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Newly discovered orally active pure antiestrogens

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Abstract—In order to develop orally active pure antiestrogens, we incorporated the carboxy-containing side chains into the 7α-position of the steroid scaffold and found that 17-keto derivative CH4893237 (**12b**) functioned as a pure antiestrogen with its oral activity much superior to clinically used pure antiestrogen, ICI182,780. Results from the pharmacokinetic evaluation indicated that the potent antiestrogen activity at oral dosing in mice attributed to both improved absorption from the intestinal wall and metabolic stability in liver.

The effects of pure antiestrogens such as ICI182,780, ICI164,384, and ZM189,154 (Fig. 1) on estrogen receptor positive breast tumor are well documented.[1–4] In particular, ICI182,780 demonstrated effectiveness in postmenopausal women with advanced breast cancer progression after tamoxifen therapy in clinical trials[5–7] and was launched in 2002 as an intramuscular injection drug. In the course of our research to develop pure antiestrogens, we found thiochroman and chroman derivatives **1** and **2** (Fig. 1) functioned as pure antiestrogens,[8] and subsequent investigation demonstrated that the carboxy, the sulfonamide, and the sulfamide moieties functioned as the alternatives to the sulfoxide moiety in compounds **1** and **2**.[9] Noteworthy is that compound **3**, in which the sulfoxide moiety in compound **1** is replaced with the carboxy moiety, exhibited oral antiestrogen activity superior to compounds **1**, **2**, and ICI182,780 in spite of its lower affinity for estrogen receptor α (ERα). Results from the pharmacokinetic evaluation indicated that the potent antiestrogen activity of compound **3** at oral dosing attributed to both improved absorption from the intestinal wall and metabolic stability in liver. Since the carboxy-containing side chains were found to be useful for the oral activities of pure antiestrogens, we here incorporated these side chains into the 7α-position of the steroid scaffold and evaluated their oral antiestrogen activities.

The 7α-steroid derivatives in Table 1 were prepared from compound **4** using the procedure described by this laboratory[10] and are summarized in Scheme 1. Hydroxylation at the 6-position followed by oxidation afforded ketone **5**, which was treated with allyl iodide in the presence of potassium hexamethyldisilazide to give 7-allyl derivative **6** as a mixture of 7α- and 7β-isomers, in which the 7β-isomer was dominant. Thermal isomerization of the 7β-isomer to the 7α-isomer, followed by deprotection of TBS group and recrystallization afforded 7α-isomer **7**. Reduction of 7α-isomer **7** followed by metathesis with the various alkene derivatives, subsequent catalytic hydrogenation and deprotection afforded 7α-steroid derivatives **10a–f**. Chiral resolution of the most potent 7α-steroid derivative **10b** using Daicel Chiralpak AD afforded chiral isomers **11a** and **11b**, which were converted to corresponding ketones **12a** and **12b** (Scheme 2).[11] Stereochemistry was assigned by X-ray crystallographic analysis of compound **14b**, which was prepared from ketone **13** and the chiral side chain[12] and converted to compounds **11b** and **12b** with the procedure in Scheme 3. Chiral ketone **14b** showed the stereochemistry of α-position of the carboxy moiety to be (*R*), which consequently suggested that of compounds **11b** and **11a** to be (*R*) and (*S*), respectively.

Keywords: Pure antiestrogen; Steroid scaffold; Carboxy moiety; estrogen receptor.
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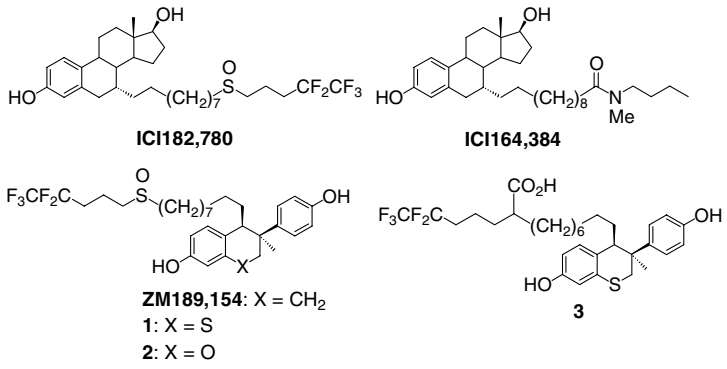
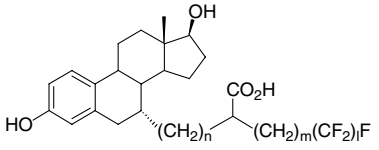


