# 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.[1] Since Echelby and coworkers[2] 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.[3] Thus, PTP-1B inhibitors could potentially ameliorate insulin resistance and normalize plasma glucose and insulin without inducing hypoglycemia.[4]

Recently, small molecule inhibitors of PTP-1B as well as peptide mimetics were reported in literatures.[5] They included oxalamides (**1**, **2**), benzoic acid (**3**), and phenoxyacetic acids (**4**-**7**) (Figure 1).[4] 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.[6]

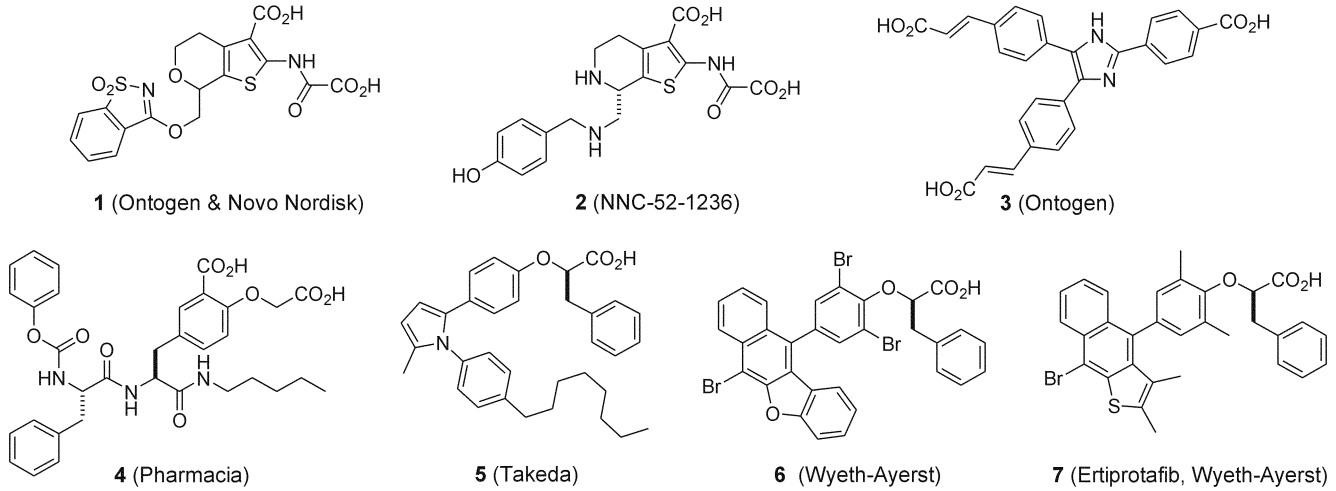
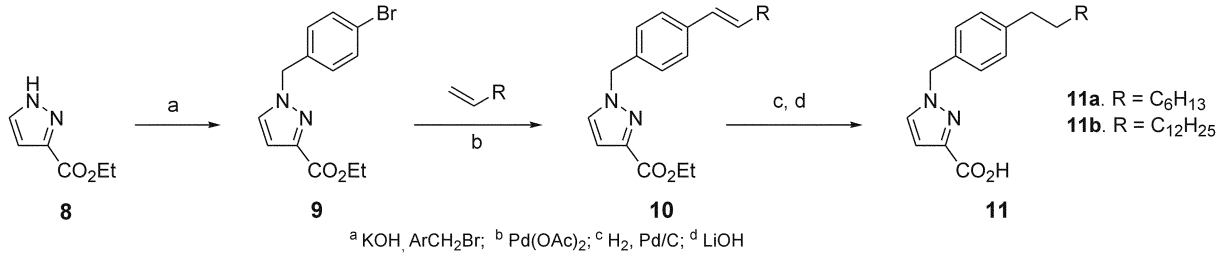



