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Function-regulating pharmacophores in a sulfonamide class of glucocorticoid receptor agonists

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ABSTRACT

A class of α-methyltryptamine sulfonamide glucocorticoid receptor (GR) modulators was optimized for agonist activity. The design of ligands was aided by molecular modeling, and key function-regulating pharmacophoric points were identified that are critical in achieving the desired agonist effect in cell based assays. Compound **27** was profiled *in vitro* and *in vivo* in models of inflammation. Analogs could be rapidly prepared in a parallel approach from aziridine building blocks.

The glucocorticoid receptor (GR) is a member of the nuclear hormone receptor superfamily (NR) that also includes the mineralocorticoid (MR), progesterone (PR), estrogen (ER), and androgen (AR) receptors.[1,2] Endogenous glucocorticoid (GC) agonists, such as cortisol, play important roles in homeostasis. They also participate in the resolution of inflammatory conditions by preventing the transcription of pro-inflammatory genes that lead to the synthesis of cytokines (e.g., IL-1, IL-2, IL-6 and TNF), and adhesion molecules.[3] The anti-inflammatory effects of endogenous GCs prompted the development of synthetic GC agonists such as prednisolone and dexamethasone (Fig. 1); however, the use of GC therapy has been limited due to the side effects associated with chronic dosing.[4] These side effects occur as a result of homeostatic disruption and include alterations in fluid and electrolyte balance, edema, weight gain, hypertension, muscle weakness, diabetes, and/or steroid induced osteoporosis.[5] Furthermore, cross-reactivity of GCs with other NRs, especially MR and PR, may also lead to a number of side effects.

Over the last decade, we and others have reported on a number of non-steroidal GR ligands targeting an improved anti-inflammatory profile with reduced side effects.[6] We have also reported that for a trifluoromethyl carbinol series of GR modulators (compound

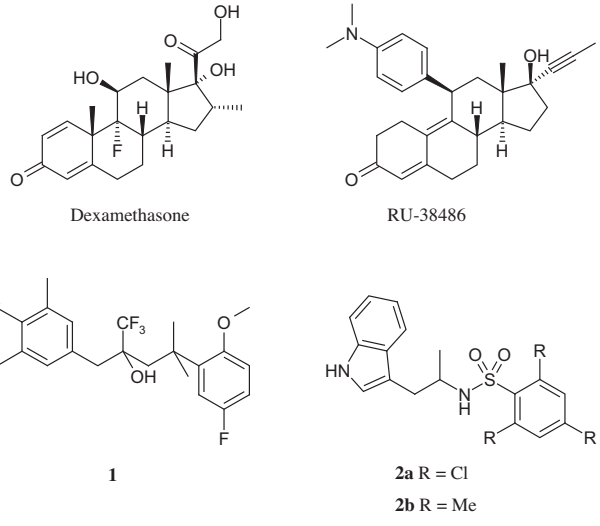

Figure 1. Synthetic glucocorticoid ligands: dexamethansone (agonist), RU-38486 (antagonist), **1** (agonist), **2a** and **2b** (GR modulators).

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1) small structural changes can have a range of effects on potency and efficacy in cell based assays for agonist activity while GR binding potency is maintained.[7] These changes are in contrast to the classical GC antagonist, RU-38486 (Fig. 1), which upon binding to the GR ligand-binding-domain (LBD) causes helix 12 to adopt an open conformation resulting in functional antagonism or 'active antagonism'.[8] Similarly, the sulfonamide series of GC modulators described in this report (e.g., compound **2a**) display a range of effects on potency and efficacy in cell based assays for agonist activity while GR binding potency is often maintained.

Our initial report disclosed the identification of α-methyltryptamine sulfonamide derivatives (e.g., **2a** and **2b**) as potent GR ligands, that were optimized for binding potency and NR selectivity.[9] These compounds failed to display the desired agonist activity in functional assays and were assumed to be GR antagonists. Since our initial publication, a number of groups have reported modifications to the sulfonamide template that have afforded GR agonist activity.[10,11] In this Letter, we describe our SAR findings for this class of GR ligands. Specifically, we report that the placement of function-regulating pharmacophoric points in three distinct regions of this scaffold afford a switch in functional activity providing potent and efficacious GR agonists relative to dexamethasone in a cellular assay.[12,13]

The IC_{50} values reported herein for binding to GR, MR and PR were determined by using a fluorescence polarization competitive binding assay.[14] The GR and MR assays measured the ability of test compounds to compete with tetramethylrhodamine (TAMRA)-labeled dexamethasone. The PR binding assay was run using TAMRA-labeled mifepristone (RU-38486). Anti-inflammatory activity (transrepression) is reported as the inhibition of IL-6 production in human foreskin fibroblasts (HFF) in response to stimulation by the pro-inflammatory cytokine IL-1.[15] It is known that circulating IL-6 levels increase during an inflammatory response and IL-6 production can be inhibited by GCs such as dexamethasone. In the IL-6 functional assay, potency and efficacy are reported, and efficacy is expressed as a percentage of the maximum response observed for dexamethasone.

