ISSN: 0975-8585

Research Journal of Pharmaceutical, Biological and Chemical Sciences

In-Silico Screening of Some Quinazolinone Derivatives as Dipeptidyl Peptidase-IV Inhibitors For Antihyperglycemic Activity

Amit G Nerkar[1]*, Ajay M Sisode[2], and Sanjay D Sawant[1].

[2]Research Scholar, [1]Faculty of Pharmaceutical Chemistry, Department of Pharmaceutical Chemistry, Sinhgad Institute's Smt. Kashibai Navale College of Pharmacy, Kondhwa, Pune-48, M.S.

ABSTRACT

In this paper research the objective is to study *in-silico* screening, synthesis, characterize and in-vitro evaluation of some Quinazolin-e/one and its derivatives as Dipeptidyl peptidase (DPP-IV) inhibitors for antihyperglycemic activity. The present study gives a new series of Quinazolin-e/one and its derivatives as potent DPP-IV inhibitors for antihyperglycemic activity. V-Life MDS 4.4 software and PreADMET software were used for *in-silico* screening and ADME studies of selected compound for actual synthesis and in-vitro evaluation. Sitagliptin (-40.61) was used as standard .*in silico* screening of 1200 Quinazoline and derivatives of Quinazoline containing molecules was carried out on DPP-IV enzyme to obtain best fit nitrogenous heterocyclic compound for DPP-IV inhibition and molecules were prioritized with their comparable docking score which are compared with Sitagliptin .ADMET parameters like HIA, Caco2 cell permeability, MDCK and PPB were considered for prioritization. Statistical data of molecules showed potent antihyperglycemic activity. Compounds ASN1, ASN2, ASN4, ASN5, ASN9 and ASN10 with higher docking score were selected which are showing potent antihyperglycemic activity. These can further serve as templates for development of antihyperglycemic agents.

Keywords: Quinazoline, Quinazolinone, *in-silico,* ADME, Molecular docking, Antihyperglycemic.

Corresponding author

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INTRODUCTION

Diabetes mellitus is metabolic disorder which is characterized by high blood glucose level and insulin resistance. Type 2 diabetes mellitus (T2DM) is major cause of mortality. Inhibition of Dipeptidyl peptidase-IV (DPP-IV) plays a major role in treatment of diabetes.

Dipeptidyl peptidase-IV (DPP-IV)

Dipeptidyl peptidase-IV having E.C. no. 3.4.14.5 is also known as adenosine deaminase complexing protein. DPP-IV is responsible for the degradation of incretins which leads to increase in blood glucose level. DPP-IV inhibitors block DPP-IV enzyme which prevent degradation of incretins and regulate blood glucose level in body.

Type 2 diabetes is a chronic metabolic disease which is produced due to inability of the β-cells in the pancreas to secrete sufficient amounts of insulin. Insulin resistance and increased hepatic glucose production increases demand for insulin. Recent treatments are not sufficient to achieve control and produces undesirable side effect like hypoglycaemia, weight gain etc. Recent study of new drugs on mechanism of insulin production and its regulation of metabolism of sugar in body .Current study of DPP-IV has been found to plays important role.[5]

Quinazolin-e/ones as DPP-IV inhibitors

Research on Quinazolin-e/one and its derivatives lead to develop a new series of antihyperglycemic agent. A new series of Quinazolin-e/one was designed to resemble Sitagliptin structural feature and fitted with functional group to enhance inhibition activity of DPP-IV enzyme. So with this aim, in this paper it was attempted to study DPP4 inhibitors by drug design. Considering importance of DPP4 enzyme, it was chosen as target and with literature of Quinazoline and quinazolinone, these were found to be potent DPP4 enzyme inhibitor hence chosen for this research. In silico prioritization of these lead moieties as DPP4 enzyme inhibitor for antihyperglycemic activity was performed by VLife science MDS 4.4 drug design software. This research work reports in silico prioritization performed before actual synthesis, in-vitro pharmacological screening and in-vivo evaluation to obtain best fit Quinazolinones as potent DPP-IV inhibitors for antihyperglycemic activity.

MATERIALS AND METHODS

In-silico ADME predictions were obtained from www.bmrd.org. VLife MDS 4.4 Drug Design software for docking simulation on windows os. Chem draw Ultra 8.0 and Marvin beans used to draw structure and conversion of 2D to3D in mol files. 2D structure of ligand were prepared in Marvin sketch and convert to 3D by V-life science MDS 4.4 Drug design software. The 3D structure was stabilized by minimizing energy using molecular mechanics followed by Merck molecular force field (MMFF).The PDB of DPP-IV inhibitor receptor was obtained from protein data base with www.rcsb.org. The PDB was subjected for docking study.

In silico docking

In silico docking study were carried out using Vlife MDS 4.4 software. In silico screening was performed with selection of appropriate protein structure. The protein data bank file 4DSA for Anti-hyperglycaemic receptor was selected after comparative analysis from PDB sum and subjected to docking study. The obtained docking score were comparable with standard sitagliptin having score of (-40.61).

