A Review of the Secondary Metabolites From the Marine Sponges of the Genus *Aaptos*

Qianqian He¹,²*, Shuang Miao¹*, Na Ni³, Yuqing Man², and Kaikai Gong¹

**Abstract**

Marine sponges, which belong to the phylum Porifera (Metazoa), are considered the single best source of marine natural products. Among them, members of the genus *Aaptos* are attractive targets for marine natural product research owing to their abundant biogenetic ability to produce aaptamine derivatives. Apart from aaptamine alkaloids, there are also reports of other compounds from *Aaptos* sponges. This work reviews the secondary metabolites isolated from *Aaptos* species from 1982 to 2020, with 46 citations referring to 62 compounds (47 for aaptamines and 15 for others). The emphasis is placed on the structure of the organic molecules, relevant biological activities, chemical ecology aspects, and biosynthesis studies, which are described in the classifications of aaptamines and other compounds in the order of the published year.

**Keywords**

marine sponge, *Aaptos*, secondary metabolites, bioactivity, alkaloids

Received: May 25th, 2020; Accepted: July 27th, 2020.

Marine secondary metabolites with wide structural diversity and multiple biological activities are important sources of unexploited drugs. Approximately 28,600 new compounds had been reported from a variety of marine sources by the end of 2018.¹ Among these, sponges, which belong to the phylum Porifera, represent a prolific source of secondary metabolites, contributing to 30% of all natural marine products identified so far.² Lead compounds from sponges have often been found to be promising pharmaceutical agents. To date, 3 approved marine drugs, the anticancer cytarabine (ara-C)³ antiviral vidarabine (ara-A), and anticancer Eribulin mesylate,⁴ have been derived from sponges. Several new sponge derivatives, such as gemcitabine,⁵ discodermolide,⁶ hemiasterlin,⁷ and PM060184,⁸ have entered clinical trials. Therefore, marine sponges have attracted the attention of natural product chemists and pharmaceutical experts worldwide to carry out chemical research for drug discovery.

The genus *Aaptos* (Porifera, Demospongiidae, Hadromerida, Suberitidae) is widely distributed in the marine ecosystem, including the South China Sea, as well as in Japanese, Indonesian, and Caribbean shallow waters. Currently, approximately 20 species have been described.⁹ Since the beginning of the 1980s, many research groups around the world have carried out chemical investigations on *Aaptos* species and have discovered the representative 1H-benzo[d,e][1,6]-naphthyridine alkaloids, known collectively as aaptamines. In addition to these diverse aaptamines, other structures have also been discovered from this genus.

To understand better and rationally exploit *Aaptos* species, the relevant studies reported between 1980 and 2020 are summarized in this review for the first time.

**Natural Products From *Aaptos* sp.**

By 2020, 62 various secondary metabolites (1-62) had been isolated and characterized from the genus *Aaptos*, including *Aaptos aaptos* (Schmidt, 1864), *Aaptos inermitis* (Brondsted, 1934),

¹Cancer Research Institute, Binzhou Medical University Hospital, Shandong, P. R. China
²Department of Pharmacy, Binzhou Medical University Hospital, Shandong, P. R. China
³Clinical Medicine Laboratory, Binzhou Medical University Hospital, Shandong, P. R. China

*Qianqian He and Shuang Miao have contributed equally to this study and should be considered as co-first authors.

**Corresponding Authors:**

Yuqing Man, Department of Pharmacy, Binzhou Medical University Hospital, Yellow River Second Road 661, Binzhou 256600, Shandong, P. R. China.
Email: myq388@126.com

Kaikai Gong, Cancer Research Institute, Binzhou Medical University Hospital, Yellow River Second Road 661, Binzhou 256600, Shandong, P. R. China.
Email: gongkaikai1005@163.com
Table 1. Secondary Metabolites From the Genus *Aaptos* and Biological Activity.

