Marine sponge compounds with antiplasmodial properties: Focus on in vitro study against *Plasmodium falciparum*

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**ABSTRACT**

Malaria continues to be a major cause of morbidity and mortality in many tropical countries. The lack of progress in drug discovery and the spread of drug resistance becomes the reason behind this. *Porifera* (sponges) is a potential source of novel bioactive compounds to provide future drugs against malaria. In this review, we summarized 243 isolated molecules belonging to 35 different genera that active against *Plasmodium falciparum* from published paper until March 2019. The molecules were classified into potent, good, moderate, low, and inactive based on their IC₅₀, and among observed bioactive metabolites, there were 57 marine sponge molecules reported to act as potent antimalarial against various strains of *P. falciparum* including drug resistance and non-drug resistance. Table 2 represents the list of isolated compounds with “potent” antimalarial activity. The class of the listed compounds includes manzamine alkaloid, guanidine alkaloids, bispyrroloiminoquinone alkaloids, pyrroloiminoquinone alkaloids, ingamine alkaloids, bromotyrosine alkaloids, sesquiterpenoids, diterpene formamides, aminoimidazole, β-galactosylceramides, β-lactam, meroterpene, trisoxazole macrolides, peroxides, thiazine alkaloids, and sterols. With this up-to-date review, we attempt to present new perspectives for the rational discovery of novel sponge metabolites that can be used as lead compounds in antimalarial drug development.

**INTRODUCTION**

Malaria is the most life-threatening and infectious disease caused by *Plasmodium* parasites such as *Plasmodium falciparum, Plasmodium ovale, Plasmodium vivax, Plasmodium malariae.* Among those protozoans, *P. falciparum* is considered to be responsible for most severe diseases and most fatal cases. The World Health Organization (2018) stated in the year of 2017 that more than 99% of estimated malaria cases in the WHO African Region followed by the WHO regions of the Western Pacific (71.9%), the Eastern Mediterranean (69%), and Southeast Asia (62.8%) were caused by this most prevalent malaria parasite. In the same period, the WHO reported approximately 219 million cases of malaria occurred worldwide including 435,000 deaths.

Nowadays, malaria continues to be a major cause of morbidity and mortality in tropical countries. It is further aggravated by an increase in a number of multidrug-resistant strains of *Plasmodium* accompanied by a lack of progress in the development of vaccines and drug discovery. As a consequence, the search of new agent that acts against malaria becomes urgent needs (Antony and Parija 2016; Burrows et al., 2011; Cui et al., 2015; Dondorp et al., 2000; Noedl et al., 2008).

Marine ecosystems are the largest part of the biosphere. More than 70% of the Earth’s surface is covered by water, and several theories believe that the life on earth originated from the ocean. In certain marine ecosystems such as coral reefs or the deep-sea floor, scientists estimate that the diversity of marine biota is even greater than the biota inhabiting tropical rainforests. Many immobile or slow-moving marine invertebrates, which usually do not have physical protection such as shells or thorns, will produce secondary metabolites as a form of defense mechanism from the environment and other creatures in the ocean (Ebada et al., 2008). These compounds attract the attention of researchers from various fields such as chemistry, pharmacology, biology, and ecology. This
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P. falciparum, 2016). Therefore, compounds (Blunt et al., 2016; Carroll et al., 2019)

Exploration of secondary metabolites from marine organisms is expected to provide new antiactive substances against various diseases (Newman and Cragg, 2007). Several studies have
managed to isolate metabolites from marine microorganisms, green, red, and brown algae, phytoplankton, Cnidaria, Bryozoa, molluscs, tunicates, echinoderms, mangroves, sponges, and terebellids which have proven to have pharmaceutical properties such as acetylcholinesterase inhibitor, radical scavenging activity, cytotoxicity, antimicrobial, anticancer, antitumor, hemolytic, anti-inflammatory, antiparasitic, antimalarial, and antifungal (Blunt et al., 2016; D’Ambrosio et al., 1996; Fattorusso and Taglialetela-Scafati 2009; Orhan et al., 2010; Rama Rao and Faulkner 2002; Setyowati et al., 2009; 2017a; 2017b).

From the perspective of drug discovery, a marine sponge is one of the invertebrate organisms which is interesting to be explored due to its potency producing new compounds (Anjum et al., 2016). The lack of physical defense of sponges resulting in secondary metabolites is estimated to vary depending on their habitats. Metabolite compounds isolated from sponges are highly diverse such as alkaloids, esters, fatty acids, glycosides, ketones, lipids, macrolides, peptides, peroxides, quinones, terpenoids, and polyketides and have shown many biological activities, in which one of them is antimalaria (Blunt et al., 2016; 2017; 2018; Carroll et al., 2019). These kinds of compounds have been found to interfere with pathogenesis at many distinct points; therefore, this can be beneficial in developing selective antimalarial drugs (Sipkema et al., 2005)

The aim of this review is to summarize compounds isolated from marine sponges which exhibit in vitro antimalarial properties, to identify the compounds with potent activity based on their IC50 values, and to highlight the most important functional groups of the compounds related to their potent activity against various strains of P. falciparum. One of the advantages of an in vitro study is that the study could thoroughly illustrate an effect of structural features of tested compounds to their activity with no interference from other factors such as biological system which can be found on in vivo study. Therefore, it can be used to generate more potent derivatives of the compounds to develop selective antimalaria drugs that work in blood-stage P. falciparum.

METHOD

A systematic search was accomplished to find all publications related to the theme until March 2019 in PubMed and Google Scholar. The keywords used to search the articles were "Plasmodium falciparum, sponge, antimalarial” or “Plasmodium falciparum, sponge, antimalosomal.” The data included in the review were primary articles in English about in vitro antimalarial study of pure compounds isolated from marine sponges against P. falciparum as shown in Table 1. The articles obtained were then removed if they are review articles, conference articles, and thesis, and there are no data available to be retrieved. All the synthetic compounds derived from naturally occurring metabolites in sponge are not mentioned in this review. Variables assessed in this review include sponge species/genus, isolated compound, strain of P. falciparum, region/country of origin, and effect on parasite growth inhibition.

EXPLORATION OF MARINE SPONGE METABOLITES FOR ANTIPLASMODIAL ASSAY

Among marine invertebrates, a sponge is the most dominant source for discovering natural products that have been used as lead compound to develop therapeutic drugs (Perdicaris et al., 2013). However, the study done in the investigation of marine sponge metabolites for antimalarial activity is relatively low compared to those of antitumor and anticancer. From literature published until March 2019, we included 50 primary articles for the review (Table 1). We identified that 35 different genera have been studied for their antiplasmodial activities and found that the most frequently studied genera were genus Agelas, Plakortis, and Xestospongia from different locations. Although many bioactive compounds have been isolated from marine sponges (Blunt et al., 2016; 2018; Carroll et al., 2019), the evaluation of their antiplasmodial activity is still relatively low. Figure 1 shows the number of studies that have been done on the examination of in vitro antiplasmodium of isolated compounds from marine sponge.

