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Discovery of thiochroman and chroman derivatives as pure antiestrogens and their structure–activity relationship

Yoshitake Kanbe,[a,*] Myung-Hwa Kim,[a] Masahiro Nishimoto,[a] Yoshihito Ohtake,[a] Nobuaki Kato,[a] Toshiaki Tsunenari,[a] Kenji Taniguchi,[a] Iwao Ohizumi,[a] Shin-ichi Kaiho,[a] Kazumi Morikawa,[a] Jae-Chon Jo,[b] Hyun-Suk Lim[b] and Hak-Yeop Kim[b]

[a]*Fuji Gotemba Research Laboratories, Chugai Pharmaceutical Co., Ltd, 1-135, Komakado, Gotemba, Shizuoka 412-8513, Japan*
[b]*C&C Research Laboratories, 146-141, Annyung, Taean, Hwasung, Kyunggi 445-976, Republic of Korea*

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Abstract—In order to develop pure antiestrogens, a series of 7-hydroxy-3-(4-hydroxyphenyl)-3-methylchroman and 7-hydroxy-3-(4-hydroxyphenyl)-3-methylthiochroman derivatives with sulfoxide containing side chains at the 4-position were designed, synthesized, and evaluated. Among them, compounds **14b** and **24b** functioned as pure antiestrogens with the ability to downregulate ER, and their in vitro and in vivo antiestrogen activities were similar to those of ICI182,780. In addition, the structure–activity relationship indicated that the (3*RS*,4*RS*)-configuration between the 3- and 4-position, the methyl group at the 3-position, the 9-methylene chain between the scaffold and the sulfoxide moiety, and the terminal perfluoroalkyl moiety play an important role in increasing estrogen receptor binding and oral antiestrogen activities.

1. Introduction

Estrogens exert a variety of physiological effects on reproductive tissue, skeletal, cardiovascular, and central nervous systems, and compounds which can modulate signals mediated via estrogen receptors (ER) have been used for the treatment of breast cancer, osteoporosis, and hormone replacement therapy.[1–3] In particular, tamoxifen has been widely used for the treatment of hormone-dependent breast cancer for more than two decades. Tamoxifen is known as an estrogen antagonist; however, it also has agonist activity, and this partial agonism has been suggested to cause deleterious effects such as development of tumor flare, endometrial stimulation, endometrial overgrowth, and endometrial cancer.[4,5] On the other hand, other antagonists such as ICI182,780, ICI164,384, and ZM189,154 with no agonist activities were also developed and are known as pure antiestrogens.[6–9] Since these pure antiestrogens exhibited no agonist activities in preclinical studies, they were expected to eliminate the deleterious effects derived from the partial agonism in tamoxifen therapy.[6,7] In fact, ICI182,780 demonstrated effectiveness in postmenopausal women with advanced breast cancer progression after tamoxifen therapy in clinical trials,[10–12] and was launched in 2002 as an intramuscular injection drug for the treatment of hormone receptor positive breast cancer with disease progression following tamoxifen therapy (Fig. 1).

Recently, X-ray crystallographic studies disclosed the binding modes of various ligands with the ER ligand binding domain (ER-LBD), and estrogen agonists, SERMs, and pure antiestrogens were found to induce different conformation changes of helix12 (H12) of ER in the ligand-ER-LBD complexes. Binding of the endogenous estrogen, 17β-estradiol (E_2), induced H12 folding over the surface of ER-LBD, creating a specific coactivator binding site composed of H3, H4, H5, and H12.[13] Coactivator binding to this specific site utilizing its LXXLL motif is suggested to be essential for an agonist-dependent transcriptional activation. Tamoxifen and raloxifene, both SERMs, were also found to bind to ER-LBD and induce H12 folding over the surface of ER-LBD.[13,14] However, the position of the folded

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* Corresponding author. Tel.: +81 550 87 6727; fax: +81 550 87 5326; e-mail: kanbeyst@chugai-pharm.co.jp

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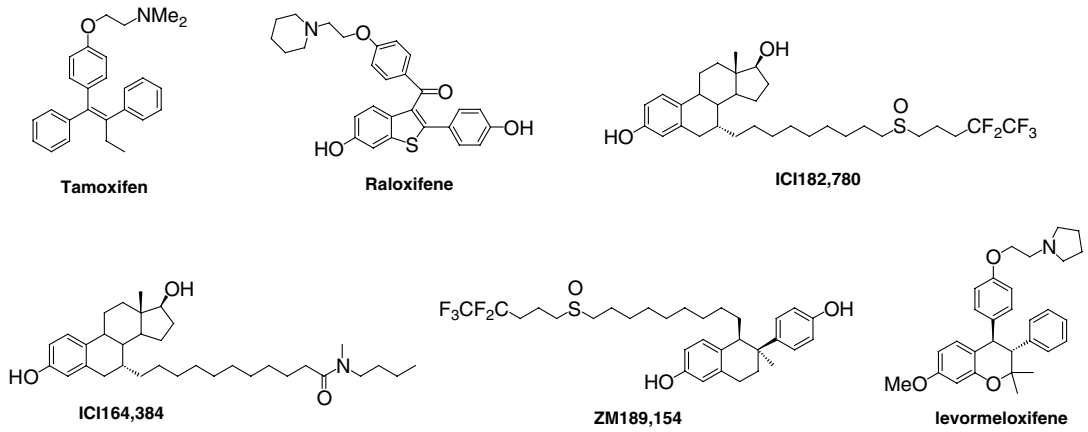


Figure 1. Structure of representative antiestrogens.

H12 was somewhat different from that in the E_2-ER-LBD complex. The amine side chain of tamoxifen or raloxifene extended toward the outside of ER-LBD, blocking the H12 folding to the same position as in the E_2-ER-LBD complex. Some parts of H12 seemed to mimic the LXXLL motif of a coactivator helix, which induced H12 folding to a coactivator binding site instead. In contrast to E_2 and SERMs, pure antiestrogen ICI164,384 did not induce the H12 folding over ER-LBD found in the X-ray crystal structure with ER-LBD.[15] The amide side chain of ICI164,384 protruded from ER-LBD, in which its amide moiety made a hydrophilic interaction with water and its terminal hydrophobic moiety was buried in the AF-2 cleft on the ER-LBD surface. The AF-2 cleft is considered a key binding site of H12 when tamoxifen and raloxifene bind to ER-LBD. These findings suggested that the protruding amide side chain of ICI164,384 blocked the H12 folding to the position observed in the E_2-ER-LBD complex as well as to the coactivator binding site observed in the tamoxifen- and raloxifene-ER-LBD complexes. Regarding the pure antiestrogen ICI182,780, X-ray crystallographic studies with ER-LBD have not been disclosed yet. However, we speculate that it would bind to ER-LBD in a fashion similar to ICI164,384, with its side chain protruding from ER-LBD, the sulfoxide moiety creating a hydrophilic interaction with water, and the terminal hydrophobic moiety buried in the AF-2 cleft. Based on the structural features of ER-LBD complexed with different ligands, we assumed that a combination of a scaffold, which could be accommodated in ER-LBD, with a side chain, which could take a spatial location similar to ICI164,384 or ICI182,780, would yield pure antiestrogens.

In this study, we first investigated whether the combination of the scaffolds such as 7-hydroxy-3-(4-hydroxyphenyl)-3-methylthiochroman and 7-hydroxy-3-(4-hydroxyphenyl)-3-methylchroman with the same side chain as ICI182,780 would afford pure antiestrogens. These scaffolds were selected because of their similarities to those of pure antiestrogen ZM189,154 and estrogen antagonist levormeloxifene.[16] Concerning the position and configuration of the attached side chain, 4-position with (3*RS*,4*RS*)-configuration was selected based on the superimposition of these

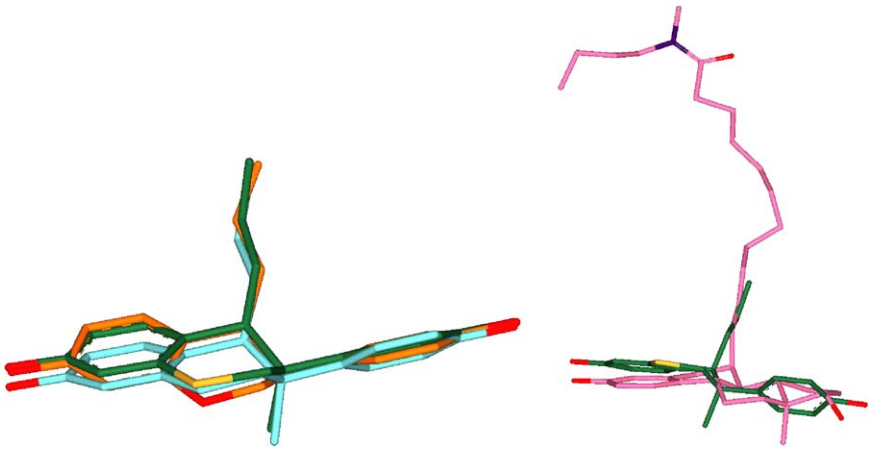
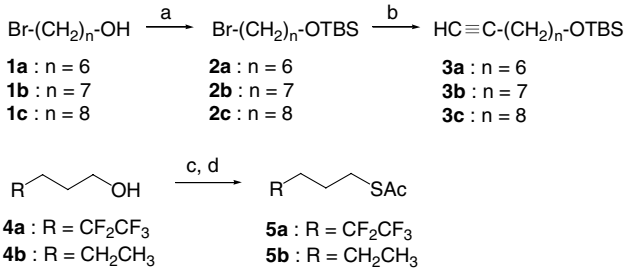


Figure 2. Superimposition of global minimum conformers of the thiochroman scaffold (green), the chroman scaffold (orange), and the tetrahydronaphthalene scaffold (light blue) (left). Superimposition of the crystal structure of ICI164,384 (purple) with the global minimum conformer of the thiochroman scaffold (green) (right). A propyl group was appended to the thiochroman, chroman, and tetrahydronaphthalene scaffold to clarify the direction of the side chain.

scaffolds with the tetrahydronaphthalene scaffold in ZM189,154 and the steroid scaffold in ICI164,384 (Fig. 2). In addition, we also investigated the structure–activity relationship studies on the relative configuration at the 3,4-position, the methyl group at the 3-position, the number of methylenes between the scaffold and the sulfoxide moiety, and the terminal perfluoroalkyl moiety.

2. Chemistry

Alkyne derivatives **3a–c** were prepared by reaction of lithium acetylide with TBS-protected bromoalkane derivatives **2a–c** (Scheme 1). The thiochroman derivatives were prepared from ketone **6**[17] according to the method described in Scheme 2. A nucleophilic 1,2-addition to ketone **6** with alkyne derivatives **3a–c** in the presence of *n*-BuLi afforded 1,2-adducts **7a–c**. Reduction of 1,2-adducts **7a–c** with $NaBH_3CN$ in the presence of ZnI_2, and subsequent repetitive catalytic hydrogenation afforded alcohol derivatives **9a–c** as a mixture of (3*RS*,4*RS*)- and (3*RS*,4*SR*)-isomers, in which the (3*RS*,4*RS*)-isomer was dominant. Alcohol derivatives **9a–c** were converted to corresponding mesylate derivatives **10a–c**, and subsequent reaction with 4,4,5,5,5-pentafluoropentyl thioacetate **5a** or pentyl thioacetate **5b** in the presence of NaOMe provided (3*RS*,4*RS*)-sulfide derivatives **11a–d** and (3*RS*,4*SR*)-sulfide derivatives **12a–d**, which were separated by column chromatography. The relative configuration of each isomer was determined based on NOESY 2D NMR spectroscopy. Between sulfide derivatives **11a** and **12a**, the NOE effect between the methylene proton at 1-position of the side chain and the methyl group at the 3-position was observed in the more polar isomer, but not in the less polar isomer. Therefore, the more polar isomer was assigned to be (3*RS*,4*SR*)-derivative **12a** and the less polar isomer to be (3*RS*,4*RS*)-derivative **11a**. As for sulfide derivatives **11b–d** and **12b–d**, a relative configuration was assigned based on the NMR patterns of (3*RS*,4*RS*)-derivative **11a** and (3*RS*,4*SR*)-derivative **12a**. Deprotection of methyl ether of sulfide derivatives **11a–d** and **12b** with BBr_3 yielded corresponding phenol derivatives **13a–d** and **15b**. Sulfide derivatives **13a–d** were also converted to corresponding sulfoxide derivatives **14a–d** by oxidation with Oxone®.



Scheme 1. Reagents: (a) TBDMSCl, imidazole, MeCN; (b) lithium acetylide ethylenediamine complex, DMSO, THF; (c) MsCl, Et_3N, CH_2Cl_2; (d) AcSK, acetone.

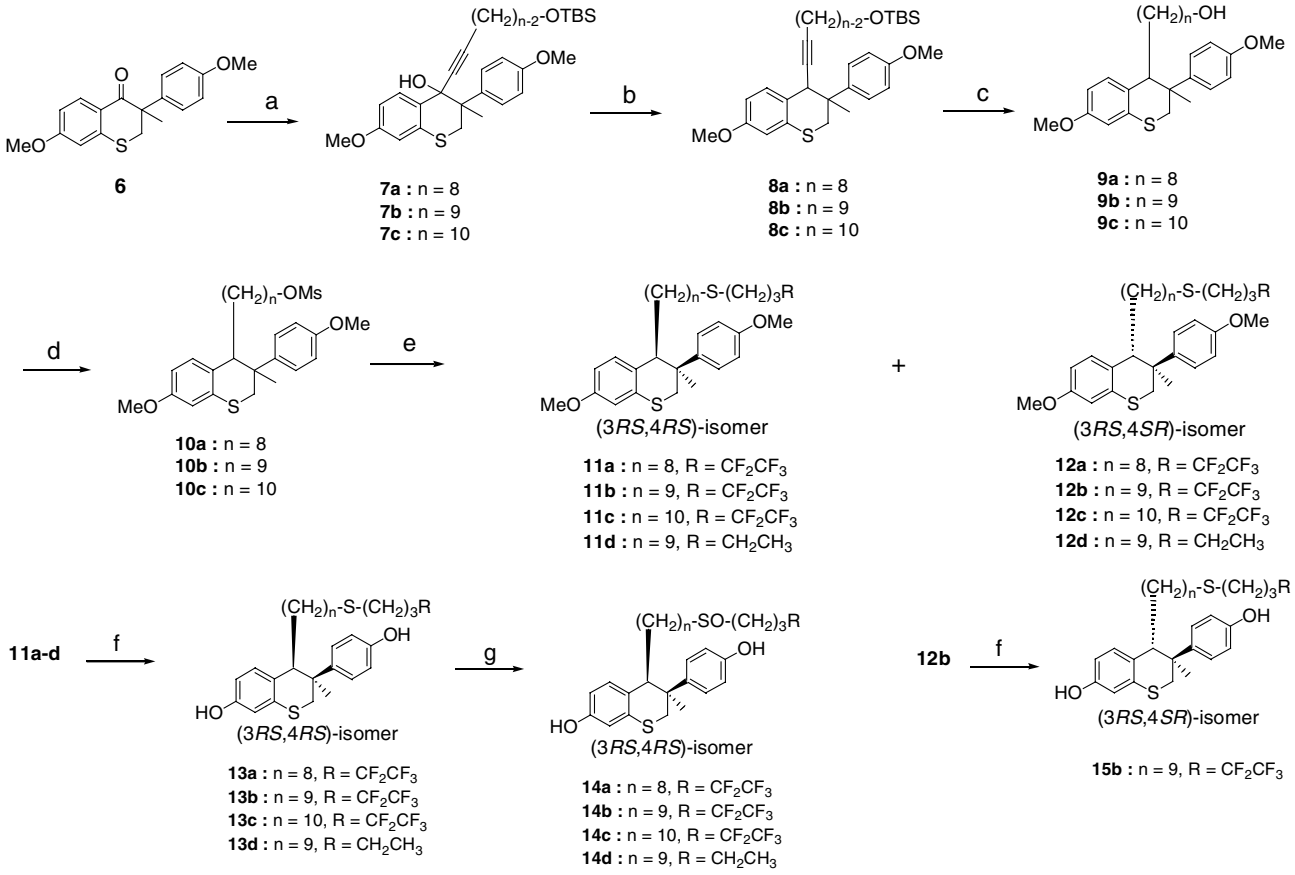
The chiral isomers of sulfoxide derivative **14b** were also prepared from chiral ketones (*R*)-**6** and (*S*)-**6** using the same method as in Scheme 2. The chiral resolution of ketone **6** with a CHIRALCEL OD column afforded chiral ketones (+)-**6** and (−)-**6**, in which (+)-**6** isomer crystallized. X-ray analysis of chiral ketone (+)-**6** showed the absolute configuration to be (*R*), which consequently suggested the other to be (*S*). Both chiral ketones (*R*)-**6** and (*S*)-**6** were converted to the corresponding (3*S*,4*S*)- and (3*R*,4*R*)-sulfoxide derivatives (Scheme 3).

