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Exploring Quantitative Structure-Activity Relationships (QSARs) for Urea-Based Dual FAAH and sEH Inhibitors

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ABSTRACT

Several urea-based compounds have been reported as dual inhibitors of fatty acid amide hydrolase (FAAH) and soluble epoxide hydrolase (sEH) enzymes which have potential as anti-inflammatory and antinociceptive agents. QSAR studies were performed on the urea analogs to identify the molecular descriptors influencing the FAAH and sEH inhibitory activity using small dataset modeler tool. Molecular descriptors (1D &2D) were computed using PaDEL-descriptor software. A set of 48 compounds was used in the present study. Statistically significant models were derived for both the enzymes [pIC50 (sEH): R2 = 0.797, Q2 = 0.762 and Q2F1 =0.747; pIC50 (FAAH): R2 = 0.642, Q2 = 0.521 and Q2F1 =0.566]. The results of QSAR on the sEH enzyme revealed the contribution of topological charge indices, ionization potential, and the number of nitrogen atoms (naaN) for defining the potency. Polarizability showed a major influence on FAAH inhibition. The predictive ability of the QSAR models was established based on the dual inhibitory potential of some newly designed molecules.

KEYWORDS

DTC Lab, FAAH Enzyme, QSAR, sEH Enzyme, Urea-Based Compounds

1. INTRODUCTION

A well-validated QSAR model guides medicinal chemists to analyze the effect of molecular features on biological activity, as well as in the design and the activity prediction of newer analogs (Maltarollo et al, 2017, Neves et al, 2018). QSAR techniques are proven strategies to reduce animal experimentation requiring cumbersome ethical obligations. Several drugs such as Zanamavir, Imatinib, Nolatrexed, Ipconazole, and Metconazole were developed based on outputs of the QSAR studies. QSAR models have been derived for several enzyme inhibitors such as esterase, methyltransferase, acyltransferase, monoamine oxidase, glycosidase, and angiotensin-converting enzymes, etc. (Gupta, 1987, Wang et al,

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2011). QSAR models aid in the lead optimization, hit identification and also assess pharmacokinetic, pharmacodynamic, and toxicity endpoints in the drug discovery process (Patel et al, 2014).

Fatty acid amide hydrolase (FAAH) is crucial for the endocannabinoid hydrolysis, anandamide. The endocannabinoid system remains an attractive target for anti-inflammatory and analgesic therapeutics. It maintains physiologic homeostasis through the cannabinoid receptors (CB1 and CB2) activated primarily by two endocannabinoids, arachidonoyl ethanolamine (AEA) or anandamide and 2-arachidonoyl glycerol. Inhibition of FAAH has been efficacious in numerous experimental rodent models of inflammatory and neuropathic pain with no functional impairment (Labar & Michaux, 2007, Ahn et al, 2009). The activity of N-palmitoyl ethanolamine (PEA), a lipid signaling molecule with nociception is also regulated by the FAAH enzyme. Hence, FAAH may represent an attractive therapeutic target for treating pain and inflammation. FAAH enzyme activity can be blocked reversibly or irreversibly by chemical groups including carbamates, substituted ureas, propane-2-ones, amides, aryloxyacetamides, oleolylethanolamides, and isoxazole derivatives (Tripathi, 2020, Ren et al, 2020).

Soluble epoxide hydrolase (sEH) is related to the epoxide hydrolase family. Through the metabolism of epoxyeicosatrienoic acids (EETs) and other lipid mediators, sEH plays a role in several diseases, including hypertension, cardiac hypertrophy, arteriosclerosis, pain, inflammation, and cancer (Zhang et al, 2013, Inceoglu et al, 2007). The production of epoxy acids from sEH can be inhibited by amides, carbamates, thioureas, and sulfonamide functionalities. Dual inhibition of FAAH and sEH enzymes showed a synergistic effect on nociceptive pathways (Pecic et al, 2013, Pecic et al, 2018).

Several urea-based compounds have been reported as dual inhibitors of FAAH and sEH enzymes which have potential as anti-inflammatory and antinociceptive agents (Fig 1). 3D-QSAR studies on piperazine carboxamides revealed the importance of hydrogen bond donor ability to increase the potency of FAAH inhibitors (Lorca et al, 2019). Zeiba et al derived COMFA and COMSIA models using a set of thirty-one 1, 3, 4-oxadiazole-2-one based FAAH inhibitors and also mentioned the importance of electrostatic and hydrogen bond donor properties to design potent FAAH inhibitors (Zieba et al, 2021). QSAR analysis of urea analogs revealed the importance of molecular descriptors like electronegativity and the presence of heteroatoms, multiple bonds for potent sEH inhibitory activity (Nazari et al, 2019). N, N$^{'}$-disubstituted urea compounds possess dual inhibitory activity on FAAH and sEH enzymes, but the potency is governed by substitution pattern on the nitrogen atoms of urea moiety. Because of the above, to investigate the molecular features that favor potency towards FAAH or sEH enzymes, QSAR analysis is performed on forty-eight urea-based compounds using DTC tools (Software tools).

2. MATERIAL AND METHODS

2.1 Computational Tools

Several well-known software tools namely PaDEL-Descriptor software, basic QSAR modeling software provided by Drug Theoretics and Cheminformatics (DTC) tools including V-WSP version

Figure 1. Urea-based compounds as dual inhibitors of FAAH and sEH enzymes