Chapter 2

Chemistry of South African Lamiaceae: Structures and Biological Activity of Terpenoids

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Additional information is available at the end of the chapter

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Abstract

South Africa flora is one of the most important mega floras with high endemic species percentage. Lamiaceae is an important family in South Africa with ±308 species in 41 genera and contains many important plants (~23%) traditionally used for treatment of different human diseases. The chemical profile of Lamiaceae is very rich in terpenoids in general and more specifically diterpenes. Genera like *Leonotis* and *Plectranthus* are well studied, while on the other hand, genus like *Stachys* (~41 species, ~50% endemic) didn't receive any attention. Different classes of diterpenes were identified and some of them demonstrating important biological activities.

Keywords: South African flora, Lamiaceae, *Leonotis*, *Plectranthus*, chemical constituents, terpenoids

This work is dedicated to Prof. Benjamin Rodriguez (Instituto de Quimica Organic General, CSIC, Spain) for his contributions in the field of natural products and specially in the chemistry of Lamiaceae family.

1. Introduction

The Green economy concept has been driven as an urgent need for addressing global challenges in vital fields like energy, environment, and health. Green economy is expected to play a very important role in changing the way that society manages the interaction of the environmental and economic domains. Consequently, a new paradigm has been established and shifted toward green economy or green growth. Natural products represent one of the most important elements required to build safe and effective economy especially in health sector. South Africa (SA) is recognized as one of the most biodiverse

country in the world with 20,456 indigenous vascular plant taxa recorded where 13,265 (65%) are endemic [1, 2].

The Lamiaceae (formerly Labiateae, mint family) is a cosmopolitan family with ~7136 species in 236 genera. Most species are shrubby or herbaceous and trees are extremely rare [3]. The Lamiaceae family has great economic value, as it contains several horticultural species, most of which are used as culinary herbs like salvia, rosemary, ocimum, mint, *Leonotis*, etc. Lamiaceae species are known to contain pharmacologically active terpenoids with a wide spectrum of bioactivity and expected to play more important roles in the process of drug discovery as well as cosmetic, food, and pesticides industries [4–6]. In the Sub-Saharan region, ~60 genera with ±980 species were reported [7]. SA considers as a diversity spot of Lamiaceae with ±308 species in 41 genera [8]. The species occur predominantly in the summer and/or winter rainfall areas. The habitats are different and vary to a great extent [9].

However, the South African flora is one of the most important mega floras for its unique diversity and endemism, it receives low attention in terms of bioprospecting, and the number of research paper every year dealing with chemical/biological profiling is still beyond the required level. This review serves as a background for the chemistry of all species belonging to the family Lamiaceae growing in SA and it covers publications till 2017. The articles information's abstracted from Sci-finder database [10] and includes all species growing in SA as well as other places. This chapter doesn't cover the essential oils and *Plectranthus barbatus*, which recently reviewed by others [11, 12].

2. Terpenoids of different genera of South African Lamiaceae

Different classes of secondary metabolites have been identified from Lamiaceae, the majority of the isolated compounds are terpenoids (~71%), and additionally other classes of compounds like flavonoids, α-pyrone derivatives, phenolic acids, and alkaloids were reported. Mono-, sesqui-, and tri-terpenoids are relatively small in number (~15%) when compared to diterpenoids and it was reported that more than 100 of different diterpene skeletons were identified which indicate the high evolutionary index of Lamiaceae [13]. According to the literature, the genera *Leonotis* (known as wild dagga) and *Plectranthus* have received the highest attention where 70 (*Leonotis*) and 94 (*Plectranthus*) compounds were identified so far, the majority of the isolated compounds are labdane diterpenes. In this chapter, the different genera have been listed alphabetically and the trivial names have been retained in the cases where they were given by authors and/or chemical abstracts.

2.1. *Aeollanthus* genus

Aeollanthus genus represented by 43 species globally and 7 in SA. From *A. buchnerianus,* an abietanediterpene,[(rel)-14α-acetoxyabiet-7-en-18-oicacid](**1**)[14],3β-acetoxy-7,15-isopimaradiene

(**2**), 3*β*-acetoxy-7,15-isopimaradien-19-ol (**3**) and 19-acetoxy-7,15-isopimaradien-3*β*-ol (**4**), 7,15-isopimaradien-19-ol (**5**, akhdarenol) and 7,15-isopimaradien-3*β*,19-diol (**6**, virescenol), a mixture of 19-isobutyryloxy- and 19-butyryloxy-8*β*-hydroxy-15-isopimarene (**7**), and a 3:1 mixture of 5-stigmasten-3*β*-ol and *β*-sitosterol were isolated from the aerial parts of *A. rydingianus*. 5 and 6 showed activity against *S. aureus* and *Enterococcus hirae* [15].

2.2. *Ballota* genus

Ballota is represented by one species in SA *vizB africana*. Hispanolone (**8**) was isolated from the aerial parts [16].

2.3. *Cedronella* genus

Cedronella genus is represented by only one species in SA *viz C. canariensis*. The phytochemical studies of the aerial parts resulted in isolation of a dimer of *d*-pinocarvone (**9**), cedronellone (**10**), and ursolic acid (**11**) [17].

2.4. *Clerodendrum* genus

Seven species were recorded in SA and clerodendrumic acid (**12**) was isolated from *C. glabrum* var. *glabrum* and showed weak antifungal, antibacterial, and cytotoxic activities [18].

