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HETEROCYCLIC COMPOUNDS CONTAINING NITROGEN AND THEIR ANTI-CANCER PROPERTY

Mir Shabeer Ahmad, Ghulam Mohammad Jan
Govt. Degree College Kulgam Jammu & Kashmir (India)
Govt. Degree College Boys Anantnag Jammu & Kashmir (India)

Abstract:
In this review, we provide for a concise overview of heterocyclic active compounds and families and their main applications in medicine. We shall focus on those suitable for cancer therapy while simultaneously addressing main biochemical modes of action, biological targets, structure-activity relationships as well as intrinsic limitation issues in the use of these compounds. Finally, considering the advent of nanotechnology for effective selective targeting of drugs, we shall discuss fundamental aspects and considerations on nanovectorization of such compounds that may improve pharmacokinetic/pharmacodynamic properties of heterocycles.

Corresponding Author

Mir Shabeer Ahmad
mirlaik2008@gmail.com

INTRODUCTION:

Defined by IUPAC as "cyclic compounds having as ring members atoms of at least two different elements" [1], heterocycles' ring structures are in essence composed by elements other than carbon, where the most frequent substituents are oxygen, nitrogen and sulfur [2,3]. According to the heteroatom(s) present in the ring structures, heterocycles can be classified as oxygen, nitrogen or sulfur based and, within each class, compounds are organized based on the size of the ring structure size determined by the total number of atoms [4]. The type and size of ring structures, together with the substituent groups of the core scaffold, impact strongly on the physicochemical properties [2,5]. Among the various clinical applications, heterocyclic compounds have a considerable active role as anti-bacterial [6,7], anti-viral [8], anti-fungal [9], anti-inflammatory [10], and anti-tumor drugs [11–13]. General applications of heterocycles are as vast as they are diverse and are not extensively encompassed in the scope of this review, hence readers are advised to refer to more detailed literature on this matter [3,14] The engineering and rationale behind drug design are closely related to the strategic incorporation of heterocyclic like fragments with specific physicochemical properties. Potency and selectivity through bioisosteric replacements, lipophilicity, polarity, and aqueous solubility can ultimately be fine-tuned to the point of altering and conditioning the possible mechanisms of action of pharmaceutical drugs in an attempt to obtain molecularly targeted agents [2]. Despite their versatility and potential, as for any other pharmaceutical, there are several issues hindering wider application and further development of such compounds into market drugs. Oncology is one of the areas where this is perhaps most noticeable, partially due to the intrinsic limitations regarding main therapeutic routes of chemotherapy, concomitant side effects and toxicity to healthy tissues. Such deleterious effects may be circumvented via selective targeting of delivery, passively or actively into cancerous cells [16]. It should be referred that for some playmakers within the chemotherapy field, the success of "molecularly targeted agents", such as imatinib are merely fortunate exceptions and that the number of success in this area is considerably low [17]. Recent advances in interdisciplinary field of nanobiotechnology have led to the development of newly inventive therapeutic strategies and drug delivery alternatives taking advantage of the architectural geniality of systems based on nanoscale devices particularly tailored to deliver drugs to a selected tissue [18–20]. In this sense, nanoparticles, and the associated nanomedicine tools, are becoming the most appealing answer to chemotherapy problems, such as low drug solubility, degradation, fast clearance rates and nonspecific toxicity [21].

