New Azolidinediones as Inhibitors of Protein Tyrosine Phosphatase 1B with Antihyperglycemic Properties

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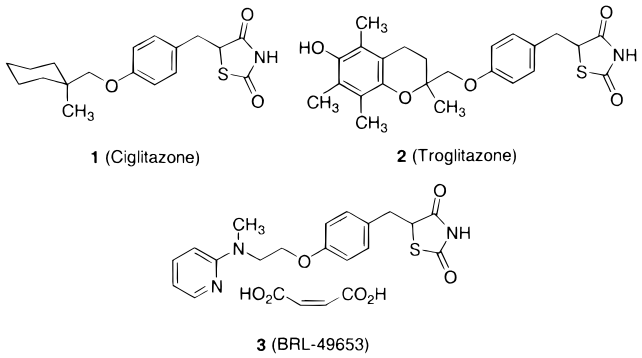
Insulin resistance in the liver and peripheral tissues together with a pancreatic cell defect are the common causes of type 2 diabetes. It is now appreciated that insulin resistance can result from a defect in the insulin receptor signaling system, at a site post binding of insulin to its receptor. Protein tyrosine phosphatases (PTPases) have been shown to be negative regulators of the insulin receptor. Inhibiton of PTPases may be an effective method in the treatment of type 2 diabetes. A series of azolidinediones has been prepared as protein tyrosine phosphatase 1B (PTP1B) inhibitors. Several compounds were potent inhibitors against the recombinant rat and human PTP1B enzymes with submicromolar IC_{50} values. Elongated spacers between the azolidinedione moiety and the central aromatic portion of the molecule as well as hydrophobic groups at the vicinity of this aromatic region were very important to the inhibitory activity. Oxadiazolidinediones **87** and **88** and the corresponding acetic acid analogues **119** and **120** were the best h-PTP1B inhibitors with IC_{50} values in the range of 0.12−0.3 μM. Several compounds normalized plasma glucose and insulin levels in the *ob/ob* and *db/db* diabetic mouse models.

Introduction

Insulin resistance in the liver and peripheral tissues together with a pancreatic cell defect are the common causes of type 2 diabetes.[1] The prevalence of insulin resistance in prediabetic or glucose-intolerant subjects has long been recognized.[2] The failure of insulin to adequately suppress hepatic glucose output postprandially combined with the reduced glucose disposal by the peripheral tissues lead to abnormal glycemic control after feeding. The increased and sustained plasma glucose levels gradually progress into a number of debilitating diabetic complications as retinopathy, neuropathy, nephropathy, atherosclerosis, and coronary artery disease.[3] Therefore, it is essential to control blood glucose at the early stages of the disease.

Treatment of type 2 diabetes usually consists of diet, exercise, and hypoglycemic agents. Sulfonylureas are the most widely used antidiabetic agents. These agents act by increasing insulin secretion but often are ineffective after 5 years of treatment.[4] Since the pioneering discovery of ciglitazone **(1)** (Chart 1) by Takeda scientists,[5] which reduced insulin resistance and normalized plasma glucose levels in genetically diabetic and/or obese animal models, a plethora of new thiazolidinediones have been developed.[6] Troglitazone **(2)**, a thiazolidinedione-type pharmacological agent, has been effectively used as an insulin-enhancing agent in a large number of insulin-resistant patients.[7] However, troglitazone has produced severe liver toxic effects in a small number of patients. Recently, SmithKline Beecham's thiazolidinedione BRL-49653 (rosiglitazone, **3**) has been approved for marketing in the United States, and patients on this new agent will also be monitored for potential liver toxicity.

Chart 1



It is now appreciated that insulin resistance is the result of a defect in the insulin receptor signaling system, at a site post binding of insulin to its receptor. Accumulated scientific evidence demonstrating insulin resistance in the major tissues which respond to insulin (muscle, liver, adipose) strongly suggests that the defect in insulin signaling resides at an early step in the signal transduction cascade, specifically at the level of the insulin receptor kinase activity, which appears to be diminished.[8]

Protein tyrosine phosphatases (PTPases) play an important role in the regulation of signal transduction pathways and the phosphorylation of proteins. The interaction of insulin with its receptor leads to the phosphorylation of certain tyrosine molecules (1146, 1150, and 1151) within the receptor protein, thus activating the receptor kinase. PTPases dephosphorylate the activated insulin receptor, attenuating the

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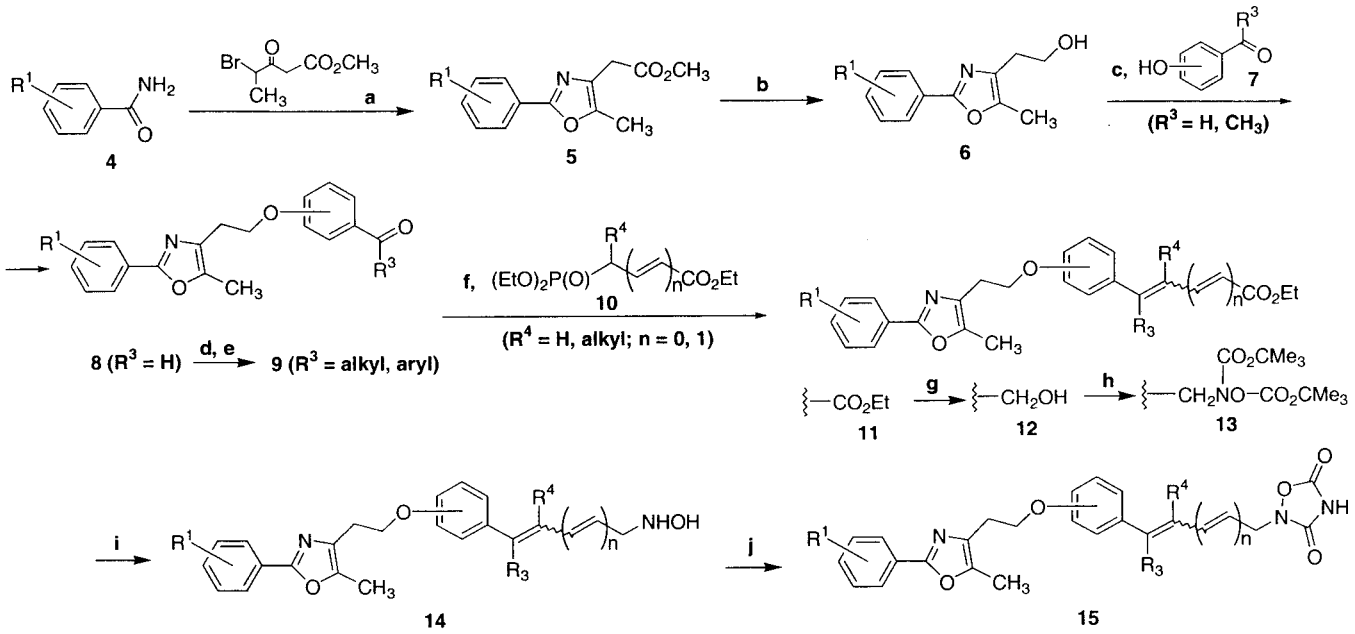
Scheme 1



Reagents: (a) $C_6H_5CH_3$, dioxane, reflux; (b) $LiAlH_4$, Et_2O; (c) Diethylazodicarboxylate, Ph_3P, THF, 7; (d) Alkyl(aryl)MgCl, Et_2O; (e) Jones Reagent, acetone; (f) NaH, $C_6H_5CH_3$, 10; (g) DIBAL, Et_2O; (h) Diethyl azodicarboxylate, Ph_3P, $Me_3CO_2CNHOCO_2CMe_3$, THF; (i) TFA, CH_2Cl_2; (j) ClCONCO, THF.

tyrosine kinase activity. PTPases can also modulate postreceptor signaling by catalyzing the dephosphorylation of cellular substrates of the insulin receptor kinase. The enzymes that appear most likely to closely associate with the insulin receptor and therefore most likely to regulate the insulin receptor kinase activity include PTP1B, LAR, PTPα, and SH-PTP2.[9]

McGuire et al.[10] demonstrated that nondiabetic glucose-intolerant subjects possessed significantly elevated levels of PTPase activity in muscle tissue vs normal subjects and that insulin infusion failed to suppress PTPase activity as it did in insulin-sensitive subjects. Meyerovitch et al.[11] observed significantly increased PTPase activity in the livers of two rodent models of type 1 diabetes, the genetically diabetic BB rat and the STZ-induced diabetic rat. Sredy et al.[12] observed similar increased PTPase activity in the livers of obese, diabetic *ob/ob* mice, a genetic rodent model of type 2 diabetes.

Vanadium-containing inhibitors of PTPase have been shown to increase insulin receptor tyrosine phosphorylation, exert insulin-like effects in vitro and in vivo, and decrease hyperglycemia in insulin-deficient animals.[13]

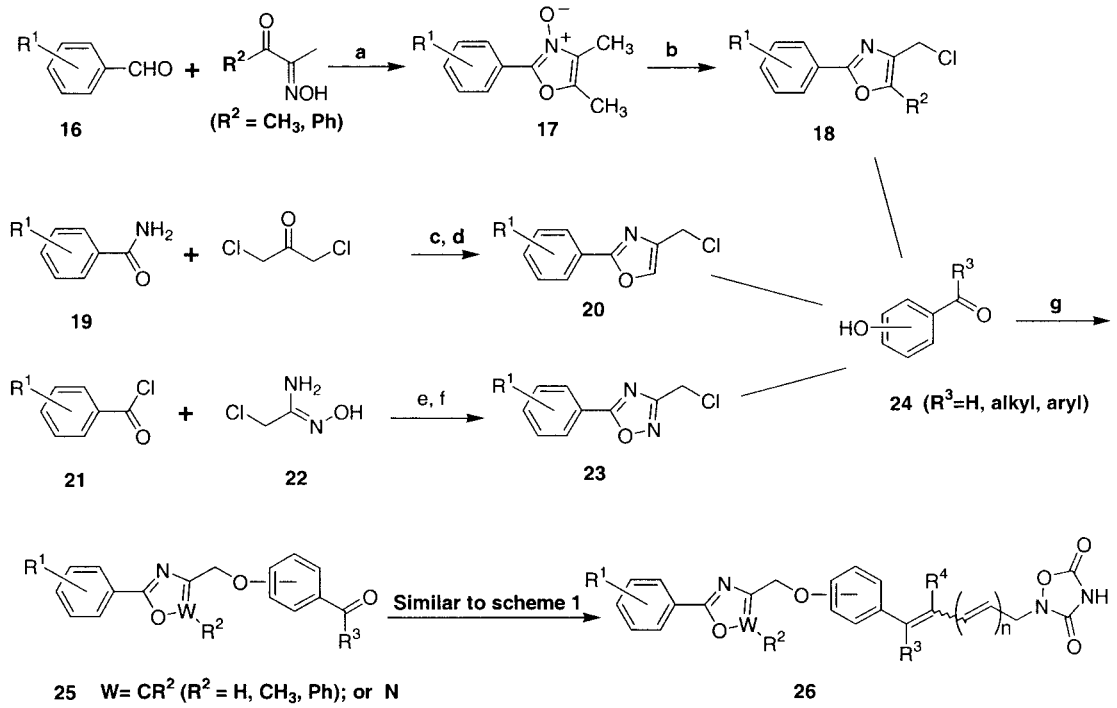
PTP1B, an intracellular nonreceptor PTPase, has shown to play a major role in the dephosphorylation of the insulin receptor in many cellular and biochemical studies.[14] A recent study with PTP1B knockout mice[15] has also demonstrated that loss of PTP1B activity resulted in an enhancement of the insulin sensitivity and resistance to weight gain. Potent and orally active PTP1B inhibitors could be potential pharmacological agents for the treatment of type 2 diabetes and obesity.

We have evaluated a number of azolidinediones previously synthesized in our laboratories and found that several azolidinediones exhibited inhibitory activity against a preparation of rat hepatic membrane, a source of PTPase enzyme(s). The active compounds belonged to an unexplored subclass of azolidinediones, where elongated spacers were introduced between the azolidinedione moiety and the central aromatic region of the compounds. In the present study, we are reporting a detailed systematic structure−activity relationship (SAR) study of azolidinediones as PTPase inhibitors and the identification of potent PTP1B inhibitors. Several azolidinediones normalized plasma glucose and insulin levels in genetically diabetic and/or obese animal models of type 2 diabetes.