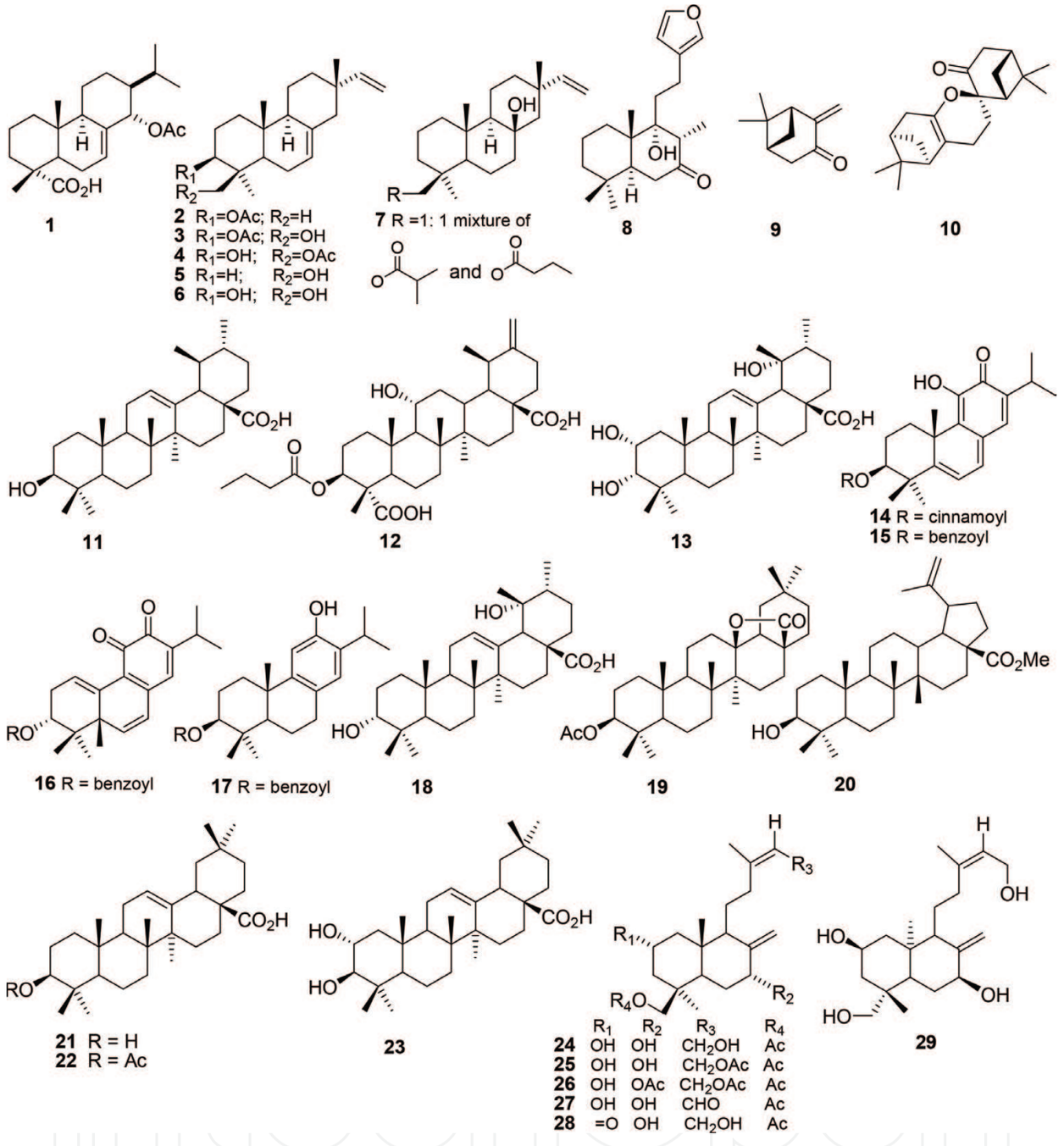
2.5. *Hoslundia* genus

Hoslundia genus is represented by one species in SA *vizH. opposite*. The phytochemical studies of the aerial parts yielded an interesting and rare pyrano and furanoflavonoid derivatives in addition to euscaphic and (**13**) ursolic acid (**11**) [19, 20]; four abietane-type esters, 3-*O*-cinnamoylhosloppone (**14**), 3-*O*-benzoylhosloppone (**15**), 3-*O*-benzoylhosloquinone (**16**), and 3-*O*-benzoylhinokiol (**17**); 13 was found to exhibit MIC of 50 μg/mL against *M. tuberculosis*, while 14 inhibits the growth of the MDR strain K_1 of *Plasmodium falciparum* in vitro with an IC_{50}-value of 0.4 μg/mL [21].

2.6. *Hyptis* genus

Three species were recorded in SA. The triterpenes 3*α*,19*α*-dihydroxyurs-12-en-28-oic acid (**18**) and 3*β*-acetoxyoleanan-13*β*,28-olide (**19**), Me betulinate (**20**), oleanolic acid/acetate (**21/22**), and ursolic (**11**) and maslinic acids (**23**) were isolated from *H. mutabilis* [22].

From *H. spicigera*, seven labdane diterpenes; 19-acetoxy-2*α*,7*α*,15-trihydroxylabda-8(17),(13*Z*)-diene (**24**); 15,19-diacetoxy-2*α*,7*α*-dihydroxylabda-8(17),(13*Z*)-diene (**25**); 7*α*,15,19-triacetoxy-2*α*-hydroxylabda-8(17),(13*Z*)-diene (**26**); 19-acetoxy-2*α*,7*α*-dihydroxylabda-8(17),(13*Z*)-dien-15-al (**27**); 19-acetoxy-7*α*,15-dihydroxylabda-8(17),(13*Z*)-dien-2-one (**28**); 2*α*,7*α*,15,19-tetrahydroxy-ent-labda-8(17), (13*Z*)-diene (**29**); and 19-acetoxy-2*R*,7*R*-dihydroxylabda-14,15-dinorlabd-8(17)-en-13-one (**30**) were isolated from the aerial parts [23].



2.7. *Leonotis* genus

Seven species were recorded in SA and two of them were extensively studied. Traditionally, this genus is used to substitute hemp and called as wild dagga; however, there is no much scientific biological evidences supporting such claim. The chemistry was started in early 60s of the last century by South African researchers. Many labdane diterpenes have been

isolated. The chemistry of the genus was covered previously by a review published by Piozzi et al.[24].

2.7.1. Leonotis leonurus

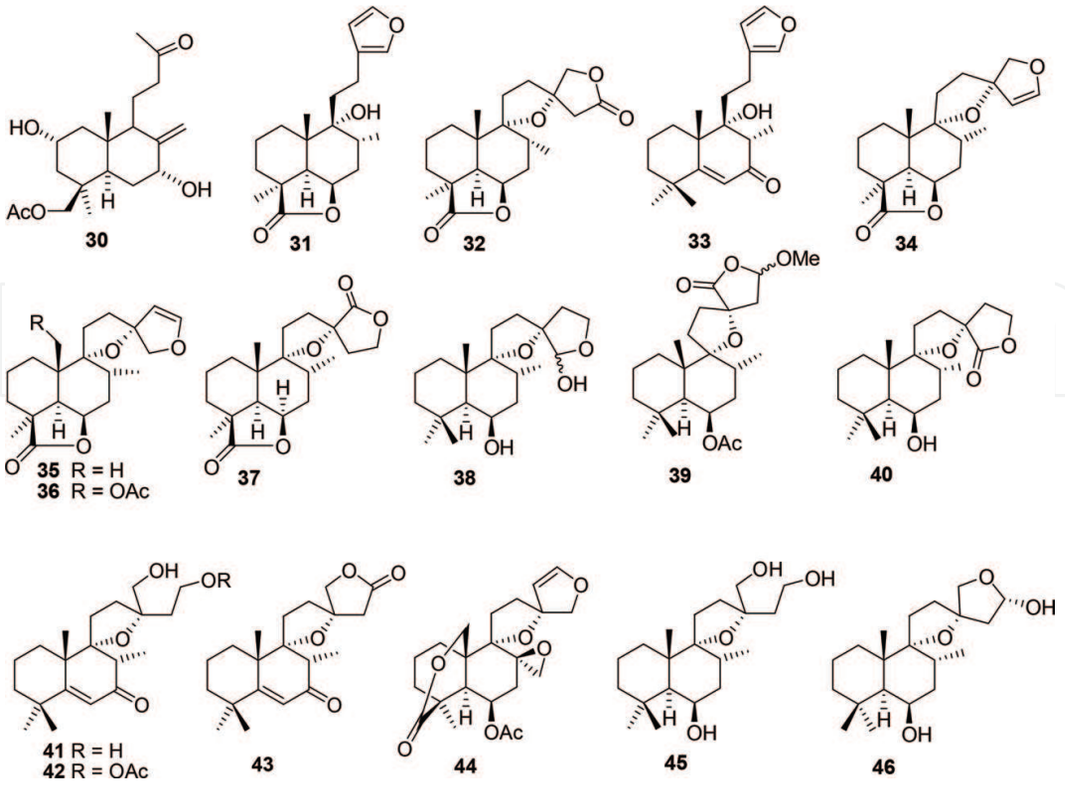
The chemistry of *Leonotis* was commenced in 1962 and some compounds were identified; marrubiin (**31**) compounds, X (**32**) and Y (**33**), the stereoisomers of premarrubiin (**34**) and (**35**) (the *C*-13 epimeric forms of premarrubiin). Leonurun (**36**) has been isolated and the relative stereochemistry was determined using single-crystal X-ray diffraction analysis [24, 25]. After two years, labdane (13*S*)-9α,13α-epoxylabda-6β(19),15(14)-dioldilactone (**37**) was isolated, this compound caused significant changes in blood pressure of anesthetized normotensive rats, and also was found to exhibit a negative chronotropic effect [26].

The organic extract of *L. leonurus* showed 99% growth inhibition against *M. tuberculosis* at 1.0 mg/mL, subsequent phytochemical studies resulted in the identification of three labdane-type diterpenoids: 9,13:15,16-diepoxy-6,16-labdanediol (**38**), 6-acetoxy-9,13-epoxy-15-methoxy-labdan-16,15-olide (**39**), and 9,13-epoxy-6-hydroxylabdan-16,15-olide (**40**). None of the isolated compounds were active against *M. tuberculosis* [27].

Recently, Fang et al. [28] identified leonurenones A–C (**41–43**), in addition to 9,13:15,16-diepoxy-6,16-labdanediol (**38**) and nepetifolin (**44**). The leonurenones contain an uncommon α,β-unsaturated enone moiety in ring B. Compound **38** was isolated as epimeric form, (at C-16, ratio 3:1). Compound **41** was isolated from aqueous extract of the leaves and the authors proposed the possible formation of **43** as an artefact *via* oxidation and lactonization of the more polar intermediate (**41**) during the isolation process. The total aqueous extract, at concentration of 1.0 g/mL, showed an 81% inhibition in a binding assay at the GABAA site. Compounds **41** and **43** did not show activity (<50% inhibition) in this assay [28].

