

Synthesis, Characterisation and Anti-inflammatory Activity of some Novel Quinazolin-4-(3H)-one Analogues

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ABSTRACT

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Some new 2-[(E)-2-(substituted phenyl) ethenyl]-3-(2/4methyl phenyl) quinazolin-4(3H)-ones (Q1_{a-f}, Q2_{a-f}) have been synthesized from 3-(2-methyl phenyl) quinazolin-4(3H)-one (Q1) and 3-(4-methyl phenyl) quinazolin-4(3H)-one (Q2) by introducing different aromatic aldehydes. The synthesized compounds have been characterized by IR, ¹H NMR, ¹³C NMR and Mass spectral techniques and screened for anti-inflammatory activity by using carrageenan induced rat paw edema method. Compounds Q1a, Q1e, Q1f and Q2f showed potent activity when compared to diclofenac sodium as standard. Examination of the relationship between lipophilicity and anti-inflammatory activity of quinazolines showed poor correlation.

Keywords: Quinazoline, Anti-inflammatory activity, Lipophilicity, Diclofenac sodium

INTRODUCTION

Quinazolin-4-(3H)-ones exhibit a wide range of activities such as Antibacterial¹, antiviral², antiinflammatory³, antihistaminic⁴, antihypertensive⁵, antiparkinsonian⁶, antitubercular⁷ and anticancer⁸. In Quinazolin-4-(3H)-one moiety, the presence of an aryl group at position three and incorporation of styryl moiety at position two enhance antibacterial, anti-inflammatory, antitubercular and chemotherapeutic activities⁹.

In the view of these observations, we planned to synthesize some new 2-[(E)-2-(substituted phenyl) ethenyl]-3-(2/4methyl phenyl) quinazolin-4(3H)-ones and to evaluate for anti-inflammatory activity.

EXPERIMENTAL

Melting points were determined on Micro-controller based melting point apparatus CL 725/726 and were uncorrected. chloro and nitro benzaldehydes were purchased from M/S Techno Chemicals, Bangalore. Other chemicals like anthranilic acid and acetic anhydride were purchased from M/S S.D. Fine Chemicals, Bangalore. Silica gel G plates (3x8cm) were used for TLC and spots were located by UV and in Iodine chamber. The IR spectra (KBr) were determined on FT-IR 8400S, SHIMADZU Spectrometer and the values were expressed in cm⁻¹. ¹H NMR and ¹³C NMR were recorded in

either CDCl₃ or DMSO-d₆ solvents using TMS as an internal reference standard at IIT Chennai and IISc Bangalore. Mass spectra were recorded on Shimadzu LCMS 2010 A Mass spectrometer.

Synthesis of 2-Methyl benzoxazin-4-one from Anthranilic acid:

5g of anthranilic acid (0.036 mol) and 7.4 g of acetic anhydride (0.0729 mol) was taken in the ratio of 1:2 in a round bottomed flask. The reaction mixture was heated gently and refluxed for 1 hr. The excess acetic anhydride was distilled off. The reaction mixture was poured into beaker containing crushed ice, stirred constantly and filtered. The crude product was recrystallized from ethyl acetate. The yield was about 64% with a M.P of 175-180 °C. IR (KBr) cm⁻¹ 1660 (C=O str), 1469 (C-N str), 788 (C-Cl str).

Synthesis of 2-Methyl-3-aryl quinazolin-4-(3H)-ones: (Q₁-Q₂)

An equimolar (0.01 mol) quantity of 2-Methyl-1, 3-benzoxazin-4-one and aryl amine was refluxed for 6 hr with glacial acetic acid. The mixture was cooled to room temperature and poured into crushed ice; the solid obtained was recrystallized from ethyl acetate.

2-Methyl-3-(2-methylphenyl)-2,3-dihydroquinazolin-4(1H)-one:(Q₁)

Colourless crystals, Yield: 65%, m.p: 170°C, Rf: 0.74 (Chloroform: methanol=9:1) Anal. Calcd. for C₁₆H₁₄N₂O (FW 250.29): C. 76.78, H. 5.64, N.11.19%. Found: C. 76.79, H. 5.66, N. 11.20 %. FTIR (KBr) cm⁻¹: 1709 (C=O), 3060 (C-H),

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1620 (C=C), 1382 (C=N). ^1H NMR (200 MHz, DMSO-d₆ δ / ppm): 7-7.9 (m, 9H, Ar-H), 2.3 (s, 3H, CH₃). MS: m/z (%) 250 (60%) [M^+]. ^{13}C NMR (200 MHz, DMSO-d₆, δ / ppm): 151.6 (C₂), 160.9 (C₄), 128.3 (C₅), 126.5 (C₆), 133.1 (C₇), 121.5 (C₈), 145.6 (C₉), 120.5 (C₁₀), 134.4 (C₁₁, C₁₂), 128.9 (C₁₃), 124.5 (C₁₄), 125.2 (C₁₅), 129.0 (C₁₆), 21.5, 22.4 (2CH₃).

2-Methyl-3-(4-methylphenyl)-2,3-dihydroquinazolin-4(1H)-one:(Q2)

Colourless crystals, Yield: 75%, m.p: 175°C, Rf: 0.76 (Chloroform: methanol=9:1) Anal. Calcd. for C₁₆H₁₄N₂O (FW 250.29): C. 76.78, H. 5.64, N.11.19%. Found: C. 76.79, H. 5.67, N. 11.20 %. FTIR (KBr) cm⁻¹:1709 (C=O), 3060 (C-H), 1620 (C=C), 1382 (C=N). ^1H NMR (200 MHz, DMSO-d₆ δ / ppm): 7-7.9 (m, 9H, Ar-H), 2.3 (s, 3H, CH₃). MS: m/z (%) 250 (60%) [M^+]. ^{13}C NMR (200 MHz, DMSO-d₆, δ / ppm): 151.3 (C₂), 160.2 (C₄), 128.7 (C₅), 126.1 (C₆), 133.5 (C₇), 121.9 (C₈), 145.7 (C₉), 120.2 (C₁₀), 134.1 (C₁₁, C₁₂), 128.2 (C₁₃), 124.3 (C₁₄), 125.6 (C₁₅), 129.0 (C₁₆), 22.3, 23.4 (2CH₃).

Synthesis of 2, 3-Disubstituted quinazolin-4-(3H)ones using aromatic substituted Aldehydes: (Q1_{a-f}, Q2_{a-f})

A mixture of appropriate quinazoline (0.1mol) and various aromatic aldehydes (0.1 mol) in 50 mL glacial acetic acid was stirred and refluxed for 24 hr. The reaction mixture was cooled and poured into ice cold water. Filtered and dried to get the final product, which was recrystallised from ethyl acetate.

2-[(E)-2-(2-Hydroxyphenyl)ethenyl]-3-(2-methylphenyl)quinazolin-4(3H)-one:(Q1_a)

Colour less Crystals, Yield: 75%, m.p: 210°C, Anal. Calcd. for C₂₃H₁₈N₂O₂ (FW 354.40): C. 77.95, H. 5.12, N. 7.90%. 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). ^1H NMR (200 MHz, DMSO-d₆ δ / ppm): 9.5 (s, 1H, OH), 7-8.2 (m, 12H, Ar-H), 6.5, 6.7(2d, 2H, CH=CH), 2.2 (s, 3H, CH₃). MS: m/z (%) 354 (55%) [M^+]. ^{13}C NMR (200 MHz, DMSO-d₆, δ / ppm): 161.0 (C₂), 160.2 (C₄), 126.3 (C₅), 127.0 (C₆), 133.6 (C₇), 121.9 (C₈), 146.7 (C₉), 119.9 (C₁₀), 111.2 (C₁₁), 135.2 (C₁₂), 115.6 (C₁₃), 153.5 (C₁₄), 115.0 (C₁₅), 128.4 (C₁₆), 120.3 (C₁₇), 126.8 (C₁₈), 134.6 (C₁₉, 20), 129.5 (C₂₁), 123.3 (C₂₂), 125.5 (C₂₃), 120.3 (C₂₄), 20.4 (CH₃).

3-(2-Methylphenyl)-2-[(E)-2-phenylethenyl]quinazolin-4(3H)-one:(Q1_b)

Pale green Crystals, Yield: 76%, m.p: 180°C, Anal. Calcd. for C₂₃H₁₈N₂O (FW 338.40): C. 81.63, H. 5.36, N. 8.28%. Found: C. 81.66, H. 5.42, N. 8.30 %. FTIR (KBr): 1711 (C=O), 3065 (C-H), 1620 (C=C), 1377(C=N). ^1H NMR (200 MHz,

DMSO-d₆ δ / ppm): 7-8.2 (m, 13H, Ar-H), 6.4, 6.7 (2d, 2H, CH=CH), 2.1(s, 3H, CH₃). MS: m/z (%) 338 (55%) [M^+]. ^{13}C NMR (200 MHz, DMSO-d₆, δ / ppm): 162.4 (C₂), 160.7 (C₄), 127.2 (C₅), 126.2 (C₆), 133.5 (C₇), 122.0 (C₈), 147.2 (C₉), 120.1 (C₁₀), 112.2 (C₁₁), 136.1 (C₁₂), 135.2 (C₁₃), 126.4 (C₁₄, C₁₈), 127.7 (C₁₅,C₁₇), 128.1 (C₁₆), 135.6 (C₁₉,20), 129.3 (C₂₁), 124.1 (C₂₂), 125.9 (C₂₃), 121.3 (C₂₄), 19.9 (CH₃).

2-[(E)-2-(2-methoxyphenyl)ethenyl]-3-(2-methylphenyl)quinazolin-4(3H)-one:(Q1_c)

Colourless Crystals, Yield: 79%, m.p: 210°C, Anal. Calcd. for C₂₄H₂₀N₂O₂ (FW 368.42): C. 78.24, H. 5.47, N. 7.60%. Found: C. 78.26, H. 5.50, N. 7.65 %. FTIR (KBr): 1711 (C=O), 3068 (C-H), 1620 (C=C), 1377 (C=N). ^1H NMR (200 MHz, DMSO-d₆ δ / ppm): 7-8.2 (m, 12H, Ar-H), 6.5, 6.7 (2d, 2H, CH=CH). 4.0 (s,3H, OCH₃), 2.1 (s,3H,CH₃), MS: m/z (%) 368 (55%) [M^+]. ^{13}C NMR (200 MHz, DMSO-d₆, 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 (CH₃), 55.3 (OCH₃).

3-(2-methylphenyl)-2-[(E)-2-(2-nitrophenyl) ethenyl]quinazolin-4(3H)-one:(Q1_d)

Pale green Crystals, Yield: 76%, m.p: 190°C, Anal. Calcd. for C₂₃H₁₇N₃O₃ (FW 338.39): C. 72.05, H. 4.47, N. 10.96%. Found: C. 72.10, H. 4.50, N.10.96% FTIR (KBr): 1709 (C=O), 3068 (C-H), 1620 (C=C), 1384 (C=N). ^1H NMR (200 MHz, DMSO-d₆ δ / ppm): 7-8.2 (m, 8H, Ar-H), 6.3, 6.5 (2d, 2H, CH=CH), MS: m/z (%) 338 (55%) [M^+]. ^{13}C NMR (200 MHz, DMSO-d₆, δ / ppm): 163.2 (C₂), 160.9 (C₄), 127.8 (C₅), 127.3 (C₆), 132.6 (C₇), 122.0 (C₈), 146.1 (C₉), 120.1 (C₁₀), 112.0 (C₁₁), 137.9 (C₁₂), 128.6 (C₁₃), 155.3 (C₁₄), 121.5 (C₁₅), 126.4 (C₁₆, C₁₈), 133.7 (C₁₇), 133.1 (C₁₉, C₂₀), 129.7 (C₂₁), 123.8 (C₂₂), 127.3 (C₂₃), 120.3 (C₂₄), 20.8 (CH₃).

2-[(E)-2-(4-Chlorophenyl)ethenyl]-3-(2-methylphenyl)quinazolin-4(3H)-one:(Q1_e)

Colourless Crystals, Yield: 86%, m.p: 220°C, Anal. Calcd. for C₂₃H₁₇N₂OCl (FW 372.84): C. 74.09, H. 4.60, N. 7.51% Found: C. 74.00, H. 4.62, N. 7.53 %. FTIR (KBr): 3081 (O-H), 1709 (C=O), 3068 (C-H), 1620 (C=C), 1384 (C=N). ^1H NMR (200 MHz, DMSO-d₆ δ / ppm):7-8.2 (m, 12H, Ar-H), 6.5, 6.7 (2d, 2H, CH=CH), 2.1 (s, 3H, CH₃). MS: m/z (%) 372 (50%) [M^+]. ^{13}C NMR (200 MHz, DMSO-d₆, δ / ppm): 162.3 (C₂), 161.9 (C₄), 127.8 (C₅), 126.4 (C₆), 132.5 (C₇), 121.4 (C₈), 146.0 (C₉), 120.2 (C₁₀), 110.8 (C₁₁), 136.2 (C₁₂), 132.2 (C₁₃), 126.8 (C₁₄), 127.8 (C₁₅), 140.4 (C₁₆), 127.8 (C₁₇), 126.8 (C₁₈),

134.3 (C_{19,20}), 127.3 (C₂₁), 123.8 (C₂₂), 125.0 (C₂₃), 120.5(C₂₄), 21.2(CH₃).

2-[(E)-2-(4-Hydroxy-3-methoxyphenyl)ethenyl]-3-(2-methylphenyl)quinazolin-4(3H)-one: (Q1_f)

Pale yellow colour crystals, Yield: 82%, m.p: 215°C, Anal. Calcd. for C₂₄H₂₀N₂O₃ (FW 384.42): C. 74.98, H. 5.24, N. 7.29% Found: C. 75.00, H. 5.32, N. 7.30 % FTIR (KBr): 3480 (O-H), 1711 (C=O), 3068 (C-H), 1620 (C=C), 1313 (C=N). ¹H NMR (200 MHZ, DMSO_{d6} δ / ppm):9.0 (s, 1H, OH), 7-8.2 (m, 12H, Ar-H), 6.5, 6.7 (2d, 2H, CH=CH), 2.1-4.0 (2s, 6H, CH₃, OCH₃). MS: m/z (%) 384 (40%) [M⁺]. ¹³C NMR (200 MHZ, DMSO_{d6}, δ / ppm): 163.0 (C₂), 161.9 (C₄), 127.8 (C₅), 125.4 (C₆), 132.3 (C₇), 121.9 (C₈), 146.1 (C₉), 120.4 (C₁₀), 112.8 (C₁₁), 137.2 (C₁₂), 127.8 (C₁₃), 111.0 (C₁₄), 150.3 (C₁₅), 140.9 (C₁₆), 115.5 (C₁₇), 119.1 (C₁₈), 133.4 (C_{19,20}), 128.3 (C₂₁), 123.3 (C₂₂), 125.0 (C₂₃), 121.5 (C₂₄), 20.1 (CH₃), 55.2 (OCH₃).

2-[(E)-2-(2-Hydroxyphenyl)ethenyl]-3-(4-methylphenyl)quinazolin-4(3H)-one: (Q2_a)

Colourless crystals, Yield: 85%, m.p: 212°C, Anal. Calcd. for C₂₃H₁₈N₂O₂ (FW 354.40): C. 77.95, H. 5.12, N. 7.90% Found: C. 77.91, H. 5.22, N. 7.96 % FTIR (KBr): 3081 (O-H), 1711 (C=O), 3068 (C-H), 1620 (C=C), 1314 (C=N). ¹H NMR (200 MHZ, DMSO_{d6} δ / ppm): 7-8.2 (m, 12H, Ar-H), 6.5, 6.7 (2d, 2H, CH=CH), 9.5 (s, 1H, OH). MS: m/z (%) 354 (50%) [M⁺]. ¹³C NMR (200 MHZ, DMSO_{d6}, δ / ppm): 163.2 (C₂), 160.2 (C₄), 127.8 (C₅), 126.4 (C₆), 132.5 (C₇), 121.4 (C₈), 146.1 (C₉), 120.0 (C₁₀), 111.1 (C₁₁), 137.2 (C₁₂), 115.1 (C₁₃), 157.3 (C₁₄), 114.9 (C₁₅), 128.0 (C₁₆), 120.3 (C₁₇), 126.2 (C₁₈), 127.3 (C₁₉), 120.5 (C_{20,24}), 133.0 (C₂₂), 128.3 (C_{21,23}), 23.4 (CH₃).

3-(4-Methylphenyl)-2-[(E)-2-phenylethenyl]quinazolin-4(3H)-one:(Q2_b)

Pale green colour crystals, Yield: 88%, m.p: 215°C, Anal. Calcd. for C₂₃H₁₈N₂O (FW 338.40): C. 81.63, H. 5.36, N. 8.28% Found: C. 81.65, H. 5.46, N. 8.32 % FTIR (KBr): 1717 (C=O), 3068 (C-H), 1620 (C=C), 1315 (C=N). ¹H NMR (200 MHZ, DMSO_{d6} δ / ppm): 7-8.2 (m, 13H, Ar-H), 6.5, 6.7 (2d, 2H, CH=CH), 2.1 (s, 3H, CH₃). MS: m/z (%) 338 (55%) [M⁺]. ¹³C NMR (200 MHZ, DMSO_{d6}, δ / ppm): 163.4 (C₂), 161.9 (C₄), 127.8 (C₅), 126.0 (C₆), 132.2 (C₇), 121.4 (C₈), 146.0 (C₉), 120.8 (C₁₀), 111.2 (C₁₁), 137.2 (C₁₂), 133.5 (C₁₃), 125.4 (C_{14,18}), 127.7 (C_{15,17}), 125.0 (C₁₆), 126.3 (C₁₉), 120.2 (C_{20,24}), 133.7 (C₂₂), 128.3 (C_{21,23}), 23.8 (CH₃).

2-[(E)-2-(2-Methoxyphenyl)ethenyl]-3-(4-methylphenyl)quinazolin-4(3H)-one: (Q2_c)

Colourless crystals, Yield: 85%, m.p: 200°C, Anal. Calcd. for C₂₄H₂₀N₂O₂ (FW 368.42): C. 78.24, H. 5.47, N. 7.60% Found:

C. 78.30, H. 5.56, N. 7.64 % FTIR (KBr): 1711 (C=O), 3068 (C-H), 1620 (C=C), 1314 (C=N). ¹H NMR (200 MHZ, DMSO_{d6} δ / ppm): 7-8.2 (m, 12H, Ar-H), 6.5, 6.7 (2d, 2H, CH=CH), 2.1-4.0 (2s, 6H, CH₃, OCH₃). MS: m/z (%) 368 (550%) [M⁺]. ¹³C NMR (200 MHZ, DMSO_{d6}, δ / ppm): 162.3 (C₂), 160.7 (C₄), 127.2 (C₅), 126.3 (C₆), 132.2 (C₇), 121.8 (C₈), 146.0 (C₉), 120.2 (C₁₀), 111.7 (C₁₁), 137.2 (C₁₂), 115.1 (C₁₃), 157.3 (C₁₄), 114.9 (C₁₅), 128.0 (C₁₆), 120.3 (C₁₇), 126.2 (C₁₈), 127.3 (C₁₉), 121.5 (C_{20,24}), 133.0 (C₂₂), 127.3 (C_{21,23}), 23.5 (CH₃).

