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COMPUTATIONAL STUDY OF CYCLIC DERIVATIVES FROM PYRIDINE-4-CARBOXYLIC ACID AS POTENTIAL ANTI-TB AGENTS

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ABSTRACT

Mycobacterium tuberculosis, the causative agent of tuberculosis (TB), is a remarkably successful pathogen that has latently infected a third of the world population. The objective is to model new molecular scaffolds by re- engineering and repositioning old drug families. Existing TB drugs isoniazid, thioamides belonging to the class of pyridine 4-carboxylic acid were substituted with an allyl or Propargylic groups at 2,6 positions. Molecular modeling tool is used to check and compare the structure and stability of existing TB drugs isoniazid, thioamides along with newly proposed molecules 2-Allyl Isoniazid, 2-Propargyl Isoniazid and 6-Alloyl Thioamides. Semi-empirical methods belonging to NDDO (neglect of double differential overlap) approximation have been used to study the stabilities of proposed molecules. The energy difference between the molecular orbitals HOMO and LUMO is in very good agreement with UV spectral data. This study concludes that these molecules can act as potent drugs to cure Tuberculosis. Further they can be synthesized and their biological activity can be studied for new drug development.

Key words : Cyclic derivatives, Mycobacterium tuberculosis, anti-TB agents, Pyridine-4-carboxylic acid

INTRODUCTION

In 1882 Robert Koch identified Mycobacterium Tuberculosis as the causative agent of tuberculosis (TB), a remarkably successful pathogen that has latently infected a third of the world population (Zhang et al., 2006). Lung Infection occurs via aerosol, and inhalation of few droplets of M. Tuberculosis bacilli (Hassan et al., 2006). M. tuberculosis pathogenesis occurs in two stages. First Stage (called as latent TB) :An asymptomatic state that can persist for many years in the host. Second stage. The symptomatic state that weakens immune system causing characteristic symptoms such as cough, chest pain, fatigue and unexplained weight loss.

While it is impossible to determine the exact number of cases, the latest World Health Organization (WHO) survey estimates that close to 2 million deaths occur every year, that there are approximately 8 million new cases annually, and that every third individual on the planet has been exposed to or infected by *M. tuberculosis* (Dye, 2006; Cole & Alzari, 2007). Although TB can be treated and even cured with chemotherapy, treatment is exceedingly lengthy and takes 6-9 months (Blumberg, et al., 2003). In addition to significant toxicity, lengthy therapy also causes poor patient compliance, which is a frequent cause for selection of drug resistant and often deadly multidrug resistant TB (MDR-TB) bacteria (Zang et al.,2006).

Treatment is also made quite difficult by the presence of metabolically silent, persistent or dormant bacteria within host lesions. These are not susceptible to the anti-mycobacterial drugs that usually kill growing but not persistent bacteria (Zhang, 2004). While there are many reasons for drug resistance, including prescription of inadequate regimens, an uncertain drug supply, and ineffective drugs, duration of lengthy treatments is one of the major contributors because some TB patients prematurely stop their therapy after an initial, rapid heath improvement. (Cole & Alzari, 2007. The emergence of Human Immunodeficiency Virus (HIV) and the resultant Acquired Immune Deficiency Syndrome (AIDS) pandemic underlined the importance of reactivation of the disease and its potentially catastrophic outcome since over 50% of deaths among HIV-infected patients results from co-infection with *M. tuberculosis* with the two pathogens inducing each other's replication, thus accelerating the collapse of the immune system (Cole & Alzari, 2007 and Estari et al, 2012).

The first-line treatment of tuberculosis includes a combination of drugs that are primarily used. The drugs are Isoniazid, Rifampin pyrazinamide, Streptomycin & Ethambutol. Second-line drugs for the treatment of tuberculosis are reserved for the treatment in multidrug-resistant tuberculosis (MDR-TB) *(special cases* (Blumberg et al., 2006). The first & second line drug treatment involves longer times. The strains developed due to TB treatment have not only become multidrug resistant (MDR), but also have become extensively drug resistant (XDR). Hence, an immense need to develop new TB drugs is urgent. The objectives of these studies were, to shorten the duration and to lower dosing frequency, to make the new drug active against MDR and XTR and to reduce the current cost of drugs.

MATERIAL AND METHODS

Objective is to model new molecular scaffolds by re- engineering and repositioning old drug families. Existing TB drugs isoniazid, thioamides belonging to the class of pyridine 4-carboxylic acid were substituted with an allyl or Propargylic groups at 2,6 positions. The new chemical entities (NCE's) are *2-Allyl Isoniazid, 2-Propargyl Isoniazid* and *6-Allyl Thioamides.* Molecular modeling tool is used to check and compare the structure and stability of existing TB drugs isoniazid, thioamides along with newly proposed molecules 2-Allyl Isoniazid, 2-Propargyl Isoniazid and 6-Alloyl Thioamides.

