SYNTHESIS OF NEW OXAZOLIDINONYL/OXAZOLIDINYL CARBAZOLE DERIVATIVES FOR β- BLOCKING ACTIVITY

Raghupathi Reddy Anumula[a], Mukkanti Kagga [b], Mahesh Reddy Ghanta[a] and Pratap Reddy Padi[a]*
[a]Department of Research and Development; Unit-IlI, Dr. Reddys Laboratories Ltd.
Plot.No.116, S.V. Co-operative Industrial Estate, IDA, Bollaram, Jinnaram
Medak Dist.-502325, Andhra Pradesh, India
*Corresponding author: Tel: +91 40 23098610, Fax: +91 40 23095438
E-mail: pratapрp@drreddys.com
[b]Institute of Science and Technology, Center for Environmental Science,
J. N. T. University, Kukatpally, Hyderabad-500 072, India

Abstract : Preparation of some new carbazolyloxy propanolamine derivatives and their cyclization into corresponding oxazolidinonyl/oxazolidinyl carbazole derivatives were described.

Introduction

β-Adrenergic blocking agents (β-blockers)[1-4] mostly comprising of β-amino alcohols are of pharmaceutical significance and have received major attention due to their utility in the management of cardiovascular disorders[5] including hypertension,[6] anginapectoris, cardiac arrhythmias, and other disorders[7] related to the sympathetic nervous system.

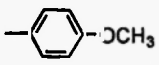
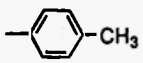
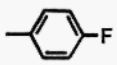
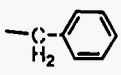
Aryloxypropanolamine structure is the key pharmacophore in β-Blockers.[8] Propranolol[3] is the prototype agent for this class of compounds. While propranolol affects β_1 and β_2 receptors, other drugs such as atenolol[9] and metoprolol[10] have greater affinity for β_1 receptors and are described as cardioselective. Betaxolol[11] is the most β_1 selective of the currently available agents.

As a part of our studies towards the synthesis of new drug candidates, we have prepared some new carbazolyloxy propanolamine derivatives and their corresponding cyclised compounds to study their β-blocking activity.

Results and discussion

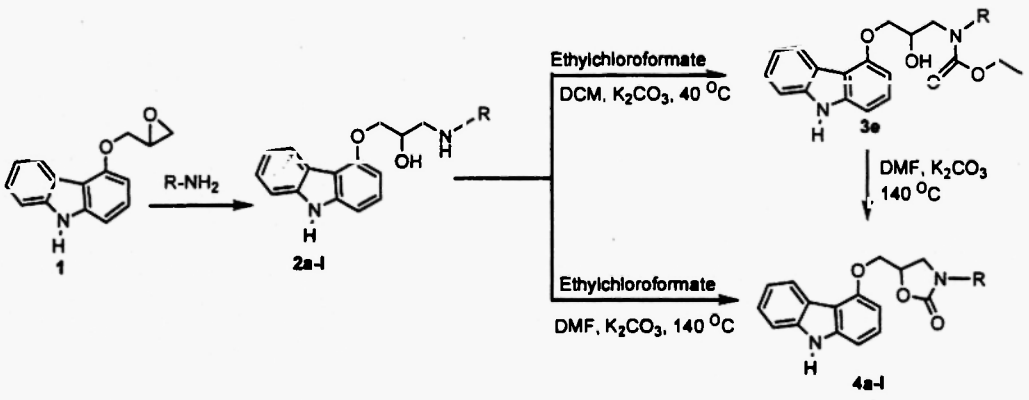
Oxirane ring opening in carbazole propyloxy epoxide **1** by using aliphatic and aromatic amines as nucleophiles served as an apt pathway in getting the desired amino alcohols. Required precursor **1** was prepared by a known procedure by condensing 4-hydroxy carbazole with epichlorohydrin.[12] Thus, epoxy compound **1** smoothly provided 1-(9*H*-carbazol-4 yloxy)-3-((4-methoxy phenyl) amino)-propan-2-ol (**2a**) on reacting with 4-methoxy aniline in refluxing toluene. Several aromatic and aliphatic amines were employed to provide corresponding amino alcohols **2b-l** (Table-1).

