Original Article

In Silico Designing, ADMET Screening, MM/GBSA Binding Free Energy of Some Novel 8-Amino Substituted Apigenin Derivatives as DPP-IV Inhibitors Targeting Type-II Diabetes Mellitus

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Abstract

Diabetes has long been a major issue for the world's health. Drugs for hypoglycemia are now administered orally and intravenously, however they have several toxic and adverse consequences. Therefore, there is an increasing demand to find anti-diabetic medications that are more potent and secure. Since it was discovered that apigenin is an edible, plant-derived flavonoid with no toxicity, scientists have been quite concerned. Plants are rich sources of apigenin (API), a well-known insulin-secretagogue and insulin-mimetic substance. In cretin enhancers known as dipeptidyl peptidase-IV (DPP-IV) inhibitors are used to treat diabetes. It is necessary to produce new agents, ideally from natural sources, with less negative consequences due to their unpleasant side effects. The purpose of this in-silico design process was to create new 8-Amino substituted apigenin derivatives (RSMS 1–50) with DPP-IV inhibitory action. Using Schrodinger suit 2020-3, docking studies of molecules RSMS1–50 are carried out against DPP–IV (PDB id–6B1E).The Glide module, the QikProp module, and the Prime-MMGBSA module of the Schrodinger suit are used to execute the molecular docking research for the designed compounds RSMS1–50. Based on the GLIDE score, the binding affinity of the proposed molecules RSMS 1–50 towards DPP–IV was selected. Many substances demonstrated effective hydrogen bonding and hydrophobic communication to obstruct DPP-IV enzyme. Comparing the compounds RSMS1-50 to conventional Vildagliptin (- 5.3) and Sitagliptin (- 5.6), they show significant Glide scores between - 4.32 and - 8.39. The proposed information concerning drug similarity includes the in-silico ADMET characteristics. The most potent inhibitor has positive MM-GBSA binding. The findings demonstrate that 8-Amino substituted apigenin derivatives should be taken into account as possible DPP-IV inhibitors. Further in vitro and in vivo studies may demonstrate the therapeutic potential of the substances, RSMS 10, 15, 35, 26, 30, 45, and 47 with substantial Glide scores.

Keywords: MM-GBSA, DPP-IV, In-silico ADMET screening, Docking investigations.

INTRODUCTION

Type-2 diabetes commonly referred to as adult-onset diabetes or non-insulin-dependent diabetic mellitus (NIDDM), makes up 90–95% of all instances of the disease. Type-2 diabetes often appears in people after the age of 45, and the chance of developing it rises with age. However, type 2 diabetes in youngsters is becoming more and more common. Due to macrovascular disease and microvascular long-term consequences, diabetes is very prevalent and is linked with increased mortality and morbidity [1, 2]. Therefore, effective treatment strategies for glycaemic management are very necessary. The pharmacological family of glucose-lowering drugs known as dipeptidylpeptidase-4 (DPP-4) inhibitors offers new opportunities for the treatment of type 2 diabetes (T2DM). These medications increase the levels of the in cretin hormones glucagon-like peptide-1 (GLP-1) and glucose-dependent insulin tropic polypeptide by inhibiting the DPP-4 enzyme, which quickly converts two important gastrointestinal hormones into inactive by products (GIP). DPP-4 inhibitors have a different mechanism of action than any other family of oral glucose-lowering medications in the market [3]. Although DPP-4 inhibitors result in comparable reductions in blood glucose levels and glycated haemoglobin (HbA1c) levels, they have a number of therapeutic benefits [4].A newer pharmacological family of glucose-lowering drugs known as dipeptidyl peptidase-4 (DPP-4) inhibitors offers new possibilities for the treatment of type 2 diabetes mellitus (T2DM). DPP-4 inhibitors have a different mechanism of action than any other family of oral glucose-lowering medications now on the market [5]. Although DPP-4 inhibitors do not have a greater ability to reduce blood glucose levels or glycated haemoglobin (HbA1c) levels, they do have a number of clinically significant benefits [6–8]. A weight-neutral profile in contrast to the weight increase often seen with SU and thiazolidinedione, and a minimal risk of hypoglycaemia that is far lower than that reported with sulphonyl urea (SU) are two of the most significant advantages (TZD). DPP-4 inhibitors have been tested both alone and in various combinations with other

glucose-lowering medications, and they have been put up against a placebo or a medication from a different pharmacological class as an active comparator [9].One of the most prevalent non-mutagenic, non-toxic flavonoids (subclass- Flavone) is apigenin (5,7-dihydroxy-2-(4-hydroxyphenyl) chromen-4-one) and is found in plants like Cynodon dactylon, chamomile, and others. Numerous studies have noted apigenin's antioxidant qualities, coupled with its anti-hyperglycaemic, anti-inflammatory, and (in myocardial ischemia) anti-apoptotic activities. Flavonoids are generally well recognised for their antioxidant characteristics. [10] In mice injected with A25-3515, apigenin is shown to be neuroprotective, increasing blood-brain barrier integrity, learning, and memory, as well as providing neurovascular protection. Apigenin is a strong antioxidant that may increase insulin production from the pancreas and the transport of glucose in peripheral tissues. It also has the ability to lengthen the half-life of incretin hormones [11–15]. In the present study, we target the DPP-IV enzyme using API as an incretin enhancer and analyse its potential anti-diabetic and DPP-IV inhibitory effects using in silico methods. The findings demonstrated that the newly constructed 8-Amino substituted apigenin derivatives displayed significant inhibition of diabetes mellitus with the DPP-4 enzyme.

