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# Synthesis and preliminary pharmacological evaluation of veratric acid ester 4-[ethyl-{2-(4-methoxyphenyl)-1-methylethyl} amino] butan-1-ol darivatives

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**Abstract**

*In a quest of novel antispasmodic agents with antimicrobial properties, the present study describes design and synthesis of novel analogs for veratric acid ester 4-[ethyl-{2-(4-methoxyphenyl)-1-methylethyl} amino] butan-1-ol, an antispasmodic drug which is expected to be a potent antimicrobial agent may be due to the presence of two benzene rings and a secondary or tertiary nitrogen in the basic structural framework of the molecule. The reaction between substituted 2-ethylamino-1-(4'-methoxyphenyl) propane and various haloaryl benzoates derivatives obtained from reaction between different homologs of benzoic acid and dibromoalkanes in a two step process to give corresponding structurally diverse analogs of lead compound has been achieved. The structures of these novel analogs were confirmed by different structure elucidation techniques. All the compounds have been screened for their anti-spasmodic activity and the study extended further to evaluate their sedative, antibacterial and antifungal potency. The novel analogs of lead compound exhibited pronounced antispasmodic activities and also gave encouraging results of antimicrobial and sedative activity as anticipated.*

**Keywords**: anti-spasmodic, sedative, antibacterial, antifungal potency.

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## INTRODUCTION

Antispasmodic drugs relieve cramps or spasms of the stomach, intestines, and bladder. Antispasmodics are classes (group) of drugs that can help to control some symptoms that arise from the gut, in particular, gut spasm. There are two main types namely "Antimuscarinics" and "Smooth muscle relaxants". Antispasmodics are commonly used in "Irritable bowel syndrome" (IBS) to help relieve some of the symptoms of IBS such as spasm (colic), bloating and abdominal (stomach) pain and to reduce the motility (movement) of the intestines (gut) [1].

After understanding further the medicinal importance of antispasmodics and their ever increasing demand worldwide, we pursue to undertake the detailed synthetic and pharmacological study of antispasmodics to identify novel candidates as potential drug substances.

Our parallel interest also lies on identifying novel antimicrobials since over the years; antibiotics are known to be the major protective agents against bacterial infections. However, the usage of antibiotics and antibacterial chemotherapeutics is becoming more and more restricted in the present age, despite the fact that there exist a large number of antibiotics. This is largely attributed to the emergence of drug-resistant bacteria, which render even some of the most broad spectrum antibiotics ineffective. In addition, most antibiotics have side effects. Thus, it becomes essential to investigate newer drugs with less resistance. Different studies on search of newer antimicrobials and antibacterial have revealed that moderate to remarkable antimicrobial or antibacterial action is present in several compounds, belonging to various pharmacological categories, such as antihistamines [2-4], tranquilizers [5], antihypertensive [6], anti-psychotics [7-11] anti-spasmodic [12] and anti-inflammatory agents [13]. Such compounds, having antibacterial properties in addition to their predesignated pharmacological actions, are termed as non-antibiotics [12].

Many of these compounds possess two or three benzene rings and nitrogen in the secondary or tertiary state in their molecular structure which is expected to be one of the bases for exhibiting antimicrobial potency [14]. Based on this rationale and to pursue our interest to identify newer antispasmodic agents with sedative and antimicrobial properties, the present study was undertaken. The incorporation of structural modifications in the main framework of the lead compound was thought to enhance the pharmacological potency. In the quest of novel antispasmodic agents with antimicrobial and sedative properties, we envisioned to synthesize novel analogs of lead compound, veratric acid ester 4-[ethyl-{2-(4-methoxyphenyl)-1-methylethyl} amino] butan-1-ol hydrochloride a potent antispasmodic agent having two benzene rings and secondary nitrogen in structural framework, incorporating diverse structural modifications.

The process for synthesis of lead compound, involves condensation of two key process intermediates i.e. 4'-bromobutyl-3, 4-dimethoxy benzoate and 2-ethylamino-1-(4'-methoxyphenyl) propane. Introducing respective modifications in the structural framework of process intermediates led us to diverse analogs of the lead compound desired for the study. This was achieved by using relevant starting materials like substituted benzoic acids analogs, different dihalo-alkanes and substituted phenyl-acetone homologs. Different analogs of intermediate 4'-bromobutyl-3, 4-dimethoxy benzoate were synthesized in a two step process by preparation of sodium salt of various substituted benzoic acids in the first step followed by reaction with different di-bromoalkanes. Condensation of these compounds with various analogs of 2-ethylamino-1-(4'-methoxyphenyl) propane intermediate synthesized in a single step by catalytic reduction of n, $n^{1}$-alkoxy- phenyl acetone homologs with hydrogen and Pt/C (5 %) catalyst followed by in-situ condensation with ethylamine yielded structurally diverse analogs of veratric acid ester 4-[ethyl-{2-(4-methoxyphenyl)-1-methylethyl} amino] butan-1-ol hydrochloride as shown in Table 1. The structures of the synthesized compounds were confirmed by physical data and different structural elucidation techniques. Synthesized compounds were then screened for their antispasmodic activity followed by their sedative, antibacterial and antifungal potential.

## RESULTS AND DISCUSSION

The structurally diverse analogs of the lead molecule synthesized and their respective yields obtained are presented in Table 1 and is supported by physical data (difference in melting ranges) as presented in Table 2. The structures of the synthesized compounds have been confirmed by the FTIR, Mass spectra (Table 2 and 3) and by $^1$H NMR spectral analysis (Table 4).

**Table 1: Analogs of lead compound and their respective yields**

| Comp. | $R^1$ | $R^2$ | $R^3$ | $R^4$ | $R^5$ | $R_1$ | $R_2$ | $R_3$ | $R_4$ | $R_5$ | n | Yield |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 5 Lead comp. | H | OCH3 | OCH3 | H | H | H | H | $OCH_3$ | H | H | 4 | 82 % |
| 5a | $OCH_3$ | $OCH_3$ | H | H | H | H | H | $OCH_3$ | H | H | 4 | 80.2% |
| 5b | H | $OCH_3$ | H | $OCH_3$ | H | H | H | $OCH_3$ | H | H | 4 | 74.3% |
| 5c | H | $CH_3$ | $CH_3$ | H | H | H | H | $OCH_3$ | H | H | 4 | 81.8% |
| 5d | $CH_3$ | $CH_3$ | H | H | H | H | H | $OCH_3$ | H | H | 4 | 82.2% |
| 5e | H | $OCH_3$ | H | H | H | H | H | $OCH_3$ | H | H | 4 | 66.5% |
| 5f | H | $CH_3$ | H | H | H | H | H | $OCH_3$ | H | H | 4 | 81.7% |
| 5g | $C_2H_5$ | H | H | H | H | H | H | $OCH_3$ | H | H | 4 | 74.6% |
| 5h | H | $C_2H_5$ | $C_2H_5$ | H | H | H | H | $OCH_3$ | H | H | 4 | 80.3% |
| 5i | $CH(CH_3)_2$ | H | H | H | H | H | H | $OCH_3$ | H | H | 4 | 79.2% |
| 5j | H | $CH(CH_3)_2$ | H | H | H | H | H | $OCH_3$ | H | H | 4 | 79.8% |
| 5k | $CH_3$ | $OCH_3$ | H | H | H | H | H | $OCH_3$ | H | H | 4 | 80.2% |
| 5l | H | $OCH_3$ | $OCH_3$ | H | H | H | H | $OCH_3$ | H | H | 2 | 84.2% |
| 5m | H | $OCH_3$ | $OCH_3$ | H | H | H | H | $OCH_3$ | H | H | 3 | 63.7% |
| 5n | H | $OCH_3$ | $OCH_3$ | H | H | H | H | $OCH_3$ | H | H | 5 | 81.5% |
| 5o | H | $OCH_3$ | $OCH_3$ | H | H | H | H | H | $OCH_3$ | H | 2 | 64.9% |
| 5p | H | $OCH_3$ | $OCH_3$ | H | H | H | H | $CH_3$ | H | H | 3 | 76.2% |

**Table 2: Physical data and Mass spectral (M/Z) results of lead compound and its analogs**

| Comp. No. | Molecular Formula (Base product) | Molecular Weight | Melting Range $^oC$ | MS (m/z) |
|---|---|---|---|---|
| 5 | $C_{25}H_{35}NO_5$ | 429 | 105-107 | 430 (M+1) |
| 5a | $C_{25}H_{35}NO_5$ | 429 | 137-141 | 430 (M+1) |
| 5b | $C_{25}H_{35}NO_5$ | 429 | 111-115 | 430 (M+1) |
| 5c | $C_{25}H_{35}NO_3$ | 397 | 151-157 | 398 (M+1) |
| 5d | $C_{25}H_{35}NO_3$ | 397 | 134-139 | 398 (M+1) |
| 5e | $C_{24}H_{33}NO_4$ | 399 | 107-109 | 400 (M+1) |
| 5f | $C_{24}H_{33}NO_3$ | 383 | 121-129 | 384 (M+1) |
| 5g | $C_{25}H_{35}NO_3$ | 397 | 141-143 | 398 (M+1) |
| 5h | $C_{27}H_{39}NO_3$ | 425 | 122-127 | 426 (M+1) |
| 5i | $C_{26}H_{37}NO_3$ | 411 | 97-103 | 412 (M+1) |
| 5j | $C_{26}H_{37}NO_3$ | 411 | 133-136 | 412 (M+1) |
| 5k | $C_{25}H_{35}NO_4$ | 413 | 148-151 | 414 (M+1) |
| 5l | $C_{23}H_{31}NO_5$ | 401 | 162-164 | 402 (M+1) |
| 5m | $C_{24}H_{33}NO_5$ | 415 | 108-111 | 416 (M+1) |
| 5n | $C_{26}H_{37}NO_5$ | 443 | 91-96 | 444 (M+1) |
| 5o | $C_{23}H_{31}NO_5$ | 401 | 121-125 | 402 (M+1) |
| 5p | $C_{24}H_{33}NO_4$ | 399 | 104-108 | 400 (M+1) |

**Table 3: FTIR spectral data of lead compound and its analogs**

| Product | Mass (m/z) | IR ($cm^{-1}$) |
|---|---|---|
| 5 | 430 (M+1) | -C-H stretching (2959-2840), -C=O stretching (1717), -C=C stretching (1605, 1514, 1459), asymmetrical -C-O-C and --C-O stretching (1265-1130), symmetrical -C-O-C stretching (1023) |
| 5a | 430 (M+1) | -C-H stretching (2958-2838), -C=O stretching (1717), -C=C stretching (1604, 1513, 1459), asymmetrical -C-O-C and --C-O stretching (1250-1131), symmetrical -C-O-C stretching (1026) |
| 5b | 430 (M+1) | -C-H stretching (2959-2840), -C=O stretching (1718), -C=C stretching (1605, 1513, 1459), asymmetrical -C-O-C and -C-O stretching (1268-1131), symmetrical -C-O-C stretching (1023) |
| 5c | 398 (M+1) | -C-H stretching (2962-2908), -C=O stretching (1720), -C=C stretching (1604, 1512, 1458), asymmetrical -C-O-C and -C-O stretching (1265-1126), symmetrical -C-O-C stretching (1026) |
| 5d | 398 (M+1) | -C-H stretching (2959-2839), -C=O stretching (1717), -C=C stretching (1604, 1514, 1459), asymmetrical -C-O-C and -C-O stretching (1291-1132), symmetrical -C-O-C stretching (1024) |
| 5e | 400 (M+1) | -C-H stretching (2959-2840), -C=O stretching (1718), -C=C stretching (1606, 1513, 1460), asymmetrical -C-O-C and -C-O stretching (1268-1132), symmetrical -C-O-C stretching (1024) |
| 5f | 384 (M+1) | -C-H stretching (2959-2839), -C=O stretching (1717), -C=C stretching (1604, 1512, 1458), asymmetrical -C-O-C and -C-O stretching (1268-1131), symmetrical -C-O-C stretching (1025) |
| 5g | 398 (M+1) | -C-H stretching (2959-2840), -C=O stretching (1718), -C=C stretching (1605, 1514, 1460), asymmetrical -C-O-C and -C-O stretching (1265-1130), symmetrical -C-O-C stretching (1023) |
| 5h | 426 (M+1) | -C-H stretching (2960-2840), -C=O stretching (1717), -C=C stretching (1605, 1514, 1460), asymmetrical -C-O-C and -C-O stretching (1268-1130), symmetrical -C-O-C stretching (1025) |
| 5i | 412 (M+1) | -C-H stretching (2962-2908), -C=O stretching (1720), -C=C stretching (1604, 1512, 1458), asymmetrical -C-O-C and -C-O stretching (1265-1126), symmetrical -C-O-C stretching (1026) |
| 5j | 412 (M+1) | -C-H stretching (2961-2839), -C=O stretching (1720), -C=C stretching (1604, 1514, 1460), asymmetrical -C-O-C and -C-O stretching (1270-1132), symmetrical -C-O-C stretching (1024) |
| 5k | 414 (M+1) | -C-H stretching (2961-2839), -C=O stretching (1714), -C=C stretching (1606, 1514, 1459), asymmetrical -C-O-C and -C-O stretching (1269-1131), symmetrical -C-O-C stretching (1023) |
| 5l | 402 (M+1) | -C-H stretching (2959-2839) -C=O stretching (1718), -C=C stretching (1604, 1513, 1459), asymmetrical -C-O-C and -C-O stretching (1268-1131), symmetrical -C-O-C stretching (1026) |
| 5m | 416 (M+1) | -C-H stretching (2960-2840), -C=O stretching (1717), -C=C stretching (1606, 1513, 1459), asymmetrical -C-O-C and --C-O stretching (1268-1131), symmetrical -C-O-C stretching (1023) |
| 5n | 444 (M+1) | -C-H stretching (2959-2839), -C=O stretching (1717), -C=C stretching (1604, 1512, 1458), asymmetrical -C-O-C and -C-O stretching (1268-1131), symmetrical -C-O-C stretching (1025) |
| 5o | 402 (M+1) | -C-H stretching (2959-2841), -C=O stretching (1717), -C=C stretching (1606, 1514, 1460), asymmetrical -C-O-C and -C-O stretching (1269-1132), symmetrical -C-O-C stretching (1024) |
| 5p | 400 (M+1) | -C-H stretching (2958-2838), -C=O stretching (1717), -C=C stretching (1604, 1513, 1459), asymmetrical -C-O-C and -C-O stretching (1269-1131), symmetrical -C-O-C stretching (1026) |

