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In silico evaluation of the antidiabetic potentials of some quercetin derivatives

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ABSTRACT

Background: Quercetin is known to exhibit antidiabetic activity in Type 2 Diabetes mellitus due to its antioxidant property. This study was aimed at designing some derivatives of quercetin and evaluating their binding affinities to target proteins implicated in diabetes mellitus.

Method: Derivatives of quercetin were designed with ChemDraw. The targets: α-amylase (AA), Dipeptidyl peptidase (DPP4); Peroxisome proliferator-activated receptor gamma (PPARG); Glycogen synthase kinases 3β (GSK3); Fructose-1,6-diphosphatase (F16DP); α-glucosidase (AG); Protein Tyrosine Phosphatase 1B (PTP1B); Glucokinase (GK) were downloaded from the Protein data bank. Ligands and targets were converted to pdbqt format using PyRx. Molecular docking of the ligands with each of the target proteins was done using Autodock Vina. Discovery Studio was used to analyse ligand-protein binding interactions. Calculated molecular and pharmacokinetic properties were obtained from molinspiration and pKCM websites, respectively.

***Results*:** Ligands with the best binding affinity on the various targets are AA (ligand 63: -9.2; quercetin: -8.8), AG (ligand 39: -7.9; quercetin: -7.5), DPP4 (ligand 15: -8.8; quercetin: -9.1), PPARG (ligand 23 and 31: -10.3; ligand 15: -10.1; quercetin: -8.8), F16DP (ligand 2, 34, and 47: -6.6; quercetin: -6.2); GSK3 (ligand 15: -8.1; quercetin: -7.9), PTP1B (ligand 26: -9.3; quercetin: -8.9), GK (ligand 37: -9.7; quercetin: -8.7). Ligands that had good binding activity on more than one target are: Ligand 15 (AA, PPARG, and DPP4), Ligand 39 (AA and DPP4), Ligands 25 and 31 (PPARG and PTB1B).

***Conclusion*:** Some of the derivatives had better binding affinity than quercetin on various targets are potential candidates for the treatment of diabetes.

***Keywords*:** Autodock, diabetes, *in silico* quercetin

1.0 INTRODUCTION

Diabetes mellitus (DM) is a disease that has existed for over 2000 years [1]. According to King and Roewers [2], an epidemic of DM is occurring in adults throughout the world. DM is currently estimated to affect about 2% of the world's population. Insulin injection has been the main remedy. However, it has been established that insulin does not restore normal glycemic levels. Therefore, in recent times, there is a resurgence in the search for non-insulin agents for the treatment of DM. Several studies support the innate potential of phenolic compounds to protect against DM associated deleterious effects by regulation of carbohydrate metabolism; improvement of glucose uptake; protection of pancreatic β-cells; enhancement of insulin action; and regulation of crucial signaling pathways to cell homeostasis. Dietary phenolic compounds constitute an easy, safe, and cost-effective way to combat the worrying scenario of DM. Polyphenols such as Quercetin are known to exhibit antidiabetic activity in Type 2 DM due to their antioxidant property [3]. Quercetin can chelate metal ions which in turn induces DNA break in the parasite by increasing intercellular ROS levels in the parasite thereby causing parasite death. This is in line with a report by [4] on intercellular parasite death by DNA invasion caused by artesunate's binding with

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the exogenous heme/ non-heme Fe^{2+} (Figure 14 b). It is hereby postulated that derivatives of quercetin may possess better antidiabetic potential than Quercetin. This study is therefore aimed at designing and evaluating the *in-silico* antidiabetic potentials of some quercetin derivatives on eight molecular targets related to carbohydrates and lipids metabolism, as well as signal transduction pathways in diabetes pathophysiology. The enzyme targets are alpha-amylase, α-glucosidase; Dipeptidyl peptidase IV; Peroxisome proliferator-activated receptor gamma; Glycogen synthase kinases 3β; Fructose -1,6-diphosphatase; Protein Tyrosine Phosphatase 1B; and Glucokinase [5, 6].

2.0 METHODOLOGY

Derivatives of quercetin were designed with ChemDraw Pro 12.0 (CambridgeSoft Corporation, USA) and saved in SDF format. The target proteins - Alpha-amylase B in complex with acarbose (3BC9), Dipeptidyl peptidase IV (2QOE); Peroxisome proliferator-activated receptor gamma (1PRG); Glycogen synthase kinases 3β (1H8F); Fructose -1,6-diphosphatase (5QUC); α-glucosidase (5KZW); Protein Tyrosine Phosphatase 1B (5T19); Glucokinase (1SZ2) were downloaded in PDB format from the Protein data bank (http://www.rcsb.org/pdb/home/home.do). Ligands and targets were converted to pdbqt format using PyRx (https://pyrx.sourceforge.io/). Molecular docking of the ligands with each of the target proteins was done using Autodock Vina (http://vina.scripps.edu/), to obtain their respective binding affinity. The grid box parameters are shown in Table 1. Discovery Studio (Dassault Systèmes), and Ligplot (https://www.ebi.ac.uk/thornton-srv/software/LIGPLOT/) were used to analyse ligand-protein binding interactions. Calculated molecular properties were obtained from molinspiration website (https://www.molinspiration.com/cgi-bin/properties), while pharmacokinetic properties from pKCMwebsite (http://biosig.unimelb.edu.au/pkcsm/prediction).

Table 1: Grid box parameters

S/N	Target	center_x	center_y	center_z	size_x	size_y	size_z
1	AA	41.4618	35.2761	15.6444	4.0968	71.9999	69.1222
2	DPP-4	45.4295	54.4219	39.5087	74.0047	75.9207	73.5099
3	PPARG	11.1795	52.1465	17.6671	52.9452	55.2913	53.9993
4	GSK3	27.7949	5.6915	40.8901	67.1973	66.0468	63.6270
5	F1,6DP	34.9929	2.5696	20.2089	57.7617	58.7643	55.2578
6	PTP1B	-2.7540	58.2487	14.6191	58.7433	49.6285	35.9518
7	GK	29.2803	0.3592	70.2534	51.1599	70.3666	57.4357
8	AG	2.2180	17.4333	16.8119	79.0173	77.6834	73.2336

AA- Alpha-amylase; DDP-4 – Dipeptidyl peptidase IV; PPARG – Peroxisome proliferator-activated receptor gamma; GSK3 – Glycogen synthase kinases 3β; F1,6DP – Fructose -1,6-diphosphatase; AG – α-glucosidase; PTB1B -Protein Tyrosine Phosphatase 1B; GK – Glucokinase

3.0 RESULTS

Table 2 shows the structural features of the quercetin derivatives (ligands) that were designed and used in this study.

