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Evaluation of O-methyl substituted quercetin analogues as DPP-4 Inhibitor: *in silico* study

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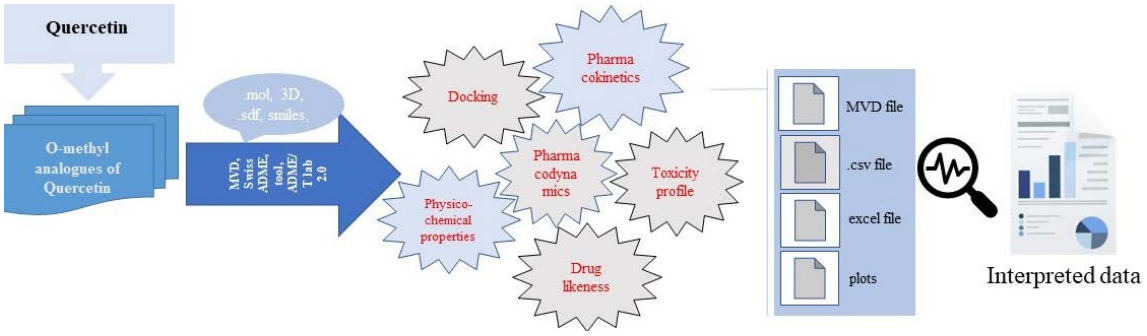
Article

ABSTRACT



Quercetin having chromone nucleus is attracting high attention due to diverse pharmacological properties. Moreover, quercetin as a dipeptidyl peptidase IV (DPP-4) inhibitors are projected to have significant potential in the treatment of diabetes. In this study, **i***n silico* evaluation of O-methyl substituted quercetin analogues as DPP-4 Inhibitor have been reported. The 2D structures of quercetin and its O-CH_3 derivatives were prepared using the ACD chem sketch software and molecular docking was run by MVD 6.0 tool with the 3-dimensional (3D) crystal structure of Human dipeptidyl peptidase IV(DPP-4) (PDB ID: 4J3J, retrieved from RCSB-PDB. Molecular properties such as molecular weight of designed compounds, donated or accepted hydrogen count, rotatable bonds, aromatic rings, partition coefficient (log P), surface area, pharmacokinetic and toxicity profile of all newly designed O-CH_3 compounds were studied by Swiss ADME and ADMET lab 2.0 tools. A series of Q1-Q5 out of total 30 compounds fulfilled the criteria for ADME/toxicity profile with high number of hydrogen interactions and exhibited potential inhibition for amino acids of DPP-4. After Docking simulation, SAR study indicated that quercetin derivatives with more hydroxyl substitutions as well as mono methyl substitution (Q1-Q5) showed stronger inhibition. A series Q1-Q5 were observed as the most effective inhibitors in terms of physicochemical, pharmacokinetic, pharmacodynamics, and docking simulation study.

Keywords: Chromone, Quercetin, Docking simulation, ADMET, DPP4, Drug likeness

INTRODUCTION

Quercetin [2-(3,4-dihydroxyphenyl)-3,5,7-trihydroxy4H-chromen-4-one], an antioxidative flavonoid or chromone isolated from nuts, herbs, vegetables, fruits and used in beverages, food supplements exhibiting diverse pharmacological activities like anticancer, anti-inflammatory, antiviral, analgesic, anti-oxidant, antidiabetic, anti-HIV, antiparasitic etc.[1–3] Generally, 100 mg of quercetin as glycosidic form, consumed by people as supplements or nutraceuticals.[4] After quercetin administration, alkylation mainly methylation was observed in metabolism along with glucuronidation and sulfonation phase reactions.[5] As of diverse biological value and very low toxicity of quercetin, a number of quercetin methyl ether or O-methylated quercetin analogues were synthesized and reported for their significant biological values in literature.[6] While we were reviewing literature about alkylated (methylated) quercetin, we have noticed that study on the synthesis and antidiabetic activity of methylated derivatives of quercetin are limited. As quercetin has 5-OH groups, CH_3 substitution yields five type of substituted quercetin methyl ether as mono, di, tri, tetra and penta-CH_3 substituted derivatives.[7] Therefore, a series of alkyl (CH_3) substituted quercetin derivatives were designed and physicochemical properties, pharmacokinetics and docking with

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DPP-4 were completely characterized in this report based upon the hypothetical concept that quercetin methyl ether derivatives can compete or possess better antidiabetic effect in comparison to synthesised parent quercetin.

Currently, DPP-4 inhibitors (sitagliptin, saxagliptin, alogliptin and linagliptin) as antidiabetic are in more use. These drugs hinder DPP-4 enzyme; responsible for the inactivation of incretin hormones e.g., activity of GLP-1, thereby prolonging the effect and release of incretin hormones which further promote insulin action against high post prandial glucose and lessens irregular glucagon secretion.[8] Usage of mono DPP-4 inhibitor or in combination with other antidiabetic drugs such as metformin, sulfonylureas, thiazolidinediones or insulin is usually suggested. But long-term use of these synthetic anti-diabetics may generate severe adverse effects, moreover less potent in management/cure of diabetic complications, therefore presently natural compounds are gaining more popularity.[9]

MATERIALS AND METHODS

In silico binding study of quercetin and all methylated (O-CH_3) substituents (Q1-Q30) was performed by Molegro Virtual Docker 6.0 (MVD) programme.[10] The 2D structures of all ligands were designed by ACD chem sketch software (**Table** 1).

2.1 Protein preparation

Using relevant literature; 3-dimensional (3D) crystal structure of Human dipeptidyl peptidase IV(**DPP-4)** (PDB ID: 4J3J, https://www.rcsb.org/structure/4J3J) was download from RCSB PDB with crystal structure resolution of 3.20 Å. It contains a unique chain (Chain A) with structural weight of 169.79 kDa. The enzyme was imported in MVD workspace after removing cofactors, water molecules and other attached interfering ligands.[10,11]

2.2 Ligand Preparation

The 2D structures of all ligands were draw up using chem draw software and 2D view of ligands were formatted to 3D as well as minimized the energy of prepared ligands by using a 3D optimization tool and saved as *.mol for docking purposes.[12,13]

2.3 Cavity prediction

The cavity or the potential ligand binding site of PDB ID:4J3J was predicted in MVD workspace.[10] with a Mol Dock grid score 0.30 and a restriction sphere of 15 radius. The top pose of each ligand was nominated for analysis of subsequent ligand-protein interaction energy.