Computational Calculations:

Semi-empirical methods belonging to NDDO (neglect of double differential overlap) approximation have been used to study the stabilities of proposed molecules. Molecular orbital calculations are performed using the reasonably accurate PM3 method on these molecules.

- Minimum energy values Emin,
- Binding energies,
- Heats of formation ΔHf ,
- Dipole moments (μ),
- UV data of the optimized geometries have been computed for gas phase molecules.

The highly negative minimum energy values Emin suggests that the molecules are extremely stable.

RESULTS AND DISCUSSION

The energy gap between HOMO and LUMO is in accordance with electronic transitions and has near UV (should be compared with experimental results) absorption. The energy difference between the molecular orbitals HOMO and LUMO is in very good agreement with UV spectral data as listed in the table-1.

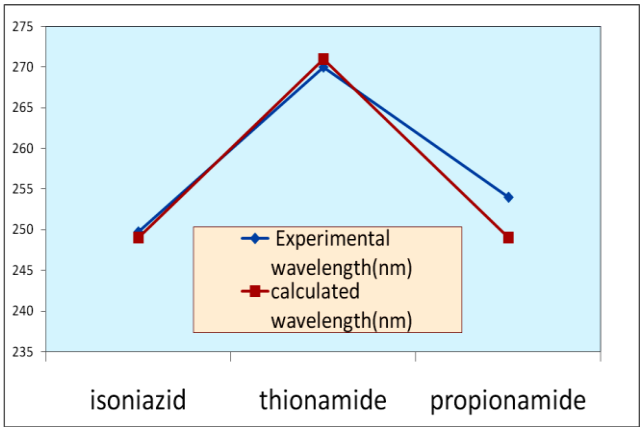
Desirable new targets should be involved in vital aspects of bacterial growth, metabolism and viability whose inactivation would lead to bacterial death or an inability to persist, thus therapy could be shortened and drug resistant strains could be eliminated or drastically reduced (Mdluli & Spigelman, 2006; Duncan, 2004). Moreover, targets involved in the pathogenesis of the disease process should also be considered for drug development (Zhang et al., 2006; Palomino et al., 2009).

Table-1. UV Spectral data of energy difference between the HOMO and LUMO molecular orbitals

MOLECULE	Total energy in kcal/mol	Binding Energy (kcal/mol)	Heat of Formation (kcal/mol)	calculated wavelength (nm)	Experimental Wavelength (nm)	Dipole moment(D)	LogP
1. Isoniazid	-36848.05	-1770.54	18.06	249	249.7	2.503	-1.37
2. 2-allyl isoniazid	-46459.13	-2480.48	29.21	250.6	256	2.54	-0.69
3. 2-propargyl isoniazid	-45717.05	-2341.363	64.12	250.6	259	2.38	-0.07
4. thionamide	-37166.93	-2131.46	49.07	249	262.7	4.873	-0.04
5. 6-allyl thionamide	-46778.21	-2841.61	59.99	267	273	4.379	1.73
6. propionamide	-40615.50	-2412.01	43.62	267	254	4.85	0.36

The molecules have highly aligned position with high net dipole moment of ~2 to ~5 D. An optimum log P value of around 21 shows CNS penetration. Evidence for this comes from a wide variety of experiments. Lipinski rule of thumb emphasizes likeness of the molecule as drug. Computed properties of already existing drug molecules and proposed new chemical entities are showed in this study (Figures 1-5).

Figure-1. Correlated graph of experimental & computed λ_{max} values of already available drug molecules. One to one correspondence of the values shows the authenticity of PM3 program for simple molecules.



The λ_{max} values of isoniazid, thionamide and propionamide in experimental drug molecules are 249.7, 262 and 254 respectively. The λ_{max} values of isoniazid, thionamide and propionamide in calculated drug molecules are 249, 249 and 267 respectively. Experimental are higher than the calculated drug molecules

Figure-2. Comparison of HOMO and LUMO orbitals of existed drug molecules and proposed new chemical entities