Table-1: Physical and spectral data of 2

Compound	R	Yield (%)	MR (^{0}C)	Mass (M+1)	IR (cm^{-1}, (OH))	^{1}H NMR#((δ ppm)
2a		61	123-127	363	3391	3.15 -3.4 (m, 2H), 3.6 (s, 3H), 4.2 (m, 3H), 5.2 (s, 1H), 5.3 (s, 1H), 6.6-8.4 (m, 11H), 11.2 (s, 1H)
2b		62	92-96	347	3328	2.1 (s, 3H), 3.15 -3.4 (m, 2H), 4.2 (m, 3H), 5.2 (s, 1H), 5.35 (s, 1H), 6.5-8.3 (m, 11H), 11.25 (s, 1H)
2c		55	128-132	351	3343	3.0-3.6 (m, 2H), 4.2-4.4 (m, 3H), 5.25 (s, 1H), 5.6 (s, 1H), 6.5-8.3 (m, 11H), 11.25 (s, 1H)
2d		65	106-110	347	3384	2.1 (s, 3H), 3.25 -3.5 (m, 2H), 4.25 (m, 3H), 4.8 (s, 1H), 5.35 (s, 1H), 6.5-8.3 (m, 11H), 11.25 (s, 1H)
2e		72	140-145	333	3350	3.2-3.5 (m, 2H), 4.25 (m, 3H), 5.25 (s, 1H), 5.65 (s, 1H), 6.5-8.3 (m, 12H), 11.2 (s, 1H)
2f		72	127-130	347	3418	2.7-2.9 (m, 2H), 3.75 (s, 2H), 4.0-4.2 (m, 3H) 5.1 (s, 1H), 6.6-8.2 (m, 12H), 11.2 (s, 1H)
2g		55	106-109	339	3317	1.0-1.9 (m, 10H), 2.4 (m, 1H), 2.7-3.0 (m, 2H), 4.0-4.3 (m, 3H), 5.0 (s, 1H), 6.6-8.25 (m, 7H), 11.2 (s, 1H)
2h	-CH_3	72	127-130	271	3336	2.3 (s, 3H), 2.7-2.85 (m, 2H) 4.0-4.2 (m, 3H), 5.1 (s, 1H) 6.65-8.25 (m, 7H), 11.2 (s, 1H)
2i	-C_2H_5	80	118-121	285	3381	1.1 (t, 3H), 2.6 (q, 2H), 2.7-2.9 (m, 2H), 4.0-4.2 (m, 3H), 5.1 (s, 1H), 6.6-8.2 (m, 7H), 11.25 (s, 1H)
2j	-n-C_3H_7	76	105-109	299	3382	0.9 (t, 3H), 1.45 (m, 2H), 2.5 (m, 2H), 2.7-2.9 (m, 2H) 4.0-4.2 (m, 3H), 5.1 (s, 1H), 6.6-8.25 (m, 7H), 11.2 (s, 1H)
2k	-n-C_4H_9	69	88-91	313	3287	0.85 (t, 3H), 1.2-1.5 (m, 4H), 2.6 (m, 2H), 2.7-2.9 (m, 2H) 4.0-4.2 (m, 3H), 5.1 (s, 1H), 6.6-8.25 (m, 7H), 11.2 (s, 1H)
2l	-n-C_5H_{11}	66	103-106	327	3303	0.85 (t, 3H), 1.2-1.5 (m, 6H), 2.6 (m, 2H) 2.7-2.9 (m, 2H) 4.0-4.2 (m, 3H), 5.1 (s,1H), 6.6-8.25 (m, 7H), 11.2 (s, 1H)

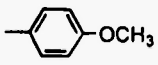
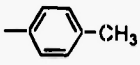
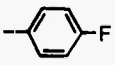
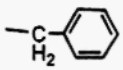
^{1}H NMR spectra of 2a, 2b, 2d, 2e, 2f, 2g,2h, 2i, 2j,2k and 2l were recorded at 400 MHz where as 2c was recorded at 200 MHz in DMSO-d_6.

