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Research Article

## Synthesis and Biological Evaluation of Some Piperazine Derivatives as Anti-Inflammatory Agents

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### ABSTRACT

Some 1-((4-methylpiperazin-1-yl)methyl)-1H-benzo[d]imidazole & 1-((4-phenylpiperazin-1-yl)methyl)-1H-benzo[d]imidazole derivatives were synthesized through reaction of 1-substituted piperazines with different benzimidazole derivatives in methanol yielded the corresponding mannich bases (42-a to 42-i). All the synthesized compounds were elucidated by IR, <sup>1</sup>H NMR and MASS spectroscopy. They were tested for anti-inflammatory activity using *in-vivo* (Carrageenan- induced rat paw edema model) method at a dose of 50mg/kg. result showed that compounds 42-c, 42-d and 42-h were found to be most potent in series.

**Keywords:** 1,4-disubstituted Piperazine, Anti-inflammatory, Mannich Base.**Article Info:** Received 13 June 2019; Review Completed 19 July 2019; Accepted 20 July 2019; Available online 15 August 2019**Cite this article as:**Patel N, Karkhanis V, Patel P, Synthesis and Biological Evaluation of Some Piperazine Derivatives as Anti-Inflammatory Agents, Journal of Drug Delivery and Therapeutics. 2019; 9(4-s):353-358 <http://dx.doi.org/10.22270/jddt.v9i4-s.3327>**\*Address for Correspondence:**

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### INTRODUCTION

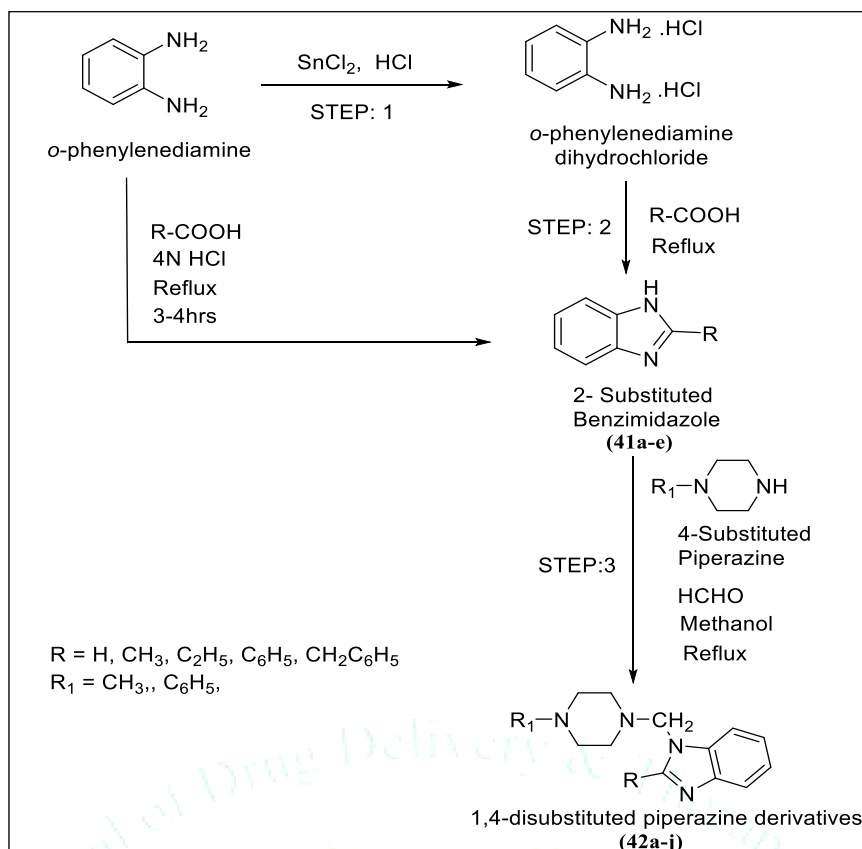
Prostaglandins, prostacyclin (PGI<sub>2</sub>) and thromboxane A<sub>2</sub> (TXA<sub>2</sub>) are produced from arachidonic acid by the enzyme cyclooxygenase which exists in a constitutive (COX-1) and an inducible (COX-2) isoforms. NSAIDs acts by blocking PG generation. The classical COX inhibitors are not selective and the main adverse effects of their use are peptic ulceration, nephrotoxicity and dyspepsia.<sup>1</sup> In designing new drug molecules, developing safer anti-inflammatory drugs without such side effects has recently been the goal of many researchers. Piperazine derivatives have been used over the

past few decades because of the wide range of activities like antimicrobials, anthelmintics, antihistamines, anti-HIV, hypotensive, anaesthetics, analgesics, anticonvulsants.<sup>2-15</sup>

