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Identification of Novel Coixol-Based Derivatives as the Potential Anti-diabetic Agents Through Molecular Docking Studies

Deepshikha Patle*, Paranjeet Kaur*, Navneet Khurana

Abstract

Objective: The objective of this study was to design and identify the novel promising anti-diabetic agents based on the naturally existing potent insulin secretagogue coixol that can improve the potency overcome the adverse effects of existing medicines. **Methods:** The Auto Dock Vina (ADT) 1.5.6 and PyMOL software were used for molecular docking and visualization purposes. The molecular structures were drawn in Chem Draw 16.0 and by the help of Chem Bio draw three dimensions, all structures were energy minimized by MM2 method and converted to PDB extension file which is readable at the ADT interface. **Result:** Total 254 designed molecules from each series 1–4 were checked for binding score with the receptor 5yw7. Out of that total 12 molecules from each series were selected on the basis of their binding affinity in each series. Among these coixol (Natural product), DP322, DP330, and DP422 were studied in-depth. **Conclusion:** Coixol-based derivatives which scored best binding affinity such as DP332, DP330, and DP422 were shown promising result on the interaction with the K^+ ATP sensitive Potassium channel protein (5yw7). The entire study suggests that these novel coixol-based derived molecules could be a promising lead for the further discovery and investigation of insulin sensitizing agents for the treatment of diabetes.

Keywords: Drug designing, Insulin secretagogues, Natural product, Potential molecules, Type II diabetes mellitus

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Introduction

Among the several metabolic diseases, diabetes has been featured as one of the major concern throughout the world.[1,2] In 2015, it was assessed that 415 million individuals had diabetes. However, this figure is relied on to ascend to 642 million in the following 25 years.[3] It is characterized by anomalous large amounts of plasma glucose in the fasting state or after the organization of glucose during an oral glucose tolerance test. DM is caused by a relative or absolute insufficiency in insulin discharge, a protection from insulin secretion or both.[4,5] About 90% of diabetes cases are type 2 diabetes mellitus, which is characterized by peripheral insulin resistance and insulin lack.[6] Type 2 is currently though to be impacted by in excess of a single gene or environmental factors resulting in improvement of insulin resistance and β-cell dysfunction.[7-9]

Natural products have a long tradition as invaluable sources of inspiration for chemistry, biology, and medicine. An overwhelming number of studies have established strategies for obtaining diverse natural products and their analogues and constructed powerful compound libraries for the development of drugs.[10] Their libraries contain specialized metabolites derived from plants, animals, and microorganisms that play a pivotal role in drug discovery due to their immense structural diversity in terms of wide range of functional groups, high degree of stereochemistry, and pharmacophores and wide variety of biological activities.[11,12]

Natural products and their analogues are meaningful for illustrating the structure-activity relationships that are key for the optimization of pharmaceutical properties of clinically relevant compounds.[13,14] Currently available drugs are associated with serious side effects like severe cardiac toxicity, hepatotoxicity and weight gain. Therefore discovery of novel anti diabetic molecules with high potency and less adverse effect have become a necessity for the researchers. Figure no 1 representing the structures of available oral hypoglycaemic agents for the treatment of Type-II diabetes.

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Coixol as a Potential Anti-diabetic Agent

In the recent studies, it is stated that coixol exhibited insulin secretory activity (Insulin secretagogues) on MIN-6 cells lines which make it an active chemical constituent for the treatment of diabetes mellitus.[15,16] It is chemically 6 methoxy benzoxazolinone (6-MBOA) which is an alkaloidal flavonoid, this potent insulin secretagogue presents majorly in the plant part of *S. Dulcis* and the seeds of Coixlacryma-jobi.[17] Perhaps, Among the available anti diabetics, sulfonylurea drugs show the mechanism as insulin secretory agents and these drugs are also commonly called as insulin secretagogues.[18] These drugs inhibit the ATP-sensitive potassium channel (K-ATPase) in the beta-cells of Pancreas. Sulfonylureas stimulate the secretion of insulin regardless of blood glucose levels. On the other side, coixol has already been reported as insulin secretagogue.[19] Considering this, we selected a protein coded as 5yw7 (K ATPase-sensitive potassium channel). All the

