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In Silico Evaluation of Heterocyclic-2-Carboxylic Acid (3-Cyano-1,4-di-Noxidequinoxalin-2-yl)amide Derivatives of Experimental in vitro Trypanosoma cruzi

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Abstract: Chagas disease affects millions of peoples each year. In present study, we have determined pharmacophoric site and pattern which governs the anti-chagas activity of Heterocyclic-2-Carboxylic Acid (3-Cyano-1,4-di-Noxidequinoxalin-2-yl)amide Derivatives. The study using POM reveals that presence of charges due to N-H and –CN group affects the activity.

Introduction: *Trypanosoma cruzi* (TC) is responsible for Chagas disease. Chagas disease affects approximately 20 million peoples. Benznidazole (Bdz) and Nifurtimox (Nfx) have been two of the few most widely used anti-*Trypanosoma cruzi* (*TC*) drugs. The success of Bdz was mainly due to its outstanding clinical efficacy, and the slow speed at which resistance developed to this drug. But the side effects and the final arrival of resistance and the alarming spread of Bdz-resistant *TC* on a global scale created an urgent need for the development of novel *TC* drugs. So novel anti-Trypanosoma drugs are strongly and urgently needed in goal to be used as new drugs without side effects and multi-drug resistance.

In present work, we have determined the pharmacophoric pattern for some Heterocyclic-2-Carboxylic Acid (3-Cyano-1,4-di-Noxidequinoxalin-2-yl)amide Derivatives (figure 1) for *in vitro Trypanosoma cruzi activity*.

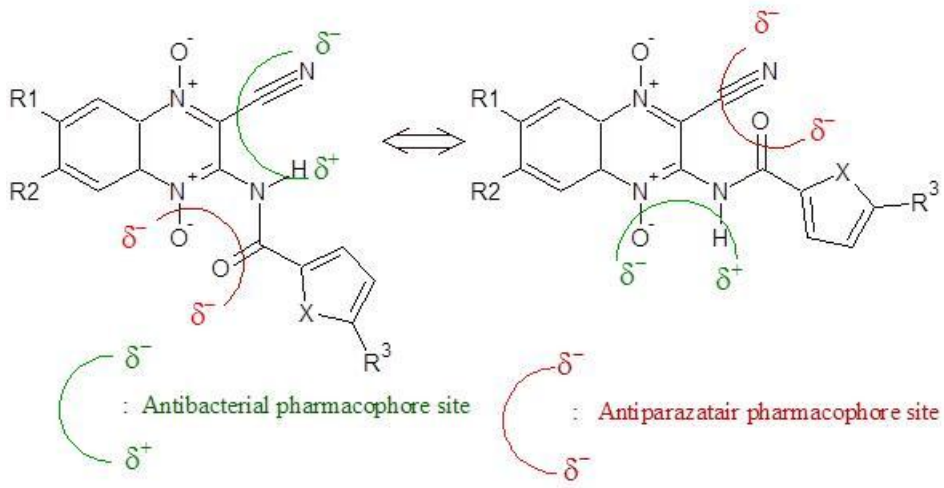

Figure 1: General structure of Heterocyclic-2-Carboxylic Acid (3-Cyano-1,4-di-Noxidequinoxalin-2-yl)amide Derivatives along with pharmacophoric pattern

Materials and methods: The well known POM (Petra/Osiris/Molinspiration) softwares were used to determine the charges and pharmacophoric pattern. To get better results, the 3d-optimised structures were drawn using ACD ChemSketch freeware 12.

Results and Discussions:

Pi-Charges Calculations

The series **1–40** of CAQDO were subjected to delocalised-charge calculations using Petra method of the nonhydrogen common atoms, obtained from the partial pi-charge of the heteroatoms, have been used to model the bioactivity against TC.

It is found that the negative charges of the oxygen of central amide moiety and nitrogen atom of nitrile and one oxygen atome N-O group contribute positively in favor of antitrypanosomal activity, more, and this is in good agreement with the hypotyhetic mode of antitrypanosomal action of the compounds bearing (X□□/Y□□) pharmacophore site (X, Y = O, N, S), Figure 1.

Conclusions:

POM analyses of the CAQDO compounds **1-40** showed that lipophilic substituents bearing electro-donor groups could be introduced in quinoxaline moiety while maintaining a high antiparasitic activity. Introduction of sulfur atom (furyl) instead oxygen atom (pyrole) on the CAQDO template provided three additional compounds **13**, **17** and **39** with no antiparasital activity.

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