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Synthesis of propiophenone derivatives as new class of antidiabetic agents reducing body weight in *db/db* mice

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ABSTRACT

A series of propiophenone derivatives (**6–23**) have been synthesized and evaluated for their in vivo antihyperglycemic activities in sucrose loaded model (SLM), sucrose challenged streptozotocin (STZ-S) induced diabetic rat model and C57BL/KsJ *db/db* diabetic mice model. Compound **15** and **16** were emerged as potent antihyperglycemics and lipid lowering agents. These compounds (**15**, **16**) further validate the potency by reducing body weight and food intake in *db/db* mice model. Possible mechanism of action for the propiophenone derivatives was established by the evaluation in various in vitro models. Interestingly some of the compounds were efficiently inhibiting PTP-1B.

1. Introduction

Diabetes mellitus is a global burden as approximately 4–5% will be affected all over the world by 2025.[1] While the rise will be of the order of 45% in developed countries and almost 200% in developing countries makes the situation more threatening.[2] Diabetes mellitus may be categorized into two subclasses (1) type I, known as insulin dependent diabetes mellitus (IDDM), (2) type II, noninsulin dependent diabetes mellitus (NIDDM). Type-2 diabetes accounts for approximately 80–90% of all diabetes cases and it is the fourth leading cause of death in developed countries.[3,4] Type-2 diabetes mellitus is characterized by hyperglycemia, insulin resistance, progressive metabolic disorder of carbohydrate and lipid metabolism.[5] Patients with type-2 diabetes often suffer from dyslipidemia in the form of high triglycerides, cholesterol and phospholipids.[6] Increase in cholesterol is a common feature of atherosclerosis by the involvement of arterial damage and lead to ischemic heart disease, myocardial infarction, and cerebro-vascular accidents. These conditions are responsible for one-third of deaths in industrialized nations.[7] Hence, in recent years several groups have focused their attention towards the development of dual acting (blood glucose as well as lipid lowering) drugs.[8] Protein tyrosine phosphatases (PTPases) plays a significant role in several diseases such as diabetes, cancer, obesity, and inflammation.[9] Recently PTP-1B has been emerged as new target to combat type-2 diabetes and obesity treatment.[10] The activation of insulin receptor in PTP-1B takes place via autophosphorylation on tyrosine part so the receptor is shut off by tyrosine phosphatase. Knockout mice of PTP-1B resulted in increased insulin sensitivity and glucose tolerance in skeletal muscle without affecting insulin action in adipose tissue, which resulted in decreased obesity.[11]

In continuation to our anti-diabetic drug discovery program,[12] we have designed and synthesized new propiophenone derivatives as antidiabetic agents. Rational behind the synthesis of propiophenone derivatives were based on previously reported propiophenone as well as acetophenone (**I**,[13] **II**,[14] **III**[15] and **IV**[16]) derivatives (Scheme 1). Benzofuran ring (heterocyclic) is attached to the prototype **I** at 3rd carbon of propiophenone scaffold, whereas benzene ring is attached to the 2nd and 3rd carbon atom on prototype **II**. Propiophenone derivatives (**I** and **II**) have better activity then acetophenone derivative (**III** and **IV**), therefore our interest has been developed towards the use of propiophenone scaffold instead of acetophenone for the search of orally active antidiabetic agents as well as potent inhibitor of PTP 1B. Herein, we have synthesized novel propiophenone derivatives and evaluated against several in vivo and in vitro models of diabetes.

2. Results and discussion

2.1. Chemistry

The synthetic strategy followed for the synthesis of novel propiophenone derivatives is depicted in Scheme 2. Synthesis of key

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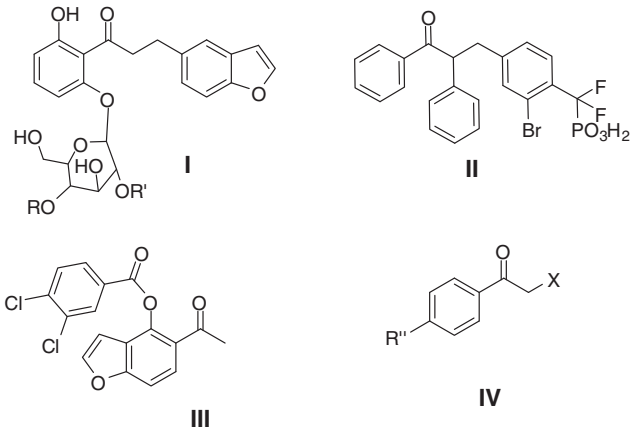


Scheme 1. Some propiophenone and acetophenone derivatives as PTP 1B inhibitors.

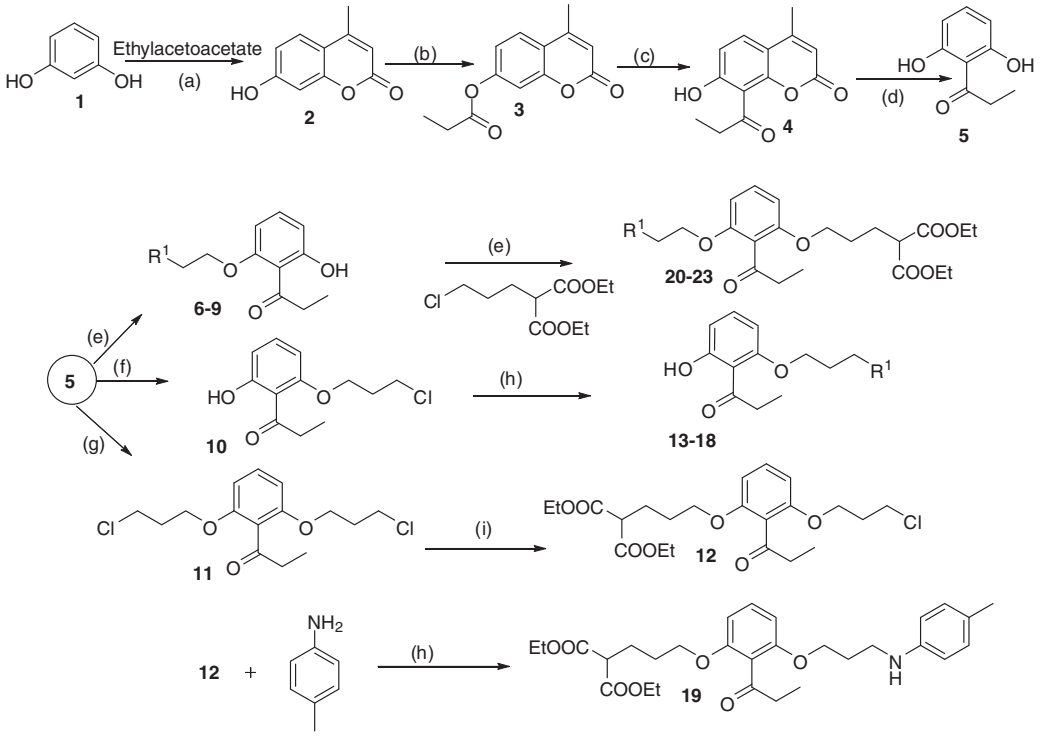
intermediate 2,6-dihydroxy propiophenone (**5**) was achieved in three steps by previously reported procedure.[17] 7-Hydroxy-4-methylcoumarin (**2**) was synthesized by the reaction of resorcinol, ethylacetoacetate and concentrated sulphuric acid. Compound (**2**) was further propionated in refluxing propionic anhydride followed by Fries rearrangement with $AlCl_3$ as catalyst afforded 8-propyl-7-hydroxy coumarin (**4**) via ortho migration of propyl group. Hydrolysis of compound **4** in 10% sodium hydroxide solution resulted 2,6-dihydroxy propiophenone **5**. Plausible mechanism for the synthesis of compound **5** via the hydrolysis of coumarin ring followed by decarboxylation and elimination of 1-propyne. The alkylation of 2,6-dihydroxy propiophenone (**5**) was achieved using different alkyl halide, and dihaloalkane in the presence of base for the synthesis of compounds **6–23.** Compounds **6**–**9** were synthesized via the alkylation of compound (**5**) using different chloroethyldialkylamino hydrochloride and diethyl 2-(3-chloropropyl)malonate. Disubstituted propiophenone derivative **11** was alkylated by diethyl malonate, $(CH_3)_3COK$, and THF as a solvent.

2.2. Biological activity

Our previous experiences in antidiabetic drug discovery[12] and antidiabetic in vivo screening program of CDRI inspired us to develop lead in vivo active compounds with the ability of glucose as well as lipid lowering potential. In course of searching potent compounds, all the synthesized compounds have been evaluated against various in vivo antidiabetic models. Some of the synthesised compounds (**7, 8, 9, 14, 15, 17, 18** and **22**) significantly lowered the blood glucose level in SLM model as compared to insulin sensitizer (metformin) and insulin secreting drug (glybenclamide).

Compounds were evaluated in STZ-S model on the basis of the glucose lowering ability in SLM. Few of the compounds (**7**, **9**, **15** and **16**) significantly lowered the blood glucose area under curve (AUC) at 0–5 h and 0–24 h. The most active compound (**15**) showed 22.1 (0–5 h) and 22.8% (0–24 h) reduction in glucose AUC in STZ-S model (Table 1). Compound **16** lowered the blood glucose in STZ-S rat model (27.5% and 21.5%) but did not have much effect on blood glucose in SLM model. No effect on the hyperglycemia of normal rats may be the possible reason behind the glucose lowering via compound **16** in SLM model. Inspired by these findings, we were evaluated these compounds in anti-hyperglycemic and lipid lowering activity in *db*/*db* mice model (Fig. 1). Compound **15** and **16** at the dose of 30 mg/kg were significant reducing the postprandial hyperglycemia by 23.9% ($p < 0.05$) and 39.6% ($p < 0.05$), respectively, as compared rosiglitazone 51.3% ($p < 0.01$).

Oral glucose tolerance in *db*/*db* mice was evaluated for their anti-hyperglycemic potential. Figs. 2 and 3 represents the effect



Scheme 2. Synthetic procedure for the synthesis of novel propiophenone derivatives. Reagent and conditions: (a) H_2SO_4, stirring at 0–8 °C; (b) Propionic anhydride, reflux; (c) Anhydrous $AlCl_3$, 170 °C; (d) Aqueous NaOH, reflux; (e) K_2CO_3, dry acetone, alkyl halides; (f) $BrCH_2CH_2CH_2Cl$, K_2CO_3, acetone; (g) $BrCH_2CH_2CH_2Cl$ (excess), K_2CO_3, dry acetone; (h) DMF, KI, amines; (i) $(CH_3)_3COK$, THF, diethyl malonate.

Table 1
In vivo anti hyperglycemic activity profile for the compounds **6–23**[a]

Compound no.	R[1]	Antihyperglycemic activity[b]		
		SLM	STZ-S	
			0–5 h	0–24 h
6	Dimethylamine	19.45*	12.1	7.4
7	Diethylamine	38.4**	23*	20.4
8	Pyrrolidine	21.08*	ND	ND
9	Piperidine	40.4**	29.2*	19.7
13	*n*-butylamine	11.0	ND	ND
14	*p*-Toludine,	28.7*	3.02	2.02
15	*p*-Anisidine	54.60**	22.1*	22.8*
16	*n*-Butylmethylamine	23.8*	27.5*	21.5*
17	Pyrrolidine	26.8*	16.9	14.8
18	Piperidine	33.2**	10.2	8.6
19	*p*-Toludine	8.49	ND	ND
20	Dimethylamine	11.5	ND	ND
21	Diethylamine	17.0	ND	ND
22	Pyrrolidine	22.9*	ND	ND
23	Piperidine	16.4	ND	ND
Metformin		18.9*	19.1	
Glybenclamide		32.3**		

[a] Single dose = 100 mg/kg; ND = Not determine.
[b] $^{*}p < 0.05$ and $^{**}p < 0.01$ versus vehicle treated control and statistical analysis was made by Dunnett's test (Prism Software). Number of experiments was 3.

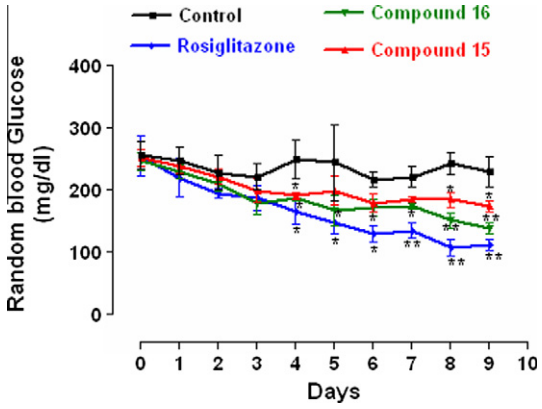


Figure 1. The blood glucose lowering activity of compound **15** and **16** till 10 day treatment of 30 mg/kg dose.

of compound **15** and **16** on day 6th and day 10th, respectively. The *db/db* mice were subjected to an oral glucose tolerance test post 3.0 g/kg oral glucose load. Significant improvement on oral glucose tolerance by 28.4% ($p < 0.05$), 26.7% ($p < 0.01$) on day 6th and 29.9% ($p < 0.05$) and 33.6% ($p < 0.01$) on day 10th were observed for the compound **15** and **16** comparable to rosiglitazone (33.9% ($p < 0.01$) on day 6th and 46.5% ($p < 0.01$) on day 10th).

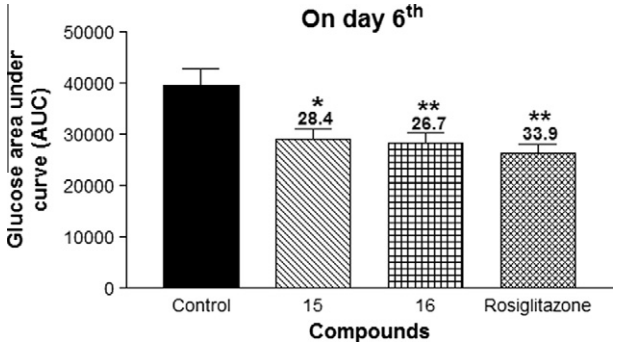


Figure 2. Post prandial OGTT on day 6th.

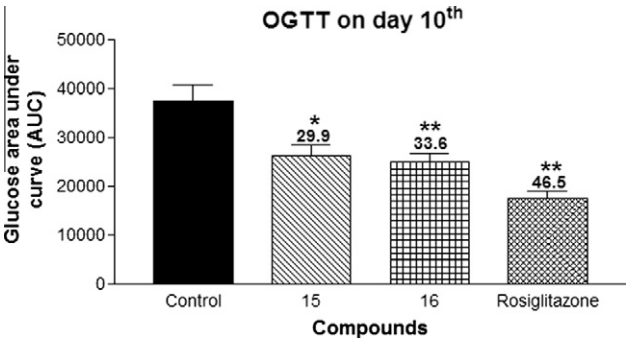


Figure 3. Post prandial OGTT on day 10th.

Compound **15** and **16** had significant improved dyslipidemia in *db/db* mice (Figs. 4a, 4b, 4c). These compounds were lowering the plasma triglycerides level (TG) by 22.0%, 23.8%, and plasma total cholesterol (T-Chol) level by 14.8%, 20.4%, respectively. Slightly increased level of HDL-cholesterol by 7.20%, 4.03% for **15** and **16** was also observed at same dose enhance the potency of compound.

We were interested to study the effect of these compounds on insulin level as hyperglycemia in *db/db* mice is due to insulin resistance. Compound **15** and **16** showed 23.6% ($p < 0.05$), 27.7% ($p < 0.05$) reduction in insulin level, respectively, as compare to the level of control mice (Fig. 5). Excessive consumption of food intake and body weight is responsible for the development of obesity and it can be directly linked with the type-2 diabetes. Further observation on body weight during the antidiabetic activity in *db/db* mice resulted decrease in body weight of mice during the treatment (Fig. 6.) of compound **15** and **16**. However, the calculated effect of compound **15** on body weight reduction was more in compare to compound **16**. We were pleased to find that compounds also had the beneficial effect on body weight besides the anti-hyperglycemic and lipid lowering activity. The reason behind the consistent lowering in body weight of mice was due to the decreased intake of food in *db/db* mice. Significant reduction in food intake was observed by the treatment of compound **15** and 16 starts from day 3rd and continues till day 10th (Fig. 7)

Synthesized compounds were evaluated against the glucose-6-phosphatase, glycogen phosphorylase, α-glucosidase, DPP-IV, and PTP-1B enzymes at 100 μM concentrations to know the possible mechanism of anti-hyperglycemic action (Table 2). All the synthesized compounds were showing poor inhibitory activities against the glucose-6-phosphatase, glycogen phosphorylase, α-glucosidase, and DPP IV enzymes. To our delight eight compounds (**13**, **14**, **15**, **17**, **19**, **20**, **21** and **22**) were inhibiting PTP-1B with more than 40% inhibition (Table 2). It may be one of the possible reason that PTP-1B inhibition plays significant role in the in vivo anti-hyperglycemic activity of the compounds. SAR studies of

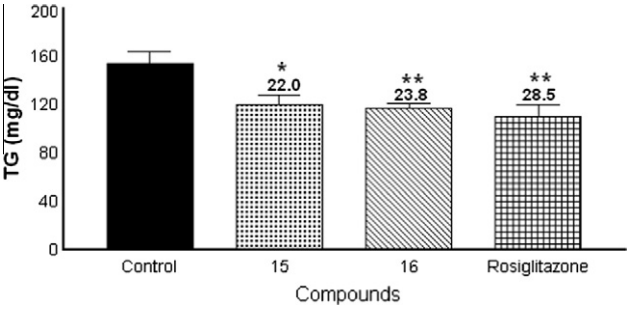


Figure 4a. Effect of compound **15** and **16** on plasma triglycerides level (TG).

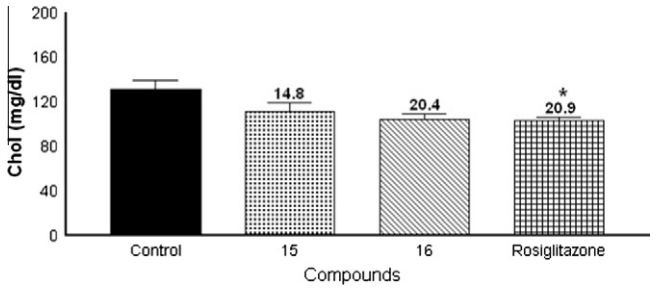


Figure 4b. Effect of compound **15** and **16** on plasma total cholesterol.

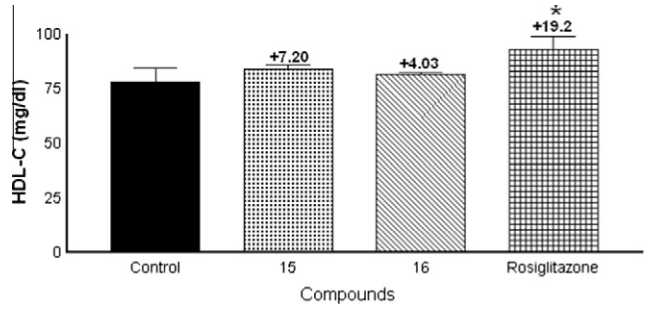


Figure 4c. Effect of compound **15** and **16** on HDL-cholesterol.

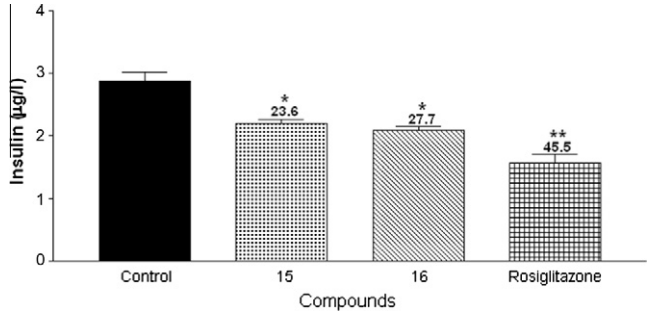


Figure 5. Effect on insulin level.

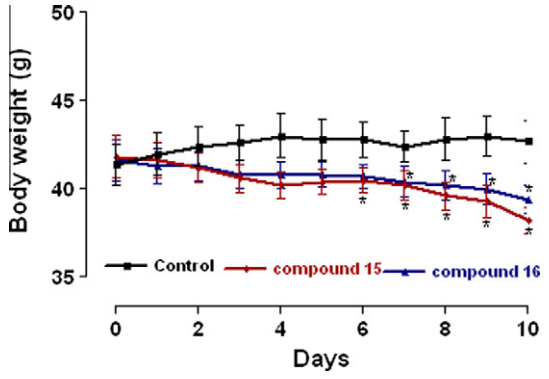


Figure 6. Effect on body weight of compounds **15** and **16**.

antidiabetic activity on synthesized compounds revealed that the two carbon chain length containing compounds (**6–9**) were less active against the PTP-1B in comparison to three carbon chain length (**13**–**18**). SAR studies on the side chain substitution indicated that the pyrrolidine ring containing compounds (**7**, **17** and **22**) gave more significant results than piperidine ring (**9**, **18** and **23**). It is noteworthy that aromatic substitution (**14** and **15**) in place of aliphatic substitution highly modulate the PTP-1B inhibition.

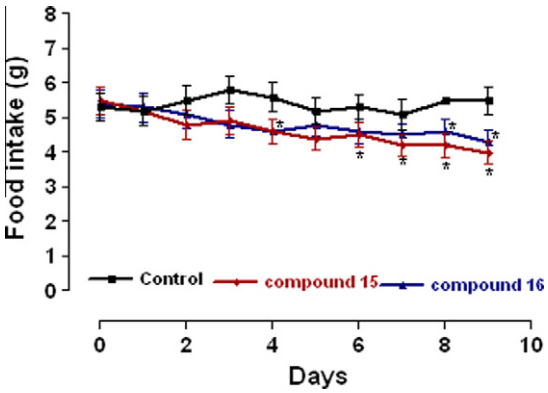


Figure 7. Effect on food intake.

3. Conclusion

In conclusion, newly synthesized propiophenone derivatives emerged as potent antidiabetic as well as lipid lowering agents. Propiophenone derivatives further signify the results by effectively reducing body weight and food intake in *db/db* mice. PTP-1B may be the potential target for the anti-hyperglycemic activity by the in vitro evaluation of synthesized compound. Most active compound of the series **15** has shown 83.6% inhibition with IC_{50} of 8.3 µM with promising in vivo activity.

4. Experimental

4.1. Chemistry

Unless otherwise specified all the reagents and catalysts were purchased from Sigma–Aldrich and were used without further any purification. The common solvents were purchased from Ranbaxy. Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator. Chromatographic purification of products was accomplished using flash chromatography on 60–120 or 100–200 mesh silica gel. Reactions were monitored by thin-layer chromatography (TLC) on 0.25 mm silica gel plates visualized under UV light, iodine or $KMnO_4$ staining. ^1H NMR spectra were recorded on a Brucker DRX-200 Spectrometer. Chemical shifts (δ) are given in ppm relative to TMS and coupling constants (J) in Hz. IR spectra were recorded on a FT IR spectrophotometer Shimadzu 8201 PC and are reported in terms of frequency of absorption (cm^{-1}). Mass spectra (ESIMS) were obtained by Micromass Quattro II instrument.

4.1.1. Typical experimental procedure for the synthesis of 2-alkoxy 1-(6-hydroxy-phenyl)-propane-1-ones derivatives (6–9)

A mixture of compound **5**, (830 mg, 5 mmol) and chloroethyldimethylamino hydrochloride (760 mg, 7 mmol) was taken in to the 50 ml round bottom flask and dry potassium carbonate (6.5 g, 50 mmol) in 30 ml dry acetone was added. Reaction mixture was refluxed on oil bath for 8 h. Reaction mixture was filtered and filtrate was concentrated to remove acetone. Reaction mixture was extracted with ethyl acetate (100 ml) and washed with (50 × 3 ml) of distilled water. Purification was done on silica gel column using hexane/chloroform solvent system to yield compound **6** in 85.23%.

4.1.1.1. 1-(2-(2-(Dimethylamino)ethoxy)-6-hydroxyphenyl)propan-1-one (6). Yield (85.23%), mp 62 °C. ESIMS (*m/z*) 238

Table 2
In vitro enzyme inhibitory activity of compounds **6–23**[a]

Compounds[a]	Glucose-6-phosphatase	Glycogen phosphorylase	α-Glucosidase	DPP IV	PTP-1B
6	11.3	NI	18.4	24.2	19.3
7	11.6	NI	19.3	NI	28.8
8	NI	13.7	28.9	NI	36.4
9	21.3	NI	NI	NI	27.5
13	18.3	24.8	NI	17.4	52.1(19.2)
14	18.9	NI	18.9	NI	79.8 (12.5)
15	NI	23	19.3	13.7	83.6(8.3)
16	17.3	NI	NI	NI	31.9
17	13.6	19.5	NI	25.6	42.1
18	NI	NI	NI	NI	31.8
19	NI	NI	11.8	NI	42.6
20	NI	NI	NI	NI	51.1(20.4)
21	NI	22.9	NI	NI	40.4
22	13.9	NI	NI	18.3	58.6(18.6)
23	NI	NI	NI	NI	19.6
Na-orthovanadate					56.0(15.2)

[a] Compounds were evaluated at 100 μM concentration; NI means no inhibition or <5%. For IC_{50} calculation against PTP inhibition, we have checked these compounds at variable doses. IC_{50} (μM) values are given in parentheses. Number of experiments-3.

$(M+H)^+$. IR (KBr) 2966, 1599, 1097 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz) δ: 1.17 (t, J = 7.2 Hz, 3H), 2.33 (s, 6H), 2.78 (t, J = 6.0 Hz, 2H), 3.14 (q, J = 7.2 Hz, 2H), 4.13 (t, J = 6.0 Hz, 2H), 6.37 (d, J = 8.2 Hz, 1H), 6.56 (d, J = 8.2 Hz, 1H), 7.28 (m, 1H), 8.23 (s, 1H). Analysis calcd for $C_{13}H_{19}NO_3$: C, 65.80; H, 8.07; N, 5.90. Found: C, 65.73; H, 8.32; N, 5.61.

4.1.1.2. 1-(2-(2-(Diethylamino)ethoxy)-6-hydroxyphenyl)propan-1-one (7). Yield (85.28%), State semisolid. ESIMS (m/z) 266 $(M+H)^+$. IR (KBr): 2972, 1621, 1058 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz) δ: 1.14 (t, J = 7.0 Hz, 3H, $COCH_2CH_3$), 1.18 (t, J = 5.0 Hz, 6H, NCH_2CH_3), 2.65 (q, J = 6.0 Hz, 4H, NCH_2CH_3), 2.90 (t, J = 6.4 Hz, 2H, OCH_2CH_2N), 3.14 (q, J = 7.0 Hz, 2H, $COCH_2CH_3$), 4.10 (t, J = 6.4 Hz, 2H, OCH_2CH_2N), 6.38 (d, J = 8.2 Hz, 1H, ArH), 6.55 (d, J = 8.2 Hz, 1H, ArH), 7.32 (m, 1H, ArH), 8.34 (s, 1H, –*OH*). Analysis calcd for $C_{15}H_{23}NO_3$: C, 67.90; H, 8.74; N, 5.28. Found: C, 67.84; H, 8.64; N 5.41.

