Design, Synthesis, and Evaluation of Quinazolinone–Triazole Hybrids as Potent Anti-Glycation Agents

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Abstract:

The devevelopment of advanced glycation end products (AGEs) through non enzymatic glyactaion of proteins is a major contributor to the pathogenesis of diabetic complications. In this study, a series of quinazolinone–triazole hybrids (4a-j) was rationally designed and synthesized to evaluate their potential as antiglycation agents. the Antiglycation activity of the synthesized compounds was assessed by employing Bovine serum albumin (BSA)-fructose to estimate the level of fructosamine, protien carbonyl contet, protien thiol and congo red binding. Among the synthesizeds hybrids, compound 4c, 4e, and 4f exhibited strong Antiglycation activity with IC_{50} values of 82.00±1.155 μM, 45.00 ± 0.577 μM, and 77.33±0.882 μM respectively in fructosamine assay compared to standard Rutin (93.16±0.441 μM). These compounds also demonstrated substantial reduction in Congo red absorbance, indicating inhibition of β-sheet-rich AGE aggregation. Furthermore, treatment with the active compounds led to a significant decrease in protien carbonyl content and preservation of free thiol groups, confirnming their role in glycation inhiobition and oxidative protection. Structure-activity relationship (SAR) analysis revealed that electron-donating groups on the triazole moety and specific substitutions at the quinazoline core greatly enhanced activity. The molecular docking simulation of these compounds with active site of the HSA-fructose complex (PDB ID: 4IW1) using also supported the potency of these hybrids (4a-j) as Antiglycation agent. These findings suggest that the synthesized quinazolinone–triazole hybrids (4a-j) represents a promising candidate for development of Antiglycation agents, warranting further investigation in AGE-related disease models.

Keywords: Quinazolinone-triazole hybrid, Antiglycation activity, Diabetic complication, BSA assay, Oxidative protection, Molecular docking.

1. Introduction

Glycation is a non-enzymatic reaction, which occurs when reducing sugars including glucose or fructose interact with free amino groups of proteins, lipids, or nucleic acids and transform into early glycation products i.e. Schiff bases and Amadori products, that evolve into a diverse and heterogenous collection of intermediates termed advanced glycation end-products (AGEs) [1]. High concentrations of AGEs in biological systems have been linked to the pathophysiology of several chronic and degenerative conditions, such as diabetes mellitus, cardiovascular disease, nephropathy, retinopathy, and neurodegenerative conditions such as Alzheimer disease and parkinsons disease. The AGEs utilize one of two ways to cause their deleterious effects by modifying the structure and activity of proteins or binding to specific cell surface receptors including the receptor of AGEs (RAGE) causing the production of oxidative stress and induction of an inflammatory response [2,3]. The existing treatment options to control AGE-related pathologies are nominal. Although standard glycemic control is essential, it still cannot always terminate the progress of AGEs formation or evade the undesirable effects of AGEs. Numerous synthetic inhibitors have also been investigated like aminoguanidine and alagebrium among other, but they have been hindered by their safety and poor efficacy [4]. Hence, there is an increasing demand of designing new safe and efficient anti-glycation agents, ideally on a rational basis drug design and molecular hybridization which should address more than one step of the glycation cascade. Over the past few years, molecular hybridization methods have become increasingly popular within the field of medicinal chemistry, which contributes to the fact that this multi-purpose approach is the most popular strategy of influencing pharmacological properties, enhancing selectivity, and regulating physicochemical characteristics [5]. Hybrid molecules have the potential of producing additive or synergistic responses and thus breaking the constraints of monofunctional agents by synthesizing two or more bioactive scaffolds into one, thus creacting a molecular framework [6]. Quinazolinone, is a fused heterocyclic system and one of the privileged scaffolds that have been broadly used to discover a wide range of their biological potential, such as anticancer, antimicrobial, anti-inflammatory, antidiabetic, and neuroprotective effects [7]. Notably, some Quinazolinone analogs have shown antioxidant and anti-glycation potentials, which have been attributed to the sacavenging activity of the reactive carbonyl and oxygen species responsible in the formation of AGEs [8]. The Quinazolinone core has drug-like properties and structural modifiability making it an ideal candidate for hybrid drug development. In

contrast, 1,2,3-triazole is a highly stable, bioisosteric, five-membered, nitrogen-based heterocycle and exhibits capability to form stable hydrogen-bonding and dipole-dipole resonance activity between the compound and a biological target. Triazole motifs are highly represented in several therapeutically active compounds in several places, and act as useful building blocks or pharmacophores in drug development. Interestingly, addition of 1,2,3-triazoles to hybrid molecules has the potential to increase aqueous solubility, metabolic stability, and binding affinity [9,10]. Although Quinazolinone and triazole scaffolds separately have been examined in a variety of therapeutic contexts, limited examination has yet been directed towards the design and synthesis of Quinazolinone-triazole conjugates as anti-glycation compounds the literature based on such scaffolds is largely investigated to their anticancer, antimicrobial or antidiabetic effect and less to their ability to block AGE formation.Furthermore, a limited number of studies have incorporated a combination of experimental and in silico methods to systematically analyse the anti-glycation activity and mechanism of action of these hybrids. This paper describes the synthesis of a series of novel Quinazolinone-triazole hybrids and screened in terms of inhibitory potential against AGE formation and their binding affinity towards the target proteins involved in glycation was examined by docking studies. In addition, the therapeutic feasibility of these compounds was evaluated through pharmacokinetic and drug-likeness profiles. The objective of this integrated approach is to recognize potential lead molecules to advance as Antiglycation agents.

2. Materials and Methods

Chemicals and solvents added during synthesis were analytical grade and provided by Sigma Alrich, Merck, SRL Chemicals, Loba Chemie and CDH Chemicals. 2,4-dinitrophenylhydrazine (DNPH), and Congo red, 2,2-diphenyl-1-picrylhydrazyl (DPPH). The progress and completion of the reaction was monitored using thin layer chromatography on silica gel G plate (E. Merck). A Bruker Advance Neo of 400 MHz was used to determine the structural characterization with regards to ^{1}HNMR and ^{13}CNMR to DMSO-D6 as a solvent using a Brucker Advance Neo Spectrometer. IR spectra were obtained on a PerkinElmer Spectrum IR version 10.6.2 FTIR spectrophotometer, whereas mass spectra were recorded on a QTOF Mass Spectrometer of Xevo G2-XS. Elemental analysis was done with the Thermo scientific flash 2000 analyzer.

Synthesis

Synthesis of (2-phenyl-4H-3,1-benzoxazin-4-one (1)[11]

Anthranillic acid (0.01mol) was dissolved in pyridine (50 mL) at 8℃. The same proportion of benzoyl chloride was added dropwise under stirring conditions over 1 hour, and the stirring was continued for an

additional 2 hours at room temperature. After neutralization with aqueous $NaHCO_3$, the resulting precipitate was filtered, washed with water, and then recrystalized in ethanol to afford pale yellow crystals.

