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Discovery of novel and potent heterocyclic carboxylic acid derivatives as protein tyrosine phosphatase 1B inhibitors

Sujay Basu [a,b,*], Uppuleti Viplava Prasad [b], Dinesh A. Barawkar [a], Siddhartha De [a], Venkata P. Palle [a], Suraj Menon [a], Meena Patel [a], Sachin Thorat [a], Umesh P. Singh [a], Koushik Das Sarma [a], Yogesh Waman [a], Sanjay Niranjan [a], Vishal Pathade [a], Ashwani Gaur [a], Satyanarayana Reddy [a], Shariq Ansari [a]

[a] Drug Discovery Facility, Advinus Therapeutics Ltd, Quantum Towers, Plot-9, Phase-I, MIDC, Hinjewadi, Pune 411057, India
[b] Department of Organic Chemistry, Andhra University, Visakhapatnam 530003, India

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ABSTRACT

A series of novel heterocyclic carboxylic acid based protein tyrosine phosphatase 1B (PTP1B) inhibitors with hydrophobic tail have been synthesized and characterized. Structure–activity relationship (SAR) optimization resulted in identification of several potent, selective (over the highly homologous T-cell protein tyrosine phosphatase, TCPTP) and metabolically stable PTP1B inhibitors. Compounds **7a**, **19a** and **19c** showed favorable cell permeability and pharmacokinetic properties in mouse with moderate to very good oral (% F = 13–70) bio-availability.

Type 2 diabetes (T2D) and obesity have emerged as major health care burden around the world. Insulin resistance has been established as a key defect in progression to and maintenance of T2D. Major current pharmacotherapies for T2D include sulfonylureas, metformin, thiazolidinediones (PPARγ agonist[1]), gliptins (DPPIV inhibitors) and liragutide (GLP-1 agonist). These pharmacotherapies have their own limitations with respect to their efficacy or side effects like nausea, diarrhea, hypoglycemia, weight gain, fluid retention and cardiovascular complications.[2] This makes discovery of new and safe treatments essential for T2D. PTP1B plays an important role in insulin receptor signaling.[3] PTP1B is an intracellular protein tyrosine phosphatase expressed in insulin responsive tissues including the classical insulin targeted tissues such as liver, muscle and fat.[4] PTP1B dephosphorylates the insulin receptor during its biosynthesis in endoplasmic reticulum as well as after it has been stimulated by the insulin and thus play a central role in negative regulation of insulin signaling pathway.[5] Recent evidence suggest that PTP1B is also involved in negative regulation of leptin signaling by inhibiting phosphorylation of JAK2, which attenuates leptin signaling in vivo.[6] Studies from two independent groups have shown that mice that lack the PTP1B gene have improved insulin sensitivity with resistance to weight gain and reduced plasma glucose on a high fat diet.[7] This unique combination of desired attributes has driven an intense search for PTP1B inhibitors for treatment of both, T2D and obesity. Reduced PTP1B levels by the use of specific antisense oligonucleotide (ISIS-113715, Phase 2, discontinued) in db/db and ob/ob mouse further reinforce the potential of this target.[8] Over the past several years, a considerable amount of efforts has been put in discovering PTP1B inhibitors for beneficial effect in T2D and obesity patients.[9] Most of the small PTP1B inhibitors bear highly charged phosphonates[10] or multiple acid and peptide functionalities.[11] These inhibitors show poor cell permeability and oral bioavailability due to presence of negatively charged polar residues. Our goal was to discover novel, potent, cell permeable and orally bio-available PTP1B inhibitors by designing low molecular weight, non-phosphonate and mono carboxylic acid phosphotyrosyl (*p*Tyr) mimetics inhibitors based on known literature compounds **I** and **II** (Fig. 1). Recently heterocyclic carboxylic acid derivatives have been reported as a new *p*Tyr surrogate.[12] The oral bio-availability of compound **I** in rats is only 13% and demonstrated in vivo efficacy.[10a] The compound **II** shows moderate cellular permeability ($P_{app} > 1 \times 10^{-6}$ cm/s) in a Caco-2 cell membrane assay and good selectivity over the TCPTP (K_i = 164 μM).[13] Structural hybridization of compound **I** and **II** was carried out with the view that (i) to lower the negative charge of compound **I** by replacing difluoromethylene phosphonate (DFMP) head group by isoxazole carboxylic acid employed in **II**, as shown in **7a**, (ii) by replacing flexible extended methyleneoxy linker of compound **II**

* Corresponding author. Tel.: +91 20 66539600; fax: +91 20 66539620.
E-mail address: sujay.basu@advinus.com (S. Basu).

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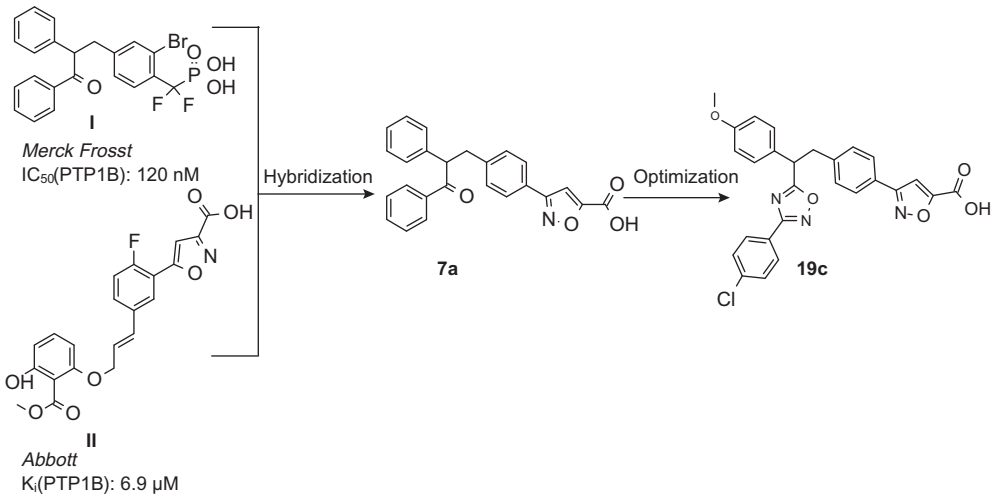


Figure 1. Structure of PTP1B inhibitors.

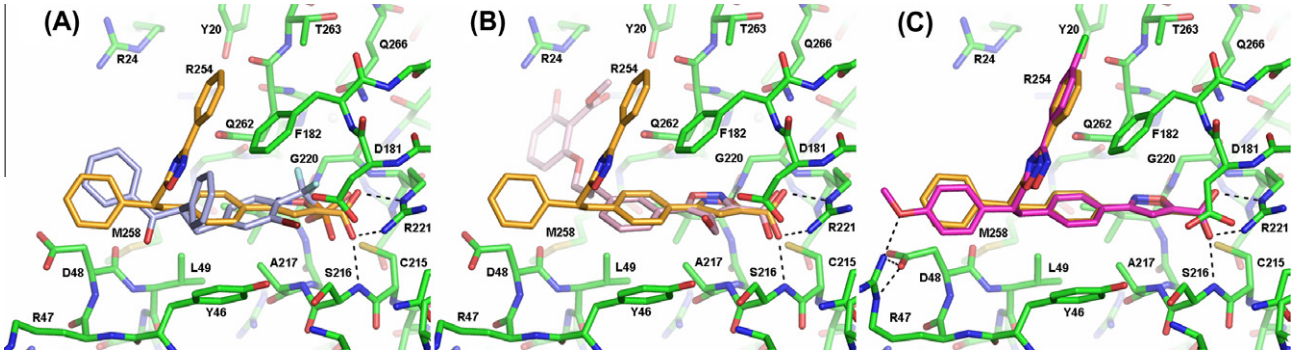


Figure 2. The docked pose of compound **19a** (bright orange) overlayed (A) with co-crystal structure of compound **I** (light blue) from pdb id 3CWE, (B) with co-crystal structure of compound **II** (light pink) from pdb id 1XBO and (C) with docked posed of **19c** (magenta). The protein structure from pdb id 3CWE was used for docking and is shown in green. The oxygen (O), nitrogen (N) and chlorine (Cl) atoms are colored in red, blue and green respectively. Docking was done using program GOLD. The docked poses of compounds were further minimized using program MOE. The putative hydrogen bonds are shown by dotted line. The atomic numbering used here is from pdb id 1XBO.

with rigid oxadiazole linker as shown **19a** in order to make molecule rigid and thus more preorganized for binding to PTP1B. Herein we report a series of heterocyclic carboxylic acid derivatives as PTP1B inhibitors that led to discovery of compound **19c** with improved pharmacokinetic profile.

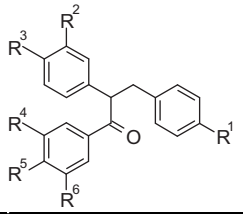
Molecular modeling was used to understand the binding mode of proposed compounds. Figure 2 shows compound **19a** docked into active site of PTP1B (pdb id 3CWE) along with ligands from pdb id 3CWE and pdb id 1XBO (Fig. 2A and B, respectively). The model exhibited that the isoxazole carboxylic acid of **19a** used to replace DFMP head group of compound **I** provided the desired complementarity for recognition by active site by providing hydrogen bond acceptor for backbone amide nitrogen of Ser216 and ionic interaction for side chain of Arg221 (Fig. 2A), similar to the carboxylic acid of compound **II** observed in crystal structure of 1XBO (Fig. 2B). The central phenyl ring shows π–π interaction with Tyr46. Replacement of flexible and extended methyleneoxy linker by rigid oxadiazole bearing terminal phenyl group in **19a** brings additional recognition element of π–π interaction with Phe182 (Fig. 2A and B) this particular interaction was not possible either with **I** or **II**. Compound **19c** (Fig. 2C) may be showing better activity due to extra putative hydrogen bonding interaction between it's methoxy group of terminal phenyl and Arg47 of PTP1B as well as increased hydrophobic interaction between inhibitors –Cl atom with the nearby hydrophobic pocket of the protein (Fig 2C).

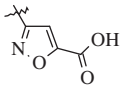
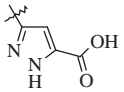
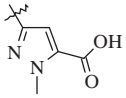
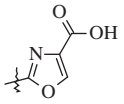
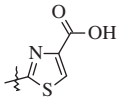
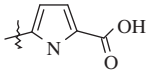
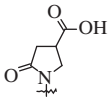
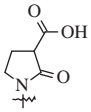
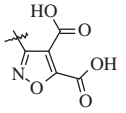
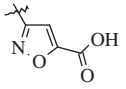
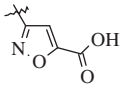
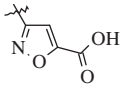
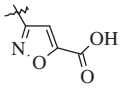
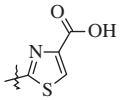
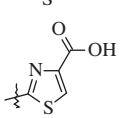
Initial SAR efforts were focused on the optimization of heterocycles containing carboxylic acid moiety as a head group, that involved replacement of DFMP group of **I** and retaining 1,2-diphenyl ethanone linker. The synthesis of target compounds **7a–h** (Table 1) involved typical synthesis of key benzyl bromide intermediates **4a–h** (Scheme 1) and is outlined in Scheme 2. The starting materials **1a–e**, **1g–h** and **2** were prepared by literature procedures.[14] Compound **2** was treated with 4-(hydroxymethyl)phenylboronic acid under Suzuki condition[15] to obtain benzyl alcohol derivative **3** which was converted to corresponding key benzyl bromide **4f** using PBr_3. Compound **1a–e** and **1g–h** were converted to corresponding key benzyl bromide intermediates (**4a–e**, **4g–h**) using *N*-bromosuccinimde (NBS) in refluxing benzene. Benzyl bromide (**4a–h**) derivative thus synthesized was treated with commercially available 1,2-diphenyl ethanone (**5**) using sodium hydride (NaH) as base in *N,N*-dimethylformamide (DMF) at temperature 10–15 °C to obtain **6a–h** (Scheme 2) which upon hydrolysis with (1 N) NaOH at room temperature provided target compound **7a–h** in overall good yields.

To further examine role of various substitutions on both the phenyl rings of 1,2-diphenyl ethanone linker with isoxazole and thiazole carboxylic acid as head group, target compounds **12a–d** and **14c–d** (Table 1) were synthesized as illustrated in Scheme 3.

Commercially available phenyl acetic acid derivatives **8a–d** were converted to corresponding Weinreb amides **9a–d** using

Table 1
Optimization of heterocycle and 1,2-diphenyl ethanone analogs as PTP1B inhibitors



Compd	R^2	R^3	R^4	R^5	R^6	R^1	K_i (μM)
7a	H	H	H	H	H		1.1
7b	H	H	H	H	H		16.3
7c	H	H	H	H	H		7.8
7d	H	H	H	H	H		7.8
7e	H	H	H	H	H		1.2
7f	H	H	H	H	H		2.9
7g	H	H	H	H	H		7.7
7h	H	H	H	H	H		5.1
7i	H	H	H	H	H		40
12a	H	F	F	H	F		2.4
12b	H	F	H	F	H		1.5
12c	H	F	F	F	H		1.4
12d	F	F	H	Cl	H		0.8
14c	H	F	F	F	H		1.8
14d	F	F	H	Cl	H		0.6

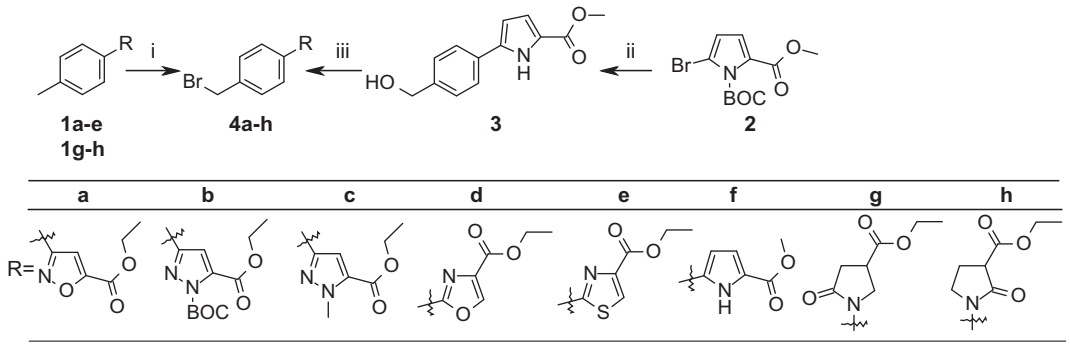
N,O-dimethylhydroxylamine hydrochloride in presence of 1,1′-carbonyldiimidazole (CDI) and triethylamine (Et_3N) in dichloromethane (DCM) at room temperature. These amides **9a–d** were then treated with an appropriate Grignard reagent in diethyl ether at temperature 0–15 °C to obtain corresponding 1,2-diphenyl ethanone derivatives **10a–d** in overall good yield. The compounds **10a–d** were treated with compound **4a** and **10c–d** with **4e** using NaH as base in DMF at temperature 10–15 °C to obtain **11a–d** and **13c–d**, respectively. Compounds **11a–d** and **13c–d** upon hydrolysis with (1 N) NaOH at room temperature provided target compounds **12a–d** and **14c–d** (Table 1).

Synthesis of target compounds **19a–c**, **21b** and **21d**, replacing flexible and extended linker of **II** by rigid oxadiazole is described in Scheme 4. Commercially available benzonitrile **15a–d** were treated with aqueous hydroxylamine hydrochloride in ethanol at reflux temperature to obtain corresponding hydroxyl benzamidine derivatives **16a–d** which were further treated with commercially available phenyl acetic acid derivatives in presence of CDI in DMF at temperature 70–75 °C to provide oxadiazole derivatives **17a–d**. These oxadiazole derivatives (**17a–d**) were condensed either with **4a** or **4e** using NaH as base in DMF at temperature 10–15 °C followed by ester hydrolysis with (1 N) NaOH to give **19a–c** or **21b** and **21d**, respectively in overall good yields.

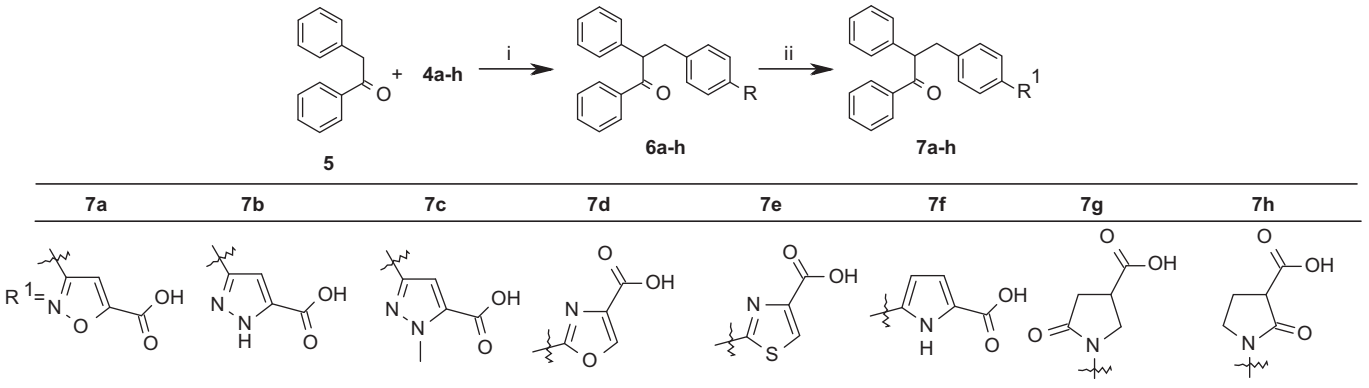
The synthesized compounds were assayed in a fluorescence-based kinetic assay using *p*-nitrophenyl phosphate (*p*NPP) as the substrate with recombinant human PTP1B enzyme. The inhibitory potency of the compounds was expressed as inhibitory constant (K_i). Our initial SAR was focused on the replacement of highly negatively charged DFMP head group of **I** carrying two negative charges by various heterocycles carrying less negatively charged group such as carboxylic acid moiety as utilized in **II** and the results are summarized in Table 1. Isoxazole containing carboxylic acid (**7a**, K_i: 1.1 μM) was found to be more potent than **II** (Fig. 1) suggesting more rigid linker is preferred over flexible linker. When other heterocycles like pyrazole, oxazole, thiazole, pyrrole, pyrrolidone were explored for improving potency, only thiazole (**7e**, K_i: 1.2 μM) and pyrrole (**7f**, K_i: 2.9 μM) showed improved potency as compared to **II** and comparable to compound **7a**. As the active site of PTP1B is highly cationic, we tried to increase the negative-charge density by introducing a second carboxylic acid moiety on isoxazole ring (**7i,** K_i: 40 μM) of **7a** (prepared similar to **7a** as shown in Scheme 1 and 2) and resulted into 40-fold loss of potency. This could be either due to steric factors or charge–charge repulsion due to presence of a negatively charged residue Asp181 close to second substituted carboxylic group in **7i**. Compound **7a** and **7e** were found to be metabolically stable in both mouse and rat liver microsomes as well as good permeability in parallel artificial membrane permeation assay (**PAMPA**)[16] (Table 3) and thus were taken for further optimization of the series. To explore SAR, different substituents on both phenyl ring of hydrophobic tail part of **7a** and **7e** were introduced. Compounds **12a–c** and **14c** are found to posses improved potency than compound **II** and were equipotent to compound **7a** and **7e** in PTP1B enzyme assay. Chloro containing compound **12d** (K_i: 0.8 μM) and **14d** (K_i: 0.6 μM) showed slightly improved inhibitory activity in PTP1B enzyme assay.

As above SAR results demonstrate that the isoxazole and thiazole containing carboxylic acid head group contributes significantly to the in vitro potency, these head groups were kept fixed to optimize the replacement of flexible linker of **II** and results are summarized in Table 2.

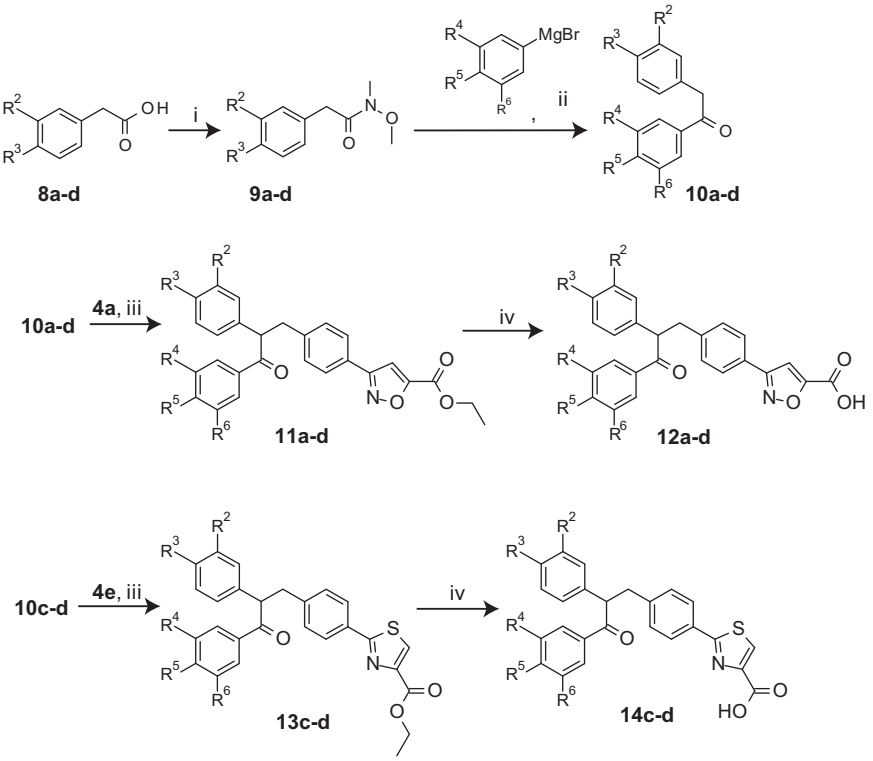
Replacing keto group of 1,2-diphenyl ethanone with more rigid oxadiazole in compound **7a** yielded compound **19a** (K_i: 4.0 μM) which is equipotent to compound **II**. Attempt was made to improve potency by introducing different substituents on tail phenyl ring in



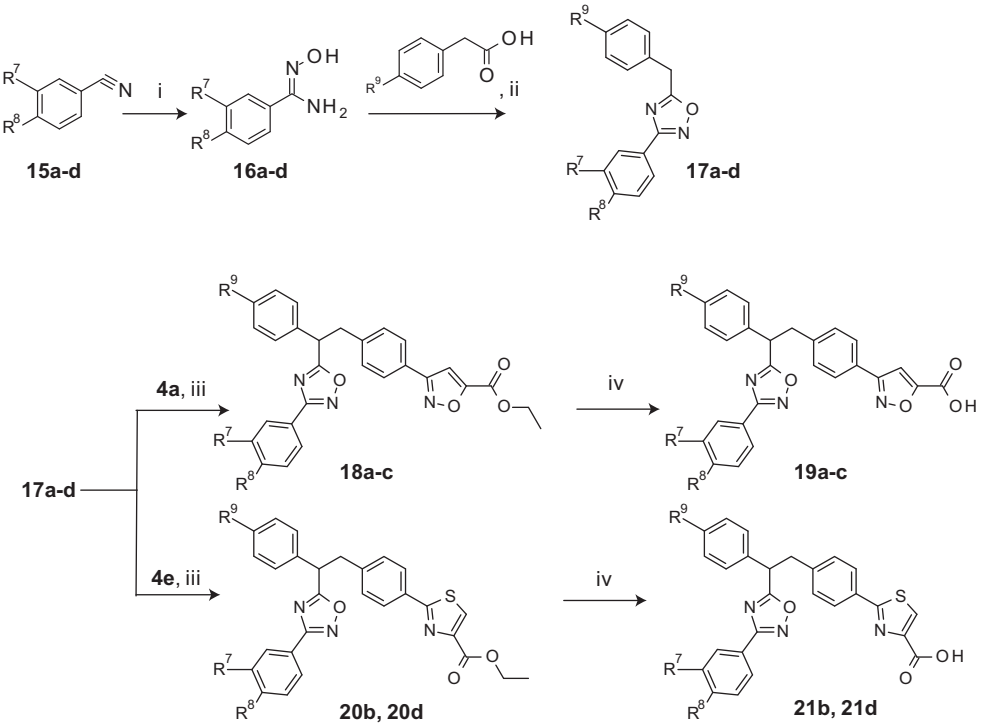
Scheme 1. Reagents and conditions: (i) NBS, AIBN, benzene, 80 °C, 24 h; (ii) 4-(hydroxymethyl)phenylboronic acid, Na_2CO_3, $Pd(PPh_3)_4$, DMF, water, 110 °C, 16 h; (iii) PBr_3, DCM, 0–5 °C, 3 h.



Scheme 2. Reagents and conditions: (i) NaH, DMF, 10–15 °C, 3 h; (ii) 1 (N) NaOH, THF/MeOH (3:2), 25 °C, 12 h.

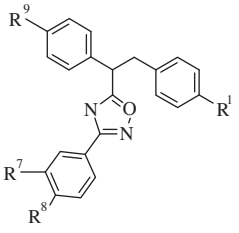


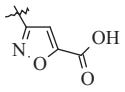
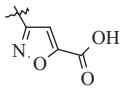
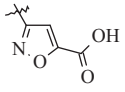
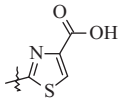
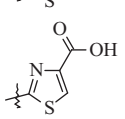
Scheme 3. Reagents and conditions: (i) CDI, *N*,*O*-dimethylhydroxylamine, HCl, Et_3N, DCM, 25 °C, 6 h; (ii) Et_2O, 0–5 °C, 4 h; (iii) NaH, DMF, 10–15 °C, 3 h; (iv) 1 (N) NaOH, THF/MeOH (3:2), 25 °C, 12 h.



Scheme 4. Reagents and conditions: (i) aq NH_2OH, EtOH, 70–75 °C, 8 h; (ii) CDI, DMF, 80 °C, 20 h; (iii) Bu^{t}OK, THF, 5–10 °C, 2 h; (iv) 1 (N) NaOH, THF/MeOH (3:2), 25 °C, 12 h.

Table 2
Oxadiazole analogs as PTP1B inhibitors



Compd	R^7	R^8	R^9	R^1	K_i (μM)
19a	H	H	H		4.0
19b	H	OMe	F		0.4
19c	H	Cl	OMe		0.3
21b	F	H	F		0.5
21d	F	H	OMe		0.5

compound **19a**. Small hydrophobic substitutions like –Cl, –F and hydrophilic substitution like –OMe (examples **19b–c**, **21b** and **21d**) significantly improved inhibitor activity as compared to compound **II**. The SAR revealed that both isoxazole and thiazole analogs were comparable in terms of potency.

Table 3
In vitro DMPK

Compd	PAMPA ($P_{app} \times 10^{-6}$ cm/s)	MR[a] (nmol/min/mg)	
		MLM	RLM
7a	103	0.06	0.02
7e	85	0.05	0.02
12b	8	0.01	0.02
12c	16	0.00	0.01
12d	168	0.00	0.00
19a	45	0.04	0.03
19b	4	0.00	0.01
19c	48	0.00	0.03
21b	10	0.00	0.01
21d	6	0.00	0.04

[a] Metabolic Rate (MR) <0.1 nmol/min/mg or 80% remaining at 30 min is considered as metabolically stable. MLM, Mouse liver microsomes; RLM, Rat liver microsomes

Selectivity with closest homologue of PTP1B particularly TCPTP is essential as its inhibition is lethal. Hence, in vitro selectivity of selected compounds from ethanone derivatives (**7a**, **12d** and **14d**) and oxadiazole derivatives (**19a–c**) were examined against TCPTP using *p*NPP assay, and found to be selective (<10% inhibition at 100 μM) over TCPTP (data not shown).

Having identified compounds with acceptable potency in PTP1B enzyme assay, we decided to further investigate metabolic stability and permeability of these compounds; results are summarized in Table 3. Compounds from ethanone derivatives (**7a**, **7e**, and **12b–d**) and oxadiazole derivatives (**19a–c**, **21b**, **21d**) were found to be metabolically stable in both mouse and rat liver microsomes. The simple unsubstitued ethanone and oxadiazole derivatives as in **7a**, **7e** and **19a**, as well as substituted ethanone in **12d** and oxadiazole in **19c** showed good permeability in **PAMPA**. The other substituted compounds from ethanone derivatives (**12b–c**) and oxadiazole derivatives (**19b**, **21b and 21d**) show a substantially reduced permeability in **PAMPA**.

