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SYNTHESIS, EVALUATION AND MOLECULAR DOCKING OF SULPHONAMIDE/ISOTHIOCYANATE LINKED QUINAZOLINONE DERIVATIVES AS ANTIDIABETIC ACTIVITY

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ABSTRACT

A series of Quinazolinone linked sulphonamide and isothiocynates derivatives was designed synthesized and evaluated for type 2 diabeties study. Designed compound were docked using AutoDock tool software with DPP-IV inhibitor protein (PDB: 3OPM). And the good dock score compounds is synthesized and evaluated for antidiabetic study in STZ- Nicotinamide model of wistar rats. Amongst all the compounds designed in the study we identified compounds A3 and C6 as potent, selective and orally active agents.

KEYWORDS: Quinazolinone, Sulphonamide, Isothiocyanate, Type 2 diabeties, Molecular Docking, STZ-Nicotinamide model.

INTRODUCTION

Type 2 diabetes is a complex metabolic syndrome resulting in high blood glucose due to impaired insulin action, which in turn stimulates glucose uptake in peripheral tissues such as muscle and fat. In normal humans, up to 80% of insulin-stimulated glucose disposal occurs in skeletal muscle, a major site of insulin resistance in type 2 diabetes.[1] Glucagon like peptide (GLP-1)[2] and glucose dependent insulinotropic polypeptide (GIP) are incretin hormones, released from the gut in response to the food intake, responsible for the glucose dependent stimulation of insulin secretion through pancreatic β-cells.[3-4] Furthermore, GLP-1 slows gastric emptying, stimulates regeneration and differentiation of pancreatic β-cells while inhibiting glucagon secretion.[5] But the therapeutic effects of both these hormones are lost due to their rapid degradation (t½ ~ 1 min) by DPP-IVenzyme. Thus inhibition of DPP-IV has emerged as a novel approach for the treatment of type 2 diabetes (T2D).[6]

Quinazoline are classes of fused heterocycles that are of considerable interest because of the diverse range of their biological properties, for example, anticancer, diuretic, anti-inflammatory, anticonvulsant and antihypertensive activities.[7] Depending upon the position of theketo or oxo group, these compounds may be classified into two types: 2-(1*H*) quinazolinones(or) 1, 2-dihydro-2-oxo quinazolines and 4(3*H*)-quinazolines or 3, 4-dihydrooxoquinazolines. Quinazoline, being the central body of the pharmacophore holds different types of substituent. Based on their various physicochemical properties, they exerted a diversified range of therapeutic efficacy.

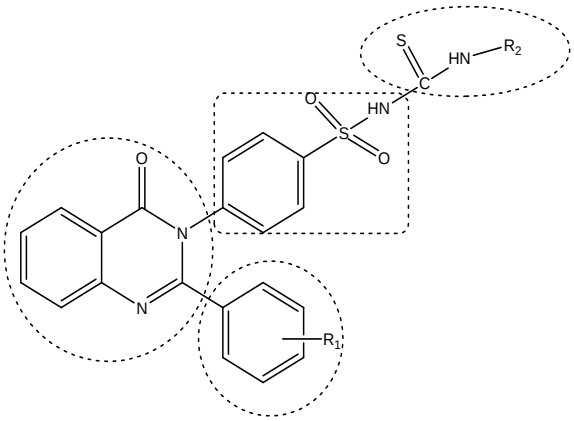


Fig. 1: Designed pharmacophore of Quinazolinone-sulfonamide/isothiocyanate for DPP-IV activity.

The quinazolinone and sulfonamide/isothiocyanatestructures were hybridized leading to the title compounds reported in this paper. In the present investigation, the designed quinazolinone-sulfonamide/ isothiocyanatehybrid derivatives (fig. 1) were synthesized in various steps that have been outlined

in Scheme 1. The synthesized derivatives were evaluated for their antidiabetic activity.

Experimental Section

Chemistry

All the chemicals and solvents were supplied by Merck Life Science Pvt. Ltd; LobaChemie and Research Lab Fine Chem Industry Pvt. Ltd. The reactions were monitored with the help of thin-layer chromatography using pre-coated aluminium sheets with silica gel, and the solvent systems used were n-Hexane-Ethyl Acetate (7:3) and Toluene: Ethyl Acetate (7:3). The spots were visualized under UV lamp. Melting points of the synthesized compounds were determined using one end open capillary tubes on Labronics LT-115 digital melting and boiling point apparatus and are uncorrected. IR spectrum was acquired on JASCO-FTIR 4100 spectrophotometer using KBr (ν max in cm^{-1}). ^1H NMR (DMSO and $CDCl_3$) spectra of the synthesized compounds were performed with $CDCl_3$ (unless specified) with TMS as internal reference (chemical shift in δ, ppm) using MERCURY VARIAN 500 MHz instrument in Pune University. All reactions were carried out under dried condition and performed using oven-dried glassware.

Step I: Synthesis of 4-(4-oxo-2-phenyl-1, 2, 3, 4-tetrahydroquinazolin-3-yl) benzene-1-sulphonamide (A to E)

A mixture of aldehyde (1 mmol) **2**, amine (1.1 mmol) **3**, andisatoic anhydride (1 mmol) **1** in 5 cm^3 acetic acid was stirredunder reflux for the appropriate time. After completion of the reaction, as indicated by TLC(Toluene: Ethyl Acetate: Methanol (7:2:1), the reaction mixture was poured into 20 cm3 ice water. On solidification, it wasfiltered, washed with ice water, and recrystallized fromethanol.[8]

{3-[4-oxo-3-(4-sulfamoylphenyl)-1, 2, 3, 4-tetrahydroquinazolin-2-yl] phenyl} azinic acid (A)

Yield: 82.60%, **Molecular formula**: $C_{20}H_{15}SN_4O_5$, **Molecular weight**: 423, **Melting point**: 220-225°C, **Rf**: 0.61 (eluent Toluene/Ethyl Acetate/Methanol, 7:2:1), **IR(KBr) in cm^{-1}**: 3415.31 cm^{-1}(N-H str. amine), 3316.96, 3214.7 cm^{-1}(N-H str. amine) 3092.3 cm^{-1} (aromatic C-H str), 1632.45 cm^{-1} (C=O str. amide), 1528.31 cm^{-1} (C=C bend. aromatic), 1330.64 cm^{-1} (S=O str.), 1170.58 cm^{-1} (S=O str.), 1248.68 cm^{-1} (C-N bend), 839 cm^{-1} (N-H bend), 749.20 cm^{-1} (S-N bend), **^1H NMR (600 MHz, DMSO) δ [ppm]**: 2.5 (s, 2H, NH_2), 6.65 (s, 1H, Ar-H), 6.18 (s, 1H, Ar-H), 7.31 (d, 1H, Ar-H), 8 (s, 1H, NH), 7.55 (d, 2H, Ar-H), 7.66 (s, 1H, Ar-H), 7.74 (d, 1H, Ar-H), 7.8 (d, 2H, Ar-H), 7.83 (s, 2H, Ar-H), 8.14 (s, 1H, Ar-H), 8.3(s, 1H, Ar-H).

4-[2-(2-hydroxyphenyl)-4-oxo-1, 2, 3, 4-tetrahydroquinazolin-3-yl] benzene-1-sulfonamide (B)

Yield: 135.80%, **Molecular formula**: $C_{20}H_{14}SN_4O_4$, **Molecular weight**: 390, **Melting point**: 188-190°C, **Rf**: 0.5 (eluent Toluene/Ethyl Acetate/Methanol, 7:2:1), **IR(KBr) in cm^{-1}**: 3369.03 cm^{-1}(N-H str. amine), 3294.79cm^{-1}(N-H str. amine) 3101.94cm^{-1}(aromatic C-H str), 1658.48 cm^{-1} (C=O str. amide), 1524.45 cm^{-1} (C=C bend. aromatic), 1331.61 cm^{-1} (S=O str.), 1185.04 cm^{-1} (S=O str.), 1039.44 cm^{-1} (C-N bend), 852.38 cm^{-1} (N-H bend), 730.88 cm^{-1} (S-N bend).

4-[2-(4-hydroxyphenyl)-4-oxo-1, 2, 3, 4-tetrahydroquinazolin-3-yl] benzene-1-sulfonamide (C)

Yield: 117, **Molecular formula**: $C_{20}H_{15}SN_3O_4$, **Molecular weight**: 377, **Melting point**: 200-210°C, **Rf**: 0.8 (eluent Toluene/Ethyl Acetate/Methanol, 7:2:1), **IR(KBr) in cm^{-1}**: 3370 cm^{-1}(N-H str. amine), 3292.86, 3217.87 cm^{-1}(N-H str. amine) 3103.87 cm^{-1}(aromatic C-H str), 1658.48 cm^{-1} (C=O str. amide), 1524.45 cm^{-1} (C=C bend. aromatic), 1372.1.64 cm^{-1}(S=O str.), 1158.04cm^{-1}(S=O str.), 1260.25 cm^{-1} (C-N bend), 827 cm^{-1} (N-H bend), 732.81 cm^{-1} (S-N bend).

