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# Synthesis, analgesic and anti-inflammatory screening of novel schiff bases of 3-amino-2-methyl quinazolin 4-(3H)-one

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#### **Abstract**

In the present study, a novel Schiff bases were synthesized by condensation of 3-amino-2-methyl quinazolin-4-(3H)-ones with different aromatic aldehydes. The 3-amino-2-methyl quinazolin-4-(3H)-one was synthesized from anthranilic acid via 2-methyl Benzoxazin-4-one. The chemical structures of the synthesized compounds were confirmed by means of IR, <sup>1</sup>H-NMR, <sup>13</sup>C-NMR, Mass spectral and Elemental analysis. These compounds were screened for the analgesic activity by tail-immersion method and also for anti-inflammatory activity by carrageenan induced paw oedema method in rats at a dose of 100 mg/kg body weight. Among the tested compound 3-(4-methylbenzylideneamino)-2-methyl quinazolin-4-(3H)-one (4f) exhibited better analgesic activity when compared to standard pentazocine. Out of twelve synthesized compounds 3-(4-hydroxybenzylideneamino)-2-methyl quinazolin-4-(3H)-one (4g) exhibited better anti-inflammatory activity when compared to standard indomethacin. From the above results it may concluded that compounds containing electron donating groups exhibits better analgesic activity than electron withdrawing groups. The substituted phenyl ring at 3<sup>rd</sup> position in the synthesized compounds was found to possess promising anti-inflammatory activity than unsubstituted phenyl ring.

**Key words**: 3-amino-2-methyl quinazolin-4-(3H)-one, schiff base, analgesic and anti-inflammatory.

## INTRODUCTION

Quinazolin-4-(3H)-ones reported to possess a wide range of biological activities such as antimicrobial [1-7], analgesic [8,9], anti-inflammatory [10], anti-convulsant [11,12], anti-cancer [13,14], anti-tubercular [15,16], anti-malarial [17], anti-viral [18,19] and anti-helmintic [20] activities. Quinazolin 4-(3H)-ones with substitution at 3<sup>rd</sup> position has been reported to be associated with antimicrobial properties [21,22]. The various substituent at 3<sup>rd</sup> position of the quinazolin-4(3H)-one which were reported, are various substituted phenyl ring moieties [23-25], bridged phenyl rings [26,27], heterocyclic rings [28,29] and aliphatic system [30,31]. In addition, In general schiff bases and presence of pharmacophores like –NO<sub>2</sub>, phenolic OH, -Cl, -CH<sub>3</sub> and – OCH<sub>3</sub> are reported to possess analgesic and anti-inflammatory activities. These observation led to the conception that a novel series of Schiff bases of 3-amino-2-methyl quinazolin-4-(3H)-ones 4a-4l were synthesized using different aromatic aldehydes by condensation and their chemical structure were confirmed by IR, <sup>1</sup>H-NMR, <sup>13</sup>C-NMR, Mass spectral and Elemental analysis. All the synthesized compounds were screened for their analgesic activity by tail-immersion method in mice using pentazocine (10 mg/kg) as a standard drug. In addition, all the title compounds were also evaluated for anti-inflammatory activity by carrageenan-induced paw oedema method in rats using indomethacin (10 mg/kg) as a standard drug.

#### MATERIALS AND METHODS

The melting points were taken in open capillary tube and are uncorrected. The IR spectra of the compounds were recorded on ABB Bomem FT-IR spectrometer MB 104 with KBr pellets. The  $^1\mathrm{H}$  (300 MHz) and  $^{13}\mathrm{C\text{-}NMR}$  (300 MHz) spectra were recorded on a Bruker 300 NMR spectrometer (with TMS for  $^1\mathrm{H}$  and CDCl<sub>3</sub> for  $^{13}\mathrm{C}$  as internal references). Mass spectra were recorded on Shimadzu GC MS QP 5000. Microanalyses were obtained with an elemental Analyses system GmbH VarioEL V300 element analyzer. The purity of the compounds was checked by TLC on pre-coated SiO<sub>2</sub> gel (HF<sub>254</sub>, 200 mesh) aluminium plates (E Merk) using ethyl acetate: n-hexane (20:80) and visualized in UV chamber. The reagent grade chemicals were purchased from the commercial sources and purified by either distillation or recrystallisation before use.

#### **Chemistry**

In the present study anthranilic acid 1 was treated with acetic anhydride to form 2-methyl benzoxazin-4-one 2 which further reacted with hydrazine hydrate resulted into 3-amino-2-methyl quinazolin-4-(3H)-ones 3. The compound 3 was subjected to react with various aromatic aldehydes in presence of ethanol as a solvent to form schiff bases.

## General method of synthesis (4a-4l)

The 3-amino 2-methyl quinazolin-4(3H)-one **3** was prepared according to reported literature [1]. Equimolar quantities (0.01 mol) of 3-amino 2-methyl quinazolin 4-(3H)-one and aromatic aldehydes were dissolved in 20 ml of ethanol and refluxed for 8 hrs, then kept aside for 3 days, the product which separated out was filtered, dried and recrystallised from absolute ethanol.

## Pharmacological screening

#### **Animals**

The animals used in the present study such as swiss albino mice weighing 20-25 gm and wistar rats weighing 150-200 gm were procured from C.L.Baid Metha College of Pharmacy, Chennai, India. Animals were maintained in colony cages at  $25\pm2^{\circ}$ C, relative humidity of 45-55%, maintained under 12 h light and dark cycle and were fed with standard animal feed and water *ad* 

*libitum*. Animals were maintained under standard conditions in an animal house approved by committee for the purpose of control and supervision on experiments on animals (CPCSEA). Institutional Animal Ethics Committee approved the experimental protocol. The entire animals were acclimatized for a week before use.

