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Synthesis and Pharmacological Evaluation of Novel *cis*-3,4-Diaryl-hydroxychromanes as High Affinity Partial Agonists for the Estrogen Receptor

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Abstract—The syntheses and in vitro pharmacological evaluation of a number of *cis*-3,4-diaryl-hydroxy-chromanes are reported, along with the results of a thorough in vivo profiling of the tissue-selective estrogen partial-agonist NNC 45-0781 [**3**, (−)-(3*S*,4*R*)-7-hydroxy-3-phenyl-4-(4-(2-pyrrolidinoethoxy)phenyl)chromane]. These studies showed that NNC 45-0781 is a very promising candidate for the prevention of post-menopausal osteoporosis, and the treatment of other health issues related to the loss of endogenous estrogen production.

Introduction

The critical role performed by estrogen in the maintenance and development of physiological tissues other than the female reproductive system has been increasingly recognized in both males and females over recent years. In particular, estrogen's roles in the maintenance of tissues such as the skeleton, the cardiovascular system, and the central nervous system have been highlighted.[1–5] This recognition of estrogen's widespread biological activity has led to the realization that a number of post-menopausal degenerative diseases, particularly osteoporosis and coronary heart disease, are linked to the decline in the production of estrogen that occurs during the menopause.[6] Indeed, the clinical use of long-term estrogen-based hormone replacement therapy (ERT) in post-menopausal women has proven to be a highly effective method for reducing the risks associated with these degenerative diseases. However, in spite of the fact that the positive effects of such long-term ERT are increasingly accepted,[7] the benefits are achieved at the expense of a number of negative side effects, including uterine bleeding, endometrial hyperplasia, endometrial cancer, and an increased risk of developing breast cancer. The uterine side effects, however, may be reduced by co-treatment with progesterone therapy.

These negative side effects, in turn, frequently lead to a reduced patient compliance and reluctance to accept ERT as a treatment form.[8,9] Taking these factors into consideration, it becomes clear that a therapeutic agent possessing the beneficial properties of estrogen, but without estrogen's negative side effects, especially on breast and endometrial tissue, has huge potential for the treatment of post-menopausal degenerative disease. A number of partial estrogens have been reported,[10] possessing these selective properties to various extents, including the compounds Raloxifene (**1**, Fig. 1), Tamoxifen (**2**, Fig. 1) and more recently, Lasofoxifene (CP-336,156),[11–14] which is currently undergoing clinical trials.

Most of these selective estrogens cannot, however be described as having 'ideal estrogen' profiles, and as such there is still a need for the development of further tissue-selective partial estrogens. In this article we report on the discovery and synthesis of a new group of non-steroidal partial estrogens, the *cis*-3,4-diaryl-hydroxy-chromanes, represented by the parent compound of the series, (−)-(3*S*,4*R*)-7-hydroxy-3-phenyl-4-(4-(2-pyrrolidinoethoxy)phenyl)chromane (Fig. 1, NNC 45-0781, **3**).

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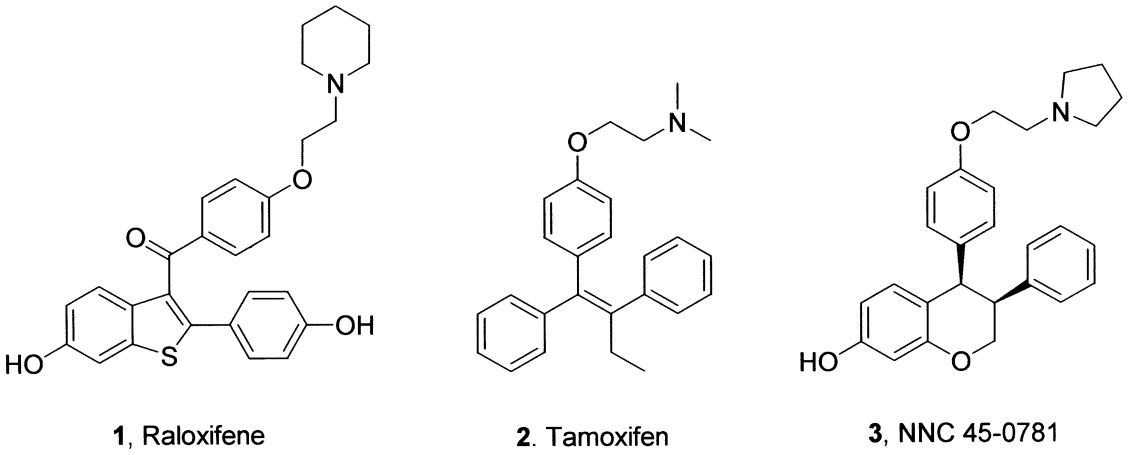


Figure 1. Tissue-selective estrogenic compounds.

The syntheses and selected in vitro and in vivo properties of a number of members of this compound series are detailed.

Chemistry

The general synthetic route used to prepare the series of target chromanes detailed in this report is shown in Scheme 1. The synthesis, which was based on a previously reported preparation of a series of analogous chromanes,[15,16] began with the condensation of 2,4′-dihydroxy-4-methoxybenzophenone[15] with a variety of substituted phenylacetic acids, to give the substituted 3,4-diarylchromen-2-ones **4a**–**j**[17] (Scheme 1). In the specific case of **4a** the *O*-acetyl group was removed by acid hydrolysis to give 4-(4-hydroxyphenyl)-7-methoxy-3-phenyl-chromen-2-one, **4a**, as described by Ray and coworkers.[15] Compound **4a** and the chromen-2-ones, **4b**–**j** were then reduced with lithium aluminium hydride to give 2,3,3-triaryl-prop-2-en-1-ol intermediates, which were immediately ring-closed, without isolation, by heating with mineral acid, giving 3-aryl-4-(4-hydroxyphenyl)-2*H*-chromenes, **5a**–**j**. These chromenes were then catalytically hydrogenated to give a series of racemic *cis*-3-aryl-4-(4-hydroxyphenyl)-7-methoxychromanes, **6a**–**j**, which were subsequently alkylated at their free phenolic positions with selected amino-alkyl chloride electrophiles, [e.g., 1-(2-chloroethyl)-pyrrolidine hydrochloride] to give products **7a**–**p**. Demethylation of **7a**–**p** by fusion with pyridine hydrochloride gave the desired racemic hydroxy-chromanes, **8a**–**p** (NB in the case of compounds **7d**, **7i**, and **7p** the pyridine hydrochloride fusion reaction also demethylated methoxy groups on the C3-aryl subunits, to give the dihydroxy products **8d**, **8i** and **8p**, respectively). Small quantities, in the order of 1–3 mg, of the separated pure enantiomers of **8a**–**o**, namely **9a**–**o** and **10a**–**o** (respectively defined as being the enantiomers with most and least potent binding to the estrogen receptor, **9a** = **3**) were then isolated by preparative chiral-HPLC separation as detailed in Table 1, and used purely for in vitro analysis. In the case of the preparation of compounds **3** (i.e., compound **9a**) and **9c** an alternative chiral resolution was carried out on a multi-gram scale, by means of the fractional crystallization of the di-*p*-toluoyl D- and L-tartaric acid salts of the intermediate methoxy-chromanes **7a** and **7c**. This allowed the preparation of substantial quantities of the optically pure enantiomers (−)-(3*S*,4*R*)-7-methoxy-3-phenyl-4-(4-(2-pyrrolidinoethoxy)phenyl)chromane [(−)-**7a**], and (−)-*cis*-7-methoxy-3-(4-trifluoromethylphenyl)-4-(4-(2-pyrrolidinoethoxy)phenyl)chromane [(−)-**7c**]. The 7-methoxy groups of (−)-**7a** and (−)-**7c** were then demethylated by heating with pyridine hydrochloride to give the optically pure 7-hydroxy compounds **3** (i.e., **9a**) and **9c**. The absolute stereochemistry of (−)-**7a**, and hence **3**, was determined by means of X-ray crystallographic analysis of its (−)-di-*p*-toluoyl-L-tartaric acid salt.[18]

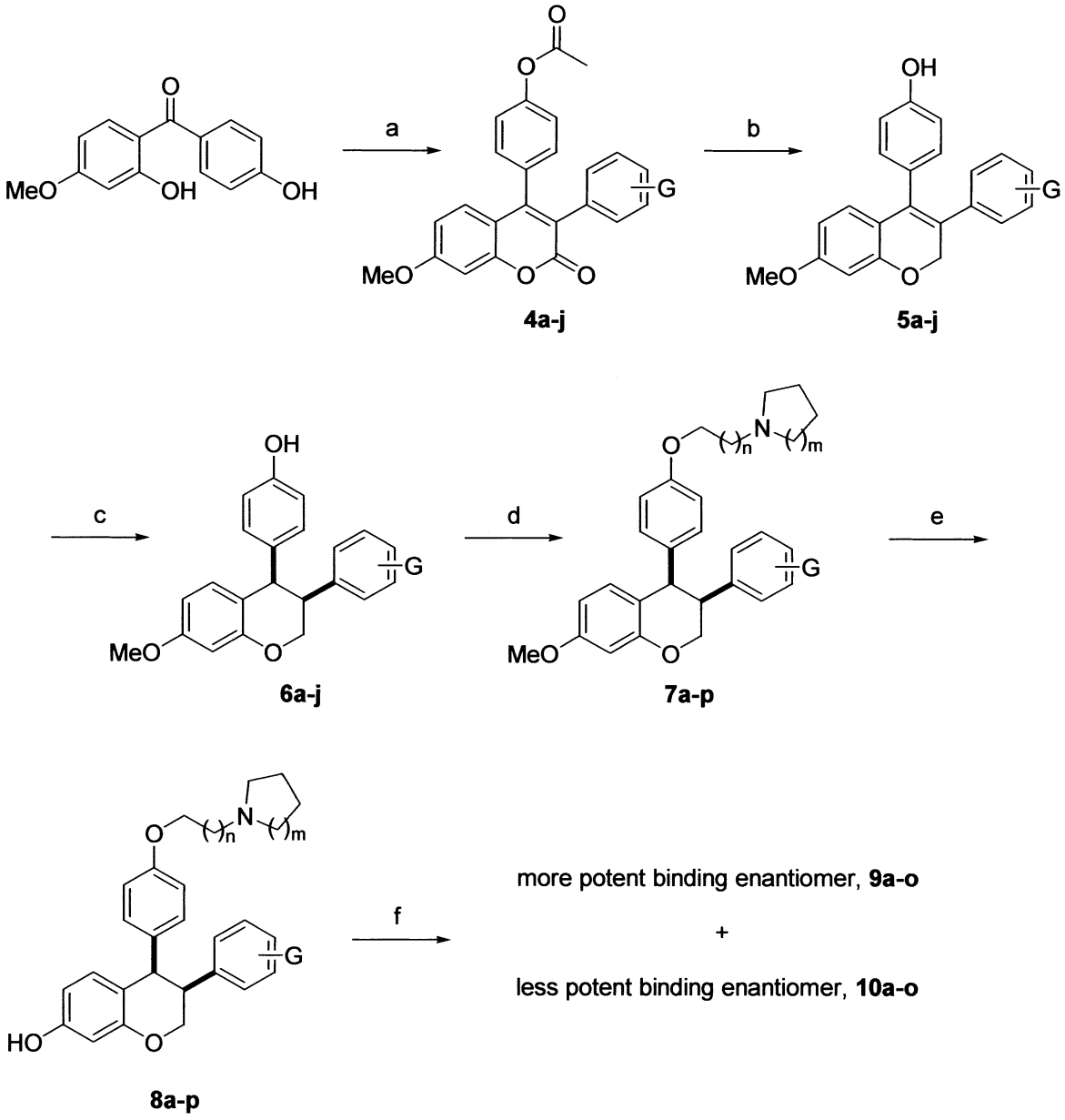
In addition to the preparation of the 7-hydroxy-chromane series, the analogous 6-hydroxy-chromane, (±)-*cis*-6-hydroxy-3-phenyl-4-(4-(2-pyrrolidinoethoxy)-phenyl)chromane, **16**, was also prepared (Scheme 2). The synthesis of **16**, which was essentially the same as that employed for the 7-hydroxychromanes, began with the reaction of *N,N*-dimethyl 2,5-dimethoxybenzamide, **11** with 4-benzyloxyphenyllithium to give 4′-benzyloxy-2,5-dimethoxybenzophenone, **12**. This was then debenzylated by treatment with hydrobromic acid in acetic acid, to give 2,4′-dihydroxy-5-methoxybenzophenone, **13**. Compound **13** was then reacted with phenylacetic acid to give the chromen-2-one, **14**, which was subsequently reduced, ring-closed, hydrogenated, alkylated and demethylated to give the target 6-hydroxychromane, **16**.

In vitro pharmacological analysis

Estrogen receptor (ER) binding assay. The IC_{50} binding affinities of the chromanes to the estrogen receptor were determined by measuring their ability to compete with [^{3}H]-17β-estradiol for receptor binding in ER-rich cytosol derived from rabbit uterine tissue in a dextran-coated charcoal (DCC) assay as described in previous publications.[19,20]

In vivo pharmacological analysis

Female Sprague–Dawley rats (supplied by M & B, Lille Skensved, Denmark), 12 weeks of age, weighing



Scheme 1. (a) Ac_2O, Et_3N, aryl-acetic acid, 110 °C. (b) i. $LiAlH_4$, THF; ii. HCl, 65 °C. (c) H_2/Pd-C, ethanol. (d) Amino-alkyl chloride hydrochloride, K_2CO_3, acetone, 65 °C. (e) Pyridine hydrochloride, 150 °C. (f) Preparative chiral HPLC.

approximately 250 g were used in these studies. All animals were allowed free access to water and a pelleted commercial diet (Altromin 1324) containing 0.9% calcium, 0.7% phosphorous, and 0.6 IU/g Vit D_3. All animal procedures were conducted according to Novo Nordisk A/S Animal Care approved protocols, and the experiments were done in compliance with internal animal welfare and national guidelines.

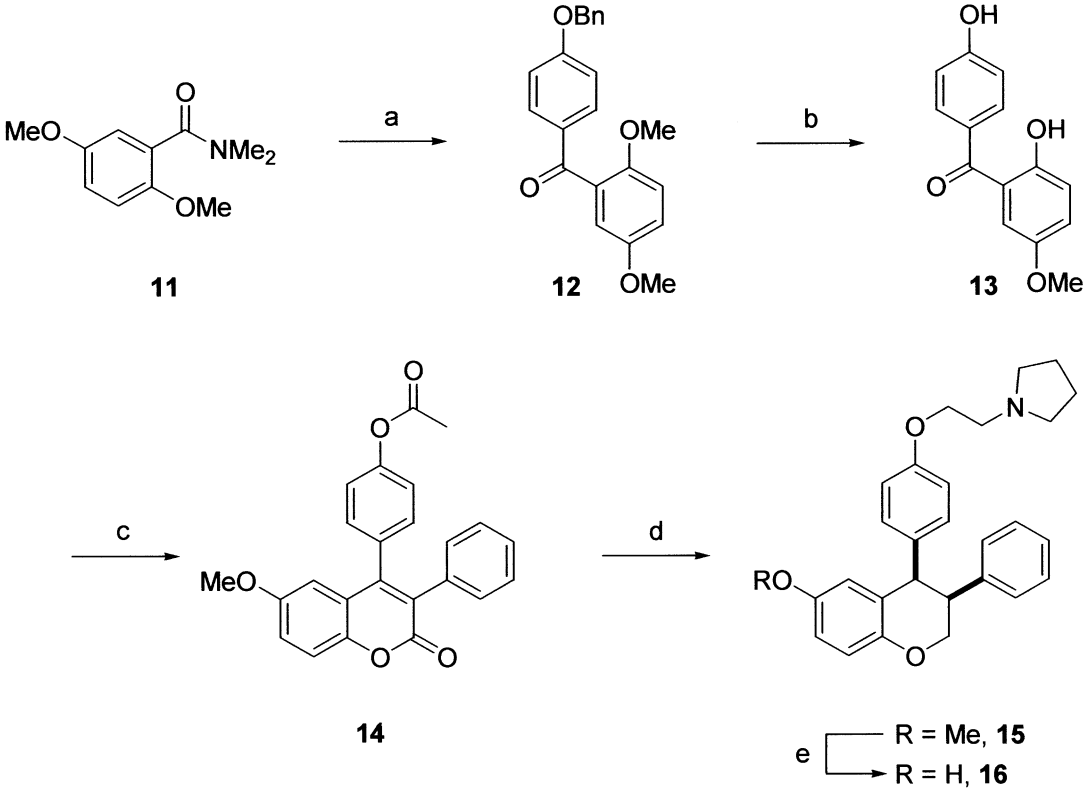
Ovariectomized rat prevention study. Vaginal cytology, serum cholesterol, uterine tissue and appendicular skeleton analysis.

Sham surgeries and ovariectomies were performed while the animals were anesthetized with a ketamine/xylazine anesthetic mixture. Ten rats were sham-operated (sham) and treated by daily oral gavage with vehicle (propylene glycol + 0.9% NaCl, 1:1 v/v), while the remaining rats ($n = 10$ per group) received bilateral ovariectomies (OVX) and were treated by oral gavage with either vehicle, 17α-ethynyl estradiol (EE) (Sigma E-4876, St. Louis, MO, USA) at doses of 1.5 nmol/g/day 3 days weekly, or test compound dosed 5 times weekly for 5 weeks beginning 3 days post surgery. Animal body weights were recorded once weekly. All animals in this study were pair-fed. The amount of food consumed ad libitum by the sham-operated, vehicle-treated animals was determined once per week. The average daily consumption of food per cage was then calculated for each pair of animals in the sham group and the cages in all other treatment groups received a daily feed ration based on this value. Food consumption of the individual cages was monitored.

Table 1. Preparative HPLC conditions for the isolation of enantiomers **9a–o** and **10a–o**

No.	Column[a]	Eluent[b]	R_t of **9** (min)	R_t of **10** (min)	Flow (mL/min)
a	Chiradex A	6:4 M/B2, pH 5.2	19.2	12.2	0.5
b	COD P	81:19 H/I, 0.1%D	36–45	29–35	6
c	COD P	7:3 H/I, 0.1%D	24–33	17–23	6
d	Chiradex A	5:5 M/B1, pH 5.0	62–80	31–45	0.8
e	Chiradex P	5:5 M/B2, pH 3.5	20–30	10–18	20
g	COD P	7:3 H/I, 0.1%D	30–38	21–28	6
h	Chiradex P	46:54 M/B1, pH 5	43–55	19–34	20
i	Chiradex P	4:6 M/B1, pH 3.5	46–64	22–34	20
j	Chiradex P	4:6 M/B2, pH 4.5	80–102	28–58	20
k	COD P	54–60:46–40 H/I, 0.1%D	17–18	20–23	6
l	COD P	6:4 H/I, 0.1%D	15–18	20–23	6
m	COD P	7:3 H/I, 0.1%D	24–31	16–22	6
n	Chiradex P	4:6 M/B1, pH 4.5	72–88	33–44	20
o	COD P	9:1 H/I, 0.1%D	64–80	50–60	6

[a]COD P = 250×20 mm Chiralcel OD preparative column; Chiradex A = 250×4 mm Chiradex analytical column; Chiradex P = 250×25 mm Chiradex preparative column.
[b]H = *n*-heptane, M = methanol, B1 = 0.1% aqueous triethylammonium acetate buffer, B2 = 0.2% aqueous triethylammonium acetate buffer, D = Diisopropylethylamine, I = Isopropyl alcohol.



