Natural Products Chemistry & Research
ISSN: 2329-6836
Al-Massarani, Nat Prod Chem Res 2014, 2:5
DOI: 10.4172/2329-6836.1000147
Review Article Open Access

Phytochemical and Biological Properties of Sesquiterpene Constituents From the Marine Red Seaweed *Laurencia:* A Review

Shaza M Al-Massarani*

Department of Pharmacognosy, Pharmacy College, King Saud University, Riyadh, Saudi Arabia

Abstract

Laurencia is an important marine red algal genus comprising of approximately 130 taxonomically accepted species. Compounds isolated from *Laurencia* species display a variety of biological activities, viz., antiviral, antibacterial, antifouling, antifungal, antioxidant, antifeedant, antimalarial, anthelmintic, antiasthmatic and cytotoxic activities. Sesquiterpenoids with, various classes and skeletons, are the main constituents of this genus. This review article has surveyed the relevant literature on *Laurencia* genus from January 2000 to May 2014 from the phytochemical and pharmacological viewpoints. All sesquiterpene compounds reported from this genus, during the mentioned period, are categorized according to their chemical class and general structural type. More than 200 sesquiterpenes isolated from *Laurencia* red algae are discussed in term of their structural type, occurrence and reported pharmacological activity.

Keywords: *Laurencia*; Sesquiterpenes; Marine algae; Seaweed

Introduction

The genus *Laurencia*, commonly known as red seaweeds, is a marine algae belonging to family Rhodomelaceae [1]. *Laurencia* has been established by JV Lamouroux in 1813, with only 8 species originally recognized. At present ~430 described species are identified, of which 134 are, taxonomically, accepted [2]. Seaweeds of the *Laurencia* genus have a wide geographical distribution and occur in all oceans and seas at all attitudes particularly in temperate to tropical shores constituting a considerable part of the flora [3]. It is estimated that over 60 species throughout the world have been investigated and more than 700 compounds possessing unique structural features have already been isolated from red algae of genus *Laurencia* [4]. In particular, species of *Laurencia* are known to be the richest producers of halogenated secondary metabolites with diverse and unique structural features depending on species, localities and season [5]. *Laurencia* species produce bromine-containing compounds in much larger numbers than either chlorine- or iodine-containing ones whereas, the Cl-containing compounds usually also possess Br atom(s) [6]. A large number of these compounds have been obtained from *Laurencia* species having an intracellular, membrane-bound vesicles known as "corps en cerise" (cherry bodies) in the outer cell layer (the cortical layer) where, these inclusions are considered as a synthesis and/or storage sites of halogenated secondary metabolites [7]. On the other hand, *Laurencia* species without "corps en cerise" does not produce any halometabolites [8].

Laurencia chemistry is dominated by the presence of sesquiterpenes which are the most abundant members in the terpenoid groups isolated from this genus, with relatively fewer reports of diterpenoids, triterpenoids, steroids, alkaloids and C15 acetogenins [9]. Many of these compounds which exhibit significant ecological role as anti-epibiosis [10] are also reported to possess a variety of biological effects, such as cytotoxic activity against various cancer cell lines [11,12], antiviral, antibacterial, antifouling, antifungal, antioxidant, antimalarial, anthelmintic, antiasthmatic, antifeedant and other activities [13-19].

More than 200 sesquiterpenoidal metabolites, isolated from *Laurencia*, will be discussed, in term of their occurrence, structural type and reported pharmacological activity and presented in an order based on their general structural type. Table 1 summarizes the taxonomical position of genus *Laurencia*. On the other hand, alphabetical listing of all cited species with the corresponding compounds isolated from each and the related references is presented in Table 2.

Sesquiterpene Constituents of Genus *Laurencia*

The genus *Laurencia* is the most attractive source of sesquiterpenes among all marine macroalgae. It has a remarkable capacity to biosynthesize a huge variety of structurally diverse sesquiterpenes, with varied skeletons including chamigrane, bisabolane, laurane, snyderane brasilane along with some unique rearranged derivatives occurring prevalently [20,21] (Table 1).

Chamigrane Skeleton Sesquiterpenes

Spirane type sesquiterpenes –chamigrenes– are the most widespread sesquiterpenes from the genus *Laurencia*. Over the *last twenty years*, large number of structurally novel chamigrane metabolites *has been isolated* from *Laurencia* [21]. In 1970, a brominated ketone spirolaurenone (**1**), was the first reported chamigrane sesquiterpene; obtained from the neutral essential oil of *Laurencia glandulifera* (Japan) [22]. The Chinese *L. okamurai,* collected from the coast of Rongcheng, China, was the source of laurokamin A (**2**), laurokamin B (**3**), laurokamin C (**4**), 10-bromo-α-chamigrene (**5**), 10-bromo-β-chamigrene (**6**), 2,10-dibromo-3-chloro-β-chamigrene (**7**), and obtusane (**8**) [23]. Compounds **6**, **7** (named as nidificene) and **8** were earlier described from *L. mariannensis*, in addition to (-)-(10*R*)-

Domain	Eukaryota
Kingdom	plantae
Subkingdom	Biliphyta
Phylum	Rhodophyta
Subphylum	Rhodophytina
Class	Florideophyceae
Order	Ceramiales
Family	Rhodomelaceae
Genus	Laurencia

Table 1: Taxonomical Position of *Laurencia*.

***Corresponding author:** Shaza M Al-Massarani, Department of Pharmacognosy, Pharmacy College, King Saud University, Riyadh, Saudi Arabia, Tel: 96-611-4960-181; E-mail: salmassarani@ksu.edu.sa

Received May 29, 2014; **Accepted** August 18, 2014; **Published** August 20, 2014

Citation: Shaza M Al-Massarani (2014) Phytochemical and Biological Properties of Sesquiterpene Constituents From the Marine Red Seaweed Laurencia: A Review. Nat Prod Chem Res 2: 147. doi:10.4172/2329-6836.1000147

Species	Sesquiterpene constituents	Reference
L. aldingensis	aldingenins A–D (75-78)	[63,64]
L.cartilaginea	isorigidol (46), ma'ilione (49)	[50]
L. composita	laurecomins A-D (16-19), 2,10-dibromo-3-chloro-7-chamigren-9-ol acetate (20), deoxyprepacifenol (21), 2-bromospironippol (22), laurencomposidiene (23), (8β)-10-bromo-3-chloro-2,7-epoxychamigr-9-en-8-ol (24), 2-bromo-3-chlorobisabola-7(14),11-diene-6,10-diol (72), 1-bromoselin-4(14),11-diene (150) and 9-bromoselin-4(14),11-diene (151)	[29-32]
L. dendroidea	dendroidone (51), dendroidiol (52), (205)	[53,110]
L. glandulifera	spirolaurenone (1), laurene (90)	[22,70]
L.gracilis	isolaurenisol, (132) reported from	[85]
L. elata	Elatol (25), cycloelatanene A (27) and B (28)	[33,40]
L. filiformis	Prepacifenol (41), 5-acetoxy-2,10-dibromo-3-chloro-7,8-epoxy-α-chamigrene (42), cycloisoallolaurinterol (125) isoallolaurinterol (126), filiformin (127), filiforminol (128), allolaurinterol (129), 10-bromolaurenisol (130)	[48,82]
L. luzonensis	luzonensin (157), luzonenone (158), luzofuran (159), 3,4-epoxypalisadin B (160), 1,2-dehydro-3,4-epoxypalisadin B (161) and 15-hydroxypalisadin A (162), 3R*, 4S*-luzonolone (165), 3S*, 4R*-luzonolone (166), luzondiol (167), luzonenone 168, 169, aplysistatin (170), palisadin B (172), palisadin A (173), aplysistatin (170), (3Z,6E)-1-bromo-2-hydroxy-3,7,11-trimethyldodeca-3,6,10-triene (200), isopalisol (201), luzonensol (202), luzonensol acetate (203)	[95,96,98]
L. microcladia	Elatol (25), hydroxy-β-bisabolene, (66), compounds 84–86 laurokamurenes A (87) and B (88), (134-137), 8-cycloeudesmane (148), calenzanol (176), debromoisocalenzanol (177), (178)	[34,60,67,68] [91,102,103]
L. majuscula	Elatol (25), Isoobtusol (26), 8-bromochamigren-1-en (29), (6R,9R,10S)-10-bromo-9-hydroxychamigra-2,7(14)-diene (30), majapolene B (197), majapolene A (198)	[8,41,108]
L. mariannensis	10-bromo-β-chamigrene (6), 2,10-dibromo-3-chloro-β-chamigrene (7), and obtusane (8), (-)-(10R)-bromo-a-chamigrene (9), 9-deoxyelatol (34), deschloroelatol (35), 36, 37, isoafricanol (189), isodactyloxene A (190)	[24,105]
L. nipponica	laurene (90)	[70]
L. obtusa	Isoobtusol (26), chamigrenelactone (31), oxachamigrene (32) and 5-acetoxyoxachamigrene (33), 12-hydroxy isolaurene (93), isolauraldehyde (94), 8,11-dihydro-12-hydroxy isolaurene (95), 3,7-dihydroxydihydrolaurene (138), (139), (141–143), brasilenol (144), epibrasilenol (145), (146), β-snyderol (152), (8R*)-8-bromo-10-epi-β-snyderol (154) (8S*)-8-bromo-β-snyderol (155), (179-182), perforenone D (183), perforatone (184), perforenol B (185), bromocyclococanol (186), 5-bromo-3-(3'-hydroxy-3'-methylpent-4'-enylidene)-2,4,4-trimethylcyclohexanone (187), (188)	[16,35,42,43] [72,86,87,93] [104]
L. okamurai	laurokamin A (2), laurokamin B (3), laurokamin C (4), 10-bromo-α-chamigrene (5), 10-bromo-β-chamigrene (6), 2,10-dibromo-3-chloro-β-chamigrene (7), and obtusane (8), 10-bromo-7α,8α-expoxychamigr-1-en-3-ol (10) and 10-bromo-β-chamigren-8-ol (11), Okamurene E (12), (13) and (14), laurenokamurin (15), (5S)-5-acetoxy-β -bisabolene (67), okamurenes A–D (79-82), 10-bromo-3-chlorocupar-5-en-2-ol (83), laurokamurene D (89), laurene (90), 7-hydroxylaurene (92), laureperoxide (96), 10-bromoisoaplysin (97), isodebromolaurinterol (98) 10-hydroxyisolaurene (99) aplysinol (100), isoaplysin (101), debromolaurinterol (102), debromolaurinterol acetate (103), laurinterol acetate (104), debromoisolaurinterol acetate (105) and isolaurinterol acetate (106), laurentristich-4-ol (112), laurepoxyene (121), 3β-hydroperoxyaplysin (122), 3α-hydroperoxy-3-epiaplysin (123), 8,10-dibromoisoaplysin (124), allolaurinterol acetate (131), 3β-hydroxyaplysin (133), seco-laurokamurone (199)	[23,25, 26,28,61] [68,71,73-75] [78,84,88]
L. pannosa	pannosanol (43), pannosane (44)	[49]
L. perforata	4-hydroxy-1,8-epi-isotenerone (191), 9-hydroxy-3-epi-perforenone A (192), 3-epi-perforenone (193)	[106]
L. rigida	9-deoxyelatol (34), deschloroelatol (35)	[13]
L. saitoi	10-bromo-3-chloro-2,7-epoxychamigr-9-en-8α-ol (38), 2,10β-dibromochamigra-2,7-dien-9α-ol (39), 2,10-dibromo-3-chlorochamigr-7-en-9α-ol (40), (9S)-2-bromo-3-chloro-6,9-epoxybisabola-7(14),10-diene (73) and (9R)-2-bromo-3-chloro-6,9-epoxybisabola-7(14),10-diene (74), isolaurenisol, (132), 2-hydroxyluzofuranone A (163), 2-hydroxyluzofuranone B (164), acetoxypalisadin B (174), 4-hydroxypalisadin C (175), 2-bromo-γ-ionone (204)	[45, 46,97,101]
L. scoparia	Scopariol (45), isorigidol (46) (+)-3-(Z)-bromomethylidene-10 β -bromo- β -chamigrene, (-)-3-(E)-bromomethylidene-10 β -bromo- β -chamigrene (47, 48) (69–71)	[17,62]
L. similis	aristolane (53), aristolan-10-ol-9-one (54), aristolan-8-en-1-one (55), aristol-1(10)-en-9-one (56), (9 β)-aristol-1(10)-en-9-ol (57), aristol-1(10),8-diene (58) aristol-1,9-diene (59) aristolan-1α-bromo-9β,10β–epoxide (60), aristol-9(10)-en-8-one (aristolone) (61), ent-1(10)-aristolen-9 β -ol (62), (+)-aristolone (63), axinysone B (64) and 9-aristolen-1 β -ol (65), (4E)-1-bromo-5-[(1'S*,3'R*)-3'-bromo-2',2'-dimethyl-6'-methylenecyclohexyl]-3-methylpent-4-ene-2,3-diol (156)	[55,56,58] [94]
L. subopposita	7-hydroxylaurene (92)	[71]
L. snackeyi	Aplysistatin (170), 5β-hydroxypalisadin B (171)	[99,100]
L. snyderae	β -snyderol (153)	[93]
L. tristicha	ar-bisabol-9-en-7,11-diol (68), laur-11-en-2,10-diol (107), laur-11-en-10-ol (108), laur-11-en-1,10-diol (109), 4-bromo-1,10-epoxylaur-11-ene (110), cyclolauren-2-ol (111) and laurentristich-4-ol (112), aplysin (113), aplysinol (100), laurebiphenyl (114), aplysin-9-ene (115), epiaplysinol (116), debromoepiaplysinol (117), -bromolaur-11-en-1,10 β -diol (118), 4-bromolaur-11-en-1,10α-diol (119), laur-11-en-1,10 α -diol (120)	[12,77,79,81]
Laurencia sp.	Ma'iliohydrin (50), 8, 10-dibromo-3, 7-epoxy- laur-13-ol (140), Tiomanene (194), acetylmajapolene B (195), acetylmajapolene A (196)	[52,57,107]

