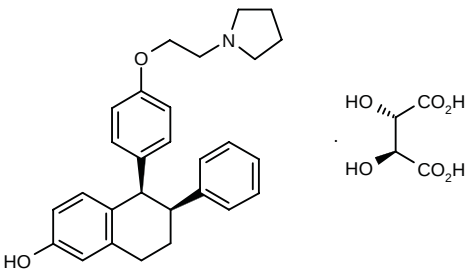
Drugs of the Future 1998, 23(10): 1066-1070

CCC: 0377-8282/98

CP-336156

Treatment of Osteoporosis
Estrogen Receptor Modulator

(–)-(5*R*,6*S*)-6-Phenyl-5-[4-[2-(1-pyrrolidinyl)ethoxy]phenyl]-5,6,7,8-tetrahydronaphthalen-2-ol (–)-D-tartrate salt



$C_{28}H_{31}NO_2.C_4H_6O_6$ Mol wt: 563.6433

CAS: 190791-29-8
CAS: 180915-85-9 (as hydrochloride)
CAS: 180916-16-9 (as free base)

EN: 236902

Synthesis

The condensation of 6-methoxy-1-tetralone (I) with 1-[2-(4-bromophenoxy)ethyl]pyrrolidine (II) by means of $CeCl_3$ and butyl lithium in THF gives 1-[2-[4-(6-methoxy-3,4-dihydronaphthalen-1-yl)phenoxy]ethyl]pyrrolidine (III), which is brominated with pyridinium bromide perbromide in THF yielding the bromo derivative (IV). The condensation of (IV) with phenylboronic acid (V) by means of tetrakis(triphenylphosphonium)palladium/Na_2CO_3 in THF affords 1-[2-[4-(6-methoxy-2-phenyl-3,4-dihydronaphthalen-1-yl)phenoxy]ethyl]pyrrolidine (nafoxidene) (VI) (1, 2). Nadoxifene is reduced with H_2 over Pd/C in ethanol/methanol giving (±)-*cis*-1-[2-[4-(6-methoxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenoxy]ethyl]-pyrrolidine (VII). The demethylation of (VII) with boron tribromide in dichloromethane or 48% HBr in hot acetic acid yields (±)-*cis*-6-phenyl-5-[4-[2-(1-pyrrolidinyl)ethoxy]-phenyl]-5,6,7,8-tetrahydronaphthalen-2-ol (VIII) (1-3), which is submitted to optical resolution by chromatography over a Chiralcell OD column in 99.95% (ethanol/heptane 5:95)/0.05% diethylamine (1), by crystallization with (–)-(*R*)-1,1'-binaphthyl-2,2'-diyl hydrogenphosphate (*R*-binaph) (1, 3) or by crystallization with D-tartaric acid (2). Scheme 1.

Description

Hydrochloride, m.p. 260-3 °C, $[\alpha]_D$ –330.6° (c 0.05, CH_2Cl_2) (1).

Introduction

Assuming that the average life span is 80 years, American women spend one-third of their lives in a postmenopausal state, with approximately 1/4 women over the age of 65 developing osteoporosis. The postmenopausal state is accompanied by a reduction in plasma 17β-estradiol to levels of < 10% of premenopausal values (4). The low bone mineral density resulting from estrogen deprivation is responsible for osteoporotic bone fractures and the significant morbidity experienced by women, often resulting in institutionalization (5). Research efforts have therefore focused on the therapeutic management of the postmenopausal state in an attempt to improve women's health and the quality of life.

Estrogen replacement therapy has been used primarily to prevent perimenopausal symptoms in addition to preventing and treating chronic postmenopausal cardiovascular disease and osteoporosis. Although many beneficial effects of estrogen replacement therapy have been described, including improvements in short-term memory and cognitive function (6, 7) and decreases in the risk of coronary disease (8), significant and serious adverse effects have also been reported to accompany this form of therapy. Evidence suggests that estrogen replacement therapy can include negative side effects such as proliferation of uterine and breast tissue (9). Thus, research efforts have focused on the design of novel, selective estrogen receptor modulators which exhibit the positive effects through estrogen receptor agonism on desired vasomotor and cardiovascular systems and liver and bone, while having minimal agonist and/or estrogen antagonist activity in breast and uterine tissues.

