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SYNTHESIS, MOLECULAR DOCKING AND ANTIDIABETIC ACTIVITY OF SOME SULPHONAMIDE BEARING QUINAZOLINONE MOIETIES

Shweta S. Gaikwad*, Shailaja B. Jadhav and Deepti D. Banadawane

[1,2]Department of Pharmaceutical Chemistry, PES's Modern College of Pharmacy, Yamunanagar, Nigdi, Pune- 44. Maharashtra, India.

***Corresponding Author: Shweta S. Gaikwad**

Department of Pharmaceutical Chemistry, PES's Modern College of Pharmacy, Yamunanagar, Nigdi, Pune- 44. Maharashtra, India.

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ABSTRACT

Type 2 diabetes (T2D) is a lifestyle disease affecting millions of people worldwide. Herein, the design and synthesis of 17 novel quinazolinone incorporating sulphonamide scaffold are described. Designed compound were docked using AutoDock (4.2.6) tool software with DPP-IV inhibitor protein (PDB: 3OPM). Synthesized compounds (**4a-q**) were evaluated for antidiabetic activity in streptozotocin-nicotinamide induced diabetic rats. Most of these synthesized compounds showed significant reduction in blood glucose level. Amongst all the compounds designed in this study, we identified compound **4q** as a potent, selective and orally active antidiabetic agent, which exhibited in vivo efficacy in diabetic rat model.

KEYWORDS: Antidiabetic agents, Quinazolinone, Sulphonamide, Type 2 Diabetes.

1. INTRODUCTION

Diabetes mellitus is characterized by chronic hyperglycemia and belongs to a group of metabolic disorders with multiple etiologies.[1] Type 2 diabetes mellitus (T2DM) is an extremely important metabolic disease with a global prevalence among adults (aged 20–79 years) suspected to reach 439 million by 2030.[2]

Dipeptidyl peptidase IV (DPP-IV, E.C.3.4.14.5, CD26) is a widely expressed serine protease found in many tissues and body fluids of mammals and, exists either as a soluble enzyme or in a membrane bound form. It functions as a protease, cleaving dipeptides comprising of either proline or alanine at the penultimate position from the N-terminal of the peptide or protein.[3-4] Glucagon like peptide 1 (GLP-1)[5] and glucose dependent insulinotropic polypeptide (GIP) are incretin hormones, responsible for the glucose dependent stimulation of insulin secretion through pancreatic β-cells.[6-9] The therapeutic effects of both these hormones are lost due to their rapid degradation (t½ ~ 1 min) by DPP-IV enzyme.[10] Thus inhibition of DPP-IV has emerged as a novel approach for the treatment of type 2 diabetes (T2D).[11]

The number of available oral hypoglycemic agents has increased significantly in the last decade, however, current therapies to reduce plasma glucose levels have inherent problems including compliance, ineffectiveness, and the occurrence of hypoglycemic episodes. Accordingly, there is a need for more effective, orally administered agents, particularly ones that normalize both glucose and insulin levels.[12] Authors have come across various fused aromatic heterocycle scaffolds in the literature study.[12-18] As a congener of bicyclic heterocycle scaffolds, we were interested in Quinazolinone scaffold since Quinazolinone derivatives were found to show diverse promising biological activities including anticancer, antihypertension, anticonvulsant, antidiabetic, antimalarial, etc.[19-21]

The hybridization of quinazolinone and sulfonamide structures led to the title compounds reported in this paper. In the present investigation, designed quinazolinone-sulfonamide hybrid derivatives (Fig. 1) were prepared by the methods that have been outlined in Scheme 1. The synthesized derivatives were evaluated for their antidiabetic activity.

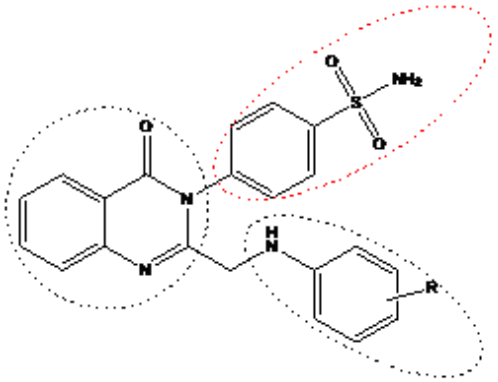


Figure 1: Designed pharmacophore.

2. MATERIALS AND METHODS

2.1 Molecular Docking

CADD are one of the most widely used and successful computational tool for structure activity relationship (SAR), protein-ligand interaction, binding energy, binding affinity etc. *In silico* studies were accomplished to study and understand the functionality and mode of action of the target Quinazolinone-Sulphonamide hybrids. Autodock is a majorly used computational docking program in binding studies. A protein namely Dipeptidyl peptidase IV (DPP-IV) was used as target for hits and number of design molecules were retrieved through Drug Data Bank and were used as ligand molecule to perform molecular docking studies.

Structure based docking approach has been implemented in our work. Active site of DDP-IV (PDB ID: 3OPM) taken from RCSB PDB in PDB format and were analysed. The protein taken was further cleaned from water and other bonds using Discovery Studio Visualiser 4.0 Client. The computer simulated docking work was performed using MGL Tools software 1.5.6 and Autodock 4.2.6 program. As a result of all procedure, both the protein and ligand were ready for docking and Sitagliptin was selected as a test ligand. Around 43 compounds were docked and screened and the dock scores were determined prior to actual synthesis.

2.2 Chemistry

2.2.1 Synthesis of 2-(2-chloroacetamido)-benzoic acid (2)

Anthranilic acid (0.1 mol) **(1)** was taken in round bottom flask in 100mL of toluene. It was made homogenous by stirring on a magnetic stirrer for 30 min. Chloro-acetyl chloride (0.1mol) was added and stirred for 2 hr. After completion of reaction, the solution was poured on crushed ice and the obtained solid was filtered and dried. The product **(2)** was recrystallized from chloroform: alcohol (9:1).

Yield 78.62%; **Melting Point** 152-154 ^{0}C; **IR (KBr,cm^{-1})** 3353.6 (OH), 1640.16 (C=O), 813.81 (C-Cl); **^{1}H NMR ($CDCl_3$)** δ 4.4 (s, 2H, CH_2), 7.2 (d, 1H, Ar-H), 7.6 (d, 1H, Ar-H), 8.0 (d, 1H, Ar-H), 8.5 (s, 1H, NH), 11.8 (s, 1H, OH), 13.7 (s, 1H, Ar-H).