**Figure 1.** PTP-1B Inhibitors.




**Scheme 1.** Synthesis of Pyrazolecarboxylic Acid Derivatives.

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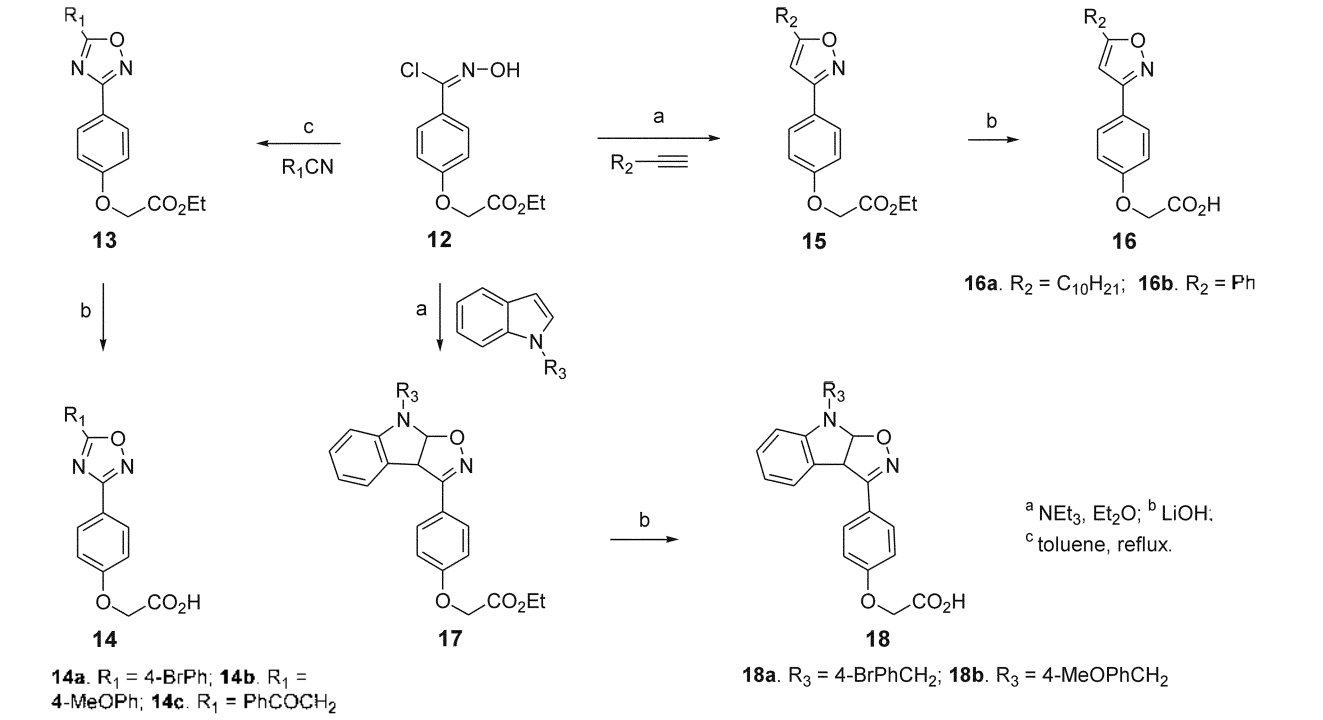
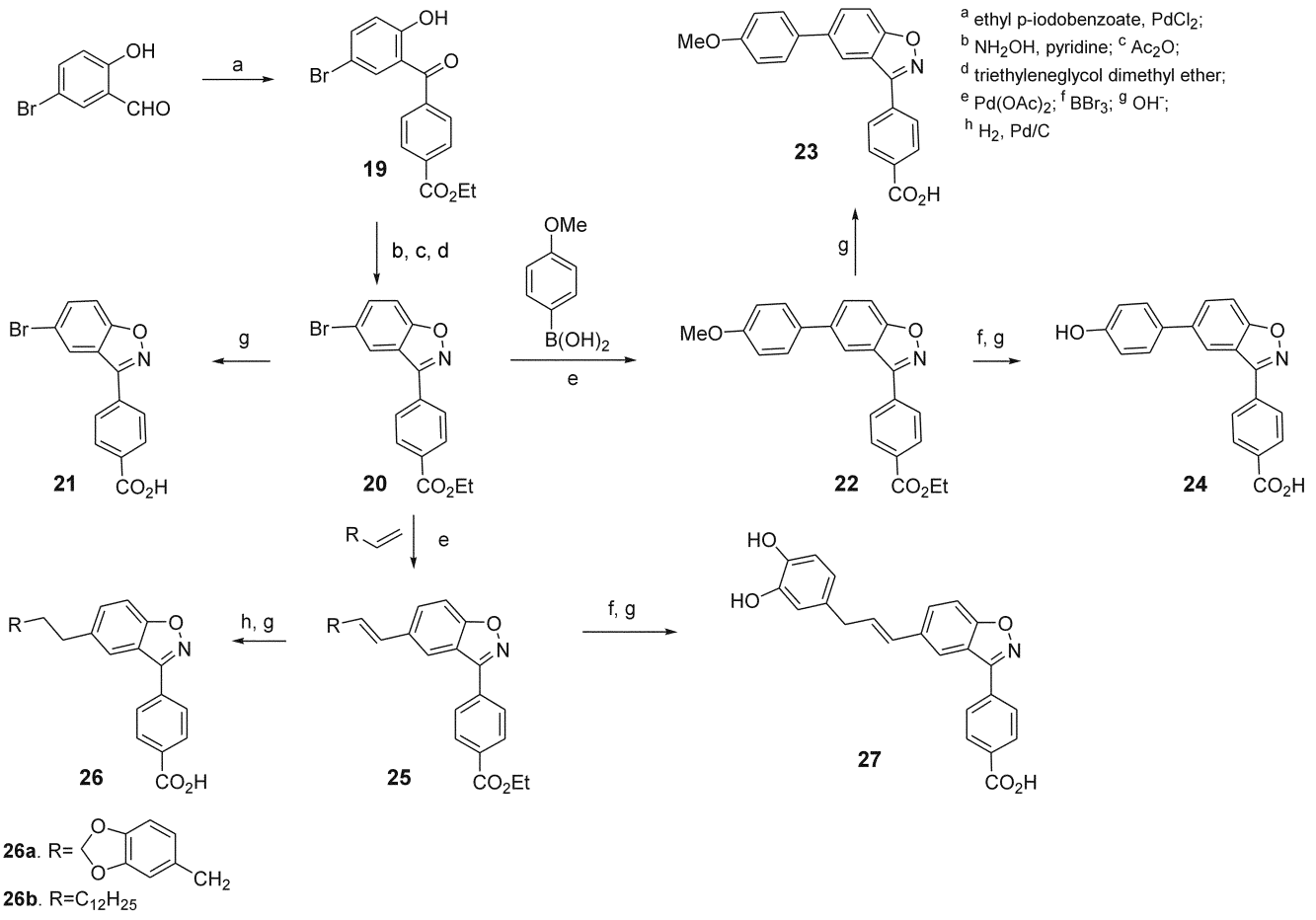



**Scheme 2.** Synthesis of Isoxazolylphenoxyacetic Acid Derivatives.

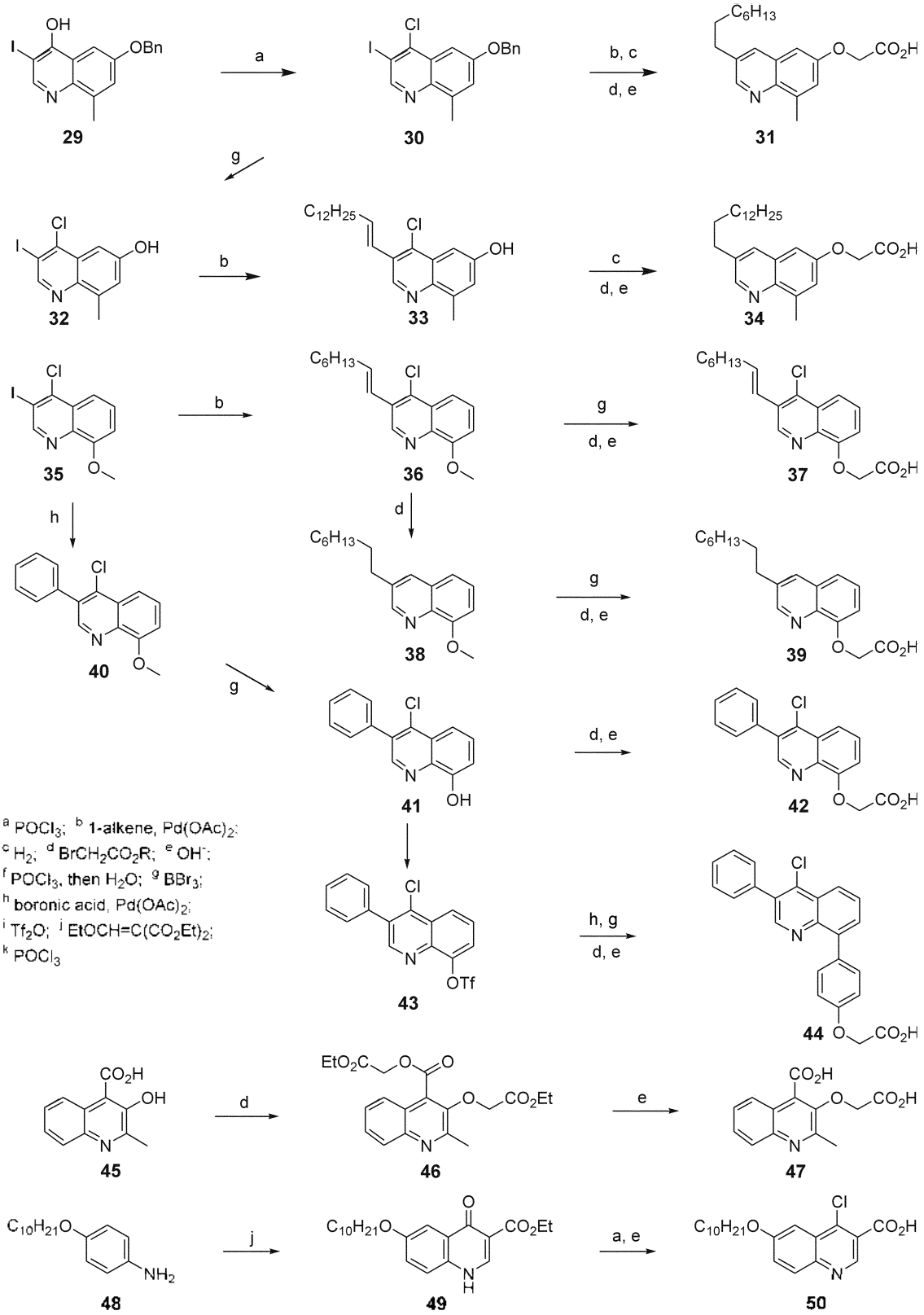



**Scheme 3.** Synthesis of Isoxazolylbenzoic Acid Derivatives.

## 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




**Scheme 4.** 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, isoxazolylphenoxy 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 phenoxyacetic acid moiety was incorporated as some of the *o*-quinones substituted with phenoxyacetic acid showed micromolar inhibitory activity in the earlier paper.[6a] and also many phenoxyacetic acid derivatives including Ertiprotafib 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 dihydroisoxazolo[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 dihydroisoxazolo[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.

**Table 1**. Inhibitory Activity against PTP-1B

| No | % inhibition | $IC_{50}$ | No | % inhibition | $IC_{50}$ |
|---|---|---|---|---|---|
| **11a** | 32.5 | | **27a** | 20.0 | |
| **11b** | 101.8 | 0.44 | **27b** | 101.1 | 0.44 |
| **14a** | na | | **28** | 40.9 | |
| **14b** | na | | **31** | 37.3 | |
| **14c** | na | | **34** | 101.3 | 0.59 |
| **16a** | 73.8 | 3.89 | **37** | 86.6 | 3.27 |
| **16b** | na | | **39** | 44.6 | |
| **18a** | 6.0 | | **42** | na | |
| **18b** | na | | **44** | 21.9 | |
| **22** | 13.1 | | **47** | na | |
| **24** | na | | **50** | 101.4 | 0.94 |
| **25** | na | | | | |

% inhibition at 20 $\mu$M and $IC_{50}$ ($\mu$M), na - not active

**Table 2**. Isozyme Selectivity ($IC_{50}$, $\mu$M)

| | **7** | **11b** | **16a** | **27b** | **34** |
|---|---|---|---|---|---|
| PTP-1B | 0.29 | 0.44 | 3.89 | 0.44 | 0.51 |
| Yop | 0.20 | 0.56 | 0.69 | 0.41 | 0.10 |
| VHR | 3.08 | ~10 | >>10 | >>10 | 5.74 |
| PP1 | 1.71 | 5.62 | 8.34 | 4.21 | 2.47 |
| CD45 | 0.41 | 1.05 | >10 | 1.49 | 1.47 |
| LAR | >10 | 2.67 | >10 | 2.74 | >10 |
| cdc25A | 1.50 | 2.60 | >10 | 1.60 | 1.73 |
| cdc25B | 0.17 | 0.33 | ~10 | 0.18 | 0.41 |
| cdc25C | 2.76 | 4.20 | >>10 | 2.95 | 2.46 |
| PP2A | ~10 | >>10 | >10 | >>10 | ~10 |

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 aryloxyacetic acid was introduced by alkylation of phenolic group with bromoacetates 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 $IC_{50}$ of 3.27 $\mu$M. Tetracedyl derivative **34** and 6-octyloxyquinoline-3-carboxylic aicd **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 1*H*-pyrazole-3-carboxylic acid ethyl ester **8** (1.00 g, 7.1 mmol), 4-bromobenzyl bromide (2.14 g, 8.6 mmol), patassium 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 $MgSO_4$, filtered, and concentrated. The residue was purified by column chromatography to give 1-(4-bromobenzyl)-1*H*-pyrazole-3-carboxylic acid ethyl ester **9** (1.7 g, 81%) as white solid: $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 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)$_4$NCl (135 mg, 0.49 mmol), and 1-octene (108.8 mg,

0.15 mL, 0.97 mmol) in pressure tube was heated for 15 h at 125 °C, and partitioned between saturated $NH_4Cl$ solution and ethyl acetate. The organic layer was dried with $MgSO_4$, and concentrated *in vacuo*. The residue was purified by column chromatography to give 1-(4-oct-1-enylbenzyl)-1*H*-pyrazole-3-carboxylic acid ethyl ester **10a** (135 mg, 82%) as a yellow oil: $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 7.34-7.30 (m, 3H) 7.18 (d, $J$ = 6.5 Hz, 2H) 6.82 (d, $J$ = 2.4 Hz, 1H) 6.41-6.28 (m, 2H) 5.36 (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-octylbenzyl)-1*H*-pyrazole-3-carboxylic acid ethyl ester (120 mg, 88%) as an yellow oil: $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 7.32 (d, $J$ = 2.2 Hz, 1H) 7.16 (s, 4H) 6.82 (d, $J$ = 2.2 Hz, 1H) 5.36 (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/$H_2O$ = 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 washed with brine, dried with $MgSO_4$, and concentrated *in vacuo* to afford **11a** (80 mg, 73%) as a yellow oil: $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 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 ($M^+$, 10), 117 (81), 104 (100), 43 (85).

**1-(4-Tetradecylbenzyl)-1*H*-pyrazole-3-carboxylic acid 11b** was prepared as **11a** from **9** using 1-dodecene in place of 1-octene: $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 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, $J$ = 7.1 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).