### MATERIAL AND METHODS

#### Synthetic Route

Schematic representation of novel piperazine derivatives is given following figure;



SCHEME-1

Figure 1: Schematic representation of novel piperazine derivatives

## Synthetic Procedure

### Synthetic Procedure for Preparation of Benzimidazole Derivatives (41a-e)

#### Synthesis of benzimidazole (41-a)<sup>16</sup>

0.025mol of *o*-phenylenediamine was placed in a 250ml RBF and 0.034mol of 90% formic acid was added. The mixture was heated on water bath for 2hrs. Cooled, 10% NaOH solution was added slowly with constant rotation of flask until the mixture is just alkaline to litmus. The crude benzimidazole was filtered off at the pump, washed with ice-cold water, drained well and washed again with 5ml of cold water. The crude product was dissolved in 40ml of boiling water, 0.2g of decolorizing carbon and digested for 15min. The product was filtered rapidly at the pump through a preheated Buchner funnel and flask. The filtrate was cooled to about 10°C, benzimidazole was filtered off, washed with 5ml of cold water and dried at 100°C.

#### Synthesis of 2-methyl benzimidazole (41-b) & 2-benzyl benzimidazole (41-e)<sup>16</sup>

A mixture of 0.03mol of *o*-phenylenediamine dihydrochloride, 20ml of water 0.09mol of acetic acid/phenylacetic acid was refluxed for 2hrs. The reaction mixture was cooled and made it distinctly basic by gradual addition of concentrated ammonia solution, the precipitated product was collected and recrystallized it from 10% aqueous methanol.

#### Synthesis of 2-ethyl benzimidazole (41-c)<sup>14</sup>

A mixture of 0.03mol of *o*-phenylenediamine dihydrochloride, 20ml of water and 0.09mol of propionic acid was refluxed for 2hrs. The reaction mixture was cooled

and made it distinctly basic by gradual addition of concentrated ammonia solution, the precipitated product was collected and recrystallized it from 10% aqueous methanol.

#### Synthesis of 2-phenyl benzimidazole (41-d)<sup>17</sup>

0.01mol *o*-phenylenediamine and 0.01mol of benzaldehyde were mixed in 10ml DMF, 0.003mol of sodium bisulphate was added and the mixture was stirred at 80°C for 6hr. The mixture was cooled to room temperature and added dropwise to cold water under vigorous stirring. The product separated as gummy material was extracted with ethylacetate. The extract was washed with water, brine solution, dried over sodium sulphate and evaporated. The residue thus obtained was recrystallized from ethanol to afford compound.

#### General procedure for the synthesis of Mannich bases (42-a-j)<sup>14,18</sup>

0.01mol of benzimidazole derivatives (41a-e) in 20ml of methanol was stirred at room temperature with 0.01mol of 1-methyl piperazine/1-phenyl piperazine, 1 ml formaldehyde solution (40%w/v) and 1ml concentrated HCl. Then the reaction mixture was refluxed for 10hrs at 70-75°C. The hot mixture was filtered and kept in refrigerator overnight. The product precipitated out and was filtered, dried and recrystallized from ethanol to give solid compound.

#### Biological Evaluation<sup>19</sup>

Albino wistar rats of either sex (150-200 g) were divided into six groups of three animals each. Animals were deprived of food for 12 hours prior to the experiment and only water was given. First group was used as a control and received 1

ml of 1 % w/v PVP suspension in saline, the second group received PVP suspension of Aspirin (50 mg/kg) orally and the remaining four groups received PVP suspension of test compounds at a dose of 50 mg/kg orally. One hour after the administration of the compounds, carrageenan suspension (0.1 ml of 1% w/v suspension in 0.9% saline solution) was injected into the sub planter region of right hind paw of the animals. Immediately, the paw thickness was measured from the ventral to the dorsal surface using a digital vernier caliper (initial paw thickness, Tc). Thereafter, the paw thickness was measured after 1 and 3hrs after carrageenan administration. Data was shown as increase in paw thickness and % inhibition of paw edema produced by treated groups.

