(RESEARCH ARTICLE)

Molecular docking studies of potent and selective orally bioavailable dihydro-pyrazole Gpr-40 agonists as Alpha-Glucosidase Inhibitors (AGIS)

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Abstract

The primary goal of this study is to bring the elevated blood sugars down to a normal range, both to improve symptoms of diabetes as well as to prevent or delay diabetic complications. Achieving this goal requires a comprehensive, coordinated, patient-centered approach on the part of the healthcare system. The potions extracted from the generated Docking models are statistically aesthetic and provide enough assumptions about the character as well as the nature of substitutions favourable to boost the biological efficiency of novel analogous. The potion provided by these computational studies helps to derive an impactful path to design more potent antihyperglycemic counterparts of dihydro-pyrazole.

Keywords: Diabetes; Molecular docking; Dihydro-pyrazole; Insulin

1. Introduction

Diabetes mellitus (DM) is a common disorder of carbohydrate, fat and protein metabolism reflected by an inappropriate fasting and postprandial high blood glucose levels (hyperglycaemia) [1, 2]. This ailment results from the absence or scantiness of insulin secretion with or without concurrent impairment of insulin action [3]. Consequently, the disease was classified into two types known as type I (insulin dependent, IDDM) and II (non-insulin dependent, NIDDM) according to the degree of the pancreatic defect. This classification has been even recognized in the book "The Canon of Medicine" by Avicenna [4]. The development of type 2 diabetes is caused by a combination of lifestyle and genetic factors [5]. While some of these factors are under personal control, such as diet and obesity, other factors are not, such as increasing age, female gender, and genetics [6]. A lack of sleep has been linked with type 2 diabetes. This is believed to act through its effect on metabolism [7].The nutritional status of a mother during fatal development may also play a role, with one proposed mechanism being that of altered DNA methylation [8]. DM is not confined to abnormal blood glucose level, but it progresses to affect other body systems. There are a number of medications and other health problems that can predispose to diabetes [9]. Some of the medications include: glucocorticoids, thiazides, beta-blockers, atypical antipsychotics, and statins [10]. Those who have previously had gestational diabetes are at a higher risk of developing type 2 diabetes [6]. Other health problems that are associated include: acromegaly, Cushing's syndrome, hyperthyroidism, pheochromocytoma, and certain cancers such as glucagonomas. Testosterone deficiency is also associated with type 2 diabetes [11]. Alpha-glucosidase inhibitors (Acarbose, Miglitol, Voglibose) are oral anti-diabetic drugs used for diabetes mellitus type 2 that work by preventing the digestion of carbohydrates (such as starch and table sugar). Carbohydrates are normally converted into simple sugars (monosaccharides), which can be absorbed through the intestine. Hence, alpha-glucosidase inhibitors reduce the impact of carbohydrates on blood sugar [12].
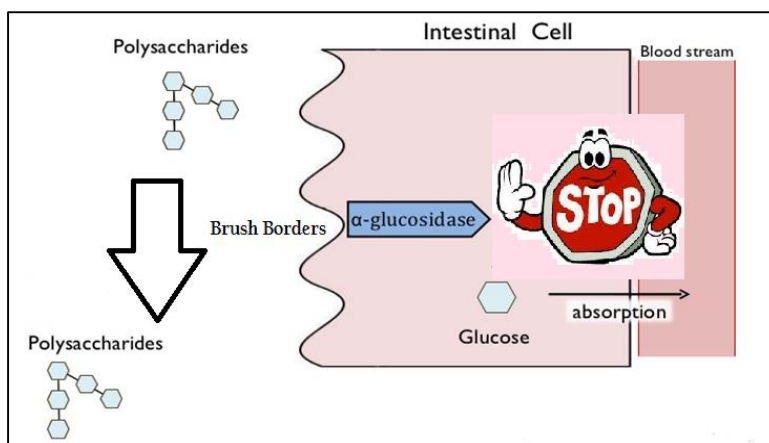
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Figure 1 Mechanism of α-Glucosidase Inhibitors

The current strategy used for the treatment of type II DM depends on combining an insulin secretagogue and an insulin sensitizer to provide a sensible therapeutic approach. Reasonable management provided by these drugs, yet over time, some of the type II diabetic patients lose response towards conventional antidiabetics, leading to inadequate control of their blood glucose level. [13]. In spite of the introduction and extensive utilization of hypoglycaemic agents, diabetes and its related complications continue to be a major health problem worldwide. Globally, around 150 millions of people are believed to be diabetic and the incidence rate is expected to double by 2025[14].

