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# Synthesis and Screening for Analgesic and Anti-inflammatory Activities of Some Novel Amino Acid-containing Bicyclo Compounds

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**ABSTRACT**

Diazabicyclo[4.3.1]decane derivatives are well known opioid receptor ligands, hence, we have developed a novel and simple method for the synthesis of 3, 4-diphenyl-2,5-diaza-bicyclo[4.3.1]deca-1(9),2,4,6(10),7-pentaene-8-carbonyl chloride derivatives containing amino acid moieties. The compounds were structurally confirmed with the help of TLC, IR, NMR, and LCMS spectra. All the title compounds were screened for analgesic activity by using the tail-flick method and for anti-inflammatory activity by using the carrageenan-induced paw edema method using diclofenac sodium as a standard.

**Key words:** Amino acids, analgesic- anti-inflammatory activity, 2, 5-diaza bicyclo [4.3.1] compounds

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## INTRODUCTION

Analogs of bicyclic systems, 8,10-diza-bicyclo [4.3.1]decane and 3,10-diza-bicyclo[4.3.1]decane bicyclo compounds, have been found to possess potent analgesic and anti-inflammatory activities and are considered to be opioid receptor ligands. More specifically, such compounds can be useful as μ opioid receptor ligands.[1-3] Bicyclo compounds are considered as interesting moieties due to their wide-ranging biological activities, which include muscarinic receptor antagonism,[4] antibacterial,[5] antiviral,[6] antiprotozoal,[7] antispasmolytic,[8] and antitumor activities.[9]

We sought to incorporate biologically innocuous amino acids into the above pharmacologically active moiety not only to minimize the side effects of the metabolites of the parent compound, but also to protect the vulnerable acidic moiety present in the nucleus and enhance the hydrophilicity of the synthesized candidates.[10] Thus, the objective of this study was to synthesize such compounds by a novel and convenient method, and to further evaluate these synthesized candidates for the analgesic and anti inflammatory activities that the parent bicyclo compounds possess.

## MATERIALS AND METHODS

Melting points (m.p.) were determined in open glass capillary tubes and have been reported without correction. Infrared (IR) spectra were recorded on an FT-IR Bruker Tensor 27 spectrometer and are expressed in $cm^{-1}$. NMR spectra of the compounds were recorded on a Bruker DRX-300 spectrometer. Chemical shifts were reported as parts per million (δ ppm) using

tetramethylsilane (TMS) as an internal standard. LC mass spectra of the compounds were recorded on a Shimadzu 8201PC spectrometer. The progress of the reaction was monitored on precoated silica gel 60 F254 plates (Merck) using different solvent systems. Spectral data (IR, NMR, and LC mass spectra) confirmed the structures of the synthesized compounds.

**General procedure**

*2-(3,5-dinitrobenzamido) acetic acid (2a)*
A solution of 3, 5-dinitrobenzoyl chloride (1 millimoles) in 1, 4-dioxan was added to glycine (1.2 millimoles) in 0.1 N sodium hydroxide (10 mL) and refluxed for six hours. The reaction mixture was allowed to cool and poured into 1 N hydrochloric acid and crushed ice. The crude product was filtered, dried, recrystallized with methanol, and subjected to column chromatography on silica gel (60-120 mesh) eluting with methanol: ethyl acetate (8:2). Mol. Formula: $C_9H_7N_3O_7$; Yield 67%; m.p. 182°C; IR ($cm^{-1}$): 3703 (-OH), 3402 ($-NH_2$), 2968 (CH-Ar), 2867 ($-CH_2$), 1714, 1634 (C=O), 1570 ($-NO_2$).

The other compounds 2b-2e were prepared by the same procedure using the corresponding amino acids.

*2-(3,5-Dinitrobenzamido) pentanedioic acid (2b)*
Mol. Formula: $C_{12}H_{11}N_3O_9$; Yield 62%; m.p. 178°C; IR ($cm^{-1}$): 3714 (-OH), 3378 ($-NH_2$), 2969 (CH-Ar), 2863 ($-CH_2$), 1713, 1630 (C=O), 1571 ($-NO_2$).

