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Research Article

# MOLECULAR DOCKING STUDY OF SOME NOVEL IMIDAZO [2,1-b] [1,3,4]-THIADIAZOLE DERIVATIVES

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**ABSTRACT**

The molecular docking studies were performed on imidazo [2,1-b] [1,3,4] – thiadiazole derivatives using Pantothenate synthetase, enoyl-acyl carrier protein reductase (InhA) and Aminoglycoside 2'-N-acetyltransferase proteins and Glycylpeptide N-tetradecanoyl transferase, mRNA-capping enzyme subunit alpha and Candidapepsin-2 which have been validated as effective anti-TB and anti-fungal targets. The compounds 6a1and 6d1 were found to show best docking score towards Pantothenate synthetase protein indicating that these compounds may be screened for in vivo Anti-TB and the same compounds showed best docking score for Glycylpeptide N-tetradecanoyl transferase protein to evaluate the Anti-Fungal activity when compared with standard drugs docking score (Isoniazid, -5.6 and fluconazole, -7.3). The results showed that amongst all the tested compounds, the compounds 6a1 [-9.7, -10.4], 6d1 [-9.7, -10.8] and methoxy substitution at 4th position of phenyl ring at 4th position of thiazole ring of the imidazo[2,1-b]-1,3,4-thiadiazole ring and nitro/chloro substitution on 4th position of the phenyl ring at 6th position of imidazo [2,1-b] [1,3,4]-thiadiazole ring was found to have the highest affinity for Pantothenate synthetase and Glycylpeptide N-tetradecanoyl transferase proteins.

**KEYWORDS:** Imidazo [2,1-b]-1,3,4thiadiazole, Dock score, Pantothenate synthetase, Glycylpeptide N-tetradecanoyl transferase, anti-tubercular and anti-fungal activity.

## INTRODUCTION

### Imidazo[2,1-b]-1,34-thiadiazole

Imidazole[1,2] and thiadiazole[3-5]moieties are accompanying with diverse applications in the field of pharmacy owing to the –N-C=N and toxophoric –N=C-S- groups. The fusion of heterocycles, the possibilities of reducing harmful effects of cytotoxic agents on the immune system also seems very attractive.

Thiazole (sulfathiazole, cefixime), Imidazo [2,1-b] thiazole and their bioisosteric derivatives such as thiadiazole (acetazolamide), imidazo [2,1-b] [1,3,4] thiadiazole are regarded as safer and better drug molecules that are found to possess diversified biological activities like anti- bacterial[2], diuretic, antifungal, and leishmanicidal[6]. The anti-tumor potential of 2-amino [1,3,4] thiadiazole skeleton was recognized in early 1950's and subsequently, its fusion with imidazo [2,1-b] ring system has resulted in compounds with antibacterial[3], anticancer[5], cardiotonic and cytotoxic activities[7].

Since imidazothiadiazole derivatives are found to be more useful, they are further focused for recent research work in green chemistry[8] which revolves around the design, development, and implementation of chemical processes and products that reduce or eliminate hazardous substances in a way that is feasible and economically viable. Imidazo [2,1-b] [1,3,4] thiadiazoles have been found to possess antisecretory[9], analgesic[10], antipyretic[10],diuretic[10], cardiotonic[10], herbicidal[10], anti-inflammatory[10], antileishmanial[11] activities in addition to their antibacterial[12], anti-tubercular[13-16] and antifungal[17] activities. The new imidazo [2,1-b] [1,3,4]-thiadiazole compounds such as 2-(2-Methylphenyl)-6-phenyl-imdidazo [2,1- b] [1,3,4]thiadiazole, 2-(2-Acetoxyphenyl)-6-phenylimidazo [ 2,1-b] [1,3,4] thiadiazole, 2-(2-Methylphenyl)-5- methyl-6-phenyl-imidazo [2,1-b] [1,3,4]-thiadiazole, 2-(2- Oxy-_-propionic-acid-ethyl-ester)-6-phenyl-imidazo [2,1- b] [1,3,4] thiadiazole, 2-Ethylphenyl-6-phenylimidazo[ 2,1-b][1,3,4]thiadiazole are found to have use solely alone or indefinite composition as antithrombotic agents and thrombolytic agents[18]. The purpose of this work is to dock molecules containing imidazo [2,1-b] [1,3,4] thiadiazole nucleus to a different type of proteins as mentioned In table 1, so as to further screen molecules for anti-Tubercular and anti-Fungal activity.

