

MINI REVIEW

A mini review on pyridoacridines: Prospective lead compounds in medicinal chemistry



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ABSTRACT

Natural products are increasingly being considered “critical and important” in drug discovery paradigms as a number of them such as camptothecin, penicillin, and vincristine serve as “lead molecules” for the discovery of potent compounds of therapeutic interests namely irinotecan, penicillin G, vinblastine respectively. Derived compounds of pharmacological interests displayed a wide variety of activity *viz.* anticancer, anti-inflammatory, antimicrobial, anti-protazoal, etc.; when modifications or derivatizations are performed on a parent moiety representing the corresponding derivatives. Pyridoacridine is such a moiety which forms the basic structure of numerous medicinally important natural products such as, but not limited to, amphimedine, ascididemin, eilatin, and sampangine. Interestingly, synthetic analogues of natural pyridoacridine exhibit diverse pharmacological activities and in view of these, natural pyridoacridines can be considered as “lead compounds”. This review additionally provides a brief but critical account of inherent structure activity relationships among various subclasses of pyridoacridines. Furthermore, the current aspects and future prospects of natural pyridoacridines are detailed for further reference and consideration.

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Introduction

The pivotal role of natural products in novel drug discovery programme can be ascertained from the fact that approximately 40% of Food and Drug Administration, USA (FDA) approved therapeutic drugs have natural origin [1]. The drugs derived via taking "lead" from nature, have shown immense potential in terms of their chemical diversity and biosynthetic molecular recognition usually absent in synthetically developed libraries. A "lead compound" can be defined as a compound responsible for synthesis of a series of compounds via chemical modifications in order to achieve optimal therapeutic activity [2]. A number of drugs derived from the natural sources are available in the market for different ailments (Table 1). In general, a lead compound is identified on the basis of its ability to bind to a therapeutic target. Once designated as a "tight-binder", this lead

compound can be chemically modified to improve the target specificity, bioavailability, and pharmacokinetics and finally tested for their therapeutic activity via pre-clinical and clinical studies [2].

Pyridoacridines, a class of marine-derived alkaloids characterized by a 11*H*-pyrido[4,3,2-*mm*]acridine, fulfil all the requirements of being lead compounds in their respective therapeutic category [32]. With varied chemical compositions and conformations differing by (1) different side chains; (2) rings fused to ring C; (3) rings fused to the acridine nitrogen; (4) bromination at C2 in ring A; and (5) varied oxidation states, pyridoacridines present an array of biological activities with respect to, but not limited to, anticancer, anti-HIV, antimicrobial, antiparasitic, anti-viral and insecticidal activities [33]. Furthermore, pyridoacridines are also associated with calcium ions release from sarcoplasmic reticulum, neuronal differentiation, metal chelation, and depict affinity towards GABA receptors [34]. Various subclasses of pyridoacridines such as amphimedines, ascididems, petrosamines, dercitins, diplamines, and eilatins provide important chemical cues and clues to act as lead compounds (Fig. 1). For example, various pyridoacridines displayed their anticancer activities *via* different mechanism like binding with DNA, inhibition of DNA/RNA/protein synthesis, inhibition of topoisomerase, cleavage/catenation/damage of DNA, cell cycle arrest and hence can be employed as "hits" in further lead optimization [32–34].

Although some comprehensive reviews are available on pyridoacridines such as Molinski's one [32] which describes the structure, synthesis and biological chemistry of pyridoacridines or the other by Marshall and Barrows [34], which reviewed the biological activities of pyridoacridines; the present review describes a correlation between various important structural aspects of pyridoacridines with respect to their biological activities demonstrating their potential as lead compounds for the future [32,34].

Different natural pyridoacridines are shown in Fig. 1. Inspired by these natural pyridoacridines, researchers around the world are synthesizing medicinally active derivatives. In view of the above mentioned facts, pyridoacridines can be considered as "Prospective lead compounds" of the future. The word "Prospective lead compounds" can be exemplified from the different representative examples of pyridoacridine deriva-

Table 1 Different medicinally important natural lead compounds and their derived drugs.

