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ORIGINAL RESEARCH ARTICLE

Synthesis and Characterization of Some Novel Alkyl-2n-butyl-[4'(2''-carboxyphenyl-1''-yl) benzyl] benzimidazole-5-sulphonates

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ABSTRACT

In the present studies, a series of Alkyl-2-n-butyl-1-[4'(2"- Carboxyphenyl-1"-yl) benzyl] benzimidazole-5-sulphonates were prepared. 2-Butyl benzimidazole was coupled with 4-Chloromethylbiphenyl-2'-carboxylic acid to form 2-Butyl-1- [(2'-carboxybiphenyl-4-yl) methyl] benzimidazole which on treatment with chlorosulphonic acid yield 2-n-Butyl-1-[4′ (2″-carboxybiphenyl-4-yl) methyl] benzimidazole-5-sulphonyl chloride. The latter on reaction with various aliphatic alcohols yield corresponding sulphonate derivatives. All the synthesized compounds were identified by IR, ^{1}H-NMR and MS.

Keywords: Benzimidazole, At-Ii Inhibitors, Sulphonyl Esters, Antihypertension

INTRODUCTION

Angiotensin-II plays an important role in Rennin-Angiotensin System [1]. It shows its action *via* AT_I and AT_{II}. The compounds which block AT_{II} receptors can be employed for the treatment of hypertension and Congestive Heart Failure [2]. Based on the literature survey, number of compounds has been reported showing antihypertensive activity [3-7]. There are varieties of potent AT_{II} antagonist available in market like Losartan [8-9] (**Fig 1**). A series of compounds have been designed and synthesized employing benzimidazole replacement for the imidazole ring in the lead compound losartan [10-12]. Keeping this in mind, new derivatives of benzimidazole have been synthesized exploring the substitution possibilities at its 5-position which can be instrumental in designing more potent and orally active AT-II antagonists.

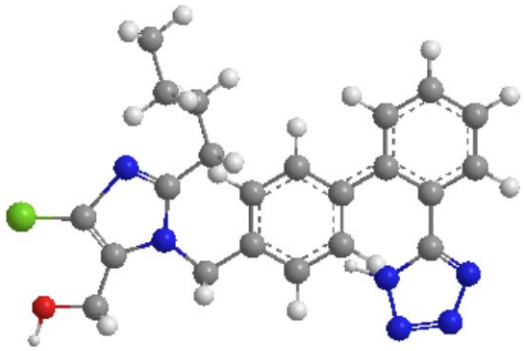

Fig 1 Losartan

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EXPERIMENTAL

All the chemicals and solvents used during the experimental studies were of analytical grade and procured form CDH, New Delhi and Sigma Chemicals, Mumbai. Melting points of all synthesized compounds were determined using open capillary tube and were uncorrected. IR data were recorded in KBr disks on Hitachi 270-30 infrared and Bruker Vector 22 spectrophotometer and H^1 NMR spectra on Bruker AC 30 of NMR spectrometer 400 MHz.Scheme shown in **Fig. 2, 3 & 4**

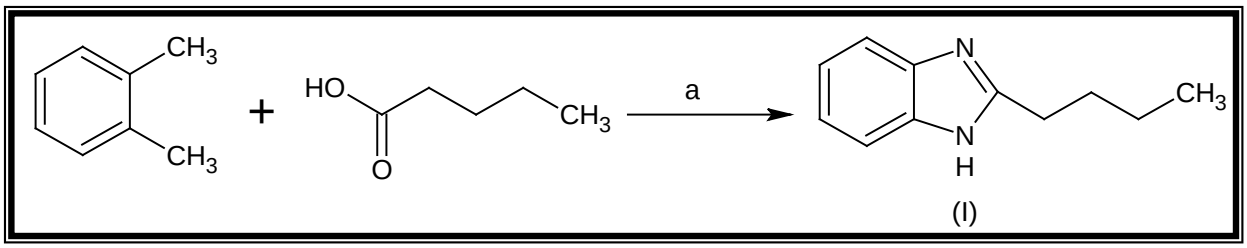

Fig. 2: Synthesis of the 2-Butyl benzimidazole; Reagents and Conditions: a). sodium hydroxide solution, 95% ethanol, H_2O, pH 7-8.