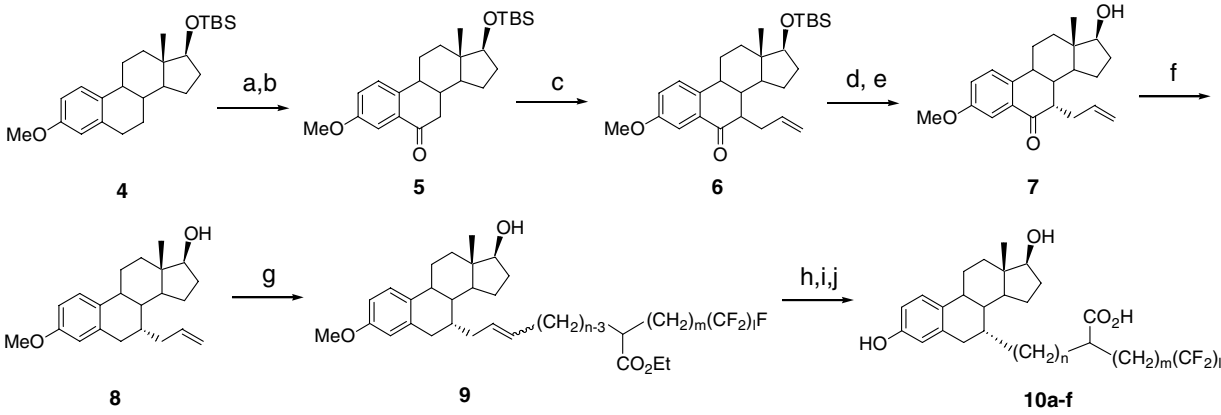
Figure 1. Structure of representative antiestrogens.

Table 1. Biological data of 7α-steroid derivatives **10a–f**



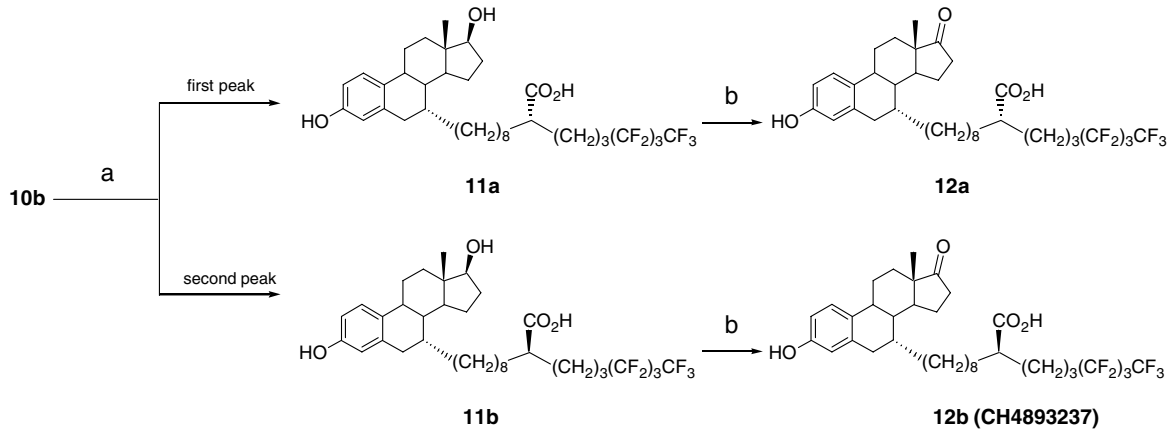
Compound	*n*	*m*	*l*	RBA[a] (%) E_2 = 100	Antiestrogen activity[b] (% inhibition ± SEM)		
					1 mg/kg po	3 mg/kg po	10 mg/kg po
10a	8	3	2	0.8	37 ± 5	67 ± 4	87 ± 1
10b	8	3	4	1.4	64 ± 3	87 ± 4	96 ± 1
10c	8	2	4	0.6	55 ± 9	80 ± 2	98 ± 2
10d	9	3	2	1.4	22 ± 5	30 ± 7	80 ± 1
10e	9	3	4	0.7	27 ± 6	42 ± 6	85 ± 1
10f	9	2	4	0.7	27 ± 9	49 ± 6	92 ± 2
	3			0.8	11 ± 6	41 ± 5	77 ± 3
	ICI182,780			138	11 ± 7	29 ± 7	54 ± 4

