CODEN [USA]: IAJPBB ISSN: 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES

Available online at: http://www.iajps.com *Research Article*

SYNTHESIS OF NOVEL (*R*)-5-BROMO-3-(*N*-METHYLPYRROLIDINE-2-YL-METHYL)-1*H* (SUBSTITUTED)-INDOLE DERIVATIVES AS POTENTIAL COX-2 INHIBITORS VIA JAPP-KLINGEMANN AND FISCHER INDOLE CYCLIZATION REACTIONS

Tasleem*[1], P. Shyam Sundar[2], R. Vasanthi[3]

[1]Associate Professor, Department of Pharmaceutical Chemistry, Deccan School of Pharmacy, Osmania University, Hyderabad, India. email-fathima.tasleem@gmail.com.

[2]Associate Professor, Department of Pharmaceutical Chemistry, NNR School of Pharmacy, JNTUH, TS-508001, India. email-shyam049@gmail.com.

[3]Associate Professor, Department of Pharmaceutical Chemistry, Geetam University, Hyderabad, T.S-500032. India. email-vasanthi.rangapuram@gmail.com.

Abstract:

A series of novel (R)-5-bromo-3-(N-methylpyrrolidine-2-yl-methyl)-1H (substituted)-indole (T1-T5) derivates were synthesized by electrophilic substitution at 1st position of (R)-5-bromo-3-(N-methylpyrrolidine-2-yl-methyl)-1H-indole with various halides. The starting material (R)-5-bromo-3-(N-methylpyrrolidine-2-yl-methyl)-1H-indole was synthesized from 4-bromo aniline by multistep synthesis. The synthesized compounds were characterized by IR, ^{1}H NMR and MASS spectroscopy and newly synthesized compounds were evaluated for their analgesic activity by tail immersion technique using wistar albino mice. Among the synthesized compounds T3, T4, T5 have shown significant activity by tail immersion technique. Compound (R)- 5-bromo-1-ethyl-3-[(1-methylpyrrolidin-2-yl)methyl]-1H-indole (T3) emerged as the most potent analgesic agent and it is equipotent when compared to the reference standard diclofenac sodium.

Keywords: *Indole derivatives; Analgesic activity; Tail immersion technique.*

Corresponding Author:

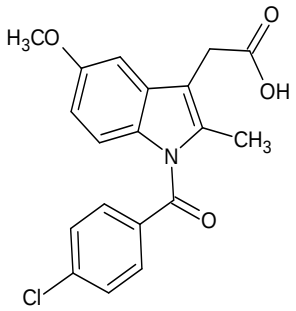
Tasleem,
Associate Professor,
Department of Pharmaceutical Chemistry,
Deccan School of Pharmacy,
Osmania University, Hyderabad,
India. email-fathima.tasleem@gmail.com.

QR code

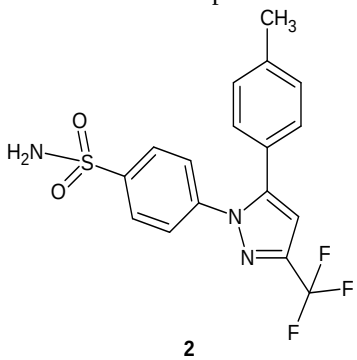
Please cite this article in press as Tasleem et al., ***Synthesis of Novel (R)-5-Bromo-3-(N-Methylpyrrolidine-2-Yl-Methyl)-1H (Substituted)-Indole Derivatives as Potential COX-2 Inhibitors via JAPP-Klingemann and Fischer Indole Cyclization Reactions,*** *Indo Am. J. P. Sci, 2018; 05(01).*

INTRODUCTION:

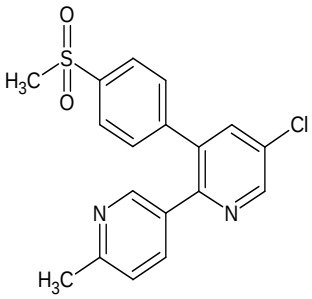
Indole is an aromatic heterocyclic organic compound possess a wide variety of pharmacological properties such as analgesic[1-4], antiinflammatory[5-8], antimicrobial[9-13], anticancer[14-15], anticonvulsant[16] and anti-HBV[17] activities. Substituted indoles like indomethacin (1) exhibits analgesic activity by inhibition of cyclooxygenase enzyme (COX) which catalyse the bioconversion of arachdonic acid to inflammatory mediator's i.e prostaglandins (PGs) and thromboxanes (TXs)[18]. Cyclooxygenase enzyme exists in two distinct isoforms, a constitutive form (COX-1) and an inducible form (COX-2). COX-1 Physiologically expressed in body and maintains the normal (house keeping) function. In contrast COX-2 induced in pathological states such as tissue damage. Despite of their activity most of anti-inflammatory agents possess side effects such as bleeding tendency, peptic ulcer and renal toxicity resulting from inhibition of constitutive COX-1. Because of selective analgesic activity exhibited by COX-2 inhibitors, many of research activities in this area were reported. Among numerous COX-2 inhibitors celecoxib (2), etoricoxib (3) and parecoxib (4) are the most popular commercial drugs currently available in the market. A large number of the studies[19-22] on indole nucleus based analgesic i.e Indomethacin analogues revealed that these derivatives were possessing selective COX-2 inhibition activity and reduced side effects. So, these results encouraged us to continue the research on such type of compounds. Our main aim is to maintain the potency of indomethacin by keeping the indole nucleus with modification of substituents at N1, C3 and C5 to increase COX-2 selectivity. We synthesized T1-T5 indole derivatives as indomethacin analogues in which i) -CH2COOH group at position -3 is replaced with proline, ii) -OCH3 group at position -5 is replaced with -Br and iii) Chlorbenzoyl group at position -1 is replaced with various halides.



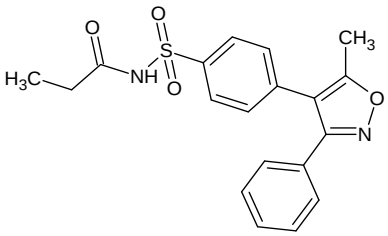
1



2



3



4

EXPERIMENTAL SECTION:

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 ^{1}H NMR spectra were recorded on Brutus-Adviser 300 MHz spectrometer. The chemical shifts were recorded as parts per million (δ 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 perform with Merck pre-coated silica gel 60 F_{254} 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 ^{0}C, 20 ml) was dropwise added. The reaction condition maintained at 5-10 ^{0}C to get good yield [23]. The resulting mixture was stirred for 30 min in an ice bath. The separated solid (2) was recrystalized 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 ^{0}C, The solution of potassium hydroxide (33.6 g, 0.6 mol) in water (30 ml) at 0-5 ^{0}C was drop wise added within 30 min and the reaction condition maintained at temperature below 8 ^{0}C[24]. The final mixture was stirred for further 30 min. The separated solid (3) was recrystalized 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 ^{0}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[25] (30 ml). The reaction mixture was stirred and heated to 50 ^{0}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_2SO_4 to pH 3. The reaction mixture was kept for boiling on water bath for 1hour at 100 ^{0}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-pyrrollidin-2-yl] carbonyl-1*H*-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 pyrrollidine (7) (2.67g, 0.01 mol) dissolved in dichlormethane (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)-1*H*-Indole (10)

A solution of (*R*)-5-bromo-3-[*N*-benzyloxycarbonyl)-2-pyrrollidin-2-yl] carbonyl-1*H*-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 ^{0}C for 1 hour. Reaction mixture was cooled to room temperature and 10% NaOH (40 ml) solution was added drop wise with stirring for 30 min. the aqueous layer was separated from the solution by using separating funnel. To this aqueous layer 1M HCl (40 ml) was added and stirred

vigorously for 30 minutes. The final compound was extracted with three portions of toluene (3*30 ml) and combined toluene extracts were evaporated to get the product. Recrystallization was done by dissolving the compound in ethanol (10 ml) and let to crystallize overnight.

