Bulletin of Environment, Pharmacology and Life Sciences
Bull. Env. Pharmacol. Life Sci., Vol 12 [3] February 2023 : 211-221

Online ISSN 2277-1808
Journal's URL:http://www.bepls.com
CODEN: BEPLAD

ORIGINAL ARTICLE **OPEN ACCESS**

Screening Phytochemical Scaffolds for Application in Antidiabetic Drug Development

Manish Bhatia[1], Pooja S. Koli[1,2]*, Priyanka Patil[1], Priyanka Mohite[2], Sukanya S. Pote[1]
[1]Department of Pharmaceutical Chemistry, Bharati Vidyapeeth College of Pharmacy, Kolhapur, Near Chitranagri, Kolhapur-416 013 (MS) India.
[2]Department of Pharmaceutical Chemistry, Womens College of Pharmacy, Peth-Vadgaon, Kolhapur-416112 (MS) India.
Corresponding Email: pkmj0855@gmail.com

ABSTRACT
Hyperglycemia is a chronic disease that arises when the pancreas does not create enough insulin or when the body's insulin is not used efficiently, resulting in abnormally high blood sugar levels. The aim of this study was an attempt to repurpose phytochemicals for designing multitarget binding ligands for diabetes treatment. Multiple targets selected from pathway systems involved in the pathophysiology of diabetes mellitus yielded significant findings that are summarized below. Objective of this work was to develop new drug like compounds targeting dipeptidyl peptidase-4, tyrosine phosphatase and glutamine fructose-6-phosphate aminotransferases proteins which are potential targets for anti-diabetic drug development. About 91 molecules were designed having indole and pyrimidine scaffolds. Docking analysis was used to conduct virtual screenings of all designed compounds. Vlife MDS 4.6 and Pyrx based molecular docking analysis was used to investigate the binding efficiency against the chosen targets. Virtual screening filters included ADME studies using Swiss ADME and toxicity studies using lazar toxicity prediction. Based on the complete in-silico analysis of the screening data 05 virtual leads were identified.
Keywords: *Diabetes; Phytochemical; Scaffold; Antidiabetic drug development*

Received 05.11.2022 Revised 21.01.2023 Accepted 27.01.2023

INTRODUCTION

Diabetes mellitus is generally chronic type of disorder that occur when the pancreas does not work properly create insulin or when the body's insulin in the body not used systematically, which leads to increasing blood sugar levels. Main function of Insulin is controlling blood sugar levels in our body. Diabetes classified into type 1, type 2, gestational, other types diabetes. In type 1 diabetes -b cell destruction occurs with lack of insulin. In type 2 diabetes -insulin resistance and relative insulin deficiency .Gestational -insulin resistance with b-cell dysfunction .Other types-genetic defects in b cell function, pancreatic disease, endocrinopathies, drug – or chemical-induced, and other rare forms. Many people are looking for ways to improve the effect of insulin on its target tissues, as well as finding chemicals that can boost insulin secretion by beta-cells. Several new oral medicines for controlling blood sugar in type 2 diabetic patients have been found in the last decade. These pharmacological drugs have a variety of methods of action and side effects. Following are most prevalent groups.11 β -Hydroxysteroid dehydrogenase (HSD), 17 β -Hydroxysteroid dehydrogenase type 1 (17β-HSD1), Glutamine fructose-6-phosphate aminotransferases (GFAT or GFPT), Protein tyrosine phosphatase 1B (PTP1B), Mono-ADP-ribosyltransferase-sirtuin-6 (SIRT6), Insulin secretagogues, Alpha-glucosidase inhibitors, Dipeptidyl peptidase 4 (DPP-4) inhibitors, Peroxisome proliferator-activated receptor (PPAR-y) [1].

MATERIAL AND METHODS

MATERIALS SOFTWARE- Pyrex , Auto dock ,V Life MDS 4.3 , DS Visualizer , Marvin Sketch , King draw , ChemDraw , Online Converter , Swiss ADME , PubChem.

METHODS

- Literature survey
- Current status of diabetes mellitus in world and its treatment.

- Identification of phytochemicals which have antidiabetic activity
- Virtual screening of phytochemicals against selected protein targets.
- Designing and modeling of ligands followed by virtual screening of designed ligands.

Pyrimidine and indole derivatives have good anti-diabetic action, according to a literature assessment. Opposing a number of well-known diabetes processes and signaling pathways that govern diabetes etiology. As a result, many indole and pyrimidinecompounds show a lot of promise as new prospective medicines with improved effectiveness and safety profiles. Taking into consideration all of the previously published findings onpyrimidine and indole derivatives, we sought to synthesis several new substituted indole and pyrimidine derivatives interaction with molecular targets in various diabetes pathways.

This work is divided into following section

- Different anti-diabetic targets have been identified.
- Drug Design selection of possible anti-diabetic targets
- Identification of Phytochemicals that may be useful.
- Molecular design for selective binding to anti-diabetic targets.
- Docking studies of designed molecules.
- ADME Prediction of designed molecules.
- Toxicity Assessment of designed molecules.

IDENTIFICATION OF DIFFERENT TARGETS

A variety of study papers were examined based on a literature review. Following dipeptidyl peptidase 4, PTP, and GFAT, the research study focusing on the protein pathway system was picked. Insulin secretagogues, HSD, 17 -HSD1, and SIRT6, Alpha-glucosidase inhibitors, PPAR-y.

DRUG DESIGN -SELECTION OF POSSIBLE ANTI-DIABETIC TARGETS

It is done after extensive literature survey. The proteins such as dipeptidyl peptidase 4, protein tyrosine phosphatase, glutamine fructose 6 phosphate aminotransferases. As a result, they've been identified as possible therapeutic targets. Protein X-ray structures that increase binding affinity were chosen using X-ray structural analysis. The PDB files for the chosen proteins were obtained from www.rcsb.org. Database of protein data [11].

