Drugs of the Future 2008, 33(2): 175-185

CCC: 0377-8282/2008
DOI: 10.1358/dof.2008.033.02.1165449

Review Article

Recent advances in the discovery and development of PTP-1B inhibitors

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CONTENTS

Abstract

Protein-tyrosine phosphatases (PTPs) play crucial roles in intracellular signaling. Regulating tyrosine phosphorylation levels ultimately controls gene transcription, metabolism, cell growth and differentiation, cell migration, the immune response, cell apoptosis and bone development. The role of the protein-tyrosine phosphatase PTP-1B in particular is well established in cellular signaling and it is believed to be involved in many human diseases, such as diabetes, obesity and cancer. Consequently, small-molecule inhibitors of PTP-1B are considered promising new therapies and a significant number of drug discovery programs around this target have been disclosed. Structural homologies in the PTP superfamily and the highly charged nature of the active site, however, make it challenging to find selective and permeable inhibitors. In this review, we discuss the role of PTP-1B in metabolic diseases and cancer, and focus on recent advances in the field of PTP-1B inhibitors.

Introduction

Protein-tyrosine phosphatases (PTPs) are enzymes that catalyze protein tyrosine dephosphorylation. Over 100 PTPs have been isolated in humans (1) and can function either as negative or positive modulators in various signal transduction pathways. The PTP superfamily is divided into the classical phosphotyrosine (pTyr)-specific phosphatases and the dual-specificity phosphatases (2). This structural diversity is indicative of the functional importance of the PTPs in the control of cell signaling and underscores the potential of PTPs to display exquisite substrate and functional specificity *in vivo*.

PTPs play essential roles in intracellular signal transduction by regulating the cellular level of tyrosine phosphorylation to control cell growth and differentiation, metabolism, cell migration, gene transcription, ion channel activity, the immune response, cell apoptosis and bone development. Among all PTPs, PTP-1B plays a seminal role in cellular signaling and in many human diseases, including cancer, diabetes and obesity (3). In this review, we will focus on the role of PTP-1B in metabolic diseases and cancer and summarize recent advances in the field of PTP-1B inhibitors.

Role of PTP-1B in metabolic diseases

The role of PTP-1B in diabetes is well documented and has been reviewed extensively (4-6). In a landmark paper that established PTP-1B as a potential therapeutic target in the treatment of type 2 diabetes and obesity, Kennedy *et al.* (7) showed that disruption of the mouse homologue of the gene encoding PTP-1B yielded healthy mice that, in the fed state, had lower blood glucose concentrations and circulating insulin levels when compared to their PTP-1B$^{+/+}$ littermates (7). The PTP-1B$^{-/-}$ mice showed increased phosphorylation of the insulin receptor (IR) in liver and muscle tissue after insulin injection in comparison to PTP-1B$^{+/+}$ mice. On a high-fat diet, the PTP-1B$^{-/-}$ and PTP-1B$^{+/-}$ mice were resistant to weight gain and remained insulin-sensitive, whereas the PTP-1B$^{+/+}$ mice rapidly gained weight and became insulin-resistant.

The *PTPN1* gene codes for PTP-1B and has been the object of several searches to identify an association with type 2 diabetes (8). This systematic approach in several populations, investigating both diabetes and metabolic traits, suggested that *PTPN1* is a significant contributor to diabetes. Another study performed in a French population showed a moderate association between the gene encoding PTP-1B and type 2 diabetes and obesity, and the authors concluded that their data

indicate that *PTPN1* variants may modulate the lipid profile, thereby influencing the susceptibility to metabolic disease (9). In a recent study, Trauriq *et al.* (10) evaluated whether a single nucleotide polymorphism (SNP) in *PTPN1* has a role in type 2 diabetes susceptibility in Pima Indians, a population with the world's highest reported prevalence and incidence rates of this disease. None of the SNPs, analyzed individually or as haplotypes, was associated with either type 2 diabetes or obesity. Based on these association results, it was concluded that SNPs within *PTPN1* are unlikely to have a major role in the etiology of type 2 diabetes or obesity in Pima Indians (10).

The role of PTB-1B in cancer

Unlike the well-established link between PTP-1B and diabetes and obesity, the exact role of this phosphatase in oncogenesis remains to be clarified. Previous studies of PTP-1B activity and expression in various cancer cells and tumors have reported variable levels of expression leading to conflicting conclusions (11, 12). Biochemical studies have implicated PTP-1B in multiple signaling pathways, including dephosphorylation of a variety of growth factor receptors, such as the insulin-like growth factor 1 receptor (IGF1R), IR, epidermal growth factor receptor (EGFR) and platelet-derived growth factor receptor (PDGFR), as well as cytosolic tyrosine kinases such as Src, BCR-ABL, JAK-2 (Janus kinase 2) and STAT5 (signal transducer and activator of transcription 5), linking this enzyme with oncogenic and cytokine signaling (13-21). The downregulation by PTP-1B of these growth factor receptors and tyrosine kinases raises the possibility that PTP-1B deficiency, or inhibition of PTP-1B, can potentially lead to increased oncogenic signaling through heightened activity of those signaling kinases. However, PTP-1B-deficient mice do not overtly develop tumors even at advanced ages. This lack of altered phenotype in knockout mice may reflect compensation by expression of other related PTPs during development (22). Interestingly, p53/PTP-1B double-null mice show a decreased survival rate and increased susceptibility towards the development of B lymphomas. This suggested a role for PTP-1B in lymphopoiesis and that PTP-1B is an important determinant of the latency and the type of tumors in a p53-deficient background through its role in the regulation of B-cell development (22).

At this point, despite an incomplete picture, recent research advances suggest that PTP-1B might have a dual role in oncogenic signaling depending on the type of cancer, and that its effect could be cell/tissue-specific.

One thing that is clear, however, is that PTPs, including PTP-1B, do not simply function as passive antagonists of protein tyrosine kinases, but rather their activity is coordinated with that of the kinases, such that they are critical regulators in their own right (23). Recent work from Tremblay's group demonstrated that mouse mammary tumor virus (MMTV)-directed overexpression of PTP-1B alone was sufficient to drive mammary tumorigenesis (24). In this study, the researchers also reported that genetic deletion or the use of a selective PTP-1B inhibitor results in delayed erbB-2-induced breast tumorigenesis, thus providing the first genetic and pharmacological evidence that PTP-1B is critical in breast tumor development. In another study, the Rochester group showed that PTP-1B plays an important role in the differentiation of neuroendocrine cells, which may in turn stimulate androgen-independent growth of prostate cancer (25). These observations highlight the potential importance of PTP-1B as a therapeutic target in cancer (23, 26).

Challenges facing the discovery and development of PTP-1B inhibitors

PTP-1B inhibitors have a highly charged active site. The electrostatic properties of the active site have been optimized for binding the dianionic phosphate moiety, and thus there is often a trade off between potency and cell permeability (27). The pTyr residue normally serves as a key recognition and binding element for signaling proteins that contain units such as Src homology 2 (SH2) and pTyr binding domains. It was determined that over 50% of the binding free energy is provided for by interactions with the pTyr residue (28). Thus, it is not surprising that pTyr and phosphate isostere mimetics were incorporated in the design of inhibitors of PTP-1B and other phosphatases (27). Such isostere mimetics include the following:

- Replacing the bridging oxygen atom with a methylene moiety, resulting in a hydrolytically stable phosphonate group
- Phosphinate isosteres with a reduced charge and potentially greater membrane permeability
- Fluoromethylenephosphonates, where the introduction of two fluorines on the methylene group of the phosphonate isostere attenuates the increased pK_a value of the phosphonate analogues
- α,α-Difluoro-β-ketophosphonic acids, where the electrophilic nature of this moiety may allow the formation of hydrates in aqueous solution, with an improved potential to mimic a bound water molecule in the active site

These efforts led to the identification of several potent PTP-1B inhibitors *in vitro,* but these compounds were still highly charged and often displayed poor cell-based activity and overall drug-like properties. To address these shortcomings, recent efforts have focused on carboxylate-based isosteres. With the aim of capturing phosphate-like electrostatic interactions in a functional group composite that is more cell-permeable than phosphate, several combinations of a carboxylate group and another polar group have been investigated (27).

In this review, we will describe the following PTP-1B inhibitors: antisense nucleotides, thiophene-based inhibitors, heterocyclic carboxylic acid mimetics, oxidoreduction-type inhibitors, monocarboxylic acid inhibitors and allosteric PTP-1B inhibitors.

PTP-1B inhibitors

Antisense oligonucleotides

ISIS-113715 is a 20-mer antisense oligonucleotide developed by Isis Pharmaceuticals for the treatment of type 2 diabetes. This is a second-generation chimeric phosphorothioate oligonucleotide whose sequence is GCTCCTTCCACTGATCCTGC, a fragment from 1035-1054 nt of the coding region of the human PTP-1B cDNA. This antisense compound is designed to target the expression of the *PTPN1* gene, which is responsible for PTP-1B synthesis. Preliminary clinical results demonstrated a dose-related glycosylated hemoglobin (HbA1c)-lowering effect not associated with hypoglycemia. This compound is currently in phase II clinical trials (29, 30).

Thiophene-based inhibitors (Fig. 1)

A novel pyridothiophene inhibitor of PTP-1B was discovered at Wyeth through rational screening of pTyr mimetics at high micromolar concentrations. This lead compound, **1**, was a reversible and competitive inhibitor of PTP-1B, with a K_i of 230 μM at pH 7.4. Inhibition of the enzyme by this compound was independent of pH (K_i = 200 μM at pH 5.5).

Binding of **1** to the enzyme active site was further confirmed by X-ray crystallography. Using this co-structure as a guide along with iterative medicinal chemistry, the Wyeth team developed a new tricyclic scaffold, as exemplified by **2**, and drove the potency down by almost three orders of magnitude (31). Upon further exploration, the scaffold was evolved into the 3-bromothiophene lead series, exemplified by **3** (32). Based on the co-crystal structure, the 3'-position of **3** offers a favorable trajectory towards the second pTyr binding site, which has been shown to offer opportunities for both potency and selectivity improvement (33, 34). Substitution at the *para*-position of the phenyl ring with a hydrogen bond donor achieved some potency improvement through the binding interaction with Asp48 (32). Substitution at the *meta*-position was found to be much more productive. The X-ray complex structure of the 3-NH-benzyl derivative with PTP-1B confirmed that the benzyl group has indeed passed through the "gateway" between the active site and the second pTyr binding site, which is lined with the Gly259 residue. Using this biostructure-based lead optimization, the Wyeth team successfully developed a potent inhibitor, **4**, with a K_i of 4 nM (35, 36). This compound showed good selectivity relative to leukocyte antigen-related (LAR) phosphatase and CD45, but was equipotent at T-cell PTP (TCPTP). As expected from the diacid structure, this compound was reported to have poor cell permeability as measured in the Caco-2 assay. Interestingly, **4** was found to be actively taken up into liver tissue through an organic anion-transporting polypeptide (OATP) mechanism. However, proof of concept for *in vivo* efficacy of this diacid compound was not provided. New studies using a prodrug approach are reportedly in progress. In a separate study, the same group developed a series of acid mimetics in an attempt to improve cellular uptake (37). The tetrazole and 1,2,5-thiadiazoliden-3-one analogues showed improved permeability, but both analogues suffered a reduction in enzyme-inhibitory activity.

Heterocyclic carboxylic acid mimetics

Significant efforts have been invested in replacing the highly charged carboxylic acids in PTP-1B inhibitors with heterocyclic mimetics. Below, we will summarize the most recently disclosed inhibitors.

