH, R_3 = α-L-rhamnopyranosyl, R_4 = H



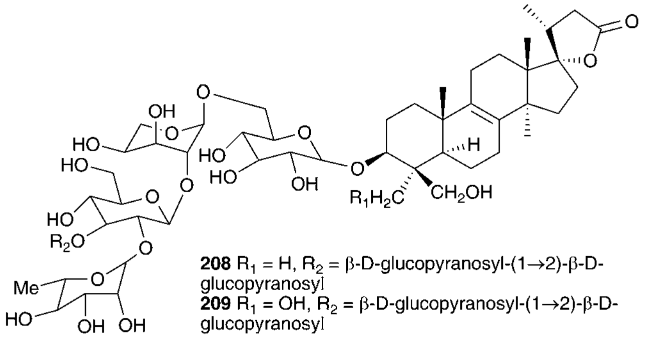
185 (23 *S)* R_1 = H, R_2 = H, R_3 = α-L-rhamnopyranosyl, R_4 = -(1→2)-O-β-D-glucopyranosyl-(1→3)-O-β-D-glucopyranosyl
186 (23 *R)* R_1 = H, R_2 = H, R_3 = α-L-rhamnopyranosyl, R_4 = -(1→2)-O-β-D-glucopyranosyl-(1→3)-O-β-D-glucopyranosyl
189 (23 *S)* R_1 = H, R_2 = H,H, R_3 = α-L-rhamnopyranosyl, R_4 = H
190 (23 *S)* R_1 = H, R_2 = H,H, R_3 = α-L-rhamnopyranosyl, R_4 = β-D-glucopyranosyl(1→2)-β-D-glucopyranosyl
191 (23 *S)* R_1 = H, R_2 = H,H, R_3 = α-L-rhamnopyranosyl, R_4 = β-D-glucopyranosyl(1→2)-β-D-galactopyranosyl
192 (23 *S)* R_1 = H, R_2 = H,H, R_3 = α-L-rhamnopyranosyl, R_4 = β-D-glucopyranosyl(1→2)-α-L-arabinopyranosyl
193 (23 *S)* R_1 = OH, R_2 = H,H, R_3 = α-L-rhamnopyranosyl, R_4 = β-D-glucopyranosyl(1→2)-β-D-galactopyranosyl
194 (23 *S)* R_1 = OH, R_2 = H,H, R_3 = α-L-arabinofuranosy, R_4 =-β-D-galactopyranosyl
195 (23 *S)* R_1 = OH, R_2 = H,H, R_3 = β-D-apiofuranosyl, R_4 = β-D-glucopyranosyl(1→2)-β-D-galactopyranosyl
196 (23 *S)* R_1 = OH, R_2 = H,H, R_3 = α-L-rhamnopyranosyl, R_4 = H
197 (23 *S)* R_1 = OH, R_2 = O, R_3 = α-L-rhamnopyranosyl, R_4 = H
198 (23 *S)* R_1 = OH, R_2 = H,H, R_3 = β-D-apiofuranosyl, R_4 = H
199 (23 *S)* R_1 = OH, R_2 = H,H, R_3 = β-D-apiofuranosyl, R_4 = β-D-glucopyranosyl
200 (23 *S)* R_1 = OH, R_2 = H, R_3 = α-L-rhamnopyranosyl, R_4 = H
201 (23 *S)* R_1 = H, R_2 = H, R_3 = α-L-rhamnopyranosyl, R_4 = -(1→2)-β-D-glucopyranosyl
202 (23 *S)* R_1 = H, R_2 = O, R_3 = α-L-rhamnopyranosyl, R_4 = -(1→2)-β-D-glucopyranosyl-(1→3)-β-D-glucopyranosyl



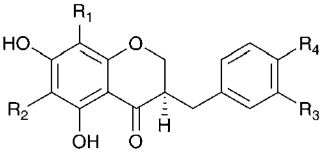
187 R = β-D-glucopyranosyl



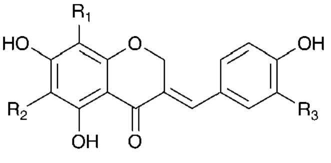
188 R = α-L-rhamnopyranosyl



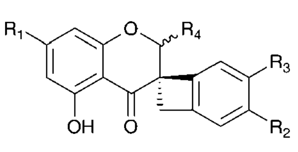
208 R_1 = H, R_2 = β-D-glucopyranosyl-(1→2)-β-D-glucopyranosyl
209 R_1 = OH, R_2 = β-D-glucopyranosyl-(1→2)-β-D-glucopyranosyl



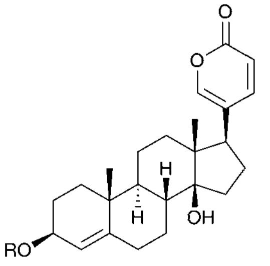
210 R_1 = OMe, R_2 = H, R_3 = OH, R_4 = OMe
211 R_1 = H, R_2 = OMe, R_3 = OH, R_4 = OMe
212 R_1 = OMe, R_2 = H, R_3 = H, R_4 = OH
213 R_1 = H, R_2 = H, R_3 = OH, R_4 = OMe
214 R_1 = H, R_2 = OMe, R_3 = H, R_4 = OH
215 R_1 = H, R_2 = H, R_3 = OH, R_4 = OH



216 R_1 = OMe R_2 = H, R_3 = OH
217 R_1 = H R_2 = OMe, R_3 = OH
218 R_1 = OMe R_2 = H, R_3 = H



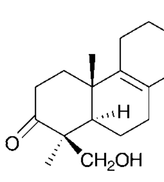
219 R_1 = OH, R_2-R_3 = O-CH_2-O, R_4 = OH
220 R_1 = OMe, R_2-R_3 = O-CH_2-O, R_4 = OH
221 R_1 = OH, R_2-R_3 = O-CH_2-O, R_4 = OH
222 R_1 = OH, R_2 = OH, R_3 = OMe, R_4 = OH



223 : R_1 = α-L-rhamnopyranoside
224 R_1 = α-L-rhamnopyranosyl-(1→4)-β-D-glucopyranoside

Barnardia japonica (Thunb.) Schult. & Schult.f. (as *Scilla scilloides* (Lind.) Druce) has been used for a long time by traditional Chinese healers to treat abscesses and to promote circulation.[112] This plant also grows extensively in the wild in Japan and Korea and has been used by traditional healers of the latter country.[113] The root extract has been evaluated for its potential as an antimicrobial agent, as an anti-inflammatory and as an antioxidant.[113] The root extract of *B. japonica* (as *Scilla scilloides*) was found to inhibit the growth of *Staphylococcus aureus*, *Salmonella enteritidis*, *Escherichia coli* and *Candida parapsilosis* down to a concentration of 0.1% of the extract. Antioxidant activity was evaluated by looking at the inhibition of hyaluronidase, an enzyme that initiates the degradation of hyaluronic acid, associated with inflammation. Inhibition was noted at concentrations of root extract of 0.1 (14.8% inhibition) and 1% (48.2% inhibition), but not below. Anti-oxidant activity was assessed by monitoring the oxidation of linoleic acid and good activity was found (anti-oxidative index of 33.2 at a concentration of 1%).[113] Extensive phytochemical investigations of the bulbs of *B. japonica* (as *Scilla scilloides*) resulted in the isolation of spirocyclic nortriterpenes (**21**, **22**, **131**, **225**, **226** and **227**),[114,115] the related oligoglycosides (**187**, **228–239** and **241–247**)[112,116–118] and homoisoflavanones (**42**, **55** and **248**).[119] Nishida *et al.*[120] reported the isolation of sixteen compounds from the methanol extract of the bulbs, including three nortriterpenes (**21**, **22**, and **225**), a lignan **249**, a xanthone **137**, two homostilbenes (**250** and **251**) and nine homoisoflavanones (**49**, **55**, C-3 epimer compound of **62**, **182**, **252**, **253**,and **254–156**). The configuration at C-3 for **253**, **254** and the epimer of compound **62** was unusually found to be *S* by circular dichroism.[120] Scillascilloside E-3 **239** and scillascilloside E-1 **237** have shown potent cytotoxicity against a range of human cancer cells (ED_{50} 1.5–3.0 nM and 1.6–5.9 nM respectively).[112,117] Patents have been filed covering the use of *B. japonica* (as *Scilla scilloides*) bulb extracts for the treatment of fungal infections[121] and as a treatment for cancer.[122] A later investigation into the methanol extract of the bulbs resulted in the isolation of two norlanostane-type triterpenoid glycosides (**257** and **258**), a phenylpropanoid glycoside **259** and two alkaloids (**260** and **261**).[123] The aqueous methanol extract of the bulbs of *B. japonica* (as *Scilla japonica*) produced some cardiac action on an isolated toad heart muscle, although the active components responsible were not identified.[124]

Othocallis siberica (as *Scilla sibirica* Haw.) is native to south-western Russia, the Caucasus and Turkey. The bulbs were found to contain 0.04% glycosides and 0.15% alkaloids, with the alkaloid fraction being able to stop the function of an isolated frog heart. The glycoside fraction showed a strong hypertensive action and was a stimulant to respiration.[125] The hot water extract of the bulbs produced an acylated glucomannan with D-mannose, D-glucose and an acyl group in a ratio of 7.7 : 1 : 2.4.[126] As part of their investigations into potential glycosidase inhibitors, Yamashita *et al.* examined the ethanol extract of the bulbs of *O. siberica* (as *Scilla sibirica*). They isolated



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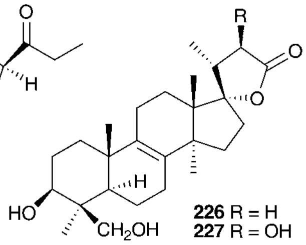
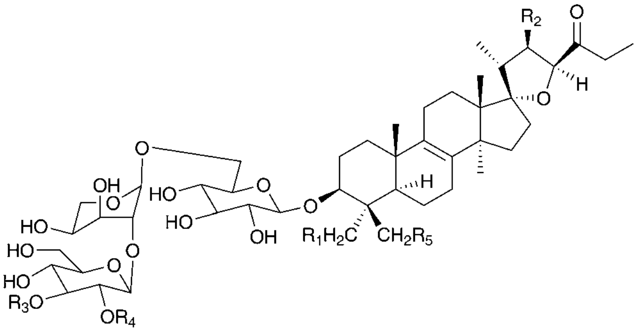
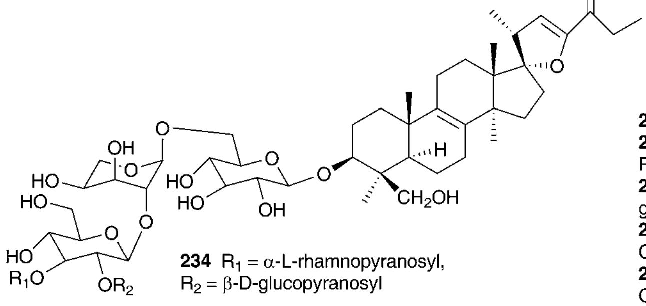


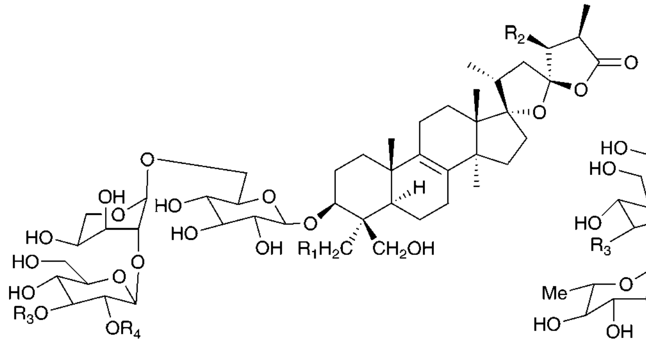
226 R = H
227 R = OH



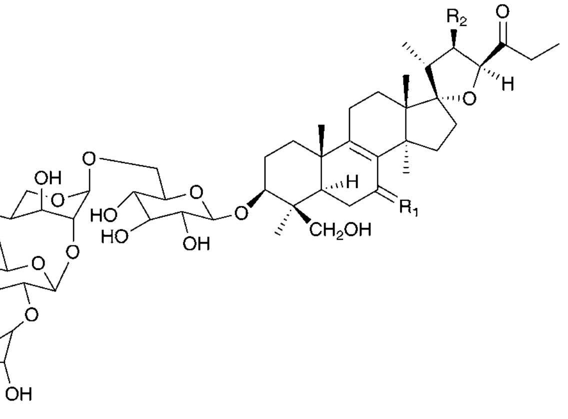
228 $R_1 = R_2 = R_4 = H$, R_3 = α-L-rhamnopyranosyl, R_5 =OH, $R_6 = H$
229 $R_1 = R_2 = H$, R_3 = α-L-rhamnopyranosyl, R_4 = β-D-glucopyranosyl, R_5 = OH, $R_6 = H$
230 $R_1 = R_2 = H$, R_3 = α-L-rhamnopyranosyl, R_4 = β-D-glucopyranosyl-(1→3)-β-D-galactopyranosyl-(1→3)-β-D-glucopyranosyl, R_5 = OH, $R_6 = H$
231 R_1 = OH, $R_2 = H$, R_3= α-L-arapinofuranosyl, R_4 = β-D-glucopyranosyl, R_5 = OH, $R_6 = H$
232 $R_1 = H$, R_2 = OAc, R_3 = α-L-rhamnopyranosyl, R_4 = β-D-glucopyranosyl, R_5 = OH, $R_6 = H$
233 $R_1 = H$, R_2 = OAc, R_3= α-L-arapinofuranosyl, R_4 = β-D-glucopyranosyl, R_5 = OH, $R_6 = H$
235 R_1 = OH, $R_2 = H$, R_5 = OH, R_3 = α-L-rhamnopyranosyl, R_4 = β-D-glucopyranosyl, $R_6 = H$
237 $R_1 = H$, $R_2 = H$, $R_5 = H$, R_3 = α-L-rhamnopyranosyl, R_4 = β-D-glucopyranosyl, $R_6 = H$
238 R_1 = OH, $R_5 = H$, R_3 = α-L-arabinofuranosyl R_4 = β-D-glucopyranosyl, $R_6 = H$
239 $R_1 = H$, $R_2 = H$, R_5 = OAc, R_3 = α-L-rhamnopyranosyl, R_4 = β-D-glucopyranosyl, $R_6 = H$
240 $R_1 = H$, $R_2 = H$, $R_5 = H$, R_3 = α-L-rhamnopyranosyl, R_4 = β-D-glucopyranosyl-(1→3)-β-D-galactopyranosyl-(1→3)-β-D-glucopyranosyl, $R_6 = H$
257 $R_1 = R_2 = H$, R_3 = β-D-galactopyranosyl-(1→3)-β-D-glucopyranosyl, R_4 = (1→2)-α-L-rhamnopyranosyl, R_5 = OH, $R_6 = O$



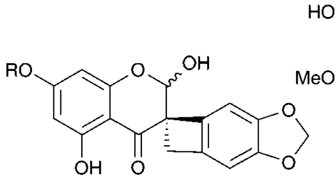
234 R_1 = α-L-rhamnopyranosyl,
R_2 = β-D-glucopyranosyl

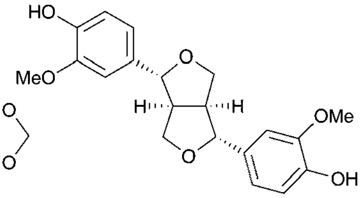


236 $R_1 = H$, $R_2 = H$, R_3 = α-L-rhamnopyranosyl, R_4 = β-D-glucopyranosyl
244 $R_1 = H$, R_2 = OH, R_3 = β-D-glucopyranosyl-(1→3)-β-D-galactopyranosyl-(1→3)-β-D-glucopyranosyl, R_4 = α-L-rhamnopyranosyl
245 $R_1 = H$, R_2 = OH, R_3 = –α-D-xylopyranosyl-β-D-glucopyranosyl-(1→3)-β-D-galactopyranosyl-(1→3)-β-D-glucopyranosyl, R_4 = α-L-rhamnopyranosyl
246 R_1 = OH, $R_2 = H$, R_3 = β-D-glucopyranosyl, R_4 = α-L-rhamnopyranosyl
247 $R_1 = H$, R_2 = OH, $R_3 = H$, R_4 = α-L-rhamnopyranosyl



241 $R_1 = O$, R_2 = OAc, R_3 = β-D-glucopyranosyl
242 $R_1 = 2H$, $R_2 = H$, R_3 = α-D-xylopyranosyl-β-D-glucopyranosyl-(1→3)-β-D-galactopyranosyl-(1→3)-β-D-glucopyranosyl,
243 $R_1 = 2H$, $R_2 = H$, R_3 = β-D-glucopyranosyl-(1→3)-β-D-galactopyranosyl-(1→3)-β-D-glucopyranosyl


248 R = Me
256 R = H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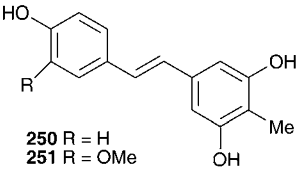
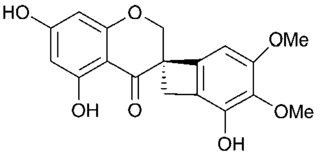

250 R = H
251 R = OMe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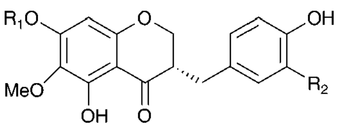
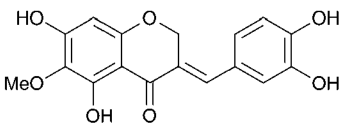

253 R_1 = Me, R_2 = OH
254 R_1 = H, R_2 = OH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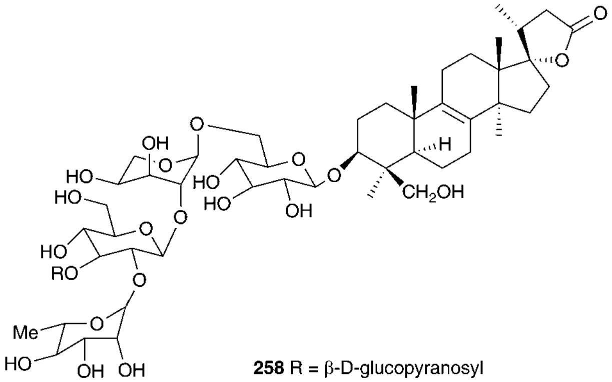
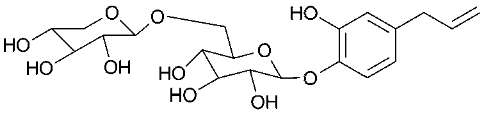

258 R = β-D-glucopyranosyl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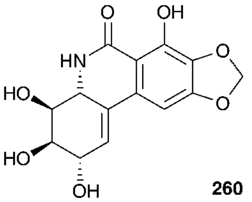
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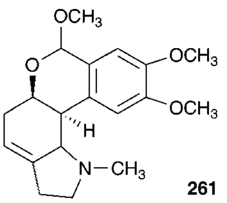
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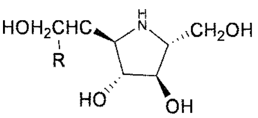
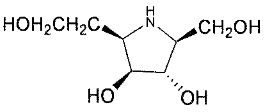
and identified five pyrrolidines (**262–266**), two pyrrolidine glycosides (**267–268**), six piperidines (**269–274**), one piperidine glycoside (**275**) and eight pyrrolizidines (**276–283**).[127] These alkaloids were tested for their inhibitory activity against various glycosidases. Compound **262** was found to be a potent inhibitor of bacterial (*Caldocellum sacchrolyticum*) β-glucosidase and mammalian β-galactosidase ($IC_{50} = 3.2$ μg ml^{-1} and 4.4 μg ml^{-1} respectively). The loss of the hydroxy group at C-6, to give compound **263**, significantly lowered the activity. Moderate or no activity was found for all other compounds isolated.[127]

The bulbs of *Oncostema peruviana* (as *Scilla peruviana*) were found to contain rearranged lanosterol glycosides (scillasaponin B **284**, peruvianoside A **285**, peruvianoside B **286**, and compounds **187–188** and **287–288**)[16,17,128,129] as well as a range of polyhydroxylated pyrrolidines (**289–291**) and pyrrolizidines (**292–295**).[130] Moderate inhibitory activity against cyclic AMP


262 R = OH
263 R = H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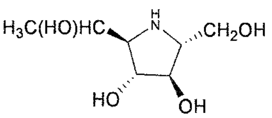
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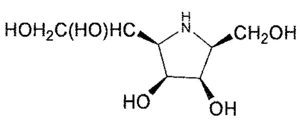
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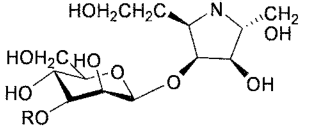
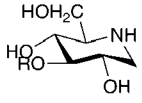
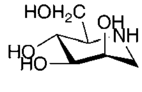

267 R = H
268 R = β-D-mannopyranosyl



269 R = H
275 R = α-D-glucopyranoside



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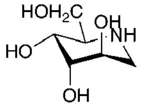

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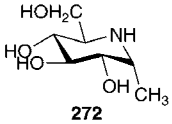

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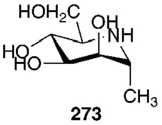

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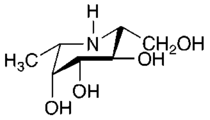

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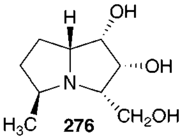

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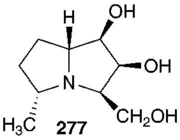

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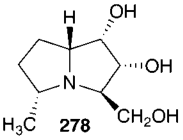

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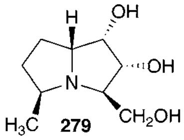

