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Dimethyl-diphenyl-propanamide Derivatives As Nonsteroidal Dissociated Glucocorticoid Receptor Agonists

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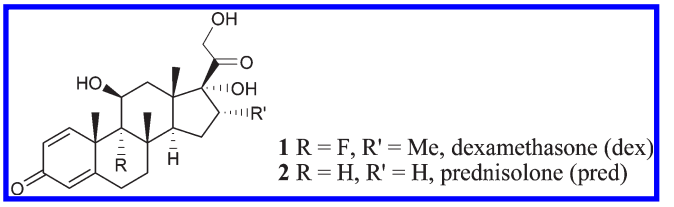
A series of 2,2-dimethyl-3,3-diphenyl-propanamides as novel glucocorticoid receptor modulators is reported. SAR exploration led to the identification of 4-hydroxyphenyl propanamide derivatives displaying good agonist activity in GR-mediated transrepression assays and reduced agonist activity in GR-mediated transactivation assays. Compounds **17** and **30** showed anti-inflammatory activity comparable to prednisolone in the rat carrageenan-induced paw edema model, with markedly decreased side effects with regard to increases in blood glucose and expression of hepatic tyrosine aminotransferase. A hypothetical binding mode accounting for the induction of the functional activity by a 4-hydroxyl group is proposed.

Introduction

Glucocorticoid receptor (GR[a]) agonists, such as dexamethasone (dex) **1** and prednisolone (pred) **2**, have been used as anti-inflammatory agents for over 60 years. However, their systemic use is limited by side effects including diabetes, osteoporosis, obesity, muscle atrophy, and glaucoma. As there is still significant unmet medical need for safe and efficacious treatments for inflammatory and autoimmune diseases, compounds which improve upon the risk−benefit ratio of steroids are highly desirable.[1] The anti-inflammatory activity of glucocorticoids is largely due to their ability to reduce the expression of pro-inflammatory genes via the inhibition of the transcription factors NFκB (nuclear factor κB) and AP-1 (activator protein-1) by ligand-bound GR, a pathway termed transrepression (TR). On the other hand, the ligand-bound GR can also induce transcription of certain genes, a process termed transactivation (TA). Several side effects of glucocorticoid therapy are thought to be predominantly or at least partially due to GR mediated transactivation of various genes involved in metabolism. Insights into the mechanism of glucocorticoid action have led to the hypothesis that the undesirable side effects originating from transactivation may be separated from the anti-inflammatory effects resulting from transrepression.[2−5] These findings have attracted extensive attention on the development of ligands termed "dissociated" glucocorticoid receptor agonists (DGRA) or "selective glucocorticoid receptor modulator/agonists (SGRM/SEGRA)", which retain similar anti-inflammatory properties as conventional steroids, but have reduced transactivation activity.[6−12]



Recently, we described a novel class of dihydro-ethanoanthracene carboxamides as potent and selective nonsteroidal GR ligands.[13] Select compounds from this series, such as compound **3** (Figure 1), had good activity in GR-mediated transrepression assays and reduced activity in transactivation assays performed with cultured cells. As part of our continuing efforts toward the optimization of GR agonists, we embarked on the study of a series of synthetically more tractable analogues related to 2,2-dimethyl-3,3-diphenyl-propanamides **4**. The structure of **4** can be perceived to be derived from excision of the methyl-substituted bridgehead carbon of dihydro-ethanoanthracene **3** (Figure 1). Computational modeling also suggested **3** and **4** should share overall similar binding poses in GR, where the polar end consisting of the amidothiazole moiety engages in several H-bonds with Gln642 and Asn564.[13] Synthetic versatility of **4** enabled the

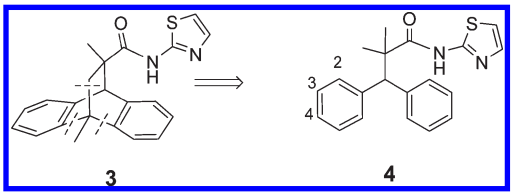


Figure 1

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[a] Abbreviations: GR, glucocorticoid receptor; TAT, tyrosine amino transferase; AP-1, activator protein-1; CPE, rat carrageenan-induced paw edema model.

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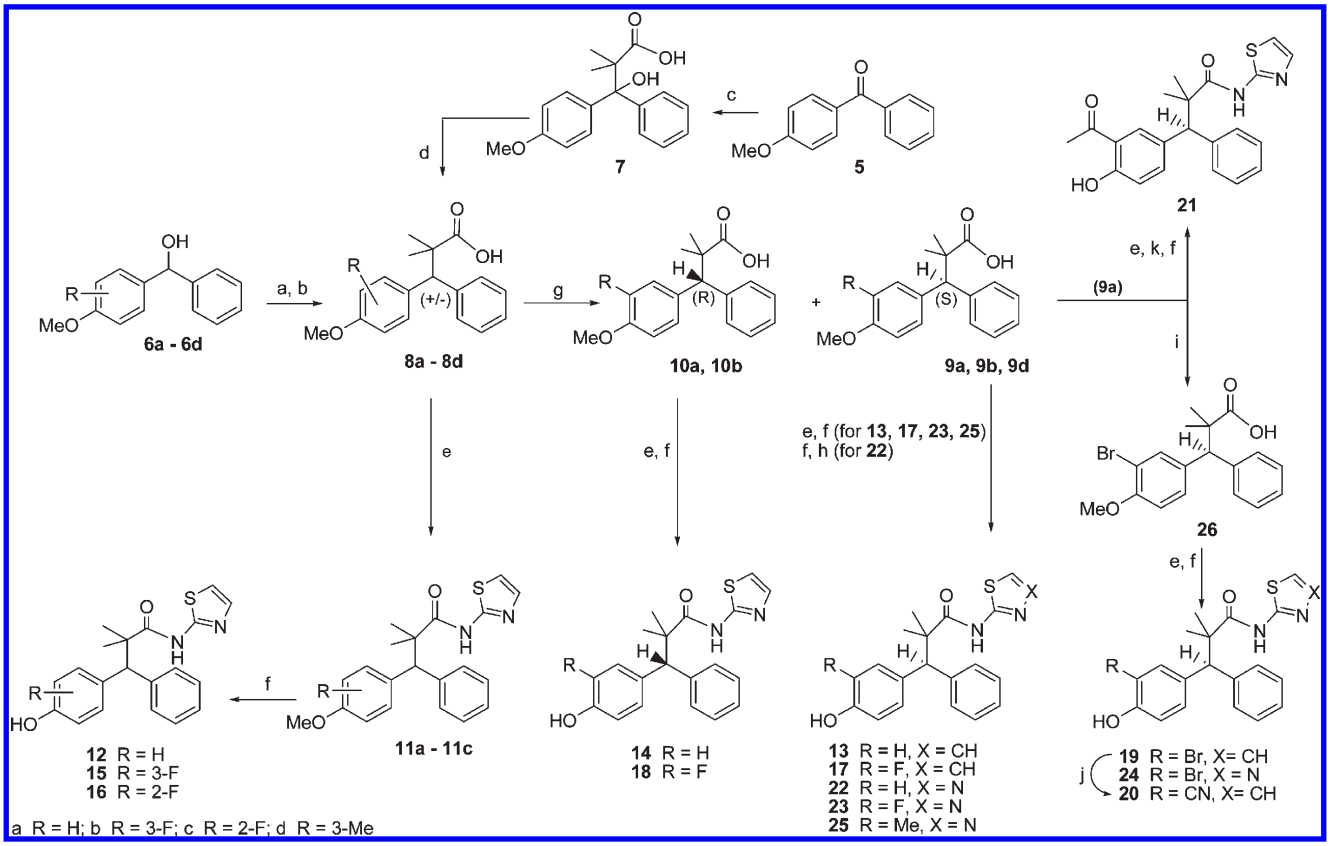
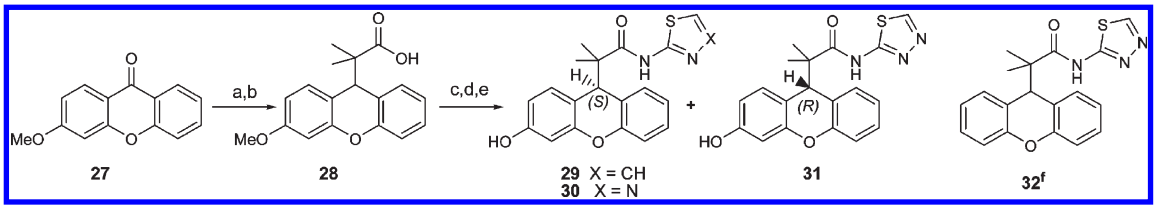
Scheme 1[a]



[a] Reagents: (a) $TiCl_4$, $(CH_3)_2C{=}C(OCH_3)$-$OSiMe_3$ THF, 0 °C then rt, 60−88%; (b) 40% aq KOH, DMSO, MeOH, 75 °C, 86−99%; (c) LDA, $(CH_3)_2CHCOOH$, THF, 0 °C−60 °C, 2 h; mixed with **5** at 0 °C, 18 h, rt, 56%; (d) Et_3SiH, $BF_3 \cdot Et_2O$, CH_2Cl_2, 0 °C, 90%; (e) 2-thiazolylamine or 1,3,4-thiadiazol-2-amine, HOBT, EDC, CH_3CN, $^iPr_2NEt$, 85 °C, 70−81%; (f) BBr_3, CH_2Cl_2, 0 °C−rt, 81−99%; (g) SFC chiral separation with various chiral columns using CO_2/MeOH as mobile phase; (h) $(CH_3)_2C{=}C(Cl)$-NMe_2, CH_2Cl_2, 0 °C, 30 min, then $^iPr_2NEt$, 1,3,4-thiadiazol-2-amine, rt, 87%; (i) Br_2, HOAc, 96%; (j) CuCN, DMF, μw, 220 °C, 50%; (k) CH_3COCl, $AlCl_3$, $ClCH_2CH_2Cl$-$PhNO_2$, rt, 1.5 h, 62.3%.