S. no.	Lead compounds	Derived drugs	Medicinal Importance	References
1	Camptothecin	Irinotecan, Topotecan	Anticancer	[3,4]
2	Paclitaxel	Docetaxel	Anticancer	[5,6]
3	Vincristine	Vinblastine, Vindesine, Vinorelbine	Anticancer	[7,8]
4	Etoposide	Teniposide	Anticancer, Cytotoxic	[8,9]
5	Quinine	Quinidine	Antimalarial, Antiarrhythmic	[10,11]
6	Digitoxin	Digoxigenin	In Cardiovascular diseases	[12,13]
7	Cephalosporin C	Cefixime, Cefuroxime	Antimicrobial	[14,15]
8	Morphine	Codeine, Pholcodeine, Ethylmorphine	Antitussives; Analgesic	[16,17]
9	Artemisinin	Artesunate, Artemether	Antimalarial	[18,19]
10	Penicillin G	Penicillin X	Antimicrobial	[20,21]
11	Tetracycline	Chlortetracyclins, Oxytetracyclins	Antimicrobial	[22,23]
12	Atropine	Hyoscine	Anticholinergic	[24,25]
13	Ergotamine	Ergotoxin, Ergometrine	α -adrenergic blockers, Uterine stimulants	[26,27]
14	Theophylline	Choline theophyllinate	Bronchodilators	[28,29]
15	Dopamine	Levodopa, Carbidopa	Parkinsonism	[30,31]

