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Original Article

MOLECULAR DOCKING STUDIES ON THIADIAZOLE DERIVATIVES AS PROTEIN KINASE INHIBITORS

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ABSTRACT

Objective: In the present study, a novel series of 1, 3, 4-thiadiazole derivatives were docked against the *mycobacterium tuberculosis* protein kinase G. 1, 3, 4–thiadiazole derivatives with a modified primary amine group at 5th position were used for docking studies.

Methods: The three-dimensional structure of the protein was obtained from PDB, and its active sites were predicted. The structures of all the compounds were drawn using chemdraw software version 8.0. The docking studies were done by using schrödinger software against the enzyme protein kinase G. Totally eighteen compounds was synthesized based on glide score

Results: In this Docking study the thiadiazole analogues were showing good binding energy. The amino acids residues GLU_{588}, SER_{412}, GLY_{410} and GLU 628 in the kinase domain active site form hydrogen bonds with the ligand.

Conclusion: The compounds D_{34}, D_{16}, D_7, D_{25}, D_{15}, and D_{27} showed better interaction with protein kinase G (pknG) more than the other drug molecules

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

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INTRODUCTION

Mycobacterium tuberculosis (MTB) is an aerobic pathogenic bacteria and is the causative agent of most cases of tuberculosis. Tuberculosis (TB) is a lung infection and is highly contagious and deadly disease. The reason for the widespread of this disease is the emergence of multi-drug resistant TB strains and less availability of a new drug with a novel mechanism of action [1].

A permanent solution to this disease will be the development of vaccines. But the most reliable will be chemotherapy, which requires effective and non-toxic antitubercular agents. The identification of new target sites will decrease the problems associated with multi-drug resistant strains, for this biochemical pathway specific to the mycobacterium disease cycle must be better understood [2].

This strategy and the conditions have indulged in the development of new thiadiazole moieties as antitubercular drugs by inhibiting the important enzymes involved in the bacterial life cycle. The enzyme protein kinase G (PKnG) is not needed for mycobacteria growth, but this enzyme is very much important for the survival of Mycobacterium in the host macrophages [3] and has marked as the best target enzyme protein for docking studies. Different 1 3 4 thiadiazole derivatives are considered as ligands or drug molecules which are going to interact with the enzyme thus inhibiting its activity [4].

Pathogenecity of mycobacteria is due to its survival in host cell macrophages. All phagocytosized microbes are rapidly transferred from host cell macrophages to lysosomes and degraded. Mycobacteria resist lysosomal delivery and also reuptake into macrophages, so they survive intracellularly. This is due to protein kinase G secreted from mycobacteria which inhibit macrophages lysosome fusion causing the survival of the bacteria. Chemical inhibition of protein kinase G causes lysosomal localization and mycobacterial cell death [5]. This enzyme inhibition is done by drug molecules or ligands binding with the enzymes. The binding capacity of the ligand with the enzyme was analysed by docking studies. The present study was carried out to evaluate the efficiency of the thiadiazole compounds against mycobacteria using molecular docking studies with the objective to find potential drug targets.

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 1, 3, 4-thiadiazoles with calculated molecular weight from 240 and its derivatives (table 2) 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 (OPLS-AA) force field [7] with the steepest descent followed by curtailed Newton conjugate gradient protocol. Partial atomic charges were computed using the OPLS-AA force field [6].

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 the present 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 a 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 [7].

RESULTS AND DISCUSSION

In this work, totally 40 compounds of thiadiazoles derivatives with modifications in the amino group of 5th position were used for the study. Six targets of 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 a chemical compound which inhibit the activity of the enzyme. Instead extra precision mode (XP) were used. More negative glide score value indicates a good interaction of the ligand with the target protein. After analyzing the different docking interactions of ligands, the compounds namely D34, D16, D7, D25, D15, and D27 showed fairly better interaction with protein kinase (PknG) with the more negative G-Score value than the other drug molecules. The amino acids residues GLU588, SER412, GLY410 and GLU 628 in the kinase domain (fig. 1, 2 and 3) form hydrogen bonds with the ligands. The amino acids like serine and glutamine form hydrogen bonds with the drug molecules of D series.

Compound D34 which is a chalcone derivative of thiadiazole contains pyridyl group at 2nd position (R Group) and a m-Hydroxy–p-Methoxy Phenyl group at substituted at the amino group of 5th position (R_1 position) possess high glide score value-6.69 and glide energy value of-42.64 which shows best ligand and enzyme interaction. Also, compound D16 which contains a p-hydroxyphenyl group at R position and a dimethyl aminophenyl group at position R1 showed high glide score with-6.62 and glide energy of-48.62. Many compounds in D series showed good interaction with the enzyme, having glide score range from-4.8 to-6.69 (table 1).