Table 2: Sesquiterpene constituents isolated from the species of genus *Laurencia*.

bromo-*a*-chamigrene (**9**) [24]. Furthermore, 10-bromo-7*α*,8*α*-expoxychamigr-1-en-3-ol (**10**) and 10-bromo-*β*-chamigren-8-ol (**11**) were isolated from another collection of the Chinese *L. okamurai* [25]. *L. okamurai*, collected along Weihai coastline in Shandong Province, China yielded okamurene E (**12**) [26]. On the other hand, compounds (**13**) and (**14**) were isolated as a 1:1 diastereoisomeric mixture from *L.*

okamurai (Qingdao, China) [27]. The same species, *L.* okamurai, was also the source of the rearranged chamigrane laurenokamurin (**15**) [28]. *L. composita* collected from Pingtan Island, China yielded laurecomins A-D (**16-19**), 2,10-dibromo-3-chloro-7-chamigren-9-ol acetate (**20**) and the known compound, deoxyprepacifenol (**21**) [29]. Compounds **16** and **17** displayed potent brine shrimp toxicity with LC_{50} values of 51.1 and 37.0, µg/mL, respectively. Additionally, compound **17** was active against the plant-pathogenic fungus *Colletotrichum lagenarium* with an inhibitory diameter of 10 mm [30]. Another Chinese *L. composita* sample (Nanji Is.) afforded 2-bromospironippol (**22**) and laurencomposidiene (**23**) (named as laurencomposene elsewhere in the same paper). The authors suggested that the occurrence of rearranged chamigranes in *L. composita* but not in *L. okamurai* could provide a useful chemotaxonomic marker to distinguish these two similar species [31]. However, several rearranged chamigranes were reported, later, from *L. okamurai* [26]. In 2010, a *L. composita* sample collected from the same area contained (8*β*)-10-bromo-3-chloro-2,7-epoxychamigr-9-en-8-ol (**24**) [32]. Elatol (**25**), isolated for the first time from *L. elata* in 1974 [33], was obtained in high yield of ca. 10% (w/w) from the ethanolic extract of *L. microcladia* [34]. Isoobtusol (**26**), described originally from *L. obtusa* [35], was isolated together with elatol (**25**) from *L. majuscula* in waters of Sabah, Malaysia and both compounds **25** and **26** were found to be active against some marine bacteria [8]. Vairappan et al. reported significant antibacterial activity for compound **25** against *Staphylococcus epidermis*, *Klebsiella pneumonia* and *Salmonella* sp, whereas, isoobtusol was significantly active against *K. pneumonia* and *Salmonella* sp. Further tests indicated that both compounds were bacteriostatic rather than bactericidal [36]. Elatol showed potent antiproliferative activity against promastigote and intracellular amastigote forms of *Leishmania amazonensis*, with an IC_{50} of 4.0 µM and 0.45 µM, respectively [37]. Recently, Desoti et al. reported the effective trypanocidal activity of (-)-elatol, extracted from *L. dendroidea,* against *Trypanosoma cruzi*. The mechanism of action was also investigated and discussed thoroughly [38]. Moreover, *in-vitro* and *in-vivo* experiments suggested that elatol acted as anti-tumor agent, against HeLa and Hep-2 human carcinoma cell lines, by activating the apoptotic process [39]. The Australian *L. elata* yeilded two C16 chamigrenes, named cycloelatanene A (**27**) and B (**28**) [40]. *L. majuscula* collected from the South China Sea was the source of 8-bromochamigren-1-en (**29**) [41], while *L. majuscula* from Okinawa was the source of (6*R*,9*R*,10*S*)-10-bromo-9-hydroxychamigra-2,7(14)-diene (**30**) in a first report of this compound from a natural source. Compound **30** showed activity against *Alcaligenes aqua-marinus*, *Azomonas agilis*, *Erwinia amylovora*, and *Escherichia coli* with MIC values in the range of 20–30µg/disk [8]. A biogenetically interesting halogen-devoid metabolite chamigrenelactone (**31**), with a high oxygen-content, has been isolated from *L. obtusa* from Isla Grande (Caribbean Panama) [42]. Two sesquiterpenes with an oxacyclic chamigrene skeleton, oxachamigrene (**32**) and 5-acetoxyoxachamigrene (**33**), were isolated from a Cuban *L. obtusa* sample [43]. In 2007, Ji et al. reported the isolation of 9-deoxyelatol (**34**), deschloroelatol (**35**); and compounds **36** and **37** from *L. mariannensis* [24]. Compounds **34** and **35** were obtained, previously, from *L. rigida* (Hainan and Weizhou Islands, China) [13], while compounds **36** and **37** were reported in 1982 as intermediates in a biomimetic synthetic study of rhodolaureol and rhodolauradiol [44].

In 2009, *L. saitoi* (Shandong Province, China) yielded 10-bromo-3-chloro-2,7-epoxychamigr-9-en-8*α*-ol (**38**) and 2,10*β*-dibromochamigra-2,7-dien-9*α*-ol (**39**), in addition to the known compound 2,10-dibromo-3-chlorochamigr-7-en-9*α*-ol (**40**) [45,46] . Prepacifenol (**41**), originally described from a *Laurencia* sp. [47], and its acetate derivative, 5-acetoxy-2,10-dibromo-3-chloro-7,8-epoxy-α-chamigrene (**42**), were isolated From *L. filiformis* collected from Taroona, Tasmania. An X-ray analysis was reported for Prepacifenol and its NMR spectra were fully assigned for the first time. Both compounds exhibited moderate activity in the brine shrimp bioassay [48]. *L. pannosa* from Malaysia was the source of two halogenated chamigranes with unusual rearranged framework named pannosanol (**43**) and pannosane (**44**). Both compounds showed antibacterial activities [49]. The rearranged chamigrane Scopariol (**45**), the *β*-chamigrene isorigidol (**46**) and the geometric isomers (+)-3-(*Z*)-bromomethylidene-10 *β* -bromo- *β* -chamigrene and (-)-3-(E)-bromomethylidene-10 *β* -bromo- *β* -chamigrene (**47**, **48**) were reported from *L. scoparia* collected in Brazilian waters. Compound **46** and ma'ilione (**49**), previously isolated from *L.cartilaginea* [50] exhibited moderate *in vitro* anthelmintic activity against the parasitant stage of *Nippostrongylus brasiliensis* [17]. From *L. scoparia* and in a separate report, Suescun et al. isolated and established the absolute stereochemistry of isorigidol (**46**) and ma'ilione (**49**) by an X-ray crystal as (3*R*,6*S*,9*S*,10*S*) and (6*S*,9*R*,10*S*) respectively [51]. Ma'iliohydrin (**50**), a cytotoxic tribrominated chamigrene with dibromohydrin functionality from a *Laurencia* sp. (Philippines) exhibited cytotoxicity in the NCI 60-cell line human tumour screen and potent activity against the NCI/ADR-RES breast cancer cell line [52]. Recently, dendroidone (**51**) and dendroidiol (**52**) were isolated from the Brazilian species *L. dendroidea* collected at Biscaia Inlet, Rio de Janeiro [53] (Figure 1).

Aristolane Skeleton Sesquiterpenes

The aristolane sesquiterpenes, derivatives of 6,11-cycloeremophilanes, are mainly reported from the species *L. similis*. A Chinese sample of *L. similis* (Hainan Is., China) yielded aristolane (**53**), formerly known as a synthetic compound [54], from a natural source for the first time. In addition, aristolan-10-ol-9-one (**54**), aristolan-8-en-1-one (**55**), aristol-1(10)-en-9-one (**56**), 9 *β* -aristol-1(10)-en-9-ol (**57**), aristol-1(10),8-diene (**58**) and aristol-1,9-diene (**59**) were also isolated and identified [55]. In 2010, Li et al. obtained aristolan-1*α*-bromo-9*β*, 10*β*–epoxide (**60**) and aristol-9(10)-en-8-one (aristolone) (**61**) from the same species [56]. A former report published in the same year, 2010, established the isolation of **61** from *Laurencia* for the first time [57]. Recently, a Bornean *L. similis* population yielded *ent*-1(10)-aristolen-9 *β* -ol (**62**) as a new optical isomer of compound **57**, in addition to (+)-aristolone (**63**), axinysone B (**64**) and 9-aristolen-1 *β* -ol (**65**) [58] (Figure 2).

Bisabolane Skeleton Sesquiterpenes

The bisabolane skeleton develops from the cyclization of the geranyl cation and results in the formation of a monocyclic ring structure [59]. In 2007, *L. microcladia* (Chios Is., North Aegean Sea) afforded the hydroxyl derivative of *β* -bisabolene, (**66**) [60], while, (5*S*)-5-acetoxy- *β* -bisabolene (**67**), was isolated, recently, from *L. okamurai* Yamada [61]. *L. tristicha* (Naozhou Island, China) yielded *ar*-bisabol-9-en-7,11-diol (**68**) [12]. On the other hand, *L. scoparia* (S˜ao Paulo, Brazil) was the source of compounds (**69–71**). The confirmation of the structure and the absolute configuration of all stereo centers of **69** were proved by **s**ingle-crystal X-ray crystallography. Compound **69** exhibited weak *in vitro* anthelmintic activity against *Nippostrongylus brasiliensis* [62]. *L. composita* from Nanji Is., China contained 2-bromo-3-chlorobisabola-7(14),11-diene-6,10-diol (**72**) [32], while, *L. saitoi* (Shandong Province, China) yielded (9*S*)-2-bromo-3-chloro-6,9-epoxybisabola-7(14),10-diene (**73**) and (9*R*)-2-bromo-3-chloro-6,9-epoxybisabola-7(14),10-diene (**74**) as an inseparable 1 : 1 mixture [46]. Biogenetic considerations were useful to assign the novel oxacyclic

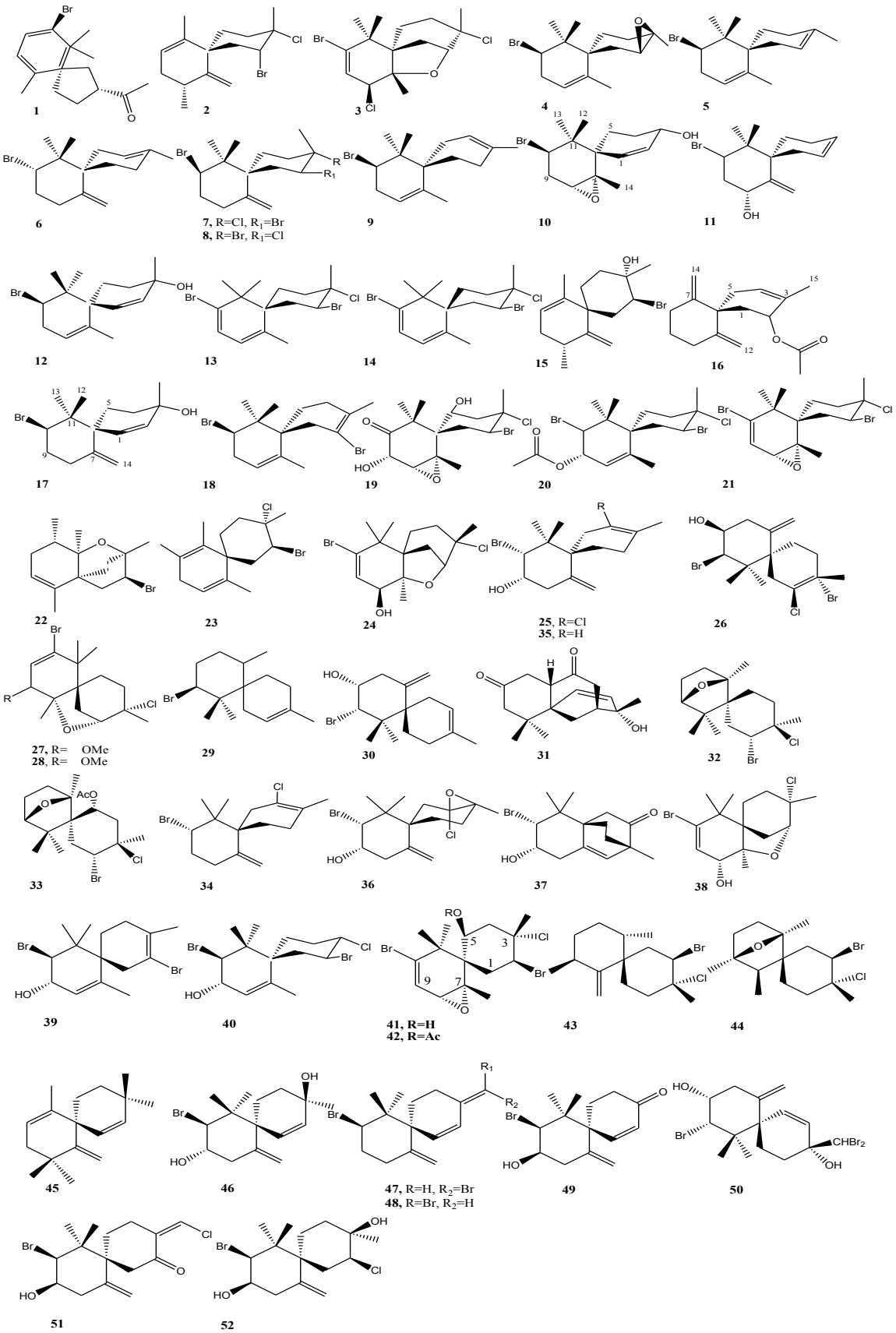

Figure 1: Chamigrane sesquiterpenes from *Laurencia*.

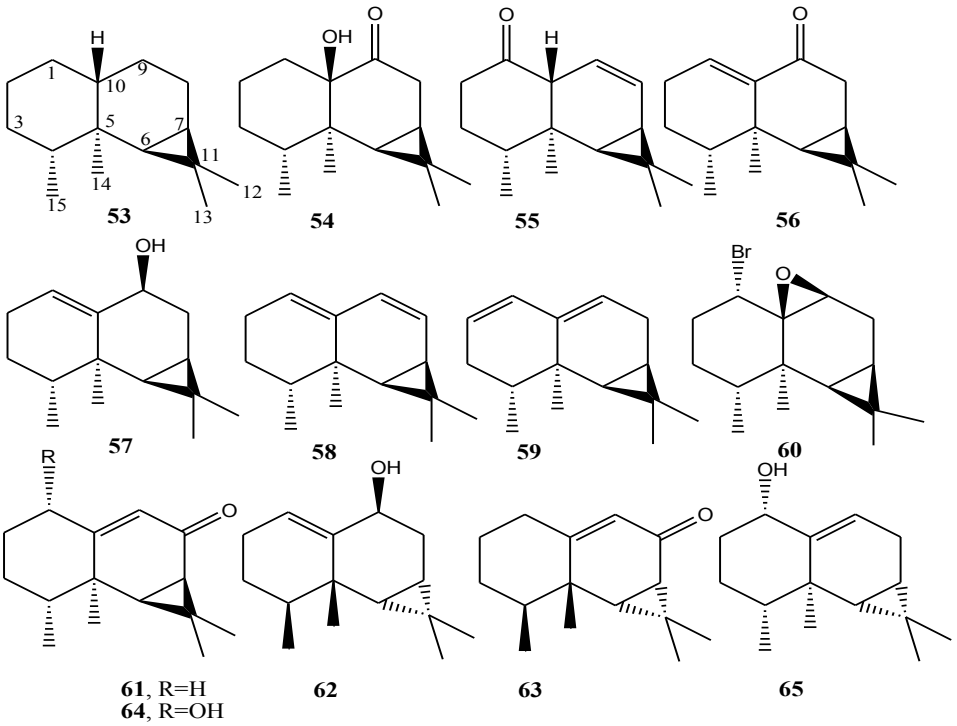

Figure 2: Aristolane sesquiterpenes from *t*

bisabolene-type structures of aldingenins A–D (**75-78**), isolated from *L. aldingensis* (Castelhanos, Brazil) [63,64]. The okamurenes A–D (**79-82**) were isolated from *L. okamurai*, whereas, okamurenes A (**79**) and B (**80**) were the first examples of bromobisabolanes possessing a phenyl moiety among sesquiterpenes derived from *Laurencia* as claimed by the authors. The isolated compounds displayed potent cytotoxicity when evaluated in the brine shrimp lethal assay [26] (Figure 3).

Cuparane Skeleton Sesquiterpenes

Cuparane skeleton is formed by cyclisation between carbons 6 and 11 of the bisabolane skeleton. In cuparane-type compounds, the three methyls in the aliphatic portion are located at positions 1, 2 and 2 [65]. In addition to marine organisms, cuparanes are found in liverworts and higher plants [66] (Figure 4).

L. okamurai, collected from the coast of Rongcheng, China, yielded 10-bromo-3-chlorocupar-5-en-2-ol (**83**) [25]. It is notable that most of the cuparane sesquiterpenes isolated from seaweeds have an aromatic ring such as compounds **84**–**86**, isolated from the Greek *L. microcladia*, collected at Chios Island in the North Aegean Sea. A strong cytotoxic activity was recognized for compounds **84**–**86** against NSCLC-N6 and A-549 lung cancer cell lines. Compound **85** showed a unique (for the cuparene class of sesquiterpenes) migration of the C-1 methyl group. The authors speculated that the aromatic hydroxyl group increased the cytotoxicity observed in compounds **85** and **86** [67]. Later on, laurokamurenes A (**87**) and B (**88**), were isolated from *L. okamurai* (Nanji Is., China) [68]. In 2007, total synthesis of the (±)-laurokamurene B (**88**) was completed, employing a combination of the Ireland–Claisen rearrangement and ring-closing metathesis reactions [69]. Lately, laurokamurene D (**89**) was isolated from *L. okamurai* Yamada [61] (Figure 5).

