Protein Tyrosine Phosphatase 1B Inhibitors: Heterocyclic Carboxylic Acids

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Several series of compounds (benzoic acids, pyrazolecarboxylic acids, phenoxyacetic acids, and quinolinoxyacetic acids) were prepared and evaluated for their inhibitory activity against PTP-1B. Several compounds showed submicromolar inhibitory activity.

Key Words: Diabetes, PTP1B inhibitor, Isoxazole, Oxadiazole, Quinoline

Introduction

Protein tyrosine phosphatase 1B (PTP-1B) plays a crucial role in the modulation of insulin signaling pathway through dephosphorylation of the activated insulin receptor. Since Echelby and coworkers reported that PTP-1B knock-out mice showed improved insulin sensitivity and resistance to weight gain, PTP-1B has emerged as an attractive therapeutic target for treatment of insulin resistance related to Type 2 diabetes. Thus, PTP-1B inhibitors could potentially ameliorate insulin resistance and normalize plasma glucose and insulin without inducing hypoglycemia.

Recently, small molecule inhibitors of PTP-1B as well as peptide mimetics were reported in literatures. They included oxalamides (1, 2), benzoic acid (3), and phenoxyacetic acids (4-7) (Figure 1). One of the inhibitors, Ertiprotafib (7) went to clinical trial, but was discontinued in Phase II due to insufficient efficacy and dose-dependent side effects. In the preceding papers from this laboratory, the 1,2-naphthoquinone and catechol derivatives were reported as new classes of PTP-1B inhibitors.

![Figure 1. PTP-1B Inhibitors.](image)

Figure 1. PTP-1B Inhibitors.

Scheme 1. Synthesis of Pyrazolecarboxylic Acid Derivatives.

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Scheme 2. Synthesis of Isoxazolylphenoxyacetic Acid Derivatives.

Scheme 3. Synthesis of Isoxazolylbenzoic Acid Derivatives.
Results and Discussion

As isoxazole and pyrazole carboxylic acids were discovered as hits from the high-throughput screening (HTS) of the library of Korea Chemical Bank, it was decided to evaluate the skeleton through structural modifications.

First, pyrazole carboxylic acid derivatives 11 were prepared as shown in Scheme 1. While acids 11 was active toward

![Chemical Structures](image)

Scheme 1. Synthesis of Quinolinyloxyacetic Acid Derivatives.
PTP-1B, esters 10 were found to be inactive. Similar trend was also observed in the result of HTS. Pyrazole derivative with octyl group 11a showed moderate activity while the tetradecyl derivative 11b showed superior activity. Further study was not pursued due to consideration of patentability.

Then the attention was moved to derivatives of isoxazoles and fused isoxazoles. First, isoxazolylphenoxycarbonylic acids were prepared as shown in Scheme 2 and tested toward PTP-1B to study the effect of structural modifications to the inhibitory activity. The pyrazoic acid moiety was incorporated as some of the o-quinones substituted with phenoxycetic acid showed micromolar inhibitory activity in the earlier paper.6a and also many phenoxycetic acid derivatives including Etiripotafib 7 have been reported as PTP-1B inhibitors. Various derivatives were easily obtained by 1,3-dipolar cycloaddition of nitriles, alkynes, and indoles with chlorooxime 12 to give oxadiazolyl derivatives 14, isoxazolyl derivatives 16, and dihydroisoxazolyl[5,4-b] indole derivatives 18, respectively.

When tested for enzyme inhibitory activity against PTP-1B, only the parent isoxazole (16a) with decyl chain showed moderate inhibitory activity. Either oxadiazolyl derivatives 14 or dihydroisoxazolyl[5,4-b] indole derivatives 18 were not effective inhibitors of PTP-1B.

The second attempt in the modification of the isoxazole series was preparation of benzoisoxazole derivatives. 4-(Benzoisoxazol-3-yl)benzoic acid derivatives were prepared as shown in Scheme 3. Hydroxybenzophenone 19 was prepared by palladium-catalyzed coupling of salicylaldehyde with aryl iodide.7 Benzoisoxazolyl benzoate 20 was prepared by cyclocondensation of 2-hydroxybenzophenone 19.8 The derivatives 23, 24, 26, and 27 were prepared from 20 with introduction of various substituents at 5-position of benzoisoxazole ring by palladium-mediated introduction of aryl and alkenyl groups.9 Aromatic derivatives, 23 and 24 did not show any significant activities, whereas alkyl derivatives 26a and 27 showed improved activity compared to parent 21. But tetradecyl derivative 26b showed submicromolar activity. Thus introduction of aromatics to the aromatic ring of 1,2-benzoisoxazoles was detrimental to the inhibitory activity, while introduction of hydrocarbon chains to the aromatics increased the inhibitory activity significantly. Similar trend was also observed in the other series.

Then quinoline derivatives were prepared because isosteres of quinoline were also discovered as hits from HTS. Alkyl groups were introduced by palladium-mediated reaction of 3-iodoquinolines,10 which was in turn prepared by chlorination of 4-hydroxy-3-iodoquinolines. The arylxoyacetic acid was introduced by alkylation of phenolic group with bromoacetate and subsequent hydrolysis.

While 3-phenyl derivative 42 and dicarboxylic acid 47 did not show activity, octyl derivatives 31, 39, and 44 (42 with insertion of benzene) showed moderate activities. Octenyl derivative with 8-acetoxy group 37 (unsaturated form of 39) showed improved activity with an IC50 of 3.27 μM. Tetracarboxylic derivative 43 and 6-octoxyquinoline-3-carboxylic acid 50 showed submicromolar activities. Thus the positive action of alkyl substitution also worked in this quinoline series.

