Table 3. CBt-PMN 30 mg/kg/day 28 日間薬物経口反復経口投与による各臓器の重量

	Males		Females	
	Vehicle	CBt-PMN	Vehicle	CBt-PMN
Weight (g)	324.3 ± 8.7	337.8 ± 4.6	213.4 ± 2.1	216.1 ± 10.7
Brain (g)	2.0 ± 0.1	2.0 ± 0.1	1.8 ± 0.0	1.7 ± 0.0
Liver (g)	9.7 ± 0.6	9.7 ± 0.4	5.9 ± 0.2	6.2 ± 0.4
Kidney (g)	2.5 ± 0.1	2.6 ± 0.1	1.6 ± 0.0	1.5 ± 0.1
Spleen (g)	0.6 ± 0.0	0.7 ± 0.1	0.4 ± 0.0	0.5 ± 0.0
Testis (g)	3.9 ± 0.2	4.5 ± 0.1 *		

データ は平均 ± s.e.m. ; 有意差: * $p < 0.05$ vs. vehicle, $n = 6$.

Table 4. CBt-PMN 30 mg/kg/day でのラット 28 日間薬物経口反復経口投与による血液生化学データ [a]

	Males			Females		
	vehicle	CBt-PMN	Reference[d]	vehicle	CBt-PMN	Reference[d]
WBC ($\times 10^2$/mL)[b]	71.7 ± 4.2	92.5 ± 18.6	–	76.5 ± 9.3	72.5 ± 7.5	–
RBC ($\times 10^4$/mL)[b]	741.8 ± 17.4	746.2 ± 11.7	–	778.3 ± 18.1	767.3 ± 12.0	–
PLT ($\times 10^4$/mL)[b]	123.3 ± 5.7	139.9 ± 13.1	–	129.3 ± 4.9	140.3 ± 7.1	–
HGB (g/dL)[b]	14.8 ± 0.2	14.4 ± 0.2	14.4 – 16.0	14.7 ± 0.2	14.5 ± 0.2	13.7 – 15.7
HCT (%)[b]	45.5 ± 0.6	45.0 ± 0.7	41.2 – 47.3	45.7 ± 0.8	44.8 ± 0.6	9.6 – 46.0
MCV (fL)[b]	61.4 ± 0.8	60.4 ± 0.4	53.0 – 59.5	58.7 ± 0.6	58.4 ± 0.6	53.6 – 58.1
MCH (pg)[b]	20.0 ± 0.2	19.3 ± 0.2 *	18.3 – 20.0	18.9 ± 0.3	18.9 ± 0.2	18.6 – 20.0
MCHC (g/dL)[b]	32.5 ± 0.1	31.9 ± 0.2 *	32.7 – 35.7	32.2 ± 0.3	32.2 ± 0.1	32.8 – 36.2
AST (U/I)[c]	65.7 ± 3.5	75.2 ± 2.8 *	87.0 – 114.0	60.2 ± 1.6	64.8 ± 2.0 *	85.0 – 123.0
ALT (U/I)[c]	27.8 ± 1.4	37.7 ± 2.0 **	28.0 – 40.0	21.5 ± 2.1	29.3 ± 1.9 **	25.0 – 36.0
γ-GTP (U/I)[c]	8.2 ± 0.4	8.3 ± 0.2	0.0 – 1.0	8.3 ± 0.2	8.7 ± 0.3	0.0 – 0.4
ALP (U/I)[c]	585.7 ± 34.3	607.5 ± 39.7	–	434.3 ± 50.7	476.5 ± 75.2	–
CRE (mg/dL)[c]	0.2 ± 0.0	0.2 ± 0.0	0.5 – 0.6	0.3 ± 0.0	0.3 ± 0.0	0.5 – 0.6
BUN (mg/dL)[c]	16.4 ± 0.7	11.8 ± 0.4 **	13.0 – 16.0	13.8 ± 0.7	14.5 ± 0.9	11.0 – 16.0
TG (mg/dL)[c]	44.8 ± 2.8	50.8 ± 2.9	61.0 – 99.0	55.0 ± 4.9	77.5 ± 5.5 **	42.0 – 74.0
TCHO (mg/dL)[c]	56.2 ± 7.5	34.0 ± 4.5 *	54.0 – 74.0	25.7 ± 3.7	44.8 ± 10.6	67.0 – 87.0
GLU (mg/dL)[c]	181.2 ± 16.1	149.8 ± 17.7	112.0 – 176.0	118.3 ± 5.7	145.5 ± 10.6 *	113.0 – 185.0

a. データ は平均 ± s.e.m. ; 有意差: * $p < 0.05$ vs. vehicle. ** $p < 0.01$ vs. vehicle.

b. 測定は pocH-100i (Sysmex)を用いた.

c. 測定は Fuji Dry Chem 4000V (Fuji Medical Co., Tokyo, Japan) を用いた.

d. Charles River®より供給されている Crl:CD(SD) Rats の Clinical Laboratory Parameters (CRL_Mar,2006) .

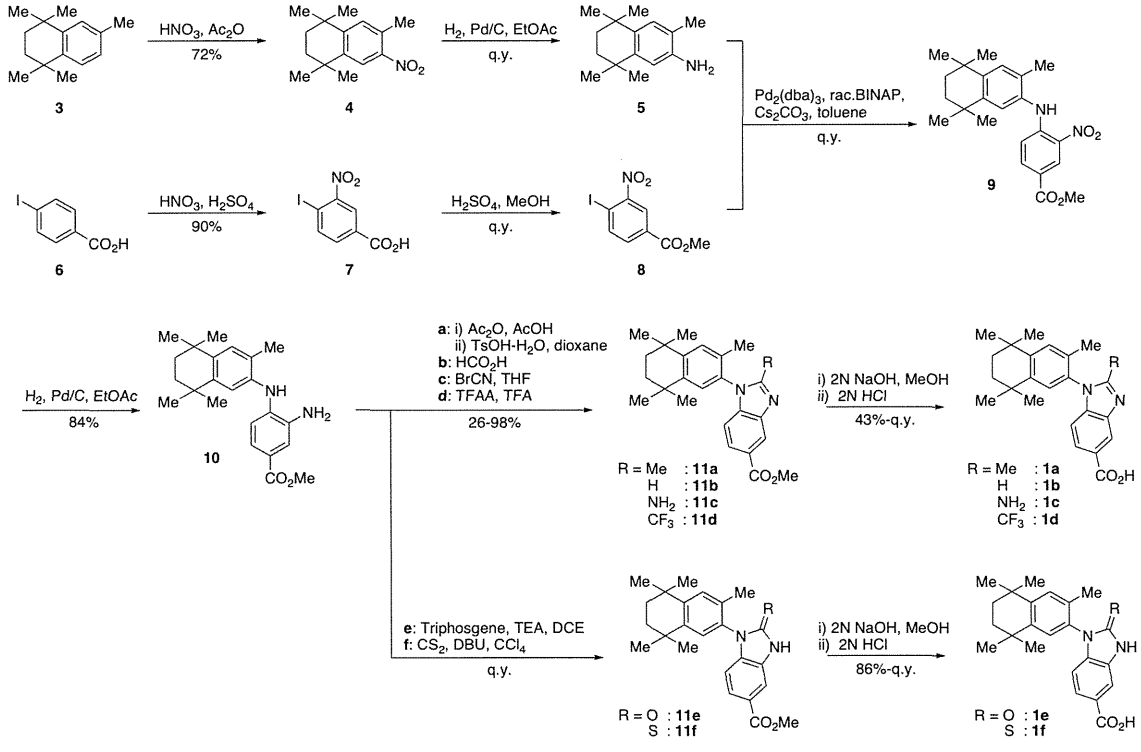
２．RXRパーシャルアゴニスト CBt-PMNのRXRパーシャルアゴニスト活性発現メカニズムの解明

