

## Recent results from natural product research at the University of Botswana\*

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**Abstract:** Marketed plants are very important items of trade in many parts of the world. The community uses these for a variety of purposes such as foods, cosmetics, flavors, spices, and medicines. It seems that plants that are used for medicinal purposes form the most common category. Four plants used for treatment of microbial infections, viz., *Bolusanthus speciosus*, *Erythrina latissima*, *Crotalaria podocarpa*, and *Elephantorrhiza goetzei*, were investigated, and these yielded several known and novel structures, some with appreciable antibiotic activity against the test organisms. The activity of some of the isolated plants and the parts of the plant from which these were obtained lend support to their traditional use. *Bulbine abyssinica* and *B. capitata* yielded phenylanthraquinones, some of which were shown to possess strong antiplasmodial activity. In addition, these yielded isofuranonaphthoquinones, which were also found to be weakly antiplasmodial and antioxidant. *Scilla nervosa* yielded several known and novel homoisoflavonoids of the 3-benzylchroman-4-ones and 3-benzylidenechroman-4-one type, as well as some stilbenoids. The homoisoflavonoids showed strong antitumor activity against various cancer cell lines. *Rhus pyroides* gave a novel bichalcone, which showed weak antifeedant activity, consistent with the observation by farmers that the plant was avoided by corn cricket. Results from investigated *Dorstenia* species originating from Cameroon, Ethiopia, and Tanzania yielded styrenes, coumarins, chalcones, and flavonoids. The chalcones and flavonoids showed various levels of prenylation or geranylation, and an observation made so far is that prenylated flavonoids are only found in *Dorstenia* species of African origin. The only example of a bis-geranylated chalcone is found in *Dorstenia*.

### INTRODUCTION

The use of plants by man is an ancient practice, perhaps as old as man himself. Plants are particularly useful as medicines, flavors, foods, insect deterrents, ornamentals, fumigants, spices, and cosmetics. Generally, the economically useful plants are sold as commodities of commercial value, and those that are sold for medicinal purposes dominate the market. Of the plants sold for medicinal purposes, those that are used for treating microbial infections constitute the biggest group. Four plants chosen from this latter category, viz., *Bolusanthus speciosus*, *Erythrina latissima*, *Crotalaria podocarpa*, and *Elephantorrhiza goetzei*, were investigated, and both chemical and biological data on them will be discussed.

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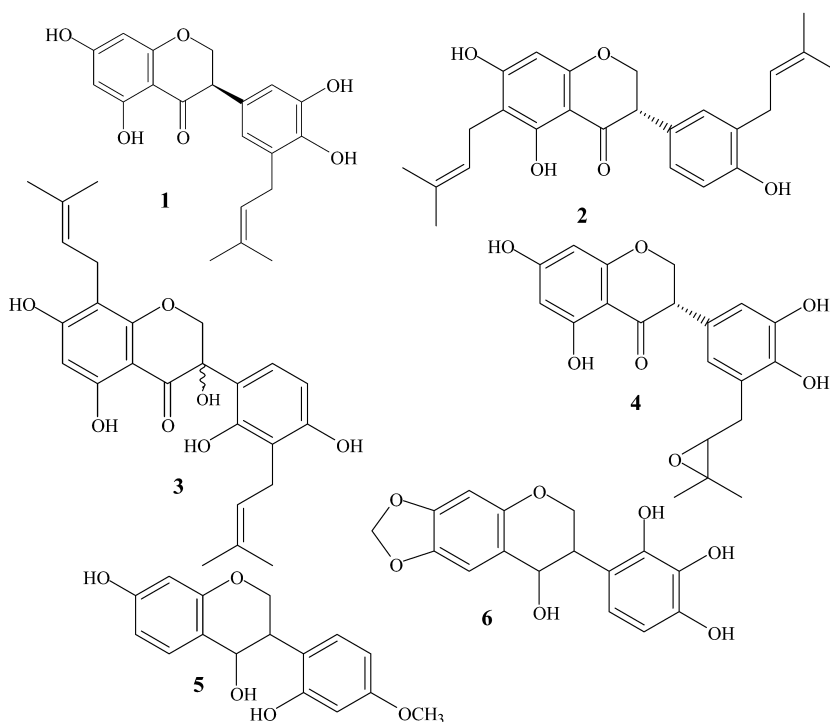
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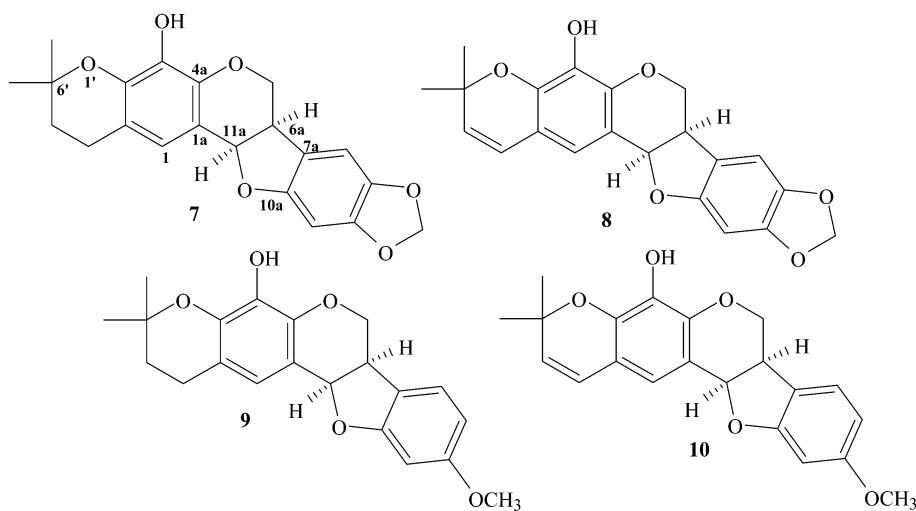
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The other area of active research is in quinone chemistry, particularly phenyl anthraquinones, which have recently generated much excitement owing to their potent antiplasmodial activity, representing a potentially new class of antimalarials. In this respect, work on *Bulbine abyssinica* and *B. capitata* will be presented. Species will be discussed. *Scilla nervosa* is used extensively as a medicine, either on its own or mixed with other plants, and results from work done on this plant will be presented. The observation by local farmers that the corn cricket avoids *Rhus* species prompted some work on *Rhus pyroides*. The corn cricket causes extensive damage to crops and hence could cause a great reduction in crop yields. Results from *Rhus* work will be presented. Finally, a summary on the recent work done on *Dorstenia* will be presented.