**{4-[5-(4-Bromophenyl)-[1,2,4]oxadiazol-3-yl]phenoxy}-acetic acid (14a).** A mixture of (4-chlorocarbooxiimidoyl-phenoxy)acetic acid ethyl ester **12** (1.3 g, 6.0 mmol) and 4-bromobenzonitrile (3.2 g, 31 mmol) in toluene (20 mL) was stirred for 2 h at room temperature, and poured into water (10 mL). The resulting mixture was extracted with ethyl acetate and the organic layer was dried with $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography to give {4-[5-(4-bromophenyl)-[1,2,4]oxa-diazol-3-yl]phenoxy}acetic acid ethyl ester **13a** (1.2 g, 51%): $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 8.10 (m, 4H), 7.71 (m, 2H), 7.03 (m, 2H), 4.71 (s, 2H), 4.31 (q, $J$ = 7.1 Hz, 2H), 1.36 (t, $J$ = 7.1 Hz, 3H); EI-MS *m/z* (relative intensity) 404 ($M^+$, 100), 402 (90), 331 (42), 185 (85). A mixture of **13a** (200 mg, 0.495 mmol) and LiOH (24 mg, 0.495 mmol) in THF : water : methanol (1 : 1 : 1, 3 mL) was stirred for 1 h and acidified by addition of 1 *N* hydrochloric acid (2 mL). The resulting mixture was extracted with ethyl acetate and the organic layer was dried with $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography to give **14a** (58 mg, 29%): $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 13.10 (brs, 1H), 7.99 (m, 6H), 7.15 (m, 2H), 4.82 (s, 2H).

**{4-[5-(4-Methoxyphenyl)-[1,2,4]-oxadiazol-3-yl]phenoxy}-acetic acid 14b and {4-[5-(2-oxo-2-phenylethyl)-[1,2,4]oxa-diazol-3-yl]phenoxy}acetic acid 14c** were prepared like **14a** using anisonitrile and benzoylacetonitrile, respectively in place of 4-bromonitrile.

**14b**: $^1$H NMR (200 MHz, DMSO-$d_6$) $\delta$ 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).

**14c**: $^1$H NMR (200 MHz, DMSO-$d_6$) $\delta$ 7.35 (m, 8H), 5.11 (s, 2H), 4.79 (s, 2H); EI-MS *m/z* (relative intensity) 339 ($M^-$, 6), 192 (17), 132 (23), 105 (100), 83 (82).

**[4-(5-Decylisoxazol-3-yl)phenoxy]acetic acid (16a).** A mixture of **12** (1.57 g, 7.00 mmol), 1-dodecyne (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 $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography to give [4-(5-decyl-isoxazol-3-yl)phenoxy]acetic acid ethyl ester **15a** (1.7 g, 87%): $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 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 $LiOH{\cdot}H_2O$ (19 mg, 0.39 mmol) in THF : water : methanol (1 : 1 : 1, 3 mL) was stirred for 1 h, and acidified by addition of 1 *N* hydrochloric acid (2 mL). The resulting mixture was extracted with ethyl acetate (30 mL) and the organic layer was dried with $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography to give **16a** (77 mg, 79%): $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 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 (m, 3H); EI-MS *m/z* (relative intensity) 359 ($M^-$, 67), 246 (100).

**[4-(5-Phenylisoxazol-3-yl)phenoxy]acetic acid 16b** was prepared like **16a** using ethynylbenzene and (1-methylprop-2-ynyloxymethyl)benzene, respectively in place of 1-dodecene: $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 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).

**{4-[8-(4-Bromobenzyl)-8,8a-dihydro-3a*H*-isoxazolo[5,4-*b*]indol-3-yl]phenoxy}acetic acid (18a).** A mixture of **12** (2.0 g, 7.0 mmol), 1-(4-bromobenzyl)-1*H*-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 $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography to give {4-[8-(4-bromobenzyl)-8,8a-dihydro-3a*H*-isoxazolo[5,4-b]indol-3-yl]phenoxy}acetic acid ethyl ester **17a** (2.3 g, 64%): $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 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 $LiOH{\cdot}H_2O$ (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 1 *N* hydrochloric acid. The resulting mixture was extracted with ethyl acetate and the organic layer was dried with $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography to give **18a** (151 mg, 99%) as white solid: $^1$H NMR (200 MHz, DMSO-$d_6$) $\delta$ 11.13 (s, 1H), 8.07 (s, 1H), 7.19 (m, 12H), 5.49 (s, 2H), 4.71 (s, 2H).

**{4-[8-(4-Methoxybenzyl)-8,8a-dihydro-3a*H*-isoxazolo[5,4-*b*]indol-3-yl]phenoxy}acetic acid 18b** was prepared like **18a** using 1-(4-methoxybenzyl)-1*H*-indole in place of 1-(4-bromobenzyl)-1*H*-indole: $^1$H NMR (200 MHz, DMSO-$d_6$) $\delta$ 11.14 (s, 1H), 8.04 (s, 1H), 7.17 (m, 12H), 5.61 (s, 2H), 4.74 (s, 2H), 3.73 (s, 3H).

**4-(5-Bromobenzo[*d*]isoxazol-3-yl)benzoic acid ethyl ester (20).** A mixture of 5-bromo-2-hydroxybenzaldehyde (10 g, 51 mmol), ethyl 4-iodobenzoate (16 g, 56 mmol), LiCl (475 mg, 11.2 mmol), $PdCl_2$ (500 mg, 2.8 mmol), $Na_2CO_3$ (11.9 g, 112 mmol) and DMF in a pressure tube was heated at 100 °C for 12 h to afford ethyl 4-(5-bromo-2-hydroxybenzoyl)benzoate **19** (6.0 g, 32%) as a yellow oil. A mixture of the above ester, $NH_2OH{\cdot}HCl$, and NaOAc in ethanol was heated for a day and partitioned between ethyl acetate and water. The organic layer was washed with water, dried with $MgSO_4$, and concentrated *in vacuo*. The residue was purified by column chromatography to afford the oxime (4.4 g, 67%). The oxime was heated in acetic anhydride for 30 min until dissolved and extracted with ethyl acetate. The organic layer was dried with $MgSO_4$, and concentrated *in vacuo* to give oxime acetate (5.3 g, 92%). The oxime acetate and $Na_2CO_3$ (2.7 g, 26 mmol) in tri(ethyleneglycol) dimethyl ether was heated for 30 min at 230 °C and the solvent was removed by vacumn distillation. The residue was partitioned between ethyl acetate and water. The organic layer was dried with $MgSO_4$, and concentrated *in vacuo* and the residue was purified by column chromatography to afford **20** (2.7 g, 65%): $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 8.24 (s, $J$ = 8.6 Hz, 1H), 8.02 (m, 2H), 7.72 (d, $J$ = 8.6 Hz, 1H), 7.56 (d, $J$ = 8.4 Hz, 1H), 4.42 (q, $J$ = 7 Hz, 2H), 1.44 (t, $J$ = 7 Hz, 3H).