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 viability [8].

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.

Table 1: Data of estimated docking parameters of thiadiazole analogues with protein kinase G

Title	Docking score	XP G score	Glide G score	Glide energy	Glide E internal	xp h bond	Glide ligand efficiency [8]
2PZI							
D34. mol	-6.3394	-6.6935	-6.6935	-42.6465	0	-2.01368	-0.26774
D16. mol	-6.2503	-6.6269	-6.6269	-48.6215	15.19324	-0.35539	-0.24544
D7. mol	-5.8741	-6.2339	-6.2339	-43.7537	4.487678	-0.9	-0.25975
D25. mol	-5.8323	-6.1465	-6.1465	-47.7566	8.266831	-1.18	-0.23641
D15. mol	-5.7560	-6.1027	-6.1027	-42.2412	9.169291	-2.85873	-0.25428
D27. mol	-5.673	-6.246	-6.2463	-43.7829	10.34215	-0.9975	-0.26026
D33. mol	-5.4844	-5.9822	-5.9822	-41.3284	11.96712	-1.95	-0.2601
D17. mol	-5.3738	-5.7475	-5.7475	-41.0715	7.604469	-0.7	-0.2299
D14. mol	-5.0956	-5.4423	-5.4423	-47.0438	0	-1.51683	-0.20932
D26. mol	-5.0464	-5.3673	-5.3673	-47.2284	13.75001	-0.7	-0.20644
D10. mol	-4.9576	-5.2905	-5.2905	-40.19	7.479155	-0.29881	-0.23002
D39. mol	-4.8320	-5.1939	-5.1939	-41.3978	12.04666	0	-0.22583
D36. mol	-4.7932	-5.2721	-5.2721	-41.488	3.481447	-0.23762	-0.22923
D9. mol	-4.6992	-5.0539	-5.0539	-41.6236	0	-0.68761	-0.21974
D30. mol	-4.6905	-5.0047	-5.0047	-41.2029	5.028046	-0.05378	-0.20853
D24. mol	-4.5593	-5.1842	-5.1842	-43.8498	17.06249	-0.7	-0.23565
D28. mol	-4.5470	-4.8612	-4.8612	-42.9364	9.682065	0	-0.20255
D8. mol	-4.5356	-4.8685	-4.8685	-41.0375	9.210653	-0.49952	-0.21168
D29. mol	-4.4410	-5.0136	-5.0136	-42.2539	6.16229	-1.37057	-0.2089
D21. mol	-4.3420	-4.6562	-4.6562	-40.4049	7.941264	-1.03888	-0.20245
D2. mol	-4.3106	-4.6435	-4.6435	-43.1724	8.176312	0	-0.19348
D22. mol	-4.2770	-4.5912	-4.591	-41.656	11.264	-0.6537	-0.1836
D5. mol	-4.2158	-4.4479	-4.4479	-40.1022	4.208613	-0.7	-0.21181
D32. mol	-4.1778	-4.5397	-4.5397	-43.5986	8.83195	-0.07374	-0.18916
D12. mol	-4.1573	-4.466	-4.46	-44.3128	7.143773	-0.56692	-0.17864
D40. mol	-4.1241	-4.8366	-4.83667	-36.6305	9.555526	-0.45638	-0.23032
D38. mol	-4.1169	-4.5018	-4.50183	-43.3633	8.564388	-0.2938	-0.19573
D13. mol	-4.0203	-4.6467	-4.64677	-41.3201	11.99485	-0.89203	-0.21122
D1. mol	-3.9445	-4.2774	-4.27743	-33.6689	13.21224	-0.084	-0.19443
D31. mol	-3.9302	-4.3940	-4.39404	-27.7501	13.77523	-0.39136	-0.19973
D6. mol	-3.9295	-4.2924	-4.29247	-42.914	11.81976	0	-0.1651
D3. mol	-3.9106	-4.2142	-4.21422	-41.3832	4.710607	-0.65721	-0.18323
D35. mol	-3.8009	-4.1932	-4.19328	-45.9145	6.055371	-0.7	-0.16773
D23. mol	-3.7838	-4.0980	-4.09804	-39.1289	6.106972	-1.31092	-0.17075
D4. mol	-3.7459	-4.2672	-4.26725	-46.0125	11.90417	-1.99717	-0.17069
D18. mol	-3.6395	-3.9862	-3.98628	-46.2679	3.122691	-1.04324	-0.1661
D11. mol	-3.5951	-4.1160	-4.11603	-48.3259	9.010351	-0.35	-0.15245
D19. mol	-3.2861	-3.6328	-3.63287	-36.1451	0.670452	-0.32319	-0.15137
D37. mol	-3.1718	-3.5337	-3.53376	-41.5995	7.738014	-1.4114	-0.15364
D20. mol	-2.1184	-2.4651	-2.46517	-43.0892	10.58537	0	-0.10272

