

Marine and Soil Derived Natural Products: A New Source of Novel Cardiovascular Protective Agents Targeting the Endothelin System

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Key words

- endothelin
- hypertension
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- microorganisms
- ecology

Abstract

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 Inhibition of the endothelin system is a recognized therapeutic approach for treating complex cardiovascular diseases. The search for natural inhibitors of the endothelin system has focused mainly on land, with recent, emerging data sug-

gesting the underestimated potential of marine microorganisms for producing leads with cardioprotective potential. The present work reviews natural products identified as inhibitors of the endothelin system, their origin, their mechanism of action, and their ecological significance.

Introduction

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 More than three decades of research on marine natural products have exposed their potential as antimicrobial, antiviral, antiparasitic, anticancer, anti-inflammatory, neuroprotective, and immunomodulatory agents [1–6]. However, very little is known about their cardioprotective potential [5,6]. Cardiovascular disorders remain the main cause of mortality, morbidity, and health care burden worldwide [7]. The endothelin system is a key player in many conditions associated with cardiovascular disorders including hypertension, heart failure [7–9], and atherosclerosis [10]. The current literature regarding the screening of marine natural products for cardioprotection focuses on well validated targets such as the angiotensin converting enzyme of renin-angiotensin-aldosterone [11] and the endothelin receptors [12–15]. The emerging data suggest that marine microorganisms are a suitable source of bioactive lead compounds. In this review, we focus on marine natural products targeting the inhibition of the endothelin system, their origin, their mechanism of action, and their ecological relevance. Other marine natural products with cardiovascular activity will also be briefly discussed.

The Endothelin System and Its Drug Targets

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 Endothelin-1 (ET-1) is a potent vasoconstrictor and the predominant compound of the endothelin family with the highest clinical relevance [16]. The biosynthesis of ET-1 starts with the large precursor protein of 212 amino acids (AA) called proendothelin-1 (PPET1), which is encoded by the ET-1 gene (EDN1) in the human chromosome 6 (○ Fig. 1). Removal of a short secretory sequence generates proendothelin-1 (proET-1, 195 AA) [16]. In the cytosol, proET-1 is then cleaved by a furin-like endopeptidase producing the 38 AA-peptide precursor big ET-1 [17]. This inactive fraction is next converted to ET-1 by endothelin converting enzyme-1 (ECE-1) which cleaves the Trp₂₁-Val₂₂ bond in the carboxylterminal of big ET-1 [18]. Big ET-1 can also be cleaved by human chymase and neutral endopeptidase (NEP) to produce ET-1 [19]. The activation of EDN1 expression may be mediated by angiotensin II (Ang II), catecholamines, cardiostrophin-1, thrombin, growth factors, cytokines, free radicals, insulin, hypoxia, shear stress, lipoproteins, cyclosporine, as well as by the same ET-1 (○ Fig. 1) [20,21]. ET-1 mediates its effects by means of two G-protein coupled receptors (GPCRs), namely ET_A, responsible for vasoconstriction and cell proliferation, and ET_B, mainly responsible for vasodilation, inhibition of cell growth and fluid retention, and ET-1 clearance [21]. ET-1 acts as an autocrine/paracrine mediator, with similar affinity for both