MATERIAL AND METHODS

Molecular docking studies

Protein preparation

The DPP-IV enzyme with co crystallized ligand (PDB ID: 6B1E, 1.77Å) was recovered from the protein data bank.The protein was built up using the Protein Preparation Wizard module of Schrödinger Suite 2020-3. Using the Schrödinger suite 2020-3 prime module, missing chain iotas are added. The protein heteroatom was given potential ionisation states, and the most steady-state candidate was chosen. In order to reorient side-chain hydroxyl groups and prevent possible steric conflicts, the protein structure energy was finally minimised under controlled conditions [16–21.]. Dipeptidyl peptidase-4 (DPP-4), commonly referred to as the T-cell antigen CD26, is a multifunctional protein that serves as a binding protein and ligand for several extracellular compounds in addition to its catalytic activity. It is a crucial membrane protein that is expressed on cells throughout the body, but it is also expelled from the membrane and circulates in the plasma as a soluble protein. DPP-4 has been shown to cleave a vast number of bioactive compounds in vitro, although only a small number of them have been shown to have physiological substrates. One of them is the in cretin hormone glucagon-like peptide-1 (GLP-1), which has been demonstrated to be the major enzyme controlling its biological activity [22–25]. GLP-1 plays a significant role in maintaining proper glucose homeostasis. The DPP-4 protein has a long intracellular tail at the N-terminus and a large extracellular domain that is fixed in the cell membrane by a flexible region connected to a trans-membrane sequence (Figure 2). The extracellular domain, which circulates in the plasma as "soluble" DPP-4 but is also present in other body fluids including seminal fluid and cerebrospinal fluid, may be cleaved at the stalk however, the extracellular domain of the protein has a cysteine-rich area and a region rich in glycosylation sites in addition to the catalytic site, which is located in the C-terminal portion of the extracellular domain. These regions are thought to play a significant role in the majority of DPP-4non-enzymatic activities, interacting with proteins like adenosine deaminase, caveolin-1, streptokinase, and plasminogen, as well as with extracellular matrix elements like collagen and fibronectin, and serving as binding sites for molecules like the chemokine CXCR4 receptor, the T-cell differentiation antigen CD45, and the sodium-hydrogen exchanger-3, among others [26-27].

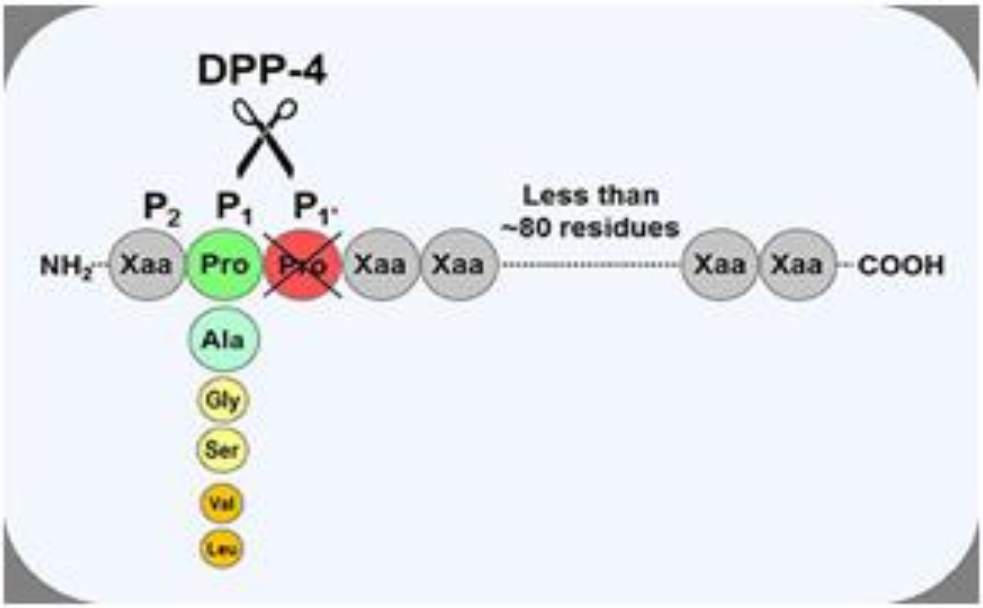


Figure 1: Substrate specificity of DPP-4, an amino peptidase called DPP-4 releases dipeptides from their substrates. Proline or alanine is preferred as the penultimate N-terminal residue in peptides or short proteins (below 80–100 residues), while certain substrates containing glycine, serine, valine, or leucine may still be cleaved at a slower rate. Proline at position three of the substrate prevents the enzyme from cleaving it [28].