2.2.2 Synthesis of 4-[2-(chloromethyl)-4-oxo-3,4-dihydroquinazolin-3-yl]benzene-1-sulfonamide (3)

20 gm of (0.09 mol) of 2-(2-chloroacetamido)-benzoic acid (**2**) and PCl_3 (18 ml) was taken in toluene (120 ml), the temperature was raised to reflux the reaction for 3 hrs. The reaction flask was cooled to room temperature. An equimolar amount of substituted aniline (0.09 mol) was added in to it. Continued stirring the reaction mixture at room temperature till completion of reaction. Added water to the residue and neutralized with sodium bicarbonate. Extracted with ethyl acetate (4 x 50 ml). Combined and washed the organic layer with water (2 x 30 ml) and then dried over Na_2SO_4. It was distilled and resulting crude compound was recrystallized from methanol to obtain 4-[2-(chloromethyl)-4-oxo-3,4-dihydroquinazolin-3-yl]benzene-1-sulfonamide **(3).**

Yield 65.39%; **Melting Point** 176-178^{0}C; **IR (KBr, cm^{-1})** 3461.6 (NH_2), 3373.85 (NH), 1637.27 (C=O), 1145.51 (S=O), 825.38 (C-Cl); **^{1}H NMR ($CDCl_3$)** δ 1.3 (s, 2H, NH_2), 4.5 (s, 2H, CH_2), 7.3 (d, 2H, Ar-H), 7.7 (d, 2H, Ar-H), 7.8 (d, 1H, Ar-H), 8.0 (d, 1H, Ar-H), 8.1 (d, 1H, Ar-H), 8.2(d, 1H, Ar-H).

2.2.3 Synthesis of 4-{2-[(substituted amino)methyl]-4-oxo-3,4-dihydroquinazolin-3-y}benzene-1-sulfonamide (4a-4o)

A mixture of compound 4-[2-(chloromethyl)-4-oxo-3, 4-dihydroquinazolin-3-yl]benzene-1-sulfonamide (3) (10 mmol, 1.0 equivalent), substituted amines (10mmol, 1.0 equivalent), K_2CO_3 (2.76 gm, 20mmol), KI (0.57gm, 3mmol, 0.3equivalent) and CH_3CN (20 ml) was heated at 80^{0}C for 90-120 min until the starting material was consumed. The reaction mixture was then diluted with water, and extracted with ethyl acetate (2 x 25ml). The combined organic layer was washed with water, brine and then dried over anhydrous Na_2SO_4. The organic layer was distilled under reduced pressure, to give the product **(4a-4o)**. Column chromatography was performed to purify the compounds.

2.2.3.1 4-(2-{[(2,5-dichlorophenyl)amino]methyl}-4-oxo-3,4-dihydroquinazolin-3-yl)benzene-1-sulfonamide (4a) Yield

56.71%; **Melting Point** 230-232 ^{0}C; **IR (KBr, cm^{-1})** 3641.91(NH_2), 3374.82(N-H), 1678.73(C=O), 1148.4 (S=O), 825.38(C-Cl). **^{1}H NMR ($CDCl_3$)** δ 2.3 (s, 2H, NH_2), 3.1 (d, 2H, CH_2), 4.2 (t, 1H, NH), 6.4 (dd, 2H, Ar-H), 6.9 (s, 1H, Ar-H), 7.6 (s, 4H, Ar-H), 7.9 (s, 2H, Ar-H), 8.1 (s, 2H, Ar-H). **MS (EI) m/z**: 474.31; **Anal. calcd for** $C_{21}H_{16}C_{l2}N_4O_3S$ C, 53.06; H, 3.39; N, 11.79; S, 6.75; **found** C, 54.69; H, 2.21; N, 11.32; S, 7.01.

2.2.3.2 4-{2-[(diphenylamino)methyl]-4-oxo-3,4-dihydroquinazolin-3-yl}benzene-1-sulfonamide (4b)

Yield 49.73%; **Melting Point** 218-220 ^{0}C; **IR (KBr, cm^{-1})** 3697.84 (NH_2), 3383.5 (NH), 1692.23cm^{-1}(C=O), 1173.47 (S=O); **^{1}H NMR ($CDCl_3$)** δ 1.3 (s, 2H, NH_2), 3.9 (d, 2H, CH_2), 6.1 (m, 4H, Ar-H), 6.3 (s, 3H, Ar-H), 6.5 (s, 2H, Ar-H), 7.3 (m, 1H, Ar-H), 7.5 (s, 2H, Ar-H), 7.6 (s, 2H, Ar-H), 7.9 (s, 2H, Ar-H), 8.1 (s, 2H, Ar-H). **MS (EI) m/z:** 482.14; **Anal. calcd for** $C_{27}H_{22}N_4O_3S$ C,67.20; H, 4.60; N, 11.61; S, 6.64; **found** C, 67.72; H, 5.41; N, 12.03; S, 5.46.

2.2.3.3 4-[2-(1H-indol-1-ylmethyl)-4-oxo-3,4-dihydroquinazolin-3-yl]benzene-1-sulfonamide (4c)

Yield 56.61%; **Melting Point.** 250-252 ^{0}C; **IR (KBr, cm^{-1})** 3407.6 (N-H), 1677.77 (C=O), 1153.22 (S=O); **^{1}H NMR ($CDCl_3$)** δ 0.8-0.9 (s, 2H, CH_2), 1.6 (s, 2H, NH_2), 6.5-6.6 (s, 2H, Ar-H), 7.14-7.17 (m, 2H, Ar-H), 7.22-7.25 (m, 4H, Ar-H), 7.42-7.44 (d, 2H, Ar-H), 7.6-7.7 (d, 2H, Ar-H), 8.16 (s, 2H, Ar-H). MS (EI) m/z 430.48. **Anal. calcd for** $C_{23}H_{18}N_4O_3S$ C, 64.17; H, 4.21; N,

13.01; S, 7.45; **found** C, 63.91; H, 5.12; N, 13.11; S, 7.54.

2.2.3.4 4-{2-[(2,3-dioxo-2,3-dihydro-1H-indol-1-yl)methyl]-4-oxo-3,4-dihydroquinazolin-3-yl} benzene-1-sulfonamide (4d) Yield 42.91%; **Melting Point** 230-232 ^{0}C; IR (KBr, cm^{-1}) 3537.77 (NH_2), 3269.72 (NH), 1638.88 (C=O), 1153.22 (S=O); **^{1}H NMR ($CDCl_3$)** δ 1.2 (d, 4H, Ar-H), 2.2 (s, 2H, NH_2), 3.89 (s, 3H, Ar-H), 4 (d, 1H, Ar-H), 6.8-6.9 (m, 1H, Ar-H), 7.2-7.3 (d, 3H, Ar-H), 7.6 (s, 2H, CH_2). **MS (EI) m/z** 460.08. **Anal. calcd for** $C_{23}H_{16}N_4O_5S$ C, 59.99; H, 3.50; N, 12.17; S, 6.96; **found** C, 59.12; H, 4.08; N, 12.74; S, 6.46.

2.2.3.5 4-{2-[(2,4-dioxo-2,4-dihydro-1H-3,1-benzoxazin-1-yl)methyl]-4-oxo-3,4-dihydroquinazolin-3-yl}benzene-1-sulfonamide (4e) Yield 40.06%; **Melting Point** 242-246 ^{0}C; **IR (KBr, cm^{-1})** 3556.09 (NH_2), 3372.89 (NH), 1691.27 (C=O), 1157.08 (S=O). **^{1}H NMR ($CDCl_3$) δ** 2.6 (s, 2H, NH_2), 3.9 (s, 2H, CH_2), 6.9 (m, 4H, Ar-H), 7.0-7.1 (m, 6H, Ar-H), 7.6 (s, 1H, Ar-H), 7.9 (s, 1H, Ar-H). MS (EI) m/z 476.52. **Anal. calcd for** $C_{23}H_{16}N_4O_6S$ C, 57.98; H, 3.38; N, 11.76; S, 6.73; **found** C, 57.88; H, 4.12; N, 12.81; S, 5.51.

