Exploring Thiazolo [4,5-d] Pyrimidinones and Derivatives: Medicinal Importance and Various Synthetic Methods

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Abstract

Thiazolo(4,5-d) pyrimidinones and derivatives have emerged as a promising class of heterocyclic compounds with various pharmacological activities like anti-inflammatory, antifungal, antiviral, antibacterial, antitumor etc. properties. This review emphasizes the medicinal importance of Thiazolo(4,5-d) pyrimidinones and their derivatives focusing on their therapeutic potential. Additionally, it summarizes various synthetic routes to construct this heterocyclic scaffold. This review throws light on the design and development of novel Thiazolo(4,5-d) pyrimidinone-based systems.

Introduction

The medicinal value of thiazole and its various derivatives has been studied a lot. However, the study of the thiazole ring fused with other heterocyclic systems is still in the growing stage. Some thiazoles are reported to show anti-inflammatory properties and are active as CNS agents [1] and pyrimidone derivatives are also reported to show medicinal properties [2]. Review papers regarding the biological activity of 4-thiazolidinone derivatives and their efficient synthetic routes have been mostly published over the last three decades [3-7].

The thiazolidine system is found to be very important in the pharmaceutical field and is used as a powerful template for the design of molecules with therapeutic value. Condensed bicyclic systems having a thiazole core fused with pyrimidine or its derivatives have a very important role in medicinal science because of their biological activities.

A large variety of cell biotargets were identified by a combination of highly efficient pharmacological screening and combinatorial chemistry. These facts leaded for more effective understanding of the mechanism of pharmacological agents as well as expanding the list of chemical compounds as drugs. This strategy has led for the fast development in the potential of condensed thiazole and thiazolidine derivatives. These chemical compounds were found to possess various biological activities.

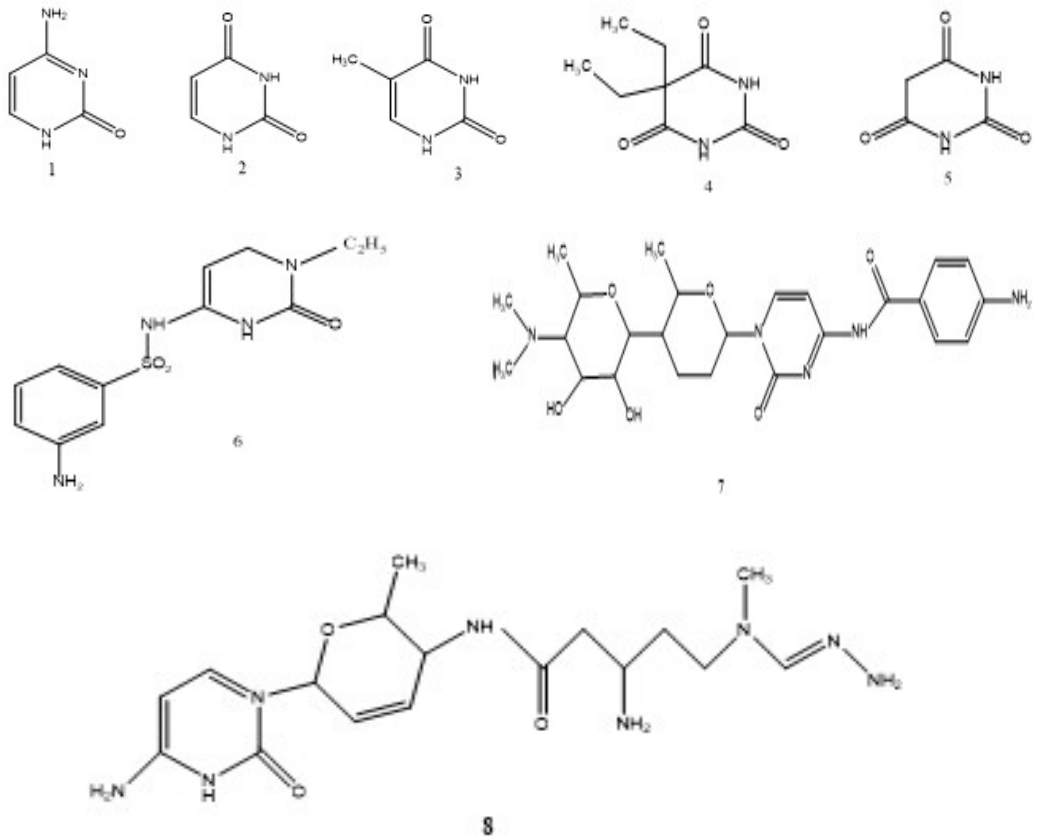
Thiazolo (4,5-d) pyrimidine-5,7-diones were found to act as anti-inflammatory agents [8]. Among various thiazolo(5,4-d) pyrimidine derivatives, it was found that 2,5-diaminothiazolo[5,4-d] pyrimidine-7-(6-H)-ones were found to act as weak inhibitors of purine nucleoside: orthophosphate rib transferase (PNPase) [9]; 5-Methyl-7-(diethylamino) thiazolo[5,4-d] pyrimidines were found to have hypertensive and vasodilating effects and to lower cholesterol level [10]. Among biologically active heterocyclic compounds triazolopyridines and their derivatives are considered to show a wide range of pharmaceutical properties like antifungal [11], antiviral [12], antibacterial [13], antitubercular [14, 15], antioxidant [16-19] and antitumor [20, 21] etc.

