

Design, synthesis and evaluation of carbazole derivatives as PPAR α / γ dual agonists and antioxidants[☆]

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Abstract—A series of hydroxycarbazole derivatives were synthesized and evaluated for PPAR α / γ dual agonist as well as antioxidant activities. While most compounds showed good antioxidant activity, some compounds were identified as potential PPAR α / γ dual agonists as well. Compounds **10a** and **16** were found to be active in animal studies.

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1. Introduction

Non-insulin dependent diabetes mellitus or type 2 diabetes is characterized by hyperglycemia due to insulin resistance.¹ A sharp increase in the incidence of type 2 diabetes especially in the developed and fast developing countries is a matter of serious concern. It is predicted that the world's diabetic population will be doubled to 300 million before 2025. Insulin resistance is a primary risk factor for type 2 diabetes mellitus.² Besides, these patients have elevated serum levels of fatty acids. Type 2 diabetic patients have an increased risk of developing various clinical complications due to microvascular or macrovascular diseases that include nephropathy, retinopathy and neuropathy.³

Since the identification of peroxisome proliferator activated receptors (PPAR α , γ and δ) of the nuclear receptor superfamily, rapid progress has been made in understanding their functions. Besides sensitizing insulin receptors, it has been established that they play a central role in regulating the storage and catabolism of lipids,

which is linked to the pathogenesis of diabetes.^{4–6} The role of PPAR γ activators in reducing hyperglycemia associated with type 2 diabetes was proved initially by use of thiazolidinediones (TZDs), which were already known to be normoglycemic.⁷ Likewise, fibrates like WY 14643, which were shown to reduce triglycerides (TG) and free fatty acids (FFA) and increase high density lipoproteins (HDL) were found to activate PPAR α .⁸

Though currently marketed TZDs, pioglitazone and rosiglitazone are effective in reducing glucose levels and have beneficial effects to some extent on TG, FFA and HDL cholesterol levels, they exhibit some undesirable effects like weight gain and edema.⁹

It was quickly realized that if ligands were designed to activate both PPAR α and PPAR γ , there could be a simultaneous control of both glucose and lipid levels in type 2 diabetic patients.¹⁰ So the inference that PPAR α / γ dual agonists could provide additive and possibly synergistic efficacy relative to selective activation of one subtype alone, lead to the reporting of many compounds having dual activation.^{11–13} The compounds of this class have a few essential pharmacophore elements. These comprise of an acidic group linked to a central flat ring and a large lipophilic substructure. Earlier, we had studied a series of glitazones replacing central phenyl ring by pyridine ring.¹⁴

Keywords: PPAR dual agonists; Hydroxycarbazoles; Hypoglycemic; Antioxidant; Transactivation; Lipid peroxidation.

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Another dimension to the complexity of the disease like diabetes is the role of oxidative stress right from its onset and all through the progression of this disease. It has been shown beyond doubt that diabetic subjects exhibit high lipid peroxides and other forms of oxidative stress.¹⁵ Oxidative stress seems to be caused by increased production of reactive oxygen species (ROS) and altered cellular redox states. Antioxidants are known to be interceptors of peroxy radicals and singlet oxygen and hence inhibit lipid peroxidation, which is implicated in the alternation of glucose transport and microangiopathic disease in diabetes. Supplementation with an antioxidant is a promising complementary treatment, which exerts beneficial effects in diabetes and provides further support for implications of oxidative stress in beta cell dysfunction in diabetes.^{16,17}

After troglitazone, which had a beneficial antioxidant activity, was withdrawn due to hepatic dysfunction and increase in lipoproteins, not much work has been carried out in designing antidiabetic compounds with antioxidant activity. Lohray et al. reported TZDs having chroman moieties and evaluated them for their euglycemic and hypolipidemic activities.¹⁸ They also found that when hydroxy group of chroman moiety of troglitazone was protected, it led to a decrease in metabolism and superior pharmacological profile.¹⁹

In a previous study, potent β - and selective α -adrenoceptor blocker carvedilol, which has hydroxycarbazole moiety, was shown to have potent antioxidant activity. Antioxidant effect of carvedilol mainly resides in carbazole moiety and substitution of hydroxyl group of carbazole resulted in an increase in antioxidant activity. The apparent mechanism of carvedilol's inhibition of lipid peroxidation was shown to be through scavenging free radicals.²⁰

2. Design concept

Compounds having tricyclic unit and α -ethoxy propionic acid group have shown good PPAR α/γ dual agonistic activity and some reached up to phase II clinical trials. Among these, carbazole analogue **1** (Fig. 1), which showed improved insulin sensitizing and lipid lowering effects in in vivo studies as compared to known TZDs, attracted us.²¹

By taking hydroxycarbazole as starting synthons, we attached the linker and receptor binding unit at oxygen and in some cases at nitrogen (Fig. 2). These compounds

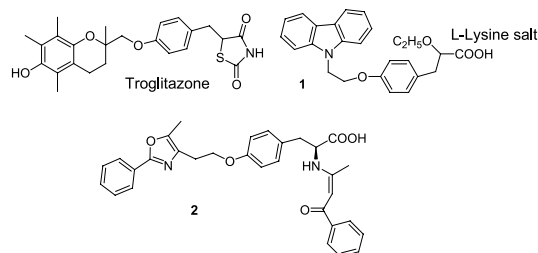


Figure 1. Some selected PPAR agonists.

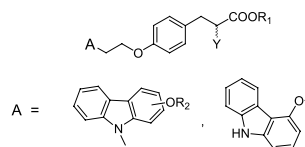


Figure 2. Designing of hydroxycarbazole derivatives.

we hoped, would show dual PPAR α/γ agonistic as well as antioxidant activities.

3. Chemistry

Starting with either 4- or 2-hydroxy carbazoles, their alkyl or aralkyl derivatives (**5a–f**) were synthesized using alkyl halides or aralkyl halides as shown in Scheme 1. These were then condensed with 4-(2-bromoethoxy) benzaldehyde (**3**), to obtain corresponding aldehyde **6**. Horner Wadsworth–Emmons reaction on these aldehydes using phosphonate (**4**),^{22,23} gave **7**. These esters were hydrogenated to get **8** and then hydrolyzed to acid **9**. The acids were then converted to their L-lysine salts **10**.

In Scheme 2, we have shown the synthesis of N-substituted L-tyrosine based derivative. Compound **13** was obtained by condensing L-tyrosine methyl ester **12** and benzoyl acetone (**11**).^{24–27} Condensing **13** with 4-(2-bromoethoxy)-9H-carbazole (**17**), gave **14**, which was then hydrolyzed to **15**. This was converted to its L-lysine salt **16**.

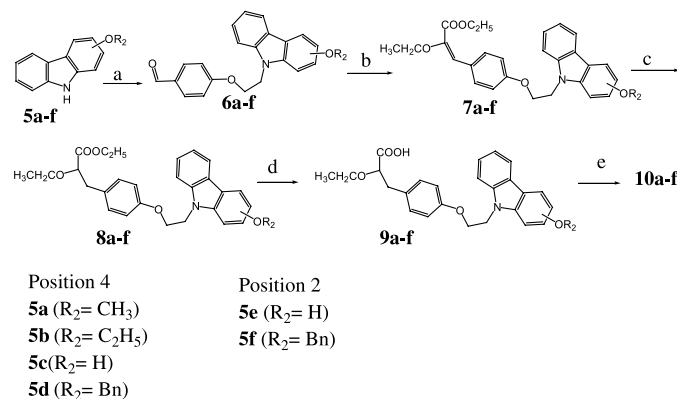
In another series, we explored some changes in the linker unit and the receptor binding unit when they are attached to oxygen of 4-hydroxycarbazole. Thus, starting from 4-(2-bromoethoxy)-9H-carbazole (**17**) various hydroxyesters like **18**, **20**, **22** and **25** were condensed to obtain compounds **19**, **21**, **23** and **26**, respectively. Compound **23** was hydrogenated to **24** and then hydrolyzed and made into L-lysine salt **24a**. Compounds **19**, **21**, **26** were hydrolyzed to give their respective carboxylic acid **19a**, **21a** and **26a** (Scheme 3).

4. Biological screening

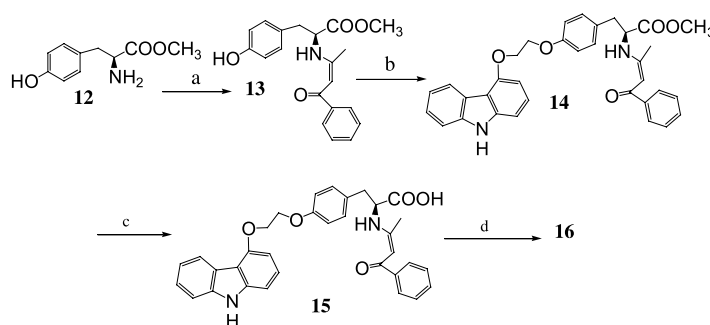
In vitro screening of compounds was done to evaluate their PPAR α/γ dual agonistic as well as their antioxidant potential.

4.1. Lipid peroxidation

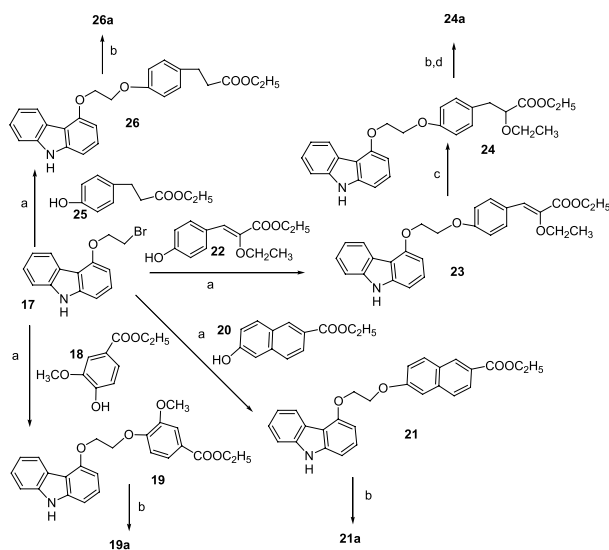
Aerobic incubation of rat brain homogenates with agents known to produce reactive oxygen species (ROS) like ferrous chloride and ascorbate, induce the process of lipid peroxidation, leading to the formation of degradation products of peroxidized lipids including malondialdehyde. This reacts with barbituric acid to yield a pink colour, whose intensity is read spectrophotometrically. The antioxidant activities of the compounds in their ester, acid and/or their L-lysine salt forms is shown in Table 1. Trolox was used as positive



Scheme 1. Reagents and conditions: (a) 4-(2-bromoethoxy)-benzaldehyde (**3**), NaH, THF; (b) ethyl-2-ethoxy-2-diethyl phosphonoacetate (**4**), NaH, THF; (c) H_2 , 10% Pd/C, ethyl acetate, 5 h; (d) 20% NaOH, ethanol, rt, 2 h; (e) L-lysine, ethanol, 1 h.



Scheme 2. Reagents and conditions: (a) benzoyl acetone (**11**), toluene, 4 Å molecular sieve, reflux; (b) 4-(2-bromoethoxy)-9H-carbazole (**17**), K_2CO_3 , acetone, reflux; (c) 20% NaOH, ethanol; (d) L-lysine, ethanol.



