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Furan-Based Hydrazone-Linked Quinazolin-4-amine Hybrids: Design, Synthesis, Spectroscopic Validation, DFT Reactivity Analysis, and Keap1-Targeted Antioxidant Studies

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Abstract

In this work, a new series of furan-based quinazoline-4-amine hydrazone (Schiff base) derivatives (**4a–h**) was rationally designed and synthesized in good yields (75–90%) through a multistep route involving nucleophilic aromatic substitution, Suzuki–Miyaura cross-coupling, and hydrazone/Schiff base condensation reactions. The synthesized compounds were characterized by FT-IR, ¹H NMR, ¹³C NMR, and ESI-mass spectrometry, which confirmed the proposed structures. Density functional theory (DFT) calculations were performed to optimize the molecular geometries and to derive frontier molecular orbital energies, global reactivity descriptors, Mulliken atomic charges, and molecular electrostatic potential (MEP) surfaces, providing insight into the stability, reactivity, and radical-scavenging propensity of the compounds. Molecular docking studies against the Kelch domain of Keap1 (PDB: 4L7B), the principal negative regulator of the Nrf2-mediated antioxidant response, were carried out using the Schrödinger Suite (Glide, Maestro interface) to rationalize the antioxidant potential of the synthesized derivatives at the molecular level; the docked compounds exhibited binding energies in the range of –7.325 to –8.603 kcal/mol, comparable to that of ascorbic acid (–7.541 kcal/mol). Computational ADMET profiling indicated drug-like physicochemical properties overall, with the dimethoxy- and phenolic-substituted analogues **4e** and **4h** showing the most favourable predicted oral bioavailability (score = 0.55) among the series. The *in vitro* antioxidant potential of compounds **4a–4h** was evaluated using the DPPH radical-scavenging assay, with IC₅₀ values ranging from 49.74 ± 2.13 to 90.40 ± 1.98 µg/mL in comparison with the standard antioxidant ascorbic acid (IC₅₀ = 41.42 ± 0.81 µg/mL). Among the series, compounds **4d** and **4f** displayed the most promising

radical-scavenging activity, correlating well with their favourable frontier orbital energy gaps and Keap1-binding profiles.

Keywords: Furan-Schiff-Based Quinazoline-4-amine Scaffolds, DFT, ADMET, Molecular Docking, Keap1-Nrf2 pathway, Antioxidant activity, DPPH radical-scavenging assay

1. Introduction

Reactive oxygen species (ROS), including the superoxide anion, hydroxyl radical, and hydrogen peroxide, are continuously generated as by-products of normal aerobic metabolism. Under physiological conditions, their levels are tightly regulated by an intricate network of enzymatic (superoxide dismutase, catalase, glutathione peroxidase) and non-enzymatic antioxidants. However, an imbalance between ROS generation and the endogenous antioxidant defence system leads to a state of oxidative stress, which causes cumulative damage to lipids, proteins, and nucleic acids. Oxidative stress is now well recognized as a central pathological driver in a wide spectrum of chronic and degenerative disorders, including cancer, diabetes mellitus, cardiovascular disease, and neurodegenerative conditions such as Alzheimer's and Parkinson's disease. Consequently, molecules capable of scavenging free radicals and reinforcing the cellular antioxidant defence machinery, such as the Keap1-Nrf2-ARE signalling axis, are of substantial therapeutic interest, and the design of new, low-toxicity synthetic antioxidants remains an actively pursued goal in medicinal chemistry.

Among the many pathological conditions linked to chronic oxidative stress, cancer remains one of the most challenging and complicated diseases in modern medicine, and it is the second leading cause of death worldwide.[1] According to the Global Cancer Observatory (GLOBOCAN) 2020 report, there were more than 10 million cancer-related deaths and approximately 19.3 million new cancer diagnoses globally. The number of new cases is expected to increase dramatically as the world's population and aging demographics increase, reaching around 420 million by 2025. Breast, colon, prostate, kidney and renal pelvis, bronchus, lung, skin melanoma, bladder, non-Hodgkin lymphoma, endometrial, pancreas, and liver cancers are the most common cancers.[2-4] The three most prevalent malignancies in women are colorectal, breast, and lung cancers, which are predicted to account for 51% of new female cancer diagnoses in 2025. In 2025, prostate, lung, and colorectal cancers are expected to make for 48% of all cancer cases worldwide.[5,6] Conventional cancer treatments, such as chemotherapy, radiation, and targeted therapy, are frequently constrained by poor selectivity, decreased efficacy, and severe side effects, despite notable advancements

in oncology. Furthermore, treatment outcomes are further compromised by the common development of multidrug resistance (MDR), which emphasizes the need for more effective and selective anticancer drugs.[7,8]

The logical construction of hybrid pharmacophores has become a potent tactic in contemporary drug discovery to get over these obstacles. A number of hybrid-based molecules are presently undergoing preclinical and clinical investigation for the treatment of cancer, as recent developments in medicinal chemistry have shown that such hybrid structures exhibit increased biological activity and therapeutic promise.[9,10] The quinazoline motif has drawn special interest among the various heterocyclic scaffolds investigated in drug design due to its broad variety of pharmacological characteristics and as a bioisosteric substitute for carbonyl-containing functions including amides, carboxylic acids, and esters. [11,12] As of their widespread and unique biological actions, quinazoline derivatives which are classified as N-containing heterocyclic compounds have raised concerns around the world. Numerous therapeutic activities of quinazoline derivatives have already been identified by researchers, such as anti-cancer [13-15], anti-inflammation [16-18], anti-bacterial [19-21], analgesia [22-24], anti-tuberculosis [25,26], anti-oxidation [27-29], anti-malarial [30,31], anti-hypertension [32,33], anti-diabetes [34,35], and more. By adding different active groups to the quinazoline moiety utilizing evolving synthetic techniques, medicinal chemists created a range of quinazoline molecules with distinct biological activity.

Schiff basederived scaffolds are very appealing building blocks for hybrid drug creation because the azomethine ($C = N$) linkage that characterizes Schiff bases provides molecular stiffness and enhanced interactions with biological macromolecules. Due to its capacity to modulate metal-dependent enzymatic activities and to stabilize free-radical intermediates, the quinazoline nucleus, a significant subclass of Schiff base-derived scaffolds, has also drawn special attention as an antioxidant pharmacophore. The goal of the current work is to maximize the antioxidant potential of quinazoline pharmacophores while minimizing toxicity by strategically utilizing the biological activity profile of the azomethine moiety through the use of a hydrazone intermediate as the essential Schiff base linker. An integrated computational-experimental strategy has been used to effectively and logically accomplish this goal. To determine the most stable molecular conformations, evaluate reactivity descriptors, and clarify the binding interactions of the proposed compounds with the Kelch domain of Keap1, the principal negative regulator of the Nrf2-mediated antioxidant response

pathway, quantum chemical calculations (DFT) and molecular docking studies are first utilized. In order to determine the most promising candidates among the synthesized compounds, ADMET profiling, DFT-assisted study, molecular docking, and in vitro antioxidant activity were carried out to assess their drug similarity and safety characteristics. Computational chemistry offers profound insights into molecule reactivity, stability, and binding behaviour while drastically cutting experimental costs and time in the early stages of drug discovery. The most stable and reactive compounds identified through these computational analyses were synthesized, and their free-radical scavenging potential was confirmed by the in vitro DPPH radical-scavenging assay. In addition to improving lead identification efficiency, this hybrid computational-experimental approach fortifies the scientific basis for the logical development of potent, selective, and less toxic antioxidant agents.

2. Methodology

2.1 Reagents and Instrument

All compounds utilized in synthesis, such as trimethyl amine, hydrazine hydrate, methanol, palladium acetate, substituted aldehydes, and others. We bought acetic acid from SRL, Loba Chemicals, and Merck. The compounds were utilized without any additional purification. Solvent was used either distilled prior to use or of spectroscopic quality. All compounds were investigated using Fourier-transform infrared (FT-IR) in the solid state using a Cary630 FT-IR spectrometer. ^1H NMR and ^{13}C NMR spectrum data were collected on an ECZ400S 400 MHz spectrometer in CDCl_3 and DMSO-d^6 . Coupling constant (J) values are in Hz.

2.2 General reaction procedure of synthesised Furan-Based Quinazoline-4-amine derivative scaffolds

In the first step, 4-chloro-6-iodoquinazoline was reacted with 3-chloro-4-((3-fluorobenzyl)oxy)aniline in ethanol as a solvent. The reaction mixture was heated at 70–80 °C for 8–10 hours under continuous stirring. During this process, the nucleophilic amine group of the substituted aniline attacks the electron-deficient C-4 position of the quinazoline ring, leading to the displacement of chloro substituent via a nucleophilic aromatic substitution ($\text{S}_{\text{N}}\text{Ar}$) mechanism. After completion of the reaction (monitored by TLC), the mixture was cooled to room temperature, resulting in the precipitation of the product. The solid was collected by filtration, washed with cold ethanol to remove impurities, and dried under

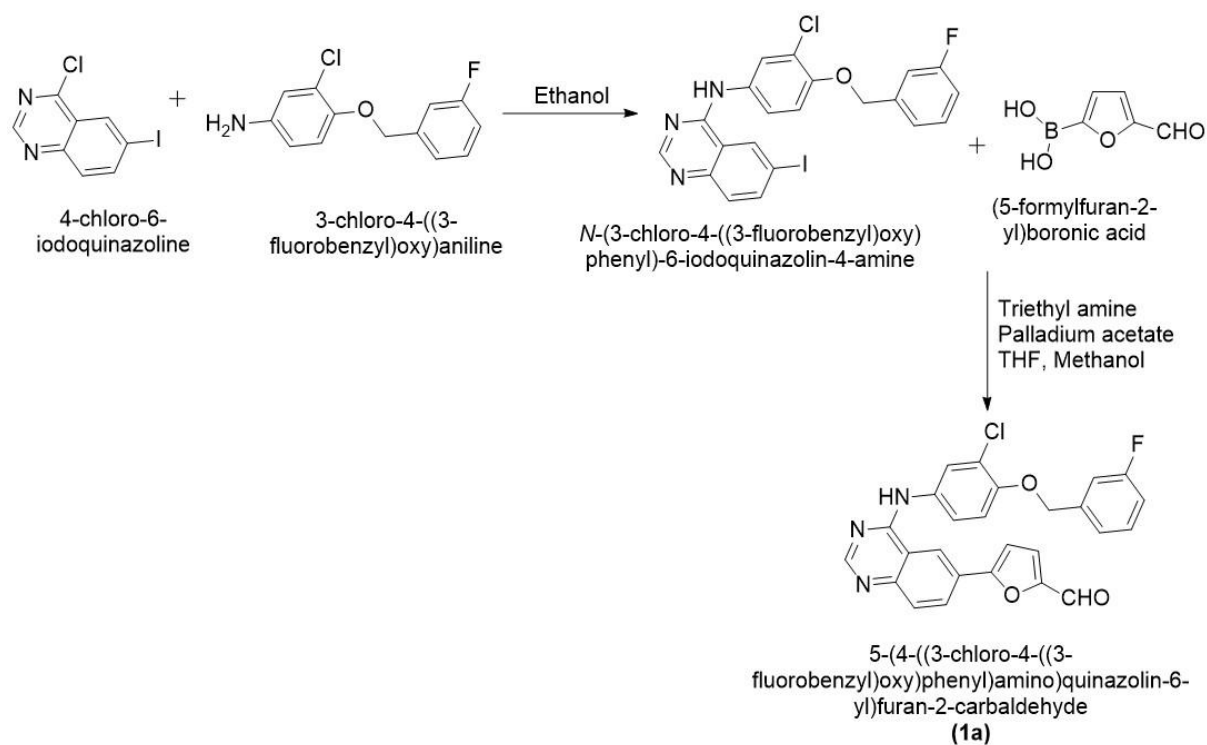
reduced pressure to afford the intermediate N-(3-chloro-4-((3-fluorobenzyl)oxy)phenyl)-6-iodoquinazolin-4-amine.

In the second step, the obtained iodoquinazoline intermediate was subjected to a Suzuki–Miyaura cross-coupling reaction with (5-formylfuran-2-yl)boronic acid (1.2 mmol). The reaction was carried out in a mixed solvent system of THF and methanol, which provides good solubility for both organic and inorganic components. To this mixture, triethylamine (2.5 mmol) was added as a base to facilitate the transmetalation step, along with a catalytic amount of palladium acetate (0.05 mmol) as the coupling catalyst. The reaction mixture was heated at 60–65 °C for 6 hours under stirring. In this step, the palladium catalyst undergoes oxidative addition with the aryl iodide, followed by transmetalation with the boronic acid and subsequent reductive elimination to form a new carbon carbon bond, introducing the furan-2-carbaldehyde moiety onto the quinazoline scaffold. The filtrate was then concentrated under reduced pressure to remove solvents, yielding the product as an aromatic aldehyde compound (1a), that is 5-(4-((3-chloro-4-((3-fluorobenzyl)oxy)phenyl)amino)quinazolin-6-yl)furan-2-carbaldehyde, in good yield.