Overall, the number of publications from year to year shows fluctuation pattern. The highest number of the published papers was in the year of 2010 with 10 articles, followed by six publications in 2009 and 2012. In regard to the number of publications from 2013 to March 2019, it seemed to be stuck at one to three studies each year. This indicates that exploration trend of marine sponge metabolites for antiplasmodial activity diminished from 31 published papers during the period of 1992–2010 to 21 publications during the period of 2011–March 2019. One of the reasons behind the trend is that many scientists are interested in microbiological sample investigations for marine natural product exploration including bacteria and fungus sponge associated, making the detriment of sponge-derived compounds (Carroll et al., 2019; Thomas et al., 2010)

Various ecological studies have shown that secondary metabolites produced by sponges often serve defensive purposes to protect them from threats such as predator attacks, microbial infections, biofouling, and overgrowth by other sessile organisms (Paul and Puglisi, 2004; Paul et al., 2006). Therefore, compounds isolated from the same sponge species are more likely to be different if their habitat is distinct due to the ecological response (Mani et al., 2012). Moreover, a review done by Qaralleh (2016) found out that among 27 species of genus Neopetrosia, there are only nine species which have been chemically studied thus far. These facts disclose significant opportunities to do the chemical constituent exploration from not only Neopetrosia but also the other genus. In terms of collection site of the sponges, Australia, Bahamas, Indonesia, and Thailand were the most explored site so far for the search of compounds which exhibit in vitro antiplasmodium (P. falciparum strains). Other sponges were collected from Turkey, Vanuatu, Madagascar, Caledonia, Fiji, China, Japan, Alaska, Jamaica, Solomon Island, Puerto Rico, Papua New Guinea, and others (Table 1).
### Table 1. Summarized data of isolated compounds which have been tested for their antiplasmodial activity.

| No | Organisms                  | Isolated compound                        | Pf Strain | IC₅₀ (µM) | Origin                                | Ref.                                      |
|----|----------------------------|------------------------------------------|-----------|----------|---------------------------------------|-------------------------------------------|
| 1  | *Acanthella klethra*       | Axisonitrile 3                           | D6        | 0.61     | Pelorus Island, Queensland, Australia | (Angerhofer et al., 1992)                |
|    |                            | Axisothiocyanate 3                       | D6        | 46.85    |                                       |                                           |
|    |                            | The eudesmane compound A⁺                | D6        | 8.50     |                                       |                                           |
|    |                            | The eudesmane compound B⁰                | D6        | 16.17    |                                       |                                           |
|    |                            | The eudesmane compound C⁺                | D6        | >37.96   |                                       |                                           |
|    |                            |                                          | W2        | 0.07     |                                       |                                           |
| 2  | *Acanthostrongylophora ingens* | (+)-8-hydroxymanzamine A                  | D6        | 0.03     | Papua New Guinea                      | (Samoylenko et al., 2009)                |
|    |                            | (+)-manzamine A                          | D6        | 0.04     |                                       |                                           |
|    |                            | (+)-8-hydroxymanzamine A hydrochloride   | D6        | 0.04     |                                       |                                           |
|    |                            | (+)-manzamine A hydrochloride            | D6        | 0.01     |                                       |                                           |
| 3  | *Acanthostrongylophora sp.* | Manzamine A                              | D6        | 0.01     | Knife Cape, Manado, Indonesia         | (Rao et al., 2006)                       |
|    |                            | (+)-8-hydroxymanzamine A                 | D6        | 0.01     |                                       |                                           |
|    |                            | Manzamine Y                              | D6        | 0.74     |                                       |                                           |
|    |                            | Manzamine E                              | D6        | 6.02     |                                       |                                           |
|    |                            | 6-hydroxymanzamine E                     | D6        | 1.36     |                                       |                                           |
|    |                            | Manzamine F                              | D6        | 1.34     |                                       |                                           |
|    |                            | 12,34-oxamanzamine A                     | D6        | 8.97     |                                       |                                           |
|    |                            | Ent-12,34-oxamanzamine F                 | D6        | 1.45     |                                       |                                           |
|    |                            | 12,28-oxamanzamine A                     | D6 and W2 | na       |                                       |                                           |
|    |                            | 12,28-oxa-8-hydroxy-manzamine A          | D6 and W2 | na       |                                       |                                           |
|    |                            | 12,34-oxamanzamine E                     | D6 and W2 | na       |                                       |                                           |
|    |                            | 12,28-oxamanzamine E                     | D6 and W2 | na       |                                       |                                           |
|    |                            | 12,34-oxa-6-hydroxymanzamine E           | D6 and W2 | na       |                                       |                                           |
| 4  | *Acanthostrongylophora sp.* | Manzamine A N-oxide                      | D6        | 0.02     | Manado, Indonesia                     | (Rao et al., 2004)                       |
|    |                            |                                          | W2        | 0.02     |                                       |                                           |
|    |                            | 3,4-dihydromanzamine A-N-oxide           | D6        | 2.82     |                                       |                                           |
|    |                            | Manzamine J                              | D6        | 2.36     |                                       |                                           |
|    |                            | 6-deoxymanzamine X                       | D6        | 2.30     |                                       |                                           |
|    |                            |                                          | W2        | 2.48     |                                       |                                           |