Scheme 2[a]



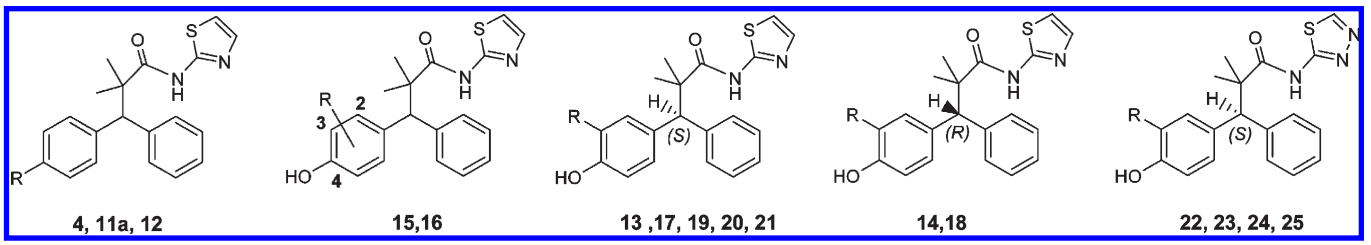
[a] Reagents: (a) LDA, $(CH_3)_2CHCOOH$ THF, −30 °C ~55 °C, 1.5 h, mixed with **27** at 0 °C, 2 h, 90%; (b) Et_3SiH, $BF_3 \cdot Et_2O$, 68%; (c) SFC chiral separation with various chiral columns using CO_2/MeOH as mobile phase; (d) NH_2PhSH, NMP, K_2CO_3, μW, 205 °C, 70%; (e) 2-thiazolylamine or 1,3,4-thiadiazol-2-amine, HOBT, EDC, CH_3CN, $^iPr_2NEt$, 85 °C, 12 h, 60−66%; (f) **32** was prepared from 9*H*-xanthen-9-one following procedures a, b, and e, 53.3%.

rapid exploration of structure−activity relationships (SAR) around the chemical space of the phenyl rings. Herein we report our studies of **4**, which led to the identification of new potent GR agonists with a favorable "dissociated" profile both in vitro and in vivo.[14]

Chemistry

The compounds described in this work were synthesized by the routes shown in Schemes 1−2. A series of *ortho*- and *meta*-substituted phenolic analogues were prepared (Scheme 1). Synthesis of the key intermediate acid **8(a−d)** was achieved through a $TiCl_4$-catalyzed addition of (1-methoxy-2-methyl-prop-1-enyloxy)trimethylsilane to diphenyl-methanol **6 (a−d)**, followed by hydrolysis of the methyl ester thus formed. Alternatively, construction of the acid **8a** could be effected under Moresch conditions.[15a] Reaction of lithium enediolate derived from isobutyric acid with ketone **5** afforded β-hydroxy acid **7**, which was deoxygenated by the action of etherated boron trifluoride and triethyl silane reducing system[15b] to give acid **8a**. Chiral HPLC separation of racemic acids **8** provided the corresponding enantiomeric acids **9** and **10**. Amidation reactions of acids **8**, as well as chiral acids **9** and **10**, with 2-thiazolylamine or 1,3,4-thiadiazol-2-amine followed by demethylation yielded a series of carboxamides, including 4-hydroxyphenyl (**13**, **14**, **22**), 3-methyl-4-hydroxyphenyl (**25**), and 3-F-4-hydroxyphenyl (**17**, **18**, **23**) propanamides. The demethylation reaction may occur prior to the amidation, as in the case of **22**. The resulting 4-hydroxyphenyl acid could offer an easy access to various 4-hydroxyphenyl carboxamides

Table 1. Activities of Diphenyl Propanamides[a]



compd	R	chirality	GR K_i (nM)	AP-1 repression EC_{50} nM (eff % dex)[b]	E-selectin repression EC_{50} nM (eff % dex)[b]	GAL 4 reporter EC_{50} nM (eff % dex)[b]	TAT induction EC_{50} nM (eff % dex)[b]
dex			1.1	2.5 (100)	1.1 (100)	4.2 (100)	5.0 (100)
pred			1.5	15.8 (97)	13.6 (97)	82.7 (97)	57.4 (97)
4	H	achiral	2.9	> 10000		> 10000	1357 (5)
11a	OCH_3	±	5.7	> 10000		> 10000	> 5000
12	OH	±	2.5	61.4 (63)	125.2 (50)	863.4 (14)	2579 (20)
13	H	*S*	1.2	40.9 (63)	29.5 (52)	372.1 (21)	250.7 (21)
14	H	*R*	18.7	> 10000		> 10000	> 10000
15	2-F	±	20.7	> 10000		> 10000	> 10000
16	3-F	±	0.6	51.1 (77)	37.7 (63)	216.4 (39)	197.0 (41)
17	F	*S*	0.7	15.9 (79)	8.6 (68)	119.0 (61)	36.1 (48)
18	F	*R*	4.6	> 10000 (16)	> 5000 (12)	> 10000	> 5000
19	Br	*S*	0.4	40.1 (83)	8.6 (71)	114.7 (48)	142.2 (29)
20	CN	*S*	0.9	506.0 (74)	205.9 (48)	> 10000	> 5000 (16)
21	$COCH_3$	*S*	7.3	> 10000	> 5000 (16)	> 10000	2325
22	H	*S*	1.2	20.3 (69)	27.5 (56)	380.2 (22)	748.5 (21)
23	F	*S*	0.7	21.2 (70)	7.9 (56)	121.0 (50)	131.8 (42)
24	Br	*S*	0.4	12.7 (87)	6.2 (75)	67.2 (54)	46.5 (57)
25	CH_3	*S*	2.2	28.6 (53)	119.3 (53)	555.8 (13)	> 5000 (21)

[a] Values are means of at least two experiments done in triplicate. [b] Efficacy represented as a percentage of the maximal response of dex (100%). % dex is not reported where < 5%.

Table 2. Activities of Xanthene Analogues[a]

compd	GR K_i (nM)	AP-1 repression EC_{50} (nM) (eff % dex)[b]	E-selectin repression EC_{50} (nM) (eff % dex)[b]	GAL 4 reporter EC_{50} nM (eff % dex)[b]	TAT induction EC_{50} nM (eff % dex)[b]
dex	1.1	2.5 (100)	1.1 (100)	4.2 (100)	5.0 (100)
29	0.3	17.5 (81)	9.3 (68)	60.1 (30)	27.1 (39)
30	0.8	7.8 (82)	3.5 (62)	85.7 (46)	91.3 (45)
31	58.7	> 5000	> 5000	> 10000	
32	6.0	> 5000	> 5000	> 10000	

[a] Values are means of at least two experiments done in triplicate. [b] Efficacy represented as a percentage of the maximal response of dex (100%). % dex is not reported where < 5%.

with the employment of 1-chloro-*N*,*N*,2-trimethylprop-1-en-1-amine. Bromination of acid **9a** or acetylation of *N*-(thiazol-2-yl)propanamide derived from **9a** proceeded regioselectively *ortho* to the methoxy group. An analogous synthetic sequence to the one described above led to 3-bromo and 3-acetyl 4-hydroxyphenyl propanamides **19**, **24**, and **21**. Bromo thiazole **19** was converted to 3-cyano-4-hydroxyphenyl thiazole **20** by reaction with copper(I) cyanide under microwave irradiation.

Conformationally constraining the diphenylpropanamides as their tricyclic xanthene derivatives **29**−**32** was accomplished by a similar sequence to that outlined in Scheme 1 (Scheme 2).

Results and Discussion

The in vitro assays used to characterize biological activities of the GR ligands including GR binding, transrepression (AP-1 and E-selectin (NFκB dependent)), and transactivation (GAL4-reporter) assays have been reported previously.[13] In addition, the transactivation potential of each compound was also evaluated by its ability to induce tyrosine amino transferase (TAT) in a human liver cell line derived from Huh7.[16] Data are provided in Tables 1 and 2.

We began our investigation by exploring phenyl ring substitution in **4**. Previous studies on the dihydroanthracene series indicated that most modifications on the aminothiazole moiety resulted in a considerable loss of binding activities.[13] For comparative purposes, the aminothiazole moiety was thus held constant. Preparations of the 2-, 3-, and 4-substituted phenyl analogues established the preference for substitution at the C-4 position (data not shown). While small alkyl, halogen, and cyano groups at C-4 of the phenyl displayed modest GR binding affinity (K_i 26−29 nM), the unsubstituted and 4-methoxyphenyl analogues, **4** and **11a**, exhibited good GR binding affinity (2.9 and 5.7 nM, respectively). However, both analogues possessed poor functional activity in the AP-1 transrepression assay (Table 1).

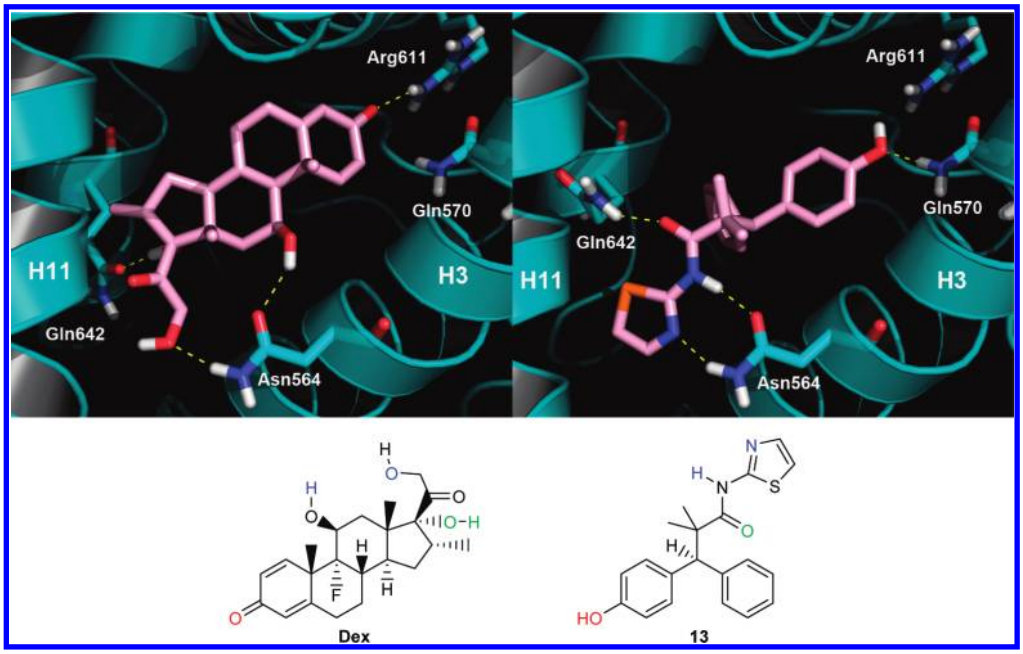


Figure 2. Comparison of GR LBD binding modes for dex (X-ray structure,[17] left) and compound **13** (model, right) illustrates a conserved set of interactions. In both cases, Arg611/Gln570 residues provide a rich source of H-bond donors, interacting with either the A-ring carbonyl in dex or the phenol OH in **13**. Asn564 provides the H3 H-bonding acceptor/donor combination to dex as well as to **13**. While Gln642 is positioned in the dex structure to H-bond to the 17-OH group, we speculated that it may undergo a slight shift in position to H-bond to the backside of the carbonyl of the amidothiazole.

The published X-ray structure of GR ligand-binding domain (LBD) bound dexamethasone reveals interactions between the C-3 carbonyl oxygen and Gln570/Arg611 residues located on helices 3 and 5, respectively.[17] We speculated that the introduction of a hydroxyl group to the phenyl ring in our nonsteroidal series might be able to engage in an H-bonding interaction with these two residues. We prepared 4-hydroxyphenyl propanamide **12**, which was found to have modest agonist activity (EC_{50} = 61 nM with 63% dex efficacy) in the AP-1 transrepression assay. Chiral separation of the stereoisomers of **12** revealed that most of the binding affinity and all of the agonist activity resided mainly with the *S*-enantiomer, **13**[18] (Table 1).

A detailed illustration of the modeled interactions of **13** in the GR binding pocket is shown in Figure 2 along with a comparison of bound dex. The model indicates that the 4-OH analogue fits well within the GR binding pocket, and a possible hydrogen-bonding network can be envisioned between the phenolic OH of **13** and neighboring residues, Gln570 and Arg611. In addition, Asn564 and Gln642 likely play a role in binding through a number of H-bonds to the amidothiazole moiety. Specifically, Asn564 may engage in two H-bonds to the amide NH and thiazole N, while Gln642 may form an additional H-bond with the amide carbonyl oxygen. This latter H-bond would require that Gln642 undergo a shift in position compared to its location in the dex complex. This model further indicates that the pocket around the phenol ring is hydrophobic and large enough to accommodate small functional groups.

The compound with a fluorine substitution *ortho* to the hydroxyl of phenol ring had improved binding affinity when compared to the compounds with substitution at the *meta* position (C-2) or with no substitution (**16** versus **15** and **4**). The improved binding potency in **16** also brought about moderate GR-mediated transrepression activity (EC_{50} = 51 nM with 77% dex efficacy in AP-1 assay). As anticipated based on the binding model, compound **17**, the *S*-enantiomer of **16**, exhibited good functional activities (EC_{50} = 16 nM with 79% dex efficacy in the AP-1 assay and EC_{50} = 8.6 nM with 68% dex efficacy in the E-selectin assay) in contrast to *R*-isomer **18**, which had minimal transrepression activity. To circumvent the potential P-450 catalyzed oxidative ring-opening of thiazole,[19] a 1,3,4-thiadiazole ring as bioisosteric replacement of the thiazole was introduced. In general, the compound pairs in which the only difference was the amide substituent (aminothiazole vs aminothiadiazole) had similar binding affinity, in accord with previous observations from the dihydro-ethanoanthracene series.[13] Of the substituents evaluated at the 3-position of the phenol ring in the *S*-isomer series, most showed GR binding affinity ranging from 0.4 to 1.2 nM, with the exception of the electron-donating methyl group (**25**, 2.2 nM) and the larger electron-withdrawing acetyl group (**21**, 7.3 nM). In the transrepression assays, 3-Br and 3-F analogues provided considerable improvement in functional activities compared to the unsubstituted phenol congeners (e.g., **13** vs **17**, **19**; **22** vs **23**, **24**). The agonistic efficacy of 3-halogen substituted analogues reached the levels of 70−87% of dex in the AP-1 assay. Methyl-substituted analogue **25** displayed weaker AP-1 efficacy (53% dex), in line with its somewhat reduced binding affinity. However, cyano-substituted analogue **20** showed much weaker agonist activity (EC_{50} = 206−506 nM in TR assays) in spite of its GR affinity being 2-fold stronger than **25**.

Several compounds in the series displayed a dissociated pharmacology with a good degree of separation between efficacies in the TA assays (TAT, GAL4-reporter) and TR assays (AP-1, E-selectin). As exemplified by **17**, its TA efficacy (48% dex in the TAT assay) was significantly weaker than the observed TR agonism efficacy (79% dex in the AP-1 assay). While exhibiting partial agonism (68−79% dex efficacy in TR assays), **17** thereby demonstrated a marked separation of TR and TA efficacies. This is in sharp contrast to pred, which displayed equal maximal efficacy in the TR and TA assays (97% dex efficacy in both AP-1 and TAT assays). The markedly

Table 3. Selectivity

		H	F	Br	CN	F	CH_3	(xanthene)	
R	Pred	**13**	**17**	**19**	**20**	**23**	**25**	**29**	**30**
GR K_i nM	1.5	1.2	0.7	0.4	0.9	0.7	2.2	0.3	0.8
PR K_i nM	> 6000	273	53	31	144	55	140	22	53
AR K_i nM		1058	1034	370	> 3000	993	> 4000	2341	696
ERα K_i μM	> 5	> 100	> 50	> 50		> 50		2.3	5.5
MR agonist[a]	0.002 (88)	> 5	> 5	> 5		> 5		> 5	> 5

[a] In A549 cell line, EC_{50} (μM)/(% maximal efficacy) determination (aldosterone as a positive control).

decreased TA agonist efficacy compared to TR agonist efficacy was also observed with compounds **19**, **23**, and **24**. In general, an increase in TR efficacy was accompanied with an increase of TA efficacy; however, a good degree separation of TR/TA was still retained for these compounds.

We also studied the effect of reintroducing a conformational constraint to the diphenylpropanamides. The tricyclic xanthene template was anticipated to share a similar binding conformation with both **3** and the acyclic diphenylpropanamides. The enantiopure hydroxylated xanthenes **29** and **30** provided promising transrepression activity (81−82% dex efficacy in AP-1) and reduced transactivation activity (39−45% dex efficacy in TAT) (Table 2). A similar binding pose for **29** and **30** compared to the corresponding acylic diphenylpropanamides (**13** and **22**) is supported by several observations. In analogy to **4**, nonhydroxylated xanthene **32** maintained a high level of binding affinity but was devoid of agonist activity. Similarly, in analogy to **14**, compound **31** (the antipode of **30**) provided only weak binding affinity and no transrepression activity. The absolute configuration of enantiomer **30** (*S*) proved to be the same as the corresponding acyclic diphenylpropanamide **22**.[20]

To monitor steroid receptor cross-reactivity, compounds listed in Tables 1 and 2 were counterscreened for binding against the progesterone receptor (PR), androgen receptor (AR) and, in some cases, the estrogen receptor (ER_α) in addition to agonist activity at the mineralocorticoid receptor (MR, activation in A549 cell) (Table 3). Compounds **13**, **17**, **19**, **23**, **25**, **29**, and **30** showed excellent selectivity between GR and AR (> 870-fold) as well as ERα (> 6800-fold), in addition to modest selectivity against PR (66−227-fold). None of the tested compounds displayed agonist activity against MR.

In Vivo Evaluation. Compounds **13**, **17**, and **30** were evaluated in the rat carrageenan-induced paw edema (CPE) model for their anti-inflammatory activity. An acute inflammatory response was generated in Sprague−Dawley rats after injections of carrageenan in the hind paws. Paw swelling was calculated by subtracting the baseline values from the post challenge measurements. Initial evaluation of **13**, following a single oral dose of 100 mg/kg, revealed a 46% inhibition of paw edema, nearly identical to that shown by pred administered orally at 30 mg/kg in the same study (42%) (Figure 3). Blood samples were collected at the conclusion of the study to measure fasting glucose levels. At an equipotent dose, **13** did not increase blood glucose while pred triggered a significant increase compared to vehicle control.

