Supporting Information

Novel 2,3-Dihydrobenzofuran-2-carboxylic Acids: Highly Potent and Subtype-Selective PPARα Agonists with Potent Hypolipidemic Activity

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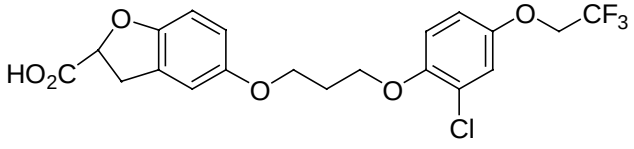
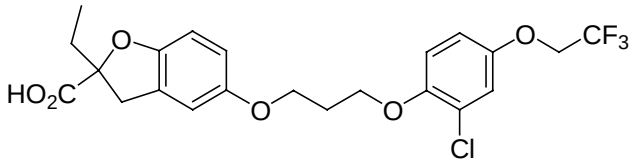
Compounds **22-23**, **26**, **28, 30-31**, **34**, **39** and **41** were prepared according to general procedure C in the experimental section.

5-{3-[2-chloro-4-(2,2,2-trifluoroethoxy)phenoxy]propoxy}-2,3-dihydro-1-benzofuran-2-carboxylic acid (22)



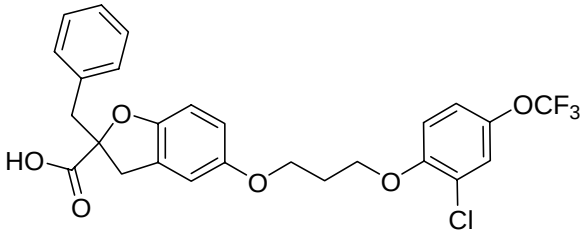
^{1}H NMR (500MHz, $CDCl_3$) δ 7.09 (d, J = 2.5 Hz, 1H), 7.04 (d, J = 9.0, 1H), 6.92 (dd, J = 9.0, 2.5 Hz, 1H), 6.82 (m, 1H), 6.70 (m, 2H), 6.67 (d, J = 8.5 Hz, 1H), 5.15 (dd, J = 10.0, 6.5 Hz, 1H), 4.48 (q, J = 8.5 Hz, 2H), 4.17 (t, J = 6.0 Hz, 2H), 4.15 (t, J = 6.0 Hz, 2H), 3.54 (dd, J = 16.5, 10.0 Hz, 1H), 3.26 (dd, J = 16.5, 6.5 Hz, 1H), 2.20 (m, 2H). LC-Mass (ESI): >97% purity at λ 220 and 254 nm; $[M+1]^+$ calculated for $C_{20}H_{18}ClF_3O_6$ 447.07 and 449.07; found, 447.10 and 449.12.

5-{3-[2-chloro-4-(2,2,2-trifluoroethoxy)phenoxy]propoxy}-2-ethyl-2,3-dihydro-1-benzofuran-2-carboxylic acid (23)



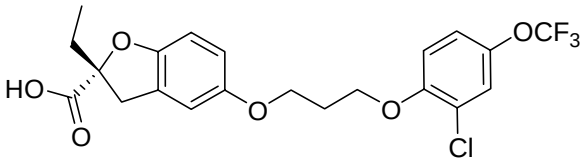
^{1}H NMR (500MHz, $CDCl_3$) δ 7.08 (d, J = 2.5 Hz, 1H), 7.02 (d, J = 9.0, 1H), 6.91 (dd, J = 9.0, 2.5 Hz, 1H), 6.79 (d, J = 2.0Hz, 1H), 6.70 (dd, J = 8.5, 2.0 Hz, 1H), 6.67 (d, J = 8.5 Hz, 1H), 4.46 (q, J = 8.5 Hz, 2H), 4.16 (t, J = 6.0 Hz, 2H), 4.11 (t, J = 6.0 Hz, 2H), 3.48 (d, J = 16.5 Hz, 1H), 3.16 (d, J = 16.5 Hz, 1H), 2.20 (m, 2H), 2.03 (dq, J = 14.5, 7.5 Hz, 1H), 1.94(dq, J = 14.5, 7.5 Hz, 1H), 0.99 (t, J = 7.5 Hz, 3H). LC-Mass (ESI): >97% purity at λ 220 and 254 nm; $[M+1]^+$ calculated for $C_{22}H_{22}ClF_3O_6$ 474.11 and 476.10; found, 474.10 and 476.12

