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Estrogen receptor ligands. Part 10: Chromanes: old scaffolds for new SERAMs

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Abstract—The discovery, synthesis, and SAR of chromanes as ERα subtype selective ligands are described. X-ray studies revealed that the origin of the ERα-selectivity resulted from a C-4 *trans* methyl substitution to the *cis*-2,3-diphenyl-chromane platform. Selected compounds from this class demonstrated very potent in vivo antagonism of estradiol in an immature rat uterine weight assay, effectively inhibited ovariectomy-induced bone resorption in a 42 days treatment paradigm, and lowered serum cholesterol levels in ovx'd adult rat models. The best antagonists **8F** and **12F** also exhibited potent inhibition of MCF-7 cell growth and were shown to be estrogen receptor down-regulators (SERDs).

As part of an evolutionary program designed to exploit the chromane skeleton for the discovery of selective ligands for the estrogen receptors, we have recently reported our findings on the flavanone,[1] **I**, Z = CO, and dihydrobenzoxathiin,[2] **I**, Z = S, classes. The reports detailed the generation of ligands with a greater affinity for the α isoform of the estrogen receptor and were therefore labeled SERAMs, selective estrogen receptor alpha modulators. Of the two classes, the more potent dihydrobenzoxathiins, typically exhibited low to sub-nanomolar binding to ERα, with 50- to 100-fold selectivity, and as a result of further study, a derivative, **II**, was targeted for development as a potential agent for the treatment of osteoporosis. This report focuses on the further extension of this research and discloses the synthesis and biological properties of another new class of orally bioavailable SERAMs containing the parent chromane core structure **III**, wherein, the size and stereogenic placement of the substituent is crucial for both receptor potency and selectivity. This series of compounds contrasts our initial finding, wherein the unsubstituted chromane **III**, Y = OH, $R^1 = R^2 = H$, exhibited equipotent affinity for both ERα and ERβ.[1] In addition, the results of this study contrast the very early studies of the Central Drug Research Institute (India) in which similar 3,4-diaryl-chromanes were exploited as potential antifertility agents and led to the development of the nonsteroidal contraceptive agent centchroman **IV**,[3] and the more recent studies of the Novo Nordisk,[4] as NSERTs (nonsteroidal estrogen receptor therapeutics) or early SERMs. Further exploitation of the chromane scaffold has also provided non-subtype selective, potent chromenes **V**[5] and **VI**,[6] as SERMs of commercial interest. The series of compounds disclosed herein represent the first reported chromanes exhibiting ERα-selectivity (see Figures 1 and 2).

Keywords: Osteoporosis; Estrogen receptor; Chromane; Subtype selectivity; Estrogen receptor alpha; SERM; SERAM; Estrogen receptor antagonist; Cancer.
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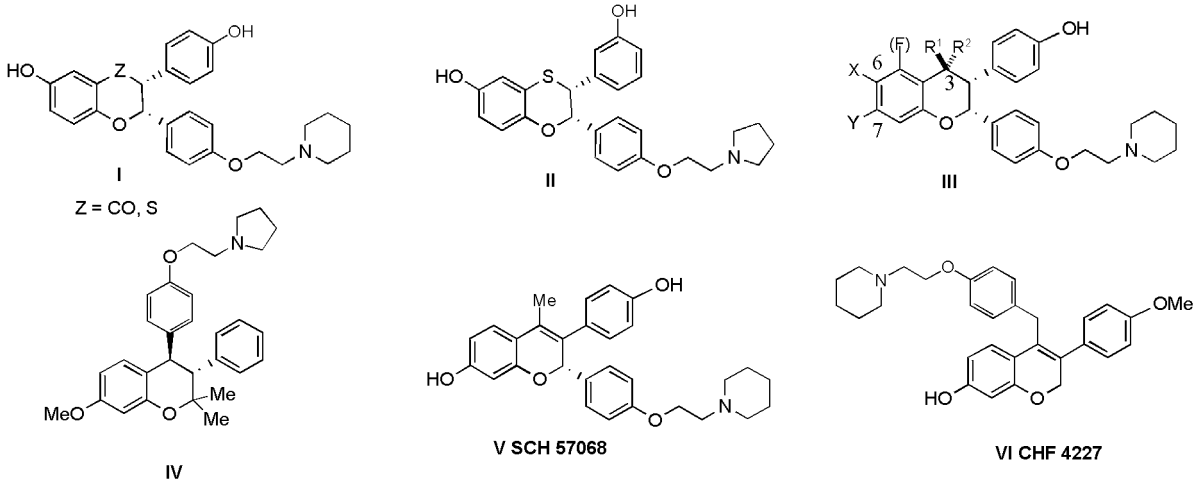


Figure 1.

