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Review article

Recent synthetic and medicinal perspectives of dihydropyrimidinones: A review

Ramandeep Kaur [a], Sandeep Chaudhary [a], Kapil Kumar [a], Manish K. Gupta [b], Ravindra K. Rawal [a, *]

[a] Department of Pharmaceutical Chemistry, Indo-Soviet Friendship College of Pharmacy (ISFCP), Moga 142001, India
[b] School of Pharmacy, Lloyd Institute of Management and Technology, Greater Noida 203207, India

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ABSTRACT

Dihydropyrimidines are the most important heterocyclic ring systems which play an important role in the synthesis of DNA and RNA. Synthetically they were synthesized using Multi-component reactions like Biginelli reaction and Hantzschdihydropyridine. In the past decades, such Biginelli type dihydropyrimidones have received a considerable amount of attention due to the interesting pharmacological properties associated with this heterocyclic scaffold. In this review, we highlight recent developments in this area, with a focus on the DHPMs, recently developed as anti-inflammatory, anti-HIV, anti-tubercular, antifungal anticancer, antibacterial, antifilarial, antihyperglycemic, antihypertensive, analgesic, anticonvulsant, antioxidant, anti-TRPA1, anti-SARS, and anti-cancer activity and α_{1a} binding affinity.

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* Corresponding author.
E-mail address: rawal.ravindra@gmail.com (R.K. Rawal).

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1. Introduction

Heterocyclic chemistry is an important branch of organic chemistry accounting for nearly one-third of modern publications [1]. Heterocyclic compounds have vital role in our biological system. They are an integral part of many pharmacologically active molecules, natural products and nucleic acids. The base pair of DNA& RNA (guanine, cytosine, adenine and thymine) are also made up of heterocyclic compounds like purine, pyrimidine etc. Heterocyclic compound are also present in large variety of drug candidate like antitumor, antibiotic, anti-inflammatory, antidepressant, antimalarial, anti-HIV, antimicrobial, antibacterial, antifungal, antiviral, antidiabetic, herbicidal, fungicidal and insecticidal agents [2]. Some naturally occurring molecules are discovered and having a good biological activity against the many diseases e.g. quinine is used as an antimalarial drug, vinblastine and vincristine are also used as anticancer agent. In this review, our focus will be on the 3,4-dihydropyrimidine (DHPM) ring. Basically it is a selective review on dihydropyrimidinones. Literature of last two decades is incorporated in this review. The pyrimidine is the most important heterocyclic moiety. Pyrimidine derivatives have various therapeutic applications in medicinal chemistry. One anticipated reason for their activity is presence of a pyrimidine base in thymine, cytosine and uracil, which are essential building blocks of nucleic acids, DNA & RNA [3]. Number of chemical compounds consisting of pyrimidine as core nucleus were synthesized and evaluated for antihypertensive [4], anticancer [5], antimicrobial [6], antihyperglycemic [7], antiarrhythmic, anti-inflammatory [8], analgesic [9], antibacterial [10], anti-HIV [11] and antitubercular activity [12]. Due to the wide range of therapeutic properties scientist have attracted towards developing new dihydropyrimidine molecules. Recently in 2013, Dragovich et al. synthesized substituted 2-thio-6-oxo-1,6-dihydropyrimidines inhibitors of human lactate dehydrogenase [5]. The DHPMs are synthesized with the help of Multi-component reactions (MCR). MCR are special types of theoretically useful organic reactions in which three or more starting materials react to give a desired product [13]. Combine synthesis pathways generally show advantages over continuous or atypical approaches with respect to time, speed, yield and reproducibility. Among organic reactions, MCR with more than two starting materials are allowed to form a complex product. Therefore, they constitute a superior tool for diversity oriented and complexity-generating synthesis for drug discovery [14]. Commonly used multi component reaction for heterocyclic synthesis are Biginelli reaction and Hantzsch dihydropyridine synthesis [15] etc. Few pharmacologically active dihydropyrimidinones are shown in Fig. 1.

Dihydroprymidinone nucleus is also found in marine natural alkaloids Batzelladine A and B which are known to inhibit the binding of HIV gp-120 to CD4 cells [16,17]. Various other synthetic analogs such as monastrol [18], L-771,688 [19], SQ 32926 [20], have been developed (Fig. 2). Monastrol is the most important anticancer compound and has an ability to cross the cell membrane. It causes mitosis by reversible and specific inhibition of Eg5 myosin kinase. Various other analogs of monstraol such as oxo-monastrol, thio and 3,4-methylenedioxy derivatives of manostrol have been developed and tested against HT-29 colon cancer cell lines. 3,4-methylenedioxy analog was found to be 30 times more potent than monastrol [18].

Various drug interactions and side effects have been reported for some of the drugs containing dihyropyrimidinone nucleus. Monastrol is well known as mitotic kinesin inhibitors [21] but it is found to have neurotoxicity as one of the major side effect. Interaction of aminophylline and topiramate has been studied carefully which revealed that aminophylline containing the dihyroprymidinone nucleus markedly attenuated the anticonvulsant potential of topiramate in the mouse maximal-electroshock-induced seizure model [22]. Seizure prolonging action of aminophylline has also been observed which is mainly attributed by blocking adenosine receptors [23]. However, seizure prolonging action was of aminophylline was antagonized by RO 15-1788, which is partial benzodiazepine agonist [23,24]. Interaction of 5-flourouracil with misonidazole has revealed that the clearance of the former was significantly reduced. Misonidazole is a radiosensitiser of hypoxic cells which has been shown to enhance antitumor activity of several chemotherapy drugs [25].

2. Synthetic strategies

Research and development in the past years have effectively accomplished the purpose of introduction of various synthetic strategies. Numerous synthetic strategies have been outlined for the synthesis of DHPMs illustrated in Scheme 1. In 1893, Pietro Bignelli's had reported the synthesis of dihydropyrimidine (monastrol) **4** by condensation of ethyl acetoacetate **3,** 3-hydroxybenzaldehyde **1** and thiourea **2** under slightly acidic condition using concentrated hydrochloric acid as catalyst in appropriate solvent such as ethanol [26]. Matthews et al. treated β-keto ester **5** with aldehyde **1** and urea **2** for the synthesis of DHPMs **6** [27]. In 2004, Holla et al. published one pot synthesis of thiazolo-dihydropyrimidinones **8** by condensing benzaldehyde**1** with 2,4-dichloro-5-fluoroacetophenones **7** and thiourea **2** in the presence of sodium hydroxide and ethanolic potassium hydroxide under the Claisen-Schmidt reaction conditions [28]. Yadlapalli et al. were synthesized DHPMs with the help of 1-(piperidin-1-yl)butane-1,3-dione **9**, benzaldehyde **1**, an excess of thiourea **2** in ethanol under mild acidic condition provided the expected DHPMs in good to excellent yield [29]. In 2010, Shaabni et al. described the synthesis of a new class of 3,4-dihydropyrimidine-2(1*H*) one derivatives in a one-pot process by a four-component condensation reaction of an aliphatic or aromatic amine **11**, diketene **12**, an aromatic aldehyde **1** and urea/thiourea **2** in the presence of *p*-toluenesulfonic acid (*p*-TsOH.H_2O) as a catalyst in dichloromethane at ambient temperature. Since the number of possible combinations in four-component reactions is greater than the three-component reactions, the diversity of Biginelli reaction is more explored under four-component reaction strategy [30].

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