Abstract: Marine and terrestrial environments are rich sources of various bioactive substances, which have been used by humans since prehistoric times. Nowadays, due to advances in chemical sciences, new substances are still discovered, and their chemical structures and biological properties are constantly explored. Drugs obtained from natural sources are used commonly in medicine, particularly in cancer and infectious diseases treatment. Naphthyridines, isolated mainly from marine organisms and terrestrial plants, represent prominent examples of naturally derived agents. They are a class of heterocyclic compounds containing a fused system of two pyridine rings, possessing six isomers depending on the nitrogen atom’s location. In this review, biological activity of naphthyridines obtained from various natural sources was summarized. According to previous studies, the naphthyridine alkaloids displayed multiple activities, i.a., antiinfectious, anticancer, neurological, psychotropic, affecting cardiovascular system, and immune response. Their wide range of activity makes them a fascinating object of research with prospects for use in therapeutic purposes.

Keywords: natural compounds; alkaloids; naphthyridines; heterocyclic compounds; canthin-6-one; aaptamine; pyridoacridines; biological activity

1. Introduction

The natural environment abounds in substances with multiple biological properties that have become an inspiration and basis for modern drugs. Since prehistoric times, secondary metabolites especially in the form of plant materials have been used for therapeutic purposes [1]. Nowadays, thanks to chemical sciences development, natural derivatives can be isolated from terrestrial and marine sources as multi-component extracts or single compounds. This provides a possibility to explore their properties, from chemical structures and general mechanisms of action to more specialized molecular targets.

Naphthyridines are a class of heterocyclic compounds that are also referred to in the chemical literature as “benzodiazines” or “diazanaphthalenes”, due to possessing a fused system of two pyridine rings. There are six positional isomers with different locations of nitrogen atoms (Figure 1).

The compounds containing the naphthyridine scaffold are found in natural products (plants and marine organisms) or can be obtained synthetically. The properties and synthesis of 1,8-isomer derivatives were most often described, mainly due to nalidixic acid (1-ethyl-7-methyl-4-oxo-1,8-naphthyridine-3-carboxylic acid), which was discovered by G. Lesher in 1962 [2] and introduced into treatment in 1967 as an antibacterial drug. In the last several decades, scientists’ interest in naphthyridines has been growing due to their broad spectrum of biological activity. In this review, biological activity of naphthyridines derived exclusively from the natural environment is presented. Many of them revealed significant bioactivity and this article may encourage researchers to further the investigation of these chemical compounds.
2. Naturally Occurring Naphthyridine Derivatives

2.1. 1,5-Naphthyridine Derivatives

1,5-Naphthyridine natural products are represented primarily by canthinone-type alkaloids. A major member of the group, canthin-6-one 1 (Figure 2), is isolated primarily from plants—the Rutaceae and Simaroubaceae families, but also from fungi [3]. The immunomodulatory activity of the compound has been determined. In rats with drug-induced colitis, canthin-6-one 1 reduced the production of pro-inflammatory mediators TNF-α (tumor necrosis factor α), IL-1β (interleukin-1β), IL-12p70 (interleukin-12p70), and VEGF (vascular endothelial growth factor). Moreover, it diminished oxidative stress in colon tissues [4].

Moreover, canthin-6-one 1 has been studied for its anticancer properties. Normally, cell death determines system homeostasis and prevents excessive proliferation and accumulation of defective cells. Major mechanisms of cell death comprise programmed apoptosis and autophagy, and traumatic necrosis. In cancer cells, cell death is disturbed due to genetic abnormalities. Restoration of a proper cell cycle together with generating cell damage in tumor tissues are key targets for anticancer compounds.

Canthin-6-one 1 was shown to activate apoptosis and necrosis in Kasumi-1 human myeloid leukemia cells, with cell cycle arrest at G0/G1 and G2, respectively, at 7 µM and 45 µM. The agent also induced cancer cells differentiation, a process which could potentially lead to the conversion of neoplastic cells into normal [5].

1,5-Naphthyridine representatives were also obtained from Zanthoxylum paracanthum Kokwaro—an endemic, tropical plant, native to Kenya and Tanzania. Canthin-6-one and
10-methoxycanthin-6-one 2 (Figure 2), isolated from the species, have been regarded as promising antibacterial and antifungal substances [6]. They displayed strong inhibitory activity against *Staphylococcus aureus* and *Escherichia coli* (MIC values respectively of 0.49 and 3.91 µg/mL), and importantly also against methicillin-resistant *Staphylococcus aureus* strain (MIC values respectively 0.98, 3.91 µg/mL). The results of stronger canthin-6-one 1 were similar to that of reference omacilin. Antifungal effects of the compounds 1–2 were presented with MIC values, respectively, of 3.91 and 7.81 µg/mL for canthin-6-one 1 and 10-methoxycanthin-6-one 2. The compounds 1–2 also exerted significant anticancer effects against DU145 prostate and HCC 1395 human breast cancer cell lines, with the most impressive activity of 10-methoxycanthin-6-one 2 against DU145 (IC₅₀ = 1.58 µg/mL, and SI = 34.15) [6].

*Ailanthus altissima Swingle* has been considered as another natural source of 1,5-naphthyridines. It is a genus of tree distributed primarily in China, but is now widespread in Europe and North America. Healing properties of the plant are known in traditional medicine, and it is used i.a. in treating bacterial infections, fever and diarrheas. Kim et al. isolated six canthinone-type compounds, containing the 1,5-naphthyridine ring, from the bark of *Ailanthus altissima Swingle* [7]. The derivatives were determined as (R)-5-(1-hydroxyethyl)-canthine-6-one 3, canthin-6-one 1, 4-hydroxycanthin-6-one 4, 10-hydroxycanthin-6-one 5, 9-hydroxycanthin-6-one 6, and 11-hydroxycanthin-6-one 7 (Figure 2). The compounds 1 and 3–7 were tested for their anti-inflammatory properties. Derivatives 1–5 showed strong inhibitory effect on LPS (lipopolysaccharides)-induced NO (nitric oxide) production in RAW 264.7 murine macrophage cell line (IC₅₀ = 7.73–15.09 µM). Moreover, 10-hydroxycanthin-6-one showed antifungal activity against *Fusarium graminearum* and *Fusarium solani* (growth inhibition rates respectively of 74.5% and 57.9%), and antibacterial effect against *Bacillus cereus* (MIC = 15.62 µg/mL) [8]. Canthin-6-one displayed antiparasitic effect in mice infected with *Trypanosoma cruzi*, both in acute and chronic infection. Due to its low toxicity, it is considered a promising candidate in Chagas disease therapy [9]. Canthin-6-one and 8-hydroxy-canthin-6-one 8 were also shown to exert antimycobacterial effects [10].

1,5-Naphthyridine alkaloids were isolated also from *Leitneria floridana*, a species of shrub, commonly known as corkwood, which is distributed in the southern regions of the United States. *Leitneria floridana*-derived 1-methoxycanthin-6-one 9 appeared to exert an effect against HIV (Human Immunodeficiency Virus) with an EC₅₀ value of 0.26 g/mL [11]. Beside antiviral properties, the compound displayed anticancer potency and was shown to induce cellular apoptosis by activation of c-Jun N-terminal kinase [12].

The protein complex NF-κB (nuclear factor kappa B) plays a key role in pro-inflammatory mechanisms and has been found chronically active in various types of tumors and autoimmune diseases. A study performed by Tran et al. showed that *Eu-rycoma longifolia*-derived alkaloids: 9-hydroxycanthin-6-one 6, 9-methoxycanthin-6-one 10 and 9,10-dimethoxycanthin-6-one 11 (Figure 2) significantly inhibited NF-κB transcription with IC₅₀ values in the range of 3.8–19.5 µM [13]. In another study, *Brueca mollis*-isolated 9-methoxycanthin-6-one 10 exerted strong cytotoxic properties against KB epidermoid carcinoma, LU-1 lung adenocarcinoma, LNCaP prostate adenocarcinoma, and HL-60 leukemia human cell lines with IC₅₀ values in the range of 0.91–3.73 µM [14].