## **Acute toxicity studies**

Acute toxicity test was performed for the entire synthesized compound to ascertain the LD<sub>50</sub> values as per OECD guidelines [32]. The experimental dose was selected between the minimum effective dose and maximal non lethal dose.

## Analgesic activity (Tail immersion method in mice)

The analgesic activity [33] was determined by tail-immersion method. Swiss mice (n=6) of either sex selected by random sampling technique was used for the study. Pentazocine at the dose of 10 mg/kg (i.p.) was administered as standard drug for comparison. The test compounds at 100 mg/kg dose level were administered orally. The animals were held in position by a suitable restrainer with the tail extending out and the tail (up to 5 cm) was taken, dipped in a beaker of water maintained at  $55\pm0.5^{\circ}$ C. The time in sec taken to withdraw the tail clearly out of water was taken as the reaction time. The first reading (0 min) was taken immediately after the administration of the test compound and subsequent reaction time was recorded at 30, 60, 120 and 180 min after the administration of compounds. A cut off point of 15 sec was observed to prevent the tail damage. The percentage analgesic activity was calculated using the following formula and the results are presented in table 1.

$$PAA = [(T_2-T_1)/T_2] \times 100$$

Where,  $T_1$  and  $T_2$  is the reaction time (in sec) before and after treatment respectively; PAA is the percentage analgesic activity.

## Anti-inflammatory activity (carrageenan- induced paw oedema method in rats)

Anti-inflammatory activity [34] was performed by carrageenan- induced paw oedema method in rats. Indomethacin (10 mg/kg, i.p) was administered as standard drug for comparison. The synthesized compounds were administered at 100 mg/kg dose level were administered orally 30 min prior to the administration of 0.1 ml/kg body weight of carrageenan in saline (1% w\v) into the lateral malleolus of the sub-planter region of the left hind paw. 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 percentage inhibition of paw odema was calculated by using the following formula and the results are depicted in table 2.

% protection = [(Control-Test)/Control] X 100

#### RESULTS AND DISCUSSION

#### Chemistry

IR, <sup>1</sup>H-NMR, <sup>13</sup>C-NMR, Mass spectra and Elemental analysis were consistent with the assigned structures.

## 3-Amino 2-methyl quinazolin-4(3H)-one (3)

Yield: 73%; m.p.141-143 °C; IR (KBr, cm<sup>-1</sup>): 3030 (Ar-CH), 2927 (CH in CH<sub>3</sub>), 1716 (C=O), 1464 (C=C), 1332 (N-H).  $^{1}$ H-NMR (CDCl<sub>3</sub>) δ: 7.41-7.82 (m, 4H; C<sub>5</sub>,C<sub>6</sub>,C<sub>7</sub>,C<sub>8</sub>,Ar-H), 1.94 (s, 2H; -NH<sub>2</sub>), 0.97 (s, 3H; -CH<sub>3</sub>).  $^{13}$ C-NMR (CDCl<sub>3</sub>) δ: 164.2 (C<sub>2</sub>), 161.7 (C<sub>4</sub>), 133.6 (C<sub>7</sub>), 128.2 (C<sub>5</sub>), 127.6 (C<sub>6</sub>), 122.3 (C<sub>8</sub>), 18.9 (-CH<sub>3</sub>). EI-MS m/z (M+): 175 (Calcd for C<sub>9</sub>H<sub>9</sub>N<sub>3</sub>O; 175.18). Anal. Calcd for C<sub>9</sub>H<sub>9</sub>N<sub>3</sub>O; C, 61.70; H, 5.18; N, 23.99. Found: C, 61.65; H, 5.18; N, 23.88.

## 3-(Benzylideneamino)-2-methyl quinazolin-4-(3H)-one (4a)

Pale yellow crystal; Yield: 80%; m.p. 153-155 °C; IR (KBr, cm<sup>-1</sup>): 3018 (Ar-CH), 2920 (CH in CH<sub>3</sub>), 1720 (C=O), 1510 (C=N), 1460 (C=C). <sup>1</sup>H-NMR (CDCl<sub>3</sub>)  $\delta$ : 8.05 (s, 1H; -N=C<u>H</u>-), 7.19-7.88 (m, 9H; C<sub>5</sub>,C<sub>6</sub>,C<sub>7</sub>,C<sub>8</sub>,C<sub>2</sub>,C<sub>3</sub>,C<sub>4</sub>,C<sub>5</sub>,C<sub>6</sub>,Ar-H), 0.86 (s, 3H; C<sub>2</sub>, -CH<sub>3</sub>). <sup>13</sup>C-NMR (CDCl<sub>3</sub>)  $\delta$ : 164.2 (C<sub>2</sub>), 160.1 (C<sub>4</sub>), 143.3 (-N=<u>C</u>H-), 133.3 (C<sub>7</sub>), 131.4 (C<sub>4</sub>), 129.4 (C<sub>2</sub> & C<sub>6</sub>), 128.9 (C<sub>3</sub> & C<sub>5</sub>), 128.6 (C<sub>5</sub>), 127.1 (C<sub>6</sub>), 19.8 (-<u>C</u>H<sub>3</sub>). EI-MS m/z (M+): 263 (Calcd for C<sub>16</sub>H<sub>13</sub>N<sub>3</sub>O; 263.29). Anal. Calcd for C<sub>16</sub>H<sub>13</sub>N<sub>3</sub>O; C, 72.99; H, 4.98; N, 15.96. Found: C, 72.95; H, 4.96; N, 15.92.