4.1.1.3. 1-(2-Hydroxy-6-(2-(pyrrolidin-1-yl)ethoxy)phenyl)propan-1-one (8). Yield (78.46%). mp 156 °C (hydrochloride salt). ESIMS (m/z) 264 $(M+H)^+$. IR (KBr): 2976, 1621, 1091 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz) δ: 1.17 (t, J = 7.2 Hz, 3H, $COCH_2CH_3$), 1.81 (m, 4H, $N(CH_2)_2(CH_2)_2$), 2.59 (m, 4H, $N(CH_2)_2(CH_2)_2$), 2.96 (t, J = 6.4 Hz, 2H, NCH_2CH_2O), 3.18 (q, J = 7.2 Hz, 2H $COCH_2CH_3$), 4.18 (t, J = 6.4 Hz, 2H, OCH_2CH_2N), 6.37 (d, J = 8.4 Hz, 1H, ArH), 6.56(d, J = 8.2 Hz, 1H, ArH), 7.32(m, 1H, ArH), 8.69 (s, 1H, –*OH*). Analysis calcd for $C_{15}H_{21}NO_3$: C, 68.42; H, 8.04; N, 5.32. Found: C, 68.54; H, 8.12; N, 5.44.

4.1.1.4. 1-(2-Hydroxy-6-(2-(piperidin-1-yl)ethoxy)phenyl)propan-1-one (9). Yield (80.57%). mp 72 °C. ESIMS (m/z) 278 $(M+H)^+$. IR (KBr): 2938, 1621, 1090 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz) δ: 1.21 (t, J = 8.0 Hz, 3H, $COCH_2CH_3$), 1.30 (m, 2H, $N(CH_2)_2(CH_2)_2CH_2$), 1.55 (m, 4H, $N(CH_2)_2(CH_2)_2CH_2$), 2.48 (m, 4H, $N(CH_2)_2(CH_2)_2CH_2$), 2.80 (t, J = 6.4 Hz, 2H, OCH_2CH_2N), 3.16 (q, J = 8.0 Hz, 2H $COCH_2CH_3$), 4.16 (t, J = 6.4 Hz, 2H, OCH_2CH_2 N), 6.37 (d, J = 8.4 Hz, 1H, ArH), 6.56 (d, J = 8.4 Hz, 1H, ArH),7.32 (m, 1H, ArH), 8.56 (s, 1H, –*OH*). Analysis calcd for $C_{16}H_{23}NO_3$: C, 69.29; H, 8.36; N, 5.05. Found: C, 69.34; H, 8.24; N, 5.14.

4.1.2. 1-(2-(3-chloropropoxy)-6-hydroxyphenyl)propan-1-one (10)

A mixture of compound **5** (830 mg, 5 mmol), anhydrous potassium carbonate (6.6 g), dry acetone (30 ml) and 1-bromo-3-chloropropane (5 mmol) were taken in 50 ml round bottom flask, and refluxed on oil bath for 6 h. After completion of the reaction on TLC, reaction mixture was filtered to remove K_2CO_3 and filtrate was concentrated. Reaction mixture was extracted with ethyl acetate (100 ml), washed with distilled water (50×3 ml) and dried over anhydrous sodium sulfate. Reaction mixture was concentrated and crystallized with benzene and hexane to yield compound **10**. Yield (76.03%). mp 70–72 °C. ESIMS (m/z) 243 $(M+H)^+$. IR (KBr): 2977, 1599, 1079 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz) δ: 1.17 (t, J = 7.2 Hz, 3H, $COCH_2CH_3$), 2.34 (m, 2H, $ClCH_2CH_2CH_2O$), 3.06(q, J = 7.2 Hz, 2H, $COCH_2CH_3$), 3.74 (t, J = 6.2 Hz, 2H, $ClCH_2$), 4.22 (t, J = 6.0 Hz, 2H, OCH_2), 6.44 (d, J = 8.2 Hz, 1H, ArH), 6.57 (d, J = 8.2 Hz, 1H, ArH), 7.33 (m, 1H, ArH), 10.48 (s, 1H, *OH*). Analysis Calcd for $C_{12}H_{15}ClO_3$: C, 59.39; H, 6.23. Found: C, 59.31; H, 6.21.

4.1.3. 1-(2,6-Bis(3-chloropropoxy)phenyl)propan-1-one (11)

A mixture of compound **5** (1.66 g, 10 mmol), anhydrous potassium carbonate (13.8 g, 100 mmol), dry acetone (50 ml) and bromochloropropane (4 ml, excess) were taken in 50 ml round bottom flask. The reaction mixture was refluxed on oil bath for 6 h. After completion of the reaction on TLC, reaction mixture was filtered, concentrated to remove acetone and extracted with ethyl acetate (100 ml) and dried over anhydrous sodium sulfate. Reaction mixture was purified by column chromatography using basic alumina as adsorbent, hexane and ethyl acetate as eluent to yield compound **11.** Yield (94.96%). Physical state. oily. ESIMS (m/z) 319 $(M+H)^+$. IR (KBr): 2967, 1591, 1051 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz) δ: 1.15 (t, J = 7.2 Hz, 3H, $COCH_2CH_3$), 2.17 (m, 4H, CH_2CH_2 CH_2), 2.77 (q, J = 7.2 Hz, 2H, $COCH_2CH_3$), 3.66 (t, J = 6.2 Hz, 4H, $ClCH_2CH_2$), 4.11 (t, J = 5.8 Hz, 4H, OCH_2 CH_2), 6.57 (d, J = 8.4 Hz, 2H, ArH), 7.25 (t, J = 8.4 Hz, 1H, ArH). Analysis Calcd for $C_{15}H_{20}Cl_2O_3$: C, 56.44; H, 6.31. Found: C, 56.59; H, 6.16.

4.1.4. Diethyl 2-(3-(3-(3-chloropropoxy)-2-propionylphenoxy) propyl)malonate (12)

In a 50 ml of round bottom flask potassium tertiary butoxide (0.6 g, 5 mmol) and THF (30 ml) was stirred for five minute and diethyl malonate (0.8 g, 5 mmol) was slowly added in to the reaction mixture. Reaction mixture was stirred for 3 h. 2,6-dichloropropyl propiophenone (1.58 g) was dissolved in THF and added drop wise to the reaction mixture and stirred for 26 h at 80–90 °C. After completion of the reaction on TLC reaction mixture was concentrated, extracted with ethyl acetate (50 ml), washed with water and dried over anhydrous sodium sulfate. Solvent was removed and purified by column chromatography with hexane and ethyl acetate to yield compound **12**. Yield (61.12%). ESIMS (m/z) 443

$(M+H)^+$. IR (KBr): 2967, 1591, 1051 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz) δ: 1.14 (t, J = 7.2 Hz, 3H, $COCH_2CH_3$), 1.26 (t, J = 7.0 Hz, 6H, $COOCH_2CH_3$), 1.9 (m, 2H, $OCH_2CH_2CH_2CH$), 2.02 (m, 2H, $OCH_2CH_2CH_2CH$), 2.12 (m, 2H, $OCH_2CH_2CH_2Cl$), 2.75 (q, J = 7.2 Hz, 2H, $COCH_2CH_3$), 3.35 (m, 1H,CH), 3.66 (t, J = 6.2 Hz, 2H, $ClCH_2$,), 4.10 (t, J = 6.0 Hz, 4H, $PhOCH_2CH_2$), 4.19 (q, J=7.0 Hz, 4H, $COOCH_2CH_3$), 6.51 (m, 2H, ArH), 7.19 (m, 1H, ArH). Analysis calcd for $C_{22}H_{31}ClO_7$: C, 59.66; H, 7.05. Found: C, 59.65; H, 7.19.