2-benzyl-5-{3-[2-chloro-4-(trifluoromethoxy)phenoxy]propoxy}-2,3-dihydro-1-benzofuran-2-carboxylic acid (26)



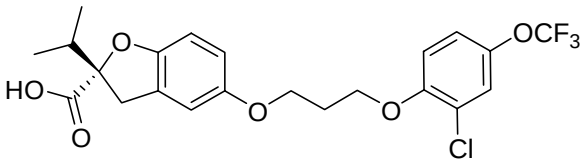
^{1}H NMR (500MHz, CD_3OD) δ 7.25 -7.50 (m, 6H), 7.17 (dd, J = 8.0, 2.5 Hz, 1H), 7.12 (d, J = 8.5 Hz, 1H), 6.78 (m, 1H), 6.69 (dd, J = 8.0, 2.0 Hz, 1H), 6.66 (d, J = 8.5 Hz, 1H), 4.22 (t, J = 6.0 Hz, 2H), 4.11 (t, J = 6.0 Hz, 2H), 3.47 (d, J = 16.0 Hz, 1H), 3.14 (d, J = 16.0 Hz, 1H), 2.40 (d, J =12.0 Hz, 1H), 2.24-2.19 (m, 3H).). LC-Mass (ESI): >97% purity at λ 220 and 254 nm; $[M+1]^+$ calculated for $C_{26}H_{22}ClF_3O_6$ 523.11 and 525.10; found, 523.10 and 525.12.

(2*R*)-2-Ethyl-5-{3-[2-chloro-4-(trifluoromethoxy)phenoxy]propoxy}-2,3-dihydro-1-benzofuran-2-carboxylic acid (28).



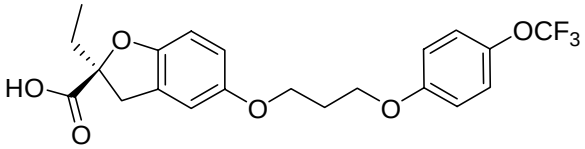
^{1}H NMR (500MHz, CD_3OD) δ 7.32 (d, J = 2.5 Hz, 1H), 7.18 (dd, J = 8.0, 2.5 Hz, 1H), 7.13 (d, J = 8.5 Hz, 1H), 6.77 (br. s, 1H), 6.69 (dd, J=8.0, 2.0 Hz, 1H), 6.67 (d, J = 8.5 Hz, 1H), 4.27 (t, J = 6.0 Hz, 2H), 4.15 (t, J = 6.0 Hz, 2H), 3.49 (d, J = 16.0 Hz, 1H), 3.16 (d, J = 16.0 Hz, 1H), 2.25-2.19 (m, 2H), 2.04 (dq, J = 14.0, 7.5 Hz, 1H), 1.94 (dq, J = 14.0, 7.5 Hz, 1H), 0.99 (t, J = 7.5 Hz, 3H). LC-Mass (ESI): >97% purity at λ 220 and 254 nm; $[M+1]^+$ calculated for $C_{21}H_{20}ClF_3O_6$ 461.09 and 463.09; found, 461.10 and 463.12.

(2*S*)-5-{3-[2-Chloro-4-(trifluoromethoxy)phenoxy]propoxy}-2-isopropyl-2,3-dihydro-1-benzofuran-2-carboxylic acid (30).



^{1}H NMR (500MHz, CD_3OD) δ 7.34 (d, J = 2.0 Hz, 1H), 7.22 (dd, J = 8.0, 2.0 Hz, 1H), 7.17 (d, J = 8.0 Hz, 1H), 6.75 (s, 1H), 6. 65-6.70 (m, 2H), 4.25 (t, J = 6.0 Hz, 2H), 4.11 (t, J = 6.0 Hz, 2H), 3.45 (d, J = 16.5 Hz, 1H), 3.20 (d, J = 16.5 Hz, 1H), 2.25 (m, 2H), 1.05(d, J = 7.5 Hz, 3H), 0.90 (d, J = 7.5 Hz, 3H). LC-Mass (ESI): >97% purity at λ 220 and 254 nm; $[M+1]^+$ calculated for $C_{22}H_{22}ClF_3O_6$ 475.11 and 477.10; found, 475.10 and 477.09.