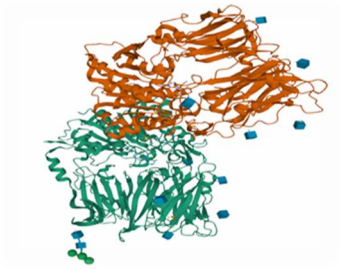


Figure 1- Crystal Structure of Human Dipeptidyl peptidase 4 (PDB ID- 4A5S)

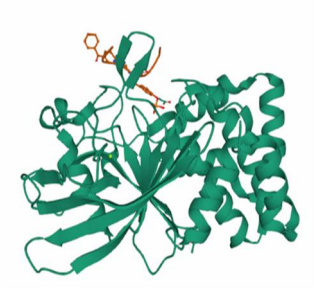


Figure 2 -Crystal Structure Of protein tyrosine phosphates 1 B (PDB ID -1EEN)

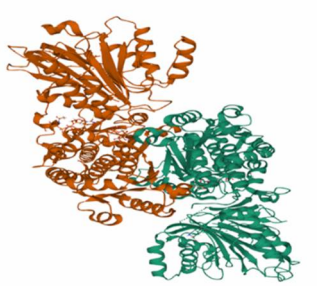
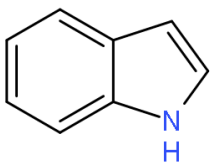


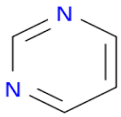
Figure 3 - Crystal Structure of Human Glutamine Fructose 6 Phosphateamidotransferase 1 (PDB ID -6SVP)

DESIGNING OF LIGANDS

From literature survey it is come to know that many antidiabetic drugs contain pyrimidine and indole as basic ring or as a scaffold so we choose pyrimidine and indole as a scaffold. Ligand designing is termed as a rational drug design. It is in-vitro process of discovering newer medication which based on understanding different biological targets. The shape of binding pockets of all ligands sites on the selected four targets was identified using pocket modelling studies. Then ligands were designed in such a way that they fits into binding pockets of targeted site.



Indole



Pyrimidine

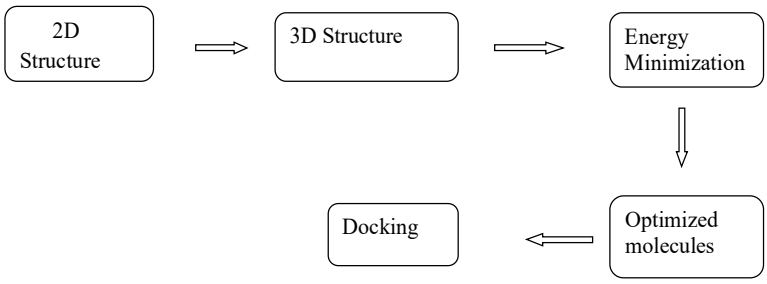
DOCKING Studies

LIGAND PREPARATION:

ChemDraw Ultra was used to create the molecular structures. Then the 2D structure was converted into 3D conformation by using Pyrex. For docking studies Ligand geometry optimization is required. Thus ligand geometries were optimized by energy minimization process .and then optimize ligand.

DOCKING ANALYSIS OF DESIGNED LIGANDS:

Docking aids in the understanding of ligand-protein interactions. In order to assess the docking score or binding energy in terms of fitness score, we ran a series of docking simulations on the active sites of the proteins.



RESULT AND DISCUSSION

SELECTION OF POTENTIAL TARGETS FOR DRUG DESIGN

From the screened database, 3 targets are selected dipeptidyl peptidase 4, glutamine fructose 6 phosphate aminotransferases, protein tyrosine phosphatase protein were selected. From these targets, macromolecule that is protein data base is selected for respective target.

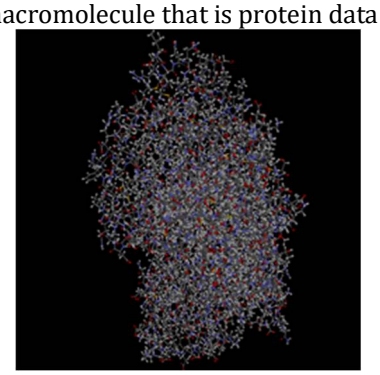


Figure 4-Ball and stick model of glutamine fructose 6 phosphateamidotransferase [PDB ID 6SVP]

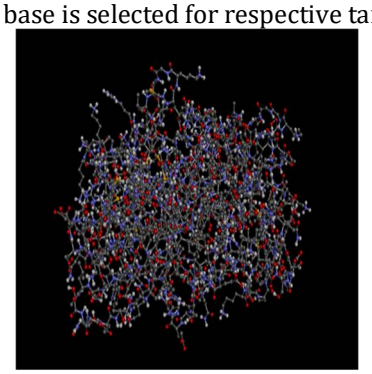


Figure 5 -Ball and stick model of Protein tyrosine phosphate [PDB ID 1EEN]

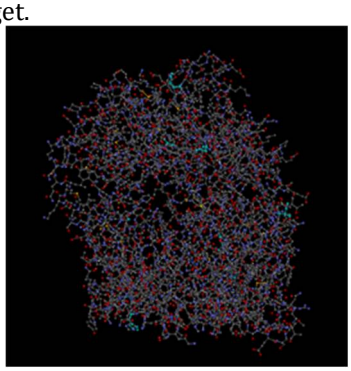
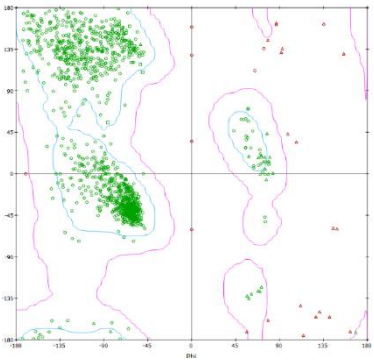