General procedure for the synthesis of compound (2a-j)

The stoichiometric mixture of compound 1 (0.01 mol) and substituted aniline was dissolved in dry pyridine (60 mL) and refluxed for 5 hours at 90-100℃. The reaction mixtures were cooled and poured into ice-cold water; the precipitate obtained was filtered, dried, and crystallized with ethanol. IR (KBr, cm^{-1}): 3307.62 (N-H), 2917.19 (Ar C-H), 1721.49 (C=O), 1643.76 (C=N), 1515.34 (Ar C=C), 1120.53 (C-N); ^{1}HNMR (400 MHz, DMSO-d_6): δ 7.44-7.49 (5H, m, ArCH), 7.57-7.58 (3H, m, ArCH), 7.77 (2H, m, ArCH) 7.50, 7.68, 7.85, 8.14 (4H, m, $ArCH_{Quinazolinone}$); ^{13}CNMR (125 MHz, DMSO-d_6), δppm: 120.8 (1C), 126.62-126.38 (2C), 127.3 (1C), 128.02-128.93 (10 C), 130.17 (1C), 132.76 (1C), 133.46 (1C), 148.72 (1C), 156.27 (1C), 160.64 (1C, >C=O).

General procedure for synthesis of 4-(3-(4-substitutedphenyl)-4-oxo-3,4-dihydroquinazolin-2-yl)benzenesulfonyl chloride (3a-j)

Chlorosulfonic acid (0.05 mol) was added dropwise to a compound 3a–j (0.01 mol) at cold condition temperature below 5 °C with constant stirring. Stirring was continued for 1 hour at 0–5 °C, followed by an additional 1-2 hour at room temperature. Upon completion, the reaction mixture was slowly poured into crushed ice with vigorous stirring to precipitate the product. The resulting solid was collected by filtration, washed with cold water, and dried.

IR (KBr, cm^{-1}): 3418.63 (N-H), 2969.91 (Ar C-H), 1678.63 (c=n), 1436.74 (Ar C=C), 1408.73 (S=O); ^{1}HNMR (400 MHz, DMSO-d_6): δ 7.43 (2H, m, ArCH), 7.57-7.58 (3H, m, ArCH), 7.50, 7.68, 7.85, 8.13 (4H, m, $ArCH_{Quinazolinone}$), 8.03-8.05 (4H, m, ArCH); ^{13}CNMR (125 MHz, DMSO-d_6), δppm: 120.8 (1C), 126.62-127.38 (7C), 127.3 (1C), 128.02-128.93 (5C), 132.72 (1C), 133.44 (1C), 135.43 (1C), 148.72 (1C), 156.27 (1C), 160.64 (1C, >C=O).

General procedure for synthesis of 4-(3-(4-substitutedphenyl)-4-oxo-3,4-dihydroquinazolin-2-yl)-N-(1H-1,2,4-triazol-3-yl)benzenesulfonamide (4a-j)

Synthesis of Quinazolinone-triazole hybrids (4a-j), for this the equimolar amount of amino triazole (0.01 mole) was dissolved in water and the pH is adjusted to around 8-9 using 10% sodium carbonate solution. The reaction mixture is cooled in an ice bath and compound 3 (0.01 mole) is added slowly with constant stirring. The mixture is then stirred for 4-5 huours, first one hour in cold and then at room

temperature, allowing the sulphonamide product to form, which precipitate out. The solid product was coolected by filteration, washed with cold water and recrystalized from ethanol.

4-(4-oxo-3-phenyl-3,4-dihydroquinazolin-2-yl)-N-(1H-1,2,4-triazol-3-yl)benzenesulfonamide (4a)

Color: canary yellow powder; m.p. 186-188ºC; % yield: 67%; IR (KBr, cm^{-1}): 3326.74 (N-H), 3168.41 (Ar C-H), 2915.73 (Alph. C-H), 1723.78 (C=O), 1619.70 (C=N), 1568.05 (Ar C=C), 1440.62 (N-N), 1165.42 (S=O), 1010.00 (N-N); ^{1}HNMR (400 MHz, DMSO-d_6): δ 7.44-7.58 (5H, m, ArCH), 7.51, 7.67, 7.86, 8.14 (4H, m, $ArCH_{Quinazolinone}$), 8.03-8.08 (4H, d, ArCH), 7.63 (1H, d, $C\text{-}H_{triazole}$), 11.68 (1H, s, $NH\text{-}SO_2$), 14.46 (1H, s, $NH_{triazole}$); ^{13}CNMR (100 MHz, DMSO-d_6), δppm: 120.8 (1C), 126.3-126.8 (4C), 127.3-127.5 (3C), 128.0-128.9 (5C), 131.8 (1C),132.8 (1C), 133.4 (1C), 141.2 (1C), 146.1 (1C), 147.8 (1C), 148.7 (1C), 156.2 (1C), 160.6 (1C, >C=O); MS m/z: 444.00 [M^+] calculated for $C_{22}H_{16}N_6O_3S$; Elemental Analysis calculated: C, 59.45; H, 3.63; N, 18.91; O, 10.80; S, 7.21; Found: C, 59.53; H, 3.71; N, 19.02; O, 10.96; S, 7.32.

4-(3-(4-substitutedphenyl)-4-oxo-3,4-dihydroquinazolin-2-yl)-N-(1H-1,2,4-triazol-3-yl)benzene sulfonamide (4b)

Color: light yellow powder; m.p. 157-159ºC; % yield: 62 %; IR (KBr, cm^{-1}): 3417.21 (N-H), 3073.36 (Ar C-H), 2889.28 (Alph. C-H), 1735.28 (C=O), 1615.52 (C=N), 1525.65 (Ar C=C), 1456.13 (N-N), 1132.50 (S=O), 1056.71 (N-N); ^{1}HNMR (400 MHz, DMSO-d_6): δ7.39-7.43 (4H, m, ArCH), 7.50, 7.67, 7.84, 8.12 (4H, d, $ArCH_{Quinazolinone}$), 7.61 (1H, s, $C\text{-}H_{triazole}$), 8.02-8.06 (4H, d, ArCH), 11.67 (1H, s, NH), 14.46 (1H, s, $NH_{triazole}$); ^{13}CNMR (100 MHz, DMSO-d_6), δppm: 120.8 (1C), 126.4-126.7 (4C), 127.3-127.4 (3C), 129.0-130.9 (5C), 131.8 (1C),133.2-133.4 (2C), 141.1 (1C), 146.1 (1C), 147.8 (1C), 148.7 (1C), 156.2 (1C), 160.6 (1C, >C=O); MS m/z: 478.01 [M^+] calculated for $C_{22}H_{15}ClN_6O_3S$; Elemental Analysis calculated: C, 55.18; H, 3.16; Cl, 7.40; N, 17.55; O, 10.02; S, 6.69; Found: C, 55.11; H, 3.08; Cl, 7.32; N, 17.45; O, 9.93; S, 6.58.

4-(3-(4-hydroxyphenyl)-4-oxo-3,4-dihydroquinazolin-2-yl)-N-(1H-1,2,4-triazol-3-yl)benzene sulfonamide (4c)

Color: dark yellow powder; m.p. 186-188ºC; % yield: 67 %; IR (KBr, cm^{-1}): 3415.72 (O-H), 3348.90 (N-H), 3227.90 (Ar C-H), 2827.20 (Alph. C-H), 1711.85 (C=O), 1614.85 (C=N), 1527.20 (Ar C=C), 1445.49 (N-N), 1173.21 (S=O), 1085.98 (N-N); ^{1}HNMR (400 MHz, DMSO-d_6): δ 6.91-7.03 (4H, d, ArCH), 7.50, 7.67, 7.84, 8.13 (4H, m, $ArCH_{Quinazolinone}$), 7.62 (1H, s, $C\text{-}H_{triazole}$), 8.02-8.06 (4H, d, ArCH), 9.44 (1H, s, Ar-OH), 11.67 (1H, s, NH), 14.46 (1H, s, $NH_{triazole}$); ^{13}CNMR (100 MHz, DMSO-

d_6), δppm: 116.1 (2C), 120.8 (1C), 126.4-126.7 (4C), 127.3-127.4 (3C), 125.4 (1C), 129.2 (2C), 131.8 (1C), 133.4 (1C), 141.1 (1C), 146.1 (1C), 147.9 (1C), 148.7 (1C), 154.2 (1C), 156.3 (1C), 160.6 (1C, >C=O); MS m/z: 460.33 [M^+] calculated for $C_{22}H_{16}N_6O_4S$; Elemental Analysis calculated: C, 57.39; H, 3.50; N, 18.25; O, 13.90; S, 6.96 Found: C, 57.43; H, 3.57; N, 18.32; O, 13.99; S, 7.03.

4-(3-(4-nitrophenyl)-4-oxo-3,4-dihydroquinazolin-2-yl)-N-(1H-1,2,4-triazol-3-yl)benzene sulfonamide (4d)

Color: yellow powder; m.p. 190-192°C; % yield: 68 %; IR (KBr, cm^{-1}): 3357.20 (N-H), 3145.82 (Ar C-H), 2943.20 (Alph. C-H), 1619.82 (C=N), 1527.40 (Ar C=C), 1445.82 (N-N), 1233.02 (NO_2), 1133.78 (S=O), 1056.71 (N-N); ^{1}HNMR (400 MHz, DMSO-d_6): δ 7.50-7.68 (2H, m, $ArCH_{Quinazolinone}$), 7.62 (1H, d, C-H $_{triazole}$), 7.81 (2H, d, ArCH), 7.85 (2H, m, $ArCH_{Quinazolinone}$), 8.02-8.07 (4H, d, ArCH), 8.13 (1H, s, ArCH $_{Quinazolinone}$), 8.42 (2H, d, ArCH), 11.68 (1H, s, -NH), 14.47 (1H, s, NH $_{triazole}$); ^{13}CNMR (100 MHz, DMSO-d_6), δppm: 120.8 (1C), 124.1 (2C), 126.4-126.7 (4C), 127.3-127.4 (3C), 129.2 (2C), 131.8 (1C), 133.4 (1C), 138.7 (1C), 141.1 (1C), 143.5 (1C), 146.0 (1C), 147.9 (1C), 148.7 (1C), 156.2 (1C), 160.6 (1C, >C=O); MS m/z: 489.12 [M^+] calculated for $C_{22}H_{15}N_7O_5S$; Elemental Analysis calculated: C, 53.99; H, 3.09; N, 20.03; O, 16.34; S, 6.55; Found: C, 53.86; H, 2.96; N, 19.93; O, 16.22; S, 6.46.

4-(4-oxo-3-(p-tolyl)-3,4-dihydroquinazolin-2-yl)-N-(1H-1,2,4-triazol-3-yl)benzenesulfonamide (4e)

Color: Reddish yellow powder; m.p. 209-211°C; % yield: 65 %; IR (KBr, cm^{-1}): 3346.79 (N-H), 3114.89 (Ar C-H), 2975.93 (Alph. C-H), 1714.95 (C=O), 1624.69 (C=N), 1574.78 (Ar C=C), 1446.76 (N-N), 1157.04 (S=O), 1072.51 (N-N); ^{1}HNMR (400 MHz, DMSO-d_6): δ 2.33 (3H, s, Ar-CH_3), 7.25-7.27 (4H, d, ArCH), 7.50, 7.67, 7.84, 8,13 (4H, m, C-H $_{Quinazolinone}$), 7.62 (1H, d, C-H $_{triazole}$), 8.02-8.06 (4H, d, ArCH), 11.68 (1H, s, NH), 14.47 (1H, s, NH $_{triazole}$); ^{13}CNMR (100 MHz, DMSO-d_6), δppm: 21.4 (1C), 120.8 (1C), 126.4-126.7 (4C), 127.3-127.4 (3C), 128.5 (2C), 129.2-129.8 (3C), 131.8 (1C), 133.4 (1C), 136.8 (1C), 141.1 (1C), 146.0 (1C), 147.9 (1C), 148.7 (1C), 156.2 (1C), 160.6 (1C, >C=O); MS m/z: 458.23 [M^+] calculated for $C_{23}H_{18}N_6O_3S$; Elemental Analysis calculated: C, 60.25; H, 3.96; N, 18.33; O, 10.47; S, 6.99; Found: C, 60.32; H, 4.05; N, 18.46; O, 10.53; S, 7.08.

4-(3-(4-isopropylphenyl)-4-oxo-3,4-dihydroquinazolin-2-yl)-N-(1H-1,2,4-triazol-3-yl)benzene sulfonamide (4f)

Color: yellowish white powder; m.p. 188-200°C; % yield: 66%; IR (KBr, cm^{-1}): 3415.68 (N-H), 3123.68 (Ar C-H), 2971.12 (Alph. C-H), 1616.36 (C=N), 1523.57 (Ar C=C), 1505.25 (N-N), 1445.75 (-CH_2-CH_3), 1165.42 (S=O), 1010.00 (N-N); ^{1}HNMR (400 MHz, DMSO-d_6): δ 1.19 (3H, m, -CH_3), 2.61 (2H, m, -CH_2), 7.32-7.42 (4H, d, ArCH), 7.50, 7.67, 7.84, 8,13 (4H, m, C-H $_{Quinazolinone}$), 7.62 (1H, d, C-H

triazole), 8.02-8.06 (4H, d, ArCH), 11.68 (1H, s, NH), 14.47 (1H, s, NH triazole); ^{13}CNMR (100 MHz, DMSO-d_6), δppm: 14.6 (1C), 28.3 (1C), 120.8 (1C), 126.4-126.6 (4C), 127.3-127.4 (3C), 127.9-128.5 (4C), 129.9 (1C), 131.8 (1C), 133.4 (1C), 141.1 (1C), 143.9 (1C), 146.0 (1C), 147.9 (1C), 148.7 (1C), 156.2 (1C), 160.6 (1C, >C=O); MS m/z: 472.17 [M^+] calculated for $C_{24}H_{20}N_6O_3S$; Elemental Analysis calculated: C, 61.01; H, 4.27; N, 17.79; O, 10.16; S, 6.78; Found: C, 60.92; H, 4.16; N, 17.66; O, 10.03; S, 6.67.