### **BOLUSANTHUS SPECIOSUS**

*Bolusanthus speciosus* Harms (Fabaceae), subfamily Papilionideae and tribe Sophoreae, commonly called tree wisteria, is a monotypic species that has a geographical distribution that extends from South Africa, through Botswana, Mozambique, and Zimbabwe to Zambia [1]. Besides its use as an ornamental plant, the dried inner bark of the tree is used to treat abdominal pains, emetism, and tuberculosis [2]. Previous work by other groups [3] on the leaves yielded quinolizidine alkaloids (*viz.*, lupanine, 5,6-dehydrolupanine, 6 $\beta$ -hydroxylupanine, cytisine, *N*-methylcytisine, 11 $\alpha$ -allylcytisine, anagryne, 13-hydroxyanagryne, sparteine, and  $\beta$ -isosparteine) while work on the seeds by us and other workers [4] gave genestein, orobol, 3'-methoxyorobol, pratensein, 3'-*O*-methylpratensein, and 3,5,7,3'-tetrahydroxy-4'-methoxyisoflavanone (bolusanthin). Further work by us [5–7] on the stem bark, twigs, and root wood of this plant gave six known compounds, *viz.*, lupeol, 5,7,3'-trihydroxy-4'-methoxy-5'- $\gamma$ , $\gamma$ -dimethylallylisoflavanone, 5,7,2'-trihydroxy-4'-methoxy-6,5'-di( $\gamma$ , $\gamma$ -dimethylallyl)isoflavanone, 3,5,7,3',4'-penta-hydroxy-6- $\gamma$ , $\gamma$ -dimethylallyl-flavone, 5,7,2',4'-tetrahydroxy-8,3'-di( $\gamma$ , $\gamma$ -dimethylallyl)-isoflavanone, and 5,4'-dihydroxy-6'',6''-dimethyl-4'',5''-dehydropyrano [2',3':7,8]-isoflavanone (derrone) and ten new compounds **1–10**.



