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RESEARCH ARTICLE

STRUCTURE BASED RATIONAL DRUG DESIGN OF SELECTIVE PHOSPHODIESTERASE-4 LIGANDS AS ANTI-INFLAMMATORY MOLECULES

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Phosphodiesterase-4 enzyme (PDE4) has been gaining increasing attention for the last two decades as a pharmacotherapeutic target, as it is involved in the etiology of a variety of pathologies that comprise a majority of inflammation problems concerning respiratory pathway in major aspect. Intense efforts have been directed towards the development of effective and selective PDE4b inhibitors, but not much success has been reported till yet. This is because of the structural similarity between the two isoforms of PDE4, PDE4b (therapeutic effect) and PDE4d (side effect of emesis). Analogues of 1,2-dihydroxy-xanthen-9*H*-one were designed as selective ligands for PDE4b using the structure based drug design. The selectivity was determined by docking of xanthone analogues in PDE4b and PDE4d active sites respectively using GLIDE docking programme from Schrodinger Inc. ADME properties of the designed ligands were also predicted using QikProp from Schrodinger Inc. Interpretation of protein-ligand interactions and binding modes of xanthone analogues showed that these ligands are more selective for PDE4b than for PDE4d.

Key words: PDE-4 (phosphodiesterase-4), Drug design, Molecular docking, ADME prediction.

INTRODUCTION

Type 4 c-AMP-specific phosphodiesterase (PDE4) is an enzyme responsible for the hydrolysis of the second messenger c-AMP to AMP in many cell types. Inhibition of this enzyme can significantly increase the intracellular c-AMP concentration, leading to major alterations in cell biochemistry and function. In particular, some inflammatory processes can be attenuated with PDE4 inhibitors. For example, LPS (lipopolysaccharides)-stimulated TNF-R (tumour necrosis factor-R) release in human blood mononuclear cells can be blocked with PDE4 inhibitors (Jin and Conti, 2002). Antigen-induced bronchospasm is another pharmacological event that can be attenuated using PDE4 inhibitors (Macdonald *et al* 2000).

The two isoforms of PDE4 *i.e.* PDE4b and PDE4d closely resemble each other (80%). Among the active site residues of PDE4b Glu413, His278, Asp275, Glu304, His274, Asp392, His238, Gln443, Gly280, His234, Phe414, Met411 and Gln417 are absolutely conserved residues in the two isoforms which play active role in getting hydrophobic and H-bond interaction with the ligand. Inhibition of PDE4b is responsible for the therapeutic effect while that of PDE4d for the side effects (Burnouf *et al* 1998). So to overcome those side effects it is needed to come up with specific inhibitors of PDE4b.

The proposed work consists of PDE4b, as the potential target for anti inflammatory molecules. The aim is to utilize the *in silico* techniques to design selective ligands for PDE4b, targeting