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Synthesis and Characterization of Some New Carbazolyloxy Substituted Oxazinane Derivatives

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Some new carbazolyloxy substituted oxazinane derivatives such as morpholinonyl, morpholinedionyl and morpholinyl were synthesized by cyclizing the corresponding carbazolyloxy propanolamine moiety using different two carbon sources.

Key Words: Synthesis, Carbazoles, Oxazinane derivatives, β-Blocking agents.

INTRODUCTION

β-Adrenergic blocking agents (β-blockers)[1-4] mostly comprising of aryloxypropanolamine moiety have been found to possess wide range of pharmacological activities and are used to treat cardiovascular disorders including hypertension[5,6], anginapectoris, cardiac arrhythmias and other disorders related to the sympathetic nervous system[7]. Aryloxypropanolamine moiety is the key pharmacophore in β-blockers[8]. Propranolol, a prototype agent for this class of compounds affects β_1 and β_2 receptors, however other drugs such as atenolol[9] and metoprolol[10] have greater affinity for β_1 receptors and are described as cardioselective. Betaxolol[11] is the best β_1 blocker among the currently available agents.

Significant pharmacological importance of these aryloxypropanolamine derivatives coupled with our continued interest[12] in the synthesis of new heterocyclic compounds having aryloxypropanolamine pharmacophore, promoted us to synthesize carbazolyloxy substituted oxazine derivatives. Herein, we described new strategy to synthesize novel β-blocker prototype.

EXPERIMENTAL

The ^{1}H NMR spectra were measured in $CDCl_3$, CD_3CN, CD_3OD and DMSO-d_6 using Gemini-2000 (200 MHz) and Mercury plus (Varian 400 MHz) FT NMR spectrometer, the chemical shifts were reported in δ ppm. IR spectra were recorded in the solid state as KBr dispersion using Perkin-Elmer 1650 FT IR spectrometer.

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The mass spectra (70 eV) were recorded on HP 5989 A LC MS spectrometer. The melting points were determined by using the capillary method on Polmon (Model MP-96) melting point apparatus. The solvents and reagents were used without further purification.

General procedure for the preparation of compounds (2a-l): A mixture of corresponding carbazolyloxy propanolamine derivative, **1a-l** (2.0 mmol), chloroacetyl chloride (2.5 mmol), potassium carbonate (3.0 mmol) and N,N-dimethyl formamide (10 mL) was refluxed for 1-3 h (depending on the amine derivative) at 130-140 °C. The reaction mixture was cooled to 25-35 °C and quenched with water (10 mL). The obtained solid was filtered and dried under vacuum.

6-(9*H*-Carbazol-4-yloxymethyl)-4-*o*-tolyl-morpholin-3-one (2a): Yield: 91 %; m.p. 125-128 °C; IR (KBr, cm^{-1}): 3269, 1665; ^1H NMR (400 MHz, $CDCl_3$, δ ppm): 8.16 (s, 1H), 6.6-8.25 (m, 11H), 4.4-4.6 (m, 4H), 4.35 (m, 1H), 3.8-4.0 (m, 2H), 2.3 (s, 3H); MS (m/z): 409 (M^+ + Na).

6-(9*H*-Carbazol-4-yloxymethyl)-4-*p*-tolyl-morpholin-3-one (2b): Yield: 90 %; m.p. 152-156 °C; IR (KBr, cm^{-1}): 3339, 1659; ^1H NMR (400 MHz, $CDCl_3$, δ ppm): 8.1 (s, 1H), 6.6-8.25 (m, 11H), 4.4-4.6 (m, 4H), 4.35 (m, 1H), 3.8-4.1 (m, 2H), 2.35 (s, 3H); MS (m/z): 409 (M^+ + Na).

6-(9*H*-Carbazol-4-yloxymethyl)-4-*p*-fluorophenyl-morpholin-3-one (2c): Yield: 79 %; m.p. 195-197 °C; IR (KBr, cm^{-1}): 3308, 1656; ^1H NMR (400 MHz, $CDCl_3$, δ ppm): 8.18 (s, 1H), 6.6-8.2 (m, 11H), 4.4-4.6 (m, 4H), 4.35 (m, 1H), 3.8-4.1 (m, 2H); MS (m/z): 391 (M^+ + H), 413 (M^+ + Na).

6-(9*H*-Carbazol-4-yloxymethyl)-4-*p*-methoxyphenyl-morpholin-3-one (2d): Yield: 82 %; m.p. 147-151 °C; IR (KBr, cm^{-1}): 3276, 1655; ^1H NMR (400 MHz, $CDCl_3$, δ ppm): 8.1 (s, 1H), 6.6-8.3 (m, 11H), 4.4-4.6 (m, 4H), 4.35 (m, 1H), 3.85-4.1 (m, 2H), 3.8 (s, 3H); MS (m/z): 425 (M^+ + Na).

6-(9*H*-Carbazol-4-yloxymethyl)-4-phenyl-morpholin-3-one (2e): Yield: 84 %; m.p. 138-141 °C; IR (KBr, cm^{-1}): 3274, 1651; ^1H NMR (400 MHz, $CDCl_3$, δ ppm): 8.1 (s, 1H), 6.6-8.3 (m, 12H), 4.4-4.6 (m, 4H), 4.35 (m, 1H), 3.9-4.2 (m, 2H); MS (m/z): 395 (M^+ + Na).

6-(9*H*-Carbazol-4-yloxymethyl)-4-benzyl-morpholin-3-one (2f): Yield: 85 %; m.p. 208-210 °C; IR (KBr, cm^{-1}): 3241, 1648; ^1H NMR (400 MHz, $CDCl_3$, δ ppm): 8.1 (s, 1H), 6.6-8.0 (m, 12H), 4.3-4.9 (m, 6H), 4.2 (m, 1H), 3.4-3.6 (m, 2H); MS (m/z): 387 (M^+ + H).

6-(9*H*-Carbazol-4-yloxymethyl)-4-cyclohexyl-morpholin-3-one (2g): Yield: 83 %; m.p. 210-215 °C; IR (KBr, cm^{-1}): 3262, 1640; ^1H NMR (400 MHz, $CDCl_3$, δ ppm): 8.1 (s, 1H), 6.6-8.3 (m, 7H), 4.2-4.6 (m, 6H), 3.4-3.65 (m, 2H), 1.0-1.9 (m, 10H); MS (m/z): 379 (M^+ + H).

6-(9*H*-Carbazol-4-yloxymethyl)-4-methyl-morpholin-3-one (2h): Yield: 88 %; m.p. 222-226 °C; IR (KBr, cm^{-1}): 3246, 1647; ^1H NMR (400 MHz, $CDCl_3$, δ ppm): 8.1 (s, 1H), 6.65-8.3 (m, 7H), 4.3-4.5 (m, 5H), 3.5-3.7 (m, 2H), 3.05 (s, 3H); MS (m/z): 311 (M^+ + H), 333 (M^+ + Na).

6-(9*H*-Carbazol-4-yloxymethyl)-4-ethyl-morpholin-3-one (2i): Yield: 80 %; m.p. 159-161 °C; IR (KBr, cm^{-1}): 3247, 1642; ^1H NMR (400 MHz, $CDCl_3$, δ ppm): 8.1 (s, 1H), 6.6-8.3 (m, 7H), 4.2-4.5 (m, 5H), 3.4-3.7 (m, 4H), 1.2 (t, 3H); MS (m/z): 325 (M^+ + H), 347 (M^+ + Na).

6-(9*H*-Carbazol-4-yloxymethyl)-4-propyl-morpholin-3-one (2j): Yield: 90 %; m.p. 105-109 °C; IR (KBr, cm^{-1}): 3254, 1645; ^1H NMR (400 MHz, $CDCl_3$, δ ppm): 8.1 (s, 1H), 6.6-8.25 (m, 7H), 4.2-4.5 (m, 5H), 3.4-3.7 (m, 4H), 1.65 (m, 2H), 0.95 (t, 3H); MS (m/z): 361 (M^+ + Na).

6-(9*H*-Carbazol-4-yloxymethyl)-4-butyl-morpholin-3-one (2k): Yield: 82 %; m.p. 185-188 °C; IR (KBr, cm^{-1}): 3257, 1644; ^1H NMR (400 MHz, $CDCl_3$, δ ppm): 8.1 (s, 1H), 6.6-8.25 (m, 7H), 4.3-4.5 (m, 5H), 3.4-3.7 (m, 4H), 1.6 (m, 2H), 1.38 (m, 2H), 0.95 (t, 3H); MS (m/z): 375 (M^+ + Na).