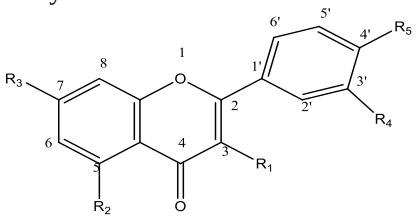

Figure 1: Quercetin nucleus

Table 2: Ligands and reference compounds

S/N	R1	R2	R3	R4	R5	Others/Name
1	OH	OH	OH	OH	OH	Quercetin
2	OH	OH	OH	----	---	C=O at C2 &Ar at C3
3	OH	OH	H	OH	OH	----

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4	OH	OH	OH	OH	H	----
5	OH	OH	OH	H	OH	
6	OH	OH	OH	OH	OH	-OH, in place of =O at C4
7	OH	OH	OH	OCH_3	OH	-------
8	OH	OCH_3	OH	OH	OH	---
9	OH	OCH_3	OCH_3	OH	OH	---
10	OH	OH	OH	OH	OCH_3	---
11	OH	OH	OH	OCH_3	OH	---
12	OH	OCH_3	OCH_3	OCH_3	OCH_3	---
13	OCH_3	OCH_3	OCH_3	OCH_3	OCH_3	---
14	OCH_3	OH	OH	OH	OH	OH at 5’
15	OH	OH	OH	OH	OH	No double bond between C2 and C3
16	OH	OH	OH	OH	OH	No double bond between C2 and C3--
17	$OCOCH_3$	OH	OH	OH	OH	No C=O at C4
18	$OCOCH_3$	OH	OH	OH	OH	No C=O at C4 No C=O at C4
19	$OCOCH_3$	OH	OH	OH	OH	No C=O at C4, No double bond between C2 & C3
20	OH	OH	OH	OH	OH	
21	H	OH	OH	OH	OH	
22	H	OH	OH	OH	OH	
23	$OCOCH_2CH_3$	OH	OH	OH	OH	
24	$OCOCH2CH_2CH_3$	OH	OH	OH	OH	
25	$OCOCH(CH_3)_2$	H	OH	OH	OH	
26	$OCOC(CH_3)_3$	H	OH	OH	OH	No double bond between C2 and C3
27	$OCOC(CH_3)_3$	OH	OH	OH	OH	No double bond between C2 and C3
28	$OCOC(CH_3)_3$	OH	OH	OH	OH	No double bond between C2 and C3
29	$OCOCH_2CH_3$	OH	OH	OH	OH	
30	$OCOCH_2CH_3$	OH	OH	OH	OH	OH, at C4
31	$OCOC(CH_3)_3$	OH	OH	OH	OH	No C=O at C4
32	H	H	H	H	H	
33	OH	H	OH	OH	OH	
34	Ar	OH	OH	-	----	$OCOCH_3$ at C2
35	Ar	OH	OH	OH	----	OCOCH2CH3 at C2
36	Ar	OH	OH	OH	----	$OCOCH_2CH_2CH_3$ at C2
37	Ar	OH	OH	OH	----	$OCOCH(CH_3)_2$ at C2
38	Ar	OH	OH	OH	-----	$OCOCH(CH_3)_2$ at C2, No C=C between C2& C3
39	Ar	OH	OH	OH	---	
40	$OCOCHCH_3CH_2CH_3$	OH	OH	OH	OH	2-Methylbutanoate
41	$OCOCHCH_3(CH_2)_2CH_3$	OH	OH	OH	OH	2-Methylhexanoate
42	$OCOCH_2CH(CH_3)_2$	OH	OH	OH	OH	3-Methylbutanoate
43	$OCOCH2CH_2CH_2(CH_3)CH_2CH_3$	OH	OH	OH	OH	4-methylhexanoate
44	$OCO(CH_2)_3CH(CH_3)_2$	OH	OH	OH	OH	5-Methylhexanoate
45	$OCOC_{19}H_{34}$	OH	OH	OH	OH	Arachidonoate
46	$OCO(CH_2)_2CH_3$	OH	OH	OH	OH	Butanoate
47	$OCOCH_2C(OH)(COOH)CH_2COOH$	OH	OH	OH	OH	Citroate
48	$OCO(CH_2)_8CH_3$	OH	OH	OH	OH	Decanoate

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49	OCHO	OH	OH	OH	OH	Formoate
50	OCOCH=CHCOOH	OH	OH	OH	OH	Fumareate
51	$OCO(CH_2)_2CHNH_2COOH$	OH	OH	OH	OH	Glutamoate
52	$OCO(CH_2)_2CH_2COOH$	OH	OH	OH	OH	Glutaroate
53	$OCO(CH_2)_4CH_3$	OH	OH	OH	OH	Hexanoate
54	$OCOCH(CH_3)_2$	OH	OH	OH	OH	Isobutanoate
55	$OCOCHOHCH_3$	OH	OH	OH	OH	Lactoate
56	$OCO(CH_2)_{10}CH_3$	OH	OH	OH	OH	Lauroate
57	$OCOC_{17}H_{29}$	OH	OH	OH	OH	Linoleoate
58	$OCOCH_2CHOHCOOH$	OH	OH	OH	OH	Maleoate
59	$OCO(CH_2)_6CH_3$	OH	OH	OH	OH	Octanoate
60	$OCOC_{19}H_{38}$	OH	OH	OH	OH	Oleate
61	$OCOC_{15}H_{34}$	OH	OH	OH	OH	Palmitate
62	$OCO(CH_2)_3CH_3$	OH	OH	OH	OH	Pentanoate
63	$OCOCH=CHCH=CHCH_3$	OH	OH	OH	OH	Sorbate
64	$OCO(CH_2)_{16}CH_3$	OH	OH	OH	OH	Stearate
65	OCOCHOHCHOHCOOH	OH	OH	OH	OH	Tartarate
66	$OCO(CHOH)_4CH_2OH$	OH	OH	OH	OH	Ascorboate
67	Acarbose	---	----	----	-----	Acarbose
68	Empagliflozin	----	----	-----	------	Empagliflozin
69	Metformin	----	----	-----	------	Metformin
70	NADH	----	----	-----	------	NADH
71	Pioglitazone	----	----	-----	------	Pioglitazone
72	Thiazolinedione	----	----	-----	------	Thiazolidinedione

The binding affinity values for the ligands and the reference compounds used are shown in Table 3.

Table 3: Binding affinity (kcal/mol) of the ligands and reference compounds obtained from Autodock vina [7].