In the following year, Wu and co-workers (2013) were successful to isolate and identify eleven labdanoides, *viz* leoleorins D–J (**41–43**, **45–48**) and 16-epi-leoleorin F (**49**), leoleorin A [corresponding to compound Y (**33**)], leoleorin B (**50**) (anhydro derivative of compound Y), and leoleorin C [9,13-epoxy-6-hydroxylabdan-15,16-olide (**40**)]. The absolute configurations of leoleorin A (**33**) and D (**41**) were established by X-ray crystallographic analyses. It is important to indicate that new compounds "leoleorins G-I", which were isolated in this study, were reported in the previous work under the names of leonurenones A–C **(41–43)** (^{13}C data showed exchange positions C_{12} and C_{14} for leonurenones C/leoleorin H between the two references) [29].

From *L. leonurus*' flowers, an acyclic diterpene ester, 1,2,3-trihydroxy-3,7,11,15-tetramethyl-hexadecan-1-yl-palmitate (**51**), along with geniposidic acid (**52**) were isolated, the compounds exhibited neither cytotoxicity on mammalian kidney fibroblasts (Vero cells) nor antimicrobial activities [30].

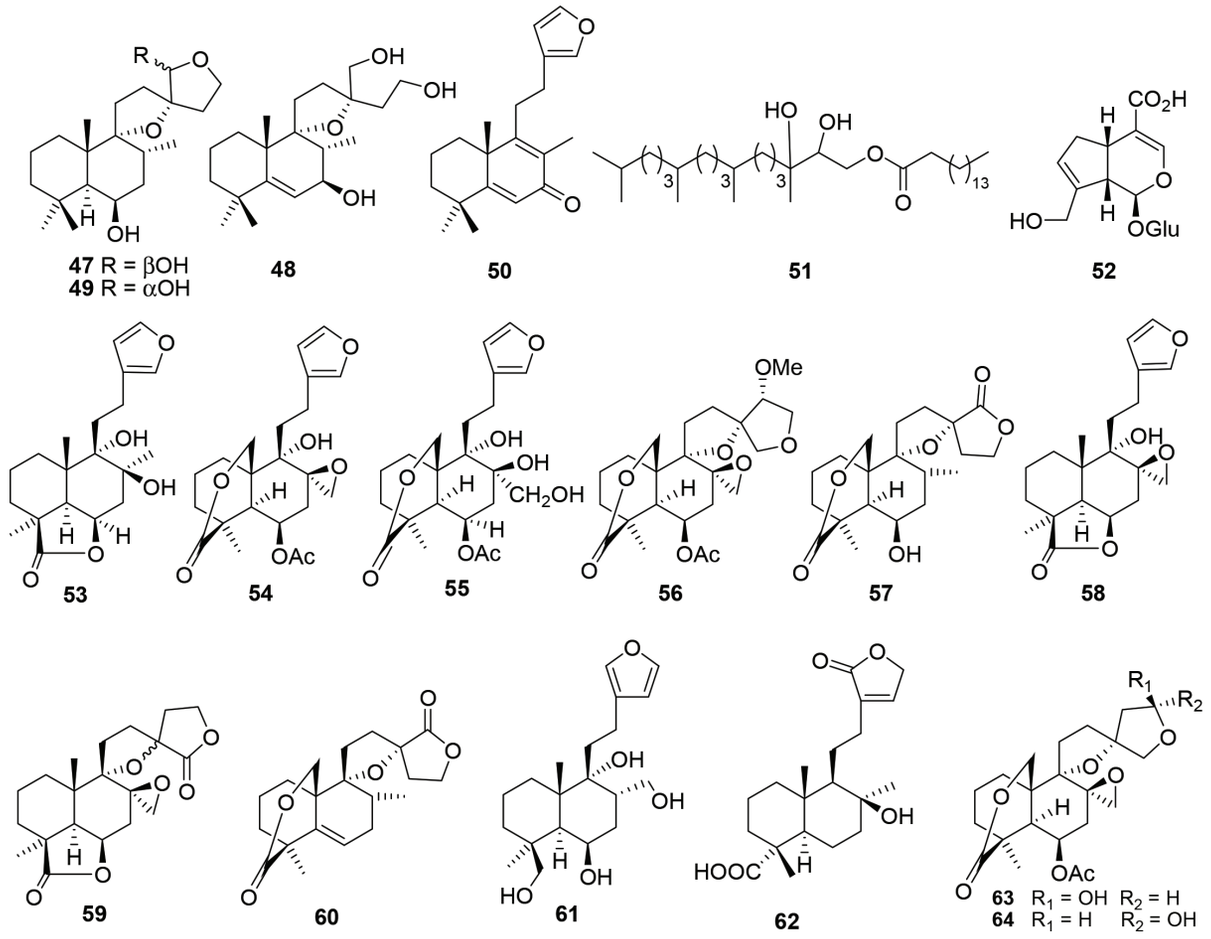


2.7.2. Leonotis nepetaefolia

The chemistry of *L. nepetaefolia* started almost simultaneously with *L. leonurus*. Leonotin (**53**), nepetaefuran (**54**), nepetaefuranol (**55**), nepetaefolin (**44**) methoxynepetaefolin (**56**), nepetaefolinol (**57**) and leonotinin (**58**) the dilactone (8*β*,17,9,13-diepoxylabdane-16,15,19,6*β*-diolactone, **59**) were characterized [31–36].

From the species collected from India, nepetaefolinol (**57**), dehydrated nepetaefolinol (**60**) and isomeric tetrol (**61**) (15,16-epoxy-labda-13(16),14-diene-6*β*,9,17,19-tetrol: the reduction product of leonotinin) were identified [37]. Leonitinic acid (**62**) with free C-17 carboxyl group was also isolated [38].