The chroman derivatives were prepared from ketone **16**[18] using a procedure similar to that used for the thiochroman derivatives (Scheme 4). Regarding the chroman derivatives, the hydroxyl group at the 4-position and the alkyne moiety of 1,2-adducts **17a–c** were easily hydrogenated with catalytic hydrogenation, yielding 4-alkyl-substituted derivatives **18a–c**. Note that a prolonged reaction time gave a mixture of the chroman derivatives in which the TBS and MOM groups were deprotected. A relative configuration of chroman derivatives **21a–c** and **22a–c** was also assigned based on NOESY 2D NMR spectroscopy and NMR patterns similar to those used for the thiochroman derivatives. Sulfoxide derivative **26b** bearing no methyl group at the 3-position was also prepared with a procedure described by this laboratory.[19]

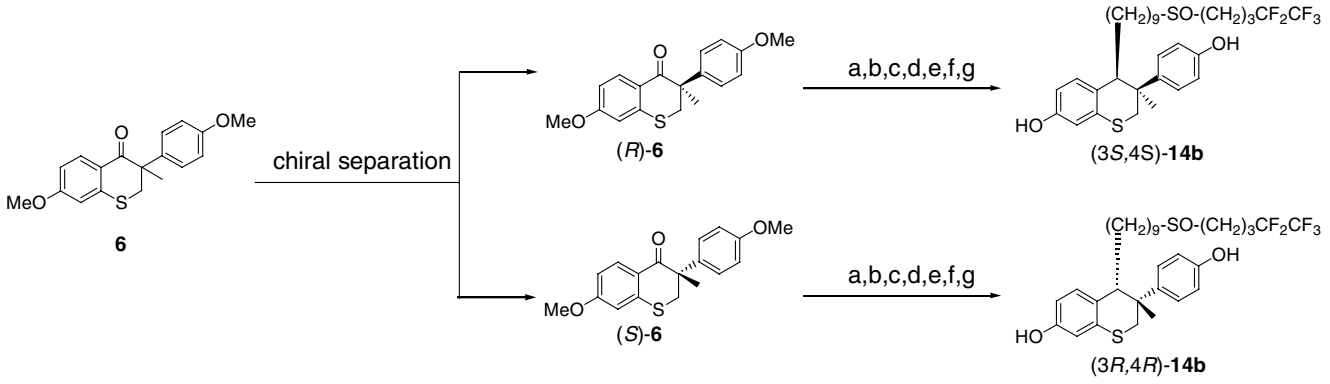
3. Results and discussion

The thiochroman and chroman derivatives prepared were assayed in vitro and in vivo to characterize their profiles and to investigate their SAR studies. In vitro, a binding affinity for ERα was determined by displacement of [^{3}H]estradiol with the test compound utilizing human recombinant 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 mice model, respectively. Agonist and antagonist activities were measured to discriminate pure antiestrogens from SERMs such as tamoxifen and raloxifen. A compound that blocked estrogen-stimulated uterine weight gain as well as exhibiting no significant uterine weight gain itself was considered a pure antiestrogen.

Based on the assumption in the introduction, we initially synthesized thiochroman and chroman derivatives **14b** and **24b** which have the same sulfoxide side chain as ICI182,780 at the 4-position. As shown in Table 1, compounds **14b** and **24b** showed considerable affinities for ERα compared to E_2. Subcutaneous administration of compound **14b** and **24b** at 300 μg/mouse almost completely inhibited estrogen-induced uterine weight gain and showed no significant uterine weight gain when dosed alone compared to vehicle. Furthermore, oral administration of compounds **14b** and **24b** at 10 and 50 mg/kg exhibited antiestrogen activities similar to those of ICI182,780. We also found compounds **14b** and **24b** exhibited ER downregulation effects in MCF-7 cells (unpublished data). These findings indicate that



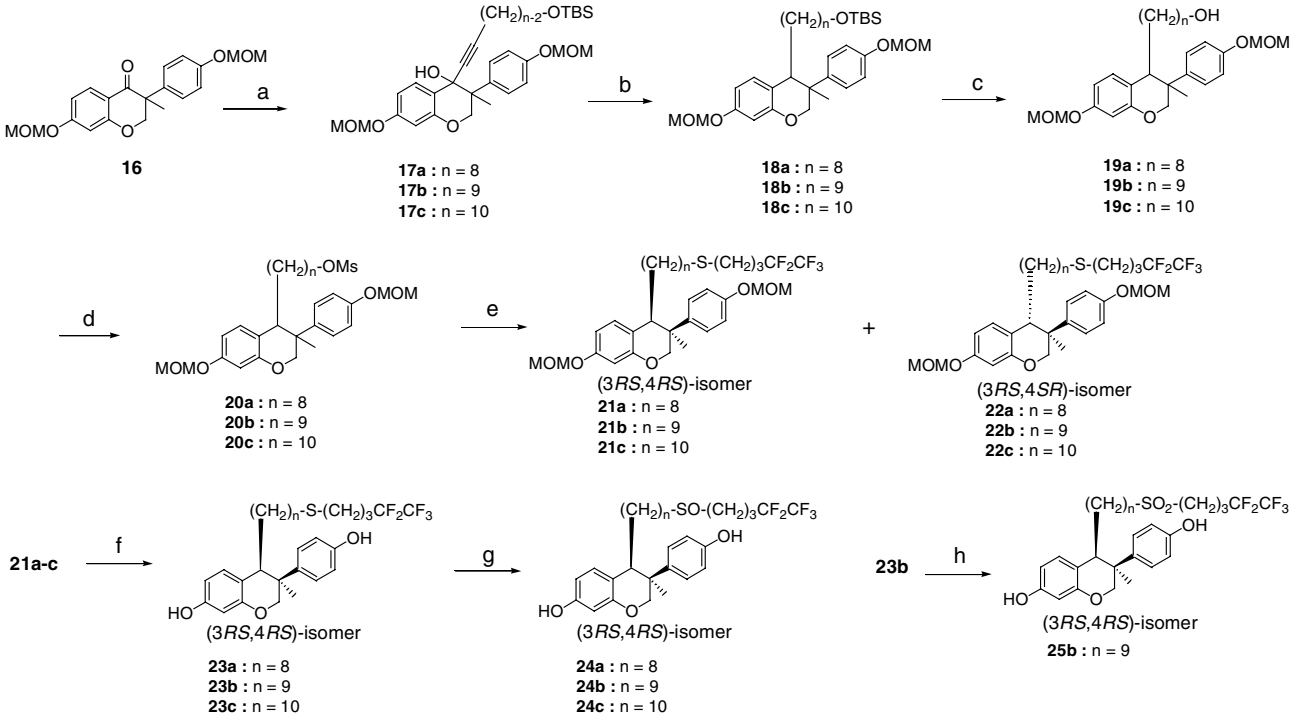
Scheme 2. Reagents: (a) **3a**–**c**, *n*-BuLi, THF; (b) ZnI_2, $NaBH_3CN$, 1,2-dichloroethane; (c) Pd/C, H_2, THF, MeOH; (d) MsCl, Et_3N, CH_2Cl_2; (e) **5a** or **5b**, NaOMe, MeOH, THF; (f) BBr_3, CH_2Cl_2; (g) oxone®, THF, H_2O.



Scheme 3. Reagents: (a) **3b**, *n*-BuLi, THF; (b) ZnI_2, $NaBH_3CN$, 1,2-dichloroethane; (c) Pd/C, H_2, THF, MeOH; (d) MsCl, Et_3N, CH_2Cl_2; (e) **5a**, NaOMe, MeOH, THF; (f) BBr_3, CH_2Cl_2; (g) oxone®, THF, H_2O.

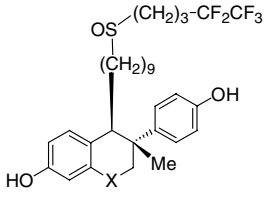
compounds **14b** and **24b** functioned as pure antiestrogens with the ability to downregulate ER, and their oral antiestrogen activities were similar to those of ICI182,780.

Having confirmed that the thiochroman and chroman scaffolds with the same side chain as ICI182,780 yielded pure antiestrogens **14b** and **24b**, chiral isomers of **14b** were then synthesized and evaluated. As shown in Table 2, both the chiral isomers of **14b**, (3*R*,4*R*)-**14b** and (3*S*,4*S*)-**14b**, showed same binding affinities for ERα and similar antiestrogen activities when dosed subcutaneously and orally. It is interesting to note that although the directions of both the side chains are completely opposite when the hydroxyl groups at the 7-position and the 4′-position of one isomer are overlaid on the respective hydroxyl groups at the 7-position and the 4′-position of the other, their binding affinities for ERα were almost the same. Flipping one scaffold 180° about its longest (hydroxy-to-hydroxy) axis and rotating it so that the hydroxyl group at the 7-position superim-



Scheme 4. Reagents: (a) **3a**–**c**, *n*-BuLi, THF; (b) Pd/C, H_2, AcOEt; (c) PPTS, CH_2Cl_2, MeOH; (d) MsCl, Et_3N, CH_2Cl_2; (e) **5a**, NaOMe, MeOH, THF; (f) HCl–MeOH; (g) oxone® (0.6 equiv), THF, H_2O; (h) oxone® (3 equiv), THF, H_2O.

Table 1. Biological data of compounds **14b** and **24b**



Compound	X	RBA[a] (%) E_2 = 100	Antiestrogen activity[b] (% inhibition)				Estrogen activity[c] (% uterine weight gain)
			30 μg/mouse (sc)	300 μg/mouse (sc)	10 mg/kg (po)	50 mg/kg (po)	300 μg/mouse (sc)
14b	S	200	83	101	51	94	−2*
24b	O	96	90	94	66	88	1*
ZM189,154	CH_2	169	79	97	42	76	4*
ICI182,780		138	75	95	54	86	−1*

[a] Relative binding affinities for the recombinant estrogen receptor (ERα), determined by competitive radiometric binding assay with [^{3}H]estradiol.
[b] Inhibition of estradiol-stimulated uterine weight gain by the test compound with subcutaneous (sc) or oral (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 2. Biological data of compounds (3*R*,4*R*)-**14b** and (3*S*,4*S*)-**14b**

Compound	RBA[a] (%) E_2 = 100	Antiestrogen activity[b] (% inhibition)		
		3 μg/mouse (sc)	30 μg/mouse (sc)	25 mg/kg (po)
(3*R*,4*R*)-**14b**	200	22	87	47
(3*S*,4*S*)-**14b**	200	13	71	37
14b	200	n.t.	83	51 (10 mg/kg)

n.t., not tested.
[a] Relative binding affinities for the recombinant estrogen receptor (ERα), determined by competitive radiometric binding assay with [^{3}H]estradiol.
[b] Inhibition of estradiol-stimulated uterine weight gain by the test compound with sc or po administration.

poses on the hydroxyl group at the 4′-position of the other isomer lead to both side chains extending almost the same axial direction and both scaffolds occupying a similar space (Fig. 3). We speculated that these conformers would equally contribute to the binding affinity for ERα and they did indeed show almost the same affinity for ERα.

We next turned our attention to the SAR studies on the relative configuration at the 3- and 4-position, the methyl group at the 3-position, the number of methylenes between the scaffold and the sulfoxide moiety, the terminal perfluoro moiety, and the oxidation state of the sulfur atom at the side chain (Table 3). With respect to the relative configuration between the 3- and 4-position, (3*RS*,4*RS*)-isomer **13b** showed higher binding affinity than corresponding (3*RS*,4*SR*)-isomer **15b**. Conformation analysis showed that the directions of the side chains of both isomers were quite different: almost axial in (3*RS*,4*RS*)-isomer **13b** and almost equatorial in (3*RS*,4*SR*)-isomer **15b**. Axial directed side chains were also observed at the 7-position of pure antiestrogens ICI164,384 and ICI182,780. This information, together with our data, suggested that (3*RS*,4*RS*)-configuration, its side chain being almost axial, was important for high affinity for ERα and potent antiestrogen activities.

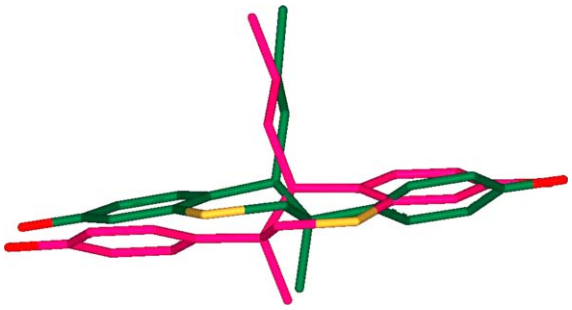
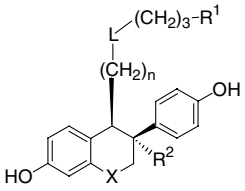


Figure 3. Superimposition of the global minimum conformers of (3*R*,4*R*)- and (3*S*,4*S*)-thiochroman derivatives (magenta and green, respectively). A propyl group was appended to the thiochroman and chroman scaffolds to simplify and clarify the scaffold and the direction of the side chains.

Replacement of the methyl group at the 3-position with a hydrogen atom decreased the binding affinity for ERα as well as antiestrogen activities with oral administration (**24b** vs **26b**). Perhaps, this is because the methyl group at the 3-position would lead the 3-aryl group to take a location almost identical to the chroman ring, in which the whole conformation would function as an alternative to the steroid scaffold and more potent activities would be observed.

Table 3. Biological data of thiochroman and chroman derivatives



Compound	*n*	X	R^1	R^2	L	RBA[a] (%) E_2 = 100	Antiestrogen activity[b] (%inhibition)		
							30 μg/mouse (sc)	10 mg/kg (po)	50 mg/kg (po)
14a	8	S	CF_2CF_3	Me	SO	230	90	43	77
13b	9	S	CF_2CF_3	Me	S	59	21	n.t.	n.t.
15b[c]	9	S	CF_2CF_3	Me	S	7	2	n.t.	n.t.
14b	9	S	CF_2CF_3	Me	SO	200	83	51	94
14d	9	S	CH_2CH_3	Me	SO	120	84	0	20
14c	10	S	CF_2CF_3	Me	SO	220	56	29	78
24a	8	O	CF_2CF_3	Me	SO	150	67	33	58[d]
23b	9	O	CF_2CF_3	Me	S	29	19	32	78[d]
24b	9	O	CF_2CF_3	Me	SO	96	90	66	81[d]
26b	9	O	CF_2CF_3	H	SO	37	0	13	46
25b	9	O	CF_2CF_3	Me	SO_2	130	88	37	63[d]
24c	10	O	CF_2CF_3	Me	SO	100	81	54	79[d]
ICI182,780						138	75	54	86

n.t., not tested.

[a] Relative binding affinities for the recombinant estrogen receptor (ERα), determined by competitive radiometric binding assay with [^{3}H]estradiol.

[b] Inhibition of estradiol-stimulated uterine weight gain by the test compound with sc or po administration.

[c] Relative configuration is (3*RS*,4*SR*).

[d] 30 mg/kg, po.

As far as the number of methylenes between the scaffold and the sulfoxide moiety is concerned, thiochroman and chroman derivatives with the 8-, 9-, and 10-methylenes, **14a–c** and **24a–c**, demonstrated similar and considerable binding affinities for ERα compared to ICI182,780. These side chains are so flexible that the sulfoxide and terminal perfluoro moieties can take similar locations to ICI182,780, which would attribute to the similar and considerable binding affinities for ERα. Furthermore, compounds **14a–c** and **24a–c** showed potent antiestrogen activities with oral administration, of which compounds bearing 9-methylenes, **14b** and **24b**, were most potent.

It is noteworthy to mention that although compounds **14b** and **14d** showed high binding affinities for ERα and similar antiestrogen activities with subcutaneous administration, oral administration at 10 and 50 mg/kg afforded quite different antiestrogen activities. The structural difference between these compounds was the terminal alkyl moiety of the side chain. We speculated that the terminal alkyl moiety would be easily metabolized by ω and ω-1 oxidation, whereas the terminal perfluoroalkyl moiety would block this oxidation, attributing to the quite different oral antiestrogen activities between these compounds. The effect of the terminal perfluoroalkyl moiety inhibiting ω and ω-1 oxidation has been mentioned in a previous study.[20]

The compounds having the sulfoxide or the sulfone moiety in the side chain, **24b** and **25b**, showed more potent receptor binding affinities than one having the sulfide moiety, **23b**. As previously mentioned, we speculated that the binding mode of these compounds would be similar to ICI164,384, and therefore, the compounds having a more hydrophilic moiety such as the sulfoxide or the sulfone moiety would create a stronger hydrophilic interaction with water and show higher affinities for ER.

4. Conclusion

In summary, we found that compounds **14b** and **24b** functioned as pure antiestrogens with the ability to downregulate ER, and their in vitro and in vivo antiestrogen activities were similar to those of ICI182,780. In addition, SAR studies indicated that (3*RS*,4*RS*)-configuration between the 3- and 4-position, the methyl group at the 3-position, the 9-methylene chain between the scaffold and the sulfoxide moiety, a more polar moiety such as the sulfoxide or the sulfone in the side chain, and the terminal perfluoroalkyl moiety play an important role in increasing ERα binding affinities and oral antiestrogen activities.

5. Experimental

Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on a JEOL JNM-ECP400 (400 MHz) or a JEOL JNM-EX270 (270 MHz) spectrometer. Chemical shifts were reported in parts per million (ppm) with tetramethylsilane as an internal standard or by reference to proton resonances resulting from incomplete deuteration of NMR solvent. All coupling constants were described in Hertz (Hz). High-resolution mass spectra (HRMS) were performed on a Micromass Q-TOF Ultima spectrometer, and low-resolution mass spectra (LRMS) were performed on a Thermo Electron LCQ-Classic spectrometer or a Waters ZQ2000 spectrometer.

5.1. 1-Bromo-6-(*tert*-butyldimethylsilyloxy)hexane (2a)

A mixture of 6-bromohexan-1-ol (**1a**) (4.84 g, 26.7 mmol), imidazole (2.79 g, 41.0 mmol), and *tert*-butyldimethylchlorosilane (6.18 g, 41.0 mmol) in acetonitrile (50 mL) was stirred at room temperature for 24 h. The precipitate was filtered off, and the residue was concentrated and purified with column chromatography (*n*-hexane/ethyl acetate = 40:1) to afford 4.25 g (54%) of **2a**. ^{1}H NMR (270 MHz, $CDCl_3$): δ 3.61 (2H, t, J = 6.3 Hz), 3.41 (2H, t, J = 6.8 Hz), 1.92–1.81 (2H, m), 1.56–1.30 (6H, m), 0.89 (9H, s), 0.05 (6H, s).

5.2. 1-Bromo-7-(*tert*-butyldimethylsilyloxy)heptane (2b)

This compound was prepared from **1b** using a procedure similar to that described for **2a**. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.60 (2H, t, J = 6.4 Hz), 3.40 (2H, t, J = 7.0 Hz), 1.87–1.84 (2H, m), 1.51–1.33 (8H, m), 0.89 (9H, s), 0.04 (6H, s).

5.3. 1-Bromo-8-(*tert*-butyldimethylsilyloxy)octane (2c)

This compound was prepared from **1c** using a procedure similar to that described for **2a**. ^{1}H NMR (270 MHz, $CDCl_3$): δ 3.59 (2H, t, J = 6.3 Hz), 3.39 (2H, t, J = 6.8 Hz), 1.88–1.77 (2H, m), 1.60–1.20 (10H, m), 0.89 (9H, s), 0.04 (6H, s).

5.4. 8-(*tert*-Butyldimethylsilyloxy)-oct-1-yne (3a)

To a stirred mixture of lithium acetylide ethylenediamine complex (90%, 2.82 g, 27.6 mmol) in dimethylsulfoxide (17 mL) and tetrahydrofuran (7 mL) was added a tetrahydrofuran solution (7 mL) of **2a** (4.07 g, 13.8 mmol) at −10 °C, and the reaction mixture was allowed to warm to room temperature overnight. The reaction mixture was poured into water and extracted with ether. The extract was dried over anhydrous magnesium sulfate and concentrated. The crude product was purified with column chromatography (*n*-hexane/ethyl acetate = 50:1) to afford 1.76 g (53%) of **3a**. ^{1}H NMR (270 MHz, $CDCl_3$): δ 3.60 (2H, t, J = 6.5 Hz), 2.21–2.15 (2H, m), 1.93 (1H, t, J = 2.6 Hz), 1.59–1.37 (8H, m), 0.89 (9H, s), 0.05 (6H, s).

5.5. 9-(*tert*-Butyldimethylsilyloxy)-non-1-yne (3b)

This compound was prepared from **2b** using a procedure similar to that described for **3a**. ^{1}H NMR (270 MHz, $CDCl_3$): δ 3.59 (2H, t, J = 6.5 Hz), 2.21–2.13 (2H, m), 1.92 (1H, t, J = 2.6 Hz), 1.52–1.23 (10H, m), 0.88 (9H, s), 0.04 (6H, s).

5.6. 10-(*tert*-Butyldimethylsilyloxy)-dec-1-yne (3c)

This compound was prepared from **2c** using a procedure similar to that described for **3a**. ^{1}H NMR (270 MHz, $CDC1_3$): δ 3.59 (2H, t, J = 6.5 Hz), 2.21–2.13 (2H, m), 1.92 (1H, t, J = 2.7 Hz), 1.64–1.30 (12H, m), 0.89 (9H, s), 0.04 (6H, s).

5.7. 4,4,5,5,5-Pentafluoropentyl thioacetate (5a)

To a dichloromethane solution (200 mL) of 4,4,5,5,5-pentafluoropentanol (23.2 g, 130 mmol) and triethylamine (27.0 g, 267 mmol) was added methanesulfonyl chloride (30.0 g, 262 mmol) at 0 °C, and the reaction mixture was allowed to warm to room temperature overnight. The reaction mixture was poured into water and extracted with chloroform. The extract was dried over anhydrous magnesium sulfate and concentrated to give 33.9 g of 4,4,5,5,5-pentafluoropentyl methanesulfonate. Then, to an acetone solution (500 mL) of the obtained 4,4,5,5,5-pentafluoropentyl methanesulfonate (33.9 g) was added potassium thioacetate (18.0 g, 158 mmol) and stirred at room temperature for 12 h. The precipitate was filtered off and the residue was concentrated. The crude product was purified with column chromatography (*n*-hexane/ethyl acetate = 20:1) to afford 15.8 g (51%) of **5a**. ^{1}H NMR (270 MHz, $CDC1_3$): δ 2.95 (2H, t, J = 6.9 Hz), 2.35 (3H, s), 2.20–1.83 (4H, m).

5.8. Pentyl thioacetate (5b)

This compound was prepared from **4b** using a procedure similar to that described for **5a**. ^{1}H NMR (270 MHz, $CDC1_3$): δ 2.86 (2H, t, J = 7.3 Hz), 2.31 (3H, s), 1.60–1.51 (2H, m), 1.36–1.30 (4H, m), 0.89 (3H, t, J = 6.8 Hz).

5.9. 4-[9-(*tert*-Butyldimethylsilyloxy)-non-1-ynyl]-7-methoxy-3-(4-methoxyphenyl)-3-methylthiochroman-4-ol (7b)

To a tetrahydrofuran solution (10 mL) of **3b** (1.66 g, 6.52 mmol) was added a 2.70 M *n*-hexane solution of *n*-butyl lithium (2.20 mL, 5.94 mmol) at −20 °C under N_2 atmosphere, and the reaction mixture was stirred for 1 h at −20 °C. Then a tetrahydrofuran solution (10 mL) of **6** (923 mg, 2.94 mmol) was added to the reaction mixture and stirred for 2 h at −10 °C. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was dried over anhydrous magnesium sulfate, concentrated, and purified with column chromatography (*n*-hexane/ethyl acetate = 10:1 → 5:1) to afford 1.64 g (98%) of **7b**. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.86 (1H, d, J = 8.8 Hz, ArH), 7.60 (2H, d, J = 8.1 Hz, ArH), 6.88 (2H, d, J = 8.1 Hz, ArH), 6.67–6.63 (2H, m, ArH), 4.26 (1H, d, J = 12.3 Hz, H-2), 3.81 (3H, s, OCH_3), 3.78 (3H, s, OCH_3), 3.60 (2H, t, J = 6.4 Hz, CH_2OTBS), 2.71 (1H, d, J = 12.3 Hz, H-2), 2.20–2.18 (3H, m, OH and C≡CCH_2), 1.59–1.26 (13H, m, C3-CH_3 and $(CH_2)_5CH_2$OTBS), 0.89 (9H, s, TBS), 0.05 (6H, s, TBS).

5.10. 4-[8-(*tert*-Butyldimethylsilyloxy)-oct-1-ynyl]-7-methoxy-3-(4-methoxyphenyl)-3-methylthiochroman-4-ol (7a)

This compound was prepared from **6** and **3a** using a procedure similar to that described for **7b**. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.85 (1H, d, J = 8.4 Hz, ArH), 7.60 (2H, d, J = 8.4 Hz, ArH), 6.88 (2H, d, J = 8.4 Hz, ArH), 6.67–6.63 (2H, m, ArH), 4.26 (1H, d, J = 12.3 Hz, H-2), 3.81 (3H, s, OCH_3), 3.78 (3H, s, OCH_3), 3.60 (2H, t, J = 6.4 Hz, CH_2OTBS), 2.71 (1H, d, J = 12.3 Hz, H-2), 2.20–2.17 (3H, m, OH and C≡CCH_2), 1.62–1.24 (11H, m, C_3-CH_3 and $(CH_2)_4CH_2$OTBS), 0.89 (9H, s, TBS), 0.05 (6H, s, TBS).

5.11. 4-[10-(*tert*-Butyldimethylsilyloxy)-dec-1-ynyl]-7-methoxy-3-(4-methoxyphenyl)-3-methylthiochroman-4-ol (7c)

This compound was prepared from **6** and **3c** using a procedure similar to that described for **7b**. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.86 (1H, d, J = 8.8 Hz, ArH), 7.60 (2H, d, J = 8.4 Hz, ArH), 6.88 (2H, d, J = 8.4 Hz, ArH), 6.67–6.63 (2H, m, ArH), 4.26 (1H, d, J = 12.4 Hz, H-2), 3.81 (3H, s, OCH_3), 3.78 (3H, s, OCH_3), 3.59 (2H, t, J = 6.4 Hz, CH_2OTBS), 2.70 (1H, d, J = 12.4 Hz, H-2), 2.19–2.16 (3H, m, OH and C≡CCH_2), 1.62–1.24 (15H, m, C3-CH_3 and $(CH_2)_6CH_2$OTBS), 0.89 (9H, s, TBS), 0.05 (6H, s, TBS).

5.12. 9-[7-Methoxy-3-(4-methoxyphenyl)-3-methylthiochroman-4-yl]-nonan-1-ol (9b)

A mixture of **7b** (1.64 g, 2.88 mmol), zinc iodide (1.30 g, 4.07 mmol), and sodium cyanoborohydride (1.30 g, 20.7 mmol) in 1,2-dichloroethane (40 mL) was stirred for 2 h at room temperature. Then, the reaction mixture was poured into water and extracted with ethyl acetate. The extract was dried over anhydrous magnesium sulfate, concentrated, and purified with column chromatography (*n*-hexane/ethyl acetate = 10:1 → 5:1) to afford 0.78 g (52%) of crude **8b**. Then a mixture of **8b** (0.78 g, 1.4 mmol) and 10% Pd/C (0.27 g) in methanol (40 mL) and tetrahydrofuran (5 mL) was stirred at room temperature for 12 h under hydrogen atmosphere. The reaction mixture was filtered to remove 10% Pd/C and concentrated. Again, methanol (30 mL), tetrahydrofuran (5 mL), and 10% Pd/C (0.27 g) were added to this residue, and the mixture was stirred for 12 h under hydrogen atmosphere. Then, the reaction mixture was filtered to remove 10% Pd/C and concentrated. Furthermore, methanol (30 mL), tetrahydrofuran (5 mL), and 10% Pd/C (0.25 g) were added to this residue, and the mixture was stirred for 12 h under hydrogen atmosphere. Then, the reaction mixture was filtered to remove 10% Pd/C and concentrated. The crude product was purified with column chromatography (*n*-hexane/ethyl acetate = 10:1 → 2:1) to afford 0.35 g (56% from **8b**, 3*RS*,4*RS*/3*RS*,4*SR* = 7:1) of **9b**. ^{1}H NMR (270 MHz, $CDCl_3$) δ: 7.29 (2H, d, J = 8.9 Hz, ArH of *cis*- and *trans*-isomer), 6.94–6.42 (5H, m, ArH of *cis*- and *trans*-isomer), 3.82–3.60 (8H + 7/8H, m, OCH_3 and CH_2OH of *cis*- and *trans*-isomer, and H-2 of *cis*-

isomer), 3.24 (2/8H, s, H-2 of *trans*-isomer), 2.99 (7/8H, d, J = 11.5 Hz, H-2 of *cis*-isomer), 2.92 (1/8H, br s, H-4 of *trans*-isomer), 2.74 (7/8H, br s, H-4 of *cis*-isomer), 1.59–1.08 (19H, m, $(CH_2)_8CH_2OH$ and C3-CH_3 of *cis*- and *trans*-isomer).

