



## MICROWAVE-ASSISTED SYNTHESIS OF NOVEL BENZOTHAZOLE DERIVATIVES CONTAINING IMIDAZOL MOIETIES AND ANTI-INFLAMMATORY ACTIVITY

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### ABSTRACT

The present work which involves the 2-phenyl-4-benzylidene oxazol-5(4H)-One can be prepared by the cyclization reaction between substituted Benzaldehydes substituted Benzyl glycine. Then it can be reaction with substituted 2-aminobenzothiazole to give novel Benzothiazole derivatives containing Imidazole moieties. The synthesized compounds were screened for Anti-inflammatory activity by carrageenan induced paw edema assay in rats. The results indicated that all the compounds reported significantly higher anti-inflammatory activity at dose of 50 mg/kg when compared to that of 20 mg/kg dose. However, the anti-inflammatory effect of compound 4j and 4n (50 mg/kg) and celecoxib (20 mg/kg) was found to be similar (82.5, 85.3% vs. 87.8%). The higher anti-inflammatory activity of compound 4j and 4n could be due to presence of higher hydrophobic planar substitutions.

### KEY WORDS

Substituted benzaldehyde, Hippuric acid, 2-amino benzothiazole, Anti-Inflammatory activity.

### INTRODUCTION:

Green chemistry is a new and rapidly emerging field of chemistry. Its growing importance is in utilization of the maximum possible resources in such a way that, there is negligible or minimum production of chemical waste. It is one of the best alternatives for traditional chemical synthesis processes. By applying the green synthesis method, we can not only avoid the use of hazardous, toxic solvents, but also the formation of by-products is avoided. Benz fused heterocyclic ring represents an area of considerable interest mainly due to its interesting pharmacological properties. The discovery of novel drugs and drug compounds has forever been the aim of pharmaceutical sciences and, especially, of medicinal chemistry, which arises from pharmaceutical chemistry. Thiazole rings are planar and aromatic. Drug design in its wide sense and structure-activity relationship studies are important and at the heart of medicinal chemistry

and it are the advancement and progress of this field of research that has made medicinal chemistry the contemporary and extremely productive science it has become in current decades [1-2]. Majority of the currently available medicinal compounds consist one or more heterocyclic ring system. From the contemporary medicinal chemistry investigation, it was found that Benzothiazole is one such significant heterocyclic system has been gained magnitude due to the broad array of biological activities.

Thiazoles are characterized by larger pi-electron delocalization than the corresponding oxazoles and have therefore greater aromaticity. This aromaticity is evidenced by the chemical shift of the ring protons in proton NMR spectroscopy (between 7.27 and 8.77 ppm), clearly indicating a strong diamagnetic ring current. The calculated pi-electron density marks C<sub>5</sub> as the primary site for electrophilic substitution, and C<sub>2</sub> as

the site for nucleophilic substitution. Since most of the benzothiazole derivatives were reported for their diversified activity [3-8] such as antimalarial, anticonvulsant, anthelmintic, analgesic, anti-inflammatory, antifungal, antitumor and antitubercular. Benzothiazole ring system is present in various marine and terrestrial natural compounds, which have useful biological activities [9-12]. 2-Aminobenzothiazoles are highly reactive compounds and extensively utilized as reactants or reaction intermediates since the  $\text{NH}_2$  and endocyclic N functions are suitably situated to enable reactions with various reactants to form a variety of fused heterocyclic compounds.

Imidazole is a five-member heterocyclic aromatic compound in which two Nitrogen atoms are present both Nitrogen atom are  $\text{sp}^2$  hybridized. Imidazole ring contains two types of lone-pair one is delocalized and second is non-delocalized (Non-Huckle-lone pair) due to this both Nitrogen has different pka. The Nitrogen has delocalized lone-pair has  $\text{pka}=7$  and other nitrogen which has non- delocalized lone- pair has  $\text{pka}=14.9$ . Hence Imidazole is amphoteric in nature i.e., it work as both acid and base, susceptible to nucleophilic and electrophilic attack [13].