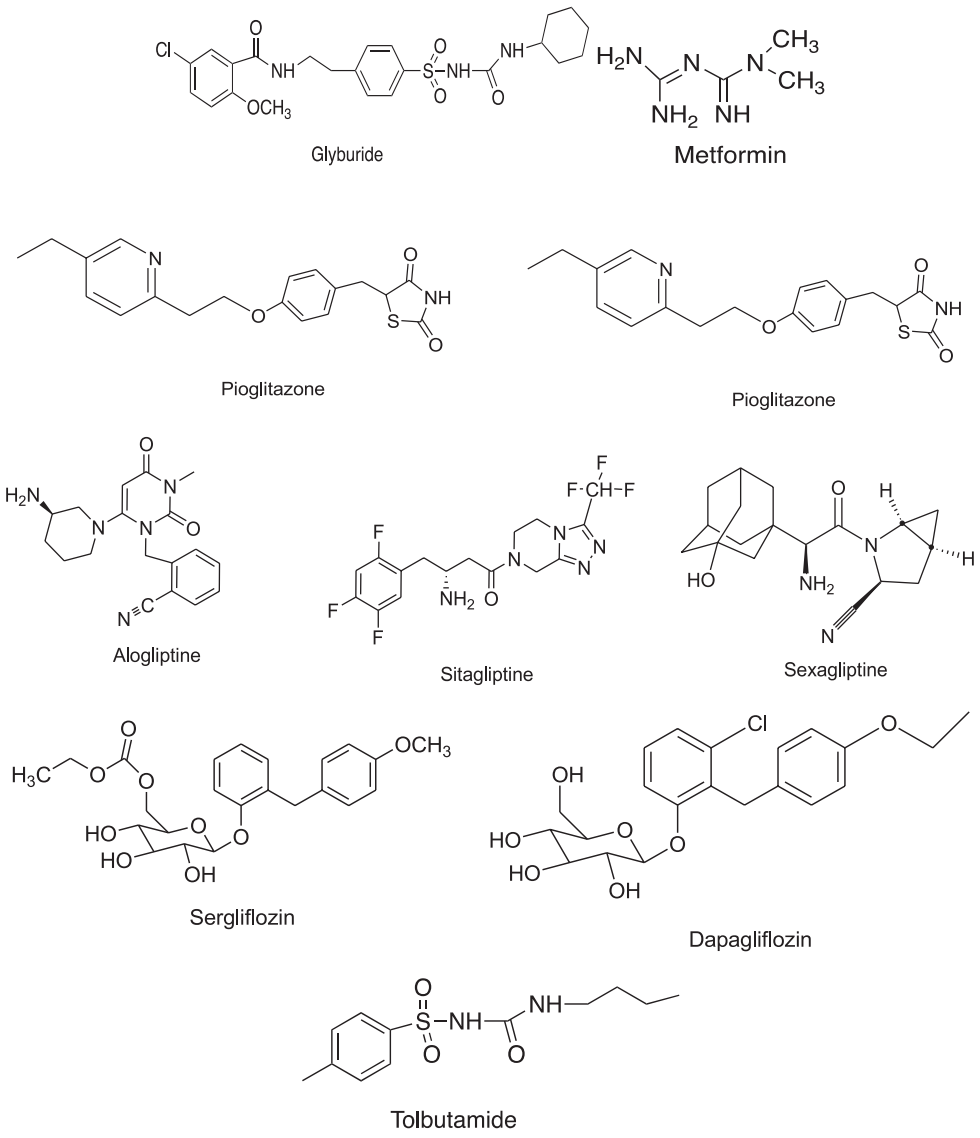


Figure 1: Structures of commonly available oral hypoglycemic agents

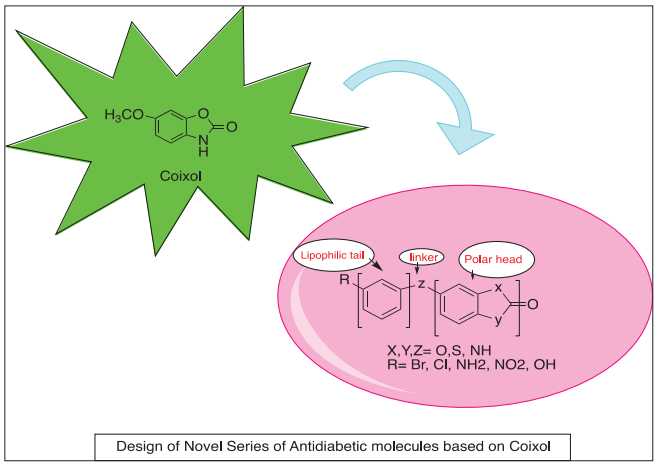


Figure 2: Design of novel series of compounds based on Coixol

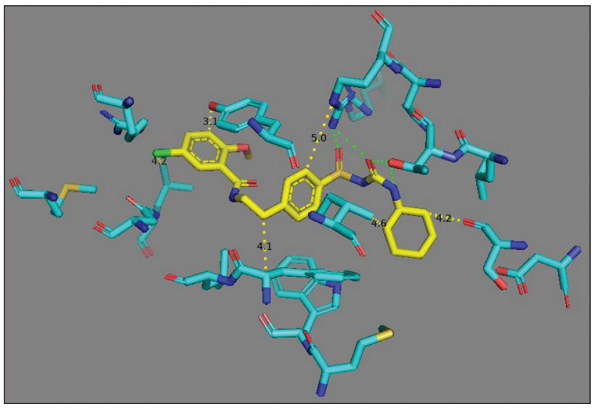


Figure 3: Binding orientation of internal ligand Glibenclamide showing possible interaction in the limit 5 A° with the amino acid residues of the protein 5yw7