4-[2-(4-methoxyphenyl)-4-oxo-1, 2, 3, 4-tetrahydroquinazolin-3-yl] benzene-1-sulfonamide (D)

Yield: 120%, **Molecular formula**: $C_{21}H_{17}SN_3O_4$, **Molecular weight**: 391, **Melting point**: 189-190°C, **Rf**: 0.42 (eluent Toluene/Ethyl Acetate/Methanol, 7:2:1), **IR (KBr) in cm^{-1}**: 3370 cm^{-1}(N-H str. amine), 3289.96 cm^{-1}(N-H str. amine) 3103.87 cm^{-1}(aromatic C-H str), 2935.13, 2849 cm^{-1}(CH str.) 1658.48 cm^{-1} (C=O str. amide), 1594.84cm^{-1} (C=C bend. aromatic), 1331.61cm^{-1} (S=O str.), 1260.25 cm^{-1} (C-N bend), 964.23 cm^{-1} (C-O str.) 853.34 cm^{-1} (N-H bend), 731.85 cm^{-1} (S-N bend).

4-[2-(4-chlorophenyl)-4-oxo-1,2,3,4-tetrahydroquinazolin-3-yl]benzene-1-sulfonamide (E)

Yield: 256.75%, **Molecular formula**: $C_{20}H_{14}SN_3O_3$, **Molecular weight**: 376, **Melting point**: 200-210°C, **Rf**: 0.55 (eluent Toluene/Ethyl Acetate/Methanol, 7:2:1), **IR(KBr) in cm^{-1}**: 3370 cm^{-1}(N-H str. amine), 3296.71 cm^{-1}(N-H str. amine) 3103.87 cm^{-1}(aromatic C-H str), 1658.48 cm^{-1} (C=O str. amide), 1594.84 cm^{-1} (C=C bend. aromatic), 1331.61 cm^{-1} (S=O str.), 1260.25 cm^{-1} (C-N bend), 853.34 cm^{-1} (N-H bend), 727.99 cm^{-1} (Cl str.).

Step II: Synthesis of 4-(4-oxo-2-phenyl-3, 4-dihydroquinazolin-3-yl) benzene-1-sulphonamide (AA to EE)

A mixture of 2, 3-dihydroquinazolin-4(1H)-ones (0.023 mol) and potassium permanganate (0.05 mol) in acetone (200 mL) was refluxed for 1h. Thereafter potassium permanganate (2.0g) was added and the mixture was refluxed for a further 1h. The $Mn0_2$ was filtered off and washed with $CHC1_3$. The filtrate and the washings were mixed and concentrated in vacuum and Recrystallized by 2-propanoldiisopropyl.[9]

{3-[4-oxo-3-(4-sulfamoylphenyl)-3,4-dihydroquinazolin-2-yl]phenyl}azinic acid (AA)
Yield: 49.18%, **Molecular formula**: $C_{20}H_{14}SN_4O_5$, **Molecular weight**: 422, **Melting point**: 118-120^oC, **Rf**: 0.57 (eluent Toluene/Ethyl Acetate/Methanol, 7:2:1), **IR(KBr) in cm^{-1}**: 3343.96 cm^{-1}(N-H str. amine) 3083.62 cm^{-1}(aromatic C-H str), 2930.31 cm^{-1}(CH str.) 1677.77 cm^{-1} (C=O str. amide), 1588.09 cm^{-1} (C=C bend. aromatic), 1530.24 cm^{-1}(N-O str.) 1348.96 cm^{-1} (S=O str.), 1159.97 cm^{-1} (S=O str.), 1098.26 cm^{-1} (C-N bend), 841 cm^{-1} (N-H bend), 774.27cm^{-1} (S-N bend), **^{1}H NMR (600 MHz, DMSO) δ [ppm]**: 2.5 (s, 2H, NH_2), 7.55 (t, 2H, Ar-H), 7.65 (d, 2H, Ar-H), 7.48 (s, 1H, Ar-H), 7.81 (s, 1H, Ar-H), 7.88 (d, 2H, Ar-H), 7.94 (s, 2H, Ar-H), 7.45 (s, 2H, Ar-H), 7.96 (s, 2H, Ar-H), 8.16 (d, 1H, Ar-H), 8.24 (d, 1H, Ar-H), 8.38(s, 1H, Ar-H).

4-[2-(2-hydroxyphenyl)-4-oxo-3, 4-dihydroquinazolin-3-yl] benzene-1-sulfonamide (BB)
Yield: 45.80, **Molecular formula**: $C_{20}H_{14}SN_3O_4$, **Molecular weight**: 392.41, **Melting point**: 115-116^oC, **Rf**: 0.53 (eluent Toluene/Ethyl Acetate/Methanol, 7:2:1), **IR(KBr) in cm^{-1}**: 3651.55 cm^{-1}(OH str.), 3343.96 cm^{-1}(N-H str. amine) 3083.62 cm^{-1}(aromatic C-H str), 2928.38 cm^{-1}(CH str.) 1677.77 cm^{-1} (C=O str. amide), 1588.09 cm^{-1} (C=C bend. aromatic), 1348.96 cm^{-1} (S=O str.), 1159.97 cm^{-1} (S=O str.), 841 cm^{-1} (N-H bend), 774.27cm^{-1} (S-N bend).

4-[2-(4-hydroxyphenyl)-4-oxo-3, 4-dihydroquinazolin-3-yl] benzene-1-sulfonamide (CC)
Yield: 47, **Molecular formula**: $C_{20}H_{14}SN_3O_4$, **Molecular weight**: 392.41, **Melting point**: 120-121^oC, **Rf**: 0.53 (eluent Toluene/Ethyl Acetate/Methanol, 7:2:1), **IR(KBr) in cm^{-1}**: 3373.95 cm^{-1}(OH str.), 3250.43 cm^{-1}(N-H str. amine) 3093.26 cm^{-1}(aromatic C-H str), 1640.16 cm^{-1} (C=O str. amide), 1598.7 cm^{-1} (C=C bend. aromatic), 1261.22 cm^{-1} (S=O str.), 1186.01 cm^{-1} (S=O str.), 825.38 cm^{-1} (N-H bend), 727.99 cm^{-1} (S-N bend).

4-[2-(4-methoxyphenyl)-4-oxo-3, 4-dihydroquinazolin-3-yl] benzene-1-sulfonamide (DD)
Yield: 48.66, **Molecular formula**: $C_{21}H_{16}SN_3O_4$, **Molecular weight**: 390, **Melting point**: 118-119^oC, **Rf**: 0.54 (eluent Toluene/Ethyl Acetate/Methanol, 7:2:1), **IR(KBr) in cm^{-1}**: 3299.61 cm^{-1}(N-H str. amine), 3093.26 cm^{-1}(aromatic C-H str), 2923.56, 2851.24 cm^{-1}(CH str.), 1656.55 cm^{-1} (C=O str. amide), 1593.88 cm^{-1} (C=C bend. aromatic), 1330.64 cm^{-1} (S=O str.), 1157.08 cm^{-1} (S=O str.), 825.34 cm^{-1} (N-H bend), 745.35 cm^{-1} (S-N bend).

4-[2-(4-chlorophenyl)-4-oxo-3, 4-dihydroquinazolin-3-yl] benzene-1-sulfonamide (EE)
Yield: 56.75, **Molecular formula**: $C_{20}H_{15}SN_3O_3Cl$, **Molecular weight**: 412.87, **Melting point**: 120-122^oC, **Rf**: 0.51 (eluent Toluene/Ethyl Acetate/Methanol, 7:2:1), **IR(KBr) in cm^{-1}**: 3251.4 cm^{-1}(N-H str. amine), 3093.26 cm^{-1}(aromatic C-H str), 2922.59, 2851.24 cm^{-1}(CH str.), 1675.84 cm^{-1} (C=O str. amide), 1593.88 cm^{-1} (C=C bend. aromatic), 1324.86 cm^{-1} (S=O str.), 1157.08 cm^{-1} (S=O str.), 834.06 cm^{-1} (N-H bend), 745.35 cm^{-1} (S-N bend), 695.21 cm^{-1}(Cl str.)

