Biomedicine & Pharmacotherapy 91 (2017) 265–277

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Review

α-pyrones: Small molecules with versatile structural diversity reflected in multiple pharmacological activities-an update

Zubair Shanib Bhat[a,b], Muzafar Ahmad Rather[a], Mubashir Maqbool[a], Hafiz UL Lah[c], Syed Khalid Yousuf[b,c], Zahoor Ahmad[a,b,*]

[a] *Clinical Microbiology and PK/PD Division, Council of scientific and industrial research (CSIR) -Indian Institute of Integrative Medicine (IIIM), Sanatnagar, Srinagar, 190005, India*
[b] *Academy of Scientific and Innovative Research (AcSIR), Indian Institute of Integrative Medicine (CSIR), Sanatnagar Srinagar, Jammu and Kashmir 190005, India*
[c] *Medicinal Chemistry Division, CSIR-Indian Institute of Integrative Medicine, Sanatnagar, Srinagar, 190005, India*

ARTICLE INFO

Article history:
Received 3 January 2017
Received in revised form 18 March 2017
Accepted 10 April 2017

Keywords:
α-pyrone
2-Pyrone
HIV
Tuberculosis
Anti-cancer
Neurodegenerative diseases
Antimicrobial agents
Human diseases

ABSTRACT

The investigations in the chemistry and biology of *α-pyrone* (*2-pyrone*) are of vital importance as they constitute an essential pharmacophore in many naturally occurring and biologically active synthetic agents. They are a promising class of biorenewable platform chemicals that provide access to an array of chemical products and intermediates. Literature survey reveals that a simple change in the substitution pattern on the *2-pyrone* ring system often leads to diverse biological activities. In this review, we present a brief overview of *2-pyrone* pharmacophore followed by highlighting their pharmacological properties and potential applicability till date. Particular attention is focused on the distinctive chemotherapeutic activities of *2-pyrones* as anti-HIV, anti-TB and anti-cancer agents followed by their potential role against neurodegeneration, hypercholesterolemia, microbial infections, chronic obstructive lung disease, inflammation, antinociception and immunomodulation. Since 2005, when *2-pyrones* came in limelight, their detailed pharmacological activities have been well documented. This review has mainly been prepared on the basis of original reports published in recent two decades with an aim to attract the attention of researchers towards this versatile scaffold for future endeavors that may lead to the development of potential drug candidates against above diseases.

Contents

* Corresponding author at: Clinical Microbiology and PK/PD Laboratory, Indian Institute of Integrative Medicine, Sanatnagar Srinagar, Jammu and Kashmir, 190005, India.
E-mail address: zahoorap@iiim.ac.in (Z. Ahmad).

http://dx.doi.org/10.1016/j.biopha.2017.04.012
0753-3322/

1. Introduction

Aromatic heterocycles represent about two-third of total organic compounds that define the history, present and future of modern drugs [1]. Benzene, a six membered aromatic organic hydrocarbon undergoes substitution in which one or more atoms in the benzene ring are replaced by heteroatoms such as nitrogen (N), Oxygen (O) and Sulphur (S) (Fig. 1**)**. O and N based heterocyclic compounds have been established to play an important role in designing new class of drugs.

Pyrones represent a class of oxygen based heterocyclic compounds that naturally occur in two isomeric forms as either *2-pyrone (α-pyrone)* or *4-pyrone(γ-pyrone*).The number 2/4 is assigned on the basis of position of the carbonyl group relative to the oxygen atom within the ring system (Fig. 2).

2-pyrone, a class of six-membered lactones, naturally exists as a part of coumarin ring system that displays chemical and physical properties similar to those of alkenes and aromatic compounds [2]. The other related natural products include polyketides, heterocycles, macrocyclic rings and saccharides.

2-pyrone is an important sub-structure of various natural products that are abundantly found in bacteria, plants, animals and insects where they are often involved in defence processes [3]. The products containing the pyrone motif show extensive diversity in structural design and function. They represent the core motifs of many key biosynthetic intermediates in microorganisms such as *Streptomycetes* [4,5] (in which they have a role in spore germination) [6], *pseudomonads* [7] and fungi [8] that is finally metabolised to acetic acid [9]. Historically, important biological compounds like pheromones [10], α-chymotrypsin [11] and elastase [12] were synthesized from simple *2-pyrone* derivative called triacetic acid lactone (TAL). In July 2013, a ketosynthase derived *2-pyrones* (Fig. 3, **1–8**) were identified as a new class of signalling molecule in bacterial communication facilitating cell–cell clumping in *Photorahabdus luminescens* [13].