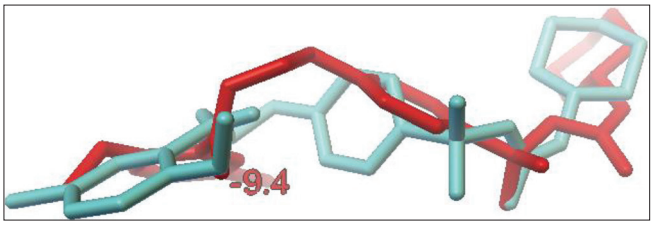


Figure 4: Validation of model by overlay of Glibenclamide (GBM) internal ligand with docked GBM (red color).

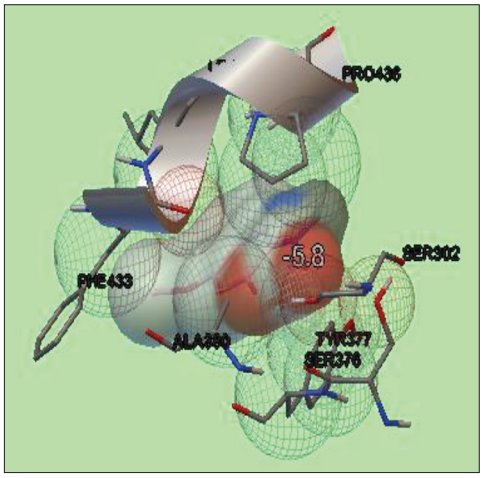


Figure 5: Visualization of active sites of protein

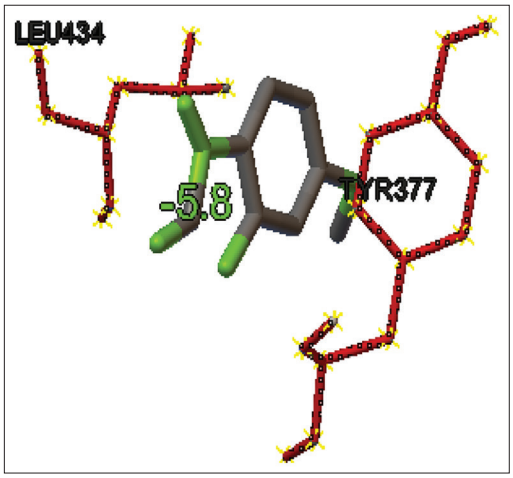


Figure 6: Overlay of close contact of Coixol with 5yw7 with NP (Coixol) neighboring amino acid residues

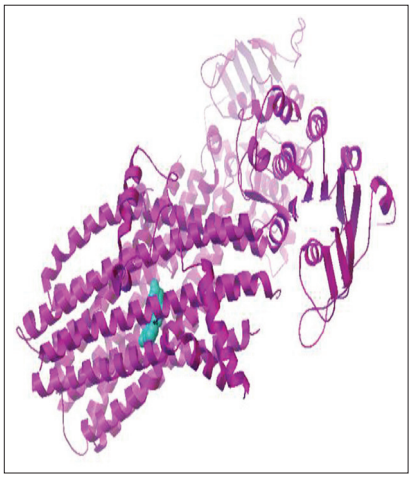


Figure 7: DP422 docked with the ribbon

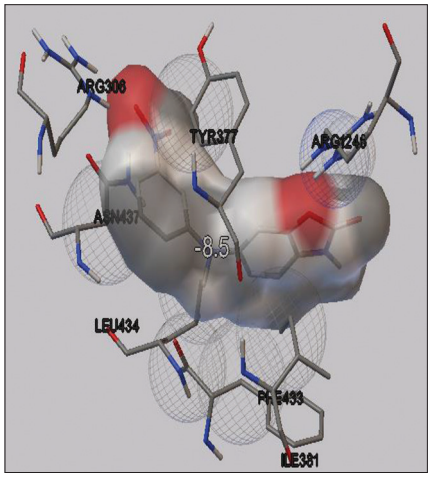


Figure 8: Overlay of Close contact of DP422 structure of the protein with amino acid residues of the protein 5yw7.