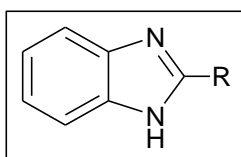
% inhibition of paw edema by using given formula:

$$\% \text{ Inhibition} = [1 - (Tt/Tc)] \times 100$$

## RESULTS

Synthesis of piperazine derivatives (42-a-j) done as per given scheme. The physical data of intermediates (41-a-e) & synthesized derivatives (42-a-j) are given in table 1 & table 2 respectively. Structures of synthesized compounds were characterized by NMR, IR, MASS spectroscopy. In the same way, the result of the biological evaluation of the prepared derivatives is also shown in table 3.

### Physical characteristics of 2-substituted benzimidazole (41a-e)

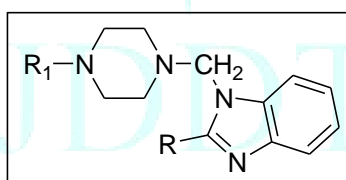


**Table 1** Physical characteristics of 2-substituted benzimidazole

| Code no. | R   | Molecular formula                              | Molecular weight (g/mol) | Melting point (°C) | Yield (%) | R <sub>f</sub> * |
|----------|---|--|--------------------------|--------------------|-----------|------------------|
| 41-a     | H   | C <sub>7</sub> H <sub>6</sub> N <sub>2</sub>   | 118.14                   | 168-170            | 59.65     | 0.52             |
| 41-b     | CH <sub>3</sub>                               | C <sub>8</sub> H <sub>8</sub> N <sub>2</sub>   | 132.16                   | 172-174            | 54.75     | 0.56             |
| 41-c     | C <sub>2</sub> H <sub>5</sub>                 | C <sub>9</sub> H <sub>10</sub> N <sub>2</sub>  | 146.19                   | 170-172            | 55.80     | 0.59             |
| 41-d     | C <sub>6</sub> H <sub>5</sub>                 | C <sub>13</sub> H <sub>10</sub> N <sub>2</sub> | 194.23                   | 286-288            | 52.68     | 0.61             |
| 41-e     | CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub> | C <sub>14</sub> H <sub>12</sub> N <sub>2</sub> | 208.26                   | 186-188            | 55.86     | 0.65             |

\*Solvent system: n-hexane: ethyl acetate (3:2)

### Physical characteristics of targeted compounds (42a-j)



**Table 2** Physical characteristics of targeted compounds

| Code no. | R   | R <sub>1</sub>                | Molecular formula                              | Molecular weight (g/mol) | Melting point (°C) | Yield (%) | R <sub>f</sub> * |
|----------|---|-------------------------------|--|--------------------------|--------------------|-----------|------------------|
| 42-a     | H   | CH <sub>3</sub>               | C <sub>13</sub> H <sub>18</sub> N <sub>4</sub> | 230.31                   | 230-232            | 47.68     | 0.60             |
| 42-b     | CH <sub>3</sub>                               | CH <sub>3</sub>               | C <sub>14</sub> H <sub>20</sub> N <sub>4</sub> | 244.34                   | 238-240            | 45.66     | 0.62             |
| 42-c     | C <sub>2</sub> H <sub>5</sub>                 | CH <sub>3</sub>               | C <sub>15</sub> H <sub>22</sub> N <sub>4</sub> | 258.36                   | 234-236            | 52.86     | 0.65             |
| 42-d     | C <sub>6</sub> H <sub>5</sub>                 | CH <sub>3</sub>               | C <sub>19</sub> H <sub>22</sub> N <sub>4</sub> | 306.40                   | >300               | 40.52     | 0.66             |
| 42-e     | CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub> | CH <sub>3</sub>               | C <sub>20</sub> H <sub>24</sub> N <sub>4</sub> | 320.43                   | 240-242            | 43.25     | 0.69             |
| 42-f     | H   | C <sub>6</sub> H <sub>5</sub> | C <sub>18</sub> H <sub>20</sub> N <sub>4</sub> | 292.38                   | 236-238            | 44.15     | 0.63             |
| 42-g     | CH <sub>3</sub>                               | C <sub>6</sub> H <sub>5</sub> | C <sub>19</sub> H <sub>22</sub> N <sub>4</sub> | 306.40                   | 242-244            | 42.50     | 0.65             |
| 42-h     | C <sub>2</sub> H <sub>5</sub>                 | C <sub>6</sub> H <sub>5</sub> | C <sub>20</sub> H <sub>24</sub> N <sub>4</sub> | 320.43                   | 238-240            | 53.56     | 0.67             |
| 42-i     | C <sub>6</sub> H <sub>5</sub>                 | C <sub>6</sub> H <sub>5</sub> | C <sub>24</sub> H <sub>24</sub> N <sub>4</sub> | 368.47                   | >300               | 41.52     | 0.70             |
| 42-j     | CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub> | C <sub>6</sub> H <sub>5</sub> | C <sub>25</sub> H <sub>26</sub> N <sub>4</sub> | 382.50                   | 246-248            | 51.86     | 0.72             |