4.1.5. Typical experimental procedure for the synthesis of compounds 13–18

A mixture of compound **10** (726 mg, 3 mmol), potassium iodide (1.66 g, 10 mmol), dry DMF (10 ml) and *n*-butyl amine (1.5 ml, excess) were taken in 50 ml round bottom flask. Reaction mixture was heated at 80 °C for 4 h. After completion of the reaction on TLC, reaction mixture was poured in distilled water (100 ml), extracted with ethyl acetate (50×4 ml) and dried over sodium sulfate. Compound was purified with silica gel column using chloroform and methanol to yield compound **13**.

4.1.5.1. 1-(2-(3-(Butylamino)propoxy)-6-hydroxyphenyl)propan-1-one (13). Yield (83.27%). mp 154 °C. ESIMS (*m/z*) 280 $(M+H)^+$. IR (KBr): 2945, 1599, 1017 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz) δ: 0.92 -1.40 (m, 13H,), 2.67 (t, J = 6.0 Hz, 2H, NCH_2), 2.83 (t, J = 7.2 Hz, 2H, NCH_2), 3.10 (q, J = 7.2 Hz, 2H, $COCH_2CH_3$), 4.10 (t, J = 6.2 Hz, 2H, OCH_2), 6.38 (d, J = 8.4 Hz, 1H, ArH), 6.55(d, J = 8.4 Hz, 1H, ArH), 7.28 (m, 1H, ArH), 9.55(s, 1H, –*OH*). Analysis calcd for $C_{16}H_{25}NO_3$: C, 68.79; H, 9.02; N, 5.01. Found: C, 68.43; H, 8.73; N, 4.89.

4.1.5.2. 1-(2-Hydroxy-6-(3-(*p*-tolylamino)propoxy)phenyl)propan-1-one (14). Yield (84.66%). mp 96 °C. ESIMS (*m/z*) 314 $(M+H)^+$. IR (KBr): 3413, 1592, 1087 cm^{-1}. ^{1}HNMR ($CDCl_3$, 200 MHz) δ: 1.18 (t, J = 7.2 Hz, 3H, $COCH_2CH_3$), 2.17(m, 2H, $PhOCH_2CH_2$ CH_2N), 3.12 (q, J = 7.2 Hz, 2H, $COCH_2CH_3$), 3.33 (t, J = 6.8 Hz, 2H, NCH_2), 3.76(s, 3H, $PhCH_3$), 4.17 (t, J = 6.0 Hz, 2H, OCH_2), 4.69(s, 1H, –*NH*), 6.38 (d, J = 8.4 Hz, 1H, ArH), 6.56 (m, 3H, ArH), 7.00 (d, J = 8.3 Hz, 2H, ArH), 7.32 (m, 1H, ArH), 8.29(s, 1H, –*OH*). Analysis calcd for $C_{19}H_{23}NO_3$: C, 72.82; H, 7.40; N, 4.47. Found: C, 72.61; H, 7.53; N, 4.49.

4.1.5.3. 1-(2-Hydroxy-6-(3-(4-methoxyphenylamino)propoxy)phenyl)propan-1-one (15). Yield (85.16%). mp 59 °C. ESIMS (*m/z*) 330 $(M+H)^+$. IR (KBr): 3317, 1615, 1033 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz) δ: 1.18 (t, J = 7.2 Hz, 3H, $COCH_2CH_3$), 2.17 (m, 2H, $NCH_2CH_2CH_2O$), 3.12 (q, J = 7.2 Hz, 2H, $COCH_2CH_3$), 3.33 (t, J = 6.8 Hz, 2H, NCH_2), 3.76 (s, 3H, $PhOCH_3$), 4.17 (t, J = 6.0 Hz, 2H, OCH_2), 4.94 (s, 1H, –*NH*), 6.38 (d, J = 8.4 Hz, 1H, ArH), 6.55 (m, 3H, ArH), 7.32 (d, J = 8.3 Hz, 2H, ArH), 7.59 (m, 1H, ArH), 8.37(s, 1H, –*OH*). Analysis calcd for $C_{19}H_{23}NO_4$: C, 69.28; H, 7.04; N, 4.25. Found: C, 69.15; H, 7.22; N, 4.29.

4.1.5.4. 1-(2-(3-(Butyl(methyl)amino)propoxy)-6-hydroxyphenyl)propan-1-one (16). Yield (91.95%). mp 106 °C. ESIMS (*m/z*) 294 $(M+H)^+$. IR (KBr): 2985, 1625, 1083 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz) δ: 0.91 (t, J = 7.2 Hz, 3H, $N(CH_2)_3CH_3$), 1.17 (t, J = 7.2 Hz, 3H, $COCH_2CH_3$), 1.30–1.41 (m, 4H, $NCH_2CH_2CH_2CH_3$), 2.06 (m, 2H, $OCH_2CH_2CH_2N$), 2.29 (s, 3H, NCH_3), 2.41 (t, J = 7.0 Hz, 2H, $NCH_2CH_2CH_2CH_3$), 2.58 (t, J = 7.0 Hz, 2H $OCH_2CH_2CH_2N$), 3.11 (q, J = 7.2 Hz, 2H, $COCH_2CH_3$), 4.10 (t, J = 6.4 Hz, 2H, $OCH_2CH_2CH_2N$), 6.38 (d, J = 8.2 Hz, 1H, ArH), 6.55 (d, J = 8.2 Hz, 1H, ArH), 6.94 (s, 1H, –*OH*), 7.32 (m, 1H, ArH). Analysis calcd for $C_{17}H_{27}NO_3$: C, 69.59; H, 9.28; N, 4.77. Found: C, 69.78; H, 9.43; N, 4.61.

4.1.5.5. 1-(2-Hydroxy-6-(3-(pyrrolidin-1-yl)propoxy)phenyl)propan-1-one (17). Yield (91.95%). mp 154 °C. ESIMS (*m/z*) 278 $(M+H)^+$. IR (KBr): 2959, 1604, 1083 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz) δ: 1.17 (t, J = 6.0 Hz, 3H, $COCH_2CH_3$), 1.82 (m, 4H, CH_2 of pyrrolidine), 2.11(m, 2H, $OCH_2CH_2CH_2N$), 2.56 (m, 4H, CH_2 of pyrrolidine), 2.62 (m, 2H, $NCH_2CH_2CH_2O$), 3.11 (q, J = 6.0 Hz, 2H, $COCH_2CH_3$), 4.12 (t, J = 6.4 Hz, 2H, $OCH_2CH_2CH_2N$), 6.38 (d, J = 8.2 Hz, 1H, ArH,), 6.55 (d, J = 8.2 Hz, 1H, ArH), 7.32 (m, 1H, ArH), 10.45 (s, 1H, –*OH*). Analysis calcd for $C_{16}H_{23}NO_3$: C, 69.29; H, 8.36; N, 5.05. Found: C, 69.38; H, 8.43; N, 4.86.

