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Research review paper

Gold from the sea: Marine compounds as inhibitors of the hallmarks of cancer

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ABSTRACT

Cancer is one of the most deadly diseases in the world. Although advances in the field of chemo-preventive and therapeutic medicine have been made regularly over the last ten years, the search for novel anticancer treatments continues. In this field, the marine environment, with its rich variety of organisms, is a largely untapped source of novel compounds with potent antitumor activity. Although many reviews of marine anticancer compounds have been published, we focus here on selected marine compounds that act on the six hallmarks of cancer presented namely self-sufficiency in growth signals, insensitivity to anti-growth signals, evasion of apoptosis, limitless replication, sustained angiogenesis and tissue invasion and metastasis.

Contents

1. Introduction

Despite considerable progress in medical research, cancer remains one of the high-ranking causes of death in the world. The National Cancer Institute estimates that "approximately 11.4 million Americans with a history of cancer were alive in January 2006. In 2010, about 569,490 Americans are expected to die of cancer, more than 1500 people a day. Cancer is the second most common cause of death in developed countries, exceeded only by heart disease. Cancer accounts for nearly 1 of every 4 deaths" (Source: Cancer Facts and Figs. 2010 of the American Cancer Society). Moreover, according to Lee Jong-Wook, former Director General of the WHO, "by the year 2020, cancer could kill more than 10.3 million people per year unless action is taken in both the field of prevention and treatment".

Accordingly, research must continue to progress to improve existing therapies and to develop novel cures. For many years, research has essentially focused on plants and terrestrial microorganisms, mainly because these specimens are easily available and folk traditions have described beneficial effects from their use. However, recent pharmaceutical research is also focusing on marine organisms that have developed biologically unique molecules.

Life began in the sea, and oceans, particularly rich in biodiversity, cover over 70% of the Earth's surface. The lack of natural defenses (e.g.

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innate immune system) in the majority of invertebrates leads to the development of biologically active secondary metabolites, especially in marine and plant organisms like shells and spines. These metabolites play a role in the defense of the host habitats and the adaption to extreme environmental challenges. The variety of marine organisms discovered to date suggests a dramatic potential for drug discovery, and much remains to be discovered in the depths of the oceans.

Although the "silent world" has a much richer biodiversity than that of terrestrial areas, efforts to exploit this biodiversity through the identification of new chemical compounds have only begun: approximately 22,000 natural products of marine origin have been discovered so far, whereas 131,000 terrestrial natural products exist (Blunt et al., 2011).

The sea covers over 70% of the earth's surface and some areas, such as coral reefs, possess a huge biodiversity, which is even greater than that of rainforests. A large proportion of the sea offers untapped sources of potential drugs with promising activities due to a large diversity of marine habitats and environmental conditions (nutrient availability, sunlight presence, and salinity levels) (Scheuer, 1990). In the area of marine research, a recent census of marine life that involved the participation of 2700 scientists from over 80 nations assessed the diversity, distribution and abundance of marine life resulted in the discovery of over 6000 potentially novel species (Butler et al., 2010; Census of marine life; Fautin et al., 2010; Miloslavich et al., 2010). As a consequence of these research efforts, it is clear that the marine environment represents an important source of unknown natural compounds whose medicinal potential must be evaluated.

Recent studies in the field of cancer research have revealed promising compounds, isolated from natural sources, with proven anticancer activity. Three examples are trabectedin, cytarabine and eribulin mesylate (Yondelis®; PharmaMar); (Cytosar-U®, Bedford, Enzon) (Halaven®; Eisai Inc.) (D'Incalci and Galmarini, 2010; Gradishar, 2011; O'Dwyer and Maslak, 2008), which represent the first three described marine anticancer drugs. Indeed, almost 50% of the antitumor agents approved in the last 50 years of the 20th century were either compounds derived from natural sources or (semi-) synthetic analogs of these products (Newman and Cragg, 2007). Natural compounds remain a high-output source of promising chemotherapeutic or chemopreventive agents in current cancer research (Dumontet and Jordan, 2010; Gullett et al., 2010; Villa and Gerwick, 2010). In addition to PharmaMar, other pharmaceutical companies including Bedford, Enzon, Eisai Inc., Novartis, Aventis, Eli Lilly, Abbott Inflazyme, Pfizer and Taiho Pharmaceuticals Co., have therapeutic compounds of marine origin under development.

It is well known that genetic changes progressively convert normal cells into cancer cells (Nowell, 1976). Although more than 100 distinct types of cancer exist, only six essential alterations in cell physiology cause malignant cell growth: self-sufficiency in growth signals, insensitivity to antigrowth signals, evasion of apoptosis, limitless replicative potential, sustained angiogenesis and metastasis. Hanahan and Weinberg reported that these six "hallmarks of cancer" are present in almost every type of human tumor (Hanahan and Weinberg, 2000).

Although a large number of reviews on marine natural compounds exist (Blunt et al., 2010; Ebada et al., 2010; Lin et al., 2010; Penesyan et al., 2010; Villa and Gerwick, 2010), in this review, we focus on selected compounds and demonstrate how they interfere with these six crucial biological pathways described by Hanahan and Weinberg.

2. The hallmarks of cancer as targets for novel marine drugs

2.1. Compounds that abolish self-sufficiency in growth signals

Published data indicate that marine compounds exert chemopreventive and chemotherapeutic effects through the inhibition of phosphorylation of membrane receptors, including epidermal growth factor receptor (EGFR), as well as downstream cell signaling cascades. Some marine compounds efficiently interrupt constitutive growth factor stimulated cell signaling pathways, typically triggering a pathway involving Ras → Raf → extracellular regulated kinase (ERK) → mitogen-activated kinase/ERK-kinase (MEK) → activator protein (AP)-1 pathway. Receptor tyrosine kinases (RTKs),including EGFR and platelet-derived growth factor receptor (PDGFR), are involved in the transduction of mitogenic signals across the plasma membrane and in the regulation of cell growth and proliferation. Enhanced RTK activity is associated with proliferative diseases, including cancer. Pathological variations of this fine-tuned regulatory network can be an interesting target for novel inhibitors that not only inhibit but also over-activate cellular mechanisms, thus leading to perturbed growth and subsequent cell death either by apoptosis or other cell death mechanisms (Fig. 1A for chemical structures **1**–**6** and Table 1 for summary of marine products that abolish self-sufficiency in growth signals).

Apratoxin A analog **1** (oz-apraA), a cyclodepsipeptide isolated from the marine cyanobacterium *Lyngbya majuscula*, promotes the degradation of Hsp90 clients through chaperone-mediated autophagy (CMA), which is a promising new anticancer strategy. Shen et al. provide an example of the ability of CMA to mediate the degradation of membrane receptors, including EGFR (Shen et al., 2009) (Fig. 1B).

Here, the natural marine product 12-epi-scalaradial **2** inhibits EGFR-mediated phosphorylation of Akt/PKB, a serine/threonine protein kinase, membrane translocation of 3-phosphoinositide-dependent protein kinase 1 (PDK1 or PDPK1),and it also inhibited phosphatidylinositol 3-kinase (PI3K) activity (Xie et al., 2005).

Results provided by Lee et al. (2008) showed that fucoidan **3** from the seaweed *Laminaria guryanovae* exerted a potent inhibitory effect on EGF-induced phosphorylation of EGFR. Subsequently, this compound suppressed the phosphorylation of ERK and JNK under the control of EGF. Interestingly, EGF-induced c-fos and c-jun transcriptional activities were inhibited by fucoidan, leading to inhibition of activator protein-1 (AP-1) activity and cell transformation induced by EGF.

On the contrary, marine compounds can also activate the EGRF cascade in a non-physiological fashion, as published by Cuadrado et al. These authors report that Aplidin® **4** induced a specific cellular stress response program, including sustained activation of EGFR, the non-receptor protein-tyrosine kinase Src and the serine/threonine kinases JNK and p38 MAPK. The authors achieved growth arrest and apoptosis in human MDA-MB-231 breast cancer cells after Aplidin treatment (Cuadrado et al., 2003).

Hinterding et al. (1998) reported that EGFR and PDGFR are inhibited by analogs of the marine compound aeroplysinin **5**. These synthetic derivatives display IC_{50} values in the low micromolar range and also show pronounced inhibitory activity in cultured cells, most likely by covalent modification of the target protein.

Ma et al. identified novel multi-targeting PTK inhibitors. Their results indicated that MdOS **6**, a novel marine-derived oligosaccharide sulfate, exhibited a broad-spectrum PTK inhibitory action. At an enzymatic level, MdOS inhibited HER2, EGFR, VEGFR, PDGFR, c-Kit, FGFR1 and c-Src, with little impact on FGFR2. In cellular settings, MdOS inhibited phosphorylation of PTKs, exemplified by HER2, EGFR and VEGFR2, and downstream molecules of Erk1/2 and AKT (Ma et al., 2008).

2.2. Compounds that re-establish sensitivity to growth-inhibitory signals

To proliferate, cancer cells need to evade anti-proliferative signals that physiologically negatively regulate growth and proliferation. Cancer cells can avoid this control step by "losing" the physiological function of the retinoblastoma suppressor protein (pRb) through which all anti-proliferative signals are controlled. This inactivation of the pRb regulatory network can occur not only *via* mutation but also *via* constitutive phosphorylation. In fact, non- or hypophosphorylated pRb actively inhibits cell cycle progression and therefore cell growth, whereas, during an active proliferative phase, cyclins hyperphosphorylate pRb and thus inhibit its braking activity. Consequently, compounds