2. Methods

2.1. Software and Tools

The 2D structures of Dihydropyrazole Gpr-40 agonist's compounds were drawn using Chemdraw Ultra 8.0software and converted into 3D by using Chem3D Ultra Software. The energy minimization was done by MM2 (Molecular Mechanics 2) and by MOPAC (Molecular Orbital Packaging) at a minimum Root Mean Square (RMS) gradient value of 0.001 followed by computation of 3D properties using the same Chem3D Ultra Software developed by Cambridge soft. The molecular docking studies were also performed using 3D structures of compounds and a targeted enzyme structure, responsible for biological activity, taken from Protein data Bank (PDB) on Molegro Virtual Docker6.0 developed by CLC drug discovery Workbench.

2.2. Ligand Preparation, Energy Minimization, and Geometrical Optimization

The structure of the compounds was prepared using ChemDraw and ChemBio 3D by Cambridge Soft. The geometry and energy of the structures were optimized using Merck Molecular Force Field 94 (MMFF94) calculation available in ChemBio 3D.

2.3. Molecular Docking

2.3.1. Software Validation

Docking studies is a type of computational approach used to study the Ligand- Enzyme interactions which are crucial for activity. The study would help to observe the binding fashion of compounds with enzyme's amino acids. Docking analysis of all 44 compounds was performed to explore the binging of compounds to the important amino acids responsible for antihyperglycemic activity. In accordance with the targeted enzyme Pdb code- 3A4A was selected for antihyperglycemic docking studies of the compounds and Pdb code- 3A4A was selected to study the binding fashion for antihyperglycemic activity. Validation of Molegro virtual Docker 6.0 is important because it is a computational approach, the result may be deviate on changing the software.

As we know that each PDB has its own co-crystalize ligand on its active site. In the process of software validation, we just re-docked that co-crystalize ligand with its PDB and observe the orientation and conformational changes on it. This will help to stabilize the software's repeatability and validate it.

2.3.2. Docking Studies and Results Visualization

Molegro virtual docker was used to identify the binding modes responsible for the activity. Protein File (PDB) was further optimized by removing water molecules and adding hydrogen atoms. The Docking grid box was set at 60 x 60 x 60 with a spacing value of 0.375Å. Genetic Algorithm (GA) with Default settings was employed as the search parameter. In the search parameter, number of runs was set At 150. The 2D interaction diagram and 3D docking results was visualized using Biovia Discovery Studio visualizer 4.0.

PDB Description Name: 3A4A

Classification: Hydrolase.

Organism: Homo sapiens

Expression System: Spodoptera fruqiperda.

PDB Ligand: ADCP2 and CD26

2.4. IUPAC

(5-Substituted-pyrrolidinyl-2-carbonyl)-2-Cyanopyrrolidines {4-{[(2R,5S) -5-{[(2S)-2-(aminomethyl) pyrrolidin-1-yl]carbonyl}pyrrolidin-2-yl] methoxy}-3-tert-butylbenzoic acid).
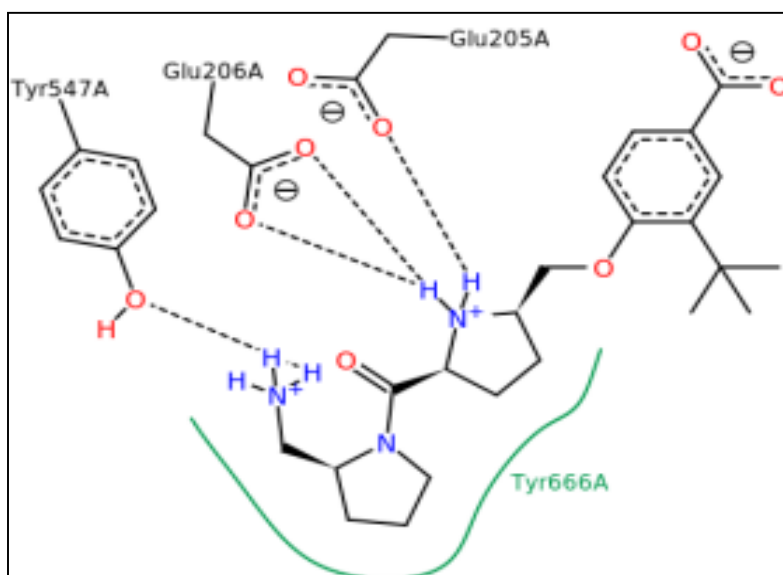

Figure 2 PDB Description Name 3A4A

Table 1 Docking score of all compounds

Compounds	MolDock Score	Rerank Score	H-Bond interaction Energy (Kcal/mol)
ADF_800 [A]	-168.623	-128.687	-6.0113
01	-140.36	-117.153	-1.86755
02	-131.198	-48.0801	-5.77622
03	-119.791	-59.6472	-1.29366
04	-168.152	-126.517	-3.12236
05	-150.268	-104.202	-2.5
06	-135.765	-91.4095	-4.75157

07	-139.807	-87.3891	-5.71479
08	-134.425	-29.1381	0
09	-136.078	-103.595	-6.45031
10	-135.523	-95.3072	-1.84517
11	-139.689	-108.305	-1.85863
12	-150.264	-94.9141	-1.67991
13	-148.045	-114.73	-1.96553
14	-135.366	-98.268	0
15	-135.717	-48.3214	-5.18917
16	-155.805	-106.866	-3.20186
17	-148.452	-106.174	-2.70533
18	-139.127	-105.893	-2.94278
19	-140.302	-90.461	-4.2237
20	-132.17	-57.2854	-2.5
21	-136.764	-108.006	-2.09335
22	-141.674	-108.17	-0.743939
23	-140.01	-108.082	-3.36936
24	-138.15	-98.378	-0.28183
25	-151.245	-113.511	-3.97086
26	-133.26	-98.4842	-6.19471
27	-129.139	-96.9758	-3.35815
28	-129.369	-87.846	-2.77128
29	-146.427	-113.49	-2.25029
30	-151.048	-113.31	0
31	-148.069	-113.58	-4.52207
32	-167.783	-118.399	0
33	-148.954	-112.059	-2.5
34	-147.363	-89.4451	-4.18106
35	-151.91	-117.448	0
36	-160.809	-124.483	-0.756457
37	-143.336	-106.119	-2.5462
38	-139.258	-30.3152	-6.98901
39	-132.674	-100.398	-0.245869
40	-146.608	-116.873	-2.61293
41	-151.467	-102.625	-4.18629
42	-147.152	-109.93	-4.37856
43	-128.029	-94.7753	-0.704791
44	-137.661	-103.833	-7.6677

