Communications to the Editor

Discovery and Preclinical Pharmacology of a Novel, Potent, Nonsteroidal Estrogen Receptor Agonist/Antagonist, CP-336156, a Diaryltetrahydronaphthalene

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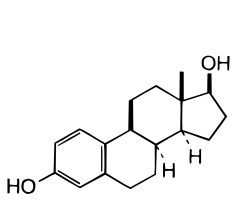
Osteoporosis is a severely debilitating skeletal disease which has special significance to the long-term health of millions of postmenopausal women.[1] Declining levels of circulating estrogen (primarily 17β-estradiol **1**) result in increased bone loss eventually leading to osteopenia (low bone mass) and an increased risk of fracture. A mainstay of osteoporosis treatment to prevent bone loss in postmenopausal women is estrogen replacement therapy (ERT). In addition, estrogen usage reduces the risk of cardiovascular disease by approximately 50%[2] due in part to beneficial effects on cholesterol, LDL and HDL. However, side effects including uterine bleeding, fluid retention, headache, and increased risk of endometrial and breast cancer result in poor compliance.[3] Therefore, from a drug discovery point of view, there is a challenge to identify an estrogen mimetic that possesses the beneficial effects and is devoid of the associated risks and negative side effects of estrogen therapy.

It has been reported that several nonsteroidal estrogen receptor agonists[4,5] such as raloxifene **2** and droloxifene **3** can maintain the benefits of estrogen both on the skeleton and cardiovascular system, while not inducing proliferation of breast and uterine tissue in rat models of osteoporosis. Raloxifene prevented[6a] ovariectomy (OVX) induced bone loss in the rat and lowered serum cholesterol with no significant proliferative effects on the endometrium. In addition, raloxifene potently inhibited[7] estrogen's proliferative actions on MCF-7 cells, a human breast cancer cell line. In clinical studies[6b] with postmenopausal women, a daily dose of raloxifene HCl (150 mg) over 2 years increased total body bone mineral density (1.86%) and lowered the levels of LDL (14.4%) and cholesterol (9.7%). However raloxifene possesses limited systemic bioavailability of intact drug upon oral administration in animals[8a] and in humans[8b] because of extensive glucuronidation at the 6- and 4′-hydroxyl groups, which we hypothesize might be the reason for raloxifene being less potent than estrogen in vivo.[9a] A synthetic program was undertaken to discover a novel, nonsteroidal agent that has good oral bioavailability and yet maintains estrogen's beneficial effects; it was our expectation that by addressing glucuronidation, a breakthrough for in vivo potency could be attained because of increased levels of circulating active drug.[9b]



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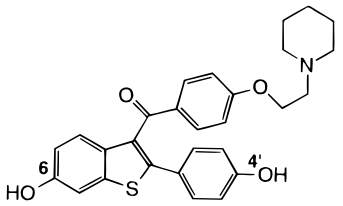

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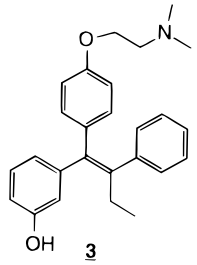

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Our chemical plan involved surveying the various structural classes known to interact with the estrogen receptor, including the benzothiophenes exemplified by raloxifene. To pursue our objective, special attention was paid to evaluate the oral pharmacokinetics of interesting estrogen mimetics in the rat and monkey. Pharmacological evaluation consisted of a three-step screening paradigm: (1) determination of the IC_{50} for inhibition of estradiol binding to the estrogen receptor,[10] (2) efficacy at preventing bone loss in the OVX rat using bone mineral density (BMD) and histomorphometry endpoints along with the monitoring of serum cholesterol levels and uterine effects,[5] and (3) antiproliferative effects in the estrogen sensitive MCF-7 breast cancer cell line.[11] A wide variety of synthetic modifications[12] at various sites of the benzothiophene produced compounds with in vitro activity similar to that of raloxifene, but oral bioavailability was not improved. Subsequent studies were conducted to monitor xenobiotic portal vein concentrations following oral administration of estrogen mimetics in the rat. These experiments demonstrated that the phenolic groups on benzothiophenes were extensively glucuronidated in the intestinal wall,[13] which would account for the poor oral bioavail-

† Medicinal Chemistry.
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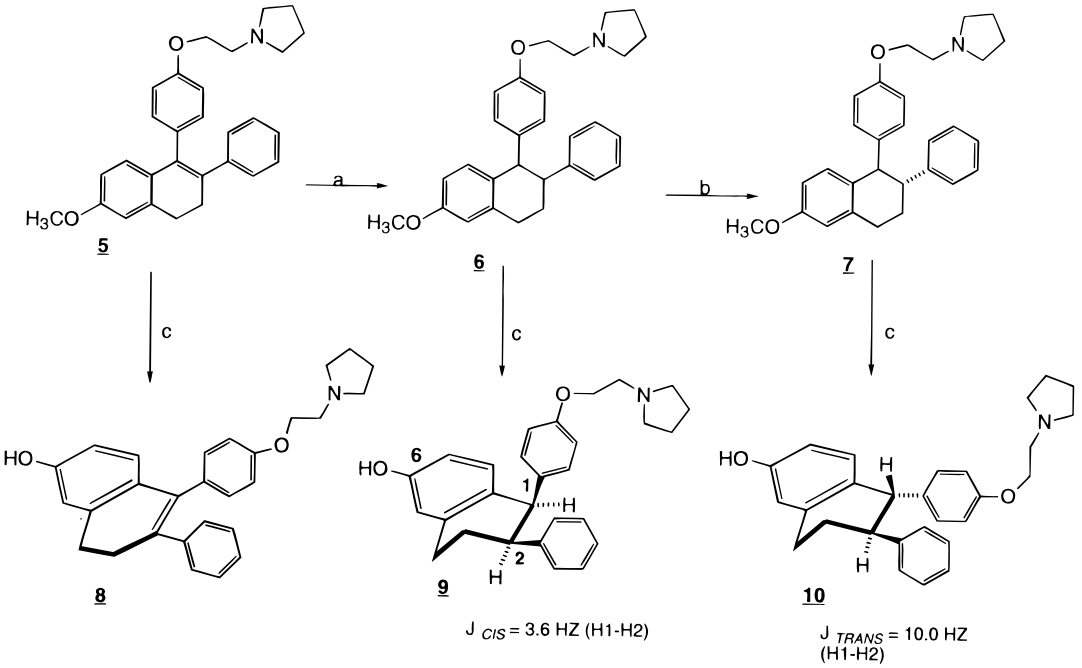
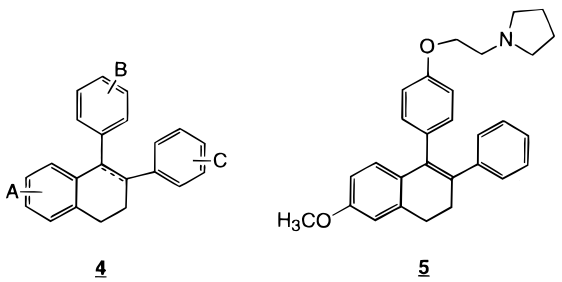
Scheme 1[a]



[a] Reagents: (a) $Pd(OH)_2/C$, H_2; (b) BuLi, DMSO;[19] (c) BBr_3.

ability of intact drug which as was stated previously is the potential limiting factor for superior in vivo potency with these analogues.

Glucuronidation within the gastrointestinal mucosa has been extensively studied;[14a] typical substrates are xenobiotics possessing phenolic functionality. In man, such a transformation is an important metabolic pathway for steroid hormones.[14b] A structural approach for minimizing conjugation was suggested by SAR studies of glucuronosyltransferases from rat intestine, where glucuronidation rates were found to depend on steric properties;[15] notably, nonplanar phenols were found to be poorer substrates. The pioneering work of Lednicer et al on dihydro-[16] and tetrahdronaphthalenes[17] provided a superb platform to test the critical concept of modulating phenolic glucuronidation to obtain pharmacokinetically superior estrogen mimetics. The tetralin template **4**, structurally related to the estrogen receptor modulator nafoxidine **5** (investigated for antifertility and breast cancer),[16] allowed us to systematically vary the spacial relationship of the crucial three aryl segments and thereby probe pharmacokinetics, along with estrogen receptor binding and in vivo pharmacology.



Accordingly, a series of tetralins (functionally similar, but topologically different) was constructed (Scheme 1) proceeding from fairly planar dihydronaphthalene **8**[18] and *trans*- tetrahydronaphthalene **10** to the *cis*-tetrahydronaphthalene **9**, where the corresponding aryl substituents at C-1 and C-2 must be in an axial, equatorial orientation; an analysis similar to an NMR structural elucidation performed on known tetralins **6** and **7** confirmed our assignments.[17]