Chemistry

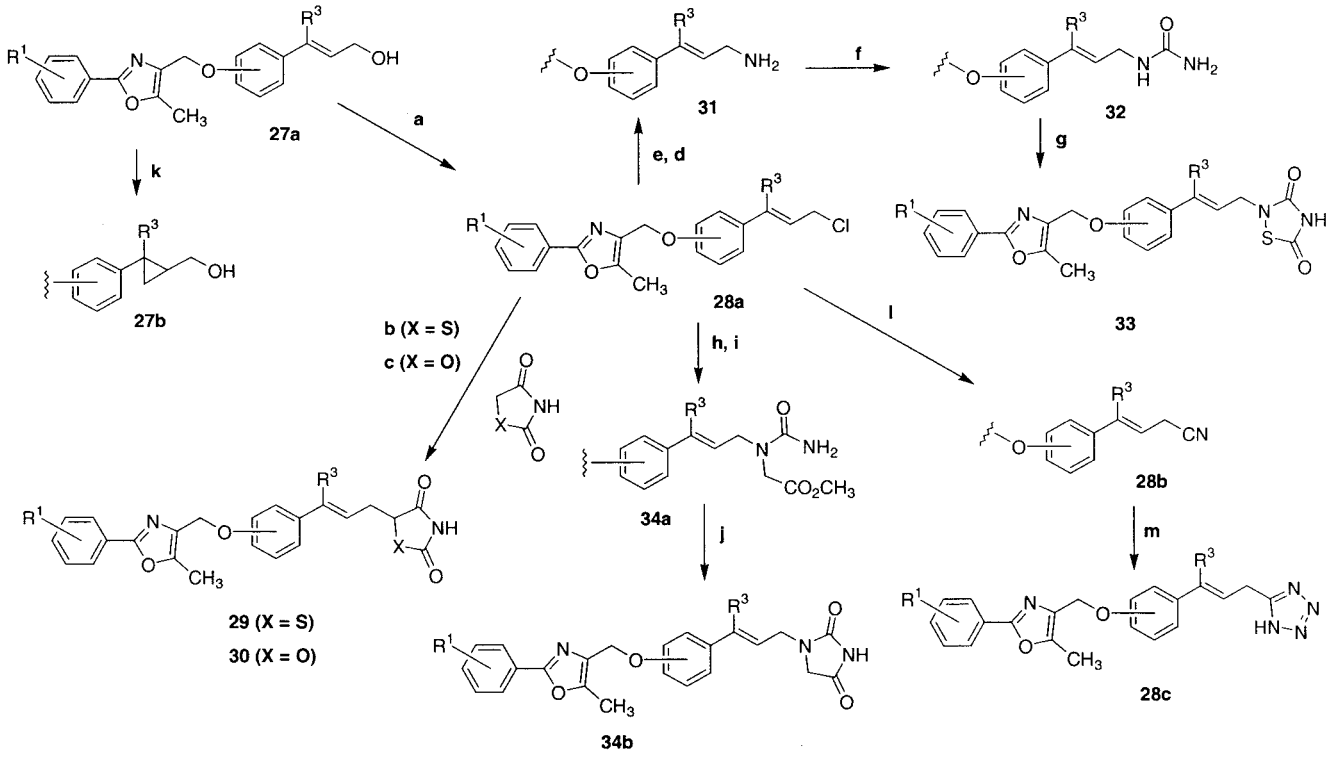
The azolidinediones described in this paper were prepared according to the synthetic Schemes 1−5. The ethoxy-linked oxadiazolidinediones (Table 1; $n = 2$) were prepared according to Scheme 1. Refluxing benzamide **4** with 4-bromopropionyl acetate produced ester **5**.[16] Reduction of ester **5** with lithium aluminum hydride afforded alcohol **6**. Coupling of compound **6** with either hydroxybenzaldehyde or hydroxyacetophenone **7**, using the Mitsunobu protocol,[17] produced phenoxy azoles **8**. Azoles **8,** where $R^3 = H$, were treated with Grignard reagents (alkyl or aromatic) followed by Jones oxidation to afford azoles **9**. Elongation of azoles **8** and **9** ($R^3 = H$, alkyl, aryl) was achieved by the Horner−Wadsworth−Emmons modification[18] of the Witting reaction using various commercially available phosponates **10** to generate **11**. Reduction of esters **11** with diisobutylaluminum hydride produced alcohols **12**, which were converted to hydroxylamines **14** by a two-step process. First, application of the Mitsunobu protocol using *tert*-butyl *N*-(*tert*-butoxycarbonyloxy)carbamate produced dicarboxylated hydroxylamines **13**, which upon treatment with trifluoroacetic acid afforded hydroxylamines **14**. The hydroxylamines **14** were converted to the oxadiazolidinediones **15** with *N*-(chlorocarbonyl)isocyanate at low temperatures (0−5 °C).

Scheme 2



Reagents: (a) HCl, EtOAc; (b) $POCl_3$, $CHCl_3$; (c) $NaHCO_3$, $ClCH_2CH_2Cl$; (d) $SOCl_2$; (e) K_2CO_3, dioxane; (f) xylenes, reflux; (g) K_2CO_3, DMF.

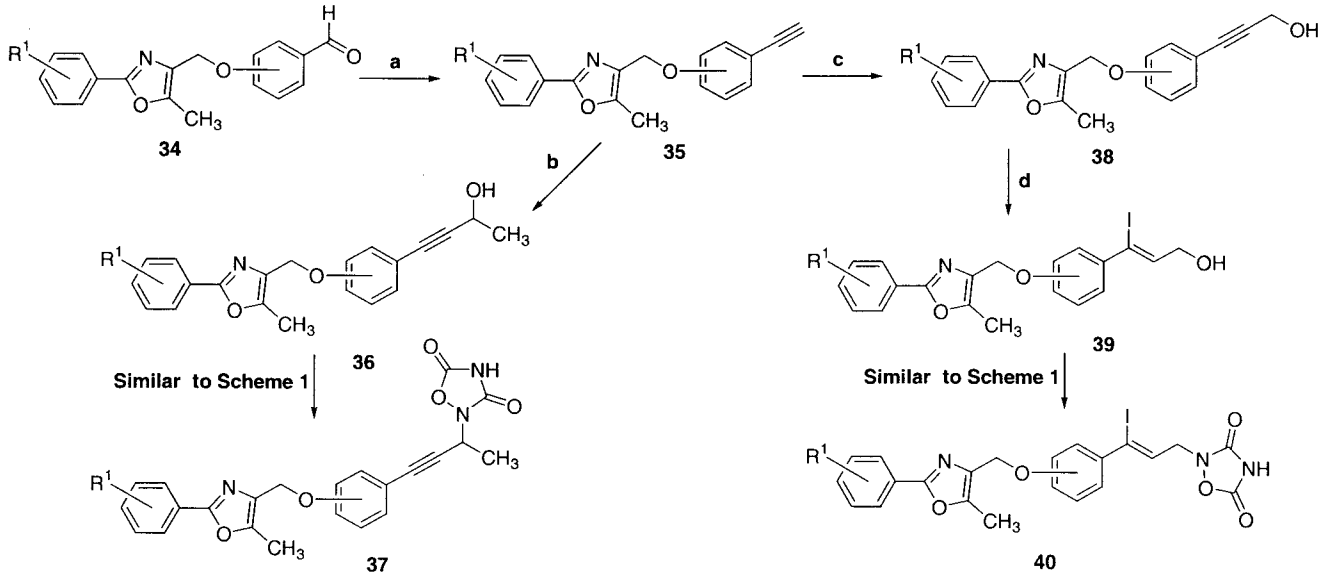
Scheme 3



Reagents: (a) PCl_5, $CaCO_3$; (b) n-BuLi, THF; (c) *tert*-BuLi, LiCl, THF; (d) NaN_3, DMF; (e) $LiAlH_4$, THF; (f) Me_3SiNCO, dioxane; (g) $ClCOSCl$, C_6H_6, reflux, (h) $NH_2CH_2CO_2CH_3$, Et_3N; (i) KNCO, AcOH, H_2O; (j) NaH, DMF; (k) Et_2Zn, $ClCH_2I$, $ClCH_2CH_2Cl$; (l) NaCN, H_2O; (m) NaN_3, NH_4Cl, DMF.

The methoxy-linked oxadiazolidinediones (Tables 1 and 2; $n = 1$) were prepared according to Schemes 1 and 2. Treatment of benzaldehyde **16** (Scheme 2) with 2,3-butanedione monoxime or 1-phenyl-1,2-propanedione 2-oxime produced oxazole *N*-oxides **17**. Deoxygenation of **17** with phosphorus oxychloride afforded ox-

Scheme 4



Reagents: (a) $BrCH_2P(C_6H_5)_3Br$, $(CH_3)_3COK$, THF; (b) $LiN(SiMe_3)_2$, CH_3CHO, THF; (c) $LiN(SiMe_3)_2$, $(CH_2O)n$, THF; (d) $NaOCH_3$, $LiAlH_4$, I_2, THF.

azoles **18**.[19] The desmethyl oxazoles **20** were prepared from the appropriately substituted amides **19** upon condensation with 1,3-dichloroacetone and subsequent dehydration with thionyl chloride. The oxadiazoles **23** were prepared from amidoxime **22** upon condensation with benzoyl chlorides **21**.[20] Phenols **24** were alkylated with either chloromethyl oxazoles **18** and **20** or oxadiazoles **23** in the presence of potassium carbonate to afford **25**. Oxa(dia)zoles **25** were converted to the final products **26** in a similar manner as described in Scheme 1.

The methoxy-linked thia-, oxa-, thiadia-, and imidazolidinediones (Table 1) were prepared according to Scheme 3. Alcohol **27a** was treated with phosphorus pentachloride and calcium carbonate to produce allylic chloride **28a**, which was further coupled with either the thiazolidinedione or oxazolidinedione dianions to produce the thia- and oxazolidinediones **29** and **30**. 2,4-Thiazolidinedione was first treated with *n*-buyllithium to generate the dilithio-2,4-thiazolidinedione and then treated with chloride **28a** to afford **29.** The dilithio-2,4-oxazolidinedione was generated with *tert*-butyllithium. Lithium chloride was very essential for the coupling of the dilithio-2,4-oxazolidinedione with chloride **28a.** Treatment of the allylic chloride **28a** with sodium azide produced the corresponding allylic azide, which was converted to amine **31** with lithium aluminum hydride. Amine **31** was first reacted with trimethylsilyl isocyanate to afford urea **32**, which upon further reaction with chlorocarbonylsulfenyl chloride produced thiadiazolidinedione **33.**

Chloride **28a** was converted to the imidazolidinedione **34b** by a three-step process. First, chloride **28a** was treated with glycine methyl ester in the presence of triethylamine, followed by urea formation (**34a**) with potassium isocyanate, and finally cyclization with sodium hydride afforded **34b**.

The acetylenic-linked oxadiazolidinediones **77** and **78** (Table 2) were prepared according to Scheme 4. Benzeldehyde **34** was treated with (bromomethyl)triphenylphosphonium bromide and potassium *tert*-butoxide to produce acetylene **35**. Compound **35** was treated with lithium bis(trimethylsilyl)amide and acetaldehyde to produce alcohol **36**. Conversion of **36** to the final product **37** was accomplished according to Scheme 1. The iodo analogue **40** was prepared from acetylene **35** upon treatment with lithium bis(trimethylsilyl)amide and formaldehyde to afford alcohol **38**, which was converted to vinyl iodide **39** with lithium aluminum hydride, sodium methoxide, and iodine.[21] Conversion of **39** to the final product **40** was accomplished according to Scheme 1.

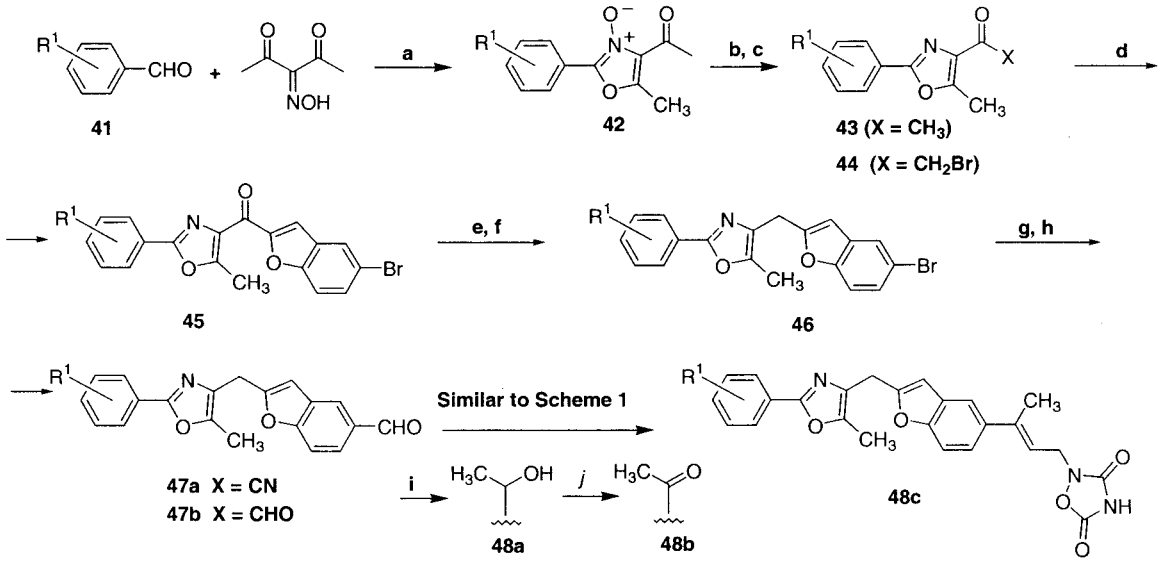
The cyclopropane analogues **79** and **80** (Table 2) were prepared from alcohols **27a** (Scheme 3). Treatment of **27a** with diethylzinc and chloroiodomethane produced the corresponding cyclopropane alcohols **27b**, which were further converted to the final products according to Scheme 1.

The saturated analogues **69** and **76** (Table 2) were prepared from the corresponding olefins by catalytic hydrogenation.