5.13. 8-[7-Methoxy-3-(4-methoxyphenyl)-3-methylthiochroman-4-yl]-octan-1-ol (9a)

This compound (3*RS*,4*RS*/3*RS*,4*SR* = 5:l) was prepared from **7a** using a procedure similar to that described for **9b**. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.29 (2H, d, J = 8.1 Hz, ArH of *cis*- and *trans*-isomer), 6.94–6.40 (5H, m, ArH of *cis*- and *trans*-isomer), 3.83–3.56 (8H + 5/6H, m, OCH_3 and CH_2OH of *cis*- and *trans*-isomer, and H-2 of *cis*-isomer), 3.24 (2/6H, s, H-2 of *trans*-isomer), 2.99 (5/6H, d, J = 11.7 Hz, H-2 of *cis*-isomer), 2.91 (1/6H, br s, H-4 of *trans*-isomer), 2.73 (5/6H, br s, H-4 of *cis*-isomer), 1.59–1.08 (17H, m, $(CH_2)_7CH_2OH$ and C3-CH_3 of *cis*- and *trans*-isomer).

5.14. 10-[7-Methoxy-3-(4-methoxyphenyl)-3-methylthiochroman-4-yl]-decan-1-ol (9c)

This compound (3*RS*,4*RS*/3*RS*,4*SR* = 7:l) was prepared from **7c** using a procedure similar to that described for **9b**. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.29 (2H, d, J = 8.1 Hz, ArH of *cis*- and *trans*-isomer), 6.94–6.39 (5H, m, ArH of *cis*- and *trans*-isomer), 3.82–3.59 (8H + 7/8H, m, OCH_3 and CH_2OH of *cis*- and *trans*-isomer, and H-2 of *cis*-isomer), 3.24 (2/8H, s, H-2 of *trans*-isomer), 2.99 (7/8H, d, J = 11.4 Hz, H-2 of *cis*-isomer), 2.91 (1/8H, br s, H-4 of *trans*-isomer), 2.73 (7/8H, br s, H-4 of *cis*-isomer), 1.61–1.08 (21H, m, $(CH_2)_9CH_2OH$ and C3-CH_3 of *cis*- and *trans*-isomer).

5.15. 9-[7-Methoxy-3-(4-methoxyphenyl)-3-methylthiochroman-4-yl]nonyl methanesulfonate (10b)

A mixture of **9b** (0.35 g, 0.79 mmol, 3*RS*,4*RS*/3*RS*,4*SR* = 7:l), methanesulfonyl chloride (0.27 g, 2.36 mmol), and triethylamine (0.24 g, 2.38 mmol) in dichloromethane (10 mL) was stirred at room temperature for 2 h. The reaction mixture was poured into water and extracted with dichloromethane. The extract was dried over anhydrous magnesium sulfate, concentrated, and purified with column chromatography (*n*-hexane/ethyl acetate = 10:1 → 3:1) to afford 0.41 g (quant.) of **10b** (3*RS*,4*RS*/3*RS*,4*SR* = 7:l). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.29–7.24 (2H, m, ArH of *cis*- and *trans*-isomer), 6.93–6.40 (5H, m, ArH of *cis*- and *trans*-isomer), 4.17 (2H, t, J = 6.6 Hz, CH_2OMs of *cis*- and *trans*-isomer), 3.81 (21/8H, s, OCH_3 of *cis*-isomer), 3.76 (21/8H, s, OCH_3 of *cis*-isomer), 3.69 (3/8H, s, OCH_3 of *trans*-isomer), 3.65 (3/8H, s, OCH_3 of *trans*-isomer), 3.63 (7/8H, d, J = 10.2 Hz, H-2 of *cis*-isomer), 3.23 (2/8H, s, H-2 of *trans*-isomer), 2.98–2.95 (3H + 7/8H, m, OMs of *cis*- and *trans*-isomer, and H-2 of *cis*-isomer), 2.90 (1/8H, br s, H-4 of *trans*-isomer), 2.73 (7/8H, br s, H-4 of *cis*-isomer), 1.70–1.07 (19H, m, $(CH_2)_8CH_2OMs$ and C3-CH_3 of *cis*- and *trans*-isomer).

5.16. 8-[7-Methoxy-3-(4-methoxyphenyl)-3-methylthiochroman-4-yl]-octyl methanesulfonate (10a)

This compound (3*RS*,4*RS*/3*RS*,4*SR* = 5:l) was prepared from **9a** (3*RS*,4*RS*/3*RS*,4*SR* = 5:l) using a procedure similar to that described for **10b**. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.30 (2H, d, J = 7.7 Hz, ArH of *cis*- and *trans*-isomer), 6.93–6.40 (5H, m, ArH of *cis*- and *trans*-isomer), 4.17 (2H, t, J = 6.6 Hz, CH_2OMs of *cis*- and *trans*-isomer), 3.83 (15/6H, s, OCH_3 of *cis*-isomer), 3.78 (15/6H, s, OCH_3 of *cis*-isomer), 3.71 (3/6H, s, OCH_3 of *trans*-isomer), 3.66 (3/6H, s, OCH_3 of *trans*-isomer), 3.65 (5/6H, d, J = 12.5 Hz, H-2 of *cis*-isomer), 3.24 (2/6H, br s, H-2 of *trans*-isomer), 3.00–2.98 (3H + 5/6H, m, OMs of *cis*- and *trans*-isomer, and H-2 of *cis*-isomer), 2.91 (1/6H, br s, H-4 of *trans*-isomer), 2.73 (5/6H, br s, H-4 of *cis*-isomer), 1.75–1.01 (17H, m, $(CH_2)_7CH_2OMs$ and C3-CH_3 of *cis*- and *trans*-isomer).

5.17. 10-[7-Methoxy-3-(4-methoxyphenyl)-3-methylthiochroman-4-yl]-decyl methanesulfonate (10c)

This compound (3*RS*,4*RS*/3*RS*,4*SR* = 7:l) was prepared from **9c** (3*RS*,4*RS*/3*RS*,4*SR* = 7:l) using a procedure similar to that described for **10b**. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.29 (2H, d, J = 8.1 Hz, ArH of *cis*- and *trans*-isomer), 6.94–6.41 (5H, m, ArH of *cis*- and *trans*-isomer), 4.20 (2H, t, J = 6.6 Hz, CH_2OMs of *cis*- and *trans*-isomer), 3.82 (21/8H, s, OCH_3 of *cis*-isomer), 3.78 (21/8H, s, OCH_3 of *cis*-isomer), 3.71 (3/8H, s, OCH_3 of *trans*-isomer), 3.66 (3/8H, s, OCH_3 of *trans*-isomer), 3.65 (7/8H, d, J = 12.5 Hz, H-2 of *cis*-isomer), 3.24 (2/8H, s, H-2 of *trans*-isomer), 2.99–2.97 (3H + 7/8H, m, OMs of *cis*- and *trans*-isomer, and H-2 of *cis*-isomer), 2.92 (1/8H, br s, H-4 of *trans*-isomer), 2.73 (7/8H, br s, H-4 of *cis*-isomer), 1.73–1.10 (21H, m, $(CH_2)_9CH_2OMs$ and C3-CH_3 of *cis*- and *trans*-isomer).

5.18. (3*RS*,4*RS*)-7-Methoxy-3-(4-methoxyphenyl)-3-methyl-4-[9-(4,4,5,5,5-pentafluoropentylsulfanyl)-nonyl]thiochroman (11b) and (3*RS*,4*SR*)-7-Methoxy-3-(4-methoxyphenyl)-3-methyl-4-[9-(4,4,5,5,5-pentafluoropentylsulfanyl)nonyl]thiochroman (12b)

To a stirred solution of **5a** (571 mg, 2.42 mmol) in methanol (3 mL) was added a 1.0 M methanol solution of sodium methoxide (2.18 mL, 2.18 mmol) and stirred for 1 h at room temperature. Then, **10b** (210 mg, 0.40 mmol, 3*RS*,4*RS*/3*RS*,4*SR* = 7:l) in tetrahydrofuran (3 mL) was added to this reaction mixture and stirred for 12 h at room temperature. The reaction mixture was neutralized with 50% acetic acid, poured into water, and extracted with ethyl acetate. The extract was washed with water, dried over anhydrous magnesium sulfate, and concentrated. The crude product was purified with chromatography (*n*-hexane/ethyl acetate = 50:1 → 20:1) to afford 197 mg (79%) of **11b** and 28 mg (11%) of **12b**.

^{1}H NMR (**11b**, 400 MHz, $CDCl_3$) δ: 7.29 (2H, d, J = 8.4 Hz, ArH), 6.94–6.89 (3H, m, ArH), 6.73 (1H, s, ArH), 6.58 (1H, d, J = 8.4 Hz, ArH), 3.82 (3H, s, OCH_3), 3.78 (3H, s, OCH_3), 3.64 (1H, d, J = 11.4 Hz,

H-2), 2.99 (1H, d, J = 11.4 Hz, H-2), 2.73 (1H, br s, H-4), 2.57 (2H, t, J = 7.0 Hz, CH_2S), 2.47 (2H, t, J = 7.3 Hz, CH_2S), 2.23–2.10 (2H, m, $CH_2CH_2CF_2CF_3$), 1.91–1.83 (2H, m, $CH_2CH_2CF_2CF_3$), 1.55–1.08 (19H, m, $(CH_2)_8CH_2S$ and C3-CH_3); MS (m/z) 619 (M+1).

^{1}H NMR (**12b**, 400 MHz, $CDCl_3$) δ: 7.30 (2H, d, J = 8.1 Hz, ArH), 6.74 (1H, d, J = 8.2 Hz, ArH), 6.70 (2H, d, J = 8.1 Hz, ArH), 6.53 (1H, s, ArH), 6.40 (1H, d, J = 8.2 Hz, ArH), 3.71 (3H, s, OCH_3), 3.66 (3H, s, OCH_3), 3.24 (2H, s, H-2), 2.91 (1H, br s, H-4), 2.59 (2H, t, J = 7.0 Hz, CH_2S), 2.50 (2H, t, J = 7.3 Hz, CH_2S), 2.24–2.10 (2H, m, $CH_2CH_2CF_2CF_3$), 1.92–1.84 (2H, m, $CH_2CH_2CF_2CF_3$), 1.67–1.25 (19H, m, $(CH_2)_8CH_2S$ and C3-CH_3).

5.19. (3*RS*,4*RS*)-7-Methoxy-3-(4-methoxyphenyl)-3-methyl-4-[8-(4,4,5,5,5-pentafluoropentylsulfanyl)octyl]thiochroman (11a) and (3*RS*,4*SR*)-7-Methoxy-3-(4-methoxyphenyl)-3-methyl-4-[8-(4,4,5,5,5-pentafluoropentylsulfanyl)octyl]thiochroman (12a)

These compounds, **11a** (76%) and **12a** (16%), were prepared from **10a** (3*RS*,4*RS*/3*RS*,4*SR* = 5:l) and **5a** using a procedure similar to that described for **11b** and **12b**.

^{1}H NMR (**11a**, 400 MHz, $CDCl_3$) δ: 7.29 (2H, d, J = 8.4 Hz, ArH), 6.93–6.89 (3H, m, ArH), 6.73 (1H, s, ArH), 6.58 (1H, d, J = 8.4 Hz, ArH), 3.82 (3H, s, OCH_3), 3.78 (3H, s, OCH_3), 3.64 (1H, d, J = 11.6 Hz, H-2), 2.99 (1H, d, J = 11.6 Hz, H-2), 2.73 (1H, br s, H-4), 2.57 (2H, t, J = 7.0 Hz, CH_2S), 2.45 (2H, t, J = 7.3 Hz, CH_2S), 2.22–2.09 (2H, m, $CH_2CH_2CF_2CF_3$), 1.90–1.83 (2H, m, $CH_2CH_2CF_2CF_3$), 1.56–1.01 (17H, m, $(CH_2)_7CH_2S$ and C3-CH_3); MS (m/z) 605 (M+1).

^{1}H NMR (**12a**, 400 MHz, $CDCl_3$) δ: 7.29 (2H, d, J = 8.4 Hz, ArH), 6.74 (1H, d, J = 8.4 Hz, ArH), 6.70 (2H, d, J = 8.4 Hz, ArH), 6.53 (1H, s, ArH), 6.40 (1H, d, J = 8.4 Hz, ArH), 3.71 (3H, s, OCH_3), 3.66 (3H, s, OCH_3), 3.24 (2H, s, H-2), 2.91 (1H, br s, H-4), 2.58 (2H, t, J = 7.0 Hz, CH_2S), 2.49 (2H, t, J = 7.3 Hz, CH_2S), 2.23–2.10 (2H, m, $CH_2CH_2CF_2CF_3$), 1.92–1.84 (2H, m, $CH_2CH_2CF_2CF_3$), 1.66–1.25 (17H, m, $(CH_2)_7CH_2S$ and C3-CH_3); MS (m/z) 605 (M+1).

5.20. (3*RS*,4*RS*)-7-Methoxy-3-(4-methoxyphenyl)-3-methyl-4-[10-(4,4,5,5,5-pentafluoropentylsulfanyl)-decyl]thiochroman (11c) and (3*RS*,4*SR*)-7-Methoxy-3-(4-methoxyphenyl)-3-methyl-4-[10-(4,4,5,5,5-pentafluoropentylsulfanyl)decyl]thiochroman (12c)

These compounds, **11c** (79%) and **12c** (13%), were prepared from **10c** (3*RS*,4*RS*/3*RS*,4*SR* = 7:l) and **5a** using a procedure similar to that described for **11b** and **12b**.

^{1}H NMR (**11c**, 400 MHz, $CDCl_3$) δ: 7.29 (2H, d, J = 8.4 Hz, ArH), 6.94–6.90 (3H, m, ArH), 6.73 (1H, s, ArH), 6.58 (1H, d, J = 8.1 Hz, ArH), 3.82 (3H, s, OCH_3), 3.78 (3H, s, OCH_3), 3.64 (1H, d, J = 11.5 Hz, H-2), 2.99 (1H, d, J = 11.5 Hz, H-2), 2.73 (1H, br s, H-4), 2.58 (2H, t, J = 7.0 Hz, CH_2S), 2.48 (2H, t, J = 7.3 Hz, CH_2S), 2.23–2.10 (2H, m, $CH_2CH_2CF_2CF_3$), 1.91–1.84 (2H, m, $CH_2CH_2CF_2CF_3$), 1.58–1.10 (21H, m, $(CH_2)_9CH_2S$ and C3-CH_3); MS (m/z) 633 (M+1).

^{1}H NMR (**12c**, 400 MHz, $CDCl_3$) δ: 7.29 (2H, d, J = 8.1 Hz, ArH), 6.75–6.69 (3H, m, ArH), 6.53 (1H, s, ArH), 6.40 (1H, d, J = 8.1 Hz, ArH), 3.71 (3H, s, OCH_3), 3.66 (3H, s, OCH_3), 3.24 (2H, s, H-2), 2.91 (1H, br s, H-4), 2.59 (2H, t, J = 7.0 Hz, CH_2S), 2.50 (2H, t, J = 7.3 Hz, CH_2S), 2.22–2.10 (2H, m, $CH_2CH_2CF_2CF_3$), 1.92–1.86 (2H, m, $CH_2CH_2CF_2CF_3$), 1.66–1.24 (21H, m, $(CH_2)_9CH_2S$ and C3-CH_3); MS (m/z) 633 (M+1).