Scheme 3. Reagents and conditions: (a) K_2CO_3 , acetone, reflux; (b) 20% NaOH, ethanol; (c) H_2 , 10% Pd/C, ethyl acetate; (d) L-lysine, ethanol.

control and compound **1**, which is also a carbazole derivative without hydroxyl group is another control.

4.2. PPAR transactivation

The cells were transfected with an expression plasmid for PPAR receptors and activation of luciferase gene

was measured. Potencies of PPAR gene activation were evaluated in cell based transcription assays using GAL4-PPAR chimeric receptors.^{28,29} Transactivation studies were done for all the compounds in 3 concentrations both for PPAR γ and PPAR α using rosiglitazone and WY 14,643 as references, respectively (fold activation for 2 concentrations are shown in Table 1). PPAR α fold activation for fenofibrate was found to be 3.2 at 100 μM concentration.

4.3. In vivo studies

In vivo studies were done on db/db mice, which were used as a type 2 diabetic animal model. Male db/db mice at 12–13 weeks of age (seven per group) received a daily oral dosing of vehicle or test compounds for 14 days. The blood was collected on the 14th day for measurement of plasma glucose level. Cholesterol fed male Sprague–Dawley (SD) rats was used as another model to evaluate hypolipidemic effect of compound **16**, **10a** and **1**. Compounds were given through oral gavage and on 3rd day of treatment, TG, TC, HDL, LDL and VLDL levels were measured.

4.4. Results and discussion

All compounds with hydroxycarbazole structural motif, showed antioxidant activity as determined by lipid peroxidation test. Compound **1** showed activity at $>300 \mu\text{M}$, while the rest, which were derivatives of

Table 1. Lipid peroxidation and PPAR fold activation

Sr. No.	Compound	Lipid peroxidation IC ₅₀ (μM)	PPARα Fold activation		PPARγ Fold activation	
			1 μM	50 μM	1 μM	50 μM
1	10a	41.88	3.3	9.7	6.7	40.4
2	10b	49.15	2.9	5.6	6.4	18.0
3	10c	07.28	1.0	3.7	5.2	14.2
4	10d	16.59	1.9	4.0	11.8	16.9
5	10e	24.09	1.2	2.4	2.2	11.8
6	10f	ND	1.1	1.9	0.7	4.1
7	14	ND	3.2	4.4	12.9	29.4
8	16	00.35	2.7	5.4	20.9	47.6
9	23	01.28	1.2	2.5	0.5	5.8
10	24	01.85	1.3	1.3	0.7	5.8
11	24a	17.09	1.0	2.0	0.6	10.2
12	19	01.29	ND	ND	ND	ND
13	19a	ND	1.1	4.2	0.9	2.0
14	21	04.71	ND	ND	ND	ND
15	21a	ND	1.1	2.2	3.0	3.7
16	26	20.01	ND	ND	0.6	1.8
17	26a	ND	ND	ND	1.1	1.8
18	1	≥300	2.5	6.2	11.5	18.3
19	Trolox	07.43	—	—	—	—
20	WY 14643	—	1.3	4.0	—	—
21	Rosiglitazone	—	—	—	15.4	22.5

ND—Not done.

hydroxycarbazole exhibited an antioxidant IC₅₀ value ranging from 49.0 μM to 0.35 μM. Among these, 4-hydroxycarbazole based compounds exhibited better antioxidant activity as compared to 2-hydroxycarbazole derivatives. Compound **16** having IC₅₀ = 0.35 μM turned out to be around 20-fold more potent than reference trolox (IC₅₀ = 7.48 μM). Compounds **19a** and **20a**, which have carboxylic acid group attached directly to the aromatic ring also exhibited good antioxidant activity (Table 1).

Transactivation studies exhibited that α-alkoxypropionic acid series showed good PPARα activity (around 2-fold higher than WY) but PPARγ activity was seen only at higher concentrations. L-Tyrosine based compound **14** and its L-lysine salt **16** have good PPARα/γ dual activity. They exhibited better activity than WY and equipotency with rosiglitazone. Comparative dose response studies of compounds **10a** and **16** were performed with rosiglitazone for PPARγ and WY for PPARα (Fig. 3). Compounds **10a** and **16** showed less potency (EC₅₀ = 11.48 μM) and (EC₅₀ = 1.68 μM), respectively, as compared to rosiglitazone (EC₅₀ = 0.78 μM). However both these compounds show more potency (EC₅₀ = 8.27 μM) and (EC₅₀ = 8.10 μM), respectively, for PPARα activation than WY 14,643 (EC₅₀ = 23.92 μM). Rest of the compounds, with variations in linker and acid chain length did not show much activity.

It is interesting to note that when the α-alkoxy propionic acid derivative **24a**, having linkage at O-atom, showed lower activity as compared to **10a**, where it is linked to N-atom of hydroxycarbazole. Compound **10a** of α-alkoxy propionic series and **16**, which is of L-tyrosine series, were chosen for in vivo studies.

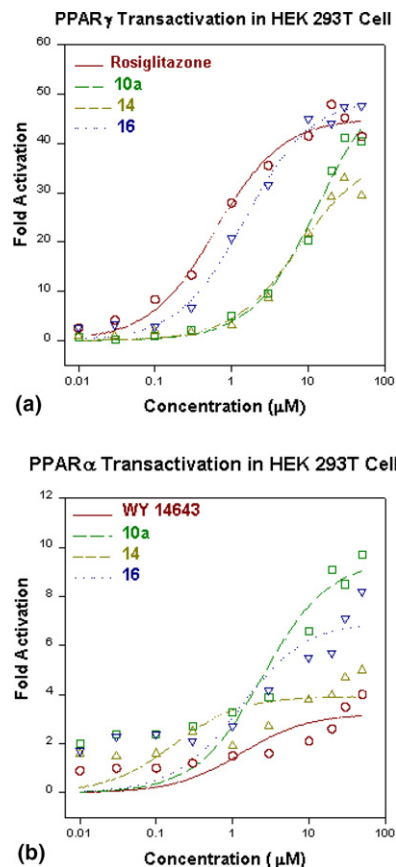


Figure 3. Note: Each compound was tested in 10 concentrations ranging from 0.01 to 50 μM.

In vivo experiments done in db/db mice for **10a**, **16** and **1** gave some very interesting results. While PG level was

significantly reduced by **10a** when given orally on 14th day by about 70%, compound **16** did not show significant reduction. Similarly, **10a** significantly reduced TG level in db/db mice by 45% when given orally while **16** did not show any TG lowering effect (Table 2).

Surprisingly, the results of PPAR transactivation assays do not correlate with the plasma glucose and triglyceride lowering activities in orally fed db/db mice studies of **16**. However, when **16** was tested in cholesterol fed SD rats orally, it showed significant lowering in TC, TG, LDL and VLDL levels and increase in HDL level (Table 3). These results can be attributed to species differences, which need to be confirmed through further studies.

Compounds **16** and **10a** show better profile than compound **1** regarding TC and LDL lowering and increase in HDL.

5. Conclusion

Our studies have shown that many hydroxycarbazole derivatives are both PPAR α/γ dual agonists as well as antioxidants. In vivo studies in fat fed SD rats show that compounds **10a** and **16** to have better profile than compound **1**. We have studied compounds linked at O-atom of hydroxycarbazole for the first time. Further pharmacological studies on these compounds are underway.

6. Experimental

6.1. General experimental details

Thin layer chromatography analyses were performed on precoated silica gel plates (GF254, Merck). Chromatography was performed on flash silica gel (230–400 mesh). Melting points were recorded on a Buchi capillary melting point apparatus and are uncorrected. Parr shaker

used for hydrogenation is from Perfit-India. Infrared (IR) spectra were recorded on a Nicolet Impact-410 FTIR spectrometer. Proton magnetic resonance (NMR) spectra were recorded on a Bruker 300 MHz spectrometer in CDCl₃, CD₃OD, D₂O or DMSO-*d*₆ solution. The chemical shifts are reported in δ (ppm) relative to internal standard tetramethylsilane (TMS) and coupling constants *J* are given in Hz. Mass spectroscopy was conducted using Shimadzu QP5000 mass spectrometer, LCQ Finnigan MAT and Bruker Daltonics MALDI Tandem TOF mass spectrometer. Elemental analyses were obtained from Elementar Vario[®]EL.

6.2. Biological study

PPAR transactivation: The response element (UAS-GAL4*5) was cloned upstream of the Pgl2-sv 40-Luc reporter (Promega, Madison, WI, USA), which contains the Simian virus early promoter for luciferase assay. GAL4 fusions were made by fusing human PPAR γ 1 or PPAR α ligand-binding domain (amino acids: 174–475) to the C-terminal end of the yeast GAL4 DNA-binding domain (amino acids: 1–147) of the pM1 vector. PadVantage (Promega, Madison, WI, USA) vector was used to enhance luciferase expression.

HEK 293T cells were grown in Dulbecco's modified Eagle's medium supplemented with 10% foetal bovine serum (DMEM-FBS) at 37 °C in 5% CO₂. At 1 day prior to transfection, cells were plated to 50–60% confluence in DMEM containing 10% delipidated FBS (DMEM-DFBS). Cells were transfected by Superfect as per the manufacturer's protocol. At 3 h after transfection, the reagent was removed and cells maintained in DMEM-DFBS. At 42 h after transfection, the cells were placed in phenol red-free DMEM-DFBS, and treated for 18 h with the test compounds or vehicle alone. The cells were lysed and assayed for luciferase activity. Luciferase activity was determined by using Lucite kit (Packard, CT, USA) in a Packard Top count and expressed as fold activation relative to untreated cells.

Table 2. Effect of **10a**, **16** and **1** on plasma glucose and plasma triglyceride in db/db mice

Group	0 day PG	14 day PG	% Reduction	0 day TG	14 day TG	% Reduction
Control	494.83 $\pm$ 37.36	454.56 $\pm$ 59.50	—	141.12 $\pm$ 30.48	154.13 $\pm$ 26.84	—
10a	495.97 $\pm$ 32.89	136.16 $\pm$ 10.46*	70	110.01 $\pm$ 24.59	66.31 $\pm$ 8.07*	45
16	477.12 $\pm$ 38.60	401.36 $\pm$ 30.23*	8	87.14 $\pm$ 7.36	170.01 $\pm$ 12.32*	NE
1	498.57 $\pm$ 25.67	200.31 $\pm$ 12.78*	56	130.18 $\pm$ 11.25	80.08 $\pm$ 5.56*	44

Note: *N* = 7/group. Values are mean $\pm$ SEM. All compounds were used at 10 mg/kg, p.o.

* *P* < 0.05 versus control group.

