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Pharmacophore modeling for antimicrobial evaluation of nitazoxanide-based analogues

Manisha Kodape[1]*, Nandkishor Gawhale[2], D.T. Mahajan[3], Syed Azhar Quazi[3]

[1] Department of Chemistry, SGBAU, Amravati, Maharashtra, India.

[2] Department of Chemistry, G. S. TompeMahavidyalaya, Amravati, Maharashtra, India.

[3] Department of Chemistry, VidyaBharatiMahavidyalaya, Amravati, Maharashtra, India- 444 602

Abstract: In the present work, Pharmacophore modeling for antimicrobial evaluation of nitazoxanide-based analogues has been performed to understand the pharmacophoric features. The analysis involves the comparison of pharmacophore model of most and least active molecules of the series. The analysis is successful in establishing the structure-activity relationships.

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

Introduction: Nitazoxanide (NTZ) (see Figure 1) is an FDA permitted drug for treating infections due to *Giardia lamblia* and *Cryptosporidium parvum*. However, its usage is restricted because of reduced solubilityand efficiency since nearly a gram per day is requisite for treatment [1,2]. Recently, a library of NTZ analogues was synthesized and evaluated for augmentedantibacterial efficiency against the pyruvate:ferredoxinoxidoreductase (PFOR) employingmicroorganisms *Helicobacter pylori* [1].Pharmacophore modeling is important computer aided technique for determining the structure-activity relationships. It is an integral part of modern process of 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.

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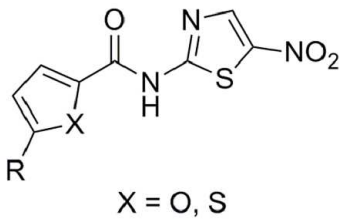

Figure 1. Nitazoxanide (NTZ) used in the present work

Experimental methodology:

A library of NTZ analogues synthesized and assessed for antibacterial efficiency against the pyruvate:ferredoxinoxidoreductase (PFOR) using microorganisms *Helicobacter pylori* [1] was used for the present work. 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 compared and depicted in figure 2. From figure 2, it is clear that the two molecules have significant difference in their pharmacophore model. The less active molecule is with few pharmacophore features as compare to most active molecule. The distances between the common pharmacophoric features are comparable in the two molecules.

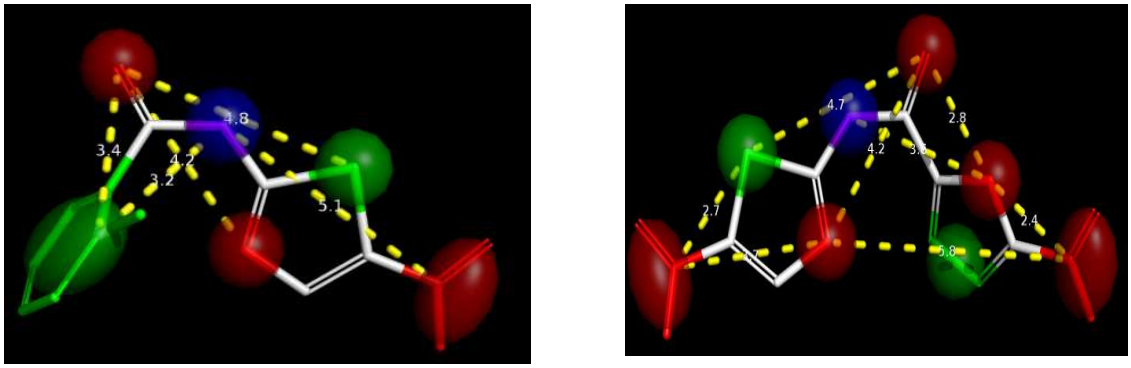

Figure 2. Pharmacophore model for least active (left) and most active molecule (right) (Red-H-bond acceptor, bue-H-bond donor and green- hydrophobic region)

Conclusions:

In the present work, the pharmacophore model derived reveals that the H-bond acceptor regions due to the nitro group and oxygen of furan ring are important for the enhanced activity. Thus, the furan ring with nitro group at position number 2 must be retained for higher activity.

References:

1] Ballard TE, X. Wang, I. Olekhnovich, T. Koerner, C. Seymour, J. Salamoun, M. Warthan, P. S. Hoffman, T. L. Macdonald, ChemMedChem, 2011, 6(2), : 362–377.

2] Ballard TE, Wang X, Olekhnovich I, Koerner T, Seymour C, Hoffman PS, Macdonald TL. BioorgMed ChemLett. 2010; 20:3537.

3] B. P. Bandgar, L. K. Adsul, H. V. Chavan, S. S. Jalde, S. N. Shringare, R. Shaikh, R. J. Meshram, R. N. Gacche, V. Masand, *Bioorg. Med. Chem. Lett.*, 2012, 22, 5839-5844.

4] S. N. Bukhari, I. Jantan, V. H. Masand, D. T. Mahajan, M. Sher, M. Naeem-ul-Hassan, M. W. Amjad, *Eur. J. Med. Chem.*, 2014, 83, 355-365.

5] V. H. Masand, D. T. Mahajan, K. N. Patil, T. B. Hadda, M. H. Youssoufi, R. D. Jawarkar, I. G. Shibi, *ChemBiol Drug Des*, 2013, 81, 527-536.

6] S. N. Bukhari, X. Zhang, I. Jantan, H. L. Zhu, M. W. Amjad, V. H. Masand, *ChemBiol Drug Des*, 2014.

7] D. T. Mahajan, V. H. Masand, K. N. Patil, T. Ben Hadda, R. D. Jawarkar, S. D. Thakur, V. Rastija, *Bioorg. Med. Chem. Lett.*, 2012, 22, 4827-4835.