[a] Relative binding affinities for the recombinant ERα, determined by competitive radiometric binding assay with [^{3}H]estradiol.
[b] Inhibition of estrogen-stimulated uterine weight gain by the test compound with po administration.

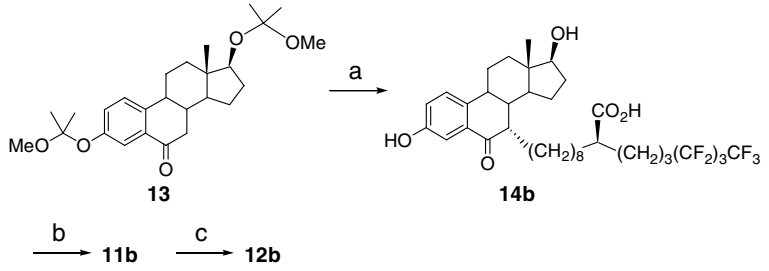


Scheme 1. Reagents and conditions: (a) *t*-BuOK, *n*-BuLi, *i*-Pr_2NH, THF, hexane, −70 °C, then $B(OMe)_3$, −70 to 0 °C, then H_2O_2 aq, rt, 82%; (b) MnO_2, MS4A, CH_2Cl_2, rt, 79%; (c) KHMDS, allyl iodide, 1,2-dimethoxyethane, −70 to 0 °C, 88% (7α/7β, 1:6); (d) NaOMe, MeOH, reflux, (7α/7β, 7:1); (e) TBAF, THF, reflux, then recrystallization, 60% from **6**; (f) Et_3SiH, BF_3–Et_2O, CH_2Cl_2, 0 °C to rt, 98%; (g) benzylidenebis(tricyclohexylphosphine)dichlororuthenium, $CH_2{=}CH(CH_2)_{n-3}$ $CH(CO_2Et)(CH_2)_m$ $(CF_2)_lF$, CH_2Cl_2, reflux, 55–67%; (h) 10% Pd–C, H_2, AcOEt, rt, 76–97%; (i) BBr_3, CH_2Cl_2, −78 °C to 0 °C, 57–81%; (j) NaOH aq, EtOH, 60 °C, 70–97%.

The 7α-steroid derivatives prepared were assayed in vitro and in vivo to characterize their biological and pharmacokinetic profiles. In vitro, the binding affinity for ERα was determined by displacement of [^{3}H]estradiol with the test compound utilizing the human recombinant ERα-ligand binding domain (ERα-LBD). In vivo, estrogen agonist and antagonist activities were measured by the ability of the test compound to increase uterine weight gain and to inhibit estrogen-stimulated uterine weight gain in an ovariectomized mouse model, respectively.[13]



Scheme 2. Reagents and conditions: (a) chiral resolution by Chiralpak AD, hexane/isopropanol/AcOH, 90:10:0.1, 42–43%; (b) Al(*t*-BuO)$_3$, cyclohexanone, toluene, 100 °C, 89%.



Scheme 3. Reagents and conditions: (a) *t*-BuOK, I-(CH$_2$)$_8$C*H(CO$_2$H) (CH$_2$)$_3$ (CF$_2$)$_3$CF$_3$, 1,2-dimethoxyethane, rt, then satd KHSO$_4$ aq, AcOEt, rt, 49%; (b) Et$_3$SiH, BF$_3$–Et$_2$O, BF$_3$(H$_2$O)$_2$, toluene, 40 °C, 75%; (c) Al(*t*-BuO)$_3$, cyclohexanone, toluene, 100 °C, 89%.