２−１）化合物の合成

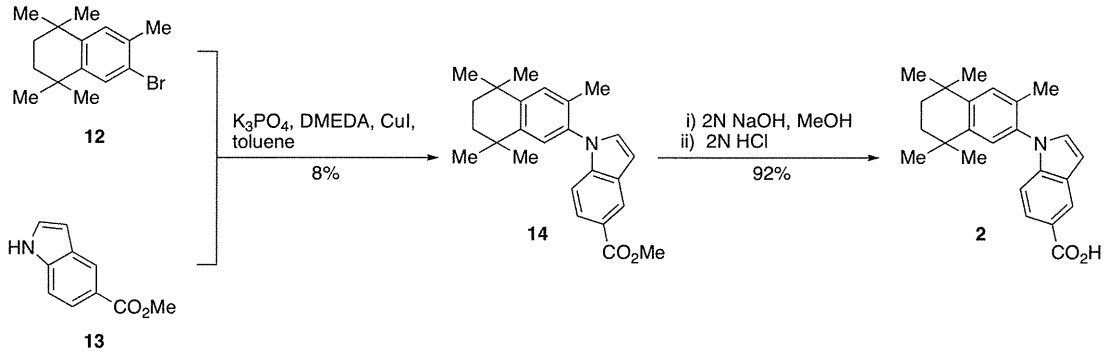
合成は，Scheme1 および 2 にしたがい行った．

文献既知の方法を用いてペンタメチルテトラリン **3** を合成し，その後のニトロ化と接触還元によりアミノ体 **5** を得た．一方，酸性部位に相当する部分を，市販の 4-iodobenzoic acid (**6**)を出発原料にニトロ化とエステル化により **8** とした．化合物 **5** と **8** を Buchwald のカップリング反応により **9** とし，その後接触還元を行うことで **10** を得た．化合物 **10** を共通中間体として，酢酸を用いた環化により **11a** を，ギ酸を用いた環化により **11b** を，ブロモシアンを用いることで **11c** を，トリフルオロ酢酸無水物を用いることで **11d** とした．さらに，**10** からトリホスゲン，二硫化炭素を用いた閉環により，カルボニル基を有する **11e** および **11f** を得た．エステル体である化合物 **10** ならびに **11** に対しエステル基の脱保護を行うことで，目的化合物 **1a–f** を得た（Scheme 1）．

Scheme 1



Scheme 2



また，インドール構造を有する **2** を，Scheme 2 により得た.

General methods.

Melting points were determined with a Yanagimoto hot-stage melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a VarianVXR-300 (300 MHz), JEOL JMN-AL-300 (300 MHz) or VarianVXR-500 (500 MHz) spectrometer. Elemental analysis was carried out with a Yanagimoto MT-5 CHN recorder elemental analyzer and results were within ±0.4% of the theoretical. FAB-MS was carried out with a VG70-SE.

HPLC conditions

The HPLC system used in this study was a Shimadzu liquid chromatographic system (Kyoto, Japan) consisting of an LC-10AD pump, SPD-10AV UV-Vis spectrophotometric detector, CTO-10AS column oven and C-R5A Chromatopac. The samples (each 20 μL) were injected. The chromatographic analyses were carried out on an Inertsil ODS-3 (4.6 i.d. x 250 mm, 5 μm, GL Sciences, Tok yo, Japan) with a guard column of Inertsil ODS-3 (4.0 i.d. x 10 mm, 5 μm, GL Sciences) kept at 40°C, using methanol : 25 mM ammonium acetate (adjusted with acetic acid to pH 5.0) (80:20 or 70:30, v/v) as a mobile phase. The flow rate was 0.7 mL/min and the absorbance at 278 nm was monitored.

1,1,4,4,6-Pentamethyl-7-nitro-1,2,3,4-tetra hydronaphthalene (4).

To an ice cooled solution of **3** (2.0 g, 9.9 mmol) in Ac_2O (10 mL) was added *conc.*HNO_3 (0.75 mL) dropwise. The reaction mixture was poured into ice, extracted with EtOAc (50 mL × 2). The organic layer was washed with H_2O (50 mL × 2) and brine (50 mL), then dried over $MgSO_4$. The solution was evaporated under reduced pressure. The residue was

re-crystallized from EtOAc/hexane to yield 4.5 g of **4** as pale yellow powder (72%).

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.96 (1H, s), 7.21 (1H, s), 2.56 (3H, s), 1.70 (4H, s), 1.30 (6H, s), 1.29 (6H, s).

3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-naphthalen-2-ylamine (5).

To a solution of **4** (2.5 g, 10 mmol) in EtOAc (20 mL) was added Pd/C (catalyst amount). The mixture was stirred at r.t. under H_2 atmosphere for 7.0 hr. The reaction mixture was filtrated through Celite. The solution was evaporated under reduced pressure to yield 2.2 g of **5** as pale yellow solid (q.y.).

^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.97 (1H, s), 6.61 (1H, s), 3.45 (2H, br s), 2.14 (3H, s), 1.64 (4H, s), 1.24 (6H, s), 1.24 (6H, s).

4-Iodo-3-nitrobenzoic acid (7).

To a solution of **6** (2.5 g, 10 mmol) in *conc.*H_2SO_4 (14 mL) were added a solution of *conc.*HNO_3 (4.9 mL) and *conc.*H_2SO_4 (4.3 mL) dropwise. The mixture was stirred at r.t. over night. The reaction mixture was poured into ice (50 mL). The mixture was filtered, then the residue was dried to yield 2.6 g of **7** as pale yellow powder (90%).

^{1}H NMR(500 MHz, $CDCl_3$) δ: 8.49 (1H, s), 8.19 (1H, d, J = 8.0 Hz), 7.92 (2H, d, J = 8.0 Hz).

4-Iodo-3-nitrobenzoic acid methyl ester (8).

To a solution of **7** (2.6 g, 9.0 mmol) in dry MeOH (10 mL) was added a *conc.*H_2SO_4 (1.9 mL) dropwise. The mixture was stirred at r.t. over night. The reaction mixture was neutralized with *sat.*$NaHCO_3$ (10 mL), extracted with EtOAc (40 mL × 3). The organic layer was washed with H_2O (40 mL) and brine (50 mL), then dried over $MgSO_4$. The solution was evaporated under reduced pressure. The residue was re-crystallized from MeOH to yield 2.8 g of **8** as yellow needles (q.y.).

^{1}H NMR(500 MHz, $CDCl_3$) δ: 8.45 (1H, d, J = 2.0 Hz), 8.15 (1H, d, J = 8.0 Hz), 7.88 (1H, dd, J = 8.0, 2.0 Hz), 3.97 (3H, s).

3-Nitro-4-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-naphthalen-2-ylamino)-benzoic acid methyl ester (9).

To a solution of **5** (0.83 g, 3.8 mmol) and **8** (1.2 g, 3.8 mmol) in dry toluene (4.0 mL) were added $Pd_2(dba)_3$ (170 mg, 0.19 mmol), (±)-BINAP (180 mg, 0.28 mmol) and Cs_2CO_3 (3.1 g, 9.5 mmol). The mixture was refluxed at 110°C under Ar atmosphere over night. The reaction mixture was filtrated through Celite. The filtrate was evaporated under reduced pressure. The residue was purified by flash column chromatography (EtOAc : *n*-hexane = 1 : 15) to yield 1.3 g of **9** as yellow foam (q.y.).

^{1}H NMR(300 MHz, $CDCl_3$) δ: 9.63 (1H, br s),

8.93 (1H, d, J = 2.0 Hz), 7.93 (1H, dd, J = 9.0, 2.0 Hz), 7.24 (1H, s), 7.17 (1H, s), 6.82 (1H, d, J = 9.0 Hz), 3.91 (3H, s), 2.19 (3H, s,) 1.70 (4H, s), 1.31 (6H, s), 1.25 (6H, s).

3-Amino-4-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-naphthalen-2-ylamino)-benzoic acid methyl ester (10).

To a solution of **9** (0.50 g, 1.3 mmol) in EtOAc (2.0 mL) was added Pd/C (catalyst amount). The mixture was stirred at r.t. under H_2 atmosphere over night. The reaction mixture was filtrated through Celite. The filtrate was evaporated under reduced pressure to yield 0.39 g of **10** as white solid (84%).

^{1}H NMR(300 MHz, $CDCl_3$) δ: 7.49 (1H, s), 7.48 (1H, d, J = 8.0 Hz), 7.13 (1H, s), 6.96 (1H, s), 6.83 (1H, d, J = 8.0 Hz), 5.39(1H, br s), 3.87 (3H, s), 3.55(2H, br s), 2.19 (3H, s), 1.67 (4H, s,), 1.28 (6H, s), 1.21 (6H, s).

2-Methyl-1-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-1H-benzoimidazole-5-carboxylic acid methyl ester (11a).

To a solution of **10** (150 mg, 0.40 mmol) in AcOH (5.0 mL) was added Ac_2O (0.50 mL). The mixture was stirred at r.t. for 15 min. The reaction mixture was poured into ice-cooled *sat.*$NaHCO_3$ (70 mL), extracted with EtOAc (50 mL × 2). The organic layer was washed with *sat.*$NaHCO_3$ (70 mL), then dried over $MgSO_4$. The solution was evaporated under reduced pressure.