2.2.3.6 4-(2-{[(3-chlorophenyl)amino]methyl}-4-oxo-3,4-dihydroquinazolin-3-yl)benzene-1-sulfonamide (4f) Yield 59.09%; **Melting Point** 228-230 ^{0}C**; IR (KBr, cm^{-1})** 3653.48 (NH_2), 3374.82 (NH), 1598.7 (C=O), 1137.8 (S=O), 800.31 (C-Cl). **^{1}H NMR ($CDCl_3$)** δ 1.3 (s, 2H, NH_2), 4.2 (s, 1H, NH), 6.1 (d, 2H, CH_2), 6.4 (s, 1H, Ar-H), 6.59 (s, 2H, Ar-H), 7.0 (s, 1H, Ar-H), 7.1-7.2 (m, 4H, Ar-H), 7.3 (s, 2H, Ar-H), 7.9-8.0 (dd, 2H, Ar-H), 8.1 (s, 2H, Ar-H). **MS (EI) m/z** 440.59. **Anal. calcd for** $C_{21}H_{17}ClN_4O_3S$ C, 57.21; H, 3.89; N, 12.71; S, 7.27; **found** C, 57.17; H, 3.91; N, 11.80; S, 6.93.

2.2.3.7 methyl2-({[4-oxo-3-(4-sulfamoylphenyl)-3,4-dihydroquinazolin-2-yl]methyl}amino) benzoate (4g) Yield 49.91%; **Melting Point** 256-258 ^{0}C; **IR (KBr, cm^{-1})** 3484.74 (NH_2), 3375.78 (NH), 1617.98 (C=O), 1173.47 (S=O). **^{1}H NMR ($CDCl_3$)** δ 2.8 (s, 2H, NH_2), 3.8 (s, 3H, CH_3), 4.1 (d, 2H, CH_2), 4.3 (s, 1H, NH), 5.9 (s, 2H, Ar-H), 6.0-6.1 (m, 2H, Ar-H), 7.3 (m, 3H, Ar-H), 7.4 (s, 1H, Ar-H), 7.9-8.1 (m, 2H, Ar-H), 8.3 (s, 2H, Ar-H). **MS (EI) m/z** 464.10. **Anal. calcd for** $C_{23}H_{20}N_4O_5S$ C, 59.47; H, 4.34; N, 12.06; S, 6.90; **found** C, 59.61; H, 4.37; N, 12.69; S, 5.71.

2.2.3.8 4-[2-({[3-(hydroxynitroso)phenyl]amino}methyl)-4-oxo-3,4-dihydroquinazolin-3-yl]benzene -1-sulfonamide (4h) Yield 66.21%; **Melting Point** 260-264 ^{0}C; **IR (KBr, cm^{-1})** 3375.78 (NH), 1625.7 (C=O), 1348.96 (NO_2), 1153.22 (S=O); **^{1}H NMR ($CDCl_3$)** δ 1.2 (s, 1H, NH), 5.8 (s, 5H, Ar-H), 6.5 (dd, 2H, NH_2), 6.89 (s, 1H, Ar-H), 6.9 (m, 2H, CH_2), 7.2-7.3 (m, 4H, Ar-H), 7.44 (dd, 2H, Ar-H); **MS (EI) m/z** 451.20. **Anal. calcd for** $C_{21}H_{17}N_5O_5S$ C, 55.87; H, 3.80; N, 15.51; S, 7.10; **found** C, 55.91; H, 3.73; N, 15.50; S, 7.58.

2.2.3.9 3-{[4-oxo-3-(4-sulfamoylphenyl)-3,4-dihydroquinazolin-2-yl]methyl}-1-phenylthiourea (4i) Yield 55.21%; **Melting Point** 280-282 ^{0}C; **IR (KBr, cm^{-1})** 3477.99 (NH), 1670.05 (C=O), 1274.72 (C=S), 1158.04 (S=O); **^{1}H NMR ($CDCl_3$)** δ 0.8 (s, 1H, NH), 1.2-1.3 (s, 3H, Ar-H), 1.7 (s, 1H, NH), 3.1-3.9 (m, 7H, Ar-H), 6.9 (dd, 2H, NH_2), 7.2-7.3 (dd, 2H, CH_2), 7.4 (s, 3H, Ar-H). **MS (EI) m/z** 465.02. **Anal. calcd for** $C_{22}H_{19}N_5O_3S_2$ C, 56.76; H, 4.11; N, 15.04; S, 13.78; **found** C, 55.97; H, 5.10; N, 15.81; S, 12.83.

2.2.3.10 4-(2-{[(3-methylphenyl)amino]methyl}-4-oxo-3,4-dihydroquinazolin-3-yl)benzene-1-sulfonamide (4j) Yield 44.25%; **Melting Point** 224-228 ^{0}C; **IR (KBr, cm^{-1})** 3640.95 (NH_2), 3375.78 (NH), 1678.63 (C=O), 1149.37 (S=O); **^{1}H NMR ($CDCl_3$)** δ 1.2 (s, 2H, NH_2), 2.1 (d, 3H, CH_3), 2.2 (s, 3H, Ar-H), 4.2 (s, 1H, NH), 6.3 (m, 2H, CH_2), 6.4 (s, 1H, Ar-H), 6.9 (m, 1H, Ar-H), 7.2 (m, 3H, Ar-H), 7.3 (m, 4H, Ar-H). **MS (EI) m/z** 420.13. **Anal. calcd for** $C_{22}H_{20}N_4O_3S$ C, 62.84; H, 4.79; N, 13.32; S, 7.63; **found** C, 62.41; H, 4.81; N, 13.44; S, 6.91.

2.2.3.11 4-(2-{[(2-chlorophenyl)amino]methyl}-4-oxo-3,4-dihydroquinazolin-3-yl)benzene-1-sulfonamide (4k) Yield 49.21%; **Melting Point** 230-232 ^{0}C; **IR (KBr, cm^{-1})** 3384.46 (NH), 1681.62 (C=O), 1153.22 (S=O), 826.34 (C-Cl). **^{1}H NMR ($CDCl_3$)** δ 1.2 (s, 2H, NH_2), 4.4 (d, 2H, CH_2), 4.6 (s, 1H, NH), 6.4 (s, 1H, Ar-H), 6.59 (s, 2H, Ar-H), 7.0 (s, 1H, Ar-H), 7.1-7.2 (m, 4H, Ar-H), 7.3 (s, 2H, Ar-H), 7.9-8.0 (dd, 2H, Ar-H), 8.1 (s, 2H, Ar-H). **MS (EI) m/z** 440.05. **Anal. calcd for** $C_{21}H_{17}ClN_4O_3S$ C, 57.21; H, 3.89; N, 12.71; S, 7.27; **found** C, 57.15; H, 3.76; N, 12.60; S, 7.20.