Laurane Skeleton Sesquiterpenes

In Laurane-type compounds, contrary to the cuparanes, the three methyls in the aliphatic portion are located at positions 1, 2 and 3. *Laurencia* is considered the main producer of laurane-type sesquiterpenes among marine organisms in general [65]. The Chinese *L. okamurai* collected from the coast of Rongcheng, yielded laurene (**90**), originally isolated from *L. glandulifera and L. nipponica* [70], and 7-hydroxylaurene acetate (**91**). Compound **90** exhibited potent antibacterial activity and lethal toxicity to brine shrimp [25]. However, 7-hydroxylaurene (**92**) was reported in 1977 as novel compound from *L. subopposita* and *L. okamurai* [71]. The compounds 12-hydroxy isolaurene (**93**), isolauraldehyde (**94**) and 8,11-dihydro-12-hydroxy isolaurene (**95**), isolated from *L. obtusa*, exhibited potent activity against the gram-positive *Bacillus subtilis* and *Staphylococcus aureus*, with **94** being the most active (MIC of 35 and 27 µg/mL, respectively). Compound **94** showed, also, significant activity against *Candida albicans* (MIC of 70 µg/mL) and promising *in vitro* activity against Ehrlich ascites carcinoma [72].

In 2005, the Chinese *L. okamurai* (Nanji Island) yielded laureperoxide (**96**), 10-bromoisoaplysin (**97**), isodebromolaurinterol (**98**) and 10-hydroxyisolaurene (**99**) as new compounds together with seven previously reported and related sesquiterpenes; aplysinol (**100**), isoaplysin (**101**), debromolaurinterol (**102**), debromolaurinterol acetate (**103**), laurinterol acetate (**104**), debromoisolaurinterol acetate (**105**) and isolaurinterol acetate (**106**) [73-75]. In the same year, 2005, *L. tristicha* (Naozhou Island, China) was the source of laur-11-en-2,10-diol (**107**), laur-11-en-10-ol (**108**), laur-11-en-1,10-diol (**109**), 4-bromo-1,10-epoxylaur-11-ene (**110**), previously reported as a synthetic racemate [76], cyclolauren-2-ol (**111**) and laurentristich-4-ol (**112**), along with the formerly known compounds aplysin (**113**), aplysinol (**100**), and the dimeric cyclolaurane sesquiterpene laurebiphenyl (**114**)

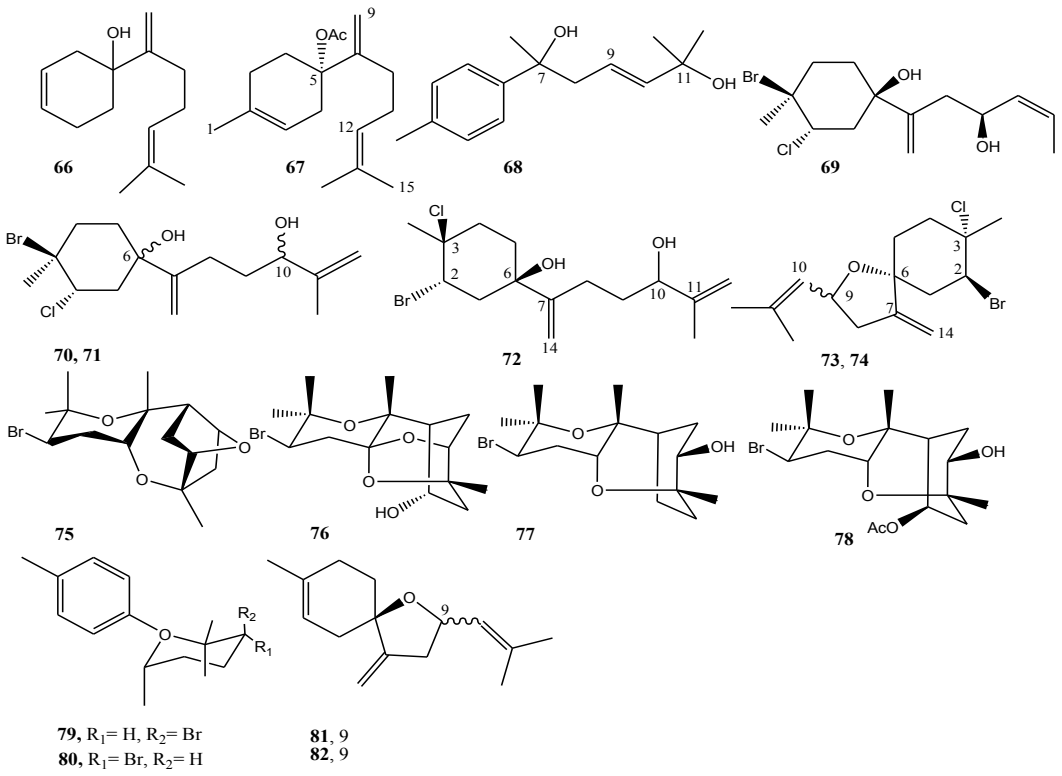

Figure 3: Bisabolane sesquiterpenes from *Laurencia*.

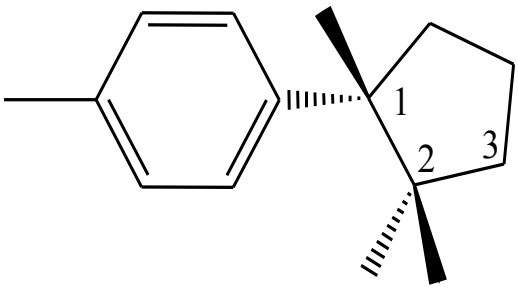

Figure 4: Structure of cuprane.

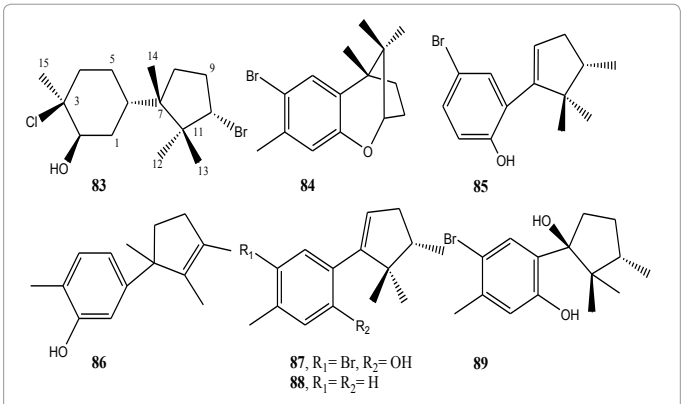

Figure 5: Cuparane sesquiterpenes from *Laurencia*.

[77,12]. Compound **112**, having a novel rearranged cyclolaurane skeleton was also reported recently from *L. okamurai* [78]. Compound **114** exhibited moderate cytotoxicity against several human cancer cell lines, while all other compounds were inactive [12]. The Chinese species *L. tristicha* produced aplysin-9-ene (**115**), epiaplysinol (**116**) and debromoepiaplysinol (**117**). Compound **117** displayed selective cytotoxicity to the HeLa cell line [79]. Another collection of *L. tristicha* (Shanwei, Guangdong Province, China) yielded the stereoisomers 4-bromolaur-11-en-1,10 β -diol (**118**) and 4-bromolaur-11-en-1,10 β -diol (**119**), along with the known laur-11-en-1,10 β -diol (**120**), but reported for the first time as a natural product [80,81].

A Chinese collection of *L. okamurai* (Nanji island) yielded laurepoxyene (**121**), 3 β -hydroperoxyaplysin (**122**), 3 β -hydroperoxy-3-epiaplysin (**123**) and 8,10-dibromoisoaplysin (**124**) [61]. The Australian *L. filiformis* (St. Paul's Beach, Australia) produced cycloisoallolaurinterol (**125**) and isoallolaurinterol (**126**) as new compounds, along with the previously reported filiformin (**127**), filiforminol (**128**), allolaurinterol (**129**) and 10-bromolaurenisol (**130**) [82]. The authors suggested that both **125** and **126** are formed as artefacts from compound **129** [83]. The previously reported allolaurinterol acetate (**131**) [84] was isolated again in 2012 from *L. okamurai* [25], while, isolaurenisol, (**132**) previously reported from *L.gracilis* [85] was obtained in 2009 from *L. saitoi* [46]. 3 β -hydroxyaplysin (**133**) was isolated from *L.okamurai* (Nanji Is., China) [68] while, *L. microcladia* (Chios Is., North Aegean Sea) provided the aromatic sesquiterpenes (**134-136**) and the dimeric brominated sesquiterpene **137** [60]. The organic extract of *L. obtusa*, collected from Serifos in the Aegean Sea afforded 3,7-dihydroxydihydrolaurene (**138**) and (**139**). Both compounds showed weak cytotoxic activity against five human tumour cell lines [86]. On the other hand, a *Laurencia* sp. collected from South

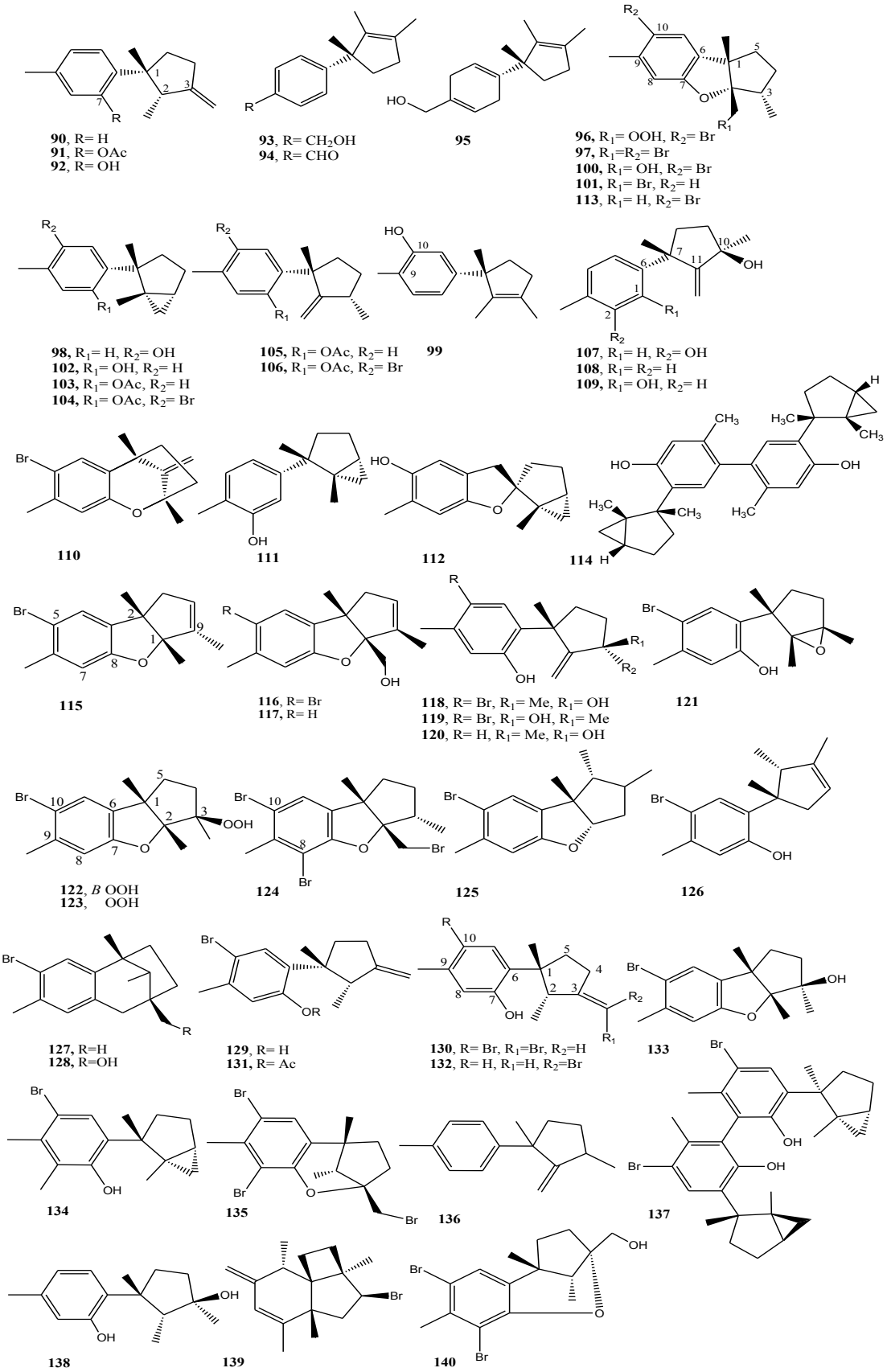

Figure 6: Laurane sesquiterpenes from *Laurencia*.

