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Discovery of novel nonsteroidal glucocorticoid receptor modulators

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Abstract—A new class of selective nonsteroidal glucocorticoid receptor modulators typified by *N*-{3-[benzyl-(4-chloro-2-fluoro-benzyl)-amino]-2-methyl-phenyl}-methanesulfonamide **19** has been discovered.

The discovery of nuclear hormone receptor modulators continues to thrive as an active and fruitful approach to drug discovery.[1] Glucocorticoid receptor (GR) agonists have been sought for antiinflamatory and other applications and antagonists have been probed as a potential treatment for diabetes.[2] Considerable research into steroids related to the potent antagonist mifepristone (RU-486, **1**) has been conducted (Fig. 1). These steroidal antagonists are perhaps more known for their progesterone receptor antagonist activity that is responsible for their abortifacient activity. Nonsteroidal agonists have also been discovered.[3] Recent activities directed toward the discovery of nonsteroidal antagonists, based on the structure of agonists, have lead to the discovery of chromene GR antagonist **2**.[4]

In order to expand our knowledge about this series and improve its properties, we sought to prepare the achiral tricycle **3**. Although the benzyl group appended to the tricycle **3** does not assume an axial orientation that is important for aryl substituents in steroids like **1** and chromene **2**, the group could potentially be structurally varied more easily leading to an unpredicted discovery. During the course of these studies, we prepared the tricyclic antagonist **3** and found it to be a potent GR binder with limited stability. A related acyclic series of readily prepared sulfonamides, typified by the dibenzyl-anilino-sulfonamide **4**, was also discovered.[5]

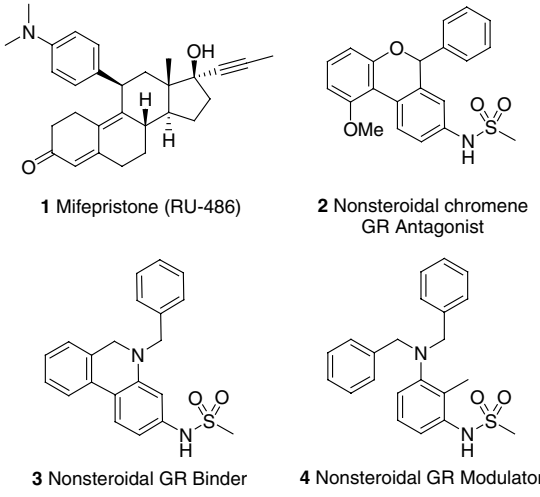

Figure 1. Steroidal and nonsteroidal glucocorticoid receptor modulators.

Retrosynthetically we sought to prepare tricycles related to **3** from the corresponding acyclic sulfonamides **5** (X = halide or triflate) from a palladium catalyzed intramolecular aryl–aryl coupling (Fig. 2).[6] The cyclization should potentially be aided by deprotonation of the sulfonamide (in analogy to the related work of Rawal with phenols),[7] blocked *ortho* position on the aniline ring, six- versus seven-membered ring formation, and reaction with the more electron rich aromatic ring.

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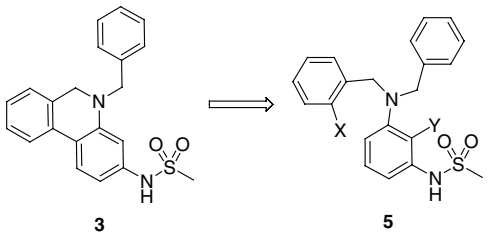
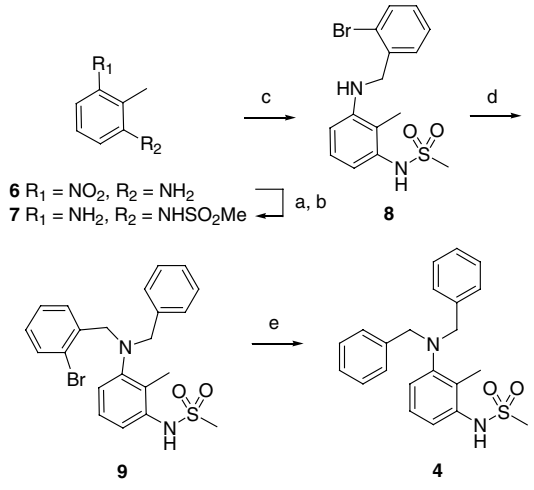


Figure 2. Proposed cyclization.

