IN SILICO SCREENING OF SULFONAMIDES DRUGS TO INHIBITORS FOR MYCOLIC ACID TRANSPORTER (MMPL3) USING SWISSDOCK SOFTWARE FOR THE THERAPY OF TUBERCULOSIS

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Abstract

Aim: The research deals with the evaluation of small molecule inhibitors for Mycolic acid transporter (Mmpl3) with respect to its role in tuberculosis using sources derived from sulfonamides.

Materials and Methods: The three-dimensional (3D) coordinates of Mmpl3 protein were retrieved from Protein Data Bank (5oeq). The structures of 15 sulfonamide drugs were collected from the NCBI-PubChem compound database. The Molecular docking analysis of Mmpl3 with the derived sulfonamides was performed using swiss Dock software. This software employs an algorithm that generates the output complexes based on the shape complementarity of the biomolecules. The best poses were analysed for non-covalent interactions using the PLIP server.

Results: Molecular docking analysis revealed compounds Azulfidine (sulfasalazine), Amaryl (glimepiride), Tikosyn (dofetilide), Flomax (tamsulosin HCl), Imitrex (sumatriptan succinate) could bind Mmpl3 protein with higher affinity, ($p=0.6$, $p>0.05$) which appears to be statistically insignificant in comparison with AU1235 and also show similar residue interaction patterns when compared with the known potent mmpl3 inhibitors and would report an affirmative prognostic factor.

Conclusion: The identified inhibitor complexes from sulfonamides are expected to bind with Mmpl3 protein with better efficiency in comparison with AU1235, hence they can be further considered for in vivo and in vitro analysis.

Keywords: Sulfonamides, Tuberculosis, Novel Inhibitor Complexes, Interaction, Molecular Docking**.**

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1. Introduction

The research deals with In silico screening of inhibitor mycolic acid transporter (Mmpl3) protein in Tuberculosis(TB) infection using sulfonamides drugs.The importance of this study is to identify inhibitors for Mmpl3, understanding their binding affinity and interaction with key residues using docking analysis Tuberculosis is a contagious infection that severely attacks the lungs.Mycobacterium tuberculosis (Mtb), the causative agent of tuberculosis (TB), is the largest cause of death caused by a single infectious pathogen worldwide.With an expected 10 million new cases and 1.2 million fatalities in 2018,(B. M. Andersen 2019; M. Chan 2018; Dibaba, Kriek, and Thoen 2019). The routine for the treatment of drugs for vulnerable tuberculosis comprises of rifampin (RIF, 1) isoniazid (INH, 2), Ethambutol, pyrazinamide (PZA), and pyrazinamide (PZA).Treatment of MDR/XDR-TB consequently utilizes a blend of normalized and individualized approaches that at last accomplish just low fix rates . MDR-TB (multidrug resistant TB) is impervious to RIF and INH furthermore, requires a mixed treatment with second-line drugs enduring something like 20 months (World Health Organization 2017).Is impervious to RIF, INH, fluoroquinolones and to something like one of the second-line injectable specialists and treatment of patients with XDR-TB depends on their drug affectability test. In 2012, bedaquiline was endorsed by the Food and Drug Administration (FDA) for the treatment of MDR-TB (Karaköse, n.d.; Olayanju et al. 2019; E. D. Chan, Strand, and Iseman 2009). As an ATP synthase inhibitor , bedaquiline is the principal new anti-TB drug to have been endorsed in almost 40 years. In 2014, delamanid was endorsed by the European Medications Agency (EMA) for the treatment of MDR-TB(Karaköse, n.d.; Olayanju et al. 2019; E. D. Chan, Strand, and Iseman 2009; Lefkowitz 2013; Hagan, Dedicoat, and Bothamley 2017; Guo et al., n.d.; Kambili 2016). A mix of nitroimidazole pretomanid with linezolid and bedaquiline was supported by FDA for the treatment of XDR-TB or treatment-bigoted MDR-TB in 2019. Moreover, various antibiotics of TB drugs are presently in clinical preliminaries(Kadura et al. 2020; Dheda et al. 2018; Howell et al. 2019).