(Continued)
| No | Organisms                          | Isolated compound                          | Py Strain | IC₅₀ (µM) | Origin                        | Ref.                           |
|----|-----------------------------------|--------------------------------------------|-----------|-----------|-------------------------------|--------------------------------|
| 5  | *Agelas cf. mauritiana*           | Agelasine J                                | FcB1      | 6.60      | Solomon Islands               | (Appenzeller et al., 2008)     |
|    |                                   | Agelasine K                                | FcB1      | 8.30      |                               |                                |
|    |                                   | Agelasine L                                | FcB1      | 18.00     |                               |                                |
| 6  | *Agelas gracilis*                 | Gracilioethers A                           | ItG       | 28.22     | Oshima-Shinsone, Japan        | (Ueoka et al., 2009)           |
|    |                                   | Gracilioethers B                           | ItG       | 1.56      |                               |                                |
|    |                                   | Gracilioethers C                           | ItG       | 31.02     |                               |                                |
| 7  | *Agelas oroides*                  | 24-ethyl-cholest-5α-7-en-3α-ol             | K1        | 38.82     | Go’ce, ceda, Turkey           | (Tasdemir et al., 2007)        |
|    |                                   | 4,5-dibromopyrrole-2-carboxylic acid methyl ester | K1     | >176.73   |                               |                                |
|    |                                   | 4,5-dibromopyrrole-2-carboxylic acid (free base) | K1     | >185.95   |                               |                                |
|    |                                   | 4,5-dibromopyrrole-2-carboxylic acid (salt) | K1        | 136.37    |                               |                                |
|    |                                   | (E)-oroidin (free base)                    | K1        | 10.02     |                               |                                |
|    |                                   | (E)-oroidin (salt)                         | K1        | 16.25     |                               |                                |
|    |                                   | 3-amino-1-(2-aminoimidazoyl)-prop-1-ene    | K1        | 53.56     |                               |                                |
|    |                                   | Taurine                                    | K1        | >399.52   |                               |                                |
| 8  | *Agelas dispar*                   | Longamide B                                | K1        | 21.19     | Little San Salvador Island    | (Scala et al., 2010)           |
| 9  | *Agelas longissima*               | Longamide A                                | K1        | >64.53    | Little San Salvador Island    | (Scala et al., 2010)           |
|    |                                   | Agelongine                                  | K1        | 32.97     |                               |                                |
| 10 | Genus Agelas (*A. conifera*, *A. clathrodes*, *A. longissima*, and *A. dispar*) | Hymenidin                                  | K1        | 40.43     |                               | (Scala et al., 2010)           |
|    |                                   | Dispacamide B                              | K1        | 4.11      |                               |                                |
|    |                                   | Dispacamide D                              | K1        | >58.45    |                               |                                |
| 11 | *Aplysinella strongylata*         | 19-hydroxypsammmaplysin E                  | 3D7       | 6.40      | Tulamben Bay, Bali, Indonesia | (Madiana et al., 2012)         |
|    |                                   | Psammmaplysin L                            | 3D7       | nat 10 µM |                               |                                |
|    |                                   | Psammmaplysin M                            | 3D7       | nat 10 µM |                               |                                |
|    |                                   | Psammmaplysin N                            | 3D7       | nat 10 µM |                               |                                |
|    |                                   | 19-hydroxypsammmaplysin P                  | 3D7       | nat 10 µM |                               |                                |
|    |                                   | Psammmaplysin T                            | 3D7       | nat 10 µM |                               |                                |
|    |                                   | Psammmaplysin V                            | 3D7       | nat 10 µM |                               |                                |
| 12 | *Axinyssa dijiferi*               | Axidjiferosides (mix-A, -B, -C)           | Fcb1      | 0.53      | Senegalese coasts, Keur Bamboung | (Farokhi et al., 2013)         |
| 13 | *Axinella verrucosa*              | Stevensine                                  | K1        | 12.61     | Calvi Bay, Corsica            | (Scala et al., 2010)           |
|    |                                   | Spongialcidin B                            | K1        | 3.34      |                               |                                |
|    |                                   | Bromoaldisine                              | K1        | >82.08    |                               |                                |
|    |                                   | Dibromopalau'amine                         | K1        | 1.48 µg/ml |                               |                                |
|    |                                   | Bromopyrrolohomoarginin                    | K1        | >20 µg/ml |                               |                                |
|    |                                   | Manzacidin A                               | K1        | >20 µg/ml |                               |                                |

(Continued)
| No | Organisms                   | Isolated compound                                                                 | Py Strain  | IC₅₀ (µM) | Origin                        | Ref.                              |
|----|-----------------------------|------------------------------------------------------------------------------------|------------|-----------|-------------------------------|-----------------------------------|
| 14 | *Bienna laboutei*           | Netamine K                                                                        | not available | 2.40     | Salary Bay, Madagascar        | (Gros et al., 2014)               |
|    |                             | Mirabilin A                                                                       | not available | 20.70    |                                |                                   |
| 15 | *Bienna laboutei*           | Netamine O                                                                        | not available | 16.99    | Salary Bay, Madagascar        | (Gros et al., 2015)               |
|    |                             | Netamine P                                                                        | not available | 32.62    |                                |                                   |
|    |                             | Netamine Q                                                                        | not available | 8.37     |                                |                                   |
|    |                             | Netamine H                                                                        | not available | na       |                                |                                   |
|    |                             | Netamine I                                                                        | not available | na       |                                |                                   |
|    |                             | Netamine N                                                                        | not available | na       |                                |                                   |
|    |                             | Netamine C                                                                        | not available | na       |                                |                                   |
|    |                             | Netamine F                                                                        | not available | na       |                                |                                   |
| 16 | *Callyspongia fibrosa*      | 24S-24- methyl-cholestane 3β,6β,25-triol-25-O-acetate                              | 3D7        | 54.81    | The Gulf of Mannar, Western Bay of Bengal, India | (Prakasa Rao et al., 2010)         |
|    |                             | 24S-24-methyl-cholestane-3β,5α,6β,25-tetraol-25-monoacetate                        | 3D7        | 30.10    |                                |                                   |
|    |                             | 24S-24-methyl-cholestane-3β,6β,8β,25-tetraol-25-O-acetate                          | 3D7        | 48.46    |                                |                                   |
|    |                             | 24S-24-methyl-cholester-3β,5α,6β,12β,25-pentaol-25-O-acetate                       | 3D7        | 48.48    |                                |                                   |
| 17 | *Clathria calla*            | Norbatzelladine L                                                                 | FcB1       | 0.40     | Island of Martinique          | (Laville et al., 2009)            |
|    |                             | Clathriadic acid                                                                  |            | 2.30     |                                |                                   |
| 18 | *Cymbastela cantharella*    | Giroline                                                                           | FcB1       | 0.21     | Caledonian sponge             | (Benoit-Vical et al., 2008)       |
|    |                             |                                                                                  | FcM29      | 0.13     |                                |                                   |
|    |                             |                                                                                  | F32        | 0.08     |                                |                                   |
| 19 | *Cymbastela hooperi*        | (1S,3S,4R,7S,8S,11S,12S,13S,15R,20R)-7-Formamido-20-isocyanoisocycloamphilectane | FCR3F86    | 0.58     | Not available                 | (Wright and Lang-Unnasch, 2009)   |
|    |                             | W2                                                                                 | 1.75       |          |                                |                                   |
|    |                             | D6                                                                                 | 2.34       |          |                                |                                   |
|    |                             | (1S,3S,4R,7S,8S,11S,12S,13S,15R,20R)-7,20-Diformamidoisocycloamphilectane          | FCR3F86    | 41.05    |                                |                                   |
|    |                             | (1S*,3S*,4R*,7S*,8S*,12S*,13S*)-7-formamidocycloamphilect-11(20)-ene               | FCR3F86    | na       |                                |                                   |
|    |                             | (1R*,3S*,4R*,7S*,8S*,12S*,13S*)-7-formamidocycloamphilecta-11(20),14-diene        | FCR3F86    | na       |                                |                                   |
|    |                             | (1S*,3S*,4R*,7S*,8S*,12S*,13S*)-7-formamidocycloamphilecta-11(20),15-diene        | FCR3F86    | na       |                                |                                   |
| 20 | *Desmapsamma anchorata*     | sulfated polysaccharides                                                          | 3D7        | 66.3 μg/ml | Not available                 | (Marques et al., 2016)            |
| 21 | *Diacarnus megaspinorhabdosa* | Diacarnuperoxide M                                                                | W2         | 4.20     | Xisha Islands                 | (Yang et al., 2010)               |
|    |                             |                                                                                  | D6         | 5.60     |                                |                                   |
|    |                             | Diacarnuperoxide N                                                                | W2         | 3.00     |                                |                                   |
|    |                             |                                                                                  | D6         | 6.60     |                                |                                   |
|    |                             | (+)-2, 3, 6-epihurghaperoxide                                                    | W2         | 1.60     |                                |                                   |
|    |                             |                                                                                  | D6         | 2.20     |                                |                                   |
|    |                             | (+)-2,3,6-epihurghaperoxide acid                                                | W2         | 4.90     |                                |                                   |

