Med Chem Res (2013) 22:1618–1623
DOI 10.1007/s00044-012-0165-0

MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Molecular modeling and synthesis of ZINC02765569 derivatives as protein tyrosine phosphatase 1B inhibitors: lead optimization study

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Received: 22 April 2012 / Accepted: 16 June 2012 / Published online: 30 June 2012

Abstract This article describes design, synthesis, and molecular modeling studies of the ZINC02765569 derivatives as potent protein tyrosine phosphatase 1B (PTP1B) inhibitors, which was previously reported as a vHTS hit (ZINC02765569) by our laboratory. Ten compounds were synthesized and characterized by IR, MASS, and NMR followed by in vitro screening for PTP1B inhibition and glucose uptake in skeletal muscle L6 myotubes. The most potent compound **3j** shows 66.4 % in vitro PTP1B inhibition and 39.6 % increase in glucose uptake. Glide was used to study the nature of interactions governing binding of designed molecules with active site of the PTP1B enzyme.

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Electronic supplementary material The online version of this article (doi:10.1007/s00044-012-0165-0) contains supplementary material, which is available to authorized users.

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Keywords Diabetes · PTP1B inhibitors · ZINC02765569 derivatives · Molecular modeling · Lead optimization study

Introduction

Diabetes mellitus (DM) is complex progressive disease, considered one of the leading non-communicable metabolic disorders, estimated to affect 300 million people worldwide and 33 million people in India by the year 2025. Indians alone may have about 1/5 of the global diabetic population by 2025. Higher blood Glucose levels for longtime may cause; slow wound healing, blurring of vision, renal collapse, increased cardiovascular risk, and may lead to premature death.

Diabetes mellitus is characterized by insulin deficiency and insulin resistance, or, both (Goodman and Gilman, 2001). The effect of insulin on the tyrosine domain of the insulin receptor (IR) for glucose metabolism is the result of counter-action of tyrosine kinases versus tyrosine phosphatases (Zhang, 2003). Imbalance between these the two enzymes' activity disrupts normal cell function, therefore entangled in diabetes, obesity, and cancer disorders (Zhang, 2001; Lund *et al.*, 2004; Seely *et al.*, 1996; Ahmad *et al.*, 1995). Tyrosine kinases phosphorylate alpha subunit of the insulin receptor, while the phosphatase family work against maintaining homeostatic balance. Protein tyrosine phosphatase 1B negatively regulates insulin signaling in vivo by dephosphorylating important tyrosine residue at α-subunit of the IR, assuaging receptor tyrosine kinase activity. (Wang *et al.*, 2001; Bandyopadhyay *et al.*, 1997; Ramachandran *et al.*, 1992; Ahmad *et al.*, 1997a, b; Kenner *et al.*, 1996; Chen *et al.*, 1999). Inhibition of PTP1B is, therefore, expected to improve insulin resistance in DM

(Zhang and Lee, 2003; Blume and Hunter, 2001; Rotella, 2004). Further, many biochemical and genetic studies justify this rationale; for example Chromosomal region 20q13.1, where the PTP1B gene is situated, is found as a risk factor for obesity and type 2 diabetes (Lembertas *et al.*, 1997). Besides these, two different PTP1B knockout mice studies in 1999 and 2000 show augmented insulin sensitivity and reduced body weight gain following a high-fat diet (Elchebly *et al.*, 1999; Klaman *et al.*, 2000). From another study, it can be stated that, over-expression of a PTP1B slice variant lead to improved plasma insulin level (Sell and Reese, 1999). In similar surveillance, the administration of PTP1B antisense Oligonucleotides to diabetic, obese mice lead to reduce plasma glucose and fetch insulin level to normal (Zinker *et al.*, 2002).

The key challenging issues in designing new PTP1B inhibitors includes: first, incorporation of the hydrolytically stable phosphotyrosine (pTyr) or phosphate mimics, in appropriate PTP1B substrate (such as phosphonates, selenates, and carboxylate); second, appropriate non-tyrosine binding lipophillic aromatic domain was incorporated which bind to allosteric site (to achieve selectivity and higher bioavailability).

The hurdles associated in development of negatively charged phosphonates are bio-availability and selectivity; may be because, inorganic phosphonates do not obey the Lipinski principles, and PTP1B shares common homology to other phosphatase (Evans and Jallal, 1999; Lipinski *et al.*, 2001; Blaskovich and Kim, 2002; Boutselis *et al.*, 2007). Therefore, intense search for phosphate mimics is continuously having low molecular weight, low charge, and improved cellular permeability, so that drug candidates will have ideal drug-like properties (Hooft van Huijsduijnen *et al.*, 2004). Therefore, in early 2000, carboxylic acid-based anions proposed as PTP1B inhibitors and many of them are in clinical phases like trodusquemine by Genaera. The comprehensive research efforts in this thrust led to the discovery and development of several PTP1B inhibitors including diaryloxamic acid isothiazolidinedione, benzofuran and benzothiophene biphenyl, trodusquemine, and many more in last decade, concise in (Table 1) (Bleasdale *et al.*, 2001; Burke *et al.*, 1996a, b; Joshi *et al.*, 2012a, b; Chen and Seto 2002; Maccari *et al.*, 2007; Liljebris *et al.*, 2002a, b; Malamas *et al.*, 2000; Xin *et al.*, 2003; Wrobel *et al.*, 2000; Fu *et al.*, 2002; Seiner *et al.*, 2007; Hussain *et al.*, 2008; and Doman *et al.*, 2002).

Our previous research efforts led to identification of a novel lead candidate, ZINC02765569, as a moderate PTP1B inhibitor with good cell permeability (as established by in vitro and in vivo experimental bioassay) by vHTS of ZINC-database using GLIDE docking algorithm (Joshi *et al.*, 2012b). The rationales for considering the hit ZINC02765569 as ideal lead molecule are mentioned in Table 2, which upon further tailoring provide an opportunity to develop better preclinical candidates with improved overall efficacy and potency.

Table 1 Classification of PTP1B inhibitors

Classification of PTP1B inhibitors
1. Competitive/Active site inhibitors
Peptidyl and peptido-mimetics
Phosphonates and fluoro-phosphonates
Carboxylic and α-keto carboxylic acids
Non-carboxylic acid derivatives: Tetrazoles, Catecholes, Malononitrile and TZD isostere
2. Non-competitive/Allosteric Site inhibitors
α -Bromo acetophenones and pyridazines

Experimental

Molecular modeling

For better understanding regarding binding mode of ZINC02765569 derivatives at the molecular level, we carried out molecular docking simulation of synthesized molecules at the PTP1B ligand-binding site. The docking studies of synthesized molecules (**3b–k**) were performed using the Schrodinger software suite (Maestro, version 9.2, 2011). The molecules were sketched in 3D format using build panel and were prepared for docking using LigPrep application. The protein for docking study was taken from Protein data Bank (PDB ID: 1XBO), was prepared by removing solvent, adding hydrogens, and minimal minimization in the presence of bound ligand (IX1) using protein preparation wizard. Grids for molecular docking were generated with bound co-crystallized ligand. Molecules (**3b–k**) were docked using Glide in extra-precision mode, with up to three poses saved per molecule.

Chemistry

Melting points determined by the open capillary method using the VEEGO, programmable digital melting point

Table 2 Rationale for selection of the hit ZINC02765569 molecule as Lead

Why *ZINC02765569* selected as Lead?
Promising biological effects in DM
Novelty of the scaffold for PTP1B
Ease of synthesis
Amenability to structural derivatization
Good Lipinski profile

apparatus and were uncorrected. TLC were carried out on Pre-coated silica gel plates (F254 Merck) using chloroform–methanol (9:1) as solvent. FT-IR spectra were obtained from FT-IR 470 plus spectrophotometer, made by JASCO using KBr as the internal standard. MASS spectra were recorded on Applied biosystems 3200 Q-Trap LC–MS/MS. The NMR spectra were recorded on Bruker (400 MHz) 1HNMR spectrophotometer in DMSO-D6. Unless stated otherwise, all materials were procured from commercial suppliers and used without further purification.

Common procedure for synthesis: first step involved synthesis of the precursor chloroacetamido derivatives, by reaction of amino benzoic acids with chloroacetyl chloride in DMF. Second step entailed coupling the methylenic carbon from precursor to thiol group of 2-mercaptobenzimidazoles in the presence of potassium carbonate as a base (Joshi *et al.*, 2012b). Scheme 1. Finally, all compounds were either recrystallized from ethyl acetate: Methanol [9:1] or purified by normal silica gel column chromatography using chloroform–methanol in appropriate ratio.

Biological evaluation

In vitro glucose uptake in differentiated myotubes

The glucose uptake was estimated by the reported method of Klip *et al.*, (1992). Skeletal muscle L6 myoblasts were differentiated into post-confluency for 4–6 days until the cells aligned to form myotubes. The myotubes were then treated with standard metformin, rosiglitazone, and test compounds in low glucose Dulbecco's modified eagles medium (DMEM) with 10 % fetal bovine serum (FBS) for 18 h. The myotubes were washed with phosphate-buffered saline (PBS) and incubated for 3 h in serum-free DMEM, followed by the Krebs–ringer phosphate hepes buffer (KRPH) containing 0.5 % Bovine serum albumin (BSA) and 100 nM Insulin for 30 min. The myotubes were then, briefly washed with KRPH containing 0.5 % BSA. The 2-deoxy-D-[U-^{14}C] glucose (2-DOG) (310 mCi/mmol; Amersham biosciences, The UK) uptake was carried out in KRPH buffer having 0.5 μCi of 2-DOG for 10 min and the myotubes were washed thrice with cold PBS. The myotubes were then lysed in 0.5 ml of 0.1 N NaOH followed by radioactivity measurement (Beckman coulter, USA). All assays were performed in triplicates, and results were expressed as picomoles/min/well. Metformin (500 μM) and rosiglitazone (100 μM) were employed as standard.

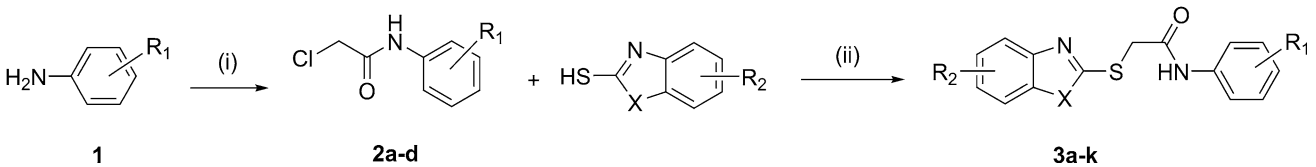
In vitro PTP1B enzyme inhibition

PTP1B enzyme inhibitory activity was determined by using the colorimetric, non-radioactive assay (PTP1B assay kit, BML-AK 822, Enzo life sciences, USA). The test compounds on PTP1B enzyme activity were determined by incubating test compounds (10 μM) and standard Suramin (10 μM) with human recombinant PTP1B enzyme and determining the PTP1B activity using phosphate detection reagent, Biomol red. The reaction was carried out in 96 well, flat-bottomed microtiter plates at 10 μm concentration using DMSO as Control. The detection of free phosphate released is based on classic Malachite green assay (Martin *et al.*, 1985). The percentage inhibition by test compounds on PTP1B enzyme was calculated based on the activity in the control tube (without inhibitor) as 100 % from three autonomous sets of experiments.

Results and discussion

From initial molecular modeling studies and understanding of synthetic organic chemistry, it ascertained that tailoring in ZINC02765569 is possible at both head and tail sites as depicted in Fig. 1. The position of carboxylic acid in ZINC02765569, head may be either varied (as in compounds **3a**–**3d**) or additional polar features in head may be incorporated (as in compounds **3b** and **3d**), to facilitate additional interaction to catalytic site.

In addition, upon binding analysis of enzyme-inhibitor complex and the literature knowledge on PTP1B, ZINC02765569 tail was modified by either substituting phenyl ring of benzimidazole (as in compounds **3e**–**3g**) or replacing cyclic NH group of benzimidazole ring by S atom (as in compounds **3h**–**3k**), to improve overall molecule cellular permeability and bioavailability (Spark *et al.*, 2007). PTP1B inhibition studies revealed that most promising PTP1B inhibitors are compound **3f** (62 %); **3i** (53.9 %); **3j** (66.4 %) and **3k** (56.2 %) at 10 μM conc. In addition, designed compounds were also evaluated for the in vitro glucose uptake assay in liver myotubes. Detailed results are mention in the (Table 3), where Compound **3b**



Scheme 1 Reagents and conditions: (*i*) Chloroacetyl-chloride, DMF, RT, 24 h (*ii*) 2-mercaptobenzimidazole, K_2CO_3, acetone, reflux, 4–6 h

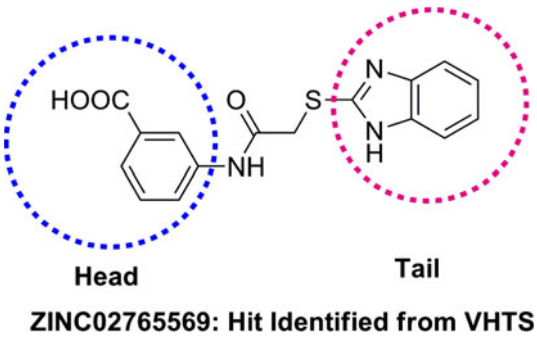


Fig. 1 Design of novel PTP1B inhibitors

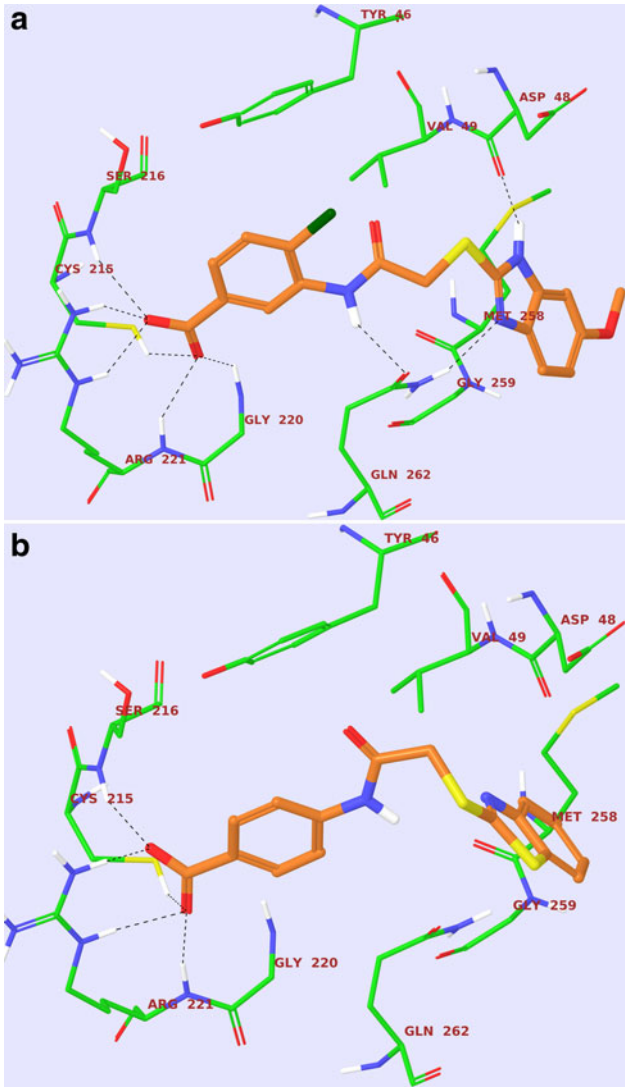


Fig. 2 Binding pattern of compound 3f (**a**) and 3j (**b**) at the catalytic site of PTP1B enzyme

(58.6 %); **3 h** (59.2 %) and **3j** (39.6 %) are found promising.

The results from the PTP1B inhibition studies were used to re-assess the docking performance to gain insight into their possible binding features and derive appropriate SAR. Upon reassessment, it was found that all compounds bind to catalytic domain in similar fashion to the ZINC02765569 by H-bonding via carboxylic acid of designed inhibitors to the Arg221, Cys215, and Ser217 (Fig. 2). Polar substituent such as hydroxyl group, in ZINC02765569 shows additional H-bonding and improved PTP1B inhibition (**3b** in comparison to **3a** and **3i** in comparison to **3h**). Unlike hydroxyl group, incorporation of halogen (Cl atom) does not show additional H-bonding to PTP1B enzyme, but improved PTP1B inhibition and glucose uptake may be due to favorable position of carboxylic acid and increased lipophilicity (35.82 % enzyme inhibition and 28.7 % increase in glucose uptake by compound **3d** in comparison to **3a** which shows 24.2 % enzyme inhibition and 18.5 increase in Glucose uptake). Therefore, halogen-incorporated head group was selected constant and further modifications were carried out on tail side of ZINC02765569 by substituting phenyl ring through methyl, methoxy, and nitro group. It was found that substitution on benzimidazole ring is favorable for PTP1B inhibition and leads to constant increase in potency.

Table 3 Structure and biological activity data of synthesized compounds

Code	R_1	R_2	X	% Glucose uptake (at 50 μM)	% PTP1B inhibition (at 10 μM)
3a (ZINC02765569)	3-COOH	H	NH	18.5	24.2
3b	5-COOH, 2-OH	H	NH	58.6	23.2
3c	4-COOH	H	NH	22.5	18.7
3d	5-COOH, 2-Cl	H	NH	28.7	35.82
3e	5-COOH, 2-Cl	4-NO_2	NH	37.6	36.56
3f	5-COOH, 2-Cl	4-OCH_3	NH	26.6	62.68
3g	5-COOH, 2-Cl	4-CH_3	NH	31.4	20.89
3h	3-COOH	H	S	59.2	24.2
3i	5-COOH, 2-OH	H	S	29.2	53.9
3j	4-COOH	H	S	39.6	66.4
3k	5-COOH, 2-Cl	H	S	28.7	56.2
Suramin	–	–	–	–	20
Metformin[a](100 μM)	–	–	–	30.2	–
Rosiglitazone[b] (500 μM)	–	–	–	25.2	–

[a] Metformin and [b] Rosiglitazone were evaluated at 100 and 500 μM concentrations, respectively, for glucose uptake assay

4-methoxy substitution on benzimidazole ring lead to potent compound **3f**, having 62 % PTP1B inhibition, in comparison with **3d** 35.82 %. This may be due to favorable van der Waal interactions to the second aryl binding site (compound **3f** shows 62 % enzyme inhibition in comparison to the **3d** 35.82 %).

Similarly, in ZINC02765569 incorporation of benzthiazole fragment instead of benzimidazole increases the potency consistently, as in compound **3i** (53.9 %); **3j** (66.4 %); and **3 k** (56.2 %); however, some of the binding interaction of ligand with Asp48 and Gln262 residue completely disappeared. However, this does not seem to affect enzyme inhibition and ultimately favor PTP1B inhibition, which may be due to the increased hydrophobicity and favorable van der Waal interactions.

Compounds **3b** (58.6 %), **3e** (37.6 %), **3 h** (59.2 %), and **3j** (39.6) are potent inducer of normal glucose uptake process in muscle myotubes and re-establishes the disease implications. However, other compounds also stimulate this process but there is little loss of enzyme inhibition activity simultaneously.

Conclusion

In this part of lead optimization process, molecule **3j** was found as potent PTP1B inhibitor and potential anti-hyperglycemic agent in glucose uptake assay by lead optimization at head and tail sites of ZINC02765569. SAR suggests that incorporation of additional polar features such as hydroxyl and chlorine at head, substitution at benzimidazole phenyl ring and replacement of NH by S atom in tail improve PTP1B inhibition significantly. Further lead optimization is under pipeline.

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