4-(3-(4-methoxyphenyl)-4-oxo-3,4-dihydroquinazolin-2-yl)-N-(1H-1,2,4-triazol-3-yl)benzene sulfonamide (4g)

Color: yellowish white powder; m.p. 185-187°C; % yield: 60%; IR (KBr, cm^{-1}): 3418.35 (N-H), 3349.91 (Ar C-H), 3222.53 (-OCH_3), 1681.96 (C=O), 1615.67 (C=N), 1525.66 (Ar C=C), 1525.66 (N-N), 1174.61 (S=O), 1024.14(N-N); ^{1}HNMR (400 MHz, DMSO-d_6): δ 3.82 (3H, s, -CH_3), 7.02-7.20 (4H, d, ArCH), 7.50, 7.67, 7.84, 8,13 (4H, m, C-H Quinazolinone), 7.62 (1H, d, C-H triazole), 8.02-8.06 (4H, d, ArCH), 11.68 (1H, s, NH), 14.47 (1H, s, NH triazole); ^{13}CNMR (100 MHz, DMSO-d_6), δppm: 55.9 (1C), 114.6 (2C), 120.8 (1C), 125.01 (1C), 126.4-126.6 (4C), 127.3-127.4 (3C), 128.8 (2C), 131.8 (1C), 133.4 (1C), 141.1 (1C), 146.0 (1C), 147.9 (1C), 148.7 (1C), 156.2 (1C), 158.9 (1C), 160.6 (1C, >C=O); MS m/z: 474.00 [M^+] calculated for $C_{23}H_{18}N_6O_4S$; Elemental Analysis calculated: C, 58.22; H, 3.82; N, 17.71; O, 13.49; S, 6.76; Found: C, 58.28; H, 3.91; N, 17.79; O, 13.57; S, 6.86.

4-(3-(2,4-dichlorophenyl)-4-oxo-3,4-dihydroquinazolin-2-yl)-N-(1H-1,2,4-triazol-3-y)benzene sulfonamide (4h)

Color: yellowish white powder; m.p. 182-184°C; % yield: 68%; IR (KBr, cm^{-1}): 3346.79 (N-H), 3114.89 (Ar C-H), 2975.93 (Alph. C-H), 1714.95 (C=O), 1624.69 (C=N), 1574.78 (Ar C=C), 1446.76 (N-N), 1157.04 (S=O), 1024.15 (N-N); ^{1}HNMR (400 MHz, DMSO-d_6): δ 7.62 (1H, d, C-H triazole), 7.63, (1H, d, ArCH), 7.78 (1H, s, ArCH), 7.92 (1H, d, ArCH), 7.50, 7.67, 7.84, 8,13 (4H, m, C-H Quinazolinone), 8.02-8.06 (4H, d, ArCH), 11.68 (1H, s, NH), 14.47 (1H, s, NH triazole); ^{13}CNMR (100 MHz, DMSO-d_6), δppm: 120.8 (1C), 123.13 (1C), 126.4-126.6 (4C), 127.3-127.4 (3C), 130.62 (1C), 131.10-131.34 (2C), 131.82-131.96 (2C), 133.43-133.87 (2C), 141.1 (1C), 146.0 (1C), 147.9 (1C), 148.7 (1C), 156.2 (1C), 160.6 (1C, >C=O); MS m/z: 512.00 [M^+] calculated for $C_{22}H_{14}Cl_2N_6O_3S$; Elemental Analysis calculated: C, 51.47; H, 2.75; Cl, 13.81; N, 16.37; O, 9.35; S, 6.25; Found: C, 51.53; H, 2.81; Cl, 13.94; N, 16.48; O, 9.45; S, 6.33.

4-(3-(2,4-dimethylphenyl)-4-oxo-3,4-dihydroquinazolin-2-yl)-N-(1H-1,2,4-triazol-3-yl)benzene sulfonamide (4i)

Color: yellowish white; m.p. 170-172ºC; % yield: 63%; IR (KBr, cm^{-1}): 3481.65 (N-H), 3056.95 (Ar C-H), 2890.73 (Alph. C-H), 1721.42 (C=O), 1621.20 (C=N), 1575.20 (Ar C=C), 1446.75 (N-N), 13 (-CH_3), 1156.27 (S=O), 1025.63 (N-N);^{1}HNMR (400 MHz, DMSO-d_6): δ 2.13-2.24 (6H. s, Ar-CH_3), 7.03, (1H, d, ArCH), 7.18 (1H, s, ArCH), 7.54 (1H, d, ArCH), 7.62 (1H, d, C-H $_{triazole}$), 7.50, 7.68, 7.84, 8,13 (4H, m, C-H $_{Quinazolinone}$), 8.02-8.06 (4H, d, ArCH), 11.68 (1H, s, NH), 14.47 (1H, s, NH $_{triazole}$); ^{13}CNMR (100 MHz, DMSO-d_6), δppm: 21.63 (1C), 24.66 (1C), 120.8 (1C), 126.4-126.6 (4C), 127.3-127.4 (3C), 131.02-131.84 (2C), 132.52 (1C), 133.42 (1C), 134.92 (1C), 136.74 (1C), 141.1 (1C), 143.46-144.23 (2C), 146.0 (1C), 147.9 (1C), 148.7 (1C), 156.2 (1C), 160.6 (1C, >C=O); MS m/z: 472.22 [M^+] calculated for $C_{24}H_{20}N_6O_3S$; Elemental Analysis calculated: C, 61.01; H, 4.27; N, 17.79; O, 10.16; S, 6.78; Found: C, 61.12; H, 4.38; N, 17.90; O, 10.26; S, 6.87.