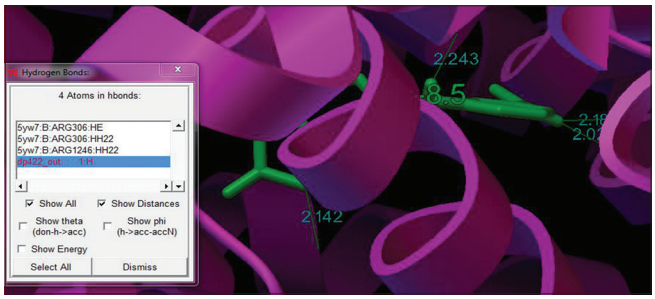


Figure 9: DP422 showing H bond interaction with 5yw7 amino acid residues

molecules were designed by considering the structural backbone of coixol and docked with the protein 5yw7 to check insulin secretory effect of the designed ligands [Figure 2].

Materials and Methods

Molecular docking is the well-known and established field of drug discovery. It minimizes the time and efforts of the researchers for identifying potent compounds. It may vary from building and visualizing simple molecules in three dimensions (3D) to performing complex computer simulations on large proteins and nanostructures. It is a computer-based technique for driving, representing, and manipulating the structures and reactions of molecules, and those properties that are dependent on these 3D structures.[20]

From a detailed survey of the literature, it can be concluded that to coixol is known to be insulin secretagogue obtained from Scoparia dulcis. It is proposed to be act on insulin receptor and leading to increased insulin secretion. Based on coixol, a

pharmacophore is proposed, in which the structural modifications was done as per scheme 1-4 via varying electron donor, electron withdrawing and other possible substitution and proposed a pharmacophore which is shown in Figure 2.

For the same purpose, we used PyMOL and Auto Dock Vina (ADT) 1.5.6 software's for visualizing active sites of protein and docking of designed ligands with the active sites of protein 5yw7. The molecular structures were drawn in Chem Bio draw ultra and by the help of Chem Bio draw 3D, all structures were energy minimized by MM2 method and converted to Pdb extension file which is readable at the ADT interface.[21] To identify the potential anti diabetic compounds, we have selected the protein 5yw7 (ATP sensitive potassium channel) which was downloaded from pdb data bank (http://www.rcsb.org/pdb/explore. do?pdbId=1z95). The outcomes of results were analyzed by ADT result which reveals close contact, hydrogen bond, hydrophilic, and hydrophobic interactions [Figure 3].

The Methodology Includes Following Steps:

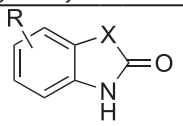
Start Auto Dock Tool → Load protein 5yw7 from molecule tab → Open dashboard for chain B, which contain water molecule and ligand Glibenclamide (GBM) → Extract the ligand from protein by selecting all AA residues and deselecting ligand → Then go to edit and delete selected atoms → Add polar hydrogens, then go to file tab and write as pdb and save as ligand.pdb file, then close the Autodock tool → Start Autodock again and open ligand.pdb, → Go to ligand tab and choose it as a ligand, choose torsion and detect root → Save it as ligand.pdbqt → Reload Protein 5yw7 and Ligand. → To fix any problem with the PDB files, such as missing bonds or atoms and to remove extraneous structures such as water molecules → Before beginning this section, inspect the PDB file to learn what such structures may be present → Keep only the protein and such cofactors as may be bound to it naturally → Delete water molecules and ligand X-ray crystallography usually does not locate hydrogens; hence, most PDB files do not include them. → However, hydrogens, particularly those that can form hydrogen bond, are important in binding ligand → Repair missing atom/residue. → Add polar hydrogen, no bond order with renumbering → Add kollaman charges → Select macromolecule and choose 5yw7 and save it as 5yw7.pdbqt file → Load ligand.pdbqt and set it as Map type by choosing ligand → Then set the Grid box by selecting "Centre on ligand" and save it by close saving current, search space volume should be <27000$_A$3 → Finall$_y$ prepare configuration file as given below parameter in grid output txt file and save as —conf.txt. → Then, Open "Command prompt" C: \users\intel>intel>cd "downloads C: \users\intel\docking "\program files (x86)\the scripps research institute\vina\vina.exe" –help C: \users\intel\dock2 "\program files (x86)\the scripps research institute\vina\vina.exe" –config conf.txt –log log.txt.

Results and Discussion

The structures were designed on the basis of known compound coixol. The designed novel molecules were analyzed by molecular docking. The designed molecules were drawn by Chem Draw and converted to 3D. Further, energy minimizations were performed using MM2 interface program on Chem3D Ultra 8.0 and molecules were saved in PDB format.