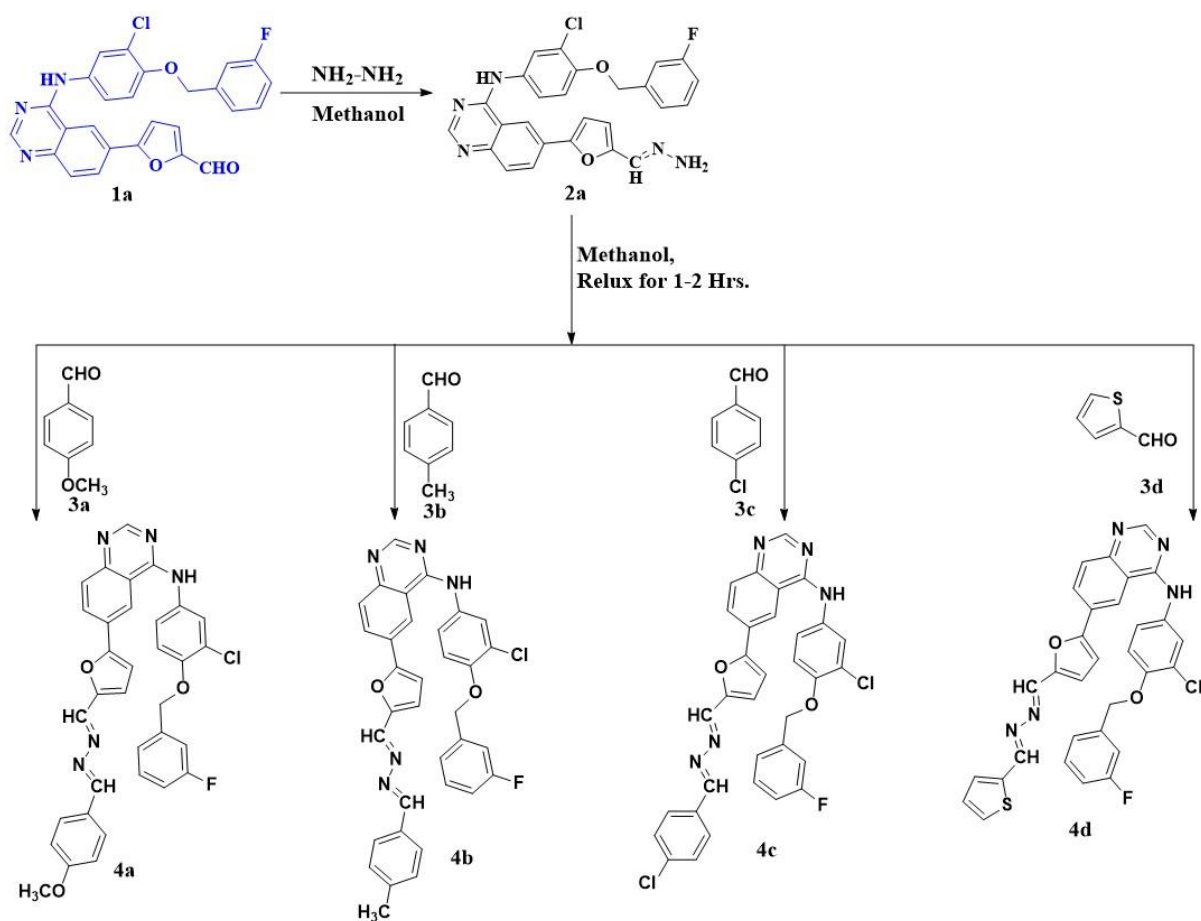
Upon dissolved 6-(5-formylfuran-2-yl)-N-(4-(3-fluorobenzyloxy)-3-chlorophenyl)quinazolin-4-amine (1a) (0.01 mol) and hydrazine hydrate (0.01 mol) in 25–30 mL of methanol, the mixture was agitated at room temperature. The matching hydrazone intermediate (2a) was subsequently obtained by refluxing the reaction mixture for one to two hours. Thin-layer chromatography (TLC) was used to track the reaction's development using silica gel plates and a suitable solvent solution (ethyl acetate: n-hexane, 1:4 ratio). The precipitated product was filtered, cleaned with cold methanol, and vacuum-dried when the reaction mixture had cooled to room temperature. Without additional purification, the resulting intermediate was utilized for the subsequent stage.

Substituted aromatic/heteroaromatic aldehydes (3a–3h) (0.01 mol) were then added after intermediate 2a (0.01 mol) was dissolved in methanol (20–25 mL). The resultant reaction mixture was continuously stirred and refluxed in methanol for one to two hours. TLC analysis verified the reaction's completion. To get pure furan-based quinazoline hydrazone derivatives, the separated solid products (4a–4h) were collected by filtering, extensively cleaned with cold methanol to remove impurities, and recrystallized from appropriate solvents after cooling to room temperature. FT-IR, ¹H NMR, ¹³C NMR, and mass

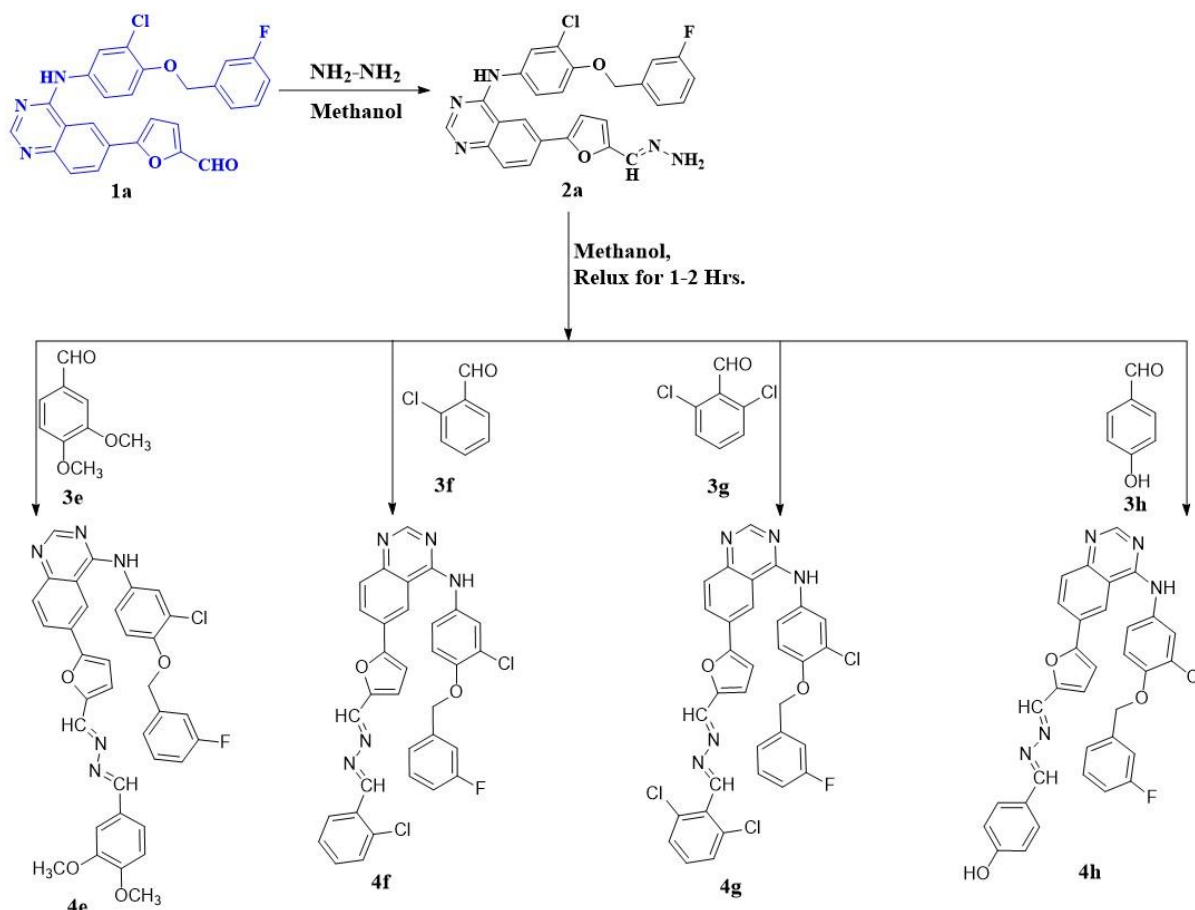
spectrometry were among the spectroscopic techniques used to characterise the products after drying.



Scheme 1. Synthesis of quinazolin-6-furan-2-carbaldehyde derivative compounds (**1a**).



Scheme 2. Reaction procedure of synthesised Furan-Based Quinazoline-4-amine derivative scaffolds (4a-4d).



Scheme 3. Reaction procedure of synthesised Furan-Based Quinazoline-4-amine derivative scaffolds (**4e-4h**).

2.2.1 Characterization of N-(3-chloro-4-((3-fluorobenzyl)oxy)phenyl)-6-(5-((E)-(((E)-4-methoxybenzylidene)hydrazono)methyl)furan-2-yl)quinazolin-4-amine(**4a**)

Cream solid; **Yield:** 87 %; **M.P.:** 240 °C; $\text{C}_{34}\text{H}_{25}\text{ClFN}_5\text{O}_3$; **M. Wt.:** 606.05g/mol; **Elemental Analysis Calc. % (found %):** C, 67.38 (67.29); H, 4.16 (4.01); N, 11.56 (11.45); **FT-IR (cm^{-1}):** 3324 (N-H), 2967 (=C-H) Ar stretching, 1602 (-C=C) stretching, 1498 (-C=N) stretching, 1252 (-C-O) stretching, 1058 (-C-F) stretching, 670 (-C-Cl) stretching. **^1H NMR (DMSO- d_6) δ [ppm]:** 10.02 (1H, s, N-H), 8.86 (1H, s, Ar-H), 8.71 (1H, s, Ar-H), 8.57 (2H, s, Ar-H), 8.25 – 8.22 (1H, d, $J = 8.8$ Hz), 7.99 (1H, s, Ar-H), 7.84 – 7.82 (3H, dd, $J_1 = 2.4$ Hz, $J_2 = 8.4$ Hz, Ar-H), 7.79 (1H, m, Ar-H), 7.47 – 7.46 (1H, m, Ar-H), 7.32 – 7.26 (5H, m, Ar-H), 7.18 – 7.10 (2H, m, Ar-H), 7.065 – 7.043 (1H, d, $J = 8.8$ Hz, Ar-H), 5.25 (2H, s, -OCH₂), 3.85 (3H, s, -OCH₃). **^{13}C NMR (DMSO- d_6) δ [ppm]:** 163.95(Ar, -C-F), 162.41(-C-O-CH₃), 161.96, 161.53(-C=N-), 158.30, 155.86, 155.36 (Ar, -C-NH-), 150.40, 150.14, 150.01(-C=N-), 140.20(=C-NH-), 140.13(Ar, -C=CH-), 133.47(Ar, -C=CH-), 131.13, 131.04, 130.75, 129.64(Ar, -C=CH -), 129.21, 127.63, 126.94(Ar, -C=CH-), 125.00, 123.86, 123.83,

123.20(Ar, -C=Cl), 121.60, 120.06, 118.78, 115.92(Ar, -C=CH-), 115.33, 115.13, 114.95, 114.80, 114.66, 114.45, 110.33(-C=CH-), 69.93(O-CH₂), 55.93(O-CH₃). **ESI-MS (m/z):** 606.74 [M+H]⁺, 608.76, 609.70, 610.77, 415.61, 411.72, 329.62, 257.28

2.2.2 Characterization of N-(3-chloro-4-((3-fluorobenzyl)oxy)phenyl)-6-(5-((E)-(((E)-4-methylbenzylidene)hydrazono)methyl)furan-2-yl)quinazolin-4-amine (4b)