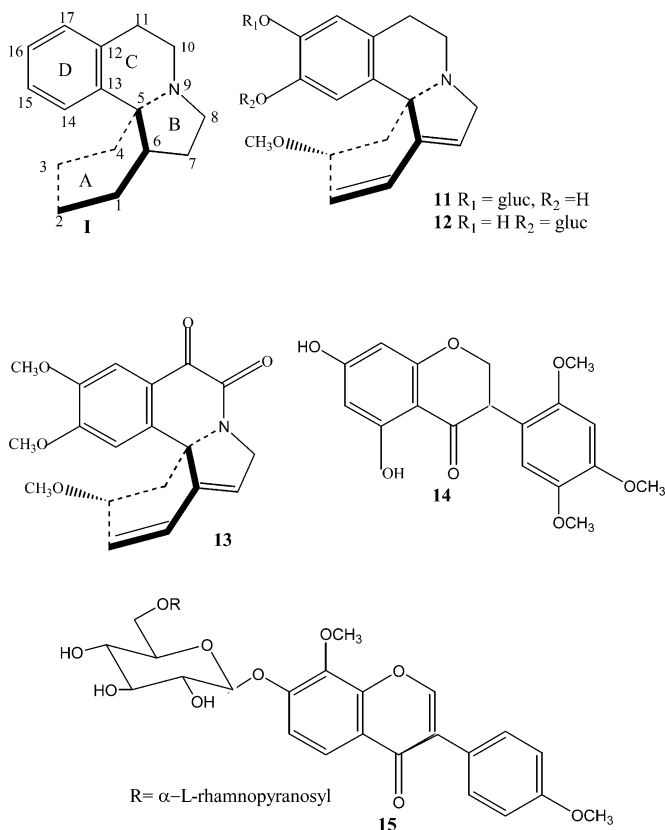


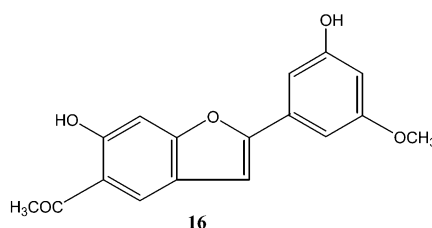
The antibiotic activity of the isolates was assessed using the thin-layer chromatography (TLC) bioautography agar overlay technique [8]. The isoflavonoids, in general, showed moderate to high antibacterial activity against *Bacillus subtilis* and *Staphylococcus aureus* and weak activity against *Escherichia coli*. The isoflavonoids (both known and new) all had 5,7,4'-oxygenation, and the most active had prenyl units at positions 6/3' or 6/5', while prenylation at 8/3' or 8/5' or 5' in that order led to reduced activity. The two isoflavan-4-ols (**5,6**) and the pterocarpans (**7–10**) displayed weak to no activity against the bacterial strains used. All isolated compounds showed moderate to weak activity against the yeasts *Saccharomyces cerevisiae* and *Candida mycoderma*.

### **ERYTHRINA LATISSIMA**

The genus *Erythrina*, a member of the Fabaceae family and subfamily Papilionideae, comprises over 110 species of trees, shrubs, and herbaceous plants that are widely distributed throughout the tropical warm regions of the world [9]. Seven species of *Erythrina* are found in southern Africa, viz., *E. caffra*, *E. decora*, *E. humeana*, *E. livingstoniana*, *E. lysistemon*, *E. abyssinica*, and *E. latissima*, with the latter three species found in Botswana [10]. *Erythrina* species are known to produce flavonoids, isoflavonoids, pterocarpans, triterpenoid saponins, and alkaloids. The alkaloids produced are of the erythrina-type, some of which have been shown to have curare-like activity on the central nervous system [11,12]. *E. latissima* E Meyer (Fabaceae) is a sturdy, small- to medium-sized deciduous tree with a spreading round crown, occurring in wooded grassland and shrub forest, often on hillsides. The name *Erythrina latissima* describes the red flowers (“erythro”) and wide leaves (“latissima”) the plant possesses and, it is a decorative tree commonly called the broad-leaved coral tree [10]. The bark of *E. latissima* is burnt and used as a dressing for open wounds [11]. Previous work on *E. latissima* concentrated mainly on the seeds and a number of erythrina-type alkaloids, all of which are dextrorotatory with 3R and 5S absolute stereochemistry, and having a classic skeleton **I**, were isolated. These were (+)-erythraline, (+)-11 $\beta$ -hydroxyerysodine, (+)-erythratidine, and (+)-erysosalvine [11]. In our detailed phytochemical investigation of the seeds, stem bark, root bark, root wood, and seed pods, (+)-erythraline was re-isolated along with six other known alkaloids—(+)-erysotrine, (+)-erysovine, (+)-erysodine, (+)- $\beta$ -D-glucoerysodine, (+)-8-oxoerythraline, and (+)-erysotramidine [11]. Three novel alkaloids, (+)-16 $\beta$ -D-gluco-erysopine **11**, (+)-15 $\beta$ -D-glucoerysopine **12** [14], and (+)-10,11-di-oxoerysotrine **13**, were also isolated. These compounds showed no antimicrobial activity against the tested organisms. However, preliminary results, from our collaborators in the United States, on (+)-erysotrine, (+)-ery-

