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Synthesis and structure–activity relationship of novel RXR antagonists: Orally active anti-diabetic and anti-obesity agents

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Abstract—A series of diazepinylbenzoic acid derivatives were synthesized and tested in the inhibition assay of the transactivation of RXR. Oral treatment of cyano derivatives (**16f**) was found to show anti-diabetic and anti-obesity effects in KK-A^y mice.

The retinoid X receptor (RXR) belongs to the superfamily of intracellular nuclear receptors. RXR is known to regulate gene transcription and control cellular differentiation and proliferation through the formation of heterodimers with other nuclear receptors, such as RAR, TR, VDR, NGFIB, LXR, FXR, and PPARs.[1–3] Therefore, RXR modulators are of potential use in disease indications, for instance, diabetes, obesity, dermatologic diseases, inflammatory diseases, and proliferative diseases.[4,5]

In the preceding paper,[6] we reported the synthesis, SAR, and pharmacokinetic study of the RXR antagonists **2** based on the diazepinylbenzoic acid scaffold **1** (Fig. 1).[7,8]

We herein describe a further modification of the diazepinylbenzoic acid structure and results of in vivo study in KK-A^y mice.

Followed by the reported procedures,[7,8] the unsubstituted diazepinylbenzoic acid **3** and its bromide **4** were prepared as shown in Scheme 1. These two compounds can be utilized as a versatile intermediate to deliver a variety of diazepinylbenzoic acid analogues. The bromide **4** was subjected to the palladium-catalyzed coupling reaction with thiols and amines to give sulfide **5** and aniline **9** derivatives in good chemical yields. Sulfonamides **8** were readily synthesized by the direct sulfonylation with chlorosulfonic acid followed by the treatment with $SOCl_2$ and then amines.

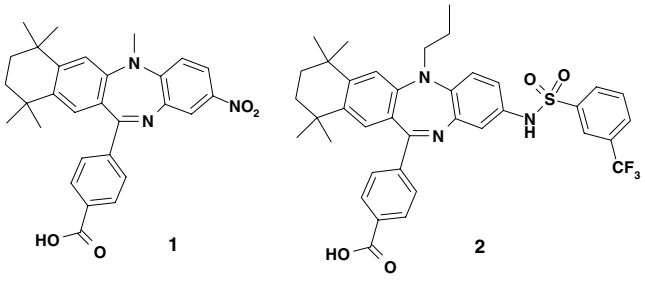

Figure 1. Diazepinylbenzoic acic analogues.

Hydroxy-diazepinylbenzoic esters **12** were served as precursors for phenoxy derivatives **13** and a triflate **14**, which was transformed into acetyl analogues **15** by the known palladium coupling.[9,11] Cyano derivatives **16** were prepared from bromo-tetrahydronaphthalene **10** and commercially available 4-amino-3-nitro-benzonitrile by slight modification of the reported procedures (Scheme 2).[7,8,10,11]

Preparation of 3-fluoro- (**21**) or 2-fluoro-terephthalic acid 4-methyl ester (**26**) was carried out as shown in Scheme 3.[11] Bromination of **18** afforded a mixture of di- and tri-bromides both of which were converted to the target **21** without separation. The same bromination