2-pyrone is a promising class of biorenewable core scaffolds that provide access to a wide array of intermediates and chemical products. They undergo a range of chemical reactions unique to their structure where the final products formed depends on the type of solvent used and the acidity of the reaction environment [9]. As such, the complexity of *2-pyrone* is diverse ranging from simple substituted derivatives, such as TAL (**9**) and tetra-acetic acid lactone (TtAL) to more complex systems like *Fusapyrone* (**53**) [3]. TAL-moiety is a yellowish *6-methyl-4-hydroxy-pyran-2-one (MHP)* derivative that is soluble in organic solvents. TAL is chemically synthesized from a related compound, dehydroacetic acid (DHA) (**10**) (Fig. 4).

However, in biological systems it is synthesized enzymatically from glucose (Fig. 5). DHA (**10**) and its simple chalcone analogues such as *3-cinnamoyl-4-hydroxy-6-methyl-2-oxo-2H-pyrans* (CHPs) represent the vital scaffolds for the synthesis of various heterocyclic compounds that display interesting applications [14,15].

2-pyrones are known for their ability to bind specific protein domains in diverse biological systems and possess anti-viral [16–18], broad-spectrum anti-bacterial [19] and anti-fungal activities [20–23].

Tricyclic *2-pyrones* are reported to be effective against Alzheimer's amyloid toxicity [24–26]. Many chlorinated *2-pyrone* based derivatives were discovered as potent anti-cancer agents [27–33]. *3-Alkyl-6-chloro-pyran-2-ones* (ACP) display cholesterol lowering property by selective inhibition of pancreatic cholesterol esterase [34]. The biological activity of pyrone based molecules in all of these examples is believed to be due to enzyme inhibition [19,35,36]. Undoubtly therefore, the probable scope of 2-*pyrones* as suitable drug candidates against various human diseases is worth pursuing.

2. Pharmacological applications

2-pyrones have attracted much attention due to their remarkable structural diversity and broad spectrum biological activities [2,3]. A single change in substitution pattern on the *2-pyrone* ring system leads to diverse biological activities. The carbonyl position on the *2-pyrone* is prone to attack by hydroxide ions leading to ring-opening. Due to this reactivity, *2-pyrone* has substitutions generally at the C-4 and C-6 positions that stabilise the intermediate species through resonance. TAL (**9**) and DHA (**10**) are two such examples. These derivatives represent an interesting template for combinatorial chemistry for the construction of condensed heterocyclic systems and makes them intimidating for exploration as possible bioactive molecules [37]. Interestingly, many *2-pyrone* based compounds are being explored as possible therapeutic options against a variety of human diseases as summarised in Table 1. Under the following subheadings, we discuss in detail about the advancement of individual *2-pyrone* based derivatives against respective disease discretely.

2.2. Anti-HIV potential

HIV is among the leading infectious diseases with approximately 36.9 million HIV positive individuals globally and 1.2 million people dying from HIV-related causes annually [38]. A key sub-class of *pyrones* are the *4-Hydroxy-pyran-2-ones* (4-HP) [39]. They have been established as one of the most important class of anti-HIV agents [40–43]. In 1996, Thaisrivongs *et al.* [44] reported the structural design of *5,6-dihydro-4-hydroxy-pyran-2-one* based *Tipranavir* (**11**) as a new class of effective anti-HIV agent. It is a dihydropyrone based sulphonamide derivative of 4-HPs (Fig. 6)

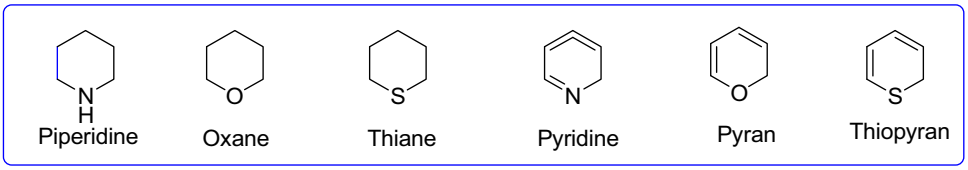

Fig. 1. Some six membered ring heterocycles.