eISSN 2330-0272

VEDIC RESEARCH INTERNATIONAL

Bioinformatics & Proteomics

JOURNAL HOME PAGE AT WWW.VEDICJOURNALS.COM

RESEARCH ARTICLE

DOI: http://dx.doi.org/10.14259/bp.v1i1.43

In silico Assessment of Factor Xa Inhibitors by Docking Studies

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Article

Received: July 2nd, 2013
Revised: July 5th, 2013
Accepted: July 16th, 2013

Keywords

Anticoagulant, FactorXa, Haemostasis, Sulfonamide, Thrombin, Thrombosis, Thiophene -Anthranilamide

ABSTRACT

Human Factor Xa (FXa), a blood coagulation enzyme which catalyses the activation of prothrombin to thrombin and plays a pivot role in haemostasis and thrombosis. Imbalance in the activation of this enzyme disturbs the normal haemostasis leading to bleeding disorders and also vascular occlusion with overproduction of thrombin. This intravascular clot formation causes many cardiovascular diseases such as acute myocardial infarction (AMI), stroke, pulmonary embolism (PE), and deep vein thrombosis (DVT). So the direct inhibition of FXa may contribute for developing effective and safe anticoagulants without effecting thrombin activity necessary for normal hemostasis. The present study initiates to provideto provide insight of FXa inhibition and facilitate the design of more potent ligands ,ligands, a series of Sulfonamide and Thiophene-Anthranilamide derivatives are docked to the X-ray structure of FXa(FXa (2P95) using Discovery Studio(Studio (DS), and their binding conformations are analyzed. The docking analysis shows the compound 1v (2-(5-Chloro-2-thienyl)-N-{(3S)-1-[(1S)-1-methyl-2-(4-morpholinyl)-2-oxoethyl]-2-oxo-3-pyrrolidinyl}-1,3-thiazole-5-sulfonamide) of sulfonamide derivatives and 12a(3-Chloro-N-[4-chloro-2-[[(5-chloro-2-pyridinyl)amino]carbonyl]-6-methoxyphenyl]-4-[[methyl(methylsulfonyl)amino]methyl]-2-thiophenecarboxamide) of Thiophene-Anthranilamides are having a high dock score of 55.722K.Cal/mol and 57.523 K.Cal/mol respectively, which may act as potent inhibitors of FXa for the development of antithrombotic drugs.

INTRODUCTION

A well-balanced and highly regulated hemostatic process is essential to normal physiology which occurs by the activation of the blood clotting or coagulation system necessary to prevent blood loss after injury. An imbalanceAn imbalance between intravascular activation and inactivation of coagulation can lead to pathological thrombosis or bleeding disorders [1, 2]. That is, if the hemostatic response is disturbed the result in life-threatening bleeding; however, if it is not limited, the result is life-threatening thrombosis. Thrombosis is a multifactorial disorder initiated by intravascular blood clotting leading to thrombus formation in an artery or vein. The resultant thrombi can be obstructive or dislodged into smaller blood vessels, depriving vital organs of oxygen (ischemia), which can be catastrophic [3]. Intravascular clot formation is an essential factor in a number of cardiovascular diseases such as myocardial infarction, unstable angina, deep vein thrombosis, pulmonary embolism, and ischemic stroke. The interruption of the coagulation cascade is one of the most important strategies for inhibition of clot formation which is, in turn, for prevention

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and treatformation which is, in turn, for prevention and treats ment of these thrombotic disorders [4-6].

Blood coagulation cascade proceeds through the sequential enzymatic activation of a number of plasma serine proteases through intrinsic and extrinsic pathways that ultimately generates fibrin, the foundation of all blood clots [7]. This intricately controlled system of enzymatic interactions and interfacial processes maintains blood in a fluid state under physiological conditions and allows rapid clotting in response to injury [8]. The blood coagulation serine protease, Factor Xa (FXa), plays a central role in this coagulation cascade linking the intrinsic pathway and extrinsic pathway to the common coagulation injury [9, 10]. When bound to factor Xa, calcium, phospholipid, and prothrombin (prothrombinase complex), FXa activates prothrombin to thrombin. Thrombin, the terminal enzyme in the cascade, has several procoagulant functions including activation of platelets, regulation of factors in the cascade, and the conversion of fibrinogen to fibrin, which polymerizes to form the insoluble matrix of a blood clot or thrombus [11]. FXa and thrombin are both enzymatically active when associated with the intravascular thrombus, so it is vitally important that an antithrombotic agent be able to inhibit the "clot-bound" activity [12]. Inhibition of thrombus-associated FXa and thrombin provide antithrombotic effect making these agents more attractive for medical interventions in thrombotic diseases [13].