EXPERIMENTAL

In-silico screening

ADME Prediction

PreADMET software is used to obtain following *In-silico* ADME parameters.

$Caco_2$: cell permeability

ISSN: 0975-8585

$Caco_2$ cell permeability is used to determine the apparent permeability values of compounds within a specific range, molecules were solvated *in silico* at pH 7.4. By using Caco2 cells the apparent permeability values of compounds were determined. The range of Caco2 cell was found to be 4-70 nm/sec.

MDCK cell permeability

MDCK means Madin-Darby Canine Kidney cell. MDCK cells are used to determine apparent permeability values of used compounds. The range of MDCK is 25- 500 nm/sec.

Human Intestinal Absorption (HIA)

HIA data is sum of absorption and bioavailability obtained from ratio of excretion/cumulative excretion in urine, bile and faces. The range of HIA is 20- 70%.

Plasma Protein Binding

A unionised drug is available for diffusion or transport across cell membranes and interaction with a pharmacological target. *In-silico* ADME prediction is shown in table1.

Table 1: It shows *in silico* ADME Prediction data for selected compound.

Compound	HIA@	Caco2 cell permeability++	MDCK+++	PPB	BBB
ASN1	95.34	19.96	0.3460	89.070	0.035
ASN2	95.26	20.20	29.100	85.970	0.120
ASN3	93.12	20.88	1.6644	87.970	0.057
ASN4	92.70	20.11	19.560	49.710	0.033
ASN5	86.32	15.60	4.2599	61.560	0.051
ASN6	90.25	20.88	4.8382	43.860	0.049
ASN7	89.01	19.86	5.7331	39.220	0.043
ASN8	96.91	34.40	0.0434	100.00	9.319
ASN9	97.63	21.92	0.0433	100.00	0.113
ASN10	94.83	20.76	2.5170	37.790	0.048

@HIA = Human Intestinal Absorption. ++$Caco_2$ cell permeability = human colon adenocarcinoma and possess multiple drug transport pathways through the intestinal epithelium. +++MDCK = Madin-Darby canine kidney cell. PPB = Plasma Protein Binding.

Docking study

VLife MDS 4.4 software is used for docking experiment. Docking studies involves following steps.

Selection of Protein data bank

In the selection process 3D structure of protein is analysed Protein (4DSA) was selected after a comparative analysis of different pdb protein structures.

Protein Validation

Ramachandran plot and Errata plot was used for protein validation. The Ramachandran plot showed residue in favoured region and allowed region. Fig.1 shows Ramachandran plot of protein PDB. Then protein subjected for active site analysis, optimization and docking study on V-Life MDS 4.4 software.

Errata plot was obtained from NIH MBI server for evaluation of protein and is showed in Fig.2

ISSN: 0975-8585

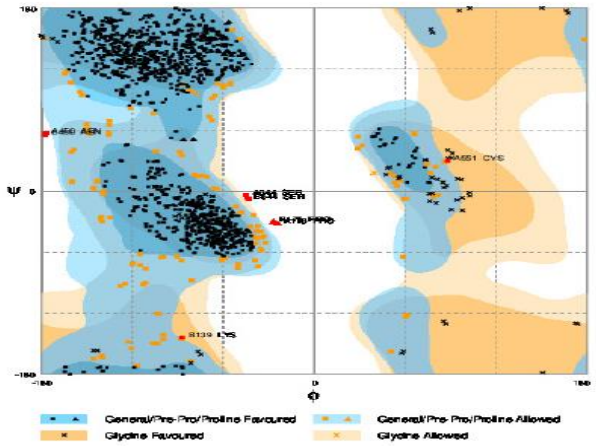

Figure 1: Ramachandran plot of PDB

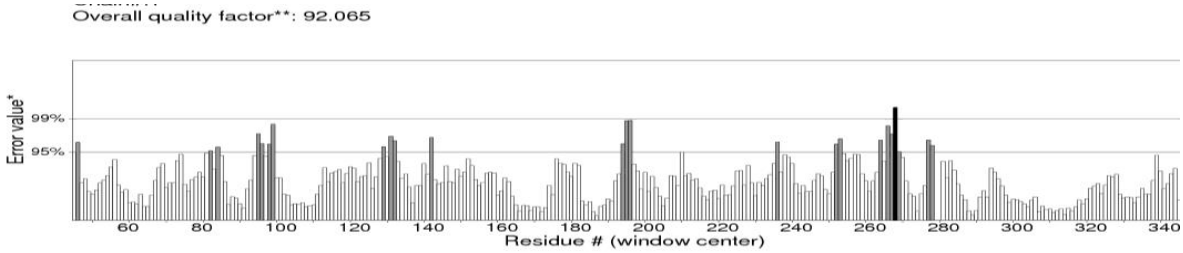

Figure 2: Errata report of PDB

Active site analysis of 4DSA:

4DSA shows 4 cavities out of which cavity 1 was selected since it contained co-crystallized ligand. This site abundantly had lipophilic residues.