**4-(5-Bromobenzo[*d*]isoxazol-3-yl)benzoic acid (21).** A mixture of **20** (34.6 mg, 0.1 mmol) and several drops of dilute sodium hydroxide solution in MeOH (5 mL) was stirred for 2 h at room temperature and acidified by addition of dilute hydrochloric acid. After extraction with ethyl acetate, the organic layer was washed with water, dried with $MgSO_4$, and concentrated *in vacuo* to give 29 mg (91%) of **21** as white crystals: $^1$H NMR (200 MHz, $CDCl_3$-DMSO-$d_6$) 8.24 (d, $J$ = 8.4 Hz, 2H), 8.12 (d, $J$ = 1.6 Hz, 1H), 8.01 (d, $J$ = 8.4 Hz, 2H), 7.76 (dd, $J$ = 8.9, 1.8 Hz, 1H), 7.65 (s, 1H), 7.62 (d, $J$ = 8.9 Hz, 1H).

**4-[5-(4-Hydroxyphenyl)benzo[*d*]isoxazol-3-yl]benzoic acid (24).** A mixture of **20** (700 mg, 2.02 mmol), $Bu_4NCl$ (561 mg, 2.02 mmol), $Cs_2CO_3$ (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 $MgSO_4$, 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: $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 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 $BBr_3$ 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 $MgSO_4$ and concentrated *in vacuo*. The residue was recrystallized to give 4-[5-(4-hydroxyphenyl)-benzo[*d*]isoxazol-3-yl]benzoic acid ethyl ester (85 mg, 98%): $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 8.16 (d, $J$ = 2 Hz, 2H), 8.02 (d, $J$ = 2.2 Hz, 2H), 7.98 (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 $LiOH{\cdot}H_2O$ (9.9 mg, 0.23 mmol) in THF/$CH_3OH$/$H_2O$ (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 extracted with ethyl acetate. The combined organic layer was washed with brine and water, and dried with $MgSO_4$, and concentrated *in vacuo*. The residue was recrystallized to give **24** (70 mg, 91%): $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 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).

**4-[5-(4-Methoxyphenyl)benzo[*d*]isoxazol-3-yl]benzoic acid (23).** A mixture of ester **22** (70 mg, 0.19 mmol) and $LiOH{\cdot}H_2O$ (16 mg, 0.38 mmol) in THF/$CH_3OH$/$H_2O$ (1 : 1 : 1) was stirred for 1 h followed by addition of ice and ethyl acetate. The resulting mixture was neutralized with 10% HCl and extracted with ethyl acetate. The organic layer was washed with brine and water, and dried with $MgSO_4$, and concentrated *in vacuo*. The residue was purified by recrystallization to give 40 mg (61%) of **23** as white crystal: $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 13.19 (s, 1H), 8.26-8.01 (m, 5H), 7.97-7.89 (m, 2H), 7.74 (d, $J$ = 8.8 Hz, 2H), 7.05 (d, $J$ = 8.8 Hz, 2H), 3.31 (s, 3H); EI-MS $m/z$ (relative intensity) 345 ($M^+$, 26), 302 (15), 224 (12), 196 (11), 153 (21), 127 (44), 76 (35), 65 (100), 51 (40).

**4-{5-[3-(3,4-Dihydroxyphenyl)propenyl]benzo[*d*]isoxazol-3-yl}benzoic acid (27).** A 1,4-dioxane solution of **20** (300 mg, 0.87 mmol), LiCl (36 mg, 0.87 mmol), $Cs_2CO_3$ (546

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), 8.03 (d, $J$ = 8.0 Hz, 2H), 7.79-7.25 (m, 3H), 6.89-6.59 (m, 3H), 5.93 (s, 2H), 4.41 (q, $J$ = 8.4 Hz, 2H), 3.67 (d, $J$ = 7.2 Hz, 1H), 3.49 (d, $J$ = 7.4 Hz, 1H), 1.25 (t, $J$ = 7.4 Hz, 3H); EI-MS $m/z$ (relative intensity) 427 ($M^-$, 100), 398 (11), 354 (30), 191 (31), 165 (83), 103 (91), 76 (75), 65 (72). To a solution of the ester (100 mg, 0.24 mmol) in methylene chloride was added $BBr_3$ at 0 °C. The resulting mixture was stirred for 1 d, quenched by addition of methanol at 0 °C and stirring for 15 min, and partitioned between water and methylene chloride. The organic layer was 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), 8.15 (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 ($M^+$, 34), 371 (100), 343 (46), 266 (73), 252 (53), 165 (36), 123 (67), 65 (56).

**4-[5-(3-Benzo[1,3]dioxol-5-ylpropenyl)benzo[*d*]isoxazol-3-yl]benzoic acid (26a).** A solution of 4-{5-[3-(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-ylpropyl)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), 6.75-6.64 (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) 429 ($M^-$, 42), 307 (30), 280 (42), 135 (100), 91 (41), 77 (60), 65 (45). The ester (70 mg, 0.17 mmol) and $LiOH{\cdot}H_2O$ (14 mg, 0.17 mmol) in $THF/CH_3OH/H_2O$ (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 extracted with ethyl acetate and the organic layer was washed with brine and water, dried with $MgSO_4$, and concentrated *in vacuo*, and recrystallized to afford acid **26a** (47 mg, 69%): $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 8.15 (s, 4H), 7.93 (s, 1H), 7.77 (d, $J$ = 7.6 Hz, 1H), 7.58 (d, $J$ = 8.6 Hz, 1H), 6.80-6.76 (m, 2H), 6.65 (d, $J$ = 7.8 Hz, 1H), 5.94 (s, 2H), 2.78 (t, $J$ = 8.2 Hz, 2H), 2.55 (t, $J$ = 8.2 Hz, 2H), 1.49 (m, 2H); EI-MS $m/z$ (relative intensity) 401 ($M^-$, 15), 252 (27), 135 (75), 77 (78), 65 (100), 51 (66).

