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Estrogen receptor ligands. Part 16: 2-Aryl indoles as highly subtype selective ligands for ERα

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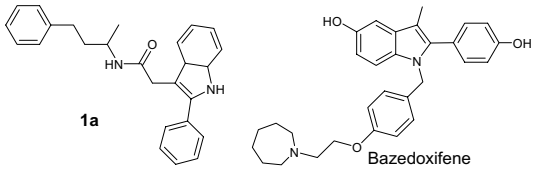
Abstract—A novel class of indole ligands for estrogen receptor α have been discovered which exhibit potent affinity and high selectivity. Substitution of the bazedoxifene skeleton to the linker present in the HTS lead **1a** provided **22b** which was found to be 130-fold α-selective and acted as an antagonist of estradiol activity in uterine tissue and MCF-7 cancer cells.

Estrogen interacts with the estrogen receptors ERα and ERβ, and controls multiple functions in mammalian tissues and plays a crucial role in female reproduction, bone formation, and cardiovascular and CNS health.[1] Since the introduction of selective estrogen receptor modulators (SERMs),[2] much interest has been focused on this class of compounds as an alternative approach for hormone replacement therapy (HRT). Although the clinical advantages of SERMs over conventional HRT are well known, current SERMs have disadvantages as well.[3] Like estrogen, raloxifene,[4] bazedoxifene,[5] as well as all other third generation SERM candidates, exhibit balanced binding to the estrogen receptors. With the recent discovery of the ERβ receptor,[6] efforts to develop subtype selective ligands have been pursued, in an effort to identify compounds with unique biological properties. We have recently disclosed our findings on the SAR of the flavanoid,[7a,c] dihydrobenzoxathiin,[7b–k] and chromane[7e,f] classes as potent selective estrogen receptor α modulators (SERAMs). We now report on the discovery of a unique class of compounds possessing a 2-aryl indole platform **1a**, uncovered from HTS screening that was further pursued as a novel SERAM. The acetamide linked 2-aryl indole **1a** demonstrated exceptional subtype selectivity for ERα (>400-fold), but exhibited agonism in an immature rat uterine weight gain model while no measurable biological activity in an MCF-7 cell proliferation assay was observed.

The introduction of the 4-hydroxyphenyl group and chiral acetamide side chain afforded **1d** (Table 1) that maintained high subtype selectivity while demonstrating a 10-fold greater affinity for ERα, however, it exhibited similar activity in MCF-7 cells. Molecular modeling of **1d** with raloxifene (Fig. 1) prompted a synthetic effort to evaluate substituted 2-aryl indoles bearing basic amino side chains at the 4–7 positions in an attempt to invoke antagonism.



The high selectivity of **1d** could be rationalized from the X-ray crystal. Complex of the ligand with ERα[8] (Fig. 1) which suggests that selectivity may be partially due to the interaction of the acetamide carbonyl and chiral

Keywords: 2-Aryl indoles; Estrogen receptor; ERα; SERAMs.
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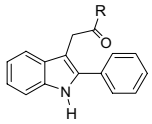
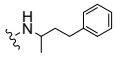
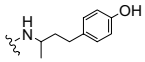
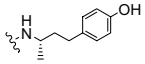
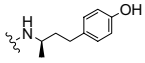
Table 1.



Compound	R	ERα/ERβ[15] IC_{50} (nM)	MCF-7[16] IC_{50} (nM)	Uterine weight[17] % inhibition/% control (antagonism/agonism)
1a		11/4900	>1000	–4/40
1b		1/78	>1000	–4/83
1c		37/1582	>1000	—
1d		1/94	>1000	—