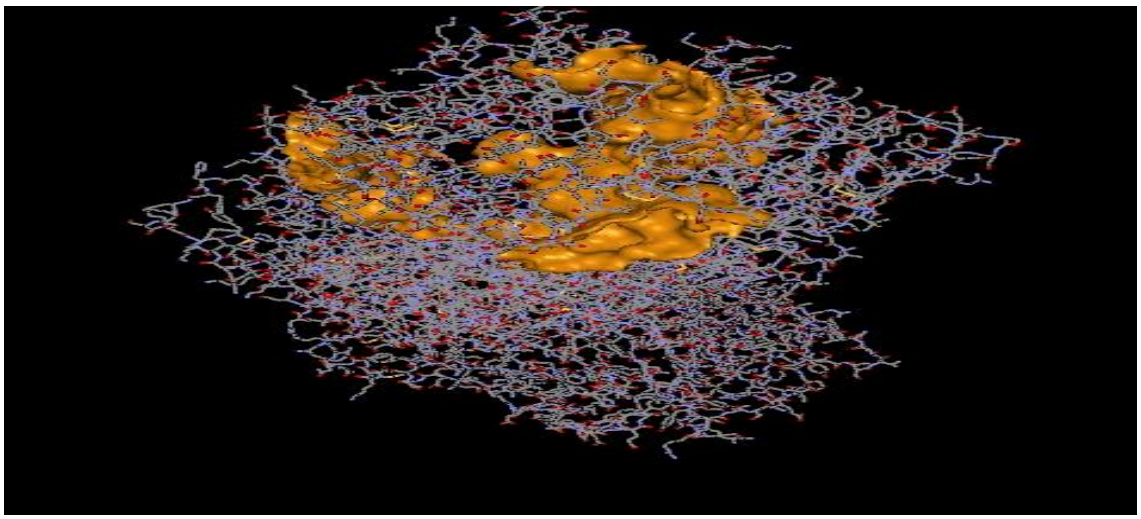

Fig. 3: It shows the co-ordinates, shape and active residues involved in 4DSA.

Protein pdb optimization

Water molecules were removed and addition of hydrogen atoms was performed and original ligand present in co-crystallized form was extracted out. Optimization of protein was done and this file used for docking studies.

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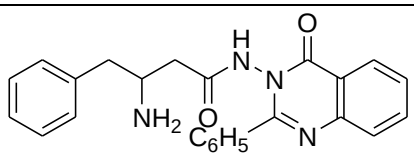
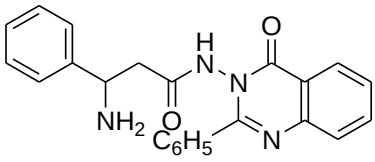
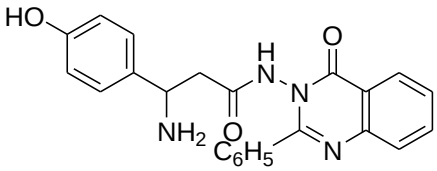
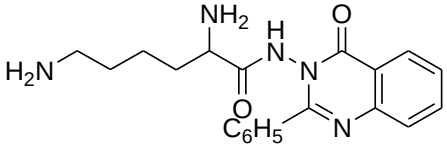
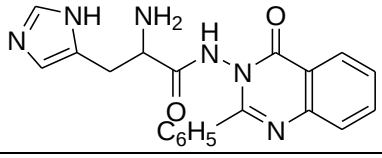
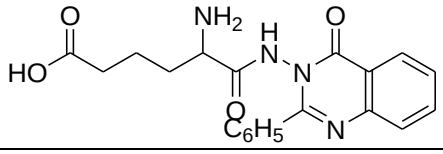
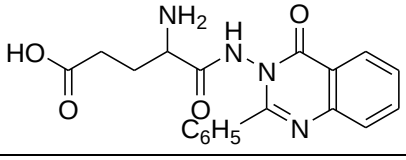
Library design and ligand preparation

Marwin bean software was used to draw molecular structure of ligands. V-Life MDS 4.4 was used to convert 2D mol files into 3D mol files. Designed molecules were series shown below. Library of total 131 compounds was developed. Structures of ligands were designed shown from series 1: 6,8-dihalo-(substituted/unsubstituted)2-alkyl-3-substituted-quinazolin-4(3H)-ones. Series8: 2-alkyl-3-substituted- N-((3-(4-substituted phenyl)-5-(9H-carbazole-3-yl)-4,5-dihydroisoxazol-4-yl)methyl)-4-substituted aniline-quinazolin-4(3H)-ones.

Docking of ligand:

Vlife MDS 4.4 software used for docking. Grip docking was done. Grip based docking id exhaustive and rigid docking method, in which conformer of ligands generated. Choice of receptor cavity was chosen and grid is generated around cavity. Cavity points are found and the centre of mass of ligand is moved to each cavity point. All rotations of ligand are scanned at each cavity point where ligand is placed. For each rotation a pose of ligand is generated and corresponding bumps are checked for each pose of ligand and pose of ligand with the best score is given as output. Result of docking score, inhibition constant and binding energy are shown below in table no. (2-11).