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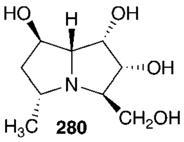

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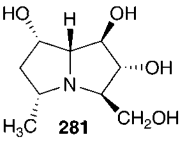

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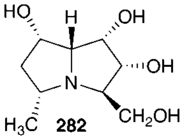

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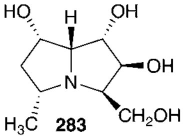
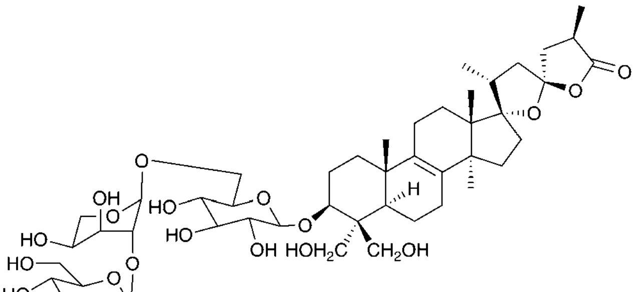
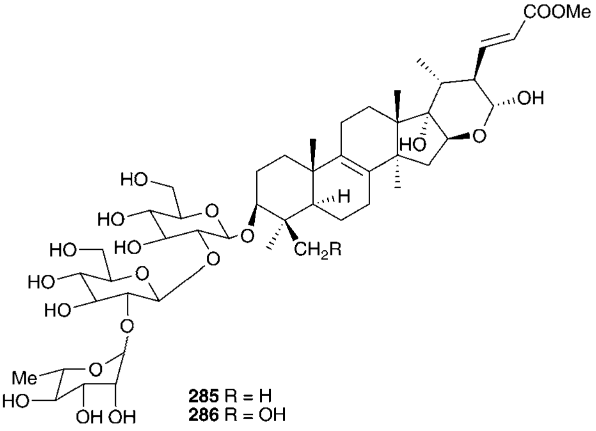


283

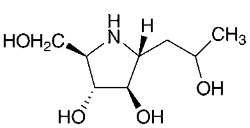
phosphodiesterase was noted for peruvianoside A **285** ($IC_{50} = 23.5 \times 10^{-5}$ M) and scillasaponin B **286** ($IC_{50} = 14.0 \times 10^{-5}$ M),[16,128] while compound **187**, a 15-deoxoeucosterol oligosaccharide, was found to be toxic to HeLa cells at a concentration of 5 μg ml^{-1}.[17] The pyrrolidine **291** was found to be a potent inhibitor of bacterial β-glucosidase (IC_{50} = 80 nM), compounds **292** and **293** showed significant inhibition of yeast α-glucosidase (IC_{50} = 6.6 and 6.3 μM respectively) with compound **293** also showing good inhibition of bacterial β-glucosidase (IC_{50} = 5.1 μM).[130]



284 R_1 = β-D-glucopyranosyl, R_2 = α-L-rhamnopyranosyl
287 R_1 = H, R_2 = α-L-rhamnopyranosyl
288 R_1 = H, R_2 = β-D-apiofuranosyl



285 R = H
286 R = OH



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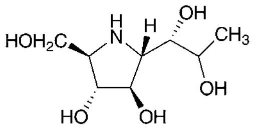

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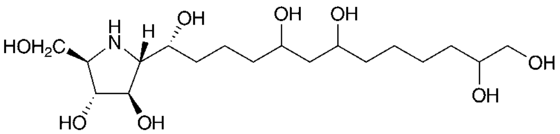

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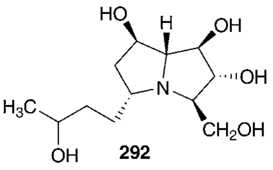

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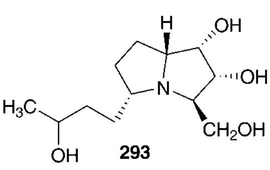

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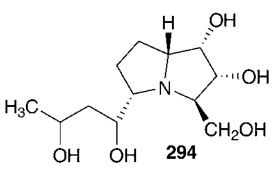

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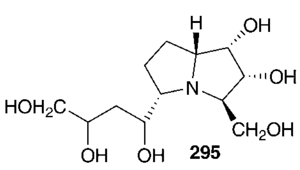
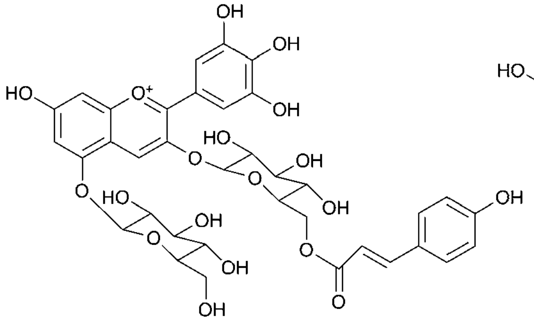


295

Phytochemical work on the Hyacinthaceae has primarily focused on the bulbs. The exception to this has been the genus *Hyacinthus*, where most of the work has been done on the flowers. *Hyacinthus orientalis* is used as an ornamental plant and can have blue, pink, yellow or white flowers. The blue flowers of *H. orientalis* have been found to contain a range of acylated anthocyanins (**296–302**).[131] The anthocyanin content was also studied in the blue flowers produced *in vitro*. The same anthocyanins were produced with some small changes in the percentage composition of the different compounds.[132] The red flowers of *H. orientalis* likewise produced a range of acylated anthocyanins (**303–316**) and, as with the blue flowers, the red flowers produced *in vitro* produced the same anthocyanins with some differences in composition.[133–135] A later investigation of the blue flowers of *H. orientalis* revealed a further seven anthocyanins (**317–323**) in addition to those isolated previously.[136] Differences in essential oil content between wild *H. orientalis* flowers and those generated *in vitro* have been studied. Four common components were found, 1-hepten-3-ol, benzyl alcohol, phenethyl alcohol and cinnamyl alcohol. The main components in the wild flowers were phenethyl alcohol (55% at stage 3 and 48% at stage 4) and cinnamyl alcohol (23% at stage 3 and 29% at stage 4) while the *in vitro* generated flowers produced 75% phenethyl alcohol as the major component.[137] The bulbs of *H. orientalis* were found to be rich in polyhydroxy alkaloids. α-Homonojirimycin **324** was the major component[138] with the compounds **325–334** being found in smaller amounts.[138,139] Compound **332** was found to be a good inhibitor of bacterial β-glucosidase (IC_{50} = 3.8 μM), mammalian β-galactosidases (IC_{50} = 4.0 μM and 4.4 μM) and mammalian trehalases (5.0 μM and 2.0 μM), while compound **333** inhibited rice α-glucosidase (IC_{50} = 2.2 μM) and rat intestinal maltase (IC_{50} = 2.5 μM) and compound **334** inhibited α-L-fucosidase (IC_{50} = 50 μM).[139]

The methanol extract of the bulbs of *Bellevalia paradoxa* (Fisch. & C.A.Mey.) Boiss. (as *Muscari paradoxum* (Fisch. et C.A. Mey.) K.Koch) yielded eight 27-norlanostane glycosides (**335–342**)[55] and seven tetranorlanosterol glycosides (**25, 343–348**).[54] All were tested



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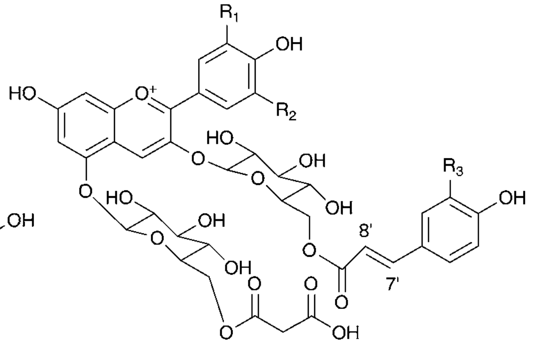
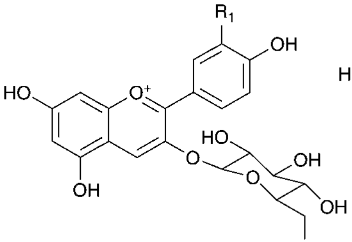


297 R_1 = OH, R_2 = OH, R_3 = OH, 7'/8' *trans*
298 R_1 = OH, R_2 = OH, R_3 = H, 7'/8' *cis*
299 R_1 = OH, R_2 = OH, R_3 = H, 7'/8' *trans*
300 R_1 = OMe, R_2 = OH, R_3 = H, 7'/8' *trans*
301 R_1 = OH, R_2 = H, R_3 = H, 7'/8' *trans*
302 R_1 = H, R_2 = H, R_3 = H, 7'/8' *trans*
322 R_1 = H, R_2 = OH, R_3 = H, 7'/8' *trans*
323 R_1 = OH, R_2 = OMe, R_3 = H, 7'/8' *trans*



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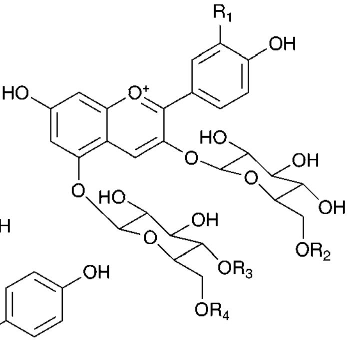
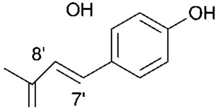
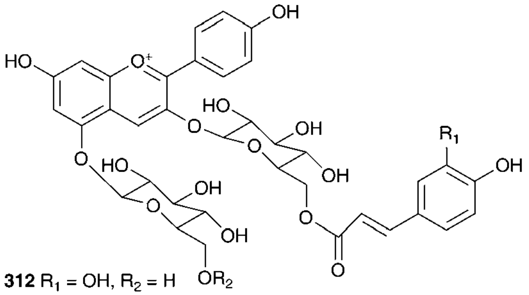
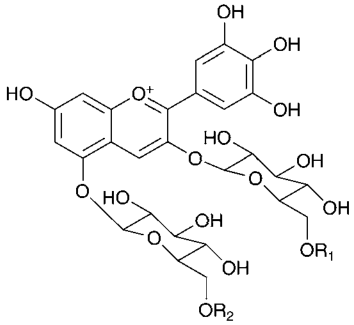


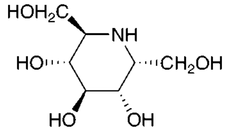


p-coumaroyl

304 R_1 = H, R_2 = H, R_3 = H, R_4 = H
305 R_1 = H, R_2 = *p*-coumaroyl, R_3 = H, R_4 = H, 7'/8' cis
306 R_1 = H, R_2 = *p*-coumaroyl, R_3 = H, R_4 = H, 7'/8' trans
307 R_1 = H, R_2 = H, R_3 = H, R_4 = malonyl
308 R_1 = H, R_2 = *p*-coumaroyl, R_3 = H, R_4 = malonyl, 7'/8' cis
309 R_1 = H, R_2 = *p*-coumaroyl, R_3 = H, R_4 = malonyl, 7'/8' trans
310 R_1 = H, R_2 = *p*-coumaroyl, R_3 = malonyl, R_4 = H, 7'/8' trans
311 R_1 = OH, R_2 = *p*-coumaroyl, R_3 = H, R_4 = malonyl, 7'/8' trans
318 R_1 = H, R_2 = caffeoyl, R_3 = H, R_4 = H
319 R_1 = H, R_2 feruloyl, R_3 = H, R_4 = H
320 R_1 = H, R_2 = feruloyl R_3 = H, R_4 = malonyl
321 R_1 = H, R_2 = caffeoyl, R_3 = H, R_4 = malonyl


312 R_1 = OH, R_2 = H
313 R_1 = OMe, R_2 = H
314 R_1 = H, R_2 = acetyl
315 R_1 = OMe, R_2 = malonyl
316 R_1 = OH, R_2 = malonyl


317 R_1 = caffeoyl, R_2 = malonyl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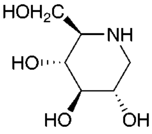
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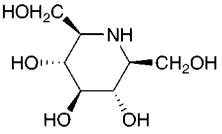
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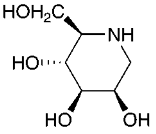
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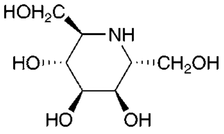
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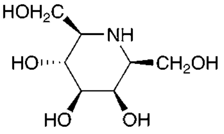
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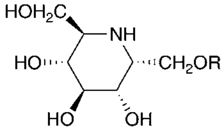
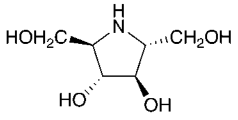

330 R = β-D-glucopyranoside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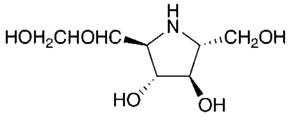
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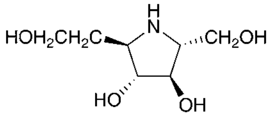
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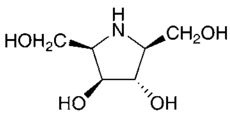
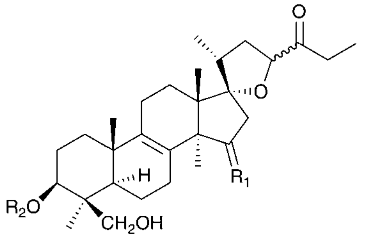

334

for cytotoxicity against HSC-2 human oral squamous cell carcinoma. Compounds **25** and **343–344** showed no activity while compounds **345–348** gave IC_{50} values of 6.3–59 μg ml^{-1}, with the standard etoposide giving an IC_{50} of 24 μg ml^{-1}. Compounds **335**, **336**, **338**, **340** and **341**, all 23*S* isomers, showed good activity relative to etoposide, but the corresponding 23*R* isomers showed no activity up to a dose of 100 μg ml^{-1}. The methanol extract of the bulbs of *Bellevalia romana* (L.) Sweet produced oligoglycosides of the eucosterol-type, four new compounds bellevaliosides A **349**, B **350**, C **351** and D **352** as well as compounds **86**, **87** and **353**, previously isolated from *Muscari* species.[140] In addition to the spirocyclic nortriterpenoids, five homoisoflavanones (**354–358**) were isolated.[141] The bulbs of *Autonoe madeirensis* (as *Scilla maderensis* Menezes), have produced a slightly unusual phytochemical profile. An investigation of the ethanol extract of the bulbs resulted in the isolation of a range of 2-hydroxy di- and tricarboxylic acids and esters, *cis*- and *trans*-hydroxycinnamate esters and a flavone diglucoside **359**.[142] A later study of the bulbs found 24*S*-ethyl-5α-cholesta-7,22*E*-dien-3-ol-β-galactopyranoside **360** to be present.[143] Dias *et al.* isolated the pyrimidine derivative 2-(4′-aminobenzenamine)-pyrimidine and found it to be an α-adrenoreceptor antagonist.[144]

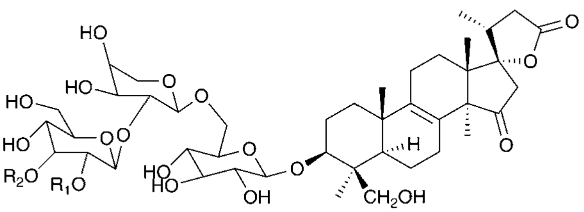
Work on the bulbs of *Hyacinthoides hispanica* (as *Scilla campanulata*) has focused on the isolation and structure determination of a mannose-specific lectin. Crystals have been grown and the structure determined by X-ray diffraction studies.[145–149] In addition to the mannose-binding lectin, a fetuin-binding lectin has been isolated and identified.[150] Polyhydroxylated alkaloids have been isolated from the ethanol extract of the bulbs of *H. hispanica* (as *Scilla campanulata*) and tested for glycosidase inhibitory activity. Compounds **361–368** were identified with compound **364** showing good inhibition of *Caldocellum saccharolyticum* β-glucosidase ($IC_{50} = 3.8$ μM) and bovine liver β-galactosidase ($IC_{50} = 4.4$ μM). Compound **366** was more active than compound **364** against *Caldocellum saccharolyticum* β-glucosidase ($IC_{50} = 0.34$ μM), but less so of bovine liver β-galactosidase ($IC_{50} = 24$ μM).[151]

Hyacinthoides non-scripta (bluebells) has long been known to be toxic to livestock. Horses suffer from abdominal pain and dysentery while cattle suffer from lethargy and dullness after consuming the plants. The toxic principles are the polyhydroxy pyrrolidine and pyrrolizidine alkaloids, common to many Hyacinthoideae.[151,152] Alkaloids **361–367**, also found in *Hyacinthoides hispanica* (as *Scilla campanulata*), have been isolated from the leaves, stalks and immature fruits of the bluebells.[151,152] A glucomannan has been isolated from the seeds of *H. non-scripta*. It is a linear polymer with D-glucopyranose and D-mannopyranose residues occurring in the ratio of 1 : 1.3.[153]

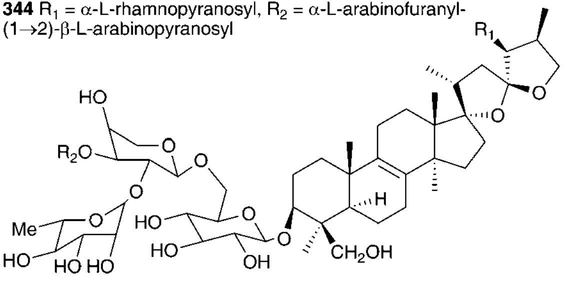
Southern African genera that have received the attention of phytochemists are *Drimiopsis*, *Resnova*, *Veltheimia*, *Merwilla*, *Lachenalia*, *Pseudoprospero*, *Schizocarphus* and *Spetaea*. The range of compounds isolated is typical of the subfamily Hyacinthoideae,



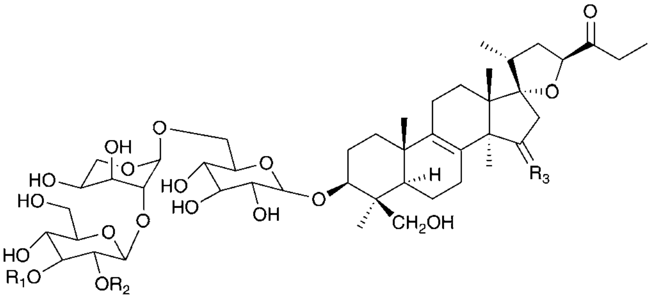
335 (23*S*) R$_1$ = 2H, R$_2$ = α-L-rhamnopyranosyl-(1→2)-β-D-glucopyranosyl-(1→2)-β-L-arabinopyranosyl-(1→6)-β-D-glucopyranoside
336 (23*S*) R$_1$ = O, R$_2$ = α-L-rhamnopyranosyl-(1→2)-β-D-glucopyranosyl-(1→2)-β-L-arabinopyranosyl-(1→6)-β-D-glucopyranoside
337 (23*R*) R$_1$ = O, R$_2$ = α-L-rhamnopyranosyl-(1→2)-β-D-glucopyranosyl-(1→2)-β-L-arabinopyranosyl-(1→6)-β-D-glucopyranoside
338 (23*S*) R$_1$ = O, R$_2$ = β-apiofuranosyl-(1→2)-β-D-glucopyranosyl-(1→2)-β-L-arabinopyranosyl-(1→6)-β-D-glucopyranoside
339 (23*R*) R$_1$ = O, R$_2$ = β-apiofuranosyl-(1→2)-β-D-glucopyranosyl-(1→2)-β-L-arabinopyranosyl-(1→6)-β-D-glucopyranoside
340 (23*S*) R$_1$ = 2H, R$_2$ =[α-L-rhamnopyranosyl-(1→2)]-[-α-D-xylopyranosyl-(1→2)-β-arabinopyranosyl-(1→3)]-β-D-glucopyranosyl-(1→2)-β-L-arabinopyranosyl-(1→6)-β-D-glucopyranoside,
341 (23*S*) R$_1$ = O, R$_2$ =[α-L-rhamnopyranosyl-(1→2)]-[–α-D-xylopyranosyl-(1→2)–β-arabinopyranosyl-(1→3)]-β-D-glucopyranosyl-(1→2)-β-L-arabinopyranosyl-(1→6)-β-D-glucopyranoside
342 (23*R*) R$_1$ = O, R$_2$ =[α-L-rhamnopyranosyl-(1→2)]-[-α-D-xylopyranosyl-(1→2)-β-arabinopyranosyl-(1→3)]-β-D-glucopyranosyl-(1→2)-β-L-arabinopyranosyl-(1→6)-β-D-glucopyranoside



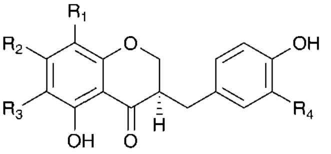
343 R$_1$ = α-L-rhamnopyranosyl, R$_2$ = β-L-arabinpyranosyl
344 R$_1$ = α-L-rhamnopyranosyl, R$_2$ = α-L-arabinofuranyl-(1→2)-β-L-arabinopyranosyl



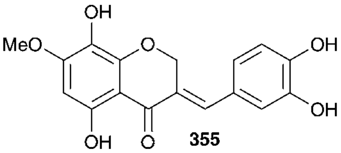
345 R$_1$ = H, R$_2$ = β-L-arabinopyranosyl
346 R$_1$ = H, R$_2$ = α-L-arabinofuranyl-(1→2)-β-L-arabinopyranosyl
347 R$_1$ = OH, R$_2$ = α-L-arabinofuranyl-(1→2)-β-L-arabinopyranosyl
348 R$_1$ = H, R$_2$ = H



