Novel Series of Potent, Nonsteroidal, Selective Androgen Receptor Modulators Based on 7*H*-[1,4]Oxazino[3,2-*g*]quinolin-7-ones

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Recent interest in orally available androgens has fueled the search for new androgens for use in hormone replacement therapy and as anabolic agents. In pursuit of this, we have discovered a series of novel androgen receptor modulators derived from 7*H*-[1,4]oxazino[3,2-*g*]quinolin-7-ones. These compounds were synthesized and evaluated in competitive binding assays and an androgen receptor transcriptional activation assay. A number of compounds from the series demonstrated single-digit nanomolar agonist activity in vitro. In addition, lead compound **(*R*)-16e** was orally active in established rodent models that measure androgenic and anabolic properties of these agents. In this assay, **(*R*)-16e** demonstrated full efficacy in muscle and only partially stimulated the prostate at 100 mg/kg. These data suggest that these compounds may be utilized as selective androgen receptor modulators or SARMs. This series represents a novel class of compounds for use in androgen replacement therapy.

Introduction

The androgen receptor (AR[a]) is a member of the intracellular receptor superfamily of ligand-dependent transcription factors.[1] The native hormones for AR are testosterone (T) and dihydrotestosterone (DHT, Figure 1). When bound to AR, these ligands play important roles in sexual development and function[2] and musculo-skeletal growth.[3] Androgen therapy is effective for the treatment of androgen insufficiency. However, the broader use of steroidal androgens for additional treatments, such as osteoporosis or frailty, is limited by undesirable AR-mediated effects, such as prostatic hypertrophy and hirsutism. A selective androgen receptor modulator (SARM) with full anabolic activity but reduced impact on the undesirable effects could have a large role on endocrine therapies to treat muscle wasting and osteoporosis.[4] Early studies on modified androgens explored alkylation at C-17, as in fluoxymesterone (**1**).[5] However, compounds from this general class are associated with potential liver toxicity and are met with limited clinical use.[2] Recently, the discovery of novel androgens has shifted toward nonsteroidal templates, and a number of SARMs derived from classical androgen antagonists flutamide and bicalutamide have been reported (**2**).[6] Ongoing publication activity in the androgen field is a testament to the high level of interest for safe, effective anabolic agents.[7] Our interest in novel SARMs was derived from our earlier studies on pyrano- and pyridono-fused quinoline agonists (**3a** and **3b**, respectively), which demonstrated potent AR agonist activity in luciferase-based reporter cell-based assays.[8] However, neither series, including lead compound **3c** (LG121071), exhibited good activity in the maintenance of levator ani (LA) muscle weight when dosed orally in castrated rats. It was hypothesized that replacing the quinoline with the corresponding benzoxazine could result in compounds less prone to metabolic oxidation and potentially lead to compounds with improved in vivo activity. This concept is supported by the fact that **3b** analogues that possess geminal alkyl disubstitution[9] at the R^3 position show improved exposure in oral pharmacokinetic studies, but converted the analogues to AR antagonists.[10] In our studies, we sought to determine if the quinoline nitrogen in **3b** could be substituted with an oxygen and if the replacement of the CR^1 group in **3b** with an NR^1 present in **5** would also be tolerated (Figure 2).[8a,b] This led to the design and preparation of a series of novel androgens derived from 7*H*-[1,4]oxazino-

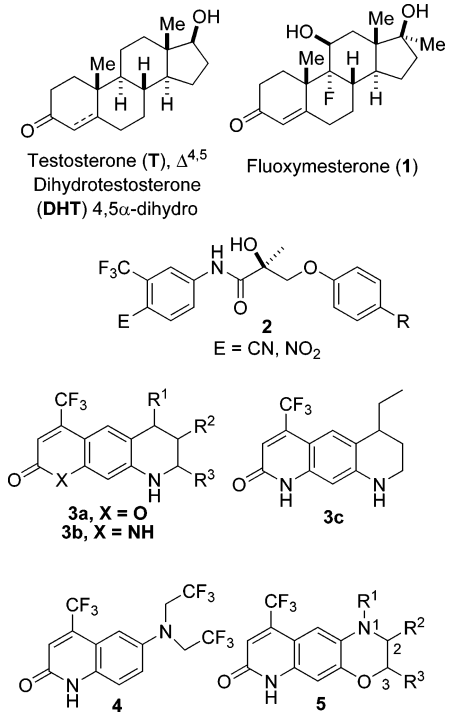

Figure 1. Steroidal and nonsteroidal androgens.

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[a] Abbreviations: AR, androgen receptor; T, testosterone; DHT, 4,5α-dihydrotestosterone; SARM, selective androgen receptor modulator; MR, mineralocorticoid receptor; GR, glucocorticoid receptor; PR, progesterone receptor; VP, ventral prostate; SV, seminal vesicle; LA, levator ani; LH, leutinizing hormone.

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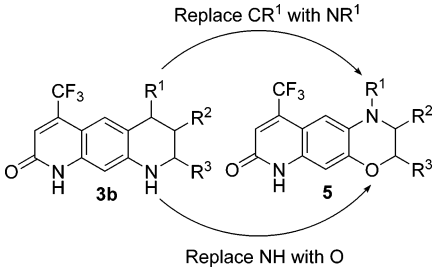
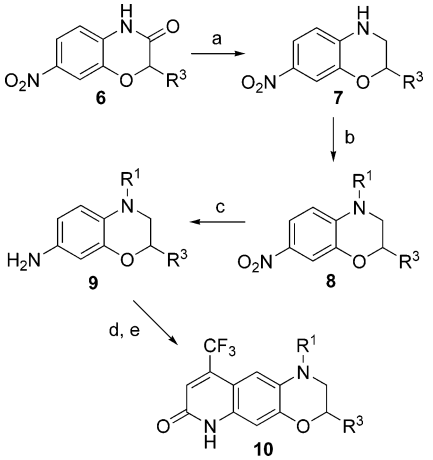


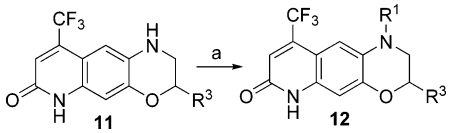
Figure 2. Design elements of AR pharmacophore **5**.

Scheme 1[a]



[a] Reagents and conditions: (a) borane dimethyl sulfide, THF, reflux; (b) R^1CHO, $NaBH_3CN$, HOAc, rt; (c) 10% Pd−C, H_2, EtOAc, EtOH, rt, or Zn dust, $CaCl_2$, EtOH/H_2O (95:5), reflux; (d) ethyl 4,4,4-trifluoroacetoacetate, benzene, reflux; (e) PPA or concd H_2SO_4, 100 °C.

Scheme 2[a]



[a] Reagents and conditions: (a) R^1CHO, $NaBH_3CN$, HOAc, rt.

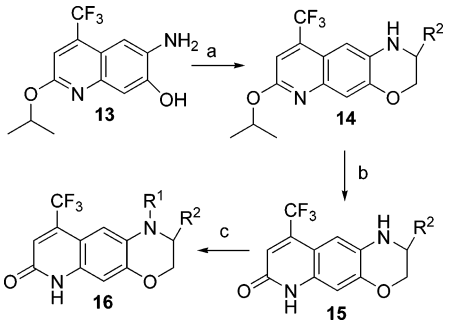
[3,2-*g*]quinolin-7-ones (**5**). Along with the 6-*N*,*N*-bis(2,2,2-trifluoroethyl)amino-4-trifluoromethylquinolin-2(1*H*)-one **4** (LGD2226) series,[11] this manuscript describes our efforts in the discovery of new nonsteroidal AR modulators.

Chemistry

A flexible synthetic strategy that allowed for facile substitutions at the 1- and 3-positions of **5** is shown in Scheme 1. Compounds **6**[12] and **7**[13] were prepared from methods described in the literature, followed by alkylation at nitrogen by treatment with an aldehyde and sodium cyanoborohydride. Reduction of the nitro group to the corresponding aniline (**9**) was followed by treatment with 4,4,4-trifluoroacetoacetate in refluxing benzene, followed by treatment of the crude acetanilide with strong acid, either polyphosphoric acid (PPA) or concentrated H_2SO_4 (Knorr reaction),[14] to afford the desired 4-substituted-7*H*-[1,4]-oxazino[3,2-*g*]quinolin-7-one (**10**). Acid-sensitive groups that do not survive the harsh Knorr reaction conditions, such as a cyclopropylmethyl group, can be prepared by reductive amination of compound **11** (Scheme 2).

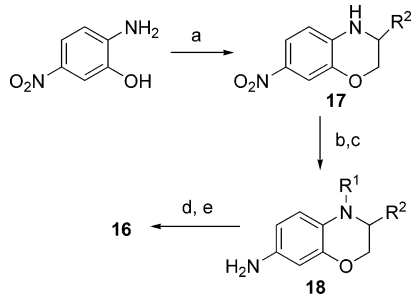
2-Substituted analogues were prepared by treatment of an aminophenol and an α-haloketone followed by $NaBH_3CN$ reduction to afford **14** (Scheme 3). Hydrolysis to the pyridone was accomplished by treatment with strong acid, then **15** was

Scheme 3[a]



[a] Reagents and conditions: (a) $R^2C(O)CH_2Cl$, K_2CO_3, acetone; then $NaBH_3CN$, TFA; (b) HOAc/HCl; (c) R^1CHO, $NaBH_3CN$, HOAc, rt.

Scheme 4[a]



[a] Reagents and conditions: (a) $R^2C(O)CH_2X$, K_2CO_3, acetone; then $NaBH_3CN$, TFA; (b) R^1CHO, $NaBH_3CN$, HOAc, rt; (c) 10% Pd−C, H_2; (d) ethyl 4,4,4-trifluoroacetoacetate, benzene, reflux; (e) PPA or concd H_2SO_4, 100 °C.

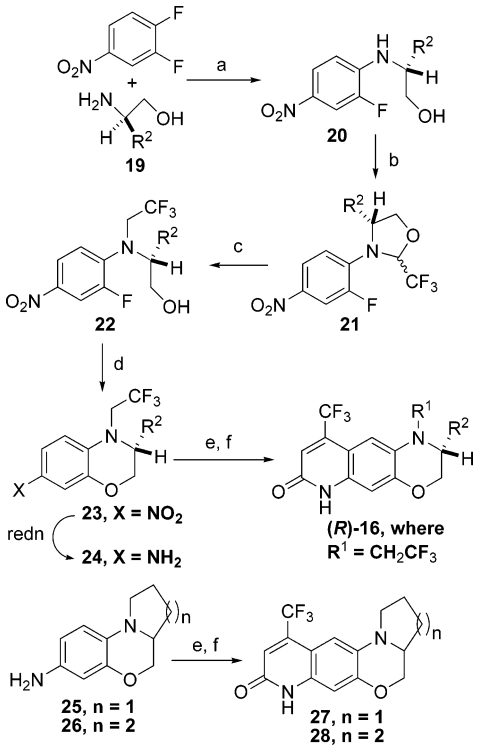
subjected to reductive amination to afford **16**. Alternatively, **16** could be prepared by the benzoxazine protocol described above to afford **17** (Scheme 4). Reductive amination, nitro reduction, followed by the Knorr reaction, as described previously, affords **16**. Chiral HPLC separation of **10** and **16** was achieved utilizing a Chiralpak AD column.

To evaluate our compounds in rodent models, an enantiospecific synthesis was desired to facilitate evaluation of compounds in longer-term models. Enantiospecific syntheses of simple 2*H*-1,4-benzoxazine systems have been reported previously;[15] however, none of the reported methods derive diversity from the amino alcohol chiral pool. The synthesis of the desired compounds is described in Scheme 5. Nucleophilic substitution of 3,4-dinitrofluorobenzene with commercially available amino alcohols afforded **20**. Acetal formation followed by Lewis acid-mediated reductive ring opening provided **22**. With the tertiary amine, closure to the benzoxazine proceeded in good yields (**23**). This scheme provides an efficient enantiospecific synthesis of both (trifluoroethyl)amino alcohols and the corresponding benzoxazines. In addition, this allows for the assignment of absolute configuration of (*R*) for the 1-(2,2,2-trifluoroethyl) analogues, which is established when the (*R*)-enantiomer of the amino alcohol is used as the starting material. This methodology was also an effective method to generate newer analogues in asymmetrically pure form.

Results and Discussion

The compounds were evaluated in a transcriptional activation assay with hAR in a mammalian cell background (CV-1), as previously described, and was the primary in vitro assay utilized to measure the AR activity.[9] Competitive receptor binding assays for AR were performed using MDA-MB-453 cells and was used to confirm the activity observed in the transactivation assay. MDA-MB-453 cells are human breast carcinoma cells that

Scheme 5[a]



[a] Reagents and conditions: (a) $NaHCO_3$, EtOH, reflux; (b) trifluoroacetaldehyde ethyl hemiacetal, *p*-TsOH, reflux; (c) $TiCl_4$ or BF_3, Et_3SiH; (d) NaH, THF, reflux; (e) ethyl 4,4,4-trifluoroacetoacetate, benzene, reflux; (f) PPA or concd H_2SO_4, 100 °C.

express high levels of AR and are responsive to androgens.[16] The unsubstituted analogue **11a** was a weakly potent AR antagonist and did not possess any agonist activity (Table 1). The introduction of an alkyl group at the 1-position converted the antagonist into an agonist, and the size of the alkyl group is critical to the AR modulating activity. For the small alkyl analogues, single-digit nanomolar potency for AR is observed for a number of the R^1-substituted analogues (**10b**−**f**, **12a**) in the AR transcriptional activation assay. The optimal size of R^1 for a full agonist is about 2−3 carbons (compounds **10b**, **10c**, and **10f**). The analogues with slightly less optimal R^1 size tend to have partial agonist activity, such as analogues with methyl (**10a**) and *t*-butyl (**10e**). Increasing the size to benzyl (**12b**) converts the compounds back to an antagonist, with no agonist activity detected. This SAR trend for the benzoxazine series (**5**) is similar to that observed for the tetrahydroquinoline (**3b**) series, where the presence of a small alkyl group is likewise beneficial for AR agonist activity. Furthermore, the utilization of the NR^1 group in **5** eliminates the chiral center present in the R^1 position in the racemic **3b** series. These initial analogues demonstrated that both the replacement of the quinoline nitrogen in **3b** with oxygen and the utilization of an NR^1 group at the 1-position are well tolerated and that **5** was a viable AR modulator scaffold suitable for further exploration.

Although many of the monosubstituted compounds at R^1 of **5** demonstrated good AR in vitro activity, they were characterized by poor exposure in 1-day oral pharmacokinetic studies. To improve oral exposure while maintaining the functional activity, we investigated analogues with a small alkyl group at the 2- or 3-position of the molecule while keeping the R^1 as an optimal small alkyl group. Unfortunately, this resulted in the introduction of a chiral center either at the R^2 or the R^3 position. The racemic 3-methyl compounds (**10g** and **10h**) show comparable AR activity to the corresponding unsubstituted analogues (**10a** and **10f**). The 3-ethyl substitution is less tolerated, where compounds **10i**, **10j**, and **10k** show weaker activity relative to that of their corresponding parent compounds **10a**, **10b**, and **10f**. To address the chirality issue, **(+)-10h** and **(−)-10h** were prepared by chiral HPLC separation of **10h** and characterized in the assays. The test result demonstrates that a majority of the AR agonist activity resides in one enantiomer, **(−)-10h**.

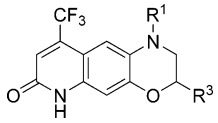
Assay results of the 2-substituted analogues are summarized in Table 2. The racemic 2-methyl analogue **15a** shows weaker AR agonist activity than that of the 1-ethyl-2-methyl analogue **16a**, which indicates the importance of the substitution at the 1-position, although **15a** is a significant improvement over parent compound **11a**. Introduction of a methyl or ethyl group at the 2-position is generally tolerated, but their relative tolerance depends on the substitution at the 1-position. When R^1 is ethyl or cyclopropylmethyl, the 2-ethyl and 2-methyl analogues have similar activity. When R^1 is trifluoroethyl, 2-methyl compound **16e** is more active than 2-ethyl compound **16f** in the transcriptional activation assay. Two pairs of enantiomers (**16e**,**f**) were prepared individually and evaluated to study the effect of the chirality on the modulating activity. Both enantiomers of **16e**,**f** are AR agonists, though the (*S*)-enantiomers of **16e** and **16f** tend toward lower agonist efficacy and potency than the corresponding *R*-enantiomers. Two enantiomerically pure analogues with a larger R^2 group [**(*R*)-16g** and **(*R*)-16h**] behave more as partial agonists. Ring-fused analogues **27** and **28** examined whether fusing the R^1- and R^2-substituents in a ring could enhance the activity. These compounds likewise were AR agonists, but this did not lead to an improvement in activity over the corresponding acyclic substituents.

Selected compounds in the series were tested in steroid hormone binding selectivity assays (Table 3). None of the compounds showed appreciable activity toward the mineralocorticoid (MR) nor glucocorticoid (GR) receptors. Some of the compounds show low micromolar affinity for the progesterone receptor (PR), but this represents significantly weaker activity compared to the AR binding affinity.

Although the in vitro potencies of the 2-substituted analogues were similar to the unsubstituted compounds, lead compound **(*R*)-16e** demonstrated improved oral exposure over **10b** and **10f**. To demonstrate in vivo proof-of-concept for this series of AR modulators, **(*R*)-16e** was evaluated in a 4-week castrated mature rat assay.[17] The male sexual accessory organs, such as the ventral prostate (VP) and the seminal vesicles (SV), play an important role in reproductive function. These glands are stimulated to grow and are maintained in size and function by the presence of endogenous androgens. This model is used to determine the androgen-dependent growth of the sex accessory organs in mature castrated rats. In addition to the VP and SV, the LA muscle demonstrates androgen-dependent growth,[17] hence, the LA muscle is a useful endpoint to evaluate anabolic effects. A SARM should have full efficacy on LA muscle and a reduced impact on VP to maximize the anabolic effects, while minimizing the risk of prostate overstimulation.

In this model, T is reported to have equivalent potency and efficacy on both the VP and the LA muscle when dosed subcutaneously, and is hence considered not muscle-selective.[11] Because T is rapidly metabolized when dosed orally and, therefore, ineffective, **1** was chosen as the orally active positive control in this experiment. As can be seen in Figure 3, 100 mg/kg of **(*R*)-16e** maintains the LA muscle weight at the intact level (Table 4). At this dose, the compound shows less activity (∼25−50%) on the VP and SV weights. The tissue selectivity profile for **(*R*)-16e** on VP and LA weight is similar to that

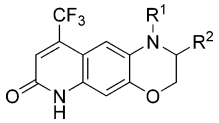
Table 1. Activity in the AR Transcriptional Activation and AR Binding Assays[a]



			hAR agonist		hAR antagonist		AR bind.
cmpd	R^1	R^3	eff (%)	EC_{50} (nM)	Eff (%)	IC_{50} (nM)	K_i (nM)
DHT			100	5.7 ± 0.1	-	-	0.3 ± 0.0
1			124 ± 9	0.3 ± 0.1	-	-	5.7 ± 0.2
3c			100 ± 7	4.1 ± 0.9	-	-	11 ± 2
11a	H	H	-	-	72 ± 3	296 ± 100	>1000[b]
10a	Me	H	56 ± 10	18 ± 3	-	-	15 ± 3[b]
10b	Et	H	92 ± 8	6.4 ± 1.7	-	-	1.2 ± 0.4
10c	Pr	H	83 ± 8	2.4 ± 0.3	-	-	9.6 ± 7.1[b]
10d	*i*-Bu	H	70 ± 11[b]	3.2 ± 0.6	27 ± 27	nd[c]	17 ± 14[b]
10e	*t*-Bu	H	62 ± 3	7.8 ± 2.6	-	-	48 ± 42[b]
10f	CH_2CF_3	H	88 ± 5	3.5 ± 1.3	-	-	4.0 ± 1.0
12a	$C_3H_6CH_2$	H	68 ± 5	1.4 ± 0.3	-	-	1.6 ± 0.2
12b	Bn	H	-	-	90 ± 2	224 ± 44	206 ± 17[b]
10g	Me	Me	50 ± 8	47 ± 5	21 ± 11	nd[c]	33 ± 10
10h	CH_2CF_3	Me	104 ± 10	8.9 ± 2.7	-	-	15 ± 5[b]
10i	Me	Et	28 ± 4	52 ± 8	32 ± 11	67 ± 24	58 ± 17
10j	Et	Et	53 ± 2	31 ± 3	-	-	34 ± 7
10k	CH_2CF_3	Et	72 ± 11	15 ± 6	-	-	30 ± 9
(+)-10h	CH_2CF_3	Me	35 ± 12	44 ± 5	29 ± 8	nd[c]	75 ± 22
(−)-10h	CH_2CF_3	Me	82 ± 3	7.8 ± 0.6	-	-	25 ± 4

[a] AR transcriptional activation and AR binding experimental results with at least three separate experiments in triplicate with SEM. [b] Mean value from two experiments. A hyphen is indicative of efficacy <20% or a potency >10 000 nM. [c] nd means the EC_{50} could not be calculated.

Table 2. AR Agonist and Binding Data for 2-Substituted Analogues[a]



			hAR agonist		AR bind.
cmpd	R^1	R^2	eff (%)	EC_{50} (nM)	K_i (nM)
15a	H	Me	80 ± 3[b]	133 ± 9	113 ± 50[b]
16a	Et	Me	61 ± 4	10 ± 7	4.2 ± 0.3[b]
16b	Et	Et	80 ± 20	3.9 ± 2.0	5.6 ± 1.6[b]
16c	$C_3H_6CH_2$	Me	65 ± 5	1.9 ± 0.3	4.0 ± 0.9[b]
16d	$C_3H_6CH_2$	Et	71 ± 8	2.3 ± 0.4	23 ± 19[b]
16e	CH_2CF_3	Me	96 ± 12	2.7 ± 0.5	7.8 ± 1.2
16f	CH_2CF_3	Et	69 ± 4	6.0 ± 1.5	9.4 ± 2.5[b]
(*S*)-16e	CH_2CF_3	Me	58 ± 4	3.8 ± 0.4	5.7 ± 1.5
(*R*)-16e	CH_2CF_3	Me	82 ± 5	1.1 ± 0.2	7.1 ± 1.9
(*S*)-16f	CH_2CF_3	Et	49 ± 3	30 ± 22	19 ± 4[b]
(*R*)-16f	CH_2CF_3	Et	85 ± 9	2.7 ± 1.1	2.8 ± 0.3[b]
(*R*)-16g	CH_2CF_3	*i*-Pr	46 ± 23	5.9 ± 0.4	51 ± 36[b]
(*R*)-16h	CH_2CF_3	*i*-Bu	65 ± 15	27 ± 13	109 ± 52[b]
(*R*)-27			46 ± 13	26 ± 14	27
28			75 ± 5	14 ± 4	16 ± 11[b]

[a] AR transcriptional activation and AR binding experimental results with at least three separate experiments in triplicate with SEM. [b] Mean value from two experiments. If no SEM is noted, value is from a single determination.

observed for **1**. This profile could be beneficial in androgen therapy, where over-stimulation of the sexual accessory tissues should be avoided to limit the risk of prostate hypertrophy or hyperplasia. **(*R*)-16e** also reduces leutinizing hormone (LH) levels, another marker of androgen activity in vivo.[8a]

Conclusion

We have described a receptor-selective and potent series of AR modulators based on 7*H*-[1,4]oxazino[3,2-*g*]quinolin-7-ones. A number of compounds, particularly those substituted at the 1- and 2-positions demonstrate potent activity in vitro. The 1-(2,2,2-trifluoroethyl) substituent exhibits very good AR activity in vitro across a number of analogues, while having minimal or no impact on GR, MR, or PR. Compound **(*R*)-16e** demonstrates in vivo activity in an established rodent model of androgen action. At 100 mg/kg, **(*R*)-16e** maintains LA muscle weight at the intact levels after oral administration for 4 weeks, while showing reduced activity in VP weight, demonstrating a muscle selectivity profile comparable to **1**. Furthermore, an enantiospecific synthesis of the benzoxazine core was developed and resulted in the establishment of the absolute configuration of the chiral center of the 2-position (*R*), as well as facilitating the evaluation of **(*R*)-16e** in vivo. This series of compounds offer good opportunities to identify new androgen modulators as anabolic agents and further studies directed toward improving the in vivo potency of these analogues will be reported in due course.

