European Journal of Medicinal Chemistry 85 (2014) 371–390

Contents lists available at ScienceDirect

European Journal of Medicinal Chemistry

journal homepage: http://www.elsevier.com/locate/ejmech

Mini-review

1,3,5-Triazine-based analogues of purine: From isosteres to privileged scaffolds in medicinal chemistry

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ARTICLE INFO

Article history:
Received 31 December 2013
Received in revised form
11 April 2014
Accepted 31 July 2014
Available online 1 August 2014

Keywords:
Isostere
Purine
Triazine
Enzyme inhibitor
Anticancer
Antiviral

ABSTRACT

Purines can be considered as the most ubiquitous and functional N-heterocyclic compounds in nature. Structural modifications of natural purines, particularly using isosteric ring systems, have been in the focus of many drug discovery programs. Fusion of 1,3,5-triazine ring with pyrrole, pyrazole, imidazole, 1,2,3-triazole or 1,2,4-triazole results in seven bicyclic heterocyclic systems isosteric to purine. Application of the isosterism concept for the development of new compounds with therapeutic potential in areas involving purinergic regulation or purine metabolism led to significant advances in medicinal chemistry of the azolo[1,3,5]triazines. These 1,3,5-triazine-based purine-like scaffolds significantly increase level of molecular diversity and allow covering chemical space in the important areas of medicinal chemistry. Some of these azolo[1,3,5]triazine systems have become privileged scaffolds in the development of inhibitors of various kinases, phosphodiesterase, xanthine oxidase, and thymidine phosphorylase, antagonists of adenosine and corticotropin-releasing hormone receptors, anticancer and antiviral agents.

1. Introduction

Purine, a nitrogen containing heterocycle, is found abundantly in nature. It is the core structure of adenine and guanine in RNA and DNA [1]. From a biological perspective, attention to purines is mainly driven by the fact that purine nucleotides (ATP, GTP, cAMP, cGMP, NAD, FAD) act as co-factors, substrates, or mediators in the functioning of many proteins [1,2]. These proteins are estimated to include half of the most druggable targets, primarily enzymes and receptors. For example, phosphorylation of ATP is carried out by protein kinases [3] while hydrolysis of cAMP and cGMP is associated with cyclic nucleotide phosphodiesterases [4]. Purine catabolism involves the key enzyme xanthine oxidase [5] whereas the ubiquitous purine nucleoside phosphorylase [6] also plays a vital role in the purine salvage pathway. Adenosine receptors constitute a very promising group of G-protein coupled receptors (GPCRs) [7].

Advancements in drug design and development on the basis of purine motif inspired parallel development in the chemistry and biology of structurally related heterocyclic system *viz.* purine isosteres. Increasing molecular diversity using various purine isosteres is ideal for the discovery of novel therapeutic agents that target selectively purine dependent enzymes and receptors.

A number of renowned drugs with purine isostere core structure are available in the market (Fig. 1), including chemotherapeutic temozolomide [8], a pro-drug functioning as a molecular transporting device to deliver a reactive methylating species to guanine-rich sequences in the major groove of DNA. One of the cornerstones of acute leukemia treatment is antimetabolite 8-azaguanine [9], while an alternative therapeutic agent forodesine [10], a second generation purine nucleoside analogue, is currently undergoing clinical trials. Forodesine exhibits highly selective purine nucleoside phosphorylase inhibitory activity in preclinical studies with malignant cells and clinical efficacy against T-cell acute lymphoblastic leukemia and cutaneous T-cell lymphoma [10]. Another structurally similar purine nucleoside phosphorylase inhibitor ulodesine (BCX-4208) [11] is also under clinical investigation as the drug for treatment of gout in hope of a synergistic therapy with hypoxanthine bioisostere allopurinol, a drug inhibiting xanthine oxidase and therefore preventing formation of uric acid [12]. Well known PDE5 inhibitors, sildenafil and vardenafil [13] have been extensively used for the treatment of erectile dysfunction while their prototype zaprinast was found to demonstrate

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http://dx.doi.org/10.1016/j.ejmech.2014.07.112
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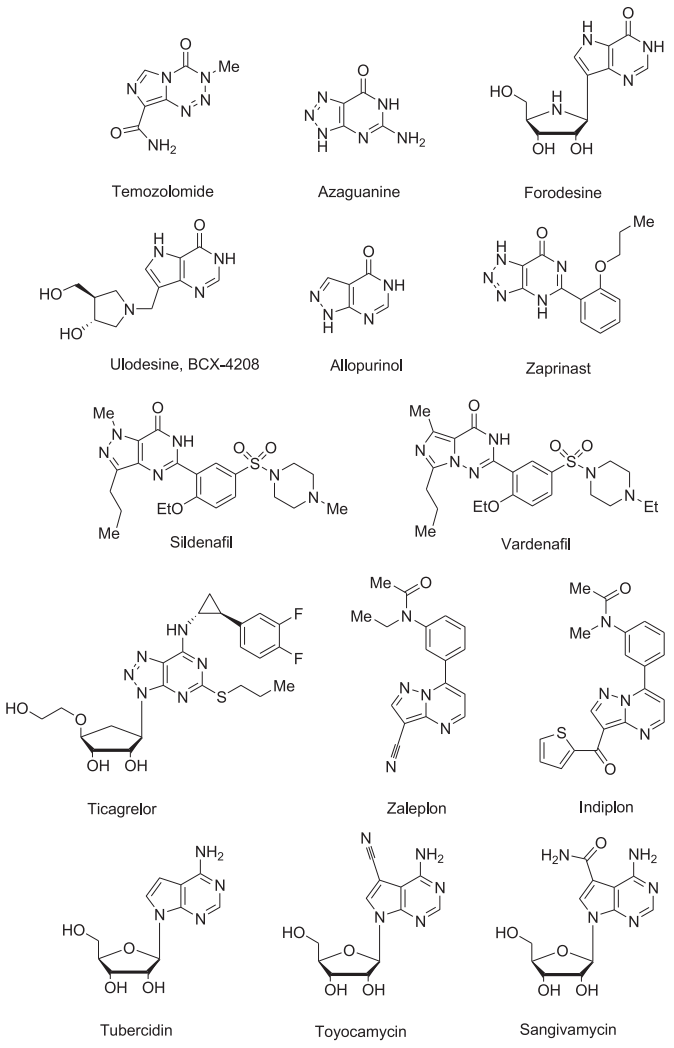