1. 1,2,5-Isothiazolidinone heterocycles (Fig. 2)

The Incyte group reportedly designed and discovered (*S*)-isothiazolidinone ([*S*]-IZD) as a heterocyclic pTyr mimetic based on a comprehensive review of the X-ray

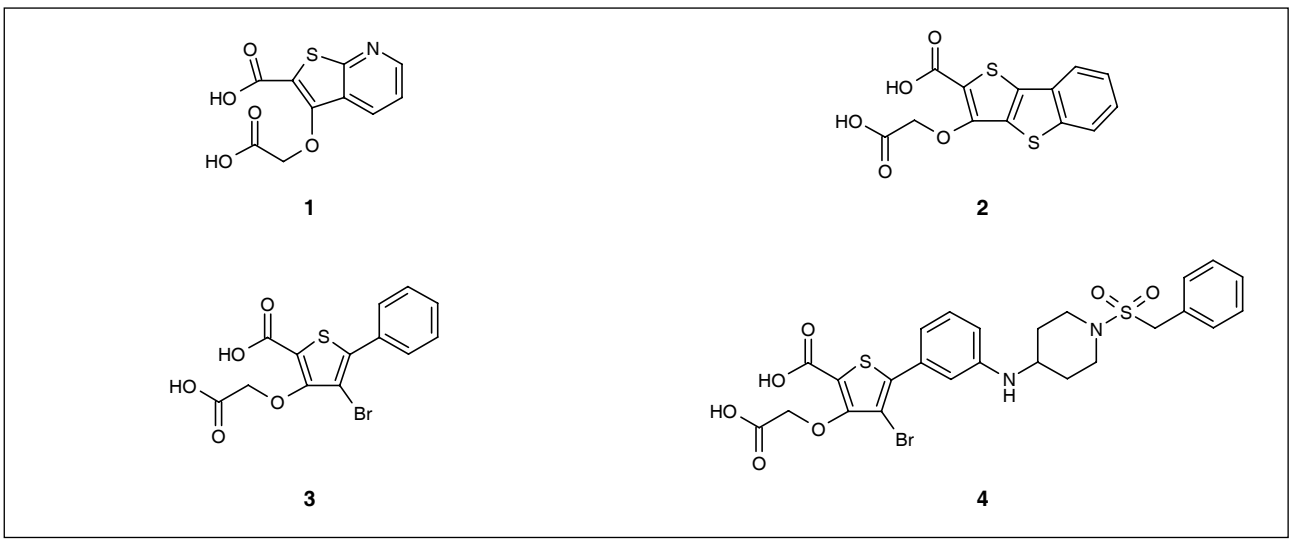

Fig. 1. Thiophene-based inhibitors.

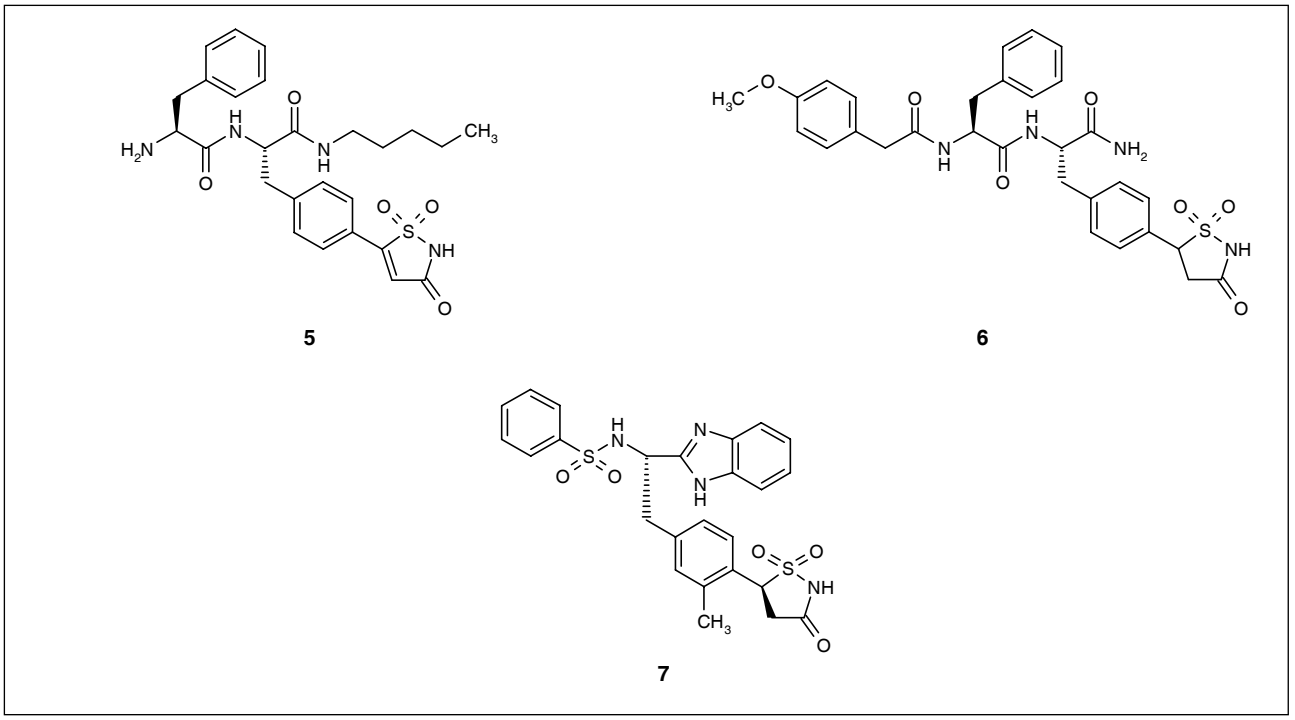

Fig. 2. Isothiazolidinone heterocycle inhibitors.

crystal structures of PTP-1B/inhibitor complexes available in the Protein Data Bank. Incorporation of this head group onto dipeptides gave exceptionally potent, competitive and reversible inhibitors of PTP-1B (38). The crystal structure of the potent inhibitor **5** revealed that the (*S*)-IZD heterocycle interacts extensively with the phosphate-binding loop precisely as designed *in silico*. Further structure-activity relationship (SAR) studies identified the saturated IZD heterocycle as an improved heterocyclic pTyr mimetic over (*S*)-IZD. The most potent compound in this series, **6**, exhibited an IC_{50} of 80 nM in the *p*-nitrophenyl phosphate (pNPP) enzyme assay (39).

The structural basis for the higher potency of the saturated IZD-containing peptides relative to unsaturated analogues was ascribed to the observation that the IZD heterocycle and phenyl ring directly attached to it bind in a nearly orthogonal orientation with respect to each other, a conformation that is close to the energy minimum of the saturated IZD phenyl moiety (40).

In order to improve the cell permeability and the overall pharmacokinetic properties of the (*S*)-IZD-containing inhibitors of PTP-1B, the Incyte group focused on eliminating the peptidic nature of their lead (**6**). Replacement of the *C*-terminal primary amide with a substituted benzimidazole retained the critical binding interaction with Asp48. Substitution of the *N*-terminal peptide portion with arylsulfonamides, however, gave a flat SAR. Rationalization of this result was difficult since modeling predicted that the arylsulfonamide NH and benzimidazole NH bidentate H-bond interaction with Asp48 would necessitate that the aryl group of the sulfonamide bind in an extended conformation against the protein in the so-called C-site. Surprisingly, X-ray co-crystal structures indicate that the aryl ring of the sulfonamide does not interact with the protein in any site, but extends into the solvent with only intermolecular interactions (41). This observation explained the failure to significantly improve the binding of these ligands by substitution on the arylsulfonamide. Further optimization was focused on the substitution at the *ortho*-position of the aryl ring in the (*S*)-IZD moiety. This strategy was found to be effective, as it achieved binding into the relatively small D-site imbedded deep into the protein adjacent to the catalytic site. The most potent compounds in this series, *e.g.,* **7**, displayed low-nanomolar enzyme-inhibitory activity. Unfortunately, these potent inhibitors also have low Caco-2 cell permeability and cellular activity in IR and Akt phosphorylation assays (42, 43).

2. 1,2,5-Thiadiazolidinones (Fig. 3)

Four patent applications from the Novartis group were published recently (44-47) in which 1,2,5-thiadiazolidinone derivatives were claimed to be inhibitors of PTPs and useful for the treatment of conditions mediated by PTPase activity. A large number of compounds are covered by these patent applications, but one common structural feature among them is the presence of an OH substituent group situated *ortho* to the 1,2,5-thiadiazolidinone ring. This arrangement draws a very close parallel with that of the Incyte lead series discussed above. In these patent applications, PTP-1B enzyme-inhibitory activity (IC_{50}) data were reported for compounds **8**-**15** and ranged from 80 to 158 nM. No other biological activity was disclosed.

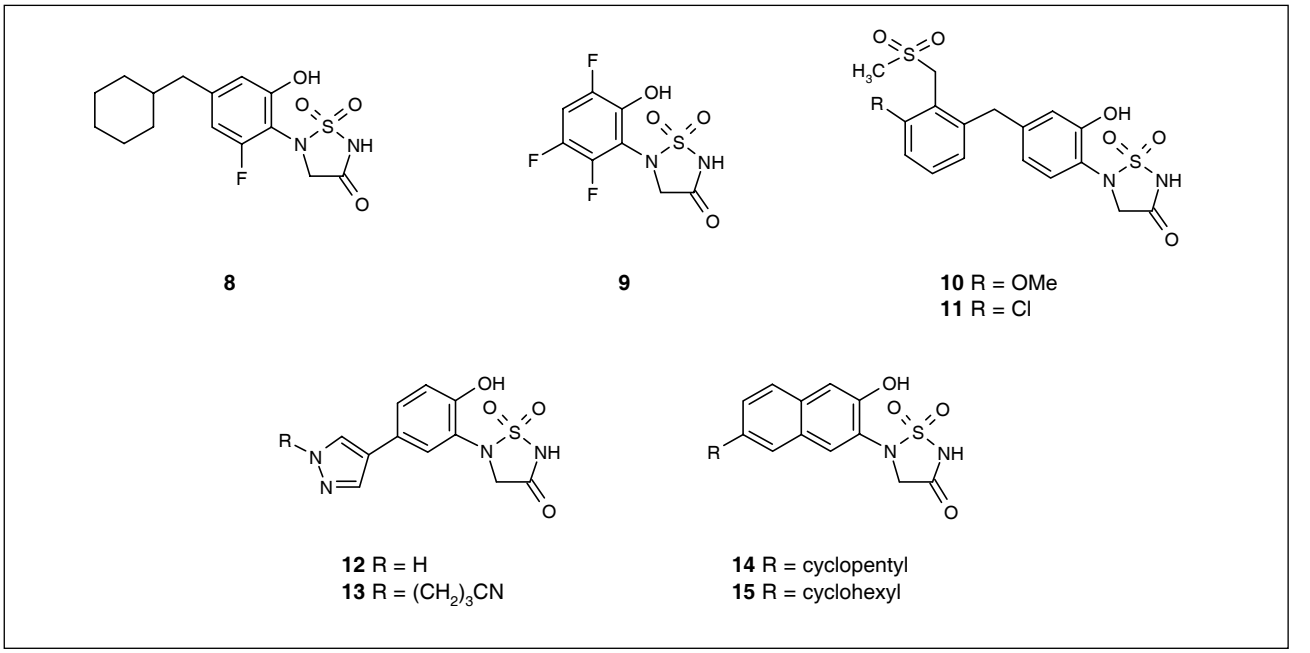

Fig. 3. 1,2,5-Thiadiazolidinones.

3. Thiazolylaminobenzoisothiazole dioxides

Thiazolylaminobenzoisothiazole dioxides were also reported as PTP-1B inhibitors (48) in a patent application. Fourteen examples of the general structure **16** (Fig. 4) exhibited IC_{50} values ranging from 2.77 to 80 μM in the enzyme assay. Based on the limited SAR information provided, bulky and lipophilic substituents are tolerable on the thiazole ring. However, the introduction of an acidic group led to a big drop in potency. No cell-based activity was reported.

Oxidoreduction-type inhibitors (Fig. 5)

The pyrimido[5,4-*e*][1,2,4]triazine-5,7-diamine **17** was identified through high-throughput screening (HTS) against LAR phosphatase (49). This compound was subsequently found to have residual PTP-1B activity as well, and served as a starting point for the development of novel PTPase inhibitors. Hydrophobic benzylic side-chains are favored on the piperazine ring, such as the 4-biphenylmethyl **18**, with an IC_{50} of 2.9 μM, and the naphthalene analogue **19**, with an IC_{50} of 3.5 μM.

The *in vitro* activity of these inhibitors appears to be sensitive to the concentration of dithiothreitol (DTT) used in the assay, suggesting a possible redox reaction between the inhibitors and DTT (49). It was also suggested that the compounds undergo redox chemistry with the PTP-1B active site cysteine residue, thus inactivating the enzyme. Shaver and co-workers (50) have speculated that the mode of PTPase inhibition by peroxovanadium compounds may involve irreversible oxidation of the catalytic cysteine residue. Under high DTT conditions, one may expect to observe less inhibition of PTP-1B with inhibitors, as competing redox chemistry with DTT would become prominent.

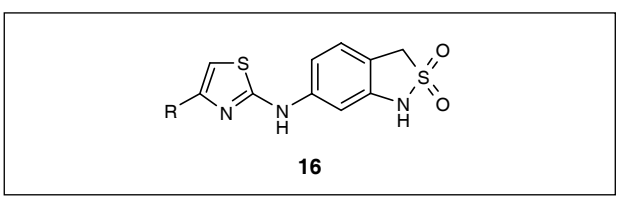

Fig. 4. Thiazolylaminobenzoisothiazole dioxides.

^{1}H NMR and MS studies performed in the presence of DTT and the absence of oxygen showed that the structurally related pyrimidotriazines rapidly and quantitatively undergo reduction to the corresponding dihydro derivatives. This reaction was found to be reversible in the presence of atmospheric oxygen. This supports the hypothesis that the triazine ring is likely responsible for the redox activity of these inhibitors.

Kinetic and reversibility experiments performed using a GST-PTP-1B (1-321) construct indicated that compounds of the pyrimido[5,4-*e*][1,2,4]triazine-5,7-diamine class are reversible and competitive inhibitors of PTP-1B in the presence of low (300 nM) DTT concentrations. Moreover, the PTP-1B-inhibitory potency of these compounds is completely abolished when the assay is conducted in the presence of catalase to sequester any generated hydrogen peroxide. This indicates that hydrogen peroxide plays a central role in the inhibition of PTP-1B. It is worth noting that Goldstein *et al*. (51) have demonstrated *in vivo* that insulin stimulation generates a burst of intracellular hydrogen peroxide that reversibly inhibits PTP-1B, thereby enhancing the early insulin cascade.

The redox hypothesis described herein for PTPase inhibitors (see Fig. 5) would suggest that these com-

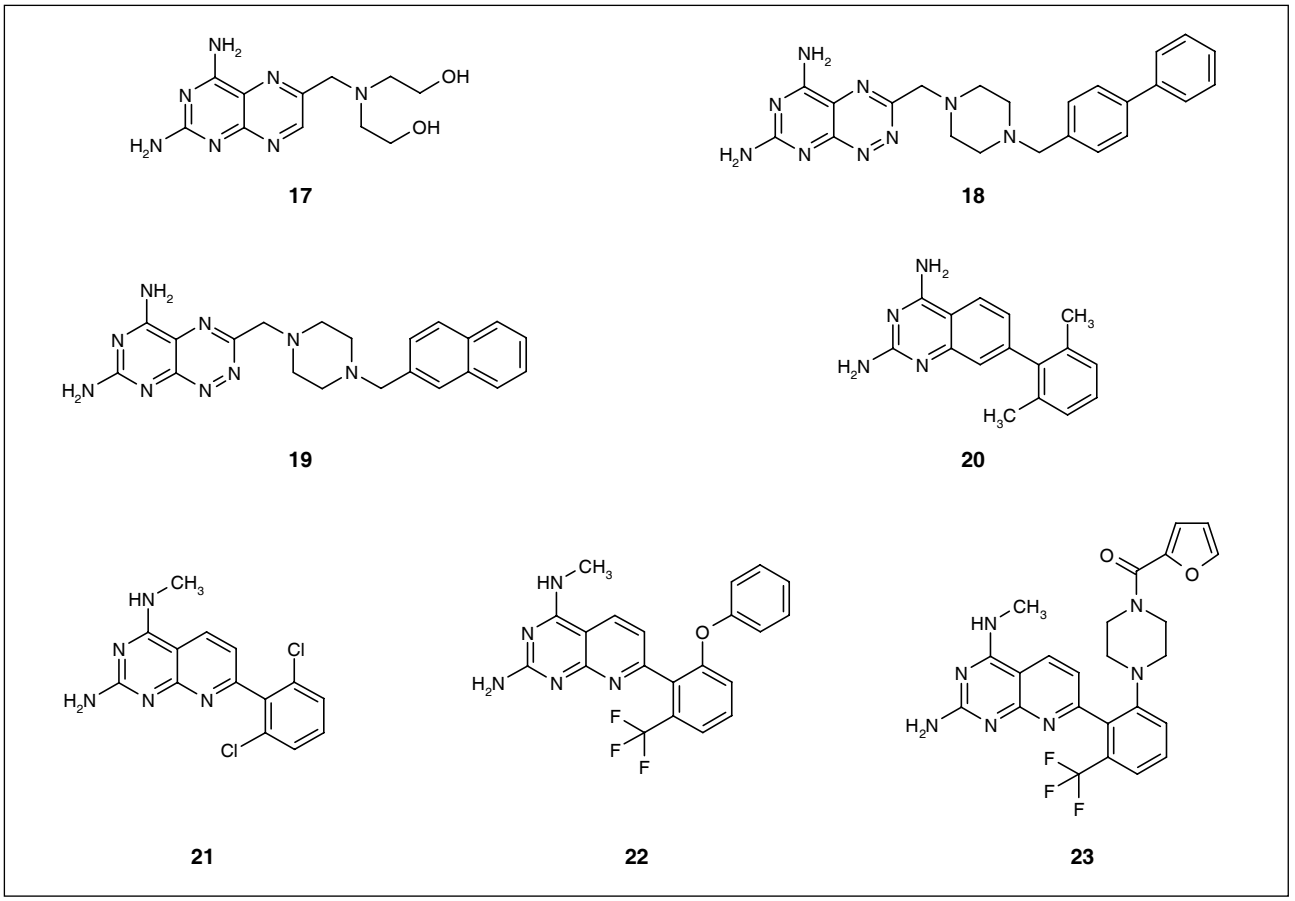

Fig. 5. Oxidoreduction inhibitors.

pounds should be rather nonselective in their redox actions, as all PTPases (cytosolic and transmembrane-bound receptor-like enzymes) contain the conserved 11-amino-acid sequence motif (I/V)HcxAGxxR(S/T)G, which specifies the active site of the phosphatase. Compounds **18** and **19** were evaluated against other PTPases (PTPα, LAR and SHP-2) and showed no selectivity in this panel.

Compounds **18** and **19** were also evaluated in the *ob/ob* mouse model. Compounds were dosed p.o. once daily for 5 days at 50 mg/kg and blood glucose was measured 2 h after dosing on day 5. These compounds displayed a significant glucose-lowering effect (23% reduction for **18** and 19% reduction for **19**).

Compound **19** was found to be rapidly and extensively distributed in mice. The compound had a favorable $t_{1/2}$ and excellent oral bioavailability. The large steady-state volume of distribution (V_{ss}) of **19** is approximately six times the total body water volume, suggesting deep tissue and cell penetration. On the other hand, the compound suffers from high systemic clearance, which exceeds the hepatic blood flow of the mouse.

Related analogues have been reported in recent patent applications filed by Roche (52, 53). Aminoquinazolines, exemplified by compound **20**, showed an IC_{50} of 0.79 μM. Similar pyridopyrimidines, exemplified by compounds **21**, **22** and **23**, all had IC_{50} values below 1 μM, with **22** being the most potent from this series (IC_{50} = 0.17 μM). No additional information was disclosed for these compounds.

Monocarboxylic acids (Fig. 6)

Monocarboxylic acids continue to emerge in the patent literature as PTP-1B inhibitors. Alkyne phenoxycarboxylic acids (54) were reported as PTP-1B inhibitors, exemplified by compound **24**, with an IC_{50} of 500 nM, and compound **25**, with an IC_{50} of 80 nM.

Representative compounds were also tested in *db/db* mice at 30 mg/kg. Compound **26** showed a reduction in blood glucose and serum insulin (37% and 28%, respectively), compound **27** showed a 20% reduction in blood glucose and a 43% reduction in serum insulin, and compound **28** showed a 46% reduction in blood glucose and a 75% reduction in serum insulin. There was no mention of peroxisome proliferator-activated receptor (PPAR) activity for these compounds.

The Institutes for Pharmaceutical Discovery revealed in five patent applications multiple series of phenylalkanoic acids as inhibitors of PTP-1B (54-59). Representative structures are shown in Figure 7. Common features in these series are the carboxylic acid group and the general lipophilic nature of the molecules.

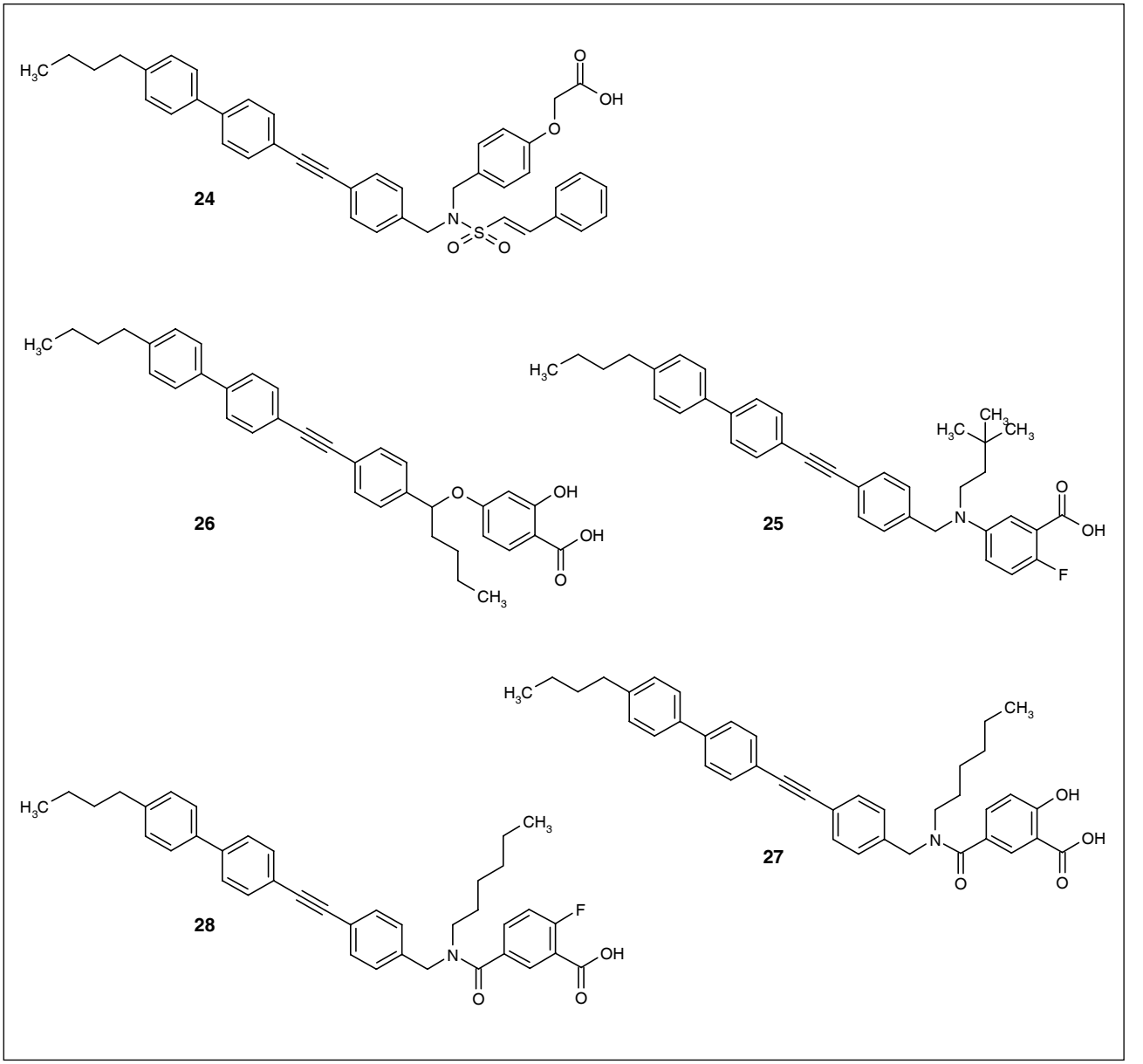

Fig. 6. Monocarboxylic acid PTP-1B inhibitors.

Particularly preferred compounds of these inventions were reported to have IC_{50} values of < 300 nM for PTP-1B inhibition. No specific data were given.

