RESEARCH ARTICLE

Synthesis and Evaluation of Novel Quinazolin-4-(3h)-one Analogues for their Anti-Inflammatory Activity

RS Kulkarni[1*], NK Sathish[2], AA Kempwade[1], SA Kavatagimath[3]

[1]*KLES's College of Pharmacy, Nipani, Karnataka, India.*
[2]*Government College of Pharmacy, Bengaluru, Karnataka, India.*
[3]*KLE College of Pharmacy, Belagavi, KLE Academy of Higher Education and Research, Belagavi, Karnataka, India.*

Received: 08th September, 2023; Revised: 18th October, 2023; Accepted: 16th November, 2023; Available Online: 25th December, 2023

ABSTRACT

New 2, 3-disubstituted quinazolin-4-(3H)ones was conceived and synthesized through the substitution of various primary amines at the 3-position and a range of aldehydes at the 2-position. These compounds were characterized using elemental analysis, IR spectroscopy, 1H NMR spectroscopy and MS. Subsequently, the anti-inflammatory activity of these newly developed quinazoline derivatives was investigated by *in-vitro* protein denaturation method. *In-vitro* studies revealed that compounds Q_{B1}, Q_{B2}, $Q_{B4,}$ Q_{B8}, $Q_{B9,}$ $Q_{F1,}$ $Q_{F3,}$ $Q_{F4,}$ Q_{F8} and Q_{F10} have significant anti-inflammatory potential. In-vivo anti-inflammatory properties of QB2 and QF8 were tested in carrageenan-induced paw edema. Research findings demonstrated that compounds Q_{B2} and Q_{F8} have significant anti-inflammatory properties.

Keywords: Quinazolin-4-(3H)ones, Anti-inflammatory, Lipophilicity, NSAID.

International Journal of Pharmaceutical Quality Assurance (2023); DOI: 10.25258/ijpqa.14.4.20

How to cite this article: Kulkarni RS, Sathish NK, Kempwade AA, Kavatagimath SA. Synthesis and Evaluation of Novel Qquinazoline-4-(3h)-one Analogues for their Anti-Inflammatory Activity. International Journal of Pharmaceutical Quality Assurance. 2023;14(4):933-941.

Source of support: Nil.

Conflict of interest: None

INTRODUCTION

Through excluding pathogens and stimulating tissue healing and recovery, inflammation serves as a defense mechanism against bacteria, viruses, toxins, and illnesses, and is thus a process that has been conserved throughout evolution.[1] Systemic or localized, the intensity and duration of inflammation determine the metabolic and neuroendocrine alterations that occur. These modifications are made to save metabolic resources and supply the active immune system with more resources.[2] One of the pivotal medical revelations within the last two decades has been the recognition of the significant role played by the immune system and inflammatory processes in the prevailing morbidity and mortality rates globally.[3]

Ischemic heart disease, stroke non-alcoholic fatty liver disease, chronic kidney disease, autoimmune circumstances have all been linked to chronic inflammation, and together they account for more than half of all deaths worldwide today.[4] Recent research has connected prenatal environments to the later risk of chronic inflammation. Furthermore, it is understood that its impact endures across the entire lifespan, influencing adult health and mortality risk.[5]

NSAIDs find extensive application in the management of inflammation. NSAIDs function by inhibiting cyclooxygenases, which are enzymes responsible for catalyzing the synthesis of cyclic endoperoxidases from arachidonic acid to produce prostaglandins. COX-1 and COX-2 are separate isoenzymes. Prostaglandins are produced in large quantities via cyclooxygenase-2 (COX-2) at inflammatory areas. The nitrogen heterocyclic molecule known as quinazoline, or 1,3-diazanaphthalene, is structurally distinguished by a double ring. The pyrimidine ring is fused to two wadjacent carbon atoms in this structure, making it look like a benzene ring. The initial synthesis of a quinazoline derivative, specifically 2-cyano-3,4-dihydro-4-oxoquinazoline, was accomplished by Griess *et al.* in the year 1869 through a condensation process. By decarboxylating the 2-carboxy molecule, Bischler and Lang were able to synthesize related quinazoline analogues.[6] Gabriel and Colman (1993) produced a variety of quinoazoline derivatives and conducted a thorough examination of their properties.[7] The quinazoline compounds can be categorized as either quinazolin-2(1H)-ones or quinazolin-4(3H)-ones, reliant on the placement of oxo or keto group. Among these, the latter type tends to prevail, appearing prominently as intermediate products in various planned organic synthetic schemes.[8] Quinazolinone derivatives have demonstrated significant and diverse biological activities, including

**Author for Correspondence: rupesh.k88@gmail.com*

antibacterial, antifungal, anticonvulsant and anti-inflammatory properties. Enhancements in the activity are attainable through subtle adjustments to the substituents on the fundamental quinazoline nucleus. Recent advancements in quinazoline derivatives have demonstrated improved efficacy and reduced toxicity, motivating our pursuit of synthesizing novel compounds.[9] In this context, in the present study, various aromatic benzaldehydes were introduced onto 2-methyl-3-aryl quinazolin-4-(3H)-ones under optimal conditions which caused formation of 2,3-disubstituted quinazolin-4-(3H)ones (Table 1). ^{13}C-NMR, IR, 1H-NMR, and MS were used to look at the chemical structures of all substances that were produced. Subsequently, composites were subjected to screening for their anti-inflammatory properties both *in-vitro* and *in-vivo* conditions using protein denaturation and carrageenan-induced paw edema test in rats respectively.[10]

MATERIALS AND METHODS

All chemicals required for the study were procured from Fine Chemicals. For TLC Silica gel G plates measuring 3 x 8 cm were employed. The melting points were ascertained using the Thermonik melting point apparatus through open glass capillary tubes, and no corrections were made. The infrared spectra (Thermo Nicolate IR-700 Spectrometer with KBr) were analyzed, and the results were presented in terms of cm^{-1}. ^{1}H-NMR spectra were collected in either $CDCl_3$ or DMSO-d6, and TMS was used as a standard. The percentage changes in chemicals are denoted in ppm. We used a 400 MHz FT-NMR Spectrometer to get our readings. The mass spectra were recorded in JMS-700. The purity of compounds was regularly assessed through TLC employing silica gel, and the spots were subsequently subjected to iodine vapor exposure.[10] The lipophilicity of the compounds was assessed utilizing the ALOGPS software. The physicochemical information of the synthesized compounds is summarized in Table 2.

