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Docking Studies of 1 3 4 Thiadiazole Derivatives against target Protein PknG from *Mycobacterium Tuberculosis*

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ABSTRACT

1,3,4 – thiadiazole derivatives derived from various reaction sequences with slight modifications in the side chain with primary amine group at 5th position in the thiadiazole ring. The docking studies were done by using scroodinger software version against the enzyme protein kinase. The structures of all the compounds were drawn using chemdraw software version 8.0. All the thiadiazole derivatives showed satisfactory ligand binding energy between -2.70 to -5.60 k.cal /mole. Compounds A_3, A_{21},M_{34}&M_{36} showed better glide score with -5.4, -4.9, -4.7 and-4.00 respectively.

Keywords: Thiadiazole derivatives, molecular docking, Schroodinger software, ligand binding energy, protein kinase enzyme, mycobacterium tuberculosis.

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INTRODUCTION

Biological activities of five membered heterocyclic rings with different hetero atoms embedded in them have gained more considerable attention. One among them is thiadiazole a 5 – membered heterocyclic ring with two nitrogens and one sulphur as the hetero atoms. Thiadiazoles are available in different isomeric forms like 1, 3, 4 thiadiazole, 1,2,4 thiadiazole, 1,2,3 thiadiazole, 1,2,5 thiadiazole. All of them found to possess excellent biological activity like fungicidal[1], bactericidal, anti cancer activity[2], anti inflammatory, anti convulsant, CNS stimulant activity, Anti viral activity, anthelmintic activity[3].

Among them 1,3,4 thiadiazole especially possess anti tubercular activity[4]. Meanwhile the treatment of air borne infectious diseases still remain a important problem due to increasing amount of drug resistance developed by the microbes. One of the common and deadly air borne infectious disease is tuberculosis (TB), caused by mycobacterium tuberculum, the most prevalent disease worldwide.

World health organization (WHO) in 2011 revealed that around 8.7 million people are infected with TB throughout the world. Nearly 1.4 million people were killed by this disease. This accounts for about 32 percent of the World's population infected with TB. India, china, South Africa, Indonesia, Pakistan are the five countries with more number of TB cases coming newly.

India alone holds around 40 percent people infected with TB globally[5]. Also anti biotic with less activitycauses of multi drug resistant and extremely drug resistant strains of TB together increases the problems of the disease. This strategy and the conditions has indulged in the development of new thiadiazole moieties as anti – tubercular drugs by inhibiting the important enzymes involved in the microbes life cycle. This inhibition is done by drug molecules or ligands binding with the enzymes. The binding capacity of the ligand can be analyzed by docking studies.

The enzyme protein kinase G (PKnG) is not needed for mycobacteria growth, but this enzyme is very much important for survival of mycobacterium in the host macrophages[6] and has marked as the target protein for docking studies. Different 1 3 4 thiadiazole derivatives are considered as ligand or drug molecules which are going to interact with the enzyme thus inhibiting its activity.

MATERIALS AND METHODS

Schrodinger software version was used for the docking studies. For the determination of protein – Ligand binding affinities and scoring function GLIDE 4.0 (Grid Based Ligand Docking with Energies) XP (Extra Precision) docking protocol was used.

Ligand Preparation

The 3D structure of the ligand 134 thiadiazoles having calculated molecular weight from 268 and its derivatives (Table 1) were drawn using chemdraw software version 8.0. The basic structure of thiadiazole was got from pubmed database. The ligand structures were constructed using the splinter dictionary of Maestro 9.4 (Schrodinger, LLC) using the Optimized Potentials for Liquid Simulations-All Atom[7] (OPLS-AA) force field with the steepest descent followed by curtailed Newton conjugate gradient protocol. Partial atomic charges were computed using the OPLS-AA force field.

Protein / Enzyme Preparation

The X-ray crystal structures protein kinase G (PDB: 2PZI) retrieved from the Research Collaboratory for Structural Bioinformatics (RCSB) Protein Data Bank was used in this study. Water molecules of crystallization were detached from the composite and the protein was optimized for docking using the protein preparation and refinement utility provided by Schrödinger LLC. Partial atomic charges were assigned according to the OPLS-AA force field.

Bind Site Analysis

Active sites or binding sites for enzymes were predicted from pictorial database of 3D structures in the protein data bank (PDB sum) and Q-Site Finder software from university of Leeds Bioinformatics was used for ligand binding site prediction . In that 6 sites where found active (1 for ligands and 5 for metals). So it was decided to keep all the amino acids in the active site of the enzyme.