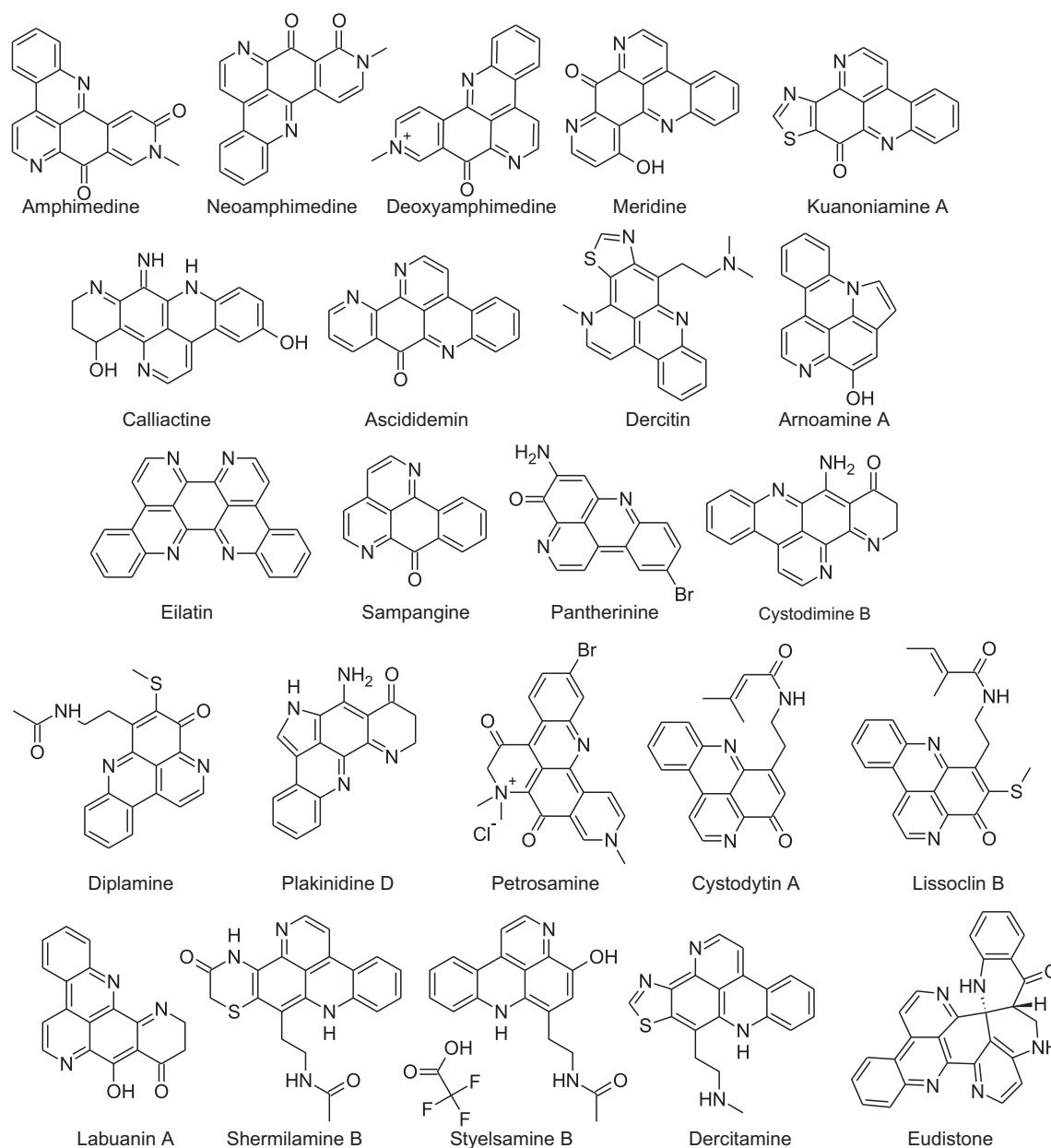


Fig. 1 Natural pyridoacridines.

tives to be covered in coming sections. In addition, structural activity relationship points may further prove their candidature as lead compounds for different ailments. Furthermore, for the interest of the readers, due care has been taken as the present review limit itself to discussion on different analogues of representative natural pyridoacridines with promising activities only and discussion has been provided with sub-heads namely: amphimedine analogues, ascidemin analogues, dercitin analogues, eilatin analogues, kuanoniamine analogues, sampangine analogues and current/future prospects.

Scope of the review

This review primarily focuses on the representative publications of last 20 years (i.e. from 1994 to 2014) related to

chemical and medicinal aspects of pyridoacridines; each representing a unique study about pyridoacridine analogues.

Search terms like pyridoacridine, pyridoacridine derivative, lead, amphimedine, ascidemin, kuanoniamine, sampangine, dercitin, eilatin were used to find out different publications on natural as well as synthetic analogues of pyridoacridines by using various E-resources and databases like Google Scholar, American Chemical Society, Wiley-Blackwell Publishing, Elsevier Science, Nature, Royal Society of Chemistry, Springer Link, Taylor and Francis, Pubmed Scopus, Reaxys, Bielstein and Scifinder.

Amphimedine analogues

A small difference in the structure of a drug may impose noticeable effect on its pharmacological activity like three natural

analogues of amphimedines namely: amphimedine, neoamphimedine, deoxyamphimedine bear only small differences in structures but neoamphimedine and deoxyamphimedine both possess antitumour activity. On the other hand, the study describes amphimedine as relatively inactive (Fig. 1). As per a study performed by Marshall and co-workers [35], neoamphimedine antitumour activity equals to well-known anticancer agent etoposide while in reference to work by Matsumoto et al. [36], authors speculate that mechanism behind anticancer activity of deoxyamphimedine could be redox cycling and reactive oxygen species (ROS) generation emanated from its iminoquinone moiety [35–37]. Authors further concluded that being a positively charged compound; deoxyamphimedine demonstrated significantly different biological activities as compared to neoamphimedine and deoxyamphimedine.

Ponder et al. [38], demonstrated the influence of carbonyl group position in biological activity with the help of molecular docking studies. Docking studies on ATPase site of TopoII α enzyme revealed that carbonyl group of neoamphimedine interacts with Ser-148 residue at ATPase but in case of amphimedine, hydrogen bonding with Ser-148 was lost which resulted in unfavourable steric interaction with the active site Mg²⁺ and ultimately loss of biological activity [38].

Different analogues of amphimedine were synthesized via Diels–Alder reaction and their cytotoxic potential was assessed on human cancer cell lines with varying histopathological types (colon, lung, glioblastomas and bladder cancers) by using MTT assay. Interestingly, it was reported that most similar analogues of amphimedine i.e. compound 1 and compound 2 were found to exhibit highest cytotoxic potential with IC₅₀ value less than 10⁻⁷ M [39].

