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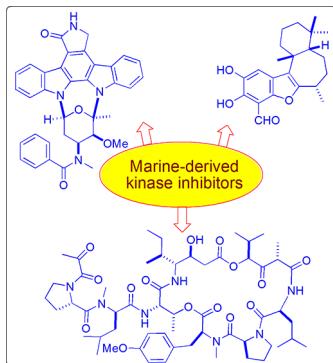
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## Kinase Inhibitors of Marine Origin

Sandip B. Bharate, Sanghapal D. Sawant, Parvinder Pal Singh, and Ram A. Vishwakarma\*

Medicinal Chemistry Division, Indian Institute of Integrative Medicine (Council of Scientific and Industrial Research), Canal Road, Jammu-180001, India

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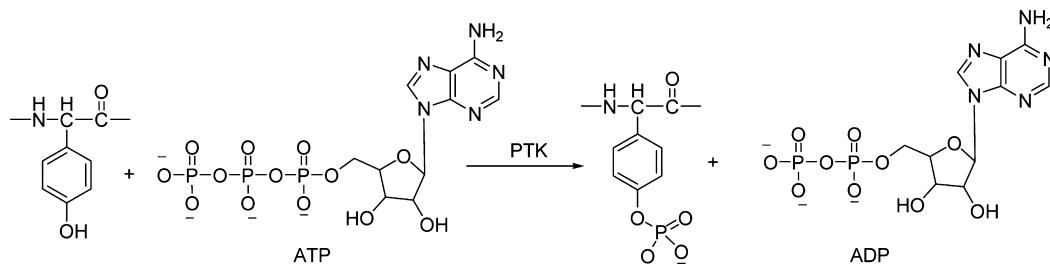
### 1. INTRODUCTION

The ocean occupies three-fourths of the Earth's surface and hosts approximately 80% of all living species. In fact, some areas of the sea such as coral reefs possess a biodiversity density greater than that of tropical rainforests. A recent census of marine life by 2700 scientists from more than 80 countries assessed the diversity, distribution, and abundance of marine life and reported over 6000 potentially novel species ([www.coml.org](http://www.coml.org)).<sup>1–3</sup> The sea offers mostly untapped sources of potential drugs with promising activities due to the diversity of marine habitats and environmental conditions (nutrient availability, sunlight density, and salinity levels).<sup>4</sup> Therefore, it is clear that the marine ecosystem represents a very rich source of novel drug-like natural products whose medicinal potential must be evaluated for a variety of pharmacological properties,<sup>5</sup> particularly for the treatment of cancer and bacterial infection.

More than 20 000 marine natural products (MNPs) have been isolated from ocean life-forms such as sponges, ascidian, aplysia, algae, corals, bryozoa, worm, sea-squirts, sea-hares, sea-cucumbers, fish species, and microorganisms.<sup>6</sup> Molecules with potential biomedical applications include alkaloids, terpenoids, steroids, polypeptides, polyethers, macrolides, and polysaccharides. Marine organisms produce secondary metabolites that are structurally distinct from those produced by terrestrial organisms, due to the unique biosynthetic milieu (high salinity, pressure, and temperature), and unusual functional groups such as isocyanate, isonitrile, dichloroimine, and halogenated functionalities that are predominantly found in marine metabolites. MNP research attracted some interest in the late 1950s with the project "Drugs from the Sea", which was launched in the U.S. and led to the discovery of two therapeutic drugs: cytarabine (an anticancer drug approved by the FDA in

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**Figure 1.** Phosphorylation of tyrosine hydroxyl by protein tyrosine kinase.

1969) and vidarabine (an antiviral drug approved by the FDA in 1976). Despite these early success stories, it was not until 2004 that the next generation of MNPs obtained global regulatory approval after successful clinical trials. During the intervening period, there was a general reluctance on the part of mainstream pharmaceutical industries to pursue drug discovery projects to translate potential hits based on marine natural product scaffolds, largely due to (a) the structural complexity of MNPs, which is not amenable to standard medicinal chemistry and lead-optimization; (b) the lack of a consistent and reproducible supply of marine flora and fauna required for scale-up to the levels necessary for research; and (c) the legal hurdles imposed by various geological territories and countries. However, natural products chemistry efforts continued unabated in several leading academic institutions worldwide, resulting in the discovery of a large number of structurally unique natural products. The majority of these MNPs were not screened against a battery of clinically validated targets in an industry setting.<sup>7–9</sup> However, recent approvals of some marine-derived drugs<sup>7–9</sup> for a number of intractable cancers have demonstrated their untapped potential for the discovery of first-in-class drugs. Considering the current dismal scenario of new drug approvals in global pharmaceutical industries, the focus will shift back to natural products-driven drug discovery sooner rather than later. This interest is likely to be enhanced by recent advances in the technologies used for deep-sea collection, extraction, large-scale aquaculture production, high-throughput isolation, dereplication, chemical synthesis, and biotechnology.

Over the past decade, drug discovery has shifted from an empirical approach characterized by random screening of large compound libraries of synthetic origin using high-throughput cell-based cytotoxicity assays to screening against clinically validated molecular targets. The goal of this new target-based discovery is to improve the efficacy and selectivity of treatment by developing drug candidates that specifically block disease mechanisms. This new approach is largely driven by the rapidly expanding knowledge of disease biology and pathology at the molecular level. This approach has been particularly successful in the area of oncology. In the late 1970s, it became clear that proteins, after synthesis by the ribosomal machinery, are not only modified post-translationally (glycosylation, lipidation, etc.) but are also reversibly modified by phosphorylation/dephosphorylation, in response to many extracellular and intracellular stimuli. In phosphorylation, a phosphate group is added to (or removed from) the hydroxyl-bearing side chain of serine or threonine or the phenolic hydroxyl of tyrosine. This phosphorylation reaction is catalyzed by specific enzymes known as protein kinases, which transfer the  $\gamma$ -phosphate from ATP to the side-chain hydroxyls of substrate proteins, as depicted in Figure 1. In mammalian signaling pathways, there are four major classes of kinases, which are broadly classified by

their substrate preferences: serine/threonine kinases, tyrosine kinases, dual function kinases (Ser/Thr kinases and Tyr kinases), and lipid kinases. The signaling events triggered by kinases are regulated by another set of enzymes known as phosphatases, which specialize in selective deprotection of phosphate groups.

After the discovery of kinase-mediated signaling pathways (for a recent review, see Dar and Shokat, 2011<sup>10</sup>), it was obvious that designing small-molecule inhibitors of kinases (or activators of phosphatases) would be an ideal way to target many dysregulated pathways, particularly in cancer progression and metastasis. However, this premise was met with significant scepticism in the scientific community due to the perceived difficulty of selectively targeting a specific kinase without affecting several other kinases (overall, 519 kinases are encoded in the human genome), due to the conservation of the ATP binding pocket of most kinases. However, in 1994, Parke-Davis scientists reported<sup>11</sup> the first generation of very potent (nM) kinase inhibitors with manifold selectivity against other kinases. This discovery spurred the development of projects throughout the pharmaceutical industry; 18 kinase inhibitors have now been approved by the FDA for various diseases, and more than 500 candidates are in active clinical development. In addition, an entirely new type of biological therapeutics (monoclonal antibodies) was created to successfully target many such kinase receptors and enzymes.<sup>12,13</sup> However, despite these remarkable success stories, target selectivity remains a formidable challenge in drug development because almost all approved kinase inhibitor drugs work by competing with ATP for the ATP binding site of the enzyme. Hence, there is a great need for next-generation kinase inhibitors that work through alternative mechanisms such as allosteric inhibition,<sup>14–17</sup> or by targeting inactive conformations of kinases.<sup>10,18–20</sup> It is our premise that structural scaffolds based on natural products will provide these next-generation kinase inhibitors because small-molecule natural products have coevolved with protein folds in cells and several natural products are known to function as regulatory switches in plant and microbial biology.<sup>21</sup> Thus, marine natural products offer a fertile and untapped source for the discovery of next-generation kinase inhibitor drugs, particularly for the treatment of cancer and bacterial infections.

The primary aim of this Review is to discuss and critically analyze marine-derived small-molecule inhibitors of protein and lipid kinases, with an emphasis on medicinal chemistry, lead optimization, patent literature, preclinical profiling, and clinical development. Over the last two decades, several reviews have been published on marine natural products and their potential in drug discovery,<sup>22–73</sup> but there has not been a comprehensive review of marine natural products as inhibitors and modulators of clinically validated protein and lipid kinases. Some of the previous reviews on marine natural products have very briefly

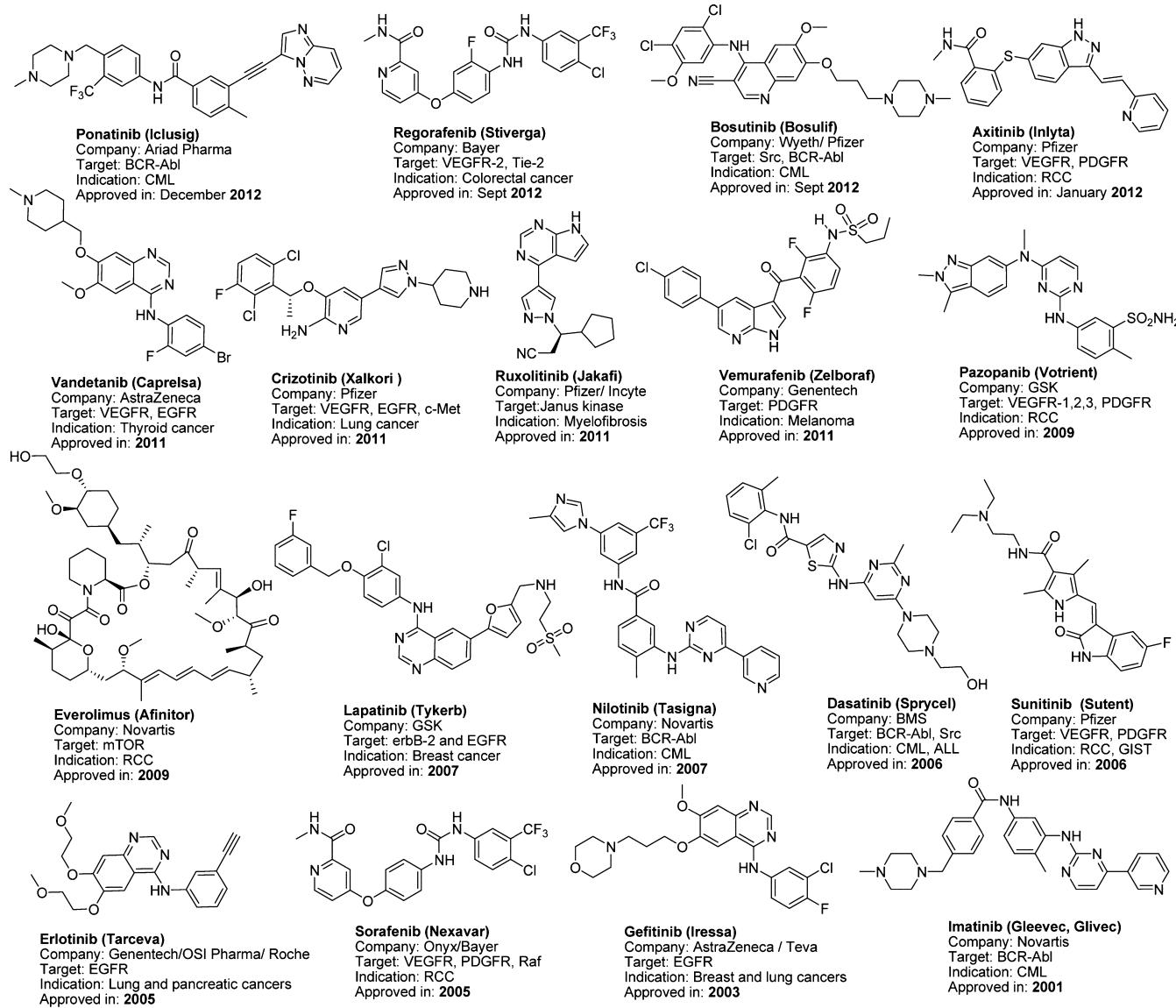


Figure 2. FDA-approved kinase inhibitors.

discussed their potential as protein kinase inhibitors. For example, Bridges (2001)<sup>74</sup> published a review on chemical inhibitors of protein kinases that contained 258 references and was mainly focused on PKC and BCR-Abl inhibitors from natural (both terrestrial plants and marine species) as well as synthetic sources. A review by Nakao and Fusetani (2007)<sup>75</sup> of enzyme inhibitors from marine invertebrates (208 references) briefly covered representative marine-derived small molecules inhibiting different kinases. Grant (2009)<sup>76</sup> reviewed therapeutic kinase inhibitors, their adverse effects, and toxicities. Morris and co-workers (2009)<sup>77</sup> reviewed variolins and related alkaloids. Marston (2011)<sup>78</sup> published a short review on natural products as a source of protein kinase activators and inhibitors that included 39 references. Recently, Skropeta et al. (2011)<sup>79</sup> reviewed kinase inhibitors from marine sponges, covering 70 natural products and 106 references with a focus on sponge-derived compounds but neglecting literature pertaining to medicinal chemistry and patents. Pla and co-workers (2011)<sup>80</sup> reviewed recent literature on lamellarins, a large group of marine-derived pyrrole alkaloids. Gao and Hamann (2011)<sup>81</sup> reviewed chemistry and biology of

kahalalides. Liu and co-workers (2012)<sup>82</sup> have summarized the history of different classes of natural product-derived kinase inhibitors, their target profiles, and structural binding modes. Recently, we have discussed the chemistry and biology of two types of marine-derived kinase inhibitors: fascaplysin<sup>83</sup> and meridianins.<sup>84</sup> The present comprehensive Review covers the natural product chemistry, synthetic/semisynthetic studies, medicinal chemistry, lead optimization, patent literature, preclinical pharmacology, and clinical status of marine-derived kinase inhibitors, including 354 compounds and 717 references. The literature was searched by using The Dictionary of Natural Products (Version 11.2, Chapman & Hall, CRC, 2010), PubMed, SciFinder, ISI Web of knowledge, Datamonitor, several patent databases (Delphion, Micropatent, Qpat, Patbase, and Total Patent), and Google Scholar.

## 2. KINASE INHIBITORS AS ANTICANCER DRUGS

Kinase inhibitors are a new class of anticancer drugs that are capable of directly interacting with the catalytic site of the target enzyme and thereby inhibiting kinase function or blocking kinase signaling. There are approximately 519 kinases in the

human genome, which are either serine/threonine or tyrosine specific. Because of the enormous progress that has been made during past few years in the elucidation of the human genome, molecular and cellular biology technologies, structural biology, and bioinformatics, a number of receptor and nonreceptor tyrosine kinases have been identified as valuable molecular targets. Currently, more than 20 different tyrosine kinase targets are under evaluation in drug discovery projects in oncology. The progress made in the crystallization of protein kinases, usually in complex with ATP-site-directed inhibitors, has confirmed that the ATP binding domain of tyrosine kinases is an attractive target for rational drug design; more than 70 ATP-competitive, low-molecular-weight inhibitors are in various phases of clinical evaluation. Several small-molecule kinase inhibitors are being intensively pursued as new anticancer therapeutics, and approximately 80 inhibitors<sup>85</sup> are in advanced stages of clinical trials and NDA approvals.

## 2.1. FDA-Approved Kinase Inhibitors in Clinical Use

The FDA has approved 18 kinase inhibitors for therapeutic use in oncology. The first kinase inhibitor used in clinical trials was tested against chronic myelogenous leukemia (CML), and after a series of preclinical and clinical successes imatinib (ST1571, Gleevec, Glivec) gained FDA approval in 2001 for the treatment of childhood leukemias.<sup>86–90</sup> This landmark success was followed by several candidates. Gefitinib (Iressa), a selective EGFR inhibitor, was approved by the FDA in May 2003 for the treatment of nonsmall-cell lung carcinoma.<sup>91–94</sup> However, FDA withdrew this approval in June 2005 for use in new patients due to lack of evidence of its efficacy in prolonging life in advanced disease states. The European regulatory agency approved gefitinib in 2009 for advanced NSCLC harboring EGFR mutations.

In 2005, two kinase inhibitors received FDA approval: the EGFR inhibitor erlotinib (OSI-774, Tarceva; Genentech/Roche), for the treatment of nonsmall cell lung cancer, pancreatic cancer, and several other types of cancer,<sup>95,96</sup> and sorafenib (Nexavar; Onyx/Bayer), a multitarget tyrosine kinase inhibitor (VEGFR, PDGFR), for the treatment of primary kidney cancer (advanced renal cell carcinoma) and advanced primary liver cancer (hepatocellular carcinoma).<sup>97–99</sup> In 2006, two multitarget tyrosine kinase inhibitors, sunitinib (SU11248 or Sutent; Pfizer) and dasatinib (BMS-354825; BMS), were approved by the FDA. Sunitinib was approved for renal cell carcinoma and imatinib-resistant gastrointestinal stromal tumors (GISTs),<sup>100–102</sup> whereas dasatinib (Sprycel) was approved for chronic myelogenous leukemia (CML) and imatinib-resistant Philadelphia chromosome-positive leukemias.<sup>85,103</sup> In 2007, the EGFR inhibitor lapatinib (Tykerb; GSK)<sup>104</sup> and the BCR-Abl inhibitor nilotinib (AMN107 or Tasigna; Novartis)<sup>105,106</sup> were approved for the treatment of breast cancer and CML, respectively. Everolimus (afinitor, Novartis), a semisynthetic analogue of rapamycin and a potent mTOR inhibitor, was approved in March 2009 for the treatment of advanced kidney cancer. In the same year, the multitargeted tyrosine kinase inhibitor pazopanib (Votrient; GSK) was approved for the treatment of advanced kidney cancer. In 2011, four tyrosine kinase inhibitors, vandetanib (Caprelsa; AstraZeneca), crizotinib (Xalkori; Pfizer), vemurafenib (Zelboraf; Genentech), and ruxolitinib (Jakafi; Incyte Pharma/Novartis), were approved by the FDA. In 2012, the FDA approved Ponatinib (Iclusig, Ariad Pharmaceuticals, for CML), Regorafenib (Stivarga, Bayer, for colorectal cancer),

Bosutinib (Bosulif, Pfizer, for CML), and Axitinib (Inlyta, Pfizer, for advanced kidney cancer).<sup>107</sup> All of these approved compounds target the ATP binding site on the kinase, even though this site is known to be highly conserved across the entire protein kinase family. The chemical structures of FDA-approved kinase inhibitors are shown in Figure 2.

## 2.2. Kinase Inhibitors in the Clinical Pipeline

Many tyrosine kinase inhibitors have advanced to various stages of clinical development. BIBF-1120 is an oral, potent tyrosine kinase inhibitor that simultaneously targets VEGFR-1–3, platelet-derived growth factor (PDGF) receptors  $\alpha$  and  $\beta$ , and fibroblast growth factor (FGF) receptors 1–3, as well as Flt-3 and Src. Currently, this molecule is in phase III development for second-line nonsmall cell lung cancer and first-line ovarian cancer patients.<sup>108</sup> Other tyrosine kinase inhibitors in clinical development include AP26113 (EGFR inhibitor, phase I/II, Ariad Pharmaceuticals),<sup>109</sup> apatinib (VEGFR-2, phase III, Bukwang Pharma),<sup>110</sup> telatinib (BAY 57-9352, VEGFR-2,3, PDGFR, phase I, ACT Biotech),<sup>111</sup> CHIR-258 (Flt-3, c-Kit, VEGFR-1/2/3, FGFR-1/3, Chiron Corp.),<sup>112</sup> BMS-540215 (VEGFR-1,2,3, FGFR-1,2,3; BMS),<sup>113</sup> vatalanib (PTK-787, VEGFR-1,2, PDGFR- $\beta$ , c-Kit, Flt-4; phase II; Bayer Schering and Novartis),<sup>114</sup> cabozantinib (XL-184; Met, VEGFR-2, Exelixis Inc.),<sup>115</sup> foretinib (GSK-1363089, XL-880, VEGFR-2/KDR; phase II; GSK),<sup>116</sup> tivozanib (VEGFR-1,2,3, phase II/III; Aveo Pharmaceuticals),<sup>117</sup> and OSI-930 (c-Kit VEGFR-2; OSI Pharma).<sup>118</sup> The phenolic compound INSM-18, which was discovered by Insmed, is a selective inhibitor of IGF-1R and Her-2 and has completed a phase I study in patients with relapsed prostate cancer. Among serine/threonine kinase inhibitors, several Aurora kinase inhibitors have advanced to clinical development phases. Tozastertib, originally developed as VX-680 by Vertex and later renamed MK-0457 by Merck, was the first Aurora kinase inhibitor to be tested in clinical trials. Tozastertib appeared to be particularly effective in bone marrow mononuclear cells obtained from acute myeloid leukemia (AML) patients with high Aurora A expression.<sup>119</sup> Other Aurora kinase inhibitors in clinical development include PHA-739358 (Nerviano Medical Sciences, Italy),<sup>120</sup> AS703569 (Merck),<sup>121</sup> AT9283 (Astellas Therapeutics),<sup>122</sup> SNS-314 (Sunesis Pharma),<sup>123</sup> PF-03814735 (Pfizer), CYC116 (Cyclacel Pharma), and MK5108 (VX-689). Several other Aurora kinase inhibitors are at the preclinical stage. IBU-PO and Tideglusib (Nypta) are GSK-3 $\beta$  inhibitors and are presently in phase I and II clinical trials for patients with Alzheimer's disease.

Among the lipid kinase inhibitors, several PI3K inhibitors have advanced to clinical studies such as XL-765 and XL-147 (Exelixis), which are class I PI3K inhibitors that have entered phase I clinical studies for advanced solid tumors. Other PI3K inhibitors in clinical studies include BEZ-235 and BKM-120 (phase II, Novartis) and GSK-1059615 (phase I, GSK) for advanced solid tumors. AstraZeneca's AZD-6482, which is a PI3K- $\beta$  inhibitor, has completed phase I trials for the treatment of thrombosis. A quinazolinone-based isoform-specific PI3K- $\delta$  inhibitor CAL-101 (GS-1101, Gilead Sciences) is in phase III, and IC-87114 (Calistoga) has entered phase I clinical trial. Other PI3K inhibitors in clinical trials include D106669 and D87503 (phase I, Aeterna Zentaris), GDC-0941 (phase I, Genentech), and PKI-587 (phase I, Pfizer). In addition, several other PI3K inhibitors are in early stages of clinical trials. A

detailed, current list of the clinical candidate pipeline is provided in the Supporting Information.

### 3. MARINE-DERIVED KINASE INHIBITORS

Almost all of the current natural product-derived drugs are of terrestrial origin; however, marine biodiversity has shown great promise and success due to the inherent potential of marine organisms to produce chemical and biological novelties. A recent comparative analysis by Kong and co-workers showed that marine natural products are superior to terrestrial natural products in terms of chemical novelty.<sup>124</sup> The analysis, which compared chemical scaffolds reported in the Dictionary of Natural Products to those in the Dictionary of Marine Natural Products, showed that approximately 71% of the scaffolds in the Dictionary of Marine Natural Products were exclusively produced by marine organisms. In addition, marine organisms showed higher incidence of significant bioactivity as compared to terrestrial organisms. For example, in a National Cancer Institute (NCI, NIH, U.S.) preclinical cytotoxicity screen, approximately 1% of the tested marine samples showed antitumor potential versus 0.1% of the tested terrestrial samples.<sup>125</sup> Furthermore, several marine drugs have successfully made it to market, and several others are in different phases of clinical trials. Mayer et al. have recently reviewed the marine pharmaceutical pipeline.<sup>53</sup> Currently, there are five FDA-approved marine or marine-derived small-molecule drugs (cytarabine, vidarabine, ziconotide, eribulin mesylate, omega-3-acid ethyl esters), in addition to an additional drug registered in the EU (trabectedin).<sup>53,126</sup> Twelve other marine or marine-derived drugs are in clinical trials.<sup>53</sup> Furthermore, there is a continuous supply of marine-derived NCEs in the preclinical pipeline, to feed the clinical pipeline. Interestingly, the number of new MNPs reported each year is increasing, and more than 1000 NCEs with different potencies and biological activities have been reported each year for the past couple of years.<sup>27–29,34,127–129</sup>

This literature precedence indicates that MNPs have great promise in the discovery of anticancer agents. 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. In recent years, a large number of kinase inhibitory MNPs have been reported. These molecules are discussed below in subsequent sections according to their targeted kinase. Broadly, two classes of kinases are covered, protein and lipid kinases.

#### 3.1. Protein Kinase Inhibitors

One of the largest groups of kinases is protein kinases, which act on and modify the activity of specific proteins. Protein kinases catalyze key phosphorylation pathways that regulate most aspects of cell life, whereas abnormal phosphorylation is a cause or a consequence of disease. Because they can be modulated by small molecules, protein kinases have now become the second most studied group of drug targets, after G-protein-coupled receptors (GPCRs). Most of the kinase inhibitor drugs approved so far are ATP-competitive with various off-target liabilities due to cross-reactivities; however, marine-derived compounds offer opportunities for the discovery of allosteric kinase inhibitors. Henceforward, all kinase inhibitors discussed in this Review are of marine origin.

##### 3.1.1. Serine/Threonine Kinase Inhibitors. 3.1.1.1. Protein Kinase C (PKC), A (PKA), and B (PKB, AKT) Inhibitors.

Protein kinase C (PKC) is a ubiquitous enzyme involved in a broad range of cellular processes such as signal transduction, growth, differentiation, and proliferation.<sup>130,131</sup> Staurosporine (1), an indolocarbazole alkaloid (first discovered in 1977 from the bacterium *Streptomyces staurosporeus*)<sup>132</sup> isolated from the marine ascidian *Eudistoma toaeensis*,<sup>133</sup> inhibits the cellular proliferation of 12 human leukemia cell lines, although the cell lines differed in their sensitivity toward the individual staurosporine derivatives. Staurosporine (1) was subsequently shown to be a potent PKC inhibitor as well as an inhibitor of cAMP-dependent protein kinases, cGMP-dependent protein kinases, and tyrosine protein kinases at similar concentrations.<sup>133</sup> Interestingly, it markedly inhibited phospholipid/Ca<sup>2+</sup>-dependent PKC from rat brain, with an IC<sub>50</sub> value of 2.7 nM. The inhibition of PKC was not competitive with phospholipid.<sup>134</sup> Differences in the efficacy of staurosporine derivatives in modulating growth may result from differences in their ability to inhibit certain kinases involved in cell growth and tumor promotion.<sup>135</sup> Staurosporine also inhibits p21 activated kinases (PAK).<sup>136</sup> The use of staurosporine has also been proposed for the inhibition of angiogenesis.<sup>137</sup> Because PKC is considered a therapeutic target for various diseases, the use of staurosporine and its derivatives has also been proposed for the treatment of different diseases such as various types of cancer,<sup>138–142</sup> respiratory syncytial virus infection,<sup>143</sup> ocular diseases,<sup>144,145</sup> several allergic diseases,<sup>146</sup> hypereosinophilic syndrome,<sup>147</sup> suppression of sustained slow postsynaptic excitation,<sup>148</sup> immunopotentiation,<sup>149,150</sup> and cardiac hypertrophy.<sup>151</sup> Two related natural products, de-O-methylstaurosporine (2)<sup>152</sup> and 11-hydroxystaurosporine (3),<sup>153</sup> isolated from the ascidian *Eudistoma* sp., are also potent inhibitors of PKC.<sup>152,153</sup> The staurosporine analogue UCN-01 (4)<sup>154</sup> is in phase II trials for various forms of cancers including pancreatic, breast, and lymphoma. UCN-01 strongly inhibits CHK-1 (*k*<sub>i</sub> = 5.6 nM), PDK-1 (IC<sub>50</sub> = 5.0 nM), and PKC $\beta$ 37 (IC<sub>50</sub> = 10 nM).<sup>155–157</sup> It also inhibits CDKs CDK-1 (*k*<sub>i</sub> = 95 nM), CDK-2 (*k*<sub>i</sub> = 30 nM), and CDK-4 (*k*<sub>i</sub> = 3.6  $\mu$ M), and isoforms of PKCs, with an IC<sub>50</sub> of less than 1  $\mu$ M. In specificity tests against a panel of 29 kinases, the kinase inhibition profile of UCN-01 was significantly distinct from staurosporine but was still rather broad.<sup>158</sup> 3-Hydroxystaurosporine (5), a natural product isolated from the flatworm *Pseudoceros* sp., displayed potent antiproliferative activity in leukemia cell lines.<sup>135</sup> The X-ray structure of 3-hydroxystaurosporine (5) in complex with Pak-1 (p21-activated kinase, PDB: 2hy8) revealed a binding mode similar to that of staurosporine (1).<sup>159</sup>

The structurally related indolocarbazole antibiotic K252b (6) and its methyl ester (K252a, 7), which were isolated from *Nocardiopsis* and *Actinomadura* species, are potent inhibitors of PKC in cell-free systems at low nanomolar concentrations.<sup>160,161</sup> K-252a (7) also inhibits cyclic nucleotide-dependent kinases with similar potency, whereas K-252b (6) is a relatively weak inhibitor of these enzymes.<sup>162</sup> The inhibition of PKC by K-252a and K-252b was reversible by higher concentrations of ATP, indicating competitive interaction with the ATP binding pocket of the enzyme.<sup>162,163</sup> Staurosporinone (8, K-252c), the aglycone of the staurosporine isolated from *Nocardiopsis* K290, inhibits PKC with an IC<sub>50</sub> of 214 nM with 10-fold selectivity over PKA. In other investigations, 8 inhibited cell-adhesion of the cell line EL-4. IL-2 and displayed activity in the KS62 bleb and neutrophil assays, in addition to micromolar and submicromolar inhibition of seven PKC isoenzymes.<sup>164,165</sup> A related natural product antibiotic contain-

Table 1. Miscellaneous Marine-Derived PKC Inhibitors

MNP	chemical class	source	ref
latrunculin A (63)	macrolide	red sea sponge <i>Latrunculia magnifica</i> and <i>Latrunculia corticata</i> ; Pacific sponges <i>Spongia mycofijiensis</i> and <i>Hyatella</i> sp.	196,197
3-bromo-5-hydroxy-4-methoxyphenylacetic acid (64)	phenol	red alga <i>Rhodomela confervoides</i>	198–200
manzamenone A (65)	bicyclic carboxylic acid	sponge <i>Plakortis</i> sp.	201
5-(methylthio)varacin A (66) and its <i>N,N</i> -dimethyl analogue 67	benzo[d][1,2,3] trithiole	ascidium <i>Lissoclinum</i> sp.	202
unidentified stereoisomer of ursolic acid	triterpenoid	black sea bryozoan <i>Conopeum seuratum</i>	203
spheciosterols A–C (68–70)	sterol sulfates	<i>Spheciopsis</i> sp.	204
fibrosterol sulfate B,C (71,72)	bis-steroids	<i>Lissodendoryx</i> ( <i>Acanthodoryx</i> ) <i>fibrosa</i>	205

ing a rhamnopyranosyl moiety, K-252d (9) isolated from *Nocardiopsis*-K290e, also showed PKC inhibition.<sup>164</sup> Interestingly, tjipanazole J (10) and its analogues 11–18,<sup>166</sup> which are indolocarbazole alkaloids structurally related to staurosporine isolated from the blue-green alga *Tolyphothrix tjipanasensi*, were inactive against rat brain PKC at concentrations up to 1 μM, which is quite high as compared to the activity threshold (10–100 nM) of other PKC inhibitory indolocarbazole alkaloids.<sup>166</sup> Three new indolocarbazoles, fradcarbazoles A–C (19–21), isolated from a mutant strain of the marine-derived actinomycete *Streptomyces fradiae* 007M135 showed significant inhibition of PKC-α, with IC<sub>50</sub> values of 4.27, 0.85, 1.03, and 0.16 μM, respectively. These compounds also showed strong cytotoxicity in HL-60 (IC<sub>50</sub> = 1.3, 1.6, 0.13 μM), KS62 (IC<sub>50</sub> = 4.58, 1.47, 0.43 μM), A-549 (IC<sub>50</sub> = 1.41, 0.001, 0.02 μM), and BEL-7402 (IC<sub>50</sub> = 3.26, 1.74, 0.68 μM) cells.<sup>167</sup>