Preparation of 2-Methyl Benzoxazin-4-one from Anthranilic acid

In a round-bottomed flask, Anthranilic acid and acetic anhydride were combined in a 1:2 ratio. The mixture was subjected to gentle heating and refluxing for one hour. The surplus acetic anhydride was subsequently removed through distillation. Carefully, we poured the resulting liquid into a beaker containing crushed ice, swirled it constantly, and then strained it. Ethyl acetate was used to re-crystallize the obtained crude product.[11]

Preparation of 2-methyl-3-aryl quinazolin-4-(3H)-ones

In a round-bottomed flask, an equimolar (0.01 mol) mixture of 2-methyl-1,3-benzoxazin-4-one, aryl amine and anhydrous zinc chloride was subjected to reflux for a duration of 9 hours in the presence of anhydrous ethanol. Subsequently, any surplus anhydrous ethanol was removed via distillation. After mixing, the liquid was left to cool to ambient temperature and then dispensed over ice. After getting solid result, it was cleaned up by re-crystallization with ethanol.[12]

Preparation of 2, 3-disubstituted quinazolin-4-(3H)ones using aromatic substituted Aldehydes

In a round-bottomed flask, an equimolar amount (0.01 mol) of the respective quinazoline, anhydrous zinc chloride and different aromatic aldehydes were combined and subjected to reflux for 22 hours with anhydrous ethanol. Any surplus anhydrous ethanol was subsequently distilled off. The resultant mixture from the reaction was allowed to cool and carefully dumped into ice-cold water. After filtration and drying, the ultimate product was obtained and subsequently purified through re-crystallization using an appropriate solvent.[13]

Anti-inflammatory Action

Anti-inflammatory action of synthesized compounds was evaluated by *in-vitro* and *in-vivo* models.

In-vitro Method

Albumin denaturation inhibition

The Mizushima method was employed with slight adjustments. The reaction mixture comprised varying concentrations of the test sample and a 1% aqueous solution of bovine albumin fraction. Slight quantity of 1N HCl was introduced to the reaction mixture to attain the desired pH. Subsequently, samples were subjected to an incubation period at 37°C for 20 minutes, heating at 57°C for an additional 20 minutes. Following the cooling process, turbidity levels were assessed spectrophotometrically at 660 nm. The same procedure was followed for the standard drug aspirin. The procedure was repeated three times.[14] The following method was used to determine the percentage of protein denaturation inhibition:

$$Percentage\ Inhibition = \frac{Abs_{control} - Abs_{sample}}{Abs_{control}} \times 100$$

In-vivo Anti-inflammatory Activity

Based on the results obtained during the *in-vitro* protein denaturation study, Q_{B2} and Q_{F8} (showing significant activity) were selected for further evaluation of their *in-vivo* anti-inflammatory action using the carrageenan-induced paw edema method.

Carrageenan-induced Paw Edema Model

Albino Wister rats, weighing between 150 to 200 grams, were selected and maintained in accordance with standard protocols at the central animal facility of the college. Ethical approval for the research was approved by the Institutional Animal Ethics Committee (Approval No. SACCP/IAEC/11/2009-10). These rats were housed in the pharmacology branch of the college for a period of 7 days to allow them to acclimate to the controlled environment at a temperature of 20ºC. Previously beginning of testing, animals underwent an overnight fast, with access to water provided *ad libitum*.

Twenty-four male albino wistar rats, with weights ranging from 150 to 200 g, were segregated into four groups (n = 6). Group I functioned as the control and was administered 1% carboxymethyl cellulose (CMC) suspension orally.

Group II, identified as the standard group, was administered Diclofenac sodium suspension at a dosage of 25 mg/kg.

Table 1: Spectral data of FTIR, ^{1}H NMR, ^{13}C NMR and Mass for newly synthesized Quinazolin-4-(3H)one analogues