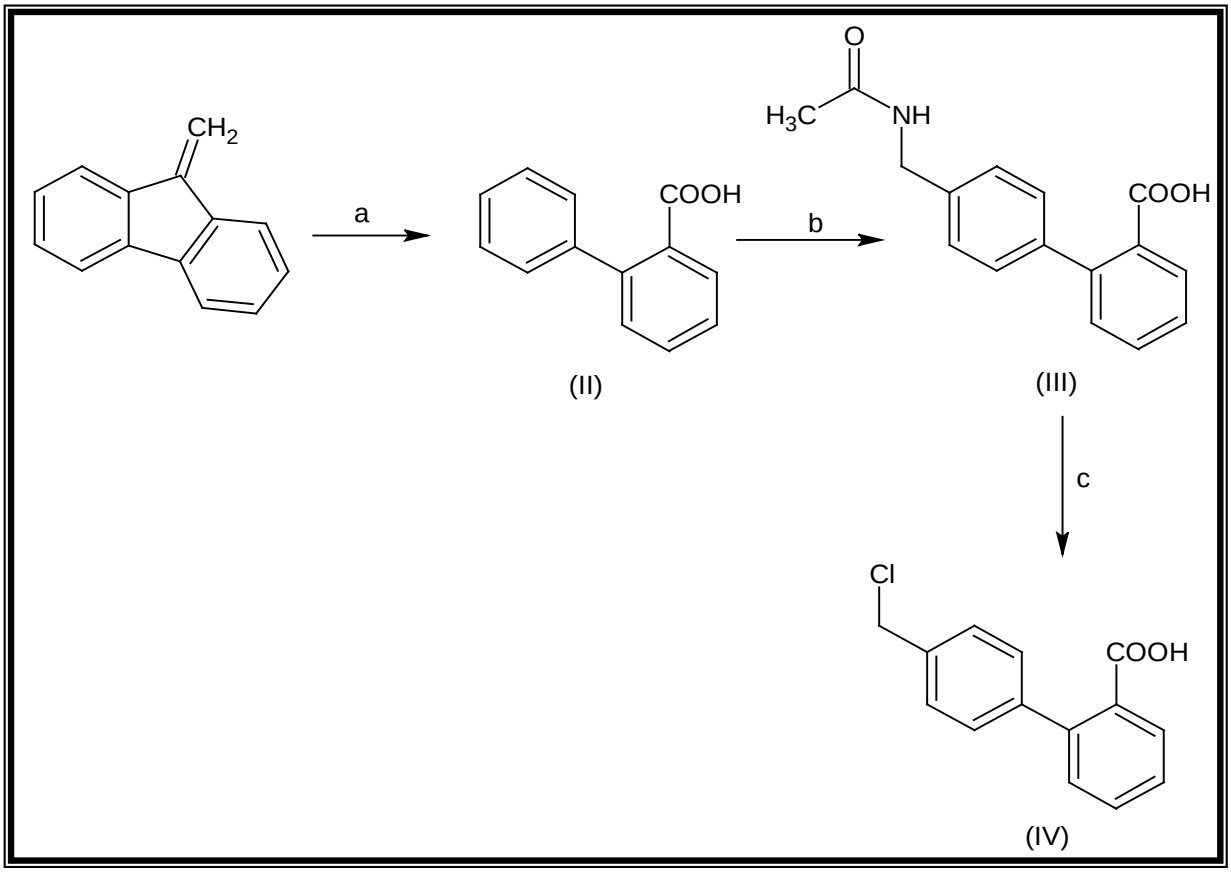

Fig. 3 Synthesis of 2-Carboxybiphenyl-4-yl methyl chloride; Reagents and Conditions: a). KOH, b). H_2SO_4, paraformaldehyde, acetamide, c). $POCl_3$, DMF/Xylene.

