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Synthesis and Evaluation of Antipsychotic and Anticonvulsant Activity of Indol-5-YL and Benzoxazepin-4-YL Carbazoles

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Abstract : Various1-(substituted indolylidenylchalconyl) carbazole**(2a-2b)**, 1-[2'-(5''-substituted indolyl)-1' , 5'-benzoxazepinyl]-carbazoles**(3a-3b)** and 1-[2'-(5''-substituted indolyl)-3'-(2'''-substitutedphenyl amino)-methyl-1', 5'-benzoxazepinyl]-carbazoles**(4a-4n)** have been synthesized according to scheme -1. These compounds were screened for antipsychotic and anticonvulsant activity as well as for acute toxicity. Compound **4d**I.E. 1-[2'-(5''-methoxy indolyl)-3'-(2''',3'''- dichlorophenyl amino)-methyl-1', 5'-benzoxazepinyl]-carbazoles showed most promising antipsyctotic and anticonvulsant activity with ALD_{50}greaterthan 2000 mg/kg i.p. The structures of all the newly synthesized compounds were confirmed by elemental (C, H, N) and spectral (IR, ^{1}H-NMR and mass) analysis.

Keywords: Indol-5-yl benzoxazepin-4-yl carbazoles, Antipsychotic activity, anticonvulsant activity, acute toxicity.

1.Introduction

Carbazole is an aromatic heterocyclic organic compound, having tricyclic structure, consisting of two six-membered benzene rings fused on either side of a five membered nitrogen containing ring. Carbazole derivatives attracted researchers due to their therapeutic potential against neurological disorders. Survey of literature shows that various biological activities like antipsychotic[1-2], anticonvulsant [3-4], anti-inflammatory [5], antimicrobial [6-7], antibacterial [8-10], anticancer [11-12] are associated with carbazole. It was also noted from chemical literature that various derivatives of indole [13-14] and benzoxazepine[15-16] were also found to possess antipsychotic as well as anticonvlsant activity. On the basis of above discussion it was thought to synthesize some new derivatives with antipsychotic activity by incorporating three heterocyclic nuclei – carbazole, indole and benzoxazepine into a single molecular framework, with the hope to get potent and safer antipsychotic agents.

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2. Experimental

2.1 Materials and method

Open capillaries were used to determine the melting points of the compounds and were uncorrected. Thin layer chromatography on silica gel-G plates were used to routinely check the homogeneity of the newly synthesized compounds. Mixture of polar and non-polar solvent in different proportions was used as eluent . Iodine was used to locate the spots. The IR spectra were recorded on Bruker IFS-66VFT-IR (ν_{max}in cm^{-1}). The ^{1}H-NMR spectra were recorded by Bruker DRX-400 FT-NMR instrument using $CDCl_3$ as solvent and tetramethylsilane (TMS) as internal reference standard.

2.2.Chemistry

The synthetic route of the compounds are outlined in series-1. Carbazole was reacted with acetyl chloride in methanol to give (1). Compound 1 on reaction with 5-asubstituted indole aldehydes yielded i.i.2a-2b which on cyclization with 2-aminophenol in presence of few drops of glacial acetic acid gave (3a-3b). Compounds 3a-3b underwent Mannich reaction with various substituted anilines and formaldehyde to furnish (4a-4n).

2.2.1. General procedure for the synthesis of N-acetyl carbazole(1a)

To a solution ofcarbazole (1.5 mole) in dry chloroform (150ml), acetyl chloride (1.5 mole)was slowly added drop by drop with constant stirring at 0-5^{0}C. The reaction mixture was further stirred on magnetic stirrer for 10 hours at room temperature and was kept overnight. The excess of solvent was distilled off with the help of distillation assembly and the residue thus obtained was washed with petroleum ether 40-60^0 a number of times and then it was poured onto ice. The solid thus obtained was filtered with the help of a filteration pump and recrystallized from ethanol to give compound 1a.

*N^9-Acetyl carbazole**(1a)***

Yield 87% (ethanol) ;m.p. 142^{0}C ; IR (KBr) ν_{max} in cm^{-1} : 1720 (C=O), 1610 (C-C of aromatic ring), 1450 (N-CH_2). ^{1}H-NMR ($CDCl_3$) δ in ppm : 2.50 (s, 3H, $COCH_3$), 7.10-6.20 (m, 8H,Ar-H). Anal.Calcd.for $C_{14}H_{11}NO$: C, 80.38 ; H, 5.26; N, 6.69; Found : C, 80.40; H, 5.25; N, 6.71%: $[M]^+$ at m/z 209.

*2.2.2. General procedure for the synthesis of 1-(substituted indolylidenylchalconyl) carbazole **(2a-2b)***

To a solution of N^9-acetyl carbazole (0.5 mole) in absolute alcohol containing 2% NaOH, various substituted indol-3-aldehyde (0.5 mole) were added and refluxed for 8-12 hours. After refluxing, mixtures were concentrated, cooled and poured onto ice. The solids thus obtained were filtered using filterationobtain compound 2a-2.

*2.2.2.1. 1-(5-Methoxy indolylidenylchalconyl) carbazole**(2a)***

Yield 82% (methanol) ;m.p. 130^{0}C ; IR (KBr) ν_{max} in cm^{-1} : 1680 (C=O), 3343 (NH), 1616 (C-C of aromatic ring), 1570 (COCH=CH). ^{1}H-NMR ($CDCl_3$) δ in ppm : 3.52 (s, 3H, OCH_3) 6.60 (d, 1H, COCH), 6.65 (d, 1H, *J*CH=CH),6.25-7.88 (m, 11H,Ar-H), 9.80 (brs, 1H, NH of indole exchangeable). Anal.Calcd. for $C_{24}H_{18}N_2O_2$: C, 78.68 ; H, 4.91; N. 7.92; Found C, 78.70; H, 4.89; N, 7.90%: $[M]^+$ at m/z 366.

