SYNTHESIS AND EVALUATION OF 2, 3-DIHYDROQUINAZOLIN-4(1H)-ONE DERIVATIVES AS ANALGESIC AND ANTI-INFLAMMATORY AGENTS

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ABSTRACT
Applying internal Mannich reaction on N’-(substituted benzoyl)-2-(methyl- amino) benzohydrazide (IIa-h), under different conditions, afforded a new series of 2, 3-dihydroquinazolin-4(1H)-one derivatives (IIIa-g). The carbohydrazide; N’-(p-chlorobenzoyl)-2-(methyl- amino) benzohydrazide (IIe) is the only exception which gives benzotriazepin- 5(2H)-one. All carbohydrazides (IV) were prepared by condensing N-methylisatoic anhydride with substituted benzoic acid hydrazides. The obtained 2, 3-dihydroquinazolin-4(1H)-one derivatives (IIIa-g) were subjected to biological screening as analgesic and anti-inflammatory. The quinazolinone (IIia, IIig) showed higher analgesic activity over celecoxib while (IIig) is more active than diclofenac sodium as anti-inflammatory.

KEY WORDS
Quinazolin4(1H)-one, anti-inflammatory, analgesic, synthesis.

INTRODUCTION
Quinazolines and their derivatives have been reported to possess varied pharmacological properties among of which analgesic1 and anti-inflammatory 2, Proquazone (1) is clinically used as a non-steroidal anti-inflammatory drug 3. In addition to N-(2-methyl-4-oxoquinazolin-3(4H)-yl)-1H-pyrrole-1-carbothioamide (2) synthesized and tested for its analgesic and anti-inflammatory activities 4. In view of these observations, we herein report the synthesis of some new 1 - methyl - 2, 3 – dihydro quinazolin - 4 (1H) -one derivatives carrying benzamide moiety in 3-position with the hope that
the resultant compounds may possess analgesic and anti-inflammatory activities.

**EXPERIMENTAL SECTION**

**General Data**

Melting points were determined with a Gallenkamp melting point apparatus (London, UK), and are uncorrected. IR spectra (KBr, cm⁻¹) were recorded on a Bruker Vector 22 FT-IR Spectrometer (Bavaria, Germany). ¹HNMR spectra were recorded on Varian Gemini-200 (200 MHz) Spectrometer (CA, USA) using DMSO-d₆ as a solvent and tetramethylsilane (TMS) as an internal standard (Chemical shift in δ, ppm). Electron impact mass spectra were determined at 70 eV using a GC/MS Shimadzu QP1000EX Spectrometer (Tokyo, Japan). Elemental analyses were determined using Heraeus or Vario EL-III (Elementar) (Hanau, Germany) or Perkin Elmer Model 2400 (USA) CHN analyzers at the National Research Center and Microanalytical Center, Faculty of Science, Cairo University, Egypt. All the results of the elemental analyses were in an acceptable error range. Thin layer chromatography (TLC) was performed on silica gel G for TLC (Merck), and spots were visualized by irradiation with ultraviolet light (UV; 254 nm). All chemicals were purchased from Acros Chemicals (Belgium).

**General procedure for preparation of 2-methylamino-N’-(substituted-benzoyl) benzohydrazide (IIa-h)**

A mixture of N-methyl isatoic anhydride (8 gm, 0.045 mol) and substituted benzoic acid hydrazide (0.045 mol) in ethanol (50 ml) containing 10 drops of glacial acetic acid was heated under reflux for (8-18 hours). The reaction mixture was cooled and the separated solid was filtered and crystallized from ethanol to give the titled compounds.

**General procedure for preparation of compounds (IIIa-g) & (IV)**

To a solution of 2-methylamino-N’- (substituted benzoyl) benzohydrazide (1.5gm,0.0047mol) in ethanol (50ml), 38% formalin (0.7 ml, 0.0052mol) and 10 drops of glacial acetic acid were added. The reaction mixture was stirred on cold for 24 hours or heated under reflux for 2 hours, the reaction mixture was poured into water (100ml), and the separated solid was filtered, dried and crystallized from ethanol to give the titled compounds.