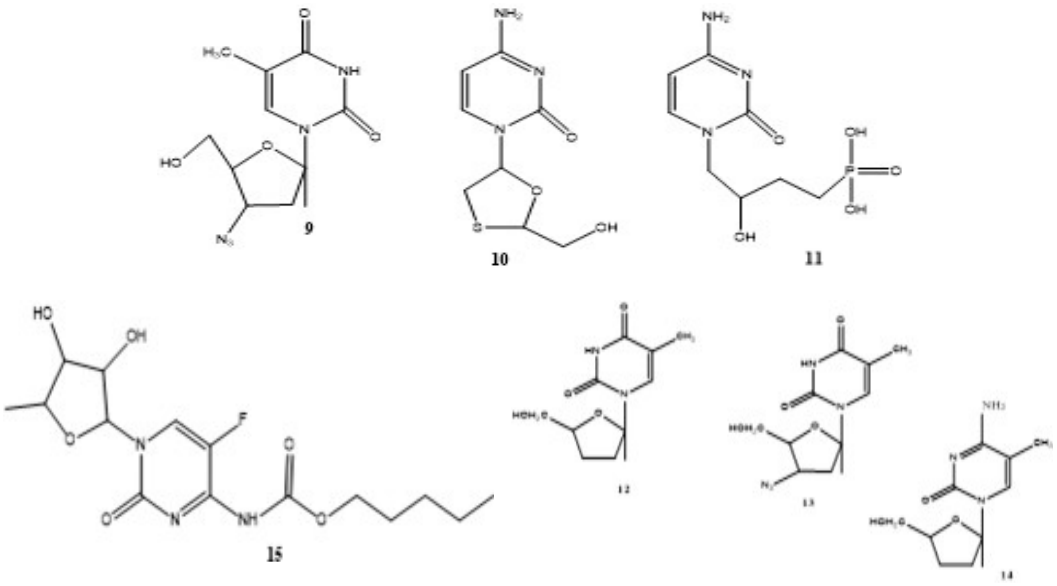
Among a few important biologically active heterocycles pyrimidines are also considered. These are present in uracil **1**, thymine **2**, which are constituents of RNA and DNA and also in cytosine **3** present in both DNA and RNA. Besides, the pyrimidone skeleton is also present in various synthetic compounds like veronal **4** and barbituric acid **5**. These are utilized as hypnotics [22]. The pyrimidone moiety is also present in a trisubstituted sulfa drug sulfacytine **6**. The potential of sulfacytine was reported to be 3 to 10 times more than already existing sulfa drugs: Sulfa isoxazole and sulfisomidine [23]. Plicecetin **7** is also found to have a Pyramidone skeleton and exhibit antibacterial activity [24]. Similarly, Gorgerin **8** is also antibacterial and shows activity against both gram-

positive and gram-negative bacteria.