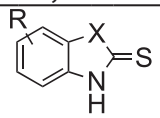
The designed molecules were analyzed by molecular modeling software for identification of the most active molecules. The selected molecule from each series 1–4 shows [Tables 1-4] the

Table 1: Binding affinity score of series 1 molecules



S. No	Code	X	R	Position of R	Affinity score
1	DP101	O	CH_3	6th	−5.8
2	DP102	O	OCH_3		−5.9
3	DP103	O	OH		−6.2
4	DP104	O	NO_2		−7.3
5	DP105	O	Cl		−6.5
6	DP106	O	Br		−6.6
7	DP107	O	OH	4th	−6.1
8	DP108	O	NO_2		−6.8
9	DP109	O	Cl		−6.0
10	DP110	O	Br		−6.1
11	DP111	O	CH_3		−6.1
12	DP112	O	OCH_3		−6.2
13	DP113	O	OH	5th	−6.1
14	DP114	O	NO_2		−5.8
15	DP115	O	Cl		−6.3
16	DP116	O	Br		−5.8
17	DP117	O	CH_3		−5.9
18	DP118	O	OCH_3		−5.9
19	DP119	O	OH	7th	−6.0
20	DP120	O	NO_2		−7.0
21	DP121	O	Cl		−6.1
22	DP122	O	Br		−6.0
23	DP123	O	CH_3		−6.3
24	DP124	O	OCH_3		−6.2
25	DP125	S	CH_3	6th	−6.0
26	DP126	S	OCH_3		−5.8
27	DP127	S	Cl		−5.9
28	DP128	S	Br		−6.0
29	DP129	S	OH		−6.1
30	DP130	S	NO_2		−6.7
31	DP131	S	CH_3	7th	−6.1
32	DP132	S	OCH_3		−6.0
33	DP133	S	Cl		−5.9
34	DP134	S	Br		−5.8
35	DP135	S	OH		−5.9
36	DP136	S	NO_2		−6.1
37	DP137	S	CH_3	5th	−6.1
38	DP138	S	OCH_3		−5.9
39	DP139	S	Cl		−5.9
40	DP140	S	Br		−6.0
41	DP141	S	OH		−6.2
42	DP142	S	NO_2		−6.6
43	DP143	S	CH_3	4th	−6.0
44	DP144	S	OCH_3		−6.0
45	DP145	S	Cl		−5.9
46	DP146	S	Br		−5.8
47	DP147	S	OH		−5.7
48	DP148	S	NO_2		−6.3
49	DP149	-NH	CH_3	6th	−6.0
50	DP150	-NH	OCH_3		−6.6
51	DP151	-NH	Cl		−6.8
52	DP152	-NH	Br		−6.7
53	DP153	-NH	OH		−6.1
54	DP154	-NH	NO_2		−7.1
55	DP155	-NH	CH_3	7th	−6.3
56	DP156	-NH	OCH_3		−6.3
57	DP157	-NH	Cl		−6.1
58	DP158	-NH	Br		−6.1
59	DP159	-NH	OH		−6.2
60	DP160	-NH	NO_2		−6.7
61	DP161	-NH	CH_3	5th	−5.9
62	DP162	-NH	OCH_3		−6.1
63	DP163	-NH	Cl		−w5.8
64	DP164	-NH	Br		−5.8
65	DP165	-NH	OH		−6.1
66	DP166	-NH	NO_2		−6.7
67	DP167	-NH	CH_3	4th	−6.3
68	DP168	-NH	OCH_3		−6.3
69	DP169	-NH	Cl		−6.1
70	DP170	-NH	Br		−6.0
71	DP171	-NH	OH		−6.2
72	DP172	-NH	NO_2		−6.5