Table 3. Hypolipidemic effect of **16** in cholesterol fed SD rats: TC, TG, HDL, LDL and VLDL levels on 3rd day of treatment

Parameter/ compd	TC (mg/dl)	% Red	TG (mg/dl)	% Redn	HDL (mg/dl)	% Incr	LDL (mg/dl)	% Redn	VLDL (mg/dl)	% Redn
Control	607.43 $\pm$ 80.39	—	160.19 $\pm$ 26.91	—	12.29 $\pm$ 0.73	—	563.11 $\pm$ 79.64	—	32.04 $\pm$ 5.38	—
16	136.54 $\pm$ 3.37*	78	91.49 $\pm$ 1.81*	43	24.82 $\pm$ 2.36*	102	93.43 $\pm$ 5.88*	83	18.30 $\pm$ 0.36*	43
10a	255.84 $\pm$ 10.32	58	83.2 $\pm$ 5.32	48	19.42 $\pm$ 1.25	58	220.23 $\pm$ 15.86	61	16.19 $\pm$ 0.81	48
1	324.79 $\pm$ 22.51	46	106.23 $\pm$ 9.57	34	15.07 $\pm$ 1.98	23	292.76 $\pm$ 10.29	48	16.96 $\pm$ 1.58	48

Note: *N* = 7/group. Values are mean SEM. All compounds were used at 3 mg/kg, p.o.

* *P* < 0.05 versus control group.

In vivo studies: Animals C57 BL/6J-db/db mice were obtained from Jackson Laboratory, Bar Harbour, ME, USA at 6 weeks of age. Sprague–Dawley rats were bred at Dr. Reddy's Laboratories-Discovery Research (DRL-DR) animal house. All animals were maintained under 12 h light and 12 h dark cycle at $25 \pm 1^\circ\text{C}$. All animals were given standard laboratory chow (National Institute of Nutrition, Hyderabad, India) and water ad libitum. Male Sprague–Dawley rats weighing 157–253 g were made hyperlipidemic by feeding a high-fat diet containing 2% cholesterol and 1% sodium cholate mixed with standard laboratory chow. All animal experiments were carried out in accordance with internationally valid guidelines, and the experimental protocols were approved by DRL-DR animal ethics committee.

6.2.1. Lipid peroxidation. Preparation of rat brain homogenates: The male SD rats weighing 280–350 g were sacrificed by decapitation and the brains were immediately taken out and cleaned with ice cold 0.9% saline. Whole brain, except cerebellum, was homogenized with a polytron homogenizer in 10 vol of ice-cold saline. Then, homogenate volume was adjusted/diluted with ice-cold saline so as to give a final concentration of 10 mg/0.8 ml and frozen as aliquots at -20°C , if studied later (within 2 days).

Measurement of lipid peroxidation in rat brain homogenate: The rates of membrane lipid peroxidation were measured by the formation of thiobarbituric acid reactive substances (TBARS) by the methodology reported by Yue et al.,³⁰ with some modification. The rat brain homogenates (10 mg tissue/0.8 ml) were incubated at 37°C for 15 min with 6–8 different concentrations of 10 μl of a test compound or vehicle. Lipid peroxidation was initiated by addition of 0.1 ml each of 0.25 mM of FeCl_2 and 1 mM ascorbic acid. A final volume of 1 ml reaction mixture was further incubated for 30 min at 37°C in water bath and then the reaction was stopped by addition of 0.1 ml of 0.2% butylated hydroxytoluene. Thiobarbituric acid (0.67%) (TBA) reagent, 1 ml was then added and the mixture heated for 30 min at 95°C in water bath. The mixture then cooled on ice for 5 min. The TBARS were extracted by adding 2.0 ml of *n*-butanol and vortexed well for a minute and centrifuged for 5 min at 3000 rpm and the 1 ml aliquot of *n*-butanol phase was taken for measuring absorbance at 535 nm. Reactions without TBA were taken as blank. The antioxidant activity of test compounds was determined as percent inhibition of TBARS formation from the control absorbance values (i.e., in the absence of the test compound), which is assumed as 100%. The reference compound used is a well known antioxidant, trolox.

6.2.2. Statistical analysis. For in vivo studies, the data were represented as mean $\pm$ SEM and analyzed by unpaired Student *t* test if two groups and one way ANOVA if more than two groups, followed by multiple comparison test (Tukey's test). A value of $P < 0.05$ was considered statistically significant. For in vitro lipid peroxidation studies, a sigmoidal curve was plotted as percent inhibition versus log concentration and IC_{50}

(inhibitory concentration at which occurs 50% inhibition of TBARS formation) value for each compound was found out by nonlinear regression curve fitting using Graph Pad Prism software. Each measurement was the average of 2 or 3 experiments performed in duplicates. Similarly, EC_{50} value of the compounds **10a** and **16** were calculated in transactivation assays.

6.3. Synthetic procedures

6.3.1. General procedure for synthesis of 5a,b,d,f. To an ethyl acetate solution of 4-hydroxycarbazole (1.0 equiv) for **5a,b,d** or 2-hydroxycarbazole (for **5f**), tetrabutyl ammonium hydrogen sulfate (0.01 equiv), alkyl halide (1.5 equiv) was added potassium carbonate (1.2 equiv). The resulting suspension was refluxed for 12–14 h. The reaction mixture was diluted with ethyl acetate and water. The organic layer was separated and dried over anhydrous sodium sulfate, decanted, concentrated and chromatographed on silica gel. Elution with a gradient mixture of ethyl acetate/hexane yielded the title compounds (60–80%).

6.3.1.1. 4-Methoxy carbazole (5a). White solid. Mp 135°C . IR (KBr, cm^{-1}) 3393, 1599, 1452, 1260, 1100. ^1H NMR (CDCl_3) δ 4.07 (s, 3H), 6.68 (d, $J = 9$ Hz, 1H), 7.04 (d, $J = 8.1$ Hz, 1H), 7.05–7.39 (m, 4H), 8.05 (s, 1H), 8.31 (d, $J = 7.8$ Hz, 1H). MS (EI): 197 (m/z M^+).

6.3.1.2. 4-Ethoxy carbazole (5b). White solid. Mp 150°C . IR (KBr, cm^{-1}) 3395, 1601, 1454, 1262, 1100. ^1H NMR (CDCl_3) δ 1.62 (m, 3H), 4.25 (q, $J = 6$ Hz, 2H), 6.66 (d, $J = 8.1$ Hz, 1H), 7.02 (d, $J = 9.3$ Hz, 1H), 7.20–7.38 (m, 4H), 8.03 (s, 1H), 8.33 (d, $J = 7.8$ Hz, 1H). MS (EI): 211 (m/z M^+).

6.3.1.3. 4-Benzyloxycarbazole (5d). Off-white solid. Mp 180°C . IR (KBr, cm^{-1}) 3400, 1584, 1439, 1258, 1099. ^1H NMR (CDCl_3) δ 5.35 (s, 2H), 6.75 (d, $J = 7.8$ Hz, 1H), 7.06 (d, $J = 8.1$ Hz, 1H), 7.25–7.43 (m, 8H), 7.59 (d, $J = 7.2$ Hz, 1H), 8.06 (s, 1H), 8.31 (d, $J = 7.8$ Hz, 1H). MS (EI): 273 (m/z M^+).

6.3.1.4. 2-Benzyloxycarbazole (5f). Light yellow solid. Mp 175°C . ^1H NMR (CDCl_3) δ 5.11 (s, 2H), 6.91–6.97 (m, 2H), 7.14 (m, 1H), 7.23 (m, 2H), 7.32–7.46 (m, 6H), 7.95–8.03 (m, 2H). MS (EI): 273 (m/z M^+).

6.3.2. General procedure for synthesis of 6a,b,d,f. A dry THF solution of **5a,b,d,f** (1.0 equiv) under nitrogen was cooled to 0°C . Sodium hydride (60% dispersion in oil, 1.5 equiv) was added and the solution stirred for 30 min at 0°C . 4-(2-Bromoethoxy)-benzaldehyde (**3**), (1.1 equiv) was added and solution stirred at room temp over night. The reaction mixture was concentrated, poured in water and extracted in diethyl ether. The organic layer was separated and dried over anhydrous sodium sulfate, decanted, concentrated and chromatographed on silica gel. Elution with a gradient mixture of ethyl acetate/hexane yielded the title compounds as yellowish oil (50–65%).

6.3.2.1. 4-(2-(4-Methoxycarbazole)-ethoxy)-benzaldehyde (6a). IR (cm^{-1}) 1691, 1601, 1262, 1157, 740. ^1H NMR (CDCl_3) δ 4.07 (s, 3H), 4.39 (t, $J = 6$ Hz, 2H), 4.71 (t, $J = 6$ Hz, 2H), 6.7 (d, $J = 8.1$ Hz, 1H), 6.86 (d, $J = 8.7$ Hz, 2H), 7.1 (d, $J = 8.1$ Hz, 1H), 7.23–7.28 (m, 1H), 7.37–7.75 (m, 3H), 7.74 (d, $J = 8.7$ Hz, 2H), 8.34 (d, $J = 7.8$ Hz, 1H), 9.82 (s, 1H). MS (EI): 345 (m/z M^+).

6.3.2.2. 4-(2-(4-Ethoxycarbazole)-ethoxy)-benzaldehyde (6b). ^1H NMR (CDCl_3) δ 1.59 (t, $J = 6.9$ Hz, 3H), 4.3 (q, $J = 7.2$ Hz, 2H), 4.41 (t, $J = 6$ Hz, 2H), 4.71 (t, $J = 6$ Hz, 2H), 6.68 (d, $J = 8.1$ Hz, 1H), 6.88 (d, $J = 9$ Hz, 1H), 6.98 (d, $J = 9$ Hz, 2H), 7.07 (d, $J = 8.1$ Hz, 1H), 7.24–7.44 (m, 2H), 7.73 (d, $J = 9$ Hz, 2H), 8.35 (d, $J = 8.1$ Hz, 2H), 9.8 (s, 1H). MS (APCI): 360 (m/z $\text{M}+1$).

6.3.2.3. 4-(2-(4-Benzylloxycarbazole)-ethoxy)-benzaldehyde (6d). ^1H NMR (CDCl_3) δ 4.36 (t, $J = 6$ Hz, 2H), 4.68 (t, $J = 6$ Hz, 2H), 5.35 (s, 2H), 6.62 (m, 1H), 6.77 (d, $J = 9$ Hz, 2H), 6.85 (d, $J = 8.1$ Hz, 1H), 6.98 (d, $J = 8.4$ Hz, 2H), 7.11 (d, $J = 8$ Hz, 1H), 7.28–7.45 (m, 5H), 7.56 (d, $J = 7.2$ Hz, 2H), 7.9 (d, $J = 8.4$ Hz, 1H), 8.34 (d, $J = 7.5$ Hz, 1H), 9.79 (s, 1H). MS (APCI): 422 (m/z $\text{M}+1$).

6.3.2.4. 4-(2-(2-Benzylloxycarbazole)-ethoxy)-benzaldehyde (6f). ^1H NMR (CDCl_3) δ 4.42 (m, 2H), 4.67 (m, 2H), 5.11 (s, 2H), 6.65 (m, 1H), 7.03 (m, 2H), 7.34 (m, 3H), 7.37–7.48 (m, 5H), 7.86 (d, $J = 7.2$ Hz, 2H), 7.97 (m, 3H), 9.83 (s, 1H). MS (APCI): 422 (m/z $\text{M}+1$).

