Supporting Information

Modification at the lipophilic domain of RXR agonists differentially influences activation of RXR heterodimers

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Contents:

Chemistry.

Melting points were determined with a Yanagimoto hot-stage melting point apparatus and are uncorrected. IR were recorded on JASCO FT/IR350 (KBr). ^{1}H NMR spectra were recorded on a VarianVXR-300 (300 MHz) or VarianVXR-500 (500 MHz) spectrometer. Elemental analysis was carried out with a Yanagimoto MT-5 CHN recorder elemental analyzer. FAB-MS was carried out with a VG70-SE.

LGD1069 (1)

This compound was prepared according to reference 1.

6-[Ethyl-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphthalen-2-yl)amino]nicotinic acid (4a)

This compound was prepared according to reference 2.

Methyl 6-[ethyl-(3-isopropoxy-4-isopropylphenyl)amino]nicotinate (6)

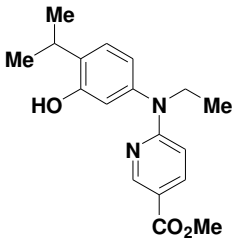
6-[Ethyl-(3-isopropoxy-4-isopropylphenyl)amino]nicotinic acid (5a)

6-[Ethyl-(3-isobutoxy-4-isopropylphenyl)amino]nicotinic acid (5b)

6-[Ethyl-(4-isopropyl-3-propoxyphenyl)amino]nicotinic acid (5g)

These compounds were prepared according to reference 3.

Methyl 6-[ethyl-(3-hydroxy-4-isopropylphenyl)amino]nicotinate (7)

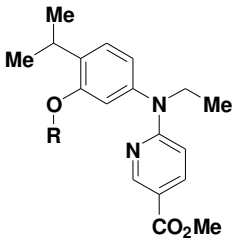


To a solution of **7** (420 mg, 1.2 mmol) in CH_2Cl_2 (5 mL) was added $AlCl_3$ (600 mg, 4.5 mmol). The mixture was stirred at room temperature for 4 h. The solution was poured into water and extracted with EtOAc (3 × 50 mL). The organic layers were combined, washed with water and brine, and dried over $MgSO_4$. The solvent was evaporated under reduced pressure and the resulting crude material was purified by flash column chromatography (3/1 *n*-hexane/EtOAc) to provide 350 mg (93%) of **7** as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.81 (d, 1H, *J* = 2.5 Hz), 7.79 (dd, 1H, *J* = 9.0, 2.5 Hz), 7.24 (d, 1H, *J* = 2.0 Hz), 6.76 (dd, 1H, *J* = 8.0, 2.0 Hz), 6.61 (d, 1H, *J* = 2.0 Hz), 6.27 (d, 1H, *J* = 9.0 Hz), 5.31 (s, 1H), 4.00 (q, 2H, *J* = 7.0 Hz), 3.86 (s, 3H), 3.23 (sep, 1H, *J* = 7.0 Hz), 1.29 (d, 6H, *J* = 7.0 Hz), 1.22 (t, 3H, *J* = 7.0 Hz).

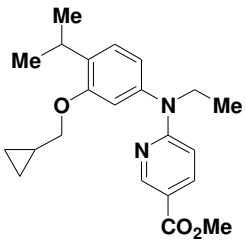
General procedure for synthesis of O-alkyl intermediates (8c-f, 8h-m) (GP-1)

To a solution of each OH-intermediate (1.0 mmol) in DMF (3 mL) were added K_2CO_3 (1.2 mmol), alkyl halide (1.5 mmol) and KI (c. a.). The reaction mixture was stirred at 60-90 ºC for 2 h, and the solution was poured into water and extracted with EtOAc (3 × 20 mL). The organic



layer was washed with water and brine, and dried over $MgSO_4$. The solution was evaporated under reduced pressure. The residue was purified by flash column chromatography to yield the O-alkyl intermediates.

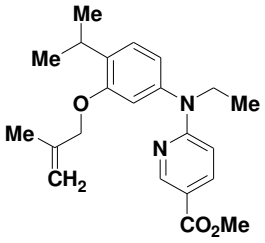
Methyl 6-[(3-cyclopropylmethoxy-4-isopropylphenyl)ethylamino]nicotinate (8c)



According to the general procedure (GP-1), **8c** was obtained as a colorless oil (67%).