Table 3. Steroid Hormone Binding Selectivity[a]

cmpd	AR K_i[b] (nM)	PR K_i (nM)	GR K_i (nM)
10b	1.2 ± 0.4	5200 ± 2700	8100 ± 1800
10f	4.0 ± 1.0	5300 ± 2700	9200 ± 840
10h	15[c] ± 5	7000 ± 3000	-
12a	1.6 ± 0.2	2000 ± 930	8800 ± 1200
16d	23[c] ± 19	5400 ± 2400	-
16e	7.8 ± 1.2	2800 ± 600	8500 ± 1500
16f	9.4[c] ± 2.5	2800 ± 240	6500 ± 3500
28	16[c] ± 11	-	-

[a] Experimental results with at least three separate experiments in triplicate with SEM. Binding experiments were carried out with baculovirus expressed receptors, except where otherwise indicated. [b] Whole-cell binding in MDA cells. [c] Mean value from two experiments. A hyphen is indicative of K_i > 10 000 nM. All compounds from Table 3 were evaluated in a MR binding assay and were found to have a K_i > 10 000 nM in all instances.

Experimental Section

Proton nuclear magnetic resonance (^{1}H NMR) and carbon-13 nuclear magnetic resonance (^{13}C NMR) were recorded at 400 and 100 MHz, respectively, on a Bruker AC 400 or at 500 and 125 MHz on a Varian Unity Inova 500. Chemical shifts are given in parts per million (ppm) downfield from internal reference tetramethylsilane in δ units. Elemental analyses were performed at

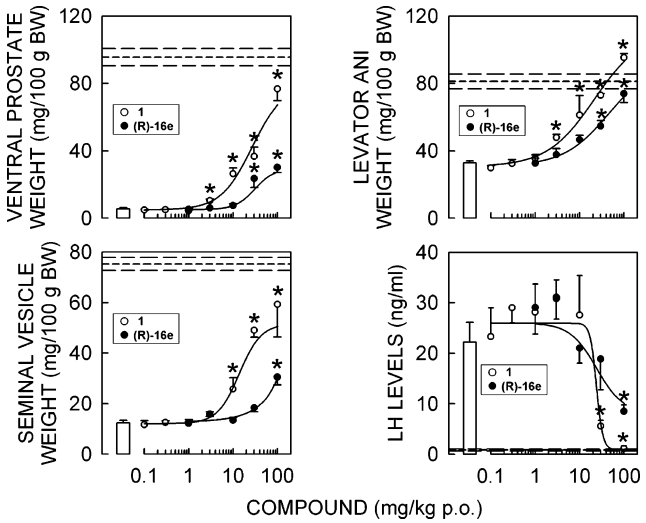


Figure 3. **(*R*)-16e** and **1** in a 4-week castrated mature rat model. The dashed lines (—) represent intact levels. $P < 0.05$ vs vehicle (one-way ANOVA, followed by Dunnett's test).

Table 4. Efficacy of **(*R*)-16e** and **1** Compared to Intact Control for VP and LA Weight

treatment (mg/kg)	LA efficacy[a]	VP efficacy[a]
(*R*)-16e (100)	85 ± 11	27 ± 3
1 (100)	129 ± 5	79 ± 8
intact	100 ± 9	100 ± 6

[a] Efficacy compared to intact control.

Quantitative Technologies, Inc., Whitehouse, NJ. Column chromatography was performed on silica gel using Merck 230−400 mesh silica gel. Analytical thin layer chromatography (TLC) was performed using Merck 60-F-254 0.25 mm precoated silica gel plates. Low- and high-resolution electrospray ionization (ESI) mass spectrometry was performed on a Micromass LCT Mass Spectrometer.

Analytical HPLC for selected compounds were performed on two systems. System A, Kromasil 100 (C18, 5 μm, 150 × 4.6 mm, 1.0 mL/min); system B, Beckman Si (5 μm, 250 × 4.6 mm, 1.0 mL/min). Using two analytical methods, the purity of the compounds was determined to be >95% using UV detection at 254 nM.

General Procedure 1: Reductive Amination with Sodium Cyanoborohydride in Acetic Acid. To a solution of **7** (1.0 equiv) in acetic acid (7.8 mL/mmol) was added an aldehyde (10 equiv), and the mixture was stirred at rt for 1 h. To this mixture was added portionwise sodium cyanoborohydride (4.8 equiv) and stirred at room temperature overnight. The resulting mixture was poured over ice, neutralized with 6 M NaOH to pH 7.0, extracted with CH_2Cl_2 (3 × 30 mL/mmol), and washed with pH 7 phosphate buffer (50 mL/mmol) and brine (50 mL/mmol). The organic solution was dried ($MgSO_4$) and concentrated under reduced pressure to afford the desired *N*-alkylated product as a yellow solid.

3,4-Dihydro-4-methyl-7-nitro-2*H*-1,4-benzoxazine (8a, R^1 = Me, R^3 = H). Compound **8a** (1.21 g, 98%) was prepared from **7a** (1.15 g, 6.38 mmol) and paraformaldehyde (1.92 g, 64.1 mmol). R_f 0.83 (11.5:1 CH_2Cl_2/MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (dd, 1H, J = 9.0, 2.6), 7.65 (d, 1H, J = 3.4), 6.56 (d, 1H, J = 8.9), 4.27 (t, 2H, J = 4.6), 3.46 (t, 2H, J = 4.5), 3.05 (s, 3H).

4-Ethyl-3,4-dihydro-7-nitro-2*H*-1,4-benzoxazine (8b, R^1 = Et, R^3 = H). Compound **8b** (984 mg, 74%) was prepared from **7a** (1.15 g, 6.39 mmol) and acetaldehyde (3.59 mL, 64.2 mmol). R_f 0.85 (11.5:1 CH_2Cl_2/MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (dd, 1H, J = 9.6, 2.6), 7.66 (d, 1H, J = 2.7), 6.29 (d, 1H, J = 9.2), 4.23 (t, 2H, J = 4.7), 3.47 (t, 2H, J = 4.7), 3.45 (q, 2H, J = 7.2), 1.22 (t, 3H, J = 7.0).

3,4-Dihydro-7-nitro-4-propyl-2*H*-1,4-benzoxazine (8c, R^1 = Pr, R^3 = H). Compound **8c** (450 mg, 69%), an orange oil, was prepared from **7a** (530 mg, 2.9 mmol) and propionaldehyde (1.61 g, 28 mmol). R_f 0.57 (2:1 EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (dd, 1H, J = 9.1, 2.6), 7.66 (d, 1H, J = 2.6), 6.56 (d, 1H, J = 9.0), 4.22 (t, 2H, J = 4.5), 3.49 (t, 2H, J = 4.5), 3.33 (t, 2H, J = 7.5), 1.67 (sext, 2H, J = 7.4), 0.98 (t, 3H, J = 7.4).

3,4-Dihydro-4-isobutyl-7-nitro-2*H*-1,4-benzoxazine (8d, R^1 = isobutyl, R^3 = H). Compound **8d** (713 mg, 99%) was prepared from **7a** (550 mg, 3.0 mmol) and isobutyraldehyde (1.65 g, 22.8 mmol). R_f 0.75 (3:2 EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (dd, 1H, J = 9.0, 2.6), 7.66 (d, 1H, J = 2.6), 6.55 (d, 1H, J = 9.2), 4.21 (t, 2H, J = 4.5), 3.52 (t, 2H, J = 4.6), 3.16 (d, 2H, J = 7.4), 3.12 (hept, 1H, J = 6.9), 0.97 (d, 6H, J = 6.7).

4-(2,2-Dimethylpropyl)-3,4-dihydro-7-nitro-2*H*-1,4-benzoxazine (8e, R^1 = 2,2-dimethylpropyl, R^3 = H). Compound **8e** (38 mg, 27%) was prepared from **7a** (100 mg, 0.55 mmol) and trimethylacetaldehyde in TFA. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (dd, 1H, J = 9.2, 2.7), 7.65 (d, 1H, J = 2.7), 6.68 (d, 1H, J = 9.2), 4.23 (t, 2H, J = 4.4), 3.54 (t, 2H, J = 4.5), 3.19 (s, 2H), 1.02 (s, 9H).

(±)-3,4-Dihydro-2,4-dimethyl-7-nitro-2*H*-1,4-benzoxazine (8g, R^1 = Me, R^3 = Me). Compound **8g** (160 mg, 99%) was prepared from **7b** (150 mg, 0.77 mmol) and paraformaldehyde (233 mg, 7.8 mmol). R_f 0.77 (3:2 EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (dd, 1H, J = 9.1, 2.5), 7.66 (d, 1H, J = 2.5), 6.55 (d, 1H, J = 8.9), 4.26−4.23 (m, 1H), 3.32 (dd, 1H, J = 12.1, 2.7), 3.22 (dd, 1H, J = 12.0, 8.2), 3.03 (s, 3H), 1.39 (d, 3H, J = 6.5).

(±)-2-Ethyl-3,4-dihydro-4-methyl-7-nitro-2*H*-1,4-benzoxazine (8i, R^1 = Me, R^3 = Et). Compound **8i** (127 mg, 99%) was prepared from **7c** (120 mg, 0.57 mmol) and paraformaldehyde (174 mg, 5.8 mmol). R_f 0.89 (11.5:1 CH_2Cl_2/MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (dd, 1H, J = 9.0, 2.5), 7.67 (d, 1H, J = 2.5), 6.54 (d, 1H, J = 9.0), 4.01 (m, 1H), 3.34 (dd, 1H, J = 12.0, 2.7), 3.23 (dd, 1H, J = 12.0, 8.1), 3.03 (s, 3H), 1.79−1.72 (m, 1H), 1.67−1.60 (m, 1H), 1.07 (t, 3H, J = 7.5).

(±)-2,4-Diethyl-3,4-dihydro-7-nitro-2*H*-1,4-benzoxazine (8j, R^1 = Et, R^3 = Et). Compound **8j** (72 mg, 42%) was prepared from **7c** (150 mg, 0.70 mmol) and acetaldehyde. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (dd, 1H, J = 9.1, 2.6), 7.68 (d, 1H, J = 2.5), 6.57 (d, 1H, J = 9.0), 3.90−4.00 (m, 1H), 3.48−3.60 (m, 1H), 3.25−3.40 (m, 2H), 3.25 (dd, 1H, J = 12.1, 8.0), 1.60−1.80 (m, 2H), 1.21 (t, 3H, J = 7.1), 1.08 (t, 3H, J = 7.4).

3,4-Dihydro-4-(*p*-methoxybenzyl)-7-nitro-2*H*-1,4-benzoxazine (8l, R^1 = 4-anisyl, R^3 = H). Compound **8l** (361 mg, 70%) was prepared from **7a** (305 mg, 1.7 mmol) and *p*-anisaldehyde (2.3 g, 17 mmol). R_f 0.79 (3:2 EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (dd, 1H, J = 9.0, 2.6), 7.70 (d, 1H, J = 2.5), 7.14 (d, 2H, J = 8.6), 6.88 (d, 2H, J = 8.6), 6.63 (d, 1H, J = 9.1), 4.54 (s, 2H), 4.26 (t, 2H, J = 4.5), 3.80 (s, 3H), 3.51 (t, 2H, J = 4.6).