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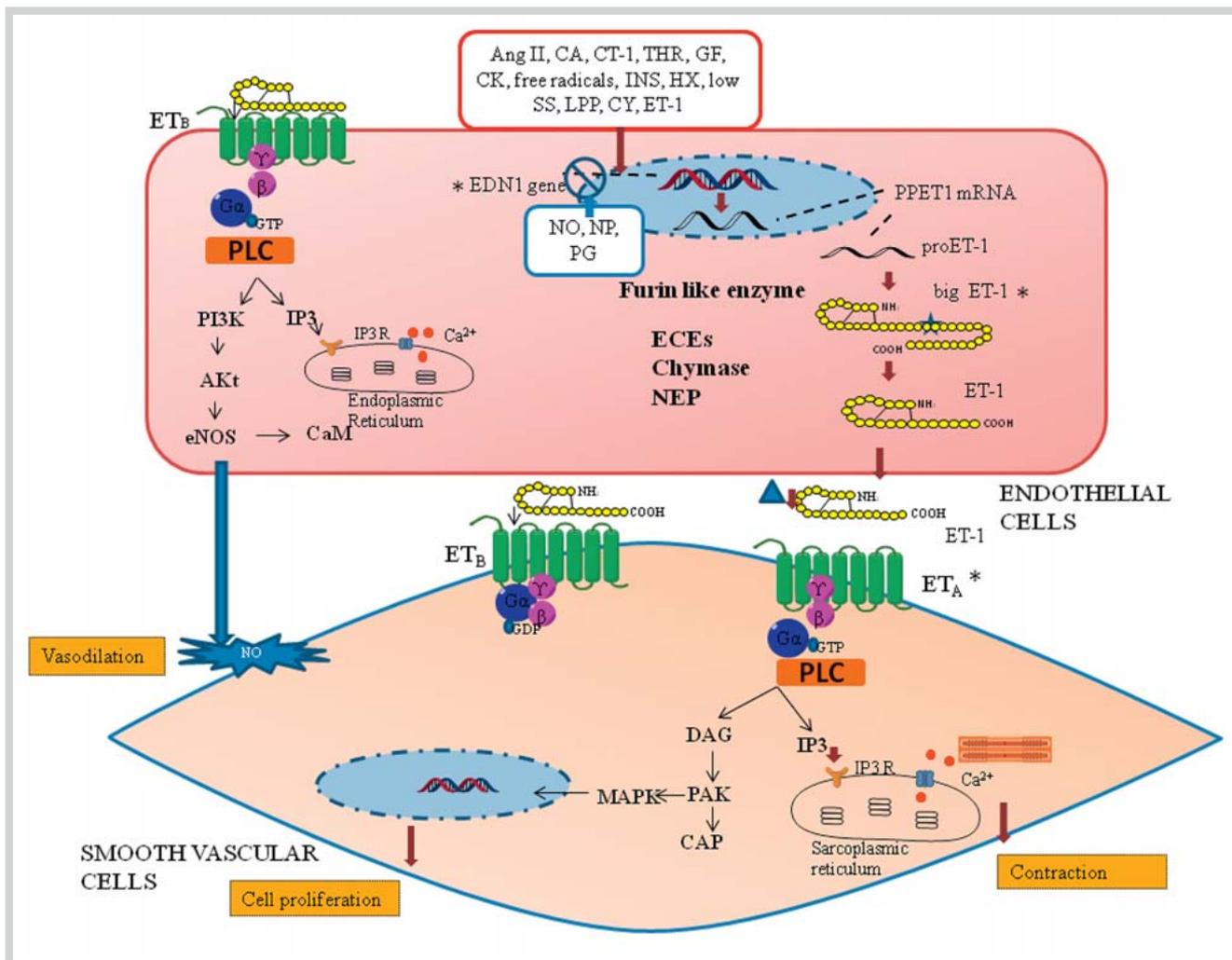


Fig. 1 Molecular overview of the endothelin system and the main drug targets for its inhibition. Abbreviations: Akt, protein kinase B; Ang II, angiotensin II; big ET-1, big endothelin-1; Ca^{2+} , calcium; CA, catecholamines; CaM, calmodulin; CAP, c-Cbl-associated protein; CK, cytokines; CT-1, cardiothrombin-1; CY, cyclosporine; DAG, diacylglycerol; ET-1, endothelin-1; ET_A , endothelin receptor A; ET_B , endothelin receptor B; EDN1, endothelin-1 gene; ECE, endothelin converting enzyme; eNOS, endothelial nitric oxide synthase; GF, growth factors; GTP, guanosine 5'-triphosphate; HX, hypoxia; IP3, inositol

1,4,5-triphosphate; IP3R, inositol 1,4,5-triphosphate receptor; INS, insulin; LPP, lipoproteins; mRNA, messenger ribonucleic acid; MAPK, mitogen-activated protein kinases; NEP, neutral endopeptidase; NO, nitric oxide; NP, natriuretic peptide; PAK, p21-activated kinase; PG, prostaglandins; PI3K, phosphoinositide 3-kinase; PLC, phospholipase C; PPET1, preproendothelin-1; proET-1, proendothelin-1; SS, shear stress; THR, thrombin. (Color figure available online only.)