Benzofuran **101** (Table 3) was prepared according to Scheme 5. Treatment of benzaldehyde **41** with 2,3,4-pentanetrione 3-oxime produced oxazole *N*-oxide **42**. Deoxygenation of **42** with phosphorus oxychloride afforded oxazole **43**. Treatment of **43** with bromine furnished **44**, which upon condensation with 3-bromo-2-hydroxybenzaldehyde in the presence of sodium methoxide afforded benzofuran **45**. Reduction of the ketone first with sodium borohydride to the corresponding alcohol and second with triethylsilane/trifluoroacetic acid produced benzofuran **46**. Conversion of the aromatic bromide of **46** to a formyl group was achieved in a two-step process: first, generation of nitrile **47a** with copper cyanide in *N*,*N*-dimethylformamide from **46**, and second reduction of **47a** with Al-Ni in formic acid afforded **47b**. Aldehyde **47b** was converted to the final product **48c** according to Scheme 1.

The *N*-acetic acid analogues **118**−**122** (Table 4) were prepared by alkylation of the corresponding oxadiazoli-

Scheme 5



Reagents: (a) HCl, EtOAc; (b) $POCl_3$, $CHCl_3$; (c) Br_2, $CHCl_3$; (d) $NaOCH_3$, EtOH, 3-Br-2-OH-C_6H_3CHO; (e) $NaBH_4$ MeOH, THF; (f) Et_3SiH, TFA, CH_2Cl_2; (g) CuCN, DMF; (h) Al-Ni, 70% HCO_2H; (i) CH_3MgCl, Et_2O; (j) Jones Reagent, acetone.

dinediones with *tert*-butyl bromoacetate/K_2CO_3 and subsequent acidic hydrolysis with trifluoroacetic acid.

Tetrazole **123** (Table 4) was prepared from the allylic chloride **28a** (Scheme 3) upon treatment with sodium cyanide to furnish the allylic nitrile **28b** and subsequent conversion of **28b** to tetrazole **28c** with sodium azide and ammonium chloride.

Results and Discussion

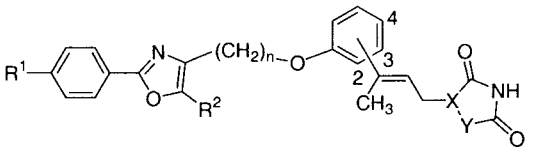
The test compounds were evaluated for their in vitro inhibitory activity against recombinant human[22] and rat[23] PTP1B, as well as a rat hepatic membrane preparation as the source of PTPase enzyme (s), with phosphotyrosyl dodecapeptide TRDI(P)YETD(P)Y(P)-YRK (corresponds to the 1142−1153 insulin receptor kinase regulatory domain, phosphorylated on the 1146, 1150, and 1151 tyrosine residues; IR-triphosphopeptide), and *p*-nitrophenyl phosphate (pNPP) as sources of the substrate.[30] Enzyme reaction progression was monitored via the release of inorganic phosphate as detected by the malachite green−ammonium molybdate method for the phosphopeptide and the amount of *p*-nitrophenolate ion released from pNPP.[24,27]

The in vitro activity was expressed either as the concentration of the test compound which inhibited enzyme activity by 50% (IC_{50}) or as the average inhibition of the test compounds at 50, 10, and 2.5 μM concentrations. Samples were prepared in quadruplicates.

The test compounds were evaluated in vivo for their ability to decrease plasma glucose levels in the genetically obese C57 B1/6J *ob/ob* and diabetic C57BL/KsJ *db/db* mouse models. The *ob/ob* animal model is severely insulin resistant, hyperinsulinemic, and glucose intolerant. Insulin resistance in this model has been associated with a reduction in insulin-induced protein tyrosine phosphorylation in tissues such as liver. Also, elevated PTPase activity in the liver of obese *ob/ob* mice has been observed, which may cause or contribute to the decline in receptor and postreceptor tyrosine phosphorylation.[12] The *db/db* model is also glucose intolerant with fasting hyperglycemia and occasional hyperinsulinemia. The in vivo activity was assessed at a daily dose of 10−100 mg/kg (po) for 4 days and measured as a specified decrease in plasma glucose and insulin levels of the drug-treated group relative to a vehicle-treated control group. A 50−60% (*db/db*) and 30−40% (*ob/ob*) decrease in plasma glucose level generally normalizes glucose to levels that are similar to the nondiabetic controls. Ciglitazone was the reference standard in all of the assays.

In Vitro Studies. In the early stage of our discovery program, we evaluated a number of azolidinediones previously synthesized in our laboratories and found that several among them exhibited inhibitory activity against a preparation of rat hepatic membrane, a source of PTPase enzyme(s), with pNPP as the substrate. Ciglitazone-like compounds, where a methylene group linked the thiazolidinedione ring with the central phenyl ring of the molecule, were either weakly active at 250 μM or inactive (data not shown). The propene-elongated analogues (Table 1) exhibited promising inhibitory activity against rat liver PTPase enzyme(s) at 50 μM concentrations. These early findings, combined with the good in vivo activity of these molecules in the *db/db* and *ob/ob* diabetic mouse models, prompted us to further explore the SAR of such compounds as PTPase inhibitors. In the initial phase of our studies we used a rat hepatic membrane preparation as the source of the enzyme(s), with pNPP as the substrate. As our program progressed, we used either recombinant rat or human PTP1B enzyme as the enzyme source and phosphotyrosyl dodecapeptide TRDI(P)YETD(P)Y(P)YRK as the substrate. This phosphopeptide, corresponding to the major site of autophosphorylation of the insulin receptor, has been shown to be an attractive substrate in

Table 1. Chemical and Biological Data of Oxazole Azolidinediones[h]



								% inhibition of PTPase activity		% decrease in plasma glucose		% decrease in plasma insulin
compd	R^1	R^2	n	P.O.A[g]	X	Y	mp. ^{0}C	pNPPase[a] (50 uM)	r-PTP1B[b] IC_{50} (uM)	db/db mouse[f] 100 mg/kg/day	ob/ob mouse 100 mg/kg/day	ob/ob mouse 100 mg/kg/day
49	H	CH_3	1	3	N	O	131-132	35		28±10*	39**	76**
50	H	CH_3	1	3	CH	O	138-139	23		18±10		
51	H	CH_3	1	3	CH	S	48-49	5		NS[e]		
52	H	CH_3	2	3	N	O	141-142	45	24 (10 uM)	38±10*		
53	H	CH_3	2	3	CH	O	99-100	36		NS		
54	CF_3O	CH_3	1	3	N	O	144-145	57		41±7*	39**	82**
55	CF_3O	CH_3	1	3	CH	O	104-105	27	46 (10 uM)	40±7*		
56	CF_3O	CH_3	1	3	CH	S	50-51	46	1.5	18±4	44**	63**
57	CF_3CH_2O	CH_3	1	3	N	O	161-162	52		44±6*		
58	CF_3CH_2O	CH_3	1	3	CH	O	119-120	37		NS		
59	CF_3	CH_3	1	3	N	O	137-138	49	1.9	62±1*	58** 20 (10 mg/kg)*	86**
60	CF_3	CH_3	1	3	N	S	60-61		3.8		29*	26*
61	CF_3	CH_3	1	4	N	O	198-199		4.3	16±5*		
62	CF_3	CH_3	2	4	N	O	180-181	63	1.6	NS		
63	CF3	CH_3	1	2	N	O	117-118		43 (10 uM)			
64	CF_3	CH_3	1	3	N	CH	154-155		13 (10 uM)			
65	CF3	Ph	1	3	N	O	159-160		0.3[c]		25	30
66	CF3	H	1	3	N	O	137-139	32	19 (10 uM)			
ciglitazone								20 (250 uM)		32[d]		
troglitazone								29 (250 uM)		34*		

[a] pNPP used as the substrate and rat hepatic membrane as the source of PTPase enzyme(s). [b] IR-triphosphopeptide used as the substrate and recombinant r-PTP1B as the enzyme. [c] IR-triphosphopeptide used as the substrate and recombinant h-PTP1B as the enzyme. [d] Mean of 38 experiments, $p < 0.05$. [e] NS: not significant, generally less than −15% change. [f] Values (mean ± SE) are percent change relative to vehicle-treated group with use of 4−6 mice/group; *$p < 0.05$ and **$p < 0.01$ when compared to vehicle-treated mice. [g] Point of attachment to the phenyl ring. [h] All compounds were prepared according to the synthetic Schemes 1−3.

varying degrees for several PTPases, including PTP1B, LAR, CD45, and TCPTPase.[26]

Results with the propene-linked oxazole azolidinediones are shown in Table 1**.** Oxadiazolidinedione **49** exhibited modest inhibitory PTPase activity at 50 μM and was similar to oxazolidinedione **50**, while the thiazolidinedione **51** was inactive. The ethoxy-linked (n = 2) oxadia- and oxazolidinediones **52** and **53** demonstrated similar in vitro activity to the methoxy-linked (n = 1) analogues **49** and **50**, respectively. Substitutions on the 2-phenyl group of the oxazole tail produced more active in vitro compounds. The trifluoromethoxy-substituted thiazolidinedione **56** inhibited PTPase activity by 46% at 50 μM, while the unsubstituted analogue **51** was inactive. Compound **56** was one of the our initial analogues that inhibited r-PTP1B at a micromolar concentration (IC_{50} = 1.5 μM). The analogous oxazolidinedione **55** was weaker than **56**. The trifluoromethyl analogue **59** of **49** was more potent with an IC_{50} value of 1.9 μM against r-PTP1B. The recombinant r-PTP1B enzyme/IR-triphosphate assay proved to be more sensitive to our compounds, as depicted by the greater degree of inhibition for examples **56** and **59**. The thiadiazolidinedione **60** and the *p*-oxadiazolidinedione **61** were 2-fold less active than **59**. The ethoxy-linked para-substituted analogue **62** was similar to **59** in vitro. The ortho-substituted oxadiazolidinedione **63** was much weaker than the meta-substituted analogue **59**. Substitutions at position-5 of the oxazole ring appeared to be more critical to the enzyme inhibition. The 5-phenyl analogue **65** was 6-fold better than the 5-methyl analogue **59** with an IC_{50} value of 0.3 μM, while the unsubstituted analogue **66** was only weakly active at 10 μM.

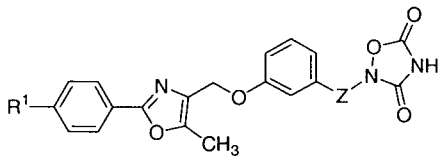
Our initial assessment indicated that meta-substituted oxadiazolidinediones have demonstrated a better in vitro profile, and we further focused our SAR studies on this series of compounds. Modifications of the linkers between the oxadiazolidinedione ring and the central aromatic region are shown in Table 2. The *E*- and *Z*-isomers **49** (Table 1) and **67** were similar in vitro. Various monomethyl and dimethyl analogues **70**−**76** were similar in vitro to **59**. The substituted trifluoromethylacetylene **78** was better than **77** in vitro. The cyclopropane analogue **80** was similar to **59** in vitro. Replacement of the methyl group, attached to the propene linker of **59**, with longer alkyl chains resulted in a marked increase in the inhibitory activity. The *E*- and *Z*-octyl analogues **87** and **88** were submicromolar inhibitors of r-PTP1B, with IC_{50} values of 0.4 and 0.2 μM, respectively. Shorter alkyl groups (ethyl, propyl, butyl) were less active in vitro. Compounds **84**, **86**, and **88** also demonstrated comparable potency against recombinant h-PTP1B with IC_{50} values in the range of 0.3−1.9 μM. The 5-phenyl oxazole analogue **117** (Table 4) of **86** exhibited a 4-fold increase in inhibitory potency (IC_{50} = 0.37 μM) against h-PTP1B. The bulky *tert*-butyl analogue **89** had an IC_{50} value of 0.6 μM against r-PTP1B. The long and/or bulky lipophilic substituents at the vicinity of the central aromatic region, which produced marked increases in inhibitory potency, may play a key role in inhibitor/protein hydrophobic interactions. Further replacement of the methyl group with iodine, cyclohexyl, phenyl, benzyl, and substituted phenyl moieties with either electron-withdrawing or electron-donating groups **(90**−**96)** produced r-PTP1B inhibitors with IC_{50} values in the range of 0.8−1.4 μM. The only exception was the 4-methoxyphenyl analogue **96**, which was modestly active at 2.5 μM. Elongation of the propene linker with pentadienes (**97** and **98**) produced similar in vitro activity to **59**.

Modifications of the central aromatic region produced weaker in vitro inhibitors (Table 3). Benzofuran **100**, where the propene linker of **59** was connected to the central phenyl ring via benzofuran formation, was found to be inactive in vitro. However, the benzofuran analogue **101**, where the propene linker is attached to the phenyl portion of the molecule, demonstrated good activity against r-PTP1B. These findings suggest that space constraints between the oxadiazolidinedione ring and the central aromatic region may be critical to the inhibitory activity of these compounds. The indan analogue **102** was also active in vitro.

Further modifications included the replacement of the oxazole tail of **59** with aromatic or heteroaromatic moieties (Table 4). Analogues **106**−**109**, where phenoxy or benzyloxy groups with electron-withdrawing groups (chlorine, trifluoromethyl) were introduced in the molecule, were active against r-PTP1B with IC_{50} values in the range of 0.8−4.1 μM. Unsubstituted (**103**) or substituted phenoxy **(104**−**105)** analogues with electron-donating groups (methyl, methoxy) were inactive against r-PTP1B. The naphthyl analogue **112** was weakly active at 2.5 μM. Benzofuran analogues **113** and **114** had IC_{50} values of 2.7 and 1.3 μM, respectively. The pyridine **115** and oxadiazole **116** were inactive at 2.5 μM.