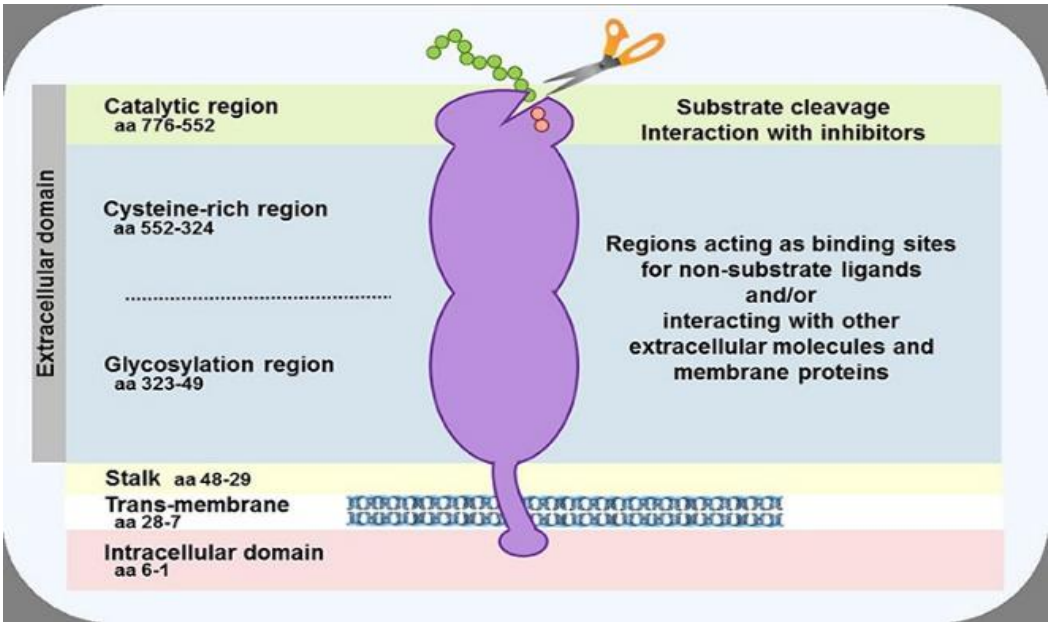


Figure 2: Shows the DPP-4 protein schematically. Two DPP-4 monomers dimerize to create a homodimer in the cell membrane. The soluble form of DPP-4, which circulates in the plasma, may be released when the monomers are split at the stalk. The catalytic pocket, which is created by residues containing serine at position 630 in the protein C-terminal region, houses the enzymatic activity. For several molecules, such as adenosine deaminase, caveolin-1, collagen, fibronectin, chemokine CXCR4 receptor, CD45, and sodium-hydrogen exchanger-3, sites within the cysteine-rich and glycosylation areas act as a receptor or ligand to mediate the non-enzymatic actions of the protein [28].

Receptor grid generation

The protein gem structure, which was created using the protein preparation wizard, included the co-crystallized ligand and was used to create the receptor lattice. In order to describe the centroid of the dynamic docking location, a Gride box was created. The Glide grid generating wizard is used to create the Grid box. The protein Glide grid box dimensions, which represent the centroid of a docked posture, were set at 14*14 *14.

Ligand preparation

The ligand structures were created using a 2D sketcher and then send to the LigPrep module of the Schrodinger suite 2020. The stereo concoction, ionisation, tautomeric variations, energy minimization and optimization for their shape, desalination, and correction for their chiralities and missing hydrogen atoms allowed the ligands to be converted from 2D to 3D structures. Using the Epik module, the ionisation and tautomeric states were generated within a pH range of 6.8 and 7.2. Mixtures were restricted using the OPLS-3 power field in the Impact bundle of Schrodinger during the last stage of LigPrep until a root mean square deviation of 1.8Å was achieved. Each ligand was given a single low-energy ring affirmation, and the streamlined ligands were then used for docking research.

Glide ligand docking

By applying the Glide module of the Schrödinger suite 2020-3, the ligands RSMS1–50 are docked into the synergist pocket of the DPP–IV protein (PDB ID: 6B1E). Based on their Glide score, ligands are selected that are best-docked. The Glide ligand docking module was used to rate the successful interactions between the ligands and the receptor. OPLS-3 power field and extra precision (XP) mode were used for the docking. The docking procedure described above was carried out in flexible docking mode, which creates conformations for each input ligand automatically. This computation penalises steric conflicts while perceiving positive hydrogen-bonding, metal-ligation, and lipophilic connections. Finally, the constrained positions were rescored using the scoring capabilities of Glide Score. The docking results were examined using the XP visualizer of the Glide module. The Glide score of the common compound including Vildagliptin and Sitagliptin were compared to the score of dynamic molecules. Majority of the time, the Gide scoring capability depends on docking features like lipophilic persistence, where the ligands are encapsulated in the lipophilic pocket that is crucial for controlling the activity. Another parameter to increase the binding affinity is hydrogen bonding with various ligands and electrostatic forces. The mobility will be reduced by several unfavourable characteristics, such as XP penalties, rotational penalties, and so on. The QikProp module of Schrodinger suit-2020.

Binding free energy calculation by using Prime/MM-GBSA approach

Molecular Mechanics-Generalized Born Surface Area (MM-GBSA) processes the binding free energies of the protein ligand complex using Schrödinger Suite 2020-3 Prime module, which integrates the OPLS3 power field and VSGB solvation model to examine computations.

Table 1: Docking studies for compounds RSMS 1-50 with DPP-IV (6B1E)