Nonsteroidal antiestrogen compounds such as tamoxifen, a triphenylethylene estrogen antagonist, have been developed as a treatment for breast cancer (10). Although significant reductions in cardiovascular disease

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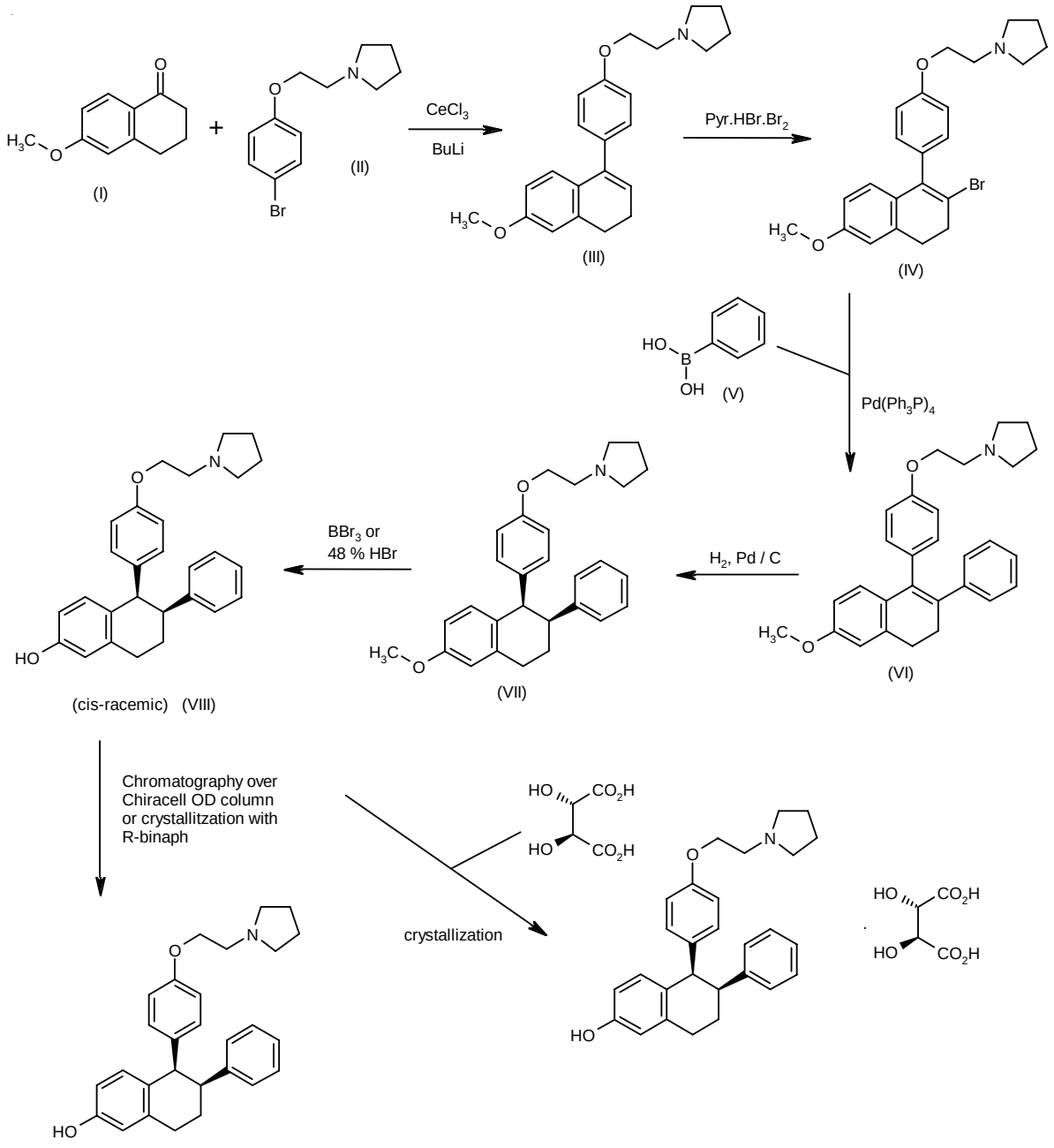
Scheme 1: Synthesis of CP-336156