## 3-(4-Methoxybenzylideneamino)-2-methyl quinazolin-4-(3H)-one (4b)

Cream solid; Yield: 72%; m.p. 191-194 °C; IR (KBr, cm<sup>-1</sup>): 3046 (Ar-CH), 2912 (CH in CH<sub>3</sub>), 1724 (C=O), 1514 (C=N), 1462 (C=C), 1124 (C-O).  $^{1}$ H-NMR (CDCl<sub>3</sub>)  $\delta$ : 8.07 (s, 1H; -N=CH-), 6.81-7.92 (m, 8H; C<sub>5</sub>,C<sub>6</sub>,C<sub>7</sub>,C<sub>8</sub>,C<sub>2</sub>,C<sub>3</sub>,C<sub>5</sub>,C<sub>6</sub>,Ar-H), 3.70 (s, 3H; -OCH<sub>3</sub>), 0.79 (s, 3H; -CH<sub>3</sub>).  $^{13}$ C-NMR (CDCl<sub>3</sub>)  $\delta$ : 163.9 (C<sub>2</sub>), 160.2 (C<sub>4</sub>),143.2 (-N=CH-), 133.2 (C<sub>7</sub>), 163.1 (C<sub>4</sub>), 130.1 (C<sub>2</sub>, & C<sub>6</sub>), 128.6 (C<sub>5</sub>), 127.3 (C<sub>6</sub>), 126.2 (C<sub>1</sub>), 122.2 (C<sub>8</sub>), 114.3 (C<sub>3</sub>, &C<sub>5</sub>), 55.6 (-OCH<sub>3</sub>), 20.2 (-CH<sub>3</sub>). EI-MS m/z (M+): 293 (Calcd for C<sub>17</sub>H<sub>15</sub>N<sub>3</sub>O<sub>2</sub>; 293.31). Anal. Calcd for C<sub>17</sub>H<sub>15</sub>N<sub>3</sub>O<sub>2</sub>; C, 69.61; H, 5.15; N, 14.33. Found: C, 69.58; H, 5.14; N, 14.28.

## 3-(2-Hydroxybenzylideneamino)-2-methyl quinazolin-4-(3H)-one (4c)

Pale yellow solid; Yield: 66%; m.p. 173-175 °C; IR (KBr, cm<sup>-1</sup>): 3040 (Ar-CH), 2915 (CH in CH<sub>3</sub>), 1722 (C=O), 1514 (C=N), 1457 (C=C) 1350,1205 (C-O). <sup>1</sup>H-NMR (CDCl<sub>3</sub>)  $\delta$ : 7.99 (s, 1H; -N=CH<sub>-</sub>), 6.78-7.88 (m, 8H; C<sub>5</sub>,C<sub>6</sub>,C<sub>7</sub>,C<sub>8</sub>,C<sub>3</sub>,C<sub>4</sub>,C<sub>5</sub>,C<sub>6</sub>,Ar-H), 5.41 (s, 1H; Ar-OH), 0.82 (s, 3H; -CH<sub>3</sub>). <sup>13</sup>C-NMR (CDCl<sub>3</sub>)  $\delta$ : 163.4 (C<sub>2</sub>), 164.5 (C<sub>2</sub>), 160.6 (C<sub>4</sub>), 142.9 (-N=CH<sub>-</sub>), 133.7 (C<sub>7</sub>), 132.2 (C<sub>4</sub>), 130.3 (C<sub>6</sub>), 128.6 (C<sub>5</sub>), 127.4 (C<sub>6</sub>), 122.1 (C<sub>8</sub>), 121.3 (C<sub>5</sub>), 118.2 (C<sub>1</sub>), 116.2 (C<sub>3</sub>), 20.1 (-CH<sub>3</sub>). EI-MS m/z (M+): 279 (Calcd for C<sub>16</sub>H<sub>13</sub>N<sub>3</sub>O<sub>2</sub>; 279.29). Anal. Calcd for C<sub>16</sub>H<sub>13</sub>N<sub>3</sub>O<sub>2</sub>; C, 68.81; H, 4.69; N, 15.05. Found: C, 68.79; H, 4.61; N, 15.01.