6-(9*H*-Carbazol-4-yloxymethyl)-4-pentyl-morpholin-3-one (2l): Yield: 84 %; m.p. 174-177 °C; IR (KBr, cm^{-1}): 3274, 1645; ^1H NMR (400 MHz, $CDCl_3$, δ ppm): 8.1 (s, 1H), 6.6-8.25 (m, 7H), 4.2-4.5 (m, 5H), 3.4-3.7 (m, 4H), 1.6 (m, 2H), 1.35 (m, 4H), 0.9 (t, 3H); MS (m/z): 367 (M^+ + H), 389 (M^+ + Na).

General procedure for the preparation of compounds (3a-l): A mixture of corresponding carbazolyloxy propanolamine derivative, **1a-l** (2.0 mmol), 10 % aqueous sodium hydroxide (3.0 mmol) and dichloromethane (10 mL) was cooled to 0-5 °C and added ethyl chlorooxoacetate (3.0 mmol). The resulted reaction mixture was stirred for 1-2 h (depending on the amine derivative) at 0-5 °C and pH of the reaction mixture was adjusted 7.0-7.5 using aqueous sodium carbonate solution. Organic layer was separated and concentrated under vacuum thus obtained residue was triturated with isopropyl alcohol (10 mL) thus afforded solid was dried under vacuum.

6-(9*H*-Carbazol-4-yloxymethyl)-4-*o*-tolyl-morpholine-2,3-dione (3a): Yield: 93 %; m.p. 185-190 °C; IR (KBr, cm^{-1}): 3341, 1762, 1684; ^1H NMR (400 MHz, DMSO-d_6, δ ppm): 11.3 (s, 1H), 6.7-8.3 (m, 11H), 5.7 (m, 1H), 3.8-4.6 (m, 4H), 2.3 (s, 3H); MS (m/z): 423 (M^+ + Na).

6-(9*H*-Carbazol-4-yloxymethyl)-4-*p*-tolyl-morpholine-2,3-dione (3b): Yield: 84 %; m.p. 202-205 °C; IR (KBr, cm^{-1}): 3321, 1761, 1689; ^1H NMR (400 MHz, DMSO-d_6, δ ppm): 11.3 (s, 1H), 6.7-8.3 (m, 11H), 5.6 (m, 1H), 4.1-4.6 (m, 4H), 2.3 (s, 3H); MS (m/z): 423 (M^+ + Na).

6-(9*H*-Carbazol-4-yloxymethyl)-4-*p*-fluorophenyl-morpholine-2,3-dione (3c): Yield: 80 %; m.p. 240-243 °C; IR (KBr, cm^{-1}): 3321, 1761, 1689; ^1H NMR (200 MHz, DMSO-d_6, δ ppm): 11.3 (s, 1H), 6.6-8.3 (m, 11H), 5.6 (m, 1H), 4.1-4.6 (m, 4H); MS (m/z): 405 (M^+ + H).

6-(9*H*-Carbazol-4-yloxymethyl)-4-*p*-methoxyphenyl-morpholine-2,3-dione (3d): Yield: 88 %; m.p. 235-240 °C; IR (KBr, cm^{-1}): 3336, 1764, 1683; ^1H NMR (400 MHz, DMSO-d_6, δ ppm): 11.3 (s, 1H), 6.7-8.2 (m, 11H), 5.6 (m, 1H), 4.1-4.6 (m, 4H), 4.1 (m, 1H), 3.78 (s, 3H); MS (m/z): 439 (M^+ + Na).

6-(9*H*-Carbazol-4-yloxymethyl)-4-phenyl-morpholine-2,3-dione (3e): Yield: 80 %; m.p. 220-225 °C; IR (KBr, cm^{-1}): 3315, 1763, 1690; ^1H NMR (200 MHz,

DMSO-d_6, δ ppm): 11.3 (s, 1H), 6.7-8.0 (m, 12H), 5.6 (m, 1H), 4.1-4.6 (m, 4H); MS (m/z): 409 (M^+ + Na).

6-(9*H*-Carbazol-4-yloxymethyl)-4-benzyl-morpholine-2,3-dione (3f): Yield: 83 %; m.p. 276-280 °C; IR (KBr, cm^{-1}): 3341, 1754, 1690; ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 11.3(s, 1H), 6.6-8.0 (m, 12H), 5.4 (m, 1H), 4.4-4.8 (m, 4H), 3.7-4.1 (m, 2H); MS (m/z): 401 (M^+ + H).

