World Journal of Pharmaceutical and Life Sciences
WJPLS
www.wjpls.org
SJIF Impact Factor: 6.129

INSILICO DESIGN AND MOLECULAR DOCKING STUDIES OF NOVEL PYRIDINE DERIVATIVES AS PPAR GAMMA AGONISTS

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Article Received on 06/06/2023 **Article Revised on 26/06/2023** **Article Accepted on 16/07/2023**

ABSTRACT

Molecular docking is one of the best data – based screening methodology of virtual screening for ligand which minimized the works cost by filtering and also helps to predicted the toxicity study for designing the formulation or synthesis of New Chemical Entity in now a day of pharmaceutical research developments. The heterocyclic compounds are widely distributed in nature and they were found to possess various physiological activities. Pyridine and related fused heterocycles are of interest as potential bioactive molecules. The present work has focused on incorporation of pyridine and tetrazole and evaluate its PPAR γ agonist effect. PPAR γ nuclear receptor agonist are therapeutically used to combat hyperglycaemia associated with the metabolic syndrome and type 2 diabetes. A new series of pyridine tetrazole derivatives were designed as PPAR gamma agonits based on docking studies and oral bioavailabity scores based on Lipinski's rule evaluation. Insilico molecular docking was carried out using ArgusLab. To identify the potential anti-tubercular lead compounds among compounds docking calculation were performed into the 3D structure of the catalytic site of PPAR γ enzyme (pdb code:3SZ1). Docking score of the novel compound showed good fit with 3SZ1when compared with standard drug rosiglitazone.

KEYWORDS: Tetrazole, PPAR γ agonist, hyperglycaemia, ArgusLab.

INTRODUCTION

PPAR agonists are drugs which act upon the peroxisome proliferator-activated receptor. They are used for the treatment of symptoms of the metabolic syndrome, mainly for lowering triglycerides and blood sugar. PPARγ (gamma) is the main target of the drug class of thiazolidinediones (TZDs), used in diabetes mellitus and other diseases that feature insulin resistance.[1] PPAR γ can be activated by dietary fatty acids and their metabolites, they act as lipid sensors that, upon activation, are able to markedly redirect metabolism. Pioglitazone and Rosiglitazone are PPARγ agonists currently licensed for the management of hyperglycemia in Type 2 diabetes mellitus. Currently used PPAR γ agonists have serious side effects, making the discovery of novel ligands highly relevant. Tetrazole derivatives are reported to show potent agonistic activity for peroxisome proliferator-activated receptor gamma.[2] Compounds containing tetrazole ring have been established as anti-inflammatory[3], antimicrobial[4] and antinociceptive[5] agents. Derivatives having tetrazole moiety are good nonpeptide angiotensin receptor antagonists[6], $SGLT_2$ inhibitors[7] and superoxide scavengers.[8] Orally active, highly potent compounds derived from the picolinaldehyde bearing tetrazole ring are mGlu5 receptor antagonist.[9] Potential antidiabetic agents are derived from tetrazole derivatives.[10] The purpose of the present study was to investigate the PPARγ agonist effect of pyridyl tetrazole derivatives on Human PPAR gamma through virtual screening methods like molecular interactions with respect to molecular docking and ligand binding.

MATERIALS AND METHODS

ACD/ChemSketch

ACD/ChemSketch is a molecular modelling program used to create and modify images of chemical structures. Also, this software allows molecules and molecular models displayed in two and three dimensions, to understand the structure of chemical bonds and the nature of functional groups. Chemical structures and SMILES notations of the compounds were obtained by using ACD labs Chemsketch version 12.0 (www.acdlabs.com/resources/freeware/chemsketch/).

Molinspiration

Molinspiration offers free on-line cheminformatics software for calculation of important molecular properties such as partition coefficient (Log P), Topological polar surface area (TPSA), Hydrogen bond donors and acceptors, rotatable bonds, number of atoms, molecular weight and violation of Lipinski's rule of five

and to predict bioactivity scores for drug targets. SMILES notations of the selected derivatives were fed in the online Molinspiration software (https://www.molinspiration.com/) to predict the drug likeness properties. Lipinski's rule of five is used in drug design and development to predict oral bioavailability of potential lead or drug molecules.