(Continued)
| No | Organisms                         | Isolated compound                           | Py/ Strain | IC₅₀ (µM) | Origin | Ref.                      |
|----|----------------------------------|---------------------------------------------|------------|-----------|---------|---------------------------|
| 22 | Fascaplysinopsis reticulata     | 8-oxo-tryptamine                            | 3D7        | 50.52     | Passe Bateau, Mayotte     | (Campos et al., 2019) |
|    |                                  | (E) and (Z)-6-bromo-20-demethyl-30-N-      |            |           |                     |                           |
|    |                                  | methylaplysinopsin                          |            |           |                     |                           |
|    |                                  | 6,6'-bis-(debrono)-gelliusine F             | 3D7        | na        |                     |                           |
|    |                                  | 6-bromo-8,1'-dihydro-isoplysin A            | 3D7        | na        |                     |                           |
|    |                                  | 5,6-dibromo-8,1'-dihydro-isoplysin A       | 3D7        | na        |                     |                           |
|    |                                  | tryptamine                                  | 3D7        | na        |                     |                           |
| 23 | Hyattella sp.                    | psammaplysin G                              | Dd2        | 98% totga 40 µM | Hervey Bay, Sponge Garden, Queensland, Australia | (Yang et al., 2010) |
|    |                                  | psammaplysin F                             | Dd2        | 1.40      |                     |                           |
| 24 | Hymeniacidon sp                  | monamphilectine A                           | W2         | 0.60      | Mona Island, Puerto Rico |                           |
| 25 | Hyrtios cf. erecta              | hormofascaplysin A                          | K1, NF54   | na        |                     |                           |
|    |                                  | fascaplysin                                 | K1, NF54   | 0.04, 0.07|                     |                           |
|    |                                  |                                              |            |           |                     |                           |
| 26 | Hyrtios erectus                 | smenotronic acid                            | Dd2        | 3.51      | Chonk Island, Federated States of Micronesia | (Ju et al., 2018) |
|    |                                  | ilimaquinone                                | Dd2        | 2.11      |                     |                           |
|    |                                  | pelorol                                     | Dd2        | 0.80      |                     |                           |
| 27 | Ircinia sp.                     | tryptophol                                  | K1         | 31.51     | Aegean Sea, Turkey     | (Orhan et al., 2010) |
|    |                                  | 4-hydroxy-3-tetraprenyl-phenylacetic acid   | K1         | 7.77      |                     |                           |
|    |                                  | demethylfiurospongin-4                      | K1         | 32.23     |                     |                           |
|    |                                  | dorisenone D                                | K1         | 1.03      |                     |                           |
|    |                                  | 11β-acetoxyspongi-12-en-16-one              | K1         | 3.02      |                     |                           |
| 28 | Genus Latrunculia               | discorhabdins A                             | D6         | 0.05      | Aleutian Islands      | (Na et al., 2010)        |
|    | (later identified as Latrunculia (L.) hamanni sp. nov. (Kelly et al., 2016)) | discorhabdins C                             | D6         | 2.80      |                     |                           |
|    |                                  | dihydrodiscorhabdin C                      | D6         | 0.17      |                     |                           |
|    |                                  |                                              | W2         | 0.13      |                     |                           |
| 29 | Lendenfeldia dendyi             | Four polybromidated diphenyl ethers        | D6         | na        | Papua New Guinea      | (Radwan et al., 2015)    |
|    |                                  |                                              | W2         | na        |                     |                           |
| 30 | Mycophora sp.                   | Crambescidin 800                            | FCR3       | 0.24      | Not available        | (Lazar et al., 2006)    |
|    |                                  |                                              | 3D7        | 0.16      |                     |                           |
| 31 | Monanchora arbuscula            | norbatzelladine A                           | FcB1       | 0.20      | island of Martinique  | (Laville et al., 2009)  |
|    |                                  | dinorbatzelladine A                         | FcB1       | 0.90      |                     |                           |
|    |                                  | dinordehydrobatzelladine B                 | FcB1       | 0.80      |                     |                           |
|    |                                  | dihomodehydrobatzelladine C                | FcB1       | 4.50      |                     |                           |