The selectivity of the inhibitors is important to minimize the undesirable side effects of a drug. Thus the selectivity of the selected inhibitors was tested likewise against nine phosphatases using the same concentration of FDP as substrate and the result is shown in Table 2. The isozyme selectivities are generally good except against YOP and cdc25B.

### Experimental Section

1-(4-Octylbenzyl)pyrazole-3-carboxylic acid (11a). A mixture of 1H-pyrazole-3-carboxylic acid ethyl ester 8 (1.00 g, 7.1 mmol), 4-bromobenzyl bromide (2.14 g, 8.6 mmol), potassium hydroxide (600 mg, 10.7 mmol) in THF (40 mL) was heated for 12 h at reflux and partitioned between brine and ethyl acetate. The organic layer was dried with MgSO4, filtered, and concentrated. The residue was purified by column chromatography to give 1-(4-bromobenzyl)-1H-pyrazole-3-carboxylic acid ethyl ester 9 (1.7 g, 81%) as white solid:1H NMR (200 MHz, CDCl3) δ 7.49 (d, J = 8.3 Hz, 2H) 7.35 (d, J = 2.4 Hz, 1H) 7.11 (d, J = 8.3 Hz, 2H) 6.84 (d, J = 2.4 Hz, 1H) 5.35 (s, 2H) 4.42 (q, J = 14.2, 7.1 Hz, 2H) 1.40 (t, J = 7.1 Hz, 3H); EI-MS m/z (relative intensity) 309 (M+, 13), 169 (100), 89 (30), 63 (24). A mixture 9 (150 mg, 0.49 mmol), DMF (7 mL), palladium acetate (22 mg, 0.1 mmol), sodium bicarbonate (90 mg, 1.07 mmol), (n-Bu)4NCl (135 mg, 0.49 mmol), and 1-octene (108.8 mg,

### Table 2. Isozyme Selectivity (IC50, μM)

<table>
<thead>
<tr>
<th>IC50</th>
<th>7</th>
<th>11b</th>
<th>16a</th>
<th>27b</th>
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<tr>
<td>PTP-1B</td>
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<td>0.44</td>
<td>3.89</td>
<td>0.44</td>
<td>0.51</td>
</tr>
<tr>
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<td>0.69</td>
<td>0.41</td>
<td>0.10</td>
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<tr>
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<tr>
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<td>5.62</td>
<td>8.34</td>
<td>4.21</td>
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<tr>
<td>CD45</td>
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<td>1.05</td>
<td>&gt;10</td>
<td>1.49</td>
<td>1.47</td>
</tr>
<tr>
<td>LAR</td>
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<td>&gt;10</td>
<td>2.74</td>
<td>&gt;10</td>
</tr>
<tr>
<td>cdc25A</td>
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<td>2.60</td>
<td>&gt;10</td>
<td>1.60</td>
<td>1.73</td>
</tr>
<tr>
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<td>~10</td>
<td>0.18</td>
<td>0.41</td>
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<tr>
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<td>~10</td>
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</table>

% inhibition at 20 μM and IC50 (μM), na - not active.
0.15 mL, 0.97 mmol) in pressure tube was heated for 15 h at 125 °C, and partitioned between saturated NH4Cl solution and ethyl acetate. The organic layer was dried with MgSO4, and concentrated in vacuo. The residue was purified by column chromatography to give 1-{4-(1-octyl-1-en-1-yl)-1H-pyrazole-3-carboxylic acid ethyl ester 10a (135 mg, 82%) as a yellow oil: 1H NMR (200 MHz, CDCl3) δ 7.34-7.30 (3 m, 3H), 7.18 (d, J = 6.5 Hz, 2H), 6.82 (d, J = 2.4 Hz, 1H), 6.41-6.28 (m, 2H), 2.56 (m, 2H), 2.26-2.13 (m, 2H), 1.40 (t, J = 7.1 Hz, 3H), 1.37-1.26 (m, 8H), 0.87 (t, J = 4.4 Hz, 3H); EI-MS m/z (relative intensity) 340 (M+, 47), 143 (54), 129 (100), 117 (45), 104 (44). Then the ester 10a (135 mg, 0.4 mmol) in ethyl acetate (10 mL) was hydrogenated for 3 h with 5% Pd/C (60 mg) as catalyst to give 1-{4-(1-octyl-1-enyl)-1H-pyrazole-3-carboxylic acid ethyl ester (120 mg, 88%) as an yellow oil: 1H NMR (200 MHz, CDCl3) δ 7.32 (d, J = 2.2 Hz, 1H), 7.16 (s, 4H), 6.82 (d, J = 2.2 Hz, 1H), 3.56 (s, 2H), 4.42 (q, J = 14.2, 7.1 Hz, 2H), 2.57 (t, J = 7.3 Hz, 2H), 1.68-1.50 (m, 2H), 1.40 (t, J = 7.1 Hz, 3H), 1.37-1.19 (m, 10H), 0.87 (t, J = 4.4 Hz, 3H); EI-MS m/z (relative intensity) 342 (M+, 7), 117 (53), 104 (100), 43 (60). Finally the ester (120 mg, 0.35 mmol) and NaOH (84 mg, 2.1 mmol) in THF/H2O (1:1) (34 mL) was heated at 80°C for 15 h. After cooling to room temperature, pH was adjusted to 6 with buffer solution (pH 4.1-4.4). The resulting mixture was extracted with ethyl acetate and the organic layer was dried with MgSO4, and concentrated in vacuo to afford 11a (80 mg, 73%) as a yellow oil: 1H NMR (200 MHz, CDCl3) δ 7.37 (d, J = 2.4 Hz, 1H), 7.17 (s, 4H), 6.87 (d, J = 2.4 Hz, 1H), 5.35 (s, 2H), 2.59 (t, J = 7.3 Hz, 2H), 1.58 (m, 2H), 1.26-1.18 (m, 10H), 0.85 (t, J = 2.0 Hz, 3H); EI-MS m/z (relative intensity) 314 (M+, 110), 117 (81), 104 (100), 43 (85).