Several reagents such as phosgene,[13] diethylcarbonate,[14] carbonyldiimidazole,[15] trichloromethyl chloroformate[16] and bis trichloromethyl carbonate[17] were hitherto used as one carbon source in bridging the hydroxy and amino functions of amino alcohols to furnish oxazolidinone derivatives. In the present work, we have used ethyl chloroformate as a gainful reagent. Thus, reaction of **2e** with ethyl chloroformate in the presence of K_2CO_3 in dichloromethane at 40 ^oC provided a white solid, characterized as [3-(9*H*-carbazol-4-yloxy)-2-hydroxy-propyl]-phenyl-carbamic acid ethyl ester (**3e**) based on its IR, ^{1}H-NMR and mass spectral data. In the mass spectrum, molecular ion peak appeared at 405 (M^{+1}). IR spectrum showed N-H (3391) and carbonyl (1668) absorptions. ^{1}H-NMR with signals at δ 1.15 (t, 3H), 3.8 (m, IH), 4.0-4.25 (m, 6H), 5.35 (d, 1H), 6.6-8.15 (m, 12H), 11.2 (s, 1H) was in conformity with the open chain structure **3e**. The carboxamido ester **3e** underwent dehydroethoxy cyclization in DMF/K_2CO_3 at 140 ^oC to yield 5-(9H-carbazol-4-yloxymethyl)-3-phenyl-oxazolidin-2-one (**4e**) whose structure was assigned based on its IR, ^{1}H-NMR and mass spectral data. Mass spectrum showed highest peak at m/z 359. IR spectrum in KBr (cm^{-1}) showed characteristic peaks at 3402 (NH) and 1729 (C=O). Chemical shift values at 4.1-4.6 (m, 4H), 5.25 (m, 1H), 6.5-7.8 (m, 12H), 11.2 (s, 1H) in the ^{1}H-NMR(DMSO-d_6) spectrum fully support the assigned structure. When compound **2a** was reacted with ethyl chloroformate in DMF in the presence of K_2CO_3 at 140 ^oC, reaction directly provided **4a** (Scheme-1). Compounds **2b-l** were directly converted in to corresponding oxazolidinone derivatives **4b-l** in good yields (Table-2) by heating with ethyl chloroformate in DMF at 140 ^oC in the presence of K_2CO_3.



Scheme-1

Table-2: Physical and spectral data of 4

Compound	R	Yield (%)	MR (°C)	Mass (M+1)	IR (cm^{-1}) NH	IR (cm^{-1}) C=O	^{1}H NMR# (δ, ppm)
4a		62	165-170	389	3377	1736	3.8 (s, 3H), 4-4.6 (m, 4H), 5.25 (m, 1H) 6.65-7.85 (m, 11H), 11.25 (s, 1H)
4b		74	202-205	373	3294	1722	2.3 (s, 3H), 4.1-4.6 (m, 4H), 5.25 (m, 1H), 6.5-7.85 (m, 11H), 11.25 (s, 1H)
4c		64	204-207	377	3304	1714	4.1-4.6 (m, 4H), 5.3 (m, 1H), 6.6-7.8 (m, 11H), 11.2 (s, 1H)
4d		93	185-190	373	3267	1731	2.25 (s, 3H), 4.0-4.6 (m, 4H), 5.3 (m, 1H), 6.7-8.2 (m, 11H), 11.25 (s, 1H)
4e		74	220-225	359	3402	1729	4.1-4.6 (m, 4H), 5.25 (m, 1H), 6.5-7.9 (m, 12H), 11.25 (s, 1H)
4f		81	205-208	373	3247	1727	3.4-3.9 (m, 4H), 4.25-4.5 (m, 2H), 5.15 (m, 1H), 6.7-8.1 (m, 12H), 11.3(s, 1H)
4g		80	182-185	365	3254	1719	1.0-1.9 (m, 10H), 3.5-3.8 (m, 3H), 4.3-4.5 (m, 2H), 5.05 (m, 1H), 6.7-8.1 (m, 7H), 11.25 (s, 1H)
4h	-CH_3	78	252-256	297	3235	1738	2.9 (s, 3H), 3.5-3.9 (m, 2H), 4.3-4.5 (m, 2H), 5.05 (m, 1H), 6.7-8.05 (m, 7H), 11.3 (s, 1H)
4i	-C_2H_5	92	190-195	311	3255	1739	1.18 (t, 3H), 3.3 (m, 2H), 3.6-3.8 (m, 2H), 4.3- 4. 45 (m, 2H), 5.1 (m, 1H) 6.7-8.1, (m, 7H), 11.3 (s, 1H)
4j	-n-C_3H_7	83	165-170	325	3246	1736	0.9 (t, 3H), 1.6 (m, 2H), 3.2-3.4 (m, 2H,) 3.6-3.9 (m, 2H), 4.3-4.5 (m, 2H), 5.1 (m, 1H) 6.7-8.1 (m, 7H), 11.3 (s, 1H)
4k	-n-C_4H_9	79	115-120	339	3246	1731	0.9 (t, 3H), 1.3 (m, 2H), 1.5 (m, 2H), 3.2-3.3 (m, 2H), 3.6-3.9 (m, 2H), 4.3-4.5 (m, 2H), 5.1 (m, 1H), 6.7-8.1 (m, 7H), 11.3 (s, 1H)
4l	-n-C_5H_{11}	81	120-125	353	3248	173 3	0.85 (t, 3H), 1.3 (m, 4H), 1.55 (m, 2H), 3.25 (m, 2H), 3.5-3.9 (m, 2H), 4.3-4.5 (m, 2H), 5.1 (m, 1H), 6.7-8.1 (m, 7H), 11.3 (s, 1H)