*Picrasma quassioides*, a genus of tree commonly growing in temperate regions of southern Asia, revealed to be the source of another natural naphthyridine agents. Jiao et al. isolated novel 1,5-naphthyridine alkaloids from *Picrasma quassioides Bennet* [15]. The compounds were determined as quassidine E 12 and canthin-16-one-14-butyrlic acid 13 (Figure 3). The novel agents 12 and 13 reduced the production of pro-inflammatory mediators: NO, IL-6, and TNF-α in LPS-induced RAW 264.7 cells, with IC₅₀ values in the range of 20.51–66.96 µM [15].
Figure 3. Structures of quassidine E 12 and canthin-16-one-14-butyric acid 13.

Natural products—cimiciduphytine 14 and eburnane derivatives 15 (Figure 4)—were evaluated as natural painkillers and antihypertensive agents, which could be used in cerebral circulation disturbance therapy [16].

Figure 4. Structures of cimiciduphytine 14 and eburnane derivatives 15.

2.2. 1,6-Naphthyridine Derivatives

Aaptos, a widely-known genus of marine sponges, is considered as a prominent natural source of 1,6-naphthyridines. Aaptos was firstly described by Gray in 1867 [17]. The genus is represented by nearly 29 species that can be found in shallow waters of coastal areas all over the world. Since the 1980s, Aaptos has been extensively researched due to being the source of at least 62 secondary metabolites with diverse biological activities [18].

Aaptamine (8,9-dimethoxy-1H-benzo[de][1,6]naphthyridine) 16 (Figure 5) isolated by Nakamura et al. [19] in 1982 from Aaptos aaptos became the first, maternity representative of aaptamines family. The anticancer activity of the compound 16 has been extensively researched. Aaptamine exhibited notable cytotoxic effects in vitro against H1299 and A549 non-small cell lung cancer [20], HeLa cervical cancer [21], and CEM-SS T-lymphoblastic leukemia cell lines [22], with IC$_{50}$ values ranging from 10.47 to 15.03 µg/mL. Moreover, aaptamine 16 displayed a potent anticancer effect in mice carrying human hepatocellular carcinoma HCC-LM3 xenografts with downregulation of SOX9 and Ki67 expression [23]. The agent 16 has been detected to intercalate into DNA [24], upregulate p21 expression, and induce apoptosis in cancer cells in a p53-independent manner [23,25]. Aaptamine 16
expressed the ability to interfere specifically with p53 and c-myc network in NT2 human embryonal carcinoma cell line [26]. Gong et al. [20] performed further investigation of the mechanism of aaptamine 16 action in non-small cell lung cancer cell lines. The agent 16 displayed antiproliferative properties with inhibition of cancer cells growth and clonogenicity in a dose-dependent manner. Aaptamine induced G1 cell cycle arrest with a reduction of CDK2 (Cyclin-dependent kinase 2), CDK4 (Cyclin-dependent kinase 4), Cyclin D1, and Cyclin E levels, and also interfered with the PI3K/AKT/GSK3b (phosphatidylinositol-3 kinase/protein kinase B/glycogen synthase kinase 3 beta) axis. It could potentially diminish the process of metastasis and tumor invasion due to downregulation of MMP-7 (matrix metalloproteinase-7) and MMP-9 (matrix metalloproteinase-9) expression [20].

Beside anticancer activity, aaptamine 16 was shown to block α-adrenoceptors in vascular smooth muscles [27]. Hence, it could be considered a antihypertensive agent. Moreover, the compound 16 has been reported to display antiviral activity against HIV-1 [24] and anti-amoebic effect towards Acanthamoeba castellanii [28]. Aaptamine 16 selectively blocked the type A MAO (Monoamine Oxidase) [29], an enzyme which is overexpressed in the brain during major depression episodes. Therefore, aaptamine 16 could be useful in depression therapy. Aaptamine 16 demonstrated a wide range of activity, nevertheless its derivatives surpassed the effect of parental agent.

Figure 5. Aaptamine derivatives 16–18.

There are several studies comparing properties of parent aaptamine 16 with its derivatives demethyl(oxy)aaptamine 17 and isoaaptamine 18 (Figure 5). Dyshlovoy et al. [30] investigated anticancer properties of these compounds 16–18, isolated from Aaptos. Evaluation of cytotoxicity on human cancer cell lines (THP-1 human leukemia monocytic, HeLa cervical cancer, SNU-C4 colorectal carcinoma, SK-MEL-28 human melanoma, MDA-MB-231 breast cancer) in MTS assay confirmed significant anticancer potency of aaptamines 16–18, and aaptamine analogues exerted impressively higher activity than the parent compound. All the agents 16–18 induced apoptosis in THP-1 cell line, and the effect was also more significant for demethyl(oxy)aaptamine 17 and isoaaptamine 18. The study confirmed p53-independent cell cycle arrest induced by these compounds 16–18. The agents 16–18 were also shown to prevent cancerogenesis induced by epidermal growth factor at low, non-toxic concentrations in the JB6 P+ Cl41 murine epidermal cell line. The mechanism of prevention is independent from the transcription of AP-1 (activator protein-1) and NF-κB.

Wu et al. [31] investigated the cytotoxicity of aaptamine 16, demethyl(oxy)aaptamine 17, and isoaaptamine 18 on breast cancer cell lines. The derivatives 17 and 18 also presented higher activity than parent compound 16. Itoaaptamine 18 exerted the highest effect on T-47D (IC$_{50} = 30.13$ µM), meanwhile demethyl(oxy)aaptamine 17 was the most potent on MCF-7 (IC$_{50} = 23.11$ µM) and MDA-MB-231 (IC$_{50} = 19.34$ µM) cell lines. Itoaaptamine 18, chosen for further research as the most prominent alkaloid (84.74%) in the active fraction isolated from sponge Aaptos sp., presented short-term and long-term antiproliferative properties. The compound 18 inhibited XIAP (X-linked inhibitor of apoptosis protein) expression, and due to caspases 3 and 7 activation and cleavage of PARP (Poly ADP-ribose polymerase), induced apoptotic cell death in cancer cells. Cytotoxic properties of
isoaaptamine 18 have also been based on autophagy induction, disruption to mitochondrial function, and over-generating reactive oxygen species. The role of isoaaptamine 18 as a significant apoptosis inducer on THP-1 cells was confirmed by Shubina et al. [32]. The compound 18 exerted the highest activity among tested aaptamine analogues.

Beside aaptamine 16 and its major analogues demethyl(oxy)aaptamine 17 and isoaaptamine 18, other 1,6-naphthyridines have been successfully isolated from marine sponge Aaptos. Liu et al. [33] obtained four novel 1,6-naphthyridine alkaloids, suberitine A-D 19–22 (Figure 6), and two known alkaloids, demethyl(oxy)aaptamine 17 (Figure 5) and 8,9,9-trimethoxy-9H-benzo[de][1,6]naphthyridine 23 (Figure 7), from the Aaptos suberitoides.

![Figure 6. Structures of suberitines A-D 19–22.](image)

Figure 6. Structures of suberitines A-D 19–22.

Cytotoxic evaluation of the compounds revealed significant antitumor activity of 20 and 22 against P388 cell line with IC$_{50}$ values, respectively, of 1.8 and 3.5 µM [33].

Toshiyuki Hamada et al. [34] isolated 8,9,9-trimethoxy-9H-benzo[de][1,6]naphthyridine 23 and 1,3-dioxolo[4,5-d]benzo[de][1,6]naphthyridine 24 (Figure 7) from the Bornean Aaptos aaptos and tested their cytotoxicity against adult T-cell leukemia cells. Compound 24 revealed a significant antitumor effect with an IC$_{50}$ value of 0.29 µM, while alkaloid 23 remained inactive.

Yu et al. [35] isolated nine novel and three previously-known aaptamine derivatives from the South China Sea sponge Aaptos aaptos. Four of the compounds: 9-Amino-2-ethoxy-8-methoxy-3H-benzo[de][1,6]naphthyridin-3-one 25, 3-isobutylaminodemethyl(oxy)
aaptamine 26, 3-(isopentylamino)demethyl(oxy)aaptamine 27, and 3-(phenethylamino)demethyl(oxy)aaptamine 28 (Figure 8) revealed potent anticancer activity with IC_{50} values in the range of 0.03–8.5 µM against human cancer cell lines: HL60 leukemia, K562 erythroleukemia, MCF-7 breast cancer, KB epidermoid carcinoma, HepG2 hepatocellular carcinoma, and HT-29 colon adenocarcinoma [35].