349 R$_1$= α-L-rhamnosyl, R$_2$ = D-apiofuranosyl-(1→2)-D-xylopyranosyl, R$_3$ = O
350 R$_1$= α-L-rhamnosyl, R$_2$ = D-xylopyranosyl, R$_3$ = O
351 R$_1$ = D-apiofuranosyl , R$_2$ = D-apiofuranosyl-(1→2)-D-xylopyranosyl, R$_3$ = O
352 R$_1$= α-L-rhamnosyl, R$_2$ = D-apiofuranosyl-(1→2)-D-xylopyranosyl, R$_3$ = OH
353 R$_1$= α-L-rhamnosyl, R$_2$ = D-apiofuranosyl-(1→2)-L-arabinopyranosyl, R$_3$ = O



354 R$_1$ = OMe, R$_2$ = OMe, R$_3$ = OH, R$_4$ = OH
356 R$_1$ = H, R$_2$ = H, R$_3$ = H, R$_4$ = OH,
357 R$_1$ = OH, R$_2$ = OMe, R$_3$ = H, R$_4$ = H
358 R$_1$ = OH, R$_2$ = OMe, R$_3$ = OMe, R$_4$ = H



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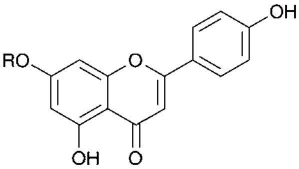
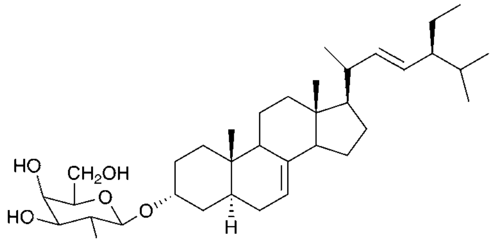
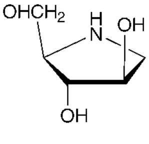




360

359 R = β-D-glucopyranosyl-(1→2)-β-D-glucopyranoside



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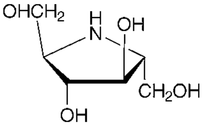

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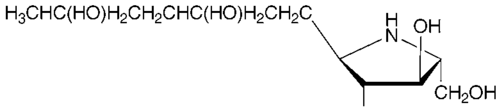

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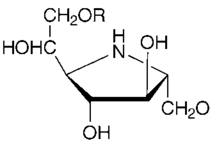
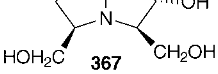


364 R = H
365 R = apiopyranoside
366 R = β-D-xylopyranoside



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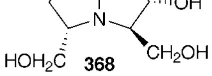

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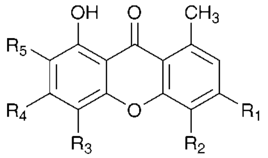
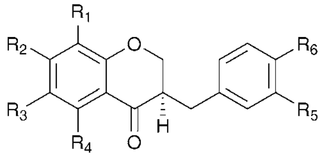
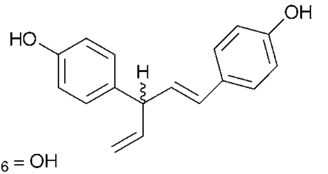
including homoisoflavanones, spirocyclic nortriterpenoids and xanthones, as well as some more unusual alkaloids. Three species of *Drimiopsis* have been studied, *Drimiopsis maculata* Lindl. & Paxton, *Drimiopsis burkei* and *Drimiopsis barteri* Baker. *Drimiopsis maculata* is a southern African species used by traditional healers for treating a variety of complaints, including stomach complaints in children and the relief of constipation. It has not been found to be toxic to livestock.[25] The bulbs of this plant have yielded scillascillin-type homoisoflavanones (compound **106**, previously isolated from *Muscari botryoides* and compound **182**, previously isolated from *M. botryoides* and *M. armeniacum*),[154] xanthones (drimiopsins A–E, **163**, **369**, **138** and **370–372**),[25] three homoisoflavanones (**30**, **59**, **373**) and a norlignan **374**.[69] *Drimiopsis burkei* is widespread throughout Botswana and Zimbabwe, occurring southward towards the Eastern Cape Province of South Africa.[69] In Botswana it is known as *thejane* and is used to treat stomach complaints.[155] A sample of this plant collected in KwaZulu-Natal, South Africa was found to contain the norlignan hinokiresinol **155** and a homoisoflavanone **375**,[69] while a sample collected in Mochudi, Botswana was found to contain the scillascillin-type homoisoflavanones (**248** and **376**), xanthones (**137**, **138**, **369**, **377–378**), the norlignan hinokiresinol **155** and the homoisoflavanones (*E*- eucomin **6**, **104**, **128** and **379–382**).[155] *Drimiopsis barteri* is the only genus member to occur in Cameroon, where it is used to treat fever.[156] The bulbs have been found to contain the unusual isoquinoline alkaloids (**383** and **384**) as well as the more expected scillascillin-type homoisoflavanones (**161**, **376**, **385–387**), 3-benzyl-4-chromanones (**61**, **214** and **388**) and *Z*-eucomin **6**. While the configuration at C-3 was not specified, the data compared favourably to known compounds of this type and would appear to be *R*.[155,156] The homoisoflavanones **144**, **373**, **375**, **387** and **389–391**, were tested against the Gram-positive, methicillin-resistant *Staphylococcus aureus*. Compound **391** was found to have significant inhibitory activity with an MIC value of 0.47 mM. Compounds **389** and **375** showed some activity, but the quantities available were insufficient for conclusive testing.[41] The homoisoflavanone **389**, showed significant vasodilating effects when tested on rat aortic rings (inhibition of the contraction elicited in aorta rings by high K^+ gave pIC_{50} of 5.31 M). This result would serve to validate the use of these bulbs for the treatment of conditions involving vasoconstriction.[157] *Resnova humifusa* (Baker) U.Müll.-Doblies & D.Müll.-Doblies, a South African species, earlier placed in *Drimiopsis* by Jessop[40] was found to contain nine homoisoflavanones (**7**, **10**, **30**, **56–60**, **392**). The same study reported seven



369 R_1 = OH, R_2 = H, R_3 = OMe, R_4 = OMe, R_5 = OMe
370 R_1 = OH, R_2 = OMe, R_3 = OMe, R_4 = OH, R_5 = H
371 R_1 = OH, R_2 = H, R_3 = OMe, R_4 = OH, R_5 = H
372 R_1 OMe, R_2 = H, R_3 = H, R_4 = OH, R_5 = OMe
377 R_1 = OH, R_2 = H, R_3 = H, R_4 = OMe, R_5 = OMe
378 R_1 = OMe, R_2 = H, R_3 = OH, R_4 = OMe, R_5 = OMe



373 R_1 = H, R_2 = OMe, R_3 = OH, R_4 = OH, R_5 = H, R_6 = OH
375 R_1 = H, R_2 = OMe, R_3 = H, R_4 = OMe, R_5 = H, R_6 = OH
379 R_1 = H, R_2 = OH, R_3 = OMe, R_4 = OMe, R_5 = H, R_6 = OH
380 R_1 = H, R_2 = OMe, R_3 = OMe R_4 = OH, R_5 = H, R_6 = OH
381 R_1 = H, R_2 = OMe, R_3 = OMe R_4 = OMe, R_5 = H, R_6 = OH
388 R_1 = H, R_2 = OH, R_3 = OH, R_4 = OH, R_5 = H, R_6 = OH
389 R_1 = H, R_2 = OH, R_3 = H R_4 = OH, R_5 =H, R_6 = OH
390 R_1 = H, R_2 = OH, R_3 = H R_4 = OH, R_5 =OMe, R_6 = OH
391 R_1 = OMe, R_2 = OMe, R_3 = H R_4 = OH, R_5 =H, R_6 = OH
392 R_1 = H, R_2 = OH, R_3 = H R_4 = OH, R_5 =OH, R_6 = OMe
394 R_1 = OH, R_2 = OMe, R_3 = OMe, R_4 = OH, R_5 = H, R_6 = OH



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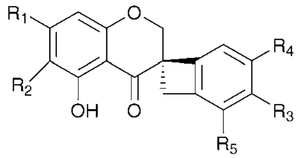
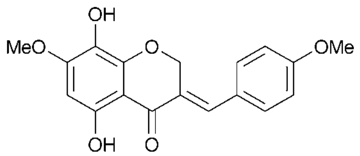


376 R_1 = OH, R_2 = H, R_3 = OMe, R_4 = OMe, R_5 = OMe
385 R_1 = OMe, R_2 = H, R_3 = OMe, R_4 = OMe, R_5 = OMe
386 R_1 = OMe, R_2 = H, R_3 = OMe, R_4 = OH, R_5 = OH
387 R_1 = OMe, R_2 = H, R_3 = OH, R_4 = OMe, R_5 = H



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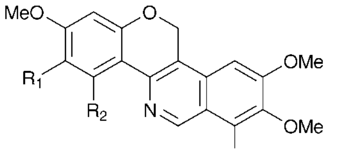
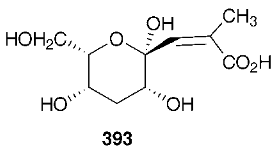


383 R_1 = H, R_2 = OH
384 R_1 = OH, R_2 = H



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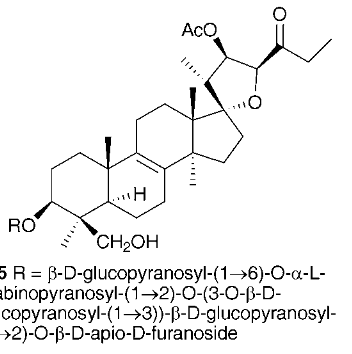
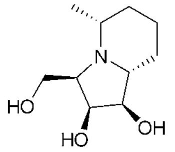


395 R = β-D-glucopyranosyl-(1→6)-O-α-L-arabinopyranosyl-(1→2)-O-(3-O-β-D-glucopyranosyl-(1→3))-β-D-glucopyranosyl-(1→2)-O-β-D-apio-D-furanoside



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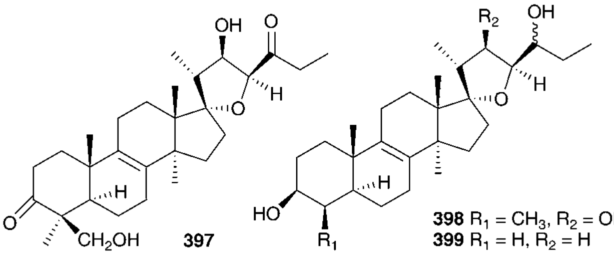
to be common with those found in the South African species *Eucomis montana* (**7**, **10**, **30**, **56**, **58**, **59**, **60**), which in addition contained compound **8**.[40] A later study on the methanol extract of the bulbs of this plant resulted in the isolation of four homoisoflavanones (**50**, **58**, **59**, **61**), a chalcone **132** and a tetrahydropyran derivative **393**.[42]

Veltheimia bracteata Harv. ex Baker is indigenous to South Africa. The petroleum ether and diethyl ether extracts of bulbs (as *Veltheimia viridifolia*) grown from seeds in Berlin have yielded two homoisoflavanones (**394** and muscomin, **97**)[158] as well as a spirocyclic nortriterpenoid **133** and its pentaglycoside **395** from the petrol and chloroform extracts respectively.[159] The homoisoflavanone **394**, was found to exhibit good inhibitory activity against phosphodiesterase (PDE).[158] Compound **394** was found to inhibit the two PDE-isoenzymes by 70% and 75% at a concentration of 100 μmol l^{-1}.[158] *Veltheimia capensis* (L.) DC., native to the Western Cape, South Africa, has been found to contain an indolizidine alkaloid, steviamine **396**. This alkaloid is also present in *Stevia rebaudiana* Bertoni (Asteraceae), but such alkaloids have not yet been isolated from any other Hyacinthaceae taxa.[160]

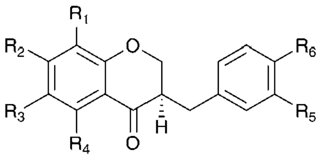
Merwilla plumbea (Lindl.) Speta is widely used by southern African traditional healers. The Zulu use it as a purgative and to facilitate full term labour. The Sotho eat the cooked bulbs as an aperient, use bulb decoctions in enemas to treat internal tumours and for the treatment of lung disease in cattle. Powdered bulbs are rubbed on sprains and fractures by the Southern Sotho, while the Tswana believe that bulbs rubbed on the body will make them resistant to witchcraft. The Swati use a lotion prepared from the bulbs to treat veldsores and boils.[161,162] Concern for the sustainability of *Merwilla plumbea* has led Ncube *et al.* to include the bulbs of this plant in a study to compare the antibacterial, anticandidal and cyclooxygenase inhibitory activity of the leaves and the, more commonly harvested, bulbs of some popular medicinal plants, harvested during different seasons in the year. Antimicrobial activities between the leaves and bulbs of *Merwilla plumbea* were found to be comparable over all four seasons and as such they concluded that the leaves could be used in many cases as a substitute for the bulbs. Likewise both the leaves and bulbs produced good cyclooxygenase inhibitory activity throughout the year.[163,164] A further study found that *in vitro* propagation of these plants could, under the right conditions, result in an increase in the flavonoid and gallotannin levels found in the shoots, which would allow for the successful mass propagation of these plants containing elevated levels of the potentially medicinally active components.[110,161] A phytochemical investigation of the bulbs (as *Scilla natalensis* Planch.) found two homoisoflavanones **62** and **72**, seven known eucosterol-type spirocyclic nortriterpenoids and the new spirocyclic nortriterpenoids **397**, **398** and **399**.[161] An extract of the lectin-like proteins from the bulbs of *M. plumbea* (as *Merwilla natalensis* Planch.) have been found to exhibit moderate inhibitory activity (47%) against cyclooxygenase (COX-1).[31] In a separate study, the homoisoflavanones **62** and **400** have been isolated from *M. plumbea* (as *Scilla natalensis* Planch.).[162] In addition *M. plumbea* (as *S. natalensis*) has been shown to have good *in vitro* activity against the parasite *Schistosoma haematobium* (LC = 0.4 mg ml^{-1}).[66] Three homoisoflavanones (**7**, **62**, **401**) have been isolated from *Merwilla dracomontana* (Hilliard & B.L. Burtt) Speta (as *Scilla dracomontana* Hillard and Burtt).[162] A southern African member of the genus *Merwilla*, under its basionym *Scilla krausii* Baker, was found to contain the homoisoflavanone, **80**.[162]

Lachenalia is the largest endemic genus of the Hyacinthaceae in southern Africa. Surprisingly, very little phytochemical work has been done on the genus.[165] A study of the leaves of *Lachenalia unifolia* Jacq. has yielded flavone sulphates (luteolin-3′-sulphate and -7,3′-disulphate, tricetin-3′-sulphate and -7,3′disulphate, diosmetin-3′-sulphate and -7,3′-disulphate)[166] while the bulbs of *L. rubida* Jacq., collected from the Western Cape, South Africa, were found to contain the homoisoflavanones **402** and **403**.[165] The bulbs of *Pseudoprospero firmifolium* (Baker) Speta have been found to contain five 3-hydroxy-3-benzyl-4-chromanone type

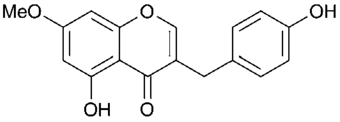


397

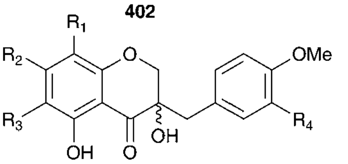
398 $R_1 = CH_3$, $R_2 = OH$
399 $R_1 = H$, $R_2 = H$



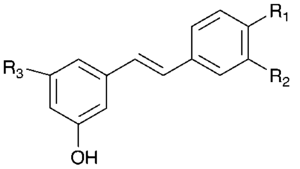
400 $R_1 = H$, $R_2 = OH$, $R_3 = OMe$, $R_4 = OH$, $R_5 = OH$, $R_6 = OMe$
401 $R_1 = H$, $R_2 = OH$, $R_3 = OMe$, $R_4 = OH$, $R_5 = H$, $R_6 = OMe$
403 $R_1 = H$, $R_2 = OMe$, $R_3 = H$, $R_4 = OH$, $R_5 = H$, $R_6 = OH$
409 $R_1 = H$, $R_2 = OMe$, $R_3 = H$, $R_4 = OH$, $R_5 = H$, $R_6 = OMe$
410 $R_1 = H$, $R_2 = OMe$, $R_3 = H$, $R_4 = OMe$, $R_5 = OH$, $R_6 = OMe$
411 $R_1 = H$, $R_2 = OMe$, $R_3 = H$, $R_4 = OMe$, $R_5 = H$, $R_6 = OH$
412 $R_1 = H$, $R_2 = OMe$, $R_3 = H$, $R_4 = OH$, $R_5 = H$, $R_6 = OMe$
417 $R_1 = H$, $R_2 = OMe$, $R_3 = H$, $R_4 = OMe$, $R_5 = H$, $R_6 = OMe$
418 $R_1 = H$, $R_2 = OMe$, $R_3 = H$, $R_4 = OH$, $R_5 = OMe$, $R_6 = OH$
419 $R_1 = H$, $R_2 = OH$, $R_3 = H$, $R_4 = OH$, $R_5 = OH$, $R_6 = OMe$
420 $R_1 = H$, $R_2 = OMe$, $R_3 = OMe$, $R_4 = OH$, $R_5 = OMe$, $R_6 = OH$
421 $R_1 = H$, $R_2 = OH$, $R_3 = OMe$, $R_4 = OH$, $R_5 = H$, $R_6 = OH$
422 $R_1 = H$, $R_2 = OH$, $R_3 = H$, $R_4 = OH$, $R_5 = OMe$, $R_6 = OMe$
423 $R_1 = H$, $R_2 = OMe$, $R_3 = OH$, $R_4 = OMe$, $R_5 = H$, $R_6 = OMe$
424 $R_1 = H$, $R_2 = OMe$, $R_3 = OMe$, $R_4 = OMe$, $R_5 = H$, $R_6 = OH$
425 $R_1 = OH$, $R_2 = OMe$, $R_3 = H$, $R_4 = OMe$, $R_5 = H$, $R_6 = OMe$
428 $R_1 = H$, $R_2 = OMe$, $R_3 = OMe$, $R_4 = OMe$, $R_5 = H$, $R_6 = OMe$
429 $R_1 = H$, $R_2 = OH$, $R_3 = OMe$, $R_4 = OMe$, $R_5 = H$, $R_6 = OMe$



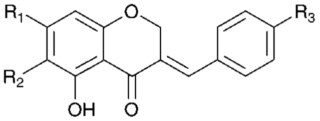
402



404 R_1 = OMe, R_2 = OMe, R_3 = H, R_4 = OMe
405 R_1 = H, R_2 = OMe, R_3 = H, R_4 = OMe
406 R_1 = OMe, R_2 = OMe, R_3 = H, R_4 = OH
407 R_1 = H, R_2 = OMe, R_3 = OH, R_4 = OH
408 R_1 = H, R_2 = OH, R_3 = H, R_4 = OH



413 R_1 = OH, R_2 = H, R_3 = OH
414 R_1 = OMe, R_2 = OH, R_3 = OH
426 R_1 = OH, R_2 = OMe, R_3 = OMe
427 R_1 = OH, R_2 = OMe, R_3 = OH



415 R_1 = OH, R_2 = OMe, R_3 = OMe
416 R_1 = OMe, R_2 = H, R_3 = OH

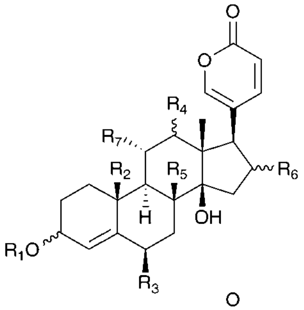
homoisoflavanones, all as racemic mixtures (**404–408**) as well as the spirocyclic nortriterpenoid, 15-deoxoeucosterol.[167] A subsequent study on the bulbs of *Pseudoprospero firmifolium* subsp. *natalensis* J.C. Manning confirmed the previous findings for the typical subspecies but, in addition, found the homoisoflavanone **59** in the dichloromethane extract.[42]

Schizocarphus nervosus (Burch.) van der Merwe is widespread in southern Africa. Although toxic to livestock,[1] it plays an important role in traditional medicine within the region. The bulbs are used by the Zulu to treat dysentery and nervous conditions in children as well as treat rheumatic fever.[168] In Botswana the bulbs are used to enhance fertility and to treat infections.[169] The methanol extract of the bulbs of *S. nervosus* (as *Scilla nervosa* (Burch.) Jessop) has been tested for anti-inflammatory and anti-microbial activity. The crude methanol extract displayed a strong, but short-acting effect on a croton-oil induced contact dermatitis in a mouse ear (66% reduction of oedema after 3 h) and the nonpolar components were active against *Staphylococcus aureus* ($IC_{50} = 1.8\ \mu g\ ml^{-1}$), *Klebsiella pneumonia* ($IC_{50} = 2.0\ \mu g\ ml^{-1}$) and *Candida albicans* ($IC_{50} = 1.0\ \mu g\ ml^{-1}$). Little discrimination was noted between the Gram-positive and Gram-negative bacteria, but some specificity for the yeast was observed.[169] Five homoisoflavanones (**49** and **409–412**) and two stilbenoids (**413, 414**) have been isolated from the bulbs.[168] A further thirteen homoisoflavanones (**41**, **49** and **415–425**) and three stilbenes (**414** and **426–427**) have been isolated from the bulbs of *S. nervosus* (as *Scilla nervosa* (Burch.) Jessop subsp. *rigidifolia*).[170,171] Compound **419** was found to be highly active against colon cancer (HT-29 cell line $ED_{50} = 0.88\ \mu g\ ml^{-1}$) and breast cancer (MDA-MB-435 cell line $ED_{50} = 0.42\ \mu g\ ml^{-1}$).[170] The yellow inter-bulbscale deposits of this subspecies were likewise investigated and eight homoisoflavanones were isolated, two of which were novel (**428–429**).[172] There has been some evidence presented to indicate that the bulbs may cause damage to liver cells.[173] A homoisoflavanone **400** has been isolated from *Spetaea lachenaliiflora* Wetschnig & Pfosser (as *Scilla plumbea* Lindl.). This is a little known species, neither toxic nor known to be used by traditional healers.[65]

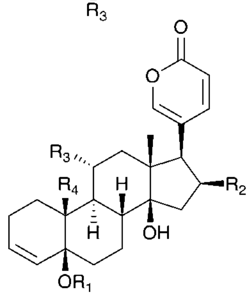
2 The Urgineoideae

The subfamily Urgineoideae, with more than 100 species,[7] has received considerable taxonomic attention in recent years, with widely differing opinions subsequently offered on generic circumscriptions. Speta recognised eleven genera,[174] several of which have been studied from both a phytochemical and a pharmacological perspective. More than any other compound type, the bufadienolides characterise the Urgineoideae. Bufadienolides are C-24 steroids possessing an α-pyrone group (doubly unsaturated six-membered lactone ring) at position 17β. The presence of these highly toxic cardioactive steroids has led to these plants being used by man in antiquity, with the ancient Egyptians reportedly using preparations to treat heart disease.[175] Research into this subfamily was further stimulated by the sometimes fatal toxicity associated with various species, both to stock[176–178] and to humans.[179,180] The systematic position of the sea onion, *Charydbis maritima* (L.) Speta, has long been debated.[181] The ancient Greeks referred to the plant as skilla, the Romans as scilla and for much of the early research on this plant, the names *Urginea maritima* or *Scilla maritima* were applied. Subsequent work by Pfosser and Speta[181] provided evidence for two genera in the subfamily Urgineoideae in the Mediterranean region, *Urginea* Steinh. and *Charydbis* Speta. Phytochemical investigations to date support this generic distinction.