6.3.3. General procedure for synthesis of 7a,b,d,f. A dry THF solution of **6a,b,d,f** (1.0 equiv) under nitrogen was cooled to 0°C . Sodium hydride (60% dispersion in oil, 1.5 equiv) was added and the solution stirred for 30 min at 0°C . Ethyl-2-ethoxy-2-diethyl phosphonoacetate (**4**) (1.5 equiv) was added and solution stirred at room temp overnight. The reaction mixture was concentrated, poured in water and extracted in diethyl ether. The organic layer was separated and dried over anhydrous sodium sulfate, decanted, concentrated and chromatographed on silica gel. Elution with a gradient mixture of ethyl acetate/hexane yielded the title compounds as yellowish oil (50–65%).

6.3.3.1. Ethyl-2-ethoxy-3-{4-[2-(4-methoxycarbazole)-ethoxy]-phenyl}-2-propenoate (7a). ^1H NMR (CDCl_3) δ 1.12–1.57 (m, 6H), 3.94 (q, $J = 6$ Hz, 2H), 4.11 (s, 3H), 4.27 (q, $J = 6$ Hz, 2H), 4.35 (t, $J = 6$ Hz, 2H), 4.70 (t, $J = 6$ Hz, 2H), 6.71 (d, $J = 7.5$ Hz, 1H), 6.79 (d, $J = 8.7$ Hz, 1H), 6.90 (s, 1H), 7.12 (d, $J = 9$ Hz, 2H), 7.27 (m, 1H), 7.37–7.46 (m, 2H), 7.60 (d, $J = 9$ Hz, 2H), 8.34 (d, $J = 7.5$ Hz, 2H). MS (EI): 459 (m/z M^+).

6.3.3.2. Ethyl-2-ethoxy-3-{4-[2-(4-ethoxy-carbazole)-ethoxy]-phenyl}-2-propenoate (7b). ^1H NMR (CDCl_3) δ 1.29–1.35 (tt, $J = 6.9, 6.9$ Hz, 6H), 1.59 (t, $J = 6.9$ Hz, 3H), 3.94 (m, 1H), 4.08 (m, 1H), 4.25–4.37 (qq, $J = 6.6, 6.6$ Hz, 4H), 4.41 (t, $J = 6$ Hz, 2H), 4.65 (t, $J = 6$ Hz, 2H), 6.68 (d, $J = 8.4$ Hz, 1H), 6.78 (d, $J = 9$ Hz, 1H), 6.89 (s, 1H), 6.98 (d, $J = 7.5$ Hz, 2H), 7.07 (d, $J = 8.1$ Hz, 1H), 7.29–7.43 (m, 3H), 7.65 (d,

$J = 8.4$ Hz, 2H), 8.35 (d, $J = 7.2$ Hz, 1H). MS (APCI): 474 (m/z $\text{M}+1$).

6.3.3.3. Ethyl-2-ethoxy-3-{4-[2-(4-benzylloxycarbazole)-ethoxy]-phenyl}-2-propenoate (7d). ^1H NMR (CDCl_3) δ 1.28–1.42 (tt, $J = 6, 6$ Hz, 6H), 3.93 (q, $J = 6.9$ Hz, 2H), 4.27 (q, $J = 6.9$ Hz, 2H), 4.36 (t, $J = 6$ Hz, 2H), 4.71 (t, $J = 6$ Hz, 2H), 5.35 (s, 2H), 6.78 (m, 4H), 6.92 (s, 1H), 7.13 (d, $J = 8.4$ Hz, 1H), 7.23 (m, 1H), 7.36–7.47 (m, 5H), 7.57 (d, $J = 7.5$ Hz, 2H), 7.68 (d, $J = 8.7$ Hz, 2H), 8.34 (d, $J = 7.2$ Hz, 1H). MS (APCI): 536 (m/z $\text{M}+1$).

6.3.3.4. Ethyl-2-ethoxy-3-{4-[2-(2-benzylloxycarbazole)-ethoxy]-phenyl}-2-propenoate (7f). ^1H NMR (CDCl_3) δ 1.12–1.57 (m, 6H), 3.63–3.75 (m, 1H), 3.9 (m, 1H), 4.34 (q, $J = 3.3$ Hz, 2H), 4.41 (m, 2H), 4.69 (m, 2H), 5.11 (s, 2H), 6.65 (m, 1H), 6.9 (s, 1H), 6.92–7.0 (m, 3H), 7.23 (m, 2H), 7.28–7.34 (m, 5H), 7.37–7.43 (m, 2H), 8.02 (m, 3H). MS (APCI): 536 (m/z $\text{M}+1$).

6.3.4. General procedure for synthesis of 8a,b,d,f. To a 10 ml ethyl acetate solution of compounds (**7a,b,d,f**) (1.0 equiv), was added 10% Pd/C (0.1 equiv). The resulting suspension was placed in a Parr shaker and hydrogenated under hydrogen atmosphere at 60 psi for 5 h. The reaction suspension was then filtered through a pad of Celite, concentrated and chromatographed on silica gel. Elution with a gradient mixture of ethyl acetate/hexane yielded the title compounds as colourless oil (80–95%).

6.3.4.1. Ethyl-2-ethoxy-3-{4-[2-(4-methoxycarbazole)-ethoxy]-phenyl}propionate (8a). ^1H NMR (CDCl_3) δ 1.13 (t, $J = 6.9$ Hz, 3H), 1.34 (t, $J = 6$ Hz, 3H), 2.9 (d, $J = 6$ Hz, 2H), 3.3 (m, 1H), 3.58 (m, 1H), 3.91 (t, $J = 6$ Hz, 1H), 4.08 (s, 3H), 4.16 (q, $J = 6$ Hz, 2H), 4.30 (t, $J = 6$ Hz, 2H), 4.68 (t, $J = 6$ Hz, 2H), 6.71 (t, $J = 9$ Hz, 2H), 7.10 (t, $J = 6$ Hz, 2H), 7.27 (m, 2H), 7.37–7.45 (m, 3H), 8.34 (d, $J = 9$ Hz, 2H). MS (APCI): 462 (m/z $\text{M}+1$).

6.3.4.2. Ethyl-2-ethoxy-3-{4-[2-(4-ethoxycarbazole)-ethoxy]-phenyl}propionate (8b). ^1H NMR (CDCl_3) δ 1.31 (t, $J = 7.2$ Hz, 3H), 1.41 (t, $J = 6.9$ Hz, 3H), 1.61 (t, $J = 6.6$ Hz, 3H), 2.90 (d, $J = 6$ Hz, 2H), 3.27–3.33 (m, 1H), 3.51–3.59 (m, 1H), 3.93 (t, $J = 6.6$ Hz, 1H), 4.05 (q, $J = 6.9$ Hz, 2H), 4.14 (q, $J = 6$ Hz, 2H), 4.30 (t, $J = 6$ Hz, 2H), 4.67 (t, $J = 6$ Hz, 2H), 6.73 (d, $J = 8.4$ Hz, 2H), 6.88 (d, $J = 8.4$ Hz, 2H), 7.9 (d, $J = 7.8$ Hz, 2H), 7.20 (m, 2H), 7.37–7.45 (m, 2H), 8.35 (d, $J = 7.5$ Hz, 1H). MS (APCI): 476 (m/z $\text{M}+1$).

6.3.4.3. Ethyl-2-ethoxy-3-{4-[2-(4-benzylloxycarbazole)-ethoxy]-phenyl}propionate (8d). ^1H NMR (CDCl_3) δ 1.15 (t, $J = 6$ Hz, 3H), 1.41 (t, $J = 6$ Hz, 3H), 2.91 (d, $J = 6$ Hz, 2H), 3.3 (m, 1H), 3.6 (m, 1H), 3.9 (t, $J = 6.9$ Hz, 1H), 4.03 (q, $J = 6$ Hz, 2H), 4.31 (t, $J = 6$ Hz, 2H), 4.68 (t, $J = 6$ Hz, 2H), 5.35 (s, 2H), 6.65 (d, $J = 8.4$ Hz, 1H), 6.73 (d, $J = 9$ Hz, 2H), 6.88 (d, $J = 8.4$ Hz, 2H), 7.11 (d, $J = 8.4$ Hz, 2H), 7.25 (m, 2H), 7.38–7.47 (m, 5H), 7.68 (d, $J = 8.7$ Hz, 1H), 8.32 (d, $J = 7.2$ Hz, 1H). MS (APCI): 538 (m/z $\text{M}+1$).

6.3.4.4. Ethyl-2-ethoxy-3-{4-[2-(2-benzylloxycarbazole)-ethoxy]-phenyl}propionate (8f). ^1H NMR (CDCl_3) δ 1.12–1.57 (m, 6H), 2.91 (d, $J = 6$ Hz, 2H), 3.33 (m, 1H), 3.68 (m, 1H), 3.94 (t, $J = 6.9$ Hz, 1H), 4.03 (q, $J = 6$ Hz, 2H), 4.31 (t, $J = 6$ Hz, 2H), 4.68 (t, $J = 6$ Hz, 2H), 5.11 (s, 2H), 6.65 (m, 1H), 7.03 (m, 4H), 7.34 (m, 4H), 7.37–7.48 (m, 5H), 8.02 (m, 2H). MS (APCI): 538 (m/z $M+1$).

6.3.4.5. Ethyl-2-ethoxy-3-{4-[2-(4-hydroxycarbazole)-ethoxy]-phenyl}propionate (8c). To a 10 ml ethyl acetate solution of compound **7d** (1.0 equiv) was added 10% Pd/C (0.1 equiv). The resulting suspension was placed in a Parr shaker and debenzylated via hydrogenation under hydrogen atmosphere at 60 psi for 6 h at 50 °C. The reaction suspension was then filtered through a pad of Celite, concentrated and chromatographed on silica gel. Elution with a gradient mixture of ethyl acetate/hexane yielded the title compounds as colourless oil (80–95%). ^1H NMR (CDCl_3) δ 1.12–1.57 (m, 6H), 2.89 (d, $J = 6$ Hz, 2H), 3.4 (m, 1H), 3.6 (m, 1H), 3.9 (t, $J = 6.9$ Hz, 1H), 4.13 (q, $J = 6$ Hz, 2H), 4.31 (t, $J = 6$ Hz, 2H), 4.6 (s, 1H), 4.66 (t, $J = 6$ Hz, 2H), 6.72 (d, $J = 8.7$, 1H), 7.01 (d, $J = 8.4$ Hz, 2H), 7.08 (d, $J = 8.4$ Hz, 2H), 7.25 (m, 1H), 7.44 (m, 2H), 7.5 (m, 2H), 8.32 (d, $J = 7.2$ Hz, 1H). MS (APCI): 448 (m/z $M+1$).

6.3.4.6. Ethyl-2-ethoxy-3-{4-[2-(2-hydroxycarbazole)-ethoxy]-phenyl} propionate (8e). This compound was prepared from **7f** according to a procedure similar to the one used for the synthesis of compound **8c**. ^1H NMR (CDCl_3) δ 1.12–1.57 (m, 6H), 2.89 (d, $J = 6$ Hz, 2H), 3.4 (m, 1H), 3.6 (m, 1H), 3.9 (t, $J = 6.9$ Hz, 1H), 4.13 (q, $J = 6$ Hz, 2H), 4.31 (t, $J = 6$ Hz, 2H), 4.66 (t, $J = 6$ Hz, 2H), 4.8 (s, 1H), 6.72 (d, $J = 8.7$, 1H), 7.01 (d, $J = 8.4$ Hz, 2H), 7.08 (d, $J = 8.4$ Hz, 2H), 7.25 (m, 1H), 7.44 (m, 2H), 7.5 (m, 2H), 8.02 (d, $J = 7.2$ Hz, 1H). MS (APCI): 448 (m/z $M+1$).