**4-(5-Tetradecylbenzo[*d*]isoxazol-3-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), $(n\text{-}Bu)_4NCl$ (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 $NH_4Cl$ solution and ethyl acetate and extracted with ethyl acetate. The combined organic layer was dried with $MgSO_4$, and concentrated *in vacuo*. The residue in ethanol (20 mL) was hydrogenated for 2 h with 5%-Pd/C (10 mol%) as catalyst under 1 atm of hydrogen. The filtrate was concentrated *in vacuo* and the residue was purified by column chromatography to give 4-(5-tetradecyl-benzo[*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-octylquinolin-6-yloxy)acetic acid (31).** A mixture of 6-benzyloxy-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 $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography to give 6-benzyloxy-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), $(n\text{-}Bu)_4NCl$ (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 $NH_4Cl$ twice, and water, dried with $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography to give 6-benzyloxy-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 10% 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-octylquinolin-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), $K_2CO_3$ (245 mg, 1.77 mmol), and methyl bromoacetate (0.202 mL, 1.77 mmol) in acetone (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 $MgSO_4$, 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: $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 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 dried with $MgSO_4$, filtered, and concentrated *in vacuo* to give **31** (100 mg, 74%) of white solid: mp 130-131 °C; $^1$H NMR (200 MHz, $CDCl_3$-DMSO-$d_6$) $\delta$ 8.71 (d, $J$ = 2.0 Hz, 1H), 7.88 (s, 1H), 7.30 (s, 1H), 6.90 (d, $J$ = 2.4 Hz, 1H), 5.80 (brs, 1H), 4.72 (s, 2H), 2.78 (s, 3H), 2.77 (t, $J$ = 7.1 Hz, 2H), 1.70-0.85 (m, 15H); EI-MS *m/z* (relative intensity) 329 ($M^+$, 100), 244 (66), 231 (40), 230 (34), 156 (30), 143 (42), 43 (68), 41 (71).

**(8-Methyl-3-tetradecylquinolin-6-yloxy)acetic acid (34).** A mixture of 4-chloro-3-iodo-8-methylquinolin-6-ol **32** (210 mg, 0.657 mmol), $Pd(OAc)_2$ (7.4 mg, 5 mol%), $NaHCO_3$ (132 mg, 1.58 mmol), ($n$-Bu)$_4$NCl (183 mg, 0.657 mmol), DMF (10 mL) and 1-tetradecene (0.333 mL, 1.31 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 $NH_4Cl$ twice, and water, dried with $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography to give 4-chloro-8-methyl-3-(tetradec-1-enyl)quinolin-6-ol **33** (159 mg, 62%) as yellow solid. A mixture of **33** (159 mg, 0.410 mmol) and 10% Pd-C (87 mg, 0.082 mmol) in ethanol was stirred for 17 h under hydrogen, filtered through Celite, and concentrated *in vacuo* to give 8-methyl-3-tetradecyl-quinolin-6-ol (136 mg, 93%) as yellow solid: EI-MS *m/z* (relative intensity) 356 ($M^+$, 71), 200 (61), 187 (47), 186 (100), 173 (38), 43 (22), 41 (19). A mixture of the quinolinol (135 mg, 0.37 mmol), $K_2CO_3$ (153 mg, 1.11 mmol), and methyl bromoacetate (0.127 mL, 1.30 mmol) in acetone (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 $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography to give (8-methyl-3-tetradecyl-quinolin-6-yloxy)acetic acid methyl ester 117 mg (74%) as white solid: $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 8.66 (d, $J$ = 2.4 Hz, 1H), 7.76 (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, $J$ = 7.1 Hz, 2H), 0.85-1.70 (m, 27H); EI-MS *m/z* (relative intensity) 427 ($M^+$, 41), 272 (24), 258 (89), 245 (100), 143 (17), 43 (25). A mixture of the ester (107 mg, 0.25 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 dried with $MgSO_4$, filtered, and concentrated *in vacuo* to give 73 mg (71%) of white solid: mp 110-111 °C; $^1$H NMR (200 MHz, $CDCl_3$-DMSO-$d_6$) $\delta$ 8.71 (d, $J$ = 2.4 Hz, 1H), 8.08 (s, 1H), 7.30 (s, 1H), 6.90 (d, $J$ = 2.4 Hz, 1H), 5.00 (brs, 1H), 4.72 (s, 2H), 2.83 (s, 3H), 2.82 (t, $J$ = 7.1 Hz, 2H), 1.70-0.85 (m, 27H); EI-MS *m/z* (relative intensity) 413 ($M^+$, 12), 258 (14), 244 (59), 231 (45), 230 (21), 156 (17), 143 (24), 57 (27), 43 (100), 41 (67).

**{4-Chloro-3-(octen-1-yl)quinolin-8-yloxy}acetic acid (37).** A mixture of 4-chloro-3-iodo-8-methoxyquinoline **35** (1.00 g, 3.12 mmol), 1-octene (1.40 mL, 8.92 mmol), $NaHCO_3$ (620 mg, 6.20 mmol), $Bu_4NCl$ (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 $MgSO_4$, and concentrated *in vacuo*. The residue was purified by column chromatography to give 650 mg (68.6%) of 4-chloro-3-(oct-1-enyl)-8-methoxyquinoline **36** as an yellow solid: $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 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 Hz, 1H), 6.50 (dq, $J$ = 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 $BBr_3$ and crystallization in ethyl acetate. A mixture of the quinolinol (0.14g, 0.49 mmol), methyl bromoacetate (60 uL, 0.63 mmol), $K_2CO_3$ (0.14 g, 0.98 mmol) in acetone (7 mL) was heated for 3 h under reflux, filtered and concentrated *in vacuo*. The residue was partitioned between ethyl acetate and brine, and the organic layer was dried with $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography to give {4-chloro-3-(octen-1-yl)quinolin-8-yloxy}acetic acid methyl ester 0.15 g (85%): $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 0.91 (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 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 $LiOH\cdot H_2O$ (17 mg, 0.42 mmol) in THF/$CH_3OH$/$H_2O$ (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%): $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 9.08 (s, 1H), 8.01 (d, $J$ = 8.3 Hz, 1H), 7.61 (t, $J$ = 8.3 Hz, 1H), 7.32 (d, $J$ = 7.9 Hz, 1H), 6.90 (d, $J$ = 15.7 Hz, 1H), 6.56 (dt, $J$ = 15.7, 6.4 Hz, 1H), 5.30 (bs, 1H), 4.78 (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-Octylquinolin-8-yloxy)acetic acid (39).** The octenyl-quinoline **36** (430 mg, 1.4 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, 84%): $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 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, 1.1 mmol) in 7 mL of methylene chloride was added 1 *N*