*2.2.2.2. 1-(5-Ethoxy indolylidenylchalconyl) carbazole**(2b)***

Yield 80% (ethanol) ;m.p. 140^{0}C ; IR (KBr) ν_{max} in cm^{-1} : 1682 (C=O), 3340 (NH), 1610 (C-C of aromatic ring), 1575 (COCH=CH). ^{1}H-NMR ($CDCl_3$) δ in ppm : 3.20 (t, 3H, CH_2CH_3), 3.60 (q, 2H, CH_2CH_3), 6.63 (d, 1H, COCH), 6.61 (d, 1H, *J*CH=CH),6.20-7.85 (m, 11H,Ar-H), 9.83 (brs, 1H, NH of indole exchangeable). Anal.Calcd.for $C_{25}H_{20}N_2O_2$: C, 78.94 ; H, 5.26; N, 7.36; Found : C, 78.95; H, 5.24; N, 7.37%: $[M]^+$ at m/z 380.

*2.2.3. General procedure for the synthesis of 1-[2$^{'}$-(5$^{''}$-substituted indolyl)-1$^{'}$, 5$^{'}$-benzoxazepinyl]-carbazoles**(3a-3b)***

An equimolar mixture (o.2 mole) of ethanolic solutions of compounds 2a-2 and 2-aminophenol (0.2 mole) was refluxed for 3-4 hours in presence of glacial acetic acid. Completion of the reaction was monitored by TLC.

Excess of solvent was distilled offunder reduced pressure and the solid thus obtained was recrystallized by suitable solvents to give compounds 3a-3.

*2.2.3.1. 1-[2'-(5''-Methoxy indolyl)-1', 5'-benzoxazepinyl]-carbazoles**(3a)***

Yield 72% (methanol) ;m.p. 145^{0}C ; IR (KBr) ν_{max} in cm^{-1} : 3340 (NH), 1612 (C-C of aromatic ring),1582 (C=N), 1070 (C-O-C). ^{1}H-NMR ($CDCl_3$) δ in ppm :3.56 (s, 3H, OCH_3),4.25 (t, 1H, C_2- H of oxazepine ring), 3.25 (d, 2H, C_3 -H_2 of oxazepine ring),6.90-7.88 (m, 15H,Ar-H), 9.84 (brs, 1H, NH of indole exchangeable). Anal.Calcd.for $C_{30}H_{23}N_3O_2$: C, 78.77; H, 5.03; N, 9.19; Found :C, 78.79; H, 5.01; N, 9.20%: $[M]^+$ at m/z 457.

*2.2.3.2. 1-[2'-(5''-Ethoxy indolyl)-1', 5'-benzoxazepinyl]-carbazoles**(3b)***

Yield 70% (methanol) ;m.p. 142^{0}C ; IR (KBr) ν_{max} in cm^{-1} : 3346 (NH), 1615 (C-C of aromatic ring),1580 (C=N), 1074 (C-O-C). ^{1}H-NMR ($CDCl_3$) δ in ppm :2.58 (t, 3H, CH_2CH_3), 3.45 (q, 2H, CH_2CH_3), 4.30 (t, 1H, C_2- H of oxazepine ring), 3.30 (d, 2H, C_3 -H_2 of oxazepine ring),6.80-7.81 (m, 15H,Ar-H), 9.83 (brs, 1H, NH of indole exchangeable). Anal.Calcd.for $C_{31}H_{25}N_3O_2$: C, 78.98; H, 5.30; N, 8.91; Found : C, 79.00; H, 5.29; N, 8.89%: $[M]^+$ at m/z 471.

*2.2.4. General procedure for the synthesis of 1-[2'-(5''-substitutedindolyl)-3'-(2'''-substitutedphenyl amino)-methyl-1', 5'-benzoxazepinyl]-carbazoles**(4a-4n)***

To the solution of compounds 3a-3 (0.1 mole) in methanol, different aromatic anilines (0.1 mole) and formaldehyde (0.1 mole) were added. The mixtures were refluxed gor 4-6 hours. The resulting mixtures were concentrated, cooled and poured onto ice. Separated solids were filtered and recrystallized from appropriate solvents to yield compounds 4a-4.

2.2.4.1. 1-[2'-(5''-Methoxy indolyl)-3'-(aminophenyl)-methyl-1', 5'-benzoxazepinyl]-carbazoles (4a)

Yield 70% (acetone) ;m.p. 135^{0}C ; IR (KBr) ν_{max} in cm^{-1} : 3338 (NH), 1620 (C-C of aromatic ring),1580 (C=N), 1040 (C-O-C). ^{1}H-NMR ($CDCl_3$) δ in ppm : 3.11 (t, 2H, CH_2NH),3.53 (s, 3H, OCH_3),4.22 (t, 1H, C_2- H of oxazepine ring), 3.21 (d, 2H, C_3 -H_2 of oxazepine ring),6.50 (brs, 1H, NH), 6.82-7.85 (m, 21H,Ar-H), 9.84 (brs, 1H, NH of indole exchangeable). Anal.Calcd.for $C_{37}H_{31}N_3O_2$: C, 80.87; H, 5.64; N, 7.65; Found : C, 80.90; H, 5.66; N, 7.67%: $[M]^+$ at m/z 549.