Table 2: Binding affinity scores of series 2 molecules



S. No.	Code	X	R	Position of R	Affinity score
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3	DP203	O	Cl		−5.8
4	DP204	O	Br		−5.8
5	DP205	O	OH		−5.7
6	DP206	O	NO_2		−6.4
7	DP207	O	CH_3	5th	−5.6
8	DP208	O	OCH_3		−5.5
9	DP209	O	Cl		−5.4
10	DP210	O	Br		−5.3
11	DP211	O	OH		−6.0
12	DP212	O	NO_2		−5.7
13	DP213	O	CH_3	6th	−5.9
14	DP214	O	OCH_3		−5.5
15	DP215	O	Cl		−5.5
16	DP216	O	Br		−5.9
17	DP217	O	OH		−6.4
18	DP218	O	NO_2		−5.7
19	DP219	O	CH_3	7th	−6.6
20	DP220	O	OCH_3		−5.8
21	DP221	O	Cl		−5.6
22	DP222	O	Br		−6.0
23	DP223	O	OH		−5.8
24	DP224	O	NO_2		−5.7
25	DP225	S	CH_3	4th	−5.7
26	DP226	S	OCH_3		−5.7
27	DP227	S	Cl		−5.5
28	DP228	S	Br		−5.4
29	DP229	S	OH		−5.5
30	DP230	S	NO_2		−6.2
31	DP231	S	CH_3	5th	−5.3
32	DP232	S	OCH_3		−5.2
33	DP233	S	Cl		−5.3
34	DP234	S	Br		−5.3
35	DP235	S	OH		−6.2
36	DP236	S	NO_2		−6.2
37	DP237	S	CH_3	6th	−5.5
38	DP238	S	OCH_3		−5.5
39	DP239	S	Cl		−5.3
40	DP240	S	Br		−5.2
41	DP241	S	OH		−6.0
42	DP242	S	NO_2		−6.2
43	DP243	S	CH_3	7th	−6.0
44	DP244	S	OCH_3		−5.5
45	DP245	S	Cl		−5.7
46	DP246	S	Br		−5.5
47	DP247	S	OH		−6.0
48	DP248	S	NO_2		−6.3
49	DP249	-NH	CH_3	4th	−6.0
50	DP250	-NH	OCH_3		−5.9
51	DP251	-NH	Cl		−5.9
52	DP252	-NH	Br		−5.6
53	DP253	-NH	OH		−5.8
54	DP254	-NH	NO_2		−6.8
55	DP255	-NH	CH_3	5th	−5.7
56	DP256	-NH	OCH_3		−5.8
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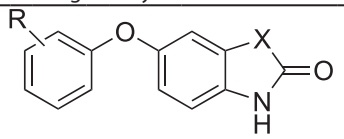
63	DP263	-NH	Cl		−6.6
64	DP264	-NH	Br		−5.3
65	DP265	-NH	OH		−6.0
66	DP266	-NH	NO_2		−6.7
67	DP267	-NH	CH_3	7th	−6.0
68	DP268	-NH	OCH_3		−5.9
69	DP269	-NH	Cl		−5.9
70	DP270	-NH	Br		−5.0
71	DP271	-NH	OH		−5.8
72	DP272	-NH	NO_2		−6.7

Table 3: Binding affinity scores of series 3 molecules



S. No.	Code	X	R	Position of R	Affinity score
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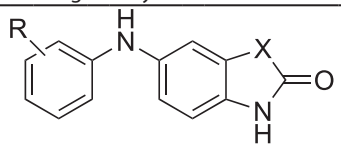
3	DP303	S	OH		−7.6
4	DP304	S	NO_2		−7.4
5	DP305	S	Cl		−7.6
6	DP306	S	Br		−7.8
7	DP307	S	NH_2		−7.9
8	DP308	S	CH_3	meta	−7.4
9	DP309	S	OCH_3		−7.6
10	DP310	S	OH		−8.3
11	DP311	S	NO_2		−7.6
12	DP312	S	Cl		−7.4
13	DP313	S	Br		−7.2
14	DP314	S	NH_2		−8.1
15	DP315	S	CH_3	para	−7.5
16	DP316	S	OCH_3		−7.5
17	DP317	S	OH		−7.6
18	DP318	S	NO_2		−7.8
19	DP319	S	Cl		−7.4
20	DP320	S	Br		−7.5
21	DP321	S	NH_2		−8.3
22	DP322	O	NO_2	meta	−9.5
23	DP323	O	OH		−8.3
24	DP324	O	Br		−9.4
25	DP325	O	Cl		−8.9
26	DP326	O	NH_2		−8.8
27	DP327	O	CH_3		−7.9
28	DP328	O	OH	ortho	−8.2
29	DP329	O	Br		−8.6
30	DP330	O	NH_2		−9.1
31	DP331	O	NO_2		−8.8
32	DP332	O	CH_3		−7.9
33	DP333	O	Cl		−8.4
34	DP334	O	OH	para	−8.3
35	DP335	O	Br		−8.7
36	DP336	O	NH_2		−8.8
37	DP337	O	NO_2		−8.6
38	DP338	O	CH_3		−7.8
39	DP339	O	Cl		−8.3
40	DP340	-NH	NH_2	Ortho	−7.8
41	DP342	-NH	CH_3		−7.9
42	DP343	-NH	OH		−8.0
43	DP344	-NH	NO_2		−7.9
44	DP345	-NH	Cl		−7.7
45	DP346	-NH	Br		−7.9
46	DP347	-NH	NH_2	Meta	−8.0
47	DP348	-NH	CH_3		−7.7
48	DP349	-NH	OH		−8.3
49	DP350	-NH	NO_2		−8.1
50	DP351	-NH	Cl		−7.8
51	DP352	-NH	Br		−7.8
52	DP353	-NH	NH_2	para	−7.9
53	DP354	-NH	CH_3		−7.5
54	DP355	-NH	OH		−8.0
55	DP356	-NH	NO_2		−8.0
56	DP357	-NH	Cl		−7.6
57	DP358	-NH	Br		−7.6

high binding affinity with selected protein (5yw7) at the binding site, as shown in Table 5.