| Number | Name                | Sources          | Locality                               | Biological activity                                                                 | Reference |
|--------|---------------------|------------------|----------------------------------------|--------------------------------------------------------------------------------------|-----------|
| 1      | Aaptamine           | *Aaptos aaptos*  | Okinawa, Japan                         | α-Adrenoceptor blocking activity                                                      | 10        |
|        |                     | A. aaptos        | Taiwan                                 | Cytotoxic activity                                                                  | 11        |
|        |                     | *Aaptos nigra*   | Manado and Derawan Island, Indonesia    | Antifouling activity                                                                | 12        |
|        |                     | *A. aaptos*      | Ku Lao Re Island, Vietnam              | Antioxidant activity                                                                 | 13        |
|        |                     | Unknown          | Unknown                                | Induced the p53 expression                                                           | 14        |
|        |                     | *Aaptos suberitoides* | North Sulawesi, Indonesia             | Proteasome inhibitory activity                                                      | 15        |
|        |                     | *A. aaptos*      | Terengganu, Malaysia                   | Antiviral activity                                                                  | 16        |
|        |                     | *A. aaptos*      | South China Sea                        | Cytotoxic activity                                                                  | 17        |
|        |                     | *A. aaptos*      | South Sulawesi, Indonesia              | Antiatherosclerotic property, antibacterial activity                                | 18        |
|        |                     | *A. lobata*      | Indonesia                              | Osteoclast formation inhibitory                                                     | 19        |
|        |                     | A. aaptos        | Tho Chu Island Vietnam                 | Stimulating activity on the growth of seedling roots                                | 20        |
| 2      | Demethylaaptamine   | *A. suberitoides* | North Sulawesi, Indonesia              | Proteasome inhibitory activity                                                      | 15        |
|        |                     | *A. aaptos*      | Vietnam                                | Apoptosis induction                                                                 | 21        |
|        |                     | *A. aaptos*      | Vietnam                                | Cytotoxic activity                                                                  | 22        |
|        |                     | *A. aaptos*      | South Sulawesi, Indonesia              | Antiatherosclerotic property, antibacterial activity                                | 18        |
|        |                     | A. aaptos        | Tho Chu Island Vietnam                 | Stimulating activity on the growth of seedling roots                                | 20        |
| 3      | Demethoxyaaptamine  | *A. aaptos*      | Okinawa, Japan                         | Antimicrobial activities                                                             | 23        |
|        |                     | A. aaptos        | Taiwan                                 | Cytotoxic activity                                                                  | 11        |
|        |                     | *A. aaptos*      | Abrolhos, Bahia, Brazil                | Antiviral activity                                                                  | 24        |
|        |                     | *A. aaptos*      | Kupang, Indonesia                      | Antimycobacterial activities                                                          | 25        |
|        |                     | *A. aaptos*      | South China Sea                        | Cytotoxic activity                                                                  | 17        |
|        |                     | *A. aaptos*      | South Sulawesi, Indonesia              | Cytotoxic activity                                                                  | 18        |
|        |                     | *A. lobata*      | Indonesia                              | Osteoclast formation inhibitory                                                     | 19        |
|        |                     | A. aaptos        | Tho Chu Island Vietnam                 | Stimulating activity on the growth of seedling roots                                | 20        |
| 4      | Aaptosine           | A. aaptos        | Taiwan                                 | Autophagy induction                                                                 | 28        |
| 5      | Isoaaptamine        | *A. nigra*       | Manado and Derawan Island, Indonesia    | Antifouling activity                                                                | 12        |
|        |                     | A. aaptos        | the Federated States of Micronesia     | Sortase A inhibitory activity                                                       | 26        |
|        |                     | *A. aaptos*      | Ku Lao Re Island, Vietnam              | Antioxidant activity                                                                 | 13        |
|        |                     | A. aaptos        | Vang Fong Bay, Vietnam                 | Apoptosis induction                                                                 | 27        |
|        |                     | *A. suberitoides* | Indonesia                              | Proteasome inhibitory activity, cytotoxic activity                                 | 15        |
|        |                     | *A. lobata*      | Indonesia                              | Osteoclast formation inhibitory                                                     | 19        |
|        |                     | A. aaptos        | Tho Chu Island Vietnam                 | Stimulating activity on the growth of seedling roots                                | 20        |
|        |                     | A. aaptos        | Taiwan                                 | Autophagy induction                                                                 | 28        |
| 6      | Aaptosamine         | A. aaptos        | Southern Caribbean                     | nd                                                                                    | 29        |
| 7      | 4-Methylaaptamine   | A. aaptos        | Abrolhos, Bahia, Brazil                | Antiviral activity                                                                  | 30        |
|        |                     | A. aaptos        | South Sulawesi, Indonesia              | Antiatherosclerotic property, antibacterial activity                                | 18        |
| 8      | 8,9-Demethylaaptamine| *A. aaptos*      | Indonesia                              | nd                                                                                    | 31        |
|        |                     | *A. aaptos*      | South Sulawesi, Indonesia              | Antiatherosclerotic property, antibacterial activity                                | 18        |
|        |                     | *A. aaptos*      | Indonesia                              | nd                                                                                    | 31        |
|        |                     | *A. aaptos*      | Indonesia                              | Antiatherosclerotic property, antibacterial activity                                | 18        |
| 9      | Bisdemethylaaptamine-9-O-sulfate| *A. aaptos* | Indonesia                              | nd                                                                                    | 31        |
| 10     | 3-N-morpholinyl-9-demethyl(oxy)aaptamine| *A. aaptos* | Vietnam                                | Cell malignant transformation inhibitory                                             | 32        |
| 11     | 3-(Phenethylamino)dimethyl (oxy)aaptamine | *A. aaptos* | Terengganu, Malaysia                   | Cytotoxic activity                                                                  | 33        |
|        |                     | *A. aaptos*      | South China Sea                        | Antifungal activity anti-HIV-1 activity                                             | 34        |
|        |                     | *A. aaptos*      | Terengganu, Malaysia                   | Induction of apoptosis                                                               | 16        |
|        |                     | *A. aaptos*      | South China Sea                        | Cytotoxic activity                                                                  | 17        |
| 12     | 3-(Isopentylamino)dimethyl (oxy)aaptamine| *A. aaptos* | Terengganu, Malaysia                   | Cytotoxic activity                                                                  | 33        |
|        |                     | *A. aaptos*      | South China Sea                        | Antifungal activity anti-HIV-1 activity                                             | 34        |

(Continued)
| Number | Name                             | Sources               | Locality                        | Biological activity                                      | Reference |
|--------|----------------------------------|-----------------------|---------------------------------|----------------------------------------------------------|-----------|
| 13     | Aaptanone                        | A. aaptos             | Vietnam                         | nd                                                       |           |
| 14     | N-demethylaaptanone              | A. aaptos             | Vietnam                         | nd                                                       |           |
|        |                                  | A. aaptos             | Tho Chu Island Vietnam          | Stimulating activity on the growth of seedling roots      | 20        |
| 15     | 2,3-Dihydro-2,3-dioxoaaptamine   | Aaptos sp.            | Vang Fong Bay, Vietnam          | nd                                                       | 27        |
|        |                                  | Aaptos sp.            | Indonesia                       | Antimycobacterial activity                               | 25        |
| 16     | 6-[(N-morpholinyl)-4,5-dihydro-5- | Aaptos sp.            | Vang Fong Bay, Vietnam          | nd                                                       | 27        |
|         | oxo demethyl(oxy)aaptamine       |                      |                                 |                                                          |           |
| 17     | 3-(Methylamino)dimethyl (oxy)aaptamine | Aaptos sp.      | Vang Fong Bay, Vietnam          | nd                                                       |           |
|        |                                  | A. aaptos             | South China Sea                 | nd                                                       |           |
|        |                                  | Aaptos sp.            | Kupang, Indonesia               | Antimycobacterial activity                               | 28        |
|        |                                  | A. aaptos             | South China Sea                 | nd                                                       | 17        |
| 18     | Suberitine A                     | A. suberitoides       | South China Sea                 | nd                                                       |           |
| 19     | Suberitine B                     | Cytoxic activity      |                                 |                                                          |           |
| 20     | Suberitine C                     |                       |                                 |                                                          |           |
| 21     | Suberitine D                     |                       |                                 |                                                          |           |
| 22     | 8,9,9-Trimethoxy-9H-benzo[de]    | A. suberitoides       | South China Sea                 | nd                                                       |           |
|         | [1,6]-naphthyridine              | A. aaptos             | South China Sea                 | Antifungal activity                                      | 54        |
|        |                                  | A. aaptos             | South Sulawesi, Indonesia       | Cytoxic activity                                         | 18        |
|        |                                  |                       |                                 | antiatherosclerotic property                             |           |
|        |                                  |                       |                                 | antibacterial activity                                   |           |
| 23     | 11-Methoxy-3H-[1,6]naphthyridino[6,5,4-| A. suberitoides       | Sepanggar Island, Malaysia      | nd                                                       | 59        |
|         | def] quinazolin-3-one            | A. aaptos             | Ambon, Indonesia                |                                                          | 40        |
| 24     | 2,11-Dimethoxy-3H-[1,6]naphthyridino[6,5,4-| A. suberitoides       |                                 | nd                                                       |           |
|         | def] quinazolin-3-one            | A. aaptos             |                                 |                                                          |           |
| 25     | 5-Benzoyldemethyl-aaptamine      | A. suberitoides       | Ambon, Indonesia                | Cytoxic activity                                         |           |
| 26     | 3-Aminodemethyl(oxy) aaptamine   | A. suberitoides       | Ambon, Indonesia                |                                                          |           |
|        |                                  | A. aaptos             | Kupang, Indonesia               | Antimycobacterial activity                               | 25        |
| 27     | 8-Methoxybenzimidazo [6,7,1-def]  | A. suberitoides       | Ambon, Indonesia                | nd                                                       | 40        |
|         | [1,6]-naphthyridine              | A. aaptos             |                                 |                                                          |           |
| 28     | Piperidine[3,2-b] demethyl(oxy)aaptamine | A. aaptos             | South China Sea                 | nd                                                       |           |
| 29     | 9-Amino-2-ethoxy-8-methoxy-3H-benzo[de] | A. aaptos             | South China Sea                 | Cytoxic activity                                         |           |
|         | [1,6]naphthyridin-3-one          | A. aaptos             |                                 |                                                          |           |
| 30     | 2- (sec-Butyl)− 7,8-dimethoxybenzo[de]imidazo [4,5,1-ij,[1,6]-naphthyridin-10(9 H)-one | A. aaptos             | South China Sea                 | nd                                                       |           |
| 31     | 2-Isobutyl-7,8-dimethoxybenzo[de]imidazo [4,5,1-ij,[1,6]-naphthyridin-10(9 H)-one | A. aaptos             | South China Sea                 |                                                          |           |
| 32     | 2-Isopropyl-7,8-dimethoxybenzo[de]imidazo [4,5,1-ij,[1,6]-naphthyridin-10(9 H)-one | A. aaptos             | South China Sea                 |                                                          |           |
| 33     | 2-Ethoxy-7,8-dimethoxybenzo[de]imidazo[4,5,1-ij,[1,6]-naphthyridin-10(9 H)-one (6) | A. aaptos             | South China Sea                 |                                                          |           |
| 34     | 3-(2-Methylbutylamino)dimethyl (oxy)aaptamine | A. aaptos             | South China Sea                 | nd                                                       |           |
| 35     | 3-Isobutylaminodemethyl (oxy)aaptamine | A. aaptos             |                                 |                                                          |           |
| 36     | 3-(N-4-ethylbutanoate)amino-demethyl(oxy) aaptamine | A. aaptos             |                                 |                                                          |           |
| 37     | 2-Isobutyl-11-methoxy-3H-[1,6]-nimethyl[6,5,4-de]quinazolin-3-one | A. aaptos             | South China Sea                 | nd                                                       |           |
| 38     | 2-(sec-Butyl)-11-methoxy-3H-[1,6]naphthyridino [6,5,4-de]quinazolin-3-one | A. aaptos             | South China Sea                 | Cytoxic activity                                         |           |
| 39     | 2-(sec-Butyl)-10-methoxyimidazo [4,5,1-ij]pyrid [2,3,4-de]quinoline | A. aaptos             | South China Sea                 | nd                                                       |           |
| 40     | 2-Isobutyl-10-methoxyimidazo [4,5,1-ij]pyrido [2,3,4-de]quinoline | A. aaptos             | South China Sea                 |                                                          |           |
| 41     | 2-Isopropyl-10-methoxyimidazo [4,5,1-ij]pyrido [2,3,4-de]quinoline | A. aaptos             | South China Sea                 |                                                          |           |
| 42     | Methoxy-3-oxoaaptamine           | Aaptos sp.            | Kupang, Indonesia               | Antimycobacterial activity                               | 25        |