![Figure 8. Structures of aaptamine derivatives 25–28.](image)

RANKL (Receptor Activator for Nuclear Factor κB Ligand) is a transmembrane protein that controls bone regeneration and remodeling. Wang et al. [36] performed biological examination of four 1,6-naphthyridines analogues, aaptodine A–D 29 (Figure 9), derived from Aaptos suberitoide. Aaptodine A–D 29 inhibited impressively RANKL-induced osteoclast formation and resorption, with the strongest effect for aaptodine D 29D. Hence, aaptodines could be considered as candidates for drugs used in treating osteoporosis and hormone therapy-induced bone loss.

![Figure 9. Structures of aaptodine A-D 29.](image)

Another rich source of 1,6-naphthyridine is constituted by Sophora derivatives. Trees and shrubs from genus Sophora, comprising approximately 62 species, are distributed in tropical and temperate zones in Eastern Europe; Asia; Australia; Pacific islands; and western, North, and South America. Natural alkaloids have been isolated from roots, seeds and epigeal parts of the plant. Sophora extracts have been used in traditional Chinese medicine [37].

Matrine 30 (Figure 10) is considered as one of the most principal and widely studied Sophora alkaloid, and the number of publications regarding the compound are constantly growing. Molecular mechanisms of matrine 30 antitumor activity have been considerably researched. Recent studies confirmed the antineoplasm effect of matrine on MCF-7 breast cancer and A549 non-small cell lung cancer cell lines by inhibiting AKT/mTOR axis [38,39]. Additionally, it reduced tumor growth of ovarian cancer cells in vivo by inducing the expression of ERK and JNK (c-Jun N-terminal kinase) pathways [40]. Matrine 30 also
exerted a significant effect in drug-resistant tumors by inducing apoptosis and inhibiting efflux-pump activity [41,42]. Beside anticancer properties, matrine 30 exerted cardioprotective effects towards cardiomyocyte damage during hyperglycemia and sepsis [43,44]. Moreover, matrine 30 properties of protecting liver function resulted in several clinical trials. Intramuscular injections of matrine 30 caused improvement of condition in patients treated for chronic Hepatitis type B and patients suffering from primary hepatic carcinoma after trans-artery chemo-embolization [45,46]. Compound 30 was also reported to decrease total bilirubin level and improve survival rates in liver transplant recipients [47]. Matrine 30 is also considered a promising candidate as an immunosuppressive drug due to inhibiting autoimmune response in experimental models of multiple sclerosis [48,49]. It also exerts antiviral activity [50,51].

Figure 10. Structures of the Sophora alkaloids 30–33.

Extract isolated from the seeds of Sophora alopecuroides matrine 30, sophocarpine 31 and sophoramine 32 (Figure 10), with contents, respectively, of 32.85%, 26.55%, and 6.91%, have alleviated morphine withdrawal in patients [52]. Moreover, these alkaloids 30–33 displayed strong antitumor properties. Matrine 30, sophoridine 33 (Figure 10), and sophocarpine 31 exerted potent cytotoxic activity against HL-60 human leukemia, U937 human myeloid leukemia, K562 human erythroleukemia, EC109 esophageal squamous cell carcinoma, A549 non-small cell lung cancer, and HepG2 hepatocellular carcinoma cell lines, with IC50 values in the range of 1.21–12.86 mM [53]. Matrine 30 and sophocarpine 31 decreased cachexia symptoms (induced by colon carcinoma) in mice, and the mechanism of action was related to the suppression of TNF-α and IL-6 production [54]. Additionally, sophoramine 32 and sophocarpine 31 displayed antinematicidal activity against Bursaphelenchus xylophilus, pine trees parasite, and it was observed that degree of unsaturation in the -lactam ring correlated with the strength of antinematicidal activity [55].

Sophora alkaloids have been tested worldwide for their anti-inflammatory properties. Tang et al. [56] evaluated the activity of five 1,6-naphthyridines analogues 34–36 (Figure 11), derived from roots of Sophora tonkinesis. The agents 34–36 significantly reduced the secretion of cytokines TNF-α and IL-6 in LPS-stimulated murine macrophages RAW 264.7. The most potent effect, higher than that of matrine 30, was exerted by 12,13-dehydrosoforidine 34 (TNF-α and IL-6 levels were 56.82% and 65.21%, respectively) [56].
Li et al. [57] isolated 43 natural alkaloids from the seeds of *Sophora alopecuroides*. Assessment of anti-inflammatory efficacy was measured as suppression of NO production in LPS-activated RAW 264.7 cells. Among *Sophora* alkaloids, 5,6-dehydrolupanine 37 (Figure 12) exerted the most potent effect (IC\textsubscript{50} value of 25.86 µM), higher than that of matrine. On the other hand, another 1,6-naphthrylidine derivative sophalode K 38 (Figure 12) decreased significantly the secretion of enzymes playing crucial role in development of inflammation: iNOS (inducible nitric oxide synthase) and COX-2 (cyclooxygenase 2).

Fan et al. [58] obtained five novel 1,6-naphthyridine alkaloid dimers, alopecuroides A–E 39–43 (Figure 13), from the aerial parts of *Sophora alopecuroides*. The study revealed strong anti-inflammatory properties of alopecuroides B 40 and C 41. TNF-α and IL-6 levels were, respectively, 50.05% and 52.87% for alopecuroides B 35b and 49.59% and 73.90% for alopecuroides C 41 in LPS-induced RAW 264.7 cells [58].

*Sophora* alkaloids were also reported to exhibit immunosuppressive properties. Alopecines A-E 44–48 (Figure 14), isolated from the seeds of *Sophora alopecuroides*, were assessed toward inhibiting proliferation of Concanavalin A-induced T lymphocytes and LPS-induced B cells [59]. Alopecine D 47 exerted the most potent effect, with IC\textsubscript{50} = 3.98 µM for inhibiting proliferation of T lymphocytes and 3.74 µM for B lymphocytes (SI ratios respectively 8.0 and 8.5).

Pan et al. [60] evaluated antiviral activity of 16 natural alkaloids, obtained from rhizomes of *Sophora tonkinensis*. 12α-Hydroxyxophocarpine 49 (Figure 15), 12β-hydroxyxyso-phocarpine 50, and sophoranol 52 inhibited Influenza Virus A/Hanfang/359/95 replication with IC\textsubscript{50} values in the range of 63.07–242.46 µM (SI ratios 3.1–5.7). 12β-Hydroxyxyso-phocarpine 50, 9α-hydroxyxophocarpine 51, sophoranol 52, and 14β-hydroxymatrine 53 (Figure 15) exerted the most potent activity against Coxsackie Virus B3 with IC\textsubscript{50} values in the range of 26.62–252.18 µM (SI ratios 3.0–6.8) [60].
Figure 13. Alopecuroides A–E 39–43.
Figure 14. Alopecines A-E 44–48.

Figure 15. Structures of 12-hydroxyoxysophocarpine 49–50, 9α-hydroxyoxysophocarpine 51, sophoranol 52, and 14β-hydroxymatrine 53.

2.3. 1,7-Naphthyridine Derivatives

Bisleuconothine A 54 (Figure 16), determined as 1,7-naphthyridine alkaloid, was derived from the bark of *Leuconotis* griffithii—a species of plant with native distribution in southern Asia [61]. The agent 54 was shown to exert antineoplasm potency by inhibiting WNT signaling pathway, and to induce G0/G1 cell cycle arrest in cancer cells. It displayed significant antiproliferative properties against SW480, HCT116, HT29, and SW620 colon cancer cells in vitro (IC\(_{50}\) values respectively 2.74, 3.18, 1.09, and 3.05 µM), and reduced tumor growth in mice carrying HCT116 Xenograft [62]. Research conducted by
Wong et al. [63] in A549 non-small cell lung cancer and MCF-7 breast cancer cell lines showed that bisleuconothine A 54 owes its cytostatic properties to inducing autophagosome formation. Additionally, the compound 54 could also play a protective role in periodontitis. Bisleuconothine A 54 was determined to reduce RANKL expression and diminish periodontal tissue infiltration by pro-inflammatory polymorphonuclear cells [64].