With much of the early research on *Charybdis maritima* focused on the plant then known as *Scilla maritima*, the trivial names of isolates of this urgineoid accordingly reflect this nomenclatural association. Notably, *Scilla* is a distinct genus currently assigned to the subfamily Hyacinthoideae, and has a very different chemical profile. Kopaczewski isolated a toxic component from the bulbs of *C. maritima* (as *Scilla maritima*) which he termed scillitin.[182] It was found to be a diuretic but the whole extract from the bulbs was found to be more poisonous to guinea pigs and rabbits than scillitin itself.[183] In contrast, Smith found scillitin to be more toxic to rats than the crude extract.[184] The bufadienolides scillaren A **224**, scilliroside **430**, proscillaridin A **223** and scillaren F **431** have also been isolated from *C. maritima* (reported as *Scilla maritima* and/or *Urginia maritima*).[185–190] Using HPLC, with proscillaridin A **223** as a reference, Tittel and Wagner showed the possible presence of bufadienolides in a plant identified as *Scilla rubra* L. (here considered synonymous with *C. maritima*).[191] Petrol extracts of bulbs of this species (as *Scilla maritima* and *Urginia maritima*) were found to contain fatty acids (lauric acid, myristic acid,



223 : R_1 = α-L-rhamnopyranoside, R_2 = CH_3, R_3 - R_7 = H
224 R_1 = α-L-rhamnopyranosyl-(1→4)-β-D-glucopyranoside, R_2 = CH_3, R_3 - R_7 = H
430 : R_1 = β-D-glucopyranoside, R_2 = CH_3, R_3 = OAc, R_4 = H, R_5 = OH, R_6 = H, R_7 = H
433 : R_1 = β-D-glucopyranoside, R_2 = CH_3, R_3 - R_7 = H
435 : R_1 = β-D-glucopyranosyl-(1→4)-β-D-glucopyranosyl-(1→4)-α-L-rhamnopyranoside, R_2 = CH_3, R_3- R_7 = H
436 : R_1 = α-L-rhamnopyranoside, R_2 = CH_3, R_3 = H, R_5 = H, R_6 = H, R_4 = α-OH, R_7 = H
437 : R_1 = β-D-glucopyranosyl-(1→4)-α-L- rhamnopyranoside, R_2 = CH_3, R_3 = H R_5 = H, R_6 = H, R_4 = α-OH
449 R_1 = α-L-rhamnopyranoside, R_2 = CHO, R_3 - R_6 = H, R_7 = OH
488 R_1 = β-D-glucopyranoside, R_2 = CHO, R_3 = H, R_4 = β-OH, R_5 - R_7 = H

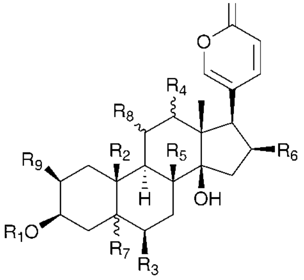


431 R_1 = β-D-glucopyranoside, R_2 = H, R_3 = H, R_4 = CHO
434 R_1 = β-D-glucopyranoside, R_2 = OAc, R_3 = H, R_4 = CHO
478 R_1 = β-D-glucopyranoside, R_2 = H, R_3 = OH, R_4 = CHO
493 R_1 = β-D-glucopyranoside, R_2 = H, R_3 = H R_4 = COOH
494 R_1 = H, R_2 = H, R_3 = H, R_4 = CHO

palmitic acid, palmitoleic acid, stearic acid, oleic acid, linoleic acid and linolenic acid) and sterols (sitosterol, stigmasterol, campesterol and cholesterol).[192–194]

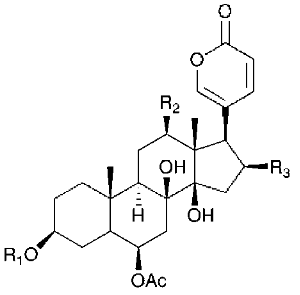
Investigations carried out in the early 1920s focused primarily on *Charydbis maritima* (squill). Both the extracts of fresh bulbs and dried powdered bulbs showed digitalis-like activity on the heart when tested on frogs and cats.[195,196] Markwalder[196] found no difference in activity between the fresh and dried bulbs and noted that neither the dried outer leaves nor the heart of the bulb exhibited much activity, while the mature middle layers of the bulb were rich in active components. The structure of scillaren A **224**, the principle active component of *C. maritima* (reported as *Urginia maritima*) was elucidated by Stoll *et al.* in 1933.[197] The interesting activity shown by the squill bufadienolides resulted in some comparative studies with digitoxigenin and strophanthidin as well as the effects of combination therapy.[198,199] Extensive work on the bulbs of *C. maritima* (as *Urginia maritima*) over the following years resulted in the isolation and identification of a large number and variety of bufadienolides. They can be divided into those having a double bond at C-4 (*e.g.*, **224**), those having a double bond at C-3 (*e.g.*, **431**) and those without either (dihydro C-4) (*e.g.*, **432**). Without exception, within *C. maritima* they contain a β-hydroxy group at C-14, a *trans* junction of rings B and C and a *cis* junction of rings C and D. They have been isolated as the aglycones as well as a variety of glycosides, with scillaren A **224** and proscillaridin A **223** being present in all specimens of *C. maritima* investigated. Samples of the plant from across its Mediterranean, European and Middle Eastern range have been investigated and this would account for the great diversity of bufadienolides isolated.

Von Wartburg and Renz[200,201] isolated five bufadienolides from *C. maritima* (as *Urginia maritima*), scilliroside **430**, scillaren A **224**, scillaren F **431**, proscillaridin A **223** and scillarenin-β-D-glucopyranoside **433**. The structures reported at that time were subsequently revised and the structures shown here reflect that revision.[202,203] Gorlich[204] found proscillaridin A **223**, scillaren A **224**, scilliglaucoside (scillaren F) **431** and scillicyanoside **434** in crystalline form as well as minor amounts of scillicoeloside (no structure given) and glucoscillaren A **435**. Later work on this plant resulted in the isolation of further minor components, scilliphaeoside **436** and glucoscilliphaeoside **437**.[205] A reinvestigation of the bulbs of *C. maritima* (as *Urginia maritima*) in 1991 by Krenn *et al.*[206] resulted in an additional four new bufadienolides, identified as 5α-4,5-dihydroproscillaridin A **432**, 5α-4,5-dihydroglucoscillaren A **438**,

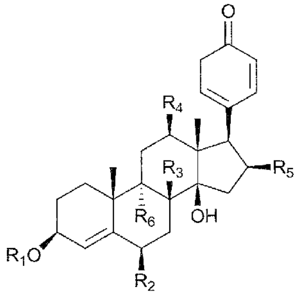


432 R_1 = α-L-rhamnopyranoside, R_2 = CH_3 R_3 - R_9 = H, R_7 = α-H
438 R_1 = β-D-glucopyranosyl-(1→4)-β-D-glucopyranosyl-(1→4)-α-L-rhamnopyranoside, R_2 = CH_3, R_3- R_9 = H, R_7 = α-H
439 R_1 = α-L- rhamnopyranosyl-β-D-glucopyranoside, R_2 = CH_3, R_3- R_6 = H, R_7 = β-H, R_8 = α-OH, R_9 = H
440 R_1 = α-L-rhamnopyranoside, R_2 = CHO R_3 - R_6 = H, R_7 = α-H, R_8 = H, R_9 = H
477 R_1 = α-L- rhamnopyranosyl-β-D-glucopyranoside, R_2 = CH_3, R_3-R_6 = H, R_7 = β-H R_8 = α-OAc, R_9 = H
490 R_1 = α-L-rhamnopyranoside, R_2 = CH_3, R_3 = H, R_4 = H, R_5 = H, R_6 = H, R_7 = H, R_8 = α-OH, R_9 = H

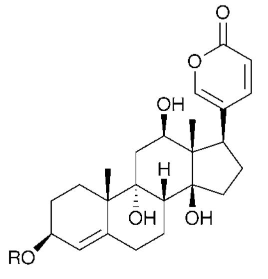
gamabufotalin-3-*O*-α-L-rhamnopyranosyl-β-D-glucopyranoside **439** and 19-oxo-5α-4,5-dihydroproscillaridin A **440**. Forty-one bufadienolides were isolated from an Egyptian sample of *C. maritima* (as *Urginia maritima*).[207] Proscillaridin A **223**, scillaren A **224** and scilliroside **430** were found as expected. In addition to 15 known bufadienolides found (**223, 224, 430, 434, 435, 436, 441–449**), 10 new glucosides of known aglycones (**450–459**) and sixteen new compounds were isolated (**460–475**). An unusual 9-hydroxy bufadienolide **476** was later isolated, also from Egyptian material.[208] From 2000 until 2012 a total of eleven additional new bufadienolides (**477–487**) have been isolated from *C. maritima* (as *Urginia maritima*). Two of the compounds **477** and **478** were isolated from Spanish material[209] and nine (**479–487**) from a plant cultivated in Japan (provenance undisclosed).[210] A comparative study of the bulbs of *C. maritima* collected in the northern and southern regions of the Mediterranean area showed some differences in both the quantity and type of bufadienolides isolated.[211] Both samples contained scilliroside **430**, scillarenin



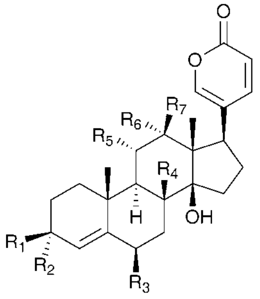
447 R_1 = α-L-thevetopyranosyl-(1→4)-β-D-glucopyranoside, R_2 = H, R_3 = H
448 R_1 = α-L-thevetopyranosyl-(1″→4′)-β-D-glucopyranosyl-(1‴→4″)-β-D-glucopyranoside, R_2 = H, R_3 = H
453 R_1 = α-L-glucomethylopyranoside, R_2 = H, R_3 = H
454 R_1 = α-L-thevetopyranoside, R_2 = H, R_3 = H
455 R_1 = β-D-glucopyranoside, R_2 = H, R_3 = H
456 R_1 = α-L-rhamnopyranosyl-(1 ›4)-β-D-glucopyranoside, R_2 = H, R_3 = H
457R_1 = α-L-glucomethylopyranosyl-(1→4)-β-D-glucopyranoside, R_2 = H, R_3 = H
458 R_1 = α-L-glucomethylopyranosyl-(1″→4′)-β-D-glucopyranosyl-(1‴→4″)-β-D-glucopyranoside, R_2 = H, R_3 = H
459 R_1 = α-L-rhamnopyranosyl-(1″→4′)-β-D-glucopyranosyl-(1‴→4″)-β-D-glucopyranoside, R_2 = H, R_3 = H
472 α-L-thevetopyranoside, R_2 = OH, R_3 = H
473 R_1 = α-L-thevetopyranosyl-4′-β-D-glucopyranoside, R_2 = OH, R_3 = H
474 R_1 = α-L-thevetopyranoside, R_2 = H, R_3 = OH
475 R_1 = α-L-thevetopyranosyl-4′-β-D-glucospyranoide, R_2 = H, R_3 = OAc



441 R_1 = β-D-glucopyranoside, R_2 = H, R_3 = H, R_4 = OH, R_5 = H, R_6 = H
442 R_1 = α-L-rhamnopyranosyl-β-D-glucopyranoside, R_2 = H, R_3 = H, R_4 = OH, R_5 = H, R_6 = H
443 R_1 = β-D-glucopyranoside, R_2 = OH, R_3 = OH, R_4 = H, R_5 = H, R_6 = H
444 R_1 = -β-D-glucopyranosyl-(1″→4′)-β-D-glucopyranoside, R_2 = OAc, R_3 = OH, R_4 = H, R_5 = H, R_6 = H
445 R_1 = H, R_2 = OAc, R_3 = OH, R_4 = OH, R_5 = H, R_6 = H
446 R_1 = β-D-glucopyranoside, R_2 = OAc, R_3 = OH, R_4 = OH, R_5 = H, R_6 = H
450 R_1 = β-D-glucopyranosyl-(1″→4′)-β-D-glucopyranoside, R_2 = H, R_3 = H, R_4 = H, R_5 = H, R_6 = H
451 R_1 = β-D-glucopyranosyl-(1″→4′)-β-D-glucopyranoside, R_2 = H, R_3 = OH, R_4 = H, R_5 = H, R_6 = H
452 R_1 = α-L-rhamnopyranosyl-(1″→4′)-β-D-glucopyranosyl-(1‴→4″)-β-D-glucopyranoside, R_2 = H, R_3 = OH, R_4 = H, R_5 = H, R_6 = H
460 R_1 = β-D-glucopyranoside, R_2 = OH, R_3 = OH, R_4 = OH, R_5 = H, R_6 = H
461 R_1 = α-L-rhamnopyranoside, R_2 = H, R_3 = OH, R_4 = OH, R_5 = H, R_6 = H
462 R_1 = α-L-rhamnopyranoside, R_2 = H, R_3 = H, R_4 = H, R_5 = OH, R_6 = H
463 R_1 = β-D-glucopyranoside, R_2 = H, R_3 = H, R_4 = H, R_5 = OH, R_6 = H
464 R_1 = α-L-rhamnopyranosyl-(1″→4′)-β-D-glucopyranosyl-(1‴→4″)-β-D-glucopyranoside, R_2 = H, R_3 = H, R_4 = H, R_5 = OH, R_6 = H
465 R_1 = α-L-rhamnopyranoside, R_2 = H, R_3 = H, R_4 = H, R_5 = OAc, R_6 = H
466 R_1 = -β-D-glucopyranoside, R_2 = H, R_3 = H, R_4 = H, R_5 = OAc, R_6 = H
467 R_1 = -β-D-glucopyranosyl-(1″→4′)-glucopyranoside, R_2 = H, R_3 = H, R_4 = H, R_5 = OAc, R_6 = H
468 R_1 = α-L-rhamnopyranosyl-(1″→4′)-β-D-glucopyranosyl-(1‴→4″)–β-D-glucopyranoside, R_2 = H, R_3 = H, R_4 = H, R_5 = OAc, R_6 = H
469 R_1 = α-L-glucomethylopyranosyl-(1″→4′)-β-D-glucopyranosyl-(1‴→4″)-β-D-glucopyranoside, R_2 = H, R_3 = H, R_4 = H, R_5 = OAc, R_6 = H
470 R_1 = β-D-glucopyranoside, R_2 = H, R_3 = OH, R_4 = H, R_5 = OAc, R_6 = H
471 R_1 = α-L-rhamnopyranoside, R_2 = H, R_3 = H, R_4 = OH, R_5 = H, R_6 = OH



476 R = α-L-rhamnopyranoside

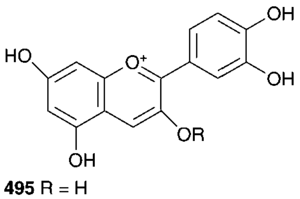


479 R_1 = OH, R_2 = OCH_3, R_3 = H, R_4 = H, R_5 = H, R_6 = H, R_7 = OH
480 R_1 = =O, R_3 = H, R_4 = H, R_5 = OH, R_6 = H, R_7 = H
481 R_1 = OH, R_2 = OH, R_3 = H, R_4 = H, R_5 = H, R_6 = OH, R_7 = H
482 R_1 = -O-β-D-glucopyranoside, R_2 = H, R_3 = OAc, R_4 = H, R_5 = H, R_6 = H, R_7 = H
483 R_1 = -O-α-L-rhamnopyranosyl-(1→4)-β-D-glucopyranoside, R_2 = H, R_3 = OAc, R_4 = H, R_5 = H, R_6 = H, R_7 =H
484 R_1 = -O-α-L-rhamnopyranosyl-(1→4)-α-L-rhamnopyranoside, R_2 = H, R_3 = H, R_4 = OH, R_5 = H, R_6 = H, R_7 = H
485 R_1 = -O-α-L-rhamnopyranosyl-(1→4)-β-D-glucopyranoside, R_2 = H, R_3 = OAc, R_4 = OH, R_5 = H, R_6 = H, R_7 = H
486 R_1 =-O-3'-OAc-α-L-rhamnopyranosyl-(1→4)-β-D-glucopyranoside, R_2 = H, R_3 = H, R_4 = H, R_5 = H, R_6 = H, R_7 = H
487 R_1 = -O-2'-OAc-α-L-rhamnopyranosyl-(1→4)-β-D-glucopyranoside, R_2 =H, R_3 = H, R_4 = H, R_5 = H, R_6 = H, R_7 = H
489 R_1 = -O-α-L-rhamnopyranosyl-α-L-rhamnopyranoside, R_2 = H, R_3 = H, R_4 = H, R_5 = H, R_6 = OH, R_7 = H
491 R_1 = -O-α-L-rhamnopyranoside, R_2 = H, R_3 = H, R_4 = OH, R_5 = H, R_6 = H, R_7 = H
492 R_1 = -O-β-D-glucopyranoside, R_2 = H, R_3 = H, R_4 = OH, R_5 = H, R_6 = H, R_7 = H

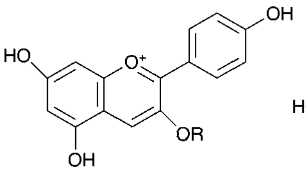
3-*O*-β-D-glucopyranoside **433**, proscillaren A **223**, scilliphaesidin 3-β-D-glucopyranoside **441**, scilliglaucoside **431**, scilliphaoside **436** and 12-*epi*-scilliphaeoside. In addition, the bulbs from Tunisia contained glucoscilliphaeoside **437**, 12-*epi*-glucoscilliphaeoside, 12β-hydroxyscilliglaucosidin 3-*O*-β-D-glucopyranoside **488**, 12-*epi*-scilliphaeosidin 3-*O*-β-D-glucopyranoside **443** and 12-*epi*-scilliphaeosidin 3-*O*-α-L-rhamnopyranosyl-α-L-rhamnopyrano- side **489**. Bulbs sourced from Sardegna also contained gamabufotalin 3-*O*-α-L-rhamnopyranoside **490**, scillirubrosidin 3-*O*-α-L-rhamnopyranoside **491**, scillirubroside **492**, 12β-hydroxyscilliroside **446**, 5α-4,5-dihydroscillirosidin 3-*O*-α-L-thevetopyranosyl-β-D-glucopyranoside **475**, deacetylscilliroside **443**, 10-carboxy-5β-14β-hydroxybufa-3,20,22-trienolide 5-*O*-β-D-glucopyranoside **493** and scilliglaucogenin **494**.

