RESEARCH ARTICLE

PHARMACOPHORE MODELING STUDIES ON XANTHONES AS MONOAMINE OXIDASE-A INHIBITORS

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Pharmacophore mapping studies were undertaken for a set of 42 xanthone as monoamine oxidase-A inhibitors. Five point pharmacophores with three hydrogen bond acceptor, and two aromatic ring as pharmacophoric features were developed. Amongst them the pharmacophore hypothesis AAARR1 yielded a statistically significant 3D-QSAR model with 0.81 as R-square value and was considered to be the best pharmacophore hypothesis. The developed pharmacophore model was externally validated by predicting the activity of test set molecules. The squared predictive correlation coefficient of 0.79 was observed between experimental and predicted activity values of test set molecules. The geometry and features of pharmacophore were expected to be useful for the design of selective MAO-A inhibitors.

Key words: Xanthone, Monoamine oxidase-A, Pharmacophore hypothesis, Regression coefficient.

INTRODUCTION

Monoamine oxidases (MAOs), widely distributed in all living organism, are flavin adenine dinucleotide cofactor covalently linked to a cysteine residue in the active centre (Santana *et al* 2006), containing enzymes present in the outer mitochondrial membranes of neuronal, glial and other cells (Chimenti *et al* 2008). MAO exists in two isoforms: MAO-A and MAO-B, differing in their substrate preferences, inhibitor selectively, tissue distribution, molecular genetics (Gallardo-Godoy *et al* 2005) and amino acid sequence (Chimenti *et al* 2004). MAO-A metabolize the principal biogenic amines, serotonin (Chimenti *et al* 2007), epinephrine and nor-epinephrine and MAO-B mainly acting on dopamine, *β*-phenylethylamine and benzylamine (Mai *et al* 2002). MOA-A is selectively inhibited by clorgyline (Medvedev *et al* 1996) and moclobemide (Medvedev *et al* 1998) and MAO-B is selectively inhibited by selegiline (Silvestri *et al* 2003). MAO-A and MAO-B have essential roles in vital physiological processes and are involved in the pathogenesis of various human disease. The MAO inhibitors are used for the treatment of psychiatric and neurological disorders (Regina *et al* 2007). Selective MAO-A inhibitors are currently used for treating neurological disorders such as anxiety (Pacher *et al* 2001) and depression (Binda *et al* 2008), while selective inhibitors of the B isoform are administered alone or together with Levo-DOPA for the treatment of Parkinson's syndrome (Sant *et al* 2005; Kalgutkar *et al* 1994) and Alzheimer's disease (Hubalek *et al* 2004). In the last decade, remarkable progress in computer technology has allowed us to perform complex computational operations in a feasible and even interactive time frame. Among such operations, pharmacophore modeling is successfully used in drug discovery. A pharmacophore model consists of a 3D arrangement of a collection of features necessary for the biological activity of the ligands (Roy *et al* 2010). These models are hypothesis on the 3D arrangement