Besides this, inappropriate down-regulation of thrombin results in a near complete disruption of clot formation which may cause hemorrhagic problems and the also the over production lead to vascular occlusion or thrombus formation in artery or vein as a consequence of many cardiovascular diseases such as acute myocardial infarction (AMI), stroke, pulmonary embolism (PE), and deep vein thrombosis (DVT) [9, 14]. However, growing realization that inhibiting the proteolytic function of thrombin results in numerous ancillary effects has led to an impetus to design selective FXa inhibitors. The inhibition of FXa compared to thrombin may allow the effective control of thrombogenesis with minimal effect upon bleeding, thus diminishing thrombin-mediated activation of both coagulation and platelets without affecting the activity of existing thrombin level necessary for primary haemostasis, a characteristic that is desirable for antithrombotic agents [15, 16]. Furthermore, inhibition of FXa seems to be more efficacious because one molecule of FXa generates many thrombin molecules [17]. Therefore, the inhibition factor Xa may provide a novel, effective antithrombotic drug that provides no risk of bleeding.

Materials and Methods

Selection of PDB structure:

The x-ray crystal structure of Factor Xa (FXa) from human is obtained from the protein databank. After evaluating number of entries, the best protein is selected based on high resolution, Ramachandran plot analysis using Procheck from SAVS server based on number of residues in disallowed regions.

Protein preparation

The high resolution X-ray crystal structure of FXa is retrieved and the pdb code is 2P95 with a resolution of 2.20 A° and the method of incorporation is X-ray diffraction method. The ligand and crystallographic water molecules are removed from the protein; and the chemistry of the protein is corrected for missing hydrogen. Crystallographic disorders and unfilled valence atoms are connected using alternate conformations and valence monitor options. Following the above steps of preparation, the protein is subjected to energy minimization using the CHARMm Force field.

Ligand generation and Optimization:

The structures of the sulfonamide and Thiophene-Anthranilamide derivatives are sketched using ACD/ ChemSketch (12.0) Software and saved in mol2 format. The saved ligand compounds are later imported in to DS and hydrogen bonds are added and the energy is minimized using CHARMm force field. The individual compounds are finally saved in mol file format for further binding studies.

Docking Studies:

Docking was carried out to find the suitable orientation and interactions of the lead in protein active site. LigandFit, one of the best docking techniques was used to dock the selected sulfonamide and Thiophene-Anthranilamide derivatives compounds. This method employs a cavity detection algorithm for detecting invaginations in the protein as candidate active site regions. A shape comparison filter is combined with a Monte Carlo conformational search for generating ligand posses consistent with the active site shape. Candidate poses are minimized in the context of the active site using a grid based method for evaluating protein-ligand interaction energies. The method appears quite promising and reproducing. Throughout the docking process top ten conformations were generated for each ligand and the determination of ligand binding affinity was evaluated and ranked using the scoring function including Ligscore1, Ligscore2, PLP1, PLP2, JAIN, PMF and DOCK score. Apart from these, other input parameters for docking were set as default options. Thus docking analysis of the suplhanamide and thiophene anthralamine derivates with FXa carried out by ligand Fit of Discovery studio (version 2.1, Accelery software Inc.). The software allows us predict the strongest binders based on scoring functions. The collection of compound and FXa complexes is identified via docking and their relative stabilities are evaluated using their binding affinities. Thus based on the scoring functions and the appropriate interactions with the critical residues are considered as a final cut off requirements to select the best inhibitors for FXa.

Results and Discussion

Selection of PDB Structure:

Based on good resolution and Ramachandran's plot analysis the X-ray crystal structure of the protein human Factor Xa (PDB ID: 2P95) is chosen from protein data bank. The crystal structure of the human FXa is in complex with the inhibitor 5-chloro-N-((1R,

2S)-2-(4-(2-oxopyridin-1(2H)-YL) benzamido) cyclopentyl) thiophene-2-carboxamide and having a resolution of 2.20 Å. It is having two chains: chain A ranging from 16-244 residues and chain L ranging from 87-138 residues which is shown in figure 1. In the Ramachandran's plot analysis, the residues are classified according to their regions in the quadrangle, which shows human FXa is having 87.3% residues in most favorable region and there is no residue in disallowed region.

Protein preparation

To prepare the protein, the crystal structure of human FXa (PDB ID: 2P95) is downloaded from PDB databank. The subsequent structure 2P95 is imported in to DS, and then protein preparation is carried out by correcting the missing residues and removing the complexes bound to receptor molecule. Water molecules and metal bonds between the ligand and protein in 2P95 are also deleted. The structure is then refined by energy minimization with appropriate charges and parameters carried out using steepest descent gradient until the convergence gradient satisfied.

