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Research Article

IN SILICO ADMET PROFILING AND MOLECULAR DOCKING OF NOVEL SUBSTITUTED THIENO[3,2-*d*] PYRIMIDINES AGAINST LIGAND BINDING DOMAIN OF THE HUMAN PEROXISOME PROLIFERATOR ACTIVATED RECEPTOR GAMMA IN COMPLEX WITH SYNTHETIC AGONIST

Amrutkar Rakesh Devidas *[1], Amrute Bhavesh Bharat [2], Ahire Ashishkumar Harishchndra [2], Ziyaul Haque s. Ahmed [3]

[1]Department of Pharmaceutical Chemistry, Mahatma Gandhi Vidyamandir's Samajshri Prashantdada Hiray College of Pharmacy, Malegaon, Nashik, Maharashtra, India

[2]Department of Pharmaceutical Chemistry, Mahatma Gandhi Vidyamandir's Pharmacy College Panchavati, Nashik, Maharashtra, India

[3]Department of Pharmaceutical Chemistry, Loknete Dr. J. D. Pawar College of Pharmacy, Mannur, Kalwan, Maharashtra, India

*Corresponding Author Email: rakesh_2504@yahoo.co.in

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ABSTRACT

Pyrimidine ring system has wide range of pharmacological activities in the form of substituted and fused ring system and its derivatives. In this study we use some new computational tools for predicting ADMET, Pharmacological profile and Molecular docking of some novel substituted Thieno[3,2-*d*]pyrimidine. The side effect during the investigation is Carcinogenicity, Hepatotoxicity, *etc*., Molecular docking by using QSAR Software (Drug-receptor Interaction) it also focuses.

Keywords: Pharmacokinetics, Toxicity, Molecular docking.

INTRODUCTION

Pyrimidines are the heterocyclic aromatic compounds containing two nitrogen atoms at positions one and three of the six membered rings. Substituted pyrimidines come very widely in living organisms[1-2]. Pyrimidine have continuing to attract widespread of interest for an extended time because of their various pharmacological activities like antiviral[3], anticancer[4], antifungal[5], activities. Thieno[3,2-*d*] pyrimidine is reported to possess significant anticonvulsant, antimalarial and anthelmintic activities. The basic aim of this study is to predict pharmacokinetics, toxicity profiles, molecular docking (drug receptor interaction) and toxic adverse effects of Thieno[3,2-*d*]pyrimidine[6].

MATERIALS AND METHOD

In Silico ADME Screening

The absorption, distribution, metabolism, excretion and drug likeness prediction of compound were performed online on SwissADME tool. SwissADME tool was used for online pharmacokinetic properties evaluation of compounds. The two dimensional structures were drawn in ChemDrawUltra[7]. SMILES of each compound were created online in SMILES translator[8]. In addition to the pharmacokinetic properties such as gastrointestinal absorption, BBB penetration, skin permeation, drug likeness prediction like Lipinski, Ghose and Veber rule, synthetic accessibility and bioavailability score [9-10].

TOXICITY PREDICTION

The PreTOX-II tool is used to predict the toxicity or adverse effect of the compounds. PreTOX-II tool predicts acute toxicity, hepatotoxicity, carcinogenicity, cytotoxicity, mutagenicity and immunogenicity and adverse outcomes pathways and toxicity targets[11-13]. The biological activity spectra and adverse effect prediction of the compound were performed using pass online tools. Prediction of activity spectra of substances is a tool for online prediction of biological activity and side effects of compounds[10, 13.]

MOLECULAR DOCKING

The molecular docking is used to predict the drug receptor interaction of the compound. VLife MDS is a comprehensive and integrated software for computer aided drug and molecular discovery. Predictions of compound were performed using pass offline tools. Prediction of docking score of substances is a tool for offline prediction of drug receptor interaction of compounds. Firstly, molecules draw in VLife MDS then it converted in two dimensional to three dimensional. Further 3D molecules are optimized, and conformers are generated then optimised molecules are used for docking purpose[14].