2.2.4.2. 1-[2'-(5''-Methoxy indolyl)-3'-(2'''-chlorophenyl amino)-methyl-1', 5'-benzoxazepinyl]-carbazoles (4b)

Yield 70% (acetone) ;m.p. 135^{0}C ; IR (KBr) ν_{max} in cm^{-1} : 3336 (NH), 1622 (C-C of aromatic ring),1583 (C=N), 1039 (C-O-C), 682 (C-Cl). ^{1}H-NMR ($CDCl_3$) δ in ppm : 3.10 (t, 2H, CH_2NH), 3.51 (s, 3H, OCH_3),4.20 (t, 1H, C_2- H of oxazepine ring), 3.23 (d, 2H, C_3 -H_2 of oxazepine ring),6.52 (brs, 1H, NH), 6.85-7.90 (m, 20H,Ar-H), 9.80 (brs, 1H, NH of indole exchangeable). Anal.Calcd.for $C_{37}H_{30}N_3O_2Cl$: C, 76.09; H, 5.14; N, 7.19; Found : C, 76.07; H, 5.12; N, 7.21%: $[M]^+$ at m/z 583.5.

*2.2.4.3. 1-[2'-(5''-Methoxy indolyl)-3'-(3'''-chlorophenyl amino)-methyl-1', 5'-benzoxazepinyl]-carbazoles**(4c)***

Yield 72% (DMF-Water) ;m.p. 145^{0}C ; IR (KBr) ν_{max} in cm^{-1} : 3334 (NH), 1626 (C-C of aromatic ring),1585 (C=N), 1040 (C-O-C), 680 (C-Cl). ^{1}H-NMR ($CDCl_3$) δ in ppm : 3.11 (t, 2H, CH_2NH), 3.49 (s, 3H, OCH_3),4.19 (t, 1H, C_2- H of oxazepine ring), 3.22 (d, 2H, C_3 -H_2 of oxazepine ring),6.50 (brs, 1H, NH), 6.81-7.85 (m, 20H,Ar-H), 9.82 (brs, 1H, NH of indole exchangeable). Anal.Calcd.for $C_{37}H_{30}N_3O_2Cl$: C, 76.09; H, 5.14; N, 7.19; Found : C, 76.10; H, 5.15; N, 7.18%: $[M]^+$ at m/z 583.5.

*2.2.4.4. 1-[2'-(5''-Methoxy indolyl)-3'-(2''',3'''- dichlorophenyl amino)-methyl-1', 5'-benzoxazepinyl]-carbazoles**(4d)***

Yield 72% (Methanol) ;m.p. 148^{0}C ; IR (KBr) ν_{max} in cm^{-1} : 3333 (NH), 1624 (C-C of aromatic ring),1583 (C=N), 1042 (C-O-C), 686 (C-Cl). ^{1}H-NMR ($CDCl_3$) δ in ppm : 3.13 (t, 2H, CH_2NH), 3.50 (s, 3H, OCH_3),4.22 (t, 1H, C_2- H of oxazepine ring), 3.20 (d, 2H, C_3 -H_2 of oxazepine ring),6.48 (brs, 1H, NH), 6.75-7.90 (m, 19H,Ar-H), 9.84 (brs, 1H, NH of indole exchangeable). Anal.Calcd.for $C_{37}H_{29}N_3O_2Cl_2$: C, 71.80; H, 4.69; N, 6.79; Found : C, 71.78; H, 4.70; N, 6.81%: $[M]^+$ at m/z 618.

*2.2.4.5. 1-[2'-(5''-Methoxy indolyl)-3'-(2'''-bromophenyl amino)-methyl-1', 5'-benzoxazepinyl]-carbazoles **(4e)***

Yield 75% (Petroleum ether) ;m.p. 138^{0}C ; IR (KBr) ν_{max} in cm^{-1} : 3335 (NH), 1624 (C-C of aromatic ring),1585 (C=N), 1041 (C-O-C), 612 (C-Br). ^{1}H-NMR ($CDCl_3$) δ in ppm : 3.09 (t, 2H, CH_2NH), 3.53 (s, 3H, OCH_3),4.22 (t, 1H, C_2- H of oxazepine ring), 3.21 (d, 2H, C_3 -H_2 of oxazepine ring),6.54 (brs, 1H, NH), 6.82-7.95 (m, 19H,Ar-H), 9.78 (brs, 1H, NH of indole exchangeable). Anal.Calcd.for $C_{37}H_{30}N_3O_2Cl$: C, 70.70; H, 4.77; N, 6.68; Found : C, 70.67; H, 4.80; N, 6.71%: $[M]^+$ at m/z 628.

*2.2.4.6. 1-[2'-(5''-Methoxy indolyl)-3'-(3'''-bromophenyl amino)-methyl-1', 5'-benzoxazepinyl]-carbazoles **(4f)***

Yield 69% (Acetone) ;m.p. 136^{0}C ; IR (KBr) ν_{max} in cm^{-1} : 3337 (NH), 1621 (C-C of aromatic ring),1583 (C=N), 1043 (C-O-C), 614 (C-Br). ^{1}H-NMR ($CDCl_3$) δ in ppm : 3.07 (t, 2H, CH_2NH), 3.55 (s, 3H, OCH_3),4.20 (t, 1H, C_2- H of oxazepine ring), 3.19 (d, 2H, C_3 -H_2 of oxazepine ring),6.56 (brs, 1H, NH), 6.80-7.90 (m, 19H,Ar-H), 9.77 (brs, 1H, NH of indole exchangeable). Anal.Calcd.for $C_{37}H_{30}N_3O_2Cl$: C, 70.70; H, 4.77; N, 6.68; Found : C, 70.68; H, 4.75; N, 6.70%: $[M]^+$ at m/z 628.