The residue (170 mg) and $TsOH \cdot H_2O$ (190 mg, 1.0 mmol) were solved into dioxane (5.0 mL). The solution was refluxed at 120°C overnight. The reaction mixture was poured into H_2O (40 mL), extracted with EtOAc (30 mL × 2). The organic layer was washed with H_2O (50 mL) and brine (30 mL), then dried over $MgSO_4$. The solution was evaporated under reduced pressure to yield 150 mg of **11a** as brown solid (98%).

^{1}H NMR(500 MHz, $CDCl_3$) δ: 8.46 (1H, d, J = 1.5 Hz), 7.92 (1H, dd, J = 8.5, 1.5 Hz), 7.30 (1H, s), 7.12 (1H, s), 6.98 (1H, s), 3.95 (3H, s), 2.42 (3H, s), 1.90 (3H, s), 1.74 (4H, s), 1.36 (6H, s), 1.26 (6H, s).

1-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetra-hydronaphthalen-2-yl)-1*H*-benzimidazole-5- carboxylic acid methyl ester (11b).

Compound **10** (150 mg, 0.40 mmol) was added formic acid (1.0 mL). The mixture was refluxed at 100°C for 4.0 hr. The reaction mixture was poured into 2N NaOH (10 mL), extracted with EtOAc (40 mL × 3). The organic layer was collected, washed with brine (10 mL), then dried over $MgSO_4$. The solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography (EtOAc : *n*-hexane = 1 : 4) to yield 140 mg of **11b** as colorless powder (93%).

^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.61 (1H, d, J = 2.0 Hz), 8.06 (1H, s), 8.03 (1H, dd, J = 9.0,

2.0 Hz), 7.33 (1H, s), 7.22 (1H, s), 7.21 (1H, d, J = 9.0 Hz), 3.98 (3H, s), 2.05 (3H, s), 1.75 (4H, s), 1.36 (6H, s), 1.29 (6H, s).

2-Amino-1-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-1*H*-benzimidazole-5-carboxylic acid methyl ester (11c)

To a solution of BrCN (48 mg, 0.45 mmol) in THF (5.0 mL) was added **10** (110 mg, 0.30 mmol). The mixture was stirred at r.t. under Ar atmosphere for 12 hr. The reaction mixture was poured into 2N NaOH (10 mL), extracted with EtOAc (60 mL × 3). The organic layer was washed with brine (20 mL) and H_2O (40 mL), then dried over $MgSO_4$. The solution was evaporated under reduced pressure. The residue was purified by flash column chromatography (CH_2Cl_2 : MeOH = 50 : 1) to yield 30 mg of **11d** as white powder (26%).

^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.14 (1H, d, J = 1.5 Hz), 7.77 (1H, dd, J = 8.5, 1.5 Hz), 7.34 (1H, s), 7.23 (1H, s), 6.81 (1H, d, J = 8.5 Hz), 3.92 (3H, s), 2.03 (3H, s), 1.74 (4H, s), 1.36 (3H, s), 1.34 (3H, s), 1.28 (3H, s), 1.27 (3H, s).

1-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydronaphthalen-2-yl)-2-trifluoromethyl-1*H*-benzimidazole-5-carboxylic acid methyl ester (11d)

To a solution of **10** (520 mg, 1.4 mmol) in TFA (8.0 mL) was added TFAA (1.0 mL, 7.0 mmol). The mixture was stirred at r.t. for 1.0 hr. The reaction mixture was poured into *sat.*$NaHCO_3$ (30 mL), extracted with EtOAc (50 mL × 3). The organic layer was washed with H_2O (50 mL) and brine (10 mL), then dried over $MgSO_4$. The solution was evaporated under reduced pressure. The residue was purified by flash column chromatography (EtOAc : *n*-hexane = 1 : 20) to yield 590 mg of **11d** as white solid (95%).

^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.68 (1H, d, J = 1.5 Hz), 8.10 (1H, dd, J = 9.0, 1.5 Hz), 7.28 (1H, d, J = 8.5 Hz), 7.20 (1H, s), 7.12 (1H, dd, J = 9.0, 0.5 Hz), 3.97 (3H, s), 1.89 (3H, s), 1.73 (4H, s), 1.35 (6H, s), 1.25 (6H, s).

2-Oxo-1-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-2,3-dihydro-1*H*-benzimidazole-5-carboxylic acid methyl ester (11e).

To a solution of **10** (110 mg, 0.30 mmol) in 1,2-dichloroethane (6.0 mL) were added Et_3N (70 μL, 0.50 mmol) and triphosgene (59 mg, 0.20 mmol). The mixture was refluxed at 110°C overnight. The reaction mixture was poured into H_2O (40 mL), extracted with EtOAc (30 mL × 2). The organic layer was washed with H_2O (60 mL), then dried over $MgSO_4$. The solvent was evaporated under reduced pressure to yield 120 mg of **11e** as pale yellow solid (q.y.).

^{1}H NMR(500 MHz, $CDCl_3$) δ: 11.35 (1H, s), 7.67 (1H, dd, J = 8.0, 1.5 Hz), 7.60 (1H, d, J

= 1.5 Hz), 7.39 (1H, s), 7.27 (1H, s), 6.66 (1H, d, J = 8.0 Hz), 3.84 (3H, s), 2.00 (3H, s), 1.68 (4H, s), 1.31 (3H, s), 1.30 (3H, s), 1.23 (3H, s), 1.23 (3H, s).

1-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-2-thioxo-2,3-dihydro-1*H*-benzimidazole-5-carboxylic acid methyl ester (11f).

To a solution of **10** (110 mg, 0.30 mmol) in CCl_4 (5.0 mL) were added CS_2 (180 μL, 3.0 mmol) and DBU (45 μL, 0.30 mmol). The mixture was refluxed at 70°C for 2.5 hr. The reaction mixture was poured into H_2O (50 mL), extracted with EtOAc (30 mL × 2). The organic layer was washed with H_2O (50 mL) and brine (30 mL), then dried over $MgSO_4$. The solvent was evaporated under reduced pressure to yield 120 mg of **11f** as pale yellow foam (q.y.).

^{1}H NMR(300 MHz, $CDCl_3$) δ: 10.41 (1H, br s), 7.95 (1H, d, J = 1.5 Hz) , 7.88 (1H, dd, J = 8.5, 1.5 Hz), 7.32 (1H, s), 7.19 (1H, s), 6.78 (1H, d, J = 8.5 Hz), 3.94 (3H, s), 2.06 (3H, s), 1.73 (4H, s), 1.36 (3H, s), 1.34 (3H, s), 1.30 (3H, s), 1.26 (3H, s).

2-Methyl-1-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-1*H*-benzimidazole-5-carboxylic acid (1a).

To a solution of **11a** (150 mg, 0.40 mmol) in MeOH (10 mL) was added 2N NaOH (10 mL). The mixture was stirred at 60°C for 20 min. The reaction mixture was poured into 1N HCl (20 mL), extracted with EtOAc (30 mL × 2). The organic layer was washed with H_2O (40 mL) and brine (30 mL), dried over $MgSO_4$. The solvent was evaporated under reduced pressure to yield 140 mg of **1a** as brown solid (93%). The residue was re-crystallized from MeOH to yield 84 mg of colorless powder.

Mp 295.0°C; ^{1}H NMR(300 MHz, DMSO-d_6) δ: 12.71 (1H, br s), 8.20 (1H, s), 7.81 (1H, d J = 8.5 Hz), 7.47 (1H, s), 7.36 (1H, s), 6.94 (1H, d, J = 8.5 Hz), 2.32 (3H, s), 1.85 (3H, s), 1.69 (4H, s), 1.33 (6H, s), 1.25 (3H, s), 1.24 (3H, s); IR (KBr): 2957-2925 (OH), 1701 (CO) cm^{-1}; FAB-MS *m/e*: 377 $[M+H]^+$; *Anal.* Calcd for $C_{24}H_{28}N_2O_2 \cdot 1/4H_2O$: C, 75.66; H, 7.54; N, 7.35. Found: C, 75.70; H, 7.42; N, 7.36.

1-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydronaphthalen-2-yl)-1*H*-benzimidazole-5-carboxylic acid (1b).

To a solution of **11b** (140 mg, 0.40 mmol) in MeOH (3.0 mL) and THF (1.0 mL) was added 2N NaOH (2.0 mL). The mixture was stirred at 60 °C for 2.0 hr. The solution was poured into 2N HCl (2,0 mL) and extracted with EtOAc (40× 3 mL). The organic layer was collected, washed with brine (20 mL), then dried over MgSO4. The mixture was evaporated under reduced pressure to yield 180 mg of **1b** (q.y.). The residue was re-crystallized from EtOAc/*n*-hexane to yield

110 mg of colorless powder.