*1-(3,5-Dinitrobenzoyl)-pyrrolidine-2-carboxylic acid (2c)*
Mol. Formula: $C_{12}H_{11}N_3O_7$; Yield 69%; m.p. 181°C; IR ($cm^{-1}$): 3609 (-OH), 3102 (CH-Ar), 2885 ($-CH_2$), 1705, 1622 (C=O), 1570 ($-NO_2$), 1346 (*tert*. N).

*2-(3,5-Dinitrobenzamido)-3-mercapto propanoic acid (2d)*
Mol. Formula: $C_{10}H_9N_3O_7S$; Yield 61%; m.p. 202°C; IR ($cm^{-1}$): 3752 (-OH), 3605 ($-NH_2$), 2978 (CH-Ar), 2873 ($-CH_2$), 1698, 1645 (C=O), 2560 (-SH), 1593 ($-NO_2$).

*2-Amino-6-(3,5-dinitro-benzoyl amino) hexanoic acid (2e)*
Mol. Formula: $C_{13}H_{16}N_4O_7$; Yield 54%; m.p. 196°C; IR ($cm^{-1}$): 3409 (-OH,$-NH_2$ merged), 2982 (CH-Ar), 2862, 2842 ($-CH_2$), 1702, 1651 (C=O), 1552 ($-NO_2$).

**General procedure**

*2-(3,5-Diamino-benzamido)acetic acid (3a)*
A suspension of 2-(3,5-dinitro benzamido)acetic acid (1 millimoles) and zinc dust (2.5 millimoles) in methanol was stirred with 5 mL of 90% formic acid at room temperature for five hours. After completion of the reaction (monitored by TLC), the reaction mixture was filtered off. The organic layer was evaporated and the residue was dissolved in ether and washed with saturated sodium chloride solution (five times) to remove the ammonium formate. The ethereal layer was evaporated to dryness[11] and the crude product was recrystallized with ethanol and purified by column chromatography on silica gel (60-120 mesh) eluting with chloroform: ethyl acetate (9:1). Mol. Formula: $C_9H_{11}N_3O_3$; Yield 65%; m.p. 173°C; IR ($cm^{-1}$): 3727 (-OH), 3634 ($-NH_2$), 2938 (CH-Ar), 2858 ($-CH_2$), 1680, 1619 (C=O).

All the other compounds 3b-3e were prepared similarly.

*2-(3,5-Diamino-benzamido)-pentanedioic acid (3b)*
Mol. Formula: $C_{12}H_{15}N_3O_5$; Yield 71%; m.p. 184°C; IR ($cm^{-1}$): 3733 (-OH), 3633 ($-NH_2$), 2987 (CH-Ar), 2865 ($-CH_2$), 1700 (C=O).

*1-(3,5-Diamino-benzoyl)–pyrrolidine-2-carboxylic acid (3c)*
Mol. Formula: $C_{12}H_{15}N_3O_3$; Yield 73%; m.p. 108°C; IR ($cm^{-1}$): 3628 (-OH), 3700, 3726 ($-NH_2$), 2977 (CH-Ar), 2873 ($-CH_2$), 1697, 1613 (C=O), 1342 (*tert*. N).

*2-(3,5-Diamino-benzamido)-3-mercapto propionic acid (3d)*
Mol. Formula: $C_{10}H_{13}N_3O_3S$; Yield 68%; m.p. 115°C; IR ($cm^{-1}$): 3732 (-OH), 3618 ($-NH_2$), 2934 (CH-Ar), 2853 ($-CH_2$), 2531 (-SH), 1618, 1702 (C=O).

*2-Amino-6-(3,5-diamino-benzamido) hexanoic acid (3e)*
Mol. Formula: $C_{13}H_{20}N_4O_3$; Yield 62%; m.p. 126°C; IR ($cm^{-1}$): 3734 (-OH), 3622 ($-NH_2$), 2924 (CH-Ar), 2865 ($-CH_2$), 1622, 1701 (C=O).