^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.83 (d, 1H, *J* = 2.5 Hz), 7.78 (dd, 1H, *J* = 9.0, 2.5 Hz), 7.25 (d, 1H, *J* = 8.0 Hz), 6.77 (d, 1H, *J* = 8.0, 2.0 Hz), 6.62 (d, 1H, *J* = 2.0 Hz), 6.23 (d, 1H, *J* = 9.0 Hz), 4.02 (q, 2H, *J* = 7.0 Hz), 3.85 (s, 3H), 3.78 (d, 2H, *J* = 6.5 Hz), 3.67 (sep, 1H, *J* = 7.0 Hz), 1.27 (d, 6H, *J* = 7.0 Hz), 1.23 (t, 3H, *J* = 7.0 Hz), 0.65-0.59 (m, 2H), 0.38-0.33 (m, 2H).

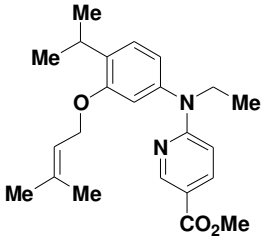
Methyl 6-{ethyl-[4-isopropyl-3-(2-methylallyloxy)phenyl]amino}nicotinate (8d)



According to the general procedure (GP-1), **8d** was obtained as a colorless oil (68%).

^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.85 (d, 1H, *J* = 2.5 Hz), 7.80 (dd, 1H, *J* = 9.0, 2.5 Hz), 7.27 (d, 1H, *J* = 8.0 Hz), 6.79 (dd, 1H, *J* = 8.0, 2.0 Hz), 6.66 (d, 1H, *J* = 2.0 Hz), 6.25 (d, 1H, *J* = 9.0 Hz), 5.10 (s, 1H), 4.99 (s, 1H), 4.39 (s, 2H), 4.03 (q, 2H, J = 7.0 Hz), 3.86 (s, 3H), 3.39 (sep, 1H, *J* = 7.0 Hz), 1.84 (s, 3H), 1.27 (d, 6H, *J* = 7.0 Hz), 1.23 (t, 3H, *J* = 7.0 Hz).

Methyl 6-{ethyl-[4-isopropyl-3-(3-methyl-but-2-enyloxy)phenyl]amino}nicotinate (8e)



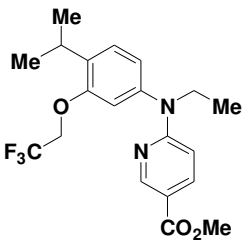
According to the general procedure (GP-1), **8e** was obtained as a colorless oil (58%).

^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.85 (d, 1H, *J* = 2.5 Hz), 7.79 (dd, 1H, *J* = 9.0, 2.5 Hz), 7.25 (d, 1H, *J* = 8.0 Hz), 6.77 (dd, 1H, *J* = 8.0, 2.0 Hz), 6.66 (d, 1H, *J* = 2.0 Hz), 6.25 (dd, 1H, *J* = 9.0 Hz), 5.45 (m, 1H), 4.48 (d, 2H, *J* = 6.5 Hz), 4.03 (q, 2H, *J* = 7.0 Hz), 3.86 (s, 3H), 3.35 (sep, 1H, *J* = 7.0 Hz), 1.77 (s, 3H), 1.69 (s, 3H), 1.24 (d, 6H, *J* = 7.0 Hz), 1.24 (t, 3H, *J* = 7.0 Hz).

Methyl 6-{ethyl-[4-isopropyl-3-(2,2,2-trifluoroethoxy)phenyl]amino}nicotinate (8f)

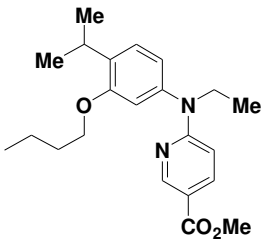
According to the general procedure (GP-1), **8f** was obtained as a colorless oil (67%).

^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.84 (d, 1H, *J* = 2.5 Hz), 7.82 (dd, 1H, *J* = 9.0, 2.5 Hz), 7.32 (d,



1H, *J* = 8.0 Hz), 6.90 (d, 1H, *J* = 8.0, 2.0 Hz), 6.64 (d, 1H, *J* = 2.0 Hz), 6.24 (d, 1H, *J* = 9.0 Hz), 4.33 (q, 2H, *J* = 8.0 Hz, OCH_2), 4.03 (q, 2H, *J* = 7.0 Hz), 3.86 (s, 3H) 3.35 (sep, 1H, *J* = 7.0 Hz), 1.27 (d, 6H, *J* = 7.0 Hz), 1.23 (t, 3H, *J* = 7.0 Hz).

