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Synthesis and PTP1B Inhibition of Novel 4-Aryl-1-Oxa-9-Thiacyclopenta[*b*]fluorenes

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Abstract—Novel 4-aryl-1-oxa-9-thiacyclopenta[*b*]fluorenes were designed, synthesized, and evaluated as inhibitors of the protein tyrosine phosphatase, PTP1B. Compounds **3** ($IC_{50}=284$ nM) and **4** ($IC_{50}=74$ nM), showed nanomolar potency against PTP1B (TRDI(P)YETD(P)Y(P)YRK as substrate). Compound **4** also lowered insulin in the diabetic ob/ob mouse at a dose of 10 mg/kg/day, po.

Protein tyrosine phosphatase 1B (PTP1B) appears to play a major role in insulin sensitivity and the dephosphorylation of the insulin receptor (IR) on the basis of many biochemical and cellular studies[1] and according to a pivotal study with PTP1B knockout mice.[2] Dephosphylation of the IR correlates with insulin resistance[3] and this, in turn, is a prime factor leading to Type II diabetes.[4] Thus, an orally active and selective PTP1B inhibitor could potentially ameliorate insulin resistance and normalize plasma glucose and insulin without inducing hypoglycemia, and could, therefore, be a major advance in the treatment of Type II diabetes.[5] We previously disclosed the PTP1B inhibition and oral antidiabetic activities of a series 11-aryl benzo[*b*]naphtho[2,3-*d*]thiophenes, such as **1**[6] (Fig. 1). In an effort to define the role and improve upon the properties of the tetracyclic ring portion of **1** and **2**, we designed, synthesized and tested 4-aryl-1-oxa-9-thiacyclopenta[*b*]fluorenes **3** and **4** (Fig. 1) and report the results herein.

Chemistry

According to Scheme 1, commercially available 2,3-dimethylfuran **5** was subjected to Vilsmeier conditions to afford 4,5-dimethylfuran 2-carboxaldehyde (method a).[7] 2-Lithio-benzo[*b*]thiophene, produced via reaction of benzo[*b*]thiophene with *n*-butyl lithium, was treated with this aldehyde (method b) and the secondary alcohol of the resulting product was reductively eliminated using conditions of Nutaitis[8] to provide methylene congener **6** (method c). Treatment of this benzothiophene-furan **6** with *p*-anisoyl chloride under standard Friedel-Crafts conditions (method d) resulted in acylation of **6**, concomitant intramolecular cyclization and aromatization to give the 1-oxa-9-thiacyclopenta[*b*]fluorene heterocycle **7**, which was the first representative of this novel heterocyclic ring system. Starting material **6** (42%) was recovered as well.

The methyl ether of **7** was demethylated with BBr_3 (method e) and the resulting phenol was bis-iodinated with molecular iodine and base to provide di-iodo phenol **8** (method f). Treatment of **8** with (*S*)-lactic acid, methyl ester under Mitsunobu conditions, followed by methyl ester hydrolysis with aqueous potassium hydroxide gave (*R*)-2-methyloxyacetic acid derivative **3** (method g). Likewise, compound **8**, when reacted with (*S*)-2-hydroxy-3-phenylpropionic acid, methyl ester under similar conditions, followed by basic hydrolysis gave (*R*)-2-benzyloxyacetic acid derivative **4** (method h).

For the preparation of **2**, compound **9**[6] was subjected to molecular iodine and base (method i) and the resulting di-iodophenol was further treated with (*S*)-2-hydroxy-3-phenylpropionic acid, methyl ester under Mitsunobu conditions. Methyl ester hydrolysis with aqueous potassium hydroxide (method j) afforded compound **2**. Analytical data for the target compounds and intermediates are provided in footnote 17.