We previously found that compound **1** and steroid derivative ICI182,780, both of which have the same sulfoxide side chain at the 4-position and the 7α-position, respectively, exhibited similar in vitro and in vivo antiestrogen activities. Furthermore, compound **3**, in which the sulfoxide moiety was replaced with the carboxy moiety, also functioned as a pure antiestrogen, and interestingly, its oral activity was superior to compound **1** and ICI182,780. The structure–activity relationship study of compound **3** derivatives showed that the 8- and 9-methylene chains between the thiochroman scaffold and the carboxy moiety were optimal for oral activities. These findings encouraged us to incorporate a variety of carboxy-containing side chains into the 7α-position of the steroid scaffold and evaluate their biological activities. As can be seen in Table 1, all the 7α-steroid derivatives exhibited antiestrogen activities superior to ICI182,780, in which compounds **10b**, **10c**, and **10f** almost completely inhibited estrogen-induced uterine weight gain at oral dosing of 10 mg/kg. It is noteworthy that the binding affinities for ERα of the 7α-steroid derivatives were much lower than ICI182,780,[14] and a clear correlation between the binding affinities and oral antiestrogen activities was not observed. The reason was not fully investigated; however, we speculate that 7α-steroid derivatives **10a**–**f** would possess well-absorbed and metabolically stable pharmacokinetic profiles similar to compound **3**, and that the potent oral activities would be mainly determined by absorption and metabolism rather than their binding affinities.

Having confirmed that the 7α-steroid derivatives displayed remarkable oral antiestrogen activities, chiral isomers of the most potent 7α-steroid derivative **10b** were then prepared, and their biological and pharmacokinetic profiles were evaluated. As shown in Table 2, the chiral isomers, compounds **11a** and **11b**, both showed similar binding affinities for ERα and similar potent oral antiestrogen activities. In addition, subcutaneous administration at 17 mg/kg showed no significant uterine weight gain when dosed alone compared to vehicle. These findings indicate that compounds **11a** and **11b** both functioned as pure antiestrogens and their oral activities were much superior to ICI182,780.

Concerning the binding mode with ERα-LBD, we speculate that both isomers would bind to ERα-LBD in a fashion similar to ICI164,384,[15] where their carboxy-containing side chains would protrude from ERα-LBD and each of the carboxy moiety would make hydrophilic interaction with water solvent existing outside of ERα. These protruding side chains would block the H12 folding to the position observed in the E_2-ER-LBD complex (PDB entry: 1ERE[16]) as well as to the coactivator binding site observed in the 4-OH-tamoxifen- and raloxifene-ER-LBD complexes (PDB entries: 3ERT[17] and 1ERR[16]), which would lead these isomers to pure antiestrogens.

The pharmacokinetic profiles of both isomers were also investigated (Table 3). The isomers, compounds **11a** and

Table 2. Biological data of compounds **11a** and **11b**

Compound	RBA[a] (%) E_2 = 100	Antiestrogen activity[b] (% inhibition ± SEM)			Estrogen activity[c] (% control ± SEM)
		1 mg/kg po	3 mg/kg po	10 mg/kg po	17 mg/kg sc
11a	1.0	58 ± 2	88 ± 3	103 ± 1	−3 ± 1[*]
11b	1.1	59 ± 6	93 ± 1	99 ± 1	−4 ± 1[*]
10b	1.4	64 ± 3	87 ± 4	96 ± 1	−4 ± 1[*]

[a] Relative binding affinities for the recombinant ERα, determined by competitive radiometric binding assay with [^{3}H]estradiol.
[b] Inhibition of estrogen-stimulated uterine weight gain by the test compound with po administration.
[c] Stimulation of uterine weight gain by the test compound with sc administration.
[*] No significant difference between the test group and the vehicle group at $P < 0.05$ using Student's t test.

Table 3. Pharmacokinetic data[a] of compounds **11a** and **11b**

Compound	10 mg/kg iv		20 mg/kg po	Bioavailability (%)
	AUC (μg h/mL)	CL_{tot}[b] (mL/h/kg)	AUC (μg h/mL)	
11a	254	39	190	37
11b	146	74	98	33
10b	207	49	144	35
3	228	47	209	46
ICI182,780	5.3	1969	1.7	16

[a] Compound dosed in Sprague–Dawley rats as a solution in water/PEG200/EtOH (3:6:1) for iv and po dosing.
[b] Total clearance.