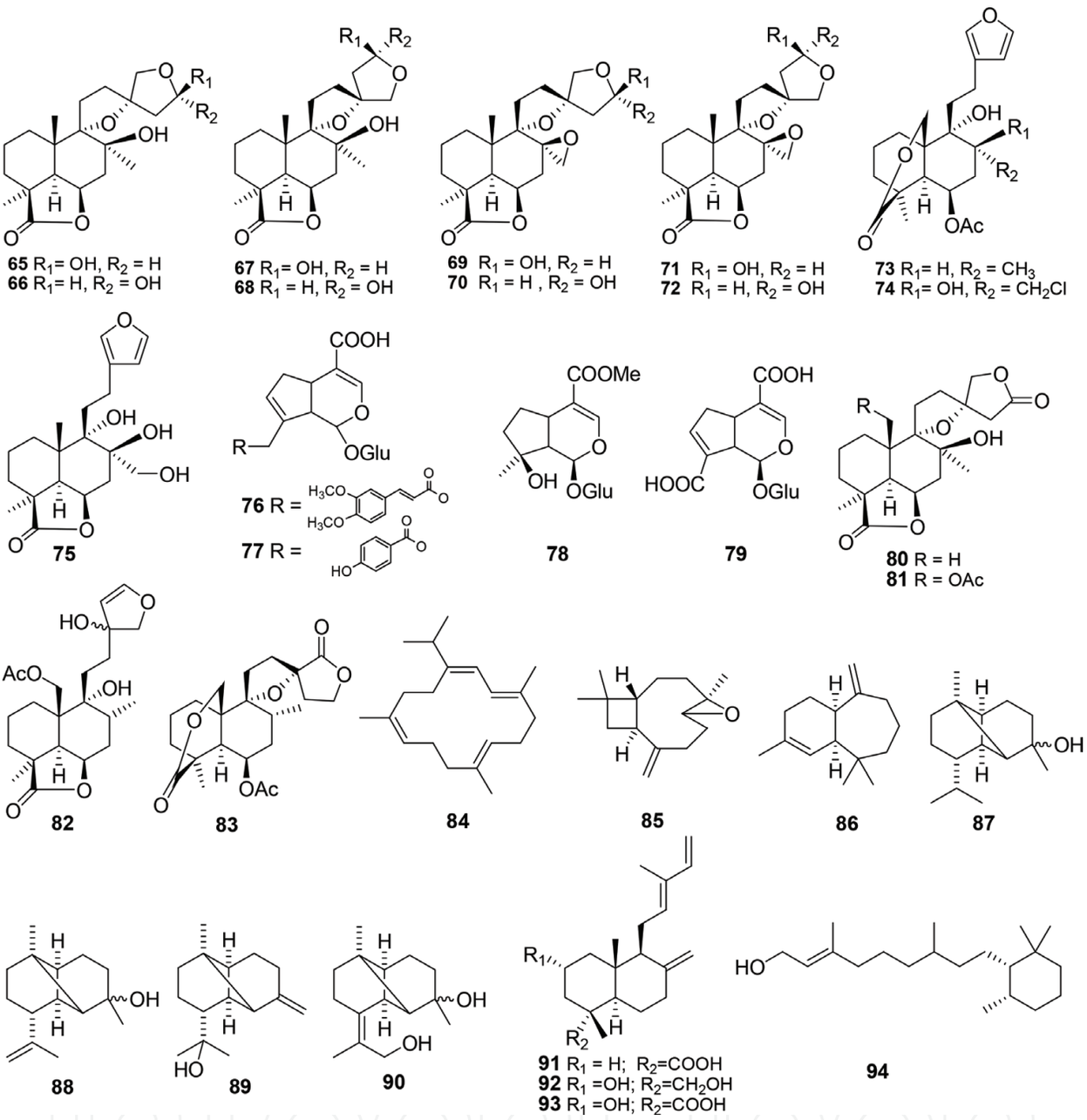
From a commercially material, originally collected from Peru, five inseparable epimeric mixtures of bis-spirolabdane diterpenoids, resulted from biosynthetic epimerization of three different structures around C-13 and C-15, have been isolated and identified as leonepetaefolin A (**63**) and its epimeric isomer 15-epi-leonepetaefolin A (**64**) (ratio 1:1), leonepetaefolin B(**65**)/15-epi-leonepetaefolin B (**66**) (2:3), leonepetaefolin C(**67**)/15-epi-leonepetaefolin C (**68**) (1,1), leonepetaefolin D (**69**)/15-epi-leonepetaefolin D (**70**) (7,10), leonepetaefolin E (**71**)/15-epi-leonepetaefolin E (**72**) (2,3) [39]. Additionally, methoxynepataefolin (**56**), nepetaefolin (**44**), nepetaefuran (**54**), dubiin (**73**), 19 chlroro derivative of nepetaefolin (**74**), leonotinin (**58**), leonotin (**53**), and LS-1 (**75**) were isolated. The absolute configuration of the epimeric mixture **63** and **64** was determined by X-ray crystallographic analysis [39].



The isolated compounds were evaluated for their binding activities to a panel of CNS G-protein-coupled receptors including adrenergic, dopaminergic, histaminic, muscarinic, opioid, and serotonergic receptors and neurotransmitter transporters and showed no interesting activity.[39]. From the material collected from Japan, five iridoid glycosides: 10-*O*-(*trans*-3,4-dimethoxycinnamoyl) geniposidic acid (**76**), 10-*O*-(*p*-hydroxybenzoyl) geniposidic acid (**77**), geniposidic acid (**52**), mussaenoside (**78**), and ixoside (**79**) were isolated [40].

2.7.3. Leonotis ocymifolia

L. ocymifolia was studied under different synonyms *viz*; *L. dubia* (*L. ocymifolia*, var. *ocymifolia*), *L. leonitis*; *L. leonitis* var. *hirtfolia* (*L. ocymifolia*, var. *ocymifolia*) and *L. dysophylla* Benth. (*L. ocymifolia* var. *raineriana*) and *L. ocymifolia* var. *raineriana* (Burm f) Iwarsson var. *raineriana* (Visiani) Iwarsson. The chemical studies resulted in the isolation of dubiin (**73**), 9α,13(*S*)-epoxy-8β-hydroxylabdane-6β,19;16,15-diolide (**80**), and leonitin (**81**). 20-acetoxy-9α,l3-dihydroxy-15(16)-epoxylabd-14-en-6β(19)-lactone (**82**) and 6β-acetoxy-9α,l3α-epoxylabda-20(19),16(15)-diol-dilactone (**83**) are from the leaves, in addition to compound X (**32**)[24, 41] Finally, nepetaefolin (**44**), leonotinin (**58**), and leonotin (**53**) were identified from the material collected from Pretoria (South Africa) [42].



2.8. *Neophyptis* genus

Neophyptis genus is represented by *N paniculata* in SA. Isoneocembrene-A (**84**), *β*-caryophyllene oxide(**85**), *α*-himachalene (**86**), the isolates showed weak to moderate antibacterial activity against five strains of *S. aureus* [43].

2.9. *Ocimum* genus

Ocimum genus comprises 65 aromatic species, distributed in tropical and subtropical regions worldwide. Species belonging to this genus are popularly used in Africa and Asia for treating diabetic symptoms. The genus is represented by 16 species in SA and the phytochemical

study of *O. amercanium* afforded four compounds of the copane series (copan-3-ol (**87**), cop-l1(12)-en-3-o1 (**88**), cop-3(15)-en-11-ol (**89**), and cop-l0(ll)-en-3,12-diol(**90**)) [44].

2.10. *Orthosiphon* genus

Orthosiphon genus comprises 40 species recorded from the old world: in tropical and sub-tropical regions including Southern Africa and Madagascar. Three species were found in SA. Three labdanoids (+)-*trans*-ozic acid (**91**), labda-8(17),12*E*,14-trien-2α,18-diol (**92**), and 2α-hydroxylabda-8(17),12*E*,14-trien-18-oic acid (**93**) have been isolated from an ethanol extract. Compound **93** exhibited activity against *M. tuberculosis*, while **92** showed cytotoxic activity against MCF-7 and decreased the production of all the pro-inflammatory cytokines. From the same source, pheophytin a, the acidic degradation product of chlorophyll a, was isolated and showed inhibition of HIV-1 protease [45, 46].

2.11. *Paltstoma* genus

Only one species was recorded in SA. From the ethyl acetate extract of *P. rotundifolium,* cassipourol (**94**), β-sitosterol, and α-amyrin were identified [47].

2.12. *Plectranthus* genus

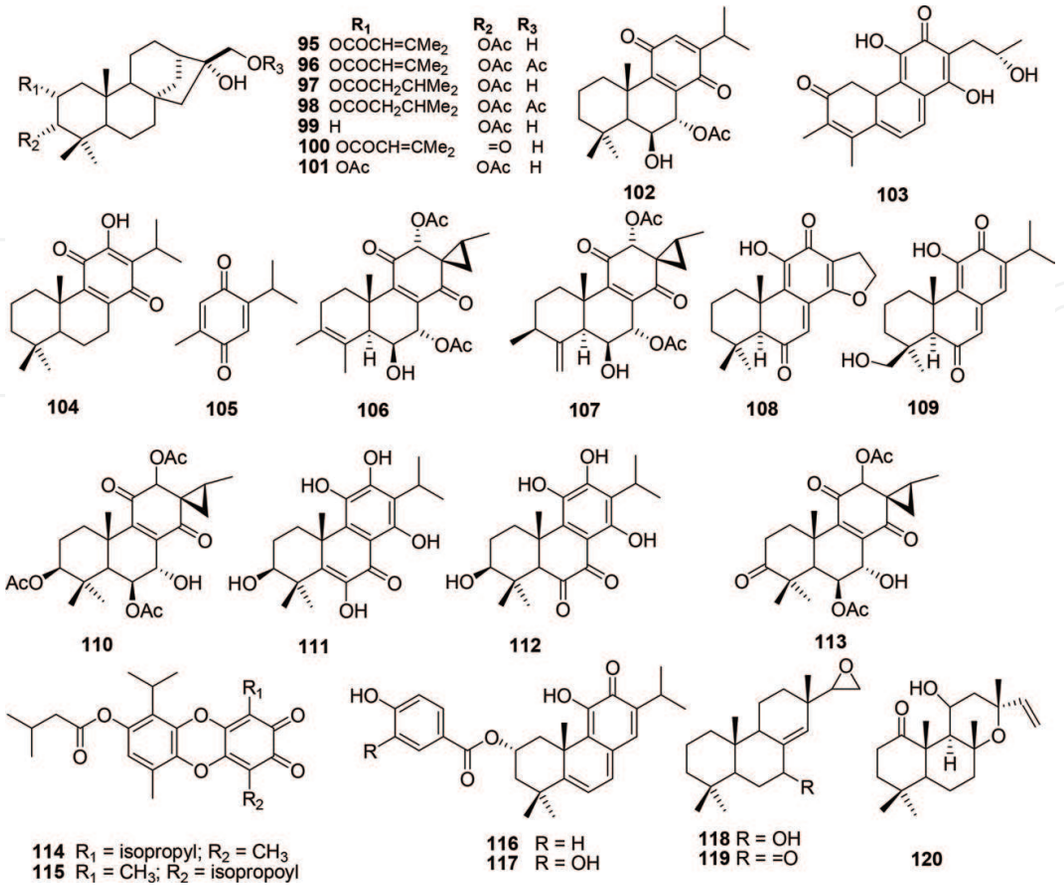
About 300 species distributed in tropical and warm regions of the old World, 45 species recorded in SA, from which 19 species were studied for their chemical and/or biological constituents. The genus is characterized by the presence of orange glands that distributed in the aerial parts and contain highly oxygenated (and modified) abietane-type diterpenoids. Others, e.g., kaurane, labdane, phyllocladane as well as the rare skeleton halimane diterpenoids were described.