Yellowish solid; **Yield:** 89%; **M.P.:** 242 °C; **C₃₄H₂₅ClFN₅O₂**; **M. Wt.:** 590.06g/mol; **Elemental Analysis Calc. % (found %):** C, 69.21 (69.05); H, 4.27 (4.35); N, 11.87 (11.95); **FT-IR (cm⁻¹):** 3339 (N-H), 1602 (-C=C) stretching, 1490 (-C=N) stretching, 1274 (-C-O) stretching, 1058 (-C-F) stretching, 678 (-C-Cl) stretching. **¹H NMR (DMSO-d₆) δ [ppm]:** 10.01 (1H, s, N-H), 8.85 (1H, s, Imine CH), 8.72 (1H, s, Imine CH), 8.57 (2H, s, Ar-H), 8.224 – 8.22 (1H, d, J = 1.6 Hz), 7.99 (1H, s, Ar-H), 7.77 (1H, d, Ar-H), 7.75 (3H, m, Ar-H), 7.47 – 7.46 (1H, m, Ar-H), 7.34 – 7.17 (7H, m, Ar-H), 7.17 (1H, m, Ar-H), 5.25 (2H, s, -OCH₂), 2.35 (3H, s, -CH₃). **¹³C NMR (DMSO-d₆) δ [ppm]:** 163.95(Ar, -C-F), 162.25(-C-O-CH₃), 161.53(-C=N-), 158.28, 156.01, 155.37(Ar, -C-NH-), 150.43, 150.40(-C=N-), 150.16(-C=N-), 149.88, 141.99, 140.20, 140.12(=C-NH-), 133.47, 131.68, 131.12, 131.03, 130.04, 129.20 (Ar, -C=CH-), 128.95, 127.58(Ar, -C=CH-), 124.98, 123.85, 123.82, 123.18(Ar, -C=Cl), 121.60, 120.39, 118.84, 115.91(Ar, -C=CH-), 115.33, 115.12, 114.78, 114.66, 114.44, 110.34 (-C=CH-), 69.92(O-CH₂), 21.71(-C-CH₃-). **ESI-MS (m/z):** 590.75 [M+H]⁺, 592.76, 593.84, 594.78, 329.73, 258.49, 257.28

2.2.3 Characterization of N-(3-chloro-4-((3-fluorobenzyl)oxy)phenyl)-6-(5-((E)-(((E)-4-chlorobenzylidene)hydrazono)methyl)furan-2-yl)quinazolin-4-amine (4c)

Yellowish solid; **Yield:** 85%; **M.P.:** 243 °C; **C₃₃H₂₂Cl₂FN₅O₂**; **M. Wt.:** 610.47g/mol; **Elemental Analysis Calc. % (found %):** C, 64.93 (65.06); H, 3.63 (3.59); N, 11.47 (11.35); **FT-IR (cm⁻¹):** 3287 (N-H), 2944 (=C-H) Ar stretching, 1595 (-C=C) stretching, 1483 (-C=N) stretching, 1259 (-C-O) stretching, 1058 (-C-F) stretching, 790 (-C-Cl) stretching. **¹H NMR (DMSO-d₆) δ [ppm]:** 10.04 (1H, s, N-H), 8.87-8.77(2H, s, Imine CH), 8.59-8.58 (2H, d, J=6.4 Hz, Ar-H), 8.25 – 8.23 (1H, d, J = 8.4Hz, Ar-H), 7.99-7.98 (1H, d, Ar-H), 7.90-7.88 (3H, m, Ar-H), 7.58-7.56 (1H, d, J = 8.4Hz, Ar-H), 7.48 (2H, d, Ar-H), 7.46 – 7.44 (1H, m, J = 8 Hz Ar-H), 7.34-7.27(5H, m, Ar-H), 7.18 (1H, m Ar-H), 5.26 (2H, s, -OCH₂). **¹³C NMR (DMSO-d₆) δ [ppm]:** 163.99, 161.53(-C=N-), 161.10, 158.33, 156.23, 155.45(Ar, -C-NH-), 151.03, 150.46, 150.18(-C=N-), 149.73, 140.23, 140.13(=C-NH-), 136.45, 133.45, 133.26, 131.13, 131.13, 131.05, 130.52, 129.70, 129.58 (Ar, -C=CH-), 129.21, 127.54, 125.01,

123.86, 123.84, 123.21, 121.60, 120.99, 118.95, 115.92, 115.34, 115.13, 114.81, 114.67, 114.45, 110.43(-C=CH-), 69.92(O-CH₂). **ESI-MS (m/z):** 610.64 [M+H]⁺, 612.79, 613.73, 614.67, 615.61, 688.73, 799.75, 473.01, 411.45, 329.46, 257.42.

2.2.4 Characterization of N-(3-chloro-4-((3-fluorobenzyl)oxy)phenyl)-6-(5-((E)-(((E)-thiophen-2-ylmethylene)hydrazono)methyl)furan-2-yl)quinazolin-4-amine (4d)

Yellowish solid; **Yield:** 86%; **M.P.:** 240 °C; **C₃₁H₂₁ClFN₅O₂S;** **M. Wt.:** 582.05g/mol; **Elemental Analysis Calc. % (found %):** C, 63.97 (64.10); H, 3.64 (3.60); N, 12.03 (11.95); **FT-IR (cm⁻¹):** 3332 (N-H), 3056 (=C-H) Ar stretching, 1595 (-C=C) stretching, 1490 (-C=N) stretching, 1252 (-C-O) stretching, 1058 (-C-F) stretching, 700 (-C-Cl) stretching. **¹H NMR (DMSO-d₆) δ [ppm]:** 10.03 (1H, s, N-H), 8.94-8.86 (2H, s, Imine CH), 8.57-8.56 (2H, m, J=6.4 Hz, Ar-H), 8.23 – 8.22 (1H, d, J = 1.2Hz, Ar-H), 7.997-7.991 (1H, d, J = 2.4Hz Ar-H), 7.85 (2H, m, Ar-H), 7.83 (2H, m, Ar-H), 7.46 (1H, m, Ar-H), 7.34 – 7.22 (5H, m, Ar-H), 7.18 (2H, m, Ar-H), 5.26 (2H, s, -OCH₂). **¹³C NMR (DMSO-d₆) δ [ppm]:** 163.95, 161.53(-C=N-), 158.30, 156.60, 156.1, 155.40 (Ar, -C-NH-), 150.41, 150.17 (-C=N-), 149.83, 140.20, 140.13(=C-NH-), 139.02, 136.97, 134.45, 133.96, 133.46, 131.65, 131.13, 131.04, 129.67 (Ar, -C=CH-), 129.20, 128.84, 127.56, 127.32 (Ar, -C=CH-), 124.99, 124.76, 123.86, 123.83, 123.20, 122.93, 121.64, 121.60, 120.76, 119.75, 118.89, 115.91, 115.33, 115.13 (Ar, -C=CH-), 114.80, 114.67, 114.45, 110.41(-C=CH-), 69.93(O-CH₂). **ESI-MS (m/z):** 582.68 [M+H]⁺, 583.76, 584.56, 585.64, 586.71, 660.77, 483.89, 411.72, 319.24, 259.43, 257.28

2.2.5 Characterization of N-(3-chloro-4-((3-fluorobenzyl)oxy)phenyl)-6-(5-((E)-(((E)-3,4-dimethoxybenzylidene)hydrazono)methyl)furan-2-yl)quinazolin-4-amine (4e)

Yellowish solid; **Yield:** 88%; **M.P.:** 238 °C; **C₃₅H₂₇ClFN₅O₄;** **M. Wt.:** 636.08g/mol; **Elemental Analysis Calc. % (found %):** C, 66.09 (66.00); H, 4.28 (4.15); N, 11.01 (11.17); **FT-IR (cm⁻¹):** 3354 (N-H), 2847 (=C-H) Ar stretching, 1610 (-C=C) stretching, 1490 (-C=N) stretching, 1252 (-C-O) stretching, 1028 (-C-F) stretching, 775 (-C-Cl) stretching. **¹H NMR (DMSO-d₆) δ [ppm]:** 10.01 (1H, s, N-H), 8.90 (1H, s, Imine CH), 8.85 (1H, s, Imine CH), 8.57-8.56 (2H, d, J=7.2 Hz, Ar-H), 8.25 – 8.23 (1H, d, J = 8.8Hz, Ar-H), 7.99 (1H, s, Ar-H), 7.98 (1H, d, Ar-H), 7.90 (1H, d, Ar-H), 7.84 (1H, d, Ar-H), 7.34 (1H, m, Ar-H), 7.32-7.27 (5H, m, Ar-H), 7.26 (1H, m, Ar-H), 6.65-6.62 (2H, m, Ar-H), 5.25 (2H, s, -OCH₂), 3.88-3.86 (3H, s, -OCH₃), 3.84-3.82 (3H, s, -OCH₃). **¹³C NMR (DMSO-d₆) δ [ppm]:** 164.23, 163.95, 161.53(-C=N-), 160.94, 158.28, 157.37, 155.76(Ar, -C-NH-), 155.34, 150.42, 150.14(-C=N-), 150.10, 149.58, 140.20(=C-NH-), 140.13, 133.47, 131.12, 131.04, 129.20(Ar, -C=CH-),

128.40, 127.66(Ar, -C=CH -), 125.08, 123.86, 123.83,123.28(Ar, -C=Cl), 121.58, 119.72, 118.64, 115.89, 115.33(Ar, -C=CH-), 115.03, 114.78, 114.67, 114.45, 110.32, 107.21, 98.75, (-C=CH-), 69.92(O-CH₂), 56.46(-C-OCH₃), 56.08(-C-OCH₃). **ESI-MS (m/z):** 636.71 [M+H]⁺, 637.79, 638.73, 639.80, 488.60, 331.61, 330.53, 329.59.

2.2.6 Characterization of N-(3-chloro-4-((3-fluorobenzyl)oxy)phenyl)-6-(5-((E)-(((E)-2-chlorobenzylidene)hydrazono)methyl)furan-2-yl)quinazolin-4-amine (4f)

Yellowish solid; **Yield:** 84%; **M.P.:** 237 °C; **C₃₃H₂₂ClFN₅O₂**; **M. Wt.:** 610.47g/mol; **Elemental Analysis Calc. % (found %):** C, 64.93 (64.99); H, 3.63 (3.60); N, 11.47 (11.42); **FT-IR (cm⁻¹):** 3362 (N-H), 3101 (=C-H) Ar stretching, 1610 (-C=C) stretching, 1490 (-C=N) stretching, 1282 (-C-O) stretching, 1058 (-C-F) stretching, 685 (-C-Cl) stretching. **¹H NMR (DMSO-d₆) δ [ppm]:** 10.03 (1H, s, N-H), 9 (1H, s, Imine CH), 8.87 (1H, s, Imine CH), 8.63 (1H, s, Ar-H), 8.57 (1H, s, Ar-H), 8.27-8.24 (1H, d, J=8.4 Hz, Ar-H), 8.1 (1H, d, Ar-H), 7.98 (1H, s, Ar-H), 7.84 (1H, d, Ar-H), 7.7 (1H, d, Ar-H), 7.57-7.46 (4H, m, Ar-H), 7.39-7.34 (5H, m, Ar-H), 7.32-7.26 (1H, t, Ar-H), 5.25 (2H, s, -OCH₂). **¹³C NMR (DMSO-d₆) δ [ppm]:** 165.19, 163.95, 161.52(-C=N-), 158.31, 158.03, 156.48, 155.44(Ar, -C-NH-), 151.68, 150.45, 150.24(-C=N-), 149.54, 140.2, 140.12(=C-NH-), 135.04, 133.41, 133.39(Ar, -C-Cl), 131.35, 131.13, 131.04, 130.68, 129.77, 129.22(Ar, -C=CH -), 128.45, 128.21(Ar, -C=CH 2 -), 127.45, 125.12, 123.86,123.32(Ar, -C=Cl), 121.58, 118.97, 115.88, 115.33, 115.12(Ar, -C=CH-), 114.79, 114.67, 114.45, 110.51(-C=CH-), 69.92(O-CH₂). **ESI-MS (m/z):** 610.77 [M+H]⁺, 612.79, 614.80, 633.76, 638.86, 703.11, 815.34, 840.47, 1388.72, 1466.27, 499.62, 411.72, 351.50, 352.56, 258.63, 257.42.

2.2.7 Characterization of N-(3-chloro-4-((3-fluorobenzyl)oxy)phenyl)-6-(5-((E)-(((E)-2,6-dichlorobenzylidene)hydrazono)methyl)furan-2-yl)quinazolin-4-amine (4g)

Yellowish solid; **Yield:** 87%; **M.P.:** 239 °C; **C₃₃H₂₁Cl₃FN₅O₂**; **M. Wt.:** 644.91g/mol; **Elemental Analysis Calc. % (found %):** C, 61.46 (61.42); H, 3.28 (3.25); N, 10.86 (10.84); **FT-IR (cm⁻¹):** 3354 (N-H), 3093 (=C-H) Ar stretching, 1610 (-C=C) stretching, 1490 (-C=N) stretching, 1252 (-C-O) stretching, 1028 (-C-F) stretching, 685 (-C-Cl) stretching. **¹H NMR (DMSO-d₆) δ [ppm]:** 10.04 (1H, s, N-H), 8.88 (1H, s, Imine CH), 8.84 (1H, s, Imine CH), 8.59-8.57 (2H, s, J=7.6 Hz, Ar-H), 8.25-8.24 (1H, s, J= 1.2 Hz, Ar-H), 7.987-7.981 (1H, d, J=2.4 Hz, Ar-H), 7.85 (1H, d, Ar-H), 7.6 (1H, d, J=7.6 Hz, Ar-H), 7.58 (2H, d, J=7.6 Hz, Ar-H), 7.5-7.49 (2H, m, J=7.2 Hz, Ar-H), 7.41-7.4 (1H, d, Ar-H), 7.35-7.31 (4H, m, Ar-H), 7.28-7.26 (1H, m, Ar-H), 5.25 (2H, s, -OCH₂). **¹³C NMR (DMSO-d₆) δ [ppm]:** 163.99,

161.56(-C=N-), 158.32, 157.53, 156.61, 155.47(Ar, -C-NH-), 151.68, 150.44, 150.27(-C=N-), 149.30, 140.24, 140.06, (=C-NH-), 134.74, 133.42(Ar, -C-Cl), 132.42(Ar, -C-Cl), 131.12, 130.72, 129.22, 129.69(Ar, -C=CH-), 127.44(Ar, -C=CH-), 125.10, 123.85, 123.82, 123.30(Ar, -C=Cl), 121.97, 121.59, 119.03, 115.88, 115.32, 115.11(Ar, -C=CH₂-), 114.77, 114.66, 114.44, 110.48(-C=CH-), 69.91(O-CH₂). **ESI-MS (m/z):** 644.78[M]⁺, 646.66, 647.73, 649.62, 715.88, 723.54, 1316.95, 638.85, 476.63, 474.48, 388.46, 319.65, 257.28.