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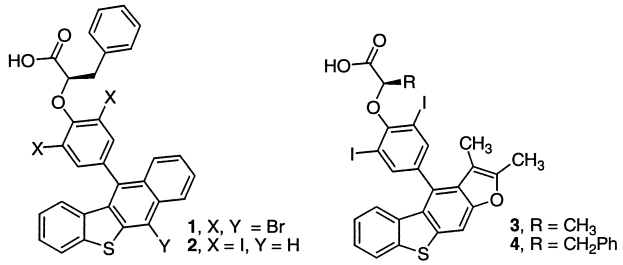


Figure 1.

Results and Discussion

The inhibitory activity of our compounds against recombinant PTP1B[9] was assessed using, as substrate, the phosphotyrosyl dodecapeptide, TRDI(P)YETD(P)Y (P)YRK, corresponding to the 1142–1153 insulin receptor kinase regulatory domain, phosphorylated on the 1146, 1150, and 1151 tyrosine residues as described previously.[6,10]

We previously reported that compound **1** had an IC_{50} against hPTP1B of 61 nM, making it among the most potent PTP1B inhibitors reported to date.[6] In our docking studies of **1** with the X-ray crystal structure PTP1B,[6] we noticed that the tetracyclic ring portion interacted with lysine-120 and lysine-116 via cation-π type interactions described by Dougherty[11] (see Fig. 2). There was a particularly strong interaction (~3 Å) between lysine-120 side-chain nitrogen atom and the naphthalene ring of the tetracycle. In an effort to capitalize on this possible interaction, we designed the 4-aryl-1-oxa-9-thiacyclopenta [*b*]fluorene ring system (as shown in analogues **3** and **4**) because the terminal furan ring of this system would provide a more electron rich aromatic environment that could potentially have stronger interactions with the ammonium side chain of lysine-120.

In order to directly compare the effect on activity of the 1-oxa-9-thiacyclopenta[*b*]fluorene ring system with the benzo [*b*]naphtho[2,3-*d*]thiophene ring system of compound **1**, the substituents of both compounds would have to be identical. Since the tribromo derivative of the 1-oxa-9-thiacyclopenta[*b*]fluorene analogous to **1** was not readily

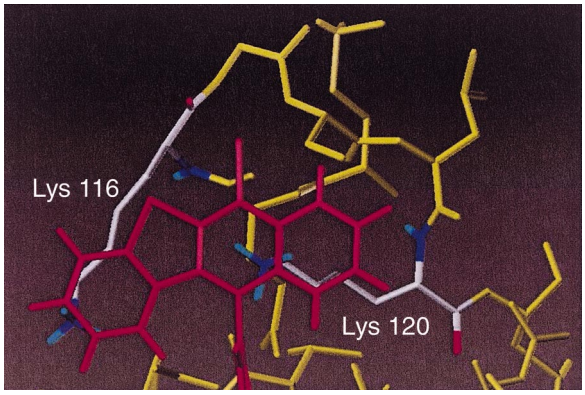
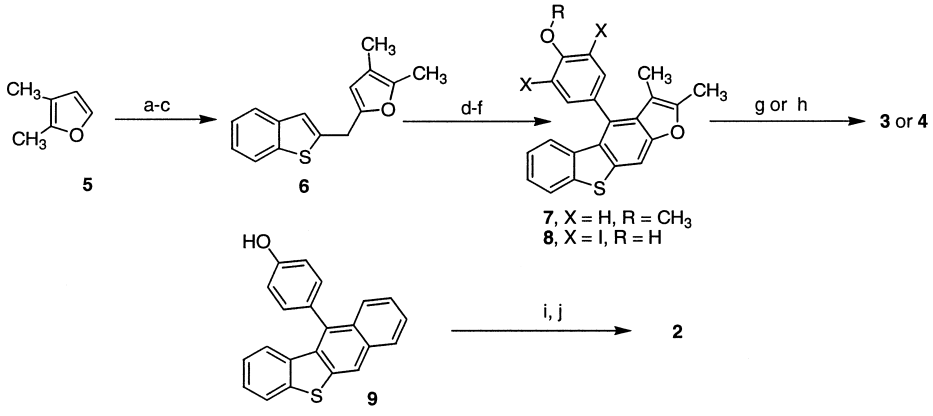