2.12.1. Plectranthus ambiguus

The plant afforded a series of tetracyclic phyllocladane-type (= 13β-kaurane) diter-penoids: (16*R*)-2α-senecioyloxy-3α-acetoxyphyllocladan-16,17-diol (**95**), (16*R*)-2α-senecioyloxy-3α,17-diacetoxy-16-hydroxyphyllocladane (**96**), (16*R*)-2α-isovaleroyloxy-3α-acetoxyphyllocladan-16, 17-diol (**97**), (16*R*)-2α-isovaleroyloxy-3α,17-diacetoxy-16-hydroxyphyllocladane (**98**), (16*R*)-3α-acetoxyphyllocladan-16,17-diol (**99**), (16*R*)-2α-senecioyloxy-16,17-dihydroxyphyllocladan-3-one (**100**), and (16*R*)-2α,3α-diacetoxyphyllocladan-16,17-diol (**101**). The authors discriminated between phyllocladane and *ent*-kaurane tetracyclic skeletons after extensive spectroscopic investigation as well as chemical transformations [48, 49].

2.12.2. Plectranthus amboinicus

Thymoquinone (**105**) was identified as an active nonpolar ingredient to suppress the expression of lipopolysaccharide-induced tumor necrosis factor-alpha (TNF-α) [50]. The total extract showed cytotoxic activity against MCF-7, using HPLC-based metabolomics approach, and 7α-acetoxy-6β-hydroxyroyleanone (**102**) was identified as the main active constituent. Other minor compounds like coleon E (**103**) and royleanone (**104**) were also identified [51].



2.12.3. Plectranthus caninus

Plectranthus caninus afforded coleons M (**106**), N (**107**), P (**108**), Q(**109**), R (**110**), S (**111**), and T (**112**) and barbatusin (**113**) [52, 53].

2.12.4. Plectranthus ecklonii

Plectranthus ecklonii is traditionally used in South Africa for treating stomach aches, nausea, vomiting, and meningitis. Ecklonoquinone A (**114**) and B (**115**) and parviflorons D (**116**) and F (**117**) were isolated [54, 55]. Compound **117** showed potent activity against *Listeria monocytogenes* and *M. tuberculosis* and both **116** and **117** were found to be very toxic against vero cell lines. The potency of parvifloron D (**116**) was further confirmed and showed fast and potent apoptotic inducer in leukemia cells [56].

2.12.5. Plectranthus ernstii

Two pimaranes rel-15(ζ),16-epoxy-7*α*-hydroxypimar-8,14-ene (**118**): rel-15(ζ),16-epoxy-7-oxopimar-8,14-ene (**119**) and a labdane 1*R*,11*S*-dihydroxy-8*R*,13*R*-epoxylabd-14-ene (**120**) were isolated. The three compounds showed activity against *M. tuberculosis* and different strains of *S. aureus* [57].

2.12.6. Plectranthus fruticosus

Plectranthus fruticosus cultivated in Porugal afforded 4 labdanes, *ent*-labda-8(17),12Z,14-trien-2*β*-ol (**121**),*ent*-2*α*-acetoxylabda-8(17),12*Z*,14-trien-3*β*-ol (**122**), ent-3*β*-acetoxylabda-8(17),

12*Z*,14-trien-2*α*-ol (**123**),3*β*-acetoxylabda-8(17),12*E*,14-trien-2*α*-ol (**124**), 10 kauranes (*ent*-12*β*-acetoxy-15*β*,16*β*-epoxykauran-19-oic acid (**125**), *ent*-7*β*-hydroxy-15*β*,16*β*-epoxykauran-19-oic acid (**126**), *ent*-15*β*,16*β*-epoxykauran-19-oic acid (**127**), *ent*-15*β*,16*β*-epoxykauran-19-ol (**128**), *ent*-12*β*-acetoxy-15*β*-hydroxykaur-16-en-19-oic acid (**129**), *ent*-12*β*-acetoxy-7*β*-hydroxykaur-16-en-19-oic acid (**130**),methyl ent-12*β*-acetoxy-16-kauren-19-oate (**131**), *ent*-7*β*-hydroxykaur-15-en-19-oic acid (**132**), methyl *ent*-12*β*-acetoxy-7*β*-hydroxykaur-15-en-19-oate acid (**133**), *ent*-12*β*-acetoxy-17-oxokaur-15-en-19-oic acid (**134**), methyl *ent*-12*β*-acetoxy-15-kauren-19-oate (**135**), additionally, armendrance (**136**), caryophyllene *α*-oxide (**137**), ursolic/oleanolic acids (2,1 mixture) *β*-sitosterol, stigmasta-5,22*E*-dien-3*β*-ol, and *β*-amyrin. Some of the compounds showed moderate anti-*staphylococcus* activity [58, 59]. *P. fruticosus* growing in India showed abietane diterpene pattern and 7*α*-acetoxy-6*β*-hydroxyroyleanone (**102**), 6,7-dehydroroyleanone (**138**) and 7*α*,6*β*-dihydroxyroyleanone (**139**) were isolated [60].

2.12.7. Plectranthus grandidentatus

In addition to 14-hydroxytaxodione (**140**), coleons U (**141**) and V (**142**), a series of abietane dimers namely grandidone A (**143**), B(**145**), and D(**147**) and their epimers 7-epigrandidone A(**144**), B(**146**), and D (**148**) and grandidone C (**149**) [61] were identified. Also, royleanone (**103**), 6,7-dehydroroyleanone (**138**), horminone (**150**), 6*β*-hydroxyroyleanone (**151**), and 7*α*-acetoxy-6*β*-hydroxyroyleanone (**102**) together with a mixture of fatty acid esters of 7*α*-acyloxy-6*β*,12-dihydroxy-abieta-8,12-diene-11,14-dione (**152**), 7*α*,6*β*,-dihydroxyroyleanone (**139**), and 9*α*-(2-oxopropyl)abietane derivative(**156**) were isolated [62–67].