Table 1: Estimated Docking Parameters of Enzyme with Thiadiazole Analogues[8]

Title	Docking score	XP gscore	Glide gscore	Glide energy	XP H bond	Glide ligand efficiency
2PZI						
A3.mol	-5.47273	-5.49143	-5.49143	-48.4703	-0.35	-0.18936
A21.mol	-4.92306	-4.92666	-4.92666	-52.8965	-1.05	-0.15396
M34.mol	-4.71408	-4.75098	-4.75098	-51.577	-1.43818	-0.12503
M36.mol	-4.00093	-4.03843	-4.03843	-57.0701	-0.62532	-0.10627
M31.mol	-3.96899	-4.00649	-4.00649	-51.3812	-1.33	-0.10828
M39.mol	-3.93779	-3.97529	-3.97529	-45.2344	-0.35	-0.10461
M29.mol	-3.64959	-3.68709	-3.68709	-50.4153	-1.19501	-0.1229
M13.mol	-3.61971	-3.61971	-3.61971	-45.3283	0	-0.11312
M42.mol	-3.41282	-5.07602	-5.07602	-49.2371	-1.27084	-0.1493
M33.mol	-3.33131	-3.36881	-3.36881	-53.7065	-0.35	-0.09105
M41.mol	-3.03894	-3.07644	-3.07644	-48.2482	-0.80502	-0.10608
M17.mol	-2.96932	-2.96932	-2.96932	-43.2522	-0.33163	-0.08025
M37.mol	-2.91041	-2.94791	-2.94791	-45.9676	-1.18156	-0.08189
A28.mol	-2.81834	-2.81834	-2.81834	-43.0981	-0.65755	-0.0854

M30.mol	-2.75391	-2.79141	-2.79141	-41.7093	-0.57453	-0.07975
M35.mol	-2.69432	-2.96702	-2.96702	-42.997	-1.33	-0.07808
M38.mol	-2.67389	-2.71139	-2.71139	-42.7521	-0.21617	-0.07532
M2.mol	-2.64239	-2.64239	-2.64239	-41.3019	0	-0.08007
M15.mol	-2.57182	-2.57182	-2.57182	-45.4625	-0.20057	-0.08573
M27.mol	-2.45105	-2.45105	-2.45105	-47.6823	0	-0.08452
A8.mol	-2.38628	-2.38628	-2.38628	-42.1066	-0.7	-0.07457
M32.mol	-2.37244	-2.40994	-2.40994	-51.1867	-1.01938	-0.06694
M16.mol	-2.21741	-2.21741	-2.21741	-35.0143	-0.1924	-0.06336
M4.mol	-2.15948	-2.15948	-2.15948	-52.5675	-0.38508	-0.06351
M19.mol	-2.06072	-2.06072	-2.06072	-52.9543	-0.32128	-0.0557
M28.mol	-2.02435	-2.02435	-2.02435	-34.3907	0	-0.05954
M22.mol	-1.82794	-1.82794	-1.82794	-28.4189	0	-0.0481
M20.mol	-1.82402	-1.82442	-1.82442	-41.5164	-1.37565	-0.04801
M21.mol	-1.79907	-2.45907	-2.45907	-51.2509	-0.33496	-0.06471
M14.mol	-1.68023	-1.68023	-1.68023	-43.1666	0	-0.06223
A8.mol	-1.66814	-1.66814	-1.66814	-34.5186	-0.35	-0.05213
M23.mol	-1.52995	-1.52995	-1.52995	-45.2313	0	-0.0425
M40.mol	-1.51639	-1.55389	-1.55389	-48.0941	-0.88341	-0.04316
M24.mol	-1.40444	-1.40444	-1.40444	-47.112	0	-0.03901
M18.mol	-1.24103	-1.24103	-1.24103	-39.4025	-0.7	-0.03447
M26.mol	-1.15823	-1.15823	-1.15823	-48.3371	-0.23108	-0.03217
M25.mol	-1.03642	-1.03642	-1.03642	-30.4791	0	-0.02727
A13.mol	-0.20502	-2.26182	-2.26182	-55.4554	-0.7	-0.07539

RESULTS AND DISCUSSION

In this work, totally 80 compounds of 1 3 4 thiadiazoles derivatives from data base were used for the study. Six targetsof binding sites on the crystallographic structure of the enzyme have been examined for ligand based docking program. The ligands are screened for their ability to dock within the active site of the enzyme. Virtual screening is not performed to find the numbers of chemical compound which inhibit the activity of the enzyme, instead extra precision mode (XP) were used. More negative GlideS core value indicates a good interaction of the ligand with the target protein. After analyzing the different docking interactions of ligands, the compounds namely A3, A21, M34 & M36 showed fairly better interaction with PknG with the more negative G-Score value than the other drug molecules. The amino acids residues GLU588, SER597, ARG371, and HIS 589 in the kinase domain form hydrogen bonds with the ligands (Figure 1 &2). The amino acids like serine &glutamine form hydrogen bonds with the drug molecules of M series. Similarly aminoacids like serine and arginine forms hydrogen bond with compound of A series.