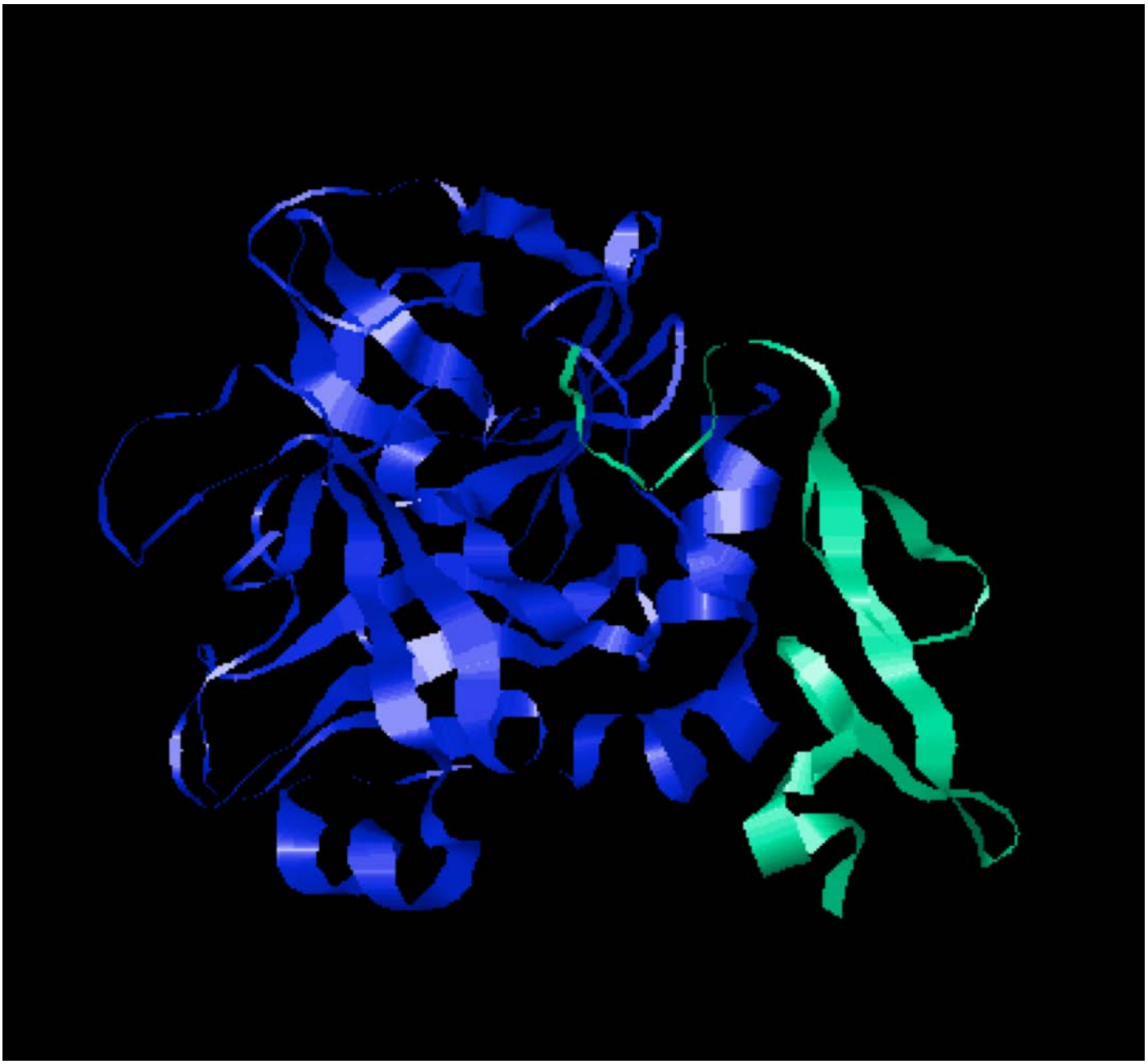
Ligand generation and Optimization

The sketched sulfonamide and Thiophene-Anthranilamide derivatives are saved in mol2 format and imported in to DS. Ligand preparation is carried out by adding hydrogen through add polar hydrogen option in the menu bar of DS and then energy minimization by applying CHARMm force field.