4-(3-(2,4-dinitrophenyl)-4-oxo-3,4-dihydroquinazolin-2-yl)-N-(1H-1,2,4-triazol-3-yl)benzene sulfonamide (4j)

Color: yellow powder; m.p. 225-227ºC; % yield: 67%; IR (KBr, cm^{-1}): 3436.94 (N-H), 3271.69 (Ar C-H),1655.76 (C=N), 1530.54 (Ar C=C), 1464.58 (N-N), 1310.10 (NO_2), 1236.25 (S=O), 1071.43 (N-N); ^{1}HNMR (400 MHz, DMSO-d_6): δ 7.62 (1H, d, C-H $_{triazole}$), 7.50, 7.68, 7.84, 8,13 (4H, m, C-H $_{Quinazolinone}$), 8.16, (1H, d, ArCH), 8.54 (1H, d, ArCH), 8.66 (1H, s, ArCH), 8.02-8.06 (4H, d, ArCH), 11.68 (1H, s, NH), 14.47 (1H, s, NH $_{triazole}$); ^{13}CNMR (100 MHz, DMSO-d_6), δppm: 120.27-120.81 (2C), 123.42 (1C), 126.4-126.7 (4C), 127.3-127.4 (3C), 130.23 (1C), 131.84 (1C), 139.46 (1C), 141.1 (1C), 143.33 (1C), 144.48 (1C), 146.0 (1C), 147.9 (1C), 148.7 (1C), 156.2 (1C), 160.6 (1C, >C=O); MS m/z: 534.02 [M^+] calculated for $C_{22}H_{14}N_8O_7S$; Elemental Analysis calculated: C, 49.44; H, 2.64; N, 20.97; O, 20.95; S, 6.00; Found: C, 49.54; H, 2.73; N, 21.06; O, 21.03; S, 6.09.

Biological Evolution

In Vitro Antiglycation Potential

Glycation of Bovine Serum Albumin

The antiglycation activity of synthesized compounds **(4a-j)** was determined using glycated BSA samples prepared by incubating BSA (10 mg/mL) with fructose (250 mM) in 200 mM phosphate buffer (pH 7.4, containing 0.02% sodium azide) along with Rutin varying concentrations of the test compounds (25, 50, 75, 100, 125, and 150 μM) at 37°C in the dark for 72 hours in sealed tubes. A positive control (BSA + fructose) was maintained under similar conditions, and all incubations were performed in triplicate. After incubation, unbound fructose was removed by dialysis against phosphate buffer (200 mM, pH 7.4) at 4°C. The resultant glycated BSA samples were analyzed for antiglycation activity by estimating

fructosamine levels using the NBT assay protein carbonyl content through the DNPH assay, protein thiol groups using Ellman's reagent (DTNB), and amyloid aggregation through Congo red binding absorbance [12, 13].

Estimation of Fructosamine

Fructosamine in glycated BSA samples was estimated by use of Nitro blue Tetrazolium (NBT) assay. The aliquots of glycated sample and positive control (10 µL) were mixed with 0.2 mL of NBT solution, then the obtained solution were incubated at 37°C for 30 minutes. Followed the incubation period, the absorbance was taken in UV- spectrophotometer at 520 nm. The degree of inhibition of fructosamine formation was calculated via the formula of Inhibitory activity (%) = [$(A_0 – A_1) / A_0$] x 100. In which the A_0 is the absorbance of the positive control (BSA + fructose) and A_1 is the absorbance of the glycated albumin samples. The assay for each compound was performed three times. The lower the absorbance of the glycated albumin samples compared to the positive control, indicated the greater inhibitory activity against fructosamine formation [14].

Protein carbonyl group estimation

The protien carbonyl content in Glycated BSA samples was estimated using 2,4-dinitrophenylhydrazine (DNPH) assay. In this assay, the aliquots of the glycated samples and the positive control were mixed with 500 µL of 10 mM DNPH in 2M HCl, and incubate at room temperature for an hour. After incubation, 0.5 µL of 20 % trichloroacetic acid (TCA) was added to precipitate proteins and then the mixture was centrifuged at 10,000 RPM for 10 minutes. The protein pellet was washed three times with an ethanol/ethyl acetate mixture (1:1) to remove excess DNPH. After this, absorbance at 365 nm was then measured by spectrophotometer and percentage inhibition was determined. [15].

Protein thiol estimation

The protein thiol groups estimated in glycated BSA samples was assesed by using a 5,5'-dithiobis-(2-nitrobenzoic acid) (DTNB) assay. Aliquots of glycated samples and the positive control (250 µL) were mixed with 750 µL of DTNB (0.5 mM) and incubated at room temperature for 15 minutes. After incubation, the absorbance was measured at 410 nm using a spectrophotometer. The percentage inhibition of thiol oxidation was calculated using the same formula as in the fructosamine assay [15].

Binding of Congo red

The estimation of amyloid aggregation in glycated BSA samples was performed using the Congo red binding assay. Glycated samples were combined with 100 µM Congo red in potassium buffer solution

(pH 7.4) that contained 10% (v/v) ethanol and incubated at RT for 20 minutes. After incubation, the absorbance at 530 nm was measured using a spectrophotometer, and the results were expressed as a calculated % inhibition [15].

Statistical Analysis

The statistical analysis was performed utilizing GraphPad Prism v 5.00. The results from three separate experiments, each conducted in triplicate, were expressed as mean ± SD. One-way ANOVA followed by Dunnett's test was used to determine statistical significance, with p-values represented as *$p<0.05$, **$P< 0.01$, and *** $p<0.001$.

Molecular docking study

Molecular docking was employed as a computational approach to evaluate ligand-protein interactions and binding affinities, thereby assisting in the structural optimization and identification of potential ligands [16]. The interaction of the synthesized quinazoline derivatives (**4a-j**) and the standard drug rutin with the human serum albumin-fructose complex (PDB ID: 4IW1) was investigated through molecular docking simulation [17]. The target protein structure was downloaded from the Protein Data Bank (http://www.rcsb.org/pdb). The two-dimensional (2D) chemical structures of the synthesized quinazoline derivatives (2a–l) and rutin were generated by using ChemDraw version 22.2.0 (64-bit). These 2D structures were further converted into Chem3D version 22.2.0 (64-bit) 3D molecular structures [18]. The energy minimization of the 3d structures was carried out using the MM2 force field algorithm to obtain the lowest energy conformations. The optimized structures were then exported in .pdb format for subsequent docking analysis. The molecular docking simulations were performed via Molegro Virtual Docker v. 6.0. The binding pocket parameters, including surface area and volume. A spherical search space with a radius of 15.0 Å centered at the binding site (X: 2.70, Y: -0.38, Z: 15.63). Docking was carried out using a grid spacing of 0.30 Å, a population size of 50 and 1500 iterations, and ten runs per ligand. [19, 20].

