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Synthesis and antihyperglycemic activity of chalcone based aryloxypropanolamines☆

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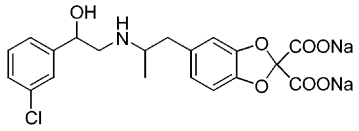
Abstract—A series of aryloxypropanolamines (**5a**–**r**) of different chalcones (**3a**–**e**) were synthesized and evaluated for antihyperglycemic activity in sucrose loaded (SLM) and streptozotocin (STZ) induced diabetic animal models. Among them compounds **5a**, **g**, **m**, **o**, **p** and **r** showed significant reduction in blood glucose levels in both SLM and STZ animal models.

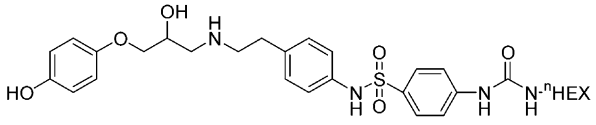
1. Introduction

Non-insulin dependent diabetes mellitus (NIDDM, type-II diabetes) is a chronic metabolic disease characterized by insulin resistance, hyperglycemia and hyperinsulinaemia. It represents 80–90% of the human population with diabetes and approximately 215 million will be afflicted worldwide by 2010.[1] The disease is often associated with obesity, dyslipidemia and hypertension leading to cardiovascular risks.[2] Primary therapy for type-II diabetes is caloric restriction and aerobic exercise[3] but only a small percentage of patients adopt them with sufficient rigor to achieve a significant improvement in hyperglycemic condition. Current therapies for type-II diabetes have inherent problems including non-compliance, ineffectiveness and hypoglycemic episodes with insulin and sulphonyl ureas.[4] Glitazone type therapeutic agents are in the market but some of them have been reported to have hepatotoxicity.[5] Therefore, here still remains a great need for more effective orally administered agents.

β_3-adrenergic receptors (β_3-AR) are found on the cell surface of both white adipose (WAT) and brown adipose tissues (BAT) where their stimulation promotes lipolysis and thermogenesis respectively.[6] BAT also plays an important role in the maintenance of glucose homeostasis; hence β_3-AR agonists are useful for treating diabetes as well as obesity.[7] The aryloxypropanolamines were first described as β_3-AR agonists in the mid 1980s.[8] Later on several pharmaceutical industries are engaged in developing potent selective β_3-AR agonists for treatment of type-II diabetes and obesity. CL-316243[9] has been reported for the treatment of type-II diabetes as well as obesity and recently L-755507[10] as highly selective β_3-AR agonist acting as metabolic rate enhancer in rodents.



CL-316243



L-755507

Chalcones either natural or synthetic are known to exhibit various biological activities. They have been reported as antioxidant,[11–14] antimalarial,[15] antileishmanial,[16] antiinflammatory[17] and antitumor[18]

Keywords: Chalcones; Aryloxypropanolamines and antihyperglycemic activity.
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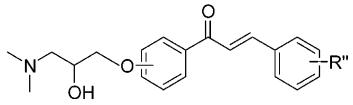


Figure 1. General structure of synthesized aryloxypropanolamines.

agents. Chalcones with proper substitution have recently been isolated from *Broussonetia papyrifera* known to selectively inhibit enzymes like protein tyrosine phosphatase 1B (PTP1B) [19] and aldose reductase.[20] Their antioxidant property attracted us to explore hybrid structures as antihyperglycemic agents, because oxidative stress also plays an important role in diabetic patients leading to vascular complications.[2,21] On this background we designed and synthesized compounds corresponding to general formula given in Figure 1 to explore their potential for antihyperglycemic activity.

2. Results and discussion

The general synthetic route used to synthesize the designated compounds is outlined in Scheme 1. The target compounds (**5a**–**r**) as typified by general structure (Fig. 1) were prepared by reacting different amines with aryloxypropeneoxides in methanol at room temperature. The structures and antihyperglycemic activities of aryloxypropanolamines are summarized in Table 1.

All the chalcones (**3a**–**e**) were prepared using the Claisen-Schmidt condensation, which has been previously reported.[22] Yields ranged from 65% to quantitative but were not optimized. The chalcones were always obtained as *trans*-alkenes (E-form) as judged by ^{1}H NMR spectroscopy. The chalcones thus obtained were alkylated at hydroxyl groups with *epi*chlorohydrin using NaH as base in dry dimethyl formamide (DMF) at room temperature.

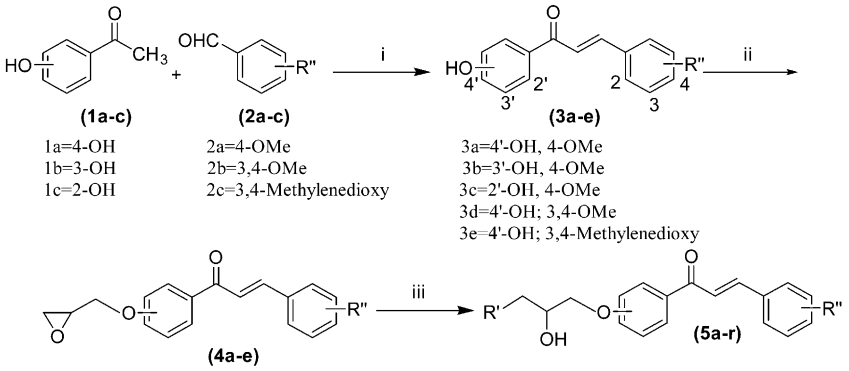
All the synthesized compounds (**5a**–**r**) were evaluated for antihyperglycemic activity[23] in sucrose-loaded model (SLM) followed by streptozotocin (STZ) induced β-cell damaged diabetic model of Sprague–Dawley strain male albino rats.