Figure 2. Cation-π interactions of lysines 116 and 120 of PTP1B with the tetracyclic-rings of **1** found via docking experiments.

obtained through our synthesis efforts, we prepared instead the diiodide-containing analogue **4**. Thus, the obvious analogue from the benzo[*b*]naphtho[2,3-*d*]thiophene series to compare to compound **4** was the diodide **2**. This latter compound contained the same ring system as **1** with the minor changes of substitution of two phenolic ring bromines by iodine atoms and the tetracyclic ring bromine by a hydrogen atom.

Consistent with our hypothesis gleaned from our docking studies, compound **4**, with an IC_{50} of 74 nM, was more potent than **2** (IC_{50} of 179 nM). Structural studies are necessary to confirm our docking results and therefore other reasons for this potency enhancement are possible. For instance, the length of the tetracyclic portion increased by 1 Å when going from **2** to **4**. This increase in length results in an extension of lipophilic moieties that are available for binding via hydrophobic interactions. Other differences that could play a role in the increased potency of **4** over **2** include differences in dipole moments and the potential *H*-bonding site of the furan oxygen atom of **4** that is not present in **2**.

The (*R*)-benzyl moiety emanating from the acetic acid α-carbon of **1** was incorporated into **1** on the basis of



Scheme 1. Reagents and conditions: (a) DMF, $POCl_3$, rt, 3.5 h, 76%; (b) 2-lithio-benzo[*b*]thiophene, THF, −78 °C, 1 h, 99%; (c) $NaBH_4$, TFA, THF, rt, 3.5 h, 42%; (d) *p*-anisoyl chloride, $SnCl_4$, CS_2, −78 to 0 °C, 9 h, 25%; (e) BBr_3, CH_2Cl_2, −78 °C to rt, 2.5 h, 94%; (f) I_2, NaOH, MeOH, 0 °C to rt, 15 h, 54%; (g) **8** to **3** (*S*)-lactic acid, methyl ester, diethyl azodicarboxylate, PPh_3, benzene, reflux, 3 h, 52%/KOH, H_2O, dioxane, rt, 32 h, 95%; (h) **8** to **4** (*S*)-$HOCH_2(CH_2Ph)CO_2Me$, diethyl azodicarboxylate, PPh_3, benzene, 60 °C, 3 h, 54%/KOH, H_2O, dioxane, rt, 24 h, 93%; (i) I_2, NaOH, MeOH, 0 °C to rt, 15 h, 54%; (j) (*S*)-$HOCH_2(CH_2Ph)CO_2Me$, diethyl azodicarboxylate, PPh_3, benzene, 60 °C, 3 h, 86%/KOH, H_2O, dioxane, rt, 24 h, 99%.

the aforementioned docking studies of **1**, and earlier analogues.[6] In these studies, the benzyl moiety of **1** filled an empty pocket within the enzyme active site. According to these docking results, a substituent smaller than a benzyl group would not fill this pocket as well, and was therefore proposed to be less active. To examine this hypothesis, the 1-oxa-9-thiacyclopenta[*b*]fluorene analogue **3** that contained an (*R*)-methyl moiety on the acetic acid α-carbon was prepared. This compound, with an IC_{50} of 284 nM, was indeed more than 4-fold less potent than **4**.

The compounds were also evaluated as antidiabetic agents in the ob/ob mouse model.[6,12,13] Insulin resistance in this model, has been associated with a reduction in insulin-induced protein tyrosine phosphorylation in tissues such as liver, and markedly elevated PTPase activities in these tissues have been observed leading to the conclusion that PTPases may cause or contribute to the reduced phosphorylation of the IR.[14] Increased abundance of PTP1B in the livers of ob/ob mice has also been noted.[15] Although neither **2** nor **4** significantly lowered plasma glucose values in these studies, the 1-oxa-9-thiacyclopenta [*b*]fluorene analogue **4** demonstrated a statistically significant ($p < 0.05$) insulin lowering effect of 43% at a dose of 10 mg/kg dose.[16] The benzo[*b*]naphtho[2,3-*d*]thiophene analogue **2** also demonstrated a statistically significant ($p < 0.05$) insulin lowering effect (68%) although it was at a considerably higher dose (25 mg/kg) than that for **4**.

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16. Ciglitazone reference standard at 100 mg/kg dose: 43% decrease in glucose and 39% decrease in insulin insulin.
17. **Analytical data**. Melting points were determined on an electrothermal capillary melting point apparatus and are not corrected. Proton magnetic resonance (^{1}H NMR) spectra were recorded at 200 MHz (Varian XL-200), 300 MHz (VXR-300 or Bruker DPX300), or at 400 MHz (Bruker AM-400 or VXR-400). Electron Impact (EI, IE = 70 eV) and chemical ionization (CI, isobutane reagent gas) mass spectra were recorded on a Finnigan model 8230 spectrometer. Fast atom bombardment (FAB) were recorded on a Kratos MS50. High Resolution MS were recorded on a Bruker 9.4 T FTMS. Analyses (C, H, N) were carried out on a modified Perkin–Elmer model 240 CHN analyzer. Analytical results for elements were within ±0.4% of the theoretical values.
4,5-Dimethyl-2-furaldehyde: yellow oil: MS (ESI): [M + H] +, 125.
Benzo[*b*]thiophen-2-yl-(2,3-dimethyl-furan-5-yl)-methanol. Yellow oil: ^{1}H NMR (DMSO-d_6) δ 7.89 (d, J = 8 Hz, 1H), 7.76 (d, J = 8 Hz, 1H), 7.26–7.356 (m, 2H), 7.25 (s, 1H), 6.36 (s, 1H), 6.08 (s, 1H), 5.92 (s, 1H), 2.13 (s, 3H), 1.86 (s, 3H); MS (EI): [M +], 258.
Benzo[*b*]thiophen-2-yl-(2,3-dimethyl-furan-5-yl)-methane (**6**). Oil: ^{1}H NMR ($CDCl_3$) δ 7.74 (d, J = 8 Hz, 1H), 7.67 (d, J = 8 Hz, 1H), 7.22–7.35 (m, 2H), 7.08 (d, J = 1 Hz, 1H), 5.93 (s, 1H), 4.15 (s, 2H), 2.17 (s, 3H), 1.90 (s, 3H); MS (EI): [M +], 242.
4-(2,3-Dimethyl-1-oxa-9-thia-cyclopenta[*b*]fluoren-4-yl)-phenyl methyl ether (**7**). Light-yellow solid: ^{1}H NMR ($CDCl_3$) δ 7.81 (s, 1H), 7.76 (d, J = 8 Hz, 1H), 7.24–7.36 (m, 3H), 7.00–7.11 (m, 3H), 6.85 (d, J = 8 Hz, 1H), 3.96 (s, 3H), 2.37 (s, 3H), 1.55 (s, 3H); MS (EI): [M +], 358.
4-(2,3-Dimethyl-1-oxa-9-thia-cyclopenta[*b*]fluoren-4-yl)-phenol. Brown: mp 174–175 °C: ^{1}H NMR ($CDCl_3$) δ 7.81 (s, 1H), 7.76 (d, J = 8 Hz, 1H), 7.27–7.31 (m, 3H), 7.00–7.08 (m, 3H), 6.87 (d, J = 8 Hz, 1H), 5.00 (s, 1H), 2.37 (s, 3H), 1.58 (s, 3H); MS (EI): [M +], 344.