**Table 4: 1H NMR spectral data of lead compound and its analogs**

| Product | $^1$H NMR (ð) |
|---|---|
| 5 | Chemical Shift ð, 1.25-1.22 ppm (t, 3H, $-CH_3$), 1.57-1.51 (m, 3H, $-CH_3$), 1.90-1.81 (d, 2H, $-CH_2$), 2.16-2.11(m, 2H, $-CH_2$), 2.54-2.25 (m, 1H, -CH), 3.11-3.05 (m, 4H, $-CH_2$), 3.58-3.54 (t, 2H, $-CH_2$), 3.77 (s, 3H, $-OCH_3$), 3.91 (s, 6H, $-OCH_3$), 4.37-4.33 (d, 2H, $-CH_2$), 6.87-6.79 (m, 3H, Ar-H), 7.14-7.12 (d, 2H, Ar-H), 7.52-7.50 (d, 1H, Ar-H), 7.68-7.65 (m, 1H, Ar-H) |
| 5a | Chemical Shift ð, 1.08-0.90 ppm (t, 3H, $-CH_3$), 1.24-1.10 (m, 3H, $-CH_3$), 1.49-1.39 (m, 2H, $-CH_2$), 2.05-1.75 (t, 2H, $-CH_2$), 2.36-2.20 (t, 2H, $-CH_2$), 2.50-2.40 (m, 2H, $-CH_2$), 2.61-2.51 (d, 2H, $-CH_2$), 3.28-3.10 (m, 1H, -CH), 3.72 (s, 6H, $-OCH_3$), 3.85 (s, 3H, $-OCH_3$), 4.12-4.25 (d, 2H, $-CH_2$), 6.80-6.72 (m, 2H, Ar-H), 6.90-6.82 (m, 2H, Ar-H), 7.17-7.01 (d, 2H, Ar-H), 7.30-7.21 (d, 1H, Ar-H) |
| 5b | Chemical Shift ð, 1.04-0.95 ppm (t, 3H, $-CH_3$), 1.40-1.15 (m, 3H, $-CH_3$), 1.67-1.42 (m, 2H, $-CH_2$), 1.89-1.80 (t, 2H, $-CH_2$), 2.35-2.22 (t, 2H, $-CH_2$), 2.49-2.38 (m, 2H, $-CH_2$), 2.69-2.50 (d, 2H, $-CH_2$), 3.22-3.18 (m, 1H, -CH), 3.70 (s, 3H, $-OCH_3$), 3.77 (s, 6H, $-OCH_3$), 4.22-4.17 (d, 2H, $-CH_2$), 6.58-6.47 (d, 1H, Ar-H), 6.74-6.57 (m, 2H, Ar-H), 7.71-7.04 (m, |