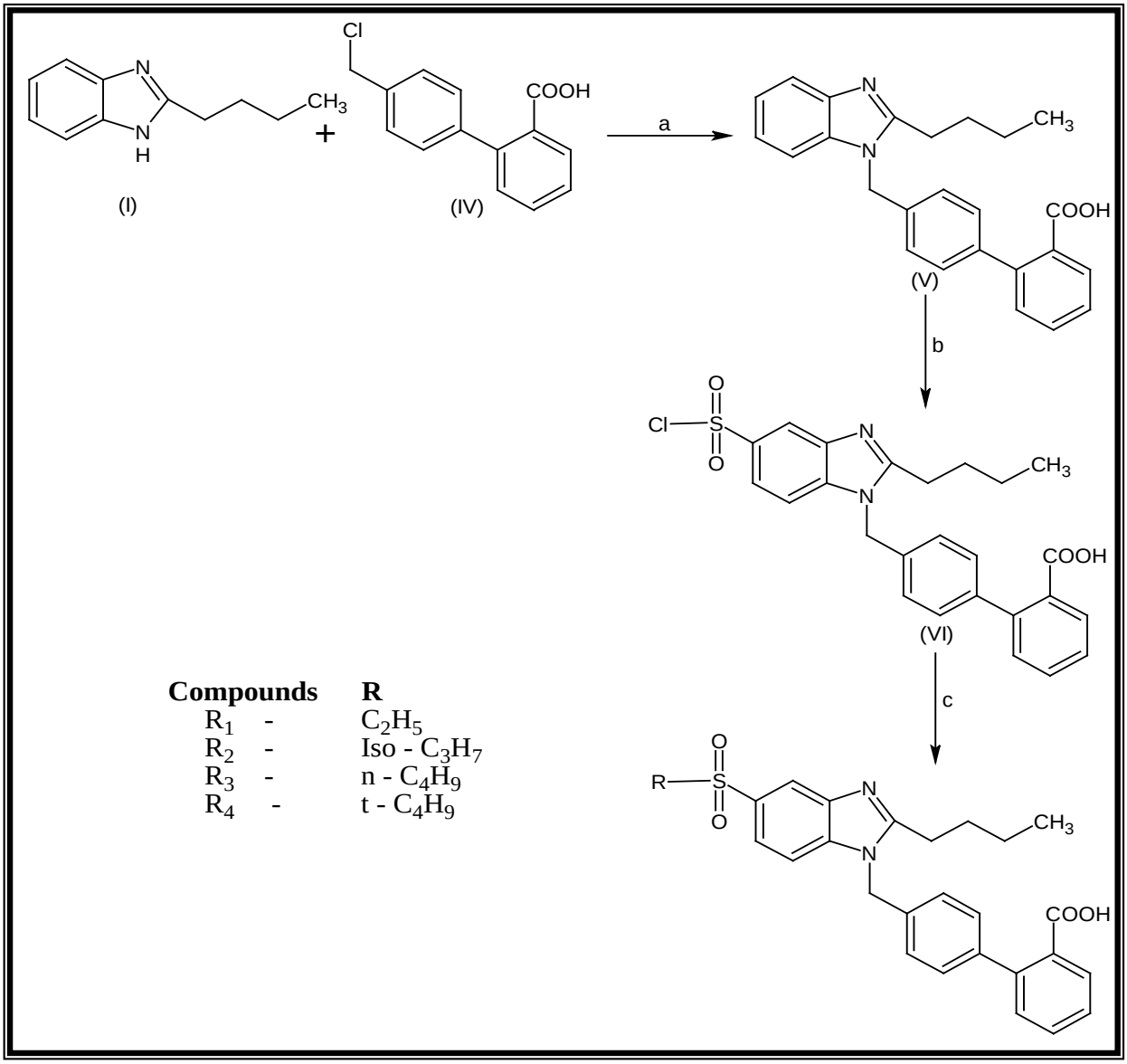

Fig. 4 Coupling of (I) and (II) and preparation of derivatives; Reagents and Conditions: a). dry pyridine b). Chlorosulphonic acid c). appropriate alcohols, conc. HCl, methanol and pyridine.