The protein 5yw7 is prepared by ADT through removing water molecules, repairing for missing atoms, adding polar hydrogen atoms only, adding Kollman charges, and saved as

Table 4: Binding affinity scores of series 4 molecules



S. No.	Code	X	R	Position of R	Affinity score
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2	DP402	S	OCH_3		−7.7
3	DP403	S	OH		−7.5
4	DP404	S	NO_2		−8.8
5	DP405	S	Cl		−7.8
6	DP406	S	Br		−7.7
7	DP407	S	CH_3	ortho	−7.5
8	DP408	S	OCH_3		−7.7
9	DP409	S	OH		−8.1
10	DP410	S	NO_2		−8.2
11	DP411	S	Cl		−7.3
12	DP412	S	Br		−7.4
13	DP413	S	CH_3	para	−7.6
14	DP414	S	OCH_3		−7.3
15	DP415	S	OH		−7.2
16	DP416	S	NO_2		−8.5
17	DP417	S	Cl		−7.3
18	DP418	O	CH_3	meta	−7.9
19	DP419	O	OCH_3		−8.2
20	DP420	O	OH		−8.4
21	DP421	O	Cl		−7.7
22	DP422	O	NO_2		−10.2
23	DP423	O	Br		−7.7
24	DP424	O	CH_3	ortho	−7.8
25	DP425	O	OCH_3		−8.1
26	DP426	O	OH		−8.5
27	DP427	O	Cl		−7.7
28	DP428	O	NO_2		−8.9
29	DP429	O	Br		−7.7
30	DP430	O	CH_3	Para	−7.9
31	DP431	O	OCH_3		−7.6
32	DP432	O	OH		−7.6
33	DP433	O	NO_2		−8.7
34	DP434	O	Cl		−7.7
35	DP435	O	Br		−7.7
36	DP436	-NH	NO_2	ortho	−8.2
37	DP437	-NH	CH_3		−7.9
38	DP438	-NH	OCH_3		−7.8
39	DP439	-NH	OH		−8.0
40	DP440	-NH	Cl		−7.9
41	DP441	-NH	Br		−7.9
42	DP442	-NH	NO_2	meta	−9.1
43	DP443	-NH	CH_3		−8.5
44	DP444	-NH	OCH_3		−8.5
45	DP445	-NH	OH		−7.6
46	DP446	-NH	Cl		−7.6
47	DP447	-NH	Br		−7.6
48	DP448	-NH	NO_2	para	−7.6
49	DP449	-NH	CH_3		−7.6
50	DP450	-NH	OCH_3		−7.6
51	DP451	-NH	OH		−7.6
52	DP452	-NH	Cl		−7.6
53	DP453	-NH	Br		−7.6

a macromolecule. The validation of method is performed by extracting the ligand GBM present in the B chain of the protein and docked which showed similar interaction as reported by Wu *et al.*[22] The results obtained from molecular docking of designed ligands

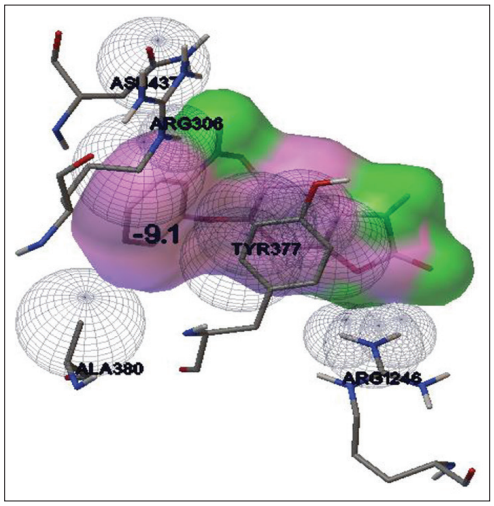
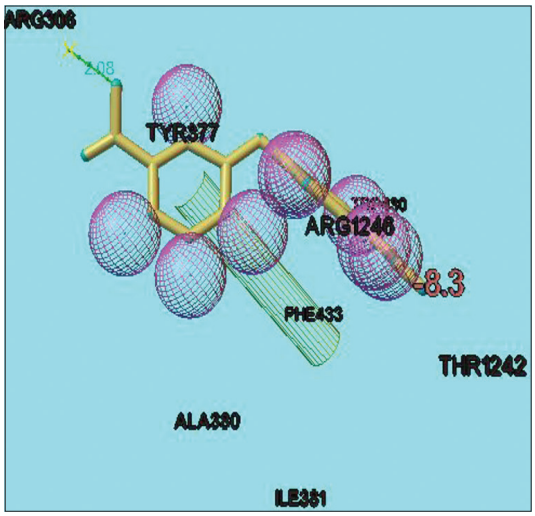


Figure10: Interaction of ligand DP330 with the neighboring amino acid residue in the wireframe