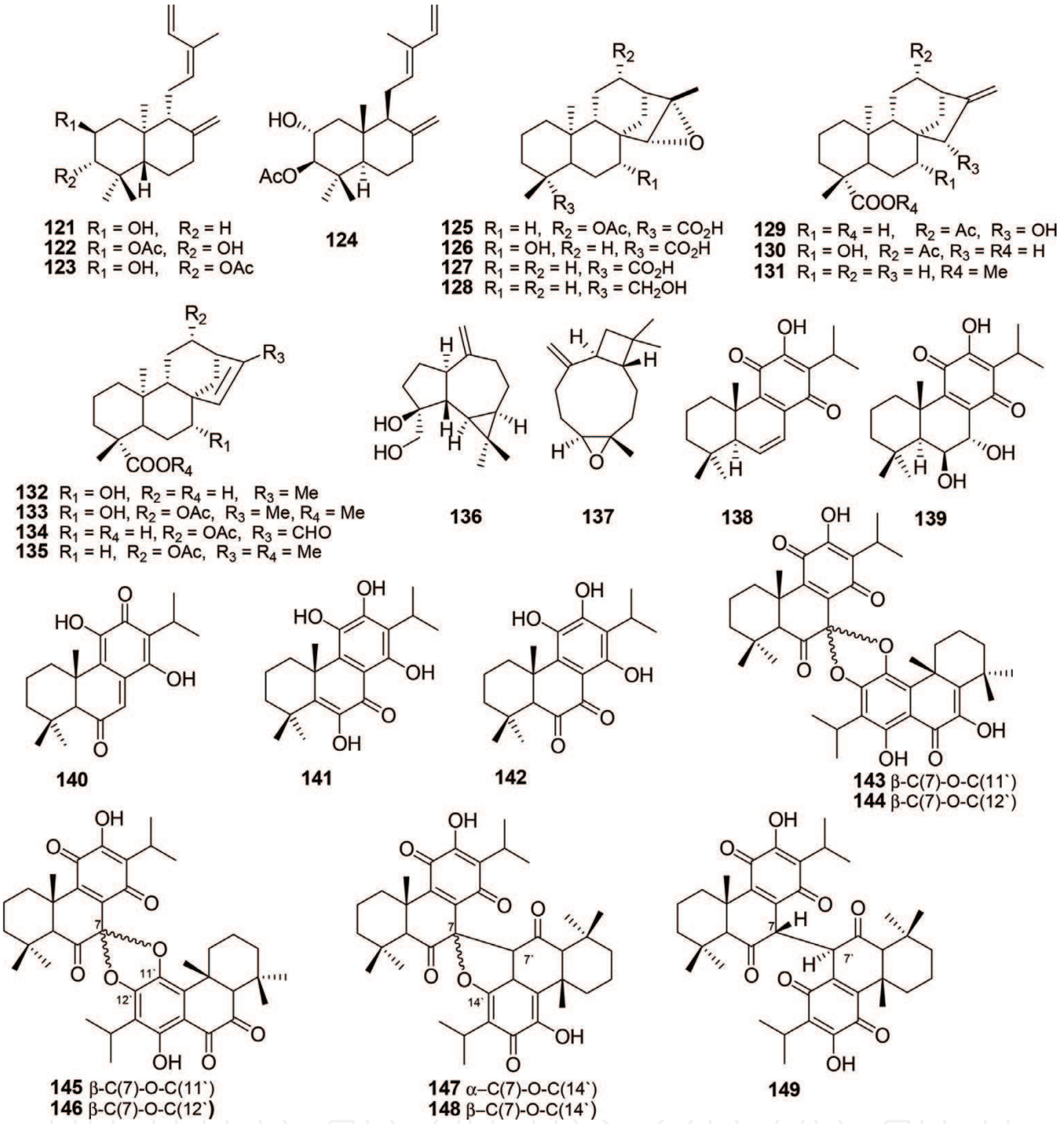
Fatty acid esters of 7*α*-acyloxy-6*β*-hydroxyroyleanone (**152**) showed moderate antibacterial activity [62]; coleon U exhibited potent cytotoxicity against a panel of human cancer cell lines [63, 65] also showed potent inhibition of mouse splenocyte proliferation induced by ConA or LPS mitogens [64]. Coleons U **141** is considered as a promising compound and deserves further evaluation as an anti-cancer drug [68]. Coleon U (**141**), 7*α*-acetoxy-6*β*-hydroxyroyleanone (**102**), and horminone (**150**) showed activity against methicillin-resistant *S. aureus* (MRSA) and vancomycin-resistant *Enterococcus faecalis* (VRE). Recently, the biological activity of **102** was reported and showed selective cytotoxicity against MCF-7. Other derivatives of the same compound showed potent cytotoxic [69, 70] and antimicrobial [66] activities.

2.12.8. Plectranthus hereroensis

Horminone (**150**), 16-acetoxy-7*α*,12-dihydroxy-8,12-abietadiene-11,14-dione (**153**) and 7*α*-12-dihydroxy-17(15→16)-abieta-8,12,16-triene-11,14-dione (**157**);3*β*-acetoxy-6*β*,7*α*-12-trihydroxy-17(15→16)18(4→3)bisabeo-abieta-4(19)8,12,16-triene-11,14-dione (**158**) were isolated [13, 66, 71], on the other hand, the structure of an aristolane sesquiterpene aldehyde (**159**) have been revised [72], all compounds showed moderate antimicrobialactivity [13, 66, 71, 72], while **158** showed antiviral activity [73].

2.12.9. Plectranthus madagascariensis

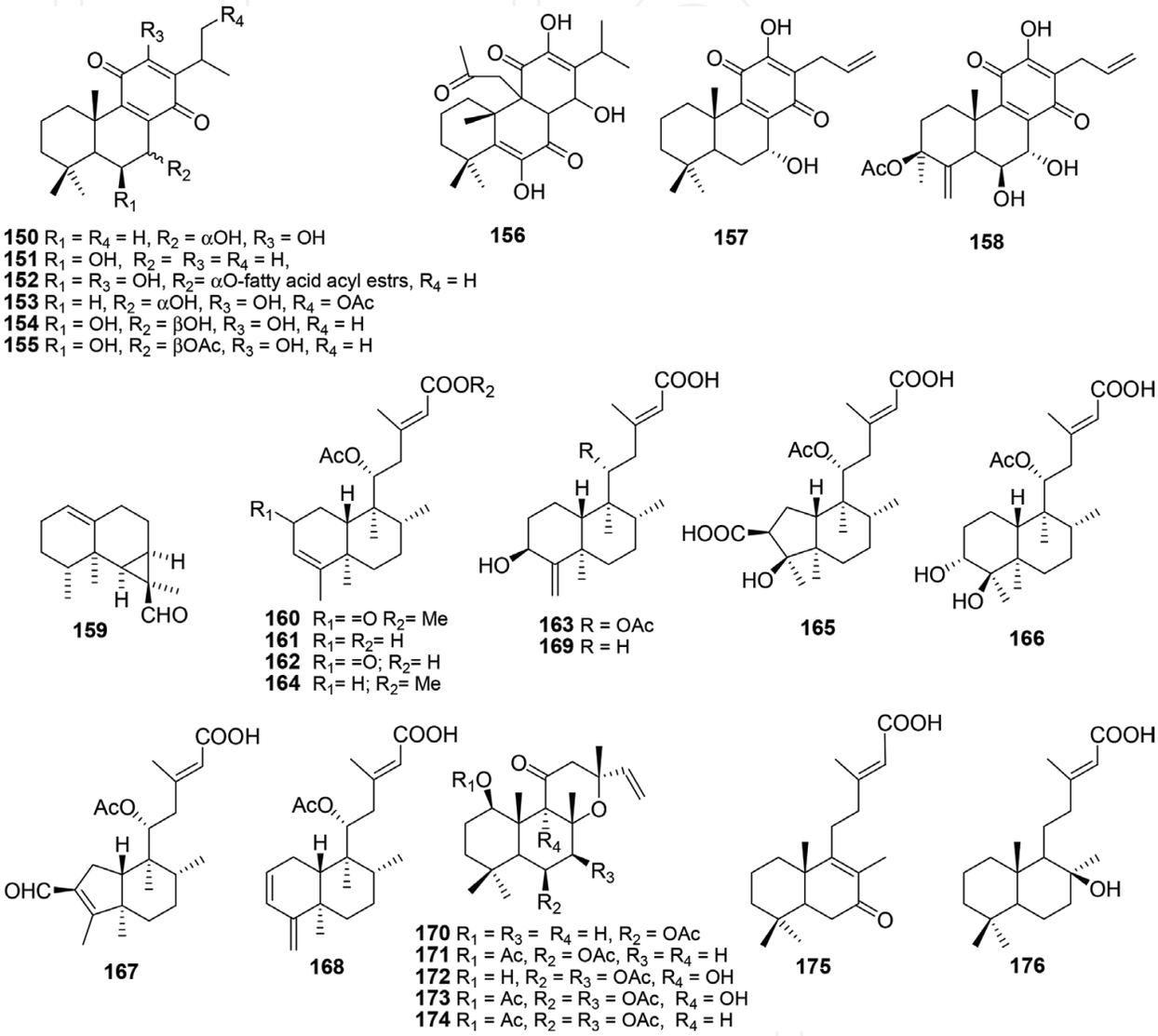
Plectranthus madagascariensis is used as a traditional medicine in Southern Africa. Three constituents were isolated and identified as 6*β*,7*β*-dihydroxyroyleanone (**154**), 7*β*-acetoxy-6*β*-hydroxyroyleanone (**155**), and coleon U (**141**). The compounds exhibited inhibitory activity on *α*-glucosidase, *S. aureus* and *Enterococcus faecalis* [74].