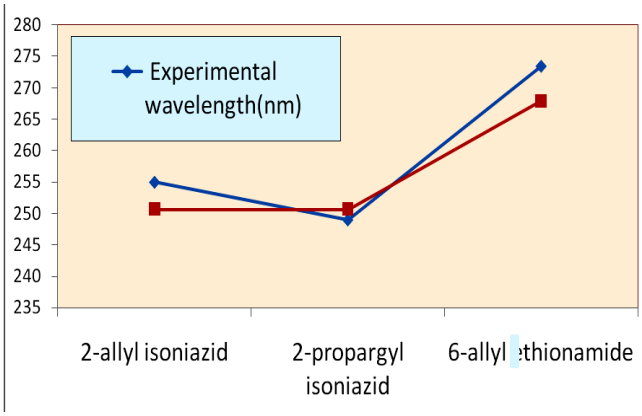


Figure-3. Comparison of HOMO and LUMO orbitals of existed drug molecules and proposed new chemical entities

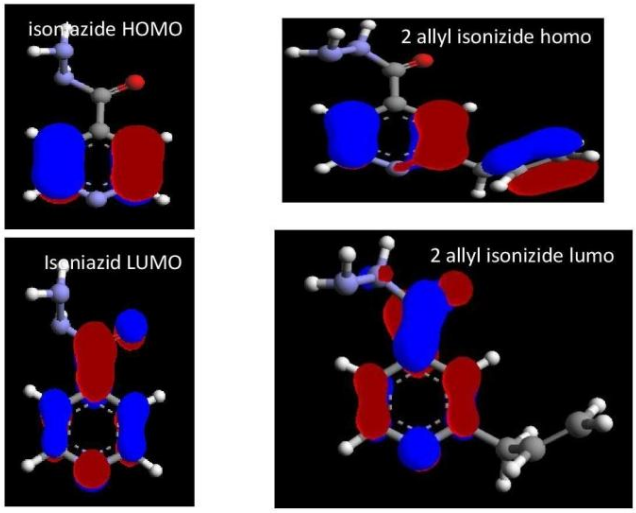


Figure-4. Comparison of HOMO and LUMO orbitals of existed drug molecules and proposed new chemical entities

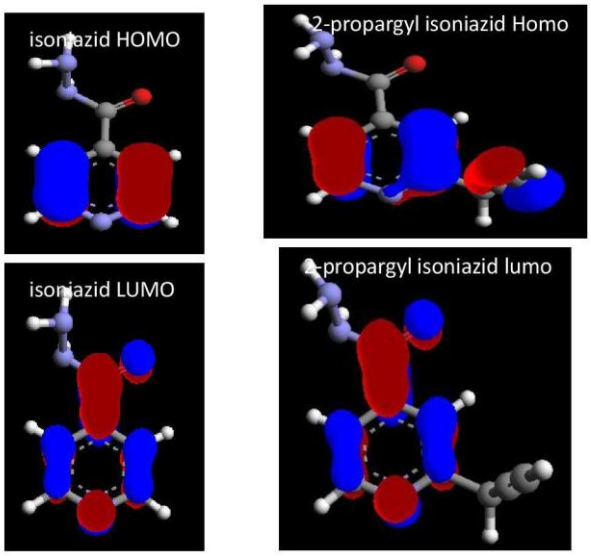
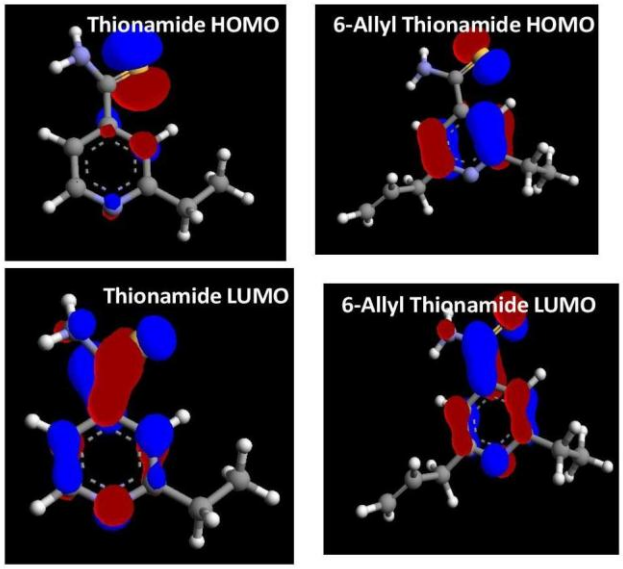


Figure-5. Comparison of HOMO and LUMO orbitals of existed drug molecules and proposed new chemical entities



CONCLUSION

NCEs (New Chemical Entities) viz., 2-Allylisoniazid, 2-Propargylisoniazid and, 6-Allyl thioamide, have comparable energies, heats of formation, dipole moments, absorption wavelengths, log p values comparable with that of existing ones. So we can conclude that these molecules can act as potent drugs to cure Tuberculosis. Further they can be synthesized and their biological activity can be studied for new drug development.

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