*2.2.4.7. 1-[2'-(5''-Methoxy indolyl)-3'-(2''',3'''- dibromophenyl amino)-methyl-1', 5'-benzoxazepinyl]-carbazoles**(4g)***

Yield 69% (Acetone) ;m.p. 136^{0}C ; IR (KBr) ν_{max} in cm^{-1} : 3334 (NH), 1624 (C-C of aromatic ring),1581 (C=N), 1044 (C-O-C), 616 (C-Br). ^{1}H-NMR ($CDCl_3$) δ in ppm : 3.08 (t, 2H, CH_2NH), 3.53 (s, 3H, OCH_3),4.23 (t, 1H, C_2- H of oxazepine ring), 3.21 (d, 2H, C_3 -H_2 of oxazepine ring),6.57 (brs, 1H, NH), 6.75-7.92 (m, 19H,Ar-H), 9.79 (brs, 1H, NH of indole exchangeable). Anal.Calcd.for $C_{37}H_{29}N_3O_2Br_2$: C, 62.80; H, 4.10; N, 5.94; Found : C, 62.78; H, 4.08; N, 5.93%: $[M]^+$ at m/z 707.

*2.2.4.8. 1-[2'-(5''-Ethoxy indolyl)-3'-(aminophenyl)-methyl-1', 5'-benzoxazepinyl]-carbazoles**(4h)***

Yield 71% (Methanol) ;m.p. 155^{0}C ; IR (KBr) ν_{max} in cm^{-1} : 3332 (NH), 1625 (C-C of aromatic ring),1581 (C=N), 1042 (C-O-C), . ^{1}H-NMR ($CDCl_3$) δ in ppm : 3.10 (t, 2H, CH_2NH), 2.58 (t, 3H, CH_2CH_3), 3.45 (q, 2H, CH_2CH_3),4.20 (t, 1H, C_2- H of oxazepine ring), 3.23 (d, 2H, C_3 -H_2 of oxazepine ring),6.52 (brs, 1H, NH), 6.85-7.90 (m, 20H,Ar-H), 9.80 (brs, 1H, NH of indole exchangeable). Anal.Calcd.for $C_{38}H_{33}N_3O_2$: C, 80.99; H, 5.86; N, 7.46; Found : C, 81.00; H, 5.85; N, 7.47%: $[M]^+$ at m/z 563.

*2.2.4.9. 1-[2'-(5''-Ethoxy indolyl)-3'-(2'''- chlorophenyl amino)-methyl-1', 5'-benzoxazepinyl]-carbazoles **(4i)***

Yield 67% (Ethanol) ;m.p. 165^{0}C ; IR (KBr) ν_{max} in cm^{-1} : 3334 (NH), 1624 (C-C of aromatic ring),1582 (C=N), 1041 (C-O-C), 680 (C-Cl). ^{1}H-NMR ($CDCl_3$) δ in ppm : 3.11 (t, 2H, CH_2NH), 2.61 (t, 3H, CH_2CH_3), 3.43 (q, 2H, CH_2CH_3), 4.24 (t, 1H, C_2- H of oxazepine ring), 3.25 (d, 2H, C_3 -H_2 of oxazepine ring),6.50 (brs, 1H, NH), 6.75-7.87 (m, 20H,Ar-H), 9.80 (brs, 1H, NH of indole exchangeable). Anal.Calcd.for $C_{38}H_{32}N_3O_2Cl$: C, 76.30; H, 5.35; N, 7.02; Found : C, 76.28; H, 5.37; N, 7.01%: $[M]^+$ at m/z 597.5.

*2.2.4.10. 1-[2'-(5''-Ethoxy indolyl)-3'-(3'''- chlorophenyl amino)-methyl-1', 5'-benzoxazepinyl]-carbazoles**(4j)***

Yield 65% (Ethanol) ;m.p. 168^{0}C ; IR (KBr) ν_{max} in cm^{-1} : 3330 (NH), 1620 (C-C of aromatic ring),1585 (C=N), 1040 (C-O-C), 684 (C-Cl). ^{1}H-NMR ($CDCl_3$) δ in ppm : 3.13 (t, 2H, CH_2NH), 2.59 (t, 3H, CH_2CH_3), 3.45 (q, 2H, CH_2CH_3), 4.25 (t, 1H, C_2- H of oxazepine ring), 3.23 (d, 2H, C_3 -H_2 of oxazepine ring),6.48 (brs, 1H, NH), 6.75-7.90 (m, 20H,Ar-H), 9.83 (brs, 1H, NH of indole exchangeable). Anal.Calcd.for $C_{38}H_{32}N_3O_2Cl$: C, 76.30; H, 5.35; N, 7.02; Found : C, 76.31; H, 5.33; N, 6.69%: $[M]^+$ at m/z 597.5.

*2.2.4.11. 1-[2'-(5''-Ethoxy indolyl)-3'-(2''',3'''- dichlorophenyl amino)-methyl-1', 5'-benzoxazepinyl]-carbazoles**(4k)***

Yield 66% (Acetone) ; m.p52; IR (KBr) ν_{max} in cm^{-1} : 3336 (NH), 1625 (C-C of aromatic ring),1584 (C=N), 1040 (C-O-C), 684 (C-Cl). ^{1}H-NMR ($CDCl_3$) δ in ppm : 3.10 (t, 2H, CH_2NH), 2.61 (t, 3H, CH_2CH_3), 3.47 (q, 2H, CH_2CH_3), 4.25 (t, 1H, C_2- H of oxazepine ring), 3.18 (d, 2H, C_3 -H_2 of oxazepine ring),6.51 (brs, 1H, NH), 6.80-7.95 (m, 19H,Ar-H), 9.86 (brs, 1H, NH of indole exchangeable). Anal.Calcd.for $C_{38}H_{31}N_3O_2Cl_2$: C, 72.15; H, 4.90; N, 6.64; Found : C, 72.18; H, 4.88; N, 6.62%: $[M]^+$ at m/z 632.