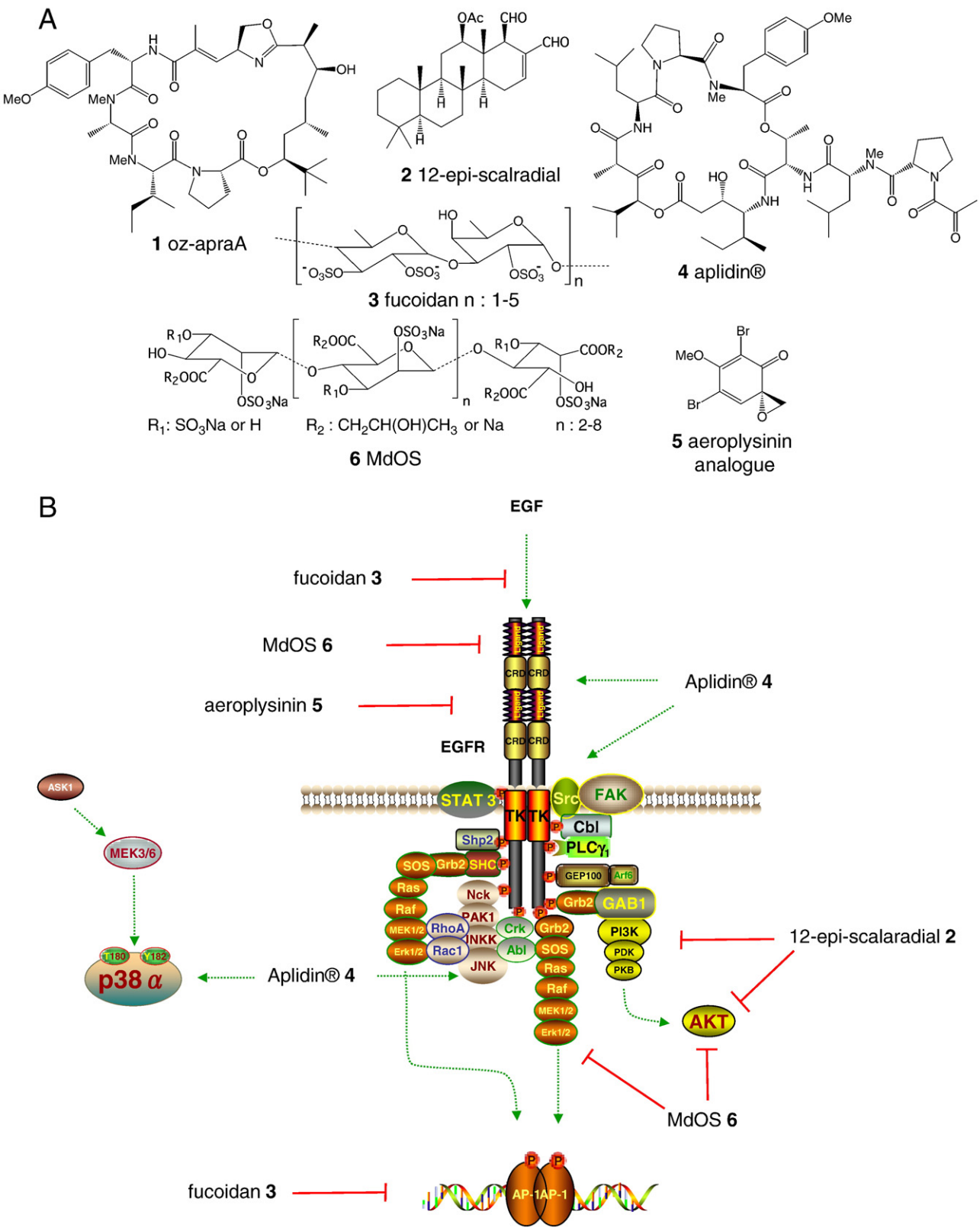


Fig. 1. A–B) Chemical structures of marine products **1–6**, that abolish self-sufficiency in growth signals.

that inhibit constitutive hyper-phosphorylation of pRb contribute efficiently to the reestablishment of regulated growth in cancer and in hyperproliferative diseases in general.

The cell cycle is a tightly controlled and highly organized process regulating cell survival, and disturbances can lead to cell cycle arrest and cell death. The molecular link between these three cell fates is an area of intense research (Maddika et al., 2007). Deregulated cell cycling might lead to uncontrolled growth and finally to tumor development. Several control mechanisms exist that avoid inappropriate cell division. CDKs, together with their positive regulators, cyclins, enable the passage from one cell cycle phase to another. These cyclin/CDK complexes are closely controlled by inhibitory phosphorylation (e.g., by the kinases Wee1 and

Table 1
Marine products that abolish self-sufficiency in growth-signals and re-establish sensitivity to growth-inhibitory signals.

Name	Chemical class	Affected hallmark	IC_{50}[a]	Reference
Aeroplysinin analog **5**	Cyclohexadienone	1	10 μM	(Hinterding et al., 1998)
Apratoxin A analog **1**	Cyclodepsipeptide	1	100 nM	(Shen et al., 2009)
Fucoidan **3**	Polysaccharide	1	10 μg/mL	(Lee et al., 2008)
MdOS **6**	Oligosaccharide	1	0.3 μg/mL	(Ma et al., 2008)
Plitidepsin/Aplidin® **4**	Cyclodepsipeptide	1	5 nM	(Cuadrado et al., 2003)
12-epi-scalaradial **2**	Sesterterpene	1	2.9 μM	(Xie et al., 2005)
Bromopyrrole **9**	Bromopyrrole	2	6.25 μg/mL	(Xiong et al., 2010)
Cyclopentenone **13**	Cyclopentenone	2	750 μM	(Ciucci et al., 2006)
Dactylone **7**	Sesquiterpene	2	40 μM	(Fedorov et al., 2007)
Dideoxypetrosynol A **8**	Polyacetylene	2	0.7 μg/mL	(Park et al., 2006)
Manzamine A **10**	β-carboline	2	10 μM	(Hamann et al., 2007)
Peloruside A **11**	Marcrocyclic lactone	2	10.1 nM	(Miller et al., 2004)
Spongistatin 1 **12**	Marcrocyclic lactone	2	1 nM	(Catassi et al., 2006)

[a] In some articles, the IC_{50} was not determined, see indicated references for further details.

MYT1) or by inhibitors (INK4 and CIP/KIP classes) (Grant and Roberts, 2003; Park and Lee, 2003; Schwartz and Shah, 2005). The transition from one cell cycle phase to the next is controlled by checkpoints (Park and Lee, 2003). Depending on the severity of cellular damage, the amount of stimuli and/or the outcome of repair processes, the cell cycle checkpoint machinery, which is mainly regulated by p53, might initiate cell-cycle arrest, senescence, differentiation, DNA repair, apoptosis or prevention of angiogenesis (Giono and Manfredi, 2006; Maddika et al., 2007). See Fig. 2A for chemical structures **7**–**13** and Table 1 for a summary of marine products that abolish self-sufficiency in growth signals.

Fedorov et al. showed that the marine natural chamigrane-type sesquiterpenoid dactylone **7** exerted its influence in part through the inhibition of cyclin D and Cdk4 expression and pRb phosphorylation. The inhibition of these cell cycle components was followed by cell cycle arrest at the G1–S transition, with subsequent p53-independent apoptosis (Fedorov et al., 2007) (Fig. 2B).

Park et al. described the suppression of U937 human monocytic leukemia cell growth by dideoxypetrosynol A **8**, a polyacetylene from the sponge *Petrosia* sp., *via* induction of Cdk inhibitor p16 and down-regulation of pRb phosphorylation (Park et al., 2006) (Fig. 2B).

The marine sponges of the genera *Agelas*, *Axinella* and *Hymeniacidon* are known as rich sources of bromopyrrole alkaloids (Kobayashi et al., 1990; Pettit et al., 1990). In 2010, the research team of Xu reported *in vitro* and, for the first time for this chemical class, *in vivo* antineoplastic activity of a novel bromopyrrole, namely N-(4, 5-dibromo-pyrrole-2-carbonyl)-L-amino isovaleric acid methyl ester **9**. This compound inhibited the proliferation of human cancer cells *in vitro* (IC_{50} of 3.8 to 17.2 μg/mL) and in xenograft mouse models (MIC at 60 mg/kg). Moreover, it has been shown that bromopyrrole inhibits cancer cell growth by mediating cell cycle arrest in the G1 phase (Xiong et al., 2010) (Fig. 2B).

Manzamine A **10** inhibited cyclin dependent kinase (CDK) 5, the later enables the passage from one cell cycle phase to another, likewise decreasing tau hyperphosphorylation in human neuroblastoma cells (Hamann et al., 2007).

Peloruside A **11**, a compound isolated from the marine sponge *Mycalehentscheli* reduces growth and enhances apoptosis in H-ras-transformed cells. Interestingly, Miller et al. showed that this compound is more cytotoxic in oncogene-transformed cells, which were subsequently blocked in G2/M phase of the cell cycle, leading to apoptosis independent of caspase activation (Miller et al., 2004).

Pettit et al. isolated the macrocyclic lactone spongistatin 1 **12** from the Porifera *Spongia* sp. in 1993 (Pettit et al., 1993). This compound exerted a strong cytotoxicity against a panel of highly chemoresistant tumor types. Several research teams evaluated the exact mechanisms of action and investigated the cell death pathways affected by spongistatin 1. The latter was found to inhibit glutamate-induced tubulin polymerization (IC_{50} of 3.6 μM in kangaroo rat kidney PtK1 cells) by interacting with the *Vinca* alkaloid domain of tubulin, thus leading to mitosis inhibition (Bai et al., 1993). Catassi et al. determined the cascade of events after treatment of lung cancer A549 cells with spongistatin 1 at a concentration of 1 nM. They found that this product caused cell cycle arrest at the G2–M phase together with the up-regulation of GADD45α-γ and down-regulation of c-Myc (Catassi et al., 2006).

Detailed mechanistic studies have indicated that cyclopentenone **13** caused cell cycle arrest by repression of cyclin D1 expression, inhibited constitutive nuclear factor kappa B (NF-κB) activity and lead to the induction of apoptosis (Ciucci et al., 2006; Hsiang and Straus, 2002).

2.3. Compounds that lead to apoptosis

Resistance to apoptosis by cancer cells can be acquired through a variety of strategies, including p53 tumor suppressor gene inactivation. p53, a DNA damage sensor, can lead to induction of the apoptotic effector cascade. Moreover, the PI3K/AKT/PKB pathway reported to transmit antiapoptotic survival signals and their inhibition by marine compound inhibitors could be of potential therapeutic value. Additionally, abrogation of FAS death signaling represents a possible target for as-yet-undiscovered compounds.(see Figs. 3A and 4 for chemical structures **14**–**37** and Table 2 for a summary of marine products which induce apoptosis).

The ester-substituted sesquiterpenoid cryptosphaerolide **14**, first isolated by Fenical's research group in 2010 from the marine-derived ascomycete fungal strain CNL-523 (*Cryptosphaeria* sp.) (Oh et al., 2010), exerts cytotoxicity with an IC_{50} of 4.5 μM upon an HCT-116 colon carcinoma cell line. Studies of a hydrolyzed analog show that the presence of a hydroxylated ester side chain, linked to the core sesquiterpenoid group, is crucial for the observed activity (Oh et al., 2010). A more detailed study revealed that this product inhibited the myeloid leukemia cell differentiation protein (Mcl)-1, which is a critical player in life/death outcomes (Michels et al., 2005), with an IC_{50} of 11.4 μM (Fig. 3B).

The main anti-apoptotic function of Mcl-1 is the sequestering of Bak on the outer mitochondrial membrane, thereby preventing Bak oligomerization and cytochrome c release from mitochondria (Willis et al., 2005). Mcl-1 up-regulation has been reported in a number of cancer cell lines (Aichberger et al., 2005; Cho-Vega et al., 2004; Derenne et al., 2002). Inhibition of Mcl-1 expression, however, leads to apoptosis in cancer cells and enhances chemosensitivity (Andersson et al., 2004; Wei et al., 2008).