## MATERIALS AND METHODS

The synthesized compounds were screened for anti-inflammatory activities. Fourier Transform IR spectrometer (model Shimadzu 8700) in the range of  $400\text{-}4000\text{ cm}^{-1}$  Using KBr pellets and values are reported in  $\text{cm}^{-1}$  and the spectra were interpreted.  $^1\text{H-NMR}$  spectra were recorded on DPX-200 MHz NMR spectrometer using  $\text{DMSO-d}_6$  and chemical shifts ( $\delta$ ) are reported in parts per million down field from internal reference Tetramethylsilane (TMS) and the Spectra were interpreted. Mass spectra were recorded on Mass spectrophotometer (model Shimadzu) by LC- MS and the spectra were interpreted. Precoated Silica gel G plates were used to monitor the progress of reaction as well as to check the purity of the compounds: n-Hexane: Ethyl acetate (7:3).

## General procedures

### Step-1. Synthesis of 2-hydrazineylbenzo[d]thiazole (1a-b) derivatives:

Concentrated HCl (10 ml) was added drop wise with stirring to hydrazine hydrate (10 ml) at  $5\text{-}10^\circ\text{C}$ ; to it ethylene glycol (22 ml) and benzothiazol-2-ylamine (0.01mol) were added and the reaction was subjected to under microwave irradiation for 6 minutes, at 300 W. The reaction was monitored by silica gel TLC. (N-Hexane: Ethylacetate 7: 3). On cooling solid separated out, this was filtered and washed with water. Further it was purified by recrystallization by ethanol.

**Step-2: Synthesis of Benzoylglycine derivatives:** In conical flask prepare 10% of sodium hydroxide solution and dissolve in it 0.03 mole of glycine. Add 0.03 mole of benzoyl chloride in 5 portions to the solution. Stopper the vessel and shake vigorously after each addition until all the chloride has reacted. Transfer the solution to a beaker and rinse the conical flask with a little water. Place a few pieces of crushed ice to the solution and add slowly 5 mL of HCl with stirring until the mixture is acid to Congo red paper. Collect the resulting crystalline precipitate of benzoylglycine. Filter the product on Büchner funnel, and dry on air on Petri dish.

**Step: 3: Synthesis of 2-phenyl-4-benzylidene oxazol-5(4H)-One derivative.** The appropriate aldehyde (1 mmol), hippuric acid (1 mmol),  $\text{Ac}_2\text{O}$  (1 ml) and  $\text{CaHPO}_4$  as a catalyst (0.2 mmol) were mixed in a conical flask. Then, the reaction mixture was irradiated using the microwave oven at a power output of 300W for the appropriate time. After completion of the reaction as indicated by TLC, the reaction mixture was cooled to room temperature. 5 ml Cold ethanol/water (1:1) was added and the mixture was stirred for 15 min until a yellow solid precipitated. An aqueous solution of  $\text{NaHCO}_3$  (10 ml, 20%) was added, the solid products and the catalyst were filtered. The solid materials were dissolved in hot ethanol to remove the catalyst. The solvent was allowed to cool in room temperature to obtain crude products.