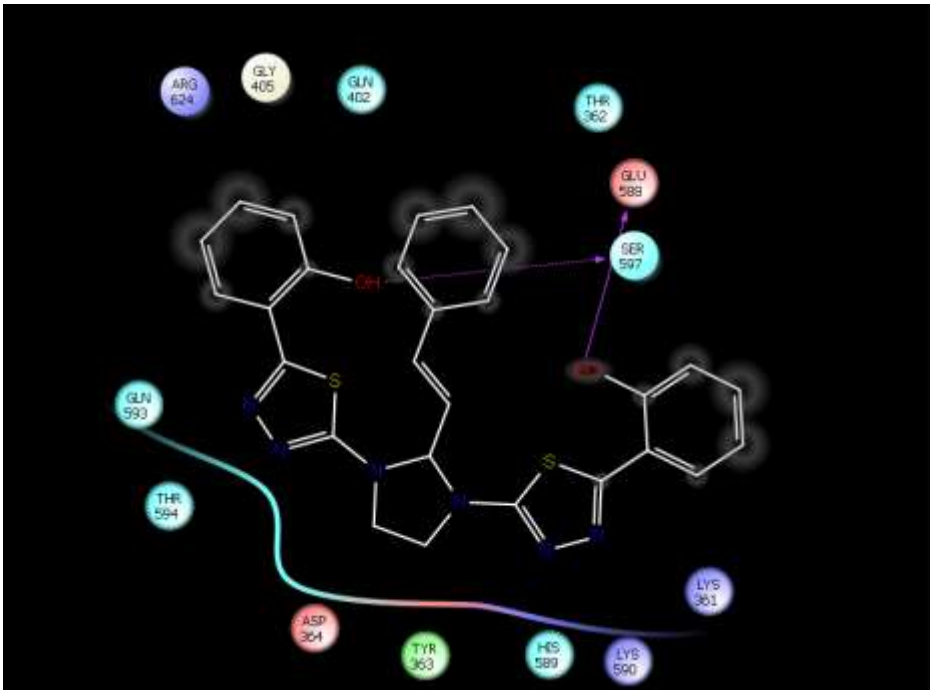

Figure 1: Docking interaction of compound M33 with the enzyme.

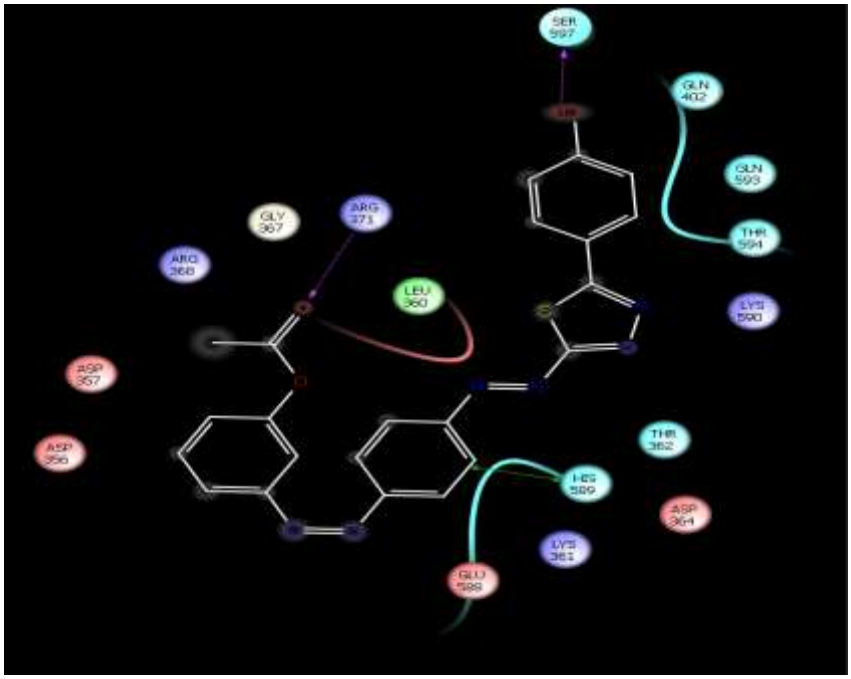

Figure 2: Docking interaction of compound A21 with the enzyme.