receptors [20]. When ET-1 interacts with the ET_A receptor, a G protein hydrolyzes phospholipase C to form diacylglycerol (DAG) and inositol 1,4,5-triphosphate (IP3). IP3 increases cytoplasmic calcium (Ca^{2+}) through activation of its receptors and transmembrane Ca^{2+} channels located on the endoplasmic reticulum resulting in vasoconstriction (● Fig. 1) [22]. DAG can also lead to activation of proto-oncogenes including those involved in the MAPK cascade [22].

Stimulation of ET_B receptors leads to activation of phosphoinositide 3-kinase (PI3K) and downstream activation of protein B kinase/Akt. The PI3K/Akt pathway is responsible for activation of endothelial nitric oxide synthase (eNOS), where nitric oxide (NO) antagonizes ET-1 synthesis via inhibition of PPET1 transcription. ET_B receptors mediate the release of other vasodilators like prostaglandins and the endothelium-derived hyperpolarizing factor [23].

The deleterious effects of ET-1 can be prevented by different mechanisms. They include suppression of the expression of

EDN1, translation of proET-1, and activation of ECE and endothelin receptors [24,25].

Endothelin-1 gene inhibitors

There is a specific gene that encodes for each precursor of the mature isoforms of the endothelin family [21]. These genes are susceptible to inhibition by diverse factors. For instance, EDN1 expression may be inhibited by endothelium-derived NO, nitrovasodilators, natriuretic peptides, heparin, and prostaglandins (● Fig. 1) [20,21], as well as high shear stress [26].

Endothelin converting enzyme, neutral endopeptidase and chymase inhibitors

Among the metalloproteases that may cleave big ET-1 to produce ET-1 are pepsin, cathepsin D, and thiol proteases [26], which are sensitive to inhibition by phosphoramidon [27]. Another ECE inhibitor is R568 [28], a calcimimetic substance that induces changes in the synthesis of endothelial vasoactive factors. In addition,

tion, NEP is an important enzymatic target which may be inhibited by both phosphoramidon and thiorphan. The combination of NEP/ECE inhibition, as in SLV 306 (daglutril), is a recent approach to reduce adverse effects produced by NEP inhibition [29].

Endothelin receptor antagonists

Effective antagonism of endothelin receptors has been achieved by compounds like bosentan (non-selective ET_A/ET_B), BQ-123 (selective ET_A), BQ-788 (selective ET_B) [24,30], sitaxentan (selective ET_A), atrasentan (selective ET_A), ambrisentan (selective ET_A), and darusentan (selective ET_A) [24]. Selective antagonism of the ET_A receptor has been effective for treating pulmonary arterial hypertension [24]. Potential underlying mechanisms include reducing pulmonary artery pressure, inhibiting vascular remodeling, improving exercise capacity and pulmonary haemodynamics, and reducing the Borg dyspnea index [21].

Although non-selective ET_A/ET_B receptor antagonism effectively decreases blood pressure, it causes vasoconstriction by blockade of tonic endothelial ET_B-receptor-mediated stimulation of NO and prostacyclin generation and affects the clearance of circulating ET-1 (● Fig. 1) [24]. Thus, the selection between selective and non-selective antagonism of endothelin receptors depends on the individual patient response.