2.4 Molecular descriptor analysis

Molecular properties such as molecular weight of designed compounds, donated or accepted hydrogen count, rotatable bonds, aromatic rings, partition coefficient (log P) and surface area of all newly designed compounds were studied by Swiss ADME software.[14]

2.5 ADME/T Prediction

ADME/T means absorption, distribution, metabolism, excretion, and toxicity which describe the pharmacokinetic detail of a molecule and also helps in the prediction of pharmacodynamics of compounds. Today, a number of online and offline software's are available, using these tools ADMET profiles of the compound can be easily generated. For such predictions, Swiss ADME and ADMET lab 2.0 tools are used. (https://admet.scbdd.com).[15,16]

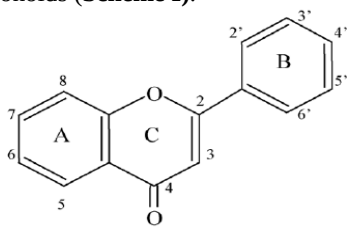
RESULT

3.1 Molecular Docking Studies

Quercetin contains chromone moiety considered as a promising agent in the treatment of T2DM by sensitizes tissues to insulin action as well as a valuable alternative in insulin-resistant diabetic patients.[17] The mechanism of action of chromane might be that it stimulated the beta islets to secrete insulin, reduced insulin resistance and give antidiabetic effect through a number of receptors.[18] The receptor targets that are suggested by many scientists for quercetin against T2DM are protein tyrosine phosphatase 1-beta (PTP-1β), glycogen phosphorylase, peroxisome proliferator activated receptor (PPAR-γ), glucokinase, aldose reductase (AR), insulin receptor (IR) and so on.[19] Therefore, in current study, available literature database and results of docking simulation with above said receptors, quercetin shows good binding resulting antidiabetic activity through the inhibition of DPP-4 protein (PDB ID: 4J3J, https://www.rcsb.org/structure/4J3J) as shown in **Figure** 1 and **Table** 2.

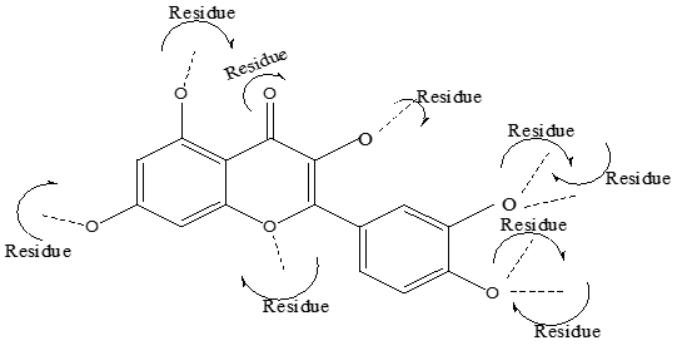
3.1.1 Structure Activity Relationship (SAR)

Hydroxylation at C-5,7 (ring A), C-3 (ring C) and C-3',4' (ring B) as well as 2,3 C=C in C-ring are significant for the inhibitory potential of flavonoids (**Scheme I)**.[20]



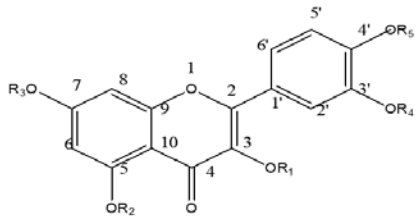
Scheme I: Parent structure of flavonoid

All -O- atoms at C3, C5, C7, C3'and C4' of proposed ligand shows highest number of H-interactions (09) with a good Mol Dock score, Rerank score and H-bond energy -79.49, -54.97 and -9.26 (Table 2). It means -O- substitution plays an important role in bindings of ligand (**Scheme II**) with corresponding amino acids of protein DPP-4.



Scheme II: Interactions of ligand with residue

Substitutions as -O substitution with small size alkyl groups like CH_3 results mono, di, tri, tetra and penta methyl substituted compounds as shown in **Scheme III** and **Table** 1.[21]



Scheme III: Parent structure of quercetin for substitution

Table 1: List of designed compounds used for docking simulation

COMPOUNDS	R_1	R_2	R_3	R_4	R_5
Quercetin	H	H	H	H	H
Q1	CH_3	H	H	H	H
Q2	H	CH_3	H	H	H
Q3	H	H	CH_3	H	H
Q4	H	H	H	CH_3	H
Q5	H	H	H	H	CH_3
Q6	CH_3	CH_3	H	H	H
Q7	H	CH_3	CH_3	H	H
Q8	CH_3	H	CH_3	H	H
Q9	H	H	H	CH_3	CH_3
Q10	CH_3	H	H	CH_3	H
Q11	H	CH_3	H	CH_3	H
Q12	H	H	CH_3	CH_3	H
Q13	CH_3	H	H	H	CH_3
Q14	H	CH_3	H	H	CH_3
Q15	H	H	CH_3	H	CH_3
Q16	CH_3	CH_3	CH_3	H	H
Q17	H	CH_3	CH_3	CH_3	H
Q18	H	H	CH_3	CH_3	CH_3
Q19	CH_3	H	H	CH_3	CH_3
Q20	CH_3	H	CH_3	H	CH_3
Q21	H	CH_3	CH_3	H	CH_3
Q22	CH_3	H	H	CH_3	CH_3
Q23	H	CH_3	H	CH_3	CH_3
Q24	CH_3	H	CH_3	CH_3	H
Q25	CH_3	CH_3	CH_3	CH_3	H
Q26	CH_3	CH_3	CH_3	H	CH_3
Q27	H	CH_3	CH_3	CH_3	CH_3
Q28	CH_3	H	CH_3	CH_3	CH_3
Q29	CH_3	CH_3	H	CH_3	CH_3
Q30	CH_3	CH_3	CH_3	CH_3	CH_3

C-4, C-5, C-7, C-3’ and C-4’ position of parent quercetin shows nine hydrogen annotations 2.60, 3.00, 2.87, 3.19, 3.312.99, 3.10, 3.24, 3.28 (Å) respectively (**Figure** 1 and **Figure** 2).