The synthesis of a cyclization precursor **9** (X = Br) began with 2-methyl-3-nitroaniline **6**, which was converted to aniline **7** by sulfonylation followed by nitro group reduction (Scheme 1). Reductive amination with 2-bromobenzaldehyde followed by a second reductive amination with benzaldehyde provided bromide **9**. Attempted cyclization under precedented conditions lead to reduction (rather than ring closure) and delivered dibenzylanilino-sulfonamide **4**.[7] The failure of this reaction may be due to the instability of the desired product **3**, however the testing of sulfonamide **4** revealed it to be a potent GR modulator. Furthermore, it has reasonable properties for a lead structure including no rule of five violations,[8] low molecular weight (MW = 380.5), $c\log P = 4.5$, and a polar surface area consistent with membrane permeability.[9]



Scheme 1. (a) MsCl, pyr, rt, 2 h; (b) H_2 (1 atm), 10% Pd on carbon, EtOAc, rt, 2 h, 84% (two steps); (c) 2-bromobenzaldehyde, AcOH, DCE, rt, 4 h; $Na(OAc)_3BH$, 12 h, 64%; (d) benzaldehyde, AcOH, DCE, rt, 4 h; $Na(OAc)_3BH$, 12 h, 14%; (e) $Pd(OAc)_2$, P(*o*-tol)$_3$, Cs_2CO_3, DMA, 85 °C, 12 h, 22%.

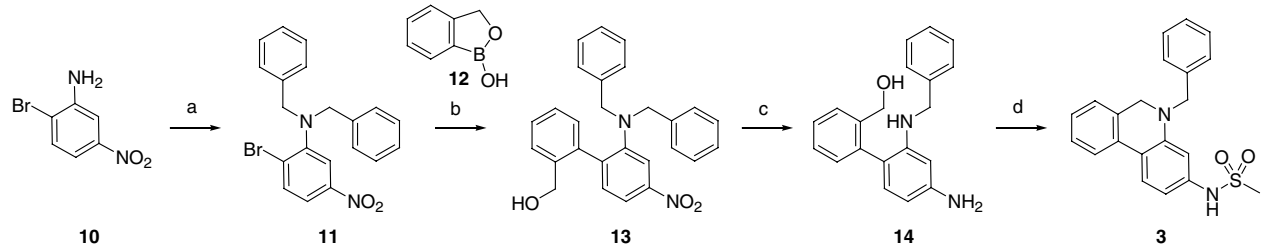
Although inefficient, an alternate route resulted in the preparation of sulfonamide **3** (Scheme 2). Aniline **10** was alkylated with benzyl bromide and Suzuki coupling with 3H-benzo[*c*][1,2]oxaborol-1-ol **12** yielded alcohol **13**. Hydrogenation removed one benzyl group, reduced the nitro group, and provided alcohol **14**. Conversion of the alcohol to the mesylate followed by spontaneous cyclization provided the tricyclic sulfonamide **3**. Tricyclic sulfonamide **3** was unstable and was stored prior to assay at low temperature (−78 °C). Room temperature storage, either neat or in solution, lead to numerous uncharacterized decomposition products.

A more efficient preparation of the dibenzylanilines related to **4** begins with 2-methyl-3-nitroaniline **15** (Scheme 3). Reductive amination with an aldehyde, like **16**, provided monoalkyl anilines like **17** in high yield. Alkylation with a reactive alkyl halide, for example, a benzyl halide, then yielded nitroarenes such as **18**. Reduction and sulfonylation provided dialkyl sulfonamides like **19**.

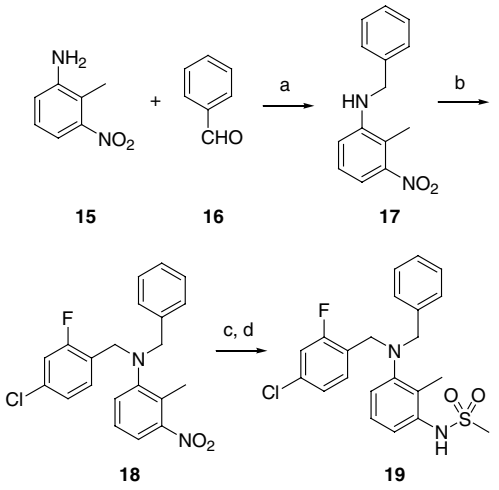
Compounds were assayed in binding assays against a panel of human nuclear hormone receptors monitoring the displacement of radiolabeled dexamethasone.[9] Functional activity was measured in a reporter cell line (GRAF) genetically engineered to express h-GR, the glucocorticoid response element, and a reporter gene encoding a secreted form of alkaline phosphatase.[10]

N-(3-Dibenzylamino-2-methyl-phenyl)-methanesulfonamide **4** is a potent binder of the human glucocorticoid receptor (h-GR) with an $IC_{50} = 28$ nM (Table 1). It has good selectivity for this receptor over the human progesterone receptor (h-PR) (>100×), mineralocorticoid receptor (h-MR>10×), androgen receptor (h-AR>6×), estrogen receptor (h-ER_a>100×, and thyroid-hormone receptor (h-TR_α and h-TR_β > 100×). Evaluation of sulfonamide **4** in the GRAF assay indicated it is an antagonist with moderate potency ($IC_{50} = 250$ nM). *N*-(5-Benzyl-5,6-dihydro-phenanthridin-3-yl)-methanesulfonamide **3** showed excellent h-GR binding potency ($IC_{50} = 20$ nM). However, its instability precluded further potency determinations and analog synthesis, so we focused our attention on sulfonamide **4**. Ultimately we were able to optimize the in vitro properties of the series as shown by dihalide **19**.