6-(9*H*-Carbazol-4-yloxymethyl)-4-cyclohexyl-morpholine-2,3-dione (3g): Yield: 85 %; m.p. 286-288 °C; IR (KBr, cm^{-1}): 3328, 1763, 1669; ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 11.3 (s, 1H), 6.7-8.2 (m, 7H), 5.3 (m, 1H), 4.5 (m, 2H), 4.2 (m, 1H), 3.9 (m, 2H), 1.0-1.8 (m, 10H); MS (m/z): 415 (M^+ + Na).

6-(9*H*-Carbazol-4-yloxymethyl)-4-methyl-morpholine-2,3-dione (3h): Yield: 78 %; m.p. 256-260 °C; IR (KBr, cm^{-1}): 3320, 1763, 1686; ^{1}H NMR (200 MHz, $CDCl_3$ + DMSO-d_6, δ ppm): 10.9 (s, 1H), 6.6-8.2 (m, 7H), 5.35 (m, 1H), 3.8-4.6 (m, 4H), 3.15 (s, 3H); MS (m/z): 325 (M^+ + H).

6-(9*H*-Carbazol-4-yloxymethyl)-4-ethyl-morpholine-2,3-dione (3i): Yield: 81 %; m.p. 262-265 °C; IR (KBr, cm^{-1}): 3324, 1761, 1687; ^{1}H NMR (400 MHz, $CDCl_3$ + CD_3CN, δ ppm): 9.0 (s, 1H), 6.6-8.2, (m, 7H), 5.25 (m, 1H), 4.5 (m, 2H), 3.8-4.2 (m, 2H), 3.6 (m, 2H), 1.2 (t, 3H); MS (m/z): 339 (M^+ + H).

6-(9*H*-Carbazol-4-yloxymethyl)-4-propyl-morpholine-2,3-dione (3j): Yield: 88 %; m.p. 248-250 °C; IR (KBr, cm^{-1}): 3327, 1763, 1691; ^{1}H NMR (400 MHz, $CDCl_3$ + CD_3CN, δ ppm): 9.0 (s, 1H), 6.6-8.2 (m, 7H), 5.25 (s, 1H), 4.5 (m, 2H), 3.8-4.1 (m, 2H), 3.5 (t, 2H), 1.7 (m, 2H), 0.95 (t, 3H); MS (m/z): 353 (M^+ + H).

6-(9*H*-Carbazol-4-yloxymethyl)-4-butyl-morpholine-2,3-dione (3k): Yield: 79 %; m.p. 220-224 °C; IR (KBr, cm^{-1}): 3335, 1758, 1687; ^{1}H NMR (400 MHz, $CDCl_3$ + CD_3CN, δ ppm): 9.1 (s, 1H), 6.6-8.2 (m, 7H), 5.2 (m, 1H), 4.5 (m, 2H), 3.8-4.2 (m, 2H), 3.55 (t, 2H), 1.6 (m, 2H), 1.35 (m, 2H), 0.9 (t, 3H); MS (m/z): 367 (M^+ + H).

6-(9*H*-Carbazol-4-yloxymethyl)-4-pentyl-morpholine-2,3-dione (3l): Yield: 80 %; m.p. 220-225 °C; IR (KBr, cm^{-1}): 3335, 1757, 1687; ^{1}H NMR (400 MHz, $CDCl_3$ + CD_3CN, δ ppm): 9.35 (s, 1H), 6.7-8.2 (m, 7H), 5.25 (m, 1H), 4.5 (m, 2H), 3.7-4.1 (m, 2H), 3.45 (t, 2H), 1.6 (m, 2H), 1.3 (m, 4H), 0.9 (t, 3H); MS (m/z): 381 (M^+ + H).

General procedure for the preparation of compounds (4a-l): A mixture of carbazolyloxy propanolamine derivative, **1a-l** (2.0 mmol), 1-bromo-2-chloroethane (3.0 mmol), potassium carbonate (3.0 mmol) and N,N-dimethylformamide (10 mL) was heated for 6-9 h (depending on the amine derivative) at 90-100 °C. The reaction mixture was cooled to 25-35 °C and quenched with water (10 mL). The organic layer was separated and concentrated under vacuum to afford the solid.

4-(4-*o*-Tolyl-morpholin-2-ylmethoxy)-9*H*-carbazole (4a): Yield: 82 %; m.p. 126-129 °C; IR (KBr, cm^{-1}): 3407; ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 6.7-8.2 (m, 11H), 4.0-4.4 (m, 3H), 3.8 (m, 2H), 3.5-3.7 (m, 2H), 2.8 (m, 2H), 2.2 (s, 3H); MS (m/z): 373 (M+ + H), 395 (M^+ + Na).