The more potent analogues, **17** and **30**, were also evaluated in the rat CPE model. Both compounds produced a dose-dependent reduction of edema after the single oral dose. The in vivo potencies (**17**: ED_{50} = 45 mg/kg; **30**: ED_{50} = 44 mg/kg) compared favorably with pred (ED_{50} = 19 mg/kg) (Figure 4). As observed with **13**, **17** and **30** also gave little or no increase in blood glucose relative to pred, even at the highest dose (**17**, 50 mg/kg; **30**, 30 mg/kg vs pred, 30 mg/kg).

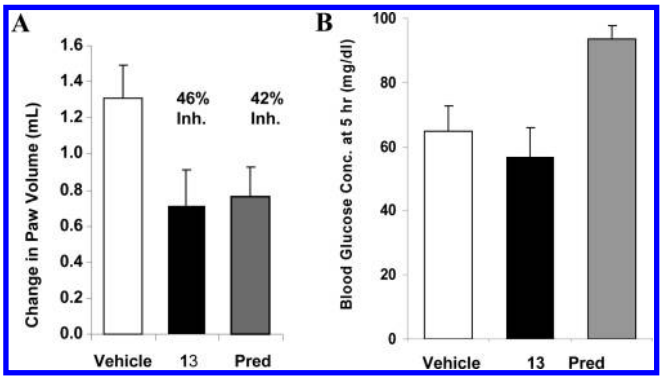


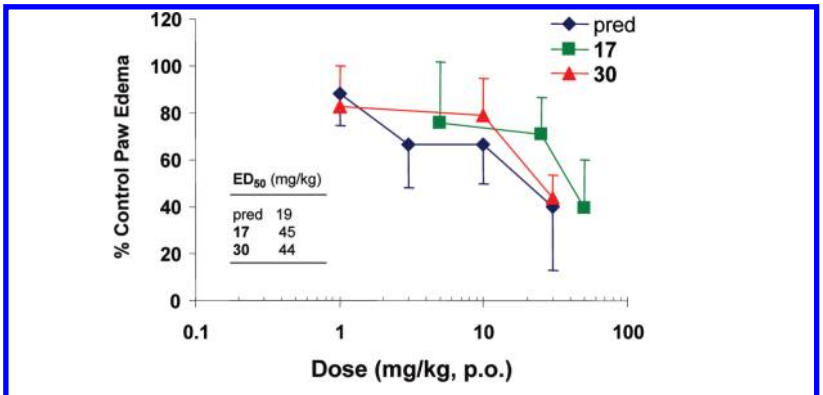
Figure 3. Compound **13** and pred in the carrageenan-induced paw edema model after oral administration in rats: (A) paw edema inhibition 5 h postdose; (B) blood glucose levels 5 h postdose. Compound **13** dosed at 100 mg/kg and pred at 30 mg/kg.

GR-mediated transactivation effects of **30** were also evaluated in normal, nondiseased Sprague−Dawley (SD) rats via its ability to induce tyrosine amino transferase (TAT) and elevate serum glucose. TAT is a liver specific gene, the hepatic expression of which is closely regulated by activated GR.[21] Fasted SD rats showed a significant increase in serum glucose and induction of TAT (6 h post dose) when orally dosed with pred at 30 mg/kg. The oral administration of **30** to SD rats at 7.5, 15, and 30 mg/kg gave a dose-proportional increase in serum exposure (as measured 6 h postdose) of 59, 157, and 311 nM, respectively. Unlike pred, **30** did not provoke measurable increases of serum glucose nor liver TAT activity at all dose levels, even at the highest dose of 30 mg/kg (Figure 5).

Overall, the anti-inflammatory activity of **30** and **17** are similar to that of pred, whereas the GR-mediated transactivation activity (as measured by induction of hyperglycemia or TAT) are significantly reduced compared with pred.

Conclusion

We have described a novel class of dimethyl-diphenylpropanamides as potent and selective nonsteroidal ligands of the glucocorticoid receptor. Select compounds from this series elicit reduced transactivation relative to steroidal agonists while retaining good transrepression activities in reporter gene assays. Compounds **30** and **17** achieved equivalent anti-inflammatory efficacy in vivo to pred in the rat carrageenan paw edema assay. Most notably, both compounds induced little or no side effects in rats with regard to blood glucose elevation and hepatic TAT induction compared with prednisolone. Taken together, the dissociation between transrepression and transactivation observed with **30** and **17** in vitro is reflected in vivo by a steroid-like anti-inflammatory activity and markedly reduced transactivation-mediated side effects.



	Edema inh. (highest dose)	Glucose increase[a] (highest dose)	Pred (30 mg/kg)[b] Edema inh.	Pred (30 mg/kg)[b] Glucose increase[a]
17	61%	<1%	66%	43%
30	56%	<1%	57%	42%

a. Compared to vehicle control; b. Pred data recorded in the same study of the compound.

Figure 4. Compounds **17** and **30** demonstrated efficacy comparable to pred in suppressing paw edema after oral administration in rats but promoted little or no blood glucose elevation.

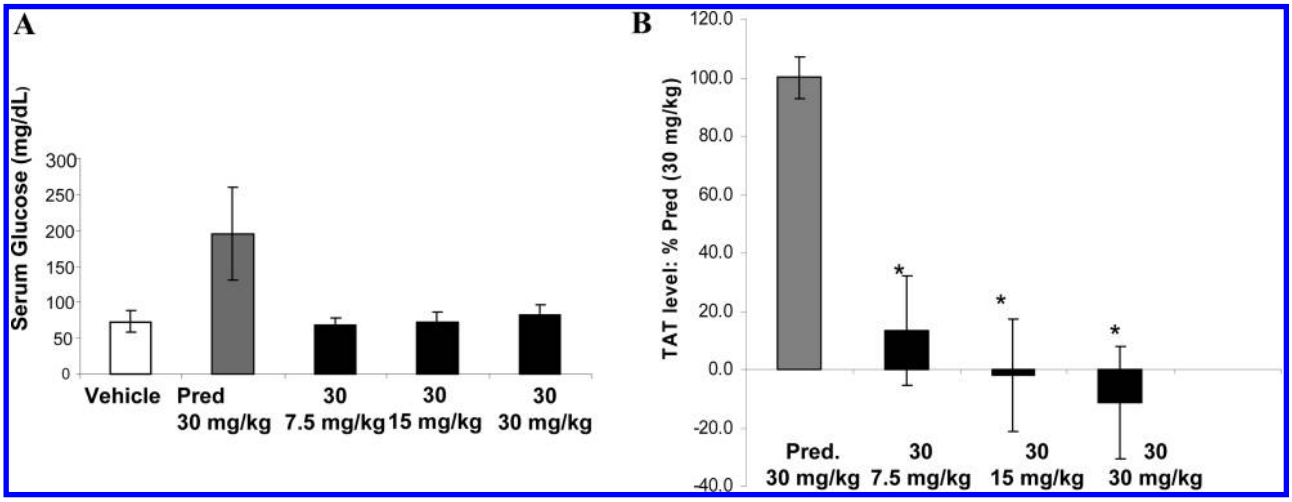


Figure 5. Compound **30** did not lead to measurable increase of serum glucose compared to vehicle control (A) and no induction of liver TAT enzyme activity relative to pred (B) in normal fasted SD rats, in contrast to pred, even at the highest (and equipotent) oral dose of 30 mg/kg.

Although compounds **30** and **17** have provided a major advance in identifying a dissociated GR agonist in our program, many opportunities remain for continued improvement. For example, phenols often suffer from the drawback of reactive metabolite formation. Optimization to circumvent the formation of reactive metabolites by exploring bioisosteric replacements of the phenolic OH is expected to improve the overall ADMET profile and will be the subject of future reports.

Experimental Section

Chemistry. All commercially available chemicals and solvents were used without further purification. Reactions are performed under an atmosphere of nitrogen. All new compounds gave satisfactory ^{1}H NMR, ESI-MS, and mass spectrometry analyses. ^{1}H NMR spectra were obtained on a Bruker 400 MHz or a Jeol 500 MHz NMR spectrometer using residual signal of deuterated NMR solvent as internal reference. Electrospray ionization (ESI) mass spectra were obtained on a Waters Micromass ESI-MS single quadrupole mass spectrometer. High-resolution mass spectral analysis was performed on an LTQ-FT mass spectrometer (Thermo Scientific, San Jose, CA) interfaced to a Waters Acquity ultra performance liquid chromatograph (UPLC) (Milford, MA). The purity of tested compounds determined by analytical HPLC system was >95% except as noted. Analytical HPLC was performed on a Shimadsu instrument. Column: YMC Combiscreen ODS-A, 4.6 mm × 50 mm; gradient elution 0−100% B/A over 4 min with 1 min hold (solvent A: water 90%/MeOH 10%/H_3PO_4 0.2%; solvent B: MeOH 90%/water 10%/H_3PO_4 0.2%); flow rate 4 mL/min; 220 or 254 nm detection wavelength.