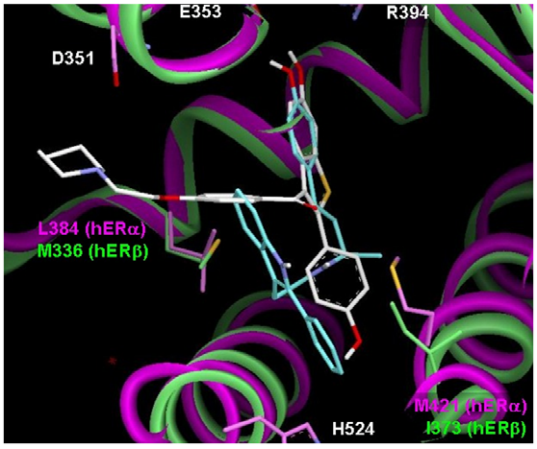
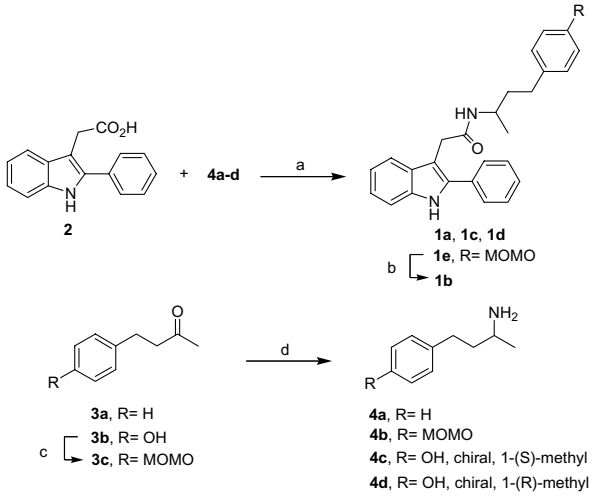


Figure 1. Comparison of crystallographic complex of **1d** (cyan) against raloxifene (white). hERα is depicted in purple and hERβ in green. Residue numbering is hERα unless otherwise indicated.

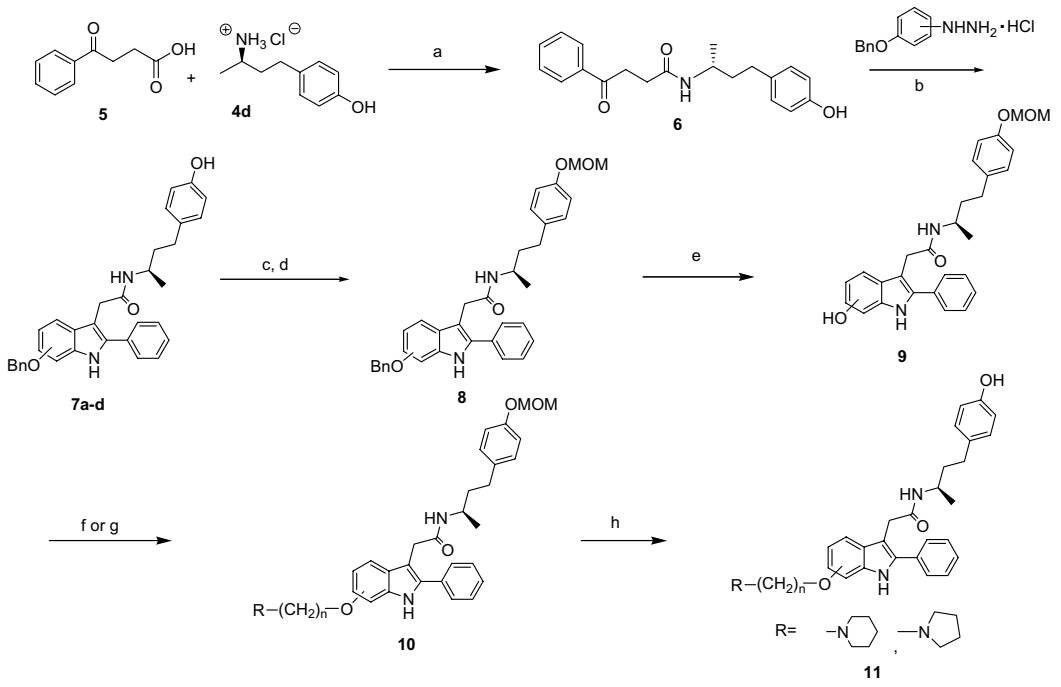
methyl substituent of **1d** with the two discriminating residues in the two receptor isoforms (Leu 384 ERα and Met 336 ERβ), which favors the less sterically constrained ERα receptor, as was similarly hypothesized with both the flavanoid[7a,c] and dihydrobenzoxathiin[7b–g] SERAMs. In addition, the increase in steric size of the pendant 2-phenyl substituent on the indole scaffold of **1d** may be further constrained due to the Il373 residue found in ERβ, but seems to be better accommodated by the conformation of the Met 421 residue found in the same position in ERα.