General Procedure 2: Reductive Amination To Form a 2,2,2-(Trifluoroethyl)amine. To a solution of a **7** (1.0 equiv) in trifluoroacetic acid (0.5 mL/mmol) was added 2,2,2-trifluoroacetaldehyde monohydrate (10 equiv), and the mixture was stirred at rt for 2 h. To this mixture was added portionwise sodium cyanoborohydride (4.8 equiv) and the mixture was stirred at room temperature overnight. [Caution: Add the sodium cyanoborohydride slowly and provide a gentle cone of nitrogen to minimize the introduction of air.] The resulting mixture was poured over ice, neutralized with 6 M NaOH solution to pH 7.0, extracted with CH_2Cl_2 (3 × 30 mL/mmol), and washed with pH 7 phosphate buffer (50 mL/mmol) and brine (50 mL/mmol). The organic solution was dried ($MgSO_4$) and concentrated under reduced pressure to afford the desired product as a yellow solid.

3,4-Dihydro-7-nitro-4-(2,2,2-trifluoroethyl)-2*H*-1,4-benzoxazine (8f, R^1 = CH_2CF_3, R^3 = H). Compound **8f** (500 mg, 88%), a yellow solid, was prepared from **7a** (388 mg, 2.1 mmol). R_f 0.59 (3:2 EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (dd, 1H, J = 8.8, 2.6), 7.72 (d, 1H, J = 2.6), 6.72 (d, 1H, J = 9.1), 4.27 (t, 2H, J = 4.5), 3.94 (q, 2H, J = 8.6), 3.61 (t, 2H, J = 4.5).

(±)-3,4-Dihydro-2-methyl-7-nitro-4-(2,2,2-trifluoroethyl)-2*H*-1,4-benzoxazine (8h, R^1 = CH_2CF_3, R^3 = Me). Compound **8h** (550 mg, 96%), a yellow solid, was prepared from **7b** (400 mg,

2.0 mmol). R_f 0.85 (3:2 EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (dd, 1H, J = 9.2, 2.6), 7.72 (d, 1H, J = 2.6), 6.72 (d, 1H, J = 9.1), 4.23 (m, 1H), 4.23−3.82 (m, 2H), 3.47 (dd, 1H, J = 12.1, 2.6), 3.37 (dd, 1H, J = 12.2, 8.2), 1.41 (d, 3H, J = 6.1).

(±)-2-Ethyl-3,4-dihydro-7-nitro-4-(2,2,2-trifluoroethyl)-2*H*-1,4-benzoxazine (8k, R^1 = CH_2CF_3, R^3 = Et). Compound **8k** (346 mg, 99%) was prepared from **7c** (250 mg, 1.2 mmol). R_f 0.75 (3:2 EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (dd, 1H, J = 8.9, 2.6), 7.73 (d, 1H, J = 2.5), 6.70 (d, 1H, J = 9.0), 4.03−3.81 (m, 3H), 3.48 (dd, 1H, J = 12.1, 2.6), 3.39 (dd, 1H, J = 12.1, 8.0), 1.80−1.62 (m, 2H), 1.08 (t, 3H, J = 7.4).

General Procedure 3: Pd−C Hydrogenation of a Nitro Compound to an Aniline. To a solution of a 4-alkyl-3,4-dihydro-7-nitro-2*H*-1,4-benzoxazine in 1:1 EtOAc/EtOH (13 mL/mmol) was added 10% Pd−C (6% by wt). The flask was flushed, evacuated with N_2 (3×), and then stirred under an atmosphere of H_2 overnight. The reaction mixture was filtered through Celite, washed with EtOAc (2 × 20 mL/mmol) and concentrated under reduced pressure to give the desired product as a light purple/tan solid, which was purified on silica gel (CH_2Cl_2/MeOH, 20:1) unless otherwise indicated.

7-Amino-3,4-dihydro-4-methyl-2*H*-1,4-benzoxazine (9a, R^1 = Me, R^3 = H). Compound **9a** (167 mg, 75%) was prepared from **8a** (262 mg, 1.35 mmol). R_f 0.36 (11.5:1 CH_2Cl_2/MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.55 (d, 1H, J = 8.2), 6.25 (d, 1H, J = 2.6), 6.22 (dd, 1H, J = 7.0, 2.7), 4.28 (t, 2H, J = 4.4), 3.32 (br s, 2H), 3.13 (t, 2H, J = 4.5), 2.79 (s, 3H).

7-Amino-4-ethyl-3,4-dihydro-2*H*-1,4-benzoxazine (9b, R^1 = Et, R^3 = H). Compound **9b** (173 mg, 77%) was prepared from **8b** (264 mg, 1.3 mmol). R_f 0.52 (11.5:1 CH_2Cl_2/MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.56 (d, 1H, J = 8.1), 6.26−6.22 (m, 2H), 4.23 (t, 2H, J = 4.4), 3.29 (br s, 2H), 3.24 (q, 2H, J = 7.1), 3.19 (t, 2H, J = 4.4), 1.11 (t, 3H, J = 7.0).

7-Amino-3,4-dihydro-4-propyl-2*H*-1,4-benzoxazine (9c, R^1 = Pr, R^3 = H). Compound **9c** (36 mg, 84%) was prepared from **8c** (50 mg, 0.2 mmol). R_f 0.43 (2:1 EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.53 (d, 1H, J = 8.9), 6.25−6.20 (m, 2H), 4.21 (t, 2H, J = 4.4), 3.28 (br s, 2H), 3.21 (t, 2H, J = 4.4), 3.08 (t, 2H, J = 7.5), 1.60 (sext, 2H, J = 7.4), 0.94 (t, 3H, J = 7.4).

7-Amino-3,4-dihydro-4-isobutyl-2*H*-1,4-benzoxazine (9d, R^1 = Isobutyl, R^3 = H). Compound **9d** (621 mg, 99%) was prepared from **8d** (712 mg, 3.0 mmol). R_f 0.43 (3:2 EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.49 (d, 1H, J = 9.1), 6.23 (m, 2H), 4.20 (t, 2H, J = 4.4), 3.28 (br s, 2H), 3.23 (t, 2H, J = 4.4), 2.85 (d, 2H, J = 7.2), 2.04−1.92 (m, 1H), 0.94 (d, 6H, J = 6.5).

7-Amino-4-(2,2-dimethylpropyl)-3,4-dihydro-2*H*-1,4-benzoxazine (9e, R^1 = 2,2-Dimethylpropyl, R^3 = H). Compound **9e** (53 mg (100%) was prepared from **8e** (60 mg, 0.24 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.57 (d, 1H, J = 9.2), 6.18−6.25 (m, 2H), 4.17 (t, 2H, J = 4.4), 3.27 (t, 2H, J = 4.4), 2.86 (s, 2H), 0.98 (s, 9H).

7-Amino-3,4-dihydro-4-(2,2,2-trifluoroethyl)-2*H*-1,4-benzoxazine (9f, R^1 = CH_2CF_3, R^3 = H). Compound **9f** (2.7 g, 98%) was prepared from **8f** (3.12 g, 12 mmol). R_f 0.47 (3:2 EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.56 (d, 1H, J = 8.2), 6.30−6.20 (m, 2H), 4.16 (t, 2H, J = 4.3), 3.65 (q, 2H, J = 9.1), 3.39 (t, 2H, J = 4.4), 3.36 (br s, 1H).

(±)-7-Amino-3,4-dihydro-2,4-dimethyl-2*H*-1,4-benzoxazine (9g, R^1 = Me, R^3 = Me). Compound **9g** (134 mg, 97%) was prepared from **8g** (160 mg, 0.77 mmol). R_f 0.35 (11.5:1 CH_2Cl_2/MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.54 (d, 1H, J = 8.0), 6.25−6.20 (m, 2H), 4.36−4.33 (m, 1H), 3.31 (br s, 2H), 3.08 (dd, 1H, J = 11.4, 2.3), 2.82 (dd, 1H, 11.4, 8.2), 2.78 (s, 3H), 1.33 (d, 3H, J = 6.2).

(±)-7-Amino-3,4-dihydro-2-methyl-4-(2,2,2-trifluoroethyl)-2*H*-1,4-benzoxazine (9h, R^1 = CH_2CF_3, R^3 = Me). Compound **9h** (345 mg (98%) was prepared from **8h** (394 mg, 1.4 mmol). R_f 0.60 (11.5:1 CH_2Cl_2/MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.57 (d, 1H, J = 9.2), 6.27−6.22 (m, 2H), 6.24 (s, 1H), 4.18 (m, 1H), 3.75−3.62 (m, 3H), 3.27 (dd, 1H, J = 12.0, 9.8), 3.10 (dd, 1H, J = 12.0, 8.5), 1.34 (d, 3H, J = 6.3).

(±)-7-Amino-2-ethyl-3,4-dihydro-4-methyl-2*H*-1,4-benzoxazine (9i, R^1 = Me, R^3 = Et). Compound **9i** (80 mg, 71%) was prepared from **8i** (130 mg, 0.6 mmol). R_f 0.5 (19:1 CH_2Cl_2/MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.53 (dd, 1H, J = 9.1, 2.7), 6.25−6.20 (m, 2H), 4.11 (m, 1H), 3.10 (dd, 1H, J = 11.4, 2.1), 2.84 (dd, 1H, J = 11.3, 8.1), 2.78 (s, 3H), 1.75−1.70 (band, 1H), 1.64−1.58 (m, 1H), 1.03 (t, 2H, J = 7.5).

(±)-7-Amino-2,4-diethyl-3,4-dihydro-2*H*-1,4-benzoxazine (9j, R^1 = Me, R^3 = Et). Compound **9j** (43 mg, 70%) was prepared from **8j** (70 mg, 0.3 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.54 (d, 1H, J = 8.1), 6.20−6.30 (m, 2H), 3.98−4.08 (m, 1H), 3.25−3.35 (m, 1H), 3.10−3.20 (m, 1H), 2.92 (dd, 1H, J = 11.4, 8.1), 1.70−1.80 (m, 1H), 1.55−1.65 (m, 1H), 1.11 (t, 3H, J = 7.2), 1.03 (t, 3H, J = 7.5).

(±)-7-Amino-2-ethyl-3,4-dihydro-4-(2,2,2-trifluoroethyl)-2*H*-1,4-benzoxazine (9k, R^1 = CH_2CF_3, R^3 = Et). Compound **9k** (151 mg, 99%) was prepared from **8k** (170 mg, 0.6 mmol). R_f 0.62 (3:2 EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.56 (d, 1H, J = 8.0), 6.25−6.20 (m, 2H), 3.93 (m, 1H), 3.70−3.64 (m, 3H), 3.43 (br s, 1H), 3.31 (m, 1H), 3.12 (dd, 1H, J = 11.9, 8.1), 1.74−1.59 (m, 2H), 1.04 (t, 3H, J = 7.5).

General Procedure 4: Zinc Reduction of a Nitrobenzene Derivative to an Aniline. A mixture of the nitrobenzene derivative (1.0 equiv) in ethanol/water (95:5), zinc dust (4.3 equiv), and calcium chloride dihydrate (2.2 equiv) was heated to reflux for approximately 4−5 h. The reaction mixture was filtered hot through a pad of celite and washed with hot EtOAc (100 mL). The solvent was removed under reduced pressure and partitioned with water (150 mL) and EtOAc (150 mL). The aqueous layer was then adjusted to a pH of 3−4 with 20% HCl, extracted with EtOAc (3 × 100 mL), washed with brine (100 mL), dried ($MgSO_4$), and concentrated under reduced pressure. Purification by flash chromatography (silica gel, 20:1, CH_2Cl_2/MeOH) afforded the desired aniline.

7-Amino-3,4-dihydro-4-(*p*-methoxybenzyl)-2*H*-1,4-benzoxazine (9l, R^3 = H, R^1 = 4-anisyl). Compound **9l** (900 mg, 99%) was prepared from **8l** (1.0 g, 3.3 mmol). R_f 0.60 (24:1 CH_2Cl_2/MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 (d, 2H, J = 8.6), 6.86 (d, 2H, J = 8.6), 6.60 (d, 1H, J = 8.4), 6.34 (d, 1H, J = 2.5), 6.30 (dd, 1H, J = 8.5, 2.4), 4.25 (s, 2H), 4.21 (t, 2H, J = 4.5), 3.80 (s, 3H), 3.17 (t, 2H, J = 4.3).