2.2.3.12 4-(2-{[(4-hydroxyphenyl)amino]methyl}-4-oxo-3,4-dihydroquinazolin-3-yl)benzene-1-sulfonamide (4l) Yield 52.17%; **Melting Point**. 284-286 ^{0}C; **IR (KBr, cm^{-1})** 3464.6 (OH), 3343.96 (NH_2), 1666.2 (C=O), 1151.29 (S=O); **^{1}H NMR ($CDCl_3$)** δ 2.1 (s, 2H, NH_2), 3.3 (s, 2H, CH_2), 3.9 (d, 1H, NH), 5.5 (s, 1H, OH), 6.4 (d, 1H, Ar-H), 6.8-6.9 (d, 1H, Ar-H), 7.0-7.3 (d, 1H, Ar-H), 7.4 (d, 1H, Ar-H), 7.5-7.6 (d, 1H, Ar-H), 7.8 (d, 1H, Ar-H), 7.9 (d, 1H, Ar-H). **MS (EI) m/z** 422.10. **Anal. calcd for** $C_{21}H_{18}N_4O_4S$ C, 59.70; H, 4.29; N, 13.26; S, 7.59; **found** C, 59.83; H, 4.34; N, 12.89; S, 7.65.

2.2.3.13 4-{2-[(1,3-dioxo-2,3-dihydro-1H-isoindol-2-yl)methyl]-4-oxo-3,4-dihydroquinazolin -3-yl}benzene-1-sulfonamide (4m) Yield 50.81%; **Melting Point** 294-296 ^{0}C; **IR (KBr, cm^{-1})** 3573.45(NH_2), 3468.35(NH), 1605.45 (C=O), 1143.58 (S=O); **^{1}H NMR ($CDCl_3$)** δ 0.8 (s, 2H, CH_2), 6.5-6.6 (s, 1H, Ar-H), 7.4 (d, 3H, Ar-H), 7.8 (s, 8H, Ar-H), 11.3 (s, 2H, NH_2). **MS (EI) m/z** 460.52**. Anal. calcd for** $C_{23}H_{16}N_4O_5S$ C, 59.99;

H, 3.50; N, 12.17; S, 6.96; **found** C, 59.84; H, 3.31; N, 12.21; S, 7.11.

2.2.3.14 4-[2-({[4-(hydroxynitroso)phenyl]amino}methyl)-4-oxo-3,4-dihydroquinazolin-3-yl]benzene -1-sulfonamide (4n) Yield 60.01%; **Melting Point** 250-252 ^{0}C; **IR (KBr, cm^{-1})** 3698.8 (NH_2), 3363.25 (NH), 1632.45 (C=O), 1306.54 (NO_2), 1184.08 (S=O); **^{1}H NMR ($CDCl_3$)** δ 1.4 (s, 1H, NH), 5.7 (s, 4H, Ar-H), 5.9 (s, 1H, Ar-H), 6.5 (dd, 2H, NH_2), 6.89 (s, 1H, Ar-H), 6.9 (m, 2H, CH_2), 7.2-7.3 (m, 4H, Ar-H), 7.44 (dd, 2H, Ar-H); **MS (EI) m/z** 453.27 (M+2H). **Anal. calcd for** $C_{21}H_{17}N_5O_5S$ C, 55.87; H, 3.80; N, 15.51; S, 7.10; **found** C, 55.89; H, 3.72; N, 15.40; S, 7.18.

2.2.3.15 4-(2-{[(4-methylphenyl)amino]methyl}-4-oxo-3,4-dihydroquinazolin-3-yl)benzene-1-sulfonamide (4o) Yield 48.21%; **Melting Point** 238-240 ^{0}C; **IR (KBr, cm^{-1})** 3461.6 (NH_2) 3373.85 (NH), 1677.77 (C=O), 1151.29 (S=O); **^{1}H NMR ($CDCl_3$)** δ 1.2 (s, 2H, NH_2), 2.3 (d, 2H, CH_2), 3.9 (d, 1H, NH), 7.2 (d, 2H, Ar-H), 7.3 (d, 2H, Ar-H), 7.4 (d, 1H, Ar-H), 7.5 (d, 3H, CH_3), 7.6 (d, 1H, Ar-H), 7.7 (d, 1H, Ar-H), 7.77-7.81(d, 2H, Ar-H), 7.8 (d, 1H, Ar-H), 7.9 (d, 1H, Ar-H), 8.0 (d, 1H, Ar-H). **MS (EI) m/z** 420.48. **Anal. calcd for** $C_{22}H_{20}N_4O_3S$ C, 62.84; H, 4.79; N, 13.32; S, 7.63; **found** C, 62.72; H, 4.91; N, 13.39; S, 7.60.

2.2.3.16 4-(2-{[tert-butyl({2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl})amino] methyl}-4-oxo-3,4-dihydroquinazolin-3-yl)benzene-1-sulfonamide (4p) Yield 39%; **Melting Point.** 308-310 ^{0}C; **IR (KBr, cm^{-1})** 3370.96 (NH), 3240.79 (OH), 1675.84 (C=O), 1151.29 (S=O.) **MS (EI) m/z 552.9. Anal. calcd** for $C_{28}H_{32}N_4O_6S$ C,60.85; H, 5.84; N, 10.14; S, 5.80; **found** C, 60.89; H, 5.81; N, 9.97; S, 5.93.

2.2.3.17 4-(4-oxo-2-{[(4-sulfamoylphenyl)amino]methyl}-3,4-dihydroquinazolin-3-yl)benzene-1-sulfonamide (4q) Yield 69.85%; **Melting Point** 250-252 ^{0}C; **IR (KBr, cm^{-1})** 3683.37 (NH_2), 3374.82 (NH), 1632.45 (C=O), 1186.97 (S=O); ^{1}H NMR ($CDCl_3$) δ 1.3 (s, 2H, NH_2), 1.6 (s, 2H, NH_2), 3.8 (s, 1H, NH), 5.3 (d,2H, CH_2), 6.7-6.8 (m, 2H, Ar-H), 6.9 (m, 2H, Ar-H), 7.6 (m, 2H, Ar-H), 7.7 (s, 1H, Ar-H), 7.8-7.9 (m, 5H, Ar-H) **MS (EI) m/z** 486.08 (M+H); 533.18 (M+Na). **Anal. calcd for** $C_{21}H_{19}N_5O_5S_2$ C, 51.95; H, 3.94; N, 14.42; S, 13.21; **found** C, 52.02; H, 3.91; N, 14.36; S, 13.48.

2.3 Biological Activity

Wistar rats weighing 150-200 gm bodyweight were housed at standard laboratory conditions (22 ± 3 ℃, 12 h day/night cycle) and fed with a rodent pellet diet and water. Before examination all animals were fasted depriving them of food for 16 h but were given free access to 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 (1091/abc/07/CPCSEA) India, and were approved by the Institutional Animal Ethics Committee (IAEC).

2.3.1 Induction of diabetes

Non insulin-dependent diabetes mellitus was induced in overnight fasted rats by a single intraperitoneal injection of 65 mg/kg Streptozotocin dissolved in cold citrate buffer (pH 4.5), 15 min after the intraperitoneal administration of 120 mg/kg of Nicotinamide. Hyperglycemia was confirmed by the elevated glucose concentration in plasma, determined at 72 h. The hyperglycemic animals (blood glucose level higher than 250 mg/dL) were used for the antidiabetic screening. Rats of experimental group were administered a suspension of desired test samples (prepared in 2% sodium CMC) orally (75mg/kg).

2.3.2 Preliminary Screening of Antihyperglycemic activity

The blood glucose levels were measured at 0-, 1-, 2-, 3-, 4-, 5-, 6-, 7- and 8-h intervals on blood samples collected via tail vein by excision. The % decrease in blood glucose from 0-8 h by test compounds was calculated.[22]

2.3.3 Determination of fasting blood glucose level

Fasting blood glucose levels (FBG) was determined in all experimental rats initially to determine the diabetic status, and thereafter, every week during the 28 day study period. Blood samples were collected via tail vein by excision and, the blood glucose levels were determined using a commercial glucometer.

2.3.4 Oral Glucose Tolerance Test

On the 28th day of treatment period, animals were subjected to an oral glucose tolerance test (OGTT). After overnight fasting, a baseline (t=0 min) blood sample was taken from rats in normal and diabetic groups. Without delay, a load of glucose was administered. Blood samples were collected via tail vein by excision at different time intervals after 0 min interval i.e. at 15, 30, 60, 90, and 120 min for estimation of blood glucose level.[23]

2.3.5 Glycogen content of liver and skeletal muscle

The skeletal muscle and liver tissue were homogenized under appropriate volume of tricholoroacetic acid (TCA) for 3 minutes and centrifuged for 15 minutes. The desired volume was made up with 5% TCA and mixed thoroughly. One ml of the TCA filtrate was pipetted into 15 ml Pyrex tube. Five volumes of 95% methanol was added to each tube and allowed to stand overnight for precipitation and then centrifuged at 3000 rpm (Remi, India) for 15 minutes. Standard glucose solution of 0.1 mg glucose in 2 ml distilled water was prepared and distilled water was used as blank. Anthrone reagent was added and glycogen content was determined colorimetrically.[24]

2.3.6 Parameters of Antihyperlipidemic, Hepatic Dysfunction and Antioxidant Activity

The Antihyperlipidemic profile of the drug was performed by estimation of total cholesterol, triglycerides and VLDL using Erba Cholesterol Kit (CHOD-PAP Method, End point), Erba Triglycerides DES Kit (GPO-TRINDER Method, End piont), Erba Direct HDL 160 Kit. Hepatic dysfunction parameters include estimation of serum transaminase and Estimation of serum alkaline phosphatase (ALP) carried out using ERBA SGPT/SGOT Kit (IFCC Method, Kinetic) and ERBA Alkaline phosphatase Kit (Tris Carbonate Buffer, Kinetic). *In vitro* antioxidant assays involving estimation of liver superoxide dismutase, estimation of reduced glutathione, estimation of liver MDA lipid peroxidation, estimation of liver catalase.[25-26]

3 RESULTS AND DISCUSSION

3.1 Molecular Docking Study

From the structure of docking conformation, we analysed that greater binding efficacy of Sitagliptin (- 7.04 kcal/mol) revealed that the ligand is tightly fixed in the pocket. Furthermore details of each docked ligand is given in **Table 1**:

Table 1: Molecular docking analysis using MGL tools 1.5.6 and autodock 4.2.6 program (PBD ID: 3OPM).

Ligand	Binding energy (kcal/mol)	No. of H Bond	Cluster RMSD	Reference RMSD
4a	-8.14	1	0.0	34.9
4b	-7.92	1	0.0	36.71
4c	-7.77	1	0.0	40.3
4d	-8.80	3	0.0	37.92
4e	-9.49	1	0.0	35.17
4f	-7.97	2	0.0	34.91
4g	-8.15	2	0.0	37.68
4h	-9.36	2	0.0	45.76
4i	-8.66	-	0.0	32.05
4j	-7.52	2	0.0	42.31
4k	-7.98	3	0.0	36.64
4l	-7.79	2	0.0	33.72
4m	-8.60	1	0.0	40.79
4n	-9.03	1	0.0	46.09
4o	-7.55	1	0.0	45.03
4p	-7.73	3	0.0	37.88
4q	-9.00	1	0.0	38.79
Standard (Sitagliptin)	-7.04	1	0.0	39.42

The minimum binding energy indicated that the DPP-IV protein was successfully docked with compounds. The results showed that the binding affinity of **4q** for the enzyme was -9.00 kcal/mol and Sitagliptin as reference was -7.04 kcal/mol. Other molecules also showed comparable binding affinities for the enzyme. We found that the molecules bound to the active site of DPP-IV residues like Tyr631, Ser630, Val656, Gly628, Val711, Tyr547, Val546, and Lys554. This study suggested that the designed molecules had the potential to act as DPP-IV inhibitors and hence synthesis of these molecules was taken up. LigPlot was used to show the interaction of the binding site residues of the protein as seen in Fig. 2 and Fig. 5 respectively. Molecular docking showing 2D binding interaction of Sitagliptin and (**4-q**) at Dipeptidyl Peptidase-IV inhibitor (PDB ID 3OPM) in Fig. 3 and Fig. 6. Molecular docking showing 3D binding interaction of Sitagliptin and (**4-q**) at Dipeptidyl Peptidase-IV inhibitor (PDB ID 3OPM) is seen in Fig. 4 and Fig. 7.

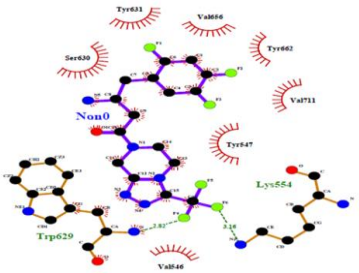


Fig. 2: Ligplot of Sitagliptin.

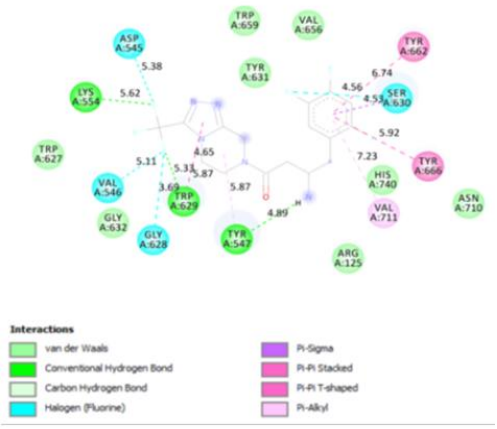


Fig. 3: Molecular docking showing 2D binding interaction of Sitagliptin at Dipeptidyl Peptidase-IV inhibitor (PDB ID 3OPM).

