



## Research Article

**SYNTHESIS AND CHARACTERIZATION OF (R)-2-{{[5-BROMO-1-(3-BROMOPROPYL)-1H(SUBSTITUTED)-INDOL-3-YL]METHYL} PYRROLIDINE-1-CARBOXYLIC ACID DERIVATIVES VIA JAPP-KLINGEMANN AND FISCHER INDOLE CYCLIZATION REACTIONS**
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## ABSTRACT

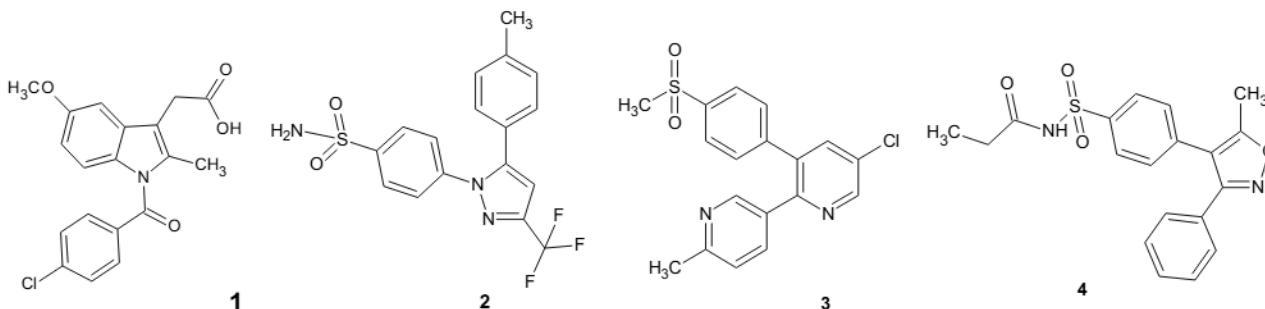
A series of novel (R)-2-{{[5-bromo-1-(3-bromopropyl)-1H (substituted)-indol-3-yl]methyl}pyrrolidine-1-carboxylic acid (T1-T5) derivatives were synthesized by electrophilic substitution at 1st position of (R)-2-{{[5-bromo-1-(3-bromopropyl)-1H-indol-3-yl]methyl}pyrrolidine-1-carboxylic acid with various halides. The starting material (R)-2-{{[5-bromo-1-(3-bromopropyl)-1H-indol-3-yl]methyl}pyrrolidine-1-carboxylic acid was synthesized from 4-bromo aniline by japp-klingsmann and fischer indole cyclization reactions. The synthesized compounds were characterized by IR, <sup>1</sup>H NMR and MASS spectroscopy.

**Keywords:** Indole derivatives, japp-klingsmann, fischer indole cyclization.

## INTRODUCTION

Indole is an aromatic heterocyclic organic compound. It has a bicyclic structure consisting of six membered benzene ring fused to a five membered nitrogen containing pyrrole ring. Indole exhibits very distinctive reactivity. Indole can undergo aromatic electrophilic substitution. At C-3 substitution shows nucleophilic substitution followed by nitrogen then C-2. These are isoelectronic analogues to Benzopyran. Indole is a popular component of fragrances and the precursor to pharmaceuticals. Indole possess a wide variety of pharmacological properties such as antifungal, antibacterial, anticancer, anticonvulsant. The indolic amino acid tryptophan is the precursor of the neurotransmitter serotonin. Substituted indoles are of the tryptan derived tryptamine alkaloids like neurotransmitter serotonin and