Figure 6 -Ball and stick model of dipeptidyl peptidase 4 PDB ID 4A5S

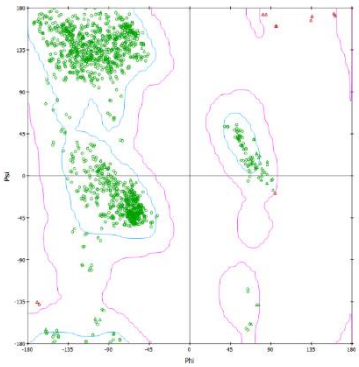
Table 01-Characterization of selected antidiabetic targets

Sr no	Protein	Resolution (A^{o})
1	glutamine fructose 6 phosphate amidotransferase(6SVP)	2.53
2	Protein tyrosine phosphate (1EEN)	1.90
3	dipeptidyl peptidase 4(4A55)	1.62

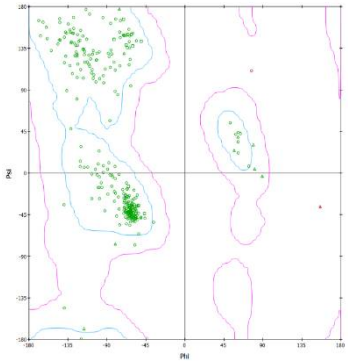
Figure 7 -Ramachandran plot of protein.



PDBID-6SVP



PDB ID- 4 A5S



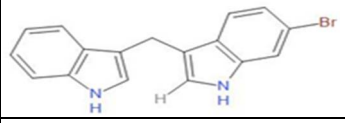
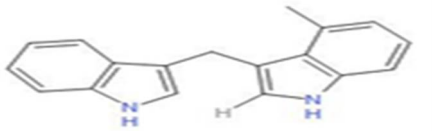
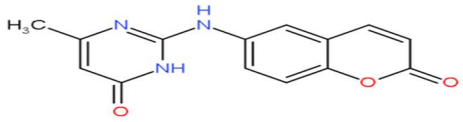
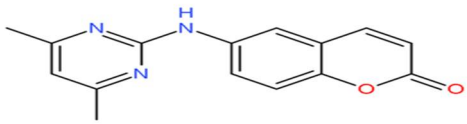
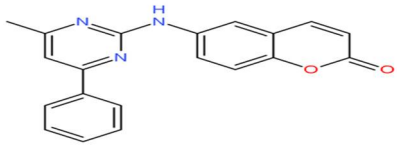
PDB ID- 1EEN

Table 02 Docking binding energy result

Sr no	Name of compound	Docking score		
		1EEN	6SVP	4A5S
1	Dasatinib	-8.3	-7.8	-8.7
2	Gliamilide	-6.9	-8.0	-9.4
3	Pioglitazone	-6.5	-6.7	-8.6
4	Repaglinide	-7.6	-7.2	-7.6
5	Rosiglitazone maleate	-6.6	-8.2	-7.6
6	Gliflumide	-7.4	-8.4	-9.5
7	Glymidine	-6.4	-7.4	-8.1
8	Glicetanile	-7.5	-9.3	-9.4
9	Imatinib	-8.3	-9.6	-9.3
10	Sorafenib	-8.2	-10.4	-8.9
11	Cycotiamine	-6.0	- 6.4	-7.1
12	Sulphamorprin	-6.2	-7.2	-7.5
13	Fenyripol	-6.1	-6.8	-7.3
14	Aditoprim	-6.1	-6.9	-6.5
15	Ormetoprim	-6.1	-6.1	-7.1
16	Beclotiamine	-5.7	-5.7	-6.3
17	Cycotiamines	-6.0	- 6.4	-7.1
18	Metioprim	-6.0	- 5.6	-6.9
19	metoprin	-7.4	- 7.7	-7.0
20	sulfadoxin	-6.5	- 6.8	-6.7
21	sulfametomidin	-6.1	-6.7	-7.2
22	aditeren	-6.0	-6.3	-6.9
23	amprolium	-5.7	-6.4	-6.8
24	baquiloprim	-6.4	-7.8	-6.7
25	isaxonine	-5.4	-4.9	-5.7
26	iprozilamine	-5.2	-5.4	-6.3
27	etoprine	-7.2	-7.4	-7.5
28	lodinixil	-6.7	- 7.4	-7.8
29	mezilamine	-5.3	-5.3	-6.1
30	Pirinixic acid	-6.4	-6.6	-7.1
31	sulfaclomide	-6.8	-6.8	-7.5
32	tasuldine	-5.5	-5.9	-6.2
33	sulfaperin	-6.6	-7.5	-7.4
34	brodimoprim	-6.0	-7.2	-7.4
35	dapivirin	-6.9	-6.98	-8.2
36	diaverdine	-6.0	-4.67	-7.2
37	sulfamonomethoxine	-6.2	-4.44	-7.2
38	sulfameter	-6.4	-7.3	-7.3
39	thiamine	-5.5	-5.7	-6.0
40	sulfisomidine	-6.7	-7.0	-7.5