S/N	AA	GSK3	F1,6DP	PPAR	GK	DPP4	AGCS	PTB
1	-8.8	-7.9	-6.2	-9.8	-8.7	-8.8	-7.5	-8.9
2	-8.8	-7.4	-6.6	-8.9	-7.8	-8.1	-7.6	-7.0
3	-8.6	-7.6	-6.2	-9.9	-8.6	-8.4	-7.2	-8.8
4	-9.1	-7.6	-6.1	-9.6	-8.7	-8.6	-7.6	-8.2
5	-8.2	-7.9	-6.2	9.5	-8.3	-8.3	-7.3	-8.1
6	-8.5	-7.9	-6.3	-9.8	-8.1	-8.8	-7.2	-8.8
7	-8.5	-7.7	-6.1	-9.5	-8.6	-8.7	-7.4	-8.7
8	-8.3	-7.8	-6.2	9.5	-8.6	-8.5	-7.0	-8.7
9	-8.0	-7.6	-6.0	9.5	-8.6	-8.5	-7.0	-8.5
10	-8.5	-7.7	-6.2	-9.6	-8.7	-8.9	-7.2	-8.4
11	-8.5	-7.5	-6.0	-9.7	-7.7	-8.1	-7.6	-8.6
12	-7.1	-7.0	-5.8	9.0	-7.4	-7.7	-6.4	-7.4
13	-6.7	6.9	5.3	8.3	-7.0	-7.5	-6.7	-7.2
14	-8.5	-7.6	-5.8	-9.4	-7.8	-8.5	-7.3	-8.7
15	-8.8	-8.1	-6.1	-10.1	-8.5	-9.1	-7.9	-8.9

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16	-8.7	7.7	-6.3	-10.0	-8.3	-8.9	-7.6	-8.6
17	-9.0	-7.7	-5.9	-9.2	-8.4	-8.2	-7.7	-8.3
18	-9.1	-7.8	-6.0	9.9	8.2	-8.5	-7.8	-9.0
19	-8.9	-7.8	-5.9	-8.8	-7.9	-8.4	-7.7	-9.2
20	-8.8	-7.8	-5.9	-9.4	-7.9	-8.7	-7.4	-9.1
21	-8.4	-7.8	-5.9	-9.0	-9.5	-8.0	-7.3	-9.1
22	-8.4	-7.5	-5.9	-8.8	-9.0	-8.3	-7.2	-9.1
23	-9.1	-7.6	-5.7	-9.8	-8.0	-8.4	-7.7	-7.0
24	-8.8	-7.5	-5.7	-9.2	-8.0	-8.4	-7.2	-8.7
25	-8.8	-7.7	-5.9	-10.0	-8.2	-8.8	-7.6	-9.2
26	-8.9	-7.5	-6.0	-10.3	-8.1	-8.7	-7.8	-9.3
27	-8.8	7.1	-6.2	-9.3	-8.0	-8.6	-7.6	-6.9
28	-8.6	7.2	-6.3	-9.8	-8.6	-8.6	-7.8	-9.1
29	-8.6	-7.7	-6.0	-9.7	-7.9	-7.8	-7.8	-8.8
30	-9.0	-7.7	-6.0	-9.9	-7.9	-8.3	-7.6	-9.1
31	-9.0	-7.4	-6.2	-10.3	-8.1	-8.8	-7.5	-9.2
32	-7.4	-6.9	-5.6	-8.5	-9.0	-7.7	-6.7	-8.0
33	-8.6	-7.7	-6.0	-9.7	-9.1	-8.8	-7.3	-8.8
34	-7.7	-7.5	-6.6	-9.2	-7.6	-8.8	-7.1	-8.6
35	-8.0	-7.0	-6.4	-9.4	-7.3	-7.8	-7.0	-8.4
36	-8.0	-6.9	-6.3	-9.4	-8.4	-8.0	-6.7	-6.4
37	-8.6	-7.6	-6.6	-9.9	-9.7	-8.2	-7.9	-8.9
38	-7.9	-7.3	-6.6	-9.7	-7.5	-8.4	-7.6	-7.2
39	-8.5	-7.6	-6.5	-9.9	-7.4	-9	-7.9	-7.4
40	-8.7	-6.9	-5.8	-8.0	-7.3	7.9	-7.3	-7.2
41	-8.5	-7.3	-5.5	-9.1	-7.2	8.1	-7.1	-6.8
42	-8.9	-7.3	-5.9	-8.9	-7.3	8.1	-7.1	-7.0
43	-8.4	-7.0	-6.1	-9.2	-8.9	-8.3	-7.5	-7.2
44	-8.6	-7.3	-5.9	-9.0	-7.4	-8.2	-7.2	-7.1
45	X	-8.0	-4.3	-8.6	-9.2	-8.1	-6.2	-7.3
46	-9.0	-6.9	-5.8	-7.8	-7.4	-7.6	-7.2	-7.0
47	-7.9	-6.0	-6.6	-9.2	-8.4	-7.7	-7.2	-7.8
48	-7.8	-6.3	-5.0	-7.0	-9.0	-7.7	6.7	-5.9
49	-8.5	-7.2	-6.1	-8.6	-7.4	-7.7	-6.9	-7.1
50	-8.9	-7.6	-6.7	-9.0	-8.0	-7.9	-7.8	-8.2
51	-8.6	-6.9	-6.3	-8.9	8.0	-7.3	-7.1	-7.9
52	-8.6	-7.8	-6.2	-8.9	-7.8	-7.7	-7.1	-7.7
53	-8.8	-7.0	-5.8	-8.7	-8.3	-7.2	-7.2	-7.2
54	-8.9	-7.6	-6.0	-9.0	-7.2	-7.9	-7.4	-7.3
55	-8.7	-7.4	-6.4	7.1	-7.8	-7.9	-7.5	-8.4
56	-8.1	-6.3	-5.3	9.0	-7.4	-7.6	-5.6	-6.3
57	-7.9	-7.2	-4.6	-10.0	-8.2	8.2	-6.0	-7.5
58	-8.8	-7.8	-6.3	-8.8	-8.3	8.1	-7.4	-7.9
59	-8.3	-6.7	-5.7	-8.8	-6.6	-7.5	-6.9	-6.9
60	-7.5	-6.6	-5.2	-9.4	-8.5	-7.0	-5.4	-6.0
61	-7.7	-5.8	-4.8	-8.7	-6.8	-6.9	-6.0	-6.0

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62	-8.9	-7.1	-5.9	-8.5	-7.4	-7.9	-7.2	-7.0
63	-9.2	-7.4	-6.4	-9.5	-7.6	-8.1	-7.6	-7.4
64	-7.61	-6.3	-4.3	-8.9	-8.4	-7.6	-5.4	-5.3
65	-8.8	-7.6	6.4	7.9	-8.4	-8.1	-7.9	-7.7
66		-7.5	-6.0	-8.8	-8.0	-7.6	-6.5	-6.8
67	-8.2	-8.6	-7.0	-8.2	-9.1	-9.6	-9.0	-7.5
68	-7.4	-7.6	-6.0	-9.5	-7.7	-8.4	-7.4	-8.2
69	-5.2	-4.8	-3.9	-5.0	-5.1	-5.0	-4.8	-4.8
70	-8.0	-8.2	-5.8	-10.0	-9.6	-8.8	-8.7	-7.9
71	-7.3	-6.8	-5.6	-9.1	-8.3	-7.5	-6.6	-7.1
72	-3.7	-4.2	-2.9	-4.3	5.1	-4.8	-4.0	-4.9

Table 4 shows the result of the biological and pharmacokinetic parameters of the ligands as obtained at the pkCSM website.

