WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.084
Volume 12, Issue 13, 1094-1107. Research Article ISSN 2277–7105

DRUG LIKENESS, BIOAVAILABILITY, VIRTUAL SCREENING AND DOCKING STUDIES OF SOME SULFONAMIDE DERIVATIVES

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Article Received on
05 June 2023,

Revised on 26 June 2023,
Accepted on 16 July 2023

DOI: 10.20959/wjpr202313-29102

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ABSTRACT

Sulfonamides selected for the computation of drug likeness and bioavilability using Molispiration software. All the compounds obey Lipinski"s rule and its extension and showed drug likeness. Resulting in, the tested compounds showed good permeability across cell membrane and can easily bind to receptor. Similarly, all compounds were taken for calculation of bioactivity score towards G protein–coupled receptors (GPCR) ligands, ion channel modulator, kinase inhibitors, nuclear receptor inhibitors and other enzyme targets based on Molinspiration software. The compounds could be found to exhibit moderately bioactivities. They were further docked into the active domain of protein: cyclooxygenase enzymes, phosphodiesterase, the peroxisome proliferator-activated receptor, carbonic anhydrase, dihydro-folate reductase, hydrolase, polymerase, microsomal P450 enzymes, protease, pyrovate kinase and N-Methyl-D-Aspartate receptor using the docking program Molegro Virtual Docker. The docking scores of all compounds were expressed in negative energy terms and exhibited a good docking score in comparison with standard sulfadiazine & furosemide.

KEYWORDS: Drug Likeness, Bioavailability, Docking Studies, Sulfonamide.

INTRODUCTION

The concept of druggability has been widely used to postulate that the binding sites on biological molecules are complementary with their ligands in terms of volume, topology and

physicochemical properties.[1] the druggability concept evaluates the probability that small drug-like molecules can bind a given protein with sufficient potency to alter its activity. about 30% of oral drugs fail in development due to poor pharmacokinetics studies.[2] The pharmacokinetic properties are actually the main reason to stopping further development of the drug.[3] Further, the lack of efficacy might be due to poor physicochemical properties of the drug candidate itself.[4] Moreover, drug withdrawal was the interaction of a drug with a single receptor, ion channel or enzyme.[5] Therefore, it can only be advantageous if a screening set already include drug-likeness and bioactivity of compounds with the right physical properties resulting in a lower risk of attrition during drug development. Consequently, the prediction of oral bioavailability is very important in the early period of drug discovery to select the most favorable compounds for further optimization and in the last stage to match candidates for further clinical development.[6] On the other hand, the chemistry of sulfonamides has received an interest because of its biological significance.[7] Many derivatives of this system showed antibacterial, fungicidal[8], antihypertensive,[9] anticancer[10] activities. Additionally, sulfa are used as PDE4 inhibitors[11], carbonic anhydrase inhibitors[12] and as anti-inflammatory drugs via blocking the NMDA response by reducing the number of NMDA channels.[13] Taken together, from the previous information have created awareness to select compounds containing sulfonamide participated with quinoxaline or phthalazine moiety for the calculation of their drug likeness and bioavailability using Molinspiration software. Subsequently, these compounds were taken for study of ligand-protein interactions using the docking program Molegro Virtual Docker. Consequently, to make proofs for further research work for the development of preferable medicinal agents and newer compounds that could be superior agents in terms of efficacy and safety.

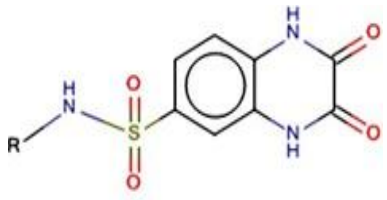
MATERIALS AND METHODS

The Quinoxaline or Phthalazine were selected for this work and given in the Scheme. Each molecule was then drawn using Marvin Sketch. The physicochemical properties and bioactivity were calculated also using Molinspiration software (www. Molinspiration.com online).

SCHEME

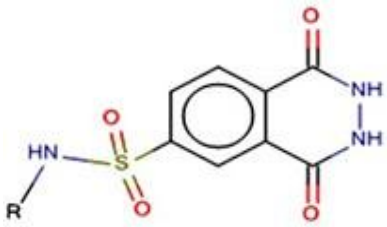
Illustrate the structures of Quinoxaline and Phthalazine derivatives.

Quinoxaline Derivatives (Q1-Q4)



[N-Ethyl-2, 3-dioxo-1, 4-dihydroquinoxaline-6-sulfonamide]

Phthalazine derivatives (P1-P4)



2, 3-dihydro-phthalazine-1, 4-dione 6-sulfonamide

R=

NH- CH2CH2OH (Hydroxyethylamine)-Q1 & P1

NH-CH2CH2OCH3 (Methoxyethylamine)-Q2 & P2

NH-CH2COOH (Glycine) -Q3 & P3

NH-p-ph-COOH (p-amino benzoic acid) -Q4 & P4

EVALUATION OF DRUG LIKENESS (DRUGGABILITY)

The utility of Druggability from a medicinal chemistry standpoint has been summarized by the rule of five (Lipinski rules, Ro5) and its extensions. The drug likeness was evaluated through the Lipinski, Ghose and Veber rules using Molinspiration software (www. Molinspiration.com).