Marine Natural Products as Inhibitors of the Endothelin System

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A number of marine natural products of diverse chemical structures have been found to possess cardiovascular activities. These include small peptides produced by enzymatic hydrolysis of marine proteins, chitosan derivatives, and phlorotannins which inhibit the angiotensin converting enzyme [11]; xestoquinone (● Fig. 2, 1), a pentacyclic quinone with inotropic activity and capacity to inhibit Na/K-ATPase [31] obtained from *Xestospongia sapra*; *D*-polymannuronic sulfate (● Fig. 2, 2) obtained from brown algae that increase NO and decrease plasma levels of Ang II and ET-1 [32]; and xestospongins C (● Fig. 2, 3) an alkaloid from *Xestospongia exigua*, spongosine (● Fig. 2, 4) a nucleoside from *Cryptotethia crypta* [34], 12-*epi*-scalaradial (● Fig. 2, 5) a sesquiterpene from *Hyrtios erecta* [33], and eledoisin (● Fig. 2, 6), a peptide from *Eledone sp.* [35] with hypotensive activity. The majority of natural products capable of inhibiting the endothelin system have been obtained from microorganisms and plants of terrestrial origin. Since the discovery of the cyclic pentapeptide BE-18257B (● Fig. 2, 7) in the bacteria *Streptomyces misakiensis* [36], which originated the first selective endothelin ET_A receptor antagonist BQ-123 [37], more attention has been given to finding endothelin antagonists within microorganisms.

Bacteria

Following the discovery of BE-18257B, two more binding inhibitors of endothelin receptors were identified in soil-born *Streptomyces*, i.e., the benzo[α]anthraquinones WS009 A and B (● Fig. 2, 8–9) (● Table 1) [38]. *Blastorbacter sp.* has been the one bacteria obtained from sea water, from which the non-peptide metalloprotease inhibitor B90063 (● Fig. 2, 10) has been obtained [39]. B90063 inhibits both ECE and NEP, preventing the generation of ET-1 (● Table 1). Other inhibitors of ECE were the benzo[α]naphthacene quinones WS79089 A, B, and C (● Fig. 2, 11–13) (● Table 1) obtained from the soil-born *Streptosporangium roseum* 79089 (● Fig. 2) [40].

Fungi

An interesting fact is that compounds obtained from soil-born fungi, which exhibited endothelin receptor binding capacity, were also found in fungi from marine habitats. This is the case of the spirocyclic drimanes stachylocin A and B (● Fig. 2, 14–15) isolated from *Stachybotrys sp.* M6222 found in soil [41] and *Stachybotrys sp.* MF347 found in driftwood [42]. Drimane sesquiterpenoids have been commonly isolated from marine-derived fungi specially those associated with mangrove [43] and sponges [44]. Dimeric spirodihydrobenzofuranlactam compounds [41, 45] and those with the sesquiterpene drimane skeleton [46,47] (● Fig. 2, 17–23) inhibited the binding of [¹²⁵I]ET-1 to both endothelin receptors, with a consistent preference for the ET_B receptor (● Table 1).

Azaphilones are another group of fungal metabolites found to be produced in fresh [13] and sea water [48–50]. In contrast to the above mentioned drimanes, the group of bioactive azaphilones found in *Penicillium sclerotium* X11853 inhibited the binding of [¹²⁵I]ET-1 to both endothelin receptors, with a consistent preference for the ET_A receptor (● Fig. 2, 24–29) (● Table 1) [13]. Other compounds like diphenyl ether RES-1214-1 and -2 (● Fig. 2, 30–31) obtained from soil-born *Pestalotiopsis sp.* also inhibited the binding of [¹²⁵I]ET-1 to the ET_A receptor [51].

Porifera

Although marine invertebrates, especially sponges, have been claimed as the largest source of chemically diverse marine natural products [52], it is intriguing why information on cardiovascular activity of compounds obtained from sponges is scarce. The literature shows that two compounds obtained from sponges have been identified as inhibitors of the endothelin systems. The first is 34-sulfatobastadin 13 (● Fig. 2, 32), a bromotyrosine derivative which inhibited the binding of [¹²⁵I]ET-1 to the ET_A receptor [12], and the second is the novel sterol sulfate halistanol disulfate B (● Fig. 2, 33) that inhibited ECE (● Table 1) [53].

Ecological Significance of Natural Inhibitors of the Endothelin System

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The majority of the active natural products found within this group are drimane sesquiterpenes. Terpenes have been thought to play a critical role in antagonistic or mutualistic interactions among organisms. They are associated with defense mechanisms in terrestrial as well as in marine environments. In both habitats, molecules with deterrent and antimicrobial activity are the typical chemical defenses of sedentary, slow-moving, or otherwise poorly defended organisms [54].