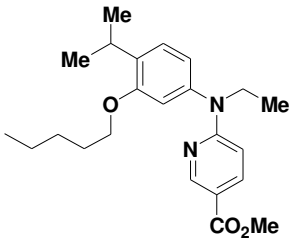
Methyl 6-[(3-butoxy-4-isopropylphenyl)ethylamino]nicotinate (8h)



According to the general procedure (GP-1), **8h** was obtained as a colorless oil (74%).

^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.84 (dd, 1H, *J* = 2.5, 0.5 Hz), 7.79 (dd, 1H, *J* = 9.0, 2.5 Hz), 7.25 (d, 1H, *J* = 9.0 Hz), 6.76 (dd, 1H, *J* = 8.0, 2.0 Hz), 6.65 (d, 1H, *J* = 2.0 Hz), 6.24 (dd, 1H, *J* = 9.0, 0.5 Hz), 4.03 (q, 2H, *J* = 7.0 Hz), 3.91 (t, 2H, *J* = 6.5 Hz), 3.86 (s, 3H), 3.33 (sep, 1H, *J* = 7.0 Hz), 1.83-1.74 (m, 2H), 1.56-1.46 (m, 2H), 1.25 (d, 6H, *J* = 7.0 Hz), 1.24 (t, 3H, *J* = 7.0 Hz) 0.99 (t, 3H, *J* = 7.5 Hz).

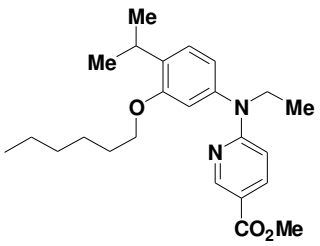
Methyl 6-[ethyl-(4-isopropyl-3-pentyloxyphenyl)amino]nicotinate (8i)



According to the general procedure (GP-1), **8i** was obtained as a colorless oil (77%).

^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.84 (d, 1H, *J* = 2.5 Hz), 7.79 (dd, 1H, *J* = 9.0, 2.5 Hz), 7.25 (d, 1H, *J* = 8.0 Hz), 6.76 (dd, 1H, *J* = 8.0, 2.0 Hz), 6.64 (d, 1H, *J* = 2.0 Hz), 6.24 (d, 1H, *J* = 9.0 Hz), 4.03 (q, 2H, *J* = 7.0 Hz), 3.90 (t, 2H, *J* = 6.5 Hz), 3.86 (s, 3H), 3.34 (sep, 1H, *J* = 7.0 Hz), 1.81-1.78 (m, 2H), 1.52-1.38 (m, 4H), 1.25 (d, 6H, *J* = 7.0 Hz), 1.24 (t, 3H, *J* = 7.0 Hz), 0.94 (t, 3H, *J* = 7.0 Hz).

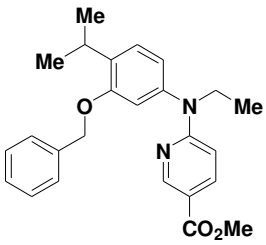
Methyl 6-[ethyl-(3-hexyloxy-4-isopropylphenyl)amino]nicotinate (8j)



According to the general procedure (GP-1), **8j** was obtained as a colorless oil (78%).

^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.84 (d, 1H, *J* = 2.0 Hz), 7.79 (dd, 1H, *J* = 9.0, 2.0 Hz), 7.25 (d, 1H, *J* = 8.0 Hz), 6.76 (dd, 1H, *J* = 8.0, 2.0 Hz), 6.65 (d, 1H, *J* = 2.0 Hz), 6.25 (d, 1H, *J* = 9.0 Hz), 4.03 (q, 2H, *J* = 7.0 Hz), 3.91 (t, 2H, *J* = 6.5 Hz), 3.85 (s, 3H), 3.34 (sep, 1H, *J* = 7.0 Hz), 1.85-1.75 (m, 2H), 1.51-1.44 (m, 2H), 1.40-1.31 (m, 4H), 1.25 (d, 6H, *J* = 7.0 Hz), 1.24 (t, 3H, *J* = 7.0 Hz), 0.91 (t, 3H, *J* = 7.0 Hz).

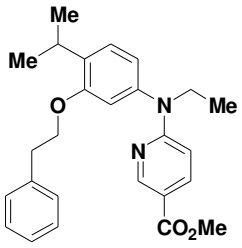
Methyl 6-[(3-benzyloxy-4-isopropylphenyl)ethylamino]nicotinate (8k)



According to the general procedure (GP-1), **8k** was obtained as a colorless oil (69%).