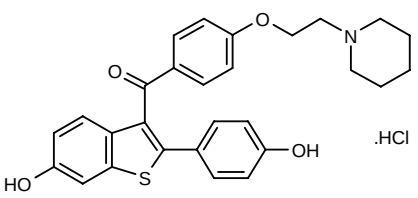
and prevention of breast cancer were reported from trials, tamoxifen therapy was also responsible for an increased risk of endometrial cancer (11). A class of drugs called selective estrogen receptor modulators (SERMs) has been identified and shown to be effective alternatives to estrogen replacement therapy. In this regard, tamoxifen is considered a SERM but only with respect to breast tissue. Another SERM, raloxifene (Evista®; Lilly) was first launched this year in the U.S., with subsequent introductions in Mexico, Brazil, Israel, Argentina, Lebanon and Peru, and was recently approved by the E.C. for the prevention of vertebral fractures in postmenopausal women at increased risk for osteoporosis. Approval was based on the 38-52% reduction in spinal fractures observed in treated women in the ongoing MORE (Multiple Outcomes of Raloxifene Evaluation) trial involving more than 7700 woman with osteoporosis (12).

Table I: Estrogen receptor modulators launched and in clinical trials.

Launched
1. Raloxifene HCl (*Evista*)
   Lilly
   L-1998

Clinical Trials
2. CP-336156
   Pfizer
3. Droloxifene
   Pfizer
4. Idoxifene
   SmithKline Beecham
5. Levormeloxifene*
   Novo Nordisk
6. LY-353381.HCl
   Lilly

Preclinical Testing
7. GW-5638
   Glaxo Wellcome
8. LY-357489
   Lilly



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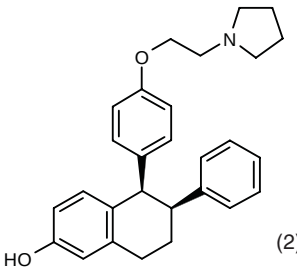

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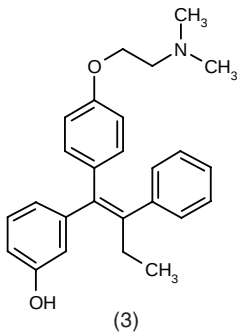

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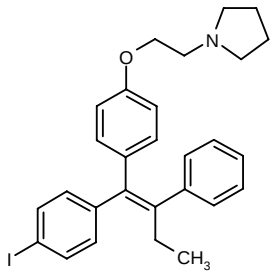

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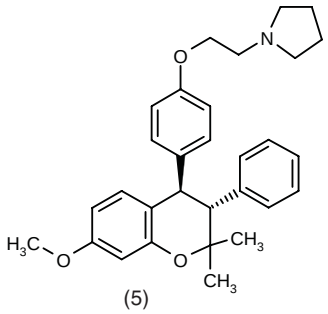

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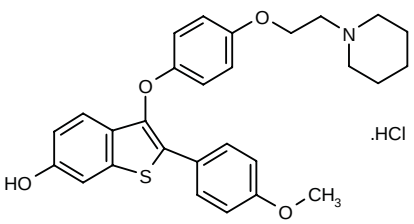

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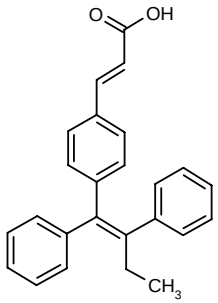

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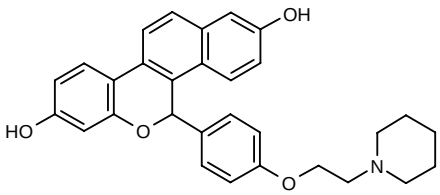

(8)

*Development recently discontinued. Source: Prous Science Ensemble database.