3. Results and discussion

Docking analysis is important to study the ligand-enzyme interaction. For the docking analysis, the compounds were chosen based on their previously evaluated for antihyperglycemic activity. Docking was carried out using Pdb code-3A4A, using Molegro Virtual Docker 6.0. Computer aided drug designing (CADD) helps the researcher to decrease the time and money for drug designing projects Molecular docking is very helpful in studying the interactions of ligand molecules with the target protein before its in vitro synthesis. Docking is performed through computer programs like Molegro virtual docker 6.0. All these molecules were taken from ligand database or draw with help of chemical organizer (draw) software like chemdraw ultra 2D & 3D in mol or pdb format and were stored in a database of MOE in mdb format or Pubchem database. All these molecules were docked against the same pocket where reference drug bound. Molecules were selected from a library of molecules and were further assessed by the interaction analysis. Finalized molecules showed the interactions with the active residue and with other residues.
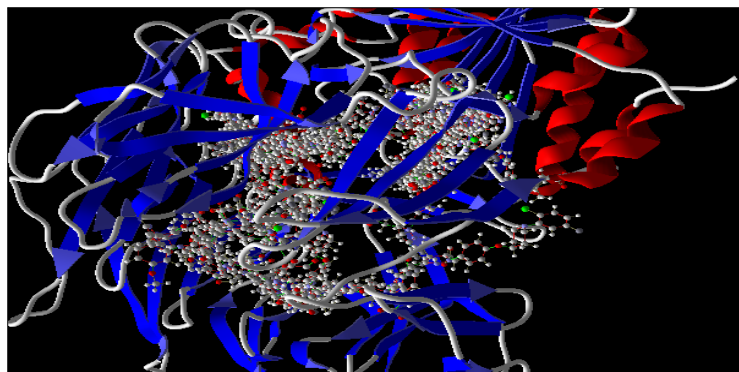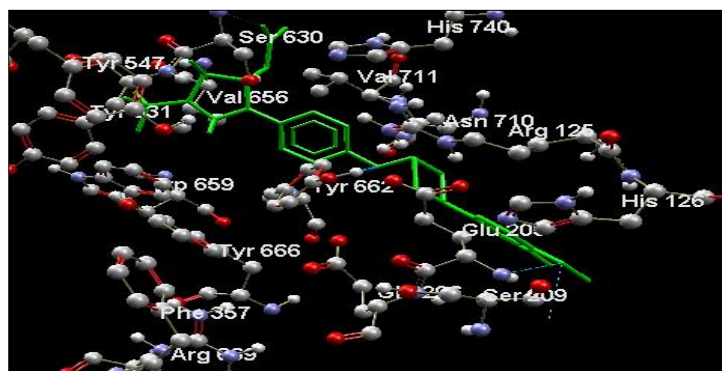

Figure 3 Docking Pose of all Compounds
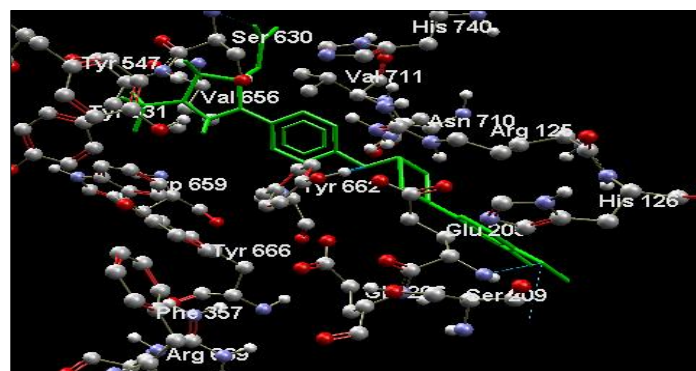

Figure 4 Docking Pose of Compound 4

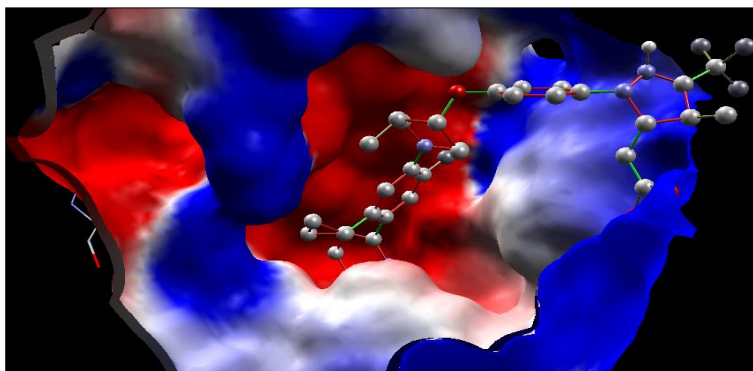**Figure 5** Docking Pose of Comp. 16
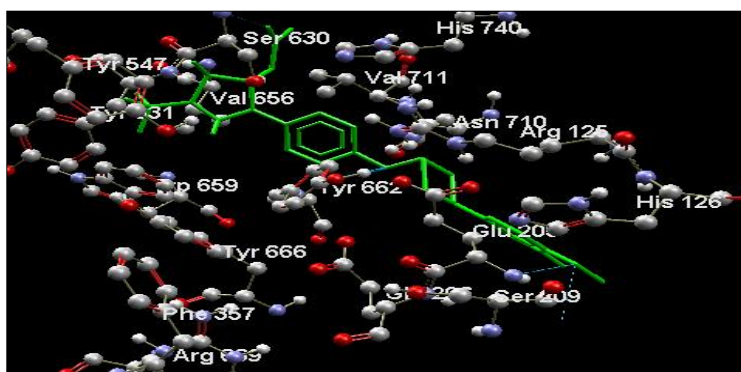
Figure 6 Cavity depth view of Comp. 25