Docking Studies

This study investigates the interaction of ligand molecule in the

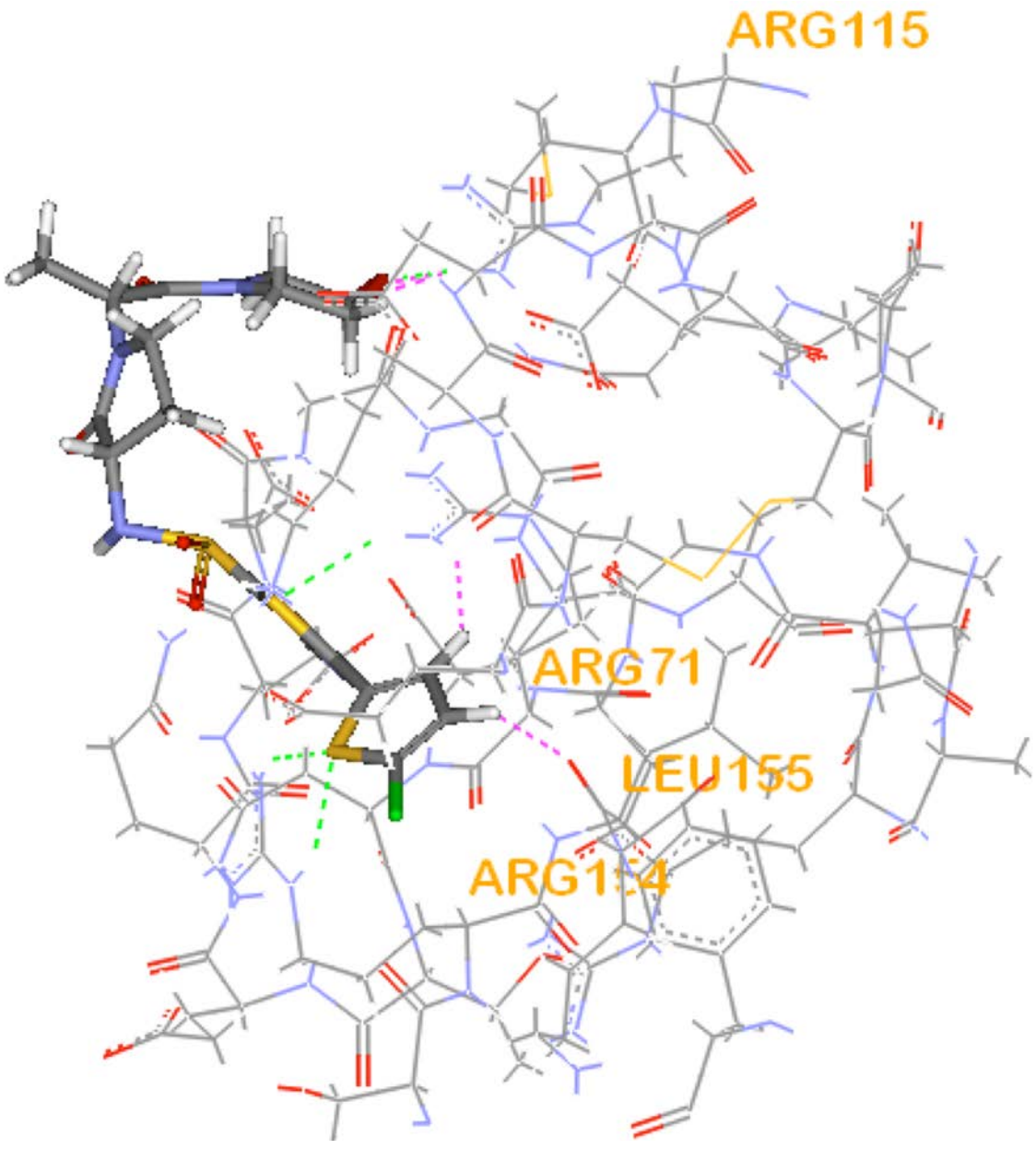
Figure 1: Secondary structure of 2P95 containing two chains: chain A (16-244) in blue color and chain L (87-138) in green colour.



active region of the protein and to predict the binding modes and affinities between the ligand and the protein molecule. The active site of the protein is first identified and it is defined as the binding site. The binding sites are defined based on the ligand present in the PDB file which is followed by site sphere definition. Here site 1 is chosen as the binding site. For accurate docking of ligands into protein active sites, the docking method used in this study is LigandFit. Dockscores are used to estimate the ligand binding energies.

The docking studies reveal that the most active compounds 1v from sulfonamide derivatives is having a high dock score of 55.722 K.Cal/mol with four hydrogen bonds, and compound 12a from Thiophene-Anthranilamide derivatives having a dock score of 57.523 K.Cal/mol with one hydrogen bond binds to protein with high affinity. Table 1 contains docking scores of all sulfonamide derivatives and Table 2 contains docking scores of all Thiophene-Anthranilamide derivatives. Of the ten conformations the compound with high dockscore is taken for interaction analysis of the hydrogen bonding. The Hydrogen bonding interaction of the compound 1v and compound 12a with protein 2P95 are analyzed. Fig 2 shows the amino acid residues involved in hydrogen bond interactions with protein 2P95 and the compound 1V of sulfonamide derivatives.The interacting amino acids are ARG115, ARG71, LEU155, ARG154. Figure 3 shows the amino acid residues involved in hydrogen bond interactions with protein 2P95 and the compound 12a of Thiophene-Anthranilamide. The interacting amino acids are ARG115, ARG71, and ARG154.

Figure 2: Shows H-bond interactions of 1v comp with activesite residues of factor Xa (2P95), here ligand molecule interacting with Arg71, 154, Leu155. (Green dotted lines H-Bond and receptor ligand bumps).



Conclusion

In the present study, sulfonamide and Thiophene-Anthranilamide derivatives are docked in to the active site of human FXa. From the docking analysis, the compounds 1v ((2-(5-Chloro-2-thienyl)-N-{(3S)-1-[(1S)-1-methyl-2-(4-morpholinyl)-2-oxoethyl]-2-oxo-3-pyrrolidinyl}-1,3-thiazole-5-sulfonamide)) of sulfonamide derivatives and compound 12a((3-Chloro-N-[4-chloro-2-[[(5-chloro-2-pyridinyl)amino]carbonyl]-6-methoxyphenyl]-4-[[methyl(methylsulfonyl)amino]methyl]-2-thiophene carboxamide)) of Thiophene-Anthranilamide shows high binding affinity with the receptor (2P95) and the interaction analysis of the compounds revealed the interacting amino acids involved in binding of the ligands to the FXa. Good interactions are found with the amino acids ARG115, ARG71, LEU155, and ARG154 of 2P95 with compound 1v of sulphanamide derivatives and ARG115, ARG71, ARG154 with compound 12a of thiophene antralamide derivative. Hence, compound 1v of sulfonamide and 12a of Thiophene-Anthranilamide derivative can be assumed to be the most potent FXa inhibitor and can be potentially act as anti-thrombotic target.