Chemistry

2-Butylbenzimidazole (I)

o-Phenylendiamine 2.16 g [0.02 mol] and pentanoic acid 3.2 g [0.04 mol] were placed in round bottom flask and refluxed for 7 hours. The reaction mixture was cooled and basified (pH 7-8) with 20% sodium hydroxide solution with continuous stirring. The crude product was dissolved in 95% ethanol and digested with activated charcoal for 45 minutes. Boiling water was then added to the filtrate till slight turbidity appeared. The solution was made clear by addition of few drops of ethanol and kept for recrystallization. The product was obtained as white, needle shaped crystals. IR: 3600-3200 (N-H stretch), 3100, 3050 (Aromatic C-H stretch), 2900, 2800 (Aliphatic C-H stretch), 1400 (C=C and C=N ring), 1240, 1220 (C – N), 880 (N-H). ^{1}H-NMR: 10.3 (s, 1H, NH), 7.5 -7.2 (m, 4H, Ar-H), 2.95 (t, 2H, CH_2, 1.84 (m, 2H, CH_2), 1.40 (m, 2H, CH_2), 0.88 (t, 3H, CH_3). MS: 174 Molecular ion peak $M^{\cdot +}$ 159 [M-

$^{\cdot}CH_3$], 132 [M- C_3H_6] 145 [M-$^{\cdot}CH_2$ CH_3], 92 [$^{+}$ C_6 H_5 NH2], 104 [m/z 132 – H, HCN], 77 [m/z 104 – HCN].

Biphenyl-2'-carboxylic acid (II)

Flourenone 10 g [0.055 mol], potassium hydroxide 26 g [0.46 mol] and boiling toluene were stirred under reflux for 4 hrs. After 4 hrs, the mixture was cooled, treated with water (100 ml) and filtered. Two layers (aqueous and organic) were separated. To the aqueous layer, concentrated hydrochloric acid was added slowly until the title compound gets precipitated. The product was recrystallized from carbon tetrachloride. However, since it gave a single spot in TLC, it could be taken as such in the next synthetic step. IR: 3600-2750 (O-H stretch), 3060, 3020 (Aromatic C-H), 1760 (C=O). ^{1}H-NMR: 11.5 (s,1H, COOH), 7.9-7.36 (m, 9H, Ar-H). MS: 198 M, 197 [M – ($^{\cdot}$H)]$^{+,}$ 181 [M – ($^{\cdot}$OH)]$^{+}$, 153 [m/z 181 – (CO)]$^{+}$, 152 [M –(H_2O, CO)]$^{\cdot +}$, ^{70} [(CH≡CCOOH)]$^{\cdot +}$.

4-Acetamidomethyl-biphenyl-2'-carboxylic acid (III)

2 g of [0.01 mol] of (**II)** was dissolved in 12.12 ml of concentrated sulfuric acid. 0.150g [0.005 mol] of paraformaldehyde was added in one portion and then 1.78g [0.03M) of acetamide was added in small portions. The solution was heated at 55°C along with stirring for 3 hours. The hot mixture was poured over ice-cold water. The resulting solid was filtered out. IR: 3610-2300(O-H and N-H), 3070 (Aromatic C-H), 2925 (Aliphatic C-H), 1713 (C=O), 1630 (C=C), 1611 (N-H bend), 1456 (C-N). ^{1}H-NMR: 10.5 (s, 1H, COOH), 7.78-7.30 (m, 8H, Ar-H), 5.1 (s, 1H, CONH), 4.33 (s, 2H, CH_2), 2.10 (s, 3H, CH_3). MS: 269 M, 198 [M – (H_2C=$NCOCH_3$)]$^{\cdot +}$, 197 [M – ($^{\cdot}CH_2NHCOCH_3$)]$^{+}$, 180 [M–(CH_3CHO, COOH)]$^{+}$, 153 [m/z 198 – ($^{\cdot}$COOH)]$^{+}$, 152 [m/z 198 – (H_2O, CO)]$^{\cdot +}$, 76 [C_6H_4]$^{\cdot +}$.

