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Structure Guided Design of 5-Arylindazole Glucocorticoid Receptor Agonists and Antagonists

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Glucocorticoid receptor (GR) agonists have been used for more than half a century as the most effective treatment of acute and chronic inflammatory conditions despite serious side effects that accompany their extended use that include glucose intolerance, muscle wasting, skin thinning, and osteoporosis. As a starting point for the identification of GR ligands with an improved therapeutic index, we wished to discover selective nonsteroidal GR agonists and antagonists with simplified structure compared to known GR ligands to serve as starting points for the optimization of dissociated GR modulators. To do so, we selected multiple chemical series by structure guided docking studies and evaluated GR agonist activity. From these efforts we identified 5-arylindazole compounds that showed moderate binding to the glucocorticoid receptor (GR) with clear opportunities for further development. Structure guided optimization was used to design arrays that led to potent GR agonists and antagonists. Several in vitro and in vivo experiments were utilized to demonstrate that GR agonist **23a** (GSK9027) had a profile similar to that of a classical steroidal GR agonist.

Introduction

Glucocorticoid receptor (GR[a]) agonists have been used for more than half a century as the most effective treatment of acute and chronic inflammatory conditions including asthma and rheumatoid arthritis.[1] Unfortunately, serious side effects, including glucose intolerance, muscle wasting, skin thinning, and osteoporosis, accompany the extended use of systemic glucocorticoid agonists.[2] Despite these side effects, GR steroidal agonists dexamethasone **1** and prednisolone **2** (Figure 1) are commonly prescribed oral treatments for rheumatoid arthritis. About 10 million prescriptions are written each year for oral glucocorticoid agonists in the U.S. alone, and it is estimated that over 50% of patients with rheumatoid arthritis are treated more or less continuously with glucocorticoid agonists.[3]

Overall, the market size for all uses of glucocorticoids is estimated as $10 billion per year.[2] Inhaled delivery of the steroid fluticasone propionate **3** is an example of one strategy for ameliorating the side effects, allowing safe and effective chronic treatment of asthma and allergic rhinitis. The drug is administered directly to the lungs or nose and is rapidly cleared from the blood, limiting side effects from systemic exposure.

Attempts to reduce the side effects of systemically administered GR agonists have led to extensive investigation into the mechanisms by which therapeutic index is determined. Researchers have postulated that the beneficial anti-inflammatory effects result from transrepression (TR) pathways and may be separated from the side effects derived from transactivation (TA) pathways. Detailed reports and descriptions of these pathways have been discussed elsewhere.[2−4] These findings have led to research into compounds that display selectivity for TR over TA, often referred to as dissociated agonists or GR modulators.[5−8,9a−9e] We have recently published the structure-guided design of nonsteroidal GR modulators exemplified by **4**−**6**.[10,11]

Aside from the therapeutic benefits of glucocorticoid agonists, steroidal glucocorticoid antagonists have been used for the treatment of depression and type 2 diabetes.[12−15] The antagonist mifepristone **7** (RU486) is the gold standard glucocorticoid antagonist, but its clinical use is severely limited by side effects resulting from a lack of selectivity over the progesterone, mineralocorticoid, and androgen receptors. Multiple groups have attempted to address these limitations through the synthesis of selective GR antagonists such as hexahydropyridazine **8**.[16−18]

We wished to discover through structure guided design novel chemical series of nonsteroidal selective GR agonists and antagonists with simplified structures compared to known nonsteroidal series to serve as starting point for the optimization of dissociated GR modulators and selective antagonists. We based our designs on the embedded pyrazole in the selective steroidal GR agonist cortivazol **9** and used an *N*-arylindazole as a selective steroid A-ring mimetic. In this paper we describe the structure-guided design of a synthetically accessible series 5-arylindazoles as potent, selective nonsteroidal GR agonists and antagonists.

Chemistry

An array of biarylindazoles was synthesized using the 5-bromoindazole intermediate **12**. This intermediate was

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[a] Abbreviations: GR, glucocorticoid receptor; AR, androgen receptor; PR, progesterone receptor; TR, transrepression; TA, transactivation; FP, fluoresence polarization; IL-1, interleukin-1; IL-6, interleukin-6; IL-8, interleukin 8; MMP-1, matrix metalloproteinase; GS, glutamine synthetase; PEPCK, phosphoenol pyruvate carboxykinase.

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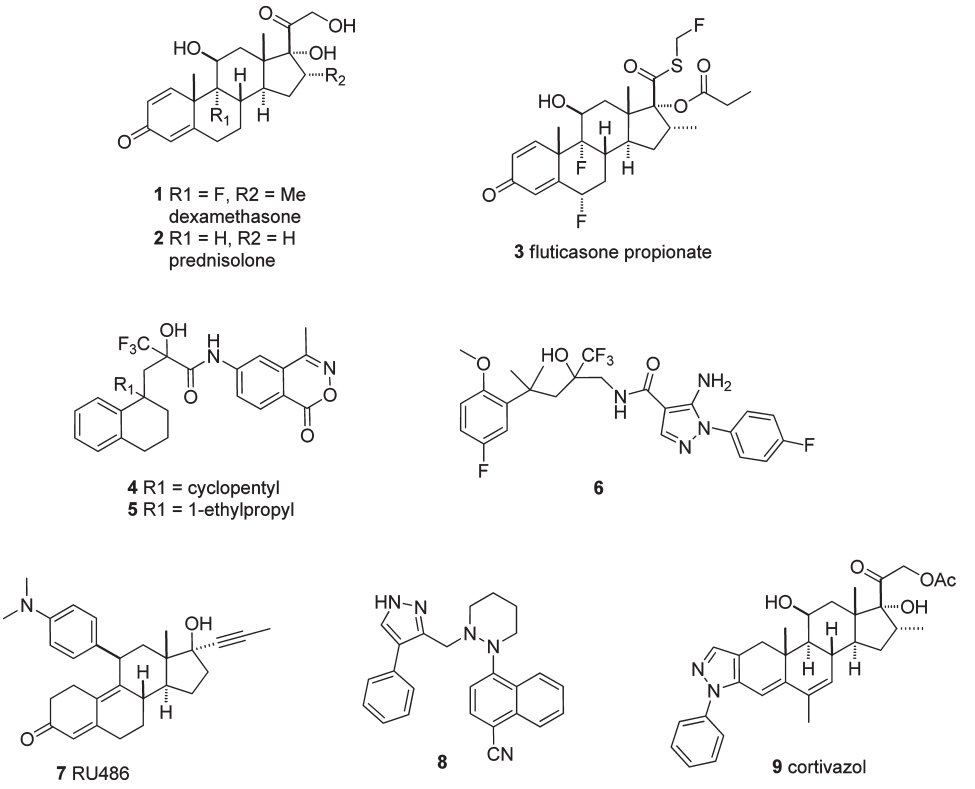
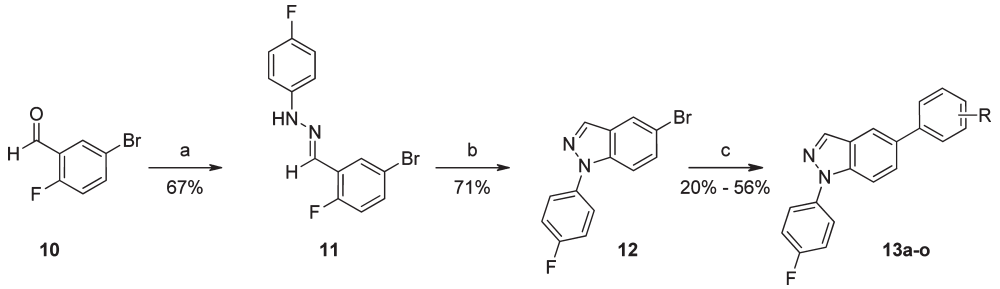


Figure 1. Steroidal and nonsteroidal glucocorticoid modulators.

Scheme 1. Synthesis of the Initial 5-Arylindazole Array[a]



[a] Reagents and conditions: (a) 4-F-phenylhydrazine, MeCN, reflux; (b) Cs_2CO_3, DMSO, 140 °C microwave; (c) arylboronic acid (ester), Na_2CO_3, $Pd(PPh_3)_4$, dioxane, water, reflux.

synthesized in two steps from the commercially available *o*-fluorobenzaldehyde **10** by hydrazone formation followed by intramolecular cyclization. The resultant 5-bromoindazole **12** was coupled to a variety of boronic acids or esters by Suzuki coupling (Scheme 1).

Further analogues for SAR exploration were prepared by using the indazole 5-boronic ester **14**. This route was used to benefit from the increased availability of monomers for Suzuki coupling (Scheme 2). The boronic ester **14** was prepared from **12** using a palladium catalyst and bis(pinacolato)-diboron. The aryl bromide intermediates **16a**−**f** and **18a**−**f** were prepared by PS-DMAP-catalyzed sulfonylation reactions. The intermediates **16a**−**f** and **18a**−**f** were then coupled using standard Suzuki protocols with boronic ester **14**. Further derivatives were obtained by subsequent alkylation of the sulfonamides **19a**−**f** with alkyl bromides and iodides to give final products **21a**−**e**.

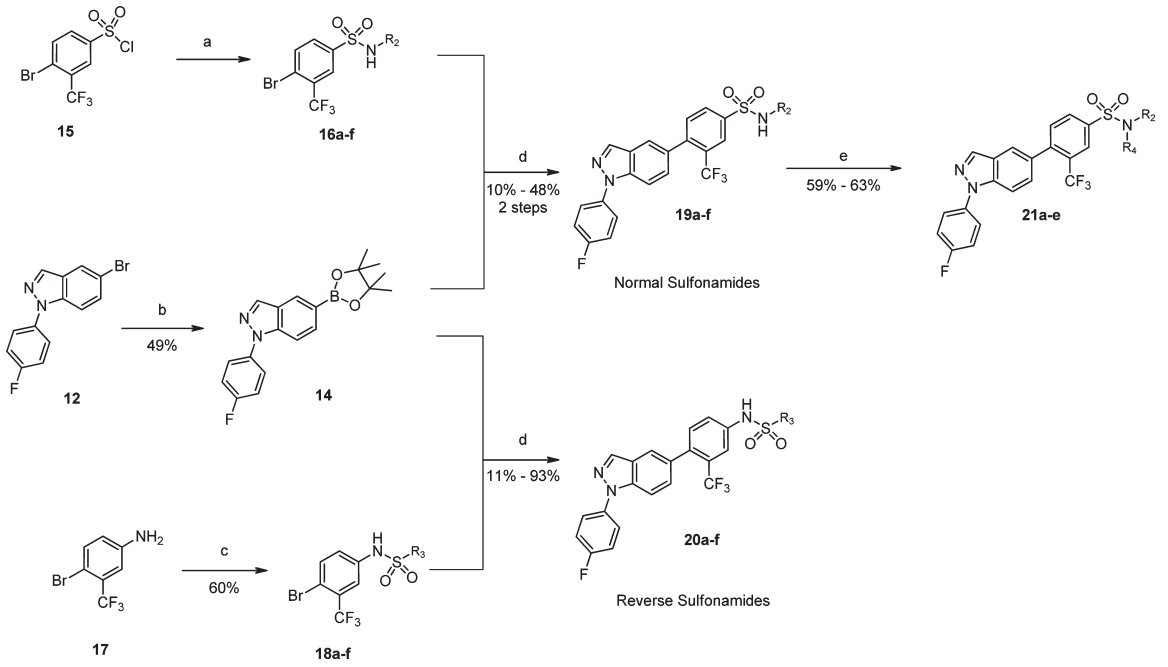
A more streamlined route for exploration of the reverse sulfonamides **23a**−**f** was developed to allow for incorporation of a larger set of monomers (Scheme 3). The boronic ester **14** was coupled with commercially available 4-bromo-3-(trifluoromethyl)aniline to give **22**, which was then reacted with a variety of sulfonyl chlorides in pyridine.