Table 4: Biological and pharmacokinetics properties of the ligands

Ligand	MW	logP	No. Acc	No. Don	Int Abs	Tot Clr	LD50	LOAEC	No. of violations
1	302	1.99	7	5	74.6	0.55	2.56	1.74	None
2	270	1.98	5	2	93.5	0.24	2.04	1.77	None
3	286	2.28	6	4	84.8	0.1	2.37	1.92	None
4	286	2.28	6	4	79.7	0.31	2.45	1.35	None
5	286	2.28	6	4	79.5	0.58	2.46	1.29	None
6	292	1.97	1	0	95.2	0.95	2.59	1.28	None
7	304	2.96	3	0	97.6	0.99	2.17	1.03	None
8	304	2.96	3	0	97.7	0.99	2.31	1.02	None
9	316	2.74	4	0	100.0	0.99	2.42	1.01	None
10	304	2.96	3	0	97.3	0.97	2.26	1.30	None
11	304	2.96	3	0	97.2	0.97	2.20	1.33	None
12	340	2.30	6	0	99.0	0.97	2.47	1.03	None
13	352	2.08	7	0	100.0	0.98	2.40	1.01	None
14	304	2.96	3	0	97.7	0.10	2.08	1.08	None
15	308	3.52	2	0	100	0.94	2.26	1.52	None
16	292	2.38	2	0	100	0.91	2.18	1.29	None
17	332	2.08	4	0	89.0	0.93	2.34	1.43	None
18	332	2.53	4	0	90.4	1.07	2.20	1.07	None
19	316	1.72	3	0	97.0	0.96	2.49	1.35	None
20	276	2.01	1	0	11.9	0.97	2.41	1.35	None
21	260	2.06	1	0	98.3	1.00	2.26	1.41	None
22	260	2.75	1	0	97.5	0.88	2.03	1.37	None
23	358	2.60	8	4	82.9	0.48	2.23	2.37	None
24	356	2.69	4	0	94.4	1.23	2.27	0.98	None
25	356	2.69	4	0	89.5	1.21	2.25	1.11	None
26	368	2.69	4	0	93.4	1.24	2.38	1.05	None

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27	368	2.24	4	0	85.3	1.13	1.88	1.79	None
28	356	2.24	4	0	86.3	1.08	1.87	1.76	None
29	344	2.16	4	0	86.8	1.03	1.86	1.72	None
30	344	1.75	3	0	90.5	1.03	2.69	1.36	None
31	368	1.83	3	0	89.1	1.20	2.63	1.44	None
32	208	3.66	1	0	96.6	0.17	1.96	1.16	None
33	276	2.84	2	0	100.0	1.01	2.29	1.29	None
34	300	1.84	4	0	93.4	1.16	2.36	1.37	None
35	312	1.92	4	0	93.1	1.24	2.41	1.35	None
36	324	2.01	4	0	92.7	1.32	2.44	1.41	None
37	324	2.01	4	0	92.5	1.29	2.45	1.36	None
38	324	1.56	4	0	93.2	0.98	2.35	1.49	None
39	324	1.15	3	0	93.1	1.17	2.18	1.52	None
40	372	1.02	8	4	68.3	0.97	2.43	1.77	None
41	396	1.18	8	4	67.3	1.14	2.50	1.82	None
42	372	1.02	8	4	64.7	0.89	2.42	2.78	None
43	396	1.18	8	4	63.7	1.04	2.43	2.82	None
44	396	1.18	8	4	67.4	1.14	2.51	1.73	None
45	552	2.24	8	4	56.2	1.8	2.30	3.18	1
46	360	0.94	8	4	68.9	0.92	2.43	1.69	None
47	467	-0.75	11	7	00.0	0.86	2.49	3.69	2
48	432	1.43	8	4	65.5	1.42	2.55	2.31	None
49	324	0.73	8	4	66.7	0.68	2.37	2.78	None
50	393	0.44	9	5	34.3	0.85	2.66	3.08	None
51	421	-0.07	10	6	32.3	0.37	2.50	2.66	None
52	405	0.52	9	5	36.4	0.85	2.69	3.10	None
53	384	1.10	8	4	67.9	1.09	2.50	1.74	None
54	360	0.94	8	4	68.7	0.89	2.38	1.80	None
55	365	0.68	9	5	64.4	0.81	2.41	1.94	None
56	456	1.59	8	4	64.2	1.59	2.54	2.61	No
57	528	2.08	8	4	60.9	1.83	2.50	3.22	1
58	410	0.26	10	6	21.7	0.77	2.58	3.55	None
59	408	1.26	8	4	66.7	1.25	2.54	1.99	None
60	528	2.08	8	4	60.5	2.01	2.50	3.21	Yes
61	504	1.91	8	4	61.6	1.92	2.52	3.11	1
62	372	1.02	8	4	68.5	1.00	2.47	1.65	None
63	384	1.10	8	4	64.7	0.93	2.41	2.85	None
64	528	2.08	8	4	60.3	-1.14	2.50	3.20	1
65	427	0.08	11	7	13.2	0.79	2.48	3.51	2
66	452	0.39	12	8	44.1	0.77	2.63	4.44	1

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3.1. Alpha-Amylase

The 3D structure of alpha-amylase and its interactions with some ligands are shown in figures 2a-2k.

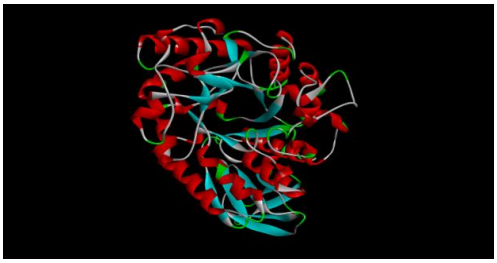


Figure 2a: 3D structure of Alpha-amylase

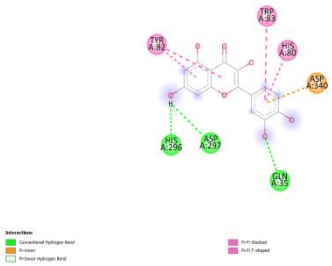


Figure 2b: Acarbose - AAM Interactions (-8.2)

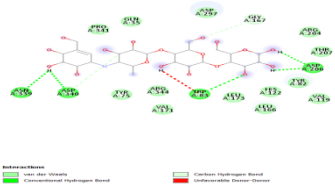


Figure 2c: Quercetin – AAM Interactions (-8.8)

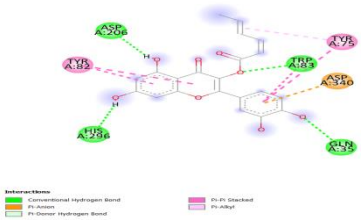
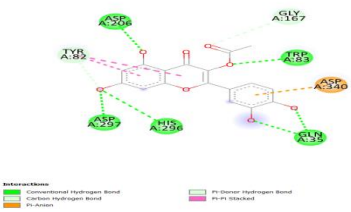


Figure 2d: Quercetin – 3-Sorboate: AAM Interactions (-9.2)