2.1. Sucrose loaded rat model (SLM)

Compounds were tested for their effect on glucose tolerance curve in rats of average body weight 160 ± 20 g, an indirect effect of measuring antihyperglycemic activity. The blood glucose levels of all animals were checked after an overnight fasting (16 h) by Glucostrips (Boehringer Mannheim). Animals showing blood glucose levels between 60–80 mg/dl (3.33–4.44 mM) were divided into groups of five to six animals in each. Animals of experimental groups were administered the suspension of the synthetic compounds orally (made in 1.0% Gum acacia) at a dosage of 100 mg/kg body weight. Animals of control group were given an equal amount of 1.0% gum acacia. A sucrose load (10.0 g/kg) was given to each animal orally exactly after 30 min post administration of the test sample/vehicle. Blood glucose profile of each animal was determined at 30, 60, 90 and 120 min post administration of sucrose. Food but not water was removed from the cages during the course of experimentation. Quantitative glucose tolerance of each animal was calculated by Area Under Curve (AUC) method. Comparing the AUC of experimental and control groups was calculated the percentage antihyperglycemic effect. Samples showing significant inhibition ($p < 0.05$) on postprandial hyperglycemia (AUC) were considered as active samples.

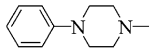
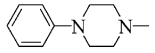
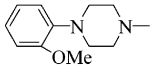
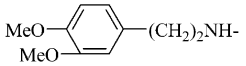
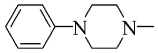
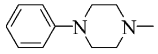
2.2. Streptozotocin-induced diabetic rats (STZ)

Sprague–Dawley strain male albino rats of average body weight 140 ± 20 g were selected having blood glucose profiles between 60–80 mg/dl. Streptozotocin (Sigma, USA) was dissolved in 100 mM citrate buffer (pH 4.5) and calculated amount of freshly prepared solution was injected to overnight fasted animals at a dose of 60 mg/kg body weight intraperitoneally. Blood glucose profile was checked after 48 h using Glucostrips (Boehringer Mannheim) and animals showing blood glucose profiles between 180–270 mg/dl were considered suitable for the experiment. These diabetic animals were again divided into groups and their blood glucose profile was again checked on the day of experiment (Day 3). Animals showing almost equal or similar blood glucose profiles were divided into groups consisting of 5 to 6 animals in each group. Animals of experimental groups were administered suspension of the test sample orally (prepared in 1% Gum acacia) at 100-mg/kg-body weight. Animals of control group were given an equal amount of 1% Gum acacia. A sucrose load (2.5 g/kg) was given to each animal orally exactly after 30 min post administration of the test sample/vehicle. Blood



Scheme 1. Reagents and conditions: (i) 50% aq NaOH, MeOH, rt; (ii) NaH, Epichlorohydrin, DMF, rt; (iii) Amine, MeOH, rt.

Table 1. In vivo antihyperglycemic activity of aryloxypropanolamines (**5a**–**r**) in STZ and SLM rat models

S.No	Compd	Position	R′	R″	%Antihyperglycemic activity	
					STZ	SLM
1	**5a**	4′		3, 4-OMe	20.3	15.4
2	**5b**	4′	$(CH_3)_3CNH$—	3, 4-OMe	NIL	11.2
3	**5c**	4′		4-OMe	NIL	7.78
4	**5d**	4′	$(CH_3)_2CHCH_2NH$—	4-OMe	ND	5.67
5	**5e**	4′	$(CH_3)_3CNH$—	4-OMe	NIL	11.8
6	**5f**	4′	$(CH_3)_2CHNH$—	4-OMe	ND	Inactive
7	**5g**	4′		4-OMe	6.18	10.8
8	**5h**	4′		4-OMe	ND	Inactive
9	**5i**	4′	CH_3NH—	4-OMe	ND	Inactive
10	**5j**	4′	$CH_3(CH_2)_3NH$—	4-OMe	NIL	38.0
11	**5k**	3′		4-OMe	ND	4.41
12	**5l**	3′	$(CH_3)_2CHNH$—	4-OMe	NIL	6.85
13	**5m**	3′	$(CH_3)_3CNH$—	4-OMe	11.3	20.0
14	**5n**	2′	$CH_3(CH_2)_3NH$—	4-OMe	NIL	33.1
15	**5o**	2′	$(CH_3)_2CHNH$—	4-OMe	2.77	47.0
16	**5p**	4′	$(CH_3)_3CNH$—	3, 4-Methylenedioxy	23.0	21.1
17	**5q**	4′		3, 4-Methylenedioxy	ND	5.03
18	**5r**	4′	$(CH_3)_2CHCH_2NH$—	3, 4-Methylenedioxy	11.58	23.8
19	**3a**				NIL	NIL
20	**3b**				NIL	NIL
21	**3c**				ND	NIL
22	**3d**				ND	ND
23	**3e**				NIL	NIL
	Metformin				19.1	12.9
	Glybenclamide				29.0	33.7

ND, Not Determined; NIL, Insignificant activity.

glucose profile of each animal was determined at 30, 60, and 90, 120, 180, 240, 300 min and at 24 h post administration of sucrose. Food but not water was withheld from the cages during the experimentation. The % fall in blood glucose by test sample was calculated according to the AUC method. The average fall in AUC in experimental group compared to control group provided % antihyperglycemic activity. Metformin and glybenclamide acting with two different mechanisms were used as standard drugs to compare the activity of compounds reported here. Chalcones (**3a**–**e**) without oxypropanolamine chain showed insignificant activities.