General procedure for synthesis of (*R*)-5-Bromo-3-(*N*-Methylpyrrolidine-2-yl-Methyl)-1*H* (substituted)-Indole (T1-T5)

A mixture of (*R*)-5-bromo-3-(*N*-methylpyrrolidine-2-yl-methyl)-1*H*-indole (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*)-1-{5-bromo-3-[(1-methylpyrrolidin-2-yl) methyl]-1*H*-indol-1-yl}-2-chloroethan-1-one (T1)

Yield: 84%, **M.P**=112 ^{0}C, **IR (KBr pellet)**- 1666 (C=O), 720 (C-Cl), 1096 (C-Br), 1256 (C-N), 3030 (Ar C-H), **NMR (DMSO-d6)**- δ-7.45-8.26 (m, 3H, Ar-H), 2.1 (s, 1H, CH indole), 1.5 (s, 2H, CH_2), 2.7(s, 1H, CH), 1.6-2.8 (m, 6H, $3CH_2$), 2.6 (s, 3H,NCH_3), 1.8 (s, 2H, $COCH_2Cl$). **MASS**- 369 $[M+1]^+$.

Synthesis of (*R*)-5-bromo-1-(2-bromoethyl)-3-[(*N*-methylpyrrolidin-2-yl) methyl]-1*H*-indole (T2)

Yield: 82%, **M.P**=120^{0}C, **IR (KBr pellet)**- 1099 (Ar C-Br), 564 (Ali C-Br), 1245 (C-N), 3035 (Ar C-H), **NMR (DMSO-d6)**- δ-7.45-8.26 (m, 3H, Ar-H), 2.0 (s, 1H, CH indole), 1.4 (s, 2H, CH_2), 2.4 (s, 1H, CH), 1.6-2.8 (m, 6H, $3CH_2$), 2.7 (s, 3H,NCH_3), 2.1-3.6 (m, 4H, NCH_2CH_2Br), **MASS**- 399 $[M+1]^+$.

Synthesis of (*R*)-5-bromo-1-ethyl-3-[(*N*-methylpyrrolidin-2-yl) methyl]-1*H*-indole (T3)

Yield =85%, **M.P**=114^{0}C, **IR (KBr pellet)**- 2895 (Ali C-H), 1088 (C-Br), 1242 (C-N), 3042 (Ar C-H), **NMR (DMSO-d6)**- δ-7.45-8.26 (m, 3H, Ar-H), 2.0 (s, 1H, CH indole), 1.6 (s, 2H, CH_2), 2.9 (s, 1H, CH), 1.6-2.8 (m, 6H, $3CH_2$), 2.5 (s, 3H,NCH_3), 1.1-2.6 (m, 5H, CH_2CH_3), **MASS**- 321 $[M+1]^+$.

Synthesis of (*R*)-{5-bromo-3-[(*N*-methylpyrrolidin-2-yl) methyl]-1*H*-indol-1-yl} (phenyl) methanone (T4)

Yield: 86%, **M.P**=116 ^{0}C, **IR (KBr pellet)**- 1654 (C=O), 1091 (Ar C-Br), 1249 (C-N), 3034 (Ar C-H), **NMR (DMSO-d6)**- δ-7.45-8.26 (m, 3H, Ar-H), 2.4 (s, 1H, CH indole), 1.5 (s, 2H, CH_2), 2.8 (s, 1H, CH), 1.6-2.8 (m, 6H, $3CH_2$), 2.5 (s, 3H,NCH_3), 7.9-8.3 (m, 5H, COC_6H_5), **MASS**-397 $[M+1]^+$.