General structure of compound D-Series

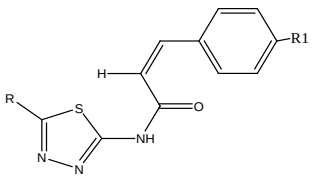

Table 2: 1 3 4 thiadiazole derivatives of D-series

Compound code	R	R1	
D1–D10	C_6H_5-phenyl	D1	Phenyl
		D2	4-methoxy phenyl
		D3	2-hydroxy phenyl
		D4	3-hydroxy-4-methoxy phenyl
		D5	Furfuryl
		D6	p-dimethyl amino phenyl
		D7	2-amino phenyl
		D8	3-amino phenyl
		D9	4-amino phenyl
		D10	4-hydroxy phenyl
D11–D20	4–Hydroxyl phenyl	D11	Phenyl
		D12	4-methoxy phenyl
		D13	2-hydroxy phenyl
		D14	3-hydroxy-4-methoxy phenyl
		D15	Furfuryl
		D16	p-dimethyl amino phenyl
		D17	2-amino phenyl
		D18	3-amino phenyl
		D19	4-amino phenyl
		D20	4-hydroxy phenyl
D21–D30	2-Hydroxy Phenyl	D21	Phenyl
		D22	4-methoxy phenyl
		D23	2-hydroxy phenyl
		D24	3-hydroxy-4-methoxy phenyl
		D25	Furfuryl
		D26	p-dimethyl amino phenyl
		D27	2-amino phenyl
		D28	3-amino phenyl
		D29	4-amino phenyl
		D30	4-hydroxy phenyl
D31–D40	Pyridyl	D31	Phenyl
		D32	4-methoxy phenyl
		D33	2-hydroxy phenyl
		D34	3-hydroxy-4-methoxy phenyl
		D35	Furfuryl
		D36	p-dimethyl amino phenyl
		D37	2-amino phenyl
		D38	3-amino phenyl
		D39	4-amino phenyl
		D40	4-hydroxy phenyl