O-substitution with mono alkyl group (methyl) also shows high number of hydrogen interactions as well as novelty and feasibility in synthesis.[3,22,23]

As we know DPP-4 inhibitors may be used as monotherapy or in combination with sulfonylureas, metformin, thiazolidinediones or insulin. So, inhibition of DPP4 receptor by quercetin and its analogues may be a better choice for the treatment of T2DM**.**

3.2 ADME/T analysis

in silico ADME/T was predicted by Swiss ADME and ADMET lab 2.0 programs. By using these online tools, physicochemical parameters including molecule description, solubility profile, lipophilicity, drug likeness, Lipinski rule, bioavailability score, medicinal chemistry, synthetic accessibility, pharmacokinetic

Table 2: The Mol Dock score, re rank score, and hydrogen bond interaction energy of the different substituents with Dipeptidyl peptidase-IV (4J3J)

Compounds	Moldock score	Rerank score	H-bond	Interactions	Energy	Distance Annotation	Ligand	Protein
Parent (Quercetin)	-79.49	-54.97	-9.26	9	-2.5	2.87	[O] C-7	Arg253 [O]
					-2.05	3.19	[O] C-7	Asp192 [O]
					-2.5	2.60	[O] C-4	Lys250 [O]
					-2.5	3.00	[O] C-5	Lys250 [N]
					-1.79	3.24	[O] C-4’	Gln123 [O]
					-1.58	3.28	[O] C-4’	Lys122 [N]
					-2.5	2.99	[O] C-3’	Ala707 [O]
					-0.71	3.31	[O] C-7	Asp192 [O]
					-2.48	3.10	[O] C-3’	Asp709 [O]
Q1	-78.55	-58.82	-8.35	9	-2.5	2.60	[O] C-4	Lys250 [N]
					-2.5	3.10	[O] C-5	Lys250 [N]
					-2.49	3.10	[O] C-7	Asp192 [O]
					-0.35	3.33	[O] C-7	Asp192 [O]
					-2.5	3.06	[O] C-7	Arg253 [O]
					-1.93	3.21	[O] C-4	Asp709 [O]
					-1.85	3.23	[O] C-4	Gln123 [O]
					-1.57	3.28	[O] C-4	Lys122 [N]
					-2.5	3.09	[O] C-3’	Ala707 [O]
Q2	-79.00	-60.05	-7.32	9	-1.14	3.37	[O] C-4’	Lys122 [N]
					-1.49	3.30	[O] C-4’	Gly123 [O]
					-2.5	3.10	[O] C-3’	Ala707 [O]
					-1.47	3.30	[O] C-3’	Asp709 [O]
					-2.5	3.64	[O] C-4	Lys250 [N]
					-2.03	3.19	[O] C-5	Lys250 [N]
					-0.08	3.34	[O] C-7	Asp192 [O]
					-2.5	3.10	[O] C-7	Arg253 [O]
					-2.5	3.04	[O] C-7	Asp192 [O]
Q3	-80.94	-66.46	-11.69	9	-2.4	3.11	[O] C-3	Asp192 [O]
					-0.49	3.32	[O] C-3	Asp192 [O]
					-2.0	3.20	[O] C-3	Arg253 [O]
					-2.22	3.15	[O] C-4	Gln123 [N]
					-1.21	3.36	[O] C-5	Gln123 [N]
					-2.5	3.60	[O] C-3’	Thr251 [O]
					-1.24	3.14	[O] C-3’	Arg253 [N]
					-1.76	2.80	[O] C-4’	Arg253 [N]
					-1.45	3.03		
Q4	-80.73	-46.58	-6.82	9	-1.48	2.92	[O] C-4’	Lys250 [N]
					-0.93	3.41	[O] C-3’	Lys250 [N]
					-2.48	2.60	[O] C-4	Tyr238 [O]
					-2.5	2.61	[O] C-5	Ala707 [O]
					-2.49	2.60	[O] C-5	Asp709 [O]
					-2.48	3.92	[O] C-5	Tyr238 [O]
					-1.90	3.22	[O] C-7	Asp739 [O]
					-2.09	3.18	[O] C-7	Asp737 [O]
					-0.48	3.23	[O] C-7	Asp739 [N]
Q5	-87.98	-63.63	-6.52	8	-2.5	3.09	[O] C-5	Lys250 [N]
					-1.5	2.48	[O] C-4	Lys250 [N]
					-2.5	3.10	[O] C-7	Asp192 [O]
					-2.5	3.08	[O] C-7	Arg253 [O]
					-0.13	3.38	[O] C-7	Asp192 [O]
					-2.3	3.13	[O] C-3’	Tyr238 [O]
					-2.5	3.10	[O] C-3’	Asp709 [O]
					-2.49	2.60	[O] C-3’	Asp707 [O]
Q6	-80.56	-71.17	-4.8	5	-2.5	2.85	[O] O-1	Lys250 [N]
					-2.5	2.78	[O] C-4’	Arg253 [N]
					-0.68	2.38	[O] C-3’	Asp192 [O]
					-1.75	3.25	[O] C-3’	Arg253 [O]
					-0.49	3.50	[O] C-4	Gln123 [N]