3-(4-bromophenyl)-2-[(*E*)-2-(4-chlorophenyl) ethenyl]quinazolin-4(3*H*)-one [Q_{B1}]	Colorless Crystals, Yield: 55%, m.p: 92ºC, Anal. Calcd. for $C_{22}H_{14}BrClN_2O$ (FW437.71): C. 64.58, H.4.52, N. 9.41% Found: C. 64.58, H. 4.52, N.9.41% FTIR (KBr): 1685.67(C=O), 1089.75 (Ar-Br), 1654.99 (C=C), 755.63 (Ar-Cl). ^{1}H NMR (200 MHz, $DMSOd_6$ δ / ppm):8-8.2 (m, 12H, Ar-H), 7.5, 7.7 (2d, 2H, CH=CH), 3.1 (s, 3H, CH_3). MS: m/z (%)437 (50%) [M^+]. ^{13}C NMR (200 MHz, $DMSOd_6$, δ / ppm): 172.3 (C_2), 171.9 (C_4), 137.8 (C_5), 136.4 (C_6), 142.5 (C_7), 131. 4 (C_8), 166.0 (C_9), 130.2 (C_{10}), 120.8 (C_{11}), 146.2 (C_{12}), 142.2 (C_{13}), 136.8 (C_{14}), 137.8 (C_{15}), 150.4 (C_{16}), 137.8 (C_{17}), 136.8 (C_{18}), 144.3 ($C_{19,20}$), 137.3 (C_{21}), 133.8 (C_{22}), 135.0 (C_{23}), 130.5(C_{24}), 31.2 (CH_3).
3-(4-bromophenyl)-2-{(*E*)-2-[4-(dimethyl amino) phenyl]ethenyl}quinazolin-4(3*H*)-one [Q_{B2}]	Pale green color crystals, Yield: 58%, m.p. 98°C, Anal. Calcd. for $C_{24}H_{20}BrN_3O$.(FW446.33): C. 64.58, H. 4.52, N. 9.41% Found: C. 64.58, H. 4.52, N. 9.41% FTIR (KBr): 1664.57(C=O), 1065.05(Ar-Br), 1654.99(C=C), 1165.04(C-N). ^{1}H NMR (200 MHz, $DMSOd_6$ δ / ppm): **δ 2.91**(s, CH_3), 6.55-7.19 (m, Ar-H), 6.6 (d, CH=CH). MS: m/z (%)446 (40%) [M^+]. ^{13}C NMR (200 MHz, $DMSOd_6$, δ / ppm): 164.0 (C_2), 161.9 (C_4), 157.8 (C_5), 145.4 (C_6), 152.3 (C_7), 131. 9 (C_8), 146.1 (C_9), 130.4 (C_{10}), 112.8 (C_{11}), 137.2 (C_{12}), 127.8 (C_{13}), 126.0 (C_{14}), 140.3 (C_{15}), 130.9 123.5 (C_{17}), 129.1 (C_{18}), 143.4 ($C_{19,20}$), 148.3 (C_{21}), 123.3 (C_{22}), 135.0 (C_{23}),
3-(4-bromophenyl)-2-[(*E*)-2-(4-nitro phenyl)ethenyl]quinazolin-4(3*H*)-one [Q_{B3}]	Colourless crystals, Yield: 53%, m.p: 136°C, Anal. Calcd. for $C_{22}H_{14}BrN_3O_3$ (FW448.26): C. 58.95, H3.15, N. 9.37% Found: C. 58.95, H. 3.15, N. 9.37 FTIR (KBr) :): 1685.73 (C=O), 1103.21 (Ar-Br), 1655.07 (C=C), 3100 (Ar-CH), 1508.77 (C-NO_2).^{1}H NMR (200 MHz, $DMSOd_6$ δ / ppm): 8-8.2 (m, 12H, Ar-H), 7.5, 8.7 (2d, 2H, CH=CH), 3.0 (s, 3H, CH_3). MS: m/z (%) 448 (55%) [M^+]. ^{13}C NMR (200 MHz, $DMSOd_6$, δ / ppm): 163.9(C_2), 170.1 (C_4), 138.2 (C_5), 136.1 (C_6), 142.6(C_7), 131.3 (C_8), 156.2 (C_9), 130.7 (C_{10}), 121.5 (C_{11}), 147.9 (C_{12}), 126.0 (C_{13}), 165.5 (C_{14}), 124.9 (C_{15}), 138.0 (C_{16}), 130.2(C_{17}), 136.5 (C_{18}), 137.3 (C_{19}), 131.5 ($C_{20, 24}$), 143.0 (C_{22}), 138.4 ($C_{21,23}$), 32.2 (CH_3).
3-(4-bromophenyl)-2-[(*E*)-2-(4-hydroxy-3-methoxyphenyl)ethenyl]quinazolin-4(3*H*)-one [Q_{B4}]	Pale green color crystals, Yield: 58%, m.p136°C, Anal. Calcd. for $C_{23}H_{17}BrN_2O_{33}$ (FW449.29): C.58.95, H. 3.15, N. 9.37% Found: C. 58.95, H. 3.15, N. 9.37% FTIR (KBr): 1685.68 (C=O), 1124.70 (Ar-Br), 1637.47 (C=C), 3490.50 (OH). ^{1}H NMR (200 MHz, $DMSOd_6$ δ / ppm):9.6 (s, 1H, OH), 8-8.2 (m, 12H, Ar-H), 7.5, 7.7 (2d, 2H, CH=CH), 3.1-5.0 (2s, 6H, CH_3, OCH_3). MS: m/z (%)449 (40%) [M^+]. ^{13}C NMR (200 MHz, $DMSOd_6$, δ / ppm): 173.0 (C_2), 171.9 (C_4), 137.8 (C_5), 135.4 (C_6), 142.3 (C_7), 131. 9 (C_8), 156.1 (C_9), 130.4 (C_{10}), 122.8 (C_{11}), 147.2 (C_{12}), 137.8 (C_{13}), 121.0 (C_{14}), 160.3 (C_{15}), 150.9 (C_{16}), 125.5 (C_{17}), 129.1 (C_{18}), 143.4 ($C_{19,20}$), 138.3 (C_{21}), 133.3 (C_{22}), 135.0 (C_{23}),
3-(4-bromophenyl)-2-[(*E*)-2-(4-hydroxy phenyl) ethenyl] quinazolin-4(3*H*)-one [Q_{B5}]	Color less Crystals, Yield: 57%, m.p: 102ºC, Anal. Calcd. for $C_{22}H_{15}BrN_2O_2$ (FW 419.27.40): C. 63.02, H. 3.61, N. 6.68%. Found: C. 77.91, H. 5.21, N. 7.92 %. FTIR (KBr): 3081 (O-H), 1709 (C=O), 3068 (C-H), 1620 (C=C), 1384 (C=N). ^{1}H NMR (200 MHz, DMSOd6 δ / ppm): 9.7 (s, 1H, OH), 8-8.2 (m, 12H, Ar-H), 7.5, 7.7(2d, 2H, CH=CH), 3.2 (s, 3H, CH3). MS: m/z (%)419 (54%) [M^+]. ^{13}C NMR (200 MHz, DMSOd6, δ / ppm): 171.0 (C2), 170.2 (C4), 136.3 (C5), 137.0 (C6), 143.6 (C7), 131. 9 (C8), 156.7 (C9), 129.9 (C10), 131.2 (C11), 145.2 (C12), 125.6 (C13), 163.5 (C14), 125.0 (C15), 138.4 (C16), 130.3 (C17), 136.8 (C18), 144.6 (C19, 20), 139.5 (C21), 133.3 (C22), 135.5 (C23), 130.3 (C24), 30.4 (CH_3).
3-(4-bromophenyl)-2-[(*E*)-2-(3-ethoxy-4-hydroxyphenyl) ethenyl]quinazolin-4(3*H*)-one [Q_{B6}]	Pale yellow crystals, Yield: 55%, MP: 220ºC, Anal. Calcd. for $C_{24}H_{19}BrN_2O_3$ (FW463.32): C. 62.22, H. 4.13, N. 6.05.% Found: C. 62.22, H. 4.13, N. 6.05.% FTIR (KBr1685.65 (C=O), 1028.43 (Ar-Br), 1637.67 (C=C), 3497.12 (OH). ^{1}H NMR (200 MHz, $DMSOd_6$ δ / ppm): 8.6 (s, 1H, OH),7-8.7 (m, 12H, Ar-H), 6.8, 6.6 (2d, 2H, CH=CH), 4.5 (s, 3H, OCH_3), 3.1 (s, 3H,CH_3). MS: m/z (%)463 (55%) [M^+]. ^{13}C NMR (200 MHz, $DMSOd_6$, δ / ppm): 166.9(C_2), 163.5 (C_4), 137.9 (C_5), 136.2 (C_6), 136.0 (C_7), 131. 7 (C_8), 126.8 (C_9), 120.3(C_{10}), 112.1 (C_{11}), 136.2 (C_{12}), 125.8 (C_{13}), 112.3 (C_{14}), 140.9 (C_{15}), 139.9 (C_{16}), 115.3 (C_{17}), 120.2 (C_{18}), 128.3 (C_{19}), 121.0 ($C_{20, 24}$), 133.0 (C_{22}), 128.8 ($C_{21,23}$), 23.1 (CH_3).

3-(4-bromophenyl)-2-[(*E*)-2-(4-methoxy phenyl)ethenyl] quinazolin-4(3*H*)-one [Q_{B7}]

Colourless Crystals, Yield: 68%, m.p: 80ºC, Anal. Calcd. for $C_{23}H_{17}BrN_2O_2$ (FW433.29): C. 63.75, H. 3.95, N. 6.47% .Found: C. 63.75, H. 3.95, N. 6.47%. FTIR (KBr1685.70 (C=O), 1024.70 (Ar-Br), 1637.51 (C=C). ^{1}H NMR (200 MHz, DMSOd6 δ / ppm): 7-8.2 (m, 12H, Ar-H), 6.5, 6.7 (2d, 2H, CH=CH). 4.0 (s,3H, OCH_3), 2.1 (s,3H,CH3), MS: m/z (%)433 (55%) [M^+]. ^{13}C NMR (200 MHz, DMSOd6, δ / ppm): 163.0 (C2), 160.8(C4), 127.8 (C5), 126.6 (C6), 132.5 (C7), 121. 4 (C8), 146.3 (C9), 119.9 (C10), 112.0 (C11), 137.2 (C12), 114.0 (C13), 156.6 (C14), 113.2 (C15), 128.4 (C16), 120.7 (C17), 126.4 (C18), 134.6 (C19,20), 128.3 (C21), 123.3 (C22), 125.0 (C23), 120.5 (C24), 20.2 (CH_3), 55.3 (OCH_3).