**General procedure**

*2-[(3,4-Diphenyl-2,5-diaza-bicyclo[4.3.1]deca-1(9),2,4,6(10),7-pentaene-8-carbonyl)-amino]- pentanedioic acid (4a)*
2-(3,5-Diamino- benzamido) acetic acid (1 millimoles) was dissolved in 10ml of 0.1 N sodium hydroxide solution. To this, an ethanolic mixture of benzil (1.1 millimoles) and sodium ethoxide (2.3 millimoles) was dissolved with continuous stirring and refluxed for 55 hours. The reaction mixture was then allowed to cool and poured into 1 N hydrochloric acid and crushed ice. The content was kept overnight at room temperature, filtered, dried, and recrystallized with methanol. The reaction was monitored by TLC and the reaction mixture purified by column chromatography on silica gel (60-120 mesh) eluting with methanol: ethyl acetate (8:2). Yield 48%; m.p. 83°C; IR ($cm^{-1}$): 3712 (-OH), 3670 ($-NH_2$), 2968 (CH-Ar), 2858 ($-CH_2$), 1681 (C=O), 1530 (C=N); $^1H$ NMR (DMSO-$d_6$) δ: 2.5 (d, 2H, $CH_2$), 9.03 (t, 1H, NH), 8.86 (s, 1H, COOH),

7.60-7.93 (m, 13H, ArH); LCMS: m/z $[M+1]^+$384.4, $[M+2]^+$ 385.4; Anal. Calcd. for $C_{23}H_{17}N_3O_3$: C, 72.05; H, 04.47; N, 10.96. Found: C, 72.16; H, 04.57; N, 10.89.

*2-[(3,4-Diphenyl-2,5-diaza-bicyclo[4.3.1]deca-1(9),2,4,6(10),7-pentaene-8-carbonyl)-amino]-pentanedioic acid (4b)*
Yield 43%; m.p. 68°C; IR ($cm^{-1}$): 3737 (-OH), 3528 ($-NH_2$), 3083 (CH-Ar), 2888 ($-CH_2$), 1675, 1699 (C=O), 1588 (C=N); $^1$H NMR (DMSO-$d_6$) δ: 1.21 (s, 1H, CH), 8.66 (s, 1H, COOH), 2.5 (m, 4H, $(CH_2)_2$), 8.88 (t, 1H, NH), 9.10 (s, 1H, COOH), 7.53-7.93 (m, 13H, Ar H); LCMS: m/z $[M+1]^+$ 456. Anal. Calcd. for $C_{26}H_{21}N_3O_5$: C, 68.56; H, 04.65; N, 09.23. Found: C, 69.18; H, 04.62; N, 09.31.

*1-(3,4-Diphenyl-2,5-diaza-bicyclo[4.3.1]deca-1(9),2,4,6(10),7-pentaene-8-carbonyl)-pyrrolidine-2- carboxylic acid (4c)*
Yield 47%; m.p. 55°C; IR ($cm^{-1}$): 3602 (-OH), 3098 (CH-Ar), 2798 ($-CH_2$), 1707, 1546 (C=O), 1493 (C=N), 1336 (*tert*. N); $^1$H NMR (DMSO-$d_6$) δ: 1.20 (t, 1H, CH), 3.75 (m, 4H, $(CH_2)_2$ pyrrolidine ring), 2.5 (m, 2H, $CH_2$), 9.0 (s, 1H, COOH), 7.23-8.02 (m, 13H, ArH); LCMS: m/z $[M+1]^+$424.4. Anal. Calcd. for $C_{26}H_{21}N_3O_3$: C, 73.74; H, 05.00; N, 09.92. Found: C, 74.46; H, 04.92; N, 09.76.