Scheme 2. (a) 4-$BnOC_6H_4Li$, THF, −78 °C. (b) HBr, AcOH, 65 °C. (c) $C_6H_5CH_2COOH$, Et_3N, Ac_2O. (d) i) $LiAlH_4$, THF, 0 °C; ii) HCl, H_2O, THF, 65 °C; iii) H_2/Pd-C, ethanol; iv) $C_4H_8NCH_2CH_2Cl$ hydrochloride, K_2CO_3, acetone, 60 °C. (e) Pyridine.HCl, 150 °C.

Vaginal cytology. On the last day of treatment, vaginal smear preparations were made using a plastic rod. The samples were transferred to a glass slide and immediately spray fixed with ESWE cytospray (Simonsen & Weel, Copenhagen, Denmark). The specimens were kept refrigerated (+4 °C) until processed further. The slides were stained according to the Papanicolau technique and the relative number of superficial, intermediate and basal cells were estimated. On average 106 cells were counted in each preparation.

Determination of serum cholesterol levels and uterine wet and dry weights. Twenty-four hours after the last dose of treatment, rats were asphyxiated by CO_2 inhalation followed by cervical dislocation. Blood samples were collected into serum vaccutainer collection tubes, allowed to clot on ice and centrifuged at 3000*g* for 10 min. Serum aliquots were stored at −80 °C until measurements of total serum cholesterol were made using enzymatic cholestryl ester hydrolysis and cholesterol oxidation, as followed by a color change reaction (CHOD-PAP, Boehringer Mannheim, Mannheim, Germany).

Uteri were rapidly excised, trimmed free of fat, pierced, and gently blotted to remove excess fluid. They were then cut just above the junction with the cervix and the junction of the uterine horns with the ovaries. The uterine wet weight was then determined immediately on a Mettler balance. Uterine dry weights were obtained by drying uteri at 70 °C for 24 h before reweighing. Uteri for histological examinations were immersion fixed in neutral buffered 4% formalin solution. A central cross-section from one of the horns was embedded in paraffin and sections (5 μm thick) were cut on a microtome. Sections were stained with hematoxylin eosin according to standard procedures, and the morphology was described qualitatively.

Bone densitometry measurements. Immediately after sacrifice of the test animals the tibiae were excised, fixed by immersion in 70% ethanol and their bone mineral density (BMD) analyzed. Tomographic measurements of total volumetric BMD (total vBMD) and trabecular vBMD were performed by pQCT using an XCT Research SA^{TM} instrument (Stratec Medizintechnik, Pforzheim, Germany). The estimates of total and trabecular vBMD were determined 5 mm below the knee joint in right proximal tibiae. The voxel size was $0.150\times0.150\times0.750$ mm, and threshold values of 730 and 214 mg/cm^3 were used for cortical and trabecular bone, respectively. Other settings used were: contour mode 1, peel mode 20, trabecular area 20%, and cortical mode 1. Employing these settings, the coefficient of variation (CV%) as assessed by ten repeated measurements (with repositioning of bone and reference line between each measurement) was 0.84% for total vBMD and 0.68% for trabecular vBMD.

Osteoclast number study

As in the prevention study described above, sham and OVX animals, 12 weeks of age, were administered vehicle, control or test compound via subcutaneous or oral route. Test compound or 17β-estradiol, as a positive control, were administered on days 2, 4, and 7 post-surgery. Twenty-four hours after the last dose of treatment, rats were asphyxiated by CO_2 inhalation followed by cervical dislocation. Tibiae were excised, fixed in 10% formalin for 24 h prior to storage in 70% ethanol, and processed for determination of osteoclast numbers using TRAcP (tartrate-resistant acid phosphatase) staining of calcified plastic embedded sections. Histological assessment of osteoclast numbers was performed following TRAcP staining, with methyl green thione as the counter-stain.

Aortic expression of endothelial nitric oxide synthase (eNOS)

One week after recovery from OVX or sham-OVX surgery, rats were randomized to subcutaneous treatment with either vehicle, test compound (10–100 nmol/g/day) or 17β-estradiol (E) (0.3 nmol/g/day) for 7 days. Rats were euthanized, the thoracic aortas quickly isolated and washed in 0.9% NaCl with 1 mM PMSF prior to storage at −80 °C. Approximately 0.5 cm lengths of vessel were added to 100 μL of extraction buffer (10% glycerol, 62.5 mM Tris–HCl pH 6.8, 2.3% SDS, 1 mM PMSF) and boiled on a water bath for 6 min. Aliquots of 15 μL of final lysate with 2% mercaptoethanol were separated on a 8–16% Tris–Glycin gel (NOVEX) at 100 V for 2 h. eNOS quantities were assessed by Western blotting [NOVEX Western Transfer Apparatus procedure, 30 V, 8 Watt, subsequent application of anti-eNOS (purified polyclonal mouse IgG1, Transduction Laboratories, N30020) and secondary anti-mouse IgG HRP conjugated antibody (Transduction Laboratories, M15345)] using an ECL Western blotting detection kit (Pharmacia, Amersham). Aortic segments from which the endothelium was gently removed were subjected to similar analysis. Quantitative levels of eNOS expression were determined by use of computerized imaging analysis software.

Statistics

Statistics were calculated using GraphPad PRISM 2.0 (GraphPad Software, Inc., San Diego, CA). The ANOVA analysis of variance test, followed by Dunnett's Multiple Comparison Test, were used to compare the differences between groups.

Results and Discussion

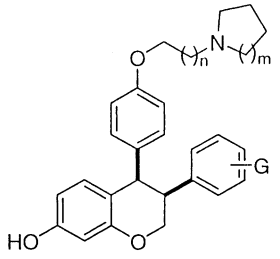
In vitro estrogenic activity studies. The data derived from the ER binding assay for the *cis*-3,4-diaryl-7-hydroxychromanes, which is summarized in Table 2, clearly shows that these compounds are extremely potent ligands for the estrogen receptor, with all but one of the racemic compounds, **8a**–**p** having IC_{50} values below 35 nM. Indeed the majority of the compounds studied had single-digit binding affinities. The analogous racemic 6-hydroxychromane, **16** is also a potent ER ligand, with an IC_{50} binding affinity of 6 nM. Furthermore, even a brief analysis of the data for the purified enantiomers, **9a**–**o** and **10a**–**o** clearly shows, not unsurprisingly, that one of the *cis*-enantiomers is always significantly more potent than the other.

Consideration of the structural–activity relationships displayed by the chromane series shows that the addition of a second hydroxyl functionality on the C-3 aryl moiety is beneficial for the binding affinity. Chromane **8i**, which carries a meta-hydroxyl functionality, possesses sub-nanomolar affinity comparable to that of 17β-estradiol itself ($IC_{50}=0.7$ nM). The trend of the binding affinities also shows that smaller substituents are generally preferred over more sterically demanding groups (compare **8f** with **8e**), and that the *meta* substitution pattern on the C3-aryl moiety is generally preferable to *para* substitution (compare **8j** with **8e**, or **8h** with **8b**).

In vivo skeletal activity. The in vitro test results summarized above clearly show that the hydroxy-chromanes **8a**–**p** are promising partial estrogens. A selection of the chromanes was, therefore, further evaluated by

means of the ovariectomized rat (OVX rat) in vivo assay; an assay designed to evaluate the skeletal estrogenic activities of the test compounds at a standard, orally administered dose of 10 nmol/gram body weight. Since we suspected that the phenolic hydroxy groups present in compounds **8a**–**p** would probably be subject to rapid metabolic turnover in vivo, we also included the methoxy chromanes, (−)-**7a**, **7c** and (−)-**7c** in the test compound set, as putative pro-drugs for their hydroxy-substituted congeners. The results of the tomographic analysis of total and trabecular vBMD of tibiae, as summarized in Table 3, showed notable changes following OVX operation. Vehicle treated rats OVX'ed for 5 weeks displayed considerable decreases in total and trabecular vBMD at the proximal tibia (~21 and 60%, respectively) relative to sham-operated controls. Oral administration of the test chromanes showed that they significantly prevented the loss of total vBMD and trabecular vBMD in the order of 43–105% and 39–81%, respectively (Table 3). Likewise, 17α-ethynyl estradiol protected tibiae against OVX-mediated loss of both total vBMD and trabecular vBMD in the order of 89 and 61.1%, respectively (Table 3). Our supposition that the presence of free hydroxy groups in our test chromanes **3**, and **8c** may lead to rapid metabolic clearance was supported by the fact that both of these compounds showed somewhat weaker in vivo activity than their methoxy analogues (−)-**7a** and **7c** (Table 3). Nevertheless the skeletal activity of NNC 45-0781 (**3**) was comparable to that of 17α-ethynyl estradiol.

Table 2. Estrogen receptor binding affinities of hydroxy-chromanes **8a**–**p**, **9a**–**o** and **10a**–**o**



No.	G	Side chain		ER Binding (IC_{50}, nM)		
		n	m	Racemate **8**	Enantiomer **9**	Enantiomer **10**
a	H	1	1	18	2	400
b	*para*-F	1	1	5	1.8	1500
c	*para*-CF_3	1	1	31	21	410
d	*para*-OH	1	1	2	1	140
e	*para*-Me	1	1	12	N/A	1100
f	*para*-Phenyl	1	1	55	N/A	N/A
g	*meta*-CF_3	1	1	13	5	550
h	*meta*-F	1	1	1	2	1700
i	*meta*-OH	1	1	0.01	0.3	160
j	*meta*-Me	1	1	0.2	0.04	320
k	H	1	2	3	1.6	85
l	H	2	2	2	2	100
m	*para*-CF_3	1	2	23	17	360
n	*para*-Me	1	2	3	2	1300
o	*para*-F	2	2	6	0.1	800
p	*meta*-OH	2	2	2	N/A	N/A

The pharmacological properties of compound **3**, which may be considered to be the parent compound of the homochiral (−)-*cis*-3,4-diaryl-7-hydroxychromane series, were then studied further through a series of in vivo experiments. A full dose-response OVX rat study, involving oral administration of compound **3** in the range of 1–100 nmol/g body weight, showed that this compound completely prevented the OVX-mediated loss of total vBMD from proximal tibiae at all doses from 10 nmol/g and above (c.f. Fig. 2).

In an effort to estimate the direct anti-resorptive activity of compound **3** in the OVX rat, its action on the number of osteoclasts found on trabecular surfaces in tibiae was assessed following both subcutaneous and oral administration at equimolar doses. Study of osteoclasts in rat tibiae, 1-week post OVX, showed a significant increase in osteoclast activity, as evaluated by means of a change in TRAcP (tartrate-resistant acid phosphatase) positive stained multinuclear cells (Fig. 3A). Administration of compound **3** in three separate doses of 2 nmol/g body weight over the course of 1-week post

Table 3. Total and trabecular vBMD determined by pQCT in ovariectomized rats following treatment with novel *cis*-3,4-diaryl-7-hydroxychromanes (**3**, **8c**, & **8e**, 10 nmol/g), *cis*-3,4-diaryl-7-methoxychromanes [(−)-**7a**, **7c**, (−)-**7c**, & **7i**, 10 nmol/g] or 17α-ethynyl estradiol (EE, 1.5 nmol/g)[c]

	Total vBMD mg/cm^3	Trabec vBMD mg/cm^3	Total vBMD % protection	Trabec vBMD % protection
Sham ($n=34$)	$702.7\pm44.7^{NA,d}$	$334.2\pm69.4^{NA,d}$	$100.0\pm25.8^{NA,d}$	$100.0\pm31.4^{NA,d}$
OVX ($n=32$)	$556.5\pm33.6^{b,NA}$	$133.7\pm42.0^{b,NA}$	$0.0\pm21.3^{b,NA}$	$0.0\pm18.3^{b,NA}$
3 = **9a** ($n=10$)	$683.1\pm36.4^{a,d}$	$288.8\pm72.8^{a,d}$	$76.5\pm22.7^{a,d}$	$62.7\ \pm35.6^{a,d}$
(−)-**7a** ($n=6$)	$645.5\pm28.7^{NS,d}$	$252.6\pm43.4^{NS,d}$	$78.3\pm32.3^{NS,d}$	$81.2\pm24.0^{NS,d}$
7c ($n=6$)	$677.6\pm9.7^{NS,d}$	$238.7\pm20.0^{NS,d}$	$105.0\pm8.1^{NS,d}$	$73.5\pm11.1^{NS,d}$
(−)-**7c** ($n=8$)	$670.9\pm28.9^{NS,d}$	$282.3\pm66.1^{NS,d}$	$96.2\pm20.1^{NS,d}$	$79.45\pm35.6^{NS,d}$
7i ($n=6$)	$638.2\pm29.6^{NS,d}$	$231.4\pm58.6^{NS,d}$	$72.2\pm24.7^{NS,d}$	$69.5\pm32.4^{NS,d}$
8c ($n=10$)	$629.8\pm35.8^{b,d}$	$240.4\pm48.4^{b,d}$	$43.3\pm22.3^{b,d}$	$39.1\pm23\ 7^{b,d}$
8e ($n=10$)	$657.4\pm55.9^{b,d}$	$226.6\pm77.5^{b,d}$	$55.5\pm37.1^{b,d}$	$47.5\pm35.0^{b,d}$
EE ($n=33$)	$685.2\pm54.7^{NS,d}$	$255.8\pm64.6^{NS,d}$	$89.0\pm33.1^{NS,d}$	$61.1\pm30.9^{NS,d}$

Data are given as the mean ± SD. Group sizes are given in brackets. The notations NS, a, b, c or d, left and right of the comma respectively indicate whether a value is different from that of the sham or the OVX group.
[a] $p<0.05$ versus sham.
[b] $p<0.01$ versus sham.
[c] $p<0.05$ versus OVX.
[d] $p<0.01$ versus OVX. NA = non-applicable; NS = non-significant.

surgery, completely prevented this change in OVX-mediated osteoclast numbers. Comparison of the effects seen following oral or subcutaneous dosing allowed an estimation of compound **3**s 'apparent oral bioavailability'[21] at the target tissue, which was calculated as being approximately 63%. It is also notable that subcutaneous administration of compound **3**, and intraperitoneal administration of 17β-estradiol produced anti-resorptive activities of the same order of magnitude (Fig. 3B).

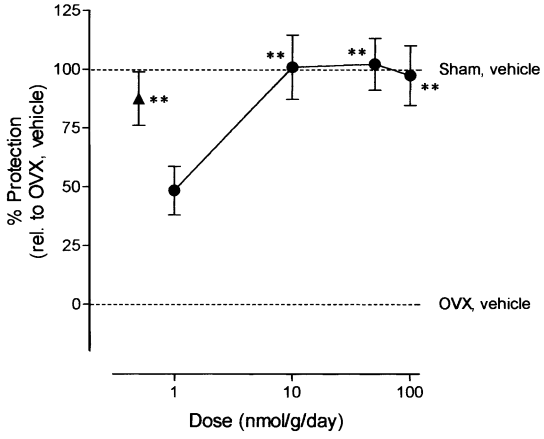


Figure 2. Skeletal activity of compound **3** (NNC 45-0781) (●) and 17α-ethynyl estradiol (▲) on total bone mineral density (BMD) in the proximal tibia of the ovariectomized rat. Data are expressed as percentage protection relative to BMD in vehicle treated OVX rats and represent mean and SEM for 10 animals per group. (**$p < 0.01$ vs OVX, vehicle).

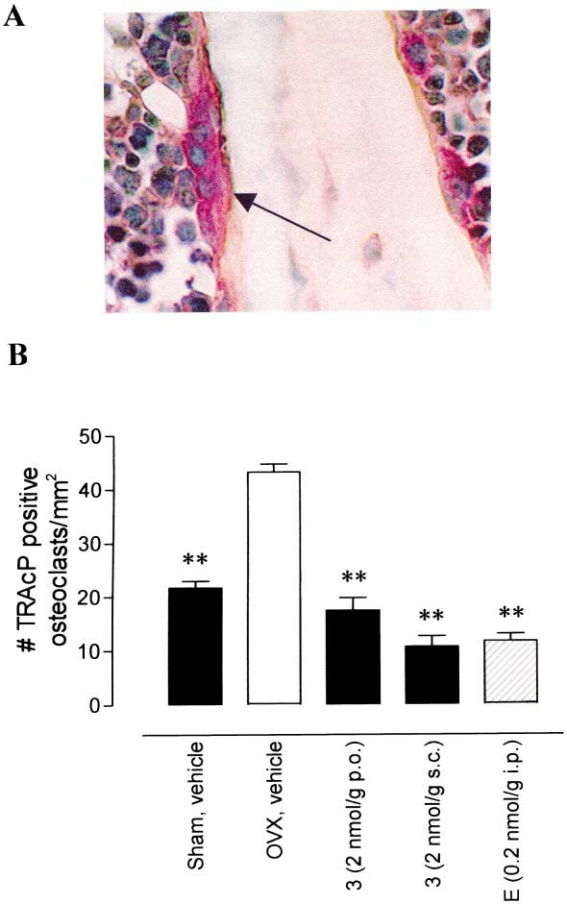


Figure 3. Oral administration of compound **3** (NNC 45-0781) reduces the osteoclast number on trabecular surfaces in tibiae of the ovariectomized rat. (**A**) Section of tibia showing TRAcP positive stained osteoclasts at the trabecular surface (arrow). (**B**) Data represent mean and SEM for 5 animals per group. (**$p < 0.01$ vs OVX, vehicle).

Effects on serum cholesterol levels and epithelial NOS expression. The effect of compound **3** on serum cholesterol levels was also assessed as part of the OVX-rat study. As can be seen from Figure 4, total serum cholesterol was significantly increased in the vehicle-treated group as compared to the sham animals. All of the animals receiving compound **3** at doses of 10 nmol/g or higher, had significantly lower levels of total serum cholesterol as compared to the vehicle treated group. Likewise, the well-known cholesterol lowering effect of estrogen treatment was clearly observed in those OVX animals dosed with 17α-ethynyl estradiol.