^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.84 (d, 1H, *J* = 2.5 Hz), 7.77 (dd, 1H, *J* = 9.0, 2.5 Hz), 7.43 (m, 5H), 7.29 (d, 1H, *J* = 8.0 Hz), 6.80 (dd, 1H, *J* = 8.0, 2.0 Hz), 6.73 (d, 1H, *J* = 2.0 Hz), 6.20 (d, 1H, *J* = 9.0 Hz), 5.05 (s, 2H), 4.01 (q, 2H, *J* = 7.0 Hz), 3.85 (s, 3H), 3.43 (sep, 1H, *J* = 7.0 Hz), 1.28 (d, 6H, *J* = 7.0 Hz), 1.20 (t, 3H, *J* = 7.0 Hz).

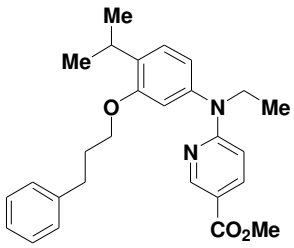
Methyl 6-[ethyl-(4-isopropyl-3-phenethyloxyphenyl)amino]nicotinate (8l)



According to the general procedure (GP-1), **8l** was obtained as a colorless oil (34%).

^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.83 (d, 1H, *J* = 2.5 Hz), 7.78 (dd, 1H, *J* = 9.0, 2.5 Hz), 7.32-7.22 (m, 6H), 6.76 (dd, 1H, *J* = 8.0, 2.0 Hz), 6.63 (d, 1H, *J* = 2.0 Hz), 6.22 (d, 1H, *J* = 9.0 Hz), 4.12 (t, 2H, *J* = 6.5 Hz), 4.00 (q, 2H, *J* = 7.0 Hz), 3.85 (s, 3H), 3.31 (sep, 1H, *J* = 7.0 Hz), 3.11 (t, 2H, *J* = 6.5 Hz), 1.21 (t, 3H, *J* = 7.0 Hz), 1.21 (d, 6H, *J* = 7.0 Hz).

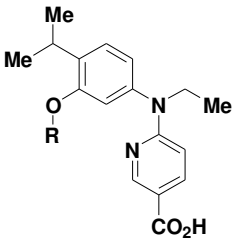
Methyl 6-{ethyl-[4-isopropyl-3-(3-phenylpropoxy)phenyl]amino}nicotinate (8m)



According to the general procedure (GP-1), **8m** was obtained as a colorless oil (86%).

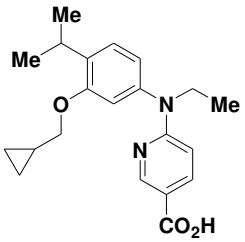
^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.83 (d, 1H, *J* = 2.5 Hz), 7.78 (dd, 1H, *J* = 9.0, 2.5 Hz), 7.31-7.19 (m, 6H), 6.77 (dd, 1H, *J* = 8.0, 2.0 Hz), 6.61 (d, 1H, *J* = 2.0 Hz), 6.23 (d, 1H, *J* = 9.0 Hz), 4.02 (q, 2H, *J* = 7.0 Hz), 3.93 (t, 2H, *J* = 6.0 Hz), 3.86 (s, 3H), 3.37 (sep, 1H, *J* = 7.0 Hz), 2.84 (t, 2H, *J* = 8.0 Hz), 2.18-2.08 (m, 2H), 1.28 (d, 6H, *J* = 7.0 Hz), 1.22 (t, 3H, *J* = 7.0 Hz).

General Procedure for Synthesis of 5c-f, 5h-m (GP-2)



To a solution of each intermediate (1.0 mmol) in MeOH (10 mL) were added 2 N NaOH (4.0 mL) and THF (3.0 mL). The reaction mixture was stirred at 60 °C for 1 hr, then neutralized with 1 N HCl (12 mL). The mixture was poured into water (40 mL) and extracted with EtOAc (3 × 20 mL). The organic layer was washed with water and brine, and dried over $MgSO_4$. The solution was evaporated under reduced pressure and the residue was recrystallized to yield the desired product.

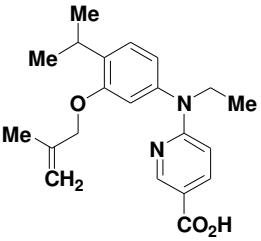
6-[(3-Cyclopropylmethoxy-4-isopropylphenyl)-ethylamino]nicotinic acid (5c)



According to the general procedure (GP-2), **5c** was obtained by re-crystallization from MeOH in 31% yield as colorless needles.