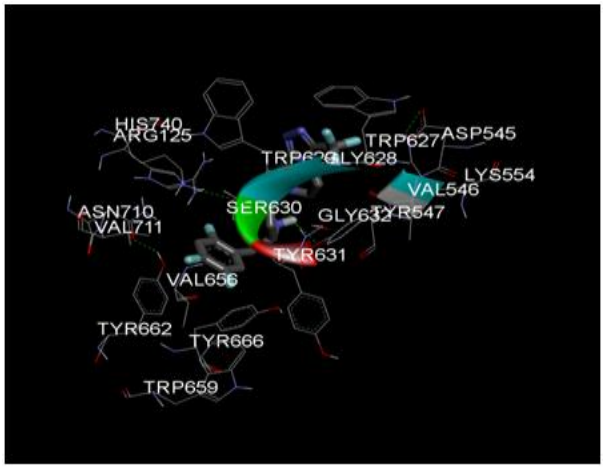


Fig. 4: Molecular docking showing 3D binding interaction of Sitagliptin at Dipeptidyl Peptidase-IV inhibitor (PDB ID 3OPM).

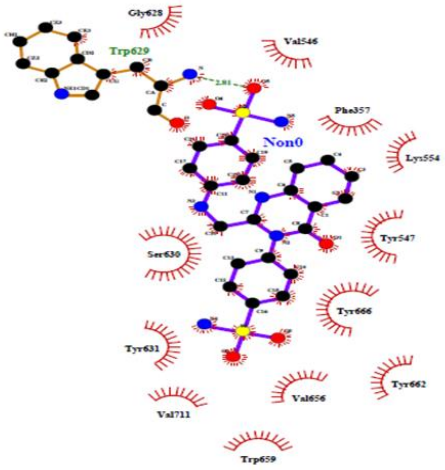


Fig. 5: Ligplot of 4-q.

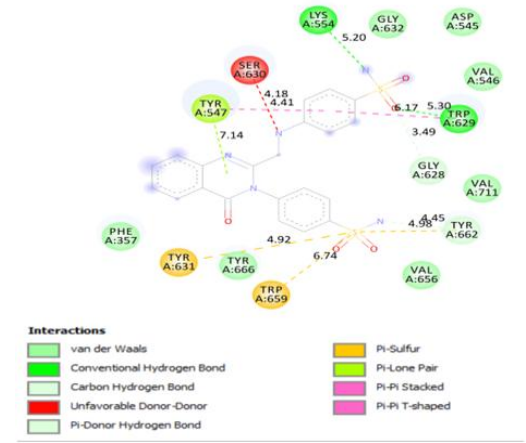


Fig. 6: Molecular docking showing 2D binding interaction of (4-q) at Dipeptidyl Peptidase-IV inhibitor (PDB ID 3OPM).

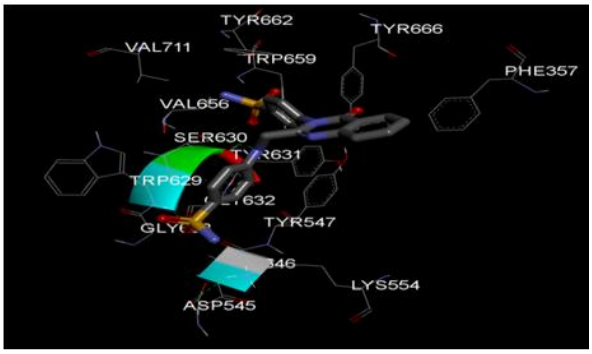
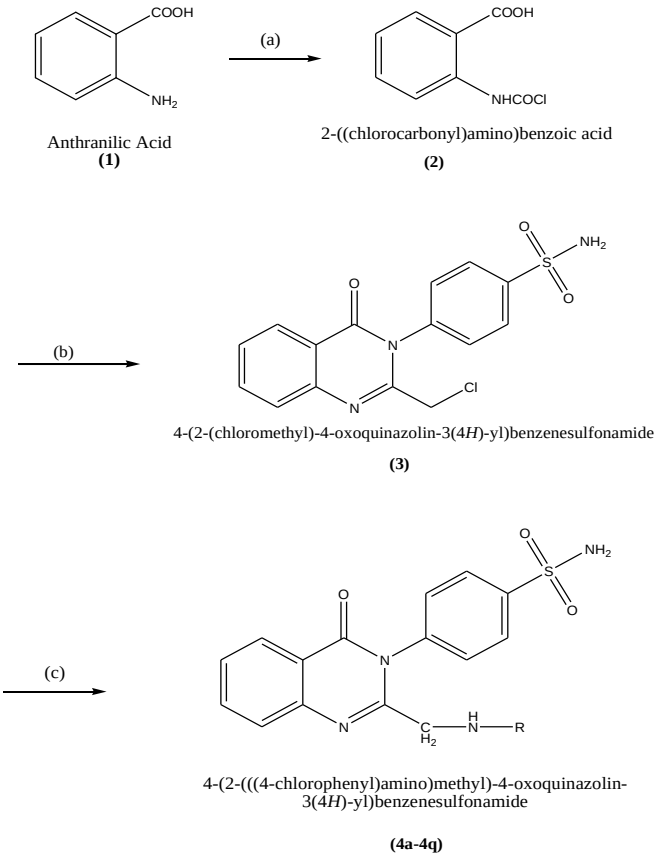


Fig. 7: Molecular docking showing 3D binding interaction of (4-q) at Dipeptidyl Peptidase-IV inhibitor (PDB ID 3OPM).

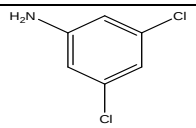
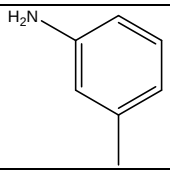
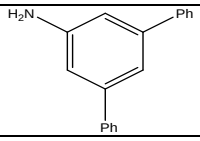
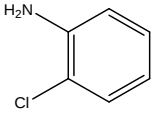
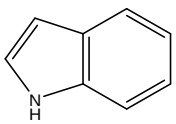
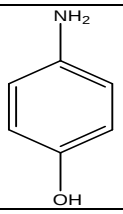
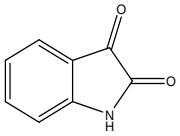
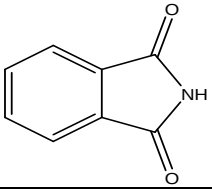
3.2 Chemistry

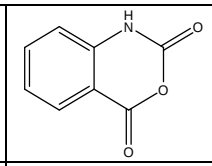
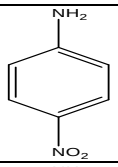
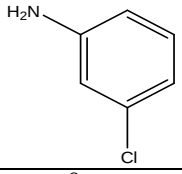
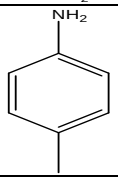
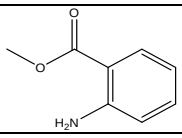
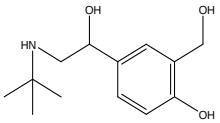
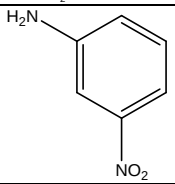
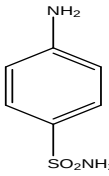
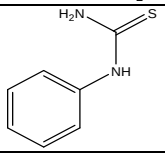
The synthesis of compounds was achieved by following the route showed in Scheme 1. The synthesis of 2-(2-chloroacetamido)-benzoic acid (**2**) was carried out using a modified Niementowski synthesis, beginning with the chloro-acetylation of anthranilic acid (**1**) to yield the corresponding 2-(2-chloroacetamido)-benzoic acid (**2**).[27-29] The acid (**2**) was then treated with trichlorophosphate (PCl_3) to obtain acid chloride which was immediately treated with substituted amine i.e. sulphanilamide insitu, to replace the chloro group of acid chloride with substituted aniline. This was then refluxed in toluene to generate the cyclized product (**3**). Finally, the title compounds (**4a-4q**) were synthesized in good yield from the intermediate **(3)** by refluxing it with various substituted amines dissolved in acetonitrile.[30] The synthesized compounds were purified by column chromatography. The structure and purity of all compounds was confirmed by spectroscopic (IR and NMR) and spectrometric (mass spectrometry) techniques. The summery of synthesized derivatives given in **Table 2.**



Scheme 1: Synthesis of compounds 4a-4q. Reagents and conditions: (a) $ClCH_2COCl$, toluene, 2.5 h; (b) PCl_3, toluene, sulphanilamide, rt; (c) R-NH_2, K_2CO_3, KI, acetonitrile, 80℃, 90-120 min.