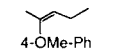
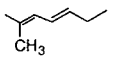
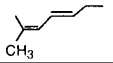
In Vivo Studies. The oxadiazolidinediones **49** and **52** (Table 1) were active in vivo at a dose of 100 mg/kg, decreasing plasma glucose levels in the *db*/*db* mouse by 28% and 38%, respectively. Compound **49** also normalized plasma glucose levels in the *ob*/*ob* mouse at 100 mg/kg. The substituted trifluoromethyl analogue **59** which was better in vitro decreased plasma glucose levels in the *ob*/*ob* mouse by 20% at a dose of 10 mg/kg and normalized glucose levels in the *db*/*db* mouse at the 100 mg/kg dose. Compound **65**, while being one of our best compounds against h-PTP1B (IC_{50} = 0.3 μM), was only weakly active in vivo. One reason of this poor correlation may due to the higher lipophilic properties of **65** (phenyl analogue) versus **59** (methyl analogue). Substitutions on the olefinic linker of the compounds (Table 2) played a more critical role on their in vivo efficacy. The monosubstituted analogues appeared to be more potent in vivo, normalizing plasma glucose levels at 100 mg/kg, while the disubstituted analogues were either weakly active or inactive. Lower alkyl groups (methyl, ethyl, propyl, butyl) were superior to the more hydrophilic groups (octyl, *tert*-butyl). The decline in the in vivo potency of the analogues with the longer lipophilic tails (octyl analogues; **87**, **88**), despite their superior in vitro properties, may be due to the higher degree of lipophilicity of these compounds (*CLog P* = 7.4). The alkyl analogues with chain lengths of 1−4 carbons (**59**, **80**, **84**, **86**) had *CLog P* values in the range of 3.8−5.3. In an attempt to improve the oral efficacy of our compounds, we prepared the acetic acid analogues **118**−**122** (Table 4) as less hydrophobic compounds. This modification produced compounds with lower lipophilic

Table 2. Chemical and Biological Data of Oxazole Azolidinediones[g]



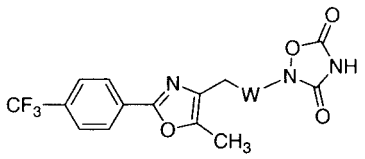
compd	R^1	Z	mp, ^0C[d]	% inhibition of PTPase activity: pNPPase[a] (50 uM)	% inhibition of PTPase activity: r-PTP1B[b] 50 uM	% decrease in plasma glucose: db/db mouse[f] 100 mg/kg/day	% decrease in plasma glucose: ob/ob mouse 100 mg/kg/day	% decrease in plasma insulin: ob/ob mouse 100 mg/kg/day
67	H		118-119	25		49±9*	30**	75**
68	CF_3		179-181	49		NS[e]		
69	CF_3		141-142	54	4.3	21±3*		
70	CF_3		144-146	IC_{50} = 71[a1]	7	36±8*	37**	28**
71	CF_3		119-121	49		41±3*	NS (50 mg/kg)	83** (50 mg/kg)
72	Cl		172-174	33		20±5		
73	CF_3		144-145	47		20±5		
74	CF_3		152-153	54		NS		
75	CF_3		55-56	38		16±4		
76	OCF_3		94-95	47		41±4*		
77	H		55-57	23				
78	CF_3		84-86	56	47 (10 uM)	30±5*	32**	91**
79	CF_3		126-128	51	28 (10 uM)	36±13*		
80	CF_3		41-42	51	1			
81	CF_3		66-67	57	90 (10 uM)	63±2*	71** 32 (20 mg/kg)**	80** 32 (20 mg/kg)
82	CF_3		126-127	56	80 (10 uM)	65±2*		
83	CF_3		124-125	58		24±10*		
84	CF_3		135-136	58	2.0[b] 1.9[c]	59±1*	58**	82**
85	CF_3		122-124	58		55±8*		
86	CF_3		123-124		1.9 1.4[c]		61**	88**
87	CF_3				0.4		43**	NS
88	CF_3		94-95	68[a1]	0.2 0.3[c]		21*	31
89	CF_3		87-88	IC_{50} = 24[a1]	0.6		NS	NS
90	CF_3		95-96	51	1.8		38**	64**
91	CF_3		58-60	66[a1]	49 (2.5 uM)			
92	CF_3		130-132	24[a1]	1.1		55**	74**
93	CF_3		159-160		0.8		23	46**
94	CF_3		141-142	IC_{50} = 28[a1]	1.2		34**	38**
95	CF_3		174-175	IC_{50} = 27[a1]	1.4			

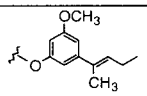
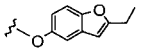
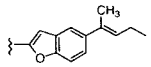
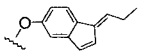
Table 2 (Continued)

compd	R^1	Z	mp, ^0C[d]	% inhibition of PTPase activity: pNPPase[a] (50 uM)	% inhibition of PTPase activity: r-PTP1B[b] 50 uM	% decrease in plasma glucose: db/db mouse[f] 100 mg/kg/day	% decrease in plasma glucose: ob/ob mouse 100 mg/kg/day	% decrease in plasma insulin: ob/ob mouse 100 mg/kg/day
96	CF_3	 4-OMe-Ph	147-148	56[a1]	34 (2.5 uM)			
97	H	 CH_3	151-152	57	1.4	NS	NS (70 mg/kg)	NS (70 mg/kg)
98	H	 CH_3	117-118	55		19±3* (50 mg/kg)		

[a] pNPP used as the substrate and rat hepatic membrane as the source of PTPase enzyme(s). [a 1]IR-triphosphopeptide used as the substrate and rat hepatic membrane as the source of PTPase enzyme(s). [b] IR-triphosphopeptide used as the substrate and recombinant r-PTP1B as the enzyme. [c] IR-triphosphopeptide used as the substrate and recombinant h-PTP1B as the enzyme. [d] Compounds without melting points were viscous oils. [e] NS: not significant, generally less than −15% change. [f] Values (mean ± SE) are percent change relative to vehicle-treated group with use of 4−6 mice/group; $*p < 0.05$ and $**p < 0.01$ when compared to vehicle-treated mice. [g] All compounds were prepared according to the synthetic Schemes 1 and 2.

Table 3. Chemical and Biological Data of Oxazole Azolidinediones[d]



compd	R^1	mp, ^0C	% inhibition of PTPase activity: PNPPase[a] (50 uM)	% inhibition of PTPase activity: r-PTP1B[b]	% decrease in plasma glucose: db/db mouse[c] 100 mg/kg/day
99	 OCH_3, CH_3	96-97	49[a1]	12 (2.5 uM)	
100		174-175	14[a1]		
101	 CH_3	163-165	57	53 (10 uM)	31±8*
102		168-170	31[a1]	83 (10 uM)	

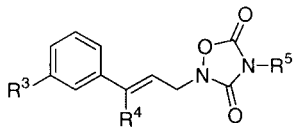
[a] pNPP used as the substrate and rat hepatic membrane as the source of PTPase enzyme(s). [a 1]IR-triphosphopeptide used as the substrate and rat hepatic membrane as the source of PTPase enzyme(s). [b] IR-triphosphopeptide used as the substrate and recombinant r-PTP1B as the enzyme. [c] Values (mean ± SE) are percent change relative to vehicle-treated group with use of 4−6 mice/group; $*p < 0.05$ when compared to vehicle-treated mice. [d] All compounds were prepared according to the synthetic Schemes 1, 2, and 5.

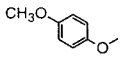
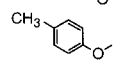
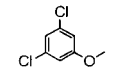
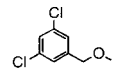
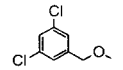
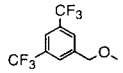
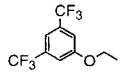
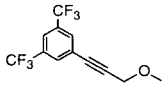
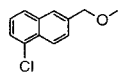
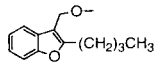
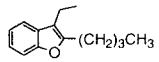
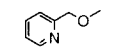
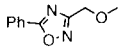
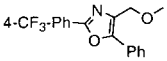
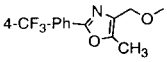
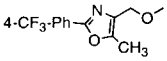
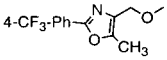
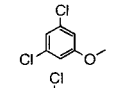
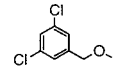
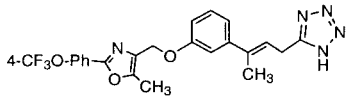
properties (*CLog P* values in the range of 1.6−3.7). However, even though the acetic acid analogues **119** and **120** were found to be very potent inhibitors against h-PTP1B, with IC_{50} values of 0.16 and 0.12 μM, they were inactive in vivo (*ob/ob*). The other acetic acid analogues maintained their in vitro inhibitory activity, with the exception of **122** which was lower. The tetrazole analogue **123** was found to be inactive against h-PTP1B.

There have been a number of reports that the thiazolidinediones are high-affinity peroxisome proliferator-activated receptor γ (PPARγ) agonists, and there is a direct correlation between the in vitro potency at the PPARγ receptor and the in vivo antihyperglycemic potency in *ob/ob* mice.[31] Since our compounds possess some structural similarities with the thiazolidinedione-type antihyperglycemic agents, an additional component (PPARγ effect) to the PTP1B inhibition may contribute to the in vivo activity of the compounds. While our present studies are outside the scope of addressing such a possible dual mechanism of our compounds, future work will be necessary to elucidate this hypothesis.

In summary, we have prepared a new series of azolidinediones as PTPase inhibitors. Several compounds were potent inhibitors against recombinant rat and human PTP1B enzymes with submicromolar IC_{50} values. Most of the compounds were also active against a less sensitive rat hepatic membrane preparation at higher concentrations (50 μM). Elongated spacers between the azolidinedione moiety and the central aromatic portion of the molecule appeared to be very important to inhibitory activity. Large hydrophobic groups at the vicinity of this aromatic central region produced the most potent inhibitors. The octyl analogues **87** and **88** and the corresponding acetic acid analogues **119** and **120** were the best h-PTP1B inhibitors with IC_{50} values in the range of 0.12−0.3 μM. The tail portion of these molecules was also important to the in vitro activity. In the case of the oxazole tail analogues,

Table 4. Chemical and Biological Data of Azolidinediones[e]



compd	R^1	R^4	R^5	mp, °C[d]	% inhibition of PTPase activity: pNPPase[a1] (50 uM)	% inhibition of PTPase activity: r-PTP1B[b] IC_{50} (uM)
103		n-butyl	H		63[a1]	2 (2.5 uM)
104		n-butyl	H		62[a1]	10 (2.5 uM)
105		n-butyl	H		62[a1]	13 (2.5 uM)
106		n-butyl	H		IC_{50} = 23[a1]	1.6
107		n-butyl	H		57[a1]	0.8
108		n-butyl (cis)	H		61[a1]	1.8
109		CH_3	H	56-57		4.1
110		CH_3	H	83-84	64[a1]	12 (2.5 uM)
111		CH_3	H		62[a1]	25 (2.5 uM)
112		CH_3	H	116-118	20[a1]	16 (2.5 uM)
113		CH_3	H		IC_{50} = 33[a1]	2.7
114		CH_3	H			1.3
115		CH_3	H	144-145	5[a1]	9 (2.5 uM)[c]
116		CH_3	H	129-130	17[a1]	3 (2.5 uM)
117		n-butyl	H	130-131	76[a1]	0.37[c]
118		Ph	CH_2CO_2H	68-69	24[a1]	0.85[c]
119		n-octyl (E)	CH_2CO_2H	89-91	57[a1]	0.16[c]
120		n-octyl (Z)	CH_2CO_2H	66-68	64[a1]	0.12[c]
121		n-butyl	CH_2CO_2H		63[a1]	1.3[c]
122		n-butyl	CH_2CO_2H		31[a1]	48[c]
123				99-100	29[a1]	13[c]

[a] [1]IR-triphosphopeptide used as the substrate and rat hepatic membrane as the source of PTPase enzyme(s). [b] IR-triphosphopeptide used as the substrate and recombinant r-PTP1B as the enzyme. [c] IR-triphosphopeptide used as the substrat and recombinant h-PTP1B as the enzyme. [d] Compounds without melting points were viscous oils. [e] All compounds were prepared according to the synthetic Schemes 1 and 2.

substitutions at position-5 of the oxazole moiety with hydrophobic substituents produced very good inhibitors. The 5-phenyl analogues **65** and **117** had IC_{50} values against h-PTP1B of 0.3 and 0.37 μM, respectively. The oxadiazolidinedione analogues exhibited the most appropriate in vitro and in vivo profile. Several compounds

normalized plasma glucose and insulin levels in the *ob/ob* and *db/db* diabetic mouse models. The in vitro enhanced activity of several compounds did not translate to higher in vivo potency. Although we did not have the opportunity to examine the pharmacokinetic properties of these compounds, our data would suggest that the increased lipophilic properties of these compounds (higher *ClogP* values) might have negatively attributed to their poor in vivo profile.

