Synthesis and Biological Evaluation of Pyridazinone derivatives as Potential Anti-inflammatory Agents

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Abstract: Cyclic nucleotide phosphodiesterase type 4 (PDE4), that controls intracellular level of cyclic nucleotide cAMP, has aroused scientific attention as a suitable target for anti-inflammatory therapy in respiratory diseases. Here we describe the development of two families of pyridazinone derivatives as potential PDE4 inhibitors and their evaluation as anti-inflammatory agents. Among these derivatives, 4,5-dihydropyridazinone representatives possess promising activity, selectivity towards PDE4 isoenzymes and are able to reduce IL-8 production by human primary polymorphonuclear cells.

Keywords: Pyridazinone - phosphodiesterase inhibitors - anti-inflammatory - PDE4

Introduction

The chemistry of pyridazinones has been an interesting field of study since decades and this six membered ring has then become a scaffold of choice for the development of potential drug-candidates [1]. Thus these nitrogen-rich heterocyclic derivatives have been known to exhibit many pharmacological actions against ulcer [2] or cardiovascular diseases [3] or as anti-proliferative agents [4,5]. Development of new pyridazinone-based analgesic and anti-inflammatory derivatives acting as selective COX-2 inhibitors was recently described as well as the design of pyrazolo pyrimidopyridazinones for the treatment of erectile dysfunction [6,7]. An identified therapeutic application of such scaffold is its anti-inflammatory activity by targeting phosphodiesterases and our interest in this heterocyclic system stems from the pyridazinone type PDE3/PDE4 dual inhibitor, Zardaverine (Scheme 1),