Ascididemin analogues

Marshall and co-workers [40] discussed structure activity relationship among different analogues of ascididemin i.e. AK37 and AK36 (Fig. 2). Structurally, the only difference between ascididemin and AK37 is the presence of an additional N-atom in ascididemin; while mechanistically AK37 act by inhibiting the catalytic activity of both topo I/II and stabilizes the DNA-Topo I cleavable complex. The DNA-Topo I cleavable complex stabilizing function of AK37, the first pyridoacridine

to show this activity, as compared to the ROS-generating function of ascididemin, can be attributed to the absence of nitrogen in the ‘A’ ring of AK37. However, complete removal of ring ‘D’ from AK37 maintained the DNA-Topo I cleavable complex stabilization in BC21 which proves that ring ‘D’ does not exhibit any important role in AK37’s Topo I activity. In case of AK36, the presence of an additional ring ‘F’ prevented DNA intercalation by AK36 and rendered it lower cytotoxicity than the related compounds. Additionally, the presence of ring ‘F’ in AK36 diminished the DNA-Topo I cleavable complex stabilizing functions observed in AK37 [40].

In a study, Lindsay et al. [41], provided the structure activity relationship of various ascididemin analogues. In brief, the authors assessed the importance of ring A and ring E of ascididemin (Fig. 2) by synthesizing different analogues of ascididemin and carried out a range of assays for the evaluation of their biological activity. Presence of nitrogen in ring A is essential for the inhibition of *Escherichia coli* and *Cladosporium resinae* while its absence results in *Trichophyton mentagrophytes* inhibition. [41]. Alternatively, dramatic increase in antitumour/antifungal/antibacterial activity was evaluated by the presence or absence of ring E in ascididemin and compound 3 respectively (Fig. 2). Furthermore, it was concluded that ascididemin acts through multiple mechanisms towards mammalian cell systems [41]. Similar to these studies, Appleton and co-workers synthesized ring A analogues of ascididemin containing furan and thiophene rings which showed considerable antitubercular activity [42].

In their study, Guittat et al. [43], determined the affinity of ascididemin for DNA quadruplexes and findings of the study indicated that large flat aromatic surface of ascididemin might be responsible for their binding with DNA quadruplexes. Furthermore, authors asserted that presence of positive charge on nitrogen atom of ascididemin would enhance, as DNA quadruplex has high negative charge density [43].

Delfourne and co-workers [44], further suggested that the cytotoxic activity of the ascididemin isomer (compound 4) can be retained even after manipulating positions 5 and 7 on ring D [44].

In a study conducted by Delfourne and co-workers in [45], ascididemin analogues were synthesized and evaluated for their cytotoxic potential by MTT assay. Some ascididemin

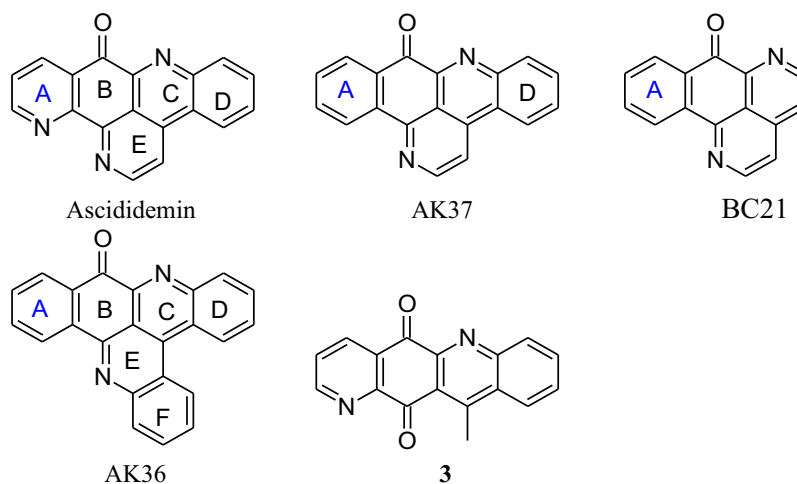


Fig. 2 The basic structure of ascididemin and their analogues.

analogues (ring D-modified) appeared to be more cytotoxic than the reference compound ascididemin (Table 2). Furthermore, it was reported that substitution at R₁ and R₃ does not have much influence on cytotoxic activity [45].

Debnath and co-workers [46], carried out QSAR studies on the above mentioned ascididemin analogues reported by Delfourne et al. [45] and emphasized that the presence of an electron withdrawing substituent with higher molar refractivity value and the presence of NHR (R is hydrogen or alkyl group) at R₁ and R₃ positions, respectively, favoured the anti-tumour activity of ascididemin analogues [Fig. 3] [45,46].