3-(4-Methylphenyl)-2-[(E)-2-(2-nitrophenyl) ethenyl]quinazolin-4(3H)-one:(Q2_d)

Pale green crystals, Yield: 74%, m.p: 190°C, Anal. Calcd. for C₂₃H₁₇N₃O₃ (FW 383.39): C. 72.05, H. 4.47, N. 10.96% Found: C. 72.10, H. 4.50, N. 10.99 % FTIR (KBr): 1710 (C=O), 3068 (C-H), 1620 (C=C), 1315 (C=N). ¹H NMR (200 MHZ, DMSO_{d6} δ / ppm): 7-8.2 (m, 12H, Ar-H), 6.5, 6.7 (2d, 2H, CH=CH), 2.0 (s, 3H, CH₃). MS: m/z (%) 383 (55%) [M⁺]. ¹³C NMR (200 MHZ, DMSO_{d6}, δ / ppm): 163.9 (C₂), 160.1 (C₄), 128.2 (C₅), 126.1 (C₆), 132.6 (C₇), 121.3 (C₈), 146.2 (C₉), 120.7 (C₁₀), 111.5 (C₁₁), 137.9 (C₁₂), 116.0 (C₁₃), 155.5 (C₁₄), 114.9 (C₁₅), 128.0 (C₁₆), 120.2 (C₁₇), 126.5 (C₁₈), 127.3 (C₁₉), 121.5 (C_{20,24}), 133.0 (C₂₂), 128.4 (C_{21,23}), 22.2 (CH₃).

2-[(E)-2-(4-Chlorophenyl)ethenyl]-3-(4-methylphenyl)quinazolin-4(3H)-one:(Q2_e)

Colourless crystals, Yield: 79%, m.p: 212°C, Anal. Calcd. for C₂₃H₁₇N₂OCl (FW 372.84): C. 74.09, H. 4.60, N. 7.51% Found: C. 74.11, H. 4.62, N. 7.52 % FTIR (KBr): 1717 (C=O), 3068 (C-H), 1620 (C=C), 1313 (C=N). ¹H NMR (200 MHZ, DMSO_{d6} δ / ppm): 7-8.2 (m, 12H, Ar-H), 6.5, 6.7 (2d, 2H, CH=CH), 2.1 (s, 3H, CH₃). MS: m/z (%) 372 (50%) [M⁺]. ¹³C NMR (200 MHZ, DMSO_{d6}, δ / ppm): 163.4 (C₂), 160.8 (C₄), 128.7 (C₅), 126.5 (C₆), 133.5 (C₇), 122.1 (C₈), 146.8 (C₉), 120.6 (C₁₀), 111.2 (C₁₁), 137.4 (C₁₂), 115.9 (C₁₃), 126.2 (C_{14,18}), 127.7 (C_{15,17}), 128.0 (C₁₆), 127.3 (C₁₉), 121.0 (C_{20,24}), 133.0 (C₂₂), 128.0 (C_{21,23}), 23.6 (CH₃).

2-[(E)-2-(4-Hydroxy-3-methoxyphenyl)ethenyl]-3-(4-methylphenyl)quinazolin-(3H)-one:(Q2_f)

Pale yellow crystals, Yield: 75%, MP: 220°C, Anal. Calcd. for C₂₄H₂₀N₂O₃ (FW 384.42): C. 74.98, H. 5.24, N. 7.29% Found: C. 75.10, H. 5.26, N. 7.30 % FTIR (KBr): 3430 (O-H), 1711 (C=O), 3068 (C-H), 1620 (C=C), 1313 (C=N). ¹H NMR (200 MHZ, DMSO_{d6} δ / ppm): 8.9 (s, 1H, OH), 7-8.2 (m, 12H, Ar-H), 6.5, 6.7 (2d, 2H, CH=CH), 3.5 (s, 3H, OCH₃), 2.1 (s, 3H, CH₃). MS: m/z (%) 384 (55%) [M⁺]. ¹³C NMR (200 MHZ, DMSO_{d6}, δ / ppm): 163.9 (C₂), 160.5 (C₄), 127.9 (C₅), 126.2

(C₆), 132.0 (C₇), 121.7 (C₈), 146.8 (C₉), 120.3 (C₁₀), 112.1 (C₁₁), 136.2 (C₁₂), 125.8 (C₁₃), 112.3 (C₁₄), 140.9 (C₁₅), 139.9 (C₁₆), 115.3 (C₁₇), 120.2 (C₁₈), 128.3 (C₁₉), 121.0 (C_{20,24}), 133.0 (C₂₂), 128.8 (C_{21,23}), 23.1 (CH₃).

***In-vivo* method**

Albino Wister rats weighing 150-200gm were taken and kept under standard conditions in the central animal house at the college and animal ethical committee clearance was obtained for carrying out the experiment (SACCP/IAEC/11/2009-10). They were housed in the pharmacology department of the college for 7 days for acclimatization in air conditioned atmosphere 20°C. Prior to the experiment, all the animals were fasted overnight with water *ad libitum*.

Procedure:

The animals were weighed and numbered by marking them on the tail. They were divided into three groups each consisting of 4 mice, for intraperitoneal, intravenous and oral routes of administration. Intraperitoneal injection was made in the abdomen where as the dorsal tail vein was used for intravenous administration. For oral route, the mouse was held by its neck muscle and the feeding needle was placed on the tongue and the solution was gently pushed in the mouth. The time of injection and time of onset of sleep was noted (loss of righting reflex). The animals were put on its back when it was asleep so that when it regains consciousness it will turn over to its normal posture (end point). Animals were placed apart so that no mouse shall disturb the other when it recovers from barbiturate induced sleep. The time of recovery was noted and the duration of action was calculated. The onset of action and duration of sleep due to diclofenac sodium when given by different routes of administration was noted.