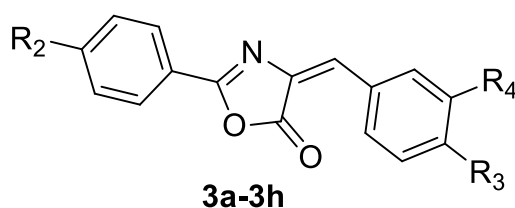


Table: Physical data of Compounds 3a-3h

| Code | Molecular Formula                                             | R <sub>2</sub>                   | R <sub>3</sub>   | R <sub>4</sub>    | Molecular Weight (gms) | M.P (°C) | %Yield |
|------|---------------------------------------------------------------|----------------------------------|------------------|-------------------|------------------------|----------|--------|
| 3a   | C <sub>16</sub> H <sub>11</sub> NO <sub>2</sub>               | H                                | H                | H                 | 249                    | 179-181  | 66     |
| 3b   | C <sub>16</sub> H <sub>10</sub> NO <sub>2</sub>               | Cl                               | H                | H                 | 283                    | 209-211  | 78     |
| 3c   | C <sub>16</sub> H <sub>10</sub> N <sub>2</sub> O <sub>4</sub> | NO <sub>2</sub>                  | H                | H                 | 294                    | 198-200  | 74     |
| 3d   | C <sub>17</sub> H <sub>13</sub> NO <sub>2</sub>               | CH <sub>3</sub>                  | H                | H                 | 263                    | 183-185  | 80     |
| 3e   | C <sub>18</sub> H <sub>16</sub> N <sub>2</sub> O <sub>2</sub> | N(CH <sub>3</sub> ) <sub>2</sub> | H                | H                 | 292                    | 207-209  | 84     |
| 3f   | C <sub>17</sub> H <sub>13</sub> NO <sub>3</sub>               | OCH <sub>3</sub>                 | H                | H                 | 279                    | 219-221  | 77     |
| 3g   | C <sub>18</sub> H <sub>15</sub> NO <sub>4</sub>               | OCH <sub>3</sub>                 | OCH <sub>3</sub> | H                 | 309                    | 227-229  | 68     |
| 3h   | C <sub>16</sub> H <sub>10</sub> N <sub>2</sub> O <sub>4</sub> | H                                | H                | 3-NO <sub>2</sub> | 294                    | 201-203  | 78     |

#### Step: 4: Synthesis of 3-(benzo[d]thiazol-2-ylamino)-5-benzylidene-2-phenyl-3,5-dihydro-4H-imidazol-4-one

Equimolar mixtures of 2-phenyl-4-benzylidene oxazol-5(4H)-One (3a-3h, 0.01) and 2-hydrazineyl benzo[d]thiazole (1a-1b, 0.01) were dissolved in 10ml glacial acetic acid. The reaction uses the microwave

irradiation in an unmodified domestic microwave oven at 160W with 30 s/cycle for 3 min and set aside. The resultant solid was washed with dilute ethanol, dried and recrystallized from an ethanol-chloroform mixture.

Table:2. Physical data of Compounds 4a-4o

| Compound | Molecular Formula                                                  | R | R <sub>1</sub> | R <sub>2</sub>  | R <sub>3</sub>                   | R <sub>4</sub>   | Molecular Weight (gms) | M.P (°C) | %Yield | R <sub>f</sub> value |
|----------|--------------------------------------------------------------------|---|----------------|-----------------|----------------------------------|------------------|------------------------|----------|--------|----------------------|
| 4a       | C <sub>23</sub> H <sub>16</sub> N <sub>4</sub> OS                  | H | H              | H               | H                                | H                | 396                    | 213-215  | 74     | 0.72                 |
| 4b       | C <sub>23</sub> H <sub>15</sub> N <sub>4</sub> OSCl                | H | H              | H               | H                                | H                | 430                    | 213-215  | 73     | 0.71                 |
| 4c       | C <sub>23</sub> H <sub>15</sub> N <sub>5</sub> O <sub>3</sub> S    | H | H              | H               | NO <sub>2</sub>                  | H                | 441                    | 233-235  | 81     | 0.62                 |
| 4d       | C <sub>24</sub> H <sub>18</sub> N <sub>4</sub> OS                  | H | H              | H               | CH <sub>3</sub>                  | H                | 410                    | 172-174  | 81     | 0.59                 |
| 4e       | C <sub>25</sub> H <sub>21</sub> N <sub>5</sub> OS                  | H | H              | H               | N(CH <sub>3</sub> ) <sub>2</sub> | H                | 439                    | 219-221  | 78     | 0.79                 |
| 4f       | C <sub>24</sub> H <sub>18</sub> N <sub>4</sub> O <sub>2</sub> S    | H | H              | H               | OCH <sub>3</sub>                 | H                | 426                    | 237-239  | 72     | 0.68                 |
| 4g       | C <sub>25</sub> H <sub>20</sub> N <sub>4</sub> O <sub>3</sub> S    | H | H              | H               | OCH <sub>3</sub>                 | OCH <sub>3</sub> | 456                    | 263-265  | 76     | 0.60                 |
| 4h       | C <sub>23</sub> H <sub>15</sub> N <sub>5</sub> O <sub>3</sub> S    | H | H              | NO <sub>2</sub> | H                                | H                | 441                    | 243-245  | 63     | 0.74                 |
| 4i       | C <sub>23</sub> H <sub>14</sub> N <sub>4</sub> OSFCl               | F | Cl             | H               | H                                | H                | 430                    | 187-189  | 78     | 0.83                 |
| 4j       | C <sub>23</sub> H <sub>13</sub> N <sub>4</sub> OSCl <sub>2</sub> F | F | Cl             | H               | Cl                               | H                | 482                    | 253-255  | 82     | 0.65                 |
| 4k       | C <sub>23</sub> H <sub>13</sub> N <sub>4</sub> O <sub>3</sub> SClF | F | Cl             | H               | NO <sub>2</sub>                  | H                | 493                    | 213-215  | 77     | 0.80                 |
| 4l       | C <sub>24</sub> H <sub>16</sub> N <sub>4</sub> OSClF               | F | Cl             | H               | CH <sub>3</sub>                  | H                | 462                    | 221-224  | 69     | 0.86                 |
| 4m       | C <sub>25</sub> H <sub>19</sub> N <sub>5</sub> OSFCl               | F | Cl             | H               | N(CH <sub>3</sub> ) <sub>2</sub> | H                | 491                    | 223-225  | 73     | 0.74                 |
| 4n       | C <sub>24</sub> H <sub>16</sub> N <sub>4</sub> SClF                | F | Cl             | H               | OCH <sub>3</sub>                 | H                | 478                    | 253-255  | 74     | 0.76                 |
| 4o       | C <sub>23</sub> H <sub>13</sub> N <sub>5</sub> OSClF               | F | Cl             | NO <sub>2</sub> | H                                | H                | 493                    | 239-241  | 78     | 0.82                 |