Mp: 255.0-257.0°C; HPLC: 13 min. 99% purity (MeOH:$AcONH_4$ = 70:30); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.76 (1H, d, *J* = 2.0 Hz), 8.17 (1H, s), 8.11 (1H, dd, *J* = 8.0, 2.0 Hz), 7.33 (1H, s), 7.27 (1H, d, *J* = 8.0 Hz), 7.26 (1H, s), 7.23 (1H, s), 2.06 (3H, s), 1.74 (4H, s), 1.36 (6H, s), 1.29 (6H, s); FAB-MS *m/z*: 363 $[M + H]^+$; Anal. Calcd for $C_{23}H_{26}N_2O_2$·1/4EtOAc: C, 74.97; H, 7.34; N, 7.29. Found: C, 75.06; H, 7.74; N, 7.74.

2-Amino-1-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-1*H*-benzimidazole-5-carboxylic acid (1c)

To a solution of **11c** (95 mg, 0.24 mmol) in MeOH (2.0 mL) and THF (2.0 mL) was added 2N NaOH (2.0 mL). The mixture was stirred at 60 °C for 0.5 hr. The solution was poured into 2N HCl (4.0 mL) and extracted with EtOAc (70× 3 mL). The organic layer was collected, washed with brine (30 mL) and H_2O (30 mL), then dried over $MgSO_4$. The mixture was evaporated under reduced pressure. The residue was purified by flash column chromatography (CH_2Cl_2 : MeOH = 10 : 1) to yield 110 mg of **1c** as white crystal (q.y.).

Mp: 265.3-266.0°C decomp.; HPLC: 25 min. 95% purity (MeOH:$AcONH_4$ = 70:30); ^{1}H NMR (300 MHz, DMSO-d_6) δ: 12.95 (1H, br s), 8.36 (2H, br s), 7.98 (1H, s), 7.79 (1H, dd, *J* = 8.5, 1.0 Hz), 7.53 (1H, s), 7.50 (1H, s), 6.79 (1H, d, *J* = 8.5 Hz), 2.01 (3H, s), 1.69 (4H, s), 1.33 (6H, s), 1.25 (3H, s), 1.23 (3H, s); FAB-MS *m/z*: 378 $[M + H]^+$.

1-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-2-trifluoromethyl-1*H*-benzimidazole-5-carboxylic acid (1d)

To a solution of **11d** (50 mg, 0.11 mmol) in MeOH (1.0 mL) and THF (2.0 mL) was added 2N NaOH (1.0 mL). The mixture was stirred at 60 °C for 1.0 hr. The solution was poured into 2N HCl (2.0 mL) and extracted with EtOAc (40× 3 mL). The organic layer was collected, washed with brine (10 mL) and H_2O (10 mL), then dried over $MgSO_4$. The mixture was evaporated under reduced pressure. The residue was re-crystallized from EtOAc/*n*-hexane to yield 21 mg of colorless powder (43%).

^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.75 (1H, d, *J* = 1.5 Hz), 8.15 (1H, dd, *J* = 8.5, 1.5 Hz), 7.30 (1H, s), 7.21 (1H, s), 7.15 (1H, d, *J* = 9.5 Hz), 1.91 (3H, s), 1.74 (4H, s), 1.36 (6H, s), 1.25 (6H, s); FAB-MS m/e: 431 [M+H]+; Anal. Calcd for $C_{24}H_{25}F_3N_2O_2$: C, 66.96; H, 5.85; N, 6.51. Found: C, 6.93; H, 6.11; N, 6.41.

2-Oxo-1-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-2,3-dihydro-1*H*-benzimidazole-5-carboxylic acid (1e).

To a solution of **11d** (120 mg, 0.30 mmol) in MeOH (10 mL) was added 2N NaOH (10 mL). The mixture was stirred at 60°C for 30

min. The reaction mixture was poured into 1N HCl (20 mL), extracted with EtOAc (30 mL × 2). The organic layer was washed with H_2O (40 mL) and brine (30 mL), then dried over $MgSO_4$. The mixture was evaporated under reduced pressure to yield 110 mg of **1e** as pale yellow solid (q.y.). The residue was re-crystallized from EtOAc/*n*-hexane to yield 45 mg of colorless powder.

Mp >300°C; ^{1}H NMR(300 MHz, DMSO-d_6) δ: 12.69 (1H, br s), 11.29 (1H, s), 7.64 (1H, dd, J = 8.0, 1.5 Hz), 7.59 (1H, d, J = 1.5 Hz), 7.39 (1H, s), 7.26 (1H, s), 6.63 (1H, d, J = 8.0 Hz), 2.01 (3H, s), 1.68 (4H, s), 1.31 (3H, s), 1.30 (3H, s), 1.24 (3H, s), 1.23 (3H, s); IR (KBr): 2959-2926 (OH), 1712 (CO), 1685 (CO) cm^{-1}; FAB-MS *m/e*: 379 $[M+H]^+$; *Anal.* Calcd for $C_{23}H_{26}N_2O_3 \cdot 1/4H_2O$: C, 72.13; H, 6.97; N, 7.31. Found: C, 72.40; H, 7.05; N, 7.18.

1-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetra-hydro-2-naphthyl)-2-thioxo-2,3-dihydro-1*H*-benzimidazole-5-carboxylic acid (1f).

To a solution of **11f** (120 mg, 0.30 mmol) in MeOH (3.0 mL), was added 2N NaOH (3.0 mL). The mixture was stirred at 60°C for 15 min. The reaction mixture was poured into 2N HCl (30 mL), extracted with EtOAc (20 mL × 2). The organic layer was washed with H_2O (30 mL × 2) and brine (30 mL), then dried over $MgSO_4$. The mixture was evaporated under reduced pressure to yield 100 mg of **1f** as pale yellow solid (86%). The residue was re-crystallized from EtOAc/*n*-hexane to yield 90 mg of pale yellow needles.

Mp >300°C; ^{1}H NMR(300 MHz, DMSO-d_6) : 13.20 (1H, br s), 12.91 (1H, br s) , 7.76 (1H, dd, J = 8.5, 1.5 Hz) , 7.75 (1H, d, J = 1.5 Hz), 7.41 (1H, s), 7.24 (1H, s), 6.68 (1H, d, J = 8.5 Hz), 1.95 (3H, s), 1.68 (4H, s), 1.33 (3H, s), 1.32 (3H, s), 1.23 (3H, s), 1.23 (3H, s); IR (KBr): 3056 (NH), 2962-2923 (OH), 1693 (CO) cm^{-1}; FAB-MS *m/e*: 395 $[M+H]^+$; *Anal.* Calcd for $C_{23}H_{26}N_2O_2S \cdot 1/2H_2O$: C, 68.48; H, 6.74; N, 6.94. Found: C, 68.39; H, 6.63; N, 6.82.

1-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetra-hydronaphthalen-2-yl)-1*H*-indole-5-carboxylic acid methyl ester (14).

To a solution of **12** (1.0 g, 3.6 mmol) and **13** (530 mg, 3.0 mmol) in dry toluene (4.0 mL) were added CuI (28 mg, 0.15 mmol), K_3PO_4 (1.3 g, 6.3 mmol), KI (600 mg, 3.6 mmol) and *N, N'*-dimethylethylenediamine (65 μL, 0.60 mmol). The mixture was refluxed at 160°C for 2.5 hr under microwave irradiation. The reaction mixture was filtrated through Celite. The filtrate was evaporated under reduced pressure. The residue was purified by flash column chromatography (EtOAc : *n*-hexane = 1 : 40) to yield 89 mg of **14** as yellow crystal (7.9%).

^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.47 (1H, d, J

= 2.0 Hz), 7.88 (1H, dd, J = 9.0, 2.0 Hz), 7.28 (1H, s), 7.25 (1H, d, J = 3.0 Hz), 7.23 (1H, s), 7.09 (1H, d, J = 9.0 Hz), 6.75 (1H, d, J = 3.0 Hz), 3.95 (3H, s), 2.00 (3H, s), 1.74 (1H, s), 1.36 (6H, s), 1.28 (6H, s).

1-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetra-hydronaphthalen-2-yl)-1*H*-indole-5-carboxylic acid (2).

To a solution of **14** (66 mg, 0.18 mmol) in MeOH (2.0 mL) and THF (1.0 mL) was added 2N NaOH (2.0 mL). The mixture was stirred at 60°C for 1.5 hr. The solution was poured into 2N HCl (2.0 mL) and extracted with EtOAc (40× 3 mL). The organic layer was collected, washed with brine (20 mL), then dried over $MgSO_4$. The mixture was evaporated under reduced pressure to yield 58 mg of **2** (92%). The residue was re-crystallized from EtOAc/*n*-hexane to yield 10 mg of colorless powder.