$BBr_3/CH_2Cl_2$ (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 $MgSO_4$, 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), $K_2CO_3$ (110 mg, 0.78 mmol) and in acetone (5 mL) was heated for 3 h under reflux, filtered and concentrated *in vacuo*. The residue was partitioned between ethyl acetate and brine, and the organic layer was dried with $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography to give (3-octylquinolin-8-yloxy)acetic acid methyl ester 100 mg (77%): $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 8.85 (d, $J$ = 2.1 Hz, 1H), 7.87 (m, 1H), 7.38 (d, $J$ = 4.8 Hz, 2H), 6.90 (t, $J$ = 4.3 Hz, 1H), 4.96 (s, 2H), 3.80 (s, 3H), 2.79 (t, $J$ = 7.3 Hz, 2H), 1.65 (m, 2H, 1.20-1.45 (m, 10H)), 0.87 (t, $J$ = 2.1 Hz, 3H). A mixture of ester (80 mg, 0.24 mmol) and $LiOH\cdot H_2O$ (15 mg, 0.36 mmol) in $THF/CH_3OH/H_2O$ (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 **39** (71 mg, 95%): $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 8.85 (s, 1H), 8.01 (s, 1H), 7.49 (m, 2H), 7.25 (m, 1H), 4.78 (s, 1H), 2.84 (t, $J$ = 7.3 Hz, 2H), 1.67 (m, 2H), 1.10-1.45 (m, 10H), 0.95 (t, $J$ = 7.2 Hz, 3H).

**(4-Chloro-3-phenylquinolin-8-yloxy)acetic acid (42).** A mixture of **35** (500 mg, 1.57 mmol), phenylboronic aicd (288 mg, 2.36 mmol), LiCl (67 mg, 1.57 mmol), $Cs_2CO_3$ (1.023 g, 3.14 mmol), $Pd(OAc)_2$ (18 mg, 0.079 mmol) and 1,4-dioxane (30 mL) was heated for 10 h at 110 °C followed by dilution with ethyl acetate. The organic layer was washed with brine, dried with $MgSO_4$, and concentrated *in vacuo*. The residue was purified by column chromatography to give 300 mg (71%) of 4-chloro-8-methoxy-3-phenylquinoline **40**: $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 8.74 (s, 1H), 7.78 (d, $J$ = 8.5 Hz, 1H), 7.16-7.50 (m, 6H), 6.99 (d, $J$ = 7.7 Hz, 1H), 3.99 (s, 3H). To a solution of **40** (300 mg, 1.12 mmol) in 5 mL of methylene chloride was added 1 M $BBr_3/CH_2Cl_2$ (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 $MgSO_4$, and concentrated *in vacuo* and the residue was purified by column chromatography to give 4-chloro-3-phenylquinolin-8-ol **41** (158 mg, 55%). A mixture of the quinolinol **41** (100 mg, 0.39 mmol), ethyl bromoacetate (78 mg, 0.47 mmol), $K_2CO_3$ (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 $MgSO_4$, 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-yloxy)acetic acid ethyl ester (51 mg, 38%): $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 8.88 (s, 1H), 7.98 (d, $J$ = 8.5 Hz, 1H), 7.26-7.61 (m, 6H), 7.05 (d, $J$ = 7.9 Hz, 1H), 5.00 (s, 2H), 4.28 (q, $J$ = 7.3 Hz, 2H), 1.28 (t, $J$ = 7.3 Hz, 3H); EI-MS *m/z* (relative intensity) 268 (100), 239 (10), 203 (18), 43 (15). A mixture of ester (40 mg, 0.12 mmol) and $LiOH\cdot H_2O$ (10 mg, 0.23 mmol) in $THF/CH_3OH/H_2O$ (1 : 1 : 1) was stirred for 1 h and concentrated. The aqueous layer was acidified with 1 *N* HCl. The precipitate was filtered and dried to give **42** (37 mg, 97%): $^1$H NMR (200 MHz, DMSO-$d_6$) $\delta$ 8.81 (s, 1H), 7.43-7.86 (m, 7H), 7.24 (d, $J$ = 7.4 Hz, 1H), 4.75 (s, 2H); EI-MS *m/z* (relative intensity) 277 (52), 248 (100), 218 (11), 190 (11), 146 (12), 109 (20), 102 (24).

**[4-(4-Chloro-3-phenylquinolin-8-yl)phenoxy]acetic acid (44).** To a mixture of 4-chloro-3-phenylquinolin-8-ol **41** (600 mg, 2.35 mmol), pyridine (1.9 mL, 23.5 mmol) in $CH_2Cl_2$ (50 mL) was added trifluoromethanesulfonic anhyride (0.79 mL, 4.7 mmol) at 0 °C. The resulting mixture was stirred for 10 h, washed with dilute hydrochloric acid, and extracted with ethyl acetate. The organic layer was dried with $MgSO_4$ and concentrated *in vacuo* and the residue was purified by column chromatography to give 4-chloro-3-phenylquinolin-8-yl trifluoromethanesulfonate **43** (346 mg, 38%): $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 8.98 (s, 1H), 8.35-8.40 (m, 1H), 7.67-7.70 (m, 2H), 7.47-7.56 (m, 5H); EI-MS *m/z* (relative intensity) 389 (M+2, 38), 387 ($M^-$, 89), 254 (74), 226 (100), 190 (39), 163 (21). A mixture of triflate (292 mg, 0.753 mmol), *p*-methoxyphenylboronic acid (172 mg, 1.13 mmol), LiCl (32 mg, 0.753 mmol), $Cs_2CO_3$ (490 mg, 1.506 mmol) and $Pd(OAc)_2$ (9 mg, 0.038 mmol) in 1,4-dioxane (15 mL) was heated for 10 h at 110 °C. The resulting mixture was washed with brine and the aqueous layer was extracted with ethyl acetate. The combined organic layer was dried with and concentrated. The residue was purified by column chromatography to give 4-chloro-8-(4-methoxyphenyl)-3-phenylquinoline (52 mg, 20%): $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 8.88 (s, 1H), 8.36 (dd, $J$ = 7.9, 2.0 Hz, 1H), 7.25-7.80 (m, 9H), 7.03-7.09 (m, 2H), 3.89 (s, 3H); EI-MS *m/z* (relative intensity) 347 (M+2, 47), 345 ($M^+$, 100), 330 (33), 133 (39). To a solution of methoxyquinoline (50 mg, 0.145 mmol) in 5 mL of methylene chloride was added dropwise 1 M $BBr_3/CH_2Cl_2$ (1.0 mL, 1.0 mmol) at 0 °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 $MgSO_4$, and concentrated *in vacuo* and the residue was purified by column chromatography to give 4-(4-chloro-3-phenylquinolin-8-yl)phenol 29 mg (60%). A mixture of the phenol (40 mg, 0.12 mmol), $K_2CO_3$ (33 mg, 0.24 mmol), KI (2 mg, 0.012 mmol) and ethyl bromoacetate (78 mg, 0.47 mmol) in DMF (5 mL) was stirred for 12 h, and washed with brine. The aqueous layer was extracted with ethyl acetate and the combined organic layer was dried with $MgSO_4$ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography to give 38 mg (75%) of [4-(4-chloro-3-phenylquinolin-8-yl)-phenoxy]acetic acid ethyl ester: $^1$H NMR (200 MHz, $CDCl_3$)