41	epirizole	-6.3	-6.3	-6.8
42	voriconazole	-6.6	-6.0	-7.8
43	Bmy-14802	-5.9	-6.8	-7.1
44	sulfamerazine	-6.8	-7.2	-7.8
45	sulfamethazine	-6.6	-7.5	-7.5
46	0(2)medc	-5.2	-4.8	-5.4
47	imanixil	-8.7	-8.9	-9.4
48	pyritidium	-7.8	-8.3	-10.0
49	Propyl 4 pyridyl ketone	-4.6	-4.5	-5.3
50	Silica aerogel	-6.8	-8.5	-8.6
51	avitriptan	-6.3	-7.2	-7.8
52	intelence	-7.2	-6.4	-7.9
53	cyprodinil	-6.6	-7.3	-7.9
54	Orotic acid	-7.4	-6.3	-6.7
55	pyrimethanil	-5.9	-7.1	-7.2
56	iclaprim	-7.0	-7.3	-8.7
57	feloprintan	-7.5	-8.1	-6.8
58	rosuvastatin	-7.5	-7.1	-8.4
59	bosentan	-7.2	-8.1	-7.7
60	thonzylamine	-5.9	-6.5	-6.4
61	talmetoprim	-7.0	-7.8	-8.7
62	ambrisentan	-6.9	-6.2	-8.0
63	Epiroprim	-6.3	-7.0	-7.6
64	buspirone	-6.5	-7.5	-8.2
65	enazadrem	-6.4	-7.3	-7.2
66	moxonidine	-6.5	-5.8	-6.1
67	tandospirone	-6.7	-7.5	-8.2
68	lesopitron	-6.9	-6.3	-7.0
69	sulfabromomethazine	-6.8	-6.8	-7.4
70	encadin	-7.1	-7.6	-7.6
71	pirinixil	-6.6	-5.9	-7.5
72	Rilpivirine	-7.6	-6.9	-8.7
73	Eptapirone	-6.7	-7.8	-7.3
74	prosultiamine	-5.4	-5.4	-6.4
75	benfotiamine	-6.8	-6.8	-8.1
76	rimoprogin	-4.2	-4.2	-4.8
77	acetiamine	-5.5	-6.6	-6.7
78	ipsapirone	-7.0	-8.3	-8.8
79	tetroxoprim	-6.1	-6.9	-6.8
80	gepirone	-6.9	-7.5	-7.8
81	fursultiamine	-6.3	-6.2	-6.4
82	inpool	-6.8	-7.8	-7.9
83	fapy	-5.0	-5.2	-5.2
84	3-[(1H-indol-3-yl)methyl]-6-methoxy-1H-indole	-7.2	-7.5	-8.4
85	4-chloro-3-[(6-chloro-1H-indol-3-yl)methyl]-1H-indole	-7.0	-7.5	-8.5
86	2-(5-methoxy-2,3-dihydro-1H-indol-3-yl)acetic acid	-6.9	-7.8	-8.0

Table 03-Compound structure, IUPAC name and compound code of lead molecule

Sr no	Structure of lead molecule	IUPAC Name	Compound code
1		6-bromo-3-[(1H-indol-3-yl)methyl]-1H-indole	A1
2		3-[(1H-indol-3-yl)methyl]-4-methyl-1H-indole	A2
3		6-(3,4-Dihydro-6-methyl-4-oxopyrimidin-2-ylamino)-2H- chromen-2-one	A3
4		6-(4,6-Dimethylpyrimidin-2-ylamino)-2H-chromen-2-one.	A4
5		6-(6-Methyl-4-phenylpyrimidin-2-ylamino)-2H-chromen-2-one	A5