1. Lipinski`s Rules

Lipinski designate those compounds as "drug-like", which have sufficiently reasonable ADMET (absorption, distribution, metabolism, excretion, and toxicity) properties to outrun through the Phase I clinical trials. The "rule of 5" provides an existential guide for determining, if a compound will be orally bioavailable. Properties such as oral bioavailability or membrane permeability have often been correlated to log P, molecular weight (MW) and number of hydrogen bond acceptors and donors in a molecule. Simple counting methods include "Lipinski's rule of 5" and its fulfillment in prediction of the drug likeness, along with

extended concept of Ghose and Veber. The Lipinski`s rules (RO5) states that molecules exhibition good absorption or permeation when they have an octanol-water partition coefficient (Milog P) < 5, molecular weight (MW) < 500, number hydrogen bond donors (n OHNH) ≤ 5, number hydrogen bond acceptor (n ON) ≤ 10.

2. Ghose`s Rules

Ghose established qualifying ranges for a log P (-0.4 to 5.6), molecular weight (160 to 480), and number of atoms (20 to 70).

3. Veber`s rules

A study conducted by Veber on rats showed, molecular flexibility, topological polar surface area (PSA) and hydrogen bond count are important determinants for oral bioavailability. Veber`s rules for good bioavailability in rats: rotatable bonds ≤ 10, topological polar surface area (PSA) ≤ 140 $Å^2$ and total H bond donors and acceptors ≤ 12. The target compounds were passed the Lipinski, Ghose and Veber rules and have properties that would make it a likely orally active drug in humans. The predicted drug likeness score of new compounds were compared with standard drugs sulfadiazine and furosemide.

a. Bioactivity score

Bioactivity of the compounds was checked by calculating the activity score toward G protein coupled receptors (GPCR ligand), ion channel modulator, nuclear receptor legand, kinase inhibitor, protease inhibitor and enzyme inhibitor. All the parameters were checked with the help of software Molinspiration drug-likeness score online. The predicted bioactivity score of the compounds and standard (sulfadiazine and furosemide).

b. Molecular docking studies

i. Protein Preparation

The three-dimensional crystal structure of thirteen (13) proteins were fetched from the Protein Data Bank (PDB) (http://www.rcsb.org/): cyclooxygenase enzymes COX-1 (3N8Y) ; phosphodiesterase (PDE) (4KP6) and (4MYQ); the peroxisome proliferator-activated receptor (PPAR) (2GTK); carbonic anhydrase (3K34); dihydro-folate reductase (5JA3); hydrolase (1YMN); polymerase (5JJS); microsomal P450 enzymes (5LIE); protease (1HSG); Pyruvate kinase (PK) (5FT4) and (2VGG) and N-methyl-D-aspartate receptor (NMDA) (5EWM). All the PDB's proteins were loaded in the Molegro virtual docker (MVD) with the removal of all water molecules and cofactors. The standard Molegro algorithm was utilized

for rendering the missing charges, protonation states, and assigning of polar hydrogen to the receptor.

ii. Ligands preparation

The Structures of ligands were drawn using Marvin Sketch and energy minimization was done. Energy minimization was done to help the docking program, Molegro Virtual Docker (MVD), to identify the bioactive conformer from the local minima. One major advantage of Molegro Virtual Docker (MVD) is that it helps in assigning the missing bond orders, charges, bonds, and hybridization states of the imported ligands.

iii. Molecular docking

Flexible ligand models were used for docking and post docking geometry optimizations. The post-docking geometry optimizations were carried out using Molegro Virtual Docker (MVD). This program uses a grid-based scheme for energies of individual atoms, allowing a quick computation of the interaction energy of the protein-ligand complex as the interaction between the ligand and the grid. So, the ligand was binding with active site of protein. A docking sphere (20 Å radius) was placed on the binding sites of each protein structure in order to allow different orientations of each ligand to be searched in the binding cavities. The title compounds were docked with the different receptors.

RESULTS AND DISCUSSION

Evaluation of drug likeness

Drug-likeness can be deduced as a smooth balance among molecular properties affecting pharmacodynamics and pharmacokinetics of molecules which finally affects their absorption, distribution, metabolism, and excretion (ADME) in human body like a drug. Molecular properties such as membrane permeability and bioavailability are always connected with some basic molecular descriptors such as logP (partition coefficient), molecular weight (MW), topological polar surface area (TPSA), or hydrogen bond acceptors and donor's counts in a molecule. It appears that, the lipophilicity is potentially linked to toxicity, which is in agreement with the observation that lipophilic binding is non-specific, whereas polar binding is related to specificity and therefore selectivity. It proof that, the toxicity are significantly higher for compounds with a clogP exceeds 3 and a topological polar surface area (TPSA) < 75 $Å^2$. Our compounds show clogP is below 3 and TPSA is more than 75 $Å^2$ but less than 140 $Å^2$ resulting in the target compounds may be safe in use. Lipinski, Ghose and Veber rules states that most molecules with good membrane permeability have logP ≤ 5,

molecular weight ≤500, number of hydrogen bond acceptors ≤10, and number of hydrogen bond donors ≤ 5, topological polar surface area (TPSA) < 140 $Å^2$ and number of rotatable bonds (n rotb) < 10 this measures molecular flexibility and also, the total number of atoms between (n Atoms) 20 and 70. These rules are widely used as a filter for drug-like properties.