Method A. Synthesis of 3-(4-Methoxyphenyl)-2,2-dimethyl-3-phenylpropanoic Acid (8a).[15]

a. To a solution of lithium diisopropylamide (LDA, 22.6 mL, 45.2 mmol) in tetrahydrofuran (THF, 10 mL) at 0 °C was added dropwise a solution of isobutyric acid (2.102 mL, 22.6 mmol) in THF (10 mL). The reaction solution was stirred at 0 °C for 30 min and 60 °C for 2 h. The flask was recooled to 0 °C, and a solution of (4-methoxyphenyl)(phenyl)-methanone **5** (4.8 g, 22.6 mmol) in THF (10 mL) was added dropwise. The solution was allowed to warm to room temperature and stirred overnight. The reaction was quenched with 1N HCl until pH ~3 and extracted with ethyl acetate (EtOAc) 3 times. The combined

organic layers were washed with 1N aqueous NaOH (3 times). The combined basic washes were acidified with concentrated HCl and extracted with EtOAc (3 times). The organic phase was washed with brine, dried over $MgSO_4$, and concentrated. The crude product mixture was purified by flash chromatography (10% EtOAc in hexanes) to give 4.1 g (60% yield) of 3-hydroxy-3-(4-methoxyphenyl)-2,2-dimethyl-3-phenyl propanoic acid **7** as an amorphous solid. ESI-MS m/z 299.30 ($[M - H]^-$). HPLC *Rt* 3.530 min.

b. To a solution of **7** (2.0 g, 6.66 mmol) in dichloromethane (25 mL) at 0 °C was added triethylsilane (10.7 mL, 66.6 mmol), followed by boron trifluoride diethyl etherate (2.5 mL, 19.98 mmol). The solution was allowed to warm to room temperature and stirred for 5 h, by which time it was quenched with saturated aqueous Na_2CO_3 solution. The aqueous phase was acidified with 1N HCl and extracted with EtOAc (3 times). Recrystallization of the crude product mixture with EtOAc and hexanes yielded 1.52 g (80% yield) of **8a** as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.29−7.35 (2 H, m), 7.17−7.29 (5 H, m), 6.81 (2 H, d, J = 8.14 Hz), 4.40 (1 H, s), 3.78 (3 H, s), 1.29 (6 H, s). ESI-MS m/z 283.28 ($[M - H]^-$). HPLC *Rt*: 3.598 min.

Method B. Synthesis of 3-(4-Methoxy-3-methylphenyl)-2,2-dimethyl-3-phenylpropanoic Acid (8d)

a. To a solution of (phenyl) magnesium bromide in THF (1M, 8 mL. Eight mmol) at 0 °C was added dropwise a solution of 4-methoxy-3-methylbenzaldehyde (0.6 g, 4 mmol) in THF (2 mL). After being stirred at 0 °C for 10 min and at room temperature for 3 h, the reaction mixture was poured onto ice-cooled saturated aqueous NH_4Cl. The solution was extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated to give (4-methoxy-3-methylphenyl)(phenyl)methanol **6d** as a colorless viscous liquid (920 mg). ESI-MS m/z 211 ($[M-OH]^+$). HPLC *Rt*: 3.226 min.

b. To a solution of **6d** (920 mg, 4 mmol) and (1-methoxy-2-methyl-propenyloxy)-trimethyl-silane (3.25 mL, 16 mmol) in dichloromethane (8 mL) at 0 °C was added a solution of titanium tetrachloride in dichloromethane (1 M solution, 8.8 mL, 8.8 mmol) slowly. The reaction mixture was stirred at 0 °C for 10 min and at room temperature for 2 h. To the reaction mixture was added water. After stirring for 10 min, the solution was adjust to pH 7 with Na_2CO_3 powder and was extracted with EtOAc. The organic layer was washed with brine, dried ($MgSO_4$), and concentrated to give the crude product. The crude product mixture was purified by flash chromatography (0−15% EtOAc in hexanes) to yield 1.154 g (92.3% for 2 steps) of methyl 3-(4-methoxy-3-methylphenyl)-2,2-dimethyl-3-phenylpropanoate. ESI-MS m/z 335.21 ($[M + Na]^+$). HPLC *Rt*: 3.983 min.

c. To a solution of the methyl ester (771 mg, 2.467 mmol) in MeOH (4 mL) and dimethyl sulfoxide (DMSO, 1 mL) was added a 40% aqueous solution of KOH (5 mL). The reaction mixture was heated at 75 °C for 15 h. After removal of methanol, the solution was adjusted to pH 2 and was extracted with ethyl ether (Et_2O). The ether layer was washed with brine, dried ($MgSO_4$), and evaporated to give **8d** as a white foam (577 mg, 78.5% yield). ^{1}H NMR (400 MHz, MeOD) δ ppm 7.33 (2 H, d, J = 7.12 Hz), 7.23 (2 H, t, J = 7.38 Hz), 7.15 (2 H, t, J = 7.38 Hz), 7.06 (1 H, d, J = 2.03 Hz), 6.78 (1 H, d, J = 8.65 Hz), 4.35 (1 H, s), 3.77 (3 H, s), 2.13 (3 H, s), 1.23 (6 H, s). ESI-MS m/z 297.43 ($[M - H]^-$). HPLC *Rt*: 3.753 min.

3-(4-Methoxy-3-fluorophenyl)-2,2-dimethyl-3-phenylpropanoic Acid (8b). Prepared from 4-methoxy-3-fluorobenzaldehyde according to method B (55% yield). ^{1}H NMR (400 MHz, MeOD) δ ppm 7.15−7.39 (5 H, m), 7.03−7.14 (2 H, m), 6.97 (1 H, t, J = 8.69 Hz), 4.38 (1 H, s), 3.83 (3 H, s), 1.25 (3 H, br s), 1.24 (3 H, br s). ESI-MS m/z 301.4. ($[M - H]^-$). HPLC *Rt*: 3.516 min.

3-(4-Methoxy-2-fluorophenyl)-2,2-dimethyl-3-phenylpropanoic Acid (8c). Prepared from (2-fluoro-4-methoxyphenyl)(phenyl)-methanone according to method A (91.2% yield). ^{1}H NMR (400 MHz, MeOD) δ ppm 7.42 (1 H, t, J = 8.65 Hz), 7.27−7.33 (2 H, m), 7.24 (2 H, t, J = 7.38 Hz), 7.14−7.20 (1 H, m), 6.69 (1 H, dd, J = 8.65, 2.54 Hz), 6.63 (1 H, dd, J = 12.21, 2.54 Hz), 4.76 (1 H, s), 1.30 (3 H, br s), 1.23 (3 H, br s). ESI-MS m/z 301.16. ($[M - H]^-$). HPLC *Rt*: 3.650 min.

Method C. (*S*)-3-(4-Methoxyphenyl)-2,2-dimethyl-3-phenylpropanoic Acid (9a) and (*R*)-3-(4-Methoxyphenyl)-2,2-dimethyl-3-phenylpropanoic Acid (10a). The acid **8a** was resolved into its corresponding enantiomers using chiral supercritical fluid chromatography (SFC) with the following conditions. Column, Chiralpak-AD, 3 cm × 25 cm; mobile phase, CO_2/MeOH/trifluoroacetic acid (TFA) = 85:15:0.1; flow rate, 60 mL/min; detection, UV (220 nm). Analytical HPLC conditions. Column, Chiralcel OJ 4.6 mm × 250 mm; 10 μm; mobile phase, 1:1 MeOH/EtOH with 0.1% TFA; temperature, ambient; flow rate, 1 mL/min; detection, UV (254 and 220 nm). Retention time (min): first eluting enantiomer, 7.82 (>99% ee); second eluting enantiomer, 8.84 (>99% ee).

A sample of the second eluting enantiomer **10a** was cocrystallized with (*S*)-(−)β-methylphenethylamine in acetonitrile (CH_3CN). An X-ray crystal structure determination of the crystalline material thus obtained proved **10a** to be of (*R*) absolute stereochemistry. The absolute configuration of the first-eluting enantiomer **9a** has been deduced to be (*S*).

(*S*) and (*R*)-3-(3-Fluoro-4-methoxyphenyl)-2,2-dimethyl-3-phenylpropanoic Acids (9b) and (10b). Obtained from chiral separation of **8b** according to a procedure similar to method C.

(*S*)-3-(4-Methoxy-3-methylphenyl)-2,2-dimethyl-3-phenylpropanoic Acid (9d). Obtained from chiral separation of **8d** according to a procedure similar to Method C.

Method D. Synthesis of 3-(4-Hydroxyphenyl)-2,2-dimethyl-3-phenyl-*N*-(thiazol-2-yl)propanamide (12). a. 3-(4-Methoxyphenyl)-2,2-dimethyl-3-phenyl-*N*-(thiazol-2-yl)propanamide (11a). To a solution of **8a** (150 mg, 0.42 mmol) in CH_3CN (1 mL) were added 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (EDC) (202 mg, 1.056 mmol) and 1-hydroxy-7-benzotriazole (HOBt) (143 mg, 1.056 mmol). The solution was stirred for 5 min, and thiazol-2-amine (69 mg, 0.69 mmol) and ^{i}Pr$_2$NEt (0.322 mL, 1.85 mmol) were added. The reaction was heated at 75 °C for 12 h. The product mixture was filtered, concentrated, and purified by silica gel flash chromatography eluted with 30% EtOAc in hexanes to give **11a** as a white solid (173 mg, 89% yield). ^{1}H NMR (400 MHz, MeOD) δ ppm 7.33−7.43 (3 H, m), 7.29 (2 H, d, J = 8.65 Hz), 7.23 (2 H, t, J = 7.38 Hz), 7.13−7.19 (1 H, m), 7.07 (1 H, d, J = 3.05 Hz), 6.80 (2 H, d, J = 8.65 Hz), 4.54 (1 H, s), 3.73 (3 H, s), 1.37 (6 H, s). ESI-MS m/z 367.26 ($[M + H]^+$). HPLC *Rt*: 3.587 min. HRMS m/z calcd for $C_{21}H_{22}N_2O_2S$ ($[M + H]^+$) 367.1475, found: 367.1475.

b. To a solution of **11a** (173 mg, 0.472 mmol) in dichloromethane (10 mL) at 0 °C was added a 1 M solution of boron tribromide in dichloromethane (1.89 mL, 1.89 mmol). The reaction solution was stirred at 0 °C for 30 min and at room temperature for 1 h and then was quenched with methanol. The reaction mixture was partitioned between water and dichloromethane. The organic solution was washed (water and brine), dried ($MgSO_4$), and concentrated. The crude product mixture was purified by reverse phase preparative HPLC (column, YMC, C-18 Ballistic, 30 mm × 100 mm; 10−90% aq CH_3OH/0.1% TFA, 25 mL/min flow rate, 220 nm detection wavelength, same for compounds hereafter unless noted) to yield 135 mg (81%) of **12** as a white solid. ^{1}H NMR (500 MHz, MeOD) δ ppm 7.40 (1 H, d, J = 3.61 Hz), 7.36 (2 H, d, J = 7.49 Hz), 7.23 (2 H, t, J = 7.49 Hz), 7.13−7.20 (3 H, m), 7.07 (1 H, d, J = 3.61 Hz), 6.66 (2 H, d, J = 8.88 Hz), 4.49 (1 H, s), 1.36 (6 H, s). ESI-MS m/z 353.29 ($[M + H]^+$). HPLC *Rt*: 3.158 min.