4.1.5.6. 1-(2-Hydroxy-6-(3-(piperidin-1-yl)propoxy)phenyl)propan-1-one (18). Yield (91.95%). ESIMS (*m/z*) 292 $(M+H)^+$. IR (KBr): 2929, 1619, 1088 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz) δ: 1.21 (t, J = 7.9 Hz, 3H, $COCH_2CH_3$), 1.30 (m, 2H, CH_2 of piperidine), 1.55 (m, 4H, CH_2 of piperidine), 2.17 (m, 2H, $NCH_2CH_2CH_2O$), 2.48 (m, 4H, $N(CH_2)_2$ of piperidine), 2.80 (t, J = 6.4 Hz, 2H, $OCH_2CH_2CH_2N$), 3.16 (q, J = 7.9 Hz, 2H $COCH_2CH_3$), 4.16 (t, J = 5.8 Hz, 2H, $OCH_2CH_2CH_2N$), 6.37 (d, J = 8.4 Hz, 1H, ArH), 6.56 (d, J = 8.4 Hz, 1H, ArH), 7.32 (m, 1H, ArH), 8.42 (s, 1H, –*OH*). Analysis calcd for $C_{17}H_{25}NO_3$: C, 70.07; H, 8.65; N, 4.81. Found: C, 70.18; H, 8.69; N, 4.69.

4.1.6. Diethyl 2-(3-(2-propionyl-3-(3-(*p*-tolylamino)propoxy)phenoxy)propyl)malonate (19)

A mixture of compound **12** (726 mg, 3 mmol), potassium iodide (1.66 g, 10 mmol) and *p*-toludine (1.20 g) were taken in dry DMF (10 ml). Reaction mixture was heated at 80 °C for 4 h. After completion of the reaction on TLC, reaction mixture was poured into distilled water (100 ml), which was extracted with ethyl acetate (50×4 ml) and dried over sodium sulfate. The organic layer was concentrated to remove excess ethyl acetate. Compound was purified on basic alumina column using hexane and ethyl acetate as a elutent to yield compound **19.** Yield (86.27%). Physical state: semisolid. ESIMS (*m/z*) 514 $(M+H)^+$. IR (KBr): 2950, 1731, 1067 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz) δ: 1.16 (t, J = 7.2 Hz, 3H, $COCH_2CH_3$), 1.26 (t, J = 7.0 Hz, 6H, $COOCH_2CH_3$), 1.99–2.34 (m, 6H,), 2.2 (s, 3H, $PhCH_3$), 2.70 (q, J = 7.2 Hz, 2H, $COCH_2$ CH_3), 3.10 (m, 1H, *CH*), 3.97 (t, J = 6.0 Hz, 2H, NCH_2), 4.01–4.08 (m, 4H, OCH_2CH_2), 4.20 (q, J = 7.0 Hz, 4H, $COOCH_2CH_3$), 4.44 (s, 1H, –*NH*), 6.55–6.92 (m, 4H, ArH), 6.97 (d, J = 8.2 Hz, 2H, ArH), 7.17 (m, 1H, ArH). Analysis calcd for $C_{29}H_{39}NO_7$: C, 67.81; H, 7.65; N, 2.73. Found: C, 67.88; H, 7.58; N, 2.62.

4.1.7. Typical experimental procedure for the synthesis of compounds 20–23

A mixture of compound **6–9**, (5 mmol) and diethyl 2-(3-chloropropyl)malonate (6 mmol) was taken in to the 50 ml round bottom flask and dry potassium carbonate (20 mmol) in 30 ml dry acetone was added. Reaction mixture was refluxed on oil bath for 8 h. Reaction mixture was filtered and filtrate was concentrated to remove acetone. Reaction mixture was extracted with ethyl acetate (100 ml) and washed with (50×3 ml) of distilled water. Purification was done on silica gel column using hexane/chloroform solvent system to yield compound **20–23**.

4.1.7.1. Diethyl 2-(3-(3-(2-(dimethylamino)ethoxy)-2-propionylphenoxy)propyl)malonate (20). Yield (64.22%). Physical state: semisolid. ESIMS (*m/z*) 438 $(M+H)^+$. IR (KBr): 2974, 1729, 1529, 758 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz) δ: 1.20 (t, J = 5.8 Hz, 3H, $COCH_2CH_3$), 1.30–2.16 (m, 10H), 2.31 (s, 6H, $N(CH_3)_2$), 2.70 (q, J = 5.8 Hz, 2H, $COCH_2CH_3$), 2.76 (m, 2H, NCH_2), 3.10 (m, 1H, *CH*), 3.96(m, 2H, $OCH_2CH_2CH_2$), 4.10 (m, 2H, OCH_2CH_2), 4.16 (t, J = 7.2 Hz, 4H, OCH_2), 6.50 (d, J = 4.2 Hz, 1H, ArH), 6.54 (d,

J = 4.2 Hz, 1H, ArH), 7.18 (m, 1H, ArH). Analysis calcd for $C_{23}H_{35}NO_7$: C, 63.14; H, 8.06; N, 3.20. Found: C, 63.21; H, 8.15; N, 2.83.

4.1.7.2. Diethyl 2-(3-(3-(2-(diethylamino)ethoxy)-2-propionylphenoxy)propyl)malonate (21). Yield (61.05%). Physical state: semisolid. ESIMS (m/z) 466 $(M+H)^+$. IR (KBr): 2976, 1723, 1324 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz) δ: 1.20 (t, J = 5.8 Hz, 3H, $COCH_2CH_3$), 1.32–2.23 (m, 10H), 2.31 (t, J = 6.8 Hz, 6H, $N(CH_2CH_3)_2$), 2.72 (q, J = 5.8 Hz, 2H, $COCH_2CH_3$), 2.76 (m, 6H, NCH_2), 3.10 (m, 1H, CH), 3.96(m, 2H, $OCH_2CH_2CH_2$), 4.10 (m, 2H, OCH_2CH_2), 4.16 (t, J = 6.4 Hz, 4H, OCH_2), 6.51 (d, J = 8.2 Hz, 1H, ArH), 6.55 (d, J = 8.2 Hz, 1H, ArH), 7.18 (m, 1H, ArH). Analysis calcd for $C_{25}H_{39}NO_7$: C, 64.49; H, 8.44; N, 3.01. Found: C, 64.35; H, 8.47; N, 2.82.