Mp: 244.0-245.0°C; HPLC: 33 min. 95% purity (MeOH:$AcONH_4$ = 80:20); ^{1}H NMR (300 MHz, DMSO) δ: 12.5 (1H, s), 8.47 (1H, d, J = 2.0 Hz), 7.74 (1H, dd, J = 9.0, 2.0 Hz), 7.58 (1H, d, J = 3.0 Hz), 7.41 (1H, s), 7.26 (1H, s), 7.09 (1H, d, J = 9.0 Hz), 6.79 (1H, d, J = 3.0 Hz), 1.94 (3H, s), 1.68 (4H, s), 1.31 (6H, s), 1.24 (6H, s); FAB-MS *m/z*: 362 $[M + H]^+$; Anal. Calcd for $C_{24}H_{27}NO_2 \cdot 1/4H_2O$: C, 78.76; H, 7.57; N, 3.83. Found: C, 78.60; H, 7.36; N, 3.93.

2－2）RXR 活性

レポータージーンアッセイの結果を，Table 5 に掲載した．なお，記載データは既知の RXR フルアゴニスト LGD1069 1 μM での転写活性化能を 100 とした相対値で掲載している．

ウレア体**1e**およびチオウレア体**1f**には RXR 活性化能が見られなかったものの，**1a** や閉環構造 2 位にアミノ基を有する **1c** に RXR フルアゴニスト活性が認められた．

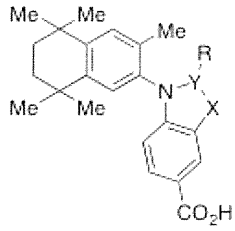
一方，無置換体 **1b** およびトリフルオロ体 **1d** (CBTF-PMN) に RXR パーシャルアゴニスト活性が見られた．なかでも **1d** の EC_{50} は CBt-PMN よりも一桁高活性な値を示した．

2－3）構造活性相関

Table 6 には，得られた RXR 転写活性化データと，電子効果であるシグマ値，立体因子を表す Es 値，置換基の脂溶性の指標である π 値を示している．いずれの指標を用いても，RXR フルアゴスト活性と RXR パーシャルアゴニスト活性の間に相関を得ることが出来ず，CBt-PMN，**1b**, **1d** が RXR パーシャルアゴニスト活性を示す要因はこれら以外によるところが大きいと考えられた．

そこで，我々は RXR フルアゴニスト，パーシャルアゴニスト表面の静電ポテンシャルに着目した (Figure 4). RXR フルアゴニスト活性を示した化合物 **1a** や **1c** は

Table 5. 本研究で新たに創出した化合物の RXR 転写活性化能



			RXRα[a]			
Compound	X	Y-R	EC_{50} (nM)[b]	E_{max} (%)	Efficacy at 1 μM (%)	Efficacy at 10 μM (%)
NEt-TMN	–	–	3.8 ± 0.2	96 ± 4	96 ± 4	98 ± 3
CBt-PMN	N	N	143 ± 2	75 ± 4	75 ± 3	69 ± 3
1a	N	C-CH_3	367 ± 130	95 ±5	70 ± 4	80 ± 5
1b	N	C-H	633 ± 33	75 ± 3	52 ± 3	72 ± 4
1c	N	C-NH_2	155 ± 10	103 ± 2	35 ± 3	96 ± 4
1d	N	C-CF_3	15 ± 0	67 ± 2	71 ± 6	66 ± 3
1e	NH	C=O	n.d.	i.a.	1 ± 0	22 ± 2
1f	NH	C=S	n.d.	i.a.	2 ± 0	37 ± 0
2	CH	C-H	83 ± 8	73 ± 2	67 ± 5	77 ± 4

a) All values represent the mean value of at least two separate experiments with triplicate determinations. Luciferase activity of LGD1069 (RXR full agonist) at 1 μM was defined as 100 percent.

b) EC_{50} values were determined from full dose-response curves in COS-1 cells.

閉環構造 2 位付近が正の静電ポテンシャルを示す一方，RXR パーシャルアゴニスト活性を示した CBt-PMN や **1b**, **1d** における当該の位置においては，弱い負の静電ポテンシャルを有すことが分かった．さらに，RXR アゴニスト活性を示さなかった **1e** や **1f** はこの部位が強く負電荷に偏っていることから，RXR アゴニスト活性と閉環構造 2 位の静電ポテンシャルとの間の相関が示唆された．

更なる考察を行うべく，RXR パーシャルアゴニストと RXR との Docking study を行った(Figure 5)．その結果，RXR パーシャルアゴニストの閉環構造2位と，RXR 中のヘリックス 5 のアスパラギン 306 の酸素原子との近接が示唆され，この酸素原子と CBt-PMN や **1d** の負の静電ポテンシャルとの弱い静電的反発が，これらの化合物が RXR パーシャルアゴニスト活性を示す要因であると推測された．

Table 6. 本研究で新たに創出した化合物の RXR 転写活性化能（図は Table 5 に同じ）

			RXRα[a]		Properties of R		
Compound	X	Y-R	EC_{50} (nM)	E_{max} (%)	σ[b]	Es[c]	π[d]
CBt-PMN	N	N	143 ± 2	75 ± 4	–	–	–
1a	N	C-CH_3	367 ± 130	95 ±5	-0.17	-1.24	0.56
1b	N	C-H	633 ± 33	75 ± 3	0.00	0.00	0.00
1c	N	C-NH_2	155 ± 10	103 ± 2	-0.66	-0.61	-1.23
1d	N	C-CF_3	15 ± 0	67 ± 2	0.54	-2.40	0.88

a) all data are the same as described in Table 3. b) σ: electronic effect, c) Es: Taft's steric substituent constants (steric effect), d) π: lipophilicity. These data were cited from Hansch, C., Leo, A. *Substituent Constants for Correlation Analysis in Chemistry and Biology,* Wiley-Interscience, NY, 1979.

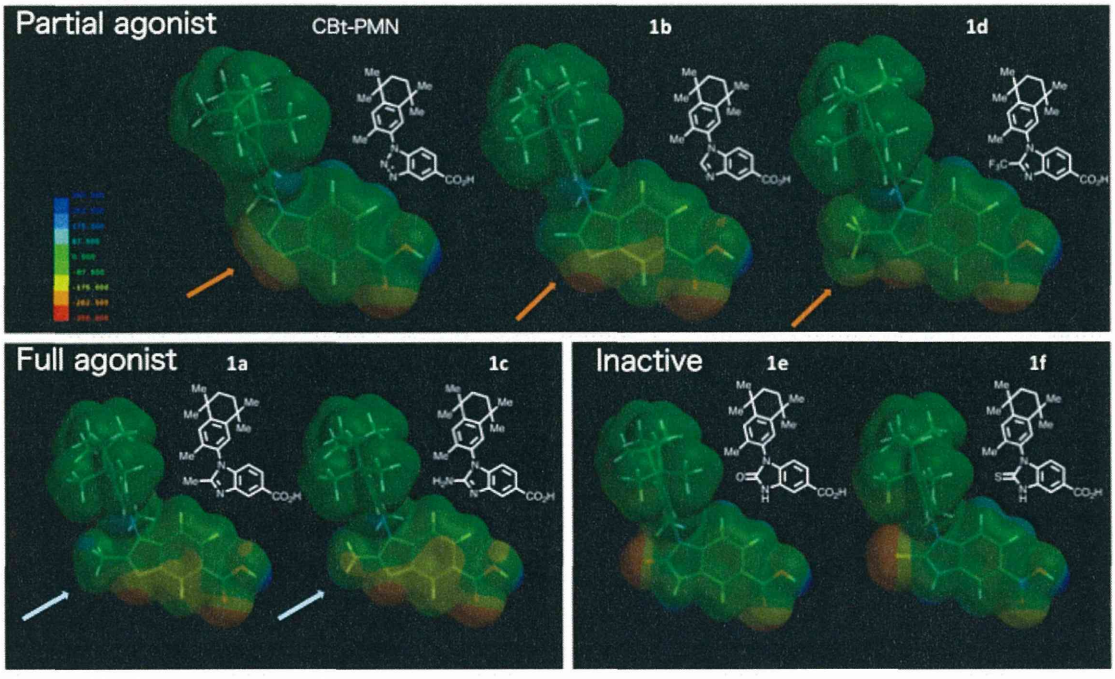


Figure 4. CBt-PMN および創出化合物の分子表面静電ポテンシャル図．フルアゴニスト活性を示した化合物は，ともに→で示す部分が弱い正の静電ポテンシャルを示し，RXR パーシャルアゴニスト活性を示した化合物は，→で示す部分に弱い負の静電ポテンシャル部位が存在することが示唆された．