4-Chloromethylbiphenyl-2'-carboxylic acid (IV)

700 mg [0.0026 mol] of the (**III)**, 0.794 g ([0.063 mol] of phosphorous oxychloride, 2 ml [0.03 mol] of dimethylformamide and 2 ml of xylene were taken in a round bottom flask and refluxed for 7 hours. The solution was cooled, washed with water and evaporated to give a light yellow crystalline product. IR: 3407 (O-H stretch), 3037 (Aromatic C-H), 2875, 2800 (Aliphatic C-H), 1713 (C=O), 1603 (C=C), 1457 (CH_2), 1296 (C-O), 650 (Aliphatic C-Cl). ^{1}H-NMR: 10.5 (s,1H, COOH), 7.65-7.29 (m, 8H, Ar-H), 4.01 (s, 2H, CH_2). MS: 210 [M – (HCl)]$^{\cdot +}$, 209 [m/z 210 – ($^{\cdot}$H)]$^{+}$, 208 [m/z 210 – (H_2)]$^{\cdot +}$, 195 [m/z 197 – (H_2)]$^{+}$, 194 [M – (CH_3Cl, H_2)]$^{\cdot +}$, 182 [M – (HCOCl)]$^{\cdot +}$, 181 [m/z 182 – ($^{\cdot}$H)]$^{+}$, 180[m/z 182 – (H_2)]$^{\cdot +}$, 179 [M – ($^{\cdot}CH_2Cl$, H_2O)]$^{+}$, 178 [M – (CH_3Cl, H_2O)]$^{\cdot +}$, 165 [m/z 210 – ($^{\cdot}$COOH)]$^{+}$, 153 [m/z 197 – (CO_2)]$^{+}$, 151 [m/z 179 – (CO)]$^{+}$, 139 [m/z 210 – (C_2H_2, COOH)]$^{+}$, 126 [M – (C_6H_3COOH)]$^{\cdot +}$, 77 [m/z 126 – ($^{\cdot}CH_2Cl$)]$^{+}$.

2-Butyl-1- [(2'-carboxybiphenyl-4-yl) methyl] benzimidazole (V)

1g [0.004 mol] of **(I)**, 1g [0.005 mol] of (**IV)** and 6ml of pyridine (previously dried over potassium hydroxide pellets) were taken in a round bottom flask fitted with a reflux condenser. The mixture was refluxed for 1 hour. The solution was kept to achieve room temperature (20^{o}C). Then it was poured dropwise with constant stirring into 200 ml of ice-cold water resulting in brick red precipitates. The product was filtered at vacuum pump to afford the product as brick red crystalline powder. IR: 3600 – 2500(O-H), 3054(Aromatic C-H), 2924, 2859(Aliphatic C-H), 1710(C=O), 1642(C=N), 1604, 1452(Aromatic C=C), 1425(COOH), 1295(C-N). ^{1}H-NMR: 7.76-7.26 (m, 12H, Ar-H), 5.1 (s, 1H, COOH), 4.0 (s, 2H, CH_2), 2.95 (t, 2H, CH_2), 1.84 (m, 2H,

CH_2), 1.40 (m, 2H, CH_2), 0.88 (t, 3H, CH_3). MS: 235 $[M - (HCl)]^{\cdot +}$, 209 [m/z 210 – $(^{\cdot}H)]^{+}$, 208 [m/z 210 – $(H_2)]^{\cdot +}$, 19 [m/z 197 – $(H_2)]^{+}$, 194 $[M - (CH_3Cl, H_2)]^{\cdot +}$, 182 $[M - (HCOCl)]^{\cdot +}$, 181[m/z 182 – $(^{\cdot}H)]^{+}$, 180[m/z 182 – $(H_2)]^{\cdot +}$, 179 $[M - (^{\cdot}CH_2Cl, H_2O)]^{+}$, 178 $[M - (CH_3Cl, H_2O)]^{\cdot +}$, 165 [m/z 210 – $(^{\cdot}COOH)]^{+}$, 153 [m/z 197 – $(CO_2)]^{+}$, 151 [m/z 179 – $(CO)]^{+}$, 139 [m/z 210 – $(C_2H_2, COOH)]^{+}$, 126 $[M - (C_6H_3COOH)]^{\cdot +}$, 77 [m/z 126 – $(^{\cdot}CH_2Cl)]^{+}$.