2,2-Dimethyl-3,3-diphenyl-*N*-(thiazol-2-yl)propanamide (4). Prepared from benzophenone according to method A and method D, Step (a). ^{1}H NMR (500 MHz, MeOD) δ ppm 7.33−7.47 (5 H, m), 7.24 (4 H, t, J = 7.38 Hz), 7.17 (2 H, t, J = 7.12 Hz), 7.07 (1 H, d, J = 3.05 Hz), 4.62 (1 H, s), 1.39 (6 H, s). ESI-MS m/z 337.32 ($[M + H]^+$). HPLC *Rt*: 3.643 min. HRMS m/z calcd for $C_{20}H_{21}N_2O_1S$ ($[M + H]^+$) 337.1369; found 337.1370.

(*S*)-3-(4-Hydroxyphenyl)-2,2-dimethyl-3-phenyl-*N*-(thiazol-2-yl)propanamide (13). Prepared from **9a** according to method D. ^{1}H NMR (500 MHz, MeOD) δ ppm 7.40 (1 H, d, J = 3.61 Hz), 7.36 (2 H, d, J = 7.49 Hz), 7.23 (2 H, t, J = 7.49 Hz), 7.13−7.20 (3 H, m), 7.07 (1 H, d, J = 3.61 Hz), 6.66 (2 H, d, J = 8.88 Hz), 4.49 (1 H, s), 1.36 (6 H, s). ESI-MS m/z 353.3 ($[M + H]^+$). HPLC *Rt*: 3.095 min. HRMS m/z calcd for $C_{20}H_{20}N_2O_2S$ ($[M + H]^+$) 353.1318; found 353.1321. Chiracel OJ (90% EtOH/MeOH/0.1%TFA; 10% Hep, 1 mL/min) *Rt* 4.80 min, ee >99.7%.

(*R*)-3-(4-Hydroxyphenyl)-2,2-dimethyl-3-phenyl-*N*-(thiazol-2-yl)-propanamide (14). Prepared from **9b** according to method D. ^{1}H NMR (500 MHz, MeOD) δ ppm 7.40 (1 H, d, J = 3.61 Hz), 7.36 (2 H, d, J = 7.49 Hz), 7.23 (2 H, t, J = 7.49 Hz), 7.13−7.20 (3 H, m), 7.07 (1 H, d, J = 3.61 Hz), 6.66 (2 H, d, J = 8.88 Hz), 4.49 (1 H, s), 1.36 (6 H, s). ESI-MS m/z 353.3 [$(M + 1)^+$]. HPLC *Rt*: 2.991 min. HRMS m/z calcd for $C_{20}H_{20}N_2O_2S$ ($[M + H]^+$) 353.1318; found 353.1321. Chiracel OJ (90% EtOH/MeOH/0.1%TFA; 10% Hep, 1 mL/min) *Rt* 6.53 min, ee >99.7%.

3-(3-Fluoro-4-hydroxyphenyl)-2,2-dimethyl-3-phenyl-*N*-(thiazol-2-yl)propanamide (15). Prepared from **10b** according to method D. ^{1}H NMR (400 MHz, MeOD) δ ppm 7.43 (1 H, br s), 7.36 (2 H, d, J = 7.12 Hz), 7.25 (2 H, t, J = 7.38 Hz), 7.18 (1 H, t, J = 7.38 Hz), 7.10 (1 H, br s), 7.06 (1 H, dd, J = 12.97, 1.78 Hz), 6.99 (1 H, d, J = 8.14 Hz), 6.78 (1 H, t, J = 8.65 Hz), 4.51 (1 H, s), 1.37 (3 H, s), 1.36 (3 H, s). ESI-MS m/z 371.12 ($[M + H]^+$). HPLC *Rt*: 3.250 min. HRMS m/z calcd for $C_{20}H_{19}FN_2O_2S$ ($[M + H]^+$) 371.1224; found 371.1224.

3-(2-Fluoro-4-hydroxyphenyl)-2,2-dimethyl-3-phenyl-*N*-(thiazol-2-yl)propanamide (16). Prepared from **8c** according to method D. ^{1}H NMR (500 MHz, MeOD) δ ppm 7.37−7.44 (1 H, m), 7.29−7.37 (3 H, m), 7.23 (2 H, t, J = 7.42 Hz), 7.16 (1 H, t, J = 7.15 Hz), 7.08 (1 H, br s), 6.53 (1 H, d, J = 8.25 Hz), 6.44 (1 H, d, J = 12.10 Hz), 4.88 (1 H, br s), 1.33 (6H, s), 1.47 (3 H, s). ESI-MS m/z 371.12 ($[M + H]^+$). HPLC *Rt*: 3.275 min. HRMS m/z calcd for $C_{20}H_{19}FN_2O_2S$ ($[M + H]^+$) 371.1224; found 371.1224.

(*S*)-3-(3-Fluoro-4-hydroxyphenyl)-2,2-dimethyl-3-phenyl-N-(thiazol-2-yl)propanamide (17). Prepared from **9b** according to method D. ^{1}H NMR (400 MHz, MeOD) δ ppm 7.33−7.42 (3 H, m), 7.25 (2 H, t, J = 7.63 Hz), 7.15−7.20 (1 H, m), 7.02−7.10 (2 H, m), 6.98 (1 H, d, J = 8.14 Hz), 6.74−6.82 (1 H, m), 4.51 (1 H, s), 1.37 (3 H, s), 1.36 (3 H, s). ESI-MS m/z 371.12 ($[M + H]^+$). HPLC *Rt*: 3.255 min. HRMS m/z calcd for $C_{20}H_{19}FN_2O_2S$ ($[M + H]^+$) 371.1224; found 371.1224.

(*R*)-3-(3-Fluoro-4-hydroxyphenyl)-2,2-dimethyl-3-phenyl-*N*-(1,3,4-thiadiazol-2-yl)propanamide (18). Prepared from **10b** according to method D. ^{1}H NMR (400 MHz, MeOD) δ ppm: same as compound **15**. ESI-MS m/z 371.06 ($[M + H]^+$). HPLC *Rt*: 3.288 min. HRMS m/z calcd for $C_{20}H_{19}FN_2O_2S$ ($[M + H]^+$) 371.1224; found 371.1224.

(*S*)-3-(3-Bromo-4-hydroxyphenyl)-2,2-dimethyl-3-phenyl-*N*-(thiazol-2-yl)propanamide (19)

a. (*S*)-3-(3-Bromo-4-methoxyphenyl)-2,2-dimethyl-3-phenyl-propanoic Acid (26). To a suspension of **9a** (1 g, 3.52 mmol) and NaOAc (433 mg, 5.28 mmol) in acetic acid (20 mL) at room temperature was added bromine (0.271 mL, 5.28 mmol) dropwise. After stirring for 3 h, the reaction mixture was poured into 10% aqueous sodium hydrosulfite ($Na_2S_2O_4$) solution. The solution was adjusted to pH 7 with concentrated NH_4OH and extracted with Et_2O. The organic extract was washed with brine, dried ($MgSO_4$), and concentrated to afford (*S*)-3-(3-bromo-4-methoxyphenyl)-2,2-dimethyl-3-phenyl-propanoic acid **26** as a white solid (1.239 g, 96.9% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.49 (1 H, d, J = 2.54 Hz), 7.26−7.30 (4 H, m), 7.25 (1 H, d, J = 2.03 Hz), 7.23 (1 H, d, J = 2.03 Hz), 6.80 (1 H, d, J = 8.65 Hz), 4.36 (1 H, s), 3.86 (3 H, s), 1.30 (6 H, s). HPLC *Rt*: 3.696 min.

b. 19 was prepared from **26** according to method D (18% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.46 (1 H, d, J = 2.03 Hz), 7.42 (1 H, d, J = 2.54 Hz), 7.30−7.35 (2 H, m), 7.18−7.30 (4 H, m), 7.01 (1 H, br s), 6.91 (1 H, d, J = 8.65 Hz), 4.60 (1 H, s), 1.43 (6 H, s). ESI-MS m/z 431.16, 433.16 ($[M + H]^+$). HPLC *Rt*: 3.428 min. HRMS m/z calcd for $C_{20}H_{19}BrN_2O_2S$ ($[M + H]^+$) 431.0428; found 431.0427.