Synthesis of (*R*)-5-bromo-1-(3-bromopropyl)-3-[(*N*-methylpyrrolidin-2-yl) methyl]-1*H*-indole (T5)

Yield: 84%, M.P=110 ^{0}C, **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)**- δ-7.45-8.26 (m, 3H, Ar-H), 1.98 (s, 1H, CH indole), 1.5 (s, 2H, CH_2), 3.0 (s, 1H, CH), 1.6-2.8 (m, 6H, $3CH_2$), 2.6 (s, 3H,NCH_3), 1.2-3.6 (m, 6H, $-CH_2CH_2CH_2Br$), **MASS**- 413 $[M+1]^+$.

Pharmacology

Analgesic Activity

The synthesized compounds were evaluated for their analgesic activity by tail immersion technique. The animals were maintained in colony cages at a temperature of 25±2 ^{0}C, relative humidity of 45–55 %, and under a 12 h light and dark cycle; they were fed standard animal feed. All the animals were acclimatized for week before the experiment. The institutional Animal Ethics committee approved the protocol adopted for the experimentation of animals.

Tail Immersion Technique

Purpose and Rationale

The method has been developed to be selective for indole-like compounds. The procedure is based on the observation that indole like drugs are selectively capable of prolonging the reaction time of the typical tail-withdrawal reflex in mice induced by immersing the end of the tail in warm water of 55 ± 0.5 °C.

Procedure

Young mice (20–30 g body weight) were used. Animals were divided into 10 groups each consists of four animals. They were placed into individual restraining cages leaving the tail hanging out freely. The animals are allowed to adapt to the cages for 30 min before testing. The lower 5 cm portion of the tail was marked. This part of the tail was immersed in a cup of freshly filled water of exactly 55 ± 0.5 °C [26]. Within a few seconds the rat reacts by withdrawing the tail. The reaction time was recorded in 0.5 s units by a stopwatch. After each determination the tail was carefully dried. Test compound and standard diclofenac sodium were administered orally at doses of 200 mg/kg and 10 mg/kg as aqueous suspension in 1% sodium carboxy methyl-cellulose (Na CMC) respectively, while the control group was fed with the same volume of 1% Na CMC. The reaction time is determined before and periodically after either oral or subcutaneous administration of the test substance, e. g., after 0.5, 1, 2 and 3h. The cut off time of the immersion was 15 s. The withdrawal time of untreated animals was between 1 and 5.5 s. A withdrawal time of more than 6 s therefore was regarded as a positive response. The Percentage of Analgesic Activity (PAA) was calculated with the following formula.