Mp 176.5-177.0 °C. IR (KBr) cm-[1]: 1681 (CO). [1]H NMR (300 MHz, DMSO-d_6) δ: 8.66 (d, 1H, *J* = 2.5 Hz), 7.78 (dd, 1H, *J* = 9.0, 2.5 Hz), 7.29 (d, 1H, *J* = 8.5 Hz), 6.81-6.79 (m, 2H), 6.24 (d, 1H, *J* = 9.0 Hz), 3.97 (q, 2H, *J* = 7.0 Hz), 3.83 (d, 2H, *J* = 6.5 Hz), 1.22 (d, 6H, *J* = 7.0 Hz), 1.13 (t, 3H, *J* = 7.0 Hz), 0.59-0.53 (m, 2H), 0.35-0.30 (m, 2H). FAB-MS *m/z*: 355 $[M + H]^+$. Anal. ($C_{21}H_{26}N_2O_3$) C, H, N.

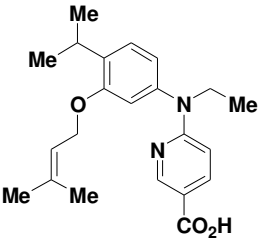
6-{Ethyl-[4-isopropyl-3-(2-methylallyloxy)phenyl]amino}nicotinic acid (5d)



According to the general procedure (GP-2), **5d** was obtained by re-crystallization from MeOH in 51% yield as colorless needles.

Mp 162.0-163.5 °C. IR (KBr) cm^{-1}: 1677 (CO). [1]H NMR (300 MHz, DMSO-d_6) δ: 12.49 (br s, 1H), 8.67 (d, 1H, *J* = 2.5 Hz), 7.78 (dd, 1H, *J* = 9.0, 2.5 Hz), 7.51 (d, 1H, *J* = 8.0 Hz), 6.84-6.81 (m, 2H), 6.25 (d, 1H, *J* = 9.0 Hz), 5.08 (s, 1H), 4.96 (s, 1H), 4.47 (s, 2H), 3.98 (q, 2H, *J* = 7.0 Hz), 3.30 (sep, 1H, *J* = 7.0 Hz), 1.78 (s, 3H), 1.22 (d, 6H, *J* = 7.0 Hz), 1.14 (t, 3H, *J* = 7.0 Hz). FAB-MS *m/z*: 355 $[M + H]^+$. Anal. ($C_{21}H_{26}N_2O_3$) C, H, N..

6-{Ethyl-[4-isopropyl-3-(3-methyl-but-2-enyloxy)phenyl]amino}nicotinic acid (5e)



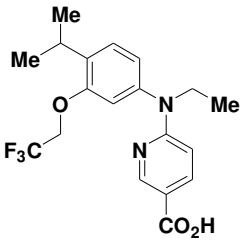
According to the general procedure (GP-2), **5e** was obtained by re-crystallization from MeOH in 51% yield as colorless needles.

Mp 139.5-141.0 °C. IR (KBr) cm-[1]: 1680 (CO). [1]H NMR (300 MHz, DMSO-d_6) δ: 12.46 (br s, 1H), 8.67 (d, 1H, *J* = 2.5 Hz), 7.78 (dd, 1H, *J* = 9.0, 2.5 Hz), 7.28 (d, 1H, *J* = 8.0 Hz), 6.85 (d, 1H, *J* = 2.0 Hz), 6.81 (dd, 1H, *J* = 8.0, 2.0 Hz), 6.25 (d, 1H, *J* = 9.0 Hz), 5.41 (t, 1H, *J* = 6.5 Hz), 4.53 (d, 2H, *J* = 6.5 Hz), 3.98 (q, 2H, *J* = 7.0 Hz), 3.25 (sep, 1H, *J* = 7.0 Hz), 1.73 (s, 3H), 1.66 (s, 3H), 1.19 (d, 6H, *J* = 7.0 Hz), 1.14 (t, 3H, *J* = 7.0 Hz). FAB-MS *m/z*: 369 $[M + H]^+$. Anal. ($C_{22}H_{28}N_2O_3$) C, H, N.