In general all the screened compounds (except **5d**, **f**, **h**, **i** and **k**) showed moderate to potent antihyperglycemic activity in SLM model but only 6 compounds (**5a**, **g**, **m**, **o**, **p** and **r**) displayed blood glucose lowering activity at 100-mg/kg doses in STZ model.

3,4-Methylenedioxy compounds **5p** and **r** lowered blood glucose level to 23.0% and 11.58% in STZ and 21.1% and 23.8% in SLM models respectively. 3,4-Dimethoxy compound **5a** displayed significant antihyperglycemic effect, 15.4% in SLM and 20.3% in STZ model. From mono methoxy series **5g** and **m** showed blood glucose lowering activity 10.8% and 20% in SLM model and moderate activity 6.18% and 11.3% in STZ model. Another active compound **5o** from the same series reduced blood glucose level significantly to 47% in SLM model but showed insignificant activity (2.77%) in STZ model. Compounds **5f**, **h** and **i** were found to be inactive in SLM model, while compounds **5d**, **k** and **q** showed insignificant blood glucose lowering activity. Rest of the compounds (**5b**, **c**, **e**, **j**, **l** and **n**) showed moderate to significant antihyperglycemic effect in SLM model but showed poor activity in STZ model. In conclusion compounds (**5a**, **b**, **p**, **q** and **r**) vicinally dioxygenated as dimethoxy and methylenedioxy substitution showed the best antihyperglycemic activity when compared to the corresponding monomethoxy compounds (**5c**, **d** and **e**). From monomethoxy series also compounds (**5e**, **g**, **j**, **m**, **n** and **o**) showed moderate to significant blood glucose lowering activity in SLM model but only **5g**, **m** showed moderate activity in STZ model. Furthermore compounds containing propanolamine chain at *para* posi-

tion showed significant activity as compared to *meta* and *ortho* substituted compounds

3. Experimental

Melting points were determined on a capillary melting point apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded in the indicated solvent on Bruker WM 200 MHz spectrometer with TMS as internal standard. Infrared spectra were recorded in KBr on Perkin–Elmer AC-1 spectrometer. FAB mass spectra were recorded on JEOL SX 102/DA 6000 mass spectrometer. Microanalyses were performed on Carlo Erba EA-1108 element analyzer and were within the $\pm$0.5% of the theoretical values. Column chromatography was performed on silica gel (Merck, 60–120 mesh).

3.1. (A) General procedure for the preparation of chalcones (3a–e)

To a well stirred solution of substituted acetophenone (50 mmol) and appropriately substituted benzaldehyde (50 mmol) in methanol (150 mL) was added a 50% w/v aq NaOH solution (30 mL). The reaction mixture was stirred overnight at room temperature. It was neutralized with 1N HCl and filtered the product; in case of the absence of precipitate it was extracted with chloroform. The combined organic layers were dried (Na_2SO_4), filtered and evaporated. The product was purified by column chromatography.

3.1.1. 4′-Hydroxy-4-methoxy-chalcone (3a). Yield 90%; mp 184–185 °C (lit. 188–190 °C) [24]; MS (EI) *m*/*z* 254 (M^+, 100), 253 (34.7), 239 (32.3), 161 (36.8), 121 (79.5); IR (KBr) 3371 (OH), 1654 (CO); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.99 (d, *J* = 8.6 Hz, 2H), 7.78 (d, *J* = 15.6 Hz, 1H), 7.60 (d, *J* = 8.6 Hz, 2H), 7.41 (d, *J* = 15.6 Hz, 1H), 6.93 (d, *J* = 7.2 Hz, 4H), 5.85 (broad s, 1H, OH), 3.86 (s, 3H, OMe).

3.1.2. 3′-Hydroxy-4-methoxy-chalcone (3b). Yield 98%; mp 93–94 °C; MS (FAB) 255 ($M^+ + 1$); IR (KBr) 3366 (OH), 1649 (CO); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.80 (d, *J* = 15.6 Hz, 1H), 7.62 (d, *J* = 7.8 Hz, 1H), 7.58 (d, *J* = 8.7 Hz, 2H), 7.55 (d, *J* = 2.3 Hz, 1H), 7.38 (d, *J* = 15.6 Hz, 1H), 7.36 (t, *J* = 7.8 Hz, 1H), 7.04 (d, *J* = 7.9 Hz, 1H), 6.92 (d, *J* = 8.6 Hz, 2H), 3.85 (s, 3H, OMe).

3.1.3. 2′-Hydroxy-4-methoxy-chalcone (3c). Yield 92%; mp 81–83 °C (lit. 93–94) [25]; MS (FAB) 255 ($M^+ + 1$); IR (KBr) 3450 (OH), 1639 (CO); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.92 (dd, *J* = 8.7 Hz, 1.4 Hz, 1H), 7.90 (d, *J* = 15.4 Hz, 1H), 7.62 (d, *J* = 8.7 Hz, 2H), 7.53 (d, *J* = 15.5 Hz, 1H), 7.49 (t, *J* = 7.4 Hz, 1H), 6.95 (d, *J* = 8.6 Hz, 2H), 7.03–6.89 (m, 2H), 3.86 (s, 3H, OMe).

3.1.4. 3,4-Dimethoxy-4′-hydroxy-chalcone (3d). Yield 69%; mp 193–195 °C; MS (FAB) 285 ($M^+ + 1$); IR (KBr) 3443 (OH), 1643 (CO); ^{1}H NMR (200 MHz, $CDCl_3$) δ 10.45 (s, 1H, OH), 8.10 (d, *J* = 8.5 Hz, 2H), 7.81 (d, *J* = 15.5 Hz, 1H), 7.66 (d, *J* = 15.5 Hz, 1H), 7.52 (s, 1H), 7.36 (d, *J* = 8.2 Hz, 1H), 7.01 (d, *J* = 8.4 Hz, 1H), 6.93 (d, *J* = 8.5 Hz, 2H), 3.95 (s, 3H, OMe), 3.92 (s, 3H, OMe).