Four polyoxygenated cholestanes **15** have been isolated from the sea whip *Leptogorgia sarmentosa*. These four steroids exhibited cytotoxic activity against mouse lymphoid neoplasma (P-388), human lung carcinoma (A 549), human colon carcinoma (HTG) and human melanoma (MEL 28) at an IC_{50} range of 1 μg/mL (Garrido et al., 2000). Based on the

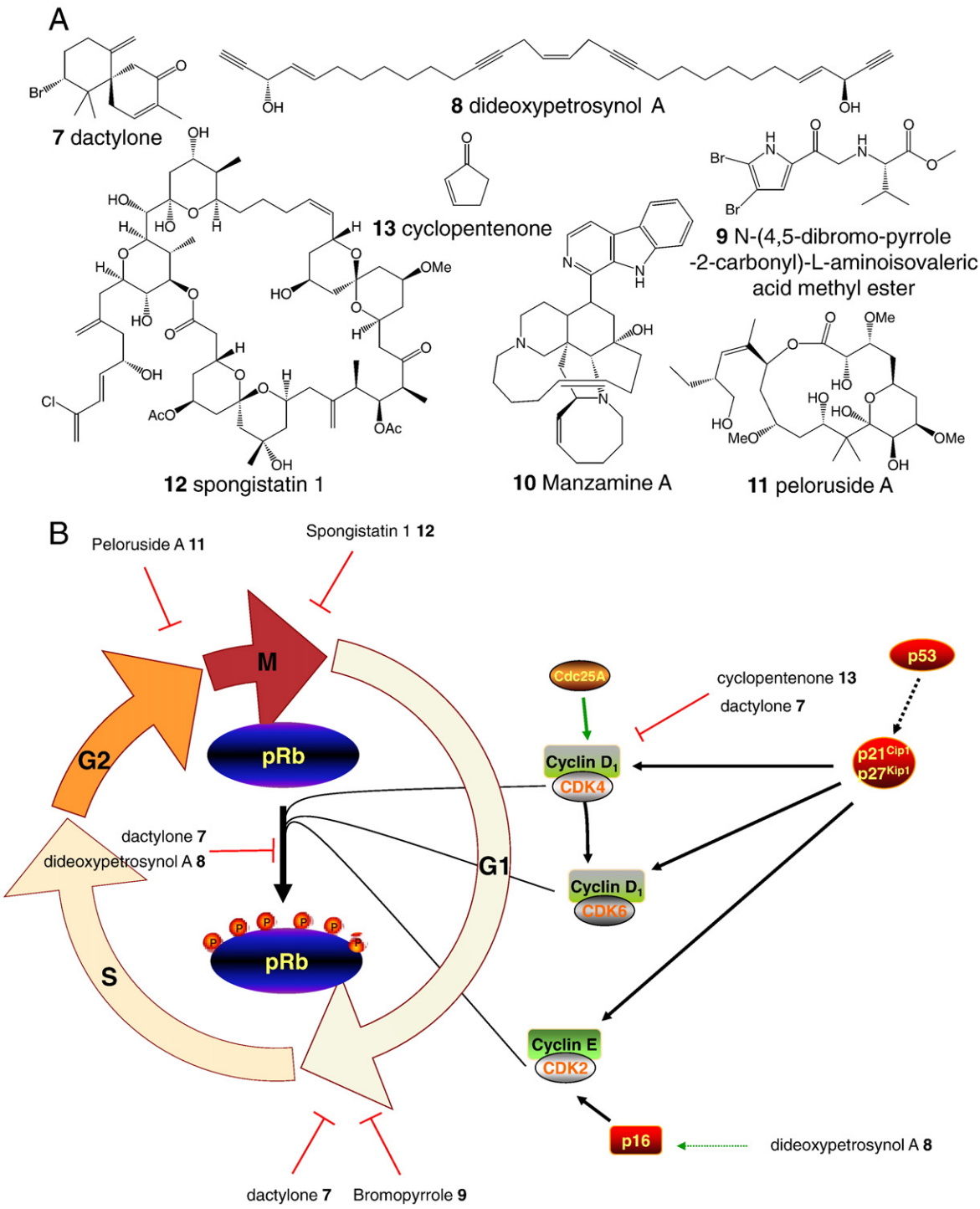
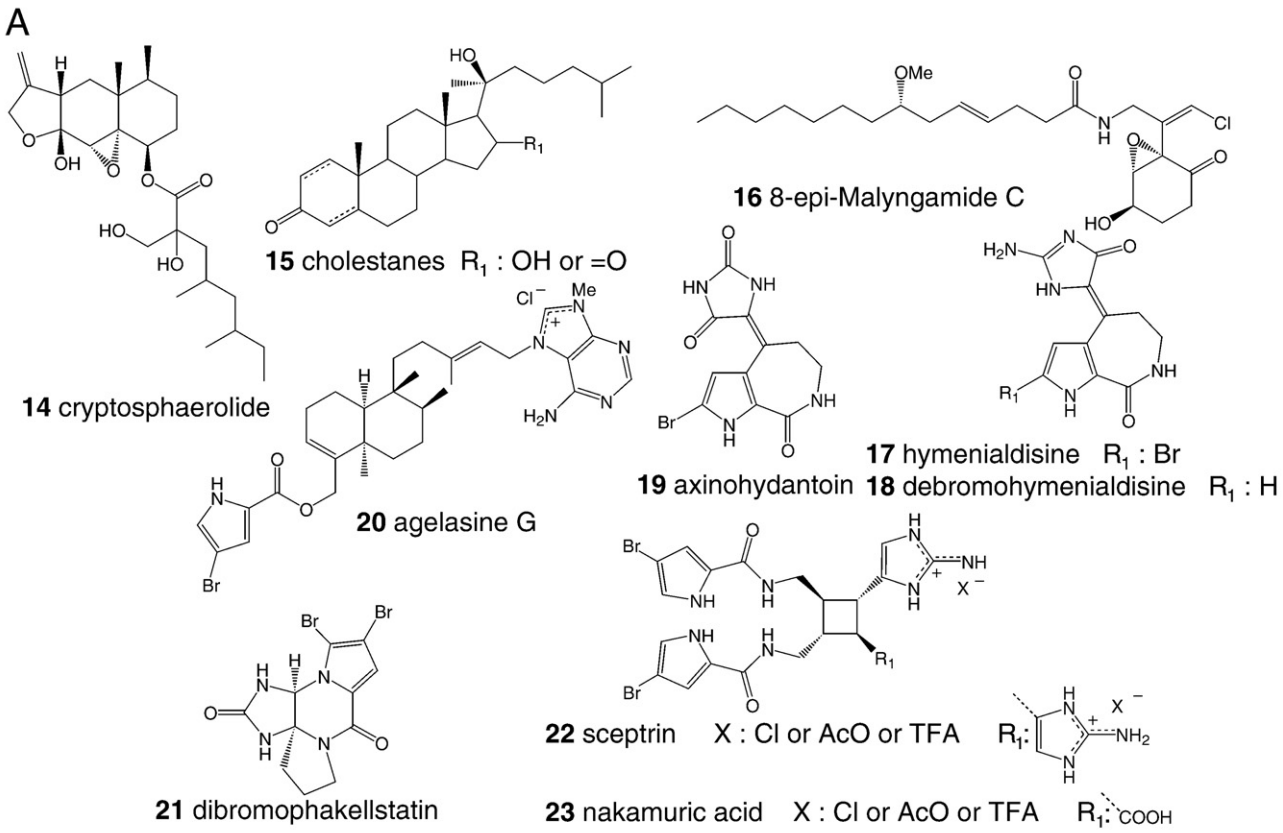


Fig. 2. A) Chemical structures of marine products **7**–**13**, that restore sensitivity to growth-inhibitory signals. B) Cell cycle regulators targeted by selected marine compounds.

observed activity and the fact that this product is only available in small quantities, Kongkathip's research group decided to synthesize these marine cholestanes. These steroids, containing aα-unsaturated ketone, showed significant cytotoxicity activity for human lung cancer cell lines (NCI) (IC_{50} of 6.2–10.5 μM) and moderate activity for MCF7 breast cancer (IC_{50} of 30.7–31.4 μM) and human oral cancer KB (IC_{50} of 41.7–42.2 μM) cell lines (Boonananwong et al., 2008). The biological pathway affected by this group of steroids must still be determined.

Malyngamide C **16**, a chlorinated amide of lyngbic acid, was first isolated by Moore's research team in 1985 from the blue-green algae *L. majuscula* (Ainnslie et al., 1985). In 2010, Kwan et al. isolated and identified an epi-isomer of malyngamide C and evaluated the bioactivity of this new stereoisomer along with the native compound. They found that the epi-isomer exerted a three-fold lower cytotoxicity against HT29 colorectal adenocarcinoma cells with IC_{50} value of 15.4 μM, in contrast to 5.2 μM (Kwan et al., 2010). Thus, the configuration of the alcohol group of the six-member cyclic ketone ring plays an important role in the observed bioactivity. No study investigating the signaling pathway used by malyngamides has been published so far.

The previously mentioned macrocyclic lactone spongistatin 1 **12** from marine *Porifera* also induces BAD dephosphorylation, leading to cytochrome C release from the mitochondria and finally to caspase-3



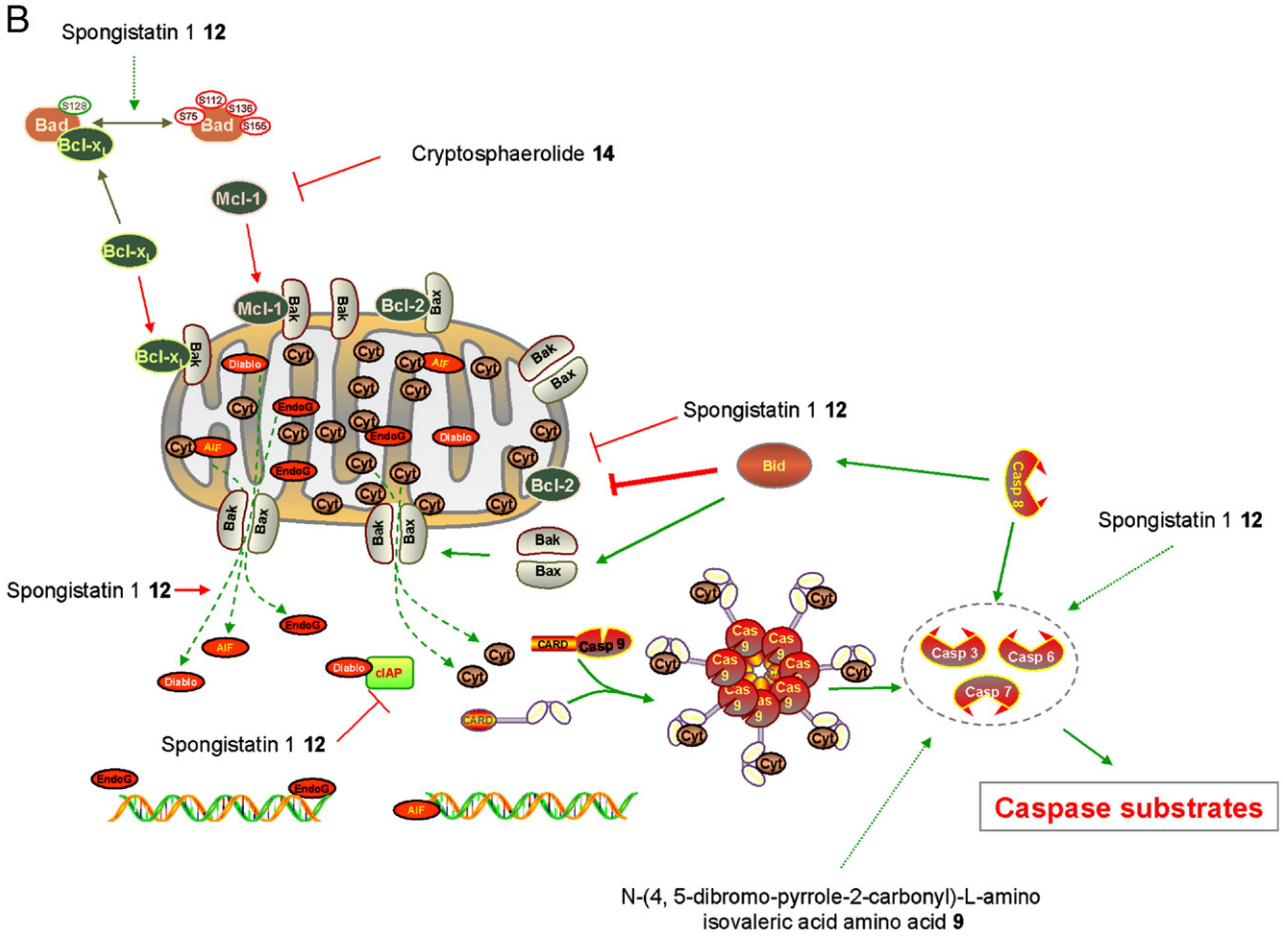


Fig. 3. A) Chemical structures of marine products **14**–**23**, that induce apoptosis. B) Cell signaling pathways involved in growth signal response targeted by selected marine compounds.