To guide our SAR and placement of pharmacophoric points we docked compound (***S***)-**2b** into the published GR-LBD binding pocket (Fig. 2).[16] A proposed binding pose of compound (***S***)-**2b** (Fig. 2b) revealed several interesting features. The central NH group of (***S***)-**2b** forms a key H-bond with Asn564 (helix 12) mimicking the interaction seen with the 11β-hydroxyl group of dexamethasone (Fig. 2).

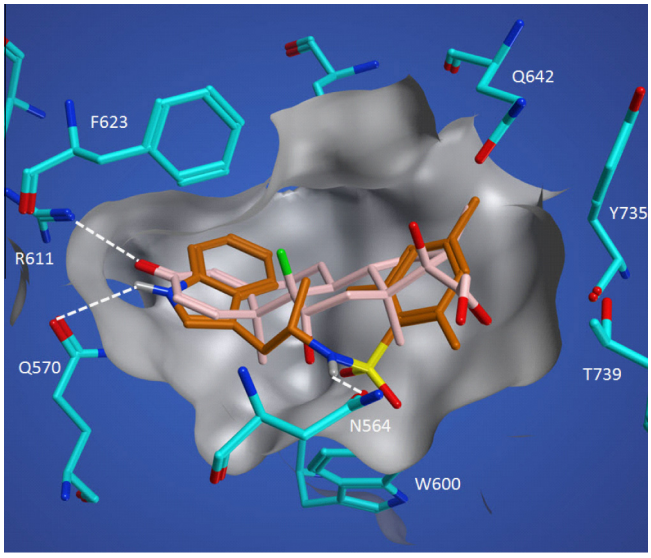


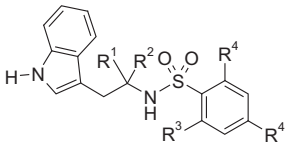
Figure 2. Overlay of docking pose of compound (***S***)-**2b** (orange) with the co-complex x-ray structure of GR-LBD and dexamethasone (rose). Docking was performed using Glide[17] and the picture was generated with MOE.[18] Dotted lines represent hydrogen bonds.

The indole moiety of (***S***)-**2b** overlays with the steroid A-ring of dexamethasone forming π-stacking interactions with Phe623. The tri-substituted phenyl occupies the space of the steroid D-ring. Based on this analysis and our experience optimizing the trifluoromethyl carbinol series (compound **1**) we targeted three strategies for facilitating a functional switch of **2b**. These included: (i) introduction of a polar residue on the phenyl sulfonamide moiety which could engage the Asn564, (ii) replacement of the α-methyl group with a trifluoromethyl moiety to improve the hydrogen bond potential of the sulfonamide N–H, and (iii) placement of a polar residue, useful as a steroid A-ring mimetic, on the indole ring to engage the Arg611 and Gln570 pair. As a proof of concept, compound **3**, containing an aniline moiety designed to engage Asn564, displayed potent GR binding, good potency (IC_{50} = 120 nM) and partial efficacy (59%) in the IL-6 assay. In comparison, compounds **2a** and **2b** are only 12 and eightfold less potent in the GR binding assay, respectively, but were not active in the IL-6 assay (max. concn = 2000 nM). Replacement of the α-methyl group of **3** with a trifluoromethyl group (compound **4**) further improved potency and efficacy in the IL-6 assay relative to compound **3**. Interestingly, the CF_3 modification alone was not sufficient to afford potency or efficacy in the IL-6 assay for compound **5**, the 2,4,6-trichlorophenyl substituted sulfonamide. However, weak efficacy in the IL-6 assay was observed for compound **6**, the 2,4,6-trimethylphenyl substituted sulfonamide. The gem-dimethyl analog **7** also failed to demonstrate efficacy in the IL-6 assay. Clearly, these results highlight the value in a multi-component SAR approach to achieving functional activity. It should be noted that compounds **3**, **4** and **7** demonstrated excellent selectivity relative to dexamethasone in the PR and MR assays. For example, compound **3** was 102-fold more selective for GR over MR in the binding assays (Table 1).

Finally, we focused our attention on the indole moiety which modeling suggests aligns with the same pocket occupied by the A-ring of dexamethasone. Our choice of functional groups was driven by our experience in the trifluoromethyl carbinol series (compound **1**).[7b] In the carbinol series, the cyano group of **1** can serve as a function-regulating pharmacophore due to critical polar interactions with the Arg611/Gln570 pair and a lipophilic component (methyl groups) in this same region can influence the level of agonist activity and efficacy observed. The use of a cyano group as a replacement for the A-ring carbonyl is known from other nuclear hormone receptors, like progesterone[19] and androgen[20] receptor.