Biological Assays

GR Fluorescence Polarization (FP) Binding Assay. The compounds were tested for their ability to bind to GR through competition with fluorescently labeled dexamethasone **1**. By use of the pooled variance from the tested compounds, the standard deviation (SD) for potency (pIC_{50}) in this assay is ±0.26.[19]

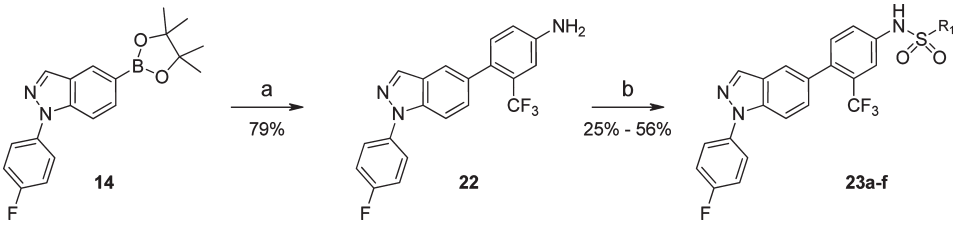
GR NFκB Transrepression Assay. The NFκB assay used human A549 lung epithelial cells engineered to contain a secreted placental alkaline phosphatase gene under the control of the distal region of the NFκB dependent ELAM promoter. In this assay, using the pooled variance from the tested compounds, the SD for pIC_{50} is ±0.34.[10] Maximum responses are quoted with reference to the maximum for

Scheme 2. Synthesis of Normal (**19a**−**f**) and Reverse (**20a**−**f**) Sulfonamides and Their Alkylated Derivatives (**21a**−**e**)[a]



[a] Reagents and conditions: (a) primary amine, PS-DMAP, DCM; (b) bis(pinacolato)diboron, $Pd(dppf)_2Cl_2$, KOAc, DMSO, 70 °C; (c) sulfonyl chloride, PS-DMAP, DCM; (d) Na_2CO_3, $Pd(PPh_3)_4$, dioxane, water, reflux; (e) K_2CO_3, DMF, alkyl bromide/iodide.

Scheme 3. Improved Synthesis of the Reverse Sulfonamides[a]



[a] Reagents and conditions: (a) 4-bromo-3-(trifluoromethyl)aniline, Na_2CO_3, $Pd(PPh_3)_4$, dioxane, water, reflux; (b) R_1SO_2Cl, pyridine.

dexamethasone **1**. By use of the pooled variance from the test compounds, the SD around the maximum response is ±7%.

GR MMTV Transactivation Assay. The MMTV transactivation assay human A549 lung epithelial cells were engineered to contain a renialla luciferase gene under the control of the distal region of the LTR from the mouse mammary tumor virus (MMTV). In this assay, using the pooled variance from the tested compounds, the SD for potency (pEC_{50}) is ±0.23.[10] Maximum responses are quoted with reference to the maximum for dexamethasone **1**. By use of the pooled variance from the test compounds, the SD around the maximum response is ±15%.

Select GR compounds were also tested for their ability to antagonize dexamethasone-induced transactivation. By use of the pooled variance from the tested compounds, the SD for potency (pIC_{50}) in this assay is ±0.2 . Maximum responses are quoted with reference to the maximum for antagonist **7**. By use of the pooled variance from the test compounds, the SD around the maximum response is ±12%.

Results and Discussion

Using a structural model of GR bound with cortivazol **9**, we performed an evaluation of potential chemical libraries to prioritize the libraries for synthesis and evaluation in the GR binding, selectivity, and functional assays. The library design technique involved a combination of shape similarity to a bound ligand **9** followed by full geometric optimization of the active-site oriented compound, a technique that had been used successfully with the androgen receptor (AR).[20] The library design selected three chemotypes, 5-amino, 5-amido, and 5-arylindazoles. Initial arrays of the 5-amino, 5-amido, and 5-arylindazoles resulted in the synthesis of greater than 400 compounds.

A number of the 5-amino and 5-amido compounds demonstrated GR binding with $pIC_{50} > 7.0$, but the SAR was difficult to interpret with highly related compounds giving disparate results. As the data did not indicate any ways to progress the series, no further synthetic efforts were made within these chemotypes (data not shown).

The initial array of 100 5-arylindazoles did not provide compounds with activity in the NFκB assay or with superior affinity compared to the other templates, but analysis of the data revealed important structural features that provided opportunities for further development (Table 1). The compounds with an ortho substitution had improved binding affinity when compared to the compounds with substitution at other positions of that aryl ring (**13b**, **13c**, **13d**), regardless of the electronic nature of the substituent (**13b** vs **13k**). Second, meta/para hydroxyl groups (**13m** and **13n**) also had improved binding affinity compared to related analogues. Almost all

compounds demonstrated binding selectivity over other oxosteroid receptors independent of their substitution.

To test the additive nature of the two observations, docking studies of compounds **13b** and **13n** revealed that the ortho position of the aryl ring could be occupied by a small hydrophobic group while simultaneously the para position of that ring could contain a polar/hydrogen-bond donor group that would potentially interact with T739 (Figure 2). Compound **13o** was shown to have improved binding affinity and selectivity, but as with other compounds, no activity in the NFκB transrepression assay.

Docking of **13o** into the active site of GR revealed additional space near the para position of the phenyl ring that could be occupied for improved potency and functional activity (Figure 2).

In general, we observed a decrease in binding affinity upon incorporation of amides at the para position of the phenyl ring (data not shown). Two initial arrays of normal and reverse sulfonamides (Table 2) showed a significant increase in binding affinity, potentially through a favorable interaction with N564 and T739. A variety of alkyl and aryl substituents were tolerated on the sulfonamide moiety, while only those compounds with the larger substituents showed significant drops in binding affinity. Despite the increase in binding affinity, we did not observe any activity in the NFκB transrepression assay. Selectivity over AR and PR was maintained.

Notably compound **19a** was identified as a GR antagonist in the MMTV transactivation assay. Although less potent than mifepristone **7**, compound **19a** is a potent GR antagonist and is selective over other oxo steroid receptors. Future communications will focus on optimization of the potency of the molecule and the investigation of its use in the treatment of diabetes.

We decided to probe the 17-α pocket of the receptor toward M560 and T739 (Figure 2) based on past observations that the GR was sensitive to the shape of nonpolar groups in this region. It had been observed that small changes in this region could yield compounds with NFκB transrepression activity.[10] The two areas we investigated further were exploration of the reverse sulfonamides and alkylation of the sulfonamide nitrogen.

Nitrogen substitutions on the sulfonamides confirmed the sensitivity of GR functional activity to minor changes in this region. Small alkyl groups provided compounds with partial NFκB transrepression and MMTV agonist activity such as **21a** and **21d** (Table 3). Over 120 alkylated sulfonamides were synthesized, but none provided an improved functional profile compared to **21d**. Groups larger than isopropyl or ones that contained polar functionality resulted in a loss of binding affinity and functional activity.

For the reverse sulfonamides, 65 additional compounds were synthesized leading to the identification of several potent compounds with NFκB transrepression activity (Table 4). Among the active compounds the benzyl analogue **23a** (GSK9027) was the most potent. Further exploration of the benzyl group provided no improvement in functional potency. Within the aryl analogues, only those with meta substitution showed activity (**23c**−**e**). These compounds retained excellent selectivity over the other oxosteroid receptors, and contrary to the sulfonamide analogues, methylation of the reverse sulfonamides resulted in compounds with reduced binding affinity for GR and no NFkB functional activity (data not shown).

The most potent compound identified, the reverse sulfonamide **23a**, was compared with dexamethasone **1** in a range of

Table 1. Data for Initial 5-Arylindazole Array

		pIC_{50} [a]			
compd	R	GR	NFκB	AR	PR
13a	H	5.5	< 5	< 5	< 5
13b	*o*-CF_3	6.6	< 5	< 5	5.6
13c	*m*-CF_3	5.5	< 5	< 5	5.8
13d	*p*-CF_3	< 5	< 5	< 5	< 5
13e	*o*-CN	6.4	< 5	< 5	< 5
13f	*m*-CN	< 5.6	< 5	< 5	< 5
13g	*p*-CN	< 5	< 5	< 5	5.7
13h	*o*-Me	5.9	< 5	< 5	5.2
13i	*m*-Me	5.5	< 5	< 5	< 5
13j	*p*-Me	< 5	< 5	< 5	< 5
13k	*o*-OEt	6.3	< 5	< 5	< 5
13l	*m*-OEt	5.6	< 5	< 5	< 5
13m	*m*-OH	6.1	< 5	< 5	5.6
13n	*p*-OH	6.2	< 5	< 5	< 5

[a] Unless otherwise indicated, the pIC_{50} values quoted are from mean values from multiple tests, $n \geq 2$.

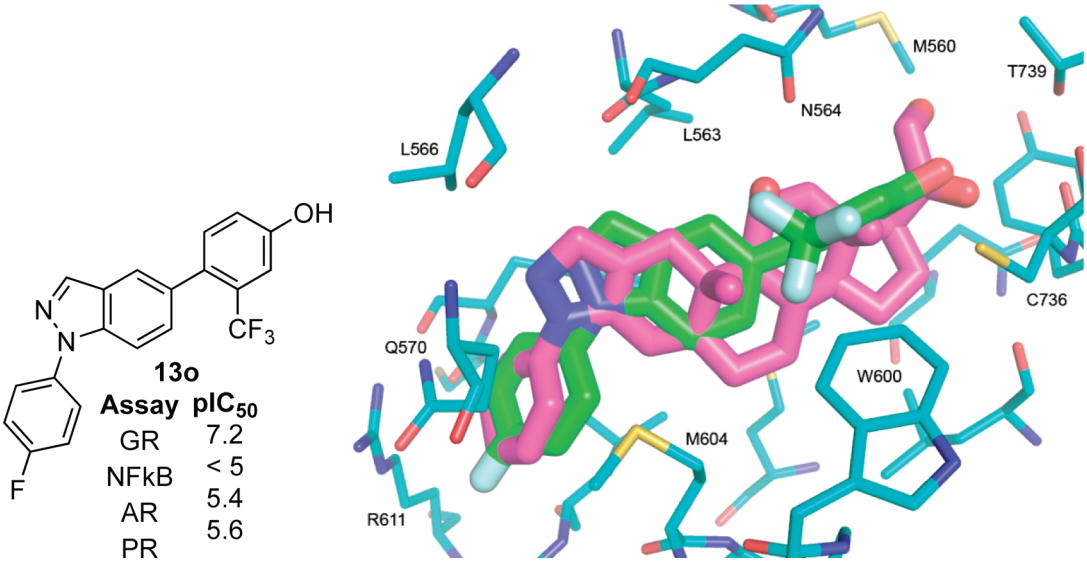


Figure 2. Structure of compound **13o** with structural diagram of **13o** overlaid with cortivazol **9**.

Table 2. Data for the Sulfonamide Arrays

compd	R_1	pIC_{50} [a] GR	pIC_{50} [a] NFκB	pIC_{50} [a] (% max) GR MMTV antag	pIC_{50} [a] AR	pIC_{50} [a] PR
19a	2-propyl	7.9	< 5	5.9 (102)	< 5	5.5
19b	phenyl	7.6	< 5	5.5 (68)	< 5	< 5
19c	ethyl	7.7	< 5	5.7 (76)	5.5	5.8
19d	2-hydroxyethyl	7.8	< 5	5.7 (90)	5.0	5.3
19e	propyl	7.5	< 5	5.5 (63)	5.2	6.1
19f	isobutyl	7.4	< 5	5.5 (74)	5.2	6.2
20a	ethyl	8.0	< 5	5.7 (72)	5.3	< 5
20b	methyl	8.0	< 5	5.8 (80)	5.3	< 5
20c	propyl	7.8	< 5	5.7 (89)	5.5	< 5
20d	phenyl	7.8	< 5	5.8 (84)	5.2	< 5
20e	4-*tert*-butylphenyl	7.3	< 5	5.0 (58)	< 5	< 5.6
20f	2,4,6-triisopropylphenyl	6.6	< 5	< 5 (52)	< 5	< 5
7		8.2	< 5	8.2 (101)	7.2	8.1

[a] Unless otherwise indicated, the pIC_{50} values quoted are from mean values from multiple tests, $n \geq 2$.

Table 3. Agonist Trigger Data

compd	R_2	R_4	pIC_{50} [a] GR	pIC_{50} [a] (% max) NFκB	pEC_{50} [a] (% max) MMTV ag	pIC_{50} [a] AR	pIC_{50} [a] PR
21a	Ph	methyl	7.9	6.4 (65)	6.2 (29)	< 5	6.1
21b	Ph	ethyl	7.8	6.9 (71)	6.7 (40)	< 5	< 5
21c	Ph	propyl	7.8	6.5 (54)	6.5 (25)	< 5	< 5
21d	Ph	isopropyl	7.8	7.3 (83)	6.9 (44)	< 5	< 5.6
21e	Ph	butyl	7.6	< 5 (29)	< 5 (3%)	< 5	< 5

[a] Unless otherwise indicated, the pXC_{50} values quoted are from mean values from multiple tests, $n \geq 2$.

Table 4. Data for Follow-Up Array of Reverse Sulfonamides

compd	R	pIC_{50} [a] GR	pIC_{50} [a] (% max) NFκB	pEC_{50} [a] (% max) MMTV ag	pIC_{50} [a] AR	pIC_{50} [a] PR
23a	benzyl	8.0	8.0 (102)	7.7 (92)	< 5	< 5
23b	isopropyl	7.9	7.3 (71)	6.8 (39)	< 5	< 5
23c	3-trifluoromethoxyphenyl	7.4	7.1 (101)	6.6 (88)	< 5	< 5
23d	3-methoxyphenyl	7.8	7.1 (91)	6.6 (79)	5.5	< 5
23e	3-trifluoromethylphenyl	7.3	7.2 (98)	6.7 (85)	5.4	< 5
23f	3-thiophene	7.9	7.0 (70)	6.6 (38)	5.6	< 5

[a] Unless otherwise indicated, the pIC_{50} and pEC_{50} values quoted are from mean values from multiple tests, $n \geq 2$.

biological systems designed to mimic aspects of glucocorticoid physiology.

The powerful anti-inflammatory activity of glucocorticoids is mediated in part through inhibition of proinflammatory cytokine release. Stimulation of primary human synovial fibroblasts with interleukin-1 (IL-1) leads to the release of interleukin-6 (IL-6), interleukin 8 (IL-8), and matrix metalloproteinase (MMP-1) (Figure 3A). The production of all three of these proinflammatory mediators was dose-dependently inhibited by pretreatment with both dexamethasone **1** and **23a**, with dexamethasone being 4−5 times more potent (Figure 3B, Table 5)

In addition to being anti-inflammatory, glucocorticoids exert metabolic effects across a range of tissues and ultimately give rise to the side effects that limit their clinical utility, including diabetogenesis, weight gain, and muscle loss. Glutamine synthetase (GS) is an enzyme involved in releasing amino acids from skeletal muscle for use as gluconeogenic substrates. GS up-regulation is thought to contribute to the muscle atrophy seen in glucocorticoid treated individuals. Treatment of primary human skeletal muscle cells with either dexamethasone **1** or **23a** resulted in a 7-fold increase in the level of the mRNA coding for GS, with dexamethasone being 5 times more potent than **23a** (Figure 4A).

Phosphoenol pyruvate carboxykinase (PEPCK) is the key enzyme in the liver that controls the rate of gluconeogenesis, leading to the release of glucose into the bloodstream. Expression of the mRNA for PEPCK in primary human hepatocytes was increased 5-fold following treatment with either **1** or **23a**, with dexamethasone again being more potent (Figure 4B). Taken together, these results strongly suggest that **23a** had a functional profile akin to that of a classical glucocorticoid.

To confirm the pharmacological activity of compound **23a**, it was progressed into rodent pharmacokinetic studies. A low clearance and a moderate volume of distribution were observed in mice and rats, resulting in a 3−4 h elimination half-life (Table 6). Following oral administration, good systemic exposure was demonstrated via a prolonged absorption phase with T_{max} in excess of 6 h in both rat and mouse. The sampling profile was limited to 7 h, and therefore, the concentration versus time profile was not completely characterized and the

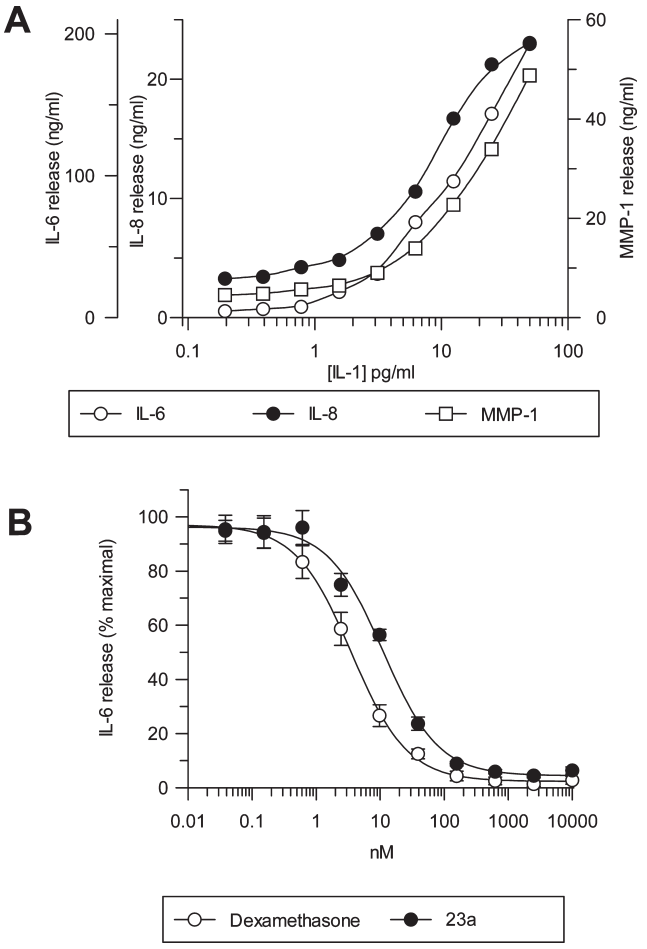


Figure 3. (A) IL-6, IL-8 and MMP-1 dose-dependent release in synovial fibroblasts treated with IL-1. Primary human synovial fibroblasts were treated with indicated concentrations of IL-1 for 18 h, and cytokine production was monitored. (B) Inhibition of IL-6 release by **1** and **23a**. Primary human synovial fibroblasts were cultured in the presence of compound for 1 h prior to stimulation with IL-1 (50pg/mL). Data are the mean ± SEM for 14 independent experiments.

bioavailability values quoted are therefore an underestimate. While dexamethasone **1** showed a moderate level of binding to plasma proteins, **23a** displayed a much lower free fraction in plasma (Table 7). To determine whether this high protein binding would restrict the biological activity of the compounds, their cellular potency in the A549 MMTV transactivation assay was compared in normal culture medium or in human plasma. When plasma from three different donors were used, the dose response curve for dexamethasone **1** shifted between 3- and 5-fold to the right, consistent with the free fraction of 0.27 measured using biophysical methods (Table 7). In contrast the potency of **23a** decreased by more than 100-fold in the presence of plasma, consistent with only the free fraction of the drug (0.002) being available to exert pharmacological activity (Figure 5).

This observation was then extended to an acute in vivo model of cytokine release. Intraperitoneal injection of mice with IL-1 resulted in a rapid and dose-dependent increase in circulating IL-6 levels (Figure 6A,B). Oral administration of dexamethasone **1** or **23a** 60 min prior to challenge gave dose-dependent inhibition of this response (Figure 6C,D).

Table 5. pIC_{50} Levels for Primary Human Synovial Fibroblasts Cultured in the Presence of Compound for 1 h Prior to Stimulation with IL-1 (50 pg/mL) for 18 h[a]

analyte	**1**	**23a**
IL-6	9.2	8.5
IL-8	9.3	8.7
MMP-1	9.5	8.9

[a] IL-6, IL-8, and MMP-1 levels were determined using MSD technology. The pIC_{50} values quoted are from mean values from multiple tests, $n \geq 2$.

To interpret the in vivo pharmacology, additional data were gathered. Systemic levels of drug at the time of IL-1 challenge were measured (Table 7). Then the potency of compounds in murine systems was assessed using a stably integrated cellular MMTV reporter system in murine NIH-3T3 cells (Table 7). The total plasma concentrations of **23a** achieved at 10 mg/kg dosing were similar to that achieved after 1 mg/kg dosing with dexamethasone **1**, and both were around 300 times higher than the in vitro IC_{50} level. However at this dose dexamethasone **1** was maximally effective, while **23a** showed only partial inhibition. The free drug concentration achieved at 100 mg/kg **23a** was only 2.4 times above the in vitro IC_{50}, while this level of free drug was exceeded at a dose of only 0.1 mg/kg dexamethasone **1**. Indeed the latter was more effective than the former.

When the potency normalized drug levels were adjusted to account for plasma protein binding, a consistent dose response relationship emerged to explain the in vivo results (Table 7). These data supported our hypothesis that only the unbound exerted pharmacological activity in vivo. Therefore, despite promising pharmacokinetic parameters, the very high plasma protein binding of **23a** was a major limiting factor in its pharmacological activity.

Conclusions

This paper described the discovery of indazole based GR agonist and antagonist through the use of structure guided design. Through several iterations of chemistry a lead GR agonist **23a** and GR antagonist **19a** were discovered that demonstrated a favorable in vitro profile. Antagonist **19a** represents a starting point for optimization of a selective GR antagonist tool. Further evaluation of indazole **23a** showed that it acts as a conventional steroidal glucocortocoid agonist, although 4−5 times less potent than dexamethasone. In vivo studies showed that compound **23a** had similar pharmacology compared to dexamethasone, but its potency was diminished by its high plasma protein binding.

Experimental Section

General Experimental Procedures. ^{1}H NMR spectra were recorded on a Varion Unity-300 or Varian Unity Plus-400. Chemical shifts are expressed in parts per million (ppm, δ units). Coupling constants are in units of hertz (Hz). Splitting patterns describe apparent multiplicities and are designated as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), or br (broad).

Two LCMS systems were used to determine purity. System 1 consisted of the following: Micromass ZMD LC/MS using a C18 Phenomenex Luna, 20 mm × 4.0 mm, 3 μm column, 90% H20, 10% MeOH to 100% MeOH in 3 min, holding at 100% MeOH for 1 min. Water contained 0.1% v/v formic acid. MeOH contained 0.075% v/v formic acid. The flow rate was 2 mL/min with 3 μL of solution injected. Mass spectra were recorded on a Micromass ZMD utilizing electrospray ionization (ESI) or atmospheric pressure chemical ionization (APCI) switching

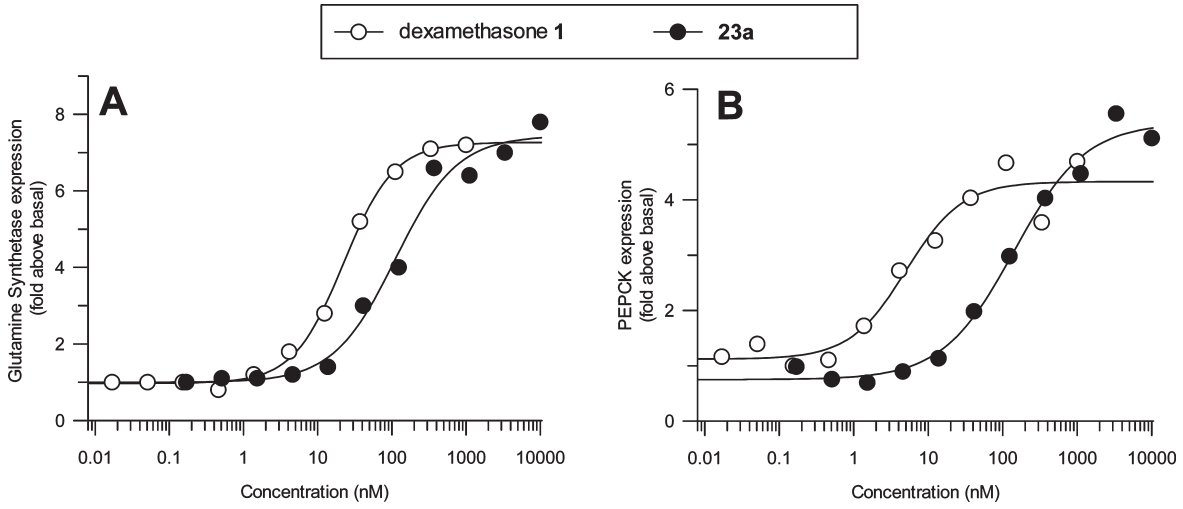


Figure 4. (A) Primary human skeletal muscle cells were treated with compound for 18 h, and the expression of glutamine synthetase was assessed by quantitative PCR. Data are from a single representative experiment. (B) Primary human hepatocytes were treated with compound for 18 h, and the expression of PEPCK was assessed by quantitative PCR. Data are from a single representative experiment.