Fig. 1. Therapeutic agents based on isosteric purine skeletons.

interesting orphan G-protein coupled receptor GPR35 activating properties [14]. Reversible purine $P2Y_{12}$ receptor antagonist ticagrelor with the 8-azapurine scaffold is an oral antiplatelet agent recently approved for the management of acute coronary syndrome [15]. Hypnotic agents zaleplon [16] and indiplon [17] exert their effects through binding to the $GABA_A$ receptors at the benzodiazepine recognition site, for which hypoxanthine and inosine are natural ligands. Also noteworthy, a group of 7-deazapurines tubercidin [18], toyocamycin [19] and sangivamycin [19] which function as antimetabolites and are used as broad spectrum antibiotics.

There are extensive and ongoing research and development activities around purine isosteres and one of the promising directions has a focus on using 1,3,5-triazine-based isosteres of purine (Fig. 2). This group of azolo[1,3,5]triazine systems has a nitrogen atom in the position 5 of the purine ring and therefore can be generally categorized as 5-aza-isosteres of purine. The present review focuses on the scope of biological activities displayed by compounds with these scaffolds (**I**–**VII**) and their potential applications as therapeutic agents. The research work on chemistry and biological activity of compounds constructed on the basis of scaffolds **I**–**VII** is not equally distributed between different groups. Thus, pyrazolo[1,5-*a*][1,3,5]triazines (5-aza-9-deazapurines, **II**) and 1,2,4-triazolo[1,5-*a*][1,3,5]triazines (5-azapurines, **V**) have undergone more active investigations [20,21], while biological properties of systems **I**, **VI** and **VII** have remained almost unexplored. Therefore, primary organization of sections in this review is based on pharmacological effects of the compounds rather than their relation to the specific heterocyclic system.

2. Enzymes inhibitors

Almost half of all marketed drugs specifically target enzymes, therefore demonstrating a huge potential for development of new therapeutic agents modulating enzyme activity [22]. The compounds constructed using 1,3,5-triazine-based isosteres of purine affect enzymes of different groups as discussed below.

2.1. Kinase inhibitors

Kinases are one of the most promising groups of enzymes in the field of drug discovery. Protein kinases represent about 20% of the druggable genome. They have been in the focus of intensive investigations resulting in 20 kinase-targeting drugs approved for clinical use over the past decade and hundreds of drug candidates undergoing clinical trials [23]. It is estimated that protein kinase inhibitors are main targets in 50–70% of current cancer drug discovery programs [23].

Cyclin-dependent kinases (CDKs) are a family of enzymes playing a key role in cell cycle regulation. Overexpression of CDKs in cancer cells makes them an attractive drug target in the fight against oncological diseases [24–28]. Development of CDK inhibitors appears to be a promising strategy in the search for new effective anticancer agents. A number of CDK inhibitors are currently at different stages of clinical trials.

Isosteric to purine system, pyrazolo[1,5-*a*][1,3,5]triazine scaffold was used as a template for new potent CDK2 inhibitors. Variously decorated 2,4-diamino substituted pyrazolo[1,5-*a*][1,3,5]triazines (**1**–**4**) demonstrated high CDK2 inhibitory activity (Fig. 3) [29–31]. The CDK inhibitory activity was translated into *in vitro* antiproliferative activity against prostate (PC3) and colon cancer (HCT116) cell lines [31]. Even though there was a decrease of about a hundred times in the potency of CDK2 inhibition between compounds **2** and **3**, macrocyclic compound **3** showed almost ten times improvement in the anticancer activity [31]. The macrocyclic lactam ring provided a less planar and more three-dimensional structure of overall molecule resulting in an increase in membrane permeability ultimately improving cellular activity. Enhancement of CDK2 inhibitory potency was successfully achieved by replacing the cyclopropylamino group with a more complex substituted arylamino moiety (compound **4**) [31]. This modification of the structure also improved aqueous solubility of **4** which led to an increase in cellular activity against both human prostate and colon cancer cell lines in *in vitro* experiments [31].

A purine based CDK inhibitor (*R*)-roscovitine (**5**) is a drug candidate currently undergoing clinical trials as an anticancer therapeutic agent [32–34]. This molecule has been serving as a lead for the development of new potent compounds targeting CDKs. An isosteric replacement of purine system of roscovitine (**5**) with the pyrazolo[1,5-*a*][1,3,5]triazine core led to the development of a potent CDK2 inhibitor **6** [33]. This isosteric modification provided more than 5 times improvement in the inhibitory activity. Roscovitine (**5**) and pyrazolo[1,5-*a*][1,3,5]triazine **6** demonstrated similar conformations and binding modes to CDK2 [33]. A similarity in the pharmacokinetic profile of **6** and roscovitine (**5**) was also observed [33].

Tested against the National Cancer Institute panel of 60 tumor cell lines, **6** was about 14 times more potent than roscovitine (**5**) with no preference towards any specific form of tumor [34]. An