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Review article

Thiazolo[4,5-*d*]pyrimidines as a privileged scaffold in drug discovery

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ABSTRACT

Thiazolo[4,5-*d*]pyrimidines are fused heterocyclic ring-systems that can be viewed at the first glance as purine isosteres. They are the 7 thia-analogs of purines via the replacement of the nitrogen at position 7 of the purine ring by a sulfur atom. Because of the structural resemblance to adenine and guanine and their related derivatives as adenosine, guanosine, cAMP, cGMP and similar biomolecules, many thiazolo [4,5-*d*]pyrimidines scaffold were developed and utilized by medicinal chemists to design novel therapeutics. Many were found to have a broad range of pharmacological activities. The outstanding development of thiazolo[4,5-*d*]pyrimidines within a short time span shows its magnitude of usefulness for medicinal chemistry research. Despite their importance from pharmacological and synthetic point of views, hardly there is a comprehensive review of thiazolo[4,5-*d*]pyrimidines applications in medicinal research to date. Thus, this review article describes the structures and medicinal significance of all classes of thiazolo[4,5-*d*]pyrimidines reported in literature to date. It describe the development of thiazolo[4,5-*d*]pyrimidines as immune-modulators, Corticotropin Releasing Factor (CRF) receptor antagonists, anti-Parkinson's, antiviral, anticancer, antibacterial, antifungal, analgesic, anti-inflammatory agents including COX inhibitors, chemokines antagonists and Fractlkine receptor antagonists.

1. Introduction

Thiazolo[4,5-*d*]pyrimidines are fused heterocyclic ring-system that can be viewed at the first glance as purine isosteres. They are the 7 thia-analogs of purines via the replacement of the nitrogen at position 7 of the purine ring by a sulfur atom. Many thiazolo[4,5-*d*] pyrimidines scaffold were developed and utilized by medicinal chemists to design novel therapeutics. Many were found to have a broad range of pharmacological activities. The reported pharmacological activities of thiazolo[4,5-*d*]pyrimidines include antibacterial [1,2], Corticotropin-releasing factor receptor antagonist [3,4], antiviral including anti-HIV, anticancer [5,6], analgesic and anti-inflammatory [7] effects.

Thiazolo[4,5-*d*]pyrimidines synthesis has been reported in the literature since the early 60's. The first synthesis of thiazolo[4,5-*d*] pyrimidines was reported by Cook et al. [8,9]. The second paper on synthesis was reported by Childress et al. [10]. The synthesis of thiazolo[4,5-*d*]pyrimidines as purine analogs was reported by Maggiolo et al. [11]. A novel synthesis of thiazolo[4,5-*d*]pyrimidines using sulfur, isothiocyanate and active methylene compounds was reported by Gewald et al. [12–14]. The versatility of Gewald's synthesis allowed multiple applications of this synthesis to prepare several classes of thiazolo[4,5-*d*]pyrimidines with various substituents and various pharmacological effects. The outstanding development of thiazolo[4,5-*d*]pyrimidines within a short time span shows its magnitude of usefulness for medicinal chemistry research.

Despite their importance from pharmacological and synthetic point of views, hardly there is a comprehensive review of thiazolo [4,5-*d*]pyrimidines applications in medicinal research to date. Thus, in this review article, the medicinal and biological significance of thiazolo[4,5-*d*]pyrimidines are reported.

2. General structures of the thiazolo[4,5-*d*]pyrimidine ring system and its common reduced analogs

The general structure and numbering system of the thiazolo [4,5-*d*]pyrimidine fused ring system and its common reduced analogs are shown in Fig. 1.

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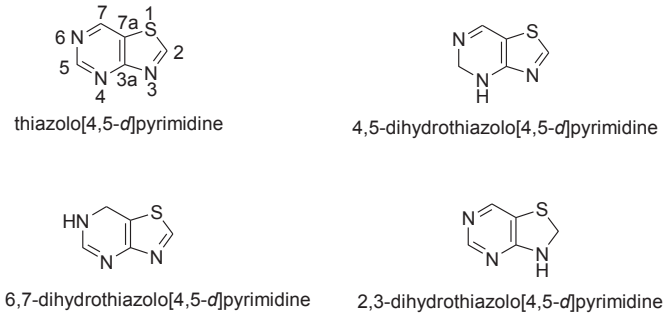

Fig. 1. General structures of the thiazolo[4,5-*d*]pyrimidine ring system and its common reduced analogs.

3. Biological and pharmacological effects of various classes of thiazolo[4,5-*d*]pyrimidines

3.1. Immune-modulators and antiviral agents

Cellular Immunity plays as important role in defending the host against vast majority of disease causing agents. Compromised immune system is responsible for a number of clinical manifestations including aging, cancer, infectious diseases, and autoimmunity [15,16]. Development of agents which can potentiate an immune response and consequently host resistance to diseases could be a valuable potential treatment option for many disease conditions.