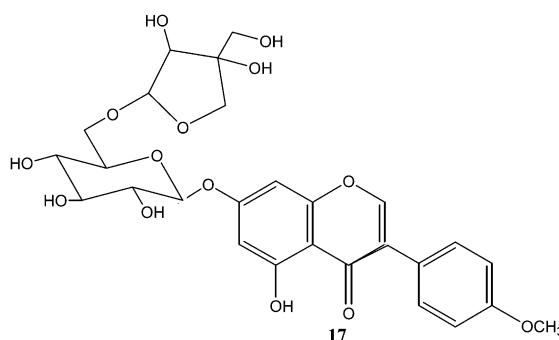
thraline, and (+)-erysodine in experiments on enzyme inhibition on Rb efflux stimulated nicotine from KX $\alpha$ 3 $\beta$ 4R2 cells and showed competitive inhibition. Seven flavanones were isolated and were identified as abyssinin II, sigmoidin B, abyssinone V, sigmoidin A, sigmoidin C, and abyssinone IV. These compounds showed strong antimicrobial activity against yeasts and gram-positive bacteria, but were only weakly active against gram negative bacteria. Seven isoflavonoids were isolated, and the first two were known genestein derivatives—prenylpratensein and erythranin B. These derivatives displayed weak to moderate antibiotic activity against test organisms. The other isoflavonoids were 7,4'-dihydroxy-3'- $\gamma,\gamma$ -dimethylallylisoflavone, 4'-hydroxyisoflavone-7-O- $\alpha$ -L-rhamnosyl(1 $\rightarrow$ 6)- $\beta$ -D-glucopyranoside, 4'-hydroxyisoflavone-7-O- $\beta$ -D-glucopyranoside, 5,7,3'-trihydroxy-4'-methoxy-5'- $\gamma,\gamma$ -dimethylallylisoflavanone, and two novel compounds—8,4'-dimethoxyisoflavone-7-O- $\alpha$ -L-rhamnosyl(1 $\rightarrow$ 6)- $\beta$ -D-glucopyranoside **15** [15] and 5,7-dihydroxy-2',4',5'-trimethoxyisoflavanone **14** [16]. Only 7,4'-hydroxy-3'- $\gamma,\gamma$ -dimethylallylisoflavone strongly inhibited growth of the yeasts *C. mycoderma* and *S. cerevisiae* and gram-positive bacteria, but was only mildly active against gram-negative bacteria. The rest of these isoflavonoids were only mildly active against gram-positive bacteria. The four pterocarpan isolated were identified as erybraedin A, neorautenol, isoneorautenol, and shinpterocarpin, and these showed strong antifungal activity against the test organisms and moderate activity against gram-positive bacteria. Furthermore, a lignan 4-hydroxy-3,5-dimethoxy-7,9':7',9'-diepoxylignan (syringaresinol), a long chain ferulic ester, (E)-octacosyl-3-(4-hydroxyphenyl)-2-propenoate, and a novel aurone, 2-(5'-hydroxy-3'-methoxyphenyl)-6-hydroxy-5-methoxybenzofuran **16** were also isolated. Compound **16** was very active against fungi and gram-positive bacteria and showed moderately good activity against gram-negative bacteria. This was the most active compound isolated so far and displayed a somewhat broad spectrum of activity against gram-positive, gram-negative bacteria and fungi. More tests are currently conducted on the compound.





### **CROTALARIA PODOCARPA**

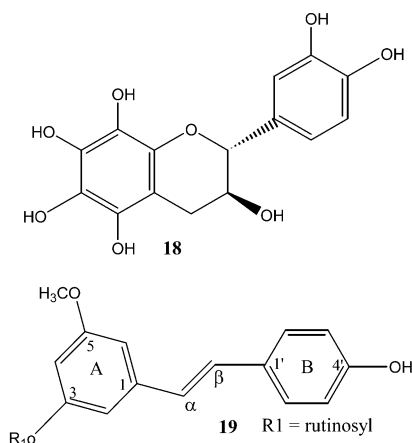
The genus *Crotalaria* (Fabaceae) is a member of the subfamily Papilionideae. These are annual or perennial herbs with alternate, simple or compound leaves. There are over 300 species of *Crotalaria* worldwide, and 60 are found in southern Africa [17]. The genus is known to produce mainly pyrrolizidine alkaloids [18], but flavonoids [19], pterocarpans [20,21], and chalcones [22,23] are also reported. Traditionally, *C. podocarpa* is used as an expectorant, anti-inflammatory, and for treatment of sore eyes and boils [24–25]. Work prior to this on *C. podocarpa* gave 7-hydroxy-1-methelenepyrrolidine [26]. Our group isolated apeginin-7-*O*- $\beta$ -D-apiofuranosyl-(1 $\rightarrow$ 6)-glucopyranoside and novel compound acetetin-7-*O*- $\beta$ -D-apiofuranosyl-(1 $\rightarrow$ 6)-glucopyranoside **17** [27], and this was the first report of flavonoids from *C. podocarpa*. The first compound was weakly active against *B. subtilis* and *S. aureus*. No alkaloids were isolated, but the use of *C. podocarpa* as medicine requires caution since pyrrolizidine alkaloids have been reported in *Crotalaria* species, which poses a potential health hazard to humans and livestock in southern Africa. Animals that ingested some *Crotalaria* plants manifested a whole range of pathological symptoms, in most cases fatal, associated with liver poisoning, a confirmation of the hepatotoxicity of these alkaloids [28]. Continual ingestion of *Crotalaria ssp.* also leads to deformation of hooves in cattle and horses, a condition called crotalariosis [28]. The meager antibacterial activity shown by the extract and isolated compounds does not justify the use of *C. podocarpa* for medicinal purposes, and the community should be advised against using these plants.