6.3.5. General procedure for synthesis of 9a–f. To ethanol solution of compounds (**8a–f**) (1.0 equiv) was added 20% aqueous sodium hydroxide (1.0 equiv) and stirred at room temperature overnight. The reaction mixture was concentrated, acidified with acetic acid (pH 4). The acidic solution was extracted with ethyl acetate. The organic layer was separated and dried over anhydrous sodium sulfate, decanted and concentrated to yield the title compounds (90–95%).

6.3.5.1. 3-(4-(2-(4-Methoxycarbazole)-ethoxy)-phenyl)-2-ethoxy propionic acid (9a). ^1H NMR (CDCl_3) δ 1.41 (t, $J = 6.9$ Hz, 3H), 2.9–3.02 (m, 2H), 3.39 (m, 2H), 3.54 (m, 2H), 3.99 (m, 1H), 4.08 (s, 3H), 4.30 (t, $J = 6$ Hz, 2H), 4.68 (t, $J = 6$ Hz, 2H), 6.73 (d, $J = 8.4$ Hz, 2H), 7.10 (t, $J = 7.5$ Hz, 2H), 7.25 (m, 1H), 7.37–7.48 (m, 4H), 8.34 (d, $J = 7.8$ Hz, 1H). MS (EI): 433 (m/z M^+).

6.3.5.2. 3-(4-(2-(4-Ethoxycarbazole)-9-yl-ethoxy)-phenyl)-2-ethoxy propionic acid (9b). ^1H NMR (CDCl_3) δ 1.41 (t, $J = 6.9$ Hz, 3H), 1.60 (t, $J = 6.9$ Hz, 3H), 2.95–3.05 (m, 2H), 3.34 (m, 1H), 3.65 (m, 1H), 4.01 (m, 1H), 4.14 (q, $J = 6$ Hz, 2H), 4.28 (m, 4H), 4.67 (t,

$J = 6$ Hz, 2H), 6.71 (m, 2H), 6.88 (d, $J = 8.4$ Hz, 2H), 7.09 (d, $J = 8.4$ Hz, 2H), 7.26 (m, 1H), 7.37–7.45 (m, 2H), 8.35 (d, $J = 7.5$ Hz, 1H). MS (EI): 447 (m/z M^+).

6.3.5.3. 3-(4-(2-(4-Benzylloxycarbazole)-9-yl-ethoxy)-phenyl)-2-ethoxy propionic acid (9d). ^1H NMR (CDCl_3) δ 1.39 (t, $J = 6$ Hz, 3H), 2.91 (m, 2H), 3.30 (m, 1H), 3.61 (m, 1H), 3.90 (t, $J = 6.9$ Hz, 1H), 4.31 (t, $J = 6$ Hz, 2H), 4.68 (t, $J = 6$ Hz, 2H), 5.35 (s, 2H), 6.73 (m, 1H), 6.88 (d, $J = 8.4$ Hz, 2H), 7.11 (d, $J = 8.4$ Hz, 2H), 7.25 (m, 2H), 7.38–7.47 (m, 5H), 7.57 (m, 1H), 7.68 (d, $J = 8.7$ Hz, 2H), 8.32 (d, $J = 7.2$ Hz, 1H). MS (EI): 509 (m/z M^+).

6.3.5.4. 3-(4-(2-(2-Benzylloxycarbazole)-ethoxy)-phenyl)-2-ethoxy propionic acid (9f). ^1H NMR (CDCl_3) δ 1.41 (t, $J = 6$ Hz, 3H), 2.92 (m, 2H), 3.32 (m, 1H), 3.60 (m, 1H), 3.91 (t, $J = 6.9$ Hz, 1H), 4.32 (t, $J = 6$ Hz, 2H), 4.69 (t, $J = 6$ Hz, 2H), 5.11 (s, 2H), 6.72 (m, 1H), 6.87 (d, $J = 8.4$ Hz, 2H), 7.12 (d, $J = 8.4$ Hz, 2H), 7.24 (m, 2H), 7.38–7.48 (m, 5H), 7.58 (m, 1H), 7.67 (d, $J = 8.7$ Hz, 2H), 8.33 (d, $J = 7.2$ Hz, 1H). MS (EI): 509 (m/z M^+).

6.3.5.5. 3-(4-(2-(4-Hydroxycarbazole)-ethoxy)-phenyl)-2-ethoxy propionic acid (9c). ^1H NMR (CDCl_3) δ 1.40 (t, $J = 6$ Hz, 3H), 2.89 (m, 2H), 3.40 (m, 1H), 3.60 (m, 1H), 3.90 (t, $J = 6.9$ Hz, 1H), 4.31 (t, $J = 6$ Hz, 2H), 4.6 (s, 1H), 4.66 (t, $J = 6$ Hz, 2H), 6.72 (d, $J = 8.7$, 1H), 7.01 (d, $J = 8.4$ Hz, 2H), 7.08 (d, $J = 8.4$ Hz, 2H), 7.25 (m, 2H), 7.44 (m, 1H), 7.5 (m, 2H), 8.32 (d, $J = 7.2$ Hz, 1H). MS (EI): 419 (m/z M^+).

6.3.5.6. 3-(4-(2-(2-Hydroxycarbazole)-ethoxy)-phenyl)-2-ethoxy propionic acid (9e). ^1H NMR (CDCl_3) δ 1.41 (t, $J = 6$ Hz, 3H), 2.91 (m, 2H), 3.30 (m, 1H), 3.61 (m, 1H), 3.92 (t, $J = 6.9$ Hz, 1H), 4.31 (t, $J = 6$ Hz, 2H), 4.56 (s, 1H), 4.68 (t, $J = 6$ Hz, 2H), 6.73 (m, 1H), 6.88 (d, $J = 8.4$ Hz, 2H), 7.11 (d, $J = 8.4$ Hz, 2H), 7.25 (m, 2H), 7.57 (m, 1H), 7.68 (d, $J = 8.7$ Hz, 2H), 8.32 (d, $J = 7.2$ Hz, 1H). MS (EI): 419 (m/z M^+).

6.3.6. General procedure for synthesis of 10a–f. L-Lysine monohydrochloride was passed through a cation exchange resin (Dowex) bed with help of water. The aqueous ammonia solution was eluted through the resin and concentrated under high vacuum to give free L-lysine. To a suspension of compounds **9a–f**, (1.0 equiv) in ethanol was added L-lysine (1.0 equiv) and stirred for 2 h. Solvent removed and residue washed with diethyl ether.

6.3.6.1. 3-(4-(2-(4-Methoxycarbazole)-ethoxy)-phenyl)-2-ethoxy propionic acid, L-lysine salt (10a). ^1H NMR (CD_3OD) δ 1.05 (t, $J = 6.9$ Hz, 3H), 1.27 (m, 4H), 1.50 (m, 2H), 1.68 (m, 2H), 1.87 (m, 2H), 2.75 (m, 1H), 2.85–2.94 (m, 3H), 3.29 (m, 1H), 3.57 (m, 2H), 3.75 (m, 1H), 4.06 (s, 3H), 4.34 (t, $J = 6$ Hz, 2H), 4.70 (t, $J = 6$ Hz, 2H), 6.75 (d, $J = 7.8$ Hz, 1H), 6.67 (d, $J = 9$ Hz, 2H), 7.16 (m, 4H), 7.40 (m, 2H), 7.53 (d, $J = 8.4$ Hz, 1H), 8.22 (d, $J = 7.8$ Hz, 1H). IR (KBr, cm^{-1}) 3416, 2928, 1583, 1511, 1459, 1402. MS (APCI): 579 (m/z $M+1$). Anal. Calcd for $\text{C}_{32}\text{H}_{41}\text{N}_3\text{O}_7$ (579.29):

C, 66.30; H, 7.13; N, 7.25. Found: C, 66.13; H, 7.11; N, 7.19.

6.3.6.2. 3-(4-(2-(4-Ethoxycarbazole)-ethoxy)-phenyl)-2-ethoxy propionic acid, L-lysine salt (10b). ^1H NMR (CD_3OD) δ 1.06 (t, $J = 6.9$ Hz, 3H), 1.48 (m, 2H), 1.56–1.68 (m, 5H), 1.82 (m, 2H), 2.6 (m, 1H), 2.86–2.90 (m, 2H), 3.25 (m, 1H), 3.50 (m, 3H), 3.75 (m, 1H), 4.28–4.36 (m, 4H), 4.67 (t, $J = 6$ Hz, 2H), 6.70 (t, $J = 7.8$ Hz, 3H), 7.09–7.19 (m, 4H), 7.32–7.39 (m, 2H), 7.53 (d, $J = 8.1$ Hz, 1H), 8.25 (d, $J = 7.8$ Hz, 1H). IR (KBr, cm^{-1}) 3909, 2929, 1586, 1505, 1458, 1402, 1336, 1244. MS (APCI): 593 (m/z M+1). Anal. Calcd for $\text{C}_{33}\text{H}_{43}\text{N}_3\text{O}_7$ (593.31): C, 66.76; H, 7.30; N, 7.08. Found: C, 66.59; H, 7.23; N, 6.89.

6.3.6.3. 3-(4-(2-(4-Benzoyloxycarbazole)-ethoxy)-phenyl)-2-ethoxy propionic acid, L-lysine salt (10d). ^1H NMR (CD_3OD) δ 1.01 (t, $J = 6.9$ Hz, 3H), 1.27 (m, 2H), 1.48 (m, 2H), 1.69 (m, 2H), 1.78 (m, 2H), 2.91 (m, 2H), 3.3 (m, 1H), 3.49 (m, 2H), 3.6 (m, 1H), 3.75 (m, 1H), 3.9 (t, $J = 6.9$ Hz, 1H), 4.38 (t, $J = 6$ Hz, 2H), 4.68 (t, $J = 6$ Hz, 2H), 5.35 (s, 2H), 6.69 (m, 2H), 6.84 (d, $J = 7.8$ Hz, 1H), 7.10–7.21 (m, 4H), 7.39–7.54 (m, 5H), 7.57 (m, 3H), 8.20 (d, $J = 7.8$ Hz, 1H). IR (KBr, cm^{-1}) 3413, 2922, 1637, 1505, 1406, 1244. MS (APCI): 656 (m/z M+1). Anal. Calcd for $\text{C}_{38}\text{H}_{45}\text{N}_3\text{O}_7$ (655.33): C, 69.60; H, 6.92; N, 6.41. Found: C, 69.29; H, 6.87; N, 6.28.