1-(4-Tetradecylbenzyl)-1H-pyrazole-3-carboxylic acid 11b was prepared as 11a from 9 using 1-dodecene in place of 1-octene: 1H NMR (200 MHz, CDCl3) δ 7.38 (d, J = 2.4 Hz, 1H), 7.17 (s, 4H), 6.88 (d, J = 2.4 Hz, 1H), 5.35 (s, 2H), 2.59 (t, J = 7.3 Hz, 2H), 1.65-1.48 (m, 2H), 1.29-1.25 (m, 22H), 0.86 (t, J = 7.1 Hz, 3H); EI-MS m/z (relative intensity) 398 (M+, 51), 353 (65), 286 (59), 145 (46), 104 (100).

1-[4-(4-Bromophenyl)-1H-pyrazole-3-carboxylic acid 14a] was prepared like 11a using anisonitrile and benzoylacetonitrile, respectively in place of 4-bromonitrile.

1H NMR (200 MHz, DMSO-δ6) δ 13.05 (s, 1H), 8.06 (m, 4H), 7.17 (m, 4H), 4.79 (s, 2H), 3.88 (s, 3H); EI-MS m/z (relative intensity) 326 (M+, 100), 193 (38), 134 (76), 105 (27).

The residue was purified by column chromatography to give [4-[5-(4-Methoxyphenyl)-1,2,4-oxadiazol-3-yl]phenoxo]acetic acid 14c were prepared like 14a using anisonitrile and benzoylacetonitrile, respectively in place of 4-bromonitrile.

A mixture of 12 (1.57 g, 7.00 mmol), 1-dodecylene (4.1 mL, 12.8 mmol) and triethylamine (0.90 mL, 12 mmol) in ether (30 mL) was stirred for 5 h at room temperature, and poured into water (15 mL). The resulting mixture was extracted with 40 mL of ethyl acetate and the organic layer was dried with MgSO4 and concentrated in vacuo. The residue was purified by column chromatography to give [4-[5-(4-isoazoloxidol-3-yl)phenoxo]acetic acid ethyl ester 15a (1.2 g, 87%): 1H NMR (200 MHz, CDCl3) δ 7.77 (m, 2H), 6.97 (m, 2H), 6.22 (s, 1H), 4.65 (s, 2H), 4.28 (q, J = 7.1 Hz, 2H), 2.78 (t, J = 7.3 Hz, 2H), 1.75 (m, 2H), 1.31 (m, 17H), 0.87 (t, J = 6.4 Hz, 3H); EI-MS m/z (relative intensity) 387 (M+, 84), 274 (100), 261 (74). A mixture of 15a (100 mg, 0.26 mmol) and LiOH·H2O (19 mg, 0.39 mmol) in THF:water: methanol (1:1:1, 3 mL) was stirred for 1 h, and acidified by addition of 1N hydrochloric acid (2 mL). The resulting mixture was extracted with ethyl acetate (30 mL) and the organic layer was dried with MgSO4 and concentrated in vacuo. The residue was purified by column chromatography to give 16a (77 mg, 79%): 1H NMR (200 MHz, CDCl3) δ 12.90 (brs, 1H), 7.78 (m, 2H), 6.98 (m, 2H), 6.61 (m, 1H), 4.64 (s, 2H), 2.74 (m, 2H), 1.64 (m, 2H), 1.25 (m, 14H), 0.82 (s, 3H); EI-MS m/z (relative intensity) 359 (M+, 67), 246 (100).

[4-(5-Phenylisoxazol-3-yl)phenoxo]acetic acid ethyl ester 16b was prepared like 16a using ethylnylbenzene and (1-methylprop-2-ynyloxyethyl)benzene, respectively in place of 1-dodecene: 1H NMR (200 MHz, CDCl3) δ 13.10 (brs, 1H), 7.85 (m, 4H), 7.58 (m, 4H), 7.19 (m, 2H), 4.79 (s, 2H); EI-MS m/z (relative intensity) 295 (M+, 31), 105 (100).

A mixture of 12 (2.0 g, 7.0 mmol), 1-(4-bromobenzyl)-1H-indole (2.0 g, 8.4 mmol) and triethylamine (1.6 mL, 7.0 mmol) in ether (20 mL) was stirred for 2 h at room temperature, and poured into water (10 mL). The resulting mixture was extracted with 20 mL of ethyl acetate and the organic layer was dried with MgSO4 and concentrated in vacuo. The residue was purified by column chromatography to give [4-[8-(4-bromobenzyl)-8,8a-dihydro-3aH-isoazolo[5,4-b]indol-3-yl]phenoxo]acetic acid ethyl ester 17a (2.3 g, 64%): 1H NMR (200 MHz, CDCl3) δ 7.78 (m, 2H), 7.45 (m, 2H), 7.27 (m, 3H), 7.14 (m,
4H), 6.61 (m, 1H), 6.39 (m, 2H), 5.21 (d, J = 8.7 Hz, 1H), 4.65 (s, 2H), 4.61 (d, J = 8.7 Hz, 1H), 4.25 (q, J = 7.1 Hz, 2H), 1.31 (m, 4H); EI-MS m/z (relative intensity) 508 (M⁺, 3), 506 (2.9), 287 (49), 285 (50), 171 (100), 169 (100). A mixture of 17a (160 mg, 0.32 mmol) and LiOH·H₂O (27 mg, 0.64 mmol) in THF: water: methanol (1 : 1 : 1) was stirred for 1 h, cooled by addition of ice water, and acidified by addition of 1N hydrochloric acid. The resulting mixture was extracted with ethyl acetate and the organic layer was dried with MgSO₄ and concentrated in vacuo. The residue was purified by column chromatography to give 18a (151 mg, 99%) as white solid: 1H NMR (200 MHz, CDCl₃) δ 11.13 (s, 1H), 8.07 (s, 1H), 7.19 (m, 12H), 5.49 (s, 2H), 4.71 (s, 2H), 2.74 (s, 2H), 1.43 (m, 4H); EI-MS m/z (relative intensity) 373 (M⁺, 100), 330 (39), 302 (17), 224 (9), 227 (22), 76 (14). A mixture of 5-bromo-2-hydroxybenzaldehyde (700 mg, 2.02 mmol), Cs₂CO₃ (1.3 g, 4.04 mmol), Pd(OAc)₂ (22.0 mg, 0.101 mmol), and p-methoxyphenylboronic acid (52 mg, 0.43 mmol) in 1,4-dioxane in a pressure tube filled with nitrogen was heated for 5 h at 120°C followed by extraction with ethyl acetate. The organic layer was washed with brine and water, dried with MgSO₄, and concentrated in vacuo. The residue was purified by column chromatography to give 210 mg (28%) of 4-[5-(4-methoxyphenyl)benzo[d]-isoxazol-3-yl]benzoic acid ethyl ester 22 as an yellow oil: 1H NMR (200 MHz, CDCl₃) δ 8.25 (d, J = 8.6 Hz, 2H), 8.07 (d, J = 8.4 Hz, 2H), 7.99-7.72 (m, 3H), 7.54 (d, J = 8.8 Hz, 2H), 7.01 (d, J = 8.6 Hz, 2H), 4.43 (q, J = 7.0 Hz, 2H), 3.87 (s, 3H), 1.43 (t, J = 7.2 Hz, 3H); EI-MS m/z (relative intensity) 373 (M⁺, 100), 330 (39), 302 (17), 224 (9), 127 (22), 76 (14). To a solution of 22 (100 mg, 0.24 mmol) in methylene chloride was added BBr₃ at 0°C and stirred for 3 h at room temperature, and the reaction was quenched by addition of methanol at 0°C. The resulting mixture was washed with water and the aqueous layer was extracted with methylene chloride. The combined organic layer was dried with MgSO₄ and concentrated in vacuo. The residue was recrystallized to give 4-[5-(4-hydroxyphenyl)-benzo[d]-isoxazol-3-yl]benzoic acid ethyl ester 23. A mixture of ester 22 (70 mg, 0.19 mmol) and LiOH·H₂O (16 mg, 0.38 mmol) in THF/CH₃OH/H₂O (1 : 1 : 1) was stirred for 1 h at room temperature followed by addition of ice and ethyl acetate. The resulting mixture was neutralized with 10% hydrochloric acid. The organic layer was washed with water. The combined aqueous layer was washed with ethyl acetate. The combined organic layer was concentrated in vacuo. The residue was washed with brine and water, and dried with MgSO₄ and concentrated in vacuo. The residue was recrystallized to give 24 (70 mg, 91%); 1H NMR (200 MHz, CDCl₃) δ 8.25-8.18 (m, 5H), 7.92 (s, 1H), 7.94 (d, J = 11.8 Hz, 2H), 7.71 (d, J = 8.8 Hz, 1H), 7.63 (d, J = 8.8 Hz, 1H), 7.37 (d, J = 8.6 Hz, 2H), 6.88 (d, J = 8.6 Hz, 2H), 4.36 (q, J = 7.2 Hz, 2H), 1.37 (t, J = 7.2 Hz, 3H). The ester and LiOH·H₂O (9.9 mg, 0.23 mmol) in THF/CH₃OH/H₂O (1 : 1 : 1) was stirred for 1 h at room temperature followed by addition of ethyl acetate. The resulting mixture was neutralized with 10% hydrochloric acid. The organic layer was washed with water. The combined aqueous layer was washed with ethyl acetate. The combined organic layer was concentrated in vacuo. The residue was washed with brine and water, and dried with MgSO₄ and concentrated in vacuo. The residue was recrystallized to give 25 (70 mg, 91%); 1H NMR (200 MHz, CDCl₃) δ 8.25-8.18 (m, 5H), 7.92 (d, J = 3.4 Hz, 2H), 7.62 (d, J = 9.0 Hz, 2H), 6.88 (d, J = 8.2 Hz, 2H); EI-MS m/z (relative intensity) 331 (M⁺, 100), 210 (35), 182 (34), 127 (27), 102 (56), 76 (86), 65 (24), 45 (47).
mg, 1.68 mmol), Pd(OAc)\(_2\) (9.9 mg, 0.044 mmol), and 3-(3,4-methylenedioxyphenyl)propene (156 mg, 1.29 mmol) in a pressure bottle filled with nitrogen was heated for 5 h at 120 °C. The resulting mixture was partitioned between brine and ethyl acetate and the combined organic layer was washed with brine and water, dried with MgSO\(_4\), and concentrated in vacuo. The residue was purified by column chromatography to give 4-[5-(3-benzo[1,3]dioxol-5-yl)-propenyl]benzo[d]isoxazol-3-yl]benzoic acid ethyl ester 25a (270 mg, 76%) as an oil: \(^1\)H NMR (200 MHz, CDCl\(_3\)) \(\delta\) 8.23 (d, \(J = 8.2\) Hz, 2H), 8.15 (m, 2H), 7.92 (s, 1H), 7.75 (m, 1H), 7.61 (m, 1H), 6.63-6.57 (m, 3H), 2.7 (m, 2H), 2.4 (m, 2H), 1.9 (m, 2H); EI-MS \(m/z\) (relative intensity) 390 (M\(^+\), 100), 371 (10), 343 (46), 266 (73), 252 (135), 123 (67), 65 (56).