2.12.10. Plectranthus ornatus

Traditionally, the plants were used for treatment of stomach and liver diseases and as a substitute of *P. barbatus*. The phytochemical studies resulted in the isolation of 11 neoclerodanes (plectrornatins A (**160**) [75], 11*R**-acetoxykolavenic acid (**161**), 11*R**-acetoxy-2-oxokolavenic acid (**162**), 11*R**-acetoxy-3*β*-hydroxyneocleroda-4(18),13*E*-dien-15-oic acid (**163**) [76], ornatins A–E (**164**-**168**), 3*β*-hydroxyneocleroda-4(18),13*E*-dien-15-oic acid (**169**) [77]; 7 labdanes (plectrornatins B (**170**), C (**171**), [75],6-*O*-acetylforskolin (**172**); 1,6-di-*O*-acetylforskolin (**173**), 1,6-di-*O*-acetyl-9-deoxyforskolin (**174**) [76, 78], rhinocerotinoic acid (**175**) [66], 8*β*-hydroxylabd-13-en-15-oic acid (**176**) [77]); 2 abietanes (14-*O*-acetyl-coleon U (**177**), coleon R (**110**)) and a halimane derivative, (11R*-acetoxyhalima-5,13E-dien-15-oic acid (**178**) [79]) in addition to *β*-sitosterol and stigmasterol, 3*β*-acetyl-*α*-amyrin, and friedelin. Inversion at C-13 of 1,6-di-*O*-acetyl-9-deoxyforskolin (**174**) was carried out based on correlations between ^{13}C NMR experimental data and HF/6-31G*

calculation [80]. **160**, **161** showed moderate antimicrobial. **178** exhibited growth inhibitory activity against five *Staphylococcus* and five *Enterococcus* strains [75]. Ornatin C, D, E and three related diterpenes displayed marginal bactericidal or bacteriostatic effects against the Gram-positive strains [77].



2.12.11. Plectranthus porcatus

(13*S*,15*S*)-6*β*,7*α*,12*α*,19-tetrahydroxy-13*β*,16-cyclo-8-abietene-11,14-dione (**179**) has been isolated and showed weak antibacterial activity against *S. aureus* [81].

2.12.12. Plectranthus saccatus

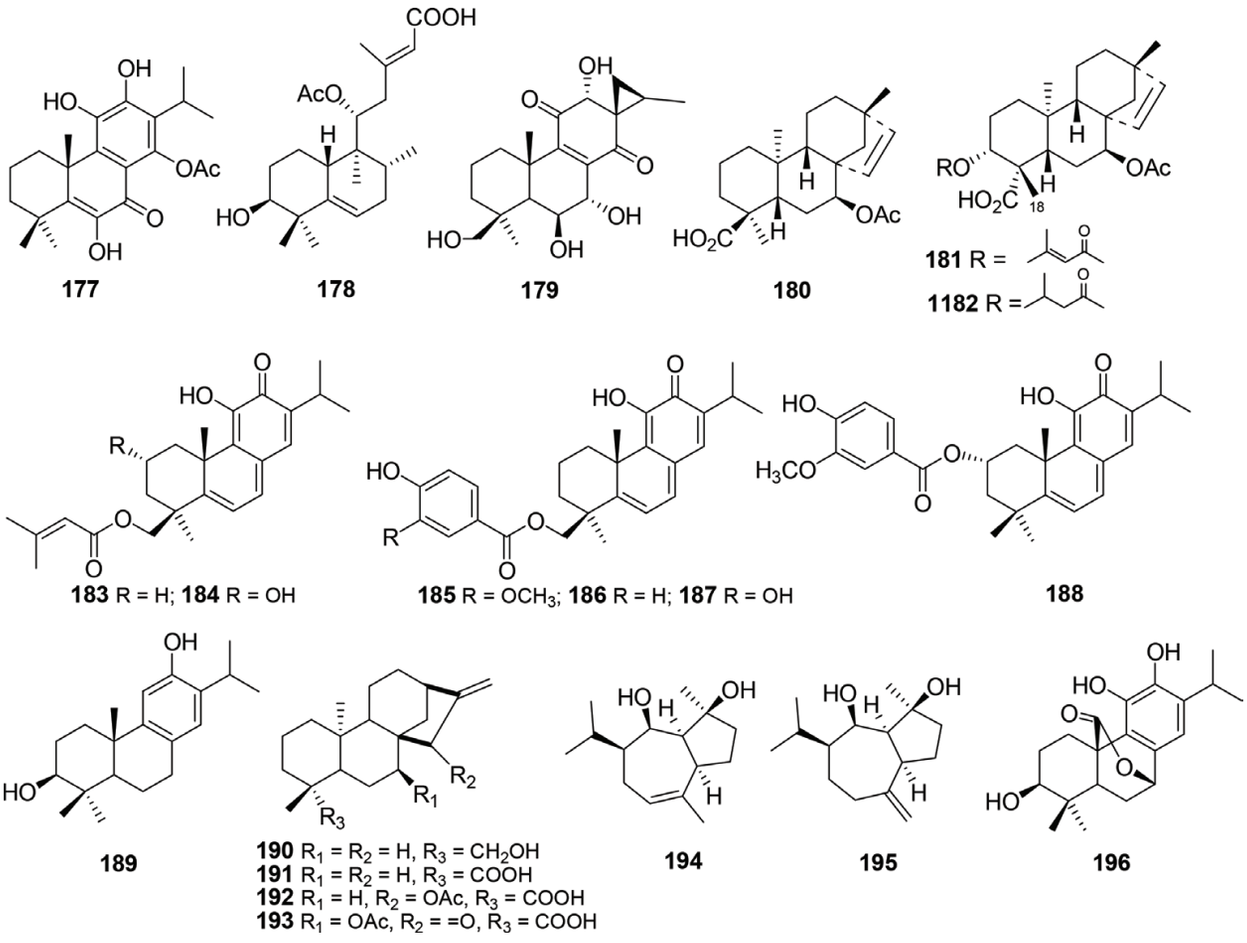
Ent-7*α*-acetoxy-15-beyeren-18-oic acid (**180**), *ent*-3*β*-(3-methyl-2-butenoyl) oxy-15-beyeren-19-oic acid (**181**), and ent-3*β*-(3-methylbutanoyl) oxy-15-beyeren-19-oic acid (**182**). Both **181** and **182** showed insect antifeedant activity against *Spodopteralittoralis*, while **180** showed no antibacterial activity [81, 82].

2.12.13. Plectranthus strigosus

9 abietanes (parviflorones A (**183**), B (**184**), C (**185**), D (**114**), E (**186**), F (**115**), G (**187**), and H (**188**) [83], and hinokiol (**189**)) [84]), 3 kauranes (*ent*-16-kauren-19-ol (**190**), *ent*-16-kauren-19-oic acid (**191**), xylopic acid (**192**), xylopinic acid (**193**)), and 2 sesquiterpens (4*β*,6*β*-dihydroxy-1*α*,5*β*(H)-guai-9-ene (**194**) 4*β*,6*β*-dihydroxy-1*α*,5*β*(H)-guai-10(14)-ene (**195**)), were isolated [84]. A bioactivity study revealed herpetic inhibitory properties for (**190**) and (**191**) [84].

2.13. *Salvia* genus

The genus *Salvia* is known as sage and is the largest genus in Lamiaceae, comprising over 900 species distributed throughout the world. *Salvia is* represented by 30 species in SA, distributed mainly in great cape region. The chemistry of *Salvia* is rich in diterpenoids and different skeletons have been reported, also, many members of this genus is well known for its curative and medicinal properties like *S. officinalis* and *S. miltiorrhiza*.



