# *Articles*

## Selective Estrogen Receptor Modulators with Conformationally Restricted Side Chains. Synthesis and Structure−Activity Relationship of ERα-Selective Tetrahydroisoquinoline Ligands

Johanne Renaud,*,† Serge François Bischoff,‡ Thomas Buhl,† Philipp Floersheim,‡ Brigitte Fournier,† Martin Geiser,§ Christine Halleux,† Joerg Kallen,§ Hansjoerg Keller,† and Paul Ramage§

*Novartis Institute for Biomedical Research, WKL-136.6.81, CH-4002 Basel, Switzerland*

*Received July 1, 2004*

We disclose herein the discovery of estrogen receptor α (ERα) selective estrogen receptor modulators (SERMs) of the tetrahydroisoquinoline series that incorporate novel conformationally restricted side chains as replacement of the aminoethoxy residue typical of SERMs. Molecular modeling studies used in conjunction with the X-ray crystal structure of the ERα ligand binding domain (LBD) with raloxifene (**7**) suggested a diazadecaline moiety as a viable mimic of the SERM side chain. On the basis of this knowledge, the piperidinylethoxy moiety of our lead compound **60** was replaced by a diazadecaline subunit, providing the novel tetrahydroisoquinoline **29**. In addition to exhibiting a binding affinity to ERα and antagonistic properties in the estrogen response element and MCF-7 assays similar to those of the parent compound **60**, ligand **29** showed a reduced agonist behavior in the MCF-7 assay in the absence of 17$\beta$-estradiol. These data point toward the fact that **29** may have a potential for breast cancer prevention/treatment in vivo, a feature which is particularly attractive in the quest for safe alternatives to hormone replacement therapy. In a pharmacokinetic experiment carried out in rats, **29** displayed an interesting profile, with a bioavailability of 49%. We also disclose the X-ray crystal structure of **29** in complex with ERα-LBD, which reveals the preferred configurations of **29** at the two chiral centers and the details of its interactions with the receptor. Finally, our structure−activity relationship studies show that other analogues bearing constrained side chains retain potency and antagonist activity and that a 3-OH substituted phenyl D-ring increases the selectivity of a set of piperazinyl-containing ligands in favor of ERα over ER$\beta$.

### Introduction

A number of endogenous estrogens are known, and three of them, 17$\beta$-estradiol (**1**), estrone (**2**), and estriol (**3**) (Figure 1), are found in greater concentrations in female plasma.[1] The most important endogenous estrogen is 17$\beta$-estradiol (**1**), which exerts its action on female reproductive functions and on numerous tissues,[1] including bone.[2] The efficacy of estrogens in the prevention and treatment of postmenopausal osteoporosis has been demonstrated by various studies.[3−5] Estrogens are typically administered in combination with progestins to women with an intact uterus to prevent endometrial hyperplasia. Recently, the Women's Health Initiative study has shown that the incidence of fractures is reduced in women taking the estrogen−progestin combination.[6] However, this study has also demonstrated that hormone replacement therapy (HRT) leads to increased risks of breast cancer (26%), heart attacks (29%), strokes (41%), blood clots (double rate), and total cardiovascular disease (22%).[6,7] The current concerns regarding treatment with estrogens are having an impact on women's willingness to take HRT, with the risks associated with the treatment overriding the benefits. In that context, an agent capable of preventing or treating postmenopausal osteoporosis (PMO) but not associated with the safety concerns of estrogens and progestins would be an important addition to the portfolio of menopausal therapies.

In recent years, substantial efforts have been put into the discovery of estrogen surrogates with better benefit−risk profiles. Agents that have the potential to act as estrogen in some tissues while antagonizing its action in others are known. The acronym SERMs—selective estrogen receptor modulators—has been ascribed to such compounds.[8] In fact, several SERMs are currently in advanced clinical trials (lasofoxifene (**4**)[8−10] and bazedoxifene (**5**)[8,11]) or on the market (tamoxifen (**6**) for the treatment of hormone-dependent breast cancer[8] and raloxifene (**7**) for prevention and treatment of osteoporosis[12,13]) (Figure 1).

Members of the SERM class are characterized by at least two common structural features: a phenolic hydroxyl group that is required for binding to the estrogen receptor α (ERα) or $\beta$ (ER$\beta$) and a side chain containing

* To whom correspondence should be addressed. Phone: +41 61 696 5399. Fax: +41 61 696 6071. E-mail: johanne.renaud@pharma.novartis.com.
† Arthritis and Bone Metabolism Therapeutic Area.
‡ Nervous System Therapeutic Area.
§ Central Technologies.

10.1021/jm040858p CCC: $30.25 
Published on Web 12/22/2004

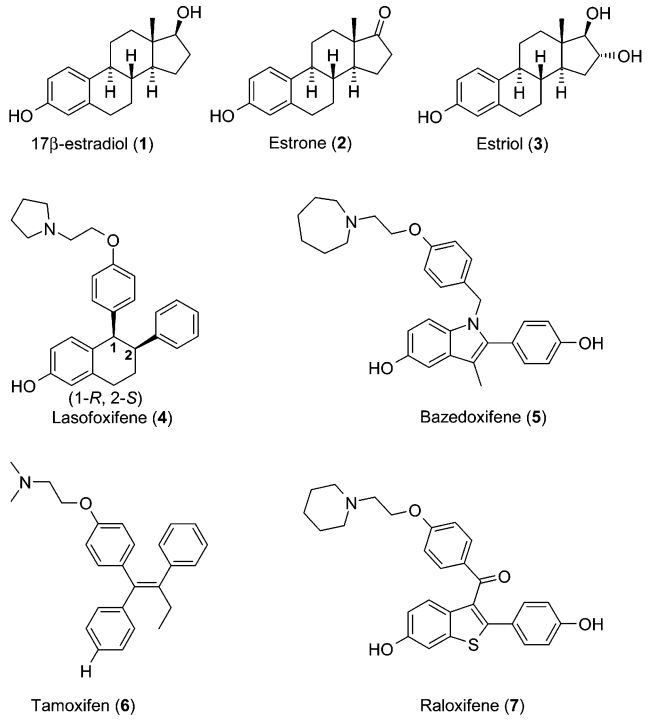



**Figure 1.** Structures of estrogens and SERMs.

a basic functionality, which confers SERMs their antagonistic properties in some tissues. The spatial orientation of the 2-aminoethoxyphenyl side chain relative to the central core of the molecule has been postulated to influence the endometrial properties of SERMs in women.[14] For example, tamoxifen (**6**), which has a relatively flat structure, is estrogenic in the uterus and has been shown to increase the risk of endometrial cancer. However, raloxifene (**7**), which is not associated with uterine side effects in humans, features a side chain oriented orthogonally to the plane of its benzothiophene framework.[14]

The mechanisms by which SERMs exert their tissue-specific actions are only partly elucidated.[15−17] SERMs bind with different affinities and selectivities to the two currently known estrogen receptors, ERα and ER$\beta$. The two receptors, which act as ligand-activated transcription factors, are found in a wide variety of tissues and show a distinct but also overlapping distribution pattern.[18−20] They regulate gene transcription either directly by binding, primarily as homo- or heterodimers, to the estrogen response element (ERE) or through protein−protein interaction with other transcription factors such as AP-1 or NF-$\kappa$B.[19] Gene transcription is stimulated via interactions that involve the receptor, chromatin complexes, and coactivators at the ER-activated promoters.[21,22] Conversely, repression of transcription occurs through recruitment of corepressors by the antagonist-bound ER.[21,22] Each SERM may induce a different conformation of the ER and alter the interaction of the ligand-bound complex with a given set of coregulators. In addition, the differential expression of ERα and ER$\beta$ or of coregulators in various tissues may very well contribute to the formation of specific ER−ligand−coregulator complexes and thus elicit a tissue-specific effect.[15]

Although the relative contributions of ERα and ER$\beta$ to the spectrum of SERMs effects have only been partly studied, there is current evidence pointing toward ERα as occupying an important role in bone remodeling. However, ER$\beta$ may also be a contributor to this process.[23] It is not yet clear what effect an ER subtype-selective ligand would trigger on bone tissue.

Considerable activity in the SERM field has contributed to the development of compounds of diverse molecular architectures. Our interest in this area led us to explore novel side chains because this is a critical moiety of the ligand. The fact that the side chain has a strong impact on the tissue-specific agonist/antagonistic properties of the molecule influences the pharmacological profile of the compound. Particularly, the stimulation of breast and endometrial tissues is a critical safety issue. Except for a report on the significance of specific elements of the aminoethoxy fragment of raloxifene analogues,[24] the effects of modification of the side chain on potency and antagonistic properties of ERα-selective SERMs have not been explored.[25] Herein, we report for the first time new cyclic residues as replacements of the aminoethoxy subunit characteristic of SERMs that retain potency and antagonistic activity. The synthesis and biological evaluation of these novel piperidinyl and piperazinyl derivatives of the tetrahydroisoquinoline series is described below. In addition, the X-ray crystal structure of one potent ligand, the tetrahydroisoquinoline **29**, is disclosed.

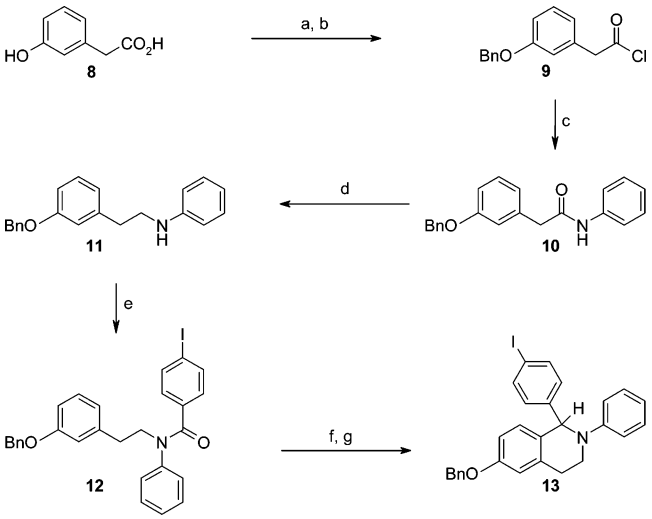
## Chemistry

The tetrahydroisoquinolines were prepared by three different routes, using either the iodophenyl intermediate **13** or bromophenyl derivatives **17a**−**d** as starting material. The syntheses of compounds **13** and **17a**−**d** are outlined in Schemes 1 and 2.

**Synthesis of Intermediate Tetrahydroisoquinoline 13 via the Bischler**−**Napieralski Route.** 3-Hydroxyphenylacetic acid (**8**) was transformed into tetrahydroisoquinoline **13** following a similar strategy as described in the literature for related compounds (Scheme 1).[26] Selective benzylation of 3-hydroxyphenylacetic acid was accomplished readily by trapping the dianion formed upon KOH treatment (2.5 equiv) with benzyl bromide (1.05 equiv).[27] Exposure of 3-benzyloxyphenylacetic acid to $(COCl)_2$ provided the corresponding acyl chloride, which was transformed into amide **10** by reaction with aniline. Reduction of 2-(3-benzyloxyphenyl)-*N*-phenyl-acetamide (**10**) with lithium aluminum hydride (LAH) led to the phenylethylphenylamine derivative **11**. Acylation of this substance with 4-iodobenzoyl chloride gave amide **12**. Ring closure was effected by refluxing compound **12** in $POCl_3$ to generate an intermediate iminium ion, which was reduced with $NaBH_4$ to the iodophenyl intermediate **13** (Scheme 1).

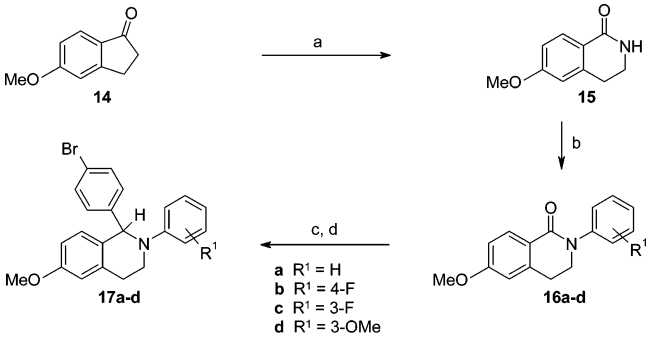
**Synthesis of Intermediate Tetrahydroisoquinolines 17a**−**d via the Schmidt Rearrangement.** The bromophenyl intermediates **17a**−**d** were assembled from 5-methoxyindanone (**14**) in four steps (Scheme 2), following a synthetic route that is shorter and is higher yielding than that described above. In addition, a broad diversity of structures could be rapidly synthesized by this flexible approach. Large quantities of bicyclic lactam **15** were accessed via the Schmidt rearrangement of indanone **14**, according to a published procedure.[28,29] The isoquinolin-1-one **15** proved to be a versatile

**Scheme 1.** Bischler−Napieralski Route to Tetrahydroisoquinoline Derivative **13**[a]




[a] Reagents: (a) benzyl bromide (1.05 equiv), KOH (2.5 equiv), NaI (0.025 equiv), EtOH (0.26 M), reflux, 16 h; HCl, 93%; (b) $(COCl)_2$, (1.5 equiv), $CH_2Cl_2$ (0.5 M), room temperature, 5 h, 99%; (c) $PhNH_2$ (1.5 equiv), $Na_2CO_3$ (3 equiv), PhH (0.1 M), reflux, 6 h, 61%; (d) lithium aluminum hydride (5 equiv), dioxane−$Et_2O$ (2:3), 35 °C, 17 h, 78%; (e) 4-iodobenzoyl chloride (1.2 equiv), $Na_2CO_3$ (3 equiv), benzene (0.1 M), reflux, 1.5 h, 69%; (f) $POCl_3$, reflux, 18 h; KI; (g) $NaBH_4$ (2.2 equiv), MeOH (0.1 M), room temperature, 4 h, 73% over 2 steps.

**Scheme 2.** Schmidt Rearrangement Route to Tetrahydroisoquinolines **17a**−**d**[a]

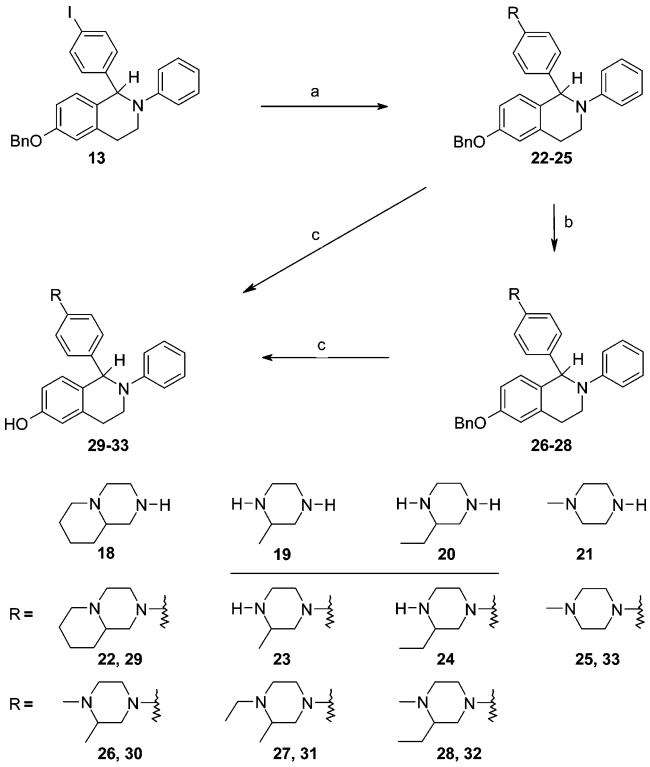



[a] Reagents: (a) ref 28; (b) ArI or ArBr, CuI, $K_2CO_3$, DMF, 150 °C, 72−120 h, 70−95%; (c) [LiArBr] (generated from *p*-dibromobenzene and *n*-BuLi), THF, −78 °C, 1.5−3.5 h; $HClO_4$, 10−15 min; (d) $NaBH_4$, MeOH, room temperature, 15−30 min, 70−86% over two steps.

intermediate of our synthetic scheme. N-Arylation of **15** was effected under Ullmann-type conditions,[30] using the appropriately substituted phenyl iodide or bromide and CuI, to provide compounds **16a**−**d**. These compounds were then converted into the tetrahydroisoquinolines **17a**−**d** by reaction with 4-bromophenyllithium followed by $NaBH_4$ reduction of the intermediate iminium salts.

**Synthesis of Piperazine Derivatives 29−33 via the Hartwig−Buchwald Reaction.** To synthesize piperazine derivatives **29**−**33**, a palladium-catalyzed amination of the aryl iodide **13** served as the key step (Scheme 3). After investigation of a few reaction conditions, $Pd_2dba_3$ (dba = dibenzylidene acetone) was found to catalyze the transformation efficiently, particularly in the presence of (2′-dicyclohexylphosphanyl-biphenyl-2-yl)-dimethylamine[31] in toluene or when used in conjunction with 1,3-bis(2,6-diisopropylphenyl)-4,5-dihydroimidazolium tetrafluoroborate[32−35] in dioxane. In the

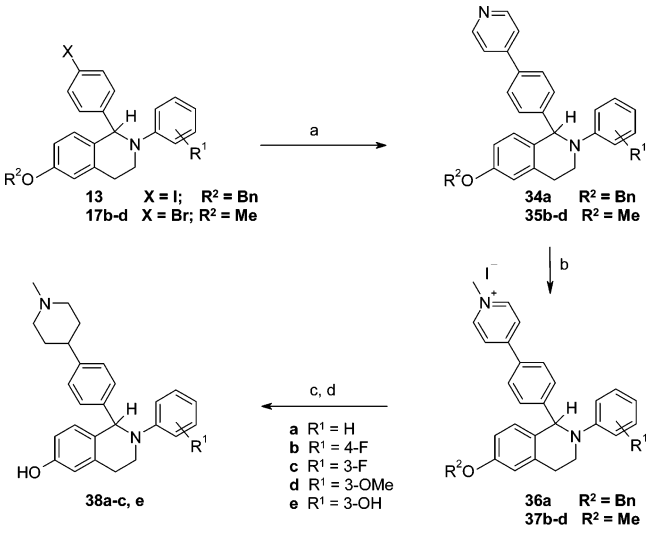
**Scheme 3.** Synthesis of Piperazine Derivatives **29**−**33** via Amination Reaction[a]




[a] Reagents: (a) for the preparation of **22** and **24**, procedure A: **18** or 2-ethyl-piperazine (**20**),$^t$BuOK, $Pd_2(dba)_3$, (2′-dicyclohexylphosphanyl-biphenyl-2-yl)-dimethylamine, PhMe, 80−85 °C, 12/19 h, 53/74%. For the preparation of **23**, procedure B: 2-methylpiperazine (**19**), $^t$BuOK, $Pd_2(dba)_3$, 1,3-bis(2,6-diisopropylphenyl)-4,5-dihydroimidazolium tetrafluoroborate,dioxane, 27 °C, 40 h; 40 °C, 4 h, 61%. For the preparation of **25**, procedure C: 4-methylpiperazine (**21**), $^t$BuOK, $Pd_2(dba)_3$, (±)-BINAP, anhydrous THF, reflux, 38 h; 53%. (b) For the preparation of **26**: 37% aqueous HCHO, AcOH, MeOH, 80 °C, 1 h; $NaBH_3CN$, $CH_2Cl_2$; 0 °C, 1 h, 81%. For the preparation of **27**: $CH_3CHO$, AcOH, $NaBH(OAc)_3$, $Cl(CH_2)_2Cl$, room temperature, 16 h, 52%. For the preparation of **28**: 37% aqueous HCHO, AcOH, $NaBH(OAc)_3$, $Cl(CH_2)_2Cl$, room temperature, 1 h, 86%. (c) 2:1 or 5:3 dioxane/concentrated HCl, 90 °C, 2−2.5 h, 34−73%.

