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Pharmacophore modeling and structure activity relationship analysis for evaluation of nitazoxanide-based analogues against *Campylobacter jejuni*

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Abstract: In the present study, pharmacophore modeling and structure-activity relationship analysis for evaluation of nitazoxanide (NTZ) analogues against *Campylobacter jejuni*has been accomplished to recognize the pharmacophoric features that steer the activity. The analysis encompasses the comparison of pharmacophore model of most and least active molecules of the series. The analysis is useful for further optimization of NTZ analogues.

Keywords: Pharmacophore modeling, antimicrobial evaluation, nitazoxanide-based analogues

Introduction: For treating infections owing to *Giardia lamblia* and *Cryptosporidium parvum*, FDA has approved Nitazoxanide (NTZ) (see Figure 1). Though, its practice is limited because of diminished solubility and proficiency as nearly a gram per day is needed for the treatment [1, 2]. Recently, a good number of NTZ analogues were prepared and assessed for improved antibacterial efficacy against the pyruvate:ferredoxinoxidoreductase (PFOR) employing microorganisms *Campylobacter jejuni*[1]. Pharmacophore modeling and structure-activity relationships are frequently employed as important computer aided technique for lead and drug optimization [3-7]. In the present work, pharmacophore modeling for antimicrobial evaluation of NTZ analogues has been performed to understand the pharmacophoric features that have correlation with the activity by comparing most and least active molecules of the series.

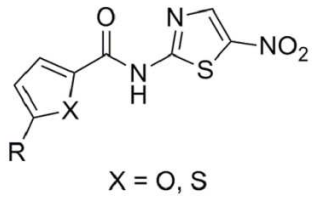

Figure 1. Nitazoxanide (NTZ) used in the present study

Experimental methodology:

A library of NTZ analogues synthesized and evaluated for antibacterial efficiency against the pyruvate:ferredoxinoxidoreductase (PFOR) using microorganisms *Campylobacter jejuni*[1] was employed for the present study. The structures were drawn using ChemSketch 12 freeware followed by 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 most active and least active has been equated and represented in figure 2. From figure 2, it is clear that the two molecules have noteworthy alteration in their pharmacophore model. The less active molecule is with two H-bond acceptor and one hydrophobic regions (depicted on left side in the figure 2a), whereas, most active molecule is with a large hydrophobic region (shown on right side in figure 2b). The distances between the common pharmacophoric features are comparable in the two molecules.

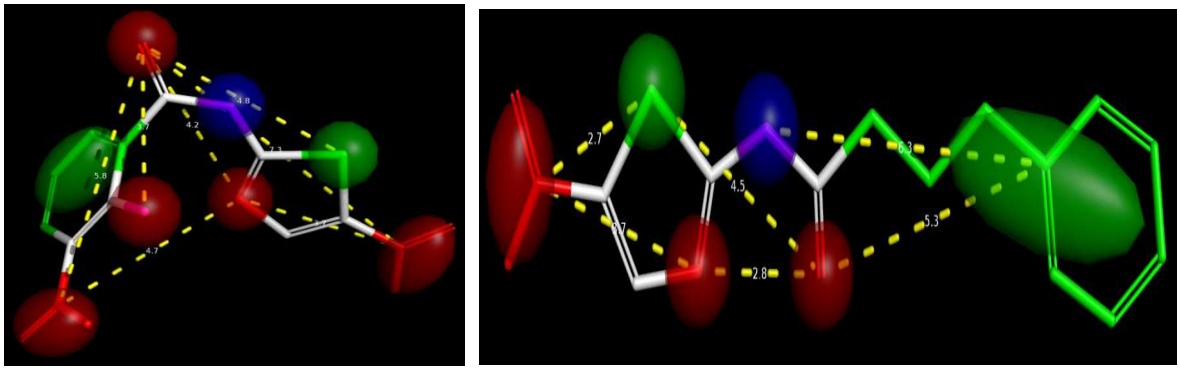

Figure 2. Pharmacophore model for least active (left2a) and most active molecule (right 2b) (Red-H-bond acceptor, bue- H-bond donor and green- hydrophobic region)

Conclusions:

In the present study, the pharmacophore model comparison discloses that the hydrophobic region due to the long chain and phenyl moiety are important for increasing the activity. Thus, the activity can be enhanced using phenyl ring with alkyl chain.

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