The synthesis of sulfur derivatives of naturally-occurring purine nucleosides with a sulfur atom replacing the nitrogen atom at position 7 was reported by Nagahara et al. [17]. The ability of these purine bioisosteres to activate murine spleen cells to proliferate *in vitro* as measured by new DNA synthesis in a [^{3}H]-thymidine incorporation assay and their ability to provide protection against a lethal Semliki Forest virus infection in mice was evaluated. Activation of Toll-Like-Receptor 7 (TLR-7), leading to an immune-stimulation, by these derivatives was reported later by Lee et al. [18].

Out of several thiazolo[4,5-*d*]pyrimidins prepared, compounds **1** and **2** (Fig. 2) showed a significant immune-reactivity in all tests compared to the known guanosine derivatives such as 8-bromoguanosine (**3a**), 8-mercaptoguanosine (**3b**), and 7-methyl-8-oxoguanosine (**4**). Furthermore, compound **1** exhibited a 4-fold increase in natural killer cell cytotoxicity, compared to the standard 7-methyl-8-oxoguanosine (**4**) and provided a 92% protection against Semliki Forest virus in mice. Moreover, compound **1** showed excellent *in vivo* activity against various RNA as well as DNA virus by stimulating both cellular and humoral immunity.

To identify the structural requirements of the sugar moiety for the biological activity of compound **1**, various derivatives of compound **1** such as 5′-monophosphate derivative **5a**, the 3′,5′-diphosphate derivative **5b**, the 5′-Sufamoyl derivative **5c**, tri-O-acetyl derivative **5d**, 5′-deoxy derivative **5e**, 2′-deoxy derivative **5f** and the open-ring sugar derivative **6** were prepared (Fig. 3) by

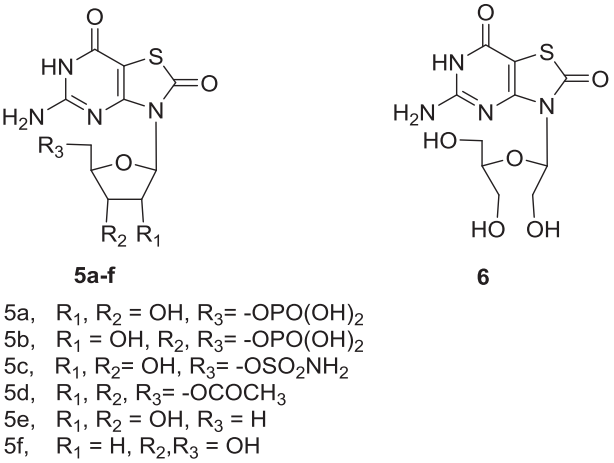

Fig. 3. Structures of antiviral thiazolo[4,5-*d*]pyrimidines **5a**–**f** and **6**.

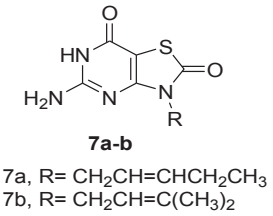

Fig. 4. Structures of antiviral thiazolo[4,5-*d*]pyrimidines **7a**–**b**.

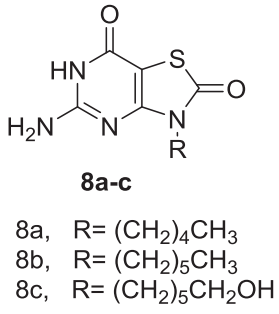

Fig. 5. Structures of immune-potentiating thiazolo[4,5-*d*]pyrimidines **8a**–**c**.

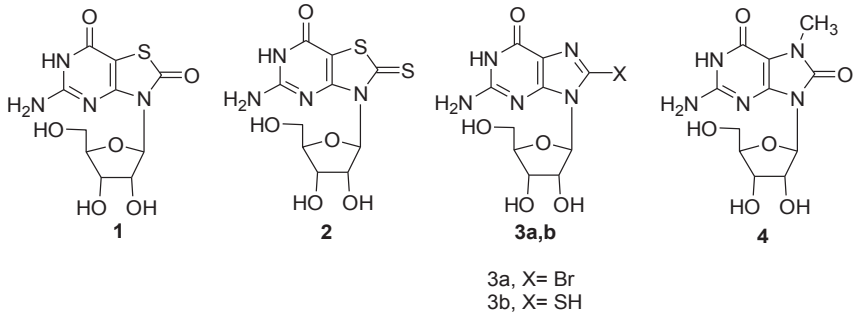

Fig. 2. Structures of immune-modulator and antiviral thiazolo[4,5-*d*]pyrimidines 1 & 2, 8-bromoguanosine (**3a**), 8-mercaptoguanosine (**3b**) and 7-methyl-8-oxoguanosine (**4**).