Mycobacterial film protein Large (MmpL) group of proteins has a place with the resistance, nodulation and cell division (RND) superfamily of carriers that rely upon the proton motive force(PMF) to trade substrates across cell layer("Mycobacterial Glycopeptidolipids (GPL) Are Transported by the MmpL4a Membrane Protein. Genetic Studies Have Identified Critical Residues within the Transmembrane Segments of MmpL Proteins Postulated to Be Couple the Proton Motive Force (PMF) to MmpL Trans" 2016; Rottem, Linker, and Wilson 1981; Hernandez-Mendoza et al. 2007) Mtb genomes contain 13 MmpL qualities . MmpL3 (Rv0206c) is the main fundamental MmpL quality in Mtb H37Rv and is saved among all individuals from the mycobacterial family . MmpL3 assumes a critical part in various significant aggregates like cell divider biosynthesis, iron take-up, energy creation, film potential, and antitoxin helplessness. Hereditary exhaustion of MmpL3 brings about Mtb demise in vitro and in vivo murine models of TB contamination, featuring its potential as an original remedial objective The importance of this study is to establish safe and efficient drugs for treating tuberculosis and eventually cure them("Mycobacterial Glycopeptidolipids (GPL) Are Transported by the MmpL4a Membrane Protein. Genetic Studies Have Identified Critical Residues within the Transmembrane Segments of MmpL Proteins Postulated to Be Couple the Proton Motive Force (PMF) to MmpL Trans" 2016; Rottem, Linker, and Wilson 1981; Hernandez-Mendoza et al. 2007; Chen, n.d.; Sun et al., n.d.; López, n.d.). The major application is to find inhibitors with higher affinity that are in use and focus on the current and future use of targeted therapy in Tuberculosis

Based on the survey, "MmpL3 inhibitors as antituberculosis drugs" (Min Shao et al.,2020) is expressed as one among the best surveys over the data identified with Mmpl3 protein. We looked for most referred articles in Google Scholar and science direct data set and wound up with 1056 articles distributed around here. Inhibitors of indole-2-carboxamides, benzothiazole amides, THPPs, pyrroles, pyrazoles, adamantyl ureas, benzimidazoles, spirocycles, and piperidinol are some medicines(Matthew McNeil et al.,2020). This Inhibition of MmpL3 weakens the mycobacterial cell wall and ultimately results in cell death in both in vitro and in vivo models ("Targeting Necrosis: Elastase-like Protease Inhibitors Curtail Necrotic Cell Death Both In Vitro and in Three In Vivo Disease Models," n.d.; Obasaju et al. 2019; Tei, Miyake, and Fujisawa 2015). Studies express the advancement cycle in discovering the drug particles docked with Mmpl3 as a protein enzyme for tuberculosis . When contrasted with the total recreated screened compounds with preferable affinity, the general energy of Amaryl(glimepiride) inhibitor interacting with the Mmpl3 is higher than stated to be the best study among the available literature.

Our institution is passionate about high quality evidence based research and has excelled in

various domains (Vickram et al. 2022; Bharathiraja et al. 2022; Kale et al. 2022; Sumathy et al. 2022; Thanigaivel et al. 2022; Ram et al. 2022; Jothi et al. 2022; Anupong et al. 2022; Yaashikaa, Keerthana Devi, and Senthil Kumar 2022; Palanisamy et al. 2022).The lacunae in the existing research results in lack of specific inhibitor molecule for Mmpl3 for therapy of Tuberculosis .The study was expected to check if inhibitors got from sulfonamides could restrain Mmpl3 enzyme than other recent drugs on the global level("Targeting Necrosis: Elastase-like Protease Inhibitors Curtail Necrotic Cell Death Both In Vitro and in Three In Vivo Disease Models," n.d.; Obasaju et al. 2019; Tei, Miyake, and Fujisawa 2015; Tischler 2020; "Warming from Rising CO2 Could Happen Faster than Expected" 2012; Mahase 2021). The authors of this study have experience in the computational biology field which allowed us to efficiently carry out our research, based on the detection of small molecular inhibitors of different mycobacterium tuberculosis medicines for targeted tuberculosis therapy as stable drugs(Bhakta 2013; Abdelwahab 2008; Vesenbeckh et al. 2016). The aim states by identifying a synthetic inhibitor molecule for Mycolic Acid transporter (Mmpl3) inhibitor enzymes using swissdock. The study aims at identifying small molecule inhibitors derived from sulfonamides against Mmpl3 in treatment of Tuberculosis(Dupont et al. 2019; Adams et al. 2021; "StructureFunction Profile of MmpL3, the Essential Mycolic Acid Transporter from Mycobacterium Tuberculosis," n.d.)).

2. Materials and Methods

The study setting of research was conducted in Saveetha School of Engineering by using swiss dock software along with that chimera to analyze the estimated ΔG and full fitness value. The study does not require any human samples and ethical approval is also not required .The power calculation was done using a pre test power .The sample in this study comprises reference and 15 test compound drugs (Td et al. 2017)).

The Three dimensional structure of 15 sulfonamides drugs was obtained from Protein Data Bank (6ajh) .The three dimensional structure of 15 sulfonamides drugs were obtained from the NCBI-Pubchem compound database. The ligand molecule was prepared using the LigPrep wizard of the Schrödinger suite and the structure was minimized using the OPLS-2005 force field (Gincel, Ptak, and Vovelle 1995; K. V. Andersen and Poulsen 1993; Gul and Zarina 2005; Yuan et al. 2012; Hinck et al. 1997; Jacobs and Dallakyan 2005; Domaille and Handel 1996; Patel and Anderson 1995; Poulsen 1993; Kirfel and Fischer 2010; Al-Manthari, n.d.)).