### **ELEPHANTORRHIZA GOETZEI**

The genus *Elephantorrhiza* is a member of the Fabaceae family and subfamily Mimosoideae and consists of shrubs, small trees, or low bushes springing from underground rhizomes [13]. Ten species of *Elephantorrhiza* are found in Africa with only four found in southern Africa, viz., *E. burkei*, *E. elephantina*, *E. goetzei*, and *E. suffruticosa* [28]. *Elephantorrhiza* species are known to produce flavonoids, gallic acid derivatives, esterified sugars, and simple phenolic derivatives [29]. *Elephantorrhiza goetzei* Harms is found in northeastern Botswana and is used medicinally as a remedy for sores of the penis and vulva, irregular menstruation, and for cleansing the womb after abortion [28]. Preliminary antimicrobial tests on the crude aqueous ethanolic extract of *E. goetzei* gave impressive activity against all test

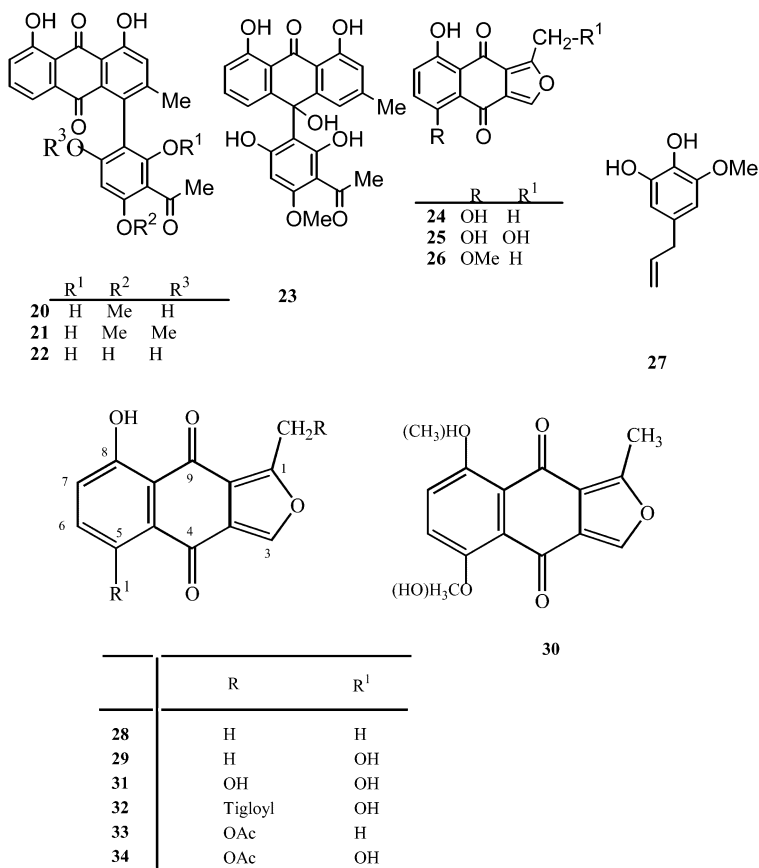
organisms, and phytochemical work led to the isolation of (+)-catechin, gallic acid, methyl gallate, 2(3',4'-dihydroxyphenyl)ethanol, a novel compound 3,3',4',5,6,7,8-heptahydroxyflavan **18** [30], (+)-gallocatechin and (–)-epigallocatechin as an enantiomeric mixture, sericoside, arjungenin, and the resveratrols, *viz.*, [E]-resveratrol, [E]-resveratrol-3-*O*-rutinosyl, and 5-methoxy-[E]-resveratrol-3-*O*-rutinosyl, **19**, as a novel compound [31]. Compound **19** and arjungenin showed weak to moderate activity against gram-positive bacteria and fungi, while gallic acid and methyl gallate were only weakly active against gram-positive bacteria.



## BULBINE

Phenyl anthraquinones are a new class of antiplasmodial compounds. This remarkable observation was made by Bringmann *et al.* when it was revealed that Knipholone anthrone and related substances possess antiplasmodial activity comparable or only slightly lower than that of chloroquine itself [32]. Knipholone was first reported from the African plant, *Kniphofia foliosa*, by Dagne and Steglich in 1984 [33]. Further work by Dagne's group in Addis and Abegaz's group in Botswana has revealed that this important class of compounds are present in *Kniphofia* [34], *bulbinella* [35], and *Bulbine* species [36,37]. Two plants belonging to the genus *Bulbine* are sold as medicinal plants in Botswana, and these are *Bulbine capitata* and *B. abyssinica*. Studies on these plants resulted in the isolation of a number of phenyl anthraquinones including knipholone itself (**20**), 6'-*O*-methylknipholone (**21**), 4'-demethylknipholone (**22**), and foliosone (**23**). The antiplasmodial activity of the phenylanthraquinones appears to be intrinsically associated with the stereogenic axis of the molecule since it has been shown that neither chrysophanol nor phloracetophenone possess any significant antiplasmodial activity. Many structurally related synthetic substances were also tested and found to be devoid of any activity ( $IC_{50}$  values were above 10  $\mu$ m). The unique attributes of knipholone have been the motivations for the work that led to the determination of the absolute configuration (**20**) as *M* by quantum chemical CD calculations [38]. Also, the first, atropo-enantioselective total syntheses, both of knipholone and 4'-*O*-demethylknipholone, was recently reported. This has opened up the possibility to explore various approaches to generate sufficient quantities of these phenyl anthraquinones for pharmacological evaluations. The group in Gaborone is exploring further sources for these class of substances. In this effort, investigations of *Bulbine* species indicated that this genus is also rich in yet another rare class of secondary metabolites, *viz.*, isofuranonaphthoquinones. Only fewer than 20 such compounds are known from natural sources with nearly half of them obtained from *Bulbine* plants in Botswana (**24–26**, **28–34**). Recent reports based on collaboration of our group with Australian researchers have indicated that isofuranonaphthoquinones possess appreciable antioxidant and weak antiplasmodial activities [39]. It is interesting to speculate the potential of these plants that contain the more active

