23. A Consensus Pharmacophoric Pattern for Benzimidazolecarboxylic Acid Derivatives as Human Prostaglandin E2 Receptor Subtype 4 (hEP4-R) Antagonists

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Abstract

Human Prostaglandin E2 Receptor Subtype 4 (hEP4-R) antagonists are important compounds to combat inflammation and pain. To develop compounds having high selectivity for hEP4-R could be achieved by identifying a consensus pharmacophoric pattern using congeneric antagonists. Consequently, in this work, such a pattern has been identified using Benzimidazolecarboxylic Acid derivatives. The analysis reveals that the activity profile is linked to three lipophilic, one H-Bond donor and four H-bond acceptor groups. The results are highly robust and could be used by medicinal chemists to develop a better Benzimidazolecarboxylic Acid derivative possessing better activity and selectivity.

Keywords: Pharmacophore modeling,Benzimidazolecarboxylic Acid, Human Prostaglandin E2 Receptor Subtype 4, hEP4-R

Introduction

Prostaglandin E_2 receptor 4 (EP_4) is a prostaglandin receptor and plays a critical role in postnatal closure of the ductus arteriosus, inflammation, lipid metabolism[1-3]. Therefore, search for a selective antagonist forhEP4-R is in progress. Recently, Bäurleet al [1] reported Benzimidazolecarboxylic Acid Derivative (BAY 1316957)for their activity and selectivity for

hEP4-R. Some of the BAY 1316957 derivatives were reported to be active in nano and sub-nano molar level. Although, Bäurleet al [1] describedSAR (Structure-Activity Relationships) in good details, however no attempt was instigatedby them to generate a consensus pharmacophore model. Therefore, the present work isintended to attain development of such pharmacophore model.

Experimental Methodology [4-6]:

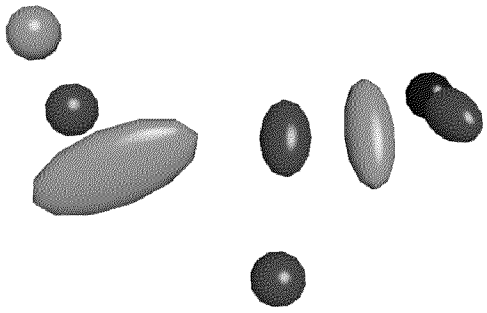
1. Selection of Dataset: The consensus pharmacophore model is developed using a dataset of 39 molecules[1]. The molecules were screened for their activity and selectivity for hEP4-R. The activity values(IC_{50} expressed as nM) were used to find most active molecules. The Table 1 contains top active molecules used for model building.

Table 1. SMILES notations and activity values IC_{50} (nM)for top five molecules used for alignment

S.N.	SMILES	IC_{50} (nM)
1	CCn1c2ccc(cc2c3cccc(C)c13)c4nc5c(C)c(ccc5n4CCOC)C(=O)O	4.2
2	CCn1c2ccccc2c3cc(ccc13)c4nc5c(F)c(ccc5n4CCOC)C(=O)O	4.3
3	CCn1c2ccc(Cl)cc2c3cc(ccc13)c4nc5c(C)c(ccc5n4CCOC)C(=O)O	4.4
4	CCn1c2ccccc2c3cc(ccc13)c4nc5cc(ccc5n4CCOC)C(=O)O	4.7
5	CCn1c2ccc(cc2c3cccc(Cl)c13)c4nc5c(C)c(ccc5n4CCOC)C(=O)O	5.2

2. Development of model: The entireprocedure is based on four main steps:

- Structure drawing: The task of structure drawing was accomplished using ChemSketch 12 freeware.
- Structure optimization: In second step, Avogadro 2 was employed to optimize the 3D-structure of thirty-nine BAY 1316957 derivatives using semi-empirical method (MMFF94).
- Alignment of molecules: This step was accomplished using Open3Dalign.



Model generation: Lastly, top five active aligned molecules were introducedinPyMOL 2.0. Then,PyMOL plugin 'LIQUID' was employed to generateconsensus model using default settings.

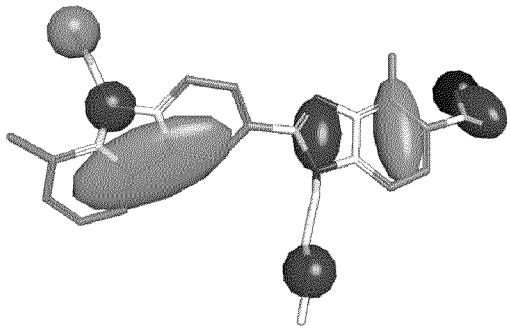


Figure 1. Consensus pharmacophore model with and without molecule and contours for different regions (Green: Lipophilic, Blue: H-Bond donor and Red: H-Bond acceptor region)

Result and Discussions

The present pharmacophore-orientedanalysis unveils that the hEP4-Rinhibitory activityof molecules selected in the present work has goodcorrelation with three lipophilic, one H-Bond donor and four H-bond acceptor groups.

A closure inspection of figure 1 reveals that hEP4-R inhibitory activity of BAY 1316957 derivatives is due to lipophilic nature of tricyclic ring and aromatic ring fused with imidazole ring. The nitrogen atoms of imidazole ring act as H-bond acceptor. The -CH2-CH3 group attached to nitrogen of tricyclic ring contributes as a lipophilic part. Therefore, a good strategy to retain the activity is to give good importance to these regions.

Conclusions

The hEP4-R inhibitory activity of BAY 1316957 derivativeswhich is associated with the presence of imidazole and aromatic ring fused to it, tricyclic ring as well as with the -CH2-CH3 group attached to nitrogen of tricyclic ring, hencesuch a combination of these moieties must be retained in future optimization to have good activity. The present study was effective in discovering useful structural features for future optimizations.

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