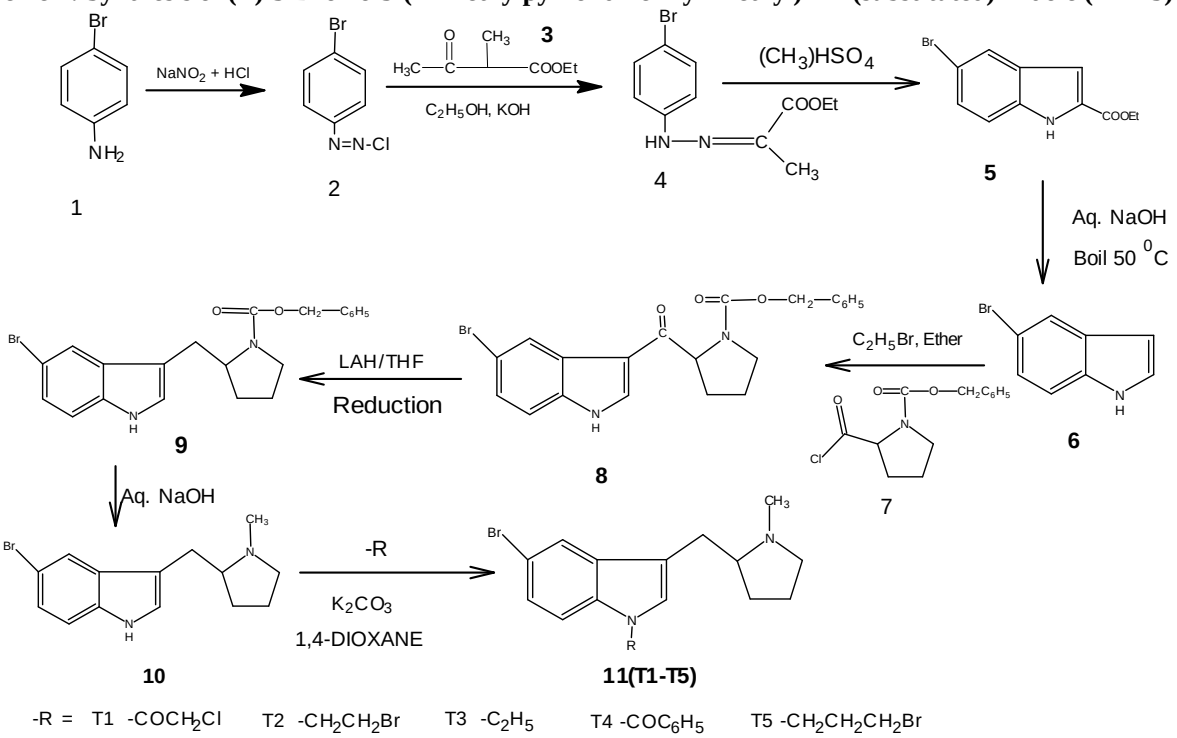
PAA = (T_2-T_1/10-T_1) *100
Were T_1 is reaction time (s) before treatment; T_2 is reaction time (s) after treatment.

RESULTS AND DISCUSSION:

Chemistry:

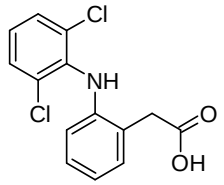
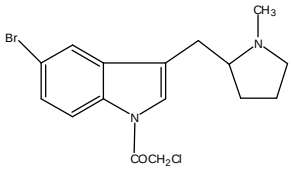
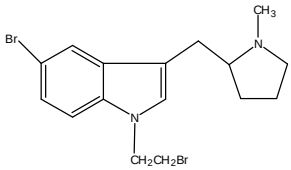
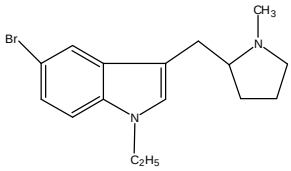
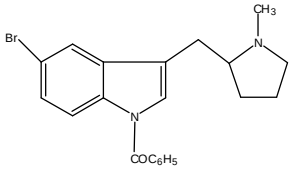
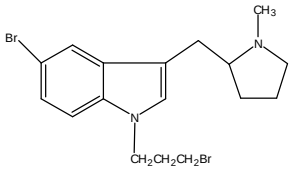
The syntheses of target compounds (R)-5-Bromo-3-(*N*-methylpyrrolidin-2-yl-methyl)-1*H* (substituted)-indole (T1-T5) were described in scheme-1. The intermediate (5) was synthesized from 4-bromo aniline and Ethyl 2-methyl-3-oxobutanoate via Ethyl 2-[2-(4-bromophenyl) hydrazinylidene] propanoate (4) by Japp-Klingemann reaction[27] and fischer indole cyclization[27] 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 pyrrolildine in presence of grignard reagent (C_2H_5MgBr) gives (R)-5-bromo-3-[*N*-benzyloxycarbonyl)-2-pyrrollidin-2-yl] carbonyl-1*H*-indole (8). The key intermediate (R)-5-Bromo-3-(*N*-methylpyrrolidin-2-yl-methyl)-1*H*-indole (10) was synthesized by stirring at hot condition a solution of (*R*)-5-bromo-3-[*N*-benzyloxycarbonyl)-2-pyrrollidin-2-yl] carbonyl-1*H*-indole (8) in tetra hydrofuran and a solution of LAH in tetra hydrofuran for 1h and ester hydrolysis by stirring with 10% NaOH. The IR spectra of compounds (*R*)-5-Bromo-3-(*N*-methyl pyrrolidine-2-yl-methyl)-1*H*-indole have shown a peak for N-H around 3120 cm^{-1}. The ^1H NMR spectra of compounds 5-Bromo-3-[(*N*-methylpyrrolidin-2-yl) methyl]-1*H*-indole have shown a singlet at δ-11.04 integrating proton is assignable to N-H, a singlet at δ 2.62 integrating to three protons is assignable to N-CH_3, a multiplet at δ-7.29 integrating to three protons is assignable to aromatic protons. Mass spectra of (R)-5-Bromo-3-(*N*-methyl pyrrolidine-2-yl-methyl)-1*H*-indole 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*)-5-Bromo-3-(*N*-methylpyrrolidin-2-yl-methyl)-1*H*-indole with variety of halides using 1,4-dioxane as solvent to afford (*R*)-5-Bromo-3-(*N*-methylpyrrolidin-2-yl-methyl)-1*H* (substituted)-indole (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^{-1} in the IR spectrum of the compounds T1. In T5 it have shown a peak for Aliphatic C-Br around 564 cm^{-1}. The ^1H NMR spectra of title compound T1 have shown peaks a singlet around δ-1.8 due to -$COCH_2Cl$ and The ^1H NMR spectra of title compound T4 have shown peaks a multiplet around δ-7.9-8.3 was observed for aromatic protons of -COC_6H_5.