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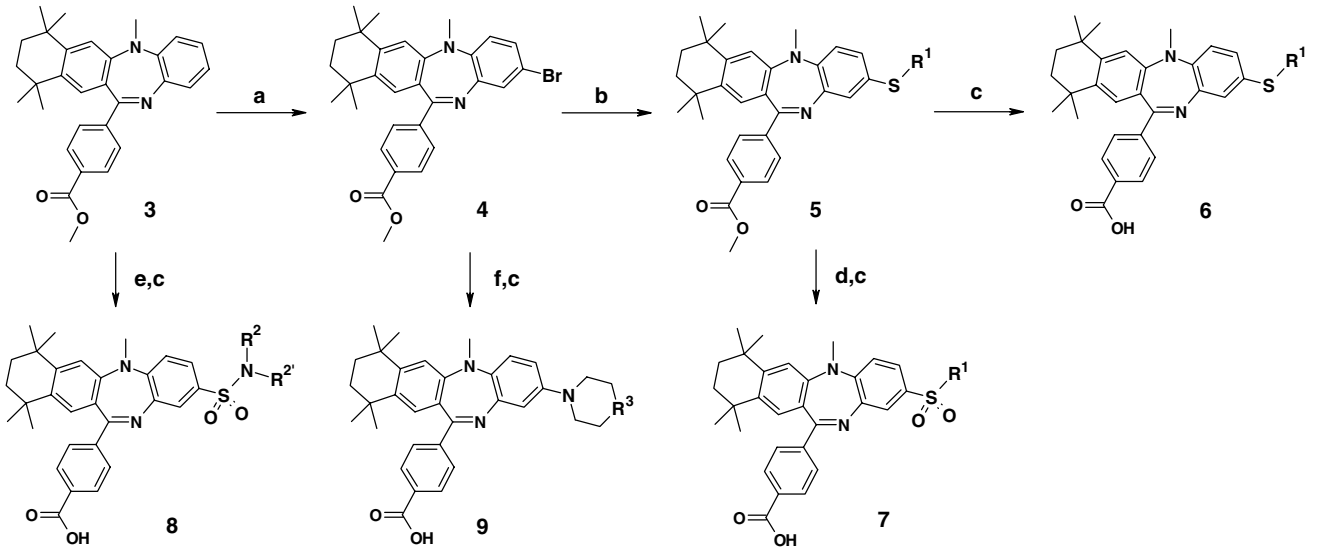
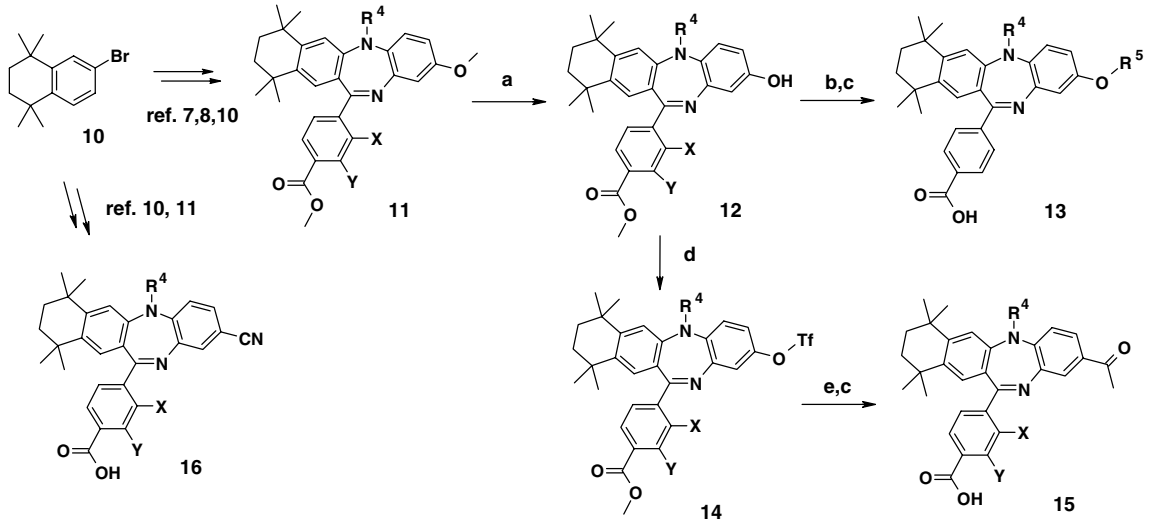
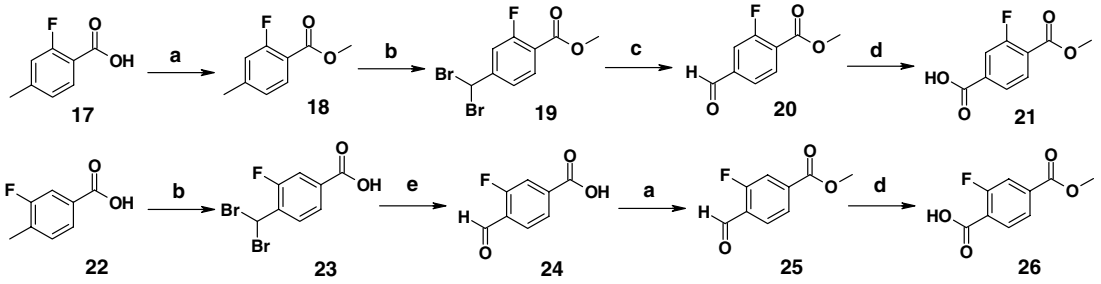


Scheme 1. Reagents: (a) Br_2, Fe, CCl_4 or Py–HBr_3, CH_2Cl_2; (b) R^1SH, $Pd(PPh_3)_4$, NaO*t*-Bu, toluene; (c) 2 M NaOH, DMF; (d) *m*-CPBA CH_2Cl_2; (e) i—$ClSO_3H$, CCl_4; ii—$SOCl_2$, DMF; iii—$R^2R^{2'}NH$, pyridine, CH_2Cl_2; (f) amine, $Pd_2(dba)_3$, 2-(di-*tert*-butylphosphino)biphenyl, NaO*t*-Bu, toluene.



