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Review article

The therapeutic journey of pyridazinone

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ABSTRACT

Pyridazinones have drawn a substantial attention within the field of research analysis and development. The moiety is a subject matter of intensive research because of its wide spectrum of biological activities and therapeutic applications. The synthesis of pyridazinone and investigation of their chemical and biological activities have gained additional importance in recent years. In this review, we have compiled and discussed various biological and therapeutic potential of pyridazinone derivatives.

Contents

1. Introduction

The chemistry of pyridazinones (Fig. 1) has been an interesting field of study since decade. The synthesis of novel pyridazinone derivatives and examination of their chemical and biological behaviour have gained much significance in recent decades for biological, medicinal and agricultural reasons. Living being finds difficulty in construction of N–N bonds that limits the natural abundance of compounds having such bonds. The pharmacological action of pyridazinones has been broadly studied and is well known for its cardiovascular effects [1–3]. In this field several compounds such as zardaverine or imazodan have been developed as PDE III

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Abbreviations

PDE- III	Phosphodiesterase-III
HIV	Human Immunodeficiency Virus
NSAIDs	Non-steroidal anti-inflammatory drugs
COX	Cyclooxygenase
TNF	Tumor necrosis factor
IL-1β	Interleukin-1 beta
μM	Micromolar
mL	Millilitre
IC_{50}	Half maximal inhibitory concentration
nM	Nanomolar
PDE3A	Phosphodiesterase 3A
PDE4B	Phosphodiesterase 4B
LOX	Lipoxygenase
ED_{50}	Effective dose
mg	Milligram
kg	Kilogram
WHO	World Health Organization
GI_{50}	Growth Inhibition
PARP1	Poly (ADP-Ribose) Polymerase 1
H_2O_2	Hydrogen peroxide
PFKFB3	Fructose-2,6-biphosphatase3
HSV-1	Human herpes simplex virus
HCMV	Human cytomegalovirus
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
Anti-TMV	Anti-tobacco mosaic virus
IC_{95}	95% inhibitory concentration
EC_{50}	Half maximal effective concentration
C. albicans	*Candida albicans*
MIC	Minimum Inhibitory Concentration
CVDs	Cardiovascular diseases
VAP-1	Vascular Adhesion Protein-1
MAP	Mean arterial pressure
mmHg	Millimeter of mercury
TB	Tuberculosis
MCH-R1	Melanin-concentrating hormone receptor 1
AD	Alzheimer's disease
AChE	Acetylcholinesterase
PDE inhibitor	Phosphodiesterase inhibitor
PGI_2	Prostaglandin I_2
Human NPCs	Human neural progenitor cell
MES	Maximal Electroshock Model
FPR	Formyl Peptide Receptors
PDE5	Phosphodiesterase-5
SRB	Sulforhodamine B
S. racemosum	*Syncephalastrum racemosum*
C. albicans	*Candida albicans*

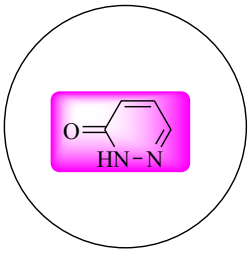

Fig. 1. Structure of pyridazinone.

inhibitors in the search for new antiplatelet or cardiotonic agents [4,5]. A survey of literature revealed that substituted pyridazinones have received much attention during recent years on account of their prominent potential as antidepressant [6], antihypertensive [7], anticonvulsant [8], cardiotonic [9], antibacterial [10], diuretics [11], anti HIV [12] and anti-cancer [13]. Pyridazinone causes direct relaxation of arteriolar smooth muscle by reducing arterial tone without affecting autonomic nervous system. The molecular mechanisms mediating this action are not clear, but may ultimately involve a fall in intracellular calcium concentrations. While a variety of changes in cellular signalling pathways are influenced by arteriolar vasodilators like hydralazine, precise molecular targets that explain its capacity to dilate arteries remain uncertain.

This six membered ring can be traced in a number of well established drugs belonging to different categories with diverse therapeutic activities. Such drugs are enlisted in Table 1.

Numerous patents published on this moiety are given in Table 2.

2. Pharmacological activities

Owing to the diverse pharmacological activities of this ring, a number of researchers across the globe are engaged in the development of pharmacologically active agents bearing it. Recent developments made by researchers in this field are documented below:

2.1. Anti-inflammatory and analgesic activity

Control of inflammation has attained considerable importance due to its application in numerous diseases like asthma, atherosclerosis, osteoarthritis, Crohn's disease, Alzheimer's, gout, *Diabetes mellitus*, multiple sclerosis, rheumatoid arthritis, carcinoma, psoriasis, viral and bacterial infections etc. Non-steroidal anti-inflammatory drugs (NSAIDs) have a wide clinical use for the treatment of inflammatory and painful conditions. The two isoforms of cyclooxygenase (COX) are COX-1 and COX-2. These isoforms are poorly distinguishable by most of the classical NSAIDs [42,43]. Several pyridazinone based analgesic and anti-inflammatory agents have been synthesized by medicinal chemists (Fig. 2).

Amongst the several pyridazinone derivatives synthesized by Mogilski et al. [44] compounds **1** and **2** exhibited anti-inflammatory activity and cytokine (TNFα, IL-1β) inhibitory activities at a concentration of 100 μM/mL. The edema formation was significantly decreased by both the compounds. Amongst the pyridazinone derivatives developed by Ochiai et al. [45] compound **3** displayed highest anti-inflammatory activity with half maximal inhibitory concentration (IC_{50}) of 5 & 6.7 nM against phosphodiesterase 3A (PDE3A) & phosphodiesterase 4B (PDE4B). Ochiai et al. also developed another series of pyridazinone derivatives, amongst them compound **4** exhibited significant *in-vivo* anti-inflammatory activity with IC_{50} value of 0.042 and0.36 μM against PDE4B and PDE3A respectively [46]. Pyridazinone analogs synthesized by Ozadali et al. were evaluated for anti-inflammatory activity. All the compounds displayed potent *in vitro* (COX-1/COX-2, 5-LOX) and *in vivo* (rat paw edema assay) anti-inflammatory activity. However, compound **5** was found to be most active with inhibition of both COX-2 (IC_{50} = 2.1 μM) and 5-LOX (IC_{50} = 6.3 μM) enzymes [47]. A