China Sea was the source of 8, 10-dibromo-3, 7-epoxy- laur-13-ol (**140**) [57] (Figure 6).

Brasilane Skeleton Sesquiterpenes

Brasilane skeleton has the basic structure of octahydro-1,6,6-trimethyl-4-(1-methyl)-1*H*-indene [65]. The rearranged halogenated compounds, with the unique 1,6-epoxy brasilane moiety (**141**–**143**) had been isolated; along with the known compounds brasilenol (**144**) and epibrasilenol (**145**) from *L. obtusa* collected off Symi Island in the Aegean Sea, Greece. Relative stereochemistries of all compounds were determined by molecular modeling [87]. *L. obtusa* (Tekirova, Turkey) produced also new brasilane-type sesquiterpene with the systemic name 2-Chloro-4-isopropyl-1,6,6-trimethylhexahydro-1*H*-indene-1,3 *β*,7 *β* -triol (**146**) [88] (Figure 7).

Eudesmane (selinane) Skeleton Sesquiterpenes

Eudesmane-type sesquiterpenes, formerly referred to as selinanes, have been recognized from several terrestrial and marine organisms and occasionally encountered from *Laurencia* [89]. Heterocladol (**147**) was the first example of a sesquiterpene with a selinane skeleton reported from *Laurencia* species and its structure was rationalized in terms of a trans-annular ring closure of a germacradiene [90]. *L. microcladia*, collected in the Baia di Calenzana, Elba Island, was the source of 8-cycloeudesmane (**148**), the first eudesmane sesquiterpene to be isolated from a marine origin [90]. In the same year, 2002, itomanol (**149**), was isolated from *L. intricata* collected in Okinawan waters [91]. In 2012, the brominated selinanes, 1-bromoselin-4(14),11-diene (**150**) and 9-bromoselin-4(14),11-diene (**151**), isolated from

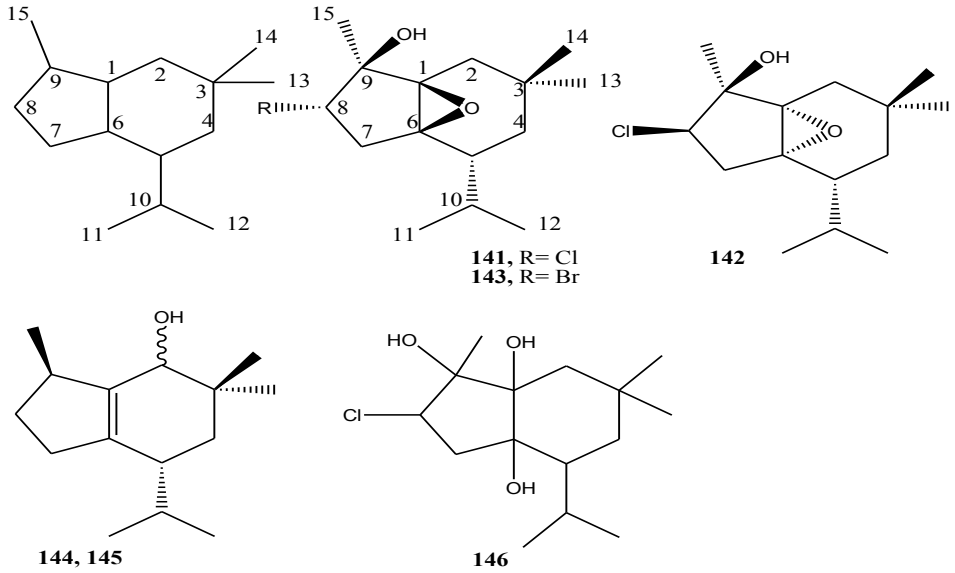

Figure 7: Brasilane sesquiterpenes from *Laurencia*.

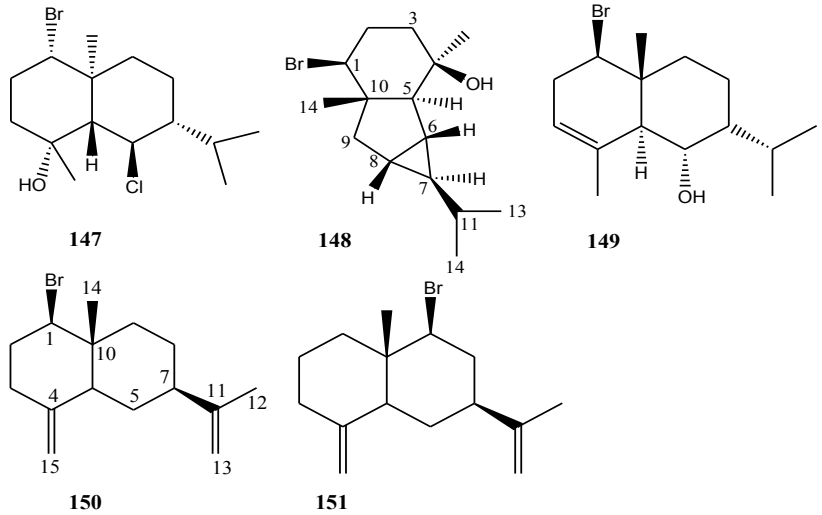

Figure 8: Eudesmane sesquiterpenes from *Laurencia*.

L. composita (Pingtan Island, China) displayed potent brine shrimp toxicity with LC_{50} of 15.2 and 78.7 µg/mL, respectively [30] (Figure 8).

Snyderane Skeleton Sesquiterpenes

The snyderane sesquiterpenes are bromo monocyclo-nerolidol derivatives. β -snyderol (**152**) and β -snyderol (**153**) were the first reported compounds having this skeleton from collections of *L. obtusa* and *L. snyderae*, respectively [92]. (8*R**)-8-bromo-10-*epi*-β-snyderol (**154**) and (8*S**)-8-bromo-β-snyderol (**155**) were isolated from *L. obtusa* collected from Bademli, Turkey. Compound **154** was active against D6 and W2 clones of the malaria parasite *Plasmodium falciparum* [16].

(4*E*)-1-bromo-5-[(1'S*,3'R*)-3'-bromo-2',2'-dimethyl-6'-methylenecyclohexyl]-3-methylpent-4-ene-2,3-diol (**156**) was isolated from *L. similis* (Sanya Bay, China) [93], while luzonensin (**157**) [94], luzonenone (**158**), luzofuran (**159**), 3,4-epoxypalisadin B (**160**), 1,2-dehydro-3,4-epoxypalisadin B (**161**) and 15-hydroxypalisadin (**162**) were obtained from *L. luzonensis*, from Okinawan waters [95]. The ethanolic extract of the Chinese *L. saitoi* (Hainan coastline) yielded 2-hydroxyluzofuranone A (**163**) and 2-hydroxyluzofuranone B (**164**) [96]. Another collection of the Okinawan *L. luzonensis*, a rich source of snyderane sesquiterpenes, afforded 3*R**, 4*S**-luzonolone (**165**), 3*S**, 4*R**-luzonolone (**166**), luzondiol (**167**), luzonenone (**158**) and the two isomeric compounds **168** and **169**, beside the known compound, aplysistatin (**170**). The authors suggested that compounds **168** and **169** were the first non-halogenated compounds, from the *Laurencia* genus, with a rearranged snyderane skeleton, as a result of a 1,2 methyl migration [97]. Aplysistatin (**170**), obtained from *L. snackeyi* in a bioassay-guided isolation, significantly inhibited NO and prostaglandin-E2 (PGE2) production. Activity was attributed to the modulation of anti-inflammatory agents *via* the inhibition of nitric oxide synthase (NOS) and cyclooxygenase-2 (COX-2) expressions in LPS-stimulated RAW 264.7 cells [98]. On the other hand, 5β-hydroxypalisadin B (**171**), isolated also from ***L.*** *snackeyi*,