Scheme 1: Synthesis of (*R*)-5-Bromo-3-(*N*-Methylpyrrolidine-2-yl-Methyl)-1*H* (substituted)-Indole (T1-T5)



Pharmacology:

Table 1: Analgesic activity of synthesized compounds T1-T5

Compound	Structure	Dose (mg/kg) Orally	30min PAA	1h PAA	2h PAA	3h PAA
Control	-	1% NaCMC	20	21	21	22
Diclofenac Sodium		10	51	60	69	82
T1		200	22	24	27	23
T2		200	28	30	32	27
T3		200	40	45	49	33
T4		200	30	32	37	28
T5		200	28	30	33	25

Evaluation of analgesic activity was performed by the tail-immersion technique using Wistar albino mice. The results of analgesic testing indicate that the test compounds (T1-T5) were exhibited moderate analgesic activity at 30 min of reaction time and an increase in activity at 1 h which reached a peak level at 2 h. declining in activity was observed at 3 h (Table 1). Compound (T3) with N-ethyl substituent showed good activity (49%); when the ethyl group was replaced by benzoyl (compound T4;

37%) the activity was retained; Aryl substituent/substituted aryl substituents showed decrease activity compare to the aliphatic and hetero aliphatic substituents. Compound (*R*)-5-Bromo-1-ethyl-3-(*N*-methylpyrrolidin-2-yl-methyl)-1*H*-indole (T3) emerged as the most active analgesic agent and it is equipotent when compared to the reference standard diclofenac sodium.

CONCLUSION:

In summary, the synthesis of novel indomethacin analogues (*R*)-5-Bromo-3-(*N*-Methylpyrrolidine-2-yl-Methyl)-1*H* (substituted)-Indole (T1-T5) have been described. The title compounds T1-T5 have shown promising analgesic activity by tail immersion technique on Wister albino mice. Among the synthesized compounds series (*R*)-5-Bromo-1-ethyl-3-(1-methylpyrrolidin-2-yl-methyl)-1*H*-indole (T3) emerged as the most potent compound with 49% (PAA) at a dose of 200 mg/kg, When compared to reference standard diclofenac sodium 79% (PAA) at a dose of 20 mg/kg. Compound (*R*)-1-{5-bromo-3-[(1-methylpyrrolidin-2-yl) methyl]-1*H*-indol-1-yl}-2-chloroethan-1-one (T1) exhibited lowest analgesic activity. Compound T3 could therefore serve as a lead molecule for further modification to obtain clinically useful novel analgesics.