The atheroprotective effect of estrogen is speculated to be mediated, in part, through the nitric oxide (NO) pathway. By use of immunoblotting of proteins from vessels of treated rats, the regulative activity of compound **3** on thoracic aortic eNOS expression in ovariectomized rats was evaluated. After one week of vehicle treatment post OVX the expression levels of eNOS were reduced to approximately 40% of those in sham-operated animals. Daily administration of 17β-estradiol (0.3 nmol/g) significantly preserved the expression of eNOS in OVX rats to the level of sham animals (Fig. 5). No estrogen-mediated response on eNOS expression was observed in endothelial-denuded aortic segments (Fig. 5). These data directly show that OVX associated down-regulation of endothelial-dependent aortic eNOS expression may be restored by estrogen replacement in vivo. Also, analysis of aortic eNOS expression from OVX rats treated with compound **3**, revealed estrogenic activity in a dose-dependent manner following 1 week of post OVX treatment (Fig. 5), although this effect did not reach statistical significance over the 1 week treatment period. The effect of compound **3** on eNOS

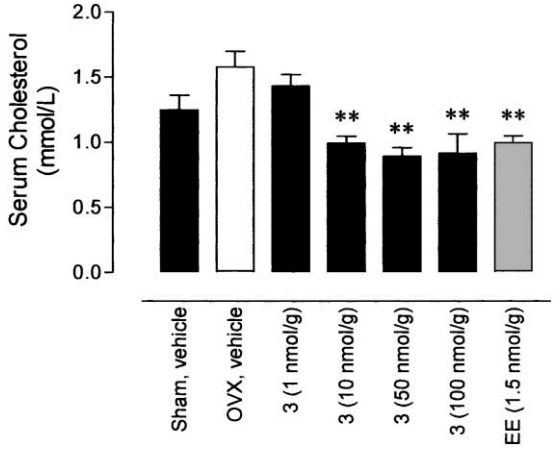


Figure 4. Activity of orally administered compound **3** (NNC 45-0781) or 17α-ethynyl estradiol on total serum cholesterol in the ovariectomized rat. Data represent mean and SEM for 10 animals per group. (**$p < 0.01$ vs OVX, vehicle).

expression did reach statistical significance, however, following extended treatment periods of up to 5 weeks post OVX.[22]

Vaginal cytology. Estrogen initiates a maturation of the vaginal mucosa both by increasing the thickness and the number of cornified superficial cells. The relative appearance of vaginal squamous epithelium cells in a vaginal smear preparation reflects the degree of estrogen stimulation in an animal. Analysis of vaginal smear preparations from OVX'ed rats following treatment with compound **3** revealed stimulatory effects on the maturation of the vaginal mucosa, which resembled the beneficial effects of estradiol treatment (Table 4). Furthermore, in smaller doses, compound **3**, like estradiol, was able to inhibit the inflammatory response, which is characteristic for the atrophic mucosa (Table 4).

Uterotrophic activity. Analysis of the uterine wet and dry weights from the OVX-rat study showed that, when compared with sham animals, the OVX-vehicle group experienced a reduction in the uterine wet weight and consequently a significant increase in relative dry matter. These relative changes were virtually reversed by estradiol treatment (Fig. 6). In contrast, 5 weeks of treatment with compound **3** at 10 and 50 nmol/g did not change the relative amount of dry matter in uterine tissue when compared to the vehicle treated animals (Fig. 6).

Morphological analyses of the uteri derived from the OXV-rat study showed that animals treated with compound **3** had non-proliferative epithelia (Fig. 7). The main effect of compound **3** on the uteri was observed to be an increase in the height of the cells in the uterine surface epithelium upon treatment with doses beyond 50 nmol/g. The nuclei of the cells, however, remained in the non-proliferative, non cancerous, basal state (i.e., the nuclei were situated at the base of the epithelial cells). Importantly, at the lower dose of 10 nmol/g, the dose at which the maximal skeletal anti-resorptive effect was observed, (Fig. 2) no significant effect of compound **3** treatment was visible. This was in contrast to the effect seen with the 17β-estradiol treated animals, or with the sham operated group, which still possessed their endogenous estradiol production (Fig. 7a, b and h). In these estradiol-exposed animals, the nuclei of the surface epithelium of the uterine cavity were stimulated. They were

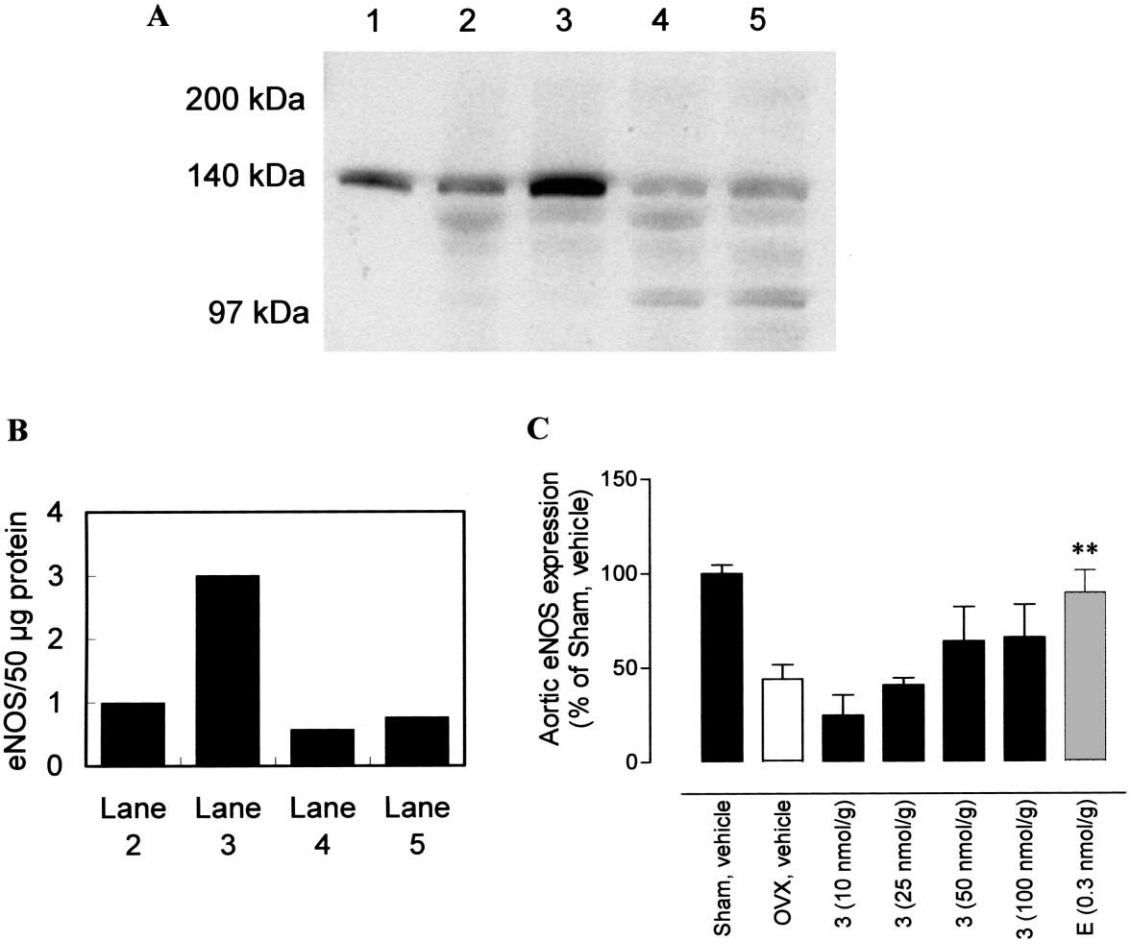


Figure 5. Changes of aortic eNOS protein expression upon administration of compound **3** (NNC 45-0781) or 17β-estradiol in the ovariectomized rat. (**A**) Western blot showing 140 kDa eNOS protein. Lane 1: human endothelial lysate; Lane 2: OVX, vehicle; Lane 3: OVX, 17β-estradiol (0.3 nmol/g/day for 7 days); Lane 4: as lane 2 with protein extract from endothelial-denuded aorta; Lane 5: as lane 3 with protein extract from endothelial-denuded aorta. (**B**) Quantitative eNOS protein levels from Western blot (A). (**C**) Animals received bilateral ovariectomies 1 week prior to daily subcutaneous administration of compound **3** or 17β-estradiol. Data represent mean and SEM from 3–9 animals per group. (**$p < 0.01$ vs OVX, vehicle).

Table 4. Percentage distribution of basal, intermediate, or superficial squamous epithelial cell types in vaginal smears, plus the number of inflammatory cells present after treatment with **3** or EE. Data represent mean and SEM from 10 animals per group

Treatment	Basal	Intermediate	Superficial	Leucocytes
Sham, vehicle	4.4±2.1*	80.4±2.5	15.2±2.4	variable
OVX, vehicle	17.9±4.1	61.7±5.5	20.4±4.4	many
OVX, **3** (1 nmol/g)	24.8±4.2	62.5±4.9	12.7±3.2	few
OVX, **3** (10 nmol/g)	14.1±1.8	51.2±3.5	34.7±5.0	few
OVX, **3** (50 nmol/g)	7.6±2.1	46.8±3.1	45.6±4.8**	few
OVX, **3** (100 nmol/g)	7.3±1.4	43.5±6.3	49.2±6.2**	few
OVX, EE (2.5 nmol/g)	8.1±1.3	50.4±4.9	41.5±5.3**	few

*$p < 0.001$ (versus OVX, vehicle).
**$p < 0.005$ (versus OVX, vehicle).

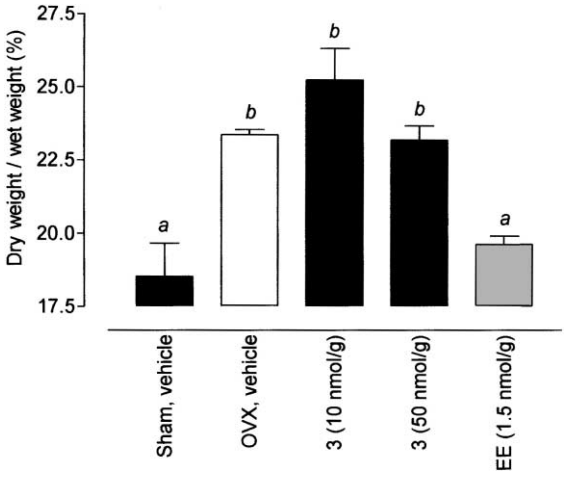


Figure 6. Changes in relative dry matter of uterine tissue after oral administration of compound **3** (NNC 45-0781) or 17α-ethynyl estradiol in the ovariectomized rat. Data represent mean and SEM for 10 animals per group. *a*: $p < 0.01$ versus OVX-vehicle; *b*: $p < 0.01$ versus sham, OVX-vehicle treated, and EE-treated groups.

enlarged, with a dense chromatin, and they were situated at all levels of the epithelial cells, giving the epithelium a stratified appearance, so-called pseudostratification. Furthermore, even at very low doses of estradiol treatment, prominent nucleoli were present in the stimulated nuclei. This characteristic could not be observed after treatment with compound **3**. Even at the higher dose levels, the glands and stroma were morphologically unaffected after treatment with compound **3** when compared with the OVX and vehicle treated groups. Consequently, since the effects of compound **3** treatment on the nuclei were observed only at doses higher than that required for the maximal skeletal antiresorptive effect, it is clear that compound **3** had a therapeutic window in which maximal bone preserving activity was achieved without stimulating endometrial tissue.

Conclusion

In summary, the various pharmacological assays detailed above clearly show that the *cis*-3,4-diarylhydroxychromanes, as represented by compound **3** (NNC 45-0781) are an extremely promising class of tissue-selective partial estrogens. Treatment of ovariectomized rats with compound **3** completely prevented the loss of bone mineral density resulting from the removal of endogenous estrogen production, and similarly brought about the same lowering of serum cholesterol levels as seen with 17α-ethynyl estradiol treatment. Positive, dose-dependent, effects on vaginal cytology, and on the levels of aortic eNOS expression, along with a dose-dependent reduction in trabecular osteoclast numbers, were also seen in those animals treated with compound **3**. Whilst compound **3** was able to bring about these beneficial estrogenic effects, the corresponding negative uterotrophic changes normally observed with estradiol treatment were not seen in those animals dosed with compound **3**. In particular, the dangerous proliferative effects on endometrial tissue were not observed. In conclusion, therefore, the pharmacological profile of the *cis*-3,4-diaryl-7-hydroxychromane, NNC 45-0781 shows that it is a very promising tissue-selective estrogen agonist.

Experimental

All reactions were carried out using conventional techniques. Those processes involving the use of moisture-sensitive reagents were performed using oven-dried glassware, under an atmosphere of dry nitrogen. Solvents were used as supplied from commercial sources except for THF, which was freshly distilled from a sodium and benzophenone mixture immediately before use. Reaction progress was monitored by means of TLC on Macherey–Nagel Alugram® SIL G/UV plates. Column chromatography was performed using Macherey–Nagel 230–400 mesh silica gel 60. Melting points were recorded using a Büchi B-545 open capillary melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded using Bruker DRX400, DRX300 or DPX200 spectrometers in suitable deuterated solvents, as indicated. Chemical shifts values (δ) are reported in parts per million relative to tetramethylsilane as an internal standard. Elemental analyses were performed by Novo Nordisk microanalysis laboratories. Mass spectra (MS) were recorded as electron impact (EI) spectra at 70 eV on a Finnigan MAT-TSQ70 mass spectrometer. High-resolution mass spectra (HR-MS) were determined at the Department of Chemistry, University of Southern Denmark, on an IonSpec HiRes MALDI (Matrix Assisted Laser Desorption Ionisation)

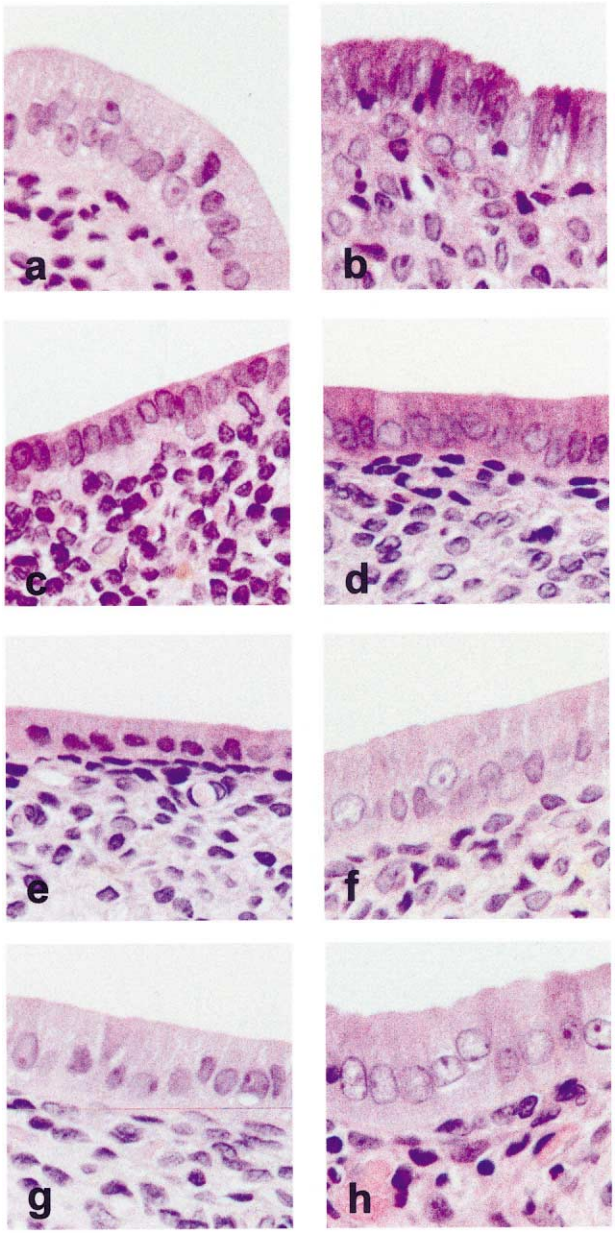


Figure 7. Photomicrographs of uterine surface epithelium in rats upon oral administration of compound **3** (NNC 45-0781). a intact untreated baseline at 5 weeks; b Sham, vehicle; c OVX-vehicle; d OVX, **3** (1 nmol/g); e OVX, **3** (10 nmol/g); f OVX, **3** (50 nmol/g); g OVX, **3** (100 nmol/g); h OVX, 17β-estradiol (0.5 nmol/g). Compound **3** and 17β-estradiol were administered 5 and 2 times weekly for 5 weeks, respectively.

Fourier Transform mass spectrometer. The intermediates, 2,4′-dihydroxy-4-methoxybenzophenone, and 4-(4-hydroxyphenyl)-7-methoxy-3-phenylchromen-2-one, **4a** were prepared according to literature procedures.[15]

4-(4-Acetoxyphenyl)-3-(4-fluorophenyl)-7-methoxychromen-2-one (4b). A mixture of 2,4′-dihydroxy-4-methoxybenzophenone (7.33 g, 30.0 mmol), acetic anhydride (15 mL), triethylamine (5.5 mL, 39.5 mmol), and 4-fluorophenylacetic acid (4.63 g, 30.0 mmol) was stirred at 135 °C for 18 h, the resulting orange solution poured into water (120 mL) and stirred for 3 h. The resulting mixture of aqueous solution plus sticky solid was diluted with ethyl acetate (300 mL) to dissolve the solid, and the organic layer separated. The aqueous phase was further extracted with ethyl acetate (2×100 mL) and the combined organic layers washed with water, saturated sodium chloride solution, dried over sodium sulfate and evaporated to give a yellow/orange solid, which was recrystallized from 2:1 ethanol/water (600 mL) to give **4b** as off-white needles, which were vacuum dried: 7.98 g (65% yield), mp 173–176 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 2.32 (s, 3H); 3.89 (s, 3H); 6.78 (dd, 1H); 6.82–6.95 (m, 3H); 7.03–7.14 (m, 6H); 7.15 (d, 1H). MS (EI): 404 (M^+), 362, 334, 319, 43. Elemental analysis; calcd for $C_{24}H_{17}FO_5$: C, 71.28; H, 4.24%; found C, 71.26; H, 4.25%.

4-(4-Acetoxyphenyl)-7-methoxy-3-(4-(trifluoromethyl)-phenyl)chromen-2-one (4c). The title compound was prepared as described for **4b**, from 4-trifluoromethylphenylacetic acid (4.63 g, 30.0 mmol) and 2,4′-dihydroxy-4-methoxybenzophenone (7.33 g, 30.0 mmol); crude product recrystallized from aqueous ethanol: 9.56 g (70% yield), mp 198–201 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 2.31 (s, 3H), 3.90 (s, 3H), 6.79 (dd, 1H), 6.93 (d, 1H), 7.05–7.15 (m, 4H), 7.17 (d, 1H), 7.21–7.27 (m, 2H), 7.42–7.49 (m, 2H). MS (EI): 454 (M^+), 412, 384, 369, 43. Elemental analysis; calcd for $C_{25}H_{17}F_3O_5$; C, 66.08; H, 3.77%; found C, 66.04; H, 3.77%.