Table 2: It shows ligand of series 1

Sr. No.	Compound no.	Structure	Docking Score
1	ASN1		-64.90
2	ASN2		-56.21
3	ASN3		-60.25
4	ASN4		-50.63
5	ASN5		-52.82
6	ASN6		-56.75
7	ASN7		-53.98

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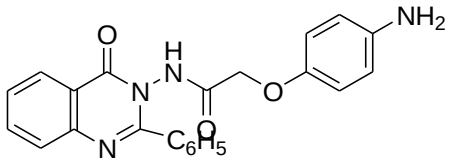
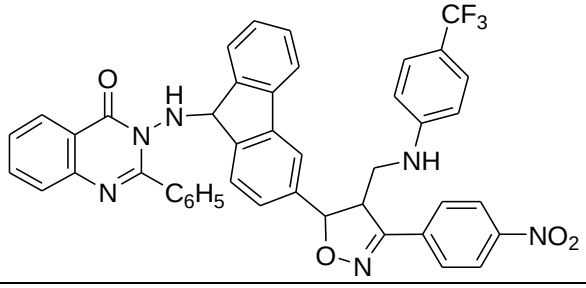
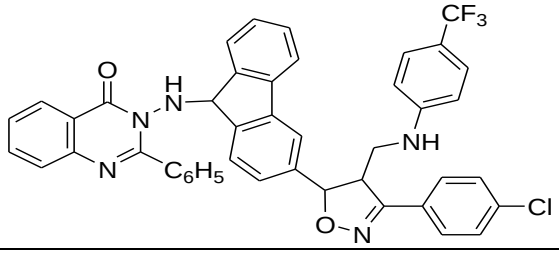
8	ASN8		-51.22
9	ASN9		-79.29
10	ASN10		-76.18
	Sitagliptin	-	-40.61

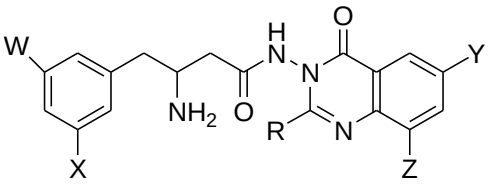


Table 3: It shows ligand of series 2

Sr. No.	Compound No.	R	W	X	Y	Z	Docking Score
11	ASN 11	CF_3	Br	Br	H	H	- 38.14
12	ASN 12	CF_3	Br	Br	H	H	-43.58
13	ASN 13	CH_3	Br	Br	H	H	-41.28
14	ASN 14	CH_3	Br	Br	Br	Br	-36.72
15	ASN 15	H	Br	Br	H	H	-42.05
16	ASN 16	H	Br	Br	Br	Br	-35.49
17	ASN 17	H	H	H	H	H	-32.70
18	ASN 18	CF_3	H	H	H	H	-34.59
19	ASN 19	CF_3	Cl	Cl	Cl	Cl	-42.00
20	ASN 20	CF_3	I	I	I	I	-40.71
21	ASN 21	CF_3	NH_2	NH_2	NH_2	NH_2	-40.97
22	ASN 22	CH_3	H	H	Br	Br	-48.09
23	ASN 23	CF_3	H	H	Br	Br	-42.83
24	ASN 24	CH_3	H	H	H	H	-30.13
25	ASN 25	C_6H_5	H	H	H	H	-64.90
26	ASN 26	C_6H_5	H	H	Br	Br	-50.75
27	ASN 27	CF_3	H	H	H	H	-39.46
28	ASN 28	C_6H_5	Br	Br	Br	Br	-43.42
29	ASN 29	C_6H_5	Br	Br	H	H	-43.66
30	ASN 30	C_6H_5	Cl	Cl	H	H	-49.32
	Sitagliptin	-	-	-	-	-	-40.61

ISSN: 0975-8585

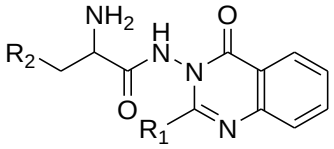
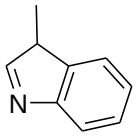
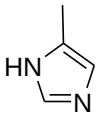
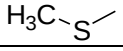


Table 4: It shows ligand of series 3

Sr. NO.	Compound No.	R_1	R_2	Docking Score
31	ASN 31	C_6H_5	C_6H_5	-38.50
32	ASN 32	C_6H_5	4-OH C_6H_4	-51.40
33	ASN 33	C_6H_5		-43.23
34	ASN 34	C_6H_5		-43.16
35	ASN 35	C_6H_5		-34.09
	Sitagliptin	-	-	-40.61

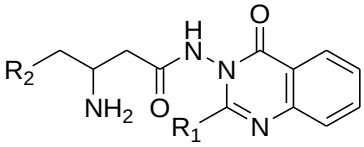
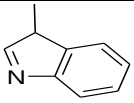
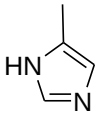
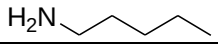
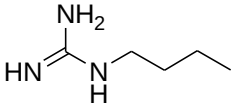
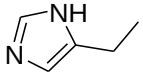
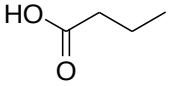
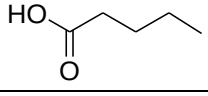