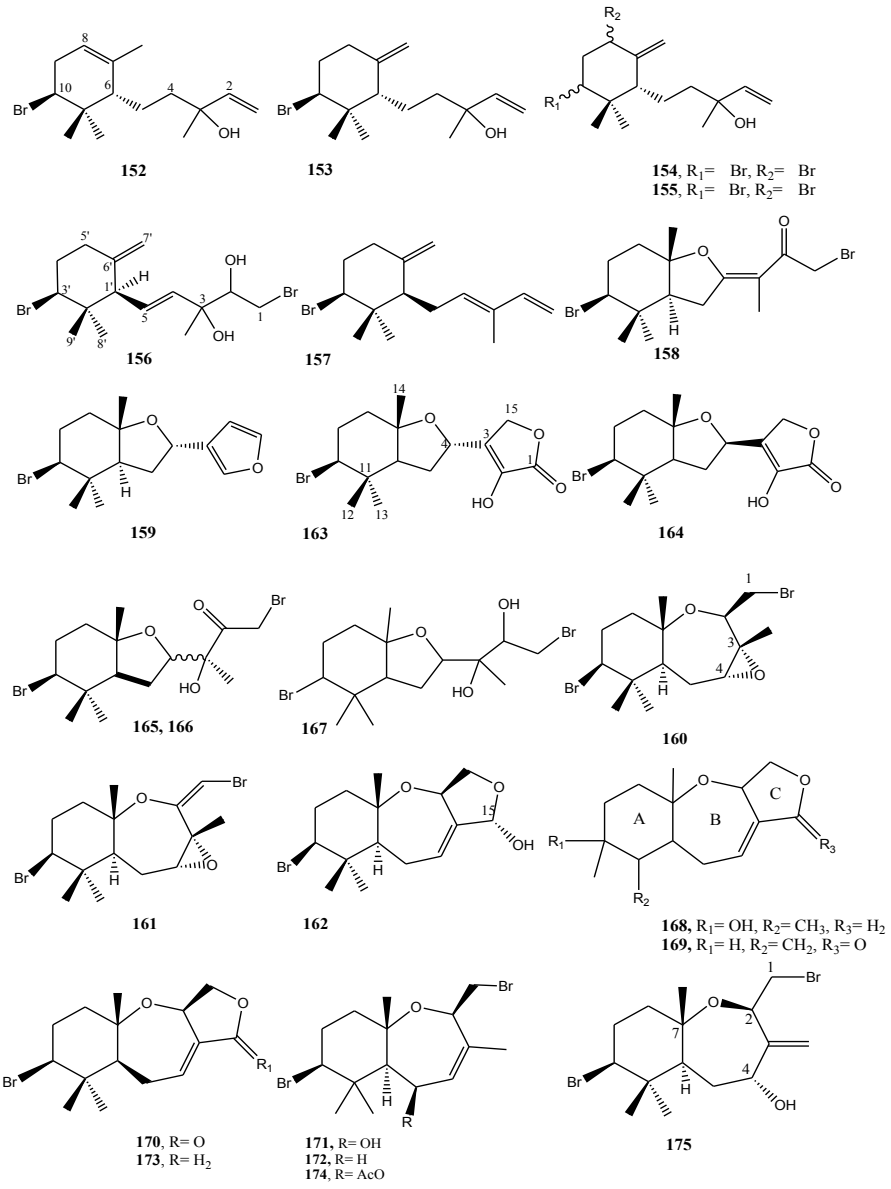

Figure 9: Snyderane sesquiterpenes from *Laurencia*.

exhibited profound anti-inflammatory activity in lipopolysaccharide (LPS)-induced nitric oxide (NO) production in zebrafish embryo. The protective effect was comparable to the anti-inflammatory agent dexamethasone with effective concentrations of the compound between 0.25- 1µg/mL [99]. On the other hand, *L. luzonensis* was the source of palisadin B (**172**), palisadin A (**173**) and its oxidized product aplysistatin (**170**) [94]. *L. saitoi* (Hainan coastline, China) was the source of 5-acetoxypalisadin B (**174**) [100] and 4-hydroxypalisadin C (**175**) [96] (Figure 9).

Other Skeletons Sesquiterpenes

In addition to the skeletons mentioned above, there are some other sesquiterpenes, reported from different species of *Laurencia* that do not fit easily into the above categories.

L. microcladia, from Elba Island, provided a novel calenzanane sesquiterpene named calenzanol (**176**) [101]. Later, debromoisocalenzanol (**177**) and an indene-type sesquiterpene (**178**) were, also, obtained from *L. microcladia,* [102]. *L. obtusa* collected at Milos Island in the Aegean Sea Greece yielded four undecane-3-one sesquiterpenes (**179-182**) and perforenone D (**183**). The relative stereochemistry of the known compound perforatone (**184**) was revised [87]. On the other hand, perforenol B (**185**), which was also, isolated from *L. obtusa,* exhibited strong cytotoxic activity [86]. Moreover, *L. obtusa* from Cayo Coco, Cuba was the source of bromocyclococanol (**186**), possessing a novel carbon skeleton of fused cyclopropane–cyclopentane rings [103]. The Turkish *L. obtusa* collected from Bademli, yielded 5-bromo-3-(3'-hydroxy-3'-methylpent-4'-enylidene)-2,4,4-trimethylcyclohexanone (**187**), and the epoxide (**188**) [16]. The previously known as a synthetic compound, isoafricanol (**189**) [104] was reported from *L. mariannensis* (Hainan and Weizhou Islands, China) as a natural product, together with a chromene type sesquiterpene, isodactyloxene A (**190**) [24]. 4-hydroxy-1,8-*epi*-isotenerone (**191**), 9-hydroxy-3-*epi*-perforenone A (**192**) and 3-*epi*-perforenone (**193**) were isolated from the lipophilic extract of *L. perforata*, collected from the Great Barrier Reef, Australia [105]. Tiomanene (**194**), acetylmajapolene B (**195**) and acetylmajapolene A (**196**) were isolated from an unrecorded *Laurencia* species collected at Pulau Tioman, Pahang (Malaysia) [106] along with the known majapolene B (**197**) and majapolene A (**198**), originally isolated from *L. majuscula* [107]. The use of vibrational circular dichroism (VCD) allowed the determination of the absolute configuration of **195** and **198** as 7*S*, 10*S* for both [108].

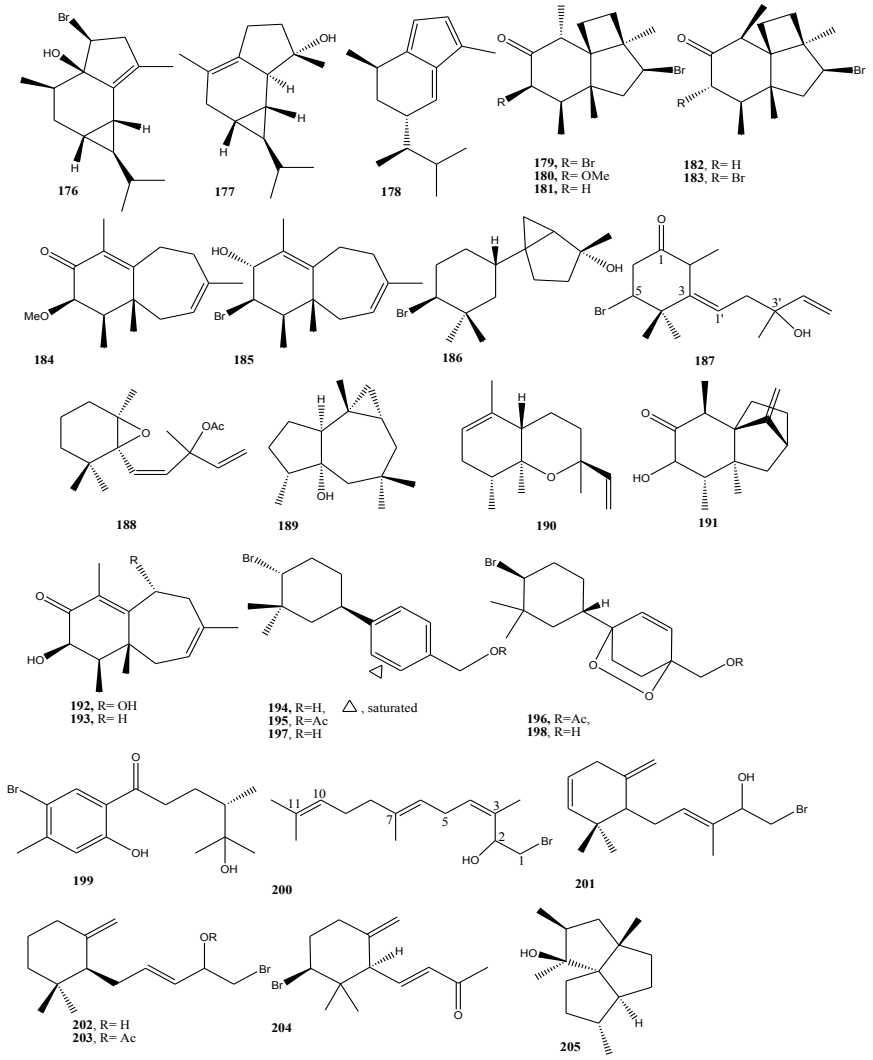

Figure 10: Other skeletons sesquiterpenes from *Laurencia*.

A ring-cleaved sesquiterpene, reported as having a novel skeleton, was isolated from *L. okamurai* Yamada and named seco-laurokamurone (**199**) [61]. *L. luzonensis* from Okinawan waters yielded (3*Z*,6*E*)-1-bromo-2-hydroxy-3,7,11-trimethyldodeca-3,6,10-triene (**200**), isopalisol (**201**), luzonensol (**202**) and luzonensol acetate (**203**) [95], while, the norsesquiterpene derivative, 2-bromo-β-ionone (**204**) was isolated from *L. saitoi* (Hainan coastline, China) [97]. A triquinane derivative (**205**) was identified from *L. dendroidea*, in the Brazilian coast, and was found to be moderately active against *Leishmania amazonensis* (IC_{50} 43.8µg/mL) [109] (Table 2 and Figure 10).

Conclusion

Among the red algae, genus *Laurencia* is known to be one of the most *important* resources to produce unique natural metabolites with novel structures. A large number of sesquiterpene compounds with unprecedented structural features have been described from different *Laurencia* species during the past years. In the present review, an attempt to congregate the phytochemical and biological information on *Laurencia* sesquiterpenes was conducted. Survey of literature revealed the presence of over 200 sesquiterpenoids isolated from different species, over the last 14 years, and reported either as novel or known compounds. The numerous chemical diversity and biological activities of genus *Laurencia* keep attracting the attentions of phytochemists and pharmacologists to further explore different species of this interesting red weed distributed in the oceans and seas around the world.

