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Original article

Sketching the historical development of pyrimidones as the inhibitors of the HIV integrase

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ABSTRACT

Heterocyclic substances perform a very unique role in drug design and discovery. This article provides the primary objectives of the analysis within pyrimidine centered new heterocyclic elements chronologically from their finding focusing on one of the essential enzyme of HIV virus particle that is integrase upon suppressing its strand transfer function. The class of compounds reviewed here includes bicyclic pyrimidines, dihydroxypyrimidines, pyrimidine-2,4-dinones, *N*-methylpyrimidones, pyranopyrimidine, pyridine–quinoline conjugates, pyrimidine-2-carboxamides, *N*-3 hydroxylated pyrimidine-2,4-diones as well as their various substituted analogues. Such initiatives released an effective drug Raltegravir as a first FDA approved anti-HIV integrase inhibitor as well as several of its derivatives along with other pyrimidones is under clinical or preclinical growth. Some of the provided scaffolds indicated dual anti-HIV efficacies against HIV reverse transcriptase and integrase enzymes at both cites as 3′-processing and strand transfer, while several scaffolds exhibited potency against Raltegravir resistant HIV mutant strains determining themselves a potent class of compounds having appealing upcoming implementations. Connections of the new compounds' molecular structure and HIV viral target has been overviewed to be able to accomplish further growth of promising anti-HIV agents in future drug discovery process.

1. Introduction

Anti-HIV drug development is one of the leading tasks in the drug discovery area due to the improving rate of sufferers with HIV and related infections. AIDS, a result of HIV infection is a serious risk to public health and can be regarded as one of the biggest reasons responsible for numbers of death annually in near future. The infection of this virus particle even invites a variety of other microbial infections, cancers and other diseases [1]. Since the beginning of the epidemic, almost 70 thousand individuals have been contaminated with the HIV virus and about 35 thousand individuals have passed away of AIDS. Globally, 34.0 thousand [31.4–35.9 million] individuals were residing with HIV at the end of 2011. An approximate 0.8% of grownups older 15–49 years are residing with HIV, although the pressure of the outbreak is constantly on the different considerably between nations and areas [2]. Though current anti-HIV drugs can suppress HIV infection at some extent, the multi-drug resistance prevalence of some HIV mutant strains is one of the major threats for the HIV arsenal [3]. To avoid the problem, current searches for new anti-HIV agents are focused on discovering compounds with novel components and different mechanisms of action [4]. Research on HIV chemistry have offered strong knowledge of the molecular activities engaged in the HIV replicative pattern, which involve several steps as entry-fusion of HIV virus particle with CD4 cell, reverse transcription, integration, gene expression, gene assembly, budding and maturation [5]. In particular, scaffolds focusing on reverse transcriptase (RT), protease (P) and integrase (IN) enzymes in the HIV replicative cycle, remain important targets in drug development. To date, several drugs are established for the treatment of this disease like zidovudine, didanosine, zalcitabine, stavudine, lamivudine, abacavir and emtricitabine as NRTIs, tenofovir as NtRTIs, nevirapine, delavirdine, efavirenz and etravirine as NNRTIs, saquinavir, ritonavir, indinavir, nelfinavir, amprenavir, lopinavir, atazanavir, fosamprenavir, tipranavir and darunavir as PIs, enfuvirtide as FIs, maraviroc as CRA and raltegravir as well as elvitegravir as INIs [6]. From this point, less numbers of anti-HIV integrase inhibitors are developed till date, hence the figures strongly recommend the development of further class of integrase inhibitors expressing a clear mode of anti-HIV action. Several scientists over the world working to discover

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new anti-HIV drug-like elements upon holding architectural difference of a particular type of substances to improve their efficiency and possibly discover new clinical trial candidates. Herein, we review a type of appealing anti-HIV substances, pyrimidones with anti-HIV potency towards IN enzyme of HIV virus. The articles are the extensive selection of pyrimidine based merged or annulated elements presenting effective anti-HIV effectiveness along with information of the key architectural features which will aid therapeutic apothecaries in their continuous drug discovery process.

A pyrimidine class of compounds is of enormous interest within anti-HIV drug discovery process for several decades, as pyrimidine based DABOs class [7], DAPYs class [8] are well known as NNRTIs as well as NRTIs. However, the overall role of a pyrimidine class of heterocycles in anti-HIV drug discovery appeared in the literature few years ago [9]. In connection with the present article, the inhibitory effects of dihydro-alkoxyl-benzyl-oxopyrimidine derivatives towards reverse transcriptase enzyme of HIV virus particle is recently reviewed [10]. Simultaneously, occurrence of similar pyrimidine congeners with potent anti-HIV integrase inhibitory profiles have been noticed by us and reviewed herewith. Developing the effective part of the pyrimidine ring system against RT enzyme of HIV, some scientists tried to provide latest pyrimidine centered substances focusing on the integrase enzyme of HIV virus particle and such developments are described in this review. To the 3′-end of the HIV pol gene, a 32 kDa protein is encoded called HIV integrase enzyme [11]. Inhibition of HIV integrase, accountable for placing the viral DNA into the host cellular genome, outcomes in arrest of the HIV life cycle and is, therefore, a very eye-catching therapeutic target. Upon inhibition of integrase, the viral DNA is turned into a circular DNA incapable to be incorporated into the host genome [12]. Incorporation of viral DNA into the infected individual's chromosomal DNA, which is catalyzed by HIV integrase, happens by a particularly described series of 3′-processing and strand transfer reactions [13,14]. In the cytoplasm, prior to the commencement of integration, there is set up of viral DNA, formerly created by reverse transcription, on HIV integrase. From each 3′-end of the viral DNA, after the assembly formation, a site-specific endonucleatic cleavage of two nucleotides is a process called 3′-processing, which produces tailored viral DNA recessed by two nucleotides and with terminal CAOH-3′. The strand transfer step is followed then, which includes joining of viral DNA's each 3′-ends with host DNA's 5′-ends via staggered nicking of chromosomal DNA. Remarkably, in the nucleus, the strand transfer step is partitioned from 3′-processing and is carried out after the transport of the processed, preintegration complex (formed through RT enzyme) from the cytoplasm into the nucleus [15].