3-(4-bromophenyl)-2-[(*E*)-2-(3-nitro phenyl)ethenyl]quinazolin-4(3*H*)-one [Q_{B8}]

Pale green Crystals, Yield: 66%, m.p: 67ºC, Anal. Calcd. for $C_{22}H_{14}BrN_3O_3$ (FW448.26): C. 58.95, H. 3.15, N. 9.37% .Found: C. 58.95, H. 3.15, N. 9.37%. FTIR (KBr): 1665.57(C=O), 1066.05(Ar-Br), 1655.99(C=C), 1166.04(C-N).. ^{1}H NMR (200 MHz, DMSO$_6$ δ / ppm): **δ** 2.99(s, CH_3), 6.7-7.19 (m, Ar-H), 6.9 (d, CH=CH). MS: m/z (%)448 (40%) [M^+]. ^{13}C NMR (200 MHz, DMSO$_6$, δ / ppm): 165.0 (C_2), 168.9 (C_4), 159.8 (C_5), 148.4 (C_6), 157.3 (C_7), 138. 9 (C_8), 148.1 (C_9), 132.4 (C_{10}), 118.8 (C_{11}), 147.2 (C_{12}), 137.8 (C_{13}), 128.0 (C_{14}), 140.3 (C_{15}), 130.9 (C_{16}), 123.5 (C_{17}), 129.1 (C_{18}), 143.4 ($C_{19,20}$), 148.3 (C_{21}), 123.3 (C_{22}), 135.0 (C_{23}),.

3-(4-bromophenyl)-2-[(*E*)-2-(3-methoxy phenyl)ethenyl] quinazolin-4(3*H*)-one [Q_{B9}]

Colourless Crystals, Yield: 52%, m.p: 142ºC, Anal. Calcd. for $C_{23}H_{17}BrN_2O_2$ (FW433.29): C. 63.75, H. 3.95, N. 6.47% .Found: C. 63.75, H. 3.95, N. 6.47%. FTIR (KBr1688.70 (C=O), 1034.70 (Ar-Br), 1647.51 (C=C).. ^{1}H NMR (200 MHz, DMSOd6 δ / ppm): 7-8.3 (m, 12H, Ar-H), 6.5, 6.8 (2d, 2H, CH=CH). 4.6 (s,3H, OCH_3), 2.8 (s,3H,CH3), MS: m/z (%)433 (55%) [M^+]. ^{13}C NMR (200 MHz, DMSOd6, δ / ppm): 163.0 (C2), 165.8(C4), 127.8 (C5), 129.6 (C6), 138.5 (C7), 131. 4 (C8), 156.3 (C9), 119.9 (C10), 112.0 (C11), 137.2 (C12), 114.0 (C13), 156.6 (C14), 113.2 (C15), 128.4 (C16), 120.7 (C17), 126.4 (C18), 134.6 (C19,20), 128.3 (C21), 123.3 (C22), 125.0 (C23), 120.5 (C24), 20.2 (CH_3), 65.3 (OCH_3).

(E)-2-(3,4,5-trimethoxystyryl)-3-(4-Bromo phenyl)Quinazoline-4(3H)-one [Q_{B10}]

Pale green colour crystals, Yield: 52%, MP: 142ºC, Anal. Calcd. for $C_{25}H_{21}BrN_2O_4$ (FW 493.34): C. 60.86, H. 4.29, N. 5.68.% Found: C. 60.86, H. 4.29, N. 5.68.% FTIR (KBr1685. 1685.74 (C=O), 1002.84 (Ar-Br), 1637.52 (C=C). ^{1}H NMR (200 MHz, DMSOd$_6$ δ / ppm): 8.8 (s, 1H, OH),7-8.8 (m, 12H, Ar-H), 7.8, 6.6 (2d, 2H, CH=CH), 4.8 (s, 3H, OCH_3), 3.9 (s, 3H,CH_3). MS: m/z (%)493(55%) [M^+]. ^{13}C NMR (200 MHz, DMSOd$_6$, δ / ppm): 166.9(C_2), 163.5 (C_4), 137.9 (C_5), 136.2 (C_6), 136.0 (C_7), 131. 7 (C_8), 126.8 (C_9), 120.3(C_{10}), 112.1 (C_{11}), 136.2 (C_{12}), 125.8 (C_{13}), 112.3 (C_{14}), 140.9 (C_{15}), 139.9 (C_{16}), 115.3 (C_{17}), 120.2 (C_{18}), 128.3 (C_{19}), 121.0 ($C_{20,24}$), 133.0 (C_{22}), 128.8 ($C_{21,23}$), 23.1 (CH_3).

2-[(*E*)-2-(4-chlorophenyl)ethenyl]-3-(4-fluorophenyl)quinazolin-4(3*H*)-one [Q_{F1}]

Colourless Crystals, Yield: 60%m.p: 92ºC, Anal. Calcd. for $C_{22}H_{14}ClFN_2O$ (FW. 367.81): C. 70.12, H. 3.74, N. 9.41% Found: C. . 70.12, H. 3.74, N.9.41% FTIR (KBr): 1686.67(C=O), 1090.75 (Ar-F), 1664.99 (C=C), 765.63 (Ar-Cl). ^{1}H NMR (200 MHz, DMSOd$_6$ δ / ppm):9-8.2 (m, 12H, Ar-H), 8.5, 8.7 (2d, 2H, CH=CH), 4.1 (s, 3H, CH_3). MS: m/z (%)367 (50%) [M^+]. ^{13}C NMR (200 MHz, DMSOd$_6$, δ / ppm): 182.3 (C_2), 181.9 (C_4), 147.8 (C_5), 146.4 (C_6), 152.5 (C_7), 141. 4 (C_8), 176.0 (C_9), 140.2 (C_{10}), 130.8 (C_{11}), 136.2 (C_{12}), 152.2 (C_{13}), 146.8 (C_{14}), 147.8 (C_{15}), 160.4 (C_{16}), 147.8 (C_{17}), 146.8 (C_{18}), 154.3 ($C_{19,20}$), 147.3 (C_{21}), 143.8 (C_{22}), 145.0 (C_{23}), 140.5(C_{24}), 41.2 (CH_3).