3.1.5. 4′-Hydroxy-3,4-methylenedioxy-chalcone (3e). Yield 65%; mp 191–193 °C; MS (FAB) 269 ($M^+ + 1$); IR (KBr) 3410 (OH), 1646 (CO); ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.15 (s, 1H, OH), 7.98 (d, *J* = 8.7 Hz, 2H), 7.72 (d, *J* = 15.5 Hz, 1H), 7.37 (d, *J* = 15.5 Hz, 1H), 7.16 (s, 1H), 7.12 (d, *J* = 8.1 Hz, 1H), 6.99 (d, *J* = 8.8 Hz, 2H), 6.82 (d, *J* = 7.9 Hz, 1H), 6.02 (s, 2H).

3.2. (B) General procedure for the *O*-alkylation of hydroxy chalcones (4a–e)

To a well stirred solution of chalcone (40 mmol) in dry DMF (160 mL) was added NaH (40 mmol) at 0–5 °C. To the above reaction mixture excess of epichlorohydrin (120 mmol) was added and stirred at room temperature approximately for 8 h. The reaction mixture was concentrated under reduced pressure, diluted with water and extracted with chloroform. The combined organic layers were dried (Na_2SO_4), filtered and evaporated. The product was purified by column chromatography.

3.2.1. 4′-(2,3-Epoxy-propoxy)-4-methoxy-chalcone (4a). Yield 60%; mp 85–87 °C; MS (FAB) 311 ($M^+ + 1$); IR (KBr) 1655 (CO); ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.02 (d, *J* = 8.8 Hz, 2H), 7.77 (d, *J* = 15.6 Hz, 1H), 7.59 (d, *J* = 8.7 Hz, 2H), 7.41 (d, *J* = 15.6 Hz, 1H), 6.99 (d, *J* = 8.8 Hz, 2H), 6.93 (d, *J* = 8.7 Hz, 2H), 4.32 (dd, *J* = 11.1 Hz, 2.9 Hz, 1H), 4.01 (dd, *J* = 11.1 Hz, 5.7 Hz, 1H), 3.84 (s, 3H, OMe), 3.40–3.35 (m, 1H), 2.92 (t, *J* = 4.5 Hz, 4.5 Hz, 1H), 2.77 (dd, *J* = 4.8 Hz, 2.6 Hz, 1H).

3.2.2. 3′-(2,3-Epoxy-propoxy)-4-methoxy-chalcone (4b). Yield 75%; mp 64–65 °C; MS (FAB) 311 ($M^+ + 1$); IR (KBr) 1658 (CO); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.79 (d, *J* = 15.5 Hz, 1H), 7.60 (d, *J* = 8.7 Hz, 1H), 7.60 (d, *J* = 8.7 Hz, 2H), 7.56 (d, *J* = 1.3 Hz, 1H), 7.41 (t, *J* = 7.9 Hz, 1H), 7.39 (d, *J* = 15.5 Hz, 1H), 7.15 (dd, *J* = 8.1 Hz, 1.4 Hz, 1H), 6.94 (d, *J* = 8.6 Hz, 2H), 4.34 (dd, *J* = 11.0 Hz, 2.8 Hz, 1H), 4.01 (dd, *J* = 11.0 Hz, 5.8 Hz, 1H), 3.86 (s, 3H, OMe), 3.40–3.38 (m, 1H), 2.93 (t, *J* = 4.5 Hz, 4.4 Hz, 1H), 2.79 (dd, *J* = 4.7 Hz, 2.6 Hz, 1H).

3.2.3. 2′-(2,3-Epoxy-propoxy)-4-methoxy-chalcone (4c). Yield 42%; mp 57–58 °C; MS (FAB) 311 ($M^+ + 1$); IR (KBr) 1644 (CO); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.64 (dd, *J* = 8.5 Hz, 1.8 Hz, 1H), 7.63 (d, *J* = 15.8 Hz, 1H), 7.60 (d, *J* = 8.6 Hz, 2H), 7.45 (t, *J* = 7.5 Hz, 1H), 7.34 (d, *J* = 15.8 Hz, 1H), 7.10–6.95 (m, 2H), 6.92 (d, *J* = 8.8 Hz, 2H), 4.36 (dd, *J* = 11.0 Hz, 2.6 Hz, 1H), 4.08 (dd, *J* = 11.0 Hz, 5.1 Hz, 1H), 3.84 (s, 3H, OMe), 3.34–3.31 (m, 1H), 2.85–2.77 (m, 2H).

3.2.4. 3,4-Dimethoxy-4′-(2,3-epoxy-propoxy)-chalcone (4d). Yield 41%; mp 95–96 °C; MS (FAB) 341 ($M^+ + 1$); IR (KBr) 1655 (CO); ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.03 (d, *J* = 8.8 Hz, 2H), 7.75 (d, *J* = 15.5 Hz, 1H), 7.39 (d, *J* = 15.5 Hz, 1H), 7.23 (dd, *J* = 8.3 Hz, 1.5 Hz, 1H),

7.16 (s, 1H), 7.00 (d, $J=8.8$ Hz, 2H), 6.89 (d, $J=8.3$ Hz, 1H), 4.32 (dd, $J=11.1$ Hz, 2.9 Hz, 1H), 4.01 (dd, $J=11.1$ Hz, 5.8 Hz, 1H), 3.95 (s, 3H, OMe), 3.93 (s, 3H, OMe), 3.40–3.36 (m, 1H), 2.93 (t, $J=4.5$ Hz, 4.6 Hz, 1H), 2.79 (dd, $J=4.8$ Hz, 2.6 Hz, 1H).