| | |
|---|---|
| | 4H, Ar-H) |
| 5c | Chemical Shift ð, 1.15-0.90 ppm (t, 3H, -$CH_3$), 1.29-1.15 (m,3H, -$CH_3$), 1.58-1.40 (m, 2H, -$CH_2$), 1.85-1.74 (m, 2H, -$CH_2$), 2.34 (s, 6H, -$CH_3$), 2.41-2.38 (t, 2H, -$CH_2$), 2.55-2.42 (m, 2H, -$CH_2$), 2.67-2.58 (d, 2H,-$CH_2$), 3.20-3.16 (m, 1H, -CH), 3.75 (s, 3H, -$OCH_3$),4.32-4.25 (d, 2H, -$CH_2$), 6.68-6.52 (m, 2H, Ar-H), 7.31-7.10 (d, 2H, Ar-H), 7.56-7.32 (m, 1H, Ar-H), 7.72-7.57 (m, 2H, Ar-H) |
| 5d | Chemical Shift ð, 0.96-1.04 ppm (t, 3H, -$CH_3$), 1.18-1.10 (m,3H, -$CH_3$), 1.44-1.37 (m, 2H, -$CH_2$), 1.81-1.70 (m, 2H, -$CH_2$), 2.36 (s, 6H, -$CH_3$), 2.41-2.38 (t, 2H, -$CH_2$), 2.52-2.42 (m, 2H, -$CH_2$), 2.59-2.53 (d, 2H,-$CH_2$), 3.25-3.18 (m, 1H, -CH), 3.72 (s, 3H, -$OCH_3$), 4.33-4.27 (d, 2H, -$CH_2$), 6.91-6.72 (m, 2H, Ar-H), 7.04-7.01 (d, 2H, Ar-H), 7.11-7.06 (m, 1H, Ar-H), 7.20-7.15 (t, 1H, Ar-H), 7.53-7.49 (m, 1H, Ar-H) |
| 5e | Chemical Shift ð, 1.03-0.98 ppm (t, 3H, -$CH_3$), 1.18-1.10 (m,3H, -$CH_3$), 1.68-1.39 (m, 2H, -$CH_2$), 1.98-1.75 (m, 2H, -$CH_2$), 2.26-2.21- (t, 2H, -$CH_2$), 2.46-2.40 (m, 2H, -$CH_2$), 2.55-2.49 (m, 2H, -$CH_2$), 2.88-2.65 (m, 1H, -CH), 3.72 (s, 6H, -$OCH_3$), 4.47-4.30 (m, 2H, -$CH_2$), 6.94-6.72 (m, 2H, Ar-H), 7.06-6.95 (d, 3H, Ar-H), 7.31-7.25 (d, 1H, Ar-H), 7.32-7.45 (m, 1H, Ar-H), 7.53-7.46 (m, 1H, Ar-H) |
| 5f | Chemical Shift ð, 1.01-0.95 ppm (t, 3H, -$CH_3$), 1.24-1.00 (m, 3H, -$CH_3$), 1.51-1.34 (m, 2H, -$CH_2$), 1.94-1.72 (m, 2H, -$CH_2$), 2.36-2.22 (t, 2H, -$CH_2$), 2.46-2.37 (m, 2H, -$CH_2$), 2.53 (s, 3H, -CH3), 2.72-2.59 (d, 2H,-$CH_2$), 3.23-3.13 (m, 1H, -CH), 3.69 (s, 3H, -$OCH_3$), 4.25-4.21 (d, 2H, -$CH_2$), 7.00-6.74 (m, 2H, Ar-H), 7.08-7.02 (d, 2H, Ar-H), 7.31-7.27 (m, 2H, Ar-H), 7.40-7.32 (m, 2H, Ar-H) |
| 5g | Chemical Shift ð, 1.10-1.00 ppm (t, 3H, -$CH_3$), 1.20-1.10 (m, 3H, -$CH_3$), 1.32-1.24 (t, 3H, -$CH_3$), 1.59-1.40 (m, 2H, -$CH_2$), 1.88-1.75 (m, 2H, -$CH_2$), 2.29-2.40 (t, 2H,-$CH_2$), 2.59-2.41 (m, 2H, -$CH_2$), 2.71-2.68 (d, 2H, -$CH_2$), 2.83-2.68 (m, 2H, -$CH_2$), 3.35-3.15 (m, 1H, -CH), 3.70 (s, 3H, -$OCH_3$), 4.26-4.20 (d, 2H, -$CH_2$), 6.84-6.72 (m, 2H, Ar-H), 7.12-7.01 (d, 2H, Ar-H), 7.25 (s, 1H, Ar-H), 7.40-7.30 (m, 1H, Ar-H), 7.59-7.71 (d, 1H, Ar-H), 7.81-7.72 (d, 1H, Ar-H) |
| 5h | Chemical Shift ð, 0.96-1.06 ppm (t, 3H, -$CH_3$), 1.24-1.01 (m, 3H, -$CH_3$), 1.38-1.21 (t, 6H, -$CH_3$), 1.63-1.36 (m, 2H, -$CH_2$), 2.02-1.75 (m, 2H, -$CH_2$), 2.36-2.22 (t, 2H, -$CH_2$), 2.50-2.41 (m, 2H, -$CH_2$), 2.62-2.51 (d, 2H, -$CH_2$), 2.79-2.62 (m, 4H, -$CH_2$), 3.36-3.16 (m, 1H, -CH), 3.67 (s, 3H, -$OCH_3$), 4.19-3.93 (d, 2H, -$CH_2$), 6.85-6.72 (d, 2H, Ar-H), 7.01-6.89 (d, 2H, Ar-H), 7.23-7.17 (d, 1H, Ar-H), 7.61-7.25 (m, 2H, Ar-H) |
| 5i | Chemical Shift ð, 0.90-1.00 ppm (m, 3H, -$CH_3$), 1.21-1.10 (m, 3H, -$CH_3$), 1.38-1.29 (d, 6H, -$CH_3$), 1.63-1.39 (m, 2H, -$CH_2$), 1.86-1.77 (t, 2H, -$CH_2$), 2.36-2.22 (t, 2H, -$CH_2$), 2.48-2.40 (m, 2H, -$CH_2$), 2.58-2.49 (d, 2H,-$CH_2$), 3.20-3.02 (m, 2H, -CH), 3.72 (s, 3H, -OCH3), 4.21-4.19 (d, 2H, -$CH_2$), 6.79-6.69 (m, 2H, Ar-H), 7.19-7.01(m, 2H, Ar-H), 7.24-7.20 (m, 2H, Ar-H), 7.39-7.30 (m, 1H, Ar-H), 7.85-7.75 (m, 1H, Ar-H) |
| 5j | Chemical Shift ð, 1.00-0.89 ppm (t, 3H, -$CH_3$), 1.05-1.00 (m, 3H, -$CH_3$), 1.25-1.11 (d, 6H, -$CH_3$), 1.38-1.21 (m, 2H, -$CH_2$), 1.90-1.71 (t, 2H, -$CH_2$), 2.36-2.28 (t, 2H, -$CH_2$), 2.50-2.40 (m, 2H, -$CH_2$), 2.66-2.50 (d, 2H,-$CH_2$), 3.40-3.16 (m, 2H, -CH), 3.62 (s, 3H, -$OCH_3$), 4.28-4.21 (d, 2H, -$CH_2$), 6.68-6.55 (m, 2H, Ar-H), 7.12-7.00 (d, 2H, Ar-H), 7.21-7.34 (m, 2H, Ar-H), 8.00-7.81 (m, 2H, Ar-H) |
| 5k | Chemical Shift ð, 1.05-0.90 ppm (t, 3H, -$CH_3$), 1.12-1.05 (m, 3H, -$CH_3$), 1.45-1.37 (m, 2H, -$CH_2$), 1.89-1.75 (t, 2H, -$CH_2$), 2.35 (s, 3H, -$CH_3$), 2.42-2.38 (t, 2H, -$CH_2$), 2.60-2.47 (m, 2H, -$CH_2$), 2.80-2.69 (d, 2H, -$CH_2$), 3.30-3.18 (m, 1H, -CH), 3.72 (s, 6H, -$OCH_3$), 4.13-4.19 (d, 2H, -$CH_2$), 6.89-6.75 (m, 2H, Ar-H), 7.21-6.90 (m, 3H, Ar-H), 7.55-7.21 (m, 2H, Ar-H) |
| 5l | Chemical Shift ð, 1.03-1.00 ppm (t, 3H, -$CH_3$), 1.30-1.03 (m, 3H, -$CH_3$), 2.40-2.28 (m, 2H, -$CH_2$), 2.51-2.49 (d, 2H, -$CH_2$), 2.95-2.83 (t, 2H, -$CH_2$), 3.32-3.18 (m, 1H, -CH), 3.71 (s, 3H, -$OCH_3$), 3.83 (s, 6H, -$OCH_3$), 4.45-4.39 (d, 2H, -$CH_2$), 6.85-6.69 (m, 2H, Ar-H), 7.09-7.03 (d, 2H, Ar-H), 7.21-7.10 (m, 1H, Ar-H), 7.44 -7.22(m, 2H, Ar-H) |
| 5m | Chemical Shift ð, 1.06-0.97 ppm (t, 3H, -$CH_3$), 1.32-1.02 (m, 3H, -$CH_3$), 2.02-1.85 (t, 2H, -$CH_2$), 2.46-2.39(t, 4H, -$CH_2$), 2.60-2.48 (d, 2H, -$CH_2$), 3.32-3.16 (m, 1H, -CH), 3.81 (s, 3H, -$OCH_3$), 3.88 (s, 6H, -OCH3), 4.25-4.15 (d, 2H, -CH2), 6.85-6.71 (m, 2H, Ar-H), 7.20-7.06 (d, 2H, Ar-H), 7.38-7.21 (m, 1H, Ar-H), 7.71-7.41 (m, 2H, Ar-H) |
| 5n | Chemical Shift ð, 1.06-0.89 ppm (t, 3H, -$CH_3$), 1.28-1.10 (m, 3H, -$CH_3$), 1.38-1.30 (t, 2H, -$CH_2$), 1.59-1.38 (m, 2H, -$CH_2$), 1.94-1.75 (t, 2H, -$CH_2$), 2.60-2.40 (t, 4H, -$CH_2$), 2.99-2.83 (d, 2H, -$CH_2$), 3.38-3.15 (m, 1H,-CH), 3.73 (s, 3H, -$OCH_3$), 3.86 (s, 6H, -$OCH_3$), 4.50-4.33 (d, 2H, -$CH_2$), 7.00-6.72(m, 2H, Ar-H), 7.15-7.01 (d, 2H, Ar-H), 7.30-7.15(d, 1H, Ar-H), 7.44-7.60 (m, 2H, Ar-H) |
| 5o | Chemical Shift ð, 1.10-1.00 (t, 3H, -$CH_3$), 1.40-1.10 ppm (m, 3H, -$CH_3$), 2.65-2.42 (m, 2H, -$CH_2$), 2.79-2.66 (d, 2H, -$CH_2$),3.00- 2.82 (t, 2H, -$CH_2$), 3.21-3.13 (m, 1H, -CH), 3.73 (s, 3H, -$OCH_3$), 3.86 (s, 6H, -$OCH_3$), 4.42-4.32 (d, 2H, -$CH_2$), 6.95-6.68 (d, 3H, Ar-H), 7.40-7.10 (m, 2H, Ar-H), 7.72-7.59 (m, 2H, Ar-H) |
| 5p | Chemical Shift ð, 1.25-1.00 (t, 3H, -$CH_3$), 1.43-1.25 ppm (m, 3H, -$CH_3$), 1.95-1.85 (t, 2H, -$CH_2$), 2.19 (s, 3H, -$CH_3$), 2.46-2.36 (m, 2H, -$CH_2$), 2.55-2.46 (m, 2H, -$CH_2$), 2.74-2.55 (d, 2H, -$CH_2$), 3.31-3.18 (m, 1H, -CH), 3.75 (s, 6H, -$OCH_3$), 4.45-4.29 (t, 2H, -$CH_2$), 7.02 (s, 4H, Ar-H), 7.31-7.11 (m, 1H, Ar-H), 7.59-7.45(d, 1H, Ar-H), 7.70-7.59 (d, 1H, Ar-H) |