2.2.8 Characterization of 4-((E)-(((E)-5-(4-((3-chloro-4-((3-fluorobenzyl) oxy) phenyl) amino) quinazolin-6-yl)furan-2-yl)methylene)hydrazono)methyl)phenol (4h)

Cream solid; **Yield:** 90%; **M.P.:** 245 °C; **C₃₃H₂₃ClFN₅O₃**; **M. Wt.:** 592.03g/mol; **Elemental Analysis Calc. % (found %):** C, 66.95 (66.91); H, 3.92 (3.89); N, 11.83 (11.78); **FT-IR (cm⁻¹):** 3056 (N-H), 2981 (=C-H) Ar stretching, 1595 (-C=C) stretching, 1490 (-C=N) stretching, 1215 (-C-O) stretching, 1058 (-C-F) stretching, 678 (-C-Cl) stretching. **¹H NMR (DMSO-d₆) δ [ppm]:** 10.16 (1H, s, O-H), 10.02 (1H, s, N-H), 8.86 (1H, s, Imine CH), 8.66 (1H, s, Imine CH), 8.55 (2H, Ar-H), 8.24-8.22 (1H, d, J= 8.8 Hz, Ar-H), 7.99 (1H, s, Ar-H), 7.74 (1H, d, Ar-H), 7.72 (3H, m, Ar-H), 7.34 (1H, m, Ar-H), 7.32-7.7.3 (5H, m, Ar-H), 7.27 (1H, m, Ar-H), 6.94-6.87 (2H, m, Ar-H), 5.25 (2H, s, -OCH₂). **¹³C NMR (DMSO-d₆) δ [ppm]:** 163.95, 162.27, 161.53(-C=N-), 161.18, 159.08, 158.29, 156.18, 155.75(Ar, -C-NH-), 155.32(Ar, -C-OH), 150.40, 150.10(-C=N-), 149.61, 148.63, 140.20, 140.12(=C-NH-), 133.48, 132.62, 131.03, 130.99, 129.64(Ar, -C=CH-), 129.17, 127.67(Ar, -C=CH-), 125.41, 125.00, 123.85, 123.20(Ar, -C=Cl), 121.60, 119.76, 118.73, 116.36, 115.92, 115.33, 115.12(Ar, -C=CH-), 114.79, 114.67, 114.45, 110.31(-C=CH-), 69.93(O-CH₂). **ESI-MS (m/z):** 592.76 [M+H]⁺, 594.78, 595.72, 672.87, 714.27, 1012.51, 411.85, 388.33, 329.59, 258.36, 257.28.

2.3 ADMET Prediction

The physicochemical and drug-likeness properties of compounds **4a–h** and the standard ascorbic acid were predicted using the SwissADME web tool (<http://www.swissadme.ch>, Swiss Institute of Bioinformatics). Canonical SMILES of each structure were submitted to the server to compute key descriptors molecular weight, heavy atoms, Csp³, rotatable bonds, hydrogen-bond acceptors/donors, and topological polar surface area (TPSA) along with compliance against the Lipinski, Ghose, Veber, Egan, and Muegge drug-likeness filters and the predicted oral bioavailability score, to assess the pharmacokinetic suitability of the synthesized derivatives.^[36,37]

2.4 Molecular Docking study

Molecular docking studies were performed to elucidate the binding mode and rationalize the antioxidant potential of the synthesized furan-quinazoline hydrazone derivatives (4a–4h) using the Schrödinger Suite (Maestro graphical interface, Schrödinger, LLC, New York, NY). The three-dimensional crystal structure of the Kelch domain of Keap1 in complex with a small-molecule inhibitor (PDB ID: 4L7B) was retrieved from the RCSB Protein Data Bank and processed using the Protein Preparation Wizard, wherein bond orders were assigned, hydrogen atoms were added, missing side chains were completed, water molecules beyond 5 Å of the co-crystallized ligand were removed, and the protonation states of ionizable residues were optimized at physiological pH (7.0 ± 2.0) using PROPKA/Epik, followed by restrained energy minimization using the OPLS4 force field. The ligand structures of compounds 4a–4h and the standard ascorbic acid were built in Maestro and prepared using LigPrep, which generated the appropriate ionization states at pH 7.0 ± 2.0 (Epik), tautomers, and low-energy 3D conformers using the OPLS4 force field. A receptor grid was generated using the Receptor Grid Generation module, centred on the centroid of the co-crystallized ligand within the Kelch β -propeller binding pocket, with an inner box of $10 \text{ Å} \times 10 \text{ Å} \times 10 \text{ Å}$ and an outer box of $20 \text{ Å} \times 20 \text{ Å} \times 20 \text{ Å}$ enclosing the binding-site residues. Molecular docking was carried out using Glide in extra-precision (XP) mode, and the resulting poses were ranked according to Glide docking score (kcal/mol). The best-scoring pose for each ligand was retained for analysis of hydrogen bonding, halogen bonding, π – π stacking, and hydrophobic interactions with the Keap1 binding-site residues. [38]

2.5 DFT calculations

Density functional theory (DFT) calculations were carried out using the Jaguar module of the Schrödinger Suite (Schrödinger, LLC, New York, NY). The ground-state geometries of compounds **4a–h** were fully optimized using the B3LYP hybrid exchange-correlation functional with the 6-31G* basis set, and the optimized structures were confirmed as true energy minima by the absence of imaginary vibrational frequencies. The frontier molecular orbital energies (E_{HOMO} , E_{LUMO}), HOMO–LUMO energy gap, global reactivity descriptors, Mulliken atomic charges, and molecular electrostatic potential (MEP) surfaces were derived from the optimized geometries at the same level of theory. [39]

3. Result and Discussion

3.1 Chemistry

3.1.1 FT-IR spectra

The effective construction of the target scaffold was verified by the FT-IR spectra of the synthesized furan-based quinazoline-4-amine derivatives (**4a–h**). The quinazoline amine functionality was indicated in all compounds by the presence of a distinctive N–H stretching band in the range of 3056–3362 cm^{-1} , whilst bands detected at 1595–1610 cm^{-1} and 1483–1498 cm^{-1} were attributed to aromatic C=C and quinazoline C=N stretching vibrations, respectively. At 3324 cm^{-1} for **4a**, 3339 cm^{-1} for **4b**, 3287 cm^{-1} for **4c**, 3332 cm^{-1} for **4d**, 3354 cm^{-1} for **4e** and **4g**, 3362 cm^{-1} for **4f**, and 3056 cm^{-1} for **4h**, the broad absorption linked to N–H stretching emerged. The presence of aromatic and heteroaromatic rings in the synthesized compounds was further supported by the observation of aromatic C–H stretching bands in the 2847–3101 cm^{-1} range. The furan moiety's integration into the quinazoline framework was confirmed by the appearance of the furan ring's C–O stretching vibration between 1215 and 1282 cm^{-1} . Furthermore, the C–Cl stretching vibrations were found between 670 and 790 cm^{-1} , and the C–F stretching bands were found between 1028 and 1058 cm^{-1} . These absorptions offer more proof of structural heterogeneity amongst the analogues and are consistent with the presence of halogen substituents in the produced derivatives. The suggested structures of compounds (**4a–h**) are supported by the measured spectrum data. The presence of N–H, aromatic C=C, quinazoline C=N, furan C–O, and halogen-related stretching bands at the same time suggests that the required substituted products were successfully synthesized and that the quinazoline core remained intact during synthesis. The compounds' slight variations in peak positions are probably caused by variations in the electronic surroundings and substituent effects surrounding the aromatic and heterocyclic systems.

3.1.2 Proton NMR

Strong support for the effective synthesis of the target compounds was provided by the ^1H NMR spectra of the furan-based quinazoline-4-amine derivatives (**4a–h**), which were congruent with the suggested structures. The presence of the amine functionality was confirmed in all derivatives by the emergence of a downfield singlet at δ 10.01–10.04 ppm, which was attributed to the quinazoline N–H proton. The presence of a hydroxyl substituent in compound **4h** was supported by an extra singlet at δ 10.16 ppm that matched the phenolic O–H proton. Throughout the series, the quinazoline ring's imine or heteroaromatic protons showed up as singlets in the δ 8.84–9.00 ppm range. There were several aromatic resonances between δ 6.62 and 8.59 ppm, which is typical for the substituted phenyl and heteroaryl rings as well as the quinazoline nucleus. The creation of the anticipated aromatic framework was

further supported by the existence of these signals, as well as their multiplicity patterns and coupling constants.

The methylene resonance at δ 5.25–5.26 ppm, which appears as a singlet and corresponds to the $-\text{OCH}_2\text{-}$ linker, was a crucial diagnostic signal for all compounds. This signal unmistakably shows that the ether-linked side chain was successfully constructed. Singlets at δ 3.85 ppm and δ 3.88–3.86/3.84–3.82 ppm, respectively, indicated the presence of methoxy substituents in compounds **4a** and **4e**. At δ 2.35 ppm, compound **4b** had a methyl singlet, which is consistent with an aromatic methyl group.

3.1.3 Carbon NMR

The ^{13}C NMR spectra of the furan-based quinazoline-4-amine derivatives (**4a-h**) were fully consistent with the proposed structures and further confirmed the successful synthesis of the target compounds. In all compounds, the most downfield resonances in the range of approximately δ 161–165 ppm were assigned to the quinazoline $\text{C}=\text{N}$ and other deshielded heteroaromatic carbons, indicating the presence of the quinazoline core. Signals observed around δ 155–156 ppm were attributed to carbons attached to nitrogen in the heteroaromatic system, while resonances near δ 140 ppm were assigned to the $\text{C}=\text{NH}$ or adjacent aromatic carbons. A large number of aromatic carbon signals appeared in the δ 110–150 ppm region, which is typical for substituted quinazoline and phenyl rings. These resonances reflected the structural complexity of the derivatives and the presence of multiple substituted aromatic environments. The furan and heteroaryl carbons were also clearly represented within this region, supporting incorporation of the heterocyclic fragment into the final products.

The methylene carbon of the ether linker was consistently observed at δ 69.91–69.93 ppm in all compounds, confirming the presence of the $-\text{OCH}_2\text{-}$ bridge. In compounds **4a** and **4b**, an additional methoxy carbon signal appeared at δ 55.93 and 21.71 ppm, respectively, corresponding to $-\text{OCH}_3$ and aromatic $-\text{CH}_3$ groups. Compound **4e** showed two methoxy signals at δ 56.46 and 56.08 ppm, consistent with the presence of two methoxy substituents. In compound **4h**, the signal at δ 155.32 ppm was assigned to the aromatic carbon bearing the hydroxyl group, supporting the presence of the phenolic substituent. The ^{13}C NMR data strongly support the assigned structures of compounds (**4a-h**). The chemical shifts and number of carbon resonances were in good agreement with the expected substitution patterns, and the data complement the FT-IR and ^1H NMR results, collectively confirming the formation of the desired furan-based quinazoline-4-amine derivatives.

3.1.4 Mass spectrometry

The electrospray ionization mass spectrometry (ESI-MS) data of the synthesized furan-based quinazoline-4-amine derivatives (**4a-h**) provided additional confirmation of their molecular identities. In each case, the observed molecular ion peaks were in good agreement with the expected molecular weights of the target compounds, thereby supporting the successful formation of the desired products. For compound **4a**, the prominent ion at m/z 606.74 was assigned to $[M + H]^+$, accompanied by isotope peaks at 608.76, 609.70, and 610.77, which are characteristic of halogen-containing molecules. Similarly, compound **4b** showed a molecular ion peak at m/z 590.75 $[M + H]^+$ with the expected isotope distribution at 592.76, 593.84, and 594.78. Compound **4c** exhibited a molecular ion at m/z 610.64 $[M + H]^+$ together with corresponding isotopic peaks at 612.79, 613.73, 614.67, and 615.61, while compound **4d** displayed $[M + H]^+$ at m/z 582.68 with associated isotopic signals at 583.76, 584.56, 585.64, and 586.71. The same pattern was observed for the remaining derivatives. Compound **4e** gave a molecular ion at m/z 636.71 $[M + H]^+$, compound **4f** at m/z 610.77 $[M + H]^+$, compound **4g** at m/z 644.78 $[M]^+$, and compound **4h** at m/z 592.76 $[M + H]^+$. The presence of multiple peaks in each spectrum is consistent with fragmentation behavior and isotopic contributions from halogen atoms such as chlorine and fluorine, further validating the substituted aromatic nature of these compounds. In addition to the molecular ion peaks, several fragment ions were observed in the lower mass region, including signals around m/z 411, 329, 257, 258, and related values. These fragments likely arose from cleavage of the ether linkage, loss of substituents, and breakdown of the quinazoline-furan framework under ionization conditions. The repeated appearance of fragment ions near m/z 257–329 across the series suggests a stable common core fragment derived from the quinazoline-based scaffold.