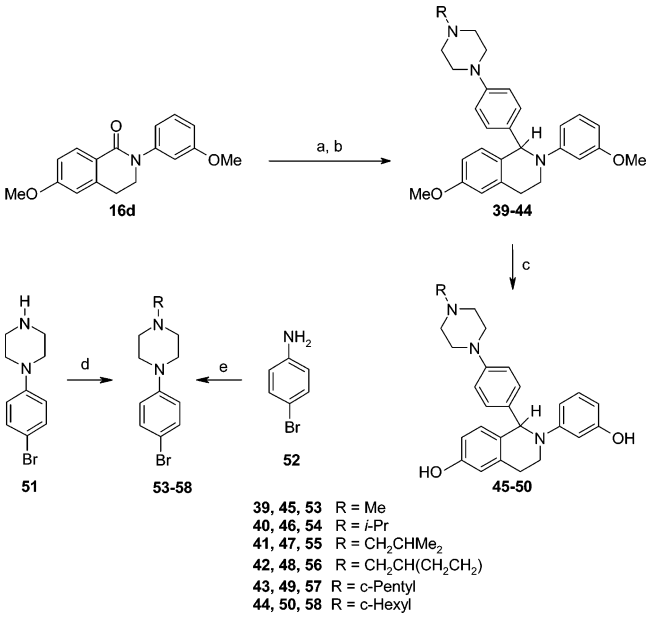
latter case, the reaction could be carried out at a temperature reduced to 40 °C. When BINAP was employed as the ligand, the coupling reactions proceeded, but the yields were generally lower. $^t$BuOK was found to be a suitable base for all cases. By use of the appropriate piperazines **18**−**21**, the analogues **22**−**25** were synthesized in 53−74% yield from **13**. The coupling of 2-methyl-piperazine (**19**) and 2-ethyl-piperazine (**20**) with **13** proceeded regioselectively via reaction of the least hindered amine to provide analogues **23** and **24**. The tetrahydroisoquinoline **23** was then converted into the corresponding *N*-methyl piperazine derivative **26** by reaction with HCHO in the presence of AcOH to generate the corresponding iminium intermediate, which was subsequently reduced with $NaBH_3CN$. The ethyl and methyl analogues **27** and **28** were prepared by the method of Abdel-Magid et al.[36] Exposure of **23** to $CH_3CHO$ and **24** to HCHO in the presence of AcOH and $NaBH(OAc)_3$ in $ClCH_2CH_2Cl$ provided the *N*-alkyl piperazine analogues **27** and **28**. Debenzylation of **22**, **25**, and **26**−**28** was achieved by treatment with HCl at 90 °C.

**Scheme 4.** Synthesis of Piperidine Derivatives **38a−c, e** via Suzuki Cross-Coupling Reaction[a]




[a] For the preparation of **35b−d**: **17b−d**, 4-pyridineboronic acid, $PdCl_2(dppf)\cdot CH_2Cl_2$, $K_2CO_3$, toluene/acetone/water (ratios of 3:3:1 or 4:4:1), reflux, 20−78 h, 45−75%. For the synthesis of **34a**: **13**, 4-pyridineboronic acid, $PdCl_2(dppf)\cdot CH_2Cl_2$, CsF, DME, 80 °C, 24 h, 56%. (b) For the syntheses of **36a**, **37b**, and **c:** MeI, DMF, 40 °C, 2 h. For the synthesis of **37d:** MeI, xylene, 140 °C, 2.5 h. (c) $H_2$, $PtO_2$, MeOH or MeOH/THF (4:1 or 1:1), room temperature, 10−45 h, 61−100%. For the reduction of **37d**: $NaBH_4$, MeOH, room temperature, 30 min; $H_2$, $PtO_2$, MeOH, r.t., 20 h, 63%. (d) For the preparation of **38b**, **c**, and **e**: EtSH, $AlCl_3$, $CH_2Cl_2$, room temperature, 2−17 h, 20−55%. For the synthesis of **38a**: 2:1 dioxane/concentrated HCl, 90 °C, 3 h, 37%.

**Scheme 5.** Synthesis of Piperazine Derivatives **45−50** from Lactam **16d**[a]




[a] (a) Phenyllithium reagent (prepared from 1-(4-bromophenyl)-4-alkylpiperazine, *n*-BuLi, THF, −78 °C, 0.5−1 h), −78 °C, 1−2.5 h. For the syntheses of **41**, **43**, and **44**: −78 °C, 10−45 min; −78 °C → room temperature, 40−60 min. (b) $NaBH_4$, MeOH or 8:1 MeOH/$CH_2Cl_2$, room temperature, 15−60 min, 59−87% over two steps. (c) EtSH, $AlCl_3$, $CH_2Cl_2$, room temperature, 0.5−4 h, 45−58%. (d) RCHO or RCOR, $NaBH(OAc)_3$, $ClCH_2CH_2Cl$, room temperature, 2−26 h, 74−99%. (e) $(ClCH_2CH_2)_2N$, THF−acetone−$H_2O$, reflux, 3.5 h, 12%.

**Synthesis of Piperidine Derivatives 38a−c,e via Suzuki Cross-Coupling Reaction.** The approach pursued for the synthesis of piperidine analogues **38a−c** and **e** is outlined in Scheme 4. Palladium-catalyzed coupling of phenyl bromides **17b−d** with 4-pyridineboronic acid was effected in the presence of $K_2CO_3$ in a toluene/acetone/water mixture to provide the pyridine derivatives **35b−d** in 45−75% yield. Compound **34a** was prepared in a similar manner using iodide **13** as the coupling partner. Treatment of **34a** and **35b−d** with MeI in dimethylformamide (DMF) at 40 °C or in xylene at 140 °C provided the pyridinium salts **36a** and **37b−d**. Reduction of these salts, followed by removal of the protecting groups, furnished the desired products **38a−c** and **e**. Debenzylation was effected via acid treatment at 90 °C whereas demethylation was promoted by reaction with $AlCl_3$ in the presence of EtSH.

**Synthesis of Piperazine Derivatives 45−50 from Lactam 16d.** The *N*-alkylpiperazinyl derivatives **45−50** were synthesized via an alternative sequence to that followed for the preparation of analogues **29−33**. This route involved condensation of the appropriate 1-(4-lithiophenyl)-4-alkyl-piperazine with lactam **16d** to generate an iminium derivative that was reduced with $NaBH_4$. The resultant tetrahydroisoquinolines **39−44** were then deprotected under Lewis-acid conditions (Scheme 5). The phenyllithium reagents needed for the transformation of **16d** into **39−44** were generated by metal−halogen exchange of the 1-(4-bromophenyl)-4-alkyl-piperazines **53−58**. 4-Methyl-piperazine reagent **53** was initially synthesized by alkylation of 4-bromophenylamine (**52**) with bis-(2-chloroethyl)methylamine in a low yield. This protocol was clearly suboptimal. The desired product could be obtained, however, in quantitative yield by reductive amination of **51**, carried out in the presence of HCHO, AcOH, and $NaBH_3CN$. The remaining piperazines **54−58** were also prepared via reductive amination of **51** with the appropriate aldehyde or ketone, but this transformation was effected according to the protocol of Abdel-Magid et al.[36]

## Biology

As part of our initial screening strategy, our compounds were tested in three in vitro assays. In a first instance, new derivatives were screened in a [$^3$H]-estradiol radioligand binding assay using recombinant human ERα and ER$\beta$ to select those substances that demonstrate affinity for the target receptor and to assess their selectivity toward one or the other receptor. The compounds were then profiled in a cellular transcription assay using HeLa cells stably transfected with human ERα or ER$\beta$ and estrogen response elements (ERE) upstream of a luciferase gene. In this assay, 17$\beta$-estradiol induces ERE reporter gene activity. Thus, compounds able to inhibit luciferase transcription in the presence of 17$\beta$-estradiol may be classified as antagonists in this cell line. Agonists would activate gene transcription in the absence of estrogen. The ERE cellular assay also allows one to determine the ability of target derivatives to regulate transcription through ERα or ER$\beta$ and thus provides information with respect to the selectivity of the ligand. The third in vitro assay was used as an indicator of the ligand's behavior on tissues/cells affected by estrogen. For this purpose, new compounds were evaluated for their ability to antago-

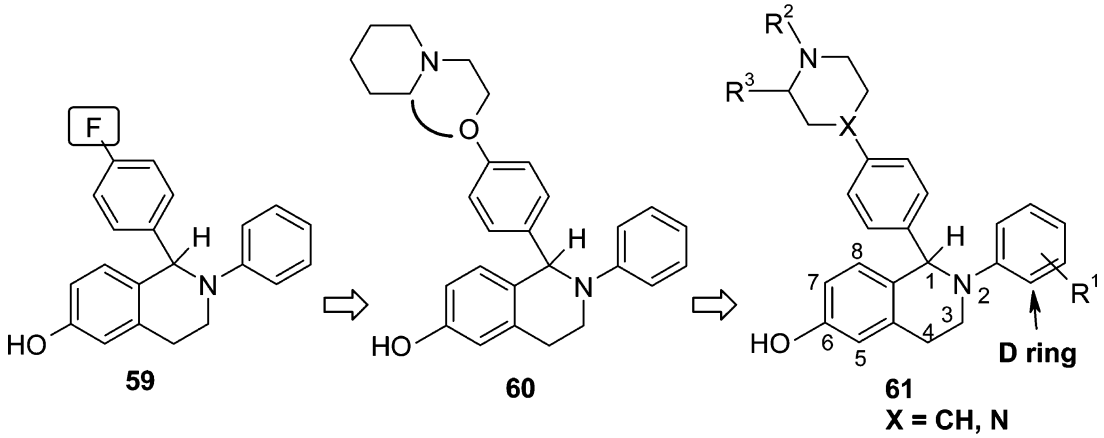



**Figure 2.** Lead identification and optimization.

nize the proliferative action of 17$\beta$-estradiol (**1**) on MCF-7 breast tumor cells. The agonist action of these analogues was also measured in the same cellular assay in the absence of estrogen. Finally, to get early insight into the pharmacokinetic properties of interesting compounds, selected candidates were profiled in rats using cassette dosing experiments.

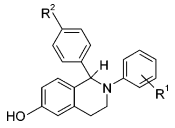
## Results and Discussion

High-throughput screening of our sample collection provided the fluorophenyl derivative **59** as our starting hit (Figure 2). Replacement of fluorine by a piperidinylethoxy side chain provided our lead compound **60**[37] (Figure 2), which displayed a binding affinity comparable to that of raloxifene (**7**) ($IC_{50}$ = 22 and 19 nM, for compounds **7** and **60**, respectively, Table 1, entries 21 and 17). When profiled in the ERE and MCF-7 assays to assess its antagonist activity, **60** potently inhibited luciferase expression in the former assay and cell proliferation in the latter with $IC_{50}$ of 16.5 and 32 nM, respectively (Table 1, entry 17).[37] In the absence of 17$\beta$-estradiol in the MCF-7 proliferation assay, both **60** and raloxifene (**7**) displayed some agonistic effects (37% and 22%, respectively). Having identified a potent lead containing the typical aminoethoxy residue, we set to evaluate ligands containing side chains with reduced conformational flexibility (Figure 2) and to evaluate the effect of these novel moieties on affinity, selectivity, and antagonist potential.

**Design of Cyclic Side Chains: Modeling Studies.** With this aim in mind, we looked for an appropriate rigidification of the amine bearing side chain while potentially maintaining the electrostatic interaction between the alkylammonium nitrogen atom and the carboxylic acid group of Asp351 (Figure 3a). Inspection of the X-ray crystal structure of raloxifene (**7**) bound to the ER$\alpha$ ligand binding domain (LBD)[38] revealed that the O−C−C−N chain adopts a near gauche conformation with a torsion angle that matches the N−C−C−N torsion angles (~60°) of a piperazine in the chair conformation. We saw that substitution of the ether oxygen of raloxifene (**7**) by a nitrogen atom and addition of a methylene group to link the 2-piperidine carbon and the new nitrogen atom leads to a derivative that incorporates an ideal *trans*-diazadecaline system without changing the orientation of the basic nitrogen in the former piperidine ring of raloxifene (**7**) (Figures 2 and 3a). Our studies also indicated that the side chain conformation would be unaltered by replacement of the oxygen by a carbon. On the basis of this knowledge, it appeared that we could make use of an analogous modification in the tetrahydroisoquinoline series, whereby the piperidine-containing side chain of the lead tetrahydroisoquinoline **60** could be substituted by a 1,4-diazadecaline system as in **29**. A model of **29** was built accordingly with the molecular modeling program Witnotp[39] and optimized with Mopac/AM1.[39] Superposition of modeled **29** on raloxifene (**7**) bound to the carboxymethylated ER$\alpha$-LBD (Figure 3b) showed that **29** has the potential to bind to ER$\alpha$ via interactions similar to those established by **7**, but with a reduced loss of torsional freedom. To confirm the validity of the model, the bicyclic piperazine derivative **29** was synthesized and its affinity for the estrogen receptors, its selectivity, and its ability to act as an antagonist in MCF-7 cells were evaluated. Other analogues, in which the diazadecaline system of **29** was replaced by 1-alkyl-, 1-alkyl-2-alkyl-piperazines, or *N*-methyl-piperidine residues, were also prepared to study the influence of the substitution pattern on potency and selectivity. A few derivatives with substituted aryl D rings within the *N*-methyl-piperidine series were synthesized to assess the influence of substituents on selectivity. At this stage of our program, the new ligands were tested either as racemates or as mixtures of diastereoisomers. The results of our investigation are reported below.

**Biological Results.** A comparison of the in vitro data obtained for **29** and **60** reveals that the bicyclic side chain replacement is an effective mimic of the aminoethoxy side chain (Table 1, entries 1 and 17). The tetrahydroisoquinoline **29** displays good binding affinity for ER$\alpha$ showing an $IC_{50}$ of 63 nM. When compared to that of **60**, the potency of **29** in this assay is slightly reduced by ~3-fold. In this context, it is thus relevant to point out that **29** was tested as a mixture of four diastereoisomers whereas **60** was evaluated as the racemate. Because there is evidence (vide infra) indicating that one isomer is responsible for the potency of the mixture, it ensues that the difference of affinity amounts to only ~1.5-fold. When profiled in the ERE and MCF-7 assays, **29** and **60** were found to exhibit similar activities, within a factor of 1.5-fold in favor of **60** in the former assay and favoring **29** in the latter (Table 1, entries 1 and 17). The two most notable differences

**Table 1.** ER Binding, ER Transcriptional Activation on an ERE, and Inhibition of MCF-7 Cell Proliferation



| Entry | No | $R^1$ | $R^2$ | Radioligand binding assay[a] | | ERE Assay[b] | | MCF-7 Assay[b] | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | ERα $IC_{50}$ (nM) | ERβ $IC_{50}$ (nM) | ERα $IC_{50}$ (nM) | ERβ $IC_{50}$ (nM) | $IC_{50}$ (nM) | Agonism (%) |
| 1 | **29** | H |  | 63 ±8 | 252 ±15 | 23.2 ±4.6 | 98 ±16 | 21 ±9 | 16 ±4 |
| 2 | **30** | H |  | 69 ±2 | 330 ±25 | 34.9 ±3.3 | 106 ±6 | 44 ±25 | 10 ±4 |
| 3 | **31** | H |  | 38[c] | 173[c] | 64 ±25 | 399 ±6 | 30 ±11 | 10 ±5 |
| 4 | **32** | H |  | 162 ±21 | 1155 ±145 | 512 ±42 | 4454 ±26 | 190 ±120 | 18 ±8 |
| 5 | **33** | H |  | 185 ±19 | 428 ±25 | 55 ±1.4 | 180 ±57 | 55 ±15 | 13 ±6 |
| 6 | **38a** | H |  | 106 ±45 | 266 ±66 | 46.6 ±4.9 | 464 ±80[d] | 45 ±19 | 12 ±4 |
| 7 | **38b** | 4-F |  | 87 ±24 | 239 ±27 | 46.1 ±6.9 | 162 ±105 | 46 ±15 | 12 ±5 |
| 8 | **38c** | 3-F |  | 163 ±61 | 879 ±202 | 153 ±86 | >1000[d] | 150 ±115 | 15 ±7 |
| 9 | **38e** | 3-OH |  | 108 ±16 | 1730 ±290 | 31 ±14 | 496 ±138 | 104 ±24 | 9.4 ±0.6 |
| 10 | **45** | 3-OH |  | 169 ±53 | 1677 ±454 | 18.2 ±5.6 | 287 ±137 | 110 ±17 | 7.6 ±1.6 |
| 11 | **46** | 3-OH |  | 83 ±6 | 943 ±41 | 18.0 ±2.8 | 286 ±210 | 51 ±27 | 15 ±11 |
| 12 | **47** | 3-OH |  | 119 ±2 | 1945 ±55 | 31.5 ±2.1 | 491 ±378[d] | 80 ±41 | 10 ±5 |
| 13 | **48** | 3-OH |  | 122 ±15 | 1370 ±100 | n.d.[e] | n.d.[e] | 46 ±5 | 10 ±4 |
| 14 | **49** | 3-OH |  | 123 ±33 | 1110 ±110 | 19.6 ±6.5 | 268 ±140 | 59 ±21 | 5 ±3 |
| 15 | **50** | 3-OH |  | 177 ±41 | 1285 ±185 | 21.8 ±5.8 | 276 ±45 | 52 ±5 | 5 ±6 |
| 16 | **59** | H | F | 285 ±34 | 421 ±5 | n.d.[e] | n.d.[e] | >1000 | 100 ±11 |
| 17 | **60** | H |  | 19 ±6 | 346 ±3 | 16.5 ±3.0 | 289 ±17 | 32 ±14 | 37 ±18 |
| 18 | **1** | - | | 28 ±13 | 24 ±7 | n.d.[e] | n.d.[e] | n.d.[e] | 100 |
| 19 | **4**[f] | - | | 4 ±2 | 13 ±12 | 3.1 ±1.0 | 24 ±1 | 2.3 ±1.0 | 29 ±12 |
| 20 | **6** | - | | n.d.[e] | n.d.[e] | 622 ±200 | >1000 | 580 ±160[d] | 42 ±10 |
| 21 | **7**[f] | - | | 22 ±6 | 260 ±70 | 2.4 ±0.7 | 341 ±71 | 1.4 ±1.0 | 22 ±9 |

[a] Average of two independent experiments run in triplicate. [b] Average of two to four independent experiments run either in duplicate or in triplicate except when indicated; the maximum antagonism in the ERE and MCF-7 assays is 100% unless otherwise noted. [c] Average of three determinations issued from one experiment. [d] Maximum antagonism for **38a**, 98%; for **38c**, 71%; for **47**, 91%; for **6**, 68%. [e] n.d. = not determined. [f] Tested as the HCl salt.

between the two ligands lie in their selectivity profile and their agonistic effect in the MCF-7 proliferation assay. Tetrahydroisoquinoline **60** displays a stronger preference by ~18-fold for ERα whereas **29** shows a ~4-fold selectivity for ERα over ER*β*. In the MCF-7 cellular assay, analogue **29** clearly shows a reduced agonism (16%) relative to that displayed by **60** (37%). These data indicate that **29** may have a potential for breast cancer prevention/treatment in vivo. This feature is particularly attractive in the quest for a safe SERM as an alternative to hormone replacement therapy (HRT).