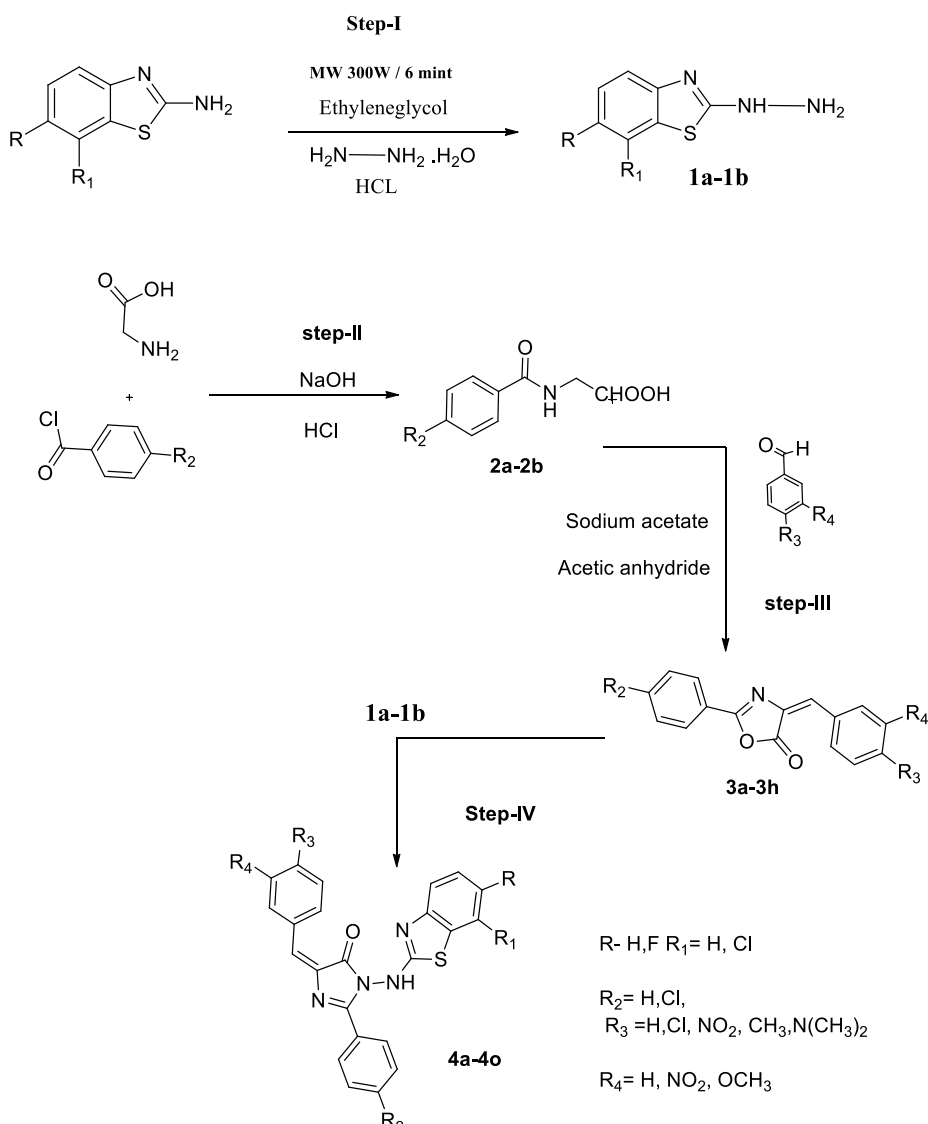
#### RESULTS AND DISCUSSION:

**Synthesis:** The present work which involves the reaction between 2-aminobenzothiazole and hydrazine hydrate to give 2-hydrazineylbenzo[d]diazole. The 2-phenyl-4-benzylidene oxazol-5(4H)-One can be prepared by the cyclization reaction between substituted Benzaldehydes substituted Benzyl glycine. Then it can be reaction with substituted 2-aminobenzothiazole to give novel Benzothiazole derivatives containing Imidazole moieties. The synthesized compounds were screened for Anti-inflammatory activity.

#### Spectral data:

##### Compound (4a): 3-(benzo[d]thiazol-2-ylamino)-5-benzylidene-2-phenyl-3,5-dihydro-4H-imidazol-4-one.

Mol. formula: C<sub>23</sub>H<sub>16</sub>N<sub>4</sub>OS, Microwave irradiation yield 74%, IR (ν cm<sup>-1</sup>): 3415 (N-H Str), 3088(A-H Str), 2977, 2863 (C-H Str, Aliphatic), 1701 (-CO Str) 1539(C=N Str), 1230(C-N Str), 664(C-S-C Str). <sup>1</sup>H-NMR (DMSO) δδ ppm: 10.93 (s, 1H, -NH), 8.53(s, 1H, -C=CH), 7.80-7.68 (d, 2H, Ar-H), 7.63-7.52 (t, 3H, Ar-H), 7.48-7.44 (t, 3H, Ar-H), 7.43-7.38 (t, 2H, Ar-H), 6.76-6.58 (d, 2H, Ar-H), 6.20-6.10 (d, 2H, Ar-H). Mass (ESI-MS): m/z 396(M), 297(M + 1, 100%).



**Compound (4b): 3-((benzo[d]thiazol-2-yl)amino)-2-(phenyl)-5-(4-chlorobenzylidene)-3,5-dihydro-4H-imidazol-4-one:** Mol. formula: C<sub>23</sub>H<sub>15</sub>N<sub>4</sub>OSCl, Microwave irradiation yield 73%, IR ( $\nu$  cm<sup>-1</sup>): 3406 (N-H Str), 3096(A-H Str), 2960, 2895(C-H Str, Aliphatic), 1710(CO Str), 1574(C=N Str), 1324(C-N Str), 795(Cl Str, Ar-Cl), 656(C-S-C Str). 1H-1H-NMR (DMSO)  $\delta\delta$  ppm: 11.93 (s, 1H, -NH), 8.49(s, 1H, -C=CH), 8.37-7.97 (d, 2H, Ar-H), 7.87-7.84 (d, 2H, Ar-H), 7.79-7.78 (d, 2H, Ar-H), 7.69-7.68 (d, 2H, Ar-H), 7.60-7.58 (t, 2H, Ar-H), 7.45-7.42 (t, 2H, Ar-H). Mass (ESI-MS): m/z 430(M), 431(M + 1, 100%).

**Compound (4c): 3-((benzo[d]thiazol-2-yl)amino)-2-(phenyl)-5-(4-nitrobenzylidene)-3,5-dihydro-4H-imidazol-4-one" (4c):** Mol. formula: C<sub>23</sub>H<sub>15</sub>N<sub>5</sub>O<sub>3</sub>S, Microwave irradiation yield 81%, IR ( $\nu$  cm<sup>-1</sup>): 3354 (N-H Str), 3164(Ar-H Str), 2965, 2932(C-H Str, Aliphatic),

1702(CO Str), 1634(NO<sub>2</sub> Str), 1545(C=N Str), 1253(C-N Str), 675(C-S-C Str). 1H-1H-NMR (DMSO)  $\delta\delta$  ppm: 11.95 (s, 1H, -NH), 8.56(s, 1H, -C=CH), 8.29-8.11 (d, 2H, Ar-H), 7.88-7.87(d, 2H, Ar-H), 7.69-7.67 (d, 2H, Ar-H), 7.55-7.54 (d, 2H, Ar-H), 7.41-7.14 (d, 2H, Ar-H), 7.42-7.11 (t, 3H, Ar-H). Mass (ESI-MS): m/z 441(M), 442(M + 1, 100%).

