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## Design and synthesis of 3-(4-Ethylphenyl)-2-substituted amino-3*H*-quinazolin-4-ones as a novel class of analgesic and anti-inflammatory agents

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### Abstract

A new series of 3-(4-ethylphenyl)-2-substituted amino-3*H*-quinazolin-4-ones were synthesized by reacting the amino group of 2-hydrazino-3-(4-ethylphenyl)-3*H*-quinazolin-4-one from 4-ethyl aniline with a variety of aldehydes and ketones. The title compounds were investigated for analgesic, anti-inflammatory and ulcerogenic index activities. The compound 2-(*N'*-3-pentylidene-hydrazino)-3-(4-ethylphenyl)-3*H*-quinazolin-4-one (**AS2**) emerged as the most active compound of the series and was moderately more potent than the reference standard diclofenac sodium. Interestingly the test compounds showed only mild ulcerogenic potential when compared to aspirin.

**Keywords:** *Quinazoline, analgesic, anti-inflammatory agents*

### Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly prescribed for the treatment of acute and chronic inflammation, pain, and fever. Most of NSAIDs act via inhibition of cyclooxygenase, thus preventing prostaglandin biosynthesis. However, this mechanism of action is also responsible for their main undesirable effects, gastrointestinal (GI) ulceration and, less frequently, nephrotoxicity. The increase in hospitalization and deaths due to GI-related disorders parallels the increased use of NSAIDs. Therefore, the discovery of new safer anti-inflammatory drugs represents a challenging goal for such a research area [1–4]. On our going medicinal chemistry research program we found that quinazolines and condensed quinazolines exhibit potent central nervous system

(CNS) activities including analgesic, anti-inflammatory [5] and anticonvulsant behavior [6]. Quinazolin-4(3*H*)-ones with 2,3-substitution are reported to possess significant analgesic, anti-inflammatory [7,8] and anticonvulsant activities [9]. Earlier we have documented some lead 2-phenyl-3-substituted quinazolines [10] (Figure 1, I), 2-methyl-3-substituted quinazolines [11] (Figure 1, II), 2-methylthio-3-substituted quinazolines [12] (Figure 1, III), and 2,3-disubstituted quinazolines [13] that exhibited good analgesic and anti-inflammatory properties. The present study is an extension of our ongoing efforts towards the development and identification of new molecules for analgesic and anti-inflammatory activities with minimal gastrointestinal ulceration side effects. With this background in the present work we have

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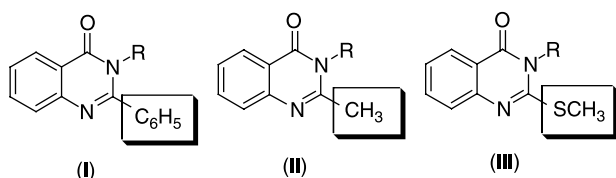


Figure 1. Lead molecule of quinazolines.

synthesized a series of 3-(4-ethylphenyl)-2-substitutedamino-3H-quinazolin-4-ones. The synthesized compounds were tested for their analgesic, anti-inflammatory and ulcerogenic index behavior.

## Materials and methods

### Chemistry

Melting points were taken in open capillaries on a Thomas Hoover melting point apparatus and are uncorrected. Infrared spectra were recorded on an FT-IR Perkin-Elmer spectrometer. The  $^1\text{H}$ -NMR spectra were recorded on a DPX-300 MHz Bruker FT-NMR spectrometer. The chemical shifts were reported as parts per million ( $\delta$  ppm) with TMS as internal standard. Mass spectra were obtained on a JEOL-SX-102 instrument using fast atom bombardment (FAB positive). Elemental analysis was performed on a Perkin-Elmer 2400 C,H,N analyzer and values were within the acceptable limits of the calculated values ( $\pm 0.4\%$ ). The progress of the reaction was monitored on silica gel plates (Merck) using chloroform-methanol (9:1) as a solvent system. Iodine was used as a developing agent. Spectral data (IR, NMR and mass spectra) confirmed the structures of the synthesized compounds and the purity of these compounds was ascertained by microanalysis. All chemicals and reagents were obtained from Aldrich (USA), Lancaster (UK) or Spectrochem Pvt.Ltd (India) and were used without further purification.

**3-(4-Ethylphenyl)-2-thioxo-2,3-dihydro-1H-quinazolin-4-one (4).** A solution of 4-ethyl aniline 1 (0.02 mol) in dimethyl sulfoxide (10 mL) was stirred vigorously. To this was added carbon disulphide (1.6 mL) and aqueous sodium hydroxide 1.2 mL (20 molar solution) drop wise during 30 min with stirring. Dimethyl sulphate (0.02 mol) was added gradually at 5-10°C. The reaction mixture was stirred for 2 h and poured into ice-water. The solid obtained was filtered, washed with water, dried and recrystallized from ethanol. Methyl anthranilate (0.01 mol) and the above prepared N-(4-ethylphenyl)-methyl dithiocarbamic acid (0.01 mol), were dissolved in ethanol (20 mL). To this anhydrous potassium carbonate (100 mg) was added and refluxed for 22 h. The reaction mixture was cooled in ice and the solid separated was filtered and purified

by dissolving in 10% alcoholic sodium hydroxide solution and re-precipitated by treating with dilute hydrochloric acid. The solid obtained was filtered, washed with water, dried and re-crystallized from ethanol. Yield = 81%, mp 265-266°C; IR (KBr)  $\text{cm}^{-1}$ : 3210 (NH), 1690 (C=O), 1218 (C=S);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 1.3-1.4 (t, 3H,  $\text{CH}_2\text{CH}_3$ ), 2.1-2.2 (q, 3H,  $\text{CH}_2\text{CH}_3$ ), 7.3-8.0 (m, 8H, ArH), 10.1 (br s, 1H, NH,  $\text{D}_2\text{O}$  Exchangeable); MS ( $m/z$ ) 282 ( $\text{M}^+$ ). *Anal.* Calcd for  $\text{C}_{16}\text{H}_{14}\text{N}_2\text{OS}$ : C, 68.06; H, 5.00; N, 9.92. Found: C, 68.09; H, 5.02; N, 9.86%.

**3-(4-Ethylphenyl)-2-methylsulfanyl-3H-quinazolin-4-one (5).** The 3-(4-ethylphenyl)-2-thioxo-2,3-dihydro-1H-quinazolin-4-one 4 (0.01 mol) was dissolved in 40 mL of 2% alcoholic sodium hydroxide solution. To this reaction mixture dimethyl sulphate (0.01 mol) was added drop wise with stirring. The stirring was continued for 1 h, the reaction mixture was then poured into ice water. The solid obtained was filtered, washed with water, dried and recrystallized from ethanol-chloroform (75:25) mixture. Yield = 85%, mp 151-153°C; IR (KBr)  $\text{cm}^{-1}$ : 1681 (C=O);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 1.5-1.6 (t, 3H,  $\text{CH}_2\text{CH}_3$ ), 2.3-2.4 (q, 3H,  $\text{CH}_2\text{CH}_3$ ), 2.7 (s, 3H,  $\text{SCH}_3$ ), 7.2-7.8 (m, 8H ArH); MS ( $m/z$ ) 296 ( $\text{M}^+$ ). *Anal.* Calcd for  $\text{C}_{17}\text{H}_{16}\text{N}_2\text{OS}$ : C, 68.89; H, 5.44; N, 9.45. Found: C, 68.86; H, 5.47; N, 9.41%.