4-(4-Acetoxyphenyl)-7-methoxy-3-(4-methoxyphenyl)-chromen-2-one (4d). The title compound was prepared as described for **4b**, from 4-methoxyphenylacetic acid (4.99 g, 30.0 mmol) and 2,4′-dihydroxy-4-methoxybenzophenone (7.33 g, 30.0 mmol); crude product triturated with hot ethanol: 5.09 g (40% yield), mp 208–212 °C. ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 2.32 (s, 3H), 3.75 (s, 3H), 3.88 (s, 3H), 6.68–6.80 (m, 3H), 6.91 (d, 1H), 6.99–7.18 (m, 7H). MS (EI): 416 (M^+), 374, 346, 331, 43.

4-(4-Acetoxyphenyl)-7-methoxy-3-(4-methylphenyl)chromen-2-one (4e). The title compound was prepared as described for **4b**, from 4-methylphenylacetic acid (4.51 g, 30.0 mmol) and 2,4′-dihydroxy-4-methoxybenzophenone (7.33 g, 30.0 mmol); crude product recrystallized from aqueous ethanol: 5.72 g (47% yield), mp 192–196 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 2.25 (s, 3H), 2.30 (s, 3H), 3.90 (s, 3H), 6.76 (dd, 1H), 6.91 (d, 1H), 6.96–7.03 (m, 4H), 7.03–7.17 (m, 5H). MS (EI): 400 (M^+), 358, 330, 315, 43. Elemental analysis; calcd for $C_{25}H_{20}O_5$; C, 74.99; H, 5.03%; found C, 75.13; H, 5.11%.

4-(4-Acetoxyphenyl)-3-(4-biphenyl)-7-methoxychromen-2-one (4f). The title compound was prepared as described for **4b**, from 4-biphenylacetic acid (6.37 g, 30.0 mmol) and 2,4′-dihydroxy-4-methoxybenzophenone (7.33 g, 30.0 mmol); crude product triturated with boiling acetone: 7.12 g (51% yield), mp 229–234 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 2.29 (s, 3H), 3.90 (s, 3H), 6.78 (dd, 1H), 6.83 (d, 1H), 7.04–7.11 (m, 2H), 7.12–7.22 (m, 5H), 7.35–7.47 (m, 5H), 7.51–7.56 (m, 2H). MS (EI): 462 (M^+), 420, 392, 377, 43. Elemental analysis; calcd

for $C_{30}H_{22}O_5$; C, 77.91; H, 4.79%; found C, 77.56; H, 4.80%.

4-(4-Acetoxyphenyl)-7-methoxy-3-(3-(trifluoromethyl)-phenyl)chromen-2-one (4g). The title compound was prepared as described for **4b**, from 3-(trifluoromethyl)phenylacetic acid (6.13 g, 30.0 mmol) and 2,4′-dihydroxy-4-methoxybenzophenone (7.33 g, 30.0 mmol); crude product recrystallized from hot ethanol: 9.52 g (69% yield), mp 150.5–151.5 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 2.30 (s, 3H), 3.90 (s, 3H), 6.80 (dd, 1H), 6.94 (d, 1H), 7.05–7.24 (m, 5H), 7.30–7.50 (m, 4H). MS (EI): 454 (M^+), 412, 384, 369, 43. Elemental analysis; calcd for $C_{25}H_{17}F_3O_5$; C, 66.08; H, 3.77%; found C, 66.13; H, 3.79%.

4-(4-Acetoxyphenyl)-3-(3-fluorophenyl)-7-methoxychromen-2-one (4h). The title compound was prepared as described for **4b**, from 3-fluorophenylacetic acid (4.63 g, 30.0 mmol) and 2,4′-dihydroxy-4-methoxybenzophenone (7.33 g, 30.0 mmol). First crop of product recrystallized from aqueous ethanol, mother liquors evaporated and resulting solid recrystallized from aqueous acetone to give a second crop of solid, which was mixed with the first: combined product 8.39 g (69% yield), mp 179–180.5 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 2.30 (s, 3H), 3.89 (s, 3H), 6.78 (dd, 1H), 6.82–6.94 (m, 4H), 7.04–7.20 (m, 6H). MS (EI): 404 (M^+), 362, 334, 319, 123, 43. Elemental analysis; calcd for $C_{24}H_{17}FO_5$; C, 71.28; H, 4.24%; found C, 71.31; H, 4.24%.

4-(4-Acetoxyphenyl)-7-methoxy-3-(3-methoxyphenyl)-chromen-2-one (4i). The title compound was prepared as described for **4b**, from 3-methoxyphenylacetic acid (4.99 g, 30.0 mmol) and 2,4′-dihydroxy-4-methoxybenzophenone (7.33 g, 30.0 mmol); crude product recrystallized from ethanol: 7.93 g (63% yield), mp 155.5–157 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 2.30 (s, 3H), 3.65 (s, 3H), 3.90 (s, 3H), 6.62 (m, 1H), 6.69–6.80 (m, 3H), 6.90 (d, 1H), 7.03–7.20 (m, 6H). MS (EI): 416 (M^+), 374, 346, 331, 43.

4-(4-Acetoxyphenyl)-7-methoxy-3-(3-methylphenyl)chromen-2-one (4j). The title compound was prepared as described for **4b**, from 3-methylphenylacetic acid (4.51 g, 30.0 mmol) and 2,4′-dihydroxy-4-methoxybenzophenone (7.33 g, 30.0 mmol); crude product recrystallized from ethanol: 7.46 g (62% yield), mp 137.5–139.5 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 2.22 (s, 3H), 2.30 (s, 3H), 3.89 (s, 3H), 6.77 (dd, 1H), 6.84–7.00 (m, 4H), 7.00–7.20 (m, 6H). MS (EI): 400 (M^+), 358, 330, 315, 43. Elemental analysis; calcd for $C_{25}H_{20}O_5$; C, 74.99; H, 5.03%; found C, 74.51; H, 5.01%.

4-(4-Hydroxyphenyl)-7-methoxy-3-phenyl-2*H*-chromene (5a). A solution of 4-(4-hydroxyphenyl)-7-methoxy-3-phenylchromen-2-one (**4a′**, 300 g, 0.87 mol) in dry tetrahydrofuran (2 L) was added over a 30 min period to a stirred suspension of lithium aluminium hydride (66.3 g, 1.75 mol) in dry tetrahydrofuran (1 L), and the resulting mixture stirred for 30 min. Hydrochloric acid (6M, 2 L) was added carefully, and the mixture stirred at 60 °C for 1 h. The resulting solution was cooled to room temperature, the aqueous layer separated and extracted twice with toluene (500 mL and 200 mL). The combined organic phases were evaporated, the solid residue dissolved in ethanol (500 mL) and the solvents evaporated again to give an orange solid, which was dissolved in hot ethanol (800 mL), diluted with water (400 mL) and cooled to room temperature. This resulted in the crystallization of the product, **5a** as colorless needles, which were collected and vacuum dried; 234 g (81% yield), mp 156–157 °C (aqueous ethanol). ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 3.80 (s, 3H), 4.82 (bs, 1H), 5.08 (s, 2H), 6.40 (dd, 1H), 6.51 (d, 1H), 6.73 (d, 2H), 6.78 (d, 1H), 6.94–7.02 (m, 4H), 7.05–7.18 (m, 3H). HR-MS; calcd for $C_{22}H_{19}O_3$ ($M+H^+$) 331.1334, found 331.1349.

3-(4-Fluorophenyl)-4-(4-hydroxyphenyl)-7-methoxy-2*H*-chromene (5b). Lithium aluminium hydride (0.76 g, 20.03 mmol) was added in small portions to a stirred tetrahydrofuran (150 mL) solution of 4-(4-acetoxyphenyl)-3-(4-fluorophenyl)-7-methoxychromen-2-one (**4b**, 4.04 g, 9.99 mmol). After complete addition, the mixture was stirred at room temperature for 30 min, and then treated dropwise with 6 M hydrochloric acid (30 mL). The resulting mixture was heated to 60–65 °C for 3 h, cooled and diluted with water (100 mL) and ethyl acetate (50 mL). The aqueous layer was separated and further extracted with ethyl acetate (3×100 mL). The combined organic phase was washed with saturated aqueous sodium chloride, dried over sodium sulfate and evaporated to give an orange solid. This was recrystallized from ethanol/water (75 mL, 4:1) to give the first crop of product **5b**, as colorless needles. The mother liquors were evaporated to give an orange gum, which was subjected to a second aqueous ethanol recrystallization to give a second crop of **5b**; the solids were combined and vacuum dried; 2.47 g (70% yield), mp 155–156.5 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 3.79 (s, 3H), 4.80 (bs, 1H), 5.20 (s, 2H), 6.40 (dd, 1H), 6.51 (d, 1H), 6.70–7.00 (m, 9H). MS (EI): 348 (M^+), 255, 253.

4-(4-Hydroxyphenyl)-7-methoxy-3-(4-(trifluoromethyl)-phenyl)-2*H*-chromene (5c). The title compound was prepared as described for **5b** from 4-(4-acetoxyphenyl)-7-methoxy-3-(4-(trifluoromethyl)phenyl)chromen-2-one (**4c**, 4.54 g, 9.99 mmol); crude product recrystallized in two crops from aqueous ethanol: 3.59 g (91% combined yield), mp 169–171 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 3.80 (s, 3H), 4.85 (bs, 1H), 5.05 (s, 2H), 6.42 (dd, 1H), 6.52 (d, 1H), 6.72–6.82 (m, 3H), 6.96 (dm, 2H), 7.07 (dm, 2H), 7.40 (dm, 2H). MS (EI): 398 (M^+), 305, 253. Elemental analysis; calcd for $C_{23}H_{17}F_3O_3$; C, 69.34; H, 4.30%; found C, 69.00; H, 4.27%.

4-(4-Hydroxyphenyl)-7-methoxy-3-(4-methoxyphenyl)-2*H*-chromene (5d). The title compound was prepared as described for **5b** from 4-(4-acetoxyphenyl)-7-methoxy-3-(4-methoxyphenyl)chromen-2-one (**4d**, 4.16 g, 9.99 mmol); crude product recrystallized in two crops from aqueous ethanol: 2.72 g (75% combined yield), mp 176–178 °C. ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 3.75 (s, 3H), 3.80 (s, 3H), 4.78 (bs, 1H), 5.04 (s, 2H), 6.39 (dd, 1H), 6.50 (d, 1H), 6.63–6.80 (m, 5H), 6.85–7.03 (m, 4H). MS (EI): 360 (M^+), 267, 253. Elemental analysis; calcd for

$C_{23}H_{20}O_4$; C, 76.65; H, 5.59%; found C, 76.59; H, 5.67%.

4-(4-Hydroxyphenyl)-7-methoxy-3-(4-methylphenyl)-2*H*-chromene (5e). The title compound was prepared as described for **5b** from 4-(4-acetoxyphenyl)-7-methoxy-3-(4-methylphenyl)chromen-2-one (**4e**, 4.00 g, 9.99 mmol); crude product recrystallized in two crops from aqueous ethanol: 2.50 g (73% combined yield), mp 184–186 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 2.25 (s, 3H), 3.80 (s, 3H), 4.68 (bs, 1H), 5.06 (s, 2H), 6.39 (dd, 1H), 6.50 (d, 1H), 6.70–6.79 (m, 3H), 6.86 (dm, 2H), 6.92–7.02 (m, 4H). MS (EI): 344 (M^+), 329, 253, 251. Elemental analysis; calcd for $C_{23}H_{20}O_3$; C, 80.21; H, 5.85%; found C, 80.20; H, 5.92%.

3-(4-Biphenyl)-4-(4-hydroxyphenyl)-7-methoxy-2*H*-chromene (5f). The title compound was prepared as described for **5b** from 4-(4-acetoxyphenyl)-3-(4-biphenyl)-7-methoxychromen-2-one (**4f**, 4.62 g, 9.99 mmol); crude product recrystallized in two crops from aqueous ethanol: 3.29 g (81% combined yield), mp 198.5–200.5 °C. ^{1}H NMR ($CDCl_3$ + drop DMSO-d_6, 300 MHz) δ: 3.80 (s, 3H), 5.10 (s, 2H), 6.40 (dd, 1H), 6.51 (d, 1H), 6.74–6.82 (m, 2H), 6.83 (d, 1H), 6.92–7.00 (m, 2H), 7.01–7.09 (m, 2H), 7.27–7.34 (m, 1H), 7.34–7.43 (m, 4H), 7.50–7.56 (m, 2H), 8.50 (s, 1H). MS (EI): 406 (M^+), 313, 152, 77.

4-(4-Hydroxyphenyl)-7-methoxy-3-(3-(trifluoromethyl)-phenyl)-2*H*-chromene (5g). The title compound was prepared as described for **5b** from 4-(4-acetoxyphenyl)-7-methoxy-3-(3-(trifluoromethyl)phenyl)chromen-2-one (**4g**, 4.54 g, 9.99 mmol); crude product recrystallized from CH_2Cl_2 and light petroleum (2:5, respectively): 3.14 g (79% yield), mp 172–175 °C. ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 3.80 (s, 3H), 4.85 (bs, 1H), 5.06 (s, 2H), 6.42 (dd, 1H), 6.52 (d, 1H), 6.70–6.79 (m, 2H), 6.80 (d, 1H), 6.90–7.00 (m, 2H), 7.09–7.40 (m, 4H). MS (EI): 398 (M^+), 305, 253.

3-(3-Fluorophenyl)-4-(4-hydroxyphenyl)-7-methoxy-2*H*-chromene (5h). The title compound was prepared as described for **5b** from 4-(4-acetoxyphenyl)-3-(3-fluorophenyl)-7-methoxychromen-2-one (**4h**, 4.04 g, 9.99 mmol); crude product recrystallized in two crops from aqueous ethanol: 2.49 g (71% combined yield), mp 139.5–140.5 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 3.80 (s, 3H), 5.05 (s, 2H), 6.41 (dd, 1H), 6.51 (d, 1H), 6.66 (dm, 1H), 6.71–6.84 (m, 5H), 6.93–7.00 (m, 2H), 7.06–7.15 (m, 1H), phenolic OH not observed. MS (EI): 348 (M^+), 255, 253.

4-(4-Hydroxyphenyl)-7-methoxy-3-(3-methoxyphenyl)-2*H*-chromene (5i). The title compound was prepared as described for **5b** from 4-(4-acetoxyphenyl)-7-methoxy-3-(3-methoxyphenyl)chromen-2-one (**4i**, 4.16 g, 9.99 mmol); crude product recrystallized in two crops from aqueous ethanol: 2.82 g (78% combined yield), mp 169.5–171 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 3.59 (s, 3H), 3.80 (s, 3H), 4.78 (bs, 1H), 5.06 (s, 2H), 6.40 (dd, 1H), 6.49 (m, 1H), 6.51 (d, 1H), 6.59 (dm, 1H), 6.66 (dm, 1H), 6.70–6.80 (m, 3H), 6.99 (dm, 2H), 7.08 (dd, 1H). MS (EI): 360 (M^+), 267, 253.

4-(4-Hydroxyphenyl)-7-methoxy-3-(3-methylphenyl)-2*H*-chromene (5j). The title compound was prepared as described for **5b** from 4-(4-acetoxyphenyl)-7-methoxy-3-(3-methylphenyl)chromen-2-one (**4j**, 4.00 g, 9.99 mmol); crude product recrystallized in two crops from aqueous ethanol: 1.88 g (54% combined yield), mp 135–137 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 2.20 (s, 3H), 3.80 (s, 3H), 4.75 (bs, 1H), 5.05 (s, 2H), 6.39 (dd, 1H), 6.51 (d, 1H), 6.68–6.83 (m, 5H), 6.87–7.06 (m, 4H). MS (EI): 344 (M^+), 253, 251.

(±)-*cis*-4-(4-Hydroxyphenyl)-7-methoxy-3-phenylchromane (6a). Palladium (10 wt% on activated carbon, 50% water, 10 g, 5 mmol) was added at 60 °C to a stirred solution of 4-(4-hydroxyphenyl)-7-methoxy-3-phenyl-*2H*-chromene (**5a**, 86.44 g, 0.26 mol) in hot ethanol (2 L) and the resulting mixture hydrogenated on a Parr apparatus at elevated pressure for 18 h. The resulting hot suspension was filtered through Celite® to remove the catalyst, and the filter cake washed with hot ethanol. The filtrate was concentrated in vacuo to approximately 1 L, and cooled in an ice bath. The resulting first crop of solid product was collected by filtration, the mother liquors evaporated to dryness, and the residue washed with ethanol to give a second crop of solid. The crops were combined to give the colorless solid product, **6a**; 76.10 g (81% yield), mp 188–190 °C. ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 3.55 (ddd, 1H), 3.73 (s, 3H), 4.18–4.25 (m, 2H), 4.35 (dd, 1H), 6.30–6.68 (m, 2H), 6.40–6.50 (m, 4H), 6.72–6.82 (m, 3H), 7.11–7.19 (m, 3H), 9.10 (s, 1H). HR-MS; calculated for $C_{22}H_{21}O_3$ ($M+H^+$) 333.1490, found 333.1482.

(±)-*cis*-3-(4-Fluorophenyl)-4-(4-hydroxyphenyl)-7-methoxychromane (6b). Palladium (10 wt% on activated carbon, 0.20 g, 0.19 mmol, 3 mol%) was added to a solution of 3-(4-fluorophenyl)-4-(4-hydroxyphenyl)-7-methoxy-2*H*-chromene (**5b**, 1.74 g, 4.99 mmol) in absolute ethanol (150 mL) and the mixture stirred under a hydrogen atmosphere at ambient pressure for 22 h. The catalyst was removed by filtration through Celite®, the filter cake washed with extra ethanol, and the filtrate evaporated to dryness. The resulting off-white solid was recrystallized from aqueous ethanol; giving the product **6b** as colorless needles, which contained 0.75 mol equiv of ethanol of crystallization; 1.46 g (75% yield), mp 163–165 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.25 (t, 2.4H, 0.75 EtOH), 3.55 (ddd, 1H), 3.73 (q, 1.6H, 0.75 EtOH), 3.81 (s, 3H), 4.16–4.25 (m, 2H), 4.38 (dd, 1H), 4.90 (bs, 1H), 6.44–6.58 (m, 6H), 6.59–6.68 (m, 2H), 6.80–6.90 (m, 3H). MS (EI): 350 (M^+), 227, 211. Elemental analysis; calcd for $C_{22}H_{19}FO_3 \cdot 0.75C_2H_5OH$; C, 73.33; H, 6.13%; found C, 73.32; H, 6.11%.