melatonin. Other indolic compounds include the plant hormone Auxin. Naturally occurring hallucinogen dimethyl tryptamine. Indole possess a wide variety of pharmacological properties such as analgesic<sup>1-4</sup>, antiinflammatory<sup>5-8</sup>, antimicrobial<sup>9-13</sup>, anticancer<sup>14-15</sup>, anticonvulsant<sup>16</sup> and anti-HBV<sup>17</sup> activities. Substituted indoles like indomethacin (1) exhibits analgesic activity by inhibition of cyclooxygenase enzyme (COX) which catalyze the bioconversion of arachidonic acid to inflammatory mediators i.e prostaglandins (PGs) and thromboxanes (TXs).<sup>18</sup> We synthesized T1-T5 indole derivatives as indomethacin analogues in which i) -CH<sub>2</sub>COOH group at position -3 is replaced with proline, ii) -OCH<sub>3</sub> group at position -5 is replaced with -Br and iii) Chlorbenzoyl group at position -1 is replaced with various halides.



## MATERIALS AND METHODS

### General

Solvents and reagents were obtained from commercial source (Sigma-Aldrich (USA) and Spectrochem Pvt. Ltd. (India)) and used without any further purification. The melting points (MP) were recorded on Electro thermal melting point apparatus and are uncorrected. The infrared absorption spectra were recorded in a solid state KBr dispersion using Perkin Elmer FT-IR spectrometer. The <sup>1</sup>H NMR spectra were recorded on Brutus-Adviser 300 MHz spectrometer. The chemical shifts were recorded as parts per million ( $\delta$  ppm) tetramethylsilane (TMS) as internal standard. The mass spectra were recorded using Perkin-Elmer SCIEX API 2000 mass spectrometer in the electro spray ionization mode. TLC was performed with Merck pre-coated silica gel 60 F254 TLC plates and compound visualization was effected under U.V light (365 nm). The structures of synthesized compounds were confirmed by spectral data (IR, NMR and MASS).

### Preparation of 4-Bromodiazonium Chloride (2)

To a solution of p-bromo aniline (1.62 g, 0.1 mol) in aqueous 5M HCl (16.6 ml), the solution of powdered sodium nitrite (1.38 g, 0.2 mol) in cold water (5 °C, 20 ml) was dropwise added. The reaction condition maintained at 5-10 °C to get good yield<sup>23</sup>. The resulting mixture was stirred for 30 min in an ice bath. The separated solid (2) was recrystallized from ethanol and used for next step.

### Preparation of ethyl 2-methyl-3-oxobutanoate anion (3)

To a solution of Ethyl 2-methyl-3-oxobutanoate (14.4 ml, 0.1 mol) in ethanol (30 ml) at 0-5 °C, The solution of potassium hydroxide (33.6 g, 0.6 mol) in water (30 ml) at 0-5 °C was drop wise added within 30 min and the reaction condition maintained at temperature below 8 °C<sup>24</sup>. The final mixture was stirred for further 30 min. The separated solid (3) was recrystallized from ethanol and used for next step directly.

### Preparation of Ethyl 2-[2-(4-bromophenyl) hydrazinylidene] propanoate (4)

4-Bromodiazonium chloride (2) was added slowly with stirring to the solution of ethyl 2-methyl-3-oxobutanoate anion (3) in water (30 ml) and stirring continued for 1hour at 40 °C. Then the mixture was allowed to cool to room temperature and the pH was adjusted to 4 by adding aqueous HCl (1M). The desired product was extracted with diethyl ether (3\*50 ml). The combined organic layers were collected and evaporated to dryness to yield Ethyl 2-[2-(4-bromophenyl) hydrazinylidene] propanoate (4).

### Preparation of 5-Bromo-2-ethyl carboxyl indole (5)

Ethyl 2-[2-(4-bromophenyl) hydrazinylidene] propanoate (4) (0.01 mol), was poured into a beaker containing hot methanesulphonic acid<sup>25</sup> (30 ml). The reaction mixture was stirred and heated to 50 °C for an additional 10 min. The hot reaction solution was added to 25 ml ice cold water with stirring. The 5-Bromo-2-ethyl carboxyl indole (5) was formed as precipitate, collected the precipitate by vacuum filtration and washed the compound 2-3 times with distilled water.