Drimane sesquiterpenes are potent antimicrobials and believed to deter feeding on plants and sponges by acting directly on taste receptors [54]. Interestingly, taste receptors belong to the GPCR family as so the endothelin receptors [55,56]. Thus, it is possible that drimanes are non-selective GPCR ligands, which might explain their ability to bind ET_A and ET_B. The microorganisms reviewed in this work, which produce these sesquiterpenes, are frequently present in association with sponges, corals, and algae, thus validating their ecological significance in the marine ecosystem.

The significance of sulfated polysaccharides as the vasoactive *D*-polymannuronic sulfate (● Fig. 2) [32] in the marine environment is not completely understood. Sulfated polysaccharides are known to be largely species-specific and involved in cell matrix

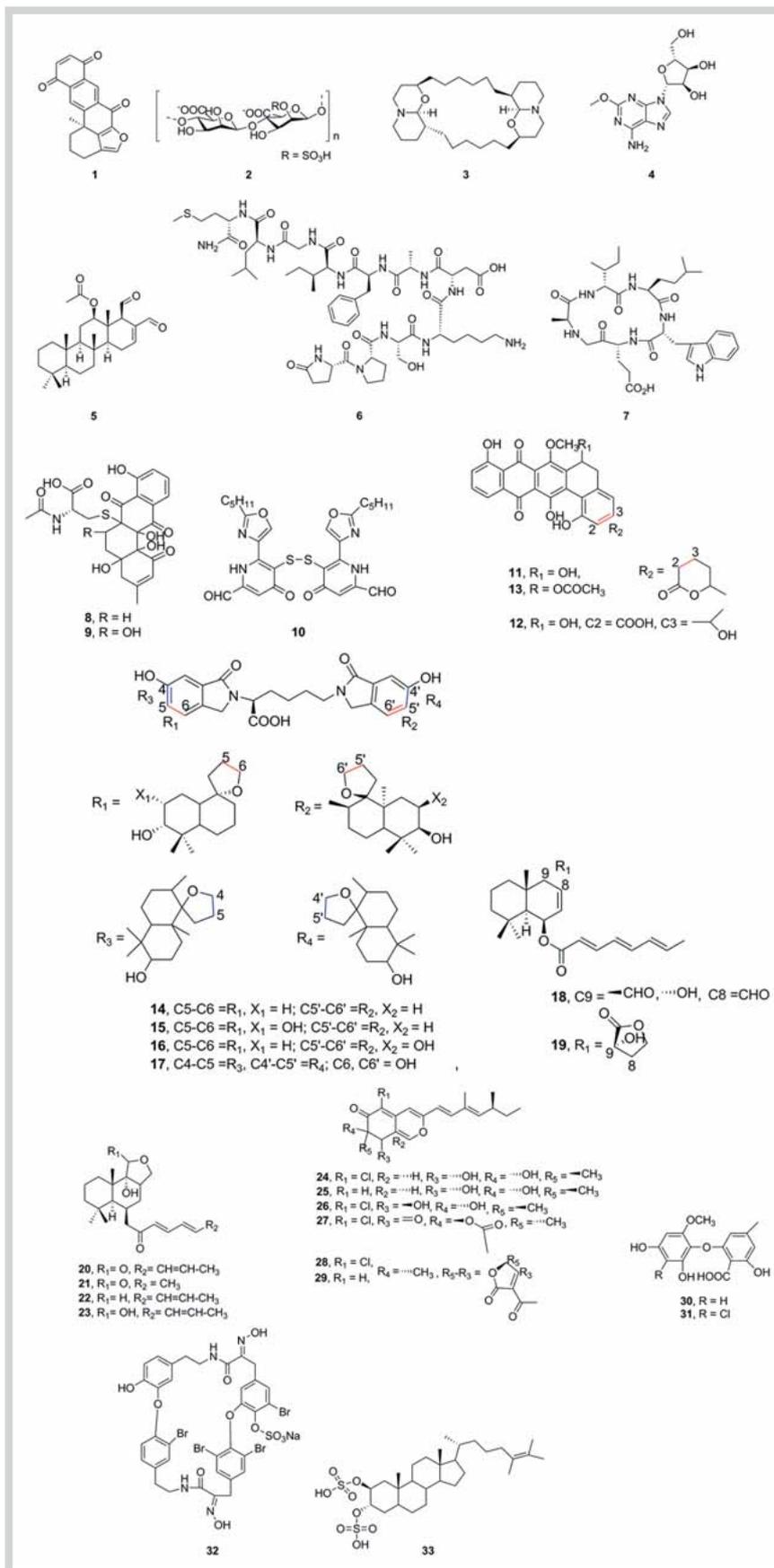


Fig. 2 Marine and soil derived natural products with cardiovascular actions. (Color figure available online only.)

interactions, cell signaling and development [57]. They represent an enormous source of different chemical structures with the advantage of a lower risk to patients [57].

Additionally, peptides are another group of compounds from microbes and sponges that act on the endothelin system. These sub-

Table 1 Natural products from microorganisms and marine sponges acting as inhibitors of the endothelin system.

Compound	Number of structure	Chemistry	ORG ^a	Species	Origin	MMOA ^b	IC ₅₀ (μM)	Ref.
BE-18257B	7	cyclic pentapeptide	BA	<i>Streptomyces misakienses</i>	Soil	ET _A	3.0	[36]
WS009 A	8	benz[α]anthraquinone	BA	<i>Streptomyces sp.</i> 89009	Soil	ET _S	5.8	[38]
WS009 B	9	benz[α]anthraquinone	BA	<i>Streptomyces sp.</i> 89009	Soil	ET _S	67.0	[41]
B-90063	10	pyridone	BA	<i>Blastobacter sp.</i> SANK 71 894	Sea water	ECE/NEP.	1.0/66.0	[39]
WS79089 A	11	benzo[α]naph-tacen quinone	EU	<i>Streptosporangium roseum</i> 79089	Soil	ECE	0.7	[40]
WS79089 B	12	benzo[α]naph-tacen quinone	EU	<i>Streptosporangium roseum</i> 79089	Soil	ECE	0.1	[40]
WS79089 C	13	benzo[α]naph-tacen quinone	EU	<i>Streptosporangium roseum</i> 79089	Soil/	ECE	3.4	[40]
Stachybocin A	14	drimane ses- quiterpene	FU	<i>Stachybotrys sp.</i> M 6222	Soil	ET _A /ET _B	13.0/7.9	[41]