*2.2.4.12. 1-[2'-(5''-Ethoxy indolyl)-3'-(2'''- bromophenyl amino)-methyl-1', 5'-benzoxazepinyl]-carbazoles **(4l)***

Yield 67% (Ethanol) ;m.p. 165^{0}C ; IR (KBr) ν_{max} in cm^{-1} : 3332 (NH), 1623 (C-C of aromatic ring),1581 (C=N), 1041 (C-O-C), 612 (C-Br). ^{1}H-NMR ($CDCl_3$) δ in ppm : 3.13 (t, 2H, CH_2NH), 2.64 (t, 3H, CH_2CH_3), 3.44 (q, 2H, CH_2CH_3), 4.26 (t, 1H, C_2- H of oxazepine ring), 3.26 (d, 2H, C_3 -H_2 of oxazepine ring),6.51 (brs, 1H, NH), 6.75-7.90 (m, 20H,Ar-H), 9.83 (brs, 1H, NH of indole exchangeable). Anal.Calcd.for $C_{38}H_{32}N_3O_2Br$: C, 71.02; H, 4.98; N, 6.54; Found : C, 71.00; H, 5.5.00; N, 6.53%: $[M]^+$ at m/z 642.

2.2.4.13. 1-[2'-(5''-Ethoxy indolyl)-3'-(3'''- bromophenyl amino)-methyl-1', 5'-benzoxazepinyl]-carbazoles ***(4m)***

Yield 65% (Methanol) ;m.p. 170^{0}C ; IR (KBr) ν_{max} in cm^{-1} : 3340 (NH), 1626 (C-C of aromatic ring),1584 (C=N), 1044 (C-O-C), 610 (C-Br). ^{1}H-NMR ($CDCl_3$) δ in ppm : 3.15 (t, 2H, CH_2NH), 2.66 (t, 3H, CH_2CH_3), 3.46 (q, 2H, CH_2CH_3), 4.24 (t, 1H, C_2- H of oxazepine ring), 3.24 (d, 2H, C_3 -H_2 of oxazepine ring),6.54 (brs, 1H, NH), 6.85-7.90 (m, 20H,Ar-H), 9.81 (brs, 1H, NH of indole exchangeable). Anal.Calcd.for $C_{38}H_{32}N_3O_2Br$: C, 71.02; H, 4.98; N, 6.54; Found : C, 71.03; H, 4.96; N, 6.55%: $[M]^+$ at m/z 642.

2.2.4.14. 1-[2'-(5''-Ethoxy indolyl)-3'-(2''',3'''- dibromophenyl amino)-methyl-1', 5'-benzoxazepinyl]-carbazoles ***(4n)***

Yield 65% (Methanol) ;m.p. 170^{0}C ; IR (KBr) ν_{max} in cm^{-1} : 3348 (NH), 1624 (C-C of aromatic ring),1586 (C=N), 1043 (C-O-C), 610 (C-Br). ^{1}H-NMR ($CDCl_3$) δ in ppm : 3.13 (t, 2H, CH_2NH), 2.67 (t, 3H, CH_2CH_3), 3.47 (q, 2H, CH_2CH_3), 4.23 (t, 1H, C_2- H of oxazepine ring), 3.22 (d, 2H, C_3 -H_2 of oxazepine ring),6.56 (brs, 1H, NH), 6.85-7.95 (m, 20H,Ar-H), 9.85 (brs, 1H, NH of indole exchangeable). Anal.Calcd.for $C_{38}H_{31}N_3O_2Br_2$: C, 63.24; H, 4.29; N, 5.82; Found : C, 63.26; H, 4.31; N, 5.80%: $[M]^+$ at m/z 721.

3.Pharmacological results and discussion

All the newly synthesizedcarbazole derivatives of series-1 were screened for antipsychotic properties viz. Amphetamine induced stereotype behaviour, induction of catalepsy, rotarod performance test, anticonvulsant activity and acute toxicity. All the test compounds were administered intraperitoneally (i.p.) to albino rats at a dose of 40 mg/kg i.p. Animals were divided into three groups of control, standard and treated , each group having five animals. Control group was treated with propylene glycol (0.5ml). Phenytoin sodium (30mg/kg i.p.) was used as standard for anticonvulsant activity. Chlorpromazine (4mg/kg i.p.) and haloperidol (0.5 mg/kg i.p) were used as a reference standard drug for amphetamine induced sterotypebehaviour (SB) and for cataleptic behaviour respectively. Biological data of all the newly synthesized compounds is depicted in Table-1.

3.1. Antipsychotic activity

3.1.1. .Amphetamine induced stereotype behaviour (SB)

All the newly synthesized compounds showed statistically significant amphetamine induced stereotype behaviour. Compounds 1a, 2a and 2b showed mild response towards amphetamine induced stereotype behaviour ranging between 2.5 to 2.8 scores. There is seen an increase in response (1.9 and 1.8 scores by compounds 3a and 3b respectively) as we to next step of the series which have additional benzoxazepine moiety. Good response towards amphetamine induced stereotype behaviour was shown by final step compounds (4a-4n) ranging between 1.5 to 0.0 scores. Moreover compound 4d namely 1-[2'-(5''-methoxy indolyl)-3'-(2''',3'''- dichlorophenyl amino)-methyl-1', 5'-benzoxazepinyl]-carbazoles has completely antagonized the amphetamine induced stereotype behaviour and hence from these results we can say that compound 4d is the most potent antipsychotic compound among all.