3. Result and Discussion

Chemistry

The synthetic route (Scheme 1) invoves synthesis of Quinazolinone-triazole hybrids (4a-j) was acheived via multistep pathways, starting with the condensation of antranillic acid with benzoyl chloride in pyridine, forming 2-phenyl-4H-3,1-benzoxazin-4-one (compound 1).this reaction was carried by Nucleophilic acyl substitution followed by cyclization, producing pale yellow crystals upon

recrystallization. Subsequently compound-1 was treated with several substituted anilines under reflux to yield Quinazolinone derivatives (2a-j) in dry pyridine. The synthesis of Quinazolinone rings was confirmed by IR spectroscopy, showing characteristic bands around 1721.49 cm^{-1} (C=O), 1643.76 cm^{-1} (C=N) and 1334 cm^{-1} (C-O). the ^{1}H NMR spectra exhibited aromatic multiplets and distinct signals corresponding to the Quinazolinone scaffold, with ^{13}C NMR further supporting the presence of carbonyl and aromatic carbons. Further chlorosulphonation of qubnazolinone deribvatives (2a-j) bearing substituted anilines produces sulphonyl chloride intermediates (3a-j). The reaction was performed under cold conditions to control high reactiovity of chlorosulphonic acid. The IR spectra for this compounds retained peaks for aromatic C-H and C=O, while the appearance of new absorptions around 1120-1408 cm^{-1} (SO_2 stretching) and N-H vibrations confirmed the presence of sulfonyl functionality. The NMR data supported these findings, showing downfield shifts due to the electron-withdrawing sulfonyl group. The presence of new signals in ^{1}H NMR corresponding to sulfonated aromatic protons further validated the successful functionalization. Finally, the key quinazolinone–triazole sulfonamide hybrids (4a–j) were synthesized by reacting sulfonyl chlorides (3a–j) with 3-amino-1H-1,2,4-triazole under mild basic aqueous conditions (pH 8–9). Compound 4a, as a representative example, was obtained in 67% yield and confirmed by comprehensive spectroscopic analysis. The IR spectrum displayed corresponding peaks at 1723.78 (C=O), 1619.70 (C=N), and 1165.42 (S=O), while ^{1}H NMR revealed triazole and sulfonamide NH signals at δ 14.46 and 11.68 ppm, respectively. Aromatic protons appeared as expected multiplets between δ 7.4–8.1 ppm. ^{13}C NMR confirmed the quinazolinone carbonyl (δ ~160 ppm) and aromatic carbon environments. Mass spectrometry showed a molecular ion peak at m/z 444 [M^+], consistent with the molecular formula ($C_{22}H_{16}N_6O_3S$), and elemental analysis closely matched theoretical values. These results confirm the successful synthesis of quinazolinone–triazole hybrids, which possess pharmacologically relevant scaffolds suitable for further biological evaluation.

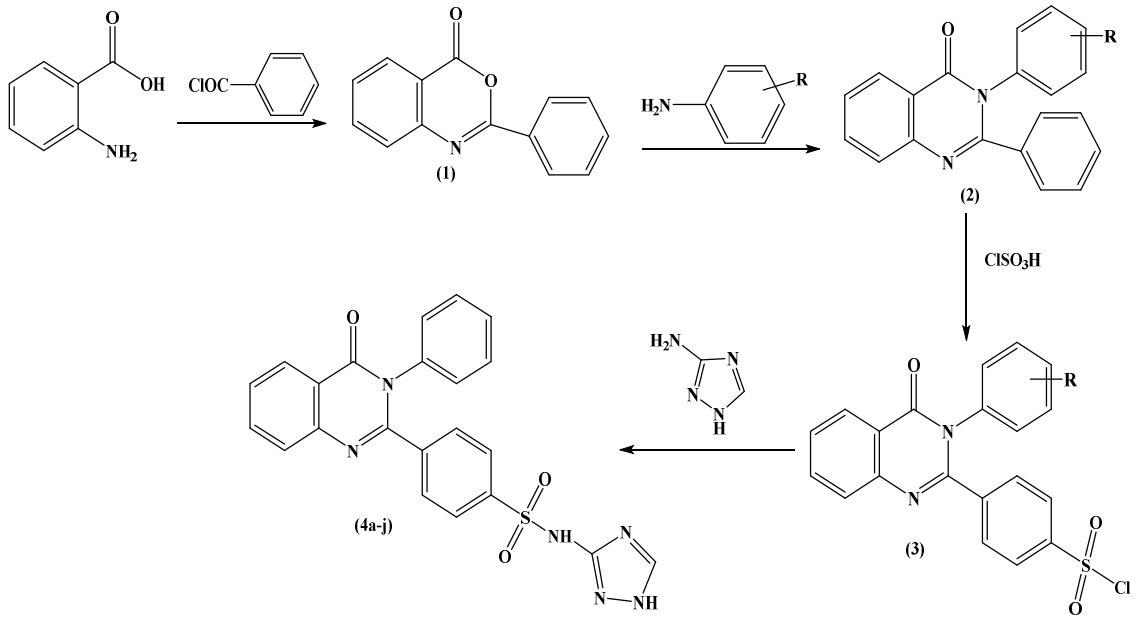

Fig.1. Schematic representation of the synthesis of Quinazolinone-triazole Hybrids (2a-j)

Reagents and Reaction Conditions: (a) Benzoyl chloride, Pyridine, Stirring at Room temperature, (b) 4-amino triazole, dry pyridine, Reflux for 5 hours at 90-100℃.

Biological Activities

***In vitro* Antiglycation Potential**

The *in-vitro* Antiglycation potential of quinazoline-triazole hybrids (4a-j) was assessed using a glucose-bovine serum albumin (BSA) assay by measuring key biomarkers-fructosamine levels, protien carbonyl content, protien thiol levels, and Congo red binding compared to the natural standard compounds. These parameters collectively quantified the Antiglycation efficacy of the compounds. Fructosamine seves as an indicator of early-stage glycation, formed through the non-enzymatic reaction between rediucing sugars and protien amino groups. Protien carbonyl contents reflects oxidative damage associated with advanced glycation, while protien thiol levels indicate the compounds ability to preserve antioxidant capacity. Congo red bindimg measures structural alterations in proteins, such as amuloid-like aggregation. Together, these markers provide a comprehensive evaluation of glycation-induced damage and protective effects of the tested compounds. The extent of glycation inhibition was measured by determining the IC_{50} values, which express the concentration of test compound required to acheve 50%

inhibition, as represented in table 2. Among all the compounds, compound 4e (4-CH_3) emerged as the strong inhibitor, showing significant lower fructosamine (45.00 ± 0.577nM), protien carbonyl (42.66 ± 0.882 nM) and Congo red binding levels (63.33 ± 0.882 nM), as well as improved protien thiol preservation (47.33 ± 1.202 nM), outperforming rutin across all parameters. Compound 4f (4-C_2H_5) also exhibited promising activity, even though slightly less potent than 4e, suggesting that small alkyl substitutions at para position enhance Antiglycation activity likely due to improved lipophilicity and sterioc compatibility. In contrast, nitro-substituted derivatives such as 4d and 4j displayed the lowest potential, with high fructosamine and carbonyl levels and poor thiol retention, indicating that strong-withdrawing groups exhibited negative impact on Antiglycation potential. Electron-donating groups like hydroxyl (4c) and methoxy (4g) demonstrated moderate activity, while compounds substituted with halogen (4b, 4h) and dimethyl (4i) groups showed inconsistent results. Overall SAR analysis suggests that para-alkyl groups (especially methyl) enhance Antiglycation activity, making compound 4e a promising lead candidate with superior efficacy compared to rutin.