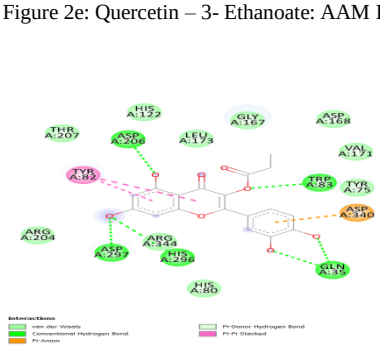


Figure 2e: Quercetin – 3- Ethanoate: AAM Interaction (-9.1)

Figure 2f: Quercetin – 3- propionoate: AAM Interaction (-9.1)

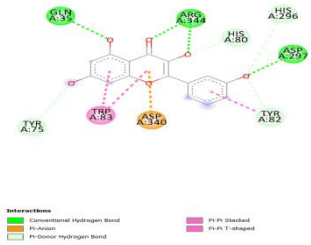


Figure 2g: Quercetin with 5' OH group missing (-9.1)

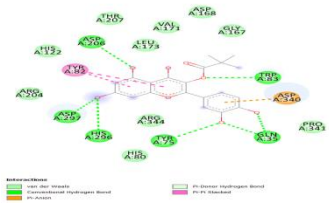


Figure 2h: Quercetin -3- Isopropanoate: AAM Interaction (-9.0)

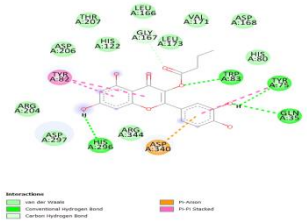


Figure 2i: Quercetin – 3- butanoate: AAM interactions(-9.0)

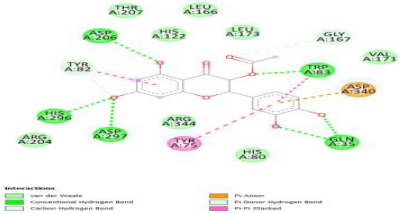


Figure 2j: Quercetin - 3- ethanoate with no double bond between C2 and C3 (-9.0)

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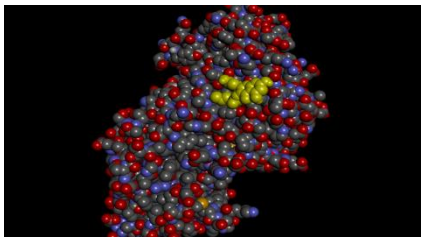

Figure 2k: AAM: Quercetin -3 –sorboate (Discovery studio)

3.2. **Alpha-glucosidase**

The 3D structure of alpha-glucosidase and its interactions with some ligands are shown in figures 3a-3b.

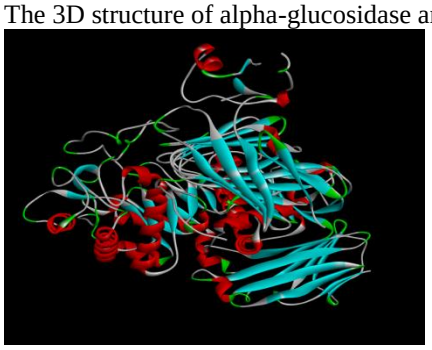

Figure 3a: 3D structure of alpha-glucosidase

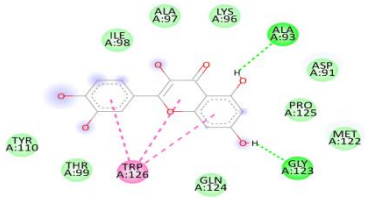

Figure 3b: Alpha-glucosidase – Quercetin interactions

3.3. Dipeptidyl peptidase-4 (DPP-4)

The 3D structure of Dipeptidyl peptidase-4 and its interactions with some ligands are shown in figures 4a-4e

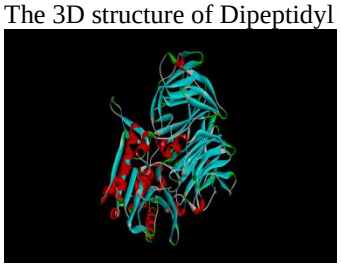

Figure 4a: 3D structure of Dipeptidyl peptidase-4 (DPP-4)

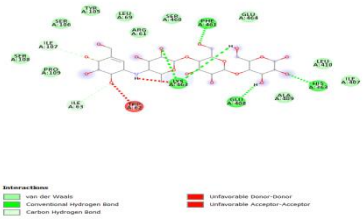

Figure 4c: DPP4 – Acarbose Interactions (-9.6)

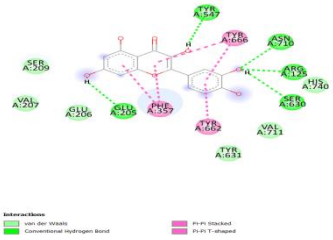

Figure 4b: DPP4 – Quercetin Interactions (-8.8)

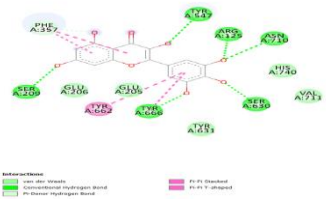

Figure 4d: DPP4 – Ligand 15 Interactions (-9.1)

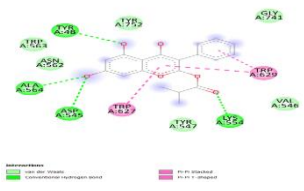

Figure 4e: DPP4 – Ligand 39 Interactions (-9.0)

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3.4. Peroxisome proliferator-activated receptor-GAMMA (PPARG)

The 3D structure of the Peroxisome proliferator-activated receptor and its interactions with some ligands are shown in figures 5a-5j.

Figure 5a: 3D structure of PPARG

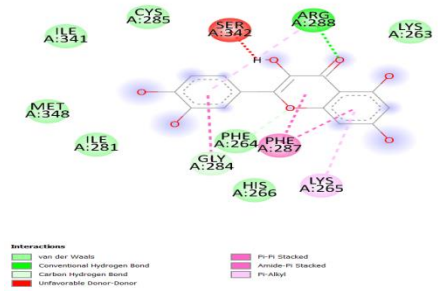

Figure 5b: PPARG – Quercetin Interactions (-8.8)

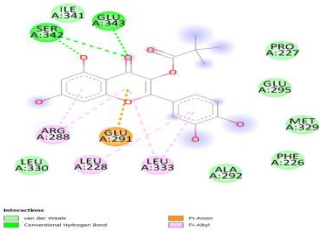

Figure 5c: PPARG – Ligand 26 Interactions (10.3)

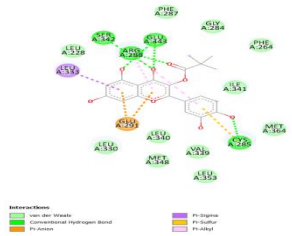

Figure 5d: PPARG – Ligand 31 Interactions (-10.3)