2.13.1. Salvia africana-lutea

Carnosol (**196**), rosmadial (**197**), and carnosic acid (**198**-characterized as its methyl ester) were isolated. Compound **198** exhibited potent activity against *M. tuberculosis* and cytotoxic activity against a breast (MCF-7) human cancer cell line [45].

2.13.2. Salvia chamelaeagnea

Four compounds were isolated: carnosol (**196**), 7-O-methylepirosmanol (**200**), oleanolic and ursolic acids as the active principles against *S. aureus* [85].

2.13.3. Salvia coccinea

Momordic acid, methyl ester (**201)** [86], salviacoccin (**202**) [87], dehydrouvaol (**203**), and uvaol (**204**) [88] were isolated.

2.13.4. Salvia disermas

The aerial parts afforded ocotillol II (**205**) [89].

2.13.5. Salvia radula

Betulafolientriol oxide (**206**) was isolated [90].

2.13.6. Salvia reflexa

Four neoclerodanes were isolated and identified as salviarin (**207**), 6β-hydroxysalviarin(**208**), 15,16-epoxy-8α-hydroxyneocleroda-2,13(16),14-triene-17,12*R*:18,19-diolide (**209**), and 5,6-secoclerodane, 7,8-didehydrorhyacophiline (**210**) [91].

2.13.7. Salvia repens

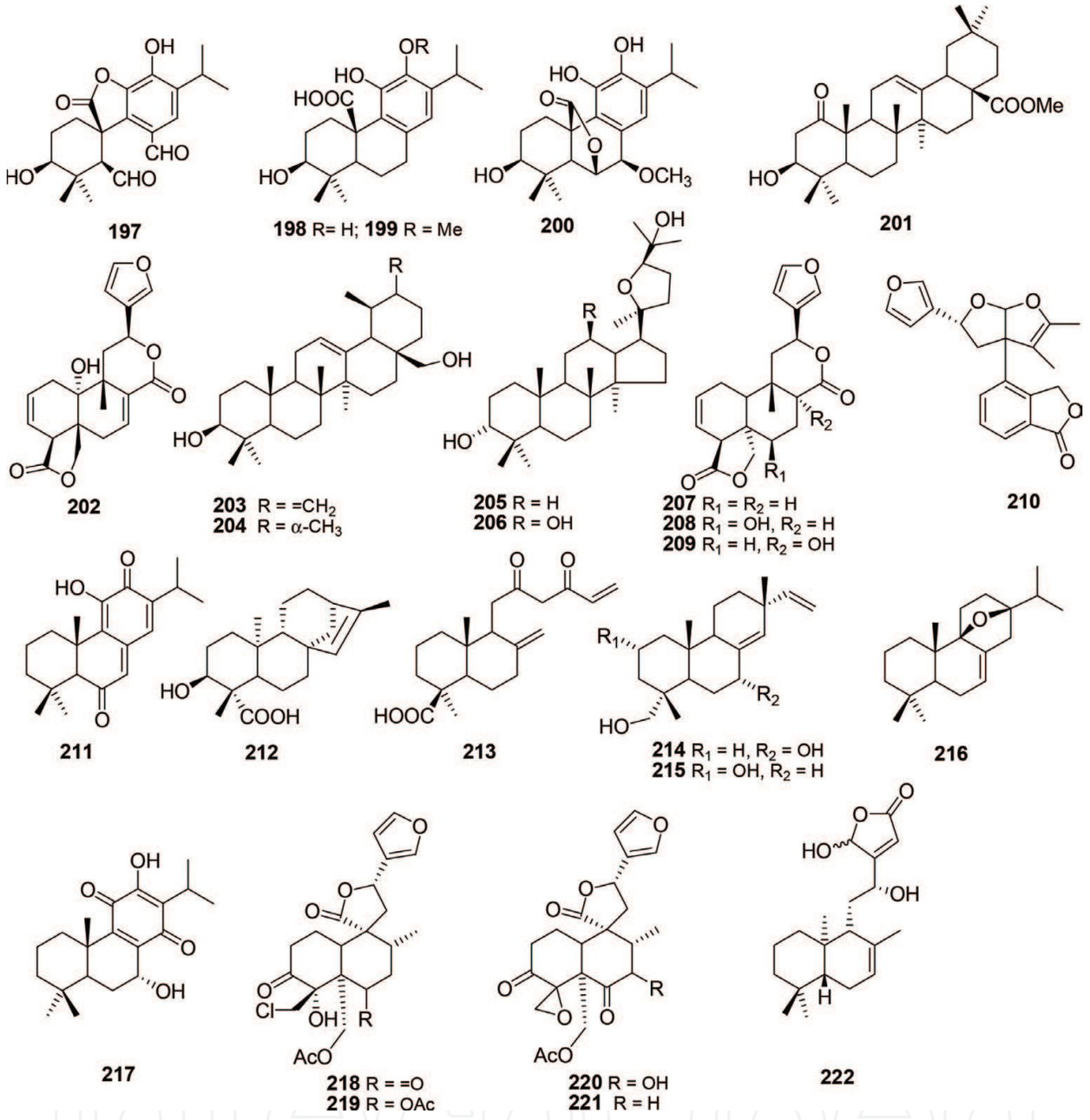
The whole plant extract yielded 12-methoxycarnosic acid (**199**) with antiprotozoal activity against *Leishmania donovani* amastigotes and cytotoxicity against the L6-cells [92].

2.13.8. Salvia verbenaca

The plant yielded β-sitosterol, ursolic acid, dehydroursolic acid, sitosteryl-3-β-D-glucoside [93], taxodione (**211**), horminone (**150**) and 7α-acetoxy-6β-hydroxyroyleanone (**102**) [94], verbenacine (**212**) and salvinine (**213**) [95].

2.14. *Solenostemon* genus

Solenostemon genus is from *S. rotundifolius*; oleanolic acid was isolated as a major component [96].



2.15. *Tetradenia* genus

Seven species were recorded in SA, one of them *T. riparia* is widely distributed in Africa and showed interesting chemical profile. Several compounds have been isolated from the leaves of this plant, including 8(14),15-sandaracopimaradiene-7α,18-diol (**214**) [97], 8(14), 15-sandaracopimaradiene-2α,18-diol (**215**) [98], 9β,13β-epoxy-7-abietene (**216**), 6,7-dehydroroyleanone (**136**) [99], and ibozol (**217**) [100].

Compound (**214**) exhibited antimicrobial activity (**213**). Compound (**215**) showed papaverine-like antispasmodic activity on guinea pig ileum contracted by methacholine, histamine, or $BaCl_2$ and on the noradrenaline-induced contractions of rabbit aorta [101]. It also showed activities against *Trichomonasvulgaris* with MIC of 20–40 μg/mL [102], wheat rootlets inhibition activity (MIC7.81 μg/mL) [103], and *M. tuberculosis*[104].

2.16. *Teucrium* genus

Three species were recorded in SA. From *T. africanum*tafricanins A (**218**) and B(**219**), teutrifidin (**220**) and 4*α*,18-epoxytafricanin A (**221**) were isolated [105].

2.17. *Vitex* genus

Vitex genus is represented by 12 species in SA. The fraction responsible for antimicrobial activity of *V. rehmannii* was purified to give a labdane diterpene as an inseparable epimeric mixture of 12*S*,16*S*/*R*-dihydroxy-*ent*-labda-7,13-dien-15,16-olide (**222**). The extract and the labdane diterpene exhibited good antimalarial activity, with the labdane diterpene being the most active IC_{50}: 2.39 ± 0.64 μg/mL [106].

3. Conclusion

South African flora characterized by high endemism and unique floral kingdom is only located in the great cape region. Lamiaceae is represented by ~308 species widely distributed all over the country. In general, the bioprospecting of SA flora including Lamiaceae is not reached; yet the required level and more attention are required to explore the potential of their chemical constituents. The present work shades the light on the isolated terpenoids of all listed species in updated SA flora checklist. It is interesting to indicate that *Plectranthus* genus contains mostly abietane diterpenes and shows potent activity as demonstrated by coleon U and parviflorons F and D. On the other hand, leoleorin C from *L. Leonurus* showed moderate binding affinity (*Ki* = 2.9 μM) to the Sigma 1 receptor. These compounds and others may be considered as a model for drug discovery for human benefits.

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Conflict of interest

The author declares no conflict of interest to disclose.

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