## MOLECULAR DOCKING STUDIES

In order to gain an insight into the mechanism of action of the new thiazole hybrids, the active molecules were subjected to molecular docking studies against various enzymes like Pantothenate synthetase, enoyl-acyl carrier protein reductase (InhA) and Aminoglycoside 2'-N-acetyltransferase of *M. tuberculosis* and Glycylpeptide N-tetradecanoyl transferase, mRNA-capping enzyme subunit alpha and Candidapepsin-2 of fungi which have

been validated as effective anti-TB and anti-fungal targets. Further, isoniazid (the first-line anti-TB drug) acts by inhibiting the enoyl-acyl carrier protein reductase (InhA). Recent studies on thiazolylhydrazone and 1, 3, 4-thiadiazole derivatives with InhA revealed the good binding interaction of these molecules with the amino acid residue of the enzyme.[19] InhA is one of the key enzymes involved in the type II fatty acid biosynthesis pathway. Tyr 158 is an important amino acid residue which interacts with the long chain fatty acyl substrates required for the synthesis of mycolic acids in the mycobacteria.[20, 21] On the other hand, Pantothenate exhibits uncompetitive inhibition toward both D-pantoate and ATP, and non-competitive inhibition toward beta-alanine. AMPCPP exhibits competitive inhibition toward ATP, uncompetitive inhibition toward beta-alanine, and non-competitive inhibition toward D-pantoate. The enzyme is most active in the presence of magnesium or manganese. Other divalent cations (cobalt, nickel, zinc) are less effective azole group of compounds.[22] and the crystal structure of the AAC(2')-Ic from Mycobacterium tuberculosis has been determined in the apo enzyme form and in ternary complexes with CoA and either tobramycin, kanamycin A or ribostamycin, representing the first structures of an aminoglycoside acetyltransferase bound to a drug the physiological function of AAC(2')-Ic is uncertain, a structural analysis of these high-affinity aminoglycoside complexes suggests that the enzyme may acetylate a key biosynthetic intermediate of mycothiol, the major reducing agent in mycobacteria, and participate in the regulation of cellular redox potential. Compound **6a1** and **6d1** had the highest docking score of −9.7 against Pantothenate synthetase of TB (In table **2)**, whereas compound **6a1 and 6d1** with a docking score of −10.4, -10.8 showed against Glycylpeptide N-tetradecanoyl transferase of Fungi (In table **3)**. The docking score of all the active molecules is given In table **4**.

## MATERIALS AND METHODS

### Docking Study of Imidazo[2,1-b]-1,3,4thiadiazole Derivatives

**Software used:** 1-Click Docking

**The protein used for docking[23]:**
Details of Proteins used for Docking studies mentioned in table 1.

**Table 1: Details of Proteins used for Docking studies**

| S.No | Name of the protein | Source | PDB ID | Organism |
|---|---|---|---|---|
| 01 | Pantothenate synthetase | sc-PDB | 1n2g | *Mycobacterium tuberculosis* |
| 02 | Enoyl-[acyl-carrier-protein] reductase [NADH] | sc-PDB | 3fne | *Mycobacterium tuberculosis* |
| 03 | Aminoglycoside 2'-N-acetyltransferase | sc-PDB | 1m4g | *Mycobacterium tuberculosis* |
| 04 | Glycylpeptide N-tetradecanoyl transferase | sc-PDB | 1iyk | *Candida albicans* |
| 05 | mRNA-capping enzyme subunit alpha | sc-PDB | 1p16 | *Candida albicans* |
| 06 | Candidapepsin-2 | sc-PDB | 1zap | *Candida albicans* |

