26. Identifying the Recurring Pharmacophoric Pattern for Trypanosoma Cruzi Inhibitoryactivity of 6-Nitro-2,3-Dihydroimidazo[2,1-b][1,3] Oxazoles

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Abstract

6-Nitro-2,3-dihydroimidazo[2,1-b][1,3]oxazoles have gained attention as a anti-tubercular agents. Recently, they were screened for activity against Trypanosoma cruzi. In the present work, we have developed consensus pharmacophore model using highly active 6-Nitro-2,3-dihydroimidazo[2,1-b][1,3]oxazoles for Trypanosoma cruzi. The results indicate that the activity has strong correlation with H-bond acceptor and lipophilic features. The results could be beneficial for developing an optimized 6-Nitro-2,3-dihydroimidazo[2,1-b][1,3]oxazole derivative with better activity profile.

Keywords: Pharmacophore modeling, 6-Nitro-2,3-dihydroimidazo[2,1-b][1,3]oxazoles, Trypanosoma cruzi

Introduction

Trypanosoma cruzi is causative agent for Chagas disease (or American trypanosomiasis) in humans, dourine and surra in horses, and a brucellosis-like disease in cattle. Chagas disease, spread mostly by insects known as Triatominae, or "kissing bugs", has high occurrence in undeveloped and developing countries and considered as neglected disease. Generally, benznidazole or nifurtimox are used as medication, but emergence of resistant for these drugs and need of a better drug with minimum or no side effects is yet to be achieved [1-3]. Recently, Thompsonet al [1-3] reported 6-Nitro-2,3-dihydroimidazo[2,1-b][1,3]oxazoles as effective

agents against T. Cruzi. Even though, extensive SAR (Structure-Activity Relationships) were discussed, but no attempt was made to develop a consensus pharmacophore model. The aim of present work is to accomplish development of such pharmacophore model.

Experimental Methodology [4-6]:

1. **Selection of Dataset:** In the present work, a dataset of 241 molecules was used for developing the consensus model [1-3]. The dataset consists of stereo, positional and functional isomers of 6-Nitro-2,3-dihydroimidazo[2,1-b][1,3]oxazoles. A variety of substituents has broadened the chemical space of the dataset. The reported activity value (IC_{50} in μM) were used to identify most active molecules. The Table 1 contains top active molecules used for model building.

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

SN	SMILES	T.cruzi IC_{50} (μM)
1	FC1=CC(C(C=N2)=CC=C2CO[C@H]3COC4=NC([N+]([O-])=O)=CN4C3)=CC=C1OC(F)(F)F	0.025
2	FC(N=C1)=CC=C1C(C=C2)=CC=C2OCC3OC4=NC([N+]([O-])=O)=CN4CC3	0.027
3	FC(C=C1)=CC=C1C(C=N2)=CC=C2OCC3OC4=NC([N+]([O-])=O)=CN4CC3	0.027
4	FC(C=C1F)=CC=C1C(C=N2)=CC=C2OCC3OC4=NC([N+]([O-])=O)=CN4CC3	0.03
5	O=[N+]([C1=CN2C(OC[C@H]3OCC3=CC=C(C4=CC=C(OC(F)(F)F)C=C4)C=N2)=N1)[O-]	0.043

2. **Development of model:** For model, the structures of molecules were drawn using ChemSketch 12 freeware. The, Avogadro 1.1 was used to optimize the molecules, followed by optimization using Open3Dalign. For modeling purpose, top five active molecules were aligned and imported to PyMOL 2.2. The PyMOL plugin 'LIQUID' was used to derive final model.

Result and Discussions: The present analysis reveals that the activity has correlation with lipophilic and H-Bond acceptor features of the present set molecules. The final pharmacophore model has been depicted in figure 1.

Figure 1 Common pharmacophore model with and without molecule and contours for different regions (Green Lipophilic and Red H-bond acceptor)

From Figure 1, it is evident that activity varies with three H-bond acceptor and one large lipophilic region. The three H-bond acceptor contours are present in ring A and B, whereas the lipophilic region extends across ring C to D. These regions must be preserved in future to have good activity.

Conclusions

The activity has good association with lipophilic and H-bond acceptor features, which must be retained for retaining activity. The present analysis was successful in identifying useful features for future optimizations.

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