*2-[(3,4-Diphenyl-2,5-diaza-bicyclo[4.3.1]deca-1(9),2,4,6(10),7-pentaene-8-carbonyl)-amino]-3- mercapto propionic acid (4d)*
Yield 50%; m.p. 73°C; IR ($cm^{-1}$): 3506 (-OH), 3399 ($-NH_2$), 3084 (CH-Ar), 2877 ($-CH_2$), 2637 (-SH), 1711, 1626 (C=O), 1532 (C=N); $^1$H NMR (DMSO-$d_6$) δ: 1.20 (s, 1H, CH), 8.65 (s, 1H, COOH), 2.5 (d, 2H, $CH_2$), 9.09 (t, 1H, NH), 8.87 (s, 1H, SH), 7.27-7.93 (m, 13H, ArH); LCMS: m/z $[M-1]^+$428.3. Anal. Calcd. for $C_{24}H_{19}N_3O_3S$: C, 67.12; H, 04.46; N, 09.78. Found: C, 66.88; H, 04.54; N, 09.65.

*3,4-Diphenyl-2,5-diaza-bicyclo[4.3.1]deca-1(9),2,4,6(10),7-pentaene-8-carboxylic acid (5-amino-6- hydroxy-6-oxo-hexyl)-amide (4e)*
Yield 42%; m.p. 77°C; IR ($cm^{-1}$): 3726 (-OH), 3647 ($-NH_2$), 2924 (CH-Ar), 2864 ($-CH_2$), 1678 (C=O), 1569 (C=N); $^1$H NMR (DMSO-$d_6$) δ: 1.21 (t, 1H, CH), 8.66 (s, 1H, COOH), 2.5 (m, 2H, $CH_2$), 9.09 (t, 1H, NH), 8.88 (d, 2H, $NH_2$), 3.58 (m, 6H, $CH_2$) 7.60-7.93 (m, 13H, ArH); LCMS: m/z $[M+1]^+$455.4, $[M-1]^+$452.8. Anal. Calcd. for $C_{27}H_{26}N_4O_3$: C, 71.35; H, 05.77; N, 12.33; Found: C, 70.90; H, 05.81; N, 12.42.

## Pharmacology

All the title compounds (4a-4e) were dissolved in DMSO. Albino mice weighing 20-25 g and Wistar rats weighing 150-200 g were used for the tail-flick method and the carrageenan-induced paw edema, respectively. The animals were housed in colony cages under conditions of constant temperature (22 ± 2°C), a 12 h light/dark schedule, and allowed free access to a standard diet and tap water except during the experiment. The animals were allowed to habituate to the laboratory environment for 2 h before the experiments were initiated. The protocol of the study was approved by the Institutional Animal Ethical Committee.

### Acute toxicity study

The tested compounds were administered intraperitoneally at different dose levels in separate groups of animals. The drug was administered in a single injection and in a single dose and after 24h of drug administration, the percent mortality in each group was observed. Approximate Lethal Dose ($ALD_{50}$) was calculated by Karber's method(> 400 mg/ kg).

### Tail-flick method

Prescreened animals (reaction time: 3-4 sec) of either sex were assigned to seven groups of six each. Diclofenac sodium (25 mg/kg) was used as a standard; DMSO was used as control. Tail-flick latency was assessed with an analgesiometer. The strength of the current passing through the naked nichrome wire was kept constant at 6 amp. The reaction time was recorded at 30 min, one, and two hours after the treatment, and the cut-off time was set at ten seconds to avoid tissue damage. The difference in reaction time (sec) was calculated by comparing the test compounds/standard drug and the normal controls. The % relative analgesic activity was calculated by using the following formula:

$$\% \text{ Relative analgesic activity} = (DRT_{test}/DRT_{drug}) \times 100$$

where $DRT_{test}$ is the difference in reaction time of the test compound with respect to (w.r.t) the control and $DRT_{drug}$ is the difference in reaction time of the standard drug used w.r.t control.