Compounds	D. Score	Lipophilic EvdW	PhobEn	H Bond	XP Electro	Low MW	Rot Penal	XP Penalties
RSMS1	-5.35	-2.54	-0.35	-1.36	-0.79	-0.46	0.24	0
RSMS2	-5.34	-2.56	-0.35	-1.33	-0.67	-0.46	0.24	0
RSMS3	-5.11	-1.91	-0.55	-1.59	-0.72	-0.5	0.18	0
RSMS4	-5.1	-2.17	-0.42	-1.83	-0.7	-0.46	0.16	0
RSMS5	-5.11	-4.99	-0.55	-1.32	-0.72	-0.5	0.16	0
RSMS6	-4.87	-2.05	-0.57	-1.32	-0.86	-0.5	0.1	0
RSMS7	-5.11	-5.11	-0.76	-1.57	-1.14	-0.32	0.32	0
RSMS8	-4.81	-2.59	-0.35	-0.74	-1.01	-0.32	0.2	0.01
RSMS9	4.98	-2.09	-0.51	-1.78	-0.65	-0.42	0.15	0
RSMS10	-6.18	-2.94	-1.4	-1.33	-0.42	-0.34	0.2	0.05
RSMS11	-7.05	-3.25	-1.05	-1.34	-1.4	-0.24	0.23	0
RSMS12	-5.79	-1.74	-0.5	-2.39	-0.93	-0.5	0.26	0
RSMS13	-4.49	-2.03	-0.38	-1.84	-0.71	-0.36	0.14	0
RSMS14	-5.83	-2.48	-1.22	-1.11	-0.77	-0.16	0.16	0
RSMS15	-6.46	-2.16	-0.71	-2.45	-1.07	-0.36	0.28	0
RSMS16	-5.15	-5.15	-0.36	-1.7	-0.52	-0.3	0.19	0.38
RSMS17	-4.52	-4.75	-1.13	-0.59	-0.35	-0.38	0.22	0
RSMS18	-5.28	-5.28	0	-1.52	-1.15	-0.24	0.17	0.03
RSMS19	-5.46	-3.18	-0.62	-0.7	-0.59	-0.3	0.25	0
RSMS20	-3.79	-2.47	0	-1.54	-0.3	-0.19	0.16	0.65
RSMS21	-4.49	-2.2	0	-1.43	-0.77	-0.29	0.19	0.09
RSMS22	-5.71	-2.52	-0.55	-2.12	-0.65	-0.19	0.16	0.22
RSMS23	-5.69	-2.5	-0.44	-1.33	-0.43	-0.2	0.17	0
RSMS24	-5.85	-2.68	-0.48	-2.15	-0.6	-0.15	0.15	0
RSMS25	-5.69	-2.58	-0.4	-2.17	-0.58	-0.1	0.14	0
RSMS26	-8.02	-2.35	-0.72	-1.26	-0.45	-0.09	0.14	0
RSMS27	-5.41	-2.61	-0.33	-1.82	-0.68	-0.1	0.14	0
RSMS28	-4.74	-2.03	0	-1.82	-0.64	-0.1	0.17	0
RSMS29	-5.72	-2.79	-5.71	-1.15	-0.91	-0.15	0.15	0
RSMS30	-5.78	-2.15	-0.65	-1.55	-1.18	-0.21	0.22	0
RSMS31	-5.73	-2.15	-0.65	-1.22	-0.72	-0.21	0.22	0
RSMS32	-4.9	-2.7	-0.5	-1.34	-0.46	-0.18	0.21	1
RSMS33	-5.4	-2.39	-0.97	-1	-0.71	-0.24	0.23	0
RSMS34	-5.51	-5.51	-0.77	-1.14	-0.64	-0.1	0.19	0
RSMS35	-6.17	-2.55	-1.26	-1.08	-1.02	-0.15	0.21	0
RSMS36	-5.45	-2.61	-0.25	-1.55	-0.72	-0.2	0.17	0.07
RSMS37	-4.94	-2.59	0	-1.61	-0.74	-0.16	0.21	0.35
RSMS38	-5.79	-2.46	-0.76	-1.8	-0.94	-0.2	0.21	0.02
RSMS39	-3.75	-2.55	-0.26	-1.78	-0.69	-0.15	0.21	1.38
RSMS40	-4.52	-2.89	-0.9	-1.12	-0.72	-0.11	0.24	3.31
RSMS41	-4.32	-1.34	0	-2	-0.97	-0.26	0.18	0
RSMS42	-5.31	-1.57	-0.15	-1.71	-0.9	-0.14	0.15	0
RSMS43	-5.35	-2.28	0	-1.33	-0.85	-0.03	0.13	1
RSMS44	-5.82	-1.62	-1.46	-2.54	-0.97	-0.2	0.16	0
RSMS45	-8.39	-3.01	-1.56	-2.34	-0.73	-0.03	0.13	0
RSMS46	-4.63	-2.8	-4.77	-1.24	-0.66	-0.19	0.16	0
RSMS47	-6.9	-3.07	-1.64	-0.72	-0.66	-0.11	0.15	0
RSMS48	-5.61	-2.77	-0.48	-0.76	-0.85	-0.26	0.18	0
RSMS49	-2.2	-2.46	-0.23	-0.98	-0.87	-0.19	0.16	2.4
RSMS50	-4.71	-2.05	-0.43	-1.76	-0.64	-0.22	0.17	0
Vildagliptin	-5.3	-2.0	-1.6	-0.8	-0.5	-0.5	0.3	0
Sitagliptin	-5.6	-1.6	-1.6	-0.6	-0.6	-0.2	0.2	0

RESULTS AND DISCUSSION

To determine the coupling affinities of the ligands, the intended molecules were sub-atomically docked to the protein dynamic targets using the advanced sub-atomic docking software Schrodinger suit2020-3. To determine the structured analogues DPP-IV (6B1E) inhibitory effect against diabetes mellitus, the DPP-IV is docked with the analogues. When compared to ordinary Vildagliptin subsidiary with antidiabetic movement Vildagliptin and against antidiabetic drug Sitagliptin, the compounds RSMS 1-50 (Figure 1) showed remarkable receptor affinity. Table 1 displays the Glide scores from docking experiments against the DPP-IV receptor (PDB id 6B1E). When compared to conventional Vildagliptin (- 5.3) and Sitagliptin(-5.6), compounds RSMS 1–50, with the exception of RSMS 20,39,49, show substantial Glide scores in the range of – 4.32 to – 8.39. Because there are groups like cyano and aromatic rings present, the docking data show that the binding affinity is mostly caused by lipophilic components. In docking scores in the majority of the mixes, lipophilic factors have a significant role. In the vicinity of the Ser 630, Glu 205, and Glu 206 build-ups, which is the active site region, the cooperatives are practically overburdened (Figure 4). Figure 5 displays the developed ligands in their optimal docking postures. In Figure 6 the compounds with the highest Glide scores, RSMS 10, 15, 25, 26, 35, and 47, are presented in their best-docked positions. Figure 7 depicts the hydrogen bonding that the ligand RSMS 28 displayed with SER630 (H-bond length: 1.96 A).