6-{Ethyl-[4-isopropyl-3-(2,2,2-trifluoroethoxy)phenyl]amino}nicotinic acid (5f)

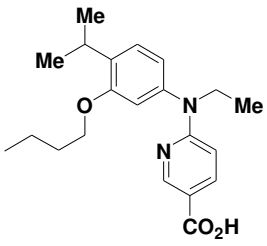
According to the general procedure (GP-2), **5f** was obtained by re-crystallization from EtOAc/*n*-hexane in 43% yield as yellow needles.

Mp 180.0-181.0 °C. IR (KBr) cm-[1]: 1668 (CO). [1]H NMR (300 MHz, DMSO-d_6) δ: 12.51 (br s, 1H), 8.67 (d, 1H, *J* = 2.5 Hz), 7.80 (dd, 1H, *J* = 9.0, 2.5 Hz), 7.35 (d, 1H, *J* = 8.0 Hz), 7.02 (d,



1H, *J* = 2.0 Hz), 6.94 (dd, 1H, *J* = 8.0, 2.0 Hz), 6.29 (d, 1H, *J* = 9.0 Hz), 4.77 (q, 2H, *J* = 8.5 Hz), 3.99 (q, 2H, *J* = 7.0 Hz), 3.26 (sep, 1H, *J* = 7.0 Hz), 1.22 (d, 6H, *J* = 7.0 Hz), 1.15 (t, 3H, *J* = 7.0 Hz). FAB-MS *m/z*: 383 $[M + H]^+$. Anal. ($C_{19}H_{21}N_2O_3F_3$) C, H, N.

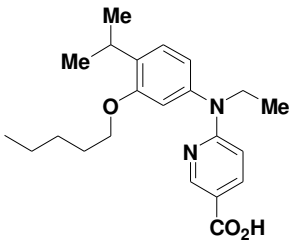
6-[(3-Butoxy-4-isopropylphenyl)-ethylamino]nicotinic acid (5h)



According to the general procedure (GP-2), **5h** was obtained by re-crystallization from EtOAc/*n*-hexane in 99% yield as a white powder.

Mp. 159.0-161.0 °C. IR (KBr) cm-[1]: 1683 (CO). ^{1}H NMR (300 MHz, DMSO-d_6) δ: 12.49 (s, 1H), 8.67 (dd, 1H, *J* = 2.5, 0.5 Hz), 7.79 (dd, 1H, *J* = 9.0, 2.5 Hz), 7.28 (d, 1H, *J* = 7.5 Hz), 6.83-6.79 (m, 2H), 6.25 (dd, 1H, *J* = 9.0, 0.5 Hz), 3.98 (q, 2H, *J* = 7.0 Hz), 3.95 (t, 2H, *J* = 6.0 Hz) 3.26 (sep, 1H, *J* = 7.0 Hz), 1.76-1.67 (m, 2H), 1.53-1.40 (m, 2H), 1.20 (d, 6H, *J* = 7.0 Hz), 1.14 (t, 3H, *J* = 7.0 Hz), 0.94 (t, 3H, *J* = 7.5 Hz). FAB-MS *m/z*: 357 $[M + H]^+$. Anal. ($C_{21}H_{28}N_2O_3$) C, H, N.

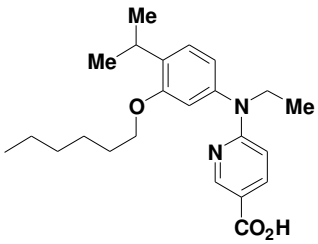
6-[Ethyl-(4-isopropyl-3-pentyloxyphenyl)amino]nicotinic acid (5i)



According to the general procedure (GP-2), **5i** was obtained by re-crystallization from EtOAc/*n*-hexane in 99% yield as a white powder.

Mp 141.0-142.0 °C. IR (KBr) cm-[1]: 1684 (CO). ^{1}H NMR (300 MHz, DMSO-d_6) δ: 12.49 (s, 1H), 8.67 (dd, 1H, *J* = 2.5, 0.5 Hz), 7.78 (dd, 1H, *J* = 9.0, 2.5 Hz), 7.28 (d, 1H, *J* = 7.5 Hz), 6.82-6.80 (m, 2H), 6.24 (d, 1H, *J* = 9.0 Hz), 3.99-3.93 (m, 4H), 3.28 (sep, 1H, *J* = 7.0 Hz), 1.75-1.68 (m, 2H), 1.45-1.31 (m, 4H), 1.20 (d, 6H, *J* = 7.0 Hz), 1.14 (t, 3H, *J* = 7.0 Hz), 0.89 (t, 3H, *J* = 7.0 Hz). FAB-MS *m/z*: 371 $[M + H]^+$. Anal. ($C_{22}H_{30}N_2O_3$) C, H, N.