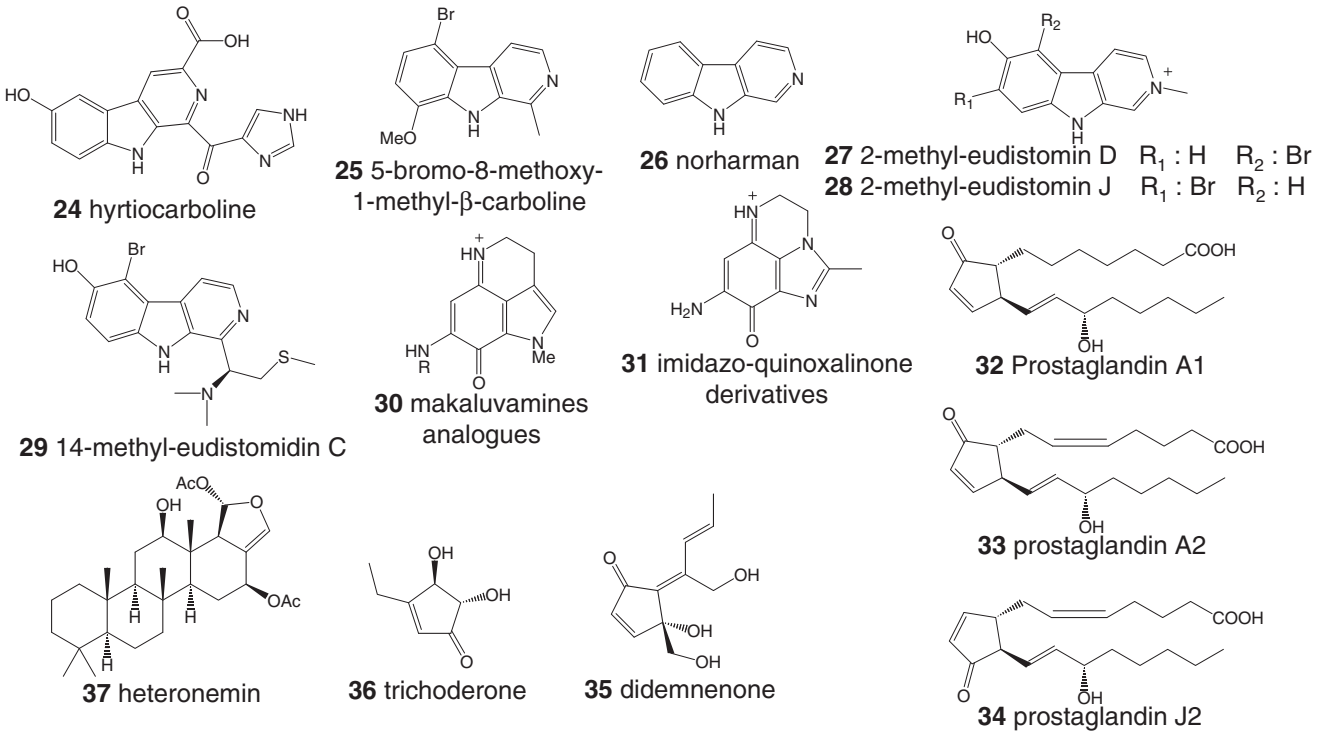


Fig. 4. Chemical structures of marine products **24**–**37**, that induce apoptosis.

triggered apoptosis (Catassi et al., 2006). Another study in leukemia cell lines by Schyschka et al. showed that spongistatin 1 mediated the release of cytochrome c, Smac/DIABLO and Omi/HtrA2 from the mitochondria to the cytosol, leading to caspase-dependent apoptosis in Jurkat cells and even in primary leukemia cell lines at a low concentrations of 1 nM (Schyschka et al., 2008). Schneiders et al. reported that this lactone acted on caspase-independent pathways by inducing the translocation from the proapoptotic proteins' apoptosis-inducing factor (AIF) and endonuclease G (EndoG) from the mitochondria to the nucleus. Bim was freed from its sequestration both by microtubules and by the antiapoptotic protein Mcl-1. Thus, the proapoptotic protein Bim was shown to be the up-stream target of spongistatin 1 responsible for the observed caspase-independent apoptosis (Schneiders et al., 2009).

The caspase-dependent apoptotic pathway is a common target in cancer therapy (Degterev et al., 2003). Two major apoptotic pathways exist in humans: 1) the extrinsic pathway activated by the death receptor Fas or the tumor necrosis factor α receptor (TNFR), followed by caspase-8 and 2) the intrinsic pathway triggered through cellular stress and implying the activation of caspase-9. Both pathways lead to a common activation process that requires the proteolytic activation of the effector caspases-3 and/or -7 (Thornberry and Lazebnik, 1998). Caspase-8 is able to cleave the BH3-only protein Bid; truncated Bid (tBid) then activates caspase-9 through cytochrome c release (Coppola and Ghibelli, 2000). Cytochrome c release is also initiated in the intrinsic pathway through Bax/Bak insertion in the mitochondrial membrane. In addition to cytochrome c, mitochondria release other polypeptides, including apoptosis inducing factor (AIF), endonuclease G (Endo G), second mitochondria derived activator of caspase (Smac)/direct inhibitor of apoptosis protein (IAP)-binding protein with low PI (DIABLO) and HtrA2/Omi. AIF and Endo G cause DNA damage and condensation; Smac/Diablo and HtrA2/Omi, in contrast, trigger caspase

Table 2
Marine products that induce apoptosis.

Name	Chemical class	Affected hallmark	IC_{50}[a]	Reference
Agelasine G **20**	Bromo-pyrrole	3	3.1 μg/mL	(Ishida et al., 1992)
Axinohydantoin **19**	Bromo-pyrrole	3	18 μg/mL	(Pettit et al., 1990)
Bromopyrrole **9**	Bromo-pyrrole	3	6.25 μg/mL	(Xiong et al., 2010)
Cryptosphaerolide **14**	Sesquiterpene	3	4.5 μM	(Oh et al., 2010)
Cyclopentenone **13**	Cyclepentenone	3	750 μM	(Ciucci et al., 2006)
Debromohymenial. **18**	Bromo-pyrrole	3	2.5 μg/mL	(Pettit et al., 1990)
Dibromophakellistatin **21**	Bromo-pyrrole	3	0.2 μg/mL	(Pettit et al., 1997)
Didemnenones **35**	Cyclepentenone	3	2–6 μg/mL	(Ogi et al., 2009)
Dihydroimidazo[1,5,4-de]quinoxalin-9-ones **30**	Pyrroloiminoquinone	3	3 μM	(Hoang et al., 2007)
Heteronemin **37**	Sesterterpene	3	5.6 μM	(Schumacher et al., 2010)
Hymenialdisine **17**	Bromo-pyrrole	3	2.0 μg/mL	(Pettit et al., 1990)
Hyrtiocarboline **24**	β-carboline	3	1.2 μg/mL	(Inman et al., 2010)
8-epi-Malyngamide C **16**	Chlorinate amide	3	15.4 μM	(Kwan et al., 2010)
Spongistatin 1 **12**	Marcrocyclic lactone	3	10 nM	(Rothmeier et al., 2010)
Trichoderone **36**	Cyclepentenone	3	43.2 μM	(You et al., 2010)
(20S)-20-hydroxycholest-1-ene-3,16-dione **15**	Polyoxygen. steroid	3	6.2 μM	(Boonananwong et al., 2008)
14-methyl-eudistomin C **29**	β-carboline	3	0.4 μg/mL	(Rashid et al., 2001)

[a] In some articles, the IC_{50} was not determined, see indicated references for further details.

activation through inhibition of IAPs (Debatin, 2004; Du et al., 2000; Li et al., 2002; Lorenzo et al., 1999; van Loo et al., 2002). Antiapoptotic Bcl-2 family members, like Bcl-2 and Bcl-xL, inhibit cytochrome c and Smac/Diablo release (Sun et al., 2002), whereas BH-3-only proteins, such as Bid and Bim, potentiate the pro-apoptotic activity of Bax and Bak (Ghavami et al., 2009). Caspase-induced apoptosis may be a promising target for anticancer therapy. Thus, one caspase-activating agent currently tested in preclinical trials is the protein apoptin, derived from chicken anemia virus, which selectively induces cell death of tumor cells *in vitro* and *in vivo* (Los et al., 2009; Pan et al., 2010) (Fig. 3B).

The lactone spongistatin 1 **12** induced the degradation of XIAP (Schyschka et al., 2008), an anti-apoptotic protein that is overexpressed in chemoresistant cancer cells (Igney and Krammer, 2002).

Inhibitors of apoptosis proteins (IAPs) are a family of endogenous caspase-inhibitors and include the human analogs X-linked Inhibitor of Apoptosis Protein (XIAP), cIAP1, cIAP2, survivin, livin/melanoma-IAP (MLIAP), apollon, NAIP and ILP-2 (Hunter et al., 2007). XIAP, the most-studied member of this group, is up-regulated in many forms of human cancer, indicating its role as a potential target for cancer therapy (Igney and Krammer, 2002). To rescue cells from caspase-dependent cell death, XIAP binds upstream to caspase 9 and downstream to caspase-3 and -7 by its Baculovirus IAP Repeat (BIR) 3 and BIR2 regions, respectively (Huang et al., 2001). Additionally, XIAP can induce apoptosis independently of the caspase pathway through induction of the NF-κB pathway by complex formation with TAK1 kinase and its cofactor, TAB1 (Lu et al., 2007). Thus, inhibition of XIAP expression might be a promising tool to restore apoptosis in cancer cells (Schimmer et al., 2004).