11b, showed 1/50 and 1/27 lower clearance in iv and 112- and 58-fold higher AUC in po, respectively, than ICI182,780 in rats. These remarkable pharmacokinetic profiles were similar to those previously observed in thiochroman derivative **3**. These findings, together with their biological data, indicated that the potent oral antiestrogen activities of 7α-steroid derivatives **11a** and **11b** were mainly due to improved absorption from the intestinal wall and metabolic stability in liver.

Although compounds **11a** and **11b** possessed remarkable pharmacokinetic profiles in rats, pharmacokinetic profiles in mice and monkeys were quite different (Table 4). In mice and monkeys, compounds **11a** and **11b** were easily converted to corresponding 17-keto derivatives **12a** and **12b**. In particular, most of them were converted to 17-keto derivatives **12a** and **12b** in monkeys. These data led to the concern that oral administration of 17-hydroxy derivatives **11a** and **11b** to humans may also give a large amount of corresponding 17-keto derivatives **12a** and **12b**. Conversion from the

Table 4. Pharmacokinetic data of rats, mice, and monkeys

Compound	Animal species	AUC, po (μg h/mL)			AUC, iv (μg h/mL)		Bioavailability (%)
		Dose (mg/kg)	Intact	17-metabolite (compound)	Dose (mg/kg)	Intact	
11a	Rat	20[a]	190	n.d.[e] (**12a**)	10[a]	254	37
	Mouse	30[b]	470	297 (**12a**)	10[d]	447	35
	Monkey	3[c]	0.30	6.64 (**12a**)	N.D.[f]	N.D.[f]	N.D.[f]
11b	Rat	20[a]	98	n.d.[e] (**12b**)	10[a]	146	34
	Mouse	30[b]	274	194 (**12b**)	10[d]	244	37
	Monkey	3[c]	0.42	3.20 (**12b**)	3[c]	88	0.48
12b (CH4893237)	Rat	20[a]	32	n.d.[e] (**11b**)	10[a]	50	32
	Mouse	30[b]	468	37 (**11b**)	10[d]	389	40
	Monkey	3[c]	2.42	0.19 (**11b**)	3[c]	77	3.1

[a] Compound dosed in Sprague–Dawley rats as a solution in water/PEG200/EtOH (3:6:1).
[b] Compound dosed in CD-1 mice as a suspension in 5% gum arabic.
[c] Compound dosed in cynomolgus monkeys as a solution in water/PEG200/EtOH (4:8:3).
[d] Compound dosed in CD-1 mice as a solution in water/PEG200/EtOH (3:6:1).
[e] n.d., not detected.
[f] N.D., no data.

Table 5. Biological data of compounds **12b** and **11b**

Compound	RBA[a] (%) E_2 = 100	Antiestrogen activity[b] (% inhibition ± SEM)			Estrogen activity[c] (% control ± SEM)
		1 mg/kg po	3 mg/kg po	10 mg/kg po	sc
12b (CH4893237)	1.0	54 ± 6	85 ± 4	96 ± 1	−1 ± 1[d] (50 mg/kg)
11b	1.1	59 ± 6	93 ± 1	99 ± 1	−4 ± 1[d] (17 mg/kg)

[a] Relative binding affinities for the recombinant ERα, determined by competitive radiometric binding assay with [^{3}H]estradiol.
[b] Inhibition of estrogen-stimulated uterine weight gain by the test compound with po administration.
[c] Stimulation of uterine weight gain by the test compound with sc administration.
[d] No significant difference between the test group and the vehicle group at $P < 0.05$ using Student's t test.