3.1.2. Cataleptic behaviour

Compounds 1a, 2a and 2b exhibited very little response towards cataleptic behaviour (2.3 to 2.6 scores). A little increase in response was noticed as we move to next step i.e. compounds 3a and 3b (1.9 and 1.9

scores respectively). Furthermore, final step compounds i.e. 4a-4n showed varying scores (0.0 to 1.2 scores) against cataleptic behaviour. On the basis of response towards cataleptic behaviour compound 1-[2'-(5''-methoxy indolyl)-3'-(2''',3'''- dichlorophenyl amino)-methyl-1', 5'-benzoxazepinyl]-carbazoles (4d) was considered as most potest as this compound elicited negligible cataleptic behaviour.

3.1.3. Rotarod performance test

On observing the results of rotarod performance test given in Table -1 , we can say that compound 1a, 2a, 2b, 3a and 3b showed mild activity ranging from 111.5 s to 118.0s in rotarod test. But at the same time it was also noticed that final step compounds i.e. 4a-4n showed better rotarod activity ranging between 92.0s to 107.2s. Compound 4d showed most potent result (i.e. 92.0s).

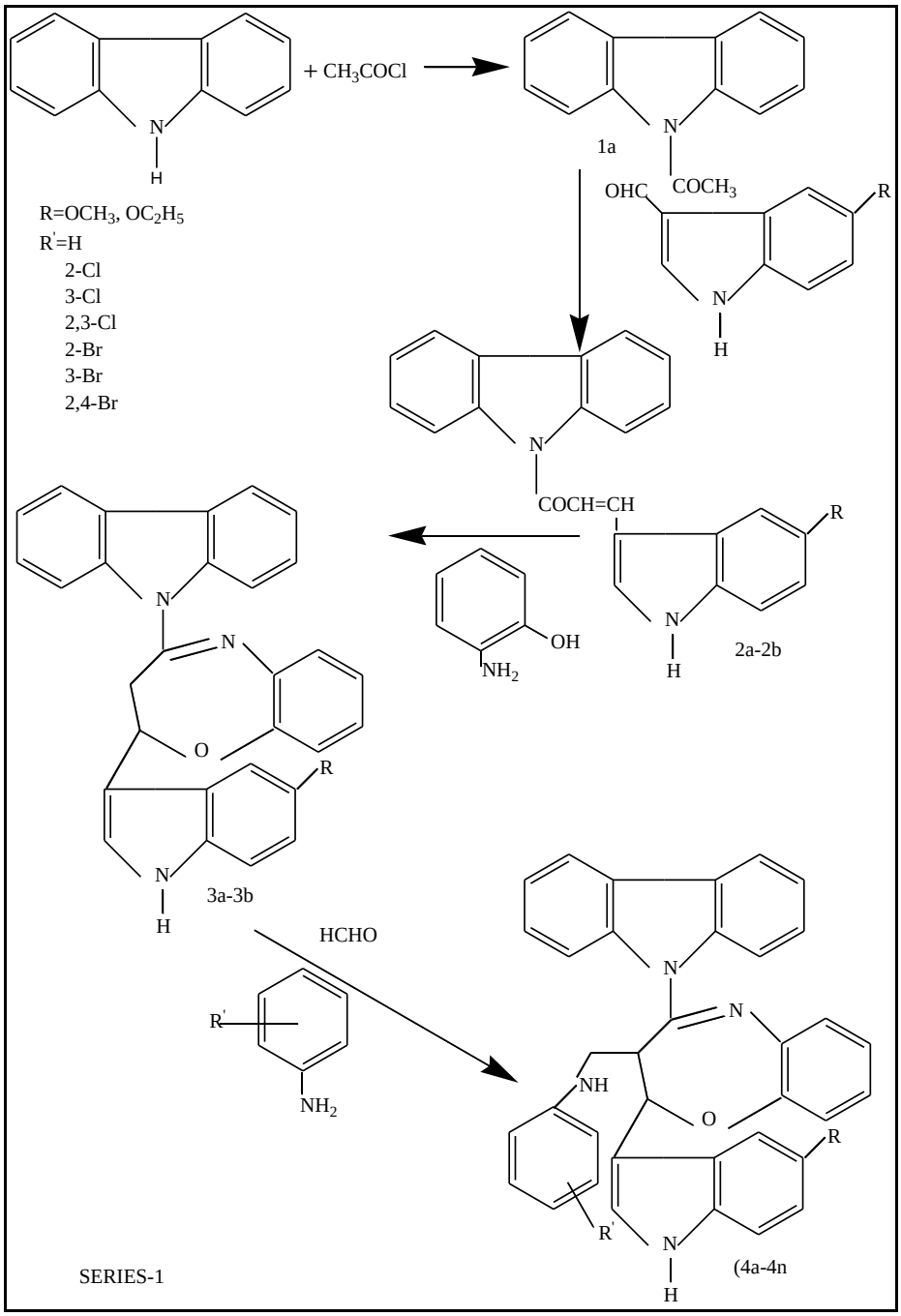

Table-1: Antipsychotic and anticonvulsant activity of compounds 1a, 2a-2b, 3a-3b, 4a-4n.