6-[Ethyl-(3-hexyloxy-4-isopropylphenyl)amino]nicotinic acid (5j)



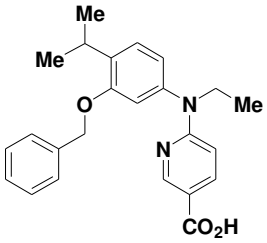
According to the general procedure (GP-2), **5j** was obtained by re-crystallization from MeOH in 79% yield as colorless needles.

Mp 113.0-114.0 °C. IR (KBr) cm-[1]: 1684 (CO). ^{1}H NMR (300 MHz, DMSO-d_6) δ: 12.48 (br s, 1H), 8.66 (d, 1H, *J* = 2.5 Hz), 7.78 (dd, 1H, *J* = 9.0, 2.5 Hz), 7.28 (d, 1H, *J* = 8.5 Hz), 6.87-6.76 (m, 2H), 6.24 (d, 1H, *J* = 9.0 Hz), 4.01-3.92 (m, 3H), 3.27 (q, 2H, *J* = 7.0 Hz), 1.74-1.70 (m, 2H), 1.47-1.42 (m, 2H), 1.34-1.27 (m, 4H), 1.20 (d, 6H, *J* = 7.0 Hz), 1.14

(t, 3H, *J* = 7.0 Hz), 0.87 (t, 3H, *J* = 7.0 Hz). FAB-MS *m/z*: 385 $[M + H]^+$. Anal. ($C_{23}H_{32}N_2O_3$) C, H, N.

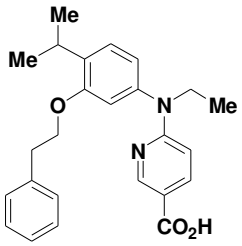
6-[(3-Benzyloxy-4-isopropylphenyl)-ethylamino]nicotinic acid (5k)

According to the general procedure (GP-2), **5k** was obtained by re-crystallization from MeOH in 37% yield as colorless needles.



Mp 178.0-179.0 °C. IR (KBr) cm-[1]: 1694 (CO). ^{1}H NMR (300 MHz, DMSO-d_6) δ: 12.51 (br s, 1H), 8.67 (d, 1H, *J* = 2.5 Hz), 7.76 (dd, 1H, *J* = 9.0, 2.5 Hz), 7.46-7.33 (m, 5H), 7.32 (d, 1H, *J* = 8.0 Hz), 6.95 (d, 1H, *J* = 2.0 Hz), 6.85 (dd, 1H, *J* = 8.0, 2.0 Hz), 6.21 (d, 1H, *J* = 9.0 Hz), 5.13 (s, 2H), 3.97 (q, 2H, *J* = 7.0 Hz), 3.32 (sep, 1H, *J* = 7.0 Hz), 1.22 (d, 6H, *J* = 7.0 Hz), 1.12 (t, 3H, *J* = 7.0 Hz). FAB-MS *m/z*: 391 $[M + H]^+$. Anal. ($C_{24}H_{26}N_2O_3$) C, H, N.

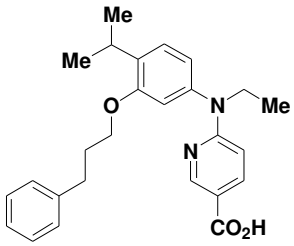
6-[Ethyl-(4-isopropyl-3-phenethyloxyphenyl)amino]nicotinic acid (5l)



According to the general procedure (GP-2), **5l** was obtained by re-crystallization from MeOH in 21% yield as colorless needles.

Mp 183.0-184.0 °C. IR (KBr) cm-[1]: 1677 (CO). ^{1}H NMR (300 MHz, DMSO-d_6) δ: 12.47 (br s, 1H), 8.66 (d, 1H, *J* = 2.5 Hz), 7.77 (dd, 1H, *J* = 9.0, 2.5 Hz), 7.31-7.21 (m, 5H), 7.26 (d, 1H, *J* = 8.0 Hz), 6.85 (d, 1H, *J* = 2.0 Hz), 6.80 (dd, 1H, *J* = 8.0, 2.0 Hz), 6.23 (d, 1H, *J* = 9.0 Hz), 4.17 (t, 2H, *J* = 6.5 Hz), 3.97 (q, 2H, *J* = 7.0 Hz), 3.19 (sep, 1H, *J* = 7.0 Hz), 3.04 (t, 2H, *J* = 6.5 Hz), 1.13 (d, 6H, *J* = 7.0 Hz), 1.13 (t, 3H, *J* = 7.0 Hz). FAB-MS *m/z*: 405 $[M + H]^+$. Anal. ($C_{25}H_{28}N_2O_3$) C, H, N.