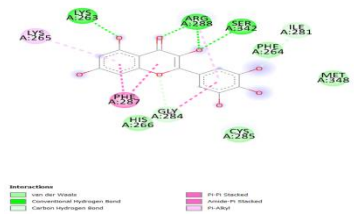

Figure 5e: PPARG – Ligand 15 Interactions (-10.1)

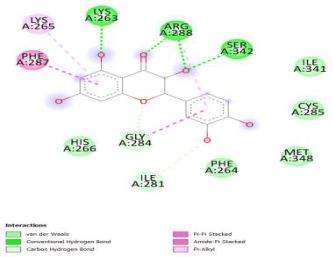

Figure 5f: PPARG – Ligand 16 Interactions (-10.0)

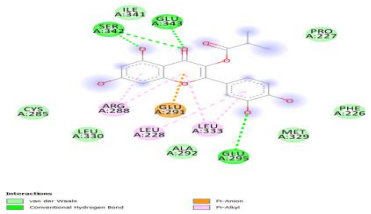

Figure 5g: PPARG – Ligand 25 Interactions (-10.0)

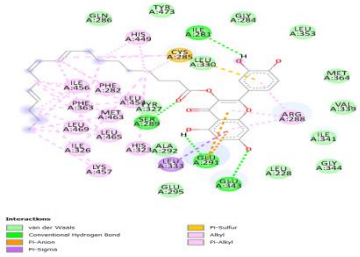

Figure 5h: PPARG – Ligand 57 Interactions (-10.0)

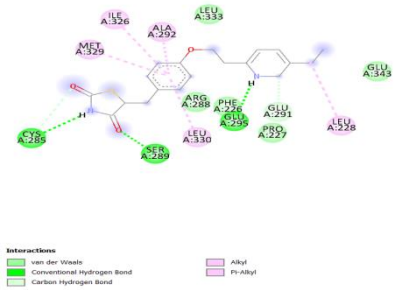

Figure 5i: PPARG – Pioglitazone Interactions (-9.1)

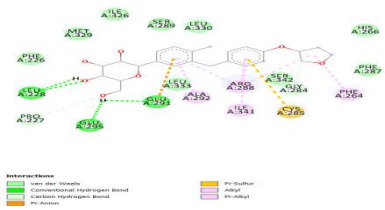

Figure 5j: PPARG - Empagliflozin Interactions (-9.5)

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3.5 Glycogen synthase kinase-3 (GSK3)

The 3D structure of Glycogen synthase kinase-3 and its interactions with some ligands are shown in figures 6a-6b

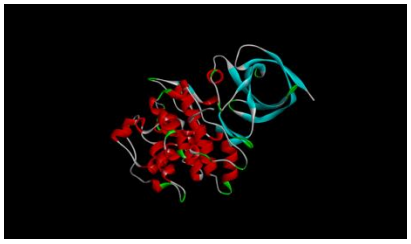

Figure 6a: 3D structure of GSK3

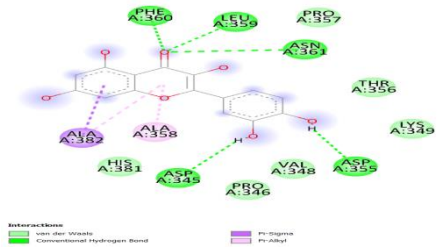

Figure 6b: GSK3-Quercetin Interactions

3.6 Fructose-1,6-biphosphate (F16DP)

The 3D structure of Fructose -1,6-biphosphate and its interactions with some ligands are shown in figures 7a-7b

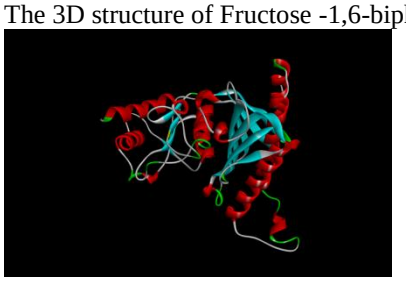

Figure 7a: 3D structure of Fructose -1,6-biphosphate

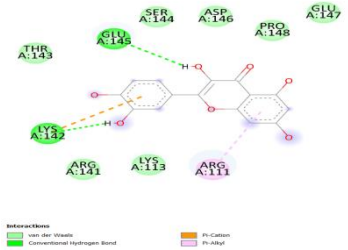

Figure 7b: F16BP – Quercetin Interactions

3.7. Protein Tyrosine Phosphatase 1B (PTP1B)

The 3D structure of Protein Tyrosine Phosphatase and its interactions with some ligands are shown in figures 8a-8b

Figure 8a: 3D structure of Protein Tyrosine Phosphatase 1B

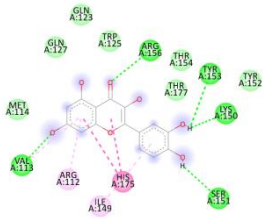

Figure 8b : PTP1B- Quercetin interaction

3.8 Glucokinase

The 3D structure of 8. Glucokinase and its interactions with some ligands are shown in figures 9a-9b

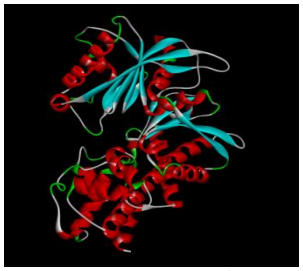

Figure 9a : 3D structure of Glucokinase

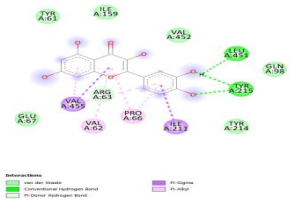

Figure 9b: GLUCK – Quercetin Interactions

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The amino acid residues of target proteins involved in interactions with ligands are shown in Table 5

Table 5: Amino acid residues of target proteins involved in interactions with ligands

S/N	Target protein	H-bonding	Pi anion/Pi sigma	Pi Cation	Pi-pi stacked	Pi alkyl
1	AA	Trp83, Asp206, His296, Asp297, Gln35	Asp340	-	Tyr82	-
2	DPP4	Arg125, Asn710, Ser630, and Tyr547	-	-	Tyr662, Phe357, Tyr666	-
3	PPARG	Mostly Arg288, Ser342, and in some cases	-	-	-	-
4	AG	Glu343, Lys263	-	-	-	-
5	F16DP	GLU145, Lys142	-	Lys142	-	Arg111
6	GSK3	Phe360, Leuc359, Asn361, Asp345, Asp355	-	-	His175	Ala358, Ala382
7	PTP1B	Val113, Ser151, Lys150, Tyr153, Arg156	-	-	-	Arg112, Val113, Ile149
8	GK	Tyr215, Leu451	Ile211, Val455	-		Pro66, Val62, Val455

AA- Alpha-amylase; DDP-4 – Dipeptidyl peptidase IV; PPARG – Peroxisome proliferator-activated receptor gamma; GSK3 – Glycogen synthase kinases 3β; F1,6DP – Fructose -1,6-diphosphatase; AG – α-glucosidase; PTB1B -Protein Tyrosine Phosphatase 1B; GK – Glucokinase