The Three dimensional structure of reference molecule AU1235 was obtained from Protein Data Bank .The Three Dimensional structure of 15 sulfonamides drugs were obtained from the NCBI-Pubchem compound database. The ligand molecule was prepared using the LigPrep wizard of the Schrödinger suite and the structure was minimized using the OPLS-2005 force field.

Swiss dock algorithm generates output complexes based on the shape complementary of biomolecules; the three dimension structure of Mmpl3 was docked with inhibitor derived from NCBI pub chem compound database(Beckford et al. 2016; Li et al. 2020; Latos-Brozio and Masek 2020; Su 2019b, [a] 2019; Pilón-Jiménez et al. 2019; Boyles, Deane, and Morris, n.d.; Kiskova et al. 2020; "Figure 5. In Silico Modelling of Binding of ID-8 and Compound 45 to DYRK1A," n.d.; Reetz 2016))

Non covalent bond interactions were determined using PLIP server. The statistical software used for the research article is IBM SPSS version 28. The dependent variables are 15 sulfonamide drugs. The analysis was done on an independent sample T test (Glaspell 2016; Ahuja 2006).The association between amino acid deposits of Mmpl3 and ligand was assessed utilizing the testing arrangement of Chimerax. Restricting partiality with the relationship of the dynamic site buildup in Mmpl3 protein are the best corroborative conditions for ligands. The ideal areas for the utilization of Chimerax and PLIP were investigated in non-covalent cooperations. PyMOL is a sub-atomic and renderer. Protein-Ligand Interaction Profiler (PLIP) is the accompanying testing methodology that is utilized to recover the Δ G estimations of drug complex inhibitors that is completely robotized identification and perception of important noncovalent protein-ligand contacts in 3D structures. PLIP is a new web service for complete recognizable proof and investigation of related non-covalent proteins–connecting contacts in 3D designs.

3. Results

The Mmpl3 was docked with 15 sulfonamides drugs using swiss dock software AU1235 has been reported as a potential Mmpl3 inhibitor in the human body. Study identified that Azulfidine (sulfasalazine), Amaryl (glimepiride), Tikosyn (dofetilide), Flomax (tamsulosin HCl), Imitrex (sumatriptan succinate) has higher binding affinity in comparison with Mmpl3. "therapeutic potential of the mycobacterium tuberculosis mycolic acid

transporter " is a similar finding of this article and opposing findings are not found.

From Table 1 Clinical trials of Azulfidine (sulfasalazine), Amaryl (glimepiride), Tikosyn (dofetilide), Flomax (tamsulosin HCl), Imitrex (sumatriptan succinate) for tuberculosis have been determined. In vitro and vivo analysis will be performed to develop the top 5 hits of sulfonamides drugs for tuberculosis(TB) infection.

From Table 2 and Fig. 1, it was found that the interaction of Amaryl(glimepiride) with Mmpl3 and the active binding site residues of Mmpl3 namely PHE2,ARG288,PHE292,VAL655, forms hydrophobic interactions. The residues namely GLN -3,ARG 288 form hydrogen interaction.

From Table 3 and Fig. 2 Interaction analysis of dofetilide sulfonamides drug were found in the active site pocket of Mmpl3 protein.The structure of Mmpl3 and dofetilide are represented in green and yellow sticks .amino acid residues of mmpl3 protein namely ARG 288, ARG 288, ARG 288, THR 289, ARG 653, GLU 656 , GLU 659 interacts with dofetilide.

From Table 4 and Fig. 3 Interaction analysis of flomax sulfonamides drug in the active site pocket of Mmpl3 protein.The structure of Mmpl3 and flomax are represented in green and yellow sticks .amino acid residues of mmple protein namely ILE 32 , LEU 25, ILE 194, LEU 251 , ALA 215 interacts with flomax.

From Table 5 and Fig. 4 Interaction analysis of imitrex sulfonamides drug in the active site pocket of Mmpl3 protein.The structure of Mmpl3 and Tolbutamide are represented in green and yellow sticks .amino acid residues of mmple protein namely VAL 655, ARG 288, GLU 656, ARG 744, GLU 659 interacts with imitrex.

From Table 6 and Fig. 5 Interaction analysis of sulfasalazine sulfonamides drug in the active site pocket of Mmpl3 protein.The structure of Mmpl3 and metolazone are represented in green and yellow sticks .amino acid residues of mmple protein namely TYR 30, ILE 228, LEU 325 interacts with sulfasalazine.