\*Solvent system: benzene: methanol (3:2)

**Spectral characteristics of targeted compounds****1-((4-methylpiperazin-1yl)methyl)-1H-benzo[d]imidazole (42-a)**

(KBr)  $\text{cm}^{-1}$ : 3058 (aromatic CH stretch), 2967 (aliphatic CH stretch), 1182 (C-N) 1656 (C=N)  $^1\text{H NMR}$  ( $\delta$ , ppm): 2.15 (s, 3H, N-CH<sub>3</sub>), 2.30 (s, 8H, 4CH<sub>2</sub> of piperazine), 4.81 (s, 2H, N-CH<sub>2</sub>-N), 7.19-7.27 (m, 2H, Ar-H), 7.62 (d, 2H, Ar-H), 8.18 (s, 1H, N-CH<sub>2</sub>=N). EIMS(m/z): 230 (M<sup>+</sup>). Elemental analysis: (found/calculated) C, 67.71/67.80; H, 7.91/7.88; N, 24.38/24.33

**2-methyl-1-((4-methylpiperazin-1yl)methyl)-1H-benzo[d]imidazole (42-b)**

(KBr)  $\text{cm}^{-1}$ : 3098 (aromatic CH stretch), 2971 (aliphatic CH stretch), 1267 (C-N), 1615 (C=N)  $^1\text{H NMR}$  ( $\delta$ , ppm): 2.14 (s, 3H, N-CH<sub>3</sub>), 2.31 (s, 8H, 4CH<sub>2</sub> of piperazine), 2.52 (s, 3H, CH<sub>3</sub> of 2-methyl benzimidazole) 4.80 (s, 2H, N-CH<sub>2</sub>-N), 7.18-7.27 (m, 2H, Ar-H), 7.52-7.64 (m, 2H, Ar-H). EIMS(m/z): 244 (M<sup>+</sup>). Elemental analysis: (found/calculated) C, 68.78/68.82; H, 8.20/8.25; N, 23.02/22.93

**2-ethyl-1-((4-methylpiperazin-1yl)methyl)-1H-benzo[d]imidazole (42-c)**

(KBr)  $\text{cm}^{-1}$ : 3053 (aromatic CH stretch), 2920 (aliphatic CH stretch), 1255 (C-N), 1638 (C=N)  $^1\text{H NMR}$  ( $\delta$ , ppm): 1.27 (t, 3H, CH<sub>3</sub> of 2-ethyl benzimidazole), 2.13 (s, 3H, N-CH<sub>3</sub>), 2.33 (s, 8H, 4CH<sub>2</sub> of piperazine), 2.81 (m, 2H, CH<sub>2</sub> of 2-ethyl benzimidazole), 4.79 (s, 2H, N-CH<sub>2</sub>-N), 7.17-7.26 (m, 2H, Ar-H), 7.53-7.64 (m, 2H, Ar-H) EIMS(m/z): 258 (M<sup>+</sup>). Elemental analysis: (found/calculated) C, 69.69/69.73; H, 8.60/8.58; N, 21.71/21.69

**1-((4-methylpiperazin-1yl)methyl)-2-phenyl-1H-benzo[d]imidazole (42-d)**

(KBr)  $\text{cm}^{-1}$ : 759 (aromatic CH out-of-plane bend), 2925 (aliphatic CH stretch), 1165 (C-N), 1626 (C=N)  $^1\text{H NMR}$  ( $\delta$ , ppm): 2.13 (s, 3H, N-CH<sub>3</sub>), 2.32 (s, 8H, 4CH<sub>2</sub> of piperazine), 4.81 (s, 2H, N-CH<sub>2</sub>-N), 7.25-7.27 (t, 2H, Ar-H), 7.49 (t, 3H, Ar-H), 7.64-7.70 (m, 2H, Ar-H), 8.26 (d, 2H, Ar-H). EIMS(m/z): 306 (M<sup>+</sup>). Elemental analysis: (found/calculated) C, 74.44/74.48; H, 7.23/7.24; N, 18.33/18.29