The flavonoid, anthocyanin and sterol content of the bulbs of *C. maritima* (as *Urginia maritima*) have been investigated. The ethanol extract of the bulbs was studied by gas-liquid chromatography and the sterols identified by comparison to known reference compounds. Sitosterol, stigmasterol, campesterol, cholesterol, Δ^5-avenasterol and Δ^7-avenasterol were found to be present.[193,194] Red bulbs of *C. maritima* (as *Urginia maritima*), collected in the Balearic Islands contained cyanidin **495**, cyanidin-3-monoglucoside **496** and pelargonidin-3-monoglucoside **497**, both in the free form and acylated with *p*-coumaric acid.[212–216] The proportion of anthocyanin was found to be higher in tetraploids than in triploids or hexaploids.[217]

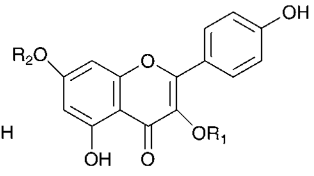
The flavonoids isolated included kaempferol-7-*O*-β-D-glucopyranoside-3-*O*-β-D-triglucopyranoside **498**, kaempferol-7-*O*-β-D-glucopyranoside-3-*O*-α-L-rhamnopyranosyl-β-D-glucopyranoside **499**, kaempferol-7-*O*-β-D-glucopyranoside-3-*O*-β-D-diglucopyranoside **500** and kaempferol-7-*O*-α-L-rhamnopyranoside-3-*O*-α-L-rhamnosyl-β-D-glucopyranoside **501**.[218] In addition the



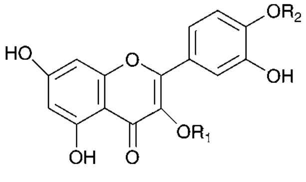
495 R = H
496 R = β-D-glucopyranoside



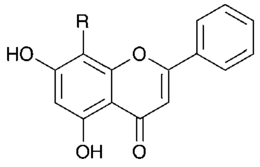
497 R = β-D-glucopyranoside



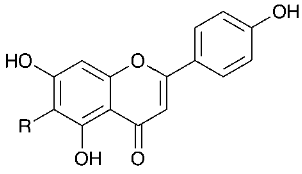
498 R_1 = tri-β-D-glucopyranoside, R_2 = β-D-glucopyranoside
499 R_1 = α-L-rhamnopyanosyl-b-D-glucopyranoside, R_2 = H
500 R_1 = di-β-D-gluciopyranoside, R_2 = H
501 R_1 = α-L-rhamnopyranosyl-β-D-glucopyranoside, R_2 = α-L-rhamnopyranoside
505 R_1 = tri-β-D-glucopyranoside, R_2 = H



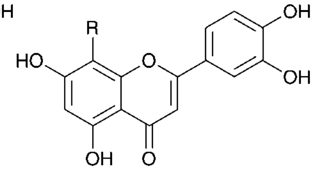
502 R_1 = H, R_2 = β-D-glucopyranoside
503 R_1 = β-D-glucopyranoside, R_2 = H
504 R_1 = H, R_2 = H



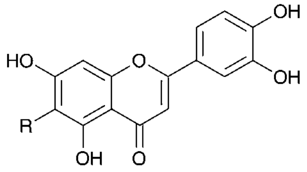
506 R = β-D-glucopyranoside



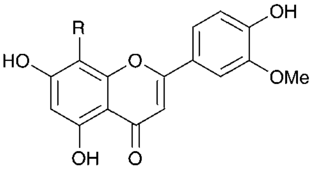
507 R = β-D-glucopyranoside



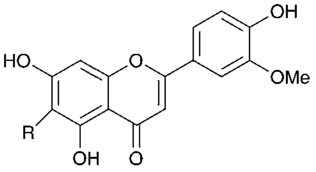
508 R = β-D-glucopyranoside



509 R = β-D-glucopyranoside



510 R = β-D-glucopyranoside

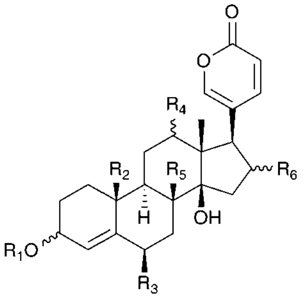


511 R = β-D-glucopyranoside

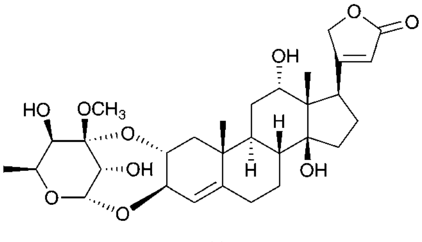
flavonoid O-glycosides **502–505**, have been isolated.[219] Five C-glycosylflavones have been isolated from the ethyl acetate extract of the bulbs. They have been identified as vitexin **506**, isovitexin **507**, orientin **508**, isoorientin **509**, scoparin **510** and isoscoparin **511**.[220–223] Fernandez *et al.* identified twenty-five flavonoids in a Spanish sample of *C. maritima* bulbs (as *Urginia maritima*). They followed a parallel series: pelargonidin, kaempferol, cyaniding, quercetin and taxifolin. A complex mixture of both C- and O-glycosides was obtained.[224] A fructan, sinistrin, has been isolated from *C. maritima* (as *Urginia maritima*) and found to be a mixed type β-D-fructan, with (2–1) linked and (2–6) linked unbranched β-D-fructofuranosyl and α-D-glucopyranoside residues.[225,226]

C. maritima (reported as *Urginia maritima*) has been used as a form of rodenticide since the 13th century.[202] The toxic component has been found to be scilliroside **430**, which affects the cardiovascular and central nervous systems, resulting in death.[202] Scilliroside has an emetic effect on humans, cats, dogs and pigeons, but rats and mice are unable to vomit and as such they die within a few hours of ingesting the bulbs. The flavonoid fraction has been found to have a diuretic effect[227] and the ethanolic extract of Spanish squill has shown good insecticidal activity against the stored grain pest *Tribolium castaneum* (red flour beetle).[228] Twelve wild populations of the bulbs were studied with the red bulbs giving 60–90% mortality if applied at 20–30 μg insect^{-1}.[228] An extract of the bulbs of *C. maritima* (as *Urginia maritima*) growing in Turkey has been found to exhibit greater toxicity than cisplatin against the A549 non-small cell lung cancer (NSCLC) cell line.[229] Tissue cultures of *C. maritima* (as *Urginia maritima*) grown both in the dark and under light showed no sign of the bufadienolides commonly associated with this species. The cultures grown in the light did though produce anthocyanins.[230]

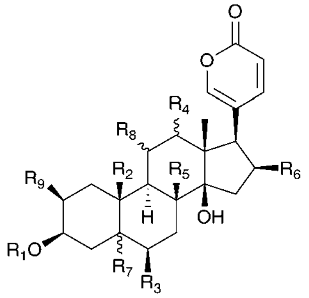
The range of bufadienolides found in the bulbs of *Charybdis hesperia* (Webb & Berthel.) Speta (as *Urginea hesperia* Webb & Berthel.) indicates a close relationship to *C. maritima*. Thirteen bufadienolides have been isolated including scillarenin (**512**) and a variety of associated glycosides.[231] *Urginea fugax* (Moris) Steinh. is a species which is widespread in the Mediterranean area. In contrast to *C. maritima* and *C. hesperia*, cardenolides



512 R_1 = H (β), R_2 = CH_3, R_3 -R_6 = H
518 R_1 = H, R_2 = CH_3, R_3 = OAc, R_4 = H, R_5 = OH, R_6 = H
519 R_1 = H, R_2 = CH_3, R_3 = OH, R_4 = H, R_5 = OH, R_6 = H
520 R_1 = β-D-glucopyranoside, R_2 = CH_3, R_3 = OH, R_4 = β-OH, R_5 = OH, R_6 = H
522 R_1 = =O, R_2 = CH_3, R_3 = OAc, R_4 = OH, R_5 = OH, R_6 = H
523 R_1 = =O, R_2 = CH_3, R_3 = H, R_4 = OH, R_5 = OH, R_6 = H
532 R_1 = H (β), R_2 = CHO, R_3 - R_6 = H
533 R_1 = =O, R_2 = CHO, R_3 - R_6 = H
534 R_1 = α-L-rhamnopyranoside, R_2 = CHO, R_3 - R_6 = H
535 R_1 =β-D-glucopyranoside, R_2 = CHO, R_3 - R_6 = H
536 R_1 = α-L-rhamnopyranosyl-(1→3)-[-β-D-glucopyranosyl(1→4)-]-α-L-rhamnopyranoside, R_2 = CH_3, R_3 - R_6 = H
546 R_1 = H, R_2 = CHO, R_3 - R_5 = H R_6 = OAc
549 R_1 = α-L-rhamnopyranoside, R_2 = CH_3, R_3 = H, R_4 = OH, R_5 - R_6 = H



513



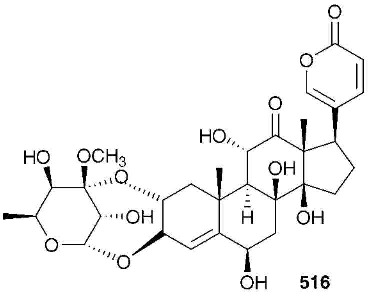
514 R_1 = α-L-rhamnopyranosido-(1→4)-β-D-glucopyranoside, R_2 = CH_3, R_3 = H, R_4 = =O, R_5 = H, R_6 = H, R_7 = β-H, R_8 = α-OH, R_9 = H
515 R_1 = α-L- rhamnopyranosyl-β-D-glucopyranoside, R_2 = CH_3, R_3 = OAc, R_4 = β-OH, R_5 = OH, R_6 = H, R_7 = β-H, R_8 = H, R_9 = H
521 R_1 = H, R_2 = CH_3, R_3 = OAc, R_4 = β-OH, R_5 = OH, R_6 = H, R_7 = β-H, R_8 = H, R_9 = H
530 R_1 = H, R_2 = CHO, R_3-R_6 = H, R_7 = β-OH, R_8 = H, R_9 = H
531 R_1 = β-D-glucopyranoside, R_2 = CHO, R_3-R_6 = H, R_7 = β-OH, R_8 = H, R_9 = H
537 R_1 = α-L-rhamnopyranoside, R_2 = CH_3, R_3 = H, R_4 = =O, R_5 = H, R_6 = H, R_7 = H, R_8 = α-OH, R_9 = H
538 R_1 = β-D-digitalopyranoside, R_2 = CHO, R_3 = H, R_4 = H, R_5 = H, R_6 = H, R_7 = β-OH, R_8 = H, R_9 = H
539 R_1 = β-D-glucopyranosyl-(1→4)-O-(2-O-acetyl-α-L-thevetopyranoside), R_2 = CHO, R_3 = H, R_4 = H, R_5 = H, R_6 = H, R_7 = β-OH, R_8 = H, R_9 = OAc
542 R_1 = H, R_2 = CH_3, R_3-R_5 = H, R_6 = β-OH, R_7 = β-H, R_8 = H, R_9 = H
543 R_1 = β-D-galactopyranoside, R_2 = CH_3, R_3-R_5 = H, R_6 = β-OH, R_7 = β-H, R_8 = H, R_9 = H
557 R_1 = H, R_2 = CHO, R_3 = H, R_4 = H, R_5 = H, R_6 = OH, R_7 = β-OH, R_8 = H, R_9 = H
558 R_1 = β-D-glucopyranoside, R_2 = CHO, R_3 = H, R_4 = H, R_5 = H, R_6 = OH, R_7 = β-OH, R_8 = H, R_9 = H
559 R_1 = β-D-glucopyranoside, R_2 = CH_3, R_3 = H, R_4 = H, R_5 = H, R_6 = H, R_7 = β-H, R_8 = H, R_9 = H
560 R_1 = 6-deoxy-3-O-methyl-β-L-glucopyranoside , R_2 = CHO, R_3-R_6 = H, R_7 = β-H, R_8 = H, R_9 = H
561 R_1 = β-D-glucopyranosyl-(1→2)-6-deoxy-3-O-methyl-β-L-glucopyranoside , R_2 = CHO, R_3-R_6 = H, R_7 = β-H, R_8 = H, R_9 = H
562 R_1 = 6-deoxy-3-O-methyl-β-L-glucopyranoside, R_2 = CHO, R_3-R_5 = H, R_6 = =O, R_7 = β-OH, R_8 = H, R_9 = H
563 R_1 = H, R_2 = CHO, R_3-R_6 = H, R_7 = β-H, R_8 = H, R_9 = H

have been isolated from the bulbs.[232] The new cardenolide fugaxin **513** has a rubellin-like carbohydrate linkage between C-3 and C-2, unlike any seen in *C. maritima* and *C. hesperia*, which lends chemotaxonomic support to recognition of both *Urginea* and *Charybdis* in the Mediterranean region.[181] Six bufadienoides have been isolated from the bulbs of *Charybdis pancration* (Steinh.) Speta (as *Urginea pancration*), scilliglaucoside **431**, scillirubroside **492**, scilliroside **430**, 5α-4,5-dihydroscillirosidin 3-*O*-α-L-thevetopyranosyl-β-D-glucopyranoside **475**, arenobufagin-3β-*O*-L-rhamnopyranosyl-4′-β-D-glucopyranoside **514** and the glycoside **515**.[233,234] *Charybdis aphylla* (Forssk.) Speta (as *Urginea aphylla* (Forssk.) Speta), growing in the northeastern Mediterranean region was found to contain eleven bufadienolides, scillicyanoside **434**, gamabufotalin-3-*O*-α-L-rhamnopyranoside **490**, scilliglaucoside **431**, gamabufotalin-3-*O*-α-L-rhamnosyl-β-D-glucopyranoside **439**, proscillaridin A **223**, scilliphaeosidin-3-*O*-β-D-glucopyranoside **437**, scillarenin-3-*O*-β-D-glucopyranoside **433**, 16β-*O*-acetylgamabufotalin-3-*O*-α-L-rhamnopyranoside (16β-*O*-acetyl **436**), 12β-hydroxyscilliroside **446** and 5α-4,5-dihydroxyscillirosidin-3-*O*-α-L-thevetopyranosyl-β-D-glucopyranosyl-β-D-glucopyranoside (**475** glucoside).[235] The similarity in chemical composition of the bulbs of *Charybdis* from across the European region highlights their close relationship.

As early as 1923, Juritz reported the presence of a glucoside in the toxic South Africa plant *Boosia macrocentra* (Baker) Speta (as *Urginea macrocentra* Baker) with digitalis-like activity and he noted that it could be used as a substitute for squill.[236] This plant has also been implicated in stock mortality and it is used by the Zulu as a vermifuge (as *Drimia macrocentra*).[237] The major component was identified as rubellin **516** by NMR spectroscopy.[237] In 1927, work by Watt[238] on South African *Sekanama burkei* (Baker) Speta (as *Urginea burkei*), yielded two glucosides, a red compound found to be toxic to animals and having a digitalis-like effect on the heart as well as a diuretic effect, and a white compound which resulted in paralysis of the central nervous system and respiration. Additional work on *S. burkei* (as *Urginea burkei*) and *Urgineopsis modesta* (Baker) Speta (as *Urginea rubella* Baker) in the 1940s and 1950s resulted in the isolation and identification of two cardiac glycosides, transvaalin and rubellin **516** respectively.[239–243] Rubellin **516** was found to behave as a cardiac poison towards rats while transvaalin was found to kill rats primarily by its effect on the central nervous system.[241,243,244] Rubellin was found to have a digitalis-like action on cats.[245] Further work by Louw *et al.*[246] on transvaalin led to the conclusion that it was either isomeric with scillaren A **224** or a stable complex of scillaren A **224** and scilliroside **430**. This was based on melting point analysis, toxicity tests and the fact that hydrolysis of transvaalin led to the same products as the hydrolysis of scillaren A, namely scillaridin A **517** and scillabiose (disaccharide). Zoller and Tamm[247] and Tschesehe and Hottemann[240] all concluded that transvaalin and scillaren A were identical compounds. The structure of rubellin **516** was fully elucidated by Steyn *et al.* in 1986[248] using high-field NMR spectroscopy. Later work by Krenn *et al.*[249] on *Sekanama sanguinea* (Schinz) Speta (as *Urginea sanguinea* Schinz) yielded eight bufadienolides as well as a steroidal sapogenin and stigmasterol. The first six bufadienolides, namely scillirosidin **518**, deacetylscillirosiden **519**, 12β-hydroxyscillirosidin **445**, 12β-hydroxydeacetylscillirosidin **520**, 12β-hydroxyscilliroside **446** and 5α-4,5-dihydro-12β-hydroxyscillirosidin **521** had been isolated previously from other members of the Urgineoideae. Two new compounds, 12β-hydroxyscillirosidin-3-one **522** and 12β-hydroxyscillirubrosidin-3-one **523** were identified using NMR spectroscopy. The steroidal saponin, 7β,15α-dihydroxyyamogenin **524** was the first such compound to be isolated from a member of the Urgineoideae. Majinda *et al.*[250] investigated another specimen of the same plant, and found stigmasterol, phloroglucinol **525**, phloroglucinol 1-β-*O*-glucopyranoside, scillaren A **224** and the novel 5α-4,5-dihydroscillaren A. In addition, salicylic acid and 3-hydroxy-4-methylbenzoic acid were isolated. An ethnopharmacological study of *S. sanguinea*, using patient records from Ga-Rankuwa Hospital in South Africa revealed a number of cases of poisoning as a result of ingestion. The amount usually prescribed by traditional healers does not result in adverse side effects, but the patients admitted to the hospital had taken more than the prescribed dose. A brine shrimp assay showed a seasonal variation in toxicity, with the plant being more toxic in February (late Summer) than in September (Spring).[251] *Sekanama sanguinea* has traditionally been used for many different conditions, including asthma and it is often taken by pregnant women. A study by Marx *et al.*[252] (as *Urginea sanguinea*) showed significant damage to chick embryos after exposure to this plant. They concluded that it should be used with extreme care by traditional healers.[253] Undoubtedly the bufadienolides dominate the chemistry of the Urgineoideae, including the *Sekanama* species. However, the isolation of a novel homoisoflavanoid from the bulbs of *Sekanama delagoensis* (Baker) Speta (as *Drimia delagoensis* (Baker) Jessop) indicates that a broader range of secondary metabolites can be expected, if not commonly found.[254] The homoisoflavonoid **526** and 3-methoxy-4-hydroxybenzoic acid **527**, were isolated from the dichloromethane and methanol extracts of the bulbs respectively.[254]

Other sub-Saharan members of the Urgineoideae to receive attention include *Urginavia altissima* (L.f.) Speta (as *Urginea altissima* (L.f.) Baker and *Drimia altissima* (L.f.) Baker), *Fusifilum physodes* (Jacq.) Raf. ex Speta (as *Urginea physodes* (Jacq.) Baker), *Urginavia epigea* (R.A.Dyer) Speta (as *Urginea epigea* R.A.Dyer), *Urginea lydenburgensis* R.A.Dyer and *Urginea riparia* Baker. Characteristic bufadienolides have been isolated and identified, many of which include either an aldehyde group at C-10 or a rubellin type carbohydrate group doubly linked to the aglycone at positions 2α and 3β. The best known of this group is the widespread *Urginavia altissima* (often referred to as *Drimia altissima* or *Urginea altissima*). Rat populations need to be controlled to limit threats to public health and minimise crop damage. The toxicity of *U. altissima* has been investigated with respect to the field rat, *Arvicanthis abyssinicus*.[255] Synthetic rodenticides affect non-target species and can be expensive. The powdered bulb was tested and found to be toxic at levels of 5% of the daily food intake. If the percentage was lower, no mortality was noted. *Urginavia brachystachys* (Baker) Speta has (as *Drimia brachystachys* (Baker) Stedje) reportedly been used as an arrow poison.[256]

Both bufadienolides and alkaloids have been isolated from *U. altissima*. The alkaloids, lycorine **528** and acetylcaranine **529** have not been found by any subsequent investigators and the identity of the plant investigated by Miyakado and co-workers[257] has been called into question as bulbs of *U. altissima* may be easily confused with those of some Amaryllidaceae, especially the genus *Crinum* L.[258,259] Six bufadienolides have been isolated from *U. altissima* collected in Kenya, all of which have an aldehyde at C-10 (**530–535**).[260,261] A South African sample of this plant was found to contain 12β-hydroxyscillirosidin **445**,[258] which has been isolated from *S. sanguinea* previously and urginin **536** with an interesting trisaccharide substituent at C-3.[258] A specimen from Ethiopia yielded different bufadienolides again, gamabufotalin-3-*O*-α-L-rhamnopyranoside **490** and arenobufagin-3-*O*-α-L-rhamnopyranoside **537**.[259] It would appear that significant regional differences exist in the type of bufadienolide found in *U. altissima*. *U. altissima* is widely used for the treatment of gout, rheumatism and a number of respiratory conditions, including asthma.[258] This plant is also used by Zimbabwean traditional healers to treat skin conditions. It has been found to produce a mild



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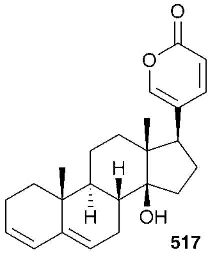

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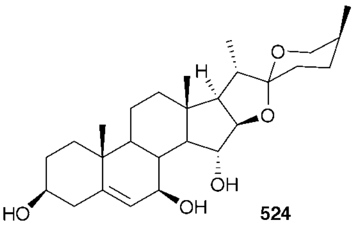

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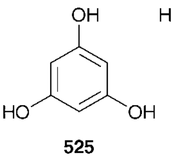

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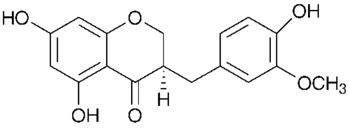

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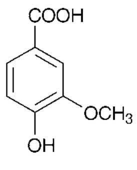

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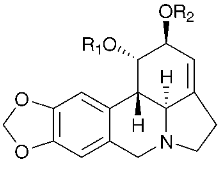
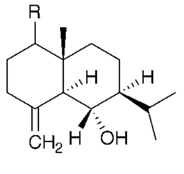


528 : R_1 = H, R_2 = OH
529 : R_1 = Ac, R_2 = H

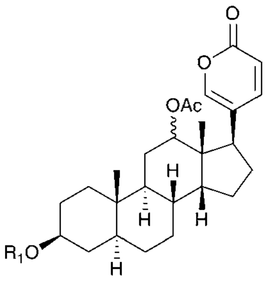


547 : R = β-OH
548 : R = =O

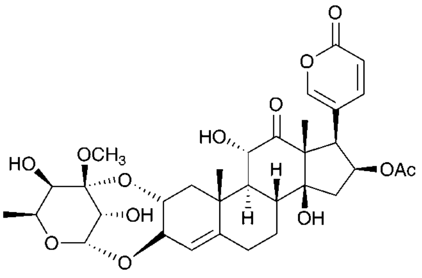
inflammation and itching if rubbed on the skin. This effect has been found to be due to the presence of calcium oxalate raphides in the bulbs and as such the appropriateness of its use as a skin treatment has been questioned.[262]