**Figure 16.** Bisleuconothine A 54 and 1-N-methyl-3-methylamino-[N-butanoic acid-3-(9-methyl-8-propen-7-one)-amide]-benzo[f][1,7]naphthyridine-2-one 55.

Streptomyces albogriseolus is a mangrove bacterium species, widely known for producing aminoglycoside antibiotics neomycin B and neomycin C. *Streptomyces albogriseolus* has also been reported to be the source of 1,7-naphthyridine compound, 1-N-methyl-3-methylamino-[N-butanoic acid-3′-(9′-methyl-8′-propen-7′-one)-amide]-benzo[f][1,7]naphthyridine-2-one 55 (Figure 16) [65]. Cytotoxic evaluation performed by Tian et al. revealed that 55 displayed anticancer potency against HGC-27 human stomach carcinoma cell line [66].

2.4. 2,6-Naphthyridine Derivatives

4-Methyl-2,6-naphthyridine 56 (Figure 17) is an alkaloid isolated from the dried plant of *Antirrhinum majus* by Harkiss and Swift in 1970 [67].

**Figure 17.** 4-Methyl-2,6-naphthyridine 56.

Some indolo[2,6]naphthyridine alkaloids were obtained from plants of *Erythrina* spp. The seeds of these tropical trees contain erythrina alkaloids of varying degrees of toxicity. Some of them are used by indigenous peoples for medicinal purposes. They have an effect on the central nervous system and exhibit hypnotic, curare-like effects and neuromuscular inhibition, as well as sedative and hypotensive activity [68,69].

Erymelanthine-methyl(2R,13bS)-2-methoxy-2,6,8,9-tetrahydro-1H-indolo[7a,1a][2,6]naphthyridine-12-carboxylate 57 (Figure 18) was isolated from *Erythrina melanacantha* and *E. velutina* [70]. This alkaloid 57 was also obtained from *Erythrina merilliana* seeds by Jackson et al. [71]. Erymelanthine 57 was evaluated regarding its TRAIL (tumor necrosis
factor-related apoptosis-inducing ligand) enhanced activity, and this alkaloid showed no cytotoxicity [72].

An example of Erythrina alkaloid containing indolo[2,6]naphthyridine scaffold is also 8-oxoerymelanthine 58, known as melanacanthine (methyl (2R,13bS)-2-methoxy-6-oxo-1,2,8,9-tetrahydroindolo[7a,1a][2,6]naphthyridine-12-carboxylate) 58 (Figure 18). This alkaloid 58 was isolated from *E. melanacantha* by Redha in 1983 [73]. Melanacanthine 58 inhibits thrombocyte agglutination and can be used in the treatment of hypertonia. The erythrina alkaloids 57–58 exhibited paralyzing activity [70,74].

Calycanthine 59 (Figure 19) was the first alkaloid isolated from the plants Calycanthaceae [75]. Calycanthine 59 was also isolated from *Meratia praecox* [76]. Toxic doses of calycanthine 59 cause excitation in mice, rats, and rabbits. After injection, calycanthine hydrochloride induces hyperglycaemia in rabbits and lowers blood pressure in cats or dogs [77]. Calycanthine 59 acts on peripheral motor nerves to cause muscle weakness associated in lower animals. In mammals, calycanthine causes seizures. The alkaloid 59 is also a strong depressant on the heart. It was reported that the anticonvulsant effect of calycanthine 59 is mainly caused by the inhibition of the release of the inhibitory neurotransmitter GABA (gamma-aminobutyric acid) [78].

Gordin [75] isolated a second alkaloid, isocalycanthine 60 (Figure 19), from the seeds of *Chimonanthus* genus. This tetradehydroisomer of calycanthine was also isolated from the leaves of *Psychotria colorata*, the plant used in folk medicine to relieve pain [79], and from *Psychotria forsteriana* [80].

Dibenzo[c,h][2,6]naphthyridine named calycanine 61 (Figure 19) was isolated from the seeds of *Chimonanthus praecox* [81]. This alkaloid 61 was also obtained by Zn dehydrogenation of calycanthine 59 [82]. Calycanthine 59 and calycanine 61 were evaluated for their antifungal activities. *Bipolaris maydis* was susceptible to calycanthine (EC$_{50}$ = 29.3 µg/mL) [83]. Calycanthine 59 was evaluated for its potent melanogenesis inhibitory activity, but showed cytotoxicity at 10 µM [84].
2.5. 2,7-Naphthyridine Derivatives

Compounds containing the 2,7-naphthyridine scaffold were isolated from plants and various marine organisms. Naturally occurring bicyclic 2,7-naphthyridine derivatives are known as polycyclic compounds with the 2,7-naphthyridine ring in their structures.

2.5.1. Bicyclic Alkaloids

Some of the monoterpenoid alkaloids of 2,7-naphthyridine structure were isolated from Oleaceae species [85]. Jasminine 62 (Figure 20) was obtained from the leaf of Ligustrum novoguineense by Hart et al. [86]. Jasminine 62 at a dose of 300 mg/kg causes a slight decrease in motor activity in mice. Cardiovascular activity of this alkaloid 62 was also evaluated, but it showed no significant effects [87].

Figure 20. Jasminine 62, jasminidine 63, and dihydrojasminine 64.

Jasminidine 63 was isolated from Syringa Vulgaris [88], and dihydrojasminine 64 (Figure 20) was isolated from Osmanthus austrocaledonica [89,90].

Benkrief et al. [89] also isolated jasminine 62, dihydrojasminine 64, and a new copyrine alkaloid—austrodimerine 65 (Figure 21) from O. austrocaledonica.

Figure 21. Austrodimerine 65.

Powel et al. [91] reported antileukemic activity of extracts from seeds of Sesbania drummondii. Three years later, scientists described the isolation of alkaloid sesbanine—(3'R,4R)-3'-hydroxyspiro[2,7]naphthyridine-4,1'-cyclopentane-1,3-dione 66 (Figure 22) from the ethanol extract of Sesbania drummondii seeds, which are poisonous [92]. The extract containing sesbanine 66 showed cytotoxic activity (KB assay) and was active in vivo in the P-388 lymphocytic leukemia system [93].
3-Acetyl-2,7-naphthyridine 67 (Figure 22) was isolated by Janot et al. [94] from the roots and rhizomes of Valeriana officinalis. This compound 67 exhibited sedative and tranquilizer activity [94].

Neozeylancine 68 (Figure 22) was isolated in 1988 from Neonauclea zeylanica by Atta-ur-Rahman [95].

Bioactive alkaloids Lophocladine A 69 and lophocladine B 70 (Figure 23) were isolated from the marine red alga Lophocladia sp. by Gross et al. [96]. 4-Phenyl-2,7-naphthyridin-1-one 69 exhibited antagonistic activity against δ-opioid receptors, and 1-amino-4-phenyl-2,7-naphthyridine 70 showed cytotoxic activity against human lung tumor and breast cancer cell lines [96].

2.5.2. Tricyclic Alkaloids

Some alkaloids containing a diazaphenanthrene (benzo[2,7]naphthyridine) scaffold were discovered in some plants and marine organisms. 8-Bromo-4,5,5-trimethyl-5,6-dihydrobenzo[c][2,7]naphthyridine named Veranamine 71 (Figure 24) was isolated from the ethanol extract of the marine sponge Verongula rigida. Veranamine 71 had a moderate affinity for serotonin receptors and was therefore assessed for antidepressant activity in mice using the forced swim test. This alkaloid 71 showed antianxiety and antidepressant activity and selective affinity for 5HT2B and sigma-1 receptors [97].
Alkaloids: 6-(3,4-dimethoxyphenyl)-3\(H\)-benzo[\(f\)][2,7]naphthyridin-6-ium-4-one called Perloline 72 and benzo[\(f\)][2,7]naphthyridin-4(3\(H\))-one called perlolidine 73 (Figure 24) were isolated from the perennial rye grass Lolium perenne [98]. These alkaloids 72–73 inhibit in vitro cellulose digestion. Perloline 72 is slightly toxic after oral administration to mice and sheep [99].