Table 2: Physical data of synthesized compounds (4a-4q).

Compd	Substitution at R	Mol. weight	% yield	Compd	Substitution at R	Mol. weight	% yield
4a		475.35	62.3%	**4j**		420.48	63.74%
4b		482.55	58.46%	**4k**		442.92	65.23%
4c		430.48	61.38%	**4l**		422.46	50.12%
4d		460.46	65.73%	**4m**		460.46	61.32%

4e		476.46	59.2%	**4n**		451.46	52.98%
4f		440.09	67.3%	**4o**		420.48	49.57%
4g		464.49	61.89%	**4p**		570.66	45.64%
4h		451.46	67.5%	**4q**		485.54	64.39%
4i		465.55	49.1%				

3.3 Biological Activity

It is well known that some quinazolinones and sulfonamides have shown anti-diabetic activity.[32-35] The anti-diabetic activity of our synthesized quinazolinone-sulfonamide hybrid was performed by *in-silico* method, with DPP-IV as target. The in vivo Antihyperglycemic activity was performed 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 as standard at a dose of 5mg/kg. 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 on blood samples collected via tail vein by excision. The % decrease in blood glucose from 0-8 h by test compounds were calculated. All the compounds were found to be active as anti-diabetic agents (Table 3). The compounds **4q, 4d, 4f, 4j** showed good potent hypoglycemic effect as compared to standard Sitagliptin, while compounds **4e, 4p, 4l, 4o, 4m, 4i** shows moderate hypoglycemic effect. The compound **4q** was studied further in detail, as it showed highest % decrease in blood glucose level in the present series of synthesized compounds.

Table 3: % decrease in Blood Sugar Level of Test compounds.

Sr no	Compound	% decrease blood glucose level
1	4-a	4.67
2	4-b	17.17
3	4-c	24.09
4	4-d	60.17
5	4-e	46.84
6	4-f	57.03
7	4-g	12.7
8	4-h	8.15
9	4-i	29.53
10	4-j	50.34
11	4-k	13.68
12	4-l	39.67
13	4-m	33.49
14	4-n	21.45
15	4-o	37.87
16	4-p	40.06
17	4-q	52.1
18	STG	50.4

During the 4 weeks of treatment period with compound **4q** and Sitagliptin, fasting blood glucose level (FBG) were estimated in normal and experimental rats on 7th, 14th, 21st and 28th day. Our results showed that STZ-NA injection in rats leads to a significant increase ($p<0.01$) in fasting blood glucose level when compared to normal control (Fig. 8). A clear reduction in fasting blood glucose levels was observed from the day one after the treatment with **4q** ($p<0.01$) when compared to STZ-NA induced diabetic control values. On comparison with diabetic control group, decrease in fasting blood glucose was observed on treatment with standard Sitagliptin and **4q** as a test compound.

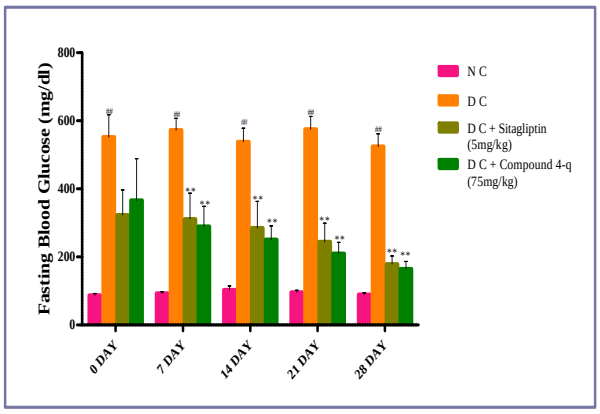


Fig 8: Effect of compound 4q (75mg/kg) and Sitagliptin (5mg/kg) on fasting blood glucose level in Streptozotocin-Nicotinamide induced diabetes rats.

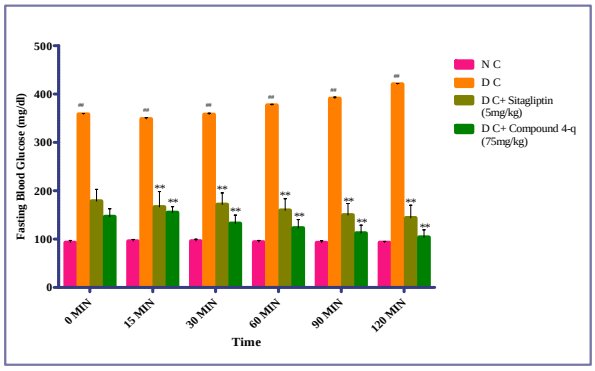


Fig 9: Effect of compound 4q (75mg/kg) and Sitagliptin (5mg/kg) on oral glucose tolerance test (OGTT) in Streptozotocin-Nicotinamide induced diabetes rats.

Fig. 9 illustrates the results of the treatment with **4q** on blood glucose levels during the Oral Glucose Tolerance Test (OGTT) in normal and Streptozotocin-Nicotinamide induced diabetic rats. A clear difference in baseline fasting blood glucose between the normal and STZ-NA induced diabetic groups was noted. After glucose loading, the level of blood glucose in normal control rats showed slight difference, while, in diabetic control; high value peak was observed from 15 min to 120 min. A high peak value at 15 min was also observed in diabetic rats treated with the dose of **4q**, and then a decline in a dose-dependent manner was noted at 30 min and thereafter. At the end of oral glucose tolerance test, it was seen that the compound **4q** at a dose of 75mg/kg was as effective as Sitagliptin at 5 mg/kg, in reducing blood glucose levels.