(±)-*cis*-4-(4-Hydroxyphenyl)-7-methoxy-3-(4-(trifluoromethyl)phenyl)chromane (6c). The title compound was prepared as described for **6b** from 4-(4-hydroxyphenyl)-7-methoxy-3-(4-(trifluoromethyl)phenyl)-2*H*-chromene (**5c**, 2.99 g, 7.51 mmol) and palladium (10 wt% on activated carbon, 0.40 g, 0.38 mmol, 5 mol%) in absolute ethanol (100 mL); crude product recrystallized in two crops from aqueous ethanol to give **6c** as colorless needles: 2.52 g (73% combined yield), mp 211–213 °C. ^{1}H

NMR ($CDCl_3$, 300 MHz) δ: 3.63 (ddd, 1H), 3.81 (s, 3H), 4.20–4.28 (m, 2H), 4.44 (dd, 1H), 4.60 (bs, 1H), 6.43–6.58 (m, 6H), 6.79 (dm, 2H), 6.84 (d, 1H), 7.41 (dm, 2H). MS (EI): 400 (M^+), 227, 211. Elemental analysis; calcd for $C_{23}H_{19}F_3O_3$; C, 68.99; H, 4.78%; found C, 69.00; H, 4.78%.

(±)-*cis*-4-(4-Hydroxyphenyl)-7-methoxy-3-(4-methoxyphenyl)chromane (6d). The title compound was prepared as described for **6b** from 4-(4-hydroxyphenyl)-7-methoxy-3-(4-methoxyphenyl)-2*H*-chromene (**5d**, 1.80 g, 4.99 mmol) and palladium (10 wt% on activated carbon, 0.10 g, 0.09 mmol, 2 mol%) in absolute ethanol (150 mL); crude product recrystallized in two crops from aqueous ethanol to give **6d** as colorless needles: 1.63 g (90% combined yield), mp 157.5–158.5 °C. ^1H NMR ($CDCl_3$ + drop DMSO-d_6, 300 MHz) δ: 3.48 (ddd, 1H), 3.75 (s, 3H), 3.78 (s, 3H), 4.11–4.22 (m, 1H), 4.13 (d, 1H), 4.36 (dd, 1H), 6.38–6.50 (m, 4H), 6.51–6.61 (m, 4H), 6.64–6.71 (m, 2H), 6.83 (d, 1H), 8.57 (bs, 1H). MS (EI): 362 (M^+), 227, 211, 134, 119, 91. Elemental analysis; calcd for $C_{23}H_{22}O_4$; C, 76.22; H, 6.12%; found C, 76.13; H, 6.25%.

(±)-*cis*-4-(4-Hydroxyphenyl)-7-methoxy-3-(4-methylphenyl)chromane (6e). The title compound was prepared as described for **6b** from 4-(4-hydroxyphenyl)-7-methoxy-3-(4-methylphenyl)-2*H*-chromene (**5e**, 1.72 g, 4.99 mmol) and palladium (10 wt% on activated carbon, 0.30 g, 0.28 mmol, 6 mol%) in absolute ethanol (200 mL); crude product recrystallized in two crops from aqueous ethanol to give **6e** as colorless needles, which contained 0.25 mol equiv of ethanol of crystallization: 1.68 g (93% combined yield), mp 165.5–166.5 °C. ^1H NMR ($CDCl_3$ + drop DMSO-d_6, 300 MHz) δ: 2.29 (s, 3H), 3.53 (ddd, 1H), 3.80 (s, 3H), 4.15–4.25 (m, 2H), 4.39 (dd, 1H), 4.74 (bs, 1H), 6.42–6.60 (m, 8H), 6.84 (d, 1H), 6.96 (dm, 2H). MS (EI): 346 (M^+), 227, 211.

(±)-*cis*-3-(4-Biphenyl)-4-(4-hydroxyphenyl)-7-methoxychromane (6f). The title compound was prepared as described for **6b** from 3-(4-biphenyl)-4-(4-hydroxyphenyl)-7-methoxy-2*H*-chromene (**5f**, 2.03 g, 4.99 mmol) and palladium (10 wt% on activated carbon, 0.30 g, 0.28 mmol, 6 mol%) in absolute ethanol (300 mL); crude product recrystallized from aqueous ethanol to give **6f** as colorless needles: 1.67 g (81% yield), mp 225–226.5 °C. ^1H NMR (DMSO-d_6, 300 MHz) δ: 3.58 (ddd, 1H), 3.74 (s, 3H), 4.21–4.30 (m, 2H), 4.39 (dd, 1H), 6.37–6.52 (m, 6H), 6.82 (d, 1H), 6.81–6.90 (m, 2H), 7.30–7.38 (m, 1H), 7.39–7.52 (m, 4H), 7.59–7.66 (m, 2H), 9.15 (s, 1H). MS (EI): 408 (M^+), 227, 211, 180. Elemental analysis; calcd for $C_{28}H_{24}O_3$; C, 82.33; H, 5.92%; found C, 82.57; H, 6.03%.

(±)-*cis*-4-(4-Hydroxyphenyl)-7-methoxy-3-(3-(trifluoromethyl)phenyl)chromane (6g). The title compound was prepared as described for **6b** from 4-(4-hydroxyphenyl)-7-methoxy-3-(3-(trifluoromethyl)phenyl)-2*H*-chromene (**5g**, 2.0 g, 5.02 mmol) and palladium (10 wt% on activated carbon, 0.30 g, 0.28 mmol, 6 mol%) in absolute ethanol (100 mL); crude product recrystallized in two crops from aqueous ethanol to give **6g** as colorless needles, which contained approximately 0.5 mol equiv of ethanol of crystallization: 1.76 g (82% combined yield), mp 97.5–99 °C. ^1H NMR ($CDCl_3$, 300 MHz) δ: 3.63 (ddd, 1H), 3.81 (s, 3H), 4.18–4.27 (m, 2H), 4.43 (dd, 1H), 4.95 (bs, 1H), 6.41–6.59 (m, 6H), 6.81–6.90 (m, 3H), 7.27 (dd, 1H), 7.44 (d, 1H). MS (EI): 400 (M^+), 227, 211.

(±)-*cis*-3-(3-Fluorophenyl)-4-(4-hydroxyphenyl)-7-methoxychromane (6h). The title compound was prepared as described for **6b** from 3-(3-fluorophenyl)-4-(4-hydroxyphenyl)-7-methoxy-2*H*-chromene (**5h**, 1.22 g, 3.50 mmol) and palladium (10 wt% on activated carbon, 0.20 g, 0.19 mmol, 5 mol%) in absolute ethanol (100 mL); crude product recrystallized in two crops from aqueous ethanol to give **6h** as colorless needles: 1.00 g (81% combined yield), mp 183–183.5 °C. ^1H NMR ($CDCl_3$, 300 MHz) δ: 3.57 (ddd, 1H), 3.81 (s, 3H), 4.20–4.27 (m, 2H), 4.38 (dd, 1H), 4.55 (s, 1H), 6.38 (dd, 1H), 6.44–6.60 (m, 7H), 6.82–6.92 (m, 2H), 7.08–7.18 (m, 1H). MS (EI): 350 (M^+), 227, 211. Elemental analysis; calcd for $C_{22}H_{19}FO_3$; C, 75.41; H, 5.47%; found C, 75.46; H, 5.53%.

(±)-*cis*-4-(4-Hydroxyphenyl)-7-methoxy-3-(3-methoxyphenyl)chromane (6i). The title compound was prepared as described for **6b** from 4-(4-hydroxyphenyl)-7-methoxy-3-(3-methoxyphenyl)-2*H*-chromene (**5i**, 2.52 g, 6.99 mmol) and palladium (10 wt% on activated carbon, 0.10 g, 0.09 mmol, 1 mol%) in absolute ethanol (300 mL); crude product recrystallized in two crops from aqueous ethanol to give **6i** as colorless needles: 2.34 g (93% combined yield), mp 195.5–196.5 °C. ^1H NMR ($CDCl_3$, 300 MHz) δ: 3.55 (ddd, 1H), 3.65 (s, 3H), 3.80 (s, 3H), 4.19–4.27 (m, 2H), 4.39 (dd, 1H), 4.58 (bs, 1H), 6.18 (m, 1H), 6.31 (dm, 1H), 6.43–6.58 (m, 6H), 6.72 (dm, 1H), 6.84 (d, 1H), 7.08 (dd, 1H). MS (EI): 362 (M^+), 227, 211. Elemental analysis; calcd for $C_{23}H_{22}O_4$; C, 76.2; H, 6.1%; found C, 75.9; H, 6.1%.

(±)-*cis*-4-(4-Hydroxyphenyl)-7-methoxy-3-(3-methylphenyl)chromane (6j). The title compound was prepared as described for **6b** from 4-(4-hydroxyphenyl)-7-methoxy-3-(3-methylphenyl)-2*H*-chromene (**5j**, 1.03 g, 2.99 mmol) and palladium (10 wt% on activated carbon, 0.16 g, 0.15 mmol, 5 mol%) in absolute ethanol (150 mL); crude product recrystallized in two crops from aqueous ethanol to give **6j** as colorless needles: 0.93 g (90% combined yield), mp 158–159 °C. ^1H NMR ($CDCl_3$, 300 MHz) δ: 2.23 (s, 3H), 3.53 (ddd, 1H), 3.80 (s, 3H), 4.16–4.25 (m, 2H), 4.39 (dd, 1H), 4.63 (bs, 1H), 6.40–6.58 (m, 8H), 6.85 (d, 1H), 6.95–7.08 (m, 2H). MS (EI): 346 (M^+), 227, 211. Elemental analysis; calcd for $C_{23}H_{22}O_4$; C, 79.74; H, 6.40%; found C, 79.77; H, 6.54%.

(±)-*cis*-7-Methoxy-3-phenyl-4-(4-(2-pyrrolidinoethoxy)-phenyl)chromane ((±)-7a). A solution of (±)-*cis*-4-(4-hydroxyphenyl)-7-methoxy-3-phenylchromane (**6a**, 74.3 g, 0.173 mol) and sodium hydroxide (24.3 g, 0.608 mol) in toluene (700 mL) and water (12 mL) was heated to 75 °C and 1-(2-chloroethyl)pyrrolidine hydrochloride (46.2 g, 0.272 mol) added in six portions at

30 min intervals. The resulting mixture was stirred at 75 °C for 4 h, diluted with water (1 L), and the aqueous phase separated and extracted with toluene (300 mL). The combined organic layers were dried (Na_2SO_4) and evaporated to give a solid, which was recrystallized from hot methanol (1 L), to give the product **7a** as colorless needles, which were collected and vacuum dried; 79.6 g (83% yield), mp 113–114 °C. ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 1.6–1.7 (m, 4H), 2.40–2.50 (m, 4H), 2.70 (t, 2H), 3.55 (ddd, 1H), 3.73 (s, 3H), 3.92 (t, 2H), 4.20–4.30 (m, 2H), 4.37 (dd, 1H), 6.41–6.50 (m, 4H), 6.60 (d, 2H), 6.74–6.80 (m, 3H), 7.11–7.19 (m, 3H). HR-MS; calcd for $C_{28}H_{32}NO_3$ ($M+H^+$) 430.2382, found 430.2372.

(±)-*cis*-3-(4-Fluorophenyl)-7-methoxy-4-(4-(2-pyrrolidinoethoxy)phenyl)chromane (7b). Potassium carbonate (13.90 g, 100.6 mmol), 1-(2-chloroethyl)pyrrolidine hydrochloride (1.87 g, 10.99 mmol) and sodium iodide (0.07 g, 0.5 mmol) were added to a stirred solution of (±)-*cis*-3-(4-fluorophenyl)-4-(4-hydroxyphenyl)-7-methoxychromane, (**6b**, 3.50 g, 9.99 mmol) in dry acetone (200 mL) and the mixture stirred at 60 °C, under reflux, for 24 h. The mixture was cooled to room temperature, the inorganic solids removed by filtration, and the filter cake washed with extra acetone. The filtrate was evaporated to give an off-white solid, which was recrystallized from ethanol to give the product, **7b** as colorless needles; 3.63 g (81% yield), mp 93–95 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.75–1.85 (m, 4H), 2.55–2.65 (m, 4H), 2.85 (t, 2H), 3.55 (ddd, 1H), 3.81 (s, 3H), 4.08 (t, 2H), 4.16–4.23 (m, 2H), 4.37 (dd, 1H), 6.43–6.53 (m, 4H), 6.57–6.66 (m, 4H), 6.80–6.88 (m. 3H). MS (EI): 447 (M^+), 84. HR-MS; calcd for $C_{28}H_{31}FNO_3$ ($M+H^+$) 448.2288, found 448.2279.

(±)-*cis*-7-Methoxy-4-(4-(2-pyrrolidinoethoxy)phenyl)-3-(4-(trifluoromethyl)phenyl)chromane (7c). The title compound was prepared as described for **7b** from (±)-*cis*-4-(4-hydroxyphenyl)-7-methoxy-3-(4-(trifluoromethyl)phenyl)chromane, (**6c**, 0.80 g, 2.0 mmol), potassium carbonate (2.76 g, 20 mmol), 1-(2-chloroethyl)pyrrolidine hydrochloride (0.38 g, 2.23 mmol) and sodium iodide (0.01 g, 0.07 mmol) in dry acetone (100 mL). The crude product was recrystallized from ethanol to give **7c** as colorless needles, which contained 0.25 mol equiv of ethanol of crystallization; 0.93 g (88% yield), mp 119–121 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.75–1.85 (m, 4H), 2.55–2.65 (m, 4H), 2.85 (t, 2H), 3.62 (ddd, 1H), 3.81 (s, 3H), 4.01 (t, 2H), 4.19–4.28 (m, 2H), 4.44 (dd, 1H), 6.44–6.54 (m, 4H), 6.64 (dm, 2H), 6.78 (dm, 2H), 6.84 (d, 1H), 7.40 (dm, 2H). MS (EI): 497 (M^+), 84. HR-MS; calcd for $C_{29}H_{31}F_3NO_3$ ($M+H^+$) 498.2256, found 498.2243. Elemental analysis; calcd for $C_{29}H_{30}F_3NO_3 \cdot 0.25C_2H_5OH$; C, 69.60; H, 6.24; N, 2.75%; found C, 69.94; H, 6.23; N, 2.67%.

(±)-*cis*-7-Methoxy-3-(4-methoxyphenyl)-4-(4-(2-pyrrolidinoethoxy)phenyl)chromane (7d). The title compound was prepared as described for **7b** from (±)-*cis*-4-(4-hydroxyphenyl)-7-methoxy-3-(4-methoxyphenyl)chromane, (**6d**, 0.54 g, 1.49 mmol), potassium carbonate (2.10 g, 15.2 mmol), 1-(2-chloroethyl)pyrrolidine hydrochloride (0.28 g, 1.67 mmol) and sodium iodide (0.01 g, 0.07 mmol) in dry acetone (35 mL). The crude product was recrystallized from aqueous ethanol to give **7d** as colorless needles; 0.47 g (69% yield), mp 133–134 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.75–1.85 (m, 4H), 2.55–2.65 (m, 4H), 2.85 (t, 2H), 3.52 (ddd, 1H), 3.76 (s, 3H), 3.81 (s, 3H), 4.02 (t, 2H), 4.15–4.23 (m, 2H), 4.37 (dd, 1H), 6.45 (dd, 1H), 6.48–6.54 (m, 3H), 6.54–6.60 (m, 2H), 6.60–6.66 (m, 2H), 6.66–6.73 (m, 2H), 6.84 (d, 1H). MS (EI): 459 (M^+), 84. HR-MS; calcd for $C_{29}H_{34}NO_4$ ($M+H^+$) 460.2488, found 460.2491. Elemental analysis; calcd for $C_{29}H_{33}NO_4$; C, 75.79; H, 7.24; N, 3.05%; found C, 75.90; H, 7.47; N, 3.12%.

(±)-*cis*-7-Methoxy-3-(4-methylphenyl)-4-(4-(2-pyrrolidinoethoxy)phenyl)chromane (7e). The title compound was prepared as described for **7b** from (±)-*cis*-4-(4-hydroxyphenyl)-7-methoxy-3-(4-methylphenyl)chromane, (**6e**, 0.69 g, 2.0 mmol), potassium carbonate (2.76 g, 20 mmol), 1-(2-chloroethyl)pyrrolidine hydrochloride (0.38 g, 2.23 mmol) and sodium iodide (0.01 g, 0.07 mmol) in dry acetone (100 mL). The crude product was recrystallized from ethanol to give **7e** as colorless needles, which contained 0.25 mol equiv of ethanol of crystallization; 0.78 g (87% yield), mp 115–116.5 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.70–1.90 (m, 4H), 2.29 (s, 3H), 2.50–2.67 (m, 4H), 2.80–2.90 (m, 2H), 3.53 (ddd, 1H), 3.80 (s, 3H), 3.94–4.05 (m, 2H), 4.15–4.25 (m, 2H), 4.40 (dd, 1H), 6.40–6.66 (m, 8H), 6.84 (d, 1H), 6.94 (dm, 2H). MS (EI): 443 (M^+), 84. HR-MS; calcd for $C_{29}H_{34}NO_3$ ($M+H^+$) 444.2538, found 444.2541. Elemental analysis; calcd for $C_{29}H_{33}NO_3 \cdot 0.25C_2H_5OH$; C, 77.86; H, 7.64; N, 3.08%; found C, 78.00; H, 7.72; N, 3.08%.

(±)-*cis*-7-Methoxy-3-(4-biphenyl)-4-(4-(2-pyrrolidinoethoxy)phenyl)chromane (7f). The title compound was prepared as described for **7b** from (±)-*cis*-3-(4-biphenyl)-4-(4-hydroxyphenyl)-7-methoxychromane, (**6f**, 0.61 g, 1.50 mmol), potassium carbonate (2.10 g, 15 mmol), 1-(2-chloroethyl)pyrrolidine hydrochloride (0.31 g, 1.82 mmol) and sodium iodide (0.01 g, 0.07 mmol) in dry acetone (100 mL). The crude product was recrystallized from aqueous acetone to give **7f** as colorless needles; 0.28 g (36% yield), mp 190.5–192 °C. ^{1}H NMR ($CDCl_3$ + drop DMSO-d_6, 300 MHz) δ: 1.60–1.70 (m, 4H), 2.42–2.50 (m, 4H), 2.70 (t, 2H), 3.60 (ddd, 1H), 3.75 (s, 3H), 3.93 (t, 2H), 4.27 (dd, 1H), 4.32 (d, 1H), 4.40 (dd, 1H), 6.45 (dd, 1H), 6.50 (d, 1H), 6.47–6.56 (m, 2H), 6.60–6.67 (m, 2H), 6.81 (d, 1H), 6.81–6.88 (m, 2H), 7.29–7.37 (m, 1H), 7.38–7.50 (m, 4H), 7.58–7.65 (m, 2H). MS (EI): 505 (M^+), 84. HR-MS; calcd for $C_{34}H_{36}NO_3$ ($M+H^+$) 506.2695, found 506.2689. Elemental analysis; calcd for $C_{34}H_{35}NO_3$; C, 80.76; H, 6.98; N, 2.77%; found C, 81.13; H, 7.05; N, 2.58%.