Table 6. Pharmacokinetic Parameters of **23a** in the Male CD Rat and Male DBA/1 Mouse after 1 mg/kg Dose iv and Oral

	Cl_p ((mL/min)/kg)	V_{ss} (L/kg)	$T_{1/2}$ (h)	oral bioavailability (%)
rat	8	2.0	3.3	>22
mouse	8	1.8	4.0	>51

between positive and negative modes with DAD (Waters 996 DAD) scanning from 210 to 400 nm.

System 2 consisted of the following: The UPLC analysis was conducted on a Waters Acquity system with BEH C18, 2 mm × 50 mm, 1.7 μm column at 40 °C, 95% H_2O, 5% MeCN to 99% MeCN in 1.1 min, holding at 100% MeCN for 40 s. Water contained 0.2% v/v formic acid. MeCN contained 0.15% v/v formic acid. The flow rate was 1 mL/min with 5 μL of solution injected. Mass spectra were recorded utilizing electrospray ionization (ESI) or atmospheric pressure chemical ionization (APCI) switching between positive and negative modes with DAD scanning from 210 to 350 nm. All compounds tested were of ≥95% purity.

Normal phase chromatography was accomplished using either Isco or Biotage equipment using prepacked silica columns.

Reverse phase HPLC was accomplished using Agilent 110 series preparative HPLC systems using C18 Phenomenex Luna, 75 mm × 30 mm, 5 μm column using the gradient described. The flow rate was 70 mL/min, and the product was collected based on UV detection at 220 or 254 nm.

5-Bromo-2-fluorobenzaldehyde (4-Fluorophenyl)hydrazone (11). To a boiling solution of (4-fluorophenyl)hydrazine (0.829 g, 8.0 mmol) in acetonitrile (36 mL) was added 5-bromo-2-fluorobenzaldehyde (1.0 g, 8.0 mmol) in boiling acetonitrile (9 mL), resulting in a bright-yellow solution. The solution was allowed to cool to room temperature and then the solvent was removed in vacuo, resulting in a yellow solid. The yellow solid was washed with isopropanol to yield 1.56 g of **11** (67%) as a yellow solid. MS (APCI) 312 $(M + H)^+$. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.19−7.33 (m, 2 H), 7.48−7.61 (m, 2 H), 7.61−7.72 (m, 2 H), 7.94−7.99 (m, 1 H), 8.15 (s, 1 H).

5-Bromo-1-(4-fluorophenyl)-1*H*-indazole (12). A mixture of **11** (100 mg, 341 mmol) and cesium carbonate (222 mg, 682 mmol) in anhydrous DMSO (2 mL) was heated to 100 °C using a microwave for 10 min. The mixture was then heated 140 °C using a microwave for 10 min. To the solution was added brine (30 mL), and the product was extracted with ethyl acetate. The organic layers were combined, dried, and concentrated in vacuo to a yellow oil. The oil was purified by normal phase chromatography using EtOAc/hexanes (1−7% gradient) to yield 66 mg of **12** (71%) as a white solid. MS (APCI) 292 $(M + H)^+$. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.19−7.33 (m, 2 H), 7.48−7.61 (m, 2 H), 7.61−7.72 (m, 2 H), 7.94−7.99 (m, 1 H), 8.15 (s, 1 H).

Compounds 13a−n were prepared in array format using the following representative procedure. 1-(4-Fluorophenyl)-5-phenyl-1*H*-indazole (13a). To a reaction vessel containing dioxane (1.0 mL) was added 440 μL of the 0.5 M DMF solution of phenylboronic acid (0.22 mmol), 200 μL of 1.0 M dioxane solution of 5-bromo-1-(4-fluorophenyl)-1*H*-indazole (0.20 mmol), 300 μL of 2.0 M aqueous sodium carobonate solution (0.600 mmol), and 800 μL of 0.0125 M dioxane solution of tetrakis(triphenylphosphino)palladium (0.01 mmol). The reaction was flushed with nitrogen and heated to 110 °C for 16 h. The solution was cooled to room temperature and added to a prepacked 5 g silica column. The product was eluted with EtOAc/hexanes (0−100% gradient) to yield 30 mg of **13a** (53%) as a solid. MS (ESI) 289 $(M + H)^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.44 (s, 1 H), 8.16 (s, 1 H), 7.79−7.91 (m, 4 H), 7.71−7.77 (m, 2 H), 7.41−7.53 (m, 4 H), 7.34−7.41 (m, 1 H).

1-(4-Fluorophenyl)-5-[2-(trifluoromethyl)phenyl]-1*H*-indazole (13b). Compound **13b** was prepared in the same manner as **13a** to yield 10.9 mg of **13b** (31%) as a solid. MS (ESI) 357 $(M + H)^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.44 (s, 1 H), 7.78−7.90 (m, 5 H), 7.75 (t, J = 7.51 Hz, 1 H), 7.65 (t, J = 7.69 Hz, 1 H), 7.39−7.52 (m, 4 H).

1-(4-Fluorophenyl)-5-[3-(trifluoromethyl)phenyl]-1*H*-indazole (13c). Compound **13c** was prepared in the same manner as **13a** to yield 36.5 mg of **13c** (51%) as a solid. MS (ESI) 357 $(M + H)^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.46 (s, 1 H), 8.30 (s, 1 H), 8.02−8.12 (m, 2 H), 7.90 (s, 2 H), 7.81−7.88 (m, 2 H), 7.70−7.77 (m, 2 H), 7.46 (t, J = 8.79 Hz, 2 H).

1-(4-Fluorophenyl)-5-[4-(trifluoromethyl)phenyl]-1*H*-indazole (13d). Compound **13d** was prepared in the same manner as **13a** to yield 20.0 mg of **13d** (20%) as a solid. MS (ESI) 357 $(M + H)^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.47 (s, 1 H), 8.27 (s, 1 H), 7.97 (d, 2 H), 7.80−7.93 (m, 6 H), 7.46 (t, J = 8.79 Hz, 2 H).

2-[1-(4-Fluorophenyl)-1*H*-indazol-5-yl]benzonitrile (13e). Compound **13e** was prepared in the same manner as **13a** to yield 8.3 mg of **13e** (27%) as a solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.50 (s, 1 H), 8.12 (s, 1 H), 7.98 (d, J = 7.57 Hz, 1 H), 7.93 (d, J = 8.55 Hz, 1 H), 7.78−7.88 (m, 3 H), 7.70 (dd, J = 8.06, 1.71 Hz, 2 H), 7.60 (t, J = 7.57 Hz, 1 H), 7.46 (t, J = 8.79 Hz, 2 H)

3-[1-(4-Fluorophenyl)-1*H*-indazol-5-yl]benzonitrile (13f). Compound **13f** was prepared in the same manner as **13a** to yield 25.9 mg

Table 7. Effect of Plasma Protein Binding on the Observed Effect of IL-6 Release

compd	potency in NFκB assay (nM)	Fu_p	dose (mg/kg)	total plasma concn 1 h (nM)	relative total plasma concn 1 h (fold above EC_{50})	unbound plasma concn 1 h (nM)	relative unbound plasma concn (fold above EC_{50})	effect (% inhib)
1	6	0.29	10	17700	2944	5123	870	83
			1	1800[a]	300	87	86	88
			0.1	236	40	11.6	8	67
			0.01	44	7	2.03	0.4	24
23a	10	0.002	100	12100	1210	24.2	2.4	57
			10	2730	273	5.46	0.5	44
			1	290	29	0.58	0.06	0
			0.1	25	2.5	0.05	0.005	0

[a] Value calculated on the basis of linear exposure with dose.

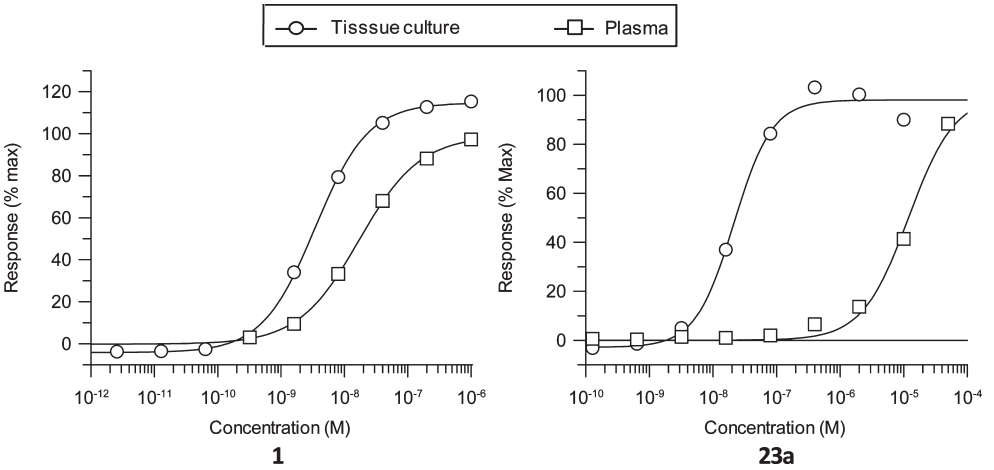


Figure 5. A549 cells containing an MMTV reporter gene were incubated with compounds for 18 h in tissue culture medium (circles) or human plasma prepared from healthy donors (squares) before luciferase reporter gene activity was determined. Results are from a single experiment representative of three.

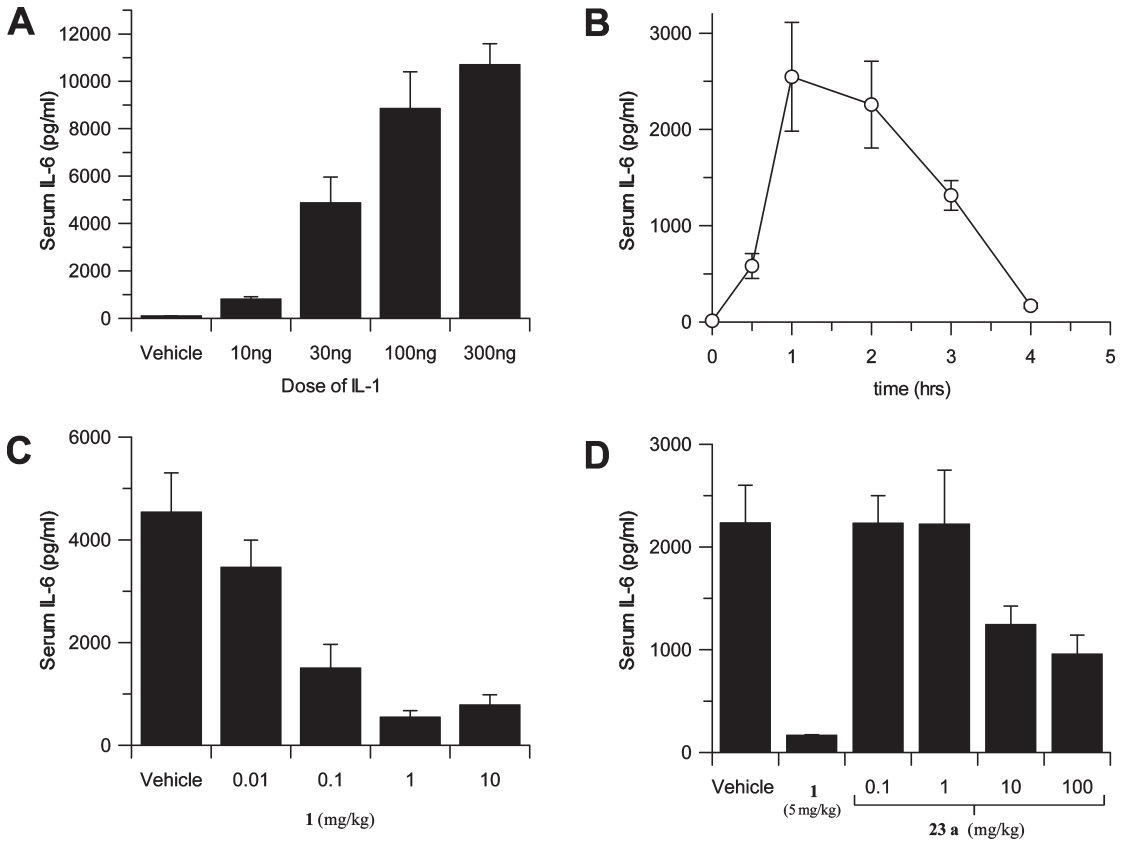


Figure 6. In vivo results for **1** and **23a**.

of **13f** (41%) as a solid. MS (ESI) 314 $(M + H)^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.46 (s, 1 H), 8.30 (s, 1 H), 8.22−8.27 (m, 1 H), 8.09−8.14 (m, 1 H), 7.90 (s, 2 H), 7.80−7.88 (m, 3 H), 7.70 (s, 1 H), 7.46 (s, 2 H).