4-[5-(3-Benzyl[1,3]dioxol-5-ylpropenyl)benzo[d][isoxazol-3-yl]benzoic acid ethyl ester (26a). A solution of 4-[5-(3,4-dihydroxyphenyl)-propenyl]-benzo[d][isoxazol-3-yl]benzoic acid ethyl ester (270 mg, 0.66 mmol) in ethanol was hydrogenated for 2 h with Pd/C (137 mg) as catalyst and the product was purified by column chromatography to afford 4-[5-(3-benzo[1,3]dioxol-5-ylpropenyl)benzo[d][isoxazol-3-yl]benzoic acid ethyl ester (124 mg, 45%): \(^1\)H NMR (200 MHz, CDCl\(_3\)) \(\delta\) 8.23 (d, \(J = 8.6\) Hz, 2H), 8.03 (d, \(J = 8.8\) Hz, 2H), 7.66-7.45 (m, 3H), 6.75-6.46 (m, 3H), 5.92 (s, 2H), 4.42 (q, \(J = 7\) Hz, 2H), 2.79 (t, \(J = 7.2\) Hz, 2H), 2.60 (t, \(J = 7.6\) Hz, 2H), 1.97 (m, 2H), 1.44 (t, \(J = 7.2\) Hz, 3H); EI-MS \(m/z\) (relative intensity) 449 (M\(^+\), 42), 307 (30), 280 (42), 135 (100), 91 (41), 77 (60), 65 (45). The ester (70 mg, 0.17 mmol) and LiOH·H\(_2\)O (14 mg, 0.17 mmol) in THF/CH\(_3\)OH/H\(_2\)O (1 : 1 : 1) was stirred for 1 h at room temperature. To the resulting mixture was added ice and ethyl acetate, and 10% hydrochloric acid until acidic. The aqueous layer was ethylated with water and the organic layer was washed with brine and water, dried with MgSO\(_4\), and concentrated in vacuo. The residue was purified by crystallization to give the corresponding acid, 27 (70 mg, 75%): \(^1\)H NMR (200 MHz, CDCl\(_3\)) \(\delta\) 8.62 (d, \(J = 16.8\) Hz, 2H), 8.23 (m, 2H), 7.92 (s, 1H), 7.75 (m, 1H), 7.61 (m, 1H), 6.63-6.57 (m, 3H), 2.7 (m, 2H), 2.4 (m, 2H), 1.9 (m, 2H); EI-MS \(m/z\) (relative intensity) 390 (M\(^+\), 100), 371 (100), 343 (46), 266 (73), 252 (135), 123 (67), 65 (56).

4-(5-Tetradecylbenzo[1,3]dioxol-5-yl)benzoic acid (26b). A DMF (5 mL) solution of 20 (110 mg, 0.317 mmol), 1-tetradecene (148 mg, 0.76 mmol), NaHCO\(_3\) (65 mg, 0.76 mmol), (n-Bu)\(_2\)NCl (90 mg, 0.317 mmol), and Pd(OAc)\(_2\) (3.6 mg, 5 mol%) in a pressure bottle filled with nitrogen was heated for 12 h. The resulting mixture was partitioned between saturated NH\(_4\)Cl solution and ethyl acetate and extracted with ethyl acetate. The combined organic layer was dried with MgSO\(_4\), and concentrated in vacuo. The residue was purified by column chromatography to give 4-(5-tetradecylbenzo[d][isoxazol-3-yl]benzoic acid ethyl ester (80 mg, 55%) as semi-solid: \(^1\)H NMR (200 MHz, CDCl\(_3\)) \(\delta\) 8.25 (m, 2H), 8.04 (m, 2H), 7.73-7.41 (m, 3H), 2.90-2.40 (m, 2H), 1.75-1.50 (m, 2H), 1.40-1.20 (m, 22H), 0.87 (t, 3H). A mixture of the ester and several drops of dilute NaOH solution in methanol was stirred for 2 h at room temperature. The resulting mixture was acidified with dilute hydrochloric acid and extracted with ethyl acetate. The organic layer was dried with MgSO\(_4\), and concentrated in vacuo to afford 26b as white crystals: \(^1\)H NMR (200 MHz, CDCl\(_3\)) \(\delta\) 8.34 (m, 2H), 8.11 (m, 2H), 7.78-7.43 (m, 3H), 2.90-2.40 (m, 2H), 1.75-1.50 (m, 2H), 1.40-1.20 (m, 22H), 0.87 (t, 3H).