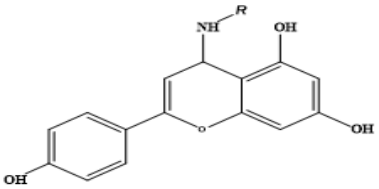


Figure 3: Structures of compounds RSMS 1-50

8-Amino substituted apigenin derivatives (1-50)

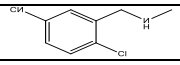
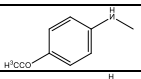
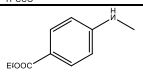
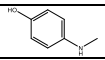
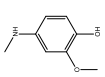
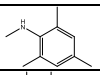
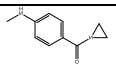
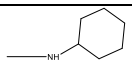
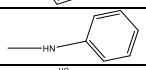
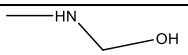
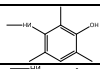
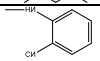
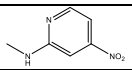
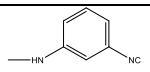
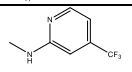
S.No	R		R		R
1	H_3CH_2CHCN——	17		34	
2	$H_3C(H_2C)_2HN$——	18		35	
3	$(H_3C)_2HCHN$——	19		36	
4	$(3HC)_3HCN$——	20		37	
5	$(H_3C)_2N$——	21		38	
6	$(C_2H_5)_2N$——	22		39	
7	$(C_3H_7)_2N$——	23		40	
8		24		41	
9		25		42	
10		26		43	
11		27		44	
12		29		45	
13		30		46	
14		31		47	
15		32		48	
16		33		49	
				50	

Figure 4: Ligand interaction of compound RSMS25 with DPP-IV (6B1E)

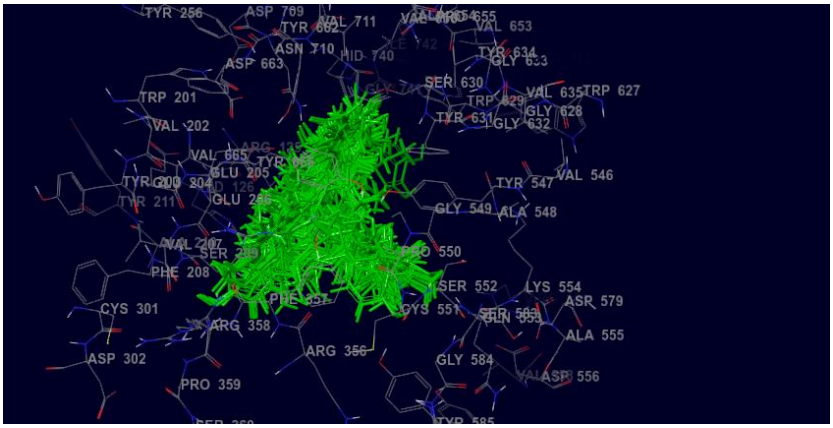
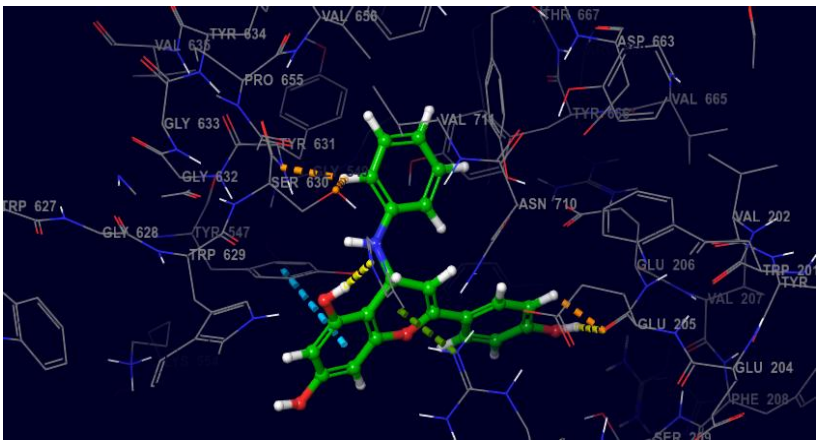
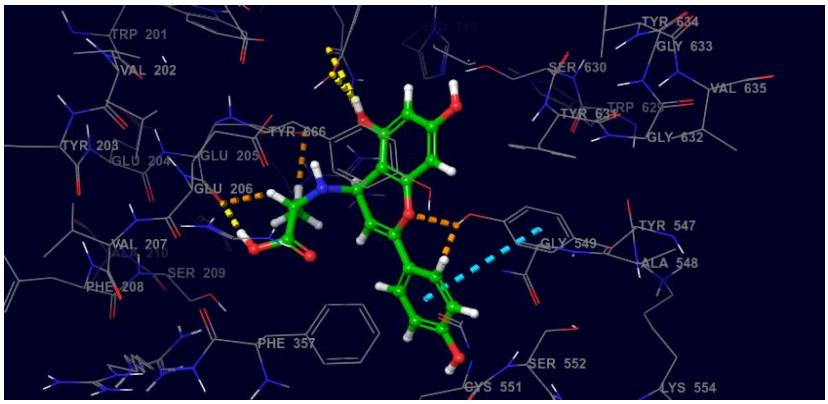


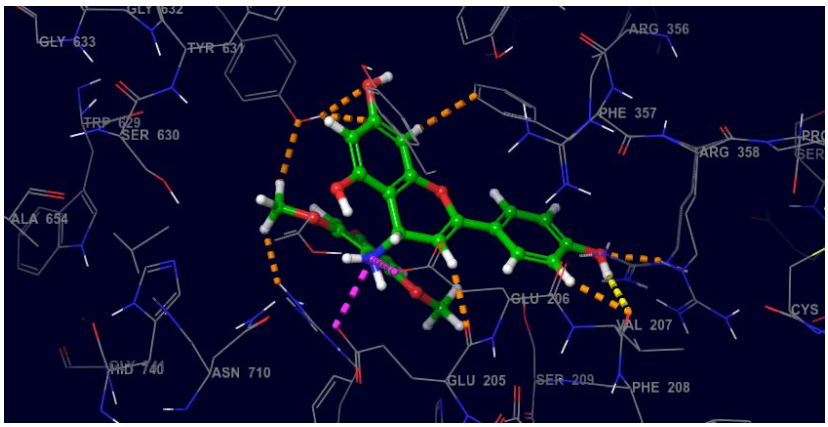
Figure 5: Docked poses of all compounds RSMS 1-50 with DPP-IV (6B1E).