Drug Likeness Of Selected Compounds Comparing With References (Sulfadiazine & Furosemide)- QUINOXALINE

Comp. No.	MiLogP	TPSA	n. A.	MW	n ON	n ONH	n. V	n.R	Vol.
Q1	-1.85	132.12	19	285.28	8	4	0	4	221.43
Q2	-1.02	128.96	20	297.29	8	3	0	3	232.15
Q3	-2.89	149.19	20	299.26	9	4	0	4	223.61
Q4	0.39	149.19	25	361.33	9	4	0	4	278.22
Sulfadiazine	-0.04	97.98	17	250.28	6	3	0	3	202.26
Furosemide	2.39	122.63	20	316.72	7	4	0	4	232.68

Notes: Milog P: Partition Coefficient; TPSA: Topological Polar Surface Area; N A: Number Of Atoms; MW: Molecular Weight; N ON: Number Of Hydrogen Acceptor; Nonh: Number Of Hydrogen Donor, Nv: Number Of Violation Of Five Lipinsky Rules; N.R: Number Of Rotatable Bonds And Vol Volume OfMolecule.

Drug likeness of selected compounds comparing with references(sulfadiazine & furosemide) -PHTHALAZINE

Comp. No.	MiLogP	TPSA	n. A.	MW	n ON	n ONH	n. V	n.R	Vol.
P1	-0.69	132.12	20	299.31	8	4	0	5	238.23
P2	-0.34	121.13	20	297.29	8	3	0	5	238.96
P3	-1.99	149.19	20	299.26	9	4	0	4	223.61
P4	1.28	149.19	25	361.33	9	4	0	4	278.22
Sulfadiazine	-0.04	97.98	17	250.28	6	3	0	3	202.26
Furosemide	2.39	122.63	20	316.72	7	4	0	4	232.68

Notes: Milog P: partition coefficient; TPSA: Topological polar surface area; n A:number of atoms; MW: molecular weight; n ON: number of hydrogen acceptor; nONH: number of hydrogen donor, nV: number of violation of five Lipinsky rules; n.R: number of rotatable bonds and vol volume of molecule.

The results reveal that all compounds obeyed the rules and showed good drug likeness score. The logP value of a compound, which is the logarithm of its partition coefficient between n-octanol and water, is a well-established measure of the compound's hydrophilicity. It has been shown that our compounds have a reasonable probability of good absorption, their logP value ranged between -2.89 to 1.28 that is not exceed 5.0. Topoligical polar surface area (TPSA) is a very useful parameter for the prediction of drug transport properties. The tested compounds were found to have topological polar surface area (TPSA) in the range of 128.96 to 149.19 that is well below 140 $Å^2$ except compounds Q3, Q4, P3 and P4 have TPSA equal 149 $Å^2$ which is somewhat higher than140 $Å^2$. Number of rotatable bond is important for conformational changes of molecules under study and ultimately for the binding of receptors

or channels. The compounds possess lower range of number of rotatable bonds (2-4) ≤ 10 therefore they exhibit low conformational flexibility. In addition, they have molecular weights (MW) ranged between 283-361.33 that is below 500, number of hydrogen bond donors (nONH) are ranged between 2-4 that is less than 5 and also hydrogen bond acceptors (nON) are 7-9 that is below 10. Finally, all compounds have number of atoms ranged 19-25 that is within 20-70. The results were compared with standard sulfadiazine and furosemide. From the results reveal that these compounds obeyed Lipinski and its extension rules and are orally bioactive.

Bioactivity score

From the previous results shows that all compounds (Q1-4 and P1-4) have physiochemical properties within the acceptable criteria. Thus, these parameter should be taken into consideration and serve as a guide for further screening investigations against various bio targets: [G-protein-coupled receptors (GPCR); Ion channel modulator (ICM); Kinase inhibitor (KI); Nuclear receptor ligand (NRL); Protease inhibitor (PI); Enzyme inhibitor (EI)]. So, by using Molinspiration software "on-line test", the bioactivity of the all compounds were estimated and represented. In general, drugs in the protease and GPCR-peptidic families are characterized by significantly higher average molecular weight, while those in the ion channel family have lower average molecular weight. Drugs in the GPCR-lipid, GPCR peptidic and nuclear hormone receptor (NHR) families have significantly higher cLogP. Also, drugs in the GPCR- peptidic and protease families have more acceptors, while those in NHR families have fewer acceptors. It proofs that only four families; CYP450, kinase, phosphodiesterase (PDE) and Transporters are the mean values of all four properties statistically similar to those of all oral drugs.

Taking into consideration, the bioactivity scores (≥ 0.00) may refer to considerable biological activities, if the bioactivity scores (-5.0 to 0.0) it is moderately active and finally if the bioactivity scores (< -5.0) it is inactive.