Motivated by these results, we set to expand our knowledge of the series by evaluating other analogues in which the piperidinyl ring of the diazadecaline system was disconnected. The data demonstrate that, among the newly prepared tetrahydroisoquinolines bearing 1-alkyl-2-alkylpiperazine residues, the 1-methyl- and 1-ethyl-2-methyl-piperazine derivatives **30** and **31** exhibit profiles similar to that of **29** (Table 1, entries 1−3). The 2-ethyl-piperazine analogue **32** is less active (Table 1, entry 4). Although **31** shows a marginal increase of binding affinity relative to **29** ($IC_{50}$ = 38 and 63 nM, respectively), this enhancement is not reflected in the ERE and MCF-7 assays, where the $IC_{50}$ values are 64 nM and 30 nM for **31** versus 23 and 21 nM for **29**. As observed for **29**, the tetrahydroisoquinoline derivatives **30**−**32** display weaker agonism (10−18%) than **60** in the MCF-7 assay in the absence of estrogen.

Next, analogues lacking the 2-position substituent were prepared to evaluate the influence of this group on binding affinity and potency in vitro. The *N*-methyl-piperazine analogue **33** (Table 1, entry 5) shows a 3- and 10-fold reduction of binding affinity relative to the parent 1-methyl-2-methyl-piperazine **30** and to the aminoethoxy derivative **60**, respectively. In the ERE and

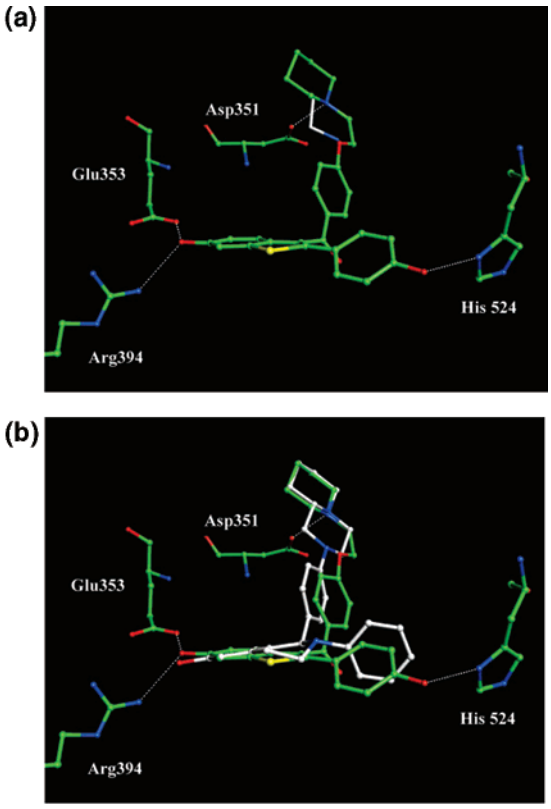



**Figure 3.** Side chain rigidification leading to **29** using raloxifene (**7**) bound to ERα-LBD (C atoms in green) as a template. Salt bridges and hydrogen bonding contacts of raloxifene (**7**) are indicated by dotted lines in white. (a) The conformation of the 2-(1-piperidinyl)ethyloxy fragment of raloxifene (**7**) forms a substructure of a *trans*-1,4-diazadecaline skeleton that is completed upon addition of one ring atom (the C atom is shown in white). (b) Model of **29** (C atoms in white) incorporating the *trans*-1,4-diazadecaline superimposed on raloxifene (**7**). The polar contacts of raloxifene (**7**) with Asp351, Glu353, and Arg394 are retained, and the phenolic A rings and piperidine rings common to both molecules overlap.

MCF-7 assays, its activity is only slightly reduced by 1.6- and 1.3-fold, respectively, relative to that of **30**.

In an attempt to further validate our modeling studies which had suggested piperidines as potential cyclic versions of the amine bearing side chain, we prepared piperidine derivative **38a** (Table 1, entry 6). The results indicate that both the piperazine and the piperidine residues (entries 5 and 6) are acceptable aminoethoxy side chain replacements, albeit the resulting ligands are slightly less potent than the parent tetrahydroisoquinolines **29** and **60** (entries 1 and 17).

Looking at the impact of the substitution pattern around the phenyl D ring for a small subset of *N*-methyl-piperidine analogues (Table 1, entries 6−9), we discovered that the presence of a 3-hydroxy group increased the selectivity toward ERα in both the binding and the ERE assays (Table 1, entry 9). Aiming to exploit this finding and to further probe the potential effect of *N*-alkyl groups on selectivity, we prepared a number of tetrahydroisoquinolines, embedding a 3-hydroxyphenyl D ring. In view of the fact that both the piperazine and the piperidine side chains have a similar impact on potency and that the piperazine analogues were more readily prepared, we carried out our studies with derivatives of the piperazine series. Comparison of the *N*-methyl piperazines **33** and **45** (Table 1, entries 5 and 10) confirms the trend observed for the piperidine analogues whereby a meta-OH group increases selectivity in favor of ERα. The other piperazine ligands **46**−**50** (Table 1, entries 11−15) display $IC_{50}$ values in the radioligand binding assay that vary from 83 to 177 nM and show selectivities for ERα over ER$\beta$ that range between 7−16-fold. These new piperazines display similar potency to that of the diazadecaline derivative **29** in the ERE assay and an activity reduced by 2−5-fold in the MCF-7 assay. Interestingly, the variation in the basic character of the nitrogen interacting with Asp351 by up to 1.4 log units does not significantly affect affinity. The p$K_a$values of the alkyl nitrogens for the *N*-methyl-piperazine **33**, the cyclopropyl-methyl-piperazine **48**, and the *N*-methyl-piperidine **38a** are 7.8, 8.0, and 9.2, respectively. In comparison, the lead tetrahydroisoquinoline **60** displays a p$K_a$ of 8.5 for its piperidine nitrogen.

As a result of our studies, we established that the aminoethoxy subunit of **60** can be replaced effectively by piperazine or piperidine moieties while maintaining activity and antagonist potential. In addition, we found that the analogues with constrained side chains present a superior profile relative to that of the parent in that they display reduced agonism in the MCF-7 assay. The diazadecaline residue was identified as the best side chain replacement. Because **29** is a mixture of four diastereoisomers, we questioned whether one or more isomers were contributing to the activity. There are literature precedents indicating that one enantiomer of SERMs such as lasofoxifene (**4**),[10] NNC 45-0781,[41] and EM-652[42] is more potent than the other. In the case of lasofoxifene (**4**),[10] for example, the 1-*R*, 2-*S* absolute configuration was attributed to the most potent enantiomer as illustrated in Figure 1. On the basis of our own results[37] and on published literature data, it appeared likely that the most active isomer of **29** would possess an *R* absolute configuration at C-1 of the tetrahydroisoquinoline nucleus. However, the importance of the configuration at the diazadecaline fragment remained to be confirmed. Our molecular modeling studies indicated that the preferred absolute configuration of the diazadecaline side chain would be *S*. An X-ray crystal structure of **29** in complex with ERα-LBD corroborated our assumption regarding the absolute configuration at C1 and the results of the modeling studies, in addition to providing the details of the ligand−protein interactions.

## X-ray Crystal Structure

Cocrystallization of the Cys → Ser triple mutant hERα-LBD 301−553 with a mixture containing the four diastereomers of **29** provided crystals diffracting to at least 2.05 Å that were suitable for X-ray analysis. This new crystal form for ERα-LBD contains four monomers (denoted A, B, C, and D) per asymmetric unit which form two dimers (AB and CD). The final model contains residues 307−330, 341−461, 464−528, and 535−548 for monomers A and C and residues 307−330, 341−461, 464−525, and 535−548 for monomers B and D (the missing regions correspond to flexible loops), as well as 374 water molecules and 4 ligand molecules **29** (denoted L, M, N, and O).

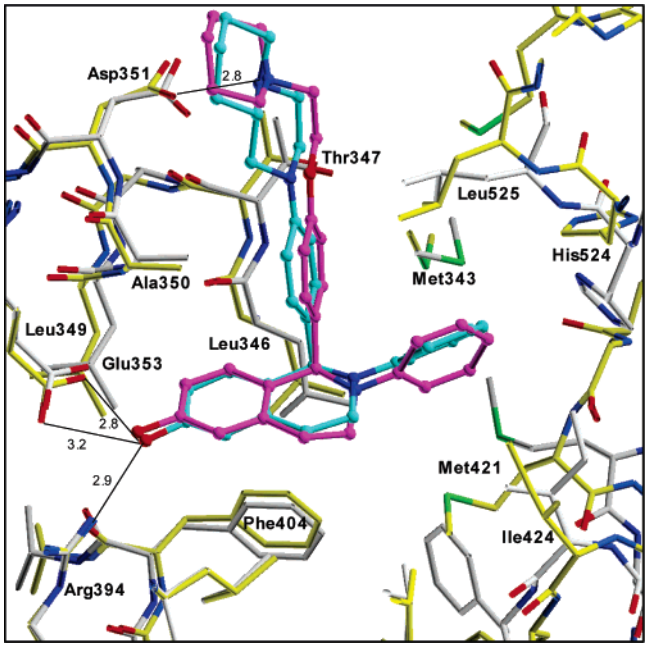



**Figure 4.** Superposition of the X-ray crystal structures of (1-*R*)(*S*)-**29** (blue) in complex with ERα-LBD301−553/C→S triple mutant (yellow) and (*R*)-**60** (magenta) in complex with ERα-LBD301−553/C→S triple mutant (gray). For details on the structure determination, see Supporting Information and our previous work.[37]

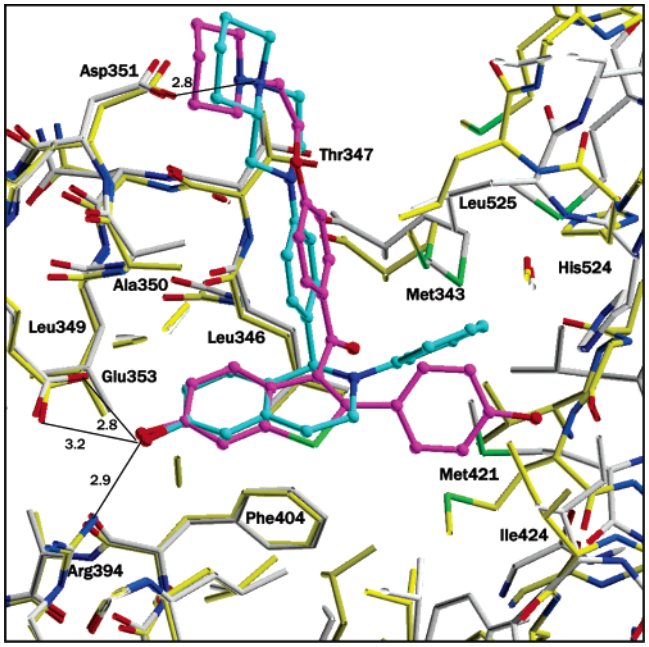



**Figure 5.** Superposition of the X-ray crystal structures of (1-*R*)(*S*)-**29** (blue) in complex with ERα-LBD301−553/C→S triple mutant (yellow) and raloxifene (**7**) (magenta) in complex with ERα-LBD301−553/carboxymethylated C (grey). For details on the structure determination, see Supporting Information.

The X-ray crystal structure ascertains that only one diastereoisomer of **29** (that with the *R*-configuration at the C1 position of the tetrahydroisoquinoline core and the *S*-configuration at the bicyclic piperazine residue) binds within the cavity of the ERα-LBD (Figure 4). Its positioning within the binding cleft is reminiscent of that observed for **60**[37] and other SERMs.[38] The backbone of tetrahydroisoquinoline **29** establishes a number of van der Waals contacts with the residues forming the binding pocket. The tetrahydroisoquinoline ligand **29** is further anchored within the binding cavity via a network of hydrogen bonds established between its phenolic hydroxyl and the side chains of Glu353 and Arg394. Its piperazinyl phenyl side chain protrudes through a narrow channel and adopts a position which allows a salt-bridge interaction with Asp351. The electron density indicates that the two anilinic nitrogens of **29** are slightly nonplanar as predicted by our model of **29**.

An overlay of the X-ray structures of ERα-LBDs bound to **29**, to the parent tetrahydroisoquinoline **60** (Figure 4) or to raloxifene (**7**) (Figure 5) shows that their basic side chains adopt similar positions (stabilized by the interaction with Asp351), despite differences in their crystal forms. As predicted by molecular modeling, the diazadecaline moiety of **29** nicely superimposes over the piperidinylethoxy side chain of **60** (Figure 4). The first ring of the bicyclic residue of **29**, apart from rigidifying the side chain, also participates in hydrophobic contacts with Trp383. However, this increased stabilization does not translate into an improvement in binding affinity.

## Pharmacokinetic Properties

To examine the pharmacokinetic properties of our ligands, we profiled a few selected candidates in a pharmacokinetic (PK) cassette dosing experiment carried out in rats (Table 2). For that purpose, the diazadecaline analogue **29**, the *N*-$^{i}$Pr-piperazine derivative **46** which incorporates a 3-position hydroxyphenyl residue, and the *N*-methyl-piperidine **38b** bearing a 4-position fluorophenyl moiety were chosen. These tetrahydroisoquinolines display good absolute oral bioavailabilities (BAV) (44−64%, Table 2, entries 3−5) and maximal blood concentrations which range between 27 and 57 nM ($C_{max}$, po, dose-normalized). The values found for **29, 38b**, and **46** compare very favorably with those obtained for the parent tetrahydroisoquinoline **60** (BAV, 42%; $C_{max}$, 31 nM; Table 2, entry 6) and are superior to those exhibited by lasofoxifene (**4**, Table 2, entry 1, BAV, 38%; $C_{max}$, 15.5 nM) and raloxifene (**7**, Table 2, entry 2; BAV, 22%; $C_{max}$, 7.5 nM). The volumes of distribution at steady state (Vss) for the various tetrahydroisoquinolines range from 9 to 16 L/kg, with the exception of the meta hydroxy derivative **46** that is associated with a lower Vss (5 L/kg), a value indicating that this compound may have a higher protein binding.

## Conclusion

In this paper, we reported the results of our investigations aimed at the discovery of selective estrogen receptor modulators with conformationally restricted side chains. The information resulting from the X-ray crystal structure of hERα in complex with raloxifene (**7**) used in conjunction with modeling studies directed our synthetic work toward the preparation of analogues of the tetrahydroisoquinoline series that incorporate cyclic side chains as surrogates for the aminoethoxy residue. Both piperazine and piperidine derivatives were found to retain affinity for ERα and, importantly, antagonistic properties when compared to the parent compound **60**. In addition, all of the new derivatives displayed weaker agonism in the MCF-7 assay relative to that of lasofoxifene (**4**), raloxifene (**7**), and tetrahydroisoquinoline **60**.

**Table 2.** Pharmacokinetic Data for Selected Compounds[a]

| entry | no. | oral BAV (%)[b] | maxi blood concn po dose-normalized ($C_{max}$) (nM) | total clearance (CL) (mL/min kg) | vol of distribn at steady state (Vss) (L $kg^{-1}$) |
|---|---|---|---|---|---|
| 1 | **4**[c] | 38 ± 5 | 15.5 ± 5.3 | 55.7 ± 4.3 | 14.7 ± 1.3 |
| 2 | **7**[c] | 22 ± 4 | 7.5 ± 2.3 | 157.7 ± 11.7 | 17.6 ± 1.8 |
| 3 | **29** | 49 ± 6 | 29.7 ± 5.4 | 28.4 ± 4.2 | 9.2 ± 1.2 |
| 4 | **38b** | 64 ± 7.5 | 26.5 ± 7.7 | 52.4 ± .8 | 15.8 ± 2.5 |
| 5 | **46** | 44 ± 6 | 57.2 ± 5.9 | 17.9 ± 4.0 | 5.0 ± 1.0 |
| 6 | **60** | 42 ± 10 | 31 ± 7 | 51.9 ± 3.2 | 13.8 ± 0.7 |

[a] Pharmacokinetic parameters calculated from blood levels after iv (1 mg/kg) and po (5 mg/kg) administration to conscious rats. [b] BAV = bioavailability. [c] Tested as the HCl salt.

The most potent analogue, tetrahydroisoquinoline **29**, embeds the diazadecaline side chain, which acts as an excellent mimic of the traditional SERM residue. In addition to being potent in functional assays, **29** displays a very good oral bioavailability (49%) in a cassette dosing experiment carried out in rats. On the basis of both its in vitro and PK profile, **29** was identified as the optimal compound within that series and warrants further in vivo evaluation.

## Experimental Section

**Chemistry. General.** All of the commercial chemicals and solvents are reagent grade and were used without further purification unless otherwise stated. All of the reactions except those in aqueous media were carried out under an atmosphere of $N_2$, in flame-dried glassware. Reactions were monitored by analytical reverse-phase high-performance liquid chromatography (RP-HPLC) using a Hewlett-Packard series 1100, equipped with a diode array spectrometer ($\lambda$ = 210−250 nm) and a Waters Symmetry C-8 column (3.5 $\mu$m, 2.1 mm × 50 mm) as the stationary phase. The mobile phases used were A, 95:5 $H_2O/CH_3CN$ containing 0.1% TFA, and B, $CH_3CN$ containing 0.1% TFA. The program employed ran as follows: 0−7 min, 5% B → 100% B; 7−8.5 min, 100% B; at 8.5 min, 5% B for 2.5 min, prior to the next run. The flow rate was maintained at 0.5 mL/min. Additionally, thin-layer chromatography on 0.25 mm silica gel plates (E. Merck, silica gel 60 $F_{254}$) was used to follow the reactions. Visualization was accomplished with UV light, $KMnO_4$, or 5% phosphomolybdic acid in 95% ethanol.