Enantiospecific Synthesis of Amino Benzoxazine Analogues. General Procedure 5: Nucleophilic Aromatic Substitution of 3,4-Difluoronitrobenzene with an Amino Alcohol. A mixture of 3,4-difluoronitrobenzene (1.2 equiv) and the amino alcohol (1 equiv) was dissolved in absolute ethanol (3.3 M) or DMF. To this solution was added sodium bicarbonate (1 equiv). The suspension was heated at reflux (EtOH) or the specified temperature for 12 h until TLC indicated complete conversion of the amino alcohol. After cooling to room temperature, the reaction mixture was filtered with the aid of additional ethanol and the filtrate was concentrated under reduced pressure, which was then purified as indicated.

(2*R*)-(+)-2-(2-Fluoro-4-nitrophenyl)amino-1-propanol (20a, R^2 = Me). Compound **20a** (68.4 g, 80%), a yellow solid, was prepared from (*R*)-(−)-2-amino-1-propanol (30 g, 0.40 mol) and sodium bicarbonate (33.6 g, 0.40 mol) in 120 mL of ethanol, after recrystallization from ethanol: mp 128.2−129.7 °C; $[\alpha]_D$ = +22.6 (EtOH, *c* 3.1); ^{1}H NMR (400 MHz, $CDCl_3$) d 7.99 (dd, 1H, J = 11.4), 7.89 (dd, 1H, J = 11.6, 2.5), 6.72 (dd, 1H, J = 8.7), 4.75 (br s, 1H), 3.8 (m, 2H), 3.69 (m, 1H), 1.31 (d, 3H, J = 6.4).

(2*R*)-2-(2-Fluoro-4-nitrophenyl)amino-1-butanol (20b, R^2 = Et). Compound **20b** (9.9 g, 99%), a yellow oil, was prepared from (*R*)-(−)-2-amino-1-butanol (4.14 mL, 0.044 mol) in 133 mL of anhydrous DMF heated at 90 °C, after flash chromatography (gradient elution, hexanes/ethyl acetate 95:5 to 50:50). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.98 (dd, 1H, J = 8.8, 1.5), 7.89 (dd, 1H, J = 11.7, 2.4), 6.71 (dd, 1H, J = 8.8, 8.8), 4.72 (br s, 1H), 3.81 (m, 1H), 3.73 (m, 1H), 3.55 (m, 1H), 1.76 (m, 1H), 1.63 (m, 1H), 1.02 (t, 3H, J = 7.8).

(2*R*)-2-(2-Fluoro-4-nitrophenyl)amino-3-methyl-1-butanol (20c, R^2 = Isopropyl). Compound **20c** (8.3 g (71%), a yellow solid,

was prepared from (*R*)-(−)-2-amino-3-methyl-1-butanol (5.00 g, 48.5 mmol) in 6 mL of EtOH heated at reflux for 22 h, after flash chromatography. R_f 0.8 (1:1 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00−7.96 (m, 1H), 7.90 (dd, 1H, J = 11.6, 2.4), 6.73 (dd, 1H, J = 8.5, 8.5), 4.75−4.69 (m, 1H), 3.87−3.79 (m, 1H), 3.79−3.70 (m, 1H), 3.47−3.39 (m, 1H), 2.06−1.97 (m, 1H), 1.03 (d, 3H, J = 3.6), 1.01 (d, 3H, J = 3.6).

(2*R*)-2-(2-Fluoro-4-nitrophenyl)amino-4-methyl-1-pentanol (20d, R^2 = Isobutyl). Compound **20d** (6.0 g (55%), a yellow solid, was prepared from (*R*)-(−)-2-amino-4-methyl-1-pentanol (5.00 g, 42.7 mmol) in EtOH heated at reflux for 16 h, after flash chromatography (gradient elution, hexanes/EtOAc 9:1 to 1:1). R_f 0.3 (3:1 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01−7.97 (m, 1H), 7.90 (dd, 1H, J = 11.7, 2.7), 6.74 (dd, 1H, J = 8.6, 8.6), 4.62−4.57 (m, 1H), 3.82−3.74 (m, 1H), 3.75−3.62 (m, 2H), 1.77−1.65 (m, 1H), 1.61−1.45 (m, 2H), 0.99 (d, 3H, J = 6.6), 0.93 (d, 3H, J = 6.6).

General Procedure 6: Formation of an Oxazolidine from an Aminoalcohol and Trifluoroacetaldehyde Ethyl Hemiacetal. A round-bottom flask equipped with a Dean−Stark condenser was charged with the amino alcohol (1 equiv), benzene (0.3−0.5 M), trifluoroacetaldehyde ethyl hemiacetal (5 equiv), and *p*-toluenesulfonic acid (catalytic). The reaction mixture was refluxed with azeotropic removal of water for 10−12 h. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure. The residue was dissolved in ethyl acetate, washed with aqueous sodium bicarbonate and brine, and dried over anhydrous $MgSO_4$. After filtration, the solvents were removed under reduced pressure to afford the desired oxazolidine. In most instances, the oxazolidine was isolated as a diastereomeric mixture and carried on directly.

cis*-(2*S*,4*R*)-(−)-3-(2-Fluoro-4-nitrophenyl)-4-methyl-2-trifluoromethyloxazolidine (*cis*-21a, R^2 = Me) and *trans*-(2*R*,4*R*)-(+)-3-(2-Fluoro-4-nitrophenyl)-4-methyl-2-trifluoromethyloxazolidine (*trans*-21a, R^2 = Me).** These compounds were prepared from **20a** (68 g, 0.317 mole) and 100 mg of *p*-toluenesulfonic acid (100 mg, 0.53 mmol) to afford **21a** as a low melting solid. The product is a mixture of two diastereoisomers (*cis*/*trans* 4:1). Crystallization from ethyl acetate−hexanes furnished the major (cis*-21a**) isomer as pale yellow needles and the minor (***trans*-21a**) isomer as a glassy solid. In subsequent examples, the compounds are carried on as mixtures of diastereomers. The combined yield of both compounds was 93.2 g (100%).

***cis*-21a:** mp 46−50 °C; $[\alpha]_D$ = −60.9 ($CHCl_3$, *c* 10.3); ^{1}H NMR ($CDCl_3$) δ 8.01 (m, 1H), 7.98 (dd, 1H, J = 12.3, 2.5), 6.96 (dd, 1H, J = 9.0), 5.75 (q, 1H, J = 4.7), 4.33 (m, 1H), 4.19 (m, 1H), 3.99 (m, 1H), 1.45 (d, 3H, J = 6.3).

***trans*-21a:** $[\alpha]_D$ = +258.9 ($CHCl_3$, *c* 8.25); ^{1}H NMR ($CDCl_3$) δ 8.02 (dd, 1H), 7.98 (dd, 1H, J = 12.9, 2.5). 6.96 (dd, 1H, J = 8.5), 5.83 (q, 1H, J = 4.7), 4.48 (m, 1H), 4.40 (m, 1H), 3.95 (m, 1H), 1.23 (d, 3H, J = 6.0).

(4*R*)-3-(2-Fluoro-4-nitrophenyl)-4-ethyl-2-(trifluoromethyl)-1,3-oxazolidine (21b, R^2 = Et). Compound **21b** (1.8 g, 85%) was prepared from **20b** (1.6 g, 70 mmol) and *p*-toluenesulfonic acid (0.13 g, 0.68 mmol) in 70 mL anhydrous benzene, after flash chromatography (gradient elution, hexanes/ethyl acetate 90:10 to 50:50). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.01 (m, 1H), 7.98 (m, 1H), 6.95 (dd, 1H, J = 8.8, 8.8), 5.68 (m, 1H), 4.30 (m, 1H), 4.08 (m, 1H), 3.92 (m, 1H), 2.00 (m, 1H), 1.67 (m, 1H), 0.97 (t, 3H, J = 7.8).

(4*R*)-3-(2-Fluoro-4-nitrophenyl)-4-isopropyl-2-(trifluoromethyl)-1,3-oxazolidine (21c, R^2 = Isopropyl). Compound **21c** (5.2 g, 47%) was prepared from **20c** (8.3 g, 34 mmol) and *p*-toluenesulfonic acid (20 mg, 0.10 mmol) in 220 mL benzene. R_f 0.7 (3:1 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04−7.97 (m, 2H), 7.22 (dd, J = 8.7, 8.7, 1H), 5.34 (q, J = 4.6, 1H), 4.27 (dd, J = 8.0, 8.0, 1H), 4.11(dd, J = 7.4, 7.4, 1H), 3.81 (q, J = 7.1, 1H), 2.02−1.93 (m, 1H), 0.96 (d, J = 6.8, 6H).

(4*R*)-3-(2-Fluoro-4-nitrophenyl)-4-isobutyl-2-(trifluoromethyl)-1,3-oxazolidine (21d, R^2 = Isobutyl). Compound **21d** (5.15 g, 65%) was prepared from **20d** (6.0 g, 23 mmol) and *p*-toluenesulfonic acid (0.020 g, 0.10 mmol) in 250 mL benzene. R_f 0.8 (3:1 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03−7.94 (m, 2H), 6.96−6.88 (m, 1H), 5.81 (q, 1H, minor diast., J = 4.7), 5.69 (q, 1H, major diast., J = 4.7), 4.45−4.40 (m, minor diast., 1H), 4.36−4.28 (m, major diast., 1H), 4.11−4.01 (m, 2H), 1.82−1.74 (m, 1H), 1.66−1.52 (m, 2H), 1.02 (d, 3H, major diast., J = 6.4), 0.99−0.95 (m, 3H), 0.91 (d, 3H, minor diast., J = 6.6).

(2*R*)-(−)-2-[2-Fluoro-4-nitro(2,2,2-trifluoroethyl)anilino]-1-propanol (22a, R^2 = Me). A solution of ***cis*-21a** and ***trans*-21a** (93 g, 0.36 mole), 600 mL of dry chloroform, and triethylsilane (183.7 g, 1.58 mol) was cooled to −78 °C and $TiCl_4$ (90 g, 0.474 mol) was added via addition funnel. The reaction mixture was allowed to warm to room temperature and stirred for another 24 h. The mixture was quenched with ice and then neutralized with aqueous Na_2CO_3. The organic layers were washed with water and brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by silica gel column chromatography (ethyl acetate/hexanes 1:9) to afford 57 g (61%) of **22a**, as a glassy solid. $[\alpha]_D$ = −205.9 (EtOH, *c* 10.15); ^{1}H NMR ($CDCl_3$) δ 7.99 (dd, 1H, J = 2.5, 9.0), 7.95 (dd, 1H, J = 2.6, 14.7), 7.32 (dd, 1H, J = 8.6), 3.94 (m, 1H), 3.74 (m, 2H), 3.65 (m, 1H), 1.86 (br s, 1H), 1.19 (d, 3H, J = 6.7).

(2*R*)-2-[2-Fluoro-4-nitro(2,2,2-trifluoroethyl)anilino]-1-butanol (22b, R^2 = Et). To a solution of **21b** (9.2 g, 29.8 mmol) and Et_3SiH (19.1 mL, 119 mmol) in 100 mL of chloroform was added BF_3OEt_2 (7.56 mL, 60 mmol). The reaction was heated to reflux for 12 h, then additional BF_3OEt_2 (7.56 mL, 60 mmol) was added, and the mixture was heated at reflux for an additional 12 h. After cooling, MeOH (5 mL) was added, and after 1 h, the reaction was poured in water (250 mL) and extracted with ethyl acetate (3 × 250 mL). The organic layers were combined, washed with water (250 mL) and brine (250 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford a brown oil. Flash chromatography (gradient elution, hexanes/ethyl acetate 95:5 to 50:50) afforded 5.4 g (59%) of **22b**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.98 (dd, 1H, J = 8.8, 2.4), 7.94 (dd, 1H, J = 13.2, 2.9), 7.37 (dd, 1H, J = 8.8, 8.8), 4.12 (m, 1H), 3.87 (m, 1H), 3.77 (m, 1H), 3.70 (m, 1H), 3.57 (m, 1H), 1.78 (dd, 1H, J = 6.8, 4.4), 1.50−1.60 (m, 2H), 0.95 (t, 3H, J = 7.3).