Bioactivity Of All Selected Compounds Comparing With Standard (Sulfadiazine & Furosemide)

Comp. No.	GPCR	ICM	KI	NRL	PI	EI
Q1	-0.11	-0.22	-0.21	-0.55	-0.14	0.04
Q2	0.11	-0.23	-0.21	-0.49	0.02	0.10
Q3	-0.05	-0.17	-0.41	-0.29	-0.03	0.13
Q4	-0.04	-0.14	-0.20	-0.06	-0.01	0.02
Sulfadiazine	-0.292	-0.392	-0.145	-0.918	-0.471	-0.012
Furosemide	-0.346	-0.598	-0.318	-0.689	-0.498	-0.06

Notes: GPCRL: GPCR ligand; ICM: Ion channel modulator; KI: Kinase inhibitor; NRL: Nuclear receptor ligand; PI: Protease inhibitor; EI: Enzyme inhibitor

Bioactivity of all selected compounds comparing with standard(Sulfadiazine & Furosemide)

Comp. No.	GPCR	ICM	KI	NRL	PI	EI
P1	-0.19	-0. 35	-0.23	-0.54	-0.05	0.12
P2	-0.24	-0.35	-0.35	-0.60	-0.16	0.01
P3	-0.21	-0.39	-0.47	-0.52	-0.04	0.15
P4	-0.17	-0.32	-0.25	-0.25	-0.02	0.04
Sulfadiazine	-0.292	-0.392	-0.145	-0.918	-0.471	-0.012
Furosemide	-0.346	-0.598	-0.318	-0.689	-0.498	-0.06

Notes: GPCRL: GPCR ligand; ICM: Ion channel modulator; KI: Kinase inhibitor; NRL:Nuclear receptor ligand; PI: Protease inhibitor; EI: Enzyme inhibitor

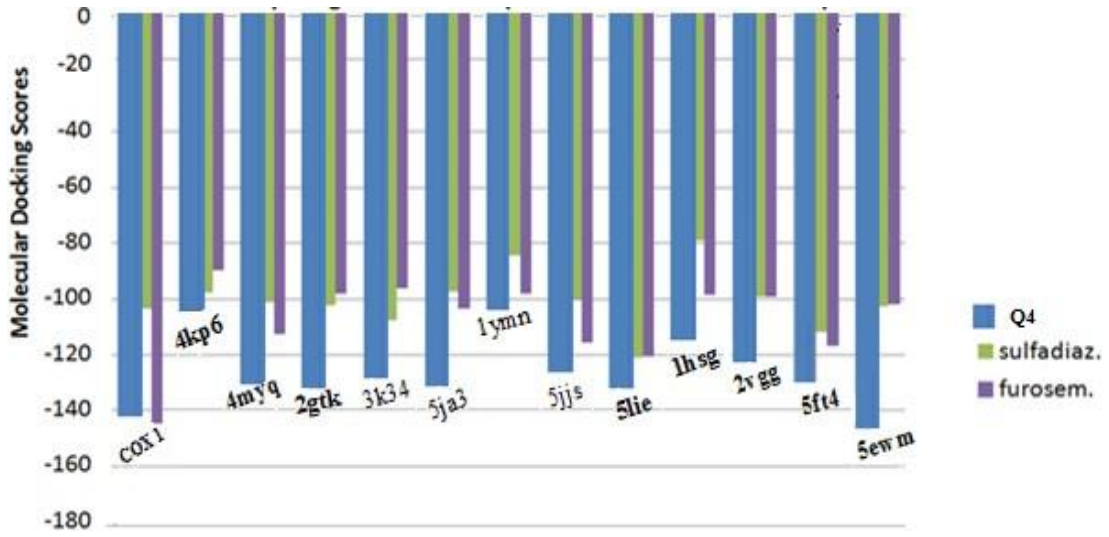
On these oversight, the results showed the following observations: for quinoxaline sulfonamides (Q1-Q4): a) GPCR ligand: all our compounds were found to be moderately bioactive, the bioactivity scores (-0.18 to -0.04) comparing with sulfadiazine and furosemide (-0.292 and -0.346 respectively). b) Ion channel modulator: all our compounds were found to be better bioactive, the bioactivity scores (-0.35 to 0.18) comparing with references (-0.392 and -0.598). c) Kinase inhibitors: the bioactivity scores (-0.41 to -0.20) comparing with sulfadiazine and furosemide (-0.145 and -0.318). d) Nuclear receptor inhibitors: all our compounds were found to be good bioactive, thus the bioactivity scores were -0.53 to 0.45 in comparison with sulfadiazine and furosemide are -0.918 and -0.689 respectively. e) Protease inhibitor: all our compounds were found to be good bioactive, the bioactivity scores (-0.11 to 0.14), while sulfadiazine and furosemide are -0.471 and -0.498 respectively. f) Enzyme inhibitor: all our compounds were found to be better bioactive; the bioactivity scores were ranged between -0.09 to 0.13, whereas standards are -0.012 and -0.06. Taken together, the results show that quinoxaline sulfonamides may have better bioactivity score (-0.53 to 0.45) than phthalazine sulfonamides (-0.76 to 0.15) in comparison with sulfadiazine and furosemide (-0.918 to -0.012 and -0.689 to -0.06 respectively). Also, quinoxaline sulfonamides may be active toward ion channel modulator; nuclear receptor inhibitors, protease inhibitor and enzyme inhibitor especially compound Q1, Q3 and Q4 may be bioactive toward enzyme inhibitor. While in the case of phthalazine sulfonamides, the compounds P1, P2, P3 and P4 are bioactive toward enzyme inhibitor only. Moreover, the designed molecules obeyed the Lipinski and its extension rules. So the selected compounds may be useful as a lead compound for various diseases like anti-inflammatory, antibacterial, HIV, cancer and others diseases.