**N-(1-methyl-4-oxo-1,2-dihydroquinazolin-3(4H)-yl)benzamide (IIIa)**

Yield: 76.7 %; m.p. = 161°C; crystallized from ethanol; ¹HNMR: δ = 2.8724 (s, 3H, NCH₃), 4.7249(s, 2H, CH₂N), 6.8448-7.9071(m, 9H, Ar-H), 11.0282 (s, 1H, NH, exchangeable) ppm. MS m/z (rel.int.) = 282(M+2, 0.8), 281(M+1, 0.6), 280(M⁺, 0.6), 161(100), 135(1.1), 134(2.0), 119(2.6), 77(33.3), 76(8.6). Analysis for C₁₆H₁₄N₃O₂ (281.31): Calcd: C, 68.31; H, 5.37; N, 14.94. Found: C, 68.10; H, 5.40; N, 14.95 %.

**N-(1-methyl-4-oxo-1,2-dihydroquinazolin-3(4H)-yl)-3-nitrobenzamide (IIIb)**

Yield: 92 %; m.p. = 213-216 °C; crystallized from ethanol; ¹HNMR: δ = 2.8816 (s, 3H, NCH₃), 4.7631(s, 2H, CH₂N), 6.8540-8.7080 (m, 8H, Ar-H), 11.3583 (s, 1H, NH, exchangeable) ppm. ¹³C NMR (CDCl₃) δ = 39.6, 68.59, 112.9, 115.7, 118.58, 123.83, 128.4, 129.16, 134.28, 137.5, 149.73, 162.56, 164.17. MS m/z (rel.int.) = 327(M+1, 0.2) ,326(M⁺, 0.4), 165(0.9), 161 (100) , 132(34.4), 91(31.9), 77(22.9) ,76(19.5) . Analysis for C₁₆H₁₄N₄O₄ (326.31): Calcd: C, 58.89; H, 4.32; N, 17.17. Found: C, 59.02; H, 4.64; N, 16.99 %.

**N-(1-methyl-4-oxo-1,2-dihydroquinazolin-3(4H)-yl)-4-nitrobenzamide (IIIc)**

Yield: 74.5 %; m.p. = 228-231°C; crystallized from ethanol; ¹HNMR: δ = 2.8785 (s, 3H, NCH₃), 4.7509 (s, 2H, CH₂N), 6.8571 - 8.3687 (m, 8H, Ar-H), 11.2972 (s, 1H, NH, exchangeable) ppm. ¹³C NMR (CDCl₃) δ = 40.16, 69.11, 113.44, 116.24, 119.08, 122.85, 127.3, 128.9, 13103, 133.83 ,134.77, 148.32, 150.22, 163.09, 164.24.MS m/z (rel.int.) = 327(M+,1.02), 326(M⁺,0.4), 165(0.9), 161 (100) , 132(34.4), 91(31.9), 77(22.9) ,76(19.5) . Analysis for C₁₆H₁₄N₄O₄ (326.31): Calcd: C, 58.89; H, 4.32; N, 17.17. Found: C, 59.02; H, 4.64; N, 16.99 %.

**N-(1-methyl-4-oxo-1,2-dihydroquinazolin-3(4H)-yl)-4-nitrobenzamide (IIIc)**

Yield: 74.5 %; m.p. = 228-231°C; crystallized from ethanol; ¹HNMR: δ = 2.8816 (s, 3H, NCH₃), 4.7631 (s, 2H, CH₂N), 6.8540-8.7080 (m, 8H, Ar-H), 11.3583 (s, 1H, NH, exchangeable) ppm. ¹³C NMR (CDCl₃) δ = 39.6, 68.59, 112.9, 115.7, 118.58, 123.83, 128.4, 129.16, 134.28, 137.5, 149.73, 162.56, 164.17. MS m/z (rel.int.) = 327(M+1, 0.2) ,326(M⁺, 0.4), 165(0.9), 161 (100) , 132(34.4), 91(31.9), 77(22.9) ,76(19.5) . Analysis for C₁₆H₁₄N₄O₄ (326.31): Calcd: C, 58.89; H, 4.32; N, 17.17. Found: C, 59.02; H, 4.64; N, 16.99 %.