(Continued)
Aaptos lobata (Calcinai, Bastari, Bertolino & Pansini, 2017), Aaptos ciliata (Wilson, 1925), Aaptos nigra (Lévi, 1961), and other unidentified Aaptos sp. In terms of their chemical structures, most Aaptos-derived products are structurally diversified aaptamines (47 for aaptamines and 15 for others; Table 1). Some chemicals have pronounced biological activities and can be used as lead drugs. These secondary metabolites are summarized below in the order of the published year.

### Aaptamines

In 1982, the first and representative member of the family aaptamine (1) was reported by Nakamura et al from *A. aaptos*, collected off the shores of Okinawa. It was found to possess α-adrenoceptor blocking activity and was a competitive antagonist of α-adrenoceptors in vascular smooth muscles. In 1993, Rudi et al isolated aaptosine (4) from the Red Sea sponge *A. aaptos*, which contained an unprecedented 5,8-diazabenz[c]azulene heterocycle. In 1997, Shen et al isolated 4 alkaloids, aaptamine (1), demethylxyaaptamine (3), aaptosine (4), and isoaaptamine (5), from Formosan *A. aaptos*. All the compounds except aaptosine (4) showed potent cytotoxicities against P-388, KB16, A549, and HT-29 tumor cells. In 1998, Tinto et al isolated a new 5,8-diazabenz[c]azulene alkaloid, aaptosamine (6), from *A. aaptos* collected in the southern Caribbean. 29

In 2002, Coutinho et al isolated a new aaptamine alkaloid, 4-methylaaptamine (7), and the known demethylxyaaptamine (3) from *Aaptos* sp. collected in Abrolhos, Bahia, Brazil. At the concentration of 2 µg/mL, both compounds showed potent antiviral activity against the herpes simplex virus type 1 (HSV-1) but displayed low toxicity to Vero cells, which suggests that they may selectively inhibit viral replication. In 2007, Souza et al disclosed that 4-methylaaptamine (7) inhibited HSV-1 replication by targeting the immediate-early protein ICP27 and impaired HSV-1 penetration without affecting viral adsorption. In 2004, Herlt et al isolated 8,9-demethylaaptamine (8) and bisdemethylaaptamine-9-O-sulfate (9) from an *Aaptos* sp. harvested off the Indonesian coast. It was proposed that 8,9-demethylaaptamine (8) is a biosynthetic precursor of the aaptamines. Bisdemethylaaptamine-9-O-sulfate (9) was the first reported sulfated aaptamine. In 2006, Diers et al evaluated the antifouling activity of aaptamine (1) and isoaaptamine (5), which were isolated from *A. nigra* collected from reef slopes of Manado and Derawan Island, Indonesia, and the semisynthetic aaptamine derivatives 4-N-methylaaptamine (7) and 4-N-demethylaaptamine (8) on biofouling by *Monosia compressa* and *Halicryptus japonicus*. In 2008, Diers et al isolated 4-N-methylaaptamine-9,10-diacetate (10) from the red alga *Chondrus crispus*. This compound showed potent antifouling activity against *Monosia compressa* and *Halicryptus japonicus*. The antifouling activity of bisdemethylaaptamine-9-O-sulfate (9) was further investigated by Diers et al. 20