Table 1: *In-vitro* Antiglycation Potential of Quinazolinone-triazole hybrids (4a-j).

Compound ID	**R**	**IC_{50} Values (nM)**			
		Estimation of Fructosamine	**Protein carbonyl estimation**	**Protein thiol estimation**	**Binding of Congo red**
Rutin	-	93.16±0.441	66.33±0.882	63.33±0.333	79.33±0.882
4a	-H	114.33±1.202	106.33±0.882	84.00±1.155	96.00±1.155
4b	4-Cl	146.33±1.453	93.66±1.202	96.66±0.882	89.33±0.882
4c	4-OH	82.00±1.155	71.33±0.667	57.66±0.882	84.66±0.882
4d	4-NO_2	172.66±1.764	136.33±1.202	115.66±1.453	123.66±1.202
4e	4-CH_3	45.00±0.577	42.66±0.882	47.33±1.202	63.33±0.882
4f	4-C_2H_5	77.33±0.882	48.00±0.577	64.66±0.882	68.66±0.333
4g	4-OCH_3	95.00±1.528	70.66±0.667	56.66±0.882	86.66±0.333
4h	2,4-$(Cl)_2$	126.66±0.882	79.33±0.882	69.33±0.882	86.00±0.577
4i	2,4-$(CH_3)_2$	107.33±0.882	67.66±0.333	75.66±0.882	76.00±1.528
4j	2,4-$(NO_2)_2$	132.66±0.882	115.33±1.202	102.33±1.453	105.00±1.528

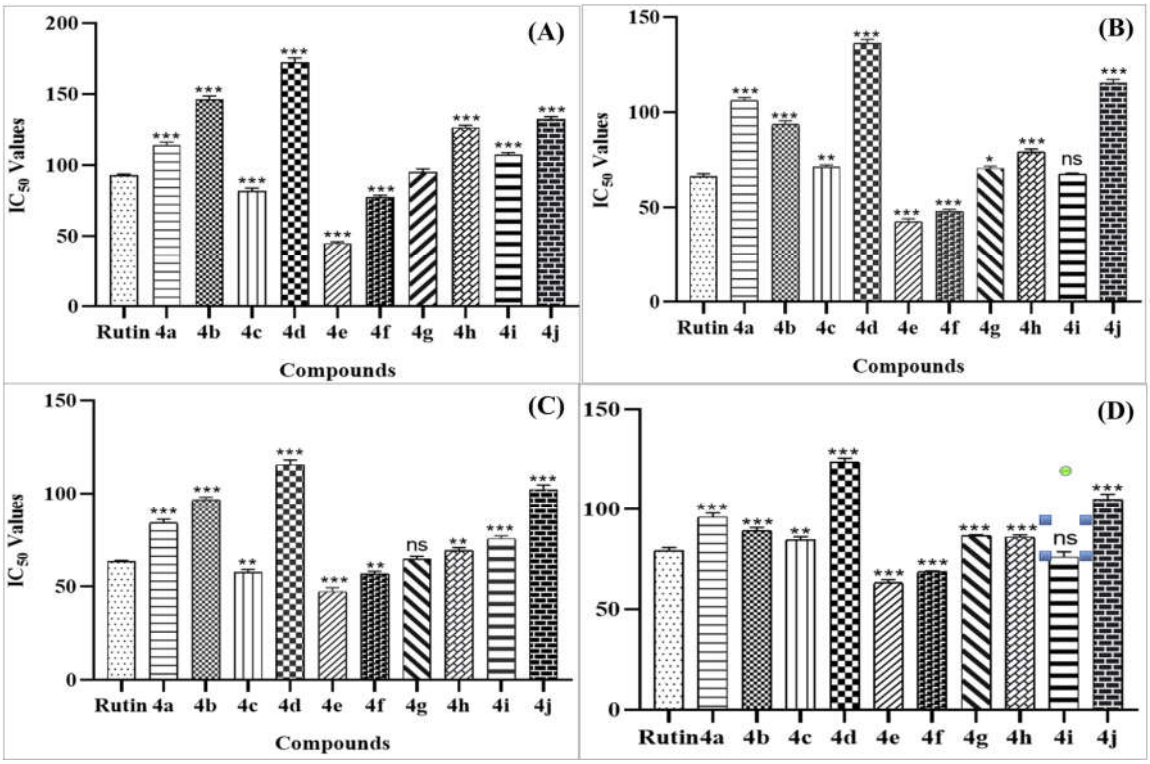

Fig.2. Antiglycation potential of Quinazolinone-triazole hybrids (4a-j) assessed by estimation level of (A) fructosamine, (B) Carbonyl protien, (C) Protien Thiol and (D) Congo red binding. All values are presented in mean ± SEM (n=3). Statistical analysis was performed using one-way ANOVA followed by Dunnett's post hoc test, significance levels: *p < 0.05, **p < 0.01, *** p < 0.001.

Molecular Docking Study

Molecular docking simulations were performed for the synthesized Quinazolinone-triazole hybrids (4a-j) and the reference drug rutin against the active site of the HSA-fructose complex (PDB ID: 4IW1) using Molegro Virtual Docker version 6.0 software. The docking simulations, assessed through the MolDock scoring function, demonstrated that all the synthesized compounds exhibited strong binding affinities within the active sites of the enzymes. The MolDock scores ranged from -119.644 kcal/mol to -145.387 kcal/mol, indicating favorable interactions between the ligands and target proteins. Among the synthesized hybrids, compound **4e** exhibited the lowest MolDock score, indicating the strongest binding affinity toward both target enzymes. However, the reference drug rutin revealed a lower MolDock score of -142.891 kcal/mol, suggesting a relatively less stable ligand-receptor interaction. A comprehensive summary of the binding affinity, H-bond interaction, H-bond, and S-bond interaction of all the designed ligands is presented in Table 1. The docking results revealed that the enhanced binding affinities of these compounds are predominantly driven by the establishment of non-covalent interactions, including

hydrogen bonding, π–π stacking, and sulfur molecule contacts with critical amino acid residues within the enzyme's active site. This can be attributed to its optimal orientation and interaction geometry within the binding pocket, which enables the stronger stabilization of the ligand-protein complex. Among the various interactions observed, the stabilizing interactions that Asp108, Ser193, and Tyr452 participate in inside the binding pocket of glycation-related proteins are essential for mediating the antiglycation effects of ligands. Ser193 hydroxyl group generates strong hydrogen bonds that protect vulnerable amino acids, including lysine and arginine, from glycation. At the same time, Asp108 provides electrostatic and hydrogen-bonding interactions that aid in stabilizing ligand binding and blocking reactive carbonyl groups. Through π–π interactions and hydrogen bonding, Tyr452 further improves binding by anchoring ligands within the active site and inhibiting the formation of advanced glycation end products (AGE) and crosslinking. Additionally, the designed derivatives also exhibited prominent steric interactions with other key residues, such as Glu188, Ala191, Lys436, Tyr452, Val455, and Gln459, as shown in Figure 1. The protein-ligand complex interaction illustrates the binding pocket interactions of compound **4e** and the reference drug with the target proteins, as shown in Figure 2. Overall, the docking results suggest that the synthesized quinoline derivatives, particularly compound **4e**, possess promising antiglycation potential by effectively interacting with the HSA–fructose complex. Their ability to form stable non-covalent interactions with key amino acid residues provides a structural basis for their inhibitory activity against the formation of advanced glycation end-products (AGEs).