Compounds **1a**–**b** were synthesized from 2-aryl indole-3-acetic acid **(2)** (commercially available) with the requisite secondary amines **4a-b** in the presence of the amide coupling agent EDC. Both **4a** and **4b** were obtained by reductive amination of the corresponding commercial ketones, using ammonium acetate and sodium cyanoborohydride (Scheme 1). The chiral 4-hydroxyphenyl butylamines **4c**–**d**[9] were coupled to afford the desired chiral acetamides **1c**–**d**. Higher yields of **1b** were observed using the MOM-protected phenol **3c**, which eliminated the ester by-products that were typically observed in ~10% yield, in the case of the non-protected phenols. Exposure of **3b** to $EtN(i\text{-}Pr)_2$, followed by MOMCl in DCM, at 0 °C, provided the MOM-protected intermediate **3c**. Deprotection of **1e** was accomplished using 2 N aq HCl to give **1b**.

The 4–7 substituted indoles were accessed from the Fischer indole synthesis using the conditions described by Hutchins and Chapman[10] and the pivotal chiral acetamide precursor **6**, which was obtained from the



Scheme 1. Reagents and conditions: (a) EDC, DMAP, CH_2Cl_2 or DMSO, rt, 47–78%; (b) 2 N aq HCl, 60 °C, 75–90%; (c), $EtN(i\text{-}Pr)_2$, MOMCl, DCM, 0 °C, 82%; (d) NH_4OAc, $NaCNBH_3$, MeOH, 3A-Sieves 43–52%.



Scheme 2. Reagents and conditions: (a) EDC, DMAP, *N*-methylmorpholine, DCM, rt, 3 h, 63%; (b) HOAc, $ZnCl_2$, 70 °C, 18 h, 54%; (c) NaH, DMF, 0 °C; (d) MOMCl, 2 h, 90%; (e) 1 wt. equiv of Pd-black, NH_4CO_2H, 7:3:1 EtOH–EtOAc–H_2O, 70 °C, 10 min, 100%; (f) 6 equiv chloroalkylpiperidine or chloroalkylpyrrolidine hydrochloride, 11 equiv Cs_2CO_3, acetone, 10% H_2O, 60 °C, 3 h, 34–65%; (g) 1—6 equiv $Br(CH_2)_nBr$, 11 equiv Cs_2CO_3, acetone, 10% H_2O, 60 °C, 1.5 h; 2—20 equiv piperidine or pyrrolidine, 1 equiv, KI, DMF, 80 °C, 1 h, 60–70%; (h) 2 N aq HCl, MeOH, 80 °C, 1 h, 81–90%.

coupling of the chiral 4-hydroxyphenyl butylamine **4d** and 3-benzoylpropionic acid (**5**), (Scheme 2). Treatment of the chiral acetamide **6** with the requisite benzyl-protected hydrazines, in the presence of zinc chloride, provided the desired indoles **7a**–**d**. Treatment of the phenols **7a**–**d**, with NaH and MOMCl, gave the desired MOM-protected indoles **8**. Removal of the benzyl protecting groups was accomplished using Pd black and ammonium formate to afford the hydroxyindole intermediates **9**, that were readily alkylated and converted to the piperidinyl or pyrrolidinyl analogs **10**. Deprotection of **10** using acidic conditions provided analogs **11a**–**n**, after purification by HPLC.

Compounds **11a**–**n** were evaluated in the estrogen receptor binding assay, an MCF-7 cell proliferation assay and an immature rat uterine weight assay (Table 2).

Although high affinity and selectivity for ERα was observed for most of the compounds obtained in this series, only partial antagonism (23%) was exhibited from the piperidinyl compounds **11f** and **11n**.

Interestingly, the X-ray crystal complex of partial antagonist, **11f**, with ERα[8] revealed a close interaction between the basic side chain nitrogen and the Asp 351 residue in ERα (Fig. 2), believed to be necessary for antagonism.

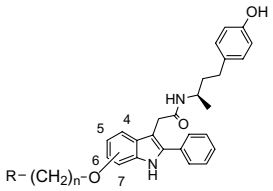
In an analogous attempt to introduce SERAM like properties to this class, several N-alkylated indole analogs (**12e**–**h**) bearing basic side chains were accessed from **1e**, where it was hoped that either benzyl or benzoyl linked basic side chains (similar to the SERMs raloxifene and bazedoxifene) could also access the Asp 351 residue.

Compounds **12e**–**h** were synthesized according to Miller's protocol,[5] followed by the deprotection of the MOM protecting groups, shown in Scheme 3.

Compounds **12e**–**h** also demonstrated high affinity and selectivity for ERα, but likewise exhibited disappointing in vivo antagonism (Table 3), based on MCF-7 cell proliferation and immature rat uterine weight evaluations. This suggested that the positioning of the basic side chain was either not proximal to the Asp 351 residue or that the necessary conformation of the basic side chain was not achieved.

It is known that both the ligand and the basic side chain must interact with the binding elements in the estrogen receptor in a specific conformation and that minor changes in orientation can greatly impact the functional activity.[4–k] The X-ray crystal structure of raloxifene with ERα demonstrates that the basic side chain exists relative to benzothiophene core in an orthogonal array.[11] It was postulated that the partial antagonism observed with **11f**, **11n**, and **12e** could be the result of an unfavorable conformation between the indole core and the basic side chain, which based on the X-ray crystal complexes resides in a skewed planar fashion.

Table 2.



Compound	Position	*n*	R	Human ERα/β[15] IC_{50} (nM) (selectivity)	MCF-7[16] inhibition IC_{50} (nM)	Uterine weight[17] % inhibition/% control (antagonism/agonism)
(11a)	4	2		1134/>10000 (–)	—	—
(11b)	5	2		378/>10000 (–)	—	—
(11c)	5	3		40/>10000 (–)	—	—
(11d)	5	4		31/5594 (180.3)	900	—
(11e)	5	5		6.6/2954 (447.6)	318	−7.8/−6.9
(11f)	6	2		8/1231 (153.8)	42.7	23/16
(11g)	6	3		13/2340 (180)	79	−3.8/−4.0
(11h)	6	4		10.1/394 (39.4)	220	—
(11i)	6	2		22/4749 (215.8)	130	—
(11j)	6	3		9.1/2653 (291.5)	28	—
(11k)	7	2		440/>10000 (–)	—	—
(11l)	7	3		69/3250 (47.1)	—	—
(11m)	7	4		23/3688 (160.3)	—	—
(11n)	7	5		13/2338 (179.8)	—	23/2

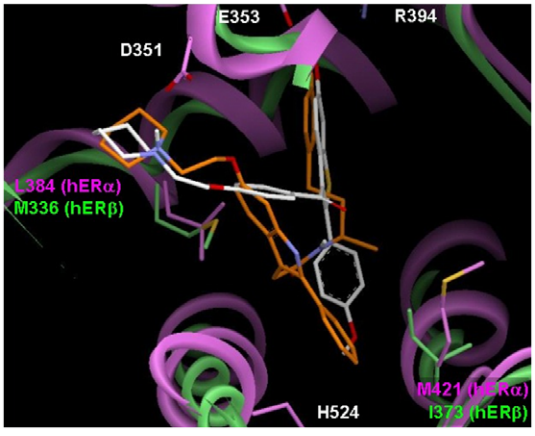
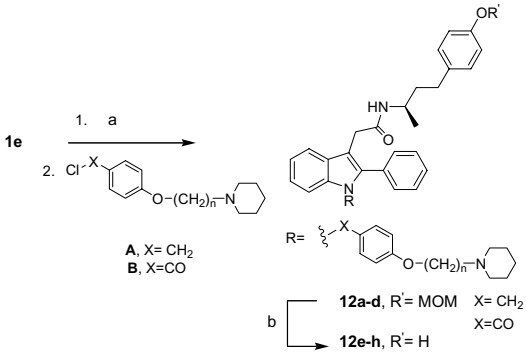


Figure 2. Comparison of crystallographic complex of **11f** (orange) against raloxifene (white). hERα is depicted in purple and hERβ in green. Residue numbering is hERα unless otherwise indicated.

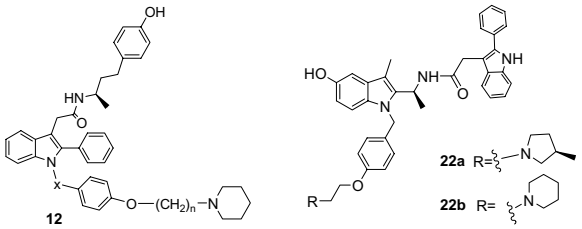
In an effort to introduce an orthogonal conformation between the basic side chain of **1d** and the ASP 351 residue in ERα, it was envisioned, based on the modeling of



Scheme 3. Reagents and conditions: (a) NaHMDS, DMF, −40 °C, addition of **A** or **B**, 60 °C, 18 h, 47–67%; (b) 2 N aq HCl, EtOH, 60 °C, 1 h, 78–91%.