Intermediates and final compounds were purified by flash chromatography (E. Merck silica gel 60, 230−400 mesh), crystallization, or semipreparative reverse-phase HPLC (RP-HPLC) using a Gilson model 306 equipped with a UV−vis detector ($\lambda$ usually set to 214 nm) and a Symmetry Prep RP18 (7 $\mu$m, 19 mm × 150 mm column) as the stationary phase. The eluents employed were A, $H_2O$ containing 0.1%TFA, and B, $CH_3CN$ containing 0.1% TFA. The program ran as follows: 0−0.5 min, 100% B; 0.5−3 min, 10% B; the compound was automatically injected at 3 min; from 3 to 4 min, 10% B; thereafter, a linear gradient was then run from 10% B to 100% B over the next 16 min followed by a 2.0 min hold at 100% B. The flow rate was held constant at 20 mL/min.

NMR spectra were recorded either on a Varian spectrometer, model Mercury-300 or -400, or on a Bruker DPX-400, DMX-500, or DRX-500. Signal positions ($\delta$ values) were calibrated using the residual undeuterated solvent resonance as the internal standard. The multiplicity is indicated by one of the following: d, doublet; t, triplet; m, multiplet; br, broad. Infrared spectra were recorded using a Perkin-Elmer i-Series FT-IR microscope coupled with a SPECTRUM 2000 FT-IR spectrometer. High-resolution mass spectra (HRMS) were recorded on a Finnigan MAT900.

**Syntheses of Piperazinyl Derivatives 29−33 via Amination. Synthesis of 6-Benzyloxy-1-(4-iodophenyl]-2-phenyl-1,2,3,4-tetrahydroisoquinoline (13).** The iodo derivative **13** was synthesized as described in Scheme 1. A similar route using intermediates with different protecting groups has been described.[26] IR (KBr) $\nu_{max}$: 2915, 2891, 2821, 1599, 1503, 1473, 1378, 1325, 1240, 1228, 1216, 1151, 1008, 751, 693 $cm^{-1}$. $^1H$ NMR (400 MHz, DMSO) $\delta$: 7.58 (d, $J$ = 8.5 Hz, 2H), 7.43−7.26 (m, 6H), 7.13 (dd, $J$ = 7.5, 8.5 Hz, 2H), 7.04 (d, $J$ = 8.5 Hz, 2H), 6.88−6.81 (m, 2H), 6.78 (d, $J$ = 8.5 Hz, 2H), 6.64 (t, $J$ = 7.5 Hz, 1H), 5.85 (s, 1H), 5.04 (s, 2H), 3.69−3.61 (m, 1H), 3.41−3.32 (m, 1H), 2.96−2.86 (m, 1H), 2.86−2.75 (m, 1H). $^{13}C$ NMR (100.7 MHz, DMSO) $\delta$: 157.0, 148.4, 143.6, 136.8, 136.6, 136.2, 129.6, 129.0, 128.7, 128.4, 128.2, 127.55, 127.4, 116.7, 113.6, 113.1, 112.6, 92.4, 69.1, 60.3, 43.1, 27.7. HRMS (ESI, M + $H^+$) calcd for $C_{28}H_{24}NOI$: 518.0981. Found: 518.0985. HPLC purity: 100%; $t_R$ 7.95 min.

**General Procedure for the Amination of 13. Procedure A. Synthesis of 22 and 24.** When two different numbers appear in parentheses, these refer to the quantities used in the preparation of bicyclic piperazine **22** and ethyl piperazine derivative **24**, respectively. A mixture containing the phenyliodide **13** (1 equiv), octahydropyrido[1,2-a]pyrazine (**18**, 1.54 equiv) or 2-ethyl-piperazine (**20**, 1.3 equiv), $^t$BuOK (1.54/2 equiv), $Pd_2(dba)_3$ (2/5% mol), and (2′-dicyclohexylphosphanyl-biphenyl-2-yl)-dimethylamine (8/10% mmol) in anhydrous toluene (0.19/0.24 M) was stirred at 80−85 °C for 12/19 h. After workup and purification by flash chromatography, the piperazine derivatives **22** and **24** were obtained in 53 and 74% yield, respectively. One detailed procedure is reported below.

**General Procedure for Debenzylation.** A solution of the piperazine derivative **22**, **25**, **26**, **27**, or **28** in a 2:1 or 5:3 dioxane/concentrated HCl mixture was stirred at 90 °C for 2−2.5 h. After workup and purification, tetrahydroisoquinolines **29**, **30**, **31**, **32**, or **33** were isolated in yields ranging from 34 to 73%. A representative example is given below.

**Procedure A. Synthesis of 6-Benzyloxy-1-[4-(3-ethyl-piperazin-1-yl)phenyl]-2-phenyl-1,2,3,4-tetrahydroisoquinoline (24) by Amination.** A mixture containing the phenyliodide **13** (1.0 g, 1.93 mmol), 2-ethyl-piperazine (**20**, 286 mg, 2.5 mmol), $^t$BuOK (432 mg, 3.86 mmol), $Pd_2(dba)_3$ (88 mg, 0.096 mmol), and (2′-dicyclohexylphosphanyl-biphenyl-2-yl)-dimethylamine (76 mg, 0.193 mmol) in anhydrous toluene (8 mL) was stirred at 85 °C for 19 h. The mixture was cooled to room temperature and poured into $H_2O$ (10 mL)/$Et_2O$ (20 mL). The layers were separated, the organic phase was washed with brine (10 mL) and dried ($MgSO_4$), and the solvent was concentrated in vacuo. The residual brown oil was purified by flash chromatography (silica gel, 19:1 → 9:1 $CH_2Cl_2$/MeOH) to provide the title compound (721 mg, 74%) as a solid. IR (KBr) $\nu_{max}$: 3427, 3058, 3031, 2957, 2930, 2818, 1597, 1502, 1453, 1381, 1231, 1156, 1025, 747, 694 $cm^{-1}$. $^1H$ NMR (400 MHz, DMSO) $\delta$: 7.44−7.22 (m, 6H), 7.12 (t, $J$ = 8.0 Hz, 2H), 7.02 (d, $J$ = 8.5 Hz, 2H), 6.86−6.74 (m, 6H), 6.61 (t, $J$ = 7.5 Hz, 1H), 5.77 (s, 1H), 5.04 (s, 2H), 3.67−3.58 (m, 1H), 3.47−3.25 (m, 3H), 2.97−2.66 (m, 4H), 2.57−2.43 (m, 2H), 2.15 (t, $J$ = 10.0 Hz, 1H), 1.40−1.27 (m, 2H), 0.89 (t, $J$ = 7.5 Hz, 3H). $^{13}C$ NMR (100.7 MHz, DMSO) $\delta$: 156.7, 149.7, 148.7, 136.9, 136.1, 133.5, 130.6, 128.65, 128.3, 128.2, 127.5, 127.4, 127.3, 116.4, 114.9, 113.5, 113.1, 112.4, 69.1, 60.3, 56.0, 54.13/54.06, 48.76/48.70, 45.1, 42.7, 27.6, 26.4, 10.3. HRMS (ESI, M + $H^+$) calcd for $C_{34}H_{37}N_3O$: 504.3015. Found: 504.3017. HPLC purity: 96%; $t_R$ 5.19 min.

**Synthesis of 6-Benzyloxy-1-[4-(3-ethyl,4-methyl-piperazin-1-yl)phenyl]-2-phenyl-1,2,3,4-tetrahydroisoquinoline (28) by Reductive Amination.** A mixture of piperazin-

yl derivative **24** (115 mg, 0.23 mmol), 37% HCHO (76 μL, 1.01 mmol), AcOH (14 μL, 0.25 mmol), and $NaBH(OAc)_3$ (73 mg, 0.34 mmol) in $Cl(CH_2)_2Cl$ (6 mL) was stirred at room temperature for 1 h. The reaction mixture was diluted with $CH_2Cl_2$ (10 mL) and washed with 1 N aqueous NaOH (6 mL). The aqueous layer was extracted with $CH_2Cl_2$ (1 × 10 mL), the combined organic phases were dried ($MgSO_4$), and the solvent was removed in vacuo. The residue was purified by flash chromatography (silica gel, 50:1:0.1 $CH_2Cl_2$/MeOH/$NH_4OH$) to furnish the title compound (101 mg, 86%) as an oil. $^1$H NMR (500 MHz, DMSO) δ: 7.43 (d, $J$ = 7.0 Hz, 2H), 7.38 (t, $J$ = 7.0 Hz, 2H), 7.34−7.29 (m, 1H), 7.27 (d, $J$ = 8.5 Hz, 1H), 7.14 (t, $J$ = 7.0 Hz, 2H), 7.04 (d, $J$ = 8.5 Hz, 2H), 6.77−6.88 (m, 6H), 6.83 (t, $J$ = 7.0 Hz, 1H), 5.79 (s, 1H), 5.06 (s, 2H), 3.64 (ddd, $J$ = 5.5, 5.5, 11.5 Hz, 1H), 3.43−3.30 (m, 3H), 2.915 (ddd, $J$ = 5.5, 5.5, 15.5 Hz, 1H), 2.87−2.74 (m, 2H), 2.68−2.61 (m, 1H), 2.44−2.37 (m, 1H), 2.20 (dm, $J$ = 11.0 Hz for d, 1H), 2.17 (s, 3H), 1.99−1.92 (m, 1H), 1.63−1.53 (m, 1H), 1.44−1.34 (m, 1H), 0.85 (t, $J$ = 7.5 Hz, 3H). $^{13}$C NMR (125.8 MHz, DMSO) δ: 157.5, 150.1, 149.5, 137.6, 136.8, 134.4, 131.3, 129.3, 129.0, 128.9, 128.2, 128.1, 128.0, 117.1, 115.5, 114.2, 113.8, 113.1, 69.6, 62.8, 60.8, 55.3, 52.6/52.5, 48.45, 43.2, 42.4, 28.1, 22.9, 9.7. HPLC purity: 98.8%; $t_R$ 5.27 min.

**Synthesis of 1-[4-(3-Ethyl-4-methyl-piperazin-1-yl)phenyl]-2-phenyl-1,2,3,4-tetrahydroisoquinolin-6-ol (32) by Debenzylation.** A solution of the piperazine derivative **28** (100 mg, 0.193 mmol) in a 2:1 dioxane/concentrated HCl mixture (15 mL) was stirred at 90 °C for 2 h. The mixture was cooled to room temperature and extracted with $Et_2O$. The aqueous layer was adjusted to pH 10 with 4 N aqueous NaOH (14 mL) and extracted with $CH_2Cl_2$ (3 × 10 mL). The combined organic phases were dried ($MgSO_4$) and concentrated. The residue was purified by flash chromatography (silica gel, 19:1 → 9:1 $CH_2Cl_2$/MeOH) to provide the tetrahydroisoquinolinol **32** (38 mg, 46%) as a solid. IR ($CH_2Cl_2$ solution) $\nu_{max}$: 3582, 3041, 2969, 2838, 2801, 1609, 1598, 1504, 1452, 1384, 1244, 1148, 928, 800 cm$^{-1}$. $^1$H NMR (500 MHz, DMSO) δ: 9.27 (s, 1H), 7.17−7.10 (m, 3H), 7.04 (d, $J$ = 8.5 Hz, 2H), 6.82−6.77 (m, 4H), 6.65−6.56 (m, 3H), 5.72 (s, 1H), 3.65−3.58 (m, 1H), 3.42−3.30 (m, 3H), 2.84 (ddd, $J$ = 5.5, 5.5, 15.5 Hz, 1H), 2.80−2.72 (m, 2H), 2.69−2.61 (m, 1H), 2.45−2.37 (m, 1H), 2.25−2.15 (m, 1H), 2.17 (s, 3H), 2.00−1.93 (m, 1H), 1.64−1.54 (m, 1H), 1.45−1.34 (m, 1H), 0.85 (t, $J$ = 7.5 Hz, 3H). $^{13}$C NMR (125.8 MHz, DMSO) δ: 156.4, 150.05, 149.5, 136.6, 134.7, 129.3, 128.9, 127.9, 116.9, 115.5, 114.65, 113.7, 113.5, 62.8, 60.9, 55.3, 52.6/52.5, 48.5/48.4, 43.3, 42.3, 28.0, 22.9, 9.7. HRMS (ESI, M + H$^+$) calcd for $C_{28}H_{33}N_3O$: 428.2702. Found: 428.2702. HPLC purity: 100%; $t_R$ 3.81 min.

**1-[4-(Octahydropyrido[1,2-a]pyrazin-2-yl)phenyl]-2-phenyl-1,2,3,4-tetrahydroisoquinolin-6-ol (29).** Derivative **22** was prepared in 53% yield from **13** using procedure A. Debenzylation provided **29** in 73% yield. IR (KBr) $\nu_{max}$: 3600−2200, 3022, 2932, 2819, 1596, 1503, 1382, 1254, 1231, 927, 748, 691 cm$^{-1}$. $^1$H NMR (400 MHz, DMSO) δ: 9.24 (s, 1H), 7.19−7.06 (m, 3H), 7.01 (d, $J$ = 8.0 Hz, 2H), 6.84−6.70 (m, 4H), 6.64−6.51 (m, 3H), 5.70 (s, 1H), 3.67−3.27 (m, 4H), 2.88−2.57 (m, 5H), 2.32−2.10 (m, 2H), 2.02−1.85 (m, 2H), 1.73−1.37 (m, 4H), 1.30−1.05 (m, 2H). $^{13}$C NMR (100.7 MHz, DMSO) δ: 155.6, 149.1, 148.8, 135.8, 133.9, 128.6, 128.4, 127.2, 116.2, 114.8, 114.0, 113.0, 112.9, 60.4/60.3, 54.8, 54.3, 54.1, 48.1, 42.8, 29.1, 27.5, 25.2, 23.5. HRMS (ESI, M + H$^+$) calcd for $C_{29}H_{33}N_3O$: 440.2702. Found: 440.2702. HPLC purity: 97%; $t_R$ 3.67 min.

**Procedure B. Synthesis of 6-Benzyloxy-1-[4-(3-methylpiperazin-1-yl)phenyl]-2-phenyl-1,2,3,4 -tetrahydroisoquinoline (23) by Amination.** A mixture containing the phenyliodide **13** (500 mg, 0.966 mmol), 2-methyl-piperazine (**19**, 116 mg, 1.16 mmol), $^t$BuOK (162 mg, 1.44 mmol), $Pd_2(dba)_3$ (8.8 mg, 0.0096 mmol), and 1,3-bis(2,6-diisopropylphenyl)-4,5-dihydroimidazolium tetrafluoroborate[32−35] (18.4 mg, 0.0386 mmol) in anhydrous dioxane (3 mL) was stirred at 27 °C for 40 h. An additional quantity of $^t$BuOK (54 mg, 0.48 mmol), $Pd_2(dba)_3$ (8.8 mg, 0.0096 mmol), and 1,3-bis(2,6-diisopropylphenyl)-4,5-dihydroimidazolium tetrafluoroborate (18.4 mg, 0.0386 mmol) was added. The mixture was stirred at 40 °C for 4 h. After being cooled to room temperature, the mixture was poured into $H_2O$ (10 mL)/$Et_2O$ (20 mL). The layers were separated, and the aqueous layer was extracted once again with $Et_2O$ (20 mL). The combined organic phases were washed with brine (10 mL) and dried ($MgSO_4$), and the solvent was removed in vacuo. The residual orange oil was purified by flash chromatography (silica gel, 9:1 $CH_2Cl_2$/MeOH) to provide the title compound (290 mg, 61%) as a yellow solid. $^1$H NMR (400 MHz, $CDCl_3$) δ: 7.51−7.35 (m, 5H), 7.31−7.10 (m, 5H), 6.94−6.75 (m, 7H), 5.78 (s, 1H), 5.09 (s, 2H), 3.74−3.65 (m, 1H), 3.57−3.46 (m, 3H), 3.14 (dt, $J$ = 12.0, 2.5 Hz, 1H), 3.08−2.85 (m, 4H), 2.71 (td, $J$ = 2.5, 12.0 Hz, 1H), 2.40 (m, 1H), 1.85 (br s, 1H), 1.15 (d, $J$ = 6.5 Hz, 3H). $^{13}$C NMR (125.8 MHz, DMSO) δ: 157.5, 150.5, 149.5, 137.6, 136.8, 134.15, 131.3, 129.35, 129.1, 128.9, 128.2, 128.1, 128.0, 117.05, 115.4, 114.2, 113.8, 113.1, 69.6, 60.8, 56.4, 50.6, 48.91/48.88, 45.7, 43.2, 28.0, 19.9. MS (APCI) $m/z$ = 490 [M + H$^+$]. HPLC purity: 97.8%; $t_R$ 5.08 min.

**Synthesis of 6-Benzyloxy-1-[4-(3,4-dimethyl-piperazin-1-yl)phenyl]-2-phenyl-1,2,3,4-tetrahydroisoquinoline (26) by Reductive Amination.** A mixture of piperazin-yl derivative **23** (450 mg, 0.919 mmol), 37% aq HCHO (829 μL, 11.0 mmol), and AcOH (63 μL, 1.1 mmol) in MeOH (8 mL) was stirred at 80 °C for 1 h. The reaction mixture was cooled to 0 °C and diluted with $CH_2Cl_2$ (1 mL), and $NaBH_3CN$ (95%, 881 mg, 13.3 mmol) was added. The resultant mixture was stirred at this temperature for 1 h and poured into saturated aqueous $NH_4Cl$ (20 mL)/$CH_2Cl_2$ (40 mL), and the layers were separated. The aqueous layer was extracted with $CH_2Cl_2$ (3 × 15 mL), the combined organic phases were dried ($Na_2SO_4$), and the solvent was removed in vacuo. The residual light brown solid was purified by crystallization (AcOEt/$Et_2O$) and flash chromatography (silica gel, 9:1 $CH_2Cl_2$/MeOH) to furnish the title compound (372 mg, 81%) as a beige solid. Acid-catalyzed removal of the benzyl group, followed by purification by flash chromatography (silica gel; 19:1 $CH_2Cl_2$/MeOH), provided the debenzylated product **30** as a pale yellow solid in 70% yield.

**1-[4-(3,4-Dimethyl-piperazin-1-yl)phenyl]-2-phenyl-1,2,3,4-tetrahydroisoquinolin-6-ol (30).** IR (KBr) $\nu_{max}$: 3600−2200, 2951, 2822, 1597, 1503, 1381, 1244, 1149, 748 cm$^{-1}$. $^1$H NMR (400 MHz, DMSO) δ: 9.24 (s, 1H), 7.16−7.08 (m, 3H), 7.02 (d, $J$ = 8.5 Hz, 2H), 6.82−6.74 (m, 4H), 6.64−6.54 (m, 3H), 5.71 (s, 1H), 3.65−3.57 (m, 1H), 3.45−3.30 (m, 3H), 2.88−2.71 (m, 3H), 2.69−2.60 (m, 1H), 2.35−2.24 (m, 1H), 2.22−2.13 (m, 1H), 2.18 (s, 3H), 2.12−2.02 (m, 1H), 1.00 (d, $J$ = 6.0 Hz, 3H). $^{13}$C NMR (100.7 MHz, DMSO) δ: 155.4, 148.9, 148.6, 135.7, 133.7, 128.45, 128.1, 127.1, 116.1, 114.55, 113.8, 112.9, 112.7, 60.2, 56.9, 54.97/54.96, 54.6, 48.0/47.97, 42.6, 41.9, 27.35, 16.6. HRMS (ESI, M + H$^+$) calcd for $C_{27}H_{31}N_3O$: 414.2545. Found: 414.2546. HPLC purity: 100%; $t_R$ 3.56 min.