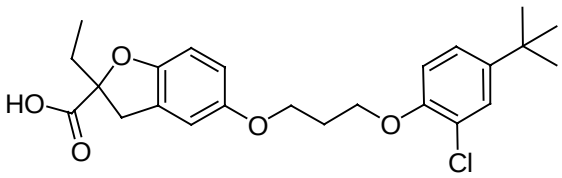
(2*S*)-2-Ethyl-5-{3-[4-(trifluoromethoxy)phenoxy]propoxy}-2,3-dihydro-1-benzofuran-2-carboxylic acid (31).



^{1}H NMR (500MHz, CD_3OD) δ 7.12 (d, J = 8.5 Hz, 1H), 6.90 (d, J = 8.5 Hz, 2H), 6.78 (d, J = 8.5 Hz, 2H), 6.69 (dd, J=8.0, 2.0 Hz, 1H), 6.66 (d, J = 8.5 Hz, 1H), 4.23 (t, J = 6.0 Hz, 2H), 4.15 (t, J = 6.0 Hz,

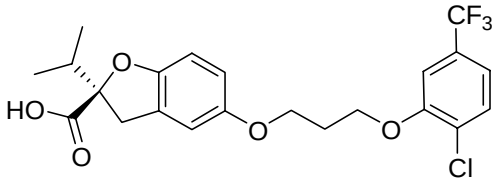
2H), 3.48 (d, J = 16.0 Hz, 1H), 3.16 (d, J = 16.0 Hz, 1H), 2.24-2.19 (m, 2H), 2.05 (dq, J = 14.0, 7.5 Hz, 1H), 1.95 (dq, J = 14.0, 7.5 Hz, 1H), 0.99 (t, J = 7.5 Hz, 3H). LC-Mass (ESI): >97% purity at λ 220 and 254 nm; $[M+1]^+$ calculated for $C_{21}H_{21}F_3O_6$ 427.13; found, 427.10.

5-[3-(4-*tert*-butyl-2-chlorophenoxy)propoxy]-2-ethyl-2,3-dihydro-1-benzofuran-2-carboxylic acid (34)



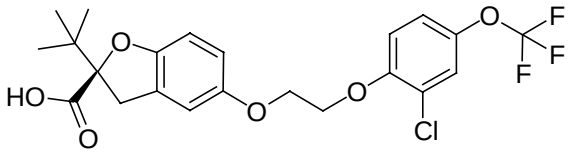
^{1}H NMR (500MHz, CD_3OD) δ 7.35 (d, J = 2.5 Hz, 1H), 7.25 (dd, J = 8.5, 2.0 Hz, 1H), 6.98 (d, J = 8.5 Hz, 1H), 6.80 (d, J = 2.5 Hz, 1H), 6.71 (dd, J = 8.5, 2.5 Hz, 1H), 6.67 (d, J = 8.5 Hz, 1H), 4.18 (t, J = 6.0 Hz, 2H), 4.13 (t, J=6.0 Hz, 2H), 3.47 (d, J = 16.0 Hz, 1H), 3.16 (d, J = 16.0 Hz, 1H), 2.20 (quintet, J = 6.0 Hz, 2H), 2.05 (dq, J = 14.0, 7.5Hz, 1H), 1.94 (dq, J = 14.0, 7.5Hz,1H), 1.28 (s, 9H), 0.99 (t, J = 7.5 Hz, 3H). LC-Mass (ESI): >97% purity at λ 220 and 254 nm; $[M+1]^+$ calculated for $C_{24}H_{29}ClO_5$ 433.17 and 435.17; found, 433.23 and 435.20.