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ethanol; IR: v = 3437.49 (amidic NH), 3181.01 (C-H aromatic), 2997.8 (C-H aliphatic), 1698.02 (CO), 1643.05 (CO), 1449.24 (C=C). 1H NMR: δ = 2.8706 (s, 3H, NCH3), 4.7267 (s, 2H, CH2N), 6.8419-7.9132 (m, 8H, Ar-H), 11.0672 (s, 1H, NH, exchangeable) ppm. MS m/z (rel.int.) = 314 (M-1, 13.3), 160 (100), 155 (43.3), 139 (70), 132 (56.7), 91 (66.7), 77 (66.7), 76 (40). Analysis for C16H14ClN3O2 (315.75): Calcd: C, 65.81; H, 5.50; N, 13.30%. Found: C, 65.82; H, 5.50; N, 13.31. 3-methoxy-N-(1-methyl-4-oxo-1,2-dihydroquinazolin-3(4H)-yl)benzamide (IIIe) Yield: 70 %; m.p. = 192-194 °C; crystallized from ethanol; 1H NMR: δ = 2.8954 (s, 3H, NCH3), 3.8034 (s, 3H, OCH3), 4.7075 (s, 2H, CH2N), 6.837-7.849 (m, 8H, Ar-H), 10.790 (s, 1H, NH, exchangeable) ppm. MS m/z (rel.int.) = 312 (M+1, 0.1), 311 (M, 0.1), 161 (100), 132 (8.9), 91 (16.1), 77 (32.4), 76 (5.8). Analysis for C17H17N3O3 (311.34): Calcd: C, 65.58; H, 5.50; N, 13.30%. 4-hydroxy-N-(1-methyl-4-oxo-1,2-dihydroquinazolin-3(4H)-yl)benzamide (IIIg) Yield: 74 %; m.p. = 160 °C; crystallized from ethanol; 1H NMR: δ = 2.8586 (s, 3H, NCH3), 4.6913 (s, 2H, CH2N), 6.8158-7.6765 (m, 8H, Ar-H), 10.1631 (s, 1H, OH, exchangeable), 10.6812 (s, 1H, NH, exchangeable) ppm. MS m/z (rel.int.) = 296 (M-1, 0.2), 161 (100), 132 (6.5), 91 (16.1), 77 (32.4), 76 (5.8). Analysis for C16H15N3O2 (297.31): Calcd: C, 64.64; H, 5.09; N, 14.13. Found: C, 64.32; H, 4.99; N, 13.90 %. 3-(4-chlorobenzoyl)-1-methyl-3,4-dihydro-1H-benzo[e][1,2,4]triazepin-5(2H)-one (IV) Yield: 78.4 %; m.p. = 231-232 °C; crystallized from ethanol IR: v = 3444.24 (amidic NH), 3174.26 (C-H aromatic), 2981.41 (C-H aliphatic), 1707.66 (CO), 1643.05 (CO), 1448.28 (C=C). 1H NMR: δ = 2.8687 (s, 3H, NCH3), 4.7209 (s, 2H, CH2N), 6.8446-7.9036 (m, 8H, Ar-H), 11.0308 (s, 1H, NH, exchangeable) ppm. MS analysis: m/z (rel.intensity) = 314 (M-1, 0.1), 161 (100), 132 (6.5), 91 (16.1), 77 (32.4), 76 (5.8). Analysis for C18H14ClN3O2 (315.75): Calcd: C, 60.86; H, 4.47; N, 13.31. 3-methoxy-N-(1-methyl-4-oxo-1,2-dihydroquinazolin-3(4H)-yl)benzamide (IIId) Yield: 74 %; m.p. = 192-194 °C; crystallized from ethanol; 1H NMR: δ = 3.308 (s, 3H, NCH3), 3.827 (s, 3H, OCH3), 4.757 (s, 2H, CH2N), 6.870-7.800 (m, 8H, Ar-H), 10.928 (s, 1H, NH, exchangeable) ppm. MS MS m/z (rel.int.) = 311 (M, 100), 161 (100), 132 (8.7), 91 (18.3), 77 (23.7), 76 (6.8). Analysis for C15H15N3O3 (311.34): Calcd: C, 65.58; H, 5.50; N, 13.30 %.