From Table 7 and Fig 6, it shows that the outcome of an independent sample t-test of the top five hits Azulfidine (sulfasalazine), Amaryl (glimepiride), Tikosyn (dofetilide), Flomax (tamsulosin HCl), Imitrex (sumatriptan succinate) revealed a higher binding affinity than AU1235 when compared to AU1235.

From Table 8, it was found that the Independent sample t-test in predicting the significant, mean difference, std error difference of Mmpl3 with different sulfonamides drugs.

4. Discussion

The research was built to identify the impeccably lead and drug components with rich affinity to Mmpl3 protein with a ligand protein complex inhibitory results .The Mmpl3 enzyme was docked with 15 sulfonamides using swiss dock software. Studies have reported AU1235 as a potential Mmpl3 protein inhibitor in tuberculosis cells. Our docking results that Azulfidine (sulfasalazine), Amaryl (glimepiride), Tikosyn (dofetilide), Flomax (tamsulosin HCl), Imitrex (sumatriptan succinate) demonstrated higher binding affinity in comparison with AU1235 were analyzed using Chimerax software (Zhang et al. 2018; Grudinin 2019; Hall, Heimbigner, and Wolf 1998; Carter et al. 2005; Viji, Balaji, and Gautham 2012; Kurcinski et al. 2020; Echartea, de Beauchêne, and Ritchie 2019)).

As Mmpl3 protein was docked with 15 sulfonamides, determined manufactured mixtures utilizing Swiss Dock software (Decker 2017). Global studies have reported Amaryl(glimepiride) as a potential Mmpl3 inhibitor in Tuberculosis. Curiously, our docking results uncovered that Azulfidine (sulfasalazine), Amaryl (glimepiride), Tikosyn (dofetilide), Flomax (tamsulosin HCl), Imitrex (sumatriptan succinate) compounds from sulfonamides that showed higher binding in correlation with amaryl(glimepiride)(Das et al. 1970). It was discovered that Amaryl(glimepiride) ties with Mmpl3 with the limiting liking of - 9.81 .kcal/mol, while the mycobacterial inhibitor, in particular Azulfidine (sulfasalazine), Amaryl (glimepiride), Tikosyn (dofetilide), Flomax (tamsulosin HCl), Imitrex (sumatriptan succinate) , ties with a higher affinity of -8.94 , -9.81 , - 9.60 , - 8.25 , -8.68 Kcal/mol, individually.

Similar findings express that Mmpl3 and its inhibitors display further developed adequacy and dissolvability with small molecules when contrasted with other protein catalysts . opposing findings results that imidazopyridine amine subordinate Q203 drug is certainly not a genuine inhibitor (Mmpl3) of mycolic carrier, so the clinical result ought not be extrapolated from the development of any tuberculosis drugs treatments(Malerczyk et al. 1994). Before the commencement of clinical investigations or clinical preliminaries of Q203 , the component of initiation of this specialist was not adequately explained when contrasted with Mmpl3 protein. So. Mmpl3 was taken and docked with synthetic compounds.

The major factor which limits this study is that the above listed top complexes will have to undergo clinical trials to determine its efficiency towards Mmpl3 for the treatment of tuberculosis . The future context of the study is to consider the compounds Azulfidine (sulfasalazine), Amaryl (glimepiride), Tikosyn (dofetilide), Flomax (tamsulosin HCl), Imitrex (sumatriptan succinate)

for in-vivo and in-vitro analysis to yield them to model and develop better sulfonamides drugs(Leone and Rabaglia, n.d.; Shi et al. 2017; M, Karthikeyan, and Balasubramanian 2016; Hennighausen and Szymaniec 1990; Brandes, n.d.; "Evaluation of a New Oral Diuretic Agent" 1967; Wilkins 2012; Tallarida 1982; Vaughan 1981; Harman 2001; &na; and &NA; 2011, 1997)).

5. Conclusion

The novel small molecules derived from sulfonamides show better inhibition activity on Mmpl3 as compared to AU1235. These novel inhibitors can be used to treat Tuberculosis after in vivo and in vitro analysis.

Declarations:

Conflict of interests: No conflict of interest in this manuscript.

Authors contributions:

Author KPS was involved in data collection, data analysis and manuscript writing. Author PR was involved in Conceptualization. Author PR was involved in data validation and critical review of the manuscript.

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Tables and Figures

Table 1 (a) : Screening of Mmpl3 inhibitors derived from sulfonamides drugs using swissdock software.