4-(4-*p*-Tolyl-morpholin-2-ylmethoxy)-9*H*-carbazole (4b): Yield: 85 %; m.p. 130-133 °C; IR (KBr, cm^{-1}): 3401; ^1H NMR (400 MHz, $CDCl_3$, δ ppm): 8.1 (s, 1H), 6.6-8.4 (m, 11H), 4.4-4.5 (m, 3H), 3.85-4.2 (m, 2H), 3.4-3.8 (m, 2H), 2.8-3.0 (m, 2H), 2.3 (s, 3H); MS (m/z): 373 (M^+ + H), 395 (M^+ + Na).

4-(4-*p*-Fluorophenyl-morpholin-2-ylmethoxy)-9*H*-carbazole (4c): Yield: 86 %; m.p. 170-172 °C; IR (KBr, cm^{-1}): 3410; ^1H NMR (400 MHz, $CDCl_3$, δ ppm): 6.5-8.3 (m, 11H), 4.7-4.9 (m, 3H), 4.4-4.5 (m, 2H), 3.6-3.8 (m, 2H), 2.8-3.0 (m, 2H); MS (m/z): 363 (M^+ + H).

4-(4-*p*-Methoxyphenyl-morpholin-2-ylmethoxy)-9*H*-carbazole (4d): Yield: 80 %; m.p. 125-128 °C; IR (KBr, cm^{-1}): 3404; ^1H NMR (400 MHz, $CDCl_3$, δ ppm): 8.1 (s, 1H), 6.6-8.4 (m, 11H), 4.3-4.5 (m, 3H), 3.9-4.2 (m, 2H), 3.8 (s, 3H), 3.3-3.7 (m, 2H), 2.8-3.0 (m, 2H); MS (m/z): 389 (M^+ + H), 411 (M^+ + Na).

4-(4-Phenyl-morpholin-2-ylmethoxy)-9*H*-carbazole (4e): Yield: 81 %; m.p. 125-128 °C; IR (KBr, cm^{-1}): 3385; ^1H NMR (400 MHz, CD_3OD, δ ppm): 6.7-8.3 (m, 12H), 4.1-4.4 (m, 4H), 3.8-4.0 (m, 2H), 3.5 (d, 1H), 2.8-3.0 (m, 2H); MS (m/z): 359 (M^+ + H).

4-(4-Benzyl-morpholin-2-ylmethoxy)-9*H*-carbazole (4f): Yield: 78 %; m.p. 198-201 °C; IR (KBr, cm^{-1}): 3404; ^1H NMR (400 MHz, $CDCl_3$, δ ppm): 6.6-8.2 (m, 12H), 4.0-4.6 (m, 5H), 3.4-3.8 (m, 2H), 2.8-3.0 (m, 2H), 2.6 (s, 2H); MS (m/z): 373 (M^+ + H).

4-(4-Cyclohexyl-morpholin-2-ylmethoxy)-9*H*-carbazole (4g): Yield: 87 %; m.p. 171-173 °C; IR (KBr, cm^{-1}): 3408; ^1H NMR (400 MHz, $CDCl_3$, δ ppm): 8.0 (s, 1H), 6.6-8.4 (m, 7H), 4.0-4.4 (m, 5H), 3.1-3.7 (m, 2H), 2.6-2.8 (m, 2H), 2.3 (m, 1H), 1.0-2.0 (m, 10H); MS (m/z): 365 (M^+ + H).

4-(4-Methyl-morpholin-2-ylmethoxy)-9*H*-carbazole (4h): Yield: 80 %; m.p. 163-167 °C; IR (KBr, cm^{-1}): 3400; ^1H NMR (400 MHz, DMSO-d_6, δ ppm): 11.2 (s, 1H), 6.6-8.3 (m, 7H), 4.0-4.4 (m, 3H), 3.1-3.6 (m, 2H), 2.6-2.8 (m, 4H), 2.5 (s, 3H); MS (m/z): 297 (M^+ + H).