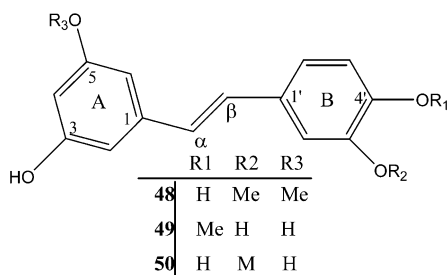
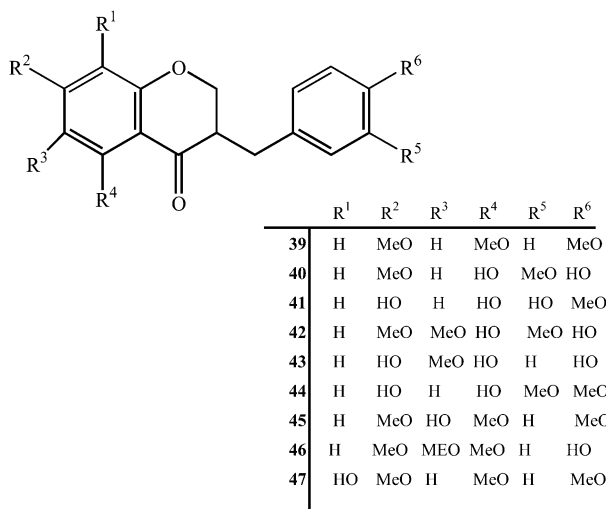
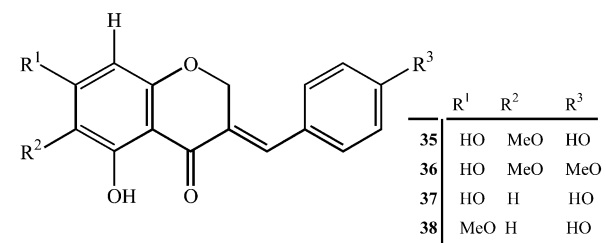
phenyl anthraquinones and the lesser active isofuranonaphthoquinones as potential phytomedicines for the treatment of malaria.



### SCILLA NERVOSA SUBSP. RIGIDIFOLIA

The genus *Scilla* is believed to globally represent 80 taxa. Four species occur in southern Africa, of which *Scilla nervosa* is the only member known to occur in Botswana [40,41]. This plant is important in Zulu medicine and is used to treat pains associated with rheumatic fever and as purges for children. In Botswana, the plant is alleged to enhance female fertility and to treat infections. Prior to work done by our group, there have been no published reports dealing with the chemical constituents of this plant, except a report that was published almost simultaneously by a group in Natal University, South Africa [42]. The results of our studies on the bulbs of *S. nervosa* (Burch.) Jessop sub-species *rigidifolia* (Hyacinthaceae) yielded 13 homoisoflavonoids, 4 of which were 3-benzylidenechroman-4-ones (**35–38**), and 9 were 3-benzylchroman-4-ones (**39–46**). Nine of these 13 compounds, viz., 3-(4-methoxybenzyl)-5,7-dimethoxychroman-4-one, **39**, 3-(4-hydroxy-3-methoxy benzyl)-5-hydroxy-7-methoxychroman-4-one, **40**, 3-(4-methoxybenzylidene)-5,7-dihydroxy-6-methoxychroman-4-one, **36**, 3-(4-hydroxybenzylidene)-5-hydroxy-7-methoxychroman-4-one, **38**, 3-(4-hydroxy-3-methoxybenzyl)-5-hydroxy-6,7-dimethoxychroman-4-one, **42**, 3-(3,4-dimethoxybenzyl)-5,7-dihydroxychroman-4-one, **44**, 3-(4-methoxybenzyl)-6-hydroxy-5,7-dimethoxychroman-4-one, **45**, 3-(4-hydroxybenzyl)-5,6,7-trimethoxychroman-4-one, **46**, and 3-(4-methoxybenzyl)-8-hydroxy-5,7-dimethoxychroman-4-one, **47**, were reported here for the first time [43]. Three known stilbene derivatives **48**, **48**, and **50** were also identified. Current work on compounds isolated from this plant show them to have antitu-

mor activity. Few of the isolated compounds were shown to be actually tumor-promoting on some cancer cell lines.