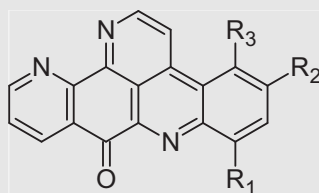
In this period of shortage of antitubercular drugs; Appleton and co-workers [42], synthesized and evaluated a series of ascididemin analogues and found thioethyl analogue i.e. compound 17 to exhibit potent antitubercular activity against *Mycobacterium tuberculosis* ((Mtb) H37Rv) strain (IC₅₀ = 0.34 μM) as compared to reference compound rifampin (IC₅₀ = 0.152 μM) [42]. Encouraged by these observations, authors made the following assertions:

1. "Size-reduced analogues of ascididemin may provide a useful scaffold for future studies."
2. Iminoquinone moiety of ascididemin is essential for antitubercular activity.

Dercitin analogues

In 1992, Taraporewal and co-workers studied the anti-HIV and anti-tumour activities of dercitin analogues. Dercitin (Fig. 1), a pyridoacridine obtained from *Dercitus* sp. sponge namely *Dercitus simplex*, *Dercitus lististinus* [47], exerts its cytotoxic effect on mammalian cells through four basic nitrogen atoms capable of binding to the acidic amino acid residues. Furthermore, progressive removal of these basic nitrogen atoms results in lowering of cytotoxic potential of dercitin. In addition to nitrogen atoms, the presence of a fused thiazole ring contributed to the cytotoxic activity of dercitin while the

Table 2 Ascididemin derivatives along with mean IC₅₀ of 12 different cell lines viz., two colon (HCT-15; LoVo); two breast (T-47D and MCF7); three glioblastomas (SW1088; U-373 MG and U-87 MG); one prostate (PC-3); two bladder (J82; T24) and two non small-cell lung (A549; A-427) cancer cell lines.



Compound	R ₁	R ₂	R ₃	Mean IC ₅₀ (nM)
5	NH ₂	H	H	53
6	H	Br	H	80
7	H	NH ₂	H	21
8	H	NHCH ₂ CH ₂ Cl	H	7
9	H	N(CH ₂ CH ₂ Cl) ₂	H	100
10	H	NHCH ₂ CH ₂ N(CH ₃) ₂	H	60
11	H	Cl	H	270
12	H	CH ₃	H	60
13	H	OCH ₃	H	90
14	H	N(CH ₃) ₂	H	37
15	H	NHBn	H	140
16	H	NH ₂	Br	140
Ascididemin	H	H	H	100

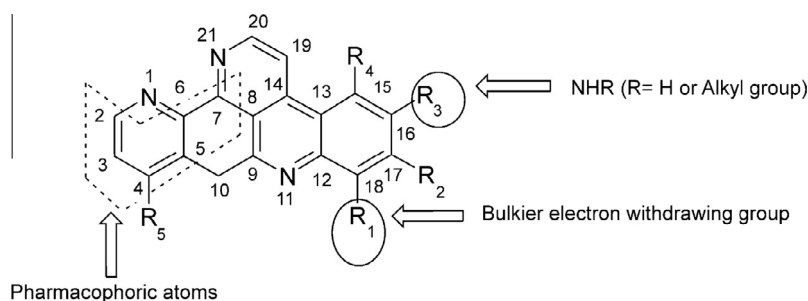
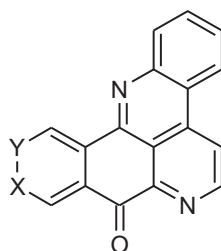


Fig. 3 Pharmacophoric atoms and required physicochemical properties of substituents at R₁ and R₃ positions of ascididemin analogues for their anti-tumour activity [46], Reproduced with permission from Elsevier B.V. Ltd.© 2003).

presence of a nonlinearly fused pyridine ring E elicited no significant benefit. Compounds **18** and **19** possessed best anti-HIV activity. The presence of a sulphur atom seemed to be essential for antiviral activity of dercitin analogues while the acidic carboxylic group decreases viral affinity towards lymphocytes. Similarly, the occurrence of a mercaptoacetic acid group at the C-2 position in compounds **18** and **19** on the tricyclic ABC acridine nucleus demonstrated highest HIV-1 neutralization activity along with the partial inhibition of viral affinity towards lymphocytes [48].