Step III: Synthesis of Isothiocyanate Derivatives (1-10)
The substituted aniline (0.1 mole) was dissolved in 50 ml benzene and treated with carbon disulfide (0.1 mole) and triethyl amine (0.1 mole) and the solution was cooled to 0^{o}C. After 72 hrs, the precipitated salt of triethylammoniumdithiocarbamate was filtered and washed with 30 mL diethyl ether and air dried for 10 min. The salt was then dissolved in 75 mL chloroform, treated with (0.1 mole) triethyl amine and cooled again to 0^{o}C. To this solution, ethyl chloroformate was added (0.1 mole) drop wise over a period of 15 minutes. The resulting solution was stirred at 0^{o}C for 10 min. and allowed to warm to room temperature during a 1 hr period. The chloroform solution was then washed with 100 mL 3M HCl solution and 2 X 75 mL water and was dried over sodium sulphate. The chloroform was evaporated in vacuum and the isothiocyanate was isolated.[10]

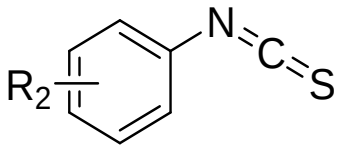


Fig. 2: Isothiocyanate Derivatives.

Table 1: Derivatives of Isothiocyante.

Sr.	R_2	MP/BP ^{0}C	% yield	RF value
1	3,4-dichloro	60-65	0.82	67.05
2	2,5-dichloro	48-50	0.73	74
3	H	100-105	0.83	71.47
4	m-NO_2	68-70	0.70	78.98
5	p-Br	78-80	0.79	70.10
6	p-NO_2	110-115	0.46	75.66
7	p-Cl	85-90	0.84	65.2
8	2-NO_2	85-90	0.70	71.03
9	o-Cl	219-220	0.89	61.2
10	Benzyl	120-122	0.76	63.48

Step IV: Synthesis of 4-(4-oxo-2-phenyl-3,4-dihydroquinazolin-3-yl) benzene sulphonylthiourea (AA1-AA3, BB1-BB3, CC1-CC3, DD-DD3, EE1-EE3)
A mixture of isothiocyanate derivative (0.01 mol) and sulfonamide derivatives in dioxane (20 mL) containing triethyl-amine (0.5 mL) was heated under reflux for 2 h. The reaction mixture then cooled and poured into cold water and acidified with HCl. The solid product was collected and recrystallized from dioxane.[11]

(3-{3-[4-({[(2, 5-dichlorophenyl) carbamothioyl] amino} sulfonyl) phenyl]-4-oxo-3, 4-dihydroquinazolin-2-yl} phenyl) azinic acid (AA2)
Yield: 42, **Molecular formula**: $C_{27}H_{17}N_5O_5SCl_2$, **Molecular weight**: 594.42, **Melting point**: 98-99^oC, **Rf**: 0.64 (eluent Toluene/Ethyl Acetate, 2:1), **IR(KBr) in cm^{-1}**: 3215 cm^{-1}(N-H str. amine), 3081.69 cm^{-1}(aromatic C-H str), 2923.56 cm^{-1}(CH str.) 1682.59 cm^{-1} (C=O str.), 1587.13 cm^{-1} (C=C bend. aromatic), 1530.24 cm^{-1}(N-O str.), 1471.42 cm^{-1}(C=S str.), 1301.72 cm^{-1} (S=O str.), 1162.87 cm^{-1} (S=O str.), 1021.12 cm^{-1} (C-N bend), 839.84 cm^{-1} (N-C-N vibration), 773.31 cm^{-1} (S-N bend). **^{1}H NMR (600 MHz, DMSO) δ [ppm]**: 2.17 (s, 1H, NH), 4.11 (d, 1H, NH), 5.59 (s, 1H, Ar-H), 6.95 (d, 1H, Ar-H), 6.97 (d, 1H, Ar-H), 7.15 (d, 2H, Ar-H), 7.31 (s, 2H, Ar-H, 7.74 (d, 2H, Ar-H), 7.92 (s, 2H, Ar-H), 7.30 (d, 1H, Ar-H), 8.15 (d, 2H, Ar-H), 8.35 (s, 1H, Ar-H).

(3-{3-[4-({[(3, 4-dichlorophenyl) carbamothioyl] amino} sulfonyl) phenyl]-4-oxo-3, 4-dihydroquinazolin-2-yl} phenyl) azinic acid (AA3)
Yield: 69.71, **Molecular formula**: $C_{27}H_{17}N_5O_5SCl_2$, **Molecular weight**: 594.42, **Melting point**: 158-160^oC, **Rf**: 0.57 (eluent Toluene/Ethyl Acetate, 2:1), **IR(KBr) in cm^{-1}**: 3345.89 cm^{-1}(N-H str. amine), 3099.05 cm^{-1}(aromatic C-H str), 2985.27 cm^{-1}(CH str.) 1701.87 cm^{-1} (C=O str.), 1588.09 cm^{-1} (C=C bend. aromatic), 1535.06 cm^{-1}(N-O str.), 1379.82 cm^{-1}(C=S str.), 1301.72 cm^{-1} (S=O str.), 1136.83 cm^{-1} (S=O str.), 1095.37 cm^{-1} (C-N bend), 869.73 cm^{-1} (N-C-N vibration), 766.56 cm^{-1} (S-N bend). **^{1}H NMR (600 MHz, DMSO) δ [ppm]**: 1.99 (s, 1H, NH), 4.12(d, 1H, NH), 7.27 (s, 1H, Ar-H), 7.45 (d, 2H, Ar-H), 7.54 (d, 1H, Ar-H), 7.55 (s, 1H, Ar-H), 7.58 (d, 2H, Ar-H), 7.68 (s, 1H, Ar-H), 7.82 (d, 2H, Ar-H), 7.8 (d, 2H, Ar-H), 7.98 (s, 2H, Ar-H), 8.1 (s, 2H, Ar-H), 8.38 (s, 2H, Ar-H).

{3-[4-oxo-3-(4-{[(phenylcarbamothioyl) amino] sulfonyl} phenyl)-3, 4-dihydroquinazolin-2-yl] phenyl} azinic acid (AA4)
Yield: 41.9, **Molecular formula**: $C_{27}H_{17}N_5O_5S$, **Molecular weight**: 523.52, **Melting point**: 95-96^oC, **Rf**: 0.35 (eluent Toluene/Ethyl Acetate, 2:1), **IR(KBr) in cm^{-1}**: 3216.68 cm^{-1}(N-H str. amine), 3086.51 cm^{-1} (aromatic C-H str), 2923.56 cm^{-1}(CH str.), 2853.17 cm^{-1} (CH str.) 1682.59 cm^{-1} (C=O str.), 1586.16 cm^{-1} (C=C bend. aromatic), 1530.24 cm^{-1}(N-O str.), 1349.93 cm^{-1} (S=O str.), 1162.87 cm^{-1} (S=O str.), 1021.12 cm^{-1} (C-N bend), 839.84 cm^{-1} (N-C-N vibration), 773.31 cm^{-1} (S-N bend).**^{1}H NMR (600 MHz, DMSO) δ [ppm]**: 2.20 (s, 1H, NH), 4.16 (d, 1H, NH), 7.25 (s, 1H, Ar-H), 7.26 (d, 2H, Ar-H), 7.24 (d, 2H, Ar-H), 7.45 (s, 1H, Ar-H), 7.59 (d, 2H, Ar-H), 7.83 (d, 2H, Ar-H), 7.96 (d, 2H, Ar-H), 7.61 (s, 1H, Ar-H), 7.73 (s, 1H, Ar-H), 8.15 (s, 2H, Ar-H), 8.35 (s, 1H, Ar-H).

1-(3, 4-dichlorophenyl)-3-({4-[2-(2-hydroxyphenyl)-4-oxo-3, 4-dihydroquinazolin-3-yl] benzene} sulfonyl) thiourea (BB3)
Yield: 75.63, **Molecular formula**: $C_{27}H_{18}N_4O_4SCl_2$, **Molecular weight**: 565.43, **Melting point**: 126-128^oC, **Rf**: 0.62 (eluent Toluene/Ethyl Acetate, 2:1), **IR(KBr) in cm^{-1}**: 3464.49 cm^{-1}(O-H str.), 3345.89 cm^{-1}(N-H str. amine), 3086.51 cm^{-1}(aromatic C-H str), 2923.56 cm^{-1}(CH str.), 2853.17 cm^{-1}(CH str.) 1702.84 cm^{-1} (C=O str.), 1598.7 cm^{-1} (C=C bend. aromatic), 1480.1 cm^{-1}(C=S str.), 1378.85 cm^{-1} (S=O str.), 1155.19 cm^{-1} (S=O str.), 1096.33 cm^{-1} (C-N bend), 827.31 cm^{-1} (N-C-N vibration), 712.33 cm^{-1} (S-N bend). **^{1}H NMR (600 MHz, DMSO) δ [ppm]**: 2.14 (s, 1H, NH), 4.12(d, 1H, NH), 5.8 (s, 1H, OH), 6.60 (d, 2H, Ar-H), 6.90 (d, 1H, Ar-H), 7.25 (s, 1H, Ar-H), 7.46 (d, 2H, Ar-H), 7.53 (s, 1H, Ar-H), 7.70 (d, 2H, Ar-H), 7.72 (d, 2H, Ar-H), 7.81 (s, 2H, Ar-H), 7.90 (s, 2H, Ar-H).