3.2 Density Functional Theory (DFT) Study

3.2.1 Molecular geometry

The ground-state geometries of compounds **4a-h**, optimized to genuine energy minima, retain the characteristic V-shaped conformation imposed by the central quinazoline-4-amine core flanked by the furan-hydrazone arm on one side and the 3-chloro-4-(3-fluorobenzyloxy)phenyl arm on the other (Figure 1). The azomethine ($-\text{CH}=\text{N}-\text{N}=\text{CH}-$) linkage connecting the furan and the substituted benzyldene ring is essentially planar in all analogues, favouring extended π -conjugation across the furan-hydrazone-benzyldene

framework, a feature expected to facilitate delocalization of an unpaired electron generated upon hydrogen-atom or single-electron transfer during radical scavenging. Minor deviations in the dihedral orientation of the pendant aryl rings among **4a–h** arise from the steric and electronic nature of the substituents (methoxy, methyl, chloro, thiophene, hydroxy), which in turn modulate the frontier orbital energies and dipole moments discussed below.

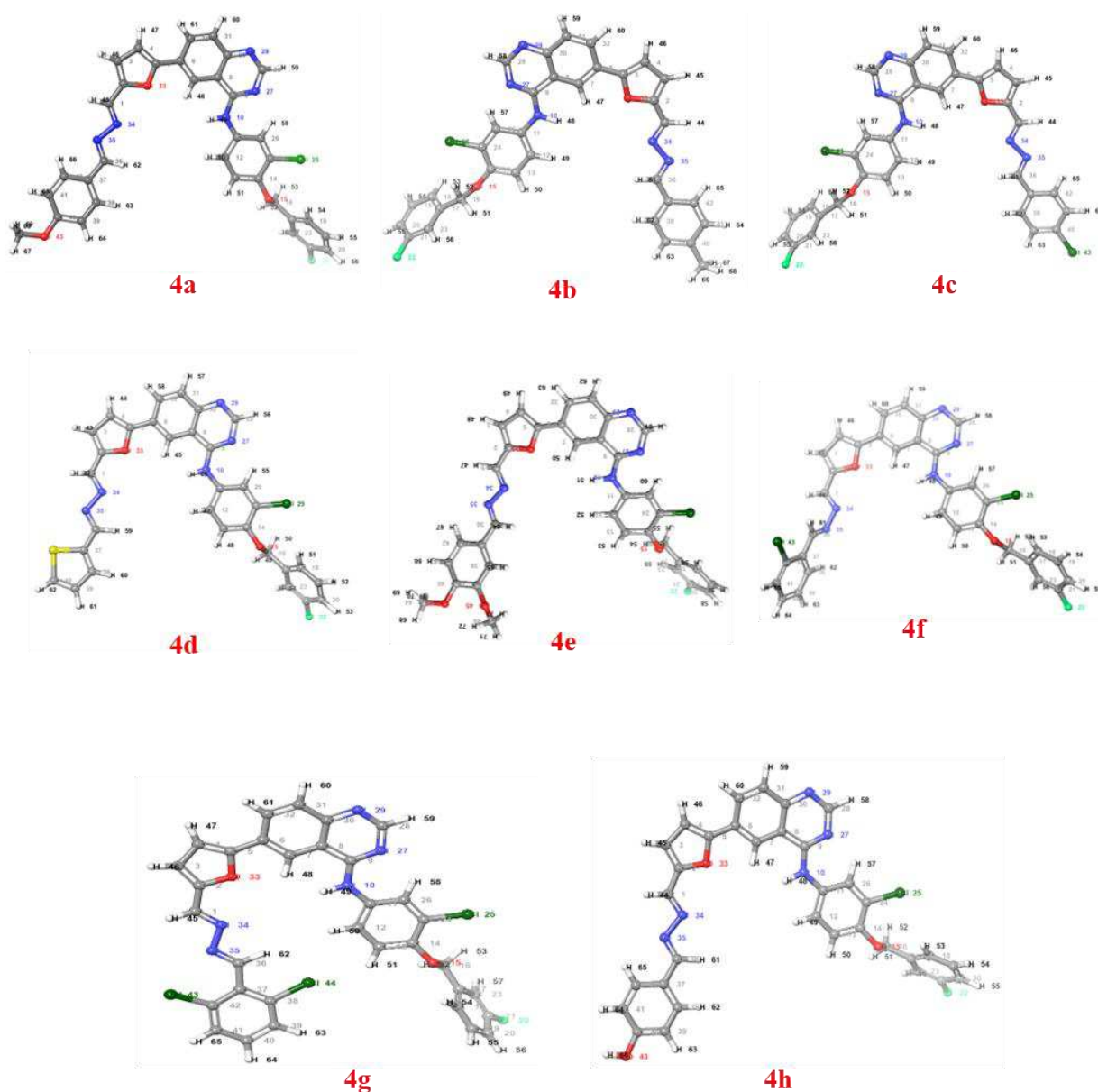


Figure 1. DFT-optimized ground-state molecular geometries of compounds **4a–h** showing the atom-numbering scheme used for structural and electronic analysis.

3.2.2 Frontier molecular orbital

The frontier molecular orbital analysis (Figure 2, Table 1) shows that the HOMO is predominantly delocalized over the furan–hydrazone–benzylidene segment and the electron-rich methoxy-/hydroxy-substituted aryl rings, whereas the LUMO is largely localized on the quinazoline ring and the adjoining azomethine linkage, indicating an intramolecular charge-transfer character on excitation. The calculated E_{HOMO} values range from -5.3788 eV (**4e**) to -5.7397 eV (**4g**), while the E_{LUMO} values span -2.1064 eV (**4f**) to -2.5437 eV (**4c**). The resulting HOMO–LUMO energy gap (ΔE) varies from 3.1236 eV (**4d**) to 3.5532 eV (**4f**); the thiophene-bearing compound **4d** and the dimethoxy-substituted compound **4e** ($\Delta E = 3.1353$ eV) show the narrowest gaps, indicating comparatively higher chemical reactivity and softness, and hence a greater propensity for single-electron or hydrogen-atom transfer to a free radical. In contrast, the 2-chlorobenzylidene compound **4f** displays the widest energy gap (3.5532 eV), consistent with a comparatively more kinetically stable, lower-reactivity electronic configuration.

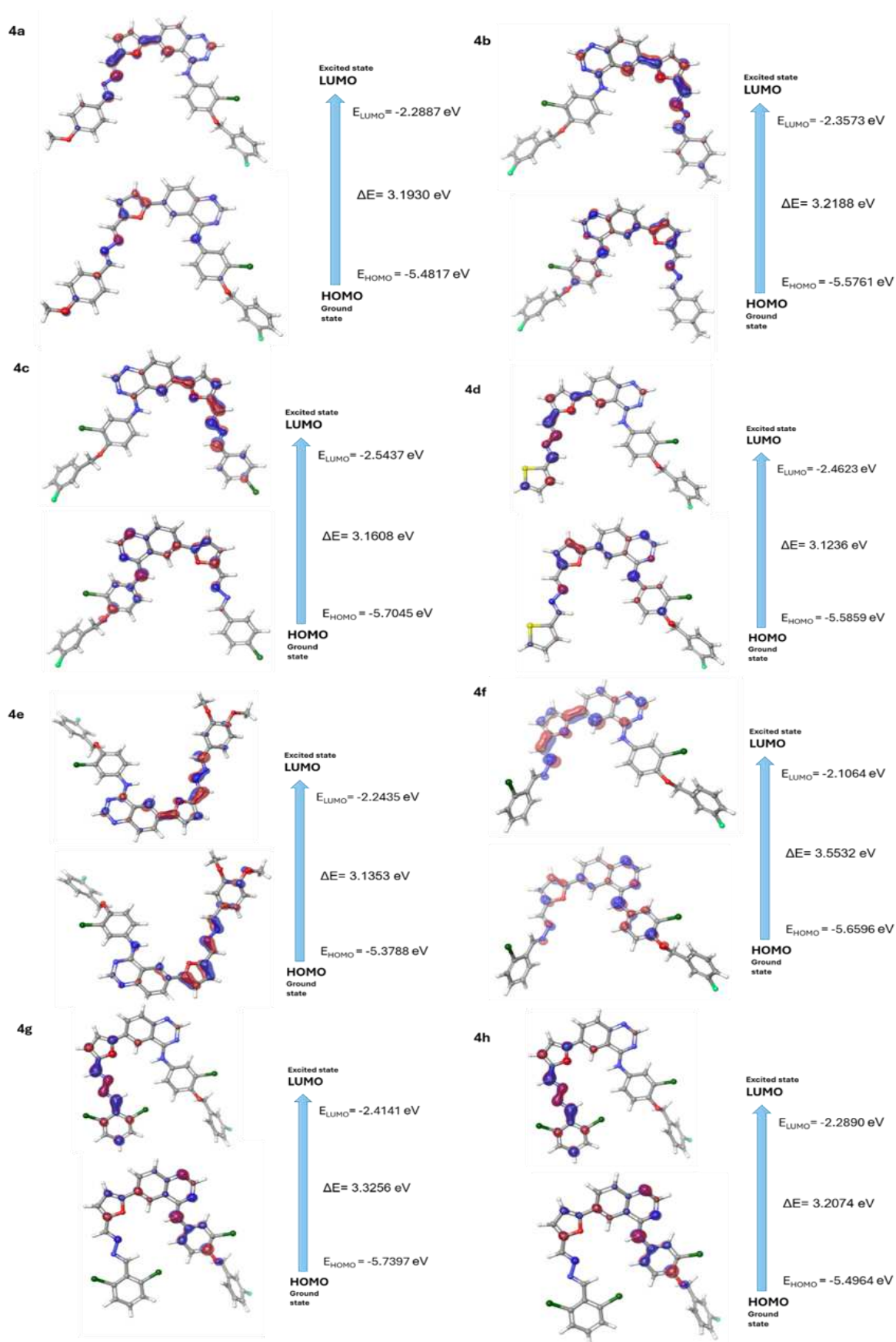


Figure 2. Frontier molecular orbital (HOMO/LUMO) surface plots and the corresponding HOMO–LUMO energy gaps (ΔE) of compounds 4a–h.

3.2.3 Global reactivity descriptors

The global reactivity descriptors derived from the frontier orbital energies (Table 1) further substantiate the reactivity trends noted above. The chemical hardness (η) values range from 1.5618 eV (**4d**) to 1.7766 eV (**4f**), mirroring the HOMO–LUMO gap trend, while the corresponding softness (S) values (0.5629–0.6403 eV⁻¹) indicate that **4d** and **4e** are the most polarizable and, therefore, the most readily oxidizable members of the series. The electrophilicity index (ω), a measure of the energy stabilization a molecule gains upon accepting additional electronic charge, is highest for **4c** (5.3810 eV) and lowest for **4f** (4.2434 eV), suggesting that **4c** behaves as a comparatively stronger electrophile whereas **4f** behaves as a comparatively better electron donor. Since efficient radical-scavenging activity is generally favoured by molecules with lower hardness (higher softness) that can readily donate an electron or hydrogen atom to neutralize a free radical, the comparatively low η and high S values calculated for **4d** and **4f** are consistent with their superior in vitro DPPH radical-scavenging activity (Section 3.5). The calculated dipole moments (2.64–6.23 Debye) reflect the asymmetric charge distribution imposed by the halogenated aryl and furan-hydrazone arms and correlate with the polarity/solubility trends observed in the ADMET predictions (Section 3.3).

Table 1. Frontier molecular orbital energies (E_{HOMO} , E_{LUMO}), HOMO–LUMO energy gap (ΔE), and global reactivity descriptors (ionization potential, electron affinity, electronegativity, chemical potential, hardness, softness, electrophilicity index) and dipole moment of compounds 4a–h.