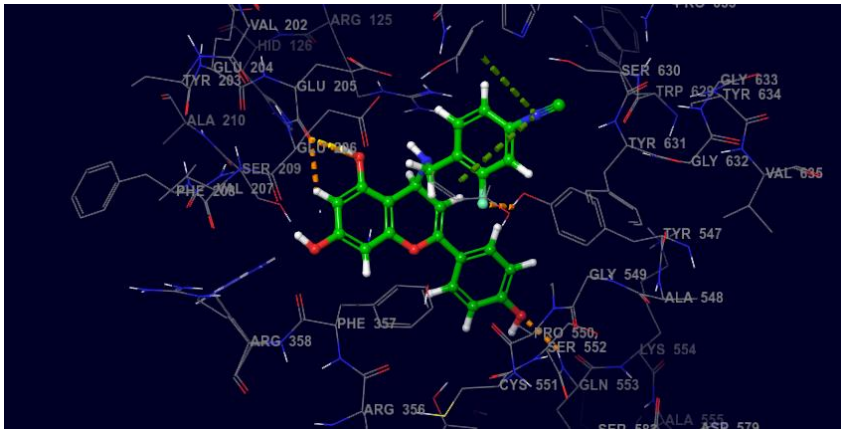
Compound RSMS10 (G Score: --6.18)



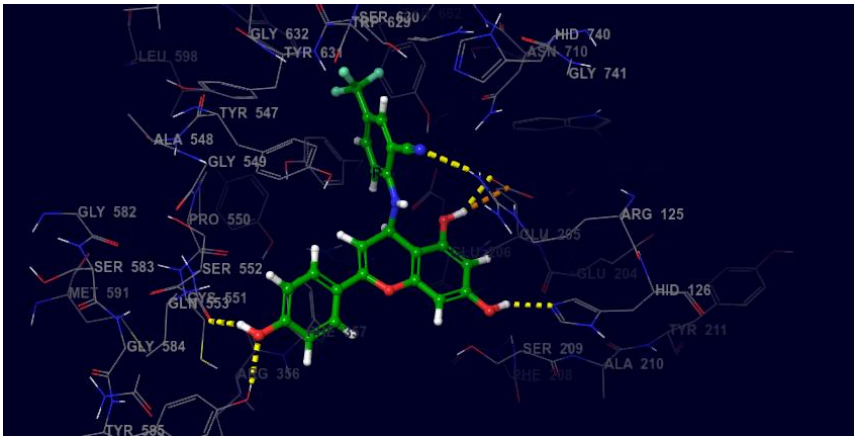
Compound RSMS15 (G Score: -6.46)



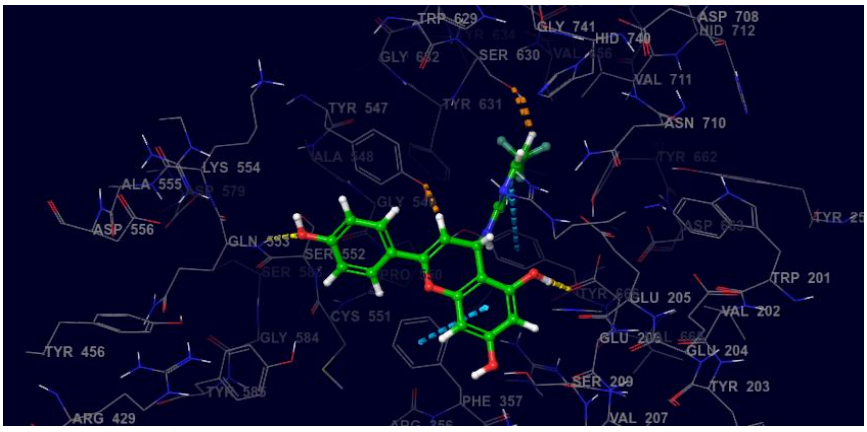
Compound RSMS26 (G Score: -8.02)



Compound RSMS35 (G Score: -6.17)



Compound RSMS45 (G Score: -8.39)



Compound RSMS47 (G Score: -6.9)

Figure 6: Best affinity mode of docked compounds with DPP-IV (6B1E)

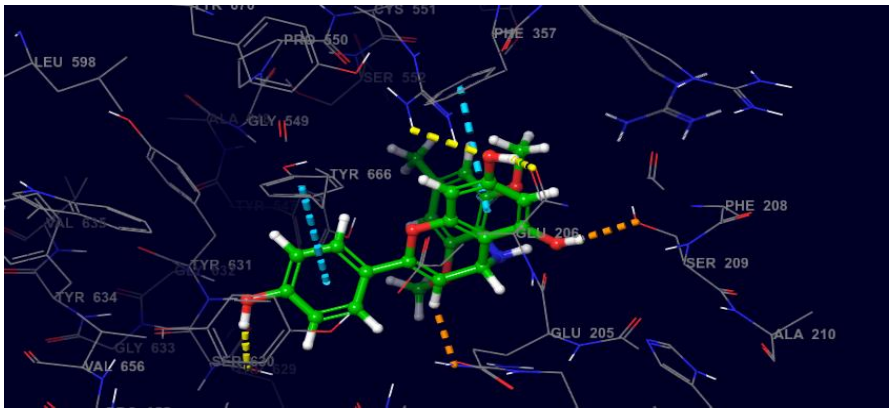


Figure 7: Hydrogen bonding interaction of compound RSMS25 with DPP-IV (6B1E).