Table 1. Continued

| Number | Name | Sources | Locality | Biological activity | Reference |
|--------|------|---------|----------|---------------------|-----------|
| 43     | 10-Methoxy-2-methylimidazo [4,5,1-ij]pyrido [2,3,4-de]quinolone | *A. aaptos* | South China Sea | Cytotoxic activity | 17        |
| 44     | 2-Isopropyl-11-methoxy-3H-[1,6]naphthyridino [6,5,4-de]quinolin-3-one | *A. aaptos* | South China Sea | nd                  |           |
| 45     | 3-(3-Hydroxyphenethylamino)dimethyl (oxy) | *A. aaptos* | nd | Cytotoxic activity | 47        |
| 46     | Aaptic acid | *A. lobata* | Indonesia | nd | 19        |
| 47     | Methyleneoxyaaptamine | *A. aaptos* | Sepanggar Island, Malaysia | Cytotoxic activity | 39        |
| 48     | 3-(13-Methyloctadecyloxy)-1,2-(3) propanediol | *Aaptos sp.* | Taiwan | nd | 41        |
| 49     | 3-(15-Methyloctadecyloxy)-1,2-(3) propanediol | *A. aaptos* | nd | Cytotoxic activity | 42        |
| 50     | Cholestanol | *A. aaptos* | the Bay of Naples | nd | 43        |
| 51     | 24-Ethylcholestanol | *A. aaptos* | nd | Cytotoxic activity | 44        |
| 52     | 3-Methoxy-β,χ-carotene | *A. aaptos* | Kagoshima, Japan | nd | 45        |
| 53     | Homoaramine | *Aaptos sp.* | Spain | nd | 46        |
| 54     | Pyridiniumbetaine B | *A. aaptos* | nd | Cytotoxic activity | 47        |
| 55     | Ciliatamides A | *A. ciliata* | Oshima-Shinsone, Japan | Antileishmanial activity | 48        |
| 56     | Ciliatamides B | *A. ciliata* | Oshima-Shinsone, Japan | Cytotoxic activity | 49        |
| 57     | Ciliatamides C | *A. ciliata* | Oshima-Shinsone, Japan | Cytotoxic activity | 50        |
| 58     | Aaptoline A | *A. suberitoides* | Indonesia | nd | 51        |
| 59     | 4-Hydroxybenzamide | *A. aaptos* | South Sulawesi, Indonesia | nd | 52        |
| 60     | 3 β,5α-Cholesterol | *A. aaptos* | Terengganu, Malaysia | nd | 53        |
| 61     | Aaptolines A | *A. aaptos* | South China Sea | Cytotoxic activity | 54        |
| 62     | Aaptolines B | *A. aaptos* | nd | Cytotoxic activity | 55        |

Abbreviations: nd, not determined.
and 8,9-demethylaaptamine (8). Aaptamine (1), isoaaptamine (5), and demethylated aaptamine (8) displayed significant antifouling activity with half maximal effective concentration values of 24.2, 11.6, and 18.6 µM, respectively. The structure-activity relationship (SAR) study indicated that the free hydroxyls were essential for the antifouling activity and the N-methyl groups could reduce the toxicity. Hence, aaptamine derivatives may be used as environmentally benign antifouling alternatives to metal-based paints.12

In 2006, Shunji et al found that aaptamine (1) activated the p21 promoter that was stably transfected in MG63 cells dose dependently at concentrations of 20-50 µM and arrested the cell cycle of MG63 cells at the G2/M phase. The activation of p21 promoter by aaptamine was led through acting on Sp1 sites between −82 and −50 bp in a p53-independent manner.50

In 2007, Jang et al reported 4 aaptamines: aaptamine (1), demethylaaptamine (2), demethlyoxyaaptamine (3), and isoaaptamine (5) from A. aaptos collected from the Federated States of Micronesia. Their inhibitory activities were evaluated against sortase A, an enzyme that plays a key role in cell wall protein anchoring and virulence in Staphylococous aureus. Isoaaptamine (5) was a potent inhibitor of sortase A, with a half-maximal inhibitory concentration (IC50) value of 3.7 µg/mL. The methyl group at the N-1 position of isoaaptamine proved to be an important factor for sortase A activity. Besides, isoaaptamine (5) reduced the fibronectin-binding activity of the bacterium, which highlighted its potential for the treatment of S. aureus infections via inhibition of sortase A activity.26

In 2009, Utikina evaluated the antioxidant activity of aaptamine (1) and isoaaptamine (5) isolated from A. aaptos. Both of these strongly reacted with 2,2-diphenyl-1-picryl-hydrazyl and showed a high reducing ability for Folin-Ciocalteau reagent.13 In 2009, Shubina et al isolated a new aaptamine-type alkaloid, 3-N-morpholinyl-9-demethyl(oxy)aaptamine (10), from an Aaptos sp. collected in Vietnamese waters. It showed inhibitory activity on the epidermal growth factor (EGF)-induced malignant transformation of mouse epidermal JB6 P+ C1 41 cells in soft agar.12 In 2009, Shaari et al used a bioassay-guided isolation method to obtain 2 new derivatives of aaptamines, 3-(phenethylamino)demethyl(oxy)aaptamine (11), and 3-(isopentylamino)demethyl(oxy)aaptamine (12), in addition to the known aaptamine (1) from A. aaptos collected from the coastal waters of Terengganu, Malaysia. This was the first report of a naturally occurring C-3 substituted aaptamine. All 3 isolated alkaloids exhibited significant cytotoxic activity against T-lymphoblastic leukemia cells with the concentration to reduce the absorbance of treated cells by 50% with reference to the control (CD50) values of 5.3 (11), 6.7 (12), and 15.0 (1) µg/mL, respectively. SAR studies suggested that hydroxylation at C-9 and parasubstituted phenyl substituents on one or both of the nitrogen are important for increased activity, and C-3 substitution may also influence the cytotoxicity of this class of compounds.35

In 2009, Utikina et al isolated a new zwitterionic compound, aaptanone (13), with a rare oxygenated 1,6-naphthyridine core, from Vietnamese A. aaptos. Aaptanone (13) is the first zwitterionic metabolite of the aaptamine class bearing 2 adjacent carbonyl groups in the 1,6-naphthyridine core. Bioactivity tests revealed that aaptanone (13) was inactive against S. aureus, Bacillus subtilis, Candida albicans, and Escherichia coli strains and displayed no cytotoxicity against mouse Ehrlich carcinoma cells.35 In another study of the same sponge from another collection, Utikina et al found another new zwitterionic compound, N-demethylaaptanone (14), with the same skeleton as aaptanone (13).36