Interestingly, this compound **12** did not induce apoptosis in healthy peripheral blood cells to a significant extent (Schyschka et al., 2008). Recently, the research team of Vollmar published a study about the impact of spongistatin 1 on highly metastatic pancreatic L3.6pl cancer cells (at 0.5 nM). The compound down-regulated tumor growth associated with up-regulation of apoptosis and long-term growth inhibition effects. In addition to these *in vitro* studies, spongistatin 1 inhibited tumor progression and reduced metastasis in mice models. The observed anticancer activities were linked to the reduced expression of metalloproteinase 9 (MMP-9) and down-regulation of the antiapoptotic protein Bcl-2 (Rothmeier et al., 2010).

As previously mentioned, the marine sponges of the genera *Agelas*, *Axinella* and *Hymeniacidon* are abundant sources of bromopyrrole alkaloids (Kobayashi et al., 1990; Pettit et al., 1990). In 1990, hymenialdisine **17** and debromohymenialdisine **18** were reported to exhibit potent activity against murine P388 lymphocytic leukemia (ED_{50} of 2.0 and 2.5 μg/mL, respectively), whereas axinohydantoin **19** was eight times less active (18 μg/mL) (Pettit et al., 1990). Another compound of the same chemical class, agelasine G **20**, showed cytotoxic activity against murine lymphoma L1210 cells (IC_{50} of 3.1 μg/mL) (Ishida et al., 1992). In addition, dibromophakellistatin **21** exerted cytotoxicity against a panel of human cancer cells at submicromolar concentrations, whereas the replacement of the urea group by a guanidine function resulted in a less active compound (Pettit et al., 1997). N-(4, 5-dibromo-pyrrole-2-carbonyl)-L-aminoisovaleric acid amino acid **9** induced apoptosis through cleavage of caspases-9 and -3 accompanied by the release of intracellular Ca^{2+} (Xiong et al., 2010). In addition, sceptrin **22**, composed of 2 bromopyrroles linked to a cyclobutane unit, inhibited cell motility in a variety of cancer cells (at 40 μM) through inhibition of cell contractibility (Cipres et al., 2010). Debromo-sceptrin and, more importantly, nakamuric acid **23** and its methyl ester exhibited lower effects on cell motility compared to the parent compound. Sceptrin did not affect cell proliferation or survival (Cipres et al., 2010). On the contrary, it has been reported to be non-toxic to monkey kidney cells (at 200 μg/disk) (Keifer et al., 1991). However, detailed mechanistic studies of the pathways affected by sceptrin must still be conducted.

The research group of Crews isolated a novel β-carboline (1-imidazolyl-3-carboxy-6-hydroxy-β-carboline alkaloid, named hyrtiocarboline **24**) from the marine sponge *Hyrtiosreticulatus*. This compound exerted cytotoxic cell death against a panel of 13 cancer cells with IC_{50} of 1.2 μg/mL, 3.0 μg/mL and 1.5 μg/mL against non-small cell lung (H522-T1), melanoma (MDA-MB-435) and lymphoma (U937) cells, respectively (Inman et al., 2010). The β-carboline core structure represents a promising chemical class in drug discovery, as stated in several publications (Daugan et al., 2003; Trujillo et al., 2007) In the past, only a few β-carboline alkaloids from marine sources have been isolated, including 5-Bromo-8-methoxy-1-methyl-β-carboline **25** (Till and Prinsep, 2009), norharman **26** (Zheng et al., 2006), 2-methyleudistomins-D-J **27**,**28** and 14-methyl-eudistomin C **29** (Rashid et al., 2001). Of these compounds, only the last one possessed cytotoxic potential in a submicromolar range. Mechanistic details on the nature of cell death have yet to be investigated (Fig. 3B).

Makaluvamines **30**, belonging to the chemical class of pyrroloiminoquinones, were first isolated from marine sponges of the genera *Zyzzya* and *Histodermella* (Carney et al., 1993; Radisky et al., 1993). These compounds are cytotoxic against a number of cancer cell lines, which may be partly explained by their DNA topoisomerase II inhibiting activity (Matsumoto et al., 1999). These promising anticancer properties led to the synthesis and biological evaluation of various related analogs. In this respect, imidazo-quinoxalinone derivatives **31**, synthesized by Skibo and coworkers, have been shown to be less potent topoisomerase II inhibitors due to the presence of an electron-deficient benzimidazole ring in contrast to the indole ring of the parent compounds. Under physiological conditions, the cationic makaluvamines were reported to be active, whereas the imidazo-quinoxalinone analogs were not charged, which explains the lower activity of the latter (Hoang et al., 2007; Labarbera and Skibo, 2005). Altogether, the data presented here clearly indicate that makaluvamine analogs represent a promising target for future clinical trials and might promote the development of a novel anticancer drug.

More than 30 years ago, cyclopentenones were reported to inhibit cellular metabolism and exert antitumor activity (Hayward et al., 1998; Lee et al., 1977). It is worth noting that prostaglandins of types A1 **32**, A2 **33** and J2 **34**, which are known to inhibit tumor cell proliferation, are characterized by the presence of an α,β-unsaturated cyclopentenone ring (Santoro et al., 1989). Indeed, the bioactivity of these compounds is mainly associated with the presence of the cyclopentenone ring, and it has been supposed that this functional group acts as an important alkylating center with cysteine in a Michael-type reaction (Haven et al., 1973; Lee et al., 1977; Santoro et al., 1989). Detailed mechanistic studies have indicated that cyclopentenone **13** caused cell cycle arrest by repression of cyclin D1 expression, inhibited constitutive nuclear factor kappa B (NF-κB) activity and lead to the induction of apoptosis (Ciucci et al., 2006; Hsiang and Straus, 2002).

Interestingly, a recent review by Mantovani et al. pointed out that cancer-related inflammation could be identified as the seventh hallmark of cancer, as inflammatory conditions in certain organs lead to an increased risk of cancer (Colotta et al., 2009; Lazebnik, 2010). The transcription factor nuclear factor kappa B (NF-κB) is strongly involved in innate immune responses, inflammatory processes and tumorigenesis. NF-κB is composed of two different classes of subunits (RELA, RELB, cREL and NF-κB1, NF-κB2, respectively) (Ghosh et al., 1998; Prasad et al., 2010). These proteins form NF-κB hetero- and homo-dimers, whose activity is triggered by two major pathways. The first canonical NF-κB regulation pathway, targeted by viral or microbial infections and inflammatory signals, triggers the IκB kinase (IKK) complex; the later phosphorylates the inhibitor of κB (IκB) protein, which is bound to NF-κB dimer in the inactivated state. After its liberation, the p50-RELA dimer translocates to the nucleus and up-regulates the transcription of target genes (Karin and Ben-Neriah, 2000; Prasad et al., 2010). Members of the TNFα-receptor family, such as B-cell activating factor (BAFF) and

CD40, initiate the second, non-canonical pathway through selective activation of the NF-κB-inducing kinase (NIK) and IKK1 and subsequent phosphorylation of p100. After nuclear translocation of the generated p52-RELB dimer, the expression of corresponding target genes is induced (Claudio et al., 2002; Coope et al., 2002; Prasad et al., 2010). The activated NF-κB pathway plays a crucial role in cancer development and malignity, because its target genes are involved in multiple steps of cancer formation. Constitutive activation of the NF-κB pathway has been reported in a variety of cancer types (Prasad et al., 2010). This pathway controls a variety of genes linked to cancer formation and progression. These include metastatic genes (e.g., ICAM-X, ICAM-1, Mel-14, GMP-140, ELAM-1, and VCAM-1) needed for cancer cell migration (Iademarco et al., 1992; Prasad et al., 2010), angiogenic genes (such as VEGF and MCP-1) associated with vascularization of tumor cells (Chilov et al., 1997; Prasad et al., 2010; Ueno et al., 2000) and pro-inflammatory genes (e.g., TNFα, IL-1, IL-12, matrix metalloproteinase (MMP-9), and iNOS) (Chung and Chang, 2003; Dong et al., 2001; Klotz et al., 1999; Noguchi et al., 1996; Ohmori et al., 1997; Pacheco et al., 2001; Prasad et al., 2010; Tomimatsu et al., 2001). Moreover, the NF-κB pathway controls the up-regulation of both apoptotic and survival genes; these opposing induced effects depend on the cell type and the activation signal. In detail, the pro-apoptotic proteins FasL, c-myc, p53 and IκBα (Chan et al., 1999; Prasad et al., 2010; Qin et al., 1999), as well as the anti-apoptotic proteins TRAF1, TRAF2, IAP-family (e.g., c-IAP1, XIAP) and the Bcl-2-group (such as Bcl-xL and Bcl-2),may be expressed *via* NF-κB pathway control (Prasad et al., 2010; Stehlik et al., 1998; Wang et al., 1998). Altogether, the variety of pathways affected by the NF-κB signaling cascade has led to the focus on this transcription factor in the field of cancer drug development in recent years (Johnson and Brown, 2010; Lopez-Guerra and Colomer, 2010).

A series of novel cytotoxic cyclopentenones, namely didemnidones and trichoderone **35, 36**, has been isolated from the didemnid ascidian *Lissoclinum* sp. and the marine-derived fungus *Trichoderma* sp. (Ogi et al., 2009; You et al., 2010). In both cases, the IC_{50} was in the micromolar range. These findings substantiate the anticancer potential of cyclopentenone groups that are soft electrophiles and recognized as antitumor pharmacophores through covalently targeting pathogenic proteins in diseased cells (Conti, 2006, 2007).

The sesterpene heteronemin **37**, a pentacyclic scalarane, was originally derived from the sponges *Heteronema erecta* and *Hytios* sp., where it is available in large quantities (Kazlauskas et al., 1976). A few years after its first isolation in 1976, the research team of Crews reported the cytotoxicity of heteronemin against brine shrimps and gametes of the giant kelp *Macrocystis pyrifera* (Walker et al., 1980). In cytotoxicity assays, heteronemin induced cell death in human thyroid carcinoma cells, and one derivative, 12-deacetoxy-23-hydroxyheteronemin, exhibited significant toxicity against K562 cells (Fontana et al., 1999; Song et al., 2008). However, the exact mechanism of the observed anticancer bioactivity was not elucidated in this study. Later, in 2004, the involved biological pathways affected by this sesterterpene were clarified, in part. Thus, it has been demonstrated that heteronemin possesses antitubercular activity and acts *via* farnesyl transferase inhibition (Ledroit et al., 2004; Wonganuchitmeta et al., 2004). In addition, results from our laboratory have clearly shown that heteronemin inhibited the activation of the NF-κB pathway by down-regulating the proteasome. Moreover, our study revealed that heteronemin triggered caspase-dependent apoptosis in K562 cells *via* the extrinsic pathway and that this marine compound sensitized K562 cells to TNFα-induced apoptosis (Schumacher et al., 2010).

2.4. Anti-angiogenic compounds

Cells within aberrant proliferation mostly lack neoangiogenic capacity. Accordingly, tumors seek to develop angiogenic ability to progress to a larger size. Vascular endothelial growth factor (VEGF) is a prominent angiogenesis-initiating signal. Tumors activate this angiogenic switch by increasing gene transcription of VEGF and by down-regulating proteases that control the bioavailability of angiogenic activators and inhibitors. Circulating VEGF binds to tyrosine kinase receptors (VEGFR) on the cell surface, called VEGF receptors, especially on endothelial cells, triggering a tyrosine kinase pathway leading to neo-angiogenesis (see Fig. 5A for chemical structures **38**–**39** and Table 3 for a summary of anti-angiogenic marine products).