6.3.6.4. 3-(4-(2-(2-Benzoyloxycarbazole)-ethoxy)-phenyl)-2-ethoxy propionic acid, L-lysine salt (10f). ^1H NMR (CD_3OD) δ 1.08 (t, $J = 6.9$ Hz, 3H), 1.27 (m, 2H), 1.48 (m, 2H), 1.69 (m, 2H), 1.78 (m, 2H), 2.91 (m, 2H), 3.3 (m, 1H), 3.49 (m, 2H), 3.6 (m, 1H), 3.75 (m, 1H), 3.9 (t, $J = 6.9$ Hz, 1H), 4.31 (t, $J = 6$ Hz, 2H), 4.68 (t, $J = 6$ Hz, 2H), 5.11 (s, 2H), 6.71 (m, 2H), 6.84 (d, $J = 7.8$ Hz, 1H), 7.10–7.21 (m, 4H), 7.39–7.54 (m, 5H), 7.57 (m, 3H), 8.12 (d, $J = 7.8$ Hz, 1H). IR (KBr, cm^{-1}) 3415, 2928, 1632, 1505, 1406, 1344. MS (APCI): 656 (m/z M+1). Anal. Calcd for $\text{C}_{38}\text{H}_{45}\text{N}_3\text{O}_7$ (655.33): C, 69.60; H, 6.92; N, 6.41. Found: C, 69.52; H, 6.88; N, 6.37.

6.3.6.5. 3-(4-(2-(4-Hydroxycarbazole)-ethoxy)-phenyl)-2-ethoxy propionic acid, L-lysine salt (10c). ^1H NMR (CD_3OD) δ 1.02 (t, $J = 6.9$ Hz, 3H), 1.26 (m, 2H), 1.49 (m, 2H), 1.69 (m, 2H), 1.84 (m, 2H), 2.75 (m, 2H), 2.95 (m, 2H), 3.2 (m, 1H), 3.5 (m, 2H), 3.6 (m, 1H), 3.76 (m, 1H), 4.02 (t, $J = 6.9$ Hz, 1H), 4.37 (t, $J = 6$ Hz, 2H), 4.6 (s, 1H), 4.69 (t, $J = 6$ Hz, 2H), 6.68 (t, $J = 9$ Hz, 2H), 7.12 (m, 3H), 7.20 (m, 2H), 7.25 (m, 1H), 7.44 (m, 1H), 7.6 (m, 1H), 8.24 (d, $J = 8.4$ Hz, 1H). IR (KBr, cm^{-1}) 3416, 2929, 2863, 1586, 1406, 1107. MS (APCI): 567 (m/z M+1). Anal. Calcd for $\text{C}_{31}\text{H}_{39}\text{N}_3\text{O}_7$ (565.28): C, 65.82; H, 6.95; N, 7.43. Found: C, 65.69; H, 6.83; N, 7.38.

6.3.6.6. 3-(4-(2-(2-Hydroxycarbazole)-ethoxy)-phenyl)-2-ethoxy propionic acid, L-lysine salt (10e). ^1H NMR (D_2O) δ 0.95 (t, $J = 6$ Hz, 3H), 1.38 (m, 2H), 1.63 (m, 2H), 1.78 (m, 2H), 2.91 (m, 4H), 3.18 (m, 1H), 3.40 (m, 1H), 3.54 (m, 2H), 3.76 (m, 1H), 3.91 (t,

$J = 6.9$ Hz, 1H), 4.31 (t, $J = 6$ Hz, 2H), 4.71 (s, 1H), 4.8 (t, $J = 6$ Hz, 2H), 6.52 (m, 2H), 6.95 (m, 2H), 7.18 (m, 2H), 7.42 (m, 3H), 8.03 (m, 2H). IR (KBr, cm^{-1}) 3420, 2922, 1583, 1402, 1347. MS (APCI): 567 (m/z M $^+$). Anal. Calcd for $\text{C}_{31}\text{H}_{39}\text{N}_3\text{O}_7$ (565.28): C, 65.82; H, 6.95; N, 7.43. Found: C, 65.71; H, 6.83; N, 7.33.

6.3.7. (S)3-{4-[2-(9H-Carbazol-4-yloxy)-ethoxy]-phenyl}-2-(1-methyl-3-oxo-3-phenyl-propenylamino)-propionic acid methyl ester (14). Step (A): Synthesis of (13) (S)3-(4-Hydroxy-phenyl)-2-(1-methyl-3-oxo-3-phenyl-propenylamino)-propionic acid methyl ester: To a 10 ml dry toluene suspension of L-tyrosine methyl ester (2.0 g, 10.2 mmol), benzoylacetone (1.7 g, 10.2 mmol) was added in presence of 4 Å molecular sieve. The suspension was refluxed overnight. Toluene was removed and residue was extracted with dichloromethane. The organic layer was separated and dried over anhydrous sodium sulfate, decanted, concentrated and chromatographed on silica gel. Elution with a gradient mixture of ethyl acetate/hexane yielded the title compounds (90–95%). IR (KBr, cm^{-1}) 3177.8, 1744.1, 1596.1, 1438.5, 1118.2, 745.6. ^1H NMR (CDCl_3) δ 1.81 (s, 3H), 2.99–3.16 (m, 4H), 3.72 (s, 3H), 5.65 (m, 1H), 6.74 (d, $J = 8.34$ Hz, 1H), 7.02 (d, $J = 6.57$ Hz, 1H), 7.38 (d, $J = 6.78$ Hz, 1H), 7.84 (d, $J = 7.02$ Hz, 1H). MS (APCI): 339 (m/z M+1). Step (B): Synthesis of (17) 4-(2-bromo-ethoxy)-9H-carbazole: To a 10 ml acetone solution of 4-hydroxycarbazole (2.0 g, 10.8 mmol) and dibromoethane (2.0 g, 12.0 mmol) was added K_2CO_3 (2.2 g, 12.0 mmol). The suspension was refluxed overnight. Acetone was removed and residue was extracted with ethyl acetate. The organic layer was separated and dried over anhydrous sodium sulfate, decanted, concentrated and chromatographed on silica gel. Elution with a gradient mixture of ethyl acetate/hexane yielded the title compounds white powder mp 115 °C (60–70%). ^1H NMR (CDCl_3) δ 3.84 (t, $J = 6$ Hz, 2H), 4.55 (t, $J = 6$ Hz, 2H), 6.64 (d, $J = 8.1$ Hz, 1H), 7.07 (d, $J = 8.1$ Hz, 1H), 7.25 (m, 2H), 7.36 (d, $J = 9$ Hz, 1H), 8.06 (s, 1H), 8.38 (d, $J = 6.9$ Hz, 1H). MS (EI): 289, 291 (m/z M+1, M+2). Step (C): To a 10 ml acetone solution of 13 (1.0 g, 2.9 mmol) and 17 (0.9 g, 3.19 mmol) was added K_2CO_3 (0.6 g, 4.35 mmol). The suspension was refluxed overnight. Acetone was removed and residue was extracted with ethyl acetate. The organic layer was separated and dried over anhydrous sodium sulfate, decanted, concentrated and chromatographed on silica gel. Elution with a gradient mixture of ethyl acetate/hexane yielded the title compounds. ^1H NMR (CDCl_3) δ 1.94 (s, 3H), 3.16 (m, 1H), 3.20 (m, 1H), 3.54 (t, $J = 6$ Hz, 1H), 3.76 (s, 3H), 4.49 (t, $J = 6$ Hz, 2H), 4.57 (t, $J = 6$ Hz, 2H), 4.74 (m, 1H), 5.6 (s, 1H), 6.74 (d, $J = 8.4$ Hz, 2H), 6.93 (t, $J = 8.4$ Hz, 1H), 7.09 (d, $J = 8.4$ Hz, 2H), 7.20 (m, 5H), 7.33 (d, $J = 9$ Hz, 2H), 7.87 (m, 3H), 8.01 (s, 1H), 8.25 (d, $J = 8.4$ Hz, 1H). MS (EI): 548 (m/z M $^+$). Anal. Calcd for $\text{C}_{34}\text{H}_{32}\text{N}_2\text{O}_5$ (548.23): C, 74.43; H, 5.88; N, 5.11. Found: C, 74.27; H, 5.76; N, 5.08.

6.3.8. (S)3-{4-[2-(9H-Carbazol-4-yloxy)-ethoxy]-phenyl}-2-(1-methyl-3-oxo-3-phenyl-propenylamino)-propionic acid, L-lysine salt (16). To ethanol solution of compound 14

(1.0 g, 1.8 mmol) was added 20% aqueous sodium hydroxide and stirred at room temperature overnight. The reaction mixture was concentrated, acidified with acetic acid (pH 4). The acidic solution was extracted with ethyl acetate. The organic layer was separated and dried over anhydrous sodium sulfate, decanted and concentrated to yield the title compounds **15** (75%). Chiral HPLC (chiral-AGP, 150 * 4 mm, 5 μ M, hexane-isopropanol (4:1), 1 ml/min), t_R = 8.2, 98% ee. MS (MALDI): 535 M^+ . To a suspension of compounds (**15**, 0.5 g, 1.0 mmol) in ethanol was added L-lysine (0.14 g, 1.0 mmol) and stirred for 2 h. Solvent removed and residue crystallized with diethyl ether. 1H NMR $CDCl_3$ δ 1.48 (m, 2H), 1.68 (m, 2H), 1.86 (m, 2H), 1.94 (s, 3H), 2.97 (m, 2H), 3.16 (m, 1H), 3.20–3.30 (m, 5H), 3.54 (t, J = 6 Hz, 1H), 3.60 (m, 1H), 4.49 (t, J = 6 Hz, 2H), 4.57 (t, J = 6 Hz, 2H), 5.6 (s, 1H), 6.74 (d, J = 8.4 Hz, 2H), 6.93 (t, J = 8.4 Hz, 1H), 7.09 (d, J = 8.4 Hz, 2H), 7.20 (m, 5H), 7.33 (d, J = 9 Hz, 2H), 7.87 (m, 3H), 8.01 (s, 1H), 8.25 (d, J = 8.4 Hz, 1H). MS (MALDI): 680 (m/z M^+). Anal. Calcd for $C_{39}H_{44}N_4O_7$ (680.32): C, 68.81; H, 6.51; N, 8.23. Found: C, 68.58; H, 6.47; N, 8.12.

6.3.9. 3-{4-[2-(9H-carbazole-4-yloxy)-ethoxy]-phenyl}-2-ethoxy acrylic acid ethyl ester (23**).** Step (A): Synthesis of (**22**) ethyl-3-(4-hydroxyphenyl) 2-ethoxy prop-2-enoate. A dry THF solution of 4-hydroxybenzaldehyde (1.0 g, 8.1 mmol) under nitrogen was cooled to 0 °C. Sodium hydride (60% dispersion in oil, 0.6 g, 24 mmol) was added and the solution stirred for 30 min at 0 °C. Ethyl-2-ethoxy-2-diethyl phosphonoacetate (**4**) (3.2 g, 12.1 mmol) was added and solution stirred at room temp overnight. The reaction mixture was concentrated, poured in water and extracted in diethyl ether. The organic layer was separated and dried over anhydrous sodium sulfate, decanted, concentrated and chromatographed on silica gel. Elution with a gradient mixture of ethyl acetate/hexane yielded the title compounds as yellowish oil (50%). 1H NMR $CDCl_3$ δ 1.3–1.42 (m, 6H), 3.95 (m, 1H), 4.14 (m, 2H), 4.28 (m, 1H), 6.83 (d, J = 8.7 Hz, 2H), 6.95 (s, 1H), 7.7 (d, J = 8.4 Hz, 2H). MS (EI): 236 (m/z M^+). Step (B): To a 10 ml acetone solution of **17** (1.0 g, 3.4 mmol) and **22** (0.76 g, 3.23 mmol) was added K_2CO_3 (0.7 g, 5.1 mmol). The suspension was refluxed overnight. Acetone was removed and residue was extracted with ethyl acetate. The organic layer was separated and dried over anhydrous sodium sulfate, decanted, concentrated and chromatographed on silica gel. Elution with a gradient mixture of ethyl acetate/hexane yielded the title compounds. 1H NMR ($CDCl_3$) δ 1.25 (t, J = 6.6 Hz, 3H), 1.38 (t, J = 6.6 Hz, 3H), 3.85 (m, 1H), 3.96 (m, 2H), 4.01 (m, 1H), 4.25 (t, J = 6 Hz, 2H), 4.56 (t, J = 6 Hz, 2H), 6.84 (d, J = 9 Hz, 2H), 6.96 (s, 1H), 7.08 (d, J = 8.4 Hz, 2H), 7.39 (m, 4H), 7.71 (d, J = 9 Hz, 2H), 8.08 (s, 1H), 8.32 (d, J = 8.4 Hz, 1H). MS (EI): 445 (m/z M^+). Anal. Calcd for $C_{27}H_{27}NO_5$ (445.19): C, 72.79; H, 6.11; N, 3.14. Found: C, 72.47; H, 5.78; N, 3.02.