4-(4-Ethyl-morpholin-2-ylmethoxy)-9*H*-carbazole (4i): Yield: 84 %; m.p. 230-233 °C; IR (KBr, cm^{-1}): 3408; ^1H NMR (400 MHz, $CDCl_3$, δ ppm): 8.0 (s, 1H), 6.6-8.4 (m, 7H), 4.0-4.4 (m, 3H), 2.6-3.1 (m, 8H), 1.2 (t, 3H); MS (m/z): 311 (M^+ + H).

4-(4-Propyl-morpholin-2-ylmethoxy)-9*H*-carbazole (4j): Yield: 79 %; m.p. 152-154 °C; IR (KBr, cm^{-1}): 3395; ^1H NMR (400 MHz, DMSO-d_6, δ ppm): 11.2 (s, 1H), 6.6-8.2 (m, 7H), 4.0-4.2 (m, 3H), 2.3-2.8 (m, 8H), 1.35 (m, 2H), 0.7 (t, 3H); MS (m/z): 325 (M^+ + H).

4-(4-Butyl-morpholin-2-ylmethoxy)-9*H*-carbazole (4k): Yield: 83 %; m.p. 127-129 °C; IR (KBr, cm^{-1}): 3407; ^1H NMR (400 MHz, DMSO-d_6, δ ppm): 11.2 (s, 1H), 6.6-8.3 (m, 7H), 4.0-4.2 (m, 3H), 2.3-2.8 (m, 8H), 1.3 (m, 2H), 1.1 (m, 2H), 0.7 (t, 3H); MS (m/z): 339 (M^+ + H).

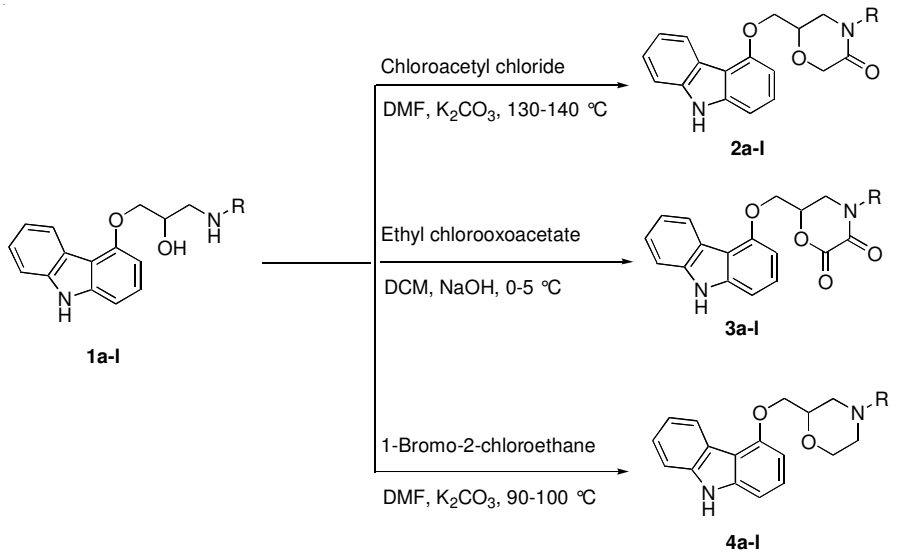
4-(4-Pentyl-morpholin-2-ylmethoxy)-9*H*-carbazole (4l): Yield: 86 %; m.p. 147-149 °C; IR (KBr, cm^{-1}): 3407; ^1H NMR (400 MHz, $CDCl_3$, δ ppm): 8.1 (s, 1H), 6.6-8.3 (m, 7H), 4.2-4.6 (m, 3H), 3.4-3.8 (m, 2H), 2.5-3.0 (m, 6H), 1.6 (m, 2H), 1.2 (m, 4H), 0.9 (t, 3H); MS (m/z): 353 (M^+ + H).

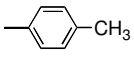
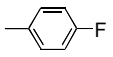
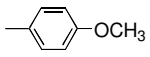
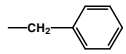
RESULTS AND DISCUSSION