4-[1-(4-Fluorophenyl)-1*H*-indazol-5-yl]benzonitrile (13g). Compound **13g** was prepared in the same manner as **13a** to yield 26.4 mg of **13g** (42%) as a solid. MS (ESI) 314 $(M + H)^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.48 (s, 1 H), 8.31 (s, 1 H), 7.81−8.01 (m, 8 H), 7.46 (s, 2 H)

1-(4-Fluorophenyl)-5-(2-methylphenyl)-1*H*-indazole (13h). Compound **13h** was prepared in the same manner as **13a** to yield 18.7 mg of **13h** (31%) as a solid. MS (ESI) 303 $(M + H)^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.41 (s, 1 H), 7.81−7.88 (m, 4 H), 7.41−7.51 (m, 3 H), 7.24−7.36 (m, 4 H), 2.26 (s, 3 H).

1-(4-Fluorophenyl)-5-(3-methylphenyl)-1*H*-indazole (13i). Compound **13i** was prepared in the same manner as **13a** to yield 30.4 mg of **13i** (50%) as a solid. MS (ESI) 303 $(M + H)^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.40 (s, 3 H), 7.19 (d, J = 7.51 Hz, 1 H), 7.38 (t, J = 7.60 Hz, 1 H), 7.46 (t, J = 8.79 Hz, 2 H), 7.52 (d, J = 7.87 Hz, 1 H), 7.56 (s, 1 H), 7.77−7.91 (m, 4 H), 8.14 (s, 1 H), 8.43 (s, 1 H).

1-(4-Fluorophenyl)-5-(4-methylphenyl)-1*H*-indazole (13j). Compound **13j** was prepared in the same manner as **13a** to yield 25.4 mg of **13j** (42%) as a solid. MS (ESI) 303 $(M + H)^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.36 (s, 3 H), 7.30 (d, J = 8.06 Hz, 2 H), 7.45 (t, J = 8.79 Hz, 2 H), 7.63 (d, J = 8.06 Hz, 2 H), 7.76−7.90 (m, 4 H), 8.12 (d, J = 0.73 Hz, 1 H), 8.42 (s, 1 H).

5-[2-(Ethyloxy)phenyl]-1-(4-fluorophenyl)-1*H*-indazole (13k). Compound **13k** was prepared in the same manner as **13a** to yield 35.6 mg of **13k** (54%) as a solid. MS (ESI) 333 $(M + H)^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.26 (t, J = 6.96 Hz, 3 H), 4.06 (q, J = 6.96 Hz, 2 H), 7.04 (t, J = 7.42 Hz, 1 H), 7.12 (d, J = 8.06 Hz, 1 H), 7.29−7.40 (m, 2 H), 7.44 (t, J = 8.70 Hz, 2 H), 7.66 (dd, J = 8.79, 1.28 Hz, 1 H), 7.76−7.88 (m, 3 H), 7.96 (s, 1 H), 8.40 (s, 1 H).

5-[3-(Ethyloxy)phenyl]-1-(4-fluorophenyl)-1*H*-indazole (13l). Compound **13l** was prepared in the same manner as **13a** to yield 32.9 mg of **13l** (50%) as a solid. MS (ESI) 333 $(M + H)^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.37 (t, 3 H), 4.13 (q, J = 6.96 Hz, 2 H), 6.93 (dd, J = 8.06, 2.01 Hz, 1 H), 7.24 (s, 1 H), 7.29 (d, J = 7.87 Hz, 1 H), 7.39 (t, J = 7.87 Hz, 1 H), 7.42−7.50 (m, 2 H), 7.78−7.90 (m, 4 H), 8.17 (s, 1 H), 8.42 (s, 1 H).

3-[1-(4-Fluorophenyl)-1*H*-indazol-5-yl]phenol (13m). Compound **13m** was prepared in the same manner as **13a** to yield 34.2 mg of **13m** (56%) as a solid. MS (ESI) 305 $(M + H)^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 6.78 (dd, 1 H), 7.09 (s, 1 H), 7.14 (d, J = 7.87 Hz, 1 H), 7.28 (t, J = 7.87 Hz, 1 H), 7.45 (t, J = 8.79 Hz, 2 H), 7.74 (dd, J = 8.79, 1.46 Hz, 1 H), 7.79−7.89 (m, 3 H), 8.08 (s, 1 H), 8.42 (s, 1 H), 9.54 (s, 1 H).

4-[1-(4-Fluorophenyl)-1*H*-indazol-5-yl]phenol (13n). To a reaction vessel was added 4-hydroxyphenylboronic acid (15.2 mg, 0.11 mmol), 100 μL of 1.0 M dioxane solution of 5-bromo-1-(4-fluorophenyl)-1*H*-indazole (0.20 mmol), 150 μL of 2.0 M aqueous sodium carobonate solution (0.300 mmol), and 200 μL of 0.0025 M dioxane solution of tetrakis(triphenylphosphino)palladium (0.005 mmol). The mixture was flushed with nitrogen and heated to 110 °C for 16 h. The solution was cooled to room temperature and added to a prepacked 5 g silica column. The product was eluted with EtOAc/hexanes (0−100% gradient) to yield 12 mg of **13n** (39%) as a solid. MS (ESI) 305 $(M + H)^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 6.87 (d, J = 8.42 Hz, 2 H), 7.39−7.48 (m, 2 H), 7.55 (d, J = 8.61 Hz, 2 H), 7.73 (dd, J = 8.88, 1.56 Hz, 1 H), 7.79−7.87 (m, 3 H), 8.03 (s, 1 H), 8.39 (s, 1 H), 9.53 (s, 1 H).

4-[1-(4-Fluorophenyl)-1*H*-indazol-5-yl]-3-(trifluoromethyl)-phenol (13o). To a mixture of 4-hydroxy-2-(trifluoromethyl)-phenylboronic acid (135.9 mg, 0.660 mmol) and tetrakis-(triphenylphosphino)palladium (34.7 mg, 0.03 mmol) in dioxane (5.0 mL) was added 600 μL of 1.0 M dioxane solution of 5-bromo-1-(4-fluorophenyl)-1*H*-indazole (0.60 mmol) and 1.0 mL of 2.0 M aqueous sodium carobonate solution (2.0 mmol). The mixture was flushed with nitrogen and heated to 110 °C for 24 h. The solution was cooled to room temperature, added to 5 g silica, and concentrated in vacuo. The product was added to a column and eluted with EtOAc/hexanes (0−100% gradient) to yield 82.7 mg of **13o** (37%) as a solid. MS (ESI) 373 $(M + H)^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.09 (dd, J = 8.33, 2.29 Hz, 1 H), 7.18 (d, J = 2.56 Hz, 1 H), 7.27 (d, J = 8.42 Hz, 1 H), 7.39 (d, J = 8.79 Hz, 1 H), 7.45 (t, J = 8.79 Hz, 2 H), 7.72−7.89 (m, 4 H), 8.41 (s, 1 H), 10.20 (s, 1 H).

1-(4-Fluorophenyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indazole (14). To a solution of 5-bromo-1-(4-fluorophenyl)-1*H*-indazole **12** (43.5 g, 0.149 mol) in degassed DMSO was added [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (5.5 g, 0.0075 mol). The mixture was allowed to stir for 10 min at room temperature followed by the addition of bis-(pinacolato)diboron (56.9 g, 0.224 mol) and potassium acetate (44.2 g, 0.447 mol). The mixture was stirred at room temperature for 10 min and then heated to 70 °C for 4 h. The mixture was allowed to cool. Ethyl acetate was added to the mixture followed by filtration though Celite. The filtrate was washed with water and then concentrated to a dark solid. The solid was submitted to column chromatography, eluting with EtOAc/hexanes (1:4) to yield an impure brown solid. The solid was suspended in boiling hexanes and then filtered. The filtrate was cooled to produce a second batch of solid. The solids were combined to yield 34.8 g of **14** (49%). MS (ESI) 339 $(M + H)^+$. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.34 (s, 1 H), 8.19 (s, 1 H), 7.84 (d, 1 H), 7.67 (m, 3 H), 7.21 (m, 2 H), 1.34 (s, 12 H).

Compounds 16a−f were synthesized as part of a larger array. 4-Bromo-*N*-(1-methylethyl)-3-(trifluoromethyl)benzenesulfonamide (16a). To a mixture of isopropylamine (33.5 mg, 0.567 mmol) and PS-DMAP (1.60 mmol/g loading, 531.2 mg, 0.85 mmol) in DCM (5 mL) was added 4-bromo-3-(trifluoromethyl)benzenesulfonyl chloride (183.3 mg, 0.567 mmol). The mixture was allowed to shake at room temperature for 24 h. The resin was filtered and washed with DCM. The filtrate was concentrated and carried on to the next step assuming quantitative yield of **16a**. MS (APCI) 346 $(M - H)^-$.

4-Bromo-*N*-phenyl-3-(trifluoromethyl)benzenesulfonamide (16b). To a mixture of aniline (52.8 mg, 0.567 mmol) and PS-DMAP (1.60 mmol/g loading, 531.2 mg, 0.85 mmol) in DCM (5 mL) was added 4-bromo-3-(trifluoromethyl)benzenesulfonyl chloride (183.3 mg, 0.567 mmol). The mixture was allowed to shake at room temperature for 24 h. The resin was filtered and washed with DCM. The filtrate was concentrated and carried on to the next step assuming quantitative yield of **16b**. MS (APCI) 379 $(M - H)^-$.

4-Bromo-*N*-ethyl-3-(trifluoromethyl)benzenesulfonamide (16c). To a mixture of ethylamine (25.6 mg, 0.567 mmol) and PS-DMAP (1.60 mmol/g loading, 531.2 mg, 0.85 mmol) in DCM (5 mL) was added 4-bromo-3-(trifluoromethyl)benzenesulfonyl chloride (183.3 mg, 0.567 mmol). The mixture was allowed to shake at room temperature for 24 h. The resin was filtered and washed with DCM. The filtrate was concentrated and carried on to the next step assuming quantitative yield of **16c**. MS (APCI) 331 $(M - H)^-$.

4-Bromo-*N*-(2-hydroxyethyl)-3-(trifluoromethyl)benzenesulfonamide (16d). To a mixture of 2-aminoethanol (34.6 mg, 0.567 mmol) and PS-DMAP (1.60 mmol/g loading, 531.2 mg, 0.85 mmol) in DCM (5 mL) was added 4-bromo-3-(trifluoromethyl)-benzenesulfonyl chloride (183.3 mg, 0.567 mmol). The mixture was allowed to shake at room temperature for 24 h. The resin was filtered and washed with DCM. The filtrate was concentrated and carried on to the next step assuming quantitative yield of **16d**. MS (APCI) 347 $(M - H)^-$.

4-Bromo-*N*-propyl-3-(trifluoromethyl)benzenesulfonamide (16e). To a mixture of propylamine (33.5 mg, 0.567 mmol) and PS-DMAP (1.60 mmol/g loading, 531.2 mg, 0.85 mmol) in DCM (5 mL) was added 4-bromo-3-(trifluoromethyl)benzenesulfonyl chloride (183.3 mg, 0.567 mmol). The mixture was allowed to shake at room temperature for 24 h. The resin was filtered and washed with DCM. The filtrate was concentrated and carried on

to the next step assuming quantitative yield of **16e**. MS (APCI) 345 $(M - H)^-$.