Two sesquiterpene aldehydes corallidictyal A,B (22,23), isolated from the marine sponge *Aka siphonodictyon coralliphagum*, inhibited PKC with an IC<sub>50</sub> of 28 μM without inhibiting other serine–threonine kinases and cAMP-dependent kinases. Using four purified recombinant human isoforms of PKC (α, ε, η, and γ), it was possible to show that the inhibitor was selective for the α isoform (IC<sub>50</sub> 30 μM) as compared to ε, η, and γ (IC<sub>50</sub> of 89, >300, and >300 μM, respectively). In addition, the corallidictyal mixture (A and B) inhibited the growth of cultured Vero (African green monkey kidney) cells with IC<sub>50</sub> = 1 μM after continuous exposure (72 h).<sup>168</sup> The structurally similar sesquiterpenes nakijiquinone C (24) and D (25) isolated from the Okinawan marine sponge of the family Spongillidae exhibited inhibitory activity against PKC with IC<sub>50</sub> values of 23 and 220 μM, respectively.<sup>169</sup> Z-Axinohydantoin (spongiacidin D, fuscin, 26) and debromo-Z-axinohydantoin (spongiacidin C, 27) isolated from the sponge *Stylorella aurantium* inhibited PKC with an IC<sub>50</sub> of 9 and 22 μM, respectively.<sup>170</sup> Betaenone derivatives 28,29 and anthraquinones 30–32 isolated from the sponge-associated fungus *Microsphaeropsis* species displayed PKC-ε inhibition with IC<sub>50</sub> values of 36, >100, 18.5, 27, and 54 μM.<sup>171</sup> The triterpenoid oligoglycosides sarasinoside D (33), G (34), and E (35) isolated from the marine sponge *Asteropus sarasinorum* displayed in vitro cytotoxic activity against several types of tumor cells as well as PKC inhibition.<sup>172</sup> The polycyclic alkaloids xestocyclamine A (36) and B (37) from the marine sponge *Xesfospongia* sp. inhibited PKC at micromolar concentrations. Xestocyclamine A (36) was moderately potent against PKC-ε (IC<sub>50</sub> 10 μM) and also exhibited activity in a whole cell IL-1 release assay with an IC<sub>50</sub> of 1 μM.<sup>173–175</sup> The guanidine alkaloids batzelladines A–D (38–41) and crambescin A (42) from the Caribbean sponge *Batzella* sp. inhibited

PKC with IC<sub>50</sub> values of 1.4, 1.5, 6.8, 11, and 9.6 μM, respectively. These alkaloids 38–42 were also cytotoxic to proliferating Vero cells, with IC<sub>50</sub> values of 1.6, 1.8, 1.1, 0.5, and 0.7 μM, respectively.<sup>176</sup>

Aaptamines are marine alkaloids. The parent member, aaptamine 43, was first isolated by Nakamura and co-workers<sup>177,178</sup> and was found to possess cancer cell growth inhibitory activity and adrenoreceptor blocking activity.<sup>179</sup> Another member of the series, isoaaaptamine (44), was first reported by Fedoreev from the sponge *Aaptos suberitoides*<sup>180</sup> and was later isolated from the sponge *Aaptos aaptos* by two different groups.<sup>181,182</sup> Isoaaaptamine displays PKC inhibitory activity<sup>180,181</sup> as well as antiproliferative effects in P-388, KB16, A549, and HT-29 cells with IC<sub>50</sub> values of 0.175, 1.75, 1.32, and 1.75 μM, respectively.<sup>183</sup> Frondosin A–E (45–49) from the sponge *Dysidea frondosa* inhibited PKC-α with IC<sub>50</sub> values of 1.8, 4.8, 20.9, 26, and 30.6 μM, respectively.<sup>184,185</sup> The indole alkaloid 16-methylpendolmycin (50), which was isolated from *Nocardiopsis* sp., inhibited phorbol ester binding to PKC with an IC<sub>50</sub> of 35 nM.<sup>186</sup>

The sphingolipid-like molecule penazetidine A (51), a constituent of the Indo-Pacific marine sponge *Penates sollasi*, is a potent PKC inhibitor. It exhibited 50% inhibition of PKC at 1 μM and displayed no inhibitory activity at the same concentration against tyrosine kinase, suggesting that 51 binds to the regulatory site of PKC.<sup>187</sup> Sargaquinoic acid (52), which was isolated from the marine brown alga *Sargassum macrocarpum*, promotes neurite outgrowth via protein kinase A and MAP kinase-mediated pathways in PC12D cells.<sup>188</sup> Bis-amino bis-hydroxy polyunsaturated lipid, BRS1 (53), which was isolated from the Australian sponge *Leucetta microraphis*, inhibited phorbol ester binding to PKC with an IC<sub>50</sub> of 98 μM.<sup>189</sup> The polyketide peroxide chondrillin (54) from the marine sponge *Plakortis lita* and a peroxide lactone plakortolide B (55) from the sponge *Plakinastrella onkodes* exhibited PKC antagonistic and agonistic activity, respectively. Chondrillin (54) induced cell adhesion in the EL-4.E-2 cell line but expressed modest antagonistic activity against the PKC isoenzymes (IC<sub>50</sub> values: PKC-α = 87, PKC-β1 = 119, PKC-β2 = 119, PKC-δ = 56, PKC-ε = 73, PKC-γ = >364, and PKC-ζ = 104 μM). Plakortolide B also induced cell adhesion in the EL-4.E-2 cell line, which corresponded to very modest agonistic activity against a suite of PKC isoenzymes (inhibition at 50 μg/mL: PKC-α = 19%, PKC-β1 = 13%, PKC-β2 = 27%, PKC-δ = 9%, PKC-ε = 38%, and PKC-γ = 9%).<sup>190</sup>

Secosterols 56–60 from *Pseudopteogorgia* sp. showed moderate activity against PKC (all isoforms α, β1, β2, γ, δ, ε, and ζ) with IC<sub>50</sub> values in the range 12–50 μM.<sup>191</sup> Shimofuridin A (61) from the marine tunicate *Apodium*

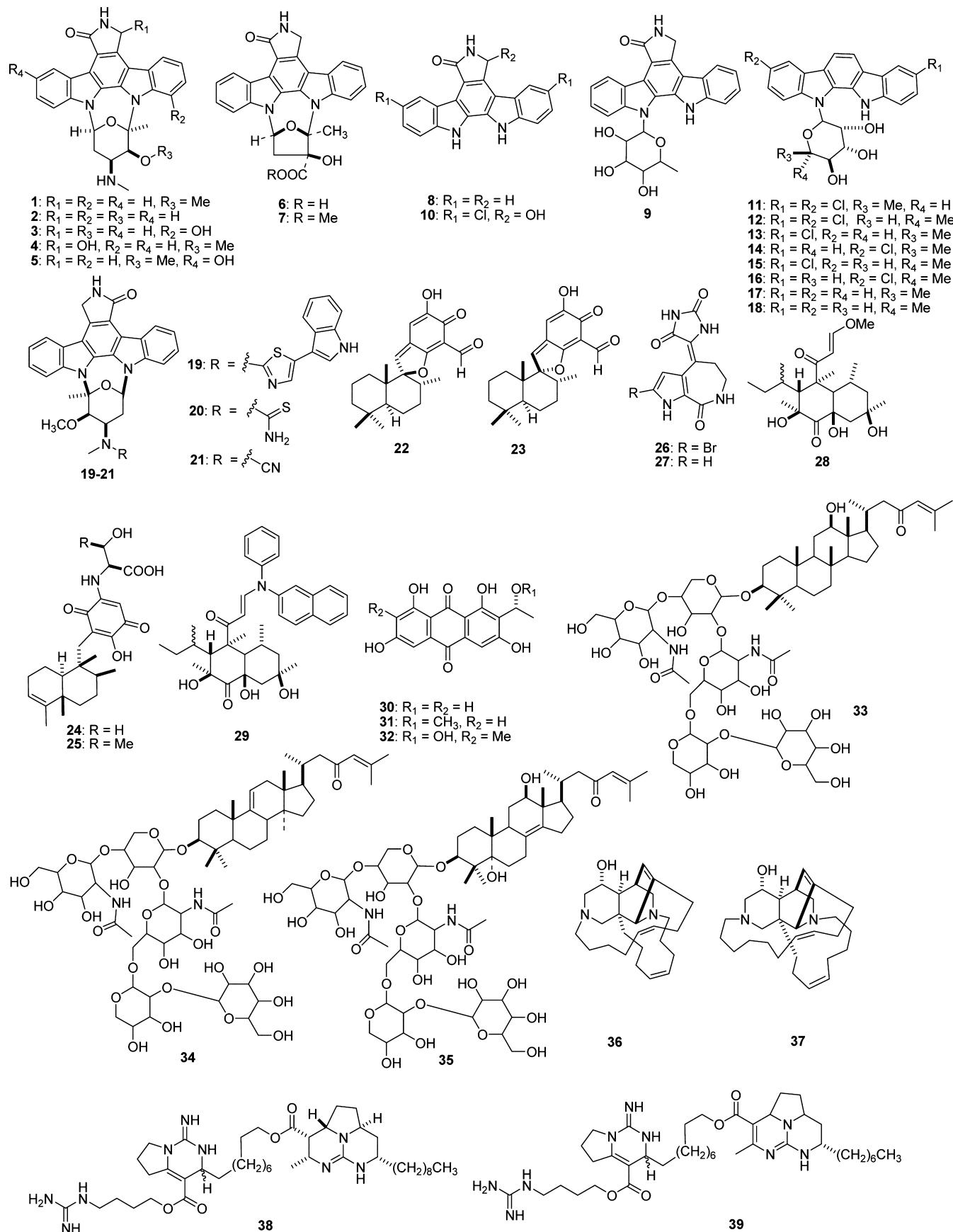


Figure 3. continued

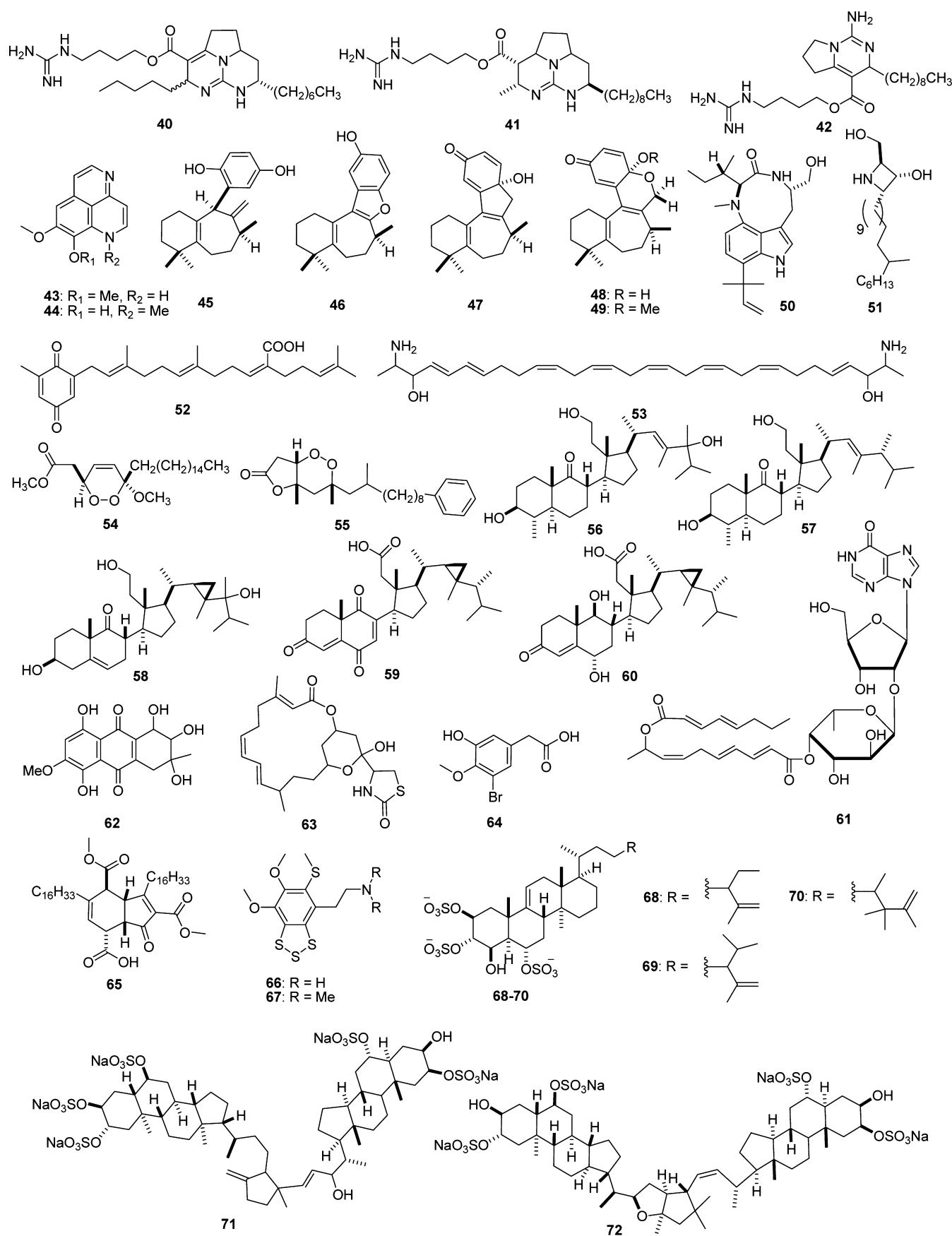


Figure 3. Marine-derived protein kinase C (PKC) and PKA inhibitors.

*multiplicatum* inhibited PKC with an  $IC_{50}$  of 28.6  $\mu\text{M}$ . This compound also exhibited cytotoxicity against murine lymphoma L1210 cells with an  $IC_{50}$  value of 13.6  $\mu\text{M}$  in vitro.<sup>192</sup> Sponge-derived hymenialdisine and its derivatives are also known to inhibit PKC (these compounds are discussed in the CDK class).<sup>193</sup> Anthraquinone SZ-685C (62) from the mangrove endophytic fungus collected from the South China Sea induced apoptosis through the Akt/FOXO pathway.<sup>194</sup> SZ-685C suppressed the proliferation of human MCF-7 (breast), PC-3 (prostate), MDA-MB-435 (melanoma), LN-444 (glioma), and Hep-3B and Huh-7 (hepatoma) cancer cell lines with  $IC_{50}$  values of 3.0–9.6  $\mu\text{M}$  and the growth of breast cancer xenografts in mice. The phosphorylation of Akt (also called protein kinase B, PKB) and its downstream effectors, forkhead box protein O1 and forkhead box protein O3a, was down-regulated in SZ-685C-treated cancer cells.<sup>195</sup> Furthermore, SZ-685C suppressed the proliferation of ADR-resistant MCF-7/ADR and MCF-7/Akt breast cancer cells as well as the growth of MCF-7/ADR xenografts.<sup>194</sup> Additional marine-derived PKC inhibitors 63–72 are listed in Table 1. The chemical structures of PKC inhibitors 1–72 are shown in Figure 3.

**3.1.1.2. Cyclin-Dependent Kinase Inhibitors.** Cyclin-dependent kinases (CDKs) are a group of protein kinases that are activated by the formation of a complex with a cyclin and are involved in the regulation of the cell cycle. CDKs are serine/threonine kinases that phosphorylate proteins on serine and threonine residues. Each cyclin associates with one or two CDKs, and most CDKs associate with one or two cyclins.<sup>206</sup> Several marine-derived small molecules inhibit various CDKs. The indole alkaloid rhopaladin B (73) from the marine Okinawan tunicate *Rhopalaea* sp. inhibited CDK-4 with an  $IC_{50}$  value of 20  $\mu\text{M}$ .<sup>207</sup> Spongiciadins A,B (74,75) from an Okinawan marine sponge *Hymeniacidon* sp. inhibited CDK-4 with  $IC_{50}$  values of 79.8 and 37.2  $\mu\text{M}$ , respectively.<sup>208</sup> Variolins, which were first isolated in 1994 from the rare, difficult to access Antarctic sponge *Kirkpatrickia variolosa* by Blunt and co-workers,<sup>209,210</sup> possess a rare pyrido[3',2':4,5]pyrrolo[1,2-c]pyrimidine skeleton, which had not previously been reported in a natural product. Five variolins have been isolated: variolin A (76), variolin B (77), deoxyvariolin B (78), N(3')-methyl tetrahydrovariolin B (79), and variolin D (80). Variolin D was found to be an artifact of the extraction process (aerial oxidation of the variolins).<sup>77</sup> Variolin B exhibited anticancer activity on P388 murine leukemia cells with an  $IC_{50}$  of 716 nM, whereas variolin A and N(3')-methyl tetrahydrovariolin B displayed only modest activities against this cell line, and variolin D was not active.<sup>209,210</sup> Variolin B (77) and deoxyvariolin B (78) inhibited CDKs in the micromolar range. CDK-1/cyclin B, CDK-2/cyclin A, and CDK-2/cyclin E complexes were inhibited at a range of concentrations similar to that required to inhibit CDK-4/cyclin D or CDK-7/cyclin H complexes.<sup>211</sup> Meridianins, structurally related compounds that share a 3-(pyrimidyl)indole motif, were isolated from the tunicate *Apidium meridianum* in 1998 by Hernandez Franco and Palermo.<sup>212,213</sup> Meridianins A–G (81–87) exhibited inhibitory activity against a panel of kinases that included CDKs, GSKs, CKs, and PKs. Meridianin E (85) inhibited CDK-1/cyclin B, CDK-2/cyclin A, CDK-2/cyclin E, CDK-4/cyclin D1, and CDK-5/p25 with  $IC_{50}$  values of 0.18, 0.80, 1.8, 3.0, and 0.15  $\mu\text{M}$ , respectively.<sup>212,214</sup> Meridianins A–F (81–86) were also evaluated for their antiproliferative effect on different cancer cell lines; only meridianins B (82) and E (85) had an effect on proliferating human teratocarcinoma NT2

cells, suggesting that only kinase-active meridianins display antiproliferative properties. The nonbrominated meridianin A (81) did not exhibit cytotoxicity even at higher concentrations, although it had a relatively good inhibitory profile against various protein kinases. By contrast, meridianins B–F (82–86) exhibited cytotoxic activity in the micromolar range.

Screening of compounds isolated from marine invertebrates for CDK inhibition led to the discovery of 10Z-hymenialdisine (88), isolated from the sponge *Hymeniacidon aldis* as a potent ( $IC_{50}$  10–40 nM) inhibitor of the protein serine/threonine kinases GSK-3 $\beta$ , CDK-1, CDK-2, CDK-5, CK-1, and MAPKK-1.<sup>215–217</sup> Wan et al. (2004)<sup>218</sup> synthesized several analogues of hymenialdisine, resulting in the discovery of new nanomolar to micromolar inhibitors of 11 different targets including p90RSK, KDR, c-Kit, Fes, MAPK-1, PAK-2, PDK-1, PKC $\epsilon$ , PKD-2, Rsk-1, and SGK.<sup>218</sup> Recently, White and co-workers<sup>219</sup> synthesized series of pyrroloazepinone and indoloazepinone oximes of hymenialdisine and screened for CDK-2/A activity. These compounds showed promising growth inhibition activity against four human cancer cell lines but did not significantly inhibit CDK-2. The hymenialdisine (88) has also been patented for use in the treatment of inflammation-related and allergic disorders.<sup>220,221</sup>

Fascaplysin (89), which was isolated from the marine sponge *Fascaplysinopsis* species, selectively inhibited CDK-4/D1 with an  $IC_{50}$  value of 0.35  $\mu\text{M}$  and also blocked the growth of cancer cells at the G0/G1 phase of the cell cycle.<sup>222,223</sup> However, fascaplysin was found to be a poor inhibitor of other CDKs such as CDK-1/B, CDK-2/A, CDK-2/E, and CDK-5/p35, with  $IC_{50}$  values of >100, >50, >50, and 20  $\mu\text{M}$ , respectively.<sup>223</sup> Molecular modeling studies further investigated the selectivity of fascaplysin for CDK-4 versus its close homologue CDK-2.<sup>224,225</sup> Fascaplysin showed 10-fold selectivity toward CDK-4/D1 as compared to CDK-6/D1 but did not significantly inhibit CDK-4/D2 and CDK-4/D3 at concentrations >100  $\mu\text{M}$ , while CDK-6/D2 was inhibited with an  $IC_{50}$  of 35  $\mu\text{M}$ . This selectivity reflects the ability of different cyclins binding to their CDK partners to subtly alter the three-dimensional geometry of the active site. Fascaplysin did not inhibit other prototype tyrosine kinases ( $IC_{50}$  for IGF-1R and v-Abl is >10  $\mu\text{M}$ ).<sup>223</sup> The selectivity of fascaplysin for CDKs versus other kinases was evidenced by another recent study by Peterson and co-workers<sup>226</sup> in which fascaplysin was screened against a panel of 300 kinases, revealing that fascaplysin was active only against CDKs among the 300 kinases tested.<sup>226</sup> Fascaplysin exhibited antiproliferation effects on HeLa human cervical cancer cells by inducing apoptosis via the extrinsic death pathway and mitochondrial pathway, without arresting cell cycle progression at G1 phase.<sup>227</sup> Fascaplysin also exhibits antiangiogenic activity via VEGF blockage and through the direct effects of cell cycle arrest and apoptosis on human umbilical vein endothelial cells (HUVEC).<sup>228,229</sup> No antitumor effect of fascaplysin was found in vivo with doses of 5–20 mg/kg in a model of Ehrlich carcinoma in mice, which is likely due to the observed suppressive action on immunocompetent cells.<sup>230</sup> Fascaplysin (89) also inhibited the growth of tumors from implanted S180 cells; the mechanism of action may involve apoptosis, antiangiogenesis, or cell cycle arrest.<sup>231</sup> The use of tryptoline and indole-containing fascaplysin analogues has shown potential for breast cancer, colorectal cancer, leukemia, retinoblastoma, and small cell lung cancer.<sup>232</sup>

Proximicin C (90), which was isolated from a Norwegian strain of *Verrucosispora*, exhibited anticancer activity in different

Table 2. Miscellaneous Marine-Derived CDK Inhibitors

MNP	chemical class	source	CDK	ref
microxine (99)	purine derivative	australian marine sponge <i>Microxina</i> sp.	p34cdc2/cyclin B ( $IC_{50}$ 13 $\mu$ M)	242
konbuacidin A (100)	alkaloid	sponge <i>Hymeniacidon</i> sp.	CDK-4	243
nakadomarin A (101)	alkaloid	sponge <i>Amphimedon</i> sp.	CDK	244
butyrolactone I (102)	butyrolactone	terrestrial and a marine-derived <i>Aspergillus terreus</i> (strains IFO-8835, DRCC-152, and HKI0499)	CDK	245
dictyonamide A (103)	decapeptide	cultures of the red alga <i>Ceradictyon spongiosum</i>	CDK-4 ( $IC_{50}$ 13 $\mu$ M)	246
indirubins	indole alkaloids	mollusc <i>Hexaplex trunculus</i>	CDK-1,5	247

cell lines through upregulation of the oncogene p53 and the cyclin kinase p21 in AGS cells.<sup>233,234</sup> The marine-derived chamigrane-type brominated sesquiterpenoid dactylone (91) inhibited cyclin D and CDK-4 expression and pRb phosphorylation. Inhibition of these cell cycle components was followed by cell cycle arrest at the G1–S transition, with subsequent p53-independent apoptosis.<sup>235</sup> Park et al.<sup>236</sup> described the suppression of U937 human monocytic leukemia cell growth by dideoxypetrosynol A (92), a polyacetylene compound from the sponge *Petrosia* sp., via induction of the CDK inhibitor p16 and downregulation of pRb phosphorylation. Scytomemin (93) from the cyanobacterium *Stigonema* sp. inhibited the serine/threonine kinases CDK-1, CHK-1, and polo-like kinase with similar potency ( $IC_{50}$  2  $\mu$ M).<sup>237</sup> Scytomemin is a yellow-green ultraviolet sunscreen pigment present in the extracellular sheaths of different genera of aquatic and terrestrial blue-green algae. It has a unique symmetrical dimeric ring structure. The monomeric subunit is closely related to nostodione A, a mitotic spindle poison from the terrestrial blue-green alga *Nostoc commune*. Furthermore, scytomemin inhibits the proliferation of human fibroblasts and endothelial cells in culture and reduced TPA-induced ear edema in mice when administered topically.<sup>238</sup> The betaenone derivatives 28,29 and anthraquinones 30–32, which were isolated from sponge-associated fungal *Microsphaeropsis* species, exhibited CDK-4/cyclin D1 inhibition with  $IC_{50}$  values of 11.5, >100, 43.5, 22.5, and 37.5  $\mu$ M, respectively.<sup>171</sup> Elatol (94), which was isolated from the red algae *Laurencia microcladia*, exhibited a cytotoxic effect by inducing cell cycle arrest in G1 and sub-G1 phases, leading to apoptosis. Mechanistic studies indicated that elatol reduces the expression of cyclin-D1, cyclin-E, and cyclin-dependent kinases CDK-2 and CDK-4.<sup>239</sup> Fucoxanthin (95) from the marine alga *Ishige okamurai* reduced the proliferation of B16F10 cells, which was accompanied by the induction of cell cycle arrest during G0/G1 phase and apoptosis. Fucoxanthin-induced G0/G1 arrest was associated with a marked decrease in the protein expression of phosphorylated-Rb (retinoblastoma protein), cyclins D1 and D2, and CDK-4.<sup>240</sup> Spiralisone A (96), B (97), and a chromone 98 from the Australian marine brown alga *Zonaria spiralis* inhibited CDK-5/p25 with  $IC_{50}$  values of 10, 3.0, and 10.0  $\mu$ M, respectively.<sup>241</sup> Additional marine-derived CDK inhibitors 99–103 are listed in Table 2. The chemical structures of the marine-derived CDK inhibitors 28–32 and 73–103 are shown in Figures 3 and 4, respectively.

Lamellarins are a family of pyrrole alkaloids (>30 alkaloids) isolated from marine invertebrates such as sponges, molluscs, and tunicates.<sup>248,249</sup> Meijer and co-workers have evaluated all lamellarins for antiproliferative activity and their ability to

inhibit protein kinases. Among the tested lamellarins, 104–117 exhibited antitumor activity and inhibited several protein kinases relevant to cancer (CDKs, Dyk-1A, CK1, GSK-3, and PIM-1). Lamellarin N (109) and lamellarin 6 (114) showed potent CDK-1/cyclin B and CDK-5/p25 activity, with  $IC_{50}$  values of 0.07 and 0.1 (for CDK-1/cyclin B) and 0.025 and 0.03  $\mu$ M (CDK-5/p25), respectively.<sup>250,251</sup> The chemical structures and kinase activity profiles of lamellarins are shown in Table 3.

**3.1.1.3. Glycogen Synthase Kinase-3 (GSK-3) Inhibitors.** GSK-3 is a multifunctional serine/threonine kinase that is involved in numerous diseases, including diabetes, cancer, inflammation, Alzheimer's, and bipolar disorder. This kinase modulates several biological processes, such as glycogen metabolism, insulin signaling, cell proliferation, neuronal function, oncogenesis, and embryonic development, and its two isoforms ( $\alpha$  and  $\beta$ ) have similar biological functions.<sup>252</sup> Indirubin (118), 6-bromoindirubin (119), 6'-bromo-indirubin (120), and 6,6'-dibromo-indirubin (121) isolated from the Mediterranean mollusc *Hexaplex trunculus* have been reported to inhibit GSK-3, CDK-1, and CDK-5.<sup>247</sup> Compounds 118–121 inhibited GSK-3 with  $IC_{50}$  values of 1, 22, 0.045, and 4.5  $\mu$ M, respectively. Manzamine A (122) and related derivatives isolated from a common Indonesian sponge, *Acanthostrongylophora*, have been identified<sup>253</sup> as a new class of GSK-3 $\beta$  inhibitors. In addition, manzamine A was shown to be effective<sup>253</sup> in decreasing tau hyperphosphorylation in human neuroblastoma cell lines, which demonstrated the ability of manzamine A to enter cells and interfere with tau pathology. Inhibition studies<sup>253</sup> of manzamine A against a panel of five different kinases, GSK-3 $\alpha/\beta$ , CDK-1, PKA, CDK-5, and MAPK, revealed specific effects on GSK-3 $\beta$  and CDK-5, two kinases involved in tau pathological hyperphosphorylation. These results suggest that manzamine A constitutes a promising scaffold from which more potent and selective GSK-3 inhibitors could be designed as potent therapeutic agents for Alzheimer's disease.<sup>253</sup> Another sponge-derived alkaloid hymenialdisine (88), a potent inhibitor of GSK-3 $\beta$ ,<sup>215,217</sup> also inhibited the phosphorylation of the human microtubule-associated protein tau, which is implicated in the pathogenesis of Alzheimer's disease.<sup>217</sup> In addition, hymenialdisine (88) reduced the production of interleukin-8 and prostaglandin E2 in human cells, indicating that it may have anti-inflammatory activity.<sup>254,255</sup> Furthermore, the ability of hymenialdisine (88) to modulate the Wnt pathway and the E-cadherin/ $\beta$ -catenin pathway has been reported.<sup>256–258</sup> The GSK-3 $\beta$  inhibitory potential of hymenialdisine may be useful for the treatment of prostate cancer,<sup>259</sup> neuroendocrine tumors,<sup>260</sup> bone-related disorders,<sup>261,262</sup> and glaucoma.<sup>263</sup>

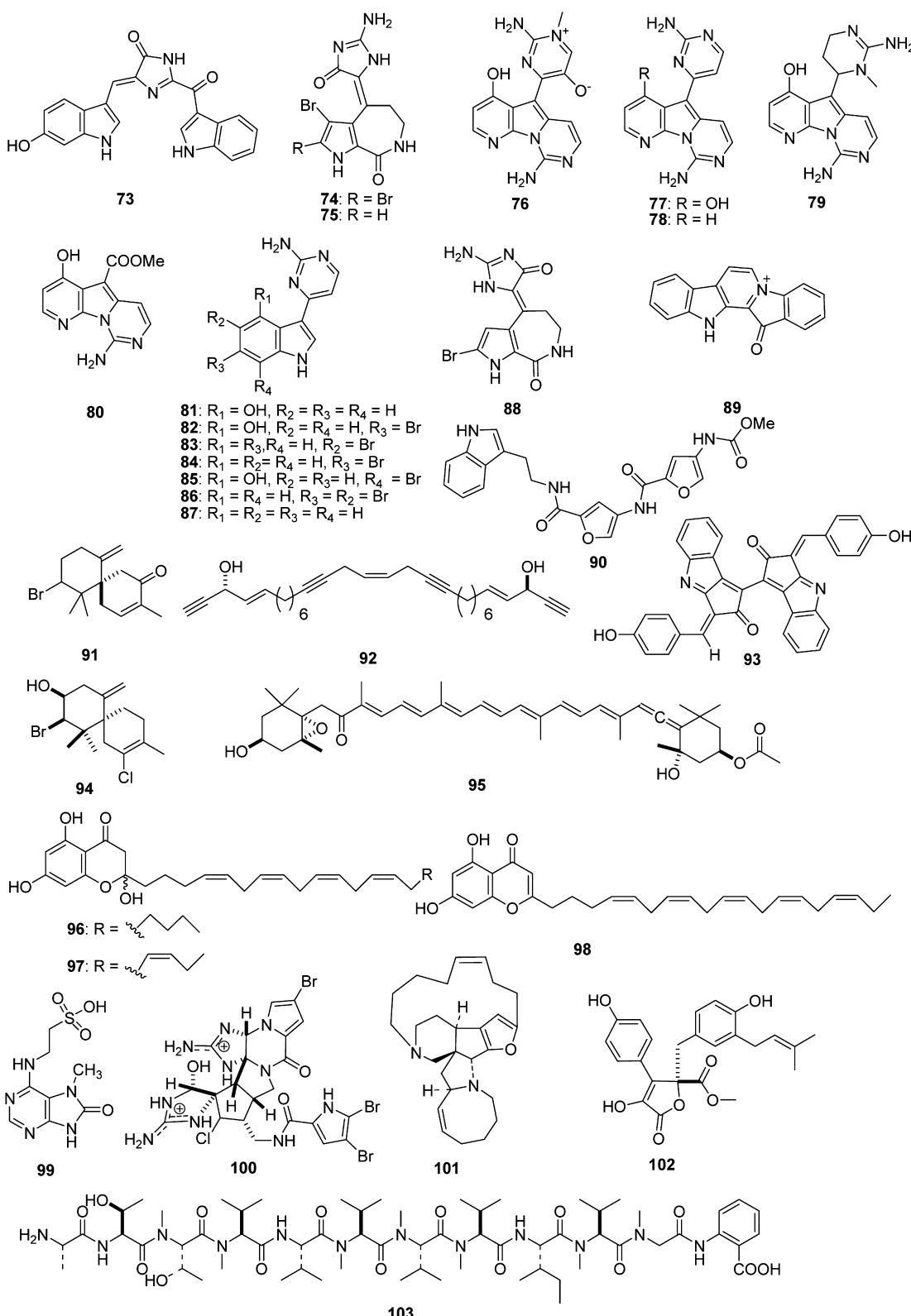


Figure 4. Marine-derived CDK inhibitors.