Descriptor	Formula	4a (eV)	4b (eV)	4c (eV)	4d (eV)
Frontier Orbital Energies					
E_{HOMO}	–	-5.4817	-5.5761	-5.7045	-5.5859
E_{LUMO}	–	-2.2887	-2.3573	-2.5437	-2.4623
ΔE	$E_{\text{LUMO}} - E_{\text{HOMO}}$	3.1930	3.2188	3.1608	3.1236
Global Reactivity Descriptors					
Ionization potential (I)	$-E_{\text{HOMO}}$	5.4817	5.5761	5.7045	5.5859
Electron affinity (A)	$-E_{\text{LUMO}}$	2.2887	2.3573	2.5437	2.4623
Electronegativity (χ)	$(I + A)/2$	3.8852	3.9667	4.1241	4.0241
Chemical potential (μ)	$-\chi$	-3.8852	-3.9667	-4.1241	-4.0241
Hardness (η)	$(I - A)/2$	1.5965	1.6094	1.5804	1.5618
Softness (S)	$1/\eta$	0.6264	0.6213	0.6328	0.6403
Electrophilicity index (ω)	$\mu^2/2\eta$	4.7275	4.8884	5.3810	5.1842
Dipole moment (μD)	-	4.1563	4.2598	3.6248	5.8943

Descriptor	Formula	4e (eV)	4f (eV)	4g (eV)	4h (eV)
Frontier Orbital Energies					
E_{HOMO}	–	-5.3788	-5.6596	-5.7397	-5.4964
E_{LUMO}	–	-2.2435	-2.1064	-2.4141	-2.2890
ΔE	$E_{\text{LUMO}} - E_{\text{HOMO}}$	3.1353	3.5532	3.3256	3.2074
Global Reactivity Descriptors					
Ionization potential (I)	$-E_{\text{HOMO}}$	5.3788	5.6596	5.7397	5.4964
Electron affinity (A)	$-E_{\text{LUMO}}$	2.2435	2.1064	2.4141	2.2890
Electronegativity (χ)	$(I + A)/2$	3.8112	3.8830	4.0769	3.8927
Chemical potential (μ)	$-\chi$	-3.8112	-3.8830	-4.0769	-3.8927
Hardness (η)	$(I - A)/2$	1.5677	1.7766	1.6628	1.6037
Softness (S)	$1/\eta$	0.6379	0.5629	0.6014	0.6236
Electrophilicity index (ω)	$\mu^2/2\eta$	4.6327	4.2434	4.9979	4.7244
Dipole moment (μD)	-	2.6357	5.2184	2.6984	6.2348

3.2.4 Mulliken charge distributions

The Mulliken atomic charge distribution plots (Figure 3) reveal a consistent charge-polarization pattern across the series, with the heteroatoms of the quinazoline and furan rings (ring nitrogens, ether/furan oxygen) and the halogen substituents (Cl, F) carrying pronounced negative charges, while the ring and azomethine carbons directly bonded to these electronegative atoms bear compensating positive charges. The imine/azomethine carbons ($-\text{CH}=\text{N}-$) consistently display the most positive charge values in each compound, identifying them as the principal electrophilic centres, whereas the furan- and quinazoline-ring nitrogen/oxygen atoms represent the most electron-rich, nucleophilic sites. This charge asymmetry supports facile delocalization of electron density along the conjugated azomethine–furan–quinazoline backbone and provides favourable sites for donor–acceptor interactions with the Keap1 Kelch domain, as well as for single-electron/hydrogen-atom abstraction from DPPH radicals during the in vitro antioxidant assay.

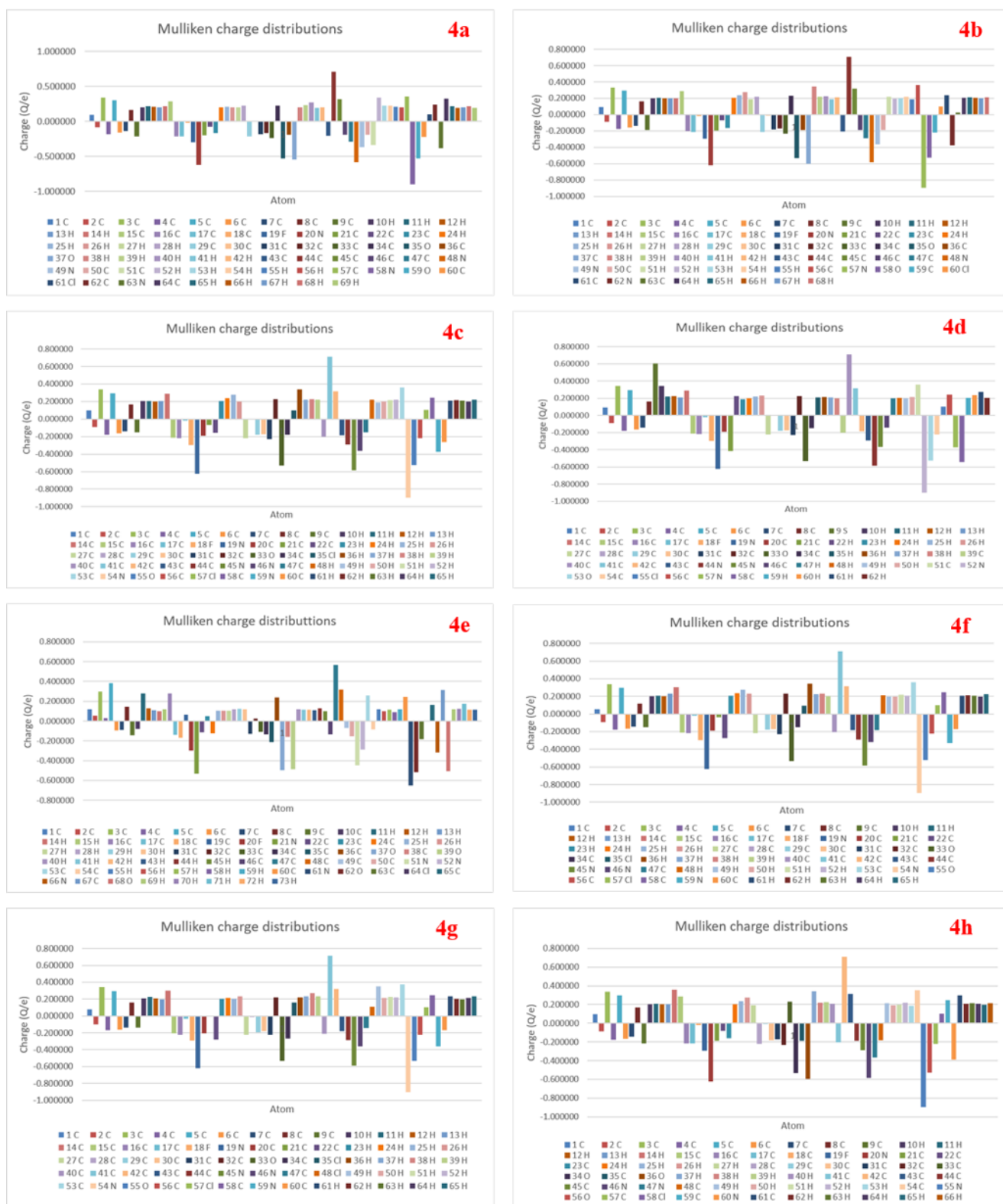


Figure 3. Mulliken atomic charge distribution profiles of compounds 4a–h.

3.2.5 Molecular electrostatic potential

The molecular electrostatic potential (MEP) surfaces (Figure 4), mapped on the total electron density with the standard red (electron-rich, nucleophilic) to blue (electron-deficient, electrophilic) colour scale, show the most negative potential (red regions) localized over the furan-ring oxygen, the azomethine/imine nitrogen atoms, and, in compound 4h, the phenolic oxygen, marking these as the preferred sites for electrophilic attack and hydrogen-bond acceptance. Conversely, the most positive potential (blue regions) is concentrated over the quinazoline N–H and aromatic C–H hydrogens, consistent with their role as hydrogen-bond donors, such as the conserved backbone hydrogen bond to Val420 observed in the Keap1 docking studies (Section 3.4). The coexistence of well-defined electron-rich (furan/azomethine) and electron-poor (N–H) regions within a single, extended conjugated framework is a favourable electronic signature for radical-scavenging molecules, since it enables both hydrogen-atom donation from the N–H/aryl–OH groups and stabilization of the resulting radical by delocalization over the electron-rich heteroaromatic system.

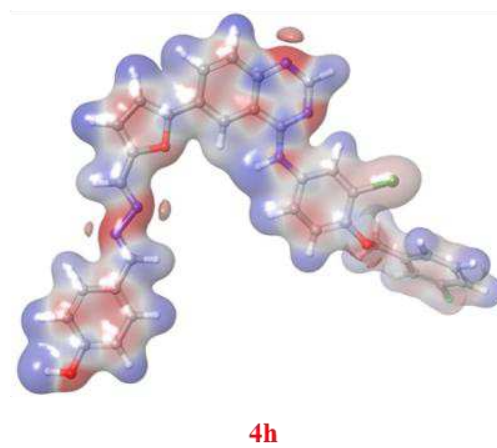
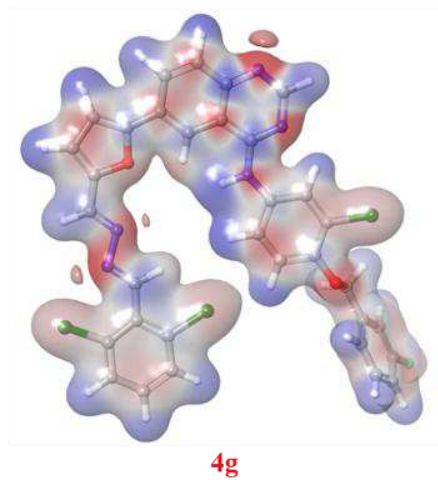
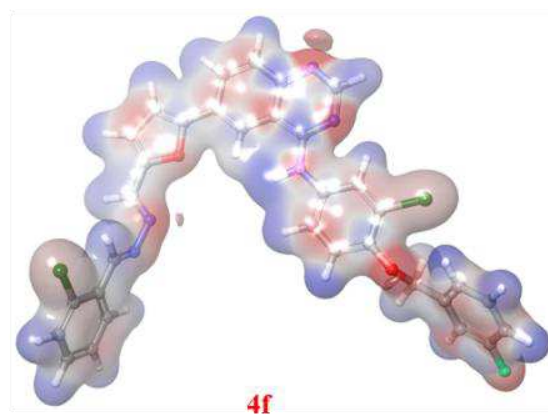
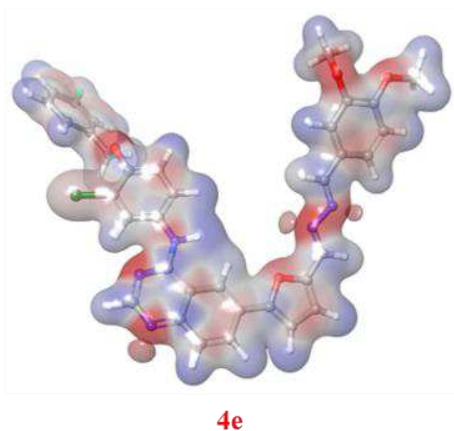
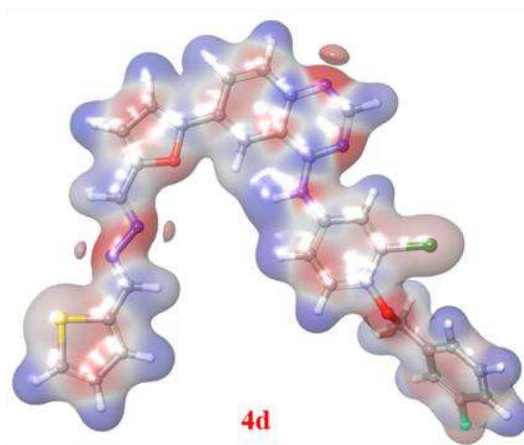
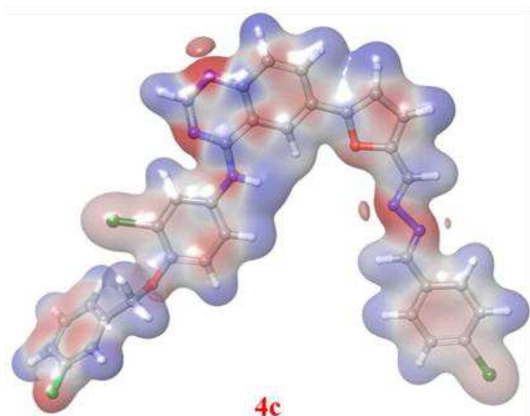
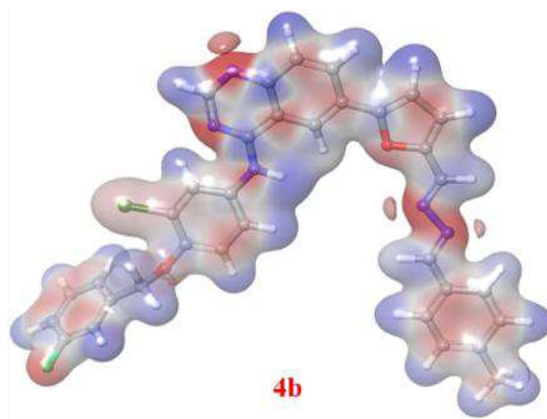
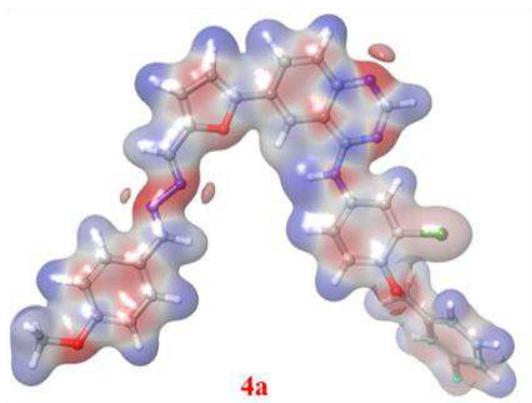