4-Bromo-*N*-(2-methylpropyl)-3-(trifluoromethyl)benzenesulfonamide (16f). To a mixture of isobutylamine (41.5 mg, 0.567 mmol) and PS-DMAP (1.60 mmol/g loading, 531.2 mg, 0.85 mmol) in DCM (5 mL) was added 4-bromo-3-(trifluoromethyl)benzenesulfonyl chloride (183.3 mg, 0.567 mmol). The mixture was allowed to shake at room temperature for 24 h. The resin was filtered and washed with DCM. The filtrate was concentrated and carried on to the next step assuming quantitative yield of **16f**. MS (APCI) 359 $(M - H)^-$.

Compounds 18a−f were synthesized as part of a larger array. *N*-[4-Bromo-3-(trifluoromethyl)phenyl]ethanesulfonamide (18a). To a mixture of 4-bromo-3-(trifluoromethyl)aniline (200 mg, 0.833 mmol) and DMAP (152.7 mg, 1.25 mmol) in DCM (2 mL) was added ethanesulfonyl chloride (107 mg, 0.833 mmol). The mixture was allowed to stir at room temperature for 2 h. The mixture was concentrated and purified by reverse phase HPLC (10−100% MeCN/water with 0.05% TFA), and the solid product was carried on to the next step assuming 60% yield of **18a**. MS (ESI) 331 $(M - H)^-$.

***N*-[4-Bromo-3-(trifluoromethyl)phenyl]methanesulfonamide (18b).** To a mixture of 4-bromo-3-(trifluoromethyl)aniline (200 mg, 0.833 mmol) and DMAP (152.7 mg, 1.25 mmol) in DCM (2 mL) was added methanesulfonyl chloride (95 mg, 0.833 mmol). The mixture was allowed to stir at room temperature for 2 h. The mixture was concentrated and purified by reverse phase HPLC (10−100% MeCN/water with 0.05% TFA), and the solid product was carried on to the next step assuming 60% yield of **18b**. MS (ESI) 317 $(M - H)^-$.

***N*-[4-Bromo-3-(trifluoromethyl)phenyl]-1-propanesulfonamide (18c).** To a mixture of 4-bromo-3-(trifluoromethyl)aniline (200 mg, 0.833 mmol) and DMAP (152.7 mg, 1.25 mmol) in DCM (2 mL) was added propanesulfonyl chloride (119 mg, 0.833 mmol). The mixture was allowed to stir at room temperature for 2 h. The mixture was concentrated and purified by reverse phase HPLC (10−100% MeCN/water with 0.05% TFA), and the solid product was carried on to the next step assuming 60% yield of **18c**. MS (ESI) 345 $(M - H)^-$.

***N*-[4-Bromo-3-(trifluoromethyl)phenyl]benzenesulfonamide (18d).** To a mixture of 4-bromo-3-(trifluoromethyl)aniline (200 mg, 0.833 mmol) and DMAP (152.7 mg, 1.25 mmol) in DCM (2 mL) was added benzenesulfonyl chloride (147 mg, 0.833 mmol). The mixture was allowed to stir at room temperature for 2 h. The mixture was concentrated and purified by reverse phase HPLC (10−100% MeCN/water with 0.05% TFA), and the solid product was carried on to the next step assuming 60% yield of **18d**. MS (ESI) 379 $(M - H)^-$.

***N*-[4-Bromo-3-(trifluoromethyl)phenyl]-4-(1,1-dimethylethyl)-benzenesulfonamide (18e).** To a mixture of 4-bromo-3-(trifluoromethyl)aniline (200 mg, 0.833 mmol) and DMAP (152.7 mg, 1.25 mmol) in DCM (2 mL) was added 4-(1,1-dimethylethyl)-benzenesulfonyl chloride (194 mg, 0.833 mmol). The mixture was allowed to stir at room temperature for 2 h. The mixture was concentrated and purified by reverse phase HPLC (10−100% MeCN/water with 0.05% TFA), and the solid product was carried on to the next step assuming 60% yield of **18e**. MS (ESI) 435 $(M - H)^-$.

***N*-[4-Bromo-3-(trifluoromethyl)phenyl]-2,4,6-tris(1-methylethyl)benzenesulfonamide (18f).** To a mixture of 4-bromo-3-(trifluoromethyl)aniline (200 mg, 0.833 mmol) and DMAP (152.7 mg, 1.25 mmol) in DCM (2 mL) was added 2,4,6-tris(1,1-dimethylethyl)benzenesulfonyl chloride (252 mg, 0.833 mmol). The mixture was allowed to stir at room temperature for 2 h. The mixture was concentrated and purified by reverse phase HPLC (10−100% MeCN/water with 0.05% TFA), and the solid product was carried on to the next step assuming 60% yield of **18f**. MS (ESI) 505 $(M - H)^-$.

Compounds 19a−f were synthesized as part of a larger array. 4-[1-(4-Fluorophenyl)-1*H*-indazol-5-yl]-*N*-(1-methylethyl)-3-(trifluoromethyl)benzenesulfonamide (19a). To a solution of **16a** (assumed 0.567 mmol), tetrakis(triphenylphosphino)palladium (29.8 mg, 0.026 mmol), and **14** (174.2 mg, 0.515 mmol) in degassed dioxane was added 1.0 mL of a 2 M sodium carbonate solution. The mixture was flushed with nitrogen and heated to 110 °C for 12 h. The solution was cooled to room temperature, added to silica (5 g), and concentrated. The product was purified by normal phase chromatography, eluting with EtOAc/hexanes (0−100% gradient) to yield 38 mg of **19a** (16%) as a solid. MS (ESI) 478 $(M + H)^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.02 (d, J = 6.41 Hz, 6 H), 3.28−3.42 (m, 1 H), 7.41−7.52 (m, 3 H), 7.73 (d, J = 8.06 Hz, 1 H), 7.82−7.97 (m, 5 H), 8.11−8.17 (m, 1 H), 8.22 (s, 1 H), 8.47 (s, 1 H).

4-[1-(4-Fluorophenyl)-1*H*-indazol-5-yl]-*N*-phenyl-3-(trifluoromethyl)benzenesulfonamide (19b). To a solution of **16b** (assumed 0.567 mmol), tetrakis(triphenylphosphino)palladium (29.8 mg, 0.026 mmol), and **14** (174.2 mg, 0.515 mmol) in degassed dioxane was added 1.0 mL of a 2 M sodium carbonate solution. The mixture was flushed with nitrogen and heated to 110 °C for 12 h. The solution was cooled to room temperature, added to silica (5 g), and concentrated. The product was purified by normal phase chromatography, eluting with EtOAc/hexanes (0−100% gradient) to yield 26 mg of **19b** (10%) as a solid. MS (ESI) 512 $(M + H)^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.11 (t, J = 7.33 Hz, 1 H), 7.17 (d, J = 7.69 Hz, 2 H), 7.30 (t, J = 7.87 Hz, 2 H), 7.45 (t, J = 8.79 Hz, 3 H), 7.69 (d, J = 8.06 Hz, 1 H), 7.78−7.90 (m, 4 H), 8.01−8.09 (m, 1 H), 8.14 (s, 1 H), 8.44 (s, 1 H), 10.54 (s, 1 H).

***N*-Ethyl-4-[1-(4-fluorophenyl)-1*H*-indazol-5-yl]-3-(trifluoromethyl)benzenesulfonamide (19c).** To a solution of **16c** (assumed 0.567 mmol), tetrakis(triphenylphosphino)palladium (29.8 mg, 0.026 mmol), and **14** (174.2 mg, 0.515 mmol) in degassed dioxane was added 1.0 mL of a 2 M sodium carbonate solution. The mixture was flushed with nitrogen and heated to 110 °C for 12 h. The solution was cooled to room temperature, added to silica (5 g), and concentrated. The product was purified by normal phase chromatography, eluting with EtOAc/hexanes (0−100% gradient) to yield 114 mg of **19c** (48%) as a solid. MS (ESI) 464 $(M + H)^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.03 (t, J = 7.23 Hz, 3 H), 2.82−2.94 (m, 2 H), 7.42−7.53 (m, 3 H), 7.74 (d, J = 8.06 Hz, 1 H), 7.81−7.95 (m, 5 H), 8.10−8.15 (m, 1 H), 8.19 (s, 1 H), 8.47 (s, 1 H).

4-[1-(4-Fluorophenyl)-1*H*-indazol-5-yl]-*N*-(2-hydroxyethyl)-3-(trifluoromethyl)benzenesulfonamide (19d). To a solution of **16d** (assumed 0.567 mmol), tetrakis(triphenylphosphino)palladium (29.8 mg, 0.026 mmol), and **14** (174.2 mg, 0.515 mmol) in degassed dioxane was added 1.0 mL of a 2 M sodium carbonate solution. The mixture was flushed with nitrogen and heated to 110 °C for 12 h. The solution was cooled to room temperature, added to silica (5 g), and concentrated. The product was purified by normal phase chromatography, eluting with EtOAc/hexanes (0−100% gradient) to yield 69 mg of **19d** (28%) as a solid. MS (ESI) 480 $(M + H)^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.91 (br s, 2 H), 3.44 (q, J = 5.86 Hz, 2 H), 4.78 (t, J = 5.49 Hz, 1 H), 7.46 (q, J = 8.73 Hz, 3 H), 7.72 (d, J = 8.06 Hz, 1 H), 7.81−7.92 (m, 4 H), 7.98 (br s, 1 H), 8.14 (d, J = 8.61 Hz, 1 H), 8.23 (s, 1 H), 8.47 (s, 1 H).

4-[1-(4-Fluorophenyl)-1*H*-indazol-5-yl]-*N*-propyl-3-(trifluoromethyl)benzenesulfonamide (19e). To a solution of **16e** (assumed 0.567 mmol), tetrakis(triphenylphosphino)palladium (29.8 mg, 0.026 mmol), and **14** (174.2 mg, 0.515 mmol) in degassed dioxane was added 1.0 mL of a 2 M sodium carbonate solution. The mixture was flushed with nitrogen and heated to 110 °C for 12 h. The solution was cooled to room temperature, added to silica (5 g), and concentrated. The product was purified by normal phase chromatography, eluting with EtOAc/hexanes (0−100% gradient) to yield 46 mg of **19e** (19%) as a solid. MS (ESI) 478 $(M + H)^+$. NMR (400 MHz, DMSO-d_6) δ ppm 0.84 (t, J = 7.33 Hz, 3 H), 1.43 (sxt, J = 7.25 Hz, 2 H), 2.80 (q, J = 6.65 Hz, 2 H), 7.41−7.53 (m, 3 H), 7.74 (d, J = 8.06 Hz, 1 H), 7.82−7.96 (m, 5 H), 8.13 (d, J = 8.06 Hz, 1 H), 8.19 (s, 1 H), 8.47 (s, 1 H).

4-[1-(4-Fluorophenyl)-1*H*-indazol-5-yl]-*N*-(2-methylpropyl)-3-(trifluoromethyl)benzenesulfonamide (19f). To a solution of **16f** (assumed 0.567 mmol), tetrakis(triphenylphosphino)palladium (29.8 mg, 0.026 mmol), and **14** (174.2 mg, 0.515 mmol) in degassed dioxane was added 1.0 mL of a 2 M sodium carbonate solution. The mixture was flushed with nitrogen and heated to 110 °C for 12 h. The solution was cooled to room temperature, added to silica (5 g), and concentrated. The product was purified by normal phase chromatography, eluting with EtOAc/hexanes (0−100% gradient) to yield 120 mg of **19f** (47%) as a solid. MS (ESI) 492 $(M + H)^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.85 (d, J = 6.59 Hz, 6 H), 1.60−1.74 (m, J = 13.37, 6.68, 6.68, 6.68, 6.68 Hz, 1 H), 2.65 (t, J = 6.41 Hz, 2 H), 7.42−7.52 (m, 3 H), 7.73 (d, J = 7.87 Hz, 1 H), 7.81−7.98 (m, 5 H), 8.09−8.15 (m, 1 H), 8.20 (s, 1 H), 8.47 (s, 1 H).