**2-benzyl-1-((4-methylpiperazin-1yl)methyl)-1H-benzo[d]imidazole (42-e)**

(KBr)  $\text{cm}^{-1}$ : 3061 (aromatic CH stretch), 2943 (aliphatic CH stretch), 1235 (C-N), 1648 (C=N)  $^1\text{H NMR}$  ( $\delta$ , ppm): 2.14 (s, 3H, N-CH<sub>3</sub>), 2.30 (s, 8H, 4CH<sub>2</sub> of piperazine), 4.00 (s, 2H, CH<sub>2</sub> of 2-benzyl benzimidazole), 4.80 (s, 2H, N-CH<sub>2</sub>-N), 7.15-7.28 (m, 9H, Ar-H), 7.51 (d, 1H, Ar-H), 7.65 (d, 1H, Ar-H) EIMS(m/z): 320 (M<sup>+</sup>). Elemental analysis: (found/calculated) C, 74.92/74.97; H, 7.56/7.55; N, 17.52/17.48

**1-((4-phenylpiperazin-1yl)methyl)-1H-benzo[d]imidazole (42-f)**

(KBr)  $\text{cm}^{-1}$ : 749 (aromatic CH), 2924 (aliphatic CH stretch), 1122 (C-N), 1612 (C=N)  $^1\text{H NMR}$  ( $\delta$ , ppm): 2.45 (t, 4H, 2CH<sub>2</sub>

of piperazine), 3.45 (t, 4H, 2CH<sub>2</sub> of piperazine), 4.81 (s, 2H, N-CH<sub>2</sub>-N), 6.80 (t, 1H, Ar-H of phenyl piperazine), 6.93 (d, 2H, Ar-H of phenyl piperazine), 7.20-7.27 (m, 4H, Ar-H), 7.61 (d, 2H, Ar-H), 8.19 (s, 1H, N-CH<sub>2</sub>=N) EIMS(m/z): 292 (M<sup>+</sup>). Elemental analysis: (found/calculated) C, 73.98/73.94; H, 6.85/6.89; N, 19.17/19.16

**2-methyl-1-((4-phenylpiperazin-1yl)methyl)-1H-benzo[d]imidazole (42-g)**

(KBr)  $\text{cm}^{-1}$ : 3053 (aromatic CH stretch), 2974 (aliphatic CH stretch), 1271 (C-N), 1622 (C=N)  $^1\text{H NMR}$  ( $\delta$ , ppm): 2.43 (t, 4H, 2CH<sub>2</sub> of piperazine), 2.51 (s, 3H, CH<sub>3</sub> of 2-methyl benzimidazole), 3.45 (t, 4H, 2CH<sub>2</sub> of piperazine), 4.82 (s, 2H, N-CH<sub>2</sub>-N), 6.77 (t, 1H, Ar-H of phenyl piperazine), 6.92 (d, 2H, Ar-H of phenyl piperazine), 7.20-7.27 (m, 4H, Ar-H), 7.51-7.63 (d, 2H, Ar-H) EIMS(m/z): 306 (M<sup>+</sup>). Elemental analysis: (found/calculated) C, 74.41/74.48; H, 7.25/7.24; N, 18.34/18.29

**2-ethyl-1-((4-phenylpiperazin-1yl)methyl)-1H-benzo[d]imidazole (42-h)**

(KBr)  $\text{cm}^{-1}$ : 3050 (aromatic CH stretch), 2988 (aliphatic CH stretch), 1222 (C-N), 1623 (C=N)  $^1\text{H NMR}$  ( $\delta$ , ppm): 1.28 (t, 3H, CH<sub>3</sub> of 2-ethyl benzimidazole), 2.45 (t, 4H, 2CH<sub>2</sub> of piperazine), 2.80 (m, 2H, CH<sub>2</sub> of 2-ethyl benzimidazole), 3.44 (t, 4H, 2CH<sub>2</sub> of piperazine), 4.80 (s, 2H, N-CH<sub>2</sub>-N), 6.80 (t, 1H, Ar-H), 6.94 (d, 2H, Ar-H), 7.21-7.27 (m, 4H, Ar-H), 7.53 (d, 1H, Ar-H), 7.64 (d, 1H, Ar-H) EIMS(m/z): 320 (M<sup>+</sup>). Elemental analysis: (found/calculated) C, 74.88/74.97; H, 7.57/7.55; N, 17.55/17.48