**3-(4-Ethylphenyl)-2-Hydrazino-3H-quinazolin-4-one (6).** The 3-(4-ethylphenyl)-2-methylsulfanyl-3H-quinazolin-4-one 5 (0.01 mol) was dissolved in ethanol (25 mL). To this hydrazine hydrate (99%) (0.1 mol) and anhydrous potassium carbonate (100 mg) was added and refluxed for 39 h. The reaction mixture was cooled and poured into ice water. The solid so obtained was filtered, washed with water, dried and recrystallized from chloroform-benzene (25:75) mixture. Yield = 85%, mp 187-189°C; IR (KBr)  $\text{cm}^{-1}$ : 3362, 3281 ( $\text{NHNH}_2$ ), 1686 (C=O);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 1.6-1.7 (t, 3H,  $\text{CH}_2\text{CH}_3$ ), 2.2-2.3 (q, 3H,  $\text{CH}_2\text{CH}_3$ ), 5.3 (br s, 2H,  $\text{NH}_2$ ,  $\text{D}_2\text{O}$  Exchangeable), 7.4-8.1 (m, 8H, ArH), 9.8 (br s, 1H, NH,  $\text{D}_2\text{O}$  Exchangeable); MS ( $m/z$ ) 280 ( $\text{M}^+$ ). *Anal.* Calcd for  $\text{C}_{16}\text{H}_{16}\text{N}_4\text{O}$ : C, 68.55; H, 5.75; N, 19.99. Found: C, 68.59; H, 5.74; N, 19.95%.

**General synthetic procedure for 3-(4-ethylphenyl)-2-substitutedamino-3H-quinazolin-4-ones (A1-A15).** A mixture of 2-hydrazino-3-(4-ethylphenyl)-3H-quinazolin-4-one (6) (0.004 mol) and appropriate ketones/aldehydes (0.004 mol) in glacial acetic acid was refluxed for 36 h. The reaction mixture was poured into ice water. The solid obtained was recrystallized from ethanol.

2-(*N'*-2-Butylidene-hydrazino)-3-(4-ethylphenyl)-3*H*-quinazolin-4-one (**AS1**). Yield = 71%, mp 265–266°C; IR (KBr)  $\text{cm}^{-1}$ : 3268 (NH), 1683 (C=O), 1612 (C=N);  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  1.0–1.1 (q, 2H,  $\text{CH}_2\text{CH}_3$ ), 1.3–1.4 (q, 3H,  $\text{CH}_2\text{CH}_3$ ), 1.6–1.7 (t, 3H,  $\text{CH}_2\text{CH}_3$ ), 1.8–1.9 (t, 3H,  $\text{CH}_2\text{CH}_3$ ), 2.3–2.4 (s, 3H,  $\text{CH}_3$ ), 7.1–7.7 (m, 8H, ArH), 8.3 (br s, 1H, NH,  $\text{D}_2\text{O}$  Exchangeable); MS ( $m/z$ ): 334 ( $\text{M}^+$ ). *Anal.* Calcd. for  $\text{C}_{20}\text{H}_{22}\text{N}_4\text{O}$ : C, 71.83; H, 6.63; N, 16.75. Found: C, 71.79; H, 6.66; N, 16.73%.

2-(*N'*-3-Pentylidene-hydrazino)-3-(4-ethylphenyl)-3*H*-quinazolin-4-one (**AS2**). Yield = 80%, mp 282–283°C; IR (KBr)  $\text{cm}^{-1}$ : 3371 (NH), 1677 (C=O), 1611 (C=N);  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  1.0–1.2 (m, 4H,  $(\text{CH}_2\text{CH}_3)_2$ ), 1.5–1.7 (m, 6H,  $(\text{CH}_2\text{CH}_3)_2$ ), 1.9–2.0 (t, 3H,  $\text{CH}_2\text{CH}_3$ ), 2.4–2.5 (q, 3H,  $\text{CH}_2\text{CH}_3$ ), 7.4–8.0 (m, 8H, ArH), 8.6 (br s, 1H, NH,  $\text{D}_2\text{O}$  Exchangeable); MS ( $m/z$ ): 348 ( $\text{M}^+$ ). *Anal.* Calcd. for  $\text{C}_{21}\text{H}_{24}\text{N}_4\text{O}$ : C, 72.38; H, 6.94; N, 16.08. Found: C, 72.35; H, 6.90; N, 16.06%.

2-(*N'*-2-Pentylidene-hydrazino)-3-(4-ethylphenyl)-3*H*-quinazolin-4-one (**AS3**). Yield = 78% yield, mp 268–269°C; IR (KBr)  $\text{cm}^{-1}$ : 3268 (NH), 1685 (C=O), 1617 (C=N);  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  1.3–1.4 (t, 2H,  $\text{CH}_2\text{CH}_2\text{CH}_3$ ), 1.5–1.6 (sext, 2H,  $\text{CH}_2\text{CH}_2\text{CH}_3$ ), 1.9–2.0 (t, 3H,  $\text{CH}_2\text{CH}_3$ ), 2.2–2.3 (q, 3H,  $\text{CH}_2\text{CH}_3$ ), 2.5–2.6 (t, 3H,  $\text{CH}_2\text{CH}_2\text{CH}_3$ ), 2.7 (s, 3H,  $\text{CH}_3$ ), 7.2–7.9 (m, 8H, ArH), 8.7 (br s, 1H, NH,  $\text{D}_2\text{O}$  Exchangeable); MS ( $m/z$ ): 348 ( $\text{M}^+$ ). *Anal.* Calcd. for  $\text{C}_{21}\text{H}_{24}\text{N}_4\text{O}$ : C, 72.38; H, 6.94; N, 16.08. Found: C, 72.40; H, 6.97; N, 16.11%.

2-(*N'*-Cyclohexylidene-hydrazino)-3-(4-ethylphenyl)-3*H*-quinazolin-4-one (**AS4**). Yield = 77%, mp 226–228°C; IR (KBr)  $\text{cm}^{-1}$ : 3328 (NH), 1679 (C=O), 1611 (C=N);  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  0.8–1.7 (m, 10H, cyclohexyl), 1.9–2.0 (t, 3H,  $\text{CH}_2\text{CH}_3$ ), 2.5–2.6 (q, 3H,  $\text{CH}_2\text{CH}_3$ ), 7.4–8.0 (m, 8H, ArH), 8.5 (br s, 1H, NH,  $\text{D}_2\text{O}$  Exchangeable); MS ( $m/z$ ): 360 ( $\text{M}^+$ ). *Anal.* Calcd. for  $\text{C}_{22}\text{H}_{24}\text{N}_4\text{O}$ : C, 73.31; H, 6.71; N, 15.54. Found: C, 73.40; H, 6.70; N, 15.60%.

2-(*N'*-1-Phenylethylidene-hydrazino)-3-(4-ethylphenyl)-3*H*-quinazolin-4-one (**AS5**). Yield = 73%, mp 279–280°C; IR (KBr)  $\text{cm}^{-1}$ : 3316 (NH), 1685 (C=O), 1610 (C=N);  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  1.5–1.6 (t, 3H,  $\text{CH}_2\text{CH}_3$ ), 1.8–1.9 (q, 3H,  $\text{CH}_2\text{CH}_3$ ), 2.4 (s, 3H,  $\text{CH}_3$ ), 7.2–8.0 (m, 13H, ArH), 8.4 (br s, 1H, NH,  $\text{D}_2\text{O}$  Exchangeable); MS ( $m/z$ ): 382 ( $\text{M}^+$ ). *Anal.* Calcd. for  $\text{C}_{24}\text{H}_{22}\text{N}_4\text{O}$ : C, 75.37; H, 5.79; N, 14.64. Found: C, 75.39; H, 5.574; N, 14.68%.

2-(*N'*-2-Oxo-indolin-2-one-3-yl-idene-hydrazino)-3-(4-ethylphenyl)-3*H*-quinazolin-4-one (**AS6**). Yield = 74%, mp 216–218°C; IR (KBr)  $\text{cm}^{-1}$ : 3279 (NH), 1687 (C=O), 1610 (C=N);  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ): 1.3–1.4 (t, 3H,  $\text{CH}_2\text{CH}_3$ ), 1.9–2.0 (q, 3H,  $\text{CH}_2\text{CH}_3$ ), 7.1–8.0 (m, 12H, ArH), 8.3 (br s, 1H, NH,  $\text{D}_2\text{O}$  Exchangeable),

8.8 (br s, 1H, NH,  $\text{D}_2\text{O}$  Exchangeable); MS ( $m/z$ ): 409 ( $\text{M}^+$ ). *Anal.* Calcd. for  $\text{C}_{24}\text{H}_{19}\text{N}_5\text{O}_2$ : C, 70.40; H, 4.68; N, 17.10. Found: C, 70.45; H, 4.71; N, 17.13%.

2-(*N'*-Benzylidene-hydrazino)-3-(4-ethylphenyl)-3*H*-quinazolin-4-one (**AS7**). Yield = 77%, mp 241–242°C; IR (KBr)  $\text{cm}^{-1}$ : 3310 (NH), 1685 (C=O), 1613 (C=N);  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  1.8–1.9 (t, 3H,  $\text{CH}_2\text{CH}_3$ ), 2.2–2.3 (q, 3H,  $\text{CH}_2\text{CH}_3$ ), 6.1 (s, 1H, CH), 7.2–8.1 (m, 13H, ArH), 8.7 (br s, 1H, NH,  $\text{D}_2\text{O}$  Exchangeable); MS ( $m/z$ ): 368 ( $\text{M}^+$ ). *Anal.* Calcd. for  $\text{C}_{23}\text{H}_{20}\text{N}_4\text{O}$ : C, 74.98; H, 5.47; N, 15.20. Found: C, 74.94; H, 5.39; N, 15.21%.

2-(*N'*-(2-Chloro-benzylidene-hydrazino))-3-(4-ethylphenyl)-3*H*-quinazolin-4-one (**AS8**). Yield = 78%, mp 286–287°C; IR (KBr)  $\text{cm}^{-1}$ : 3290 (NH), 1681 (C=O), 1610 (C=N);  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  1.1–1.2 (t, 3H,  $\text{CH}_2\text{CH}_3$ ), 2.5–2.6 (q, 3H,  $\text{CH}_2\text{CH}_3$ ), 6.4 (s, 1H, CH), 7.1–8.1 (m, 12H, ArH), 8.6 (br s, 1H, NH,  $\text{D}_2\text{O}$  Exchangeable); MS ( $m/z$ ): 402 ( $\text{M}^+$ ). *Anal.* Calcd. for  $\text{C}_{23}\text{H}_{19}\text{N}_4\text{OCl}$ : C, 68.57; H, 4.75; N, 13.91. Found: C, 68.59; H, 4.71; N, 13.90%.

2-(*N'*-(4-Chloro-benzylidene-hydrazino))-3-(4-ethylphenyl)-3*H*-quinazolin-4-one (**AS9**). Yield = 77% yield, mp 239–240°C; IR (KBr)  $\text{cm}^{-1}$ : 3243 (NH), 1679 (C=O), 1610 (C=N);  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  1.8–1.9 (t, 3H,  $\text{CH}_2\text{CH}_3$ ), 2.1–2.2 (q, 3H,  $\text{CH}_2\text{CH}_3$ ), 6.0 (s, 1H, CH), 7.3–8.2 (m, 12H, ArH), 8.8 (br s, 1H, NH,  $\text{D}_2\text{O}$  Exchangeable); MS ( $m/z$ ): 402 ( $\text{M}^+$ ). *Anal.* Calcd. for  $\text{C}_{23}\text{H}_{19}\text{N}_4\text{OCl}$ : C, 68.57; H, 4.75; N, 13.91. Found: C, 68.63; H, 4.70; N, 13.87%.

2-(*N'*-(2-Nitro-benzylidene-hydrazino))-3-(4-ethylphenyl)-3*H*-quinazolin-4-one (**AS10**). Yield = 81%, mp 221–222°C; IR (KBr)  $\text{cm}^{-1}$ : 3041 (NH), 1686 (C=O), 1615 (C=N);  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  1.6–1.7 (t, 3H,  $\text{CH}_2\text{CH}_3$ ), 2.1–2.2 (q, 3H,  $\text{CH}_2\text{CH}_3$ ), 6.2 (s, 1H, CH), 7.3–8.2 (m, 12H, ArH), 8.5 (br s, 1H, NH,  $\text{D}_2\text{O}$  Exchangeable); MS ( $m/z$ ): 413 ( $\text{M}^+$ ). *Anal.* Calcd. for  $\text{C}_{23}\text{H}_{19}\text{N}_5\text{O}_3$ : C, 66.82; H, 4.63; N, 16.93. Found: C, 66.85; H, 4.68; N, 16.91%.

2-(*N'*-(4-Nitro-benzylidene-hydrazino))-3-(4-ethylphenyl)-3*H*-quinazolin-4-one (**AS11**). Yield = 71%, mp 263–264°C; IR (KBr)  $\text{cm}^{-1}$ : 3263 (NH), 1689 (C=O), 1615 (C=N);  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  1.2–1.3 (t, 3H,  $\text{CH}_2\text{CH}_3$ ), 2.4–2.5 (q, 3H,  $\text{CH}_2\text{CH}_3$ ), 6.2 (s, 1H, CH), 7.2–8.1 (m, 12H, ArH), 8.6 (br s, 1H, NH,  $\text{D}_2\text{O}$  Exchangeable); MS ( $m/z$ ): 413 ( $\text{M}^+$ ). *Anal.* Calcd. for  $\text{C}_{23}\text{H}_{19}\text{N}_5\text{O}_3$ : C, 66.82; H, 4.63; N, 16.93. Found: C, 66.81; H, 4.66; N, 16.97%.

2-(*N'*-(4-Methoxy-benzylidene-hydrazino))-3-(4-ethylphenyl)-3*H*-quinazolin-4-one (**AS12**). Yield = 79%, mp 229–230°C; IR (KBr)  $\text{cm}^{-1}$ : 3381 (NH), 1680 (C=O), 1610 (C=N);  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  1.4–1.5 (t, 3H,  $\text{CH}_2\text{CH}_3$ ), 2.0–2.1 (q, 3H,  $\text{CH}_2\text{CH}_3$ ), 3.2 (s, 3H,  $\text{OCH}_3$ ), 6.6 (s, 1H, CH), 7.0–7.9 (m, 12H, ArH), 8.5 (br s, 1H, NH,  $\text{D}_2\text{O}$  Exchangeable); MS ( $m/z$ ):



398 ( $M^+$ ). *Anal.* Calcd. for  $C_{24}H_{22}N_4O_2$ : C, 72.34; H, 5.56; N, 14.06. Found: C, 72.37; H, 5.59; N, 14.04%.

2-( $N^1$ -(2-Methyl-benzylidene-hydrazino))-3-(4-ethyl-phenyl)-3H-quinazolin-4-one (**AS13**). Yield = 77%, mp 208-209°C; IR (KBr)  $cm^{-1}$ : 3327 (NH), 1689 (C=O), 1610 (C=N);  $^1H$ -NMR ( $CDCl_3$ ):  $\delta$  1.7-1.8 (t, 3H,  $CH_2CH_3$ ), 2.5-2.6 (q, 3H,  $CH_2CH_3$ ), 2.9 (s, 3H,  $CH_3$ ), 6.2 (s, 1H, CH), 7.1-8.0 (m, 12H, ArH), 8.3 (br s, 1H, NH,  $D_2O$  Exchangeable); MS (m/z): 382 ( $M^+$ ). *Anal.* Calcd. for  $C_{24}H_{22}N_4O$ : C, 75.35; H, 5.80; N, 14.66. Found: C, 75.41; H, 5.78; N, 14.69%.

2-( $N^1$ -(4-Methyl-benzylidene-hydrazino))-3-(4-ethyl-phenyl)-3H-quinazolin-4-one (**AS14**). Yield = 74%, mp 261-263°C; IR (KBr)  $cm^{-1}$ : 3274 (NH), 1690 (C=O), 1615 (C=N);  $^1H$ -NMR ( $CDCl_3$ ):  $\delta$  1.3-1.4 (t, 3H,  $CH_2CH_3$ ), 2.1-2.2 (q, 3H,  $CH_2CH_3$ ), 2.6 (s, 3H,  $CH_3$ ), 6.4 (s, 1H, CH), 7.0-8.0 (m, 12H, ArH), 8.5 (br s, 1H, NH,  $D_2O$  Exchangeable); MS (m/z): 382 ( $M^+$ ). *Anal.* Calcd. for  $C_{24}H_{22}N_4O$ : C, 75.35; H, 5.80; N, 14.66. Found: C, 75.33; H, 5.81; N, 14.67%.

2-( $N^1$ -Phenyl-benzylidene-hydrazino)-3-(4-ethylphenyl)-3H-quinazolin-4-one (**AS15**). Yield = 79%, mp 238-239°C; IR (KBr)  $cm^{-1}$ : 3278 (NH), 1690 (C=O), 1613 (C=N);  $^1H$ -NMR ( $CDCl_3$ ):  $\delta$  1.5-1.6 (t, 3H,  $CH_2CH_3$ ), 2.3-2.4 (q, 3H,  $CH_2CH_3$ ), 3.1 (s, 3H,  $OCH_3$ ), 7.1-8.3 (m, 18H, ArH), 8.6 (br s, 1H, NH,  $D_2O$  Exchangeable); MS (m/z): 444 ( $M^+$ ). *Anal.* Calcd. for  $C_{29}H_{24}N_4O$ : C, 78.35; H, 5.44; N, 12.60. Found: C, 78.41; H, 5.47; N, 12.61%.

### Pharmacology

The synthesized compounds were evaluated for analgesic, anti-inflammatory, ulcerogenic index and antimicrobial activities. Student t-test was performed to ascertain the significance of all the exhibited activities. The test compounds and the standard drugs were administered in the form of a suspension (1% carboxymethyl cellulose as a vehicle) by oral route of administration for analgesic and anti-inflammatory. For ulcerogenicity studies the drug were administered by intraperitoneally as suspension in 10% v/v Tween 80. Each group consisted of six animals. The animals were procured from the Tetrex Biological Center, Madurai, India, and were maintained in colony cages at  $25 \pm 2^\circ C$ , relative humidity of 45-55%, under a 12 h light and dark cycle; they were fed standard animal feed. All the animals were acclimatized for a week before use. The Institutional Animal Ethics committee has approved the protocol adopted for the experimentation of animals.

### Analgesic activity

Test for analgesic activity was performed by tail-flick technique [14,15] using Swiss albino mice (25-35 gm)

of either sex selected by random sampling technique. Diclofenac sodium at a dose level of 10 mg/kg and 20 mg/kg was administered orally as reference drug for comparison. The test compounds at two dose levels (10 and 20 mg/kg) were administered orally. The reaction time was recorded at 30 min, 1, 2 and 3 h after the treatment, and cut-off time was 10. The percent analgesic activity (PAA) was calculated by the following formula,

$$PAA = \left[ \frac{T_2 - T_1}{10 - T_1} \right] \times 100$$

where  $T_1$  is the reaction time (s) before treatment, and  $T_2$  is the reaction time (s) after treatment.

### Anti-inflammatory activity

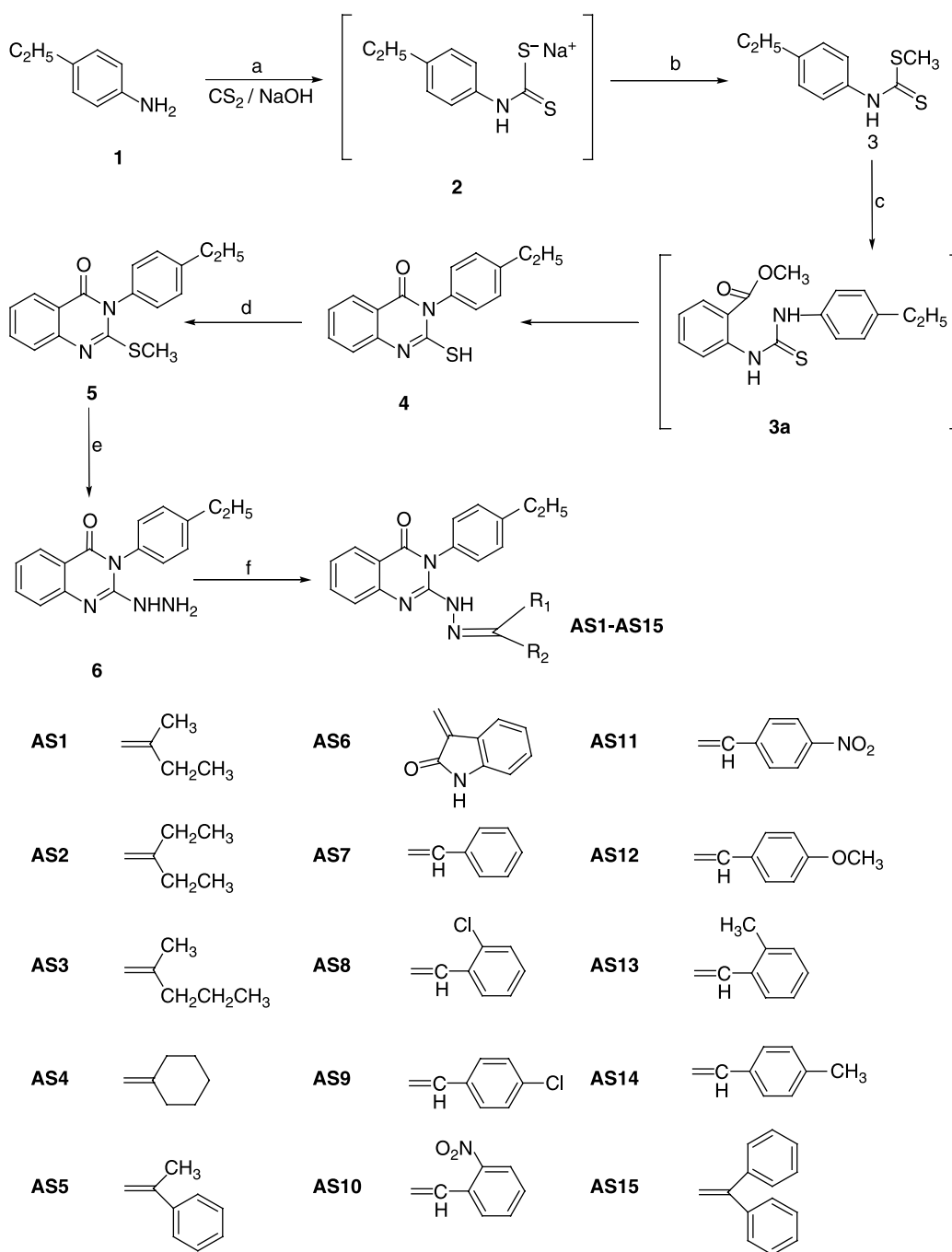
Anti-inflammatory activity was evaluated by carrageenan-induced paw oedema test in Albino rats of Wistar strain [16]. Diclofenac sodium 10 and 20 mg/kg was administered as a standard drug for comparison. The test compounds were administered at two dose levels (10 mg & 20 mg/kg). The paw volumes were measured using the mercury displacement technique with the help of a plethysmograph immediately before and 30 min, 1, 2 and 3 h after carrageenan injection. The percent inhibition of paw oedema was calculated using the following formula