RESULTS AND DISCUSSION

Chemistry:

2-Methyl benzoxazin-4-one, was obtained by a reported procedure⁴ and 3-(2-Methyl phenyl) quinazolin-4(3H)-one (**Q1**) and 3-(4-Methyl phenyl) quinazolin-4(3H)-one (**Q2**) synthesized by reacting with substituted anilines. Then the derivatives there of were prepared from the reaction of different aromatic aldehydes to give 2-[(E)-2-(substituted phenyl) ethenyl]-3-(2/4methyl phenyl) quinazolin-4(3H)-ones (**Q1_{a-f}**, **Q2_{a-f}**). The structures were confirmed based on their chemical and spectral data.

All the synthesized compounds were recrystallized with ethyl acetate. The IR, ¹H NMR, ¹³C NMR and Mass spectral data showed their chemical properties. The IR spectral data showed the presence of major functional groups in the compounds. The data is in complete agreement with all the structures of the quinazolinones. The IR spectral data

presented the expected characteristic absorption bands. The characteristic frequency ranges of the showed peaks at the region of 1709-1717 cm⁻¹, 1620 cm⁻¹ and 1313-1384 cm⁻¹, resembles the C=O, C=C and C=N.

¹H NMR spectra of the compounds showed a two doublet at about δ 6.3-6.7 ppm integrated for two protons attributed to CH=CH protons and a multiplet at about δ 7-8.2 ppm integrated for aromatic protons. These two doublets and multiplet protons are belonging to the CH=CH bridge between quinazolinone and substituted aromatic aldehydes. The assignment of the ¹³C-resonance of quinazolinone derivatives is in close agreement with analogous compounds. Mass spectra of the compounds showed molecular ions in the form of M⁺. The ions were usefulness for characterization of the derivatives.

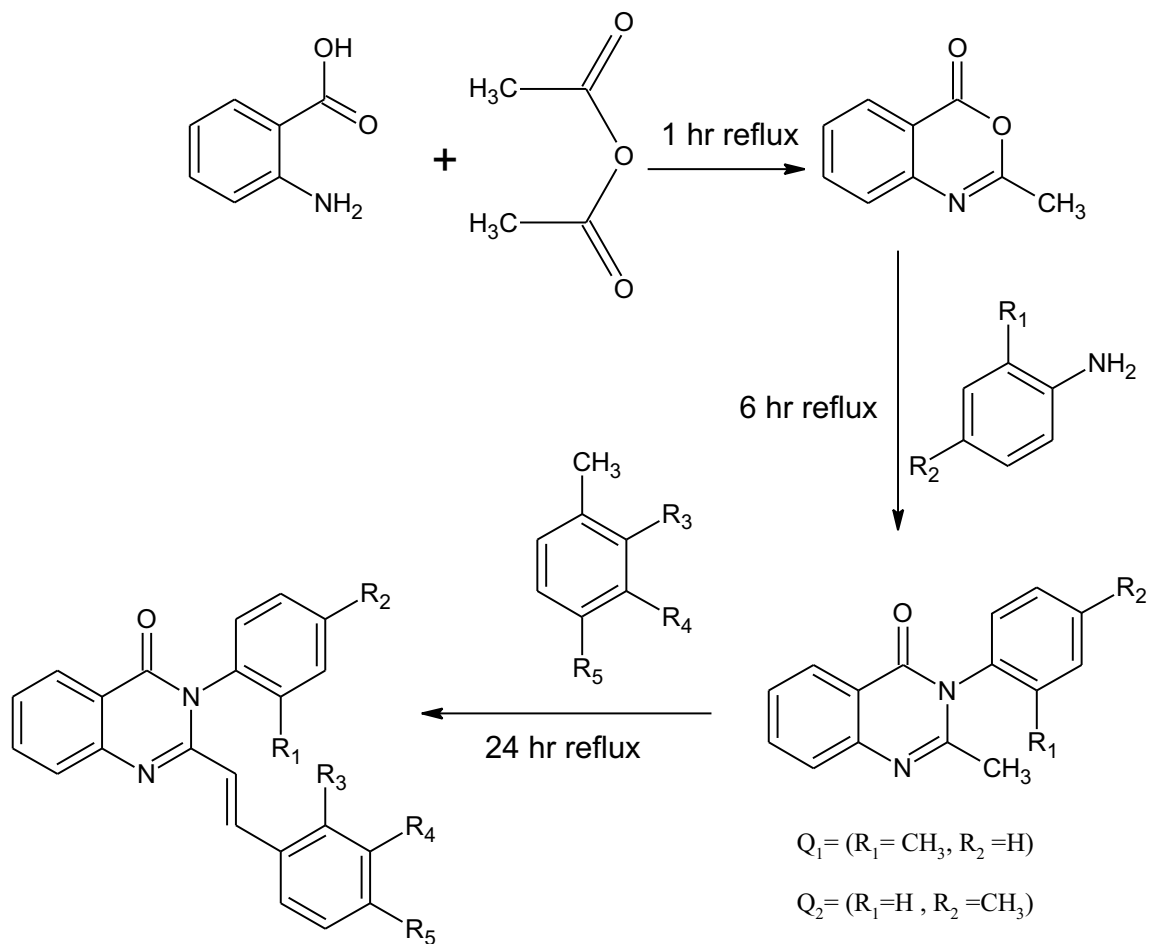
Anti-inflammatory activity:

Quinazolin-4-one derivatives were synthesized (**Scheme**) and screened for anti-inflammatory activity by *In-vivo* method¹⁰ on rats. The activity of synthesized compounds was done on paw of Wister Albino rats. The animals were divided into different groups each consisting of 6 animals. The synthesized compounds were divided into 2 batches (**Q_{1a}**, **Q_{1b}**, **Q_{1c}**, **Q_{1d}**, **Q_{1e}**, **Q_{1f}** and **Q_{2a}**, **Q_{2b}**, **Q_{2c}**, **Q_{2d}**, **Q_{2e}**, **Q_{2f}**) as test compounds and compared with Diclofenac sodium, which is the standard drug. The standard was administered orally as an aqueous suspension of 1% CMC. The control group was fed with the same amount of 1% CMC. The paw volumes were recorded within 1 hr. interval time duration and the SEM values were calculated by using SPSS software. The study indicated that compounds **Q_{1a}**, **Q_{1e}**, **Q_{1f}** and **Q_{2f}** exhibited potent anti-inflammatory activity. Other compounds exhibited less anti-inflammatory activity.

Lipophilicity:

The lipophilicity of the synthesised compounds was determined by using n-octanol and aqueous phases. The aqueous and n-octanol phases were assayed using UV spectrometer¹¹. The efficiency of an anti-inflammatory drug will depend in part on its ability to accumulate in cells. Lipophilicity of compounds plays a vital role in anti-inflammatory effect of the compounds. The quinazolinones are strong bases and able to exist in both charged (protonated) and uncharged (unprotonated) forms. The lipophilicity data of (**Q1_{a-f}**, **Q2_{a-f}**) varying from 4.66-5.71 expressed in log₁₀P are given in **Table-1**. Substitution of aryl group at position C-2 and C-4 and styryl moieties with OCH₃, OH, NO₂ and C-1 in positions C-2, C-3 and C-4 resulted in an enhancement in the log₁₀P values. Analysis of the relationship between log₁₀P values and the anti-inflammatory activity showed poor correlation. The major outlier in this analysis was **Q1e** with

Scheme:



$Q_{1a} = (R_1 = \text{CH}_3, R_2 = \text{H}, R_3 = \text{OH}, R_4 = \text{H}, R_5 = \text{H})$

$Q_{1b} = (R_1 = \text{CH}_3, R_2 = \text{H}, R_3 = \text{H}, R_4 = \text{H}, R_5 = \text{H})$

$Q_{1c} = (R_1 = \text{CH}_3, R_2 = \text{H}, R_3 = \text{OCH}_3, R_4 = \text{H}, R_5 = \text{H})$

$Q_{1d} = (R_1 = \text{CH}_3, R_2 = \text{H}, R_3 = \text{NO}_2, R_4 = \text{H}, R_5 = \text{H})$

$Q_{1e} = (R_1 = \text{CH}_3, R_2 = \text{H}, R_3 = \text{H}, R_4 = \text{H}, R_5 = \text{Cl})$

$Q_{1f} = (R_1 = \text{CH}_3, R_2 = \text{H}, R_3 = \text{H}, R_4 = \text{OCH}_3, R_5 = \text{OH})$

$Q_{2a} = (R_1 = \text{H}, R_2 = \text{CH}_3, R_3 = \text{OH}, R_4 = \text{H}, R_5 = \text{H})$

$Q_{2b} = (R_1 = \text{H}, R_2 = \text{CH}_3, R_3 = \text{H}, R_4 = \text{H}, R_5 = \text{H})$

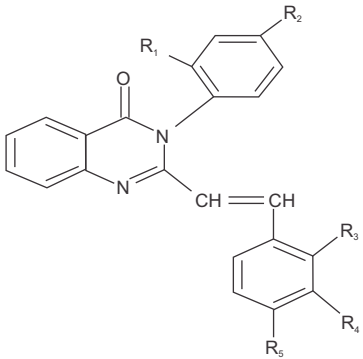
$Q_{2c} = (R_1 = \text{H}, R_2 = \text{CH}_3, R_3 = \text{OCH}_3, R_4 = \text{H}, R_5 = \text{H})$

$Q_{2d} = (R_1 = \text{H}, R_2 = \text{CH}_3, R_3 = \text{NO}_2, R_4 = \text{H}, R_5 = \text{H})$

$Q_{2e} = (R_1 = \text{H}, R_2 = \text{CH}_3, R_3 = \text{H}, R_4 = \text{H}, R_5 = \text{Cl})$