5.21. (3*RS*,4*RS*)-7-Methoxy-3-(4-methoxyphenyl)-3-methyl-4-[9-(pentylsulfanyl)nonyl]thiochroman (11d) and (3*RS*,4*SR*)-7-Methoxy-3-(4-methoxyphenyl)-3-methyl-4-[9-(pentylsulfanyl)nonyl]thiochroman (12d)

These compounds, **11d** (79%) and **12d** (10%), were prepared from **10b** (3*RS*,4*RS*/3*RS*,4*SR* = 7:l) and **5b** using a procedure similar to that described for **11b** and **12b**.

^{1}H NMR (**11d**, 400 MHz, $CDCl_3$) δ: 7.29 (2H, d, J = 8.4 Hz, ArH), 6.93–6.89 (3H, m, ArH), 6.73 (1H, s, ArH), 6.58 (1H, d, J = 8.4 Hz, ArH), 3.82 (3H, s, OCH_3), 3.78 (3H, s, OCH_3), 3.64 (1H, d, J = 11.4 Hz, H-2), 2.99 (1H, d, J = 11.4 Hz, H-2), 2.73 (1H, br s, H-4), 2.50–2.45 (4H, m, CH_2S CH_2), 1.56–0.88 (28H, m, $(CH_2)_8CH_2SCH_2(CH_2)_3CH_3$ and C3-CH_3); MS (m/z) 529 (M+1).

^{1}H NMR (**12d**, 400 MHz, $CDCl_3$) δ: 7.30 (2H, d, J = 8.8 Hz, ArH), 6.74 (1H, d, J = 8.4 Hz, ArH), 6.70 (2H, d, J = 8.8 Hz, ArH), 6.53 (1H, d, J = 2.6 Hz, ArH), 6.40 (1H, dd, J = 8.4, 2.6 Hz, ArH), 3.71 (3H, s, OCH_3), 3.66 (3H, s, OCH_3), 3.24 (2H, s, H-2), 2.91 (1H, br s, H-4), 2.51–2.48 (4H, m, CH_2SCH_2), 1.57–0.88 (28H, m, $(CH_2)_8CH_2SCH_2(CH_2)_3CH_3$ and C3-CH_3).

5.22. (3*RS*,4*RS*)-3-(4-Hydroxyphenyl)-3-methyl-4-[9-(4,4,5,5,5-pentafluoropentylsulfanyl)nonyl]thiochroman-7-ol (13b)

To a stirred solution of **11b** (120 mg 0.19 mmol) in dichloromethane (8 mL) was added a 1.0 M dichloromethane solution of boron tribromide (2.0 mL, 2.0 mmol) at −78 °C under N_2 atmosphere. The reaction mixture was stirred for 1 h at −78 °C and then allowed to warm to room temperature overnight. The reaction mixture was poured into water and extracted with dichloromethane. The extract was dried over anhydrous magnesium sulfate, concentrated, and purified with column chromatography (*n*-hexane/ethyl acetate = 50:1 → 5:1) to afford 85 mg (74%) of **13b**. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.24 (2H, d, J = 8.1 Hz, ArH), 6.87 (1H, d, J = 8.3 Hz, ArH), 6.83 (2H, d, J = 8.1 Hz, ArH), 6.67 (1H, s, ArH), 6.50 (1H, d, J = 8.3 Hz, ArH), 4.86 (1H, br s, OH), 4.68 (1H, br s, OH), 3.62 (1H, d, J = 11.4 Hz, H-2), 2.96 (1H, d,

J = 11.4 Hz, H-2), 2.70 (1H, br s, H-4), 2.58 (2H, t, J = 7.1 Hz, CH_2S), 2.48 (2H, t, J = 7.3 Hz, CH_2S), 2.23–2.10 (2H, m, $CH_2CH_2CF_2CF_3$), 1.92–1.84 (2H, m, $CH_2CH_2CF_2CF_3$), 1.57–1.07 (19H, m, $(CH_2)_8CH_2S$ and C3-CH_3); HRMS (ES-NEG) calculated for $C_{30}H_{39}F_5O_2S_2$: 589.2233. Found: 589.2243 (+1.6 ppm).

5.23. (3*RS*,4*RS*)-3-(4-Hydroxyphenyl)-3-methyl-4-[8-(4,4,5,5,5-pentafluoropentylsulfanyl)octyl]thiochroman-7-ol (13a)

This compound was prepared from **11a** using a procedure similar to that described for **13b**. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.24 (2H, d, J = 8.4 Hz, ArH), 6.87 (1H, d, J = 8.2 Hz, ArH), 6.83 (2H, d, J = 8.4 Hz, ArH), 6.67 (1H, s, ArH), 6.50 (1H, d, J = 8.2 Hz, ArH), 4.91 (1H, br s, OH), 4.68 (1H, br s, OH), 3.63 (1H, d, J = 11.4 Hz, H-2), 2.96 (1H, d, J = 11.4 Hz, H-2), 2.70 (1H, br s, H-4), 2.58 (2H, t, J = 7.0 Hz, CH_2S), 2.46 (2H, t, J = 7.3 Hz, CH_2S), 2.17–2.14 (2H, m, $CH_2CH_2CF_2CF_3$), 1.89–1.86 (2H, m, $CH_2CH_2CF_2CF_3$), 1.56–1.07 (17H, m, $(CH_2)_7CH_2S$ and C3-CH_3); MS (m/z) 577 (M+1).

5.24. (3*RS*,4*RS*)-3-(4-Hydroxyphenyl)-3-methyl-4-[10-(4,4,5,5,5-pentafluoropentylsulfanyl)decyl]thiochroman-7-ol (13c)

This compound was prepared from **11c** using a procedure similar to that described for **13b**. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.24 (2H, d, J = 7.7 Hz, ArH), 6.88 (1H, d, J = 8.1 Hz, ArH), 6.83 (2H, d, J = 7.7 Hz, ArH), 6.67 (1H, s, ArH), 6.50 (1H, d, J = 8.1 Hz, ArH), 4.90 (1H, br s, OH), 4.72 (1H, br s, OH), 3.62 (1H, d, J = 11.7 Hz, H-2), 2.96 (1H, d, J = 11.7 Hz, H-2), 2.71 (1H, br s, H-4), 2.59 (2H, t, J = 7.0 Hz, CH_2S), 2.50 (2H, t, J = 7.3 Hz, CH_2S), 2.23–2.10 (2H, m, $CH_2CH_2CF_2CF_3$), 1.92–1.84 (2H, m, $CH_2CH_2CF_2CF_3$), 1.61–1.07 (21H, m, $(CH_2)_9CH_2S$ and C3-CH_3); MS (m/z) 605 (M+1).

5.25. (3*RS*,4*RS*)-3-(4-Hydroxyphenyl)-3-methyl-4-[9-(pentylsulfanyl)nonyl]thiochroman-7-ol (13d)

This compound was prepared from **11d** using a procedure similar to that described for **13b**. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.22 (2H, d, J = 7.7 Hz, ArH), 6.87 (1H, d, J = 8.2 Hz, ArH), 6.84 (2H, d, J = 7.7 Hz, ArH), 6.67 (1H, s, ArH), 6.50 (1H, d, J = 8.2 Hz, ArH), 4.99 (1H, br s, OH), 4.71 (1H, br s, OH), 3.63 (1H, d, J = 11.5 Hz, H-2), 2.96 (1H, d, J = 11.5 Hz, H-2), 2.70 (1H, br s, H-4), 2.52–2.48 (4H, m, CH_2SCH_2), 1.56–0.88 (28H, m, $(CH_2)_8CH_2SCH_2(CH_2)_3CH_3$ and C3-CH_3).

5.26. (3*RS*,4*RS*)-3-(4-Hydroxyphenyl)-3-methyl-4-[9-(4,4,5,5,5-pentafluoropentylsulfinyl)nonyl]thiochroman-7-ol (14b)

To a stirred mixture of **13b** (33 mg, 0.056 mmol) and Oxone (21 mg, 0.034 mmol) in tetrahydrofuran (10 mL) was added water (1 mL) and stirred for 10 min at room temperature. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was dried over anhydrous magnesium sulfate and concentrated. The crude product was purified with column chromatography (n-hexane/ethyl acetate = 5:1 → 1:1) to afford 29 mg (86%) of **14b**. ^{1}H NMR (400 MHz, $CDCl_3$ + D_2O) δ: 7.23–7.20 (2H, m, ArH), 6.87–6.83 (3H, m, ArH), 6.67 (1H, d, J = 2.6 Hz, ArH), 6.52–6.49 (1H, m, ArH), 3.67–3.63 (1H, m, H-2), 2.96–2.61 (6H, m, H-2, H-4, and CH_2SOCH_2), 2.32–2.17 (4H, m, $CH_2CH_2CF_2CF_3$), 1.80–1.01 (19H, m, $(CH_2)_8CH_2SO$ and C3-CH_3); HRMS (ES-POS) calculated for $C_{30}H_{39}F_5O_3S_2$: 607.2339. Found: 607.2345 (+1.0 ppm).

5.27. (3*RS*,4*RS*)-3-(4-Hydroxyphenyl)-3-methyl-4-[8-(4,4,5,5,5-pentafluoropentylsulfinyl)octyl]thiochroman-7-ol (14a)

This compound was prepared from **13a** using a procedure similar to that described for **14b**. ^{1}H NMR (400 MHz, $CDCl_3$ + D_2O) δ: 7.22 (2H, d, J = 8.8 Hz, ArH), 6.87–6.85 (3H, m, ArH), 6.67 (1H, d, J = 2.6 Hz, ArH), 6.50 (1H, dd, J = 8.1, 2.6 Hz, ArH), 3.65 (1H, d, J = 11.4 Hz, H-2), 2.94 (1H, d, J = 11.4 Hz, H-2), 2.90–2.56 (5H, m, CH_2SOCH_2 and H-4), 2.33–2.16 (4H, m, $CH_2CH_2CF_2CF_3$), 1.69–0.91 (17H, m, $(CH_2)_7CH_2SO$ and C3-CH_3); HRMS (ES-POS) calculated for $C_{29}H_{37}F_5O_3S_2$: 593.2183. Found: 593.2175 (−1.3 ppm).

5.28. (3*RS*,4*RS*)-3-(4-Hydroxyphenyl)-3-methyl-4-[10-(4,4,5,5,5-pentafluoropentylsulfinyl)decyl]thiochroman-7-ol (14c)

This compound was prepared from **13c** using a procedure similar to that described for **14b**. ^{1}H NMR (400 MHz, $CDCl_3$ + D_2O) δ: 7.21 (2H, d, J = 8.8 Hz, ArH), 6.87–6.83 (3H, m, ArH), 6.67 (1H, d, J = 1.8 Hz, ArH), 6.51–6.49 (1H, m, ArH), 3.66–3.62 (1H, m, H-2), 2.96–2.64 (6H, m, H-2, H-4, and CH_2SOCH_2), 2.31–2.18 (4H, m, $CH_2CH_2CF_2CF_3$), 1.82–0.97 (21H, m, $(CH_2)_9CH_2SO$ and C3-CH_3); HRMS (ES-POS) calculated for $C_{31}H_{41}F_5O_3S_2$: 621.2496. Found: 621.2473 (−3.6 ppm).

5.29. (3*RS*,4*RS*)-3-(4-Hydroxyphenyl)-3-methyl-4-[9-(pentylsulfinyl)nonyl]thiochroman-7-ol (14d)

This compound was prepared from **13d** using a procedure similar to that described for **14b**. ^{1}H NMR (400 MHz, $CDCl_3$ + D_2O) δ: 7.22–7.20 (2H, m, ArH), 6.87–6.84 (3H, m, ArH), 6.67 (1H, d, J = 2.6 Hz, ArH), 6.53–6.49 (1H, m, ArH), 3.67–3.63 (1H, m, H-2), 2.96–2.58 (6H, m, H-2, H-4, and CH_2SOCH_2), 1.82–0.91 (28H, m, $(CH_2)_8CH_2SOCH_2(CH_2)_3CH_3$ and C3-CH_3); HRMS (ES-POS) calculated for $C_{30}H_{44}O_3S_2$: 517.2810. Found: 517.2806 (−0.8 ppm).

5.30. (3*RS*,4*SR*)-3-(4-Hydroxyphenyl)-3-methyl-4-[9-(4,4,5,5,5-pentafluoropentylsulfanyl)nonyl]thiochroman-7-ol (15b)

This compound was prepared from **12b** using a procedure similar to that described for **13b**. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.25 (2H, d, J = 8.4 Hz, ArH), 6.68 (1H, d, J = 8.1 Hz, ArH), 6.62 (2H, d, J = 8.4 Hz,

ArH), 6.47 (1H, s, ArH), 6.32 (1H, d, J = 8.1 Hz, ArH), 4.56 (1H, br s, OH), 4.49 (1H, br s, OH), 3.23 (2H, s, H-2), 2.88 (1H, br s, H-4), 2.59 (2H, t, J = 7.0 Hz, CH_2S), 2.50 (2H, t, J = 7.3 Hz, CH_2S), 2.24–2.10 (2H, m, $CH_2CH_2CF_2CF_3$), 1.92–1.84 (2H, m, $CH_2CH_2CF_2CF_3$), 1.66–1.24 (19H, m, $(CH_2)_8CH_2S$ and C3-CH_3); HRMS (ES-NEG) calculated for $C_{30}H_{39}F_5O_2S_2$: 589.2233. Found: 589.2240 (+1.1 ppm).

5.31. 4-[9-(*tert*-Butyldimethylsilyloxy)-non-1-ynyl]-7-methoxymethyloxy-3-(4-methoxymethyloxyphenyl)-3-methylchroman-4-ol (17b)

To a tetrahydrofuran solution (10 mL) of **3b** (1.58 g, 6.21 mmol) was added a 2.70 M hexane solution of n-butyl lithium (2.0 mL, 5.4 mmol) at −20 °C under N_2 atmosphere, and the reaction mixture was stirred for 1 h at −20 °C. Then a tetrahydrofuran solution (10 mL) of **16** (0.97 g, 2.71 mmol) was added to the reaction mixture and stirred 2 h at −10 °C. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was dried over anhydrous magnesium sulfate, concentrated and purified with column chromatography (n-hexane/ethyl acetate = 10:1 → 5:1) to afford 1.61 g (97%) of **17b**. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.66 (1H, d, J = 8.8 Hz, ArH), 7.48 (2H, d, J = 9.0 Hz, ArH), 7.05 (2H, d, J = 9.0 Hz, ArH), 6.67 (1H, dd, J = 8.8, 2.6 Hz, ArH), 6.56 (1H, d, J = 2.6 Hz, ArH), 5.19 (2H, s, OCH_2OCH_3), 5.16 (2H, s, OCH_2OCH_3), 4.91 (1H, d, J = 10.4 Hz, H-2), 4.06 (1H, d, J = 10.4 Hz, H-2), 3.60 (2H, t, J = 6.6 Hz, CH_2OTBS), 3.50 (3H, s, OCH_3), 3.47 (3H, s, OCH_3), 2.26 (2H, t, J = 7.0 Hz, C≡CCH_2), 2.05 (1H, s, OH), 1.58–1.32 (13H, m, C3-CH_3 and $(CH_2)_5CH_2$OTBS), 0.89 (9H, s, TBS), 0.05 (6H, s, TBS).