3.2.5. 4′-(2,3-Epoxy-propoxy)-3,4-methylenedioxy-chalcone (4e). Yield 80%; mp 83–84 °C; MS (FAB) 325 ($M^+ +1$); IR (KBr) 1650 (CO); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.98 (d, $J=8.8$ Hz, 2H), 7.72 (d, $J=15.5$ Hz, 1H), 7.36 (d, $J=15.5$ Hz, 1H), 7.16 (s, 1H), 7.12 (d, $J=8.1$ Hz, 1H), 6.99 (d, $J=8.8$ Hz, 2H), 6.83 (d, $J=7.9$ Hz, 1H), 6.02 (s, 2H), 4.32 (dd, $J=11.1$ Hz, 3.0 Hz, 1H), 4.02 (dd, $J=11.1$ Hz, 5.7 Hz, 1H), 3.38–3.36 (m, 1H), 2.93 (t, $J=4.4$ Hz, 4.3 Hz, 1H), 2.78 (dd, $J=4.8$ Hz, 2.6 Hz, 1H).

3.3. General procedure for the opening of epoxides with amines (5a–r)

To a solution of epoxide (5 mmol) in methanol (80 mL) was added required amount of amine (5 mmol, excess of amine required in case of primary amine ≈4 times) and stirred at room temperature approximately for 6 h. Methanol was removed under vaccum and product purified by column chromatography.

3.3.1. 3,4-Dimethoxy-4′-[2-hydroxy-3-(4-phenylpiperazin-1-yl)-propoxy]-chalcone (5a). Yield 85%; mp 126–127 °C; MS (FAB) 503 ($M^+ +1$); IR (KBr) 3426 (OH), 1652 (CO); ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.03 (d, $J=8.8$ Hz, 2H), 7.76 (d, $J=15.5$ Hz, 1H), 7.39 (d, $J=15.5$ Hz, 1H), 7.31–7.20 (m, 3H), 7.16 (d, $J=1.3$ Hz, 1H), 7.01 (d, $J=8.8$ Hz, 2H), 6.93 (d, $J=7.8$ Hz, 1H), 6.95–6.87 (m, 3H), 4.19–4.08 (m, 3H), 3.95 (s, 3H, OMe), 3.92 (s, 3H, OMe), 3.23 (t, $J=4.7$ Hz, 4H), 2.90–2.85 (m, 2H), 2.69–2.61 (m, 1H); ^{13}C NMR δ 189.2 (CO), 162.8, 151.8, 151.6, 149.7, 144.6, 132.1, 131.1, 129.6, 128.5, 123.4, 120.3, 116.6, 114.8, 111.7, 110.7, 70.9 (OCH_2), 65.9 (CH), 60.8 (CH_2N), 56.5 (2*OMe) 53.8 (NCH_2,CH_2), 49.7 (NCH_2,CH_2). Anal. calcd for $C_{30}H_{34}N_2O_5$: C, 71.69; H, 6.82; N, 5.57. Found: C, 71.18; H, 6.93; N, 5.32.

3.3.2. 4′-[3-*tert*-Butylamino-2-hydroxy-propoxy]-3,4-dimethoxy-chalcone (5b). Yield 87%; mp 62–64 °C; MS (FAB) 414 ($M^+ +1$); IR (KBr) 3450 (broad, OH, NH), 1650 (CO); ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.03 (d, $J=8.8$ Hz, 2H), 7.76 (d, $J=15.5$ Hz, 1H), 7.40 (d, $J=15.5$ Hz, 1H), 7.26 (s, 1H), 7.17 (dd, $J=8.2$ Hz, 1.6 Hz, 1H), 7.0 (d, $J=8.8$ Hz, 2H), 6.90 (d, $J=8.3$ Hz, 1H), 4.07–4.05 (m, 3H), 3.95 (s, 3H, OMe), 3.93 (s, 3H, OMe), 2.88 (dd, $J=11.9$ Hz, 4.0 Hz, 1H), 2.68 (dd, $J=11.9$ Hz, 7.5 Hz, 2H), 1.13 (s, 9H). Anal. calcd for $C_{24}H_{31}NO_5$: C, 69.71; H, 7.56; N, 3.39. Found: C, 69.82; H, 7.41; N, 3.16.

3.3.3. 4′-[2-Hydroxy-3-(4-phenylpiperazin-1-yl)-propoxy]-4-methoxy-chalcone (5c). Yield 70%; mp 165–167 °C; MS (FAB) 473 ($M^+ +1$); IR (KBr) 3392 (OH), 1652 (CO); ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.03 (d, $J=8.8$ Hz, 2H), 7.78 (d, $J=15.6$ Hz, 1H), 7.60 (d, $J=8.6$ Hz, 2H), 7.42 (d, $J=15.5$ Hz, 1H), 7.31–7.24 (m, 2H), 7.01 (d, $J=8.7$ Hz, 2H), 6.94 (d, $J=8.7$ Hz, 2H), 6.96–6.84 (m, 3H), 4.19–4.09 (m, 3H), 3.86 (s, 3H, OMe), 3.24 (t, $J=4.9$ Hz, 4H), 2.89–2.84 (m, 2H), 2.74–2.64 (m, 4H). Anal. calcd for $C_{29}H_{32}N_2O_4$: C, 73.70; H, 6.83; N, 5.93. Found: C, 73.32; H, 6.41; N, 5.69.

