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Mini-review

Living on pyrrolic foundations – Advances in natural and artificial bioactive pyrrole derivatives

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ABSTRACT

Pyrrole, a simple heterocyclic system, is an important building block for numerous biologically active compounds both natural and synthetic in origin, which boast an immense array of qualities, baleful and beneficial alike. The latter have given rise to a bountiful variety of pyrrole-based drugs, with many more being designed, developed and applied each year, as evidenced by the amount of entries in the Cambridge Structural Database skyrocketing from about six hundred in 2004 to more than a thousand over the course of the last decade. Particularly important in light of the ever-encroaching menace of drug-resistant bacteria, the vast progress in the field necessitates a sound organisational framework and summary - a task, to which we contribute this summary and checklist of the most recent developments, indicating the classes of compounds, which have attracted the most significant research attention.

1. Introduction

Perusing the papers published worldwide, an emerging trend of preparing various novel heterocyclic compounds for pharmacological applications is evident. Recent years have brought increased interest in pyrrole and its derivatives in particular. This rediscovery can be derived from the fact that, as a building block, pyrrole is one of the foundations of biochemistry, as its flat and electron-rich ring is susceptible to electrophilic attack and can react with numerous biomolecules, both through hydrogen bonds and through π–π stacking interactions. These properties make it a key element of a vast array of compounds, that are crucial to life, ranging from natural to artificial pharmaceuticals, designed to combat viruses, bacteria and fungi [1], treat cancer [2], and combat hypercholesterolemia [3]. Natural compounds, containing a pyrrole ring are present in numerous alkaloids of varying complexity and biological activity, which have been obtained from sources such as marine organisms [4–10], insects, fungi and bacteria [11]. Pyrrole-bearing moieties have also been discovered in vertebrates, such as birds and frogs [11]. Conversely, flora is also a rich source of such systems, as 2-acetylpyrrole has been found in a multitude of plants, including African mango [12], cocoa, coffee, valerian and tobacco [13]. The pyrrole core occurs in fragments of haemoglobin, myoglobin, cytochromes, chlorophyll and vitamin B12 [14]. Pyrrole is an important constituent of numerous, well-established drugs, such as Tolmetin, Atorvastatin, Chlorfenapyr, Premazepam, Pyrvinium, Roseophilin and Zomepirac [15]. Currently, more than a thousand compounds, in which pyrrole is the primary structural moiety, have been identified. This figure has doubled over the last decade, as at the end of 2004, the Cambridge Structural Database contained 500 registered compounds with a 2-substituted pyrrole ring in their structure and a 100 more compounds, where the system is present as pyrrol-2-yl carbonyl [16]. The constant broadening of this set addresses the necessity of developing new antibiotics and disinfectants, in order to combat the ever-increasing drug resistance of bacteria.

The aim of our work is to summarise and report on the progress in the field of bioactive pyrrole derivatives in the last decade. New compounds are being reported on a daily basis, therefore it is naught but prudent to organise these works, so as to underline the primary development trends and refer the reader to specific information rather than to undertake an encyclopaedic comparison of the plentiful amount of relevant systems.

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2. Bioactive pyrrole derivatives

We have based our review on three main groups of bioactive pyrrole derivatives: (a) alkaloids isolated from flora and fauna, along with their synthetically-prepared analogues; (b) those obtained through biosynthesis, with the use of microorganisms; and (c) artificially-prepared pyrrole derivatives.

2.1. Alkaloids and their derivatives

Alkaloids are a class of organic bases, found in nature, whose heterocyclic rings contain at least one nitrogen atom. The interest in this class of compounds is driven by their vast potential for affecting our bodies, effecting either positive or negative changes. In the latter case, they are employed to treat cancer [7,17,18], HIV [19,20] and malaria [21], as well as act as psychotropic [22], antibacterial [10] and antifungal agents [23]. Considering alkaloids containing a pyrrole ring as a constituent of their structure, alkaloids obtained from marine creatures are of particular interest [4–10]. Research is being also carried out on systems produced by plants [24]. In recent years, lamellarins (Fig. 1a), bromopyrrole (Fig. 1b), pyrrolo[1,2-*a*]quinoxaline (Fig. 1c) and pyrrolo [2,3-*b*] quinoxaline (Fig. 1d) have attracted significant research attention.