In 2010, Shubina et al isolated 3 new aaptamines, 2,3-dihydro-2,3-dioxaaptamine (15), 6-(N-morpholinyl)-4,5-dihydro-5-oxodemethyl(oxy)aaptamine (16), and 3-(methylamino)demethyl(oxy)aaptamine (17), in addition to 4 known compounds (1, 3, 11, 12) from an Aaptos sp. collected in Vang Fong Bay, Vietnam. The apoptosis-inducing activity of these compounds and isoaaptamine (5) on human leukemia THP-1 cells was evaluated. Isoaaptamine (5) was shown to be the most active inducer of apoptosis. The side chain length at position 3 may decrease the apoptosis-inducing activity.25 In 2010, Arif et al found that aaptamine (1), at a concentration of 10 µM, induced benzoylpyrene (BP)-derived deoxyribonucleic acid adduct formation. At a concentration of 50 µM, aaptamine induced the p53 expression by 40%, which indicated its anticancer potential.14 In 2010, Tsukamoto et al examined the proteasome inhibitory activity of aaptamine (1), demethylaaptamine (2), and isoaaptamine (5) isolated from A. suberitoides collected in Indonesia. They inhibited the chymotrypsin-like and caspase-like activities of the proteasome with IC50 values of 1.6-4.6 µg/mL and displayed weak inhibition of the trypsin-like activity of the proteasome. These 3 compounds also showed cytotoxic activities against HeLa cells with IC50 values of 15, 1.4, and 3.1 µg/mL, respectively, but their cytotoxicity did not correlate with their potency as proteasome inhibitors.15 In 2011, Jin et al investigated the antiproliferative effect of aaptamine on chronic myeloid leukemia (CML) K562 cells. Aaptamine inhibited the growth of K562 with the concentration that causes 50% inhibition of the growth of cells (GI50) of 10 µM and arrested the cell cycle at the G2/M phase. Western blot assays indicated that aaptamine induced the p53 expression by 40%, which indicated its antiproliferative effect. Aaptamine induced the p53 expression by 40%, which indicated its antiproliferative effect. Aaptamine induced the p53 expression by 40%, which indicated its antiproliferative effect. Western blot assays indicated that aaptamine induced the p53 expression by 40%, which indicated its antiproliferative effect.
Figure 1. Chemical structures of compounds 1-22.
Figure 2. Chemical structures of compounds 23-47.
treatment with either demethylxyaaptamine or isoxyaaptamine. In the same year, they also reported the anticancer activity of these 3 compounds. Aaptamine (1), demethylxyaaptamine (2), and isoxyaaptamine (5) demonstrated anticancer activity in THP-1, HeLa, SNU-C4, SK-MEL-28, and MDA-MB-231 human cancer cell lines. Additionally, all compounds were found to prevent the EGF-induced neoplastic transformation of murine JB6 Cl41 cells, and the nuclear factors AP-1, NF-B, and p53 were involved in the cellular response following treatment with high and nontoxic concentrations of aaptamine alkaloids. In 2012, Liu et al isolated 4 new bis-aaptamines, suberine A-D (18-21), along with 2 monomers, 8,9,9-trimethoxy-9H-benzo[de][1,6]-naphthyridine (22) and demethylxyaaptamine (3), from A. suberitoides collected from Xisha island. The 4 unusual dimers structurally linked 2 aaptamine units, 8,9,9-trimethoxy-9H-benzo[de][1,6]-naphthyridine (22) and demethylxyaaptamine (3), through a rare C-3-C-3′ or C-3-C-6′ σ-bond. This was the first isolation of aaptamine dimers in nature. The cytotoxicity of the 6 compounds was evaluated against P388,
activity against the murine lymphoma L5178Y cell line, with IC_{50} values of 1.8 and 3.5 µM, respectively, whereas suberitine A and C were inactive toward the same cell line. In 2013, Pham et al isolated 4 new aaptamine derivatives (23-26), along with 4 related compounds (1, 2, 22, 27), from the ethanol extract of *A. suberitoides* collected in Indonesia. Compounds 25, 1, and 2 showed cytotoxic activity against the murine leukemia L1578Y cell line, with IC_{50} values ranging from 0.9 to 8.3 µM. SAR studies suggested that the hydroxyl at C-9, loss of aromaticity in ring C, hydrogenation of ring B substitution at both C-9 and N-1, and an additional carboxyl group at C-12 negatively affected the activity. In 2014, Yu et al. isolated 13 new alkaloids of the aaptamine family (28-40) and 5 known derivatives (11, 12, 17, 22, 41) from *A. aaptos* from the South China Sea. Structurally, compound 28 possesses a piperidyl group fused to a demethyl(oxy)aaptamine moiety, compounds 30-33 and 39-40 share an imidazole-fused 1H-benzo[d][1,6]naphthyridin-2(4H)-1 skeleton, and compounds 37-38 are characterized by a triazaperylene lactam skeleton. Compounds 29, 39, 11, and 12 showed potent cytotoxicity against HL60, K562, MCF-7, KB, HepG2, and HT-29 cells, with IC_{50} values in the range of 0.03-8.5 µM. Compounds 22, 11, and 12 showed antifungal activity against 6 fungi, with minimum inhibitory concentration (MIC) values in the range of 4-64 µg/mL. At a concentration of 10 µM, compounds 11 and 12 exhibited anti-HIV-1 activity, with inhibitory rates of 88.0% and 72.3%, respectively. In 2014, Arai et al isolated a new aaptamine class alkaloid, designated as 2-methoxy-3-oxoaaptamine (42), together with 7 known aaptamines (1, 3, 15, 17, 26, 27, 39), as anticybacterial substances against active and dormant bacilli from an *Aaptos* sp. collected at Kupang, Indonesia. Compound 42 showed anticybacterial activity against *Mycobacterium smegmatis* in both active growing and dormancy-inducing hypoxic conditions with a MIC of 6.25 µg/mL, and compounds 3, 15, 17, and 26 showed anticybacterial activities under hypoxic conditions selectively, with MIC values of 1.5-6.25 µg/mL. In 2015, Li et al evaluated the antiproliferative effect of aaptamine on hepatocellular carcinoma cells in vitro and in vivo and analyzed the mechanisms. The results demonstrated that aaptamine led to cell cycle arrest and suppressed the expression of SOX9 and CDK2. The mechanisms were associated with the increased binding of p21 to Cdk2-cyclin D/E complexes and inhibition of CDK2 kinase activity in hepatocellular carcinoma cells. In 2015, Zalilawati et al evaluated the cytotoxic and anti-HSV-1 activities of 3-(phenethylamino)demethyl(oxy)aaptamine (II) and aaptamine (I). Both strongly reduced HL-60 viability and also displayed cytotoxicity against WEHI-3B through the induction of apoptosis. In addition, aaptamine (I) also exhibited good antiviral activity on HSV-1. In 2015, Gan et al isolated 3 new aaptamine derivatives (43-45), together with 6 known related compounds (1, 3, 11, 17, 22, 27), from the South China Sea sponge *A. aaptos*. Compounds 1, 3, 11, 17, and 43 showed cytotoxic activities against HeLa, K562, MCF-7, and U937 cell lines with IC_{50} values in the range of 0.90-12.32 µM. In 2017, Mohamad et al obtained 5 known aaptamines, aaptamine (I), demethylaaptamine (2), 4-N-methylaaptamine (7), 9-methoxyaaptamine (22), and demethyloxyaaptamine (3) by bioactivity-guided isolation from the butanol extract of *A. aaptos* collected from South Sulawesi, Indonesia. The cytotoxic activity, antithrombotic properties, and antibacterial activity of the compounds were determined. Compounds 3 and 22 exhibited cytotoxic activity against the HepG2 cell line. Compounds 1, 2, 7, and 22 increased the transcriptional activity of the SRB1 promoter and PPRE and may be potential drug candidates to reduce the progression of atherosclerosis. In addition, compounds 1, 2, 7, and 22 displayed antibacterial activity against shrimp pathogenic bacteria, *Vibrio harveyi*, and *Vibrio* sp. In 2018, Fukumoto et al isolated a new aaptamine homolog, aptic acid (46), as well as aaptamine (I), demethyl(oxy)aaptamine (3), and isoaptamine (5), from *A. lobata* collected in Indonesia. The inhibitory effect of RAW264 cells on osteoclast formation was determined. Dosing at 5 µM of 1, 3, and 5 inhibited receptor activator of nuclear factor kappa B ligand-induced multuncleated osteolast formation by 25%, 54%, and 17%, respectively. In contrast, 46 did not inhibit osteoclastogenesis, even at a concentration of 50 µM. In the same year, Utkina et al evaluated the agricultural plant growth stimulatory effect of aaptamine (I), 9-demethylaaptamine (2), isoaptamine (5), aaptanone (15), and N-demethylaaptanone (14) isolated from Vietnamese *A. aaptos*. Aaptamine (I) displayed stimulatory activity on the roots of seedlings of soy, maize, and buckwheat at a wide range of concentrations. 9-Demethylaaptamine (2) stimulated the root growth of soy and maize in the concentration range of 0.001-10 µg/mL. Isoaptamine (5) stimulated the root growth of soy and wheat, while only aaptanone (14) stimulated barley roots at a concentration of 0.1 µg/mL. The structural motif of aaptamines 1, 2, and 5 is essential for their stimulating activity on the growth of seedling roots of soy, maize, and wheat. The presence of carbonyl groups in aaptanones 13 and 14 leads to a lack of growth-stimulating activity, while the oxygenated core of aaptanone 14 is important for its growth stimulating activity on barley roots. In 2018, Wu et al isolated aaptamine (I), demethyl (oxy) aaptamine (3), and isoaptamine (5) from an *Aaptos* sp. using a bioactivity-guided method. The cytotoxic activity of the isolated compounds was evaluated, revealing that isoaptamine exhibited potent cytotoxic activity against breast cancer T-47D cells. This study also deciphered that isoaptamine induced apoptosis and autophagy through p62-dependent oxidative stress in breast cancer T-47D cells. In 2019, Hamada et al obtained an aaptamine-related alkaloid methylenedioxyaaptamine (47) and compound 22 from Malaysian *A. aaptos*. Methylenedioxyaaptamine (47) was previously reported as a synthetic product, and this was the first report of it from a natural source. Compound 47 displayed moderate cytotoxic activity against adult T-cell leukemia with an IC_{50} of 0.29 µM (Figure 2).