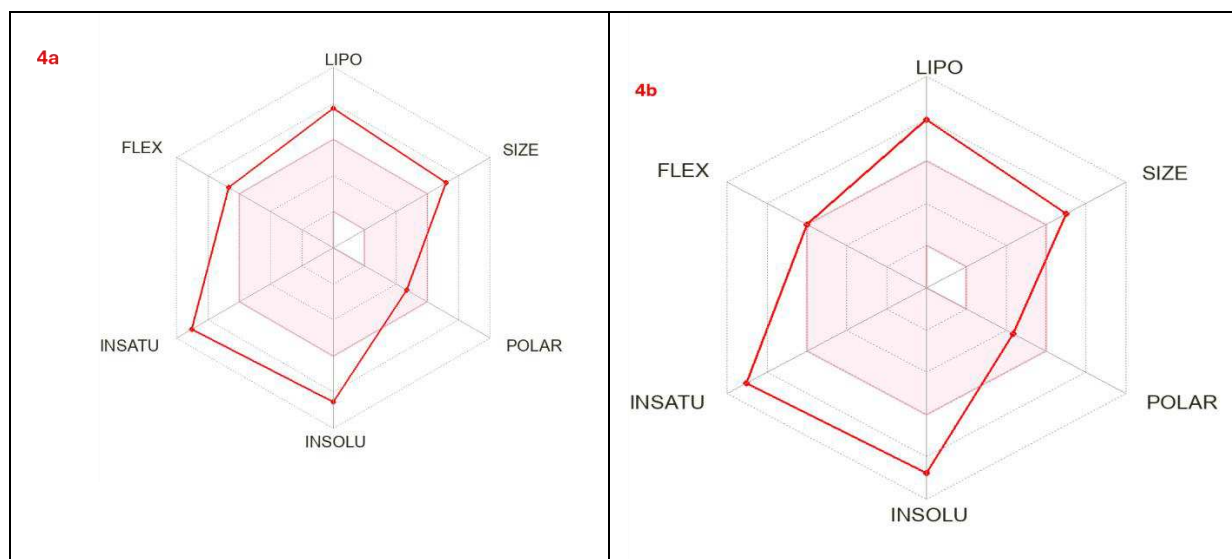
Figure 4. Molecular electrostatic potential (MEP) surface maps of compounds 4a–h (red = electron-rich/nucleophilic region; blue = electron-deficient/electrophilic region).

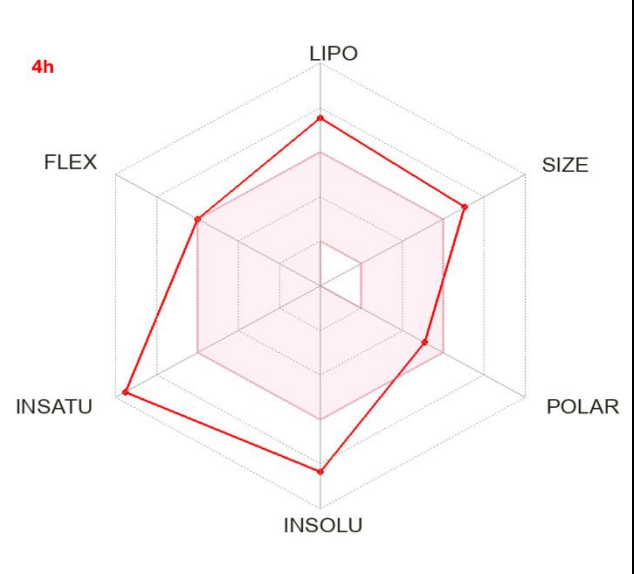
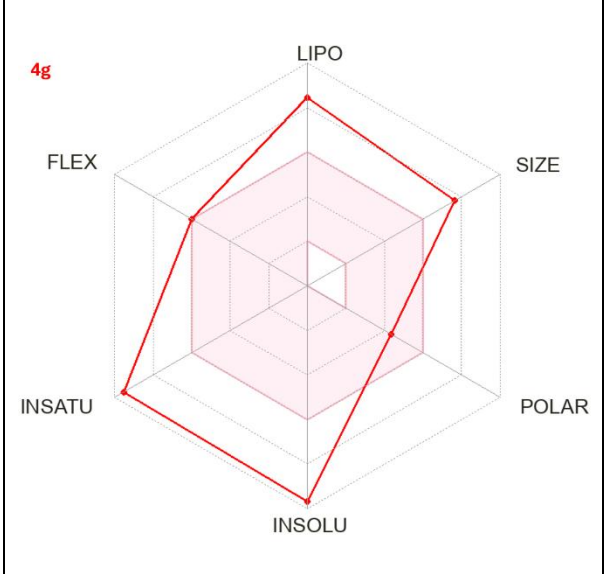
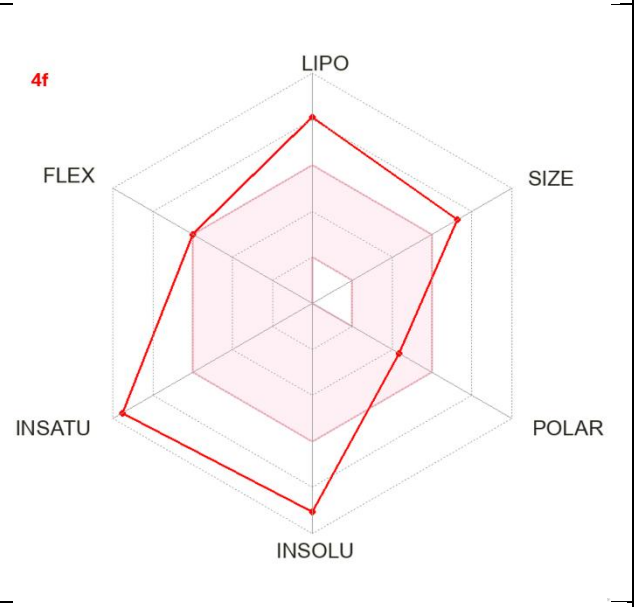
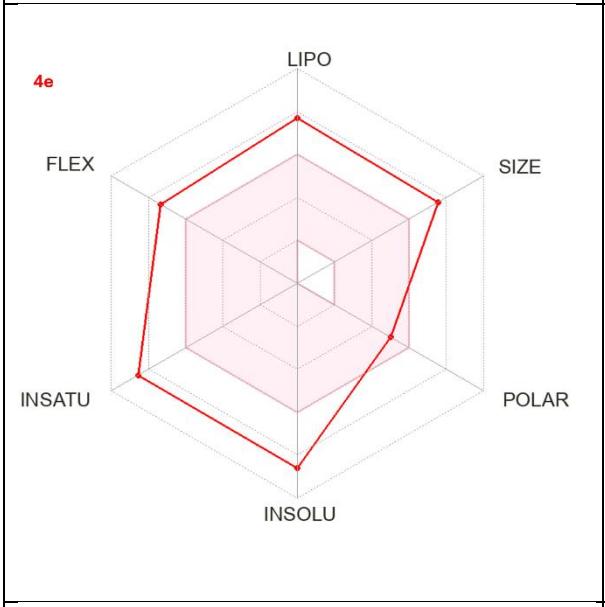
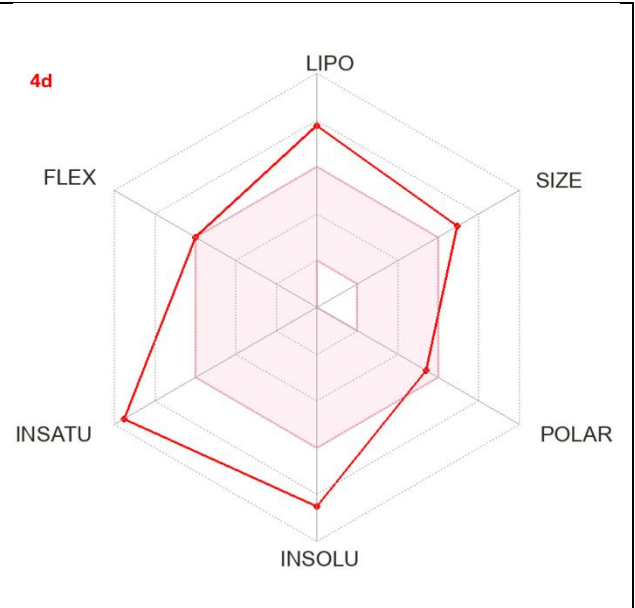
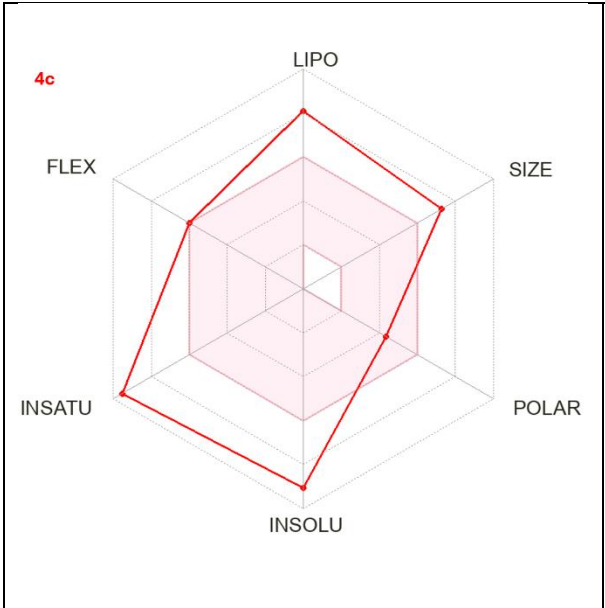
3.3 ADMET Analysis

The predicted physicochemical and drug-likeness properties of compounds 4a–h, computed using SwissADME, are summarized in Table 2 and visualized as bioavailability radar plots in Figure 5. All eight derivatives possess molecular weights in the range of 582.05–644.91 g/mol, appreciably higher than the 500 g/mol threshold recommended by Lipinski's rule of five, a consequence of the extended furan-hydrazone-quinazoline architecture bearing halogenated aryl substituents. Consistently, all compounds returned at least one Lipinski violation on the basis of molecular weight alone, while **4a**, **4b**, **4c**, **4d**, **4f**, and **4g** accumulated a second violation (attributable to a calculated lipophilicity beyond the recommended limit), whereas the more polar dimethoxy- (**4e**) and phenolic (**4h**) analogues incurred only a single violation, reflecting their comparatively lower lipophilicity. The topological polar surface area (TPSA) values (84.90–113.14 Å²) remain below the ~140 Å² threshold generally associated with poor passive membrane permeability, and the number of rotatable bonds (9–11) and hydrogen-bond acceptors/donors (7–9 HBA; 1–2 HBD) fall largely within acceptable medicinal-chemistry ranges, with the exception of **4e**, which alone registers a Veber-rule violation owing to its eleven rotatable bonds. In line with these trends, the calculated oral bioavailability scores are 0.55 for **4e** and **4h**, appreciably higher than the 0.17 recorded for the remaining six analogues, a difference that is also visually reflected in the more balanced, contracted radar profiles of **4e** and **4h** relative to the LIPO/INSATU-skewed profiles of the other derivatives (Figure 5). Notably, this places the two most drug-like compounds of the series (**4e**, **4h**) in partial contrast with the two most potent radical scavengers identified by the DPPH assay (**4d**, **4f**; Section 3.5) a common trade-off encountered in early-stage lead identification between potency and pharmacokinetic optimality, which could be addressed in future analogues through targeted reduction of molecular weight and lipophilicity without compromising the core radical-scavenging pharmacophore. As expected for a small, highly polar natural antioxidant, ascorbic acid violated none of the Lipinski, Ghose, Veber, Egan, or Muegge filters and returned the highest bioavailability score (0.56) among all compounds evaluated.

Table 2. Physicochemical, drug-likeness, and bioavailability parameters of compounds 4a–h and ascorbic acid predicted using SwissADME.