Pharmacokinetic parameters and toxicity potential

ADME refers to the absorption, distribution, metabolism and excretion of a molecule in an organism. All these factors are important for a molecule which acts as a drug. Having favourable ADME characteristics is the most pre-requisite for drug development. The identification and elimination of unfavourable compounds makes the research process more cost-effective and efficient. For this reason, prediction of the pharmacokinetic properties of the new drug candidates as early as possible in the drug development process is very important.

PkCSM software

pkCSM provides a platform for the analysis and optimization of pharmacokinetic and toxicity properties implemented in a user-friendly, freely available web interface (http://structure.bioc.cam.ac.uk/pkcsm). This is a novel method for predicting and optimizing small-molecule pharmacokinetic and toxicity properties which relies on distance-based graph signatures.

Molecular docking studies

To perform docking one first needs to define atoms that make up the ligand and the binding sites of the protein where the ligand should bind. The prepared 3D structure of 3SZ1 protein was downloaded into the ArgusLab program and binding sites were made by choosing "Make binding site for this protein" option. The ligand was then introduced and docking calculation was allowed to run using shapebased search algorithm and AScore scoring function. The scoring function is responsible for evaluating the energy between the ligand and the protein target. Flexible docking was allowed by constructing grids over the binding sites of the protein and energy-based rotation is set for that ligand's group of atoms that do not have rotatable bonds. For each rotation, torsions are created and poses (conformations) are generated during the docking process. For each complex 10 independent runs were conducted and one pose was returned for each run. The best docking model was selected according to the lowest A score calculated by ArgusLab and the most suitable binding conformation was selected on the basis of hydrogen bond interactions between the ligand and protein near the substrate binding site. The lowest energy poses indicate the highest binding affinity as high energy produces the unstable conformations.[11]

RESULTS AND DISCUSSION

General structure of novel pyridine derivatives

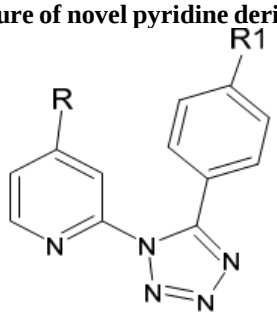

Table 1: Various derivatives used.

Cpd code	R	R1	Cpd code	R	R1
1A	4-Cl	H	2A	3-Cl	H
1B	4-Cl	4-Cl	2B	3-Cl	4-Cl
1C	4-Cl	4-OCH3	2C	3-Cl	4-OCH3
1D	4-Cl	3-Cl	2D	3-Cl	3-Cl
1E	4-Cl	$C_6H_5CH_2$	2E	3-Cl	$C_6H_5CH_2$
1F	4-Cl	2-Cl	2F	3-Cl	2-Cl
1G	4-Cl	3,5-Cl	2G	3-Cl	3,5-Cl
1H	4-Cl	2-F	2H	3-Cl	2-F
1I	4-Cl	3-F	2I	3-Cl	3-F
1J	4-Cl	3,5-F	2J	3-Cl	3,5-F

Table 2: Lipinski rule analysis of proposed derivatives.

Cpd code	Log P	Molecular Weight	Hydrogen Donors	Hydrogen Acceptor	No. of Violations
1A	2.86	257.68	5	0	0
1B	3.54	292.13	5	0	0
1C	2.92	287.71	6	0	0
1D	3.52	292.13	5	0	0
1E	2.81	271.71	5	0	0
1F	3.49	292.13	5	0	0
1G	4.15	326.57	5	0	0

1H	2.98	275.67	5	0	0
1I	3.00	275.67	5	0	0
1J	3.12	293.66	5	0	0
2A	3.08	257.68	5	0	0
2B	3.76	292.13	5	0	0
2C	3.14	287.71	6	0	0
2D	3.73	292.13	5	0	0
2E	3.03	271.71	5	0	0
2F	3.71	292.13	5	0	0
2G	4.36	326.57	5	0	0
2H	3.20	275.67	5	0	0
2I	3.22	275.67	5	0	0
2J	3.33	293.66	5	0	0

All the proposed derivatives obeyed Lipinski rule of five.

Table 3: Adme Prediction By Pkcsm Software.