**Synthesis of 6-Benzyloxy-1-[4-(4-ethyl-3-methylpiperazin-1-yl)phenyl]-2-phenyl-1,2,3,4-tetrahydroisoquinoline (27) by Reductive Amination.** A mixture of piperazin-yl derivative **23** (290 mg, 0.59 mmol), $CH_3CHO$ (401 μL, 7.1 mmol), AcOH (37 μL, 0.65 mmol), and $NaBH(OAc)_3$ (188 mg, 0.887 mmol) in $Cl(CH_2)_2Cl$ (6 mL) was stirred at room temperature for 16 h. The reaction mixture was diluted with $CH_2Cl_2$ (40 mL) and poured into 1 N aqueous NaOH (20 mL). The layers were separated. The aqueous layer was extracted with $CH_2Cl_2$ (1 × 15 mL), the combined organic phases were dried ($MgSO_4$), and the solvent was removed in vacuo. The residual orange oil was purified by flash chromatography (silica gel, 19:1 $CH_2Cl_2$/MeOH) to furnish the title compound (160 mg, 52%) as a yellow solid. Acid-catalyzed removal of the benzyl group, followed by purification by flash chromatography (silica gel, 19:1 $CH_2Cl_2$/MeOH), provided the debenzylated product **31** in 55% yield.

**1-[4-(4-Ethyl-3-methyl-piperazin-1-yl)phenyl]-2-phenyl-1,2,3,4-tetrahydroisoquinolin-6-ol (31).** IR (KBr) $\nu_{max}$: 3650−2200, 2967, 2820, 1597, 1503, 1456, 1382, 1326, 1242, 1173, 1154, 923, 748, 692 cm$^{-1}$. $^1$H NMR (400 MHz, DMSO) δ: 9.22 (s, 1H), 7.16−7.08 (m, 3H), 7.01 (d, $J$ = 8.5 Hz, 2H), 6.81−6.73 (m, 4H), 6.64−6.53 (m, 3H), 5.70 (s, 1H), 3.65−3.55

(m, 1H), 3.40−3.20 (m, 3H), 2.90−2.65 (m, 5H), 2.45−2.35 (m, 2H), 2.33−2.19 (m, 2H), 1.00 (d, $J$ = 5.0 Hz, 3H), 0.95 (t, $J$ = 7.0 Hz, 3H). $^{13}$C NMR (125.8 MHz, DMSO) $\delta$: 155.9, 149.5, 149.0, 136.1, 134.1, 128.9, 128.5, 127.45, 116.4, 115.0, 114.2, 113.2, 113.1, 60.4, 55.5, 53.8, 49.6, 48.4, 46.35, 42.9, 27.5, 15.8, 10.6. HRMS (ESI, M + H$^+$) calcd for $C_{28}H_{33}N_3O$: 428.2702. Found: 428.2701. HPLC purity: 99%; $t_R$ 3.57 min.

**Procedure C. Synthesis of 6-Benzyloxy-1-[4-(4-methyl-piperazin-1-yl)phenyl]-2-phenyl-1,2,3,4 -tetrahydroisoquinoline (25) by Amination.** A mixture containing the phenyliodide **13** (300 mg, 0.58 mmol), 4-methyl-piperazine (**21**, 80 $\mu$L, 0.72 mmol), $^t$BuOK (78 mg, 0.81 mmol), $Pd_2(dba)_3$ (2 mg, 0.0022 mmol), and (±)-BINAP (4 mg, 0.0064 mmol) in anhydrous tetrahydrofuran (THF) (3 mL) was refluxed for 4 h. Additional quantities of $Pd_2(dba)_3$ (4 mg, 0.0044 mmol), (±)-BINAP (8 mg, 0.0128 mmol), and 4-methyl-piperazine (**21**, 80 $\mu$L, 0.72 mmol) were added. The mixture was refluxed for 17 h prior to the addition of $^t$BuOK (80 mg, 0.83 mmol). After being stirred for another 17 h at the same temperature, the mixture was cooled to room temperature and poured into $H_2O$ (10 mL)/AcOEt (30 mL). The layers were separated. The organic phase was washed with water (10 mL) and dried ($MgSO_4$), and the solvent was removed in vacuo. The residue was filtered over silica gel, using MeOH as eluent to provide the title compound (152 mg, 53%, 87% purity by HPLC), which was used in the next step (HCl-promoted debenzylation) without further purification. The debenzylated product **33** was isolated as a solid in 34% yield after purification by flash chromatography (silica gel, 19:1 $CH_2Cl_2$/MeOH) and recrystallization in AcOEt.

**1-[4-(4-Methyl-piperazin-1-yl)phenyl]-2-phenyl-1,2,3,4-tetrahydroisoquinolin-6-ol (33).** IR (KBr) $\nu_{max}$: 3650−2000, 3023, 2977, 2935, 2906, 2815, 2683, 2569, 1596, 1503, 1325, 1287, 1238, 1151, 1006, 989, 925, 859, 785, 749, 694 cm$^{-1}$. $^1$H NMR (400 MHz, DMSO) $\delta$: 9.30 (s, 1H), 7.16−7.08 (m, 3H), 7.04 (d, $J$ = 8.5 Hz, 2H), 6.82−6.74 (m, 4H), 6.64−6.55 (m, 3H), 5.72 (s, 1H), 3.66−3.57 (m, 1H), 3.42−3.32 (m, 1H), 3.14−3.03 (m, 4H), 2.88−2.70 (m, 2H), 2.62−2.52 (m, 4H), 2.29 (s, 3H). $^{13}$C NMR (100.7 MHz, DMSO) $\delta$: 155.6, 148.9, 148.7, 135.8, 134.2, 128.6, 128.5, 128.2, 127.2, 116.2, 114.9, 114.0, 112.95, 112.85, 60.3, 54.0, 47.45, 44.85, 42.8, 27.5. HRMS (ESI, M + H$^+$) calcd for $C_{26}H_{29}N_3O$: 400.2389. Found: 400.2388. HPLC purity: 100%; $t_R$ 3.44 min.

**Syntheses of Piperidine Derivatives 38a−c, e. General Procedure for the Synthesis of 16a−d via N-Arylation of 15.**[30] 6-Methoxy-3,4-dihydro-2*H*-isoquinolin-1-one (**15**)[28] was N-arylated by reaction with an aryl iodide or an aryl bromide (2 equiv) in the presence of CuI (0.1 equiv initially; portions of 0.1 equiv were added, for a maximal amount of 0.4 equiv, in cases where the reaction slowed) and $K_2CO_3$ (1 equiv) in DMF (0.5−0.6 M) at 150 °C for 72−120 h. The yields of the arylated products ranged from 70 to 95%. A representative procedure is given below.

**Synthesis of 2-(3-Fluorophenyl)-6-methoxy-3,4-dihydro-2*H*-isoquinolin-1-one (16c).** A mixture of 6-methoxy-3,4-dihydro-2*H*-isoquinolin-1-one (**15**, 1.0 g, 5.64 mmol), 1-fluoro-3-iodobenzene (2.5 g, 11.3 mmol), $K_2CO_3$ (780 mg, 5.64 mmol), and CuI (107 mg, 0.56 mmol) in DMF (10 mL) was heated at 150 °C for 72 h under $N_2$ atmosphere. After being cooled to room temperature, the mixture was poured into aqueous $NH_4OH$ (50 mL)/AcOEt (50 mL). The layers were separated, and the aqueous layer was extracted with portions of AcOEt (3 × 50 mL). The combined organic phases were washed with brine (75 mL), dried ($MgSO_4$), and concentrated in vacuo. The resulting solid was recrystallized from $CH_2Cl_2$−$Et_2O$ to provide the title compound (1.06 g, 69%) as a beige solid. IR (KBr) $\nu_{max}$: 2956, 2894, 2839, 1648, 1605, 1492, 1410, 1322, 1270, 1208, 1025, 897, 779, 687 cm$^{-1}$. $^1$H NMR (400 MHz, DMSO) $\delta$: 7.86 (d, $J$ = 9.0 Hz, 1H), 7.41 (ddd, $J$ = 8.0, 8.0, 8.0 Hz, 1H), 7.28 (ddd, $J$ = 2.5, 2.5, 11.0 Hz, 1H), 7.23 (dm, $J$ = 8.0 Hz for d, 1H), 7.04 (ddd, $J$ = 2.5, 8.0, 8.0 Hz, 1H), 6.92 (d, $J$ = 2.5 Hz, 1H), 6.90 (s, 1H), 3.93 (t, $J$ = 6.5 Hz, 2H), 3.82 (s, 3H), 3.08 (t, $J$ = 6.5 Hz, 2H). $^{13}$C NMR (100.7 MHz, DMSO) $\delta$: 162.7, 161.9, 161.5 (d, $J_{C-F}$ = 242 Hz), 144.6 (d, $J_{C-F}$ = 10 Hz), 141.0, 129.8, 129.6 (d, $J_{C-F}$ = 9 Hz), 121.5, 120.9 (d, $J_{C-F}$ = 3 Hz), 112.8, 112.3 (d, $J_{C-F}$ = 23 Hz), 112.0 (d, $J_{C-F}$ = 21 Hz), 111.7, 55.4, 48.6, 28.0. HRMS (ESI, M + H$^+$) calcd for $C_{16}H_{14}NO_2F$: 272.1087. Found: 272.1088. HPLC purity: 97%; $t_R$ 5.38 min.

**General Procedure for the Conversion of Lactams 16a−d into Tetrahydroisoquinolines 17a−d. Lactam 16a−d** was allowed to undergo reaction with 4-bromophenyllithium in THF (0.08−0.1 M) for 1.5−3.5 h. (The phenyllithium reagent was generated by treatment of *p*-dibromobenzene (1.1 equiv) with *n*-BuLi (1.1 equiv) in THF at −78 °C for 25−150 min.) After aqueous workup and isolation, the iminium salt was dissolved in MeOH (0.06−0.085 M) and treated with $NaBH_4$ (2.2 equiv) at room temperature for 15−30 min. After that period of time, the product was isolated and purified. Tetrahydroisoquinolines **17a−d** were obtained in yields ranging from 70 to 86%. A representative example is given below.

**Synthesis of 1-(4-Bromophenyl)-2-(3-fluorophenyl)-6-methoxy-1,2,3,4-tetrahydroisoquinoline (17c).** To a cold (−78 °C) solution of *p*-dibromobenzene (2.39 g, 10.14 mmol) in anhydrous THF (50 mL), a solution of *n*-BuLi in hexanes (1.6 M, 6.3 mL, 10.14 mmol) was added over a period of 5 min. After the resultant suspension was stirred at this temperature for 25 min, a solution of lactam **16c** (2.5 g, 9.22 mmol) in anhydrous THF (50 mL) was added dropwise over 30 min. Stirring was continued for an additional 3 h at this temperature. The mixture was poured onto $H_2O$ (100 mL)/AcOEt (100 mL). $HClO_4$ (70%, 2.4 mL) was added, the mixture was stirred for 15 min at room temperature, and the phases were separated. The aqueous layer was extracted with AcOEt (100 mL), and the combined organic layers were washed with brine (75 mL) and dried ($MgSO_4$), and the solution was concentrated in vacuo yielding an iminium salt that was used directly in the next step.

To a solution of the iminium intermediate in MeOH (150 mL), portions of solid $NaBH_4$ (770 mg, 20.35 mmol) were added over 5 min. The resultant mixture was stirred at room temperature for 30 min. The mixture was poured into $H_2O$ (100 mL). The aqueous layer was extracted with $CH_2Cl_2$ (2 × 100 mL). The combined organic phases were washed with brine (50 mL), dried ($MgSO_4$), and concentrated in vacuo. The resultant yellow solid was purified by flash chromatography (75 g silica gel; 19:1 → 9:1 hexanes/AcOEt) to provide the title compound **17c** (3.12 g, 82%) as a white solid. IR (KBr) $\nu_{max}$: 2958, 2906, 2862, 1615, 1576, 1494, 1475, 1381, 1157, 818, 752 cm$^{-1}$. $^1$H NMR (400 MHz, DMSO) $\delta$: 7.46−7.34 (m, 3H), 7.26−7.10 (m, 3H), 6.81−6.76 (m, 2H), 6.63−6.52 (m, 2H), 6.45−6.39 (m, 1H), 5.93 (s, 1H), 3.74−3.65 (m, 1H), 3.71 (s, 3H), 3.42−3.32 (m, 1H), 2.96−2.88 (m, 1H), 2.85−2.74 (m, 1H). $^{13}$C NMR (100.7 MHz, DMSO) $\delta$: 163.1 (d, $J_{C-F}$ = 239 Hz), 158.0, 150.2 (d, $J_{C-F}$ = 11 Hz), 142.7, 136.1, 130.9, 130.1 (d, $J_{C-F}$ = 11 Hz), 129.2, 128.7, 128.3, 119.6, 112.7, 112.0, 108.7, 102.6 (d, $J_{C-F}$ = 21 Hz), 99.4 (d, $J_{C-F}$ = 25 Hz), 59.9, 55.0, 43.3, 27.6. HRMS (ESI, M + H$^+$) calcd for $C_{22}H_{19}BrFNO$: 412.0707. Found: 412.0708. HPLC purity: 99%; $t_R$ 7.79 min.

**General Procedure for the Suzuki Cross-Coupling Reaction.** A solution containing phenylbromide **17b**, **c**, or **d** (1 equiv), 4-pyridineboronic acid (1−1.2 equiv), $K_2CO_3$ (2 equiv), and $PdCl_2(dppf)\cdot CH_2Cl_2$ (0.05−0.1 equiv) in toluene/acetone/water (ratio 3:3:1 or 4:4:1; ∼0.1 M) was refluxed for 20−78 h. After being cooled to room temperature, the mixture was poured into saturated aqueous $NaHCO_3$/AcOEt. The phases were separated. The aqueous layer was extracted with AcOEt, the combined organic layers were washed with brine and dried ($MgSO_4$), and the solution was concentrated to provide pyridines **35b−d** in yields ranging from 45 to 75%. For the synthesis of **34a**, the iodo derivative **13** served as the coupling partner, CsF (3 equiv) was used instead of $K_2CO_3$, and the toluene/acetone/water mixture was replaced by 1,2-dimethoxyethane (DME) as a solvent.

**Synthesis of 2-(3-Fluorophenyl)-6-methoxy-1-[4-pyridin-4-yl-phenyl]-1,2,3,4-tetrahydroisoquinoline (35c).** A solution containing phenylbromide **17c** (500 mg, 1.21 mmol), 4-pyridineboronic acid (179 mg, 1.46 mmol), $K_2CO_3$ (335 mg,

2.42 mmol), and $PdCl_2(dppf)\cdot CH_2Cl_2$ (50 mg, 0.061 mmol) in 3:3:1 toluene/acetone/water (10.5 mL) was refluxed for 42 h. After being cooled to room temperature, the mixture was poured into saturated aqueous $NaHCO_3$ (10 mL)/AcOEt (20 mL). The phases were separated. The aqueous layer was extracted with AcOEt (15 mL), the combined organic layers were washed with brine (15 mL) and dried ($MgSO_4$), and the solution was concentrated. The resulting brown oil was purified by flash chromatography (75 g silica gel; 19:1 $CH_2Cl_2$/MeOH) to furnish the pyridine **35c** (368 mg, 74%) as a beige solid. IR (KBr) $\nu_{max}$: 3027, 2909, 2834, 1615, 1596, 1577, 1496, 1163, 817, 788, 756, 682 $cm^{-1}$. $^1H$ NMR (400 MHz, DMSO) $\delta$: 8.56 (d, $J$ = 5.5 Hz, 2H), 7.67 (d, $J$ = 8.0 Hz, 2H), 7.61 (d, $J$ = 5.5 Hz, 2H), 7.43 (d, $J$ = 8.0 Hz, 1H), 7.39 (d, $J$ = 8.0 Hz, 2H), 7.15 (ddd, $J$ = 8.0, 8.0, 8.0 Hz, 1H), 6.82 (d, $J$ = 2.5 Hz, 1H), 6.79 (s, 1H), 6.65−6.55 (m, 2H), 6.42 (ddd, $J$ = 2.5, 8.0, 8.0 Hz, 1H), 6.01 (s, 1H), 3.81−3.68 (m, 4H, includes a 3-H s at $\delta$ = 3.72), 3.45−3.36 (m, 1H), 2.99−2.80 (m, 2H). $^{13}C$ NMR (100.7 MHz, DMSO) $\delta$: 163.1 (d, $J_{C-F}$ = 239 Hz), 157.9, 150.2 (d, $J_{C-F}$ = 11 Hz), 149.8, 146.3, 144.5, 136.1, 135.3, 130.1 (d, $J_{C-F}$ = 11 Hz), 129.5, 128.4, 127.2, 126.6, 120.8, 112.7, 112.0, 108.6, 102.5 (d, $J_{C-F}$ = 21.5 Hz), 99.3 (d, $J_{C-F}$ = 26 Hz), 60.2, 55.0, 43.4, 27.7. HRMS (ESI, M + $H^+$) calcd for $C_{27}H_{23}FN_2O$: 411.1873. Found: 411.1876. HPLC purity: 97%; $t_R$ 5.38 min.

**General Procedures for Methylation and Reduction Reactions. Preparation of 38a, b, c, and e.** A mixture of pyridine derivative **34a**, **35b**, **c**, or **d** and MeI (5 equiv) in DMF (0.2−0.3 M) was stirred at 40 °C for 2 h. Removal of solvent in vacuo provided the crude pyridinium salt **36a**, **37b**, **c**, or **d** as a solid, which was used directly in the next step. For the synthesis of **37d**, xylene was used as solvent (M = 0.5) in replacement of DMF, and the mixture was heated to 140 °C for 2.5 h.

A mixture of the pyridinium salt **36a**, **37b**, or **c** and $PtO_2$ (20% w/w) in MeOH or MeOH/THF (4:1 or 1:1) was stirred under an atmosphere pressure of $H_2$ at room temperature for 10−45 h. The reaction mixture was filtered through Celite, and the solvent was removed in vacuo. The residue was purified to provide the corresponding piperidine derivative. For the reduction of **37d**, a two-step procedure was used. The pyridinium salt was reduced with $NaBH_4$ (3.3 equiv) in MeOH (0.04 M) at room temperature for 30 min. The resultant alkene (tetrahydropyridine) in MeOH (0.04 M) was hydrogenated at atmospheric pressure and room temperature in the presence of $PtO_2$ (20% w/w). Yields of products ranged from 61 to 100%.