(Continued)
| No | Organisms                  | Isolated compound                  | Pf/Strain | IC$_{50}$ (µM) | Origin                                      | Ref.                      |
|----|---------------------------|------------------------------------|-----------|-----------------|---------------------------------------------|---------------------------|
| 32 | *Monanchora unguiculata*  | Unguiculin A                       | 3D7       | 12.89           | Mitsio Islands, Madagascar                  | (Campos et al., 2019)     |
|    |                           | Ptilomyacin E                      | 3D7       | 0.35            |                                             |                           |
|    |                           | Ptilomyacin F                      | 3D7       | 0.23            |                                             |                           |
|    |                           | Ptilomycalins G + H                | 3D7       | 0.46            |                                             |                           |
|    |                           | Crambescidin 800                   | 3D7       | 0.52            |                                             |                           |
|    |                           | Fromiamycalin                      | 3D7       | 0.24            |                                             |                           |
| 33 | New Caledonian Sponge     | Alisiaquinones A                   | FeMC29    | 8.50            | the Norfolk Rise                           | (Desouzadanne et al., 2008) |
|    |                           |                                    | FeB1      | 7.40            |                                             |                           |
|    |                           |                                    | F32       | 9.10            |                                             |                           |
|    |                           | Alisiaquinones B                   | FeMC29    | 2.60            |                                             |                           |
|    |                           |                                    | FeB1      | 8.40            |                                             |                           |
|    |                           |                                    | F32       | 7.10            |                                             |                           |
|    |                           | Alisiaquinones C                   | FeMC29    | 0.08            |                                             |                           |
|    |                           |                                    | FeB1      | 0.21            |                                             |                           |
|    |                           |                                    | F32       | 0.15            |                                             |                           |
|    |                           | Alisioaquinol                      | FeMC29    | 7.90            |                                             |                           |
|    |                           |                                    | FeB1      | 6.40            |                                             |                           |
|    |                           |                                    | F32       | 9.90            |                                             |                           |
| 34 | *Pachastrissa nux*        | Kabiramide J                       | K1        | 0.31            | Kab-Tao, Surat-Thani Province and Chumphon Islands National Park, Chumphon Province, Thailand | (Sirirak et al., 2011)   |
|    |                           | Kabiramide K                       | K1        | 0.39            |                                             |                           |
|    |                           | Kabiramide B                       | K1        | 1.67            |                                             |                           |
|    |                           | Kabiramide C                       | K1        | 4.79            |                                             |                           |
|    |                           | Kabiramide D                       | K1        | 1.87            |                                             |                           |
|    |                           | Kabiramide G                       | K1        | na              |                                             |                           |
| 35 | *Pachastrissa nux*        | Kabiramide L                       | K1        | 2.60            | Chumphon Islands National Park, Thailand    | (Sirirak et al., 2011)   |
|    |                           | Kabiramide I                       | K1        | 4.50            | Kab Tao, Surat Thani Province, Thailand     |                           |
| 36 | *Petrosid Ng5 Sp5*        | Ingamine A                         | D6        | 0.20            | Not available                               | (Fattorusso et al., 2010) |
|    |                           |                                    | W2        | 0.16            |                                             |                           |
|    |                           | 22(S)-hydroxyingamine A            | D6        | 0.47            |                                             |                           |
|    |                           |                                    | W2        | 0.30            |                                             |                           |
|    |                           | Dihydroingenamine D                | D6        | 0.18            |                                             |                           |
|    |                           |                                    | W2        | 0.30            |                                             |                           |
| 37 | *Plakortis cfr. simplex*  | Manadoperoxide A                   | D10       | 6.88            | Bunaken Marine Park of Manado, Indonesia     | (Fattorusso et al., 2010) |
|    |                           |                                    | W2        | 3.74            |                                             |                           |
|    |                           | Manadoperoxide B                   | D10       | 6.76            |                                             |                           |
|    |                           |                                    | W2        | 3.69            |                                             |                           |
|    |                           | Manadoperoxide C                   | D10       | 4.54            |                                             |                           |
|    |                           |                                    | W2        | 2.33            |                                             |                           |

(Continued)
| No | Organisms | Isolated compound | Pf Strain | IC₅₀ (µM) | Origin | Ref. |
|----|-----------|-------------------|-----------|----------|--------|------|
| 38 | *Plakortis halichondrioides* | Epiplatinic acid F methyl ester | W2 | 0.01 | Mona Island, Puerto Rico | (Jiménez-Romero et al., 2010) |
|    |           | Epiplatinidioic acid | W2 | 0.95 |        |      |
|    |           | Epiplatinic acid F | W2 | 7.93 |        |      |
|    |           | Plakortolide J | W2 | na |        |      |
|    |           | Plakortolide F | W2 | na |        |      |
| 39 | *Plakortis lita* | Thiaplakortones A | 3D7 | 0.05 | Melville Passage, Tydeman Reef, Queensland, Australia | (Davis et al., 2012) |
|    |           | Dd2 | 0.01 |
|    |           | Thiaplakortones B | 3D7 | 0.65 |
|    |           | Dd2 | 0.09 |
|    |           | Thiaplakortones C | 3D7 | 0.31 |
|    |           | Dd2 | 0.17 |
|    |           | Thiaplakortones D | 3D7 | 0.28 |
|    |           | Dd2 | 0.16 |
| 40 | *Plakortis simplex* | Plakortin | D10 | 1.26 | Berry Island (Bahamas) | (Fattorusso, 2002) |
|    |           | W2 | 0.73 |
|    |           | Dihydroplakortin | D10 | 1.12 |
|    |           | W2 | 0.76 |
|    |           | Plakortide E | D10 | na |
|    |           | W2 | na |
| 41 | *Plakortis sp.* | Plakortide F | D6 | 1.35 | Discovery Bay, Jamaica | (Gochfeld and Hamann, 2001) |
|    |           | W2 | 1.10 |
|    |           | Plakortene G | D6 | 15.09 |
|    |           | W2 | 17.10 |
| 42 | Genus *Pseudoceratina* | Psammaplysin H | 3D7 | 0.41 | Not available | (Xu et al., 2011) |
|    |           | Psammaplysin G | 3D7 | 5.22 |
|    |           | Psammaplysin F | 3D7 | 1.92 |
| 43 | *Pseudoceratina sp.* | Ceratinadin E | K1 | 0.90 | Okinawa, Japan | (Kurimoto et al., 2018) |
|    |           | FCR3 | 0.67 |
|    |           | Ceratinadin F | K1 | >8.16 |
|    |           | Psammaplysin F | K1 | 5.16 |
|    |           | FCR3 | 3.35 |
| 44 | *Pseudoceratina sp.* | Methyl (2,4-dibromo-3,6-dihydroxyphenyl) acetate | FcB1 | 12 | Rowa islands, Banks Territory (Vanuatu) | (Lebouvier et al., 2009) |
| 45 | *Smenospongia aurea* | 6'-chloroaureol | D6 | 9.74 | Discovery Bay, Jamaica | (Hu et al., 2002) |
|    |           | Isoplysin A | D6 | 3.54 |
|    |           | 6-bromo-2'-de-N-methylaplysinopsin | D6 | 3.45 |
|    |           | 6-bromotaplysinopsin | D6 | 1.02 |
|    |           | Makaluvamine O | D6 | 3.52 |
|    |           | Aureol | D6 | na |
|    |           | Aureol acetate | D6 | na |
|    |           | 2'-de-N-methylaplysinopsin | D6 | na |
|    |           | N,3'-methylaplysinopsin | D6 | na |
|    |           | N,3'-ethaplysinopsin | D6 | na |