References

1. Masuda M, Kogame K, Arisawa S, Suzuki M (1998) Morphology and halogenated secondary metabolites of three Gran Canarian species of Laurencia ceramiales, Rhodophyta. Botanica Marina 41: 265-277.
2. Sentíes A, Díaz-Larrea J, Cassano V, Gil-Rodríguez MC, Mutue T, et al. (2011) Laurencia marilzae (ceramiales, rhodophyta) from the mexican caribbean: a new record for the tropical western atlantic. Bulletin of Marine Science 87: 681-686.
3. http://www.algaebase.org/
4. Suzuki M, Vairappan CS (2005) Halogenated secondary metabolites from Japanese species of the red algal genus Laurencia (Rhodomelaceae, Ceramiales. Curr Top Phytochem 7: 1–34.
5. Wang BG, Gloer JB, Ji NY, Zhao JC (2013) Halogenated organic molecules of Rhodomelaceae origin: chemistry and biology. Chem Rev 113: 3632-3685.
6. Suzuki M, Takahashi Y, Nakano S, Abe T, Masuda M, et al. (2009) An experimental approach to study the biosynthesis of brominated metabolites by the red algal genus Laurencia. Phytochemistry 70: 1410-1415.
7. Young DN, Howard BM, Fenical W (1980) Subcellular localization of brominated secondary metabolites in the red alga Laurencia snyderae. J Phycol 16: 182-185.
8. Vairappan CS, Suzuki M, Abe T, Masuda M (2001) Halogenated metabolites with antibacterial activity from the Okinawan Laurencia species. Phytochemistry 58: 517-523.
9. Amsler, Charles D (2008) Algal chemical ecology. Springer-Verlag press.
10. Cabrita MT, Vale C, Rauter AP (2010) Halogenated compounds from marine algae. Mar Drugs 8: 2301-2317.
11. Juagdan EG, Kalidindi R, Scheuer P (1997) Two new chamigranes from an hawaiian red alga, Laurencia cartilaginea.Tetrahedron 53: 521-528.
12. Sun J, Shi D, Ma M, Li S, Wang S, et al. (2005) Sesquiterpenes from the red alga Laurencia tristicha. J Nat Prod 68: 915-919.
13. König GM, Wright AD (1997) Laurencia rigida: chemical investigations of its antifouling dichloromethane extract. J Nat Prod 60: 967-970.
14. Alarif WM, Al-Lihaibi SS, Abdel-Lateff A, Ayyad SE (2011) New antifungal cholestane and aldehyde derivatives from the red alga Laurencia papillosa. Nat Prod Commun 6: 1821-1824.
15. Li YX, Li Y, Qian ZJ, Kim MM, Kim SK (2009) In vitro antioxidant activity of 5-HMF isolated from marine red alga Laurencia undulata in free-radical-mediated oxidative systems. J Microbiol Biotechnol 19: 1319-1327.
16. Topcu G, Aydogmus Z, Imre S, Gören AC, Pezzuto JM, et al. (2003) Brominated sesquiterpenes from the red alga Laurencia obtusa. J Nat Prod 66: 1505-1508.
17. Davyt D, Fernandez R, Suescun L, Mombrú AW, Saldaña J, et al. (2001) New sesquiterpene derivatives from the red alga Laurencia scoparia. Isolation, structure determination, and anthelmintic activity. J Nat Prod 64: 1552-1555.
18. Jung WK, Choi I, Oh S, Park SG, Seo SK, et al. (2009) Anti-asthmatic effect of marine red alga (Laurencia undulata) polyphenolic extracts in a murine model of asthma. Food Chem Toxicol 47: 293-297.
19. Kurata K, Taniguchi K, Agatsuma Y, Suzuki M (1998) Diterpenoid feeding-deterrents from Laurencia saitoi. Phytochemistry 47: 363-369.
20. Dembitsky VM, Tolstikov GA (2004) Natural halogenated sesquiterpens from marine organisms, chemistry for sustainable development 12: 1-12.
21. Erickson KL (1983) Marine natural products. Academic Press.
22. Suzuki M, Kurosawa E, Irie T (1970) Spirolaurenone, a new sesquiterpenoid containing bromine from Laurencia glandulifera Kützing. Tetrahedron Lett 11: 4995-4998.
23. Li XD, Ding W, Miao FP, Ji NY (2012) Halogenated chamigrane sesquiterpenes from Laurencia okamurae. Magn Reson Chem .
24. Ji NY, Li XM, Li K, Ding LP, Gloer JB, et al. (2007) Diterpenes, sesquiterpenes, and a C15-acetogenin from the marine red alga Laurencia mariannensis. J Nat Prod 70: 1901-1905.
25. Li XD, Miao FP, Li K, Ji NY (2012) Sesquiterpenes and acetogenins from the marine red alga Laurencia okamurai. Fitoterapia 83: 518-522.
26. Liang Y, Li XM, Cui CM, Li CS, Sun H, et al. (2012) Sesquiterpene and acetogenin derivatives from the marine red alga Laurencia okamurai. Mar Drugs 10: 2817-2825.
27. Ji NY, Li XM, Zhang Y, Wang BG (2007) Two new halogenated chamigrane-type sesquiterpenes and other secondary metabolites from the marine red alga Laurencia okamurai and their chemotaxonomic significance. Biochem Syst Ecol 35: 627-630.
28. Liang Y, Li XM, Cui CH, Li CS, Wang GW (2009) A new rearranged chamigrane sesquiterpene from Laurencia okamurai. Chinese Chemical Letters 20: 190-192.
29. de Nys R, Coll JC, Bowden BF (1993) Tropical marine algae IX A new sesquiterpenoid metabolite from the red alga Laurencia mariannensis. Aust J Chem 46: 933-937.
30. Li XD, Miao FP, Yin XL, Liu JL, Ji NY (2012) Sesquiterpenes from the marine red alga Laurencia composita. Fitoterapia 83: 1191-1195.
31. Ji NY, Li XM, Li K, Gloer JB, Wang BG (2008) Halogenated sesquiterpenes and non-halogenated linear C15-acetogenins from the marine red alga Laurencia composita and their chemotaxonomic significance. Biochem Syst Ecol 36: 938-941.
32. Ji NY, Li XM, Wang BG (2010) Sesquiterpenes and other metabolites from the marine red alga Laurencia composita (Rhodomelaceae). Helv Chim Acta 93: 2281-2286.
33. Sims JJ, Lin GHY, Wing RM (1974) Marine natural products X elatol, a halogenated sesquiterpene alcohol from the red alga Laurencia elata. Tetrahedron Lett 15: 3487-3490.
34. Lhullier C, Donnangelo A, Caro M, Palermo JA, Horta PA, et al. (2009) Isolation of elatol from Laurencia microcladia and its palatability to the sea urchin Echinometra lucunter. Biochem Syst Ecol 37: 254–259.
35. Gonzalez AG, Darias J, D'iaz A, Fourneron JD, Martin JD, et al. (1976) Evidence for the biogenesis of halogenated chamigrenes from the red alga Laurencia obtusa. Tetrahedron Lett 17: 3051-3054.
36. Vairappan CS (2003) Potent antibacterial activity of halogenated metabolites from Malaysian red algae, Laurencia majuscula (Rhodomelaceae, Ceramiales). Biomol Eng 20: 255-259.
37. Dos Santos AO, Veiga-Santos P, Ueda-Nakamura T, Filho BP, Sudatti DB, et al. (2010) Effect of elatol, isolated from red seaweed Laurencia dendroidea, on Leishmania amazonensis. Mar Drugs 8: 2733-2743.
38. Desoti VC, Lazarin-Bidóia D, Sudatti DB, Pereira RC, Alonso A, et al. (2012) Trypanocidal action of (-)-elatol involves an oxidative stress triggered by mitochondria dysfunction. Mar Drugs 10: 1631-1646.
39. Campos A, Souza CB, Lhullier C, Falkenberg M, Schenkel EP, et al. (2012) Anti-tumour effects of elatol, a marine derivative compound obtained from red algae Laurencia microcladia. J Pharm Pharmacol 64: 1146-1154.
40. Dias DA, Urban S (2011) Phytochemical studies of the southern Australian marine alga, Laurencia elata. Phytochemistry 72: 2081-2089.

41. Blunt JW, Copp BR, Munro MHG, Norhcote, PT, Prinsep MR (2003) Marine natural products. Nat Prod Rep 20: 1-48.

42. Dorta E, Díaz-Marrero AR, Cueto M, D'Croz L, Maté JL, et al. (2004) Chamigrenelactone, a polyoxygenated sesquiterpene with a novel structural type and devoid of halogen from Laurencia obtusa. Tetrahedron Lett 45: 7065-7068.

43. Brito I, Cueto M, Díaz-Marrero AR, Darias J, San Martín A (2002) Oxachamigrenes, new halogenated sesquiterpenes from Laurencia obtusa. J Nat Prod 65: 946-948.

44. Gonza´lez AG, Marti´n JD, Marti´n VS, Norte M, Pe´rez R (1982) Biomimetic approach to the synthesis of rhodolaureol and rhodolauradiol. Tetrahedron Lett 23: 2395-2398.

45. Suzuki M, Kurosawa E, Furusaki A (1988) The structure and absolute stereochemistry of a halogenated chamigrene derivative from the red alga Laurencia species. Bull Chem Soc Jpn 61: 3371-3373.

46. Ji NY, Li XM, Li K, Wang BG (2009) Halogenated sesquiterpenes from the marine red alga Laurencia saitoi (Rhodomelaceae). Helv Chim Acta 92: 1873-1879.

47. Howard BM, Fenical W (1975) Structures and chemistry of two new halogen-containing chamigrene derivatives from Laurencia. Tetrahedron Lett 16: 1687.

48. Jongaramruong J, Blackman AJ, Skelton BW, White AH (2002) Chemical relationships between the sea hare Aplysia parvula and the red seaweed Laurencia filiformis from Tasmania. Aust J Chem 55: 275-280.

49. Suzuki M, Daitoh M, Vairappan CS, Abe T, Masuda M (2001) Novel halogenated metabolites from the Malaysian Laurencia pannosa. J Nat Prod 64: 597-602.

50. Juagdan EG, Kalidindi R, Scheuer PJ (1997) Two new chamigranes from an hawaiian red alga, Laurencia cartilaginea. Tetrahedron 53: 521-528.

51. Suescun L, Mombrú AW, Mariezcurrena RA, Davyt D, Fernández R, et al. (2001) Two natural products from the algae Laurencia scoparia. Acta Crystallogr C 57: 286-288.

52. Francisco ME, Erickson KL (2001) Ma'iliohydrin, a cytotoxic chamigrene dibromohydrin from a Philippine Laurencia species. J Nat Prod 64: 790-791.

53. da Silva Machado FL, Ventura TL, Gestinari LM, Cassano V, Resende JA, et al. (2014) Sesquiterpenes from the Brazilian red alga Laurencia dendroidea J. Agardh. Molecules 19: 3181-3192.

54. Rucker R, Kretzuschmar U (1971) 9-Aristolen-1a-ol and 1,2,9,10-tetradehydroaristolane, new aristolane type sesquiterpenes. Liebigs Ann Chem 748: 214-217.

55. Ji NY, Li XM, Ding LP, Wang BG (2007) Aristolane sesquiterpenes and highly brominated indoles from the marine red alga Laurencia similis (Rhodomelaceae). Helv Chim Acta 90: 385-391.

56. Li CS, Li XM, Cui CM, Wang BG (2010) Brominated metabolites from the marine red alga Laurencia similis. Z. Naturforsch 65: 87-89.

57. Su S, Sun WS, Wang B, Cheng W, Liang H, et al. (2010) A novel brominated cuparene-derived sesquiterpene ether from the red alga Laurencia sp. J Asian Nat Prod Res 12: 916-920.

58. Kamada T, Vairappan CS (2013) New bioactive secondary metabolites from Bornean red alga, Laurencia similis (Ceramiales). Nat Prod Commun 8: 287-288.

59. Fraga BM (1997) Natural sesquiterpenoids. Nat Prod Rep 14: 145-162.

60. Kladi M, Vagias C, Papazafiri P, Furnari G, Serio D, et al. (2007) New sesquiterpenes from the red alga Laurencia microcladia. Tetrahedron 63: 7606-7611.