Pyrimidone derivatives are found to show very good antiviral properties. e.g., 1-(3-Azido-2,3-dideoxy-â-D-ribofuranosyl)-5-methylpyrimidine-2,4(1H,3H)-dione **9**commonly known as AZT or Zidovudine, is a prime example. It has been approved for treating AIDS as a potent inhibitor of HIV replication. It's a potent inhibitor of HIV replication and has been approved for treating AIDS. [25]. Lamivudine **10** when used with zidovudine, works as a potential anti-AIDS agent.

Cidofovir **11** is used against cytomegalovirus [26]. Stavudine **12** is used along with zidovudine against HIV virus [27]. Zidovudine **13** is used against retroviruses. These viruses are responsible for causing AIDS and T-cell leukemia. Zalcitabine **14** in combination with zidovudine is also used as a useful drug [28]. Some Pyrimidone derivatives like capecitabine **15** are found to act as anticancer agents [29].



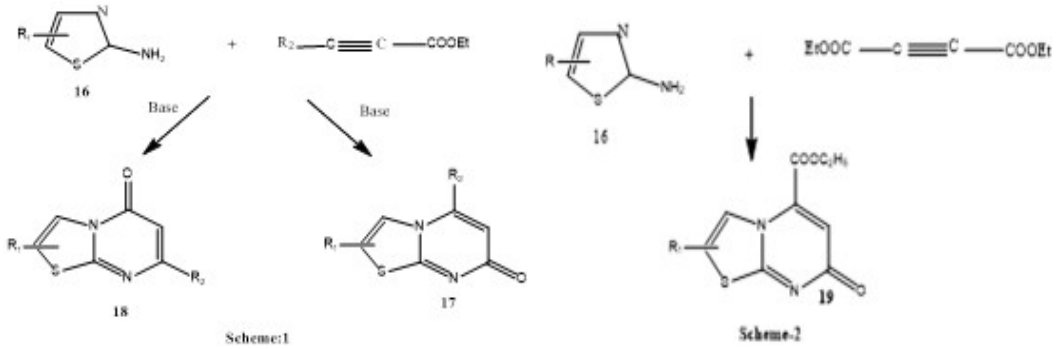


Synthesis of Triazolopyridines

Synthesis of Thiazolo[3,2-a] pyrimidin-7(3H)-ones:

Synthesis of Thiazolo[3,2-a] pyrimidin-7(3H)-ones can be possible from 2-mercapto pyrimidone or 2-aminothiazoles as described by the following reactions:

1. Synthesis of thiazolo[3,2-a] pyrimidines from 2-amino thiazoles: It was shown by Rominger [30] and Dunwell et al. [31] that 2-amino thiazolino **16** on condensation with propiolic acid or the ester of it in presence of basic medium gives Thiazolo[3,2-a] pyrimidin-7(3H)-ones **17** and Thiazolo[3,2-a] pyrimidin-5(7H)-ones **18**. **17** is the major product (Scheme-1). While **16** on condensing with acetylene dicarboxylic ester gives 5-ethoxy carbonyl derivative **19** (scheme-2).