17-hydroxy to the 17-keto derivative is well documented in the metabolism of estradiol (E_2) in monkeys and humans,[18–27] in which orally administered 17-hydroxy derivative E_2 is easily converted to 17-keto derivative estrone (E_1), whereas orally administered E_1 is not easily converted to E_2. These data provoked us to investigate the pharmacokinetic profiles and biological activities of 17-keto derivatives **12a** and **12b**. Since the genotoxic concern was suggested in 17-keto derivative **12a**, we then evaluated 17-keto derivative **12b**. As can be seen in Table 4, 17-keto derivative **12b** was found to be metabolically much more stable than 17-hydroxy derivative **11b** in mice and monkeys, in which conversion from 17-keto derivative **12b** to corresponding 17-hydroxy derivative **11b** was much slower than that from compound **11b** to **12b** when dosed orally. These findings were consistent with the metabolism of E_1 and E_2 in monkeys and humans in that conversion from the 17-keto to the 17-hydroxy moiety is much slower than that from the 17-hydroxy to the 17-keto moiety. So, we speculate that the 17-position of 17-keto derivative **12b** would be metabolically much more stable than that of 17-hydroxy derivative **11b** when orally administered to humans.

Other metabolites we obtained in plasma when compound **12b** was orally dosed were the CO_2H glucuronate conjugate, the 3-OH sulfate conjugate, and the CO_2H glucuronate and 3-OH sulfate conjugate. These conjugates were scarcely observed in mouse plasma and less than 1/10 of compound **12b** in rat plasma when orally dosed. However, oral administration of compound **12b** to monkeys afforded total amounts of these conjugates almost 20 times as much as compound **12b** in plasma, which would lower its AUC and bioavailability in monkeys.

Regarding the biological activities, 17-keto derivative **12b** was also found to function as a pure antiestrogen with its oral antiestrogen activity similar to corresponding 17-hydroxy derivative **11b** (Table 5). In addition, 17-keto derivative **12b** exhibited ER downregulation effects in MCF-7 cells,[28] and its oral antitumor activity was almost equal to the maximum antitumor activity of subcutaneous administration of ICI182,780 in the MCF-7 xenograft model.[28]

In summary, we incorporated the carboxy-containing side chains into the 7α-position of the steroid scaffold and found that 17-keto derivative CH4893237 (**12b**) functioned as a pure antiestrogen and ER downregulator with its oral activity much superior to clinically used pure antiestrogen, ICI182,780. The potent antiestrogen activity of **12b** at oral dosing in mice was found to be attributed to improved absorption from the intestinal wall and metabolic stability in liver.

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12. The chiral side chain used in Scheme 3 was prepared by chiral resolution of 2-(4,4,5,5,6,6,7,7,7-nonafluoroheptyl)-10-iododecanoic acid using Chiralpak® AD column with the eluent, hexane/isopropanol/AcOH, 980:20:1. The (−)-isomer was first eluted, and the (+)-isomer used in Scheme 3 was eluted second.
13. Antiestrogen activity was determined as anti-uterotrophic effect of the test compound in ovariectomized (OVX) mice. OVX mice were treated with 0.1 μg of 17β-estradiol benzoate in peanut oil solution subcutaneously along with the indicated dose of the test compound in 5% gum arabic-water suspension orally once a day for three consecutive days. Approximately 24 h after the last administration, mice were euthanized, and their uterine weights were measured. Antiestrogen activity, determined by percent inhibition of estrogen-stimulated uterine weight gain by the test compound, was calculated according to the following equation: % inhibition = $100 \times (1 - (T - C)/(E - C))$. Estrogen activity was determined as uterotrophic effect of the test compound in OVX mice. OVX mice were treated with the indicated dose of the test compound in 10% EtOH-peanut oil solution subcutaneously once a day for three consecutive days. Approximately 24 h after the last administration, mice were euthanized, and their uterine weights were measured. Estrogen activity, determined by percent uterine weight gain by the test compound, was calculated according to the following equation: % uterine weight gain = $100 \times (T - C)/(E - C)$. T, E, and C refer to uterine weight gain per body weight by the test compound, by 17β-estradiol benzoate, and by vehicle, respectively.
14. The RBA value for ICI182,780 we obtained appears higher than other published values, which may be due to the experimental condition. The condition we used mainly differs from other reports in that the temperature we used is 25 °C, whereas the temperature other reports used is 0 or 4 °C. We speculate that ER degradation by ICI182,780 at 25 °C proceeded faster than at 0 or 4 °C, which led to

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