(2*R*)-2-[2-Fluoro-4-nitro(2,2,2-trifluoroethyl)anilino]-3-methyl-1-butanol (22c, R^2 = Isopropyl). To a solution of **21c** (1.8 g, 5.6 mmol) and Et_3SiH (1.88 g, 16.1 mmol) in 15 mL of $CHCl_3$ was added $TiCl_4$ (6 mL of a 1 M solution in CH_2Cl_2, 6 mmol) at −78 °C. The solution was stirred for 2 h, then allowed to warm to 0 °C, and stirred for 2 h. The mixture was poured into 150 mL of water and neutralized with 6 N NaOH. The aqueous layer was extracted with $CHCl_3$ (3 × 100 mL), and the combined organic layers were washed with brine (150 mL), dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (gradient elution, hexanes/EtOAc 9:1 to 3:1) afforded 1.6 g (88%) of **22c**, an orange oil. R_f 0.3 (3:1 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (dd, 1H, J = 8.8, 2.3), 7.92 (dd, 1H, J = 13.4, 2.5), 7.37 (dd, 1H, J = 8.8, 8.8), 4.33−4.23 (m, 1H), 4.03−3.86 (m, 2H), 3.81−3.74 (m, 1H), 3.36−3.27 (m, 1H), 1.97−1.88 (m, 1H), 1.85 (br s, 1H), 0.99 (d, 3H, J = 6.6), 0.94 (d, 3H, J = 6.6).

(2*R*)-2-[2-Fluoro-4-nitro(2,2,2-trifluoroethyl)anilino]-4-methyl-1-pentanol (22d, R^2 = Isobutyl). To a solution of **21d** (4.8 g, 14.3 mmol) and Et_3SiH (21.6 g, 186 mmol) in 60 mL of $CHCl_3$ was added BF_3OEt_2 (14.2, 60 mmol). The reaction was heated at reflux for 1 day. After cooling, the reaction was poured in water (200 mL) and extracted with $CHCl_3$ (3 × 150 mL). The organic layers were combined, washed sequentially with water (200 mL) and brine (200 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford a brown oil. Flash chromatography (gradient elution, hexanes/ethyl acetate 95:5 to 3:1) afforded 2.1 g (44%) of **22d**, an orange oil. R_f 0.8 (3:1 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (dd, 1H, J = 9.3, 2.4), 7.94 (dd, 1H, J = 12.9, 2.5), 7.40 (dd, 1H, J = 8.7, 8.7), 4.21−4.10 (m, 1H), 3.89−3.78 (m, 1H), 3.79−3.65 (m, 3H), 1.96−1.89 (m, 1H), 1.67−1.54 (m, 1H), 1.55−1.44 (m, 1H), 1.32−1.22 (m, 1H), 0.91 (d, J = 6.6, 3H), 0.77 (d, J = 6.6, 3H).

General Procedure 7: Intramolecular Benzoxazine Cyclization. A solution of the aminoalcohol (1 equiv) in dry THF (1 M)

was added to a suspension of NaH (1.5 equiv) in dry THF (2 M), and the mixture was heated at reflux for 3 h or until TLC indicated the reaction was completed. After cooling, methanol (50 mL/mol) was added. The reaction mixture was poured into cold water and extracted with ethyl acetate. The organic portions were combined, washed with brine, and dried over $MgSO_4$. After filtration, the solvents were evaporated under reduced pressure and purified as indicated.

(3*R*)-(+)-3,4-Dihydro-3-methyl-7-nitro-4-(2,2,2-trifluoroethyl)-2*H*-1,4-benzoxazine (23a, R² = Me). Compound **23a** (36.5 g, 68%), a yellow crystalline solid, was prepared from **22a** (57 g, 0.193 mol), heated at reflux for 3 h, after purification by flash chromatography. Mp 95.5−96.4 °C; $[\alpha]_D = +57.8$ (EtOH, *c* 2.25); ^{1}H NMR ($CDCl_3$) δ 7.80 (dd, 1H, J = 9.1, 2.5), 7.73 (d, 1H, J = 2.6), 6.71 (d, 1H, J = 9.1), 4.13 (m, 2H), 4.03 (m, 1H), 3.84 (m, 1H), 3.69 (m, 3H), 1.31 (d, 3H, J = 6.6).

(3*R*)-3-Ethyl-3,4-dihydro-7-nitro-4-(2,2,2-trifluoroethyl)-2*H*-1,4-benzoxazine (23b, R² = Et). Compound **23b** (3.78 g, 75%) was prepared from **22b** (5.4 g, 17.3 mmol) in 45 mL of THF and NaH (1.4 g, 35 mmol) in 10 mL of THF, after purification by flash chromatography (gradient elution, hexanes/ethyl acetate 95:5 to 50:50). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81 (dd, 1H, J = 8.8, 2.4), 7.73 (d, 1H, J = 2.9), 6.72 (d, 1H, J = 8.8), 4.34 (dd, 1H, J = 11.2, 1.5), 4.13 (m, 1H), 4.03 (dd, 1H, J = 11.2, 2.4), 3.8 (m, 1H), 3.37 (m, 1H), 1.67 (m, 1H), 1.01 (t, 3H, J = 7.3).

(3*R*)-3,4-Dihydro-3-isopropyl-7-nitro-4-(2,2,2-trifluoroethyl)-2*H*-1,4-benzoxazine (23c, R² = Isopropyl). Compound **23c** (0.80 g, 54%), a yellow oil, was prepared from **22c** (1.58 g, 4.87 mmol), after purification by flash chromatography (gradient elution, hexanes/EtOAc 9:1 to 3:1). R_f 0.5 (3:1 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (dd, 1H, J = 9.1, 2.5), 7.72 (d, 1H, J = 2.6), 6.79 (d, 1H, J = 9.1), 4.49 (dd, 1H, J = 11.1, 0.92), 4.37−4.26 (m, 1H), 3.95 (dd, 1H, J = 11.1, 2.4), 3.80−3.69 (m, 1H), 3.14 (d, 1H, J = 8.5), 2.08−1.98 (m, 1H), 1.01 (d, 3H, J = 6.9), 0.99 (d, 3H, J = 6.9).

(3*R*)-3,4-Dihydro-3-isobutyl-7-nitro-4-(2,2,2-trifluoroethyl)-2*H*-1,4-benzoxazine (23d, R² = Isobutyl). Compound **23d** (0.87 g, 50%), a yellow oil, was prepared from **22d** (1.95 g, 5.76 mmol). R_f 0.6 (3:1 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (dd, 1H, J = 9.1, 2.7), 7.71 (d, 1H, J = 2.5), 6.72 (d, 1H, J = 9.1), 4.30 (dd, 1H, J = 11.0, 1.5), 4.19−4.06 (m, 1H), 4.06−4.01 (m, 1H), 3.82−3.73 (m, 1H), 3.53−3.47 (m, 1H), 1.71−1.61 (m, 2H), 1.38−1.29 (m, 1H), 0.99 (d, 3H, J = 6.5), 0.96 (d, 3H, J = 6.5).

(3*R*)-(−)-7-Amino-3,4-dihydro-3-methyl-4-(2,2,2-trifluoroethyl)-2*H*-1,4−benzoxazine (24a, R² = Me). Compound **24a** (31 g, 98%), an off-white solid, was prepared according to General Procedure 3 (Pd−C reduction) from **23a** (35.5 g, 0.128 mol) and 10% palladium on carbon (3 g) in 400 mL of ethyl acetate, after purification by flash chromatography (ethyl acetate/hexanes). $[\alpha]_D = -39.4$ (EtOH, *c* 1.7); ^{1}H NMR ($CDCl_3$) δ 6.58 (d, 1H, J = 8.2), 6.40 (m, 1H), 6.37 (m, 1H), 4.05 (dd, 1H, J = 11.0, 2.3), 3.98 (dd, 1H, J = 10.6, 2.9), 3.66 (m, 2H), 3.38 (m, 1H), 3.40 (br s, 2H), 1.18 (d, 3H, J = 6.6).

(3*R*)-7-Amino-3-ethyl-3,4-dihydro-4-(2,2,2-trifluoroethyl)-2*H*-1,4−benzoxazine (24b, R² = Et). Compound **24b** (4.8 g, 95%) was prepared according to General Procedure 3 (Pd−C reduction) from **23b** (5.6 g, 19.3 mmol) and 10% Pd/C (cat.) in 60 mL ethyl acetate, and carried on without purification.

(3*R*)-7-Amino-3,4-dihydro-3-isopropyl-4-(2,2,2-trifluoroethyl)-2*H*-1,4−benzoxazine (24c, R² = Isopropyl). Compound **24c** (0.284 g, 90%) was prepared according to General Produre 3 (Pd−C reduction) from **23c** (0.350 g, 1.15 mmol) and 10% Pd/C (0.14 g) in 7 mL of EtOAc, after purification by flash chromatography (gradient elution, hexanes/EtOAc 9:1 to 3:1). R_f 0.2 (3:1 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.71 (d, 1H, J = 8.5), 6.27 (dd, 1H, J = 8.5, 2.6), 6.20 (d, 1H, J = 2.5), 4.34 (dd, 1H, J = 11.0, 1.5), 3.84 (dd, 1H, J = 11.3, 2.2), 3.71−3.47 (m, 2H), 3.41 (br s, 2H), 2.62 (d, 1H, J = 9.8), 1.81−1.70 (m, 1H), 0.98 (d, 3H, J = 6.7), 0.96 (d, 3H, J = 6.7).

(3*R*)-7-Amino-3,4-dihydro-3-isobutyl-4-(2,2,2-trifluoroethyl)-2*H*-1,4−benzoxazine (24d, R² = Isobutyl). Compound **24d** (0.13 g, 65%) was prepared according to General Procedure 3 (Pd−C reduction) from **24c** (0.22 g, 0.69 mmol) and 10% Pd/C (0.075 g) in 5 mL ethyl acetate. R_f 0.3 (3:1 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.63 (d, 1H, J = 8.5), 6.27 (dd, 1H, J = 8.5, 2.6), 6.23 (d, 1H, J = 2.5), 4.10 (dd, 1H, J = 10.6, 1.8), 3.97 (dd, 1H, J = 10.6, 2.3), 3.70−3.51 (m, 2H), 3.38 (br s, 2H), 3.19−3.13 (m, 1H), 1.75−1.63 (m, 1H), 1.47−1.25 (m, 2H), 0.93 (d, 3H, J = 6.6), 0.89 (d, 3H, J = 6.6).

General Procedure 8: Condensation of a 7-Amino-3,4-dihydro-2*H*-1,4-benzoxazine with Ethyl 4,4,4-Trifluoroacetoacetate Followed by Treatment with Polyphosphoric Acid or Sulfuric Acid (Knorr Reaction). To a solution of a 7-amino-3,4-dihydro-2*H*-1,4-benzoxazine (1.0 equiv) in benzene (10 mL/mmol) under N_2 at room temperature was added ethyl 4,4,4-trifluoroacetoacetate (1.2 equiv), and the reaction was heated at reflux for 12−16 h, whereupon the mixture was concentrated under reduced pressure. The crude reaction mixture was diluted in PPA (8 mL/mmol) or concd sulfuric acid (2−3 mL/mmol) and heated to 100 °C for 12−16 h. The resulting mixture was poured over ice, neutralized with 6 M NaOH solution to pH 7.0, extracted with CH_2Cl_2 (3 × 30 mL/mmol), and washed with pH 7 phosphate buffer (50 mL/mmol) and brine (50 mL/mmol). The organic solution was dried ($MgSO_4$) and concentrated under reduced pressure. Purification by flash chromatography (silica gel, 20:1, CH_2Cl_2/MeOH, or as otherwise indicated) afforded the desired quinolone as a yellow solid.