The sanofi-aventis group has reported two series of salicyclic acid-based PTP-1B inhibitors (60, 61). In the first series (Fig. 8), 17 examples of the general structure **33** exhibited IC_{50} values ranging from 0.7 to 46 μM in the PTP-1B enzyme assay. This limited set of data offered very little information on SAR. It showed that quite a variety of substituents, except a COOH group, are tolerable at the biphenyl ring and replacement of the biphenyl with a naphthyl group caused a loss of potency. In the second series (Fig. 8), 24 examples of the general structure **34** exhibited IC_{50} values ranging from 0.5 to 1.9 μM in the PTP-1B enzyme assay. The SAR for these compounds was very flat. In these examples, all R_1 and R_2 groups are lipophilic and mostly aromatic. Compound **35** is a representative structure, with an IC_{50} of 0.5 μM in the PTP-1B enzyme assay. No other biological data were given.

Allosteric inhibitors (Fig. 9)

The need for alternative strategies for inhibiting PTP-1B prompted researchers at Sunesis to initiate a search for non-pTyr-like inhibitors (62). During a screening effort, compound **36** was identified as a weak inhibitor (IC_{50} = 350 μM) and was not competitive with the substrate, sug-

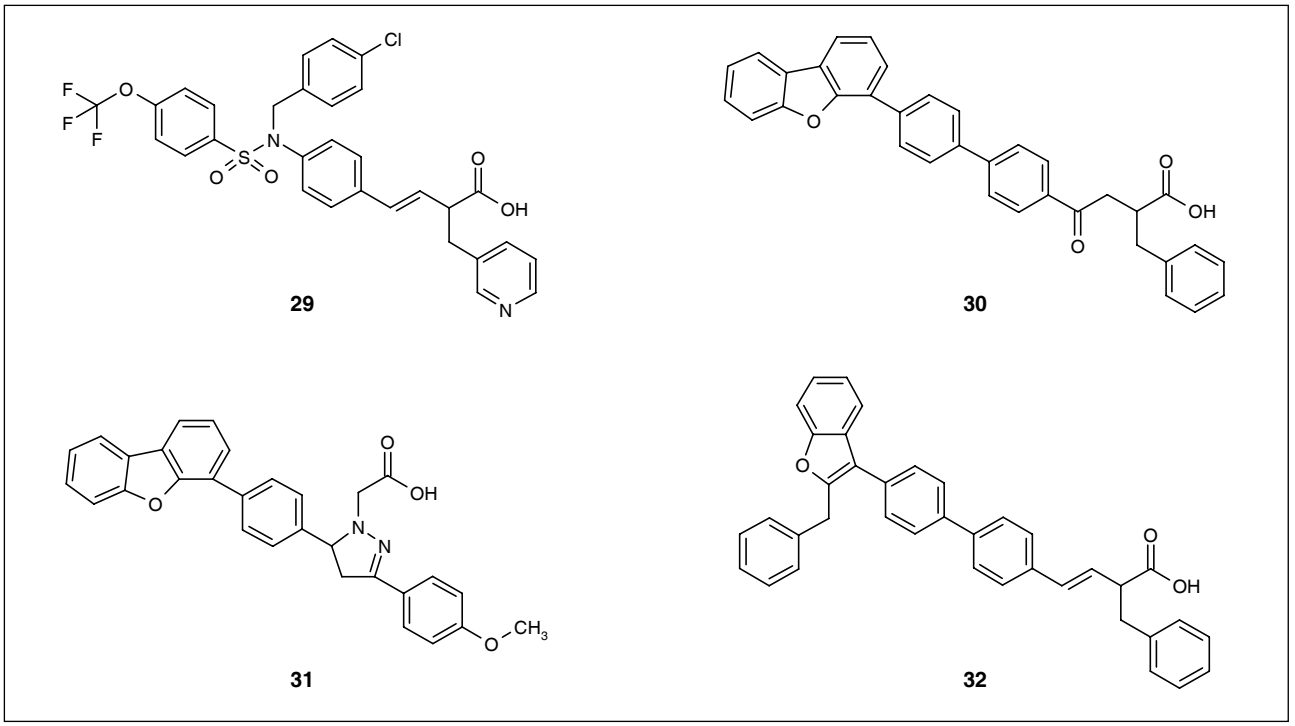

Fig. 7. Additional monocarboxylic acid PTP-1B inhibitors.

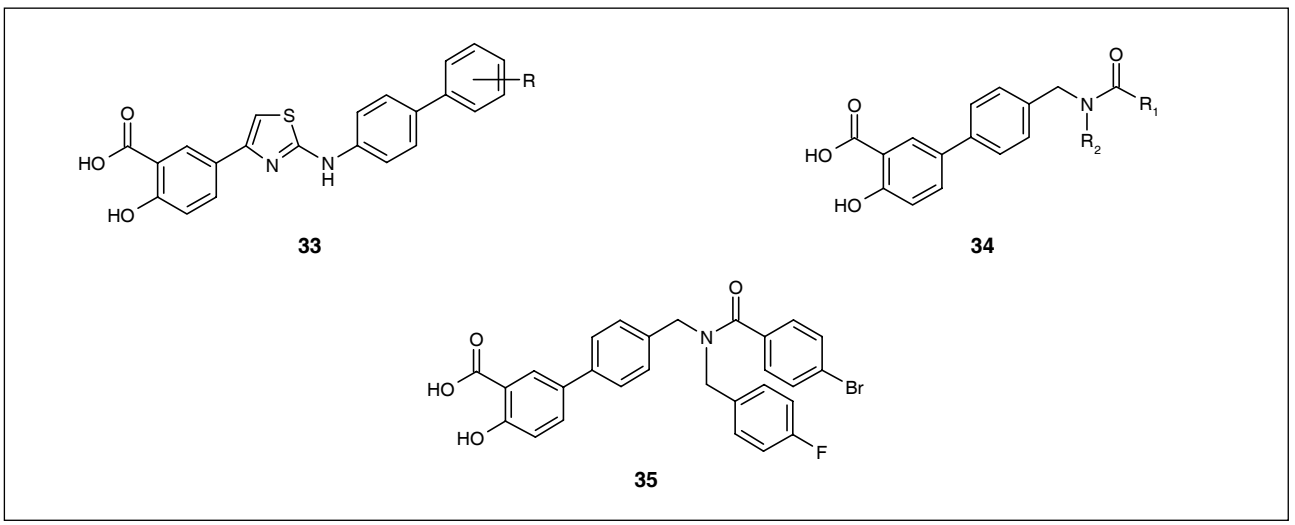

Fig. 8. Salicylic acid PTP-1B inhibitors.

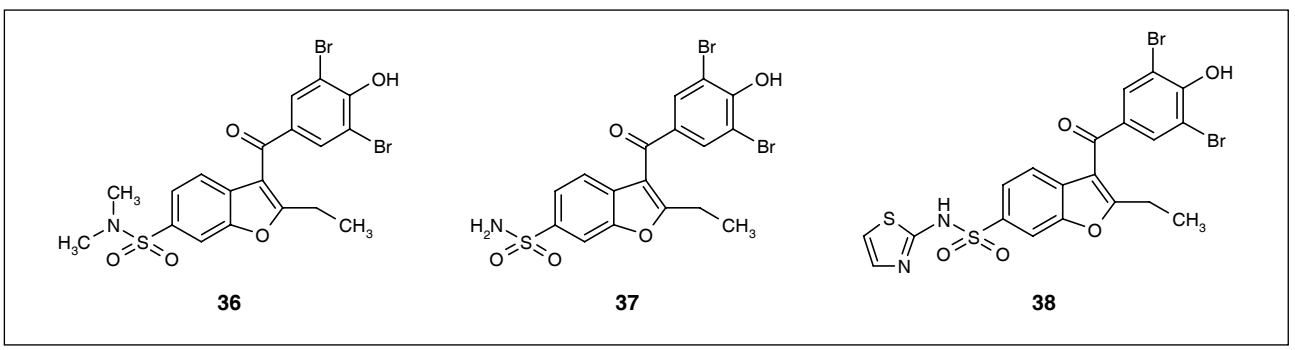

Fig. 9. Benzofurane PTP-1B inhibitors.

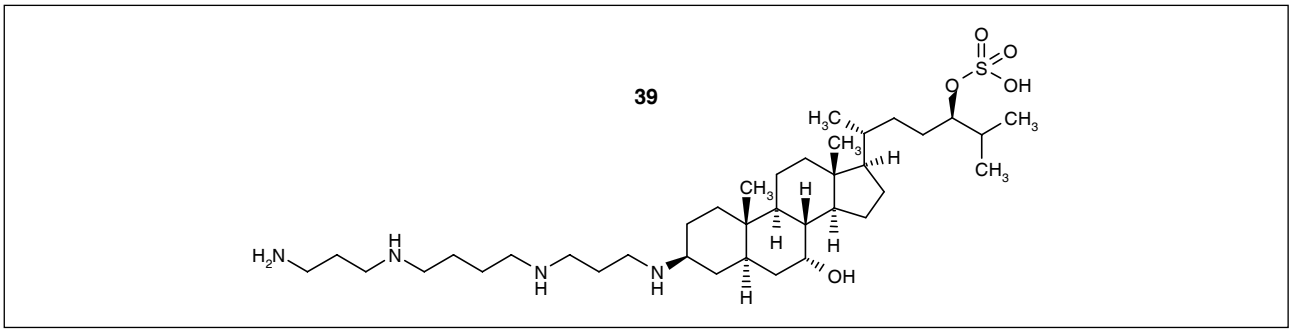

Fig. 10. Structure of trodusquemine.

gesting a mechanism of inhibition not directed at the active site. Optimization of compound **36** led to the identification of compounds **37** (IC_{50} = 22 μM) and **38** (IC_{50} = 8 μM). Compound **37** exhibited no time-dependent inhibition, showed over 90% reversibility and maintained inhibition at low compound-to-protein stoichiometry (consistent with a site-specific binding mechanism) (62). Compound **36** showed selectivity for PTP-1B over the related phosphatase LAR (IC_{50} > 500 μM). High-resolution crystal structures of PTP-1B revealed that these inhibitors bind to a novel site located 20 Å away from the catalytic pocket.

Compound **38** was tested in Chinese hamster ovary (CHO) cells overexpressing the human IR (CHO-hIR) and produced a clean phosphorylation pattern comparable to that of insulin, while being devoid of the promiscuous phosphorylation seen with pervanadate (IC_{50} = 250 μM). Compound **38** also induced phosphorylation of IRS-1 and Akt, proteins downstream of the insulin receptor. The authors concluded that the discovery of an allosteric site in PTP-1B offers new hope for the development of PTP-1B inhibitors with pharmacological properties that are suitable for the treatment of obesity and diabetes (62).

Trodusquemine (MSI-1436, **39**; Fig. 10) is a centrally acting appetite suppressant developed by Genaera for the treatment of diabetes and obesity. MSI-1436 induces consistent and sustained weight loss in a variety of animal models and reverses co-morbidities associated with obesity, such as abnormal glucose metabolism and elevated cholesterol (63).

The appetite-suppressing activity of this compound was discovered serendipitously during a search for antimicrobial compounds in the dogfish shark (64, 65). Early last year, the company reported inhibition of PTP-1B as the mechanism of action for the weight-reducing effect of MSI-1436 (66), and *in vitro* kinetic data demonstrated that trodusquemine is an allosteric, noncompetitive, reversible inhibitor of PTP-1B and can cross the blood-brain barrier. However, other mechanisms of action have been proposed for trodusquemine, including binding to receptors in the central nervous system or to a putative polyaminosterol receptor. The compound is currently undergoing early clinical evaluation for the treatment of obesity.

Conclusions

There is a significant body of evidence supporting the role of PTP-1B as a negative regulator of IR phosphorylation and signaling. More recently, emerging data suggest a role for PTP-1B in various cancer cells and tumors, indicating that PTP-1B inhibition could be useful for oncology applications. Tremendous drug discovery efforts have been invested on this target and numerous potent PTP-1B inhibitors have been identified. Newly disclosed analogues are focused on addressing the lack of cell permeability and oral bioavailability by replacing the highly charged phosphate group and identifying heterocyclic carboxylic acid mimetics, inhibitors that act through an oxidoreduction mechanism, as well as allosteric inhibitors with improved physicochemical properties. Despite all these efforts, potent, selective, cell-permeable and orally available agents remain elusive and new strategies are needed to identify PTP-1B inhibitors with the requisite properties.

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