### Preparation of 5-Bromo indole (6)

A solution of 5-Bromo-2-ethyl carboxyl indole (5) in 20% Aq. NaOH (30 ml) was stirred for 30 min then acidified with 1M

H<sub>2</sub>SO<sub>4</sub> to pH 3. The reaction mixture was kept for boiling on water bath for 1hour at 100 °C. The hot reaction solution was added to 50 ml ice cold water with stirring. 5-bromo indole (6) formed as precipitate was collected from the solution by vacuum filtration and washed the compound 2-3 times with distilled water.

### Preparation of 5-bromo-3-[N-benzyloxycarbonyl]-2-pyrrolidin-2-yl] carbonyl-1H-indole (8)

Ethyl magnesium bromide (1.33 g, 0.01 mol) was added to a solution of 5-bromo indole (6) (1.96 g, 0.01 mol) in ether (30 ml) the mixture was stirred at room temperature for 10 min and refluxed for 2hrs. Then reaction mixture was cooled to room temperature to this 2-carbonyl chloride N-Benzyloxy carbonyl pyrrolidine (7) (2.67g, 0.01 mol) dissolved in dichloromethane (10 ml) was added drop wise. The mixture was stirred for 1hour followed by addition of ether (25 ml) and saturated aqueous sodium bicarbonate solution (10 %w/v, 13 ml) and stirring continued for 10 minutes. The separated solid was collected from the solution, washed and dried.

### Preparation of (R)-5-Bromo-3-(N-Methylpyrrolidine-2-yl-Methyl)-1H-Indole (9)

A solution of (R)-5-bromo-3-[N-benzyloxycarbonyl]-2-pyrrolidin-2-yl] carbonyl-1H-indole (8) (2.85 g, 0.01mol) in dry tetra hydrofuran (30 ml) was added drop wise over the period of 60 min to the solution of Lithium Aluminium Hydride (LAH) (1.52 g) in tetra hydrofuran (30 ml). The mixture was stirred and heated to 50 °C for 1 hour. Then the reaction mixture was poured into crushed ice. The solid obtained was filtered, washed, dried and recrystallized from ethanol.

### Preparation of 2-[(5-bromo-1H-indol-3-yl) methyl] pyrrolidine-1-carboxylic acid (10)

To a stirring solution of ester (1gm) and methanol (5ml), KOH (2mol) was added at 35 °C. The reaction was allowed to continue for 1hr then quenched by addition of water (20 ml). The unreacted ester was removed by ether extraction and the aqueous layer was acidified with dil. HCl. The resulting acid precipitated out and collected by vacuum filtration.

### General procedure for synthesis of (R)-2-[[5-bromo-1-(3-bromopropyl)-1H (substituted)-indol-3-yl]methyl]pyrrolidine-1-carboxylic acid (T1-T5)

A mixture of (R)-2-[[5-bromo-1-(3-bromopropyl)-1H (substituted)-indol-3-yl]methyl]pyrrolidine-1-carboxylic acid (T1-T5) (2.78g, 0.01mol) in dry 1, 4-dioxan (20 ml), anhydrous potassium carbonate (100 mg) and desired halide (0.01 mol) was refluxed for 5 h. Then the reaction mixture was poured into crushed ice. The solid obtained was filtered, washed, dried and recrystallized from ethanol.

### Synthesis of (R)- 2-[[5-bromo-1-(chloroacetyl)-1H-indol-3-yl]methyl]pyrrolidine-1-carboxylic acid (T1)

Yield: 84%, M.P=112 °C, IR (KBr pellet)- 1666 (C=O), 720 (C-Cl), 1096 (C-Br), 1256 (C-N), 3030 (Ar C-H), NMR (DMSO-d<sub>6</sub>)-  $\delta$ -7.45-8.26 (m, 3H, Ar-H), 2.1 (s, 1H, CH indole), 1.5 (s, 2H, CH<sub>2</sub>), 2.7(s, 1H, CH), 1.6-2.8 (m, 6H, 3CH<sub>2</sub>), 2.6 (s, 3H,NCH<sub>3</sub>), 1.8 (s, 2H, COCH<sub>2</sub>Cl ). MASS- 369 [M+1]<sup>+</sup>.

