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QSAR and Toxicity profile of Synthesized Derivatives of 5-aryl/di fluro phenyl substituted-1,3,4-Thidiazole-2-amine

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ABSTRACT
The synthesized series of derivatives of 5-substituted-alkyl/aryl-1,3,4-thidiazole-2-amine were confirmed by spectral techniques such as IR, ^{1}HNMR, LCMS etc. Computational study of the synthesized molecule gives us clear cut idea about the toxicity and ADMET parameters. The synthesized derivatives didn't show any toxicity issues which was predicted in result. Toxicity profile of the synthesized derivatives were check out in silicon regarding mutagenic, tumorigenic, effect on reproductive system, eye irritant properties. Antimicrobial studies of synthesized molecules are the parameter of screening of synthesized derivatives which was also produces acceptable result. In that molecular modelling and docking study reveals the antimicrobial properties with selected protein target via literature survey and PDB. Due to increase in AMR problem day by day cause the resistance to antibiotic drugs and it affects the severe problems to community and hospitalized patients as well as healthy persons. Mainly these problems arises due to population, industrialization, pollution and deforestation, new microorganisms are continuously producing and cause diseases such as swine flu, antiviral infection, and asthma in short infectious diseases increased day by day. To fight against these harmful microorganisms there was continuous and consistent effort of scientist to develop new molecules which could be used for the treatment of infections.

Key words: -substituted-alkyl/aryl-1,3,4-thidiazole-2-amine, mutagenic, tumerogenic, effect on reproductive system, eye irritant, IR, ^{1}HNMR, LCMS, AMR etc.

INTRODUCTION

Heterocyclic compounds are wide range of pharmaceutical, agrochemicals, veterinary, antioxidant, corrosion inhibitors, as a copolymer, dye stuff, useful for synthetic purpose [1]. These are very much interest in our daily life, some of them as an antibiotics such as penicillin's, cephalosporin; alkaloids such as vinblastine, morphine, reserpine etc. had heterocyclic moiety. The cyclic organic compounds which contain at least one hetero atom, the most common heteroatom are the nitrogen, oxygen and sulphur but heterocyclic rings containing other hetero atoms are also widely known. [2-3]. To solve the medical life issues synthetic chemistry joined with medicinal chemistry, computational chemistry, drug chemistry which is becomes an important fields of chemistry. Modern drug discovery focuses on the synthesis of specific bimolecular targets, which invariably contain a heterocyclic component or design drug which has been structural and functional analogues to mimic or study the change in pharmacological properties. A key challenge in the synthesis of such targets continues to be the development of new pathways and improvement of existing pathways [4]. Structure based drug discovery (SBDD) is a proven strategy for the rational development of small molecules of therapeutic interest without necessitating its synthesis at the preliminary stages [5-6].

In this research work we especially emphasis on molecular modelling and docking study of synthesized derivatives of 5-substituted -1,3,4-thidiazole-2-amine by computational method chosen for the identification of potential target specific ligands (lead generation), synthesis and computational screening were carried out in pursuit of designing some potential novel antimicrobial compounds carrying 1,3,4-Thiadiazoles rings as core nucleus.

1, 3, 4- thiadiazole core containing drugs are currently in the market: acetazolamide®) and methazolamide® are diuretics, acting through inhibition of carbonic anhydrase; their derivatives display additional activities, including anticonvulsant and selective cerebral vasodilation, as well as the anticipated inhibition of carbonic anhydrase, cefazolin sodium® (CFZL; 3) and cefazedon® (CFZD; 4)-first-generation cephalosporins and megazol® an antiparasitic drug [7-10].