$$\text{Percent inhibition } I = 100[1 - (a - x)/(b - y)]$$

Where  $x$  is the mean paw volume of rats before the administration of carrageenan and test compounds or reference compound (test group),  $a$  is the mean paw volume of rats after the administration of carrageenan in the test group (drug treated),  $b$  is the mean paw volume of rats after the administration of carrageenan in the control group,  $y$  is the mean paw volume of rats before the administration of carrageenan in the control group.

### Evaluation of ulcerogenicity index

Ulceration in rats was induced as described by Goyal et al [17]. Albino rats of Wistar strain (150-200 g) of either sex were divided into various groups each of six animals. The control groups of animals were administered only with 10% v/v Tween 80 suspension intraperitoneally. One group was administered with Aspirin (German Remedies) intraperitoneally in a dose of 200 mg/kg once daily for three days. The remaining group of animals was administered with test compounds intraperitoneally in a dose of 20 mg/kg. On fourth day, pylorus was ligated as per the method of Shay et al [18]. Animals were fasted for 36 h before the pylorus ligation procedure. Four hours after the ligation, animals were sacrificed.



Scheme 1. Synthesis of 3-(2-ethylphenyl)-2-substitutedamino-3H-quinazolin-4-ones. **Reagents and conditions:** (a) DMSO, rt, 30 min; (b)  $(\text{CH}_3)_2\text{SO}_4$ , 5–10°C, 2 h; (c) Methyl anthranilate (3),  $\text{K}_2\text{CO}_3$ , ethanol reflux for 22 h; (d) 2% alcoholic NaOH,  $(\text{CH}_3)_2\text{SO}_4$ , rt, 1 h; (e)  $\text{NH}_2\text{NH}_2$ ,  $\text{K}_2\text{CO}_3$ , ethanol reflux for 39 h; (f)  $(\text{R}_2\text{R}_1)\text{CO}$ ;  $\text{CH}_3\text{COOH}$  reflux, 36 h.

The stomach was removed and opened along Table the greater curvature. Ulcer index was determined by the method of Ganguly and Bhatnagar [19] and recorded in Table III.

#### Statistical analysis

Statistical analysis of the biological activity of the synthesized compounds on animals was evaluated

using a one-way analysis of variance (ANOVA). In all cases, post-hoc comparisons of the means of individual groups were performed using Tukey's test. A significance level of  $P < 0.05$  denoted significance in all cases. All values are expressed as mean  $\pm$  SD (standard deviations). For statistical analysis we have used GraphPad Prism 3.0 version. (GraphPad Prism 3.0 version, GraphPad Software, Inc.11452 El Camino Real, #215, San Diego, CA 92130 USA).

## Results and discussion

### Synthesis and characterization of AS1-AS 15

The key intermediate 3-(4-ethylphenyl)-2-thioxo-2,3-dihydro-1*H*-quinazolin-4-one **4** was synthesized by reacting 4-ethyl aniline (**1**) with carbon disulphide and sodium hydroxide in DMSO to give sodium dithiocarbamate, which was methylated with dimethyl sulphate to afford the dithiocarbamic acid methyl ester (**2**) (Scheme 1). Compound **2** on reflux with methyl anthranilate (**3**) in ethanol yielded the desired 3-(4-ethylphenyl)-2-thioxo-2,3-dihydro-1*H*-quinazolin-4-one (**4**) via the thiourea intermediate in good yield (81%). The product obtained was cyclic and not an open chain thiourea **3a**. It was confirmed by IR spectra of compound **4** showed intense peaks at  $3210\text{ cm}^{-1}$  for cyclic thio urea (NH),  $1690\text{ cm}^{-1}$  for carbonyl (C=O) and  $1218\text{ cm}^{-1}$  for thioxo (C=S) stretching.  $^1\text{H}$  NMR spectra of **4** showed a triplet at  $\delta$  1.3-1.4 ppm due to  $\text{CH}_3$  group; a quartet at  $\delta$  2.1-2.2 due to  $\text{CH}_2$  and a multiplet at  $\delta$  7.3-8.0 ppm for aromatic (8H) protons and a broad singlet at  $\delta$  10.1 ppm indicating the presence of NH. Data from the elemental analyses were found to be in conformity with the assigned structure. Further the molecular ion recorded in the mass spectra is also in agreement with the molecular weight of the compound.

The 3-(4-ethylphenyl)-2-methylsulfonyl-3*H*-quinazolin-4-one **5** was obtained by dissolving **4** in 2% alcoholic sodium hydroxide solution and methylating with dimethyl sulphate with stirring at room temperature. The IR spectra of **5** showed disappearance of NH and C=S stretching signals of cyclic thiourea. It showed a peak for carbonyl (C=O) stretching at  $1681\text{ cm}^{-1}$ . The  $^1\text{H}$  NMR spectra of compound **5** showed triplet at  $\delta$  1.5-1.6 ppm due to  $\text{CH}_3$ ; a quartet at  $\delta$  2.3-2.4 due to  $\text{CH}_2$ ; a singlet at  $\delta$  2.7 ppm  $\text{SCH}_3$  and multiplet at  $\delta$  7.2-7.8 ppm was observed for aromatic (8H) protons. Data from the elemental analyses and molecular ion recorded in the mass spectra further confirmed the assigned structure.