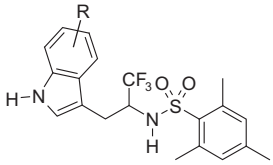
To study polar and lipophilic modifications to the indole moiety we chose the 2,4,6-trimethylphenyl sulfonamide analog **6**, and prepared methylindoles **8**–**11** and cyanoindoles **12**–**15** (Table 2). Interestingly, the methylated indole analogs **8**–**11** are all of similar potency in the GR binding assay (GR IC_{50}'s = 10–37 nM). However, a range of GR binding potencies is observed for the cyano analogs **12**–**15**. Thus, the 4-cyanoindole **12** was not potent at the highest concentration tested (GR IC_{50} >10 μM). However, the 7-cyanoindole **15** (GR IC_{50} = 10 nM) is 28 and 32-fold more potent than 6-cyanoindole **14** and 5-cyanoindole **13**, respectively. Consistent with a lipophilic component in this region useful for improving functional activity, the 5-methylindole (compound **9**) afforded partial agonist activity (60% efficacy) in the functional assay. At the same time, consistent with our binding hypothesis (Fig. 2b) that a polar component in the steroid A-ring region is useful for functional activity, the 7-cyanoindole analog **15**, which can engage the Arg611/Gln570 pair, displayed potent binding activity and partial agonism (70% efficacy) in the functional assay. Compound **16**, containing both of these function-regulating pharmacophoric points (the 5-methyl-7-cyanoindole), gave further improvements

Table 1
Aniline analogs display partial agonist activity

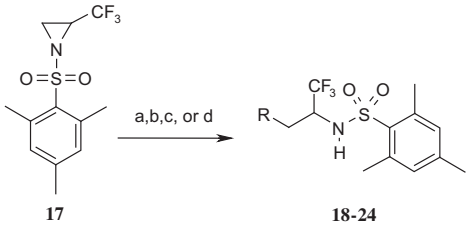


Compound	R^1	R^2	R^3	R^4	GR IC_{50} (nM)	PR IC_{50} (nM)	MR IC_{50} (nM)	IL-6 IC_{50} (nM)	IL-6 efficacy (%)
Dex	—	—	—	—	3.5	>2000	33	0.5	96
2a	CH_3	H	Cl	Cl	64	570	130	>2000	0
2b	CH_3	H	CH_3	CH_3	40	1400	290	>2000	0
3	CH_3	H	NH_2	Cl	5	>2000	510	120	59
4	CF_3	H	NH_2	Cl	10	>2000	270	56	82
5	CF_3	H	Cl	Cl	35	3500	80	>2000	0
6	CF_3	H	CH_3	CH_3	15	3600	80	>2000	30
7	CH_3	CH_3	NH_2	Cl	15	5300	470	>2000	0

Table 2
Substituted C3-linked indole analogs display agonist activity



Compound	R	GR IC_{50} (nM)	PR IC_{50} (nM)	MR IC_{50} (nM)	IL-6 IC_{50} (nM)	IL-6 efficacy (%)
6	H	15	3600	80	>10,000	30
8	4-Methyl	18	>2000	80	>2000	0
9	5-Methyl	10	6000	90	210	60
10	6-Methyl	37	>2000	140	>2000	5
11	7-Methyl	20	5900	90	>10,000	25
12	4-Cyano	>10000	>10,000	170	NT	NT
13	5-Cyano	320	>10,000	210	>10,000	0
14	6-Cyano	280	2000	280	>10,000	15
15	7-Cyano	10	540	70	45	70
16	5-Methyl-7-cyano	5	750	110	15	85



Scheme 1. Reagents and conditions: (a) indole, NaH, DMF; (b) $PhNH_2$, KHMDS, DMSO; (c) PhOH, NaH, DMF; (d) PhSH, NaH, DMF.

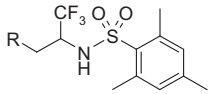
in GR potency (GR IC_{50} = 5 nM) and IL-6 activity (IC_{50} = 15 nM, 85% efficacy) as compared to the mono-substituted indoles **9** and **15**. Within this SAR, for compounds **6**, **8**–**16**, PR binding potency (IC_{50} = 2000 to >10000 nM) was similar to earlier analogs **3**–**5**, and **7**. MR/GR selectivity, on the other hand, for analogs **8**–**11** and **13**–**15** was between 1 and ninefold and only compound **16** is 22-fold selective. Interestingly, analog **12** was not active in either the GR or PR binding assays yet displayed good MR potency (IC_{50} = 170 nM). The earlier aniline compounds **3**, **4**, and 7 showed increased MR/GR selectivity, supporting our hypothesis for the role of the aniline.