**Compound(4d):3-((benzo[d]thiazol-2-yl) amino)-2-(phenyl)-5-(4-methyl benzylidene -3,5-dihydro-4H-imidazol-4-one.** Mol. formula: C<sub>24</sub>H<sub>18</sub>N<sub>4</sub>OS, Microwave irradiation yield 81%, IR ( $\nu$  cm<sup>-1</sup>): 3405 (N-H Str), 3038(A-H Str), 2998, 2917, 2874(C-H Str, Aliphatic), 1716(CO Str), 1555(C=N Str), 1216(C-N Str), 681(C-S-C Str). 1H-NMR (DMSO)  $\delta\delta$  ppm: 12.04(s, 1H, -NH), 8.47(s, 1H, -N=CH), 7.97-7.85 (d, 2H, Ar-H), 7.79-7.74(t, 3H, Ar-H), 7.66-7.64 (d, 2H, Ar-H), 7.50-7.49 (d, 2H, Ar-

H), 7.35-7.26(t, 2H), 7.25(d, 2H, Ar-H), 2.24(s, 3H, -CH<sub>3</sub>)<sub>2</sub>. Mass (ESI-MS): m/z 410(M), 411(M + 1, 100%).

**Compound (4i): 3-((7-chloro-6-fluorobenzo[d]thiazol-2-yl) amino)-2-(phenyl)-5 (benzyl idene)-3, 5-dihydro-4H-imidazol-4-one.** Mol. formula: C<sub>23</sub>H<sub>14</sub>N<sub>4</sub>OS, Microwave irradiation yield 65%, IR (ν cm<sup>-1</sup>): 3408 (N-H Str), 3102, 3087(A-H Str), 2989, 2954, 2894(C-H Str, Aliphatic), 1720(CO Str), 1541(C=N Str), 1284(C-N Str), 789(Cl Str), 692(C-S-C Str). <sup>1</sup>H-NMR (DMSO) δδ ppm: 10.34 (s, 1H, -NH), 8.43(s, 1H, -C=CH), 8.23-8.20 (d, 2H, Ar-H), 7.98-7.67 (d, 2H, Ar-H), 7.54-7.50 (d, 2H, Ar-H), 7.38-7.32 (t, 3H, Ar-H), 6.98-6.94 (t, 3H, Ar-H). Mass (ESI-MS): m/z 448(M), 449(M + 1, 100%).

#### Pharmacological Evaluation:

**Anti-Inflammatory:** [14-15] Anti-inflammatory activity of the newly synthesized compounds was determined by carrageenan induced paw edema assay in rats. Two dose levels (20 mg/kg and 50 mg/kg) of synthesized compounds and Celecoxib (10mg/kg) as standard were administered. The change in the paw volumes were measured before and 1h after carrageenan injection, using the mercury displacement technique with the help of plethysmograph. The percent inhibition of paw edema was calculated from percent inhibition formula. % inhibition (I) = 100[1 - (a - x) / (b - y)]

Where,

x = mean paw volume of rats before the administration of carrageenan and test compounds or reference compound (test group)

a = mean paw volume of rats after the administration of carrageenan in the test group (drug treated)