5.32. 4-[8-(*tert*-Butyldimethylsilyloxy)-oct-1-ynyl]-7-methoxymethyloxy-3-(4-methoxymethyloxyphenyl)-3-methylchroman-4-ol (17a)

This compound was prepared from **16** and **3a** using a procedure similar to that described for **17b**. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.66 (1H, d, J = 8.8 Hz, ArH), 7.48 (2H, d, J = 9.0 Hz, ArH), 7.05 (2H, d, J = 9.0 Hz, ArH), 6.67 (1H, dd, J = 8.8, 2.6 Hz, ArH), 6.56 (1H, d, J = 2.6 Hz, ArH), 5.19 (2H, s, OCH_2OCH_3), 5.16 (2H, s, OCH_2OCH_3), 4.91 (1H, d, J = 10.4 Hz, H-2), 4.06 (1H, d, J = 10.4 Hz, H-2), 3.61 (2H, t, J = 6.4 Hz, CH_2OTBS), 3.50 (3H, s, OCH_3), 3.47 (3H, s, OCH_3), 2.27 (2H, t, J = 7.0 Hz, C≡CCH_2), 2.05 (1H, s, OH), 1.59–1.35 (11H, m, C3-CH_3 and $(CH_2)_4CH_2$OTBS), 0.89 (9H, s, TBS), 0.05 (6H, s, TBS).

5.33. 4-[10-(*tert*-Butyldimethylsilyloxy)-dec-1-ynyl]-7-methoxymethyloxy-3-(4-methoxymethyloxyphenyl)-3-methylchroman-4-ol (17c)

This compound was prepared from **16** and **3c** using a procedure similar to that described for **17b**. ^{1}H NMR ($CDCl_3$) δ: 7.66 (1H, d, J = 8.4 Hz, ArH), 7.48 (2H, d, J = 9.0 Hz, ArH), 7.05 (2H, d, J = 9.0 Hz, ArH), 6.67 (1H, dd, J = 8.4, 2.6 Hz, ArH), 6.56 (1H, d, J = 2.6 Hz, ArH), 5.19 (2H, s, OCH_2OCH_3), 5.16 (2H, s, OCH_2OCH_3), 4.91 (1H, d, J = 10.4 Hz, H-2), 4.06 (1H, d, J = 10.4 Hz, H-2), 3.60 (2H, t, J = 6.8 Hz, CH_2OTBS), 3.50 (3H, s, OCH_3), 3.47 (3H, s, OCH_3), 2.26 (2H, t, J = 7.0 Hz, C≡CCH_2), 2.05 (1H, s, OH), 1.58–1.22 (15H, m, C3-CH_3 and $(CH_2)_6CH_2$OTBS), 0.89 (9H, s, TBS), 0.04 (6H, s, TBS).

5.34. 4-[9-(*t*-Butyldimethylsilyloxy)nonyl]-7-methoxymethyloxy-3-[4-(methoxymethyloxy)phenyl-3-methylchroman (18b) and 9-[7-Methoxymethyloxy-3-(4-methoxymethyloxy)phenyl-3-methylchroman-4-yl]-nonan-1-ol (19b)

A mixture of **17b** (756 mg, 1.23 mmol) and 10% Pd/C (110 mg, ACROS) in ethyl acetate (40 mL) was stirred at room temperature for 7 h under hydrogen atmosphere. Then, the reaction mixture was filtered to remove 10% Pd/C and concentrated. The crude product was purified with column chromatography (n-hexane/ethyl acetate = 10:1 → 2:1) to afford 309 mg (51%, 3*RS*,4*RS*/3*RS*,4*SR* = 5:1) of **18b** and 106 mg (18%,3*RS*,4*RS*/3*RS*,4*SR* = 1:1) of **19b**.

^{1}H NMR (**18b**, 400 MHz, $CDCl_3$) δ: 7.30–6.94 (5H, m, ArH of *cis*- and *trans*-isomer), 6.58–6.48 (2H, m, ArH of *cis*- and *trans*-isomer), 5.18 (10/6H, s, OCH_2OCH_3 of *cis*-isomer), 5.15 (10/6H, s, OCH_2OCH_3 of *cis*-isomer), 5.14 (2/6H, s, OCH_2OCH_3 of *trans*-isomer), 5.11 (2/6H, s, OCH_2OCH_3 of *trans*-isomer), 4.52 (5/6H, d, J = 10.3 Hz, H-2 of *cis*-isomer), 4.27–4.21 (1H, m, H-2 of *cis*- and *trans*-isomer), 3.93 (1/6H, d, J = 11.0 Hz, H-2 of *trans*-isomer), 3.60–3.55 (2H, m, CH_2OTBS of *cis*- and *trans*-isomer), 3.50 (15/6H, s, OCH_3 of *cis*-isomer), 3.49 (15/6H, s, OCH_3 of *cis*-isomer), 3.47 (3/6H, s, OCH_3 of *trans*-isomer), 3.46 (3/6H, s, OCH_3 of *trans*-isomer), 3.04 (1/6H, br s, H-4 of *trans*-isomer), 2.65 (5/6H, br s, H-4 of *cis*-isomer), 1.53–1.07 (19H, m, C3-CH_3 and $(CH_2)_8CH_2$OTBS of *cis*- and *trans*-isomer), 0.89 (9/6H, s, TBS of *trans*-isomer), 0.88 (45/6H, s, TBS of *cis*-isomer), 0.04 (6/6H, s, TBS of *trans*-isomer), 0.03 (30/6H, s, TBS of *cis*-isomer).

^{1}H NMR (**19b**, 400 MHz, $CDCl_3$) δ: 7.30–6.94 (5H, m, ArH of *cis*- and *trans*-isomer), 6.58–6.48 (2H, m, ArH of *cis*- and *trans*-isomer), 5.18 (2/2H, s, OCH_2OCH_3 of *cis*-isomer), 5.15 (2H, s, OCH_2OCH_3 of *cis*- and *trans*-isomer), 5.11 (2/2H, s, OCH_2OCH_3 of *trans*-isomer), 4.52 (1/2H, d, J = 10.6 Hz, H-2 of *cis*-isomer), 4.28–4.21 (1H, m, H-2 of *cis*- and *trans*-isomer), 3.93 (1/2H, d, J = 11.0 Hz, H-2 of *trans*-isomer), 3.67–3.59 (2H, m, CH_2OH of *cis*- and *trans*-isomer), 3.50 (3/2H, s, OCH_3 of *cis*-isomer), 3.49 (3/2H, s, OCH_3 of *cis*-isomer), 3.47 (3/2H, s, OCH_3 of *trans*-isomer), 3.46 (3/2H, s, OCH_3 of *trans*-isomer), 3.05 (1/2H, br s, H-4 of *trans*-isomer), 2.65 (1/2H, br s, H-4 of *cis*-isomer), 1.54–1.07 (19H, m, C3-CH_3 and $(CH_2)_8CH_2$OH of *cis*- and *trans*-isomer).

5.35. 4-[8-(*t*-Butyldimethylsilyloxy)octyl]-7-methoxymethyloxy-3-[4-(methoxymethyloxy)phenyl-3-methylchroman (18a)

A mixture of **17a** (550 mg, 0.92 mmol) and 10% Pd/C (50 mg, ACROS) in ethyl acetate (30 mL) was stirred

at room temperature for 45 min under hydrogen atmosphere. Then, the reaction mixture was filtered to remove 10% Pd/C and concentrated. The crude product was purified with column chromatography (*n*-hexane/ethyl acetate = 10:1) to afford 423 mg (78%, 3*RS*,4*RS*/3*RS*,4*SR* = 2:l) of **18a**. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.30–6.94 (5H, m, ArH of *cis*- and *trans*-isomer), 6.58–6.48 (2H, m, ArH of *cis*- and *trans*-isomer), 5.18 (4/3H, s, OCH_2OCH$_3$ of *cis*-isomer), 5.15 (4/3H, s, OCH_2OCH$_3$ of *cis*-isomer), 5.14 (2/3H, s, OCH_2OCH$_3$ of *trans*-isomer), 5.11 (2/3H, s, OCH_2OCH$_3$ of *trans*-isomer), 4.52 (2/3H, d, J = 10.3 Hz, H-2 of *cis*-isomer), 4.27–4.21 (1H, m, H-2 of *cis*- and *trans*-isomer), 3.93 (1/3H, d, J = 11.0 Hz, H-2 of *trans*-isomer), 3.60–3.54 (2H, m, CH_2OTBS of *cis*- and *trans*-isomer), 3.50 (6/3H, s, OCH$_3$ of *cis*-isomer), 3.49 (6/3H, s, OCH$_3$ of *cis*-isomer), 3.47 (3/3H, s, OCH$_3$ of *trans*-isomer), 3.46 (3/3H, s, OCH$_3$ of *trans*-isomer), 3.04 (1/3H, br s, H-4 of *trans*-isomer), 2.65 (2/3H, br s, H-4 of *cis*-isomer), 1.53–1.07 (17H, m, C3-CH$_3$ and $(CH_2)_7CH_2$OTBS of *cis*- and *trans*-isomer), 0.89 (9/3H, s, TBS of *trans*-isomer), 0.88 (18/3H, s, TBS of *cis*-isomer), 0.04 (6/3H, s, TBS of *trans*-isomer), 0.03 (12/3H, s, TBS of *cis*-isomer).

5.36. 4-[10-(*t*-Butyldimethylsilyloxy)decyl]-7-methoxymethyloxy-3-[4-(methoxymethyloxy)phenyl-3-methylchroman (18c)

This compound (3*RS*,4*RS*/3*RS*,4*SR* = 5:2) was prepared from **17c** using a procedure similar to that described for **18a**. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.30–6.94 (5H, m, ArH of *cis*- and *trans*-isomer), 6.57–6.48 (2H, m, ArH of *cis*- and *trans*-isomer), 5.18 (10/7H, s, OCH_2OCH$_3$ of *cis*-isomer), 5.15 (10/7H, s, OCH_2OCH$_3$ of *cis*-isomer), 5.14 (4/7H, s, OCH_2OCH$_3$ of *trans*-isomer), 5.11 (4/7H, s, OCH_2OCH$_3$ of *trans*-isomer), 4.52 (5/7H, d, J = 10.3 Hz, H-2 of *cis*-isomer), 4.27–4.21 (1H, m, H-2 of *cis*- and *trans*-isomer), 3.93 (2/7H, d, J = 11.0 Hz, H-2 of *trans*-isomer), 3.61–3.56 (2H, m, CH_2OTBS of *cis*- and *trans*-isomer), 3.50 (15/7H, s, OCH$_3$ of *cis*-isomer), 3.49 (15/7H, s, OCH$_3$ of *cis*-isomer), 3.47 (6/7H, s, OCH$_3$ of *trans*-isomer), 3.46 (6/7H, s, OCH$_3$ of *trans*-isomer), 3.04 (2/7H, br s, H-4 of *trans*-isomer), 2.65 (5/7H, br s, H-4 of *cis*-isomer), 1.52–1.09 (21H, m, C3-CH$_3$ and $(CH_2)_9CH_2$OTBS of *cis*- and *trans*-isomer), 0.89 (18/7H, s, TBS of *trans*-isomer), 0.88 (45/7H, s, TBS of *cis*-isomer), 0.05 (12/7H, s, TBS of *trans*-isomer), 0.04 (30/7H, s, TBS of *cis*-isomer).

5.37. 9-[7-Methoxymethyloxy-3-(4-methoxymethyloxy)phenyl-3-methylchroman-4-yl]-nonan-1-ol (19b)

A mixture of **18b** (138 mg, 0.23 mmol, 3*RS*,4*RS*/3*RS*,4*SR* = 5:l) and pyridinium *p*-toluenesulfonate (140 mg) in methanol (5 mL) and dichloromethane (2 mL) was stirred at room temperature for 2 h. Then, the reaction mixture was concentrated, and purified with column chromatography (*n*-hexane/ethyl acetate = 2:1) to afford 102 mg (91%, 3*RS*,4*RS*/3*RS*,4*SR* = 5:l) of **19b**. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.30–6.94 (5H, m, ArH of *cis*- and *trans*-isomer), 6.58–6.48 (2H, m, ArH of *cis*- and *trans*-isomer), 5.18 (10/6H, s, OCH_2OCH$_3$ of *cis*-isomer), 5.15 (2H, s, OCH_2OCH$_3$ of *cis*- and *trans*-isomer), 5.11 (2/6H, s, OCH_2OCH$_3$ of *trans*-isomer), 4.52 (5/6H, d, J = 10.6 Hz, H-2 of *cis*-isomer), 4.28–4.21 (1H, m, H-2 of *cis*- and *trans*-isomer), 3.93 (1/6H, d, J = 11.0 Hz, H-2 of *trans*-isomer), 3.67–3.59 (2H, m, CH_2OH of *cis*- and *trans*-isomer), 3.50 (15/6H, s, OCH$_3$ of *cis*-isomer), 3.49 (15/6H, s, OCH$_3$ of *cis*-isomer), 3.47 (3/6H, s, OCH$_3$ of *trans*-isomer), 3.46 (3/6H, s, OCH$_3$ of *trans*-isomer), 3.05 (1/6H, br s, H-4 of *trans*-isomer), 2.65 (5/6H, br s, H-4 of *cis*-isomer), 1.54–1.07 (19H, m, C3-CH$_3$ and $(CH_2)_8CH_2$OH of *cis*- and *trans*-isomer).

5.38. 8-[7-Methoxymethyloxy-3-(4-methoxymethyloxy)phenyl-3-methylchroman-4-yl]-octan-1-ol (19a)

This compound (3*RS*,4*RS*/3*RS*,4*SR* = 2:l) was prepared from **18a** (3*RS*,4*RS*/3*RS*,4*SR* = 2:l) using a procedure similar to that described for **19b**. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.30–6.94 (5H, m, ArH of *cis*- and *trans*-isomer), 6.58–6.48 (2H, m, ArH of *cis*- and *trans*-isomer), 5.18 (4/3H, s, OCH_2OCH$_3$ of *cis*-isomer), 5.15 (4/3H, s, OCH_2OCH$_3$ of *cis*-isomer), 5.14 (2/3H, s, OCH_2OCH$_3$ of *trans*-isomer), 5.11 (2/3H, s, OCH_2OCH$_3$ of *trans*-isomer), 4.52 (2/3H, d, J = 10.6 Hz, H-2 of *cis*-isomer), 4.28–4.21 (1H, m, H-2 of *cis*- and *trans*-isomer), 3.93 (1/3H, d, J = 11.0 Hz, H-2 of *trans*-isomer), 3.65–3.57 (2H, m, CH_2OH of *cis*- and *trans*-isomer), 3.50 (6/3H, s, OCH$_3$ of *cis*-isomer), 3.49 (6/3H, s, OCH$_3$ of *cis*-isomer), 3.47 (3/3H, s, OCH$_3$ of *trans*-isomer), 3.46 (3/3H, s, OCH$_3$ of *trans*-isomer), 3.05 (1/3H, br s, H-4 of *trans*-isomer), 2.64 (2/3H, br s, H-4 of *cis*-isomer), 1.54–1.07 (17H, m, C3-CH$_3$ and $(CH_2)_7CH_2$OH of *cis*- and *trans*-isomer).