Piperidine derivatives **38b**, **c**, and **e** were obtained after demethylation, achieved by treatment of the methoxy analogues with $AlCl_3$ (~6 equiv) in $CH_2Cl_2$ (0.020−0.025 M) in the presence of EtSH (5 equiv) at room temperature for 2−17 h. Yields of purified products ranged from 20 to 55%. Tetrahydroisoquinoline **38a** was isolated after debenzylation effected as described above for the preparation of piperazine derivatives **29**−**33**.

A representative example for this series of transformations is provided below.

**Synthesis of 2-(3-Fluorophenyl)-1-[4-(1-methyl-piperidin-4-yl)phenyl]-1,2,3,4-tetrahydroisoquinolin-6-ol (38c).** A mixture of pyridine derivative **35c** (300 mg, 0.731 mmol) and MeI (228 $\mu$L, 3.65 mmol) in DMF (4 mL) was stirred at 40 °C for 2 h. Removal of the solvent in vacuo provided the crude pyridinium salt as a solid, which was used directly in the next step. A mixture of the pyridinium salt and $PtO_2$ (20% w/w) in 4:1 MeOH/THF (15 mL) was reduced under an atmosphere of $H_2$ (1013 mbar) at room temperature for 10 h. The reaction mixture was filtered through Celite using MeOH as eluent, and the solvents were removed in vacuo. The residue was purified by flash chromatography (30 g of silica gel; 13:1:0.1 $CH_2Cl_2$/MeOH/$NH_4OH$) to furnish the corresponding piperidine (193 mg, 61%) as a white solid. IR (KBr) $\nu_{max}$: 2935, 2842, 2780, 2735, 2678, 1617, 1577, 1497, 1380, 1279, 1163, 995, 821, 683 $cm^{-1}$. $^1H$ NMR (400 MHz, DMSO) $\delta$: 7.35 (d, $J$ = 9 Hz, 1H), 7.17−7.07 (m, 5H), 6.79−6.74 (m, 2H), 6.62−6.50 (m, 2H), 6.39 (ddd, $J$ = 2.0, 8.0, 8.0 Hz, 1H), 5.88 (br s, 1H), 3.75−3.65 (m, 1H), 3.70 (s, 3H), 3.43−3.31 (m, 1H), 2.95−2.75 (m, 4H), 2.40−2.30 (m, 1H), 2.14 (s, 3H), 1.94−1.83 (m, 2H), 1.69−1.50 (m, 4H). $^{13}C$ NMR (100.7 MHz, DMSO) $\delta$: 163.1 (d, $J_{C-F}$ = 238 Hz), 157.8, 150.3 (d, $J_{C-F}$ = 11 Hz), 144.3, 140.8, 136.0, 130.0 (d, $J_{C-F}$ = 11 Hz), 129.9, 128.3, 126.35, 126.31, 112.6, 111.8, 108.4, 102.2 (d, $J_{C-F}$ = 21.5 Hz), 99.1 (d, $J_{C-F}$ = 25 Hz), 60.2, 55.7, 54.9, 46.1, 43.2, 40.7, 32.9, 27.5. HRMS (ESI, M + $H^+$) calcd for $C_{28}H_{31}FN_2O$: 431.2499. Found: 431.2498. HPLC purity: 97%; $t_R$ 5.39 min.

A mixture of the piperidin-1-yl derivative from above (145 mg, 0.337 mmol), $AlCl_3$ (269 mg, 2.02 mmol), and EtSH (125 $\mu$L, 1.69 mmol) in $CH_2Cl_2$ (15 mL) was stirred at room temperature for 17 h. The mixture was diluted with $CH_2Cl_2$ (15 mL), and saturated aqueous $NaHCO_3$ (10 mL) was added to the mixture. The layers were separated, and the aqueous layer was further extracted with $CH_2Cl_2$ (20 mL). The combined organic phases were washed with brine (20 mL), dried ($MgSO_4$), and concentrated in vacuo. The yellow residue was purified by reverse phase HPLC, followed by extraction of the clean fractions with $CH_2Cl_2$/aqueous $NaHCO_3$. Compound **38c** was isolated as a yellow solid (77 mg, 55%). IR (KBr) $\nu_{max}$: 3600−2200, 3023, 2937, 2851, 2801, 1618, 1577, 1496, 1380, 1277, 1249, 1162, 991, 820, 764, 682 $cm^{-1}$. $^1H$ NMR (500 MHz, DMSO) $\delta$: 9.34 (s, 1H), 7.26 (d, $J$ = 8.5 Hz, 1H), 7.18−7.10 (m, 5H), 6.63−6.59 (m, 2H), 6.58 (d, $J$ = 2.5 Hz, 1H), 6.54 (dt, $J$ = 13.5, 2.5 Hz, 1H), 6.40 (ddd, $J$ = 2.5, 8.5, 8.5 Hz, 1H), 5.83 (br s, 1H), 3.74−3.67 (m, 1H), 3.40−3.30 (m, 1H), 2.88−2.72 (m, 4H), 2.40−2.31 (m, 1H), 2.15 (s, 3H), 1.93−1.85 (m, 2H), 1.69−1.52 (m, 4H). $^{13}C$ NMR (125.8 MHz, DMSO) $\delta$: 163.4 (d, $J_{C-F}$ = 239 Hz), 156.2, 150.6 (d, $J_{C-F}$ = 11 Hz), 144.5, 141.3, 136.1, 130.3 (d, $J_{C-F}$ = 10 Hz), 128.5, 126.6, 126.5, 114.2, 113.2, 108.5, 102.3 (d, $J_{C-F}$ = 21 Hz), 99.1 (d, $J_{C-F}$ = 26 Hz), 60.4, 55.8, 46.2, 43.4, 40.8, 33.0, 27.5. HRMS (ESI, M + $H^+$) calcd for $C_{27}H_{29}FN_2O$: 417.2342. Found: 417.2339. HPLC purity: 100%; $t_R$ 4.42 min.

**1-[4-(1-Methyl-piperidin-4-yl)phenyl]-2-phenyl-1,2,3,4-tetrahydroisoquinolin-6-ol (38a).** IR (KBr) $\nu_{max}$: 3600−2200, 3021, 2925, 2852, 2800, 2680, 1596, 1503, 1469, 1380, 1325, 1277, 1252, 1223, 1152, 749, 692 $cm^{-1}$. $^1H$ NMR (500 MHz, $CD_3OD$) $\delta$: 7.18−7.06 (m, 7H), 6.84 (d, $J$ = 8.0 Hz, 2H), 6.69 (t, $J$ = 7.5 Hz, 1H), 6.65 (dd, $J$ = 2.5, 8.0 Hz, 1H), 6.60 (d, $J$ = 2.5 Hz, 1H), 5.74 (s, 1H), 3.66−3.60 (m, 1H), 3.44−3.38 (m, 1H), 3.08 (dm, $J$ = 12.0 Hz for d, 2H), 2.90−2.78 (m, 2H), 2.53 (tt, $J$ = 4.0, 12.0 Hz, 1H), 2.43 (s, 3H), 2.34 (td, $J$ = 12.0, 2.5 Hz, 2H), 1.87−1.71 (m, 4H). $^{13}C$ NMR (125.8 MHz, $CD_3OD$) $\delta$: 157.3, 151.1, 145.0, 143.4, 138.1, 130.4, 130.0, 129.9, 128.7, 127.5, 118.6, 115.5, 115.4, 114.2, 63.3, 56.8, 45.8, 44.7, 41.9, 33.6/33.5, 29.1. HRMS (ESI, M + $H^+$) calcd for $C_{27}H_{30}N_2O$: 399.2431. Found: 399.2429. HPLC purity: 100%; $t_R$ 4.13 min.

**2-(4-Fluorophenyl)-1-[4-(1-methyl-piperidin-4-yl)phenyl]-1,2,3,4-tetrahydroisoquinolin-6-ol (38b).** IR (KBr) $\nu_{max}$: 3650−2200, 3049, 2936, 2800, 1610, 1507, 1379, 1276, 1230, 1151, 991, 810 $cm^{-1}$. $^1H$ NMR (400 MHz, DMSO) $\delta$: 9.27 (s, 1H), 7.17−7.05 (m, 5H), 6.96 (t, $J$ = 8.5 Hz, 2H), 6.80−6.70 (m, 2H), 6.60−6.53 (m, 2H), 5.71 (s, 1H), 3.64−3.55 (m, 1H), 3.43−3.26 (m, 1H), 2.88−2.69 (m, 4H), 2.42−2.30 (m, 1H), 2.16 (s, 3H), 1.99−1.87 (m, 2H), 1.70−1.49 (m, 4H). $^{13}C$ NMR (100.7 MHz, DMSO) $\delta$: 155.7, 154.4 (d, $J_{C-F}$ = 233 Hz), 145.6, 144.1, 141.4, 135.75, 128.3 (d, $J_{C-F}$ = 16 Hz), 126.7, 126.2, 115.0 (d, $J_{C-F}$ = 21.5 Hz), 114.3, 114.2, 114.0, 113.0, 61.1, 55.7, 46.0, 43.4, 40.6, 32.8, 27.5. HRMS (ESI, M + $H^+$) calcd for $C_{27}H_{29}FN_2O$: 417.2342. Found: 417.2341. HPLC purity: 99%; $t_R$ 4.07 min.

**2-(3-Hydroxyphenyl)-1-[4-(1-methyl-piperidin-4-yl)phenyl]-1,2,3,4-tetrahydroisoquinolin-6-ol (38e).** IR (KBr) $\nu_{max}$: 3650−2200, 3399, 3023, 2924, 2853, 1678, 1610, 1499, 1468, 1380, 1276, 1248, 1202 $cm^{-1}$. $^1H$ NMR (400 MHz, DMSO) $\delta$: 9.26 (s, 1H), 8.98 (s, 1H), 7.19 (d, $J$ = 8.0 Hz, 1H), 7.14 (d, $J$ = 8.5 Hz, 2H), 7.09 (d, $J$ = 8.5 Hz, 2H), 6.89 (t, $J$ = 8.0 Hz, 1H), 6.57 (d, $J$ = 8.0 Hz, 1H), 6.55 (s, 1H), 6.21 (br d, $J$ = 8.0 Hz, 1H), 6.14 (br s, 1H), 6.05 (br d, $J$ = 8.0 Hz, 1H), 5.68 (s, 1H), 3.68−3.57 (m, 1H), 3.40−3.20 (m, 1H), 2.95−2.64 (m, 4H), 2.56−2.35 (m, 1H), 2.24 (s, 3H), 2.15−2.00 (m, 2H), 1.75−1.55 (m, 4H). $^{13}C$ NMR (125.8 MHz, DMSO) $\delta$: 158.1, 156.1, 150.2, 143.9, 142.0, 136.3, 129.5, 128.7, 128.4, 126.7, 126.4, 114.2,

113.1, 104.1, 103.9, 99.9, 60.7, 55.4, 45.6/45.5 (maxima of br signal), 43.25, 32.4 (br signal), 27.5. HRMS (ESI, M + $H^+$) calcd for $C_{27}H_{30}N_2O_2$: 415.2386. Found: 415.2390. HPLC purity: 93%; $t_R$ 3.36 min.

**Syntheses of Piperazines 45−50. Synthesis of 6-Methoxy-2-(3-methoxyphenyl)-3,4-dihydro-2*H*-isoquinolin-1-one (16d).** A mixture of 6-methoxy-3,4-dihydro-2*H*-isoquinolin-1-one (**15**, 7.2 g, 40.6 mmol), 3-bromoanisole (98%, 10.5 mL, 81.3 mmol), $K_2CO_3$ (99%, 5.67 g, 40.6 mmol), and CuI (0.774 g, 4.06 mmol) in DMF (70 mL) was heated at 150 °C for 30 h under $N_2$ atmosphere. After that period of time, a second portion of CuI (0.774 g, 4.06 mmol) was added. Heating was continued for another 40 h prior to the addition of a last portion of CuI (0.774 g, 4.06 mmol). After being heated for a further 48 h, for a total reaction time of 118 h, the mixture was cooled to room temperature and poured into aqueous $NH_4OH$ (300 mL)/AcOEt (300 mL). The layers were separated, and the aqueous layer was extracted with portions of AcOEt (3 × 300 mL). The combined organic phases were washed with brine (500 mL), dried over $MgSO_4$, and concentrated in vacuo until crystallization started. Hexane was added slowly to the solution. The resulting solid was filtered, washed with hexane, and dried in vacuo to provide **16d** (10.96 g, 95%). IR (KBr) $\nu_{max}$: 1653, 1597, 1472, 1403, 1327, 1312, 1295, 1262, 1214, 1194, 1172, 1157, 1034, 1022, 851 $cm^{-1}$. $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$: 8.10 (d, $J$ = 8.5 Hz, 1H), 7.30 (t, $J$ = 8.0 Hz, 1H), 6.98−6.94 (m, 2H), 6.88 (dd, $J$ = 2.5, 8.5 Hz, 1H), 6.80 (dm, $J$ = 8.0 Hz for d, 1H), 6.72 (d, $J$ = 2.5 Hz, 1H), 3.96 (t, $J$ = 6.5 Hz, 2H), 3.88 (s, 3H), 3.83 (s, 3H), 3.10 (t, $J$ = 6.5 Hz, 2H). $^{13}C$ NMR (125.8 MHz, $CDCl_3$) $\delta$: 163.8, 162.1, 159.5, 144.0, 140.0, 130.6, 129.1, 122.1, 117.0, 112.3, 111.6, 111.5, 110.9, 55.05, 55.0, 49.0, 28.6. HRMS (ESI, M + $H^+$) calcd for $C_{17}H_{17}NO_3$: 284.1287. Found: 284.1285. HPLC purity: 98%; $t_R$ 5.43 min.

**General Synthesis of 1-(4-Bromophenyl)-4-alkylpiperazine 54−58 by Reductive Amination.** To a solution of 1-(4-bromophenyl)-piperazine·HCl (**51**)(1 equiv) and the appropriate ketone or aldehyde (1−2 equiv) in $ClCH_2CH_2Cl$ (0.22−0.26 M), was added $NaBH(OAc)_3$ (1.4−1.5 equiv), and the resultant mixture was stirred at room temperature for 2−26 h.[36] Following workup, piperazines **54**−**58** were isolated. They were used without further purification in cases where the purity was acceptable. Otherwise, the product was either triturated with solvent, crystallized, or purified by flash chromatography. The bromophenylpiperazines **54**−**58** were obtained in yields ranging from 74 to 99%. A representative example is given below.

**Synthesis of 1-(4-Bromophenyl)-4-isopropylpiperazine (54).** To a solution of 1-(4-bromophenyl)-piperazine·HCl (**51**) (98%, 3.0 g, 10.6 mmol) and anhydrous acetone (98%, 628 mg, 10.6 mmol) in $ClCH_2CH_2Cl$ (40 mL), was added $NaBH(OAc)_3$ (3.37 g, 15.9 mmol), and the resultant mixture was stirred at room temperature for 1 h. Another portion of anhydrous acetone (98%, 628 mg, 10.6 mmol) was added. Stirring was continued for 25 h. The mixture was then treated with 1 N aqueous NaOH (20 mL) and diluted with $Et_2O$ (100 mL). The layers were separated, and the aqueous phase was extracted once again with $Et_2O$ (50 mL). The combined organic layers were washed with brine (75 mL), dried ($MgSO_4$), and concentrated in vacuo. Crystallization of the resultant beige solid from hexane at −4 °C provided the title compound (2.53 g, 84%) as a white solid. $^1H$ NMR (300 MHz, DMSO) $\delta$: 7.30 (d, $J$ = 9.0 Hz, 2H), 6.86 (d, $J$ = 9 Hz, 2H), 3.08 (t, $J$ = 5 Hz, 2H), 2.65 (septet, $J$ = 6.5 Hz, 1H), 2.54 (t, $J$ = 5 Hz, 2H), 0.98 (d, $J$ = 6.5 Hz, 6H). $^{13}C$ NMR (100.7 MHz, DMSO) $\delta$: 150.2, 131.4, 117.15, 109.8, 53.65, 48.2, 47.9, 18.2. MS (ESI) $m/z$ 283 [M + $H^+$]. HPLC purity: 96%; $t_R$ 4.04 min.

**Synthesis of 1-(4-Bromophenyl)-4-methyl-piperazine (53).** This compound was synthesized by reductive amination of **51** according to the conditions described for the preparation of **26**. $^1H$ NMR (300 MHz, DMSO) $\delta$: 7.30 (d, $J$ = 9.0 Hz, 2H), 6.86 (d, $J$ = 9.0 Hz, 2H), 3.10 (t, $J$ = 5.0 Hz, 2H), 2.42 (t, $J$ = 5.0 Hz, 2H), 2.20 (s, 3H). $^{13}C$ NMR (100.7 MHz, DMSO) $\delta$: 150.1, 131.4, 117.2, 109.8, 54.4, 47.7, 45.7. MS (ESI) $m/z$ 255 [M + $H^+$]. HPLC purity: 91%; $t_R$ 3.81 min.

**General Procedure for the Conversion of Lactam 16d into Tetrahydroisoquinolines 39−44.** The phenyllithium reagent was generated from the reaction of *n*-BuLi (0.9−1.4 equiv) with 1-(4-bromophenyl)-4-alkylpiperazine **53**, **54**, **55**, **56**, **57**, or **58** (1−1.3 equiv) in THF (0.1−0.3 M) for 0.5−1 h. Lactam **16d** was allowed to undergo reaction with the appropriate phenyllithium reagent in THF (0.04−0.05 M) for 1−2.5 h at −78 °C. For the syntheses of **41** and **43**, the reaction mixtures were stirred for 10 min at −78 °C and then allowed to warm to room temperature, for total reaction times of 60 and 40 min, respectively. In the case of **44**, the mixture was stirred at −78 °C for 45 min following addition of the amide **16d** and allowed to warm to room temperature for 45 min. After aqueous workup and isolation, the iminium salt was dissolved in MeOH or 8:1 MeOH/$CH_2Cl_2$ (0.06−0.09 M) and treated with $NaBH_4$ (2−2.2 equiv) at room temperature for 15−60 min. After that period of time, the product was isolated and purified. Tetrahydroisoquinolines **39**−**44** were obtained in yields ranging from 59 to 87%. A representative example is given below.

