**Ligand Based Optimization, Synthesis and Docking of 1,2,3-Triazoles Inhibitors of P450 14 α-Sterol Demethylase (CYP51)**

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**Introduction**

- Ergosterol is one of the major components of cell membrane of fungi which is crucial for their survival.
- Cytochrome P450 14α-sterol demethylase (CYP51) is a key enzyme which plays an important role in the biosynthesis of ergosterol in fungi by catalyzing the oxidative removal of 14α-methyl group of lanosterol. As it plays a key role in the synthesis of ergosterol therefore it has been proved to be an effective target for antifungals.
- The first generation of antifungal includes Fluconazole (FLU), Itraconzaole, etc., which have revolutionized the treatment of some serious fungal infection. However, other drugs suffer from serious side effects and their results are still far from satisfactory.
- In this report, we have employed the ligand based drug designing methodology which uses field based approach to describe a biologically active molecule, to identify 1,2,3-triazoles as sterol inhibitors and their efficacy was then evaluated on various fungi. Furthermore, the results were confirmed by molecular docking.

**Ligand Based Optimization**

- Ligand based optimization was carried out using Croesswt software "Forge", which uses 3-D field points to define binding interactions.
- These field points were used to rank different molecules on their ability to match the generic field points of standard drug Fluconazole. Along with field points, shape plays a key role in Substrate – Ligand binding therefore, similarity index (Sli) was chosen as parameter which employs 30-50 combination of both shape and field points.
- In this way different molecules were screened and 1,2,3 triazoles, a structurally diverse molecule exhibited impressive results. Based on the results, same molecule was optimized and the similarity index of its different derivatives was evaluated. Interestingly, substitution on ring A increases the Sli whereas substitution on ring B decreases the similarity index.

**Synthesis**

- A total of 29 analogues of 1,2,3-triazole were evaluated against five common human pathogenic fungi, in vitro, by measuring minimal inhibitory concentration (MIC).
- Nearly all the tested compounds were found to be highly potent against candida albicans, candida haemulonii and candida parapsilosis.
- Noticeably, 12 compounds were found to be most active with comparable cytotoxicity.

**Results and Discussion**

- MICs (µg/ml) against candida albicans.
- MICs (µg/ml) against candida haemulonii.
- MICs (µg/ml) against candida parapsilosis.
- Cytotoxicity (IC50) values.

**Conclusion**

- We have designed and synthesized twenty nine analogues of 1,2,3 triazoles, out of which nineteen compounds were found to be potent P450 14α-sterol demethylase (CYP51) inhibitors with comparable cytotoxicity to the Fluconazole and Voriconazole.

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**References**