Compd.	R	R'	Dose (mg/k	Amphe-tamine	Catalepsy scored	Rotarod perform-	Anticonvulsant activity	ALD_{50} (mg/kg)

No.			**g)**	**induced SB (mean score)**		**ance (mean score)**	**(%inhibition) in mice (for MES model)**	
P.G.	-	-	0.5ml	3.8	-	120.0	0	
P.S.	-	-	30	-	-	-	80***	
CPZ	-	-	4.0ml	0.0	-	100.0	0	
HPL	-	-	0.5ml	-	1.8	-	0	
1a	OCH_3	-	40	2.8	2.6	118.0	20	>1000
2a	OCH_3	-	40	2.5	2.3	117.0	20	>1000
2b	OC_2H_5	-	40	2.6	2.3	116.8	30	>1000
3a	OCH_3	-	40	1.5	1.9	112.0	40	>1000
3b	OC_2H_5	-	40	1.2	1.8	111.5	30	>1000
4a	OCH_3	H	40	1.0	1.5	111.0	50*	>1000
4b	OCH_3	2-Cl	40	0.7	0.7	110.6	60**	>1000
4c	OCH_3	3-Cl	40	0.5	0.6	101.0	70***	>1000
4d	OCH_3	2,3-Cl	40	0.0	0.0	92.0	90***	>2000
4e	OCH_3	2-Br	40	0.8	0.7	102.0	60**	>1000
4f	OCH_3	3-Br	40	0.6	1.0	108.4	60**	>1000
4g	OCH_3	2,4-Br	40	0.1	0.3	105.5	70***	>1000
4h	OC_2H_5	H	40	1.3	1.2	112.2	50*	>1000
4i	OC_2H_5	2-Cl	40	1.1	0.9	107.2	60**	>1000
4j	OC_2H_5	3-Cl	40	0.6	0.8	104.2	60**	>1000
4k	OC_2H_5	2,3-Cl	40	0.2	0.3	94.0	80***	>1000
4l	OC_2H_5	2-Br	40	1.0	1.0	100.4	60**	>1000
4m	OC_2H_5	3-Br	40	0.8	0.9	102.2	60**	>1000
4n	OC_2H_5	2,4-Br	40	0.4	0.1	100.2	70***	>1000

P.G.-Propylene glycol, P.S.- Phenytoin sodium standard drug for SMES pattern test, CPZ-Chlorpromazine, HPL= Haloproid

***P < 0.05, **P < 0.01, ***P < 0.001**

3.2. Anticonvulsant activity

Least activity against MES test was shown by compounds 1a, 2a and 2b varying from 20% to 30%, which increases upto 40% in the next step compounds (3a and 3b). Compound 3a, having 5-methoxy indole moiety exhibited better anticonvulsant activity than 3b having 5-ethoxy indole moiety. Better response againt convulsions was observed in Mannich products. Final step compounds (4a-4n) are much stronger than their parent compounds (3a and 3b). These compounds exhibited 50% to 90% protection against seizures induced by MES.

3.3. Acute toxicity

All the newly synthesized compounds of series-1 were also evaluated for acute toxicity. All the compounds showed a high value of ALD_{50} of greater than 1000 mg/kg i.p. thereby suggesting a good safety margin. A much higher value of ALD_{50} value of more 2000 mg/kg i.p. was shown by compound **4a**.

4.Conclusion

On analysing the biological data of the synthesized compounds of the series-1, it may be concluded that:

1.Introduction of benzoxazepine ring by cyclization of chalconyl moiety was found to enhance the antipsychotic as well as anticonvulsant properties.

2. Remarkable increase in antipsychotic activity was noticed in compounds having 2,3-dichlorophenyl moiety.

5. Biological methods

5.1. Antipsychotic activity

5.1.1. Effect of amphetamine induced stereotype behaviour (SB)

Method of Castall and Nayor]17] was used foe amphetamine induced stereotype behaviour. Animals were deprived of food during experiments and were fasted for 12 hour before administering test drugs. Stereotype induced (SB) behaviour in albino rats was induce by administering amphetamine at a dose of 4 mg/kg i.p. in albino rats. After 30 min of test compounds treatment, the intensity of SB was assessed and following system for scoring was used-

Periodic sniffing = 1 score,
Continuous sniffing = 2 scores,
Periodic bitting, gnawing or licking = 3 scores,
Continuous biting, gnawing or licking = 4 scores.

The mean value of the group was computed by taking the maximam intensity of stereotype behaviour scored by each rat in the respective group. The standard drug used was chlorpromazine (4 mg/kg i.p), which was injected 30 minutes prior to challenge. Test compounds and propylene glycol (0.5 ml i.p.)were given 20 minutes before injecting amphetamine.

5.1.2. Induction of catalepsy

It was done by the method of Castall and Nayor [17]. According to this method, the forelimbs of the rats were placed over a wooden block of 8 cm high and the time for which animals maintained the imposed posture was noted .Those animals were considered as cataleptic, which maintained the imposed posture for more than 10 seconds. Following scoring system was used for testing the catalepsy in animals to maintain the impose posture-

0 – 10 sec = 0 score,
11 – 30 sec = 1 score,
31 – 60 sec = 2 scores,
61 – 120 sec = 3 scores.

After injecting propylene glycol (0.5ml i.p.) or test compounds (40 mg/kg i.p.) or standard drug haloperidol (0.5 mg/kg i.p.)

5.1.3. Rotarod performance test

The rotarod performance was essentially the same as described by Dunham and Miya [18]. This activity was use to test the co-ordination movement and strength of the animals. Rotarod rotating at 6 rpm was used a day before the test session, to give training to the animals. As soon as the rat fell of the rotarod, it was immediately placed back, Training was terminated when the rat remained on the rod continuously for 2 minutes. On the second day, after administration of test compound, the rats were given the trials on the rotarod for 60 minutes and the cumulated time spent on rotarodwas recorded with a cut Soff of 2 minutes.