3-({4-[2-(2-hydroxyphenyl)-4-oxo-3, 4-dihydroquinazolin-3-yl] benzene} sulfonyl)-1-phenylthiourea (BB4)
Yield: 72, **Molecular formula**: $C_{27}H_{18}N_4O_4S$, **Molecular weight**: 494.52, **Melting point**: 84-85^0C, **Rf**: 0.46 (eluent Toluene/Ethyl Acetate, 2:1), **IR(KBr) in cm^{-1}**: 3508.16 cm^{-1}(O-H str.), 3375.78 cm^{-1}(N-H str. amine), 3086.51 cm^{-1}(aromatic C-H str), 1619.91 cm^{-1} (C=O str.), 1625.42 cm^{-1} (C=C bend. aromatic), 1505.17 cm^{-1}(C=S str.), 1316.18 cm^{-1} (S=O str.), 1146.47 cm^{-1} (S=O str.), 1081.87 cm^{-1} (C-N bend), 808.028 cm^{-1} (N-C-N vibration), 669.53 cm^{-1} (S-N bend). **^{1}H NMR (600 MHz, DMSO) δ [ppm]**: 2.14 (s, 1H, NH), 3.37 (d, 1H, NH), 5.8 (s, 1H, OH), 6.58 (d, 2H, Ar-H), 6.60 (d, 2H, Ar-H), 6.89 (s, 1H, Ar-H), 7.24 (s, 1H, Ar-H), 7.45 (s, 2H, Ar-H), 7.46 (d, 2H, Ar-H), 7.72 (d, 2H, Ar-H), 7.76 (s, 2H, Ar-H).

(3-{[({4-[2-(2-hydroxyphenyl)-4-oxo-3, 4-dihydroquinazolin3yl] benzene} sulfonyl) carbamothioyl] amino} phenyl) azinic acid (BB6)
Yield: 59.09, **Molecular formula**: $C_{27}H_{18}N_5O_6S$, **Molecular weight**: 540.5, **Melting point**: 94-96^0C, **Rf**: 0.67 (eluent Toluene/Ethyl Acetate, 2:1), **IR(KBr) in cm^{-1}**: 3464.49 cm^{-1}(O-H str.), 3371.92 cm^{-1}(N-H str. amine), 1659.45 cm^{-1} (C=O str.), 1612.45 cm^{-1} (C=C bend. aromatic), 1595.81 cm^{-1}(C=S str.), 1317.14 cm^{-1} (S=O str.), 1186.01 cm^{-1} (S=O str.), 1097.3 cm^{-1} (C-N bend), 829.41 cm^{-1} (N-C-N vibration), 736.67 cm^{-1} (S-N bend). **^{1}H NMR (600 MHz, DMSO) δ [ppm]**: 2.14 (s, 1H, NH), 4.15 (d, 1H, NH), 5.81 (s, 1H, OH), 6.60 (d, 2H, Ar-H), 7.24 (d, 2H, Ar-H), 7.45 (s, 2H, Ar-H), 7.24 (s, 1H, Ar-H), 7.47 (s, 2H, Ar-H), 7.77 (d, 2H, Ar-H), 8.47 (d, 2H, Ar-H).

(3-{[({4-[2-(4-hydroxyphenyl)-4-oxo-3, 4-dihydroquinazolin3yl] benzene} sulfonyl) carbamothioyl] amino} phenyl) azinic acid (CC6)
Yield: 87.99, **Molecular formula**: $C_{27}H_{18}N_5O_6S$, **Molecular weight**: 540.5, **Melting point**: 120-122^{0}C, **Rf**: 0.87 (eluent Toluene/Ethyl Acetate, 2:1), **IR(KBr) in cm^{-1}**: 3608.16 cm^{-1}(O-H str.), 3355.53 cm^{-1}(N-H str. amine), 1671.02 cm^{-1} (C=O str.), 1621.84 cm^{-1} (C=C bend. aromatic), 1531.2 cm^{-1}(C=S str.), 1314.25 cm^{-1} (S=O str.), 1151.29 cm^{-1} (S=O str.), 1080.91 cm^{-1} (C-N bend), 801.27 cm^{-1} (N-C-N vibration), 661.46 cm^{-1} (S-Nbend).**^{1}H NMR (600 MHz, DMSO) δ [ppm]**: 2.14 (s, 1H, NH), 4.15 (d, 1H, NH), 5.81 (s, 1H, OH), 6.5 (d, 2H, Ar-H), 6.90 (s, 1H, Ar-H), 7.22 (s, 2H, Ar-H), 7.32 (s, 2H, Ar-H), 7.53 (s, 2H, Ar-H), 7.78 (d, 2H, Ar-H), 8.08 (d, 2H, Ar-H). 8.47(s, 2H, Ar-H).

1-(4-bromophenyl)-3-({4-[2-(4-hydroxyphenyl)-4-oxo-3, 4-dihydroquinazolin-3-yl] benzene} sulfonyl) thiourea (CC8)
Yield: 78.66, **Molecular formula**: $C_{27}H_{18}N_4O_4SBr$, **Molecular weight**: 574.42, **Melting point**: 110-111^{0}C, **Rf**: 0.5 (eluent Toluene/Ethyl Acetate, 2:1), **IR(KBr) in cm^{-1}**: 3477.99 cm^{-1}(O-H str.), 3308.29 cm^{-1}(N-H str. amine), 3109.65 cm^{-1} (C-H str. Aromatic), 2979.48 cm^{-1} (C-H str.), 1698.02 cm^{-1} (C=O str.), 1595.77 cm^{-1} (C=C bend. aromatic), 1536.02 cm^{-1}(C=S str.), 1305.57 cm^{-1} (S=O str.), 1153.22 cm^{-1} (S=O str.), 1076.08 cm^{-1} (C-N bend), 828.27 cm^{-1} (N-C-N vibration), 753.05 cm^{-1} (Br str.).

(4-{[({4-[2-(4-hydroxyphenyl)-4-oxo-3, 4-dihydroquinazolin3yl] benzene} sulfonyl) carbamothioyl] amino} phenyl) azinic acid (CC10)
Yield: 65.21, **Molecular formula**: $C_{27}H_{18}N_5O_6S$, **Molecular weight**: 540.5, **Melting point**: 115-116^{0}C, **Rf**: 0.62 (eluent Toluene/Ethyl Acetate, 2:1), **IR(KBr) in cm^{-1}**: 3462.56 cm^{-1}(O-H str.), 3376.75 cm^{-1}(N-H str. amine), 2989.12 cm^{-1} (C-H str.), 1638.23 cm^{-1} (C=O str.), 1551.45 cm^{-1} (C=C bend. aromatic), 1515.78 cm^{-1}(C=S str.), 1309.43 cm^{-1} (S=O str.), 1112.73 cm^{-1} (S=O str.), 1098.33 cm^{-1} (C-N bend), 825.38 cm^{-1} (N-C-N vibration), 726.06 cm^{-1} (S-N bend). **^{1}H NMR (600 MHz, DMSO) δ [ppm]**: 2.09 (s, 1H, NH), 4.16 (s, 1H, NH), 5.81 (s, 1H, OH), 6.59 (d, 2H, Ar-H), 7.25 (d, 2H, Ar-H), 7.47 (s, 2H, Ar-H), 7.69 (s, 1H, Ar-H), 7.75 (s, 1H, Ar-H), 7.78 (d, 2H, Ar-H), 7.89 (d, 2H, Ar-H), 8.19(d, 2H, Ar-H).

(3-{[({4-[2-(4-methoxyphenyl)-4-oxo-3, 4-dihydroquinazolin3yl] benzene} sulfonyl) carbamothioyl] amino} phenyl) azinic acid (DD6)
Yield: 76.25, **Molecular formula**: $C_{28}H_{21}N_5O_6S$, **Molecular weight**: 555.28, **Melting point**: 136-138^{0}C, **Rf**: 0.65 (eluent Toluene/Ethyl Acetate, 2:1), **IR(KBr) in cm^{-1}**: 3306.36 cm^{-1}(N-H str. amine), 3108.69 cm^{-1}(C-H str. aromatic), 2934.3 cm^{-1} (C-H str.), 1598.7 cm^{-1} (C=O str.), 1533.13 cm^{-1} (C=C bend. aromatic), 1402.96 cm^{-1} (C=S str.), 1309.54 cm^{-1} (S=O str.), 1093.44 cm^{-1} (S=O str.), 1067.41 cm^{-1} (C-N bend), 1013.41 cm^{-1}(C-O str.), 828.27 cm^{-1} (N-C-N vibration), 744.38 cm^{-1} (S-N bend). **^{1}H NMR (600 MHz, DMSO) δ [ppm]**: 2.08 (s, 1H, NH), 4.15 (s, 1H, NH), 3.38 (s, 3H, CH_3), 7.25 (s, 2H, Ar-H), 7.57 (d, 2H, Ar-H), 7.66 (s, 2H, Ar-H), 7.67 (s, 2H, Ar-H), 7.75 (s, 2H, Ar-H), 7.76 (d, 2H, Ar-H), 7.84 (d, 2H, Ar-H), 8.46 (s, 2H, Ar-H).