3-(4-fluorophenyl)-2-[(*E*)-2-(4-nitro phenyl)ethenyl]quinazolin-4(3*H*)-one [Q_{F2}]

Pale yellow crystals, Yield: 54%, m.p. 110°C, Anal. Calcd. for $C_{22}H_{14}FN_3O_3$.(FW385.43): C. 74.79, H. 5.23, N. 10.90% Found: C. 74.79, H. 5.23, N. 10.90%. FTIR (KBr): 1664.57(C=O), 1118.12 (Ar-F), 1654.99(C=C), 1165.04(C-N).. ^{1}H NMR (200 MHz, DMSOd$_6$ δ / ppm): **δ** 2.91(s, CH_3), 7.55-7.19 (m, Ar-H), 7.6 (d, CH=CH). MS: m/z (%)487 (40%) [M^+]. ^{13}C NMR (200 MHz, DMSOd$_6$, δ / ppm): 174.0 (C_2), 171.9 (C_4), 167.8 (C_5), 145.4 (C_6), 162.3 (C_7), 141. 9 (C_8), 156.1 (C_9), 140.4 (C_{10}), 122.8 (C_{11}), 147.2 (C_{12}), 137.8 (C_{13}), 136.0 (C_{14}), 140.3 (C_{15}), 140.9 (C_{16}), 133.5 (C_{17}), 139.1 (C_{18}), 123.4 ($C_{19,20}$), 138.3 (C_{21}), 113.3 (C_{22}), 125.0 (C_{23}),

3-(4-fluorophenyl)-2-[(*E*)-2-(4-nitro phenyl)ethenyl]quinazolin-4(3*H*)-one [Q_{F3}]

Pale yellow crystals, Yield: 66%, m.p: 128ºC C, Anal. Calcd. for (FW387.36): C. 68.21, H.3.64, N. 10.85% Found: C. 68.21, H. 3.15, N.10.85
FTIR (KBr): 1676.06 (C=O), 1104.12 (Ar-F), 1637.59 (C=C). ^{1}H NMR (200 MHz, DMSOd$_6$ δ / ppm): 8-8.8 (m, 12H, Ar-H), 8.5, 8.7 (2d, 2H, CH=CH), 4.0 (s, 3H, CH_3). MS: m/z (%)387(55%) [M^+]. ^{13}C NMR (200 MHz, DMSOd$_6$, δ / ppm): 173.9(C_2), 180.1 (C_4), 148.2 (C_5), 146.1 (C_6), 152.6(C_7), 141.3 (C_8), 166.2 (C_9), 140.7 (C_{10}), 131.5 (C_{11}), 157.9 (C_{12}), 136.0 (C_{13}), 175.5 (C_{14}), 134.9 (C_{15}), 148.0 (C_{16}), 140.2(C_{17}), 136.5 (C_{18}), 137.3 (C_{19}), 141.5 ($C_{20,\ 24}$), 153.0 (C_{22}), 148.4 ($C_{21,23}$), 42.2 (CH_3).

3-(4-fluorophenyl)-2-[(*E*)-2-(4-hydroxy- 3-methoxyphenyl) ethenyl]quinazolin-4(3*H*)-one [Q_{F4}]

Pale yellow crystals, Yield: 55% m.p 88ºC C, Anal. Calcd. for $C_{23}H_{17}FN_2O_3$ (FW388.39): C. 71.13, H. 4.41, N. 7.21% Found: C. 71.13, H. 4.41, N. 7.21%
FTIR (KBr): 1655.12 (C=O), 1162.57 (Ar-F), 1648.60 (C=C), 3401.089 (OH).. ^{1}H NMR (200 MHz, DMSOd$_6$ δ / ppm):9.2 (s, 1H, OH),8-8.7 (m, 12H, Ar-H), 7.7, 7.9 (2d, 2H, CH=CH), 4.1-5.8 (2s, 6H, CH_3, OCH_3). MS: m/z (%)388 (40%) [M^+]. ^{13}C NMR (200 MHz, DMSOd$_6$, δ / ppm): 183.0 (C_2), 181.9 (C_4), 147.8 (C_5), 145.4 (C_6), 152.3 (C_7), 141. 9 (C_8), 166.1 (C_9), 140.4 (C_{10}), 132.8 (C_{11}), 157.2 (C_{12}), 147.8 (C_{13}), 131.0 (C_{14}), 170.3 (C_{15}), 140.9 (C_{16}), 135.5 (C_{17}), 139.1 (C_{18}), 153.4 ($C_{19,20}$), 148.3 (C_{21}), 143.3 (C_{22}), 145.0 (C_{23}),

3-(4-fluorophenyl)-2-[(*E*)-2-(4-hydroxy phenyl)ethenyl] quinazolin-4(3*H*)-one [Q_{F5}]

Pale yellow crystals, Yield: 64%, m.p: 85°C, Anal. Calcd. for $C_{22}H_{15}FN_2O_2$. (FW358.36): C73.73, H. 4.42, N. 7.82%. Found: C73.73, H. 4.42, N. 7.82%.
FTIR (KBr): 3089 (O-H), 1712 (C=O), 3078 (C-H), 16410 (C=C), 1388 (C=N). ^{1}H NMR (200 MHz, DMSOd6 δ / ppm): 9.4 (s, 1H, OH), 8-8.9 (m, 12H, Ar-H), 7.5, 7.9(2d, 2H, CH=CH), 4.2 (s, 3H, CH3). MS: m/z (%)388 (54%) [M^+]. ^{13}C NMR (200 MHz, DMSOd6, δ / ppm): 181.0 (C2), 180.2 (C4), 146.3 (C5), 147.0 (C6), 153.6 (C7), 141. 9 (C8), 166.7 (C9), 139.9 (C10), 141.2 (C11), 155.2 (C12), 135.6 (C13), 173.5 (C14), 135.0 (C15), 148.4 (C16), 140.3 (C17), 146.8 (C18), 154.6 (C19, 20), 149.5 (C21), 143.3 (C22), 145.5 (C23), 140.3 (C24), 34 (CH_3).

2-[(*E*)-2-(3-ethoxy-4-hydroxyphenyl) ethenyl]-3-(4-fluorophenyl)quinazolin-4(3*H*)-one [Q_{F6}]

Pale yellow crystals, Yield: 48%, MP: 150ºC, Anal. Calcd. for $C_{24}H_{19}BrN_2O_3$ (FW402.41): C. 62.22, H. 4.13, N. 6.05.% Found: C. 62.22, H. 4.13, N. 6.05.%
FTIR (KBr1683.65 (C=O), 1022.41 (Ar-Br), 1635.67 (C=C), 3491.12 (OH).. ^{1}H NMR (200 MHz, DMSOd$_6$ δ / ppm): 8.8 (s, 1H, OH),7-8.3 (m, 12H, Ar-H), 6.2, 6.8 (2d, 2H, CH=CH), 4.5 (s, 3H, OCH_3), 3.9 (s, 3H,CH_3). MS: m/z (%)402 (55%) [M^+]. ^{13}C NMR (200 MHz, DMSOd$_6$, δ / ppm): 176.9(C_2), 168.5 (C_4), 139.9 (C_5), 145.2 (C_6), 151.0 (C_7), 144. 7 (C_8), 136.8 (C_9), 130.3(C_{10}), 122.1 (C_{11}), 146.2 (C_{12}), 135.8 (C_{13}), 122.3 (C_{14}), 150.9 (C_{15}), 149.9 (C_{16}), 125.3 (C_{17}), 130.2 (C_{18}), 138.3 (C_{19}), 131.0 ($C_{20,\ 24}$), 143.0 (C_{22}), 138.8 ($C_{21,23}$), 43.1 (CH_3).