なお，インドール骨格を有する **2** が RXR パーシャルアゴニスト活性を示したのは，上述した負の静電ポテンシャルではなく，**1a** や **1c** が RXR フルアゴニスト活性を示していることに鑑み，閉環構造 2 位の正の静電ポテンシャルに加えて立体

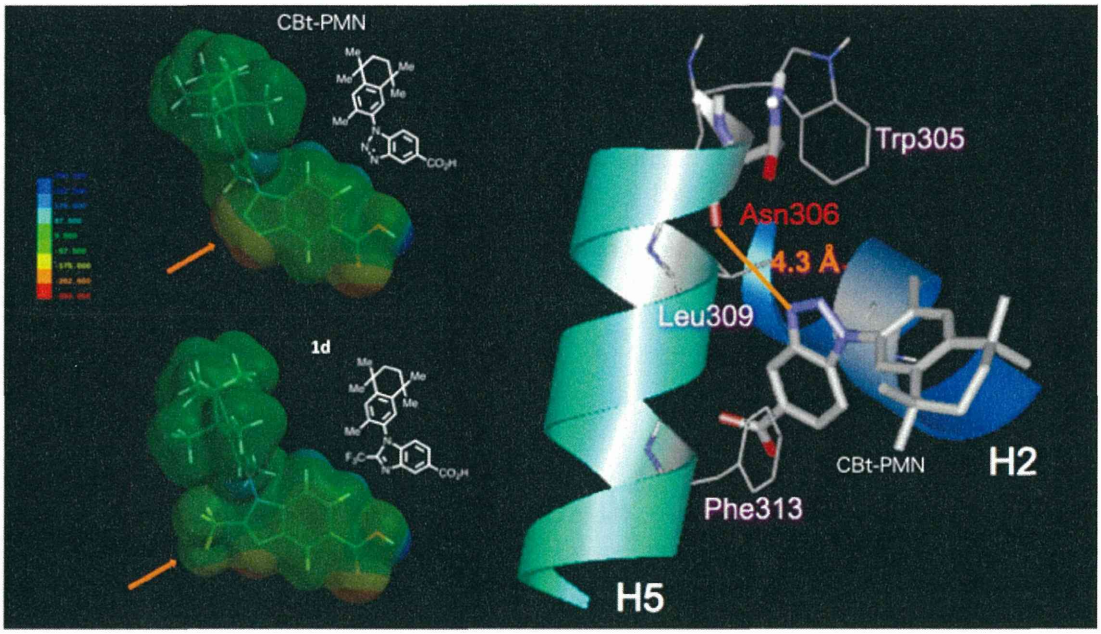


Figure 5. CBt-PMN および **1d** の分子表面静電ポテンシャル図と RXR のリガンド結合部位における CBt-PMN のドッキング図．閉環部位に見られる弱い負の静電ポテンシャル部分と RXR ヘリックス 5 上の Asn306 との静電反発が示唆された．

構造的に小さいことに起因するものと思われる．これは，**1b** についても言えることである．

３．RXRパーシャルアゴニスト CBTM-PMNの反復投与における副作用発現に関して

３－１）CBTM-PMN の経口投与時の血中移行性

CBTF-PMN (**1d**) の副作用発現評価に先立ち，化合物の経口投与による血中移行性を調べた．なお，比較対象としてRXRフルアゴニストであるNEt-TMNの血中濃度についても調べた．Figure 6に，それぞれの化合物の30 mg/kgでのICRマウスへの単回投与時の血中濃度を示す．CBTF-PMN (**1d**)は，投薬後30分で10 μM程度の血中濃度を与えたのに対し，RXRフルアゴニストであるNEt-TMNは1 μM程度であった．さらにCBTF-PMNは投与後3時間から6時間後であっても，その血中濃度は6 μMであり，本化合物の最大活性（E_{max}）を与えるのに十分であることも分かった．

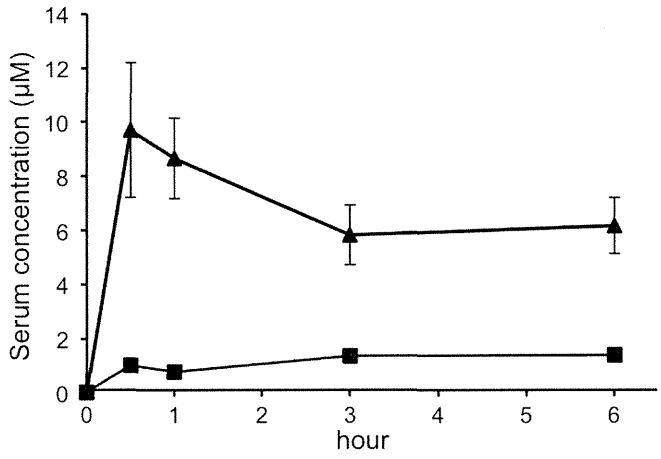


Figure 6. Plasma concentrations of NEt-TMN and CBTF-PMN (**1d**) in ICR mice after single oral administration of 30 mg/kg. Closed Squares and triangles indicate NEt-TMN and CBTF-PMN (**1d**), respectively. The data (n = 5–9) represent the mean ± SEM.

つぎに, ICRマウスに対して30 mg/kgで7日間連続経口投与した際の, 血清パラメータについて述べる. このデータについては, Table 7に示している. ここに示す化合物**1a**はRXRフルアゴニストである. RXRフルアゴニストNEt-TMNや**1a**がAST, ALT, ALPを顕著に上昇させたのに対し, CBTF-PMN (**1d**)の投与群においては, ASTを除いてNEt-TMNや**1a**に比べ低く, 薬物非投与群と変わらない程度であった.

Table 7. Plasma parameters of male ICR mice after oral administration of vehicle, NEt-TMN, **1a** or CBTF-PMN (**1d**) at 30 mg/kg/day for 7 consecutive days (n = 7–16)

	Vehicle	NEt-TMN	**1a**	CBTF-PMN (**1d**)
AST (U/I)	54.6 ± 3.8	87.9 ± 18.9**	51.3 ± 3.9	70.1 ± 6.5
ALT (U/I)	22.3 ± 1.5	43.5 ± 6.0**	32.7 ± 6.4*	26.5 ± 2.1
γ-GTP (U/I)	6.1 ± 0.7	7.1 ± 0.3	6.4 ± 0.3	4.5 ± 0.6
ALP (U/I)	281.3 ± 15.7	968.9 ± 115.0**	456.0 ± 51.5*	381.6 ± 58.9
CRE (mg/dL)	D.L.[a]	D.L.	D.L.	D.L.
BUN (mg/dL)	24.1 ± 1.0	26.0 ± 1.8	24.1 ± 2.1	24.8 ± 2.1

a) D.L. means below the detection limit (0.2 mg/dL).
AST: aspartate aminotransferase, ALT: alanine aminotransferase, γ-GTP : γ-glutamyltranspeptidase, ALP: alkaline Phosphatase, CRE: creatinine, BUN: blood urea nitrogen.
b) Data are mean ± SEM. Statistical analysis was performed by analysis of variance (ANOVA). Significant differences: * $p < 0.05$ vs. vehicle. ** $p < 0.01$ vs. vehicle.