**Synthesis of (R)- 2-[[5-bromo-1-(2-bromoethyl)-1H-indol-3-yl]methyl]pyrrolidine-1-carboxylic acid (T2)**

Yield: 82%, M.P=1200C, IR (KBr pellet)- 1099 (Ar C-Br), 564 (Ali C-Br), 1245 (C-N), 3035 (Ar C-H), NMR (DMSO-d6)-  $\delta$ -7.45-8.26 (m, 3H, Ar-H), 2.0 (s, 1H, CH indole), 1.4 (s, 2H, CH2), 2.4 (s, 1H, CH), 1.6-2.8 (m, 6H, 3CH2), 2.7 (s, 3H,NCH3), 2.1-3.6 (m, 4H, NCH2CH2Br), MASS- 399 [M+1]<sup>+</sup>.

**Synthesis of (R)- 2-[[5-bromo-1-ethyl-1H-indol-3-yl]methyl]pyrrolidine-1-carboxylic acid (T3)**

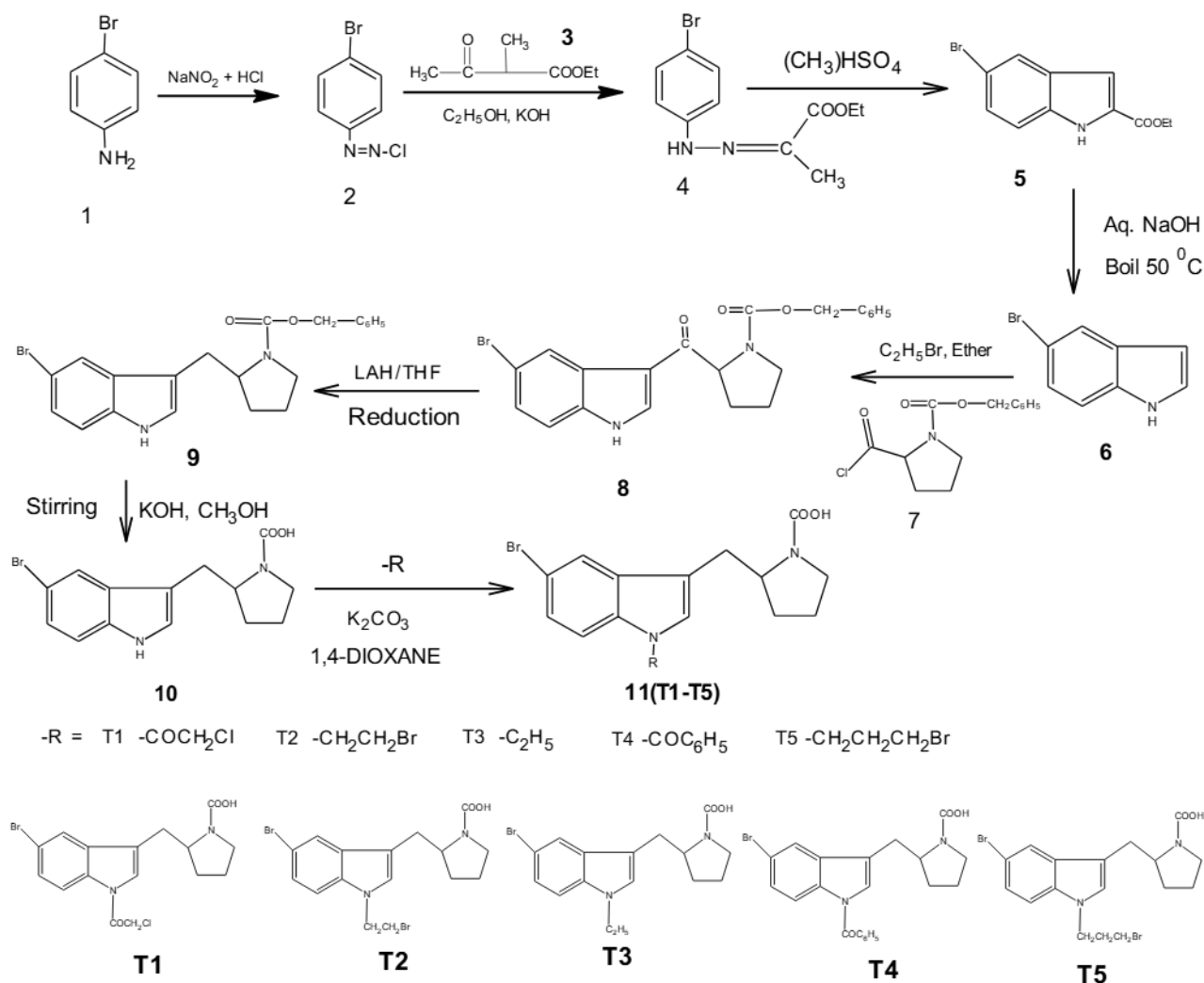
Yield =85%, M.P=1140C, IR (KBr pellet)- 2895 (Ali C-H), 1088 (C-Br), 1242 (C-N), 3042 (Ar C-H), NMR (DMSO-d6)-  $\delta$ -7.45-8.26 (m, 3H, Ar-H), 2.0 (s, 1H, CH indole), 1.6 (s, 2H, CH2), 2.9 (s, 1H, CH), 1.6-2.8 (m, 6H, 3CH2), 2.5 (s, 3H,NCH3), 1.1-2.6 (m, 5H, CH2CH3), MASS- 321 [M+1]<sup>+</sup>.