(Continued)
| No | Organisms              | Isolated compound                                      | Pf Strain | IC<sub>50</sub> (µM) | Origin                                      | Ref.                      |
|----|------------------------|--------------------------------------------------------|-----------|-----------------------|--------------------------------------------|--------------------------|
| 46 | *Spongia* sp.          | Squalene                                               | K1        | 2.82 µM               | Aegean Sea, Turkey                        | (Orhan et al., 2010)     |
|    |                        | Furonospinulosin-1                                    | K1        | 31.53 µM              |                                            |                          |
|    |                        | Furospongine                                           | K1        | 42.42 µM              |                                            |                          |
|    |                        | 2-(hexaprenylmethyl)-2-methylchroomenol                | K1        | >34.19 µM             |                                            |                          |
|    |                        | Heptaprenyl-p-quinol                                   | K1        | >33.28 µM             |                                            |                          |
|    |                        | 12-epi-deoxoscalarin                                   | K1        | 17.37 µM              |                                            |                          |
|    |                        | 4-hydroxy-3-octaprenylbenzoic acid                     | K1        | 2.29 µM               |                                            |                          |
|    |                        | furospinulosin-2                                       | K1        | 8.30 µM               |                                            |                          |
| 47 | *Spongosorites* sp.    | Nortopsentin A                                         | 3D7       | 0.46                  | Lucaya, Bahamas                           | (Alvarado et al., 2013)  |
| 48 | *Stylissa caribica*    | Stevensin                                              | D6        | 4.65                  | Columbus Park, Jamaica                     | (Mohammed et al., 2006)  |
|    |                        | oroidin                                                | D6        | 3.08                  |                                            |                          |
|    |                        | Stylistin 1                                            | D6        | na                    |                                            |                          |
|    |                        | Stylistin 2                                            | D6        | na                    |                                            |                          |
|    |                        | Phakellistatin 13                                      | D6        | na                    |                                            |                          |
|    |                        | sceptrin                                               | D6        | na                    |                                            |                          |
| 49 | *Stylissa cf. massa*   | 8-isocyanato-15-formamidoamphilect-11(20)-ene          | K1        | 8.85                  | Kob-Tao, Surat-Thani Province, Thailand (10°7.569′ N, 99°48.665’ E) | (Chanthathamrongsiri et al., 2012) |
|    |                        | 8-isothiocyanato-15-formamidoamphilect-11(20)-ene      | K1        | 8.07                  |                                            |                          |
|    |                        | 8-isocyanato-15-formamidoamphilect-11(20)-ene          | K1        | 0.52                  |                                            |                          |
|    |                        | 7-formamidoamphilect-11(20),15-diene                   | K1        | na                    |                                            |                          |
| 50 | *Suberea ianthelliformis* | Araplysillin I                                       | FcB1      | 4.5                   | Anuta Paina Island (Malaita)               | (Mani et al., 2012)      |
|    |                        |                                                       | 3D7       | 4.6                   |                                            |                          |
|    |                        | Araplysillin II                                        | FcB1      | 34.2                  |                                            |                          |
|    |                        | Araplysillin N20-formamide                             | FcB1      | 3.6                   |                                            |                          |
|    |                        |                                                       | 3D7       | 7.0                   |                                            |                          |
|    |                        | Araplysillin IV                                        | FcB1      | 27.6                  |                                            |                          |
|    |                        | Araplysillin V                                         | FcB1      | 50.5                  |                                            |                          |
|    |                        | Araplysillin VI                                        | FcB1      | 37.4                  |                                            |                          |
|    | *Suberea ianthelliformis* | Aerophobin I                                         | FcB1      | 59.0                  | New Georgia Island                        | (Mani et al., 2012)      |
|    |                        | Aerophobin II                                          | FcB1      | 24.9                  |                                            |                          |
|    |                        |                                                       | 3D7       | 19.9                  |                                            |                          |
|    |                        | Purealidin Q                                           | FcB1      | 3.6                   |                                            |                          |
|    |                        | Araplysillin N20-hydroxyformamide                      | FcB1      | 5.0                   |                                            |                          |
|    |                        |                                                       | 3D7       | 4.1                   |                                            |                          |
|    | *Suberea ianthelliformis* | Aerothionin                                           | FcB1      | 3.4                   | North West of Nggela Island               | (Mani et al., 2012)      |
|    |                        |                                                       | 3D7       | 4.2                   |                                            |                          |
|    |                        | Homoserothionin                                        | FcB1      | 2.8                   |                                            |                          |
|    |                        |                                                       | 3D7       | 4.0                   |                                            |                          |
|    |                        | 11,19-Dideoxyfistularin 3                              | FcB1      | 2.1                   |                                            |                          |
|    |                        |                                                       | 3D7       | 0.9                   |                                            |                          |
|    |                        | 11-Hydroxyfistularin 3                                 | FcB1      | 2.1                   |                                            |                          |
|    |                        |                                                       | 3D7       | 2.6                   |                                            |                          |
|    |                        | Aplysinone D                                           | FcB1      | 1.0                   |                                            |                          |
|    |                        |                                                       | 3D7       | 3.1                   |                                            |                          |

(Continued)
| No | Organisms          | Isolated compound                        | IC₅₀ (µM) | Origin                                      | Ref.                      |
|----|--------------------|------------------------------------------|----------|---------------------------------------------|---------------------------|
| 51 | *Verongula rigida* | Purealidin B                             | 23.2%    | Urabá Gulf, Caribbean Sea, Colombia (8°40′14″N, 77°21′28″W) | (Galeano et al., 2011)   |
|    |                    | 11-hydroxyaerothionin                    | 8.0%     |                                             |                           |
|    |                    | Aeroplysinin                             | 35.3%    |                                             |                           |
|    |                    | Dihydroxyaerothionin                     | 7.9%     |                                             |                           |
|    |                    | Purealidin R                             | 7.1%     |                                             |                           |
|    |                    | 3,5-dibromo-N,N,N-trimethyltyraminium    | na       |                                             |                           |
|    |                    | 3,5-dibromo-N,N,N,O-tetramethyltyraminium| na       |                                             |                           |
|    |                    | 19-deoxyfistularin 3                     | na       |                                             |                           |
| 52 | *Xestospongia exigua* | Araguspongine C                         | 1.4      | Bayadha, Saudi Arabian Red Sea coast       | (Orabi et al., 2002)    |
|    |                    | W2                                       | 0.58     |                                             |                           |
|    |                    | (+)- Araguspongine K                     | na       |                                             |                           |
|    |                    | W2                                       | na       |                                             |                           |
|    |                    | (+)- Araguspongine L                     | na       |                                             |                           |
|    |                    | W2                                       | na       |                                             |                           |
| 53 | *Xestospongia sp.*  | Kaimanol                                 | 0.36     | Kaimana, West Papua, Indonesia             | (Murtihapsari et al., 2019) |
|    |                    | Saringoster                             | 2.50 × 10⁻⁴|                                              |                           |
| 54 | *Xestospongia sp.*  | Xestoquinone                             | 3        | Malvoror reef, Vanuatu                     | (Laurent et al., 2006)  |
| 55 | genus Xestospongia  | Halenaquinone                            | >30      | South Pacific                              | (Longeon et al., 2010)  |
|    |                    | 3-Ketoadociaquinone A                    | 1.08     |                                             |                           |
|    |                    | 3-Ketoadociaquinone B                    | 1.67     |                                             |                           |
|    |                    | Tetrahydrohalenaquinone A               | 3.89     |                                             |                           |
|    |                    | 3-Ketoadociaquinone B                    | 4.12     |                                             |                           |
|    |                    | Tetrahydrohalenaquinone B               | 3.89     |                                             |                           |
|    |                    | Halenaquinol sulfate                     | 3.89     |                                             |                           |
|    |                    | Xestosaprol C methylacetul               | 3.89     |                                             |                           |
|    |                    | Orhalquinone                             | 9.22     |                                             |                           |
|    |                    | 3-D7                                     | 0.01     | Rodda Reef, Queensland, Australia          | (Davis et al., 2012)    |
|    |                    | Dd2                                      | 0.02     |                                             |                           |
|    |                    | makaluvamines J                          | 0.02     |                                             |                           |
|    |                    | Dd2                                      | 0.02     |                                             |                           |
|    |                    | makaluvamines G                          | 0.04     |                                             |                           |
|    |                    | Dd2                                      | 0.04     |                                             |                           |
|    |                    | makaluvamines L                          | 0.04     |                                             |                           |
CLASSIFICATION OF ANTIPLASMODIAL ACTIVITY OF ISOLATED COMPOUND FROM SPONGES