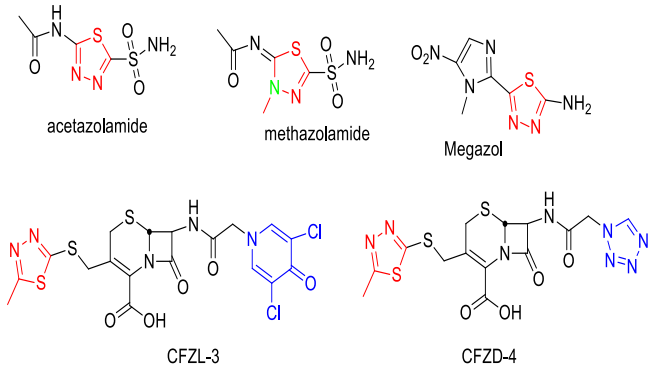


Fig.1: Structures of 1, 3, 4- thiadiazole core containing drugs available in the market

METHODOLOGY

Methods to study the *in silico* activity:

Software and program

Chemsketch was used to draw the ligand compounds. Accelry's Discovery studio v4.0 and Schrodinger's maestro visualization program v9.6 [11] were utilized to visualize the protein-ligand structures, H-bonds, measurement of bond lengths and to render images. Manual Pharmacophore hypothesis generation module of Schrodinger's maestro v9.6 was used for pharmacophore features mapping of the compounds along with location and calculation of distance between the pharmacophore features. MGL Tools version 1.5.6 was used for the preparation of the ligands and protein receptors in pdbqt format and to visualize and estimate the grid box size for docking calculations. Autodock 4.0 [12] is the software used for the docking calculation. Molinspiration and Orisis property explorer and programs were used to predict the ADMET properties of the compounds.

QSAR study of the synthesized derivatives:

Based on the descriptor values predicted by the Molinspiration and Osiris property explorer online servers [13] all the synthesized compounds successfully satisfied all the parameters of Lipinski's rule of five [14] (the mol. wt. must be less than 500 Da, the number of hydrogen donors and log P values should be less than five; the refractivity molar range shall be between 40 to 130 and the number of

hydrogen bond acceptors should not exceed ten.) and all the present investigated synthesized compounds show that all the compounds have a promising oral bioavaibility and ADME. As per the Veber's rule, oral bioavailability of drugs could be measured by the total polar surface area (TPSA) of the compound along with molecular weight, number of H-bonds and the number of rotatable bonds. Good orally bioavailabe small molecules is marked by small molecular weight (less than 500 Da); the number hydrogen donor/ acceptors combined shall be less than 12, TPSA values less than 140 and the number of rotatable bonds must be less than ten [15].

Prediction of toxicity:

The toxicity predictions of the present studied synthesized derivatives using Osiris Property Explorer [16] were based on the functional group similarity for the query molecule with the *in vitro* and *in vivo* validated compounds in the database.

The result of toxicity analysis of all the analyzed compounds is described as follows "HIGH" means high tendency of toxicity; "MEDIUM" means the midcore and "NONE" means low toxic tendency as evident tabulated in table no. 1 and 2.

RESULTS AND DISCUSSION

All these synthesized computational screened *in silco* activity predicted the compounds possessed no toxic tendency, only TDB_3 (2-(3-(5-(2,3-difluorophenyl)-1,3,4-thiadiazol-2-yl) ureido) acetic acid) has showed high eye irritant toxicity. Otherwise remaining all synthesized derivatives of 1,3,4-thidiazole having urea moiety (as pharmacophore) as bridge connected with bioactive molecule used as cyclopentyl amine,morpholine and glycine (optically inactive aminoacid) showed acceptable pharmacological properties based on analogues.

Table 1: ADME parameters of the synthesized derivatives:

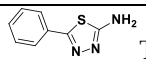
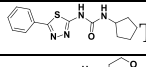
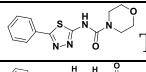
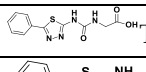
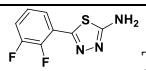
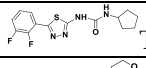
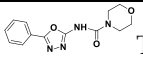
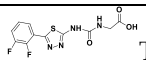
Sr. No	synthesized derivative	Molecular Formula	Mol. wt.	Log P	H-bond donors	H-Bond acceptors	Rotatable bonds	TPSA
1	 TDA	$C_8H_7N_3S$	177.2	1.6	1	3	1	80.0
2	 TDA_1	$C_{14}H_{16}N_4OS$	288.3	2.9	2	5	3	95.1
3	 TDA_2	$C_{13}H_{14}N_4O_2S$	290.3	1.9	1	6	2	95.5
4	 TDA_3	$C_{11}H_{10}N_4O_3S$	278.2	0.8	3	7	4	132.4
5	 TDB	$C_8H_5N_3F_2S$	213.2	1.8	1	3	1	80.0
6	 TDB_1	$C_{14}H_{14}N_4OF_2S$	324.3	3.1	2	5	3	95.1
7	 TDB_2	$C_{13}H_{12}N_4O_2F_2S$	326.3	2.1	1	6	2	95.5
8	 TDB_3	$C_{12}H_{12}N_4O_3F_2S$	310.3	1.3	3	7	4	132.4