Results from ongoing clinical trials indicate that idoxifene (SmithKline Beecham) is demonstrating excellent progress as a treatment and/or prevention of postmenopausal diseases. Studies evaluating idoxifene in osteopenic postmenopausal woman have described reductions in markers of bone resorption and formation similar to those observed with estrogen without concomitant estrogenic effects on the endometrium (13). Similarly, the development of drolixifene, an estrogen agonist/antagonist from Pfizer, has been accelerated based on interim clinical preliminary results demonstrating the efficacy and safety of this compound for the prevention of osteoporosis (14). CP-336156, a third-generation estrogen receptor agonist/antagonist identified by Pfizer in collaboration with Ligand and now being developed by Pfizer alone, is currently under phase III trials (15).

Several other SERMs are currently under various stages of clinical evaluation, including LY-353381 hydrochloride and LY-357489 (Lilly) and GW-5638 (Glaxo Wellcome) (Table I), while new compounds of this class continue to appear in the patent literature (Table II).

Table II: Estrogen receptor modulators from recent patent literature.

Lilly	
EP 731098	EP 832882
EP 729964	EP 832888
EP 731101	EP 832890
EP 729951	EP 838464
EP 733620	EP 838461
EP 791590	EP 838459
EP 791591	US 5552401
EP 816360	WO 9628146
EP 818453	WO 9628155
EP 826670	WO 9713764
EP 826680	WO 9708187
EP 826683	WO 9706796
EP 831089	WO 9704778
EP 827959	WO 9701549
EP 823437	WO 9741851
EP 832883	WO 9808797
EP 832881	Pfizer
EP 832880	WO 9621656

Source: Prous Science Ensemble database.

Table III: Receptor affinity of selected SERMs.

Compound	IC_{50} (nM)	References
17β-Estradiol	0.354 ± 0.69	3
CP-336156	11.3 ± 3.46	3
Droloxifene	~11	24
Nafoxidene	40.9 ± 9.32	3
Raloxifene	1.85 ± 0.28	3
Tamoxifene	272	24

Source: Prous Science MFLine database.

Levormeloxifene, a partial estrogen receptor agonist and member of the SERM family of compounds previously in phase III trials at Novo Nordisk, was recently discontinued as a treatment for osteoporosis due to increased incidences of adverse gynecological effects, specifically urinary incontinence and uterovaginal prolapse. Although levormeloxifene demonstrated desirable effects on bone and plasma lipid levels at the doses used in the phase III trials, the risk/benefit profile was considered unfavorable for an osteoporosis indication (16).

Pharmacological Actions

CP-336156 is a novel orally active nonsteroidal estrogen agonist/antagonist under clinical evaluation for the prevention and treatment of osteoporosis in postmenopausal women. *In vitro* binding studies in rat tissues have demonstrated that CP-336156 has an IC_{50} value reflecting estrogen receptor affinity of 11.3 ± 3.46 nM, as compared to IC_{50} values of 0.354 ± 0.69 and 1.85 ± 0.28 nM, for 17β-estradiol and raloxifene, respectively (3). Table III shows the affinity for the estrogen receptor of selected SERMs. Other studies have shown that CP-336156 displays high affinity and selective binding to the human estrogen receptor α with half-inhibition occurring at a concentration of 1.5 nM and similar to a half-inhibition concentration of 4.8 nM observed for estradiol (17).