2-n-Butyl-1-[4' (2''-carboxybiphenyl-4-yl) methyl] benzimidazole-5-sulfonyl chloride (VI)

1.2 ml [0.018 mol] chlorosulphonic acid was cooled to 10–15°C in a dry two necked 100 ml round bottom flask. 1g of **(V)** [0.0026 mol] was added with continuous stirring over a period of half an hour. Stirring was further continued for 3.5 hour maintaining the temperature at 10-15°C. Formation of sulphonyl chloride derivative was ascertained by TLC data. IR: 3545 – 2525 (O-H), 3039(Aromatic C-H), 2922, 2840 (Aliphatic C-H), 1735 (C=O), 1645 (C=N), 1601, 1435 (Aromatic C=C), 1420 (COOH), 1285 (C-N). ^{1}H-NMR: 7.72-7.21 (m, 12H, Ar-H), 5.3 (s, 1H, COOH), 4.1 (s, 2H, CH_2), 2.89 (t, 2H, CH_2), 1.81 (m, 2H, CH_2), 1.42 (m, 2H, CH_2), 0.82 (t, 3H, CH_3). MS: 325 $[M-(C_6H_{12}O_2)]^{\cdot +}$, 180 $[M- (C_{14}H_{20}N_2SO_4)]^{\cdot +}$, 165 [m/z 372 – $C_8H_6N_2SO_3)]^{\cdot +}$, 152 [m/z 180 – $(CO)]^{\cdot +}$, 132 $[M - (C_{20}H_{26}SO_3)]^{+}$, 126 [m/z 152 – $(C_2H_2)]^{\cdot +}$, 64 $[M - (C_{26}H_{28}O_3N_2)]^{\cdot +}$, 48 $[M - (C_{25}H_{24}O_3N_2)]^{\cdot +}$.

Ethyl-2-n-butyl-1 [4 -(2''-carboxyphenyl-1-yl) benzyl] benzimidazole- 5-sulfonate (R1)

4 ml ethanol [0.06 mol] in 9.6 [0.12 mol] of dry pyridine was placed in a round bottomed flask. The mixture was cooled to 10°C and then 1 ml of **(VI)** [0.27 mol] was added in portions during 20 minutes. The mixture was stirred for 3 hrs at a temperature below 20°C. After 3 hrs, concentrated hydrochloric acid (5 ml) in ice cold water was added to mixture. The ester formed was collected on chilled Buchner funnel. To the collected ester 15 ml methanol was added and the mixture was heated on steam bath until the ester melted. Then the solution was cooled and stirred vigorously. The ester was separated in finely divided state. Then the product was filtered. IR: 3600-2800(O-H), 3050(Aromatic C-H), 2917(Aliphatic C-H), 1711(C=O), 1607, 1458 (Aromatic C=C), 1369 (S=O), 1292(C-O), 1178 (S=O). ^{1}H-NMR: 8.1 (s,1H, COOH), 7.75-7.26 (m,11H, Ar-H), 4.05 (d, 2H, CH_2), 3.2 (m, 2H, CH_2), 2.89-1.44 (m, 2H, CH_2), 1.24-0.98 (t, 2H, CH_3). MS: 372 $[M- (C_6H_{12}O_2)]^{\cdot +}$, 180 $[M-(C_{14}H_{20}N_2SO_4)]^{\cdot +}$, 165 [m/z 372 – $C_8H_6N_2SO_3)]^{\cdot +}$, 152 [m/z 180 – $(CO)]^{\cdot +}$, 132 $[M - (C_{20}H_{26}SO_3)]^{+}$, 126 [m/z 152 – $(C_2H_2)]^{\cdot +}$, 64$[M - (C_{26}H_{28}O_3N_2)]^{\cdot +}$, 48$[M - (C_{25}H_{24}O_3N_2)]^{\cdot +}$.