Q7	-83.24	-71.85	-10.58	6	-2.23 -2.5 -1.99 -1.84 -2.35 -1.35	3.15 3.10 3.18 3.07 2.58 3.19	[O] C-1 [O] C-3 [O] C-3′ [O] C-4′ [O] C-4′ [O] C-4′	Lys250 [N] Arg253 [O] Arg253 [N] Arg253 [N] Thr251 [O] Arg253 [N]
Q8	-89.17	-72.43	-8.68	4	-2.5 -2.5 -2.5 -2.5	2.60 3.07 2.99 2.63	[O] C-4 [O] C-5 [O] C-4′ [O] C-3′	Lys250 [N] Lys250 [N] Gln123 [O] Ala707 [O]
Q9	-93.47	-76.71	-4.83	4	-2.5 -2.5 -2.37 -0.38	2.87 2.60 2.59 3.52	[O] C-5 [O] C-5 [O] C-7 [O] C-4′	Gln123 [O] Lys122 [O] Ala707 [O] Arg253 [N]
Q10	-92.44	-76.46	-7.70	6	-2.5 -2.5 -2.5 -1.31 -2.5 -0.58	2.69 3.09 2.67 3.34 2.96 3.48	[O] C-7 [O] C-5 [O] C-5 [O] C-4′ [O] C-3′ [O] C-3′	Ala707 [O] Gln 123 [O] Lys122 [O] Lys 250 [N] Arg253 [O] Asp192 [O]
Q11	-57.74	-45.03	-6.92	5	-2.08 -2.49 -1.71 -2.5 -2.5	3.10 3.10 3.26 2.81 2.73	[O] C- 3′ [O] C-3 [O] C-4 [O] C-3′ [O] C-7	Arg253 [N] Thr251 [O] Lys250 [N] Arg253[N] Gln123[N]
Q12	-65.61	-30.0067	-7.93	6	-2.5 -2.5 -2.01 -1.58 -2.5 -1.53	2.74 2.61 2.54 3.28 2.71 2.48	[O] C-5 [O] C-5 [O] C-4 [O] C-3 [O] C-3′ [O] C-4′	Asp709 [O] Ala707 [O] Tyr238 [O] Tyr238 [O] Lys 250[N] Lys 250 [N]
Q13	-51.86	-24.52	-8.41	7	-2.33 -2.5 -2.5 -2.5 -2.5 -0.92 -0.29	2.58 3.00 2.60 2.72 2.76 3.03 3.54	[O] C- 3 [O] C-4′ [O] C-4 [O] C-5 [O] C-5 [O] C-7 [O] C-3	Lys250 [N] Lys250 [N] Tyr238 [O] Asp709 [O] Ala707 [O] Asp739 [O] Tyr238 [O]
Q14	-54.91	-39.61	-9.93	7	-1.78 -1.96 -1.93 -2.50 -2.32 -0.79 -0.40	3.09 3.01 3.08 2.68 3.14 3.44 3.52	[O] C-5 [O] C-5 [O] C-4 [O] C-3 [O] C-3′ [O] C-3 [O] C-1	Arg253 [N] Arg253 [N] Arg253 [N] Arg253 [O] Arg253 [O] Asp192 [O] Lys250 [N]
Q15	-64.118	-46.96	-7.42	7	-2.43 -1.27 -2.38 -2.48 -2.09 -2.5 -2.5	3.01 3.10 3.12 3.10 3.18 2.69 3.10	[O] C-5 [O] C-5 [O] C-7 [O] C-4 [O] C-3 [O] C-3′ [O] C-3′	Asp192 [O] Asp192 [O] Arg253 [N] Gln123 [N] Gln123 [N] Gln123 [O] Lys122 [O]
Q16	-44.61	-11.92	-8.89	7	-0.89 -2.50 -2.28 -2.26 -2.50 -2.23 -0.47	2.41 3.08 2.73 3.15 3.10 3.15 3.51	[O] C-3′ [O] C-3′ [O] C-3′ [O] C-4′ [O] C-4 [O] C-5 [O] C-3′	Asp739 [O] Glu738 [O] Asp739 [N] Glu738 [O] Tyr238 [O] Tyr238 [O] Asp737 [O]
Q17	-64.73	-46.64	-5.76	4	-2.49 -2.47 -2.50 -0.99	2.95 2.60 2.68 3.40	[O] C-5′ [O] C-3 [O] C-3 [O] C-4′	Arg253 [N] Asp192 [O] Arg253 [O] Gln123 [N]
Q18	-56.69	-28.16	-6.57	7	-2.50 -2.50 -1.70 -2.47 -2.33 -0.05 -0.63	2.60 2.60 2.50 2.60 2.58 3.59 3.29	[O] C-5 [O] C-5 [O] C-4 [O] C-3′ [O] C-4′ [O] C-3 [O] C-7	Ala707 [O] Asp709 [O] Tyr238 [O] Lys250 [N] Lys250 [N] Tyr238 [O] Asp739 [N]
Q19	-46.34	-20.23	-10.44	7	-2.50 -2.49 -0.77 -2.49 -2.50 -2.50 -2.16	2.77 2.60 3.44 2.60 2.60 2.82 3.07	[O] C-4′ [O] C-3′ [O] C-3 [O] C-4 [O] C-5 [O] C-5 [O] C-7	Lys250 [N] Lys250 [N] Tyr238 [O] Tyr238 [O] Ala707 [O] Asp709 [O] Asp739 [O]
Q20	-42.07	-35.05	-4.58	5	-2.50 -1.48 -2.15 -2.50 -0.94	3.03 2.48 3.16 2.90 3.41	[O] C-4′ [O] C-3′ [O] C-7 [O] C-7 [O] C-7	Lys250 [N] Lys250 [N] Asp739 [O] Asp739 [O] Gln123 [O]
Q21	-43.71	-30.17	-5.54	5	-2.50 -2.50 -2.50 -2.19 -0.70	2.64 2.91 2.84 3.16 3.46	[O] C-3′ [O] C-4′ [O] C-7 [O] C-7 [O] C-7	Lys250 [N] Lys250 [N] Asp709 [O] Asp709 [O] Gln123 [O]
Q22	-46.24	-33.88	-6.96	7	-0.44 -2.50 -2.50 -0.49 -2.50 -2.43 -2.50	3.51 2.60 2.60 3.35 2.75 3.11 3.10	[O] C-4′ [O] C-7 [O] C-7 [O] C-7 [O] C-7 [O] C-5 [O] C-5	Lys250 [N] Ala707 [O] Asp709 [O] Asp709 [N] Tyr238 [O] Lys122 [N] Gln123 [O]
Q23	-48.30	-31.78	-6.28	5	-0.21 -1.84 -1.72 -2.50 -2.50	3.54 3.07 3.10 3.10 2.62	[O] C-3′ [O] C-4′ [O] C-4′ [O] C-3 [O] C-3	Arg253 [N] Arg253 [N] Arg253 [N] Asp192 [O] Arg253 [O]
Q24	-70.90	-53.99	-6.40	5	-2.47 -1.98 -2.50 -2.50 -2.40	2.60 3.20 2.61 2.74 3.12	[O] C-5 [O] C-5 [O] C-4 [O] C-4′ [O] C-3′	Ala707 [O] Asp709 [O] Tyr238 [O] Lys250 [N] Lys250 [N]
Q25	-58.72	-47.75	-3.71	3	-2.50 -2.50 -2.50	2.72 3.02 2.99	[O] C-4′ [O] C-4′ [O] C-3	Arg253 [O] Asp192 [O] Lys250 [N]
Q26	-59.01	-45.08	-4.89	3	-2.5 -2.5 -2.39	3.10 2.60 3.10	[O] C-4′ [O] C-3′ [O] C-3′	Arg253 [N] Asp192 [O] Arg253 [O]
Q27	-62.99	-46.14	-4.89	3	-2.5 -2.5 -2.39	2.74 2.60 3.07	[O] C-3 [O] C-3 [O] C-5	Arg253 [O] Asp192 [O] Arg253 [N]
Q28	-46.04	-19.23	-6.10	6	-1.78 -2.5 -2.5 -0.62 -0.97 -2.5	2.51 2.62 2.66 3.34 2.42 2.91	[O] C-4 [O] C-5 [O] C-5 [O] C-7 [O] C-3′ [O] C-4′	Tyr238 [O] Ala707 [O] Asp709 [O] Asp739 [N] Lys250 [N] Lys250 [N]
Q29	-40.37	-31.54	-5.17	5	-1.91 -0.52 -2.5 -2.23 -2.5	3.18 3.59 2.78 2.57 2.94	[O] C-7 [O] C-7 [O] C-7 [O] C-3′ [O] C-4′	Asp739 [O] Gln123 [O] Asp709 [O] Lys250 [N] Lys250 [N]
Q30	-36.60	-10.92	-3.35	4	-0.59	3.34	[O] C-7	Asp739 [N]