PHARMACOLOGY
Male albino rats and male mice, weighing 150–200 g and 20–25 g each, respectively, were used. All experimental animals were provided by Faculty of Veterinary Medicine, Zagazig University, Egypt. All animals were held under standard laboratory conditions in the animal house (temperature 27°C) with 12/12 light-dark cycle. They were fed laboratory diet and water ad libitum. All experiments were carried out using 5 animals per group. The animal experiments were performed in accordance with international guidelines.

Acetic-acid-induced writhing
The test was carried out using the previously described technique.6 Mice were divided into 6 groups each of 5 mice and were injected intraperitoneally (i.p) with 0.1 ml/10 g body weight of 0.6% acetic acid solution in normal saline 1 h after the oral administration of tested compounds (IIIe, IIIg) at a dose of 50 mg/kg. The frequency of writhing was recorded within 25 min from the injection of acetic acid. Celecoxib was administrated to one group of mice at a dose level of 50 mg/kg as a positive control. One group of mice was left as a control.

Carrageenan-induced edema method
The effects of test compounds (IIIe, IIIg) on rat paw edema induced by carrageenan were studied as described by 7. The substances were tested at 50 mg/kg. Test substances and diclophenac sodium were suspended in gum acacia (7% suspension). Diclophenac sodium were tested at 5 mg/kg. The diameter of the right paw of each animal was determined using a micrometer. The test substances...
were administered by means of oral administration. The control group received only the corresponding vehicle. Thirty minutes later, paw edema was induced by subcutaneous injection of 0.1 ml carrageenan (0.1%) into the subplantar surface of the right hind paw of all animals. The paw diameter was measured 1, 2, 3, 4, 5 and 24 h after the injection. The AUC relating variation of edema to time was obtained using the trapezoidal rule. Total inhibition (TI, %) was obtained for each group and at each record, using the following ratio: 

\[
TI (\%) = \frac{[\text{AUC control} - \text{AUC treat}] \times 100}{\text{AUC control}}
\]

Data were expressed as mean ± standard error of mean (SEM) of 5 animals.

**Statistics**

Since the time course of the effect was followed, it was possible to use the cumulative anti-inflammatory effect during the whole observation period as the area under the curve (AUC). Because the AUC curve represents the integrated anti-inflammatory effect (variation of paw diameter) during the observation period, it then includes both the maximal response and the duration of action. The AUC relating variation of edema to time was obtained using the trapezoidal rule. Total inhibition (TI, %) was obtained for each group and at each record, using the following ratio: 

\[
TI (\%) = \frac{[\text{AUC control} - \text{AUC treat}] \times 100}{\text{AUC control}}
\]

Data were expressed as mean ± standard error of mean (SEM) of 5 animals.

**Ulcerogenic activity**

All tested compounds were investigated for their ulcerogenic activity using indomethacin as a reference drug. Male albino rats weighing 150-200 gm were fasted for 12 hours prior to drug administration. Water was supplied ad-libitum. The animals were divided into 9 equal groups (each of 5). The first group received 7% gum acacia (suspending vehicle) orally once a day and left as a control, whereas, the second and third groups received diclofenac sod. and celecoxib at a dose of 50 mg/ kg/ day orally, respectively. Groups from 4\text{th} to 9\text{th} received the tested compounds at 50 mg/ kg/ day. The tested compounds were administered once a day for 3 successive days. The animals were killed by overdose of ether 6 hours after the last dose. The stomachs were removed, opened along the greater curvature and examined for ulceration. The number and diameter of discrete areas of damage in the glandular mucosa were scored. The ulcer score was calculated according to 1 to 10 scoring system of.

