Journal of Enzyme Inhibition and Medicinal Chemistry

http://informahealthcare.com/enz
ISSN: 1475-6366 (print), 1475-6374 (electronic)

J Enzyme Inhib Med Chem, 2015; 30(4): 550–563
© 2014 Informa UK Ltd. DOI: 10.3109/14756366.2014.951349

informa healthcare

REVIEW ARTICLE

Synthesis of the inosine 5′-monophosphate dehydrogenase (IMPDH) inhibitors

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Abstract

Inosine 5′-monophosphate dehydrogenase (IMPDH) is important molecular target for potential anticancer, antiviral, antibacterial and immunosuppressive agents. A lot of compounds were obtained to establish their activity toward this enzyme, and to improve therapeutic properties of IMPDH inhibitors used as the drugs. Some of the recently reported analogs exhibited promising results during *in vitro* and *in vivo* examinations in comparison to substances applied in clinic. In this review, we describe synthesis and biological activity evaluations of the newly designed IMPDH inhibitors.

Keywords

Anticancer activity, antiviral activity, IMPDH inhibitors, mycophenolic acid, organic synthesis

History

Received 2 April 2014
Revised 16 July 2014
Accepted 31 July 2014
Published online 1 September 2014

Introduction

Inosine 5′-monophosphate dehydrogenase [IMPDH; IMP-NAD oxidoreductase, Enzyme Classification (EC) 1.2.1.14] catalyzes a metabolic branch point reaction in purine synthesis and has been an area of intellectual convergence in biological and medicinal chemistry[1]. This enzyme is responsible for the catalysis of NAD-dependent oxidation of inosine monophosphate (IMP) as a substrate to xanthosine 5′-monophosphate (XMP), which is used in the *de novo* biosynthesis of guanine. XMP is converted to guanosine monophosphate (GMP) with glutamine as an amino donor. The *de novo* pathway of purine synthesis is considered as a more significant source of nucleotides for B and T cells than the salvage pathway, in order that IMPDH inhibitors are potential immunosuppressive agents[2,3]. In this review, we focus mainly on synthesis and biological activity of human IMPDH inhibitors.

The inhibition of IMPDH induces a reduction in guanine nucleotide pools that produce an interruption of DNA and RNA synthesis[4], a decline in intracellular signaling[5], and down-regulation of c-myc and K_i-ras oncogenes *in vitro*[6–8] and in leukemic cells of patients treated with inhibitors[8]. IMPDH inhibition results in apoptosis in both neoplastic cell lines and activated T-lymphocytes[6,9].

The role of IMPDH as a chemotherapeutic target was further advanced by the discovery, in 1990 by Natsumeda et al.[10], that the enzyme exists as two isoforms: labeled type I and type II[10]. These isoforms are of identical size and share 84% sequence identity. However, the type I ''housekeeping'' isoform is constitutively expressed in both normal and neoplastic cells[11], while type II expression is preferentially up-regulated in human neoplastic cell lines[10,12].

The type II isoform is also a target for immunosuppression. The role of this isoform in immunosuppression has been elucidated by a series of mice knockout models described by Gu et al.[13]. While the type II enzyme is the major isoform in normal human T-lymphocytes, these cells appear to induce both type I and type II enzymes when stimulated by mitogen[13]. Recently, hIMPDH-I has been identified as anti-angiogenic drug target and mycophenolic acid (MPA) was found to block tumor-induced angiogenesis *in vivo*[14]. Therefore, in this review newly designed compounds are also discussed, which indicated interesting selectivity between both isofoms of hIMPDH.

Enzymes of purine nucleotide biosynthesis pathways are attractive targets for the design of potential anticancer, immunosuppressant, antiviral and antibacterial agents[14–20]. There were obtained many of the compounds that inhibit IMPDH activity, but only a few have been used in medicine.

IMPDH inhibitors used in clinic

IMPDH is recognized as a validated target for several major therapeutic areas[21]. A number of potent and selective inhibitors of IMPDH are used in clinic (Figure 1). Ribavirin (**1**) is a prodrug of corresponding 5′-monophosphate, which as a competitive inhibitor interacts with the IMP domain of IMPDH[22,23].

Ribavirin (**1**) (1-β-D-ribofuranosyl-1,2,4-triazole-3-carboxamide, Virazole®, Valeant Pharmaceuticals, Laval, Quebec, Canada) is a broad spectrum antiviral agent inhibiting the replication of a wide range of DNA and RNA viruses *in vitro* and *in vivo*, the most sensitive being HSV-1, HSV-2, vaccinia, influenza, parainfluenza, measles, rhino, respiratory syncytial and some tumor viruses[24–26]. It is also active against various retroviruses including HIV and is used for treatment of AIDS

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