Leucettamine B<sup>264</sup> (**123**) from the sponge *Leucetta microraphis* and its synthetic analogue **124** inhibited GSK-3 with IC<sub>50</sub> values of 15 and 0.86  $\mu\text{M}$ .<sup>265</sup> Further optimization of the leucettamine scaffold by a group at CNRS (France)<sup>266</sup> yielded leucettamine B analogues **125–127**, which inhibit GSK-3 $\alpha/\beta$  with IC<sub>50</sub> values of 0.6, 0.7, and 0.41  $\mu\text{M}$ , respectively. Analogue

L41 (**127**) inhibited GSK-3 $\alpha$  and GSK-3 $\beta$  with IC<sub>50</sub> values of 0.21 and 0.38  $\mu\text{M}$ , respectively.<sup>267</sup> (Z)-5-(4-Hydroxybenzylidene)-hydantoin (**128**) from the red sea sponge *Hemimycale arabica* inhibited GSK-3 $\beta$  with an IC<sub>50</sub> of 13.7  $\mu\text{M}$ .<sup>268</sup> The potent PKC inhibitor staurosporine also possesses GSK-3 inhibitory activity and has been reported to maintain the

Table 3. Kinase Inhibitory Profile of Lamellarins<sup>a</sup>

Sr. No	Lamellarin							Kinase activity (IC <sub>50</sub> in μM)				Cell line (IC <sub>50</sub> in μM)				
		R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>	R <sub>4</sub>	R <sub>5</sub>	R <sub>6</sub>	5-6	a-f	e*	f*	g*	h*			
<b>104</b>	Lamellarin D	OH	OMe	OH	OMe	OMe	OH	=	0.5	0.55	0.3	0.1	0.45	13	0.02	0.01
<b>105</b>	Lamellarin α	OH	OMe	OH	OMe	OMe	OMe	=	8	>10	1.4	0.59	5	7.9	10	
<b>106</b>	Di-H-Lamellarin D	OH	OMe	OH	OMe	OMe	OH	-	1.8	0.11	0.9	0.2	0.5	5.9	0.41	nt
<b>107</b>	Lamellarin H	OH	OH	OH	OH	OH	OH	=	10	10	9.5	10	10	5.3	0.45	>100
<b>108</b>	Di-H-Lamellarin H	OH	OH	OH	OH	OH	OH	-	10	10	0.67	10	10	5.2	2.55	Nt
<b>109</b>	Lamellarin N	OH	OMe	OMe	OH	OMe	OH	=	0.0 7	0.025	0.005	0.055	0.035	10	0.025	nt
<b>110</b>	Lamellarin L	OH	OMe	OMe	OH	OMe	OH	-	0.3 8	0.1	0.04	0.25	0.14	10	0.7	Nt
<b>111</b>	Lamellarin 3	OH	H	OH	OMe	OMe	OH	=	0.5 3	0.60	0.58	0.15	0.06	0.41	0.056	0.04
<b>112</b>	Lamellarin 4	H	OMe	OH	OMe	OMe	OH	=	2.0	0.6	0.05	0.05	0.08	1.3	0.79	0.85
<b>113</b>	Lamellarin 5	OH	OMe	OMe	OMe	OMe	OMe	=	10	10	10	2	10	10	8	2.5
<b>114</b>	Lamellarin 6	OH	OMe	OH	H	OMe	OH	=	0.1	0.03	0.13	0.33	0.09	0.8	0.11	0.04
<b>115</b>	Lamellarin 7	OH	OMe	H	OMe	OMe	H	=	4.3	2.1	2.1	10	10	10	0.14	0.07
<b>116</b>	Lamellarin 8	H	H	OH	OMe	OMe	OH	=	5	0.9	2.2	0.7	1.0	10	2.65	4.0
<b>117</b>	Lamellarin K	OH	OMe	OH	OMe	OMe	OMe	-	10	10	10	0.6	10	6	30	nt

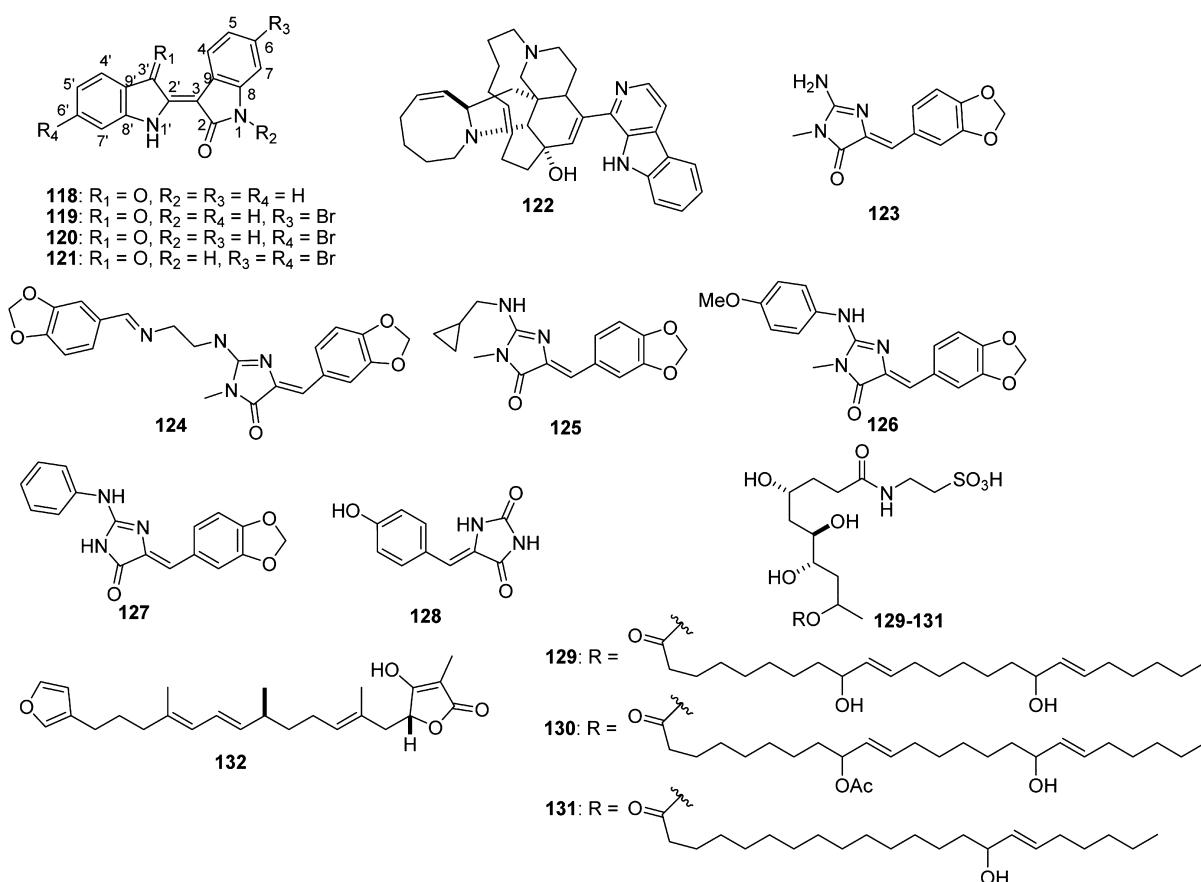
<sup>a</sup>a, CDK-1/cyclin B; b, CDK-5/p25; c, GSK-3α/β; d, PIM-1; e, Dyk-1A; f, CK-1; g, SHSY5Y cell line; h, HeLa cell line.

pluripotency of cultured cells.<sup>269</sup> Staurosporine has also been reported to have potential for use in the treatment of autoimmune diseases.<sup>257</sup> Meridianin E (**85**) also potently inhibited GSK-3α and GSK-3β, with IC<sub>50</sub> values of 0.9 and 2.5 μM, respectively.<sup>214</sup> Carteriosulfonic acids A–C (**129–131**) from *Carteriospongia* sp. were shown to inhibit the kinase GSK-3β.<sup>270</sup> The pyrrole alkaloid lamellarin N (**109**, structure shown in Table 3) displayed potent GSK-3 inhibitory activity, with an IC<sub>50</sub> of 0.005 μM.<sup>250</sup> An isopropanolic extract of the sponge *Ircinia dendroides* yielded 90% inhibition of human recombinant GSK-3β at 50 mg/mL. Bioactivity-guided fractionation led to the discovery of the furanosesquiterpene palinurin (**132**) as potent inhibitor of GSK-3α and GSK-3β, with IC<sub>50</sub> values of 1.6 and 1.9 μM. Palinurin was inactive against CDK-5 (IC<sub>50</sub> > 25 μM), CDK-1 (IC<sub>50</sub> > 100 μM), MAPK (IC<sub>50</sub> > 100 μM), and CK-2 (IC<sub>50</sub> > 100 μM), indicating a good degree of selectivity for GSK-3. Enzyme kinetic and molecular modeling studies indicated that palinurin is an allosteric inhibitor of GSK-3β.<sup>271</sup> The chemical structures of the marine-derived GSK-3 inhibitors **118–132** are shown in Figure 5. The chemical structures of the GSK-3 inhibitors **85** and **88** are shown in Figure 4, and the structure of **109** is shown in Table 3.

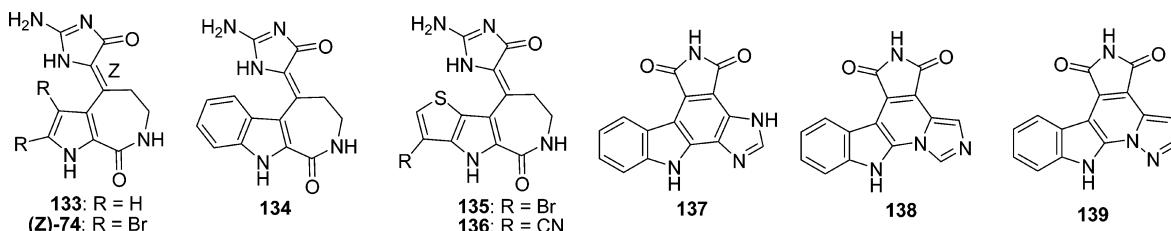
**3.1.1.4. Check-Point Kinase (CHK) Inhibitors.** The serine/threonine check-point kinase CHK-1 regulates G2/M and intra-S check-points and plays an important role in cell-cycle progression, particularly in p53-defective cancer cells (50–70% of all cancers). The marine natural products (Z)-hymenialdisine (**88**), (Z)-2-debromohymenialdisine (**133**), and (Z)-3-bromo-hymenialdisine (**74**) inhibited a large panel of kinases, including

CHK-1.<sup>215,272</sup> These three natural products inhibited CHK-1 with IC<sub>50</sub> values of 1.9, 0.33, and 0.10 μM, respectively. Hymenialdisine (**88**) also inhibited CHK-2 with an IC<sub>50</sub> of 42 nM.<sup>273</sup> Chemically spongiacidin A (**74**)<sup>208</sup> and (Z)-3-bromohymenialdisine (**74**) differ with respect to the E/Z-stereochemistry of the double bond. The former exists as the E-isomer, while the latter is the Z-isomer. Sharma and Tepe (2004)<sup>273</sup> synthesized indoloazepine analogue **134**, which exhibited potent CHK-1 and CHK-2 inhibition (IC<sub>50</sub> of 237 and 8 nM, respectively).<sup>273</sup> Recently, Parmentier et al. (2009)<sup>274</sup> synthesized a series of hymenialdisine analogues and discovered the potent CHK-1 inhibitors **135,136**, which have IC<sub>50</sub> values of 14 and 29 nM, respectively.<sup>274</sup> Two alkaloids granulatimide (**137**) and isogranulatimide (**138**) isolated from the ascidian *Didemnum granulatum* have triggered considerable attention as cell cycle G2 check-point inhibitors. The mitotic index for G2/M check-point abrogation by granulatimide (**137**), isogranulatimide (**138**), and a pyrazolic analogue **139** was 17.2, 19.4, and 23.9 (reference standard AZD, 75.0). These alkaloids **137–139** showed cytotoxicity against a panel of cancer cell lines (A549, U373, LoVo, MCF-7, HS683, PC-3, OE-21, and B16F10).<sup>275–279</sup> The chemical structures of the marine-derived CHK inhibitors **88** (Figure 4) and **74, 133–139** (Figure 6) are shown.

**3.1.1.5. Casein Kinase (CK) Inhibitors.** Casein kinases are multifunctional serine/threonine protein kinases that are ubiquitously expressed in eukaryotic organisms and yeast.<sup>280,281</sup> These enzymes function as regulators of signal transduction pathways in eukaryotic cells. Marine ascidian-



**Figure 5.** Marine-derived GSK-3 inhibitors.



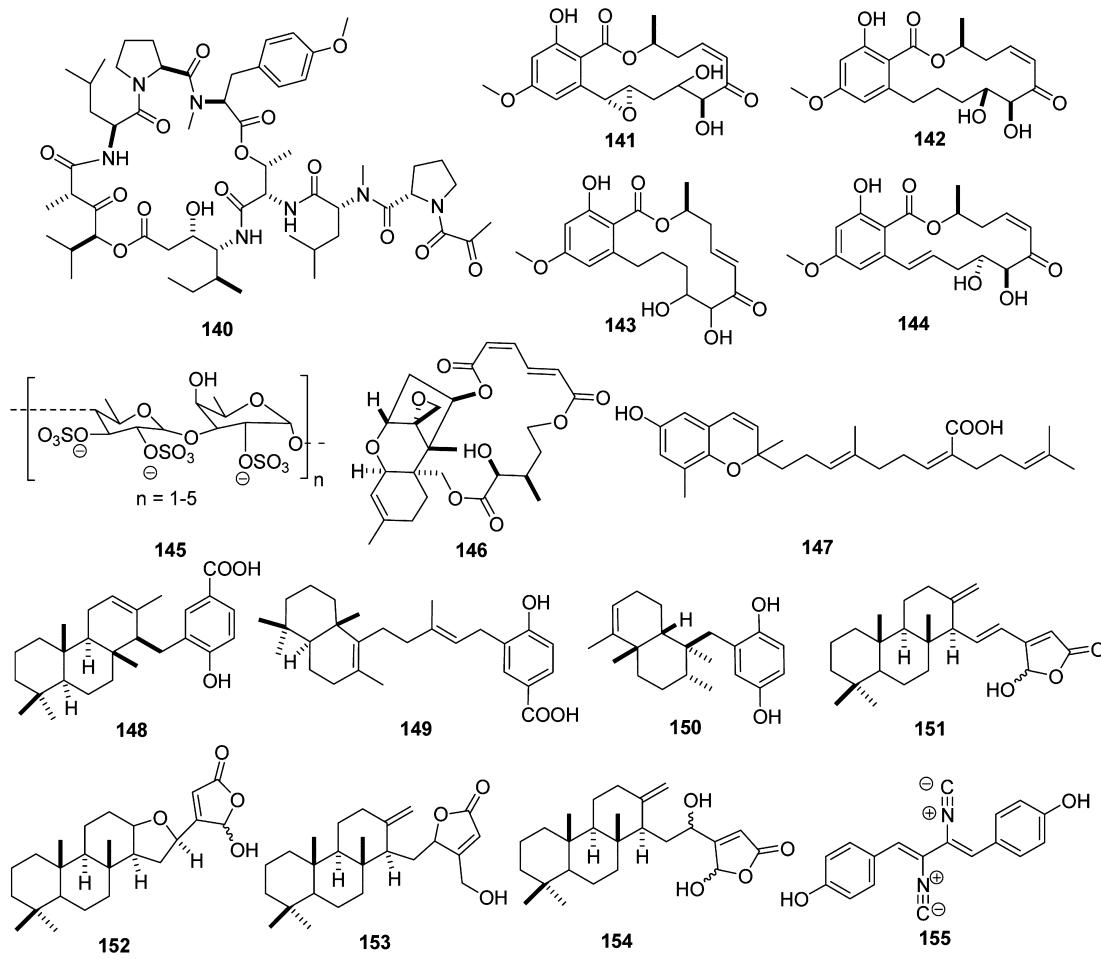
**Figure 6.** Marine-derived check-point kinase (CHK) inhibitors.

derived meridianins are inhibitors of different protein kinases such as CDKs, PKA, and GSK-3 at a low micromolar range. These compounds prevent cell proliferation and induce apoptosis. Meridianin E (**85**) was also tested against a panel of 25 kinases, and exhibited inhibitory activity against most of them at the micromolar range, with the exception of Erk-1, Erk-2, MAPKK, and CK-2. The IC<sub>50</sub> value for CK-1 inhibition is 0.4  $\mu\text{M}$ , while meridianin E is inactive against CK-2 (IC<sub>50</sub> > 100  $\mu\text{M}$ ),<sup>214</sup> thus representing an interesting but very nonspecific scaffold. In addition, meridianin E exhibited cytotoxic effects in different cell lines (Hep2, U937, LMM3, and PTP). Furthermore, it was reported that the CK-1 inhibitor meridianin reduces amyloid- $\beta$  peptide accumulation and thus has a potential for the treatment of Alzheimer's disease.<sup>282</sup>

The pyrrole alkaloids lamellarin 3 (111) and lamellarin 6 (114) inhibited CK-1 with an  $IC_{50}$  of 0.41 and 0.8  $\mu M$ , respectively.<sup>249,250</sup> Hymenialdinsine (88), which was isolated from a Caribbean sponge, was discovered in a random screen to discover new CDK inhibitors. Hymenialdinsine is a potent inhibitor of CK-1 in an ATP-competitive manner with an  $IC_{50}$

of 35 nM. It is very nonspecific and inhibits other protein kinases implicated in Alzheimer's disease, such as GSK-3 $\beta$ , CDKs, and presenilin-2.<sup>215,282</sup> The chemical structures of the marine-derived CK inhibitors 85, 88 and 111, 114 are shown in Figure 4 and Table 3, respectively.

**3.1.1.6. Mitogen-Activated Protein (MAP) Kinase Inhibitors.** Mitogen-activated protein (MAP) kinases are serine/threonine kinases that respond to extracellular stimuli such as mitogens, osmotic stress, heat-shock, and proinflammatory cytokines and regulate various cellular activities, such as gene expression, mitosis, growth, differentiation, proliferation, and cell survival/apoptosis. Sargaquinoic acid (**52**) from the marine brown alga *Sargassum macrocarpum* promotes neurite outgrowth via protein kinase A and MAP kinase-mediated signaling pathways in PC12D cells.<sup>188</sup> Aplidin (dehydroidemnin B, **140**) from the Mediterranean tunicate *Aplidium albicans*<sup>283</sup> activates p38 mitogen-activated protein kinases (MAPKs) and jNK.<sup>284,285</sup> The resorcyclic acid lactone hypothemycin (**141**), which was isolated from a marine fungus *Phoma sp.*,<sup>286</sup> is a MEK inhibitor. In cell culture, hypothemycin



**Figure 7.** Marine-derived mitogen-activated protein kinase inhibitors.

displays potent cytotoxicity against cancer cell lines that are dependent on certain activating kinase mutations. In addition, hypothemycin exhibited significant tumor growth inhibition in at least three separate murine xenograft models.<sup>287,288</sup> 11,12-Dihydro derivatives of hypothemycin, the antibiotics L783277 (**142**) and L783290 (5-E isomer of L783277, **143**), which were isolated from *Phoma* sp., and the 11,12-double bond-containing antibiotic L783278 (also known as antibiotic LL-Z1640-2, **144**), which was isolated from *Deuteromyces* sp., also inhibited MEK kinase. Hypothemycin, antibiotic L783277, and antibiotic L783290 inhibited MEK with IC<sub>50</sub> values of 15, 4, and 300 nM, respectively, as well as lck kinase inhibition with IC<sub>50</sub> values of 2.8, 0.75, and 45 μM, respectively. These compounds did not inhibit RAF, PKC, or PKA.<sup>289–291</sup>

Hymenialdisine (**88**) from the sponge *Hymeniacidon aldis* potently inhibited mitogen-activated protein kinase kinase-1 with an IC<sub>50</sub> value of 10–40 nM.<sup>215–217</sup> Fucoidan (**145**) from the seaweed *Laminaria guryanova* inhibits smooth muscle cell proliferation and reduces MAP kinase activity.<sup>292</sup> Recently, fucoidan was isolated from the brown alga *Ascophyllum nodosum*,<sup>293</sup> and was shown to have antiproliferative and apoptotic effects on HCT116 colon carcinoma cells. Verrucarin A (**146**) isolated from the Palauan marine fungus *Myrothecium roridum* significantly inhibited interleukin-8 production from human promyelocytic leukemia cells via inhibition of the activation of the mitogen-activated kinases c-Jun and p38 (IC<sub>50</sub> > 20 nM).<sup>294</sup> Verrucarin A exhibited antitumor activity in several cell lines, including the prostatic carcinoma cells LNCaP

and DU-145 with IC<sub>50</sub> values of 5.6 and 0.039 nM, respectively. It also inhibited the hepatic cancer cell lines Hep3B and HepG2 and lung cancer cell line A549 with IC<sub>50</sub> values of 4.6, 20.3, and 2.2 nM, respectively.<sup>295</sup>

The diterpene polyketide sargachromenol (**147**) from the marine brown alga *Sargassum macrocarpum* promotes NGF-dependent neurogenesis in PC12D cells (ED<sub>50</sub> 9 μM). Mechanistic studies demonstrated that both cyclic AMP-mediated protein kinase and MAP kinase-signal transduction pathways are required for neurite growth stimulated by sargachromenol.<sup>296</sup> MAP kinase-activated protein kinase 2 (MK-2) has been shown to be critical in the regulation of the production of TNF-α, a pleiotropic cytokine involved in various inflammatory processes. Therefore, MK-2 kinase inhibitors represent potential therapeutic agents to treat inflammatory diseases in which TNF-α plays a key role, such as rheumatoid arthritis. (+)-Makassaric acid (**148**) and (+)-subersic acid (**149**), isolated from the marine sponge *Acanthodendrilla* sp. collected in Indonesia, inhibited MK-2 inhibitory activity with IC<sub>50</sub> values of 20 and 9.6 μM, respectively.<sup>297</sup> Isoarenarol (**150**) isolated from a Papua New Guinean collection of *Dysidea arenaria* showed potent protein kinase inhibitory activity.<sup>298</sup>

Four cheilanthane sesterterpenoids, 25-hydroxy-13(24),15,17-cheilanthatrien-19,25-olide (**151**), 13,16-epoxy-25-hydroxy-17-cheilanthen-19,25-olide (**152**), 25-hydroxy-13(24),17-cheilanthadien-16,19-olide (**153**), and 16,25-dihydroxy-13(24),17-cheilanthadien-19,25-olide (**154**), isolated from the marine sponge *Ircinia* sp. inhibited MSK1 (mitogen

and stress activated kinase) and MAPKAPK-2 (mitogen activated protein kinase activated protein kinase), two protein kinases involved in mitogen and stress signal transduction with  $IC_{50}$  values of 4 and 90  $\mu\text{M}$ , respectively.<sup>299</sup> SD118-Xanthocillin X (**155**), which was isolated from *Penicillium commune* in a deep-sea sediment sample, exhibited growth inhibition of HepG2 cells and induced autophagy in these cells, which was found to be associated with the suppression of the MEK/ERK signaling pathway and the enhancement of class III PI3K/Beclin 1 signaling.<sup>300</sup> The chemical structures of the marine-derived MAP/MEK inhibitors **88** and **140–155** are shown in Figures 4 and 7, respectively.

**3.1.1.7. Polo-like Kinase Inhibitors.** Polo-like kinases are serine/threonine kinases that are involved in cell cycle regulation. Scytomemin (**93**) from the cyanobacterium *Stigonema* sp. inhibited polo-like kinase with an  $IC_{50}$  of 2  $\mu\text{M}$ ; polo-like kinase plays an important role in the regulation of mitotic spindle formation as well as other kinases involved in cell cycle control. The monomeric subunit of scytomemin is closely related to nostodione A, a mitotic spindle poison from the terrestrial blue-green alga *Nostoc commune*.<sup>237</sup> Scytomemin exhibited anticancer activity by preventing cell cycle progression or intracellular signaling.<sup>301</sup> Hymenialdisine (**88**) inhibited polo-like kinase (PLK-1) with an  $IC_{50}$  of 10  $\mu\text{M}$ .<sup>302</sup> The chemical structures of the marine-derived polo-like kinase inhibitors **88** and **93** are shown in Figure 4.

**3.1.1.8. CaMK Inhibitors.**  $\text{Ca}^{2+}$ /calmodulin-dependent protein kinase-II (CaMK-II) is a serine/threonine kinase. Autophosphorylation of threonine 286 in the presence of  $\text{Ca}^{2+}$  and calmodulin activates CaMK-II and produces substantial  $\text{Ca}^{2+}$ /calmodulin-independent activity. Leptosin M (**156**) isolated from a strain of *Leptosphaeria* species (which was originally separated from the marine alga *Sargassum tortile*) exhibited significant cytotoxicity against cultured P388 cells and human cancer cell lines, and also inhibited specifically CaMK-III and a protein tyrosine kinase.<sup>303</sup> Stauroporine (**1**) inhibited  $\text{Ca}^{2+}$ /calmodulin-dependent protein kinase-II (CaM kinase-II) purified from rat brain with an  $IC_{50}$  value of 20 nM.<sup>304,305</sup> The chemical structures of the marine-derived CaMK inhibitors **1** and **156** are shown in Figures 3 and 8.

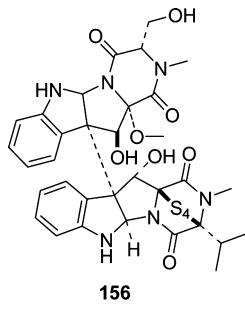


Figure 8. Marine-derived CaMK inhibitor.

**3.1.2. Tyrosine Kinase Inhibitors.** There are primarily two major types of tyrosine kinases, receptor and nonreceptor kinases. Receptor tyrosine kinases include the Erb-B family, the VEGFR family, and p60lck, while nonreceptor tyrosine kinases include src and Abl kinases.

**3.1.2.1. Erb-B (Epidermal Growth Factor Receptor, EGFR) Family Inhibitors.** This family includes four structurally related receptor tyrosine kinases: ErbB-1 (also named as EGFR), ErbB-2 (also named HER-2 in humans and neu in rodents), ErbB-3

(also named HER3), and ErbB-4 (also named HER-4). More than 50% of all tyrosine kinase inhibitors described to date have been evaluated with the ErbB-1 (EGFR) in mind. ErbB-3 and ErbB-4 are the more recently discovered members of the ErbB family. High levels of the ErbB-1 and ErbB-2 have been reported to occur in nearly one-third of primary breast cancer tumors.<sup>306</sup> The marine sesquiterpene nakijiquinone C (**24**) and D (**25**) isolated from the Okinawan sponge of the family Spongiidae inhibited c-erbB-2 with  $IC_{50}$  values of 26 and 29  $\mu\text{M}$  and ErbB-1 with  $IC_{50}$  values of 170 and  $\sim 400 \mu\text{M}$ , respectively.<sup>169</sup> Nakijiquinone C was also found to be a selective Her-2/Neu inhibitor.<sup>169,307</sup> An unidentified sponge of the family Spongiidae yielded the modestly cytotoxic nakijiquinones G–I (**157–159**), which also inhibited HER-2 kinase.<sup>308</sup>

Aeroplysinin-1 (**160**), a brominated metabolite isolated from the sponge *Verongia aerophoba*, inhibited ErbB-1 by blocking EGF-stimulated proliferation of cancer cell lines and induced apoptosis and suppressed angiogenesis in vivo.<sup>309–312</sup> Aeroplysinin-1 analogues **161,162** inhibited ErbB-1 with  $IC_{50}$  values of 10 and 35  $\mu\text{M}$ , respectively.<sup>310</sup> These synthetic analogues also showed inhibitory activity in cultured cells; this inhibition most likely occurred through covalent modification of the target protein. The use of aeroplysinin-1 (**160**) and its analogues for the treatment of angiogenic diseases and as an antibacterial and antiviral has been patented.<sup>313</sup>

Pericosine A (**163**), which was isolated from a culture of a strain of *Periconia byssoides*, displayed significant in vivo inhibitory activity against P388 in mice and inhibited ErbB-1 and topoisomerase II.<sup>314</sup> Paeciloquinone A–F (**164–169**), the methyl ester of paeciloquinone B **170** and varsicolol (**171**), which was isolated from the culture broth of the fungus *Paecilomyces carneus* p-177, exhibited activity against ErbB-1, v-Abl, and c-Src kinases. Compounds **164–171** inhibited ErbB-1 with  $IC_{50}$  values of 11, 21, 6.7, 10.5, 38, >100, 17, and 21  $\mu\text{M}$ , respectively.<sup>315</sup> The betaenone derivatives **28,29** and anthraquinones **30–32** isolated from the sponge-associated fungus *Microsphaeropsis* species inhibited ErbB-1 with  $IC_{50}$  values of 10.5, >100, 37.5, 27.5, and 41  $\mu\text{M}$ , respectively.<sup>171</sup> The sesquiterpenoid quinones metachromins L–Q (**172–177**) from the Okinawan marine sponge *Spongia* sp. (SS-103)<sup>316</sup> inhibited ErbB-1 and HER-2 kinases. All metachromins inhibited HER-2, with  $IC_{50}$  values of 312, 197, 427, 61, 42, and 51  $\mu\text{M}$ , respectively, while only metachromin L inhibited ErbB-1, with an  $IC_{50}$  value of 491  $\mu\text{M}$ .<sup>317</sup> Three alkaloids naamidine A (**178**), isonaamidine B (**179**), and isonaamidine C (**180**), isolated from the Fijian sponge *Leucetta* sp., inhibited ErbB-1, with  $IC_{50}$  values of 11.3, 22.7, and 36.9  $\mu\text{M}$ , respectively. These compounds also showed modest antitumor activity in EGF-dependent A431 tumors in athymic mice.<sup>318</sup> Naamidine A also potently inhibited EGF-stimulated DNA synthesis, with complete inhibition of DNA synthesis at 0.78  $\mu\text{M}$  in A-431 cells after 30 h. At 1.56  $\mu\text{M}$ , naamidine A caused cells to arrest in the G1 phase of the cell cycle. Subsequent studies revealed that extracellular signal-regulated kinases ERK-1 and ERK-2 are primary molecular targets for naamidine A in A-431 cells.<sup>319</sup> The trimeric hemibastadin congener sesquibastadin (**181**) and bestaldins 3, 6, 7, 11, and 16 (**182–186**) isolated from the marine sponge *Ianthella basta* collected in Indonesia inhibited several protein kinases. Compounds **181–184** and **186** inhibited ErbB-1 with  $IC_{50}$  values of 0.6, 1.3, 2.0, 1.5, and 2.9  $\mu\text{M}$ , respectively. Bastaldins 6, 7, 11, and 16 (**183–186**) inhibited proliferation of mouse lymphoma L5178Y cells

Table 4. Miscellaneous Marine-Derived ErbB-1 Inhibitors

MNP	chemical class	source	kinase	ref
rhopaladin B (73)	alkaloid	Okinawan tunicate <i>Rhopalaea</i> sp.	c-ErbB-2 ( $IC_{50}$ of 20 $\mu$ M)	207
spongicidins A,B (74,75)	alkaloid	Okinawan marine sponge <i>Hymeniacidon</i> sp.	c-ErbB-2 ( $IC_{50}$ of 21.2 and 18.6 $\mu$ M)	208
halenaquinone (188)	polyketide	Okinawan sponge <i>Xestospongia exigua</i>	ErbB-1	325,326
gracilin L (189)	norditerpenoid	<i>Spongionella</i> sp.	ErbB-1	327
pendolmycin (190)	alkaloid	<i>Nocardiopsis</i> sp.	inhibited EGF-induced phosphatidylinositol turnover in A43 cells with an $IC_{50}$ of 2.7 nM	328
tauroacidin A (191) and B (192)	alkaloid	sponge <i>Hymeniacidon</i> sp.	ErbB-1 and c-ErbB-2 ( $IC_{50}$ of 38 and 44.6 $\mu$ M)	329
(+)-purealidin J (193) and K (194)	alkaloids	Okinawan marine sponge <i>Psammaphysilla purpurea</i>	ErbB-1	330
staurosporine (1)	alkaloid	marine ascidian <i>Eudistoma toealensis</i>	ErbB-1	323

with  $IC_{50}$  values of 1.5, 5.3, 3.7, and 1.9  $\mu$ M, respectively, whereas compounds **181** and **182** had no activity.<sup>320</sup> Maedamine A (**187**) isolated from the Okinawan marine sponge *Suberea* sp. inhibited c-ErbB-2 kinase in vitro with an  $IC_{50}$  value of 10.7  $\mu$ M. Maedamine A (**187**) also exhibited cytotoxicity against murine leukemia L1210 cells with an  $IC_{50}$  of 6.9  $\mu$ M.<sup>321,322</sup> Staurosporine (**1**) also inhibited ErbB-1 at low micromolar concentrations,<sup>323</sup> and its use has been claimed for the prevention of dermatitis.<sup>324</sup> The additional marine-derived ErbB-1 inhibitors **1**, **73–75**, and **188–194** are listed in Table 4.