Table 2: Insilico ADMET screening for proposed compounds (RSMS1-50)

Compounds	Mol. Wt	Dipole	Donor HB	Accept HB	QPlog o/w	#metab	Rule of five	%Human oral absorption
RSMS1	313.352	2.644	4	4.250	2.060	5	0	73.205
RSMS2	313.352	2.644	4	4.250	2.060	5	0	73.205
RSMS3	299.326	2.141	4	4.250	1.604	5	0	69.738
RSMS4	313.352	2.329	4	4.250	1.839	5	0	71.850
RSMS5	299.326	2.141	4	4.250	1.604	5	0	69.738
RSMS6	285.299	2.116	4	4.250	1.173	5	0	65.595
RSMS7	355.433	2.391	4	4.250	3.005	5	0	79.191
RSMS8	355.433	2.380	4	4.250	2.564	4	0	78.935
RSMS9	323.348	2.371	3	4.750	2.142	6	0	74.969
RSMS10	347.370	4.615	4	3.750	3.286	7	0	91.180
RSMS11	377.396	4.356	5	5.00	2.397	7	0	70.926
RSMS12	301.298	3.979	5	5.950	0.187	6	0	50.080
RSMS13	341.363	4.106	3	6.450	1.558	5	0	72.059
RSMS14	401.341	4.243	4	3.750	3.887	5	0	95.466
RSMS15	343.335	0.896	5	6.250	-0.651	6	0	34.281
RSMS16	361.396	4.421	4	3.750	3.585	6	0	92.938
RSMS17	335.359	5.159	4	3.750	2.498	6	0	75.685
RSMS18	377.396	4.660	4	4.500	3.417	7	0	91.938
RSMS19	361.396	2.267	4	4.250	2.904	6	0	78.449
RSMS20	392.367	12.070	4	4.750	2.632	6	0	77.780
RSMS21	363.369	4.860	5	4.50	2.509	7	0	77.375
RSMS22	393.395	6.224	5	4.250	2.697	8	0	78.946
RSMS23	389.450	2.875	4	3.750	4.088	8	0	100
RSMS24	405.449	3.037	4	4.500	4.086	9	0	100
RSMS25	421.449	2.939	4	5.250	3.950	9	0	95.891
RSMS26	423.421	2.377	5	6.00	2.884	8	0	80.343
RSMS27	419.476	3.070	4	4.50	4.395	9	0	100
RSMS28	389.450	2.802	4	3.750	4.050	9	0	100
RSMS29	405.449	2.909	5	4.500	3.424	9	0	89.235
RSMS30	386.406	6.165	4	5.250	2.958	6	0	77.855
RSMS31	386.406	3.758	4	5.250	2.495	6	0	77.213
RSMS32	395.841	4.966	4	4.250	`3.350	6	0	81.417
RSMS33	379.387	3.563	4	4.250	3.116	6	0	79.400
RSMS34	420.851	1.822	4	5.250	3.214	6	0	81.212
RSMS35	404.397	3.264	4	5.250	2.683	6	0	77.888
RSMS36	389.407	7.889	4	5.750	2.872	6	0	79.808
RSMS37	403.434	7.423	4	5.750	3.197	5	0	83.050
RSMS38	390.395	8.776	6	6.250	1.691	6	0	49.995
RSMS39	404.421	8.261	5	6.250	2.700	5	0	78.042
RSMS40	416.432	7.966	4	5.750	3.321	5	0	82.915
RSMS41	372.379	5.699	4	5.250	2.681	6	0	77.269
RSMS42	406.824	7.414	4	5.250	3.155	6	0	80.921
RSMS43	440.378	9.457	4	5.250	3.641	6	0	84.812
RSMS44	390.370	5.824	4	5.250	2.777	4	0	80.165
RSMS45	440.378	7.947	4	5.250	3.645	5	0	82.915
RSMS46	393.355	8.194	4	5.250	2.322	7	0	68.400
RSMS47	416.356	4.799	4	4.250	3.936	6	0	94.448
RSMS48	373.367	4.461	4	5.250	2.990	6	0	88.318
RSMS49	393.355	6.774	4	5.250	2.434	6	0	73.140
RSMS50	382.802	3.289	4	4.250	3.413	5	0	91.371
Vildagliptin	303.4.3	6.322	2	6.750	0.438	4	0	59.478
Sitagliptin	393.291	4.456	2	6	2.24	5	0	75.455
Recommended Values	13.-725	1-12.5	0-6	2-20	-2-6.5	1-8	Max 4	>80% is high <25% is poor

MW- Molecular weight of the molecule,
Dipole – Computed dipole moment
donorHB - Estimated number of hydrogen bonds that would be donated by the solute to water molecules in an aqueous solution.
accptHB- Estimated number of hydrogen bonds that would be accepted by the solute from water molecules in an aqueous solution
QPlogPo/w - Predicted octanol/water partition coefficient.
#metab- Number of likely metabolic reactions.
RuleOfFive Number of violations of Lipinski's rule of five.
%Human- Oral absorption- Predicted human oral absorption on 0 to 100% scale.