(2*R*)-5-{3-[2-chloro-5-(trifluoromethyl)phenoxy]propoxy}-2-isopropyl-2,3-dihydro-1-benzofuran-2-carboxylic acid (39)



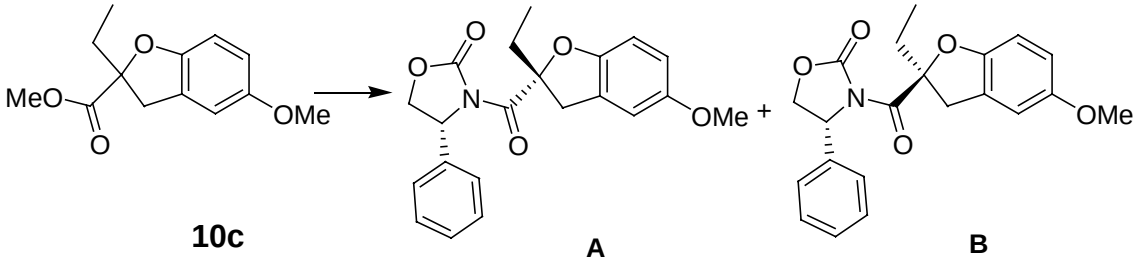
^{1}H NMR (500MHz, CD_3OD) δ 7.35 (d, J = 2.5 Hz, 1H), 7.25 (dd, J = 8.5, 2.0 Hz, 1H), 6.98 (d, J = 8.5 Hz, 1H), 6.80 (d, J = 2.5 Hz, 1H), 6.71 (dd, J = 8.5, 2.5 Hz, 1H), 6.67 (d, J = 8.5 Hz, 1H), 4.18 (t, J = 6.0 Hz, 2H), 4.13 (t, J=6.0 Hz, 2H), 3.47 (d, J = 16.0 Hz, 1H), 3.16 (d, J = 16.0 Hz, 1H), 2.20 (quintet, J = 6.0 Hz, 2H), 2.05 (dq, J = 14.0, 7.5Hz, 1H), 1.94 (dq, J = 14.0, 7.5Hz,1H), 1.28 (s, 9H), 0.99 (t, J = 7.5 Hz, 3H). LC-Mass (ESI): >97% purity at λ 220 and 254 nm; $[M+1]^+$ calculated for $C_{22}H_{22}ClF_3O_5$ 459.11 and 461.11; found, 459.12 and 461.09.

(2*R*)-2-*tert*-butyl-5-{2-[2-chloro-4-(trifluoromethoxy)phenoxy]ethoxy}-2,3-dihydro-1-benzofuran-2-carboxylic acid (41)



^{1}H NMR (600MHz, CD_3OD) δ 7.33 (br.s, 1H), 7.17-7.21 (m, 2H), 6.77 (br. s, 1H), 6.67-6.63 (m, 2H), 4.35-4.32 (m, 2H), 4.26-4.23 (m, 2H), 3.46 (d, J=16.2 Hz, 1H), 3.35 (d, J=16.2 Hz, 1H), 1.04 (s, 9H). LC-Mass (ESI): >97% purity at λ 220 and 254 nm; $[M+1]^+$ calculated for $C_{22}H_{22}ClF_3O_6$ 474.11 and 476.10; found, 474.10 and 476.10.

Determination of the Absolute Stereochemistry of 11c (S-isomer)



10c **A** **B**

The racemic compound **10c** (2.3 g, 10 mmol) in methanol (50 mL) was treated with 3*N* NaOH (10 mL) for 1h. The reaction mixture was acidified with 2*N* HCl and extracted with ethyl acetate. The organic phase was washed with brine, dried over $MgSO_4$ and concentrated. The residue was dissolved in dichloromethane (20 mL) and treated with oxalyl chloride (20 mmol) and 2 drops of DMF at refluxing temperature for 1 h. The volatiles were removed under reduced pressure and the residue was co-evaportated with toluene (2 × 50 mL) to give the corresponding acid chloride of **10c**. The crude acid chloride was added to a solution of the lithium amide of (4*R*)-4-phenyl-1,3-oxazolidin-2-one (20 mmol) (generated with *n*-BuLi) in THF (50 mL) cooled at –75 C. The reaction mixture was warmed to room temperature and quenched with a saturated solution of NH_4Cl. The organic phase was washed with brine, dried ove $MgSO_4$ and concentrated. The residue was purified by chromatography on silica gel eluting with 7:3 hexane:ethyl acetate to give a mixture of diastereomers **A** and **B**, which were separated by preparative HPLC on a RP C-18 column (30 × 300 mm) using 45% acetonitrile in water-containing 0.1% TFA as the eluent.