**Pharmacology**
**Structure activity relationships**
**Antispasmodic activity**

Based on the data presented in Table 5, the activities of different analogs were compared with lead compound "5" (Reference standard 1) and also with papaverine (Reference standard 2).

The data indicated that altering the positions of two methoxy substitutions on phenyl ring as in "5a" and "5b" lead to reduced antispasmodic potency, against lead compound "5".

Comparable antispasmodic potential to lead compound "5" were exhibited by compounds "5h" and "5k" with 3, 4-diethyl and 2-methyl, 3-methoxy substitututions respectively. Compound "5c" with 3, 4-dimethyl substitution on phenyl ring showed encouraging antispasmodic activity which is equivalent to the lead compound but further alteration in methyl group positions as in compound "5d" lead to reduced potency.

Extremely low antispasmodic potency compare to the lead compound "5", was observed in compounds "5e", "5f" and "5g" with single proton substitutions on phenyl ring by methoxy, methyl and ethyl group respectively. But surprisingly the activity of these compounds is found comparable with papaverine (Reference standard 2) and observed similar to the compounds "5i" and "5j" with isopropyl substitutions at respective positions on phenyl ring.

Substitution of butyl linker in basic structural framework of lead compound "5" with ethyl, propyl or pentyl linkers has lead to diminished antispasmodic potency as exhibited by compounds "5l", "5m" and "5n" with respective alterations.

**Table 5: Antispasmodic activity of lead compound and its analogs**

| Sr. No. | Compound | % Relaxation at various concentrations (µM, 500µL) | | | |
|---|---|---|---|---|---|
| | | 150 | 100 | 50 | 10 |
| Standard-1 | "5" Lead Compound | 85.46±3.25 | 65.29±2.15 | 44.86±3.90 | 19.89±1.13 |
| Standard-2 | Papaverine | 68.46 ± 3.49 | 43.90±2.72 | 26.70±0.32 | 7.80±0.27 |
| 1 | 5a | 75.37±2.25 | 55.19±2.35 | 34.66±2.70 | 10.79±0.73 |
| 2 | 5b | 79.36±2.25 | 62.19±1.45 | 42.96±2.97 | 17.79±1.07 |
| 3 | 5c | 80.46±2.25 | 62.15±1.25 | 40.76±2.10 | 16.79±0.67 |
| 4 | 5d | 75.36±1.75 | 57.05±1.65 | 37.76±1.19 | 13.71±0.59 |
| 5 | 5e | 61.24±2.37 | 53.24±1.39 | 31.73±2.16 | 10.37±1.27 |
| 6 | 5f | 52.59±1.49 | 43.78±1.87 | 22.58±2.79 | 07.97±1.25 |
| 7 | 5g | 60.29 ± 2.39 | 52.92±2.12 | 31.70±0.58 | 10.71±0.34 |
| 8 | 5h | 84.15 ± 2.76 | 63.72±2.89 | 42.50±0.31 | 18.11±0.27 |
| 9 | 5i | 65.73 ± 1.89 | 40.52±2.75 | 24.83±0.64 | 6.51±0.24 |
| 10 | 5j | 67.59 ± 1.39 | 42.12±1.13 | 25.10±0.23 | 6.95±0.84 |
| 11 | 5k | 83.51 ± 2.19 | 62.12±1.32 | 41.70±0.18 | 17.36±0.29 |
| 12 | 5l | 72.59 ± 1.39 | 51.62±1.12 | 30.90±0.38 | 9.71±0.17 |
| 13 | 5m | 76.16±1.85 | 56.75±0.95 | 36.96±1.09 | 12.71±0.39 |
| 14 | 5n | 80.24±1.37 | 59.24±1.19 | 40.73±1.16 | 15.37±1.17 |
| 15 | 5o | 83.36±2.25 | 63.15±1.95 | 42.76±2.80 | 17.79±0.97 |
| 16 | 5p | 81.66±2.85 | 61.15±1.75 | 41.76±2.19 | 16.19±0.17 |

No appreciable benefits in the antispasmodic activities were observed by modifications on second phenyl ring as in compound "5o" and "5p" and were comparable with compound "5a" and "5b".