c. Molecular docking studies

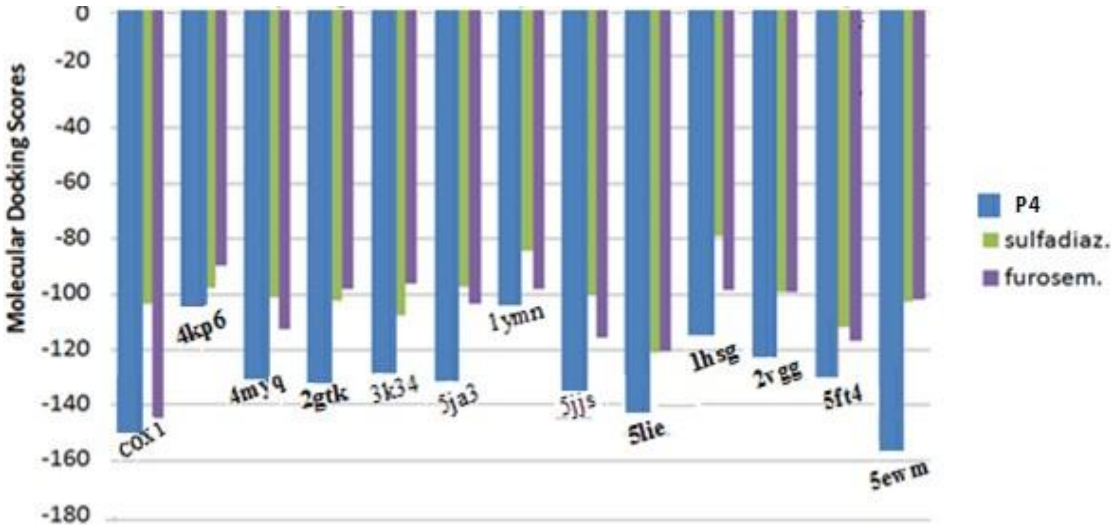
In order to understand the interactions at a molecular level of our derivatives with their bio targets, I have selected model of protein structures which are available in the Protein Data Bank (PDB) (www.rcsb.org/pdb). The structures of bio target have been instrumental in orientation not only lead optimization and target identification but also lead discovery and screening.[35] So, several proteins were fetched from the Protein Data Bank. The molecular docking study was performed to investigate the binding affinities and interaction modes between our compounds and the target protein using the Molegro Virtual Docker (MVD).

The eight (8) selected compounds and two references (sulfadiazine and furosemide) were incorporated into the active site of the preferable protein only herein we selected thirteen protein which have a higher binding scores: cyclooxygenase enzymes COX-1 (3N8Y); phosphodiesterase (PDE) (4KP6) and (4MYQ); the peroxisome proliferator-activated receptor (PPAR) (2GTK); carbonic anhydrase (3K34); dihydro-folate reductase (5JA3); hydrolase (1YMN); polymerase (5JJS); microsomal P450 enzymes (5LIE); protease (1HSG); pyrovate kinase (PK) (5FT4) and (2VGG) and N-methyl-D-aspartate receptor (NMDA) (5EWM). The docking scores were expressed in negative energy terms; the lower binding free energy is the better binding affinity. To further improve docking accuracy, a re-ranking scoring function is introduced. As we realize binding free energies can serve as a powerful tool in drug design, where correct ranking of inhibitors is often conformed.

The Molecular Docking Scores of Q4 with all selected proteincomparing with standard (Sulfadiazine and Furosemide)



The Molecular Docking Scores of P4 with all selected protein comparing with standard (Sulfadiazine and Furosemide)