S.no	Cpd code	Intestinal absorption	$Caco_2$ Permeability	Vd_{ss} Distribution	Fraction Unbound	Clearance
1	1A	98.421	1.382	-0.042	0.242	0.129
2	1B	97.463	1.422	-0.012	0.189	-0.098
3	1C	99.396	1.409	-0.06	0.181	0.061
4	1D	97.608	1.419	0.009	0.195	0.005
5	1E	98.937	1.36	-0.287	0.206	0.007
6	1F	97.667	1.415	0.036	0.205	0.095
7	1G	96.799	1.445	0.035	0.188	-0.06
8	1H	98.569	1.382	-0.078	0.216	0.085
9	1I	98.51	1.386	-0.106	0.206	-0.012
10	1J	98.647	1.333	-0.168	0.204	-0.035
11	2A	98.274	1.395	-0.009	0.23	0.132
12	2B	97.368	1.401	0.085	0.202	-0.118
13	2C	99.3	1.375	0.036	0.193	0.059
14	2D	97.506	1.398	0.105	0.208	0.019
15	2E	98.79	1.37	-0.254	0.196	0.011
16	2F	97.572	1.394	0.134	0.219	0.092
17	2G	96.704	1.424	0.13	0.201	-0.063
18	2H	98.474	1.361	0.022	0.23	0.082
19	2I	98.408	1.365	-0.007	0.22	0.002
20	2J	98.552	1.312	-0.07	0.216	-0.038

ADME parameters of proposed compounds (1A-2J) are calculated with the help of pkCSM software. Results shows that most of the dervatives exhibit good ADME properties. Table 3 presents predicted ADME properties of the compounds. It can be suggested that the designed compounds may possess a good pharmacokinetic profile, increasing their pharmacological importance.

Table 4: Toxicity prediction of analogs.

S.no	Compound Code	Carcinogenicity	Mutagenicity
1	1A	-ve	+ve
2	1B	-ve	+ve
3	1C	-ve	+ve
4	1D	-ve	+ve
5	1E	-ve	+ve
6	1F	-ve	+ve
7	1G	-ve	+ve
8	1H	+ve	+ve
9	1I	+ve	+ve
10	1J	+ve	+ve
11	2A	-ve	-ve

12	2B	-ve	+ve
13	2C	-ve	+ve
14	2D	-ve	+ve
15	2E	-ve	+ve
16	2F	-ve	+ve
17	2G	-ve	+ve
18	2H	+ve	+ve
19	2I	+ve	+ve
20	2J	+ve	+ve

The mutagenic and carcinogenic effects of designed compounds on human body were predicted using pkCSM software and results showed that all of the compounds are mutagenic and some compounds are carcinogenic also (Table 4).

Table 5: Docking scores of proposed derivatives.

S.NO	COMPOUND CODE	BINDING ENERGY (KCAL/MOL)
1	1A	-11.6095
2	1B	-12.7994
3	1C	-9.39512
4	1D	-10.759
5	1E	-11.7008
6	1F	-11.7813
7	1G	-12.1241
8	1H	-11.0076
9	1I	-10.7185
10	1J	-10.8877
11	2A	-10.488
12	2B	-11.3727
13	2C	-10.0252
14	2D	-12.0997
15	2E	-11.687
16	2F	-12.0087
17	2G	-11.7244
18	2H	-11.4535
19	2I	-10.1405
20	2J	-9.94111

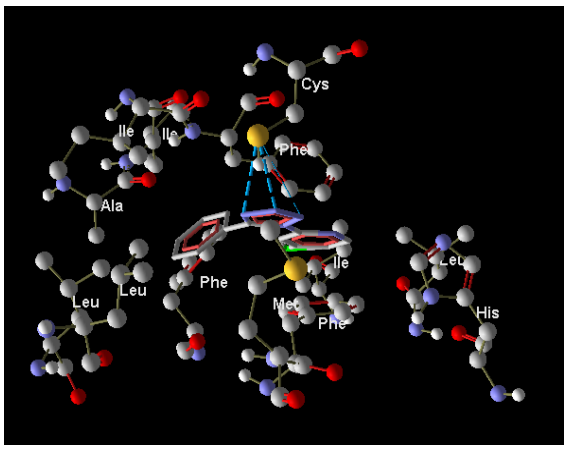

Fig. 1: Hydrogen bond interaction of 1A, bond length: 2.907A°.

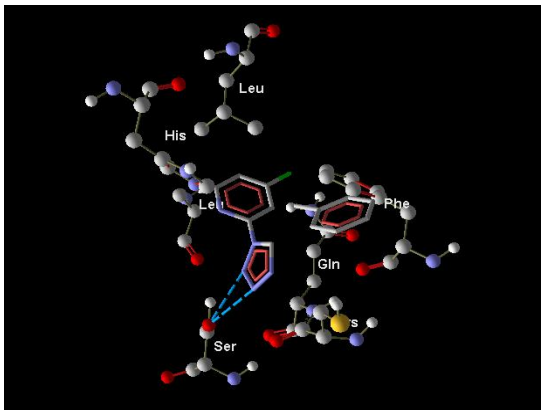

Fig. 2: Hydrogen bond interaction of 1E, bond length:2.999A°.