Nucleophilic displacement of methylthio group of **5** with hydrazine hydrate was carried out using ethanol as solvent to afford 3-(4-ethylphenyl)-2-hydrazino-3*H*-quinazolin-4-one **6**. The long duration of reaction (39 h) required might be due to the presence of bulky aromatic ring at position 3, which might have reduced the reactivity of quinazoline ring system at C-2 position. The formation of **6** was confirmed by the presence of NH and  $\text{NH}_2$  signals at  $3362\text{--}3281\text{ cm}^{-1}$  in the IR spectra. It also showed a peak for carbonyl (C=O) at  $1686\text{ cm}^{-1}$ . The  $^1\text{H}$  NMR spectra of the compound **6** showed triplet at  $\delta$  1.6-1.7 ppm due to  $\text{CH}_3$  group; a quartet at  $\delta$  2.2-2.3 due to  $\text{CH}_2$ , broad singlet at  $\delta$  5.3 ppm and 9.8 ppm due to  $\text{NH}_2$  and NH respectively, a multiplet at  $\delta$  7.4-8.1 ppm was observed for aromatic (8H) protons. Data from the elemental analyses were found to be in conformity with the

assigned structure. Further the molecular ion recorded in the mass spectra is also in agreement with the molecular weight of the compound.

The title compounds 3-(4-ethylphenyl)-2-substituted amino-3*H*-quinazolin-4-ones **AS1-AS15** were obtained by the condensation of amino group of 2-hydrazino-3-(4-ethyl phenyl)-3*H*-quinazolin-4-one (**6**) with a variety of aldehydes and ketones. The formation of title product is indicated by the disappearance of peak due to  $\text{NH}_2$  of the starting material in IR and  $^1\text{H}$ -NMR spectrum of all the compounds **AS1-AS15**. The IR and  $^1\text{H}$ -NMR spectrum these compounds showed the presence of peaks due to ( $\text{N}=\text{CR}^1\text{R}^2$ ) carbonyl (C=O), NH and Aryl groups. The mass spectrum of these compounds showed molecular ion peaks corresponding to their molecular formula and are in confirmed with the assigned structure. In mass spectrum of compounds **AS1-AS15** a common peak at  $m/z$  144 corresponding to quinazolin-4-one moiety appeared in all mass spectra. Elemental (C, H, N) analyses satisfactorily confirmed elemental composition and purity of the synthesized compounds.

### Pharmacology

**Analgesic activity.** Evaluation of analgesic activity was performed by the tail-flick technique [14,15] using Swiss albino mice. The results of analgesic testing indicate that the test compounds exhibited moderate analgesic activity at 30 minutes of reaction time and an increase in activity at 1 h which reached a peak level at 2 hours. Decline in activity was observed at 3 hours (Table I). Compound **AS1** with 1-methylpropylidene substituent showed good activity; with the increased lipophilicity (1-ethylpropylidene group, compound **AS2**) showed increase in activity. Replacement of 1-ethylpropylidene group with its isomer 1-methylbutylidene group (compound **AS3**) retains the activity. Replacement of C-2 alkyl chain with a cycloalkyl group and an aralkyl group (compounds **AS4** and **AS5** respectively) leads to a moderate decrease in activity. Placement of aryl group at the N-3 position (compounds **AS6**, **AS7** and **AS13-AS15**) also results in decreasing the activity. Placement of electron withdrawing group at N-3 aryl ring (compounds **AS8-AS12**) leads to further decrease of activity. Compound 2-(1-ethylpropylidene)-hydrazino-3-(4-ethylphenyl)-quinazolin-4(3*H*)-one (**AS2**) emerged as the most active analgesic agent and it is moderately more potent when compared to the reference standard diclofenac.

**Anti-inflammatory activity.** Anti-inflammatory activity was evaluated by the carragenenan-induced paw edema test in Albino rats of Wistar strain [16]. The anti-inflammatory activity data (Table II) indicated that

Table I. Analgesic activity of **AS1-AS15**.

Compound	Dose (mg/kg)	Percent Analgesic activity			
		30 min	1 h	2 h	3 h
<b>AS1</b>	10	58 ± 1.36**	60 ± 1.39**	63 ± 1.63***	35 ± 1.81*
	20	70 ± 1.29***	73 ± 1.63***	77 ± 1.48***	41 ± 1.57*
<b>AS2</b>	10	60 ± 1.72***	65 ± 1.29***	68 ± 1.74***	40 ± 1.53*
	20	74 ± 1.48***	78 ± 1.64***	80 ± 1.82***	51 ± 1.48*
<b>AS3</b>	10	55 ± 1.62**	63 ± 1.57***	66 ± 1.94***	36 ± 1.93*
	20	58 ± 1.92**	74 ± 1.29***	78 ± 1.56***	42 ± 1.52*
<b>AS4</b>	10	44 ± 1.38*	47 ± 1.47*	53 ± 1.84*	33 ± 1.47*
	20	53 ± 1.58*	61 ± 1.52**	62 ± 1.92**	39 ± 1.94*
<b>AS5</b>	10	45 ± 1.26*	49 ± 1.83*	57 ± 1.68**	32 ± 1.43*
	20	56 ± 1.74**	61 ± 1.55**	63 ± 1.82***	40 ± 1.23*
<b>AS6</b>	10	42 ± 1.28*	46 ± 1.59*	48 ± 1.38*	31 ± 1.53*
	20	52 ± 1.49*	55 ± 1.48**	57 ± 1.54**	38 ± 1.22*
<b>AS7</b>	10	43 ± 1.72*	50 ± 1.54*	51 ± 1.39*	28 ± 1.85*
	20	55 ± 1.39*	55 ± 1.52**	58 ± 1.85**	39 ± 1.52*
<b>AS8</b>	10	37 ± 1.56*	38 ± 1.93*	44 ± 1.65*	31 ± 1.94*
	20	48 ± 1.82*	49 ± 1.56*	55 ± 1.86**	38 ± 1.43*
<b>AS9</b>	10	37 ± 1.54	42 ± 1.93*	45 ± 1.62*	29 ± 1.29*
	20	50 ± 1.82*	51 ± 1.67*	58 ± 1.43**	37 ± 1.85*
<b>AS10</b>	10	35 ± 1.43*	44 ± 1.52*	48 ± 1.59**	30 ± 1.23*
	20	46 ± 1.49*	53 ± 1.56*	56 ± 1.85**	39 ± 1.39*
<b>AS11</b>	10	37 ± 1.95*	46 ± 1.93*	50 ± 1.53*	30 ± 1.74*
	20	48 ± 1.64*	51 ± 1.46*	53 ± 1.49**	37 ± 1.84*
<b>AS12</b>	10	37 ± 1.63*	45 ± 1.45*	51 ± 1.90**	29 ± 1.22*
	20	46 ± 1.71*	51 ± 1.60*	58 ± 1.62**	35 ± 1.49*
<b>AS13</b>	10	48 ± 1.59*	53 ± 1.54*	57 ± 1.49**	31 ± 1.33*
	20	57 ± 1.93**	61 ± 1.39***	66 ± 1.73***	38 ± 1.69*
<b>AS14</b>	10	42 ± 1.83*	51 ± 1.58*	59 ± 1.60*	30 ± 1.60*
	20	55 ± 1.27**	59 ± 1.63***	67 ± 1.53**	36 ± 1.35*
<b>AS15</b>	10	43 ± 1.65*	46 ± 1.52*	53 ± 1.82*	32 ± 1.95*
	20	51 ± 1.60**	55 ± 1.72**	60 ± 1.59**	39 ± 1.39*
<b>Control Diclofenac</b>		2 ± 0.35	6 ± 0.49	4 ± 0.59	4 ± 0.91
	10	37 ± 1.69*	43 ± 1.42*	45 ± 0.92*	33 ± 0.96*
	20	46 ± 0.95*	55 ± 1.16**	62 ± 1.49***	39 ± 1.13*