(8-Methyl-3-octylquinolinol-6-ol)acetic acid (31). A mixture of 6-benzoxy-4-hydroxy-3-iodo-8-methylquinoline 29 (1.21 g, 3.09 mmol) and POCl\(_3\) (50 mL) in a 100-mL flask was heated for 1 h at 110 °C. The excess POCl\(_3\) was removed in vacuo and the residual POCl\(_3\) was decomposed by addition of ice. The mixture was neutralized with saturated sodium bicarbonate solution and extracted with ethyl acetate. The organic layer was washed with water, dried with MgSO\(_4\), and concentrated in vacuo. The residue was purified by column chromatography to give 6-benzoxy-4-chloro-3-iodo-8-methylquinoline 30 (614 mg, 48%) as white solid: mp 120-122 °C; \(^1\)H NMR (200 MHz, CDCl\(_3\)) \(\delta\) 8.94 (s, 1H), 7.32-7.50 (m, 7H), 5.18 (s, 2H), 2.72 (s, 3H); EI-MS \(m/z\) (relative intensity) 411 (M+2, 21), 409 (55), 290 (3), 163 (12), 128 (14), 101 (7), 92 (22), 91 (100), 65 (25). A mixture of 30 (295 mg, 0.72 mmol), Pd(OAc)\(_2\) (8.1 mg, 5 mol%), NaHCO\(_3\) (145 mg, 1.73 mmol), (n-Bu)\(_2\)NCl (200 mg, 0.72 mmol), DMF (10 mL) and 1-octene (0.226 mL, 1.44 mmol) in a pressure tube was heated for 15 h at 120 °C. After cooling, the mixture was extracted with ethyl acetate and the organic layer was washed with NH\(_4\)Cl twice, and water, dried with MgSO\(_4\), and concentrated in vacuo. The residue was purified by silica gel column chromatography to give 6-benzoxy-4-chloro-8-methyl-3-(oct-1-enyl)quinoline 274 mg (96%) as yellow solid: EI-MS \(m/z\) (relative intensity) 395 (M+2, 2), 393 (4), 92 (8), 91 (100), 65 (5), 41 (4). A mixture of octenylquinoline (274 mg, 0.696 mmol) and Pd/C (148 mg, 0.139 mmol) in ethanol was stirred for 17 h under hydrogen, filtered through Celite, and concentrated in vacuo to give 8-methyl-3-octylquinolinol-6-ol (170 mg, 90%) as yellow solid: EI-MS \(m/z\) (relative intensity) 271 (M\(^+\), 95), 186 (100), 172 (23), 41 (9). A mixture of the quinolinol (162 mg, 0.59 mmol), K\(_2\)CO\(_3\) (245 mg, 1.77 mmol), and methyl bromoacetate (0.202 mL, 1.77 mmol) in aceton (50 mL) was heated for 14 h under reflux, filtered and concentrated in vacuo. The residue was...
partitioned between water and ether and the organic layer was dried with MgSO₄, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography to give (8-methyl-3-octylquinolin-6-yl-oxy)acetic acid methyl ester (157 mg, 77%) as tan-colored oil: ¹H NMR (200 MHz, CDCl₃) δ 8.66 (d, J = 2.0 Hz, 1H), 7.56 (s, 1H), 7.27 (s, 1H), 6.81 (d, J = 2.8 Hz, 1H), 4.74 (s, 2H), 3.83 (s, 3H), 2.77 (s, 3H), 2.76 (t, J = 7.8 Hz, 2H), 0.85-1.70 (m, 15H); EI-MS m/z (relative intensity) 343 (M⁺, 100), 258 (38), 245 (26), 244 (20), 156 (9), 143 (9), 43 (5). A mixture of the ester (142 mg, 0.413 mmol) and 5 mL of 2 N NaOH in methanol (10 mL) was stirred for 2 h and concentrated. The resulting mixture was diluted with water and acidified with dilute hydrochloric acid and extracted with ethyl acetate. The organic layer was washed with brine and water, dried with MgSO₄, filtered, and concentrated in vacuo.

A mixture of 4-chloro-3-iodo-8-methylquinolin-6-ol (80 mg, 0.25 mmol) and 5 mL of 2 N NaOH in methanol (15 mL) was heated for 17 h under reflux, filtered, concentrated in vacuo, and partitioned between ethyl acetate and water. The organic layer was washed with brine and water, dried with MgSO₄, filtered, and concentrated in vacuo.