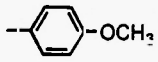
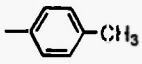
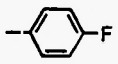
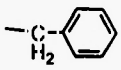
^{1}H NMR spectra of 4d, 4g,4h,4i,4j,4k and 4l were recorded at 400 MHz where as 4a, 4b,4c,4e and 4f were recorded at 200 MHz in DMSO-d_6.

^{13}C -NMR of 4a (DMSO-d_6): 38.25,38.66,39.08,39.5,39.91,40.33,40.75,46.41,55.25,68.18,70.51,100.37,104.38,110.32,111.36,114.15, 118.5,119.53,121.39,122.09, 124.55,126.4,131.68,138.84,141.09,154.25,154.46,155.50.

^{13}C-NMR of 4d (DMSO-d_6): 17.48,38.23,38.65,39.07,39.5,39.9,40.32,40.74,48.77,68.04,71.83,100.71, 104.45,110.45,111.53,118.54, 121.49,122.34, 124.71,126.42, 126.68,127.77,130.97,135.62,136.29,138.96,141.15,154.34,155.31.

The oxazolidine derivatives **5a-u** were synthesized from the condensation of *N*-substituted amino alcohols **2** with various aromatic/aliphatic aldehydes (Scheme-2). For example, reaction of **2a** with formaldehyde in methanol at 25-35 ^{O}C yielded a crystalline solid, characterized as 4-[3-(4-methoxy-phenyl)-oxazolidin-5-ylmethoxy]-9H-carbazole [**5a**, MS: 375 (M^{+}); IR: 3399 cm^{-1} (indole N-H); ^{1}H-NMR ($CDCl_3$, δ ppm): 3.75 (s, 3H), 3.6-3.7 (m, 2H), 4.4 (m, 2H), 4.9-5.2 (m, 3H), 6.6-8.3 (m, 11H)]. This reaction was extended to twenty other aliphatic and aromatic aldehydes and in all the cases corresponding oxazolidine derivatives **5b-u** were obtained in good yields (Table-3 & 4).

