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Original article

Novel 2-aryl-naphtho[1,2-*d*]oxazole derivatives as potential PTP-1B inhibitors showing antihyperglycemic activities

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Abstract

A series of 2-aryl-naphtho[1,2-*d*]oxazole derivatives have been synthesized and evaluated for PTP-1B inhibitory activity. The compounds have been screened *in vivo* for antidiabetic activity under sucrose loaded model (SLM), sucrose-challenged streptozotocin-induced diabetic rat model (STZ-S) and db/db mice model. Compounds **8** and **12** have shown promising PTP-1B inhibitory activity, significant antidiabetic activity, moderate lipid and triglyceride lowering activity.

Keywords: 2-Aryl-naphtho[1,2-*d*]oxazole; Protein tyrosine phoshatase-1B inhibitors; Antidiabetic activity; Lipid and triglyceride lowering activity

1. Introduction

Protein tyrosine phosphatase-1B (PTP-1B) has emerged as new target for the treatment of diabetes and obesity [1–7]. These enzymes belong to a family of tyrosine phosphatase, which have about 90 members. The insulin receptor is activated via autophosphorylation on tyrosine residue, so a tyrosine phosphatase is required to shut off the receptor. PTP-1B knockout mice have shown increased insulin sensitivity and also exhibited decreased tendency of obesity [8,9].

Enhanced IR as well as IRS-1 phosphorylation have been observed in liver and skeleton muscles of PTP-1B knockout mice. The results suggest that the target have potential to address the defects in hepatic glucose output as well as defects in hepatic glucose uptake. PTP-1B inhibitors are negative in insulin and leptin signaling cascades. Thus, they play a critical role in diabetes and obesity [10,11]. Therefore, the search for potent small molecules as protein tyrosine phosphatase-1B inhibitors is a major thrust area in the management of diabetes and obesity.

Recently, the interest in the development of small molecules such as PTP-1B inhibitors has dramatically increased [12]. Majority of PTP-1B inhibitors are peptidomimics or tyrosine-mimicking structures with negatively charged motifs such as phosphonate and carboxylates [13,14]. Wrobel and coworkers have reported Ertiprotafib (**I**) as potent PTP-1B inhibitor [15]. These compounds have PPARγ agonistic activity also, which could contribute to their *in vivo* efficacy. Recently, *Broussonetia papyrifera* root extract having flavonides and flavones (**II**) were reported as potent PTP-1B inhibitors [16]. Malamas et al. have reported [17,18] benzofuran, benzothiophene and oxazole derivatives (**III**, **IV**, **V**) as potent PTP-1B inhibitors (Fig. 1). Based on reported PTP-1B inhibitors, we have designed and synthesized 2-aryl-naphtho[1,2-*d*]oxazole derivatives as potential PTP-1B inhibitors.

In this paper we wish to report synthesis, PTP-1B inhibitory activity and *in vivo* antidiabetic activity of 2-aryl-naphtho [1,2-*d*]oxazole derivatives.

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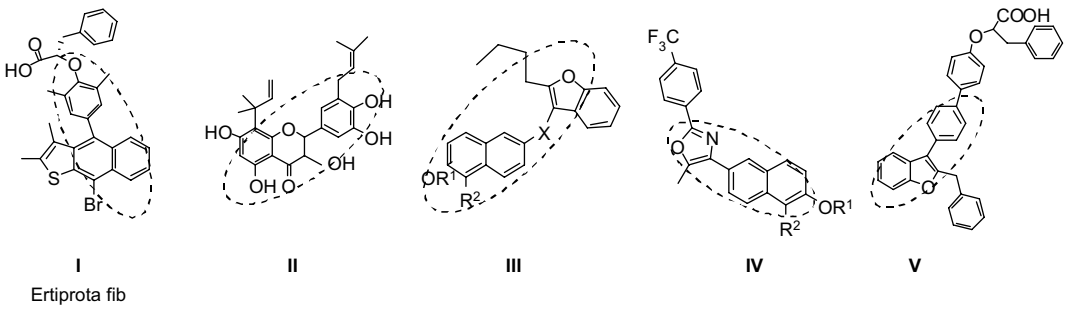


Fig. 1. Structures of some Potent PTP-1B inhibitors

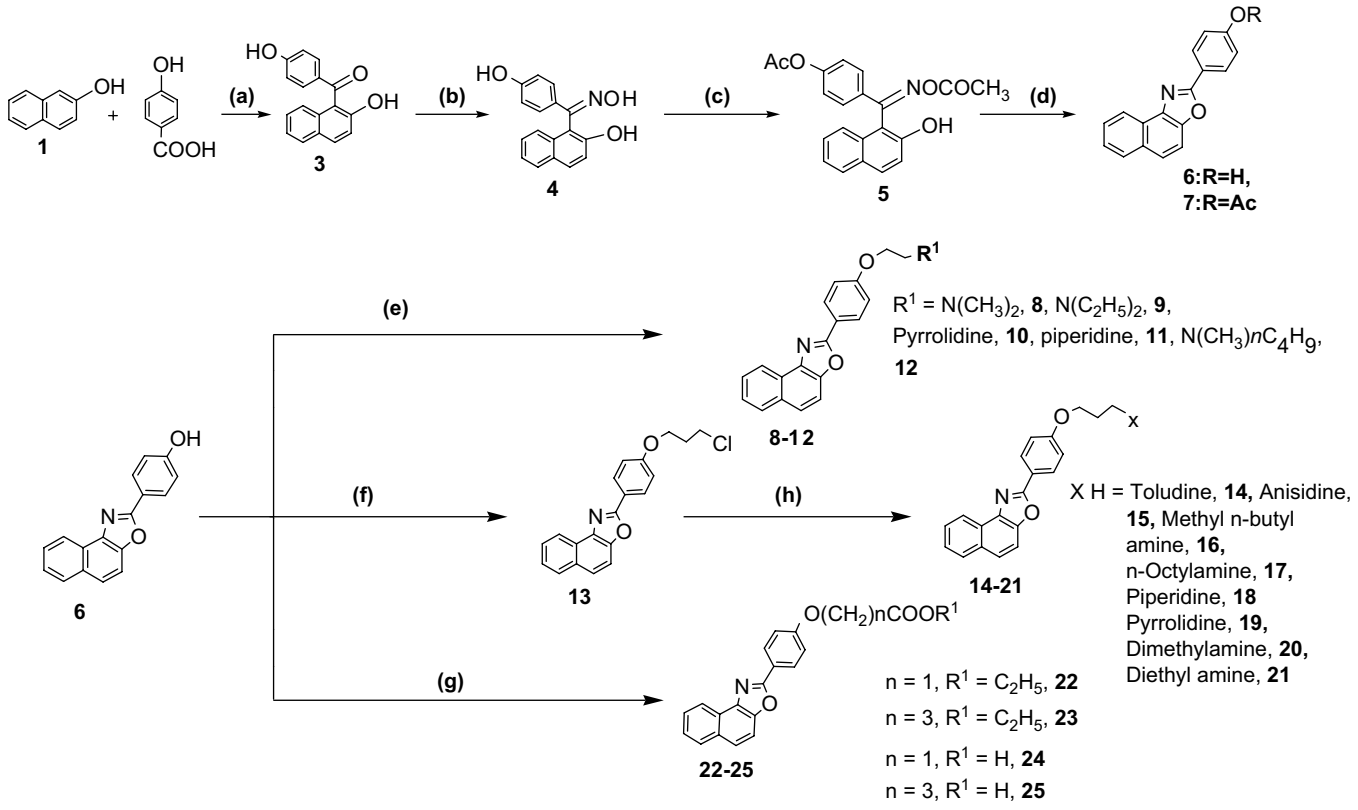
2. Results and discussion

2.1. Chemistry

It seems from the structure of potent PTP-1B inhibitors (Fig. 1) that a 6/6 fused bicyclic system (**I**, **II**, **III**, **IV**) along with a five member heterocyclic ring (**I**, **III**, **IV**, **V**) are keys for their activity. Based on these we have designed a 6/6/5 fused heterocylic system **6**. We provided a phenolic group (OH) in **6** for the addition of amine side chains and thus giving additional amine binding site.

Synthesis of key intermediate of the series 4-naphtho[1,2-*d*]-oxazole-2-yl-phenol (**6**) was achieved via a multi-step synthetic route starting from β-naphthol (Scheme 1). Friedel Crafts benzoylation of β-naphthol (**1**) with 4-hydroxybenzoic acid (**2**) in presence of $BF_3 \cdot Et_2O$ at 100 °C gave corresponding naphthophenone (**3**) in good yields. Naphthophenone (**3**) on reaction with hydroxylamine hydrochloride and sodium acetate in refluxing ethanol gave naphthophenone oxime (**4**) in very good yield.

Compound (**4**) on reaction with neat acetic anhydride at room temperature gave naphthophenone oxime acetate (**5**). Naphthophenone oxime acetate on reaction with neat pyridine at 110 °C under goes Beckmann type rearrangement to give exclusively 2-aryl-naphtho [1,2-*d*]oxazole (**6**). Compound **6** on Williamson type *O*-alkylation reaction with different 1-(2-chloro-ethyl)-substituted amine hydrochloride in presence of potassium carbonate/potassium iodide in acetone/DMF gave 2-[4-(2-substituted amino ethoxy) phenyl]-naphtho[1,2-*d*] oxazoles. All the synthesized compounds are characterized by spectroscopic analysis.



Scheme 1. Reagents and condition: (a) $BF_3 \cdot Et_2O$, 100 °C, (b) hydroxylamine hydrochloride, sodium acetate. Ethanol, reflux, (c) acetic anhydride, RT, (d) pyridine, reflux, (e) K_2CO_3, acetone, $ClCH_2CH_2R^1 \cdot HCl$, (f) $BrCH_2CH_2CH_2Cl$, K_2CO_3, acetone, (g) K_2CO_3, acetone, bromoalkyl esters, (h) DMF, KI, XH (amines).

2.2. Biological activity

The synthesized compounds were tested for protein tyrosine phosphatase-1B (PTP-1B) inhibition study by pre-incubating 100 μM of compounds in the test system for 10 min and the residual PTPase activity was determined according to the method of Goldstein et al. [19]. Vanadate (sodium ortho vanadate) a non-selective PTP's inhibitor was taken as a control. All 2-aryl-naphtho[1,2-*d*]oxazole derivatives were evaluated as PTP-1B inhibitors. The structure–activity relationship of 2-aryl-naphtho[1,2-*d*]oxazoles reveals that although the parent compound **6** has exhibited moderate activity, compounds having side chains at phenolic OH of **6** have shown promising PTP-1B inhibitory activity.

Compounds **8**–**12** having the two carbon chain along with amines showed better activity than corresponding three carbon chain compounds **14**–**21**.

Activity data suggest that side chain having open chain aliphatic amines (**8**, **9**, **12**, **20** and **21**) were more active than compounds containing cyclic/aromatic amines (**14**, **15**). Surprisingly, compounds having ester and acid functionality did not exhibit good inhibition. To rule out the possibility of promiscuous inhibition in our results, we selected compounds **8**–**12**, **20** and **21** in the presence and absence of Triton X-100 (detergent). The values of PTP-1B inhibitory activity revealed that there is no significant variation in activity by addition of Triton X-100 due to promiscuous inhibition. The IC_{50} and dissociation constant K_i of the active compounds are given in Table 1.

All the compounds were screened for their *in vivo* antidiabetic activity in sucrose loaded model (SLM) male albino rats. Compounds **8** (35.9%), **9** (21.7%), **11** (26.9%), **12** (35.3%), **18** (25.0%), **20** (25.2%), and **21** (20.5%) have shown significant blood glucose lowering activity. Compounds showing good blood glucose lowering activity were further tested for antidiabetic activity in sucrose-challenged streptozotocin (STZ-S) induced diabetic rat model and in db/db mice model. Compounds **8**, **12** and **20** have shown significant antidiabetic activity in STZ-S model as well as in db/db mice model (Table 1). Two compounds (**8**, 18.9% and **12**, 22.3%) have shown better blood glucose lowering profiles than standard drugs (metformin, 11.2%; glybenclamide, 13.6%; glyclazide, 17.4%) in db/db mice model.

Two compounds (**8** and **12**) were further tested for their antidiabetic as well as antidyslipidemic activity in db/db mice model under 6 days' and 10 days' protocol (Table 2). Interestingly, these compounds (**8** and **12**) have shown promising *in vivo* antidiabetic, lipid, triglyceride and cholesterol lowering activity.

3. Conclusion

In conclusion, we have synthesized 2-aryl-naphtho[1,2-*d*]oxazoles and evaluated these compounds for their protein

Table 1
In vitro PTP-1B inhibitory activity as well as *in vivo* antidiabetic activity of 2-aryl-naphtho[1,2-*d*]oxazole derivatives in SLM, STZ-S and db/db mice model

Entry	Compound	PTP-1B inhibitory activity					% Antihyperglycemic activity			
		Inhibition[a] (%)	−Triton 100[a,b]		+Triton 100[a,b]		SLM	STZ-S		db/db mice[c]
			IC_{50} (μM)	Ki (μM)	IC_{50} (μM)	Ki (μM)		5 h	24 h	
1	**6**	23.6	–	–	–	–	10.8	ND	ND	–
2	**7**	31.1	–	–	–	–	16.8	ND	ND	–
3	**8**	89.4	3.51	25.1	3.56	28.7	35.9	27.9	25.7	18.9
4	**9**	86.8	4.60	35.0	4.55	355	21.7	11.4	9.7	–
5	**10**	84.2	5.71	34.2	5.70	37.0	8.7	ND	ND	–
6	**11**	98.2	1.90	27.5	1.86	27.1	26.9	16.4	15.7	10.4
7	**12**	95.0	2.50	44.4	2.52	41.0	35.3	17.4	18.7	22.3
8	**13**	ND	–	–	–	–	7.4	ND	ND	–
9	**14**	44.2	–	–	–	–	17.2	14.6	15.2	–
10	**15**	43.6	–	–	–	–	11.8	ND	ND	–
11	**16**	44.5	–	–	–	–	14.7	7.8	9.2	–
12	**17**	39.7	–	–	–	–	15.0	ND	ND	–
13	**18**	34.2	–	–	–	–	25.0	13.4	11.2	–
14	**19**	46.7	–				17.2	12.6	12.9	–
15	**20**	87.8	3.50	34.1	3.52	36.3	25.2	15.6	20.3	16.7
16	**21**	88.4	3.40	40.5	3.36	41.0	20.5	11.5	13.6	10.8
17	**22**	30.7	–	–	–	–	11.4	ND	ND	–
18	**23**	ND	–	–	–	–	9.5	ND	ND	–
19	**24**	21.3	–	–	–	–	4.6	ND	ND	–
20	**25**	25.4	–	–	–	–	5.8	ND	ND	–
21	Na_2VO_3	80.5	7.70							
22	Metformin						12.9	19.1	20.2	11.2
23	Glybenclamide						33.9	32.8		13.6
24	Glyclazide						44.8	27.7		17.4

ND = not done.
[a] Values are mean from three independent sets of experiments screened at 100 μM concentration.
[b] Compounds were tested in the presence of 0.01% Triton X-100.
[c] a 3 day protocol experiment.

Table 2
Antihyperglycemic and antidyslipidemic activity in db/db mice model

Entry (compound number)	Antihyperglycemic and antidyslipidemic activity in db/db mice (% efficacy, 6 and 10 days) (100 mg/kg)				
	Antihyperglycemic		Antidyslipidemic activity		
	6 Days	10 Days	TG	CHOL	HDL
8	21.4	23.6	−10.5	−17.6	+3.0
12	22.4	24.1	−7.5	−12.2	+1.3

tyrosine phosphatase-1B inhibitory activity. Several compounds of this series have shown significant PTP-1B inhibitory activity. The compounds were also screened for *in vivo* antidiabetic activity in SLM, STZ-S and db/db mice models. Compounds **8** and **12** have exhibited most promising activity. The compounds **8** and **12** were also tested for their dyslipidemic activity and compound **8** has shown slightly better triglyceride as well as lipid lowering profile.

4. Experimental

4.1. Chemistry

All the chemical reagents were purchased from Sigma–Aldrich chemical company and were used directly without any further purification. NMR spectra were obtained using the Brucker DRX 200 MHz spectrometer. Chemical shifts (δ) are given in parts per million relative to TMS, coupling constants (J) in hertz. Mass spectra were obtained by 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. Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm silica gel plates visualized with UV light.

*4.1.1. Typical experimental procedure for the synthesis of 2-hydroxy-4[1]-hydroxy naphthophenone (**3**)*

To a stirred solution of β-naphthol **1** (1.44 g, 10 mmol) in 10 ml of boron trifluoride etherate, 4-hydroxybenzoic acid **2** (1.51 g, 11 mmol) was added and the reaction mixture was heated at 100 °C for 6 h. Then, the reaction mixture was poured in water and extracted with ethyl acetate. The organic layer was separated, dried over anhydrous sodium sulphate and concentrated to give a crude oil. The oil was then chromatographed on silica gel using a gradient mixture of hexane/ethyl acetate to yield **3**. Yield (1.2 g, 49.9%); mp 178–179 °C; FABMS (*m/z*) 265 $(M+1)^+$; IR (KBr, cm^{-1}) 3364, 1573, 1508; ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 6.80 (d, $J = 8.4$ Hz, 2H), 7.26 (m, 3H), 7.40 (d, $J = 7.8$ Hz, 1H), 7.69 (d, $J = 8.7$ Hz, 2H), 7.76 (d, $J = 8.4$ Hz, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 195.4, 161.6, 151.4, 131.2, 131.1, 129.5, 128.9, 127.0, 126.9, 125.7, 122.9, 122.0, 119.0, 117.4, 114.4. Anal. calcd for $C_{21}H_{12}O_3$, C, 77.26; H, 4.58; Found: C, 77.39; H, 4.61.

*4.1.2. Typical experimental procedure for the synthesis of 2-hydroxy-4[1]-hydroxy naphthophenone oxime (**4**)*

2-Hydroxy-4[1]-hydroxy naphthophenone **3** (2.64 g, 10 mmol) was taken in 20 ml of ethyl alcohol. To it hydroxylamine hydrochloride (3.0 g) and sodium acetate (3.0 g) were added. Reaction mixture was then refluxed at water bath for 2 h. After completion (TLC), ethyl alcohol was removed and reaction mixture was extracted with ethyl acetate. The organic layer was concentrated, dried over anhydrous sodium sulphate and chromatographed on silica gel using a gradient mixture of hexane/ethyl acetate to yield compound **4**. Yield (2.62 g, 93.90%); mp 199–202 °C; FABMS (*m/z*) 280 $(M^+ + 1)$; IR (KBr, cm^{-1}), 3364, 1602, 1247; ^{1}H NMR (DMSO-d_6, 200 MHz) δ: 7.05 (d, $J = 8.4$ Hz, 2H), 7.36 (m, 4H), 7.78 (d, $J = 8.6$ Hz, 2H), 7.90 (m, 1H), 10.1 (bs, 1H). Anal. calcd for $C_{17}H_{13}NO_3$, C, 73.11; H, 4.69; N, 5.02; Found: C, 72.97; H, 4.61; N, 4.83.

*4.1.3. Typical experimental procedure for the synthesis of acetate of naphthophenone oximes (**5**)*

2-Hydroxy-4[1]-hydroxy-naphthophenone oxime **4** (2.79 g, 10 mmol) was taken in 10 ml of acetic anhydride and stirred for 30 min. The reaction mixture was then poured in ice water and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulphate and concentrated to remove ethyl acetate yielding compound **5**. Yield (2.84 g); physical state (oil); FABMS (*m/z*) 364 $(M^+ + 1)$; ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 2.27 (s, 3H); 2.06 (s, 3H); 7.21 (d, $J = 8.8$ Hz, 2H); 7.59 (m, 4H); 7.90 (d, $J = 8.4$ Hz, 1H); 8.27 (d, $J = 8.8$ Hz); 8.50 (d, $J = 8.2$ Hz, 1H). Anal. calcd for $C_{21}H_{17}NO_5$, C, 59.41; H, 4.72; N, 3.85; Found: C, 59.39; H, 4.61; N, 3.73.

*4.1.4. Typical experimental procedure for the synthesis of naphtho[1,2-d]oxazole-2-yl-phenol (**6**)*

(a) Naphthophenone oxime acetate **5** (2.79 g, 10 mmol) was dissolved in10 ml of pyridine and heated at 80 °C for 18 h. The reaction was quenched with ice water and extracted with ethyl acetate. The organic layer was dried on sodium sulphate and evaporated under vacuum yielding naphtho[1,2-*d*]oxazole-2-yl-phenol **6** and acetic acid-4-naphtho[1,2-*d*]oxazole-2-yl-phenyl ester **7** (70:30).
(b) Naphthophenone oxime acetate **5** (2.79 g, 10 mmol) was dissolved in 10 ml of pyridine and refluxed for 14 h. The reaction was quenched with ice water and extracted with ethyl acetate. The organic layer was dried on sodium

sulphate and evaporated under vacuum yielding exclusively naphtho[1,2-*d*]oxazole-2-yl-phenol **6**. Yield (2.07 g, 79%); mp 278 °C; FABMS (*m/z*) 262 $(M)^+$; IR (KBr, cm^{-1}), 3450, 1610, 1437; ^1H NMR (DMSO-d_6, 200 MHz) δ: 6.98 (d, $J = 8.7$ Hz, 2H); 7.46 (m, 1H); 7.58 (m, 2H); 7.92 (m, 2H); 8.09 (m, 3H); 8.41 (d, $J = 8.1$ Hz, 1H); 9.6 (bs, IH). Anal. calcd for $C_{17}H_{11}NO_2$, C, 78.12; H, 4.25; N, 5.36; Found: C, 78.22; H, 4.26; N, 5.48.

*4.1.5. Typical experimental procedure for the synthesis of acetic acid-4-naphtho[1,2-d]oxazole-2-yl-phenyl ester (**7**)*

2-Hydroxy-4[1]-hydroxy naphthophenone oxime **4** (2.79 g, 10 mmol) was dissolved in 14 ml of acetic anhydride and cooled. Then 18 ml of pyridine was added to it. The reaction mixture was heated at 80 °C for 13 h to afford exclusively acetic acid-4-naphtho[1,2-*d*]oxazole-2-yl-phenyl ester **7**. Yield (2.87 g, 94.91%), mp 185–187 °C FABMS (*m/z)* 304 $(M + 1)^+$ IR (KBr cm^{-1}), 3416, 1748, 1605 ^1H NMR ($CDCl_3$, 200 MHz) δ: 2.27 (s, 3H); 7.22 (m, 2H); 7.68 (m, 4H); 7.90 (d, $J = 8.06$, 1H); 8.28 (m, 2H); 8.51(d, $J = 8.1$, 1H) Anal. calcd for $C_{19}H_{13}NO_3$, C, 75.24; H, 4.32; N, 4.62. Found: C, 75.34; H, 4.42; N, 4.83.

*4.1.6. General synthetic procedure for synthesis of **8–12***

To a solution of **6** (2 mmol) in 35 ml of dry acetone, 1-(2-chloro-ethyl)-alkyllamino hydrochloride (2.5 mmol) and potassium carbonate (6.9 g, 50 mmol) was added. The reaction mixture was then refluxed for 8 h. After completion (TLC), the reaction was filtered and concentrated to remove acetone. Then, the reaction mixture was extracted with ethyl acetate (100 ml) and dried over sodium sulphate to give a crude oil. The crude oil was purified by column chromatography using ethyl acetate/hexane as an eluent on basic alumina to yield compounds **8–12**.

*4.1.6.1. Dimethyl-[2-(4-naphtho[1,2-d]oxazol-2-yl-phenoxy)-ethyl]-amine (**8**).* Yield (92.%); mp 102–104 °C; FABMS (*m/z*) 333 $(M + 1)^+$; IR (KBr, cm^{-1}), 3417, 1609, 1210; ^1H NMR ($CDCl_3$, 200 MHz) δ: 2.3 (s, 6H); 2.78 (t, $J = 5.6$ Hz); 4.16 (t, $J = 5.6$ Hz, 2H); 7.07 (d, $J = 8.2$ Hz, 2H); 7.68 (m, 4H); 7.74 (d, $J = 5.4$ Hz, 1H); 7.76 (m, 2H); 8.26 (d, $J = 9.8$ Hz, 1H); Anal. calcd for $C_{21}H_{20}N_2O_2$, C, 75.58; H, 5.65; N, 8.26; Found: C, 75.68; H, 5.86; N, 8.33.

*4.1.6.2. Diethyl-[2-(4-naphtho[1,2-d]oxazol-2-yl-phenoxy)-ethyl]-amine (**9**).* Yield (93%); mp 98–100 °C; FABMS (*m/z*) 361 $(M + 1)^+$; IR (KBr, cm^{-1}), 3437, 1608, 1246; ^1H NMR ($CDCl_3$, 200 MHz) δ: 1.06 (m, 6H); 2.60 (m, 4H); 2.91 (t, $J = 5.4$ Hz, 2H); 4.13 (t, $J = 5.6$ Hz, 2H); 7.04 (d, $J = 9.2$ Hz, 2H); 7.68 (m, 4H); 7.96 (d, $J = 8.2$ Hz, 1H); 8.25 (d, $J = 8.8$ Hz, 2H); 8.56 (d, $J = 8.2$, 1H); Anal. calcd for $C_{23}H_{24}N_2O_2$, C, 76.58; H, 6.85; N, 8.26; Found: C, 76.64; H, 6.71; N, 8.07.

*4.1.6.3. 2-[4-(2-Pyrrolidin-1-yl-ethoxy)-phenyl]-naphtho[1,2-d] oxazole (**10**).* Yield (89%); mp 98–100 °C; FABMS (*m/z*) 359 $(M + 1)^+$; IR (KBr, cm^{-1}), 3446, 1607, 1245; ^1H NMR ($CDCl_3$, 200 MHz) δ: 1.84 (m, 4H); 2.64 (m, 4H); 2.95 (t, $J = 5.8$ Hz, 2H); 4.2 (t, $J = 5.9$ Hz, 2H); 7.06(d, $J = 8.4$ Hz, 2H); 7.68 (m, 4H); 7.95 (d, $J = 8.2$ Hz, 1H); 8.25(d, $J = 8.8$ Hz, 2H); 8.57 (d, $J = 8.2$ Hz, 1H); Anal. calcd for $C_{23}H_{22}N_2O_2$, C, 77.07; H, 6.19; N, 7.82; Found: C, 77.22; H, 6.26; N, 7.68.

*4.1.6.4. 2-[4-(2-Piperidine-1-yl-ethoxy)-phenyl]-naphtho[1,2-d]oxazole (**11**).* Yield (92.6%); mp 118–120 °C; FABMS (*m/z*) 373 $(M + 1)^+$; IR (KBr, cm^{-1}), 3436, 1612, 1256; ^1H NMR ($CDCl_3$, 200 MHz) δ: 1.47 (m, 2H); 1.62 (m, 4H); 2.52 (m, 4H); 2.80 (t, $J = 5.8$ Hz, 2H); 4.18 (t, $J = 5.9$ Hz, 2H); 7.04 (d, $J = 7.4$, 2H); 7.68 (m, 4H); 7.95 (d, $J = 8.2$ Hz, 1H); 8.25 (d, $J = 8.8$ Hz, 2H); 8.57 (d, $J = 8.2$, 1H); Anal. calcd for $C_{24}H_{24}N_2O_2$, C, 77.39; H, 6.49; N, 7.52; Found: C, 77.32; H, 6.36; N, 7.63.

*4.1.6.5. Butyl-methyl-[2-(4-naphtho[1,2-d]oxazol-2-yl-phenoxy)-ethyl]-amine (**12**).* Yield (80%); mp 125–128 °C (HCl salt); FABMS (*m/z*) 375 $(M + 1)^+$; ^1H NMR ($CDCl_3$, 200 MHz) δ: 1.09 (t, $J = 5.4$ Hz, 3H); 1.35 (m, 4H); 2.23 (s, 3H); 2.36 (t, $J = 5.2$ Hz, 2H); 2.53 ($J = 4.6$ Hz, 2H); 4.08 (t, $J = 2.6$ Hz, 2H); 7.02 (d, $J = 6$ Hz, 2H); 7.68 (m, 4H); 7.93 (m, 1H); 8.25 (m, 2H); 8.57 (d, $J = 5.2$ Hz, 1H); Anal. calcd for $C_{24}H_{26}N_2O_2$, C, 76.98; H, 7.00; N, 7.48; Found: C, 77.14; H, 7.27; N, 7.63.

*4.1.7. Typical experimental procedure for the synthesis of 4-(3-chloro-propoxy)-phenyl]-naphtho[1,2-d]oxazole (**13**)*

Compound **6** (1.32 g, 5 mmol) was taken in 35 ml of dry acetone. To it 1-bromo-3-chloropropane (1.22 ml, 11 mmol) and potassium carbonate (13.8 g) were added. The reaction mixture was refluxed for 8 h. After completion (TLC), the reaction mixture was filtered and concentrated to remove acetone. Then it was dissolved in ethyl acetate and washed with water. Compound **13** was obtained by crystallization of ethyl acetate layer with hexane. Yield (3.21 g, 95%); mp 108–110 °C; FABMS (*m/z*) 338 $(M + 1)^+$; ^1H NMR ($CDCl_3$, 200 MHz) δ: 4.20 (t, $J = 5.8$ Hz, 2H,); 3.77 (t, $J = 6.40$ Hz, 2H); 2.28 (m, 2H); 7.04 (d, $J = 8.7$ Hz, 2H); 7.68 (m, 4H); 7.86 (d, $J = 8.2$ Hz, 1H); 8.25 (d, $J = 8.8$ Hz, 2H); 8.57 (d, $J = 8.0$ Hz, 1H). Anal. calcd for $C_{20}H_{16}ClNO_2$, C, 71.11; H, 4.77; N, 4.15; Found: C, 71.23; H, 4.87; N, 4.02.

*4.1.8. General synthetic procedure for synthesis of **14–21***

Compound **13** (675 mg, 2 mmol) was taken in 15 ml of dry DMF. To it amines (2.5 mmol) and potassium iodide (830 mg, 5 mmol) were added. The reaction mixture was stirred at 100 °C for 4 h and then extracted with ethyl acetate. Organic layer was dried over sodium sulphate and chromatographed on basic alumina. Elution with a gradient mixture of hexane/ethyl acetate yielded compounds **14–21**, respectively.

*4.1.8.1. [3-(4-Naphtho[1,2-d]oxazol-2-yl-phenoxy)-propyl]-p-tolyl-amine (**14**).* Yield (92%); mp 118–120 °C; FABMS (*m/z*) 409 $(M + 1)^+$; ^1H NMR ($CDCl_3$, 200 MHz) δ: 2.11 (m,

2H); 2.23 (s, 3H); 3.34 (t, $J = 4.4$ Hz, 2H); 4.14 (t, $J = 3.8$ Hz, 2H); 5.27 (s, 1H); 6.57 (d, $J = 5.6$ Hz, 2H); 6.99 (t, $J = 6.0$ Hz, 4H); 7.52 (m, 1H); 7.68 (m, 3H); 7.95 (d, $J = 5.4$ Hz, 1H); 8.25 (m, 2H); 8.57 (d, $J = 5.2$ Hz, 1H); Anal. calcd for $C_{27}H_{24}N_2O_2$, C, 79.39; H, 5.92; N, 6.86; Found: C, 79.44; H, 5.74; N, 6.86.

*4.1.8.2. 4-(Methoxy-phenyl)-[3-(4-naphtho[1,2-d] oxazol-2-yl-phenoxy)-propyl]-amine (**15**).* Yield (84%); mp 136–140 °C; FABMS (*m/z*) 425 $(M + 1)^+$; ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 2.11 (m, 2H); 3.37 (t, $J = 6.4$ Hz, 2H); 3.77 (s, 3H); 4.14 (t, $J = 4.0$ Hz, 2H); 6.67 (d, $J = 6.6$ Hz, 2H); 6.82 (d, $J = 6.6$ Hz, 2H); 7.07 (d, $J = 5.8$ Hz, 2H); 7.77 (m, 4H); 7.99 (d, $J = 5.4$ Hz, 1H); 8.28 (d, $J = 6.6$ Hz, 2H); 8.59 (d, $J = 5.8$ Hz, 1H); Anal. calcd for $C_{27}H_{24}N_2O_3$, C, 76.39; H, 5.70; N, 6.60; Found: C, 76.54; H, 5.55; N, 6.74.

*4.1.8.3. Butyl-methyl-[2-(4-naphtho[1,2-d]oxazol-2-yl-phenoxy)-propyl]-amine (**16**).* Yield (90%); mp 115–118 °C (HCl salt); FABMS (*m/z*) 389 $(M + 1)^+$; IR (KBr, cm^{-1}), 3443, 1611, 1246; ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 0.99 (t, $J = 5.4$ Hz, 3H); 1.35 (m, 4H); 1.97 (t, $J = 4.8$ Hz, 2H); 2.24 (s, 3H); 2.36 (t, $J = 5.2$ Hz, 2H); 2.53 ($J = 4.6$ Hz, 2H); 4.08 (t, $J = 2.6$ Hz, 2H); 7.02 (d, $J = 6$ Hz, 2H); 7.68 (m, 4H); 7.94 (d, $J = 5.6$ Hz, 1H); 8.25 (d, $J = 5.8$ Hz, 2H); 8.57 (d, $J = 5.2$ Hz, 1H); Anal. calcd for $C_{25}H_{28}N_2O_2$, C, 77.29; H, 7.26; N, 7.28; Found: C, 77.34; H, 7.37; N, 7.43.

*4.1.8.4. [3-(4-Naphtho[1,2-dloxazol-2-yl-phenoxy)-propyl]-octyl-amine (**17**).* Yield (82.5%); mp 67–69 °C; FABMS (*m/z*) 431 $(M + 1)^+$; IR (KBr, cm^{-1}), 3463, 1659, 1250; ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 0.88 (t, $J = 4.2$ Hz, 3H); 1.20 (m, 8H); 1.52 (m, 4H); 2.01 (m, 2H); 2.63 ($J = 4.0$ Hz, 2H); 2.83 (t, $J = 5.4$ Hz, 2H); 4.13 (t, $J = 6.4$ Hz, 2H); 7.04 (d, $J = 6.0$ Hz, 2H); 7.68 (m, 4H); 7.96 (d, $J = 4.2$ Hz, 1H); 8.25 (d, $J = 6.0$ Hz, 2H); 8.57 (d, $J = 8.2$ Hz, 1H); Anal. calcd for $C_{28}H_{34}N_2O_2$, C, 78.10; H, 7.96; N, 6.51; Found: C, 78.24; H, 7.83; N, 6.63.

*4.1.8.5. 2-[4-(Piperidin-1-yl-propoxy)-phenyl]-naptho[1,2-d] oxazole (**18**).* Yield (87%); mp 119 °C; FABMS (*m/z*) 387 $(M + 1)^+$; IR (KBr, cm^{-1}), 3432, 1604, 1250; ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 1.65 (m, 2H); 1.70 (m, 4H); 2.05 (m, 2H); 2.48 (m, 4H); 2.56 (t, $J = 8.0$ Hz, 2H); 4.09 (t, $J = 6.2$ Hz, 2H); 7.02 (d, $J = 6.9$ Hz, 2H); 7.72 (m, 4H); 7.95 (d, $J = 7.2$ Hz, 1H); 8.23 (d, $J = 7.2$ Hz, 2H); 8.57 (d, $J = 7.6$ Hz, 1H); Anal. calcd for $C_{25}H_{26}N_2O_2$, C, 77.69; H, 6.75; N, 7.25; Found: C, 77.42; H, 6.56; N, 7.38.

*4.1.8.6. 2-[4-(3-Pyrrolidin-1-yl-propoxy)-phenyl]-naphtho [1,2-d]oxazole (**19**).* Yield (80%); mp 127–130 °C; FABMS (*m/z*) 373 $(M + 1)^+$; ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 1.47 (m, 2H); 1.67 (m, 4H); 2.48 (m, 4H); 2.56 (t, $J = 8.0$ Hz, 2H); 4.09 (t, $J = 6.2$ Hz, 2H); 7.02 (m, 2H); 7.72 (m, 4H); 7.95 (m, 1H); 8.23 (d, $J = 7.2$ Hz, 2H); 8.57 (d, $J = 7.6$ Hz, 1H); Anal. calcd for $C_{24}H_{24}N_2O_2$, C, 77.39; H 6.49, N, 7.52; Found: C, 77.30; H, 6.66; N, 7.68.

*4.1.8.7. Dimethyl-[3-(4-naphtho[1,2-d]oxazol-2-yl-phenoxy)-propyl]-amine (**20**).* Yield (75%); mp 128–134 °C; FABMS (*m/z*) 347 $(M + 1)^+$; ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 2.3 (s, 6H); 1.72 (m, 2H); 2.78 (t, $J = 5.6$ Hz, 2H); 4.16 (t, $J = 5.6$ Hz, 2H); 7.07 (m, 2H); 7.68 (m, 4H); 7.74 (m, 1H); 7.76 (m, 2H); 8.26 (m, 1H); Anal. calcd for $C_{22}H_{22}N_2O_2$, C, 76.28; H, 6.40; N, 8.09; Found: C, 76.11; H, 6.26; N, 8.23.

*4.1.8.8. Diethyl-[3-(4-naphtho[1,2-d]oxazol-2-yl-phenoxy)-propyl]-amine (**21**).* Yield (72%); mp 136–140 °C; FABMS (*m/z*) 375 $(M + 1)^+$; ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 1.03 (s, 6H); 1.72 (m, 2H); 2.28 (m, 2H); 2.68 (m, 2H); 4.16 (t, $J = 5.6$ Hz, 2H); 7.07 (m, 2H); 7.68 (m, 4H); 7.74 (m, 1H); 7.76 (m, 2H); 8.26 (m, 1H); Anal. calcd for $C_{24}H_{26}N_2O_2$, C, 76.98; H, 7.00; N, 8.54; Found: C, 76.82; H, 7.16; N, 8.39.

*4.1.9. Typical experimental procedure for the synthesis of 4-(4-naphtho[1,2-d]oxazole-2yl-phenoxy)-acetic acid ethyl ester (**22**)*

Naphtho[1,2-*d*]oxazole-2-yl-phenol **6** (1.31 g, 5 mmol) was taken in 30 ml of dry acetone. To it bromoethyl acetate (0.66 ml, 6 mmol) and potassium carbonate (13.8 g, 100 mmol) were added. The reaction mixture was refluxed for 8 h. After completion (TLC), the reaction mixture was filtered and concentrated to remove acetone. The reaction mixture was extracted with ethyl acetate and dried over sodium sulphate to give a crude oil. The crude oil was purified by column chromatography using silica gel as adsorbent and hexane/ethyl acetate as an eluent to yield compound **22**. Yield (1.51 g, 87%); mp 138 °C; FABMS (*m/z*) 348 $(M + 1)^+$; ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 1.30 (t, $J = 7.0$ Hz, 3H); 4.29 (q, $J = 7.2$ Hz, 2H); 4.69 (s, 2H); 7.04 (d, $J = 5.2$ Hz, 2H); 7.72 (m, 4H); 7.95 (d, $J = 8.0$ Hz, 1H); 8.25 (d, $J = 7.0$ Hz, 2H); 8.56 (d, $J = 8.2$ Hz, 1H). Analysis calcd for $C_{21}H_{17}NO_4$: C, 72.61; H, 4.93; N, 4.03; Found C, 72.49; H, 4.80; N, 3.91.

*4.1.10. Typical experimental procedure for the synthesis of 4-(4-naphtho[1,2-d]oxazole-2yl-phenoxy)-butyric acid ethyl ester (**23**)*

4-Naphtho[1,2-*d*]oxazole-2-yl-phenol **6** (1.31 g, 5 mmol) was taken in 30 ml of dry acetone. To it ethyl-4-bromobutyrate (0.90 ml, 6 mmol) and potassium carbonate (13.8 g) were added. The reaction mixture was refluxed for 8 h. After completion (TLC), the reaction mixture was filtered and concentrated to remove acetone. The reaction mixture was extracted with ethyl acetate and dried over sodium sulphate to give a crude oil. The crude oil was purified by column chromatography using silica gel as adsorbent and hexane/ethyl acetate as a eluent to yield compound **23**. Yield (1.51 g, 87%); mp 83–85 °C; FABMS (*m/z*) 376 $(M + 1)^+$; ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 1.27 (t, $J = 7.0$ Hz, 3H), 2.16 (m, 2H), 2.53 (m, 2H), 4.13 (m, 4H), 7.02 (d, $J = 8.8$ Hz, 2H), 7.27 (m, 4H), 7.74 (d, $J = 5.4$ Hz, 2H), 8.25 (d, $J = 5.4$ Hz, 2H);

Analysis calcd for $C_{23}H_{21}NO_4$: C, 73.58; H, 5.64; N, 3.73; Found C, 73.47; H, 5.60; N, 3.61.

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. [19]. 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 coefficient 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.

4.2.2. Sucrose loaded rat model (SLM)

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 antihyperglycemic activity.

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

Male albino rats of Sprague Dawley strain of body weight 160 ± 20 g were selected for this study. Streptozotocin 13 (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 (45 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 termed 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. Antihyperglycemic activity in db/db mice

The db/db mouse is a well-characterized 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 12–18 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 (five males and five females) were used in the experiments. The mice were housed in groups of five (same sex) in a room controlled for temperature (23 ± 2.0 °C) and 12/12 h light/dark cycle (lights on at 6.00 a.m.). 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 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 serum insulin measurements 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 g/kg to all the groups including vehicle. The blood glucose levels were checked at 30, 60, 90 and 120 min post-glucose administration. Compound 8 showed blood glucose lowering effect on postprandial protocol on days 3, 6 and 10 in db/db (Tables 1 and 2).

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