2D Representative interaction of lead compound with PDB ID
1]6SVP
2]1EEN
3]4A5S

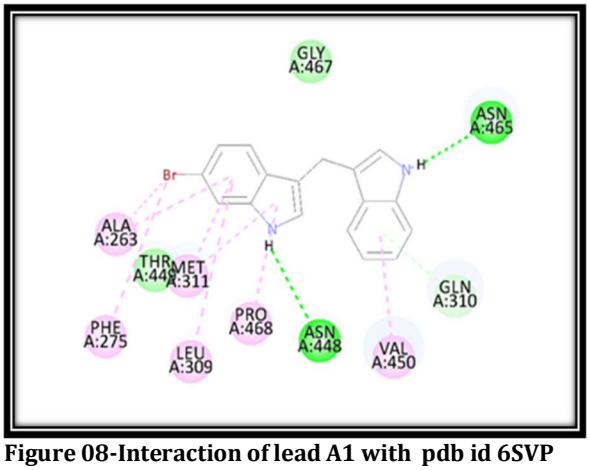


Figure 08-Interaction of lead A1 with pdb id 6SVP

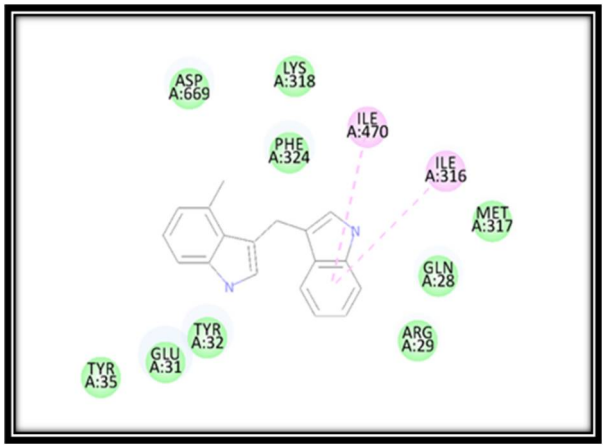


Figure 09- Interaction of lead A2 with pdb id 6SVP

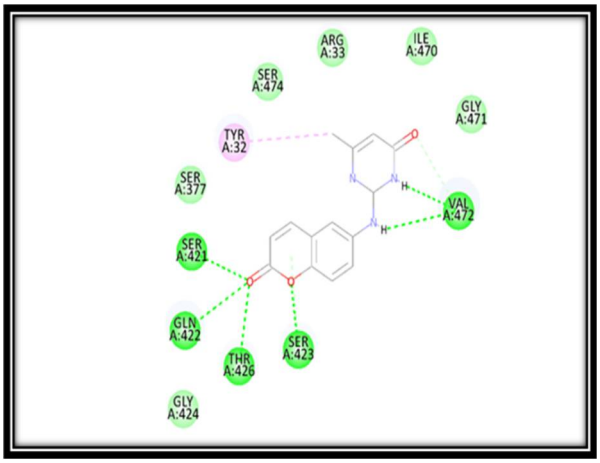


Figure 10- Interaction of lead A3 with pdb id 6SVP

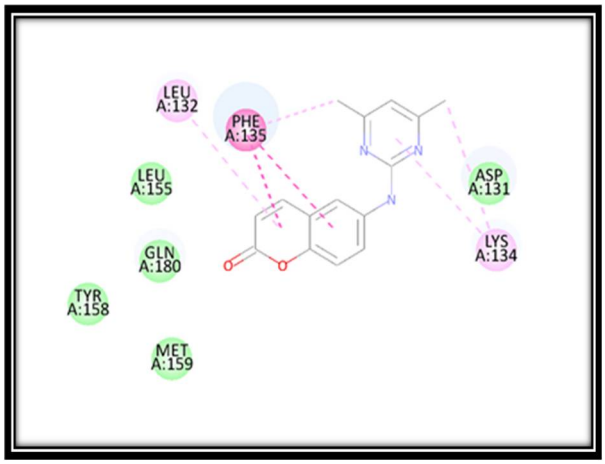


Figure 11-Interaction of lead A4 with pdb id 6SVP

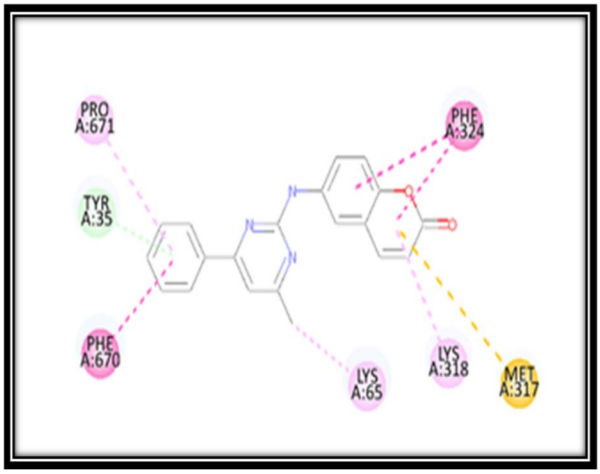


Figure 12-Interaction of lead A5 with pdb id 6SVP

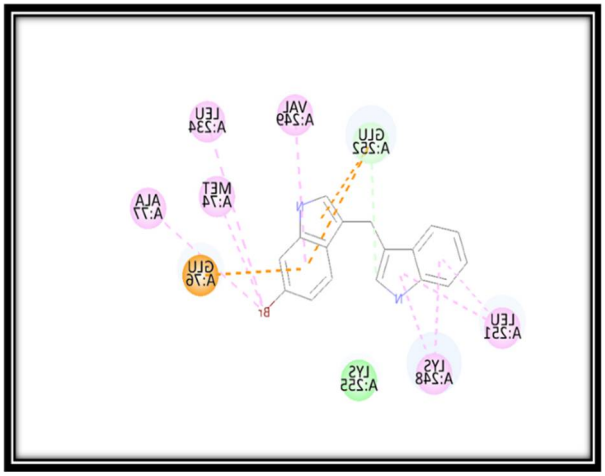


Figure 13-Interaction of lead A1 with pdb id 1EEN

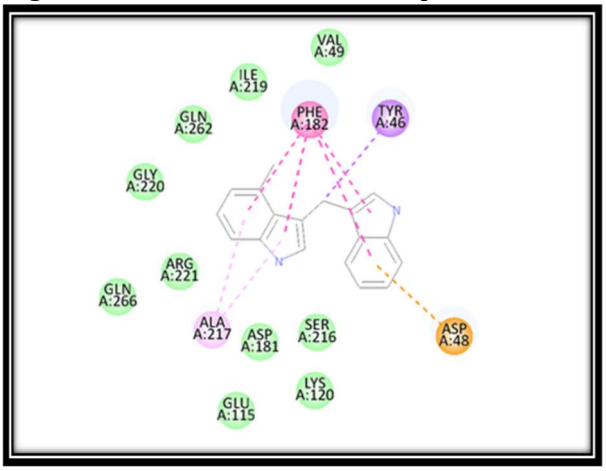


Figure 14-Interaction of lead A2 with pdb id 1EEN

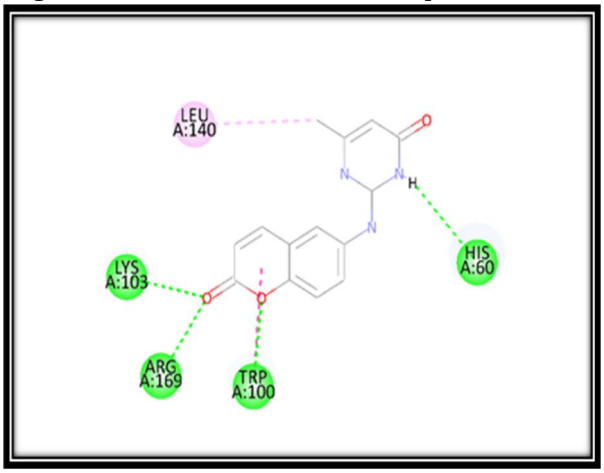