$Q_{2f} = (R_1 = \text{H}, R_2 = \text{CH}_3, R_3 = \text{H}, R_4 = \text{OCH}_3, R_5 = \text{OH})$

Table 1: Lipophilicity of the Quinazolin-4(3H)-ones



COMPOUNDS	R ₁	R ₂	R ₃	R ₄	R ₅	log ₁₀ P ^a
Q ₁	CH ₃	H	-	-	-	-
Q ₂	H	CH ₃	-	-	-	-
Q _{1a}	CH ₃	H	OH	H	H	4.76
Q _{1b}	CH ₃ H	H	H	H	H	5.10
Q _{1c}	CH ₃	H	OCH ₃	H	H	5.01
Q _{1d}	CH ₃	H	NO ₂	H	H	4.90
Q _{1e}	CH ₃	H	H	H	Cl	5.71
Q _{1f}	CH ₃	H	H	OCH ₃	OH	4.66
Q _{2a}	H	CH ₃	OH	H	H	4.74
Q _{2b}	H	CH ₃	H	H	H	5.09
Q _{2c}	H	CH ₃	OCH ₃	H	H	5.04
Q _{2d}	H	CH ₃	NO ₂	H	H	4.90
Q _{2e}	H	CH ₃	H	H	Cl	5.66
Q _{2f}	H	CH ₃	H	OCH ₃	OH	4.65

Table 2: Anti-Inflammatory Activity of Quinazolin-4(3H)-ones

S.No	Group	0hr	1hr	2hr	3hr	4hr
1	Control	1.466± 0.1212	1.616± 0.079	1.633± 0.250	1.676± 0.074	1.75± 0.061 ^a
2	Standard	1.616± 0.0793	1.45± 0.067	1.35± 0.151	1.45± 0.099	1.283± 0.060
3	Q 1 _a	1.53± 0.042	0.973± 0.074 ^{a**}	0.816± 0.147 ^{a***}	1.066± 0.042 ^{a**}	0.806± 0.047 ^{a***}
4	Q 1 _b	1.5± 0.0774	1.05± 0.067 ^{a*}	0.833± 0.150 ^{a**}	1.2± 0.051 ^a	1.000± 0.026 ^{a*}
5	Q 1 _c	1.533± 0.055	1.366± 0.071	0.916± 0.221 ^{a*}	1.116± 0.060 ^{a*}	0.923± 0.045 ^{a***}
6	Q 1 _d	1.5± 0.093	0.983± 0.064 ^{a**}	0.866± 0.140 ^{a**}	1.1± 0.063 ^{a*}	0.923± 0.045 ^{a***}
7	Q 1 _e	1.5± 0.093	1.366± 0.074	0.933± 0.176 ^{a*}	1.066± 0.049 ^{a**}	0.893± 0.037 ^{a***}
8	Q 1 _f	1.45± 0.056	1.016± 0.064 ^{a*}	1.016± 0.193 ^{a*}	0.966± 0.066 ^{a***}	0.856± 0.056 ^{a***}
9	Q 2 _a	1.616± 0.83	0.975± 0.073 ^{a**}	0.85± 0.174 ^{a**}	1.083± 0.047 ^{a**}	0.733± 0.023 ^{a***}
10	Q 2 _b	1.616± 0.94	1.433± 0.0988	0.883± 0.184 ^{a**}	1.073± 0.0792 ^{a**}	0.85± 0.076 ^{a**}
11	Q 2 _c	1.583± 0.011	1± 0.113 ^{a*}	1± 0.243 ^{a*}	1.0± 0.056 ^{a*}	0.873± 0.060 ^{a***}
12	Q 2 _d	1.65± 0.076	1.466± 0.656	0.85± 0.232 ^{a**}	1.106± 0.060 ^{a*}	0.906± 0.060 ^{a**}
13	Q 2 _e	1.133± 0.088	0.966± 0.080 ^{a**}	0.966± 0.186 ^{a**}	1.083± 0.050 ^{a**}	0.856± 0.066 ^{a***}
14	Q 2 _f	1.55± 0.076	1.4± 0.816	0.783± 0.116 ^{a***}	1.083± 0.050 ^{a**}	0.7± 0.057 ^{a***}

All values are expressed as mean ± SEMs, ^ap<0.001, ^bp<0.05, ^cp<0.01 V_s Control, ^{***}p<0.001, ^{**}p<0.05, ^{*}p<0.01 V_s Standard.

$\log_{10}P$ values (5.71) is comparatively having higher $\log_{10}P$ values than any of other substituted derivatives and very effective at increasing anti-inflammatory activity. In contrast, compounds **Q2e** with $\log_{10}P$ values (5.66) did not show the maximum activity. Therefore, the degree of lipophilicity of each drug would seem to be important, but it is not the sole determinant for anti-inflammatory activity of Quinazolones.

CONCLUSION

The quinazoline moieties are already known for the different pharmacological activities. Here we fused the two moieties (Aryl amines and aromatic substituted aldehydes) to quinazoline with the view to get good anti-inflammatory activity. Structural activity studies of the title compounds for anti-inflammatory activity reveals that the compounds having -OH, -Cl and -OCH₃ groups showed more activity.

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