**RESULTS AND DISCUSSION**

**Chemistry**

In the present work, the carbohydrazides; N’-(substituted benzoyl)-2-(methylamino) benzo hydrazides (II_{a-h}) were prepared by condensation of N-methyl isatoic anhydride with different substituted benzoic acid hydrazide. The resultant carbohydrazides (II_{a-b}) were subjected to cyclization with formaldehyde in acidified ethanol either on cold or by reflux. The final compounds were examined to be either 2,3-dihydroquinazolin-4(1H)-one (III_{a-g}) or 1H-benzo [e] [1,2,4] triazepin-5(2H)-one (IV) depending on the electronic effect of the substituent on the benzamide rather than that of anthranilamide moieties.

Applying internal Mannich conditions on 2-methylamino-N-(substituted benzoyl) benzo hydrazide (II_{a-d}, II_{f-g}) yielded 2,3-dihydroquinazolin-4(1H)-one derivatives (III_{a-g}) except the intermediate (II_{e}) cyclized to 3-(p-chloro benzoyl)-1-methyl-3,4-dihydro-1H-benzo[e][1,2,4]- triazepine-5(2H)-one (IV) as shown in scheme (I). This may be attributed to the high electron density on N\text{1} (anthranilamide nitrogen) rather than on N\text{2} (benzamide nitrogen), in the azomethene intermediate, which promotes the formation of quinazolin-4(1H)-one derivatives. Where the only exception is the cyclization of the intermediate (II_{e}) to 1H-benzo [e][1,2,4] triazepin-5(2H)-one (IV), here the mesomeric effect of p-chloride atom keeps the electron density on N\text{2} in a magnitude higher than that on N\text{1} which permits the ring closure of (II_{e}) to (IV).

The general criteria of $^1$HNMR spectra indicates the cyclization of the 2- methylamino - N - (m-nitro benzoyl) benzo- hydrazide (II_{e}), for example, to the appropriate 1, 2-dihydroquinazolinone derivative (III_{b}) where the peaks indicating three (NH) in (II_{b})
were restricted to one singlet peak at $\delta = 11.35$ ppm refers the exocyclic amidic NH, and one singlet peak at $\delta = 4.76$ ppm for the methylene group. The $^1$HNMR spectrum of benzotriazepinone derivative (IV) showed characteristic peak at $\delta = 11.03$ ppm indicating the endocyclic amidic NH, and singlet peak at $\delta = 4.72$ ppm for the methylene group. In addition to a singlet peak at $\delta = 2.8$ ppm due to N-CH$_3$ protons.

The mass spectra are the differential tool between the quinazolinone series and benzotriazepinone one. By comparison between mass spectra of (III$_d$) and (IV), which have the same molecular weight, where the fragment of m/z =160 [1-methyl-2,3-dihydroquinazolin-4(1H)-one-diradical] is present by intensity of 100% in compound (III$_d$) and restricted to 23.3% in (IV) while, the fragment of m/z =174 [1-methyl-3,4-dihydro-1H-benzo[e][1,2,4]triazepin-5(2H)-one-triradical] is present by intensity of 4.2% in compound (IV) and absent from the mass spectrum of (III$_d$) this make us to say that compound (IV) is seven-membered benzotriazepinone derivative and compound (III$_d$) belongs the 1,2-dihydroquinazolinone series.

**Pharmacology**
The newly synthesized 2,3-dihydroquinazolin-4(3H)-one derivatives (III$_a$-c, III$_e$-g) were tested for their analgesic activity using acetic-acid-induced writhing method in mice using celecoxib as a reference, anti-inflammatory using Carrageenan-induced paw edema using diclophenac sodium as a reference also these compounds tested for their ulcerogenic effect.

In this work we explored the highly active compounds with lesser side effects in comparison with reference drugs.

**Analgesic activity**
The results of the analgesic activity are listed in table 1. It was observed that the ranking order of potency for the compounds was (III$_g>$ III$_b>$ Celecoxib>III$_e>$ III$_c>$ III$_f>$ III$_a$). The results obtained from table 1 revealed that activity increases by substitution of benzamide moiety.