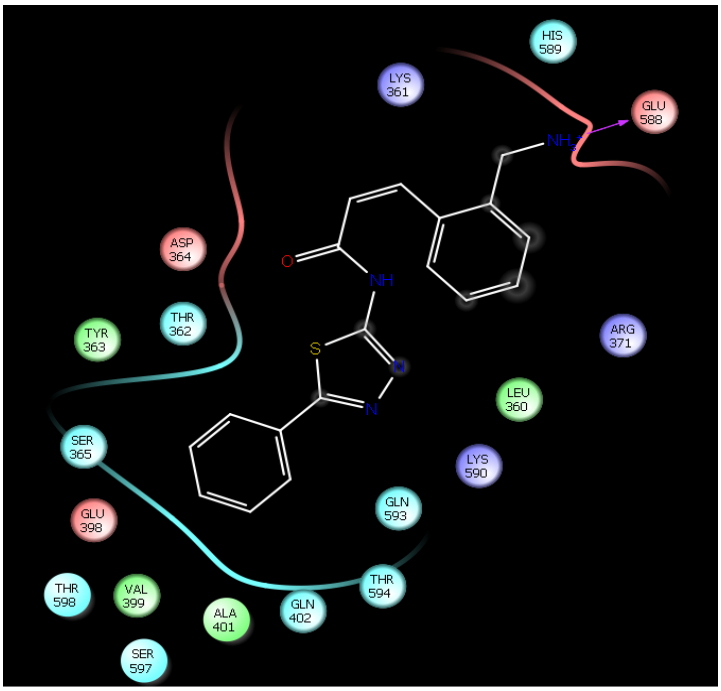

Fig. 1: Interaction of the compound D7 with the enzyme

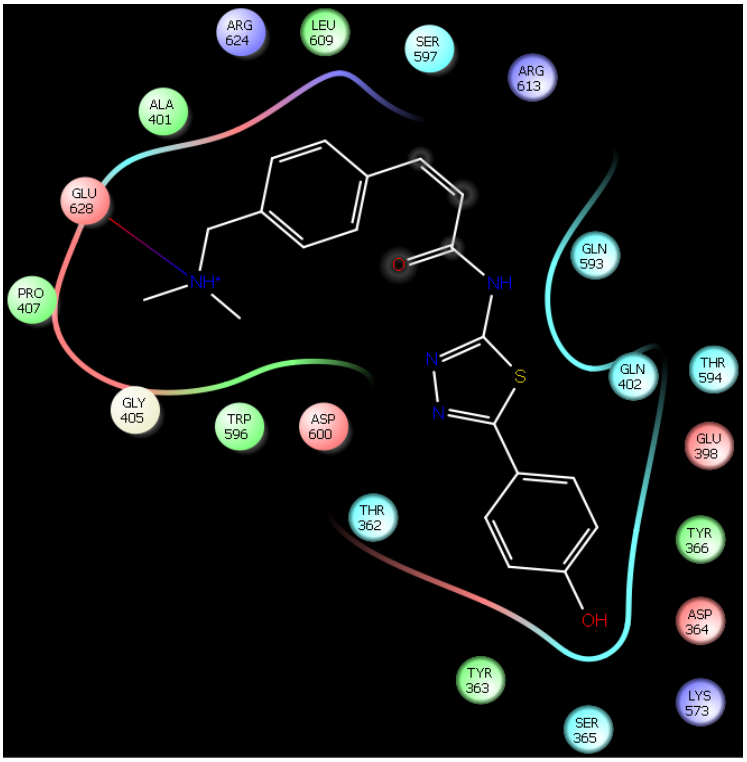

Fig. 2: Interaction of compound D16 with the enzyme

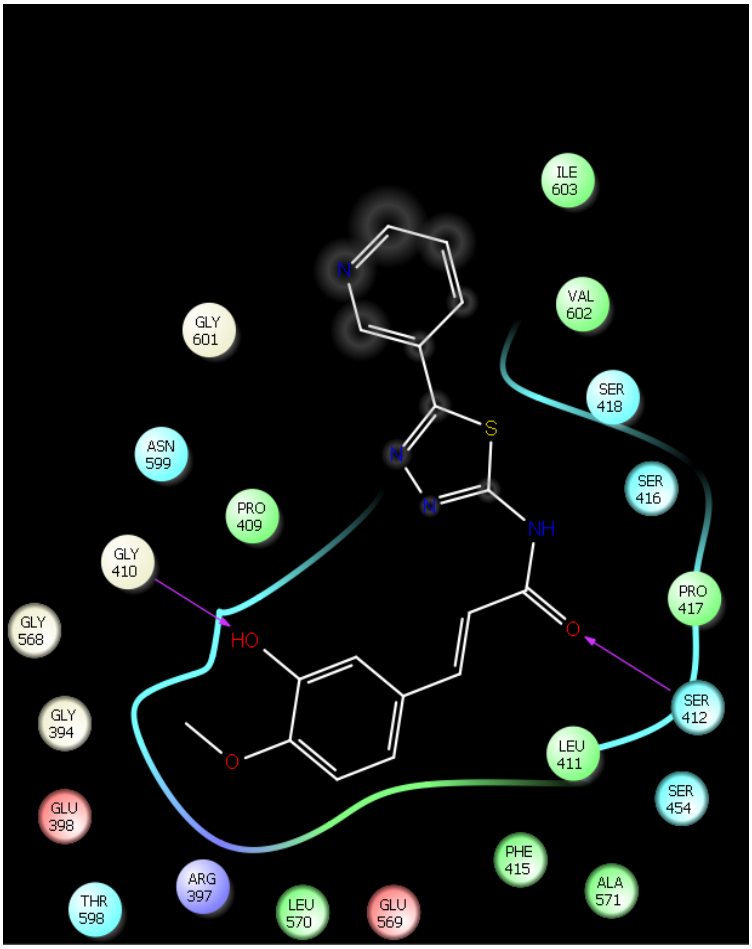

Fig. 3: Interaction of compound D34 with the enzyme

CONCLUSION

On comparing the glide score values, the better interaction was shown by compounds D_{34}, D_{16}, D_7, and D_{25} with glide score values-6.69,-6.62,-6.23 and-6.14 respectively. Thus by analyzing these datas 1 3 4 thiadiazole derivatives can be considered as a potent inhibitor against the enzyme protein kinase in *Mycobacterium tuberculosis*.

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AUTHORS CONTRIBUTIONS

All the experimental work was carried out by the first author, whereas, the second author, supervised them.

CONFLICT OF INTERESTS

Declared none

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