Experimental Section

Chemistry. Melting points were determined in open capillary tubes on a Thomas-Hoover apparatus and are reported uncorrected. ^{1}H NMR spectra were determined in the cited solvent on a Bruker AM 400 (400 MHz) or a Varian XL-300 (300 MHz) instrument, with tetramethylsilane as an internal standard. Chemical shifts are given in ppm and coupling constants are in hertz. Splitting patterns are designated as follows: s, singlet; br s, broad singlet; d, doublet; t, triplet; q, quartet; m, multiplet. The infrared spectra were recorded on a Perkin-Elmer 781 spectrophotometer as KBr pellets or as solutions in chloroform. Mass spectra were recorded on either a Finnigan model 8230 or a Hewlett-Packard model 5995A spectrometer. Elemental analyses (C, H, N) were performed on a Perkin-Elmer 240 analyzer and all compounds are within ±0.4% of theory unless otherwise indicated. All products, unless otherwise noted, were purified by "flash chromatography" with use of 220−400 mesh silica gel. Thin-layer chromatography was done on silica gel 60 F-254 (0.25 mm thickness) plates. Visualization was accomplished with UV light and/or 10% phosphomolybdic acid in ethanol. Unless otherwise noted, all materials were obtained commercially and used without further purification. All reactions were carried out under an atmosphere of dried nitrogen.

General Procedure for the Synthesis of the Oxazole Azolidinediones. The oxadiazolidinediones described in this paper (Tables 1−5) were synthesized from alcohols **6** (Scheme 1), chloromethyl oxazoles **18** and **20** (Scheme 2), and oxadiazoles **23** (Scheme 2) by the following representative procedures. Alcohols **6** were obtained from commercially available benzamides **4** according to literature methods.[16]

4-(Chloromethyl)-5-methyl-2-[4-(trifluoromethyl)phenyl]-1,3-oxazole (18, $R^1 = CF_3$, $R^2 = CH_3$). Hydrogen chloride (gas, 16.0 g) was passed through a cold (0 °C) solution of 4-trifluorobenzaldehyde (50.0 g, 287 mmol) and 1,3-butadione monoxime (26.4 g, 261 mmol) in ethyl acetate (100 mL). The reaction mixture was then warmed to 5 °C and stirred for 3 h. Cold (0 °C) ethyl ether was added and the precipitated solid filtered and dried to give a white solid (54.8 g, 65% yield). The solid was dissolved in chloroform (280 mL), cooled to 5 °C, and phosphorus oxychloride (19.7 mL, 211 mmol) in chloroform (125 mL) was added dropwise over a 15 min period. The reaction mixture was refluxed for 2.5 h, poured into cold water, and the organic layer was washed with NaOH (1 N). The organic extracts were dried over $MgSO_4$. Evaporation of the volatiles and crystallization of the residue from ethyl ether/hexane gave a yellow solid (30.0 g, 30% yield): mp 84−85 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.46 (s, 3H, CH_3), 4.77 (s, 2H, CH_2), 7.88 (d, J = 8.09 Hz, 2H, Ar-*H*), 8.1 (d, J = 8.09 Hz, 2H, Ar-*H*); MS *m/e* 275 (M^+). Anal. ($C_{12}H_9F_3ClNO$) C, H, N.

1-[3-({5-Methyl-2-[4-(trifluoromethyl)phenyl]-1,3-oxazol-4-yl}methoxy)phenyl]-1-ethanone (25, $R^1 = CF_3$, R^2, $R^3 = CH_3$, W = C). Potassium carbonate was added into a mixture of 4-(chloromethyl)-5-methyl-2-[4-(trifluoromethyl)-phenyl]-1,3-oxazole (8.0 g, 29 mmol), 3-hydroxyacetophenone (3.95 g, 29 mmol) and DMF (100 mL). The reaction mixture was stirred at 65 °C for 10 h and then poured into water and extracted with ethyl acetate. The organic extracts were dried over $MgSO_4$. Evaporation of the volatiles and purification by flash chromatography on silica gel (hexane/ethyl acetate 4/1) gave a white solid (8.9 g, 82% yield): mp 90−91 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.49 (s, 3H, CH_3), 2.57 (s, 3H, CH_3), 5.1 (s, 2H, CH_2), 7.29−7.32 (m, 1H, Ar-*H*), 7.45 (t, J = 8.09 Hz, 1H, Ar-*H*), 7.56−7.59 (m, 2H, Ar-*H*), 7.85 (d, J = 8.3 Hz, 1H, Ar-*H*), 8.1 (d, J = 8.09 Hz, 2H, Ar-*H*); IR (KBr, cm^{-1}) 1690 (CO); MS *m/e* 375 (M^+). Anal. ($C_{20}H_{16}F_3NO_3$) C, H, N.

Ethyl (*E*)-3-[3-({5-Methyl-2-[4-(trifluoromethyl)phenyl]-1,3-oxazol-4-yl}methoxy)phenyl]-2-butenoate (11, $R^1 = CF_3$, $R^3 = CH_3$, R^4 = H, *n* = 0, *m*-methoxy linker). Triethyl phosphonoacetate (4.2 mL, 21.3 mmol) was added dropwise into a mixture of sodium hydride (80% in mineral oil, 0.57 g, 19 mmol) and toluene (100 mL). The reaction mixture was stirred for 1 h, and then 1-[3-({5-methyl-2-[4-(trifluoromethyl)-phenyl]-1,3-oxazol-4-yl}methoxy)phenyl]-1-ethanone (5.7 g, 15.2 mmol) in THF (20 mL) was added dropwise. The mixture was stirred for 48 h, poured into water, acidified with HCl (1 N) and extracted with ethyl acetate. The organic extracts were dried over $MgSO_4$. Evaporation of the volatiles and purification by flash chromatography on silica gel (hexane/ethyl acetate 5/1) gave a white solid (5.5 g, 81% yield): mp 88−89 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.22 (t, J = 7.05 Hz, 3H, CH_3), 4.12 (q, J = 7.05 Hz, 2H, CH_2), 5.08 (s, 2H, CH_2), 6.17 (s, 1H, C*H*), 7.05−7.07 (m, 1H, Ar-*H*), 7.15 (d, J = 7.9 Hz, 1H, Ar-*H*), 7.23 (m, 1H, Ar-*H*), 7.32 (t, J = 8.09 Hz, 1H, Ar-*H*), 7.84 (d, J = 8.5 Hz, 2H, Ar-*H*), 8.1 (d, J = 8.3 Hz, 1H, Ar-*H*); IR (KBr, cm^{-1}) 1705 (CO); MS *m/e* 445 (M^+). Anal. ($C_{24}H_{22}F_3NO_4$) C, H, N.

(*E*)-3-[3-({5-Methyl-2-[4-(trifluoromethyl)phenyl]-1,3-oxazol-4-yl}methoxy)phenyl]-2-buten-1-ol (12, $R^1 = CF_3$, $R^3 = CH_3$, R^4 = H, *n* = 0, *m*-methoxy linker). Diisobutylaluminum hydride (1 M, 28.1 mL, 28.1 mmol) was added dropwise into a cold (−78 °C) solution of ethyl (*E*)-3-[3-({5-methyl-2-[4-(trifluoromethyl)phenyl]-1,3-oxazol-4-yl}methoxy)-phenyl]-2-butenoate (5.0 g, 11.23 mmol) in ethyl ether (100 mL). The mixture was stirred for 30 min, quenched with MeOH, poured into HCl (1 N), and extracted with ethyl acetate. The organic extracts were dried over $MgSO_4$. Evaporation of the volatiles and purification by flash chromatography on silica gel (hexane/ethyl acetate 2/1) gave a clear oil (4.3 g, 95% yield): ^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.97 (s, 3H, CH_3), 2.48 (s, 3H, CH_3), 4.14 (d, J = 6.2 Hz, 1H, O*H*), 5.05 (s, 2H, CH_2), 5.93 (m, 1H, C*H*), 6.91−6.94 (m, 1H, Ar-*H*), 7.0−7.02 (m, 1H, Ar-*H*), 7.08−7.09 (m, 1H, Ar-*H*), 7.25 (t, J = 8.09 Hz, 1H, Ar-*H*), 7.87 (d, J = 8.09, 1H, Ar-*H*), 8.13 (d, J = 8.3 Hz, 2H, Ar-*H*); IR (KBr, cm^{-1}) 3400 (OH); MS *m/e* 404 (M^+). Anal. ($C_{22}H_{20}F_3NO_3$) C, H, N.

***tert*-Butyl (*tert*-Butoxycarbonyl)oxy{(*E*)-3-[3-({5-methyl-2-[4-(trifluoromethyl)phenyl]-1,3-oxazol-4-yl}methoxy)-phenyl]-2-butenyl}carbamate (13, $R^1 = CF_3$, $R^3 = CH_3$, R^4 = H, *n* = 0, *m*-methoxy linker).** Diethyl azodicarboxylate (1.45 mL, 9.23 mmol) in THF (10 mL) was added dropwise into a cold (−20 °C) solution of (*E*)-3-[3-({5-methyl-2-[4-(trifluoromethyl)phenyl]-1,3-oxazol-4-yl}methoxy)phenyl]-2-buten-1-ol (3.1 g, 7.69 mmol), triphenylphosphine (2.42 g, 9.23 mmol), *tert*-butyl *N*-(*tert*-butoxycarbonyloxy)carbamate (2.15 g, 9.23 mmol), and THF (50 mL). After the addition, the mixture was allowed to come to 0 °C, stirred for 1 h, poured into water and extracted with ethyl acetate. The organic extracts were dried over $MgSO_4$. Evaporation of the volatiles and purification by flash chromatography on silica gel (hexane/ethyl acetate 6/1) gave a light yellow oil (4.6 g, 97% yield): ^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.41 (s, 9H, *tert*-butyl), 1.42 (s, 9H, *tert*-butyl), 2.01 (s, 3H, CH_3), 2.49 (s, 3H, CH_3), 4.38 (brs, 2H, CH_2), 5.05 (s, 2H, CH_2), 5.82 (m, 1H, C*H*), 6.92−7.1 (m, 2H, Ar-*H*), 7.08−7.1(m, 1H, Ar-*H*), 7.27 (t, J = 8.09 Hz, 2H, Ar-*H*), 8.12 (d, J = 8.09 Hz, 2H, Ar-*H*); IR (KBr, cm^{-1}) 1780 (CO), 1710 (CO); MS *m/e* 618 (M^+). Anal. ($C_{32}H_{37}F_3N_2O_7$) C, H, N.

Hydroxy{(*E*)-3-[3-({5-methyl-2-[4-(trifluoromethyl)-phenyl]-1,3-oxazol-4-yl}methoxy)phenyl]-2-butenyl}carbamic Acid (14, $R^1 = CF_3$, $R^3 = CH_3$, R^4 = H, *n* = 0, *m*-methoxy linker). Trifluoracetic acid (10 mL) was added into a solution of *tert*-butyl (*tert*-butoxycarbonyl)oxy{(*E*)-3-[3-({5-methyl-2-[4-(trifluoromethyl)phenyl]-1,3-oxazol-4-yl}methoxy)phenyl]-2-butenyl}carbamate (4.5 g, 7.28 mmol) and dichloromethane (40 mL). The reaction mixture was stirred for 8 h, and the volatiles were removed in vacuo. The residue was taken in

ethyl acetate and washed with NaOH (1 N). The organic extracts were dried over $MgSO_4$. Evaporation of the volatiles and purification by flash chromatography on silica gel (methyl alcohol/ethyl acetate 1/10) gave a clear oil (2.7 g, 89% yield): ^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.98 (s, 3H, CH_3), 2.47 (s, 3H, CH_3), 3.5 (d, J = 6.4 Hz, 2H, CH_2), 5.02 (s, 2H, CH_2), 5.8 (brs, 1H, N*H*), 5.95 (m, 1H, C*H*), 6.93−7.1 (m, 2H, Ar-*H*), 7.18 (m, 1H, Ar-*H*), 7.5−7.6 (m, 2H, Ar-*H*, O*H*), 7.88 (d, J = 8.3 Hz, 2H, Ar-*H*), 8.12 (d, J = 8.09 Hz, 1H, Ar-*H*); IR (KBr, cm^{-1}) 3280 (NH), 2590 (OH); MS *m/e* 419 (M + H)$^+$. Anal. ($C_{22}H_{21}F_3N_2O_3$) C, H, N.

2-{(*E*)-3-[3-({5-Methyl-2-[4-(trifluoromethyl)phenyl]-1,3-oxazol-4-yl}methoxy)phenyl]-2-butenyl}-1,2,4-oxadiazolidine-3,5-dione (59). *N*-(Chlorocarbonyl)isocyanate (0.5 mL, 6.22 mmol) was added dropwise into a cold (−5 °C) solution of hydroxy{(*E*)-3-[3-({5-methyl-2-[4-(trifluoromethyl)-phenyl]-1,3-oxazol-4-yl}methoxy)phenyl]-2-butenyl}carbamic acid (2.6 g, 6.22 mmol) and THF (25 mL). The reaction mixture was stirred for 30 min, poured into HCl (1 N), and extracted with ethyl acetate. The organic extracts were dried over $MgSO_4$. Evaporation of the volatiles and purification by flash chromatography on acid washed (5% H_3PO_4/MeOH) silica gel (hexane/ethyl acetate 3/1) gave a white solid (1.85 g, 62% yield): mp 136−138 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.06 (s, 3H, CH_3), 2.48 (s, 3H, CH_3), 4.43 (d, J = 7.05 Hz, 2H, CH_2), 5.06 (s, 2H, CH_2), 5.9 (t, J = 7.05 Hz, 1H, C*H*), 6.9 (dd, J = 8.09, 1.87 Hz,0.1H, Ar-*H*), 7.03 (d, J = 8.3 Hz, 1H, Ar-*H*), 7.12 (t, J = 1.87 Hz, 1H, Ar-*H*), 7.28 (t, J = 7.9 Hz, 1H, Ar-*H*), 7.88 (d, J = 8.3 Hz, 2H, Ar-*H*), 8.12 (d, J = 8.09 Hz, 2H, Ar-*H*), 12.4 (brs, 1H, N*H*); IR (KBr, cm^{-1}) 3020 (NH), 1750 (CO); MS *m/e* 488 (M + H)$^+$. Anal. ($C_{24}H_{20}F_3N_3O_5$) C, H, N.

