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Design and synthesis of 3,5-diarylisoxazole derivatives as novel class of anti-hyperglycemic and lipid lowering agents ☆

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ABSTRACT

We have designed 1,3-disubstituted-5-membered heteroaromatic ring system as a common core motif from known anti-hyperglycemic agents. Designed compounds were synthesized and screened for in vivo anti-hyperglycemic activity in sucrose loaded model (SLM), sucrose-challenged streptozotocin-induced diabetic rat model (STZ-S) as well as db/db mice model. Some of the synthesized compounds showed promising in vivo anti-hyperglycemic as well as moderate lipid lowering activity. Synthesized Compounds were screened in various in vitro models of type-2 diabetes such as DPP-4, PTP1B and PPARγ to know the mechanism of their anti-hyperglycemic action. None of the synthesized compounds showed DPP-4 inhibitory as well as PPARγ activity. These compounds have shown promising PTP-1B inhibitory activity there by revealing that compounds exhibit anti-diabetic activity by PTP1B pathway.

1. Introduction

Type-2 diabetes (T2D) is complex, chronic metabolic disorder mainly associated with three basic pathophysiological abnormalities: (1) insulin resistance in target tissue, (2) excessive hepatic glucose production and (3) insulin resistance in skeleton muscle, liver and adipose tissue.[1–5] Diabetes mellitus has now treated as epidemic disease and considered as one of the main threats to human health. The primary therapy for type-2 diabetes is caloric restriction and exercise.[6] There are four major types of pharmacological agents available for the treatment of type-2 diabetes: (1) insulin secretagogues sulfonylureas,[7–9] like Glucotrol, Micronase, Glynase and DiaBeta (2) bigunides[10–14] like metformin which delay gastrointestinal glucose absorption, (3) insulin sensitivity enhancers like glitazones[15–19] and (4) acarbose.[20–22] But none of these agents are having final answer to type-2 diabetes and also carrying undesirable side effects like hepatotoxicity, weight gain, edema, etc.

Since current available therapies cannot prevent disease's progression, many research groups are focusing their efforts towards the identification of novel approaches.[23,24] Protein Tyrosine Phosphatase-1B (PTP-1B), Dipeptidyl Peptidase IV and Peroxisome proliferator-activated receptor (PPAR) have been identified as potential target of type-2 diabetes (T2D).

Several small molecules such as hydroxy phenyl thiazole derivative (Japan Tobacco **I**),[25,26] **II**,[27] **III**, **IV, V, VI** and **VII**[28–32] have been reported as potential anti-hyperglycemic agents. After a careful observation of the structural frame work of these anti-hyperglycaemic agents, we found a very interesting structural resemblance among these molecules (Fig. 1). The structural analysis of these molecules revealed that all these molecules have a common core motif 1,3-disubstituted-5-membered heteroaromatic ring. Although all these structures have different aryl substitution basically due to presence of heteroatom in the ring system, the relative position of substituents is 1,3 in five membered heteroaromatic ring system.

Utilizing the identified core motif of compounds shown in Figure 1 for future drug design, we have designed and synthesized 3,5-diarylisoxazole moiety having 1,3-disubstituted 5-membered heteroaromatic framework as potential anti-hyperglycemic agents. Some of these design compounds have exhibited significant antidiabetic, triglyceride and cholesterol lowering activity along with promising PTP-1B inhibitory activity.

2. Results and discussion

2.1. Chemistry

The key intermediate 3,5-diarylisoxazole **5** having 1,3-disubstituted-5-membered heteroaromatic framework was synthesized from 2,4-dihydroxy acetophenone **1** in four steps. 2,4-Dihydroxy acetophenone **1** was treated with dimethyl sulphate and K_2CO_3

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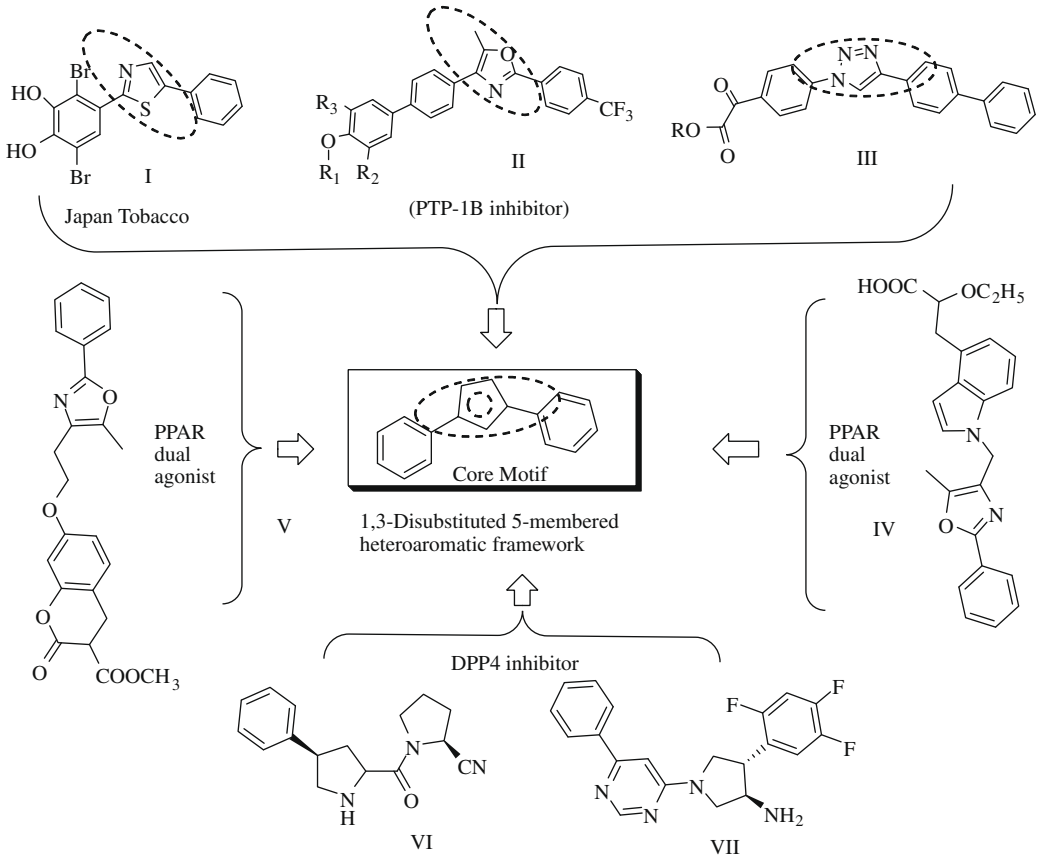


Figure 1. Design or 1,3-disubstituted five-membered heteroaromatic framework (3,5-diaryl isooxazole) based on known antihyperglycemic agents.

in acetone to yield 2-hydroxy-4-methoxy acetophenone **2**, which on reaction with benzoylchloride in pyridine gave *ortho*-benzoylated derivative **3** in 88% yield. Benzoyl group of compound **3** was migrated on treatment with KOH–pyridine resulting to the formation of diketone **4** via Baker Venkataraman rearrangement.[33] Diketone **4**, when refluxed with hydroxylamine hydrochloride afforded 3,5-diaryl isoxazole **5** in 45% yields.

The isoxazole **5** on Williamson type O-alkylation reaction with different 1-(2-chloro-alkyl) substituted amine hydrochloride gave alkyl substituted amino diaryl isoxzoles (**6**–**11**). 3,5-Diarylisoxazole on Williamson type O-alkylation with diholoalkyl compound gave compound **12,** which on reaction with amines gave compounds **13–17**. 3,5-Diarylisoxazole **5** on reaction with haloalkyl esters gave compounds **18**–**21**. Compound **5** on reaction with epichlrohydrine afforded compound **22** in very good yield. Compound **22** on reaction with appropriate amines gave compound **23–25** in good yields (Scheme 1).

2.2. Biological activity

All the synthesized compounds were evaluated for in vivo antihyperglycemic activities are given in Table 1.

Compounds were screened in vivo antidiabetic activity in sucrose loaded model (SLM) male albino rats for anti-hyperglycemic activity. Compounds **7** (29.9%), **8** (21.7%), **10** (36.9%), **11** (27.6%), **16** (21.2%), **17** (20.8%) and **24** (26.8%) were showing significant blood glucose lowering activity in SLM model (Table 1 and Fig. 2). The compounds which showed greater than 12.0% blood glucose lowering activity in SLM model, were further tested for anti-hyperglycemic activity in sucrose challenged streptozotocin (STZ-S) induced diabetic rats. Compound **7**, **10, 11** and **24** have shown promising antidiabetic activity in STZ-S model (Table 1 and Fig. 3).

2.2.1. Dose dependant anti-hyperglycemic effect of 7, 10, 11 and 24 in sucrose challenged streptozotocin-induced diabetic rats

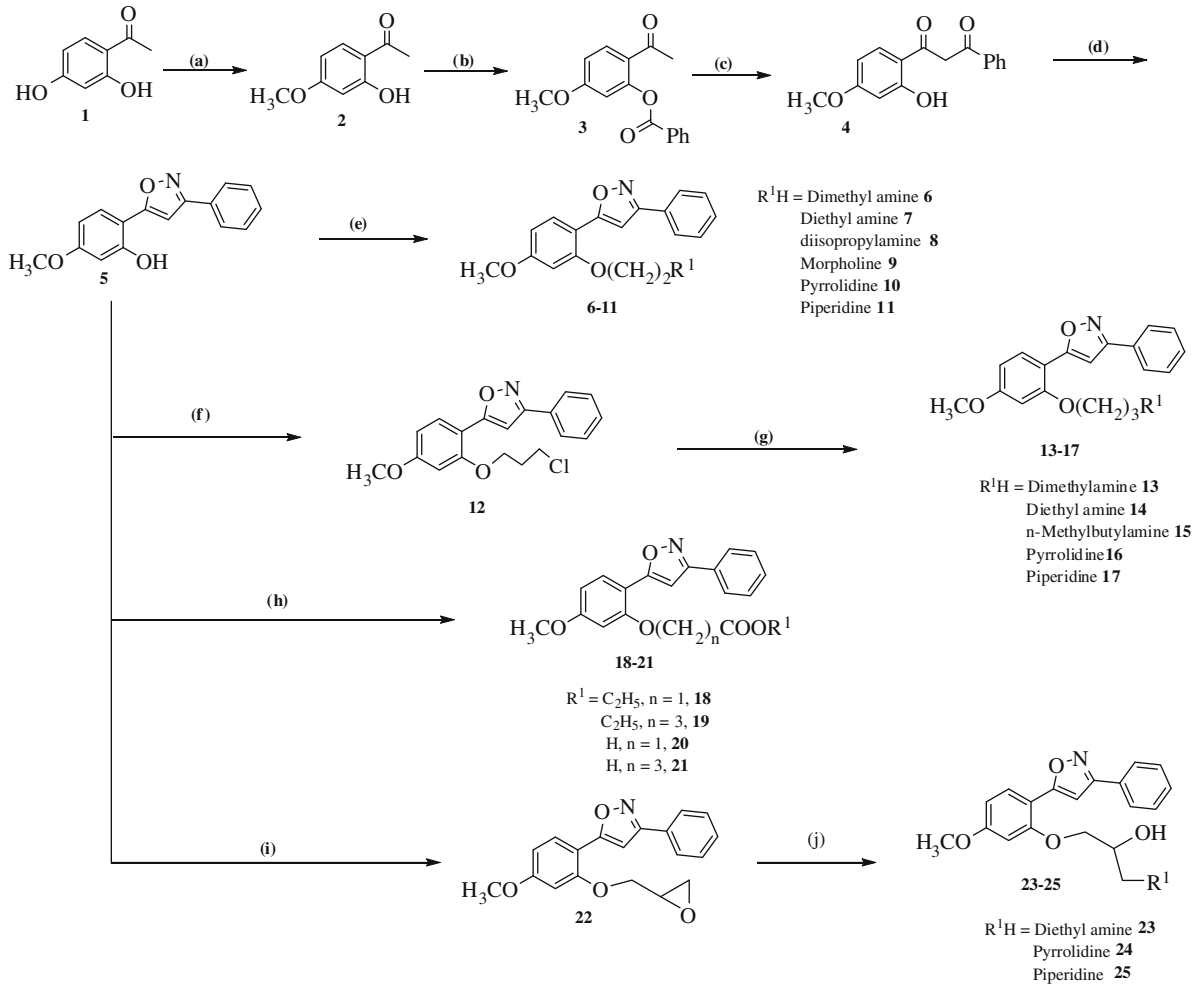
Dose dependency of compounds **7**, **10**, **11 and 24** was studied by administering different doses of test compound to streptozotocin-induced diabetic rats (Table 2). Doses ranges from 7.5 to 100 mg/kg were given and blood glucose level was measured at 30, 60, 90, 120, 180, 240, 300, 1440 min post administration of sucrose load as described in sucrose challenged streptozotocin-induced diabetic rats' protocol. Compounds **7, 10, 11 and 24** showed dose dependency and their ED_{50} were found to be 45.3 mg/kg, 54.8 mg/kg, 64.5 mg/kg and 80.2 mg/kg respectively.

Four compounds (**7**, **10, 11 and 24**) were further tested for their anti-hyperglycemic as well as lipid lowering activity (Table 3 and Figs. 4–6) in db/db mice model 6 days and 10 days protocol. These compounds (**7**, **10, 11** and **24**) showed promising in vivo anti-diabetic and anti-dyslipidemic activity in db/db mice.

In order to know the mode of action for anti hyperglycemic activity of compounds, we screened these compounds in protein-tyrosine-phosphatase-1B inhibitory activity, DPP-4 enzyme inhibition assay and tested for PPARγ transactivation assay (Table 4). Compounds **7–11**, **16–18**, **20** and **23–25** exhibited significant PTP-1B inhibitory activity (>80%). Vanadate (Sodium ortho vanadate) a non-selective PTPs inhibitor was taken as a control.

The structure–activity relationship studies of diarylisoxazole revealed that compounds with two carbon side chains (**7–11**) have shown better activity than compounds with three carbon side chains (**13–17** and **23–25**).

Compounds (**7, 8, 10, 11, 16, 17, 24**) were also tested for DPP-4 enzyme inhibition assay and PPARγ transactivation assay. None of the compounds has shown any significant activity in DPP-4 as well as PPAR assay.



Scheme 1. Reagent and condition: (a) $(CH_3)_2SO_4$, K_2CO_3, acetone; (b) benzoylchloride, pyridine, 1 h, rt; (c) KOH, pyridine, 8 h, rt; (d) $NH_2OH{\cdot}HCl$, pyridine; (e) K_2CO_3, acetone, $Cl(CH_2)_2R^1{\cdot}HCl$, 8–10 h, reflux; (f) K_2CO_3, acetone, $Cl(CH_2)_3Br$, 6 h, reflux; (g) DMF, KI (catalytic), amine, heat, 8–10 h; (h) K_2CO_3, acetone, $Cl\,(CH_2)_nCOOR^1$, 8–10 h, reflux; (i) K_2CO_3, acetone, epichlorohydrin, 7 h, reflux; (j) DMF/ethanol, amine, heat, 8–10 h.

3. Conclusion

In conclusion, we have designed and synthesized a series of 3,5-diarylisoxazole derivatives as potential anti-hyperglycemic agents. Compounds were screened for their in vivo anti-hyperglycemic activity in sucrose loaded rat model (SLM), sucrose-challenged streptozotocin-induced diabetic rat model (STZ-S) and db/db mice model. Compounds (**7, 10, 11** and **24**) were showing promising anti-hyperglycemic activity in SLM and STZ-S models. Four compounds (**7, 10, 11** and **24**) were showing promising anti-hyperglycemic and lipid lowering activity in db/db mice model. In order to know the mode of anti-hyperglycemic action of the compounds, we screened them in various models such as DPP-4, PTP1B and PPARγ. Compounds did not show any significant activity in PPAR and DPP-4 assays. The compounds exhibited promising PTP-1B inhibitory activity thereby revealing their mode of anti-hyperglycemic action via PTP1B inhibition.

4. Experimental

4.1. Chemistry

All the chemical reagents were purchased from Sigma–Aldrich Chemical Company and were used directly without further any purification. NMR spectra were obtained using the Brucker DRX 200 MHz spectrometer. Chemical shifts (δ) are given in ppm relative to TMS, coupling constants (J) in hertz. Mass spectra were obtained by the using a JEOL SX-102 (FAB) instrument. IR spectra were taken on a VARIAN FT-IR spectrometer as KBr pellets. Elemental analysis was preformed at a Perkin Elmer Autosystem XL Analyzer. Melting points were measured on a COMPLAB melting point apparatus and all the melting points were uncorrected. Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm silica gel plates visualized with UV light.

4.1.1. Benzoic acid 2-acetyl-5-methoxy-phenyl ester (3)

2-Hydroxy-4-methoxy acetophenone **2** (1.66 g, 10 mmol) was taken in 10 ml of dry pyridine and benzoyl chloride (1.38 ml, 12 mmol) was added to it. The reaction mixture was stirred for 1 h. After completion the reaction mixture was poured in 100 ml of water, extracted with ethyl acetate (50 × 3 ml) and dried over sodium sulphate. Organic layer was concentrated to yield **3**. Yield: (2.4 g, 81.48%); FAB MS: (m/z) = 271 (M+1). IR (KBr, cm^{-1}): 2961, 2362, 1732.

4.1.2. Typical experimental procedure for the synthesis of 1-(2-hydroxy-4-methoxyphenyl)-3-phenylpropane-1,3-dione (4)

Compound **3** (1.35 g, 5 mmol), potassium hydroxide (0. 84 g, 15 mmol) in 25 ml of pyridine was stirred at 25 °C for 8 h followed by T.L.C. monitoring. After completion reaction mixture was

Table 1
In vivo antihyperglycemic activity in SLM, STZ-S and db/db mice models

Entry	Compound	% Anti-hyperglycemic activity in vivo[a]			
		SLM[b]	STZ-S[b]		db/db-mice model[b,c]
			5 h	24 h	
1	5	9.8	ND	ND	—
2	6	16.8	15.3	15.9	—
3	7	29.9**	26.9***	25.7***	21.0*
4	8	21.7*	11.4	9.7	—
5	9	2.8	ND	ND	—
6	10	36.9**	27.7***	28.7***	22.8*
7	11	27.6**	17.6*	18.7**	18.5*
8	12	9.24	ND	ND	—
9	13	11.8	ND	ND	—
10	14	14.3	7.8	9.2	—
11	15	15.0	12.6	14.2	—
12	16	21.2*	13.4	11.2	—
13	17	20.8*	14.7	15.0	—
14	18	10.4	ND	ND	—
15	19	4.6	ND	ND	—
16	20	11.7	ND	ND	—
17	21	14.2	14.9	14.2	—
18	22	10.7	ND	ND	—
19	23	13.8	11.6	11.4	—
20	24	26.8**	18.5**	17.6*	15.7
21	25	17.0	15.8	16.8	—
22	Na_2VO_3	—	—	—	
23	Metformin	12.9	19.1	20.2	11.2
24	Glybenclamide	33.9	32.8	—	13.6
25	Glyclazide	44.8	27.7	—	17.4

[a] Experiments were carried out at 100 mg/kg dose.
[b] Values are expressed as mean ± SD, $n = 5$, *$p < 0.05$, **$p < 0.01$ and ***$p < 0.001$ versus vehicle treated control.
[c] Three days protocol.

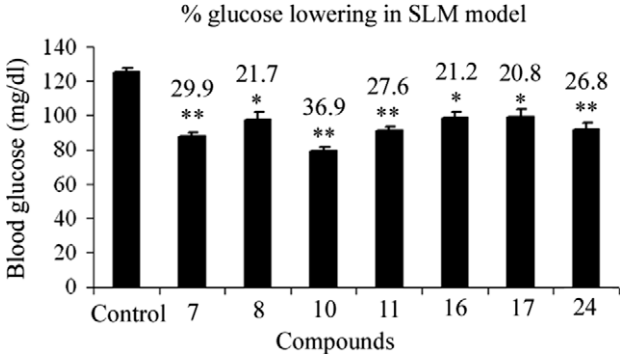


Figure 2. Anti-hyperglycemic activity of compounds **7**, **8**, **10**, **11**, **16**, **17** and **24** in SLM model. Statistical analysis was made by Dunnet test (Prism Software 3). Values were expressed as mean ± SD, $n = 5$.

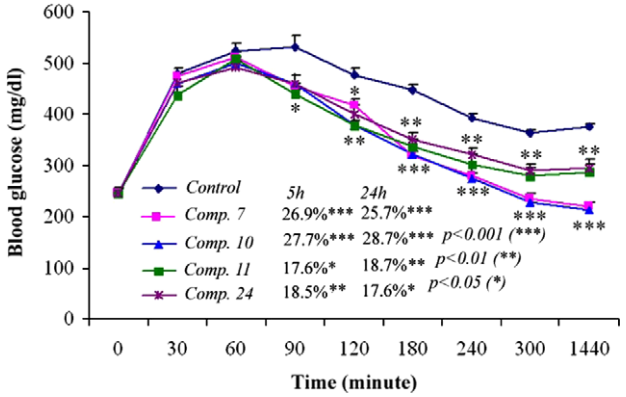


Figure 3. Anti-hyperglycemic activity of compounds **7**, **8**, **10**, **11**, **16**, **17** and **24** in STZ model. Statistical analysis was made by Dunnet test (Prism Software 3). Values were expressed as mean ± SD, $n = 5$.

Table 2
Dose dependent anti-hyperglycemic effect of **7, 10, 11** and **24** in diabetic rats

Compound	Dose (mg/kg)	% Glucose lowering	ED_{50} (mg/kg)
7	7.5	10.3	45.3
	15	15.5*	
	25	19.5**	
	50	21.7**	
	100	25.4**	
10	7.5	11.5	54.8
	15	13.7	
	25	15.2*	
	50	18.5**	
	100	27.7**	
11	7.5	9.8	64.5
	15	12.6	
	25	14.0*	
	50	16.7**	
	100	20.7**	
24	7.5	8.4	80.2
	15	11.6	
	25	13.8*	
	50	17.9*	
	100	18.5**	

Values are expressed as mean ± SD, $N = 5$, $p < 0.05$ (*), $p < 0.01$ (**) and $p < 0.001$ (***) versus control. Statistical analysis was made by Dunnett's test (Prism Software).

Table 3
Anti-hyperglycemic and lipid lowering activity in db/db mice model

Entry (Compd No.)	Anti hyperglycemic and lipid lowering activity in db/db mice (% efficacy, 6 and 10 days) (100 mg/kg)				
	Anti-hyperglycemic			Lipid lowering activity	
	6 Days	10 Days	TG	CHOL.	HDL
7	22.6**	21.5**	−12.0	−14.5*	+3.9
10	21.4**	21.6**	−10.5	−17.6*	+3.0
11	17.4*	16.1*	−7.5	−12.2	+1.3
24	15.9*	15.5*	−8.5	−9.8	+1.8

Values are expressed as mean ± SD, $N = 5$, $p < 0.05$(*), and $p < 0.01$(**) versus control. Statistical analysis was made by Dunnett's test (Prism Software).

poured in 150 ml of water and neutralized with 10% CH_3COOH solution. Reaction mixture was extracted with ethyl acetate (50 × 4 ml) washed with sodium bicarbonate solution and dried over sodium sulphate. The ethyl acetate layer was concentrated to give crude product. The crude product was purified by silica gel column chromatography using hexane, ethylacetate (4:1) as eluent to yield compound **4.** Yield: (1.10 g, 81.48%), FAB MS: (m/z) = 271 (M+1). IR: (KBr, cm^{-1}): 2961, 2362, 1602. ^1H NMR: $CDCl_3$, 200 MHz) δ: 3.73 (s, 3H, OCH_3,), 6.35 (m, 2H, ArH), 6.60 (s, 1H,

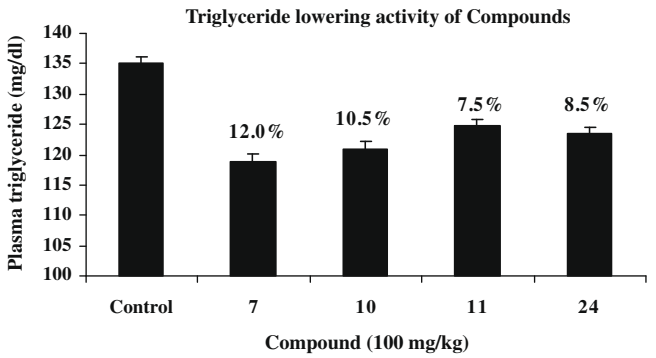


Figure 4. Triglyceride lowering activity of compounds **7**, **10**, **11** and **24** in db/db mice model. Statistical analysis was made by Dunnet's test (Prism Software 3).

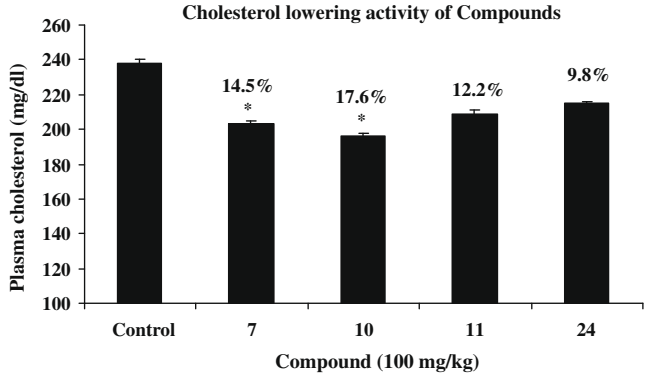


Figure 5. Cholesterol lowering activity of compounds **7**, **10**, **11** and **24** in db/db mice model. Statistical analysis was made by Dunnet's test (Prism Software 3).

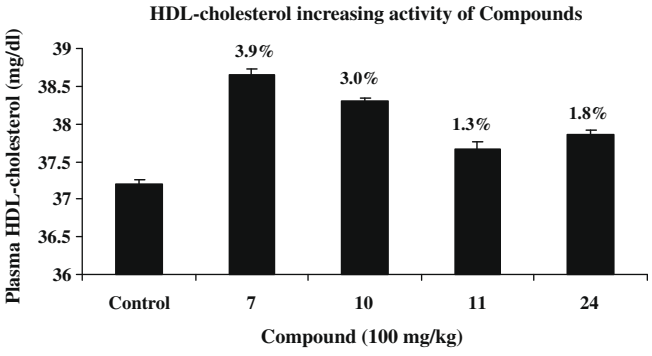


Figure 6. HDL-cholesterol increasing activity of compounds **7**, **10**, **11**, **24** on plasma lipid profiles in db/db mice, values are expressed as mean ± SD, $n = 5$, $^{*}p < 0.05$ versus vehicle treated control db/db mice.

Table 4
PTP1B inhibitory activity for the active compounds of in vivo models

Entry	Compound	PTP-1B inhibitory activity[a]		
		Inhibtion[a] (%)	−Triton 100[a,b] IC_{50} (μM)	+Triton 100[a,b] IC_{50} (μM)
1	**5**	21.8	27.45	27.63
2	**6**	33.5	24.16	24.29
3	**7**	**94.7**	**2.97**	**2.90**
4	**8**	89.4	5.50	5.44
5	**9**	82.9	**2.50**	**2.61**
6	**10**	**99.2**	**1.50**	**1.51**
7	**11**	76.3	8.80	9.00
8	**12**	9.0	56.78	56.89
9	**13**	22.3	25.28	25.34
10	**14**	21.8	28.03	28.16
11	**15**	14.4	37.31	37.46
12	**16**	82.7	**3.50**	**3.46**
13	**17**	89.5	4.40	4.42
14	**18**	79.3	5.25	5.35
15	**19**	20.1	26.73	26.71
16	**20**	75.2	9.10	9.30
17	**21**	24.4	22.32	22.36
18	**22**	11.8	31.11	31.32
19	**23**	82.8	4.30	6.89
20	**24**	**86.2**	**3.40**	**4.20**
21	**25**	85.9	6.80	3.31
22	Na_2VO_3	94.0	7.70	
23	Metformin	—	—	—
24	Glybenclamide	—	—	—
25	Glyclazide	—	—	—

[a] Values are mean from three independent sets of experiments screened at 10 μM concentration, ND = not done.
[b] Compounds were tested with Triton X-100.

enolic), 7.43 (m, 4H, ArH), 7.82 (m, 2H, ArH). Anal. Calcd for $C_{16}H_{14}O_4$: C, 71.10; H, 5.22. Found: C, 71.04; H, 5.15.

4.1.3. Typical experimental procedure for the synthesis of 5-methoxy-2-(3-phenylisoxazol-5-yl)phenol (5)

Compound **4** (2.7 g, 10 mmol) and $NH_2OH{\cdot}HCl$ (1.3 g, 13 mmol) was taken in 30 ml of dry pyridine. Reaction mixture was stirred at 25 °C for 30 min. After completion (TLC), the reaction mixture was neutralised with 6 M HCl. Then the reaction mixture was extracted with ethylacetate (50 × 5 ml) and dried over sodium sulphate. Organic layer was concentrated to remove ethyl acetate to yield a solid which was recrystallized with acetone to yield compound **5**, Yield: (1.20 g, 44.94%); mp 235 °C (acetone); FAB MS (m/z) = 268 (M+1). ^{1}H NMR ($DMSOd_6$, 200 MHz) δ: 3.86 (s, 3H, OCH_3), 6.59 (s, 1H, ArH), 6.62 (m, 1H, ArH), 7.20 (s, 1H, isoxazole), 7.53 (m, 3H, ArH), 7.92 (d, J = 2.0 Hz, 1H, ArH), 7.94 (m, 2H, ArH). Anal. Calcd for $C_{16}H1_{13}NO_3$: C, 71.90; H, 4.90; N, 5.24. Found: C, 71.84; H, 5.00; N, 5.16.

4.1.4. Typical experimental procedure for the synthesis of compounds (6–11)

Compound **5** (1.34 g, 5 mmol), $Cl(CH_2)_2R^1.HCl$ (6 mmol) and K_2CO_3 (2.07 g, 15 mmol) were taken in 30 ml of acetone. It was refluxed for 8 h. After completion the reaction, K_2CO_3 was filtered off and the filtrate was concentrated to yield crude product. The crude product was subjected to column chromatography to yield pure product **6–11**.

4.1.4.1. 2-(5-Methoxy-2-(3-phenylisoxazol-5-yl)phenoxy)-*N*,*N*-dimethylethanamine (6). Yield (90.50%), mp 97 °C (ethyl acetate/hexane). FAB MS (m/z) = 339 (M+H). ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 2.30 (s, 6H, NCH_3), 2.85 (t, J = 5.8 Hz, 2H, NCH_2), 3.86 (s, 3H, OCH_3), 4.19 (t, J = 5.8 Hz, 2H, OCH_2), 6.55 (s, 1H, ArH), 6.59 (m,1H, ArH), 7.26 (s, 1H, isoxazole), 7.47 (m, 3H, ArH), 7.89 (m, 3H, ArH). Anal. Calcd for $C_{20}H_{22}N_2O_3$: C, 70.99; H, 6.55; N, 8.28. Found: C, 71.10; H, 6.48; N, 8.19.

4.1.4.2. Diethyl-{2-[5-methoxy-2-(3-phenyl-isoxazol-5-yl)-phenoxy]-ethyl}-amine (7). Yield (84.42%), mp 58 °C. FAB MS (m/z) = 367 (M+H). ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 1.07 (t, J = 7.2 Hz, 6H, CH_3), 2.60–2.78 (m, 4H, NCH_2), 2.97 (t, J = 6.2 Hz, 2H, NCH_2), 3.83 (s, 3H, OCH_3), 4.16 (t, J = 6.8 Hz, 2H, OCH_2), 6.56 (s, 1H, ArH), 6.62 (m, 1H, ArH), 7.17 (s, 1H, isoxazole), 7.46 (m, 3H, ArH), 7.89 (m, 3H, ArH). Anal. Calcd for $C_{22}H_{26}N_2O_3$: C, 72.11; H, 7.15; N, 7.64. Found: C, 72.04; H, 7.11; N, 7.56.

4.1.4.3. *N*-Isopropyl-*N*-(2-(5-methoxy-2-(3-phenylisoxazol-5-yl) phenoxy)ethyl)propan-2-amine (8). Yield (86.40%), MS (m/z) = 395 (M+H). ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 1.08 (d, J = 6.2 Hz, 12H, CH_3), 2.60–2.74 (m, 2H, NCH_2), 3.75–3.79 (m, 4H, NCH, OCH_2), 3.83 (s, 3H, OCH_3), 6.56 (s, 1H, ArH), 6.60–6.62 (m, 1H, ArH), 7.17 (s, 1H, isoxazole), 7.42–7.52 (m, 3H, ArH), 7.82–7.90 (m, 3H, ArH). Anal. Calcd for $C_{24}H_{30}N_2O_3$: C, 73.07; H, 7.66; N, 7.10. Found: C, 73.04; H, 7.54; N, 6.96.

4.1.4.4. 4-(2-(5-Methoxy-2-(3-phenylisoxazol-5-yl)phenoxy) ethyl) morpholine (9). Yield (85.09%), mp 140 °C (ethyl acetate/hexane). FAB MS (m/z) = 381 (M+H). ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 2.30–2.56 (m, 6H, NCH_2), 3.60–3.76 (m, 4H, OCH_2), 3.83 (s, 3H, OCH_3), 4.02 (t, J = 7.3 Hz, 2H, OCH_2), 6.50 (s,1H, ArH), 6.54–6.59 (m, 1H, ArH), 7.18 (s, 1H, oxazole), 7.44–7.62 (m, 3H, ArH), 7.80–7.91 (m, 3H, ArH). Anal. Calcd for $C_{22}H_{24}N_2O_4$: C, 69.46; H, 6.46; N, 7.36. Found: C, 69.38; H, 6.40; N, 7.24.

4.1.4.5. [4-Methoxy-2-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-3-phenyl-isoxazole (10). Yield (85.85%), mp 98 °C (ethyl acetate/

hexane). FAB MS (*m/z*) 365 (M+H), ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 1.78–1.88 (m, 4H, CH_2), 2.62–2.78 (m, 4H, NCH_2), 3.02 (t, J = 5.8 Hz, 2H, NCH_2), 3.85 (s, 3H, OCH_3), 4.23 (t, J = 4.2 Hz, 2H, OCH_2), 6.53 (s, 1H, ArH), 6.56–6.59 (m, 1H, ArH), 7.24 (s, 1H, isoxazole), 7.48 (m, 3H, ArH), 7.80–7.92 (m, 3H, ArH). Anal. Calcd for $C_{22}H_{24}N_2O_3$: C, 72.50; H, 6.64; N, 7.69. Found: C, 72.58; H, 6.60; N, 7.58.

4.1.4.6. 1-{2-[5-Methoxy-2-(3-phenyl-isoxazole-5-yl)-phenoxy]-ethyl}-piperidine (11). Yield (83.59%), mp 124 °C (ethyl acetate/hexane). FAB MS (*m/z*) = 379 (M+H). ^{1}H NMR ($CDCl_3$, 200 MH$_2$) δ: 1.46 (m, 2H, CH_2), 1.64–1.76 (m, 4H, CH_2), 2.53–2.66 (m, 4H, NCH_2 of piperidine ring), 2.87 (t, J = 6.0 Hz, 2H, NCH_2), 3.81 (s, 3H, OCH_3), 4.20 (t, J = 5.8 Hz, 2H, OCH_2), 6.53 (s,1H, ArH), 6.56–6.59 (m, 1H, ArH), 7.18 (s, 1H, oxazole), 7.42–7.55 (m, 3H, ArH), 7.82–7.95 (m, 3H, ArH). Anal. Calcd for $C_{23}H_{26}N_2O_3$: C, 72.99; H, 6.92; N, 7.40. Found: C, 73.08; H, 6.81; N, 7.30.

4.1.5. Typical experimental procedure for the synthesis of 5-(2-(3-chloropropoxy)-4-methoxyphenyl)-3-phenyl isoxazole (12)

Compound **5** (1.34 g, 5 mmol), $Cl(CH_2)_3Br$ (0.93 g, 6 mmol) and K_2CO_3 (2.07 g, 15 mmol) were taken in 30 ml of acetone. The reaction mixture was refluxed for 8 h. After completion the reaction, K_2CO_3 was filtered off and the filtrate was concentrated to yield crude product. The crude product was subjected to column chromatography to yield pure product **12**. Yield (92.50%), FAB MS (*m/z*) = 344 (M+H). ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 1.90–2.10 (m, 2H, CH_2), 3.50 (t, J = 7.2 Hz, 2H, $ClCH_2$), 3.81 (s, 3H, OCH_3), 4.10 (t, J = 6.8 Hz, 2H, OCH_2), 6.56 (s, 1H, ArH), 6.58–6.60 (m, 1H, ArH), 7.17 (s, 1H, isoxazole), 7.40–7.53 (m, 3H, ArH), 7.80–7.91 (m, 3H, ArH). Anal. Calcd for $C_{19}H_{18}ClNO_3$: C, 66.38; H, 5.28; N, 4.07. Found: C, 66.45; H, 5.24; N, 3.94.

4.1.6. General synthetic procedure for synthesis of compounds (13–17)

Compound **12** (0.343 g, 1 mmol), amine (2 mmol) in 10 ml DMF were taken. To it KI (0.1 g) was added and the reaction mixture was refluxed for 8–10 h. After completion the reaction mixture was cooled and poured in 100 ml of water and extracted with ethyl acetate (50 ml). The ethyl acetate layer was dried over anhydrous sodium sulphate and concentrated to yield crude product. The crude product was purified by silica gel column chromatography to yield compounds **13–17**.

4.1.6.1. 3-(5-Methoxy-2-(3-phenylisoxazol-5-yl)phenoxy)-*N*,*N*-dimethylpropan-1-amine (13). Yield (80.58%), FAB MS (*m/z*) = 353 (M+H). ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 1.94–2.02 (m, 2H, CH_2), 2.32 (s, 6H, NCH_3), 2.76 (t, J = 5.8 Hz, 2H, NCH_2), 3.79 (s, 3H, OCH_3), 4.02 (t, J = 6.9 Hz, 2H, OCH_2), 6.50 (s, 1H, ArH), 6.60–6.63 (m, 1H, ArH), 7.18 (s, 1H, isoxazole), 7.40–7.54 (m, 3H, ArH), 7.80–7.93 (m, 3H, ArH). Anal. Calcd for $C_{21}H_{24}N_2O_3$: C, 71.57; H, 6.86; N, 7.95. Found: C, 71.48; H, 6.74; N, 8.08.

4.1.6.2. *N*,*N*-Diethyl-3-(5-methoxy-2-(3-phenylisoxazol-5-yl) phenoxy)propan-1-amine (14). Yield (78.80%), FAB MS (*m/z*) = 381 (M+H). ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 1.07 (t, J = 7.2 Hz, 6H, CH_3), 1.92–2.02 (m, 2H, CH_2), 2.64–2.90 (m, 6H, NCH_2), 3.80 (s, 3H, OCH_3), 4.04 (t, J = 7.1 Hz, 2H, OCH_2), 6.48 (s, 1H, ArH), 6.60–6.62 (m, 1H, ArH), 7.19 (s, 1H, isoxazole), 7.40–7.53 (m, 3H, ArH), 7.78–7.90 (m, 3H, ArH). Anal. Calcd for $C_{23}H_{28}N_2O_3$: C, 72.60; H, 7.42; N, 7.36. Found: C, 72.56; H, 7.44; N, 7.24.

4.1.6.3. *N*-(3-(5-Methoxy-2-(3-phenylisoxazol-5-yl)phenoxy) propyl)-*N*-methylbutan-1-amine (15). Yield (83.70%), FAB MS (*m/z*) = 395 (M+H). ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 0.98 (t, J = 6.7 Hz, 3H, CH_3), 1.32–1.46 (m, 4H, CH_2), 1.90–2.02 (m, 2H, CH_2), 2.30 (s, 3H, CH_3), 2.44–2.60 (m, 4H, NCH_2), 3.80 (s, 3H, OCH_3), 4.00 (t, J = 7.1 Hz, 2H, OCH_2), 6.50 (s, 1H, ArH), 6.60–6.63 (m, 1H, ArH), 7.19 (s, 1H, isoxazole), 7.42–7.54 (m, 3H, ArH), 7.79–7.90 (m, 3H, ArH). Anal. Calcd for $C_{24}H_{30}N_2O_3$: C, 73.07; H, 7.66; N, 7.10. Found: C, 72.96; H, 7.54; N, 7.00.

4.1.6.4. 5-(4-Methoxy-2-(3-(pyrrolidin-1-yl) propoxy) phenyl)-3-phenylisoxazole (16). Yield (82.50%), FAB MS (*m/z*) = 379 (M+H). ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 1.68–1.84 (m, 4H, CH_2), 1.89–2.00 (m, 2H, CH_2), 2.46–2.74 (m, 6H, NCH_2), 3.80 (s, 3H, OCH_3), 4.02 (t, J = 7.2 Hz, 2H, OCH_2), 6.49 (s, 1H, ArH), 6.60–6.62 (m, 1H, ArH), 7.20 (s, 1H, isoxazole), 7.40–7.53 (m, 3H, ArH), 7.80–7.90 (m, 3H, ArH). Anal. Calcd for $C_{23}H_{26}N_2O_3$: C, 72.99; H, 6.92; N, 7.40. Found: C, 72.90; H, 7.00; N, 7.30.

4.1.6.5. 5-(4-Methoxy-2-(3-(piperidin-1-yl) propoxy) phenyl)-3-phenylisoxazole (17). Yield (80.35%), FAB MS (*m/z*) = 393 (M+H). ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 1.68–1.84 (m, 4H, CH_2), 1.89–2.00 (m, 2H, CH_2), 2.46–2.74 (m, 6H, NCH_2), 3.80 (s, 3H, OCH_3), 4.02 (t, J = 7.2 Hz, 2H, OCH_2), 6.49 (s, 1H, ArH), 6.60–6.62 (m, 1H, ArH), 7.20 (s, 1H, isoxazole), 7.40–7.53 (m, 3H, ArH), 7.80–7.90 (m, 3H, ArH). Anal. Calcd for $C_{24}H_{28}N_2O_3$: C, 73.44; H, 7.19; N, 7.14. Found: C, 73.49; H, 7.10; N, 7.02.

4.1.7. Typical experimental procedure for the synthesis of compounds (18–21)

Compound **5** ((1.34 g, 5 mmol)), $Cl(CH_2)_nCOOR^1$ (6 mmol) and K_2CO_3, (2.07 g, 15 mmol) were taken in 30 ml of acetone. The reaction mixture was refluxed for 8–10 h. After completion the reaction, K_2CO_3 was filtered off and the filtrate was concentrated to yield crude product. The crude product was subjected to column chromatography to yield pure product **18–21**.

4.1.7.1. Ethyl 2-(5-methoxy-2-(3-phenylisoxazol-5-yl)phenoxy) acetate (18). Yield (88.80%), FAB MS (*m/z*) = 354 (M+H). ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 1.17 (t, J = 7.1 Hz, 3H, CH_3), 3.80 (s, 3H, OCH_3), 4.05 (t, J = 7.1 Hz, 2H, OCH_2), 5.10 (s, 2H, OCH_2), 6.50 (s, 1H, ArH), 6.60–6.62 (m, 1H, ArH), 7.19 (s, 1H, isoxazole), 7.40–7.53 (m, 3H, ArH), 7.78–7.90 (m, 3H, ArH). Anal. Calcd for $C_{20}H_{19}NO_5$: C, 67.98; H, 5.42; N, 3.96. Found: C, 67.86; H, 5.44; N, 3.85.

4.1.7.2. Ethyl 4-(5-methoxy-2-(3-phenylisoxazol-5-yl)phenoxy) butanoate (19). Yield (90.50%), FAB MS (*m/z*) = 382 (M+H). ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 1.19 (t, J = 7.1 Hz, 3H, CH_3), 2.16–2.36 (m, 4H, CH_2), 3.81 (s, 3H, OCH_3), 4.00–4.10 (m, 4H, OCH_2), 5.10 (s, 2H, OCH_2), 6.50 (s, 1H, ArH), 6.60–6.62 (m, 1H, ArH), 7.20 (s, 1H, isoxazole), 7.42–7.55 (m, 3H, ArH), 7.79–7.94 (m, 3H, ArH). Anal. Calcd for $C_{22}H_{23}NO_5$: C, 69.28; H, 6.08; N, 3.67. Found: C, 69.22; H, 6.00; N, 3.55.

4.1.7.3. 2-(5-Methoxy-2-(3-phenylisoxazol-5-yl)phenoxy)acetic acid (20). Yield (92.50%), FAB MS (*m/z*) = 326 (M+H). ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 3.82 (s, 3H, OCH_3), 5.00 (s, 2H, OCH_2), 6.50 (s, 1H, ArH), 6.60–6.62 (m, 1H, ArH), 7.20 (s, 1H, isoxazole), 7.42–7.55 (m, 3H, ArH), 7.79–7.94 (m, 3H, ArH). Anal. Calcd for $C_{18}H_{15}NO_5$: C, 66.46; H, 4.65; N, 4.31. Found: C, 69.22; H, 4.56; N, 4.19.

4.1.7.4. 4-(5-Methoxy-2-(3-phenylisoxazol-5-yl)phenoxy) butanoic acid (21). Yield (90.65%), FAB MS (*m/z*) = 354 (M+H). ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 2.12–2.30 (m, 4H, CH_2), 3.81 (s, 3H, OCH_3), 4.20 (s, 2H, OCH_2), 6.50 (s, 1H, ArH), 6.60–6.62 (m, 1H, ArH), 7.20 (s, 1H, isoxazole), 7.42–7.55 (m, 3H, ArH), 7.79–7.94 (m, 3H, ArH). Anal. Calcd for $C_{20}H_{19}NO_5$: C, 67.98; H, 5.42; N, 3.96. Found: C, 67.92; H, 5.54; N, 4.09.

4.1.8. Typical experimental procedure for the synthesis of 5-(4-methoxy-2-(oxiran-2-ylmethoxy)phenyl)-3-phenyl isoxazole (22)

Compound **5** (1.34 g, 5 mmol), epichlorohydrin (0.92 g, 10 mmol) and K_2CO_3 (2.07 g, 15 mmol) were taken in 30 ml of acetone. The reaction mixture was refluxed for 7 h. After completion the reaction, K_2CO_3 was filtered off and the filtrate was concentrated to yield crude product. The crude product was subjected to column chromatography to yield pure product **22**. Yield (80.60%), FAB MS (m/z) = 324 (M+H). ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 3.12 (s, 1H, CH), 3.42–3.56 (m, 2H, OCH_2), 3.81 (s, 3H, OCH_3), 4.00–4.20 (m, 2H, OCH_2), 6.50 (s, 1H, ArH), 6.60–6.62 (m, 1H, ArH), 7.20 (s, 1H, isoxazole), 7.42–7.55 (m, 3H, ArH), 7.79–7.94 (m, 3H, ArH). Anal. Calcd for $C_{19}H_{17}NO_4$: C, 70.58; H, 5.30; N, 4.33. Found: C, 70.50; H, 5.24; N, 4.20.

4.1.9. Typical experimental procedure for the synthesis of compounds (23–25)

Compound **22** (5 mmol) and amine (10 mmol) were taken in 10 ml of DMF and heated for 8–10 h. After completion, the reaction mixture was poured in 100 ml of water and extracted with ethyl acetate (50 ml × 2). The ethyl acetate layer was dried over anhydrous sodium sulphate and concentrated to yield crude product. The crude product was purified by column chromatography to tield compound **23–25**.

4.1.9.1. 1-(Diethylamino)-3-(5-methoxy-2-(3-phenylisoxazol-5-yl)phenoxy)propan-2-ol (23). Yield (90.56%), FAB MS (m/z) = 397 (M+H). ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 1.10 (t, J = 7.2 Hz, 6H, CH_3) 2.42–2.60 (m, 6H, CH_2), 3.22 (s, 1H, OH), 3.84 (s, 3H, OCH_3), 3.95–4.21 (m, 3H, OCH, OCH_2), 6.50 (s, 1H, ArH), 6.60–6.62 (m, 1H, ArH), 7.20 (s, 1H, isoxazole), 7.42–7.55 (m, 3H, ArH), 7.79–7.94 (m, 3H, ArH). Anal. Calcd for $C_{23}H_{28}N_2O_4$: C, 69.67; H, 7.12; N, 7.07. Found: C, 69.55; H, 7.20; N, 6.91.

4.1.9.2. 1-(5-Methoxy-2-(3-phenylisoxazol-5-yl)phenoxy)-3-(pyrrolidin-1-yl)propan-2-ol (24). Yield (89.70%), FAB MS (m/z) = 395 (M+H). ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 1.10 (t, J = 7.2 Hz, 6H, CH_3) 2.42–2.60 (m, 6H, CH_2), 3.30 (s, 1H, OH), 3.84 (s, 3H, OCH_3), 3.95–4.21 (m, 3H, OCH, OCH_2), 6.50 (s, 1H, ArH), 6.60–6.62 (m, 1H, ArH), 7.20 (s, 1H, isoxazole), 7.42–7.55 (m, 3H, ArH), 7.79–7.94 (m, 3H, ArH). Anal. Calcd for $C_{23}H_{26}N_2O_4$: C, 70.03; H, 6.64; N, 7.10. Found: C, 69.95; H, 6.50; N, 6.90.

4.1.9.3. 1-(5-Methoxy-2-(3-phenylisoxazol-5-yl)phenoxy)-3-(piperidin-1-yl)propan-2-ol (25). Yield (85.50%), FAB MS (m/z) = 409 (M+H). ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 1.40–1.58 (m, 6H, CH_2) 2.40–2.68 (m, 6H, NCH_2), 3.42 (s, 1H, OH), 3.80 (s, 3H, OCH_3), 4.00–4.19 (m, 3H, OCH & OCH_2), 6.50 (s, 1H, ArH), 6.60–6.62 (m, 1H, ArH), 7.20 (s, 1H, isoxazole), 7.42–7.55 (m, 3H, ArH), 7.79–7.94 (m, 3H, ArH). Anal. Calcd for $C_{24}H_{28}N_2O_4$: C, 70.57; H, 6.91; N, 6.86. Found: C, 70.48; H, 6.80; N, 6.78.

4.2. Pharmacology

4.2.1. Protein-tyrosine-phosphatase-1B inhibitory assay

Protein tyrosine phosphatase inhibitory activity of compounds was determined by modified method of Goldstein et al.[34] The test compounds were pre-incubated for 10 min with the enzyme in the absence and presence of 0.01% Triton X–100. Assay was performed in final volume of 1.0 ml in test mixture containing 10 mM of pNPP in 50 mM HEPES buffer (pH 7.0) with 1 mM DTT and 2 mM EDTA. The reaction was stopped after 30 min of incubation at 37 °C by addition of 500 μl of 0.1 N NaOH and the absorbance was determined at 410 nm. A molar extinction coeffcient of $1.78 \times 10^4\ M^{-1}\ cm^{-1}$ was utilized to calculate the concentration of *p*-nitrophenolate ion generated in the reaction mixture. Sodium orthovanadate was taken as standard in enzyme assay. The IC_{50} of the compounds were determined by constructing a dose-response curve and examining the effect of different concentrations of compounds.

4.2.2. Sucrose loaded rat model (SLM)[35]

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 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.

4.2.3. Sucrose-challenged streptozotocin-induced diabetic rat model (STZ-S)[35]

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 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 non-responders. 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.

4.2.4. Anti-hyperglycemic activity in db/db mice[36]

The db/db mouse is a well-characterised model of type 2 diabetes. The background for the db/db mouse is the C57BL/Ks strain. The optimal age of db/db mice used for experiments is from week 12 to 18 when they have developed NIDDM with diabetic dyslipidemia but still have functional β-cells in the pancreas. C57BL/KsBom-db mice 12–18 weeks, 40–50 g bred in the animal house of CDRI, Lucknow. Ten mice (5 males and 5 females) were used in the experiments. 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). 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 post-

prandial 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 8, blood was collected for estimation of serum lipid parameters and finally 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 gm/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.

4.2.5. DPP4 enzyme inhibition essay

Enzyme inhibition essay was done as described in the literature.[37] Enzymatic activity was determined at 37 °C by the cleavage rate of a substrate, Gly-Pro-AMC (30 lM) (Sigma–Aldrich, USA). Briefly, 10 μL of DPP-IV solution was added to each well of a 96-well flat-bottomed microtiter plate, followed by the addition of 50 μL of 60 μL Gly-Pro-AMC, 10 μL of 500 mM Tris–HCl (pH 7.4), 20 μL of distilled water, and 10 μL of a test compound. The change of fluorescence was monitored at 37 °C using a spectrofluorometer (excitation at 355 nm/emission at 460 nm) (fmax, Molecular Devices, USA). The initial rate of DPP-IV enzyme activity was calculated over the first 15 min of the reaction, with units/mL being defined as the rate of increase in the fluorescence intensity (arbitrary units) under these conditions.

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