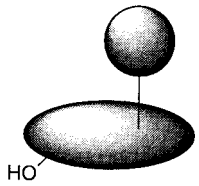
Table 1.[a] Receptor Affinity, Pharmacokinetics, and in Vivo Activity

		oral bioavailability (%)		oral OVX rat ED_{50} (μg/kg/day)[25a,b]	
structure	IC_{50} (nM)[10]	rat	cyno monkey	bone loss prevention[b]	serum cholesterol reduction
1[c,26]	0.354 ± 0.69			10	10
2	1.85 ± 0.28	10 ± 2.5	5 ± 0.4	500	500
5[27]	40.9 ± 9.32				
6	132.0 ± 18.7				
8	47.1 ± 10.1				
9	11.1 ± 2.11	60[d]			
10	9.75 ± 3.19	16[e]			
12	11.1 ± 2.35	27 ± 4		175	175
13	270.0 ± 34.0	29 ± 5		>500	>500
14	11.3 ± 3.46	62 ± 18	45[f]	<1	10

[a] The HCl salt form of new compounds was used for structural characterization (^{1}H NMR, MS, CHN), and biological profiling; amine containing reference compounds (**2**, **5**, **6**, **8**, and **12**) were tested as HCl salts. [b] Derived from analysis of BMD measurements and histomorphometry of lumbar vertebrae. [c] In vivo experiments were performed with 17α-ethynylestradiol. [d] 59−60 (2). [e] 15−17 (2). [f] 40−50 (2).

The biological profiles of these target substances along with intermediates **5** and **6** are summarized in Table 1. Because of the presumed overlap of the C-3 hydroxyl of estradiol with the C-6 hydroxyl of **9**, the latter was expected to be superior to anisole **6** in the binding assay, which was in fact observed (11.1 and 132.0 nM, respectively). With dihydronaphthalenes **5** and **8**, contrary to expectation, there was surprisingly less preference for the phenolic modification (40.9 versus 47.1 nM). Noteworthy are **9** and **10**, which although topologically different, possess similar potent receptor binding affinities. However, pharmacokinetic analyses performed

on these tetrahydronaphthalenes revealed remarkably improved oral bioavailability in the rat for cis analogue **9** ($F = 60\%$), compared to trans analogue **10** ($F = 16\%$) and raloxifene **2** ($F = 10\%$). The markedly improved oral bioavailability of **9** is attributed to resistance to intestinal wall glucuronidation, as evidenced by the low levels of the glucuronide conjugate of **9** detected in the portal vein after oral dosing. These observations have led to the proposal of a structural model **11** predictive for resistance to gut wall glucuronidation, the key structural feature being nonplanar topology. Only **9** with its axial/equatorial disposition of pendant aryl groups is consistent with our model. It should be noted that steric bulk must be in close proximity to the plane of the fused bicyclic aromatic system; although raloxifene, which is extensively glucuronidated, is also nonplanar based on X-ray structural studies, its out of plane bulk is more distant.[20] More evidence for our hypothesis came from studies on a different class of SERM, exemplified by benzopyran **12**,[21] which possesses a topological motif similar to our model **11**. On comparison to **2**, **12** exhibited less glucuronidation, which translated to significantly improved oral bioavailability and in turn better in vivo potency (Table 1).



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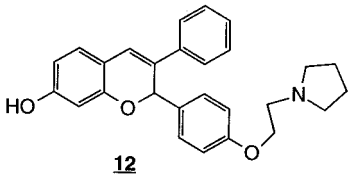
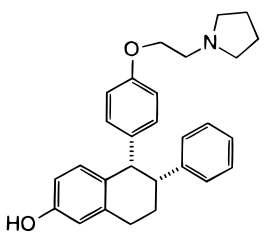


12

Selective crystallization of the (*R*)-(−)-1,1′-binaphthyl-2,2′-diyl hydrogen phosphate diastereomeric salts of **9** resulted in the dextrorotatory enantiomer **13** and the levorotatory enantiomer **14**. The receptor binding assay (Table 1) indicated that **14** was significantly more potent (11.3 versus 270.0 nM). In oral bioavailability studies, likewise **14** proved superior to its enantiomer (62% versus 29%); we ascribe this difference to mediation by the well precedented process of enantioselective glucuronidation.[22] The absolute configuration of the active enantiomer was determined through an X-ray diffraction study[23,24] of the corresponding hydrochloride salt and was found to correspond to an estradiol-like absolute configuration at C-1.



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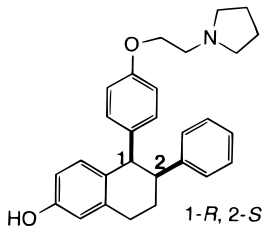

14

In the OVX rat model, **14** (Table 1) completely prevented lumbar vertebral bone loss ($ED_{50} < 1$ μg/kg/day, po), compared to 17α-ethynylestradiol (EE) ($ED_{50} = 10$ μg/kg/day) and raloxifene **2** ($ED_{50} = 500$ μg/kg/day). In addition, a reduction in total serum cholesterol was observed at a potency level similar to that of EE ($ED_{50} = 10$ μg/kg/day). Thus estrogen-like agonism with respect to both efficacy and potency for not only cardiovascular, but also bone endpoints is observed with **14**. Therefore, our expectation that addressing glucuronidation would afford a breakthrough in potency is justified.