61. Yu XQ, He WF, Liu DQ1, Feng MT, Fang Y, et al. (2014) A seco-laurane sesquiterpene and related laurane derivatives from the red alga Laurencia okamurai Yamada. Phytochemistry 103: 162-170.

62. Davyt D, Fernandez R, Suescun L, Mombrú AW, Saldaña J, et al. (2006) Bisabolanes from the red alga Laurencia scoparia. J Nat Prod 69: 1113-1116.

63. de Carvalho LT, Fujii MT, Roque NF, Kato MJ, Lago JHG (2003) Aldingenin A, new brominated sesquiterpene from red algae Laurencia aldingensis. Tetrahedron Lett 44: 2637-2640.

64. de Carvalho LR, Fujii MT, Roque NF, Lago JH (2006) Aldingenin derivatives from the red alga Laurencia aldingensis. Phytochemistry 67: 1331-1335.

65. Conolly JD, Hill RA. (1991)Dictionary of Terpenoids, Volume 1, mono and sesquiterpenoids, Chapman and Hall, London, UK.

66. Zhan ZJ, Ying YM, Ma LF, Shan WG (2011) Natural disesquiterpenoids. Nat Prod Rep 28: 594-629.

67. Kladi M, Vagias C, Furnari G, Moreau D, Roussakis C, et al. (2005) Cytotoxic cuparene sesquiterpenes from Laurencia microcladia. Tetrahedron Lett 46: 5723-5726.

68. Mao SC, Guo YW (2006) A laurane sesquiterpene and rearranged derivatives from the Chinese red alga Laurencia okamurai Yamada. J Nat Prod 69: 1209-1211.

69. Srikrishna A, Khan IA, Ramesh Babu R, Sajjanshetty A (2007) The first total synthesis of (±)-laurokamurene B. Tetrahedron 63: 12616-12620.

70. Irie T, Suzuki T, Yasunari Y, Kurosawa E, Masamune T (1969) Laurene, a sesquiterpene hydrocarbon from Laurencia species. Tetrahedron 25: 459-468.

71. Wratten SJ, Faulkner DJ (1977) Metabolites of the red alga Laurencia subopposita. J Org Chem 42: 3343-3349.

72. Alarif WM, Al-Lihaibi SS, Ayyad SE, Abdel-Rhman MH, Badria FA (2012) Laurene-type sesquiterpenes from the Red Sea red alga Laurencia obtusa as potential antitumor-antimicrobial agents. Eur J Med Chem 55: 462-466.

73. Yamamura S, Hirata Y (1963) Structures of aplysin and aplysinol, naturally occurring bromo-compounds. Tetrahedron 19: 1485–1496.

74. Elzen GW, Williams HJ, Vinson SB (1984) Isolation, identification, and bioassay of cotton synomones mediating searching behavior by parasitoid Campoletis sonorensis. Journal of Chemical Ecology 10: 1251-1264.

75. Mao S, Guo Y (2005) Cuparene-Derived sesquiterpenes from the Chinese red alga Laurencia okamurai YAMADA Helv Chim Acta 88: 1034-1039.

76. Goldsmith J, John TK, Kwong, CD, Painter III GR (1980) Preparation and rearrangement of trichothecane-like compounds. Synthesis of aplysin and filiformin. J Org Chem 45: 3989-3993.

77. Shizuri Y, Yamada K (1985) Laurebiphenyl, a dimeric sesquiterpene of the cyclolaurane-type from the red alga Laurencia nidifica. Phytochemistry 24: 1385–1386.

78. Liang Y, Li XM, Li CS, Sun H, Wang BG (2014) Laurane-, cyclolaurane-, and cuparane-type sesquiterpenes from the marine red alga Laurencia okamurai. Nat Prod Commun 9: 323-324.

79. Sun J, Han LJ, Shi DY, Fan X, Wang SJ et al. (2005) Sesquiterpenes from red alga Laurencia tristicha. Chin Chem Lett 16: 1611-1614.

80. Nemoto H, Nagamochi M, Ishibashi H, Fukumoto K (1994) A remarkable substituent effect on the enantioselectivity of tandem asymmetric epoxidation and enantiospecific ring expansion of cyclopropylidene alcohols: a new enantiocontrolled synthesis of (-)-debromoaplysin and (-)-aplysin. J Org Chem 59: 74-79.

81. Ji NY, Li XM, Li K, Ding LP, Wang BG (2008) Laurane-derived sesquiterpenes from the marine red alga Laurencia tristicha (Rhodomelaceae). Nat Prod Res 22: 715-718.

82. Kaslauskas R, Murphy PT, Quin RJ, Wells RJ (1976) New laurene derivatives from Laurencia filiformis. Aust J Chem 29: 2533-2539.

83. Dias DA, White JM, Urban S (2009) Laurencia filiformis: phytochemical profiling by conventional and HPLC-NMR approaches. Nat Prod Commun 4: 157-172.

84. Appleton DR, Babcock RC, Copp BR (2001) Novel tryptophan-derived dipeptides and bioactive metabolites from the sea hare Aplysia dactylomela. Tetrahedron 57: 10181–10189.

85. Kçnig GM, Wright AD (1994) New C15 Acetogenins and sesquiterpenes from the red alga Laurencia sp. cf. L. gracilis. J Nat Prod 57: 477-485.

86. Kladi M, Xenaki H, Vagias C, Papazafiri P Roussis V (2006) New cytotoxic sesquiterpenes from the red algae Laurencia obtusa and Laurencia microcladia Tetrahedron 62: 182 189.

87. Iliopoulou D, Roussis V, Pannecouque C, De Clercq E, Vagias C (2002) Halogenated sesquiterpenes from the red alga Laurencia obtusa. Tetrahedron 58: 6749-6755.

88. AydoÄŸmuÅŸ Z, Imre S, Ersoy L, Wray V (2004) Halogenated secondary metabolites from Laurencia obtusa. Nat Prod Res 18: 43-49.

89. Brennan MR, Erickson KL (1982) Austradiol acetate and austradiol diacetate, 4,6-dihydroxy-(+)-selinane derivatives from an Australian Laurencia sp. J Org Chem 47: 3917-3921.

90. Kazlauskas R, Murphy PT, Wells RJ, Daly JJ, Oberhansli WE (1977) Heterocladol, a halogenated selinane sesquiterpene of biosynthetic significance from the red alga Laurencia filiformis: Its isolation, crystal structure and absolute configuration. Australian Journal of Chemistry 30; 2679 - 2687

91. Guella G, Skropeta D, Mancini I, Pietra F (2002) The First 6,8-cycloeudesmane

sesquiterpene from a marine organism: The red seaweed Laurencia microcladia from the Baia di Calenzana, Elba island. Z. Naturforsch, B: Chem Sci 57: 1147-1151.

92. Suzuki M, Takahashi Y, Mitome Y, Itoh T, Abe T, et al. (2002) Brominated metabolites from an Okinawan Laurencia intricata. Phytochemistry 60: 861-867.

93. Reward BM, Fenical W (1976) a- and ß-snyderol; new bromo-monocyclic sesquiterpenes from the seaweed Laurencia. Tetrahedron Lett 17: 41-44.

94. Su H, Shi DY, Li J, Guo SJ, Li LL, et al. (2009) Sesquiterpenes from Laurencia similis. Molecules 14: 1889-1897.

95. Kuniyoshi M, Marma MS, Higa T, Bernardinelli G, Jefford CW (2001) New bromoterpenes from the red alga Laurencia luzonensis. J Nat Prod 64: 696-700.

96. Kuniyoshi M, Wahome PG, Miono T, Hashimoto T, Yokoyama M, et al. (2005) Terpenoids from Laurencia luzonensis. J Nat Prod 68: 1314-1317.

97. Su H, Yuan ZH, Li J, Gua SJ, Deng LP, et al. (2009) Sesquiterpenes from the marine red alga Laurencia saitoi. Helv Chim Acta 92: 1291-1297.

98. Makhanu DS, Yokoyama M, Miono T, Maesato T, Maedomari M, et al. (2006) New sesquiterpenes from the Okinawan red alga Laurencia luzonensis. Bull Fac Sci Univ Ryukyus 81: 115-120.

99. Vairappan CS, Kamada T, Lee WW, Jeon YJ (2013) Anti-inflammatory activity of halogenated secondary metabolites of Laurencia snackeyi (Weber-van Bosse) Masuda in LPS-stimulated RAW 264.7 macrophages. J Appl Phycol 25: 1805-1813.

100. Wijesinghe WA, Kim EA1, Kang MC1, Lee WW1, Lee HS2, et al. (2014) Assessment of anti-inflammatory effect of 5Î²-hydroxypalisadin B isolated from red seaweed Laurencia snackeyi in zebrafish embryo in vivo model. Environ Toxicol Pharmacol 37: 110-117.

101. Su H, Yuan Z, Li J, Guo S, Han L, et al. (2009) [Studies on chemical constituents of Laurencia saitoi]. Zhongguo Zhong Yao Za Zhi 34: 871-874.

102. Guella G, Skropeta D, Mancini I, Pietra F (2003) Calenzanane sesquiterpenes from the red seaweed Laurencia microcladia from the Bay of Calenzana, Elba Island: acid-catalyzed stereospecific conversion of calenzanol into indene- and guaiazulene-type sesquiterpenes. Chemistry 9: 5770-5777.

103. Brito I, Cueto M, Dorta E, Darias J (2002) Bromocyclococanol,a halogenated sesquiterpene with a novel carbon skeleton from the red alga Laurencia obtusa. Tetrahedron Lett 43: 2551-2553.

104. Fan W, White JB (1993) Total synthesis of (+-.)-africanol and (+-)-isoafricanol. J Org Chem 58: 3557-3562.

105. Wright AD, Goclik E, König GM (2003) Three new sesquiterpenes from the red alga Laurencia perforata. J Nat Prod 66: 435-437.

106. Vairappan CS, Suzuki M, Ishii T, Okino T, Abe T, et al. (2008) Antibacterial activity of halogenated sesquiterpenes from Malaysian Laurencia spp. Phytochemistry 69: 2490-2494.

107. Erickson KL, Beutler JA, Gray GN, Cardellina JH 2nd, Boyd MR (1995) Majapolene A, a cytotoxic peroxide, and related sesquiterpenes from the red alga Laurencia majuscula. J Nat Prod 58: 1848-1860.

108. Monde K, Taniguchi T, Miura N, Vairappan CS, Suzuki M (2006) Absolute configurations of brominated sesquiterpenes determined by vibrational circular dichroism. Chirality 18: 335-339.

109. da Silva Machado FL, Pacienza-Lima W, Rossi-Bergmann B, de Souza Gestinari LM, Fujii MT, et al. (2011) Antileishmanial sesquiterpenes from the Brazilian red alga Laurencia dendroidea. Planta Med 77: 733-735.