3-(4-fluorophenyl)-2-[(*E*)-2-(4-methoxy phenyl)ethenyl] quinazolin-4(3*H*)-one [Q_{F7}]

Pale yellow crystals, Yield: 70%, m.p: 74ºC, Anal. Calcd. for $C_{23}H_{17}FN_2O_2$ (FW372.39): C. 74.18, H. 4.60, N. 7.52% .Found: C. 63.75, H. . 4.60, N. 7.52%.
FTIR (KBr): 1676.01 (C=O), 1118.12 (Ar-F), 1637.87 (C=C)). ^{1}H NMR (200 MHz, DMSOd6 δ / ppm): 7-8.2 (m, 12H, Ar-H), 6.5, 6.7 (2d, 2H, CH=CH). 4.0 (s,3H, OCH_3), 2.1 (s,3H,CH3), MS: m/z (%)372(55%) [M^+]. ^{13}C NMR (200 MHz, DMSOd6, δ / ppm): 163.0 (C2), 160.8(C4), 127.8 (C5), 126.6 (C6), 132.5 (C7), 121. 4 (C8), 146.3 (C9), 119.9 (C10), 112.0 (C11), 137.2 (C12), 114.0 (C13), 156.6 (C14), 113.2 (C15), 128.4 (C16), 120.7 (C17), 126.4 (C18), 134.6 (C19,20), 128.3 (C21), 123.3 (C22), 125.0 (C23), 120.5 (C24), 20.2 (CH_3), 55.3 (OCH_3).

3-(4-fluorophenyl)-2-[(*E*)-2-(3-nitro phenyl)ethenyl]quinazolin-4(3*H*)-one [Q_{F8}]

Pale yellow crystals, Yield: 69%, m.p. 70°C, Anal. Calcd. for $C_{22}H_{14}FN_3O_3$.(FW387.36): C. 74.18, H. 4.60, N. 7.52% Found: C. 74.18, H. 4.60, N. 7.52%
FTIR (KBr): 1685.64 (C=O), 1161.43 (Ar-F), 1637.57 (C=C). ^{1}H NMR (200 MHz, DMSOd$_6$ δ / ppm): **δ** 3.91(s, CH_3), 8.0-8.19 (m, Ar-H), 7.6 (d, CH=CH). MS: m/z (%)387 (40%) [M^+]. ^{13}C NMR (200 MHz, DMSOd$_6$, δ / ppm): 178.0 (C_2), 177.9 (C_4), 168.8 (C_5), 148.4 (C_6), 169.3 (C_7), 148. 9 (C_8), 166.1 (C_9), 148.4 (C_{10}), 127.8 (C_{11}), 149.2 (C_{12}), 138.8 (C_{13}), 136.0 (C_{14}), 140.3 (C_{15}), 140.9 (C_{16}), 133.5 (C_{17}), 139.1 (C_{18}), 133.4 ($C_{19,20}$), 132.3 (C_{21}), 119.3 (C_{22}), 165.0 (C_{23}),

3-(4-fluorophenyl)-2-[(*E*)-2-(3-methoxy phenyl)ethenyl]quinazolin-4(3*H*)-one [Q_{F9}]	Pale yellow crystals, Yield: 55%, m.p: 155ºC, Anal. Calcd. for $C_{23}H_{17}FN_2O_2$ (FW372.39): C. 74.18, H. 4.60, N. 7.52% .Found: C. 63.75, H. . 4.60, N. 7.52%. FTIR (KBr): 1677.01 (C=O), 1128.12 (Ar-F), 1647.87 (C=C)). ^{1}H NMR (200 MHz, DMSOd6 δ / ppm): 7-8.8 (m, 12H, Ar-H), 6.5, 6.9 (2d, 2H, CH=CH). 4.8 (s,3H, OCH_3), 2.8 (s,3H,CH3), MS: m/z (%)372(55%) [M$^+$]. ^{13}C NMR (200 MHz, DMSOd6, δ / ppm): 163.0 (C2), 160.8(C4), 127.8 (C5), 126.6 (C6), 132.5 (C7), 121. 4 (C8), 146.3 (C9), 119.9 (C10), 112.0 (C11), 137.2 (C12), 114.0 (C13), 156.6 (C14), 113.2 (C15), 128.4 (C16), 120.7 (C17), 126.4 (C18), 134.6 (C19,20), 128.3 (C21), 123.3 (C22), 125.0 (C23), 120.5 (C24), 20.2 (CH_3), 55.3 (OCH_3).
(E)-2-(3,4,5-trimethoxystyryl)-3-(4-Fluro phenyl)Quinazoline-4(3H)-one [Q_{F10}]	Pale yellow crystals, Yield: 48%, MP: 150ºC, Anal. Calcd. for $C_{25}H_{21}FN_2O_4$ (FW432.44): C. 69.44, H. 4.89, N. 6.48. % Found: C. 69.44, H. 4.89, N. 6.48. % FTIR (KBr1683.65 (C=O), 1322.41 (Ar-F), 1636.67 (C=C), 3481.12 (OH).. ^{1}H NMR (200 MHz, DMSO$_6$ *δ* / ppm): 8.7 (s, 1H, OH), 7-8.3 (m, 12H, Ar-H), 6.2, 6.8 (2d, 2H, CH=CH), 4.5 (s, 3H, OCH_3), 3.9 (s, 3H, CH3). MS: m/z (%) 432(55%) [M$^+$]. ^{13}C NMR (200 MHz, DMSOd$_6$, *δ* / ppm): 176.9(C_2), 168.5 (C_4), 139.9 (C_5), 145.2 (C_6), 151.0 (C_7), 144. 7 (C_8), 136.8 (C_9), 130.3(C_{10}), 122.1 (C_{11}), 146.2 (C_{12}), 135.8 (C_{13}), 122.3 (C_{14}), 150.9 (C_{15}), 149.9 (C_{16}), 125.3 (C_{17}), 130.2 (C_{18}), 138.3 (C_{19}), 139.0 ($C_{20,\ 24}$), 133.0 (C_{22}), 148.8 ($C_{21,23}$), 42.1 (CH_3).

Groups III and IV received orally administered quinazoline derivatives that were synthesized, with a dosage of 25 mg/kg, suspended in Tween-80.

One hour following the administration, a 0.4 mL dose of a 1% carrageenan solution was introduced below sub-plantar surface of right hind paw for all subjects involved.

To evaluate the anti-inflammatory potential, a mercury Plethysmometer was utilized to measure paw volume at intervals of 0, 15, 30, 60, and 120 minutes following the administration of carrageenan, spanning a two-hour duration.[15,16]

RESULTS AND DISCUSSION

Anthranilic acid (2-amino benzoic acid) was gently heated and refluxed with acetic anhydride in a 1:2 ratio for one hour. This process yields 2-methyl Benzoxazin-4-one. Upon condensation with several substituted primary amines, in the presence of anhydrous ZnCl2 catalyst, it forms 2-methyl-3-aryl quinazolin-4-(3H)-ones. Finally, in optimal conditions, using equimolar quantities of different substituted aromatic benzaldehydes that are substituted on 2-methyl-3-aryl quinazolin-4-(3H)-ones, and employing anhydrous ZnCl2 as a catalyst, 2,3-disubstituted quinazolin-4-(3H) ones are obtained (Scheme 1).