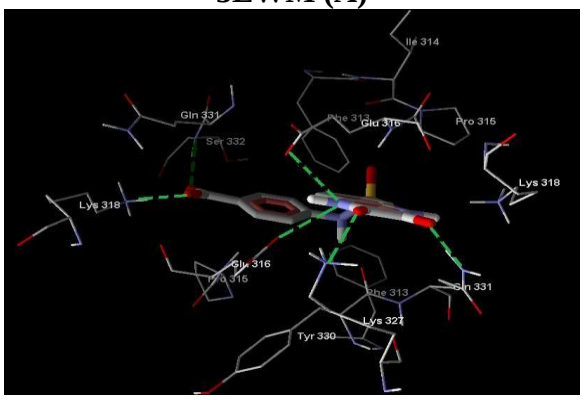


In general, the docking study displayed that all of target compounds showed superior binding interactions in terms of hydrogen bond, electrostatic and hydrophobic interactions with the residues of protein amino acids so these molecules were able to inhibit all selected enzymes by fitting inside the pocket of the active site better than standard (sulfadiazine and furosemide). As indicated from docking analysis, higher total scores (comparable to the other derivatives and with standard) were observed for compounds Q4 and P4 Revealing that, both compounds had electrostatic and hydrophobic interactions as well as hydrogen bonds with pharmacophoreic residues of protein. These interactions play significant roles in the overall binding energy. Moreover, in silico modelling good binding affinity was observed between all compounds and NMDA receptors (5EWM) that they have lowest binding free energies and thus able to inhibit NMDA receptors comparing with other enzymes and standard. As well as both Q4 and P4 were potentially an interesting hit compound due to the molecular criteria analysis and affinity binding with active site of this receptor.

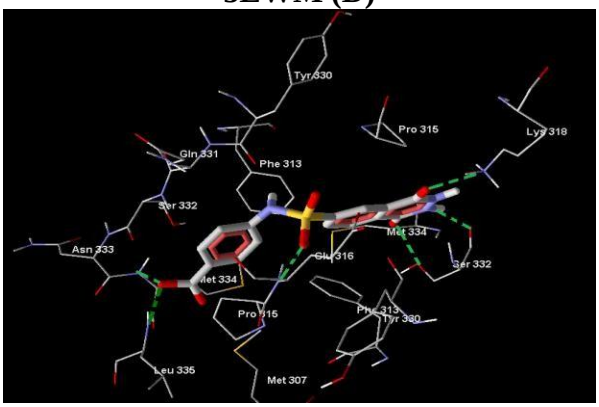
3D structure of compound Q4 **3D structure of compound P4**

3D structure of compound Q4 and P4, Hydrogen bond, Hydrophobicity and Electrostatic interactions between the compounds Q4, P4 and the active site of 5EWM.

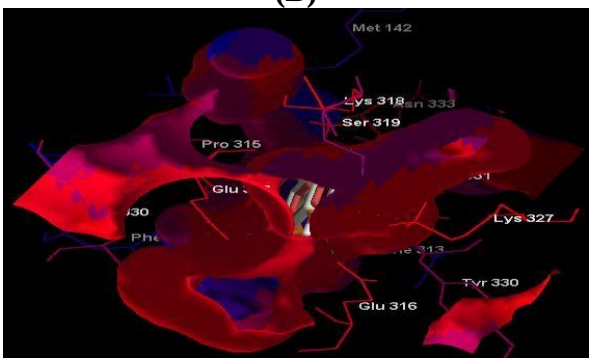
Hydrogen bond between comp. Q4 with 5EWM (A)



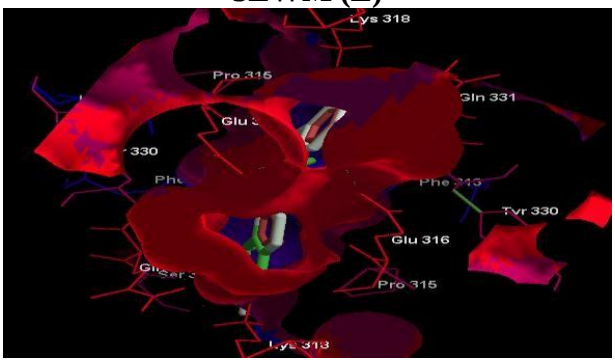
Hydrogen bond between comp. P4 with 5EWM (D)



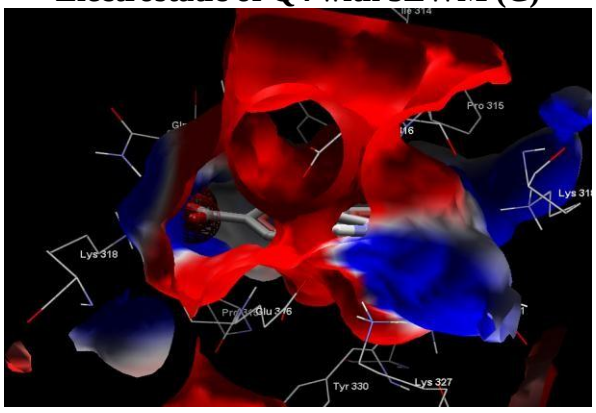
Hydrophobicity of comp. Q4 with 5EWM (B)



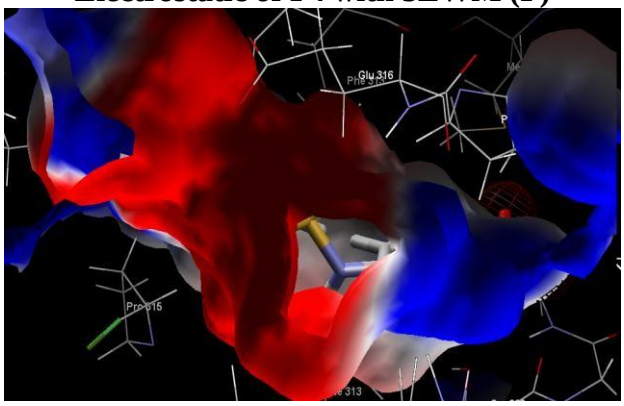
Hydrophobicity of comp. P4 with 5EWM (E)