Figure 3: Shows H-bond interactions of Comp12a with active site residues of 2p95 such as Lys23, Asp24, Glu77, and Arg154. (Green dotted lines H-Bond and receptor ligand bumps).

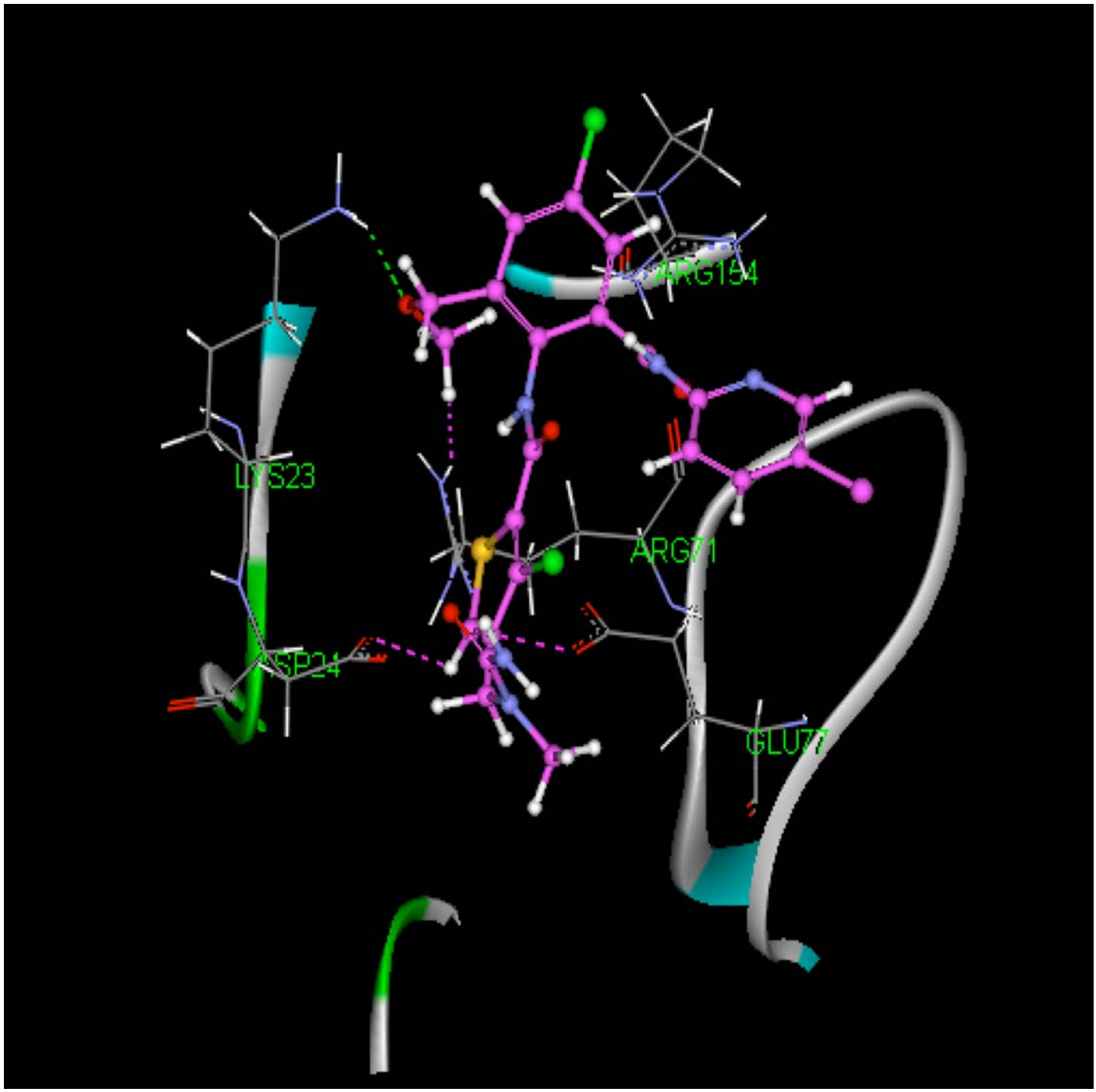


Table 1: docking results of sulfonamides

NAME	LIGSCORE1_	LIGSCORE2_	-PLP1	-PLP2	JAIN	-PMF	DOCK_SCORE	INTERACTING AMINO ACID	INTERACTING ATOMS
l a	1.19	3.23	42.84	44.6	0.68	66.88	36.019	ARG115 , ASP24, GLY78, GLU77	compound 1:C29 - A:ARG115:HH22 compound 1:H49 - A:ASP24:OD2
l j	2.92	2.8	26.16	35.77	1.98	84.81	39.487	ASP24, GLU77, LYS23, ARG115	Compound 10:N17 - A:ASP24:OD2 Compound 10:C23 - A:GLU77:OE1 A:LYS23:HZ3 - Compound 10:O4 A:ARG115:HH21 - Compound 10:Cl30 Compound 10:H48 - A:ASP24:OD2
l k	0.74	3.24	16.38	13.51	-1.08	50.35	42.319	ARG115, ASP24	A:ARG115:HH12 - compound 11:Cl30 compound 11:H48 - A:ASP24:OD2
l o	2.67	3.65	26.64	24.16	-0.15	81.84	34.875	ARG154, LYS23, GLU77	Comp14:H32 - A:ARG154:HH21 A:LYS23:HZ3 - Comp14:O4 A:ARG154:HH22 - Comp14:O8 Comp14:H48 - A:GLU77:OE1
l p	2.32	3.35	22.88	29.68	1.26	78.94	39.894	ASP24, GLU77, ARG115, LYS23	Comp15:N17 - A:ASP24:OD2 Comp15:C23 - A:GLU77:OE1 Comp15:C29 - A:ARG115:HH22 A:LYS23:HZ3 - Comp15:O4 A:ARG115:HH21 - Comp15:Cl30 Comp15:H48 - A:ASP24:OD2
l q	2.3	3.67	50.99	43.69	0.06	59.03	36.793	ARG115, ASN117, ARG71	Comp16:C24 - A:ARG115:HH22 Comp16:C28 - A:ASN117:HD21 Comp16:H51 - A:ARG71:HH21 A:ARG115:HH12 - Comp16:O19 A:ARG115:HH22 - Comp16:N22