### Anti-inflammatory activity

Anti-inflammatory activity was determined *in vivo* using the carrageenan-induced rat paw edema test. Animals of either sex were divided into seven groups of four each. A solution of 0.1 mL of 1% carrageenan in saline was injected subplantarly into the right hind paw of the rats 1 h after *i.p.* administration of the compounds. Paw thickness was measured from the ventral to the dorsal surfaces immediately prior to carrageenan injection and then at each hour, up to four hours after the subplantar injection. Edema was calculated as the thickness variation

between the carrageenan- and control treated paws.[12] Anti-inflammatory activity was expressed as the percent of inhibition of the edema when compared with the control group and was calculated by using the formula:

% inhibition of edema = $(V_c - V_t/V_c) \times 100$

where $V_t$ and $V_c$ are the mean paw volumes of the test and control groups, respectively.

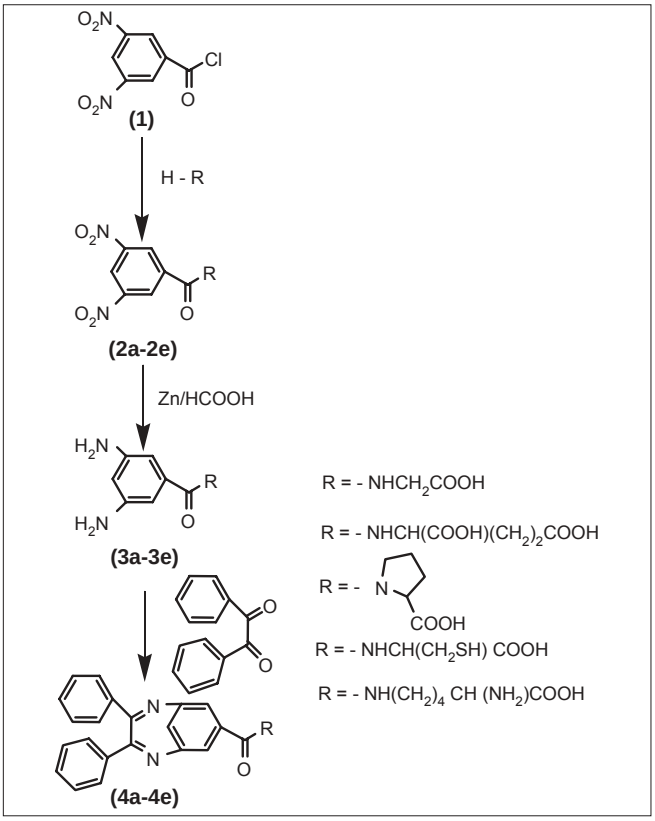
### Statistics

The results are expressed as the mean ± SEM per group and the data were statistically analyzed by one-way analysis of Variance (ANOVA) followed by Dunnett's test as *post hoc* test. $P < 0.05$ was considered to be statistically significant.

## RESULTS AND DISCUSSION

All title compounds were synthesized as per scheme 1 and were characterized by determining the m.p., and using TLC, IR, NMR, and LCMS spectra. Analgesic and anti- inflammatory activities were determined for all the five amino acid-containing bicyclo compounds. The analgesic activity was determined by the tail-flick method using diclofenac sodium as the reference drug. The data have been reported as the difference in the reaction time w. r. t. the control followed by % relative activity in comparison with the standard as shown in Table 1 and Figure 1. The anti-inflammatory activity was assessed by using carrageenan-induced rat paw edema using Diclofenac sodium as the reference drug. The data have been expressed in % inhibition as shown in Table 2 and Figure 2.

All the test compounds exhibited significant analgesic activity [Table 1]. The compound 4d, i.e., the cysteine derivative and compound 4e with the lysine moiety showed good analgesic activity, whereas compound 4a, the glycine derivative, and 4b, the glutamic acid derivative, showed lower analgesic activity. Compound 4c, the proline derivative, showed potent analgesic activity (69-82%) at 30 min to two hour intervals as compared to standard diclofenac sodium. However, as seen in Table 2, compound 4c showed excellent anti-inflammatory activity in the 81-88% inhibition seen at the 3rd and 4th hour intervals,