3-([5-Methyl-2-(4-(trifluoromethyl)phenyl)oxazol-4-yl]-methoxy)benzaldehyde [25(1), R^1 = CF_3, R^2 = CH_3, R^3 = H, W = C, meta-substituted]. Potassium carbonate (3.77 g, 27.3 mmol) was added into a mixture of 4-chloromethyl-5-methyl-2-(4-trifluoromethylphenyl)oxazole (5.25 g, 19.1 mmol), 3-hydroxylbenzaldehyde (2.33 g, 19.1 mmol), and DMF (50 mL). The mixture was stirred at 80 °C for 3 h, poured into water, acidified with HCl (2 N) and extracted with ethyl acetate. The organic extracts were dried over $MgSO_4$. Evaporation of the volatiles and crystallization from ethyl ether/hexane gave a yellow solid (4.47 g, 65% yield): mp 104−105 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.49 (s, 3H, CH_3), 5.13 (s, 2H, CH_2), 7.37−7.4 (m, 1H, Ar-*H*), 7.53−7.6 (m, 2H, Ar-*H*), 7.87 (d, J = 8.5 Hz, 2H, Ar-*H*), 8.13 (d, J = 8.09 Hz, 2H, Ar-*H*), 9.98 (s, 1H, C*H*O); IR (KBr, cm^{-1}) 1695 (CO); MS *m/e* 361 (M$^+$). Anal. ($C_{19}H_{14}F_3NO_3$) C, H, N.

1-{3-([5-Methyl-2-(4-(trifluoromethyl)phenyl)oxazol-4-yl]methoxy)phenyl}propan-1-one [25(2), R^1 = CF_3, R^2 = CH_3, R^3 = CH_2CH_3, W = C, meta-substituted]. Ethylmagnesium bromide (11.1 mL, 33.24 mmol) was added dropwise in to a cold (0 °C) solution of 3-[5-methyl-2-(4-trifluoromethylphenyl)oxazol-4-ylmethoxy)benzaldehyde (12.0 g, 33.24 mmol) and THF (50 mL). After stirring for 30 min, the reaction mixture was quenched with aqueous NH_4Cl, poured into water, acidified with HCl (2 N) and extracted with EtOAc. The organic extracts were dried over $MgSO_4$. Evaporation gave a yellowish oil (13.0 g), which was dissolved in acetone (200 mL). The mixture was cooled to 5 °C, and freshly prepared Jones reagent (40 mL) was added dropwise. After the addition, the mixture was stirred for 30 min, poured into water and extracted with EtOAc. The organic extracts were dried over $MgSO_4$. Evaporation and crystallization from ethyl ether/hexane (after cooling to 0 °C) gave a white solid (9.6 g, 74% yield): mp 73−74 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ_1.07 (t, J = 7.25 Hz, 3H, CH3), 2.49 (s, 3H, CH3), 3.02 (q, J = 7.26 Hz, 2H, CH2), 5.11 (s, 2H, CH2), 7.3 (m, 1H, Ar−H), 7.45 (t, J = 7.9 Hz, 1H, Ar−H), 7.58−7.6 (m, 2H, Ar−H), 7.87 (d, J = 8.09 Hz, 2H, Ar−H), 8.12 (d, J = 8.3 Hz, 2H, Ar−H); IR (KBr, cm^{-1}) 1695 (CO); MS *m/e* 389 (M$^+$). Anal. ($C_{21}H_{18}F_3NO_3$) C, H, N.

The thia- and oxazolidinediones **29** and **30** (Scheme 3) were prepared according to the following procedures.

(*E*)-4-[3-(3-Chloro-1-methylpropenyl)phenoxymethyl]-5-methyl-2-phenyloxazole (28a, R^1 = CF_3, R^3 = CH_3). 3-[3-(5-Methyl-2-phenyloxazol-4-ylmethoxy)phenyl]but-2-en-1-ol (10.0 g, 29.9 mmol) in ethyl ether (50 mL) was added into a cold (0 °C) suspension of phosphorus pentachloride (9.31 g, 44.7 mmol), calcium carbonate (4.47 g, 44.7 mmol), and ethyl ether (300 mL). The reaction mixture was stirred for 30 min and poured into water. The organic layer was separated and washed with water and brine. The organic extracts were dried over $MgSO_4$. Evaporation of the volatiles and purification by flash chromatography on silica gel (hexane/ethyl acetate 5/1) gave a clear oil (9.1 g, 86% yield): ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.1 (s, 3H, CH_3), 2.45 (s, 3H, CH_3), 4.42 (d, J = 8.09 Hz, 2H, CH_2), 5.04 (, S, 2H, CH_2), 6.05 (t, J = 8.09 Hz, 1H, C*H*), 6.97 (dd, J = 8.3, 2.49 Hz, 1H, Ar-*H*), 7.04 (d, J = 7.7 Hz, 1H, Ar-*H*), 7.13 (t, J = 2.49 Hz, 1H, Ar-*H*), 7.28 (t, J = 7.9 Hz, 1H, Ar-*H*), 7.5 (m, 3H, Ar-*H*), 7.94 (m, 2H, Ar-*H*); MS *m/e* 353 (M$^+$). Anal. ($C_{21}H_{20}ClNO_2$) C, H, N.

(*E*)-5-{3-[3-(5-Methyl-2-phenyloxazol-4-ylmethyl)phenyl]-but-2-enyl}oxazolidine-2,4-dione (30). *tert*-Butyllithium (17.5 mL, 29.7 mmol) was added dropwise in to a rapidly stirred cold (−78 °C) solution of lithium chloride (3.6 g, 84.8 mmol) and oxazolidine-2,4-dione (1.43 g, 14.1 mmol) in THF (90 mL). The mixture was stirred at −78 °C for 30 min and then gradually warmed to 0 °C. After recooling to −78 °C, (*E*)-4-[3-(3-chloro-1-methylpropenyl)phenoxymethyl]-5-methyl-2-phenyloxazole (5.0 g, 14.1 mmol) in THF (5 mL) was added all at once. After stirring for 10 min at −78 °C, the mixture was gradually warmed to room temperature and stirred for 5 h. Then, the reaction mixture was quenched with aqueous NH_4Cl, poured into water, acidified with HCl, and extracted with ethyl acetate. The organic extracts were dried over $MgSO_4$. Evaporation of the volatiles and purification by flash chromatography on silica gel (hexane/ethyl acetate 3/1), gave a white solid (3.5 g, 59% yield): mp 138−139 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.0 (s, 3H, CH_3), 2.45 (, 3H, CH_3), 2.76−2.8 (m, 2H, CH_2), 5.02 (s, 2H, CH_2), 5.12 (t, J = 5.2 Hz, 1H, C*H*), 5.76 (m, 1H, C*H*), 6.85−6.95 (m, 2H, Ar-*H*), 7.02 (t, J = 2.07 Hz, 1H, Ar-*H*), 7.26 (t, J = 7.9 Hz, 1H, Ar-*H*), 7.56 (m, 3H, Ar-*H*), 7.94 (m, 2H, Ar-*H*), 11.87 (brs, 1H, N*H*); IR (KBr, cm^{-1}) 1750 (CO); MS *m/e* 419 (M + H)$^+$. Anal. ($C_{24}H_{22}N_2O_5$) C, H, N.

(*E*)-5-{3-[3-(5-Methyl-2-phenyloxazol-4-ylmethoxy)-phenyl]but-2-enyl}thiazolidine-2,4-dione (29). *n*-Butyllithium (16.6 mL, 41.6 mmol) was added dropwise in to a cold (−78 °C) solution of thiazolidine-2,4-dione (2.31 g, 19.8 mmol) and THF (80 mL). The mixture was stirred at −78 °C for 15 min and then gradually warmed to 0 °C and stirred for 30 min, to complete the dianion formation. After recooling to −78 °C, 4-[3-(3-chloro-1-methylpropenyl)phenoxymethyl]-5-methyl-2-phenyloxazole (7.0 g, 19.8 mmol) in THF (15 mL) was added all at once. The mixture was stirred for 30 min at −78 °C and then was gradually warmed to room temperature and stirred for 2 h. The reaction mixture was quenched with aqueous NH_4Cl, poured into water, acidified with HCl, and extracted with ethyl acetate. The organic extracts were dried over $MgSO_4$. Evaporation of the volatiles and purification by flash chromatography on acid washed (5% H_3PO_4/MeOH) silica gel (hexane/ethyl acetate 3/1), gave a white solid (2.9 g, 33% yield): mp 48−49 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.01 (s, 3H, CH_3), 2.45 (s, 3H, CH_3), 2.82 (m, 2H, CH_2), 4.7 (t, J = 5.6 Hz, 1H, C*H*), 5.01 (s, 2H, CH_2), 5.74 (m, 1H, C*H*), 6.98 (m, 2H, Ar-*H*), 7.02 (t, J = 1.86 Hz, 1H, Ar-*H*), 7.28 (t, J = 8.09 Hz, 1H, Ar-*H*), 7.51 (m, 3H, Ar-*H*), 7.94 (m, 2H, Ar-*H*), 12.06 (brs, 1H, N*H*); IR (KBr, cm^{-1}) 1700 (CO); MS *m/e* 435 (M + H)$^+$. Anal. ($C_{24}H_{22}N_2O_4S$·0.25H_2O) C, H, N.

The thiadiazolidinedione **60** was prepared according to the following procedure.

(*E*)-3-{3-[5-Methyl-2-(4-trifluoromethylphenyl)oxazol-ylmethoxy]phenyl}but-2-enylurea (32, R^1 = CF_3, R^3 = CH_3, meta-substituted). (*E*)-3-{3-[5-Methyl-2-(4-trifluoromethylphenyl)oxazol-4-ylmethoxy]phenyl}but-2-en-1-ol (6.0 g, 14.9 mmol) in ethyl ether (50 mL) was added to a cold (0 ×b0°C) suspension of phosphorus pentachloride (4.4 g, 20.8 mmol),

calcium carbonate (1.5 g, 14.9 mmol), and ethyl ether (50 mL). The reaction mixture was stirred for 30 min and then poured into water. The organic layer was separated, washed with water and brine. The organic extracts were dried over $MgSO_4$. Evaporation of the volatiles and purification by flash chromatography on silica gel (hexane/ethyl acetate 20/1) gave a clear oil (2.1 g, 35% yield). The oil (2.1 g, 4.97 mmol), sodium azide (0.9 g, 14.2 mmol) and DMF (40 mL) was stirred at 80 ×b0°C for 18 h. The reaction mixture was then poured into water (100 mL), acidified to pH 3 with HCl (2 N), and extracted with ethyl acetate. The organic extracts were dried over $MgSO_4$. Evaporation gave a brown oil (1.8 g), which was dissolved in THF (30 mL) and cooled to 0 ×b0°C. Lithium aluminum hydride (2.2 mL, 1.0 M, 2.2 mmol) was added dropwise over a 20 min period. The reaction mixture was quenched with ethyl acetate (10 mL) and NaOH (30 mL, 2.5 N) and extracted with ethyl ether. The organic extracts were dried over $MgSO_4$. Evaporation and purification by flash chromatography on silica gel (ethyl acetate/methyl alcohol 1:1) gave a yellow oil (0.8 g, 42% yield). The amine (0.8 g) was dissolved in dioxane (10 mL) and treated with trimethylsilyl isocyanate (0.67 mL, 4 mmol). The reaction mixture was stirred for 18 h, poured into a mixture of water (40 mL) and saturated NH_4Cl (40 mL). The aqueous layer was extracted with ethyl acetate, and the organic extracts were dried over $MgSO_4$. Evaporation of the volatiles and purification by flash chromatography on silica gel (ethyl acetate/ethanol) gave a white solid (0.5 g, 55% yield): ^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.07 (s, 3H, CH_3), 2.48 (s, 3H, CH_3), 3.6 (m, 2H, CH_2), 5.05 (s, 2H, CH_2), 5.4 (s, 2H, NH2), 5.78 (t, J = 6.8 Hz, 1H, NH), 6.03 (t, J = 6.8 Hz, 1H, C*H*), 6.95−7.01 (m, 2H, Ar-*H*), 7.03 (s, 1H, Ar−H), 7.22 (t, J = 8.5 Hz, 1H, Ar-*H*), 7.82 (d, J = 8.12 Hz, 2H, Ar-*H*), 8.12 (d, J = 8.13 Hz, 2H, Ar-*H*); MS *m/e* 445 (M^+). Anal. ($C_{23}H_{22}F_3N_3O_3$) C, H, N.