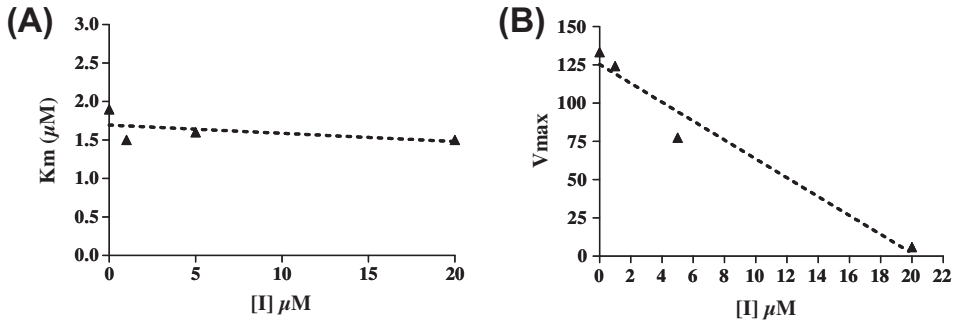


Figure 3. Inhibition of compound **19c** on the hydrolysis of *p*NPP by PTP1B suggesting that **19c** is a non competitive inhibitor.

Table 4
Pharmacokinetic profile[a] of compounds **12d**, **19a** and **19c** in male C57BL/6J mice

Compd	**12d**		**19a**		**19c**	
Route of administration	iv	po	iv	po	iv	po
Dose (mg/kg)	3	30	3	30	3	30
C_{max} (μM)	4.5	1.9	1.5	7.2	1.87	1.34
T_{max} (h)	0.083	1.0	0.08	1.0	0.083	1.0
AUC_{0-t} (μM h)	2.4	3.0	1.8	13	0.98	3.60
V_{ss} (L/Kg)	4	NA	4.8	NA	4.00	NA
CL (mL/min/Kg)	38	NA	63	NA	99.0	NA
$t_{1/2}$(h)	1.9	NA	1.0	NA	1.08	NA
F (%)	NA	13	NA	70	NA	36

[a] Values indicate mean for $n = 3$. iv formulation: *N*-methyl-2-pyrrolidinone (10%), PEG300 (15%), 0.1 M ammonium acetate buffer qs; po (oral) formulation: Tween 80 (1%), 0.5% w/v NaCMC qs; NA: not applicable.

To understand the inhibitory modality of this class of compounds, the most potent inhibitor **19c** was selected for enzymatic kinetic analysis on PTP1B using *p*NPP as substrate. The effect of compound **19c** on PTP1B catalyzed reaction was studied at three different concentrations (Fig. 3). The data suggests that compound **19c** is a non-competitive inhibitor as the Km value retained invariable while V_{max} value decreases with increasing compound concentration.

As compounds **12d**, **19a** and **19c** showed good metabolic stability and intrinsic permeability, we further evaluated them in mouse pharmacokinetic study and the results are summarized in Table 4. Compound **12d** displayed moderate plasma clearance (~50% of hepatic blood flow) with elimination half-life of 2 h with marginal oral bio-availability (% $F = 13$). Compound **19a** exhibited excellent oral bioavailability (% $F = 70$) and good plasma exposure ($C_{max} = 7.2$ μM at 30 mg/kg, po). The most potent compound **19c** showed high plasma clearance (equivalent to hepatic blood flow) with elimination half-life of 1 h and acceptable oral bioavailability (% $F = 36$).

In summary, we have identified potent heterocyclic carboxylic acid based PTP1B inhibitors containing a hydrophobic tail and systematic optimization helped to establish the SAR of this class of compounds. The presence of an isoxazole, thiazole ring and 1,2-diphenyl ethanone group is sufficient to afford potent PTP1B inhibitors (**12d**, **14d**) and even more potent inhibitors obtained by incorporation of an oxadiazole (**19b–c**, **21b** and **21d**) ring into the molecules. Compound **19c** displayed good in vitro potency, selectivity, acceptable ADME and pharmacokinetic properties in mice and showed 36% oral bioavailability. Further optimization and evaluation of this series of compounds and their in vivo efficacy study will be reported in due course of time.

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Supplementary data

Supplementary data (PTP1B, TCPTP, metabolic stability, kinetic study screening assay protocol; in vivo pharmacokinetics; spectral characterization of key compounds) associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2012.02.070.

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