The issue of tissue selectivity among estrogen target organs is key for this class of agents. In OVX rat studies (28 days, 1−1000 μg/kg/day), no uterine hypertrophic effects were observed;[25c] in contrast, ethynylestradiol and to a lesser extent nafoxidene exhibit uterotrophic behavoir in similar studies.[9a] In addition with the estrogen dependent MCF-7 breast cancer cell line, where estradiol exhibits stimulatory behavoir, **14** was determined to be an extremely potent antagonist to growth ($IC_{50} = 0.05$ nM).[28]

In conclusion, our studies culminated in the discovery of CP-336156 (**14**), a nonsteroidal estrogen agonist/antagonist with excellent oral bioavailability, which is as potent and efficacious as estrogen at preventing bone loss and lowering total serum cholesterol in rats. In addition, estrogen-like proliferative effects on breast and uterine tissue were not observed. The superior oral kinetics, achieved by minimizing intestinal glucuronidation through the application of our structural model, translated into a breakthrough for in vivo potency. Currently **14** is undergoing clinical evaluation in postmenopausal women.

Supporting Information Available: X-ray crystallographic information for CP-336156 (9 pages). Ordering information is given on any current masthead page.

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(23) X-ray data was acquired and the structure solved by Dr. J. Bordner of Pfizer Central Research: space group $P2_12_12$; cell dimensions $a = 10.373(1)$ Å, $b = 13.397(1)$ Å, $c = 17.499(1)$ Å, $\alpha = 90.0°$, $\beta = 90.0°$, $\gamma = 90.0°$, $v = 2431.8(3)$ Å^3, R index = 6.10%.

(24) All new compounds exhibited consistent spectral data and CHN analyses.

(25) The in vivo procedures employed for the OVX studies are described in detail in ref 5. There were four dose levels (1, 10, 100, and 1000 μg/kg/day) with 10 animals in each group. (a) The OVX procedure resulted in a 50% decrease in BMD. The ED_{50} is defined as the half efficaceous dose for restoration of BMD to sham-operated level from the vehicle-treated OVX control. The standard deviation for BMD at each dose level varied by no more than 2% of the mean ($n = 10$). The positive control was EE (30 μg/kg/day) which completely restored BMD to sham level (significance level: $p < 0.05$); the range of individual ED_{50}'s ($n = 5$) used to calculate the cited value varied by no more than a factor of 10. (b) Total serum cholesterol in the vehicle-treated OVX group was signficantly increased compared to sham control. The ED_{50} is defined as the half efficaceous dose for restoration of total serum cholesterol to sham-operated level from the vehicle-treated OVX control. The standard deviation for total serum cholesterol at each dose level varied by no more than 10% of the mean ($n = 10$). The positive control was EE (30 μg/kg/day) which decreased cholesterol levels to sham value (significance level: $p < 0.05$); the range of individual ED_{50}'s ($n = 5$) used to calculate the cited value varied by no more than a factor of 10. (c) The OVX procedure resulted in a 66% reduction in uterine weight. EE (30 μg/kg/day) increased the uterine weight from OVX to the level of sham control (significance level: $p < 0.05$). Drug performance assessment was based on measurement of uterine weight and observations of histology.

(26) The oral bioavailability of ethynyl estradiol was not measured; a value of 15−25% has been reported. See: Bawarshi-Nassar, R. N.; Hussain, A.; Crooks, P. A. Nasal Absorption of 17α−ethynyloestradiol in the Rat. *J. Pharm. Pharmacol.* **1989**, *41*, 214−215.

(27) In vivo studies were not performed. For comparison purposes, we cite published rat OVX data on nafoxidene, which appears to be less potent than raloxifene for restoration of BMD. See ref 9a.

(28) The procedure for growing the cells is described in ref 11; instead of IGF-I or EGF, fetal bovine serum was used to stimulate cell growth. The assay was conducted for 5 days in absence of exogenously added estradiol **1** and antiproliferative effects were measured by direct cell counting compared to vehicle-treated control (significance: $p < 0.05$). The standard deviation of the mean for % growth inhibition at each dose level (10^{-12} through 10^{-6} M) varied by no more than 10% of the mean ($n = 5$). Inactive enantiomer **13** exhibited no effect on MCF-7 proliferation, and active enantiomer **14** exhibited no effect on growth of the estrogen receptor negative MDA-MD231 cell line (10^{-6} M).

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