1d with raloxifene or bazedoxifene, that the introduction of the chiral tether of **1d** at the 2-position of a known SERM scaffold (i.e., bazedoxifene) may provide novel compounds with SERAM properties (Fig. 3).

Table 3.



Compound	*n*	X	Human ERα/β[15] IC_{50} (nM) (selectivity)	MCF-7[16] inhibition IC_{50} (nM)	Uterine weight[17] % inhibition/% control (antagonism/agonism)
12e	2	CH_2	20/606 (30.3)	>1000	2/16
12f	2	CO	175/2236 (12.8)	>1000	—
12g	3	CH_2	7.8/426 (54.6)	>1000	—
12h	4	CH_2	4.9/161 (32.9)	>1000	—
22a	—	—	4.0/522 (130.5)	23	18/15
22b	—	—	2.0/259 (129.5)	30	76/27
Estradiol	—	—	1.0/1.0 (1)	—	–/100

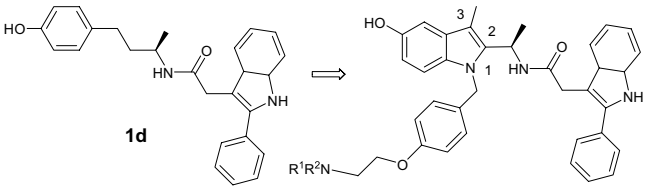
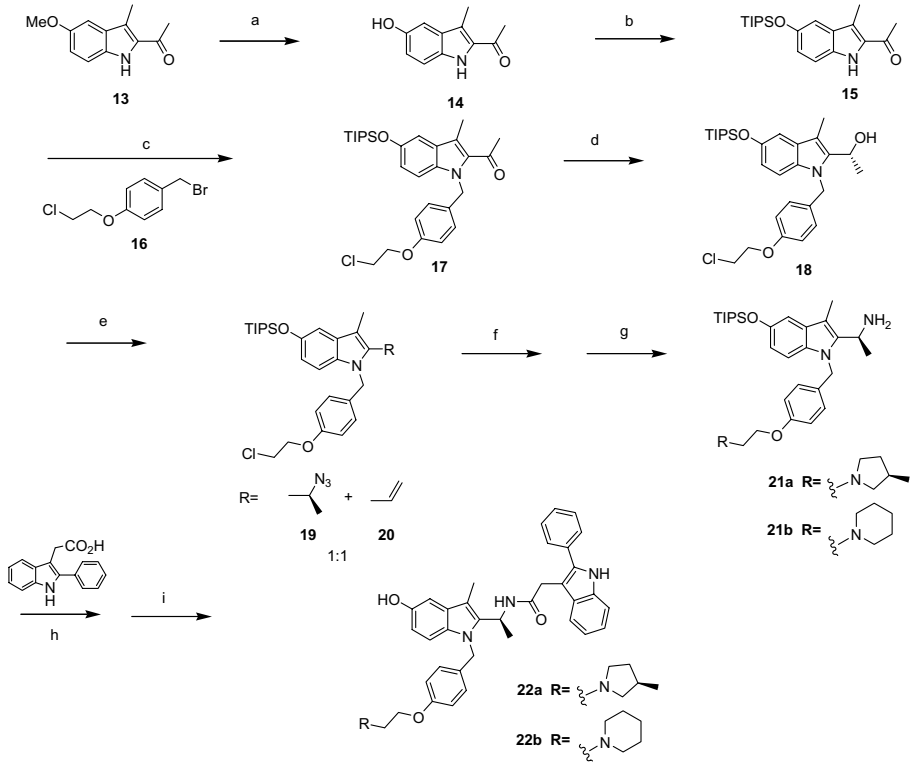


Figure 3.

This hypothesis was readily explored from the synthons on hand using the synthetic route detailed in Scheme 4.