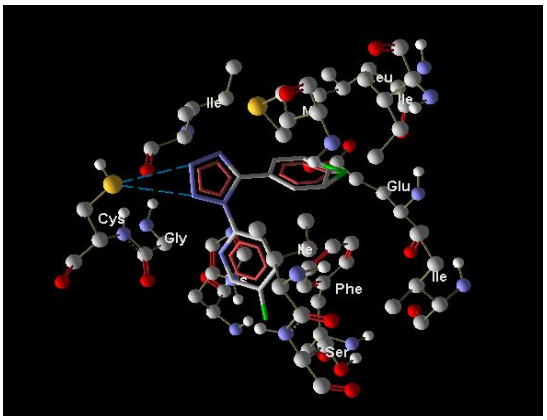

Fig. 3: Hydrogen bond interaction of 2B, bond length: 3.2607A°.

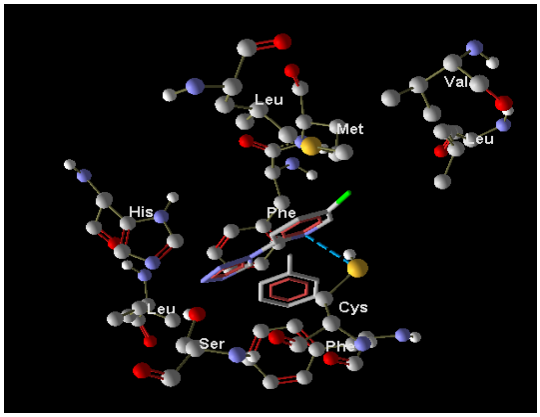

Fig. 4: Hydrogen bond interaction of 2E, bond length: 2.762A°.

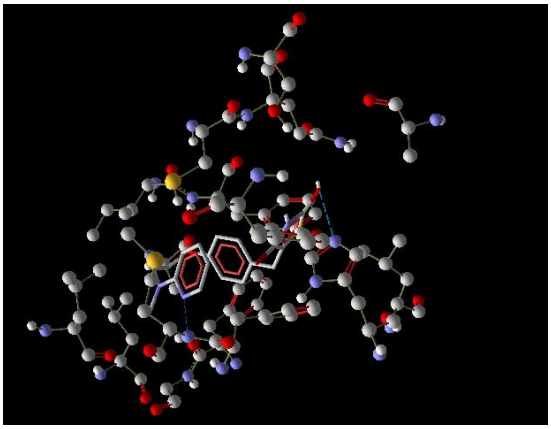

Fig. 5: Hydrogen bond interaction of rosiglitazone, bond length:3.293A^{o}.

Molecular docking studies of 20 derivatives of pyridine clubbed tetrazole was carried out to explore the possible binding interaction as well as to compare the binding pattern of these designed compounds to the standard ligand using Arguslab software. The docking scores of the derivatives are shown in Table 5. From the docking calculation study, it was observed that the top ranked conformations of almost all compounds were well accommodated inside the active site of PPAR gamma enzyme. Compounds 1B, 2D and 2F showed potent activity on PPAR γ.

CONCLUSION

Insilico drug design was carried out using ArgusLab. To identify the potential anti-diabetic agents lead compounds among compounds 1A-2J docking calculation were performed into the 3D structure of the catalytic site of PPAR gamma enzyme (pdb code:3sz1). Docking score of the novel compound showed good fit against 3SZ1 when compared with standard inhibitor rosiglitazone. All the analogues in the drug design obeyed Lipinski'sRule of five. Molecular docking in drug design shows that hydrogen bond interactions and ligand pose energy of novel compounds. In the study of insilico drug design molinspiration, chemdraw and chemsketch play very important role. Preadmet toxicity prediction in QSARs are mathematical models used to predict measures of toxicity from the physical characteristics of the structure of chemicals and binding site prediction is a foundation for functional annotation of protein and structure based drug design. From the present study it can be concluded that the pyridine derivatives were found to possess good 3SZ1 agonist activity.

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