The residue was purified by column chromatography to give 4-chloro-3-iodo-8-methoxyquinoline 35 (1.00 g, 3.12 mmol), 1-octene (1.40 mL, 8.92 mmol), NaHCO₃ (620 mg, 6.20 mmol), Bu₄NCI (860 mg, 3.12 mmol), Pd(OAc)₂ (40 mg, 5 mol%), and DMF (15 mL) was heated overnight at 100 °C followed by dilution with ethyl acetate. The organic layer was washed with brine and water, dried with MgSO₄, and concentrated in vacuo. The residue was purified by column chromatography to give 650 mg (68.6%) of 4-chloro-3-(oct-1-enyl)-quinolin-6-yl-oxy)acetic acid methyl ester 36 as an yellow solid: ¹H NMR (200 MHz, CDCl₃) δ 9.00 (s, 1H), 7.81 (dd, J = 8.5, 1.2 Hz, 1H), 7.53 (t, J = 8.4 Hz, 1H), 7.05 (d, J = 7.7 Hz, 1H), 6.90 (d, J = 15.9, 1H), 6.50 (d, J = 15.9, 6.3 Hz, 1H), 4.09 (s, 3H), 2.35 (q, J = 6.3 Hz, 2H), 2.35 (q, J = 6.3 Hz, 2H), 1.48 (m, 2H), 1.10-1.42 (m, 6H), 0.90 (t, J = 6.9 Hz, 3H). The quinolinol (210 mg, 73%) was obtained by BBr₃ and crystallization in ethyl acetate. A mixture of the quinolinol (0.14 g, 0.49 mmol), methyl bromoacetate (60 µL, 0.63 mmol), K₂CO₃ (0.14 g, 0.98 mmol) in methanol (7 mL) was stirred for 1 h under reflux, filtered, and concentrated in vacuo. The residue was partitioned between ethyl acetate and water, dried with MgSO₄, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography to give 4-chloro-3-(octen-1-yl)quinolin-8-yl-oxy)acetic acid methyl ester 37 (1.00 g, 5.72 mmol), 1-oc-tene (1.08 mL, 6.66 mmol), NaHCO₃ (620 mg, 6.20 mmol), Bu₄NCI (860 mg, 3.12 mmol), Pd(OAc)₂ (40 mg, 5 mol%), and DMF (15 mL) was heated overnight at 100 °C followed by dilution with ethyl acetate. The organic layer was washed with brine and water, dried with MgSO₄, and concentrated in vacuo. The residue was purified by column chromatography to give 650 mg (68.6%) of 4-chloro-3-(oct-1-enyl)-quinolin-6-yl-oxy)acetic acid methyl ester 36 as an yellow solid: ¹H NMR (200 MHz, CDCl₃) δ 9.00 (s, 1H), 7.81 (dd, J = 8.5, 1.2 Hz, 1H), 7.53 (t, J = 8.4 Hz, 1H), 7.05 (d, J = 7.7 Hz, 1H), 6.90 (d, J = 15.9, 1H), 6.50 (d, J = 15.9, 6.3 Hz, 1H), 4.09 (s, 3H), 2.35 (q, J = 6.3 Hz, 2H), 2.35 (q, J = 6.3 Hz, 2H), 1.48 (m, 2H), 1.10-1.42 (m, 6H), 0.90 (t, J = 6.9 Hz, 3H). The quinolinol (210 mg, 73%) was obtained by BBr₃ and crystallization in ethyl acetate. A mixture of the quinolinol (0.14 g, 0.49 mmol), methyl bromoacetate (60 µL, 0.63 mmol), K₂CO₃ (0.14 g, 0.98 mmol) in methanol (7 mL) was stirred for 1 h under reflux, filtered, and concentrated in vacuo. The residue was partitioned between ethyl acetate and water, dried with MgSO₄, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography to give 4-chloro-3-(octen-1-yl)quinolin-8-yl-oxy)acetic acid methyl ester 0.15 g (78%) as yellow solid: ¹H NMR (200 MHz, CDCl₃) δ 9.01 (t, J = 6.9 Hz, 3H), 1.2-1.61 (m, 8H), 2.36 (q, J = 6.7 Hz, 2H), 3.81 (s, 3H), 4.97 (s, 2H), 6.49 (dt, J = 16.0, 6.3 Hz, 1H), 6.88 (d, J = 16.0, 6.3 Hz, 1H), 6.99 (d, J = 7.6 Hz, 1H), 7.43 (t, J = 8.3 Hz, 1H), 7.85 (d, J = 8.3 Hz, 1H), 9.03 (s, 1H). A mixture of ester (0.10 g, 0.28 mmol) and LiOH·H₂O (17 mg, 0.42 mmol) in THF/CH₂OH/H₂O (1 : 1 : 1, 6 mL) was stirred for 1 h and concentrated. The aqueous layer was washed with ether, adjusted to pH 3 with 1 N HCl. The precipitate was filtered and dried to give 37 (87 mg, 90%): ¹H NMR (200 MHz, CDCl₃) δ 8.75 (s, 1H), 3.85 (q, J = 6.9 Hz, 2H), 2.38 (t, J = 7.1 Hz, 2H), 7.32 (d, J = 7.9 Hz, 1H), 6.90 (d, J = 15.7, 1H), 6.56 (dt, J = 15.7, 6.4 Hz, 1H), 5.55 (bs, 1H), 4.72 (s, 2H), 2.34 (q, J = 7.3 Hz, 2H), 1.20-1.61 (m, 8H), 0.91 (t, J = 7.1 Hz, 3H). 3-(Octylnylquinolin-8-yl)acetic acid (39). The octenylquinoline 36 (430 mg, 1.44 mmol) in methanol (15 mL) was hydrogenated overnight with 10%-Pd/C (0.2 g) as catalyst. The residue was filtered through Celite, concentrated in vacuo and the residue was purified by column chromatography to give 3-octyl-8-methoxyquinoline 38 (320 mg, 85%): ¹H NMR (200 MHz, CDCl₃) δ 8.85 (s, 1H), 7.96 (s, 1H), 7.38 (m, 2H), 7.05 (d, J = 7.9 Hz, 1H), 4.10 (s, 3H), 2.81 (t, J = 7.7 Hz, 1H), 1.65 (m, 2H), 1.10-1.42 (m, 10H), 0.87 (t, J = 6.9 Hz, 3H). To a solution of methoxyquinoline 38 (300 mg, 1.11 mmol) in 7 mL of methylene chloride was added 1 N
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BBr₃/CH₂Cl₂ (2.2 mL, 2.2 mmol) at 0 °C. The resulting mixture was stirred overnight at room temperature, quenched by addition of small amount of water, and partitioned between water and ethyl acetate. The organic layer was washed with saturated sodium bicarbonate solution and water, dried with MgSO₄, and concentrated in vacuo. 3-Octylquinolin-8-ol (210 mg, 73%) was obtained by crystallization in ethyl acetate and washing with ether. A mixture of the quinolinol (100 mg, 0.39 mmol), methyl bromoacetate (0.045 mL, 0.47 mmol), K₂CO₃ (110 mg, 0.78 mmol) and KI (6 mg, 0.039 mmol) in acetone (5 mL) was heated for 12 h at 110 °C. The resulting mixture was washed with dilute hydrochloric acid, and extracted with ethyl acetate. The organic layer was dried with MgSO₄ and concentrated. The aqueous layer was washed with brine and saturated sodium bicarbonate solution, and extracted with ethyl acetate. The organic layer was dried with MgSO₄ and concentrated in vacuo. A mixture of triflate (292 mg, 0.23 mmol) in THF/CH₃OH/H₂O (1 : 1 : 1) was stirred for 12 h, and washed with brine. The aqueous layer was acidified with 1 N HCl. The precipitate was filtered and dried to give 4-(4-chloro-3-phenylquinolin-8-yl)phenol 29 (346 mg, 38%).