Isomer **A** (first eluted isomer). ^{1}H NMR (500MHz, $CDCl_3$) δ 7.25-7.38 (m, 5H), 6.79 (dd, J = 8.5, 2.0 Hz, 1H0, 6.68-6.73 (m, 2H), 5.50 (dd, J = 8.5, 4.5 Hz, 1H), 4.74 (t, J = 8.5Hz, 1H), 4.33 (dd, J = 8.5, 4.5 Hz, 1H), 3.78 (s, 3H), 3.58 (d, J = 16.5 Hz, 1H0, 3.44 (d, J = 16.5 Hz, 1H), 2.39 (m, 1H), 2.19 (m, 1H), 0.82 (t, J = 7.0 Hz, 3H).

Isomer **B** (second eluted isomer). ^{1}H NMR (500MHz, $CDCl_3$) δ 7.25-7.39 (m, 5H), 6.78 (dd, J = 8.5, 2.0 Hz, 1H0, 6.65-6.77 (m, 2H), 5.60 (dd, J = 8.5, 4.5 Hz, 1H), 4.84 (t, J = 8.5Hz, 1H), 4.43 (dd, J = 8.5, 4.5 Hz, 1H), 3.87 (s, 3H), 3.65 (d, J = 16.5 Hz, 1H0, 3.54 (d, J = 16.5 Hz, 1H), 2.29 (m, 1H), 2.09 (m, 1H), 0.85 (t, J = 7.0 Hz, 3H).

X-Ray Crystal Structure of Isomer A

Crystals suitable for diffraction studies were grown from a mixture of acetonitrile/water. The crystals obtained are orthorhombic with space group $P2_12_12_1$ and cell constants of a = 6.108(2), b = 11.040(3), c = 26.546(7) Å, with V = 1790(1) Å^3, and Z = 4. The calculated density is 1.363 g cm^{-3}· All diffraction measurements were made using monochromatized Mo K_α radiation (λ = 0.71073 Å) on a CCD area-detector equipped diffractometer, at T = 100 K, to a θ limit of 26.39°. There are 3674 unique reflections out of 19712 measured with 2464 observed at the $I \geq 2\sigma$ (I) level.The structure was solved by direct methods and refined using full-matrix least-squares on F^2 using 246 parameters and all unique reflections. The refinement converged with agreement statistics of R = 0.041, wR = 0.066, S = 0.93 with $(\Delta/\sigma)_{max}$ = 0.01.

A computer-generated perspective view of isomer **A** is shown in Figure 1. Lists of interatomic distances and angles are given in Tables 1 and 2, respectively. These data established that isomer **A** has *R* configuration at the chiral center. Since isomer **B** can be converted to **11c** derived from the Sharpless AD reaction in Scheme 3, this established compound **11c** in Scheme 3 has the *S* configuration.

Figure 1

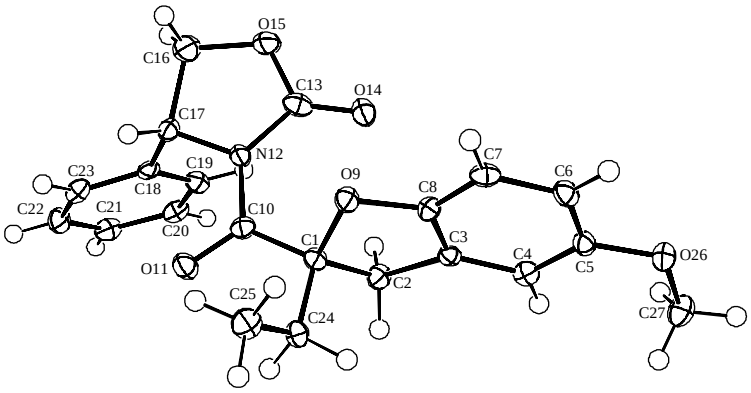


Table 1 Interatomic Distances (Å)