**2-phenyl-1-((4-phenylpiperazin-1yl)methyl)-1H-benzo[d]imidazole (42-i)**

(KBr)  $\text{cm}^{-1}$ : 3004 (aromatic CH stretch), 2835 (aliphatic CH stretch), 1268 (C-N), 1622 (C=N)  $^1\text{H NMR}$  ( $\delta$ , ppm): 2.45 (t, 4H, 2CH<sub>2</sub> of piperazine), 3.45 (t, 4H, 2CH<sub>2</sub> of piperazine), 4.76 (s, 2H, N-CH<sub>2</sub>-N), 6.83 (t, 1H, Ar-H), 6.96 (d, 2H, Ar-H), 7.20-7.27 (m, 4H, Ar-H), 7.52 (d, 3H, Ar-H), 7.63-7.69 (m, 2H, Ar-H), 8.29 (d, 2H, Ar-H) EIMS(m/z): 368 (M<sup>+</sup>). Elemental analysis: (found/calculated) C, 78.18/78.23; H, 6.59/6.57; N, 15.23/15.21

**2-benzyl-1-((4-phenylpiperazin-1yl)methyl)-1H-benzo[d]imidazole (42-j)**

(KBr)  $\text{cm}^{-1}$ : 3063 (aromatic CH stretch), 2942 (aliphatic CH stretch), 1286 (C-N), 1668 (C=N)  $^1\text{H NMR}$  ( $\delta$ , ppm): 2.44 (t, 4H, 2CH<sub>2</sub> of piperazine), 3.42 (t, 4H, 2CH<sub>2</sub> of piperazine), 4.00 (s, 2H, CH<sub>2</sub> of 2-benzyl benzimidazole), 4.82 (s, 2H, N-CH<sub>2</sub>-N), 6.80 (t, 1H, Ar-H), 6.94 (d, 2H, Ar-H), 7.16-7.28 (m, 9H, Ar-H), 7.51 (d, 1H, Ar-H), 7.65 (d, 1H, Ar-H) EIMS(m/z): 382 (M<sup>+</sup>). Elemental analysis: (found/calculated) C, 78.43/78.50; H, 6.87/6.85; N, 14.70/14.65

**Anti-inflammatory Activity**

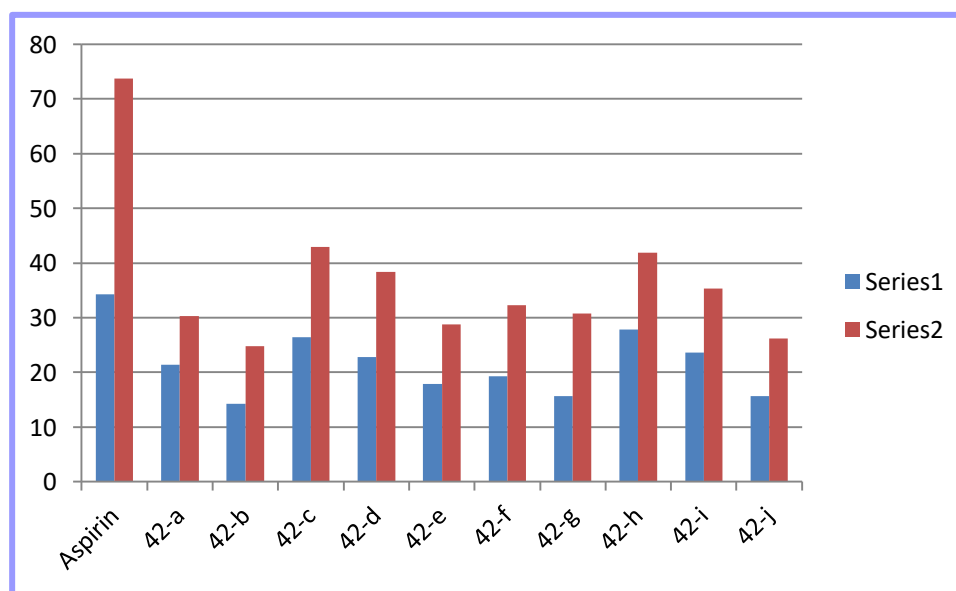
The anti-inflammatory activity of the target compounds (42-a to 42-j) were tested by carrageenan induced inflammation in rat paw edema.