Subarine-methyl 2-(5-oxo-6\(H\)-benzo[\(f\)][2,7]naphthyridin-4-yl)pyridine-3-carboxylate 74 (Figure 24) was isolated from Singaporean ascidian by Nilar et al. [100]. This marine alkaloid 74 was evaluated by in vitro screening against yeast and many Gram-positive and Gram-negative bacteria, but it exhibited no significant activity. Subarine 74 was also tested for in vitro cytotoxic activity on 60 human tumor cell lines, but did not show antiproliferative effect [101,102].

2.5.3. Tetracyclic Alkaloids

The extract of the plant Alangium lamarckii has been used by Indians to treat many human disorders [103]. In Thailand, it is useful in the treatment of asthma, coughs, hemorrhoids, diarrhea; and in India to treat leprosy, fever, or as an anthelmintic agent [104,105]. Pakrashi et al. [106,107] isolated tetracyclic alkaloids from the seeds of A. lamarckii. This alangium alkaloids namely: alamaridine 75, alangimaridine 76, dihydroalamarine 77, alangimarine 78, alamarine 79, alangimarinone 80, isoalangimarine 81 isoalamarine 82, and dihydroisoalamarine 83 (Figure 25) contain the isoquino[2,1-\(b\)][2,7]naphthyridine scaffold [108,109].
Some tetracyclic alkaloids possess 2,7-naphthyridine ring in the structure of azaaporphine: eupomatidines 1–3\textsuperscript{84–86} and imbilines 1–3\textsuperscript{87–89} (Figure 26) were isolated from \textit{Eupomatia bennettii} and \textit{E. laurina}\textsuperscript{110}.

Kitahara et al.\textsuperscript{111} synthesized eupomatidines 1–3\textsuperscript{84–86} and evaluated their antifungal activity against \textit{Candida albicans}, \textit{Paecilomyces variotii}, and \textit{Trichophyton mentagrophytes}. Eupomatidine-1\textsuperscript{84} exhibited activity against those tree fungi with \(EC_{50}\) values of 50 µg/mL, 6.25 µg/mL, and 0.4 µg/mL, respectively. Eupomatidine-2\textsuperscript{85} and eupomatidine-3\textsuperscript{86} were active only toward \textit{T. mentagrophytes} with \(EC_{50}\) values 3.1 µg/mL and 6.25 µg/mL, respectively. Khan et al.\textsuperscript{112} evaluated eupomatidine-1\textsuperscript{84} against over a dozen Gram-positive and Gram-negative bacteria strains, a protozoan and nine fungi. This alkaloid\textsuperscript{84} turned out to be much better than the applied standard (ketoconazole and griseofulvin), both in terms of scope and level of antifungal activity. Eupomatidine-1\textsuperscript{84} showed comparable antimicrobial activity to chloramphenicol.
Imbiline-1 87 (Figure 26) was also isolated from a large tree *Duguetia hadrantha* and then evaluated for its antimalarial and antimicrobial activity [113]. Imbiline-1 87 showed a weak antimalarial potency, but it was more active against chloroquine-resistant than chloroquine-sensitive *Plasmodium falciparum* clones. Imbiline-1 87 was found to be inactive against *C. albicans*, *C. neoformans*, and *S. aureus*. This alkaloid 87 exhibited cytotoxic activity in vitro against human malignant melanoma and human ovary carcinoma cell lines with IC$_{50}$ values of 2 µg/mL and 5 µg/mL, respectively [113].

The scientists [113] isolated also new imbiline-type alkaloids: hadranthine A 90a and hadranthine B 90b from the ethanolic extract of *Duguetia hadrantha* (Figure 27).

![Figure 27. Hadrantines A 90 and hadranthine B 91, and sampangines 92–96.](image)

Hadrantline A (7,10-dimethoxy-6-methyl-4,5-dihydronaphthol[1,2,3-ij][2,7] naphthyridine-4,5-(6H)-dione) 90 showed in vitro antimalarial activity against chloroquine-resistant *P. falciparum* with IC$_{50}$ = 120 ng/mL. This alkaloid was active against *C. albicans* with MIC = 20 µg/mL. Hadrantline B (7-methoxy-4,5-dihydronaphthol[1,2,3-ij][2,7]naphthyridine-4,5-(6H)-dione) 91 did not show antimalarial activity, but it exhibited in vitro cytotoxic activity against human malignant melanoma, epidermoid carcinoma, ductal carcinoma, and ovary carcinoma cell lines with IC$_{50}$ values between 3–6 µg/mL [113]. This alkaloid 91 was also evaluated for its in vitro effects on immune response and inflammation, but did not show significant potency [113].

Sampangine 92–96 (Figure 27) also are tetracyclic alkaloids containing the 2,7-naphthyridine scaffold. Sampangine 92 was isolated first from the stem bark of plant *Cananga odorata* by Rao et al. [114]. 3-Methoxy derivative 93 was isolated from *Cleistopholis patens* by Liu et al. [115]. Sampangine 92 and 3-methoxysampangine 93 were also isolated from *Duguetia hadrantha* and then evaluated for their antimalarial, antifungal, and cytotoxic potency [115]. Both alkaloids 92–93 exhibited activity against *P. falciparum* with no cytotoxicity toward VERO cells. Sampangine 92 showed cytotoxicity to human malignant melanoma with IC$_{50}$ = 0.37 µg/mL and inhibited cell aggregation (MIC < 0.15 µg/mL) [113]. Sampangine 92 isolated from the stem bark of *Anaxagorea dolichocarpa* by Lucio et al. [116] demonstrated antitumor activity against human leukemic strains with IC$_{50}$ values of 10.15–11.80 µg/mL. Sampangine 92 and 11-methoxysampangine 94 isolated from the roots of *Ambavia gerrardii* were evaluated for their antiproliferative activity [117]. Alkaloids 92 and 94 showed strong activity against human non-small cell lung cancer cell line with IC$_{50}$ values of 0.57–0.58 µM, but sampangine 92 was more active against human ovarian cancer cell line (IC$_{50}$ = 0.60 µM) than its 11-methoxy derivative 94 (IC$_{50}$ = 10.30 µM) [117].
scientists under Kluza [118] directions has shown that sampangine 92 induces apoptosis in HL-60 cells. In low concentrations, it caused G1 arrest and at the same time induced mitochondrial hyperpolarization. At higher concentrations, it elicited mitochondrial depolarization [118]. The treatment of human leukemia cells with sampangine 92 (40 µM) induced apoptosis due to an oxidative stress [119]. The ability of sampangine 92 to produce reactive oxygen species was confirmed by using an in vitro biochemical assay, and the participation of this alkaloid 92 in binding and damaging DNA was excluded [120].

Sampangine 92, and two derivatives: 9-methoxysampangine 95 and 8,9-dimethoxysampangine 96, were isolated from the barks of Polyalthia nemoralis [121] and evaluated for their cytotoxic activity. Obtained alkaloids 92, 94, 95 exhibited significant cytotoxicity against human carcinoma in the mouth, human breast cancer, human lung cancer, human hepatoma cancer, human prostate cancer, human ovarian adenocarcinoma, and human colon adenocarcinoma [121].

Sampangines 92–93 exhibited antimicrobial activity against C. albicans, C. neoformans, and S. aureus [113,122]. Sampangine 92 was found to be a strong antifungal agent against Paecilomyces variotii, and Trichophyton mentagrophytes with EC_{50} = 0.2 µg/mL [111]. Scientists reported that the antifungal activity of sampangine 92 may be due to perturbations in heme biosynthesis or metabolism [123].

3-Methoxysampangine 93 showed significant in vitro antifungal activity against C. albicans and C. neoformans and A. fumigatus, better than amphotericin B [115]. These alkaloids 92–93 also showed excellent antimycobacterial activity against Mycobacterium intracellulare, comparable to rifampin [124]. The dependence of the activity of sampangine derivatives 92–96 on the type of substituents in the naphtho[1,2,3-ij][2,7]naphthyridine scaffold is presented in Table 1.