MdOS, a novel marine-derived oligosaccharide sulfate (**195**), exhibited broad-spectrum tyrosine kinase inhibitory activity against HER-2, EGFR, VEGFR, PDGFR, c-Kit, FGFR-1, and c-Src. MdOS exhibited ATP-competitive inhibition via directly binding to the residues of entrance rather than those within the ATP-binding pocket. Furthermore, MdOS inhibited proliferation and tube formation in human microvascular endothelial cells (HMEC), arrested microvessel outgrowth of rat aortic rings, and hindered the neovascularization of chick allantoic membranes. Overall, MdOS exhibited antiangiogenic activity in a tyrosine kinase-dependent manner.<sup>331</sup> Fucoidan 3 (**145**) isolated from the seaweed *Laminaria guryanova* or *Fucus vesiculosus*<sup>332</sup> potently inhibited EGF-induced phosphorylation of EGFR. Furthermore, 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 also inhibited by fucoidan, leading to inhibition of activator protein-1 (AP-1) activity and cell transformation induced by EGF.<sup>333</sup> Fucoidan also inhibited smooth muscle cell proliferation and reduced MAP kinase activity.<sup>292</sup> Fucoidan has been used in various pharmaceutical compositions as an anticancer agent,<sup>334</sup> a hair-restoring agent,<sup>335,336</sup> an antibacterial,<sup>337</sup> antiviral,<sup>338–340</sup> for the treatment of bleeding disorders,<sup>341</sup> for reducing blood coagulation,<sup>342</sup> for the treatment of psoriasis,<sup>343,344</sup> an antimalarial,<sup>345</sup> for the treatment of prion disease,<sup>346</sup> and for the treatment of a variety of other diseases.

Marine-derived compounds can also activate the EGFR cascade in a nonphysiological fashion. Aplidin (**140**) induced a specific cellular stress response, including sustained activation of EGFR, the nonreceptor protein-tyrosine kinase Src, and the serine/threonine kinases JNK and p38 MAPK. Growth arrest and apoptosis were observed in human MDA-MB-231 breast cancer cells after aplidin treatment.<sup>347</sup> In ALL-PO cells, 20 nM aplidin treatment blocked VEGF secretion via down-regulation of its mRNA. However, aplidin cytotoxicity was found not related to VEGF inhibition alone because the sensitivity of ALL-PO cells to aplidin was comparable to that of other

cells.<sup>348</sup> The use of aplidin has been patented for the treatment of obesity<sup>349</sup> and cancer.<sup>350–356</sup> Aplidin has been tested in combination with known anticancer agents;<sup>357–360</sup> for example, it potentiated the activity of gemcitabine.<sup>358</sup> Aplidin also showed antiangiogenic activity<sup>361</sup> and beneficial effects in chronic myeloproliferative disorders.<sup>362</sup> It was demonstrated that aplidin has a role in inhibiting angiogenesis, complementing its antitumor activity.<sup>363</sup> Three dibenzofurans isolated from an extract of the ascomycete Super1F1-09 isolated from the Fijian marine sponge *Acanthella cavernosa* exhibited mild inhibition of EGFR.<sup>364</sup> Kahalalide F (**196**), a C75 cyclic tridecapeptide isolated from the sacoglossan (sea slug) *Elysia rufescens*, inhibited ErbB-2 and suppressed tumors over-expressing ErbB-2 kinase.<sup>365</sup> The effect was linked to the inhibition of downstream targets of the PI3K pathway including Akt, which is thought to be the main point of action in kahalalide F-induced apoptosis.<sup>365</sup> Kahalalide F is currently being investigated in phase II clinical trials in patients with melanoma, hepatic carcinoma, and NSCLC. The chemical structures of the marine-derived Erb kinase inhibitors **24,25** and **28–32** (Figure 3), **140**, **145** (Figure 7), **157–194** (Figure 9), and **195,196** (Figure 10) are shown in Figures 3, 7, 9, and 10.

**3.1.2.2. Vascular Endothelial Growth Factor Receptor (VEGFR) Family Inhibitors.** VEGF is a prominent angiogenesis-initiating signal that helps tumors increase in size. 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 called VEGF receptors on the cell surface, especially on endothelial cells, triggering a tyrosine kinase pathway leading to neo-angiogenesis. The VEGFR family includes growth kinases such as KDR (kinase domain receptor, also called VEGFR-2 and Flt-1), Flt-4 (Fms-like tyrosine kinase-4, also called VEGFR-3 and Tie-2), PDGFR (platelet-derived growth factor receptor), IGF-1R (insulin-like growth factor receptor-1 receptor), and FGFR (fibroblast growth factor receptor).<sup>366,367</sup> The synthetic C-2 epimer **197** of the marine-derived sesquiterpene nakijinquinone C is a potent and selective inhibitor of the VEGFR-2 (KDR) receptor, a tyrosine kinase involved in tumor angiogenesis. Najiquinones A, C, and D are poor inhibitors of these kinases.<sup>368</sup> The compound **197** inhibited VEGFR-2 with an  $IC_{50}$  value of 21  $\mu$ M (at 25  $\mu$ M ATP) and does not display activity toward other kinases (Her-2/Neu, EGFR, IGF-1R, and VEGFR-3), suggesting that the stereochemistry of the terpenoid core structure is an important determinant of its

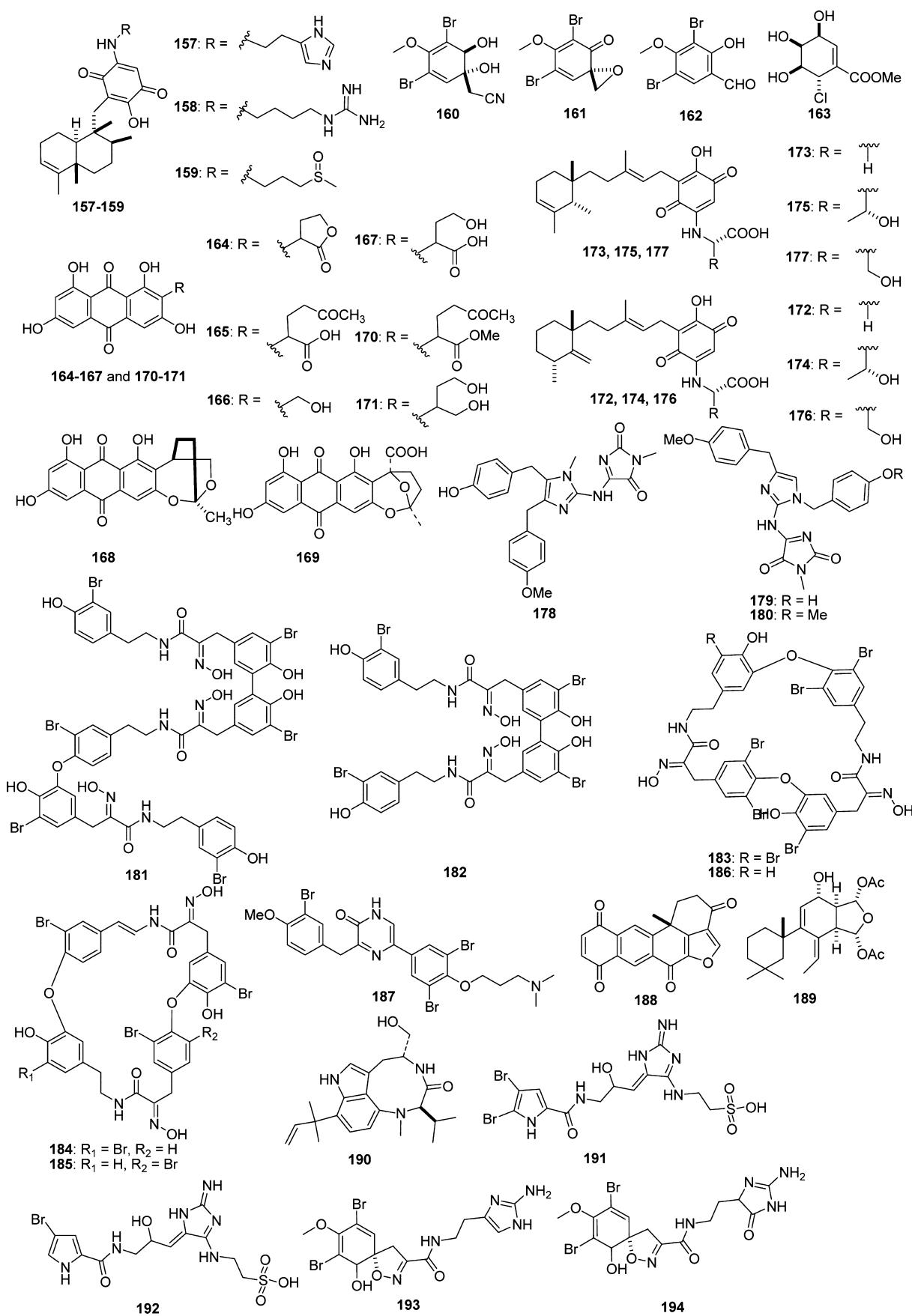


Figure 9. Marine-derived small-molecule Erb family inhibitors.

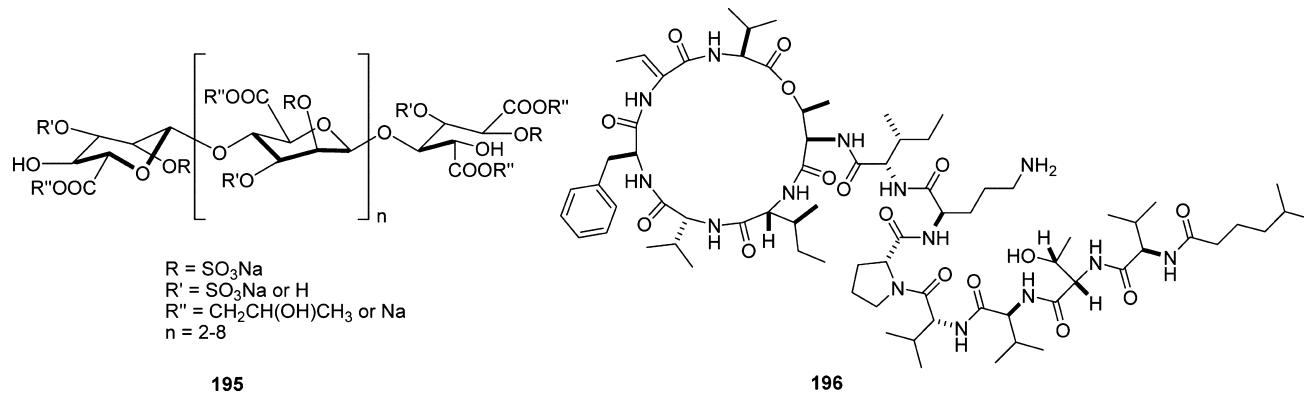


Figure 10. Marine-derived oligosaccharides and decapeptides as Erb family inhibitors.

kinase inhibitory activity. In particular, this feature determines its selectivity for individual kinases, as nakijiquinone C selectively inhibits Her-2/Neu and 2-epnakijiquinone C targets VEGFR-2.<sup>368</sup> Several staurosporine analogues have been reported to inhibit Flt-3 receptor tyrosine kinase activity.<sup>150,369-372</sup>

Aplidin (140), which was obtained from the Mediterranean tunicate *Aplidium albicans*,<sup>283</sup> activates p38 mitogen-activated protein kinases (MAPKs) and JNK<sup>284,285</sup> and inhibits the secretion of VEGF.<sup>373,374</sup> The use of aplidin for the treatment of multiple myeloma has been patented.<sup>375</sup> Terrestrol G (198) isolated from the marine-derived fungus *Penicillium terestre* displayed moderate KDR kinase inhibitory activity (32% inhibition at 10  $\mu M$ )<sup>376</sup> and cytotoxicity to cancer cell lines. Eurotinone (199) produced by the fungi *Aspergillus variecolor* B-17 and *Eurotium echinulatum* DSM-1387 potently inhibited KDR kinase.<sup>377</sup> By fermenting *Eurotium echinulatum* Delacroix (DSM-13872), Aventis Pharma<sup>378</sup> isolated the methylated eurotinone derivatives 2,12-dimethyl eurotinone (200) and 2-methyl eurotinone (201) as KDR-kinase inhibitors useful for inhibiting angiogenesis and treating malignant diseases. Sesquibastadin (181), bestaldin 3 (182), and bestaldin 7 (184) isolated from the marine sponge *Ianthella basta* inhibited VEGFR-2 and VEGFR-3 with IC<sub>50</sub> values of 0.6, 1.2, and 1.3  $\mu M$  and 1.6, 2.8, and 3.2  $\mu M$ , respectively. These compounds also inhibited IGF-1R with IC<sub>50</sub> values of 1.0, 2.3, and 1.7  $\mu M$ , respectively.<sup>320</sup> The chemical structures of the marine-derived VEGFR inhibitors 140 and 197–201 are shown in Figures 7 and 11, respectively.

**3.1.2.3. Src Kinase Inhibitors.** The Src kinases are a family of nonreceptor tyrosine kinases that includes nine members: Src, Yes, Fyn, Fgr, Lck, Hck, Blk, Lyn, and Frk. Src family kinases interact with many cellular cytosolic, nuclear, and membrane proteins, modifying these proteins by phosphorylation of

tyrosine residues. Several marine-derived Src kinase inhibitors have been reported. Crews and co-workers<sup>325,326</sup> examined the effect of several polyketide quinones/hydroquinones on v-Src kinase activity. Quinones isolated from two Indo-Pacific collections of the sponge *Xestospongia cf. carbonaria* inhibited pp60<sup>v-src</sup> kinase. Halenaquinone (188), xestoquinone (202), halenaquinol (203), 14-methoxyhalenaquinone (204), and xestoquinolide A (205) inhibited v-Src with IC<sub>50</sub> values of 1.5, 60, 0.6, 5.0, and 80  $\mu M$ , respectively.<sup>325,326,379</sup> Xestoquinone (202) and related polycyclic quinones also displayed cytotoxic activity.<sup>380</sup> Terrestrol G (198) isolated from a marine-derived fungus moderately inhibited Src kinase (36% inhibition at 10  $\mu M$ ).<sup>376</sup> The anthraquinones paeciloquinones 164–169 and varsicolol (171) isolated from the culture broth of the fungus *Paecilomyces carneus* p-177 inhibited c-Src protein tyrosine kinase with IC<sub>50</sub> values of 2, >100, >100, 9, 35, 51, 36, and >100  $\mu M$ , respectively.<sup>315</sup> Sesquibastadin (181), bestaldin 3 (182), and bestaldin 7 (184) isolated from the marine sponge *Ianthella basta* inhibited Src kinase with IC<sub>50</sub> values of 0.7, 1.9, and 2.0  $\mu M$ , respectively.<sup>320</sup> Staurosporine (1) also inhibited p60v-Src kinase with an IC<sub>50</sub> of 6 nM.<sup>323</sup> The chemical structures of the marine-derived Src kinase inhibitors 1 (Figure 3), 164–169 and 171 (Figure 9), 198 (Figure 11), and 202–205 (Figure 13) are shown in Figures 3, 9, 11, and 12.

Several sulfated marine natural products are known to inhibit tyrosine kinase pp60v-Src. For example, malhamensilipin A (206), a chlorosulfolipid isolated from a chrysophyte *Poterioochromonas malhamensis*, inhibited protein tyrosine kinase pp60v-Src with an IC<sub>50</sub> of 35  $\mu M$ .<sup>381,382</sup> Bioactivity-guided fractionation of an extract of the green brittle star *Ophiararhina inmassata* using a protein tyrosine kinase pp60 v-Src inhibition assay led to the isolation of five sterol sulfates 207–211. These compounds moderately inhibited protein tyrosine kinase pp60v-Src with IC<sub>50</sub> values of 62, 65, 31, 11, and 12  $\mu M$ , respectively.<sup>383</sup> Similarly, bioactivity-directed fractionation of the extract of the green alga *Tydemania expeditionis* using the protein tyrosine kinase pp60v-Src inhibition assay led to the isolation of three cycloartenol disulfates 212–214, all of which moderately inhibited the enzyme.<sup>384</sup> Halistanol trisulfate (215) inhibited v-Src kinase with an IC<sub>50</sub> of 4  $\mu M$ .<sup>385</sup> The chemical structures of the marine-derived sulfated lipid/sterol as Src kinase inhibitors 206–215 are shown in Figure 13.

Lck is a member of the Src family of tyrosine kinases, and it phosphorylates tyrosine residues of certain proteins involved in the intracellular signaling pathways of lymphocytes containing the lck protein. Ulocladol (216) isolated from a marine isolate

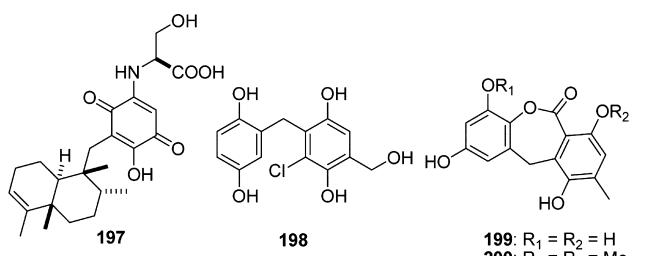
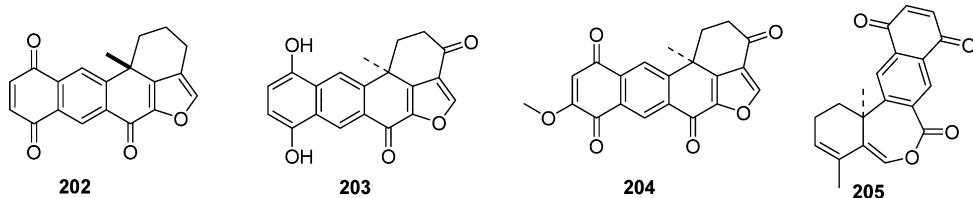
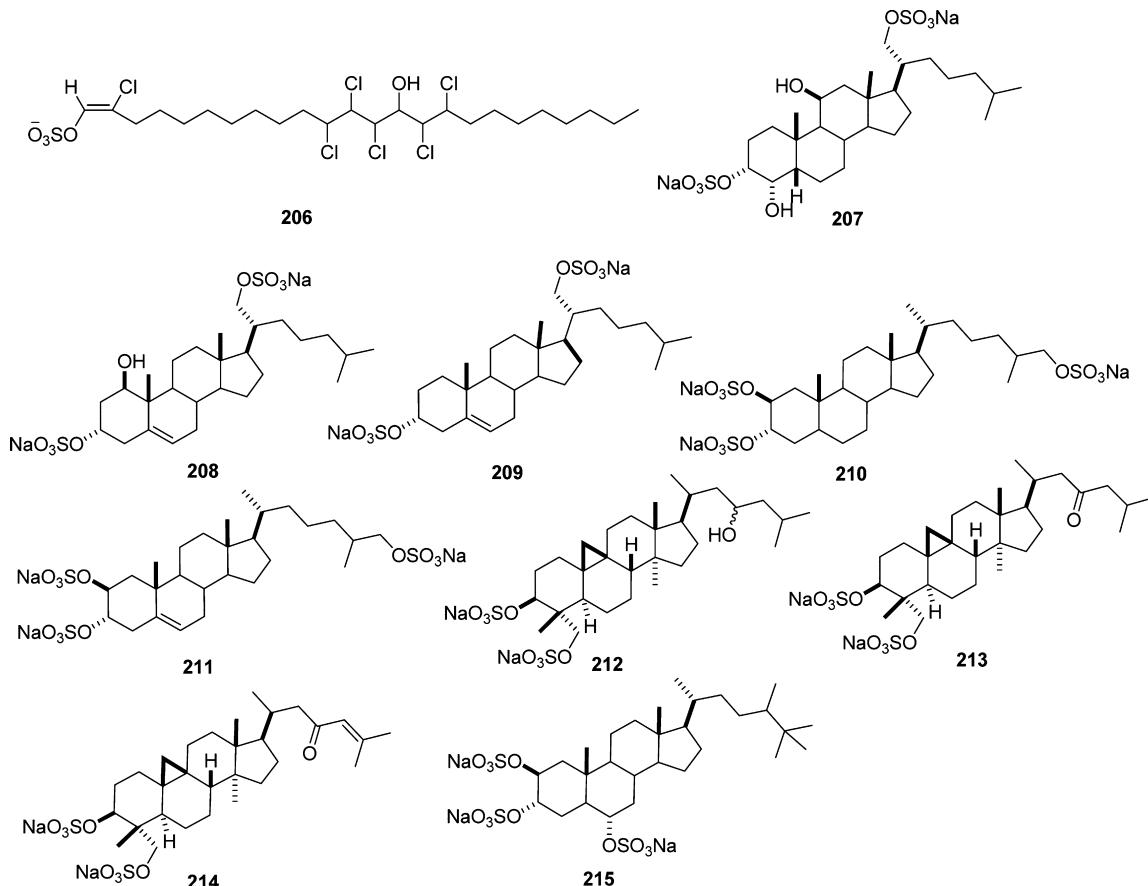


Figure 11. Marine-derived VEGFR inhibitors.



**Figure 12.** Marine-derived quinones as Src kinase inhibitors.



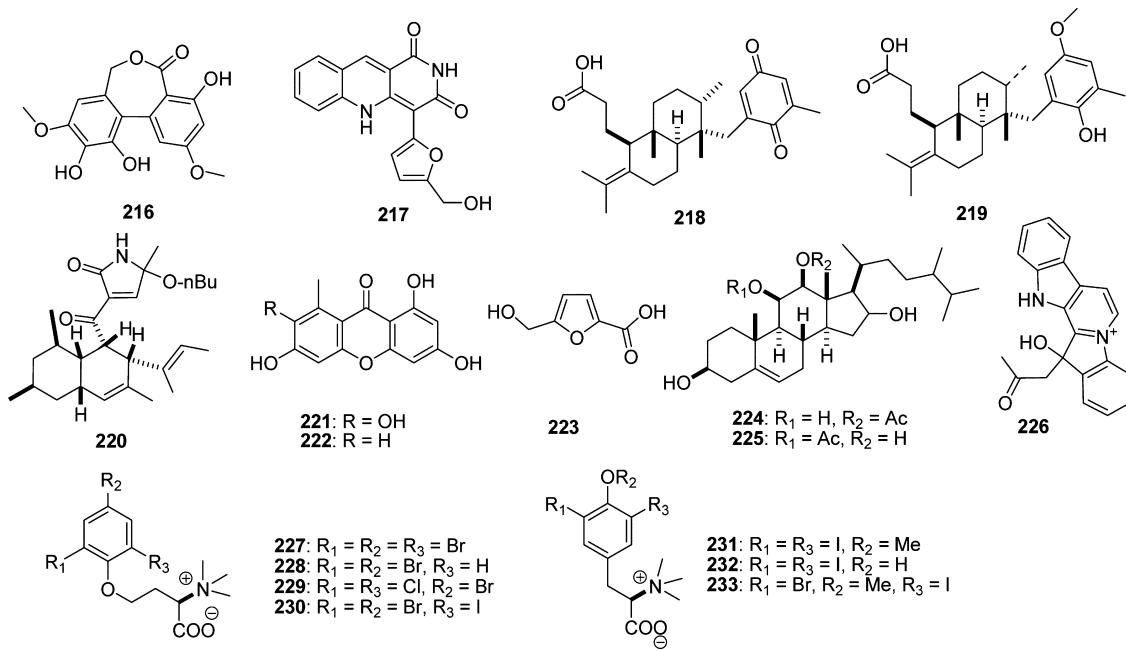
**Figure 13.** Marine-derived sulfated lipids/sterols as src kinase inhibitors.

of *Ulocladium botrytis* inhibited the tyrosine kinase p56lck, reducing enzyme activity to 7% at 0.02  $\mu\text{g}/\text{mL}$ .<sup>386</sup> The benzophenone derivative chaetominedione (217), which was isolated from the algicolous marine fungus *Chaetomium* sp., exhibited significant inhibitory activity against p56lck with 94% enzyme inhibition at 649  $\mu\text{M}$ .<sup>387</sup> Styloquinonic acid (218) and atomaric acid (219), which were isolated from the lipophilic extract of the marine brown alga *Styropodium zonale* (Dictyotaceae), inhibited p56lck with IC<sub>50</sub> values of 187 and 208  $\mu\text{M}$ , respectively.<sup>388</sup> Ascosalipyrrolidine A (220) isolated from the endophytic marine fungus *Ascochyta salicorniae* inhibited the tyrosine kinase p56lck.<sup>389</sup> Two xanthone derivatives, 2,3,6,8-tetrahydroxy-1-methylxanthone (anomalin A, 221) and 3,6,8-trihydroxy-1-methylxanthone (222), and a furan derivative, 5-(hydroxymethyl)-2-furan carboxylic acid (223), isolated from the marine fungus *Wardomyces anomalus* inhibited p56lck tyrosine kinase (100% enzyme inhibition at 200  $\mu\text{g}/\text{mL}$ ).<sup>390</sup> Ergosterol derivatives 224,225, which were isolated from a Great Barrier Reef collection of *Capnella lacertiliensis*, inhibited p56lck at a concentration of 408  $\mu\text{M}$ .<sup>391</sup> Homofascaplysin A (226) isolated

from the sponge *Hyrtios erecta* and from *Fascaplysinopsis reticulata* also inhibited p56lck.<sup>392,393</sup> Purpuorines A–D (227–230) and F–H (231–233) isolated from the marine sponge *Iotrochota purpurea* inhibited lck kinase with IC<sub>50</sub> values of 5, 33, 13, 2.1, 14.7, 25, and 17.9  $\mu\text{M}$ , respectively.<sup>394</sup> The chemical structures of the marine-derived p56lck inhibitors 216–233 are shown in Figure 14.

**3.1.2.4. v-Abl Tyrosine Kinase Inhibitors.** The v-Abl oncogene of Abelson murine leukemia virus encodes a deregulated form of the cellular nonreceptor tyrosine kinase. The anthraquinones paeciloquinones 164–169 and varsicolol (171), which were isolated from the fungus *Paecilomyces carneus* p-177, inhibited v-Abl protein tyrosine kinase with IC<sub>50</sub> values of 0.59, 83, 11, 0.56, 11, 220, 3.6, and 23  $\mu\text{M}$ , respectively.<sup>315</sup> The chemical structures of the v-Abl tyrosine kinase inhibitors 164–169 and 171 are shown in Figure 9.

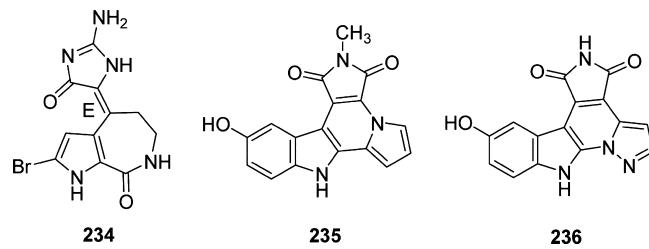
**3.1.2.5. Dual-Specificity Protein Kinase (Dyrk and CLK) Inhibitors.** A dual-specificity kinase is a kinase that can act as a tyrosine kinase and a serine/threonine kinase. Examples of such kinases are MEKs, Dyrk's, and CLKs. Dyrk's ("dual-specificity" tyrosine phosphorylation-regulated kinases) and CLKs (cdc2-



**Figure 14.** Marine-derived lck tyrosine kinase inhibitors.

like kinases) are implicated in the onset and development of Alzheimer's disease and Down syndrome. Leucettamine B (**123**) isolated from the sponge *Leucetta microraphis*<sup>264</sup> inhibited “dual-specificity” kinases Dyrk-1A, Dyrk-2, CLK-1, and CLK-3 with IC<sub>50</sub> values of 2.8, 1.5, 0.40, and 6.4 μM, respectively. Medicinal chemistry efforts<sup>266</sup> to modify leucettamine B led to the identification of potent inhibitors of these “dual-specificity” kinases. The most promising, leucettine L41 (**127**), inhibited Dyrk-1A, Dyrk-2, CLK-1, and CLK-3 with IC<sub>50</sub> values of 0.040, 0.035, 0.015, and 4.5 μM, respectively. Leucettine L41 (**127**) displayed neuroprotective effects on glutamate-induced HT22 cell death. Leucettine L41 (**127**) also reduced amyloid precursor protein-induced cell death in cultured rat brain slices. The selectivity profile of leucettamine B and leucettine L41 (**127**) was recently explored by the same group.<sup>267</sup> These compounds were poor inhibitors of CDKs (1,2,5,7,9) and CK-1δ. They were primarily found to be potent inhibitors of all Dyrk’s (1A, 2, 3, and 4) and CLKs (1 and 2). Co-crystal structures of leucettine L41 (**127**) with Dyrk-1A, Dyrk-2, and CLK-3 have been reported.<sup>267</sup> The aldisine alkaloids 10E-hymenialdsine (**234**) and 10Z-hymenialdsine (**88**) isolated from the Philippine sponge *Styliissa massa* potently inhibited MAP kinase kinase-1 (MEK-1) with IC<sub>50</sub> values of 3 and 6 nM, respectively. Compounds **234** and **88** also inhibited the growth of human tumor LoVo cells with IC<sub>50</sub> values of 586 and 710 nM, respectively.<sup>217</sup> Analogues **235** and **236** of the marine-derived alkaloid granulatimide (**137**) potently inhibited the “dual-specificity” kinases Dyrk-1A (IC<sub>50</sub> values of 0.2 and 0.18 μM) and CLK-1 (IC<sub>50</sub> values of 0.26 and 0.09 μM).<sup>279</sup> The chemical structures of the dual-specificity protein kinase (Dyrk and CLK) inhibitors **88**, **123**, **127**, and **234–236** are shown in Figures 4, 5, and 15, respectively.

**3.1.2.6. Miscellaneous Tyrosine Kinase Inhibitors.** Marine-derived tyrosine kinase inhibitors for whom specific tyrosine kinase inhibitory activity has not been reported are included in this section. Three metabolites SC2051 (**237**) and hypochromins A (**238**) and B (**239**) isolated from the marine-derived fungus *Hypocreah vinoso* showed tyrosine kinase inhibitory



**Figure 15.** Marine-derived “dual-specificity” protein kinase (Dyrk and CLK) inhibitors.

activity with IC<sub>50</sub> values of 42.1, 58.7, and 18.0 μM, and these compounds also exhibited inhibitory effects on proliferation, migration, and tubule formation.<sup>395</sup> Hydroxylated 2-heptaprenylhydroquinone (**240**), isolated from *Ircinia* sp., inhibited tyrosine kinase activity with an IC<sub>50</sub> of 10.8 μM.<sup>396</sup> Other marine natural products with tyrosine kinase inhibitory activity include leptosin M (**156**) (alga *Sargassum tortile*),<sup>303</sup> mauritamide A (**241**, sponge *Agelas mauritiana*),<sup>397</sup> melemeleone B (**242**, sponge *Dysidea avara*),<sup>398</sup> aplyroseol 5 and 6 (**243** and **244**, sponge *Aplysilla rosea*),<sup>399,400</sup> psammaplin D (**245**, sponge *Psammaplysilla purpura*),<sup>401</sup> and malonganenone D (**246**, south China sea gorgonian *Euplexaura robusta*).<sup>402</sup> The chemical structures of the miscellaneous tyrosine kinase inhibitors **156** and **237–246** are shown in Figures 8 and 16, respectively.