SNO	COMPOUND NAME	Full fitness (Kcal/mol)	Estimated (Kcal/mol)	Estimated (Kcal/mol)
1	Tolbutamide	-3912.58	-7.59	-7.60
2	Bumetanide	-3895.76	-7.01	-7.14
3	Chlorthalidone	-3929.55	-7.46	-7.45
4	Azulfidine (sulfasalazine)	-3860.64	-8.79	-8.77
5	Amaryl (glimepiride)	-3989.51	-9.81	-9.81
6	Lasix (furosemide)	-3937.63	-6.98	-6.71
7	Indapamide	-3859.93	-7.22	-7.22
8	Metolazone	-3907.52	-6.91	-6.91
9	Zonegran (zonisamide)	-3896.73	-6.94	-6.72
10	Celebrex (celecoxib)	-3811.11	-7.75	-7.75
11	Tikosyn (dofetilide)	-3912.21	-8.36	-8.37
12	Betapace (sotalol HCl)	-3877.73	-7.22	-7.22
13	Flomax (tamsulosin HCl)	-3879.35	-8.32	-8.32

14	Imitrex (sumatriptan succinate)	-3889.04	-8.29	-8.39
15	Methazolamide	-3860.10	-7.63	-7.63
REF	AU1235	-3884.06	-7.71	-7.72

Table 1(B):The Binding Affinity Of The Reference Molecule(Au1235) 0f -7.71 Estimated Δ G Value Is Given In The Data Below

SNO	COMPOUND NAME	Full fitness (Kcal/mol)	Estimated (Kcal/mol)	Estimated (Kcal/mol)
REF	AU1235	-3884.06	-7.71	-7.72

Table 2: Interaction Of Amaryl(Glimepiride) With Mmpl3,The Active Binding Site Residues Of Mmpl3 Namely Phe , Arg288 , Phe292 And Val655, Forms Hydrophobic Interactions.The Residues Namely Gln -3 , Arg 288 Forms Hydrogen Interaction

SNO	COMPOUND NAME	RESIDUE	AA	DISTANCE	NATURE OF INTERACTIONS
1	Amaryl(GLIMEPIRIDE)	2A	PHE	3.76	Hydrophobic
		288A	ARG	3.67	Hydrophobic
		292A	PHE	3.91	Hydrophobic
		655A	VAL	3.61	Hydrophobic
		-3A	GLN	3.76	Hydrogen
		288A	ARG	3.69	Hydrogen
		288A	ARG	3.59	Hydrogen
		288A	ARG	3.08	Hydrogen

		288A	ARG	3.74	Hydrogen
		288A	ARG	3.50	Hydrogen

Table 3 :Interaction Of Dofetilide With Mmpl3,The Active Binding Site Residues Of Mmpl3 Namely Glu 656 Forms Hydrophobic Interaction And Arg 288, Arg 288, Arg 288, Thr 289, Arg 653, Glu 656 Forms An Hydrogen Bond And Glu 659 Forms Salt Bridges Bond With Dofetilide

SNO	COMPOUND NAME	RESIDUES	AA	DISTANCE	INTERACTIONS
1	Dofetilide	656A	GLU	3.65	Hydrophobic interaction
		288A	ARG	3.85	hydrogen
		288A	ARG	2.97	hydrogen
		288A	ARG	4.08	hydrogen
		289A	THR	3.18	hydrogen
		653A	ARG	3.86	hydrogen
		656A	GLU	3.01	hydrogen
		659A	GLU	4.66	Salt bridges

Table 4 : Interaction Of Flomax With Mmpl3 ,The Active Binding Site Residues Of Mmpl3 Namely Ile 32 , Leu25, Ile194, Leu251 Forms Hydrophobic Interactions Bond And Ala215 Hydrogen Bond With Flomax

SNO	COMPOUND NAME	RESIDUES	AA	DISTANCE	INTERACTIONS
1	Flomax	25A	LEU	3.99	hydrophobic
		32A	ILE	3.99	hydrophobic
		194A	ILE	3.55	hydrophobic
		251A	LEU	3.59	hydrophobic

		215A	ALA	3.06	hydrogen

Table 5: Interaction Of Imitrex With Mmpl3, The Active Binding Site Residues Of Mmpl3 Namely Val655 Forms Hydrophobic Bond Arg288, Glu656, Arg744 ,Forms Hydrogen Interactions Glu659 , Forms Salt Bridge Bond With Imitrex

S NO	COMPOUND NAME	RESIDUES	AA	DISTANCE	INTERACTIONS
1	Imitrex	655A	VAL	3.90	hydrophobic
		288A	ARG	3.49	Hydrogen
		656A	GLU	2.93	Hydrogen
		744A	ARG	4.08	hydrogen
		659A	GLU	3.93	Salt bridges

Table 6 : Interaction Of Sulfasalazine With Mmpl3 Protein.The Active Binding Site Residues Of Mmpl3 Namely Tyr30, Ile228, Leu325 Forms Only Hydrophobic Interaction With Sulfasalazine

S NO	COMPOUND NAME	RESIDUES	AA	DISTANCE	INTERACTIONS
1	Sulfasalazine	30A	TYR	3.45	hydrophobic
		228A	ILE	3.87	hydrophobic
		325A	LEU	3.94	hydrophobic