ACKNOWLEDGEMENT

The authors are very thankful to Deccan School of Pharmacy, Hyderabad for providing necessary facilities to carry out the present research work.

REFERENCES:

1.Lundt B.F. and Anderson W.; "Analgesic 3-(aminoalkoxy) Indoles"; *Ger. Offen.*, 2.024,966 (1970); *Chem. Abstr.* 74, 53520 (1971).

2.Chowdhury MA, Huang Z, Abdellatif KR, et al.; "Synthesis and biological evaluation of indomethacin analogs possessing a N-difluoromethyl-1,2-dihydropyrid-2-one ring system: a search for novel cyclooxygenase and lipoxygenase inhibitors"; *Bioorg Med Chem Lett*; 20:5776–80(2010).

3.Bandgar BP, Sarangdhar RJ, Viswakarma S, Ahamed FA.; "Synthesis and biological evaluation of orally active prodrugs of indomethacin"; *J Med Chem;2011;*54:1191–201.

4.Kaur J, Bhardwaj A, Huang Z, Knaus EE.; "N-1 and C-3 substituted indole Schiff bases as selective COX-2 inhibitors: synthesis and biological evaluation"; *Bioorg Med Chem Lett*; 2012;22:2154–9.

5.Mohamed A. A., Radwan Eman A., Ragab Nermien M., Sabry Siham M., El-Shenawy, "Synthesis and biological evaluation of new 3-substituted indole derivatives as potential anti-inflammatory and analgesic agents"; *Bioorganic & Medicinal Chemistry*,2007;3832-3841.

6.Szmuszkovicz, J., Glenn, E.M., Heinzelman, R.V., Hester Jr., J.B. and Youngdale, G.A.; "Synthesis and antiinflammatroy activity of 2,3-bis(*p*-methoxyphenyl) indole and related compounds"; *J. Med. Chem.* 1966;9: 527.

7.Szmuszkovicz J.: "Antiinflammatory 5-alkanoy-2,3-bis (*p*-methoxyl phenyl) indoles"; *U.S.* 3,565,912 (1971);*Chem. Abstr.* 75, 35734 (1971).

8.Szmuszkovicz J.; "Antiinflammatory 2, 3-bis (*p*-methoxy phenyl) indole-5-carboxylic acid derivatives" *U.S.* 1972, 3,654,308; *Chem. Abstr.* 77, 34319 (1972).

9.Vijai Nath Pathak*, Ragini Gupta and Neetu Gupta; "Synthesis and biological evaluation of some new 4,5-dihydro-3-(2-aryl-indol-3-yl)-5-(4-chlorophenyl)-N^1-phenylpyrazoles"; *Journal of chemistry*,2008; 8: 106-109.

10.L. C. Heda, Rashmi Sharma, C. Pareek and P. B. Chaudhari; "Synthesis and Antimicrobial Activity of Some Derivatives of 5-Substituted Indole Dihydropyrimidines"; *E-Journal of Chemistry*,2009; 6(3): 770-774.

11.Dekker W.H., Selling H.A. and Overeem J.C.; "Structure activity relations of some antifungal indoles"; *J. Agric. Food Chem.,1975;* 23, 785.; *Chem. Abstr.* 83, 109650 (1975).

12.Hishmat, O.H., Abdel Rahman, A.H. and Nasef, A.M.M. et al; "Synthesis and antimicrobial activity of some indole derivatives", *Arch. Pharm. Res.*, 11, 266(1988).

13.Jaishree Badiger, Manjulatha K., Girish M., Adil Sharif and Purohit M. G., "Synthesis and biological evaluation of some N-substituted indole analogues"; *ARKIVOC* (xii) 217-231(2009).

14.Schoentjes, Bruno, Sophie Descamps, and Nathalie Claudie Isabelle Amblard; "Indole derivatives as anticancer agents." *U.S.* Patent No. 8,541,442. 24 Sep. (2013).