The potency exhibited by compounds "5c", "5h" and "5k" was promising and are recommended for further studies.

**Sedative activity**

The seven compounds viz. 5, 5a, 5b, 5c, 7d, 5h and 7k were found to be statistically significant against standard "Thiopental sodium" at P<0.05 by applying Scheffe's Post Hoc method at 100 mg/kg (Table 6).

In conclusion the lead compound "5" and its above stated novel analogs with diverse structural modifications have demonstrated significant sedative activity and are recommended for further studies.

**Table 6: Sedative activity of lead compound and its analogs**

| Sr. No. | Compound | Mean Sleeping Time min ± S.E. |
|---|---|---|
| 1 | Control | - |
| 2 | Standard | 13.16 ± 1.66 |
| 3 | 5 | 23.13 ± 0.86* |
| 4 | 5a | 21.06 ± 0.45* |
| 5 | 5b | 20.18 ± 0.66* |
| 6 | 5c | 22.12 ± 0.37* |
| 7 | 5d | 21.15 ± 0.55* |
| 8 | 5e | 16.15 ± 0.87 |
| 9 | 5f | 14.16 ± 1.36 |
| 10 | 5g | 14.16 ± 0.86 |
| 11 | 5h | 23.61 ± 0.95* |
| 12 | 5i | 12.19 ± 0.78 |
| 13 | 5j | 11.56 ± 0.76 |
| 14 | 5k | 22.77 ± 0.54* |
| 15 | 5l | 15.25 ± 0.67 |
| 16 | 5m | 14.36 ± 0.76 |
| 17 | 5n | 15.16 ± 0.87 |
| 18 | 5o | 14.15 ± 0.47 |
| 19 | 5p | 13.15 ± 0.55 |

*a) Dose: 100 mg/Kg b) Results are significant (*) at p<0.0*

**Antibacterial and Antifungal activity**

From Table 7, it is clearly evident that the compounds are active against the bacterial and fungal stains. Among seventeen compounds ("5-5p"), the compounds "5", "5c" and "5h" has activity comparable to that of reference standard Penicillin.

The compounds "5a" and "5b" exhibited reduced antibacterial potency than the lead compound "5", where functional group positions on phenyl ring were altered. Similar moderate potency was shown by compounds 5d and 5k with two methyl groups and methyl and methoxy group substitution of phenyl ring respectively.

**Table 7: Antibacterial activity of lead compound and its analogs**

| Sr. No. | Compound | Microorganisms | | | | | |
|---|---|---|---|---|---|---|---|
| | | Gram-positive | | | Gram-negative | | |
| | | *B. subtilis* | *B. sphaericus* | *S. aureus* | *P. aeruginosa* | *K. aerogenes* | *C. violaceum* |
| Reference Standard | Penicillin | 28 | 26 | 22 | 20 | 15 | 15 |
| 1 | 5 | 25 | 25 | 15 | 18 | 12 | 13 |
| 2 | 5a | 22 | 23 | 13 | 16 | 10 | 11 |
| 3 | 5b | 21 | 23 | 13 | 14 | 10 | 12 |
| 4 | 5c | 23 | 23 | 14 | 15 | 11 | 11 |
| 5 | 5d | 22 | 19 | 11 | 12 | 10 | 09 |
| 6 | 5e | 15 | 14 | 09 | 07 | 06 | 07 |
| 7 | 5f | 12 | 13 | 07 | 09 | 05 | 04 |
| 8 | 5g | 11 | 11 | 05 | 08 | 05 | 07 |
| 9 | 5h | 24 | 22 | 14 | 16 | 10 | 11 |
| 10 | 5i | 16 | 18 | 10 | 12 | 12 | 09 |
| 11 | 5j | 17 | 14 | 10 | 08 | 09 | 06 |
| 12 | 5k | 21 | 18 | 10 | 11 | 11 | 10 |
| 13 | 5l | 18 | 16 | 11 | 14 | 10 | 11 |
| 14 | 5m | 16 | 15 | 13 | 11 | 12 | 12 |
| 15 | 5n | 14 | 15 | 10 | 10 | 09 | 07 |
| 16 | 5o | 16 | 14 | 06 | 06 | 04 | 07 |
| 17 | 5p | 13 | 17 | 04 | 09 | 08 | 09 |

**Table 8: Antifungal activity of lead compound and its analogs**

| Sr. No. | Compound | Zone of inhibition in mm | | | | |
|---|---|---|---|---|---|---|
| | | *A.niger* | *C.tropicum* | *R.oryzae* | *F.moniliforme* | *C.lunata* |
| Reference Standard | Clotrimazole | 26 | 29 | 23 | 27 | 28 |
| 1 | 5 | 24 | 26 | 21 | 24 | 25 |
| 2 | 5a | 19 | 18 | 19 | 17 | 17 |
| 3 | 5b | 18 | 16 | 19 | 16 | 18 |
| 4 | 5c | 23 | 27 | 20 | 26 | 25 |
| 5 | 5d | 17 | 19 | 17 | 16 | 15 |
| 6 | 5e | 12 | 13 | 12 | 12 | 10 |
| 7 | 5f | 13 | 12 | 15 | 11 | 10 |
| 8 | 5g | 11 | 10 | 13 | 10 | 13 |
| 9 | 5h | 14 | 14 | 11 | 10 | 11 |
| 10 | 5i | 12 | 12 | 10 | 11 | 12 |
| 11 | 5j | 12 | 12 | 12 | 13 | 13 |
| 12 | 5k | 19 | 17 | 16 | 19 | 17 |
| 13 | 5l | 12 | 12 | 12 | 12 | 11 |
| 14 | 5m | 12 | 13 | 14 | 12 | 13 |
| 15 | 5n | 10 | 10 | 13 | 09 | 08 |
| 16 | 5o | 11 | 09 | 12 | 11 | 12 |
| 17 | 5p | 13 | 12 | 09 | 12 | 13 |

Rest all the compounds “5e-5g”, “5i”, “5j” and “5l -5p” has shown extremely low antibacterial potency. The data also indicated that replacing the butyl linker from the basic structural

framework of lead compound "5" with ethyl, propyl or pentyl linkers has lead to diminished potency of the respective compounds. None of the compounds tested have exhibited MIC more than that of the reference standard Penicillin.

The antibacterial activity of "5", "5c" and "5h" when compared to the standard drug is promising and can be evaluated further with next phase studies.

The antifungal activity studies as presented in Table 8 indicate that the compounds "5a", "5b", "5d" and "5k" have shown moderate activity (< 20), whereas compounds "5" and "5c" exhibited an excellent antifungal activity (21-27) close to reference standard Clotrimazole (23-29) and can be exploited for formulation of fungicide. Surprisingly the compound "5h" which had exhibited an excellent antibacterial potency close to reference standard has not shown promising antifungal potency (< 15). All other compounds "5e-5g", "5i", "5j" and "5l -5p" can be claimed as inactive (< 15) based on data.
It is clear from the results that replacing the butyl linker in structural framework of lead compound with ethyl, propyl or pentyl linkers lead to diminished antifungal potency of respective compounds as similarly observed during antibacterial testing.