Table 5: It shows ligand of series 4

Sr. NO.	Compound No.	R_1	R_2	Docking Score
36	ASN 36	C_6H_5	C_6H_5	-60.88
37	ASN 37	C_6H_5	4-OH C_6H_4	-47.88
38	ASN 38	C_6H_5		-45.27
39	ASN 39	C_6H_5		-50.44
40	ASN 40	C_6H_5	$(CH_3)_2CH$-	-42.22
41	ASN 41	C_6H_5		-39.62
42	ASN 42	C_6H_5		-40.74
43	ASN 43	C_6H_5		-48.53
44	ASN 44	C_6H_5		-54.89
45	ASN 45	C_6H_5		-50.61
	Sitagliptin	-	-	-40.61

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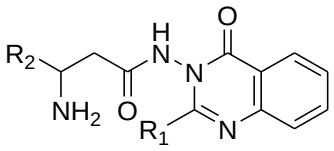
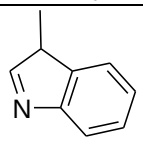
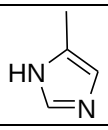


Table 6: It shows ligand of series 5

Sr. NO.	Compound No.	R_1	R_2	Docking Score
46	ASN 46	C_6H_5	C_6H_5	-50.86
47	ASN 47	C_6H_5	4-OH C_6H_4	-60.25
48	ASN 48	C_6H_5		-50.03
49	ASN 49	C_6H_5		-38.17
	Sitagliptin	-	-	-40.61

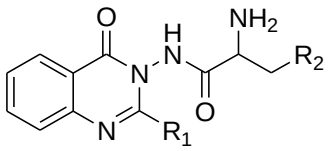
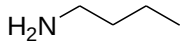
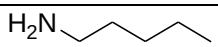
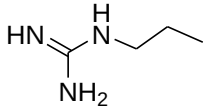
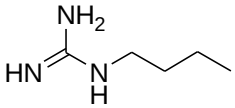
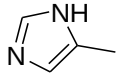
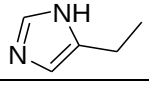
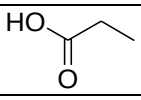
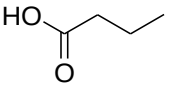
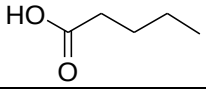


Table 7: It shows ligand of series 6

Sr. NO.	Compound No.	R_1	R_2	Docking Score
50	ASN 50	C_6H_5	$(CH_3)_2CH$-	-41.62
51	ASN 51	C_6H_5		-50.63
52	ASN 52	C_6H_5		-43.15
53	ASN 53	C_6H_5		-44.45
54	ASN 54	C_6H_5		-38.54
55	ASN 55	C_6H_5		-52.82
56	ASN 56	C_6H_5		-41.49
57	ASN 57	C_6H_5		-50.37
58	ASN 58	C_6H_5		-56.75
59	ASN 59	C_6H_5		-37.80
	Sitagliptin	-	-	-40.61

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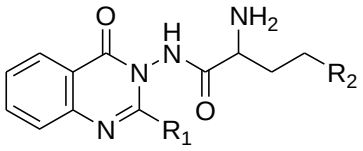
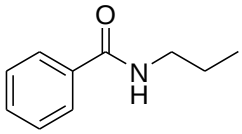
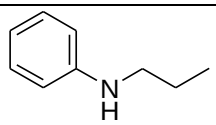
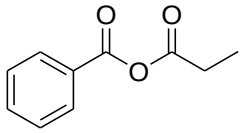
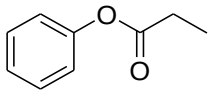
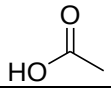
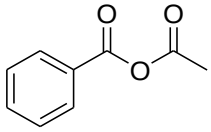
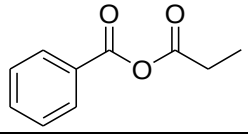


Table 8: It shows ligand of series 7

Sr. NO.	Compound No.	R_1	R_2	Docking Score
60	ASN 60	C_6H_5		-44.83
61	ASN 61	C_6H_5		-52.53
62	ASN 62	C_6H_5		-28.01
63	ASN 63	C_6H_5		-35.85
64	ASN 64	C_6H_5		-53.98
65	ASN 65	C_6H_5		-48.62
66	ASN 66	C_6H_5		-44.36
	Sitagliptin	-	-	-40.61

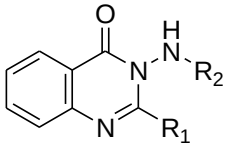
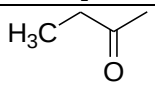
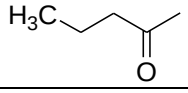
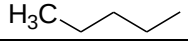
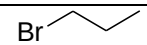
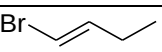
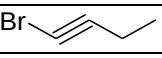