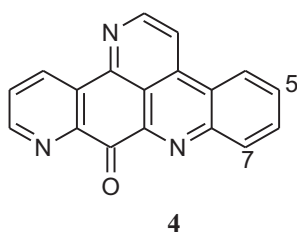
Eilatin analogues

Eilatin (Fig. 1) is a highly symmetrical heptacyclic alkaloid isolated in 1988 from the red sea tunicate *Eudistoma* sp. A new family of eilatin-containing metal complexes is under investigation for their unusual nucleic acid binding specificity [49]. In a similar study, Zeglis and Barton [50], investigated the DNA-binding properties of $\text{Ru}(\text{bpy})_2(\text{eilatin})^{2+}$ (compound **20**) to determine specificity of sterically expansive eilatin ligand for DNA [50]. From the results it was concluded that extended planar surface presented by eilatin is responsible for its specificity and anti-HIV activity [49,51].

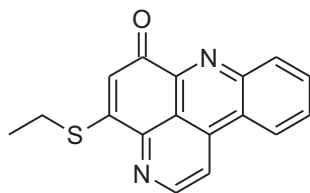


1: Y=N

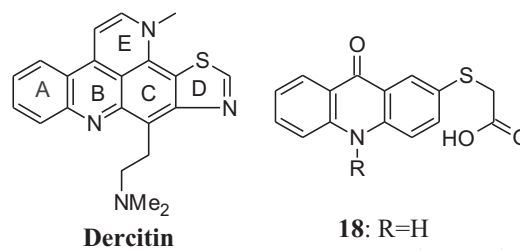
2: X=N



4



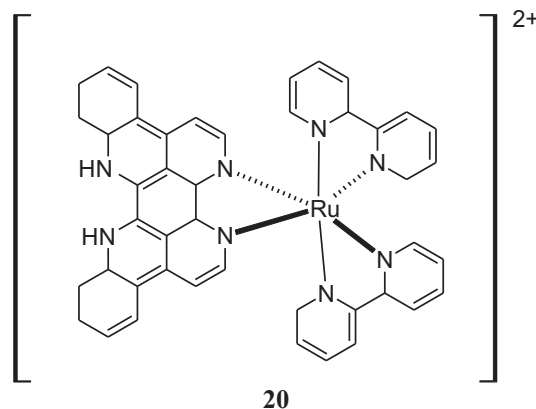
17



Dercitin

18: R=H

19: R=cyclopropyl



20

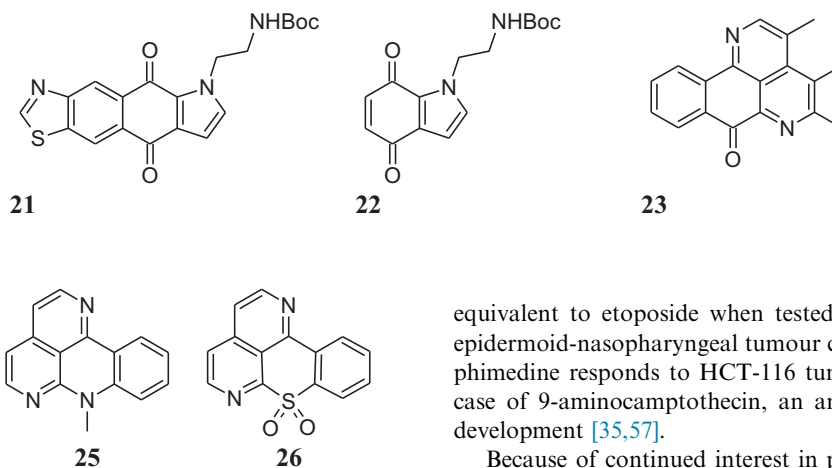
Kuanoniamine analogues

Different pentacyclic analogues of kuanoniamine A (Fig. 1) were synthesized for their antiprotozoal activity against virulent strains i.e. *Leishmania donovani*; *Leishmania major* and *Toxoplasma gondii*. As reported, most of the synthesized compounds were found to be more active than well-known drugs pentamidine, pyrimethamine, sulfadiazine and spiramycin against *T. gondii*. On the other hand, compound **21** and compound **22** displayed an IC_{50} of 6 nM against *L. major* as compared to reference compound pentamidine ($\text{IC}_{50} = 1.8$ nM). Authors neither discussed any structure activity relationship points nor they proposed any mechanism behind antiprotozoal activity. Although lipophilicity was mentioned as an important factor behind antiprotozoal activity while the presence of *boc* group and quinoneimine function might be responsible for antiprotozoal activity [52,53].