Fusifilum physodes (as *Urginea physodes* (Jacq.) Baker) was found to contain four bufadienolides, physodines A **538**, B **539**, C **540** and D **541**. Two of which, physodines A and B, both having a C-10 aldehyde group, were found to be toxic to weaned guinea pigs (fractions not causing death in 48 h at 200 mg kg^{-1} were considered non toxic). Physodines C and D were of interest in that they were the first naturally occurring 14-deoxybufadienolides to be isolated.[263] An ethanolic extract of the bulbs has been shown to have antifungal activity.[264] The methanol extract of the bulbs of *Fusifilum depressum* (Baker) U.Müll.-Doblies J.S.Tang & D.Müll.-Doblies (as *Drimia depressa* (Baker) Jessop) was found to contain two bufadienolides, **542** and **543**.[265] The leaves of this plant are toxic to cattle, sheep and rabbits and the plants are used by the Sotho as a good luck charm or to cause harm to one's enemy.[265] Novel rubellin type bufadienolides, riparianin **544** and lydenburgenin **545**, have been isolated from *Urginea riparia* and *Urginea lydenburgensis* R.A.Dyer respectively.[237,266] In addition, *Urginea lydenburgensis* was found to contain the novel bufadienolide, scillicyanosidin **546**, with an aldehyde group at C-10. Riparianin **544** showed moderate activity against MCF7 (breast), TK10 (renal) and UACC62 (melanoma) cell lines (total growth inhibition of <3.5, <7 and <10.5 ppm respectively). *Urginavia epigea* is used locally to treat backaches or as a soap. The smoke from smouldering bulbs is also used as a treatment for headaches and colds.[267] In addition to the buadienolide **517**,[268] two eudesmane sesquiterpenoids were isolated, **547** and **548**. These were the first to be reported from the Hyacinthaceae and due to their occurrence in *U. epigea* but not the oft-confused *U. altissima*, provide species level taxonomic markers.[267] The bufadienolide **517**, has an unusual 3,5-diene system, readily obtained synthetically, but not commonly isolated directly from plant sources.[268] The butanol extract of the bulbs of *U. epigea* was found to have significant molluscicidal activity against the bilharzia-carrying snail, *Bulinus africanus*. This result has raised some concern with regards its use as soap and the potential toxic affect it may have on other aquatic biota.[269]

An Indian member of the Urgineoideae, known locally as 'jungli-piyaz' or 'bhuikanda' and Indian squill has been used traditionally for stomach complaints, as a cardiac stimulant, a diuretic, as well as to treat asthma, cough or bronchitis and various infections.[270] Commercially available samples vary with some plants having a truncated bulb and others a scaly bulb.[271] For much of the work reported, the plant has been identified as *Urginea indica* (Roxb.) Kunth or *Scilla indica* Baker. The name *Indurgia indica* (Roxb.) Speta is currently accepted. Extracts of the bulbs have shown some activity against *Neisseria gonorrhoeae* infections[272] and have had outstanding antimicrobial activity attributed to them in a survey of medicinally used plants in India.[273] The ethanolic extract of the bulbs of *I. indica* (as *Scilla indica* Baker) has been found to have good antioxidant activity (protection against lipid peroxidation induced by ferrous sulphate in a dose-dependant manner, with 49% protection for hydroxyl radical-mediated hydroxylation at a concentration of 250 μg ml^{-1}) as well as to possess cardiac activity on a par with ouabain.[271,274] Rao and Rangaswami have detected bufadienolides in extracts of the bulbs of *I. indica* (as *Scilla indica* Roxb.) and have isolated scillaren A **224** as the principle active component.[275,276] Jha and Sen, however, found no trace of scillaren A **224** in a plant identified as *Scilla indica* at the time.[277] The principle bufadienolides isolated from this plant (as *Urginia indica* Kunth) by various investigators are scillaren A **224** and proscillaridin A **223**,[275,278–281] with scillaren A being reported as early as 1956. These are also the principle bufadienolides of the European squill *C. maritima*. In small doses, the action of *I. indica* is the same as *C. maritima*, in that it slows the heart beat and increases urine flow and it can successfully be used as a substitute for *C. maritima*.[282] Jha and Sen[278,280] have studied the twelve different cytotypes of *I. indica* (as *Urginea indica*), belonging to four ploidy levels. Scillaren A **224** and proscillaridin A **223** were present in all twelve. Bulbs were investigated through three successive years. The tetraploids showed the highest concentration of these bufadienolides, followed by diploids and then triploids. Significant variation in the bufadienolide concentration was also noted between samples collected in northern and southern India, with the northern samples showing much lower levels of proscillaridin A **223** and scillaren A **224**.[283] In addition, two minor components, scilliphaeoside **436** and anhydroscilliphaeosidin, were found to be present in the tetraploid cytotypes and



540 R_1 = β-D-xylopyranosyl-(1→4)-O-α-L-rhamnopyranoside
541 R_1 = β-D-glucopyranosyl-(1→3)-O-4-acetyl-α-L-rhamnopyranoside



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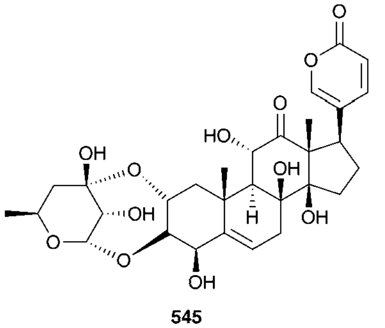

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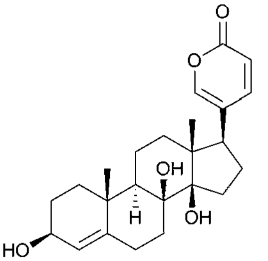

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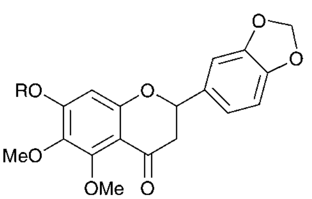
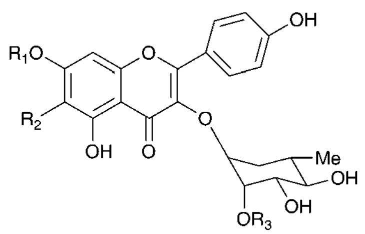


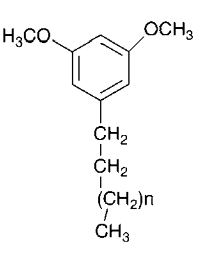
551 R = 6"- β-D-glucopyranosyl-β-D-glucopyranoside



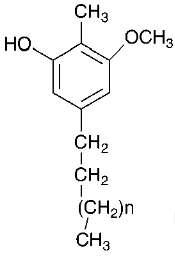
552 R_1 = 6-*p*-coumaroyl-β-D-glucopyranoside, R_2 = C-glucopyranoside, R_3 = H
553 R_1 = 6-*p*-coumaroyl-β-D-glucopyranoside, R_2 = -C-glucopyranoside, R_3 = -β-D-glucopyranosyl

scilliphaeoside **436** in the triploids. Likewise the sterol content was investigated with only minor differences noted between the ploidy levels. Stigmasterol predominated, with sitosterol and campesterol being found in the tetraploid cytotypes and some of the triploids respectively.[284,285] Kopp and Danner[281] found the bulbs of *I. indica* (as *Urginia indica*) to contain six bufadienolides, scillarenin **512**, proscillaren A **223**, scillarenin A **224**, scilliphaeosidin 3-*O*-α-L-rhamnopyranoside **549**, scilliglaucosidin 3-*O*-α-L-rhamnopyranoside **534** and scilliglaucosidin 3-*O*-β-D-glucopyranoside **535**, while Saxena and Chaturvedi isolated 6-desacetoxy scillirosidin **550**.[286] In addition to the bufadienolides and sterols, Sultana *et al.* have isolated three novel flavonoid glycosides (**551**–**553**) from bulbs collected in Bangladesh.[287]

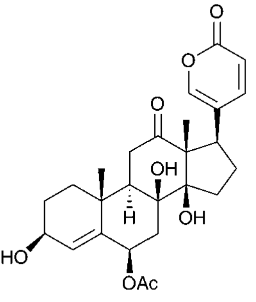
Seasonal variation in the glycosidal content of the bulbs has been observed with the highest such levels found during October at the onset of dormancy. The levels steadily decrease to reach a minimum in June.[288] Sterol content has been found to peak during the pre-flowering and pre-vegetative growth stages and it has been suggested that the sterols could be a trigger for the onset of reproductive and vegetative growth in the species.[289] Significant antifungal activity has been noted and attributed to the presence of a 29-kDa glycoprotein which inhibited growth of *Fusarium oxysporum* at a concentration of 10 μg protein well^{-1}.[290,291] This protein has in addition shown good antitumour activity against the growth of an ascites tumour and mouse mammary carcinoma (tested *in vivo* using 6–8 week old female mice).[292] The bulbs of *I. indica* (as *Urginia indica* L.) collected in Nigeria were found to contain six alkylresorcinols of the structure types shown in **554** and **555**.[293] An ethanolic extract of *I. indica* (as *Scilla indica*), has reportedly shown good inhibition of the Semliki Forest Virus and the active principal found to be a diosgenin saponin.[294]



554 : n = 17, 19, 21



555 : n = 12, 14, 17



556

The genus *Drimia* Jacq. is closely related to *Urginea*. *Drimia robusta* Baker is widely used in southern Africa by traditional healers. It has been used as a diuretic, as a treatment for feverish colds, to promote the healing of broken bones, to treat diseases of the uterus and to relieve stabbing pains in the chest.[258,295] Luyt *et al.*[295] investigated the biological activity of this plant in order to substantiate its use in traditional medicine. Anti-bacterial activity was found to be present in the ethyl acetate extract of the bulbs. An ethanolic extract of the bulbs showed higher inhibitory activity than indomethacin in the screening for inhibition of cyclooxygenase. This inhibition of prostaglandin synthesis (tested for with the cyclooxygenase assay) could explain the plant's use as a treatment for feverish colds. Further work on the COX-1 inhibition of a water extract of the bulbs showed activity above 70%.[264] Evidence for the presence of proscillaridin A **223** was presented: TLC and NMR data were compared with a standard sample. Luyt *et al.*[296] then compared bulbs derived from tissue culture with those grown naturally. A standard proscillaridin A **223** was used for comparison and the UV spectra and qualitative TLC results were compared. The results indicated that the bufadienolide content was the same in the *in vitro*-derived plants as in those grown naturally. This is in contrast to the work done on *C. maritima*, where no bufadienolides were found in the tissue cultured bulbs.[230] Phytochemical studies of the bulbs of *D. robusta* yielded eight bufadienolides, 12β-hydroxyscillirosidin **445**, 6β-acetoxy-3β,8β,14β-trihydroxy-12-oxobufa-4,20,22-trienolide **556**, scilliroside **430**, 12β-hydroxyscilliroside **446**, hellebrigenin-3-*O*-β-glucopyranoside **531**, 16β-hydroxyhellebrigenin **557**, 16β-hydroxyhellebrigenin-3-*O*-β-glucopyranoside **558** and 5β,16β-dihydroxybufalin-3-*O*-β-glucopyranoside **559** as well as three common aromatic acids, 4-hydroxy-3-methoxybenzoic acid, 3,4-dihydroxybenzoic acid and *trans*-3-(4′-hydroxyphenyl)-2-propenoic acid.[258,268,297] The toxicity of *Rhodocodon madagascariensis* Baker, a plant endemic to Madagascar, has been tested against the embryo-larvae of medaka fish (*Oryzias latipes*) and an LD_{50} of 1 mg ml^{-1} was established.[298]

Work on the genus *Bowiea* Harv. ex Hook.f. has centred on *Bowiea volubilis* Harv. ex Hook.f. Most of the investigations were carried out in the 1950s and early 1960s. This African species is toxic and as early as 1938, the presence of a cardioactive glucoside was reported.[299] Katz and Tschesche *et al.* have between them reported the presence of several bufadienolides (bovisides A **560**, B, C, D, bovogenin E, bowieasubstanz G, glucobovoside A **561**, nabogenin (scilliglaucosidin) **532**, bovoruboside **562** and bovogenin A **563**) between the years of 1950 and 1959.[300–314] Structures have been reported for nabogenin **532**, bovoruboside **562**, bovoside A **560**, glucobovoside A **561** and bovogenin A **563**, although the structure reported for bovoruboside is not certain. The cardioactive glycosides from *B. volubilis* attracted much attention in the early years of their discovery. The activity was initially found to be in the region of strophanthin,[315] the action was as rapid and lasting with a cumulative effect, though not as much as digitoxin.[316–318] Solutions of bovoside A were found to be unstable, due to the aldehyde group at C-19 being vulnerable to oxidation. Reduction of this group to the alcohol (bovosidol A) gave a stable solution which could then be assessed for activity.[319,320] Material from East Africa (as *Bowiea kilimandscharica* Mildbr.) was initially reported to contain two bufadienolides, kilimanscharogenins A and B. Katz concluded that kilimanscharogenin A was the same compound as bovogenin A **563**.[321]

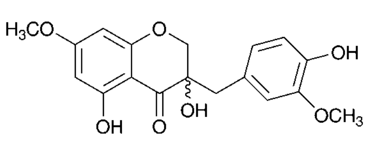
Chen and Henderson[322,323] carried out a comparative survey of the cardioactivity of twenty-nine bufadienolides and cardenolides from various sources. Included in the survey were bufadienolides from *B. volubilis*. The tests were carried out on etherised cats by slow continuous intravenous injection and the electrocardiograms were recorded to confirm the digitalis-like action of these compounds. The potency of each compound was determined in terms of lethal dose (LD), the amount (mg kg^{-1}) needed to kill a cat of approximately 2 kg in 30–60 min. The bufadienolides were found to be more potent than the cardenolides, with the glycosides seldom showing more activity than the aglycones. The methyl C-10 analogues were less active than the compounds with an aldehyde group in the C-10 position and 3-epimerisation and 5α-configuration reduced the activity. A later study by Chen increased the number of cardenolides and bufadienolides to fifty and similar profiles were obtained using the same assay system.[324]

3 The Ornithogaloideae

The Ornithogaloideae are widespread throughout Africa, Europe and southwest Asia. This group consists of approximately 280 species,[5] with a recent phylogenetic analysis by Martínez-Azorín *et al.*[6] recognising nineteen monophyletic genera. Phytochemical studies on the Ornithogaloideae have centred on *Ornithogalum* L. and *Galtonia* Decne., primarily driven by the significant biological activity attributed to the compounds isolated. In addition, a small amount of work has been done on *Albuca* L., *Eliokarmos* Raf., *Stellarioides* Medik., *Loncomelos* Raf. and *Honorius* Gray. The types of compounds isolated are strongly linked to the geographic region the plant species derive from, with the African taxa containing primarily cholestane glycosides and spirosterols, and the European taxa cardenolides. Some flavonoids and sterols have been isolated from plants sourced from all regions studied. Additionally, a limited number of homoisoflavanones have been identified from the bulbs.

The genus *Albuca* L. is widespread in southern Africa, with some species occurring in the Arabian Peninsula. The bulbs of *Albuca fastigiata* Dryand. have been investigated and only one compound was isolated, a homoisoflavonoid, **564**.[325] *Albuca fastigiata* is found on the East coast of South Africa and is used by the Zulu as a protective charm and to treat malicious food poisoning.[325] Another southern African species, *Albuca setosa* Jacq., has been tested for anti-inflammatory activity in a carrageenan-induced rat paw edema assay.[326] This plant is used by traditional healers to treat wounds, among other conditions, and was found to significantly inhibit carrageenan-induced paw edema for a 3-hour challenge (43–55% over 3 h at 150 mg kg^{-1} and 68–85% for 300 mg kg^{-1}). *Albuca setosa* has also been used by traditional healers in the Nkonkobe municipality in South Africa for the treatment of diabetes.[327] As part of a study on the steroidal saponins of various monocot families, Okanishi *et al.*[328] found *Albuca nelsonii* N.E.Br. to contain ruscogenin **565**. This was identified by comparison of melting points, mixed melting points, optical rotations, infrared and mass spectra with an authentic sample.

Galtonia candicans (Baker) Decne. is native to South Africa, and was investigated by the laboratories of Kuroda and Mimaki[329–333] who used bioassay-directed fractionation to isolate the active components of the bulbs. The methanol extract was found to be active against leukemia HL-60 cells (IC$_{50}$ = 0.017 μM). This was further partitioned between n-butanol and water, with the activity being retained in the n-butanol fraction (IC$_{50}$ = 0.0056 μM). This was found to contain the hexacyclic rearranged cholestane diglycoside, candicanoside A **566**, the polyoxygenated 5β-cholestane diglycoside galtonioside A **567**, six cholestane



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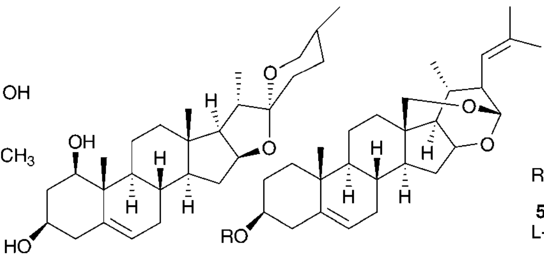
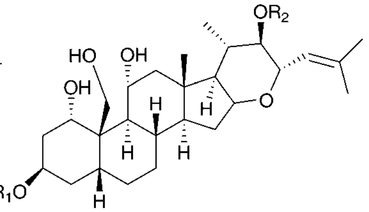
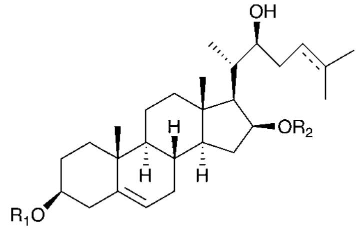


565

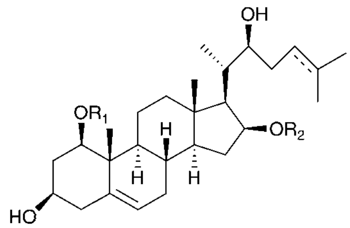
566 R = α-L-rhamnopyranosyl-(1→2)-β-D-glucopyranoside



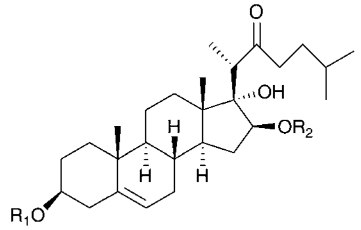
567 R$_1$ = 3,4,5-trimethoxybenzoyl ester, R$_2$ = α-L-arabinopyranosyl-(1→4)-β-D-glucopyranoside



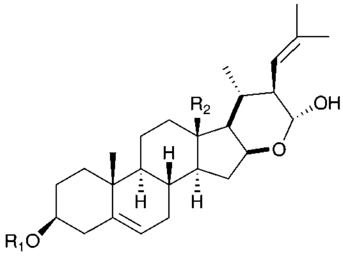
568 R$_1$ = β-D-glucopyranoside, R$_2$ = 3-O-acetyl-α-L-rhamnopyranoside
569 R$_1$ = β-D-glucopyranoside, R$_2$ = 3-O-acetyl-α-L-rhamnopyranoside, Δ^{24}



570 R$_1$ = β-D-glucopyranoside, R$_2$ = β-D-glucopyranoside
571 R$_1$ = β-D-glucopyranosyl-(1→6)-β-D-glucopyranoside, R$_2$ = β-D-glucopyranoside, Δ^{24}
572 R$_1$ = β-D-glucopyranosyl-(1→6)-β-D-glucopyranoside, R$_2$ = β-D-glucopyranoside
573 R$_1$ = α-L-rhamnopyranoside, R$_2$ = β-D-glucopyranoside
574 R$_1$ = β-D-glucopyranoside, R$_2$ = β-D-glucopyranoside



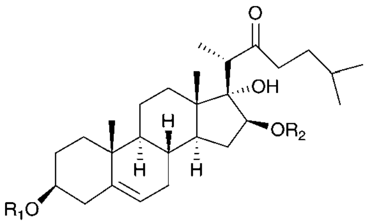
575 R$_1$ = β-D-glucopyranoside, R$_2$ = (2-*O*-(E)-cinnamoyl-β-D-xylopyranosyl)-(1→3)-2-*O*-acetyl-α-L-arabinopyranoside
576 R$_1$ = β-D-glucopyranoside, R$_2$ = (2-*O*-3,4-dimethoxybenzoyl-β-D-xylopyranosyl)-(1→3)-2-*O*-acetyl-α-L-arabinopyranoside
577 R$_1$ = β-D-glucopyranoside, , R$_2$ = β-D-xylopyranosyl)-(1→3)-2-*O*-acetyl-α-L-arabinopyranoidel
578 R$_1$ = β-D-glucopyranoside, R$_2$ = α-L-arabinopyranoside
580 R$_1$ = H, R$_2$ = α-L-arabinopyranoside



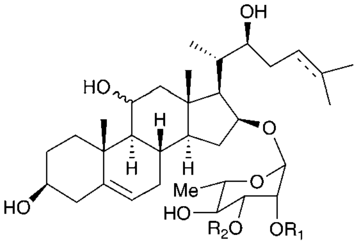
579 : R$_1$ = α-L-rhamnopyranosyl-(1→2)-β-D-glucopyranoside, R$_2$ = CH$_2$OH

bisdesmosides **568–573** and six cholestane glycosides **574–579**.[329–333] Candicanoside A **566** and galtonioside A **567** were found to have potent activity against leukemia HL-60 cells (IC$_{50}$ = 0.032 μM and 0.057 μM respectively) and further testing on a 38 cell line assay showed differential cytotoxicities against breast cancer, CNS cancer and lung cancer lines, while colon cancer, ovarian cancer and stomach cancer cell lines were resistant to them.[330,331] Compound **569** showed moderate activity against leukemia HL-60 cell lines ((IC$_{50}$ = 6.8 μM)[332] and compounds **575–578** showed good activity using the same assay (IC$_{50}$ = 0.00012 μM, 0.00048 μM, 0.0024 μM and 0.053 μM respectively).[333] Tang and Yu have achieved the total synthesis of candicanoside A **566**, using a 27-step synthesis.[334,335] Another southern African species of *Galtonia* that has received some attention is *Galtonia princeps* (Baker) Decne.[336] A methanol extract of the bulbs yielded the cholestane derivative **580**. Both the bulbs and aerial leaves of *Galtonia viridiflora* I.Verd. were found to contain monoglycosides of caffeic acid, principally rhamnose and glucose.[337]