Table 7: studies have reported au1235 as a potential mmpl3 protein inhibitor in tb. The independent sample t-test results that azulfidine (sulfasalazine), amaryl (glimepiride), tikosyn (dofetilide), flomax (tamsulosin hcl), imitrex (sumatriptan succinate) demonstrated higher binding affinity in comparison with au1235 were analysed using ibm spss software version

GROUP	N	MEAN	Std. Deviation	Std. Error Mean
AU1235(REF)	3	-7.7267	.01528	.00882
DOFETILIDE	3	-9.5933	0.005774	.00333
SULFASALAZINE	3	-8.7967	.13204	.07623
IMITREX	3	-8.2900	.33867	.19553
FLOMAX	3	-8.2500	.00000	.00000
AMARYL	3	-9.8167	.01155	.00667

Table 8 independent sample t-test in predicting the significant,mean difference,std error difference of mmpl3 with different sulfonamides drugs.these appears to be a statistically insignificant difference (p>0.05).

INDEPENDENT SAMPLE TEST OF AMARYL(GLIMEPIRIDE)									
	Levene's Test for equality of variances		t-test for Equality of means						
ENERGY	F	Sig.	t	df	significance	Mean difference	Std.Error Difference	95% Confidence Interval of the Difference	
								Lower	Upper
Equal variances assumed	.235	.653	189.048	4	.000	2.09000	.01106	2.05931	2.12069

Equal variances not assumed			189.048	3.723	.000	2.09000	.01106	2.05838	2.12162

Figures

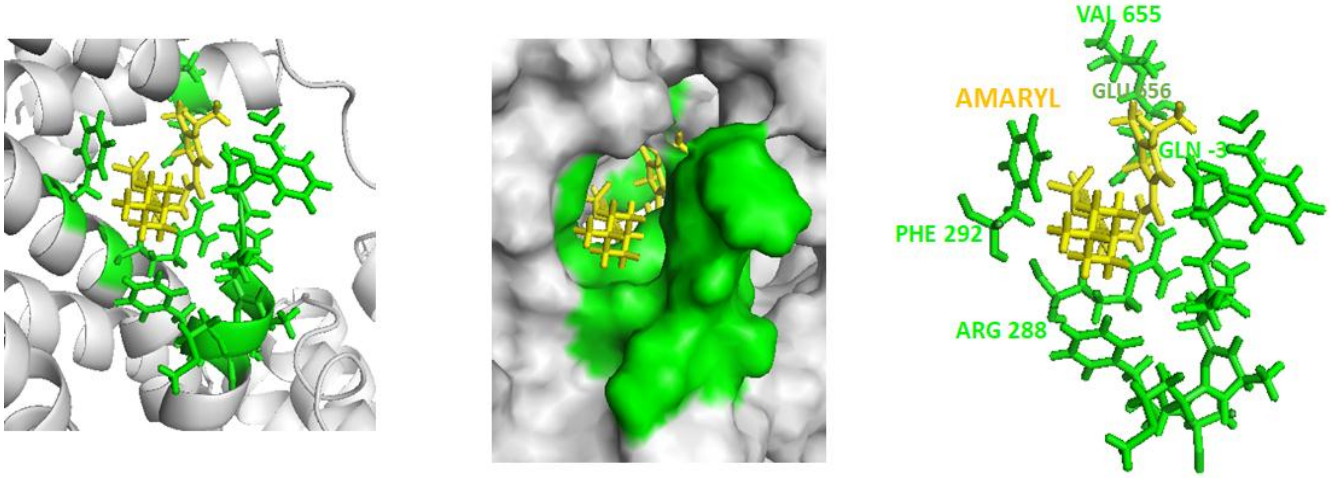

Fig. 1 Interaction analysis of amaryl(glimepiride) sulfonamides drug in the active site pocket of Mmpl3 protein.The structure of Mmpl3 and Amaryl (glimepiride) are represented in green and yellow sticks .amino acid residues of mmple protein namely VAL 655,PHE 292,ARG 288,GLN-3,GLU 256 interacts with Amaryl