Compositions of the compounds were determined by analyzing their spectroscopic data. The IR spectrum exhibited absorption peaks at 1685.67 cm^{-1} (indicative of C=O stretching), 1654.99 cm^{-1} (representing C=C stretching), 1089.75 cm^{-1} (corresponding to Ar-Br stretching), and 1161.43 cm^{-1} (associated with Ar-F stretching).

The 1H NMR spectra of the compounds displayed distinctive peaks: a multiplet at approximately δ (6.55-7.19) ppm, representing 12 protons associated with Ar-H moieties; a singlet at approximately δ (2.91) ppm, indicating six protons from 2CH_3 groups; and a doublet at around δ (6.6 and 9.6) ppm, signifying two protons attributed to CH=CH groups. These respective multiplet, singlet, and doublet signals corresponded to the aromatic ring, methyl group, and ethylene group. The remaining protons exhibited chemical shifts consistent with expectations.

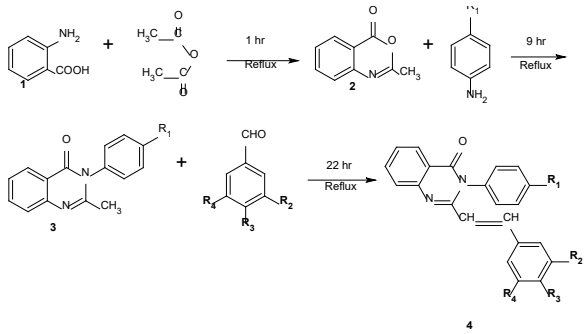
The ^{13}C-NMR spectra of the compounds displayed signals at approximately δ 123.15 to 132.05 ppm, representing the integration of sixteen carbons associated with Ar-C functionalities, and at δ 161.08 ppm, indicating the integration of one carbon linked to a C=O group. The mass spectra of the compounds exhibited molecular ions as M+ and M+1 ions, which proved to be valuable for the characterization of the derivatives.

In-vitro Anti-inflammatory Activity

As part of an inquiry into the mechanism behind the anti-inflammatory properties, we examined capacity of quinazoline analogs to impede protein denaturation. The Q_{B2} and Q_{F8} compounds demonstrated notable effectiveness in preventing the denaturation of albumin induced by heat, as detailed in Table 3. The highest observed inhibition, at 73%, was achieved at a concentration of 300 µg/mL. notably, aspirin, a well-known typical anti-inflammatory drug, also displayed a comparable 73% inhibition at the same concentration. These findings have been summarized in Table 4 for reference.

Anti-inflammatory Action

Quinazolin-4-one derivatives were prepared following the outlined Scheme and subsequently evaluated their anti-inflammatory action using an *in-vivo* carrageenan-induced paw edema method conducted on rats. The experiment involved the administration of synthesized compounds on the paws of wistar albino rats. Animals were categorized into distinct groups, every comprised of six individuals. Animals were distributed into four groups namely Control (Group I), Standard (Group II), Test 1 (Q_{B2}) and test 2 (Q_{F8}). The control group received an equivalent dosage of 1% CMC orally. The standard group was administered with diclofenac sodium suspension (25 mg/kg) while other groups were received 25 mg/kg dose of respective synthesized compounds. The paw volumes were measured at one-hour intervals, and SEM values were computed by the



Scheme 1: Synthesis of quinazoline-4-(3H)-one analogues

Table 2: Physico-chemical characteristics of synthesized compounds

Compounds	R_1	R_2	R_3	R_4	*Compounds*	R_1	R_2	R_3	R_4
Q_{B1}	Br	H	Cl	H	Q_{F1}	F	H	Cl	H
Q_{B2}	Br	H		H	Q_{F2}	F	H		H
Q_{B3}	Br	H	NO_2	H	Q_{F3}	F	H	NO_2	H
Q_{B4}	Br	OCH_3	OH	H	Q_{F4}	F	OCH_3	OH	H
Q_{B5}	Br	H	OH	H	Q_{F5}	F	H	OH	H
Q_{B6}	Br	OC_2H_5	OH	H	Q_{F6}	F	OC_2H_5	OH	H
Q_{B7}	Br	H	OCH_3	H	Q_{F7}	F	H	OCH_3	H
Q_{B8}	Br	NO_2	H	H	Q_{F8}	F	NO_2	H	H
Q_{B9}	Br	OCH_3	H	H	Q_{F9}	F	OCH_3	H	H
Q_{B10}	Br	OCH_3	OCH_3	OCH_3	Q_{F10}	F	OCH_3	OCH_3	OCH_3

Table 3: Lipophilicity of Quinazoline derivatives

Compounds	*M.P. (°C)*	*Yield %*	*Average Log P*	*Compounds*	*M.P. (°C)*	*Yield %*	*Average Log P*
Q_{B1}	105	55	5.56 (+-0.63)	Q_{F1}	92	63	5.51(+-0.55)
Q_{B2}	98	58	5.58(+-0.59	Q_{F2}	110	54	5.03(+-0.55)
Q_{B3}	136	53	5.33(+-0.55)	Q_{F3}	128	66	4.77(+-0.56)
Q_{B4}	114	58	4.93(+-0.52)	Q_{F4}	88	55	4.38(+-0.47)
Q_{B5}	102	57	5.04(+-0.48)	Q_{F5}	85	64	4.53(+-0.47)
Q_{B6}	133	55	5.29(+-0.57)	Q_{F6}	150	48	4.77(+-0.49)
Q_{B7}	80	68	5.38(+-0.60)	Q_{F7}	74	70	4.87(+-0.56)
Q_{B8}	66	66	5.33(+-0.55)	Q_{F8}	70	69	5.91 (+-0.55)
Q_{B9}	142	52	5.38(+-0.64)	Q_{F9}	155	55	4.86(+-0.56)
Q_{B10}	160	53	5.03(+-0.65)	Q_{F10}	117	58	4.48(+-0.55)

SPSS software. Research findings witnessed that compounds Q_{B2} and Q_{F8} have significant anti-inflammatory properties. The findings are as shown in Table 5.

Lipophilicity of Quinazoline Derivatives

The lipophilicity of the compounds was assessed utilizing the ALOGPS software. The lipophilicity of the compounds significantly contributes to their anti-inflammatory effect. Notably, in this analysis, the quinazoline derivatives Q_{B2} and Q_{F8} emerged as major outliers, exhibiting higher values in comparison to other substituted derivatives. This may be the underlined reason for their higher anti-inflammatory activity.