Table 9: It shows ligand of series 8

Sr. NO.	Compound No.	R_1	R_2	Docking Score
67	ASN 67	C_6H_5		-40.83
68	ASN 68	C_6H_5		-37.37
69	ASN 69	C_6H_5		-38.62
70	ASN 70	C_6H_5		-35.29
71	ASN 71	C_6H_5		-34.91
72	ASN 72	C_6H_5		-36.82

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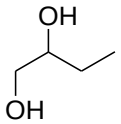
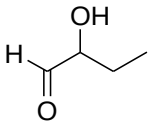
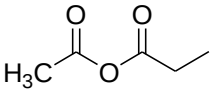
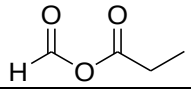
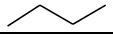
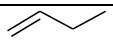
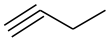
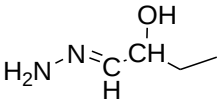
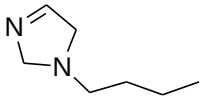
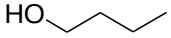
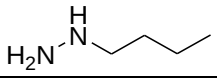
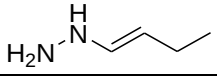
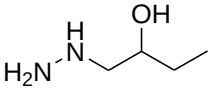
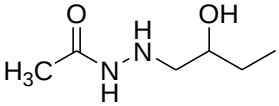
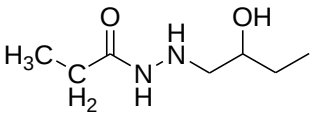
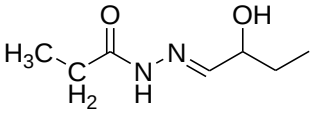
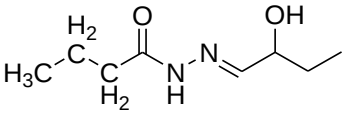
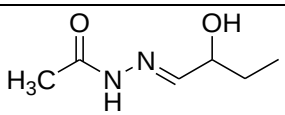
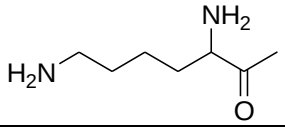
73	ASN 73	C_6H_5		-41.80
74	ASN 74	C_6H_5		-44.99
75	ASN 75	C_6H_5		-40.08
76	ASN 76	C_6H_5		-41.46
77	ASN 77	C_6H_5		-45.86
78	ASN 78	C_6H_5		-41.65
79	ASN 79	C_6H_5		-38.97
80	ASN 80	C_6H_5		-46.88
81	ASN 81	C_6H_5		-47.66
82	ASN 82	C_6H_5		-42.17
83	ASN 83	C_6H_5		-42.35
84	ASN 84	C_6H_5		-42.34
85	ASN 85	C_6H_5		-39.86
86	ASN 86	C_6H_5		-40.03
87	ASN 87	C_6H_5		-35.06
88	ASN 88	C_6H_5		-43.34
89	ASN 89	C_6H_5		-41.56
90	ASN 90	C_6H_5		-45.04
91	ASN 91	C_6H_5		-44.33

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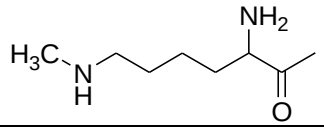
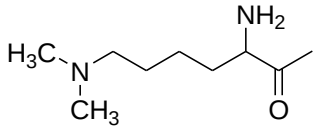
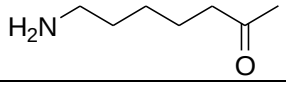
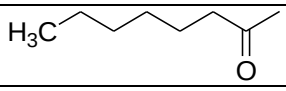
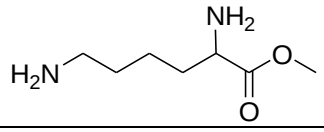
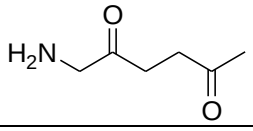
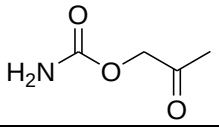
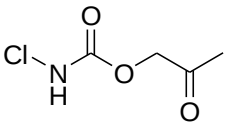
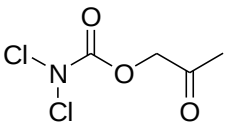
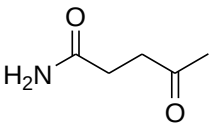
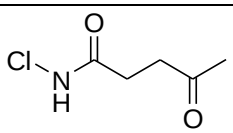
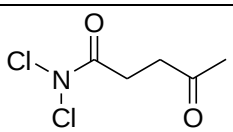
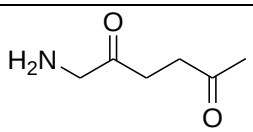
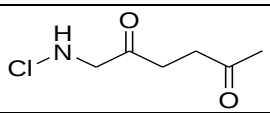
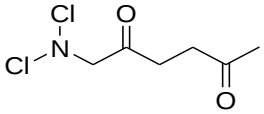
92	ASN 92	C_6H_5		-46.62
93	ASN 93	C_6H_5		-33.56
94	ASN 94	C_6H_5		-45.09
95	ASN 95	C_6H_5		-36.86
96	ASN 96	C_6H_5		-43.83
97	ASN 97	C_6H_5		-55.54
98	ASN 98	C_6H_5		-42.83
99	ASN 99	C_6H_5		-44.98
100	ASN 100	C_6H_5		-56.41
101	ASN 101	C_6H_5		-42.76
102	ASN 102	C_6H_5		-52.84
103	ASN 103	C_6H_5		-56.51
104	ASN 104	C_6H_5		-49.72
105	ASN 105	C_6H_5		-37.99
106	ASN 106	C_6H_5		-45.49
	Sitagliptin	-	-	-40.61