## 3-(4-N,N-dimethylaminobenzylideneamino)-2-methyl quinazolin-4-(3H)-one (4d)

Bright yellow crystal; Yield: 68%; m.p. 187-190 °C; IR (KBr, cm<sup>-1</sup>): 3032 (Ar-CH), 2920 (CH in CH<sub>3</sub>), 1720 (C=O), 1518 (C=N), 1453 (C=C). <sup>1</sup>H-NMR (CDCl<sub>3</sub>)  $\delta$ : 8.02 (s, 1H; -N=C<u>H</u>-), 6.75-7.89 (m, 8H; C<sub>5</sub>,C<sub>6</sub>,C<sub>7</sub>,C<sub>8</sub>,C<sub>2</sub>,C<sub>5</sub>,C<sub>6</sub>,Ar-H), 2.86 (s, 6H; -N-(C<u>H</u><sub>3</sub>)<sub>2</sub>), 0.82 (s, 3H; -C<u>H</u><sub>3</sub>). <sup>13</sup>C-NMR (CDCl<sub>3</sub>)  $\delta$ : 163.4 (C<sub>2</sub>), 159.2 (C<sub>4</sub>) 151.2 (C<sub>4</sub>), 142.2 (-N=<u>C</u>H-), 133.6 (C<sub>7</sub>), 130.3 (C<sub>2</sub>·&C<sub>6</sub>·), 128.6 (C<sub>5</sub>), 127.6 (C<sub>6</sub>), 123.2 (C<sub>1</sub>·), 122.3 (C<sub>8</sub>), 113.8 (C<sub>3</sub>·&C<sub>5</sub>·), 55.6 (-O<u>C</u>H<sub>3</sub>), 20.1 (-<u>C</u>H<sub>3</sub>). EI-MS m/z (M+): 306 (Calcd for C<sub>18</sub>H<sub>18</sub>N<sub>4</sub>O; 306.36). Anal. Calcd for C<sub>18</sub>H<sub>18</sub>N<sub>4</sub>O; C, 70.57; H, 5.92; N, 18.29. Found: C, 70.48; H, 5.94; N, 18.31.

#### 3-(3-Nitrobenzylideneamino)-2-methyl quinazolin-4-(3H)-one (4e)

Cream solid; Yield: 65%; m.p. 190-194 °C; IR (KBr, cm<sup>-1</sup>): 3017 (Ar-CH), 2922 (CH in CH<sub>3</sub>), 1715 (C=O), 1524 (C=N), 1522 and 1335 (N=O), 1450 (C=C).  $^{1}$ H-NMR (CDCl<sub>3</sub>)  $\delta$ : 8.09 (s, 1H; -N=CH<sub>-</sub>), 7.41-7.92(m, 7H; C<sub>5</sub>,C<sub>6</sub>,C<sub>7</sub>,C<sub>8</sub>,C<sub>4</sub>,C<sub>5</sub>,C<sub>6</sub>,Ar-H), 0.92 (s, 3H; -CH<sub>3</sub>).  $^{13}$ C-NMR (CDCl<sub>3</sub>)  $\delta$ : 163.9 (C<sub>2</sub>), 159.8 (C<sub>4</sub>), 148.6 (C<sub>3</sub>), 143.1 (-N=CH<sub>-</sub>), 134.3 (C<sub>1</sub>), 135.3 (C<sub>6</sub>), 133.6 (C<sub>7</sub>), 129.8 (C<sub>5</sub>), 128.8 (C<sub>5</sub>), 127.4 (C<sub>6</sub>), 124.2 (C<sub>2</sub>), 123.2 (C<sub>4</sub>), 122.4 (C<sub>5</sub>), 20.3 (-CH<sub>3</sub>). EI-MS m/z (M+): 308 (Calcd for C<sub>16</sub>H<sub>12</sub>N<sub>4</sub>O<sub>3</sub>; 308.29). Anal. Calcd for C<sub>16</sub>H<sub>12</sub>N<sub>4</sub>O<sub>3</sub>; C, 62.33; H, 3.92; N, 18.17. Found: C, 62.31; H, 3.83; N, 18.14.

## 3-(4-Methylbenzylideneamino)-2-methyl quinazolin-4-(3H)-one (4f)

Cream crystal; Yield: 76%; m.p. 164-166 °C; IR (KBr, cm<sup>-1</sup>): 3041 (Ar-CH), 2926 (CH in CH<sub>3</sub>) 1718 (C=O), 1522 (C=N), 1448 (C=C). <sup>1</sup>H-NMR (CDCl<sub>3</sub>)  $\delta$ : 8.12 (s, 1H; -N=C $\underline{\text{H}}$ -), 7.09-7.81 (m, 8H; C<sub>5</sub>,C<sub>6</sub>,C<sub>7</sub>,C<sub>8</sub>,C<sub>2</sub>,C<sub>3</sub>,C<sub>5</sub>,C<sub>6</sub>,Ar-H), 2.36 (s, 3H; -C $\underline{\text{H}}$ <sub>3</sub>), 0.92 (s, 3H; -C $\underline{\text{H}}$ <sub>3</sub>). <sup>13</sup>C-NMR (CDCl<sub>3</sub>)  $\delta$ : 164.2 (C<sub>2</sub>), 160.3 (C<sub>4</sub>), 143.1 (-N= $\underline{\text{C}}$ H-), 133.8 (C<sub>7</sub>), 130.8 (C<sub>1</sub>), 129.4 (C<sub>3</sub>, & C<sub>5</sub>), 129.1 (C<sub>2</sub>, & C<sub>6</sub>), 128.6 (C<sub>5</sub>), 127.4 (C<sub>6</sub>), 122.6 (C<sub>8</sub>), 24.3 (- $\underline{\text{C}}$ H<sub>3</sub>), 20.3 ( $\underline{\text{C}}$ H<sub>3</sub>). EI-MS m/z (M+): 277 (Calcd for C<sub>17</sub>H<sub>15</sub>N<sub>3</sub>O; 277.32). Anal. Calcd for C<sub>17</sub>H<sub>15</sub>N<sub>3</sub>O; C, 73.63; H, 5.45; N, 15.15. Found: C, 73.53; H, 5.41; N, 15.14.