**Anti-inflammatory**
The results which can be drawn from table 2 revealed that the order of anti-inflammatory activity was (III$_g>$ diclophenac > celecoxib >III$_b>$ III$_c>$ III$_f>$ III$_a$).

**Ulcerogenic activity**
Administration of diclophenac sodium resulted in obvious ulcers in all tested animals while celecoxib showed less ulcerogenic activity. Furthermore, compound III$_f$ didn't show any ulcerogenic activity.

**Table No.1:** Analgesic activity of compounds (III$_a$, III$_b$, III$_c$, III$_e$, III$_f$, III$_g$) administered in a dose of 50 mg/kg against acetic acid-induced writhing.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>0-5</th>
<th>5-10</th>
<th>10-15</th>
<th>15-20</th>
<th>20-25</th>
<th>Total</th>
<th>% reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>28.5 ± 1.9</td>
<td>21 ± 1.8#</td>
<td>18 ± 0.8</td>
<td>22.2 ± 0.8#</td>
<td>20.75 ± 0.8#</td>
<td>110.5</td>
<td>0</td>
</tr>
<tr>
<td>Celecoxib</td>
<td>32 ± 1</td>
<td>11.5 ± 0.6*</td>
<td>14.7 ± 1.6</td>
<td>8.75 ± 0.8*</td>
<td>6 ± 0.9*</td>
<td>73</td>
<td>33.9</td>
</tr>
<tr>
<td>III$_g$</td>
<td>13.2 ± 1.1*#</td>
<td>15 ± 1.8</td>
<td>13.5 ± 2.7</td>
<td>11.75 ± 2*</td>
<td>9.25 ± 0.7*#</td>
<td>62.75</td>
<td>43.2</td>
</tr>
<tr>
<td>III$_b$</td>
<td>12.2 ± 3.3*#</td>
<td>17.5 ± 1.8#</td>
<td>16.5 ± 1.4</td>
<td>14.5 ± 0.2*#</td>
<td>9 ± 1*</td>
<td>69.75</td>
<td>36.8</td>
</tr>
<tr>
<td>III$_c$</td>
<td>19.6 ± 2.9*#</td>
<td>19 ± 1.5#</td>
<td>19 ± 3.2</td>
<td>15.3 ± 1.8*#</td>
<td>9 ± 1.1*</td>
<td>82</td>
<td>25.7</td>
</tr>
<tr>
<td>III$_f$</td>
<td>21.6 ± 1.7*#</td>
<td>21.6 ± 1.2#</td>
<td>17 ± 1.1</td>
<td>14.6 ± 0.8*#</td>
<td>11.6 ± 0.8*#</td>
<td>86.6</td>
<td>21.5</td>
</tr>
<tr>
<td>III$_a$</td>
<td>18.7 ± 0.7*#</td>
<td>20.5 ± 2.5#</td>
<td>22.2 ± 3.3</td>
<td>18.2 ± 1.5#</td>
<td>11.2 ± 1.1*#</td>
<td>91</td>
<td>17.6</td>
</tr>
</tbody>
</table>

* Significantly different from control group at p<0.05.
# Significantly different from celecoxib group at p<0.05.

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Table No.2: Anti-inflammatory activity of compounds (III_a-c, III_e-g) at a dose level of 50 mg/kg against rat hind paw edema induced by carrageenan