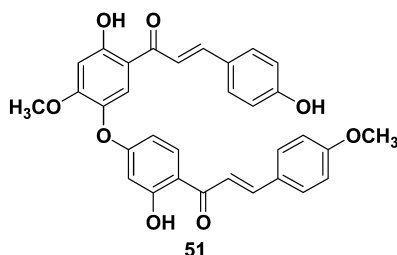
## RHUS PYROIDES

The genus *Rhus* consists of *ca.* 200 species and is known to be rich in biflavonoids. Interest in biflavonoids has increased in recent times due to the realization of a variety of biological activities manifested by them. Biflavonoids agathisflavone, robustaflavone, and hinokiflavone from *Rhus succedanea* have been shown to have HIV-1 reverse transcriptase activity [44]. Hinokiflavone was identified as one of 65 natural flavonoids to inhibit the interleukin-1 $\beta$ -induced procoagulant activity of adherent human monocytes [45].

*Rhus pyroides* is a shrub growing to a medium-sized tree found widely distributed in the eastern part of Botswana. It has been observed that this plant is avoided by the corn cricket (*Heterodes popus* L) (private communication between Dr. J. Woollard and local farmers), which often invades agricultural farms and devours a wide range of crops and plants. Intrigued by this observation, we decided to investigate the plant in an effort to identify possible antifeedants from the plant and isolated and characterized a novel bichalcone, rhuschalcone-1, **51**, which has weak antifeedant activity [46]. More bichal-



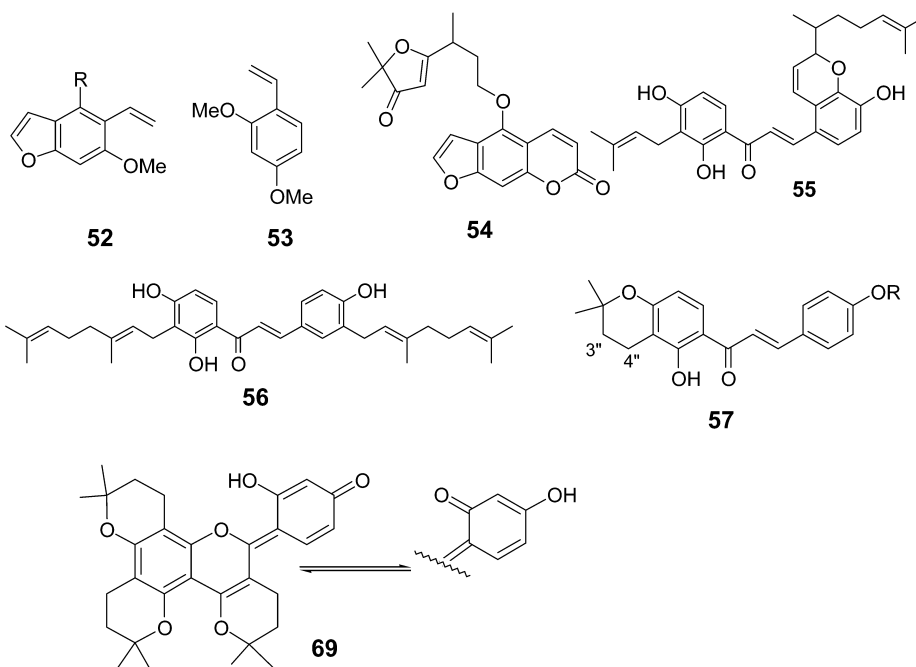
cones have since been isolated, and a total chemical synthesis of one of these bichalcones has been achieved. Results just received from our collaborators show these compounds to have strong anticancer activity.