**Other Compounds**

In 1983, Do et al isolated 3-(13-methylhexadecyloxy)-1,2-(5)-propanediol (48) and 3-(15-methyloctadecyloxy)-1,2-(5)-propanediol (49) from *Aaptos* sp. collected from Taiwanese waters. The configuration of C-2 in the glyceryl moiety was determined by...
derivatization with (S)-(+) α-methoxy-α-trifluoromethyl phenylacetyl chloride. They also reported the total synthesis of compound 48. In 1984, Dini et al analyzed the sterols in A. aaptos collected in the Bay of Naples and found that cholestanol (50) and 24-ethylcholesterol (51) were the principal sterols present. In 1985, Tanaka et al isolated a new aromatic carotenoid, 3-methoxy-β, γ-carotene (52), from A. aaptos collected from the littoral zone of Amamioshima, Kagoshima. In 2000, Granato et al described the isolation of homarine (53) and pyridiniumbetalaine B (54) from an Aaptos sp. collected in Spain. In 2008, Nakao et al isolated 3 new lipopeptides, ciliatamides A-C (55-57), from the deep-sea sponge A. ciliata collected off Oshima-Shirone. Ciliatamides A-C (55-57) were evaluated for antileishmanial activity in a fluorometric microplate assay using Leishmania major/egfp promastigotes. Ciliatamides A (55) and B (56) showed 50% and 45.5% growth inhibition at 10 µg/mL, respectively, while C (57) was inactive. Ciliatamides A (55), B (56), and C (57) also inhibited the growth of HeLa cells with IC50 values of 50, 4.5, and 50 µg/mL, respectively. In 2014, Kudo et al isolated a new quinoline alkaloid, aaprotline A (58), from A. suberitoides collected in Indonesia, along with the known alkaloids aaptamine (1), demethylaaptamine (2), and isoaprotamine (5). All 4 compounds were presumably biosynthesized from the common precursors, 1,3-dihydroxyphenylalanine and β-alanine aldehyde. In 2017, Mohamad et al isolated 4-hydroxybenzamide (59) and 3β,5α-cholesterol (60) from Indonesian A. aaptos. 3β,5α-Cholesterol (60) exhibited cytotoxic effects and potential antiatherosclerotic properties. In 2018, Rashid et al investigated the phenolics, fatty acid composition, and biological activities of Malaysian A. aaptos. The chloroform, ethyl acetate, and methanol extracts produced higher portions of straight-chain saturated fatty acids, while the hexane extract mainly consisted of unsaturated fatty acids. The chloroform extract inactivated the HSV-1 and exhibited strong cytox-toxicity on HL-60, MCF-7, K562, CEM-SS, and WEHI-3B cells, but displayed weak cytotoxic activity against normal Vero cells. 4-Hydroxybenzamide (59) was also isolated from this sponge. In 2020, Tang et al obtained 2 new quinoline alkaloids, aaprotlines A (61) and B (62), from A. aaptos collected off the coast of Xisha Island. Structurally, aaprotline A was characterized as possessing a quinoline skeleton fused with a 1,4-dioxane motif at the C(7)-C(8) position, whereas 62 possessed an intriguing 1H-pyrrolo[2,3-g] quinoline moiety. Both showed cytotoxicity toward HepG2, A549, and PC9 cancer cell lines at a concentration of 20 µM (Figure 5).

Conclusion

This review summarizes the secondary metabolites and biological activities of the sponge genus Aaptos. The most common secondary metabolites are aaprotamine alkaloids possessing a variety of beneficial biological activities such as antiviral, antimicrobial, antifungal, and cytotoxic activities. Some aaprotamine alkaloids have significant cell toxicity against a variety of tumors. However, the mechanism is not yet clear, and in vivo studies have only been conducted on a few compounds; therefore, further research is required. Although approximately 20 species of Aaptos have been described, the chemical profiles of only 5 identified species (A. aaptos, A. suberitoides, A. lobata, A. ciliata, and A. nigra) and several other unidentified Aaptos sp. have been investigated. With the increasing development of oceanographic technology and the use of advanced separation methodologies, more bioactive secondary metabolites will be discovered from Aaptos species in the near future.

Declaration of Conflcting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was supported by Science and Technology Development Foundation of Binzhou (2015ZC0304), Research Foundation of Binzhou Medical University (BY2015KYQD31 and BY2017KJ17), Traditional Chinese Medicine Technology Development Foundation of Shandong (2019-0521), Natural Science Foundation of Shandong Province (ZR2018BB024), National Natural Science Foundation of China (81903537).

