Med Chem Res (2014) 23:2062–2069
DOI 10.1007/s00044-013-0784-0

MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Synthesis and characterization of 2-(4-((1-alkyl or aryl-1*H*-1,2,3-triazol-4-yl)methoxy)phenyl)naphtho[1,2-*d*]oxazoles for protein tyrosine phosphatase 1B inhibitory activity

Sridhar Madabhushi · Narsaiah Chinthala · Abhinav Kanwal · Gagandeep Kaur · Sanjay K. Banerjee

Received: 4 April 2013 / Accepted: 7 September 2013 / Published online: 4 October 2013

Abstract 2-(4-((1-Alkyl/aryl-1*H*-1,2,3-triazol-4-yl)methoxy) phenyl)naphtho[1,2-*d*] were prepared and evaluated as protein tyrosine phosphatase 1B (PTP1B) inhibitors. In this study, two new compounds with potent PTP1B inhibitory activity were identified.

Keywords Naphtho[1,2-*d*]oxazole derivatives · PTP1B inhibitor · Antidiabetic activity

Introduction

Type II diabetes is a progressive disease caused by insulin resistance in peripheral tissues and/or impaired insulin secretion by the pancreas (King *et al*., 1998). At the molecular level, the mechanism of insulin resistance in type II diabetes is believed to be due to defects in post-receptor signal transduction pathway (Montalibet and Kennedy, 2005; Youngren and Goldfine, 1997; Vats *et al*., 2005). Phosphorylation of protein tyrosyl residues is considered to be the controlling factor, which activates or attenuates the intracellular signaling pathways involved in cell proliferation, differentiation, and metabolism (Kennedy and Ramachandran, 2000).

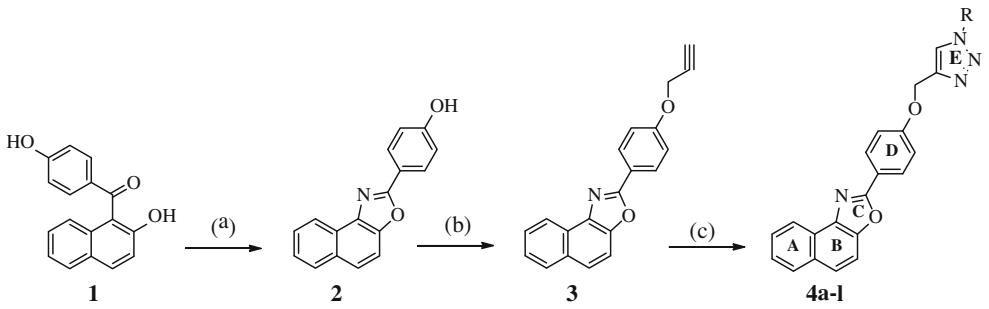
Earlier, Elchebly *et al*., (1999) showed that PTP1B deficiency in mice results in enhanced insulin sensitivity. Protein tyrosine phosphatase-1B (PTP1B), which is a member of the PTP family, directly interacts with the activated insulin receptor or insulin receptor substrate-1 (IRS-1) and dephosphorylate the phosphotyrosine residue. Thus, PTP1B acts as a negative regulator of insulin signaling pathway and leads to hyperglycemia by reducing the metabolic action of insulin (Elchebly *et al*., 1999; Goldstein *et al*., 2000). Molecular modeling studies also proved that treatment of type II diabetes is possible using potent and orally active PTP1B inhibitors (Taha *et al*., 2007). In recent years, studies have been extensively focused to identify small molecules, which exhibit high PTP1B inhibition and high in vivo efficacy with minimum side effects (Bialy and Waldmann, 2005; Srinivasan *et al*., 2006; Shim *et al*., 2003; Popov, 2011; Van Huijsduijnen *et al*., 2002; Ibrahimi *et al*., 2000; Tjernberg *et al*., 2004; Adams *et al*., 2007; Ye *et al*., 2010; Xie *et al*., 2011). In this communication, we report the synthesis and characterization of 2-(4-((1-alkyl/aryl-1*H*-1,2,3-triazol-4-yl)methoxy)phenyl) naphtho[1,2-*d*]oxazoles **4a–l** as new class of PTP1B inhibitors.

Chemistry

In the present study, a small library of 2-(4-((1-alkyl/aryl-1*H*-1,2,3-triazol-4-yl)methoxy)phenyl)naphtho[1,2-*d*]oxazoles **4a–l** was prepared using an efficient three-step method as shown in Scheme 1. To obtain **4a–l**, we first carried out reaction of 2-(2-hydroxynaphthalen-1-yl) (4-hydroxyphenyl) methanone **1** and acetohydroxamic acid using H_2SO_4 as the catalyst under microwave heating at 80 °C to obtain 4-(naphtho[1,2-*d*]oxazol-2-yl)phenol **2** in 45 % yield (Sridhar *et al*., 2011). In the next step, **2** was reacted with propargyl bromide using K_2CO_3 as a base under reflux

S. Madabhushi (✉) · N. Chinthala
Fluoroorganics Division, Indian Institute of Chemical Technology, Hyderabad 500607, India
e-mail: smiict@gmail.com

A. Kanwal · G. Kaur · S. K. Banerjee (✉)
Pharmacology Division, Indian Institute of Chemical Technology, Hyderabad 500607, India
e-mail: skbanerjee@iict.res.in



4a (R = Ph); **4b** (R = 4-MeOPh); **4c** (R = 3-CF_3Ph) ;4**d**(R = 3-ClPh); **4e** (R=3-Cl,4-FPh); **4f** (R = 3,4-diFPh); **4g** (R = n-Bu); **4h** (R = n-hexyl); **4i** (R = $CF_3(CF_2)_5CH_2CH_2$); **4j** (R = $CF_3(CF_2)_7CH_2CH_2$); **4k** (R = 4-Me Ph); **4l** R = 4-CF_3Ph).

Scheme 1 Synthesis of 2-(4-((1-alkyl/aryl-1*H*-1,2,3-triazol-4-yl)methoxy)-phenyl)naphtho[1,2-*d*]oxazoles. Reagents and conditions: (*a*) acetohydroxamic acid, H_2SO_4 (catalyst), acetonitrile, MW, 80 °C, 10 min, 45 %; (*b*) K_2CO_3, propargyl bromide, acetone, reflux, 4 h, 98 %; (*c*) CuI, R-N_3, dry THF, 50 °C, 4–6 h, 87–98 %

in acetone and the corresponding *O*-propargyl ether **3** in 98 % yields was obtained . Next, Huisgen reaction of **3** and alkyl or aryl azide under copper(I) iodide catalysis (Huisgen, 1984) gave the desired products **4a–l** in high 87–98 % yields as shown in Scheme 1.

Results and discussion

Initially, test systems were prepared by pre-incubating the PTP-1B enzyme (3 µL) derived from rat liver homogenate with compound **4a–l** (10 µM, 5 µL) for 30 min. Next, we estimated the residual PTPase activity in these test systems by Goldstein method (Goldstein *et al*., 2000) using sodium orthovanadate (10 µM, 5 µL), a non-selective PTP's inhibitor, as a standard. In this study, we observed PTP1B inhibitory activity only with compounds **4k** (41.62 %) and **4l** (68.32 %) with respect to the standard sodium orthovanadate, (60.63 %) as shown in Table 1. In this study, compounds **4k** and **4l** gave IC_{50} of 20.43 and 8.61 µM, respectively, as shown in Table 2. Both these compounds also showed dose-dependent inhibitory activity as shown in Figs. 1 and 2.

We also studied in vivo PTP-1B inhibitory activity of compounds **4k** and **4l** in Sprague-Dawley (SD) rats, which were treated with these compounds after oral glucose challenge. In this study, compounds **4k** and **4l** reduced the blood glucose level by 62.64 and 78.59 %, respectively, while the standard drug, metformin, lowered the blood glucose level by 57.10 % under similar experimental conditions as shown Table 3. We also estimated the cytotoxicity of **4k** and **4l** against the standard doxorubicin on two cell lines A549 (lung cancer cell line) and HEK-293 (human embryonic kidney cell line) and the results are given in Table 4. The results obtained in this study suggest that the compounds **4k** and **4l** are safer than doxorubicin.

Table 1 Study of PTP1B inhibitory activity of molecule **4a–l**

Compounds	% Inhibition
4a	−29.21
4b	−30.81
4c	−31.54
4d	−24.95
4e	−21.34
4f	−29.29
4g	−17.25
4h	−24.23
4i	−12.68
4j	−19.02
4k	41.62
4l	68.32
Sod. Vandate	60.68

Table 2 PTB1B inhibitor activity (IC_{50}) of compounds **4k** and **4l**

Serial no.	Compound	IC_{50} (µM)
1	**4k**	20.43
2	**4l**	8.61

The compounds **4a–l** contain identical core structure, which is designated as A, B, C, D, and E ring system and they have different groups such as alkyl, aryl, or fluoroalkyl on their E ring (triazole ring). In our study, discouraging results were observed with compounds **4a–j,** which did not act as PTP1B inhibitors, while the compounds **4k** and **4l** showed good PTP-1B inhibitory activity. The

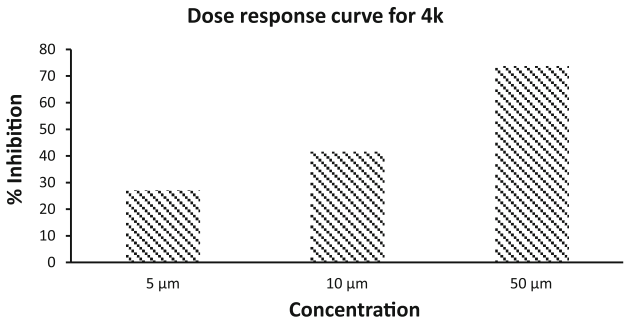


Fig. 1 Dose–response curve for **4k**

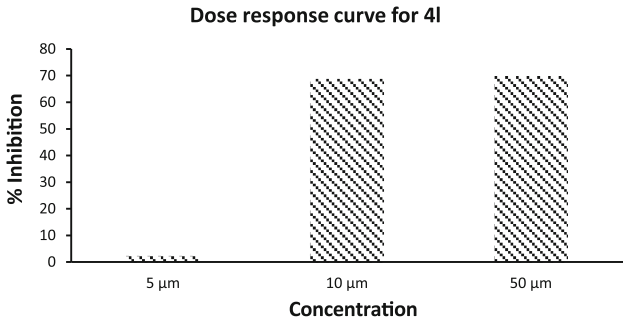


Fig. 2 Dose–response curve for **4l**

Table 3 Blood glucose level after 10 min of oral glucose challenge in SD rats

Compound	Blood glucose level 10 min after oral glucose (mg/dL)	% Inhibition of blood glucose from control
Control	257	–
Metformin	110	57.10
4k	96	62.64
4l	55	78.59

Table 4 Cytotoxicity (IC_{50}) assay of**4k** and **4l**

Compound	IC-50 values (µM) A549- cells	IC-50 values (µM) HEK293-cells
4k	>1,000	>1,000
4l	>1,000	>1,000
Doxorubicin	3.98	1.006

compounds **4k** and **4l** contain 4-CH_3Ph and 4-CF_3Ph as the pendent groups on the E ring of their structures, respectively, and CF_3 and CH_3 groups are known to be bioisosteres (Yamazaki *et al*., 2009). However, in this study, **4l** was found to be substantially more active than **4k** and it could be possibly because CF_3 group is more lipophilic and exhibits better metabolic stability than CH_3 group. However, compound **4c,** which is a structural isomer of **4l** having 3-CF_3Ph functionality on ring E, did not act as a PTP1B inhibitor. This observation suggests that possibly the orientation of CF_3 group in **4l** plays an important role in binding with PTP1B enzyme effectively and thereby inhibiting its activity.

Phosphatase-1B inhibitory assay protein tyrosine

Protein tyrosine phosphatase inhibitory activity was determined according to the modified method of Goldstein *et al*. (2000). As a rat liver is very rich in PTP-1B enzyme, we used rat liver homogenate as a source of protein tyrosine phosphatase 1B. Initially to standardize this method, we used a range of given homogenate (1–10 µL) to find the PTP-1B activity. The test compounds (5–50 µM, 5 µL) were pre-incubated with liver homogenate (3 µL) in 4-(2-hydroxyethyl)-1-piperazine ethanesulfonic acid (HEPES) buffer (total volume 50 µL) for 30 min. Drug assay was performed in a final volume of 200 µL in a test mixture containing 10 mM of *p*-nitro phenyl phosphate (*p*-NPP) in 50 mM HEPES buffer (pH 7.0) and 1 mM DTT. After 10 min of incubation at 37 °C, the reaction was stopped by addition of 50 µL of 0.1 N NaOH and the absorbance was determined at 410 nm. Sodium orthovanadate was taken as a standard for this enzyme assay (Goldstein *et al*., 2000).

In vivo glucose assay

The method described by Goldstein *et al*., (2000) was used for determination of in vivo glucose level after oral glucose challenge in male albino rats of Sprague-Dawley strain, which are having average body weight 250–300 g. The blood glucose level of each animal was checked by glucometer using glucostrips (one touch horizon) after 12 h starvation. Animals of experimental group were administered dimethylsulfoxide (DMSO) solution of the synthetic compounds (50 mg/kg) and metformin (300 mg/kg) through intraperitoneal (i.p.) route. Animal of a control group was given an equal amount of DMSO and 10 min after the administration of test compound, glucose (5 g/kg body wt.) was administered orally to each animal. Blood glucose was measured exactly after 10 min of post administration of the glucose solution by glucometer. Percentage inhibition was calculated from the blood glucose levels of both rats that received 5 g/kg glucose orally in the presence and absence of test compounds, respectively.

Cytotoxicity assay cell line

A549-cells (Human Lung Adenocarcinoma Epithelial Cell Line) and HEK293 cells (Human Embryonic Kidney Cell Line) were purchased from National Centre for Cell Science (NCCS), Pune. Both cell lines were maintained in

Dulbecco's modified Eagle's medium (DMEM, Sigma, USA) containing 10 % heat-inactivated fetal bovine serum (FBS, Lonza), 100 U/mL penicillin, 100 U/mL streptomycin, and 2 mM L-glutamine at 37 °C in a humidified atmosphere of 5 % CO_2. Cells were passaged every 2–3 days to maintain exponential growth.

In vitro cytotoxicity assay

The cytotoxicity of the different compounds (shown below) was studied by means of a colorimetric micro culture assay using MTT(3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide (Botta *et al*., 2007). 1×10^4 cells/well were seeded in 100 µL DMEM, supplemented with 10 % FBS in each well of 96-well micro culture plates and incubated for 24 h at 37 °C in a CO_2 incubator. The desired concentrations of the compounds were made and added to the wells with respective vehicle control. After 24 h of incubation, 10 µL MTT (5 mg/mL) was added to each well and the plates were further incubated for 4 h. Then the supernatant from each well was carefully removed, formazan crystals were dissolved in 100 µL of DMSO, and absorbance was recorded at 540-nm wavelength.

Conclusion

In summary, we prepared a small library of 2-(4-((1-alkyl/aryl-1*H*-1,2,3-triazol-4-yl)methoxy)phenyl)naphtho[1,2-*d*]-oxazoles by an efficient three-step protocol and studied their in vitro and in vivo protein tyrosine phosphatase 1B (PTP1B) inhibitory activity. In this study, two of the compounds **4k** and **4l** were found to exhibit good PTP1B inhibitory activity and low cytotoxicity.

Experimental

The melting points of all the compounds were recorded on Veego melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer FT-IR 240-C spectrophotometer using KBr optics. NMR spectra were obtained using the Bruker Avance 300 MHz and Inova 400 MHz instruments in DMSO-d_6 or $CDCl_3$ using TMS as the internal standard. Electron impact (EI) and chemical ionization (CI) mass spectra were recorded on a VG 7070 H 5 instrument at 70 eV. All high-resolution spectra were recorded on QSTARXL hybrid MS/MS system (Applied Biosystems, USA) under electrospray ionization. All the reactions were monitored by thin-layer chromatography (TLC) on precoated silica gel 60 F254 (mesh); spots were visualized with UV light. Merck silica gel (60–120 mesh) was used for column chromatography.

Typical procedure for the preparation of 2-aryl-naphtho [1,2-*d*]oxazole **2**

2-(2-Hydroxynaphthalen-1-yl)(4-hydroxyphenyl) **1** (1.0 g, 3.78 mmol), acetohydroxamic acid (0.45 g, 5.68 mmol), acetonitrile (5 mL), and conc. H_2SO_4 (catalyst, 0.3 mL) were taken into a 10 mL pressure tube and subjected to microwave heating (CEM discover, 360 W, 80 °C, 25 psi) for 10 min. Next, the reaction mixture was diluted with ethyl acetate (5 mL) and to this saturated sodium bicarbonate solution (5 mL) was added dropwise. The mixture was extracted with ethyl acetate (2×10 mL) and the combined organic layer was washed with saturated NaCl solution, dried over anhy. Na_2SO_4, and concentrated under reduced pressure. Purification of the mixture was performed by normal column chromatography (silica gel 60–120 mesh, ethyl acetate/hexane: 1:10) to obtain 4-(naphtho[1,2-*d*]oxazol-2-yl)phenol **2**(0.43 g, 45 %, m.p. 275–278 °C) and it was characterized by the following spectral data: EI (*m*/*z*) 261 $(M)^+$ IR (KBr, cm^{-1}), 3450, 1610, 1437; ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 6.98 (d, 2H, $J = 8.7$ Hz); 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, –OH); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 111.1 (Ar–C_3), 116.2 (O–Ph–C_3&C_5), 117.7 (O–Ph–C_2&C_6), 121.7 (Ar–C_{10}), 125.5 (Ar–C_9), 125.7 (Ar–C_5), 127.1 (Ar–C_4), 128.8 (Ar–C_7&C_8), 129.1 (Ar–C_6), 131.0 (O–Ar–C_1), 137.07 (Ar–C_1), 147.4 (Ar–C_2), 160.8 (O–Ph–C_4), 162.5 (oxazole–C=N).

Synthesis of 2-(4-(prop-2-yn-1-yloxy)phenyl)-naphtho[1,2-*d*]oxazole **3**

4-(Naphtho[1,2-*d*]oxazole-2-yl)phenol **2** (1.3 g, 4.98 mmol), propargyl bromide (0.89 g, 7.47 mmol), dry acetone (15 mL), and K_2CO_3 (2 g, 14.9 mmol) were taken into a 25 mL round bottomed flask fitted with a condenser and nitrogen balloon. The mixture was refluxed for 4 h and after completion of the reaction (TLC), the reaction mixture was cooled to room temperature and filtered. The filtrate was concentrated under reduced pressure and the crude product was purified by normal column chromatography (silica gel 60–120 mesh, ethyl acetate–hexane: 1:10) to obtain 2-(4-(prop-2-yn-1-yloxy)phenyl)naphtho[1,2-*d*]oxazole **3b** (1.45 g, 98 %, m.p. 117–120 °C) in the form of a white powder. The spectral data obtained for **3b** are as follows: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.49 (s, 1H), 4.73 (s, 2H), 7.04–7.09 (d, $J = 9.0$ Hz, 2H), 7.45–7.50 (t, $J = 7.0$ Hz, 1H), 7.57–7.62 (t, $J = 7.0$ Hz, 1H), 7.63–7.67 (d, $J = 8.0$ Hz, 1H), 7.69–7.73 (d, $J = 8.0$ Hz, 1H), 7.87–7.92 (d, $J = 8.0$ Hz, 1H), 8.21–8.26 (d, $J = 9.0$ Hz, 2H), 8.51–8.55 (d, $J = 9.0$ Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz,): δ 56.1 (OCH_2), 78.8 (acetylene–C_2), 79.7 (acetylene–C_1), 111.4

(Ar–C_3), 116.0 (O–Ph–C_3&C_5), 120.2 (O–Ph–C_2&C_6), 122.1 (Ar–C_{10}), 125.8 (Ar–C_9), 126.1 (Ar–C_5), 127.4 (Ar–C_4), 129.1 (Ar–C_7&C_8), 131.2 (Ar–C_6), 137.2 (Ar–C_1), 147.8 (Ar–C_2), 160.1 (O–Ph–C_4), 162.1 (oxazole–C=N); EI (*m/z*) 299 $(M)^+$; IR (KBr, cm^{-1}): 3350, 2218, 1615, 1435.

Typical procedure for the synthesis of 1,2,3-triazole-functionalized 2-aryl-naphtho[1,2-*d*]oxazoles **4a–l**

2-(4-(Prop-2-yn-1-yloxy)phenyl)naphtho[1,2-*d*]oxazole **3** (50 mg, 0.17 mmol), phenyl azide (30 mg, 0.25 mmol), dry THF (7 mL), and CuI (3 mg, 0.016 mmol) were taken into a 25 mL round bottomed flask fitted with a condenser and nitrogen balloon. The mixture was heated at 50 °C for 6 h and after completion of the reaction (TLC), the reaction mixture was cooled to room temperature and filtered. The filtrate was concentrated under reduced pressure and the crude product obtained was purified by normal column chromatography (silica gel 60–120 mesh, ethyl acetate–hexane: 1:2) to obtain **4a** (65 mg, 93 %, m.p. 189–191 °C) in the form of a white powder.

Characterization data obtained for **4a–l**

*2-(4-((1-Phenyl-1H-1,2,3-triazole-4-yl)phenyl)-naphtho[1,2-d]oxazole (**4a**)*

White powder, Yield (92 %); m.p. 189–191 °C; ^{1}HNMR (DMSO-d_6, 300 MHz): δ 5.37 (s, 2H), 7.29–7.31 (d, $J = 8.0$ Hz, 2H), 7.46–7.49 (t, $J = 7.0$ Hz, 1H), 7.55–7.60 (m, 3H), 7.67–7.70 (t, $J = 7.0$ Hz, 1H), 7.87–7.88 (d, $J = 5.0$ Hz, 2H), 7.90–7.91 (d, $J = 8.0$ Hz, 2H), 8.04–8.06 (d, $J = 8.0$ Hz, 1H), 8.23–8.25 (d, $J = 9.0$ Hz, 2H), 8.44–8.46 (d, $J = 8.0$ Hz, 1H), 8.90 (s, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz,): δ 61.1 (O–CH_2), 110.8 (Ar–C_3), 115.3 (O–Ph–C_3&C_5), 119.5 (triazole–C_2) 119.9 (O–Ph–C_2&C_6),), 121.5 (triazole–Ph–C_2&C_6), 122.7 (Ar–C_{10}), 125.2 (O–Ph–C_1), 125.5 (Ar–C_9), 126.8 (Ar–C_5), 128.5 (triazole–Ph–C_3&C_5), 128.5 (Ar–C_4), 128.7 (Ar–C_7&C_8), 129.6 (Ar–C_6), 130.7 (triazole–ph–C_4), 136.5 (triazole–ph–C_1), 136.8 (Ar–C_1), 143.2 (triazole–C_2), 147.3 (Ar–C_2), 160.4 (O–Ph–C_4), 161.6 (oxazole–C=N); ESI (*m/z*) 419 $([M+H]^+)$; ESI-HRMS: *m/z* obtained for $C_{26}H_{19}N_4O_2$ $([M+H]^+)$: 419.1508 (Calcd. 419.1504).

*2-(4-((1-(4-Methoxyphenyl)-1H-1,2,3-triazol-4yl)methoxy)phenyl)naptho[1,2-d]oxazole (**4b**)*

White powder, Yield (87 %); m.p. 158–162 °C; ^{1}H NMR (DMSO-d_6, 500 MHz): δ 3.86 (s, 3H), 5.35 (s, 2H), 7.01–7.04 (d, $J = 8.6$ Hz, 2H), 7.20–7.23 (d, $J = 8.6$ Hz, 2H), 7.49–7.54 (t, $J = 7.5$ Hz, 1H), 7.61–7.66 (t, $J = 7.5$ Hz, 1H), 7.71–7.73 (d, $J = 9.2$ Hz, 2H), 7.74–7.77 (d, $J = 7.1$ Hz, 2H), 7.94–7.97 (d, $J = 7.9$ Hz, 1H), 8.24–8.27(d, $J = 8.6$ Hz, 2H), 8.42 (s, 1H), 8.48–8.50 (d, $J = 7.7$ Hz, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 28.9 (OCH_3), 61.1 (Ar–OCH_2), 110.3 (Ar–C_3), 113.8 (triazole–Ar–C_3&C_5), 114.2 (O–Ph–C_3&C_5), 114.8 (O–Ph–C_2&C_6), 119.6 (triazole–C_2), 121.3 (triazole–Ph–C_2&C6), 121.5 (O–Ph–C_1), 121.9 (Ar–C_{10}), 124.7 (Ar–C_5), 125.7 (Ar–C_4), 128.1 (Ar–C_9), 128.4 (Ar–C_6), 28.5 (Ar–C_7&C_8), 129.2 (O–Ph–C_1), 129.8 (triazole–Ar–C_1), 130.5 (triazole–C_1), 142.8 (nap–C_1), 143.5 (nap–C_2), 155.4 (O–Ar–C_4), 159.04 (triazole–Ar–C_4), 160.2 (oxazole–C=N); ESI (*m/z*) 449 $([M+H]^+)$; ESI-HRMS: *m/z* obtained for $C_{27}H_{21}N_4O_3$ $([M+H]^+)$: 449.1467 (Calcd. 449.1454).

*2-(4-((1-(3-(Trifluoromethyl)phenyl)-1H-1,2,3-triazol-4-yl)methoxy)phenyl)naphtho[1,2-d]oxazole (**4c**)*

White powder, Yield (93 %); m.p. 185–189 °C; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 5.38 (s, 2H), 7.27–7.29 (d, $J = 8.6$ Hz, 2H), 7.52–7.57 (t, $J = 7.3$ Hz, 1H), 7.64–7.69 (t, $J = 7.7$ Hz, 1H), 7.83–7.84 (d, $J = 4.1$ Hz, 2H), 8.00–8.03 (d, $J = 8.1$ Hz, 1H), 8.23–8.24 (d, $J = 8.6$ Hz, 2H), 8.25–8.28 (d, $J = 5.6$ Hz, 2H), 8.44–8.47 (d, $J = 8.1$ Hz, 1H), 9.08 (s, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz,): δ 61.1 (OCH_2), 110.8 (Ar–C_3), 115.4 (O–Ph–C_3&C_4), 116.6 (O–Ph–C_2&C_6), 119.4 (triazole–C_1), 121.2 (triazole–Ar–C_2), 123.2 (Ar–C_{10}), 123.8 (O–Ph–C_1), 125.0 (Ar–C_9), 125.2 (triazole–Ar–C_4), 125.5 (Ar–C_5), 126.9 (Ar–C_4), 128.5 (Ar–C_6), 128.7 (Ar–C_7&C_8), 130.7 (triazole–Ar–C_1), 131.0 (triazole–Ar–C_3), 132.7 (triazole–Ar–C_5), 136.7 (Ar–CF_3), 136.8 (triazole–C_1), 143.6(Ar–C_1), 147.2 (Ar–C_2), 160.4 (O–Ph–C_4), 161.6 (oxazole–C=N); ESI (*m/z*) 486 $([M+H]^+)$; ESI-HRMS: *m/z* obtained for $C_{27}H_{17}N_4O_2F_3Na$ $([M+Na]^+)$: 509.1201 (Calcd. 509.1191).

*2-(4-((1-(3-Chlorophenyl)-1H-1,2,3-triazol-4yl)methoxyphenyl)naptho[1,2-d]oxazole (**4d**)*

White powder, Yield (98 %); m.p. 144–148 °C; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 5.36 (s, 2H), 7.20–7.21 (d, $J = 8.0$ Hz, 2H), 7.40–7.41 (d, $J = 7.0$ Hz, 1H), 7.49–7.52 (m, 1H), 7.61–7.64 (t, $J = 8.0$ Hz, 1H), 7.71–7.73 (d, $J = 9.0$ Hz, 1H), 7.76–7.78 (d, $J = 9.0$ Hz, 1H), 7.80–8.82 (d, $J = 8.0$ Hz, 1H), 7.93–7.95 (d, $J = 7.0$ Hz, 2H), 8.24–8.26 (d, $J = 8.0$ Hz, 2H), 8.48–8.50 (d, $J = 8.0$ Hz, 1H), 8.64 (s, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz,): δ 61.3 (OCH_2), 111.3 (Ar–C_3), 114.8 (O–Ph–C_3&C_5), 115.4 (O–ph–C_2&C_6), 119.2 (triazole–C_2), 121.2 (triazole–Ar–C_5), 121.6 (triazole–Ar–C_6), 122.5 (triazole–Ar–C_2), 122.7 (O–Ph–C_1), 123.6 (Ar–C_{10}), 124.0 (Ar–C_9), 125.7 (Ar–C_5), 126.0 (Ar–C_4&C_6), 127.4 (Ar–C_7&C_8), 129.3 (triazole–Ar–C_4), 131.1 (triazole–Ar–C_3), 135.2 (triazole–Ar–C_1), 140.3 (Ar–C_1), 143.7 (triazole–C_2), 148.9 (Ar–C_2), 160.4

(O–Ph–C_4), 161.6 (oxazole–C=N); ESI (*m/z*) 553 ($[M+H]^+$); ESI-HRMS: *m/z* obtained for $C_{26}H_{18}N_4O_2Cl$ ($[M+H]^+$): 553.1408 (Calcd. 553.1395).

*2-(4-((1-(3-Chloro-4-fluorophenyl)-1H-1,2,3-triazol-4yl)methoxy)phenyl)naptho[1,2-d]oxazole (**4e**)*

(White powder, 96 %, m.p. 193–196 °C): ^{1}H NMR (DMSO-d_6, 300 MHz): δ 5.40 (s, 2H), 7.33–7.35 (d, J = 8.8 Hz, 2H), 7.59–7.62 (t, J = 7.8 Hz, 1H), 7.67–7.69 (d, J = 8.8 Hz, 1H), 7.71–7.74 (t, J = 7.8 Hz, 1H), 7.96 (s, 1H), 7.97–8.01 (m, 3H), 8.11–8.12 (d, J = 7.8 Hz, 1H), 8.24–8.25 (d, J = 8.8 Hz, 2H), 8.44–8.45 (d, J = 7.8 Hz, 1H), 9.03 (s, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz,): δ 61.4 (OCH_2), 111.3 (Ar–C_3), 115.1 (O–Ph–C_3&C_5), 118.2 (O–Ph–C_2&C_6), 121.2 (triazole–C_2), 121.5 (Ar–C_9), 121.7 (triazole–Ar–C_3), 122.0 (Ar–C_{10}), 122.7 (O–Ph–C_1), 123.6 (triazole–Ar–C_5), 125.7 (Ar–C_5), 126.0 (Ar–C_4&C_6), 127.4 (Ar–C_7&C_8), 129.1 (triazole–Ar–C_2), 131.0 (triazole–Ar–C_1), 140.1 (Ar–C_1), 143.8 (triazole–C_1), 148.8 (Ar–C_2), 158.3 (O–Ph–C_4), 160.7 (triazole–Ar–C_4), 162.5 (oxazole–C=N); ESI (*m/z*) 471 ($[M+H]^+$); ESI-HRMS: *m/z* obtained for $C_{26}H_{17}N_4O_2FCl$ ($[M+H]^+$): 471.1205 (Calcd. 471.1201).

*2-(4-((1-(2,4-Difluorophenyl)-1H-1,2,3-triazol-4yl)methoxy)phenyl)naptho[1,2-d]oxazole (**4f**)*

White powder, Yield (95 %); m.p. 151–155 °C; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 5.37 (s, 2H), 7.24–7.26 (d, J = 8.8 Hz, 2H), 7.33–7.38 (m, 1H), 7.52–7.55 (t, J = 7.9 Hz, 1H), 7.63–7.66 (t, J = 7.9 Hz, 1H), 7.77–7.79 (d, J = 8.8 Hz, 1H), 7.81–7.83 (d, J = 8.8 Hz, 1H), 7.89–7.91 (d, J = 8.8 Hz, 1H), 7.92–7.94 (d, J = 7.9 Hz, 1H), 7.98–8.01 (d, J = 8.8 Hz, 1H), 8.23–8.25 (d, J = 8.8 Hz, 2H), 8.45–8.47 (d, J = 7.9 Hz, 1H), 8.51 (s, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz,): δ 61.01 (OCH_2), 111.1 (Ar–C_3), 112.8 (O–Ph–C_2&C_6), 115.5 (O–Ph–C_3&C_5), 119.4 (triazole–C_2), 121.5 (Ar–C_{10}), 124.3 (Ar–C_9), 125.4 (triazole–Ar–C_2&C_5), 125.6 (triazole–Ar–C_6), 125.7 (Ar–C_5), 126.5 (Ar–C_4), 127.1 (Ar–C_6), 127.6 (Ar–C_7&C_8), 128.8 (O–Ph–C_1), 130.8 (triazole–Ar–C_1), 136.7 (Ar–C_1), 142.8 (triazole–C_2), 145.9 (Ar–C_2), 147.4 (triazole–Ar–C_3&C_4), 160.5 (O–Ph–C_4), 161.7 (oxazole–C=N); ESI (*m/z*) 455 ($[M+H]^+$); ESI-HRMS: *m/z* obtained for $C_{26}H_{17}N_4O_2F_2$ ($[M+H]^+$): 455.2137 (Calcd. 455.2134).

*2-(4-((1-Butyl)-1H-1,2,3-triazol-4yl)methoxy)-phenyl)naptho[1,2-d]oxazole (**4g**)*

White powder, Yield (90 %); m.p. 114–117 °C; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 0.86–0.89 (t, J = 6.1 Hz, 3H), 0.92–1.85 (m, 4H), 4.34–4.37 (t, J = 7.1 Hz, 2H), 5.38 (s, 2H), 7.17–7.19 (d, J = 9.2 Hz, 2H), 7.50–7.53 (t, J = 7.1 Hz, 1H), 7.62–7.65 (t, J = 7.1 Hz, 1H), 7.73–7.75 (d, J = 9.2 Hz, 1H), 7.77–7.78 (d, J = 9.2 Hz, 1H), 7.94 (s, 1H), 7.95–7.97 (d, J = 9.2 Hz, 1H), 8.21–8.23 (d, J = 9.2 Hz, 2H), 8.47–8.48 (d, J = 8.1 Hz, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz,): δ 13.6 (CH_3), 20.3 (CH_2), 29.5 (CH_2), 48.2 (CH_2–N), 61.2 (OCH_2), 110.8 (Ar–C_3), 115.3 (O–Ph–C_3&C_5), 119.5 (O–Ph–C_2&C_6), 119.9 (triazole–C_2), 121.5 (Ar–C_{10}), 122.7 (Ar–C_9), 125.2 (O–Ph–C_1), 125.5 (Ar–C_5), 126.8 (Ar–C_4), 128.2 (Ar–C_6), 128.5 (Ar–C_7), 128.7 (Ar–C_8), 136.8 (Ar–C_1), 143.2 (triazole–C_1), 147.3 (Ar–C_2), 160.4 (O–Ph–C_4), 161.6 (oxazole–C=N); ESI (*m/z*) 399 ($[M+H]^+$); ESI-HRMS: *m/z* obtained for $C_{24}H_{23}N_4O_2$ ($[M+H]^+$): 399.1743 (Calcd. 399.1737).

*2-(4-((1-Hexyl-1H-1,2,3-triazol-4yl)methoxy)phenyl)naptho[1,2-d]oxazole (**4h**)*

White powder, Yield (92 %); m.p. 109–112 °C; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 0.86–0.89 (t, J = 6.1 Hz, 3H), 1.28–1.35 (m, 6H), 1.86–1.90 (m, 2H), 4.34–4.37 (t, J = 7.1 Hz, 2H), 5.26 (s, 2H), 7.17–7.19 (d, J = 9.2 Hz, 2H), 7.50–7.53 (t, J = 7.1 Hz, 1H), 7.62–7.65 (t, J = 7.1 Hz, 1H), 7.73–7.75 (d, J = 9.2 Hz, 1H), 7.77–7.78 (d, J = 9.2 Hz, 1H), 7.94 (s, 1H), 7.95–7.97 (d, J = 9.2 Hz, 1H), 8.21–8.23 (d, J = 9.2 Hz, 2H), 8.47–8.48 (d, J = 8.1 Hz, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz,): δ 14.1 (CH_3), 22.8 (CH_2), 26.5 (CH_2), 28.4 (CH_2), 31.6 (CH_2–N), 61.0 (OCH_2), 110.8 (Ar–C_3), 114.3 (O–Ph–C_3&C_5), 119.5 (O–Ph–C_2&C_6), 120.1 (Ar–C_{10}), 123.8 (Ar–C_9), 125.0 (O–Ph–C_1), 125.3 (Ar–C_5), 126.5 (Ar–C_4), 127.3 (Ar–C_6), 136.5 (Ar–C_1), 142.3 (triazole–C_1), 147.2 (Ar–C_2), 60.3 (O–Ph–C_4), 161.5 (oxazole–C=N); ESI (*m/z*) 427 ($[M+H]^+$); ESI-HRMS: *m/z* obtained for $C_{26}H_{27}N_4O_2$ ($[M+H]^+$): 427.2137 (calcd. 427.2134).

*n2-(4-((1-(3,3,4,4,5,5,6,6,7,7,8,8-Tridecafluorooctyl)-1H-1,2,3-triazol-4yl)methoxy)phenyl)naptho [1,2-d]oxazole (**4i**)*

White powder, Yield (87 %); m.p. 153–157 °C; ^{1}H NMR (DMSO-d_6, 500 MHz): δ 2.83–2.88 (m, 2H), 4.73–4.76 (t, J = 7.9 Hz, 2H), 5.28 (s, 2H), 7.15–7.17 (d, J = 8.9 Hz, 2H), 7.49–7.52 (t, J = 7.9 Hz, 1H), 7.61–7.64 (t, J = 7.9 Hz, 1H), 7.70–7.72 (d, J = 8.9 Hz, 1H), 7.75–7.77 (d, J = 8.9 Hz, 1H), 7.93–7.95 (d, J = 7.9 Hz, 1H), 8.09 (s, 1H), 8.23–8.25 (d, J = 8.9 Hz, 2H), 8.48–8.50 (d, J = 7.9 Hz, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz,): δ 34.3 (CH_2), 37.4 (CH_2–N), 61.0 (OCH_2), 109.0 (CF_2), 111.1 (Ar–C_3), 112.8 (CF_2), 115.5 (O–Ph–C_3&C_5), 117.5 (CF_2), 118.2 (CF_3), 119.4 (O–Ph–C_2&C_6), 121.5 (triazole–C_2), 122.3 (Ar–C_{10}), 125.4 (O–Ph–C_1), 125.6 (Ar–C_9), 125.7 (Ar–C_5), 126.5 (Ar–C_4), 127.1 (Ar–C_6), 127.6 (Ar–C_7), 128.7 (Ar–C_8), 136.7 (Ar–C_1), 142.8 (triazole–C_1), 147.4

(Ar–C_2), 160.5 (O–Ph–C_4), 161.7 (oxazole–C=N); ESI (*m/z*) 689 ($[M+H]^+$); ESI-HRMS: *m/z* obtained for $C_{28}H_{18}N_4O_2F_{13}$($[M+H]^+$): 689.1222 (Calcd. 689.1219).

*2-(4-((1-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-Heptadecafluorodecyl)-1H-1,2,3-triazol-4yl)methoxy)phenyl)naptho[1,2-d]oxazole (**4j**)*

White powder, Yield (93 %); m.p. 158–162 °C; ^{1}H NMR (DMSO-d_6, 500 MHz): δ 2.81–2.99 (m, 2H), 4.71–4.75 (t, $J = 6.7$ Hz, 2H), 5.20 (s, 2H), 7.21–7.24 (d, $J = 8.1$ Hz, 2H), 7.48–7.55 (t, $J = 6.9$ Hz, 1H), 7.61–7.67 (t, $J = 6.6$ Hz, 1H), 7.74–7.77 (d, $J = 8.8$ Hz, 1H), 7.79–7.82 (d, $J = 8.8$ Hz, 1H), 7.92 (s, 1H), 7.96–7.99 (d, $J = 7.7$ Hz, 1H), 8.23–8.26 (d, $J = 8.3$ Hz, 2H), 8.47–8.49 (d, $J = 8.1$ Hz, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz,): δ 34.0 (CH_2), 37.3 (CH_2–N), 61.0 (OCH_2), 111.1 (O–Ph–C_3&C_5), 112.8 (CF_2), 114.5 (CF_2), 118.9 (O–Ph–C_2&C_6), 120.0 (CF_3), 121.5 (triazole–C_2), 122.1 (Ar–C_{10}), 125.4 (O–Ph–C_1), 125.4 (Ar–C_9), 126.5 (Ar–C_5), 127.6 (Ar–C_4), 128.7 (Ar–C_6), 128.8 (Ar–C_7), 130.8 (Ar–C_8), 136.7 (Ar–C_1), 142.8 (triazole–C_1), 147.4 (Ar–C_2), 160.2 (O–Ph–C_4), 161.5 (oxazole–C=N); ESI (*m/z*) 789 ($[M+H]^+$); ESI-HRMS: *m/z* obtained for $C_{30}H_{18}N_4O_2F_{17}$ ($[M+H]^+$): 789.1231 (Calcd. 789.1223).

*2-(4-((1-p-Tolyl-1H-1,2,3-triazol-4yl)methoxy)-phenyl)naptho[1,2-d]oxazole (**4k**)*

White powder, Yield (97 %); m.p. 180–183 °C; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 2.43 (s, 3H), 5.35 (s, 2H), 7.20–7.21 (d, $J = 8.0$ Hz, 2H), 7.31–7.32 (d, $J = 8.0$ Hz, 2H), 7.49–7.52 (t, $J = 8.0$ Hz, 1H), 7.61–7.64 (t, $J = 8.0$ Hz, 1H), 7.68–7.70 (d, $J = 8.0$ Hz, 2H), 7.71–7.73 (d, $J = 9.0$ Hz, 1H), 7.76–7.78 (d, $J = 9.0$ Hz, 1H), 7.93–7.95 (d, $J = 8.0$ Hz, 1H), 8.24–8.26 (d, $J = 9.0$ Hz, 2H), 8.42 (s, 1H), 8.48–8.50 (d, $J = 8.0$ Hz, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz,): δ 19.1 (Ar–CH_3), 59.7 (OCH_2), 109.0 (Ar–C_3), 113.5 (O–Ph–C_3&C_5), 118.4 (O–Ph–C_2&C_6), 120.1 (triazole–C_2), 120.6 (Ar–C_{10}), 123.4 (Ar–C_9), 123.7 (O–Ph–C_1), 124.3 (Ar–C_5), 125.0 (Ar–C_4), 126.8 (Ar–C_6), 127.1 (Ar–C_7&C_8), 128.3 (triazole–Ar–C_3&C_5)), 129.2 (triazole–Ar–C_2&C_6), 135.5 (triazole–Ar–C_4), 136.5 (Ar–C_1), 141.6 (triazole–C_1), 142.4 (Ar–C_2), 158.9 (O–Ph–C_4), 160.1 (oxazole–C=N); ESI (*m/z*) 433 ($[M+H]^+$); ESI-HRMS: *m/z* obtained for $C_{27}H_{21}N_4O_2$ ($[M+H]^+$): 433.1664 (Calcd. 433.1658).

*2-(4-((1-(4-(Trifluoromethyl)phenyl)-1H-1,2,3-triazol-4yl)methoxy)phenyl)naptho[1,2-d]oxazole (**4l**)*

White powder, Yield (95 %); m.p. 199–202 °C; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 5.42 (s, 2H), 7.34–7.36 (d, $J = 9.0$ Hz, 2H), 7.59–7.62 (t, $J = 7.0$ Hz, 1H), 7.71–7.74 (t, $J = 7.0$ Hz, 1H), 7.96 (s, 1H), 8.00–8.02 (d, $J = 8.0$ Hz, 2H), 8.11–8.13 (d, $J = 8.0$ Hz, 1H), 8.19–8.21 (d, $J = 8.0$ Hz, 2H), 8.24–8.26 (d, $J = 9.0$ Hz, 2H), 8.44–8.45 (d, $J = 8.0$ Hz, 1H), 9.15 (s, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz,): δ 61.1 (OCH_2), 110.8 (Ar–C_3), 115.4 (O–Ph–C_3&C_5), 116.6 (O–Ph–C_2&C_6), 119.4 (triazole–C_2), 121.4 (Ar–C_{10}), 123.1 (O–Ph–C_1), 123.8 (triazole–Ar–C_3&C_5), 125.0 (Ar–C_5), 125.2 (Ar–C_9), 125.5 (Ar–C_4), 126.9 (Ar–C_6), 128.5 (Ar–C_7), 128.7 (Ar–C_8), 130.7 (triazole–C_2&C_6), 131.0 (triazole–Ar–C_1), 132.7 (Ar–C_1), 136.7 (triazole–Ar–C_4), 136.8 (Ar–CF_3), 143.6 (triazole–C_1), 147.2 (Ar–C_2), 160.4 (O–Ph–C_4), 161.6 (oxazole–C=N); ESI (*m/z*) 486 ($[M+H]^+$); ESI-HRMS: *m/z* obtained for $C_{27}H_{17}N_4O_2F_3Na$ ($[M+Na]^+$): 509.1191 (Calcd. 509.1201).

Acknowledgments Authors are thankful to the Director, IICT for the encouragement and support. NC is thankful to UGC, New Delhi for the award of SRF; and AK is thankful to CSIR, New Delhi for the award of SRF. SKB is thankful to DBT for the financial support (Project No. BT/HRD/35/02/09/2008).

References

Adams DR, Abraham A, Asano J, Breslin C, Dick CAJ, Ixkes U, Johnston BF, Johnston D, Kewnay J, Mackay SP, MacKenzie SJ, McFarlane M, Mitchell L, Spinks D, Takano Y (2007) 2-Aryl-3,3,3-trifluoro-2-hydroxypropionic acids: a new class of protein tyrosine phosphatase 1B inhibitors. Bioorg Med Chem Lett 17:6579–6583

Bialy L, Waldmann H (2005) Inhibitors of protein tyrosine phosphatases: next-generation drugs. Angew Chem Int Ed 44:3814–3839

Botta M, Armaroli S, Castagnolo D, Fontana G, Perad P, Bombardelli E (2007) Synthesis and biological evaluation of new taxoids derived from 2-deacetoxytaxinine. Bioorg Med Chem Lett 17:1579–1583

Elchebly M, Payette P, Michaliszyn E, Cromlish W, Collins S, Loy AL, Normandin A, Cheng J, Himms-Hagen CC, Chan C, Ramachandran MJ, Gresser ML, Tremblay D, Kennedy BP (1999) Increased insulin sensitivity and obesity resistance in mice lacking the protein tyrosine phosphatase-1B gene. Science 283:1544–1548

Goldstein BJ, Bittner-Kowalezyk A, White MF, Harbeck M (2000) Tyrosine dephosphorylation and deactivation of insulin receptor substrate-1 by protein-tyrosine phosphatase 1B. J Biol Chem 275:4283–4289

Huisgen R (1984) 1,3-Dipolar cycloadditions—introduction, survey, mechanism. In: Padwa A (ed) 1,3-Dipolar cycloaddition chemistry. Wiley, New York, pp 1–176

Ibrahimi OA, Wu L, Zhao K, Zhang ZY (2000) Synthesis and characterization of a novel class of protein tyrosine phosphatase inhibitors. Bioorg Med Chem Lett 10:457–460

Kennedy BP, Ramachandran C (2000) Protein tyrosine phosphatase-1B in diabetes. Biochem Pharmacol 60:877–883

King H, Aubert R, Herman W (1998) Global burden of diabetes, 1995–2025 prevalence, numerical estimates, and projections. Diabetes Care 21:1414–1431

Montalibet J, Kennedy BP (2005) Therapeutic strategies for targeting h-PTP 1B in diabetes. Drug Discov Today Ther Strateg 2:129–135

Popov D (2011) Novel protein tyrosine phosphatase 1B inhibitors: interaction requirements for improved intracellular efficacy in type 2 diabetes mellitus and obesity control. Biochem Biophys Res Commun 410:377–388

Shim YS, Kim KC, Chi DY, Lee KH, Cho H (2003) Formylchromone derivatives as a novel class of protein tyrosine phosphatase 1B inhibitors. Bioorg Med Chem Lett 13:2561–2563

Sridhar M, Narsaiah C, Sairam VV, Kondal Reddy G, Raveendra J, Kishore Kumar Reddy M, China Ramanaiah B (2011) Microwave-assisted efficient one-step synthesis of amides from ketones and benzoxazoles from (2-hydroxyaryl) ketones with acetohydroxamic acid using sulfuric acid as the catalyst. Tetrahedron Lett 52:6103–6107

Srinivasan R, Uttamchandani M, Yao SQ (2006) Rapid assembly and in situ screening of bidentate inhibitors of protein tyrosine phosphatises. Org Lett 8:713–716

Taha MO, Bustanji Y, Al-Bakri AG, Yousef AM, Zalloum WA, Al-Masri IM, Atallah N (2007) Discovery of new potent human protein tyrosine phosphatase inhibitors via pharmacophore and QSAR analysis followed by in silico screening. J Mol Graph Model 25:870–884

Tjernberg A, Halle′n D, Schultz J, James S, Benkestock K, Bystrom S, Weigelt X (2004) Mechanism of action of pyridazine analogues on protein tyrosine phosphatase 1B (PTP1B). Bioorg Med Chem Lett 14:891–895

Van Huijsduijnen RH, Bombrun A, Swinnen D (2002) Selecting protein tyrosine phosphatises as drug targets. Drug Discov Today 7:1013–1019

Vats RK, Kumar V, Kothari A, Mital A, Ramachandran U (2005) Emerging targets for diabetes. Curr Sci 88:241–249

Xie J, Tian J, Su L, Huang M, Zhu X, Ye F, Wan Y (2011) Pyrrolo[2,3-*c*]azepine derivatives: a new class of potent protein tyrosine phosphatase 1B inhibitors. Bioorg Med Chem Lett 21:4306–4309

Yamazaki T, Taguchi T, Ojima I (2009) Unique properties of fluorine and their relevance to medicinal chemistry and chemical biology. In: Ojima I (ed) Fluorine in medicinal chemistry and chemical biology. Wiley, Chichester, pp 3–46

Ye D, Zhang Y, Wang F, Zheng M, Zhang X, Luo X, Shen X, Jiang H, Liu H (2010) Novel thiophene derivatives as PTP1B inhibitors with selectivity and cellular activity. Bioorg Med Chem Lett 18:1773–1782

Youngren JF, Goldfine ID (1997) The molecular basis of insulin resistance. Sci Med 4:18–27