Compound A3 which is a azo dye derivative of thiadiazole contains phenyl group at 2nd position (R –Group) and a 4-Hydroxy – 2 Methyl Phenyl group at R1 position, possess high glide score value -5.47 and glide energy value of -48.47 which shows best ligand and enzyme interaction. Also compound A21 which contains a p-Hydroxy phenyl group at R position and a acetyl phenyl group at position R1 showed high glide score with -4.9 and glide energy of -52.9 (Table 1).

Many compounds in M series showed good interaction with the enzyme, out of which compound M34 with o-Hydroxy phenyl group as R group & Furfuryl ring as R1 groups have glide score of -4.71 and M36 with o-Hydroxy phenyl group as R group& dimethyl amino group as R1 have a glide score of -4.00.

A SERIES

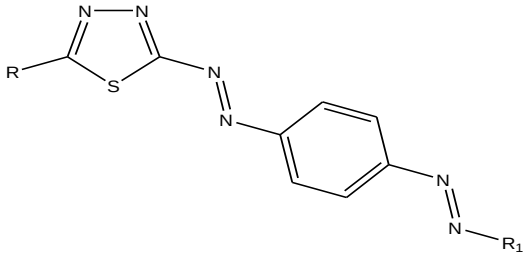

Table 1: 1,3,4 Thiadiazole derivatives of A series

Compound Code	R	R1	
A1 –A10	Phenyl (C6H5-)	A1	4-Hydroxy Phenyl
		A2	4-Hydroxy-3-Methyl Phenyl
		A3	4-Hydroxy – 2 Methyl Phenyl
		A4	3,5-Dimethyl-4-Hydroxy Phenyl
		A5	3-Isopropyl-4-Hydroxy-6-Methyl Phenyl
		A6	1-Napthyl Phenyl
		A7	2-Napthyl Phenyl
		A8	3-Isopropyl-4-Hydroxy-6-Methyl Cyclohexyl
		A9	2-Hydroxy-3-Methoxy-5-Vinyl Phenyl
		A10	3-Acetyl Phenyl
A11 –A21	p-Hydroxy Phenyl	A11	4-Hydroxy Phenyl
		A12	4-Hydroxy-3-Methyl Phenyl
		A13	4-Hydroxy – 2 Methyl Phenyl
		A14	3-Isopropyl-4-Hydroxy-6-Methyl Phenyl
		A15	1-Napthyl Phenyl
		A17	3-Isopropyl-4-Hydroxy-6-Methyl Cyclohexyl
		A18	2-Napthyl Phenyl
		A19	3,5-Dimethyl-4-Hydroxy Phenyl
		A20	2-Hydroxy-3-Methoxy-5-Vinyl Phenyl
		A21	3-Acetyl Phenyl
A21Q-A30	4- Chloro Phenyl	A21Q	4-Hydroxy Phenyl
		A22	4-Hydroxy-3-Methyl Phenyl
		A23	4-Hydroxy – 2 Methyl Phenyl
		A24	3,5-Dimethyl-4-Hydroxy Phenyl
		A25	3-Isopropyl-4-Hydroxy-6-Methyl Phenyl
		A26	1-Napthyl Phenyl
		A27	2-Napthyl Phenyl
		A28	3-Isopropyl-4-Hydroxy-6-Methyl Cyclohexyl
		A29	2-Hydroxy-3-Methoxy-5-Vinyl Phenyl
		A30	2-Hydroxy-3-Methoxy Phenyl Carbaldehyde