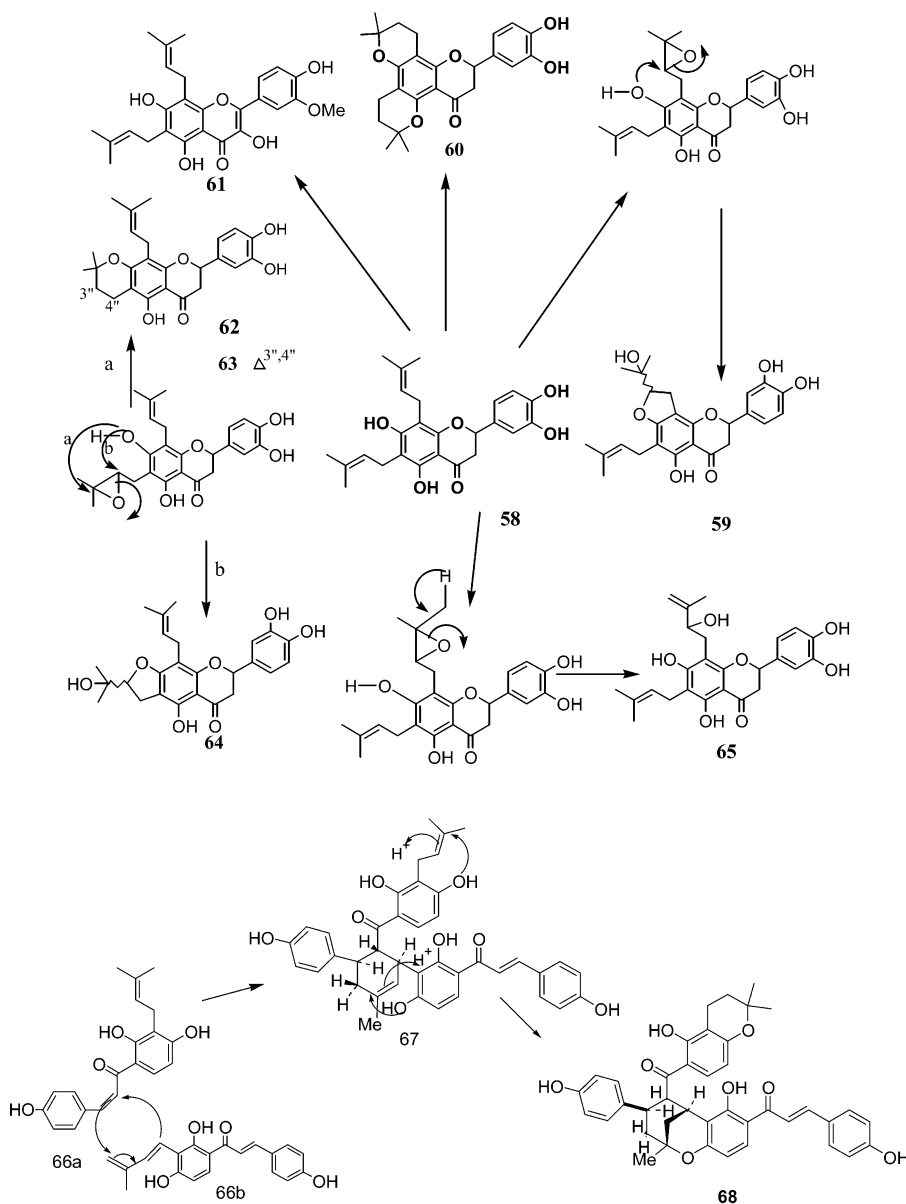
## DORSTENIA

The genus *Dorstenia* (Moraceae) is represented by about 170 species worldwide. There is now increasing interest in this genus, during the last decade close to 40 papers have appeared dealing with investigations of over 25 *Dorstenia* species. These reports appear to be based on studies conducted from plants originating in Brazil, Cameroon, Ethiopia, Mexico, Panama, and Tanzania. Our own work is based on 13 species of plants from Africa. Many *Dorstenia* species have significant medicinal values in the culturally developed medical practices of many countries. Interestingly, different species of this genus are used as snakebite remedy in many communities. *D. psilurus* in Cameroon, *D. brasiliensis* in Brazil, and *D. contrajerva* in Panama and Mexico are used for such purposes. In Addis Ababa, Ethiopia, *D. barnimiana* (vernacular name: *Worq bameda*) is an important medicinal plant, and the tubers are sold in Merkato for the treatment of a variety of diseases, but most significantly as a remedy for gout [47]. In Cameroon, these plants are generally used to treat infections and wounds. *D. elleptica* is particularly used for the treatment of eye infections. "Carapia" is a drug formulation based on *Dorstenia* species in the cultural medicine of Brazil used for the treatment of skin diseases.

The first examples of naturally occurring styrenes (**52,53**) were reported from *D. barnimiana* [47]. The geranyl-substituted furocoumarin (**54**) has been found in many species. *D. poinsettifolia* fur-



nished the unusual 4-phenyl-substituted dihydrocoumarin, and the rare geranyl- and prenyl-substituted chalcone (**55**). Prenylated flavonoids have so far been reported from African *Dorstenia* only. Compound **56** from *D. proropens* is the only example of a bis-geranylated chalcone in the literature [48] *D. manni* furnished the novel chalcone (**57**), and many more prenylated flavonoids, some of which (**58–65**) are shown below, have been isolated from *D. manni*. Many of these dorsmannins appear to be derived from 6,8-diprenyleriodictyol, and a possible biosynthetic scheme for them is presented. Compound **68** was reported from *D. zenkeri* and is believed to arise from **67**. The latter is probably formed via an enzymatic Diels–Alder reaction of isobavachalcone (**66a**) and its dehydroderivative (**66b**). *D. psilurus* provided all the triprenylated compounds found in *Dorstenia*, and of these, **69** is unique in having ring B of the flavonoid structure modified to a dienone [48]. The pharmacological data on this genus are scanty. Extracts of *D. multiradiata* show antileishmanial activity. Extracts and/or compounds from other species show anti-inflammatory, analgesic, anti-oxidant, and cytotoxic activities.



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