(±)-*cis*-7-Methoxy-4-(4-(2-pyrrolidinoethoxy)phenyl)-3-(3-(trifluoromethyl)phenyl)chromane (7g). The title compound was prepared as described for **7b** from (±)-*cis*-4-(4-hydroxyphenyl)-7-methoxy-3-(3-(trifluoromethyl)phenyl)chromane, (**6g**, 0.40 g, 1.0 mmol), potassium carbonate (1.38 g, 10 mmol), 1-(2-chloroethyl)pyrrolidine hydrochloride (0.19 g, 1.12 mmol) and sodium iodide

(0.01 g, 0.07 mmol) in dry acetone (50 mL). The crude product was recrystallized from aqueous ethanol to give **7g** as colorless needles; 0.33 g (65% yield), mp 98.5–99.5 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.70–1.90 (m, 4H), 2.55–2.65 (m, 4H), 2.85 (t, 2H), 3.63 (ddd, 1H), 3.81 (s, 3H), 3.94–4.06 (m, 2H), 4.17–4.27 (m, 2H), 4.44 (dd, 1H), 6.42–6.57 (m, 4H), 6.64 (dm, 2H), 6.80–6.90 (m, 3H), 7.26 (dd, 1H), 7.43 (d, 1H). MS (EI): 497 (M^+), 84. HR-MS; calcd for $C_{29}H_{31}F_3NO_3$ ($M+H^+$) 498.2256, found 498.2243. Elemental analysis; calcd for $C_{29}H_{30}F_3NO_3$; C, 70.01; H, 6.08; N, 2.82%; found C, 69.90; H, 6.12; N, 2.77%.

(±)-*cis*-3-(3-Fluorophenyl)-7-methoxy-4-(4-(2-pyrrolidinoethoxy)phenyl)chromane (7h). The title compound was prepared as described for **7b** from (±)-*cis*-3-(3-fluorophenyl)-4-(4-hydroxyphenyl)-7-methoxychromane, (**6h**, 0.35 g, 1.0 mmol), potassium carbonate (1.38 g, 10 mmol), 1-(2-chloroethyl)pyrrolidine hydrochloride (0.19 g, 1.12 mmol) and sodium iodide (0.01 g, 0.07 mmol) in dry acetone (50 mL). The crude product was purified by column chromatography on silica gel (5% methanol in CH_2Cl_2 eluent) to give **7h** as a colorless glass; 0.35 g (79% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.70–1.90 (m, 4H), 2.55–2.65 (m, 4H), 2.85 (t, 2H), 3.56 (ddd, 1H), 3.80 (s, 3H), 4.02 (t, 2H), 4.19–4.27 (m, 2H), 4.38 (dd, 1H), 6.38 (dm, 1H), 6.42–6.55 (m, 5H), 6.59–6.68 (m, 2H), 6.81–6.90 (m, 2H), 7.06–7.16 (m, 1H). MS (EI): 447 (M^+), 84. HR-MS; calcd for $C_{28}H_{31}FNO_3$ ($M+H^+$) 448.2288, found 448.2262.

(±)-*cis*-7-Methoxy-3-(3-methoxyphenyl)-4-(4-(2-pyrrolidinoethoxy)phenyl)chromane (7i). The title compound was prepared as described for **7b** from (±)-*cis*-4-(4-hydroxyphenyl)-7-methoxy-3-(3-methoxyphenyl)chromane (**6i**, 0.73 g, 2.01 mmol), potassium carbonate (2.76 g, 20 mmol), 1-(2-chloroethyl)pyrrolidine hydrochloride (0.38 g, 2.23 mmol) and sodium iodide (0.01 g, 0.07 mmol) in dry acetone (100 mL). The crude product was recrystallized from ethanol to give **7i** as colorless needles; 0.67 g (yield 72%), mp 110.5–111.5 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.70–1.88 (m, 4H), 2.53–2.67 (m, 4H), 2.85 (t, 2H), 3.55 (ddd, 1H), 3.64 (s, 3H), 3.80 (s, 3H), 4.00 (t, 2H), 4.18–4.27 (m, 2H), 4.39 (dd, 1H), 6.19 (m, 1H), 6.29 (dm, 1H), 6.45 (dd, 1H), 6.48–6.58 (m, 3H), 6.58–6.67 (m, 2H), 6.71 (dm, 1H), 6.85 (d, 1H), 7.07 (dd, 1H). MS (EI): 459 (M^+), 84. HR-MS; calcd for $C_{29}H_{34}NO_4$ ($M+H^+$) 460.2488, found 460.2464. Elemental analysis; calcd for $C_{29}H_{33}NO_4$; C, 75.79; H, 7.24; N, 3.05%; found C, 75.48; H, 7.24; N, 2.93%.

(±)-*cis*-7-Methoxy-3-(3-methylphenyl)-4-(4-(2-pyrrolidinoethoxy)phenyl)chromane hydrochloride (7j). The title compound was prepared as described for **7b** from (±)-*cis*-4-(4-hydroxyphenyl)-7-methoxy-3-(3-methylphenyl)-chromane, (**6j**, 0.69 g, 2.0 mmol), potassium carbonate (2.76 g, 20 mmol), 1-(2-chloroethyl)pyrrolidine hydrochloride (0.38 g, 2.23 mmol) and sodium iodide (0.01 g, 0.07 mmol) in dry acetone (100 mL). The crude product was purified by column chromatography on silica gel (5% methanol in CH_2Cl_2 eluent) to give a yellow gum, which was dissolved in ether and an excess of an ether solution of hydrochloric acid added. The solvents were evaporated, giving a sticky yellow gum which was treated with ethanol (1 mL) and ether (30 mL) and stirred, resulting in the precipitation of the hydrochloride salt of **7j** an off-white solid; 0.51 g (53% yield), mp 167–170 °C. ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 1.80–2.05 (bm, 4H), 2.18 (s, 3H), 2.95–3.15 (bm, 2H), 3.45–3.60 (bm, 5H), 3.74 (s, 3H), 4.15–4.40 (m, 5H), 6.40–6.55 (m, 5H), 6.62 (m, 1H), 6.68–6.84 (m, 3H), 6.95–7.08 (m, 2H), 10.74 (bs, 1H). MS (EI): 443 (M^+ of free base), 84. HR-MS; calcd for $C_{29}H_{34}NO_3$ ($M+H^+$) 444.2538, found 444.2532.

(±)-*cis*-7-Methoxy-3-phenyl-4-(4-(2-piperidinoethoxy)-phenyl)chromane (7k). The title compound was prepared as described for **7b** from (±)-*cis*-4-(4-hydroxyphenyl)-7-methoxy-3-phenyl-chromane, (**6a**, 0.332 g, 1.0 mmol), potassium carbonate (1.40 g, 10.1 mmol), 1-(2-chloroethyl)piperidine hydrochloride (0.19 g, 1.03 mmol) and sodium iodide (0.01 g, 0.07 mmol) in dry acetone (25 mL). The crude product was purified by recrystallization from aqueous acetone to give the colorless solid, **7k**; 0.388 g (87% yield), mp 113–117 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.38–1.48 (m, 2H), 1.52–1.63 (m, 4H), 2.42–2.52 (m, 4H), 2.71 (t, 2H), 3.58 (ddd, 1H), 3.80 (s, 3H), 4.00 (t, 2H), 4.22 (d, 1H), 4.24 (dd, 1H), 4.43 (dd, 1H), 6.43–6.54 (m, 4H), 6.60 (m, 2H), 6.64–6.71 (m, 2H), 6.84 (d, 1H), 7.10–7.19 (m, 3H). MS (EI): 443 (M^+), 84. HR-MS; calcd for $C_{29}H_{34}NO_3$ ($M+H^+$) 444.2538, found 444.2534. Elemental analysis; calcd for $C_{29}H_{33}NO_3$; C, 78.52; H, 7.50; N, 3.16%; found C, 78.26; H, 7.85; N, 2.92%.

(±)-*cis*-7-Methoxy-3-phenyl-4-(4-(3-piperidinopropoxy)-phenyl)chromane (7l). The title compound was prepared as described for **7b** from (±)-*cis*-4-(4-hydroxyphenyl)-7-methoxy-3-phenyl-chromane, (**6a**, 0.332 g, 1.0 mmol), potassium carbonate (1.40 g, 10.1 mmol), 1-(3-chloropropyl)piperidine hydrochloride (0.20 g, 1.01 mmol) and sodium iodide (0.01 g, 0.07 mmol) in dry acetone (25 mL). The crude product was purified by recrystallization from aqueous acetone to give the colorless solid, **7k**; 0.367 g (80% yield), mp 116.5–118 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.38–1.48 (m, 2H), 1.52–1.63 (m, 4H), 1.91 (pentet, 2H), 2.31–2.46 (m, 6H), 3.58 (ddd, 1H), 3.80 (s, 3H), 3.90 (t, 2H), 4.22 (d, 1H), 4.25 (dd, 1H), 4.43 (dd, 1H), 6.43–6.54 (m, 4H), 6.59 (m, 2H), 6.64–6.71 (m, 2H), 6.84 (d, 1H), 7.10–7.19 (m, 3H). MS (EI): 457 (M^+), 124, 98. HR-MS; calcd for $C_{30}H_{36}NO_3$ ($M+H^+$) 458.2695, found 458.2679.

(±)-*cis*-7-Methoxy-4-(4-(2-piperidinoethoxy)phenyl)-3-(4-(trifluoromethyl)phenyl)chromane (7m). The title compound was prepared as described for **7b** from (±)-*cis*-4-(4-hydroxyphenyl)-7-methoxy-3-(4-(trifluoromethyl)phenyl)chromane, (**6c**, 0.80 g, 2.0 mmol), potassium carbonate (2.76 g, 20.0 mmol), 1-(2-chloroethyl)piperidine hydrochloride (0.41 g, 2.23 mmol) and sodium iodide (0.01 g, 0.07 mmol) in dry acetone (100 mL). The crude product was purified by recrystallization from ethanol to give the colorless solid, **7m**; 0.97 g (95% yield), mp 119–120.5 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.35–1.50 (m, 2H), 1.50–1.65 (m, 4H), 2.40–2.55 (m, 4H), 2.71 (t, 2H), 3.62 (ddd, 1H), 3.81 (s, 3H), 4.10 (t,

2H), 4.18–4.28 (m, 2H), 4.44 (dd, 1H), 6.43–6.56 (m, 4H), 6.62 (dm, 2H), 6.79 (dm, 2H), 6.84 (d, 1H), 7.40 (dm, 2H). MS (EI): 511 (M^+), 98. HR-MS; calcd for $C_{30}H_{33}F_3NO_3$ ($M+H^+$) 512.2412, found 512.2406. Elemental analysis; calcd for $C_{30}H_{32}F_3NO_3$; C, 70.43; H, 6.30; N, 2.74%; found C, 70.32; H, 6.51; N, 2.64%.

(±)-*cis*-7-Methoxy-3-(4-methylphenyl)-4-(4-(2-piperidinoethoxy)phenyl)chromane (7n). The title compound was prepared as described for **7b** from (±)-*cis*-4-(4-hydroxyphenyl)-7-methoxy-3-(4-methylphenyl)chromane (**6e**, 0.69 g, 2.0 mmol), potassium carbonate (2.76 g, 20.0 mmol), 1-(2-chloroethyl)piperidine hydrochloride (0.41 g, 2.23 mmol) and sodium iodide (0.01 g, 0.07 mmol) in dry acetone (100 mL). The crude product was purified by recrystallization from ethanol to give the colorless solid, **7n**; 0.82 g (85% yield), mp 109–110.5 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.38–1.50 (m, 2H), 1.50–1.78 (m, 4H), 2.29 (s, 3H), 2.40–2.55 (m, 4H), 2.72 (t, 2H), 3.53 (ddd, 1H), 3.80 (s, 3H), 4.01 (t, 2H), 4.16–4.24 (m, 2H), 4.39 (dd, 1H), 6.40–6.65 (m, 8H), 6.84 (d, 1H), 6.95 (dm, 2H). MS (EI): 457 (M^+), 98. HR-MS; calcd for $C_{30}H_{36}NO_3$ ($M+H^+$) 458.2695, found 458.2685. Elemental analysis; calcd for $C_{30}H_{35}NO_3$; C, 78.74; H, 7.71; N, 3.06%; found C, 78.37; H, 7.92; N, 2.93%.

(±)-*cis*-3-(4-Fluorophenyl)-7-methoxy-4-(4-(3-piperidinopropoxy)phenyl)chromane (7o). The title compound was prepared as described for **7b** from (±)-*cis*-3-(4-fluorophenyl)-4-(4-hydroxyphenyl)-7-methoxychromane, (**6b**, 0.708 g, 2.0 mmol), potassium carbonate (2.76 g, 20.0 mmol), 1-(3-chloropropyl)piperidine hydrochloride (0.44 g, 2.22 mmol) and sodium iodide (0.01 g, 0.07 mmol) in dry acetone (100 mL). The crude product was purified by recrystallization from aqueous acetone to give the product, **7k** as colorless needles; 0.777 g (81% yield), mp 92–94.5 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.38–1.50 (m, 2H), 1.50–1.65 (m, 4H), 1.92 (pentet, 2H), 2.30–2.50 (m, 6H), 3.55 (ddd, 1H), 3.81 (s, 3H), 3.91 (t, 2H), 4.15–4.24 (m, 2H), 4.28 (dd, 1H), 6.42–6.54 (m, 4H), 6.57–6.66 (m, 4H), 6.80–6.89 (m, 3H). MS (EI): 475 (M^+), 124, 98. HR-MS; calcd for $C_{30}H_{35}FNO_3$ ($M+H^+$) 476.2601, found 484.2604.

(±)-*cis*-7-Methoxy-3-(3-methoxyphenyl)-4-(4-(3-piperidinopropoxy)phenyl)chromane (7p). The title compound was prepared as described for **7b** from (±)-*cis*-4-(4-hydroxyphenyl)-7-methoxy-3-(3-methoxyphenyl)chromane (**6i**, 3.62 g, 9.99 mmol), potassium carbonate (13.8 g, 99.9 mmol), 1-(3-chloropropyl)piperidine hydrochloride (2.22 g, 11.2 mmol) and sodium iodide (0.01 g, 0.07 mmol) in dry acetone (100 mL). The crude product was purified by recrystallization from aqueous ethanol to give the product, **7p** as colorless platelets; 4.61 g (94% yield), mp 112–113 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.37–1.49 (m, 2H), 1.50–1.63 (m, 4H), 1.92 (pentet, 2H), 2.30–2.48 (m, 6H), 3.54 (ddd, 1H), 3.63 (s, 3H), 3.80 (s, 3H), 3.90 (t, 2H), 4.18–4.26 (m, 2H), 4.39 (dd, 1H), 6.19 (m, 1H), 6.30 (dm, 1H), 6.45 (dd, 1H), 6.48–6.56 (m, 3H), 6.61 (dm, 2H), 6.72 (dm, 1H), 6.84 (d, 1H), 7.07 (dd, 1H). MS (EI): 487 (M^+), 98. HR-MS; calcd for $C_{31}H_{38}NO_4$ ($M+H^+$) 488.2801, found 488.2795.

(−)-(3*S*,4*R*)-7-Methoxy-3-phenyl-4-(4-(2-pyrrolidinoethoxy)phenyl)chromane [(−)-7a]. A mixture of (±)-*cis*-7-methoxy-3-phenyl-4-(4-(2-pyrrolidinoethoxy)phenyl)-chromane, [(±)-**7a**, 85.92 g, 0.20 mol] and (−)-di-*p*-toluoyl-L-tartaric acid (85.92 g, 0.22 mol) in 1-butanol (1.9 L) was heated to 60 °C and filtered to remove insoluble material. The resulting solution was stirred for 2 h, cooling slowly to room temperature, and the precipitated solid collected by filtration. The solid was re-dissolved in fresh 1-butanol (1.6 L) heated to 75 °C, and the solution again slowly cooled to room temperature over 2 h. The resulting precipitated solid, (−)-**7a** (−)-di-*p*-toluoyl-L-tartrate salt, was collected by filtration, washed with ice-cold ethanol, and vacuum dried. The solid was partitioned between water (400 mL) and a mixture of toluene (400 mL) and ethyl acetate (300 mL). The aqueous layer was basified to pH 11 with 10 M sodium hydroxide, separated and extracted with ethyl acetate (300 mL). The combined organic phases were dried ($MgSO_4$), and evaporated to give an off-white solid, which was recrystallized from aqueous ethanol to give the product, (−)-**7a** as a colorless powder, which contained both water (0.2 mol equiv) and ethanol (0.4 mol equiv) of crystallization; 18.32 g (40% yield), mp 56–60 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.24 (t, 1.2H, ethanol), 1.58 (bs, water + ethanol), 1.73–1.85 (m, 4H), 2.54–2.65 (m, 4H), 2.84 (t, 2H), 3.58 (ddd, 1H), 3.72 (q, 0.8H, ethanol), 3.81 (s, 3H), 4.01 (t, 2H), 4.19–4.28 (m, 2H), 4.43 (dd, 1H), 6.42–6.55 (m, 4H), 6.58–6.72 (m, 4H), 6.85 (d, 1H), 7.10–7.20 (m, 3H). MS (EI): 429 (M^+), 84. Chiral HPLC: ChiraDex 5 μ, 250×4 mm (Merck) column; eluent, 7:3 methanol/0.25% triethylammonium acetate buffer, pH = 5.2; flow, 0.5 mL/min; UV 220 nm; R_t = 17.3 min, 95%ee. Elemental analysis: calcd for $C_{28}H_{31}NO_3 \cdot 0.4C_2H_5OH \cdot 0.2H_2O$; C, 76.60; H, 7.54; N, 3.10; water, 0.80%; found C, 76.50; H, 7.25; N, 3.07; water, 0.73%. $[\alpha]_D^{20} = -329.5°$ (c = 1%, 95:5 methanol/DMSO).