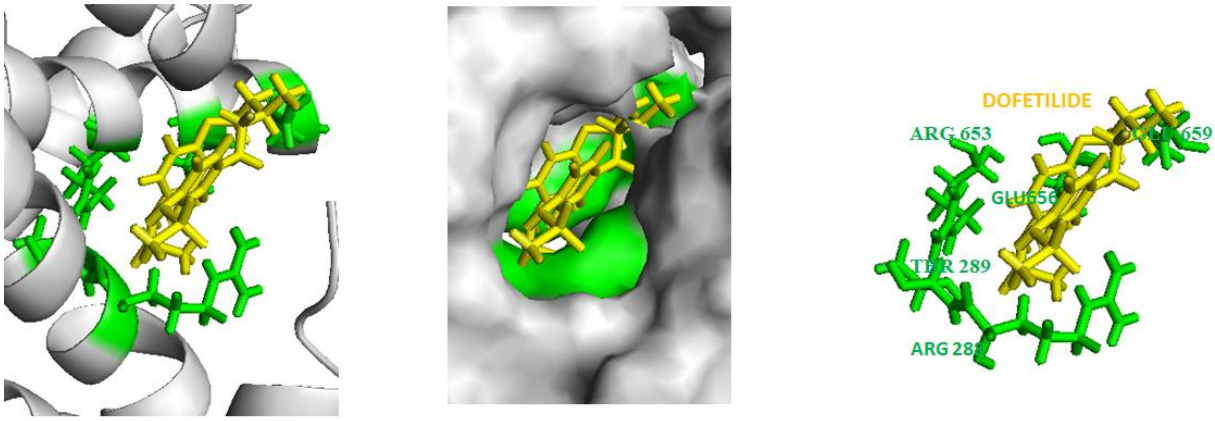

Fig. 2 Interaction analysis of dofetilide sulfonamides drug in the active site pocket of Mmpl3 protein.The structure of Mmpl3 and dofetilide are represented in green and yellow sticks .amino acid residues of mmpl3 protein namely ARG 288, ARG 288, ARG 288, THR 289, ARG 653, GLU 656 , GLU 659 interacts with dofetilide

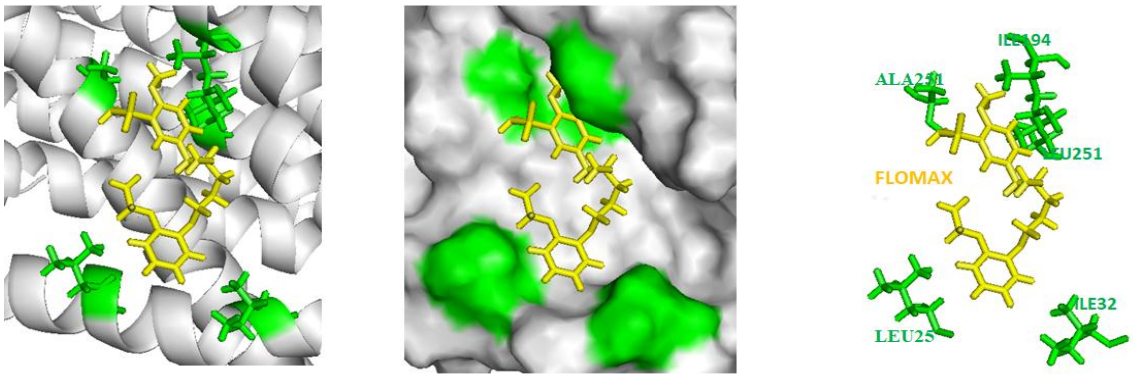

Fig. 3 Interaction analysis of flomax sulfonamides drug in the active site pocket of Mmpl3 protein.The structure of Mmpl3 and flomax are represented in green and yellow sticks .amino acid residues of mmple protein namely ILE 32 , LEU25, ILE194, LEU251 , ALA215 interacts with flomax

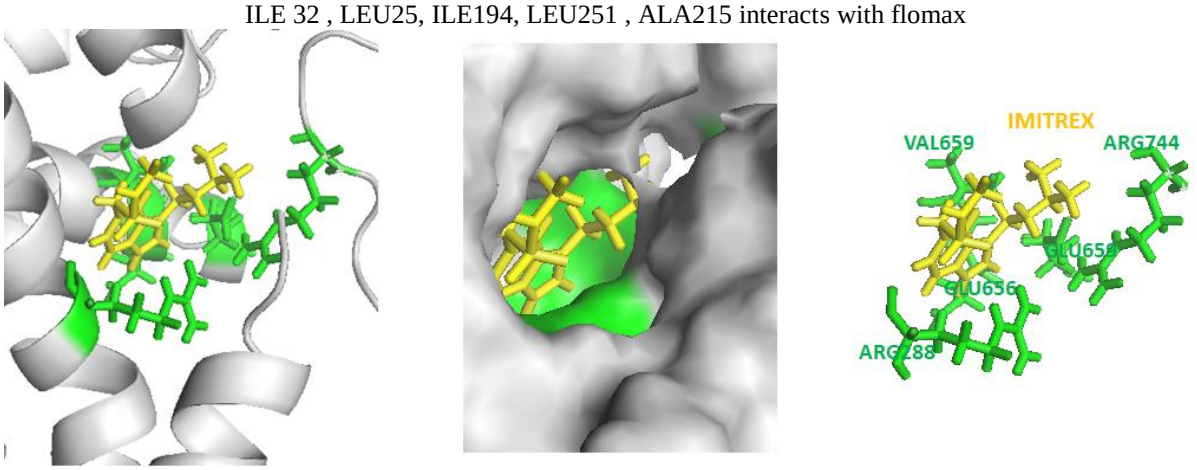

Fig. 4 Interaction analysis of imitrex sulfonamides drug in the active site pocket of Mmpl3 protein.The structure of Mmpl3 and Tolbutamide are represented in green and yellow sticks .amino acid residues of mmple protein namely VAL655, ARG288, GLU656, ARG744, GLU659 interacts with imitrex