Bridging the amino and hydroxyl functions of carbazolyloxy propanolamine derivatives **1** by using appropriate two carbon source was hypothesized as one of the approaches to access the desired oxazinane derivatives. Carbazolyloxy propanolamine derivatives **1** were prepared[12] by opening of epoxy ring present in carbazolyloxy epoxy propane using different aromatic and aliphatic amines. Thereafter, as a representative example, 1-(9*H*-carbazol-4-yloxy)-3-*o*-tolylamino-propan-2-ol (**1a**) was reacted with chloroacetyl chloride in the presence of K_2CO_3 in N,N-dimethyl formamide (DMF) medium at 130-140 °C and the resulted compound was characterized as 6-(9*H*-carbazol-4-yloxymethyl)-4-*o*-tolyl-morpholin-3-one (**2a**) based on its IR, ^{1}H NMR and mass spectral data. Mass spectrum displayed the molecular ion peak at m/z 409 (M^+ + Na). IR spectrum (KBr, cm^{-1}) showed characteristic absorptions at 3269 cm^{-1} (carbazole NH) and 1665 cm^{-1} (C=O). Chemical shift values at δ 2.3 (s, 3H), δ 3.8-4.0 (m, 2H), δ 4.35 (m, 1H), δ 4.4-4.6 (m, 4H), δ 6.6-8.25 (m, 11H) and δ 8.16 (s, 1H) in the ^{1}H NMR ($CDCl_3$) spectrum fully supported the assigned cyclic structure **2a**. Series of other morpholinonyl derivatives (**2b-l**) were synthesized by conducting the reaction of corresponding carbazolyloxy propanolamine derivatives (**1b-l**) with chloroacetyl chloride in a similar manner (**Scheme-I**). Spectral data of these compounds are provided in the experimental section.

In order to synthesize other functionalized derivatives, we employed ethyl chlorooxoacetate as a two carbon source to afford 6-(9*H*-carbazol-4-yloxymethyl)-4-*o*-tolyl-morpholine-2,3-dione (**3a**) by performing the reaction of 1-(9*H*-carbazol-4-yloxy)-3-*o*-tolylamino-propan-2-ol (**1a**) in the presence of sodium hydroxide in dichloromethane at 0-5 °C. IR, ^{1}H NMR and mass spectral data support the morpholine-2,3-dione structure of **3a**. Mass spectrum with molecular ion peak at m/z 423 (M^+ + Na), IR spectrum with absorptions corresponding to carbazole NH (3341 cm^{-1}), O-C=O (1762 cm^{-1}) and N-C=O (1684 cm^{-1}) functions, ^{1}H NMR spectrum (DMSO-d_6) with chemical shift values at δ 2.3 (s, 3H), δ 3.8-4.6 (m, 4H), δ 5.7 (m, 1H), δ 6.7-8.3 (m, 11H) and δ 11.3 (s, 1H) are in conformity with the assigned structure of **3a**. Similar protocol was practiced to synthesize the other morpholinedionyl derivatives (**3b-l**) (**Scheme-I**).

To extend the synthesis of other derivatives, 1-bromo-2-chloroethane easily reacted with 1-(9*H*-carbazol-4-yloxy)-3-*o*-tolylamino-propan-2-ol (**1a**) in the presence of potassium carbonate in N,N-dimethyl formamide at 90-100 °C and yielded 4-(4-*o*-tolyl-morpholin-2-ylmethoxy)-9*H*-carbazole (**4a**) as a crystalline solid. Mass spectrum [molecular ion m/z 373 (M^+ + H), 395 (M^+ + Na)], IR spectrum [3407 cm^{-1} (carbazole NH)] and ^{1}H NMR (DMSO-d_6) spectral data [δ 2.2 (s, 3H), δ 2.8 (m, 2H) δ 3.5-3.7 (m, 2H), δ 3.8 (m, 2H), δ 4.0-4.4 (m, 3H) δ 6.7-8.2 (m, 11H)] are in agreement with the assigned structure of **4a**. Reaction of **1a** with 1-bromo-2-chloroethane was extended to eleven other carbazolyloxy propanolamine derivatives (**1b-l, Scheme-I**) and in all the cases corresponding morpholinyl derivatives (**4b-l)** were obtained in excellent yields.



1, 2, 3 and 4	a	b	c	d	e	f
R=						

1, 2, 3 and 4	g	h	i	j	k	l
R=		-CH_3	-C_2H_5	-C_3H_7	-C_4H_9	-C_5H_{11}

Scheme-I: Synthetic scheme of carbazolyloxy substituted oxazinane derivatives

Conclusion

Several new carbazolyloxy substituted oxazinane derivatives such as morpholinonyl, morpholinedionyl and morpholinyl were synthesized in good yields by reacting the corresponding carbazolyloxy propanolamine derivatives with different two carbon sources, chloroacetyl chloride, ethyl chlorooxoacetate and 1-bromo-2-chloroethane, respectively aiming to identify potential lead structures as β-blocking agents.

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