Table 1. The dependence of the activity of alkaloids 92–96 on the types of substituents.

| Activity       | Substituents |
|----------------|-------------|
|                | R  | R¹ | R² | R³ |
| anticancer     | H  | H  | OCH₃ | H  | OCH₃ |
| antimalarial   | H, CH₃ | H | H | H |
| antifungal     | H, CH₃ | H | H | H |
| antibacterial  | H, CH₃ | H | H | H |

Eupolauridines are tetracyclic alkaloids containing the 2,7-naphthyridine scaffold condensed with an indene ring (Figure 28).

Eupolauridine (indeno[1,2,3-ij][2,7]naphthyridine) 97 was isolated from Cananga odorata [125] and from Eupomatia laurina [126]. Pan et al. [117] isolated eupolauridine 97, 8-hydroxyeupolauridine 98, 9-methoxyeupolauridine-1-oxide 100, and eupolauridine N-oxide 101 from Ambavia gerrardii. Alkaloids were screened for their in vitro antiproliferative activity. Among eupolauridine analogues, compound 101 was the most active against
human ovarian cancer cell line with $IC_{50} = 3.5 \mu M$, and only this derivative 101 showed antitumor activity against non-small-cell lung cancer cell line ($IC_{50} = 1.77 \mu M$) [117]. 7-Methoxy-8-hydroxyeupolauridine 99 isolated from Polyalthia nemoralis by Oanh et al. [121] did not show cytotoxicity against seven tested cancer cell lines (human carcinoma in the mouth, human breast cancer, human lung cancer, human hepatoma cancer, human prostate cancer, human ovarian adenocarcinoma, and human colon adenocarcinoma). Eupolauridine 97 extracted from the root bark of Cleistopholis patens by Hufford et al. [127] exhibited a significant activity against C. albicans with MIC = 1.56 µg/mL.

2.5.4. Pentacyclic Alkaloids

Pentacyclic derivatives of indolo[2′3′:3,4]pyrido[1,2-b][2,7]naphthyridine (Figure 29) were isolated from different plants. Alkaloids: nauclefine 102, naucletine 103, angustine 105, angustoline 106, and angustidine 107 isolated from Neuclea officinalis [128], and neonaucline 104 and cadamine 109 isolated from Ochreinauclea mainaguii exhibited potent vasorelaxant activity on isolated rat aorta [129]. Neuclefine 102 isolated from the bark of Nauclea subdita also induced apoptosis of diverse cancer cells and inhibited tumor xenograft growth [130]. Normalindine 111 and norisomalindine 110 were isolated from Strychnos johnsonii [131]. Isomalindine 113 and normalindine 111 were isolated from Ophiorrhiza sp. [132]. 19-O-ethylangustoline 99 and other alkaloids were isolated from the stem bark of Sarcocephalus latifolius [133]. Malindine 112 and isomalindine 113 were isolated from the stem bark of Strychnos usambarensis [134].

![Figure 29. Structures of indolo[2′3′:3,4]pyrido[1,2-b][2,7]naphthyridine derivatives 102–113.](image)

2.5.5. Polycyclic Alkaloids—Pyridoacridine Analogs

Pyridoacridines are polyheterocyclic compounds containing pyrido[4,3,2-mn]acridine skeleton (Figure 30) and are a large number of marine-derived alkaloids.
Pyridoacridine alkaloids possess 2,7-naphthyridine scaffold in their structures and can be classified into tetracyclic, pentacyclic, hexacyclic, heptacyclic, and octacyclic compounds due to the number of rings attached to the pyrido[4,3,2-mn]acridine skeleton. Calliactine 114 (Figure 31) was the first pyridoacridine derivative that was obtained. This alkaloid 114 was isolated from the sea anemone Calliactis parasitica in 1940 by E. Lederer et al. [135].

Since then, about a 100 pyridoacridine analogs have been found in many marine organisms. They have been isolated from ascidians, sponges, anemone, and certain mollusks. Most pyridoacridine derivatives were reported to possess significant pharmacological activities, including anticancer, antimicrobial, and antiparasitic activities [136–139].

Tetracyclic Pyridoacridine Derivatives

The first tetracyclic members of pyridoacridines were cystodytines 115–125 (Figure 32). These alkaloids 115–125 were isolated from the yellow tunicate Cystodytes dellechiajei by Kobayashi et al. [140,141]. Cystodytines A–K 115–125 were found to be cytotoxic. Cystodytine A–C 115–117 showed in vitro potent cytotoxicity against mouse leukemia cell lines with IC\textsubscript{50} values of 0.22–0.24 \text{µg/mL} [140] and Cystodytines D–I 118–123 against murine lymphoma and human epidermoid carcinoma KB cells with IC\textsubscript{50} values of 0.068–1.4 \text{µg/mL} [141]. Cystodytine J 124 isolated from Cystodytes sp. exhibited cytotoxic activity in vitro against the human colon tumor cell line with IC\textsubscript{50} = 1.6 \text{µM} and inhibited the topoisomerase II with IC\textsubscript{50} = 8.4 \text{µM}. The DNA binding ability of Cystodytine J 124 has also been reported [142]. 12-Methoxy derivatives 125 of cystodytine J were isolated from the ascidian Lissoclinum notti. Cystodytine K 125 showed cytotoxic activity in vitro against a murine leukemia cell line (IC\textsubscript{50} = 1.3 \text{µM}) [143].

Styelsamines A–D 126–129 (Figure 33) were isolated from the ascidian Eusynstyela latericius [144]. Obtained alkaloids 126–129 showed cytotoxicity toward the human colon tumor cell line with IC\textsubscript{50} values of 33, 89, 2.6, and 1.6 \text{µM}, respectively [144]. Styelsamines C 129 and D 128 were also isolated from the purple morph of the ascidian Cystodytes dellechiajei [145].
Fong and Copp [146] evaluated styelsamines 126–129 and cystodytines 115–125 for their DNA binding affinity and cytotoxic activity towards a panel of human tumor cell lines. Tested compounds showed moderate antiproliferative activity. Styelsamines B 127 and D 128 have particularly high affinity for calf thymus (CT)DNA, but cystodytines exhibited lower affinity [146].

Methylsulfanyl derivative of cystodytine J was isolated from the tunicate Diplosoma sp. by Charyulu et al. and named diplamine 130 [147]. Diplamine 130 and its isomer isodiplamine 131 (Figure 34) were also isolated from the ascidian Lissoclinum notti and were tested for their cytotoxicity against murine leukemia, human colon tumor, and non-malignant African Green Monkey kidney cell lines. Diplamine 130 was more cytotoxic towards BSC-1 cells than isodiplamine 131. Diplamine 130 turned out to be a stronger topoisomerase II inhibitor than etoposide and showed the ability to intercalate into DNA [142].
Figure 34. Diplamines 130–132.

Diplamines 130–131 also exhibited moderate antimicrobial activity towards *Bacillus subtilis*, *Escherichia coli*, *Candida albicans*, and *Trichophyton mentagrophytes* [143]. Diplamine B 132 was isolated from the ascidian *Lissoclinum badium* and tested by immunoblotting for its effects on cellular p53 and Hdm2 in the tert-immortalized human retinal pigment epithelial cells (the potency was similar to proteasome inhibitor N-acetyl-leucyl-leucyl-norleucinal) [148].

The dependence of the activity of diplamine derivatives 130–132 on the type of substituents in the pyridoacridine scaffold is presented in Table 2.

Table 2. The dependence of the activity of alkaloids 130–132 on the type of substituents.

| Activity         | Substituent | R   | R¹     | R²     |
|------------------|-------------|-----|--------|--------|
| anticancer       | H, COCH₃    | SCH₃| H      |
| antimicrobial    | COCH₃       | H, SCH₃| H, SCH₃|

Another pyridoacridine alkaloid containing thiomethyl substituents—varamine A 133, veramine B 134, lissoclin A 135, and lissoclin B 136 (Figure 35)—was isolated from the ascidian *Lissoclinum* sp. [149,150]. Varamines 133–134 showed cytotoxicity towards L-1210 murine leukemia cells with IC₅₀ values of 0.03 and 0.05 µg/mL, so they proved to be more toxic than cystoditines, which have the same skeleton but without the thiomethyl group [150].

Figure 35. Veramines 133, 134 and lissoclins 135 and 136.