6-{Ethyl-[4-isopropyl-3-(3-phenylpropoxy)phenyl]amino}nicotinic acid (5m)



According to the general procedure (GP-2), **5m** was obtained by re-crystallization from MeOH in 77% yield as colorless needles.

Mp 154.5-156.5 °C. IR (KBr) cm-[1]: 1683 (CO). ^{1}H NMR (300 MHz, DMSO-d_6) δ: 8.65 (d, 1H, *J* = 2.0 Hz), 7.75 (dd, 1H, *J* = 9.0, 2.0 Hz), 7.30-7.14 (m, 6H), 6.81-6.77 (m, 2H), 6.23 (d, 1H, *J* = 8.5 Hz), 3.98-3.93 (m, 4H), 2.76 (t, 2H, *J* = 8.0 Hz), 2.06-2.01 (m, 2H), 1.23 (d, 6H, *J* = 7.0 Hz), 1.14 (t, 3H, *J* = 7.0 Hz). FAB-MS *m/z*: 419 $[M + H]^+$. Anal. ($C_{26}H_{30}N_2O_3$) C, H, N.

Luciferase Reporter Gene Assay

Culture of COS-1 cells.

COS-1 cells were maintained in Dulbecco's modified Eagle's medium supplemented with 10% FBS in a humidified atmosphere of 5% CO_2 at 37 ºC.

Luciferase reporter gene assay.

Luciferase reporter gene assays were performed using COS-1 cells transfected with three kinds of vectors, containing a receptor subtype cDNA, a luciferase reporter gene under the control of the appropriate RXR response element, and secreted alkaline phosphatase (SEAP) gene as a background. CRBPII-tk-Luc, tk-PPREx3-Luc, or tk-rBARx3-Luc reporter for RXR, PPAR, LXR and plasmid DNA, respectively, was purified with a QIA filter Plasmid Midi kit. For heterodimer assay, RXRα (0.5 e.q.), a receptor subtype (PPARγ or LXRα, 0.5 e.q.) and partner response element (4 e.q.) were used. COS-1 cells were transfected with QIA Effectene Transfection reagent according to the supplier's protocol. Test compound solutions whose DMSO concentrations were below 1% were added to the suspension of transfected cells, which were seeded at about 4×10^4 cells/mL in 96-well white plates. For vehicle and positive controls, the same volume of DMSO and LGD1069 (**1**) or TIPP-703[4] or carba-T0901317[5] solution in DMSO were added, respectively. After incubation in a humidified atmosphere of 5% CO_2 at 37 ºC for 18 h, some of the medium was used for SEAP and the remaining cells were used for luciferase reporter gene assays with a Steady-Glo Luciferase Assay system (Promega) according to the supplier's protocol. The luciferase activities were normalized using secreted alkaline phosphatase (SEAP) activities. The assays were carried out in triplicate three times.

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Table S1. Combustion analysis data for compounds **5c–5m**

compound	Formula	Calculated			Found		
		C	H	N	C	H	N
5c	$C_{21}H_{26}N_2O_3$	71.16	7.39	7.90	71.12	7.30	7.87
5d	$C_{21}H_{26}N_2O_3$	71.16	7.39	7.90	71.21	7.51	7.86
5e	$C_{22}H_{28}N_2O_3$	71.71	7.66	7.60	71.48	7.64	7.48
5f	$C_{19}H_{21}N_2O_3F_3$	59.68	5.54	7.33	59.47	5.62	7.11
5h	$C_{21}H_{28}N_2O_3$	70.76	7.92	7.86	70.60	8.02	7.83
5i	$C_{22}H_{30}N_2O_3$	71.32	8.16	7.56	71.14	8.27	7.61
5j	$C_{23}H_{32}N_2O_3$	71.84	8.39	7.29	71.68	8.41	7.23
5k	$C_{24}H_{26}N_2O_3$	73.82	6.71	7.17	73.82	6.85	7.10
5l	$C_{25}H_{28}N_2O_3$	74.23	6.98	6.93	74.16	7.09	6.85
5m	$C_{26}H_{30}N_2O_3$	74.61	7.22	6.69	74.84	7.36	6.63