**Scheme 1**

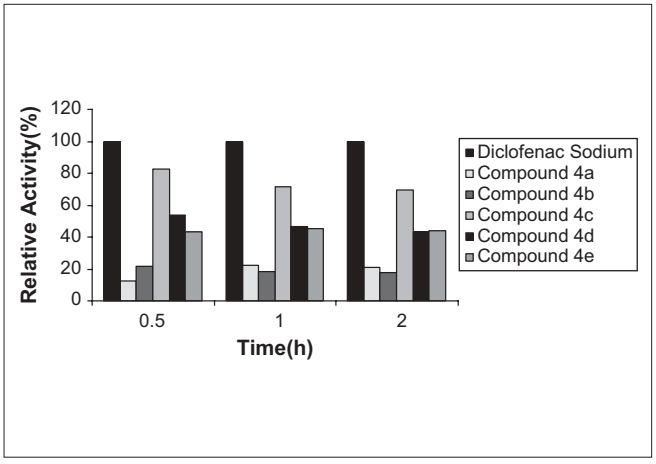



**Figure 1:** Graphical representation of the analgesic activity of amino acid-containing bicyclo compounds (4a-4e) compared to diclofenac sodium

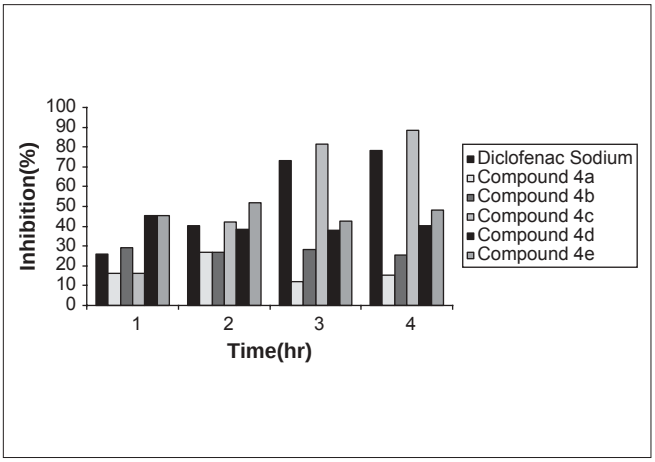



**Figure 2:** Graphical representation of the anti-inflammatory activity of amino acid-containing diazabicyclo compounds (4a-4e) compared to diclofenac sodium

**Table 1: Analgesic activity (Tail-flick technique) of amino acid-containing bicyclo compounds (4a-4e)**

| Compound | Time (h) | Dose (mg/kg) | Reaction time (sec) | Difference in reaction time (sec) | Relative analgesic Activity (%) |
|---|---|---|---|---|---|
| Control | 0.5 | - | 3.117 ± 0.09458 | - | - |
| (DMSO) | 1 | - | 3.217 ± 0.07923 | - | - |
| | 2 | - | 3.300 ± 0.09661 | - | - |
| Diclofenac | 0.5 | 25 | 7.983 ± 0.06009 | 4.866 [b] | |
| sodium | 1 | 25 | 8.783 ± 0.04773 | 5.567 [b] | 100 |
| | 2 | 25 | 9.117 ± 0.08333 | 5.817 [b] | |
| 4a | 0.5 | 25 | 3.717 ± 0.07923 | 0.600 [a] | 12.33 |
| | 1 | 25 | 4.467 ± 0.12820 | 1.250 [b] | 22.45 |
| | 2 | 25 | 4.517 ± 0.10780 | 1.217 [b] | 20.92 |
| 4b | 0.5 | 25 | 4.183 ± 0.06009 | 1.066 [b] | 21.90 |
| | 1 | 25 | 4.250 ± 0.06191 | 1.033 [b] | 18.45 |
| | 2 | 25 | 4.333 ± 0.09888 | 1.033 [b] | 17.76 |
| 4c | 0.5 | 25 | 7.133 ± 0.07149 | 4.016 [b] | 82.53 |
| | 1 | 25 | 7.183 ± 0.08333 | 3.967 [b] | 71.26 |
| | 2 | 25 | 7.333 ± 0.06667 | 4.033 [b] | 69.33 |
| 4d | 0.5 | 25 | 5.733 ± 0.13820 | 2.616 [b] | 53.76 |
| | 1 | 25 | 5.817 ± 0.13520 | 2.600 [b] | 46.70 |
| | 2 | 25 | 5.800 ± 0.15060 | 2.500 [b] | 42.98 |
| 4e | 0.5 | 25 | 5.867 ± 0.20760 | 2.116 [b] | 43.48 |
| | 1 | 25 | 5.733 ± 0.26670 | 2.517 [b] | 45.21 |
| | 2 | 25 | 5.850 ± 0.26430 | 2.550 [b] | 43.84 |