					-2.5 -2.02 -0.73	3.10 2.54 3.45	[O] C-4' [O] C-3' [O] C-4	Lys250 [N] Lys250 [N] Tyr238 [O]
Reference (Sitagliptin)	-83.15	-70.30	-7.75	5	-2.5 -2.49 -2.5 -2.5 -2.5	3.03 2.60 2.61 2.65 3.07	[O] C- [O] [O] [O] [O]	Lys250 [N] Lys250 [N] Asp709 [O] Ala707 [O] Tyr238 [O]

parameters like GI absorption, Blood Brain Barrier (BBB) penetration, P-gp substrate, CYP1A2 inhibition, CYP2D6 inhibition and skin penetration were predicted for Quercetin and 30 designed derivatives (Q1-Q30). Predicted results were further compared with standard limits. Toxicity profile which includes acute toxicity and LD_{50} values were estimated using ADME/T evaluation and ADME/T systematic assessment tools of ADMET lab 2.0.(https://admet.scbdd.com/).[24,25]

Table 3 shows various physicochemical parameters like molecular formula, molecular weight (MW), heavy atoms, aromatic heavy atoms, rotatable bonds, Hydrogen bond acceptors, Hydrogen bond donors, Molar refractivity (MR), Total polar surface area (TPSA), lipophilicity(clogP), and solubility criteria. All compounds are in acceptable range as compared to standard specifications and may be considered like a drug or showed drug likeness features.

Drug likenesses parameter establish the relation between physicochemical properties and biological activity, were mainly evaluated by Lipinski's rule of five (MW ≤ 500, Mlog P ≤ 4.15), Ghose (MW ≤ 480, Wlog P ≤ 5.6, MR≤130, atoms≤70), veber (Rotatable bonds≤10, TPSA≤140), Egan (WlogP≤5.88, TPSA≤131.6), Muegge (Bayer) filter (MW≤200-600, XlogP≤5, TPSA≤150) and bioavailability score of a drug candidate.[26] All 30 designed compounds along with parent quercetin shows 0 violation by following Lipinski's rule of five and meet the criteria of designed compounds having a drug likeness character (**Table 4**). However, all compounds showed appropriate oral bioavailability with a good bioavailability score (0.55) and TPSA value lies between 76.36-131.36 (≤140 Å) as shown in **Table 3**. Better values of performed parameters indicate that the designed compounds are more likely to become a drug candidate as compared to reference sitagliptin.

The correlation of cLogP values and hydrophilicity expresses the dependency of hydrophilicity value of a drug candidate on cLogP, as cLogP value rises above 5 permeability and absorption decreases. From **Table 3**, it is clear that all compounds are in acceptable range i.e., having cLogP lower than 5.

Pharmacokinetic study includes ADME/T parameters that evaluate human therapeutic use of compounds. *in silico* pharmacokinetic study is necessary for the prevention of failure of ADME experiment during clinical trials, severe toxicity of new compounds to animals and also prevent loss of synthetic yield of compounds for *in vivo* trials.

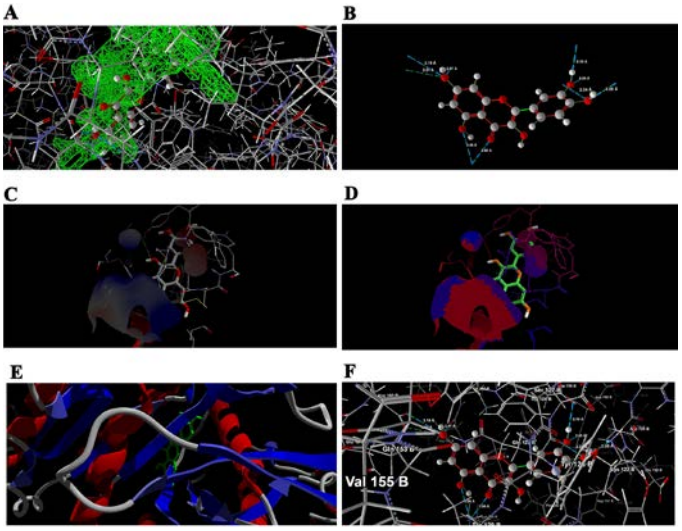


Figure 1: [A] Ligand quercetin is in selected cavity (PDB id: 4J3J) [B] H-interactions with annotations [C] Electrostatic interactions [D] Hydrophilicity (orange color) and Hydrophobicity (Green color) [E] Secondary structure [F] Hydrogen interactions of quercetin with 4J3J (DPP4)