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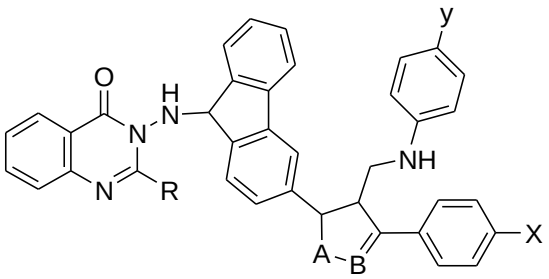


Table 10: It shows ligand of series 9

Sr. No.	Compound No.	R	A	B	X	Y	Docking Score
107	ASN 107	C_6H_5	O	N	H	H	-44.62
108	ASN 108	C_6H_5	O	N	Cl	Cl	-52.92
109	ASN 109	C_6H_5	O	N	Cl	CF_3	-76.18
110	ASN 110	C_6H_5	O	N	NO_2	CF_3	-79.29
111	ASN 111	C_6H_5	S	N	Cl	CF_3	-43.82
112	ASN 112	C_6H_5	S	N	NO_2	CF_3	-32.82
113	ASN 113	C_6H_5	S	N	Br	CF_3	-40.29
114	ASN 114	C_6H_5	S	N	F	CF_3	-24.89
115	ASN 115	C_6H_5	S	N	CF_3	CF_3	-42.56
116	ASN 116	C_6H_5	S	N	H	H	-50.21
	Sitagliptin	-	-	-	-	-	-40.61

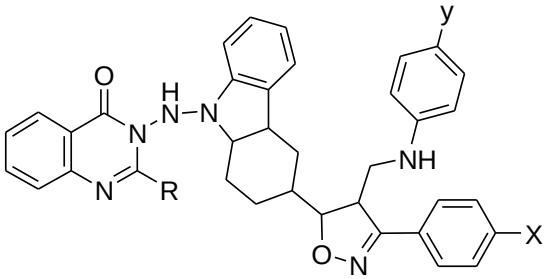
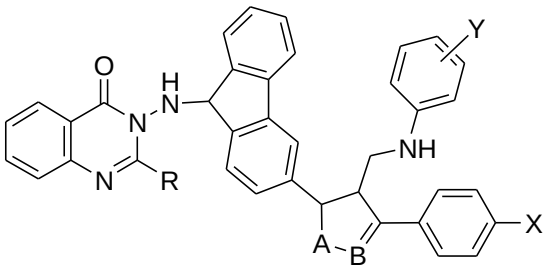


Table 11: It shows ligand of series 10

Sr. No.	Compound No.	R	X	Y	Docking Score
117	ASN 117	C_6H_5	H	H	-38.45
118	ASN 118	C_6H_5	NO_2	CF_3	-54.30
119	ASN 119	C_6H_5	Cl	CF_3	-57.94
120	ASN 120	C_6H_5	CF_3	CF_3	-43.17
	Sitagliptin	-	-	-	-40.61



Sr. No.	Compound No.	R	A	B	X	Y	Docking Score
121	ASN 121	C_6H_5	NH	N	Cl	p-CF_3	-58.43
122	ASN 122	C_6H_5	N	N	NO_2	p-CF_3	-58.52
123	ASN 123	C_6H_5	O	N	OH	p-CF_3	-58.47

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124	ASN 124	C_6H_5	O	N	Cl	p-CF_3	-64.12
125	ASN 125	C_6H_5	O	N	Cl	p-Cl	-50.36
126	ASN 126	C_6H_5	O	N	Cl	p-NO_2	-58.67
127	ASN 127	C_6H_5	O	N	NO_2	p-NO_2	-49.99
128	ASN 128	C_6H_5	O	N	Cl	m- NO_2	-55.33
129	ASN 129	C_6H_5	O	N	Cl	m-Cl, p-F	-57.35
130	ASN 130	C_6H_5	O	N	Cl	o-Cl, p-NO_2	-61.78
	Sitagliptin	-	-	-	-	-	-40.61

RESULT AND DISCUSSION

Form figure 1 and 2 the protein structure was validated. Around 1200 molecules was docked and screened best score prior to actual synthesis. Changes were made in substituent's position carried out. Alkyl/phenyl substitution on Quinazoline ring results in increased score and activity and it was found that it may results in increased anti-hyperglycemic activity.