Electrostatic of Q4 with 5EWM (C)

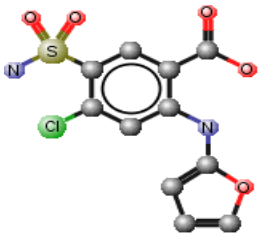


Electrostatic of P4 with 5EWM (F)

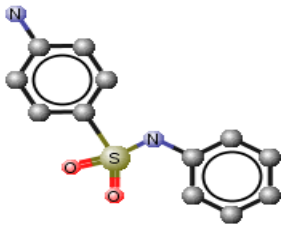


3D structure of compound Q4 and P4 and the ligands-receptor (5EWM) complex. The docking results suggest that the compound Q4 has good orientation shape with active site by hydrogen bonds (**A**), hydophobicity (**B**) and electrostatic interaction indicating (**C**) that the molecule has a good interaction with the receptor. Six H-bonding interactions between the top pose of compound Q4 and receptor; H- bonds involving oxygen atoms of the carbonyl of quinoxaline moiety with $–NH_2$ group of Lys^{327} and second C=O with $–NH_2$ of Gln^{331}; -NH of quinoxaline moiety with -C=O of two amino acids of Glu^{316} and two H-bonds are formed between –COOH of compound 3d and $–NH_2$ group of Lys^{318} and –NH of Ser^{332}.

3D structures of standard



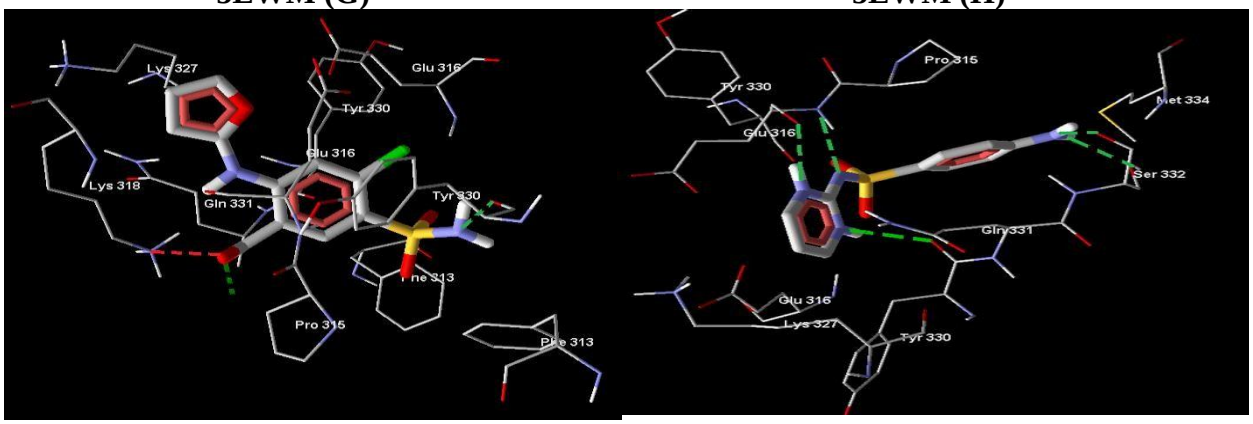
Furosemide



Sulfadiazine

Hydrogen bond between furosemide with 5EWM (G)

Hydrogen bond between sulfadiazine with 5EWM (H)



3D structure of compound of standards (sulfadiazine and furosemide), Hydrogen bond interactions between the furosemide and sulfadiazine with active site of 5EWM

Furthermore, the molecule of the compound P4 has shown affinity to or preference for its orientation in pocket of active site of receptor as shown **(D, E and F)**. As indicated from **(D)** show that a six H-bonds interactions between the top pose of compound P4 and active site of receptor. It makes hydrogen bonds oxygen atoms of the one carbonyl of phthalazine moiety with $–NH_2$ group of Lys^{318} and second C=O with –OH of Ser^{332}; -NH of phthalazine moiety with -C=O group of Ser^{332}; H-bonds between -COOH with -NH of Ieu^{335} and –NH of Asn^{333}, latter –S=O group with –NH of Glu^{316}. In comparison with two references (furosemide and sulfadiazine), the docking analysis for furosemide (**G**) reveals that, it performs hydrogen bonds between –COOH group with $–NH_2$ group of Lys^{318} and with 1 mol of water, and -NH group of sulfonamide group with C=O group of Tyr^{330}. While sulfadiazine (**H**) formed hydrogen bonds between -NH of pyrimidine moiety with -C=O group of Glu^{316}; second -NH of pyrimidine moiety with -C=O group of Tyr^{330}; -NH of sulfonyl group with -NH of Glu^{316} and finally $-NH_2$ of phenyl group with -C=O of Ser^{332} and with -OH of Ser^{332}. From docking analysis of the putative interactions of Q4 and P4 with binding site of human 5EWM receptor indicated that these hits candidates may be useful as guide for further optimization.