5.39. 10-[7-Methoxymethyloxy-3-(4-methoxymethyloxy)phenyl-3-methylchroman-4-yl]-decan-1-ol (19c)

This compound (3*RS*,4*RS*/3*RS*,4*SR* = 5:2) was prepared from **18c** (3*RS*,4*RS*/3*RS*,4*SR* = 5:2) using a procedure similar to that described for **19b**. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.30–6.94 (5H, m, ArH of *cis*- and *trans*-isomer), 6.58–6.48 (2H, m, ArH of *cis*- and *trans*-isomer), 5.18 (10/7H, s, OCH_2OCH$_3$ of *cis*-isomer), 5.15 (10/7H, s, OCH_2OCH$_3$ of *cis*-isomer), 5.14 (4/7H, s, OCH_2OCH$_3$ of *trans*-isomer), 5.11 (4/7H, s, OCH_2OCH$_3$ of *trans*-isomer), 4.52 (5/7H, d, J = 10.6 Hz, H-2 of *cis*-isomer), 4.27–4.21 (1H, m, H-2 of *cis*- and *trans*-isomer), 3.93 (2/7H, d, J = 11.4 Hz, H-2 of *trans*-isomer), 3.63 (2H, br s, CH_2OH of *cis*- and *trans*-isomer), 3.50 (15/7H, s, OCH$_3$ of *cis*-isomer), 3.49 (15/7H, s, OCH$_3$ of *cis*-isomer), 3.47 (6/7H, s, OCH$_3$ of *trans*-isomer), 3.46 (6/7H, s, OCH$_3$ of *trans*-isomer), 3.04 (2/7H, br s, H-4 of *trans*-isomer), 2.65 (5/7H, br s, H-4 of *cis*-isomer), 1.57–1.07 (21H, m, C3-CH$_3$ and $(CH_2)_9CH_2$OH of *cis*- and *trans*-isomer).

5.40. 8-[7-Methoxymethyloxy-3-(4-methoxymethyloxy)phenyl-3-methylchroman-4-yl]octyl methanesulfonate (20a)

This compound (3*RS*,4*RS*/3*RS*,4*SR* = 2:1) was prepared from **19a** (3*RS*,4*RS*/3*RS*,4*SR* = 2:1) using a procedure similar to that described for **10b**. ^{1}H NMR

(400 MHz, $CDCl_3$) δ: 7.30–6.93 (5H, m, ArH of *cis*- and *trans*-isomer), 6.58–6.48 (2H, m, ArH of *cis*- and *trans*-isomer), 5.18 (4/3H, s, OCH_2OCH$_3$ of *cis*-isomer), 5.15 (4/3H, s, OCH_2OCH$_3$ of *cis*-isomer), 5.14 (2/3H, s, OCH_2OCH$_3$ of *trans*-isomer), 5.11 (2/3H, s, OCH_2OCH$_3$ of *trans*-isomer), 4.52 (2/3H, d, J = 10.6 Hz, H-2 of *cis*-isomer), 4.28–4.18 (3H, m, H-2 and CH_2OMs of *cis*- and *trans*-isomer), 3.93 (1/3H, d, J = 11.0 Hz, H-2 of *trans*-isomer), 3.50 (6/3H, s, OCH$_3$ of *cis*-isomer), 3.49 (6/3H, s, OCH$_3$ of *cis*-isomer), 3.47 (3/3H, s, OCH$_3$ of *trans*-isomer), 3.46 (3/3H, s, OCH$_3$ of *trans*-isomer), 3.04 (1/3H, br s, H-4 of *trans*-isomer), 3.00 (3/3H, s, OMs of *trans*-isomer), 2.98 (6/3H, s, OMs of *cis*-isomer), 2.64 (2/3H, br s, H-4 of *cis*-isomer), 1.72–1.07 (17H, m, C3-CH$_3$ and $(CH_2)_7CH_2$OMs of *cis*- and *trans*-isomer).

5.41. 9-[7-Methoxymethyloxy-3-(4-methoxymethyloxy)phenyl-3-methylchroman-4-yl]nonyl methanesulfonate (20b)

This compound (3*RS*,4*RS*/3*RS*,4*SR* = 3:1) was prepared from **19b** (3*RS*,4*RS*/3*RS*,4*SR* = 3:1) using a procedure similar to that described for **10b**. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.30–6.93 (5H, m, ArH of *cis*- and *trans*-isomer), 6.58–6.48 (2H, m, ArH of *cis*- and *trans*-isomer), 5.18 (6/4H, s, OCH_2OCH$_3$ of *cis*-isomer), 5.15 (6/4H, s, OCH_2OCH$_3$ of *cis*-isomer), 5.14 (2/4H, s, OCH_2OCH$_3$ of *trans*-isomer), 5.11 (2/4H, s, OCH_2OCH$_3$ of *trans*-isomer), 4.52 (3/4H, d, J = 10.3 Hz, H-2 of *cis*-isomer), 4.28–4.18 (3H, m, H-2 and CH_2OMs of *cis*- and *trans*-isomer), 3.93 (1/4H, d, J = 11.0 Hz, H-2 of *trans*-isomer), 3.50 (9/4H, s, OCH$_3$ of *cis*-isomer), 3.49 (9/4H, s, OCH$_3$ of *cis*-isomer), 3.47 (3/4H, s, OCH$_3$ of *trans*-isomer), 3.46 (3/4H, s, OCH$_3$ of *trans*-isomer), 3.04 (1/4H, br s, H-4 of *trans*-isomer), 3.00 (3/4H, s, OMs of *trans*-isomer), 2.99 (9/4H, s, OMs of *cis*-isomer), 2.65 (3/4H, br s, H-4 of *cis*-isomer), 1.72–1.07 (19H, m, C3-CH$_3$ and $(CH_2)_8CH_2$OMs of *cis*- and *trans*-isomer).

5.42. 10-[7-Methoxymethyloxy-3-(4-methoxymethyloxy)phenyl-3-methylchroman-4-yl]decyl methanesulfonate (20c)

This compound (3*RS*,4*RS*/3*RS*,4*SR* = 3:1) was prepared from **19c** (3*RS*,4*RS*/3*RS*,4*SR* = 3:1) using a procedure similar to that described for **10b**. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.30–6.94 (5H, m, ArH of *cis*- and *trans*-isomer), 6.58–6.48 (2H, m, ArH of *cis*- and *trans*-isomer), 5.18 (6/4H, s, OCH_2OCH$_3$ of *cis*-isomer), 5.15 (6/4H, s, OCH_2OCH$_3$ of *cis*-isomer), 5.14 (2/4H, s, OCH_2OCH$_3$ of *trans*-isomer), 5.11 (2/4H, s, OCH_2OCH$_3$ of *trans*-isomer), 4.52 (3/4H, d, J = 10.6 Hz, H-2 of *cis*-isomer), 4.28–4.19 (3H, m, H-2 and CH_2OMs of *cis*- and *trans*-isomer), 3.93 (1/4H, d, J = 11.0 Hz, H-2 of *trans*-isomer), 3.50 (9/4H, s, OCH$_3$ of *cis*-isomer), 3.49 (9/4H, s, OCH$_3$ of *cis*-isomer), 3.47 (3/4H, s, OCH$_3$ of *trans*-isomer), 3.46 (3/4H, s, OCH$_3$ of *trans*-isomer), 3.04 (1/4H, br s, H-4 of *trans*-isomer), 3.00 (3/4H, s, OMs of *trans*-isomer), 2.99 (9/4H, s, OMs of *cis*-isomer), 2.65 (3/4H, br s, H-4 of *cis*-isomer), 1.76–1.02 (21H, m, C3-CH$_3$ and $(CH_2)_9CH_2$OMs of *cis*- and *trans*-isomer).

5.43. (3*RS*,4*RS*)-7-Methoxymethyloxy-3-(4-methoxymethyloxyphenyl)-3-methyl-4-[8-(4,4,5,5,5-pentafluoropentylsulfanyl)octyl]chroman (21a) and (3*RS*,4*SR*)-7-methoxy-methyloxy-3-(4-methoxymethyloxyphenyl)-3-methyl-4-[8-(4,4,5,5,5-pentafluoropentyl-sulfanyl)octyl]chroman (22a)

These compounds, **21a** (59%) and **22a** (19%), were prepared from **20a** (3*RS*,4*RS*/3*RS*,4*SR* = 2:l) and **5a** using a procedure similar to that described for **11b** and **12b**.

^{1}H NMR (**21a**, 400 MHz, $CDCl_3$) δ: 7.13 (2H, d, J = 8.8 Hz, ArH), 7.03 (2H, d, J = 8.8 Hz, ArH), 6.96–6.93 (1H, m, ArH), 6.57–6.55 (2H, m, ArH), 5.18 (2H, s, OCH_2OCH$_3$), 5.15 (2H, s, OCH_2OCH$_3$), 4.52 (1H, d, J = 10.6 Hz, H-2), 4.26 (1H, d, J = 10.6 Hz, H-2), 3.50 (3H, s, OCH$_3$), 3.49 (3H, s, OCH$_3$), 2.65 (1H, br s, H-4), 2.57 (2H, t, J = 7.1 Hz, CH_2S), 2.46 (2H, t, J = 7.5 Hz, CH_2S), 2.22–2.09 (2H, m, $CH_2CH_2CF_2CF_3$), 1.90–1.83 (2H, m, $CH_2CH_2CF_2CF_3$), 1.56–1.02 (17H, m, C3-CH$_3$ and $(CH_2)_7CH_2$S); MS (*m*/*z*) 649 (M+1).

^{1}H NMR (**22a**, 400 MHz, $CDCl_3$) δ: 7.29 (2H, d, J = 8.8 Hz, ArH), 7.01 (1H, d, J = 8.8 Hz, ArH), 6.96 (2H, d, J = 8.8 Hz, ArH), 6.54–6.48 (2H, m, ArH), 5.14 (2H, s, OCH_2OCH$_3$), 5.11 (2H, s, OCH_2OCH$_3$), 4.22 (1H, d, J = 11.2 Hz, H-2), 3.93 (1H, d, J = 11.2 Hz, H-2), 3.47 (3H, s, OCH$_3$), 3.46 (3H, s, OCH$_3$), 3.04 (1H, br s, H-4), 2.58 (2H, t, J = 7.0 Hz, CH_2S), 2.49 (2H, t, J = 7.3 Hz, CH_2S), 2.22–2.10 (2H, m, $CH_2CH_2CF_2CF_3$), 1.92–1.84 (2H, m, $CH_2CH_2CF_2CF_3$), 1.59–1.21 (17H, m, C3-CH$_3$ and $(CH_2)_7CH_2$S); MS (*m*/*z*) 649 (M+1).

5.44. (3*RS*,4*RS*)-7-Methoxymethyloxy-3-(4-methoxymethyloxyphenyl)-3-methyl-4-[9-(4,4,5,5,5-pentafluoropentylsulfanyl)nonyl]chroman (21b) and (3*RS*,4*SR*)-7-Methoxymethyloxy-3-(4-methoxymethyloxyphenyl)-3-methyl-4-[9-(4,4,5,5,5-pentafluoropentyl-sulfanyl)nonyl]chroman (22b)

These compounds, **21b** (54%) and **22b** (10%), were prepared from **20b** (3*RS*,4*RS*/3*RS*,4*SR* = 3:l) and **5a** using a procedure similar to that described for **11b** and **12b**.

^{1}H NMR (**21b**, 400 MHz, $CDCl_3$) δ: 7.13 (2H, d, J = 8.8 Hz, ArH), 7.02 (2H, d, J = 8.8 Hz, ArH), 6.96–6.93 (1H, m, ArH), 6.57–6.55 (2H, m, ArH), 5.18 (2H, s, OCH_2OCH$_3$), 5.15 (2H, s, OCH_2OCH$_3$), 4.52 (1H, d, J = 10.3 Hz, H-2), 4.26 (1H, d, J = 10.3 Hz, H-2), 3.50 (3H, s, OCH$_3$), 3.49 (3H, s, OCH$_3$), 2.64 (1H, br s, H-4), 2.57 (2H, t, J = 7.0 Hz, CH_2S), 2.48 (2H, t, J = 7.3 Hz, CH_2S), 2.21–2.09 (2H, m, $CH_2CH_2CF_2CF_3$), 1.91–1.83 (2H, m, $CH_2CH_2CF_2CF_3$), 1.58–1.01 (19H, m, C3-CH$_3$ and $(CH_2)_8CH_2$S); MS (*m*/*z*) 663 (M+1).

^{1}H NMR (**22b**, 400 MHz, $CDCl_3$) δ: 7.29 (2H, d, J = 8.8 Hz, ArH), 7.01 (1H, d, J = 8.4 Hz, ArH), 6.96 (2H, d, J = 8.8 Hz, ArH), 6.54–6.48 (2H, m, ArH), 5.14 (2H, s, OCH_2OCH$_3$), 5.11 (2H, s, OCH_2OCH$_3$), 4.22 (1H, d, J = 11.4 Hz, H-2), 3.93 (1H, d,

J = 11.4 Hz, H-2), 3.47 (3H, s, OCH_3), 3.46 (3H, s, OCH_3), 3.04 (1H, br s, H-4), 2.59 (2H, t, J = 7.0 Hz, CH_2S), 2.50 (2H, t, J = 7.3 Hz, CH_2S), 2.24–2.10 (2H, m, $CH_2CH_2CF_2CF_3$), 1.92–1.84 (2H, m, $CH_2CH_2CF_2CF_3$), 1.60–1.20 (19H, m, C3-CH_3 and $(CH_2)_8CH_2S$); MS (m/z) 663 (M+1).

5.45. (3*RS*,4*RS*)-7-Methoxymethyloxy-3-(4-methoxymethyloxyphenyl)-3-methyl-4-[10-(4,4,5,5,5-pentafluoropentylsulfanyl)decyl]chroman (21c) and (3*RS*,4*SR*)-7-Methoxymethyloxy-3-(4-methoxymethyloxyphenyl)-3-methyl-4-[10-(4,4,5,5,5-pentafluoropentylsulfanyl)decyl]chroman (22c)

These compounds, **21c** (60%) and **22c** (16%), were prepared from **20c** (3*RS*,4*RS*/3*RS*,4*SR* = 3:l) and **5a** using a procedure similar to those described for **11b** and **12b**.

^{1}H NMR (**21c**, 400 MHz, $CDCl_3$) δ: 7.13 (2H, d, J = 9.2 Hz, ArH), 7.02 (2H, d, J = 9.2 Hz, ArH), 6.96–6.94 (1H, m, ArH), 6.57–6.55 (2H, m, ArH), 5.18 (2H, s, OCH_2OCH_3), 5.15 (2H, s, OCH_2OCH_3), 4.52 (1H, d, J = 10.3 Hz, H-2), 4.26 (1H, d, J = 10.3 Hz, H-2), 3.50 (3H, s, OCH_3), 3.49 (3H, s, OCH_3), 2.65 (1H, br s, H-4), 2.58 (2H, t, J = 7.0 Hz, CH_2S), 2.49 (2H, t, J = 7.5 Hz, CH_2S), 2.21–2.10 (2H, m, $CH_2CH_2CF_2CF_3$), 1.91–1.84 (2H, m, $CH_2CH_2CF_2CF_3$), 1.59–1.07 (21H, m, C3-CH_3 and $(CH_2)_9CH_2S$); MS (m/z) 677 (M+1).