l r	1.49	3.01	28.84	20.13	-1.98	83.13	38.11	ARG154	Comp17:H32 - A:ARG154:HH21 A:ARG154:HH21 - Comp17:O8 A:ARG154:HH21 - Comp18:H35
l s	2.92	3.54	19.93	22.5	-0.46	88.74	39.17	ARG154, GLU77	A:ARG154:HE - Comp18:O4 A:ARG154:HH21 - Comp18:O4 Comp18:H48 - A:GLU77:OE1 Comp18:H49 - A:GLU77:OE1
l t	2.53	3.88	21.62	17.82	-0.29	73.09	37.498	GLU77, ARG115	Comp19:N23 - A:GLU77:OE1 A:ARG115:HH12 - Comp19:Cl30 Comp19:H50 - A:GLU77:OE1
l v	**3.13**	**3.92**	**52.81**	**45.3**	**2.21**	**98.45**	**55.722**	**ARG115,ARG71,LEU155,ARG154**	**Comp21:C2 - A:ARG115:HH22 Comp21:H35 - A:ARG115:HH22 Comp21:H51 - A:ARG71:HH11 Comp21:H52 - A:LEU155: O A:ARG71:HH12 - Comp21:S22 A:ARG115:HH22 - Comp21:O4 A:ARG154:HE - Comp21:S28 A:ARG154:HH21 - Comp21:S28**
l w	3.51	5.13	49.97	40.54	-0.26	78.18	54.18	ARG115, ARG154	comp22:C6 - A:ARG115:HH22 comp22:C26 - A:ARG154:HH21 A:ARG115:HH12 - comp22:O4 A:ARG115:HH22 - comp22:O4 A:ARG154:HH21 - comp22:S28
l x	3.31	4.27	30.82	29.55	-0.12	77.74	53.015	ARG71, ARG115, ASP24	Comp23:C26 - A:ARG71:HH12 Comp23:H50 - A:ARG71:HH22 A:ARG71:HH12 - Comp23:S28 A:ARG115:HH12 - Comp23:O4 Comp23:H49 - A:ASP24:OD2
l u	2.92	3.67	57.12	47.37	1.55	103.97	44.877	LYS23, ARG154, ARG115	Comp25:H50 - A:LYS23:HZ3 Comp25:H53 - A:ARG154:HE A:ARG115:HH22 - Comp25:O4