In this review, we give an overview of the bioactive metabolites recently isolated from marine sponges that have shown activity in in vitro study against P. falciparum. To compare the IC<sub>50</sub> values, the units in μg/ml and nM were converted to μM. All the isolated compounds were then classified based on their IC<sub>50</sub> values by following the definition of Batista et al. (2009), who grouped compounds into potent activity: IC<sub>50</sub> < 1 μM, good activity: IC<sub>50</sub> of 1–20 μM, moderate activity: IC<sub>50</sub> of 20–100 μM, low activity: IC<sub>50</sub> of 100–200 μM, and inactive: IC<sub>50</sub> >200 μM (Batista et al., 2009). To be noted, the mechanism of the in vitro continuous cultures of P. falciparum approach is only related to the inhibition of growth in erythrocytic stages of the parasite (Chin et al., 1979). Consequently, this IC<sub>50</sub>-based classification would exclude compounds that may have other specific mechanism of action. It would be wise to re-evaluate “not active compounds” with other assay or holistic approach such as the reverse pharmacology technique (Simoes-Pires et al., 2014).

As shown in Figure 2, among observed bioactive metabolites, there were 57 different compounds that have potent activity, 101 with good activity, and 26 compounds with moderate activity against various strains of P. falciparum. Some of the compounds could not be classified because, in the highest tested concentration, their activity was low or inactive and some reports use inhibition concentration instead of IC<sub>50</sub> making it incomparable. In regard to the dependency of IC<sub>50</sub> to plasmodium strains, it seems that antiplasmodial activity of some isolated compounds did not depend on chloroquine/drug sensitivity of the strain (Fattorusso et al., 2010; Longeon et al., 2010; Mani et al., 2012).

The class of compounds which exhibit potent antiplasmodial activity includes manzamine alkaloid (Rao et al., 2004; 2006; Samoylenko et al., 2009), guanidine alkaloids (Campos et al., 2017; Laville et al., 2009), bispyrroloiminoquinone alkaloid (Davis et al., 2012), pyrroloiminoquinone alkaloids (Na et al., 2010), ingamine alkaloids (Ilias et al., 2012), sesquiterpenoids (Angerhofer et al., 1992), diterpene formamides (Wright and Lang-Unnasch, 2009), aminoimidazole (Benoit-Vical et al., 2008), β-galactosyl ceramides (Farokhi et al., 2013), β-lactam (Avilés and Rodríguez, 2010), meroterpene (Desoubzdanne et al., 2008), trisoxazole macrorides (Sirirak et al., 2011), peroxides, thiazine alkaloids (Davis et al., 2012), bromotyrosine alkaloids (Kurimoto et al., 2018; Xu et al., 2011), and sterols (Murtihapsari et al., 2019).

FUNCTIONAL GROUP IN POTENT ANTIPLASMODIAL ACTIVITY

Some marine isonitriles show various biological activities such as antimalarial, antitubercular, antifouling, and antiplasmodial effect. Marine isonitriles differ from terrestrial isonitriles in terms of their biosynthetic pathways. Most of the marine compounds containing isonitrile were derived from terpenoid, whereas terrestrial isonitriles originate from α-amino acids (Emsermann et al., 1979).
Table 2. List of isolated compounds with potent antiplasmodial activity based on IC\textsubscript{50} measurement.

| No. | Isolated Compound                      | P. falciparum strain |
|-----|---------------------------------------|---------------------|
| 1   | Axisonitrile 3                         | D6 and W2           |
| 2   | (+)-8-hydroxymanzamine A              | D6 and W2           |
| 3   | (+)-manzamine A                       | D6 and W2           |
| 4   | (+)-8-hydroxymanzamine A hydrochloride| D6 and W2           |
| 5   | (+)-manzamine A hydrochloride         | D6 and W2           |
| 6   | Manzamine A                           | D6 and W2           |
| 7   | Manzamine Y                           | D6                  |
| 8   | Manzamine A N-oxide                   | D6 and W2           |
| 9   | Axidjiferosides                        | FcB1                |
| 10  | Norbatzelladine L                     | FcB1                |
| 11  | Giroline                              | FcB1; W2; FcM29; F32|
| 12  | (1S,3S,4R,7S,8S,11S,12S,13S,15R,20R)-7-Formamido-20-isocyanoisocycloamphilectane| FCR3F86 |
| 13  | Monamphilectine A                     | W2                  |
| 14  | Homofascaplysin A                     | K1 and NF54         |
| 15  | Fascaplysin                           | K1 and NF54         |
| 16  | Pelorol                               | Dd2                 |
| 17  | Discorhabdins A                       | D6 and W2           |
| 18  | Dihydrodisorhabdin C                  | D6 and W2           |
| 19  | Crambescidin 800                      | FCR3 and D37        |
| 20  | Norbatzelladine A                     | FcB1                |
| 21  | Dinorbatzelladine A                   | FcB1                |
| 22  | Dinordehydrobatzelladine B            | FcB1                |
| 23  | Batzelladine A                        | FcB1                |
| 24  | Batzelladine L                        | FcB1                |
| 25  | Ptilomycalin A                        | FcB1                |
| 26  | Ptilomycalin E                        | 3D7                 |
| 27  | Ptilomycalin F                        | 3D7                 |
| 28  | Ptilomycalin G + H                    | 3D7                 |
| 29  | Fromiamycalin                         | 3D7                 |
| 30  | Alisiaquinone C                       | FeMC29; FcB1; and F32|
| 31  | Kabiramide J                          | K1                  |
| 32  | Kabramide K                           | K1                  |
| 33  | Ingamine A                            | D6 and W2           |
| 34  | 22(S)-hydroxyingamine A               | D6 and W2           |
| 35  | Dihydroergotamine D                   | D6 and W2           |
| 36  | Epiplakinic acid F methyl ester       | W2                  |
| 37  | Epiplakimidioic acid                  | W2                  |
| 38  | Thiaplatokorne A                      | 3D7 and Dd2         |
| 39  | Thiaplatokorne B                      | 3D7 and Dd2         |
| 40  | Thiaplatokorne C                      | 3D7 and Dd2         |
| 41  | Thiaplatokorne D                      | 3D7 and Dd2         |
| 42  | Plakortin                             | W2                  |
| 43  | Dihydroplakortin                      | W2                  |
| 44  | Psammaplysin H                        | 3D7                 |
| 45  | Ceratinadin E                         | FCR3                |
| 46  | Nortopsentin A                        | 3D7                 |
| 47  | 8-isocyano-15-formamidoamphilect-11(20)-ene | K1   |

