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AcylAminoBenzothiazole Series as Inhibitors of Trypanosoma Cruzi : A Pharmacophore Modelling Approach

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Abstract: ***Modern drug designing incorporates smart use of computer-aided techniques like QSAR, Molecular docking, pharmacophore modelling, etc. In the present work, pharmacophore modelling has been accomplished for acylaminobenzothiazole series as inhibitors of Trypanosoma cruzi. The selected dataset consists of acylaminobenzothiazole derivatives having variety of substituents. The structures were drawn, optimized (MMFF94), aligned and later used to generate a robust consensus pharmacophore model. The results indicate that aromatic rings, H-bond donor/acceptor and lipophilic moieties govern the anti-Chagas activity of selected acylaminobenzothiazole derivatives. The results could be used for future optimization of acylaminobenzothiazole derivatives as Trypanosoma cruzi inhibitors.***

Keywords: Pharmacophore modelling, acylaminobenzothiazole derivatives, Trypanosoma cruzi, Chagas disease

I. INTRODUCTION

Chagas disease or sleeping sickness is a neglected disease with high occurrence in Western Africa, especially in Sub-Saharan region. The causative agent '*Trypanosoma cruzi*' (T. cruzi) is a protozoan kinetoplastid parasite [1-3]. This parasite gets transmitted to humans by an insect of the family *reduviidae*, commonly known as the 'kissing bug'. Unfortunately, there is no vaccine, and the existing available drugs, benznidazole and nifurtimox, were discovered decades ago [1-3]. The recent studies suggest that these drugs are inefficient to cure the disease for all patients due to emergence of resistance, inefficacy in chronically infected subjects, higher economical burden and long treatment duration. Therefore, there is a need to develop a new drug for this disease [1-3].

Recently, Fleau et al. [1] reported a good number of acylaminobenzothiazole derivatives as *Trypanosoma cruzi* inhibitors to cure Chagas disease. These newly synthesized and tested molecules revealed modlerate to excellent activity against *Trypanosoma cruzi*. But, future optimizations are required to achieve optimum ADMET (Absorption, Distribution, Metabolism, Excretion and Toxicity) profile to get a lead/drug candidate. While optimizing different parameters of ADMET, it is essential to retain structural features responsible for higher desired activity. Hence, knowing the pharmacophoric pattern and features could be beneficial in future optimizations [4-6].

II. EXPERIMENTAL METHODOLOGY [7-9]

1) *Selection of Dataset:* A crucial step to get successful pharmacophore model is to select appropriate dataset comprising stereo, positional and functional isomers. The present pharmacophore model is based on a dataset of 34 molecules [1] containing stereo, positional and functional isomers, thus representing a wide chemical space. The molecules were tested for their *T.cruzi* 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 four molecules used for alignment

S.N.	SMILES	T.cruzi IC_{50} (µM)
1	CCOc1ccc2nc(NC(=O)C3CC3)sc2c1	0.04
2	Clc1ccc2nc(NCC3CC3)sc2c1	0.079
3	Fc1ccc2nc(NC(=O)C3CC3)sc2c1	0.1
4	COc1cc2nc(NC(=O)C3CC3)sc2cc1C(F)(F)F	0.13
5	CCOc1ccc2nc(NC(=O)C3CC3)sc2c1	0.04

2) Development of Model: The methodology for the present work can be explained in four main steps [7-9]:

a) Structure drawing: The structures of 34 molecules were drawn using ChemSketch 12 freeware (www.acdlabs.com).

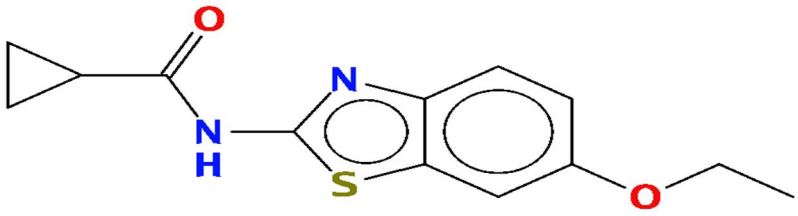
b) Structure minimization and optimization: then, Avogadro 1.2 was used to optimize the 3D- structure of all the molecules using semi-empirical method (MMFF94).

c) Alignment of active molecules: This phase was completed using Open3Dalign.