Figure 4: Graphical representation of dock score for Sulfonamides

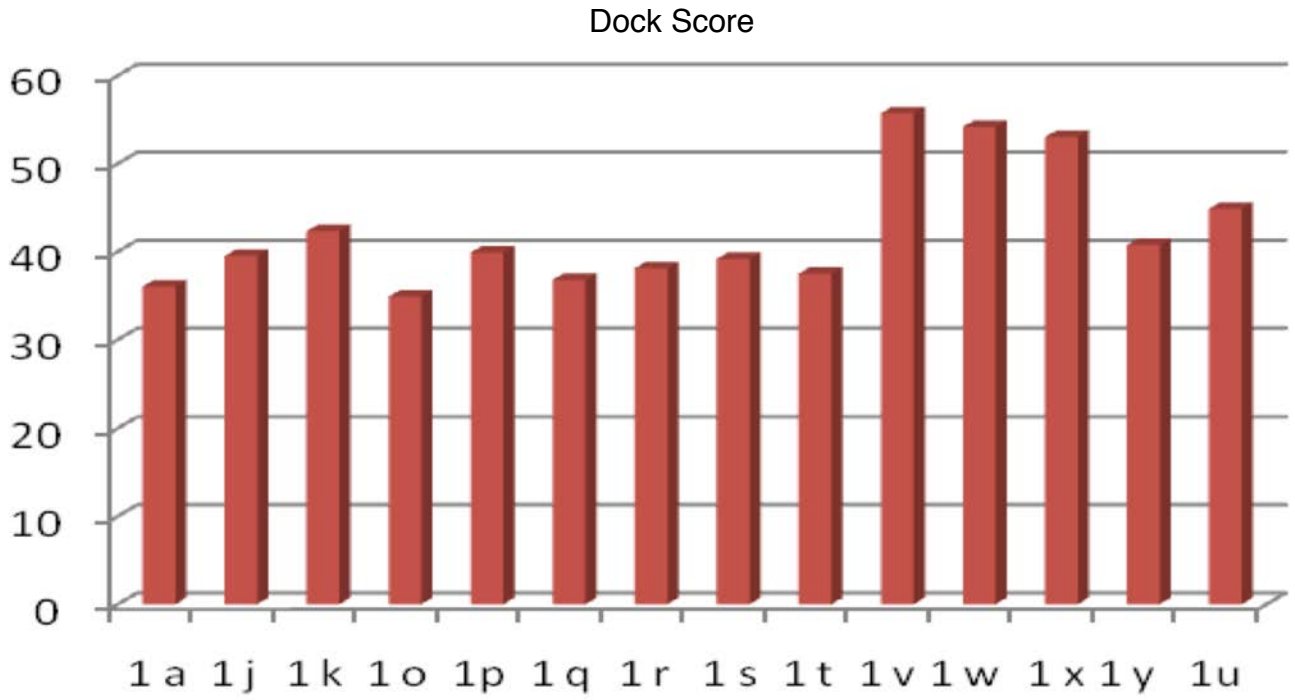


Figure 5: Graphical representation of Dock score for Thiophene-Anthranilamide

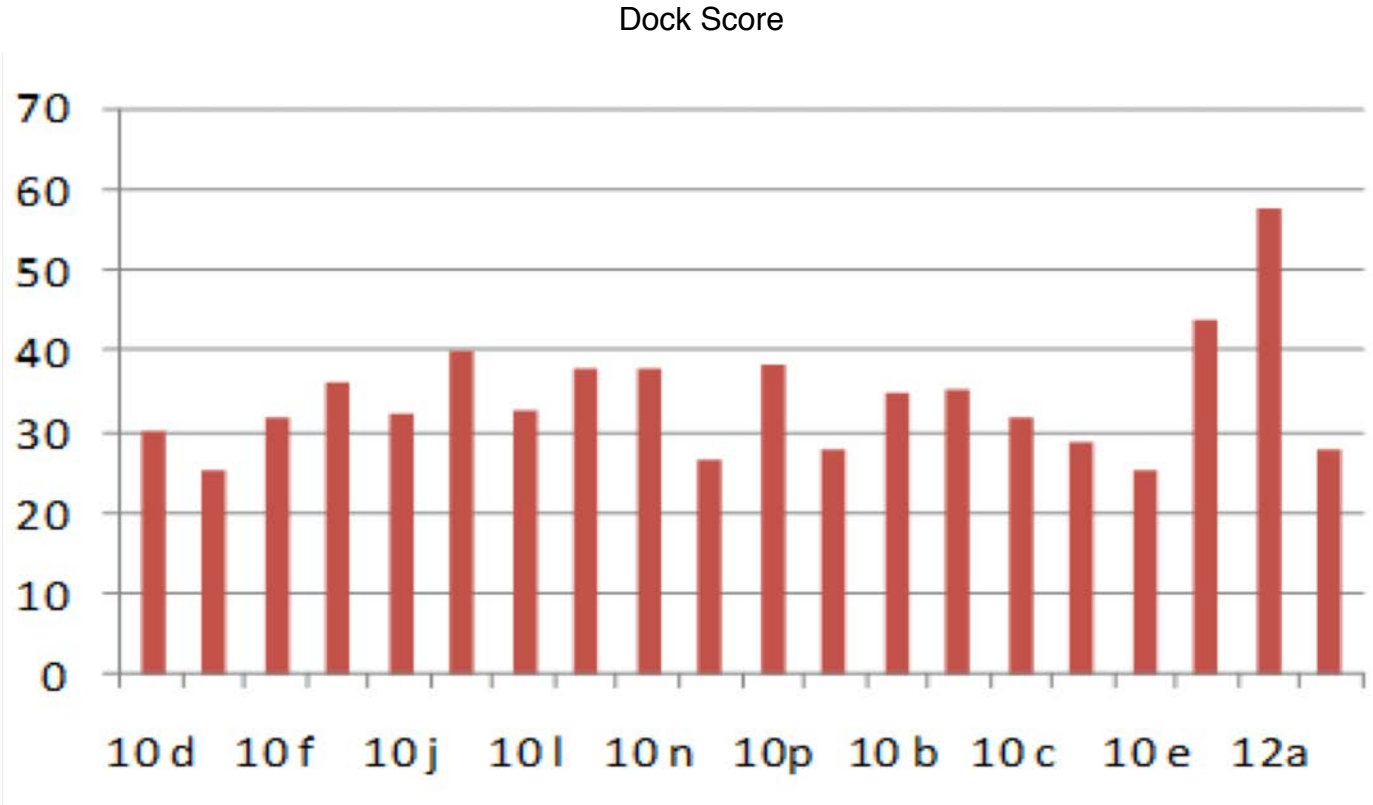


Table2: Docking results of Thiophene Anthranilamide

NAME	LIGSCORE 1	LIGSCORE 2	-PLP1	-PLP2	JAIN	PMF	DOCK_SCORE	INTERACTING AMINO ACIDS	INTERACTING ATOMS
10 d	0.95	2.23	22.36	23.59	-1.45	36.92	30.11	GLU77, ARG115	10 d:N7 - A:GLU77:OE1 10 d:H37 - A:GLU77:CD A:ARG115:HH12 - 10 d:Cl16 10 d:H37 - A:GLU77:OE1
10 e tab2	1.67	2.33	24.72	31.04	-2.36	70.8	25.324	GLU77, ARG71, ARG115	10 e tab2:Cl16 - A:GLU77:HB1 10 e tab2:H35 - A:ARG71:HH21 A:ARG115:HH12 - 10 e tab2:O15 A:ARG115:HH22 - 10 e tab2:N3
10 f	2.78	3.01	33.97	34.49	-1.57	88.63	31.566	ASN117, ARG71, GLU77, ASP24	10 f:C2 - A:ASN117:HD21 A:ARG71:HH22 - 10 f:S21 10 f:H38 - A:GLU77:OE1 10 f:H41 - A:ASP24:OD2
10 j	1.18	2.86	15.58	17.95	-4.19	39.09	36.153		NIL
10 j(2)	1.76	3	34.7	35.05	-1.6	51.45	32.401	ARG154, ARG71	10 j:H52 - A:ARG154:HH21 10 j:H53 - A:ARG71:HH11 A:ARG71:HH12 - 10 j:N30
10 k	2.74	3.6	35.39	34.53	-1.05	61.22	39.905	LYS23, GLU77	A:LYS23:HZ3 - 10 k:O28 10 k:H58 - A:GLU77:OE1
10 l	2.36	3.05	19.8	26.08	-0.25	84.14	32.644	LYS23, ARG71, ARG115	10 l:H56 - A:LYS23:HD1 A:ARG71:HH22 - 10 l:Cl27 A:ARG115:HH22 - 10 l:N3
10 m	2.55	3.6	39.19	38.8	-2.37	83.17	37.767	ARG115	A:ARG115:HH22 - 10 m:N3
10 n	2.01	3.07	24.42	24.84	-2.54	30.85	37.681	ASP24	10 n:N7 - A:ASP24:OD2 10 n:H40 - A:ASP24:OD2