Each value represents the mean ± SD (n = 6). Significance levels \*p < 0.5, \*\*p < 0.01 and \*\*\*p < 0.001 as compared with the respective control.

all the test compounds protected rats from carrageenan-induced inflammation moderately at 30 minutes of reaction time with increased activity at 1 hours that reached a peak level at 2 h. Decline in activity was observed at 3 hours. The compound 2-(1-ethylpropylidene)-hydrazino-3-(4-ethylphenyl)-quinazolin-4(3*H*)-one (**AS2**) showed the most potent anti-inflammatory activity of the series and it is moderately more potent when compared to the reference standard diclofenac sodium.

**Ulcer index.** The ulcer index of the test compounds (Table III) reveal that the compounds with aliphatic substituents (compounds **AS1-AS4**) showed negligible ulcer index, whereas aryl substituents (compounds **AS5-AS7** and **AS13-AS15**) exhibited little increase in ulcer index and the aryl substituents containing electron withdrawing groups (compounds **AS8-AS12**) exhibited higher ulcer index over other test compounds. When

compared to the reference standards aspirin (ulcer index 1.73 ± 0.41) and diclofenac (ulcer index 1.65 ± 0.59) the test compounds exhibited about 35% to 50% of the ulcer index of the reference standards. The compound 2-(*N'*-3-Pentylidene-hydrazino)-3-(4-ethylphenyl)-3*H*-quinazolin-4-one (**AS2**) and 2-(*N'*-2-Pentylidene-hydrazino)-3-(4-ethylphenyl)-3*H*-quinazolin-4-one (**AS3**) exhibited least ulcer index (0.51 ± 1.39 and 0.48 ± 1.61 respectively) among the test compounds which is about one third of the ulcer index of reference standards aspirin and diclofenac. The compound 2-(*N'*-(4-Chloro-benzylidene)-hydrazino)-3-(4-ethylphenyl)-3*H*-quinazolin-4-one (**AS9**) showed the highest ulcer index (0.83 ± 1.55) among the test compounds which is about 50% of the ulcer index of reference standards aspirin and diclofenac.

In our earlier studies [10–13] we observed that the presence of alkyl groups exhibited more analgesic and anti-inflammatory activities over aryl groups at the



Table II. Anti-inflammatory activity of synthesized compounds (AS1-AS15).

Compound	Dose (mg/kg)	Percent protection			
		30 min	1 h	2 h	3 h
AS1	10	41 ± 1.91*	45 ± 1.36**	46 ± 1.63**	30 ± 1.39*
	20	51 ± 1.57***	56 ± 1.52***	61 ± 1.57***	36 ± 1.71
AS2	10	46 ± 1.52**	48 ± 1.48*	53 ± 1.96***	33 ± 1.75*
	20	55 ± 1.57***	65 ± 1.52***	69 ± 1.65***	40 ± 1.28**
AS3	10	44 ± 1.85**	46 ± 1.28***	50 ± 1.94**	31 ± 1.75*
	20	53 ± 1.47***	62 ± 1.92***	66 ± 1.54***	39 ± 1.39**
AS4	10	32 ± 1.95*	36 ± 1.59	41 ± 1.48*	28 ± 1.65*
	20	43 ± 1.43**	48 ± 1.72**	52 ± 1.52***	35 ± 1.49*
AS5	10	35 ± 1.49*	40 ± 1.59**	41 ± 1.95**	27 ± 1.96*
	20	43 ± 1.94**	50 ± 1.83**	50 ± 1.54**	36 ± 1.69*
AS6	10	32 ± 1.53*	36 ± 1.34*	41 ± 1.93*	29 ± 1.53
	20	40 ± 1.48*	43 ± 1.58*	49 ± 1.50***	37 ± 1.82
AS7	10	31 ± 1.59*	35 ± 1.94*	38 ± 1.63**	28 ± 1.53*
	20	39 ± 1.63*	45 ± 1.74**	46 ± 1.68**	36 ± 1.94*
AS8	10	29 ± 1.50*	33 ± 1.34*	33 ± 1.93*	25 ± 1.74*
	20	37 ± 1.67*	42 ± 1.95**	42 ± 1.55**	33 ± 1.95*
AS9	10	32 ± 1.53*	34 ± 1.53*	37 ± 1.59*	28 ± 1.63*
	20	41 ± 1.39*	42 ± 1.65**	44 ± 1.48**	36 ± 1.35
AS10	10	33 ± 1.50*	36 ± 1.60*	41 ± 1.85*	28 ± 1.28*
	20	40 ± 1.53*	42 ± 1.83**	45 ± 1.83**	37 ± 1.65*
AS11	10	30 ± 1.39*	35 ± 1.49*	35 ± 1.63*	27 ± 1.59*
	20	41 ± 1.63*	44 ± 1.63**	46 ± 1.39**	36 ± 1.39*
AS12	10	31 ± 1.52*	32 ± 1.59*	32 ± 1.74*	28 ± 1.73*
	20	40 ± 1.73*	42 ± 1.36**	43 ± 1.49*	36 ± 1.65*
AS13	10	36 ± 1.02	41 ± 1.60*	34 ± 1.38*	29 ± 1.49*
	20	44 ± 1.49**	50 ± 1.63**	43 ± 1.60**	37 ± 1.54
AS14	10	32 ± 1.81*	34 ± 1.52	37 ± 1.54**	29 ± 1.59*
	20	45 ± 1.49**	47 ± 1.40**	48 ± 1.50***	36 ± 1.62*
AS15	10	36 ± 1.51*	35 ± 1.73*	36 ± 1.74*	26 ± 1.47*
	20	45 ± 1.63**	48 ± 1.96**	49 ± 1.53**	37 ± 1.93*
Control Diclofenac		5.1 ± 0.29	6.1 ± 0.27	5.7 ± 0.32	3.2 ± 0.93
	10	32 ± 0.63*	38 ± 1.58*	39 ± 1.97*	33 ± 0.93*
	20	45 ± 1.61**	52 ± 0.92***	60 ± 1.52***	42 ± 1.36**

Each value represents the mean ± SD (n = 6). Significance levels \*p < 0.5, \*\*p < 0.01 and \*\*\*p < 0.001 as compared with the respective control.