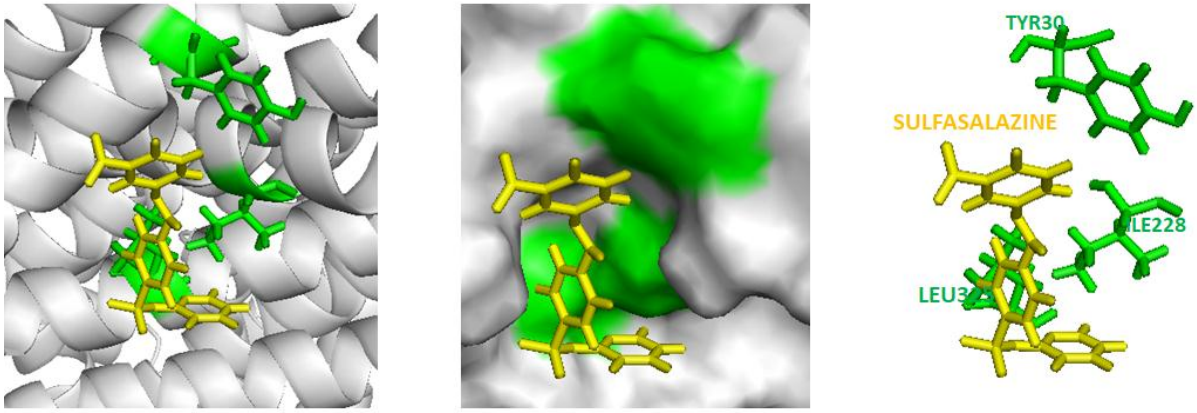

Fig. 5 Interaction analysis of sulfasalazine sulfonamides drug in the active site pocket of Mmpl3 protein.The structure of Mmpl3 and metolazone are represented in green and yellow sticks .amino acid residues of mmple protein namely TYR30, ILE228, LEU325 interacts with sulfasalazine

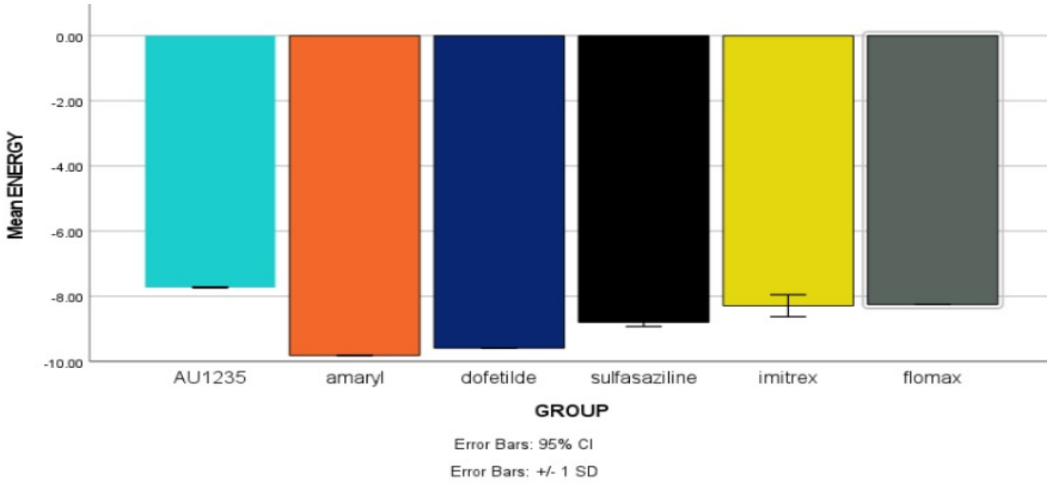

Fig. 6 : Statistical analysis of binding energy for various sulphonamide drugs.

The above graph shows the comparison of top 5 hit compounds .The highest binding affinity is amaryl(glimepiride) results in ΔG measurement of -9.81 in the orange colour. Sulfa drugs namely, Azulfidine (sulfasalazine), Amaryl (glimepiride), Tikosyn (dofetilide), Flomax (tamsulosin HCl), Imitrex (sumatriptan succinate)are represented in black, yellow, blue,sky blue,purple,grey respectively.X axis represents the screening of sulfonamides drugs and Y axis binding energy of the targeted molecules. Energy differences between the molecules were represented by ±1SD.