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Short Communication

Molecular docking studies of 1,3,4 -thiadiazoles as myeloperoxidase inhibitors

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ABSTRACT

Background: Myeloperoxidase (MPO) is a heterodimeric, cationic and glycosylated haeme enzyme which gets released under increased oxidative stress producing neutrophil oxidant, hypochlorous acid having the capacity to modify various biomolecules by chlorination and/or oxidation of sulfhydryl groups in proteins causing their inactivation and promoting inflammatory tissue damage. Different levels of hypochlorus acid are used as a trait marker for prescribing the disorders e.g. atherosclerosis, rheumatoid arthritis, lung cancer, Immuno-reactivity.

Methods: Mini library of 22500 2,5disubstituted 1,3,4 thiadiazoles were docked with Myeloperoxidase in order to identify the potent inhibitor against the enzyme. The chemical nature of the protein and ligands greatly influence the performance of docking process. Keeping this fact in view, critical evaluation of the performance was performed by GLIDE by HTVS, SP and XP. The ADME parameters by QIKPROP and protein-ligand binding free energies were calculated using the Prime/MM-GBSA module of Schrödinger.

Results: Both hydrogen bonding and hydrophobic interactions contributed significantly for its ligand binding and core influence the target site through prominent hydrophobic and charged interaction with the backbone and side chain residues in the target site that improves the affinity of the molecule. The compound selected as potent inhibitor is having minimum binding affinity, maximum GScore and minimum FlexX energy. The amino acids residues ASP98, ASP94, THR100 and GLU 102 in the MPO gene domain active site form hydrogen bonds with the ligand. Compounds 3350-5150 showed better interaction with haeme enzyme for further understanding of structures, reliability and Biomolecularactivityy in connection with oxidative stress induced disorders.

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1. Background

In humans, oxidative stress may be involved in many diseases including atherosclerosis.[1], Parkinson's disease[2], heart failure, myocardial infarction[3], Alzheimer's disease[4], schizophrenia, cancer[5,6] etc. Myeloperoxidase is a haeme enzyme abundant in granules of human inflammatory cells. The enzyme MPO as the prominent generator of reactive oxidizing species in neutrophils uses H_2O_2 and (pseudo) halides mostly chloride ion due to its increased concentration in body fluids to produce hypo (pseudo) halous acids (HOX, HOSCN). Myeloperoxidase gets released outside the phagocytes producing the most powerful and stable neutrophil oxidant, hypochlorous acid. This production of HOCl contributes to tissue damages. HOCl has the capacity to modify various biomolecules by chlorination and/or oxidation of sulfhydryl groups in proteins causing their inactivation. MPO is implicated in a growing number of diseases like atherosclerosis, rheumatoid arthritis, lung cancer and many others.HOCl has the capacity to modify various biomolecules by chlorination and/or oxidation of sulfhydryl groups in proteins causing their inactivation.[7,8] HOCl act as an immunological tool to identify chlorinated biomarkers in kidney disease, ischemia reperfusion, Parkinson's diseaseand atherosclerosis.[9],[10],[11]

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In the present study, combinatorial technology was applied to design and generate a small library consisting of 22,500 molecules 1, 3, 4- thiadiazole scaffold. Myeloperoxidase was selected as target for identification of lead molecules with good ADME properties and effective binding affinity with target enzyme myeloperoxidase.

2. Materials and Methods

Schrodinger software version was used for the docking studies. For the determination of protein–Ligand binding affinities and scoring function GLIDE 9.1 (Grid Based Ligand Docking with Energies) XP (Extra Precision) docking protocol was used. Combinatorial technology[9,10] was applied to design and generate a small library consisting of 22,500 molecules 1, 3, 4- thiadiazole scaffold. Myeloperoxidase was selected as target for identification of lead molecules with good ADME properties and effective binding affinity with target enzyme myeloperoxidase.

2.1. Myeloperoxidase

(4C1M) -Resolution of Myeloperoxidase (4C1M) selected was 2.00 A° and the R value and r free value was found to be (0.225, 0.278). The target protein was prepared and viewed through the ramachandran plot which shows clearly for all the essential aminoacids to be in the favourable region (Red colour), some in slightly favourable region (yellow) and none in unfavourable region (White).

As per the literature of this particular pdb file 4CIM gives information that the preferable conserved H-bonding interactions of inhibitors with hinge region residues Lys 308c, Phe 407, Arg 239 and Gln 91a are observed in most of the inhibitor-myeloperoxidase complex structures.

2.2. Ligand database preparation

The structure of ligand molecules was built in the panel of Maestro and store (in. mae) format by using the build tool and the fragments which had been used were shown in the figure 2. A**D**ME studies: A set of ADMET-related properties (a total of 50 molecular descriptors) Table 1 was calculated by using the QikProp program (Schrödinger 2011d) running in normal mode.

2.3. Ligand receptor docking and predicting activity

After the preparation of protein, the prepared ligands were docked with the respective proteins. The ligands Database which consist of 22500 molecules which had been already prepared by ligprep were filtered by qikprop and first initially docked by using Glide in HTVS (high throughput virtual screening) mode and Standard mode (sp).

2.4. Specifying the Receptor Grid

The receptor grid image of myeloperoxidase with its active site is shown below.

After investigating the results of docking study and predicted activity top 20 molecules were selected and then the common scaffold was identified using the thiadiazolescaffholdThese molecules were than tagged as 3205 to 5150. The molecules molecular name was again investigated as a literature review to find out the information. 5150 tagged compound was found to have effective binving affinity.

2.5. 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]

3. MM-GBSA Calculations of Protein-Ligand Binding Free Energies

3.1. Molecular mechanics/generalized born surface area (MM/GBSA)

In this study, computational methods were applied to identify binding site interaction details between thiadiazoles scaffold and myeloperoxidase. The protein-ligand binding free energies during the last 2 ns were calculated using the Prime/MM-GBSA module of Schrödinger suite[8,11] to get the averaged binding property. The binding free energy ΔGbind was estimated using the equation:

3.2. ΔGbind = gcomplex — (gprotein + gligand) (2)

WhereG complex is the optimized free energy for the complex, Gprotein and Gligand are the optimized free energy for the free protein and free ligand, each energy term was calculated by a combination of molecular mechanics energy, implicit solvation energy and surface area energy. Residues in binding pockets of the protein were treated as flexible and the ligand partial charges were assigned by the initial Charm charges. MM/GBSA has been successfully applied to various protein-ligands but their performance is system dependent.[12,13]

4. Results

In this work, library ofthiadiazoles derivatives with modifications in the 2^{nd} position and amino group of 5th position were used for the study. QikProp predicted physically significant descriptors and pharmaceutically relevant properties of organic molecules, in batches.

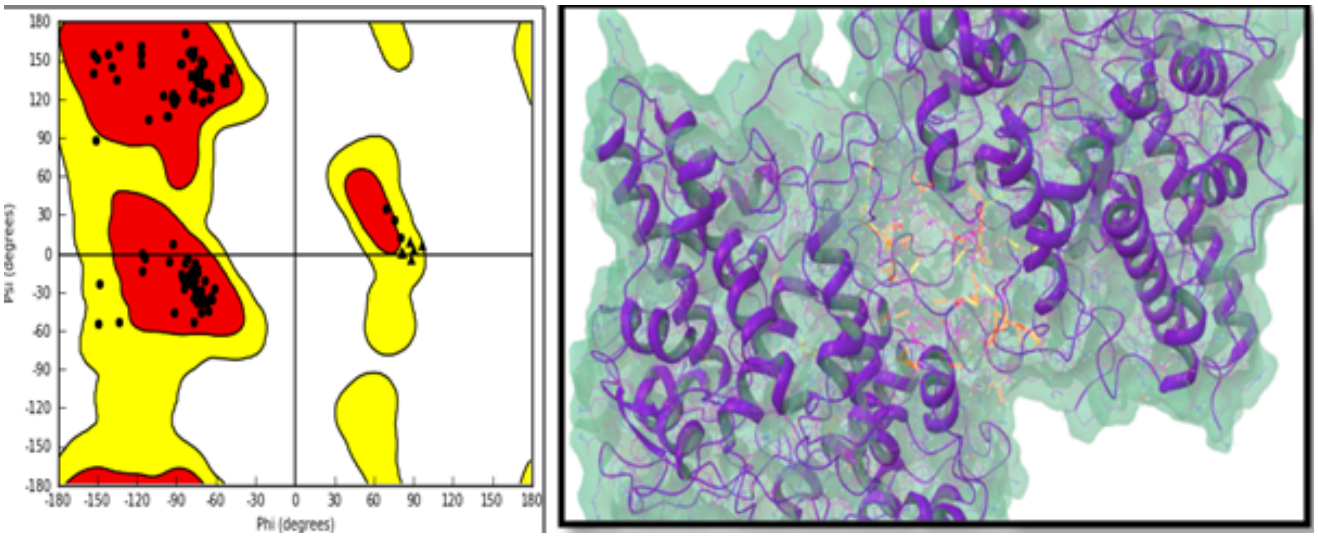

Fig. 1: Receptor site of Myeloperoxidase (4C1M)& Ramachandran plot of Myeloperoxidase receptorpdb file (4C1M)

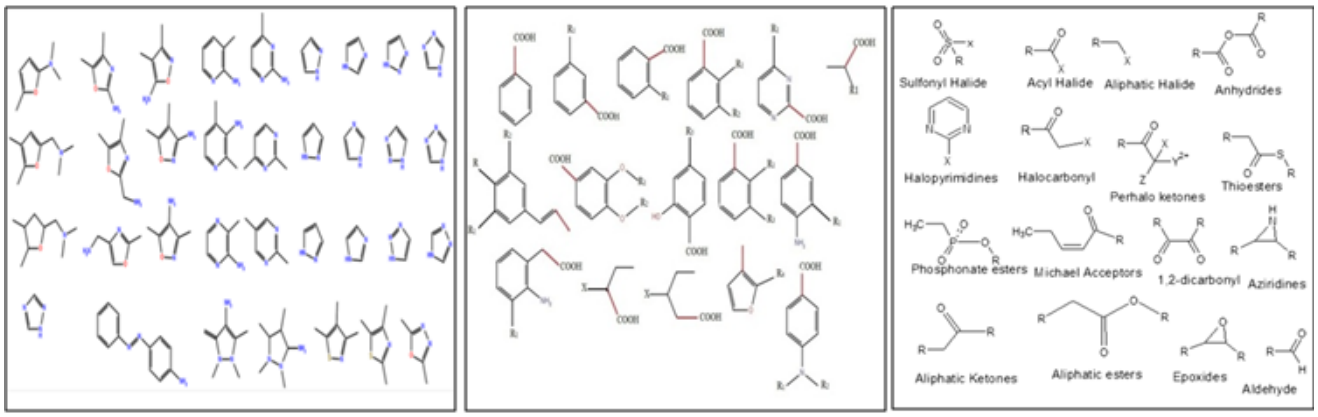

Fig. 2: Heterocyclic nucleus used as Reagent 1, Reagent2 & toxicity filters in the corelibrary generation

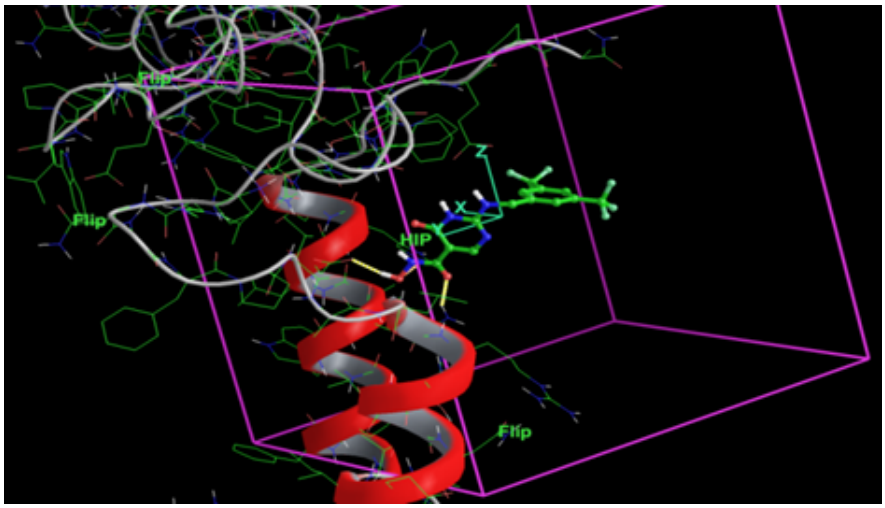

Fig. 3: Receptor grid image of myeloperoxidase receptor(4C1M)

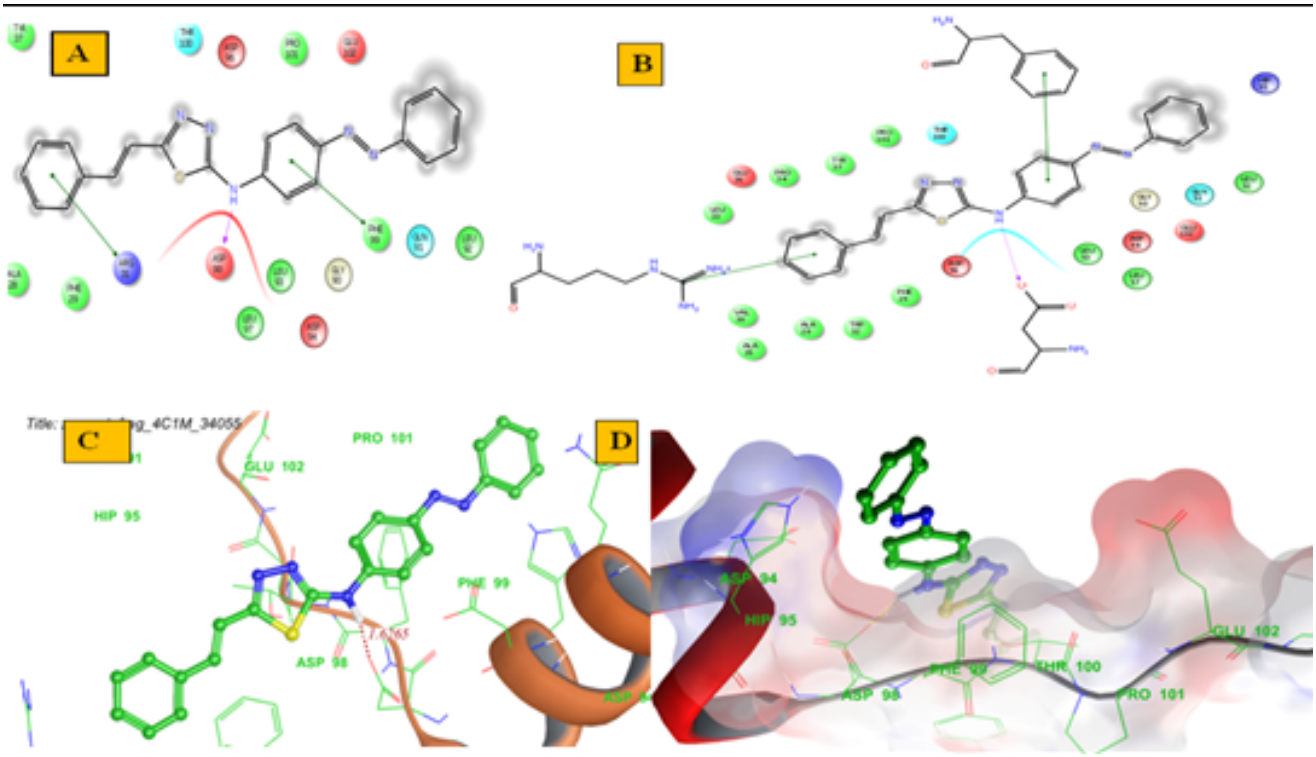

Fig. 4: Compound 5150 in mesh form.(A). 2D ligandInteraction showing interaction of 5150 with myeloperoxidase receptor aminoacid residue Arg 30, Asp 98 and Phe 99 (B) NH amine in ligand 5150 formingH-bond with the O in Carboxyl group ofAsp 98, Aromatic ring of ligand forming hydrophobic bond with aromatic ring inPhe 99 and C-Chain in Arg 30 (D) Compound 5150 been docked with themyeloperoxidase receptor

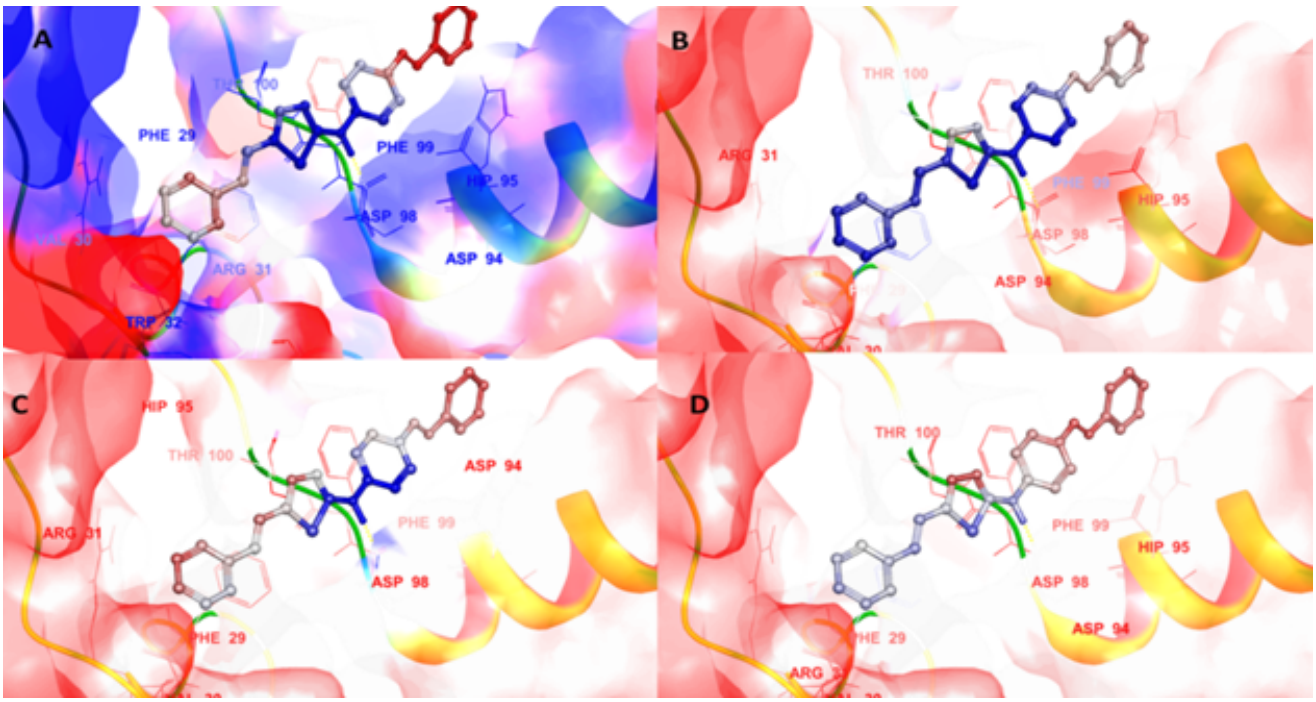

Fig. 5: Visualization of Prime energy and ΔG bindingenergy of compound 5150 with enzyme myeloperoxidase

Table 1: ADME parameters prediction of the screene1, 3, 4-thiadiazoles

ID	RO3	QPPCaCo	MDCK	QPLog KHSA	Jm	Metabolism	QPlogHERG
3205	0	351.307	216.715	-0.68	0.3	3	-5.037
3350	0	529.258	450.343	-0.548	1.484	1	-5.802
3500	1	3.066	1.911	-1.184	0.002	2	-3.407
3650	0	853.918	571.97	0.045	0.031	4	-5.266
3800	0	842.567	748.567	0.171	0.065	2	-5.884
3950	1	4.604	2.675	-0.68	0	3	-3.572
4100	1	1377.079	1147.187	0.412	0.005	4	-6.418
4250	1	1366.183	1261.64	0.606	0.009	2	-7.097
4400	1	6.843	4.812	-0.301	0	3	-4.726
4550	0	1225.518	807.363	0.281	0.027	6	-5.557
4700	0	1836.642	1734.43	0.42	0.112	4	-6.339
4850	1	11.074	7.64	-0.508	0.001	5	-3.877
5000	1	1460.013	986.66	0.705	0.006	4	-7.493
5150	1	1452.113	1091.19	0.855	0.016	2	-3.124
5300	1	12.396	8.639	-0.172	0	3	-5.78
5450	0	3148.614	2775.842	0.193	0.759	5	-5.435
5600	0	3136.279	3080.97	0.317	1.996	3	-6.141
5750	1	18.105	14.099	-0.563	0.008	4	-3.721
Range	Max 3	<25 p, >500 great	<25 poor,>500 great	-1.5 to +1.5		1-8	Concern below-7

Table 2: Data of estimated docking parameters of thiadiazole analogues with myeloperoxide

ID	Docks core[a]	Lipophilic EvdWb	H Bondc	Electrod	Site mape	Low MWf	Expos Penalg	Rot Penalh	Good vdw	Bad vdw	Ugly vdw
3205	-2.8	-1.7	-0.3	-0.2	-0.4	-0.5	0.1	0.3	110	3	0
3350	-1.8	-1.1	-0.3	-0.5	0.0	-0.5	0.1	0.4	207	5	0
3500	-4.1	-0.5	-1.7	-2.0	0.0	-0.4	0.2	0.3	105	4	0
3650	-2.8	-0.8	-1.4	-0.6	0.0	-0.4	0.1	0.2	146	5	0
3800	-2.5	-2.1	-0.3	-0.2	0.0	-0.5	0.1	0.4	181	4	0
3950	-3.9	-1.1	-1.4	-1.5	0.0	-0.3	0.1	0.3	153	3	0
4100	-1.6	-0.9	-1.2	-0.5	0.0	-0.1	0.9	0.2	136	5	0
4250	-1.5	-1.3	-0.7	-0.2	0.0	-0.2	0.6	0.3	145	6	0
4400	-2.2	-1.2	-1.1	-0.9	0.0	0.0	0.8	0.2	130	0	0
4550	-2.8	-0.8	-1.4	-0.5	0.0	-0.4	0.1	0.2	144	2	0
4700	-2.3	-0.5	-1.3	-0.6	0.0	-0.5	0.3	0.4	107	0	0
4850	-3.5	-0.5	-1.7	-1.9	0.0	-0.3	0.5	0.2	99	4	0
5000	-2.1	-0.8	-1.5	-0.5	0.0	-0.1	0.6	0.2	140	4	0
5150	-5.3	-0.9	-0.3	-0.6	0.0	-0.2	0.4	0.3	167	2	0
5300	-3.5	-0.9	-1.2	-1.6	0.0	0.0	0.0	0.2	157	5	0
5450	-2.8	-0.7	-1.6	-0.6	0.0	-0.4	0.1	0.3	129	3	0
5600	-1.8	-1.1	-0.3	-0.5	0.0	-0.5	0.2	0.5	124	4	0
5750	-3.3	-0.5	-1.7	-1.8	0.0	-0.3	0.8	0.3	110	4	0

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. Instead extra precision mode(XP) were used. After analyzing the different docking interactions of ligands, the compounds namely 3350, 3500, 3950, 4400, 4850, 5300 and 5750 showed fairly better interaction with Myeloperoxidase with the more negative G-Score value than the other drug molecules. The docking scores summarized in with glide score ranging from -5.3 to -1.3. The free energy of binding of various conformers of ethambutol with the receptor was calculated employing Prime MM-GBSA approach

5. Discussion

The designed library was filtered for drug like properties with the help of qikprop. The pharmacokinetic properties (ADMET) were predicted and the results are tabulated (table 1). In drug likeliness assessment 50 % showed lead like

Table 3: Free energy of binding of various conformers ofthiadiazole scaffold with the receptor myeloperoxidase (4C1M)

ID	Prime MMGBSA Complex Energy	Prime MMGBSA Ligand Energy	Prime MMGBSA Receptor Energy	Prime MMGBSA DG bind (ΔGbind =kcal/mol)	Prime MMGBSA DG bind Coulomb	Prime MMGBSA DG bind vdW
3205	-3895.3	-16.752	-3843.57	-30.534	-25.135	-23.549
3350	-3886.6	-4.367	-3843.57	-32.682	-17.011	-21.644
3500	-3905.4	-20.482	-3843.57	-35.37	-46.125	-19.964
3650	-3919.1	-32.299	-3843.57	-37.26	-16.817	-24.038
3800	-3927.5	-35.14	-3843.57	-42.838	-3.678	-27.52
3950	-3925.7	-54.865	-3843.57	-32.989	-21.636	-20.985
4100	-3870.1	23.553	-3843.57	-44.136	-16.683	-30.219
4250	-3874.6	18.952	-3843.57	-44.051	-9.442	-25.123
4400	-3891.6	2.699	-3843.57	-44.78	-12.885	-33.611
4550	-3929.8	-41.175	-3843.57	-39.069	-12.601	-27.313
4700	-3931.2	-48.298	-3843.57	-33.319	-16.701	-18.951
4850	-3943.1	-63.608	-3843.57	-35.841	-36.428	-20.08
5000	-3880	7.343	-3843.57	-37.758	-11.708	-31.894
5150a	-3896.6	1.688	-3843.57	-48.725	-9.844	-29.853
5300	-3925.7	-32.856	-3843.57	-43.333	-31.448	-23.514
5450	-3894.5	-13.611	-3843.57	-31.314	-15.97	-21.186
5600	-3907.7	-17.733	-3843.57	-40.401	-11.88	-23.77
5750	-3923.2	-34.84	-3843.57	-38.767	-31.256	-22.99

[a] most stable conformer

and 30% of the screened compounds showed fragment like property. All compounds satisfied the jorgenson rule of 3, fell within the range for Caco-2 permeability test so they are likely to be more orally bioavailable. As MDCK cells serve as good mimic for BBB it was estimated that about 66% of compound had apparent MDCK cell permeability falling within the recommended range for 95% of known drugs. The predicted maximum transdermal rates Jm fell within the predicted range. The plasma protein binding was predicted using logkHSA more than 96% of compounds are compliant to this parameter indicating free circulation with in the blood stream and ascess to target site. 100% of the compound predicted to undergo the recommended no of metabolism reactions (1-8) with 10% in drug like (5-6), 50% in lead like (3-4) and 40% in fragment like subset. logIC_{50} values for blockage of HERGk+ channel is >-5. The parameter was found to be in recommended range for majority of compounds.

As per the results obtained core influence the target site through prominent hydrophobic and charged interaction with the backbone and side chain residues in the target site that improves the affinity of the molecule. Overall the core had good influence in the target site, and there is large scope for the optimization of the core keeping all the facts in the mind. The major interactions formed by ligands with the receptor myeloperoxidase may be categorized as hydrogen bond, hydrophobic bond, π-π stacking and electrostatic interactions All the ligands showed selected strong hydrogen bond interactions with the amino acids Arg31, Thr 100, Gln 91, Glu 102, Asp 98, Asp94, Hip 95, Asp 98 and Leu 97 of myeloperoxidase. Thr 100 forms hydrogen bond with its back bone carbonyl oxygen and NH of ligand. The aromatic nature of the compound showed common Pi-Pi interactions with aromatic ring of Phe 99, imidazole ring in Hip95,Overallthe hydrogen bond and hydrophobic interactions formed by amino acids Asp98, Asp94, Thr100 and Glu102. Hydrophobic interactions were found with amino acids Pro101, Ala104, Ala105, Phe29, Leu97, Met87, Phe99 and Phe29 are all critical for stabilizing the inhibitors inside the binding pocket of the myeloperoxidase receptor. The thiadiazole derivatives and its different analogues were found to bind with Myeloperoxidase enzymeFigure 4 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.

The most stable conformer (ΔG_{bind} = -48.725 kcal/mol) of the screened subset of compounds was found to compound 5150. The compound showed that its amine group hydrogen was exposed to the hydrophilic region of receptor indicated in blue colour Figure 5 and formed strong H-Bond interactions with crucial amino acid residue Asp98, at a distance of 1.626 A°. The aryl unsaturated chain of compound 5150 was found to be embedded in the hydrophobic region of the receptor shown as blue colour in the Figure 5 which indicates the probability of binding of compound 5150 is in competition with the natural substrate of the receptor. The other stable conformers from

the screened subset were found as Compound 3350, 3800, 4100, 4250, 4400, 4700, 5300 and 5600 showing ΔGbind = kcal/mol) binding values in the range of (-33.319 to -48.725)

6. Conclusion

The present work deals with generation of a small combinatorial library of 22500 ligands using virtual screening method of thiadiazole scaffold. Myeloperoxidase was selected as target for the study and the designed ligands were screened for their binding affinity of ligands was calculated by MMGBSA approach and Molecular docking was carried out at three levels (HTVS, SP and XP) and top myeloperoxidase inhibitors were identified On comparing the glide score values, the better interaction was shown by compounds with glide score values-5.3 respectively. Thus by analyzing these datas 1 3 4 thiadiazole derivatives can be considered as a potent inhibitor against the enzyme myeloperoxidase in oxidative stress.

7. Source of Funding

None.

8. Conflict of Interest

None.

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Author biography

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