$\delta$ 8.87 (s, 1H), 8.37 (dd, $J$ = 7.7, 1.5 Hz, 1H), 7.48-7.76 (m, 9H), 7.06 (dd, $J$ = 6.5, 2.0 Hz, 2H), 4.69 (s, 2H), 4.28 (q, $J$ = 7.3 Hz, 2H), 1.28 (t, $J$ = 7.3 Hz, 3H); EI-MS $m/z$ (relative intensity) 419 (M+2, 19), 417 ($M^-$, 53), 330 (100), 314 (22), 278 (25), 139 (34). A mixture of ester (10 mg, 0.024 mmol) and $LiOH{\cdot}H_2O$ (2.0 mg, 0.048 mmol) in $THF/CH_3OH/H_2O$ (1 : 1 : 1, 1 mL) was stirred for 1 h and concentrated. The aqueous layer was acidified with 1 *N* HCl at 0 °C. The precipitate was filtered and dried to give **44** (9.0 mg, 95%): $^1$H NMR (200 MHz, DMSO-$d_6$) $\delta$ 8.88 (s, 1H), 8.31-8.36 (m, 1H), 7.85-7.88 (m, 2H), 7.50-7.63 (m, 7H), 7.01-7.06 (m, 2H), 4.75 (s, 2H); EI-MS $m/z$ (relative intensity) 197 (2), 194 (2), 145 (5), 83 (7), 58 (11), 43 (100).

**(4-Carboxy-2-methylquinolin-3-yl)oxyacetic acid (47).** A mixture of 4-carboxy-2-methylquinolin-2-ol **45** (300 mg, 1.43 mmol), methyl bromoacetate (0.270 mL, 1.43 mmol), and potassium carbonate (400 mg, 2.86 mmol) in 15 mL of acetone was heated for 5 h under reflux and concentrated. The residue was diluted with ethyl acetate and washed with brine, dried with $MgSO_4$, and concentrated. The residue was purified by column chromatography to give 150 mg (30%) of methyl (4-methoxycarbonylmethoxycarbonyl-2-methylquinolin-3-yl)oxyacetate **46**: $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 2.77 (s, 3H), 3.83 (s, 3H), 3.87 (s, 3H), 4.71 (s, 2H), 4.98 (s, 2H), 7.62 (m, 2H), 8.10 (m, 2H). A mixture of **46** (140 mg, 0.40 mmol) and $LiOH{\cdot}H_2O$ (67 mg, 1.6 mmol) in THF : water : methanol (1 : 1 : 1, 12 mL) was stirred for 1 h, concentrated *in vacuo*, washed with ether, and acidified by addition of 1 *N* hydrochloric acid. The resulting precipitate was filtered and dried to give **47** (80 mg, 75%): $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 7.96 (d, $J$ = 7.2 Hz, 1H), 7.45-7.70 (m, 3H), 4.68 (s, 2H), 2.66 (s, 3H).

**4-Chloro-6-decyloxyquinolin-3-carboxylic acid (50).** A mixture of 4-decyloxyaniline **48** (1.00 g, 4.01 mmol) and diethyl ethoxymethylene malonate (0.810 mL, 4.01 mmol) in ethanol (50 mL) was heated for 30 min at 90 °C, cooled to room temperature, and concentrated *in vacuo*. The residue and diphenyl ether (100 mL) was heated for 2 h at 260 °C. After cooling to room temperature, the mixture was stirred for 30 min with addition of petroleum ether (100 mL). The precipitate was filtered to give 6-deyloxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid ethyl ester **49** (1.67 g, 99%): $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ 0.88 (t, $J$ = 6.6 Hz, 3H), 1.60-1.27 (m, 17H), 1.89-1.82 (m, 2H), 4.10 (t, $J$ = 6.5 Hz, 2H), 4.48-4.22 (m, 3H), 7.93-7.41 (m, 3H), 8.99 (s, 1H). A mixture of the quinolone **49** (1.00 g, 2.68 mmol) and $POCl_3$ was heated under reflux and excess $POCl_3$ was quenched by addition of ice-water. The resulting mixture was neutralized with saturated sodium bicarbonate and extracted with ethyl acetate. The organic layer was washed with brine, dried with $MgSO_4$, and concentrated *in vacuo*. The residue was purified by column chromatography to give 4-chloro-6-decyloxyquinoline-3-carboxylic acid ethyl ester (0.932 g, 89%) as yellow solid: $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ 0.88 (m, 3H), 1.65-1.21 (m, 16H), 1.86 (quintet, $J$ = 7.6 Hz, 2H), 4.14 (t, $J$ = 6.6 Hz, 2H), 4.49 (q, $J$ = 7 Hz, 2H), 7.60-7.29 (m, 3H), 8.02 (d, $J$ = 9.2 Hz, 1H), 9.04 (s, 1H); EI-MS $m/z$ (relative intensity) 391 ($M^+$, 0.3), 384 (24), 292 (1.2), 264 (8.8) 251 (100). A mixture of the ester (927 mg, 2.36 mmol) and 2 *N* NaOH in ethanol (30 mL) was heated at reflux. The resulting mixture was cooled to room temperature and neutralized with 1 *N*-HCl to give white crystalline **50** (691 mg, 80%): $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 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).

***in vitro* Enzyme Assay.** The tests were performed against recombinant human PTP-1B using fluorescein diphosphate (FDP) as a substrate. The medium was 30 mM Tris, 75 mM NaCl, 0.67 mM EDTA in 1 mM DTT (pH 8.0) buffer with 20 $\mu$M FDP, and 0.1 $\mu$g of PTP-1B. After an hour at room temperature with inhibitor, the enzyme activity was determined by measuring the fluorescence of the product, fluorescein monophosphate (FMT) at 485 nm (excitation) and 538 nm (emission). $IC_{50}$ ($\mu$M) values were determined from direct regression curve analysis. Isozyme selectivity was determined likewise using appropriate phosphatases.

## Conclusion

Several classes of compounds (heteroarylcarboxylic acids, phenoxyacetic 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 $IC_{50}$, suggesting that the inhibition can be enhanced by lipophilic substitution within these classes of compounds.

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