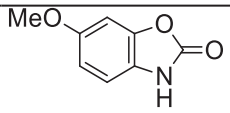
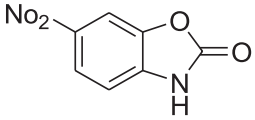
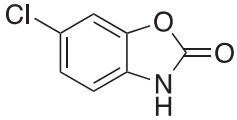
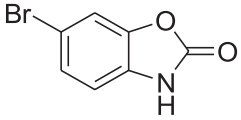
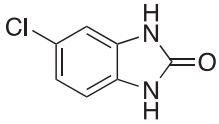
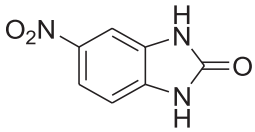
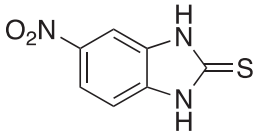
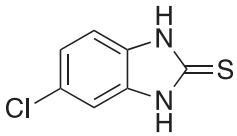
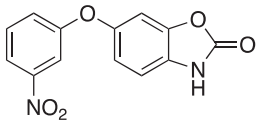
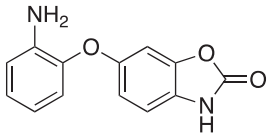
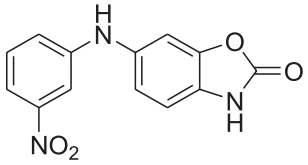
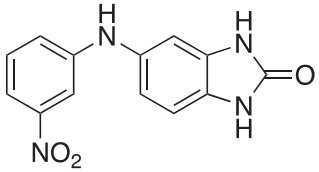
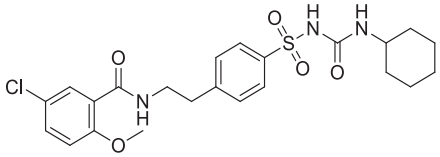
Figue 11: H-Bond interaction of DP322 with Arginine amino acid residues

on the validated protein 5yw7 are summarized in Tables 1–4 for the series 1–4. The result of best binding affinity of ligands from series 1–4 is described in Table 5.

In the current work, we have designed all possible different novel Coixol like compounds by changing its substitution on different position and replacement of oxygen with other hetero atom with the help of Chem Draw and docked using ADT. Among the all possible derivatives, we isolated and synthesized best ligands from each series [Table 5] on the basis of their affinity and binding score.

Validation was done by docking study of internal ligand (GBM) and docking of itself with 5yw7 protein (A pancreatic ATP-sensitive potassium channel K_{ATP}), as showed in Figure 4 below with good overlay with least rmsd. This is a hetero-octameric membrane protein complexes distribute on pancreatic beta cells and responsible for regulation of insulin release. On binding of

Table 5: Best molecules on the basis of best binding affinity from each series 1-4

Series	*Code*	*Structure*	*Binding Affinity (kcal/mol)*
1	Coixol/6-methoxy benzoxazolinone		−5.8
2	DP104		−7.3
3	DP105		−6.5
4	DP106		−6.6
5	DP150		−6.8
6	DP154		−7.1
7	DP260		−6.8
7	DP263		−6.6
9	DP322		−9.5
10	DP330		−9.1
11	DP422		−10.2
12	DP442		−9.1
13	GBM		−9.4

GBM: Glibenclamide

glibenclamide (GBM) inhibit KAT_p and release insulin. The same model was used for further to evaluate the newly designed coixol-based molecules series 1–4 and compared with GBM and coixol [Tables 1-4]. Figure 5 and 6 represents the interaction of Coixol with the proteins and its neighboring amino acids. Figures 7-9 depicted the in depth interaction of coded compound DP422 with 5yw7 protein. One H bond observed in DP322 as shown in Figure 10 Whereas, Figure 11 represents the interaction of ligand DP330 with neighboring amino acids of the protein 5yw7.

Conclusion

Diabetes is continuously observed as a serious illnesses developing worldwide. Medications presently available are correlated with varied adverse effects. From the comprehensive analysis of the literatures, we conclude that to enhance the potency and to minimize serious adverse effects linked with available drugs, we derived some coixol like derivatives through extensive molecular docking studies. Herein, we designed 254 novel promising anti-diabetic molecules on the basis of known structure coixol through substitution of various electron withdrawing and releasing groups on the aromatic ring and attachment of aromatic rings with ether or amine linkage. All the designed ligands were docked with the protein 5yw7 to check the compatibility with the receptor. Among these compounds, 12 most feasible and potent derivatives were identified. The potent compounds which showed best binding affinity than coixol such as DP332, DP330, and DP422 were, further, analyzed for their interactions. The entire study suggests that these novel coixol-based derived molecules could be a promising lead for the discovery and further investigation of insulin sensitizing agents for the treatment of diabetes.

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