Isopropyl-2-n-butyl-1 [4'-(2''-carboxyphenyl-1-yl) benzyl] benzimidazole-5-sulphonate (R2)

4 ml isopropyl alcohol [0.05 mol] in 8.49 [0.10 mol] of dry pyridine was placed in a round bottomed flask. The mixture was cooled to 10°C and then 1 ml of **(VI)** [0.27 mol] was added in portions during 20 minutes. The mixture was stirred for 3 hrs at a temperature below 20°C.After 3 hrs; concentrated hydrochloric acid (5 ml) in ice-cold water was added to mixture. The ester formed was collected on chilled buchner funnel. To the collected ester 15 ml methanol was added and the mixture was heated on steam bath until the ester melted. Then the solution was cooled and stirred vigorously. The ester was separated in finely divided state. Then the product was filtered. IR: 3600 – 2800(O-H), 3061(Aromatic C-H), 2918(Aliphatic C-H), 1711(C=O), 1640(C-N), 1607, 1454(Aromatic C=C), 1382, 1365 (C-H), 1370(S=O), 1293(C-O). ^{1}H-NMR: 8.0-7.81 (m, 1H, COOH), 7.75-7.31 (m, 11H, Ar-

H), 4.0 (d, 2H, CH_2), 4.7 (m, 1H, CH), 3.18-1.44 (m, 6H, CH_2), 1.4-0.97 (m, 9H, CH_3). MS: 372 [M- $(C_7H_{14}O_2)]^{\cdot +}$, 180 [M-$(C_{15}H_{22}N_2SO_4)]^{\cdot +}$, 166 [M-$(C_6H_{26}N_2SO_5)]^{\cdot +}$, 152 [m/z 180 – (CO)]$^{\cdot +}$, 146 [M – $(C_{18}H_{23}N_2SO_3)]^{+}$, 145 [m/z 146 – $(H^{\bullet})]^{+}$, 132 [M - $(C_{20}H_{27}N_2SO_4)]^{\cdot +}$, 64 [M - $(C_{27}H_{30}N_2O_3)]^{\cdot +}$, 48 [M - $(C_{26}H_{26}N_2O_5)]^{\cdot +}$.

Butyl 2-n-butyl-1 [4 -(2''-carboxyphenyl-1-yl) benzyl] benzimidazole-5-sulphonate (R3)

4 ml n-butyl alcohol [0.04 mol] in 6.3ml [0.08 mol) of dry pyridine was placed in a round bottomed flask. The mixture was cooled to 10°C and then 1 ml of **(VI)** [0.27 mol] was added in portions during 20 minutes. The mixture was stirred for 3 hrs at a temperature below 20°C. After 3 hrs, concentrated hydrochloric acid (5 ml) in ice cold water was added to mixture. The ester formed was collected on chilled Buchner funnel. To the collected ester 15ml methanol was added and the mixture was heated on steam bath until the ester melted. Then the solution was cooled and stirred vigorously. The ester was separated in finely divided state. Then the product was filtered. IR: 3600 – 2800(O-H), 3061(Aromatic C-H), 2928(Aliphatic C-H), 1710(C=O), 1606, 1462(Aromatic C=C), 1375(S=O), 1289(C-O). ^{1}H-NMR: 8.06 (m, 1H, COOH), 7.76-7.29 (m, 11H, Ar-H), 4.33-1.41 (m, 14H, CH_2), 0.98-0.90 (t, 6H, CH_3). MS: 210 [M-$(C_{20}H_{27}O_2)]^{\cdot +}$, 180 [M-$(C_{16}H_{24}N_2SO_4)]^{\cdot +}$, 132 [M- $(C_{21}H_{29}N_2SO_4)]^{\cdot +}$, 111 [M-$(C_{22}H_{21}SO_5)]^{\cdot +}$, 64 [M – $(C_{28}H_{32}N_2O_3)]^{+}$, 56 [M- $(C_{24}H_{28}N_2SO_5)]^{+}$.

t-Butyl 2-n-butyl-1[4'-(2''-carboxyphenyl-1-yl)benzyl]benzimidazole-5-sulfonate (R4)