4-(2,3-Dimethyl-1-oxa-9-thia-cyclopenta[*b*]fluoren-4-yl)-2,6-diiodo-phenol (**8**). White solid: ^{1}H NMR ($CDCl_3$) δ 7.83 (s, 1H), 7.81 (s, 2H), 7.80 (d, J = 8 Hz, 1H), 7.33 (dd, J = 8, 7 Hz, 1H), 7.15 (dd, J = 8, 7 Hz, 1H), 6.98 (d, J = 8 Hz, 1H), 5.99 (s, 1H), 2.37 (s, 3H), 1.61 (s, 3H); MS (EI): [M +], 596.
(*R*)-2-[4-(2,3-Dimethyl-1-oxa-9-thia-cyclopenta[*b*]fluoren-4-yl)-2,6-diiodo-phenoxy]-propionic acid (**3**). Off-white solid: mp 218–219 °C: ^{1}H NMR ($CDCl_3$) δ 7.97 (s, 2H), 7.85 (s, 1H), 7.81 (d, J = 8, Hz, 1H), 7.34 (ddd, J = 8, 7, 1 Hz, 1H), 7.12 (ddd, J = 8, 7, 1 Hz, 1H), 6.87 (d, J = 8 Hz, 1H), 5.46 (q, J = 7 Hz, 1H, CH), 2.38 (s, 3H), 1.77 (d, J = 7 Hz, 3H), 1.61 (s, 3H); MS (+FAB): [M +], 667.8, [M + H] +, 668.9. Anal. calcd for $C_{25}H_{18}I_2O_4S$: C, 44.93; H, 2.72; N, 0.00. Found: C, 44.77; H, 2.63; N, 0.20.
(*R*)-2-[4-(2,3-Dimethyl-1-oxa-9-thia-cyclopenta[*b*]fluoren-4-yl)-2,6-diiodo-phenoxy]-3-phenyl-propionic acid (**4**). White solid: mp 215–217 °C ^{1}H NMR (DMSO-d_6) δ 8.20 (s, 1H), 7.96 (d, J = 8 Hz, 1H), 7.92 (d, J = 2 Hz, 2H), 7.45–7.30 (m, 5H), 7.27 (dd, J = 7 Hz, 1H), 7.16 (dd, J = 7, 1 Hz, 1H), 6.84 (d, J = 8 Hz, 1H), 5.36 (t, J = 6 Hz, 1H), 3.43 (dd, J = 6 Hz, 2H), 2.37 (s, 3H), 1.57 (s, 3H); MS (+FAB): [M + H] +, 745; High-resolution MS (ESI) calcd for $C_{31}H_{22}I_2O4S$: [M + H] + 744.94010. Found: 744.94090.
4-(Benzo[*b*]naphtho[2,3-d]thiophen-11-yl)-2,6-diiodo-phenol. White solid: mp 213–214 °C: MS (-FAB): $[M-H]^-$, 576.8. Anal.

calcd for $C_{22}H_{12}I_2OS$: C, 45.70; H, 2.09; N, 0.00. Found: C, 45.82; H, 2.07; N, 0.30.

(*R*)-Benzo[*b*]naphtho[2,3-d]thiophen-11-yl-2,6-diiodo-phenoxy)-3-phenyl-propionic acid (**2**). White solid: mp 115–117 °C: NMR ($CDCl_3$) δ 8.36 (s, 1H), 7.95 (dd $J=8$, 1 Hz, 1H), 7.87 (d, $J=2$ Hz, 1H), 7.85 (d, $J=2$ Hz, 1H), 7.78 (dd, $J=8$, 1 Hz, 1H), 7.27–7.58 (m, 9 H), 7.12 (ddd, $J=8$, 7, 1 Hz, 1H), 6.77 (d, $J=8$, 1 Hz, 1H), 5.56 (t, $J=7$ Hz, 1H), 3.67–3.55 (m, 2H); MS (EI): [M+], 726. Anal. calcd for $C_{31}H_{20}I_2O_3S$: C, 51.26; H, 2.77; N, 0.00. Found: C, 51.49; H, 2.87; N, 0.13.