6.3.10. 3-{4-[2-(9H-Carbazole-4-yloxy)-ethoxy]-phenyl}-2-ethoxy propionic acid ethyl ester (24**).** To a 10 ml ethyl acetate solution of compound **23** (1.0 g, 2.2 mmol) was

added 50 mg 10% Pd/C. The resulting suspension was placed in a Parr shaker and debenzylated via hydrogenation under hydrogen atmosphere at 60 psi for 5 h at 50 °C. The reaction suspension was then filtered through a pad of Celite, concentrated and chromatographed on silica gel. Elution with a gradient mixture of ethyl acetate/hexane yielded the title compounds as colourless oil (80–95%). 1H NMR ($CDCl_3$) δ 1.23 (t, J = 6.6 Hz, 3H), 1.37 (t, J = 6.6 Hz, 3H), 2.9 (d, J = 6 Hz, 2H), 3.85 (m, 1H), 3.95 (m, 2H), 4.01 (m, 2H), 4.25 (t, J = 6 Hz, 2H), 4.56 (t, J = 6 Hz, 2H), 6.84 (d, J = 9 Hz, 2H), 6.96 (s, 1H), 7.08 (d, J = 8.4 Hz, 2H), 7.39 (m, 4H), 7.69 (d, J = 9 Hz, 2H), 8.06 (s, 1H), 8.30 (d, J = 8.4 Hz, 1H). MS (EI): 447 (m/z M^+). Anal. Calcd for $C_{27}H_{29}NO_5$ (447.20): C, 72.46; H, 6.53; N, 3.13. Found: C, 72.39; H, 6.55; N, 3.11.

6.3.11. 3-{4-[2-(9H-Carbazole-4-yloxy)-ethoxy]-phenyl}-2-ethoxy propionic acid L-lysine salt (24a**).** To ethanol solution of compound **24** (0.5 g, 1.1 mmol) was added 20% aqueous sodium hydroxide (1.1 equiv) and stirred at room temperature overnight. The reaction mixture was concentrated, acidified with acetic acid (pH 4). The acidic solution was extracted with ethyl acetate. The organic layer was separated and dried over anhydrous sodium sulfate, decanted and concentrated to yield the carboxylic acid (70–80%). The carboxylic acid (0.25 g, 0.5 mmol) in ethanol was added L-lysine (0.09 g, 0.5 mmol) and stirred for 2 h. Solvent removed and residue crystallized with diethyl ether. 1H NMR $CDCl_3$ δ 1.35 (t, J = 6.6 Hz, 3H), 1.48 (m, 2H), 1.65 (m, 2H), 1.87 (m, 2H), 2.95 (m, 4H), 3.32 (m, 4H), 3.57 (m, 1H), 3.85 (m, 1H), 4.01 (m, 2H), 4.25 (t, J = 6 Hz, 2H), 4.56 (t, J = 6 Hz, 2H), 6.84 (d, J = 9 Hz, 2H), 7.08 (d, J = 8.4 Hz, 2H), 7.39 (m, 4H), 7.71 (d, J = 9 Hz, 2H), 8.08 (s, 1H), 8.32 (d, J = 8.4 Hz, 1H). MS (MALDI): 564 (m/z M^+). Anal. Calcd for $C_{31}H_{39}N_3O_7$ (565.28): C, 65.82; H, 6.95; N, 7.43. Found: C, 65.68; H, 6.87; N, 7.41.

6.3.12. 4-Hydroxy-3-methoxy-benzoic acid ethyl ester (18**).** 4-Hydroxy-3-methoxy-benzoic acid (2.0 g, 11.9 mmol) was refluxed with $SOCl_2$ in ethanol for 30 min. The reaction mixture was concentrated, extracted with ethyl acetate. The organic layer was separated and dried over anhydrous sodium sulfate; decanted and concentrated to yield the title compounds **24a** (70–80%). 1H NMR $CDCl_3$ δ 1.38 (t, J = 7.2 Hz, 3H), 4.35 (q, J = 7.2 Hz, 2H), 6.44 (s, 1H), 6.93 (d, J = 8.1 Hz, 1H), 7.55 (s, 1H), 7.64 (d, J = 8.4 Hz, 1H). MS (EI): 196 (m/z M^+).

6.3.13. 6-Hydroxy-naphthalene-2-carboxylic acid ethyl ester (20**).** The title compound **20** was prepared from 6-hydroxy naphthalene-2-carboxylic acid (2.0 g, 10.6 mmol) by a procedure similar to followed for synthesis of **18**. 1H NMR $CDCl_3$ δ 1.44 (t, J = 7.2 Hz, 3H), 4.43 (q, J = 7.2 Hz, 2H), 5.6 (s, 1H), 7.15 (d, J = 8.7 Hz, 1H), 7.18 (s, 1H), 7.69 (d, J = 8.7 Hz, 1H), 7.86 (d, J = 8.7 Hz, 1H), 8.02 (d, J = 8.7 Hz, 1H), 8.53 (s, 1H). MS (EI): 216 (m/z M^+).

6.3.14. 3-(4-Hydroxy phenyl)-propionic acid ethyl ester (25). The title compound **25** was prepared from 3-(4-hydroxy phenyl)-propionic acid (2.0 g, 12.0 mmol) by a procedure similar to followed for synthesis of **18**. ^1H NMR CDCl_3 δ 1.23 (t, $J = 7.2$ Hz, 3H), 2.58 (t, $J = 7.8$ Hz, 2H), 2.87 (t, $J = 7.5$ Hz, 2H), 4.12 (q, $J = 6.9$ Hz, 2H), 5.30 (s, 1H). MS (EI): 194 (m/z M^+).

6.3.15. 4-[2-(9H-Carbazol-4-yloxy)-ethoxy]-3-methoxy-benzoic acid ethyl ester (19). To a 10 ml acetone solution of **17** (1.0 g, 3.4 mmol) and **18** (0.6 g, 3.1 mmol) was added K_2CO_3 (0.7 g, 5mmol). The suspension was refluxed overnight. Acetone was removed and residue was extracted with ethyl acetate. The organic layer was separated and dried over anhydrous sodium sulfate, decanted, concentrated and chromatographed on silica gel. Elution with a gradient mixture of ethyl acetate/hexane yielded the title compounds. ^1H NMR CDCl_3 δ 1.25 (t, $J = 6.6$ Hz, 3H), 3.91 (s, 3H), 4.13 (q, $J = 6$ Hz, 2H), 4.36 (t, $J = 6$ Hz, 2H), 4.64 (t, $J = 6$ Hz, 2H), 6.73 (m, 1H), 6.93 (d, $J = 9$ Hz, 1H), 7.07 (m, 2H), 7.18 (m, 2H), 7.36–7.41 (m, 2H), 7.55 (s, 1H), 7.64 (d, $J = 9$ Hz, 1H), 8.25 (m, 1H). MS: 405 (m/z M^+). Anal. Calcd for $\text{C}_{24}\text{H}_{23}\text{NO}_5$ (405.19): C, 71.10; H, 5.72; N, 3.45. Found: C, 71.03; H, 5.63; N, 3.32.

6.3.16. 4-[2-(9H-Carbazol-4-yloxy)-ethoxy]-3-methoxy-benzoic acid (19a). To ethanol solution of compound **19** was added 20% aqueous sodium hydroxide and refluxed for 30 min. The reaction mixture was concentrated and extracted with ethyl acetate. The organic layer was separated and dried over anhydrous sodium sulfate, decanted and concentrated to yield the title compounds **19a**. ^1H NMR CDCl_3 δ 3.96 (s, 3H), 4.36 (t, $J = 6$ Hz, 2H), 4.64 (t, $J = 6$ Hz, 2H), 6.73 (m, 1H), 6.96 (d, $J = 9$ Hz, 1H), 7.07 (m, 2H), 7.18 (m, 2H), 7.36–7.41 (m, 2H), 7.62 (s, 1H), 7.73 (d, $J = 9$ Hz, 1H), 8.24 (m, 1H). MS: 377 (m/z M^+). Anal. Calcd for $\text{C}_{22}\text{H}_{19}\text{NO}_5$ (377.13): C, 70.02; H, 5.07; N, 3.71. Found: C, 70.05; H, 5.01; N, 3.68.

6.3.17. 6-[2-(9H-Carbazol-4-yloxy)-ethoxy]-naphthalene-2-carboxylic acid ethyl ester (21). This compound was prepared from **17** (1.0 g, 3.4 mmol) and 6-hydroxy-naphthalene-2-carboxylic acid ethyl ester (**20**) (0.7 g, 3.0 mmol) according to a procedure similar to the used for synthesis of compound **19**. ^1H NMR CDCl_3 δ 1.44 (t, $J = 6.9$ Hz, 3H), 4.14 (q, $J = 6.9$ Hz, 2H), 4.42 (t, $J = 6$ Hz, 2H), 4.66 (t, $J = 6$ Hz, 2H), 6.73 (t, $J = 6.9$ Hz, 1H), 7.07–7.35 (m, 3H), 7.45–7.55 (m, 2H), 7.68 (d, $J = 8.4$ Hz, 1H), 7.85 (d, $J = 8.4$ Hz, 1H), 8.01 (d, $J = 8.4$ Hz, 1H), 8.16 (d, $J = 8.7$ Hz, 2H), 8.25 (m, 1H), 8.50–8.55 (m, 2H). MS: 425 (m/z M^+). Anal. Calcd for $\text{C}_{27}\text{H}_{23}\text{NO}_4$ (425.16): C, 76.22; H, 5.45; N, 3.29. Found: C, 76.07; H, 5.40; N, 3.23.