10 o	1.92	2.73	29.05	30.03	-0.46	76.63	26.591	LYS23, ARG115, GLU77	10 o:C31 - A:LYS23:HZ3 10 o:H51 - A:LYS23:HZ3 A:ARG115:HH22 - 10 o:N3 10 o:H43 - A:GLU77:OE1
10 p	1.86	3.47	33.5	30.4	-3.13	84.58	38.299	ARG154	A:ARG154:HH21 - 10 p:N3 A:ARG154:HH22 - 10 p:N3
10 a	1.48	3.07	18.5	20.98	-3.1	41.77	28.126	ASP24	10 a:H34 - A:ASP24:OD2
10 b tab2	1.28	3.41	46.98	42.33	-1.75	31.31	34.676	ARG115	A:ARG115:HH22 - 10 b tab2:N3
10 b	2.11	3.84	35.02	23.13	-0.61	80.06	35.171	MET116, LYS23, ARG71, GLU77	10 b:H35 - A:MET116:HG1 10 b:H46 - A:LYS23:HZ3 A:ARG71:HH12 - 10 b:Cl28 A:ARG71:HH22 - 10 b:Cl28 10 b:H37 - A:GLU77:OE1
10 c tab2	1.43	3.56	30.65	27.32	-2.61	65.44	31.852	ASP24	10 c tab2:H39 - A:ASP24:OD2
10 e	0.6	2.55	12.29	12.51	-3.17	51.24	28.684		NIL
10 e(2)	1.53	3.33	24.79	17.49	-2.28	67.75	25.49	GLU77	10 e:H42 - A:GLU77:OE1 10 e:H43 - A:GLU77:OE1
12 a	**2.73**	**3.31**	**44.42**	**40.46**	**-0.99**	**76.75**	**57.523**	**ARG115, ARG71, ARG154**	**12 a:C5 - A:ARG115:HH22 12 a:C6 - A:ARG115:HH22 12 a:H54 - A:ARG71:HH12 12 a:H57 - A:ARG154:HH21 A:ARG71:HH12 - 12 a:O34 A:ARG115:HH22 - 12 a:N3**
12 b	2.94	3.68	33.69	28.36	-0.65	64.33	43.926	GLU77	12 b:H39 - A:GLU77:OE1 12 b:H44 - A:GLU77:OE1
12 c	3.05	3.52	24.04	24.96	-0.97	80.5	27.753	GLU77, ARG154	A:GLU77:OE1 - 12 c:S24 12 c:H58 - A:ARG154:HH21 12 c:H58 - A:ARG154:HH21 12 c:H46 - A:GLU77:OE1

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