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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-protozoal, 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-*mn*]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, ascididemins, 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, Antiarrythmic	[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]