### 3.2. Lipid Kinase Inhibitors

**3.2.1. Phosphoinositide 3-Kinase (PI3K) Inhibitors.** PI3Ks constitute a family of lipid kinases involved in the regulation of a network of signal transduction pathways that control a range of cellular processes.<sup>403–405</sup> PI3K signaling plays a central role in cellular processes critical for cancer progression, metabolism, growth, survival, and motility. Therefore, significant efforts have been made to discover inhibitors of the PI3K pathway to treat cancers. Liphagal (**247**), which was isolated from the marine sponge *Aka coralliphaga*, showed remarkable activity against PI3K-α, with an IC<sub>50</sub> of 100 nM and

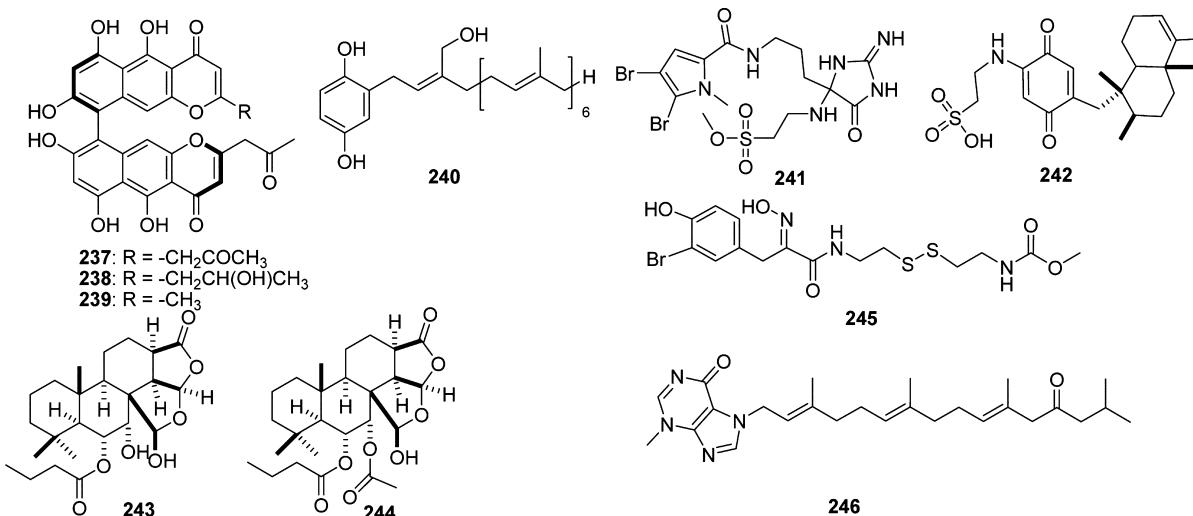


Figure 16. Marine-derived miscellaneous tyrosine kinase inhibitors.

10-fold selectivity for PI3K- $\alpha$  as compared to PI3K- $\gamma$  in a fluorescence polarization enzyme bioassay.<sup>406</sup> Liphagal (247) also exhibited antiproliferative activity in LoVo, Caco, and MDA-468 cells with IC<sub>50</sub> values of 0.58, 0.67, and 1.58  $\mu\text{M}$ , respectively.<sup>407</sup> The marine natural product 12-epi-scalaradial (248) isolated from the marine sponge *Cacospongia* sp. inhibited EGFR-mediated phosphorylation of Akt/PKB, a serine/threonine protein kinase, membrane translocation of 3-phosphoinositide-dependent protein kinase 1 (PDK-1 or PDPK-1), and PI3K activity.<sup>408</sup> 12-Epi-scalaradial also induced apoptosis in human carcinoma cells.<sup>409</sup> Halenaquinone (188), which was isolated from a sponge, inhibited PI3K with an IC<sub>50</sub> of 3  $\mu\text{M}$ . Halenaquinone inhibited PI3K activity at lower concentrations than those at which it induced apoptosis in PC12 cells, suggesting that the mechanism of apoptosis may be partially explained by the inhibition of PI3K activity.<sup>410</sup> Kahalalide F (196), a C75 cyclic tridecapeptide from the sacoglossan (sea slug) *Elysia rufescens*,<sup>411–413</sup> induced cell death by oncosis in human prostate and breast cancer cell lines.<sup>414</sup> In addition, a necrosis-like process was observed in several human kahalalide-F-sensitive breast, vulval, NSCLC, and hepatic and colon carcinoma cell lines,<sup>365</sup> in which down-regulation of the ERB-3 protein and inhibition of the PI3K/Akt signaling pathway were identified as determinants of its cytotoxicity.<sup>415</sup> The chemical structures of the marine-derived PI3K inhibitors 188 (Figure 9), 196 (Figure 10), and 247,248 (Figure 17) are shown in Figures 9, 10, and 17.

**3.2.2. Sphingosine Kinase Inhibitors.** Sphingosine kinase (SphK) is a conserved lipid kinase that catalyzes the formation of sphingosine-1-phosphate (S1P) from its precursor sphingosine. Sphingosine kinase-1 is also an oncogene that is overexpressed in many tumors and protects cancer cells from

apoptosis. Sphingosine kinase-1 has emerged as a target of interest for therapeutic intervention.<sup>416</sup> The antibiotic F-12509a (249), which was isolated from a marine bacterium and the discomycete *Trichopezella barbata*, inhibited sphingosine kinase 1, with *ki* value (for the recombinant SphK-1 isoform) of 4  $\mu\text{M}$  as compared to 3.2  $\mu\text{M}$  for dimethylsphingosine. Lineweaver–Burk plots analysis indicated that F-12509a inhibited SphK-1 competitively (like dimethylsphingosine) with respect to sphingosine, suggesting that the sesquiterpene moiety of F-12509a may mimic the conformation of sphingosine in the binding to the active site of SphK-1.<sup>417,418</sup> Antibiotics B-5354a–c (250–252), which are produced by the marine bacterium SANK 71896, displayed sphingosine kinase inhibitory activity with IC<sub>50</sub> values of 21, 58, and 38  $\mu\text{M}$ , respectively.<sup>418–420</sup> Compounds S-15183a (253) and S-15183b (254) isolated from the fungus *Zopfiella inermis* inhibited SphK-1 in a cell-free system with IC<sub>50</sub> values of 2.5 and 1.6  $\mu\text{M}$ , respectively.<sup>421</sup> The chemical structures of the marine-derived sphingosine kinase inhibitors 249–254 are shown in Figure 18.

### 3.3. Miscellaneous Kinase Inhibitors

Adenosine kinase, the most abundant nucleoside kinase in mammals, catalyzes the phosphorylation of riboflavinyl-containing nucleoside analogues at the 5'-hydroxyl using ATP or GTP as the phosphate donor. The marine natural product 5-iodotubercidin (255) is a powerful inhibitor of adenosine kinase,<sup>422,423</sup> as well as a strong promoter of glycogen synthesis in liver cells.<sup>424</sup> Although 5-iodotubercidin exerts no effect on protein phosphatases, it does exhibit inhibitory behavior against an array of protein kinases, including InsR (IC<sub>50</sub> 3.5  $\mu\text{M}$ ), casein kinase-1 (IC<sub>50</sub> 0.4  $\mu\text{M}$ ), casein kinase-2 (IC<sub>50</sub> 11  $\mu\text{M}$ ), and PKC (IC<sub>50</sub> 28  $\mu\text{M}$ ).<sup>425</sup> 5-Iodotubercidin acts as an ATP-competitive inhibitor. Interestingly, tubercidin (256), a constituent of the sponge *Caulospongia biflabellata*, is a much poorer (300 times) inhibitor of protein kinases; however, it is a known antibiotic and has been used in the treatment of cancer, mycosis fungoides,<sup>426,427</sup> allergies, and atopic disorders.<sup>428</sup> 5-Deoxy-5-iodotubercidin (257) isolated from the red marine algae *Hypnea valentiae* inhibited adenosine kinase.<sup>429</sup> 5-Iodotubercidin (255) and 5-deoxy-5-iodotubercidin (257) have been tested for their use in the treatment of cancer<sup>142</sup> and brain diseases.<sup>282,430</sup>

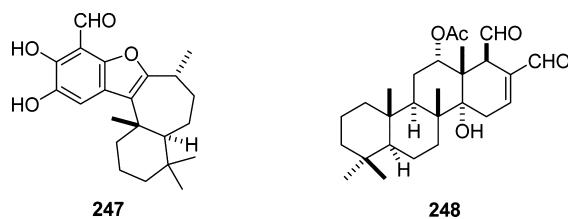


Figure 17. Marine-derived PI3K inhibitors.

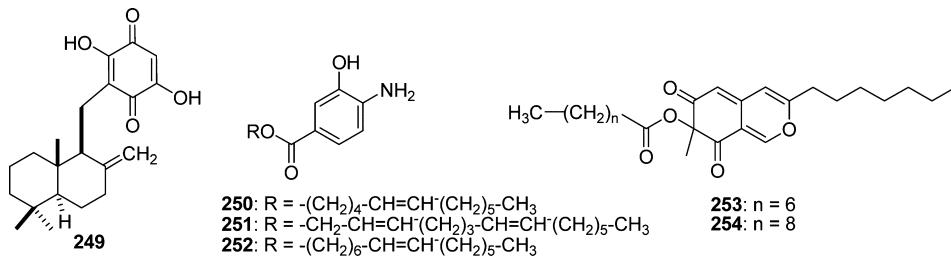


Figure 18. Marine-derived sphingosine kinase inhibitors.

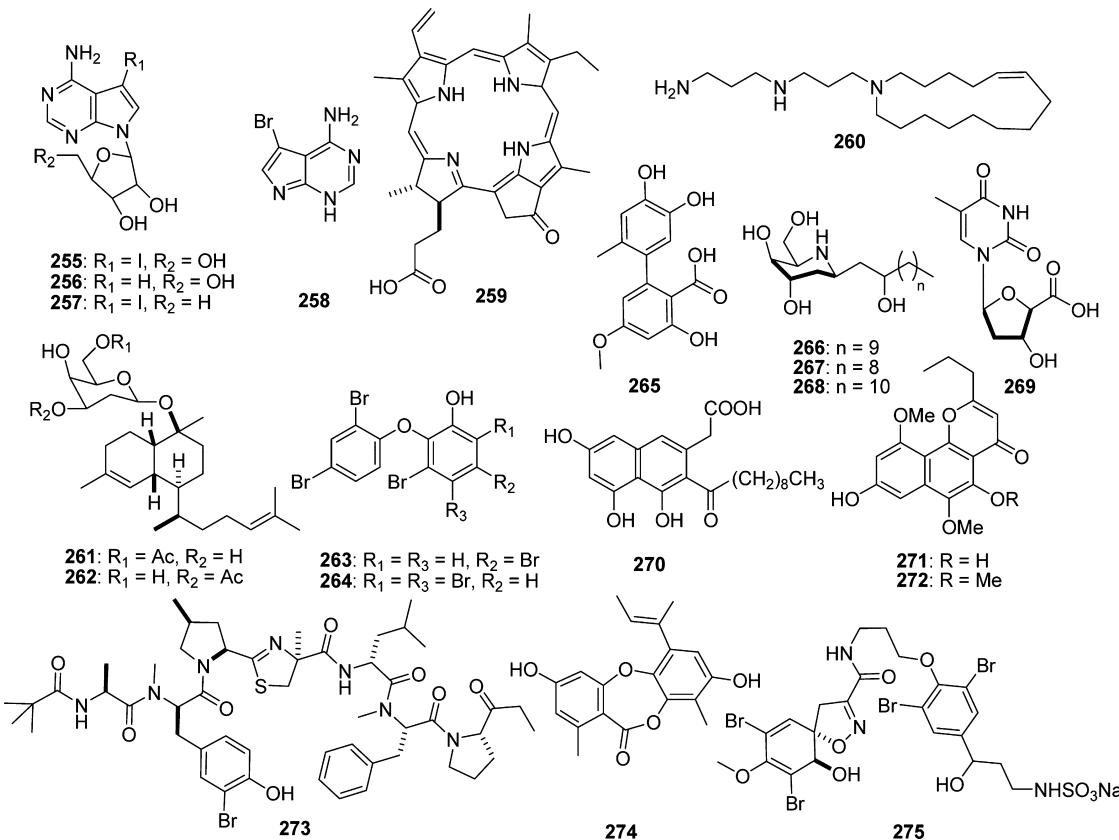
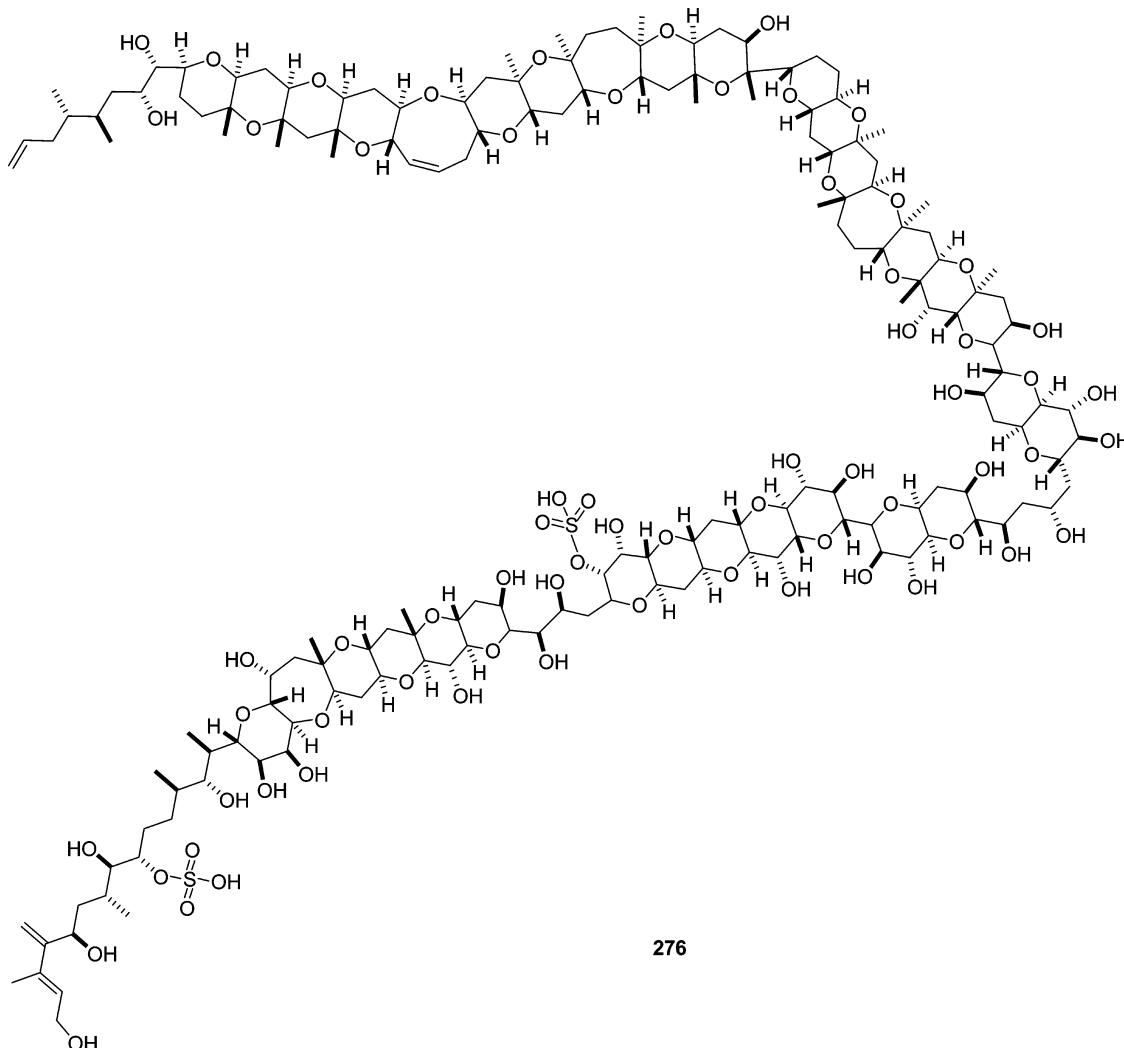


Figure 19. Marine-derived miscellaneous kinase inhibitors.

4-Amino-5-bromopyrrolo[2,3-*d*]pyrimidine (**258**) isolated from the sponge *Echinodictyon* sp. inhibited adenosine kinase activity.<sup>431</sup> Hymenialdisine (**88**) also inhibited JAK-3/STAT, which is involved in the progression of osteoarthritis or rheumatoid arthritis.<sup>262,432</sup> Staurosporine potently inhibited ZAP-70 and JAK-2 tyrosine kinases.<sup>323</sup> A tetrapyrrole compound, pyropheophorbide a (**259**), isolated from the sponge *Stellella clavosa* exhibited c-Raf-1 kinase inhibitory activity ( $IC_{50} < 578$  nM). This compound was also screened against a panel of 85 kinases covering a diverse range of biochemical pathways, and excellent selectivity (>80% inhibition) was observed against three enzymes Aurora-A, PRAK, and Syk.<sup>433</sup> Furthermore, conjugates of pyropheophorbide as well as several synthetic analogues have been reported for the treatment of cancer.<sup>434,435</sup> An alkaloid motuporamine C (**260**) isolated from the Papua New Guinea marine sponge *Xestospongia exigua* stimulated concentration-dependent neuronal growth cone collapse,<sup>436</sup> and its intracellular mechanism showed significant upregulation of the Rho–Rho–kinase

collapse pathway, suggesting that **260** might be useful for studying neuronal outgrowth.<sup>436</sup>

Xestoquinone (**202**), which was isolated from the Pacific Ocean sponge *Xestospongia* sp., showed significant in vitro antiplasmoidal activity ( $IC_{50}$  3  $\mu$ M), and inhibited Pfnek-1 ( $IC_{50}$  1  $\mu$ M), a protein kinase of *P. falciparum* of unknown function.<sup>437</sup> Lemnalosides A,B (**261,262**) isolated from the soft coral *Lemnalia* sp. were active in a hyphae formation inhibition assay, acting as a prescreen for cytotoxins and protein kinase inhibitors.<sup>438</sup> The polybrominated diphenyl ether **263**, which was isolated from the marine sponge *Dysidea* sp., exhibited kinase inhibitory activities against *Streptomyces* 85E in the hyphae formation inhibition (HFI) assay and displayed antiproliferative activities against the human breast adenocarcinoma cancer cell line MCF-7.<sup>439</sup> Another pentabrominated diphenyl ether **264**, which was isolated from *Dysidea herbacea*, inhibited Tie-2 kinase, which is involved in angiogenesis.<sup>440</sup> Altenusin (**265**), which was isolated from the marine fungus *Alternaria tenuis*, inhibits myosin light chain kinase.<sup>441,442</sup>



**Figure 20.** Structure of maitotoxin, a protein kinase inhibitor.

A series of iminosugar-like N-cyclized sphingolipids obtained from *Batzella* species, batzellasides A–C (266–268), were identified as inhibitors of Raf kinase.<sup>443</sup> Thymidine-5'-carboxylic acid (269) isolated from the ascidian *Aplidium fuscum* was found to be an inhibitor of thymidine and thymidylate kinase.<sup>444</sup> 4,5,7-Trihydroxy-3-(1-oxodecyl)-2-naphthaleneacetic acid (270) isolated from an acetone extract of solid cultures of the aquatic hypomycete *Articulospora* sp. inhibited bacterial histidine kinase.<sup>445</sup> Naphthopyrones 271,272 isolated from the crinoids *Comanthus parvicirrus* inhibited TNF- $\alpha$  induced NF- $\kappa$ B activation by inhibiting IKK $\beta$ -kinase.<sup>446–448</sup> Bisebromoamide (273) isolated from the marine cyanobacterium *Lyngbya* sp. exhibited potent protein kinase inhibition. The phosphorylation of ERK in NRK cells by PDGF-stimulation was selectively inhibited by treatment with 10–0.1  $\mu$ M of bisebromoamide. This compound had no effect on the phosphorylation of AKT, PKD, PLC $\gamma$ 1, or S6 ribosomal protein at 10–0.1  $\mu$ M.<sup>449,450</sup> Unguinol (also called Yasimin, 274) was isolated from the fungus *Aspergillus unguis* (*Ianthella reticulata*) as an inhibitor of the C4 plant enzyme pyruvate phosphate dikinase (PPDK).<sup>451</sup> 19-Hydroxyaraplysillin-I N-20 sulfamate (275) from *Ianthella flabelliformis* exhibited non-selective inhibition of plant pyruvate phosphate dikinase.<sup>452</sup> The sulphated polyether antibiotic maitotoxin (276) isolated

from the marine dinoflagellate *Gambierdiscus toxicus* is a protein kinase activator.<sup>453</sup> The chemical structures of the marine-derived miscellaneous kinase inhibitors 88 (Figure 4), 202 (Figure 13), 255–275 (Figure 19), and 276 (Figure 20) are shown in Figures 4, 13, 19, and 20.

#### 4. ATP-COMPETITIVE VERSUS ALLOSTERIC INHIBITORS

Protein kinases represent an attractive target in oncology drug discovery. Most kinase inhibitors are ATP-competitive; these inhibitors are known as type I inhibitors. The ATP-binding pocket is highly conserved among members of the kinase family, complicating the development of selective agents. Alternative approaches to inhibitor development, such as targeting sites other than the ATP cleft, are increasingly being pursued in the search for new therapeutics based on protein kinase inhibition. While recently approved kinase inhibitor drugs offer benefits for cancer treatment, further advances are required to effect tumor selective cell killing, avoid off-target related toxicities, and improve survival rates. Thus, exploiting allosteric pockets may increase selectivity while avoiding decreased efficacy as a result of competition with high ATP concentrations.<sup>454,455</sup> ATP-competitive inhibitors must compete with high intracellular ATP levels, leading to

discrepancies between  $IC_{50}$  values measured by biochemical versus cellular assays. Non ATP-competitive inhibitors, which are referred to as type II and type III inhibitors, have the potential to overcome these problems. These inhibitors act by inducing a conformational change in the target enzyme such that the kinase is no longer able to function. Marine natural products have great potential as a source of allosteric inhibitors.

Within the kinase domain of several protein kinases (e.g., Abl, p38MAP kinase, MEK, and JNK), an allosteric site has also been identified adjacent to the ATP site that is amenable to small-molecule inhibitor design.<sup>456</sup> Compounds that target this allosteric site are noncompetitive with ATP and can form an inactive, ternary complex with the enzyme. The clinical candidates CI-1040 (PD184352, Pfizer),<sup>457,458</sup> PD0325901 (Pfizer),<sup>459</sup> and ARRY-142886 (AZD6244, Array Biopharma/AstraZeneca)<sup>460</sup> represent allosteric inhibitors of MEK-1, a Ser/Thr kinase within the RTK/RAF/MEK/ERK signaling pathway. The attractiveness of designing ATP noncompetitive inhibitors targeted at this allosteric site is that they are expected to be independent of high cellular ATP concentrations and demonstrate greater selectivity toward inhibition of other protein kinases.

Manzamine A (**122**), a complex alkaloid isolated from an Okinawan sponge of the genus *Haliclona*, displayed non-competitive inhibition of GSK-3 $\beta$  with an  $IC_{50}$  value of 10.2  $\mu\text{M}$ .<sup>253</sup> The furano-sesquiterpene palinurin (**132**) isolated from the sponge *Ircinia dendroides* exhibited allosteric inhibition of GSK-3 $\beta$  with an  $IC_{50}$  of 1.9  $\mu\text{M}$ .<sup>271</sup>

## 5. MEDICINAL CHEMISTRY OF POTENTIAL CANDIDATES

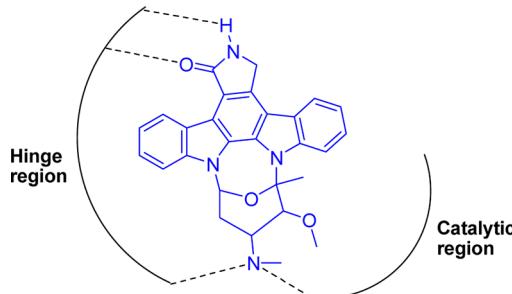
As discussed in previous sections, many structurally diverse MNPs exhibit activity against a variety of kinases. Many of these MNPs exhibited remarkable biological activity profiles and were subsequently explored for lead optimization, and preclinical and clinical development. The medicinal chemistry and SAR of selected promising marine-derived kinase inhibitors is discussed in this section. Candidates discussed herein include staurosporine, aaptamine/isoaaptamine, variolins/meridianins/meriolins, fascaplysin, indirubins, and liphagal.

### 5.1. Staurosporine

Staurosporine (**1**) is an indolocarbazole alkaloid containing an indolo[2,3-*a*]-pyrrolo[3,4-*c*]carbazole core that is attached to a sugar moiety. First discovered in 1977 by Omura and co-workers<sup>132</sup> from the bacterium *Streptomyces staurosporeus*, more than 50 related indolocarbazoles from a variety of natural sources were subsequently discovered.<sup>154,461–463</sup> Staurosporine was initially identified as an antifungal and hypotensive agent; however, the discovery of its potent PKC inhibitory activity as well as its strong cytotoxic effects on cancer cells attracted greater attention to staurosporine.<sup>134</sup> Staurosporine has greatest affinity for Ser/Thr protein kinases but also showed high affinity toward many druggable tyrosine kinases.<sup>464,465</sup> Staurosporine itself is too toxic for use as a drug, but its promising biological profile established it as a key starting point for lead optimization to design analogues with better selectivity and inhibition profiles. Several natural analogues were produced by combinatorial biosynthesis<sup>466</sup> utilizing the natural diversity of metabolic pathways in recombinant form; synthetic medicinal chemistry was also used to create several synthetic analogues. Because of these efforts, some staurosporine analogues have

entered advanced phases of clinical trials against cancer,<sup>467</sup> Alzheimer's disease, and other neurodegenerative disorders.<sup>467</sup>

Extensive efforts have been made to elucidate the kinase binding sites of staurosporine and its analogues. To date, nearly 50 3D sets of coordinate of protein kinase domains (40 with staurosporine and 10 with close analogues of staurosporine) have been cocrystallized with staurosporine and its analogues. Co-crystal structures of staurosporine with kinases revealed a common binding mode with the ATP binding site, which is formed where the N- and C-terminal folding domains are linked by hinge segment.<sup>468–471</sup> Key interaction points of staurosporine with kinase domains are shown in Figure 21. In

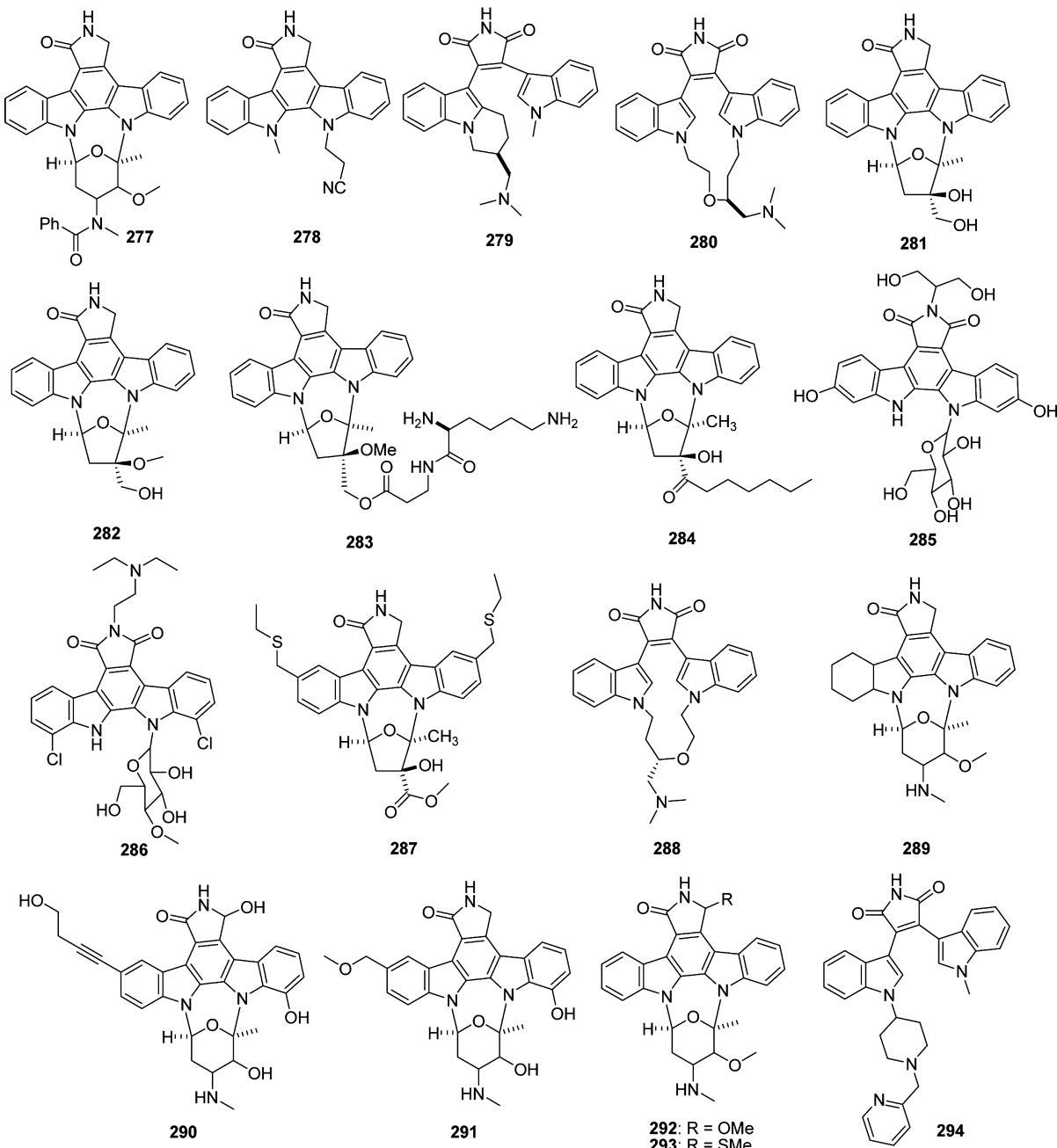


**Figure 21.** Interactions of staurosporine with cAMP-dependent protein kinase.

the biologically active form, the sugar ring of staurosporine occupies a perpendicular position with respect to the indolocarbazole plane, forming boat-shaped conformation and occupying the space in the ATP pocket that is bound by the ribose in the ATP/ADP-bound forms of the kinase,<sup>472</sup> whereas the broad aromatic planar structure of the indolocarbazole plane is sandwiched by hydrophobic residues from the N-lobe and C-lobe. In addition to the van der Waals interactions between the side-chains of these residues with the aromatic plane of staurosporine, many CH- $\pi$  interactions between the CH moieties of these residues and the conjugated plane of staurosporine have also been identified.<sup>470</sup>

The binding affinity of staurosporine for a particular kinase can be correlated with two factors: the size of the gatekeeper residue and the distance between the first Gly of the GxGxxG motif and the Asp of the DFG loop.<sup>473</sup> This distance represents the closure of the N-lobe and the C-lobe, and binding affinity increases with an increasing number of H-bonds between the methylamino group of the glycosidic ring and the surrounding residues. On the basis of this structural information, extensive medicinal chemistry explorations of the staurosporine scaffold have been performed to generate more potent and more selective analogues, particularly by modification of the indolocarbazole ring and sugar moiety (Figure 21).

Several staurosporine analogues have been derived via modification of the sugar ring. A very close analogue of staurosporine, midostaurin (**277**, PKC-412, *N*-benzoyl staurosporine), is a semisynthetic derivative generated by the introduction of a benzoyl group at the *N*-methyl of the sugar moiety. SAR investigations<sup>464</sup> revealed that benzoylation leads to a 2-fold decrease in PKC inhibition. Midostaurin inhibited several serine/threonine and tyrosine kinases, including PKC isoforms ( $\alpha$ ,  $\beta$ , and  $\gamma$ ), PKA, c-Kit, Syk, Flk-1, Akt, c-Src, C-Fgr, PDFR $\beta$ , Flt-3, VEGFR-1, and VEGFR-2 at nanomolar concentrations, and has been proposed for the treatment for myeloproliferative disease.<sup>474,475</sup> It selectively inhibited PKC



**Figure 22.** Drug candidates based on staurosporine scaffold.

and inhibited cell growth of aRMS cells, inducing apoptosis due to enhanced caspase 3 activity. Midostaurin inhibited growth or induced apoptosis in many cancer cell types blocking angiogenesis in tumors and sensitizing cancer cells to ionizing radiation, thereby supporting its use in cancer therapy.<sup>474</sup> Tenzer et al.<sup>476</sup> showed that the cytotoxic effect of midostaurin is mediated via the PI3K/Akt pathway, and tumor growth was also shown to be inhibited *in vivo* in a mouse xenograft tumor model.<sup>477,478</sup> Furthermore, midostaurin slowed the growth and delayed lung metastasis of a melanoma cell line in a mouse model, whereas in phase II clinical trials, it failed to show activity in metastatic melanoma.<sup>479</sup> Midostaurin targets Flt-3, a receptor tyrosine kinase that is activated by mutation in approximately one-third of AML patients<sup>480,481</sup> and also inhibits several other targets such as VEGFR-2, c-Kit, and

PDGFR, which are involved in the pathogenesis of acute myeloid leukemia (AML).