4.1.7.3. Diethyl 2-(3-(2-propionyl-3-(2-(pyrrolidin-1-yl)ethoxy)phenoxy)propyl)malonate (22). Yield (66.92%). Physical state: semisolid. ESIMS (m/z) 464 $(M+H)^+$. IR (KBr): 2966, 1721, 752 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz) δ: 1.17–1.81(m, 17H), 2.61 (m, 4H, NCH_2 of pyrrolidine), 2.72 (q, J = 6.2 Hz, 2H, $COCH_2CH_3$), 2.98 (t, J = 6.3 Hz, 2H, OCH_2), 3.10 (m, 1H, CH), 3.96–4.18 (m, 8H), 6.34 (d, J = 8.3 Hz, 1H, ArH), 6.56 (d, J = 8.3 Hz, 1H, ArH), 7.32(m, 1H, ArH). Analysis calcd for $C_{25}H_{37}NO_7$: C, 64.77; H, 8.05; N, 3.02. Found: C, 64.68; H, 8.21; N, 3.08.

4.1.7.4. Diethyl 2-(3-(3-(2-(piperidin-1-yl)ethoxy)-2-propionylphenoxy)propyl)malonate (23). Yield (79.65%). Physical state: semisolid. ESIMS (m/z) 478 $(M+H)^+$. IR (KBr): 2964, 1725, 1352, 757 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz) δ: 1.14–1.84(m, 17H), 2.60 (m, 6H, NCH_2 of piperidine), 2.73 (q, J = 6.0 Hz, 2H, $COCH_2CH_3$), 2.98 (t, J = 6.3 Hz, 2H, OCH_2), 3.10 (m, 1H,, 3.92–4.16 (m, 8H), 6.35 (d, J = 8.1 Hz, 1H, ArH), 6.52 (d, J = 8.1 Hz, 1H, ArH), 7.31(m, 1H, ArH). Analysis calcd for $C_{26}H_{39}NO_7$: C, 65.39; H, 8.23; N, 2.93. Found: C, 65.31; H, 8.27; N, 2.98.

4.2. Pharmacology

4.2.1. Sucrose loaded rat model (SLM)[12d]

Male albino rats of Charles Foster/Wistar strain of average body weight 160 ± 20 g were selected for this study. The blood glucose level of each animal was checked by glucometer using glucostrips (Boehringer Mannheim) after 16 h starvation. Animals showing blood glucose levels between 3.33 and 4.44 mM (60–80 mg/dl) were divided into groups of five to six animals in each. Animals of experimental group were administered suspension of the desired synthetic compound orally (made in 1.0% gum acacia) at a single dose 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 rat was again determined at 30, 60, 90 and 120 min post administration of sucrose by glucometer Food but not water was withheld from the cages during the course of experimentation. Quantitative glucose tolerance of each animal was calculated by Area Under Curve (AUC) method (Prism Software). Comparing the AUC of experimental and control groups determined the percentage anti-hyperglycemic activity.

4.2.2. Sucrose-challenged streptozotocin-induced diabetic rat model (STZ-S)[18]

Male albino rats of Sprague Dawley strain of body weight 160 ± 20 g were selected for this study. Streptozotocin (Sigma, USA) was dissolved in 100 mM citrate buffer pH 4.5 and calculated amount of the fresh solution was injected to overnight fasted rats (60 mg/kg) intraperitoneally. Blood glucose level was checked 48 h later by glucostrips and animals showing blood glucose values between 144 and 270 mg/dl (8–15 mM) were included in the experiment and considered as diabetic. The diabetic animals were divided into groups consisting of five to six animals in each group. Animals of experimental groups were administered suspension of the desired test samples orally (made in 1.0% gum acacia) at a single dose of 100 mg/kg body weight. Animals of control group were given an equal amount of 1.0% gum acacia. A sucrose load of 2.5 g/kg body weight was given after 30 min of compound administration. After 30 min of post sucrose load blood glucose level was again checked by glucostrips at 30, 60, 90, 120, 180, 240, 300 min and at 24 h, respectively. Animals not found diabetic after 24 h post treatment of the test sample were not considered and omitted from the calculations and termed as non-responders. The animals, which did not show any fall in blood glucose profile in a group while the others in that group, showed fall in blood glucose profile were also considered as nonresponders. Food but not water was withheld from the cages during the experimentation. Comparing the AUC of experimental and control groups determined the percent antihyperglycemic activity.

4.2.3. Anti-hyperglycemic activity in *db/db* mice[19]

The background for the *db/db* mouse is the C57BL/Ks strain. The major deficiency of the C57BL/KsBom-db mouse (*db/db*) is lack of a functional leptin receptor. This leads to defective leptin signaling and a complete lack of feedback from leptin. Both hypothalamic Neuropeptide Y (NPY) content and secretion are consequently elevated, and this result in hyperphagia and decreased energy expenditure, obesity, insulin-resistance, hyperinsulinemia, hyperglycaemia and dyslipidemia. The *db/db* mouse develops non insulin dependent diabetes mellitus (NIDDM) from around week 10. The disease is stable until week 20, where destruction of pancreatic β-cells can be recognized clinically as decreasing levels of plasma insulin and very severe hyperglycaemia. The *db/db* mouse has a maximal life span of 9 -12 months. The male mice are more diabetic than, and will normally die earlier than the females. The advantage of using male mice for experimental purposes is that the fluctuations in plasma parameters are less than in the females where the oestrogen cycle affects the clinical diabetes. The C57BL/KsBom-db mice 12–18 weeks, 40–50 g bred in the animal house of CDRI, Lucknow. The mice were housed in groups of 5 (same sex) in a room controlled for temperature (23 ± 2.0 °C) and 12/12 h light/dark cycle (lights on at 6.00 am). Animal of experimental groups were dosed 30 mg/kg body weight for 10 days and control groups were given 1% gum acacia at the same volume. Body weight was measured daily from day 1 to day 10. All animals had free access to fresh water and to normal chow except on the days of the postprandial protocol day 6 and during the overnight fast before the OGTT on day 10. The animals always had access to water during experimental periods. Blood glucose was checked every morning up till day 5. On day 6 postprandial protocol was employed, in this method blood glucose was checked at −0.5 h and 0 h Test drugs were given to the treatment group whereas vehicle received only gum acacia (1.0%); the blood glucose was again checked at 1, 2, 3, 4 and 6 h post test drug treatment. On day 10 an oral glucose tolerance test (OGTT) was performed after an overnight fasting. Blood glucose was measured at −30.0 min and test drugs were administered. The blood glucose was again measured at 0.0 min post treatment and at this juncture glucose solution was given at a dose of 3 g/kg to all the groups including vehicle. The blood glucose levels were checked at 30 min, 60 min, 90 min and 120 min post glucose administration. At the end of the experiment blood has been withdrawn from the retro-orbital plexus of mice for the estimation of serum insulin and lipid profile. Quantitative glucose tolerance of each animal was calculated by area under curve (AUC) method (Prism software). Comparing the AUC of experimental and control

groups determined the% anti-hyperglycemic activity. Statistical comparison was made by Dunnett's test.

4.2.4. In vitro enzyme inhibition

For the enzyme inhibition essay of synthesized compounds against glucose-6-phosphatase, glycogen phosphorylase, α-glucosidase, DPP-IV and PTP-1B, according to our previously reported procedure.[12d]

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