Table 2: Toxicology profile of the synthesized derivatives

Sr.No	**Compound Code**	Mutagenic	Tumerogenic	Effect on Reproductive system	Eye Irritant
1	TDA	NONE	NONE	NONE	NONE
2	TDA_1	NONE	NONE	NONE	NONE
3	TDA_2	NONE	NONE	NONE	NONE
4	TDA_3	NONE	LOW	NONE	NONE
5	TDB	NONE	NONE	NONE	NONE
6	TDB_1	NONE	NONE	NONE	NONE
7	TDB_2	NONE	NONE	NONE	NONE
8	TDB_3	NONE	LOW	NONE	HIGH

CONCLUSION

In Silco study of synthesized derivatives e.g (2-(3-(5-(phenyl/2,3-difluorophenyl)-1,3,4-thiadiazol-2-yl)ureido)acetic acid,1-cyclopentyl-3-(5-phenyl-1,3,4-thiadiazol-2-yl)urea has been acceptable pharmacological properties which can be extend our research work. With the help of urea moiety by further modification novel molecule metal complex can be synthesized. Before synthesis designed and virtual screening is essential. Computational drug designing is very good tool in drug chemistry to step in synthesized analogues of standard drug.

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REFERENCES

1. Arora Pragi, Arora Varun, Lamba HS, Wadhwa Deepak, Importance of Heterocyclic Chemistry: A Review IJPSR, 2012; Vol. 3(9): 2947-2954.
2. Kunied T, Mutsanga H, The chemistry of heterocyclic compounds,Palmer,B,2002:175
3. Abbas Al-Mulla, A Review: Biological Importance of Heterocyclic Compounds, Der Pharma Chemica, 2017; 9(13):141-147.
4. Katritzky AR & Boulton AJ, "Advances in Heterocyclic Chemistry", Volume 7 Academic Press New York and London, 1966
5. Whittle Peter J., and Tom L. Blundell. *Annual review of biophysics and biomolecular structure* 1994; 23: 349-375.
6. Blundell, Tom L. *Nature* 1996; 23: 384.6604 .
7. Masereel B, Rolin S, Abbate F, Scozzafava A, Supuran CT, J. Med.Chem. 2002; 45: 312– 320.
8. Burger's Medicinal Chemistry and Drug Discovery, 6th ed, (Ed.: D. J. Abraham), Hoboken, Wiley, 2003; 1: 690.
9. Li Y, Geng J, Liu Y, Yu S, Zhao G. Chem Med Chem, 2013; 8: 27-41.
10. Martınez A, Alonso M, Castro A, Pe´rez C, Moreno F. J Med Chem, 2002; 45: 1292-1299.
11. Maestro (Version 9.6). 2013 New York, NY: Schrödinger, LLC
12. Goodsell, David S., Garrett M. Morris, and Arthur J. Olson. *Journal of Molecular Recognition* 1996; 9.1: 1-5.
13. Vanommeslaeghe, Kenno, *et. al,* "CHARMM general force field: A force field for drug-like molecules compatible with the CHARMM all-atom additive biological force fields." Journal of computational chemistry 2010; 31.4: 671-690.
14. http://accelrys.com/products/discoverystudio/visualization-download.php.
15. Morris, Garrett M., *et. al,* Journal of computational chemistry 1998; 19.14: 1639-1662
16. Maestro (Version 9.6). New York, NY: Schrödinger, LLC ,2013.