Figure15-Interaction of lead A3 with pdb id 1EEN

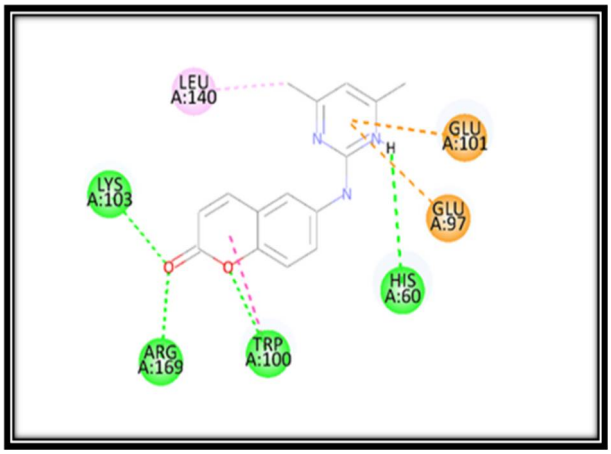


Figure 16-Interaction of lead A4 with pdb id 1EEN

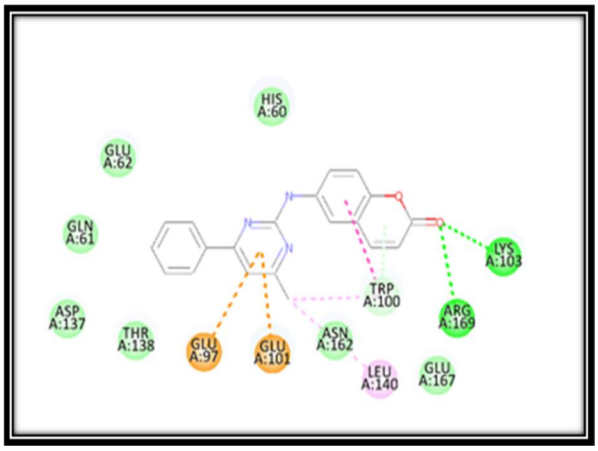


Figure 17-Interaction of lead A5 with pdb id 1EEN

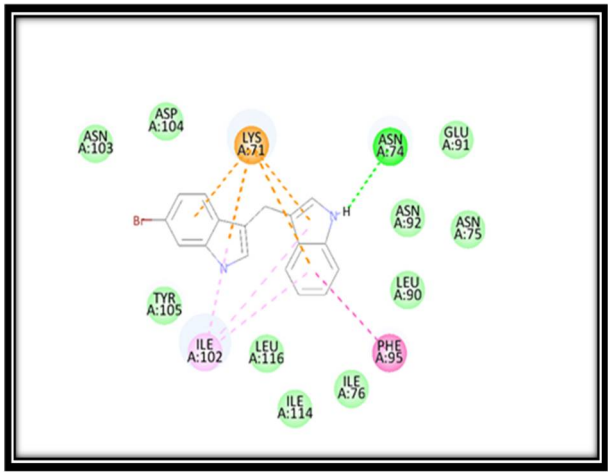


Figure 18-Interaction of lead A1 with pdb id 4A5S

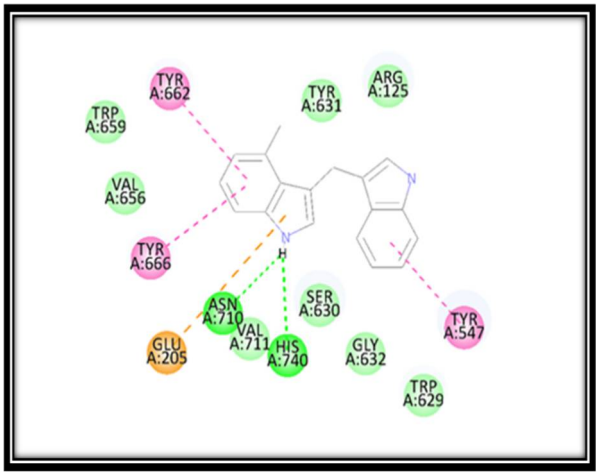


Figure 19-Interaction of lead A2 with pdb id 4A5S

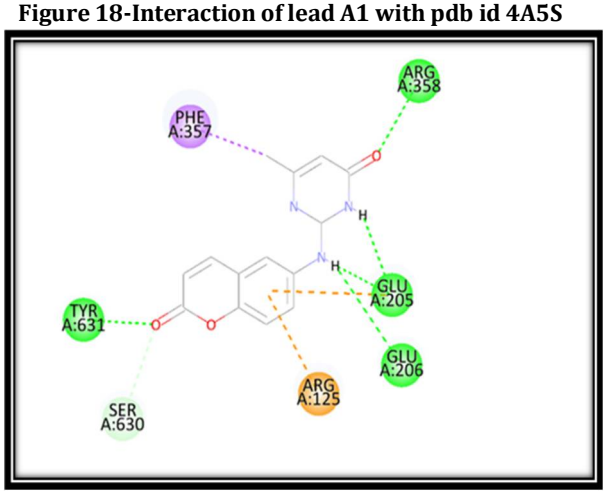


Figure 20-Interaction of lead A3 with pdb id 4A5S

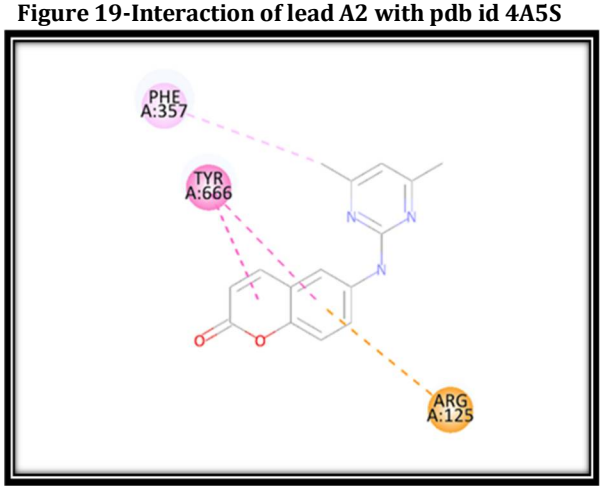


Figure 21-Interaction of lead A4 with pdb id 4A5S

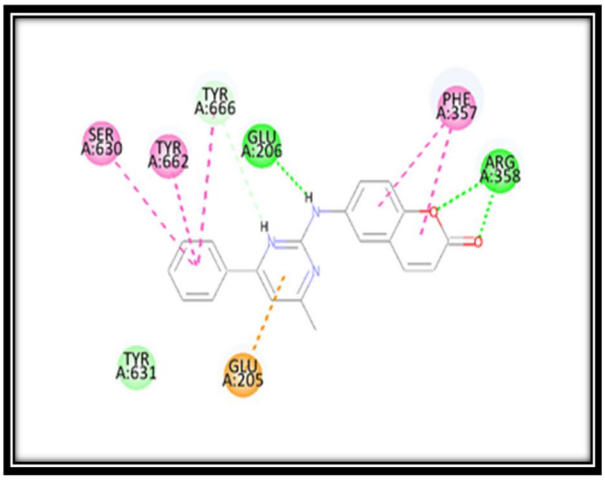


Figure 22-Interaction of lead A5 with pdb id 4A5S

Table 04 List of docking scores and interactions of lead molecules on PDB ID-6SVP