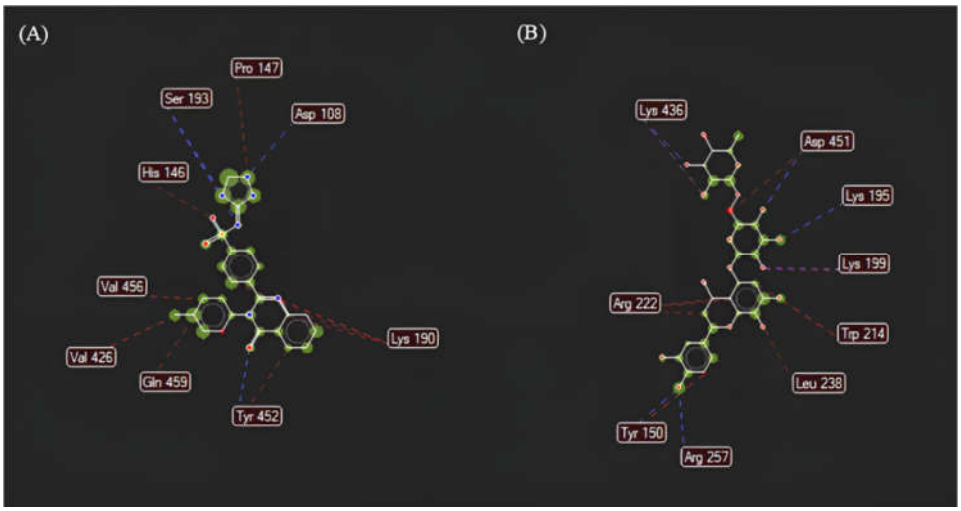

Fig.3. The protein-ligand complex interaction of compound **4e** and rutin. The blue dotted line represents the H-bond, while the red dotted line represents the S-bond interaction with the target protein.

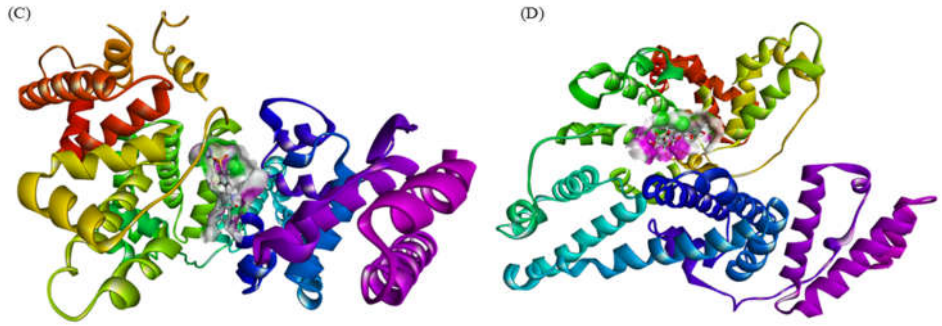

Fig.4. Binding interactions of compound **4e** and rutin within the active site of the HAS fructose complex.

Table 2: Molecular docking simulation of synthesized quinazoline derivatives.

Compound ID	R	MolDock (kcal/mol)	H-bond (kcal/mol)	H-bond Interaction	S-bond Interaction
Rutin	-	-142.891	-6.09035	Tyr150, Lys195, Lys199, Arg257, Lys436, Asp451	Tyr150, Leu238, Trp214, Arg222, Lys436, Asp451
4a	-H	-126.876	-2.28375	His146, Ser193, Tyr452, Gln459	His146, Lys190, Ser193, Asn429, Val452, Val456, Gln459,
4b	4-Cl	-132.973	-1.84553	Asp108, Ser193, Tyr452	His146, Pro147, Lys190, Tyr452, Val456, Gln459
4c	4-OH	-140.611	-2.40306	His146, Ser193, Asn429	Arg145, His146, Pro147, Lys190, Ala194, Arg197, Val456, Leu463
4d	4-NO_2	-119.644	-1.85849	Lys195, Lys436	Asp187, Lys190, Lys195, Asn429, Tyr452, Val455, Val456, Gln459
4e	4-CH_3	-145.387	-4.07674	Asp108, Ser193, Tyr452	His146, Pro147, Lys190, Val426, Tye452, Val456
4f	4-C_2H_5	-142.498	-4.37939	Asp187	Glu188, Ala191, Lys436, Tyr452, Val455, Gln459
4g	4-OCH_3	-140.792	-3.01832	Asp108, Ser193, Tyr452	His146, Pro147, Lys190, Val426, Asn429, Tyr452, Gln459
4h	2,4-$(Cl)_2$	-126.044	-2.43046	His146, Ser193	His146, Pro147, Lys190, Ala194, Arg197, Val456,
4i	2,4-$(CH_3)_2$	-139.802	-2.18256	His146, Ser193, Asn429	Asp108, Arg145, Lys190, Ser193, Ala194, Arg197, Val456, Gln459,

					Leu463
4j	2,4-$(NO_2)_2$	-122.044	-1.28375	His146, Tyr452, Asn429	Asp108, His146, Arg145, Pro147, Lys190, Ala191, Asn429, Val456, Leu463

4. Conclusion

In this study, a novel series of Quinazolinone-triazole hybrids (4a-j) was successfully designed, synthesized and evaluated for their antiglycation potential by estimating the level of certain biomarkers including fructosamine, protien carbonyl, protien thiol and congo red binding. The synthesized compounds were found to have considerable Antiglycation activity and oxidative protection. Among the synthesized hybrids, compound 4e exhibited the superior activity compared to standard rutin. Structure-activity relationship (SAR) analysis revealed that the presence of electon donating groups especially small alkyl group substituted at the para position of the quinazolinone phenyl ring significant enhanced the antiglycation potential due to interaction with key active site residues of the glycation intermediates. Molecular docking simulation further supported the biological findings, demonstrating strong binding affinity of the most active compound toward the target protien with key hydrogen binding and hydrophobic interactions stabilizing the ligand –protien complex. The docking profile of compound 4e correlated well with its experimental potency, validating the rational design approach employed in this study. These findings suggest that Quinazolinone-triazole hybrids, particularly alkyl substituted compound (4e) represents promising lead candidates for the development of new therapeutic ailments targeting protien glycation-related pathologies. Further *in vivo* studies and ADMET profiling are defensible to establish their comprehensive pharmacological potential.

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