Norsegoline 137 (Figure 36) was isolated from tunicate *Eudistoma* sp. [151,152]. Einat et al. [153] evaluated the inhibitory effect of norsegoline on the growth of myeloid progenitors obtained from bone marrow and peripheral blood of chronic myelogenous leukemia (CML) patients. Norsegoline 137 showed antiproliferative activity and may be
an effective agent for use in removing ex vivo Philadelphia-positive cells from peripheral blood of CML patients in conjunction with autologous bone marrow transplantation [153].

Kim et al. [154] isolated a brominated alkaloid pantherinine \textsuperscript{138} (Figure 36) from the ascidian \textit{Aplidium pantherinum}, which showed cytotoxic activity against murine leukemia cells (ED\textsubscript{50} = 4.5 \(\mu\)g/mL).

**Penta- and Hexacyclic Pyridoacridine Derivatives**

Lissoclinidine \textsuperscript{139} (Figure 37) was isolated from the ascidian \textit{Lissoclinum notti} [143]. This pentacyclic alkaloid \textsuperscript{139} is a product of diplamine photoreduction, where the thiomethyl group is cyclised into a 1,3-oxathiolane ring. Lissoclinidine \textsuperscript{139} showed moderate antiproliferative activity [143].

Deacetyl derivative, lissoclinidine B \textsuperscript{140}, was isolated from \textit{Lissoclinum cf. badium} [155]. Lissoclinidine B \textsuperscript{140} selectively induces cell apoptosis in a p53-dependent manner with IC\textsubscript{50} values of 98.1 ± 6 \(\mu\)M and a dose-dependent increase in luciferase activity. The results of the studies showed that lissoclinidin B \textsuperscript{140} is an inhibitor of Hdm2 auto-ubiquitylation and stabilizes p53 and Hdm2 in cells [148].

Kuanoniamine alkaloids \textsuperscript{141}–\textsuperscript{149} contain a thiazole ring fused to pyridoacridine scaffold (Figure 38). Kuanoniamines A–D \textsuperscript{141}–\textsuperscript{144} were first isolated from the mollusk \textit{Chelynotus semperi} [156], and kuanoniamines E–F \textsuperscript{145}–\textsuperscript{146} were isolated by Nilar et al. [100] from Singaporean ascidians. N-Deacetylkuanoniamine C \textsuperscript{147} was isolated from the Micronesian sponge \textit{Oceanapia sp} [157]. Dehydrokuanoniamine B \textsuperscript{148} and F \textsuperscript{149} were isolated from South-Pacific Ocean ascidian \textit{Cystodytes violatinctus} [158].
Cytotoxicity of kuanoniamines C 143 and D 144, and N-deacetylkuanoniamine C 147 were studied in vitro, using two human cell lines (HeLa cells and MONO-MAC 6 cells) and exhibited similar activity with IC_{50} values of 1.2–2.0 µg/mL [157]. Kuanoniamine D 144 exhibited affinity to A1- and A2A-adenosine receptors (K_i values of 2.94 and 13.7 µM, respectively), and all derivatives showed moderate affinity to benzodiazepine binding sites of GABA-A receptors [157]. Dehydrokuanoniamine F 149 showed cytotoxic activity toward the SW480 colon cancer cell line with IC_{50} values of 3.30 µM [158].

Sagitols are hydroxy analogs of kuanoniamines (Figure 39). Sagitol 150 and sagitol C 151 were isolated from the Indonesian sponge Oceanapia sp. [159,160]. Sagitol C 151 exhibited antiproliferative activity towards mouse lymphoma, human cervix carcinoma, and rats brain tumor cell lines in MTT (the microculture tetrazolium) assay [161]. Sagitol D 152 was isolated from Vietnamese ascidians and showed a weak antioxidant activity with IC_{50} values of 92 µM in the DPPH (2,2-diphenyl-1-picryl-hydrazyl-hydrate) assay [160].

Other pyridoacridine alkaloids containing a thiazole ring fused with pyridoacridine skeleton are Dercitin 153 isolated from Dercitus sp. sponges and its analogs isolated from Stelletta sp. sponges (Figure 40) [162–164]. Dercitin 153 exhibited in vivo antitumor activity. This alkaloid 153 inhibited the proliferation of murine leukemia and human leukemia, and lung, melanoma, and colon tumor cells with IC_{50} values of 63–150 nM. Dercitin 153 was a potent inhibitor of DNA polymerase I and showed an effect on the stabilization of protein–DNA complexes [165]. Dercitine analogs: nordecitine 154, dercitamide 155, dercitamine 156, cyclocerdicine 157, dehydrocyclocerdicine 158, and stellettamine 159 also showed antiproliferative activity, but were less potent than dercitine 153 (Table 3) [166].
Figure 40. Dercitin analogs 153–159.

Table 3. Antiproliferative activity of dercitine analogs 153–159.

| Alkaloid | Activity                                      | IC<sub>50</sub>  |
|---------|-----------------------------------------------|------------------|
| 153     | antiproliferative inhibition of polymerase I  | 63–150 nM        |
|         | stabilization of protein-DNA complexes        |                  |
| 154     | antiproliferative                             | 4.8 µM           |
| 155     | antiproliferative                             | 26.7 µM          |
| 156     | antiproliferative                             | 12.0 µM          |
| 157     | antiproliferative                             | 1.9 µM           |
| 158     | antiproliferative                             | 9.9 µM           |
| 159     | antiproliferative                             | 60.0 µM          |

Sebastianine A 160 has a pyrrole ring and sebastianine B 161 has a pyrrolidine ring fused with the pyridoacridine scaffold (Figure 41). These alkaloids 160–161 were isolated from the ascidian Cystodytes dellichiagei and showed cytotoxic activity against the HCT-116 colon carcinoma cells, indicating a p53-dependent mechanism [167].
Arnoamines 162–165 have a pyrrole ring fused to the pyridoacridine scaffold (Figure 42). These cytotoxic alkaloids 162–165 were isolated from the ascidian Cystodytes sp. [158,168]. Arnoamine A 162 showed good antitumor activity against breast cancer cell lines with GI\textsubscript{50} value of 0.3 \(\mu\)g/mL and weak activity against lung and colon cell lines with GI\textsubscript{50} of 2.0 and 4.0 \(\mu\)g/mL, respectively. Arnoamine B 163 exhibited weak antiproliferative activity against the same cancer cell lines (GI\textsubscript{50} of 2.0–3.0 \(\mu\)g/mL) [168]. Cytotoxic activity of arnoamine C 164 and arnoamine D 165 were evaluated against melanoma and colon cancer cell lines. Arnoamine D 165 was found to be more active than arnoamine C 164 (with IC\textsubscript{50} values of 4.32–8.48 \(\mu\)M) [158].

The first analog of pyridoacridine obtained from marine organisms was amphimedine 166. This alkaloid 166 containing a pyridoquinoline skeleton was isolated from an Amphimedon sp. sponge [169]. Later, more amphimedine-type alkaloids (Figure 43) 166–178 were isolated from the marine sponge Xestospongia sp. and the ascidian Cystodytes dellechiajei [145,155].