Sampangine analogues

A series of sampangine analogues were synthesized and screened for their antitubercular activity by Claes and co-workers [54]. As reported, most of the compounds showed promising activity against *M. tuberculosis* (Mtb) H37Rv strain of tuberculosis and minimal inhibitory concentrations (MIC) were measured for most potent sampangine derivative i.e. compound **23** as low as 0.39 μM [54].

In another study, sampangine analogues were synthesized to evaluate their antimicrobial activity and to investigate the role of azaquinoid partial structure in the pharmacological activity. The microbial strains selected were namely *Pseudomonas aeruginosa*, *E. coli*, *Staphylococcus aureus*, *Candida albicans* and *Aspergillus niger*. In this study, authors concluded that presence of amino group in compound **24** and compound **25**



while presence of sulphone moiety in compound **26** might be responsible for their significant antimicrobial activity [55].

In order to convert hit into lead, and lead into drug candidate it is very important to study their structural activity relationships; so that characteristic aspects like the nature of functional group, bulkiness of the molecule, electronegative effect, and inductive effect caused by the presence of a moiety/group, etc. should be considered. After discussing the representative pyridoacridine analogues and their important structure activity relationship (SAR) points, it can now be easily concluded that the “pyridoacridine moiety” will be helpful to design new medicinally active molecules and in view of these assertions, pyridoacridines can be designated as “lead compounds”.

Current status and future prospects

The literature discloses the biological potential of naturally available pyridoacridines, and the total synthesis of almost every natural pyridoacridine is available [32–34]. With the help of these available procedures, nowadays it is easy for medicinal chemists to prepare analogues of pyridoacridines in order to improve their biological activity and to lay down some interesting structure–activity relationship points for future research. Currently, search is in progress to identify novel biologically active pyridoacridine analogues on the basis of structure–activity relationship, such as, Marshall and co-workers [40], claimed AK37 as the first pyridoacridine reported to inhibit the catalytic activity of both topoisomerase I/II and stabilize the DNA-topo I cleavable complex [40]. Furthermore, in a similar study on pyridoacridine analogues, Delfourne and coworkers reported that some of the synthesized analogues are more cytotoxic than the reference compound ascididemin while Nukoolkarn et al. [56] opinionated that the quaternary ammonium group plays an important role in acetylcholinesterase inhibitory activity of ascididemin [56]. On the other hand, Guittat and co-workers identified quaternary ammonium group responsible for high affinity towards DNA quadruplex, due to high negative charge density present on DNA quadruplex [43].

Pyridoacridines were also found to possess biological activity equivalent to some well-known biologically active agents. For example, neoamphimedine showed anticancer activity

equivalent to etoposide when tested in mice bearing human epidermoid-nasopharyngeal tumour cell line. Similarly neoamphimedine responds to HCT-116 tumours as effectively as in case of 9-aminocamptothecin, an anticancer drug in clinical development [35,57].

Because of continued interest in pyridoacridine analogues, a new class of “pyridoacridine-metal complexes” (like $\text{Ru}(\text{bpy})_2(\text{eilatin})^{2+}$) was discovered where due to planar surface presented by the eilatin, affinity towards nucleic acid binding improves [51].

Heterocyclic derivatives are well known for their biological potential [58,59] and similarly heterocyclic-pyridoacridine analogues were reported by some researchers in their studies. For example Appleton and coworkers, in their study published in 2010 reported furan and thiophene analogues of ascididemin with significant antitubercular activity [42] while in case of non-heterocyclic analogues like thioethyl analogue, which displayed considerable antitubercular activity and authors pointed out that this analogue could be considered as a useful scaffold for future studies [42]. The search is underway in some cases where the pyridoacridine analogues were synthesized but their biological activity and mechanism of action remain to be explored, for example synthesis of ascididemin analogues by Plodek and co-workers [60]; preparation of pyridoacridine analogues by Godard and co-workers [61]; and synthesis of sampanine derivatives by Vasilevsky and co-workers [62], etc. Looking at the promising results, the research in this area could provide some useful drugs of future.

Conflict of interest

The author has declared no conflict of interest.

Compliance with Ethics Requirements

This article does not contain any studies with human or animal subjects.

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