Sr no	code	Binding Energy	Hydrophobic interaction	hydrogen bond interaction	Aromatic interaction
1	A1	-8.3	THR A:449;GLY A:467	ASN A:448 ASN A:465 GLN A:465	VALA:450;PRO A:468 LEUA:309;PHE A:275 META:311; ALAA:263
2	A2	-8.1	TYR A:35;GLU A:31 TYR A:32;PHE A:324 LYS A:318;ASP A:669 MET A:317;GLN A:28 ARG A:29		ILE A:470;ILE A:316
3	A3	-7.5	SER A:474;ARG A:33 ILE A:470;GLY A:471	SER A:421;GLN A:422 THR A:426;SER A:423 VALA:472;GLY A:424 GLY A:471	TYR A:32
4	A4	-7.5	MET A:159;TYR A:158 GLN A:180;LEU A:155 ASP A:131		LYSA:134;LEU A:132 PHE A:135
5	A5	-8.8		TYR A:35	LYS A:65;LYS A:318 PROA:671;PHE A:324 PHE A:670

Table 05 List of docking scores and interactions of lead molecules on PDB ID-1EEN

Sr no	code	Binding energy	Hydrophobic interaction	Hydrogen bond interaction	Aromatic interactions
1	A1	-7.3	LYS A :255	GLU A:252	LEU A:251; LYS A:248 VAL A:249; LEU A:234 MET A:74; ALA:77
2	A2	-7.6	SER A:216;LYS A:120 ASP A:181;GLU A:115 ARG A:221;GLN A:266 GLY A:220;GLN A:262 ILE A:219;VAL A :49	ALA A:217	PHE A:181;ASP A:48 TYR A:46
3	A3	-7.3	HIS A:60;LYS A:103 TRP A:100;ARG A:169		LEU A:140
4	A4	-7.4		LYS A:103 ARG A:169 TRP A:100 HIS A:60	LEU A:140;GLU A:101 GLU A:97
5	A5	-8.4	THR A:138;ASP A:137 GLN A:61;GLU A:62 HIS A:60;ASN A:162 GLU A:167	TRP A:100 ARG A:169 LYS A:103	TRP A:100;GLU A:101 GLU A:97;ASN A:162

Table 06 List of docking scores and interactions of lead molecules on PDB ID-4A5S

Sr no	code	Binding energy	Hydrophobic interaction	Hydrogen bond interaction	Aromatic interaction
1	A1	-8.7	ILE A:76;ILE A:114 LEU A:116;TYR A:105 LEU A:90;ASN A:92 ASN A:75;GLU A:91 ASP A:104;ASN A:103	ASN A:74	PHE A:95;ILE A:102 LYS A:71
2	A2	-8.7	TRP A:629;GLY A:632 SER A:630;VAL A:711 VAL A:656;TRP A :659 TYR A:631;ARG A :125	ASN A:710; HIS A:740	TYR A:547;GLU A:205 TYR A:662;TYR A:547
3	A3	-8.8		GLU A:206;GLU A:205 ARG A:358;TYR A:631 SER A:630	PHE A:357 ARG A:125
4	A4	-8.4			ARG A:125;TYR A:666 PHE A:357
5	A5	-10.4	TYR A:631	ARG A:358;GLU A:206 TYR A:666	SER A:630;TYRA:662;PHE A:357;GLU A:205

ADME prediction and Toxicity assessments of lead molecules:

ADME studies: Virtual ADME studies of all 05 lead molecules were performed using Swiss ADME software, which is freely available online.All the lead molecules exhibited low violation to the Lipinski rule of five which includes hydrogen bond acceptor, hydrogen bond donor, log P and molecular weight.

Table 07 Table showing the molecules having desired drug like properties

Molecules	MW (g/mol)	Rotatable bonds	H- bond acceptor	H- bond donors	LOGP	Lipinski violations	Bioavailability Score
Lead A1	246.31	2	0	2	1.99	0	0.55
Lead A2	325.20	2	0	2	2.31	0	0.55
Lead A3	269.26	2	4	2	1.58	0	0.55
Lead A4	239.23	2	4	1	2.05	0	0.55
Lead A5	315.33	3	4	2	2.72	0	0.55

TOXICITY ASSESSMENTS:

In silico toxicity study of lead molecule was carried out using lazarin-silico -de/predict server. Lazar is a web-based application or server for medicinal chemists toxicologists, and chemical informatics. Toxicity studies were performed for designed set of molecules. The molecules which were found non-toxic.

PHYSICOCHEMICAL CHARACTERIZATION

Melting Point Detection

An open capillary technique was used to determine the melting points of designed /lead molecule substances. Sharp melting point indicates purity of compound. The determination of MP is the most important and easy way of differentiating one compound from other.

Table 08 Physicochemical characterization

Compound code	MW(g/mol)	Melting point (0 C)
Lead A1	246.31	240-242
Lead A2	325.20	204-206
Lead A3	269.26	>300
Lead A4	239.23	231-233
Lead A5	315.33	>300

CONCLUSION

Attempts of repurposing Phytochemical to design multitarget binding ligands for diabetes treatment targeting the pathway systems of diabetes mellitus yielded significant findings that are summarized below. Identification and validation of proteins from the pathogenetic pathway systems as targets for antidiabetic drug design and discovery has been successfully carried out. From different protein pathway systems associated with diabetes. The following three targets namely dipeptidyl peptidase 4, protein tyrosine phosphatase, glutamine fructose 6 phosphate amidotransferase were selected for drug design.