N-3 position. Hence in the C-2 position also we made a substitution in such a way to increase lipophilicity of the molecule. The placement of such a group enhanced the analgesic and anti-inflammatory activities. The most active compound of the C-2 phenyl series 1-diethyl-3-(2-phenyl quinazolin-3-yl-4(3*H*)-one) thiourea (Figure 1, **I**) showed 44% & 58% analgesic and 38% & 53% anti-inflammatory activity at the dose of 10 & 20 mg/kg respectively, at the reaction time of 2 hours [10]. Whereas the C-2 methyl series lead molecule 1-pyrrolidinyl-3-(2-methyl quinazolin-3-yl-4(3*H*)-one) thiourea (Figure 1, **II**) exhibited 50% & 65% analgesic and 44% & 60% anti-inflammatory activity at the dose of 10 & 20 mg/kg respectively at the reaction time of 2 hours [11]. Introduction of sulphur atom at C-2 position in the above series i.e. by placing methylthio group at C-2 position [12] compound 1-diethyl-3-(2-methylthio quinazolin-3-yl-4(3*H*)-one) thiourea (Figure 1, **III**) exhibited 56% & 67% analgesic activity, 40% & 62% anti-inflammatory activity at 10 & 20 mg/kg respectively at the reaction time of 2 hours.

Table III. Evaluation of ulcerogenicity index.

Compound	Ulcer index
AS1	0.53 ± 1.35*
AS2	0.51 ± 1.39*
AS3	0.48 ± 1.61*
AS4	0.55 ± 1.84*
AS5	0.57 ± 1.67*
AS6	0.59 ± 1.94*
AS7	0.63 ± 1.05*
AS8	0.77 ± 1.63*
AS9	0.83 ± 1.55*
AS10	0.78 ± 1.61*
AS11	0.80 ± 1.72*
AS12	0.74 ± 1.73*
AS13	0.61 ± 1.39*
AS14	0.67 ± 1.44*
AS15	0.63 ± 1.55*
Control	0.15 ± 0.32
Diclofenac	1.65 ± 0.59**
Aspirin	1.73 ± 0.41**

Each value represents the mean ± SD (n = 6). Significance levels \*p < 0.05 and \*\*p < 0.01 as compared with the respective control.

Results of analgesic and anti-inflammatory activities of the present series showed that moderate enhancement of activity, compound **AS2** exhibited 68% & 80% analgesic activity at 10 and 20 mg/kg dose level respectively at the reaction time of 2 hours. The compound **AS2** showed 53% & 69% anti-inflammatory activity at the dose of 10 and 20 mg/kg respectively at the reaction of 2 hours. Interestingly these compounds showed one third of the ulcer index of the reference NSAID's aspirin and diclofenac. Hence this series could be developed as a novel class of analgesic and anti-inflammatory agents.

## References

- [1] Van Ryn J, Botting RM. New insights into the mode of action of anti-inflammatory drugs. *Inflamm Res* 1995;44:1–10.
- [2] Van Ryn J, Trummlitz G, Pairet M. COX-2 selectivity and inflammatory processes. *Curr Med Chem* 2000;7:1145–1161.
- [3] Van Ryn J. Inhibition of prostaglandin synthesis as a mechanism of action for aspirin-like drugs. *Nature: New Biology* 1971;231:232–235.
- [4] Beuck M. Nonsteroidal Anti-inflammatory drugs: A new generation of Cyclooxygenase inhibitors. *Angew Chem Int Ed* 1999;38:631–633.
- [5] Alagarsamy V, Revathi R, Vijayakumar S, Ramseshu KV. Synthesis and pharmacological investigation of some novel 2,3-disubstituted quinazolin-4(3*H*)-ones as analgesic and anti-inflammatory agents. *Pharmazie* 2003;58:233–236.
- [6] Alagarsamy V, Thangathirupathy A, Mandal SC, Rajasekaran S, Vijayakumar S, Revathi R, Anburaj J, Arunkumar S, Rajesh S. Pharmacological evaluation of 2-substituted (1,3,4) thiadiazolo quinazolines. *Indian J Pharm Sci* 2006; 68: 108–111.
- [7] Abdel-Rahman AE, Bakhite EA, Al-Taifi EA. Synthesis and antimicrobial testing of some new S-substituted-thiopyridines, thienopyridines, pyridothienopyrimidines and pyridothienotriazines. *Pharmazie* 2003;58:372–377.
- [8] Chambhare RV, Khadse BG, Bobde AS, Bahekar RH. Synthesis and preliminary evaluation of some N-[5-(2-furanyl)-2-methyl-4-oxo-4*H*-thieno[2,3-*d*]pyrimidin-3-yl]-carboxamide and 3-substituted-5-(2-furanyl)-2-methyl-3*H*-thieno[2,3-*d*]pyrimidin-4-ones as antimicrobial agents. *Eur J Med Chem* 2003; 38: 89–100.
- [9] Santagati NA, Caruso A, Cutuli VMC, Caccamo F. Synthesis and pharmacological evaluation of thieno[2,3-*d*]pyrimidin-2,4-dione and 5*H*-pyrimido [5,4-*b*]indol-2,4-dione derivatives. *Il Farmaco* 1995;50:689–695.
- [10] Alagarsamy V, Solomon VR, Vanikavitha G, Paluchamy V, Chandran MR, Sujin AA, Thangathirupathy A, Amuthalakshmi S, Revathi R. Synthesis, analgesic, anti-inflammatory and antibacterial activities of some novel 2-phenyl-3-substituted quinazolin-4(3*H*) ones. *Biol Pharm Bull* 2002; 25: 1432–1435.
- [11] Alagarsamy V, Murugananthan G, Venkateshperumal R. Synthesis, analgesic, anti-inflammatory and antibacterial activities of some novel 2-methyl-3-substituted quinazolin-4-(3*H*)-ones. *Biol Pharm Bull* 2003;26:1711–1714.
- [12] Alagarsamy V, Rajesh R, Meena R, Vijaykumar S, Ramseshu KV, Duraianandakumar T. Synthesis, analgesic, anti-inflammatory and antibacterial activities of some novel 2-methylthio-3-substituted quinazolin-4(3*H*)-ones. *Biol Pharm Bull* 2004; 27:652–656.
- [13] Alagarsamy V, Muthukumar V, Pavalarani N, Vasanthanathan P, Revathi R. Synthesis, analgesic and anti-inflammatory activities of some novel 2,3-disubstituted quinazolin-4(3*H*)-ones. *Biol Pharm Bull* 2003;26:557–559.
- [14] Kulkarni SK. Heat and other physiological stress-induced analgesia: Catecholamine mediated and naloxone reversible response. *Life Sci* 1980;27:185–188.
- [15] D'Armour RE, Smith DL. A method for determining loss of pain sensation. *J Pharm Exp Therap* 1941;72:74–78.
- [16] Winter CA, Risely EA, Nuss GW. Carageenin induced oedema in hind paw of the rat as assay for anti-inflammatory drugs. *Exp Biol Med* 1962;111:544–547.
- [17] Goyal RK, Chakrabarti A, Sanyal AK. The effect of biological variables on the anti-ulcerogenic effect of vegetable plantain banana. *Planta Medica* 1985;29:85–88.
- [18] Shay M, Komarov SA, Fels D, Meranze D, Grunstein H, Siplet H. A simple method for the uniform production of gastric ulceration in the rats. *Gastroenterol* 1945;5:43–61.
- [19] Ganguly AK, Bhatnagar OP. Effect of bilateral adrenalectomy on production of restraint ulcers in the stomach of albino rats. *Can J Phys Pharmacol* 1973;51:748–750.