**Synthesis of (R)- 2-[[1-benzoyl-5-bromo-1H-indol-3-yl]methyl]pyrrolidine-1-carboxylic acid (T4)**

Yield: 86%, M.P=116 0C, IR (KBr pellet)- 1654 (C=O), 1091 (Ar C-Br), 1249 (C-N), 3034 (Ar C-H), NMR (DMSO-d6)-  $\delta$ -7.45-8.26 (m, 3H, Ar-H), 2.4 (s, 1H, CH indole), 1.5 (s, 2H, CH2), 2.8 (s, 1H, CH), 1.6-2.8 (m, 6H, 3CH2), 2.5 (s, 3H,NCH3), 7.9-8.3 (m, 5H, COC6H5), MASS-397 [M+1]<sup>+</sup>.

**Synthesis of (R)-2-[[5-bromo-1-(3-bromopropyl)-1H-indol-3-yl]methyl]pyrrolidine-1-carboxylic acid (T5)**

Yield: 84%, M.P=110 0C, IR (KBr pellet)- 572 (Ali C-Br), 2888 (Ali C-H), 1099 (Ar C-Br), 1248 (C-N), 3027 (Ar C-H), NMR (DMSO-d6)-  $\delta$ -7.45-8.26 (m, 3H, Ar-H), 1.98 (s, 1H, CH indole), 1.5 (s, 2H, CH2), 3.0 (s, 1H, CH), 1.6-2.8 (m, 6H, 3CH2), 2.6 (s, 3H,NCH3), 1.2-3.6 (m, 6H, -CH2CH2CH2Br), MASS- 413 [M+1]<sup>+</sup>.