## 3-(4-Hydroxybenzylideneamino)-2-methyl quinazolin-4-(3H)-one (4g)

Pale yellow crystal; Yield: 77%; m.p. 210-214 °C; IR (KBr, cm<sup>-1</sup>): 3024 (Ar-CH), 2924 (CH in CH<sub>3</sub>), 1722 (C=O), 1514 (C=N), 1454 (C=C), 1355 and 1208 (C-O). <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 7.99 (s, 1H; -N=C<u>H</u>-), 6.82-7.88 (m, 8H; C<sub>5</sub>,C<sub>6</sub>,C<sub>7</sub>,C<sub>8</sub>,C<sub>2</sub>,C<sub>3</sub>,C<sub>5</sub>,C<sub>6</sub>,Ar-H), 5.44 (s, 1H; Ar-O<u>H</u>), 0.88 (s, 3H; -C<u>H</u><sub>3</sub>). <sup>13</sup>C-NMR (CDCl<sub>3</sub>) δ: 165.1 (C<sub>2</sub>), 160.4 (C<sub>4</sub>·), 159.2 (C<sub>4</sub>), 144.2 (-N=<u>C</u>H-), 134.2 (C<sub>7</sub>), 130.5 (C<sub>2</sub>· & C<sub>6</sub>·), 129.2 (C<sub>5</sub>), 127.4 (C<sub>6</sub>), 122.8 (C<sub>8</sub>), 115.6 (C<sub>3</sub>· & C<sub>5</sub>·), 20.1 (-<u>C</u>H<sub>3</sub>). EI-MS m/z (M+): 279 (Calcd for C<sub>16</sub>H<sub>13</sub>N<sub>3</sub>O<sub>2</sub>; 279.29). Anal. Calcd for C<sub>16</sub>H<sub>13</sub>N<sub>3</sub>O<sub>2</sub>: C, 68.81; H, 4.69; N, 15.05. Found: C, 68.79; H, 4.64; N, 15.07.

## 3-(4-Chlorobenzylideneamino)-2-methyl quinazolin-4-(3H)-one (4h)

Pale yellow powder; Yield: 74%; m.p. 259-263 °C; IR (KBr, cm<sup>-1</sup>): 3036 (Ar-CH), 2932 (CH in CH<sub>3</sub>), 1726 (C=O), 1520 (C=N), 1446 (C=C), 729 (C-Cl). <sup>1</sup>H-NMR (CDCl<sub>3</sub>)  $\delta$ : 8.12 (s, 1H; -N=CH-), 6.91-7.82 (m, 8H; C<sub>5</sub>,C<sub>6</sub>,C<sub>7</sub>,C<sub>8</sub>,C<sub>2</sub>,C<sub>3</sub>,C<sub>5</sub>,C<sub>6</sub>,Ar-H), 0.92 (s, 3H; -CH<sub>3</sub>). <sup>13</sup>C-NMR (CDCl<sub>3</sub>)  $\delta$ : 163.4 (C<sub>2</sub>), 160.8 (C<sub>4</sub>), 144.2 (-N=CH-), 136.2 (C<sub>4</sub>), 133.4 (C<sub>7</sub>), 132.5 (C<sub>1</sub>), 130.8 (C<sub>2</sub>, & C<sub>6</sub>), 129.2 (C<sub>3</sub>, & C<sub>5</sub>), 128.6 (C<sub>5</sub>), 126.9 (C<sub>6</sub>), 122.4 (C<sub>8</sub>), 19.8 (-CH<sub>3</sub>). EI-MS m/z (M+): 297 (Calcd for C<sub>16</sub>H<sub>12</sub>ClN<sub>3</sub>O; 297.73). Anal. Calcd for C<sub>16</sub>H<sub>12</sub>ClN<sub>3</sub>O; C, 64.54; H, 4.06; N, 14.91. Found: C, 64.50; H, 4.01; N, 14.81.

## 3-(4-Nitrobenzylideneamino)-2-methyl quinazolin-4-(3H)-one (4i)

Yellow crystal; Yield: 75%; m.p. 222-225 °C; IR (KBr, cm<sup>-1</sup>): 3048 (Ar-CH), 2926 (CH in CH<sub>3</sub>), 1715 (C=O), 1524 (C=N), 1518 and 1342 (N=O), 1452(C=C). <sup>1</sup>H-NMR (CDCl<sub>3</sub>)  $\delta$ : 8.12 (s, 1H; -N=CH-), 7.35-7.99 (m, 8H; C<sub>5</sub>,C<sub>6</sub>,C<sub>7</sub>,C<sub>8</sub>,C<sub>2</sub>,C<sub>3</sub>,C<sub>5</sub>,C<sub>6</sub>,Ar-H), 0.82 (s, 3H; -CH<sub>3</sub>). <sup>13</sup>C-NMR (CDCl<sub>3</sub>)  $\delta$ : 165.2 (C<sub>2</sub>), 161.2 (C<sub>4</sub>), 150.2 (C<sub>4</sub>), 143.2 (-N=CH-), 140.1 (C<sub>1</sub>), 134.0 (C<sub>7</sub>), 129.4 (C<sub>2</sub>, & C<sub>6</sub>), 128.9(C<sub>5</sub>), 127.6 (C<sub>6</sub>), 122.6 (C<sub>8</sub>), 121.2 (C<sub>3</sub>, & C<sub>5</sub>), 0.92 (-CH<sub>3</sub>). EI-MS m/z (M+): 308 (Calcd for C<sub>16</sub>H<sub>12</sub>N<sub>4</sub>O<sub>3</sub>; 308.29). Anal. Calcd for C<sub>16</sub>H<sub>12</sub>N<sub>4</sub>O<sub>3</sub>; C, 62.33; H, 3.92; N, 18.17. Found: C, 62.22; H, 3.94; N, 18.21.