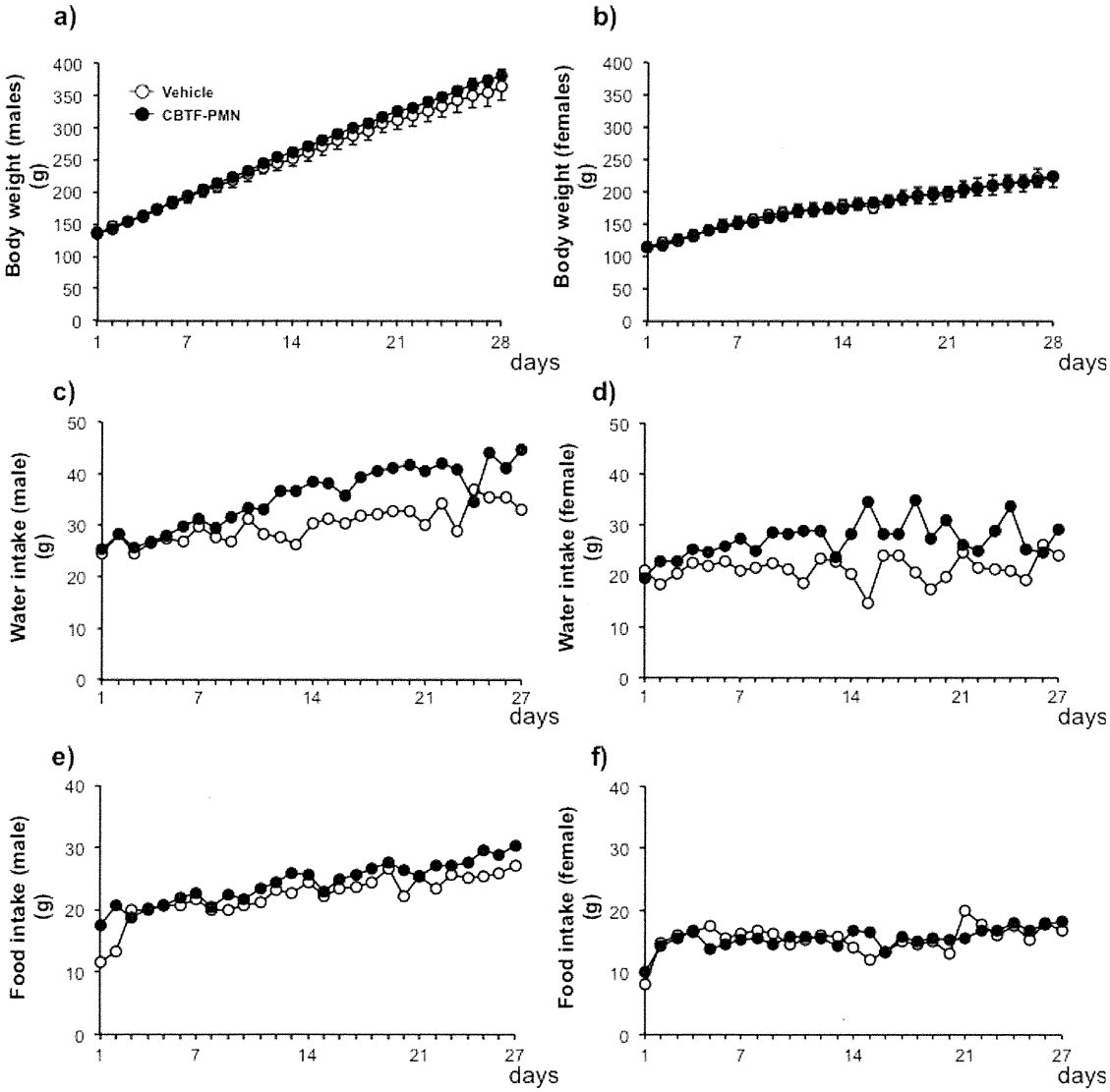


Figure 7. Changes in body weight gain, water intake, and food intake of male or female SD rats treated with oral administration of vehicle or CBTM-PMN (**1d**) at 30 mg/kg/day for 28 consecutive days (n = 3–6). a–b) Body weight gain. c–d) Water intake change. e–f) Food intake change. Males: a, c, and e. Females: b, d, and f. Open and closed circles indicate vehicle and **1d** treatment, respectively.

ラットに対する28日間反復経口投与の結果は，Figure 7，Table 8およびTable 9に示している．CBTF-PMN（**1d**）は，RXRアゴニストに報告されている体重増加は顕著でなく，肝肥大，トリグリセリド上昇についても，薬物非投与群に比べ有意な差は認められなかった．なお，臓器重量において肝臓の重量が有意に増加しており，この点については，今後の検討課題である．また，血液成分に関する生化学検査の結果，薬物非投与群に比べ有意な差が見られるものもあったが，ラット購入元である

Table 8. Plasma parameters of male and female SD rats after oral administration of vehicle or CBTF-PMN (**1d**) at 30 mg/kg/day for 28 consecutive days (n = 2–6).

	Male		
	Vehicle	CBTF-PMN (**1d**)	Reference[a]
AST (U/I)	65.7 ± 6.3	91.7 ± 3.7**	87.0–114.0
ALT (U/I)	30.0 ± 1.7	50.2 ± 2.3**	28.0–40.0
γ-GTP (U/I)	6.7 ± 0.9	7.0 ± 0.0	0.0–1.0
ALP (U/I)	703.7 ± 58.6	864.0 ± 94.2	–
CRE (mg/dL)	0.2 ± 0.0	0.2 ± 0.0	0.5–0.6
BUN (mg/dL)	15.5 ± 0.4	14.4 ± 1.4	13.0–16.0
TG (mg/dL)	61.3 ± 9.9	49.0 ± 4.6	61.0–99.0
TCHO (mg/dL)	50.0 ± 2.5	60.3 ± 4.0	54.0–74.0

	Female		
	Vehicle	CBTF-PMN (**1d**)	Reference[a]
AST (U/I)	69.7 ± 4.8	67.8 ± 2.1	85.0–123.0
ALT (U/I)	21.7 ± 1.2	37.0 ± 1.2**	25.0–36.0
γ-GTP (U/I)	7.0 ± 0.6	5.8 ± 0.2*	0.0–0.4
ALP (U/I)	382.5 ± 46.5	387.7 ± 31.4	–
CRE (mg/dL)	0.2 ± 0.0	0.2 ± 0.0	0.5–0.6
BUN (mg/dL)	14.5 ± 0.6	15.5 ± 2.0	11.0–16.0
TG (mg/dL)	18.7 ± 4.1	45.2 ± 4.6**	42.0–74.0
TCHO (mg/dL)	57.7 ± 6.9	99.7 ± 6.4**	67.0–87.0

a. These data are taken from the Clinical Laboratory Parameters for Crl:CD(SD) Rats (CRL_Mar, 2006) by Charles River®.

b. Data are mean ± SEM. Statistical analysis was performed by t-test. Significant differences: * $p < 0.05$ vs. vehicle. ** $p < 0.01$ vs. vehicle.

Charles River社から提供されている平均データと比較すると，正常範囲であると判断出来る．

4．TPA誘発皮膚炎（乾癬様）モデルにおける薬効評価

本実験は，参考文献12を参考に，TPAの塗布を1日行った後，耳の厚さを測定する方法にて行ったところ，ばらつきが多いことから，TPAの塗布ならびに薬物塗布を4日間繰返す方法に変え実施した．なお，薬効評価は耳の厚さならびにトレパンと呼ばれるサンプリング用小刀を用いて得

Table 9. Organ weights of male or female SD rats after oral administration of vehicle or **6c** at 30 mg/kg/day for 28 consecutive days (n = 3–6).

	Male		Female	
	Vehicle	**6c**	Vehicle	**6c**
Weight (g)	339.0 ± 19.1	352.1 ± 7.0	210.2 ± 13.7	206.1 ± 5.4
Brain (g)	1.9 ± 0.1	1.9 ± 0.1	1.7 ± 0.0	1.8 ± 0.0
Liver (g)	10.2 ± 0.8	12.7 ± 0.6*	5.7 ± 0.4	7.6 ± 0.1**
Kidney (g)	2.7 ± 0.1	2.7 ± 0.1	1.7 ± 0.1	1.6 ± 0.1
Spleen (g)	0.6 ± 0.0	0.7 ± 0.0*	0.5 ± 0.0	0.5 ± 0.1
Testis (g)	6.1 ± 0.2	6.4 ± 0.2		

Data are mean ± SEM; Statistical analysis was performed by t-test. Significant differences: * $p < 0.05$ vs. vehicle. ** $p < 0.01$ vs. vehicle.

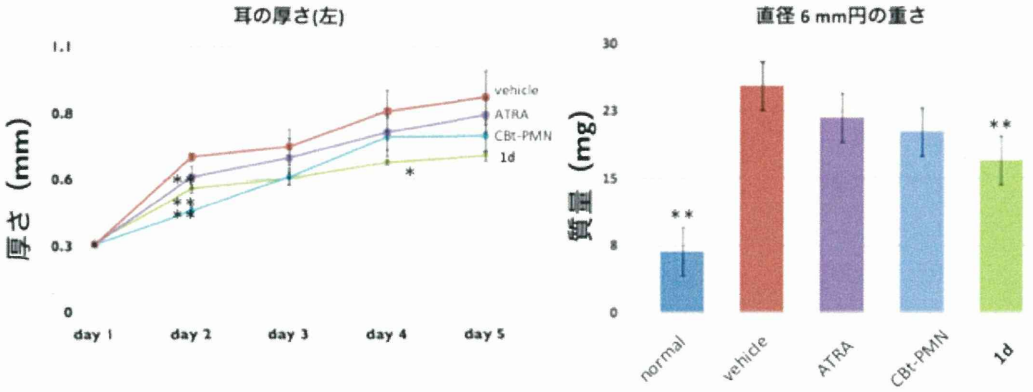


Figure 8. TPA 誘発皮膚炎モデルマウスの耳の厚さ変化ならびに直径 6 mm 円での耳重量. 左) 耳の厚さ変化. Vehicle: 薬物非投与群, ATRA: all-*trans* retinoic acid 5 mM in acetone 塗布群, CBt: CBt-PMN 5 mM in acetone 塗布群, および **1d** 5 mM in acetone 塗布群. 右) day5 における直径 6 mm 円での耳重量. Normal: 非炎症群, vehicle: 炎症・非薬物投与群, ATRA: all-*trans* retinoic acid 5 mM in acetone 塗布群, CBt: CBt-PMN 5 mM in acetone 塗布群, および **1d** 5 mM in acetone 塗布群. データ は平均 ± s.e.m. ; 有意差: * $p < 0.05$ vs. vehicle. n = 5.

