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DEVELOPMENT OF QSAAR, PHARMACOPHORE MODELS AND DOCKING ANALYSES FOR EXPLORING SELECTIVITY OF PPAR MODULATOR SUBTYPES

Ashis Nandy[1], Kunal Roy[2] and Achintya Saha[1]

[1]University of Calcutta, India
[2]Jadavpur University, India

The peroxisome proliferator-activated receptor (PPAR), a subfamily of the neuclear receptor, is involved in regulation of metabolism, inflammation, and cell differentiation. The molecular and physiological role of three isoform (PPAR , and) receptors has become extremely important to develop of new drug to treat metabolic disorder. In the present study, quantitative structure activity-activity relationship (QSAAR) has been performed to investigate the presence of any correlation among the subtypes' activity. Pharmacophore models and molecular docking analyses have been performed to provide an idea about the pharmacophoric features in 3D space and identify the involvement of catalytic residues on subtypes' modulation. The QSAAR models recommend that presence of a tertiary N- atom attached with one aryl and two aliphatic moieties, and trifluro methyl have beneficial effect for PPARα modulation. Presence of alkyl halide has detrimental effect on the γ subtype modulation. The aliphatic ether linkage has also detrimental effect on the δ activity. The pharmacophore model for α subtype suggests four pharmacophoric features (2xH, NI and RA) are mainly responsible for its selectivity, whereas five different pharmacophoric features (HBA, 2xH, AlipH and NI) are liable for modulation of δ subtype, but for γ subtype only four features (H, 2xAlipH and RA) have been accounted for selective modulation (Figure 1). The NI feature of pharmacophore models for α and δ modulator, mapped with COOH group in the compound, is mainly responsible for H-bond interaction with the catalytic residues of the active site of the α and δ receptors, respectively. Essential structural features have been explored for each subtypes of PPAR to raise the selectivity issue for designing new modulators with improved activity/selectivity.

pharma.ashis@gmail.com

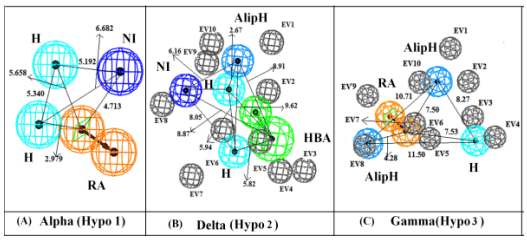

Figure 1: The pharmacophoric features of three subtypes of PPAR modulators