Cyclopropyl urea derivatives as potent soluble epoxide hydrolase inhibitors for potential decrease of renal injury without hypotensive action: A pharmacophore analysis

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Abstract:
In the present work, pharmacophore modeling for cyclopropyl urea derivatives as potent soluble epoxide hydrolase inhibitors for potential decrease of renal injury without hypotensive action has been accomplished to rationalize the pharmacophoric characteristics. The analysis comprises the comparison of pharmacophore model of most and least active molecules of the series. The analysis is successful in developing the structure-activity associations.

Keywords:
Pharmacophore modeling, hydrolase inhibitors, urea derivatives

Introduction:
Epoxyeicosatrienoic acids (EETs), which are produced from arachidonic acid by CYP 2C and CYP 2J in four distinct regioisomers due to oxidation, are biologically metabolized via numerous paths by soluble epoxide hydrolase (sEH). Therefore, an advantageous approach for the treatment of certain cardiovascular events involves keeping high blood EETs levels by inhibition of sEH [1-2].

Pharmacophore modeling is highly successful computer based modern technique for establishing the pharmacophore-activity relationships. It is an inexpensive, relatively simple and popular technique. In the present work, in silico analysis involving pharmacophore modeling was performed for cyclopropyl urea derivatives as potent soluble epoxide hydrolase inhibitors for potential decrease of renal injury without hypotensive action.
Experimental methodology [2-6]:

A library of NTF1836 and its thirty-nine analogues synthesized and evaluated for inhibitors of the mycothiol biosynthetic enzyme MshC in growing and non-replicating Mycobacterium tuberculosis [1] has been used for the present work. The structures were drawn using ChemSketch 12 freeware followed by optimization using MMFF94 force field in TINKER. The optimized structures were aligned using Open3dAlign software. The aligned structures were imported in PyMol 1.7 for pharmacophore modeling using the default settings [3-7].

Results and discussion:

The pharmacophore model for maximal and least active has been compared and showed in figure 2. From figure 2, it is visible that the two molecules have noteworthy variance in their pharmacophore model.

![Least active molecule](image1.png)

![Most active molecule](image2.png)

Conclusion:

In conclusion, the pharmacophore analysis reveals that the additional H-bond acceptor and hydrophobic region in most active molecule has significant influence and correlation with the activity.
References:


