

Novel Approach of Quinazoline Scaffold as Anti-inflammatory Agents: Design, Synthesis, Pharmacological Evaluation, and Molecular Docking Study

Deepika Dinesh Adottu ¹, Pattilthodika Suhail ^{2,*}, Arun Rasheed ^{1,*}, Shebina Pareed Rasheed ¹

¹ Department of Pharmaceutical Chemistry, Al Shifa College of Pharmacy, Affiliated to Kerala University of Health Sciences, Perinthalmanna, Kerala, 679325; deepikadinesha26@gmail.com (D.D.A.); arunrasheed@gmail.com (A.R.); shebinaniz@gmail.com (S.P.R.);

² Department of Pharmacology, Al Shifa College of Pharmacy, Affiliated to Kerala University of Health Sciences, Perinthalmanna, Kerala, 679325; ptsuhl@gmail.com;

* Correspondence: ptsuhl@gmail.com (P.T.S.); arunrasheed@gmail.com (A.R.);

Scopus Author ID 57887581500

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Abstract: Quinazoline, an aromatic heterocycle, is composed of two fused six-membered aromatic rings, a benzene ring, and a pyrimidine ring. Numerous quinazoline compounds have been shown to have biological action. The present study aims to synthesize novel quinazoline molecules with second and fourth-substitution patterns to test them as anti-inflammatory agents, with the goal of identifying a dual, selective COX-2/LOX inhibitor that maintains anti-inflammatory benefits without causing GI or asthmatic side effects. After the synthesis of the quinazoline scaffolds, the structures were established based on ¹H NMR, IR, and ¹³C NMR. Q-ToF, Micro mass (ESI-MS) was employed to record the mass spectrometry of all synthesized derivatives. The anti-inflammatory activity of the synthesized compounds was assessed using an in vitro COX inhibition assay, and most showed significant activity. In general, all of our synthetic drugs are more active against both cyclooxygenase enzymes than celecoxib. The IC₅₀ values for COX-2 of the best four derivatives ranged from 0.024 to 0.038 μM, while the reference drug has an IC₅₀ of 0.06 μM. To explain the potential of our synthesized compounds as anti-inflammatory medicines, molecular modeling was also conducted to predict binding affinities, binding modes, and optimal orientations at the COX enzyme active site.

Keywords: quinazoline; anti-inflammatory activity; COX inhibition assay; molecular docking.

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1. Introduction

Quinazoline is an aromatic heterocycle with a bicyclic structure made up of a pyrimidine ring, a benzene ring, and two fused six-membered aromatic rings. It has been discovered that a wide range of quinazoline derivatives exhibit biological activity. There are about 200 known quinazoline and quinoline alkaloids that are physiologically active [1,2]. One of the most potent classes of substances is quinazolines and their derivatives, which exhibit a variety of biological activities, including antibacterial, analgesic, antimicrobial, anti-inflammatory, anticancer, antihypertensive, antifungal, anti-HIV, antioxidant, anticonvulsant, antimalarial, antitumor, and antitubercular [3]. On the other hand, throughout the last several

decades, there has been a lot of research done on the potential connection between the use of non-steroidal anti-inflammatory drugs and increased cancer incidence [4].

Nitrogen- and sulfur-containing heterocyclic rings are highly desirable due to their greater pharmacological and therapeutic activity. These substances serve as the foundation for several pharmacological products. Quinazoline has been selected for this study among all heterocyclic moieties because it exhibits a wide range of pharmacological activity and few adverse effects [5]. The chemical formula for quinazoline, a well-known heterocyclic molecule, is $C_8H_6N_2$. Quinazoline, sometimes called 1,3-diazanaphthalene, is a light-yellow crystalline substance made up of one pyrimidine and one benzene ring. In 1895, August Bischler and Lang reported the synthesis of quinazoline by decarboxylating a 2-carboxy derivative [6]. Quinazolines are also the fundamental units of over 200 naturally occurring alkaloids that have been identified in plants, microbes, and mammals [7,8].

Two essential enzymes in the metabolic pathway, cyclooxygenase (COX) and lipoxygenase (LOX), generate a wide range of inflammatory mediators, the biological precursors of which are arachidonic acid (AA) [9-11]. COX-1 and COX-2 convert AA to the hydroxy endoperoxide PGH₂, which is then broken into its component parts prostaglandins (PGs), prostacyclin (PGI₂), and thromboxane A₂ (TXA₂), in the setting of gastrointestinal tract cytoprotection, control of platelet aggregation, and preservation of renal function. Constitutively active COX-1, which synthesizes prostaglandins [9,11,12]. Proinflammatory stimuli induce COX-2 expression, leading to the production of inflammatory signaling PGs [13,14]. The induction of PGs and LTs is linked to the pathophysiology of a number of inflammatory diseases, including multiple sclerosis, rheumatoid arthritis, psoriasis, COPD, and osteoarthritis. In view of the aforementioned information and the need for a dual-selective COX-2/LOX inhibitor that can sustain anti-inflammatory benefits without causing GI or asthmatic side effects, we decided to synthesize novel quinazoline molecules with second and fourth-substitution patterns to test them as anti-inflammatory agents.

2. Materials and Methods

2.1. Synthesis.

In the first technique, 2-2.5 equivalents of the selected amine in 10 ml of acetonitrile were added to a solution of quinazoline (4 mmol), and the mixture was heated and agitated at 35-50°C for 30-90 minutes. Following the filtration and drying of the precipitate (intermediate), a combination of the intermediate (2 mmol) and the 2-2.5 equivalents of a selected amine in 10 ml of dimethyl formamide was heated at 120-150°C for three to ten hours while a catalyst was present in an inert environment. This was the second procedure. To obtain a crude solid, the reaction mixture was diluted with water after the reaction was complete. After being cleaned with water and allowed to dry at room temperature, the solid was reconstituted into ethanol and acetone.

2.2. Characterisation.

Thin-layer chromatography (TLC) on pre-coated silica G plates was used to assess the purity of the produced derivatives, and a UV chamber was used to view the results. The solvent system used was a 2:1 mixture of n-hexane and ethyl acetate. Using the capillary fusion technique, the melting-point determination device (Sigma Instrument, Mumbai, India) was used to estimate the melting points of the derivatives. The results obtained were not adjusted.

To determine the molecular weight, mass spectra of derivatives were recorded by field desorption in the mass spectrometer's magnetic sector. A voltage of 70 eV was supplied to cause the molecular ions to fragment. The experiment was conducted at SAIF Punjab using a mass spectrophotometer (Waters, Q-ToF, Micro mass (ESI-MS)).

2.3. Spectral analysis.

The predicted structures of the synthesized derivatives were characterized using a variety of spectral studies, including mass spectrometry, ^1H NMR, IR, and ^{13}C NMR spectroscopy. All synthesized derivatives' IR spectra were recorded using a Bruker ATR instrument, and ^1H and ^{13}C NMR spectra were recorded at Al Shifa College of Pharmacy. The Bruker Avance Neo 500 NMR Spectrometer was used to record the spectra of all synthesized derivatives, while Waters, Q-ToF, Micro mass (ESI-MS) was employed to record the mass spectrometry of all samples at the University of Punjab, Chandigarh's Sophisticated Analytical Instrument Facility.

2.3.1. N4-(4-fluorophenyl)-N2-(pyridin-2-yl) quinazoline-2,4-diamine (DD1).

Off-white colored powder, Rf value = 0.52 (n-hexane: ethylacetate, 2:1), IR (ZnSe) peaks 3447cm^{-1} (C=N Stretching), 3190cm^{-1} (-NH- Stretching), 1097cm^{-1} (C-F stretching), ^1H NMR (500) MHz CDCl_3 δ ppm, 10.18(s, ^1H , -NH-), 7.5(s, ^1H , -NH-), ^{13}C NMR(500MHz) CDCl_3 160.66, 159.32, 158.33, 157.40, 135.97, 134.15, 134.13, 133.31, 126.80, 124.22, 124.15, 122.73, 121.18, 121.12, 120.38, 115.78, 115.60, 115.19, 111.42. Mass of 332.12.

2.3.2. N2-(4-chlorophenyl)-N4-(3-(trifluoromethyl) phenyl) quinazoline-2,4-diamine (DD2).

Off-white crystal, Rf value = 0.81 (n-hexane: ethylacetate, 2:1), IR (ZnSe) peaks 3029cm^{-1} (-NH- stretching), 925, 1010, 1147, 1206 (C-F stretching), ^1H NMR (500) MHz DMSO δ ppm, 13.14(s, ^1H , -NH-), 11.09 (s, ^1H , -NH-), ^{13}C NMR(500MHz) DMSO 159.69, 151.86, 137.73, 135.78, 129.88, 129.78, 129.49, 129.23, 128.98, 128.23, 125.82, 124.93, 124.81, 124.76, 124.72, 122.65, 122.43, 120.89, 120.48, 118.36, 110.69. Mass of 415.09.

2.3.3. N2-(2,4-difluorophenyl)-N4-(3-(trifluoromethyl) phenyl) quinazoline-2,4-diamine (DD3).

White color crystal, Rf value = 0.73 (n-hexane: ethylacetate, 2:1), IR (ZnSe) peaks 3378cm^{-1} (-NH- stretching), 1557, 1493, 1450 (C=C, aromatic), ^1H NMR (500) MHz DMSO δ ppm, 10.92(s, ^1H , -NH-), 10.42(s, ^1H , -NH-), ^{13}C NMR (500MHz) DMSO 159.36, 129.71, 129.60, 129.53, 129.34, 129.27, 127.64, 124.94, 124.43, 124.22, 122.90, 120.16, 111.02. Mass of 417.11.

2.3.4 N2-(4-fluorophenyl)-N4-(3-(trifluoromethyl) phenyl) quinazoline-2,4-diamine (DD4).

Pale blue colored crystal, Rf value = 0.69 (n-hexane: ethylacetate, 2:1), IR (ZnSe) peaks 3029cm^{-1} (-NH stretching), 1579, 1536, 1500cm^{-1} (C=C, aromatic), ^1H NMR (500) MHz DMSO δ ppm, 13.16(s, ^1H , -NH), 11.05(s, ^1H , -NH), ^{13}C NMR (500 MHz) DMSO 159.69, 151.86, 137.73, 135.78, 129.88, 129.78, 129.65, 129.49, 126.96, 126.23, 125.82, 124.93, 124.76, 124.72, 122.65, 122.60, 122.43, 120.69, 120.46, 116.36, 110.69. Mass of 400.12.

2.3.5. N4-(4-fluorophenyl)-N2-(3-(trifluoromethyl) phenyl) quinazoline-2,4-diamine (DD5).

White color crystal, Rf value = 0.58 (n-hexane: ethylacetate, 2:1), IR (ZnSe) peaks 3029 cm^{-1} (-NH- stretching), 1579, 153,6 1500 (C=C, aromatic), ^1H NMR (500) MHz DMSO δ ppm, 10.33(s, ^1H , -NH-), 9.76 (S, ^1H , -NH-), ^{13}C NMR (500MHz) CDCl_3 159.95, 134.26, 125.53, 123.71, 123.27, 122.94, 115.19, 115.12, 115.01, 114.94, 111.07. Mass of 399.12.

2.3.6. N2-(p-tolyl)-N4-(3-(trifluoromethyl) phenyl) quinazoline-2,4-diamine (DD6).

Buff color crystal, Rf value = 0.45 (n-hexane: ethylacetate, 2:1), IR (ZnSe) peaks 3029 cm^{-1} (-NH- stretching), 1579, 153,6 1500 (C=C, aromatic), ^1H NMR (500) MHz DMSO δ ppm, 11.32(s, ^1H , -NH-), 11.16 (S, ^1H , -NH-), ^{13}C NMR (500MHz) CDCl_3 178.44, 170.06, 150.05, 140.39, 136.58, 134.91, 132.86, 131.57, 130.35, 129.06, 128.23, 127.85, 124.88, 122.36, 119.49, 118.66, 117.79, 116.52, 115.33, 114.02, 113.20, 109.82, 20.48. Mass of 393.87.

2.3.7. N2-(4-chloro-3-fluorophenyl)-N4-(4-fluorophenyl) quinazoline-2,4-diamine (DD7).

Pale yellow color crystal, Rf value = 0.74 (n-hexane: ethylacetate, 2:1), IR (ZnSe) peaks 3029 cm^{-1} (-NH- stretching), 1579, 153,6 1500 (C=C, aromatic), ^1H NMR (500) MHz DMSO δ ppm, 12.89(s, ^1H , -NH-), 10.71 (S, ^1H , -NH-), ^{13}C NMR (500MHz) CDCl_3 159.04, 134.85, 126.05, 124.02, 115.29, 115.23, 115.11, 115.05, 110.74, 55.90, 18.43. Mass of 383.09.

2.3.8. N4-(p-tolyl)-N2-(3-(trifluoromethyl) phenyl) quinazoline-2,4-diamine (DD8).

Pale yellow color crystal, Rf value = 0.63 (n-hexane: ethylacetate, 2:1), IR (ZnSe) peaks 3029 cm^{-1} (-NH- stretching), 1579, 153,6 1500 (C=C, aromatic), ^1H NMR (500) MHz DMSO δ ppm, 12.84 (s, ^1H , -NH-), 10.79 (S, ^1H , -NH-), 3.33(t, 3H, -CH₃), ^{13}C NMR (500MHz) CDCl_3 178.44, 170.06, 150.05, 140.39, 136.58, 134.91, 132.86, 131.57, 130.35, 129.06, 128.23, 127.85, 124.88, 122.36, 119.49, 118.66, 117.79, 116.52, 115.33, 114.02, 113.20, 109.82, 20.48. Mass of 394.11.

2.3.9. N4-(3,4-difluorophenyl)-N2-(3-(trifluoromethyl) phenyl) quinazoline-2,4-diamine (DD9).

Pale brown color crystal, Rf value = 0.68 (n-hexane: ethylacetate, 2:1), IR (ZnSe) peaks 3110 cm^{-1} (-NH- stretching), 1595, 1508, 1300 (C=C, aromatic), ^1H NMR (500) MHz DMSO δ ppm, 13.16(s, ^1H , -NH-), 11.11 (S, ^1H , -NH-), ^{13}C NMR (500MHz) CDCl_3 160.66, 159.32, 158.33, 157.40, 156.43, 152.00, 135.97, 134.15, 134.15, 132.31, 126.20, 124.22, 124.15, 122.73, 121.12, 120.28, 115.78, 115.60, 115.35, 115.18, 111.42. Mass of 417.11.

2.3.10. N2-(3,4-difluorophenyl)-N4-(3-(trifluoromethyl) phenyl) quinazoline-2,4-diamine (DD10).

Pale brown color crystal, Rf value = 0.68 (n-hexane: ethylacetate, 2:1), IR (ZnSe) peaks 3496 cm^{-1} (-NH- stretching), 1590, 1500, 1300 (C=C, aromatic), ^1H NMR (500) MHz δ ppm, 13.34 (s, ^1H , -NH-), 11.28 (S, ^1H , -NH-), ^{13}C NMR (500MHz) CDCl_3 160.66, 159.32, 158.33, 157.40, 156.42, 152.00, 135.97, 134.15, 134.18, 133.31, 126.80, 124.22, 124.15, 122.73, 121.12, 120.38, 115.78, 115.60, 115.38, 115.19, 111.42. Mass of 417.11.

2.4. Biological screening.

2.4.1. *In vitro* cyclooxygenase inhibition assay.

Each newly developed material's ability to inhibit COX-1 and COX-2 enzymes *in vitro* was examined. For this, Cayman Chemicals, USA, supplied the Cayman colorimetric COX (ovine) inhibitor screening test kit. According to a previously published method and the instructions that came with the assay kit, the reagents were prepared and tested.

2.4.2. Molecular docking.

The study used Glide v5.6 163 in Maestro Suite for *in silico* enzymatic inhibition studies, performing grid-based ligand docking with energetics to identify favorable interactions between small ligand molecules and larger receptor molecules, with residues from the PDB file defining the active site. Here, utilized X-ray crystallographic 3D structures of Cyclooxygenase-2 (PDB ID: 1CX2) complexed with SC-558 (celecoxib), a selective inhibitor, from the RCSB protein data bank, <https://www.rcsb.org/structure/1CX2>, to evaluate its selective COX-2 inhibitory activity *in silico*. The crystallographic structure was analyzed using the Schrodinger suite, and protein preparation was done using Maestro 9.3108's 'protein preparation wizard'. Side chains were corrected, hydrogens were added, and steric clashes were minimized using the Impact refinement module. Water molecules were deleted, and energy was minimized using the OPLS-2005 force field. A receptor grid was generated, including all amino acids within 20 Å. Ligand docking calculations were performed using the "extra Precision" scoring function for all enzymes, with the glide score generating the single best pose for a particular ligand [15].

2.4.3. *In silico* prediction of ADME.

The ADMET properties were predicted using the Qikprop setting in the Maestro panel, with vsqb as the solvation model and opsl4 as the force field for energy minimization. Physical descriptors were used to demonstrate properties, including hydrogen bond acceptors, hydrogen bond donors, surface area, polarizability, IC₅₀ value, and human oral absorption. Lipinski's "Rule of Five" was used to evaluate a compound's drug-likeness. The test assessed molecular weights, lipophilicity, hydrogen bond acceptors, and donors. A drug-like molecule should have a molecular weight below 500 Da, a hydrogen bond donor ratio below five, and a hydrogen bond acceptor ratio below 10. The water-octanol coefficient ratio should also be below five.

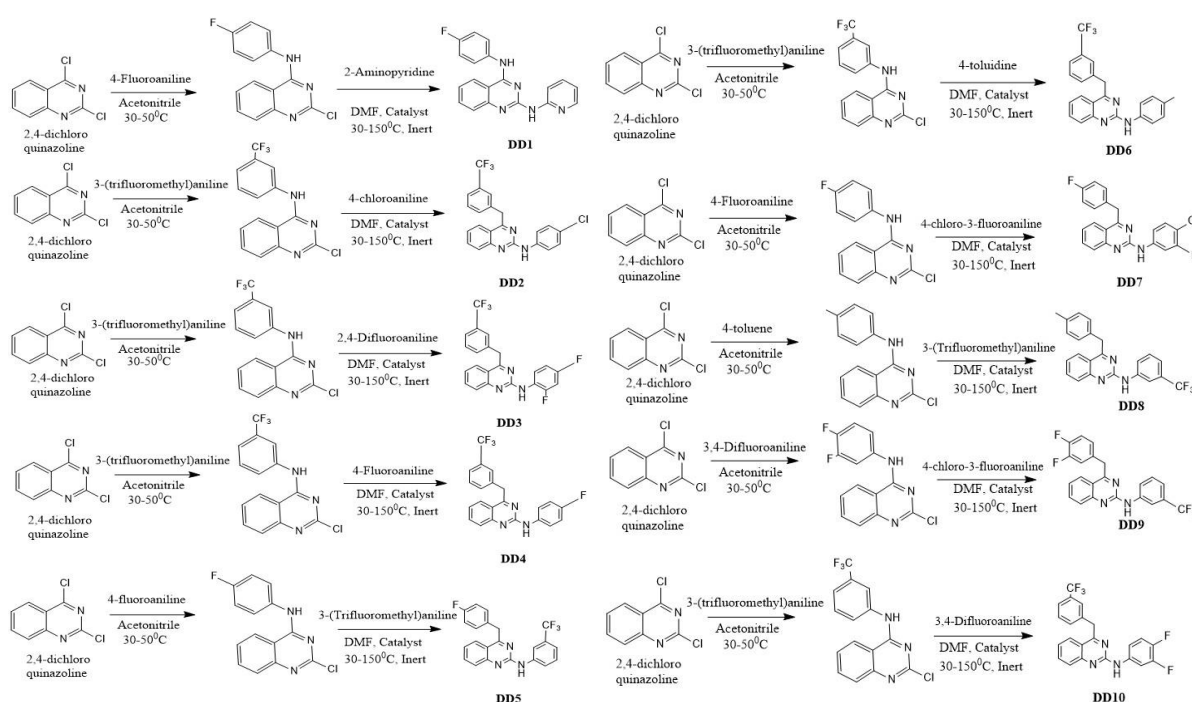
3. Results and Discussion

Inflammation and pain are the hallmarks of almost all illnesses, as they arise from various causes, such as accidents, infections, etc. Pain and inflammation are signs that COX and 5-LOX are present. The constitutive enzyme is called COX-1, whereas the inducible enzyme is called COX-2. Abnormal conditions such as inflammation, arthritis, and carcinogenesis are known to be associated with high levels of these enzymes. Although they block COX-2, non-steroidal anti-inflammatory medicines (NSAIDs) have a number of negative side effects, including stroke, stomach ulcers, and heart failure [16].

3.1. Chemistry.

The current study aims to create a range of substituted quinazolines with distinct amino substituents at the second and fourth positions.

Scheme 1 depicts the synthesis approach for the target compounds. The 2,4-dichloroquinazoline reacts with different aniline reagents to form a 4-substituted quinazoline intermediate. In the second step, these intermediates react with the same reagents to get the second and fourth substituted final products. DD1-10 was prepared from 2,4-dichloroquinazoline as the starting compound. The second and fourth substituted quinazolines (DD1-10) were prepared by refluxing (10-12 hours) 2,4-dichloroquinazoline with 4-fluoroaniline; acetonitrile at 30-50°C forms an intermediate with substitution in the second position; and 2-aminopyridine and DMF at 30-150°C form DD1. The reaction intermediates for the production of DD2-10 were 3-(trifluoromethyl)aniline and 4-chloroaniline [17,18].



Scheme 1. Synthesis of second and fourth substituted quinazolines. DD1-10 was synthesized from 2,4-dichloroquinazoline in the presence of different aniline reagents, at 30-150°C, and in inert conditions. DMF-dimethylformamide.

3.2. Biological activity.

3.2.1. *In vitro* COX inhibition assay.

Using an ovine COX test kit, all produced compounds were put through an *in vitro* COX inhibition experiment. Table 1 displays the formula $SI = IC_{50}(COX-1)/IC_{50}(COX-2)$, which was used to compute selectivity index (SI) values and identify half-maximal inhibitory concentrations (IC_{50} μ M). Comparing the DD2-5 to the maligned drugs celecoxib and indomethacin, the test of the newly synthesized quinazoline derivatives showed that the former was more effective in inhibiting COX-1. They demonstrated a 5-7-fold selectivity index towards COX-2 and around 5-10-fold inhibitory activity of the medication that was maligned. However, DD2-5 was much less selective and active than celecoxib, which may be considered a plus as it might lessen the harmful effects of highly selective COX-2 inhibitors on the cardiovascular system [19,20].

Table 1. COX-1/COX-2 inhibition assay result of synthesized quinazoline derivatives.

Derivative Code	COX-1 IC ₅₀ μM	COX-2 IC ₅₀ μM	Selectivity index (SI) ¹
Indomethacin	0.052	0.49	0.11
Celecoxib	13.6	0.06	226.7
DD1	12.6	1.78	7.08
DD2	8.2	0.024	341.7
DD3	6.5	0.038	171.05
DD4	10.4	0.501	20.76
DD5	4.3	0.5	8.6
DD6	3.6	1.02	3.53
DD7	13.4	2.15	6.2
DD8	8.7	1.87	4.65
DD9	12.6	11.04	1.14
DD10	15.6	10.58	1.47

¹Each and every IC₅₀ result are given as a triple mean with a standard deviation of less than 10% of the mean.

The selectivity index (SI) was calculated using the formula:

$$SI = \frac{IC_{50} \text{ of COX } - 1}{IC_{50} \text{ of COX } - 2}$$

3.2.2. Molecular docking study.

Our goal is to forecast the binding affinities, binding modes, and optimal orientations of synthetic compounds at the COX enzyme active site (PDB ID: 1CX2) to justify their potential as anti-inflammatory medicines. For all docking and scoring calculations, Schrödinger Maestro version 10.4 and Glide version 6.9 were used. The docked compounds' relative orientation to the co-crystallized ligands, the hydrogen bonds they produced with the surrounding amino acids, and the scoring functions were used to estimate the binding affinities to the COX-2 active site [21,22]. It is known that DD2-4 had a hydrogen bond between the nitrogen atom and the substituted aniline group with Tyr 355 amino acid of the COX-2 active binding pocket (Figure 1). Our findings also indicate that COX-1 inhibitors may also inhibit COX-2, indicating equipotency. This finding can be explained by the possibility that these ligands engage with the active site and adopt a different orientation from that in the initial reference. It also showed the least energy-conformer molecules of the selected compounds DD2-DD5. In relation to the celecoxib reference, the 2D and 3D binding models of compounds DD2-5 into the crystal structures of COX-2 were shown. Table 2 displays the binding energies of these substances.

Table 2. Docking score of selected ligands against the COX-2 enzyme.

Compound Code	Docking score (kcal/mol)
Celecoxib	-11.94
DD1	-8.834
DD2	-10.405
DD3	-10.254
DD4	-10.091
DD5	-10.004
DD6	-7.964
DD7	-4.77
DD8	-5.748
DD9	-4.85
DD10	-9.829

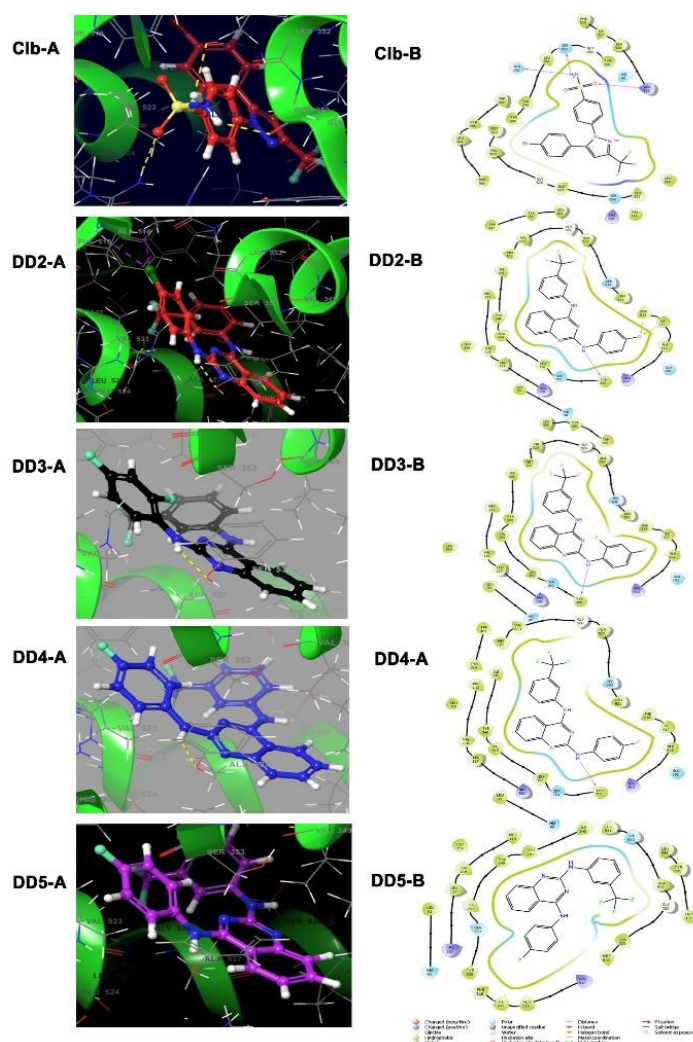


Figure 1. Docking and binding pattern of celecoxib (Cib) along with the synthesized quinazoline derivatives (DD2-5) into the COX-2 active site (PDB ID: 1CX2). A-indicated the 3D view, and B-indicated the 2D view.