## 3-(3,4,5,-Trimethoxybenzylideneamino)-2-methyl quinazolin-4-(3H)-one (4j)

Bright yellow powder; Yield: 70%; m.p. 261-264 °C; IR (KBr, cm<sup>-1</sup>): 3024 (Ar-CH), 2922 (CH in CH<sub>3</sub>), 1724 (C=O), 1514 (C=N), 1463 (C=C), 1132 (C-O). <sup>1</sup>H-NMR (CDCl<sub>3</sub>)  $\delta$ : 8.10 (s, 1H; -N=C<u>H</u>-), 7.38-7.92 (m, 4H; C<sub>5</sub>,C<sub>6</sub>,C<sub>7</sub>,C<sub>8</sub>,Ar-H), 6.61 (s, 1H; C<sub>2</sub>,Ar-H), 6.64 (s, 1H; C<sub>6</sub>,Ar-H), 3.82 (s, 9H; [OC<u>H</u><sub>3</sub>]<sub>3</sub>), 0.91 (s, 3H; -C<u>H</u><sub>3</sub>). <sup>13</sup>C-NMR (CDCl<sub>3</sub>)  $\delta$ : 164.5 (C<sub>2</sub>), 160.2 (C<sub>4</sub>), 150.8 (C<sub>3</sub>: & C<sub>5</sub>·), 143.3 (-N=<u>C</u>H-), 141.9 (C<sub>4</sub>·), 135.2 (C<sub>7</sub>), 129.9 (C<sub>5</sub>), 128.2(C<sub>1</sub>·), 127.6 (C<sub>6</sub>), 122.6 (C<sub>8</sub>), 107.1 (C<sub>2</sub>· & C<sub>6</sub>·), 56.5 (-O<u>C</u>H<sub>3</sub>), 21.2 (-<u>C</u>H<sub>3</sub>). EI-MS m/z (M+): 353 (Calcd for C<sub>19</sub>H<sub>19</sub>N<sub>3</sub>O<sub>4</sub>; 353.37). Anal. Calcd for C<sub>19</sub>H<sub>19</sub>N<sub>3</sub>O<sub>4</sub>; C, 64.58; H, 5.42; N, 11.89. Found: C, 64.49; H, 5.38; N, 11.85.

## 3-(4-Hydroxy-3-methoxybenzylideneamino)-2-methylquinazolin-4-(3H)-one (4k)

Cream solid; Yield: 65%; m.p. 122-124 °C; IR (KBr, cm<sup>-1</sup>): 3032 (Ar-CH), 2925 (CH in CH<sub>3</sub>), 1722 (C=O), 1518 (C=N), 1455 (C=C), 1352 and 1208 (C-O).  $^{1}$ H-NMR (CDCl<sub>3</sub>)  $\delta$ : 7.92 (s, 1H; -N=CH-), 7.42-7.82 (m, 4H;  $C_5$ ,  $C_6$ ,  $C_7$ ,  $C_8$ , Ar-H), 7.10 (s, 1H; Ar-H), 6.66-6.69 (d, J=6.7 Hz;  $C_5$ ;

Ar-H), 7.01-7.05 (d, J=5.8 Hz;  $C_{6'}$ , Ar-H), 5.12 (s, 1H; Ar-OH), 3.90 (s, 3H;  $-OC\underline{H}_3$ ), 0.92 (s, 3H;  $-C\underline{H}_3$ ).  $^{13}C$ -NMR (CDCl<sub>3</sub>)  $\delta$ : 165.1 ( $C_2$ ), 161.0 ( $C_4$ ), 151.2 ( $C_{3'}$ ), 148.2 ( $C_{4'}$ ), 143.4 (-N= $\underline{C}$ H-), 133.6 ( $C_7$ ), 128.6 ( $C_5$ ), 127.6 ( $C_6$ ), 127.4( $C_{1'}$ ), 122.9 ( $C_{6'}$ ), 122.6 ( $C_8$ ), 56.2 ( $-O\underline{C}$ H<sub>3</sub>), 20.2 ( $-\underline{C}$ H<sub>3</sub>). EI-MS m/z (M+): 309 (Calcd for  $C_{17}H_{15}N_3O_3$ ; 309.31). Anal. Calcd for  $C_{17}H_{15}N_3O_3$ ; C, 66.01; H, 4.89; N, 13.58. Found: C, 66.06; H, 4.78; N, 13.62.