In conclusion, the tested novel compounds have moderate to excellent activity towards the bacteria and fungi under investigation. Some of the analogs especially "5", "5c" and "5h" can be exploited for formulations of bactericidal and fungicide after detailed evaluation.

In conclusion the lead compound "5" and some of its above stated novel analogs with diverse structural modifications have well demonstrated desired antibacterial and antifungal activity and are recommended for advance studies.

## MATERIALS AND METHODS

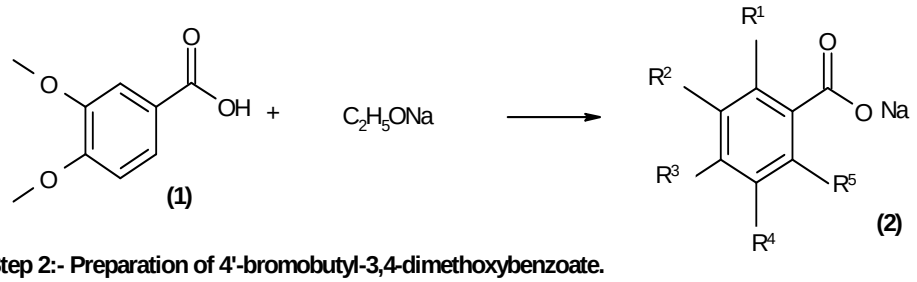
**For synthesis and characterization of compounds**
Synthesis of veratric acid ester 4-[ethyl-{2-(4-methoxyphenyl)-1-methylethyl} amino] butan-1-ol hydrochloride, as described in Scheme I, involves condensation of 4'-Bromobutyl-3, 4-dimethoxy benzoate (Intermediate I) with 2-ethylamino-1-(4'-methoxyphenyl) propane (Intermediate II) in the solvent ethyl methyl ketone at 75-80 $^{o}$C for 32 h. The "Intermediate I" is prepared by simple condensation of sodium-3, 4-dimethoxybenzoic acid and dibromo-butane in two step process. Preparation of "Intermediate II" is carried out in laboratory autoclave reactor by catalytic reduction of 4-methoxyphenyl acetone using hydrogen and Pt/C (5 %) as catalyst followed by in-situ condensation of reduction product with ethylamine.

Melting points of the synthesized compounds were determined on a melting point apparatus MP II and are uncorrected. FTIR spectra of the synthesized compounds were determined on FTIR-8300, KBr press, Shimadzu. $^{1}$H NMR, spectra were taken on Bruker 300MHz NMR spectrometer.

## SCHEME 1: Reaction Scheme

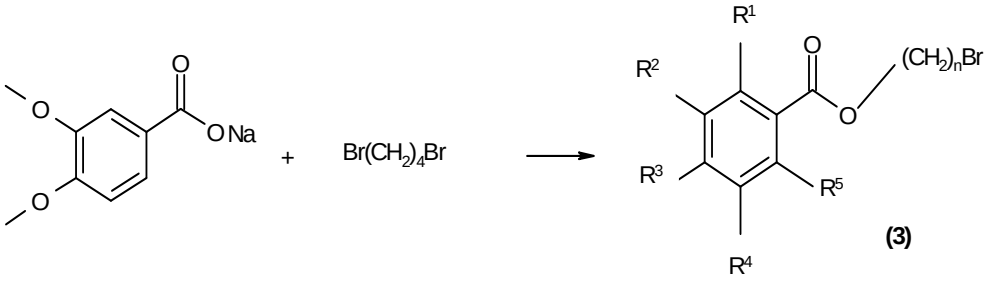
**STAGE I:- Preparation of 4'-bromobutyl-3,4-dimethoxybenzoate (Intermediate- I)**

**Step 1 :- Preparation of sodium- 3,4-dimethoxybenzoate.**



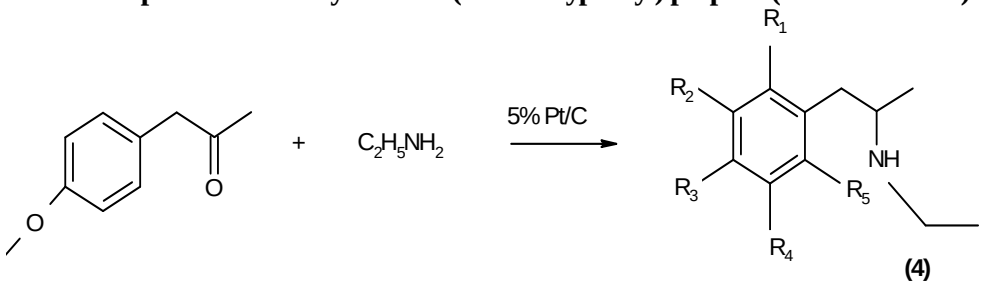

**(1)** **(2)**

**Step 2:- Preparation of 4'-bromobutyl-3,4-dimethoxybenzoate.**



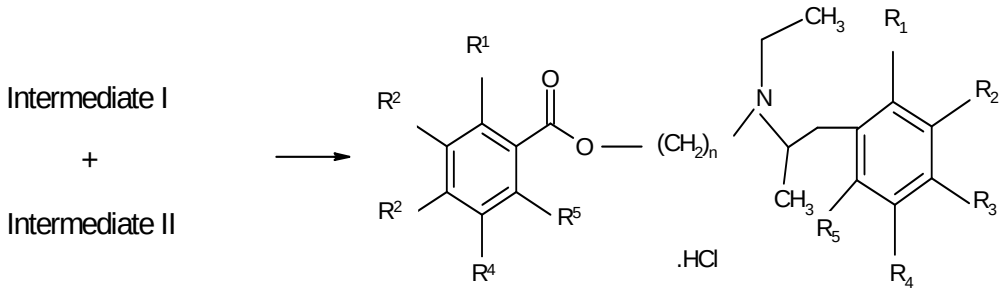

**(3)**

**STAGE II:- Preparation of 2-ethylamino-1-(4-methoxyphenyl) propane (Intermediate- II)**




**(4)**

**STAGE III: Final Condensation- Preparation of Lead Compound**




**(5a-5p)**

**General method for preparation of sodium-3, 4-dimethoxy benzoate (2) and its analogs**

To a solution of 3, 4-dimethoxy benzoic acid (200 g, 1.1 mol) in methanol (3000 ml), sodium methoxide solution (205 ml, 29 %) was added. The mixture was then warmed to 45$^{o}$C and maintained for one hour. The methanol is recovered by distillation till thick product slurry is obtained (~60 %). The solid product was filtered & slurry washed with methanol. Yield: 204 g, 91%,