**Table 2: Docking score of active compounds against different enzymes of TB**

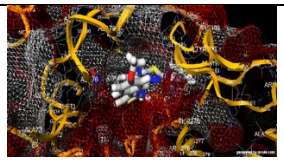
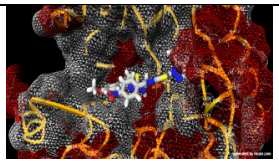
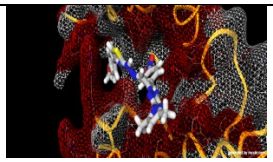
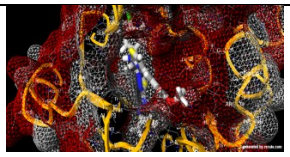
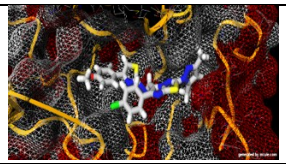
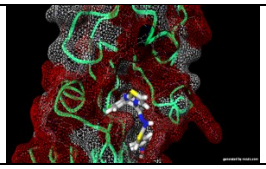
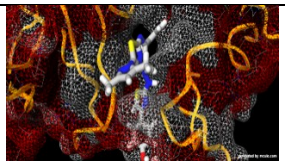
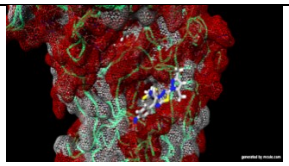
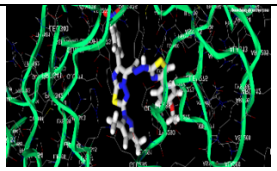
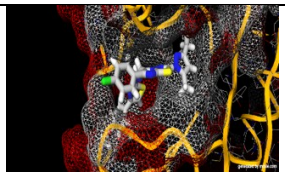
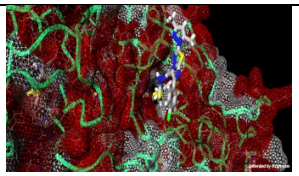
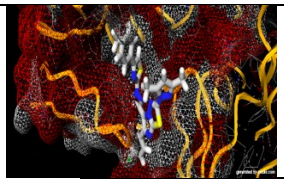
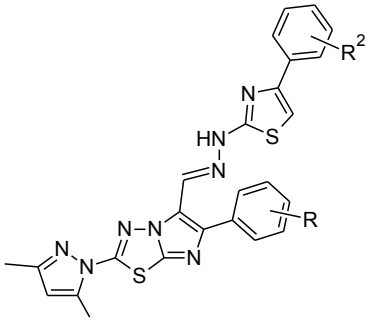
| Product name | Pantothenate synthetase | Enoyl-[acyl-carrier-protein] reductase [NADH] | Aminoglycoside 2'-N-acetyltransferase |
|---|---|---|---|
| 6a1 | -9.7 | -8.7 | -8.0 |
| 6d1 | -9.7 | -8.8 | **-8.4** |
| 6a1 |  |  |  |
| 6d1 |  |  |  |

**Table 3: Docking score of active compounds against different enzymes of Fungi**

| Product name | Glycylpeptide N-tetradecanoyltransferase | mRNA-capping enzyme subunit alpha | Candidapepsin-2 |
|---|---|---|---|
| 6a1 | **-10.4** | **-9.7** | -8.9 |
| 6d1 | **-10.8** | -9.3 | **-9.4** |
| 6a1 |  |  |  |
| 6d1 |  |  |  |

More negative values indicate higher binding affinity and highly reactive.