Celecoxib was successfully molecularly docked onto the COX-2 isoenzyme as a reference. As seen in Figure 1, it forms hydrogen bonds with Arg513, Ser353, and Gln192 to bind to the following amino acids. The compound DD2 interacts with Tyr 355 via a favorable hydrogen bond. It also forms a halogen bond with Phe518 and Ile517. This indicates a potentially stabilizing non-covalent interaction between the compound and COX-2. The DD3-4 compounds interacted with Tyr355 in the side pocket of COX-2 through a hydrogen bond.

3.2.3. ADME prediction.

Lipinski's "Rule of Five" was used to evaluate a compound's drug-likeness. The test assessed molecular weights, lipophilicity, hydrogen bond acceptors, and hydrogen bond donors. A drug-like molecule should have a molecular weight of less than or equal to 500 Da, fewer hydrogen bond donors than 5, and fewer hydrogen bond acceptors than or equal to 10. The water-octanol coefficient ratio should also be less than five [23-25]. Jorgensen's "Rule of Three" states that a compound is more likely to be orally available if it complies with all or some of the rules. According to this rule, a compound must comply with some factors like the aqueous solubility (QLogS) > -5.7, the apparent Caco-2 cell permeability (QPPCaco) > 22 nm/s, where less than 25 is poor, and above 500 is great, and the number of primary metabolites < 7 [26]. Table 3 shows that the ADME properties of all synthesized molecules were satisfactory, indicating they may be non-toxic and have a high affinity for the drug target's <https://biointerfaceresearch.com/>

binding pocket. All derivatives followed the "Lipinski Rule Five" and were predicted to have human oral absorption and cell permeability.

Table 3. *In silico* ADME and Lipinski Rule Five properties of Quinazoline Scaffolds.

Compound Code	CNS	DonorHB	acceptHB	QPlogP O/W	QPPCaco	%Human oral absorption
DD1	1	2	3	5.84	4549.646	100
DD2	1	2	3	5.049	4159.209	100
DD3	2	2	3	5.257	5015.209	100
DD4	2	2	3	5.065	4597.543	100
DD5	1	2	3	5.739	4534.361	100
DD6	1	2	3	5.5	4163.072	100
DD7	1	2	3	5.682	4603.457	100
DD8	1	2	3	5.463	4494.11	100
DD9	1	2	3	5.38	4385.163	100
DD10	1	2	3	5.933	4377.354	100

4. Conclusions

A new series of amino-substituted quinazoline derivatives was synthesized and evaluated for *in silico* and *in vitro* anti-inflammatory activity. The results revealed that all the tested compounds exhibited marked activity when compared with the reference drug. DD2-5 showed high *in vitro* anti-inflammatory activity for the synthesized compounds and high docking scores in molecular docking studies. In the *in vitro* anti-inflammatory assay, the IC₅₀ values against the COX-2 enzyme were 0.024, 0.038, 0.501, and 0.5 μ M, indicating a higher affinity for COX-2 than for COX-1. After docking into the COX-2 active site, compounds DD2, DD3, DD4, and DD5 showed excellent binding pocket fit and significant interactions with key amino acid residues. Using the ADMET program, appropriate physicochemical characteristics and good predictions of pharmacokinetic parameters were demonstrated. As a result, these active substances show promise and warrant further investigation as potential concurrent COX-2 inhibitors.

Author Contributions

Conceptualization, D.D.A., P.T.S., and A.R.; methodology, D.D.A. and P.T.S.; software, D.D.A. and P.T.S.; validation, D.D.A., P.T.S., and A.R.; formal analysis, P.T.S. and A.R.; investigation, D.D.S. and P.T.S.; resources, S.P.R. and A.R.; data curation, P.T.S. and S.P.R.; writing-original draft preparation, P.T.S.; writing-review and editing, P.T.S. and A.R.; supervision, A.R. and P.T.S. All authors have read and agreed to the published version of the manuscript.

Institutional Review Board Statement

Not applicable.

Informed Consent Statement

Not applicable.

Data Availability Statement

Data supporting the findings of this study are available upon reasonable request from the corresponding author.

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Conflicts of Interest

The authors declare no conflict of interest.

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