3.3.4. 4′-[3-*iso*-Butylamino-2-hydroxy-propoxy]-4-methoxy-chalcone (5d). Yield 74%; mp 76–77 °C; MS (FAB) 384 ($M^+ +1$); IR (KBr) 3423 (broad, OH, NH), 1653 (CO); ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.02 (d, $J=8.6$ Hz, 2H), 7.78 (d, $J=15.6$ Hz, 1H), 7.60 (d, $J=8.5$ Hz, 2H), 7.42 (d, $J=15.6$ Hz, 1H), 6.99 (d, $J=8.8$ Hz, 2H), 6.93 (d, $J=8.6$ Hz, 2H), 4.21–3.97 (m, 3H), 3.85 (s, 3H, OMe), 2.91–2.72 (m, 2H), 2.48 (d, $J=6.7$ Hz, 2H), 1.83–1.66 (m, 1H), 0.93 (d, $J=6.6$ Hz, 6H). Anal. calcd for $C_{23}H_{29}NO_4$: C, 72.04; H, 7.62; N, 3.65. Found: C, 72.12; H, 7.43; N, 3.52.

3.3.5. 4′-[3-*tert*-Butylamino-2-hydroxy-propoxy]-4-methoxy-chalcone (5e). Yield 85%; mp 70–71 °C; MS (FAB) 384 ($M^+ +1$); IR (KBr) 3391 (broad, OH, NH), 1640 (CO); ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.02 (d, $J=8.7$ Hz, 2H), 7.78 (d, $J=15.7$ Hz, 1H), 7.60 (d, $J=8.7$ Hz, 2H), 7.41 (d, $J=15.6$ Hz, 1H), 6.99 (d, $J=8.9$ Hz, 2H), 6.93 (d, $J=8.7$ Hz, 2H), 4.13–4.05 (m, 3H), 3.86 (s, 3H, OMe), 2.95–2.73 (m, 2H), 1.21 (s, 9H). Anal. calcd for $C_{23}H_{29}NO_4$: C, 72.04; H, 7.62; N, 3.65. Found: C, 72.09; H, 7.13; N, 3.72.

3.3.6. 4′-[2-Hydroxy-3-*iso*-propylamino-propoxy]-4-methoxy-chalcone (5f). Yield 59%; mp 105–106 °C; MS (FAB) 370 ($M^+ +1$); IR (KBr) 3420 (OH), 3289 (NH), 1654 (CO); ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.02 (d, $J=8.6$ Hz, 2H), 7.78 (d, $J=15.7$ Hz, 1H), 7.60 (d, $J=8.5$ Hz, 2H), 7.42 (d, $J=15.6$ Hz, 1H), 6.99 (d, $J=8.9$ Hz, 2H), 6.93 (d, $J=8.7$ Hz, 2H), 4.23–4.09 (m, 3H), 3.85 (s, 3H, OMe), 2.96–2.74 (m, 3H), 1.11 (d, $J=6.2$ Hz, 6H). Anal. calcd for $C_{22}H_{27}NO_4$: C, 71.52; H, 7.37; N, 3.79. Found: C, 71.33; H, 7.42; N, 3.63.

3.3.7. 4′-[2-Hydroxy-3-{4-(2-methoxyphenyl)-piperazin-1-yl}-propoxy]-4-methoxy-chalcone (5g). Yield 66%; mp 97–98 °C; MS (FAB) 503 ($M^+ +1$); IR (KBr) 3451 (OH), 1652 (CO); ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.03 (d, $J=8.3$ Hz, 2H), 7.78 (d, $J=15.5$ Hz, 1H), 7.60 (d, $J=8.1$ Hz, 2H), 7.43 (d, $J=15.4$ Hz, 1H), 7.03–6.85 (m, 8H), 4.13–4.09 (m, 3H), 3.87 (s, 3H, OMe), 3.86 (s, 3H, OMe), 3.14–3.10 (m, 4H), 2.90–2.88 (m, 2H), 2.67–2.63 (m, 4H). Anal. calcd for $C_{30}H_{34}N_2O_5$: C, 71.69; H, 6.82; N, 5.57. Found: C, 71.62; H, 6.91; N, 5.42.

3.3.8. 4′-[3-{2-(3,4-Dimethoxyphenyl)-ethylamino}-2-hydroxy-propoxy]-4-methoxy-chalcone (5h). Yield 59%; mp 120–121 °C; MS (FAB) 492 ($M^+ +1$); IR (KBr) 3431 (broad, OH, NH), 1654 (CO); ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.01 (d, $J=8.8$ Hz, 2H), 7.78 (d, $J=15.6$ Hz, 1H), 7.60 (d, $J=8.7$ Hz, 2H), 7.42 (d, $J=15.5$ Hz, 1H), 6.97 (d, $J=8.6$ Hz, 2H), 6.93 (d, $J=9.1$ Hz, 2H), 6.78–6.73 (m, 3H), 4.09–4.01 (m, 3H), 3.87 (s, 3H, OMe), 3.85 (s, 6H, 2*OMe), 2.91–2.77 (m, 6H). Anal. calcd for $C_{29}H_{33}NO_6$: C, 70.86; H, 6.77; N, 2.85. Found: C, 70.81; H, 6.72; N, 2.91.

3.3.9. 4′-[2-Hydroxy-3-methylamino-propoxy]-4-methoxy-chalcone (5i). Yield 43%; mp 114–115 °C; MS (FAB) 342 ($M^+ + 1$); IR (KBr) 3487 (OH), 3344 (NH), 1652 (CO); ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.01 (d, $J = 8.6$ Hz, 2H), 7.77 (d, $J = 15.6$ Hz, 1H), 7.59 (d, $J = 8.5$ Hz, 2H), 7.41 (d, $J = 15.6$ Hz, 1H), 6.98 (d, $J = 8.9$ Hz, 2H), 6.93 (d, $J = 8.7$ Hz, 2H), 4.07–4.05 (m, 3H), 3.85 (s, 3H, OMe), 2.93–2.82 (m, 2H), 2.50 (s, 3H). Anal. calcd for $C_{20}H_{23}NO_4$: C, 70.36; H, 6.79; N, 4.10. Found: C, 70.40; H, 6.72; N, 4.13.