To understand the SAR of staurosporine, several natural as well as synthetic analogues with substitutions/modifications in the indolocarbazole ring have been studied. Modifications of the sugar moiety led to the development of the lead candidates Go-6976 (278), Ro-32-0432 (279), and LY-333531 (280).<sup>482–484</sup> Replacement of pyran with a furan ring led to a few clinical candidates, the most promising of which are lestaurtinib (281, CEP-701) and CEP-751 (282), which have advanced to clinical development. Lestaurtinib inhibited tyrosine kinases as well as other kinases such as Flt-3, JAK-2, Trk-A, Trk-B, and Trk-C.<sup>485,486</sup> Cephalon is developing CEP-2563 (283), a prodrug ester of CEP-751, because of the limited aqueous solubility of CEP-751 (282).<sup>487</sup> Another analogue, KT-5720 (284), a semisynthetic derivative of K252a, was found

to be a selective inhibitor of PKA ( $IC_{50}$  56 nM), with excellent selectivity against PKC.<sup>162</sup> KT-5720 (284) was recently cocrystallized with a Ser/Thr kinase PknB receptor from *Mycobacterium tuberculosis* (PDB: 3F69),<sup>488</sup> opening new possibilities for anti-TB drug design.

Several staurosporine analogues have been prepared by substitutions on the aromatic moiety to yield the potent clinical candidates edotecarin (285) and becatecarin (286), which were prepared by modification of the sugar and maleimide nitrogen of the aromatic plane. These candidates are currently in clinical phase II/III trials for a number of cancers. Although both edotecarin (285) and becatecarin (286) were not very potent kinase inhibitors, they have shown excellent activities in stabilizing DNA topoisomerase-1.<sup>158</sup> Another analogue, CEP-1347 (287), derived from substitution on the indolocarbazole and sugar ring, is being investigated for Parkinson's diseases in a phase II clinical trial. Ruboxistaurin (288), which was obtained by breaking the bond between the two indole moieties, inhibited PKC- $\beta$  ( $IC_{50}$  = 4.7 nM for PKC- $\beta$ 1 and 5.9 nM for PKC- $\beta$ 2). Tetrahydrostaurosporine (289), which was derived by partial hydrogenation to break planarity and reduce aromaticity, displayed increased solubility<sup>489</sup> and has been cocrystallized with several kinase domains such as active Abl kinase,<sup>490</sup> focal adhesion kinase,<sup>491</sup> and JAK-3 kinase.<sup>489</sup>

Staurosporine (1) and its analogues have been evaluated against the human lung cancer cell line A-549, and two compounds, 290 and 291, displayed potent growth inhibition with  $IC_{50}$  values of 0.0051 and 0.0092  $\mu$ M, respectively.<sup>492</sup> Researchers from Japan have patented a series of staurosporine analogues with PKC/PKA inhibitory activity and anticancer activity in HeLa S3 and CoLo-320DM cell lines. Staurosporine (1) and its analogues 292 and 293 inhibited PKC with  $IC_{50}$  values of 2.1, 1.4, and 23.4 nM, respectively. These compounds also showed inhibited PKA, albeit poorly, with  $IC_{50}$  values of 8.6, 242, and 29 nM, respectively. Staurosporine (1) and 293 also displayed anticancer activity, with  $IC_{50}$  values of 343 and 97.7 nM in HeLa-S3 cell line and 38.6 and 172 nM in the CoLo-320DM cell line, respectively.<sup>493</sup> Staurosporine analogue enzastaurin (294) in which sugar moiety is replaced by pyridin-2-yl-methyl-piperidinyl moiety is a potent PKC- $\beta$  inhibitor and is presently in phase III trial for diffuse large B-cell lymphoma.<sup>494</sup> The chemical structures of the drug candidates discovered based on staurosporine scaffold are shown in Figure 22.

## 5.2. Aptamine and Isoaptamine

The aptamine family of natural products isolated from marine sponge genera *Aaptos* and *Suberites* that contain a 1H-benzo[de][1,6]-naphthyridine framework.<sup>495,496</sup> The first member of this family, aptamine (43), was isolated by Nakamura and co-workers<sup>177,178</sup> and showed excellent cancer cell growth inhibitory activity and adrenoreceptor blocking activity.<sup>179</sup> Another member of the series, isoaptamine (44), was later reported by Fedoreev from a sponge of the genus *Suberites*<sup>180</sup> and later isolated from *Aaptos aaptos* by two different groups.<sup>181,182</sup> Structurally, aptamine and isoaptamine differ only in the position of one methyl group; in aptamine, the methyl group is at the C-9 position, while in isoaptamine, it is at the N1 position. Other key natural products of this family are 9-demethylaaptamine (295), bisdemethylaaptamine (296) and its 9-O-sulfate (297), 9-demethoxyaptamine (298), and 4-N-methyaptamine (299), as shown in Figure 23.

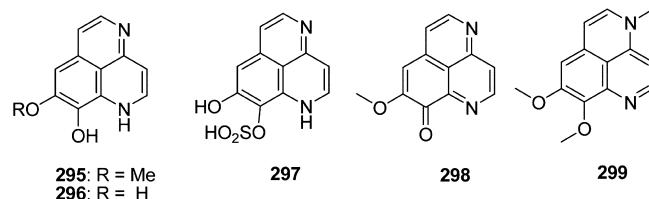


Figure 23. Structures of aptamine family of compounds.

Aptamine and analogues have shown significant activity in various tumor cell lines such as murine leukemia P388, KB16 cells, Ehrlich tumor cells, HeLa cells, A549 cells, and HT29 transfected human osteosarcoma MG63 cells. The isoaptamines were initially reported to have potent cytotoxic activity via PKC inhibition ( $IC_{50}$  100–200 nM).<sup>497</sup> This interesting profile attracted the attention of chemists around the world, and many synthetic approaches have been published.<sup>498</sup>

In the aptamines series, compounds 43, 44, and 298 showed significant cytotoxicity against human tumor cell lines such as KB16, A549, and HT29.<sup>182</sup> Shen and co-workers prepared 17 acylated analogues based on aptamine 43 and dihydroaptamine 300 ( $IC_{50}$  7.8  $\mu$ M).<sup>183</sup> All compounds were evaluated against murine P388 and human tumor cell lines (KB16, A549, and HT29), and among them, isoaptamine-based analogues 301–303 showed significant cytotoxicity against P-388 cells ( $IC_{50}$  112–149 nM). These acylated analogues were as potent as isoaptamine (44) ( $IC_{50}$  132 nM) and demethyl(oxo)-aptamine (298) ( $IC_{50}$  47 nM) and were more potent than aptamine 44 ( $IC_{50}$  2.6  $\mu$ M). From this study, it was concluded that the hydroxyl group at C<sub>9</sub> was critical and that the replacement of the hydroxyl with an oxo group in compound 298 resulted in an increase in activity. An optimal acyl chain length (C<sub>9</sub>–C<sub>11</sub>) preserved activity as compared to shorter acyl chains, but the decrease in activity with longer acyl chains may be explained by low water solubility and low bioavailability. Furthermore, analogue 300 was less active than 44, indicating that aromaticity in ring B was also important for activity.

To further elucidate the SAR for antitumor activity, Pettit and co-workers studied<sup>499</sup> methylation and demethylation of aptamine. O-Demethylation led to an increase in antitumor activity; for example, 9-demethyaptamine (295) ( $ED_{50}$  0.85  $\mu$ M against P388) and diphenol (296) ( $ED_{50}$  0.61  $\mu$ M against P-388) were more potent inhibitors than aptamine (43) itself. Methylation at N-4 led to inactive derivatives 299 ( $ED_{50}$  > 25  $\mu$ M) that showed potent antiviral activity against herpes simplex virus type 1 (HSV-1) and low toxicity in Vero cells. Interestingly, the quaternary ammonium salts 304 and 305 exhibited significant inhibitory activity against the murine P388 lymphocytic leukemia cell line ( $ED_{50}$  8.2 and 0.59  $\mu$ M, respectively) and human cancer cell lines. On the basis of these findings, Pettit and co-workers<sup>500</sup> synthesized the aptamine-based quaternary salts 306 (hystatin 2) and 307, which exhibited significant cell growth inhibitory activity against the murine P388 lymphocytic leukemia cell line ( $ED_{50}$  0.57 and 2.77  $\mu$ M, respectively) and a minipanel of human cancer cell lines. The quaternary salts 306 and 307 inhibited PKC catalytic activity in the range of 71–85% at 30 fM and blocked the S-phase of the cell cycle. In addition, these salts had broad-spectrum antimicrobial activities, and salt 306 was selected for further development. Introduction of a benzyl or para-substituted benzyl group at one or both of the nitrogen positions increased activity. Recently, Gul and co-workers<sup>501</sup>

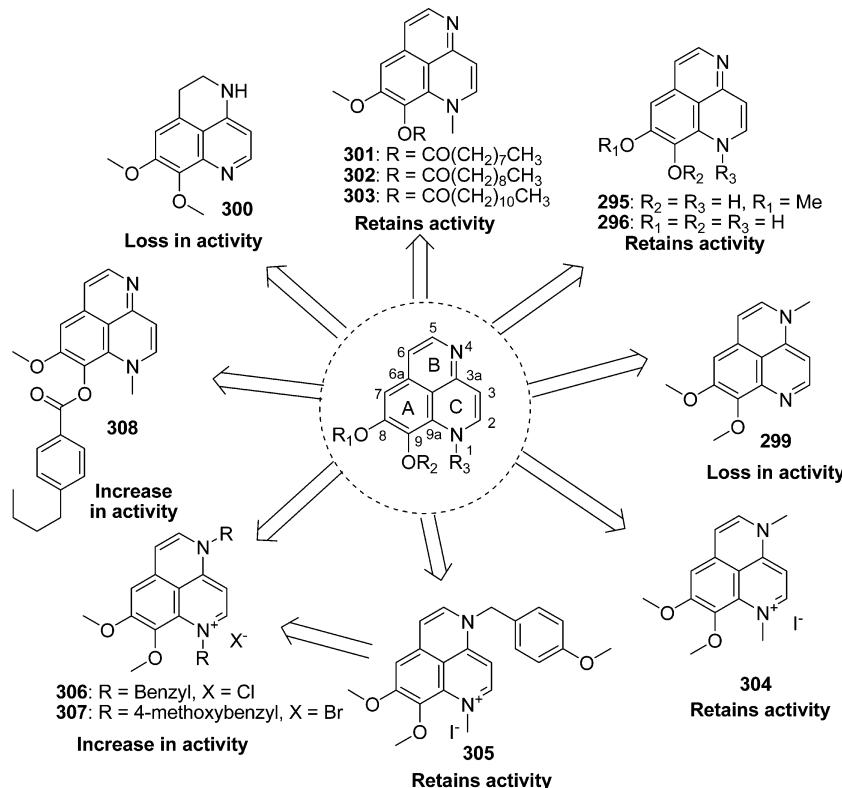


Figure 24. SAR of aaptamine.

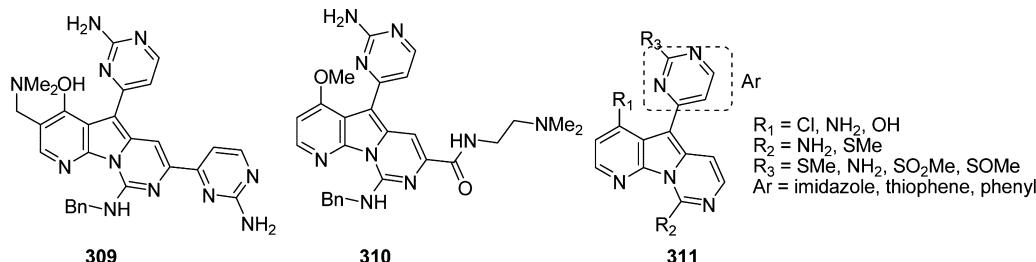


Figure 25. Lead candidates based on variolin scaffold.

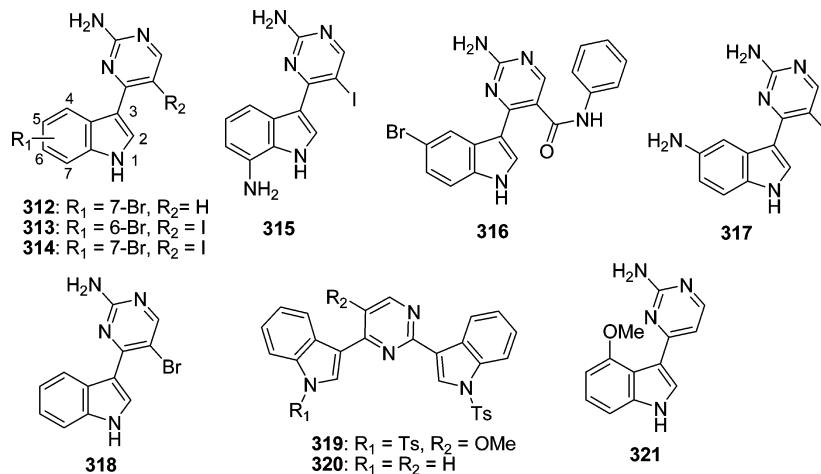
synthesized analogues containing benzoyl esters at the C<sub>9</sub> position of isoaaaptamine, among which compound 308 exhibited an EC<sub>50</sub> of 0.05 μM against the leukemia cell line K-562, demonstrating that substitution of a phenyl ester moiety was more effective than the acylation previously reported by Shen and co-workers.<sup>183</sup>

Initially aaptamine and its congeners were reported to act via PKC inhibition (IC<sub>50</sub> 100–200 nM),<sup>497</sup> but proteasome inhibitory activities have also been reported recently. However, their cytotoxicity did not correlate with their potency as inhibitors. The interesting biological profile of natural and semisynthetic naphthyridine derivatives suggests that these molecules represent another important marine-based scaffold that requires further exploration for lead optimization. The SAR of aaptamine is depicted in Figure 24.

### 5.3. Variolins, Meridianins, and Meriolins

**5.3.1. Variolins.** As discussed previously, variolins were isolated from a rare Antarctic sponge. Among various natural variolins, variolin B exhibited potent anticancer activity in P388 murine leukemia cells. The interesting biological profile and low natural occurrence of variolins<sup>502</sup> limited their further

biological exploration. Because of their limited availability from biological materials and the unique skeleton of variolins, a lot of effort has been devoted to their chemical synthesis. To date, four total syntheses of variolin B have been reported.<sup>77,503–509</sup> The Spanish pharmaceutical company PharmaMar, in collaboration with D’Incalci et al.,<sup>211</sup> synthesized variolin B (77) and deoxyvariolin B (78) and studied<sup>211</sup> their biological properties, revealing that both possess IC<sub>50</sub> values of 50–100 nM against a variety of cell lines. Studies to identify the molecular target revealed that variolins B and deoxyvariolins B inhibited the phosphorylation of histone H1 mediated by CDK-2/cyclin E, CDK-2/cyclin A, CDK-1/cyclin B, CDK-7/cyclin H, and CDK-4/cyclin D, with preferential inhibition of CDK-1 and CDK-2 over CDK-4 and CDK-7.<sup>211</sup> PharmaMar performed preclinical investigations on variolins and deoxyvariolin B<sup>510–512</sup> and selected deoxyvariolin B for further development due to its favorable physicochemical properties. Meijer and co-workers<sup>513,514</sup> confirmed the inhibition of the CDKs and also reported the inhibition of CDK-9 (IC<sub>50</sub> 26 nM) by variolin B. In addition, inhibition of several other kinases was reported, including CK-1, FMS-like tyrosine kinase 3, and GSK-3. On the basis of the SAR results of the initial screen, a medicinal



**Figure 26.** Lead candidates based on meridianin scaffold.

chemistry program was initiated by PharmaMar in collaboration with Molina and Fresneda, and 16 novel analogues with different substituents at positions C-5 and C-7 were synthesized and tested against a panel of 16 tumor cell lines.<sup>515</sup> From this study, two derivatives, 309 and 310, were identified that displayed activity similar to that of natural variolin B. Derivative 309 contained a (dimethylamino)methyl amino alkyl chain at C-3 and 3-aminopyrimidine at position C-7, as well as 3-aminopyridine at position C-5. Derivative 310 contained 2-(dimethylamino)ethyl carboxamide at C-7 and 3-aminopyridine at C-5. PharmaMar<sup>511,516</sup> discovered a series of variolin analogue with general structure 311 that showed potent cytotoxicity against a panel of colon, breast, melanoma, lung, ovary, cervix, kidney, pancreas, and endothelium cell lines, with GI<sub>50</sub> in the micromolar to nanomolar range. The structures of variolin analogues are shown in Figure 25.

**5.3.2. Meridianins.** Meijer and co-workers<sup>212,214</sup> observed that molecules of the meridianin family possessed cytotoxic properties as well as the ability to inhibit several protein kinases, including CDK-1, GSK-3, and protein kinase A. On the basis of the structural diversity of natural meridianins, an initial SAR could be established. The unsubstituted meridianin G (87, IC<sub>50</sub> 150 μM for CDK-1) was only weakly inhibitory, while a single bromine substitution at the 5- or 6-position of the indole ring (meridianin C (83, IC<sub>50</sub> 3 μM for CDK-1) and D (84, IC<sub>50</sub> 13 μM for CDK-1), respectively) resulted in considerable improvements in potency, with up to 1000-fold decreases in IC<sub>50</sub> observed in favorable cases. Interestingly, in meridianin F (86, IC<sub>50</sub> 20 μM for CDK-1), the presence of bromine atoms at both the 5- and the 6-positions resulted in improved potency relative to meridianin G (87) but decreased potency as compared to either monobrominated meridianin C (83) or D (84).<sup>77</sup> Substitution of a hydroxyl group for hydrogen at the indole 4-position, as in meridianin A (81, IC<sub>50</sub> 2.5 μM for CDK-1), resulted in smaller improvements in potency, while a bromine at 7-position and a hydroxyl group at the 4-position in meridianin E (85, IC<sub>50</sub> 0.18 μM for CDK-1) resulted in the most potent compounds, which had IC<sub>50</sub> values in the nanomolar range.

Because of the promising biological activity profile of meridianins, several synthetic protocols have been reported. Fresneda and co-workers (2000)<sup>517</sup> were the first to report the synthesis of meridianins, which was followed by the development of a large number of synthetic routes for these molecules.

To date, there are 20 reports on the synthesis of meridianins and its analogues/derivatives that have been published.<sup>517–536</sup> Synthetic meridianins have been prepared with varying substituents, mainly on the pyrimidine ring. Moreu et al.<sup>530,536</sup> identified analogues 312–314, which exhibited 45-fold selectivity toward Dyrk-1A and CLK-1 kinases over other kinases. The compound 313 potently inhibited Dyrk-1A and CLK-1 kinases, with IC<sub>50</sub> values of 34 and 32 nM, respectively. Although less number of compounds were active toward other tested kinases (CDK-5, CK-1, GSK-3), few compounds displayed good IC<sub>50</sub> values against other kinases. These include compounds 315 (CLK-1: 26 nM; CDK-5: 660 nM), 316 (GSK: 400 nM), and 317 (CK-1: 270 nM). Analogue 313 displayed good antiproliferative activity in all cell lines. Giraud et al.<sup>536</sup> studied the binding mode and orientation of the potent meridianin analogue 312 against Dyrk-1A and CLK-1 using molecular docking studies of the respective available PDB structures, 2WO6 and 1Z57. Rossignol et al. (2008)<sup>537</sup> evaluated a series of synthetic meridianin analogues against different kinases, including KDR, IGF-1R, c-Met, Ret, c-Src, c-Abl, PKA, CDK-2/A, and HER-1, and three cell lines, fibro, MCF-7, and PA1. Among the tested analogues, compound 318 exhibited good activity, inhibiting KDR, IGF-1R, C-Abl, PKA, and CDK-2 with IC<sub>50</sub> values of 1.1, 3.1, 7.8, 2.5, and 5.9 μM, respectively. The same group of researchers also evaluated meridianin G and its bromo derivative 318 against several other kinases including MKK-1, ERK-2, RSK-2, PKC-α, GSK-3β, CDK-2/A, CK-2, and MST-2. Meridianin G displayed 66%, 36%, 9%, 56%, 43%, 54%, 38%, and 31% inhibition of these kinases at 10 μM, whereas the bromo derivative 318 displayed 98%, 92%, 85%, 91%, 87%, 85%, 93%, and 96% inhibition at 10 μM, respectively.<sup>526</sup> The bisindolyl pyrimidine 319 exhibited significant inhibitory activity against leukemia SR, CNS cancer SF-539, and breast cancer MDA-MB-435 cell lines, with GI<sub>50</sub> values of 0.22, 0.16, and 0.22 μM, respectively. Another bisindolyl pyrimidine 320 displayed strong selective cytotoxic activity against the IGROV1 tumor cell line with GI<sub>50</sub> values below 0.01 μM.<sup>520</sup> Recently, Lebar et al. (2011)<sup>538</sup> reported the antimarial and CNS activity of a series of meridianin analogues. Meridianin A (81) and 4-methoxy analogue of meridianin A (321) inhibited *Plasmodium falciparum* with IC<sub>50</sub> values of 12 and 40 μM, respectively. Compounds 81 and 321 also showed good binding to the 5-HT2B receptor, with *k<sub>i</sub>* values of 0.15 and 0.088 μM,

respectively. The chemical structures of the synthetic meridianins are shown in Figure 26.

**5.3.3. Meriolins.** The resemblance between the chemical structures of meridianins and variolin B inspired the discovery of 7-azaindoles, a hybrid structure referred to as meriolins by Meijer and co-workers that displayed potent inhibitory activity toward CDKs with marked potency for CDK-2 and CDK-9.<sup>513,514</sup> This class of compounds (meriolins 1–14, 322–335, Figure 27) exhibited better antiproliferative and proapoptotic

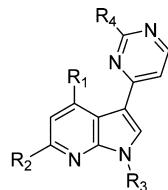
two mouse xenograft cancer models (Ewing sarcoma and LS174T colorectal carcinoma), meriolin 3 (324) exhibited potent *in vivo* activity. These results suggest that meriolins constitute a new CDK inhibitory scaffold with promising antitumor activity.

#### 5.4. Fascaplysin

Fascaplysin (89) and its natural analogues have been synthesized by several researchers, and more than 10 syntheses have been reported.<sup>539–548</sup> Because fascaplysin (89) has a flat structure and intercalates with DNA,<sup>549</sup> extensive medicinal chemistry efforts toward the discovery of nontoxic and selective fascaplysin-based nonplanar CDK-4 inhibitors have been reported.<sup>550–558</sup> A series of 1,3-linked bis-indoles, 1,1-linked bis-indoles, a tryptamine class of synthetic analogues, and N-substituted  $\beta$ -carboline class of fascaplysin-inspired analogues have been synthesized. Among these, analogue CA224 (336) displayed an IC<sub>50</sub> of 6.2  $\mu$ M against CDK-4/D1 and 84-fold selectivity over CDK-2/cyclin A.<sup>552–554</sup> On the basis of the CDK-4 homology model, analogue 336 was predicted to be located in the ATP binding site in a fashion similar to fascaplysin (89) but with a double H-bonding interaction with the backbone of His 95/Val 96 and an extra stabilization by  $\pi$ - $\pi$  stacking interaction between the biphenyl moiety of the ligand and the side chains of Phe 93 and Phe 159.<sup>554</sup> Like the tryptamine analogue 336, the biphenyl ring containing N-substituted  $\beta$ -carboline 337 was most potent, with a CDK-4 IC<sub>50</sub> of 9  $\mu$ M and 82-fold selectivity over CDK-2. The C-linked  $\beta$ -carboline 338 also showed good selectivity for CDK-4. Compound 338 exhibited 74-fold selectivity for CDK-4 over CDK-2.<sup>556</sup> Recently, we discovered anticholinesterase activity of fascaplysin (IC<sub>50</sub> 1.49  $\mu$ M).<sup>546</sup> The structures of fascaplysin-inspired synthetic CDK-4 inhibitors are shown in Figure 29.

#### 5.5. Indirubins

Several synthetic analogues of indirubins have been discovered as potent GSK-3 inhibitors, including analogues 339–346, among which 339 and 341 inhibited GSK-3 with IC<sub>50</sub> values of 0.005 and 0.022  $\mu$ M, respectively. The molecular geometry of GSK-3 $\beta$  inhibition by 339 was determined by a cocrystallization X-ray study.<sup>559</sup> The N-methyl indirubin, meisoindigo (340), a debromo derivative of 6-bromoindirubin, showed significant activity against cancer cells via CDK inhibition. Meisoindigo (340) induces cell differentiation, promotes apoptosis, arrests cells in the G0/G1 phase of the cell cycle, and inhibits tumor growth in HT-29 colon cancer xenografts



- 322 (Meriolin 1): R<sub>1</sub> = R<sub>2</sub> = R<sub>3</sub> = H, R<sub>4</sub> = NH<sub>2</sub>
- 323 (Meriolin 2): R<sub>1</sub> = OH, R<sub>2</sub> = R<sub>3</sub> = H, R<sub>4</sub> = NH<sub>2</sub>
- 324 (Meriolin 3): R<sub>1</sub> = OMe, R<sub>2</sub> = R<sub>3</sub> = H, R<sub>4</sub> = NH<sub>2</sub>
- 325 (Meriolin 4): R<sub>1</sub> = OEt, R<sub>2</sub> = R<sub>3</sub> = H, R<sub>4</sub> = NH<sub>2</sub>
- 326 (Meriolin 5): R<sub>1</sub> = OPr, R<sub>2</sub> = R<sub>3</sub> = H, R<sub>4</sub> = NH<sub>2</sub>
- 327 (Meriolin 6): R<sub>1</sub> = OiPr, R<sub>2</sub> = R<sub>3</sub> = H, R<sub>4</sub> = NH<sub>2</sub>
- 328 (Meriolin 7): R<sub>1</sub> = O(CH<sub>2</sub>)<sub>2</sub>OMe, R<sub>2</sub> = R<sub>3</sub> = H, R<sub>4</sub> = NH<sub>2</sub>
- 329 (Meriolin 8): R<sub>1</sub> = OH, R<sub>2</sub> = H, R<sub>3</sub> = Me, R<sub>4</sub> = NH<sub>2</sub>
- 330 (Meriolin 9): R<sub>1</sub> = OMe, R<sub>2</sub> = H, R<sub>3</sub> = Me, R<sub>4</sub> = NH<sub>2</sub>
- 331 (Meriolin 10): R<sub>1</sub> = Cl, R<sub>2</sub> = R<sub>3</sub> = H, R<sub>4</sub> = NH<sub>2</sub>
- 332 (Meriolin 11): R<sub>1</sub> = H, R<sub>2</sub> = Br, R<sub>3</sub> = H, R<sub>4</sub> = NH<sub>2</sub>
- 333 (Meriolin 12): R<sub>1</sub> = OMe, R<sub>2</sub> = R<sub>3</sub> = H, R<sub>4</sub> = SMe
- 334 (Meriolin 13): R<sub>1</sub> = OH, R<sub>2</sub> = R<sub>3</sub> = R<sub>4</sub> = H
- 335 (Meriolin 14): R<sub>1</sub> = OMe, R<sub>2</sub> = R<sub>3</sub> = R<sub>4</sub> = H

Figure 27. Structures of synthetic meriolins.

properties in cell cultures than their inspirational parent molecules. Meriolin 3 (324) and meriolin 5 (326), which have an alkoxy group at position 4 of the 7-azaindole ring, exhibited cytotoxicity and cyclin-dependent kinase IC<sub>50</sub> values in the nanomolar range.

The crystal structures of meriolin 5 and variolin B with CDK-2/A demonstrated that these two inhibitors bind within the ATP binding site of the kinase in different orientations, as shown in Figure 28. The observed difference in orientation in the CDK-2 binding site is significant, as a selectivity study showed that meriolins display enhanced specificity toward CDKs as compared to variolin B. Interestingly, meriolins showed better antiproliferative and pro-apoptotic activity in human tumor cell lines than their parent natural products. In

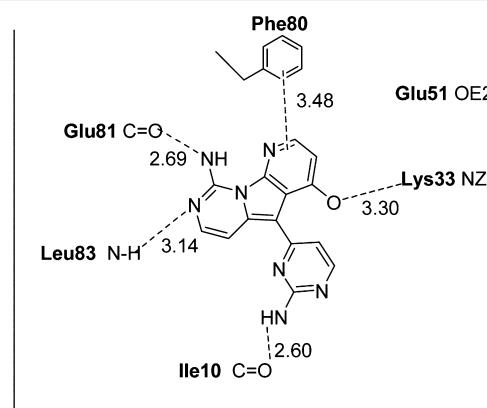
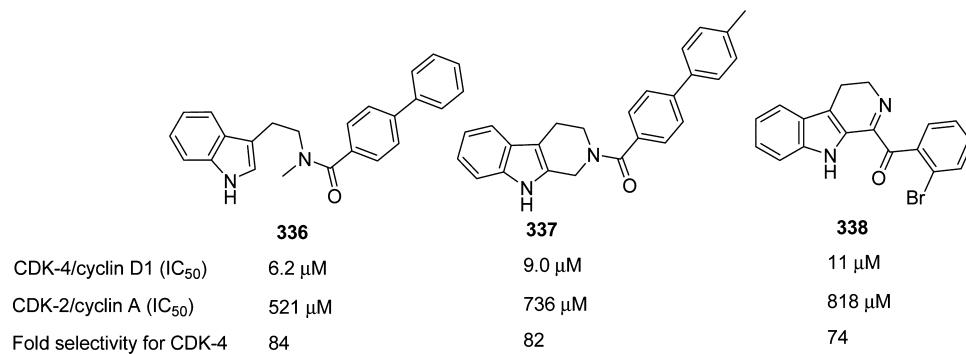
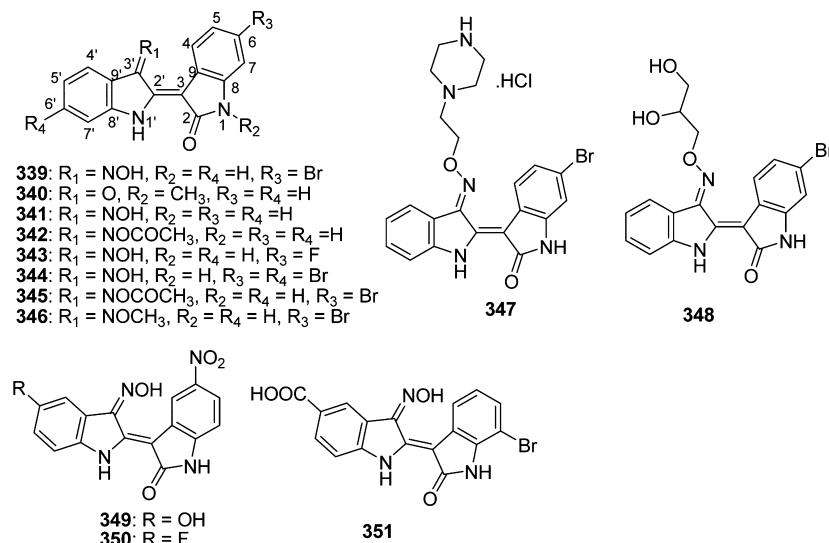


Figure 28. Interactions of meriolin 5 (326) and valiolin B (77) with CDK-2/cyclin A. Distances (Å) between the donor and acceptor atoms are shown.

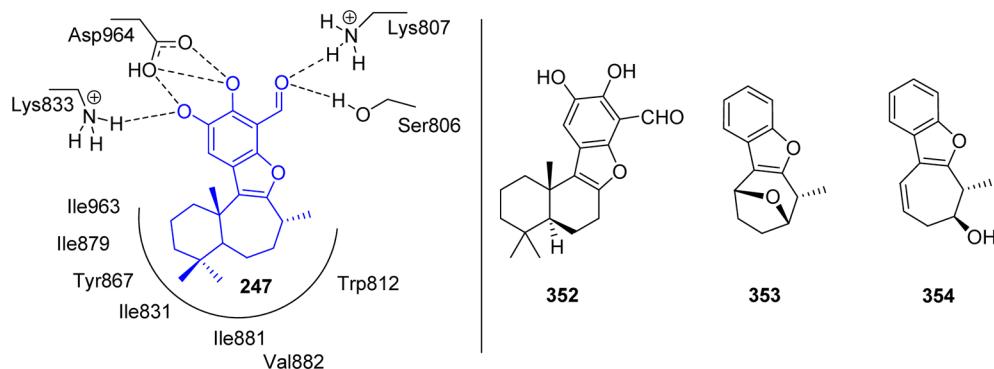
**Figure 29.** Fascaplysin-inspired synthetic analogues as CDK-4 inhibitors.**Figure 30.** Lead candidates based on indirubin scaffold.