1-(4-bromophenyl)-3-({4-[2-(4-methoxyphenyl)-4-oxo-3, 4-dihydroquinazolin-3-yl] benzene} sulfonyl) thiourea (DD8)
Yield: 56.22, **Molecular formula**: $C_{28}H_{21}N_4O_4SBr$, **Molecular weight**: 509.28, **Melting point**: 140-141^{0}C, **Rf**: 0.46 (eluent Toluene/Ethyl Acetate, 2:1), **IR(KBr) in cm^{-1}**: 3308.29 cm^{-1}(N-H str. amine), 3112.55 cm^{-1} (C-H str. Aromatic), 2979.48 cm^{-1} (C-H str.), 1698.02 cm^{-1} (C=O str.), 1595.77 cm^{-1} (C=C bend. aromatic), 1536.02 cm^{-1}(C=S str.), 1305.57 cm^{-1} (S=O str.), 1153.22 cm^{-1} (S=O str.), 1076.08 cm^{-1} (C-N bend), 1094.4 cm^{-1}(C-O str.)827.31 cm^{-1} (N-C-N vibration), 696.17 (Br str.). **^{1}H NMR (600 MHz, DMSO) δ [ppm]**: 2.07 (s, 1H, NH), 4.10 (s, 1H, NH), 3.59 (s, 3H, CH_3), 6.58 (s, 2H, Ar-H), 6.60 (s, 1H, Ar-H), 6.90 (s, 2H, Ar-H), 7.25 (d, 2H, Ar-H), 7.44 (s, 2H, Ar-H), 7.45 (d, 2H, Ar-H), 7.46 (s, 1H, Ar-H), 7.72 (s, 2H, Ar-H), 7.73(d, 2H, Ar-H).

1-(4-chlorophenyl)-3-({4-[2-(4-methoxyphenyl)-4-oxo-3, 4-dihydroquinazolin-3-yl] benzene} sulfonyl) thiourea (DD9)
Yield: 72.17, **Molecular formula**: $C_{28}H_{21}N_4O_4SCl$, **Molecular weight**: 544.51, **Melting point**: 90-92^{0}C, **Rf**: 0.65 (eluent Toluene/Ethyl Acetate, 2:1), **IR(KBr) in cm^{-1}**: 3306.36 cm^{-1}(N-H str. amine), 3073.98 cm^{-1} (C-H str. Aromatic), 2984.3 cm^{-1} (C-H str.), 1598.7 cm^{-1} (C=O str.), 1533.13 cm^{-1} (C=C bend. aromatic), 1402.96 cm^{-1}(C=S str.), 1306.54 cm^{-1} (S=O str.), 1093.44 cm^{-1} (S=O str.), 1067.41^1 (C-N bend), 1013.41 cm^{-1}(C-O str.), 828.27 cm^{-1} (N-C-N vibration), 688.46 cm^{-1} (Br str.), 744.38 cm^{-1}(Cl str.). **^{1}H NMR (600 MHz, DMSO) δ [ppm]**: 1.18 (d, 1H, NH), 4.19 (s, 1H, NH), 3.75 (s, 3H, CH_3), 6.77 (s, 2H, Ar-H), 6.79 (s, 1H, Ar-H), 7.20 (s, 2H, Ar-H), 7.33 (s, 1H, Ar-H), 7.51 (s, 2H, Ar-H), 7.53 (d, 2H, Ar-H), 7.71 (d, 2H, Ar-H), 7.72 (s, 2H, Ar-H), 7.73(s, 1H, Ar-H).

(3-{[({4-[2-(4-chlorophenyl)-4-oxo-3, 4-dihydroquinazolin3yl] benzene} sulfonyl) carbamothioyl] amino} phenyl) azinic acid (EE1)
Yield: 46, **Molecular formula**: $C_{27}H_{18}N_5O_5SCl$, **Molecular weight**: 559.53, **Melting point**: 128-130^{0}C, **Rf**: 0.85 (eluent Toluene/Ethyl Acetate, 2:1), **IR(KBr) in cm^{-1}**: 3353.6 cm^{-1}(N-H str. amine), 3179.08 cm^{-1}(C-H str. aromatic), 2935.46 cm^{-1} (C-H str.), 1660.41 cm^{-1} (C=O str.), 1624.73 cm^{-1} (C=C bend. aromatic), 1568.81 cm^{-1}(C=S str.), 1345.11 cm^{-1}(S=O str.), 1018.23 cm^{-1} (S=O str.), 872.631 cm^{-1} (N-C-N vibration), 663.93 cm^{-1} (S-N bend), 742.46 cm^{-1}(Cl str.) **^{1}H NMR (600 MHz, DMSO) δ [ppm]**: 2.15 (s, 1H, NH), 4.20 (d, 1H, NH), 6.79 (s, 2H, Ar-H), 7.18 (d, 2H, Ar-H), 7.18 (d, 2H, Ar-H), 7.25 (s, 1H, Ar-H), 7.35 (s, 2H, Ar-H), 7.52 (d, 2H,

Ar-H), 7.58 (d, 2H, Ar-H), 7.60 (s, 2H, Ar-H), 8.30 (s, 1H, Ar-H), 8.32 (d, 2H, Ar-H).

3-({4-[2-(4-chlorophenyl)-4-oxo-3, 4-dihydroquinazolin-3-yl] benzene} sulfonyl)-1-(3, 4-dichlorophenyl) thiourea (EE3)

Yield: 60.55, **Molecular formula**: $C_{27}H_{18}N_4O_3SCl_3$, **Molecular weight**: 584.43, **Melting point**: 116-117^{0}C, **Rf**: 0.74 (eluent Toluene/Ethyl Acetate, 2:1), **IR(KBr) in cm^{-1}**: 3311.18 cm^{-1}(N-H str. amine), 3179.08 cm^{-1}(C-H str. aromatic), 2979.48 cm^{-1} (C-H str.), 1698.02 cm^{-1} (C=O str.), 1627.63 cm^{-1} (C=C bend. aromatic), 1595.81 cm^{-1}(C=S str.), 1306.54 cm^{-1}(S=O str.), 1076.08 cm^{-1} (S=O str.), 872.31 cm^{-1} (N-C-N vibration), 663.93 cm^{-1} (S-N bend), 746.31 cm^{-1}(Cl str.).**^{1}H NMR (600 MHz, DMSO) δ [ppm]**: 2.15 (s, 1H, NH), 4.20 (d, 1H, NH), 6.79 (s, 2H, Ar-H), 7.18 (d, 2H, Ar-H), 7.18 (d, 2H, Ar-H), 7.25 (s, 1H, Ar-H), 7.35 (s, 2H, Ar-H), 7.52 (d, 2H, Ar-H), 7.58 (d, 2H, Ar-H), 7.60 (s, 2H, Ar-H), 8.30 (s, 1H, Ar-H), 8.32 (d, 2H, Ar-H).

1-(4-chlorophenyl)-3-({4-[2-(4-chlorophenyl)-4-oxo-3, 4-dihydroquinazolin-3-yl] benzene} sulfonyl) thiourea (EE9)

Yield: 79.82, **Molecular formula**: $C_{27}H_{18}N_4O_3SCl_2$, **Molecular weight**: 548.98, **Melting point**: 92-94^{0}C, **Rf**: 0.71 (eluent Toluene/Ethyl Acetate, 2:1), **IR(KBr) in cm^{-1}**: 3308.29 cm^{-1}(N-H str. amine), 3179.08 cm^{-1}(C-H str. aromatic), 2981.41 cm^{-1} (C-H str.), 1697.05 cm^{-1} (C=O str.), 1593.88 cm^{-1} (C=C bend. aromatic), 1533.13 cm^{-1}(C=S str.), 1307.5 cm^{-1}(S=O str.), 1094.7 cm^{-1} (S=O str.), 830.20 cm^{-1} (N-C-N vibration), 683.57 cm^{-1} (S-N bend), 770.42 cm^{-1}(Cl str.).**^{1}H NMR (600 MHz, DMSO) δ [ppm]**: 2.88 (s, 1H, NH), 5.1 (d, 1H, NH), 6.07 (s, 2H, Ar-H), 6.66 (d, 2H, Ar-H), 6.70 (d, 1H, Ar-H), 6.81 (s, 1H, Ar-H), 7.22 (d, 2H, Ar-H), 7.37 (d, 2H, Ar-H), 7.57 (d, 2H, Ar-H), 7.91 (s, 1H, Ar-H), 8.10 (d, 2H, Ar-H).