3.3.10. 4′-[3-*n*-Butylamino-2-hydroxy-propoxy]-4-methoxy-chalcone (5j). Yield 72%; mp 163–164 °C; MS (FAB) 384 ($M^+ + 1$); IR (KBr) 3367 (broad, OH, NH), 1629 (CO); ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.02 (d, $J = 8.7$ Hz, 2H), 7.77 (d, $J = 15.3$ Hz, 1H), 7.59 (d, $J = 8.7$ Hz, 2H), 7.41 (d, $J = 15.5$ Hz, 1H), 6.99 (d, $J = 8.9$ Hz, 2H), 6.93 (d, $J = 8.7$ Hz, 2H), 4.20–3.95 (m, 3H), 3.86 (s, 3H, OMe), 2.93–2.55 (m, 2H), 2.55 (t, $J = 5.9$ Hz, 2H), 1.57–1.39 (m, 4H), 0.93 (t, $J = 6.9$ Hz, 3H). Anal. calcd for $C_{23}H_{29}NO_4$: C, 72.04; H, 7.62; N, 3.65. Found: C, 71.97; H, 7.58; N, 3.61.

3.3.11. 3′-[2-Hydroxy-3-(4-phenylpiperazin-1-yl)-propoxy]-4-methoxy-chalcone (5k). Yield 82%; mp 153–154 °C; MS (FAB) 473 ($M^+ + 1$); IR (KBr) 3485 (OH), 1652 (CO); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.79 (d, $J = 15.6$ Hz, 1H), 7.60 (d, $J = 8.8$ Hz, 1H), 7.60 (d, $J = 8.8$ Hz, 2H), 7.58 (d, $J = 2.9$ Hz, 1H), 7.41 (t, $J = 7.8$ Hz, 1H), 7.39 (d, $J = 15.6$ Hz, 1H), 7.31–7.23 (m, 2H), 7.16 (dd, $J = 8.1$ Hz, 1.9 Hz, 2H), 6.94 (d, $J = 8.7$ Hz, 2H), 6.96–6.83 (m, 2H), 4.19–4.08 (m, 3H), 3.86 (s, 3H, OMe), 3.23 (t, $J = 4.9$ Hz, 4H), 2.89–2.81 (m, 2H), 2.70–2.62 (m, 4H). Anal. calcd for $C_{29}H_{32}N_2O_4$: C, 73.70; H, 6.83; N, 5.93. Found: C, 71.63; H, 6.54; N, 5.91.

3.3.12. 3′-[2-Hydroxy-3-*iso*-propylamino-propoxy]-4-methoxy-chalcone (5l). Yield 76%; mp 102–103 °C; MS (FAB) 370 ($M^+ + 1$); IR (KBr) 3391 (OH), 3131 (NH) 1650 (CO); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.79 (d, $J = 15.7$ Hz, 1H), 7.60 (d, $J = 8.6$ Hz, 1H), 7.60 (d, $J = 8.6$ Hz, 2H), 7.55 (d, $J = 1.9$ Hz, 1H), 7.40 (t, $J = 7.9$ Hz, 1H), 7.38 (d, $J = 15.6$ Hz, 1H), 7.14 (dd, $J = 7.6$ Hz, 1.6 Hz, 2H), 6.94 (d, $J = 8.7$ Hz, 2H), 4.09–4.01 (m, 3H), 3.86 (s, 3H, OMe), 2.92–2.74 (m, 3H), 1.10 (d, $J = 6.2$ Hz, 6H). Anal. calcd for $C_{22}H_{27}NO_4$: C, 71.52; H, 7.37; N, 3.79. Found: C, 71.13; H, 7.29; N, 3.81.

3.3.13. 3′-[3-*tert*-Butylamino-2-hydroxy-propoxy]-4-methoxy-chalcone (5m). Yield 69%; mp 83–84 °C; MS (FAB) 384 ($M^+ + 1$); IR (KBr) 3387 (broad, OH, NH), 1653 (CO); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.78 (d, $J = 15.6$ Hz, 1H), 7.60 (d, $J = 8.7$ Hz, 1H), 7.60 (d, $J = 8.7$ Hz, 2H), 7.56 (d, $J = 2.5$ Hz, 1H), 7.40 (t, $J = 7.9$ Hz, 1H), 7.38 (d, $J = 15.6$ Hz, 1H), 7.14 (dd, $J = 7.6$ Hz, 1.7 Hz, 1H), 6.94 (d, $J = 8.7$ Hz, 2H), 4.09–4.01 (m, 3H), 3.86 (s, 3H, OMe), 2.92–2.81 (m, 3H), 1.14 (s, 9H). Anal. calcd for $C_{23}H_{29}NO_4$: C, 72.04; H, 7.62; N, 3.65. Found: C, 72.08; H, 7.57; N, 3.58.