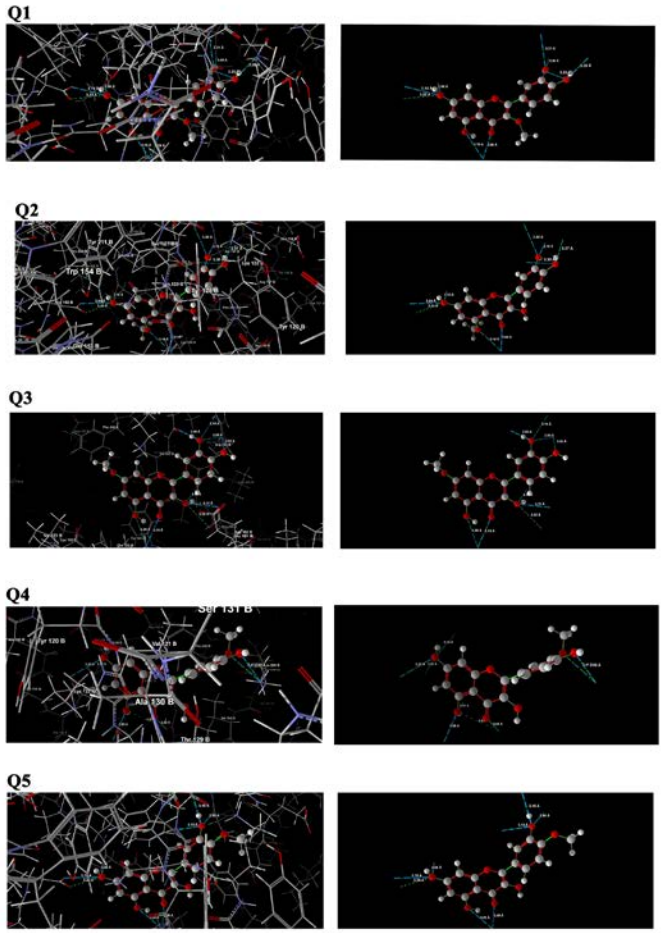


Figure 2: H-interactions of Q1-Q5 with 4J3J

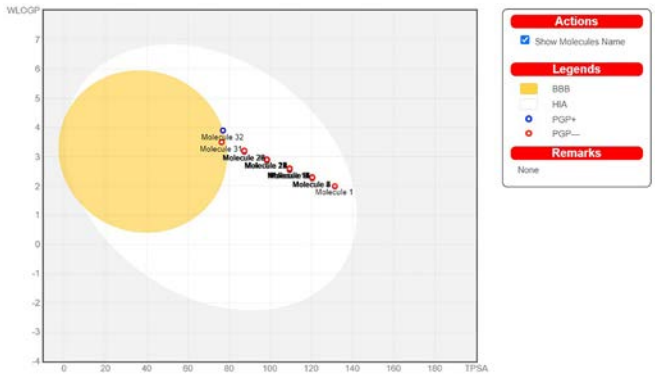


Figure 3: Boiled egg graph between WlogP and TPSA showing GI absorption (Quercetin, Q1-Q30 compounds)

DISCUSSION

The quercetin with its anti-oxidant potential have shown applicability promise in treatment of different diseases, including diabetes.[27-31] In the efforts towards development of derviatives of quercetin as potential therapeutics, the simulations studies are proving beneficial in prediction of pharmcological properties of proposed derivatives. In current study, *In silico* studies by MVD programme reveals that -O substitution with mono alkyl group (methyl) showed high number of H-interactions with good moldock and rerank score as compared to parent quercetin and Reference sitagliptin. From this series compound Q1-Q5 were reported as best docked ligand with larger number H-interactions (9) and good moldock score. Predicted data from Swiss ADME tool showed physicochemical aspects of these compounds with biological activity. ADME analysis of parent and 30 compounds (best docked compounds) are in acceptable range therefore more likely to behave as a good drug candidate. In medicinal chemistry assessment, these compounds showed synthetic accessibility <10 (Q1-Q5 in range 3.23-3.33) so possibilities of synthesis are good according to specifications. Boiled egg graph (**Figure** 3) of Swiss ADME tool between WlogP and TPSA showed quercetin and 30 compounds passively absorbed by GI tract and no BBB crossing. Moreover, these compounds were found to have low toxicity (>500mg/kg), no skin sensitization, very less human hepatotoxicity and LD_{50} in the range of 2.63-2.90 as shown in **Table** 5.

(PS: Table 3-5 have been included after the references section)

CONCLUSION

In this study, quercetin and its O-CH_3 derivatives were investigated for ligand-protein (PDB ID: 4J3J, DPP-4) binding study using MVD 6.0 software and molecular properties such as molecular weight of designed compounds, donated or accepted hydrogen count, rotatable bonds, aromatic rings, partition coefficient (log P), surface area, pharmacokinetic and toxicity profile of all newly designed O-CH_3 compounds were studied by Swiss ADME and ADMET lab 2.0 tools. A series of Q1-Q5 out of total 30 compounds fulfilled the criteria for ADME/toxicity profile with high number of hydrogen interactions and exhibited potential inhibition for amino acids of DPP-4. Therefore, following *in silico* report of O-methyl substituted quercetin; some future aspects are generated that highly docked ligands (Q1-Q5) possess significant moldock score, acceptable physicochemical aspects, good pharmacokinetics and less toxicity as compared to other docked compounds (Q6-Q30). So, only mono methyl substituted compounds (Q1-Q5) are suggested for synthesis; producing good practical yield and to explore their *in vivo* antidiabetic examination along with diabetic neuropathy and nephropathy study.

CONFLICT OF INTEREST STATEMENT

No conflict of interest is there for this work.

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Table 3: *in silico* prediction of physicochemical properties, lipophilicity and solubility criteria of Quercetin and its O-alkyl derivatives

	Physicochemical properties								Water solubility				Lipophilicity					
Parent (Quercetin)	C15H10O7	302.24	22	16	5	7	78.03	131.36	-3.16	2.11E-01	6.98E-04	Soluble	1.63	1.54	1.99	-0.56	1.54	1.23
Q1	C16H12O7	316.26	23	16	4	7	82.5	120.36	-3.89	4.07E-02	1.29E-04	Soluble	2	2.71	2.29	-0.31	2.06	1.75
Q2	C16H12O7	316.26	23	16	4	7	82.5	120.36	-3.02	3.05E-01	9.66E-04	Soluble	1.71	1.32	2.29	-0.31	2.06	1.41
Q3	C16H12O7	316.26	23	16	4	7	82.5	120.36	-3.36	1.38E-01	4.35E-04	Soluble	2.23	1.87	2.29	-0.31	2.06	1.63
Q4	C16H12O7	316.26	23	16	4	7	82.5	120.36	-3.36	1.38E-01	4.35E-04	Soluble	2.35	1.87	2.29	-0.31	2.06	1.65
Q5	C16H12O7	316.26	23	16	4	7	82.5	120.36	-4.04	2.87E-02	9.08E-05	Moderately soluble	2.24	2.95	2.29	-0.31	2.06	1.85
Q6	C17H14O7	330.29	24	16	3	7	86.97	109.36	-3.61	8.05E-02	2.44E-04	Soluble	1.99	2.27	2.59	0.07	2.59	1.88
Q7	C17H14O7	330.29	24	16	3	7	86.97	109.36	-3.22	2.01E-01	6.08E-04	Soluble	2.31	1.64	2.59	0.07	2.59	1.81
Q8	C17H14O7	330.29	24	16	3	7	86.97	109.36	-4.1	2.63E-02	7.97E-05	Moderately soluble	2.51	3.04	2.59	0.07	2.59	2.13
Q9	C17H14O7	330.29	24	16	3	7	86.97	109.36	-3.56	9.04E-02	2.74E-04	Soluble	2.51	2.19	2.59	-0.07	2.59	1.96
Q10	C17H14O7	330.29	24	16	3	7	86.97	109.36	-4.25	1.86E-02	5.63E-05	Moderately soluble	2.61	3.28	2.59	-0.07	2.59	2.2
Q11	C17H14O7	330.29	24	16	3	7	86.97	109.36	-3.22	2.01E-01	6.08E-04	Soluble	2.36	1.64	2.59	-0.07	2.59	1.82
Q12	C17H14O7	330.29	24	16	3	7	86.97	109.36	-3.56	9.04E-02	2.74E-04	Soluble	2.81	2.19	2.59	-0.07	2.59	2.02
Q13	C17H14O7	330.29	24	16	3	7	86.97	109.36	-4.25	1.86E-02	5.63E-05	Moderately soluble	1.84	3.28	2.59	-0.07	2.59	2.05
Q14	C17H14O7	330.29	24	16	3	7	86.97	109.36	-3.9	4.13E-02	1.25E-04	Soluble	2.36	2.73	2.59	-0.07	2.59	2.04