**General method for preparation of 4$^{l}$-bromobutyl-3, 4-dimethoxy benzoate (3) and its analogs**

A mixture of sodium-3, 4-dimethoxy benzoate (204 g, 1.0 mol) and dibromo-butane (1800 ml) was heated in an oil bath at 150-155°C for 3h.The progress of the reaction was monitored by thin layer chromatography (TLC) to ensure reaction completion. The product is recovered by distillation under reduced pressure (1mm/Hg, 75$^{o}$C) Yield: 190.2 g, 60%,

**General method for preparation of 2-ethylamino-1-(4'-methoxyphenyl) propane (4) and its analogs**

To the mixture of 4-methoxy-phenylacetone (175 g, 1.06 mol) in methanol (1005 ml) was added Pt/C catalyst (5 %, 5 g), and cooled to 15$^{o}$C. To this pre-cooled mixture ethylamine solution (135 g, 70 %, 2.1 mol) was added. The mixture was transferred to laboratory autoclave reactor and started purging hydrogen gas. The reaction continued further maintaining the temperature 50$^{o}$C at pressure at 6 Kg/cm$^{2}$. The progress of the reaction was monitored by TLC to ensure reaction completion. After 15 hours on reaction completion, the reaction mass was cooled to 30$^{o}$C and catalyst was filtered off. The product is isolated by distillation after the initial methanol recovery as first fraction under reduced pressure (1 mm/Hg, 89$^{o}$C). Yield: 173 g, 84%;

**General method of preparation of veratric acid ester 4-[ethyl-{2-(4-methoxyphenyl)-1-methylethyl} amino] butan-1-ol hydrochloride (5) and its analogs (5a-5p)**

A mixture of compound (3) (149 g, 0.47 mol) and Compound (4) (183 g, 0.95 mol) in ethyl methyl ketone (MEK) was refluxed for a period of 30 h at 75-80$^{o}$C. The progress of the reaction was monitored by TLC to ensure formation of product and complete conversion of starting. On reaction completion solvent was distilled off and water (750 ml) was added to the reaction mass followed by toluene (300 ml). The resulting solution was cooled to 30$^{o}$C and stirred for 30 minutes before layer separation. The organic layer was washed further with water (2x100 ml) and dried over sodium sulphate. To the organic layer IPA-HCl (72 g, 20 %) was added till pH is acidic (2-2.5).The product precipitated as solid hydrochloride salt was isolated by filtration and recrystallized from methanol. Yield: 181 g, 82% m.p., 105-107°C.

**Pharmacology**

**Animals used for biological activity studies**

Study was performed using healthy Wistar rats of average weight of either sex. Wistar rats weighing in the range of 300-500 g were procured and anti-spasmodic, sedative activity was carried out on approval of Institutional Animal Ethics Committee constituted for the purpose.

**Antispasmodic activity**

The work includes muscle relaxation studies of synthesized compounds (5a-5p) on isolated wistar rat`s ileum, contracted with acetylcholine [15-16]. Wistar rats (n=6) of both sexes (300-500 g.) were used for the study. The animals were sacrificed by using ether as anaesthetic agent, until death. The ileum was removed immediately and placed in aerated krebs saline at 37$^{o}$C.The saline contained (in mm.): NaCl, 120.7; KCl, 5.9; CaCl2, 2.5; MgCl2, 1.2; NaHCO3, 15.5; and glucose, 11.5 at pH 7.3.For tension recording 2 cm ileum strips were mounted in a 10 mL organ bath and were connected to physiograph (polyrite, recorders and medicare systems) through force tension transducer. In the concentration range 10 µM-150 µM, the standard Papaverine, lead compound and all its analogs caused relaxation of spontaneous rhythmic contractions of both wistar rat ileum accompanied by a fall in resting tension.

The inhibition contraction was measured simply as percentage reduction in the height of spontaneous contractions. The percentage relaxation of all the analogs is compared. The results are expressed as mean ± S.E. The statistical significance was treated with the paired student`s t-test. P value < 0.01 was considered to be significant. Increase or decrease in tension was expressed as percent of maximal response to lead compound and standard "Papaverine".

**Sedative activity**

Male Wister rats weighing in the range of 200-400 g were selected from an inbred strain colony. They were maintained at constant temperature and relative humidity. Acute toxicity was done by following the proposed test method from literature [17]. "Thiopental sodium" (Thiosol ®) was used as standard drug, 2% CMC suspension was used as control and suspensions of the synthesized compounds were used. The mean sleeping times of compounds were compared with the standard, using one-way ANOVA followed by Scheffe's post hoc analysis to find out the significance.

**Antibacterial activity**

Antibacterial activity of the synthesized compounds (5, 5a-5p) was evaluated using acetone as a solvent and MIC was done by broth dilution method [17]. The bacterial stains used for the assay include, against gram-positive organisms B.Subtilis (MTCC 441), B.sphaericus (MTCC 511) & S.aureus (MTCC 96) and Gram-negative organisms P.aeruginosa (MTCC 741) K.aerogenes (MTCC 39) & C.violaceum (MTCC 2656) at 100µg/ml concentration. Standard antibacterial drugs were also screened under similar conditions for comparison. Penicillin (100µg/ml) from stock solution of 1000mg/ml was used as standard for B.Subtilis, B.sphaericus & S.aureus and Gentamycin (100 µg/ml) from stock solution of 1000 mg/ml was used as a standard for other organisms.

**Antifungal activity**

The antifungal activity of compounds (5,5a-5p) was evaluated against A. niger (MTCC 282), C. tropicum (MTCC 2821), R.oryzae (MTCC 262), F.moliliforme (MTCC 1848) and C. lunata (MTCC 2030) using Acetone as a solvent by cup diffusion method [18] at 100 µg/mL concentrations. The fungal susceptibility testing was done by cup-diffusion method using Clotrimazole (100 µg/mL) from stock solution of 1000 mg/ml as standard. The zone of inhibition was measured after 24 h of incubation at 37$^{o}$C. The zone of inhibition developed if any, was then accurately measured and recorded.

## CONCLUSION

The novel analog of the lead compound veratric acid ester 4-[ethyl-{2-(4-methoxyphenyl)-1-methylethyl} amino] butan-1-ol with diverse structural modifications have exhibited promising results when screened over various pharmacological activities like antispasmodic, sedative, antibacterial and antifungal potentials. The definite structure-activity relationship could be established based on acquired test results of different pharmacological potentials against induced structural modifications in compounds.

The novel analogs of lead compound with promising potency in respective therapeutic areas are recommended for advance studies to evaluate their formulation potential that can replace some of the existing drugs in respective areas of medicine as a better alternative to existing drugs with minimal side effect characteristics.

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