Further examination *in vitro* demonstrated that rat bone marrow osteoclast cultures exposed to CP-366156 (10 nM for 3 h) responded with a dose-dependent reduction in the population of tartrate-resistant acid phosphatase-positive multinuclear cells, which increases following ovariectomy, and a 2- to 3-fold increase in the number of apoptotic cells as compared to vehicle-treated cultures. In addition, p53 expression was enhanced in apoptotic cells, suggesting that apoptosis may be the mechanism of action responsible for the estrogenic activities of CP-336156. Results also revealed that 15-25% of the cells undergoing apoptosis in CP-366156-treated cultures expressed CD61, indicating that some of the apoptotic bone marrow cells were of osteoclastic lineage. *In vitro* experiments exposing an estrogen-dependent breast cancer cell line (MCF-7) to estradiol resulted in induction of proliferative activity, while CP-336156 treatment potently antagonized growth (IC_{50} = 0.05 nM) (3).

In *in vivo* pharmacological studies, 17α-ethynylestradiol treatment (30 μg/kg/day for 3 or 28 days in immature and aged rats, respectively) significantly increased uterine dry weight by 57-58% in both aged and immature rats, whereas no uterotrophic activity was observed in CP-336156-treated immature and aged female rats administered doses of 0.1-100 μg/kg/day p.o. for 3 days and 10 or 100 μg/kg/day for 28 days, respectively. In addition, total serum cholesterol was reduced by 54% and 73%, respectively, with administration of 10 and 100 μg/kg/day of CP-336156 in aged rats. Weight loss in aged rats treated with the compound was due entirely to loss of fat body mass; no alterations in lean body mass were noted.

When ovariectomized rats were administered CP-336156 (1, 10, 100 or 1000 μg/kg/day for 28 days), ovariectomy-induced lumbar vertebral bone loss was prevented with an ED_{50} of < 1 μg/kg/day, which was much more potent than the activity seen in the same model with 17α-ethynylestradiol (ED_{50} = 10 μg/kg/day) and raloxifene (ED_{50} = 500 μg/kg/day). CP-336156-treated ovariectomized rats displayed a dose-dependent inhibition of ovariectomy-induced increases in body weight gain. Furthermore, the 66% decrease in uterine weight observed with ovariectomy and inhibited by 17α-ethynylestradiol was not affected by CP-336156 (17).

Several patents have been published claiming the use of CP-336156 in various pathological conditions such as osteoporosis (18, 19), atherosclerosis (20), immune, gynecological and dermatological disorders (21) and Alzheimer's disease, uterine fibrosis, autoimmune diseases and premenstrual and premenopausal syndromes (22).

Pharmacokinetics

Through minimization of intestinal glucuronidation, CP-366156 exhibits excellent pharmacokinetics and high oral bioavailability, making it potentially superior to estrogen for the treatment and/or prevention of postmenopausal osteoporosis. Pharmacokinetic studies have demonstrated that the respective oral bioavailabilities of CP-336156 in the rat and cynomolgus monkey were 62 ± 18% and 45%, as compared to 10 ± 2.5% and 5 ± 0.4% for raloxifene (3).

Clinical Studies

Phase III clinical trials evaluating CP-336156 are in progress (23).

Manufacturer

Pfizer, Inc. (US), identified through a collaboration with Ligand.

References

1. Cameron, K.O., Jardine, P.A. (Pfizer, Inc.). *Estrogen agonists/antagonists.* EP 802910, JP 98503215, US 5552412, WO 9621656.

2. Chiu, C.K., Meltz, M. (Pfizer, Inc.). *(–)-cis-6(S)-Phenyl-5(R)-[4-(2-pyrrolidin-1-ylethoxy)phenyl]-5,6,7,8-tetrahydronaphthalen-2-ol D-tartrate.* WO 9716434.