5.2. Anticonvulsant activity- supra maximal electroshock seizure pattern test (SMES)

Method of Tomen et al was used for performing the anticonvulsant activity. Rats of Charles Foster strain were used . Rats of both the sex weighing between 90 to 120 grams were used. Activity was performed by dividing the rats into groups. Each group contains 10 animals 9rats).The rata were treated with dufferent doses of test drugs and phenytoin sodium 30 mg/kg i.p. The rats were subjected to a shock of 150 M.A. by convulsiometer after i hour of drug treatment through ear electrodes for 0.2 s. The presence or absence of extensor response was noted. Animals in which extensor response was abolished were taken as protected rats. The results are depicted in Table-1

5.3. Acute toxicity

Acute toxicity in mice was investigated in mice by following the method of Smith [20] and the results are depicted in Table-1.

References

1. Zhu D., Chen M., LI M., Luo B., Zhao Y., Huang P., Xue F., Rapposelli S., Pi R., Wen S. Discovery of novel N-substituted carbazoles as neuroprotective agents with potent anti-oxidative activity. Eur. J. Med. Chem. 2013, 68, 81-88.
2. Rastogi S.N., Anand N. Synthesis, neuroleptic and anti-inflammatory activities of 4a, 11a-cis and trans-[γ-(p-fluorobenzoyl)propyl]-1,2,3,4,4a,5,11,11a-octahydro-6H-pyrido[4,3-b]carbazoles and related derivatives. Indian J. Chem. 1987, 26B, 335-340.
3. Srivastava S.K., Srivastava S, Srivastava S.D. Synthesis of new carbazolyl-thiadiazol-2-oxo-azetidines: Antimicrobial, anticonvulsant and anti-inflammatory agents. Indian J Chem. 1999, 38B, 183-187.
4. Yogendra K.S. Savitri D.S. Synthesis of N-substituted mono and bihetreocycles as anti-inflammatory, anti-convulsant and anthelmintic agents. Indian J. Chem.. 1994, 33B, 397-399.
5. Bandgar B.P. Adsul L.K, Chavan H.V., Jalde S.S., Shrigare S.N., Shaik R., Meshram R.J., Gacche R.N., Masand V. Synthesis, biological evaluation and docking studies of 3-(substituted)-aryl-5-(9-mrthyl-3-carbazole)-1H-32-pyrazolines as potent anti-inflammatory and anti-oxidant agents. Bioorg. Med. Chem. Lett. 2013, 23, 28-29.
6. Gu W., Qiao C., Wang S.F., Hao Y., Miao T.T. Synthesis and biological evaluation of novel N-substituted 1H-dibenzo[a,c]carbazole derivatives of dehydrobietic acid as potential antimicrobial agents. Bioorg. Med. Chem.Lett. 2014, 24, 328-331.
7. Reddy S.V.L., Naresh K., Raju C.N. New sulphonamide and carbamate derivatives of 4-(oxiran-2-ylmethoxy)-9Hcarbazole : Synthesis, characterization, antimicrobial and antioxidant activities. Der. Pharm. Lett. 2013, 5, 221-231.
8. Hagiwara H., Choshi T., Fujimoto H., Sugino E. Hibino S. Anovel total synthesis of antibiotic carbazole alkaloid carbazomycin G. Tetrahedron 2000, 22, 1428-1434.
9. Danish A.I., Prasad K.J.R. A one pot synthesis 0f 1,2,4,5-tetraazaspiro [5.5]-6,7,8,9-tetrahydrocarbazol-3-thiones and their antibacterial activities. Indian J. Heterocycl, Chem. 2006, 14, 19-22.
10. Zhang F.F., Gan L.L., Zhou G.H. Synthesis, anti-bacterial and anti-fungal activitied of some carbazole derivatives. Bioorg. Med. Chem. 2010, 20, 1881-1884.

11. Howorko R.J., Tylinska B., Biadun B., Gebarowski T., Gasiorowski K. New pyridocarbazole derivatives. Synthesis and their in vitro anticancer activity. Act. Pol. Pharm. Drug. Res. 2013, 70, 823-832.
12. Li B., Yue Z.Z., Feng J.M., He Q., Miao Z.H., Yang C.H. Design and synthesis of pyrido [3,2-α] carbazole derivatives and their analogs as potent antitumor agents. Eur. J. Med Chem. 2013, 66, 531-539.
13. Bajaj K., Srivastava V.K., Lata S., Chandra R., Kumar A. Synthesis of some new benzothia/oxazepinylindoles as an antipsychotic agents. Indian J. Chem. 2003, 42B, 1723-1728.
14. Kumar A., Kumar D., Mohd. A., Kaur H. Synthesis and evaluation of some newer indole derivatives as anticonvulsant agents. Int. J. Pharm. Bio. Archives. 2011, 2, 744-750.
15. Archana. Synthesis and biological evaluation of some novel benzodiazepine containing benzothiazepine/benzoxazepine derivatives as potent anticonvulsant agents. Indian Drugs 2018, 55, 7-13.
16. Kaur H., Kumar S., Chaudhary A., Kumar A. Synthesis and biological evaluation of some new substituted benzoxazepine and benzothiazepine as antipsychotic as well as anticonvulsant agents. Arabian J. Chem. 2012, 5, 271-283.
17. Castell L., Nayor R. Mesolimbic involvement with behavioural effects indicating antipsychotic activity, Eur. J. Pharmacol. 1974, 27, 46-58.
18. Dunham S.M., Miya T.S. A note on simple apparatus for detecting neurological deficits in rats and mice. J. Am. Pharm. Assoc. 1957, 426, 208-209.
19. Toman J.E.P., Swinyard E.A, Goodman L.S. Properties of maximal seizures and their alteration by their anticonvulsant drugs and other agents. J. Neurophysiol. 1946, 9, 231-240.
20. Smith Q.E. In: Pharmacological screening tests progress in medicinal chemistry-1, Butterwort's London. Medicinal Chem. 1960, 1, 1-33.

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