Stachybocin B	15	drimane ses- quiterpene	FU	<i>Stachybotrys sp.</i> M 6222	Soil	ET _A /ET _B	12.0/9.5	[41]
Stachybocin C	16	drimane ses- quiterpene	FU	<i>Stachybotrys sp.</i> M 6222	Soil	ET _A /ET _B	15.0/9.4	[41]
Spirodihydro-ben- zofuranlactam VI	17	drimane ses- quiterpene	FU	<i>Stachybotrys charta- rum</i>	Soil	ET _A	1.5	[45]
RES-1149-1	18	drimane ses- quiterpene	FU	<i>Aspergillus sp.</i> RE- 1149	UN ^c	ET _A /ET _B	25.8/1.6	[46]
RES-1149-2	19	drimane ses- quiterpene	FU	<i>Aspergillus sp.</i> RE- 1149	Soil	ET _B	20.0	[46]
Drimane 1	20	drimane ses- quiterpene	FU	<i>Aspergillus ustus</i> var. <i>pseudodeflectus</i> X3811	Desert soil	ET _A /ET _B	155.0/50	[47]
Drimane 2	21	drimane ses- quiterpene	FU	<i>Aspergillus ustus</i> var. <i>pseudodeflectus</i> X3811	Desert soil	ET _A /ET _B	80.0/55.0	[47]
Drimane 3	22	drimane ses- quiterpene	FU	<i>Aspergillus ustus</i> var. <i>pseudodeflectus</i> X3811	Desert soil	ET _A /ET _B	65.0/21.0	[47]
Drimane 5	23	drimane ses- quiterpene	FU	<i>Aspergillus ustus</i> var. <i>pseudodeflectus</i> X3811	Desert soil	ET _A /ET _B	50.0/70.0	[47]
Isochromophilone III	24	azaphilones	FU	<i>Penicillium sclerotio- rum</i> X11853	Tropical for- est stream	ET _A /ET _B	9.0/77.0	[13]
Isochromophilone III dechloro ana- logue	25	azaphilones	FU	<i>Penicillium sclerotio- rum</i> X11853	Tropical for- est stream	ET _A /ET _B	28.0/172.0	[13]
(8R)-7-deacetyl- O ⁸ ,8-dihydro-7-epi- sclerotiorin	26	azaphilones	FU	<i>Penicillium sclerotio- rum</i> X11853	Tropical for- est stream	ET _A /ET _B ; ARA	5.0/50.0; 33.0	[13]
(+)-sclerotiorin	27	azaphilones	FU	<i>Penicillium sclerotio- rum</i> X11853	Tropical for- est stream	ET _A /ET _B	75.0/12.0	[13]
5-chloroisrotiorin	28	azaphilones	FU	<i>Penicillium sclerotio- rum</i> X11853	Tropical for- est stream	ET _A /ET _B	35.0/8.0	[13]
Ochrephilone	29	azaphilones	FU	<i>Penicillium sclerotio- rum</i> X11853	Tropical for- est stream	ET _A /ET _B	26.0/85.0	[13]
RES-1214-1	30	diphenyl ether	FU	<i>Pestalotiopsis sp.</i>	Soil	ET _A	14.9	[51]
RES-1214-2	31	diphenyl ether	FU	<i>Pestalotiopsis sp.</i>	Soil	ET _A	49.7	[51]
34-Sulfatobastadin 13	32	bromotyrosine	PO	<i>Ianthella sp.</i>	Sandy-rubble reef	ET _A	39.0	[12]
Halistanol disulfate B	33	sulfated sterol	PO	<i>Pachastrella sp.</i>	Marine rocky substrate	ECE	2.1	[53]