ORCID ID

Kaikai Gong https://orcid.org/0000-0003-2575-5533

References

1. Blunt JW, Carroll AR, Copp BR, et al. Marine natural products. Nat Prod Rep. 2018;35(1):8-53. doi:10.1039/C7NP00052A
2. Calcabrini C, Catanzaro E, Bishayee A, Turrini E, Fimognari C. Marine sponge natural products with anticancer potential: an updated review. Mar Drugs. 2017;15(10):310 doi:10.3390/md151010310
3. Bishop JF, Matthews JP, Young GA, et al. A randomized study of high-dose cytarbine in induction in acute myeloid leukemia. Blood. 1996;87(5):1710-1717. doi:10.1182/blood.V87.5.1710.1710
4. Shetty N, Gupta S. Eribulin drug review. South Asian J Cancer. 2014;3(1):57-59. doi:10.4103/2278-330X.126527
5. Krege S, RE, vom Dorp F, et al. Prospective randomized double-blind multicentre phase II study comparing gemcitabine and cisplatin plus sorafenib chemotherapy with gemcitabine and cisplatin plus placebo in locally advanced and/or metastasized urothelial cancer: SUSE (AUO-AB 31/05). BJU Int. 2014;113(3):429-436. doi:10.1111/bju.12437
6. Longley RE, Caddigan D, Harmody D, Gunasekera M, Gunasekera SP. Deschloromodile—a new, marine-derived immuno-suppressive compound. II. In vivo studies. Transplantation. 1991;52(4):656-661. doi:10.1097/00007890-199110000-00015
7. Anderson HJ, Coleman JE, Andersen RJ, Roberge M. Cytotoxic peptides hemiasterlin, hemiasterlin A and hemiasterlin B induce mitotic arrest and abnormal spindle formation. Cancer Chemother Pharmcol. 1997;39(3):223-226. doi:10.1007/s002800050564
8. Martínez-Diez M, Guillén-Navarro MJ, Perá B, et al. PM060184, a new tubulin binding agent with potent antitumor activity including P-glycoprotein over-expressing tumors. Biochem Pharmacol. 2014;88(3):291-302. doi:10.1016/j.bcp.2014.01.026

9. Carvalho MDS, Da Silva SM, Pinheiro U. Two new species of Aiptos (Demospongiae, Hadromerida) from Brazil (western Atlantic. Zootaxa. 2015;3750:357-366. doi:10.11646/zootaxa.3750.4.4

10. Ohizumi Y, Kajiwara A, Nakamura H, Kobayashi J. Alpha-Adrenoceptor blocking action of aaptamine, a novel marine natural product, in vascular smooth muscle. J Pharm Pharmacol. 1984;36(11):785-786. doi:10.1111/j.2042-7158.1984.tb04876.x

11. Shen Y, Chein C, Hsieh P, Duh C. Bioactive constituents from marine sponge Aiptos aaptos. Taiwan Shuichan Xuehuikan. 1997;24(2):117-125.

12. Diers JA, Bowling JJ, Duke SO, et al. Zebra mussel antifouling activity of the marine natural product aaptamine and analogs. Mar Biotechnol. 2006;8(4):366-372. doi:10.1007/s10126-005-6055-4

13. Utkina NK. Antioxidant activity of aromatic alkaloids from the marine sponge Aaptos aaptos and Hyrtios sp. Chem Nat Compd. 2009;45(6):849-853. doi:10.1007/s10126-010-9940-z

14. Arif JM, Kunhi M, Siddiqui YM, et al. Differential modulation of benzo[α]pyrene-derived DNA adducts in MCF-7 cells by marine compounds. Int J Cancer. 2008;1(4):259-268.

15. Tsukamoto S, Yamanokuchi R, Yoshitomi M, et al. Aaptamine, an alkaloid from the sponge Aiptos suberitoides, functions as a proteasome inhibitor. Bioorg Med Chem Lett. 2010;20(11):3341-3343. doi:10.1016/j.bmcl.2010.04.029

16. Zalilawati MR, Andriani Y, Shaari K, et al. Induction of apoptosis and anti HSV-1 activity of 3-(Phenethylamino) demethyl(oxy) aaptamine from a Malaysian Aiptos aaptos. J Chem Pharm Res. 2015;7(10):330-341.

17. Gan J-H, Hu W-Z, Yu H-B, et al. Three new aaptamine derivatives from the South China Sea sponge Aiptos aaptos. J Asian Nat Prod Res. 2015;17(12):1231-1238. doi:10.1080/10286020.2015.1118465

18. Mohamad H, Muhammad TST, et al. Potential secondary metabolites from marine sponge Aiptos aaptos for atherosclerosis and virbirosis treatments. Nat Prod Commun. 2017;12(8):1934578. doi:10.1177/1934578X1701200819

19. Tsukamoto S, Fukumoto A, Hitora Y, et al. Isolation of aaptic acid from the marine sponge Aiptos lobata and inhibitory effect of aaptamines on RANKL-induced formation of multinuclear osteoclasts. Heterocycles. 2018;97(2):1219-1225. doi:10.3987/COM-18-S(7)73

20. Utkina NK, Chaikina EL, Anisimov MM. Influence of aaptamine alkaloids on the growth of seedling roots of agricultural plants. Nat Prod Commun. 2017;12(9):1437-1438. doi:10.1177/1934578X1701200913

21. Dyshlovoy SA, Venz S, Shubina LK, et al. Activity of aaptamine and two derivatives, demethoxyaaptamine and isoaaptamine, in cisplatin-resistant germ cell cancer. J Proteomics. 2014;96:223-239. doi:10.1016/j.jprot.2013.11.009

22. Dyshlovoy SA, Fedorov SN, Shubina LK, et al. Aaptamines from the marine sponge Aiptos sp. display anticaner activities in human cancer cell lines and modulate AP-1, NF-κB, and p53-dependent transcriptional activity in mouse J6B CH1 cells. BioMed Res Int. 2014;2014:469309-. doi:10.1155/2014/469309

23. Nakamura H, Kobayashi J, Ohizumi Y, Hirata Y. Physiologically active marine natural products from Prolifera. Part 10. Aaptamines. Novel benzo[d][1,6]naphthyridines from the Okinawan marine sponge Aiptos aaptos. J Chem Soc Perkin Trans 1. 1987;1:173-176.

24. Coutinho AF, Chanas B, Souza TML, E, Frugulhetti I, Epifanio RD. Anti HSV-1 alkaloids from a feeding deterrent marine sponge of the genus Aiptos. Heterocycles. 2002;57(7):1265-1272.