Table-3: Physical and spectral data of 5

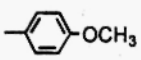
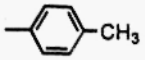
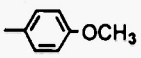
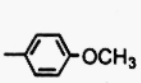
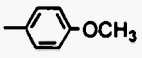
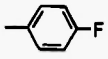
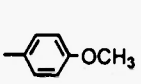
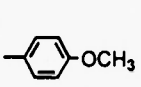
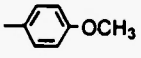
Compound	R	Yield (%)	MR (^{0}C)	Mass (M+1)	IR (cm^{-1}, NH)	^{1}H NMR#(δ, ppm)
5a		77	156-159	375	3399	3.6-3.75 (m, 2H), 3.8 (s, 3H), 4.3-4.5 (m, 2H), 4.9-5.1 (m, 3H), 6.6-8.3 (m, 11H)
5b		76	135-138	359	3391	2.3 (s, 3H), 3.6-3.8 (m, 2H), 4.3-4.4 (m, 2H), 4.9 -5.2 (m, 3H), 6.5-8.3 (m, 11H)
5c		76	170-172	363	3410	3.6-3.8 (m, 2H), 4.4–4.5 (m, 2H), 4.9-5.2 (m, 3H), 6.5-8.3 (m, 11H)
5d		77	125-127	359	3407	2.4 (s, 3H), 3.5-3.7 (m, 2H), 4.2-4.5 (m, 2H), 4.6-5.0 (m, 2H), 6.5-8.3 (m, 11H)
5e		77	101-103	345	3393	3.6-3.8 (m, 2H), 4.3-4.5 (m, 2H), 4.9-5.2 (m, 3H), 6.6-8.3 (m, 12H)
5f		58	134-136	359	3409	2.6 (s, 2H), 2.8-3.2 (m, 2H) 4.0-4.6 (m, 5H), 6.6-8.2 (m, 7H)
5g		40	110-113	351	3222	1.0-1.8 (m, 10H), 2.3 (m, 1H), 2.9-3.3 (m, 2H), 4.2-4.7 (m, 5H), 6.7-8.3 (m, 7H)
5h	-CH_3	76	139-144	283	3220	2.4 (s, 3H), 2.8-3.2 (m, 2H), 4.0-4.6 (m, 5H), 6.6-8.2 (m, 7H), 11.2 (s, 1H)
5i	-C_2H5	77	120-122	297	3400	0.9 (t, 3H), 2.6 (m, 2H), 2.8-3.2 (m, 2H), 4.0-4.6 (m, 5H), 6.6-8.2 (m, 7H)
5j	-n-C_3H_7	77	129-131	311	3401	0.9 (t, 3H), 1.5 (m, 2H), 2.5 (m, 2H), 2.8-3.2 (m, 2H), 4.1-4.5 (m, 5H), 6.7-8.2 (m, 7H), 11.2 (s, 1H)
5k	-n-C_4H_9	77	101-103	325	3408	0.9 (t, 3H), 1.3-1.6 (m, 4H), 2.5-2.7 (m, 2H), 3.0-3.4 (m, 2H), 4.2-4.7 (m, 5H), 6.6-8.3 (m, 7H)
5l	-n-C_5H_{11}	58	130-133	339	3219	0.9 (t, 3H), 1.2-1.6 (m, 6H), 2.6-2.7(m, 2H), 3.0-3.4 (m, 2H), 4.2-4.6(m, 5H), 6.6-8.3 (m, 7H)

1. ^{1}H NMR spectra of **5a,5b, 5d, 5g ,5i and 5j** were recorded at 400 MHz where as **5c,5e,5f,5h,5k**, and **5l** were recorded at 200 MHz.
2. ^{1}H-NMR spectra of **5a,5b,5c, 5d, 5e, 5f, 5g, 5i, 5k** and **5l** were recorded in $CDCl_3$; **5h** and **5j** were recorded in DMSO-d_6

^{13}C -NMR of 5a: 38.07,38.48,38.89,39.32,39.74,48.26,54.52,67.85,75.35,76.35,77,77.65,81.38,99.29,103.32,109.25,111.08,113.34,113.56,113.84,117.83, 119.87,120.97, 121.67,123.54,125.23,138.11,139.24,140.37,151.35,153.73.

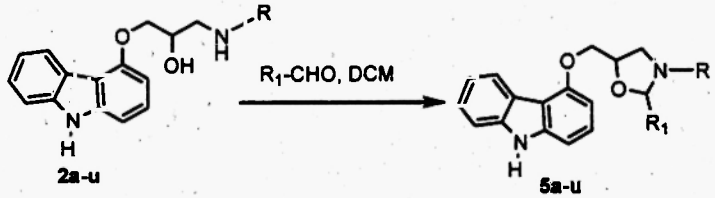
^{13}C -NMR of 5e: 38.24,38.65,39.08,39.5,39.91,40.33,40.75,47.62,65.63,68.35,76.06,77.07,77.72,78.37,81.01,99.83,103.91, 109.8,111.58,112.27,115.32,117.19, 118.37, 121.49, 122.19,124.09,125.79,128.81,138.67,140.93,144.90,154.25.