4 ml t-butyl alcohol [0.04 mol] in 6.3ml [0.08 mol] of dry pyridine was placed in a round bottomed flask. The mixture was cooled to 10°C and then 1 ml of **(VI)** [0.27 mol] was added in portions during 20 minutes. The mixture was stirred for 3 hrs at a temperature below 20°C. After 3 hrs, concentrated hydrochloric acid (5 ml) in ice-cold water was added to mixture. The ester formed was collected on chilled Buchner funnel. To the collected ester 15ml methanol was added and the mixture was heated on steam bath until the ester melted. Then the solution was cooled and stirred vigorously. The ester was separated in finely divided state. Then the product was filtered. IR: 3600 – 2800(O-H and N-H), 3090(Aromatic C-H), 2955(Aliphatic C-H), 1711(C=O), 1607, 1465(Aromatic C=C), 1369 (S=O), 1288(C-O). ^{1}H-NMR: 8.14 (m, 3H, COOH) 7.93-7.28(m, 11H, Ar-H), 4.02-1.95 (m, 6H, CH_2), 1.5 (m, 9H, CH_3), 1.43 (m, 2H, CH_2), 0.96 (t, 3H, CH_3). MS: 209 [M $(C_{14}H_{23}N_2SO_3)]^{\cdot +}$, 180 [M-$(C_{16}H_{24}N_2SO_4)]^{\cdot +}$, 152 [m/z 180 – (CO)]$^{\cdot +}$, 111[M – $(C_{22}H_{21}SO_5)]^{\cdot +}$, 64 [M - $(C_{28}H_{32}N_2O_3)]^{\cdot +}$, 48 [M - $(C_{27}H_{28}N_2O_5)]^{\cdot +}$.

Table: 1 Physical data of the compounds synthesized

Comp.	Mol. Formula	Mol Wt	M.P. (^{o}C)	% Yield
I	$C_{11}H_{14}N_2$	174	160	66%
II	$C_{13}H_{10}O_2$	198	110	81%
III	$C_{16}H_{15}NO_3$	269	147	56%
IV	$C_{14}H_{11}ClO_2$	247	128	48%
V	$C_{25}H_{24}N_2O_2$	384	135	63%
VI	$C_{25}H_{23}ClN_2O_4S$	483	190	55%
R1	$C_{27}H_{30}N_2O_5S$	490	202	58%
R2	$C_{29}H_{32}N_2O_5S$	504	235	52%
R3	$C_{31}H_{32}N_2O_5S$	530	250	48%
R4	$C_{31}H_{32}N_2O_5S$	530	272	43%

RESULTS AND DISCUSSIONS

The efficient synthetic route for the synthesis of benzimidazole derivatives was shown in Fig 3 to Fig 5. *o*-Phenylenediamine and pentanoic acid were refluxed for 7 hrs to yield 2- Butyl benzimidazole **(I).** Flourenone

was treated with KOH to yield Biphenyl-2'-carboxylic acid **(II)** which in the presence of paraformaldehyde and acetamide yield 4-Acetamidomethyl-biphenyl-2'-carboxylic acid **(III)**. The compound **(III)** on reaction with $POCl_3$/X xylene produces 4-Chloromethylbiphenyl-2'-carboxylic acid **(IV).** The **(I)** was coupled with **(IV)** to form 2-Butyl-1- [(2'-carboxybiphenyl-4-yl) methyl] benzimidazole **(V)** which on treatment with chlorosulphonic acid yield 2-n-Butyl-1-[4′ (2″-carboxybiphenyl-4-yl) methyl] benzimidazole-5-sulphonyl chloride **(VI)**. The latter on reaction with various aliphatic alcohols yield corresponding sulphonate derivatives **(R1-R4)**. The structures of the compounds **(R1-R4)** were determined by using spectroscopic methods including IR and ^{1}H-NMR and MS. These derivatives would be evaluated for antihypertensive activity. Further 5, 6-disubstituted benzimidazole compounds can also be synthesized which may be more potent than the current AT-II inhibitors. In conclusion Alkyl-2n-butyl-[4'(2"-carboxyphenyl-1"-yl) benzyl] benzimidazole-5-sulphonates may be potential AT-II receptor antagonist.

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