**Synthesis of 6-Methoxy-2-(3-methoxyphenyl)-1-[4-(4-methyl-piperazin-1-yl)phenyl]-1,2,3,4-tetrahydroisoquinoline (39).** To a cold (−78 °C) solution of 1-(4-bromophenyl)-4-methyl-piperazine (**53**) (100 mg, 0.39 mmol) in anhydrous THF (1.5 mL), was added a solution of *n*-BuLi in hexanes (1.6 M, 0.244 mL, 0.39 mmol). After the resultant suspension was stirred at this temperature for 30 min, a solution of lactam **16d** (122 mg, 0.43 mmol) in anhydrous THF (3 mL) was added dropwise. Stirring was continued for an additional 60 min. The mixture was poured onto $H_2O$ (40 mL). $HClO_4$ (70%, 75 $\mu$L) was added, the mixture was stirred for 10 min, and the organic solvent was removed in vacuo. The aqueous layer was extracted with AcOEt (4 × 30 mL) and $CH_2Cl_2$ (2 × 20 mL). The combined organic layers were washed with brine (30 mL) and dried ($MgSO_4$), and the solution was concentrated in vacuo yielding an iminium salt that was used directly in the next step.

To a solution of the iminium intermediate in 8:1 MeOH/$CH_2Cl_2$ (4.5 mL), was added solid $NaBH_4$ (97%, 30.5 mg, 0.78 mmol) in two portions. The resultant mixture was stirred at room temperature for 15 min. The suspension was poured into saturated aqueous $NaHCO_3$ (30 mL). The organic solvents were removed in vacuo. The aqueous layer was extracted with AcOEt (3 × 20 mL), and the combined organic phases were washed with brine (20 mL), dried ($MgSO_4$), and concentrated in vacuo. The resultant brown wax was purified by flash chromatography (25 g of silica gel, 12:1 $CH_2Cl_2$/MeOH) to provide the title compound **39** (129 mg, 68%) as a yellow wax. IR (KBr) $\nu_{max}$: 2994, 2935, 2832, 2794, 2746, 1676, 1609, 1496, 1380, 1239, 1167, 1038, 817 $cm^{-1}$. $^1H$ NMR (500 MHz, DMSO) $\delta$: 7.26 (d, $J$ = 8.5 Hz, 1H), 7.06−7.00 (m, 3H), 6.81−6.72 (m, 4H), 6.42 (dd, $J$ = 2.0, 8.5 Hz, 1H), 6.32 (t, $J$ = 2.0 Hz, 1H), 6.23 (dd, $J$ = 2.0, 8.5 Hz, 1H), 5.77 (s, 1H), 3.71 (s, 3H), 3.66 (s, 3H), 3.68−3.60 (m, 1H), 3.42−3.28 (m, 1H), 3.03 (t, $J$ = 5.0 Hz, 4H), 2.94−2.78 (m, 2H), 2.39 (t, $J$ = 5.0 Hz, 4H), 2.18 (s, 3H). $^{13}C$ NMR (125.8 MHz, DMSO) $\delta$: 160.2, 157.8, 150.3, 149.6, 136.2, 134.0, 130.5, 129.5, 128.5, 127.4, 115.0, 112.7, 111.9, 106.2, 101.6, 99.6, 60.3, 55.0, 54.7, 54.6, 48.0, 45.7, 42.9, 27.6. HRMS (ESI, M + $H^+$) calcd for $C_{28}H_{33}N_3O_2$: 444.2646. Found: 444.2644. HPLC purity: 91%; $t_R$ 4.30 min.

**General Procedure for Demethylation. Synthesis of 45−50.** Demethylation was achieved by treatment of **39**−**44** with $AlCl_3$ (5.9−6 equiv) in $CH_2Cl_2$ (0.02−0.03 M) in the presence of EtSH (5 equiv) at room temperature for 0.5−4 h. Yields of purified products varied between 45 and 58%. A representative example is described below.

**Synthesis of 2-(3-Hydroxyphenyl)-1-[4-(4-methylpiperazin-1-yl)phenyl]-1,2,3,4-tetrahydroisoquinolin-6-ol (45).** A mixture of the piperazin-1-yl derivative **39** (120 mg, 0.27 mmol), $AlCl_3$ (99%, 224 mg, 1.66 mmol), and EtSH (97%, 107.5 $\mu$L, 1.41 mmol) in $CH_2Cl_2$ (12 mL) was stirred at room temperature for 4 h. The mixture was diluted with $CH_2Cl_2$ (50 mL) and poured onto saturated aqueous $NaHCO_3$ (30 mL). The layers were separated, and the aqueous layer was

extracted with $CH_2Cl_2$ (3 × 50 mL). The combined organic phases were washed with brine (50 mL), dried ($MgSO_4$), and concentrated in vacuo. The yellow residue was purified by flash chromatography (25 g silica gel, 9:1 $CH_2Cl_2$/MeOH) to provide the title compound as a yellow solid (67.8 mg, 58%). IR (KBr) $\nu_{max}$: 3600−2200, 3318, 3027, 2947, 2841, 1609, 1512, 1453, 1389, 1366, 1292, 1248, 1220, 1208, 1164, 1000, 922, 829, 812, 792, 750, 686 cm$^{-1}$. $^1$H NMR (400 MHz, DMSO) $\delta$: 9.25 (s, 1H), 8.98 (s, 1H), 7.14 (d, $J$ = 8.0 Hz, 1H), 7.02 (d, $J$ = 8.5 Hz, 2H), 6.90 (t, $J$ = 8.0 Hz, 1H), 6.79 (d, $J$ = 8.5 Hz, 2H), 6.60−6.54 (m, 2H), 6.24 (dd, $J$ = 2.0, 8.0 Hz, 1H), 6.17 (t, $J$ = 2.0 Hz, 1H), 6.06 (dd, $J$ = 2.0, 8.0 Hz, 1H), 5.63 (s, 1H), 3.62−3.55 (m, 1H), 3.40−3.26 (m, 1H), 3.04 (t, $J$ = 5.0 Hz, 4H), 2.86−2.69 (m, 2H), 2.40 (t, $J$ = 5.0 Hz, 4H), 2.19 (s, 3H). $^{13}$C NMR (100.7 MHz, DMSO) $\delta$: 157.8, 155.6, 150.2, 149.2, 136.0, 134.0, 129.2, 128.8, 128.2, 127.1, 114.8, 114.0, 112.8, 104.2, 103.8, 100.0, 60.5, 54.6, 48.0, 45.7, 43.0, 27.6. HRMS (ESI, M + H$^+$) calcd for $C_{26}H_{29}N_3O_2$: 416.2338. Found: 416.2337. HPLC purity: 96%; $t_R$ 2.88 min

**2-(3-Hydroxyphenyl)-1-[4-(4-isopropylpiperazin-1-yl)-phenyl]- 1,2,3,4-tetrahydroisoquinolin-6-ol (46).** IR (KBr) $\nu_{max}$: 3700−2100, 3382, 2968, 2829, 1609, 1511, 1455, 1383, 1237, 1173, 1008, 929, 973, 919, 818, 755, 689 cm$^{-1}$. $^1$H NMR (400 MHz, DMSO) $\delta$: 9.26 (s, 1H), 8.99 (s, 1H), 7.13 (d, $J$ = 8.0 Hz, 1H), 7.02 (d, $J$ = 8.5 Hz, 2H), 6.90 (t, $J$ = 8.0 Hz, 1H), 6.77 (d, $J$ = 8.5 Hz, 2H), 6.61−6.54 (m, 2H), 6.24 (d, $J$ = 8.0 Hz, 1H), 6.18 (s, 1H), 6.07 (d, $J$ = 8.0 Hz, 1H), 5.63 (s, 1H), 3.63−3.54 (m, 1H), 3.34−3.25 (m, 1H), 3.04 (br s, 4H), 2.86−2.63 (m, 3H), 2.56 (br s, 4H), 0.99 (d, $J$ = 6.5 Hz, 6H). $^{13}$C NMR (100.7 MHz, DMSO) $\delta$: 157.8, 155.7, 150.2, 149.3, 136.0, 134.1, 129.3, 128.8, 128.2, 127.1, 114.8, 114.0, 112.8, 104.2, 103.8, 100.0, 60.5, 53.9, 48.4, 48.0, 43.1, 27.6, 18.2. HRMS (ESI, M + H$^+$) calcd for $C_{28}H_{33}N_3O_2$: 444.2646. Found: 444.2646. HPLC purity: 99%; $t_R$ 3.14 min.

**2-(3-Hydroxyphenyl)-1-[4-(4-isobutylpiperazin-1-yl)-phenyl]- 1,2,3,4-tetrahydroisoquinolin-6-ol (47).** IR (KBr) $\nu_{max}$: 3700−2200, 3390, 2954, 2826, 1610, 1511, 1456, 1382, 1234, 1172, 1008, 929, 817 cm$^{-1}$. $^1$H NMR (400 MHz, DMSO) $\delta$: 9.25 (s, 1H), 8.99 (s, 1H), 7.14 (d, $J$ = 8.0 Hz, 1H), 7.02 (d, $J$ = 8.5 Hz, 2H), 6.90 (t, $J$ = 8.0 Hz, 1H), 6.78 (d, $J$ = 8.5 Hz, 2H), 6.61−6.52 (m, 2H), 6.24 (br d, $J$ = 8.0 Hz for d, 1H), 6.18 (d, $J$ = 2.0 Hz, 1H), 6.07 (br d, $J$ = 8.0 Hz, 1H), 5.63 (s, 1H), 3.63−3.52 (m, 1H), 3.34−3.23 (m, 1H), 3.04 (br s, 4H), 2.86−2.67 (m, 2H), 2.45 (br s, 4H), 2.08 (br s, 2H), 1.84−1.71 (m, 1H), 0.86 (d, $J$ = 6.5 Hz, 6H). $^{13}$C NMR (100.7 MHz, DMSO) $\delta$: 157.8, 155.7, 150.2, 149.2, 136.0, 134.1, 129.2, 128.8, 128.2, 127.2, 114.8, 114.0, 112.9, 104.2, 103.8, 100.0, 60.5, 53.0, 48.1, 43.1, 27.6, 24.7, 20.8. HRMS (ESI, M + H$^+$) calcd for $C_{29}H_{35}N_3O_2$: 458.2802. Found: 458.2800. HPLC purity: 100%; $t_R$ 3.41 min.

**1-[4-(4-Cyclopropylmethyl-piperazin-1-yl)phenyl]-2-(3-hydroxyphenyl)-1,2,3,4-tetrahydroisoquinolin-6-ol (48).** IR (KBr) $\nu_{max}$: 3600−2100, 3384, 3002, 2916, 2827, 1609, 1511, 1455, 1380, 1336, 1235, 1168, 1002, 920, 817, 792, 753, 687 cm$^{-1}$. $^1$H NMR (400 MHz, DMSO) $\delta$: 9.24 (s, 1H), 8.98 (s, 1H), 7.13 (d, $J$ = 8.0 Hz, 1H), 7.01 (d, $J$ = 8.5 Hz, 2H), 6.89 (t, $J$ = 8.0 Hz, 1H), 6.78 (d, $J$ = 8.5 Hz, 2H), 6.60−6.53 (m, 2H), 6.24 (dd, $J$ = 2.0, 8.5 Hz, 1H), 6.16 (t, $J$ = 2.0 Hz, 1H), 6.06 (dd, $J$ = 2.0, 8.0 Hz, 1H), 5.62 (s, 1H), 3.62−3.54 (m, 1H), 3.42−3.24 (m, 1H), 3.05 (t, $J$ = 5.0 Hz, 4H), 2.85−2.68 (m, 2H), 2.58−2.50 (m, 4H), 2.20 (d, $J$ = 6.5 Hz, 2H), 0.88−0.77 (m, 1H), 0.49−0.42 (m, 2H), 0.10−0.04 (m, 2H). $^{13}$C NMR (100.7 MHz, DMSO) $\delta$: 157.8, 155.6, 150.2, 149.3, 136.0, 134.1, 129.2, 128.8, 128.2, 127.1, 114.8, 114.0, 112.8, 104.2, 103.8, 100.0, 62.7, 60.5, 52.6, 48.2, 43.0, 27.6, 8.2, 3.8. HRMS (ESI, M + H$^+$) calcd for $C_{29}H_{33}N_3O_2$: 456.2651. Found: 456.2654. HPLC purity: 100%; $t_R$ 3.42 min.

**1-[4-(4-Cyclopentylpiperazin-1-yl)phenyl]-2-(3-hydroxyphenyl)-1,2,3,4-tetrahydroisoquinolin-6-ol (49).** IR (KBr) $\nu_{max}$: 3650−2200, 3400, 2954, 2827, 1610, 1511, 1453, 1381, 1237, 1170, 1000, 927, 817, 753, 688 cm$^{-1}$. $^1$H NMR (400 MHz, DMSO) $\delta$: 9.23 (s, 1H), 8.97 (s, 1H), 7.12 (d, $J$ = 8.0 Hz, 1H), 7.01 (d, $J$ = 8.5 Hz, 2H), 6.88 (t, $J$ = 8.0 Hz, 1H), 6.77 (d, $J$ = 8.5 Hz, 2H), 6.59−6.51 (m, 2H), 6.22 (br d, $J$ = 8.0 Hz, 1H), 6.15 (br s, 1H), 6.05 (br d, $J$ = 8.0 Hz, 1H), 5.61 (s, 1H), 3.62−3.53 (m, 1H), 3.42−3.20 (m, 1H), 3.03 (br s, 4H), 2.85−2.65 (m, 2H), 2.58−2.40 (m, 5H), 1.85−1.73 (m, 2H), 1.65−1.42 (m, 4H), 1.41−1.28 (m, 2H). $^{13}$C NMR (100.7 MHz, DMSO) $\delta$: 157.8, 155.6, 150.2, 149.2, 136.0, 134.1, 129.2, 128.8, 128.2, 127.1, 114.7, 114.0, 112.8, 104.2, 103.8, 100.0, 66.6, 60.5, 51.6, 48.2, 43.0, 29.8, 27.6, 23.7. HRMS (ESI, M + H$^+$) calcd for $C_{30}H_{35}N_3O_2$: 470.2808. Found: 470.2815. HPLC purity: 98%; $t_R$ 3.64 min.

**1-[4-(4-Cyclohexylpiperazin-1-yl)phenyl]-2-(3-hydroxyphenyl)-1,2,3,4-tetrahydroisoquinolin-6-ol (50).** IR (KBr) $\nu_{max}$: 3390, 3024, 2931, 2826, 2598, 1612, 1576, 1497, 1380, 1286, 1233, 977, 918 cm$^{-1}$. $^1$H NMR (400 MHz, DMSO) $\delta$: 9.24 (s, 1H), 8.98 (s, 1H), 7.13 (d, $J$ = 8.0 Hz, 1H), 7.01 (d, $J$ = 8.5 Hz, 2H), 6.89 (t, $J$ = 8.0 Hz, 1H), 6.76 (d, $J$ = 8.5 Hz, 2H), 6.60−6.52 (m, 2H), 6.23 (br d, $J$ = 8.0 Hz, 1H), 6.16 (br s, 1H), 6.06 (br d, $J$ = 8.0 Hz, 1H), 5.62 (s, 1H), 3.62−3.53 (m, 1H), 3.45−3.25 (m, 1H), 3.01 (br s, 4H), 2.85−2.67 (m, 2H), 2.59 (br s, 4H), 2.30−2.19 (m, 1H), 1.82−1.66 (m, 4H), 1.59−1.51 (m, 1H), 1.26−1.00 (m, 5H). $^{13}$C NMR (100.7 MHz, DMSO) $\delta$: 157.8, 155.6, 150.2, 149.3, 136.0, 134.0, 129.2, 128.8, 128.2, 127.1, 114.8, 114.0, 112.8, 104.2, 103.8, 100.0, 62.5, 60.5, 48.6, 48.4, 43.0, 28.3, 27.6, 25.9, 25.3. HRMS (ESI, M + H$^+$) calcd for $C_{31}H_{37}N_3O_2$: 484.2964. Found: 484.2965. HPLC purity: 97%; $t_R$ 3.71 min.

**Crystallography.** See Supporting Information. The structure factors and the coordinates of the refined structure were deposited in the protein structure database (PDB ID code: 1XQC).

**Biological Assays. Radioligand Binding Studies.** The radioligand binding assay was performed by using 96-well microtiterplates (Picoplates, Packard) in volumes of 0.2 mL of incubation buffer (50 mM Tris, pH 7.4). The incubation mixture contained 5 nM ERα (PanVera, USA) or 6 nM ER$\beta$ long form human recombinant receptors (PanVera,), 8 nM [$^3$H] 17$\beta$-estradiol (~180 000 total counts, Perkin-Elmer NET 517, USA), and the compound to be tested and 0.25 mg/well SPA-beads (Amersham RPNQ 0001). After incubation at room temperature for 2−4 h, the reaction was terminated by centrifugation at room temperature (10 min at 1000*g*). The radioactivity was counted at least 3 h after completion of the experiment in a Packard Topcount scintillation counter. Nonspecific binding was defined as the remaining radioactivity in the presence of 10 $\mu$M nonradioactive 17$\beta$-estradiol (Sigma). Assays were performed in triplicate.

**MCF-7 Proliferation Assay.** The human breast adenocarcinoma cell line, MCF-7 (ATCC HTB-22), was routinely cultivated in DMEM (Dulbecco's modified eagle medium, high glucose, Gibco Invitrogen Corporation, Paisley, U.K.) supplemented with 10% fetal bovine serum (FBS), 2 mM l-glutamine, 10 mM Hepes (4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid), 50 IU/mL penicillin, and 50 $\mu$g/mL streptomycine (pen/strep) at 37 °C in a 5% $CO_2$ humidified incubator. Three days prior to an assay, MCF-7 cells were switched to DMEM low glucose phenol red free,[43] supplemented with 10% dextran-coated charcoal-stripped FBS (sFBS) to deplete internal stores of steroids, 2 mM L-glutamine, 10 mM Hepes, and penicillin/streptomycin. Cells were trypsinized from the maintenance flask with phenol red free trypsin (0.05%)−EDTA (0.02%) (HyClone, Logan, UT) and seeded in a 96-well plate (Nunc) at a density of $10^3$ cells per final volume of 100 $\mu$L DMEM low glucose phenol red free, supplemented with 5% sFBS, 2 mM l-glutamine, 10 mM Hepes, and penicillin/streptomycin. After 24 h, fresh medium, supplemented with serial dilutions of compounds or DMSO as diluent control, was prepared and added in the presence or absence of $10^{-10}$ M 17$\beta$-estradiol to triplicate microcultures. Cells were incubated for 6 days, and medium with compounds was changed once after 3 days. At the end of the incubation time, proliferation was assessed using the CellTiter 96 aqueous one solution cell proliferation assay kit from Promega (Madison, WI) according to the manufacturer's instructions. The absorbance at 490 nm was measured. This parameter relates to the amount of formazan

produced, the quantity of which is directly proportional to the number of living cells in the culture.