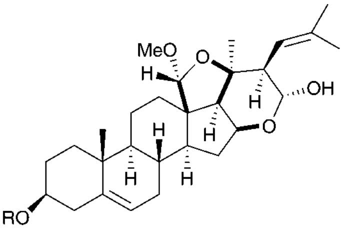
Work on the bulbs of *Galtonia saundersiae* (Baker) Mart.-Azorín, M.B.Crespo & Juan (as *Ornithogalum saundersiae*), a native of the East coast of South Africa, began in the early 1990s with the isolation of three acylated cholestane glycosides **581–583**. All three were examined for their inhibitory effect on cyclic AMP phosphodiesterase. Compounds **582** and **583** showed good activity (IC$_{50}$ = 0.00025 μM and 0.00020 μM respectively), suggesting that the presence of a benzoyl group attached to the sugar moiety is essential for activity.[338] Six additional cholestane glycosides **584–589** were isolated and tested for their inhibitory activity on cyclic AMP phosphodiesterase. Compounds **585** and **588**, with the acyl group at the C-3 hydroxyl position of the rhamnose group, showed good activity (IC$_{50}$ = 9.9 × 10^{-5} μM and 10.9 × 10^{-5} μM respectively), as did compound **589** (40% inhibition at 0.08 mg ml^{-1}), while the other compounds were inactive.[339,340] Compound **590**, isolated from the bulbs of *G. saundersiae* (as *Ornithogalum saundersiae*), showed significant inhibition (IC$_{50}$ = 3.1 μM) of the proliferation of peripheral blood lymphocytes produced by a patient with chronic renal failure, suggesting potential as an immunosuppressive agent. Rearranged cholestane glycosides (**591–599**) with a six-membered hemiacetal ring E, between C-16 and C-23, have been isolated. The conformation of ring E was determined through molecular mechanics and molecular dynamics calculations.[341] These compounds were tested for anti-tumour activity, primarily against leukaemia HL-60 cells and MOLT-4 cells. Compounds **591** (IC$_{50}$ = 21.0 nM and 18.0 nM), **592** (IC$_{50}$ = 9.2 nM and 3.2 nM) and **597–599** (IC$_{50}$ = 0.019, 0.063 and 0.052 μM for HL-60 cells) showed significant cytotoxic activity, primarily through the induction of apoptosis. These results would indicate that the presence of an aromatic ester group at the glycoside moiety is essential for good activity.[342–348] Further investigation of the methanol extract of the bulbs resulted in the isolated of the related cholestane glycoside **600**.[349] In addition to the rearranged cholestane glycosides mentioned above, ten new (**575**, **601–609**) and three previously isolated (**567–569**) cholestane glycosides, with a glycosidic moiety at C-16 have been



581 R$_1$ = H, R$_2$ = β-D-xylopyranosyl-2-*O*-acetyl-(1→3)-α-L-arabinopyranoside
582 R$_1$ = H, R$_2$ = 2-*O*-4-methoxybenzoyl- β-D-xylopyranosyl-2-*O*-acetyl-(1→3)-α-L-arabinopyranoside
583 R$_1$ = H, R$_2$ = 2-*O*-3,4-dimethoxybenzoyl-β-D-xylopyranosyl-2-*O*-acetyl-(1→3)-α-L-arabinopyranoside
602 R$_1$ = H, R$_2$ = 2-*O*-(*E*)-cinnamoyl-β-D-xylopyranosyl-2-*O*-acetyl-(1→3)-α-L-arabinopyranoside
603 R$_1$ = β-D-glucopyranoside, R$_2$ = 2-*O*-4-methoxybenzoyl-β-D-xylopyranosyl-2-*O*-acetyl-(1→3)-α-L-arabinopyranoside
608 R$_1$ = H, R$_2$ = β-D-glucopyranosyl-2-*O*-3,4-dimethoxybenzoyl-β-D-xylopyranosyl-2-*O*-acetyl-(1→3)-α-L-arabinopyranoside
609 R$_1$ = H, R$_2$ = β-D-glucopyranosyl-2-*O*-3,4,5-trimethoxybenzoyl-β-D-xylopyranosyl-2-*O*-acetyl-(1→3)-α-L-arabinopyranoside

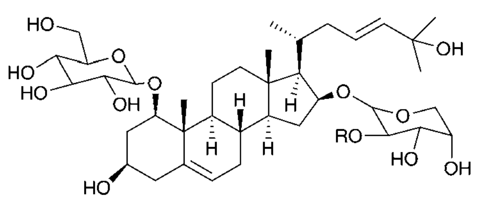


584 R$_1$ = H, R$_2$ = H, C-11α
585 R$_1$ = H, R$_2$ = Ac, C-11β
586 R$_1$ = Ac, R$_2$ = H, C-11β
587 R$_1$=H, R$_2$ = H, C-11α, Δ^{24}
588 R$_1$ = H, R$_2$ = Ac, C-11β, Δ^{24}
604 R$_1$ = Ac, R$_2$ = Ac, C-11α
605 R$_1$ = Ac, R$_2$ = 3,4,5-trimethoxybenzoyl, C-11α
606 R$_1$ = Ac, R$_2$ = *p*-methoxybenzoyl, C-11α
607 R$_1$ = Ac, R$_2$ = Ac, C-11α, Δ^{24}

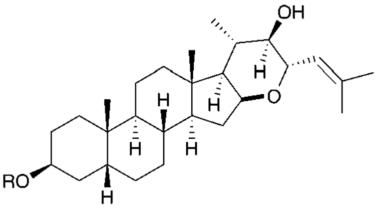


589 R = α-L-rhamnopyranosyl-(1→2)-β-D-glucopyranosyl-(1→2)-β-D-glucopyranoside
592 R = 4-*O*-4-methoxybenzoyl-α-L-rhamnopyranosyl-(1→2)-β-D-glucopyranoside
593 R = α-L-rhamnopyranosyl-(1→2)-β-D-glucopyranoside
594 R = 4-*O*-4-methoxybenzoyl-α-L-rhamnopyranosyl-(1→2)-β-D-glucopyranoside

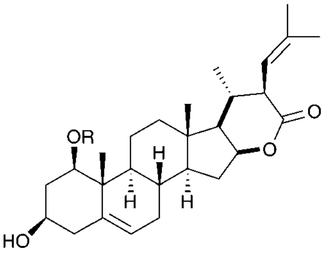
tested for their inhibitory activity against leukemia HL-60 cells and MOLT-4 cells. All these compounds showed significant activity, with a loss of activity noted each time the ester group on the sugar moiety was removed.[350–353] Due to the significant anti-tumour activity shown by these plant extracts, a number of patents have been filed in Japan and China covering the extract methods used, the use of the saponins and, in some cases, the synthesis of the active components.[354–358] In particular, 567



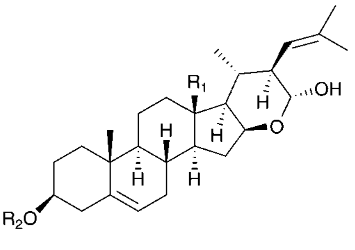
601 R = 3,4,5-trimethoxybenzoyl



590 R = α-L-rhamnopyranosyl-(1→2)-β-D-glucopyranosyl-(1→2)-β-D-glucopyranoside



600 R = β-D-glucopyranosyl-(1→6)-β-D-glucopyranoside



591 R$_1$ = CHO, R$_2$ = 4-*O*-4-hydroxybenzoyl-α-L-rhamnopyranosyl-(1→2)-β-D-glucopyranoside
595 R$_1$ = CHO, R$_2$ = α-L-rhamnopyranosyl-(1→2)-β-D-glucopyranosyl-(1→2)-β-D-glucopyranoside
596 R$_1$ = CHO, R$_2$ = α-L-rhamnopyranosyl-(1→2)-β-D-glucopyranoside
597 R$_1$ = CHO, R$_2$ = 4-*O*-4-methoxybenzoyl-α-L-rhamnopyranosyl-(1→2)-β-D-glucopyranoside
598 R$_1$ = CH$_2$OH, R$_2$ = 4-*O*-4-hydroxybenzoyl-α-L-rhamnopyranosyl-(1→2)-β-D-glucopyranoside
599 R$_1$ = CH$_2$OH, R$_2$ = 4-*O*-4-methoxybenzoyl-α-L-rhamnopyranosyl-(1→2)-β-D-glucopyranoside

(called OSW1) has been the subject of much synthetic work. The full synthesis of the compound itself has been accomplished, and a large number of analogues have been produced for structure–activity relationship studies. Studies indicate that OSW1 acts by damaging the mitochondria and inducing apoptosis through an increase of cytosolic calcium and thus the activation of calcium dependent apoptosis. It has been demonstrated that OSW1 is active against some cells that are resistant to conventional anti-cancer agents, in particular fludarabine-resistant chronic lymphocytic leukemia cells.[359] In addition to the work on the anti-tumour activity of *G. saundersiae*, the ethanol extract of the whole dried plant has been tested for its protective effects against acute hepatic failure. The authors concluded that it did provide some benefit, primarily through suppressing oxidative stress, lipid peroxidation and apoptosis of hepatocytes, as well as reducing inflammation.[360,361]

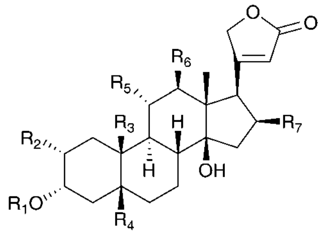
Species from the genus *Ornithogalum* have received substantial attention. While early work on the genus began in the 1950s on the European members of the genus, later work has included species from Turkey and Iran.

Work on the European species of *Ornithogalum* was initially centred on *Ornithogalum umbellatum* L. (common Star of Bethlehem). European species of *Ornithogalum* are characterised by the presence of cardenolides, with some flavonoids also identified. Extracts of the bulbs of *O. umbellatum* were found to have a digitalis-like effect on frog, rabbit and cat hearts. In all cases, a positive inotropic action was noted, decreased conduction and finally systolic standstill.[362–364] A clinical trial found that when tablets of *O. umbellatum* were substituted for digitoxin there was a loss of activity and fluid retention increased. When the tablets were coated to protect them from stomach acid, the digitalis-like action was re-established but at only half the expected strength. It was concluded that only half the active components were being absorbed. When compared to digitoxin, the drug showed less slowing of the heart, a greater diuretic effect and less gastrointestinal nausea.[365] The principal active component of *O. umbellatum* was found to be the cardenolide convallatoxin **610**.[366] The cytotoxicity of convallatoxin **610** was studied. It was found to have an IC_{50} of 002 $\mu g\ ml^{-1}$ when assayed against Eagle's KB strain of human carcinoma and structure–activity studies showed that the glycosidic portion was essential for activity and that the β-hydroxy groups at C-5 and C-14 and the aldehyde at C-10 significantly enhanced the activity.[367] The convallatoxin **610** content in the bulbs can be increased by defloration of the plant.[368] In total, sixteen cardenolides (**610–626**) have been isolated from the bulbs of *O. umbellatum* L.[366,369–371] Later phytochemical investigations of the bulbs resulted in the isolation and identification of two flavonoids (**627** and **628**)[372] while the four flavonoids (**627–630**) were isolated from the leaves.[372,373] Compounds **629** and **630** were also isolated from the leaves of *Ornithogalum algeriense* Boiss. and *Ornithogalum kochii* Parl.[373] Sabudak and Oyman reported the presence of 3-*O*-(2′-methoxy-4′-(2-pentenal))-phenylsitosterol in the bulbs of *O. umbellatum*[374] and a study of the roots colonized by the fungus *Glomus intraradices* found a complex range of apocarotenoids.[375] A range of cardenolides have been isolated from the species *Loncomelos magnum* (Krasch. & Schischk.) Speta (as *Ornithogalum magnum*) (**610**, **614**, **631–635**),[376–382] *Honorius nutans* (L.) Gray (as *Ornithogalum nutans*) (**610**, **631**, **632**, **636–664**),[383,384] *Ornithogalum gussonei* Ten. (**631**, **635**, **665**)[385] and *Honorius boucheanum* (Kunth) Holub (as *Ornithogalum boucheanum*) (**666–673**).[386] The aerial parts of *O. gussonei* yielded two flavonoids saponaretin **674** and saponarin **675**.[387] A terpene glucoside (**676**) has been isolated from *Ornithogalum montanum* Cyr.[388] and the main water soluble polysaccharide of the bulbs of *Ornithogalum ponticum* (Zahar.) Speta was found to be a neutral glucofructan with a glucose : fructose ratio of 30 : 1.[57,389]

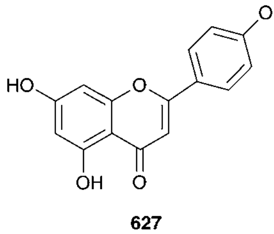
A comparative study on the Bulgarian species *Ornithogalum nanum* Sibth. & Sm., *O. gussonei*, *Loncomelos narbonense* (L.) Raf. (as *O. narbonense*), and *O. montanum* Cyr. resulted in cardenolides (**677–681**) being found in the bulbs of *O. nanum* and *O. gussonei* but not in the bulbs of the other two species.[390]

The leaves and bulbs of the Turkish species *Ornithogalum alpigenum* Stapf. have been tested for antioxidant activity, antimicrobial activity and as free radical scavengers. The leaf extracts were found to be good free radical scavengers (90.9%) and the bulb extracts (methanol, ethanol, acetone and benzene) showed variable activity against *Candida albicans*, *Bacillus subtilis* and *Bacillus cereus*. The highest antioxidant activity was found in the methanol extract of the bulbs (88.1% on a β-carotene-linoleic acid system) and the lowest in the benzene extract of the bulbs.[391] The Iranian species *Ornithogalum procerum* Stapf. and *Ornithogalum cuspidatum* Bertol. have received some attention. The aerial parts of *O. cuspidatum* are used in Iran as food additives as well as an anti-irritant and relaxant to soothe the throat when suffering from a dry cough. The essential oils in the leaves, flowers and bulbs have been determined by GC-MS. The flowers and bulbs contained primarily saturated hydrocarbons, while the leaves contained oxygenated hydrocarbons and terpenoid compounds.[392] In addition, a GS-MS analysis of the methanol extract of the bulbs has allowed for the identification of thirteen phytosterols (cholesterol, 3,5-didehydrostigmastan-6,22-diene, 4,4-dimethyl-5α-cholest-7-en-3-one, 4β-methylcholesterol, 5-cholestene-3β,7β-diol, campesterol, cholest-4-ene-3,6-dione, stigmast-4-en-3-one, stigmasta-3,5-dien-7-one, stigmasterol, Δ^5-ergostenol, β-sitosterol and γ-sitosterol).[393] A GC-MS analysis of the aerial parts and bulbs of *O. procerum* resulted in the identification of twenty-three essential oils in the aerial parts and four polysterol-type compounds in the bulbs.[394] *Ornithogalum sintensii* Freyn, another Iranian species, has been tested for antioxidant activity. A higher phenolic and flavonoid content in the aerial parts of the plant relative to the bulbs, accounted for the greater antioxidant activity in those extracts (IC_{50} for DPPH radical scavenging activity of 368 and 669 $\mu g\ ml^{-1}$ for leaves and bulbs respectively).[395]

Eliokarmos thyrsoides (Jacq.) Raf. is found in southwestern South Africa. Although not reportedly used by traditional healers it has been strongly linked to stock poisoning.[1] Accordingly, the bulbs have been the subject of many phytochemical investigations. An initial investigation of the methanol extract of the bulbs in 1992 (as *Ornithogalum thyrsoides*) resulted in the isolation of four cholestane bisdesmosides (**682–685**), with **685** showing some inhibitory activity on cyclic AMP phosphodiesterase ($IC_{50} = 15.3 \times 10^{-5}$ M).[396] Following the discovery that the methanol extract of the bulbs showed potent



610 R_1 = α-L-rhamnopyranoside, R_2 = H, R_3 = CHO, R_4 = OH, R_5 = H, R_6 = H, R_7 = H
611 R_1 = β-D-glucopyranosyl-(1→4)-α-L-fucopyranoside, R_2 = H, R_3 = HO, R_4 = OH, R_5 = H, R_6 = H, R_7 = H
612 R_1 = α-L-rhamnopyranoside, R_2 = H, R_3 = CH_2OH, R_4 = OH, R_5 = H, R_6 = H, R_7 = H
613 R_1 = 6-deoxy-β-D-gulopyranoside, R_2 = H, R_3 = CHO, R_4 = OH, R_5 = H, R_6 = H, R_7 = H
614 R_1 = α-L-rhamnopyranoside, R_2 = H, R_3 = CH_3, R_4 = H, R_5 = OH, R_6 = H, R_7 = H
615 R_1 = α-L-rhamnopyranosyl-β-D-glucopyranoside, R_2 = H, R_3 = CH_3, R_4 = H, R_5 = OH, R_6 = H, R_7 = H
616 R_1 = 6-desoxy-β-D-allopyranoside, R_2 = H, R_3 = CHO, R_4 = OH, R_5 = H, R_6 = H, R_7 = H
617 R_1 = β-D-allopyranoside, R_2 = H, R_3 = CHO, R_4 = OH, R_5 = H, R_6 = H, R_7 = H
618 R_1 = 3-acetyl-β-digitopyranosyl-β-D-glucopyranosyl-α-L-rhamnopyranoside, R_2 = H, R_3 = CHO, R_4 = OH, R_5 = H, R_6 = H, R_7 = H
619 R_1 = α-L-rhamnopyranoside, R_2 = H, R_3 = CHO, R_4 = OH, R_5 = OH, R_6 = H, R_7 = H
620 R_1 = 6-desoxy-β-D-allopyranoside, R_2 = H, R_3 = CH_3, R_4 = OH, R_5 = H, R_6 = H, R_7 = H
621 R_1 = 6-desoxy-β-D-gulopyranoside, R_2 = H, R_3 = CH_3, R_4 = H, R_5 = OH, R_6 = H, R_7 = H
622 R_1 = 6-desoxy-β-D-allopyranoside, R_2 = H, R_3 = CH_3, R_4 = H, R_5 = OH, R_6 = H, R_7 = H
623 R_1 = β-D-allopyranoside, R_2 = H, R_3 = CH_3, R_4 = H, R_5 = OH, R_6 = H, R_7 = H
624 R_1 = 6-desoxy-α-L-glucopyranose, R_2 = H, R_3 = CH_3, R_4 = OH, R_5 = OH, R_6 = H, R_7 = H
625 R_1 = α-L-rhamnopyranoside, R_2 = H, R_3 = CH_3, R_4 = OH, R_5 = OH, R_6 = H, R_7 = H
626 R_1 = β-D-ribose, R_2 = H, R_3 = CH_3, R_4 = OH, R_5 = OH, R_6 = H, R_7 = H
631 R_1 = α-L-rhamnopyranoside, R_2 = H, R_3 = CH_3, R_4 = H, R_5 = OH, R_6 = H, R_7 = H
632 R_1 = α-L-rhamnopyranosyl-β-D-glucopyranoside, R_2 =H, R_3 = CH_3, R_4 = H, R_5 = OH, R_6 = H, R_7 = H
633 R_1 = α-L-arabinopyranoside, R_2 = H, R_3 = CH_3, R_4 = H, R_5 = OH, R_6 = H, R_7 = H
642 R_1 = 6'-desoxy-β-D-allopyranosyl-4'-β-D-xylopyranosyl-3''-β-D-apiofuranoside, R_2 = H, R_3 =CHO, R_4 = OH, R_5 = H, R_6 = H, R_7 = H
643 R_1 = α-L-rhamopyranosyl-4'-β-D-apiofuranoside, R_2 = H, R_3 = CH_3, R_4 = H, R_5 = H, R_6 = H, R_7 = OH
644 R_1 = β-D-digitoxopyranosyl-4'-β-D-xylpyranosyl-3''-β-D-apiofuranoside, R_2 = H, R_3 = CH_3, R_4 = H, R_5 = H, R_6 = H, R_7 = OAc
645 R_1 = 2'-desoxy-β-D-allopyranosyl-4'-β-D-xylopyranosyl-3''-β-D-apiofuranoside , R_2 = H, R_3 = CH_3, R_4 = H, R_5 = H, R_6 = H, R_7 = OAc
646 R_1 = β-D-digitoxopyranosyl-4'-β-D-xylpyranosyl-3''-β-D-apiofuranoside, R_2 = H, R_3 = CH_3, R_4 = H, R_5 = H R_6 = OH, R_7 = OAc
653 R_1 = 6 - desoxy-α-L-glucopyranoside, R_2 = H, R_3 = CHO, R_4 = OH, R_5 = H, R_6 = H, R_7 = H
654 R_1 = α-L-rhamnopyranosyl-β-D-glucopyranoside, R_2 = H, R_3 = CHO, R_4 = OH, R_5 = H, , R_6 = H, R_7 = H
655 R_1 = β-D-allopyranosyl-β-D-xyloside, R_2 = H, R_3 = CHO, R_4 = OH, R_5 = H, R_6 = H, R_7 = H
656 R_1 = β-D-digitoxopyranosyl-4'-glucopyranoside, R_2 = H, R_3 = H, R_4 = OH, R_5 = H , R_6 = H, R_7 = H
657 R_1 = α-L-rhamnopyranoside, R_2 = H, R_3 = CHO, R_4 = OH, R_5 = OH, R_6 = H, R_7 = H
658 R_1 = 6 - desoxy-α-L-glucopyranoside, R_2 = H, R_3 = CHO, R_4 = OH, R_5 = OH, R_6 = H, R_7 = H
659 R_1 = α-L-rhamnopyranosyl-4'-β-D-apiofuranoside, R_2 = H, R_3 = CH_3, R_4 = H, R_5 = OH, R_6 = H, R_7 = H
660 R_1 = α-L-rhamnopyranosyl-4'-α-L-rhamnopyranoside, R_2 = H, R_3 = CH_3, R_4 = H, R_5 = OH, R_6 = H, R_7 = H
661 R_1 = β-D-digitoxpyranosyl-β-D-xylpyranosyl-α-L-rhamnopyranoside, R_2 = H, R_3 = CH_3, R_4 = H, R_5 = OH, R_6 = H, R_7 = H
662 R_1 = α-L-rhamnopyranoside, R_2 = H, R_3 = CH_3, R_4 = OH, R_5 = OH, R_6 = H, R_7 = H
663 R_1 = β-D-glucopyranoside, R_2 = H, R_3 = CH_3, R_4 = OH, R_5 = OH, R_6 = H, R_7 = H
664 R_1 = 2-desoxy-β-D-allopyranoside, R_2 = OH, R_3 = CH_3, R_4 = OH, R_5 = OH, R_6 = H, R_7 = H