To that end, the syntheses of **22a** and **22b** were accomplished, starting from the indole **13**.[12] Demethylation of **13** was accomplished using BBr_3 and subsequent protection of the 5-hydroxyindole **14** with TIPS gave **15**. Alkylation of the indole **15** was carried out using NaH



Scheme 4. Reagents and conditions: (a) BBr_3, CH_2Cl_2, −78 to 0 °C, 2 h,74%; (b) NaH, DMF, 0 °C, TIPSCl, 92%; (c) 1—NaH, DMF, 0 °C, 2—**16**, 60 °C, 18 h, 90%; (d) (*R*)-2-methyl-cbs-oxazaboroline, THF, 0 °C, 1 h, 100%; (e) DPPA, DBU, THF, 0 °C to rt, 4 h, 41% isolated yield of azide; (f) piperidine or 3-methyl(*R*)-pyrrolidine, DMF, KI, 80 °C, 90%; (g) $LiEt_3BH$, THF, 0 °C, 100%; (h) EDC, DMAP, B, 1:1 CH_2Cl_2/DMSO, rt, 65%; (i) TBAF, HOAc, THF, 0 °, **22a** 34% and **22b** 45%.

in DMF at 0 °C followed by the addition of the benzyl bromide **16** to provide **17** in 90% yield.

The reduction of the ketone **17** with (*R*)-2-methyl-CBZ-oxazoboroline in THF at 0 °C afforded the desired chiral alcohol **18** (81% ee).[13] Conversion of **18** to the azide using DPPA and DBU afforded separable mixtures of the desired azide **19** and the vinyl product **20**. Similar attempts to prepare **19** from activating the alcohol **18** via the mesylate or using Mitsunobu conditions afforded only the elimination by-product **20**.

The displacement reaction of **19** using piperidine or with β-methyl pyrrolidine,[7j] followed by reduction of the azide, yielded the pivotal amines **21a**–**b**. In turn, **21a**–**b** were coupled using EDC in 1:1 DCM/DMSO with catalytic DMAP and 3-indole acetic acid (**2**), followed by subsequent deprotection of the TIPS protecting group using TBAF and chiral resolution of the enantiomerically enriched products using chiral HPLC[14] to afford the desired bazedoxifene-like derivatives **22a**–**b**.

The biological evaluation of **22b** (Table 3) demonstrated high affinity and selectivity for ERα (~130-fold) while showing moderately improved antagonism (76%). Interestingly, **22a** bearing a chiral β-methyl pyrroline side chain, found to impart exceptional antagonism in the dihydrobenzoxathiin series,[7i] provided only a modest gain in antagonism. This observation was similarly reported by Blizzard et al.[7k] regarding the SAR of SERMs possessing the super antagonist side chains.

Although excellent potency and selectivity for this class was maintained, measures of MCF-7 cell proliferation for both **22a** and **22b** were less than those observed with our prior classes of compounds.

In conclusion, we have discovered a novel class of 2-aryl indoles that have high subtype selectivity and high affinity for ERα, while demonstrating in vivo antagonism. The interactions of the basic side chain, in the case of **11f**, with the Asp 351 residue in ERα confirmed our molecular modeling hypothesis.

In addition, the combination of bazedoxifene or similar SERM platforms that adopt the required antagonist confirmation, with the subtype selective acetamide linker, could lead to novel SERAMs with unique biological profiles and tissue selectivities.