Pharmacological activity

Animals

Wistar rats weighing 180-200 gm bodyweight were procured from National Institute of Bioscience, Chaturshrungi, Pune. All animals were housed at standard laboratory conditions and fed with a rodent pellet diet and water. They were maintained at room temperature. Before examination all animals were fasted for 16 h with water. All experimental procedures were carried out in strict accordance with the guidelines prescribed by the Committee for the Purpose of Control and Supervision on Experimentation on Animals i.e. CPCSEA (Reg No. 884/PO/Re/S/05/CPCSEA) and were approved by the Institutional Animal Ethics Committee (IAEC).

Induction of diabetes

Streptozotocin (STZ) was dissolved in citrate buffer (pH 4.5) and Nicotinamide (NA) was dissolved in normal physiological saline solution. Non-insulin-dependent diabetes mellitus was induced in overnight fasted rats by a single intraperitoneal injection of 65 mg/kg Streptozotocin, 15 min after the i.p. administration of 120 mg/kg of Nicotinamide. Hyperglycemia was confirmed by the elevated glucose concentration in plasma, determined at 72 h by commercial glucometer. The animals with blood glucose concentration higher 250 mg/dL, were used for the antidiabetic screening. The diabetic animals were divided into groups of six animals each. Rats of experimental group were administered a suspension of desired test samples (prepared in 1% sodium CMC) orally (75mg/kg).

Antihyperglycemic activity

Male Wistar rats weighing 180-200gm having blood glucose level higher 250 mg/dL were selected for antihyperglycemic activity. Animals of diabetic control group received vehicle and standard group received sitagliptin (10mg/kg). Animals of experimental group were administered single oral dose of test compounds (suspension in 1% sodium CMC) of 75mg/kg boy weight. The blood glucose levels were measured at 0-,1-, 2-, 3-, 4-, 5-, 6-, 7- and 8-h intervals using DrMorepenGluco One BG-03 Blood Glucose Test Strips and DrMorepenGluco One BG-03 Meter on blood samples collected via tail vein by excision. The % decrease in blood glucose from 0-8 h by test compounds was calculated.

Statistical evaluation

The statistical data were expressed as mean ± SEM IC50 values were determined using non-linear regression analysis. Statistical evaluation was performed by one-way ANOVA followed by Dunnett's post-test. Statistical studies and data analyses were performed using GRAPHPAD PRISM Version7.04.

Molecular docking studies

All the molecular modeling studies were carried out on AUTODOCK tool software. The X-ray crystallographic structure of Human DPP4 Bound to TAK-294 with their ligands (PDB ID: 3OPM) were obtained from the protein data bank. The enzymes were prepared for docking studies where: (i) Ligand molecule was removed from the enzyme active site. (ii) Hydrogen atoms were added to the structure with their standard geometry. (iii) The obtained model was then used in predicting the ligand enzymes interactions at the active site.

ADME prediction

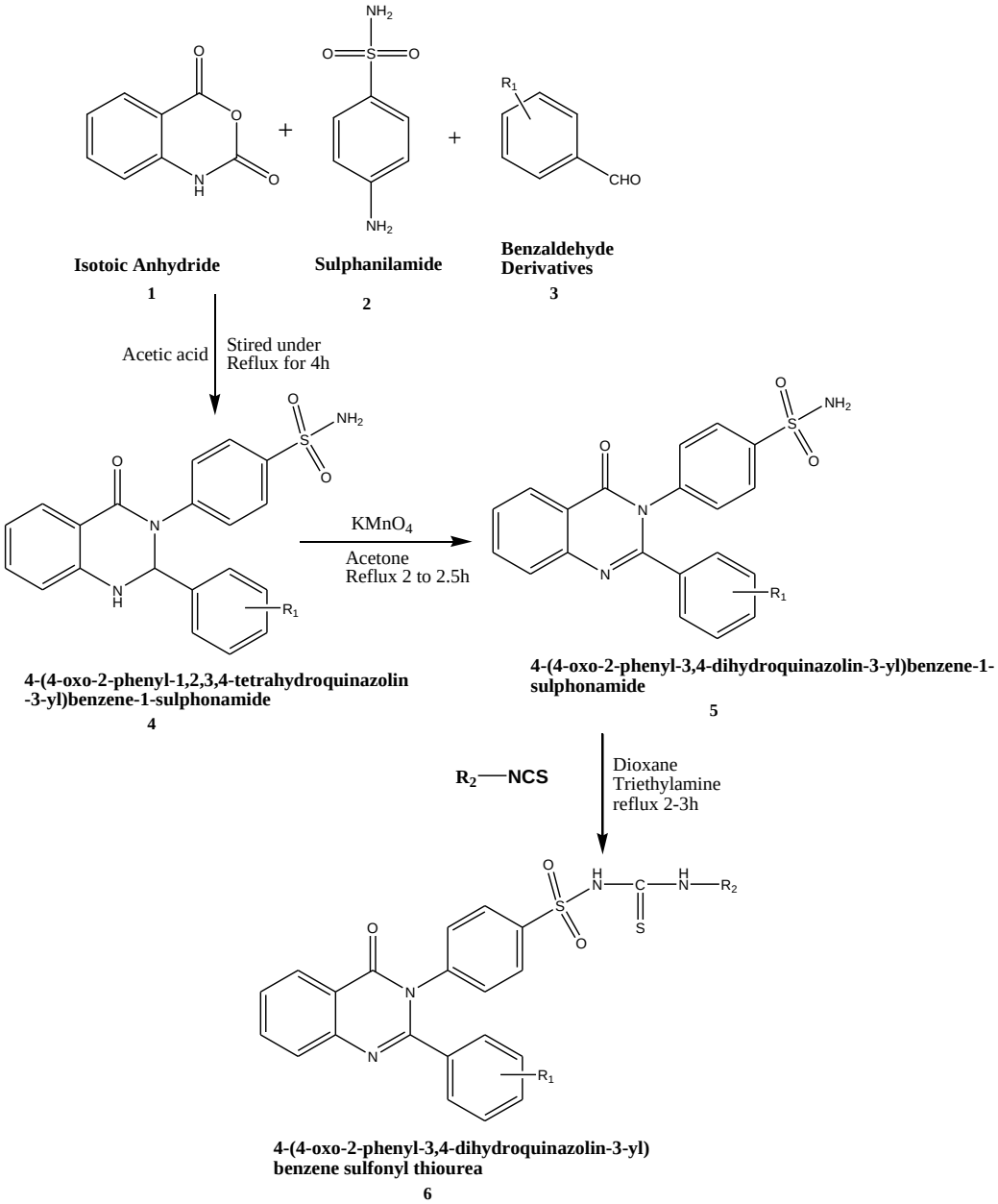
ADME properties were predicted for designed compounds using computational methods. In this study, we have calculated CaCO-2, BBB, HIA, plasma protein binding and skin permeability, Ames test, rodent carcinogenicity assay, druglikeness score and Lipinski's rule of five.

RESULT AND DISCUSSION

Chemical Synthesis

The synthesis of compounds was achieved by following the route shown in Scheme 1. The synthesis of 4-(4-oxo-

2-phenyl-1, 2, 3, 4-tetrahydroquinazolin-3-yl) benzene-1-sulphonamide (4) is done by reacting Isotoic anhydride (1) Sulphanilamide (2) and Benzaldehyde derivatives (3) in the presence of Acetic acid to yield the corresponding 4-(4-oxo-2-phenyl-1, 2, 3, 4-tetrahydroquinazolin-3-yl) benzene-1-sulphonamide(4).[8] Compound 4 was dehydrogenated with $KMnO_4$ and Acetone[9] to obtain 4-(4-oxo-2-phenyl-3, 4-dihydroquinazolin-3-yl)benzene-1-sulphonamide (5) which was immediately treated with synthesized substituted isothiocyanate[10], to obtain 4-(4-oxo-2-phenyl-3,4-dihydroquinazolin-3-yl) benzene sulfonylthiourea (6). The title compounds (AA1-AA10, BB1-BB10, CC1-CC10, DD1-DD10, and EE1-EE9) were obtained in good yield from the intermediate 5 by refluxing it with various substituted isothiocyanate dissolved in dioxane and triethylamine.[11] The synthesized compounds were purified by recrystallization and column chromatography. These title compounds were characterized by spectroscopic (IR and NMR), spectrometric (mass spectrometry) techniques.