Ma et al. demonstrated that the marine-derived oligosaccharide sulfate (MdOS) **6**, a novel multiple tyrosine kinase inhibitor, combats tumor angiogenesis both *in vitro* and *in vivo*. The authors conclude that MdOS exhibited anti-angiogenic activity in a PTK-dependent manner, making it a promising agent for further evaluation in PTK-associated cancer therapy (Ma et al., 2008) (Fig. 5B).

The alkaloid manzamine A **10**, isolated from a variety of marine sponges, exhibited cytotoxic effects againstcancer cells with an IC_{50} in the range of 1–6 μM after 72 h (Guzman et al., 2010). The authors further provided evidence that manzamine A inhibited cell migration of pancreatic cancer cells AsPC-1 *in vitro* and likewise found their metastatic potential decreased. Positive Annexin V staining upon 48 h of treatment indicated phosphatidylserine exposure as a marker for apoptosis induction (Guzman et al., 2010). Guzman et al. first reported the potential antimetastatic and proapoptotic effect of this alkaloid. Hence, manzamine A can be used in a combination therapy, as it sensitizes cancer cells to TRAIL-induced apoptosis. This sensitization results from an inhibition of glycogen synthase kinase GSK3β (Guzman et al., 2010).

This enzyme is involved in numerous diseases, including diabetes, inflammation, cancer, Alzheimer's disease and bipolar disorder. It multi-targets several biological processes, such as glycogen metabolism, insulin signaling, cell proliferation, neuronal function, oncogenesis and embryonic development (Rayasam et al., 2009). GSK3α and GSK3β present a different molecular weight but the two isoforms have similar biological functions. GSK3β is, for example, involved in Wnt signaling, where it functions as an on/off trigger. In the case of Wnt-stimulated cells, GSK3β is inactivated, and stabilized β-catenin accumulates in the cytosol. Stabilized β-catenin then translocates to the nucleus, leading to the gene expression of target genes including c-myc and cyclin D1, which leads to enhanced cell proliferation (Rayasam et al., 2009). Moreover, phosphorylation by GSK3β is crucial in the regulation of tau's binding and stabilizing ability in microtubules (Cho and Johnson, 2004). Although GSK3β inhibitors are responsible for chromosome instability and promote tumorigenesis (Tighe et al., 2007), it has been reported that inhibition of GSK3 alone in untransformed cells does not affect β-catenin levels (Frame and Zheleva, 2006). Inhibitors of GSK3β have been reported as a novel therapeutic class against colon cancer (Shakoori et al., 2007).

A study of Rothmeier et al. reported antiangiogenic effects of spongistatin 1 **12** *in vitro* in human umbilical endothelial vein cells and *in vivo* in mice models. This product exerted its influence on endothelial proliferation beginning at a concentration of 100 pM. Because at this low concentration neither apoptosis nor cytotoxicity was induced, the antiproliferative property seemed to be independent of the microtubule-depolymerization effect (at 2 nM), leading to the reduction of directed migration by polarization (at 1 nM) and to the inhibition of PKCα translocation (at 5 nM) (Rothmeier et al., 2009). In addition to endothelial cells, spongistatin 1 induced apoptosis in breast cancer MCF-7 cells at a concentration 1000-fold lower (500 pM) than Taxol.

The work described by Sallam et al. shows the design and synthesis of dibromotyrosine-inspired phenolic ester and ether analogs **38**,**39** with anti-angiogenic, anti-proliferative and anti-migratory properties and negligible cytotoxicity. Bioactive secondary metabolites originating from dibromotyrosine are common in marine sponges, such as sponges of the *Aplysina* species (Sallam et al., 2010).

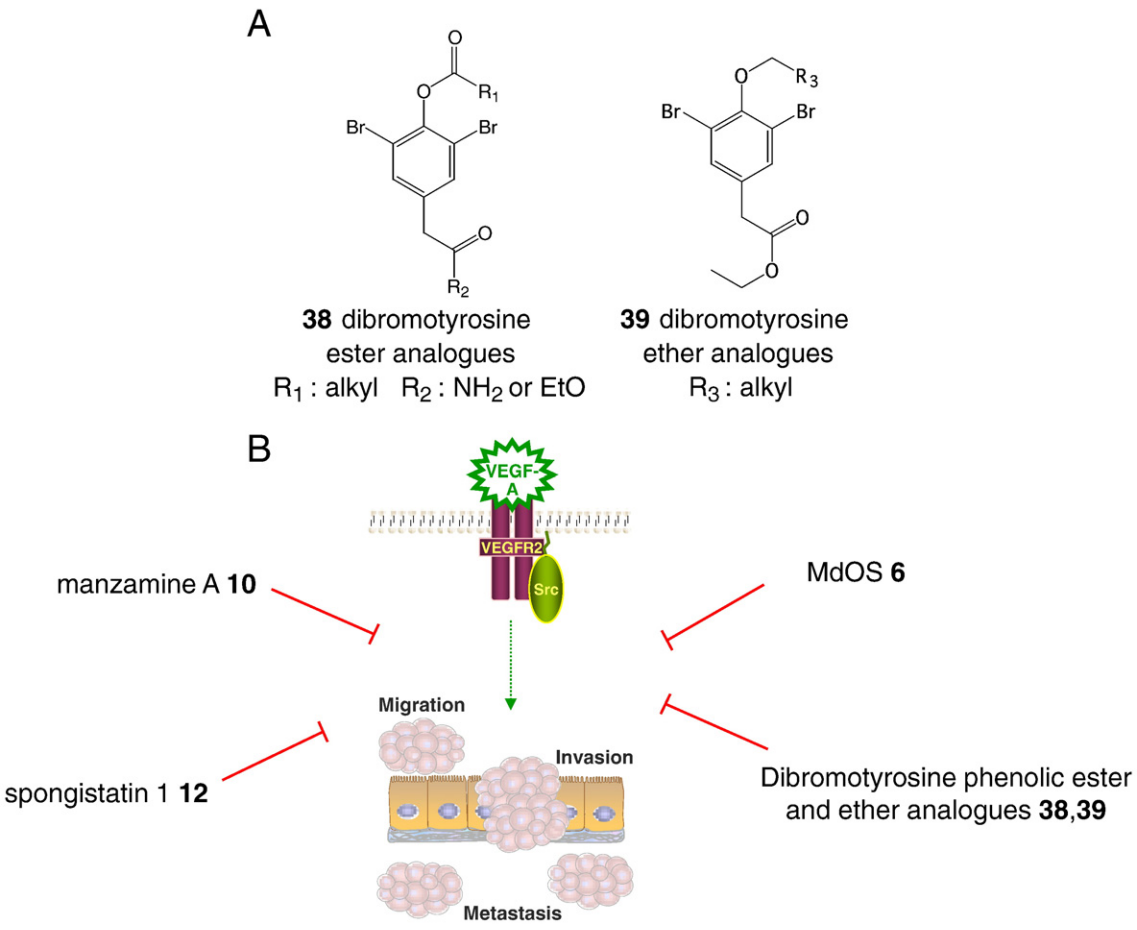


Fig. 5. A) Chemical structures of anti-angiogenic marine products **38**–**39**. B) Marine compounds targeting VEGF response.

2.5. Compounds that reduce the replicative potential

Healthy cells auto-limit their replicative potential through a fine-tuned program that limits their multiplication, known as senescence. Normal human cell types have the capacity for 60–70 doublings. The progressive erosion of telomeres through successive cycles of replication eventually causes cells to lose their ability to protect the ends of chromosomal DNA and subsequently leads to cell death. Cancer cells, however, maintain telomere length by up-regulation of the telomerase enzyme, which adds hexanucleotide repeats onto the ends of telomeric DNA and is thus considered to confer unlimited replicative potential. Compounds that would provide efficient and specific inhibition of telomerase would interfere with this feature of cancer cells and have been studied by various research teams (see

Table 3
Marine products that exert anti-angiogenic properties, reduce replicative potential and prevent metastasis and migration.

Name	Chemical class	Affected hallmark	IC_{50}[a]	Reference
Dibromotyrosine anal. **38**–**39**	Dibrominated phenols	4	20–50 μM	(Sallam et al., 2010)
MdOS **6**	Oligosaccharide	4	50 μg/mL	(Ma et al., 2008)
Spongistatin 1 **12**	Marcrocyclic lactone	4	1 nM	(Rothmeier et al., 2009)
Ascididemin **47**	Pyridoacridine	5	87 μM	(Guittat et al., 2005)
Axinelloside A **46**	Lipopolysaccharide	5	2.0 μg/mL	(Warabi et al., 2005)
Dictyodendrins A-E **41**–**45**	Pyrrolocarbazole	5	<50 μg/mL	(Warabi et al., 2003)
Dideoxypetrosynol A **8**	Polyacetylene	5	0.6 μg/mL	(Park et al., 2007a)
Meridine **48**	Pyridoacridine	5	11 μM	(Guittat et al., 2005)
Microalgal polysaccharide	Polysaccharide	5	<10 μg/mL	(Sogawa et al., 1998)
(Z)-stellettic acid C **40**	Acetylenic acid	5	30 μg/mL	(Park et al., 2007b)
Azaspiracids **51**	Polycycle	6	50 nM	(Vilarino, 2008)
KRN7000 **55**	α-galactosylceramide	6	100 μg/kg	(Nakagawa et al., 1998)
Latrunculins A and B **50**	Macrolide	6	4.2 μM	(Khanfar et al., 2010)
Manzamine A **10**	β-carboline	6	5 μM	(Guzman et al., 2010)
Motuporamine C **54**	Marcocycle	6	3 μM	(Roskelley et al., 2001)
Neopetrosiamide A	Tricyclic peptide	6	>10 μM	(Austin et al., 2010)
Oligomannurarate Sulfate **53**	Oligosaccharide	6	100 μg/mL	(Zhao et al., 2006)
Pachycladin A **56**	Diterpene	6	<50 μM	(Hassan et al., 2010)
Phenylmethyl. hydantoins **49**	Heterocycle	6	>10 μM	(Khanfar and El Sayed, 2010)
Sulfated polysaccharide **52**	Polysaccharide	6	50 μg/mL	(Tang et al., 2006)

[a] In some articles, the IC_{50} was not determined, see indicated references for further details.