et al., 2016). Axisonitrile-3 (1) is a sesquiterpene derived from chloroform fraction of sponge Acanthella kleithra containing isomitrile group which appears to be crucial for activity since the corresponding isothiocyanate derivative compound 2 (moderate activity) is less active than 1 (potent activity) (Angerhofer et al., 1992). The eudesmane compounds 3 and 4 which contain isothiocyanate still showed good antiplasmodial activity, whereas the reversal of the stereochemical configuration between 4 and 5 exhibits a significant change on their antiplasmodial effect (see Figure 3).

The manzamines are a group of marine alkaloids characterized by a fused and bridged tetra- or pentacyclic ring system attached to a β-carboline moiety. Since manzamine was isolated in different genus of sponges, it is thought that manzamine is actually produced by associated microorganism. An interesting review had been done by Fattorusso and Taglialetela-Scafati (2009) who described the key role of the eight member rings as well as other functional groups that affect the antimalarial activity of manzamines; therefore, we will not discuss it in this review.

A mixture of new glycosphingolipids named axidjiferoside A (6), axidjiferoside B (7), and axidjiferoside C (8) shows a potent antimalarial activity (Figure 3). Compounds 6, 7, and 8 were isolated from Senegal marine sponge Axinysa djiferi (Farokhi et al., 2013). These compounds contain sphingolipid structure which are found in ceramide analogs, PPMP (d,1-threo-1-phenyl-2-decanoylamino-3-morpholino-1-propanol), and PDMP (1-phenyl-2-decanoylamino-3-morpholino-1-propanol). These analogs are known to inhibit the parasite sphingomyelin synthase activity and block parasite development by preventing the formation of the tubovesicular network that extends from the parasitophorous vacuole to the red cell membrane and delivers essential extracellular nutrients to the parasite (Labaied et al., 2004; Zhang et al., 2010).

Bioactive guanidine alkaloids including norbatzelladine A (9), dinorbatzelladine A (10), batzelladine A (11), dinordehydrobatzelladine B (12), norbatzelladine L (13), and batzelladine L (14) are potent against the growth of P. falciparum. The aromatization in the tricyclic core of 11 (compared to 9 and 8) did not change the antimalarial activity. Batzelladine A, with one bicyclic and one tricyclic guanidine core, has similar properties with 9, 13, and 14 in terms of the activity against P. falciparum strain FcB1, where 13 and 14 have two tricyclic guanidine cores. The reduction of bicyclic core in dihodehydrobatzelladine C seems to affect its activity to be less active than 9–12 (Figure 3).
Figure 3. Structure of antimalarial compounds (Angerhofer et al., 1992; Benoit-Vical et al., 2008; Farokhi et al., 2013; Mudianta et al., 2012; Wright and Lang-Unnasch 2009; Xu et al., 2011).
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Giroline (15), 2-aminimidazole derivative, isolated from *Cymbastela cantharella* showed a potent activity against *P. falciparum* strains, whereas its analogs 5-deazathioigirrolines (16 and 17) were considered to be inactive (Benoit-Vical et al., 2008). This indicates that imidazole ring in 15 plays an important role in the antiplasmodial activity.

Sponge *Cymbastela hooperi* sp. nov. described by Soest et al. (1992) produces a plethora of chemical compounds structurally related to diterpene isonitrile derivatives which exhibit significant *in vitro* antimalarial activity. (1S, 3S, 4R, 7S, 8S, 11S, 12S, 13S, 15R, 20R)-7-Formamido-20-isocyanoisocycloamphilectane (18), (1S, 3S, 4R, 7S, 8S, 11S, 12S, 13S, 15R, 20R)-7,20-Diformamidoisocycloamphilectane (19), and (1S*, 3S*, 4R*, 7S*, 8S*, 12S*, 13S*)-7-Formamidoisocycloamphilect-11(20)-ene (20) were new diterpene formamides which were isolated from *C. hooperi* (Figure 3). Compound 18 is a unique molecule since it contains both formamide and isonitrile functionalities where such a feature is rarely found in natural product. Based on its IC$_{50}$ against *P. falciparum* FCR3F86, this substituent is classified into potent (Wright and Lang-Unnasch, 2009). The loss of isonitrile in the structure of 19 decreases the activity to be moderate. This finding is supported by the activity of compound 1 that possesses isonitrile too (Angerhofer et al., 1992).

Psammaplysin H (21) derived from sponge genus *Pseudoceratina* is also included in the potent activity group against *P. falciparum* 3D7 with IC$_{50}$ 0.41 µM. This activity is more likely caused by the presence of quaternary amine in the R group at C-20 (see Figure 3). However, the secondary amine at the same position in psammaplysin F (22) reduced antimalarial activity 4-fold lower than compound 21. In addition, when the alkyl amine is substituted with a urea at C-20 in Psammaplysin G (23), the activity decreased to have IC$_{50}$ 5.99 µM (Xu et al., 2011). Consistently, the loss of amine substituent in psammaplysin K (24) dispelled the antiplasmodial activity (Mudianta et al., 2012).

CONCLUSION

Data presented in the review indicate that marine sponges could be used as sources for lead compounds in drug discovery program including the development of non-resistance antimalarial drugs in this case. The summarized “potent” isolated compounds highlight the most promising candidates which include manzamine alkaloids, guanidine alkaloids, bispyrroloiminoquinone alkaloid, pyrroloiminoquinone alkaloids, ingamine alkaloids, sesquiterpenoids, diterpene formamides, aminoimidazoles, β-galactosyl ceramides, β-lactam, meroterpenes, trisoxazole macrolides, peroxides, thiazine alkaloids, bromotymoines, alkaloids, and sterols. A holistic approach for their pharmacological evaluation is still needed since in *vitro* *P. falciparum* assay could only evaluate a specific mechanism of action for antiplasmodium. To reproduce the compounds for their further evaluation, the possibility of bioengineering or/and bacterial fermentation could be worth.

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