4.0 DISCUSSION

Alpha-amylase

Interactions essential to AAM inhibitory activity are H-bonging of the OH groups and ether Oxygen of ligand to Trp83, Asp206, His296, Asp297, Gln35. Pi anion interaction between Asp340 residue and ring B of the ligand. Pi-Pi interaction between Tyr82 and ring A of ligand. Pi –pi interaction between Tyr82 and either Ring B or cyclic ring of the ligand. For ligand 63 (quercetin-3-sorboate) with the lowest binding affinity, there are 4 Pi-pi stacked interactions: 1 with Tyr75, 2 with Tyr82, and 1 with Trp83. Sorbic acid has 3 alternate (conjugated) double bonds. Its 6 Pi electrons can therefore be delocalized. Unlike the other ligands, Tyr75 is also involved in Pi-alkyl interactions with the second double bond on the hydrocarbon side chain. An increase in the chain length of ligands did not lead to an increase in binding. Acids with straight chains showed better activities than their respective branch chains. One of the two OH groups on Ring B is sufficient for activity. Ligand 18, 23, 24 and 63 (ethanoate, propionate, butanoate, and Sorbate esters of quercetin) exhibited higher *in silico* alpha-amylase inhibitory activity and could therefore serve as leads for more potent anti-diabetic compounds. α-Amylase catalyzes the hydrolysis of α-1,4-glucan bonds in starch, maltodextrins and maltooligosaccharides thereby aiding in the digestion of carbohydrates [5]. Inhibition of this enzyme, therefore, retards the production of glucose in the GIT and its attendant hyperglycaemia.

Alpha-glucosidase

Binding affinities of acarbose and quercetin are -9.0 and -7.5, respectively. None of the ligands had a binding affinity that was better than acarbose, the reference compound. Ligands 15, 37, and 39 had a binding affinity of -7.9, while ligand 50 had -7.8. In the target – quercetin binding interactions, Ala93 Gly123 were H-bonded to the OH group at positions 6 and 8, respectively. The pi-pi stacked interaction involved Trp126 and rings A and B, plus the cyclic ring. Alpha-glucosidase is a member of the glycoside hydrolase enzyme which breaks the glycosidic linkage from carbohydrates, thereby increasing their absorption. Inhibition of this enzyme in the small intestine, therefore, slows down the digestion of carbohydrates thereby preventing hyperglycemia [5]. Ligands 15, 37, 39 and 50 which had binding affinity that was comparable to or slightly better than that of quercetin could be considered good candidate compounds for the treatment of diabetes based on their action on this enzyme.

Dipeptidyl peptidase-4 (DPP-4)

Bonds involved in the interactions between DPP-4 and quercetin (Binding Affinity of -8.8 (kcal/mol)) are Hydrogen bonding: Arg125, Asn710, and Ser630 with C3' OH; Glu205 with C7 OH; Tyr547 with C3 OH. Pi pi stacked Interactions: Tyr662, Phe357, Tyr666. Ligand 15 (Binding Affinity of -9.1 (kcal/mol)). Hydrogen bonding: Arg125, Asn710, and Ser630 with C3' OH; Tyr547 with C3 OH; Ser209 with C7 OH; Tyr 666 – C5' OH; Phe357 – C5 OH. Pi pi stacked Interactions: Tyr662, Phe357, Tyr666. Ligand 39 (Binding Affinity of -9.0 (kcal/mol)). Hydrogen bonding: Tyr48 – C5 OH, Lys554 – ester carbonyl group, Asp545 – C7 OH (twice), Ala564 – C7 OH. Pi - pi stacked Interactions: Trp627-cyclic group, Trp629 - cyclic, Trp625-Aryl group. Key protein residues involved in H-bonding are Arg125, Asn710, and Ser630 with C3' OH; Glu205 with C7 OH; Tyr547. Important ligand residues are C3' OH, C7 OH. Ligand 15 had additional ones: C5' OH and C5 OH. Key residues involved in pi-pi stacked interactions are Tyr662, Phe357, Tyr666. DPP-4, an attractive target diabetes treatment,

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hydrolyzes Glucagon-Like Peptide-1 (GLP1) which is an incretin hormone that is secreted in the digestive tract. GLP1 is involved in insulin and glucagon secretion, increase in pancreatic P-cell mass, and reduction of gastric emptying [8]. Ligands 15 and 39 which had better binding affinity than that of quercetin could serve as lead compounds in the management of diabetes through their action on DPP4.

PPARG

Bonds involved in the interactions between PPARG, and quercetin are Hydrogen bonding: Arg288 with C4 carbonyl group. Pi - pi Interactions: Phe287 with ring A and cyclic ring, Gly287 with ring B. Pi alkyl interactions: Ring B with Arg288. Bonds involved in the interactions between PPARG, and other ligands are Ligand 26 (Binding Affinity of -10.3 (kcal/mol)). Hydrogen bonding: Ser342 with C4 carbonyl and C5 hydroxyl group, Glu343 with C4 carbonyl group. Pi Anion Interactions: Glu 291. Pi - pi Interactions: None. Pi alkyl interactions: Leu333 with ring B, Leu228 and Arg288 with ring B and cyclic ring Ligand 31 (Binding Affinity of -10.3 (kcal/mol)). Hydrogen bonding: Arg288 with C4 carbonyl oxygen, Ser342 with C4 OH group and C5 OH groups, Cys285 with 4' OH Pi Anion Interactions: Glu 291 with ring A and cyclic ring, Leu383 with ring A (Pi Sigma), Cys285 with ring B (Pi sulfur). Pi - pi Interactions: None. Pi alkyl interactions: Arg288 with ring B and cyclic ring. Ligand 15 (Binding Affinity of -10.1 (kcal/mol)). Hydrogen bonding: Arg288 with C3 OH and C4 carbonyl groups, Ser342 with C3 OH, Lys263 with C5 OH, Gly284 with O1 and 3' OH. Pi Anion Interactions: None. Pi-pi Interactions: Phe287 with ring A and cyclic ring, Gly284 with ring B. Pi alkyl interactions: Lys265 with ring A, and Arg288 with ring B. Ligand 16 (Binding Affinity of -10.0 (kcal/mol)). Hydrogen bonding: Arg288 with C3 OH and C4 carbonyl groups, Ser342 with C3 OH, Lys263 with C5 OH, Gly284 with O1 and 3' OH. Pi Anion Interactions: None. Pi- pi Interactions: Phe287 with ring A and cyclic ring. Pi alkyl interactions: Lys265 with ring A, Ile281 with ring A, and Arg288 with ring B. Ligand 25 (Binding Affinity of -10.0 (kcal/mol)). Hydrogen bonding: Ser342 with C4 carbonyl group and C5 OH groups, Glu343 with C4 carbonyl group, Glu285 with C3' OH. Pi Anion Interactions: None. Pi - pi Interactions: None. Pi alkyl interactions: Leu333 with ring B and cyclic ring, Leu228 with ring B, Glu291 with the cyclic ring, Arg288 with ring A and cyclic ring. In the binding of ligands to PPARG, Hydrogen bonding involved mostly Arg288, Ser342, and in some cases Glu343, Lys263. C3-, C4- and C5- OH, and C4 carbonyl groups of the ligands were the prominent sites of Hydrogen bonding. C3' OH groups were also involved in a few cases. pi alkyl interactions were more predominant than Hydrogen bonding. Most prominent pi alkyl interactions involved rings A and cyclic ring, and in a few cases ring B. Pi anion did not play any role while Pi pi interactions were involved only in a few cases. Peroxisome proliferator-activated receptor-gamma is a member of the nuclear receptor superfamily of transcription factors. The protein is an important regulator of target genes implicated in glucose homeostasis and has therefore been identified as a therapeutic target for Type 2 Diabetes [9, 10, 11]. Ligands 15, 16, 25, 26, and 31 all had better binding affinity than quercetin (9.8) and reference compounds (pioglitazone, -9.1 and empagliflozin, -9.5) and therefore high potential of serving as antidiabetic agents by acting on PPARG.