Acknowledgments

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References and notes

1. (a) Mendelsohn, M. E.; Karas, R. H. *New Engl. J. Med.* **1999**, *340*, 1801; (b) Epperson, C. N.; Wisner, K. L.; Yamamoto, B. *Psychosom. Med.* **1999**, *61*, 676; (c) Crandall, J. *Womens Health Gender Based Med.* **1999**, *8*, 1155; (d) Hurn, P. D.; Macrae, I. M. *J. Cereb. Blood Flow Metab.* **2000**, *20*, 631; (e) Toran-Allerand, C. D. *J. Steroid Biochem. Mol. Biol.* **1996**, *56*, 169; (f) Ritzen, E. M.; Nilsson, O.; Holst, M.; Savendahl, L.; Wrobelwski, J. *J. Steroid Biochem. Mol. Biol.* **2000**, *74*, 383.
2. (a) Jordan, V. C. *J. Med. Chem.* **2003**, *46*, 883; (b) Jordan, V. C. *J. Med. Chem.* **2003**, *46*, 1081; (c) Veeneman, G. H. *Curr. Med. Chem.* **2005**, *12*, 1077.
3. (a) Maricic, M.; Gluck, O. *Expert Opin. Pharmacother.* **2002**, *3*, 767; (b) Miller, C. P. *Curr. Pharm. Des.* **2002**, *8*, 2089; (c) White, I. N. H. *Carcinogenesis* **1999**, *20*, 1153.
4. Grese, T. A.; Pennington, L. D.; Sluka, J. P.; Adrain, M. D.; Cole, H. W.; Fuson, T. R.; Magee, D. E.; Phillips, D. L.; Rowley, E. R.; Shelter, P. K.; Short, L. L.; Venugopalan, M.; Yang, N. N.; Sato, M.; Glasebrook, A. L.; Bryant, H. U. *J. Med. Chem.* **1998**, *41*, 1272.
5. 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. *J. Med. Chem.* **2001**, *44*, 1654.
6. (a) Kuiper, G. G. J. M.; Enmark, E.; Pelto-Huikko, M.; Nilsson, S.; Gustafsson, J. A. *Proc. Natl. Acad. Sci. USA* **1996**, *93*, 5925; (b) Mosselman, S.; Polman, J.; Dijkema, R. *FEBS Lett.* **1996**, *392*, 49.
7. (a) Chen, H. Y.; Dykstra, K. D.; Birzin, E. T.; Frisch, K.; Chan, W.; Yang, Y. T.; Mosley, R. T.; DiNinno, F.; Rohrer, S. P.; Shaeffer, J. M.; Hammond, M. L. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 1417; (b) Kim, S.; Wu, J. Y.; Birzin, E. T.; Frisch, K.; Chan, W.; Pai, L. Y.; Yang, Y. T.; Mosley, R. T.; Fitzgerald, P. M. D.; Sharma, N.; DiNinno, F.; Rohrer, S. P.; DiNinno, F.; Rohrer, S. P.; Schaeffer, J. M.; Hammond, M. L. *J. Med. Chem.* **2004**, *47*, 2171; (c) Chen, H. Y.; Kirn, S.; Wu, J. Y.; Birzin, E. T.; Chan, W.; Yang, Y. T.; Dahllund, J.; DiNinno, F.; Rohrer, S. P.; Schaeffer, J. M.; Hammond, M. L. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 2551; (d) Kim, S.; Wu, J. Y.; Chen, H. Y.; Birzin, E. T.; Chan, W.; Yang, Y. T.; Colwell, L.; Li, S.; Dahllund, J.; DiNinno, F.; Rohrer, S. P.; Schaeffer, J. M.; Hammond, M. L. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 2741; (e) Tan, Q.; Birzin, E. T.; Chan, W.; Yang, Y. T.; Pai, L. Y.; Hayes, E. C.; DaSilva, C. A.; DiNinno, F.; Rohrer, S. P.; Schaeffer, J. M.; Hammond, M. L. *Bioorg. Med. Chem. Lett.* **2004**, 3747; (f) Tan, Q.; Blizzard, T. A.; Morgan, J. D., II; Birzin, E. T.; Chan, W.; Yang, Y. T.; Pai, L. Y.; Hayes, E. C.; Dasilva, C. A.; Warrier, S.; Yudkovitz, J.; Wilkinson, H. A.; Sharma, N.; Fitzgerald, P. M. D.; Li, S.; Colwell, L.; Fisher, J. E.; Adamski, S.; Reszka, A. A.; Kimmel, D.; DiNinno, F.; Rohrer, S. P.; Freedman, L. P.; Shaeffer, J. M.; Hammond, M. L. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 1675; (g) Blizzard, T. A.; DiNinno, F.; Morgan, J. D., II; Chen, H. Y.; Wu, J. Y.; Gude, C.; Kim, S.; Chan, W.; Birzin, E. T.; Yang, Y. T.; Pai, L. Y.; Zhang, Z.; Hayes, E. C.; DaSilva, C. A.; Tang, W.; Rohrer, S. P.; Schaeffer, J. M.; Hammond, M. L. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 3861; (h) Blizzard, T. A.; DiNinno, F.; Morgan, J. D., II; Wu, J. Y.; Chen, H. Y.; Kim, S.; Chan, W.; Birzin, E. T.; Yang, Y.; Pai, L. Y.; Zhang, Z.; Hayes, E. C.; Dasilva, C. A.; Tang, W.; Rohrer, S. P.; Schaeffer, J. M.; Hammond, M. L. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 3865; (i) Blizzard, T. A.; DiNinno, F.; Morgan, J. D., II; Chen, H.