Scheme 1: Synthesis of (R)-2-[[5-bromo-1-(3-bromopropyl)-1H (substituted)-indol-3-yl]methyl]pyrrolidine-1-carboxylic acid (T1-T5)

**RESULTS AND DISCUSSION****Chemistry**

The synthesis of target compounds (R)-2-{{5-bromo-1-(3-bromopropyl)-1H (substituted)-indol-3-yl}methyl}pyrrolidine-1-carboxylic acid (T1-T5) were described in scheme-1. The intermediate (5) was synthesized from 4-bromo aniline and Ethyl 2-methyl-3-oxobutanoate via Ethyl 2-[2-(4-bromophenyl)hydrazinylidene] propanoate (4) by Japp-Klingemann reaction<sup>26</sup> and Fischer indole cyclization<sup>26</sup> process as shown in scheme 1. This intermediate (5) upon ester hydrolysis by 20% NaOH and decarboxylation by heating gives 5-Bromo indole (6). 5-Bromo indole (6) was allowed to react with 2-carbonyl chloride N-benzyloxy carbonyl pyrrolidine in presence of Grignard reagent (C<sub>2</sub>H<sub>5</sub>MgBr) gives (R)-5-bromo-3-[N-benzyloxycarbonyl]-2-pyrrolidin-2-yl carbonyl-1H-indole (8). The key intermediate (R)-2-{{5-bromo-1-(3-bromopropyl)-1H-indol-3-yl}methyl}pyrrolidine-1-carboxylic acid (10) was synthesized by stirring at hot condition a solution of (R)-5-bromo-3-[N-benzyloxycarbonyl]-2-pyrrolidin-2-yl carbonyl-1H-indole (8) in tetrahydrofuran and a solution of LAH in tetrahydrofuran for 1h and ester hydrolysis by stirring with 10% NaOH. The IR spectra of compounds (R)-2-{{5-bromo-1-(3-bromopropyl)-1H-indol-3-yl}methyl}pyrrolidine-1-carboxylic acid have shown a peak for N-H around 3120 cm<sup>-1</sup>. The <sup>1</sup>H NMR spectra of compounds (R)-2-{{5-bromo-1-(3-bromopropyl)-1H-indol-3-yl}methyl}pyrrolidine-1-carboxylic acid have shown a singlet at δ-11.04 integrating proton is assignable to N-H, a singlet at δ 11.9 integrating to proton is assignable to N-COOH, a multiplet at δ-7.29 integrating to three protons is assignable to aromatic protons. Mass spectra of (R)-2-{{5-bromo-1-(3-bromopropyl)-1H-indol-3-yl}methyl}pyrrolidine-1-carboxylic acid gave molecular ion 293[M+1]. The titled compounds were obtained in fair to good yield through the displacement of N-H group from (R)-2-{{5-bromo-1-(3-bromopropyl)-1H-indol-3-yl}methyl}pyrrolidine-1-carboxylic acid with variety of halides using 1,4-dioxane as solvent to afford (R)-2-{{5-bromo-1-(3-bromopropyl)-1H (substituted)-indol-3-yl}methyl}pyrrolidine-1-carboxylic acid (T1-T5). The formation of titled compounds is indicated by the disappearance of N-H peak from the starting material and the appearance C-Cl signal at 756 cm<sup>-1</sup> in the IR spectrum of the compounds T1. In T5 it has shown a peak for Aliphatic C-Br around 564 cm<sup>-1</sup>. The <sup>1</sup>H NMR spectra of title compound T1 have shown peaks a singlet around δ-1.8 due to -COCH<sub>2</sub>Cl and the <sup>1</sup>H NMR spectra of title compound T4 have shown peaks a multiplet around δ-7.9-8.3 was observed for aromatic protons of -COC<sub>6</sub>H<sub>5</sub>.

**CONCLUSION**

In summary, the synthesis of novel indomethacin analogues (R)-2-{{5-bromo-1-(3-bromopropyl)-1H (substituted)-indol-3-yl}methyl}pyrrolidine-1-carboxylic acid (T1-T5) from 4-bromo aniline and beta keto ester by Japp-Klingemann and Fischer indole cyclization reactions with good yield have been described. The synthesized compounds were characterized by IR, <sup>1</sup>H NMR and MASS spectroscopy.

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