Fructose-1,6-biphosphate (F16DP)

Quercetin had a binding affinity of -6.2. Only ligands 2, 34, and 47 had a slightly stronger binding affinity of -6.6 which was lower than that of acarbose (-7.0) but better than empagliflozin (-6.0). The target-quercetin binding interactions show the presence of two H-bonding. One between Glu145 and 3-OH. The second is between Lys142 and 3' OH group. The Pi cation and pi alkyl interactions involved Lys142 vs ring B and Arg111 versus ring A of quercetin. Fructose 1,6-bisphosphatase is an important enzyme in gluconeogenesis. It is a potential drug target in the treatment of type II diabetes. It acts by catalysing the hydrolysis of fructose 1,6-bisphosphate to fructose 6-phosphate, a reaction that occurs in gluconeogenesis and the Calvin cycle [12]. Ligands 2, 34, and 47 could be useful in the management of diabetes through their effect on this enzyme.

GSK3

The binding affinity for quercetin was -7.9 while that of acarbose (-8.6) was the highest among the reference compounds. Ligands 45 and 15 had a binding affinity of -8.0 and -8.1, almost the same as that of quercetin. Phe360, Leu359 and Asn361 were hydrogen bonded to the 3 – ketone oxygen of quercetin. While Asp345 and Asp355 were hydrogen-bonded to the 4' – OH and 3' – OH groups, respectively. Ala382 had pi sigma interactions with the A ring while Ala358 and Ala382 had pi alkyl interactions with the cyclic ring. Glycogen synthase kinases 3β (GSK 3β) are an important target in the treatment of Type 2 Diabetes. It has been implicated in insulin resistance and regulation of glycogen synthesis. Inhibitors of this enzyme possess antidiabetic properties because they improve insulin sensitivity, glycogen synthesis, and glucose metabolism in skeletal muscles [13, 14, 15]. None of the ligands has a significantly better binding affinity to this enzyme than quercetin.

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PTP1B
While quercetin had a binding affinity of -8.9; ligand 18 had 9.0; ligands 20, 21, 22, 28 and 30 had -9.1; ligands 19, 25 and 31 had -9.2; ligand 26 had the best affinity (-9.3). In the interactions between target and quercetin, H-bonding is as follows: Val113 and 8- OH, Ser151 and 4'-OH, Lys150 and 3'-OH, Tyr153 and 3' -OH, Arg156 and Ketone Oxygen. Pi - pi interactions were between His 175 and, ring A and the cyclic ring. While Pi- alkyl interactions existed between Arg112, Val113 and ring A, and Ile149 and ring B. PTP-1B is known to be involved in the regulation of negated insulin signal transduction pathways. Its inhibition enhances the level of insulin receptor phosphorylation, translocation of glucose transporters and glucose uptake in insulin-sensitive cells [16]. Ligands 19, 20, 21, 22, 25, 26, 28, 30 and 31 could therefore serve as leads for antidiabetic compounds through their effect on the activity of PTB1B.

Glucokinase (GK)
The binding affinity for quercetin was -8.7 which was better than that of all the reference compounds except acarbose (-9.1). Ligands that showed better binding affinities than that of quercetin were ligand 43 (-8.9); ligands 22, 32, and 48 (-9.0); ligands 33(-9.1); ligand 45 (-9.2); and ligand 37 which has the best binding affinity of -9.7. Target – quercetin interactions showed the presence of H-bonding between theTyr215, Leu451 and 3' -OH and 4' – OH, respectively. The Pi-sigma interactions were between Ile211, Val455 and ring B, cyclic ring, respectively. Pi alkyl interactions involved Pro66 and ring B and cyclic ring, Val62 and cyclic ring, Val455 and ring A.
Glucokinase is a cytoplasmic enzyme found in both the pancreas and liver where it functions by regulating the level of glucose. It enhances liver glucose, hepatic glycogenesis and pancreatic insulin secretion [17]. Its activation through phosphorylation results in lower blood glucose levels irrespective of the cause of hyperglycemia. It is therefore a good drug target for type 2 diabetes. Ligands 22, 32, 33, 37, 43, and 45 show promising antidiabetic potential by their activity on this enzyme. Ligands that had good binding activity on more than one target are Ligand 15 (Alpha-glucosidase, PPARG, and DPP4), Ligand 39 (alpha-glucosidase and DPP4), Ligands 25 and 31 (PPARG and PTB1B).

Molecular Properties of Ligands (https://dev.drugbank.com/guides/terms/lipinski-s-rule-of-five). Lipinski's Rule of 5: The rule states, that most "drug-like" molecules have logP <= 5, molecular weight <= 500, number of hydrogen bond acceptors <= 10, number of hydrogen bond donors <= 5. Molecules violating more than one of these rules may have problems with bioavailability. Ligands 45, 47, 57, 61, 64, 65, and 66 may therefore have problems with bioavailability. This is confirmed by their poor intestinal absorption of 56.2, 0.00, 60.9, 61.6, 60.3, 13.2, and 44.1 % respectively. These are 3- O-esters of arachidonic, citric, linoleic, palmitic, stearic, tartaric, and ascorbic acid, respectively. This could be partly because of the long fatty acyl chain. In the case of ligand 47 (citroate), 65 (tartaroate) and 66 (ascorboate) the logP were -0.75, 0.08, and 0.39 due to the presence of polyhydroxy groups.

5.0 CONCLUSION
Some of the derivatives of quercetin had better binding affinity than quercetin on various targets. Some of the ligands had good binding activity on more than one target. They are Ligand 15 (Alpha glucosidase, PPARG, and DPP4), Ligand 39 (alpha glucosidase and DPP4), Ligands 25 and 31 (PPARG and PTB1B). These derivatives are potential candidate compounds that could be useful in the treatment of diabetes.

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