(*S*)-3-(3-Bromo-4-hydroxyphenyl)-2,2-dimethyl-3-phenyl-*N*-(1,3,4-thiadiazol-2-yl)propanamide (20). An Emry process vial was charged with **19** (38 mg, 0.088 mmol) and copper(I) cyanide (40 mg, 0.45 mmol) in dimethylformamide (DMF). The reaction mixture was sealed and exposed to microwave irradiation for 60 min at 220 °C. The reaction was cooled, filtered, and purified by preparative HPLC to give the TFA salt of **20** as an off-white solid. (16.5 mg, 50% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.43−7.51 (3 H, m), 7.23−7.26 (4 H, m), 7.21 (1 H, d, J = 6.10 Hz), 7.03 (1 H, d, J = 4.07 Hz), 6.88 (1 H, d, J = 8.65 Hz), 4.72 (1 H, s), 1.42 (6 H, s). ESI-MS m/z 378.27 ($[M + H]^+$). HPLC *Rt*: 3.195 min. HRMS m/z calcd for $C_{21}H_{19}N_3O_2S$ ($[M + H]^+$) 378.1271; found 378.1271.

(*S*)-3-(3-Acetyl-4-hydroxyphenyl)-2,2-dimethyl-3-phenyl-*N*-(thiazol-2-yl)propanamide (21). a. To a solution of $AlCl_3$ in nitrobenzene (1M, 4.1 mL, 4.1 mmol) was added acetyl chloride (76 μL, 1.065 mmol) at room temperature. After 10 min, a solution of **13** (300 mg, 0.819 mmol) in dichloroethane (2 mL) was added dropwise. The reaction mixture was stirred at ambient temperature for 1.5 h and was quenched with ice-cooled 10% aqueous NH_4OH. After stirring for 15 min, the solution was extracted with EtOAc. The organic phase was washed (water and brine), dried ($MgSO_4$), and concentrated. The crude product was purified by silica gel flash chromatography (30% EtOAc in hexanes) to give 3-(3-acetyl-4-methoxyphenyl)-2,2-dimethyl-3-phenyl-*N*-(thiazol-2-yl)propanamide as a white solid (208 mg, 62.3% yield). ESI-MS m/z 409.2 ($[M + H]^+$). HPLC *Rt*: 3.386 min.

b. 3-(3-Acetyl-4-methoxy-phenyl)-2,2-dimethyl-3-phenyl-*N*-(thiazol-2-yl)- propanamide was treated with boron tribromide, according to method D, step (b) to provide **21** (30% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 12.12 (1 H, s), 7.70 (1 H, d, J = 2.03 Hz), 7.49 (1 H, dd, J = 8.65, 2.54 Hz), 7.42 (1 H, br s), 7.23−7.36 (5 H, m), 6.99 (1 H, br s), 6.89 (1 H, d, J = 8.65 Hz), 4.39 (1 H, s), 2.52 (3 H, s), 1.43 (3 H, s), 1.39 (3 H, s). ESI-MS m/z 395.26 ($[M + H]^+$). HPLC *Rt*: 3.600 min. HRMS m/z calcd for $C_{22}H_{122}N_2O_3S$ ($[M + H]^+$) 395.1424; found 395.1424.

(*S*)-3-(4-Hydroxyphenyl)-2,2-dimethyl-3-phenyl-*N*-(1,3,4-thiadiazol-2-yl)propanamide (22). a. To a solution of **8a** (100 mg, 0.352 mmol) in dichloromethane (3 mL) at 0 °C was added a solution of boron tribromide in dichloromethane (1M, 1.41 mL, 1.41 mmol). The reaction solution was stirred at 0 °C for 30 min and at room temperature for 1 h. After it was cooled at 0 °C, the reaction mixture was quenched with 10% NH_4OH and extracted with dichloromethane. The aqueous layer was acidified with concentrated HCl and extracted with dichloromethane (3 times). The combined organic phase was washed (water and brine), dried ($MgSO_4$), and concentrated to afford (*S*)-3-(4-hydroxyphenyl)-2,2-dimethyl-3-phenylpropanoic acid as an off-white solid (95 mg, 99% yield). ESI-MS m/z 269.15 ($[M - H]^-$). HPLC *Rt*: 3.123 min.

b. To a solution of (*S*)-3-(4-hydroxyphenyl)-2,2-dimethyl-3-phenylpropanoic acid (15 mg, 0.055 mmol) in dichloromethane (2 mL) at 0 °C was added 1-chloro-*N*,*N*,2-trimethylprop-1-en-1-amine (15 μL, 0.111 mmol). The reaction was stirred at 0 °C for 30 min, at which time ^{i}Pr$_2$NEt (24 μL, 0.138 mmol) was added, followed by 1,3,4-thiadiazol-2-amine (17 mg, 0.165 mmol). After 5 min, the reaction mixture was allowed to warm to room temperature and stirred for 1 h. The solvent was removed. The crude product mixture was purified by reverse phase preparative HPLC to yield 17 mg (87%) of **22** as an off-white solid. 1H NMR (400 MHz, MeOD) δ ppm 8.96 (1 H, s), 7.36 (2 H, d, J = 7.63 Hz), 7.06−7.31 (5 H, m), 6.66 (2 H, d, J = 8.14 Hz), 4.54 (1 H, s), 1.38 (6 H, s). ESI-MS m/z 354.1 ($[M + H]^+$). HPLC *Rt*: 3.032 min. HRMS m/z calcd for $C_{19}H_{19}N_3O_2S$ ($[M + H]^+$) 354.1276; found 354.1274. Chiracel OJ (mobile phase: 100% 1:1 EtOH/MeOH with 0.1% TFA; 220 and 254 nm; 1 mL/min) *Rt*: 5.40 min; ee >99%.

(*S*)-3-(3-Fluoro-4-hydroxyphenyl)-2,2-dimethyl-3-phenyl-*N*-(1,3,4-thiadiazol-2-yl)propanamide (23). Prepared from **9b** according to

method D with the employment of 1,3,4-thiadiazol-2-amine in the amidation step. ^{1}H NMR (400 MHz, MeOD) δ ppm 8.97 (1 H, s), 7.36 (2 H, d, J = 7.12 Hz), 7.25 (2 H, t, J = 7.63 Hz), 7.14−7.21 (1 H, m), 7.06 (1 H, dd, J = 12.97, 2.29 Hz), 6.99 (1 H, d, J = 8.14 Hz), 6.78 (1 H, t, J = 8.90 Hz), 4.54 (1 H, s), 1.38 (6 H, s). ESI-MS m/z 372.12 ([M + H]$^+$). HPLC *Rt*: 3.030 min. HRMS m/z calcd for $C_{19}H_{18}FN_3O_2S$ ([M + H]$^+$) 372.1177; found 372.1179.

(*S*)-3-(3-Bromo-4-hydroxyphenyl)-2,2-dimethyl-3-phenyl-*N*-(1,3,4-thiadiazol-2-yl)propanamide (24). Prepared from **26** according to method D with the employment of 1,3,4-thiadiazol-2-amine in the amidation step. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.54 (1 H, s), 7.23 (1 H, d, J = 2.54 Hz), 7.04−7.11 (4 H, m), 7.02 (1 H, d, J = 2.54 Hz), 6.97−7.01 (1 H, m), 6.70 (1 H, d, J = 8.65 Hz), 4.27 (1 H, s), 1.24 (6 H, s). ESI-MS m/z 432.15, 434.15 ([M + H]$^+$). HPLC *Rt*: 3.272 min. HRMS m/z calcd for $C_{19}H_{18}BrN_3O_2S$ ([M + H]$^+$) 432.0381; found 432.0380.

(*S*)-3-(4-Hydroxy-3-methylphenyl)-2,2-dimethyl-3-phenyl-*N*-(1,3,4-thiadiazol-2-yl)propanamide (25). Prepared from **9d** according to method D with the employment of 1,3,4-thiadiazol-2-amine in the amidation step ^{1}H NMR (400 MHz, MeOD) δ ppm 8.97 (1 H, s), 7.36 (2 H, d, J = 7.63 Hz), 7.23 (2 H, t, J = 7.63 Hz), 7.11−7.18 (1 H, m), 6.97−7.06 (2 H, m), 6.61 (1 H, d, J = 8.14 Hz), 4.49 (1 H, s), 2.09 (3 H, s), 1.37 (6 H, s). ESI-MS m/z 368.2 ([M + H]$^+$). HPLC *Rt*: 3.216 min. HRMS m/z calcd for $C_{20}H_{21}N_3O_2S$ ([M + H]$^+$) 368.1427; found 368.1428.

(*S*)-2-(3-Hydroxy-9*H*-xanthen-9-yl)-2-methyl-*N*-(thiazol-2-yl)-propanamide (29)

a. According to method A, 2-(3-methoxy-9*H*-xanthen-9-yl)-2-methylpropanoic acid **28** was prepared from 3-methoxy-9*H*-xanthen-9-one **27** in 61.2% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.31−7.25 (m, 2 H), 7.20−7.05 (m, 3 H), 6.71 (d, J = 2.6 Hz, 1 H), 6.67 (dd, J = 8.5, 2.5 Hz, 1 H), 4.36 (s, 1 H), 3.82 (s, 3 H), 1.04 (d, J = 2.2 Hz, 6 H). ESI-MS m/z 299.20 ([M + H]$^+$). HPLC *Rt*: 3.710 min.

b. According to a procedure similar to method C, chiral separation of **28** afforded two enantiomers, (*S*) and (*R*)-2-(3-methoxy-9*H*-xanthen-9-yl)-2-methylpropanoic acids.

c. To a solution of (*S*)-**28** (200 mg, 0.67 mmol) in 1-methyl-2-pyrrolidinone (NMP, 4 mL) in a microwave vessel was added 2-aminothiophenol (92 mg, 0.74 mmol) and K_2CO_3 (102 mg, 0.74 mmol). The reaction mixture was irradiated by microwave at 205 °C for 1.5 h and then partitioned between EtOAc and water. The organic layer was extracted with 1N aqueous NaOH. The combined aqueous layers were acidified to ∼pH 2.0 and were extracted with EtOAc. The organic phase was washed with brine, dried over Na_2SO_4, and concentrated. Purification of the crude product by preparative HPLC provided (*S*)-2-(3-hydroxy-9*H*-xanthen-9-yl)-2-methylpropanoic acid as an amorphous solid (133 mg, 70% yield).

d. According to method D, Step (a), amidation of (*S*)-2-(3-hydroxy-9*H*-xanthen-9-yl)-2-methylpropanoic acid with 2-aminothiazole afforded **29** (60% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.51 (d, 1H), 7.23−7.31 (m, 1 H), 7.09−7.17 (m, 3 H), 6.95−7.06 (m, 2 H), 6.65 (d, J = 2.64 Hz, 1 H), 6.51 (dd, J = 8.25, 2.53 Hz, 1 H), 4.45 (s, 1 H), 1.18 (s, 6 H). ESI-MS m/z 367.21 ([M + H]$^+$). HPLC *Rt*: 3.175 min. HRMS m/z calcd for $C_{20}H_{19}O_3N_2S$ ([M + H]$^+$) 367.1111; found 367.1113.