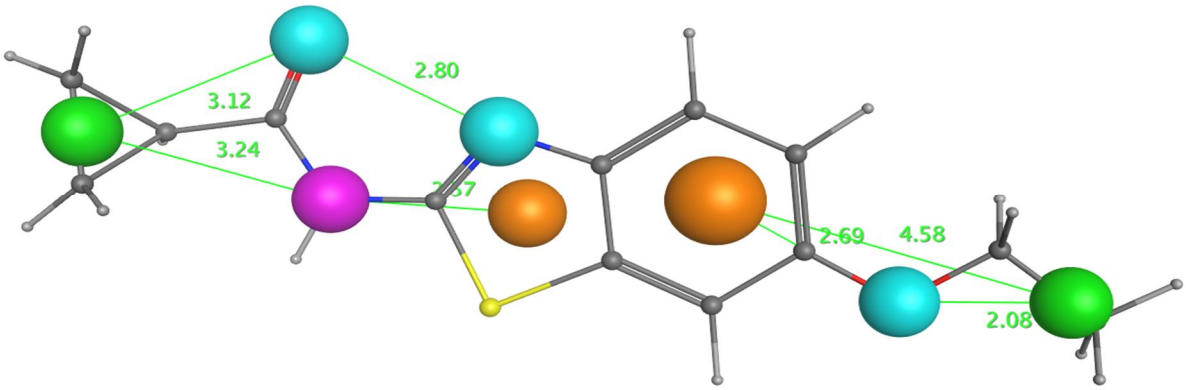
d) Model formation: Lastly, top four active aligned molecules were introduced in PyMOL 2.2, followed by generation of consensus pharmacophore model using LIQUID (a PyMOL plugin) using the default settings.

III. RESULTS AND DISCUSSION

The present work indicates that the pharmacophoric pattern for acylaminobenzothiazole derivatives as *Trypanosoma cruzi* inhibitors comprises H-bond donor/acceptor, aromatic rings and lipophilic regions. A broad aromatic region, three H-bond acceptors, one H-bond donor and two lipophilic regions are important parts of consensus pharmacophore model. The pharmacophore model has been depicted in figure 1.



(a)



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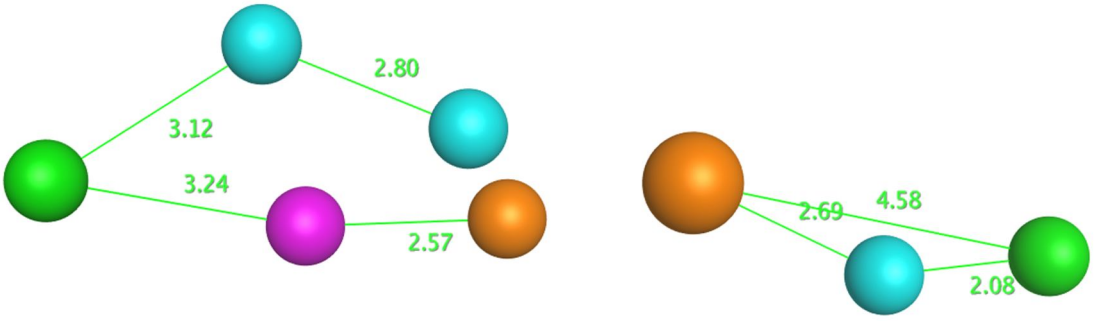

(c)

Figure 1. (a) 2d- representation of most active molecule 1 (b) 3D-representation of consensus pharmacophore patter using the most active molecule 1 (c) 3D-representation of consensus pharmacophore patter without the most active molecule 1 (Green: lipophilic, Cyan: H-bond acceptor, Purple: H-bond donor and Golden yellow: Aromatic region)

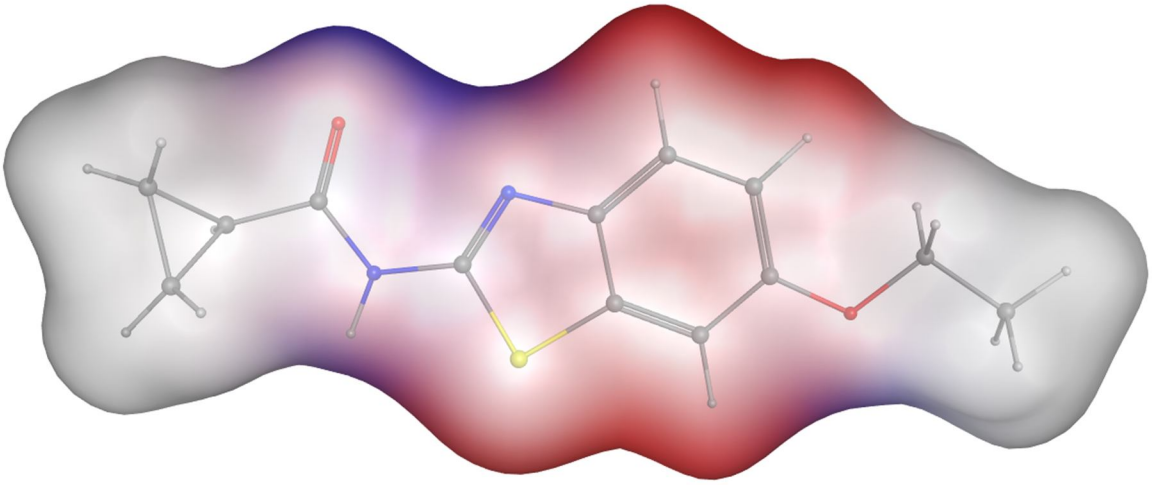

Figure 2. Molecular surface area for most active molecule **1** (Red: Polar, Blue: H-bond acceptor and White: lipophilic region)

In addition, molecular surface area was also analysed, which has been depicted in figure 2. A comparison of figure 1 and 2 indicates that pharmacophore modelling and molecular surface area analysis provided consensus and complementary results. Therefore, the results could be useful for lead/drug optimizations.