Compounds 20a−f were synthesized as part of a larger array. *N*-[4-[1-(4-Fluorophenyl)-1*H*-indazol-5-yl]-3-(trifluoromethyl)-phenyl]ethanesulfonamide (20a). To a solution of **18a** (assumed 0.495 mmol), tetrakis(triphenylphosphino)palladium (29.8 mg, 0.026 mmol), and **14** (152.2 mg, 0.450 mmol) in degassed dioxane was added 1.0 mL of a 2 M sodium carbonate solution. The mixture was flushed with nitrogen and heated to 110 °C for 12 h. The solution was cooled to room temperature, added to silica (5 g), and concentrated. The product was purified by normal phase chromatography, eluting with EtOAc/hexanes (0−100% gradient) to yield 104.5 mg of **20a** (50%) as a solid. MS (ESI) 462 $(M - H)^-$. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.24 (s, 1 H), 7.67−7.77 (m, 4 H), 7.57 (d, J = 2.32 Hz, 1 H), 7.50 (dd, J = 8.29, 2.23 Hz, 1 H), 7.39 (d, J = 8.38 Hz, 2 H), 7.21−7.31 (m, 2 H), 6.66 (s, 1 H), 3.25 (q, J = 7.31 Hz, 2 H), 1.47 (t, J = 7.40 Hz, 3 H).

***N*-[4-[1-(4-Fluorophenyl)-1*H*-indazol-5-yl]-3-(trifluoromethyl)-phenyl]methanesulfonamide (20b).** To a solution of **18b** (assumed 0.495 mmol), tetrakis(triphenylphosphino)palladium (29.8 mg, 0.026 mmol), and **14** (152.2 mg, 0.450 mmol) in degassed dioxane was added 1.0 mL of a 2 M sodium carbonate solution. The mixture was flushed with nitrogen and heated to 110 °C for 12 h. The solution was cooled to room temperature, added to silica (5 g), and concentrated. The product was purified by normal phase chromatography, eluting with EtOAc/hexanes (0−100% gradient) to yield 188.8 mg of **20b** (93%) as a solid. MS (ESI) 450 $(M + H)^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.26 (s, 1 H), 8.43 (s, 1 H), 7.79−7.90 (m, 4 H), 7.64 (d, J = 2.01 Hz, 1 H), 7.52−7.59 (m, 1 H), 7.39−7.50 (m, 4 H), 3.13 (s, 3 H).

***N*-[4-[1-(4-Fluorophenyl)-1*H*-indazol-5-yl]-3-(trifluoromethyl)-phenyl]-1-propanesulfonamide (20c).** To a solution of **18c** (assumed 0.495 mmol), tetrakis(triphenylphosphino)palladium (29.8 mg, 0.026 mmol), and **14** (152.2 mg, 0.450 mmol) in degassed dioxane was added 1.0 mL of a 2 M sodium carbonate solution. The mixture was flushed with nitrogen and heated to 110 °C for 12 h. The solution was cooled to room temperature, added to silica (5 g), and concentrated. The product was purified by normal phase chromatography, eluting with EtOAc/hexanes (0−100% gradient) to yield 96.3 mg of **20c** (49%) as a solid. MS (ESI) 478 $(M + H)^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.29 (s, 1 H), 8.43 (s, 1 H), 7.77−7.91 (m, 4 H), 7.64 (d, J = 2.01 Hz, 1 H), 7.51−7.59 (m, 1 H), 7.38−7.50 (m, 4 H), 3.15−3.26 (m, 2 H), 1.74 (sxt, J = 7.51 Hz, 2 H), 0.98 (t, J = 7.42 Hz, 3 H).

***N*-[4-[1-(4-Fluorophenyl)-1*H*-indazol-5-yl]-3-(trifluoromethyl)-phenyl]benzenesulfonamide (20d).** To a solution of **18d** (assumed 0.495 mmol), tetrakis(triphenylphosphino)palladium (29.8 mg, 0.026 mmol), and **14** (152.2 mg, 0.450 mmol) in degassed dioxane was added 1.0 mL of a 2 M sodium carbonate solution. The mixture was flushed with nitrogen and heated to 110 °C for 12 h. The solution was cooled to room temperature, added to silica (5 g), and concentrated. The product was purified by normal phase chromatography, eluting with EtOAc/hexanes (0−100% gradient) to yield 81.3 mg of **20d** (35%) as a solid. MS (ESI) 511 $(M + H)^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.87 (s, 1 H), 8.40 (s, 1 H), 7.77−7.91 (m, 5 H), 7.75 (s, 1 H), 7.56−7.72 (m, 3 H), 7.52 (d, J = 2.01 Hz, 1 H), 7.40−7.48 (m, 3 H), 7.31−7.40 (m, 2 H).

4-(1,1-Dimethylethyl)-*N*-[4-[1-(4-fluorophenyl)-1*H*-indazol-5-yl]-3-(trifluoromethyl)phenyl]benzenesulfonamide (20e). To a solution of **18e** (assumed 0.495 mmol), tetrakis(triphenylphosphino)palladium (29.8 mg, 0.026 mmol), and **14** (152.2 mg, 0.450 mmol) in degassed dioxane was added 1.0 mL of a 2 M sodium carbonate solution. The mixture was flushed with nitrogen and heated to 110 °C for 12 h. The solution was cooled to room temperature, added to silica (5 g), and concentrated. The product was purified by normal phase chromatography, eluting with EtOAc/hexanes (0−100% gradient) to yield 28.8 mg of **20e** (11%) as a solid. MS (ESI) 568 $(M + H)^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.84 (s, 1 H), 8.39 (s, 1 H), 7.72−7.88 (m, 6 H), 7.64 (d, J = 8.42 Hz, 2 H), 7.29−7.55 (m, 6 H), 1.27 (s, 9 H).

***N*-[4-[1-(4-Fluorophenyl)-1*H*-indazol-5-yl]-3-(trifluoromethyl)-phenyl]-2,4,6-tris(1-methylethyl)benzenesulfonamide (20f).** To a solution of **18f** (assumed 0.495 mmol), tetrakis(triphenylphosphino)palladium (29.8 mg, 0.026 mmol), and **14** (152.2 mg, 0.450 mmol) in degassed dioxane was added 1.0 mL of a 2 M sodium carbonate solution. The mixture was flushed with nitrogen and heated to 110 °C for 12 h. The solution was cooled to room temperature, added to silica (5 g), and concentrated. The product was purified by normal phase chromatography, eluting with EtOAc/hexanes (0−100% gradient) to yield 43.2 mg of **20f** (15%) as a solid. MS (ESI) 638 $(M + H)^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.75 (s, 1 H), 8.40 (s, 1 H), 7.77−7.87 (m, 3 H), 7.74 (s, 1 H), 7.44 (t, J = 8.79 Hz, 2 H), 7.24−7.40 (m, 6 H), 4.18 (dt, J = 13.37, 6.68 Hz, 2 H), 2.92 (dt, J = 13.73, 6.87 Hz, 1 H), 1.18 (dd, J = 6.68, 4.30 Hz, 18 H).

Compounds 21a−f were synthesized as part of a larger array. 4-[1-(4-Fluorophenyl)-1*H*-indazol-5-yl]-*N*-methyl-*N*-phenyl-3-(trifluoromethyl)benzenesulfonamide (21a). To a solution of **19b** (25 mg, 0.049 mmol) and potassium carbonate (33.8 mg, 0.244 mmol) in DMF (1.0 mL) was added methyl iodide (15 μL, 0.244 mmol). The mixture was allowed to stir at room temperature for 48 h. The mixture was filtered and purified by reverse phase HPLC (30−100% MeCN/water with 0.05% TFA) to yield 16.0 mg of **21a** (61%) as a solid. MS (ESI) 526 $(M + H)^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 3.22 (s, 3 H), 7.21 (d, J = 7.51 Hz, 2 H), 7.32−7.52 (m, 6 H), 7.68 (d, J = 1.10 Hz, 1 H), 7.74 (d, J = 8.06 Hz, 1 H), 7.81−7.94 (m, 5 H), 8.48 (s, 1 H).

***N*-Ethyl-4-[1-(4-fluorophenyl)-1*H*-indazol-5-yl]-*N*-phenyl-3-(trifluoromethyl)benzenesulfonamide (21b).** To a solution of **19b** (25 mg, 0.049 mmol) and potassium carbonate (33.8 mg, 0.244 mmol) in DMF (1.0 mL) was added ethyl iodide (20 μL, 0.244 mmol). The mixture was allowed to stir at room temperature for 48 h. The mixture was filtered and purified by reverse phase HPLC (30−100% MeCN/water with 0.05% TFA) to yield 16.1 mg of **21b** (61%) as a solid. MS (ESI) 540 $(M + H)^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.02 (t, J = 7.05 Hz, 3 H), 3.68 (q, J = 7.08 Hz, 2 H), 7.16 (d, J = 6.41 Hz, 2 H), 7.35−7.54 (m, 6 H), 7.71−7.79 (m, 2 H), 7.81−7.98 (m, 5 H), 8.48 (s, 1 H).

4-[1-(4-Fluorophenyl)-1*H*-indazol-5-yl]-*N*-phenyl-*N*-propyl-3-(trifluoromethyl)benzenesulfonamide (21c). To a solution of **19b** (25 mg, 0.049 mmol) and potassium carbonate (33.8 mg, 0.244 mmol) in DMF (1.0 mL) was added *n*-propyl bromide (25 μL, 0.244 mmol). The mixture was allowed to stir at room temperature for 48 h. The mixture was filtered and purified by reverse phase HPLC (30−100% MeCN/water with 0.05% TFA) to yield 17.1 mg of **21c** (63%) as a solid. MS (ESI) 554$(M + H)^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.87 (t, J = 7.33 Hz, 3 H), 1.36 (sxt, J = 7.14 Hz, 2 H), 3.59 (t, J = 6.87 Hz, 2 H), 7.16 (d, J = 6.59 Hz, 2 H), 7.34−7.54 (m, 6 H), 7.69−7.78 (m, 2 H), 7.81−7.99 (m, 5 H), 8.48 (s, 1 H).

4-[1-(4-Fluorophenyl)-1*H*-indazol-5-yl]-*N*-(1-methylethyl)-*N*-phenyl-3-(trifluoromethyl)benzenesulfonamide (21d). To a solution of **19b** (25 mg, 0.049 mmol) and potassium carbonate (33.8 mg, 0.244 mmol) in DMF (1.0 mL) was added isopropyl iodide (25 μL, 0.244 mmol). The mixture was allowed to stir at room

temperature for 48 h. The mixture was filtered and purified by reverse phase HPLC (30−100% MeCN/water with 0.05% TFA) to yield 16.0 mg of **21d** (59%) as a solid. MS (ESI) 554 $(M + H)^+$. NMR (400 MHz, DMSO-d_6) δ ppm 1.03 (d, $J = 6.78$ Hz, 6 H), 4.46−4.69 (m, 1 H), 7.04−7.15 (m, 2 H), 7.40−7.57 (m, 6 H), 7.75 (d, $J = 8.06$ Hz, 1 H), 7.82−7.99 (m, 5 H), 8.07−8.13 (m, 1 H), 8.48 (s, 1 H).

***N*-Butyl-4-[1-(4-fluorophenyl)-1*H*-indazol-5-yl]-*N*-phenyl-3-(trifluoromethyl)benzenesulfonamide (21e).** To a solution of **19b** (25 mg, 0.049 mmol) and potassium carbonate (33.8 mg, 0.244 mmol) in DMF (1.0 mL) was added *n*-butyl iodide (30 μL, 0.244 mmol). The mixture was allowed to stir at room temperature for 48 h. The mixture was filtered and purified by reverse phase HPLC (30−100% MeCN/water with 0.05% TFA) to yield 17.8 mg of **21e** (63%) as a solid. MS (ESI) 568 $(M + H)^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.73−0.92 (m, 3 H), 1.27−1.36 (m, 4 H), 3.63 (t, $J = 5.95$ Hz, 2 H), 7.16 (d, $J = 6.59$ Hz, 2 H), 7.33−7.54 (m, 6 H), 7.68−7.78 (m, 2 H), 7.80−7.98 (m, 5 H), 8.48 (s, 1 H).

4-[1-(4-Fluorophenyl)-1*H*-indazol-5-yl]-3-(trifluoromethyl)aniline (22). To a solution of **14** (2.0 g, 5.9 mmol), tetrakis(triphenylphosphino)palladium (340 mg, 0.29 mmol), and 4-bromo-3-(trifluoromethyl)aniline (1.56 g, 6.5 mmol) in degassed dioxane (50 mL) was added 10.0 mL of a 2 M sodium carbonate solution. The mixture was flushed with nitrogen and heated to 110 °C for 12 h. The solution was cooled to room temperature and concentrated. The product residue was purified by normal phase chromatography, eluting with EtOAc/hexanes (0−100% gradient) to yield 1.77 g of **22** (79%) as a solid. MS (APCI) 372 $(M + H)^+$. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.21 (s, 1 H), 7.69−7.78 (m, 3 H), 7.67 (d, $J = 8.56$ Hz, 1 H), 7.35−7.44 (m, 1 H), 7.20−7.31 (m, 2 H), 7.16 (d, $J = 8.20$ Hz, 1 H), 7.06 (d, $J = 2.50$ Hz, 1 H), 6.87 (dd, $J = 8.20$, 2.32 Hz, 1 H), 3.91 (br s, 2 H).

Compounds 23a−f were synthesized as part of a larger array. *N*-[4-[1-(4-Fluorophenyl)-1*H*-indazol-5-yl]-3-(trifluoromethyl)-phenyl]-1-phenylmethanesulfonamide (23a). A solution of **22** (25 mg, 0.067 mmol) in pyridine (2 mL) was added to phenylmethanesulfonyl chloride (38.5 mg, 0.202 mmol). The solution was allowed to stir at room temperature overnight. The solution was concentrated and purified by HPLC (30−100% MeCN/water with 0.05% TFA) to yield 15.8 mg of **23a** (45%) as a solid. MS (ESI) 526 $(M + H)^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.31 (s, 1 H), 8.44 (s, 1 H), 7.81−7.90 (m, 3 H), 7.80 (s, 1 H), 7.27−7.52 (m, 11 H), 4.62 (s, 2 H)

***N*-[4-[1-(4-Fluorophenyl)-1*H*-indazol-5-yl]-3-(trifluoromethyl)-phenyl]-2-propanesulfonamide (23b).** A solution of **22** (25 mg, 0.067 mmol) in pyridine (2 mL) was added to phenylmethanesulfonyl chloride (28.8 mg, 0.202 mmol). The solution was allowed to stir at room temperature overnight. The solution was concentrated and purified by HPLC (30−100% MeCN/water with 0.05% TFA) to yield 7.9 mg of **23b** (25%) as a solid. MS (ESI) 478 $(M + H)^+$. ^{1}H NMR (400 MHz, DMSO-*d*6) δ ppm 10.31 (s, 1 H), 8.44 (s, 1 H), 7.81−7.90 (m, 3 H), 7.80 (s, 1 H), 7.27−7.52 (m, 11 H), 4.62 (s, 2 H)

***N*-[4-[1-(4-Fluorophenyl)-1*H*-indazol-5-yl]-3-(trifluoromethyl)-phenyl]-3-[(trifluoromethyl)oxy]benzenesulfonamide (23c).** A solution of **22** (25 mg, 0.067 mmol) in pyridine (2 mL) was added to phenylmethanesulfonyl chloride (52.6 mg, 0.202 mmol). The solution was allowed to stir at room temperature overnight. The solution was concentrated and purified by HPLC (30−100% MeCN/water with 0.05% TFA) to yield 21.0 mg of **23c** (53%) as a solid. MS (ESI) 594 $(M - H)^-$. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.95 (s, 1 H), 8.41 (s, 1 H), 7.66−7.91 (m, 8 H), 7.29−7.53 (m, 6 H)

***N*-[4-[1-(4-Fluorophenyl)-1*H*-indazol-5-yl]-3-(trifluoromethyl)-phenyl]-3-(methyloxy)benzenesulfonamide (23d).** A solution of **22** (25 mg, 0.067 mmol) in pyridine (2 mL) was added to phenylmethanesulfonyl chloride (41.7 mg, 0.202 mmol). The solution was allowed to stir at room temperature overnight. The solution was concentrated and purified by HPLC (30−100% MeCN/water with 0.05% TFA) to yield 10.8 mg of **23d** (30%) as a solid. MS (ESI) 540 $(M - H)^-$. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.84 (s, 1 H), 8.40 (s, 1 H), 7.78−7.87 (m, 3 H), 7.76 (s, 1 H), 7.50−7.59 (m, 2 H), 7.30−7.49 (m, 7 H), 7.24 (dd, $J = 8.24$, 2.01 Hz, 1 H), 3.80 (s, 3 H).

***N*-[4-[1-(4-Fluorophenyl)-1*H*-indazol-5-yl]-3-(trifluoromethyl)-phenyl]-3-(trifluoromethyl)benzenesulfonamide (23e).** A solution of **22** (25 mg, 0.067 mmol) in pyridine (2 mL) was added to phenylmethanesulfonyl chloride (49.4 mg, 0.202 mmol). The solution was allowed to stir at room temperature overnight. The solution was concentrated and purified by HPLC (30−100% MeCN/water with 0.05% TFA) to yield 10.6 mg of **23e** (27%) as a solid. MS (ESI) 578 $(M - H)^-$. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.96 (s, 1 H), 8.41 (s, 1 H), 8.11 (dd, $J = 14.83$, 8.06 Hz, 2 H), 8.04 (s, 1 H), 7.89 (t, $J = 7.87$ Hz, 1 H), 7.79−7.86 (m, 3 H), 7.74 (s, 1 H), 7.31−7.52 (m, 6 H).

***N*-[4-[1-(4-Fluorophenyl)-1*H*-indazol-5-yl]-3-(trifluoromethyl)-phenyl]-3-thiophenesulfonamide (23f).** A solution of **22** (50 mg, 0.135 mmol) in pyridine (2 mL) was added to phenylmethanesulfonyl chloride (73.8 mg, 0.404 mmol). The solution was allowed to stir at room temperature overnight. The solution was concentrated and purified by HPLC (30−100% MeCN/water with 0.05% TFA) to yield 39.4 mg of **23f** (56%) as a solid. MS (ESI) 516 $(M - H)^-$. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.80 (s, 1 H), 8.41 (s, 1 H), 8.28−8.34 (m, 1 H), 7.74−7.87 (m, 5 H), 7.54 (d, $J = 1.83$ Hz, 1 H), 7.31−7.51 (m, 6 H).

Library Design. The library design procedure utilized for these chemistries is similar to one used previously.[20] This process was carried out in three steps: (1) enumeration of the virtual library, (2) evaluation of the compounds using a 3D virtual screening procedure, and (3) monomer selection based on the results. First, a large virtual library of compounds was enumerated using all commercially and in-house available building blocks appropriate for the chemistry of interest. Each enumerated virtual library was constructed using the CombiLibMaker software (version 4.3.2) (Tripos, Inc., St. Louis, MO, 2005). Our evaluation procedure required the generation of 3D conformers for each member of the virtual libraries. The database of compound conformations was constructed using CONCORD (version 5.1.2) to generate an initial 3D representation of each compound followed by conformer ensemble generation using the OMEGA program (version 1.8.1) with the constraint of a maximum of 200 low energy conformers per compound. A low energy conformer was defined as a conformation with a calculated energy of no more than 5 kcal/mol greater than the calculated minimum energy conformation.[21] For chiral compounds that lacked stereochemical designations, each enantiomer was created and conformationally expanded. Using the ROCS program (version 2.0), we carried out a shape overlay of each of the virtual conformers onto the conformation of cortivazol as dictated by a GR structural model.[22] For each of the virtual compounds, we selected the conformer with the best shape Tanimoto score. That particular conformer, preoriented in the active site by the shape algorithm, was energy minimized by full geometry optimization in the active site of the protein using the in-house program MVP.[23] Using the Tanimoto shape scores, the optimized energy values, and visual inspection of the bound conformations of the virtual compounds, we selected monomers that were appropriate for the chosen chemistry and provided compounds characteristic of GR modulators.

Structural Model of GR Bound with Cortivazol. Prior to the availability of a GR crystal structure bound with cortizavol, we utilized a structural model of the same in our initial library design efforts as well as many of the early structure-guided design procedures. This GR structural model was derived through the manipulation of key "A-ring" residues in the crystal structure of GR bound with dexamethasone.[24] As an initial starting point, we manually overlaid a CONCORD generated conformation (version 5.1.2) of cortivazol onto the crystal-bound conformation of dexamethasone and transposed that

oriented cortivazol conformer into the GR crystal after removing the GR-bound dexamethasone molecule.[21a] We then carried out a manual amino acid side chain conformer search for R611 and Q570 using the HOMOLOGY package available in the INSIGHTII program; the conformers were selected from an in-house database of amino acid side chain conformers that had been integrated into INSIGHTII. We selected conformers of R611 and Q570 that provided adequate space for the presence of the phenylindazole portion of cortivazol. After initial positioning of cortivazol in the GR active site and selection of appropriate residue conformers, we carried out a full geometry optimization of the cortivazol and all residues in the protein within 16 Å of the active site using the MVP program.[23] This procedure resulted in a structural model suitable for the purposes of library and structure-guided design of phenylindazole-containing compounds.

Docking Procedure for Structure-Guided Design. Initially, we utilized the GR/cortivazol structural model for our docking procedure; however, when the GR crystal structure bound with cortivazol became available, we exclusively used that conformation of the protein for our modeling purposes. Target compounds were represented using SMILES strings, and an initial starting conformation was generated using CONCORD (version 5.1.2).[21a,b] The SMILES strings for these compounds were written such that the atoms and the connectivity of the phenylindazole moiety preceded those of the remainder of the compound. This consistent atom numbering allowed for easy orientation of the initial conformation onto the bound cortivazol compounds in the GR active site. Once an initial conformation was generated in MOL2 format, the conformer was oriented in the GR active site via a simple atom-number-based matching procedure in MVP followed by coordinate transpositioning of the target compound using the same program.[23] This matching procedure is simple, requiring only a one-to-one correspondence of the atom numbers in both compounds and an appropriate translation/rotation matrix. Once adequately oriented in the active site, the energy-minimized conformation of the target compound was derived using a sequential build-up, greedy-based docking algorithm available in the MVP program. The atom located at the 5-position of the phenylindazole was used as the "anchor point" from which the remainder of the compound was "grown" into the active site. Scoring of the final ensemble of docked conformations was accomplished thermodynamically using a ΔG of binding calculated by MVP, the difference in the calculated, Boltzman-weighted energy of the bound and unbound-solvated state of the compound. This calculated binding energy was used as a guide in evaluating and rank-ordering compounds of interest for synthesis.

Pharmacokinetic Studies. Pharmacokinetic (PK) studies were performed using male CD rats and male DBA/1 mice (Charles River Laboratories, U.K.). The dose formulation for intravenous administration and for oral administration to the rat was 10% DMSO/45% polyethylene glycol 200/45% water (v/v) administered at 1 mg/kg for both routes. The dose formulation for oral administration to the mouse was 1% DMSO/99% of 1% (w/v) methylcellulose administered at 3 mg/kg. Following administration blood samples of approximately 0.2 mL volume were collected into heparin coated tubes at time points up to 7 h. Plasma samples were harvested and stored at −20 °C prior to analysis.

Plasma samples were precipitated using acetonitrile containing an analogue to act as an analytical internal standard and the resulting extracts analyzed using LC−MS/MS analysis. Plasma standard curves were generated by plotting peak area ratio of analyte to internal standard against nominal concentrations. The acceptance criterion for inclusion of a calibration standard was ±20% of the nominal value.

Pharmacokinetic parameters were determined using an in-house developed macro operating within Microsoft Excel. Calculations were performed using noncompartmental analysis and using standard formula.

Plasma Protein Binding. Plasma protein binding was determined using a modified ultrafiltration technique according to the following method. The reference is as follows: Taylor, S. J.; Harker, A. Modification of the Ultrafiltration Technique To Overcome Solubility and Nonspecific Binding Challenges Associated with the Measurement of Plasma Protein Binding of Corticosteroids. *J. Pharm. Biomed. Anal.* **2006**, *41*, 299−303.

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Supporting Information Available: Analytical data and spectra for compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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