6.3.18. 6-[2-(9H-Carbazol-4-yloxy)-ethoxy]-naphthalene-2-carboxylic acid (21a). This compound was prepared from **21** according to a procedure similar to the used for synthesis of compound **19a**. ^1H NMR CDCl_3 δ 4.43 (t, $J = 6$ Hz, 2H), 4.66 (t, $J = 6$ Hz, 2H), 6.73 (t, $J = 6.9$ Hz, 1H), 7.07 (m, 2H), 7.19 (m, 1H), 7.32 (d, $J = 9$ Hz, 1H), 7.45–7.55 (m, 2H), 7.68 (d, $J = 8.4$ Hz,

1H), 7.85 (d, $J = 8.4$ Hz, 1H), 7.98 (d, $J = 9$ Hz, 1H), 8.12 (m, 1H), 8.20 (d, $J = 9$ Hz, 1H), 8.50–8.55 (m, 2H). MS: 397 (m/z M^+). Anal. Calcd for $\text{C}_{25}\text{H}_{19}\text{NO}_4$ (397.13): C, 75.55; H, 4.82; N, 3.52. Found: C, 75.58; H, 4.77; N, 3.41.

6.3.19. 3-{4-[2-(9H-Carbazol-4-yloxy)-ethoxy]-phenyl}-propionic acid ethyl ester (26). This compound was prepared from **17** (1.0 g, 3.4 mmol) and 3-(4-hydroxy phenyl)-propionic acid ethyl ester **25** (0.6 g, 3.23 mmol) according to a procedure similar to the used for synthesis of compound **19**. ^1H NMR CDCl_3 δ 1.25 (t, $J = 6.9$ Hz, 3H), 2.60 (t, $J = 6$ Hz, 2H), 2.87 (t, $J = 6$ Hz, 2H), 4.12 (q, $J = 6$ Hz, 2H), 4.49 (t, $J = 6$ Hz, 2H), 4.56 (t, $J = 6$ Hz, 2H), 6.69 (d, $J = 9$ Hz, 2H), 6.95 (d, $J = 9$ Hz, 2H), 7.04 (d, $J = 9$ Hz, 2H), 7.15 (d, $J = 9$ Hz, 2H), 7.25 (s, 1H), 7.35 (m, 2H), 8.26 (m, 1H). MS (MALDI): 403 (m/z M^+). Anal. Calcd for $\text{C}_{25}\text{H}_{25}\text{NO}_4$ (403.18): C, 74.42; H, 6.25; N, 3.47. Found: C, 74.28; H, 6.19; N, 3.40.

6.3.20. 3-{4-[2-(9H-Carbazol-4-yloxy)-ethoxy]-phenyl}-propionic acid (26a). This compound was prepared from **26** according to a procedure similar to the used for synthesis of compound **19a**. ^1H NMR CDCl_3 δ 2.61 (t, $J = 6$ Hz, 2H), 2.87 (t, $J = 6$ Hz, 2H), 4.49 (t, $J = 6$ Hz, 2H), 4.56 (t, $J = 6$ Hz, 2H), 6.69 (d, $J = 9$ Hz, 2H), 6.95 (d, $J = 9$ Hz, 2H), 7.04 (d, $J = 9$ Hz, 2H), 7.16 (d, $J = 9$ Hz, 2H), 7.25 (s, 1H), 7.35 (m, 2H), 8.26 (m, 1H). MS: 375 (m/z M^+). Anal. Calcd for $\text{C}_{23}\text{H}_{21}\text{NO}_4$ (375.15): C, 73.58; H, 5.64; N, 3.73. Found: C, 73.47; H, 5.58; N, 3.71.

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References and notes

1. Rotella, D. P. *J. Med. Chem.* **2004**, *47*, 4111.
2. Skyler, J. S. *J. Med. Chem.* **2004**, *47*, 4113.
3. Takashi, S.; Katsutoshi, M.; Hiroyuki, T.; Uasuo, S.; Takeshi, F.; Yataka, K. *Chem. Pharm. Bull.* **1982**, *30*, 3563.
4. Ramarao, P.; Kaul, C. L. *Drugs Today* **1999**, *35*, 895.
5. Willson, T. M.; Brown, P. J.; Sternbach, D. D.; Henke, B. R. *J. Med. Chem.* **2000**, *43*, 527.
6. Willson, T. M.; Cobb, J. E.; Cowan, D. J.; Wiethe, R. W.; Correa, I. D.; Prakash, S. R.; Beck, K. D.; Moore, L. B.; Kliever, S. A.; Lehman, J. M. *J. Med. Chem.* **1996**, *39*, 665.
7. Lehmann, J. M.; Moore, L. B.; Smith-Oliver, T. A.; Wilkinson, W. O.; Willson, T. M.; Kliwer, S. A. *J. Biol. Chem.* **1995**, *270*, 12953.
8. Li, Z.; Liao, C.; Ko, B. C. B.; Shan, S.; Tong, E. H. Y.; Yin, Z.; Pan, D.; Wong, V. K. W.; Shi, L.; Ning, Z. Q.; Hu, W.; Zhou, J.; Chung, S. S. M.; Lu, X. P. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 3507.
9. Henke, B. R. *J. Med. Chem.* **2004**, *47*, 4118.
10. Koyama, H.; Miller, D. J.; Boueres, J. K.; Desai, R. C.; Jones, A. B.; Berger, J. P.; MacNaul, K. L.; Kelly, L. J.

- Doebber, T. W.; Wu, M. S.; Zhou, G.; Wang, P.; Ippolito, M. C.; Chao, Y.; Agarwal, A. K.; Franklin, R.; Heck, J. V.; Wright, S. D.; Moller, D. E.; Sahoo, S. P. *J. Med. Chem.* **2004**, *47*, 3255.
11. Lohray, B. B.; Lohray, V. B.; Bajji, A. K.; Kalchar, S.; Poondra, R. R.; Padakanti, S.; Chakrabarti, R.; Vikramadithyan, R. K.; Misra, P.; Juluri, S.; Rao, N. V. S. M.; Rajagopalan, R. *J. Med. Chem.* **2001**, *44*, 2675.
12. Brooks, A. D.; Etgen, G. J.; Rito, C. J.; Shuker, A. J. *J. Med. Chem.* **2001**, *44*, 2061.
13. Shinkai, H.; Onogi, S.; Tanaka, M.; Shibata, T.; Iwao, M.; Wakitani, K.; Uchida, I. *J. Med. Chem.* **1998**, *41*, 1927.
14. Ramachandran, U.; Mital, A.; Bharatum, P. V.; Khanna, S.; Rao, P. R.; Srinivasan, K.; Kumar, R.; Chawla, H. P. S.; Kaul, C. L.; Raichur, S.; Chakrabarti, R. *Bioorg. Med. Chem.* **2004**, *12*, 655.
15. Guigliano, D.; Ceriello, A.; Paolisso, G. *Diabetes Care* **1996**, *19*, 257.
16. Kaneto, H.; Kajimoto, Y.; Miyagawa, J.; Matsuo, T.; Fujitani, Y.; Umayahara, Y.; Hanafusa, T.; Matsuzawa, Y.; Yamasaki, Y.; Hori, M. *Diabetes* **1999**, *48*, 2398.
17. Rudich, A.; Tirosh, A.; Potashnik, R.; Hemi, R.; Kanety, H.; Bashan, N. *Diabetes* **1998**, *47*, 1562.
18. Lohray, B. B.; Bhushan, V.; Rao, B. P.; Madhavan, G. R.; Murli, N.; Rao, K. N.; Reddy, A. K.; Rajesh, B. M.; Reddy, P. G.; Chakrabarti, R.; Vikramadithyan, R. K.; Rajagopalan, R.; Mamidi, N. V. S.; Jajoo, H. K.; Subramaniam, S. *J. Med. Chem.* **1998**, *41*, 1619.
19. Reddy, K. A.; Lohray, B. B.; Bhushan, V.; Reddy, A. S.; Rao, N. V. S. M.; Reddy, P. P.; Saibaba, V.; Reddy, N. J.; Suryaprakash, A.; Misra, P.; Vikramadithyan, R. K.; Rajagopalan, R. *J. Med. Chem.* **1999**, *42*, 1538.
20. Feuerstein, G. Z.; Poste, G.; Ruffolo, R. R. *Drugs Today* **1995**, *31*, 1–23.
21. Sauerberg, P.; Pettersen, I.; Jeppesen, L.; Bury, P. S.; Mogensen, J. P.; Wassermann, K.; Brand, C. L.; Sturis, J.; Woldike, H. F.; Fleckner, J.; Anderson, A. T.; Mortensen, S. B.; Svensson, L. A.; Rasmussen, H. B.; Lehmann, S. V.; Polivka, Z.; Sindelar, K.; Panajotova, V.; Ynddal, L.; Wolff, E. M. *J. Med. Chem.* **2002**, *45*, 789.
22. Buckle, D. R.; Cantello, B. C. C. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 2121.
23. Buckle, D. R.; Cantello, B. C. C. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 2127.
24. Henke, B. R.; Blanchard, S. G.; Brackeen, M. F.; Brown, K. K.; Cobb, J. E.; Collins, J. L.; Harrington, W. W.; Hashim, M. A.; Hull, E. A.; Kaldor, I.; Kliever, S. A.; Lake, D. H.; Leesnitzer, L. M.; Lehmann, J. M.; Lenhard, J. M.; Orband-Miller, L. A.; Miller, J. F.; Mook, R. A.; Noble, S. A.; Oliver, W.; Parks, J. L.; Plunkett, K. D.; Szweczyk, J. R.; Willson, T. M. *J. Med. Chem.* **1998**, *41*, 5020.
25. Collins, J. L.; Blanchard, S. G.; Boswell, G. E.; Charifson, P. S.; Cobb, J. E.; Henke, B. R.; Hull, E. A.; Kazmierski, W. M.; Lake, D. H.; Leesnitzer, L. M.; Lehmann, J. M.; Orband-Miller, L. A.; Gray-Nunez, Y.; Parks, D. J.; Plunkett, K. D.; Tong, W. Q. *J. Med. Chem.* **1998**, *41*, 5037.
26. Cobb, J. E.; Blanchard, S. G.; Boswell, G. E.; Brown, K. K.; Charifson, P. S.; Cooper, J. P.; Collins, J. L.; Dezube, M.; Henke, B. R.; Hull, E. A.; Lake, D. H.; Lenhard, J. M.; Oliver, W.; Oplinger, J.; Pentti, M.; Parks, D. J.; Plunkett, K. D.; Tong, W. Q. *J. Med. Chem.* **1998**, *41*, 5055.
27. Roman, D.; Andrew, K. Patent WO 01/57001A1, **2001**.
28. Chakrabarti, R.; Misra, P.; Vikramadithyan, R. K.; Premkumar, M.; Hiriyani, J.; Datla, S. R.; Damarla, R. K. B.; Suresh, J.; Rajagopalan, R. *Eur. J. Pharmacol.* **2004**, *491*, 195.
29. Chakrabarti, R.; Vikramadithyan, R. K.; Misra, P.; Hiriyani, J.; Suryaprakash, R.; Damarla, R. K.; Cynthia, G.; Suresh, J.; Rajagopalan, R. *Br. J. Pharmacol.* **2003**, *140*, 527.
30. Yue, T.-L.; Cheng, H.-Y.; Lysko, P. G.; McKenna, P. J.; Feuerstein, R.; Gu, J.-L.; Lysko, K. A.; Davis, L. L.; Feuerstein, G. *J. Pharmacol. Exp. Ther.* **1992**, *263*, 92–98.