1,2,3,6-Tetrahydro-1-methyl-9-(trifluoromethyl)-7*H*-[1,4]oxazino[3,2-*g*]quinolin-7-one (10a, R¹ = Me, R³ = H). Compound **10a** (125 mg, 44%) was prepared from **9a** mg, 0.98 mmol). R_f 0.44 (EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.65 (br s, 1H), 6.90 (s, 1H), 6.87 (s, 1H), 6.72 (s, 1H), 4.39 (t, 2H, J = 4.6), 3.31 (t, 2H, J = 4.5), 2.94 (s, 3H).

1-Ethyl-1,2,3,6-tetrahydro-9-(trifluoromethyl)-7*H*-[1,4]oxazino-[3,2-*g*]quinolin-7-one (10b, R¹ = Et, R³ = H). Compound **10b** (100 mg, 35%) was prepared from **9b** (170 mg, 0.95 mmol). R_f 0.21 (11.5:1 CH_2Cl_2/MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.47 (br s, 1H), 6.92 (s, 1H), 6.88 (s, 1H), 6.81 (s, 1H), 4.35 (t, 2H, J = 4.5), 3.4 (q, 2H, J = 7.1), 3.34 (t, 2H, J = 4.5), 1.19 (t, 3H, J = 7.1). Anal. ($C_{14}H_{13}F_3N_2O_2$): C, H, N.

1,2,3,6-Tetrahydro-1-propyl-9-(trifluoromethyl)-7*H*-[1,4]oxazino[3,2-*g*]quinolin-7-one (10c, R¹ = Pr, R³ = H). Compound **10c** (100 mg, 16%) was prepared from **9c** (395 mg, 2.0 mmol) after purification by flash chromatography (3:2 EtOAc/hexanes) and recrystallization from MeOH. R_f 0.24 (3:2 EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) 11.79 (br s, 1H), 6.88 (s, 1H), 6.87 (s, 1H), 6.83 (s, 1H), 4.32 (t, 2H, J = 4.5), 3.37 (t, 2H, J = 4.5), 3.26 (t, 2H, J = 7.4), 1.66 (sext, 2H, J = 7.4), 0.99 (t, 3H, J = 7.4). HRMS (ESI) calcd for $C_{15}H_{16}F_3N_2O_2$ $(M + H)^+$, 313.1164; found, 313.1150.

1,2,3,6-Tetrahydro-1-isobutyl-9-(trifluoromethyl)-7*H*-[1,4]oxazino[3,2-*g*]quinolin-7-one (10d, R¹ = Isobutyl, R³ = H). Compound **10d** (241 mg (25%) was prepared from **9d** (620 mg, 3.0 mmol) after purification by flash chromatography (3:2 EtOAc/hexanes) and recrystallization from MeOH. R_f 0.2 (3:2 EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.62 (br s, 1H), 6.87 (s, 2H), 6.74 (s, 1H), 4.31 (t, 2H, J = 4.5), 3.41 (t, 2H, J = 4.5), 3.05 (d, 2H, J = 7.0), 2.05−1.95 (m, 1H), 0.98 (d, 6H, J = 6.5). HRMS (ESI) calcd for $C_{16}H_{18}F_3N_2O_2$ $(M + H)^+$, 327.1320; found, 327.1316. Anal. ($C_{16}H_{14}F_6N_2O_2$): C, H, N.

1-(2,2-Dimethylpropyl)-1,2,3,6-tetrahydro-9-(trifluoromethyl)-7*H*-[1,4]oxazino[3,2-*g*]quinolin-7-one (10e, R¹ = 2,2-Dimethylpropyl, R³ = H). Compound **10e** (20 mg, 24%) was prepared from **9e** (53 mg, 0.24 mmol) after purification by flash chromatography (3:2 EtOAc/hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.54 (br s, 1H), 7.03 (s, 1H), 6.89 (s, 1H), 6.88 (s, 1H), 4.31 (t, J = 4.5, 2H), 3.42 (t, J = 4.5, 2H), 3.06 (s, 2H), 1.02 s, 9H). HRMS (ESI) calcd for $C_{17}H_{20}F_3N_2O_2$ $(M + H)^+$, 341.1477; found, 341.1477.

1,2,3,6-Tetrahydro-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)-7*H*-[1,4]oxazino[3,2-*g*]quinolin-7-one (10f, R¹ = CH_2CF_3, R³ = H). Compound **10f** (790 mg, 19%) was prepared from **9f** (2.7 g, 11.6 mmol) after purification by flash chromatography (3:2 EtOAc/

hexanes) and recrystallization from MeOH. R_f 0.25 (11.5:1 CH_2Cl_2/MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.95 (br s, 1H), 7.04 (br s, 1H), 6.91 (s, 1H), 6.90 (s, 1H), 4.33 (t, 2H, J = 4.5), 3.88 (q, 2H, J = 8.9), 3.56 (t, 2H, J = 4.5). Anal. ($C_{14}H_{10}F_6N_2O_2$): C, H, N.

(±)-1,2,3,6-Tetrahydro-1,3-dimethyl-9-(trifluoromethyl)-7*H*-[1,4]oxazino[3,2-*g*]quinolin-7-one (10g, R^1 = Me, R^3 = Me). Compound **10g** (50 mg, 40%) was prepared from **9g** (75 mg, 0.42 mmol). R_f 0.42 (11.5:1 CH_2Cl_2/MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.17 (br s, 1H), 6.88 (s, 1H), 6.87 (s, 1H), 6.78 (s, 1H), 4.45 (m, 1H), 3.24 (dd, 1H, J = 11.7, 2.5), 3.02 (dd, 1H, J = 11.5, 8.2), 2.93 (s, 3H), 1.40 (d, 3H, J = 6.5).

(±)-1,2,3,6-Tetrahydro-3-methyl-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)-7*H*-[1,4]oxazino[3,2-*g*]quinolin-7-one (10h, R^1 = CH$_2$CF$_3$, R^3 = Me). Compound **10h** (52 mg, 34%) was prepared from **9h** (345 mg, 1.4 mmol). R_f 0.26 (11.5:1 CH_2Cl_2/MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.84 (br s, 1H), 7.05 (s, 1H), 6.90 (s, 1H), 6.82 (s, 1H), 4.35 (m, 1H), 3.91 (m, 1H), 3.83 (m, 1H), 3.44 (dd, 1H, J = 12.1, 2.0), 3.21 (dd, 1H, J = 11.7, 7.8), 1.42 (d, 3H, J = 6.2). Anal. ($C_{15}H_{12}F_6N_2O_2$): C, H, N.

(±)-3-Ethyl-1,2,3,6-tetrahydro-1-methyl-9-(trifluoromethyl)-7*H*-[1,4]oxazino[3,2-*g*]quinolin-7-one (10i, R^1 = Me, R^3 = Et). Compound **10i** (26 mg, 20%) was prepared from **9i** (80 mg, 0.4 mmol). R_f 0.19 (19:1 CH_2Cl_2/MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.5 (br s, 1H), 6.89 (s, 2H), 6.83 (s, 1H), 4.22 (m, 1H), 3.26 (dd, 1H, J = 11.6, 2.4), 3.05 (dd, 1H, J = 11.6, 8.2), 2.94 (s, 3H), 1.76 (m, 1H), 1.67 (m, 1H), 1.08 (t, 3H, J = 7.5).

(±)-1,3-Diethyl-1,2,3,6-tetrahydro-9-(trifluoromethyl)-7*H*-[1,4]oxazino[3,2-*g*]quinolin-7-one (10j, R^1 = Et, R^3 = Et). Compound **10j** (25 mg, 38%) was prepared from **9j** (43 mg, 0.2 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.9 (br s, 1H), 6.90 (s, 1H), 6.89 (s, 1H), 6.86 (s, 1H), 4.10−4.20 (m, 1H), 3.45−3.55 (m, 1H), 3.25−3.35 (m, 1H), 3.26 (dd, J = 11.9, 2.7, 1H), 3.10 (dd, J = 11.9, 8.1, 1H), 1.60−1.80 (m, 2H), 1.19 (t, J = 7.2, 3H), 1.08 (t, J = 7.5, 3H). HRMS (ESI) calcd for $C_{16}H_{18}F_3N_2O_2$ (M + H)$^+$, 327.1320; found, 327.1321.

(±)-3-Ethyl-1,2,3,6-tetrahydro-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)-7*H*-[1,4]oxazino[3,2-*g*]quinolin-7-one (10k, R^1 = CH$_2$CF$_3$, R^3 = Et). Compound **10k** (75 mg, 51%) was prepared from **9k** (100 mg, 0.38 mmol). R_f 0.18 (19:1 CH_2Cl_2/MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.05 (br s, 1H), 7.03 (s, 1H), 6.95 (s, 1H), 6.92 (s, 1H), 4.15−4.05 (m, 1H), 3.98−3.88 (m, 1H), 3.88−3.75 (m, 1H), 3.44 (dd, 1H, J = 11.8, 2.5), 3.32 (dd, 1H, J = 11.9, 8.1), 1.76 (m, 1H), 1.68 (m, 1H), 1.09 (t, 3H, J = 7.6). Anal. ($C_{16}H_{14}F_6N_2O_2$): C, H, N.

1,2,3,6-Tetrahydro-9-(trifluoromethyl)-7*H*-[1,4]oxazino[3,2-*g*]quinolin-7-one (11, R^3 = H). Compound **11** (533 mg, 30%) was prepared from **9l** (1.78 g, 6.58 mmol). R_f 0.17 (3:2 EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.73 (br s, 1H), 6.94 (s, 1H), 6.87 (s, 1H), 6.75 (s, 1H), 4.35 (t, 2H, J = 4.4), 3.99 (br s, 1H), 3.50−3.42 (m, 1H). HRMS (ESI) calcd for $C_{12}H_{10}F_3N_2O_2$ (M + H)$^+$, 271.0694; found, 271.0693.

1-Cyclopropylmethyl-1,2,3,6-tetrahydro-9-(trifluoromethyl)-7*H*-[1,4]oxazino[3,2-*g*]quinolin-7-one (12a, R^1 = Cyclopropylmethyl, R^3 = H). Compound **12a** (64 mg, 98%) was prepared using General Procedure 1 (reductive amination) from **11** (55 mg, 0.21 mmol), cyclopropanecarboxaldehyde (100 mg, 1.5 mmol), and $NaBH_3CN$ (65 mg, 1.01 mmol). R_f 0.29 (19:1 CH_2Cl_2/MeOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.04 (br s, 1H), 7.00 (s, 1H), 6.88 (s, 1H), 6.78 (s, 1H), 4.36 (t, 2H, J = 4.4), 3.46 (t, 2H), J = 4.4), 3.19 (d, 2H, J = 6.3), 1.05 (m, 1H), 0.62−0.58 (m, 2H), 0.27 (m, 2H). HRMS (ESI) calcd for $C_{16}H_{16}F_3N_2O_2$ (M + H)$^+$, 325.1164; found, 325.1158. Anal. ($C_{16}H_{15}F_3N_2O_2 \cdot 0.2H_2O$): C, H, N.

1-Benzyl-1,2,3,6-tetrahydro-9-(trifluoromethyl)-7*H*-[1,4]oxazino-[3,2-*g*]quinolin-7-one (12b, R^1 = Benzyl, R^3 = H). Compound **12b** (9 mg, 36%) was prepared using General Procedure 1 (reductive amination) from **11** (19 mg, 0.07 mmol) and benzaldehyde. R_f 0.20 (19:1 CH_2Cl_2/MeOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.2 (br s, 1H), 7.33 (m, 5H), 6.94 (s, 1H), 6.83 (s, 1H), 6.80 (s, 1H), 4.46 (s, 2H), 4.38 (t, 2H, J = 4.5), 3.42 (t, 2H, J = 4.5). HRMS (ESI) calcd for $C_{19}H_{16}F_3N_2O_2$ (M + H)$^+$, 361.1164; found, 361.1165.