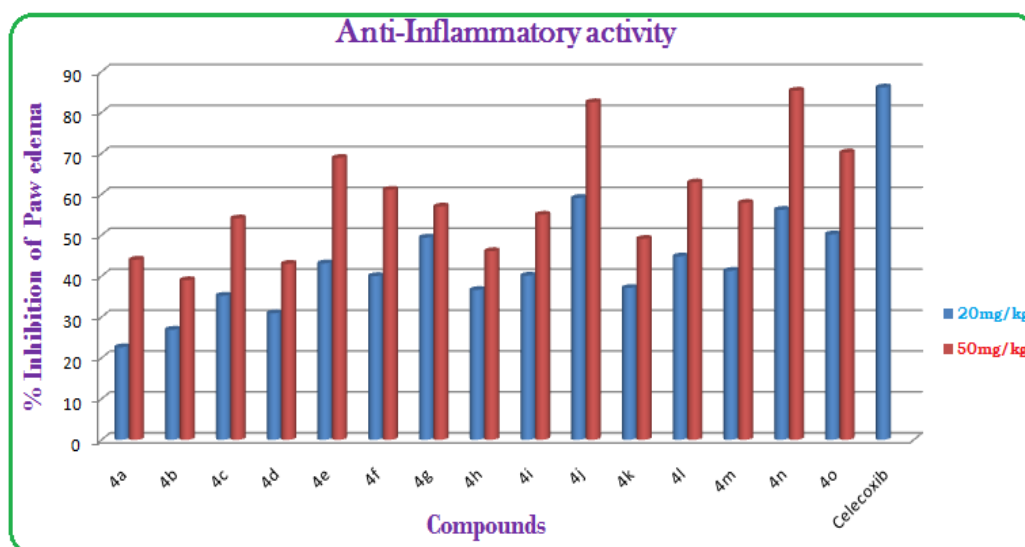
b = is the mean paw volume of rats after the administration of carrageenan in the control group

y = mean paw volume of rats before the administration of carrageenan in the control group.

Anti-inflammatory activity of newly synthesized Novel Benzothiazole Derivatives Containing Imidazol Moieties was evaluated by carrageenan induced paw edema bioassay in rats with Celecoxib (20 mg/kg) as reference standard. Percentage inhibitions of the molecules are tabulated in Table 3 and Figure 2. % inhibition of paw edema with test compounds dose of 20 mg/kg is ranged between 22.6 (compound 4a) and 59.9 (compound 4j), whereas with 50 mg/kg dose, it is between 39.1% (compound 4b) and 85.3% (compound 4n). The results indicated that all the compounds reported significantly higher anti-inflammatory activity at dose of 50 mg/kg when compared to that of 20 mg/kg dose. However, the anti-inflammatory effect of compound 4j and 4n (50 mg/kg) and celecoxib (20 mg/kg) was found to be similar (82.5, 85.3% vs. 87.8%). The higher anti-inflammatory activity of compound 4j and 4n could be due to presence of higher hydrophobic planar substitutions.

**Table.3: Anti-Inflammatory activity of novel Benzothiazole derivatives containing Imidazol moieties (% inhibition of paw edema)**

| % Inhibition of Paw edema | Compounds |      |      |      |      |      |      |      |      |       |      |      |      |      |      |      |
|---------------------------|-----------|------|------|------|------|------|------|------|------|-------|------|------|------|------|------|------|
|                           | Celecoxib | 4a   | 4b   | 4c   | 4d   | 4e   | 4f   | 4g   | 4h   | 4i    | 4j   | 4k   | 4l   | 4m   | 4n   | 4o   |
| 20mg/kg                   | 87.8      | 22.6 | 26.9 | 35.2 | 30.9 | 43.1 | 40.0 | 49.4 | 36.6 | 40.1  | 59.9 | 37.1 | 44.8 | 41.3 | 56.2 | 50.2 |
| 50mg/kg                   | -         | 44.0 | 39.0 | 54.1 | 43.0 | 68.9 | 61.1 | 57.0 | 46.1 | 555.0 | 82.5 | 49.1 | 62.9 | 57.9 | 85.3 | 70.2 |



**Figure.1: Comparison of Anti-Inflammatory activity of novel Benzothiazole derivatives containing Imidazol moieties (% inhibition of paw edema)**

#### CONCLUSION:

The objective of the present work was to synthesize, purify, characterize and evaluate the biological activity of newly synthesized structural analogs of novel Benzothiazole derivatives containing Imidazol moieties. The yield of the synthesized compounds was found to be in the range from 62-86 %. In conclusion, the present study highlights the importance of benzothiazole derivatives having various heterocyclic moiety features responsible for the anti-inflammatory activities and may serve as a lead molecule for further modification to obtain clinically useful novel entities.

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