The synthesis of the compounds described in the present work has been reported elsewhere.[13] However, one aspect to this chemistry should be noted since it enabled the rapid production of screening libraries and the exploration of the SAR within this class of analogs beyond C3-linked indoles as A-ring mimetics (Scheme 1). The preparation and ring opening of benzenesulfonylaziridines, such as compound **17**, is well known.[21] Exemplified by compound **17** (Scheme 1), upon treatment with substituted indoles, phenol or thiophenol in the presence of NaH in DMF and aniline in the presence of KHMDS, aziridine building blocks provided ring opened analogs **18**–**24** (Table 3).

Indoles **18**–**21** displayed a range of GR potency and poor functional activity. Compound **18** was comparable to the C3-linked indole compound **6** in the GR, PR and MR binding assays but lacked functional activity (Table 3). The 4-azaindole **19** and 3-cyanoindole **20** displayed weak agonist activity in the functional assay and further improvements would be necessary. Analogs **22**–**24** displayed encouraging GR binding potency but lacked functional activity and subsequent analogs were pursued using parallel synthesis and will be the topic of a future report.

Next, we chose to optimize the N-linked indole analog **18** with the goal of building in agonist activity based on the strategy outlined earlier. Select compounds are shown in Table 4. Compounds **25**–**27** all had excellent activity in the GR binding assay, but only compounds **26** and **27** displayed good potency ($IC_{50} \leqslant 10$ nM) and efficacy (87%) in the IL-6 functional assay and have a similar profile in the binding and functional assay as compound **16**. Furthermore, compound **27** demonstrated excellent PR and MR selectivity of 1500 and 330-fold, respectively.

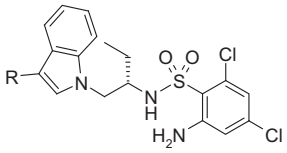
Table 3
Aziridine Library SAR



Compound	R	GR IC_{50} (nM)	PR IC_{50} (nM)	MR IC_{50} (nM)	IL-6 IC_{50} (nM)	IL-6 efficacy (%)
6	Indole[a]	15	3600	80	>2000	30
18	Indole[b]	25	2400	120	>10,000	0
19	4-Azaindole[b]	340	>10,000	220	>2000	36
20	3-Cyanoindole[b]	15	530	65	>2000	25
21	4-Cyanoindole[b]	60	700	100	>10,000	0
22	PhNH–	95	3200	260	>10,000	0
23	PhO–	210	6400	340	>10,000	0
24	PhS–	20	2000	280	>10,000	0

[a] Denotes C3-linked indole.
[b] Denotes N-linked indoles.

Table 4
Optimization of N-linked indoles for agonist and in-vivo activity



Compound	R	GR IC_{50} (nM)	PR IC_{50} (nM)	MR IC_{50} (nM)	IL-6 IC_{50} (nM)	IL-6 efficacy (%)	CYP3A4[a] IC_{50} (nM)	HLM $t_{1/2}$ (min)
25	H	2	>10,000	510	>2000	46	570	3
26	CH3	2	5000	260	10	87	940	2
27	CN	1	1500	330	7	87	5800	3

[a] Substrate 7-benzyloxy-4-trifluoromethylcoumarin (BFC).

Compound **27** was profiled in a LPS stimulated TNF-α mouse model and demonstrated an ED_{50} of 10 mg/kg. In a collagen antibody-induced arthritis model (CAIA) compound **27** displayed an ED_{50} of 100 mg/kg. However, in general, this series of compounds displayed high *in vitro* microsomal clearance and potent CYP inhibition which is consistent with other reports that have appeared in the literature for this class of compounds.

In summary, we have described a general strategy for designing GR agonists involving the strategic placement of function-regulating pharmacophoric points in three distinct regions of a sulfonamide class of GC ligands. Compound **27** is highlighted as being potent in a LPS mouse model and a CAIA model. Taken together, these findings have made this series attractive for further studies; however, a number of *in vitro* parameters will need to be addressed before compounds from this class can advance further.

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14. GR, PR and MR binding assays were performed in a fluorescence polarization format that measures competition for binding to the nuclear receptor, present in lysates of baculovirus-infected insect cells, between a test compound and a fluorescently labeled receptor ligand, or probe. IC_{50} values were determined by fitting the fluorescence polarization signal data to a 4-parameter logistic equation. All IC_{50} values shown represent the mean of at least two independent determinations. Repeated testing of reference compounds in these assays demonstrate typical IC_{50} standard deviations of 20–40% about the mean.
15. Human foreskin fibroblasts are stimulated with 1 ng/mL recombinant human IL-1 in the presence of test compound. After 24 h, the degree of GR agonist activity (transrepression) is determined by measuring IL-6 in the tissue culture media and calculating IC_{50} values. Top concentration in the assay was 2000 nM.
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