Table 1: Molecules of Pyrimidine considered in this study

Compound Code	SMILES
A7	ClCC1=NC2C(C(=N1)O)Sc1c2c(C)cc(n1)C
A8	ClCC1=NC2C(C(=N1)O)Sc1c2c(OC)ccc1
A9	ClCC1=NC2C(C(=N1)Cl)Sc1c2c(C)cc(n1)C
A10	ClCC1=NC2C(C(=N1)Cl)Sc1c2c(OC)ccc1
A11	CC(=O)OCC1=NC2C(C(=N1)O)Sc1c2c(C)cc(n1)C
A12	OC1=NC(=NC2C1Sc1c2c(C)cc(n1)C)COC(=O)c1ccccc 1
A13	OC1=NC(=NC2C1Sc1c2c(C)cc(n1)C)COC(=O)c1cccnc 1
A14	COc1cccc2c1C1N=C(COC(=O)C)N=C(C1S2)O
A15	COc1cccc2c1C1N=C(COC(=O)c3ccccc3)N=C(C1S2)O
A16	COc1cccc2c1C1N=C(OCC(=O)c3cccnc3)N=C(C1S2)O
A17	CC(=O)OCC1=NC2C(C(=N1)Cl)Sc1c2c(C)cc(n1)C
A18	ClC1=NC(=NC2C1Sc1c2c(C)cc(n1)C)COC(=O)c1cccc c1
A19	ClC1=NC(=NC2C1Sc1c2c(C)cc(n1)C)COC(=O)c1cccn c1
A20	COc1cccc2c1C1N=C(COC(=O)C)N=C(C1S2)Cl
A21	COc1cccc2c1C1N=C(COC(=O)c3ccccc3)N=C(C1S2)Cl
A22	COc1cccc2c1C1N=C(COC(=O)c3cccnc3)N=C(C1S2)Cl

RESULT AND DISCUSSION

Table 1 indicates **simplified molecular-input line-entry system** (**SMILES**) **SMILES** of the target compounds which gives specification in the form of a line notation for describing the structure of organic compound. The results of SwissADME and Toxicity predictions are summarised in Table 3. The result presented in Table 2 indicates that all the determined compounds present a high gastrointestinal absorption, good skin permeation and they inhibit cytochrome CYP1A and CYP2D6 involved in the metabolism of xenobiotics. These determinations are in agreement with few available studies concerning human oral administration conducting to fast absorption and fast metabolism. The PreTOX-II computational tools revealed that all investigated Thieno[3,2-*d*] pyrimidines produce some hepatotoxicity and mutagenicity[3,4]. The radar picture (Figure.1) shows the predicted toxicity in percentage. The molecular docking score is presented in Table.4. The molecular docking by using VLife MDS Software which is determined drug-receptor interaction. In drug molecule interactions shown in Hydrogen bond (Figure.2), Hydrophobicity (Figure.3), Pi stacking (Figure.4). The molecular docking function is a fundamental component worth being further improved upon in docking. Successful application examples show that computational approaches have the power to screen hits from a huge database and design small molecules[15]. However, the realistic interaction between small molecules and receptor are still relied on experimental technology. Accurate as well as low computational cost scoring functions may bring molecular docking application to a new stage[6, 15].

Table 2: Pharmacokinetic profile of Molecules

Com. Code	Mol. Wt. (g/mol)	TPSA (Å2)	GIA	BBB	P- group	CYP 1A2	CYP 2D6	Log Kp (Cm/s)	Bioavailability Score
A7	281.76	83.14	High	No	No	No	No	-6.58	0.55
A8	282.75	79.48	High	No	No	No	No	-6.63	0.55
A9	300.21	62.91	High	Yes	No	Yes	No	-5.99	0.55
A10	301.19	59.25	High	Yes	No	Yes	No	-6.04	0.55
A11	305.35	109.44	High	No	No	No	No	-7.22	0.55
A12	367.42	109.44	High	No	No	No	No	-6.43	0.55
A13	368.41	122.33	High	No	No	No	No	-7.19	0.55
A14	306.34	105.78	High	No	No	No	No	-7.27	0.55
A15	368.41	105.78	High	No	No	Yes	No	-6.47	0.55
A16	369.49	118.67	High	No	No	No	No	-7.07	0.55
A17	323.80	89.21	High	No	No	No	No	-6.64	0.55
A18	385.87	89.21	High	No	No	Yes	Yes	-5.84	0.55
A19	386.86	102.10	High	No	No	No	Yes	-6.60	0.55
A20	324.78	85.55	High	No	No	Yes	No	-6.68	0.55
A21	386.85	85.55	High	No	No	Yes	Yes	-5.88	0.55
A22	387.84	98.44	High	No	No	Yes	Yes	-6.65	0.55

