Optimization of Azole- Antifungal Drugs: An Attempt for Search of Better Drug for Treatment of TB with CYP450 from Mycobacterium Tuberculosis.

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Abstract- **CYP450 from Mycobacterium tuberculosis is an important enzyme responsible for many biochemical reactions like metabolism, detoxification etc. These enzymes react with Azole - antifungal drug and give fruitful results helpful in treatment of tuberculosis. But the search of better drugs is still a tough task which can be achieved by study of catalytic reactions and associated reaction barriers in reaction mechanism. The drug molecules attach to enzymes in various configurations. In this study, by the optimization of "Azole- antifungal drugs", an attempt for search of better drug is carried out so as to get a potential candidate amongst all these antifungal drugs.**

Keywords: CYP450, Optimization, Mycobacterium Tuberculosis

1. INTRODUCTION

Tuberculosis is rapidly spreading all over the world. World Health Organization (WHO) data indicate that every year, approximately 2 million people are dead due to tuberculosis [1]. There are many reasons for resurgence of the Mycobacterium tuberculosis (Mtb) infection rate around the whole world. But the major factors are synergy with the Human Immunodeficiency Virus (HIV), and development of drug-resistant (DR) and multi drug resistant (MDR) strains of the pathogen [2,3]. In all HIV infected people, 15% people ultimately die due to tuberculosis. So, treatment of tuberculosis has become so important for whole world. The complete treatment duration of Tuberculosis (TB), is 6-12 month, which is a long time period. So, the search of new drugs for treatment of TB as well as decreasing the time duration, is imperative work of research. Therefore, it is urgent to identify biochemical pathway in M. tuberculosis treatment that for new anti-mycobacterial drugs [4]. There are many compounds which are treated as anti-TB drug also used in metabolism.

Azole is antifungal drug, which is treated as a substrate and reacts with MT CYP450 [5,6], gives a biochemical pathway for understanding the metabolism process and also shows good results against the anti- mycobacterium tuberculosis [7]. There are many azole compounds, but which proves to be the best for both, anti TB as well as metabolism is still a tough task. The stability of their configuration is not same with respect to CYP450. So, it is imperative to find out the most stable configuration against the Mtb. In this study, by the optimization of "Azole- antifungal drugs", an attempt for search of better drug is carried out so, as to get a potential candidate amongst all these antifungal drugs.

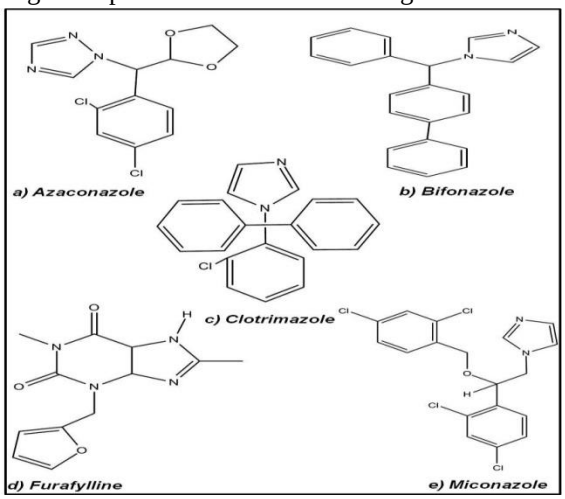

Figure 1: Structures of Azoles.

1.2. AZOLE-ANTIFUNGAL DRUGS

Azole-antifungals, containing an Azole ring, are

the group of medicine used for the inhabitation of wide range of fungal infection. They are classified into two groups: (a) Azole ring with two nitrogen called imidazole, [i.e. miconazole, clotrimazole, econazole, etc], (b) Azole ring with three nitrogen called triazoles, [i.e. fluconazole, itraconazole, posaconazole etc]. Azole antifungal inhibiting the lanosterol 14-alpha-demethylase enzyme, which is member of cytochrome P450 enzyme family, converts lanosterol to erosterol, which damages the cell membrane resulting in the death of cell [8]. But the configuration of azole-antifungal drugs are not equally stable. So finding the most stable configuration amongst all azole-antifungal drugs is primarily requirement for understanding the metabolism and anti-TB drugs properties.