Scheme 1: Synthesis of compounds AA1-AA10, BB1-BB10, CC1-CC10, DD1-DD10, EE1-EE9.

Reagents and conditions: (a) Acetic acid, stirred under reflux, 4h; (b) $KMnO_4$, Acetone, reflux, 2-2.5h; (c) R-NCS, dioxane, TEA, reflux, 2-3h.

Biological Activity

It has been well known that quinazolinones and sulfonamides have shown anti-diabetic activity.[12-15] The anti-diabetic activity of our synthesized quinazolinone-

sulfonamide hybrid was performed by in-silico method, with DPP-IV as target. In order to confirm this, we tested compounds for their in vivo activity on an experimental Streptozotocin (STZ) -Nicotinamide (NA) induced diabetic rat model. Compounds were evaluated at a dose of 75mg/kg while the standard Sitagliptin was used at a dose of 5mg/kg.

In the preliminary screening of antidiabetic activity, the synthesized compounds were administered orally. The blood glucose levels were measured at 0-, 1-, 2-, 3-, 4-, 5-, 6-, 7- and 8-h intervals using DrMorepenGluco One BG-03 Blood Glucose Test Strips and DrMorepenGluco One BG-03 Meter on blood samples collected via tail vein by excision. The % decrease in blood glucose from 0-8 h by test compounds was calculated. All the compounds were found to possess anti-diabetic activity (Table 1). The compounds AA3, AA4, CC6, CC10 and DD6 showed more potent activity as compared to standard Sitagliptin (STG).

Table 2: % decrease in Blood Sugar Level of all the synthesized test compounds.

Sr no	Compound	% decrease blood glucose level
1	AA2	9.44
2	AA3	83.47
3	AA4	64.34
4	BB3	29.20
5	BB4	50.10
6	BB6	45.63
7	CC6	83.15
8	CC8	9.17
9	CC10	58.36
10	DD6	50.07
11	DD8	14.84
12	DD9	3.85
13	EE1	35.58
14	EE3	4.41
15	EE9	17.87
16	STG	50.4

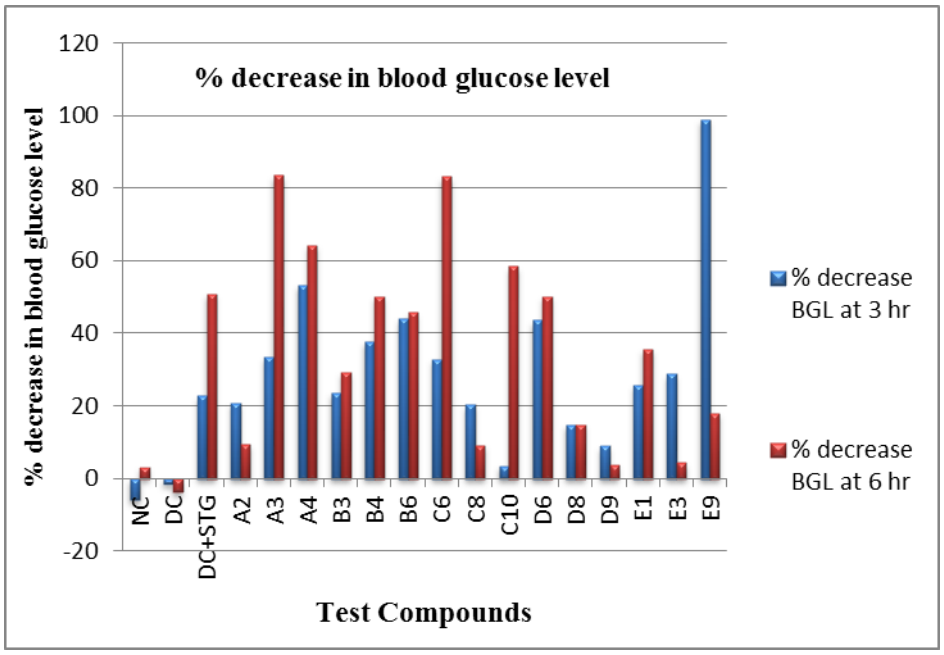


Fig. 3: % decrease in blood glucose level after 3 hrs and 6 hrs.

Molecular Docking Study

In silico studies were accomplished to study and understand the functionality and mode of action of the Quinazolinone-Sulphonamide/isothiocyanate hybrids. A dimeric protein DPP-IV, binding site residue of chain A,B,C,D of DPP-IV (PDB ID: 3OPM)[16] and resolution of 2.72 ^{0}A, was selected to perform the docking studies. 3OPM was the only crystallized structure of human DPP-IV complex and hence was chosen for the study. It was complexed with TAK-285. Designed pharmacophore has structural similarity with protein ligand TAK-285 **(**2-{[3-(aminomethyl)-2-(2-

methylpropyl)-1-oxo-4-phenyl-1, 2-dihydroisoquinolin-6-yl] oxy} acetamide**)** rather than sitagliptin which is used as standard compound for molecular docking and biological activity. Around 50 compounds were docked and screened and the dock scores were determined prior to actual synthesis. Docking results (Table 2) indicate that all the compounds interact with DPP-IV with good binding energies.

Table 3: Molecular Docking Score of compounds docked in DPP-IV inhibitor (PBD ID: 3OPM).

Ligand	Binding Energy	Ligand	Binding Energy
AA1	-9.65	**BB8**	-9.58
AA2	-10.56	**BB9**	-9.89
AA3	-11.20	**BB10**	-9.79
AA4	-10.76	**CC1**	-9.63
AA5	-9.71	**CC2**	-9.57
AA6	-10.08	**CC3**	-10.09
AA7	-10.08	**CC4**	-9.77
AA8	-10.21	**CC5**	-9.02
AA9	-10.41	**CC6**	-11.28
AA10	-9.80	**CC7**	-9.81
BB1	-9.91	**CC8**	-10.15
BB2	-9.73	**CC9**	-10.00
BB3	-10.34	**CC10**	-10.64
BB4	-10.89	**DD1**	-10.26
BB5	-9.12	**DD2**	-9.99
BB6	-10.74	**DD3**	-9.84
BB7	-9.96	**DD4**	-10.03
DD5	-10.00	**EE3**	-10.84
DD6	-10.56	**EE4**	-10.52
DD7	-10.49	**EE5**	-10.51
DD8	-10.73	**EE6**	-10.13
DD9	-10.50	**EE7**	-10.83
DD10	-9.80	**EE8**	-10.56
EE1	-10.83	**EE9**	-10.60
EE2	-10.22	**STD (Sitagliptin)**	-6.79

The minimum binding energy indicated that the DPP-IV protein was successfully docked with compounds. The results showed that the binding affinity of **CC6** for the enzyme was -11.28 kcal/mol and Sitagliptin taken as reference was -6.79 kcal/mol. Other molecules also showed comparable binding affinities for the enzyme. The docking results revealed that the compound (Sitagliptin) binds to the active site of DPP-IV through the formation hydrophilic interaction of fluorine group with Ser209 and Tyr662, also the heterocyclic nitrogen form the intraction with Arg669. Also the other structure was located in the hydrophobic binding cleft lined with Tyr670, Tyr666, Tyr547, Trp659, Ser630 and His740. The compound CC6 also bind to the same pocket of DPP-IV through the formation of hydrophilic bonding between Quinazolinone group with Arg125 and amine with Glu205. Also the remaining structure was located in hydrophobic binding cleft lined with Lys554, Asn710, Val711, Tyr631, Phe357, and Gly741. This study suggested that the designed molecules had the potential to act as DPP-IV inhibitors and hence the synthesis of these molecules was taken up. LigPlot was used to indicate the interaction of the binding site residues of the protein as seen in fig. 4 and fig. 7 respectively. Molecular docking shows 2D binding interaction of Sitagliptin and (**CC6**) at Dipeptidyl Peptidase-IV (PDB ID 3OPM) in fig. 5 and fig. 8. Molecular docking also shows 3D binding interaction of Sitagliptin and (**CC6**) at Dipeptidyl Peptidase-IV (PDB ID 3OPM) in fig.6 and fig. 9.

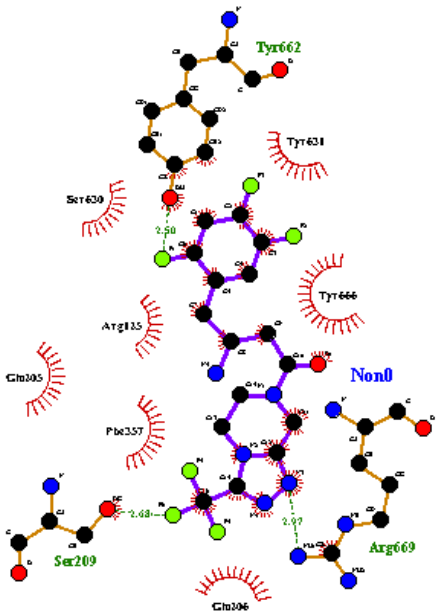


Fig. 4: LigPlot of Standard ligand.