(−)-*cis*-7-Methoxy-4-(4-(2-pyrrolidinoethoxy)phenyl)-3-(4-(trifluoromethyl)phenyl)chromane [(−)-7c]. A mixture of (±)-*cis*-7-methoxy-4-(4-(2-pyrrolidinoethoxy)phenyl)-3-(4-(trifluoromethyl)phenyl)chromane [(±)-**7c**, 14.9 g, 0.03 mol] and (−)-di-*p*-toluoyl-L-tartaric acid (20.86 g, 0.054 mol) in 1-butanol (300 mL) was heated to 50 °C and filtered to remove insoluble material. The resulting solution was cooled slowly to room temperature, and the precipitated solid collected by filtration. The solid was re-dissolved at 75 °C in 1-butanol (200 mL), the solution again cooled to room temperature, and the resulting precipitated solid, (−)-**7c** (−)-di-*p*-toluoyl-L-tartrate salt, was collected by filtration, washed with ice-cold ethanol, and dried. The solid was partitioned between water (100 mL) and ethyl acetate (150 mL), and the aqueous layer basified to pH 12 with 10 M sodium hydroxide. The aqueous layer was separated, extracted twice with ethyl acetate (100 mL), and the combined organic phases dried ($MgSO_4$) and evaporated to give a gum, which was dissolved in hot 4:1 ethanol/water (80 mL) and cooled slowly to give the product, (−)-**7c** as colorless needles, which were collected by filtration and vacuum dried. The mother liquors from the crystallization were evaporated to give

a small amount of a colorless gum, which was repeat crystallized from aqueous ethanol, giving a second crop of colorless needles, which was mixed with the first crop to give the combined product (−)-**7c**; 3.11 g (21% combined yield), mp 146–147 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.75–1.85 (m, 4H), 2.55–2.65 (m, 4H), 2.85 (t, 2H), 3.62 (ddd, 1H), 3.81 (s, 3H), 4.01 (t, 2H), 4.19–4.28 (m, 2H), 4.44 (dd, 1H), 6.44–6.55 (m, 4H), 6.64 (dm, 2H), 6.78 (dm, 2H), 6.84 (d, 1H), 7.40 (dm, 2H). MS (EI): 497 (M^+), 84. Chiral HPLC: ChiraDex 5μ, 250×4 mm (Merck) column; eluent, 7:3 methanol/0.25% triethylammonium acetate buffer, pH = 5.2; flow, 0.5 mL/min; UV 220 nm; R_t 33.0 min, 90%ee. HR-MS; calcd for $C_{29}H_{31}F_3NO_3$ ($M+H^+$) 498.2256, found 498.2251. Elemental analysis: calcd for $C_{29}H_{30}F_3NO_3$; C, 70.01; H, 6.08; N, 2.82; found C, 69.88; H, 6.08; N, 2.77%. $[\alpha]_D^{20} = -273.8°$ (c = 0.6%, methanol).

(±)-*cis*-7-Hydroxy-3-phenyl-4-(4-(2-pyrrolidinoethoxy)-phenyl)chromane hydrochloride (8a). Pyridine (9.5 mL) was added carefully to concentrated hydrochloric acid (10 mL), the solution heated to reflux, and water (5 mL) removed by distillation until the mixture reached 140 °C. (±)-*cis*-7-Methoxy-3-phenyl-4-(4-(2-pyrrolidinoethoxy)phenyl)chromane (**7a**, 2.0 g, 4.66 mmol) was added, and the temperature of the resulting melt raised to 150 °C. The mixture was stirred at 150 °C for 6 h, then water (30 mL) was added and the resulting solution cooled to 30 °C. Toluene (30 mL) was added, and the mixture basified to pH 12 with 32.5 wt% sodium hydroxide solution. The organic phase was separated, washed with water (20 mL), dried (K_2CO_3) and evaporated. The residue was dissolved in ethanol (5 mL) and water (20 mL), and the solution acidified to pH 3 with concentrated hydrochloric acid. The resulting precipitated solid was collected, and recrystallized from hot ethanol (10 mL) to give a colorless solid which was collected, washed with cold ethanol and vacuum dried to give **8a** as its hydrochloride salt; 1.0 g (47% yield), mp 243–245 °C. ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 1.77–2.05 (m, 4H), 2.98–3.13 (m, 2H), 3.45–3.60 (m, 5H), 4.13–4.30 (m, 4H), 4.32 (dd, 1H), 6.30 (dd, 1H), 6.34 (d, 1H), 6.49 (d, 2H), 6.62–6.72 (m, 3H), 6.73–6.81 (m, 2H), 7.10–7.18 (m, 2H), 9.37 (s, 1H), 10.75 (bs, 1H). MS (EI): 415 (free base M^+), 84. Elemental analysis; calcd for $C_{27}H_{30}ClNO_3$; C, 71.75; H, 6.69; N, 3.10; Cl, 7.84%; found C, 71.92; H, 6.97; N, 2.91; Cl, 7.58%.

(±)-*cis*-3-(4-Fluorophenyl)-7-hydroxy-4-(4-(2-pyrrolidinoethoxy)phenyl)chromane (8b). A mixture of (±)-*cis*-3-(4-fluorophenyl)-7-methoxy-4-(4-(2-pyrrolidinoethoxy)-phenyl)chromane (**7b**, 0.90 g, 2.01 mmol) and anhydrous pyridine hydrochloride (11.60 g, 100 mmol) was heated to 150–155 °C as a melt/fusion for 18 h. The mixture was cooled to room temperature, and the resulting orange colored wax dissolved in a mixture of water (100 mL), hot ethanol (20 mL) and dichloromethane (150 mL). The aqueous layer was basified to pH 14 by addition of 10 M sodium hydroxide, then 1 M hydrochloric acid was added until pH 8–9. The organic layer was collected, and the aqueous layer further extracted with dichloromethane (2×150 mL). The combined organics were washed with saturated sodium chloride, dried over sodium sulfate and evaporated to give a dark colored gum, which was purified by column chromatography on silica gel (7% methanol in CH_2Cl_2 eluent), giving the product as a colorless glass. This was dissolved in a minimum of acetone (5 mL), then petroleum ether (50 mL) was added to precipitate the product, **8b** as an off-white amorphous solid, which was vacuum dried; 0.632 g (72% yield), mp 164–167 °C. ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 1.55–1.80 (m, 4H), 2.40–2.60 (m, 4H), 2.70 (t, 2H), 3.50–3.61 (m, 1H), 3.93 (t, 2H), 4.13–4.25 (m, 2H), 4.29 (dd, 1H), 6.25–6.35 (m, 2H), 6.46 (d, 2H), 6.60–6.70 (m, 3H), 6.74–6.81 (m, 2H), 6.98 (t, 2H), 9.30 (s, 1H). MS (EI) 433 (M^+), 84. HR-MS; calcd for $C_{27}H_{29}FNO_3$ ($M+H^+$) 434.2131, found 434.2110. Elemental analysis; calcd for $C_{27}H_{28}FNO_3$; C, 74.81; H, 6.51; N, 3.23%; found C, 74.79; H, 6.78; N, 3.08%.

(±)-*cis*-7-Hydroxy-4-(4-(2-pyrrolidinoethoxy)phenyl)-3-(4-(trifluoromethyl)phenyl)chromane (8c). The title compound was prepared as described for **8b** from (±)-*cis*-7-methoxy-4-(4-(2-pyrrolidinoethoxy)phenyl)-3-(4-(trifluoromethyl)phenyl)chromane, (**7c**, 0.30 g, 0.60 mmol) and pyridine hydrochloride (3.5 g, 30.3 mmol). The crude product was purified by column chromatography on silica gel (6% methanol in CH_2Cl_2 eluent) giving the product, **8c** as a colorless powder; 0.20 g (68% yield), mp 100 °C (dec). ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 1.80–1.95 (m, 4H), 2.65–2.82 (m, 4H), 2.82–2.94 (m, 1H), 3.0–3.12 (m, 1H), 3.62 (ddd, 1H), 3.77–4.08 (m, 2H), 4.16 (dd, 1H), 4.21 (d, 1H), 4.38 (dd, 1H), 6.36 (dd, 1H), 6.41 (d, 1H), 6.41–6.45 (m, 4H), 6.72–6.79 (m, 3H), 7.37–7.44 (m, 2H), phenol OH not observed. MS (EI) 483 (M^+), 84. HR-MS; calcd for $C_{28}H_{29}F_3NO_3$ ($M+H^+$) 484.2099, found 484.2084.

(±)-*cis*-7-Hydroxy-3-(4-hydroxyphenyl)-4-(4-(2-pyrrolidinoethoxy)phenyl)chromane (8d). The title compound was prepared as described for **8b** from (±)-*cis*-7-methoxy-3-(4-methoxyphenyl)-4-(4-(2-pyrrolidinoethoxy)-phenyl)chromane (**7d**, 0.23 g, 0.50 mmol) and pyridine hydrochloride (3.0 g, 26 mmol). The crude product was purified by column chromatography on silica gel (15% methanol in CH_2Cl_2 eluent) giving the product, **8d** as a colorless solid; 0.158 g (73% yield), mp 112–116 °C. ^{1}H NMR (CD_3OD, 300 MHz) δ: 1.85–2.00 (m, 4H), 2.88–3.04 (m, 4H), 3.15 (t, 2H), 3.44 (ddd, 1H), 4.11 (t, 2H), 4.06–4.20 (m, 2H), 4.32 (dd, 1H), 6.29 (dd, 1H), 6.34 (d, 1H), 6.47–6.59 (m, 6H), 6.64–6.72 (m, 3H), phenolic OH not observed. MS (EI) 431 (M^+), 84. HR-MS; calcd for $C_{27}H_{30}NO_4$ ($M+H^+$) 432.2175, found 432.2156.

(±)-*cis*-7-Hydroxy-3-(4-methylphenyl)-4-(4-(2-pyrrolidinoethoxy)phenyl)chromane (8e). The title compound was prepared as described for **8b** from (±)-*cis*-7-methoxy-3-(4-methylphenyl)-4-(4-(2-pyrrolidinoethoxy)phenyl)-chromane (**7e**, 0.444 g, 1.0 mmol) and pyridine hydrochloride (5.8 g, 50 mmol). The crude product was purified by column chromatography on silica gel (5–7% methanol in CH_2Cl_2 eluent) giving the product as a colorless glass. This was triturated with a mixture of ethanol, CH_2Cl_2 and petroleum ether to give the first crop of colorless solid. The triturate was evaporated and

the resulting solid repeat triturated with ethanol, CH_2Cl_2 and petroleum ether to give a second crop of solid. The two crops were combined to give the product, **8e** as a colorless solid; 0.30 g (71% yield), mp 161–165 °C. ^{1}H NMR (CD_3OD, 300 MHz) δ: 1.80–1.95 (bm, 4H), 2.30 (s, 3H), 2.64–2.80 (m, 4H), 2.81–2.92 (m, 1H), 2.97–3.10 (m, 1H), 3.52 (ddd, 1H), 3.96–4.06 (m, 2H), 4.08–4.19 (m, 2H), 4,32 (dd, 1H), 6.34 (dd, 1H), 6.39 (d, 1H), 6.40–6.49 (m, 4H), 6.50–6.56 (m, 2H), 6.75 (d, 1H), 6.92–6.98 (m, 2H), phenol OH not observed. MS (EI) 429 (M^+), 84. HR-MS; calcd for $C_{28}H_{32}NO_3$ ($M+H^+$) 430.2382, found 430.2366.

(±)-*cis*-3-(4-Biphenyl)-7-hydroxy-4-(4-(2-pyrrolidinoethoxy)phenyl)chromane (8f). The title compound was prepared as described for **8b** from (±)-*cis*-3-(4-biphenyl)-7-methoxy-4-(4-(2-pyrrolidinoethoxy)phenyl)chromane (**7f**, 0.202 g, 0.399 mmol) and pyridine hydrochloride (2.5 g, 21.6 mmol). The crude product was purified by column chromatography on silica gel (5% methanol in CH_2Cl_2 eluent) giving the product, **8f** as an off-white solid; 43 mg (22% yield). ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 1.70–1.90 (m, 4H), 2.90–3.10 (m, 4H), 3.15–3.25 (m, 2H), 3.55–3.65 (m, 1H), 4.05–4.15 (m, 2H), 4.20–4.45 (m, 3H), 6.27–6.37 (m, 2H), 6.50–6.58 (m, 2H), 6.62–6.75 (m, 3H), 6.82–6.90 (m, 2H), 7.29–7.40 (m, 1H), 7.40–7.52 (m, 4H), 7.57–7.66 (m, 2H), 9.30 (s, 1H)1.85-2.00 (m, 4H), 2.88–3.04 (m, 4H), 3.15 (t, 2H), 3.44 (ddd, 1H), 4.11 (t, 2H), 4.06–4.20 (m, 2H), 4.32 (dd, 1H), 6.29 (dd, 1H), 6.34 (d, 1H), 6.47–6.59 (m, 6H), 6.64–6.72 (m, 3H), phenolic OH not observed. MS (EI) 491 (M^+), 84. HR-MS; calcd for $C_{33}H_{34}NO_3$ ($M+H^+$) 492.2538, found 492.2523.

(±)-*cis*-7-Hydroxy-4-(4-(2-pyrrolidinoethoxy)phenyl)-3-(3-(trifluoromethyl)phenyl)chromane (8g). The title compound was prepared as described for **8b** from (±)-*cis*-7-methoxy-4-(4-(2-pyrrolidinoethoxy)phenyl)-3-(3-(trifluoromethyl)phenyl)chromane (**7g**, 0.25 g, 0.50 mmol) and pyridine hydrochloride (2.90 g, 25 mmol). The crude product was purified by column chromatography on silica gel (7% methanol in CH_2Cl_2 eluent) giving the product **8g** as an off-white solid; 0.131 g (53% yield), mp 87–89 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.85–2.00 (m, 4H), 2.75–2.90 (m, 4H), 2.90–3.01 (m, 1H), 3.04–3.16 (m, 1H), 3.55–3.66 (m, 1H), 3.77–4.21 (m, 4H), 4.34 (m, 1H), 6.30–6.48 (m, 6H), 6.72 (d, 1H), 6.79 (d, 1H), 6.82 (s, 1H), 7.20–7.30 (m,1H), 7.40 (d, 1H), phenol OH not observed. MS (EI) 483 (M^+), 84. HR-MS; calcd for $C_{28}H_{29}F_3NO_3$ ($M+H^+$) 484.2099, found 484.2090.

(±)-*cis*-3-(3-Fluorophenyl)-7-hydroxy-4-(4-(2-pyrrolidinoethoxy)phenyl)chromane (8h). The title compound was prepared as described for **8b** from (±)-*cis*-3-(3-fluorophenyl)-7-methoxy-4-(4-(2-pyrrolidinoethoxy)phenyl)chromane (**7h**, 0.224 g, 0.50 mmol) and pyridine hydrochloride (2.90 g, 25 mmol). The crude product was purified by column chromatography on silica gel (7% methanol in CH_2Cl_2 eluent) giving a sticky gum, which was triturated with CH_2Cl_2 and petroleum ether to give the product, **8h** as an off-white solid; 0.107 g (49% yield), mp 146–150 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.85–2.00 (m, 4H), 2.65–2.88 (m, 4H), 2.88–3.14 (m, 2H), 3.50–3.60 (m, 1H), 4.00–4.10 (m, 2H), 4.10–4.23 (m, 2H), 4.32 (dd, 1H), 6.30–6.55 (m, 8H), 6.74 (d, 1H), 6.80–6.90 (m, 1H), 7.05–7.17 (m, 1H), phenol OH not observed. MS (EI) 433 (M^+), 84. HR-MS; calcd for $C_{27}H_{29}FNO_3$ ($M+H^+$) 434.2131, found 434.2131.

(±)-*cis*-7-Hydroxy-3-(3-hydroxyphenyl)-4-(4-(2-pyrrolidinoethoxy)phenyl)chromane (8i). The title compound was prepared as described for **8b** from (±)-*cis*-7-methoxy-3-(3-methoxyphenyl)-4-(4-(2-pyrrolidinoethoxy)-phenyl)chromane (**7i**, 0.345 g, 0.75 mmol) and pyridine hydrochloride (4.34 g, 37.5 mmol). The crude product was purified by column chromatography on silica gel (10% methanol in CH_2Cl_2 eluent) giving the product, **8i** as a colorless solid; 0.25 g (77% yield), mp 126 °C (dec). ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 1.65–1.80 (m, 4H), 2.60–2.80 (m, 4H), 2.85–3.00 (m, 2H), 3.30–3.60 (m, 1H plus water from solvent), 4.00 (t, 2H), 4.12–4.30 (m, 3H), 6.17–6.22 (m, 2H), 6.22–6.34 (m, 2H), 6.44–6.60 (m, 3H), 6.0–6.70 (m, 3H), 6.92 (t, 1H), 9.20 (s, 1H), 9.30 (s, 1H). MS (EI) 431 (M^+), 84. HR-MS; calcd for $C_{27}H_{30}NO_4$ ($M+H^+$) 432.2175, found 432.2175.

(±)-*cis*-7-Hydroxy-3-(3-methylphenyl)-4-(4-(2-pyrrolidinoethoxy)phenyl)chromane (8j). The title compound was prepared as described for **8b** from (±)-*cis*-7-methoxy-3-(3-methylphenyl)-4-(4-(2-pyrrolidinoethoxy)phenyl)-chromane (**7j**, 0.360 g, 0.75 mmol) and pyridine hydrochloride (4.35 g, 37.6 mmol). The crude product was purified by column chromatography on silica gel (7% methanol in CH_2Cl_2 eluent) giving the product, **8j** as a colorless solid; 0.228 g (70% yield), mp 85–90 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.85–2.00 (m, 4H), 2.20 (s, 3H), 2.75–2.90 (m, 4H), 2.90–3.03 (m, 1H), 3.03–3.17 (m, 1H), 3.52 (ddd, 1H), 4.00–4.10 (m, 2H), 4.10–4.20 (m, 2H), 4.32 (dd, 1H), 6.32–6.52 (m, 8H), 6.72 (d, 1H), 6.94–7.06 (m, 2H), phenol OH not observed. MS (EI) 429 (M^+), 84. HR-MS; calcd for $C_{28}H_{30}NO_3$ ($M+H^+$) 430.2382, found 430.2363.

(±)-*cis*-7-Hydroxy-3-phenyl-4-(4-(2-piperidinoethoxy)-phenyl)chromane (8k). The title compound was prepared as described for **8b** from (±)-*cis*-7-methoxy-3-phenyl-4-(4-(2-piperidinoethoxy)phenyl)chromane, (**7k**, 0.89 g, 2.01 mmol), and pyridine hydrochloride (11.6 g, 100 mmol). The crude product was purified by column chromatography on silica gel (7% methanol in CH_2Cl_2 eluent) giving an off-white solid, which was recrystallized from aqueous ethanol to give the product, **8k** as colorless needles; 0.424 g (49% yield), mp 168–170 °C. ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 1.30–1.40 (m, 2H), 1.40–1.55 (m, 4H), 2.35–2.45 (m, 4H), 2.60 (t, 2H), 3.53 (ddd, 1H), 3.72 (t, 2H), 4.15–4.26 (m, 2H), 4.13 (dd, 1H), 6.28 (dd, 1H), 6.31 (d, 1H), 6.44 (d, 2H), 6.61 (d, 2H), 6.66 (d, 1H), 6.71–6.80 (m, 2H), 7.10–7.20 (m, 3H), 9.30 (s, 1H). MS (EI) 429 (M^+), 98. Elemental analysis; calcd for $C_{28}H_{31}NO_3$; C, 78.29; H, 7.27; N, 3.26%; found C, 78.46; H, 7.26; N, 3.21%. HR-MS; calcd for $C_{28}H_{32}NO_3$ ($M+H^+$) 430.2382, found 430.2381.