3. METHODOLOGY

For finding the most stable configuration. commonly used method is **Quantum Mechanical (QM)** method.

Quantum Mechanical Calculations:

In this method, various quantum mechanical theories [9] are utilized to calculate the ground state energy of molecule. In this approach, Schrodinger wave equation for multi-electron system, is used [10]. And after the calculation, it gives the ground state energy, which leads to the most stable configuration. Solution of modified Schrodinger wave equation is based on **Density Functional Theory (DFT)** that utilizes concept of correlation between electron density of given system to its related physical properties**.**

Density Functional Theory:

In this method, density of electron is used instead of wave function. This theory, in contrast to wave function of quantum mechanics, describes the energy as a functional of electron density.[11]. Kohn et. al. derived a set of multi- electron system equation to calculate the electron density as well as total energy of the system. Results using this method have shown to be less computationally expensive as well as have demonstrated reasonable agreement with experimental results for the large molecular system.[12,13].

Basis Sets:

Basis sets are basically a set of functions, which described the shape of orbitals in an atom. In a single electron system, one atomic orbital for each electron. So, in case of multi-electron system, basis set is the linear combination of atomic orbital, which gives the molecular wave function through molecular orbit. Here 6-31* basis set is used for the optimization of structures. Commonly used basis sets are-

- 3-21G
- 3-21G*
- 3-21G**
- 4-21G
- 4-31G
- 6-21G
- 6-31G*
- Lan2DZ

Table 1: HOMO-LUMO bandgap of Azoles.

S.No.	Azole	HOMO-LUMO Bandgap (in a.u.)	HOMO-LUMO Bandgap (in ev)
1.	Azaconazole	0.22112	6.0168
2.	Bifonazole	0.13259	3.6079
3.	Clotimazole	0.18519	5.0266
4.	**Miconazole**	**0.13177**	**3.5855**
5.	Furafylline	0.18519	5.0392

Table 2: Energy of Azoles.

S.No.	Azole	Energy (in a.u.)	Energy (in ev)
1.	Azaconazole	-1698.96	-46,230.40
2.	Bifonazole	-958.08	-26,070.31
3.	Clotimazole	-1418.27	-38,592.54
4.	**Miconazole**	**-2719.81**	**-74,008.74**
5.	Furafylline	-909.23	-24,741.05

4. RESULTS AND DISCUSSION

The results obtained by optimization of azoles are shown in tables 1 and 2. HOMO-LUMO bandgap of Azaconazole is highest, indicating that it's configuration is less stable. Bifonalzole's HOMO-LUMO bandgap is much smaller, so it's configuration is more stable than other optimized azoles. But it is less stable than Miconazole, because HOMO- LUMO gap is the smallest (table 1). The optimization energy of Furafylline is the highest amongst the azoles, due to this, it has less stable configuration. But Miconazole has the lowest energy (table 2), that's why may be said to have the most stable configuration amongst all azoles. It may be inferred that Miconazole has the most stable structure in all given azoles. The most stable configuration means, when it is act as substrate, in any biochemical reaction, it has the most probability to bind tightly with the enzymes. This property of substrate helps in understanding the reaction mechanism of many biochemical reactions.

5. CONCLUSION

Optimization results of Azoles-antifungal drugs show that all azoles have good stability, Miconazole has the most stable structural configuration which means it can bind tightly with the enzymes. This result acts as an aid in understanding the reaction mechanism of many biochemical reactions. So, it is concluded that Miconazole is a good anti-fungal drug as well as a good substrate to react with enzymes. Further research work in such field may reveal a wide range of mysteries in understanding the metabolism, detoxification and many other biochemical reactions as well as help in search of good anti-fungal drugs also.

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