25. Arai M, Han C, Yamano Y, Setiawan A, Kobayashi M. Aaptamines, marine sponge alkaloids, as anti-dormant mycobacterial substances. J Nat Med-Tokyo. 2014;68(2):372-376. doi:10.1007/s11418-013-0811-y

26. Jiang KH, Chung S-C, Shin J, et al. Aaptamines as sortase A inhibitors from the tropical sponge Aiptos aaptos. Bioorg Med Chem Lett. 2007;17(19):5366-5369. doi:10.1016/j.bmcl.2007.08.007

27. Shubina LK, Kalinovsky AI, Fedorov SN, et al. Three new aaptamines from the marine sponge Aiptos sp. and their proapoptotic properties. Nat Prod Commun. 2010;5(12):1881-1884. doi:10.1177/1934578X100501208

28. Wu C-F, Lee M-G, El-Shazy M, et al. Isoaaptamine induces T47D cells apoptosis and autophagy via oxidative stress. Mar Drugs. 2018;16(1):18. doi:10.3390/md16010018

29. Aaptosomes TWF. A new 5,8-diazabenzo[c]diazulene alkaloid from the Caribbean sponge Aiptos aaptos. An unprecedented base-catalyzed rearrangement of 9-demethoxyaaptamine. Heterocycles. 1998;48(10):2089-2093.

30. Souza TML, Abrantes JL, de A Epifanio R, Leite Fontes CF, Frugulhetti ICPP. The alkaloid 4-methylaaptamine isolated from the sponge Aiptos aaptos impairs herpes simplex virus type 1 penetration and immediate-early protein synthesis. Plantas Med. 2007;73(3):200-205. doi:10.1055/s-2007-967109

31. Herlt A, Mander L, Romhang W, et al. Alkaloids from marine organisms. Part 8: Isolation of bisdemethylaaptamine and bisdemethylaaptamine-9-O-sulfate from an Indonesian Aiptos sp. marine sponge. Tetrahedron. 2004;60(29):6101-6104. doi:10.1016/j.tet.2004.05.068

32. Shubina I.K, Kalinovsky AI, Fedorov SN, et al. Aaptamine alkaloids from the Vietnamese sponge Aiptos aaptos. Biomed Res Int. 2014;2014:469309-. doi:10.1155/2014/469309

33. Shaari K, Ling KC, Rashid ZM, et al. Cytotoxic aaptamines from the marine sponge Aiptos aaptos sp. and their proapoptotic activities. Nat Prod Commun. 2010;4(11):785-786. doi:10.1111/j.2042-7158.1984.tb04876.x

34. Yu H-B, Yang F, Sun F, et al. Aaptamine derivatives with antifungal and anti-HIV-1 activities from the South China Sea sponge Aiptos aaptos. Mar Drugs. 2014;12(12):2580-2582. doi:10.1016/j.mdr.2014.03.096
36. Utkina NK, Denisenko VA. N-Demethylaaptanone, a new congener of aaptamine alkaloids from the Vietnamese marine sponge Aaptos Aaptos. Nat Prod Commun. 2016;11(9):1259-1260. doi:10.1177/1934578X1601100916

37. Yu H-B, Yang F, Sun F, et al. Cytotoxic aaptamine derivatives from the South China Sea sponge Aaptos aaptos. J Nat Prod. 2014;77(9):2124-2129. doi:10.1021/np500583z

38. Liu C, Tang X, Li P, Li G. Suberitine A-D, four new cytotoxic dimeric aaptamine alkaloids from the marine sponge Aaptos suberitoides. Org Lett. 2012;14(8):1994-1997. doi:10.1021/ol3004589

39. Hamada T, Matsumoto Y, Phan C-S, et al. Aaptamine-related alkaloid from the marine sponge Aaptos aaptos. Nat Prod Commun. 2019;14(9):1934578X1986393. doi:10.1177/1934578X19863935

40. Pham C-D, Hartmann R, Müller WEG, et al. Aaptamine derivatives from the Indonesian sponge Aaptos suberitoides. J Nat Prod. 2013;76(1):103-106. doi:10.1021/np300794b

41. MN D, Erickson KL. Branched chain mono-glycerol ethers from a Taiwanese marine sponge of the genus Aaptos. Tetrahedron Lett. 1983;24(51):5699-5702.

42. Dini A, Falco B, Ferrigni M, Marino A, Sica D. The sterols of two hadromerida sponges. Experientia. 1984;40(2):170-171. doi:10.1007/BF01963582

43. Tanaka Y, Ito Y. The structure of a new carotenoid aaptopurpurin in sea sponge Aaptos aaptos. Nippon Suisan Gakk. 1985;51(10):1743 doi:10.2331/suisan.51.1743

44. Granato AC, Berlinck RGS, Magalhaes A, et al. Natural products from the marine sponges Aaptos sp. and Hymeniacidon aff. heliophila, and from the nudibranch Doris aff. verruca. Quim Nova. 2000;23(5):594-599.

45. Nakao Y, Kawatsu S, Okamoto C, et al. Gliatamides A-C, bioactive lipopeptides from the deep-sea sponge Aaptos ciliata. J Nat Prod. 2008;71(3):469-472. doi:10.1021/np8000317

46. Rashid Z, Ali A, Douzenel P, et al. Phenolics, fatty acids composition and biological activities of various extracts and fractions of Malaysian Aaptos aaptos. Asian Pac J Trop Biomed. 2018;8(11):554

47. Tang Wei-Zhuo, Yu Hao-Bing, Lu Jing-Rong, et al. Aaptolines A and B, Two New Quinoline Alkaloids from the Marine Sponge Aaptos aaptos. Chem Biodivers. 2020;17(4):e2000074-n/a doi:10.1002/cbdv.202000074

48. Nakamura H, Kobayashi Jun’ichi, Ohizumi Y, Hirata Y. Isolation and structure of aaptamine a novel heteroaromatic substance possessing α-blocking activity from the sea sponge. Tetrahedron Lett. 1982;23(52):5555-5558. doi:10.1016/S0040-4039(00)85893-1

49. Rudi A, Kashman Y. Aaptosine - a new cytotoxic 5,8-diazabenz[c]azulene alkaloid from the Red Sea sponge. Tetrahedron Lett. 1993;34(29):4683-4684. doi:10.1016/S0040-4039(00)60656-1

50. Aoki S, Kong D, Suna H, et al. Aaptamine, a spongean alkaloid, activates p21 promoter in a p53-independent manner. Biochem Biophys Res Commun. 2006;342(1):101-106. doi:10.1016/j.bbrc.2006.01.119

51. Jin M, Zhao W, Zhang Y, et al. Antiproliferative effect of aaptamine on human chronic myeloid leukemia K562 cells. Int J Mol Sci. 2011;12(11):7352-7359. doi:10.3390/ijms12117352

52. Dyshlovoy SA, Naeth I, Venz S, et al. Proteomic profiling of germ cell cancer cells treated with aaptamine, a marine alkaloid with antiproliferative activity. J Proteome Res. 2012;11(4):2316-2330. doi:10.1021/pr300170p

53. Li Q-lu, Zhang P-ping, Wang P-qin, et al. The cytotoxic and mechanistic effects of aaptamine on hepatocellular carcinoma. Anticancer Agents Med Chem. 2015;15(3):291-297. doi:10.2174/187152061466141141201027

54. Tsukamoto S, Kudo Y, Kato H, et al. Aaptoline a, a new quinoline alkaloid from the marine sponge Aaptos suberitoides. Heterocycles. 2014;88(1):591-594. doi:10.3987/COM-13-S(S)3