2. HIV integrase inhibitory activity of pyrimidones

Development of new heterocycles active against deadly HIV virus is always welcomed by the scientific community due to its globally widespread infection. Especially, several Pyrimidine based scaffolds have gained much interest due to their significant anti-HIV activities along with their structural diversity. Vast research is being conducted into the synthesis and study of pyrimidine based derivatives and their intriguing pharmacological effects. Varying the fused, linked or clubbed substituents accompanying pyrimidine ring has been found to induce enhanced anti-HIV significance of the resultant molecules withy unique mode of action, i.e. in this case, inhibition of HIV IN strand transfer. In this article, numerous examples of the biological activities of such pyrimidone scaffolds are presented, in order to provide an important knowledge base for both chemists and biologists working in the field of structure based drug design and discovery. The review enlightens briefly the development of following derivatives as anti-HIV agents as next generation antiretrovirals.

Pyrimidine entity is the essential ring found in the core structure of all essential nucleobases. The anti-HIV drug discovery within pyrimidine class of nucleoside scaffolds initiated with the synthesis of pyrimidine 3′-azido-2′,3′-dideoxynucleosides and 3′-substituted purine and pyrimidine 2′,3′-dideoxynucleosides and the discovery of AZT [16] inspired several researchers in the world to develop newer NRTIs class of anti-HIV drugs and such attempts then resulted in the discovery of several potent anti-HIV drugs like abacavir, emtricitabine, lamivudine, didanosine, apricitabine, stampidine, elvucitabine, racivir, amdoxovir, stavudine, zalcitabine, festinavir and tenofovir (Fig. 1).

In addition to the pyrimidine class of NNRTIs, an FDA approved drug (12th October 2007) Raltegravir [17,18] is the best example of a pyrimidone class of HIV-1 INIs targeting strand transfer function. Raltegravir (N-[(4-fluorophenyl)methyl]-1,6-dihyro-5-hydroxy-1-methyl-2-[1-methyl-1-[[(5-methyl-1,3,4-oxadiazol-2-yl)carbonyl] amino]ethyl]-6-oxo-4-pyrimidinecarboxamide monopotassium salt) can be synthesized according to the chemical transformation shown in Scheme 1 [19].

Raltegravir has *in vitro* IC_{95} level of 31 ± 20 nmol/L against HIV-1 type in human CD4 cells with 83% binding to human plasma proteins with a huge range of potency against drug-resistant and wild-type HIV mutant strains. In some cases, the drug was found active against HIV-2 too, with 6 mmol/L of IC_{95} level as inspected in CEMx174 cells [20]. During the life cycle of HIV within CD4 cell, reverse transcriptase, a key enzyme of HIV virus particle forms the preintegration complex, which allows passing of HIV-1 viral DNA into the nucleus, where DNA strand transfer happens. Then, viral DNA is bonded to the integrase enzyme of HIV virus particle and links it with host CD4 cell DNA. After this process viral DNA is then sealed in the chromosome via viral cellular repair activities. Catalytic core, is the main part of the integrase enzyme and its divalent cations enables this enzyme to create covalent bonds with a phosphodiester backbone of DNA. The drug Raltegravir suppress this formation of covalent bond with CD4 cell DNA hence inhibits the activity of integrase enzyme [21,22] (Fig. 2). It has highly efficient pharmacokinetic profile [23,24] and well tolerance among a variety of HIV infected individuals as confirmed during clinical trials [25–30] (see Figs. 3–19).

Following the discovery of β-diketo compounds S-1360 [31] and L-731988 [32] as anti-HIV integrase inhibitors, a group of researchers discovered a potent pyrimidine based derivative (**1**) as the inhibitor of HIV integrase functioning at the 3′-processing and strand transfer steps of HIV integrase. Bioassay examining the inhibition of wild-type HIV-1 integrase by **1**, indicated 3.7 μM and 0.2 μM of IC_{50}s against 3′-processing and strand transfer, respectively. Compound **1** inhibited HIV-1_{TEKI} and HIV-1_{NL4-3} strains with 50 nM and <20 nM of IC_{50}s and >200 of CC_{50} level with >4000 and >10,000 selectivity indexes, respectively in PBMC cells, which was even better than the selectivity of AZT with >7143 and >5556 of SI, respectively. In addition, three more congeners of 1 were generated as bis-(*o*-F-Bn) analogue of **1**, bis-(*p*-F-Bn) analogue of (**1**) and **1** minus N^3-benzyl, which indicated 4.1 μM, 3.9 μM and 10 μM as well as <0.6 μM, <0.7 μM and 0.5 μM of IC_{50}s against 3′-processing and strand transfer, respectively [33].

Some dihydroxypyrimidine carboxamides (**2**) were synthesized and checked for their HIV integrase strand transfer suppression action. SAR at carboxamide (**2a**), heteroaryl amide (**2b**) and benzylamide (**2c**) was determined and analogues **2c** exhibited good potency than the remaining two series, in which compounds **$2c_{vi}$**, **$2c_{ix}$**, **$2cx_{i}$**, **$2c_{xiv}$** and **$2c_{xv}$** exerted 40 nM, 50 nM, 20 nM, 10 nM and 10 nM of IC_{50}s, respectively. The last two analogues were the most potent among the all tested to suppress IN enzyme. Furthermore,

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