## 3-(3-Phenylallylideneamino)-2-methyl quinazolin-4-(3H)-one (4l)

Lemon yellow crystal; Yield: 75%; m.p. 155-157 °C; IR (KBr, cm<sup>-1</sup>): 3019 (Ar-CH), 2916 (CH in CH<sub>3</sub>), 1728 (C=O), 1512 (C=N), 1458 (C=C). <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 7.61 (s, 1H; -N=C<u>H</u>-), 7.14-7.88 (m, 9H; C<sub>5</sub>,C<sub>6</sub>,C<sub>7</sub>,C<sub>8</sub>,C<sub>2</sub>,C<sub>3</sub>,C<sub>4</sub>,C<sub>5</sub>,C<sub>6</sub>·Ar-H), 6.59-6.62 (d, 1H; J=7.2 Hz; C<sub>6</sub>H<sub>5</sub>-C<u>H</u>=CH-), 5.61-5.63 (d, 1H; J=6.5 Hz; C<sub>6</sub>H<sub>5</sub>-CH=C<u>H</u>-), 0.92 (s, 3H; -C<u>H</u><sub>3</sub>). <sup>13</sup>C-NMR (CDCl<sub>3</sub>) δ: 164.2 (C<sub>2</sub>), 160.6 (C<sub>4</sub>), 139.2 (C<sub>6</sub>H<sub>5</sub>-<u>C</u>H=CH-) 137.6 (-N=<u>C</u>H-), 135.2 (C<sub>1</sub>·), 134.6 (C<sub>7</sub>), 128.8 (C<sub>5</sub>), 128.6 (C<sub>3</sub>· &C<sub>5</sub>·), 128.1 (C<sub>4</sub>·), 127.6 (C<sub>6</sub>), 126.6 (C2' & C6'), 126.3 (C<sub>6</sub>H<sub>5</sub>-CH=<u>C</u>H-), 20.2 (-<u>C</u>H<sub>3</sub>). EI-MS m/z (M+): 289(Calcd for C<sub>18</sub>H<sub>15</sub>N<sub>3</sub>O; 289.33). Anal. Calcd for C<sub>18</sub>H<sub>15</sub>N<sub>3</sub>O; C, 74.72; H, 5.23; N, 14.52. Found: C, 74.36; H, 5.08; N, 14.38.

### Pharmacological screening

Synthesized compounds were evaluated for analgesic activity by tail-immersion method. The activity was studied at 100 mg/kg b.w. (p.o) and their effects were measured at the time interval of 30, 60, 120 and 180 min. Most of the synthesized compounds showed significant analgesic activity. Highest analgesic activity was observed at 120 min for all the compounds. When compared with standard drug (Pentazocin, 10 mg/kg, i.p) the compound 4f exhibited comparable analgesic activity at 100 mg/kg b.w. Compounds 4d and 4g exhibited moderate analgesic activity. Among the compounds synthesized compound 4l exhibited lowest analgesic activity. From the above results it may concluded that compounds containing electron donating groups exhibits better analgesic activity than electron withdrawing groups.

Anti-inflammatory activity of the synthesized compounds was evaluated by carrageenan induced rat paw oedema method. The activity was studied at 100 mg/kg b.w, p.o. and their effects were measured at 30, 60, 120 and 180 min. Mild to good anti-inflammatory activity was observed for all the synthesized compounds. All compounds exhibited highest activity at 120 min. Among the test compounds, when compared with Indomethacin (10 mg/kg, i.p) 3-(4-hydroxy benzylideneamino)-2-methyl quinazoline-4(3H)-one **4g** exhibited better anti-inflammatory activity. Compounds **4d** and **4f** exhibited moderate anti-inflammatory activity. Compound **4a** showed the least activity among the synthesized compounds. The substituted phenyl ring at 3<sup>rd</sup> position in the synthesized compounds was found to possess promising anti-inflammatory activity than unsubstituted phenyl ring.

## Scheme 1. Synthesis of schiff bases of 3-amino-2-methyl quinazolin-4(3H)-one

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Table-1. Analgesic activity of the synthesized compounds

COMPOUNDS	DOSE (mg/kg)	0 min	) min 30 min		60 min		120 min		180 min	
		MEAN ± SEM	MEAN ± SEM	PAA	MEAN ± SEM	PAA	MEAN ± SEM	PAA	MEAN ± SEM	PAA
4a	100	3.50 <u>+</u> 0.34	7.50 <u>+</u> 0.56*	53.33	8.00 <u>+</u> 0.45*	56.25	8.33 <u>+</u> 0.42*	57.98	6.70 <u>+</u> 0.03*	47.76
4b	100	3.17 <u>+</u> 0.17	6.33 <u>+</u> 0.42*	49.92	7.50 <u>+</u> 0.43*	57.73	7.83 <u>+</u> 0.40*	59.51	6.00 <u>+</u> 0.52*	47.16
4c	100	3.83 <u>+</u> 0.40	6.50 <u>+</u> 0.43*	41.07	7.67 <u>+</u> 0.33*	50.06	8.33 <u>+</u> 0.42*	54.02	6.17 <u>+</u> 0.31*	37.92
4d	100	3.83 <u>+</u> 0.40	6.83 <u>+</u> 0.31**	43.92	9.33 <u>+</u> 0.56**	58.94	9.67 <u>+</u> 0.33**	60.39	6.50 <u>+</u> 0.34**	41.07
4e	100	3.50 <u>+</u> 0.34	5.67 <u>+</u> 0.33 <sup>NS</sup>	38.27	7.17 <u>+</u> 0.40*	51.18	8.33 <u>+</u> 0.42*	57.98	6.67 <u>+</u> 0.42*	47.52
<b>4</b> f	100	3.17 <u>+</u> 0.17	7.67 <u>+</u> 0.61*	58.67	8.50 <u>+</u> 0.34**	62.70	11.67 <u>+</u> 0.67**	72.83	10.17 <u>+</u> 0.48**	68.82
<b>4</b> g	100	3.67 <u>+</u> 0.33	7.33 <u>+</u> 0.42*	49.93	7.83 <u>+</u> 0.70*	53.12	9.83 <u>+</u> 0.40**	62.66	7.83 <u>+</u> 0.48**	53.12
4h	100	3.67 <u>+</u> 0.33	$7.33 \pm 0.21^{NS}$	49.93	8.33 <u>+</u> 0.42 <sup>NS</sup>	55.94	7.67 <u>+</u> 0.42*	56.06	5.00 <u>+</u> 0.26**	26.60
4i	100	3.83 <u>+</u> 0.40	6.00 <u>+</u> 0.52*	36.16	6.33 <u>+</u> 0.61*	39.49	7.33 <u>+</u> 0.49*	47.14	5.83 <u>+</u> 0.42**	34.31
<b>4</b> j	100	3.67 <u>+</u> 0.33	6.33 <u>+</u> 0.49*	42.02	7.67 <u>+</u> 0.49*	52.15	7.83 <u>+</u> 0.47*	53.12	6.83 <u>+</u> 0.48*	46.26
4k	100	4.17 <u>+</u> 0.31	7.17 <u>+</u> 0.48*	41.84	7.83 <u>+</u> 0.60*	46.74	9.17 <u>+</u> 0.31**	54.52	6.83 <u>+</u> 0.48**	38.94
41	100	4.00 <u>+</u> 0.37	6.33 <u>+</u> 0.42 <sup>NS</sup>	36.80	7.50 <u>+</u> 0.67 <sup>NS</sup>	46.66	8.33 <u>+</u> 0.56*	51.98	6.67 <u>+</u> 0.42**	40.02
Pentazocine	10	3.33 <u>+</u> 0.21	9.83 <u>+</u> 0.48**	66.12	11.50 <u>+</u> 0.62**	71.04	14.00 <u>+</u> 0.37**	76.21	12.67 <u>+</u> 0.42**	73.71