**Table 3:** Anti-inflammatory activity of the piperazine derivatives (42-a to 42-j)

| Treatment   | Dose (mg/kg) | Carrageenan induced paw edema |              |                            |              |
|-------------|--------------|-------------------------------|--------------|----------------------------|--------------|
|             |              | Increase in paw edema (mm)    | % inhibition | Increase in paw edema (mm) | % inhibition |
|             |              | After 1 hour                  |              | After 3 hour               |              |
| 1           | control      | 1.40±0.17                     | -            | 1.98±0.14                  | -            |
| 2 (Aspirin) | 50           | 0.92±0.18                     | 34.28        | 0.52±0.16                  | 73.73        |
| 42-a        | 50           | 1.10±0.15                     | 21.42        | 1.38±0.17                  | 30.30        |
| 42-b        | 50           | 1.20±0.15                     | 14.28        | 1.49±0.18                  | 24.74        |
| 42-c        | 50           | 1.03±0.16                     | 26.42        | 1.13±0.13                  | 42.92        |
| 42-d        | 50           | 1.08±0.13                     | 22.85        | 1.22±0.17                  | 38.38        |
| 42-e        | 50           | 1.15±0.11                     | 17.86        | 1.41±0.16                  | 28.78        |
| 42-f        | 50           | 1.13±0.18                     | 19.28        | 1.34±0.17                  | 32.32        |
| 42-g        | 50           | 1.18±0.14                     | 15.71        | 1.37±0.15                  | 30.80        |
| 42-h        | 50           | 1.01±0.16                     | 27.85        | 1.15±0.13                  | 41.91        |
| 42-i        | 50           | 1.07±0.15                     | 23.57        | 1.28±0.15                  | 35.35        |
| 42-j        | 50           | 1.18±0.11                     | 15.71        | 1.45±0.14                  | 26.26        |

Number of Animals used n = 3

Dose of the test compounds and standard drug = 50 mg/kg

**Figure 2:** Column chart showing % inhibition

## DISCUSSION

Compounds (42-a to 42-j) were screened for anti-inflammatory activity by inhibition of carrageenan induced rat paw edema method at the dose of 10 mg/kg. Significant anti-inflammatory activity was observed with inhibition in the range of after 3 h. Aspirin showed 73.73% inhibition after 3 h. Among all the screened compounds, 42-c & 42-h were found to be the most potent in the series with inhibition after 3 h. Among all the screened compounds, 42-b & 42-j were found least potent in the series with respect to standard after 3 h.

## CONCLUSION

In conclusion, we reported here a series of 1,4-disubstituted piperazine derivatives as anti-inflammatory agents. Synthesized compounds (42-c, 42-d & 42-h) exhibit good anti-inflammatory activity but two of them (42-b and 42-i) are less potent, while another five (42-a, 42-e, 42-f, 42-g and 42-j) have significant activity. Compound (42-c) was most

potent among the series of synthesized compounds as anti-inflammatory agents.

## ACKNOWLEDGEMENTS

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## REFERENCES

- Vane JR, Bakhle YS, Botting RM, Cyclooxygenase 1 and 2, Annual Review of Pharmacology and Toxicology, 1998; 38: 97-120.
- Jain VK, Jain B, Sharma UK, Saha D, Synthesis, characterization and antimicrobial screening of some 4-substituted-1-(4-substituted phenyl) piperazine derivatives, International Journal of Current Pharmaceutical Research, 2011; 3(1): 66-70.
- Hussein MA and Diab AK, Synthesis of some new 1,4-disubstituted piperazine-2,3-dione derivatives of potential anthelmintic activity, Bulletin of Pharmaceutical Science, 2005; 28: 37-44.