(2*R*-)-(−)-1,2,3,6-Tetrahydro-2-methyl-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)-7*H*-[1,4]oxazino[3,2-*g*]quinolin-7-one [(*R*)-16e, R^1 = CH$_2$CF$_3$, R^2 = Me]. (*R*)-16e (2.6 g, 42%) was prepared from **24a** (4.14 g, 16.8 mmol), after silica gel chromatography (ethyl acetate/hexanes), followed by recrystallization from ethyl acetate−hexanes. Mp 219−223 °C; $[\alpha]_D$ = −81.7 (EtOH, *c* 2.4); ^{1}H NMR ($CDCl_3$) δ 7.05 (1H, s), 6.91 (1H, s), 6.89 (1H, s), 4.23 (dd, 1H, J = 2.4, 10.8), 4.14 (dd, 1H, J = 2.7, 10.7), 3.92 (1H, m), 3.78 (1H, m), 3.61 (1H, m), 1.27 (d, 3H, J = 6.6). ^{13}C (100 MHz, DMSO-d_6) 160.0, 147.7, 135.6 (q, J = 30.4), 134.3 (m), 129.9, 125.8 (q, J = 282), 122.7 (q, J = 275), 118.4 (br s), 108.1, 106.0, 102.8, 68.8, 51.7, 50.9 (q, J = 32.2), 15.0. Anal. ($C_{15}H_{12}F_6N_2O_2$): C, H, N.

(2*R*)-2-Ethyl-1,2,3,6-tetrahydro-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)-7*H*-[1,4]oxazino[3,2-*g*]quinolin-7-one [(*R*)-16f, R^1 = CH$_2$CF$_3$, R^2 = Ethyl]. (*R*)-16f (1.5 g, 21%) was prepared from **24b** (4.8 g, 18.4 mmol), after flash chromatography (gradient elution, hexanes/ethyl acetate 95:5 to 50:50), followed by additional purification using reverse phase HPLC (Kromasil C18, 50 × 250 mm; 65:35 MeOH/water; flow rate of 80 mL/min). ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.75 (br s, 1H), 7.06 (s, 1H), 6.91 (s, 1H), 6.89 (s, 1H), 6.89 (s, 1H), 4.34 (dd, J = 10.7, 1.5, 1H), 4.14 (dd, J = 11.2, 2.4, 1H), 3.99 (m, 1H), 3.75 (m, 1H), 3.28 (m, 1H), 1.64 (dq, J = 7.6, 7.3, 2H), 1.00 (t, J = 7.3, 3H). Anal. ($C_{16}H_{14}F_6N_2O_2$): C, H, N.

(2*R*)-1,2,3,6-Tetrahydro-2-isopropyl-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)-7*H*-[1,4]oxazino[3,2-*g*]quinolin-7-one [(*R*)-16g, R^1 = CH$_2$CF$_3$, R^2 = Isopropyl]. (*R*)-16g (0.15 g, 38%) was prepared from **24c** (0.284 g, 1.04 mmol), after purification by flash chromatography (19:1 CH_2Cl_2/MeOH). Further purification was performed by reverse phase HPLC (ODS, 5 microm, 10 × 250 mm), 80% MeOH/water, 2.6 mL/min). R_f 0.2 (19:1 CH_2Cl_2/MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.52 (br s, 1H), 7.14 (br s, 1H), 6.95 (s, 1H), 6.92 (s, 1H), 4.50 (d, 1H, J = 11.0), 4.18−4.06 (m, 1H), 4.05 (dd, 1H, J = 11.0, 2.5), 3.75−3.60 (m, 1H), 2.98 (d, 1H, J = 8.7), 1.98−1.88 (m, 1H), 1.00 (d, 3H, J = 7.3), 0.98 (d, 3H, J = 7.3). Anal. ($C_{17}H_{16}F_6N_2O_2$): C, H, N.

(2*R*)-1,2,3,6-Tetrahydro-2-isobutyl-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)-7*H*-[1,4]oxazino[3,2-*g*]quinolin-7-one [(*R*)-16h, R^1 = CH$_2$CF$_3$, R^2 = Isobutyl). (*R*)-16h (17 mg, 9%) was prepared from **24d** (0.13 g, 0.45 mmol), after purification by flash chromatography (95:5 CH_2Cl_2/MeOH) and recrystallization from EtOAc/hexanes. R_f 0.2 (19:1 CH_2Cl_2/MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.58 (br s, 1H), 7.05 (br s, 1H), 6.97 (s, 1H), 6.91 (s, 1H), 4.30 (dd, 1H, J = 11.0, 1.1), 4.16 (dd, 1H, J = 11.0, 1.3), 4.01−3.91 (m, 1H), 3.75−3.65 (m, 1H), 3.42−3.37 (m, 1H), 1.71−1.62 (m, 1H), 1.62−1.54 (m, 1H), 1.35−1.27 (m, 1H), 0.96 (d, 3H, J = 6.9), 0.93 (d, 3H, J = 7.5). HRMS (ESI) calcd for $C_{18}H_{20}F_6N_2O_2$ (M + H)$^+$, 409.1351; found, 409.1345.

(*R*)-2,3,3a,4-Tetrahydro-10-(trifluoromethyl)-1*H*-pyrrolo[1′,2′:4,5][1,4]oxazino[3,2-g]quinolin-8(7*H*)-one [(*R*)-27]. (*R*)-27 (120 mg, 20%) was prepared from (*R*)-7-amino-2,3,3a,4-tetrahydro-1*H*-pyrrolo[2,1-*c*][1,4]benzoxazine [(*R*)-25] (0.390 g, 2.05 mmol), after purification by flash chromatography (92:8 CH_2Cl_2/MeOH). Further purification was performed by reverse phase HPLC (ODS, 5 micron, 10 × 250 mm, 3 mL/min). ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.42 (br s, 1H), 6.91 (s, 1H), 6.89 (s, 1H), 6.76 (br s, 1H), 4.54 (dd, 1H, J = 9.6, 2.7), 3.61 (t, 1H, J = 9.6), 3.50−3.60 (m, 1H), 3.40−3.50 (m, 1H), 3.30−3.40 (m, 1H), 2.12−2.22 (m, 2H), 2.00−2.10 (m, 1H), 1.40−1.50 (m, 1H). Anal. ($C_{15}H_{13}F_3N_2O_2$): C, H, N.

(±)-1,2,3,4,4a,5-Hexahydro-11-(trifluoromethyl)-pyrido[1′,2′:4,5][1,4]oxazino[3,2-g]quinolin-9(8*H*)-one (28). Compound **28** (0.110 g, 30%) was prepared from (±)-3-amino-6,6a,7,8,9,10-hexahydropyrido[2,1-*c*][1,4]benzoxazine (**26**; 0.232 g, 1.13). R_f 0.15 (2:3, EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.73 (br s, 1H), 7.09 (s, 1H), 6.87 (s, 1H), 6.73 (s, 1H), 4.26 (dd, 1H, J = 10.5, 2.6), 4.06 (dd, 1H, J = 10.5, 9.0), 3.80 (m, 1H), 3.02−2.97 (m, 1H), 2.60 (td, 1H, J = 12.2, 2.9), 1.92 (m, 2H), 1.74−1.65 (m, 2H), 1.50−1.42 (m, 1H), 1.29−1.21 (m, 1H). Anal. ($C_{16}H_{15}F_3N_2O_2 \cdot 0.2\ H_2O$): C, H, N.

MDA Whole-Cell Binding Assay. Receptor binding assays for hAR were performed in a whole cell format using MDA-MB-453

cells plated in DMEM+10% FBS in 96-well microtiter plates. Four days after cell plating, the media were changed to DMEM+10% charcoal-absorbed FBS (CA-FBS) to remove any endogenous ligand complexed with hAR in the cells. After 24 h, either a saturation analysis to determine the K_d for [^{3}H]DHT on hAR or a competition binding assay to evaluate the ability of test compounds to compete with [^{3}H]DHT for hAR was performed. For the saturation analysis, media (DMEM+10% CA-FBS) containing [^{3}H]DHT (1.8 − 0.04 nM) in the absence (total binding) or presence (nonspecific binding) of a 100-fold molar excess of unlabeled DHT were added to the cells. For the competition binding assay, media containing 0.3 nM [^{3}H]DHT and test compounds in concentrations ranging from 10^{-10} to 10^{-6} M were added to the cells. Three replicates were used for each sample. After 3 h at 37 °C, an aliquot of the total binding media at each concentration was removed to determine the amount of free [^{3}H]DHT. The media from the plates for the saturation analysis and the competition binding assay was aspirated, and the cells were washed twice with phosphate-buffered saline to remove unbound ligand. Scintillation fluid (250 μL of Microscint 20, Packard Instruments) was added to each well, and the amount of [^{3}H]DHT present was measured using a scintillation counter (TopCount, Packard Instruments, CT). For the saturation analysis, the difference between the total binding and nonspecific binding was defined as specific binding, which was evaluated by Scatchard analysis to determine the K_d for [^{3}H]DHT. For the competition binding assay, the amount of specific binding was determined for each replicate as: (Total CPM Bound) − (Average Nonspecific CPM Bound).

Nonspecific binding is defined as that binding remaining in the presence of an excess of unlabeled specific ligand (i.e., 1000 nM of unlabeled DHT). After correcting for nonspecific binding, IC_{50} values were determined. The IC_{50} value is defined as the concentration of competing ligand required to decrease specific binding by 50%. The IC_{50} value was determined with the aid of the log−logit (Hill) method, which linearized the concentration response curve. Linear regression was then used to determine the IC_{50} value. The K_i values were determined by the application of the Cheng−Prusoff equation to the IC_{50} values, using previously determined K_d values for each specific ligand.[18]

$$K_i = IC_{50}/(1 + [L]/K_d)$$

where $[L]$ = the concentration of labeled ligand and K_d = the dissociation constant of the labeled ligand determined in the saturation analysis.

PR, GR, and MR Binding Assays. The procedure for the cross-reactivity receptor binding assays using baculovirus-expressed receptors was previously described.[19] The radioligands used in the competitive receptor binding assays are progesterone for hPR-A, dexamethasone for hGR, and aldosterone for hMR.

Four-Week Mature Castrated Rat Assay. Mature (approximately 8 weeks old; weighing 200 g) male Sprague−Dawley rats from Harlan (Indianapolis, IN) were housed 2−3 per cage under controlled lighting conditions on a 12-h cycle, with the lights on at 0600. Rat chow (Harlan Teklad 8604) and water were available ad libitum. Mature male rats arrived and were castrated under isoflurane anesthesia after a one-week acclimation period. One group of animals was sham-operated and treated with vehicle and served as one control group. After surgery, the rats were sorted into groups of five such that no statistically significant differences in body weight were observed. They began receiving treatment the same day of the surgery after the surgical procedure. The compounds were suspended in a vehicle of 9.995% polyethylene glycol (PEG-400; Sigma), 0.005% Tween 80 (Sigma), and 90.0% of a 1% carboxymethylcellulose (CMC; Sigma) solution in NanoPure water. The appropriate amount of **(*R*)-16e** for the highest concentration to be gavaged was weighed out and dissolved completely into absolute ethanol. A mixture of 99.5% PEG 400 and 0.5% Tween 80 was added to the ethanol mixture to a total volume of $^1/_{10}$ the final volume. Water was added to the organic mix in a sufficient volume to precipitate the drug. The alcohol/water mix was evaporated under nitrogen, and a 1% CMC solution was added to complete the volume ($^9/_{10}$) of the formulation. The high concentration formulation is then diluted using vehicle to obtain the proper volumes.

Animals were treated orally via gavage each morning for the next 28 days, with 4 mL/kg dosing with either control vehicle, (**1**), or **(*R*)-16e** at various doses. Twenty-four h after the last dose, the rats were sacrificed by decapitation and organs were collected. The VP, SV, and LA muscle were dissected out, blotted dry, and weighed individually. Serum was collected for determination of serum LH levels.

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Supporting Information Available: Preparation of compounds **6b**,**c**, **7a**−**c**, **(+)-10h**, **(−)-10h**, **13**, **16a**−**f**, **(*S*)-16e**, **(*S*)-16f**, **25**, and **26**, elemental and HPLC analyses, and the data analysis for the 4-week castrated rat assay. This material is available free of charge via the Internet at http://pubs.acs.org.

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