Table 4: *In-vitro anti-inflammatory activity of compounds*

% inhibition of protein denaturation				*% inhibition of protein denaturation*			
Drugs/Std	*100 µg/mL*	*200 µg/mL*	*300 µg/mL*	*Drugs/Std*	*100 µg/mL*	*200 µg/mL*	*300 µg/mL*
Q_{B1}	39.6	50.6	69.5	Q_{F1}	26.6	41.9	50.6
Q_{B2}	41.7	53.2	73.0	Q_{F2}	11.2	21.6	33.2
Q_{B3}	24.8	39.7	59.1	Q_{F3}	41.0	46.7	63.0
Q_{B4}	31.7	41.8	65.6	Q_{F4}	27.3	40.4	52.1
Q_{B5}	30.6	41.6	63.8	Q_{F5}	22.2	15.5	22.9
Q_{B6}	32.8	45.2	65.8	Q_{F6}	29.6	32.0	38.6
Q_{B7}	9.25	21.5	36.0	Q_{F7}	24.4	34.0	44.3
Q_{B8}	39.5	47.5	66.7	Q_{F8}	38.5	56.7	70.2
Q_{B9}	37.6	48.8	65.9	Q_{F9}	26.2	35.2	45.4
Q_{B10}	21.9	41.9	47.1	Q_{F10}	32.4	53.2	65.2
Standard	41.7%	53.2%	73.0%	Standard	41.7%	53.2%	73.0%

Table 5: *In-vivo* Anti-inflammatory activity of the compounds Q_{B2}- Q_{F8}

Compounds	*0 Minute*	*15 Minutes*	*30 Minutes*	*60 Minutes*	*120 Minutes*	*% Increase in reaction time*
Control	0.05	0.05	0.09	0.15	0.14	0.14 + 0.008539
	0.07	0.07	0.11	0.13	0.12	
	0.08	0.08	0.12	0.18	0.16	
	0.07	0.07	0.11	0.13	0.12	
Q_{B2}	0.08	0.11	0.13	0.10	0.08	0.10 + 0.004082
	0.07	0.11	0.12	0.11	0.07	
	0.06	0.08	0.12	0.09	0.06	
	0.07	0.11	0.12	0.10	0.07	
Q_{F8}	0.07	0.09	0.13	0.12	0.07	0.11 + 0.008539
	0.07	0.10	0.14	0.10	0.07	
	0.09	0.12	0.13	0.11	0.09	
	0.08	0.09	0.13	0.10	0.08	
Standard	0.06	0.06	0.07	0.09	0.07	0.07+ 0.004082
	0.07	0.08	0.09	0.10	0.08	
	0.06	0.06	0.08	0.08	0.07	
	0.06	0.06	0.07	0.09	0.07	

CONCLUSION

A set of innovative quinazoline derivatives was created and subjected to screening for anti-inflammatory properties. The synthesis involved the integration of two components, namely aromatic-substituted aldehydes and aryl amines, into the quinazoline structure with the aim of enhancing anti-inflammatory efficacy. Examination of the structural activity of these compounds unveiled that those bearing -Br, -F, and -NO_2 groups exhibited noteworthy anti-inflammatory potential.

REFERENCES

1. Furman D, Campisi J, Verdin E, Carrera-Bastos P, Targ S, Franceschi C, Ferrucci L, Gilroy DW, Fasano A, Miller GW, Miller AH. Chronic inflammation in the etiology of disease across the life span. Nature medicine. 2019 Dec;25(12):1822-32.
2. Furman D, Chang J, Lartigue L, Bolen CR, Haddad F, Gaudilliere B, Ganio EA, Fragiadakis GK, Spitzer MH, Douchet I, Daburon S. Expression of specific inflammasome gene modules stratifies older individuals into two extreme clinical and immunological states. Nature medicine. 2017 Feb;23(2):174-84.
3. Netea MG, Balkwill F, Chonchol M, Cominelli F, Donath MY, Giamarellos-Bourboulis EJ, Golenbock D, Gresnigt MS, Heneka MT, Hoffman HM, Hotchkiss R. A guiding map for inflammation. Nature immunology. 2017 Aug 1;18(8):826-31.
4. Slavich GM. Understanding inflammation, its regulation, and relevance for health: A top scientific and public priority. Brain, behavior, and immunity. 2015 Mar;45:13.
5. Bennett JM, Reeves G, Billman GE, Sturmberg JP. Inflammation–nature's way to efficiently respond to all types of challenges: implications for understanding and managing "the epidemic" of chronic diseases. Frontiers in medicine. 2018 Nov 27;5:316.
6. Roth GA, Abate D, Abate KH, Abay SM, Abbafati C, Abbasi N, Abbastabar H, Abd-Allah F, Abdela J, Abdelalim A, Abdollahpour I. Global, regional, and national age-sex-specific mortality for 282 causes of death in 195 countries and territories, 1980–2017:

a systematic analysis for the Global Burden of Disease Study 2017. The Lancet. 2018 Nov 10;392(10159):1736-88.
7. Miller GE, Chen E, Parker KJ. Psychological stress in childhood and susceptibility to the chronic diseases of aging: moving toward a model of behavioral and biological mechanisms. Psychological bulletin. 2011 Nov;137(6):959.
8. Fleming TP, Watkins AJ, Velazquez MA, Mathers JC, Prentice AM, Stephenson J, Barker M, Saffery R, Yajnik CS, Eckert JJ, Hanson MA. Origins of lifetime health around the time of conception: causes and consequences. The Lancet. 2018 May 5;391(10132):1842-52.
9. Renz H, Holt PG, Inouye M, Logan AC, Prescott SL, Sly PD. An exposome perspective: Early-life events and immune development in a changing world. Journal of Allergy and Clinical Immunology. 2017 Jul 1;140(1):24-40.
10. Kotas ME, Medzhitov R. Homeostasis, inflammation, and disease susceptibility. Cell. 2015 Feb 26;160(5):816-27.
11. Straub RH, Cutolo M, Pacifici R. Evolutionary medicine and bone loss in chronic inflammatory diseases—a theory of inflammation-related osteopenia. InSeminars in arthritis and rheumatism 2015 Oct 1 (Vol. 45, No. 2, pp. 220-228). WB Saunders.
12. Straub RH, Schradin C. Chronic inflammatory systemic diseases: An evolutionary trade-off between acutely beneficial but chronically harmful programs. Evolution, medicine, and public health. 2016 Jan 1;2016(1):37-51.
13. Ryn JV, Trummlitz G, Pairet M. COX-2 selectivity and inflammatory processes. Current medicinal chemistry. 2000 Nov 1;7(11):1145-61.
14. Beuck M. Nonsteroidal antiinflammatory drugs: a new generation of cyclooxygenase inhibitors. Angewandte Chemie International Edition. 1999 Mar 1;38(5):631-3.
15. Asif M. Chemical characteristics, synthetic methods, and biological potential of quinazoline and quinazolinone derivatives. International journal of medicinal chemistry. 2014;2014.
16. Kumar A, Rajput CS. Synthesis and anti-inflammatory activity of newer quinazolin-4-one derivatives. European journal of medicinal chemistry. 2009 Jan 1;44(1):83-90.