Synthesis and Docking Studies of Novel Series of Pyridazin[6,1-C][1,2,4] Triazines

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ABSTRACT: The potential use of phoshodiesterase inhibitors (PDE4) as anti-inflammatory agents for the treatment of asthma and other inflammatory disorders has generated greater interest in this area. In our present work we have synthesized a novel series of 7-(substituted phenyl)-8,9-dihydro-2H-pyridazino[6,1-c][1,2,4]triazin-3(4H)-ones and 7-(substituted phenyl)-2H-pyridazino[6,1-c][1,2,4]triazin-3(4H)-ones. Molecular Docking studies of these compounds were performed to evaluate the binding affinities of the compounds with phosphodiesterase type4B enzyme (PDB ID IXMU). The current results showed good correlation in enzyme inhibitory activity with roflumilast (co-crystallized ligand).

KEYWORDS: Phoshodiesterase inhibitors; Pyridazines; synthesis; docing.

Introduction

The key role of cyclic nucleotides in regulating the function of airway smooth muscles, inflammatory cells and immune cells is well established. cAMP is the key secondary messenger that both mediates airway smooth muscle relaxation and exerts a broad inhibitory effect on the immune and inflammatory cells1-8. The intracellular concentration of cAMP can be elevated by stimulation of adenyl cyclase (which increases the rate of synthesis of cAMP) or by inhibiting cyclic nucleotide phosphodiesterase(PDEs) to decrease the rate at which cAMP is metabolized7-10.

Cyclic nucleotide PDEs comprise a family of distinct cell-associated isoenzymes that inactivate cAMP or cyclic 3’,5’-guanosine monophosphate (cGMP) by catalyzing hydrolysis of the 3’-phosphodiester bond to form the corresponding inactive 5’-nucleotide products7-10. Of the seven PDE isoenzymes isolated to date, cAMP-specific PDE (PDE4) is abundant in nearly all immune and inflammatory cells and airway smooth muscles11-18. Thus by inhibiting this isoenzyme, the cAMP levels can be elevated in pulmonary smooth muscles and inflammatory cells which leads to bronchodilation and anti-inflammatory effects in patients with asthma.

In our present work, we have synthesized a novel series of 7-(substituted phenyl)-8,9-dihydro-2H-pyridazino[6,1-c][1,2,4]triazin-3(4H)-ones and 7-(substituted phenyl)-2H-pyridazino[6,1-c][1,2,4]triazin-3(4H)-ones as per scheme. As the binding affinity studies between ligands and their receptors form the basis of physiological activity and pharmacological effects of chemical compounds19, our present study attempts to explore the pharmacological benefits by using molecular docking studies on PDE4 enzyme.

Chemistry

A series of 7-(substituted phenyl)-8,9-dihydro-2H-pyridazino[6,1-c][1,2,4]triazin-3(4H)-ones and 7-(substituted phenyl)-2H-pyridazino[6,1-c][1,2,4]triazin-3(4H)-ones were prepared as per scheme. The Friedel Craft acylation of aromatic hydrocarbons with succinic anhydride afforded the β-substituted benzoyl propionic acids in presence of lewis acid, aluminum chloride. Thus formed β-benzoyl propionic acid on reaction with hydrazine hydrate gave 6-aryl 4,5-dihydro pyridazin-3(2H)-ones. These pyridazinones were subjected to N-2-alkylation followed by cyclization with hydrazine hydrate to yield final compounds VIa-e(scheme).

6-(substituted phenyl) 4,5-dihydro pyridazin-3(2H)-ones were subjected to dehydrogenation with chloranil and the resulted 6-aryl pyridazin 3(2H)-ones were subjected to alkylation followed by cyclization to obtain final compounds IXa-e (scheme).

Experimental Section: Pyridazin[6,1-C][1,2,4] Triazines

General procedure for synthesis of 6-(substituted phenyl)4,5- dihydro Pyridazin 3(2H)-ones: To stirred solution containing mixture of aromatic hydrocarbon (2.25 moles) and succinic anhydride (0.34 moles), aluminum chloride (0.75 mole) was added in small portions over a period of 30 minutes at temperature below 10 °C and refluxed for 1 hour. The resulting solution was poured into