- Savaliya MD, Dobaria JG, Bhuvu VV, Purohit HD, Purohit DM, Synthesis and biological screening of 1-N-{4'-[4'',4'''-difluoro diphenyl]-methyl]-piperazine-1'-yl}-4-arylidene-2-phenyl-5-oxo-imidazolines, *Indian Journal of Chemistry*, 2012; 51: 1517-1520.
- Narendra SC, Sadashiva CT, Kavitha CV, Rangappa KS, Synthesis and in vitro antimicrobial studies of medicinally important novel N-Alkyl and N-Sulfonyl derivatives of 1-[bis (4 fluorophenyl)- methyl]piperazine, *Bioorganic and Medicinal Chemistry Letters*, 2006; 14: 6621-6627.
- Thakran AK, Gupta S, Kumari S, Mourya AK, Alok S, Synthesis and pharmacological evaluation of 1-benz-hydryl piperazine derivatives, *International Journal of Pharmaceutical Sciences and Research*, 2012; 3: 213-217.
- Purohit DM, Patoliya VN, Patel AU, Guna JV, Synthesis and antimicrobial activity of new aryl amides in Piperazine molecules, *Indian Journal of Organic Chemistry*, 2009; 5(1): 96-99.
- Serradji N, Bensaid O, Martin M, Bosquet ND, Redeuilh C, Huet C, Heymans F, Lamouri A, Clayette P, Dong CZ, Dormont D, Godfroid J, Synthesis and anti HIV activity of analogues 1-[4-methoxy-3,5-dimethyl benzyl]-4-[3-(ethyl amino)-2-pyridyl]piperazine hydrochloride, *Journal of Medicinal Chemistry*, 2000; 43: 2149.
- Agrawal SK, Saxena AK, Jain PC, Sur RN, Srimal RC, Dhwan BN, Anand N, Synthesis and CNS depressant, hypotensive,  $\alpha$ -adrenoceptor blocking activities of 1-(3-carboxyphenoxy)-3-(N1-N4-phenyl piperazinyl) -propane, *Indian Journal of Chemistry*, 1987; 26B: 642.
- Savaliya MD, Ph.D. Thesis, Synthesis and therapeutic activity of some new piperazine derivatives, Saurashtra University, 2010.
- Venable JD, Cai H, Chai W, Dvorak CA, Grice CA, Jablonowski JA, Shah CR, Kwoke AK, Ly KS, Pio B, Wei J, Desai PJ, Jiang W, Nguyen S, Ling P, Wilson SJ, Dunford PJ, Thrumond RL, Lowenberg RL, Karlsson L, Carruthers NI, Edwards JP, Preparation and biological evaluation of (5-methyl-1H-indole-2-yl)-4-methyl-piperazine-1-yl)-methanone as potent human histamine H<sub>4</sub> antagonists, *Journal of Medicinal Chemistry*, 2005; 48: 8289.
- Rastogi R, Sharma S, Lyer RN, Synthesis and antihookworm activity of N-(2-substituted-ethyl)-N'-aryl piperazine, *Indian Journal of Chemistry*, 1980; 19B: 1003.
- Kargaonkar UV, Deodhkar KD, Kulkarni RA, Samant SD, Synthesis and anti-inflammatory activity of ethyl-8-[4-(3-chlorophenyl)-1 piperazinyl methyl]-2-oxocoumarin-4-acetate, *Journal of the Indian Chemical Society*, 1984; 61: 554.
- Mariappan G, Bhuyan NR, Kumar P, Kumar D, Murali K, Synthesis and biological evaluation of mannich bases of benzimidazole derivatives, *Indian Journal of Chemistry*, 2011; 50B: 1216-1219.
- Hatnapure GD, Keche AP, Rodge AH, Birajdar SS, Tale RH, Kaamble VM, Synthesis and biological evaluation of novel piperazine derivatives of flavones as potent anti-inflammatory and anti-microbial agents, *Bioorganic Medicinal Chemistry Letters*, 2012; 22: 6385-6390.
- Furniss BS, Hannaford AJ, Smith PW, Tatchell AR. *Vogel's Textbook of Practical Organic Chemistry*. 5<sup>th</sup> Ed. Pearson Publication; 1989. P.1161.
- Ranawat MS, Soni B, Sharma P, Synthesis and evaluation of new benzimidazole derivatives as potential antimicrobial agents, *International Journal of Comprehensive Pharmacy* 2012; 9(05): 1-4.
- Srivastava S, Pandeya SN, Yadav MK, Singh BK, Synthesis and analgesic activity of novel derivatives of 1,2-Substituted benzimidazoles, *Journal of Chemistry*, 2013; 1-6.
- Winter CA, Risley EA, Nuss GW, Carrageenan induced edema in hind paw of rat as an assay for anti-inflammatory drugs, *Proceedings of the Society for Experimental Biology and Medicine*, 1962; 111: 544-547.