CONCLUSIONS

The selected compounds (Q1-4 and P1-4) met Lipinski"s rule and its extension and showed drug likeness (MiLog P value < 5, TPSA < 140 Å2, n violation = 0, molecular mass < 500, N rotb < 5, n HBD <5 and n HBA<8). These indicated that the tested compounds showed good permeability across cell membrane and can easily bind to receptor. In addition, the prediction of bioactivity for all compounds towards G protein–coupled receptors (GPCR) ligands, ion channel modulator, kinase inhibitors, nuclear receptor inhibitors and other enzyme targets based on Molinspiration software. The compounds were found to exhibit good to moderately bioactivities comparing with standard (sulfadiazine and furosemide). Furthermore, in silico modelling, revealed that they had a good binding to the pocket of active domain of fetched protein. The heterocyclic atoms and carboxylic group within compounds played a key contributor to exploiting polar interactions such as hydrogen bonding. The compounds Q4 and P4 are potentially an interesting hit compound due to the molecular criteria analysis and their affinity into the active sites of all protein especially NMDA receptors (5EWM) as indicated by the in silico modeling. Based on these overall results and in silico modeling studies reveal that the compounds especially Q4 and P4 could be considered as possible hit as therapeutic agents.

ACKNOWLEDGEMENTS

RMES's College of Pharmacy, Gulbarga for providing the necessary facilities to carry out this work.

REFERENCES

1. Hopkins A. L. and Groom C. R., Target analysis: a priori assessment of druggability, Ernst Schering Res. Found. Workshop, 2003; 42: 11–17.
2. Waterbeemd, H.V. de, Gifford E., ADMET in silico modelling: towards prediction paradise? Nat. Rev. Drug Discov, 2003; 2: 192-204.
3. Hou T., Wang J., Zhang W., Xu X., ADME evaluation in drug discovery. 6. Can oral bioavailability in humans be effectively predicted by simple molecular property-based rules, J. Chem. Inf. Model, 2007; 47: 460-463.
4. Leeson P. D. and Davis A. M., Time-Related Differences in the Physical Property Profiles of Oral Drugs, J. Med. Chem, 2004; 47: 6338–6348.
5. Smith D. A. and Schmid E. F., Drug withdrawals and the lessons within, Curr. Opin. Drug Discov. Dev, 2006; 9: 38–46.

6. Aneta K., Iwona F., Justyna Ł., Danuta B., Biological activity and synthesis of sulfonamide derivatives: a brief review, CHEMIK, 2014; 68(7): 620-628.
7. Tailor, S. M., Patel, U. H., Synthesis, spectroscopic characterization, antimicrobial activity and crystal structure of silver and copper complexes of sulfamethazine, Journal of Coordination Chemistry, 2015; 68: 2192-2207.
8. Zeng Z., Gao, T., Li, Y., Wang, X., Yang, X. and Wu, M., Synthesis and biological activity of arylsulfonamide derivatives containing 2-arylamino-4(3*H*)-quinazolinone, J. Pestic. Sci.; 2016; 41(4): 171–174.
9. Doungsoongnuen S., Worachartcheewan A., Pingaew R., Suksrichavalit T., Prachayasittikul S., Ruchirawat S., Prachayasittikul V., Investigation on biological activities of anthranilic acid sulfonamide analogs, EXCLI Journal, 2011; 10: 155-161.
10. Scozzafava, A., Owa, T., Mastrolorenzo, A., Supuran, C.T., Anticancer and antiviral sulfonamides, Curr Med Chem, 2003; 10(11): 925-53.
11. Nunes, IKdC, de Souza, ET, Cardozo, SVS, Carvalho, VdF, Romeiro, NC, Silva, PMRe, et al., Synthesis, Pharmacological Profile and Docking Studies of New Sulfonamides Designed as Phosphodiesterase-4 Inhibitors. PLoS ONE, 2016; 11(10): e0162895.
12. Temperini C., Cecchi A., Scozzafava A. and Supuran C. T., Carbonic anhydrase inhibitors. Sulfonamide diuretics revisited-old leads for new applications? Org. Biomol. Chem., 2008; 6: 2499-2506.
13. Noh JH, Gwag BJ, Chung JM, Underlying mechanism for NMDA receptor antagonism by the anti-inflammatory drug, sulfasalazine, in mouse cortical neurons, Neuropharmacology, 2006; 50(1): 1-15.
14. Gupta G. and Verma P., Antimicrobial Activity of Quinoxaline Derivatives, Chemical Science Transactions, 2014; 3(3): 876-884.
15. Peraman, R., Kuppusamy, R., Killi, S. K., and Reddy, Y. P., New Conjugates of Quinoxaline as Potent Antitubercular and Antibacterial Agents, International Journal of Medicinal Chemistry, 2016, Volume Article ID 6471352, 8 pages.
16. Rajamanickam G. et al, Synthesis, characterization and pharmacological evaluation of some potent 2-(substituted phenylimino) quinoxaline-3-one for their analgesic activity, J. Chem. Pharm. Res, 2015; 7(7): 961-966.