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Recent developments in the synthesis and biological activity of acridine/acridone analogues

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Many people in the world struggle with cancer or bacterial, parasitic, viral, Alzheimer's and other diseases. Therefore, many scientists seek new, more effective, more selective and less toxic drugs. Acridine/acridone derivatives constitute a class of compounds with a broad spectrum of biological activity and are of great interest to scientists. To date, many acridine/acridone analogues have been obtained, which, *inter alia*, exhibit antitumour (*e.g.*, (**1–5**)), antimicrobial (*e.g.*, (**59**)), and antiviral (*e.g.*, (**61**)) activities and are applicable in the treatment of Alzheimer's disease (*e.g.*, (**26**)). However, in many cases, their clinical application is limited and excluded because of side effects. In this survey, we describe acridine and acridone derivatives reported since 2013, methods of their synthesis and their potential clinical applications.

Introduction

Acridine derivatives form an important class of heterocycles containing nitrogen due to their broad range of pharmaceutical properties. Acridine derivatives are characterized by unique physical and chemical properties, biological activities, and industrial applications. In the nineteenth century, acridine derivatives were already used industrially as pigments and dyes.[1] More critical to the pharmaceutical industry, acridine derivatives have exhibited bioactivities such as anti-inflammatory,[2,3] anticancer,[4] antimicrobial,[5] antitubercular,[6,7] antiparasitic,[8] antimalarial,[9–11] antiviral[12,13] and fungicidal activities.[14] Acridine derivatives have been shown to be effective as inhibitors of acetylcholinesterase.[15] Furthermore, acridines are used as dyes, fluorescent materials for visualization of biomolecules, and in laser technologies.[16] These properties of acridines are attributed to their semi-planar heterocyclic structure, which appreciably interacts with different biomolecular targets. Acridine/acridone derivatives are found in natural plants and various marine organisms.[17,18] Notably, the anticancer activity of acridine/acridone derivatives has attracted increasing interest. To date, many derivatives of acridine have been synthesized and tested for antitumour activity. The unique planar ring structure allows acridone derivatives to act as DNA intercalators[19,20] and to inhibit topoisomerase or telomerase enzymes.[21–24] A variety of acridine/acridone derivatives have been synthesized; analogues such as *N*-(2-(dimethylamino)ethyl)acridine-4-carboxamide (DACA) (**1**),[25–27] triazoloacridone (C-1305) (**2**)[28] and amsacrine (*m*-AMSA) (**3**)[29] (Fig. 1) have entered clinical studies. Among them, *m*-AMSA (**3**) was the first synthetic drug exhibiting clinical efficacy as a topoisomerase inhibitor. Many *m*-AMSA derivatives (AHMA (**4**), D3CLP (**5**)) (Fig. 1) have been developed for stronger anti-cancer properties and removal of many harmful side effects.[27,30]

Intermolecular interactions in acridine and acridinium derivatives determine their biological and physical properties including their chemiluminogenic abilities. Therefore, hydrogen bonding and π–π interactions within the Hirshfeld surface have been studied. Recently, Wera and co-workers reported the synthesis and structural investigations of some new acridine and acridinium derivatives.[31]

Naturally occurring acridine/acridone

Acridine/acridone alkaloids

Alkaloids are naturally occurring chemical compounds, which have a wide range of pharmacological activities (*e.g.*, antimalarial, anticancer, and antibacterial).[32] To date, the literature describes a number of acridine/acridone alkaloids, which have been tested as anticancer, antibacterial and antimalarial agents and against Alzheimer's disease.[18] Examples of these compounds are cystodytin A (**6**) (isolated from various marine organisms) and acronycine (**7**) (isolated from bark of Australian scrub ash tree) (Fig. 2).[33–35]

Arai *et al.* describe the bioassay-guided fractionation and Ngn2 promoter activity of acridine alkaloids (**8–10**) from an extract of a culture of *Streptomyces* sp. IFM 11440.[17] Inubosin B (**9**) bearing a hydroxy group at the 4 position showed potent Ngn2 promoter activity, which was dose-dependent. Moreover, compound (**9**) demonstrated more activity than the positive control baicalin (**11**), while Insubosin A (**8**) and Insubosin C (**10**), which have a hydroxy group at the 5 position, did not show significant activity (Fig. 3).[17]

The Wouatsa group isolated acridone alkaloids (**12–21**) (Fig. 4) from the MeOH extract of the fruits of *Zanthoxylum zanthoxyloides* and *Zanthoxylum leprieurii*, of which six were new

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