Lamellarins are a group of DOPA-(2-amino-3-(3′,4′-dihydroxyphenyl)propionic acid)-derived pyrrole alkaloids (Fig. 1a). They have been isolated from marine organisms and comprise more than 70 known compounds. Hui Fan et al., in their review on lamellarins [25] have divided them into two groups, depending on whether the central pyrrole ring is fused or not fused, proceeding to describe the structure of these compounds, their bioactivity and the methods for their preparation in great detail. The biological activity of these systems is a subject in its own right, as they have been reported to exhibit cytotoxicity and antitumour activity [26], reversal of multidrug resistance (MDR) [27], HIV-1 integrase inhibition [28], antibiotic activity [29], human aldose reductase (h-ALR2) inhibition [30], cell division inhibition [31], immunomodulation [32], antioxidant activity [28], and feeding deterrence [33], making these compounds extremely promising for pharmacological applications.

Bromopyrrole alkaloids (Fig. 1b) are a family of compounds isolated from marine sponges [34] and are known to possess a broad range of biological activities like antihistaminic, antiserotonergic, antimicrobial and antitubercular [1,10]. Within this group of bioactive compounds, many contain pyrrole-imidazole structures, whose oxidation, cyclisation and dimerisation yield a vast array of compounds. More than 100 derivatives of bromopyrrole alkaloids have been identified and had their biological properties studied. Among those is oroidin (**4**), a structural building block, constituting the basic scaffold of a broad range of marine alkaloids [35].

In 2011, Kumar and Rawat have published the fruits of their

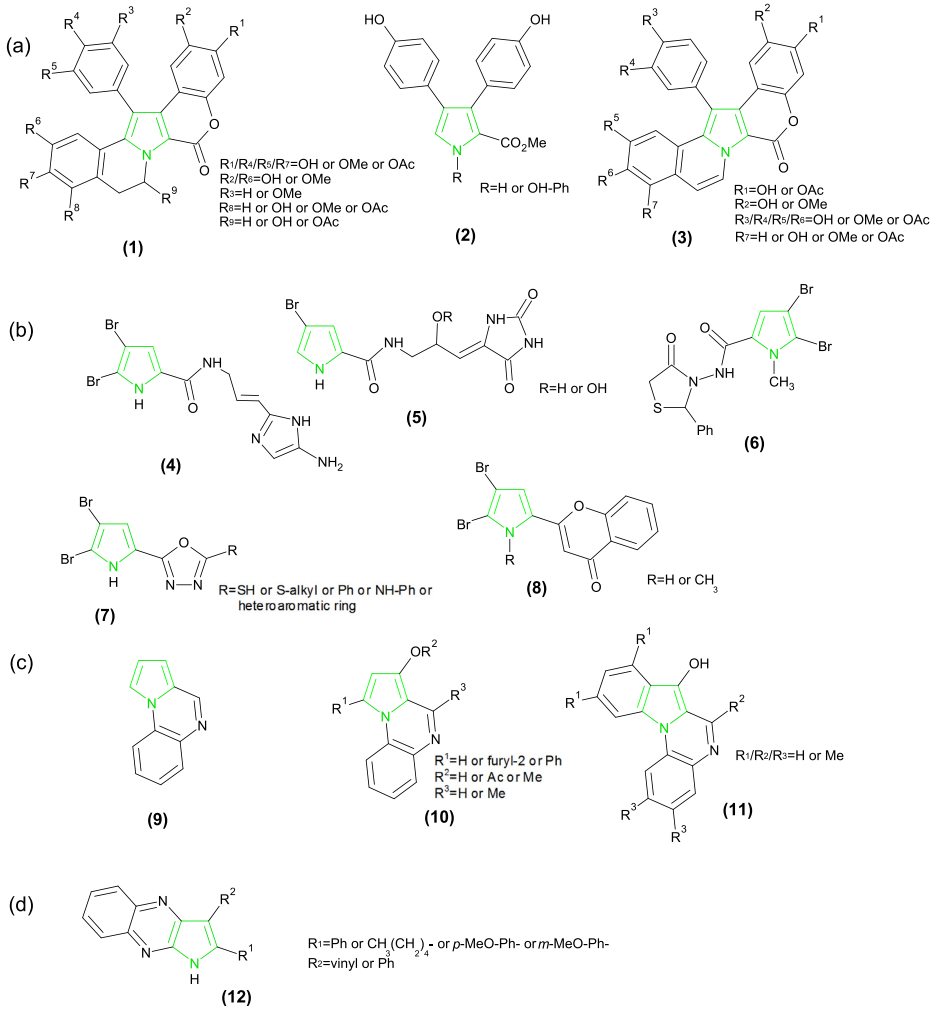

Fig. 1. Structure of selected alkaloids (a) lamellarins; (b) bromopyrrole; (c) pyrrolo[1,2-*a*]quinoxaline; (d) pyrrolo [2,3-*b*]quinoxaline.