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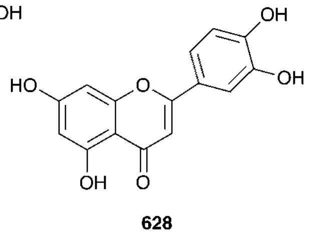

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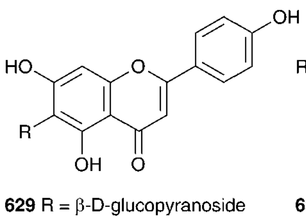
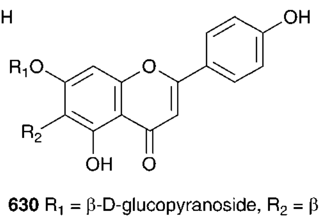
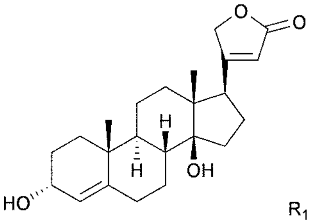


629 R = β-D-glucopyranoside



630 R_1 = β-D-glucopyranoside, R_2 = β-D-glucopyranosyl-β-D-glucopyranoside



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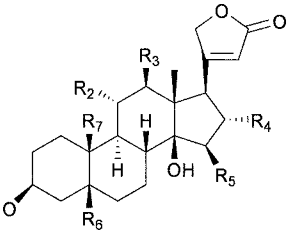
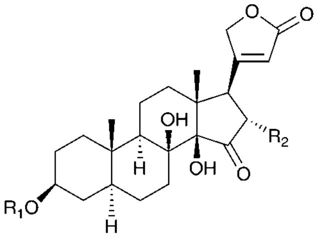
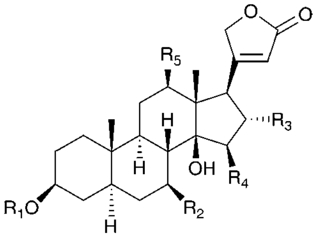


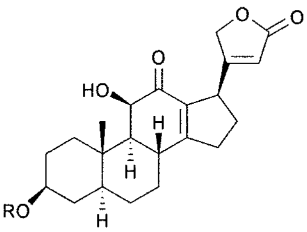
635 R_1 = α-L-rhamnopyranoside, R_2 = H, R_3 = H, R_4 = β-OH, R_5 = H, R_6 = H, R_7 = CH_3
665 R_1 = H, R_2 = OH, R_3 = H, R_4 = H, R_5 = H, R_6 = H, R_7 = CH_3
666 R_1 = 6'-deoxy-β-D-allpyranosyl-β-D-xylopyranosyl-α-L-rhamnoside, R_2 = OH, R_3 = H, R_4 = H, R_5 = H, R_6 = H, R_7 = CH_3
667 R_1 = 6'-deoxy-β-D-allopyranosyl-β-D-xylpyranosyl-β-D-apiofuranoside, R_2 = OH, R_3 = H, R_4 = H, R_5 = H, R_6 = H, R_7 = CH_3
668 R_1 = β-D-digitoxopyranosyl-β-D-xylpyranosyl-α-L-rhamnopyranoside, R_2 = H, R_3 = H, R_4 = OH, R_5 = OH, R_6 = H, R_7 = CH_3
669 R_1 = β-D-digitoxpyranosyl-β-D-xylpyranosyl-β-D-apiofuranoside, R_2 = OH, R_3 = H, R_4 = H, R_5 = H, R_6 = H, R_7 = CH_3
670 R_1 = β-D-digitoxopyranosyl-β-D-xylopyranosyl-α-L-rhamnopyranoside, R_2 = H, R_3 = OH, R_4 = H, R_5 = H, R_6 = H, R_7 = CH_3
671 R_1 = α-L-rhamnopyranosyl-β-D-apiofuranoside, R_2 = OH, R_3 = H, R_4 = H, R_5 = H, R_6 = H, R_7 = CH_3
672 R_1 = β-D-digitoxopyranosyl-β-D-xylopyranosyl-α-L-rhamnopyranoside, R_2 = H, R_3 = H, R_4 = H, R_5 = H, R_6 = H, R_7 = CH_3
673 R_1 = 6'-deoxy-β-D-allopyranosyl-β-D-xylopyranoside, R_2 = H, R_3 = H, R_4 = H, R_5 = H, R_6 = H, R_7 = CH_3
677 R_1 = H, R_2 = H, R_3 = H, R_4 = H, R_5 = H, R_6 = OH, R_7 = CH_3
678 R_1 = H, R_2 = OH, R_3 = H, R_4 = H, R_5 = H, R_6 = OH, R_7 = CHO
679 R_1 = H, R_2 = OH, R_3 = H, R_4 = H, R_5 = H, R_6 = OH, R_7 = CH_3
680 R_1 = H, R_2 = H, R_3 = H, R_4 = H, R_5 = H, R_6 = OH, R_7 = CH_2OH
681 R_1 = 6-deoxy-β-D-allopyranoside, R_2 = H, R_3 = H, R_4 = H, R_5 = H, R_6 = OH, R_7 = CH_3



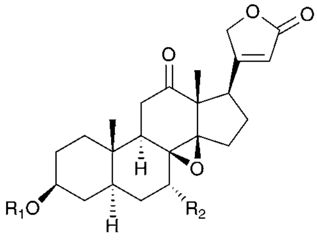
637 R_1 = β-D-digitoxopyranosyl-β-D-xylopyranosyl-α-L-rhamnopyranoside, R_2 = OH
638 R_1 = 3'-O-acetyl-β-D-digitoxopyranosyl-β-D-xylopyranosyl-α-L-rhamnopyranoside, R_2 = OH
639 R_1 = β-D-digitoxopyranosyl-β-D-xylopyranosyl-β-D-apiofuranoside, R_2 = H
640 R_1 = -3'-O-acetyl-β-D-digitoxopyranosyl-β-D-xylopyranosyl-α-L-rhamnopyranoside, R_2 = H
641 R_1 = β-D-digitoxopyranosyl-β-D-xylopyranosyl-α-L-rhamnopyranoside, R_2 = H



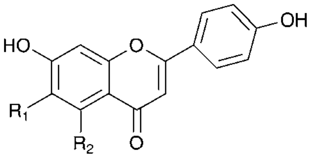
636 R_1 = β-D-digitoxopyranosyl-4'-β-D-xylopyranosyl-4''-α-L-rhamnopyranoside, R_2 = OH, R_3 = OH, R_4 = OH, R_5 = H
652 R_1 = 3'-O-acetyl-β-D-digitoxopyranosyl-4'-β-D-xylopyranosyl-4''-α-L-rhamnopyranoside, R_2 = H, R_3 = H, R_4 = H, R_5 = OH



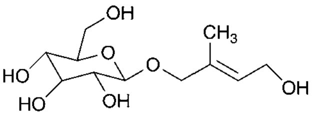
647 R = 3'-O-acetyl-β-D-digitoxopyranosyl-4'-β-D-xylopyranosyl-4''-α-L-rhamnopyranoside
648 R = β-D-digitoxopyranosyl-4'-β-D-xylopyranosyl-4''-α-L-rhamnopyranoside
650 R = β-D-digitoxopyranosyl-4'-β-D-xylopyranosyl-4''-α-L-rhamnopyranoside



649 R_1 = 3'-O-acetyl-β-D-digitoxopyranosyl-4'-β-D-xylopyranosyl-4''-α-L-rhamnopyranoside, R_2 = H
651 R_1 = β-D-digitoxopyranosyl-4'-β-D-xylopyranosyl-4''-α-L-rhamnopyranoside, R_2 = OH



674 R_1 = β-D-glucopyranoside, R_2 = OH
675 R_1 = OH, R_2 = β-D-glucopyranoside



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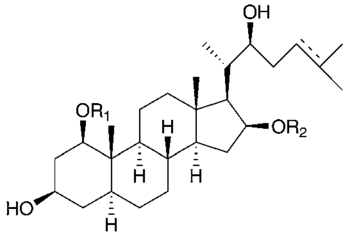
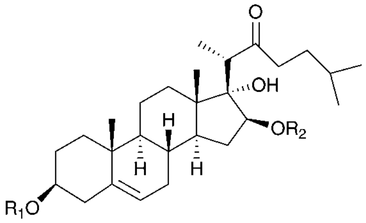
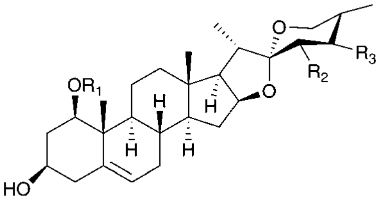
cytotoxicity against leukemia HL-60 cells ($IC_{50} = 0.79$ μg ml^{-1}), fractionation of this extract resulted in the isolation of twelve bisdesmosidic cholestane glycosides (**577–578**, **686–694**),[397] seven cholestane glycosides (**695–701**) and nine spirocyclic glycosides (**702–710**).[398,399] The bisdesmosidic cholestane glycosides with an aromatic acyl group at the C-16 diglycoside were found to be the most cytotoxic (**686** and **576**) with IC_{50} values of 0.00016 and 0.00013 μg ml^{-1} respectively. Compounds **687** and **696**, the deacyl derivatives of compounds **688** and **689** and compounds **691** and **692** respectively did not show any activity at all.[400] Only moderate activity against leukemia HL-60 cells was found for the spirocyclic glycosides (IC_{50} of 1.6–5.3 μg ml^{-1}).[401] An arabinoglucuronomannoglycan has been isolated from the leaves of *E. thyrsoides* (as *O. thyrsoides*).[402] South African bulbs of *Stellarioides longibracteata* (Jacq.) Speta are used extensively by the Zulu as an anti-inflammatory, and regionally to treat diabetes. A phytochemical investigation of the bulbs (as *Ornithogalum longibracteatum* Jacq.) revealed one major compound, the homoisoflavanone **711**.[403] The water extract of the bulbs produced a significant increase in glucose utilisation in Chang liver cells.[404] *Stellarioides longibracteata* was introduced to China many years ago and it is used in Chinese folk medicine to treat cancer, as an antimicrobial, anti-inflammatory and to treat hepatitis and parotitis.[405] This species was known earlier as *Ornithogalum caudatum* Ait. and as such many papers and in particular patents, have been filed under that name. Spirosterols, caudaside A **712** and hecogenin **713** have been isolated as well as β-sitosterol[406] and three homoisoflavanones (**714–716**).[407] Compounds **714–716** were tested for anti-tumour activity against P388 (mouse leukemia) and A-549



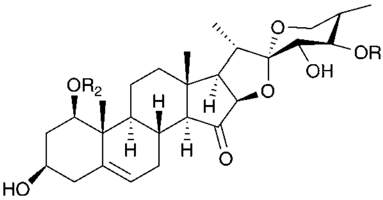
682 R_1 = α-L-rhamnopyranoside, R_2 = β-D-glucopyranoside
683 R_1 = α-L-rhamnopyranoside, R_2 = 6-*O*-acetyl-β-D-glucopyranoside
684 R_1 = α-L-rhamnopyranoside, R_2 = β-D-glucopyranoside, Δ^{24}
685 R_1 = α-L-rhamnopyranoside, R_2 = 6-*O*-acetyl-β-D-glucopyranoside, Δ^{24}
695 R_1 = α-L-rhamnopyranoside, R_2 = β-apiofuranosyl-6-*O*-acetyl-β-D-glucopyranoside
696 R_1 = β-D-glucopyranoidel, R_2 = β-D-glucopyranoside
697 R_1 = 6-*O*-3,4,5-trimethoxybenzoyl-β-D-glucopyranoside, R_2 = β-D-glucopyranoside
698 R_1 = 6-*O*-3,4,5-trimethoxybenzoyl-β-D-glucopyranoside, R_2 = β-D-glucopyranoside, Δ^{24}
699 R_1 = α-L-rhamnopyranoside, R_2 = α-L-rhamnopyranoside, Δ^{5}
700 R_1 = α-L-rhamnopyranoside, R_2 = α-L-rhamnopyranoside, Δ^{24}
701 R_1 = α-L-rhamnopyranoside, R_2 = α-L-rhamnopyranoside , Δ^{5}, Δ^{24}



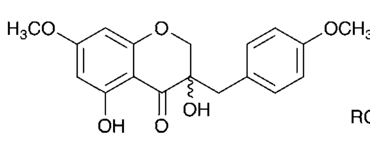
686 R_1 = β-D-glucopyranoside, R_2 = 2-*O*-3,4,5-trimethoxybenzoyl- β-D-xylopyranosyl-2-*O*-acetyl-(1→3)-α-L-arabinopyranoside
687 R_1 = β-D-glucopyranosyl-(1→6)-β-D-glucopyranoside, R_2 = β-D-xylopyranosyl-2-*O*-acetyl-(1→3)-α-L-arabinopyranoside
688 R_1 = β-D-glucopyranosyl-(1→6)-β-D-glucopyranoside, R_2 = 2-*O*-3,4-dimethoxybenzoyl–β-D-xylopyranosyl-2-*O*-acetyl-(1→3)-α-L-arabinopyranoside
689 R_1 = β-D-glucopyranosyl-(1→6)-β-D-glucopyranoside, R_2 = 2-*O*-3,4,5-trimethoxybenzoyl–β-D-xylopyranosyl-2-*O*-acetyl-(1→3)-α-L-arabinopyranoside
690 R_1 = β-D-glucopyranosyl- (1→4)-β-D-glucopyranosyl-(1→6)-β-D-glucopyranoside, R_2 = β-D-xylopyranosyl-2-*O*-acetyl-(1→3)-α-L-arabinopyranoside
691 R_1 = β-D-glucopyranosyl- (1→4)-β-D-glucopyranosyl-(1→6)-β-D-glucopyranoside, R_2 = 2-*O*-3,4-dimethoxybenzoyl– β-D-xylopyranosyl-2-*O*-acetyl-(1→3)-α-L-arabinopyranoside
692 R_1 = β-D-glucopyranosyl- (1→4)-β-D-glucopyranosyl-(1→6)-β-D-glucopyranoside, R_2 = 2-*O*-3,4,5-trimethoxybenzoyl– β-D-xylopyranosyl-2-*O*-acetyl-(1→3)-α-L-arabinopyranoside
693 R_1 = β-D-glucopyranosyl- (1→4)-β-D-glucopyranosyl-(1→6)-β-D-glucopyranoside, R_2 = 2-*O*-4-hydroxy-3-methoxybenzoyl– β-D-xylopyranosyl-2-*O*-acetyl-(1→3)-α-L-arabinopyranoside
694 R_1 = β-D-glucopyranosyl- (1→4)-β-D-glucopyranosyl-(1→6)-β-D-glucopyranoside, R_2 = 3-*O*-3,4-dimethoxybenzoyl– β-D-xylopyranosyl-2-*O*-acetyl-(1→3)-α-L-arabinopyranoside



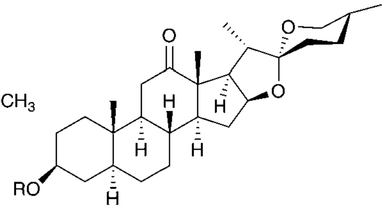
702 R_1 = β-D-glucopyranoside, R_2 = H, R_3 = H
703 R_1 = α-L-rhamnopyranosyl-(1→2)-α-L-arabinopyranoside, R_2 = H, R_3 = H
704 R_1 = α-L-rhamnopyranosyl-(1→2)-[β-D-xylopyranosyl-(1→3)-α-L-arabinopyranoside, R_2 = H, R_3 = H
705 R_1 = α-L-rhamnopyranosyl-(1→2)-α-L-arabinopyranoside, R_2 = H, R_3 =OH
706 R_1 = α-L-rhamnopyranosyl-(1→2)-[β-D-xylopyranosyl-(1→3)-α-L-arabinopyranoside, R_2 = H, R_3 = OH
712 R_1 = α-L-rhamnopyranosyl-(1→2)-[β-D-xylopyranosyl-(1→3)-α-L-arabinopyranoside, R_2 = OH, R_3 = OH



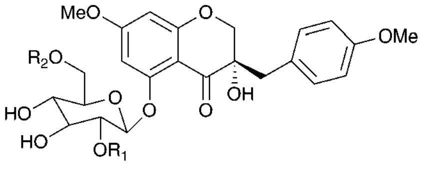
707 R_1 = H, R_2 = α-L-rhamnopyranosyl-(1→2)-α-L-arabinopyranoside
708 R_1 = 6-deoxy-β-D-gulopyranoside, R_2 = α-L-rhamnopyranosyl-(1→2)-α-L-arabinopyranoside
709 R_1 = 6-deoxy-β-D-gulopyranoside, R_2 = [α-L-rhamnopyranosyl-(1→2)-O-[-β-D-xylopyranosyl-(1→3)]-α-L-arabinopyranoside
710 R_1 = 6-deoxy-β-D-gulopyranoside, R_2 = [2,3,4 - tri-O-acetyl-α-L-rhamnopyranosyl-(1→2)-O-[-β-D-xylopyranosyl-(1→3)]-α-L-arabinopyranoside



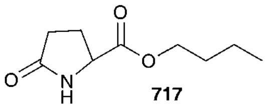
711



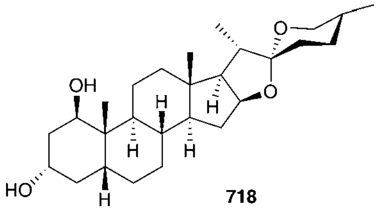
713 R = [β-D-glucopyranosyl-(1→2)-]β-D-xylopyranosyl-(1→3)-β-D-glucopyranosyl-(1→4)-β-D-galactopyranoside



714 R_1 = H, R_2 = H
715 R_1 = H R_2 = α-L-rhamnopyranoside
716 R_1 =α-L-rhamnopyranoside, R_2 = H



717



718

(human pulmonary adenocarcinoma) but no activities were noted. Later investigations of the bulbs of *S. longibracteata* (as *O. caudatum*) resulted in the isolation of n-butyl pyroglumate **717**, 26 additional known flavonoids, sterols and acids[408] and a monoterpene lactone (6-hydroxy-4,4,7α-trimethyl-5,6,7,7α-tetrahydro-4*H*-benzofuran-2-one).[409] A number of patents have been filed in China and Russia outlining methods for the extraction of *S. longibracteata* (as *O. caudatum*) and use as a treatment for cancer,[410,411] cholecystitis and cholecystitis-related diseases[412] and for the isolation of the flavonoid components for use as an anti-inflammatory and analgesic.[413,414] Extracts from *S. longibracteata* (as *O. caudatum*) have shown some benefit in the treatment of liver conditions.[415,416] Four water soluble polysaccharide fractions have been extracted from *S. longibracteata* (as *O. caudatum*) and have been found to have potential as antitumour agents.[417–419] Further work on the anti-cancer effects of this species has shown inhibition of MDA-MB-231 breast cancer cells in a dose and time dependant manner.[420] The bulbs of *Stellarioides tenuifolia* (Redoute) Speta (as *Ornithogalum tenuifolium* Delaroche) yielded a crystalline steroidal saponin, **718**, with an unusual 5β configuration.[421] This unusual configuration at C-5, together with the 1β,3α hydroxyl group configuration, results in a molecule with a shape that is able to undergo self-recognition, similar to single-strand DNA, and thus form a supramolecular zipper.

A review of steroidal glycosides isolated from various monocot families (including *Galtonia saundersiae*, as *Ornithogalum saundersiae*) and their biological activities has been published as well as a review of cholestane glycosides from *G. saundersiae*, *G. candicans* and *Eliokarmos thyrsoides* (as *Ornithogalum thyrsoides*).[422,423]

4 The Oziroëoideae

The genus *Oziroë* Raf. (*syn. Fortunatia* Macbr.), is widespread in South America and can be found in Peru, Chile, Bolivia, Paraguay and north to central Argentina.[424] No phytochemical investigations have been recorded on these plant species.

5 Conclusions

Research into the chemistry of the Hyacinthaceae has spanned over 90 years and resulted in the isolation of over 700 compounds. The need to understand the chemistry was largely fuelled by both the toxicity of the plants to stock and the significant ethnomedicinal applications associated with representative species. In addition to the isolation of many compounds of medicinal significance, the phytochemical studies have shed light on the classification of many of the species. A thorough understanding of the chemistry and pharmacology of these important plant species allows for the potential discovery of new medical applications and further aids the conservation of those taxa threatened with unsustainable utilisation by indicating alternatives with similarly active constituents.

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