(100 mg/kg, i.p.). Meisoindigo was developed to increase the solubility in water and reduce the side effects of indirubin. Meisoindigo is undergoing a phase III clinical trial in China for the treatment of chronic myelogenous leukemia (CML).<sup>560–563</sup> Another compound, 6-bromoindirubin-3-oxime (339, 6-BIO), has been extensively studied for its ability to activate the Wnt/ $\beta$ -catenin signaling pathway, and extensive patent literature is available on its role in stem cell differentiation as well as for the treatment of various neurodegenerative diseases and cancer.<sup>258,564–581</sup> The use of the GSK-3 inhibitor 6-BIO to induce immune tolerance in patients with systemic lupus erythematosus, diabetes mellitus, asthma, and arthritis via activation of the E-cadherin/ $\beta$ -catenin pathway in dendritic cells has also been patented.<sup>257</sup> Several patents exist on the role of GSK-3 inhibitors (e.g., 6-bromoindirubin-3-oxime 339 and staurosporine) in the treatment of Alzheimer's disease. This class of compounds act via inhibition of amyloid- $\beta$  production and tau phosphorylation.<sup>582</sup> Researchers from CNRS<sup>583</sup> have patented 3'- and 7-substituted indirubin analogues 341–343, which inhibit GSK-3 and CDK-5/1 for their potential development as antitumor agents. The same group<sup>584,585</sup> has patented 3',6'-substituted indirubins for the treatment of Alzheimers disease, diabetes, and heart hypertrophy. The  $IC_{50}$  values for compound 339 (6-BIO) and the oxime-substituted analogues 347 and 348 were 0.005, 0.0013, and 0.034  $\mu$ M for GSK-3 and 0.083, 0.18, and 0.025  $\mu$ M for CDK-5, respectively.<sup>586</sup> The indirubin derivative meisoindigo (340) also showed the effect on activity

of PI3K component in insulin signal conducting passage. Meisoindigo also activated Akt and inhibited mTOR to promote the transfer of the insulin signal and sensitize the peripheral tissue in utilizing insulin. Thus, the indirubin derivative meisoindigo (340) has potential as a treatment for type II diabetes.<sup>587</sup> Medicinal chemistry efforts by Kim and co-workers<sup>588</sup> identified the 5-nitro-5'-hydroxy indirubin analogue 349 and the 5-nitro-5'-fluoro indirubin analogue 350, which exhibit potent CDK-2 inhibitory activity with  $IC_{50}$  values of 1.9 and 1.7 nM, respectively. These derivatives also showed antiproliferative activity against several human cancer cell lines with  $IC_{50}$  values of 0.2–3.3  $\mu$ M. Analogue 349 showed greater than 500-fold selectivity for CDK relative to a selected kinase panel, as well as potent *in vivo* anticancer activity. Recently, Skaltsounis and co-workers<sup>589</sup> identified indirubin analogue 351, which exhibits potent inhibition of Dyk-1A and Dyk-2, with  $IC_{50}$  values of 0.21 and 0.13  $\mu$ M, respectively. The structures of the synthetic indirubin analogues are shown in Figure 30.

### 5.6. Liphagal

Liphagal (247), a tetracyclic meroterpenoid natural product, was isolated by Andersen and co-workers in 2006 from the Caribbean sponge *Aka coralliphaga*, during a program to discover new inhibitors of the PI3K signaling pathway.<sup>406</sup> The PI3K is the most frequently activated signaling pathway in cancer, and the PI3K- $\alpha$  isoform has been found to be activated by mutation in several cancers as the most frequently mutated



**Figure 31.** Structure of liphagal (247) and its analogues 352–354. Interaction map of liphagal with PI3K is also shown.

**Table 5. Clinical Status of Marine-Derived Small-Molecule Drug Candidates (Multiple Mechanisms of Action)<sup>a</sup>**

sr. no.	compound name	marine organism	chemical class	company or institution	disease area	current status
1	cytarabine, ara-C (cytosar-U)	sponge	nucleoside	Bedford, Enzon	cancer	approved (1969)
2	vidarabine, ara-A (vira-A)	sponge	nucleoside	King Pharmaceuticals	antiviral	approved (1976)
3	ziconotide (prialt)	cone snail	peptide	Elan Corp.	pain	approved (2004)
4	omega-3-acid ethyl esters (lovaza, omacor)	fish	omega-3 fatty acids	GlaxoSmithKline	hyper-triglyceridemia	approved (2004)
5	trabectedin (ET-743, yondelis) (EU registered only)	tunicate	alkaloid	PharmaMar	cancer	approved (2007)
6	eribulin mesylate (E7389) (halaven)	sponge	macrolide	Eisai Inc.	cancer	approved (2010)
7	plitidepsin (aplidin)	tunicate	depsipeptide	PharmaMar	cancer	phase III
8	sobolidin (TZT 1027, auristatin PE)	synthetic derivative of dolastatin 10	peptide	Aska Pharmaceuticals Daiichi Sankyo Inc.	cancer	phase III
9	DMXBA (GTS-21)	worm	alkaloid	Comentis	cognition schizophrenia	phase II
10	plinabulin (NPI-2358)	fungus	diketopiperazine	Nereus Pharmaceuticals	cancer	phase II
11	plitidepsin	tunicate	depsipeptide	PharmaMar	cancer	phase II
12	elisidepsin	mollusc	depsipeptide	PharmaMar	cancer	phase II
13	PM1004 (zalypsis)	nudibranch	alkaloid	PharmaMar	cancer	phase II
14	tasidotin, synthadotin (ILX-651)	synthetic derivative of dolastatin 15	peptide	Genzyme Corp.	cancer	phase II
15	pseudopterosins	soft coral	diterpene glycoside	University of Prince Edward Island, Canada	wound healing	phase II
16	bryostatin -1	bryozoa	polyketide	National Cancer Institute	cancer	phase I
17	hemiasterlin (E7974)	sponge	tripeptide	Eisai Inc.	cancer	phase I
18	marizomib (dalinosporamide A; NPI-0052)	bacterium	$\beta$ -lactone- $\gamma$ -lactam	Nereus Pharmaceuticals	cancer	phase I

<sup>a</sup>This table is compiled using the information published in refs 53, 599, and 600.

kinase in the human genome. The inhibitory activity of liphagal (**247**) was noteworthy due to its selective inhibition of the PI3K- $\alpha$  isoform, which plays a central role in several cancers. Liphagal showed selective and potent inhibition of PI3K- $\alpha$  with an IC<sub>50</sub> of 100 nM and 10-fold selectivity toward PI3K- $\alpha$  versus PI3K- $\gamma$ . In addition, liphagal was cytotoxic to LoVo (human colon, IC<sub>50</sub> 0.58  $\mu$ M), Caco-2 (human colon, IC<sub>50</sub> 0.67  $\mu$ M), and MDA-468 (human breast, IC<sub>50</sub> 1.58  $\mu$ M) cells in secondary *in vitro* cell assays and has emerged as an important scaffold for the development of selective kinase inhibitors as clinical candidates. The interesting biological profile and complex tetracyclic skeleton have attracted significant attention, and eight syntheses have been reported so far.<sup>406,590–596</sup>

Andersen and co-workers<sup>406,407</sup> synthesized desformyl, desmethyl, and spirolipagal analogues enabling SAR analysis

of the liphagal scaffold and its liabilities. The key structural features of the scaffold are the catechol and aldehyde functionalities that are present in the natural product. Efforts toward more potent, stable, and selective analogues have been initiated; for example, Pereira et al.<sup>590</sup> synthesized a library of 12 liphagal analogues and showed that the catechol and aldehyde functionalities on the benzofuran scaffold were required for potency and PI3K- $\alpha$  isoform selectivity.<sup>590</sup> Furthermore, the importance of the formyl group and the gem-methyl group to the potency and selectivity of liphagal was indicated by the work of Andersen et al.,<sup>407</sup> who showed that desformyl liphagal (IC<sub>50</sub> 250 nM), desmethyl liphagal (IC<sub>50</sub> 600 nM), and spirolipagal (IC<sub>50</sub> 600 nM) have decreased potency relative to liphagal.<sup>407</sup> On the basis of these findings, Pereira and co-workers<sup>590</sup> synthesized a more potent ring B contracted

**Table 6.** Preclinical and Clinical Status of Marine-Derived Kinase Inhibitors

compound name (trademark)	target	marine source	chemical class	company or institution	therapeutic area	status	refs
plitidepsin (Aplidin, 140) <sup>277</sup>	EGFR, Src, JNK, and p38 MAPK	tunicate	depsipeptide	PharmaMar	cancer	phase III	600–602
midostaurin (277)	Flt-3, PKC, VEGFRs	ascidian; semisynthetic analogue of 1	indolocarbazole	National Cancer Institute	cancer	phase III	600,603
meisoindigo (338)	CDK	mollusc; semisynthetic analogue of 119	indole	Cooperative Study Group of phase III Clinical Trial on Meisoindigo	cancer	phase III	560–563,604
lestaurtinib (CEP-701, 281)	Flt-3, JAK-2, Trk-A, Trk-B, and Trk-C	ascidian; synthetic analogue of 1	indolocarbazole	National Cancer Institute	cancer	phase III; received orphan drug status for AML (FDA, 2007)	485,600,605–611
edotecarin (J-107088, 285)	not inhibitor of protein kinases <sup>a</sup>	ascidian; synthetic analogue of 1	indolocarbazole	Pfizer	cancer	phase III	600,612,613
enzastaurin (LY317615, 294) <sup>286</sup>	PKC $\beta$ , GSK-3 $\beta$ not inhibitor of protein kinases <sup>a</sup>	ascidian; synthetic analogue of 1	indolocarbazole	Eli Lilly	cancer	phase III; orphan drug status for diffuse large B-cell lymphoma (EMEA, 2007)	614
bevacatin (XL119, 286)	PKC	ascidian; synthetic analogue of 1	indolocarbazole	National Cancer Institute	cancer	phase II/III	600,615–626
UCN-01 (4)		ascidian; synthetic analogue of 1	indolocarbazole	National Cancer Institute	cancer	phase II	600,627,628
kahalalide F (196) CEP-2563 (283, produng of CEP-751) CEP-1347 (KT7515, 287)	Erb-B2, PI3K/Akt Trk-A, Trk-B, Trk-C JNKs	sea slug ascidian; synthetic analogue of 1	tridecapeptide indolocarbazole	PharmaMar Cephalon	cancer	phase II	629
isokahalalide F (PM02734, elisidepsin)	ErbB2	sea slug	indolocarbazole	Cephalon	cancer	phase II	630
stauroporine (AM- 2282, 1) <sup>277</sup>	PKC, JAK2, CamKII	ascidian	tridecapeptide	PharmaMar	Parkinsons	phase II	600
variolin B (PM-01220, 77)	CDK-1, CDK-2	sponge	pyrrolo- pyrimidine bisindole	Kyowa Hakko Kirin (originator)	cancer	preclinical	464,465
fascaplysin (89)	CDK-4	sponge		Cornell University, University of Utah	cancer	preclinical	510–512
							231

<sup>a</sup>Edotecarin and bevacatin are staurosporine analogues, but they do not inhibit protein kinases. They are potent stabilizers of DNA topoisomerases.

analogue **352** ( $IC_{50}$  66 nM against PI3K- $\alpha$  and 1840 nM against PI3K- $\gamma$ ), which exhibited a 27-fold preference for PI3K- $\alpha$  and enhanced chemical stability/selectivity as compared to the natural product. Recently, Zhang and co-workers<sup>593</sup> evaluated the binding of liphagal with the target protein (PI3K) computationally and identified key interactions. The simplified tricyclic scaffolds **353** and **354** were designed but have not yet been validated. We recently discovered a new boronic acid analogue of liphagal as a potent PI3k- $\alpha$  inhibitor.<sup>597</sup> The structures of liphagal and its analogues and the interaction of liphagal with the PI3K active site are shown in Figure 31.

## 6. PRECLINICAL AND CLINICAL CANDIDATES

In the past decade, a number of new experimental anticancer agents derived from marine sources have entered preclinical and clinical trials. For example, 592 NCEs based on marine natural product scaffolds are currently in preclinical phase for various cancers, as are 666 NCEs for other therapeutic areas such as bacterial and viral infections, inflammation, etc.<sup>53,54,598</sup> Currently, there are five FDA-approved marine or marine-derived drugs (cytarabine, vidarabine, ziconotide, eribulin mesylate, omega-3-fatty acid esters) on the market, in addition to an additional drug registered in the EU (Trabectedin). In addition to these approved candidates, the current marine-derived clinical pipeline includes 12 molecules in various phases of clinical development as shown in Table 5.<sup>53</sup>

In the kinase inhibitor portfolio, several marine-derived kinase inhibitors are currently under different phases of clinical development. In 2006, the FDA granted orphan drug status to lestaurtinib for the treatment of acute myeloid leukemia (AML), and in 2007, European Medicines Agency (EMEA) granted orphan drug status to enzastaurin for the treatment of diffuse large B-cell lymphoma. This suggests the potential of marine-based kinase inhibitors as a continued source of new drug candidates in future. Among the promising candidates, the majority of the candidates are derived from staurosporine scaffold. Staurosporine (**1**) itself was too toxic for clinical development; however, several of its analogues exhibited improved toxicity profiles and have advanced to various stages of clinical development. The staurosporine analogues that are currently in active development are midostaurin (**277**), lestaurtinib (**281**), CEP-2563 (**283**), edotecarin (**285**), becatecarin (**286**), UCN-01 (**4**), CEP-1347 (**287**), and enzastaurin (**294**). A list of marine-derived kinase inhibitors that have entered clinical trials is shown in Table 6. The preclinical data and results of clinical studies for selected and most promising clinical candidates are discussed below.

### 6.1. Pharmacokinetics and Pharmacological Profile of Most Promising Clinical Candidates

**6.1.1. Aplidin (140).** Aplidin (**140**), a cyclic depsipeptide also known as a second-generation didemnin, was being developed by the Spanish company PharmaMar. In the *in vitro* investigations, aplidin showed induction of apoptosis in human cancer cells via glutathione depletion and sustained activation of the EGFR, Src, JNK, and p38 MAPK.<sup>284</sup> Further, it showed dual effect on the human SK-MEL-28 and UACC-257 melanoma cell lines at 45 nM and also inhibited the cell cycle by inducing G1 and G2/M arrest, whereas at higher concentrations it induced apoptosis. It activated Rac1 GTPase and c-Jun NH<sub>2</sub>-terminal kinase (JNK) and also induced AKT and p38MAPK phosphorylation.<sup>633</sup> Didemnin (didemnin B)

was the first ascidiacea cytotoxin but exhibited dose-limiting toxicities (DLTs) during a phase II study and was withdrawn from clinical trials. By contrast, aplidin showed a unique cytotoxic profile and more potent activity against a broad spectrum of cancer types, such as melanomas and nonsmall-cell lung, prostate, ovarian, and colorectal cancers with  $IC_{50}$  values of 0.18–0.45 nM. Aplidin exhibited potent *in vitro* activity against primary multiple myeloma tumor cells and a broad spectrum of human multiple myeloma cell lines, including cells resistant to conventional (e.g., dexamethasone, alkylating agents, and anthracyclines) or novel (e.g., thalidomide and bortezomib) antimultiple myeloma agents. Aplidin suppressed a group of proliferative/antiapoptotic genes (e.g., Myc, Mybl2, Bub1, Mcm2, Mcm4, Mcm5, and survivin) and showed up-regulation of several potential regulators of apoptosis (including c-Jun, Trail, Casp9, and Smac). The cytotoxic activity of aplidin in CLL is mediated by a direct effect on leukemic cells and an indirect effect on monocyte-derived cells.<sup>634</sup> Aplidin exhibited *in vivo* antimyeloma activity in a mouse xenograft model with favorable toxicity profile. A delay in tumor growth and prolongation of survival in aplidin-treated multiple myeloma-bearing mice was observed.<sup>635,636</sup> Aplidin also showed *in vivo* activity in *Gata1<sup>low</sup>* myelofibrosis mouse model. Aplidin-treatment prevented development of myelofibrosis by partially restoring progenitor cell and microenvironmental functions in the marrow of the mice.<sup>637</sup> Aplidin showed synergistic effects with Ara-C<sup>638</sup> and rituximab<sup>639</sup> in both *in vitro* as well as *in vivo* models. Addition of low-dose aplidin to Ara-C resulted in significant reduction in tumor size in CCRF-CEM and SK-DLCL xenograft models.<sup>638</sup> Aplidin also showed antitumor and antiangiogenic effects in the STMM syngeneic models of multiple myeloma.<sup>640</sup>

The PK of aplidin was investigated in several phase I trials.<sup>602,641–643</sup> The phase I study<sup>642</sup> of aplidin in children with advanced solid tumors indicated that aplidin treatment was beneficial with manageable toxicity, and the recommended dose was 5 mg/m<sup>2</sup>. In preclinical PK studies,<sup>644</sup> no bone marrow toxicity was observed in experimental models, and the MTDs in the mouse and rat were 3.75 and 3.42 g/m<sup>2</sup>/mo, respectively. Aplidin displayed rapid clearance in rats, and its antitumor activity in mice bearing human xenografts was maximal when the drug was administered by continuous intravenous infusion or via the intraperitoneal route. A phase I trial was conducted to determine the MTD and recommended dose of aplidin, to describe the DLTs, to assess its PK profile, and to document any antitumor activity in patients with advanced malignancies.<sup>643</sup> Sixty-seven patients received aplidin at a dose ranging from 0.2 to 8 mg/m<sup>2</sup>. Dose-limiting myotoxicity and muscle weakness occurred in 2–6 patients; however, no cardiac toxicity was observed. Grade-3 muscle toxicity occurred in 3 of 14 patients at the recommended dose of 5 mg/m<sup>2</sup>. During the course of the study, patient plasma levels of aplidin were found to be lower than that expected from the animal PK data. Aplidin exhibited a long half-life (21–44 h), low clearance (45–49 L/h), and a high volume of distribution (1036–1124 L) with high interpatient variability in plasma; however, in whole blood, clearance ranged from 3.0 to 6.2 L/h. The recommended dose of aplidin was 5 and 7 mg/m<sup>2</sup> without and with carnitine, respectively. Several phase I and phase II studies were subsequently conducted that suggested the recommended dose and method of administration for aplidin is 5.0 mg/m<sup>2</sup> over a 3-h i.v. infusion every 2 weeks.<sup>641,645–650</sup> In phase II studies<sup>650,651</sup> in advanced or metastatic transitional cell

Table 7. Pharmacokinetics and Pharmacological Profile of Aplidin (140)

Chemical structure	
Other names	Plitidepsin
Source	Natural (Mediterranean tunicate <i>Aplidium albicans</i> )
Target kinase	P38MAPK, jNK, EGFR, Src
In vivo activity <sup>635,638</sup>	In a mouse xenograft model; Gata <sup>low</sup> myelofibrosis mouse model, 5TMM syngeneic models of multiple myeloma; synergistic effect with Ara-C
PK data <sup>601,642,643</sup>	<p><u>Phase I study</u> in advanced malignancies<sup>643</sup>  Dose: 0.2 to 8 mg/m<sup>2</sup> (i.v.)  PK parameters for plasma samples: C<sub>max</sub> 5.1-31.9 ng/ml; t<sub>1/2</sub> 21-44 h; AUC 148.1-1113.5 ng.h/ml; V<sub>ss</sub> 1036-1124 L; recommended dose 5 mg/m<sup>2</sup>.  PK parameters for whole blood samples: C<sub>max</sub> 75.2 -131.2 ng/ml; AUC 2446.5-5429.7 ng.h/ml; V<sub>ss</sub> 102.4 -144.6 L.</p> <p><u>Phase I PK study</u> in children with advanced solid tumors<sup>642</sup>  Dose 5 mg/m<sup>2</sup>; C<sub>max</sub> 22.3 ng/ml; AUC 282.7 ng.h/ml; CL 23 L/h/m<sup>2</sup>; V<sub>ss</sub> 628 L/m<sup>2</sup>; recommended dose 5 mg/m<sup>2</sup>.</p> <p><u>Phase II study</u> in relapsed/refractory multiple myeloma<sup>601</sup>  PK parameters for plasma samples: dose 5 mg/m<sup>2</sup> (i.v.); C<sub>max</sub> 29.10 ng/ml; t<sub>1/2</sub> 50.35 h; AUC 255.78 ng.h/ml; V<sub>ss</sub> 2053.15 L.  PK parameters for whole blood samples: dose 8.78 mg/m<sup>2</sup> (i.v.); C<sub>max</sub> 56.17 ng/ml; t<sub>1/2</sub> 44.38 h; AUC 874.68 ng.h/ml; V<sub>ss</sub> 491.91 L.</p>
Current status	Phase III trial in patients with relapsed/refractory multiple myeloma, being developed by PharmaMar (ClinicalTrial# NCT01102426)

carcinoma of the urothelium, and nonsmall cell lung cancer (NSCLC), aplidin did not show significant antitumor activity despite its favorable safety profile.

Because aplidin did not show any bone marrow toxicity, it was considered an ideal candidate to treat heavily pretreated multiple myeloma patients, who usually have a poor bone marrow reserve. PharmaMar conducted a phase II trial with the objective of evaluating the efficacy and safety of aplidin in relapsed/refractory multiple myeloma.<sup>601</sup> Aplidin alone and with dexamethasone was feasible, well tolerated, and showed a safe cardiac profile.<sup>652</sup> Currently, aplidin is being evaluated in a phase III randomized trial in patients with relapsed/refractory multiple myeloma. The PK and pharmacological profile of aplidin is shown in Table 7.

**6.1.2. Kahalalide F (196).** Kahalalide F is a C<sub>75</sub> cyclic tridecapeptide isolated from sea slug *Elysia rufescens* that inhibited ErbB-2 and suppressed tumors overexpressing ErbB-2 kinase. To date, 14 kahalalides have been isolated; however, only kahalalide F and isokahalalide F have been advanced to clinical studies.<sup>81</sup> Kahalalide F showed antitumor activities, both in transformed cell lines and in tumor specimens derived from a variety of solid human tumors.<sup>414,653-656</sup> It showed anti-proliferative effect on a panel of cancer cell lines, viz., NSCL (AS49, NCI-H322M), leukemia (RPMI-8226), colon (COLO-205, HCC-2998, HCT-15, HT-29, KM-12), ovarian (SK-OV-3), renal (ACHN), breast (HS578T), and prostate (PC-3, DU-145) cancers. Moreover, kahalalide F is effective against human prostate cancer xenografts in mouse models, and it is currently under distinct phases of clinical trials for the treatment of prostate cancer<sup>655</sup> and in patients with severe psoriasis. Although the molecular basis of the anticancer activity of

kahalalide F is not fully established, the permeabilization of the plasma membrane leading to oncosis,<sup>414,415</sup> alterations in lysosome morphology,<sup>657,658</sup> and inhibition of the ErbB-3 signaling pathways<sup>365,658,659</sup> are involved in the mechanisms of this activity. Furthermore, kahalalide F have also showed antimicrobial<sup>658</sup> and antileishmanial<sup>660</sup> activity. Albericio and co-workers<sup>661</sup> showed that the selective delivery and activity of kahalalide F analogues can be improved by conjugating the peptides to gold nanoparticles. Kahalalide F appears to act on cell lysosomes, with treated cells swelling dramatically and forming large vacuoles. Cell death is thought to occur via oncosis,<sup>662</sup> with kahalalide F inducing subG1 cell-cycle arrest and cytotoxicity independently of MDR, HER-2, p53, and bcl-2.<sup>663</sup> Kahalalide F and its two semisynthetic analogues exhibited in vivo antitumor effect in hollow fiber assay.<sup>664</sup> The MTD for kahalalide F in mice was 280 µg/kg after a single bolus intravenous injection.

In the phase I study,<sup>665,666</sup> kahalalide F showed clinical benefit in patients with advanced androgen refractory prostate cancer and other advanced tumors. The phase II efficacy study<sup>629</sup> of kahalalide F (650 µg/m<sup>2</sup> given as a 1-h weekly infusion) in advanced malignant melanoma patients was discontinued after the first stage because of the lack of efficacy despite its safety profile. Currently, the antitumor activity of kahalalide F (196) is being investigated in phase II clinical trials in patients with hepatic carcinoma and NSCLC. Isokahalalide F (PM02734, elisidepsin), a close structural analogue of kahalalide F, showed enhanced efficacy against breast and prostate tumor cell lines. Currently, isokahalalide F has entered phase I clinical trials in malignant solid tumors.<sup>81,631,632</sup> The PK

Table 8. Pharmacokinetics and Pharmacological Profile of Kahalalide F (196)<sup>665</sup>

Chemical structure	
Other names	KF
Source	Natural (sea slug <i>Elysia rufescens</i> )
Kinase target	Erbb-2, PI3K/Akt
Cell line data	GI <sub>50</sub> values (μM): 0.004 (A549), 0.013 (NCI-H322M), 0.002 (RPMI-8226), 0.003 (COLO-205), 0.003 (HCC-2998), 0.158 (HCT-15), 0.002 (HT-29), 0.004 (KM-12), 0.008 (SK-OV-3), 0.398 (ACHN), 0.003 (HS-578T), 0.004 (PC-3), 0.005 (DU-145)
In vivo activity <sup>664</sup>	In hollow-fiber model
PK data	<p><u>Phase I study</u> in advanced androgen refractory prostate cancer<sup>665</sup>  Dose: 320-930 mg/m<sup>2</sup>/d (i.v.); C<sub>max</sub> 38-184 ng/ml; AUC 53-280 ng.h/mL; t<sub>1/2</sub> 0.47-0.88 h; CL 6.89-14.47 L/h; Vss 7.09-9.79 L; recommended dose 930 μg/m<sup>2</sup>/day; MTD 560 μg/m<sup>2</sup>/day.</p> <p><u>Phase I study</u> in advanced solid tumors<sup>666</sup>  Dose: 266-1200 μg/m<sup>2</sup> (i.v.); C<sub>max</sub> 52.7-277 ng/ml; AUC<sub>inf</sub> 46-520 ng.h/mL; t<sub>1/2</sub> 0.33-1.02 h; CL 3.97-10.38 L/h; Vss 4.04-6.19 L; recommended dose 800 μg/m<sup>2</sup>.</p>
Current status	Phase II in patients with melanoma, hepatic carcinoma and NSCLC (PharmaMar)

Table 9. Pharmacokinetics and Pharmacological Profile of Midostaurin (277)

Chemical structure	
Other names	PKC-412, CGP- 41251, N-benzoyl staurosporine
Source	Semisynthetic analog of staurosporine
Kinase target	Flt-3, PKC, VEGFRs
Cell line data	Inhibited growth of human HEL and K562 cells
PK data	<p><u>Phase I PK study</u> in patients with diabetes mellitus<sup>672</sup>  Dose: 25-100 mg (single oral dose); C<sub>max</sub> 832.3-2326.1 ng/mL; t<sub>max</sub> 1-4 h; AUC<sub>0-8 h</sub> 4242.8-9525.5 ng.h/mL.</p> <p>Dose: 25-75 mg (multiple oral dose); C<sub>max</sub> 1084.4-1605.9 ng/mL; t<sub>max</sub> 1.32-1.44 h; AUC<sub>0-12 h</sub> 7627.9-15 304.5 ng.h/mL.</p>
Current status	Phase III trial in treating patients with newly diagnosed AML, being developed by National Cancer Institute (ClinicalTrial# NCT00651261)

and pharmacological profile of kahalalide F (196) is shown in Table 8.

**6.1.3. Midostaurin (277).** Midostaurin (277), a multitarget protein kinase inhibitor,<sup>667</sup> is a widely investigated staurosporine analogue. Midostaurin showed growth inhibition of various tumor cells. It inhibited cell growth and induced megakaryocytic differentiation and apoptosis in the human erythroleukemia HEL and K562 cells.<sup>668</sup> Midostaurin also modulated the differentiation, maturation, and function of myeloid dendritic cells.<sup>669</sup>

In the phase I study<sup>670</sup> (75 mg twice daily for 2 days; 75 mg once on day 3), which was performed to investigate the effect

of midostaurin on cardiac repolarization, midostaurin demonstrated a good safety profile in healthy volunteers, with no prolonged cardiac repolarization or other changes on the electrocardiogram. In the phase II study,<sup>671</sup> it showed good systemic exposure through the oral route and was well tolerated in patients with AML or myelodysplastic syndrome (MDS). Midostaurin showed hematologic activity in both patients with Flt-3 mutant and wild-type. In a phase I PK study of midostaurin following multiple doses of midostaurin for 28 days at 4 dose levels (25 mg bid, 50 mg bid, 75 mg bid, and 75 mg tid), as well as a single-dose administration of midostaurin at 100 mg, dose-dependent pharmacokinetics were observed.

Midostaurin was absorbed rapidly, with peak plasma concentrations occurring at a mean of 1.3–1.7 h following the first single dose; however, upon repeated dosing, midostaurin exhibited a slight accumulation. Midostaurin was primarily metabolized via hydroxylation of *N*-CH<sub>2</sub> of the pyrrolidinone ring (metabolite: CGP-62221) and demethylation of OMe of the pyran ring (metabolite: CGP-52421). The steady-state peak plasma concentrations of midostaurin were 1084–1605 ng/mL (1.9–2.8 μM) with a half-life of 1.3–1.6 h. A dose of 50–225 mg/day was found to be safer for midostaurin.<sup>672</sup> After successful phase II clinical trials,<sup>671</sup> midostaurin is currently being evaluated in a multinational phase III trial in newly diagnosed AML with Flt-3 mutations, as well as in a phase II trial for aggressive systemic mastocytosis (ASM). The PK and pharmacological profile of midostaurin (277) is shown in Table 9.