M - SERIES

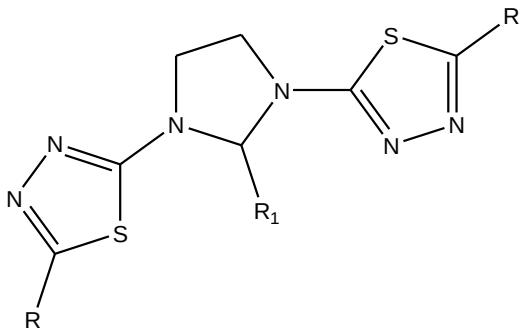

Table 2: 1,3,4 Thiadiazoles of M series

Compound code	R	R^1
M1 –M10	Phenyl	-H, -OCH_3, -2 OH, furan 2(OH) 3(OCH_3), N(CH_3)2 2-NO_2, 3-NO_2, 4-NO_2, -OH,
M11 –M20	P – Chloro Phenyl	H, -OCH_3, -2 OH, furan 2(OH) 3(OCH_3), N(CH_3)2 2-NO_2, 3-NO_2, 4-NO_2, -OH,
M21 –M30	Benzylidene	H, -OCH_3, -2 OH, furan 2(OH) 3(OCH_3), N(CH_3)2 2-NO_2, 3-NO_2, 4-NO_2, -OH,
M31 – M40	o- Hydroxy Phenyl	H, -OCH_3, -2 OH, furan 2(OH) 3(OCH_3), N(CH_3)2 2-NO_2, 3-NO_2, 4-NO_2, -OH,

Mycobacterium tuberculosis PknG is an essential receptor-like protein kinase involved in cell growth control. M. tuberculosis PKnG is a trans-membrane Ser/Thr protein kinase (STPK) highly conserved in Gram-positive bacteria and apparently essential for mycobacterial viability[9]. The thiadiazole derivatives and its different analogues were found to bind with protein kinase enzyme. The docking screening was performed by employing the scoring function. The result was based on the score of estimated free energy, inhibition constant, and hydrogen bonding.

CONCLUSION

On comparing the glide score values, better interaction was shown by compoundsA3, A21, M34&M36 with glide score values -5.4, -4.9, -4.7 and -4.00 respectively. Thus by analyzing these datas 1 3 4 thiadiazole derivatives can be considered as potent inhibitor against the enzyme protein kinase in *Mycobacterium tuberculosis*.

REFERENCES

1. Sattar Ebrahimi. Synthesis of some pyridyl and cyclohexyl substituted 1,2,4 triazole, 1,3,4 thiadiazole and 1,3,4 thiadiazole derivatives. Eur J Chem 2010; 1 (4): 322 – 24
2. Shrivastava K, Vivek Daniel, Pramod S. Kunwar, Swapnil Goyal, Gupta V.D. Synthesis

and biological activity of some novel 1,2,4-Triazole[3,4-B][1,3,4] thiadiazole derivatives J Global Pharma Technology 2010; 2(1): 72 – 80

3. Mullican MD, Wilson MW, Connar DT, Kostlan CR, Schrier DJ, Dyer RD.Design of 5-(3,5-di-tert-butyl-4-hydroxyphenyl)-1,3,4-thiadiazoles, -1,3,4-oxadiazoles, and -1,2,4-triazoles as orally-active, nonulcerogenic antiinflammatory agents. J MedChem 1993;36: 1090 – 99
4. Ankit Tripathi, Nupur Wadia, Deepak Bindal, Tarakanta Jana. Docking studies on novel alkaloid tryptanthrin and its analogues against enoyl-acyl carrier protein reductase (InhA) of *Mycobacterium tuberculosis.* Indian J. Biochem. Biophys 2012;48: 435 – 41
5. Anuja Randi, Saroj Rani, Savitha Kumari, Sudhir Kumar, Manoj Giri. An analysis of docking study on tuberculosis inhibitors. International Journal of Bioinformatics research 2010; 2 (1): 38 – 43
6. Natchimuthu Santhi, Sekar Aiswarya. Insights from the molecular docking of with anolide derivatives to the target protein PknG from *Mycobacterium tuberculosis.* Bioinformation 2011;7 (1): 1 -5
7. Richard A Friesner, Robert B Murphy, Matthew P Repasky, Leah L Frye, Jeremy R Greenwood, Thomas A Halgren, et al. Extra precision glide: docking and scoring incorporating a model of hydrophobic enclosure for protein-ligand complexes. J Med Chem. 2004: 47: 1739 -49
8. Meena Chandran, Vijey Aanandhi M, KrishnaKumar K. Comparative study on conventional and microwave assisted synthesis and molecular docking studies: Mannich bases of Benzimidazoles and their derivatives.JPR: BioMedRx An International Journal 2013;1 (10); 974 -80
9. Arshi Naquvi, Mohd Shanawaz, Asif Naquvi. N'-(Substituted benzylidene)-3-(2-nitrophenylamino)-3- oxopropanehydrazide: Synthesis, molecular docking studies and anti-mycobacterial screenings. 16th International electronic conference on synthetic organic chemistry (ECSOC -16). www.sciforum.net/conf/ecsoc - 16