られた，直径6 mm円状の耳サンプルの重量により比較した. Figure 8に示すように，耳の厚さおよび直径6 mm円状の耳サンプルの重量ともに，CBt-PMNは炎症を減少させる傾向は見られたものの，有意差は見られなかった. 一方で，より低濃度でRXR活性化能を示すRXRパーシャルアゴニストCBTF-PMN (**1d**)では，有意な炎症の抑制が認められた.

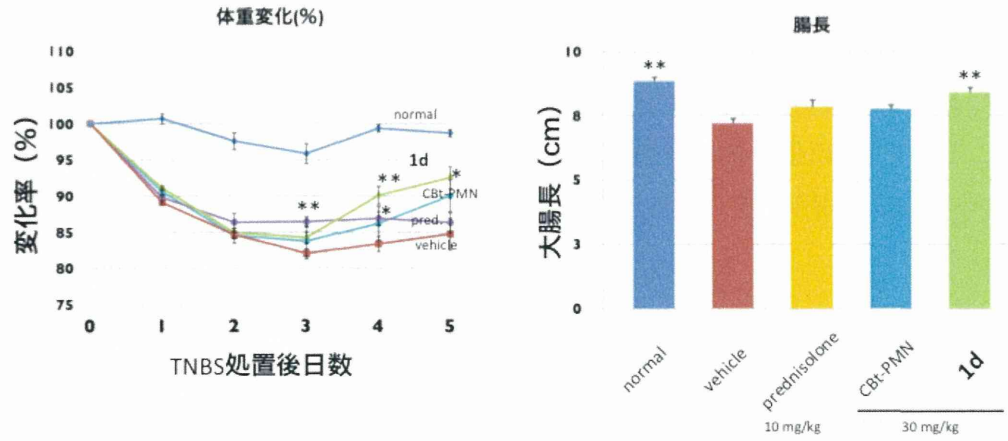


Figure 9. TNBS 誘発腸炎モデルマウスの体重推移（変化率）．TNBS 注腸時を 0 日目として示してある．Normal: 非炎症群，vehicle: 炎症・非薬物投与群，pred: prednisolone 10 mg/kg/day 投与群，CBt: CBt-PMN 30 mg/kg/day 投与群，**1d**: **1d** 30 mg/kg/day 投与群．データ は平均 ± s.e.m.；有意差: * $p < 0.05$ vs. vehicle. n = 5.

5．2,4,6-トリニトロベンゼンスルホン酸（TNBS）誘発腸炎モデルでの薬効評価

クローン病モデルの作成方法としては，TNBSやNBD-Clを用いた方法が知られる．本研究でも，いずれのモデル作成を実施したところ，TNBSモデルが再現よく作成出来たことから，こちらのモデルを用いた薬効評価を行った．その結果，CBt-PMNは，30 mg/kg/dayでの経口投与では，顕著な薬効が認められなかった（Figure 9）．一方で，より低濃度でRXR活性化能を示すRXRパーシャルアゴニスト**1d**は，有意な抗炎症作用を示した．

6．マウスリウマチモデルでの薬効評価系の構築

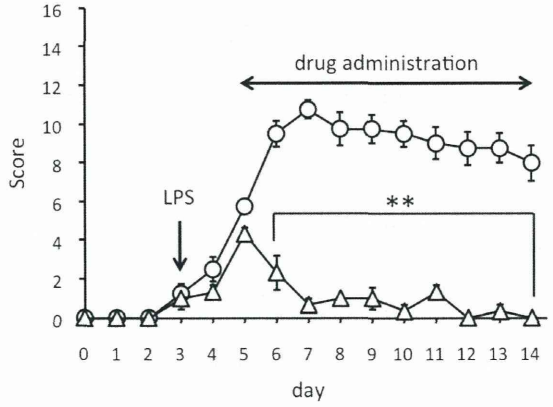


Figure 10. コラーゲン抗体誘発リウマチモデルマウスの炎症スコア．○：vehicle，△：prednisolone 10 mg/kg/day 経口投与群．データ は平均 ± s.e.m.；有意差: * $p < 0.05$ vs. vehicle. n = 5.

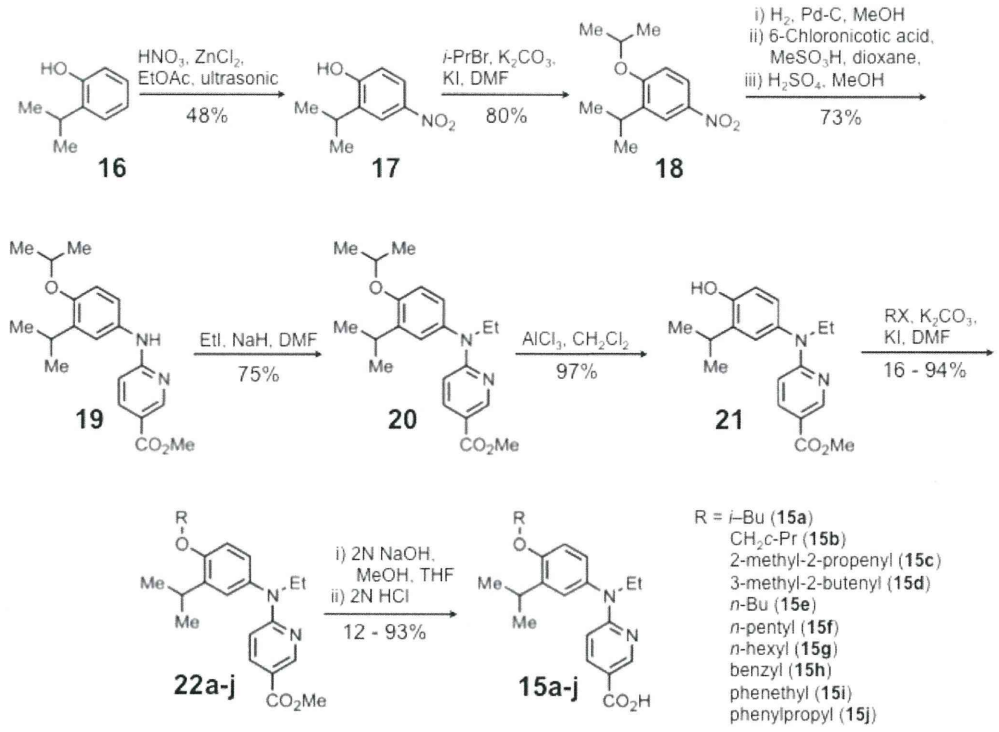
Figure 10に，リウマチモデルでの炎症スコアの結果を示す． prednisoloneの薬効評価を行ったところ，10 mg/kg/dayでの薬効を示せたことから，創出化合物の薬効評価を行うモデルとして利用可能であると判断された．

7．新規RXRパーシャルアゴニストの探索

7－1）化合物の合成

合成は，Scheme 3 にしたがい行った．なお，スキーム中の化合物番号は，目的化合物群の化合物番号を **15a–j** として記してある．

2-isopropylphenol (**16**) を出発原料とし，超音波条件下にて，硝酸と塩化亜鉛を用いてニトロ化することで **17** を合成した．化合物 **17** のフェノール性ヒドロキシ基をイソプロポキシ基に置換することで **18** を合成し，ニトロ基の接触還元後，メシル酸触媒下にて 6-chloronicotinic acid とのカップリングを行い，カルボン酸のメチルエステル化によって **19** を得た．その後，化合物 **19** のアミノ基を N-エチル化することで **20** を合成した．次に，塩化アルミニウムを用いて **20** のイソプロピル基を脱保護し，共通中間体 **21** を合成した．化合



Scheme 3. Synthesis scheme of **15a–j**.