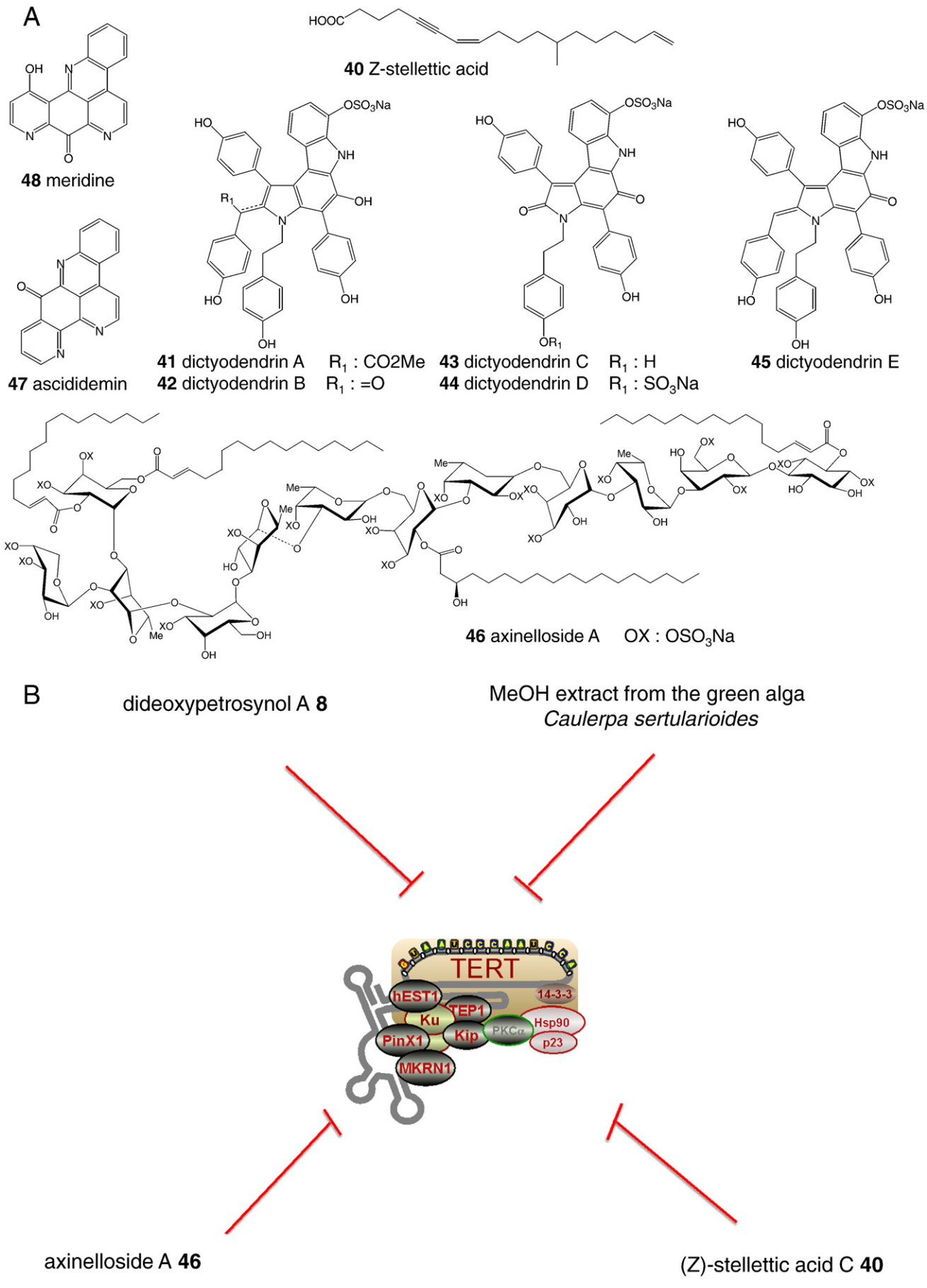


Fig. 6. A) Chemical structures of marine compounds **40**–**48** that reduce replicative potential. B) Marine compounds targeting telomerase activity.

Fig. 6A for chemical structures **40**–**48** and Table 3 for summary of marine products reducing the replicative potential).

Kanegawa et al. screened 304 marine algae samples that were collected from various Japanese coasts. In particular, the MeOH extract from the green alga *Caulerpa sertularioides* strongly inhibited telomerase activity when added to a MOLT-4 cell culture (Kanegawa et al., 2000) (Fig. 6B).

Induction of apoptosis by (Z)-stellettic acid C **40**, an acetylenic acid from the sponge *Stelletta* sp., is associated with inhibition of telomerase activity in human leukemic U937 cells, as published by Park et al. (2007b).(Z)-Stellettic acid C treatment markedly inhibited the activity of telomerase in a dose-dependent fashion. Additionally, the expression of human telomerase reverse transcriptase was progressively down-regulated by this treatment.

The same team (Park et al., 2007a) reported similar results for dideoxypetrosynol A **8**, a polyacetylene from the marine sponge *Petrosia* sp. that is known to exhibit significant selective cytotoxic activity against several human cancer cell lines. Compound treatment markedly inhibited the activity of telomerase, and the expression of human telomerase reverse transcriptase (hTERT), a main determinant of telomerase enzymatic activity, was progressively down-regulated by dideoxypetrosynol A treatment in a dose-dependent fashion.

Five alkaloids, dictyodendrins A-E **41**–**45**, were isolated from the Japanese marine sponge *Dictyodendrilla verongiformis* as telomerase inhibitors (Warabi et al., 2003). Later, Furstner et al. (2006) described full synthesis of the marine telomerase inhibitors dictyodendrin B, C, and E.

In recent years, researchers have been able to identify several telomerase inhibitors that are able to inhibit various cancer cell models: Warabi et al. described axinelloside A **46** that was isolated from the lipophilic extract of the Japanese marine sponge *Axinella infundibula* as a strong human telomerase inhibitor (IC_{50} 2.0 μg/mL) (Warabi et al., 2005). Guittat et al. reported that ascididemin **47** and meridine **48** stabilize G-quadruplexes and inhibit telomerase *in vitro*. Meridine is a stronger quadruplex ligand and therefore a stronger telomerase inhibitor than ascididemin (Guittat et al., 2005). Sogawa et al. (1998) described the inhibitory effect of a marine microalgal polysaccharide on telomerase activity in K562 cells.

2.6. Compounds that prevent invasion and metastasis

It is well known that primary tumor seed cells that acquire the capacity to invade adjacent tissues. E-cadherin serves as a widely acting suppressor of invasion and metastasis by epithelial cancers, and the functional elimination of E-cadherin represents a key step in the acquisition of metastatic capability. Moreover, changes in integrin expression are also described in invasive and metastatic cancers (see Fig. 7 for chemical structures **49**–**56** and Table 3 for a summary of marine products that prevent invasion and metastasis).

In the process of discovery of new antiproliferative and anti-metastatic agents against prostate cancer, marine-derived phenylmethylene hydantoin (PMH) derivatives **49** were identified with an activity-level range between 50 and 200 μM. A 3D-QSAR CoMFA model was used in virtual screening of commercially available derivatives of PMH. PMH derivatives with manifold increase in anti-migratory and anti-invasive activities were discovered using wound-healing and Cultrex invasion assays (Khanfar and El Sayed, 2010).

Khanfar et al. described semisynthetic latrunculin derivatives as inhibitors of metastatic breast cancer. The microfilament cytoskeleton protein actin plays an important role in cell biology and affects cytokinesis, morphogenesis and cell migration. These functions usually fail and become abnormal in cancer cells. The marine-derived macrolide latrunculins A **50** and B, from the Red Sea sponge *Negombata magnifica*, are known to reversibly bind actin monomers, forming 1:1 stoichiometric complexes with G-actin and disrupting its polymerization (Khanfar et al., 2010).

The azaspiracids (AZAs) **51** are a group of marine phycotoxins discovered during the second half of the 1990s. One of the *in vitro*

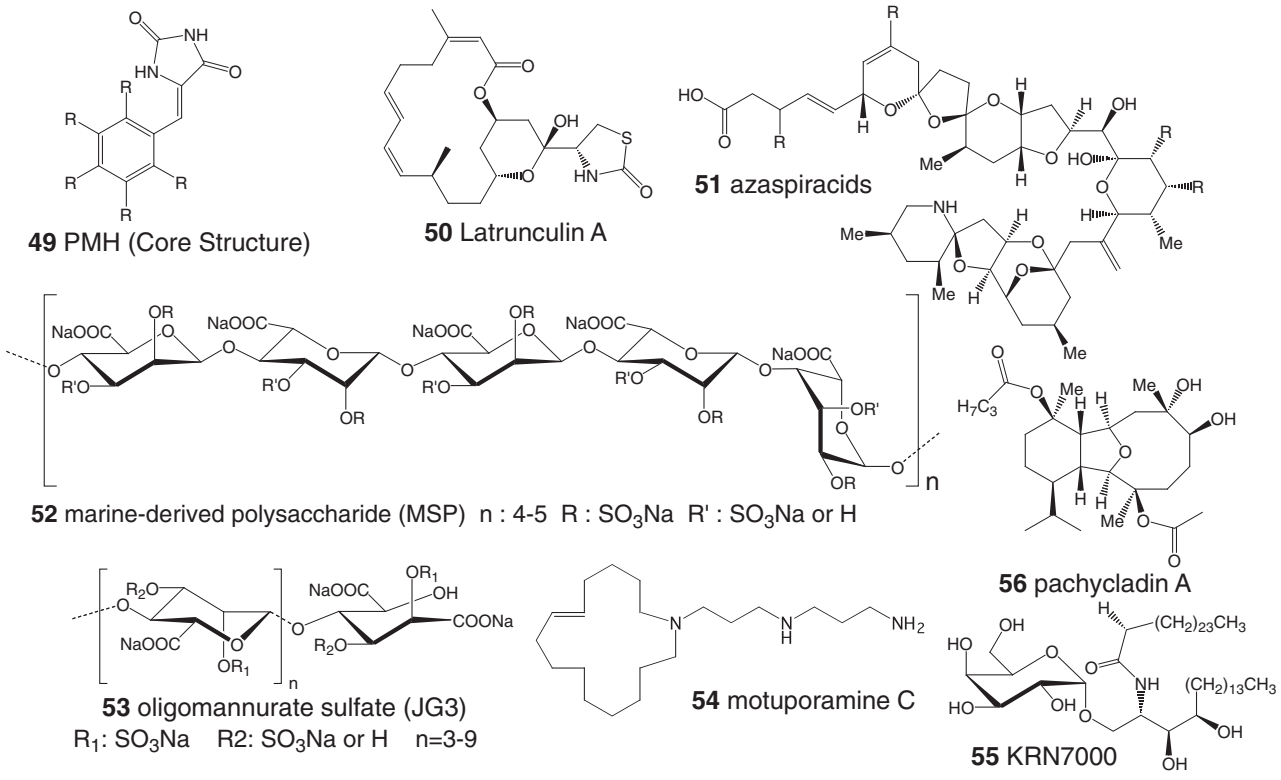


Fig. 7. Chemical structures of products **49**–**56**, that suppress metastasis and migration.