Table 3: Binding free energy calculation using Prime/MM-GBSA approach

Compounds	ΔG bind (Kcal/mol)	ΔG bind columb	ΔG bind covalent	ΔG bind vander	ΔG Bind H Bond	ΔG bind Lipophilic
RSMS1	-13.80	-26.59	8.64	-36	-1.68	-14.43
RSMS2	-13.80	-16.98	8.01	-36.62	-1.69	-14.43
RSMS3	-24.89	-26.39	8.25	-35.56	-1.82	-15.43
RSMS4	-16.38	-29.16	6.72	-34.13	-1.5	-16.38
RSMS5	-17.83	-26.41	8.29	-35.33	-2.21	-15.12
RSMS6	-15.78	-27.11	2.2	-33.32	-2.18	-14.17
RSMS7	-20.68	-33.61	7.16	-29.75	-2.57	-19.71
RSMS8	-2.75	-23.51	2.1	-39.25	-1.55	-18.66
RSMS9	-10.22	-24.87	7.5	-34.75	-1.5	-19.83
RSMS10	-21.59	-13.13	5.96	-26.96	-1.44	-16.05
RSMS11	-18.81	-27.16	3.07	-40.95	-2.07	-23.26
RSMS12	-20.64	-35.27	3.8	-27.4	-3.61	-20.76
RSMS13	-23.24	-24.61	5.84	-34.86	-2.25	-14.53
RSMS14	-5.85	-31.93	2.66	-37.76	-2.23	-17.85
RSMS15	-24.22	-25.76	6.72	-34.23	-3.14	-11.48
RSMS16	-14.82	-11.82	7.21	-39.61	-1.86	-20.5
RSMS17	-19.45	-21.03	2.81	-30.55	-1.46	-17.66
RSMS18	-17.67	-30.81	7.81	-41.08	-2.15	-22.32
RSMS19	-24.97	-26.1	2.61	-37.08	-1.38	-22.31
RSMS20	-36.45	-17.03	7.36	-46.04	-2.05	-19.13
RSMS21	-13.47	-37.23	10.08	-30.16	-3.95	-21.81
RSMS22	-24.21	-21.52	9.44	-47.5	-2.65	-21.97
RSMS23	18.25	-26.49	5.26	-41.42	-1.58	-26.03
RSMS24	-23.96	-13.37	4.91	-42.77	-2.14	-21.26
RSMS25	-24.07	-10.48	7.99	-45.62	-2.2	-20.97
RSMS26	6.42	-50.72	11.85	-40.69	-1.28	-18.99
RSMS27	-22.04	-9.33	6.33	-49.2	-1.43	-18.51
RSMS28	-15.96	-23.11	3.67	-37.73	-2.22	-18.75
RSMS29	-30.31	-33.9	8	-39.79	-2.18	-24.66
RSMS30	-46.23	-17.79	3.32	-43.74	-2.66	-20.34
RSMS31	-32.41	-17.71	4.41	-36.47	-1.49	-22.42
RSMS32	-30.02	-24.86	5.31	-36.62	-1.65	-20.56
RSMS33	-22.27	-32.81	1.77	-38.32	-2.3	-22.75
RSMS34	-14.84	-12.26	4.06	-38.06	-1.78	-18.33
RSMS35	-22.54	-15.42	4.74	-36.01	-1.34	-21
RSMS36	-26.59	-19.51	10.56	-43.77	-2.03	-19.25
RSMS37	-22.21	-32.43	8.22	-43.26	-2.78	-15.81
RSMS38	-31.79	-41.22	10.91	-36.8	-1.7	-19
RSMS39	-16.34	-19.17	8.84	-44.57	-2.33	-15.03
RSMS40	-26.52	-20.06	8.43	-46.56	-2.19	-21.42
RSMS41	-22.54	-34	7.18	-34.08	-2.56	-15.13
RSMS42	-31.24	-34	8.81	-39.87	-2.82	-19.67
RSMS43	-29.77	-31	5.6	-36.14	-1.51	-19.81
RSMS44	-15.61	-35.89	2.77	-29.54	-3.15	-18.87
RSMS45	-18	-37.39	9.88	-42.28	-2.56	-15.33
RSMS46	-28.37	-0.32	6.03	-42.58	-2.18	-17.25
RSMS47	-8.33	-14.02	3.59	-41.07	-1.26	-16.13
RSMS48	-24.75	-8.29	8.54	-40.15	-2.19	-16.43
RSMS49	-26.02	-14.7	8.94	-45.02	-3.53	-16.64
RSMS50	-10.08	-23.11	8.02	-38.57	-1.25	-22
Sitagliptin	-18.2	-20.31	3.05	-33.79	-1.63	-13.89
Vildagliptin	-10.85	-32.05	0.02	-31.07	-1.96	-16.37

By applying the qikprop module of the Schrödinger suite 2020-3, the ADMET characteristics for the planned ligands RMMS1–50 may be foreseen in-silico. Compounds with molecular weights between 285 and 440. The molecules processed dipole moments range from 1.822 to 12.070. In a fluid configuration of the mixtures, it is estimated that the solute would provide 2–6 hydrogen bonds to the water atoms. The range of 3.750 to 6.750 is the estimated number of hydrogen bonds that would be recognised by the solute from water particles in a fluid arrangement of the compounds. The compounds QPlogP values are the highest. There are a variety of 4–8 possible metabolic reactions to the chemicals. There have been 0 instances of Lipinski's rule of five being broken. Human oral absorption of the substance's ranges from 75 to 100%. According to the in-silico ADMET screening findings, the majority of the chemicals fall within the advised ranges. Table 2 illustrates the finer points of the ADMET characteristics for compounds RSMS1–50. Additionally, MM-GBSA free restricting vitality, which is discovered using the post scoring technique for the DPP-IV (PDB ID: 6B1E) target, was used to evaluate molecular docking. Examining the lowest energy postures predicted by the scoring function demonstrates the accuracy of docking. The experimental binding mode identified by X-ray crystallography and the Glide scores match one other nearly perfectly. The docking of ligands into the coupling pocket

results in the Glide score and MM-GBSA free energy values. Table 3 illustrates the intricacies of the MM-GBSA free restricting vitality for the compounds RSMS1-50.

CONCLUSION

Generally, 8-Amino apigenin analogues demonstrated a variety of biological actions, including the ability to fight off bacteria and treat diabetes. According to the molecular docking investigation, 8-Amino apigenin analogues showed improved organisation at dynamic site by interacting with multiple amino along with cyano corrosive build-ups. In this manner, the in-silico structuring approach used in the current study assisted in identifying the lead atoms and may also aid to partially explain their helpful influence for further tests like in vitro and in vivo evaluation. Based on this assumption, researchers recently shown that the 8-Amino apigenin analogues arrangement used DPP-IV enzyme restraint as harmful to antidiabetic action. The in-silico study's findings clearly showed that a large number of the 8-Amino apigenin analogues family may demonstrate fascinating anti-diabetic activity. After further refining, the compounds RSMS 10, 15, 35, 26, 30, 45, and 47 are likely to be useful analogues since they exhibit strong DPP-IV Inhibitory anti-diabetic action with potential for remedy.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

HUMAN AND ANIMAL RIGHTS

No animals/humans were used for studies that are the basis of this research.

CONSENT FOR PUBLICATION

Not applicable.

AVAILABILITY OF DATA AND MATERIALS

Not applicable.

FUNDING

RGPV RDF Fellowship.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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