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# Synthesis and biological activity of N (substituted) benzylidine ortho-amino benzoic acid and N (substituted) benzyl ortho-amino benzoic acid

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**ABSTRACT**

A new series of N –(substituted) benzylidine and benzyl ortho – amino benzoic acids consisting of 12 compounds were synthesized. The use $NaBH_4$ as a reducing agent for the reduction of N-(substituted) benzylidine ortho –amino benzoic acid to N- (substituted) benzyl ortho- amino benzoic acid appears to be new. The synthesized compounds were screened for their anti -inflammatory activity by carrageenan induced rat paw edema method. Some of these compounds have shown promising anti- inflammatory activity. ortho-amino benzoic acids are compounds with remarkable anti-inflammatory potential. These are a result of the application of classical medicinal chemistry bioisosteric drug design concepts since these derivatives are nitrogen isosteres of salicylic acid.

**Key words:** N –(substituted) benzylidine and benzyl ortho – amino benzoic acid.

## INTRODUCTION

Winder et al[1] (1962) tested the presence of anti-inflammatory, antipyretic & analgesic properties of N- (2, 3-xylyl) anthranilic acid (Mefenamic Acid) [1-3]. Another analog N- ($\alpha$,$\alpha$,$\alpha$)-m-tolyl –o-amino benzoic acid (Flufenamc acid) was tested for the presence of anti-inflammatory potential. 2. polp et al synthesized N-(2, 6 – dichloro –m- tolyl) o – amino benzoic acid (Meclofenamic acid) reported to be more potent than flufenamic acid. Recently the amino benzoic acids have been reported to possess a wide varity of activities ranging from anti-inflammatory to anti-cancer activity[4-6].

These observations prompted the authors to synthesize a few new o-amino benzoic acid derivatives with improved therapeutic result.

## EXPERIMENTAL

IR spectra were recorded on Double beam infrared spectrophotometers using KBr pellets. HNMR spectra were recorded on a Varian A 60-D instrument using TMS as an internal reference (chemical shift in $\alpha$). N- (substituted) benzylidline – o-amino benzoic acid were synthesized using the methods described in literature [3, 4] & N- (substituted) benzyl o-amino benzoic acid by reducing N-(substituted) benzylidine –o-amino benzoic acids with $NaBH_4$. Reduction by $NaBH_4$ for such reaction has been done for the first time.

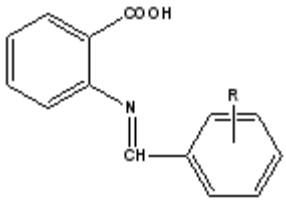
**Preparation of n – (substituted) benzylidine o – amino benzoic acids; general procedure:**

These compounds were prepared by mixing ethanolic solution of equimolar quantities of o-amino benzoic acid and an aromatic aldehyde and refluxing it for 5 – 6 hrs on a water bath. After the heating was over, the ethanolic solution was poured on crushed ice and the separated solid was filtered, washed with water and recrystallised from ethanol (Table 1).

**Reduction of n – (substituted) benzylidine o – amino benzoic acids; general procedure:**

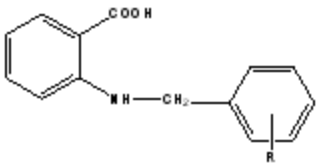
A solution of N – benzylidine o – amino benzoic acid (0.014 M) in methanol (75 ml) was placed in a 3 – necked round bottom flask fitted with a mechanical stirrer and a condenser. Sodium borohydride (0.028 M) was added in small lots to the refluxing methanolic solution. When the addition of sodium borohydride was over, the reaction solution was refluxed an additional 30 mins and the solvent was removed under reduced pressure. Water (25 ml) was added to the residue and the aqueous solution, after filtration was acidified with hydrochloric acid. The solid that separated was collected, washed with water and recrystallised from ethanol (Table 2).

**Table 1: N – (substituted) benzylidine ortho- amino benzoic acid (i)**




| Comp. No. | Substitution | Mol. for. (Mol.Wt) | m.p. ( $^{o}$C) | % yield |
|---|---|---|---|---|
| 1a | - H | $C_{14}H_{11}O_2N$ (225) | 126 – 127 | 25% |
| 1b | 2 – OH | $C_{14}H_{11}O_3N$(241) | 196 – 197 | 81.21% |
| 1c | 3- $NO_2$ | $C_{14}H_{10}O_4N_2$(270) | 168 - 169 | 83.33% |
| 1d | 4 –$OCH_3$ | $C_{15}H_{13}O_3N$(255) | 128 – 129 | 41.18% |
| 1e | 4 – N $(CH_3)_2$ | $C_{16}H_{16}O_2N_2$(272) | 180 -181 | 76.24% |
| 1f | 4 – OH, 3– $OCH_3$ | $C_{15}H_{13}O_4N$(271) | 162 – 163 | 68.52% |

**Table 2: N – (substituted) benzyl ortho- amino benzoic acid (ii)**




| Compound No. | Substitution | Mol. For. (Mol.Wt) | m.p.($^{0}$C ) | % yield |
|---|---|---|---|---|
| 2a | - H | $C_{14}H_{13}O_2N$(227) | 175-176 | 20.34% |
| 2b | 2 – OH | $C_{14}H_{13}O_3N$(243) | 152 – 153 | 38.66% |
| 2c | 3- $NO_2$ | $C_{14}H_{12}O_4N_2$(272) | 188 - 189 | 27.86% |
| 2d | 4 – $OCH_3$ | $C_{14}H_{15}O_3N$(245) | 102 – 103 | 28.63% |
| 2e | 4 – N $(CH_3)_2$ | $C_{16}H_{18}O_2N_2$(274) | 192 – 193 | 21.262% |
| 2f | 4 – OH, 3-$OCH_3$ | $C_{15}H_{15}O_4N$(273) | 178 – 179 | 45% |

**Statistical analysis**

Results were expressed as Mean ± SEM and evaluated by Dunnett test. Values of P< 0.001 were considered statistically significant.

