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RESEARCH PAPER

INDOLIZINE DERIVATIVES AS PHOSPHODIESTERASE IV INHIBITORS: DEVELOPMENT AND VALIDATION OF PHARMACOPHORE MODELS

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The challenges of drug discovery are largely overcome by computer aided designing and among various drug designing techniques, ligand based drug designing proves to be an effective one. Looking at the usefulness, in the present investigation ligand-based pharmacophore models has been developed by analyzing common chemical features of phosphodiesterase IV (PDE4) inhibitors. A dataset of 38 indolizine derivatives was selected in order to built pharmacophore models which were developed by using pharmacophoric features *viz.* hydrogen bond acceptor (A) and aromatic ring (R). In order to build up a statistically significant model, ARRRR.30 hypothesis was selected among different developed hypothesis with a R^2 value 0.880. The selected hypothesis ARRRR.30 was further validated by performing external validation on a test set where R^2 was found to be 0.804 (between experimental and predicted activity). The developed model could be an efficient tool to develop new PDE4 inhibitors.

Key words: Indolizine; Phosphodiesterase IV inhibitors; QSAR; Rational Drug Design; Pharmacophore.

INTRODUCTION

Recognition of cyclic adenosine monophosphate (cAMP) as second messenger (Sutherland *et al* 1968), can be considered as an important discovery as cAMP mediates a wide range of cellular processes (Gloerich and Bos, 2010; Hofer and Lefkimmiatis, 2007) *viz*. inflammation (Moore and Willoughby, 1995), T-cell proliferation (Muñoz *et al* 1990), cardiac actions (Haikala *et al* 1997), CNS activity (Han *et al* 2006) etc. The control over cAMP is an important area where research is under progress in order to have potent drug against different ailments.

Phosphodiesterases (PDEs) regulates cAMP and cyclic guanosine monophosphate (cGMP) levels in cells and further catalyze their degradation into AMP and GMP, respectively (Chen *et al* 2011). Role of PDE4 isozyme in cAMP degradation which in turn mediates key inflammatory cytokines is widely recognized (Bäumer *et al* 2007; Oger *et al* 2005) and considering the fact that PDE4 inhibitors played an important role in ailments like inflammation, Alzheimer's disease, Parkinson's, asthma etc. (Castro *et al* 2005; Banner and Trevethick, 2004; Jeffery, 2005; O'Donnell and Zhang, 2004; Spina, 2004; Houslay *et al* 2005). Chen and coworkers (Chen *et al* 2011) designed and synthesized a series of novel indolizine-2-oxoacetamides as PDE4 inhibitors.

Different heterocyclic derivatives like pyrazole, quinoline, furan, indolizine etc. were designed in recent past as PDE4 inhibitors and availability of