Q15	C17H14O7	330.29	24	16	3	7	86.97	109.36	-4.25	1.86E-02	5.63E-05	Moderately soluble	2.83	3.28	2.59	-0.07	2.59	2.25
Q16	C18H16O7	344.32	25	16	2	7	91.44	98.36	-3.82	5.26E-02	1.53E-04	Soluble	2.6	2.59	2.9	-0.17	3.12	2.28
Q17	C18H16O7	344.32	25	16	2	7	91.44	98.36	-3.82	5.26E-02	1.53E-04	Soluble	3.09	2.59	2.9	0.17	3.12	2.38
Q18	C18H16O7	344.32	25	16	2	7	91.44	98.36	-3.77	5.82E-02	1.69E-04	Soluble	2.7	2.52	2.9	0.17	3.12	2.28
Q19	C18H16O7	344.32	25	16	2	7	91.44	98.36	-4.46	1.20E-02	3.48E-05	Moderately soluble	2.9	3.61	2.9	0.17	3.12	2.54
Q20	C18H16O7	344.32	25	16	2	7	91.44	98.36	-4.11	2.66E-02	7.72E-05	Moderately soluble	2.56	3.06	2.9	0.17	3.12	2.36
Q21	C18H16O7	344.32	25	16	2	7	91.44	98.36	-4.11	2.66E-02	7.72E-05	Moderately soluble	3	3.06	2.9	0.17	3.12	2.45
Q22	C18H16O7	344.32	25	16	2	7	91.44	98.36	-4.46	1.20E-02	3.48E-05	Moderately soluble	2.9	3.61	2.9	0.17	3.12	2.54
Q23	C18H16O7	344.32	25	16	2	7	91.44	98.36	-3.43	1.29E-01	3.75E-04	Soluble	2.68	1.97	2.9	0.17	3.12	2.17
Q24	C18H16O7	344.32	25	16	2	7	91.44	98.36	-4.46	1.20E-02	3.48E-05	Moderately soluble	3.26	3.61	3.2	0.17	3.12	2.61
Q25	C19H18O7	358.34	26	16	1	7	95.91	87.36	-4.03	3.37E-02	9.40E-05	Moderately soluble	3.26	2.92	3.2	0.4	3.66	2.69
Q26	C19H18O7	358.34	26	16	1	7	95.91	87.36	-4.03	3.37E-02	9.40E-05	Moderately soluble	3.27	2.92	3.2	0.4	3.66	2.69
Q27	C19H18O7	358.34	26	16	1	7	95.91	87.36	-4.03	3.37E-02	9.40E-05	Moderately soluble	3.41	2.92	3.2	0.4	3.66	2.72
Q28	C19H18O7	358.34	26	16	1	7	95.91	87.36	-4.37	1.52E-02	4.23E-05	Moderately soluble	3.58	3.47	3.2	0.4	3.66	2.86
Q29	C19H18O7	358.34	26	16	1	7	95.91	87.36	-4.03	3.37E-02	9.40E-05	Moderately soluble	2.96	2.92	3.2	0.4	3.66	2.63
Q30	C20H20O7	372.37	27	16	0	0	100.38	76.36	-4.24	2.15E-02	5.77E-05	Moderately soluble	3.59	3.25	3.5	0.63	4.21	3.04
Reference (Sitagliptin)	C16H15F6N5O	407.31	28	11	1	7	87.25	77.04	-2.7	8.11E-01	1.99E-03	Soluble	2.35	0.7	3.9	2.52	3.08	2.51

Table 4: *in silico* drug likeness and medicinal chemistry predictions of Quercetin and its O-alkyl derivatives