(Mol. Wt.-Molecular Weight, TPSA-Topological Polar Surface Area, GI-Gastrointestinal Absorption, BBB-Blood Brain Barrier, P-group-Protein group, CYP-Cytochrome P450, Log Kp-Skin Permeation Coefficient)

Table 3: Toxicity Prediction of Molecules

Compound Code	Predicted LD50 (mg/kg)	Predicted Accuracy	Hepatotoxicity	Carcinogenicity	Immunotoxicity	Mutagenicity	Aryl Hydrocarbon Receptor Toxicity	Average Similarity (%)
A7	750	23	Inactive	Inactive	Inactive	Inactive	Inactive	33.17
A8	450	23	Inactive	Inactive	Inactive	Inactive	Inactive	36.35
A9	750	23	Inactive	Inactive	Inactive	Inactive	Inactive	33.01
A10	450	23	Inactive	Inactive	Inactive	Inactive	Inactive	36.06
A11	830	23	Inactive	Inactive	Inactive	Inactive	Inactive	33.45
A12	375	23	Inactive	Inactive	Inactive	Inactive	Inactive	34.57
A13	375	23	Inactive	Inactive	Inactive	Inactive	Inactive	34.36
A14	450	23	Inactive	Inactive	Inactive	Inactive	Inactive	37.51
A15	450	23	Inactive	Inactive	Inactive	Inactive	Inactive	37.16
A16	450	23	Active	Inactive	Active	Inactive	Inactive	35.25

A17	750	23	Inactive	Inactive	Inactive	Inactive	Inactive	32.94
A18	335	23	Active	Inactive	Inactive	Inactive	Inactive	34.22
A19	375	23	Active	Inactive	Inactive	Inactive	Inactive	33.94
A20	450	23	Inactive	Inactive	Inactive	Inactive	Inactive	37.32
A21	450	23	Inactive	Inactive	Inactive	Inactive	Inactive	37.06
A22	450	23	Active	Inactive	Active	Inactive	Inactive	36.84

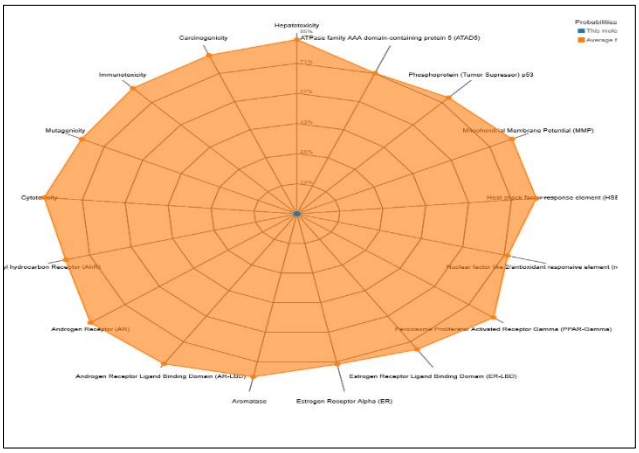

Figure 1: Radar picture of predicted toxicity of compounds

Table 4: Dock Score of Target Compounds

Compound Code	Molecular Docking Score
A7	218.68
A8	192.65
A9	193.63
A10	212.42
A11	-64.13
A12	271.42
A13	268.39
A14	177.24
A15	163.42
A16	177.03
A17	-65.69
A18	192.22
A19	222.11
A20	215.05
A21	199.21
A22	173.24