A simple glance at FDA databases reveals the structural significance of nitrogen-based heterocycles in the drug design and engineering of pharmaceuticals, with nearly 60% of unique small-molecule drugs containing a nitrogen heterocycle [24]. Recently, Edon Vitaku and colleagues comprehensively compiled the structural diversity, substitution patterns and frequency of nitrogen heterocycles among U.S. FDA approved pharmaceuticals. Noteworthy, the average number of nitrogen atoms per drug, being around 2.3, while in those containing a nitrogen heterocycle an increase to 3.1 nitrogen atoms per drug is evidenced [24]. Ultimately, the structure dynamics involved in nitrogen-based heterocycles (and other classes of heterocycles), alongside with fundamental aspects such as ring size and aromaticity, translates into a vast array of chemical structures by which their molecular mechanisms of action can vary significantly [2,5,14]. Indoles and indole derivatives for instance comprehend one of the most versatile and common nitrogen-based heterocyclic like fragments that are frequently used in the synthesis of fundamental FDA approved drugs for common pathological conditions, ranking in the ninth position of the top 25 most frequent nitrogen heterocycles among the U.S. FDA approved drugs [24]. There has been particular emphasis on the synthesis of indole derivatives in recent decades due to the virtually endless possibilities for architectural design of polycyclic structures by the incorporation of multiple fused heterocyclic scaffolds in an attempt to achieve promising new heterocycles with chemical and biomedical relevance [25,26]. The indole structure plasticity observable in drug rational design is translated to the wide range of biological targets that these have been found to affect often ranging from topoisomerase inhibitors to G2/M abrogators and others [27]. However, application of the indole basic core structure for the synthesis of several potent tubulin polymerization inhibitors has lately been receiving increasing attention, in particular in oncology [26–29], often being present among renowned FDA approved drugs and others reported in clinical trials

More recently, novel 1,2,4-triazoles, triazolothiadiazines and triazolothiadiazoles have been synthetized and their anticancer potential evaluated. Kamel and coworkers reported to have

obtained seven compounds with considerable cytotoxic activity against a broad spectrum of cancer cell lines (NUGC; DLD1, HA22T, HEPG2, HONE1, MCF7) amongst which the compound 6-(4-chlorophenyl)-3-(pyridin- 4-yl)-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazole, (13) [30-36] presented an IC50 of 25 nM against gastric cancer cell line (NUGC). Noteworthy, toxicological testing employing normal fibroblast cells (WI38), in order to assess potential side effects, demonstrated significant differences, being approximately 400-fold less toxic to normal cells compared to the NUGC cell line [37]. Despite their potential, no particular correlation between the nitrogen-based heterocycle fragments and potential families of target molecules seems to exist. Nonetheless, the bulk of these fragments or pharmaceutical drugs in which they are incorporated appear to be responsible, or to take part in coordination to major biomolecules in key regulatory pathways. Tubulin coordination/inhibition, DNA cleavage, ROS induction, and cell cycle arrest through inhibition of cyclins are several possible targets that support the previous statement but are most likely not restricted to these. The perspective covered here has only taken into consideration the most recent developments regarding the application of nitrogen-based heterocycles as potential chemotherapeutic cancer drugs, given that the vast structural diversity does not allow to present all currently investigated compounds nor the majority of the nitrogen-based heterocycle scaffolds currently incorporated into renowned pharmaceuticals. For a more complete review on other major nitrogen-based scaffolds (e.g., piperidines, pyridines, piperazines, cephems, pyrolidines, pyrazoles, purines, pyrimidines, and others), their structural diversity, substitution patterns and role as fundamental components of FDA approved pharmaceuticals, the reader is referred to a more comprehensive review on this matter [24].

CONCLUSION:

Naturally occurring heterocycles seem to play an important role in biochemical reactions in cells' metabolism. Their reactivity with cells and tissues makes the regulation of these molecules so tightly controlled that as a consequence any disturbance may be associated with pathological conditions. Therefore, the use of synthetic cyclic compounds as anticancer drugs tries to mimic natural ligands and substrates in order to disturb the delicate balance in cells. Heterocyclic compounds or heterocyclic fragments also play an important role in improving pharmacokinetics and pharmacodynamics properties of anticancer drugs by enhancing lipophilicity, polarity or other physicochemical features. Hence, heterocycles play an important role in current drug design as they are present in the majority of marketed drugs. Only in 2015, about 30% of FDA-approved anticancer drugs have one or more cyclic rings containing nitrogen or oxygen. A correlation between heterocycle fragments' structure and potential families of targeted molecules seems to not be evidenced by any literature addressed. However, mechanisms of action of these compounds are being established and pass through interactions with major biomolecules or by intervening in metabolic pathways.

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