^{1}H NMR (**22c**, 400 MHz, $CDCl_3$) δ: 7.29 (2H, d, J = 8.8 Hz, ArH), 7.01 (1H, d, J = 8.4 Hz, ArH), 6.96 (2H, d, J = 8.8 Hz, ArH), 6.54–6.48 (2H, m, ArH), 5.14 (2H, s, OCH_2OCH_3), 5.11 (2H, s, OCH_2OCH_3), 4.22 (1H, d, J = 11.0 Hz, H-2), 3.93 (1H, d, J = 11.0 Hz, H-2), 3.47 (3H, s, OCH_3), 3.46 (3H, s, OCH_3), 3.04 (1H, br s, H-4), 2.59 (2H, t, J = 7.0 Hz, CH_2S), 2.50 (2H, t, J = 7.5 Hz, CH_2S), 2.24–2.10 (2H, m, $CH_2CH_2CF_2CF_3$), 1.92–1.84 (2H, m, $CH_2CH_2CF_2CF_3$), 1.60–1.20 (21H, m, C3-CH_3 and $(CH_2)_9CH_2S$); MS (m/z) 677 (M+1).

5.46. (3*RS*,4*RS*)-3-(4-Hydroxyphenyl)-3-methyl-4-[9-(4,4,5,5,5-pentafluoropentylsulfanyl)nonyl]chroman-7-ol (23b)

A mixture of **21b** (33 mg, 0.050 mmol) and a 10% methanol solution of hydrogen chloride (1 mL) was heated at 60 °C for 15 min. Then, the reaction mixture was concentrated and purified with column chromatography (*n*-hexane/ethyl acetate = 2:1) to afford 27 mg (94%) of **23b**. ^{1}H NMR (400 MHz,$CDCl_3$) δ: 7.08 (2H, d, J = 8.8 Hz, ArH), 6.90 (1H, d, J = 8.1 Hz, ArH), 6.83 (2H, d, J = 8.8 Hz, ArH), 6.39–6.35 (2H, m, ArH), 4.93 (1H, br s, OH), 4.73 (1H, br s, OH), 4.51 (1H, d, J = 10.4 Hz, H-2), 4.24 (1H, d, J = 10.4 Hz, H-2), 2.60–2.57 (3H, m, H-4 and CH_2S), 2.49 (2H, t, J = 7.5 Hz, CH_2S), 2.23–2.10 (2H, m, $CH_2CH_2CF_2CF_3$), 1.92–1.84 (2H, m, $CH_2CH_2CF_2CF_3$), 1.57–1.03 (19H, m, C3-CH_3 and $(CH_2)_8CH_2S$); HRMS (ES-NEG) calculated for $C_{30}H_{39}F_5O_3S$: 573.2462. Found: 573.2451 (−2.0 ppm).

5.47. (3*RS*,4*RS*)-3-(4-Hydroxyphenyl)-3-methyl-4-[8-(4,4,5,5,5-pentafluoropentylsulfanyl)octyl]chroman-7-ol (23a)

This compound was prepared from **21a** using a procedure similar to that described for **23b**. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.08 (2H, d, J = 8.6 Hz, ArH), 6.89 (1H, d, J = 8.1 Hz, ArH), 6.83 (2H, d, J = 8.6 Hz, ArH), 6.39–6.35 (2H, m, ArH), 5.07 (1H, br s, OH), 4.75 (1H, br s, OH), 4.51 (1H, d, J = 10.3 Hz, H-2), 4.24 (1H, d, J = 10.3 Hz, H-2), 2.61–2.56 (3H, m, H-4 and CH_2S), 2.47 (2H, t, J = 7.5 Hz, CH_2S), 2.23–2.10 (2H, m, $CH_2CH_2CF_2CF_3$), 1.91–1.84 (2H, m, $CH_2CH_2CF_2CF_3$), 1.57–1.07 (17H, m, C3-CH_3 and $(CH_2)_7CH_2S$); MS (m/z) 561 (M+1).

5.48. (3*RS*,4*RS*)-3-(4-Hydroxyphenyl)-3-methyl-4-[10-(4,4,5,5,5-pentafluoropentylsulfanyl)decyl]chroman-7-ol (23c)

This compound was prepared from **21c** using a procedure similar to that described for **23b**. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.07 (2H, d, J = 8.8 Hz, ArH), 6.89 (1H, d, J = 8.1 Hz, ArH), 6.83 (2H, d, J = 8.8 Hz, ArH), 6.39–6.35 (2H, m, ArH), 5.37 (1H, br s, OH), 5.12 (1H, br s, OH), 4.51 (1H, d, J = 10.6 Hz, H-2), 4.23 (1H, d, J = 10.6 Hz, H-2), 2.60–2.57 (3H, m, H-4 and CH_2S), 2.49 (2H, t, J = 7.3 Hz, CH_2S), 2.23–2.10 (2H, m, $CH_2CH_2CF_2CF_3$), 1.92–1.84 (2H, m, $CH_2CH_2CF_2CF_3$), 1.60–1.00 (21H, m, C3-CH_3 and $(CH_2)_9CH_2S$); MS (m/z) 589 (M+1).

5.49. (3*RS*,4*RS*)-3-(4-Hydroxyphenyl)-3-methyl-4-[8-(4,4,5,5,5-pentafluoropentylsulfinyl)octyl]chroman-7-ol (24a)

This compound was prepared from **23a** using a procedure similar to that described for **14b**. ^{1}H NMR (400 MHz, $CDCl_3$ + D_2O) δ: 7.06 (2H, d, J = 8.8 Hz, ArH), 6.91–6.85 (3H, m, ArH), 6.39–6.35 (2H, m, ArH), 4.48 (1H, d, J = 10.6 Hz, H-2), 4.24 (1H, d, J = 10.6 Hz, H-2), 2.87–2.55 (5H, m, H-4 and CH_2SOCH_2), 2.34–2.19 (4H, m, $CH_2CH_2CF_2CF_3$), 1.72–0.88 (17H, m, C3-CH_3 and $(CH_2)_7CH_2SO$); HRMS (ES-POS) calculated for $C_{29}H_{37}F_5O_4S$: 577.2411. Found: 577.2402 (−1.5 ppm).

5.50. (3*RS*,4*RS*)-3-(4-Hydroxyphenyl)-3-methyl-4-[9-(4,4,5,5,5-pentafluoropentylsulfinyl)nonyl]chroman-7-ol (24b)

This compound was prepared from **23b** using a procedure similar to that described for **14b**. ^{1}H NMR (400 MHz, $CDCl_3$ + D_2O) δ: 7.07–7.05 (2H, m, ArH), 6.89 (1H, d, J = 8.1 Hz, ArH), 6.84 (2H, d, J = 8.4 Hz, ArH), 6.40–6.35 (2H, m, ArH), 4.50 (1H, d, J = 10.3 Hz, H-2), 4.24–4.20 (1H, m, H-2), 2.89–2.56 (5H, m, H-4 and CH_2SOCH_2), 2.31–2.18 (4H, m, $CH_2CH_2CF_2CF_3$), 1.80–1.03 (19H, m, C3-CH_3 and $(CH_2)_8CH_2SO$); HRMS (ES-POS) calculated for $C_{30}H_{39}F_5O_4S$: 591.2567. Found: 591.2566 (−0.3 ppm).

5.51. (3*RS*,4*RS*)-3-(4-Hydroxyphenyl)-3-methyl-4-[10-(4,4,5,5,5-pentafluoropentylsulfinyl)decyl]chroman-7-ol (24c)

This compound was prepared from **23c** using a procedure similar to that described for **14b**. ^{1}H NMR (400 MHz, $CDCl_3$ + D_2O) δ: 7.05 (2H, d, J = 8.8 Hz, ArH), 6.89 (1H, d, J = 7.7 Hz, ArH), 6.84 (2H, d, J = 8.8 Hz, ArH), 6.39–6.36 (2H, m, ArH), 4.51 (1H, d, J = 10.3 Hz, H-2), 4.24 (1H, d, J = 10.3 Hz, H-2), 2.89–2.57 (5H, m, H-4 and CH_2SOCH_2), 2.33–2.16 (4H, m, $CH_2CH_2CF_2CF_3$), 1.84–1.02 (21H, m, C3-CH_3 and $(CH_2)_9CH_2SO$); HRMS (ES-POS) calculated for $C_{31}H_{41}F_5O_4S$: 605.2724. Found: 605.2711 (−2.1 ppm).

5.52. (3*RS*,4*RS*)-3-(4-Hydroxyphenyl)-3-methyl-4-[9-(4,4,5,5,5-pentafluoropentylsulfonyl)nonyl]chroman-7-ol (25b)

To a stirred mixture of **23b** (64 mg, 0.11 mmol) and oxone (205 mg, 0.33 mmol) in tetrahydrofuran (2 mL) was added water (1 mL) and stirred for 3 h at room temperature. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was dried over anhydrous magnesium sulfate, concentrated, and purified with column chromatography (*n*-hexane/ethyl acetate = 1:1) to afford 64 mg (95%) of **25b**. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.08 (2H, d, J = 8.8 Hz, ArH), 6.90 (1H, d, J = 8.1 Hz, ArH), 6.84 (2H, d, J = 8.8 Hz, ArH), 6.39–6.35 (2H, m, ArH), 5.42 (1H, br s, OH), 4.85 (1H, br s, OH), 4.51 (1H, d, J = 10.3 Hz, H-2), 4.24 (1H, d, J = 10.3 Hz, H-2), 3.07 (2H, t, J = 7.5 Hz, SO_2CH_2), 2.99 (2H, t, J = 8.1 Hz, SO_2CH_2), 2.59 (1H, br s, H-4), 2.35–2.17 (4H, m, $SO_2CH_2CH_2CF_2CF_3$), 1.84–1.06 (19H, m, , C3-CH_3 and $(CH_2)_8CH_2SO_2$); HRMS (ES-NEG) calculated for $C_{30}H_{39}F_5O_5S$: 605.2360. Found: 605.2357 (−0.6 ppm).

5.53. (3*RS*,4*RS*)-3-(4-Hydroxyphenyl)-4-[9-(4,4,5,5,5-pentafluoropentylsulfinyl)nonyl]chroman-7-ol (26b)

Compound **26b** was prepared with a procedure described by this laboratory.[19]

^{1}H NMR (270 MHz, $CDCl_3$) δ: 7.65–7.54 (1H, br s, OH), 7.02–6.92 (3H, m, ArH), 6.80 (2H, d, J = 8.2 Hz, ArH), 6.40 (1H, dd, J = 8.3 and 2.3 Hz, ArH), 6.36 (1H, d, J = 2.3 Hz, ArH), 5.59–5.52 (1H, br s, OH), 4.43–4.32 (2H, m, C2-H), 3.38–3.24 (1H, m, H-3), 2.95–2.58 (5H, m, CH_2SOCH_2 and H-4), 2.38–2.10 (4H, m, $SOCH_2CH_2CH_2CF\ _2CF_3$), 1.82–0.90 (16H, m, $(CH_2)_8CH_2SO$); HRMS (ES-POS) calculated for $C_{29}H_{37}F_5O_4S$: 577.2411. Found: 577.2406 (−0.9 ppm).

5.54. Chiral resolution of racemate 6

The enantiomers, (*R*)-**6** and (*S*)-**6**, were separated from racemate **6** by CHIRALCEL® OD column using the following conditions: column CHIRALCEL® OD $\Phi 2 \times 25$ cm; eluent hexane/isopropanol 70/30; flow rate 14.0 mL/min.

(+)-**6** was first eluted at 9.6 min and (−)-**6** was second eluted at 11.2 min. Injection of 30 mg of **6** was repeated 109 times, and the total amounts of 1.03 g of (+)-**6** and 1.10 g of (−)-**6** were obtained. (+)-**6** then crystallized and X-ray analysis showed the absolute configuration to be (*R*), which consequently indicated the other to be (*S*).

(3*R*)-**6**: $[\alpha]_D$ +327.4 (*c* 1.008, EtOH), 99.9% ee.

(3*S*)-**6**: $[\alpha]_D$ −318.7 (*c* 0.996, EtOH), 98.7% ee.

^{1}H NMR (400 MHz, $CDCl_3$) of each enantiomer was the same as that of **6**.

5.55. (3*R*,4*R*)-3-(4-Hydroxyphenyl)-3-methyl-4-[9-(4,4,5,5,5-pentafluoropentylsulfinyl)nonyl]thiochroman-7-ol ((3*R*,4*R*)-14b)

(3*R*,4*R*)-**14b** was prepared from (*S*)-**6** using the same procedure as that described for **14b**. ^{1}H NMR (400 MHz, $CDCl_3$) was the same as that of **14b**; HRMS (ES-POS) calculated for $C_{30}H_{39}F_5O_3S_2$: 607.2339. Found: 607.2325 (−2.3 ppm).

5.56. (3*S*,4*S*)-3-(4-Hydroxyphenyl)-3-methyl-4-[9-(4,4,5,5,5-pentafluoropentylsulfinyl)nonyl]thiochroman-7-ol ((3*S*,4*S*)-14b)

(3*S*,4*S*)-**14b** was prepared from (*R*)-**6** using the same procedure described for **14b**. ^{1}H NMR (400 MHz, $CDCl_3$) was the same as that of **14b**; HRMS (ES-POS) calculated for $C_{30}H_{39}F_5O_3S_2$: 607.2339. Found: 607.2330 (−1.5 ppm).

5.57. Antiestrogenic activity

Antiestrogenic activity was determined as anti-uterotrophic effect of the test compound in ICR mice. Mice (6-weeks old) were ovariectomized (OVX) two weeks before the administration of the compounds. 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 10% EtOH-peanut oil solution subcutaneously or 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. Antiestrogenic activity, determined by percent inhibition of estradiol-stimulated uterine weight gain from a compound, was calculated according to the following equation.

% Inhibition = $100 \times (1 - (T - C)/(E - C))$, where T, E, and C refer to uterine weight gain per body weight by the test compound, by 17β-estradiol benzoate, and by vehicle, respectively.

5.58. Estrogenic activity

Estrogenic activity was determined as uterotrophic effect of the test compound in ICR mice. Mice (6-weeks old) were ovariectomized (OVX) two weeks before the administration of the test compound. 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. Estrogenic activity, determined by percent uterine weight gain by the test compound, was calculated according to the following equation.

% uterine weight gain = $100 \times (T - C)/(E - C)$, where T, E, and C refer to uterine weight gain per body weight by the test compound, by 17β-estradiol benzoate, and by vehicle, respectively.

5.59. Receptor binding assay

Relative binding affinities for ER were determined by competition studies between estradiol and increasing concentrations of the test compound. A 100-mL mixture of 10 nM recombinant human ER, 20 nM of [^{3}H]estradiol, the test compound, 10% glycerol, 1 mM EDTA, 1 mM EGTA, 1 mM $NaOVO_4$, 0.1% BSA, 0.5 mM PMSF, 0.2 mM leupeptin, and 1 mM DTT in 10 mM Tris–HCl (pH 7.4) was incubated at 25 °C for 6 h and cooled on ice for 10 min. At the end of this incubation, 15 mL DCC solution containing 2.5% charcoal and 0.25% dextran in 10 mM Tris–HCl (pH 7.4) was added to the mixture, and centrifuged at 800g for 10 min at 4 °C . The supernatants were counted with a scintillation counter. Specific binding was obtained after correction for nonspecific binding as evaluated with 100-fold excess of nonradioactive estradiol. The RBA was calculated according to the following equation.

RBA = $100 \times IC_{50}$ of estradiol/IC_{50} of the tested compound, where IC_{50} is the concentration of estradiol or the tested compound that inhibited [^{3}H]estradiol binding by 50%.

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