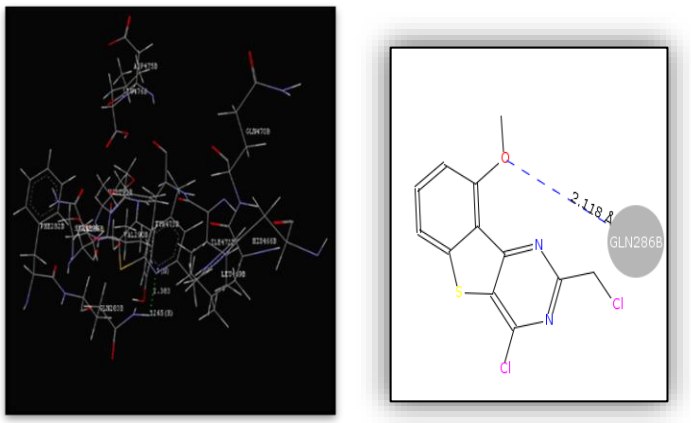

Figure 2: Hydrogen Bond Molecular-Drug Interaction

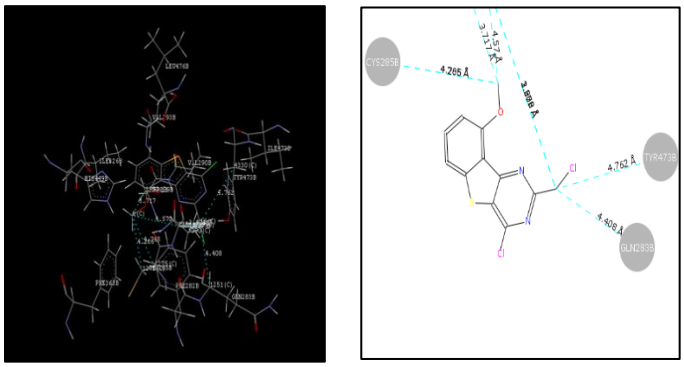

Figure 3: Hydrophobic Molecular-Drug Interaction

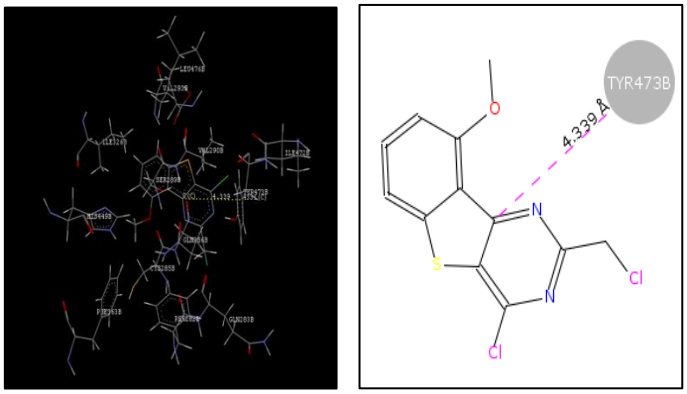

Figure 4: Pi Stacking Molecule-Drug Interaction

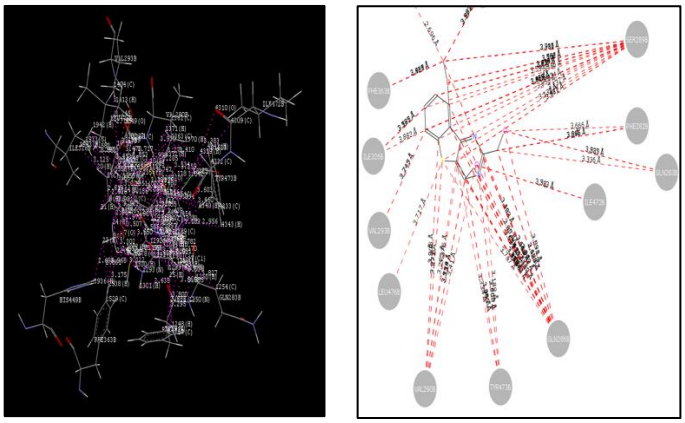

Figure 5: Vander Waal Molecule-Drug Interaction

CONCLUSION

The present study we predicted *in vivo* biological activities and side effects of Thieno[3,2-*d*]pyrimidine. Our study confirmed that the investigated compounds reveal good oral bioavailability and skin permeability and also high gastrointestinal absorption. Some investigated Thieno[3,2-*d*]pyrimidine several hepato-toxicity and mutagenicity. Some pyrimidines inhibit cytochrome CYP1A and CYP2D6 which affects the metabolism. All these results are important for researchers for the development of new chemical entities. The results are obtained by computational tools can complete the *in silico* toxicity test to improve predictive toxicity, the molecular docking to improve some drug receptor interactions and safety assessment of some Thieno[3,2-*d*]pyrimidines.

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