**6.1.4. Lestaurtinib (281).** Lestaurtinib is a polyaromatic indolocarbazole compound, derived from a parent molecule, K-252a. K-252a was first isolated from a culture broth of *Nonomuraea longicatena* and reported by a Japanese pharmaceutical group, Kyowa Hakko Kogyo, in 1985.<sup>673</sup> Derivatives of K-252a were later isolated in collaboration with another pharmaceutical company, Cephalon. Lestaurtinib initially designated as CEP-701 was initially identified as an inhibitor of Trk-A. Therefore, early preclinical and clinical studies, including phase I and II trials of this compound, were focused on its effect on Trk-A and its translation to clinical efficacy in pancreatic and prostatic malignancies.<sup>674–676</sup>

Lestaurtinib inhibited the growth of neuroblastoma, a pediatric tumor of the sympathetic nervous system, both in vitro and in vivo and substantially enhanced the efficacy of conventional chemotherapy, presumably by inhibition of the Trk/brain-derived neurotrophic factor autocrine survival pathway.<sup>677</sup> Although lestaurtinib was initially developed and licensed by multiple companies, including Cephalon and TAP Pharmaceuticals (a joint venture between Takeda Chemical Industries Ltd. and Abbott Laboratories), it is currently solely licensed to Cephalon. In 2001, investigators at Johns Hopkins identified lestaurtinib as a potent inhibitor of the Flt-3 tyrosine kinase.<sup>678</sup> Flt-3 (FMS-like tyrosine kinase 3) plays an important role in the survival and proliferation of blasts, and it gets overexpressed in most patients with AML. Lestaurtinib inhibited phosphorylation of ITD and wild-type (WT) Flt-3 with an IC<sub>50</sub> of 3 nM. Lestaurtinib induced apoptosis in leukemia cells harboring Flt-3/ITD mutations. The inhibition of phosphorylation and the resultant cell death were also demonstrated in primary leukemia samples, as well as in vivo using mouse models.<sup>678</sup> It showed cytotoxicity in human AML cell lines expressing both mutant and WT Flt-3 at doses similar to those required to inhibit phosphorylation of the Flt-3 receptor, and it prolonged survival in a mouse model of Flt-3 internal tandem duplication leukemia.<sup>678</sup> Lestaurtinib induced cytotoxicity in a synergistic fashion with cytarabine in Flt-3 mutant AML blast samples.<sup>679</sup> Lestaurtinib also showed cytotoxicity to oxaliplatin-resistant transitional cell carcinoma cell line T24 in vitro.<sup>680</sup>

Lestaurtinib has been tested against several other kinases to assess its relative selectivity for Flt-3. Inhibition of PDGFR-β, FMS, and Kit, which are structurally related to Flt-3, was considerably weaker, measured at concentrations of 500–1000 nM or greater.<sup>678</sup> However, lestaurtinib was able to effectively inhibit other tyrosine kinases, such as RET, JAK-2, and TRK.<sup>486,681–683</sup> Lestaurtinib showed potent inhibition of wild-

type JAK-2 kinase activity with IC<sub>50</sub> value of 1 nM.<sup>486</sup> Furthermore, it also inhibited the growth of HEL-92.1.7 cells, which are dependent on mutant JAK-2 activity for growth in vitro and in xenograft models.<sup>486</sup> Lestaurtinib showed additive or synergistic effect with isotretinoin in a spectrum of neuroblastoma cell lines.<sup>605</sup> Lestaurtinib induced growth inhibition and apoptosis activation in Hodgkin lymphoma cells through dysregulation of the JAK-2/STAT-5 signaling pathway.<sup>684</sup> Lestaurtinib also inhibited protein kinase C related kinase 1 (PRK-1) very potently in vitro and in vivo.<sup>685</sup>

The PK of lestaurtinib was assessed in phase I studies in patients with AML and solid-tumor malignancies.<sup>686,687</sup> It is an orally bioavailable Flt-3 inhibitor,<sup>607</sup> which is rapidly absorbed from the gastro-intestinal tract, with measurable blood levels after 1 h. It has been reported that the levels of lestaurtinib reach to a steady-state after 8 days and accumulation does not progressively increase with continued daily dose administration.<sup>686,687</sup> Lestaurtinib displays high plasma protein binding, particularly to acid glycoprotein (AGP). Lestaurtinib is primarily metabolized by the CYP3A4 in liver. In the first phase I study<sup>686</sup> of lestaurtinib in healthy volunteers, PK studies after a single dose of oral lestaurtinib showed an AUC of 929–7889 ng·h/mL and a half-life of 6.8–9.2 h. In clinical studies, there was a strong dose relationship with adverse events, and gastrointestinal side effects were the most common adverse events occurring in 83% of patients. With a median duration of treatment of 5 weeks, lestaurtinib failed to produce any objective tumor responses. However, three patients had stable disease for 6 months and one patient with lung cancer had a stable disease for a year. The clinical responses observed in this phase II study were similar in frequency, depth, and duration to those observed in the phase I study.<sup>688</sup>

In the phase I study<sup>606</sup> in children with refractory neuroblastoma, drug was rapidly absorbed; however, inter-patient variability was large. Plasma inhibition of phospho TrkB activity was observed 1 h postdosing at 85 mg/m<sup>2</sup> with uniform inhibition at 120 mg/m<sup>2</sup>. In the phase II study<sup>689</sup> in older patients with AML not considered fit for intensive chemotherapy, lestaurtinib (60–80 mg twice daily) was well-tolerated and showed favorable clinical activity. Clinical responses occurred where the presence of sustained Flt-3-inhibitory drug levels was combined with in vitro cytotoxic sensitivity of blasts to lestaurtinib. These clinical studies indicated that lestaurtinib possesses modest clinical activity as a single agent and was well tolerated as an oral drug. When administered in sequence with standard chemotherapeutic regimens, it was found to be effective in patients with Flt-3-activating mutations, specifically when inhibition of Flt-3 phosphorylation in vivo was also demonstrated. Presently lestaurtinib (281) is being evaluated in phase II/III trials for AML patients at first relapse who have a Flt-3 activating mutation. A phase III study<sup>690</sup> was conducted in 220 patients, after which Cephalon announced its preliminary findings that the study had not met its primary end point in these patients, because chemotherapy plus lestaurtinib yielded similar rates of responses and no benefit in overall survival as compared to standard chemotherapy alone. Currently, another phase III study is underway to examine the efficacy of lestaurtinib in combination with cytotoxic chemotherapy. In 2007, the FDA-approved lestaurtinib as an orphan drug for the treatment of AML as an orally bioavailable potent tyrosine kinase inhibitor.<sup>691</sup> The PK and pharmacological profile of lestaurtinib (281) is shown in Table 10.

Table 10. Pharmacokinetics and Pharmacological Profile of Lestaurtinib (281)

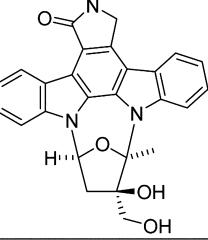
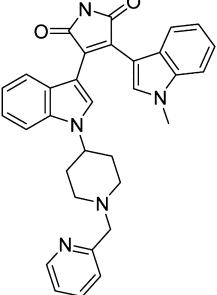
Chemical structure	
Other names	CEP- 701
Source	Synthetic analog of staurosporine
Kinase target <sup>486,678</sup>	Flt-3 (IC <sub>50</sub> of 3 nM), JAK-2 (IC <sub>50</sub> of 1 nM), Trk-A, Trk-B, Trk-C
Cell line data	IC <sub>50</sub> (in μM): 0.17 (SH-SY5Y-BR6); 0.08 (SH-SY5Y); 0.08 (IMR-5); 0.09 (CHP-134); 0.16 (E6-NBLS); 0.3 (NLF-A); 0.08 (NLF-B); 0.09 (NLF). <sup>605</sup>
PK data	<p>Phase I study<sup>686</sup> in healthy volunteers Dose: 40-60 mg/day (single dose, oral); AUC 929-7889 ng.h/ml; t<sub>1/2</sub> 6.8-9.2 h.</p> <p>Phase I study<sup>606</sup> in children with refractory neuroblastoma Dose: 120 mg/m<sup>2</sup> BID (oral); C<sub>max</sub> 3513.9 ng/mL; t<sub>max</sub> 1.5 h; AUC<sub>inf</sub> 39509 ng.h/mL; t<sub>1/2</sub> 7.9 h; recommended phase 2 dose of 120 mg/m<sup>2</sup>/dose BID</p>
Current status	<ul style="list-style-type: none"> <li>Phase III in infants with newly diagnosed acute lymphoblastic leukemia; being developed by National Cancer Institute (ClinicalTrial# NCT00557193)</li> <li>Received orphan drug status for acute myeloid leukemia (FDA, 2007)</li> </ul>

Table 11. Pharmacokinetics and Pharmacological Profile of Enzastaurin (294)

Chemical structure	
Other names	LY317615
Source	Synthetic analog of staurosporine
Kinase target <sup>692,706</sup>	PKC-β (IC <sub>50</sub> 6 nM), GSK-3β
Cell line data	Inhibited growth of human colon cancer and glioblastoma xenografts
PK data <sup>707,708</sup>	<p>Phase I PK study<sup>707</sup> of enzastaurin in combination with single-agent temozolomide in patients with gliomas</p> <ul style="list-style-type: none"> <li>Dose: Enzastaurin 250 mg QD; C<sub>max</sub> 1340 nmol/L; t<sub>max</sub> 3.97 h; AUC 17 500 nmol. h/L; CL 27.7 L/h.</li> <li>Dose: Enzastaurin 250 mg QD + temozolomide; C<sub>max</sub> 1120 nmol/L; t<sub>max</sub> 4.0 h; AUC 15 600 nmol. h/L; CL 31.1 L/h.</li> <li>Enzastaurin 500 mg QD; C<sub>max</sub> 739 nmol/L; t<sub>max</sub> 4.00 h; AUC 9190 nmol. h/L; CL 106 L/h.</li> <li>Enzastaurin 500 mg QD + temozolomide; C<sub>max</sub> 985 nmol/L; t<sub>max</sub> 4.00 h; AUC 12100 nmol. h/L; CL 80.1 L/h.</li> </ul>
Current status	<ul style="list-style-type: none"> <li>Phase II trials for the treatment of colon cancer, refractory glioblastoma and diffuse large B cell lymphoma<sup>705</sup></li> <li>In 2007, EMEA has granted orphan drug status to enzastaurin for the treatment of diffuse large B-cell lymphoma.</li> </ul>

**6.1.5. Enzastaurin (294).** Enzastaurin (LY317615, 294), a sugar ring modified analogue of staurosporine, inhibited PKC-β with IC<sub>50</sub> of 6 nM and also showed inhibition of other PKC isoforms including PKC-γ, PKC-δ, PKC-θ, PKC-ε, PKC-ξ, PKC-η, PKC-ζ, and PKC-α at micromolar concentrations.<sup>692</sup> In preclinical studies, enzastaurin suppressed signaling through AKT pathway, induced apoptosis, and suppressed growth of human colon cancer and glioblastoma xenografts.<sup>692</sup> Enzastaurin suppressed VEGF-induced angiogenesis in the rat corneal micropocket assay, decreased microvessel density, and prevented VEGF secretion from human tumor cell xenografts

in nude mice; in addition, prolonged courses of enzastaurin increased chemotherapy or radiation tumor growth delay of breast, glioma, and small cell lung cancer xenografts.<sup>693-696</sup> Enzastaurin showed antiproliferative activity against uveal melanoma cells carrying GNAQ mutations through inhibition of the PKC/Erk-1/2 pathway and induction of G1 arrest and apoptosis.<sup>697</sup> Enzastaurin also reduced the growth of SQ-20B and CAL27 tumor xenografts, decreased proliferation in these cell lines, inhibited putative target phosphorylation, and induced cell cycle arrest.<sup>698,699</sup> Enzastaurin also suppressed the proliferation of cultured gastric cancer cells and the growth

Table 12. Pharmacokinetics and Pharmacological Profile of UCN-01 (4)

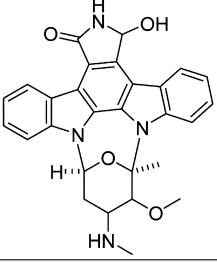
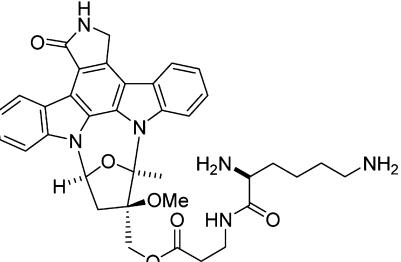
Chemical structure	
Source	Synthetic analog of staurosporine
Kinase target <sup>712-714</sup>	$IC_{50}$ in nM: 1.1 (cPKC); 8 (nPKC- $\delta$ ); 5.5 (nPKC- $\epsilon$ ) $k_1$ : 0.44 nM (PKC- $\alpha$ ), 3.8 uM (PKC- $\zeta$ )
Cell line data	Human CLL cells ( $IC_{50}$ 0.4 $\mu$ M) <sup>710</sup>
PK data	<ul style="list-style-type: none"> <li>• <u>PK in mice</u><sup>711</sup> Dose: 9 mg/kg (bolus IV administration); <math>CL_{tot}</math> 1930 mL/h/kg; <math>Vd_{ss}</math> 7.95 L/kg; <math>t_{1/2}</math> 3.98 h; <math>AUC_{inf}</math> 4.67 <math>\mu</math>g.h/mL.</li> <li>• <u>PK in rats</u><sup>711</sup> Dose: 3.5 mg/kg (bolus IV administration); <math>CL_{tot}</math> 3490 mL/h/kg; <math>Vd_{ss}</math> 16.9 L/kg; <math>t_{1/2}</math> 4.46 h; <math>AUC_{inf}</math> 1.02 <math>\mu</math>g.h/mL.</li> <li>• <u>PK in dogs</u><sup>711</sup> Dose: 0.5 mg/kg (bolus IV administration); <math>CL_{tot}</math> 616 mL/h/kg; <math>Vd_{ss}</math> 6.09 L/kg; <math>t_{1/2}</math> 11.6 h; <math>AUC_{inf}</math> 0.925 <math>\mu</math>g.h/mL.</li> <li>• <u>PK study in patients with cancer</u><sup>711</sup> Dose: 0.15 mg/kg (i.v.), administered over 72 h at 5.4 mg/m<sup>2</sup>; <math>CL_{tot}</math> 0.168 mL/h/kg; <math>Vd_{ss}</math> 0.113 L/kg; <math>t_{1/2}</math> 581 h; <math>AUC_{inf}</math> 871 <math>\mu</math>g.h/mL.</li> </ul>
Current status	Phase-II clinical trials for various forms of cancers including pancreas, breast and lymphoma

Table 13. Pharmacokinetics and Pharmacological Profile of CEP-2563 (283)

Chemical structure	
Source	Synthetic analog of staurosporine; prodrug of CEP-751
Other names	KT-8391
Kinase target	Trk-A, Trk-B, Trk-C <sup>715</sup>
PK data	<p>Phase I study in in patients with refractory solid tumors<sup>630</sup></p> <ul style="list-style-type: none"> <li>• Dose: 1 mg/m<sup>2</sup> (i.v. infusion); PK paramaters on day 1/ day 4: <math>C_{max}</math> 143.7/ 171.8 ng/ml; <math>t_{1/2}</math> 8.7/ 48.2 h; <math>AUC_{last}</math> 1334/ 1651 ng.h/ml; <math>CL</math> 0.63/ 0.35 L/h/m<sup>2</sup>; <math>Vss</math> 7.4/ 8.7 L/m<sup>2</sup>.</li> <li>• Dose: 8 mg/m<sup>2</sup> (i.v. infusion); PK paramaters on day 1/ day 4: <math>C_{max}</math> 2573.6/ 4463.2 ng/ml; <math>t_{1/2}</math> 21.9/ 93 h; <math>AUC_{last}</math> 37422/ 92739 ng.h/ml; <math>CL</math> 0.12/ 0.01 L/h/m<sup>2</sup>; <math>Vss</math> 3.5/ 1.8 L/m<sup>2</sup>.</li> <li>• Dose: 320 mg/m<sup>2</sup> (i.v. infusion); PK paramaters on day 1: <math>C_{max}</math> 29645.2 ng/ml; <math>t_{1/2}</math> 17.1 h; <math>AUC_{last}</math> 281377 ng.h/ml; <math>CL</math> 1.1 L/h/m<sup>2</sup>; <math>Vss</math> 25.3 L/m<sup>2</sup>.</li> </ul>
Current status	Phase I in patients with refractory solid tumors (completed). Phase II study planned.

of gastric carcinoma xenografts through Rsk-mediated and Bad-mediated pathways, besides inhibiting the Akt signal cascade. Enzastaurin showed synergistic or additive effects when combined with 5-fluorouracil, cisplatin, paclitaxel, or irinotecan.<sup>700</sup>

In phase I studies,<sup>701</sup> the combination of enzastaurin with erlotinib was well tolerated and did not alter the PK of individual drugs, with clinical activity seen. Further, it was

evaluated in phase II trials by Eli Lilly in NSCLC patients and was well tolerated.<sup>702,703</sup> In another phase II study<sup>704</sup> in patients with persistent or recurrent epithelial ovarian or primary peritoneal carcinoma, although enzastaurin was well tolerated it showed insufficient efficacy. Presently, enzastaurin is under phase III trials for the treatment of diffuse large B-cell lymphoma.<sup>494,705</sup> In 2007, European Medicines Agency (EMEA) granted orphan drug status to enzastaurin for the

Table 14. Pharmacokinetics and Pharmacological Profile of Variolin B (77)

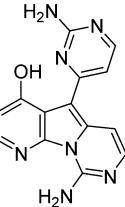
Chemical structure	
Source	Antarctic sponge <i>Kirkpatrickia variolosa</i>
Kinase target	CDK-1, CDK-2
Cell line data <sup>209,515</sup>	$GI_{50}$ in $\mu\text{M}$ : 0.89 (DU-145), 0.05 (LN-caP), 1.21 (SKOV-3), 1.14 (IGROV), 1.28 (IGROV-ET), 0.85 (SK-BR-3), 1.20 (MEL-28), 0.27 (H-MEC-1), 0.98 (A-549), 1.55 (K-562), 1.68 (PANC-1), 2.85 (HT-29), 0.80 (LoVo), 1.02 (LoVo-DOX). $IC_{50}$ ( $\mu\text{M}$ ): 0.72 (P388 murine leukemia)
PK data	PK in CD-1 mice <sup>717</sup> Dose: 17 mg/kg (i.v.) $C_{max}$ 1.62 $\mu\text{g}/\text{mL}$ ; $t_{1/2}$ 0.22 h; terminal $t_{1/2}$ 1.42 h.
Current status	Preclinical (PharmaMar)

Table 15. Comparative Analysis of PK Data of Marine-Derived Clinical Candidates (Kinase Inhibitors)<sup>a</sup>

candidate	species	route	clinical phase	pharmacokinetics				recommended dose	MTD	ref
				dose	AUC (ng·h/mL)	$C_{max}$ (ng/mL)	$t_{1/2}$ (h)			
midostaurin (277)	human	oral	I	100 mg single dose/day	9525 (0–8 h)	2326	1.62 ( $T_{max}$ )	50–225 mg/day <sup>b</sup>	nr	672
midostaurin (277)	human	oral	I	25–75 mg bid/tid	6436–15304	1084–1605	1.32–1.56	50–225 mg/day <sup>b</sup>	nr	672
lestautinib (281)	human	oral	I	60 mg orally twice/day	929–7889	nr	6.8–9.2 h	nr	nr	686,687
CEP-2563 (283)	human	IV	I	8 mg/m <sup>2</sup>	92 739 (day 4)	4463 (day 4)	93 (day 4)	256 mg/m <sup>2</sup> /d	320 mg/m <sup>2</sup>	630
CEP-2563 (283)	human	IV	I	320 mg/m <sup>2</sup>	281 377 (day 1)	29645 (day 1)	17.1 (day 1)	256 mg/m <sup>2</sup> /d	320 mg/m <sup>2</sup>	630
UCN-01 (4)	human	IV	I	72-h infusion at 5.4 mg/m <sup>2</sup>	871 000	nr	581	nr	42.5 mg/m <sup>2</sup> /d	711
aplidin (140)	human	IV	I	0.2–8 mg/m <sup>2</sup>	148–1113	5–32	21–44	5 mg/m <sup>2</sup>	nr	601,643
aplidin (140)	human	IV	II	5 mg/m <sup>2</sup> (3-h infusion every 2 weeks)	255	29	50.35	5 mg/m <sup>2</sup>	nr	601,643
kahalalide F (196)	human	IV	I	20–930 $\mu\text{g}/\text{m}^2/\text{day}$	53–280	38–184	0.47–0.88	930 $\mu\text{g}/\text{m}^2/\text{day}$	560 $\mu\text{g}/\text{m}^2/\text{day}$	665
variolin B (77)	mice	IV	preclinical	17 mg/kg	nr	1620	1.42	nr		717

<sup>a</sup>nr: not reported. <sup>b</sup>Safer dose range.

treatment of diffuse large B-cell lymphoma (DLBCL).<sup>614</sup> The PK and pharmacological profile of enzastaurin (294) is shown in Table 11.

**6.1.6. UCN-01 (4).** UCN-01, a 7-hydroxystaurosporine, inhibited the retinoblastoma susceptibility gene product kinase activity of three types of CDKs (CDK-2, 4, and 6) with  $IC_{50}$  values of 42, 32, and 58 nM, respectively. UCN-01 inhibited cell cycle progression at G1 to S transition in A549 cells at the concentration of 100 nM<sup>709</sup> and also showed significant in vitro activity against human CLL cells ( $IC_{50}$  0.4  $\mu\text{M}$ ).<sup>710</sup>

The PK of UCN-01 in laboratory animals was characterized by rapid clearance with a large distribution volume, despite a high degree of protein binding. In the phase I PK study in patients with cancer, after administration of drug over 72 h infusion, extremely low clearance (0.0613–0.390 mL/h/kg), a small distribution volume (0.097–0.276 L/kg), and unusually long  $t_{1/2}$  (535–2700 h) were observed.<sup>711</sup> In clinical studies, short infusions of UCN-01 (4) resulted in the distribution of the drug to peripheral tissues. The optimal duration of exposure to UCN-01 for antiproliferative activity against tumor cells, induction of apoptosis, and sensitization to other anticancer

drugs ranged from 10 to 72 h.<sup>711</sup> UCN-01 (4) is presently in phase II clinical trials for various forms of cancer including pancreatic and breast cancer and lymphoma.<sup>154</sup> The PK and pharmacological profile of UCN-01 (4) is shown in Table 12.

**6.1.7. CEP-2563 (283).** Cephalon<sup>487</sup> developed a prodrug ester of CEP-751 (the dipeptide proform Lys- $\beta$ -Ala; CEP-2563/KT-8391, 283), which was identified for advancement to clinical trials. CEP-2563 (283) was developed because of the limited aqueous solubility of the earlier candidate CEP-751 (282). CEP-751 possessed very poor aqueous solubility (7  $\mu\text{g}/\text{mL}$ ); however, its prodrug ester CEP-2563 (283) showed exceptional aqueous solubility (>200 mg/mL) and stability.<sup>715</sup> In toxicology studies, administration of CEP-2563 in rats and dogs at doses above their respective maximum tolerated dose (MTD) resulted in cardiovascular dysfunction, gastrointestinal effects (emesis and diarrhea), hypersensitivity reactions, and neurological effects.<sup>630</sup> In the phase I study of CEP-2563, the observed dose-limiting toxicities were grade 3 hypotension and grade 2 allergic reaction. PK analysis evidenced that CEP-2563 is converted to the parent molecule CEP-751. The recommended dose of CEP-2563 for phase II studies was 256 mg/

$\text{m}^2/\text{d}$ .<sup>630</sup> The PK and pharmacological profile of CEP-2563 (283) is shown in Table 13.

**6.1.8. Variolin B (77).** The variolins<sup>77</sup> have been isolated via P388 murine leukemia bioassay-guided isolation from the Antarctic sponge *Kirkpatrickia varialosa*. Variolin B showed cytotoxicity in the P388 murine leukemia with an  $\text{IC}_{50}$  of 0.72  $\mu\text{M}$ .<sup>209</sup> Variolin B induced apoptosis and showed potent cytotoxic activity against a variety of human cancer cell lines, including sublines overexpressing PGP, that were each resistant to other natural products.<sup>716</sup> Variolins inhibited CDKs in the micromolar range. CDK-1/cyclin B, CDK-2/cyclin A, and CDK-2/cyclin E complexes were inhibited in a range of concentrations lower than those required to inhibit the activity of CDK-4/cyclin D or CDK-7/cyclin H complexes.<sup>211</sup>

PharmaMar has conducted investigations on the variolin B (77) and deoxyvariolin B<sup>510–512</sup> and is currently focusing on deoxyvariolin B for further development because of its favorable physicochemical properties. PharmaMar reported<sup>717</sup> the PK data for variolin B (77) and its 4-dehydroxyl analogue PM01218 in CD-1 mice following a single IV administration at doses of 17 and 7.5 mg/kg, respectively. The  $C_{\max}$  of variolin B and PM01218 was 1.62 and 2.49  $\mu\text{g}/\text{mL}$ , respectively. The initial  $t_{1/2}$  was 0.22 h for variolin B and 0.13 h for PM01218; the terminal  $t_{1/2}$  was 1.42 h for variolin B and 2.92 h for PM01218. The overall results indicated that PM01218 has a better PK profile than variolin B in terms of  $C_{\max}$ , plasma clearance, and the terminal plasma half-life. The PK and pharmacological profile of variolin (77) is shown in Table 14.

The comparative PK data of marine-derived clinical candidates are summarized in Table 15.

## 7. SUMMARY AND OUTLOOK

As the marine environment covers 70% of the Earth's surface and is characterized by unique growth conditions, it produces chemodiversity and the potential for discovering novel therapeutics with novel mechanisms of action. This Review has provided a comprehensive and critical account of the natural-product chemistry, kinase inhibitory activity, medicinal chemistry, patent literature, preclinical pharmacology, and clinical development of marine-derived kinase inhibitors. As discussed, several marine natural products have successfully reached the market as therapies for different diseases, and several others are in various phases of clinical trials; consequently, this unique resource has great potential to produce many first-in-class drugs in the near future. With current advances in (a) sampling techniques, (b) nanomole structure determination, (c) analytical techniques and the availability of new methods for genetic and chemical dereplication, (d) systems biology-based screening in different animal models (zebrafish, *Caenorhabditis elegans*), (e) genome sequencing, (f) directed biosynthesis and biosynthetic pathways, (g) genome mining for cryptic pathways, (h) molecular biology tools, and (i) high-throughput screening, the efficiency of exploring marine samples to discover novel therapeutics has increased significantly. Furthermore, to overcome the supply problem, chemical synthesis and microbial fermentation methods have shown great promise. Several marine natural products that are in various phases of preclinical and clinical development, such as aplidin, kahalalide F, and staurosporine analogues, have great potential to reach the market. With the discovery of a large number of novel scaffolds from marine sources, we can expect the next decade to yield even more promising therapeutic candidates from the sea.

Because kinases are the most important signaling proteins implicated in growth, differentiation, and proliferation of eukaryotic cells, successful targeting of these proteins has resulted in a number of novel drugs for cancer and neurodegenerative diseases. However, most of the kinase inhibitors approved as drugs are ATP-competitive inhibitors and therefore have significant off-target liabilities due to cross-reactivity. Hence, there is a greater unmet need to discover and develop next-generation kinase inhibitors that function through alternative mechanisms (such as allosteric inhibition). Because of their remarkable pharmacophoric diversity and biosynthetic origin, marine-derived natural products offer a potentially rich source of such inhibitors.

## ASSOCIATED CONTENT

### S Supporting Information

A detailed list of kinase inhibitors approved as drugs by the FDA and lists of serine/threonine, tyrosine, and lipid kinase inhibitors currently in various phases of clinical trials. This material is available free of charge via the Internet at <http://pubs.acs.org>.

## AUTHOR INFORMATION

### Corresponding Author

\*Tel.: +91-191-2569111. Fax: +91-191-2569333. E-mail: ram@iim.ac.in, ravboc@gmail.com.

### Notes

The authors declare no competing financial interest.  
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### Biographies



Sandip B. Bharate obtained his B. Pharm. degree from the University of Pune in 2001 and received a M.S. (Pharm.) degree from the National Institute of Pharmaceutical Education and Research (NIPER), Mohali (India), in 2002. In 2003, he worked in the discovery research unit of Dr. Reddy's Laboratories, Hyderabad, for 6 months before commencing his Ph.D., which he completed under the supervision of Dr. Inder Pal Singh at NIPER Mohali in January 2007. Subsequently, he worked as a Research Scientist in the Department of Medicinal Chemistry, Piramal Life Sciences Ltd, Mumbai (formerly, Nicholas Piramal Research Center), for 1.5 years. He subsequently pursued postdoctoral studies (2008–2010) at the University of Montana (U.S.) with Professor Charles M. Thompson in the area of neuroscience. Presently, he is working as a Senior Scientist in the Medicinal Chemistry Division of the Indian Institute of Integrative Medicine (Council of Scientific and Industrial Research), Jammu, India. His current research interests are in the field of medicinal

chemistry of marine natural products to discover new therapeutics for the treatment of Alzheimer's disease and cancer. He is the recipient of several innovative awards in the area of new drug discovery.



Sanghapal D. Sawant was educated in chemistry at SRTM University, Nanded (India), and received his Ph.D. under the supervision of Dr. H. M. Sampath Kumar in Medicinal Chemistry from CSIR-Indian Institute of Integrative Medicine, Jammu (India). His doctoral thesis work was in the area of skin care product development and the synthesis of anticancer molecules. In 2006, he acquired a position as Scientist at CSIR-IIIM, Jammu (India). His areas of research interest include medicinal chemistry for cancer and tuberculosis as well as synthetic method development and target-oriented synthesis of natural product scaffolds. He is actively involved in the cancer and tuberculosis drug discovery programs at the Institute. His research work in the area of cancer focuses on the design and synthesis of libraries of molecules using medicinal chemistry approaches from marine-derived natural product scaffolds as PI3k/Akt/mTOR inhibitors as lead preclinical candidates.



Parvinder Pal Singh is from the Jammu and Kashmir region (a northern state of India) and was born in Poonch in 1979. He obtained his Ph.D. from Guru Nanak Dev University, Amritsar, under the supervision of Dr. H. M. Sampath Kumar at the CSIR-Indian Institute of Integrative Medicine. His doctoral research was focused on the synthesis of small molecule-based immune adjuvants and immunomodulators. In 2008, he obtained a scientific position in IIIM Jammu as a Junior Scientist. His current research interests are medicinal chemistry for the development of novel anti-TB and anticancer agents, the development of new synthetic methodologies, and the synthesis of bioactive molecules.



Ram A. Vishwakarma studied chemistry at the Central Drug Research Institute (CDRI), Lucknow, and completed his Ph.D. in 1986 under the joint supervision of Drs. S. P. Popli and R. S. Kapil. After working for a few years as a research scientist at CIMAP, Lucknow, he moved to the Cambridge University in 1991 to work with Sir Alan Battersby on the biosynthesis of cyanocobalamin (vitamin B<sub>12</sub>) and related porphyrins/correns. In the end of 1993, he joined as a staff-scientist at the National Institute of Immunology at New Delhi and initiated a research program on chemical biology of Glycosyl Phosphatidyl Inositol (GPI) anchors of parasitic protozoa (Leishmania and Malaria). In 2005, he moved to Piramal Life Sciences (Mumbai) as vice-president and head of medicinal chemistry & natural product groups. During this period, he worked on the clinically validated disease targets relevant to cancer (PI3K/mTOR, IGFR1), diabetes (DGAT1), and infection (VRE/MRSA), learned the "intricacies" of drug-discovery under the guidance of Dr. Somesh Sharma, and realized the potential of marine natural products. In 2009, he joined as Director of Indian Institute of Integrative Medicine (Council of Scientific and Industrial Research) at Jammu, where his primary focus remain natural-products driven drug discovery for cancer and infection. His scientific work has been published in over 100 papers and >25 patent applications filed. Ram Vishwakarma is an elected Fellow of the National Academy of Sciences, India.

#### LIST OF ABBREVIATIONS AND ACRONYMS

ALL	acute lymphoblastic leukemia
AML	acute myeloid leukemia
ASM	aggressive systemic mastocytosis
BCR-Abl	breakpoint cluster region-Abelson
Caco-2	human epithelial colorectal adenocarcinoma cell line
CaMKII	calmodulin-dependent protein kinase II
CDK	cyclin-dependent kinase
CHK	check-point kinase
CK	casein kinase
<i>C</i> <sub>max</sub>	maximal concentration
CML	chronic myelogenous leukemia
DLBCL	diffuse large B-cell lymphoma
DLT	dose limiting toxicity
Dyrk-1A	dual-specificity tyrosine-phosphorylation-regulated kinase 1A
EGFR	epidermal growth factor receptor
EMEA	European Medicines Agency
ERK	extracellular signal-regulated kinase
FDA	Food and Drug Administration
FGFR	fibroblast growth factor receptor
Flt-3	FMS-like tyrosine kinase-3
GSK-3	glycogen synthase kinase-3

GIST	gastrointestinal stromal tumor
HIV	human immunodeficiency virus
HMEC	human microvascular endothelial cell line
HUVEC	human umbilical vein endothelial cells
IGF-1R	insulin-like growth factor-1 receptor
jNK	c-Jun N-terminal kinase
KDR	kinase insert domain receptor
LoVo	human colon adenocarcinoma cell line
MAP	mitogen-activated protein
MCF-7	Acronym of Michigan Cancer Foundation; it is a human breast adenocarcinoma cell line
MDA-468	human breast cancer cell line
MDS	myelodysplastic syndrome
MNPs	marine natural products
MST-2	mammalian STE20-like kinase 2
MTD	maximum tolerated dose
NDA	new drug application
NSCLC	nonsmall-cell lung carcinoma
PA1	human ovarian cancer cell line
PAK	p21 activated kinases
PDGFR	platelet-derived growth factor receptor
PI3K	phosphoinositide-3-kinase
PKA	protein kinase A
PKB	protein kinase B (also named as AKT)
PKC	protein kinase C
PKD	protein kinase D
Pfnek	<i>Plasmodium falciparum</i> NIMA-related kinase
PLK	polo-like kinase
PPDK	pyruvate phosphate dikinase
PRAK	p38-regulated/activated protein kinase
RCC	renal cell carcinoma
RSK	ribosomal S6 kinase
RSV	respiratory syncytial virus
SAR	structure–activity relationship
S1P	sphingosine-1-phosphate
SGK	serum and glucocorticoid-inducible kinase
SLE	systemic lupus erythematosus
SphK	sphingosine kinase
STAT	signal transducers and activators of transcription
Syk	spleen tyrosine kinase
$t_{1/2}$	terminal half-life
VEGFR	vascular endothelial growth factor receptor
Vss	volume of distribution

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