O9—C8	1.396(2)	C21—C22	1.378(3)
O9—C1	1.460(2)	C21—C20	1.393(3)
O15—C13	1.348(3)	C3—C2	1.510(3)
O15—C16	1.455(3)	C18—C23	1.388(3)
O26—C5	1.384(2)	C18—C19	1.390(3)
O26—C27	1.440(3)	C18—C17	1.518(3)
O11—C10	1.224(2)	C20—C19	1.387(3)
O14—C13	1.194(3)	C2—C1	1.553(3)
C4—C5	1.387(3)	C23—C22	1.388(3)
C4—C3	1.395(3)	N12—C10	1.393(3)
C13—N12	1.406(3)	N12—C17	1.478(3)
C8—C7	1.378(3)	C25—C24	1.528(3)
C8—C3	1.379(3)	C24—C1	1.535(3)
C7—C6	1.397(3)	C1—C10	1.527(3)
C5—C6	1.392(3)	C16—C17	1.530(3)

Table 2. Interatomic Angles (deg.)

C8—O9—C1	105.38(16)	C3—C2—C1	99.71(16)
C13—O15—C16	110.84(18)	C22—C23—C18	120.6(2)

C5—O26—C27	116.48(17)	C10—N12—C13	130.33(18)
C5—C4—C3	118.1(2)	C10—N12—C17	117.90(18)
O14—C13—O15	122.9(2)	C13—N12—C17	111.52(18)
O14—C13—N12	128.9(2)	C5—C6—C7	120.8(2)
O15—C13—N12	108.24(19)	C20—C19—C18	120.5(2)
C7—C8—C3	122.7(2)	C25—C24—C1	115.57(18)
C7—C8—O9	124.5(2)	O9—C1—C10	108.26(17)
C3—C8—O9	112.80(18)	O9—C1—C24	108.17(16)
C8—C7—C6	117.2(2)	C10—C1—C24	110.40(18)
O26—C5—C4	123.6(2)	O9—C1—C2	106.49(16)
O26—C5—C6	115.24(19)	C10—C1—C2	114.32(17)
C4—C5—C6	121.1(2)	C24—C1—C2	108.97(18)
C22—C21—C20	120.0(2)	O15—C16—C17	105.89(18)
C8—C3—C4	120.1(2)	N12—C17—C18	113.36(17)
C8—C3—C2	108.89(19)	N12—C17—C16	100.16(17)
C4—C3—C2	131.0(2)	C18—C17—C16	113.32(18)
C23—C18—C19	119.06(19)	C21—C22—C23	120.0(2)
C23—C18—C17	118.74(19)	O11—C10—N12	117.37(19)
C19—C18—C17	122.12(19)	O11—C10—C1	120.7(2)
C19—C20—C21	119.8(2)	N12—C10—C1	121.9(2)

Results of elemental analysis

compound	formula	calculated		found	
		C%	H%	C%	H%
21	$C_{21}H_{20}ClF_3O_6$	54.73	4.37	54.77	4.41
24	$C_{24}H_{26}ClF_3O_5$	59.20	5.38	59.25	5.43
25	$C_{21}H_{17}ClF_6O_5$	50.57	3.44	50.60	3.47
27	$C_{21}H_{20}ClF_3O_6$	54.73	4.37	54.70	4.31
29	$C_{22}H_{22}ClF_3O_6$	55.65	4.67	55.53	4.41
32	$C_{24}H_{27}F_3O_5S$	59.49	5.62	59.55	5.69
33	$C_{21}H_{20}ClF_3O_5$	56.70	4.53	56.65	4.50
35	$C_{21}H_{20}ClF_3O_5S$	52.89	4.23	52.85	4.17
36	$C_{25}H_{31}ClO_5$	67.18	6.99	67.22	7.02
37	$C_{22}H_{22}ClF_3O_5$	57.59	4.83	58.06	5.06
38	$C_{23}H_{24}ClF_3O_5$	58.42	5.12	58.44	5.14
40	$C_{21}H_{20}ClF_3O_6$	54.73	4.37	54.80	4.41
41	$C_{21}H_{20}ClF_3O_6$	54.73	4.37	54.71	4.17