All the molecules were found to be fitting the actual binding pocket of molecule Sitagliptin. Most of the good scoring ligands from the synthetic series 1,3,4,5,8 were obtained. From above work prioritized compounds are shown in fig. 4.

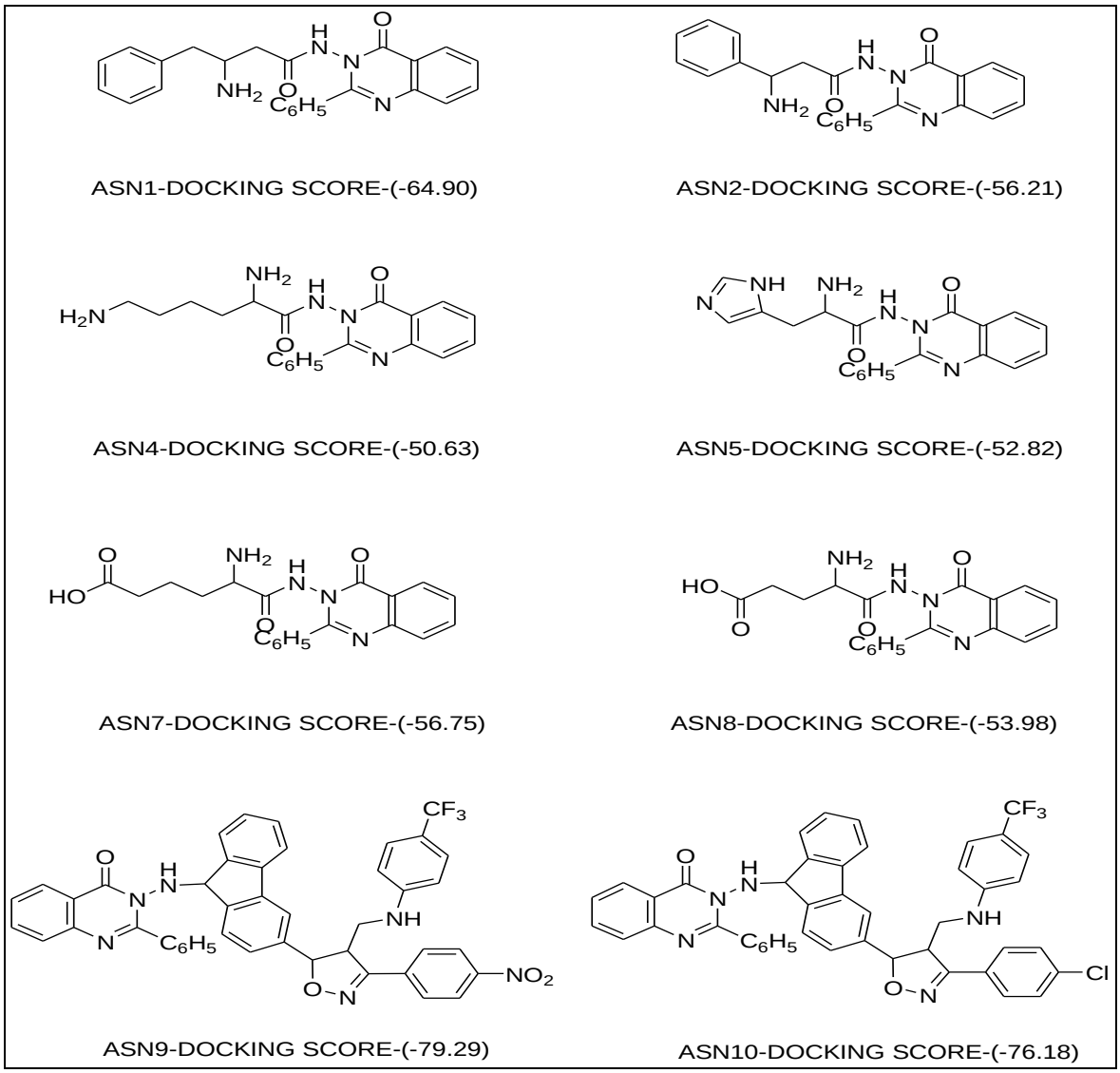

Fig.04: Prioritized Molecules

ISSN: 0975-8585

CONCLUSION

Most of ligands were found to be interacting with the amino acid residues of the active sites. The present work leads to the development of Quinazoline derivatives as an antihyperglycemic lead by *In-Silico* design. Compound ASN1, ASN2, ASN4, ASN5, ASN9 and ASN10 were found to be active *In Silico* as compared with Sitagliptin used as standard and can be considered as useful template for antihyperglycemic lead development.

ACKNOWLEDGEMENTS

The authors acknowledge Indian council for Medical Research (ICMR), a constituent of Ministry of Health and Family Welfare, New Delhi, autonomous for Medical Research in India.

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