**Table 4: structural details and Docking score**




| Product | R1 | R2 | Docking Score | |
|---|---|---|---|---|
| | | | Pantothenate synthetase | Glycylpeptide N-tetradecanoyl transferase |
| 6a1 | **p-$NO_2$** | **p-$OCH_3$** | **-9.7** | **-10.4** |
| 6a2 | p-$NO_2$ | p-$NO_2$ | -8.8 | -9.0 |
| 6a3 | p-$NO_2$ | p-$CH_3$ | -8.2 | -8.7 |
| 6a4 | p-$NO_2$ | p-Cl | -8.9 | -9.1 |
| 6a5 | p-$NO_2$ | p-Br | -8.3 | -8.9 |
| 6a6 | p-$NO_2$ | m-$NO_2$ | -8.6 | -8.8 |
| 6b1 | p-Br | p-$NO_2$ | -8.4 | -8.6 |
| 6b2 | p-Br | p-$OCH_3$ | -9.2 | -9.4 |
| 6b3 | p-Br | p-$CH_3$ | -8.1 | -8.4 |
| 6b4 | p-Br | p-Cl | -8.3 | -8.7 |
| 6b5 | p-Br | p-Br | -8.2 | -8.7 |
| 6b6 | p-Br | m-$NO_2$ | -8.6 | -8.9 |
| 6c1 | p-$OCH_3$ | p-$NO_2$ | -8.4 | -8.8 |
| 6c2 | p-$OCH_3$ | p-$OCH_3$ | -8.0 | -8.2 |
| 6c3 | p-$OCH_3$ | p-$CH_3$ | -8.2 | -8.7 |
| 6c4 | p-$OCH_3$ | p-Cl | -8.4 | -8.8 |
| 6c5 | p-$OCH_3$ | p-Br | -8.5 | -8.8 |
| 6c6 | p-$OCH_3$ | m-$NO_2$ | -8.7 | -9.0 |
| 6d1 | **p-Cl** | **p-$OCH_3$** | **-9.7** | **-10.8** |
| 6d2 | p-Cl | p-$NO_2$ | -8.5 | -8.9 |
| 6d3 | p-Cl | p-$CH_3$ | -8.0 | -8.2 |
| 6d4 | p-Cl | p-Cl | -8.2 | -8.7 |
| 6d5 | p-Cl | p-Br | -8.3 | -8.7 |
| 6d6 | p-Cl | m-$NO_2$ | -8.7 | -9.1 |
| Standard drugs used | | | Isoniazid | Fluconazole |
| Docking Score | | | **-5.6** | **-7.3** |

More negative values indicate higher binding affinity and highly reactive.

**RESULTS AND DISCUSSION**

The docking studies were performed for all synthesized compounds on Tubercular protein (Pantothenate synthetase) and Fungal protein (Aminoglycoside 2'-N-acetyltransferase). From the studies it was found that the compound 6a1 (dock score -9.7) was found to have the greatest affinity to Tubercular protein (Pantothenate synthetase) followed by 6d1 (dock score -9.7) and compound 6a1 (dock score -10.4) 6d1 (dock score -10.8) against Fungal protein (Aminoglycoside 2'-N-acetyltransferase), and all other compounds showed moderate affinity towards the same proteins.

It is concluded that when R1 and R2 substituents are electron withdrawing groups(-Cl, $-OCH_3$ & $-NO_2$) for the 6a1 and 6a2 compounds shows a greater affinity for different proteins compared to compounds which contain R1/R2 substituted with electron withdrawing groups (-Br & 3-NO2). The compounds with electron releasing groups (-CH3) were found to have the least affinity which shown In table 4. But they have more affinity when compared with the standard drugs (which shows docking score -5.6 for Isoniazid and -7.3 for Fluconazole).

**CONCLUSION**

Docking is the best tool to produce effective moieties with this regard our finding will have more impact on Chemist to discover new entities since with small modification on the basic ring with structural based drug design can produce an excellent result for Anti-TB and anti-Fungal activity.

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