Figure 7 Cavity depth view of Comp. 32

3.1. Docking Pose Analysis

Docking of standard drug metformin and co-crystallized ligand (ADCP2 and CD26) explore the common amino acid interaction like: Tyr 127 (B), Leu 227 (A_1), Ser 66 (B), Gly 230 (A_1), Gly 68 (B), Gly 65 (B) and Asn 64 (B) which are considered to be the active amino acids important for binding of ligand on active site. Compound-3 exhibit common binding interaction like: Ser 203 (A), Cys 218 (A), Lie 217 (A_1), Arg 223 (A_1), Ser 66 (B), Gly 65 (B) and Asn 65 (B) to that of standard active amino acids.Compound-24 exhibit common binding interaction Tyr 127 (B), Leu 227 (A_1), Ser 66 (B), Gly 230 (A_1), Gly 68 (B), Gly 65 (B) and Asn 64 (B) with amino acids responsible for activity. Compound-15 has common binding interactions Arg 96 (B), Ser 203 (A), Lys 85 (A), Ser 66 (A) and Leu 88 (A) with amino acids. Compound-29 exhibit binding with essential amino acids like: Ala 204 (A), Arg 96 (A), Asn 95 (A), Gly 202 (A), Asp 200 (A), Leu 88 (A), Gly 65 (A) and Asn 64 (A) with amino acids. Compound-31 exhibit binding with Asn 64 (B), Gly 65 (B), Arg 223 (A_1), Ser 215 (A) and The 232 (A_1) with amino acids.Compound-40 exhibit common amino acid bindings with Gly 262 (A_1), Asn 64 (B), Gly 65 (B), Gly 68 (B), Tyr 127 (B), Arg 223 (A_1), Lie 217 (A_1), Gly 230 (A_1) and Leu 227 (A_1) with amino acids. Compound-19 exhibit common amino acid bindings with Lie 62 (A), Gln 185 (A), Asp 200 (A) and Cys 199 (A) with amino acids. Compound-13 exhibit common amino acid bindings with Glu 97 (B), Gly 202 (B), Lie 100 (B), Gln 99 (B), Arg 96 (B), Lys 94 (B) and Gln 206 (B) with amino acids. Compound-12 exhibit common amino acid bindings with Arg 220 (B_1), Gly 262 (B_1), Arg 223 (B_1), Lie 228 (B_1), Asp 64 (A), Cys 218 (B_1), Leu 227 (B_1), Lie 217 (B_1) and Ser 215 (B) with amino acids. Compound-06 exhibit common amino acid bindings with Leu 227 (B_1), Ser 215 (B), Arg 223 (B_1), Leu 88 (A), Ser 66, Gly 65 (A), Gly 68 (A), Phe 67 (A), Gly 202 (A) and Glu 97 (A) with amino acids.

4. Conclusion

The molecular docking approach can be used to model the interaction between a small molecule and a protein at the atomic level, which allow us to characterize the behavior of small molecules in the binding site of target proteins as well as to elucidate fundamental biochemical processes. The potions extracted from the generated Docking models are statistically aesthetic and provide enough assumptions about the character as well as nature of substitutions favorable to boost the biological efficiency of novel analogous. Results generated from molecular docking of the same series are also in apple-pie-order and further supports the similar contribution of molecular variables towards the biological

outcome. The potion provided by these computational studies helps to derive an impactful path to design more potent antihyperglycemic counterparts of dihydropyrazole.

Compliance with ethical standards

Disclosure of conflict of interest

We all authors are agree and interested to publish this article in this journal.

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