**Biological evalution**

**Anti-inflammatory activity**

The synthesized compounds were tested for anti-inflammatory activity by carrageenan induced paw edema in rats. For this method albino mice (25 – 30 gm) were divided into 10 groups each consisting of 6 animals. One group served as positive control (received indomethacin 20 mg/kg), one group as negative control (received 10 % v/v honey 1ml/kg) and rest of the groups received N - benzyl anthranilic acid and p- amino benzoic acid derivatives (80 mg /kg), orally, 30 mins prior to the injection of inflammatory agent (0.1ml of 1% w/v suspension of carrageenen), was injected at the subplantar region of the left hind paw of all groups.

**Table 3: Anti-inflammatory activities of synthesized compounds**

| N – (Substituted) benzylidine ortho – amino benzoic acid | | |
|---|---|---|
| **Compound No** | **Dose (mg/kg body weight)** | **% Inhibition of paw volume at 60 min interval** |
| 1a | 80 | 56% |
| 1b | 80 | 65.69% |
| 1c | 80 | 42.25 |
| 1d | 80 | 55.68% |
| 1e | 80 | 39.32% |
| 1f | 80 | 55% |
| Contorl | 80 | - |
| **N- (Substituted) benzyl o -amino benzoic acid** | | |
| 2a | 80 | 66.6% |
| 2b | 80 | 71.23% |
| 2c | 80 | 56.46% |
| 2d | 80 | 68.54% |
| 2e | 80 | 43.33% |
| 2f | 80 | 65.54% |
| Control | 80 | - |

## RESULTS AND DISCUSSION

A new series of N (substituted) benzylidene and benzyl o- amino benzoic acids were synthesized by the steps mentioned in experimental part. The structure of the synthesized compounds was confirmed by IR and $^1$HNMR method. All the compounds were evaluated for anti – inflammatory activity.compounds 1b,2a,2d,2f have shown promising anti – inflammatory activity. Indomethacin was used as standard drug for comparison.

**Spectral data**

1. N- (2-hydroxy) benzylidine o – amino benzoic acid (1b) : IR (KBr) : 1612 (C=O), 1350 (Phenol), 1652 (N=C). $^1$HNMR (MeOH) : δ 4.2 (s,1H,OH), 5.1 (s,1H,CH), 6.3-7.8 (m,7H,ArH), 10.6(s,1H,COOH)
2. N- (2-hydroxy) benzyl o – amino benzoic acid (2b): IR (KBr) : 1672(C=O), 3350 (N-H), 1346 (Phenol). $^1$HNMR (MeOH): δ3.6-3.7 (s, 2H,$CH_2$), 4.5 (s, 2H,NH, OH), 6.7-7.8 (m, 7H,ArH), 10.5 (s, 1H,COOH)
3. N- (3-nitro) benzylidine o – amino benzoic acid: IR (KBr) 1667 (C=O), 1365 (N=O), 1210 (N=C).
4. N- (3-nitro) benzyl o- amino benzoic acid: IR (KBr): 1636 (C=O), 1310 (N=O), 3390 (N-H)
5. N- (4-methoxy) benzylidine o- amino benzoic acid (1d): IR (KBr): 1622 (C=O), 1267 (N=C), 2964 (OCH3). $^1$HNMR (MeOH): δ 3.3 (s, 3H, $OCH_3$), 5.31(s, 2H,CH), 6.5-7.8 (m, 8H,ArH), 10.5(s, 1H,COOH)
6. N- (4-methoxy) benzyl o- amino benzoic acid (2d): IR (KBr): 1654(C=O), 3394(N-H Ar), 2900-3033(OCH3), 1245($CH_2$). $^1$HNMR (MeOH): δ 3.3 (s, 3H,OCH3), 3.7 (s, 1H,$CH_2$), 4.3 (s, 2H,NH, OH), 6.5-7.9 (m, 7H,ArH), 10.6 (s, 1H,COOH)
7. N- (4- hydroxy, 3-methoxy) benzylidine o-amino benzoic acid (1f) :IR (KBr): 1678 (C=O), 1365 (Phenol), 2950 ($OCH_3$), 1278 (N=C). $^1$HNMR (MeOH): δ 3.3 (s, 3H, $OCH_3$), 3.9 (s, 1H,OH), 5.2 (s1H, CH), 6.5-7.8(m, 7H,ArH), 10.5(s, 1H,COOH)
8. N- (4- hydroxy, 3-methoxy) benzyl o- amino benzoic acid (2f): IR (KBr): 1710(C=O), 3390(N-H Ar), 1380 (Phenol), 2963 ($OCH_3$). $^1$HNMR (MeOH): δ 3.3 (s, 3H,$OCH_3$), 3.7-

3.8 (s, 2H,$CH_2$), 4.3 (s, 1H,OH), 6.5-7.9 (m, 7H,ArH), 10.6(s, 1H,COOH)

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