It was observed that the liver and muscle glycogen was significantly ($p<0.01$) reduced in STZ-NA induced diabetic rats as compared to the normal rats (Fig. 10). Since STZ causes selective destruction of β-cells of pancreas, it results into marked decrease in insulin levels.[36]

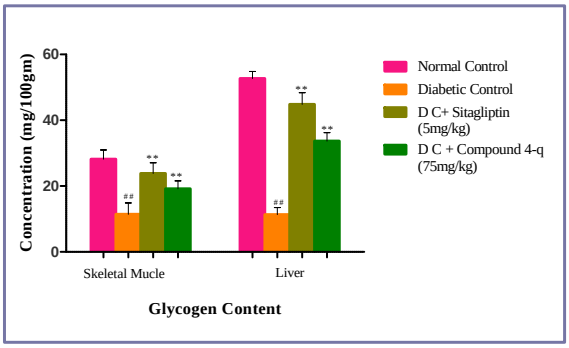


Fig 10: Effect of compound 4q (75mg/kg) and Sitagliptin (5mg/kg) on glycogen content of liver and skeletal muscle in Streptozotocin-Nicotinamide induced diabetes rats.

In lipid profile, it was observed that treatment of diabetic control rats showed significantly ($p<0.01$) higher levels of Total Cholesterol (T-CH), Triglyceride (TG), Low Density Lipoprotein (LDL), Very Low Density Lipoprotein (VLDL) associated with lower levels of High Density Lipoprotein (HDL). Moreover, a significant ($p<0.01$) elevation in the ratios was noted in this group, compared to normal control ratios. Treating diabetic animals with compound **4q** reversed the levels i.e. reduced the concentration of T-CH, TG, LDL, VLDL to near normal values and significantly ($p<0.01$) when compared to diabetic control values, whereas there was significant ($p<0.01$) increase in HDL level as compared to diabetic control.

Diabetes Mellitus is usually associated with several abnormalities of fats and lipoproteins. Abundance of TG-rich lipoproteins such as chylomicrons and VLDL in the blood was observed in STZ-NA diabetic animals along with an elevation in plasma concentration of T-CH, TG, LDL associated with reduced levels of HDL.

Oral treatment of diabetic rats with **4q** decreased the disturbance of lipid profile (Fig. 11). This hypolipidemic effect may be attributed to the augmented circulating levels of the antilipolytic hormone, insulin, which is considered as a potent activator of lipoprotein lipase (LPL), the enzyme that catalyzes the hydrolysis of the plasma TG-rich lipoprotein.[36]

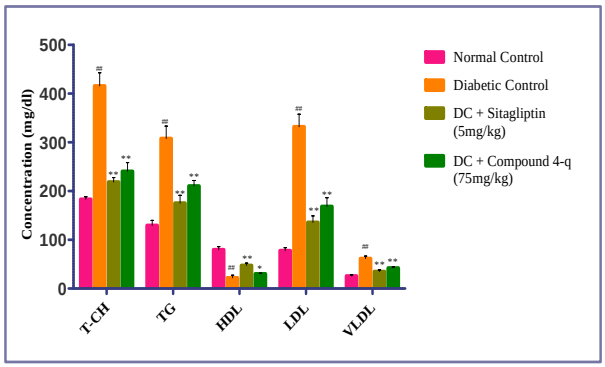


Fig 11: Effect of compound 4q (75mg/kg) and Sitagliptin (5mg/kg) on Lipid profile in STZ-Nicotinamide induced diabetes rats.

In our study, experimental Diabetes Mellitus (DM) has increased activities of plasma enzymes (Fig. 12); ALT, AST, and ALP. This might be primarily due to the leakage of these enzymes, and more specifically ALT, from liver cytosol into blood stream, demonstrating hepatocellular damage. However, the high activities of aminotransferases (ALT and AST) during DM, could also be due to excessive accumulation of gluconeogenic AAs (alanine and glutamate) as a result of AAs mobilization from peripheral protein stores. The elevated activity of circulating ALP may be secondary to the hyperphagia or to a direct toxic effects of STZ on the intestine.[23]

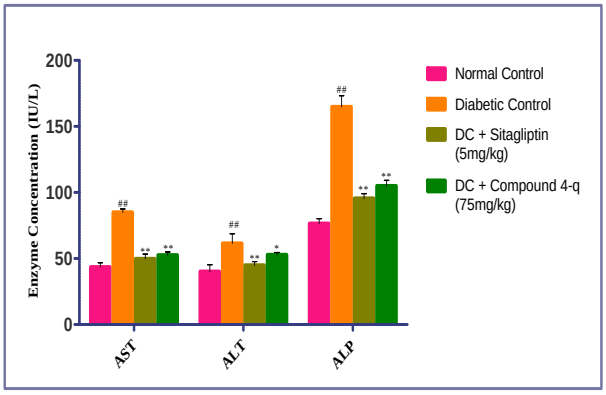


Fig 12: Effect of Compound 4q (75mg/kg) and Sitagliptin (5mg/kg) on Hepatospecific Marker in STZ-Nicotinamide induced diabetes rats.

The determination of malondialdehyde (MDA) level provides a good measure of peroxidation, which is one of the chief mechanisms of cell damage leading to necrosis or apoptosis. Our present study showed a significant elevation in liver MDA content of diabetic rats suggesting involvement of peroxidation injury in development of diabetic complications. The increase in lipid peroxidation might be an indication of a decrease in enzymatic and non-enzymatic antioxidants of defense mechanisms. In our study, the test sample group significantly reduced the MDA level in the liver tissue (Fig. 13) of diabetic rats indicating its protective role during oxidative damage. Associated with the changes in lipid peroxidation, diabetic animals showed decreased activity of the key antioxidant enzymes viz. superoxide dismutase (SOD), and reduced glutathione (GSH), which play an important role in scavenging the toxic intermediates of incomplete oxidation. The treatment showed a significant restoration in SOD and GSH contents in diabetic rats.

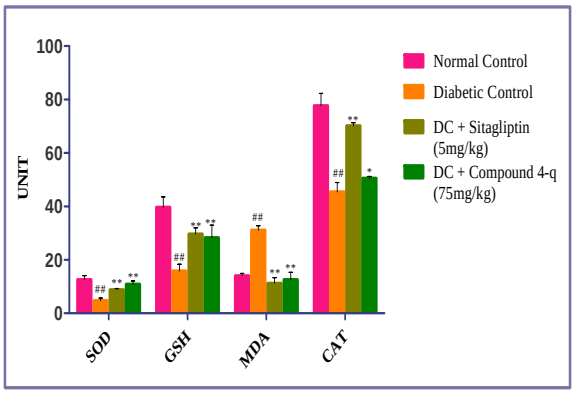


Fig 13: Effect of compound 4q (75mg/kg) and Sitagliptin (5mg/kg) on antioxidant status in STZ-Nicotinamide induced diabetes rats.

4 CONCLUSIONS

In search of novel DPP-IV inhibitors, the different scaffolds were designed and their binding affinities for the enzyme as compared with Sitagliptin were determined by *in silico* studies. The data obtained from our research study indicates that quinazolinone and sulfonamide hybrid molecules have potential to lower blood glucose level, regenerating β-cells and modulating the disturbances of lipid metabolism caused by STZ-NA induced DM. In our present study we have synthesized 17 quinazolinone-sulfonamide hybrids (**4a-4q)** and reported the findings here. The *in silico* docking study has shown the potential of these hybrids to possess antidiabetic activity through inhibition of DPP-IV enzyme. The antihyperglycemic effects exhibited by the novel synthesized molecules were comparable with those of Sitagliptin, a standard drug of type 2 DM.

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