15.Weng JR, Tsai CH, Kulp SK and Chen CS; "Indole-3-carbinol as a chemopreventive and anti-cancer agent". *Cancer letters*, 262(2):153-63; (2008).

16.James L. Stanton and Michael H. Ackerman; "Synthesis and anticonvulsant activity of some tetracyclic indole derivatives"; *J. Med. Chem.*, 1983;*26* (7):986–989.

17.Huifang Chai, YanfangZhao, ChunshenZhao and PingGong; "Synthesis and in vitro anti-hepatitis B virus activities of some ethyl 6-bromo-5-hydroxy-1*H*-indole-3-carboxylates"; *Bioorganic & Medicinal Chemistry*,2006;14: 911-917.

18.Ahmed H. Abdelazeem, Ahmed M. Gouda, Hany A. Omar Mai F. Tolba; "Design, synthesis and biological evaluation of novel diphenylthiazole-based

cyclooxygenase inhibitors as potential anticancer agents"; *Bioorganic Chemistry*,2014; 132-141..
19.WenhuiHu, ZongruGuo, XiangYi, ChangbinGuo, FengmingChu and GuifangCheng; "Discovery of 2-Phenyl-3-sulfonylphenyl-indole derivatives as a new class of selective COX-2 inhibitors*"; Bioorganic & Medicinal Chemistry*;2003;11(24): 5539-5544.
20.Amit S.Kalgutkar, Brenda C. Crews, Sam Saleh, Daniel Prudhomme and Lawrence J. Marnett; "Indolyl esters and amides related to indomethacin are selective COX-2 inhibitors"; *Bioorganic & Medicinal Chemistry*, 2005;13(24):810-6822.
21.Smriti Khanna, ManjulaMadan, Akhila Vangoori, Rahul Banerjee, Ram Thaimattam, S.K.Jafar Sadik Basha, MullangiRamesh and Seshagiri RaoCasturi; "Evaluation of glycolamide esters of indomethacin as potential cyclooxygenase-2 (COX-2) inhibitors"; *Bioorganic & Medicinal Chemistry*, 2006; 14(14***):*** 4820-4833.
22.Khaled R. A. Abdellatif, Phoebe F. Lamie and Hany A. Omar; "3-Methyl-2-phenyl-1-substituted-indole derivatives as indomethacin analogs: design, synthesis and biological evaluation as potential anti-inflammatory and analgesic agents"; *Journal of Enzyme Inhibition and Medicinal Chemistry*, 2016; 31(2):318-324.
23.Practical Organic Chemistry, F. G. Mann, 86-88, 1960.
24.Younis Baqi, Samer Alshaibani, Kirsten Ritter, Aliaa Abdelrahman, Andreas Spinrath, Evi Kostenis and Christa E. Müller; "Improved synthesis of 4-/6-substituted 2-carboxy-1*H*-indole-3-propionic acid derivatives and structure-activity relationships as GPR17 agonists"; *Med. Chem. Commun.*, 5, 86-92 (2014).
25.Modi, Monarch, Perriello, Pohland, and Minard; "Fisher Indole Synthesis of 2-Phenylindole"; A.I. Vogel's Elementary Practical Organic Chemistry, (1966). Revised 4/9/01.
26.P. A. Janssen, C. J. E. Niemegeers, and J. G. H. Dony; "The inhibitory effect of fentanyl and other morphine-like analgesics on the warm water induced tail withdrawal reflex in rats"; *Arzneimittelforschung*, vol. 13, pp. 502–507(1963).
27.Yihui Chen, Masayuki Shibata, Manju Rajeswaran, Thamarapu Srikrishnan, Sundeep Dugar and Ravindra K. Pandey; "Utility of Japp–Klingemann reaction for the preparation of 5-carboxy-6-chloroindole via Fischer indole protocol"; *Tetrahedron Letters,2007;* 489(13):26,2353–2356.