(*E*)-2-(3-{3-[5-Methyl-2-(4-trifluoromethylphenyl)oxazol-4-ylmethoxy]phenyl}but-2-enyl)-[1,2,4]thiadiazolidine-3,5-dione (60). Chlorocarbonylsulfenyl chloride (0.54 mL, 6.4 mmol) was added dropwise into a mixture of (*E*)-3-{3-[5-methyl-2-(4-trifluoromethylphenyl)oxazol-ylmethoxy]phenyl}-but-2-enylurea (2.2 g, 4.94 mmol) and toluene (40 mL). The reaction mixture was heated to 60 °C for 4 h, poured into water, acidified with HCl (2 N) and extracted with ethyl acetate. The organic extracts were dried over $MgSO_4$. Evaporation of the volatiles and purification by flash chromatography on acid washed (5% H_3PO_4/MeOH) silica gel (hexane/ethyl acetate 3/1) gave an off-white solid (0.63 g, 25% yield): mp 60−61 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.07 (s, 3H, CH_3), 2.48 (s, 3H, CH_3), 4.33 (d, J = 6.8 Hz, 2H, CH_2), 5.05 (s, 2H, CH_2), 5.85 (t, J = 6.8 Hz, 1H, C*H*), 6.95−7.05 (m, 3H, Ar-*H*), 7.29 (t, J = 8.56 Hz, 1H, Ar-*H*), 7.87 (d, J = 8.03 Hz, 2H, Ar-*H*), 8.12 (d, J = 8.13 Hz, 2H, Ar-*H*), 12.14 (brs, 1H, N*H*); IR (KBr, cm^{-1}) 1710 (CO); MS *m/e* 503 (M^+). Anal. ($C_{24}H_{20}F_3N_3O_4S$) C, H, N.

The imidiazolidinedione **64** was prepared according to the following procedure.

Methyl 2-((Aminocarbonyl){(*E*)-3-[3-({5-methyl-2-[4-(trifluoromethyl)phenyl]-1,3-oxazol-4-yl}methoxy)phenyl]-2-butenyl}amino)acetate (34a, R^1 = CF_3, R^3 = CH_3, meta-substituted). Triethylamine (4.4 mL, 31.3 mmol) was added into a mixture of 4-({3-[(*E*)-3-chloro-1-methyl-1-propenyl]-phenoxy}methyl)-5-methyl-2-[4-(trifluoromethyl)phenyl]-1,3-oxazole (2.1 g, 5.21 mmol), glycine methyl ester hydrochloride (0.66 g, 5.21 mmol), and THF (10 mL). The reaction mixture was refluxed 18 h and the volatiles were removed in vacuo. The residue was then dissolved in ethyl acetate and washed with NH_4Cl. The organic extracts were dried over $MgSO_4$. Evaporation of the volatiles and purification by flash chromatography on silica gel (hexane/ethyl acetate/methyl alcohol 70/12/1) gave brown oil (2.0 g). The oil was then dissolved in acetic acid (6 mL), and then water (10 mL) and potassium cyanate (0.7 g) were added. The mixture was stirred at 40 °C for 20 min, poured into water and extracted with ethyl acetate. The organic extracts were dried over $MgSO_4$. Evaporation of the volatiles and purification by flash chromatography on silica gel (hexane/ethyl acetate/ethyl alcohol 6/4/0.5) gave an off-white solid (1.3 g, 51% yield): ^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.92 (s, 3H, CH_3), 2.48 (, 3H, CH_3), 3.44 (s, 3H, CH_3), 3.52 (d, J = 7.4 Hz, 2H, CH_2), 3.8 (s, 2H, CH_2), 5.03 (s, 2H, CH_2), 5.4 (t, J = 7.4 Hz, 1H, C*H*), 5.87 (s, 2H, NH_2), 6.95 (m, 2H, Ar-*H*), 7.2 (t, J = 8.4 Hz, 1H, Ar-*H*), 7.26 (m, 1H, Ar-*H*), 7.89 (d, J = 8.5 Hz, 2H, Ar-*H*), 8.12 (d, J = 8.12 Hz, 2H, Ar-*H*); IR (KBr, cm^{-1}) 1700 (CO), 1750 (CO); MS *m/e* 517 (M^+). Anal. ($C_{26}H_{26}F_3N_3O_5$) C, H, N.

1-{(*E*)-3-[3-({5-Methyl-2-[4-(trifluoromethyl)phenyl]-1,3-oxazol-4-yl}methoxy)phenyl]-2-butenyl}-2,4-imidazolidinedione (64). Sodium hydride (60% in mineral oil, 0.1 g, 2.76 mmol) was added into a mixture of methyl 2-((aminocarbonyl){(*E*)-3-[3-({5-methyl-2-[4-(trifluoromethyl)phenyl]-1,3-oxazol-4-yl}methoxy)phenyl]-2-butenyl}amino)acetate 91.3 g, 2.51 mmol) and *N*,*N*-dimethylformamide (20 mL). The mixture was stirred for 1 h, poured into water, acidified with HCl (2 N), and extracted with ethyl acetate. The organic extracts were dried over $MgSO_4$. Evaporation of the volatiles and purification by flash chromatography on silica gel (hexane/ethyl acetate/ethyl alcohol 6/4/0.5) gave an off-white solid (0.89 g, 73% yield): ^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.93 (s, 3H, CH_3), 2.46 (s, 3H, CH_3), 3.6 (d, J = 7.4 Hz, 2H, CH_2), 3.76 (s, 2H, CH_2), 5.03 (s, 2H, CH_2), 5.4 (t, J = 7.4 Hz, 1H, C*H*), 6.95 (d, J = 7.5 Hz, Ar-*H*), 7.07 (dd, J = 7.25, 1.75 Hz, 1H, Ar-*H*), 7.4 (t, J = 8.3 Hz, 1H, Ar-*H*), 7.36 (m, 1H, Ar-*H*), 7.89 (d, J = 8.12 Hz, 2H, Ar-*H*), 8.12 (d, J = 8.12 Hz, 2H, Ar-*H*); IR (KBr, cm^{-1}) 1710 (CO); MS *m/e* 485 (M^+). Anal. ($C_{25}H_{22}F_3N_3O_4$) C, H, N.

The acetylenic oxadiazolidinediones **77** and **78** were prepared from alcohol **36** according to the above-described methodology.

4-(3-Ethynylphenoxymethyl)-5-methyl-2-(4-trifluoromethylphenyl)oxazole (35, R^1 = CF_3, meta-substituted). (Bromomethyl)triphenylphosphonium bromide (21.2 g, 48.6 mmol) was added portionwise to a −78 °C mixture of potassium *tert*-butoxide (10.9 g, 97.2 mmol) in THF (200 mL). The mixture was stirred for 2 h, then 3-[5-methyl-2-(4-trifluoromethylphenyl)oxazol-4-ylmethoxy]benzaldehyde (11.7 g, 32.4 mmol) in THF (50 mL) was added dropwise. The mixture was stirred for 1 h at −78 °C and then at room temperature for 2 days. The reaction mixture was quenched with aqueous NH_4Cl, poured into water, acidified with HCl (2 N), and extracted with ethyl acetate. The organic extracts were dried over $MgSO_4$. Evaporation of the volatiles and purification by flash chromatography on silica gel (hexane/ethyl acetate 8/1) gave a white solid (7.5 g, 67% yield): mp 62−64 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.47 (s, 3H, CH_3), 4.18 (s, 1H, C*H*), 5.05 (, 2H, CH_2), 7.07 (m, 2H, Ar-*H*), 7.16 (m, 1H, Ar-*H*), 7.3 (t, J = 7.9 Hz, 1H, Ar-*H*), 7.88 (d, J = 8.09 Hz, 2H, Ar-*H*), 8.12 (d, J = 8.09 Hz, 2H, Ar-*H*); MS *m/e* 357 (M^+). Anal. ($C_{20}H_{14}F_3NO_2$·0.25 H_2O) C, H, N.

4-{3-[5-Methyl-2-(4-trifluoromethylphenyl)oxazol-4-ylmethoxy]phenyl}but-3-yn-2-ol (36, R^1 = CF_3, meta-substituted). Lithium bis(trimethylsilyl)amide (10.5 mL, 10.5 mmol) was added into a cold (0 °C) solution of 4-(3-ethynylphenoxymethyl)-5-methyl-2-(4-trifluoromethylphenyl)oxazole (3.0 g, 8.7 mmol) in THF (100 mL). After 1 h at 0 °C, acetaldehyde (0.59 mL, 10.5 mmol) was added dropwise. The mixture was stirred for 30 min, quenched with aqueous NH_4Cl, poured into water, acidified with HCl (2 N), and extracted with ethyl acetate. The organic extracts were dried over $MgSO_4$. Evaporation and purification by flash chromatography on silica gel (hexane/ethyl acetate 4/1) gave a yellow solid (2.1 g, 59% yield): mp 86−87 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.38 (d, J = 6.64 Hz, 3H, CH_3), 2.47 (s, 3H, CH_3), 4.6 (m, 1H, C*H*), 5.04 (s, 2H, CH_2), 5.45 (d, J = 4.98 Hz, 1H, O*H*), 7.01−7.08 (m, 3H, Ar-*H*), 7.29 (t, J = 7.9 Hz, 1H, Ar-*H*), 7.89 (d, J = 8.3 Hz, 2H, Ar-*H*), 8.12 (d, J = 8.09, 1H, Ar-*H*); IR (KBr, cm^{-1}) 3300 (OH); MS *m/e* 401 (M^+). Anal. ($C_{22}H_{18}F_3NO_3$) C, H, N.

The cyclopropane analogues **79** and **80** were prepared from alcohol **25b** according to the above-described methodology.

(*E*)-2-{3-[5-Methyl-2-(4-trifluoromethylphenyl)oxazol-4-ylmethoxy]phenyl}cyclopropylmethanol (27b, R^1 = CF_3, R^3 = H, meta-substituted). Chloroiodomethane (3.37

mL, 46.3 mmol) was added dropwise in to a cold (0 °C) solution of diethyzinc (23.14 mL, 23.14 mmol) and dichloroethane (40 mL). After stirring for 10 min (*E*)-{3-[5-methyl-2-(4-trifluoromethylphenyl)oxazol-4-ylmethoxy]phenyl}prop-2-en-1-ol (4.5 g, 11.57 mmol) in dichloromethane (10 mL) was added dropwise. The reaction mixture was stirred for 1 h and quenched with aqueous NH_4Cl. The new mixture was stirred for 15 min, poured into water and extracted with ethyl ether. The organic extracts were dried over $MgSO_4$. Evaporation of the volatiles and purification by flash chromatography on silica gel (hexane/ethyl acetate 3/2) gave a clear oil (2.8 g, 80% yield): ^{1}H NMR (DMSO-d_6, 400 MHz) δ 0.85 (t, J = 6.9 Hz, 2H, CH_2), 1.26 (m, 1H, C*H*), 1.74 (m, 1H, C*H*), 2.47 (s, 3H, CH_3), 3.37 (m, 1H, CH_2), 3.41 (m, 1H, CH_2), 4.6 (t, J = 5.6 Hz, 1H, O*H*), 4.99 (s, 2H, CH_2), 6.68 (d, J = 7.9 Hz, 1H, Ar-*H*), 6.73 (m, 1H, Ar-*H*), 6.8 (m, 1H, Ar-*H*), 7.14 (t, J = 7.9 Hz, 1H, Ar-*H*), 7.89 (d, J = 8.09 Hz, 2H, Ar-*H*), 8.14 (d, J = 8.3 Hz, 2H, Ar-*H*); IR (KBr, cm^{-1}) 3360 (OH); MS *m/e* 403 (M^+). Anal. ($C_{22}H_{20}F_3NO_3$) C, H, N.

The iodooxadiazolidinedione **90** was prepared from alcohol **39** according to the above-described methodology.

(*Z*)-3-Iodo-3-[3-({5-methyl-2-[4-(trifluoromethoxy)-phenyl]-1,3-oxazol-4-yl}methoxy)phenyl]-2-propen-1-ol (39, R^1 = CF$_3$, meta-substituted). Lithium bis(trimethylsilyl)amide (1 M, 14 mL, 14 mmol) was added into a cold (0 °C) solution of 4-{4-[(3-ethynylphenoxy)methyl]-5-methyl-1,3-oxazol-2-yl}phenyl trifluoromethyl ether (5.0 g, 14 mmol) in THF (80 mL). After 1 h formaldehyde (gas) was passed through the mixture for 20 min. The mixture was stirred for 1 h, quenched with aqueous NH_4Cl, poured into water, acidified with HCl (2 N), and extracted with ethyl acetate. The organic extracts were dried over $MgSO_4$. Evaporation and purification by flash chromatography on silica gel (hexane/ethyl acetate 4/1) gave a yellow oil (2.8 g). The oil was dissolved in tetrahydrofuran (60 mL) and added slowly into a mixture of sodium methoxide (1.02 g, 18.8 mmol), lithium aluminum hydride (1 M, 9.4 mL, 9.4 mmol) and tetrahydrofuran (50 mL). The reaction mixture was then refluxed for 1 h, cooled to −78 °C, and then iodine (5.5 g, 43.4 mmol) in THF (20 mL) was added dropwise. The mixture was allowed to come to room temperature, poured into NH_4Cl, and extracted with ethyl acetate. The organic extracts were washed with sodium bisulfite, and dried over $MgSO_4$. Evaporation and purification by flash chromatography on silica gel (hexane/ethyl acetate 4/1) gave a yellow oil (1.55 g, 22% yield): ^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.47 (s, 3H, CH_3), 4.2 (m, 2H, CH_2), 5.05 (s, 2H, CH_2), 5.2 (m, 1H, O*H*), 6.4 (m, 1H, CH), 7.01−7.08 (m, 2H, Ar-*H*), 7.2 (t, J = 1.9 Hz, 1H, Ar-*H*), 7.4 (t, J = 7.9 Hz, 1H, Ar−H), 7.89 (d, J = 8.3 Hz, 2H, Ar-*H*), 8.12 (d, J = 8.09, 1H, Ar-*H*); IR (KBr, cm^{-1}) 3300 (OH); MS *m/e* 515(M^+). Anal. ($C_{21}H_{17}F_3INO_3$) C, H, N.