Sr. No	Physiological properties					Drug Likeness properties (#violations)							
	MW	Heavy atoms	Csp3	nROTB	HBA	HBD	TPSA	Lipinski	Ghose	Veber	Egan	Muegge	Bio. Score
4a	606.05	44	0.06	10	8	1	94.13	2	3	0	1	2	0.17
4b	590.05	43	0.06	9	7	1	84.9	2	3	0	1	1	0.17
4c	610.46	43	0.03	9	7	1	84.9	2	3	0	1	2	0.17
4d	582.05	41	0.03	9	7	1	113.14	2	3	0	1	1	0.17
4e	636.07	46	0.09	11	9	1	103.36	1	4	1	1	2	0.55
4f	610.46	43	0.03	9	7	1	84.9	2	3	0	1	2	0.17
4g	644.91	44	0.03	9	7	1	84.9	2	3	0	1	2	0.17
4h	592.02	43	0.03	9	8	2	105.13	1	3	0	1	1	0.55
Ascorbic acid	176.12	12	0.5	2	6	4	107.22	0	2	0	0	1	0.56





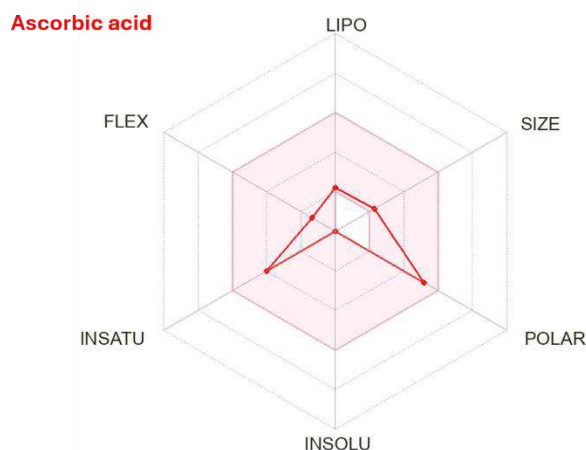


Figure 5. SwissADME bioavailability radar plots of compounds 4a–h and ascorbic acid; the pink hexagonal region represents the optimal physicochemical range for oral bioavailability (LIPO, SIZE, POLAR, INSOLU, INSATU, FLEX).

3.4 Molecular Docking Results

All the synthesized derivatives (**4a–h**) successfully occupied the Kelch domain binding pocket of Keap1 (PDB: 4L7B), the site through which Keap1 normally sequesters and targets the transcription factor Nrf2 for proteasomal degradation, with docking scores ranging from -7.325 to -8.603 kcal/mol (Table 3), values comparable to or more negative than that obtained for the reference antioxidant ascorbic acid (-7.541 kcal/mol). Compound **4f** exhibited the most favourable binding energy (-8.603 kcal/mol), followed by **4d** (-8.325 kcal/mol) and **4g** (-8.126 kcal/mol), while **4h** and **4a** showed comparatively weaker affinities (-7.325 and -7.549 kcal/mol, respectively). A hydrogen bond to the backbone of Val420 was consistently observed for compounds bearing an unsubstituted or para-substituted benzylidene arm (**4a**, **4b**, **4f**, **4h**), anchoring the quinazoline nitrogen within the Kelch β -propeller cavity, whereas the halogenated analogues **4d**, **4e**, and **4g** additionally engaged Arg326 through a halogen bond to their aromatic chlorine substituents, an interaction that mimics the arginine-mediated recognition normally used by Keap1 to clamp the ETGE/DLG degron motifs of Nrf2. Compound **4g**, bearing two ortho-chlorine atoms, formed the most extensive halogen-bonding network (five halogen contacts with Val418, Val465, Val606, Ile559, and Asn517) alongside a cation– π -type contact between Arg326 and the hydrazone ring, consistent with its high binding score. Across the series, the hydrophobic pocket lined by Leu365, Ala366, Cys368, Ile416, Val418, Cys513, Val514, Leu515, Ile559, Thr560, Val561, and the Val604–Ala607 loop provided the principal stabilizing contacts for the

quinazoline-furan core, mirroring the hydrophobic contacts made by ascorbic acid within the same pocket (Ile559, Leu557, Gly558, Val604/605, Ala510, Gly511, Cys513, Ala366). The ability of the synthesized hybrids to competitively occupy the Keap1 Kelch domain suggests that, beyond direct radical quenching, these compounds may also contribute to cellular redox homeostasis indirectly by disrupting the Keap1–Nrf2 protein–protein interaction and thereby facilitating Nrf2 nuclear translocation and up-regulation of downstream antioxidant-response-element (ARE)-driven genes. The docking trends are in good agreement with the DPPH radical-scavenging results (Section 3.5), wherein **4d** and **4f**, which showed among the most negative docking scores, also displayed the lowest (best) IC₅₀ values in the *in vitro* assay.

Table 3. Glide docking scores (kcal/mol) and key binding interactions of compounds 4a–h and ascorbic acid within the Kelch domain of Keap1 (PDB: 4L7B).

Compound	Binding Energy (kcal/mol)	H-Bonds (backbone)	Halogen Bonds	π -Interactions	Key Hydrophobic Contacts
4a	-7.549	Val420	—	—	Leu365, Ala366, Cys368, Ile416, Val418, Ile559, Thr560, Val561, Cys513, Val514, Leu515, Val604, Val606, Ala607
4b	-8.087	Val420	—	—	Leu365, Ala366, Cys368, Ile416, Val418, Val512, Cys513, Val514, Leu515, Val467, Leu468, Ile559, Thr560, Val561, Val604/606
4c	-7.891	—	—	—	Leu365, Ala366, Gly367/368, Val369/370, Val463–467, Ile416, Val418, Ile421, Val512–514, Val604 (purely hydrophobic pocket; no polar contacts marked)
4d	-8.325	—	Arg326 → Cl	Hie516 ↔ fluorophenyl ring (π – π)	Leu365, Cys368, Val369, Ile559, Thr560, Val561, Val604/606/608, Ala607, Leu610, Cys513, Val512/514, Leu515
4e	-8.038	Val467	Arg326 → Cl	—	Ile416, Val418, Val463/465, Ala466, Leu365, Ala366, Val514, Leu515, Ala556, Leu557, Ile559, Val561, Val604/606/608
4f	-8.603	Val420	—	—	Leu365, Ala366, Cys368, Ile416, Val418, Cys513, Val514, Leu515, Ile559, Thr560, Val561, Val604/606
4g	-8.126	Arg326 → ring N; Val514 → HN	Val418 → Cl; Val465 → Cl; Val606 → Cl; Ile559 → Cl; Asn517 → Cl (5 total)	—	Ile416, Leu365, Ala366, Val463/467/468, Cys513, Leu515, Val604/608/610

3.5 Antioxidant assay

The *in vitro* free-radical-scavenging potential of the synthesized furan-quinazoline hydrazone derivatives (**4a–h**) was evaluated using the DPPH radical-scavenging assay, and the results are summarized in Table 4. All eight compounds exhibited concentration-dependent scavenging of the stable DPPH radical, with IC_{50} values ranging from 49.74 ± 2.13 to 90.40 ± 1.98 $\mu\text{g/mL}$, compared with 41.42 ± 0.81 $\mu\text{g/mL}$ for the standard antioxidant ascorbic acid. Among the series, compound **4d** ($IC_{50} = 49.74 \pm 2.13$ $\mu\text{g/mL}$), bearing a thiophen-2-ylmethylene arm, and compound **4f** ($IC_{50} = 55.44 \pm 2.34$ $\mu\text{g/mL}$), bearing a 2-chlorobenzylidene arm, emerged as the most potent radical scavengers, showing activity that approached that of ascorbic acid, followed by **4h** (64.12 ± 3.89 $\mu\text{g/mL}$, phenolic –OH substituent) and **4a** (65.44 ± 1.65 $\mu\text{g/mL}$, 4-methoxybenzylidene). Compounds **4b**, **4g**, **4e**, and **4c** displayed comparatively weaker scavenging activity ($IC_{50} = 69.77\text{--}90.40$ $\mu\text{g/mL}$), with the 3,4-dimethoxy- (**4e**) and 4-chloro-substituted (**4c**) analogues being the least active members of the series. The superior activity of **4d** and **4f** is consistent with the DFT-derived reactivity indices (Section 3.2), which identified these two compounds as possessing the narrowest HOMO–LUMO energy gap and lowest chemical hardness among the series, favouring facile single-electron/hydrogen-atom transfer to the DPPH radical, and is further corroborated by their comparatively strong binding affinities toward the Keap1 Kelch domain in the molecular docking study (Section 3.4). Notably, the presence of an electron-rich heteroaromatic thiophene ring (**4d**) or a halogen substituent capable of stabilizing the resulting radical through inductive/resonance effects (**4f**) appears to enhance radical-scavenging efficiency more effectively than simple alkoxy substitution (**4e**), while the free phenolic –OH group in **4h**, although classically associated with antioxidant activity via direct H-atom donation, showed only moderate activity in this scaffold, suggesting that the overall electronic environment of the conjugated furan-quinazoline-hydrazone framework, rather than any single substituent, governs the radical-scavenging efficiency of this series. Overall, these results indicate that the furan-Schiff-based quinazoline-4-amine scaffold constitutes a promising, structurally tunable antioxidant pharmacophore, with compounds **4d** and **4f** warranting further investigation as lead candidates. The anti-oxidant study of synthesised compounds (4a-4h) graph are shown in Supplementary material 6.

Table 4. DPPH radical-scavenging activity of quinazolin-4(3H)-one derivatives (**4a–4i**) and ascorbic acid^a.

Compound	IC ₅₀ (Mean ± SD, µg/mL)
4a	65.44 ± 1.65
4b	69.77 ± 2.37
4c	90.40 ± 1.98
4d	49.74 ± 2.13
4e	86.85 ± 2.39
4f	55.44 ± 2.34
4g	79.44 ± 3.34
4h	64.12 ± 3.89
Ascorbic acid	41.42 ± 0.81

^aData were expressed as mean ± SD of three experiments

4. Conclusion

In summary, a new series of furan-based quinazoline-4-amine hydrazone (Schiff base) derivatives (**4a–h**) was successfully designed and synthesized in good yields (75–90%) through a sequential nucleophilic aromatic substitution, Suzuki–Miyaura cross-coupling, and hydrazone condensation strategy, and unambiguously characterized by FT-IR, ¹H NMR, ¹³C NMR, and ESI-mass spectrometry. DFT calculations revealed that all the synthesized compounds adopt an extended, planar azomethine-conjugated geometry, with frontier orbital energy gaps ($\Delta E = 3.12\text{--}3.55$ eV), global reactivity descriptors, Mulliken charge distributions, and molecular electrostatic potential surfaces that collectively identified compounds **4d** and **4f** as the most electronically reactive and, hence, the most promising radical-scavenging candidates of the series. Molecular docking of the synthesized derivatives against the Kelch domain of Keap1 (PDB: 4L7B), the master negative regulator of the Nrf2-ARE antioxidant signalling pathway, showed favourable binding energies (-7.325 to -8.603 kcal/mol) comparable to that of ascorbic acid, mediated through a conserved hydrogen bond to Val420, halogen bonding to Arg326, and extensive hydrophobic contacts within the Kelch β -propeller pocket, suggesting a possible dual mode of antioxidant action via both direct radical quenching and Keap1–Nrf2 pathway modulation. Computational ADMET profiling revealed generally drug-like physicochemical properties across the series (molecular weight 582.05–644.91 g/mol; TPSA 84.90–113.14 Å²), with the dimethoxy- and phenolic-substituted analogues **4e** and **4h** showing only a single Lipinski violation and the highest predicted oral

bioavailability scores (0.55) of the series, in partial trade-off with the superior radical-scavenging potency of **4d** and **4f**. Finally, the in vitro DPPH radical-scavenging assay confirmed the antioxidant potential of the series, with compounds **4d** ($IC_{50} = 49.74 \pm 2.13 \mu\text{g/mL}$) and **4f** ($IC_{50} = 55.44 \pm 2.34 \mu\text{g/mL}$) emerging as the most active analogues, in good agreement with their computational reactivity and docking profiles. Taken together, these findings validate the furan-Schiff-based quinazoline-4-amine scaffold as a promising and structurally tunable platform for the future development of potent, selective, and low-toxicity synthetic antioxidant agents, warranting further lead optimization and in vivo evaluation of the most active candidates.

CRedit authorship contribution statement

Sunil D. Narode: Methodology, Investigation, Formal analysis. **Miral Vora:** Original draft, Visualization, Software, Writing – review & editing, Validation, Supervision, Methodology, Investigation, Data curation, Conceptualization, **Jay B Maheta:** Visualization, Investigation, Formal analysis, **Yogesh O. Bhola:** Software, Data curation, manuscript writing, **Darshna K Lakhnotra:** Software, Formal analysis, Data curation, **Nikita J. Patel:** Visualization.

Funding Declaration

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Data availability

All data supporting the findings of this study, including NMR, FT-IR, Mass spectra, computational DFT files, molecular docking results, and ADME analysis, are provided within the manuscript and the Supplementary Information. Additional raw data can be made available from the corresponding author upon reasonable request.

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