Data represent Mean  $\pm$  S.E.M (Standard Error Mean) (n = 6); \*p < 0.05; \*\*p < 0.01; \*\*\*p < 0.001; NS (Non significant); PAA (Percentage analgesic activity)

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Table-2. Anti-inflammatory activity of the synthesized compounds

COMPOUND S	DOSE (mg/kg	30 min		60 min		120 min		180 min	
		MEAN±SEM	%	MEAN±SEM	%	MEAN <u>+</u> SEM	%	MEAN <u>+</u> SEM	%
4a	100	0.717 <u>+</u> 0.01 <sup>NS</sup>	0.82	0.803 <u>+</u> 0.01*	11.07	0.993 <u>+</u> 0.01*	31.18	0.773 <u>+</u> 0.02*	27.95
4b	100	0.667 <u>+</u> 0.01*	7.74	0.740 <u>+</u> 0.01*	18.05	0.913 <u>+</u> 0.01*	36.72	0.853 <u>+</u> 0.02*	20.50
4c	100	0.603 <u>+</u> 0.02*	16.59	0.653 <u>+</u> 0.02**	27.68	0.807 <u>+</u> 0.03**	44.07	0.700 <u>+</u> 0.01**	34.76
4d	100	0.617 <u>+</u> 0.03*	14.66	0.687 <u>+</u> 0.01**	23.92	0.813 <u>+</u> 0.01**	43.65	0.607 <u>+</u> 0.02**	43.42
4e	100	0.650 <u>+</u> 0.02*	10.09	0.777 <u>+</u> 0.02*	13.95	0.903 <u>+</u> 0.02*	37.42	0.753 <u>+</u> 0.01**	29.82
4f	100	0.587 <u>+</u> 0.02*	18.81	0.707 <u>+</u> 0.02*	21.70	0.843 <u>+</u> 0.02**	41.58	0.687 <u>+</u> 0.02**	35.97
4g	100	0.617 <u>+</u> 0.02*	14.66	0.663 <u>+</u> 0.01**	26.57	0.777 <u>+</u> 0.02**	46.15	0.643 <u>+</u> 0.01**	40.07
4h	100	0.667 <u>+</u> 0.01*	7.74	0.720 <u>+</u> 0.01**	20.26	0.887 <u>+</u> 0.02*	38.53	0.760 <u>+</u> 0.02*	29.17
4i	100	0.667 <u>+</u> 0.02*	7.74	0.740 <u>+</u> 0.02*	18.05	0.927 <u>+</u> 0.02**	35.75	0.810 <u>+</u> 0.02**	24.01
<b>4</b> j	100	0.670 <u>+</u> 0.01*	7.33	0.763 <u>+</u> 0.01*	15.50	0.910 <u>+</u> 0.02*	36.93	0.783 <u>+</u> 0.01*	27.02
4k	100	0.717 <u>+</u> 0.01*	0.82	0.787 <u>+</u> 0.01*	12.84	0.883 <u>+</u> 0.01*	38.8	0.743 <u>+</u> 0.02**	30.75
41	100	0.703 <u>+</u> 0.01*	2.76	0.817 <u>+</u> 0.01*	9.52	0.940 <u>+</u> 0.01*	34.85	0.753 <u>+</u> 0.02*	29.20
Indomethacin	10	0.523 <u>+</u> 0.02**	27.66	0.583 <u>+</u> 0.02**	35.43	0.667 <u>+</u> 0.02**	53.77	0.540 <u>+</u> 0.02**	49.67
Control	-	0.723 <u>+</u> 0.01	-	0.903 <u>+</u> 0.02	-	1.443 <u>+</u> 0.03	-	1.073 <u>+</u> 0.03	-

Data represent Mean  $\pm$  S.E.M (Standard Error Mean) (n = 6); \*p < 0.05; \*\*p < 0.01; \*\*\*p < 0.001; NS (Non significant); % (Percentage reduction of oedema)

#### **CONCLUSION**

In conclusion, the present study highlights the importance of aromatic imino substitution at 3<sup>rd</sup> position of the quinazolin-4(3H)-one ring features responsible for the analgesic, anti-inflammatory activity and therefore may serves as a lead molecule to obtain clinically useful novel entities in the new millennium.

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