Benzofuran **101** was prepared from methyl ketone **48b** according to the above-described methodology.

1-[2-(5-Methyl-2-phenyloxazol-4-ylmethyl)benzofuran-5-yl]ethanol (48a, R^1 = H). Methylmagnesium chloride (4.2 mL, 12.6 mmol) was added into a cold (0 °C) solution of 2-(5-methyl-2-phenyloxazol-4-ylmethyl)benzofuran-5-carbaldehyde (prepared according to EP 0 428 312 A2, 4.0 g, 12.6 mmol) and THF (20 mL). The reaction was stirred at 0 °C for 20 min and then at room temperature for 30 min. The mixture was poured into water, acidified with HCl (2 N) and extracted with ethyl acetate. The organic extracts were dried over $MgSO_4$. Evaporation of the volatiles and purification by flash chromatography on silica gel (hexane/ethyl acetate 2/1) gave a yellow solid (3.75 g, 88% yield): mp 103−105 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.33 (d, J = 6.2 Hz, 3H, CH_3), 2.37 (s, 3H, CH_3), 4.06 (s, 2H, CH_2), 4.8 (q, J = 6.3 (1H, C*H*), 5.14 (brs, 1H, O*H*), 6.61 (s, 1H, C*H*), 7.2 (dd, J = 8.51, 1.66 Hz, 1H, Ar-*H*), 7.4−7.5 (m, 5H, Ar-*H*), 7.91 (m, 2H, Ar-*H*); IR (KBr, cm^{-1}) 3380 (OH); MS *m/e* 333 (M^+). Anal. ($C_{21}H_{19}F_3NO_3$) C, H, N.

1-[2-(5-Methyl-2-phenyloxazol-4-ylmethyl)benzofuran-5-yl]ethanone (48b, R^1 = H). Freshly prepared Jones reagent (6.5 mL, 10.5 mmol) was added dropwise into a cold (10 °C) solution of 1-[2-(5-methyl-2-phenyloxazol-4-ylmethyl)benzofuran-5-yl]ethanol (3.5 g, 10.51 mmol) and acetone (50 mL). After 30 min, the mixture was poured into water and extracted with ethyl ether/ethyl acetate 1/1. The organic extracts were dried over $MgSO_4$. Evaporation of the volatiles and purification by flash chromatography on silica gel (hexane/ethyl acetate 2/1) gave a yellow solid (3.4 g, 97% yield): mp 108−109 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.39 (s, CH_3), 2.6 (3H, CH_3), 4.12 (s, 2H, CH_2), 6.8 (s, 1H, C*H*), 7.48 (m, 3H, Ar-*H*), 7.6 9d, J = 8.7 Hz, 1H, Ar-*H*), 7.85−7.9 (m, 3H, Ar-*H*), 8.2 (d, J = 1.87 Hz, 1H, Ar-*H*); IR (KBr, cm^{-1}) 1675 (CO); MS *m/e* 331 (M^+). Anal. ($C_{21}H_{17}F_3NO_3$) C, H, N.

Tetrazole **123** was prepared according to the following procedure.

(*E*)-4-[3-({5-Methyl-2-[4-(trifluoromethoxy)phenyl]-1,3-oxazol-4-yl}methoxy)phenyl]-3-pentenenitrile (28b, R^1 = CF$_3$, R^3 = CH$_3$, meta-substituted). Sodium cyanide (0.1 g, 2.02 mmol) in water (0.5 mL) was added into a mixture of 4-({3-[(*E*)-3-chloro-1-methyl-1-propenyl]phenoxy}methyl)-5-methyl-2-[4-(trifluoromethoxy)phenyl]-1,3-oxazole (0.68 g, 1.55 mmol) and acetonitrile (10 mL). The reaction mixture was refluxed for 3 h, poured into water, acidified with HCl (2 N) and extracted with ethyl acetate. The organic extracts were dried over $MgSO_4$. Evaporation of the volatiles and purification by flash chromatography on silica gel (hexane/ethyl acetate 2/1) gave a yellow oil (0.65 g, 66% yield): ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.03 (s, 3H, CH_3), 2.46 (s, 3H, CH_3), 3.5 (d, J = 7.03 Hz, 2H, CH_2), 5.04 (s, 2H, CH_2), 5.8 (t, J = 7.03 Hz, 1H, C*H*), 6.95 (dd, J = 8.13, 2.4 1H, Ar-*H*), 7.02 (d, J = 7.68 Hz, 1H, Ar-*H*), 7.1 (t, J = 1.98 Hz, 1H, Ar-*H*), 7.25 (t, J = 7.9 Hz, 1H, Ar-*H*), 7.5 (d, J = 7.9 Hz, 2H, Ar-*H*), 8.05 (d, J = 8.78 Hz, 2H, Ar-*H*); MS *m/e* 428 (M^+). Anal. ($C_{21}H_{17}F_3NO_3$) C, H, N.

4-[5-Methyl-4-({3-[(*E*)-1-methyl-3-(2*H*-1,2,3,4-tetrazol-5-yl)-1-propenyl]phenoxy}methyl)-1,3-oxazol-2-yl]phenyl Trifluoromethyl Ether (123). Sodium azide (1.6 g, 24.7 mmol) was added into a mixture of (*E*)-4-[3-({5-methyl-2-[4-(trifluoromethoxy)phenyl]-1,3-oxazol-4-yl}methoxy)phenyl]-3-pentenenitrile (2.12 g, 4.95 mmol), NH_4Cl (1.33 g, 24.7 mmol), and *N*,*N*-dimethylformamide (50 mL). The reaction mixture was stirred at 130 °C for 5 h, cooled to room temperature, poured into water, acidified with HCl (2 N), and extracted with ethyl acetate. The organic extracts were dried over $MgSO_4$. Evaporation of the volatiles and purification by flash chromatography on acid washed (5% H_3PO_4/methyl alcohol) silica gel (hexane/ethyl acetate 5/1) gave an off-white solid (0.75 g, 33% yield): mp 100−101 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.07 (s, 3H, CH_3), 2.44 (s, 3H, CH_3), 3.85 (d, J = 7.25 Hz, 2H, CH_2), 5.03 (s, 2H, CH_2), 6.07 (t, J = 7.03 Hz, 1H, C*H*), 6.95 (dd, J = 7.91, 2.4 1H, Ar-*H*), 7.02 (d, J = 7.91 Hz, 1H, Ar-*H*), 7.1 (t, J = 1.98 Hz, 1H, Ar-*H*), 7.25 (t, J = 7.91 Hz, 1H, Ar-*H*), 7.5 (d, J = 8.13 Hz, 2H, Ar-*H*), 8.05 (d, J = 8.56 Hz, 2H, Ar-*H*), 16.05 (brs, 1H, N*H*); MS *m/e* 471 (M^+). Anal. ($C_{21}H_{17}F_3NO_3$) C, H, N.

Biological Methods. 1. In Vitro Inhibition of *p*-Nitrophenylphosphatase (pNPPase, orthophosphoric monoester phosphohydrolase) Activity in Membranes Isolated from Rat Liver. Preparation of membranes: Male Sprague−Dawley rats (Charles River, Kingston, NY) weighing 100−150 g, maintained on standard rodent chow (Purina), were sacrificed by asphyxiation with CO_2. The liver was removed and washed in cold 0.85% (w/v) saline and weighed. The tissue was homogenized on ice in 10 volumes of buffer A and the membranes were isolated essentially as described by Meyerovitch et al.[25] with minor modifications. The liver homogenate was filtered through silk to remove any remaining tissue debris and then was centrifuged at 10000*g* for 20 min. The pellet, membrane fraction, was resuspended and lightly homogenized in: 20 mM TRIS-HCl (pH 7.4), 50 mM mercaptoethanol, 250 mM sucrose, 2 mM EDTA, 10 mM EGTA, 2 mM AEBSF, 0.1 mM TLCK, 0.1 mM TPCK, 0.5 mM benzamidine, 25 μg/mL leupeptin, 5 μg/mL pepstatin A, 5 μg/mL antipain, 5 μg/mL chymostatin, 10 μg/mL aprotinin to a final concentration of approximately 750 μg protein/mL. Protein concentration was determined by the Bio-Rad protein assay using crystalline bovine serum albumin as a standard (Bio-Rad Laboratories, Richmond, CA).

Measurement of pNPPase activity: The assay was conducted as described by Moss[26] and Tonks et al.[27] with minor modifications. The incubation mixture contains in a final volume of 0.24 mL: 50 mM HEPES (pH 7.4), 6.33 mM pNPP, and 5/50/150 μM compound suspended in 1.25% DMSO. Membranes were preincubated with compound in HEPES buffer for 10 minutes at 37 °C. The reaction was started by the additions of pNPP and after 30 min at 37 °C, the reaction was terminated by adding 1 mL of NaOH (0.1 N). The assay was performed in triplicate. The reaction mixture contained approximately 30 μg protein, of the above components, plus 3.33 mM TRIS-HC1, 8.33 mM 2-mercaptoethanol, 41.67 mM sucrose, 0.33 mM EDTA, 1.67 mM EGTA, 0.33 mM AEBSF, 0.02 mM TLCK, 0.02 mM TPCK, 0.08 mM benzamidine, 4.17 μg/mL leupeptin, 0.83 μg/mL pepstatin A, 0.83 μg/mL antipain, 0.83 μg/mL chymostatin, and 1.67 μg/mL aprotinin. The samples were read at 410 nm in a spectrophotometer and were evaluated based on a calibration curve of *p*-nitrophenol standard solution.

Calculations: The results were expressed as percent of control, in that the amounts of *p*-nitrophenol formed in the compound treated samples (nmol/min/mg protein) were compared to the amount (nmol/min/mg protein) formed in the untreated samples. The mean and standard error of the mean were calculated (Lotus 1-2-3) and the IC_{50} values were calculated by a regression analysis of the linear portion of the inhibition curves (STAT80 release 3.00, EDOSE version 2.00). pNPPase activity was also determined in every experiment and expressed per mg protein.

2. Inhibition of Triphosphorylated Insulin Receptor Dodecaphosphopeptide Dephosphorylation by r-PTP1B. Preparation of recombinant r-PTP1B: Rat recombinant PTP1B, prepared as described by Goldstein et al.,[23] was suspended in 33 mM TRIS-HCl, 2 mM EDTA, 10% glycerol and 10 mM β-mercaptoethanol.

Measurement of PTPase activity: The malachite green−ammonium molybdate method, as described by Lanzetta et al.[24] and adapted for the platereader, was used for the nanomolar detection of liberated phosphate by recombinant r-PTP1B. The assay used, as substrate, a dodecaphosphopeptide custom synthesized by AnaSpec, Inc. (San Jose, CA). The peptide, TRDIYETDYYRK, corresponding to the 1142−1153 catalytic domain of the insulin receptor, is phosphorylated on tyrosine residues 1146, 1150, and 1151. The recombinant r-PTP1B was diluted with buffer, pH 7.4, containing 33 mM TRIS-HCl, 2 mM EDTA and 50 mM β-mercaptoethanol to obtain an approximate activity of 1000−2000 nmol/min/mg protein. The diluted enzyme (83.25 mL) was preincubated for 10 min at 37 °C with or without test compound (6.25 μL) and 305.5 mL of the 81.83 mM HEPES reaction buffer, pH 7.4. Peptide substrate, 10.5 μL at a final concentration of 50 μM, was equilibrated to 37 °C in a LABLINE Multi-Blok heater. The preincubated recombinant enzyme preparation (39.5 mL) with or without drug was added to initiate the dephosphorylation reaction, which proceeded at 37 °C for 30 min. The reaction was terminated by the addition of 200 μL of the malachite green−ammonium molybdate−Tween 20 stopping reagent (MG/AM/Tw). The stopping reagent consisted of 3 parts 0.45% malachite green hydrochloride, 1 part 4.2% ammonium molybdate tetrahydrate in 4 N HCl, and 0.5% Tween 20. Sample blanks were prepared by the addition of 200 mL MG/AM/Tw to substrate and followed by 39.5 μL of the preincubated recombinant enzyme with or without drug. The color was allowed to develop at room temperature for 30 min and the sample absorbances were determined at 650 nm using a plate reader (Molecular Devices). Samples and blanks were prepared in quadruplicates.

Calculations: PTPase activities, based on a potassium phosphate standard curve, were expressed as nmol of phosphate released/min/mg protein. Inhibition of recombinant r-PTP1B by test compounds was calculated as percent of phosphatase control. A four-parameter nonlinear logistic regression of PTPase activities using SAS release 6.08, PROC NLIN, was used for determining IC_{50} values of the test compounds.

3. Inhibition of Triphosphorylated Insulin Receptor Dodecaphosphopeptide Dephosphorylation by h-PTP1B. Preparation of recombinant h-PTP1B: Human recombinant PTP1B (321 aa form) was prepared as described.[22] Measurements and calculations of h-PTP1B activity were determined similar to the r-PTP1B assay.

4. *ob/ob* and *db/db* Mouse Models. Experimental details for the *ob/ob* and *db/db* diabetic mouse models were previously described.[28]

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