IV. CONCLUSIONS

The present work was thriving to identify important structural features useful for future optimizations of acylaminobenzothiazole derivatives as *Trypanosoma cruzi* inhibitors. The patterns identified by pharmacophore modelling and molecular surface area are beneficial in consensus.

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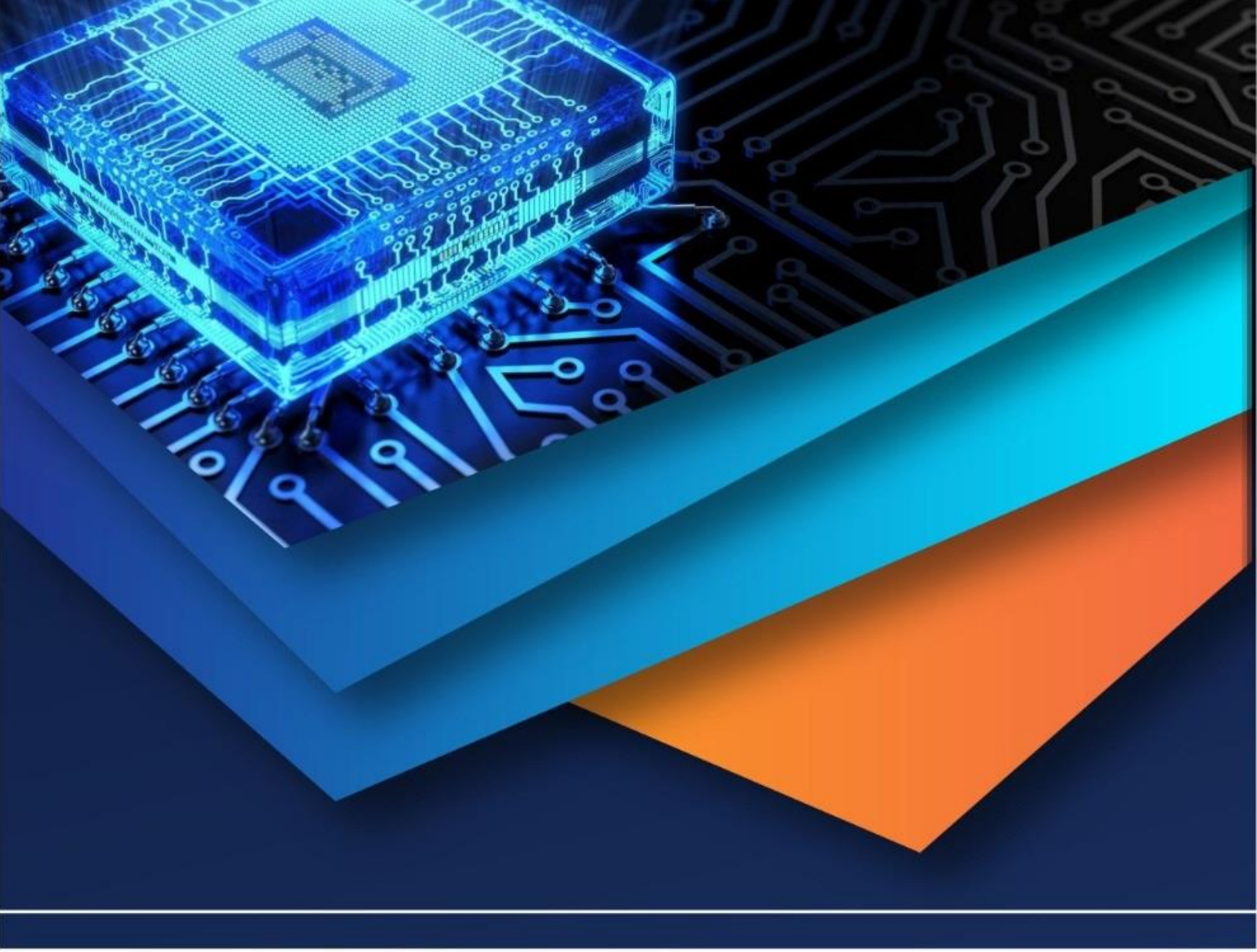

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