Table-4: Physical and spectral data of 5

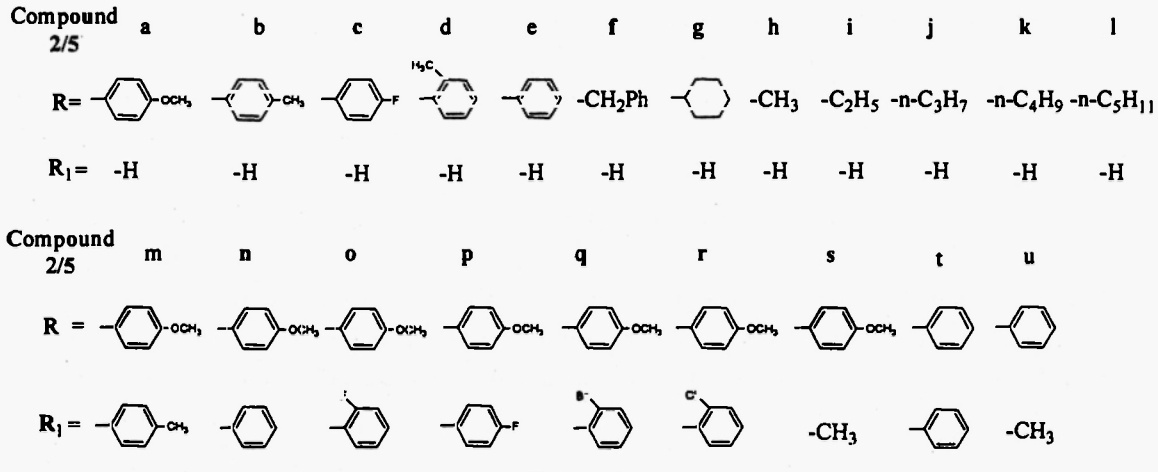
Compound	R	R_1	Yield (%)	MR (^{0}C)	Mass (M+1)	IR (cm^{-1}, N-H)	^{1}H NMR#(δ ppm)
5m			60	130-134	465	3326	2.3 (s, 3H), 3.5-3.7 (m, 5H), 4.0-4.5 (m, 3H), 4.9 (m, 1H), 6.4-8.3 (m, 15H,), 11.2 (s, 1H)
5n			64	153-155	451	3361	3.5-3.7 (m, 5H), 4.1-4.5 (m, 3H), 4.9 (m, 1H), 6.5-8.1 (m, 16H), 11.2 (s, 1H)
5o			46	140-145	469	3399	3.7 –3.8 (m, 5H), 4.1-4.6 (m, 3H), 4.9 (m, 1H), 6.4-8.3 (m, 15H)
5p			46	131-135	469	3352	3.6-3.8 (m, 5H), 4.1-4.5 (m, 3H), 4.9(m, 1H), 6.5-8.4 (m, 15H)
5q			54	120-123	530	3407	3.7-3.8 (m, 5H), 4.1-4.6 (m, 3H), 4.9 (m, 1H), 6.4-8.3 (m, 15H)
5r			60	144-147	485	3399	3.7 –3.8 (m, 5H), 4.1-4.6 (m, 3H), 4.9 (m, 1H), 6.4-8.3 (m, 15H)
5s		-CH_3	81.4	205-208	389	3467	1.5 (m, 3H), 3.4-3.7 (m, 6H), 4.1-4.5 (m, 2H), 4.9 (m, 1H), 6.6-7.5 (m, 11H)
5t			79	150-155	421	3400	3.7-3.9 (m, 2H), 4.1-4.5(m, 3H), 4.9 (m, 1H), 6.5-8.3 (m, 17H), 10.5 (s, 1H)
5u		-CH_3	74.5	202-205	389	3410	1.4 (m, 3H), 3.4-3.7 (m, 3H), 4.1-4.5 (m, 2H), 4.9 (m, 1H), 6.6-7.5 (m, 11H)

1. ^{1}H NMR spectra of 5m, 5n, 5o, 5p, 5q, 5r, 5s, 5t and 5u were recorded at 400 MHz
2. ^{1}H NMR spectra of 5o, 5p, 5q, 5r, and 5u were recorded in $CDCl_3$; 5m, 5n and 5s were recorded in DMSO-d_6; 5t was recorded in $CDCl_3$+DMSO-d_6

Compounds 2, 3, 4 and 5 will be screened for their activity and results will be reported in due course.