Scheme 2. Reagents: (a) BBr_3, CH_2Cl_2; (b) R^5Cl (or Br), NaH, DMF; (c) 2 M NaOH, DMF; (d) Tf_2O, pyridine, CH_2Cl_2; (e) butyl vinyl ether, $Pd(OAc)_2$, dppf, Et_3N, DMF, H_2O.



Scheme 3. Reagents: (a) MeI, K_2CO_3, MeCN; (b) NBS, cat.BPO, CCl_4; (c) $AgNO_3$, *t*-BuOH, H_2O; (d) $NaClO_2$, H_2NSO_3H, MeCN, H_2O; (e) $AgNO_3$, EtOH, H_2O

using NBS was initially applied to the methyl ester of **22**, however the reaction took a few days for completion. However, direct bromination of the acid **22** turned out to proceed more smoothly. The synthetic method for **21** and **26** is applicable to a hundred gram scale preparation (Table 2).

These derivatives prepared were tested in the inhibition assay[10] of the transactivation activity for RXRα homodimer (Tables 1 and 2). In general, the diazepinylbenzoic acid analogues possessing an electron-withdrawing group (**7**, **8**, **15**, and **16**) showed a higher antagonistic activity than the ones having an electron-donating group (**6**, **9**, and **13**). The comparison between sulfides and sulfones bearing a same substituent (e.g., **6b** vs **7c** or **6e** vs **7f**) gave the same result. The effect of fluorine introduction to the phenyl group was examined for acetyl **15** and cyano **16** derivatives. Both 2- and 3-fluorine substitutions were found to generally decrease the antagonistic activity to some extent, however the 3-fluorination was more tolerable than the 2-fluorination in both cases of the acetyl and cyano derivatives (**15d** and **16f**).

Table 1. Inhibition of the transactivation of RXRα with diazepinylbenzoic acid derivatives (**6**–**9**, **13**)

Compound	**6**, **7**: R^1 **8**: R^2, $R^{2'}$ **9**: R^3 **13**: R^5	LG[a] IC_{50} (μM)	9-RA[b] IC_{50} (μM)
6a	Me	3.0	2.0
6b	4-MeO–Phenyl	1.6	0.72
6c	4-CF_3O–Phenyl	1.0	0.39
6d	4-Cl–Benzyl	1.6	0.67
6e	4-MeO–Benzyl	4.9	5.5
7a	Me	1.7	1.4
7b	*n*-Pr	0.92	0.45
7c	4-MeO–Phenyl	0.36	0.17
7d	4-CF_3O-Phenyl	0.24	0.13
7e	4-Cl–Benzyl	0.95	0.42
7f	4-MeO–Benzyl	1.4	0.78
8a	Me, H	1.3	1.3
8b	Me, Me	2.2	2.0
8c	*n*-Bu, H	0.41	0.19
8d	4-CF_3O–Phenyl, H	0.96	0.46
8e	Pyrrolidinyl	1.0	0.45
8f	Morpholinyl	1.0	0.45
8g	*N*-Methylpiperazinyl	1.9	1.0
9a	O	7.0	3.9
9b	*N*-Me	11	—
13a	Me	3.6	4.2
13b	Et	5.4	3.0
13c	*n*-Pr	5.9	3.7
13d	*i*-Pr	6.8	4.0
13e	CF_3	7.0	5.0
13f	3-F-*n*-Pr	4.3	3.8
13g	2-Morpholinyl–Et	1.6	1.2
13h	4-F-Benzyl	0.64	0.34
13i	4-Cl-Benzyl	1.4	0.58
13j	4-CF_3-Benzyl	2.7	1.2
13k	Cl–Py–Me[c]	0.55	0.29
13l	4-CHF_2O-Benzyl	0.85	0.68
13m	Morpholinyl–Bz[d]	0.84	0.85

Values are means of three independent experiments measured in duplicate.
[a] LG100268.
[b] 9-*cis*-retinoic acid.
[c] 5-Cl-Pyridine-3-yl-methyl.
[d] 4-*N*-Me-Morpholinyl-benzyl.

Table 2. Inhibition of the transactivation of RXRα with diazepinylbenzoic acid derivatives (**15**–**16**)

Compound	R^4	*X*, *Y*	LG[a] IC_{50} (μM)	9-RA[b] IC_{50} (μM)
15a	Me	H, H	1.1	0.89
15b	Et	H, H	0.97	0.79
15c	Me	F, H	4.6	—
15d	Me	H, F	1.7	1.1
15e	Et	F, H	3.3	3.0
16a	Me	H, H	0.82	0.43
16b	Et	H, H	0.48	0.32
16c	*n*-Pr	H, H	2.1	2.1
16d	Me	H, F	1.2	0.52
16e	Et	F, H	1.1	0.53
16f	Et	H, F	0.77	0.50

Values are means of three independent experiments measured in duplicate.
[a] LG100268.
[b] 9-*cis*-retinoic acid.