**ERE−Luciferase Reporter Assay.** HELNα and HELN$\beta$, two human cervix adenocarcinoma cell lines derived from HeLa cells stably transfected with the reporter gene ERE-$\beta$Glob-Luc-SVNeo and the expression plasmids ERα or ER$\beta$, respectively, were used to quantify the antiestrogenic and estrogenic effects of compounds on ERE.[44,45] These cells were routinely cultivated in DMEM phenol red free, supplemented with 5% sFBS, 2 mM glutamine, 1% penicillin/streptomycin, 1 mg/mL Geneticin, and 0.5 $\mu$g/mL puromycin to ensure appropriate antibiotic selection. For the assay, cells were trypsinized from the maintenance flask with phenol red free trypsin (0.05%)−EDTA (0.02%) (HyClone, Logan, UT) and seeded in an opaque 96-well plate (Nunc) at a density of $7.5 \times 10^4$ cells/well in a final volume of 100 $\mu$L of assay medium (DMEM, phenol red free, supplemented with 3% sFBS, 2 mM glutamine, and penicillin/streptomycin). Five hours later, cells were adherent. Serial dilutions of compounds or DMSO as diluent control were then added in the presence of a fixed concentration of 17$\beta$-estradiol ($10^{-10}$ M in HELNα and $10^{-9}$ M in HELN$\beta$) to triplicate microcultures. Faslodex (Tocris, $10^{-8}$ M) was used as a baseline indicator. Cells were incubated for 20 h at 37 °C in a 5% $CO_2$ humidified incubator before being processed for luciferase determination. Medium was aspirated and 100 $\mu$L of a 1:1 mixture of LucLite (Perkin-Elmer, Life Science, Boston, MA)/assay medium was added to each well. Plates were then sealed with a Topseal and left in the dark for 10 min before luminescence activity was determined by counting the plates for 6 s in a $\beta$-TopCount (Packard Instrument Company, Meriden, CT). Protein concentrations were determined using the Bradford Micromethod (Bio-Rad). Luciferase was expressed in relative luminescence units/$\mu$g protein.

**Cassette Dosing Experiments. Rat Pharmacokinetic Cassette Standard Assay.** A set of seven novel compounds plus the internal standard raloxifene (**7**) was administered intravenously via the femoral vein at a dose level of 1 mg/kg of body weight (for each individual compound) to four female rats. Cannulas were implanted into the femoral vein for intravenous compound administration and into the femoral artery for rapid blood sampling. Compounds were administered orally by gavage at a dose level of 5 mg/kg of body weight. Blood was sampled over a 24 h time period postdose (from 5 min for iv and 15 min for po). Blood samples were then processed through steps involving protein precipitation by $CH_3CN$ addition, centrifugation of the supernatant, and evaporation of the supernatant in a vacuum centrifuge. Dried residues were dissolved in MeOH/$H_2O$ (60:40 v/v) containing 1% HCOOH and analyzed by HPLC on an Uptisphere C18 reversed-phase HPLC column (particle size, 3 $\mu$m; column dimensions, 2 mm × 50 mm). Eluents used consisted of A, 10% $CH_3CN$ in $H_2O$ with 0.1% HCOOH (pH 2.1), and B, 90% $CH_3CN$ with 10% $H_2O$ and 0.1% HCOOH (pH 2.1). A linear gradient was run from 5 to 100% B over 7 min followed by a 3 min hold at 100% B at a constant temperature of 50 °C in the column compartment. The flow rate was held constant at 0.4 mL/min. Sample injection volume was 10 $\mu$L. The flow from the HPLC system was directly introduced into the ion source of an Agilent 1100 series MS detector (single quadrupole mass analyzer) and subjected to atmospheric pressure electrospray ionization (positive mode). All compounds were detected as protonated quasi-molecular ions $[M + H]^+$. A structurally closely related SERM was used as an analytical internal standard. Quantification of blood levels of the parent compounds was based on a seven-level calibration curve (in triplicate) using blank rat blood samples spiked with stock solutions of external and internal standards.

**Rat Pharmacokinetic Cassette Validation.** Raloxifene (**7**) alone was administered iv (1 mg/kg) and po (3 mg/kg) to four female rats each. Blood samples were taken and analyzed as described above. The pharmacokinetic data generated from this validation study were compared with those obtained for raloxifene (**7**) in cassette dosing experiments to check for potential pharmacokinetic interactions. Deviations exceeding the typical range of biological variability (approximately ±50% maximum for individual parameters) were considered strongly indicative for pharmacokinetic interactions between compounds in the cassette, and the respective data were discarded.

**Acknowledgment.** We would like to thank our collaborators for their important contribution to the work disclosed herein: Nadine Braendlin, Patrick Lerch, Pierre Martin, Nicole Reymann, Hans Rudolf Zihlmann, Diana Latscha, Roland Feifel, Jean-Louis Runser, Yves Seltenmeyer, Tanja Grabenstaetter, and Erika Kuhn. In addition, the support of M. Mahnke and P. Graff for the expression and mass spectrometry analysis of ERα-LBD, the experimental assistance of Lukas Oberer for NMR experiments, and the staff of the Swiss−Norwegian Beam Lines at the European Synchrotron Radiation Facilities in Grenoble are gratefully acknowledged. We also wish to thank Drs. J.-C. Nicolas and P. Balaguer (INSERM U439, Montpellier, France) for their precious advice on the use of the HELNα and HELN$\beta$ cell lines.

**Supporting Information Available:** Protein preparation, crystallization, data collection, and structure resolution. This material is available free of charge via the Internet at http://pubs.acs.org.

## References

(1) Palacios, S. Current Perspectives on the Benefits of HRT in Menopausal Women. *Maturitas* **1999**, *33*, S1−S13.
(2) Compston, J. E. Sex Steroids and Bone. *Physiol. Rev.* **2001**, *81*, 419−447.
(3) Albertazzi, P.; Purdie, D. W. Oestrogen and Selective Oestrogen Receptor Modulators (SERMs): Current Roles in the Prevention and Treatment of Osteoporosis. *Best Pract. Res., Clin. Rheumatol.* **2001**, *15*, 451−468.
(4) Kanis, J. A. Estrogens, the Menopause, and Osteoporosis. *Bone* **1996**, *19*, 185S-190S.
(5) Sato, M.; Grese, T. A.; Dodge, J. A.; Bryant, H. U.; Turner, C. H. Emerging Therapies for the Prevention or Treatment of Postmenopausal Osteoporosis. *J. Med. Chem.* **1999**, *42*, 1−24.
(6) Rossouw, J. E.; Anderson, G. L.; Prentice, R. L.; LaCroix, A. Z.; Kooperberg, C.; Stefanick, M. L.; Jackson, R. D.; Beresford, S. A. A.; Howard, B. V.; Johnson, K. C.; Kotchen, J. M.; Ockene, J. Risks and Benefits of Estrogen Plus Progestin in Healthy Postmenopausal Women: Principal Results from the Women's Health Initiative Randomized Controlled Trial. *JAMA, J. Am. Med. Assoc.* **2002**, *288*, 321−333.
(7) Hendrix, S. L. Hormone Therapy: Evolving Concepts. *Curr. Opin. Rheumatol.* **2003**, *15*, 464−468.
(8) Miller, C. P. SERMs: Evolutionary Chemistry, Revolutionary Biology. *Curr. Pharm. Des.* **2002**, *8*, 2089−2111.
(9) Ke, H. Z.; Brown, T. A.; Thompson, D. D. Lasofoxifene (CP-336156), a Novel Selective Estrogen Receptor Modulator, in Preclinical Studies. *J. Am. Aging Assoc.* **2002**, *25*, 87−99.
(10) Rosati, R. L.; Jardine, P. D. S.; Cameron, K. O.; Thompson, D. D.; Ke, H. Z.; Toler, S. M.; Brown, T. A.; Pan, L. C.; Ebbinghaus, C. F.; Reinhold, A. R.; Elliott, N. C.; Newhouse, B. N.; Tjoa, C. M.; Sweetnam, P. M.; Cole, M. J.; Arriola, M. W.; Gauthier, J. W.; Crawford, D. T.; Nickerson, D. F.; Pirie, C. M.; Qi, H.; Simmons, H. A.; Tkalcevic, G. T. Discovery and Preclinical Pharmacology of a Novel, Potent, Nonsteroidal Estrogen Receptor Agonist/Antagonist, CP-336156, a Diaryltetrahydronaphthalene. *J. Med. Chem.* **1998**, *41*, 2928−2931.
(11) Miller, C. P.; Collini, M. D.; Tran, B. D.; Harris, H. A.; Kharode, Y. P.; Marzolf, J. T.; Moran, R. A.; Henderson, R. A.; Bender, R. H. W.; Unwalla, R. J.; Greenberger, L. M.; Yardley, J. P.; Abou-Gharbia, M. A.; Lyttle, C. R.; Komm, B. S. Design, Synthesis, and Preclinical Characterization of Novel, Highly Selective Indole Estrogens. *J. Med. Chem.* **2001**, *44*, 1654−1657.
(12) Hochner-Celnikier, D. Pharmacokinetics of Raloxifene and its Clinical Application. *Eur. J. Obstet. Gynecol. Reprod. Biol.* **1999**, *85*, 23−29.
(13) Maricic, M.; Gluck, O. Review of Raloxifene and its Clinical Applications in Osteoporosis. *Exp. Opin. Pharmacother.* **2002**, *3*, 767−775.

(14) Grese, T. A.; Sluka, J. P.; Bryant, H. U.; Cullinan, G. J.; Glasebrook, A. L.; Jones, C. D.; Matsumoto, K.; Palkowitz, A. D.; Sato, M.; Termine, J. D.; Winter, M. A.; Yang, N. N.; Dodge, J. A. Molecular Determinants of Tissue Selectivity in Estrogen Receptor Modulators. *Proc. Natl. Acad. Sci. U.S.A.* **1997**, *94*, 14105−14110.
(15) Katzenellenbogen, B. S.; Choi, I.; Delage-Mourroux, R.; Ediger, T. R.; Martini, P. G. V.; Montano, M.; Sun, J.; Weis, K.; Katzenellenbogen, J. A. Molecular Mechanisms of Estrogen Action: Selective Ligands and Receptor Pharmacology. *J. Steroid Biochem. Mol. Biol.* **2000**, *74*, 279−285.
(16) Rickard, D. J.; Subramaniam, M.; Spelsberg, T. C. Molecular and Cellular Mechanisms of Estrogen Action on the Skeleton. *J. Cell. Biochem.* **1999**, *32*/*33*, 123−132.
(17) Riggs, L.; Hartmann, L. C. Selective Estrogen-Receptor Modulators − Mechanisms of Action and Application to Clinical Practice. *N. Engl. J. Med.* **2003**, *348*, 618−629.
(18) Mosselman, S.; Polman, J.; Dijkema, R. ER$\beta$: Identification and Characterization of a Novel Human Estrogen Receptor. *FEBS Lett.* **1996**, *392*, 49−53.
(19) Dechering, K.; Boersma, C.; Mosselman, S. Estrogen Receptors $\alpha$ and $\beta$: Two Receptors of a Kind? *Curr. Med. Chem.* **2000**, *7*, 561−576.
(20) Taylor, A. H.; Al-Azzawi, F. Immunolocalisation of Oestrogen Receptor Beta in Human Tissues. *J. Mol. Endocrinol.* **2000**, *24*, 145−155.
(21) Lee, K. C.; Lee Kraus, W. Nuclear Receptors, Coactivators and Chromatin: New Approaches, New Insights. *Trends Endocrinol. Metab.* **2001**, *12*, 191−197.
(22) Shang, Y.; Brown, M. Molecular Determinants for the Tissue Specificity of SERMs. *Science* **2002**, *295*, 2465−2468.
(23) Sims, N. A.; Dupont, S.; Krust, A.; Clement-Lacroix, P.; Minet, D.; Resche-Rigon, M.; Gaillard-Kelly, M.; Baron, R. Deletion of Estrogen Receptors Reveals a Regulatory Role for Estrogen Receptors-$\beta$ in Bone Remodeling in Females but Not in Males. *Bone* **2002**, *30*, 18−25.
(24) Schmid, C. R.; Sluka, J. P.; Duke, K. M.; Glasebrook, A. W. Novel Nonsteroidal Selective Estrogen Receptor Modulators. Carbon and Heteroatom Replacement of Oxygen in the Ethoxypiperidine Region of Raloxifene. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 523−528.
(25) ER$\beta$-selective 1,3,5-triazine derivatives which include N-substituted piperazines moieties have been reported. See: Henke, B. R.; Consler, T. G.; Go, N.; Hale, R. L.; Hohman, D. R.; Jones, S. A.; Lu, A. T.; Moore, L. B.; Moore, J. T.; Orband-Miller, L. A.; Robinett, R. G.; Shearin, J.; Spearing, P. K.; Stewart, E. L.; Turnbull, P. S.; Weaver, S. L.; Williams, S. P.; Wisely, G. B.; Lambert, M. H. A New Series of Estrogen Receptor Modulators that Display Selectivity for Estrogen Receptor $\beta$. *J. Med. Chem.* **2002**, *45*, 5492−5505.
(26) Nagarajan, K.; Talwalker, P. K.; Kulkarni, C. L.; Shah, R. K.; Shenoy, S. J.; Prabhu, S. S. Antiimplantation Agents: Part II − 1,2-Diaryl-1,2,3,4-Tetrahydroisoquinolines. *Indian J. Chem., Sect. B* **1985**, *24B*, 83−97.
(27) Jones, B. A.; Bradshaw, J. S.; Nishioka, M.; Lee, M. L. Synthesis of Smectic Liquid-Crystalline Polysiloxanes from Biphenylcarboxylate Esters and Their Use as Stationary Phases for High-Resolution Gas Chromatography. *J. Org. Chem.* **1984**, *49*, 4947−4951.
(28) Sathya Shanker, P.; Subba Rao, G. S. R. Synthesis of Isoquinolines from Indanones: Total Synthesis of Illudinine. *Indian J. Chem., Sect. B* **1993**, *32B*, 1209−1213.
(29) Tomita, M.; Minami, S.; Uyeo, S. The Schmidt Reaction with Benzocycloalkenones. *J. Chem. Soc. C* **1969**, 183−188.
(30) Sugahara, M.; Ukita, T. A Facile Copper-Catalyzed Ullmann Condensation: *N*-Arylation of Heterocyclic Compounds Containing an −NHCO− Moiety. *Chem. Pharm. Bull.* **1997**, *45*, 719−721.
(31) Ali, M. H.; Buchwald, S. L. An Improved Method for the Palladium-Catalyzed Amination of Aryl Iodides. *J. Org. Chem.* **2001**, *66*, 2560−2565.
(32) Arduengo, A. J., III; Krafczyk, R.; Schmutzler, R.; Craig, H. A.; Goerlich, J. R.; Marshall, W. J.; Unverzagt, M. Imidazolylidenes, Imidazolinylidenes and Imidazolidines. *Tetrahedron* **1999**, *55*, 14523−14534.
(33) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. Synthesis and Activity of a New Generation of Ruthenium-Based Olefin Metathesis Catalysts Coordinated with 1,3-Dimesityl-4,5-Dihydroimidazol-2-ylidene Ligands. *Org. Lett.* **1999**, *1*, 953−956.
(34) Lee, S.; Beare, N. A.; Hartwig, J. F. Palladium-Catalyzed $\alpha$-Arylation of Carboxylic Acid and Amino Acid Esters. *J. Am. Chem. Soc.* **2001**, *123*, 8410−8411.
(35) Stauffer, S. R.; Lee, S.; Stambuli, J. P.; Hauck, S. I.; Hartwig, J. F. High Turnover Number and Rapid, Room-Temperature Amination of Chloroarenes Using Saturated Carbene Ligands. *Org. Lett.* **2000**, *2*, 1423−1426.
(36) Abdel-Magid, A. F.; Carson, K. G.; Harris, B. D.; Maryanoff, C. A.; Shah, R. D. Reductive Amination of Aldehydes and Ketones with Sodium Triacetoxyborohydride. Studies on Direct and Indirect Reductive Amination Procedures. *J. Org. Chem.* **1996**, *61*, 3849−3862.
(37) Renaud, J.; Bischoff, S. F.; Buhl, T.; Floersheim, P.; Fournier, B.; Halleux, C.; Kallen, J.; Keller, H.; Schlaeppi, J.-M.; Stark, W. Estrogen Receptor Modulators: Identification and Structure−Activity Relationships of Potent ER$\alpha$-Selective Tetrahydroisoquinoline Ligands. *J. Med. Chem.* **2003**, *46*, 2945−2957
(38) Brzozowski, A. M.; Pike, A. C. W.; Dauter, Z.; Hubbard, R. E.; Bonn, T.; Engström, O.; Öhman, L.; Greene, G. L.; Gustafsson, J.-Å.; Carlquist, M. Molecular Basis of Agonism and Antagonism in the Oestrogen Receptor. *Nature* **1997**, *389*, 753−758.
(39) Widmer, A. Novartis Pharma: Basel, 2003. Unpublished Work
(40) Stewart, J. J. P. MOPAC93; Fujitsu Limited: Tokyo, 1993.
(41) Bury, P. S.; Christiansen, L. B.; Jacobsen, P.; Jørgensen, A. S.; Kanstrup, A.; Naerum, L.; Bain, S.; Fledelius, C.; Gissel, B.; Hansen, B. S.; Korsgaard, N.; Thorpe, S. M.; Wassermann, K. Synthesis and Pharmacological Evaluation of Novel *cis*-3,4-Diaryl-Hydroxychromanes as High Affinity Partial Agonists for the Estrogen Receptor. *Bioorg. Med. Chem.* **2002**, *10*, 125−145.
(42) Gauthier, S.; Caron, B.; Cloutier, J.; Dory, Y. L.; Favre, A.; Larouche, D.; Mailhot, J.; Ouellet, C.; Schwerdtfeger, A.; Leblanc, G.; Martel, C.; Simard, J.; Mérand, Y.; Bélanger, A.; Labrie, C.; Labrie, F. (*S*)−(+)-4-[7-(2,2-Dimethyl-1-oxopropoxy)-4-methyl-2-[4-[2-(1-piperidinyl)-ethoxy]phenyl]-2*H*-1-benzopyran-3-yl]-phenyl 2,2-Dimethylpropanoate (EM-800): A Highly Potent, Specific, and Orally Active Nonsteroidal Antiestrogen. *J. Med. Chem.* **1997**, *40*, 2117−2122.
(43) Berthois, Y.; Katzenellenbogen, J. A.; Katzenellenbogen, B. S. Phenol Red in Tissue Culture Media is a Weak Estrogen: Implications Concerning the Study of Estrogen-Responsive Cells in Culture. *Proc. Natl. Acad. Sci. U.S.A.* **1986**, *83*, 2496−2500.
(44) Balaguer, P.; François, F.; Comunale, F.; Fenet, H.; Boussioux, A.-M.; Pons, M.; Nicolas, J.-C.; Casellas, C. Reporter Cell Lines to Study the Estrogenic Effects of Xenoestrogens. *Sci. Total Environ.* **1999**, *233*, 47−56.
(45) Balaguer, P.; Boussioux, A.-M.; Demirpence, E.; Nicolas, J.-C. Reporter Cell Lines Are Useful Tools for Monitoring Biological Activity of Nuclear Receptor Ligands. *Luminescence* **2001**, *16*, 153−158.

JM040858P