Scheme:1 Scheme-2

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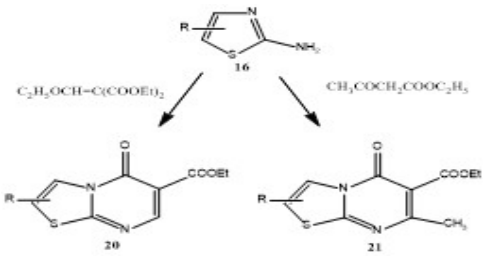
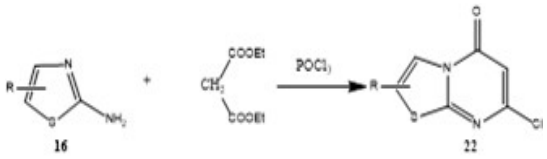
It was reported by Dunwell et al. [31] that 6-carboethoxy-5H-thiazolo[3,2-a] pyrimidin-5-ones **20** and 7-methyl-5H-thiazolo-[3,2-a]-pyrimidin-5-ones **21** can be synthesized by condensing 2-aminothiazoles **16** with diethyl ethoxy methylene malonate or ethyl acetoacetate respectively (Scheme-3).

Similarly, 7-Chloro-5H-thiazolo[3,2-a] pyrimidin-5-one **22** can also be synthesized from 2-amino thiazoles **16** by reacting it with diethyl malonate in the presence of polyphosphoric acid (PPA) and $POCl_3$ (Scheme-4) [32].



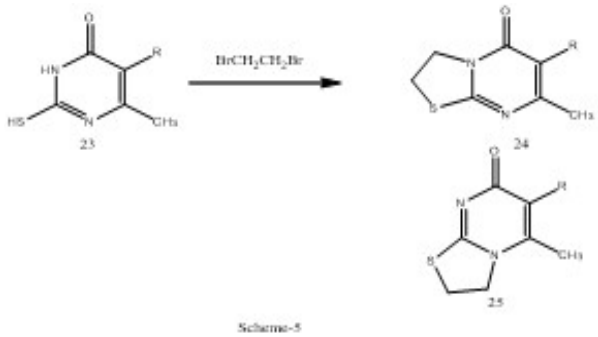
Scheme-3



Scheme-4

2. Synthesis of thiazolo[3,2-a] pyrimidinones from 2-mercapto thiazoles: A mixture of 7-methyl-5-oxo thiazolidine[3,2-a] pyrimidinones **24** and 5-methyl-7-oxo thiazolidine [3,2-a] pyrimidinones **25** can be obtained by reacting 4-methylthiouracil **23** with 1,2-dibromoethane in the presence of propan-2-ol and sodium hydrogen carbonate [33] or dimethyl formamide [34] (Scheme-5). Compounds **24** and **25** can be easily separated due to the difference in their solubilities.

Similarly, a mixture of 3-Ethoxythiazolo[3,2-a] pyrimidin-7(3H)-one **26** and 3-Ethoxythiazolo[3,2-a] pyrimidin-5(3H)-one **27** can be synthesized from 4-methyl thiouracil **23** by condensing it with Bromo acetaldehyde diethyl acetate. **26** and **27** were separated by chromatography (Scheme-6).