Based on the literature review, many phytochemicals with possible anti-diabetic activity were identified, and phytochemicals with comparable scaffolds were sorted in order to analyze desired interactions with targets. Phytochemicals containing indole and pyrimidine subunits were examined and found to be worthy of future investigation. Indole and pyrimidine containing phytochemicals with potential of interaction as a subunit of designed ligands targeting dipeptidyl peptidase 4, protein tyrosine

phosphatase, glutamine fructose 6 phosphate amidotransferase were utilized successfully for design of ligands for interaction with these targets. Finally about 91 molecules were designed having scaffold i.e.indole and pyrimidine. Docking analysis was used to conduct virtual screenings of all 91 compounds. Virtual screening filters included ADME studies using Swiss ADME and toxicity studies using lazar toxicity prediction. Molecular docking analysis was used to investigate the binding efficiency against the chosen targets on Vlife MDS 4.6 and pyrx. Based on the complete in-silico analysis of the virtual hits 05 leads identified. The designed and virtually screened leads have yielded promising data that could be explored in furthering this work to its logistic end to generate promising antidiabetic compounds.

CONFLICT OF INTEREST

No any conflict of interest

REFERENCES

1. Nguyen, N. D. T., & Le, L. T. (2012). Targeted proteins for diabetes drug design. *Advances in Natural Sciences: Nanoscience and Nanotechnology*, *3*(1), 013001.
2. Mechchate, H., Es-Safi, I., Bourhia, M., Kyrylchuk, A., El Moussaoui, A., Conte, R., . & Bousta, D. (2020). In-Vivo Antidiabetic Activity and In-Silico Mode of Action of LC/MS-MS Identified Flavonoids in Oleaster Leaves. *Molecules*, *25*(21), 5073.
3. Prottoy, N. I., Sarkar, B., Ullah, A., Hossain, S., Boby, A. S., & Araf, Y. (2019). Molecular docking and pharmacological property analysis of antidiabetic agents from medicinal plants of bangladesh against type II diabetes: a computational approach. *PharmaTutor*, *7*(9), 6-15.
4. Amin, K. M., Awadalla, F. M., Eissa, A. A., Abou-Seri, S. M., & Hassan, G. S. (2011). Design, synthesis and vasorelaxant evaluation of novel coumarin–pyrimidine hybrids. *Bioorganic & medicinal chemistry*, *19*(20), 6087-6097.
5. Sutton, J. M., Clark, D. E., Dunsdon, S. J., Fenton, G., Fillmore, A., Harris, N. V., ... & Baeschlin, D. K. (2012). Novel heterocyclic DPP-4 inhibitors for the treatment of type 2 diabetes. *Bioorganic & medicinal chemistry letters*, *22*(3), 1464-1468.
6. Sarmiento, M., Puius, Y. A., Vetter, S. W., Keng, Y. F., Wu, L., Zhao, Y., ... & Zhang, Z. Y. (2000). Structural basis of plasticity in protein tyrosine phosphatase 1B substrate recognition. *Biochemistry*, *39*(28), 8171-8179.
7. Ruegenberg, S., Horn, M., Pichlo, C., Allmeroth, K., Baumann, U., & Denzel, M. S. (2020). Loss of GFAT-1 feedback regulation activates the hexosamine pathway that modulates protein homeostasis. *Nature communications*, *11*(1), 1-16.
8. Pillaiyar, T., Uzair, M., Ullah, S., Schnakenburg, G., & Müller, C. E. (2019). Decarboxylative Coupling Reaction of 2-(1H-Indol-3-yl) acetic Acids with Indole, Azaindole, Benzimidazole and Indazole Derivatives. *Advanced Synthesis & Catalysis*, *361*(18), 4286-4293.
9. Ganugapati, J., & Swarna, S. (2014). Molecular docking studies of antidiabetic activity of cinnamon compounds. *Asian Journal of Pharmaceutical and Clinical Research*, *7*(supplement2), 31-34.
10. Hsing, H. Y., Rathnasamy, S., Dianita, R., & Wahab, H. A. (2020). Docking-based virtual screening in search for natural PTP1B inhibitors in treating type-2 diabetes mellitus and obesity. *Biomedical Research and Therapy*, *7*(1), 3579-3592.
11. Begum, S. M. F. M., Fathima, S. Z., Priya, S., Sundararajan, R., & Hemalatha, S. (2017). Screening Indian Medicinal Plants to Control Diabetes–An In silico and.
12. Sangeetha, K., Selvakumar, S., Das, M. (2020). Identification of potential bioactive compounds as dpp-iv inhibitors for diabetes treatment. *Journal of critical reviews*, 7(10) , 1805-1813
13. Natarajan, A., Sugumar, S., Bitragunta, S., & Balasubramanyan, N. (2015). Molecular docking studies of (4 Z, 12 Z)-cyclopentadeca-4, 12-dienone from Grewia hirsuta with some targets related to type 2 diabetes. *BMC complementary and alternative medicine*, *15*, 1-8.
14. http://zinc.docking.org/scaffolds/#
15. https://pubchem.ncbi.nlm.nih.gov/
16. https://www.rcsb.org/search.

CITATION OF THIS ARTICLE

Manish Bhatia, Pooja S. Koli, Priyanka Patil, Priyanka Mohite, Sukanya S. Pote. Screening Phytochemical Scaffolds for Application in Antidiabetic Drug Development. Bull. Env. Pharmacol. Life Sci., Vol 12[3] Feb 2023. Bull. Env. Pharmacol. Life Sci., Vol 12[3] Feb 2023 : 211-221.