^a ORG: type of organism. BA: Bacteria; EU: Eubacteria; FU: Fungi; PO: Porifera. ^b MMOA: molecular mechanism of action. ET_A/ET_B: receptor binding inhibition of [¹²⁵I]ET-1; ET_S: undetermined endothelin receptors; ECE: inhibition of endothelin converting enzyme; NEP: inhibition of neutral endopeptidase; ARA: receptor mediated arachidonic acid release.

^c UN: undetermined

stances are believed to belong to their classical chemical defense machinery [58,59].

Discussion

Microorganisms are a major source for new drugs with more than 50 000 microbial natural products playing an important role in drug discovery [60]. The majority of these have been isolated from terrestrial-borne microbes [60], possibly because they were more readily available when compared to marine microbes. The available literature shows that the search for natural inhibitors of the endothelin system has been done mainly in land, yielding a wide variety of chemical compounds. Even though this search produces a biased sampling, it is exciting to note that the results accentuate the underestimated potential of microorganisms for producing leads with cardioprotective potential. While the question may rise whether the inhibitory activities found for the compounds described in this review are of therapeutic relevance or not, it is worth mentioning that lead compounds may have considerably low activities (IC_{50} values in the micromolar range) and still hold the potential to become very potent drugs after few modifications. For example, the selective ET_A receptor antagonist BQ123 ($IC_{50} = 7.3$ nM) [37], is a semisynthetic product obtained from the natural product BE-18257B ($IC_{50} = 3.0$ μ M) (● Table 1).

Oceans encompass a stressful and competitive habitat with unique conditions of pH, temperature, pressure, oxygen, light, nutrients, and salinity, all of which force organisms to adapt both chemically and physiologically to survive in it [1,40]. The corresponding modifications in gene regulation and metabolic pathways increase the chances of finding unique and complex natural products that differ from organisms living in terrestrial habitats [1,40].

The large display of novel and complex chemical structures found in marine natural products as well as the extension of their therapeutic applications, support the marine environment as a promising source of new drugs. The increasing number of bioactive natural products from marine-derived fungi presents a great challenge and sets high expectations in finding, in these groups of organisms, new leads for the protection of the cardiovascular system.

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Conflict of Interest

The authors declare no conflict of interest.

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