Pharmacophore modeling for second generation analogues of the cancer drug clinical candidate tipifarnib for anti-Chagas disease drug discovery

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Abstract:
Pharmacophore modeling for second generation analogues of the cancer drug clinical candidate tipifarnib for anti-Chagas disease has been carried out to determine the associated pharmacophoric features. The study comprises the assessment of pharmacophore model of most and least active molecules of tipifarnib and its analogues. The analysis is successful in establishing the structure-activity inferences.

Keywords:
Pharmacophore modeling, tipifarnib, anti-Chagas

Introduction:
The protozoan parasite, Trypanosoma cruzi (T. cruzi), is the causative agent for Chagas disease. Though, the disease is prevalent in developing countries from Africa and Latin America, its ill-effects are global. Although, nifurtimox and benznidazole are recommended drugs, their toxicity is associated with their mode of action, and treatment is inevitably accompanied by many adverse side effects [1,2]. Recently, Gelb et al [1] synthesized and assayed the cancer drug clinical candidate tipifarnib against causative agent of Chagas disease, Trypanosoma cruzi. The study revealed that tipifarnib blocks ergosterol biosynthesis at the level of inhibition of lanosterol 14α-demethylase. Yet, search for tipifarnib analogue with desired biological profile is still continuing.
Pharmacophore modeling is an inexpensive, very successful computer aided technique to institute pharmacophore-activity relationships. In the present work, pharmacophore modeling was employed to rationalize the pharmacophoric features that have correlation with the activity.

**Figure 1. Structure of anti-cancer and anti-chagas drug tipifarnib**

**Experimental methodology:**

A library of tipifarnib and its thirty-three analogues prepared and assessed for anti-Chagas activity[1] has been selected from literature for the present work. The structures were drawn using ChemSketch 12 freeware followed by energy 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 LIQUID plugin using the default settings [3-7].

**Results and discussion:**

The pharmacophore model for the most and least active has been compared and revealed in figure 2, as representatives. From figure 2, it is evident that the two representativemolecules have importantdifference in their pharmacophore model.
The most active compound possesses a triad of H-bond acceptor region, which is absent in least active molecule. In addition, the least active molecule has hydrophobic region in place of third H-bond acceptor region.

Conclusion:

The pharmacophore analysis unveils that the additional H-bond acceptor, which is a part of triad of H-bond acceptor regions in most active molecule has noteworthy effect and relationship with the activity.

References:

