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A Pharmacophoric Pattern for 6-Nitro-2,3-Dihydroimidazo [2,1-B][1,3]Oxazoles for Leishmania Infantum

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ABSTRACT

The present work is a first ever attempt to identify a common pharmacophoric pattern for *Leishmania infantum* inhibitory activity of 6-Nitro-2,3-Dihydroimidazo [2,1-b][1,3]oxazole derivatives. The dataset used in this work covers a wide chemical space and contains 224 molecules. The analysis reveals that the activity has link with the presence of nitro group, imidazole and oxazole rings. The results of present analysis could be useful to develop a better derivative of 6-Nitro-2,3-Dihydroimidazo [2,1-b][1,3]oxazole having augmented activity against *Leishmania infantum*.

Keywords: modeling,6-Nitro-2,3-Dihydroimidazo [2,1-b][1,3]oxazole, *Leishmania infantum*

I. INTRODUCTION

It is an established fact that *Leishmania infantum* (*L.Inf.*) is the causative agent of infantile visceral leishmaniasis (kala-azar), a fatal disease, if left untreated. It is a neglected disease and also known as *Leishmania chagasi.* The emergence of resistant against existing marketed drugs have been reported. Therefore, a fresh quest for a new drug for this disease is essential [1-3]. Recently, Thompson*et al* [1-3] screened 6-Nitro-2,3-Dihydroimidazo [2,1-b][1,3]oxazolefor their *Leishmania infantum* inhibitory activity.Some of the tested compounds are found to be active in micro and sub-micro molar level. Although, Thompson*et al* [1-3] describedexhaustive and varied SAR (Structure-Activity Relationships), but no attempt was implemented by them to develop a consensus pharmacophore model. Hence, the present work isdesigned to achieve development of such pharmacophore model.

II. EXPERIMENTAL METHODOLOGY [4-6]

1. Selection of Dataset: The development of consensus pharmacophore model is based on a dataset of 224 molecules [1-3]. The selected dataset comprises stereo, positional and functional isomers, thus covering a broad chemical space. The molecules were screened for their *Leishmania infantum* inhibitory activity. The activity

values(IC_{50} expressed as μM) 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} (μM)for top five molecules used for alignment

S.N.	SMILES	L. inf IC_{50} (μM)
1	FC(C=C1)=CC=C1C(N=C2)=CC=C2OCC3CN4C(O3)=NC([N+]([O-])=O)=C4	0.03
2	FC(C=C1)=CC=C1C(N=C2)=CC=C2OC[C@@H]3CN4C(O3)=NC([N+]([O-])=O)=C4	0.03
3	FC(C=C1F)=CC=C1C(N=C2)=CC=C2OCC3OC4=NC([N+]([O-])=O)=CN4CC3	0.03
4	FC(C=C1F)=CC=C1C(C=N2)=CC=C2OCC3OC4=NC([N+]([O-])=O)=CN4CC3	0.037
5	O=[N+](C1=CN2C(OC(COC3=CC=C(OC(F)(F)F)C=C3)CC2)=N1)[O-]	0.047

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

1. Structure drawing: The structures of 224 molecules were drawn using ChemSketch 12 freeware.
2. Structure optimization: in second step, Avogadro 1.1 was used to optimize the 3D- structure of all the molecules using semi-empirical method (MMFF94).
3. Alignment of molecules: This step was accomplished using Open3Dalign.
4. Model generation: Finally, top five active aligned molecules were introducedinPyMOL 2.0. Then,PyMOL plugin 'LIQUID' was employed to createconsensus model using default settings.

III. RESULT AND DISCUSSIONS

The present *in-silico*analysis discloses that the *Leishmania infantum* inhibitory activityof molecules used in the present work has strong correlation with nitro group on imidazole ring and oxazole ring.The developed consensus pharmacophore model has been shown in figure 1.

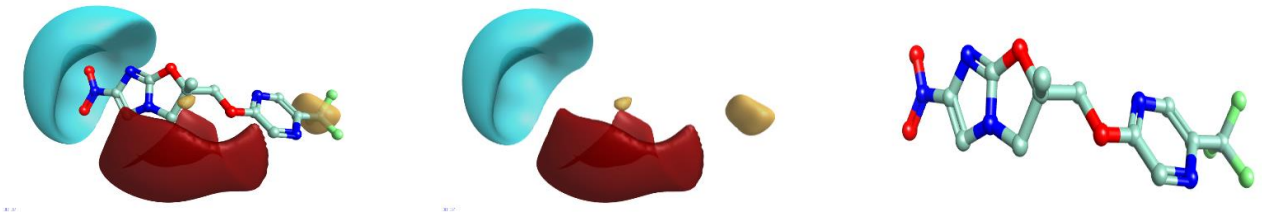

Figure 1. Consensus pharmacophore model with and without molecule and contours for different regions (Yellow: Lipophilic, Blue: negative and Red: positively charged region)

A simple analysis of figure 1 reveals that *Leishmania infantum* inhibitory of 6-Nitro-2,3-Dihydroimidazo [2,1-b][1,3]oxazoles is influenced by the negatively charged region due to the nitro group attached to imidazole ring and a big positively charged region due to oxazole ring. It also varies with a small lipophilic region near to aromatic ring. Therefore, a good strategy to retain the activity is to give good importance to these regions.

IV. CONCLUSIONS

The 6-Nitro-2,3-Dihydroimidazo [2,1-b][1,3]oxazoles have fascinating *Leishmania infantum* inhibitory which is associated with the presence of imidazole and oxazole rings as well as with the nitro group, such 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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