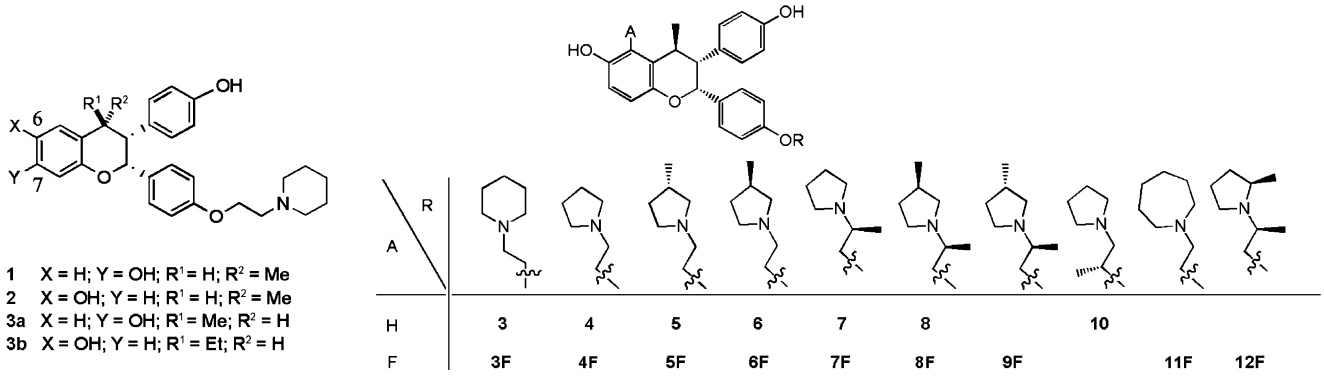
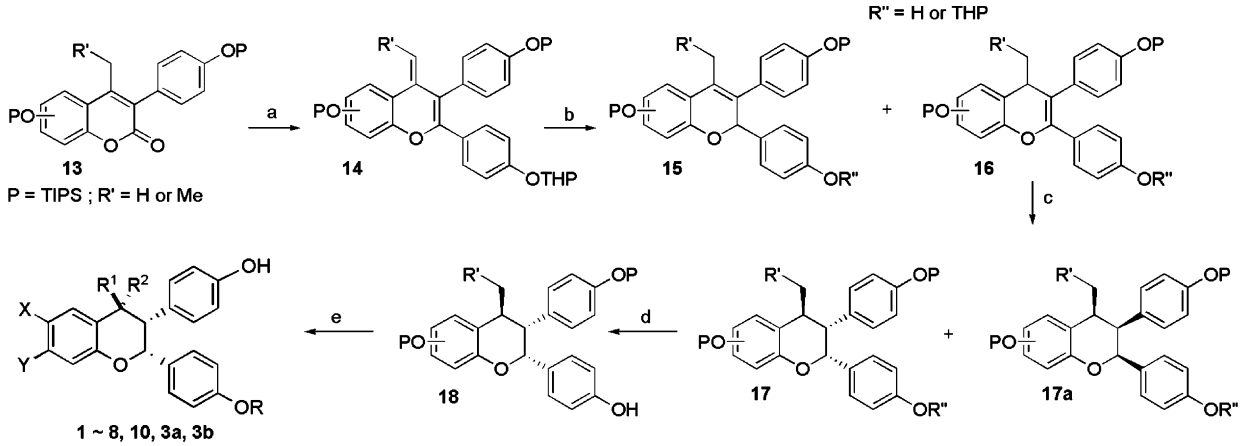


Figure 2. Novel chromanes **III**. **1**, **2**, and **3b** are racemic and the remainder are chiral.

The synthesis of the series **1**–**8**, **10**, **3a,** and **b** is depicted in Scheme 1 and featured diene **14**, which was obtained from the acid-induced elimination of the carbinol adduct formed by the addition of the Grignard reagent to coumarin **13**. Hydrogenation with Rh on carbon gave a mixture of alkenyl isomers **15** and **16**, in a ratio which averaged at 1:2.5. It was also found upon scale-up that the THP group was partially cleaved to give a mixture of protected and unprotected products. A second hydrogenation of **16** with Pd on carbon, with or without the THP group, provided chromanes **17** and **17a** (approximate ratio of **17**:**17a** = 1:1.4, R^1 = H; 1:4.5, R^1 = Me),



Scheme 1. Synthesis of **1**–**8**, **10**, **3a**, and **b**. Reagents and conditions: (a) (i) 4-(2-tetrahydro-2*H*-pyranoxy)phenylmagnesium bromide, THF, rt; (ii) 2 N anhydrous HCl in ether, 0 °C; (b) 1 atm H_2, EtOAc, 5% Rh–C, rt, ca 50% two steps; (c) 1 atm H_2, EtOAc, 10% Pd–C, rt; (d) (i) TFA, triethylsilane, CH_2Cl_2, 0 °C; skipped if THP is already completely removed in step c; (ii) chromatographic separation of isomers, ca 60% two steps; (e) (i) triphenylphosphine, DIAD, ROH, THF, rt; (ii) TBAF, THF, rt, ca 50%.