3.3.14. 2′-[3-*n*-Butylamino-2-hydroxy-propoxy]-4-methoxy-chalcone (5n). Yield 86%; mp 106–107 °C; MS (FAB) 384 ($M^+ + 1$); IR (KBr) 3430 (OH), 3295 (NH), 1644 (CO); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.60 (d, $J = 8.9$ Hz, 1H), 7.58 (d, $J = 15.8$ Hz, 1H), 7.56 (d, $J = 8.4$ Hz, 2H), 7.45 (t, $J = 7.1$ Hz, 1H), 7.28 (d, $J = 15.8$ Hz, 1H), 7.08–7.01 (m, 2H), 6.91 (d, $J = 8.6$ Hz, 2H), 4.15–4.04 (m, 3H), 3.84 (s, 3H, OMe), 2.84–2.68 (m, 2H), 2.52 (t, $J = 5.9$ Hz, 2H), 1.40–1.25 (m, 4H), 0.87 (t, $J = 6.9$ Hz, 3H). Anal. calcd for $C_{23}H_{29}NO_4$: C, 72.04; H, 7.62; N, 3.65. Found: C, 71.96; H, 7.57; N, 3.61.

3.3.15. 2′-[2-Hydroxy-3-*iso*-propylamino-propoxy]-4-methoxy-chalcone (5o). Yield 73%; mp 88–89 °C; MS (FAB) 370 ($M^+ + 1$); IR (KBr) 3450 (OH), 3284 (NH), 1645 (CO); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.60 (d, $J = 8.9$ Hz, 1H), 7.58 (d, $J = 15.6$ Hz, 1H), 7.55 (d, $J = 8.4$ Hz, 2H), 7.44 (t, $J = 7.5$ Hz, 1H), 7.28 (d, $J = 15.8$ Hz, 1H), 7.08–6.97 (m, 2H), 6.91 (d, $J = 8.6$ Hz, 2H), 4.14–3.95 (m, 3H), 3.84 (s, 3H, OMe), 2.83–2.61 (m, 3H), 0.97 (d, $J = 6.0$ Hz, 6H). Anal. calcd for $C_{22}H_{27}NO_4$: C, 71.52; H, 7.37; N, 3.79. Found: C, 71.48; H, 7.41; N, 3.71.

3.3.16. 4′-[3-*tert*-Butylamino-2-hydroxy-propoxy]-3,4-methylenedioxy-chalcone (5p). Yield 89%; mp 122–124 °C; MS (FAB) 398 ($M^+ + 1$); IR (KBr) 3401 (broad, OH, NH), 1660 (CO); ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.00 (d, $J = 8.7$ Hz, 2H), 7.71 (d, $J = 15.5$ Hz, 1H), 7.36 (d, $J = 15.5$ Hz, 1H), 7.15 (s, 1H), 7.10 (d, $J = 8.1$ Hz, 1H), 6.98 (d, $J = 8.7$ Hz, 2H), 6.82 (d, $J = 7.9$ Hz, 1H), 6.00 (s, 2H), 4.12–3.99 (m, 3H), 2.87 (dd, $J = 11.8$ Hz, 3.6 Hz, 1H), 2.68 (dd, $J = 11.6$ Hz, 6.7 Hz, 1H), 1.13 (s, 9H); ^{13}C NMR δ 188.9 (CO), 162.9, 150.1, 148.8, 144.8, 131.9, 131.1, 129.9, 125.4, 120.3, 114.8, 109.0, 107.1, 101.9 (OCH_2O), 71.2 (OCH_2), 68.9 (CH), 45.0 (CH_2N), 29.4 (3*CH_3). Anal. calcd for $C_{23}H_{27}NO_5$: C, 69.50; H, 6.85; N, 3.52. Found: C, 68.84; H, 6.94; N, 3.42.

3.3.17. 4′-[2-Hydroxy-3-(4-phenylpiperazin-1-yl)-propoxy]-3,4-methylenedioxy-chalcone (5q). Yield 68%; mp 153–154 °C; MS (FAB) 487 ($M^+ + 1$); IR (KBr) 3396 (OH), 1651 (CO); ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.02 (d, $J = 8.8$ Hz, 2H), 7.71 (d, $J = 15.5$ Hz, 1H), 7.38 (d, $J = 15.5$ Hz, 1H), 7.27 (t, $J = 7.9$ Hz, 2H), 7.16 (s, 1H), 7.12 (d, $J = 8.0$ Hz, 1H), 7.01 (d, $J = 8.8$ Hz, 2H), 6.97 (d, $J = 7.2$ Hz, 1H), 6.91–6.82 (m, 3H), 6.02 (s, 2H), 4.17–4.09 (m, 3H), 3.23 (t, $J = 4.8$ Hz, 4H), 2.89–2.81 (m, 2H), 2.69–2.62 (m, 4H). Anal. calcd for $C_{29}H_{30}N_2O_5$: C, 71.59; H, 6.21; N, 5.76. Found: C, 71.62; H, 6.30; N, 5.81.

3.3.18. 4′-[3-*iso*-Butylamino-2-hydroxy-propoxy]-3,4-methylenedioxy-chalcone (5r). Yield 80%; mp 122–123 °C; MS (FAB) 398 ($M^+ + 1$); IR (KBr) 3325 (broad, OH, NH), 1657 (CO); ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.00 (d, $J = 8.8$ Hz, 2H), 7.72 (d, $J = 15.5$ Hz, 1H), 7.36 (d, $J = 15.5$ Hz, 1H), 7.15 (s, 1H), 7.10 (dd, $J = 8.7$ Hz, 1.3 Hz, 1H), 6.98 (d, $J = 8.8$ Hz, 2H), 6.83 (d, $J = 7.9$ Hz, 1H), 6.01 (s, 2H), 4.09–4.03 (m, 3H), 2.85–2.76 (m, 2H), 2.47 (d, $J = 6.5$ Hz, 2H), 1.78–1.72 (m, 1H), 0.93 (d, $J = 6.6$ Hz, 6H). Anal. calcd for $C_{23}H_{27}NO_5$: C, 69.50; H, 6.85; N, 3.52. Found: C, 69.53; H, 6. 71; N, 3.14.

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