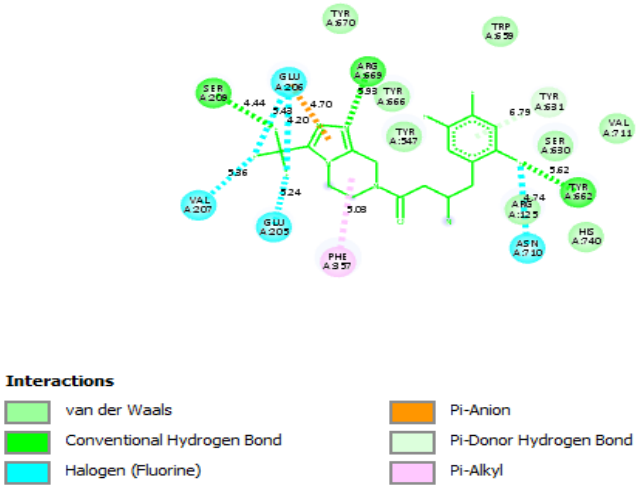


Fig. 5: 2D structure of binding interaction of the standard ligand in the DPP-IV binding site.

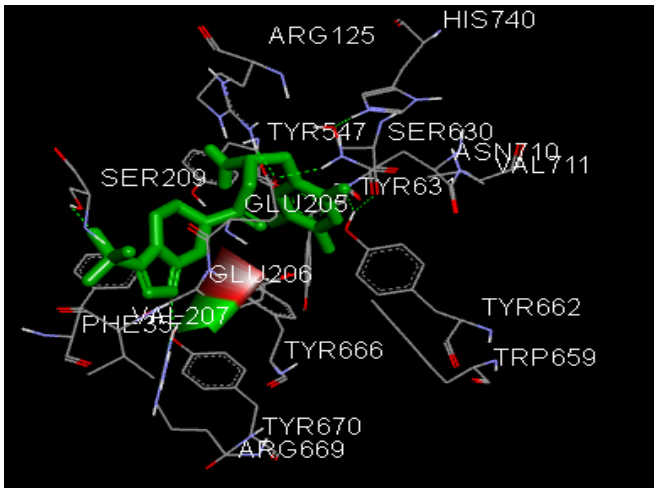


Fig. 6: 3D structure of binding interaction of the standard ligand in the DPP-IV binding site.

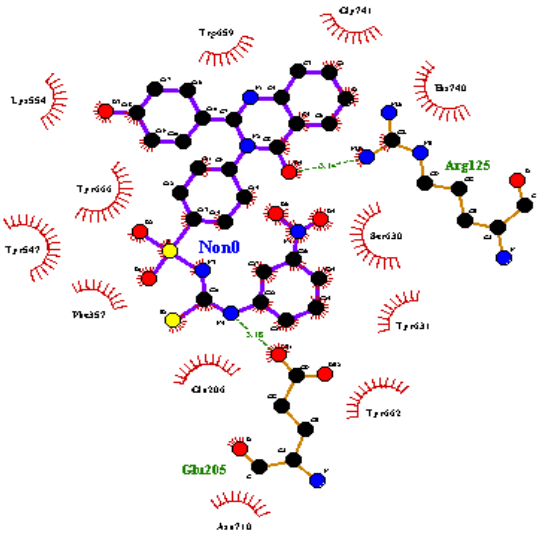


Fig. 7: LigPlot of CC6.

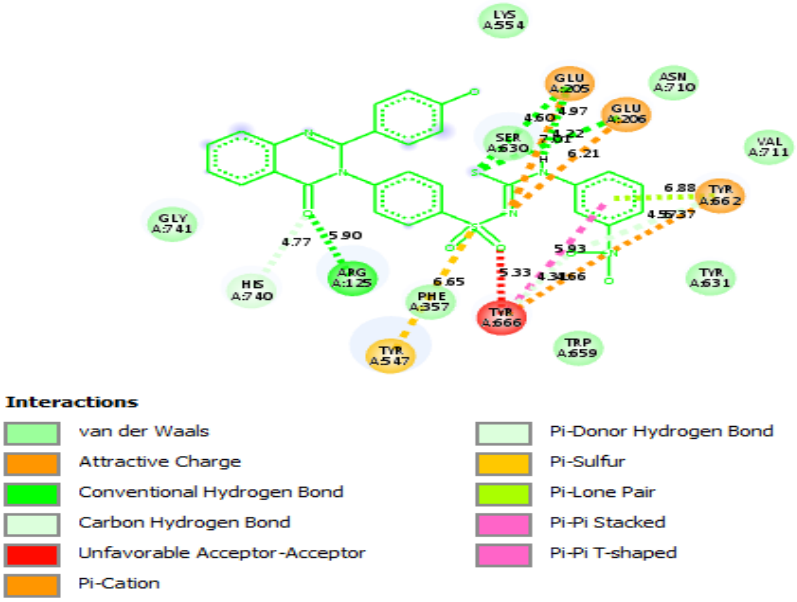


Fig. 8: Molecular docking showing 2D binding interaction of (CC6) at Dipeptidyl Peptidase-IV inhibitor (PDB ID 3OPM).

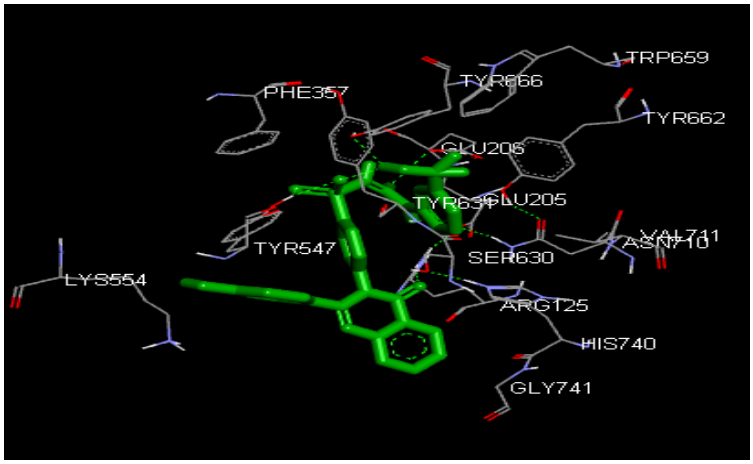


Fig. 9: Molecular docking showing 3D binding interaction of (CC6) at Dipeptidyl Peptidase-IV inhibitor (PDB ID 3OPM).

Table 4: ADMET Properties of all the designed molecules.

Drug Likeness score	-0.36	0.15	-0.03	-0.14	-0.04	-0.26	0.18	-0.08	0.18	-0.19
H Bond acceptor	9	7	7	7	7	9	7	7	7	7
H Bond donar	2	2	2	2	2	2	2	2	2	2
Mol log p	4.08	5.78	5.78	4.47	4.44	4.20	5.07	5.32	5.19	4.20
Caecino rat	positive	positive	negative	Positive	negative	positive	negative	negative	negative	Positive
Carcino mouse	positive	negative	negative	Positive	negative	positive	negative	negative	negative	Positive
Ames Test	mutagen	mutagen	Non mutagen	Mutagen	mutagen	mutagen	mutagen	mutagen	Non mutagen	Mutagen
Skin Permeability	-2.31	-2.37	-2.33	-2.32	-2.28	-2.49	-2.33	-2.39	-2.34	-2.31
PPB	96.2	93.8	100	93.0	94.6	97.6	100	96.9	100	94.8
HIA %	94.77	96.62	94.87	96.37	96.46	97.36	93.82	96.47	93.82	94.77
$CaCO_2$ nm/sec^2	0.405	2.145	1.001	0.73	0.925	0.52	0.66	2.35	0.89	0.41
BBB	0.126	0.018	0.89	0.05	0.089	0.055	0.46	0.01	0.48	0.107
Rule of 5	1	2	2	2	2	2	2	2	2	2
CMC like rule	2	3	3	3	3	2	3	3	3	3
Compound	A1	A2	A3	A4	A5	A6	A7	A8	A9	A10

CONCLUSIONS

To verify docking scores in practice, the designed compounds were synthesized and their antidiabetic activity was evaluated. The docking scores and predicted antidiabetic activity of synthesized compounds were well correlated. The finding of this study evidently indicates that oral treatment of diabetic rats with the synthesized compound **CC6** has lowered percentage blood glucose levels as compared to STD, regenerating β-cells and modulated the disturbances of lipid metabolism caused by STZ-NA induced DM.

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