3. Rosati, R.L., Da Silva Jardine, P., Cameron, K.O. et al. *Discovery and preclinical pharmacology of a novel, potent, nonsteroidal estrogen receptor agonist/antagonist, CP-336156, a diaryltetrahydronaphthalene.* J Med Chem 1998, 41: 2928-31.

4. Kauffman, R.F., Bryant, H.U. *Selective estrogen receptor modulators.* Drug News Perspect 1995, 8: 531-9.

5. Peck, W.A., Riggs, B.L., Bell, N.H. et al. *Research directions in osteoporosis.* Am J Med 1988, 84: 275-82.

6. Furuhjelm, M., Fedor-Freybergh, P. *The influence of estrogens on the psyche in climacteric and post-menopausal women.* In: Consensus on Menopause Research, P.A. Van Keep, R.B. Greenblatt, M.M. Albeaux-Fernet (Eds.), University Park Press, Baltimore, 1976, 84-93.

7. Sherwin, B.B. *Estrogen and/or androgen replacement therapy and cognitive functioning in surgically menopausal women.* Psychoneuroendocrinology 1988, 13: 345-57.

8. Stampfer, M.J., Col*ditz, G.A. Estrogen replacement therapy and coronary disease: A quantitative assessment of the epidemiological evidence.* Prev Med 1991, 20: 47-63.

9. Barrett-Connor, E. *Hormone replacement and cancer.* Br Med J 1992, 48: 345-55.

10. Early Breast Cancer Trialists' Collaborative Group. *Systemic treatment of early breast cancer by hormonal, cytotoxic, or immune therapy.* Lancet 1992, 339: 71-85.

11. Fisher, B., Constantino, J.P., Redmond, C.K., Fisher, E.R., Wickerham, D.L., Cronin, W.M. *Endometrial cancer in tamoxifen-treated breast cancer patients: Findings from the National Surgical Adjuvant Breast and Bowel Project.* J Natl Cancer Inst 1994, 86: 527-37.

12. *EC approval granted for Lilly's SERM, Evista.* Daily Essentials August 17, 1998.

13. *Idoxifene: Another SERM with clinical potential in post-menopausal disorders.* Daily Essentials July 14, 1998.

14. *Pfizer updates development pipeline.* Daily Essentials January 26, 1998.

15. *Spotlight on selective estrogen receptor modulators.* Daily Essentials November 21, 1997.

16. *Novo Nordisk discontinues development of osteoporosis drug.* Daily Essentials September 28, 1998.

17. Ke, H.Z., Paralkar, V.M., Grasser, W.A. et al. *Effects of CP-336,156, a new, nonsteroidal estrogen agonist/antagonist, on bone, serum cholesterol, uterus, and body composition in rat models.* Endocrinology 1998, 139: 2068-76.

18. Ke, H.Z., Thompson, D.D. (Pfizer, Inc.). *Combination therapy for osteoporosis.* WO 9731640.

19. MacLean, D.B., Thompson, D.D. (Pfizer, Inc.). *Combination therapy for osteoporosis.* EP 792645, JP 98007562.

20. Aiello, R.J. (Pfizer, Inc.). *Atherosclerosis treatment.* EP 842661.

21. MacLean, D.B., Thompson, D.D. (Pfizer, Inc.). *Use of estrogen antagonists and estrogen agonists in inhibiting pathological conditions.* EP 792641, JP 98007563.

22. MacLean, D.B., Thompson, D.D. (Pfizer, Inc.). *Method of treating conditions with estrogen agonists.* EP 792642, JP 98007564.

23. *CP-336156 development status.* Pfizer, Inc. Company Communication October 9, 1998.

24. Martel, C., Provencher, L., Li, X., St. Pierre, A., Leblanc, G., Gauthier, S., Mérand, Y., Labrie, F. *Binding characteristics of novel nonsteroidal antiestrogens to the rat uterine estrogen receptors.* J Steroid Biochem Mol Biol 1998, 64: 199-205.