Y.; Wu, J. Y.; Kim, S.; Chan, W.; Birzin, E. T.; Yang, Y. T.; Pai, L. Y.; Fitzgerald, P. M. D.; Sharma, N.; Li, Y.; Zhang, Z.; Hayes, E. C.; DaSilva, C. A.; Tang, W.; Rohrer, S. P.; Schaeffer, J. M.; Hammond, M. L. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 107; (j) Blizzard, T. A.; DiNinno, F.; Chen, H. Y.; Kim, S.; Wu, J. Y.; Chan, W.; Birzin, E. T.; Yang, Y. T.; Pai, L. Y.; Hayes, E. C.; DaSilva, C. A.; Rohrer, S. P.; Schaffer, J. M.; Hammond, M. L. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 3912; (k) Blizzard, T. A.; Morgan, J. D., II; Chan, W.; Birzin, E. T.; Pai, L. Y.; Hayes, E. C.; DaSilva, C. A.; Mosley, R. T.; Yang, Y. T.; Rohrer, S. P.; DiNinno, F.; Hammond, M. L. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 5124.

8. A complex of the ligand binding domain of ERα (residues 307–554) with the ligands **11f** was crystallized by vapor diffusion, using a precipitant containing 100 mM $MgCl_2$, 6% PEG 3350, and 100 mM imidazole buffer, pH 7.1. The space group of the crystal was $P6_522$, with cell dimensions $a = b = 58.22$ Å, $c = 276.66$ Å. Diffraction data were measured at beamline 17-ID of the Advanced Photon Source. The data were processed with program X-GEN, which yielded an R_{merge} of 0.117 for the data from ∞ to 1.6 Å. Data for a complex of the ligand binding domain of ERα with ligand **1d** were provided by our collaborators at Karo-Bio. The space group was $P4_1$, with cell dimensions $a = b = 99.86$ Å, $c = 54.90$ Å. Both structures were refined using program SHELXL, with final values for R_{work} and R_{free} of 0.218 and 0.336 for the data from 10.0 to 1.60 Å resolution (**11f**), and 0.215 and 0.323 for the data from 10.0 to 2.40 Å (**1d**). The data for the complex with **1d** were merohedrally twinned, and the refined value for the twin percentage was 0.398. Coordinates and structures factors have been deposited with the Protein Data Bank (entries 2IOG and 2IOK).
9. European Pat. # 0007204.
10. Hutchins, S. M.; Chapman, K. T. *Tetrahedron Lett.* **1996**, *37*(28), 4869.
11. Brzozowski, A. M.; Pike, A. C. W.; Dauter, Z.; Hubbard, R. E.; Bonn, T.; Engstrom, O.; Ohman, L.; Greene, G. L.; Gustafsson, J.-A.; Carlquist, M. *Nature* **1997**, *389*, 753.
12. Rajur, S. B.; Merwade, A. Y.; Bajanagoudar, L. D. *Synth. Commun.* **1992**, *22*, 421.
13. Calculation of ee based on proton NMR spectrum of Mosher ester (a) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512; (b) Sullivan, G. R.; Dale, J. A.; Mosher, H. S. *J. Org. Chem.* **1973**, *38*, 2143.
14. Chiral resolution was required due to low ee's resulting from the reduction step of the ketone and subsequent racemization found to occur during the azide formation step.
15. The single IC_{50} values were generated in an estrogen receptor ligand binding assay. This scintillation proximity assay was conducted in NEN basic flash plates using tritiated estradiol and full length recombinant human ERα and ERβ proteins with a 3 h incubation time. This assay provides IC_{50} values that are reproducible to within a factor of 2–3.
16. In the MCF-7 proliferation assay, estrogen depleted MCF-7 cells were plated into a 96-well cell culture plates at a density of 1000 cells/well. To determine the antagonist activity of a compound, the test compounds and 3 pmol estradiol were applied to the cells on days 1 and 4. The assay was terminated between days 8 and 10, and the cellular protein content/well used to determine the IC_{50}.
17. Twenty-day-old intact Sprague–Dawley rats were treated (sc) with the tested compounds for 3 days at 1 mpk. The anti-estrogenic activity of compounds was determined by co-administration of the compound with a subcutaneous injection of 17-β-estradiol one hour after compound at 4 μg/kg dose and reported as % inhibition. The estrogenic activity (partial agonism) of the compounds was determined by administering the test compound without estradiol and reported as % control.