Amphimedine analogs: amphimedine 166, neoamphimedine 168, deoxyamphimedine 171, 3-hydroxy-deoxyamphimedine 172, and debromopetrosamine 176 were evaluated in a zebrafish phenotype-based assay and only amphimedine 166 caused embryo necrosis, pericardial edema, and an enlarged yolk with a thin extension at 30 \(\mu\)M [170]. Amphimedine 166 exhibited cytotoxic activity toward P388 murine leukemia cells, but it did not inhibit topoisomerase II [169,171,172]. Neoamphimedine 168 was cytotoxic toward normal CHOAA8 cells and deoxyamphimedine 170 against human colon tumor cells [173]. Neoamphimedine 168 also showed antityrpanosomal activity against T. brucei with IC\textsubscript{50} = 0.21 \(\mu\)M, but amphimedine 166 was inactive [171,173]. Demethyldesoxyamphimedine 173 showed antibacterial activity against L. anguillarum and M. luteus [145].
The presence of a bromine atom on the benzene ring determines the activity of these derivatives (Table 4). Petrosamine 177 isolated from Petrosia sp. sponge was found to be about six times more potent an AChE inhibitor than galanthamine ($IC_{50} = 0.091 \mu M$) [174]. Petrosamine B 178 weakly inhibited the Helicobacter pylori aspartyl semialdehyde dehydrogenase ($IC_{50} = 306 \mu M$) [175].
Table 4. The dependence of the activity of petrosamine analogs 176–178 on the type of substituents.

| Activity                  | Substituent | R  | R¹  |
|---------------------------|-------------|----|-----|
| AChE inhibitor            | H           | Br |     |
| antibacterial (H. pylori) | Br          | H  |     |
| inactive                  | H           | H  |     |

Ascididemin analogs also possess a pyridine ring fused to the pyridoacridine scaffold (Figure 44). Ascididemin 179 was isolated from the tunicate Didemnum sp. and the ascidian Cystodytes dellechiajei [155], and later with 12-deoxyascididemin 181 from the ascidian Polysyncrator echinatum [176]. These alkaloids 179 and 181 showed potent activity against T. brucei with IC₅₀ values of 0.077 and 0.032 µM, respectively [176]. Ascididemin 179 also exhibited antimicrobial activity against C. resinae, E. coli, and B. subtilis [177], and very good potency against M. tuberculosis (MIC = 0.35 µM) [178]. Ascididemin 179 causes release of calcium ions in the sarcoplasmic reticulum seven times more than caffeine [140]. Ascididemin analogs showed cytotoxic activities. Ascididemin 179 and 12-deoxyascididemin 181 exhibited cytotoxic activity toward the human embryonic kidney cell line with IC₅₀ values of 1.48 and 7.63 µM, respectively [176]. Ascididemin 179 showed cytotoxic effects against murine leukemia cells (IC₅₀ = 0.39 µg/mL) [140]. 11-Hydroxyascididemin 180 showed cytotoxic activity against the human prostate cancer (PC3) cell line with IC₅₀ = 1.9 µM [179].

Figure 44. Structures of ascididemin analogs 179–186.
Meridine 182 (Figure 44) isolated from the ascidian *Amphicarpa meridiana* [180] and from the marine sponge *Ecionemia geodides* [181] also showed cytotoxic activity against the invasive bladder cancer cell lines (IC50 values of 3.76–4.56 µM) [181].

Ecionines A 183 and B 184 (Figure 44) possessing an imine moiety were isolated from *Ecionemia geodides* sponge [181]. Ecionine A 183 showed moderate cytotoxic activity against a panel of human bladder cancer cell lines with IC50 values of 3–7 µM [181].

Ancorine 185 and cnemidine A 186 are analogs of hydroxyascididemines (Figure 44). Ancorine 185 was isolated from the sponge *Ancorina geodides*, and cnemidine A 186 was isolated from the tunicate *Cnemidocarpa stolonifera* [182]. Cnemidine A 186 selectively inhibited PC3 with IC50 = 1.1 µM [182].

Shermilamines are alkaloids with the 3-thiomorpholinone ring fused to pyridoacridine scaffold (Figure 45). These alkaloids 187–190 were first isolated from the tunicate *Trididemnum* sp. [183,184], and later also from the ascidians *Cystodytes* sp. [142,185]. Shermilamines A 187 and B 188 exhibited cytotoxicity to murine leukemia cells. Shermilamine B 188 showed in vitro cytotoxic activity against KB cells with IC50 = 5 µg/mL, and human colon tumor cells with IC50 = 13.8 µM [156]. Shermilamines B and C 188–189 inhibit topoisomerase II and have the ability to intercalate into calf thymus DNA [142]. Shermilamine B 188 and N-deacetylshermilamine 190 were evaluated for their antibacterial activity against *E. coli* and *M. luteus*, but they were found to be less potent than reference gentamicin [138].

![Shermilamines 187–190.](image)

Hepta- and Oxacyclic Pyridoacridine Derivatives

Eilatin 191 is a symmetrical, heptacyclic alkaloid containing two pyridoacridine moieties (Figure 46). This alkaloid 191 was isolated from the tunicate *Eudistoma* sp. [151,152] and also from the ascidians *Cystodytes* sp. and *Polysyncraton echinatum* [142,169]. Eilatin 191 showed in vitro antiproliferative activity against the human colon tumor cell line and the human embryonic kidney cell line [176]. It also inhibited topoisomerase II and intercalated into DNA [142]. Eilatin 191 has two sets of nitrogen atoms capable of metal ion chelation. Complexes of eilatin–Ru(II) exhibited strong anti-HIV activity [186].

Biemnadin 192 is the octacyclic alkaloid containing the 2,7-naphthyridine ring in its skeleton (Figure 46). This alkaloid 192 was isolated from *Biemna* sp. sponges [187]. Biemnadin 192 showed weak cytotoxic activity toward the superficial bladder cancer cell line [181] and induced multipolar neuritogenesis [188].
2.6. Naphthyridines Molecular Mechanisms of Action—What Do We Know?

Naturally occurring naphthyridines are characterized by diverse mechanisms of action. Some of their biomolecular activities have been discovered, nevertheless there is still much to explore in this field.

Naphthyridines obtained from natural sources are characterized by anticancer potency. The compounds exhibit features of topoisomerase inhibitors and DNA intercalators [142]. They were documented to induce apoptosis in cancer cells in both p53-dependent and p53-independent manner [23,25,148,167]. Moreover, the compounds interfere with procytotoxic signaling pathways, i.a., AKT/mTOR, ERK, JNK, WNT [38–40,62]. Antineoplastic properties against drug-resistant tumors could be elucidated by inhibiting efflux-pumps activity, however, this topic requires further study [41,42].

Anti-inflammatory activity of naphthyridines is based on reducing iNOS and COX-2 release, decrease in NO production, and IL-6 and TNF-α secretion [7,15,54,56,57]. They suppress autoimmune reactions through an IFN-β/IL-27/IL-10 pathway, and by targeting proautoimmunity gene expression including angiogenin and stratifin [48,49].

The compounds modulate neurotransmission by affinity to GABA A and MAO A receptors, and inhibiting AchE activity [29,157,174].

Natural naphthyridines antiinfectious properties were widely screened against many infectious species [6,8,111,112,178]. However, molecular mechanisms of their action are still poorly researched and described. This issue is an interesting target for deeper research.

Natural naphthyridines have an extensive background of preliminary research, which is a solid foundation for molecular studies. Further investigations are still needed.

3. Conclusions

The natural environment, including marine and terrestrial organisms, should be considered as a rich source of bioactive substances. Naturally-derived naphthyridines, isolated mostly from sea species and terrestrial plants, have been shown as potent chemical compounds with multidirectional activity. Natural naphthyridines are most abundantly represented by 1,6- and 2,7-naphthyridine isomeric forms. Until now, research studies revealed their impressive antimicrobial [6,8,177], antifungal [6,8,111,112], and antimiococobacterial [10,178] effects, and some of them displayed activity superior or comparable to those presented by chloramphenicol [112], amphotericin B [115], and rifampin [124]—drugs used in standard therapeutic regimens. Moreover, naphthyridines were shown to present significant properties including antiinfectious: antiviral [11,24,50,51], antiparasitic [9,176], and antimalarial [113]; anticancer [5,6,23,35]; influencing cardiovascular system: hypotensive [16,27], cardioprotective [43,44]; neurological: sedative [94], analgesic [15], anticonvulsant [78], stimulating neuritogenesis [188]; psychotropic: anxiolytic [97], antidepressant [29,97]; and affecting immune system: anti-inflammatory [7,56,57], immunosuppressant [48–50]. The spectrum of activity of naturally-derived naphthyridines is wide, thus these compounds are undeniably fascinating subjects of research. An undoubted advantage of naphthyridines is their wide availability thanks to the possibility...
of obtaining them both from natural sources and synthetically. The versatility of naphthyridines is expressed by the occurrence of multiple activities within a single compound. Moreover, many of the representatives are considered as safe and nontoxic, and constitute a great alternatives for standard therapies [9,48]. We strongly believe that this work will contribute to further exploration of naphthyridine derivatives— their natural sources and bioactive properties—and will result in the use of these chemical compounds for therapeutic purposes in the future.

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