Scheme-5

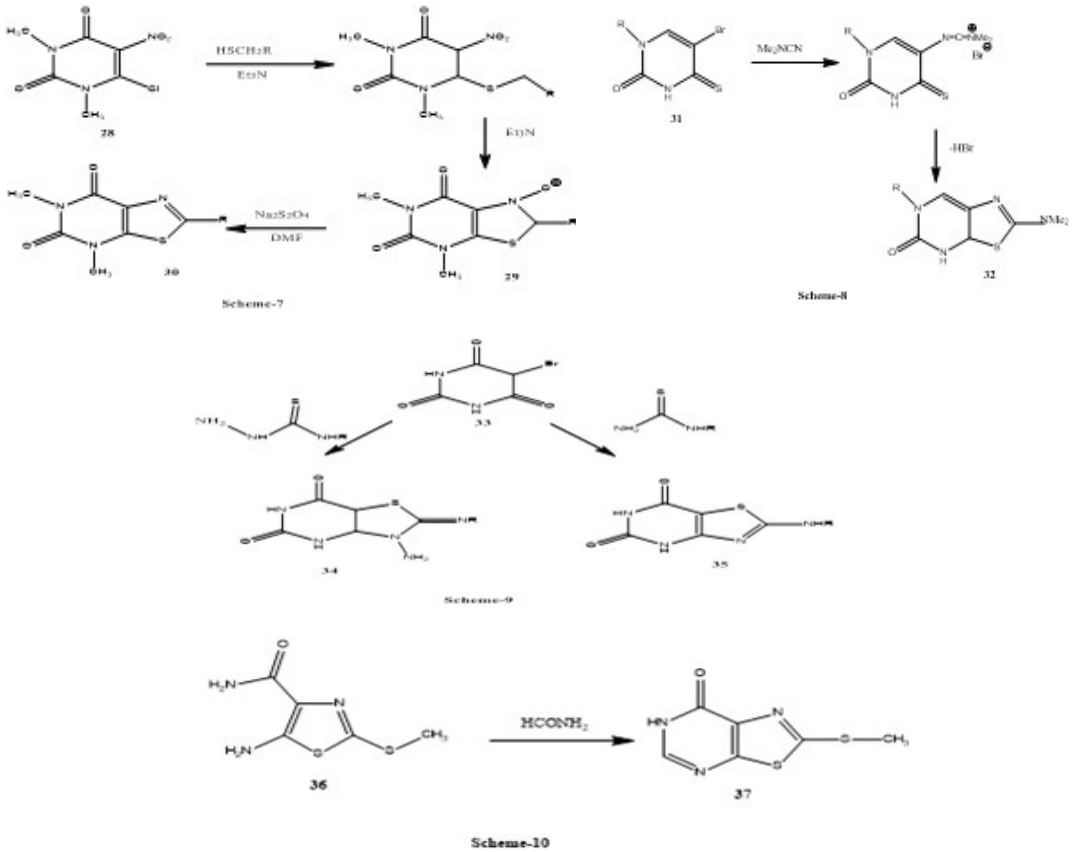
Synthesis of thiazolo[5,4-d] pyrimidinones:

6-Chloro-5-nitro-1,3-dimethyluracil **28** reacts with mercaptans in the presence of triethyl amine to form triazolopyridine oxides **29**. Thiazolopyrimidinone derivative **30** can be synthesized from **29** by treating it with sodium dithionite in dimethyl formamide (Scheme-7) [35].

A.F.S. Ahmed [36] reported that 5-bromo-4-thioxopyrimidine-2-ones **31** on reacting with N, N-dimethyl cyanamide gives an intermediate carbodiimide that undergoes intermolecular cyclization to give thiazolo[5,4-d] pyrimidinone derivative **32** (Scheme-8).

Thiazolopyrimidinone derivative **34** can be prepared by reacting 5-bromobarbituric acid **33** with thiosemicarbazone. However, **33** on condensation with thiourea derivatives gives another derivative of triazolopyridines **35** (Scheme-9) [37, 38].

5-Amino-2-methylsulfanylthiazolyl-4-carboxylic acid amide **36** on treatment with formamide gives thiazolo[4,5-d] pyrimidinone derivative **37** (Scheme-10) [39].



Scheme-7

Scheme-8

Scheme-9

Scheme-10

Conclusion:

Thiazolo [4,5-d] pyrimidinones and their derivatives have emerged as heterocyclic compounds of significant therapeutic potential, exhibiting a variety of biological activities like anti-inflammatory, antifungal, antiviral, antibacterial, antitumor etc. Various synthetic routes available to synthesize this scaffold offer opportunities for making structural modifications as per medical needs and optimizing the properties. Therapeutic significance and availability of various synthetic methods of thiazolo[4,5-d] pyrimidinones and their derivatives leads for further development of effective novel and safer drugs for the treatment of various diseases.

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