<table>
<thead>
<tr>
<th>Time (hr)</th>
<th>Carrageenan</th>
<th>Celecoxib</th>
<th>Diclophenac</th>
<th>III_b</th>
<th>III_c</th>
<th>III_e</th>
<th>III_f</th>
<th>III_g</th>
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<tr>
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<tr>
<td>1</td>
<td>155±2.6</td>
<td>141±6.3</td>
<td>130±4.6</td>
<td>125.6±5*</td>
<td>120.3±3.6</td>
<td>125.73±2.8</td>
<td>128.25±3.6</td>
<td>124.76±3.5</td>
</tr>
<tr>
<td>2</td>
<td>164±6.6</td>
<td>122±0.9*</td>
<td>115.9±1.1*</td>
<td>129.21±5.4*</td>
<td>125.04±1.05*</td>
<td>134.17±3.7*</td>
<td>139.36±2.9*</td>
<td>133.29±4.6*</td>
</tr>
<tr>
<td>3</td>
<td>160±6.7</td>
<td>112±1.8*</td>
<td>111.14±2*</td>
<td>122.23±6.1*</td>
<td>113.94±5.4*</td>
<td>117.41±4.3*</td>
<td>126.41±3.5*</td>
<td>134.42±7.1</td>
</tr>
<tr>
<td>4</td>
<td>151±4.9</td>
<td>108±1.7*</td>
<td>108.6±3.6*</td>
<td>116.92±6.4*</td>
<td>106.06±4*</td>
<td>115.04±1.8*</td>
<td>122.82±2.8*</td>
<td>125.05±5.5*</td>
</tr>
<tr>
<td>5</td>
<td>144±5</td>
<td>104±0.7*</td>
<td>103.49±1.5*</td>
<td>109.13±5.6*</td>
<td>103.56±5.11*</td>
<td>117.52±1.6*</td>
<td>120.62±2.8*</td>
<td>116.85±5.6*</td>
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<tr>
<td>24</td>
<td>1036±2.2</td>
<td>96±1.4</td>
<td>99.18±5</td>
<td>102.01±3.5</td>
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<td>102.56±1.6</td>
<td>99.23±2.6</td>
<td>103.67±3.1*</td>
</tr>
</tbody>
</table>

AUC 3099 2495 2493 2604 2482 2692 2716 2721 2869

% Reduction 0 20.45 20.51 16.76 20.89 13.77 12.97 12.79 7.786

Data expressed as mean ± SEM from six different experiments; *: p < 0.05 compared with carrageenan

Table No.3: Ulcerogenic activity of test compounds III_a-f, V_c, VII_c, VII_o, celecoxib and diclophenac sod.(n=5)

<table>
<thead>
<tr>
<th>S.No</th>
<th>Treatment</th>
<th>Ulcer index</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Diclophenac sod.</td>
<td>8.9 ± 0.7</td>
</tr>
<tr>
<td>2</td>
<td>Celecoxib</td>
<td>4.7 ± 0.3 *</td>
</tr>
<tr>
<td>3</td>
<td>III_a</td>
<td>2.8 ± 0.1 * #</td>
</tr>
<tr>
<td>4</td>
<td>III_b</td>
<td>1.1 ± 0.1 * #</td>
</tr>
<tr>
<td>5</td>
<td>III_c</td>
<td>0.9 ± 0.1 * #</td>
</tr>
<tr>
<td>6</td>
<td>III_d</td>
<td>0.01 ± 0.0 * #</td>
</tr>
<tr>
<td>7</td>
<td>III_e</td>
<td>3.0 ± 0.3 * #</td>
</tr>
<tr>
<td>8</td>
<td>III_f</td>
<td>3.7 ± 0.2 *</td>
</tr>
</tbody>
</table>

* significantly different from diclophenac sod. group at p<0.05.
# significantly different from celecoxib group at p<0.05.

Figure No.1: structures of Proquazone , N-(2-methyl-4-oxoquinazolin-3(4H)-yl)-1H-pyrrole-1-carbothioamide, III_a-g.
Figure No.2: Synthetic Pathway of Compounds III\textsuperscript{a-g} & IV
CONCLUSION
Our conclusion herein is the achievement of an excellent synthetic pathway of new series of 2,3-quinazolin-4(1H)-one derivatives III<sub>a-c</sub>, III<sub>e-g</sub>, which was done by different condensation of the benzohydrazides (II<sub>a-h</sub>) with a carbon source synthone. In the pharmacological screening, quinazolinones (III<sub>g</sub>, III<sub>c</sub>) showed higher analgesic activity over celecoxib while (III<sub>g</sub>) is more active than piroxicam. All the screened compounds as analgesic and anti-inflammatory showed no ulcerogenic activity.

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BIBLIOGRAPHY