Molecule	Drug likeness (0 means yes)						Medicinal chemistry				Absorption and Metabolism						
	Lipinski violations	Ghose violations	Veber violations	Egan violations	Muegge violations	Bioavailability Score	PAINS alerts	Brenk alerts	Leadlikeness violations	Synthetic Accessibility	GI absorption	BBB permeant	Pgp substrate	CYP1A2 inhibitor	CYP2D6nihibitor	CYP3A4 inhibitor	log Kp (cm/s)
Parent	0	0	0	0	0	0.55	1	1	Yes	3.23	High	No	No	Yes	Yes	Yes	-7.05
Q1	0	0	0	0	0	0.55	1	1	Yes	3.29	High	No	No	Yes	Yes	Yes	-6.31
Q2	0	0	0	0	0	0.55	1	1	Yes	3.33	High	No	No	Yes	Yes	Yes	-7.29
Q3	0	0	0	0	0	0.55	1	1	Yes	3.3	High	No	No	Yes	Yes	Yes	-6.9
Q4	0	0	0	0	0	0.55	0	0	Yes	3.26	High	No	No	Yes	Yes	Yes	-6.9
Q5	0	0	0	0	0	0.55	0	0	Yes	3.26	High	No	No	Yes	Yes	Yes	-6.13
Q6	0	0	0	0	0	0.55	1	1	Yes	3.46	High	No	No	Yes	Yes	Yes	-6.7
Q7	0	0	0	0	0	0.55	1	1	Yes	3.43	High	No	Yes	Yes	Yes	Yes	-7.15
Q8	0	0	0	0	0	0.55	1	1	Yes	3.43	High	No	No	Yes	Yes	Yes	-6.16
Q9	0	0	0	0	0	0.55	0	0	Yes	3.36	High	No	No	Yes	Yes	Yes	-6.76
Q10	0	0	0	0	0	0.55	0	0	Yes	3.4	High	No	No	Yes	Yes	Yes	-5.99
Q11	0	0	0	0	0	0.55	0	0	Yes	3.44	High	No	Yes	Yes	Yes	Yes	-7.15
Q12	0	0	0	0	0	0.55	0	0	Yes	3.41	High	No	No	Yes	Yes	Yes	-6.76
Q13	0	0	0	0	0	0.55	0	0	Yes	3.4	High	No	No	Yes	Yes	Yes	-5.99
Q14	0	0	0	0	0	0.55	0	0	Yes	3.43	High	No	No	Yes	Yes	Yes	-6.38
Q15	0	0	0	0	0	0.55	0	0	Yes	3.41	High	No	No	Yes	Yes	Yes	-5.99
Q16	0	0	0	0	0	0.55	1	1	Yes	3.56	High	No	No	Yes	Yes	Yes	-6.56
Q17	0	0	0	0	0	0.55	0	0	Yes	3.54	High	No	No	Yes	Yes	Yes	-6.56
Q18	0	0	0	0	0	0.55	0	0	Yes	3.51	High	No	No	Yes	Yes	Yes	-6.61
Q19	0	0	0	0	0	0.55	0	0	Yes	3.5	High	No	No	Yes	Yes	Yes	-5.84
Q20	0	0	0	0	0	0.55	0	0	Yes	3.57	High	No	No	Yes	Yes	Yes	-6.23
Q21	0	0	0	0	0	0.55	0	0	Yes	3.54	High	No	No	Yes	Yes	Yes	-6.23
Q22	0	0	0	0	0	0.55	0	0	Yes	3.5	High	No	No	Yes	Yes	Yes	-5.84
Q23	0	0	0	0	0	0.55	0	0	Yes	3.53	High	No	Yes	Yes	Yes	Yes	-7
Q24	0	0	0	0	0	0.55	0	0	Yes	3.54	High	No	No	Yes	Yes	Yes	-5.84
Q25	0	0	0	0	0	0.55	0	0	Yes	3.67	High	No	No	Yes	Yes	Yes	-6.41
Q26	0	0	0	0	0	0.55	0	0	Yes	3.67	High	No	No	Yes	Yes	Yes	-6.41

Q27	0	0	0	0	0	0.55	0	0	Yes	3.64	High	No	No	Yes	Yes	Yes	-6.41
Q28	0	0	0	0	0	0.55	0	0	Yes	3.64	High	No	No	Yes	Yes	Yes	-6.02
Q.29	0	0	0	0	0	0.55	0	0	Yes	3.67	High	No	No	No	Yes	Yes	-6.41
Q30	0	0	0	0	0	0.55	0	0	Yes	3.78	High	YES	No	No	No	Yes	-6.26
Sitagliptin	0	0	0	0	0	0.55	0	1	Yes	3.5	High	YES	Yes	No	No	No	-8.29

Table 5: Systematic ADME/T evaluation of Quercetin and its O-alkyl derivatives

Compounds	**LD_{50}** (-log mol/kg)	**Toxicity** (mg/kg)	**FDAMDD**	**H-HT**	**Skin Sensitization**	**DILI**	**hERG Blocker**	**Ames Mutagenicity**	**$T_{1/2}$ (Half Life Time,h)**	**CL (Clearance Rate** mL/min/kg**)**	**LogP (Distribution coefficient P)**
Quercetin	2.636	698.794	0.586	+	---	+++	-	++	0.2	2.045	1.988
Q1	2.712	613.834	-	+	---	++	-	-	0.665	1.954	2.291
Q2	2.727	592.995	+	+	---	+++	-	++	0.708	1.94	2.291
Q3	2.739	576.834	-	+	---	+++	-	++	0.716	1.939	2.291
Q4	2.719	604.02	+	+	---	+++	-	---	0.658	1.951	2.291
Q5	2.711	615.249	+	+	---	+++	-	---	0.629	1.941	2.291
Q6	2.76	573.982	-	+	---	+++	-	+	1.12	1.887	2.594
Q7	2.786	540.627	-	+	---	+++	-	+	1.161	1.858	2.594
Q8	2.767	564.804	-	+	---	+++	-	+	1.132	1.864	2.594
Q9	2.759	575.305	+	+	---	++	-	---	1.054	1.894	2.594
Q10	2.754	581.967	+	+	---	++	-	---	1.098	1.893	2.594
Q11	2.768	563.505	+	+	---	+++	-	---	1.291	1.886	2.594
Q12	2.782	545.63	+	+	---	+++	-	---	1.117	1.884	2.594
Q13	2.738	603.807	+	+	---	++	-	---	1.078	1.888	2.594
Q14	2.772	558.339	+	+	---	+++	-	---	1.107	1.868	2.594
Q15	2.787	539.384	+	+	---	+++	-	---	1.107	1.875	2.594

Q16	2.846	490.864	-	+	---	+++	+	-	1.717	1.829	2.897
Q17	2.859	476.388	+	+	---	+++	+	---	1.741	1.843	2.897
Q18	2.868	466.617	+	+	---	+++	+	---	1.678	1.854	2.897
Q19	2.821	519.949	+	+	---	++	+	---	1.65	1.868	2.897
Q20	2.835	503.455	+	+	---	+++	+	---	1.65	1.844	2.897
Q21	2.861	474.199	+	+	---	+++	+	---	1.704	1.842	2.897
Q22	2.821	519.949	+	+	---	++	+	---	1.65	1.868	2.897
Q23	2.842	495.406	+	+	---	+++	+	---	1.721	1.864	2.897
Q24	2.853	483.015	+	+	---	+++	+	---	1.67	1.839	2.897
Q25	2.901	450.093	+	+	---	+++	+	-	1.786	1.77	3.2
Q26	2.898	453.213	+	+	---	+++	+	-	1.773	1.774	3.2
Q27	2.878	474.572	+	+	---	+++	+	-	1.769	1.792	3.2
Q28	2.903	448.025	+	+	---	+++	+	-	1.739	1.787	3.2
Q.29	2.897	454.258	+	+	---	+++	+	-	1.731	1.789	3.2
Q30	2.711	724.4	+	+	---	+++	+	-	1.796	1.75	3.503
Sitagliptin	3.144	292.371	+	+++	-	+	---	-	1.218	1.25	2.017