**4-(4-Chloro-3-phenylquinolin-8-yl)phenoxyacetic acid (42).** A mixture of 35 (300 mg, 1.57 mmol), phenylboronic acid (288 mg, 2.36 mmol), LiCl (67 mg, 1.57 mmol), Cs₂CO₃ (1.023 g, 3.14 mmol), Pd(OAc)₂ (18 mg, 0.079 mmol) and Cs₂CO₃ (33 mg, 0.24 mmol), KI (2 mg, 0.012 mmol) and in acetone (15 mL) was heated for 10 h at 110 °C. The resulting mixture was stirred for 4 h at room temperature, quenched by sequential addition of methanol and saturated sodium bicarbonate solution, and extracted with ethyl acetate. The organic layer was dried with MgSO₄ and concentrated in vacuo. 4-(4-Chloro-3-phenylquinolin-8-yl)-phenoxycetic acid ethyl ester 51 mg, 97%): 1H NMR (200 MHz, CDCl₃) δ 8.88 (s, 1H), 8.36 (dd, J = 8.5 Hz, 1H), 7.67-7.70 (m, 2H), 7.47-7.56 (m, 5H); EI-MS (relative intensity) 374 (M+2, 47), 372 (M⁺, 100), 357 (33), 133 (39). A solution of methoxyquinoline (50 mg, 0.145 mmol) in 5 mL of methylene chloride was added 1 M BBr₃/CH₂Cl₂ (1.23 mL, 1.23 mmol) at 0 °C. The resulting mixture was stirred for 3 h at room temperature, quenched by addition of small amount of methanol and saturated sodium bicarbonate solution, and partitioned between water and ethyl acetate. The organic layer was dried with MgSO₄, and concentrated in vacuo. A mixture of the quinolinol 41 (100 mg, 0.39 mmol), ethyl bromoacetate (78 mg, 0.47 mmol), K₂CO₃ (108 mg, 0.78 mmol) and KI (6 mg, 0.039 mmol) in acetone (5 mL) was heated for 12 h under reflux, filtered and concentrated in vacuo. The residue was partitioned between ethyl acetate and brine, and the organic layer was dried with MgSO₄, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography to give 28 mg (28%) of recovered starting material and (4-chloro-3-phenyl-quinolin-8-yl)ace tic acid ethyl ester (51 mg, 38%).
POCl₃ was heated under reflux and excess POCl₃ was added.

A mixture of the quinolone was precipitated with brine, dried with MgSO₄, and concentrated.

The residue was diluted with ethyl acetate and washed with water : methanol (1 : 1 : 1, 1 mL) was stirred for 1 h, and concentrated. The mixture was cooled to room temperature and neutralized with 1 N HCl to give white crystalline 50 (691 mg, 80%). ¹H NMR (200 MHz, CDCl₃) δ 8.22 (d, J = 9.2 Hz, 1H), 7.65 (d, J = 2.8 Hz, 1H), 7.52 (dd, J = 9.1 Hz, 2.9 Hz, 1H), 4.16 (m, 2H), 1.86 (m, 1H), 1.57-1.27 (m, 16H), 0.89 (m, 3H).

### Conclusion

Several classes of compounds (heteroarylethoxyxyl acid, phenoxycetic acids, and quinolinoxyacetic acids) were prepared and tested as PTP-1B inhibitors. Some of the compounds showed remarkable inhibition in in vitro assays. Compounds with long chain alkyl substituents showed submicromolar IC₅₀, suggesting that the inhibition can be enhanced by lipophilic substitution within these classes of compounds.

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### References