[a] Shows significant as compared to normal control ($P < 0.01$); [b] shows significant as compared to normal control ($P < 0.001$)

**Table 2: Anti-inflammatory activity (Carrageenan-induced rat paw edema method) of amino acid-containing bicyclo compounds (4a-4e)**

| Compound | Time (h) | Dose (mg/kg) | Volume of edema (mL) | Inhibition (%) |
|---|---|---|---|---|
| Control | 1 | - | 0.1938 ± 0.01875 | - |
| (DMSO) | 2 | - | 0.3250 ± 0.02700 | - |
| | 3 | - | 0.5125 ± 0.02165 | - |
| | 4 | - | 0.4938 ± 0.01197 | - |
| Diclofenac | 1 | 25 | 0.1438 ± 0.015730 [a] | 25.80 |
| sodium | 2 | 25 | 0.1938 ± 0.006250 [b] | 40.37 |
| | 3 | 25 | 0.1375 ± 0.007217 [b] | 73.17 |
| | 4 | 25 | 0.1063 ± 0.011970 [b] | 78.47 |
| 4a | 1 | 25 | 0.1625 ± 0.023940 [a] | 16.15 |
| | 2 | 25 | 0.2375 ± 0.033070 [a] | 26.92 |
| | 3 | 25 | 0.4500 ± 0.010210 [a] | 12.19 |
| | 4 | 25 | 0.4188 ± 0.015730 [a] | 15.19 |
| 4b | 1 | 25 | 0.1375 ± 0.012500 [a] | 29.05 |
| | 2 | 25 | 0.2375 ± 0.016140 [a] | 26.92 |
| | 3 | 25 | 0.3688 ± 0.018750 [b] | 28.04 |
| | 4 | 25 | 0.3688 ± 0.021350 [b] | 25.31 |
| 4c | 1 | 25 | 0.1625 ± 0.016140 [a] | 16.15 |
| | 2 | 25 | 0.1875 ± 0.016140 [b] | 42.30 |
| | 3 | 25 | 0.09375 ± 0.00625 [b] | 81.70 |
| | 4 | 25 | 0.05625 ± 0.00625 [b] | 88.60 |
| 4d | 1 | 25 | 0.1063 ± 0.011970 [b] | 45.15 |
| | 2 | 25 | 0.2000 ± 0.022820 [b] | 38.46 |
| | 3 | 25 | 0.3188 ± 0.021350 [b] | 37.80 |
| | 4 | 25 | 0.2938 ± 0.031250 [b] | 40.50 |
| 4e | 1 | 25 | 0.1063 ± 0.006250 [b] | 45.15 |
| | 2 | 25 | 0.1563 ± 0.032870 [b] | 51.90 |
| | 3 | 25 | 0.2938 ± 0.031250 [b] | 42.67 |
| | 4 | 25 | 0.2563 ± 0.041300 [b] | 48.09 |

[a] shows Insignificant as compared to normal control ($P > 0.05$); [b] shows Significant as compared to normal control ($P < 0.01$)

which is greater than the 73-78% inhibition by the standard diclofenac sodium used and greater than the other four compounds, 4a, 4b, 4d, and 4e.

## CONCLUSIONS

The present study describes a simple, cost-effective, and novel method for the synthesis of bicyclo compounds without using any drastic conditions as such. The incorporation of amino acid moieties favors analgesic and anti-inflammatory activities, especially in the case of the proline derivative, 4c.

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