(*S*)-2-(3-Hydroxy-9*H*-xanthen-9-yl)-2-methyl-*N*-(1,3,4-thiadiazol-2-yl)propanamide (30). Prepared from (*S*)-2-(3-hydroxy-9*H*-xanthen-9-yl)-2-methyl-propanoic acid and 1,3,4-thiadiazol-2-amine according to method D, step (a) (66% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.87 (1 H, s), 7.26 (1 H, d), 7.14 (2 H, dd, J = 7.4, 2.8 Hz), 6.96−7.05 (2 H, m), 6.66 (1 H, d, J = 2.5 Hz), 6.50 (1 H, dd, J = 8.4, 2.8 Hz), 4.41 (1 H, s), 1.20 (6 H, s). ESI-MS m/z 368.30 ([M + H]$^+$). HPLC *Rt*: 3.090 min. HRMS m/z calcd for $C_{19}H_{18}O_3N_3S$ ([M + H]$^+$) 368.1063; found 367.1066.

(*R*)-2-(3-Hydroxy-9*H*-xanthen-9-yl)-2-methyl-*N*-(1,3,4-thiadiazol-2-yl)propanamide (31). Prepared from (*R*)-**28** according to the procedures (c) and (d) of **29** with the employment of 1,3,4-thiadiazol-2-amine at the amidation step (42% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.86 (1 H, s), 7.26 (1 H, d), 7.14 (2 H, dd, J = 7.4, 2.8 Hz), 6.96−7.05 (2 H, m), 6.66 (1 H, d, J = 2.5 Hz), 6.50 (1 H, dd, J = 8.4, 2.8 Hz), 4.41 (1 H, s), 1.20 (6 H, s). ESI-/MS m/z 368.06 ([M + H]$^+$). HPLC *Rt*: 3.097 min. HRMS ([M + Na]$^+$) calcd for $C_{12}H_{16}O_{10}N_5$ 390.0892; found 390.0892.

α,α-Dimethyl-*N*-1,3,4-thiadiazol-2-yl-9*H*-xanthene-9-acetamide (32)

a. According to method A, α,α-dimethyl-9*H*-xanthene-9-acetic acid was prepared from 9*H*-xanthen-9-one in 65% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.32−7.26 (m, 4 H), 7.16 (dd, J = 8.6, 1.1 Hz, 2 H), 7.12−7.06 (m, 2 H), 4.41 (s, 1 H), 1.05 (s, 6 H). ESI-MS m/z 267.42 ([M − H]$^-$). HPLC *Rt*: 3.725 min.

b. According to method D, step (a), **32** was prepared from α,α-dimethyl-9*H*-xanthene-9-acetic acid and 1,3,4-thiadiazol-2-amine (82% yield). ^{1}H NMR (400 MHz, acetone-d_6) δ ppm 9.09 (s, 1 H), 7.35−7.32 (m, 2 H), 7.31−7.30 (m, 2 H), 7.25−7.23 (m, 2 H), 7.08−7.04 (m, 2 H), 4.71 (s, 1 H), 1.20 (s, 6 H). ESI-MS m/z 350.11 ([M − H]$^-$). HPLC *Rt*: 3.525 min. HRMS ([M + Na]$^+$) calcd for $C_{12}H_{16}O_9N_5$ 374.0943; found 374.0941.

Glucocorticoid Receptor Binding Assay. The GR ligand binding assay was conducted in fluorescence polarization format which measures the competition between a test compound and a fluorescently labeled ligand (GS-red) for binding to the full length or ligand binding domain of GRα (Invitrogen, cat. no. P2893). Compounds were tested in concentrations ranging from 5 μM to 85 pM. IC_{50} values were determined by fitting the fluorescence polarization signal data using a four parameter logistic equation. The K_i values were determined by application of the Cheng−Prusoff equation[22] to the IC_{50} values, where $K_i = IC_{50}/(1 + \text{ligand concentration}/K_d)$. The K_d value used for GR was 0.3 nM as supplied by the assay manufacturer (Invitrogen, cat. no. P2893). Data shown represent the means of two or more experiments.

PR, ER, and AR ligand binding assays were also conducted in the fluorescence polarization format to the full length or ligand binding domain of each nuclear hormone receptor.

Transrepression Assays. AP-1 (activator protein-1) activity was measured using an AP-1 response element (5 copies) cloned into a luciferase reporter vector. This reporter was stably transfected into the human A549 lung epithelial cell line. AP-1 activity was induced for by addition of phorbol myristate acetate (PMA) (15 ng/mL), and inhibition of induction by compounds was quantitated by measuring decreased luciferase activity. NFκB was measured using a truncated, NFκB dependent, E-selectin promoter (−383 bp from transcriptional start) cloned into a luciferase reporter vector. This reporter was stably transfected into the human A549 lung epithelial cell line. NFκB activity was induced using IL-1β (0.5 ng/mL), and inhibition of induction by compounds was quantitated by measuring decreased luciferase activity.

Transactivation Assays. a. GAL4DBD-GR(LBD) Reporter Assay. The direct transcriptional activity was measured using a chimera between the GAL4 DNA-binding domain (DBD) and the human GR ligand-binding domain (GR-LBD) cloned into a GAL4 Luciferase reporter system. This reporter system was stably transfected into an NP-1 HeLa cell line.[23] The hormone-binding domains of the estrogen and glucocorticoid receptors contain an inducible transcription activation function. Response to ligand/compound induced binding was quantitated by measuring luciferase activity. Direct activation of the GR-LBD by compounds (agonist) can be measured as increased luciferase activity.

b. TAT Induction Assay.[24] An enzymatic assay used to measure the induction of tyrosine aminotransferase activity in cultured hepatoma cell line, human 13D3/Huh7 (derivative isolated under glucose-limiting condition). Briefly, on day one, the hepatoma cell line 3D3/Huh7 was plated at 20 K cells/well in a 96-well flat bottom, tissue culture treated assay plate and incubated overnight at 37 °C/5% CO_2. On day 2, the growth medium was removed from the wells and replaced with assay medium containing 20 μM forskolin and test compounds, which was then incubated overnight at 37 °C with 5% CO_2. On day 3,

the assay medium was removed and 100 μL/well of lysis buffer (125 mM potassium phosphate buffer, pH 7.6, 140 mM KCl, 1 mM EDTA, and 0.1% NP-40) was added. The lysates were assayed for TAT activity. In a new 96-well plate, 136 μL/well of TAT substrate (200 mM potassium phosphate buffer, pH 7.6, 5.4 nM tyrosine sodium salt, 0.06 mM pyridoxal 5′-phosphate, and 10.8 mM α-ketoglutarate) and 50 μL/well of lysate were added and mixed. The plates were incubated at 37 °C for 4 h. The TAT enzymatic reaction was stopped with KOH and incubated an additional 30 min at 37 °C. The absorbance was measured at 340 nm. Results were expressed as percent activation and EC_{50}s were calculated.

Carageenan Paw Edema (CPE) Assay. SD male rats were isolated and fasted overnight and up to six additional hours on the day of the study. Baseline paw volume measurements were obtained by immersing each hind paw to the level of the hair line in a water-based plethysmometer. Rats were administered a single oral dose of test compound(s) in biologically acceptable medium. Two hours postdosing, while under anesthesia, both hind paws were injected subcutaneously with 1% carrageenan in PBS. Paw volume measurements were obtained 3 h post challenge. Paw swelling was calculated by subtracting the baseline values from the post challenge measurements. In the same study, a baseline blood glucose level and glucose levels at 5 h post dosing were measured, using a glucometer, on blood samples collected by tail nicks.

Normal (Nondiseased) Rat Glucose Model and TAT Induction. SD male rats were fasted overnight and up to six additional hours on the day of the study. Rats were administered a single oral dose of test compounds in biologically acceptable medium. At the conclusion of the study (6 h post treatment), blood samples were collected, via intracardiac puncture following euthanasia with CO_2 gas, into serum separator tubes for glucose analysis. Quantitative determination of multiple serum analytes was performed with the Roche/Hitachi 917 fully automated chemistry analyzer by using hexokinase method.

In the same study, TAT induction was evaluated 6 h after compound administration by determination of TAT activity in liver homogenates. Biopsies were taken from the liver and snap frozen. Biopsies were homogenized in 150 mM KCl solution using a PT 3100 polytron and centrifuged. Supernatants were collected and protein levels were determined. Supernatants (normalized protein amount/well) were assayed in a similar manner as described above for TAT induction in vitro. TAT induction in rats, measured as OD at 340 nm, was defined as % in TAT activity in comparison to the TAT activity in prednisolone-treated animals (30 mg/kg).

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