2a-u 5a-u



Scheme-2

Experimental

The ^{1}H and ^{13}C-NMR spectra were measured in DMSO and $CDCl_3$ using 400 and 200 MHz respectively, on a Varian Gemini & Varian Mercury plus 2000 FT NMR spectrometer; the chemical shift were reported in δ ppm. IR spectrum recorded in the solid state as KBr dispersion using Perkin Elmer 1650 FT IR spectrometer. The mass spectrum (70 eV) was 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 with out further purification.

General procedure for the preparation of compounds 2a-l

A mixture of 4-(2,3-epoxypropoxy) carbazole (**1**, 1.0 g, 0.004 mol) appropriate amine (0.008 mol) in toluene (10 mL) was refluxed for 10-24 hrs and reaction was monitored by thin layer chromatography. The reaction mixture was cooled to 25-35°C, maintained at same temperature for 30-45 min and filtered. Resulted compound 2 was dried under vacuum and used in the subsequent stage with out further purification.

Preparation of [3-(9*H*-carbazol-4-yloxy)-2-hydroxy-propyl]-phenyl-carbamic acid ethyl ester (3e)

A mixture of 1-(9*H*-carbazol-4 yloxy)-3- phenyl amino)-propan-2-ol (2e, 1.0 g, 0.0027 mol) and potassium carbonate (0.95 g, 0.0068 mol) in dichloromethane (10 mL) was cooled to 0-5°C, ethyl chloroformate (0.52 mL, 0.004 mol) was added to the reaction mass at the same temperature and reaction mixture was refluxed on water bath for 3 hrs at 40°C. After the completion of the reaction (vide TLC), the reaction mixture was cooled to 25-35°C, diluted with water (10 mL). Compound 3e was filtered and dried under vacuum.

Conversion of compound 3e to 4e

A mixture of [3-(9H-carbazol-4-yloxy)-2-hydroxy-propyl]-phenyl-carbamic acid ethyl ester (3e, 1.0 g, 0.0024 mol) and potassium carbonate (0.7 g, 0.005 mol) in dimethyl formamide (10 mL) was refluxed on oil bath for 3 hrs at 130-140°C. Reaction mixture was cooled to 25-35°C, diluted with water (10 mL) and compound 4e, which was obtained as a white solid, was filtered, dried.

General procedure for the preparation of compounds 4a-l

A mixture of 1-(9*H*-carbazol-4-yloxy)-3-(4-methoxy-phenylamino)-propan-2-ol (2a, 1.0 g 0.0027 mol) and potassium carbonate (2.5 mol) in dimethyl formamide (10 mL) was cooled to 0-5°C and ethyl chloroformate (1.5 mol) was added to it at the same temperature. Reaction mixture was refluxed on oil bath for 2-3 hrs at 130-140°C till the completion of reaction (vide TLC), cooled to 25-35°C and diluted with water (10 mL) the obtained residue was triturated with isopropyl alcohol (10 mL) and the resulted solid was filtered, dried.

General procedure for the preparation of compounds 5a-l

A mixture of 1-(9*H*-carbazol-4-yloxy)-3-(4-methoxy-phenylamino)-propan-2-ol (**2a**, 1.0 g, 0.0027 mol), methanol (5 mL), and formalin (40 % formaldehyde solution in water, 10 mL) was maintained at 25 – 35°C for 8 hrs till the completion of reaction (vide TLC). Reaction mixture was filtered and the obtained solid **5**, triturated with methanol and dried.

General procedure for the preparation of compounds 5m-u

To a solution of 1-(9*H*-carbazol-4-yloxy)-3-(4-methoxy-phenylamino)-propan-2-ol (**2a**, 1.0 g, 0.0027 mol) in DCM (5 mL), was added appropriate aldehyde (1.0 mol) and reaction mixture was maintained at 25-35°C for 12-16 hrs (vide TLC). Reaction mixture was treated with 10% sodium bicarbonate solution (10 mL), organic layer was separated and concentrated under vacuum, obtained solid **5**, triturated with methanol and dried.

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