Ameliorative effects of **16f** on KK-A^y mice fed a high-fat diet were investigated. Male 8-week-old KK-A^y mice prefed a high-fat diet (32% safflower oil) for 9 days were treated with **16f** (0.01 and 0.03%) as a food admixture for 14 days. Treatment with **16f** resulted in a decrease in body weight gain. Total food intake was not significantly changed in the treated groups. Plasma glucose and insulin concentrations were decreased following treatment with the compound as shown in Figure 2.

A series of diazepinylbenzoic acid derivatives were designed and synthesized by employing the versatile intermediates **4** and **12**. A simple preparation method of 2- or 3-fluoroterephthalic acid half ester was also developed. The method can be utilized for a hundred gram scale

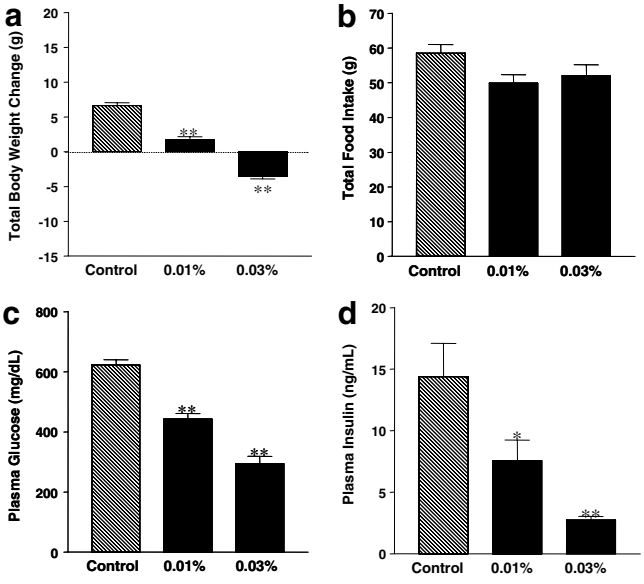


Figure 2. Ameliorative effects of compound **16f** in obese/diabetic KK-A^y mice fed a high-fat diet ((a) total body weight change, (b) total food intake, (c) plasma glucose concentration, (d) plasma insulin concentration). Values are means ± SEM for 8 animals per group. $^*P < 0.05$, $^{**}P < 0.01$, significant difference from the control group (one-way ANOVA with Dunnett's multiple comparison tests).

preparation. A functional group on the diazepinyl ring of the antagonists synthesized (**6**–**9**, **13**, and **15**–**16**) was found to effect on the RXR antagonistic activity. The cyano derivative (**16f**) was evaluated as food admixture in the KK-A^y mice model. The compound was found to decrease a body weight gain without changing food intake and also decrease both glucose and insulin levels, demonstrating its potential for anti-diabetic and anti-obesity agent.

Acknowledgments

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9. See Ref. 6 and references cited therein.
10. Synthesis of compound **16f**: To a solution of 4-(2-cyano-5-ethyl-7,7,10,10-tetramethyl-7,8,9,10-tetrahydro-5*H*-5,13-diazabenzo[4,5]-cyclohepta[1,2-*b*]naphthalene-12-yl)-2-fluorobenzoic acid methyl ester (5.36 g, 10.5 mmol) in DMF (100 ml) and THF (100 ml) was added 2 N NaOH (50 ml, 0.10 mol) at room temperature. The reaction mixture was stirred at the same temperature for 2 h. The mixture was acidified with 1 N HCl, diluted with H_2O, and extracted with ether. The organic layer was washed with H_2O twice, dried over $MgSO_4$, and evaporated in vacuo. The resulting solid was washed with hexane/ether (1:1) and dried to give **16f** (4.02 g, 88%) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 0.99 (3H, s), 1.07 (3H, t), 1.09 (3H, s), 1.19 (3H, t), 1.22 (3H, s), 1.51–1.58 (4H, m), 3.56–3.66 (1H, m), 3.74–3.82 (1H, m), 6.92 (1H, s), 7.02 (1H, s), 7.17 (1H, d), 7.45 (1H, dd), 7.59–7.65 (3H, m), 7.92 (1H, dd), 13.46 (1H, br).
11. For experimental details, see: Sakaki, J; Konishi, K; Kishida, M; Kimura, M; Uchiyiama, H; Mitani, H; WO2004/089916.