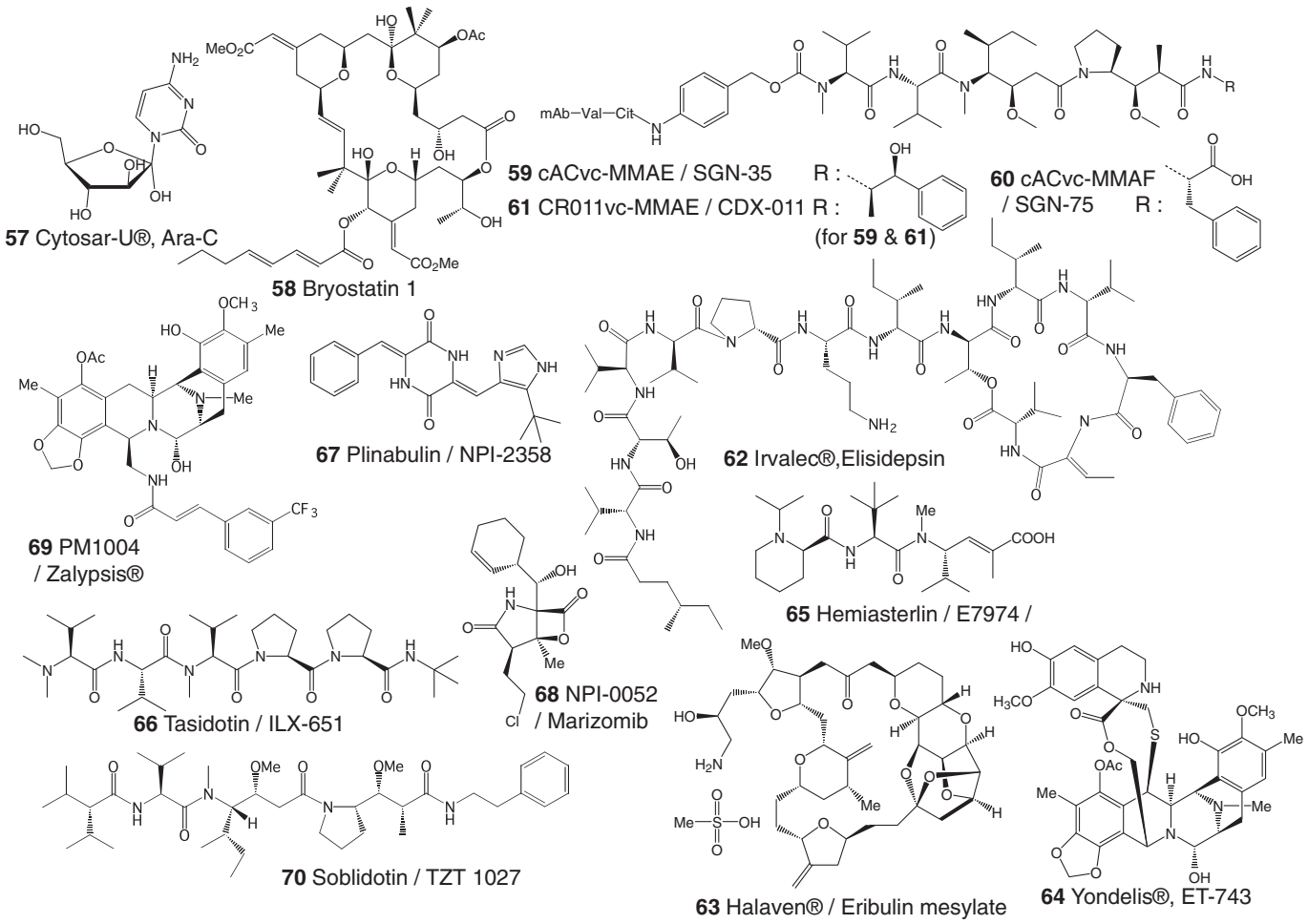


Fig. 8. Chemical structures of marine derived anticancer drugs **57**–**67**, that are approved or in clinical trials.

signs of AZA toxicity is the alteration of the actin cytoskeleton arrangement, which is accompanied by changes in cell shape and loss of cell adherence to the substrate. The cytoskeletal damage is irreversible after toxin withdrawal. Several other *in vitro* effects of AZAs have been described that may be related to cytoskeletal changes, such as E-cadherin degradation, caspase activation/apoptosis, membrane cholesterol reduction and gene expression alterations, although evidence for a direct relationship between any of these effects and AZA-induced cytoskeletal damage is still nonexistent (Vilarino, 2008).

Tang et al. reported that marine-derived sulfated polysaccharide (MSP) **52**, a new kind of polysaccharide extracted from a brown alga, exhibits an anti-migration effect *in vitro* and potently suppresses metastasis of Lewis lung carcinoma *in vivo*. Adhesion assays demonstrated that MSP inhibits the heterogenous adhesion on fibronectin. Further studies revealed that MSP decreased FN-induced MDA-MB-435 migration, accompanied by its potent regulatory effect on actin filament reassembling. In addition, MSP significantly inactivated the phosphorylation of FAK and subsequent ERK1/2 in MDA-MB-435 cells. All these

Table 4
Marine-derived products in clinical trials or approved as anticancer drugs.

Name	Chemical class	Affected hallmark	IC_{50}[a]	Reference
Ara-C/Cytosar-U® **57**	Pyrimidine nucleoside	2	10 μM	(Tuominen and Kenney, 1972)
Bryostatin 1 **58**	Macrocyclic lactone	1	10 nM	(Jones et al., 1990)
cAC10vc-MMAE; SGN-35 **59** (Brentuximab vedotin)	Antibody-drug conjugate	2	12 ng/mL	(Sutherland et al., 2006)
cAC10vc-MMAF; SGN-75 **60**	Antibody-drug conjugate	2	4.4 ng/mL	(Sutherland et al., 2006)
CR011-vcMMAE **61**	Antibody-drug conjugate	6	216 nM	(Pollack et al., 2007)
Elisidepsin/Irvalec® **62**	Cyclic peptide	1	0.6 μM	(Ling et al., 2009)
Eribulin Mesylate, Halaven® **63**	Macrocycle	2	100 nM	(Kuznetsov et al., 2004)
ET-743/Yondelis® **64**	Tetrahydroisoquinoline	2	80 nM	(Erba et al., 2001)
E7974/Hemiasterlin anal. **65**	Tripeptide	2	10 nM	(Kuznetsov et al., 2009)
ILX-651/Tasidotin **66**	Linear peptide	2	72 nM	(Ray et al., 2007)
NPI-2358/Plinabulin **67**	Diketopiperazine	2	18 nM	(Nicholson et al., 2006)
NPI-0052/Marizomib **68**	Bicyclic lactone	3	200 nM	(Miller et al., 2007)
Plitidepsin/Aplidin® **4**	Cyclodepsipeptide	1	5 nM	(Cuadrado et al., 2003)
PM1004/Zalypsis® **69**	Tetrahydroisoquinoline	2	7 nM	(Leal et al., 2009)
Soblidotin/TZT 1027 **70**	Peptide	4	0.1 ng/mL	(Watanabe et al., 2007)

[a] In some articles, the IC_{50} was not determined, see indicated references for further details.

actions may be the results of MSP binding to FN, promising the therapeutic potential of MSP in tumor metastasis (Tang et al., 2006).

Inhibitors of tumor angiogenesis and metastasis are increasingly emerging as promising agents for cancer therapy. Recently, heparanase inhibitors have offered a new avenue for such work, because heparanase is thought to be critically involved in the metastatic and angiogenic potentials of tumor cells. Here, we report that oligomannurarate sulfate (JG3) **53**, a novel marine-derived oligosaccharide, acts as a heparanase inhibitor. Our results revealed that JG3 significantly inhibited tumor angiogenesis and metastasis, both *in vitro* and *in vivo*, by combating heparanase activity *via* binding to the KKDC and QPLK domains of the heparanase molecule (Zhao et al., 2006).

A screen of marine sponge extracts identified motuporamines as micromolar inhibitors of invasion of basement membrane gels by MDA-231 breast carcinoma, PC-3 prostate carcinoma, and U-87 and U-251 glioma cells. Motuporamine C **54** inhibits cell migration in monolayer cultures and impairs actin-mediated membrane ruffling at the leading edge of lamellae. Motuporamine C also reduces beta1-integrin activation, raising the possibility that it interferes with "inside-out" signaling to integrins (Roskelley et al., 2001).

Marginisporum crassissimum (Yendo) Ganesan, a marine red alga found in the ordinal coastal sea around Japan, revealed antimetastatic effects *in vitro* and *in vivo*. In *in vivo* experiments, the lung metastasis of B16–BL6 cells inoculated *via* the tail vein of B57BL/6J mice was inhibited by intraperitoneal administration of an extract from the alga (Hiroishi et al., 2001).

Glycosphingolipids called agelasphins have been isolated as anti-tumor compounds from an extract of the marine sponge *Agelas mauritianus*. KRN7000 **55**, (2S,3S,4R)-1-O-(alpha-D-galactopyranosyl)-2-(N-hexacosanoylamino)-1,3,4-octadecanetriol, markedly stimulated lymphocytic proliferation in allogeneic MLR and showed potent tumor growth inhibitory activities in B16-bearing mice and strongly inhibited tumor metastasis (Natori et al., 1997).

In several cases, the affected biological pathways that prevent invasion and metastasis need to be elucidated, as reported in the following cases. Neopetrosiamide A (NeoA) is a 28-amino acid tricyclic peptide originally isolated from a marine sponge as a tumor cell invasion inhibitor. It is an anti-adhesive peptide that decreases cell surface integrin levels through a novel, yet-to-be-elucidated mechanism that involves the release of adhesion molecule-containing vesicles from the cell surface (Austin et al., 2010). *Alcyonaria* species are among the important marine invertebrate classes that produce a wealth of chemically diverse bioactive diterpenes. These compounds were evaluated for their ability to inhibit growth, proliferation, invasion and migration of the prostate cancer cells PC-3; Pachycladin A **56** exerted the highest activity (Hassan et al., 2010). Manzamine A **10** appears to have a formerly unrecognized activity in blocking tumor cell invasion as well as in restoring cancer cell susceptibility to apoptosis *in vitro* and, therefore, has the potential to be used as an adjuvant to existing cancer therapies (Guzman et al., 2010).

3. Conclusion

This review has presented a survey of different marine compounds acting on the six hallmarks of cancer. Interestingly, most of the natural compounds reported in this review lead to apoptosis induction in cancer cells, thus eliminating the source of the disease. This programmed cell death is targeted by most of the marine-derived anticancer drugs reported in this review, as shown in Table 2. Hence, it has to be pointed out that only the sixth hallmark reported by Hanahan and Weinberg (prevention of metastasis and migration) is exclusively associated to malignant tumors in contrast to the remaining first five hallmarks that are characteristic by both benign and malign cancers (Lazebnik, 2010). Therefore, the marine products, targeting this sixth hallmark are the most potent medical defense line against metastatic tumors. Regarding the latest advancements in drug discovery research from marine sources, it is not surprising that more than ten marine-derived compounds are actually approved anticancer drugs or in clinical trials (phase I–III) as reviewed by Mayer and co workers (Fig. 8 and Table 4, (Mayer et al., 2010)) and highlighted by the recent drug approval of the marine-derived product eribulin mesylate (Halaven®; Eisai Inc.) by the FDA in mid November 2010 (FDA) (Gradishar, 2011). Altogether, the marine products and their associated bioactivity, discussed in this review, underline the importance of marine derived compounds as promising in the drug discovery research area.

The data presented here undoubtedly indicate the great value of marine products as well as marine-derived analogs of marine products that make them important candidates for further pharmaceutical studies for feeding the anticancer drug pipeline. Thus, isolation or modification of novel marine products as well as their analogs and the subsequent evaluation of their bioactivity will propel the discovery of novel promising chemotherapeutic drugs. In conclusion, we remain convinced that the sea still contains valuable "nuggets" waiting to be mined by inquiring medicinal chemists as well as cancer researchers.

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