(±)-*cis*-7-Hydroxy-3-phenyl-4-(4-(3-piperidinopropoxy)-phenyl)chromane (8l). The title compound was prepared as described for **8b** from (±)-*cis*-7-methoxy-3-phenyl-4-

(4-(3-piperidinopropoxy)phenyl)chromane (**7l**, 0.114 g, 0.25 mmol), and pyridine hydrochloride (0.60 g, 5.19 mmol). The crude product was purified by column chromatography on silica gel (7% methanol in CH_2Cl_2 eluent) giving the product, **8l** as an off-white solid; 52 mg (47% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.45–1.60 (m, 2H), 1.70–1.85 (m, 4H), 2.05–2.20 (m, 2H), 2.65–2.85 (m, 6H), 3.54 (ddd, 1H), 3.86 (t, 2H), 4.14–4.23 (m, 2H), 4.37 (dd, 1H), 6.39 (dd, 1H), 6.42–6.56 (m, 5H), 6.61–6.68 (m, 2H), 6.72 (d, 1H), 6.70–6.90 (bs, 1H), 7.10–7.20 (m, 3H). MS (EI) 443 (M^+), 98. HR-MS; calcd for $C_{29}H_{34}NO_3$ ($M+H^+$) 444.2538, found 444.2523.

(±)-*cis*-7-Hydroxy-4-(4-(2-piperidinoethoxy)phenyl)-3-(4-(trifluoromethyl)phenyl)chromane (8m). The title compound was prepared as described for **8b** from (±)-*cis*-7-methoxy-4-(4-(2-piperidinoethoxy)phenyl)-3-(4-(trifluoromethyl)phenyl)chromane (**7m**, 0.512 g, 1.0 mmol), and pyridine hydrochloride (5.80 g, 50 mmol). The crude product was purified by column chromatography on silica gel (5–7% methanol in CH_2Cl_2 eluent) to give an orange gum, which was triturated with ether to give the product, **8m** as an off-white powder; 0.30 g (61% yield), mp 117–119 °C. ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 1.30–1.60 (m, 6H), 2.35–2.45 (m, 4H), 2.55–2.65 (m, 2H), 3.60–3.72 (m, 1H), 3.87–4.0 (m, 2H), 4.19–4.42 (m, 3H), 6.25–6.35 (m, 2H), 6.43–6.52 (m, 2H), 6.60–6.70 (m, 3H), 6.95–7.03 (m, 2H), 7.46–7.55 (m, 2H), 9.35 (s, 1H). MS (EI) 497 (M^+), 98. HR-MS; calcd for $C_{29}H_{31}F_3NO_3$ ($M+H^+$) 498.2256, found 498.2241.

(±)-*cis*-7-Hydroxy-3-(4-methylphenyl)-4-(4-(2-piperidinoethoxy)phenyl)chromane (8n). The title compound was prepared as described for **8b** from (±)-*cis*-7-methoxy-3-(4-methylphenyl)-4-(4-(2-piperidinoethoxy)phenyl)chromane (**7n**, 0.458 g, 1.0 mmol) and pyridine hydrochloride (5.8 g, 50 mmol). The crude product was purified by column chromatography on silica gel (7% methanol in CH_2Cl_2 eluent) to give a colorless foam, which was triturated with CH_2Cl_2 and petroleum ether to give the product, **8n** as an off-white powder; 0.315 g (70% yield), mp 146–147 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.45–1.55 (m, 2H), 1.64–1.75 (m, 4H), 2.32 (s, 3H), 2.50–2.70 (m, 4H), 2.70–2.82 (m, 1H), 2.82–2.95 (m, 1H), 3.53 (ddd, 1H), 3.96–4.10 (m, 2H), 4.10–4.20 (m, 2H), 4.33 (dd, 1H), 6.37 (dd, 1H), 6.40 (d, 1H), 6.41–6.50 (m, 4H), 6.50–6.58 (m, 2H), 6.77 (d, 1H), 6.92–7.00 (m, 2H), phenol OH not observed. MS (EI) 443 (M^+), 98. HR-MS; calcd for $C_{29}H_{34}NO_3$ ($M+H^+$) 444.2538, found 444.2532.

(±)-*cis*-3-(4-Fluorophenyl)-7-hydroxy-4-(4-(3-piperidinopropoxy)phenyl)chromane (8o). The title compound was prepared as described for **8b** from (±)-*cis*-3-(4-fluorophenyl)-7-methoxy-4-(4-(3-piperidinopropoxy)phenyl)-chromane (**7o**, 0.476 g, 1.0 mmol), and pyridine hydrochloride (5.80 g, 50 mmol). The crude product was purified by column chromatography on silica gel (7% methanol in CH_2Cl_2 eluent) to give the product, **8o** as an off-white solid; 0.264 g (57% yield), mp 78–84 °C. ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 1.30–1.60 (m, 6H), 1.75–7.90 (m, 2H), 2.30–2.60 (m, 6H), 3.50–3.60 (m, 1H), 3.86 (t, 2H), 4.05–4.35 (m, 3H), 6.25–6.35 (m, 2H), 6.42–6.52 (m, 2H), 6.58–6.69 (m, 3H), 6.73–6.83 (m, 2H), 6.91–7.03 (m, 2H), 9.30 (s, 1H). MS (EI) 461 (M^+), 98. HR-MS; calcd for $C_{29}H_{33}FNO_3$ ($M+H^+$) 462.2444, found 462.2431.

(±)-*cis*-7-Hydroxy-3-(3-hydroxyphenyl)-4-(4-(3-piperidinopropoxy)phenyl)chromane (8p). The title compound was prepared as described for **8b** from (±)-*cis*-7-methoxy-3-(3-methoxyphenyl)-4-(4-(3-piperidinopropoxy)-phenyl)chromane (**7p**, 0.49 g, 1.0 mmol), and pyridine hydrochloride (5.8 g, 50 mmol). The crude product was purified by column chromatography on silica gel (10% methanol in CH_2Cl_2 eluent) to give the product, **8p** as a yellow solid; 0.28 g (58% yield), mp 117–119 °C. ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 1.30–1.42 (m, 2H), 1.42–1.54 (m, 4H), 1.80 (pentet, 2H), 2.25–2.44 (m, 6H), 3.40 (ddd, 1H), 3.87 (t, 2H), 4.00–4.32 (m, 3H), 6.15–6.22 (m, 2H), 6.27 (dd, 1H), 6.31 (d, 1H), 6.47 (dm, 2H), 6.54 (dm, 1H), 6.57–6.69 (m, 3H), 6.93 (dd, 1H), 9.15 (bs, 1H), 9.28 (s, 1H). MS (EI) 459 (M^+), 98. HR-MS; calcd for $C_{29}H_{34}NO_4$ ($M+H^+$) 460.2488, found 460.2469.

(−)-(3*S*,4*R*)-7-Hydroxy-3-phenyl-4-(4-(2-pyrrolidinoethoxy)phenyl)chromane (3, = 9a). A mixture of (−)-(3*S*,4*R*)-7-methoxy-3-phenyl-4-(4-(2-pyrrolidinoethoxy)-phenyl)chromane [(−)-**7a**, 3.43 g, 8.0 mmol], pyridine (20 mL) and concentrated hydrochloric acid (24 mL) was heated to reflux and water removed by distillation until the temperature of the mixture reached 150 °C. The resulting melt was stirred for 5 h at 150 °C, cooled to room temperature, and diluted with water (30 mL), toluene (30 mL) and basified to pH 10 with 32.5 wt% sodium hydroxide solution. The aqueous phase was separated, extracted with toluene (30 mL), and the combined organic phases dried (K_2CO_3) and evaporated. The resulting solid residue was dissolved in ethanol (200 mL) and water (20 mL), acidified to pH 2 with concentrated hydrochloric acid and the solution filtered through activated charcoal. The solvents were evaporated, the residue dissolved in ethanol (20 mL), the solution filtered, diluted with more ethanol (100 mL) and neutralized to pH 7 with 32.5 wt% sodium hydroxide. The resulting precipitated solid was collected, triturated with water (30 mL), collected again by filtration, and vacuum dried to give the colorless powder **3**, which contained 0.25 mol equiv of ethanol of crystallization; 0.90 g (27% yield), mp 221–223 °C. ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 1.60–1.73 (m, 4H), 2.40–2.50 (m, 4H), 2.69 (t, 2H), 3.47–3.57 (m, 1H), 3.92 (t, 2H), 4.14–4.25 (m, 2H), 4.32 (dd, 1H), 6.27 (dd, 1H), 6.30 (d, 1H), 6.44 (d, 2H), 6.60 (d, 2H), 6.65 (d, 1H), 6.70–6.80 (m, 2H), 7.09–7.20 (m, 3H), 9.25 (s, 1H). MS (EI): 415 (M^+), 84. HR-MS; calcd for $C_{27}H_{30}NO_3$ ($M+H^+$) 416.2225, found 416.2198. HR-MS; calcd for $C_{28}H_{32}NO_3$ ($M+H^+$) 430.2382, found 430.2376. Chiral HPLC: Chiradex A, 5μ, 250×4 mm (Merck) column; eluent, 6:4 methanol/0.2% aqueous triethylammonium acetate buffer, pH = 5.2; flow, 0.5 mL/min; UV 220 nm; R_t = 19.2 min, >98%ee. Elemental analysis; calcd for $C_{27}H_{29}NO_3 \cdot 0.25C_2H_5OH$; C, 77.35; H, 7.20; N, 3.28%; found C, 77.39; H, 7.29; N, 3.12%. $[\alpha]_D^{20} = -283°$ (c = 1.004% in ethanol/3M HCl, 80:20).

(−)-*cis*-7-Hydroxy-4-(4-(2-pyrrolidinoethoxy)phenyl)-3-(4-(trifluoromethyl)phenyl)chromane (9c). The title compound was prepared from (−)-*cis*-7-methoxy-4-(4-(2-pyrrolidinoethoxy)phenyl)-3-(4-(trifluoromethyl)phenyl)chromane, [(−)-**7c**, 0.50 g, 1.00 mmol] and pyridine hydrochloride (5.81 g, 50.3 mmol) using the method described for the preparation of **8b**. The crude product was purified by column chromatography on silica gel (10% methanol in CH_2Cl_2 eluent) giving the product, **9c** as a off-white solid; 0.236 g (48% yield), mp 92–96 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.82–1.95 (m, 4H), 2.65–2.84 (m, 4H), 2. 92 (dt, 1H), 3.02 (dt, 1H), 3.62 (m, 1H), 4.04 (t, 2H), 4.12–4.22 (m, 2H), 4.40 (dd, 1H), 6.35 (dd, 1H), 6.40–6.50 (m, 5H), 6.70–6.80 (m, 3H), 7.38–7.46 (m, 2H), phenol OH not observed. MS (EI) 483 (M^+), 84. HR-MS; calcd for $C_{28}H_{29}F_3NO_3$ ($M+H^+$) 484.2099, found 484.2093. $[\alpha]_D^{20} = -234.8°$ (c = 1.00% in methanol).

General method for the small-scale separation of compounds 9a–o and 10a–o. Small quantities of the compounds **9a**–**o** and **10a**–**o** (approximately 3 mg of each) were isolated by means of preparative chiral HPLC separation of 10–15 mg quantities of compounds **8a**–**o**. Table 1 gives details of the separations, including the type of chiral column used, the flow rate, the eluents employed, and the collection retention times (R_t) of the different enantiomers.

4′-Benzyloxy-2,5-dimethoxybenzophenone (12). Butyllithium (2.0 M in hexanes, 6.6 mL, 13.2 mmol) was added dropwise at −78 °C to a stirred THF (20 mL) solution of 4-benzyloxybromobenzene (3.15 g, 11.97 mmol) to give a yellow colored suspension, which was stirred for 10 min. A THF (10 mL) solution of *N*,*N*-dimethyl 2,5-dimethoxybenzamide (**11**, 2.09 g, 9.99 mmol) was then added slowly, and the resulting mixture warmed to room temperature over 20 h. The mixture was diluted with 1 M aqueous hydrochloric acid (50 mL) and the product extracted into dichloromethane (4×50 mL). The combined extracts were washed with brine, dried over sodium sulfate and evaporated. The crude product was purified by column chromatography on silica gel (20% ethyl acetate in petroleum ether eluent), to give a colorless solid, which was recrystallized from ethanol to give **12** as colorless platelets; 1.61 g (46% yield), mp 111–113 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 3.70 (s, 3H), 3.78 (s, 3H), 5.13 (s, 2H), 6.85–7.02 (m, 5H), 7.30–7.47 (m, 5H), 7.82 (dm, 2H). MS (EI) 348 (M^+), 257, 91. HR-MS; calcd for $C_{22}H_{21}O_4$ ($M+H^+$) 349.1440, found 349.1450.

2,4′-Dihydroxy-5-methoxybenzophenone (13). Hydrogen bromide (33% w/w in acetic acid, 0.70 mL, 3.94 mmol) was added to a stirred acetic acid (5 mL) solution of (4-benzyloxyphenyl)-(2,5-dimethoxyphenyl)-methanone (**12**, 0.87 g, 2.50 mmol) and the resulting mixture heated to 75 °C for 4 h. The mixture was diluted with water (10 mL) and the solution stirred at room temperature for 18 h, diluted with CH_2Cl_2 (50 mL) and water (40 mL), and neutralized to pH 7 by addition of 2 M sodium hydroxide. The aqueous layer was separated and extracted with CH_2Cl_2 (50 mL). The combined organic layers were washed with brine, dried over magnesium sulfate, and evaporated to give a yellow gum, which was purified by column chromatography on silica gel (30% ethyl acetate in petroleum ether eluent) to give **13** as a yellow solid; 0.12 g (19% yield), mp 144.5–147.5 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 3.74 (s, 3H), 6.30 (bs, 1H), 6.92 (dm, 2H), 7.01 (d, 1H), 7.10 (d, 1H), 7.13 (dd, 1H), 7.68 (dm, 2H), 11.50 (s, 1H). MS (EI) 244 (M^+), 150.

4-(4-Acetoxyphenyl)-3-phenyl-6-methoxychromen-2-one (14). A mixture of 2,4′-dihydroxy-5-methoxybenzophenone (**13**, 0.59 g, 2.42 mmol), acetic anhydride (1.15 mL, 12.1 mmol), triethylamine (0.44 mL, 3.16 mmol), and phenylacetic acid (0.33 g, 2.42 mmol) was stirred at 135 °C for 18 h. The resulting orange colored solution was poured into water (20 mL), stirred for 3 h, and the resulting mixture diluted with ethyl acetate (20 mL). The aqueous layer was separated, and extracted with ethyl acetate (2×20 mL). The combined organic layers were washed with water, brine, dried over sodium sulfate and evaporated to give a yellow/orange gum, which was dissolved in a minimum of ether. Petroleum ether was then added to precipitate the product, which was collected by filtration and vacuum dried to give **14** as an off white powder; 0.49 g (52% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 2.28 (s, 3H), 3.72 (s, 3H), 6.70 (d, 1H), 7.04–7.25 (m, 10H), 7.48 (d, 1H). MS (EI) 386 (M^+), 344, 327, 316, 43.

(±)-*cis*-6-Methoxy-3-phenyl-4-(4-(2-pyrrolidinoethoxy)-phenyl)chromane (15). Lithium aluminium hydride (0.96 g, 2.54 mmol) was added in small portions to a stirred solution of 4-(4-acetoxyphenyl)-3-phenyl-6-methoxychromen-2-one (**14**, 0.49 g, 1.27 mmol) in tetrahydrofuran (75 mL) and the resulting mixture stirred for 30 min. Hydrochloric acid (6 M, 4 mL) was then added dropwise, and the resulting mixture heated to 65 °C for 3 h. The resulting solution was cooled to room temperature, diluted with water (100 mL) and the products extracted into ethyl acetate (2×100 mL). The combined extracts were washed with brine, dried over sodium sulfate and evaporated to give crude 4-(4-hydroxyphenyl)-6-methoxy-3-phenyl-2*H*-chromene as a yellow gum. This gum was dissolved in ethanol (100 mL), palladium (5 wt% on activated carbon, 0.045 g, 0.02 mmol) added, and the mixture stirred under a hydrogen atmosphere for 18 h. The palladium catalyst was removed by filtration through Celite® and the solvents evaporated to give crude (±)-*cis*-4-(4-hydroxyphenyl)-6-methoxy-3-phenylchromane. This chromane was dissolved in dry acetone (20 mL), potassium carbonate (1.87 g, 13.50 mmol), 1-(2-chloroethyl)pyrrolidine hydrochloride (0.257 g, 1.51 mmol) and sodium iodide (0.01 g, 0.07 mmol) were added, and the mixture heated to 60 °C for 20 h. The solid inorganic products were removed by filtration, and the solvent evaporated to give an orange gum, which was purified by column chromatography on silica gel (10% methanol in CH_2Cl_2 eluent). This gave **15** as a pale orange gum; 0.34 g (62% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.70–1.90 (m, 4H), 2.55–2.70 (m, 4H), 2.85 (t, 2H), 3.56 (ddd, 1H), 3.69 (s, 3H), 4.02 (t, 2H), 4.15–4.28 (m, 2H), 4.40 (dd, 1H), 6.45–6.55 (m, 3H), 6.55–6.72 (m, 4H), 6.79 (dd, 1H), 6.90 (d, 1H), 7.10–7.20 (m, 3H).

(±)-*cis*-6-Hydroxy-3-phenyl-4-(4-(2-pyrrolidinoethoxy)-phenyl)chromane (16). A mixture of (±)-*cis*-6-methoxy-3-phenyl-4-(4-(2-pyrrolidinoethoxy)phenyl)chromane (**15**, 0.34 g, 0.79 mmol) and pyridine hydrochloride (0.91 g, 7.9 mmol) was stirred at 135 °C for 18 h, cooled to room temperature and the resulting dark solid dissolved in a mixture of methanol (10 mL), water (50 mL) and CH_2Cl_2 (50 mL). The aqueous layer was separated and further extracted with 4:1 CH_2Cl_2/methanol (50 mL). The combined organic layers were washed with brine, dried over magnesium sulfate, and evaporated to an orange gum, which was purified by column chromatography on silica gel (5% methanol in CH_2Cl_2 eluent) to give a yellow solid. This solid was dissolved in CH_2Cl_2, washed with sodium hydrogen carbonate solution, brine, dried over magnesium sulfate and evaporated to give **16** as a pale yellow solid; 70 mg (21% yield). ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 1.70–1.90 (m, 4H), 2.55–2.75 (m, 4H), 2.85 (t, 2H), 3.55 (ddd, 1H), 3.90–4.10 (m, 2H), 4.15–4.28 (m, 2H), 4.40 (dd, 1H), 6.38 (d, 1H), 6.42–6.60 (m, 4H), 6.60–6.75 (m, 3H), 6.85 (d, 1H), 7.05–7.25 (m, 3H), phenol OH not observed. HR-MS; calcd for $C_{27}H_{30}NO_3$ ($M+H^+$) 416.2225, found 416.2230.

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