SAR studies of dialkyl anilines related to sulfonamide **4** indicated aryl groups, particularly benzyl groups, are



Scheme 2. (a) BnBr, *i*-Pr_2Net, DMF, 120 °C, 12 h, 75%; (b) $Pd(PPh_3)_4$, **12**, Na_2CO_3, EtOH, tol, 80 °C, 7 h, 95%; (c) H_2, 10% Pd/C, EtOAc, rt, 4 h, 9%; (d) MsCl, pyr, rt, 12 h, 13%.



Scheme 3. (a) AcOH, DCE, rt, 4 h; $Na(OAc)_3BH$, 12 h, 87%; (b) 4-chloro-2-fluorobenzylbromide, *i*-Pr_2NEt, DMF, 90 °C, 12 h, 85%; (c) Fe, NH_4Cl, EtOH, H_2O, 80 °C, 1 h; (d) MsCl, pyr, 0 °C, 30 min, 83% (over two steps).

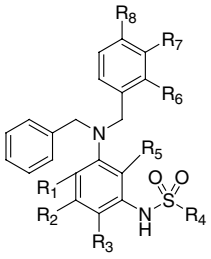
preferred (data not shown). Anilino-sulfonamides are also more potent than the corresponding aniline, phenol, acylaniline, carboxylic acid, ester, carbamide, and the benzylic alcohol (data not shown). Alkylation of the sulfonamide also decreases potency. Substitutions at positions 1, 2, and 3 dramatically weakened binding potency as illustrated by **20**–**25** (Table 2). Amongst R_4 substituents methylsulfonamide is preferred, although the ethylsulfonamide **26** is also tolerated. At the carbon between the two aniline nitrogens, small alkyl groups are preferred as illustrated by **4** and **34**. Hydrogen substitution leads to decreased potency as in **28**. Polar and larger groups decrease potency as in **29**–**33**. A broader range of substitution of the benzyl rings increase or maintain binding potency. Fluorine at the *ortho* position, as in **35**, increases potency, although larger groups—even electron-withdrawing groups—lose potency (e.g., **36**–**41**). No substitution at the *meta* position maintained, or increased, potency (see examples **42**–**51** of which the most potent is fluoride **42**). The R_8 position tolerated the greatest diversity of substitution (compounds **52**–**61**). Halogens and ethers both lead to potency improvements. Notable amongst the ethers were the allyl ether **60** ($IC_{50} = 12.7$ nM) and dihalo analogs like **61** ($IC_{50} = 15$ nM). One potent sulfonamide **19** shows excellent binding potency (h-GR $IC_{50} = 5.7$ nM) and good receptor selectivity over h-PR

Table 1. h-GR binding IC_{50}, h-PR binding IC_{50}, h-MR binding IC_{50}, h-AR binding IC_{50}, and GRAF IC_{50} assay results for compounds **3**,**4**, and **19**

Compounds	h-GR binding IC_{50}, nM[a]	h-PR binding IC_{50}, nM[a]	h-MR binding IC_{50}, nM[a]	h-AR binding IC_{50}, nM[a]	GRAF IC_{50}, nM[a]
3	20	nd	nd	nd	nd
4	28	7600	310	170	250
19	5.7	790	4000	300	210

[a] Values are means of two experiments (nd = not determined).

Table 2. h-GR binding IC_{50} and GRAF IC_{50} results for compounds **3** and **19**–**31**

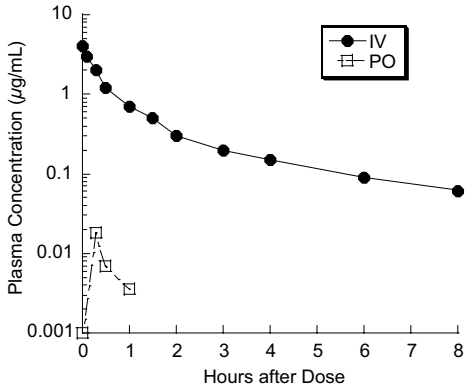


Compounds	Substituents R_n where $R_n \neq H$	h-GR binding IC_{50}, nM[a]	GRAF IC_{50}, nM[a]
4	$R_5 = Me$	28	250
19	$R_5 = Me$, $R_6 = F$, $R_8 = Cl$	5.7	210
20	$R_1 = Me$, $R_5 = Me$	1100	nd
21	$R_1 = CONMe_2$, $R_5 = Me$	14,000	nd
22	$R_1 = Br$, $R_5 = Me$	2700	nd
23	$R_1 = OMe$, $R_5 = Me$	3800	nd
24	$R_2 = Me$, $R_5 = Me$	1100	nd
25	$R_3 = Me$, $R_5 = Me$	6600	nd
26	$R_4 = Et$, $R_5 = Me$	138	400
27	$R_4 =$ *i*-Pr, $R_5 = Me$	320	nd
28	$R_5 = H$	2200	nd
29	$R_5 = CH_2OH$	56	nd
30	$R_5 = OEt$	850	nd
31	$R_5 = COMe$	580	nd
32	$R_5 = CH_2OEt$	290	nd
33	$R_5 = Ph$	450	nd
34	$R_5 = Et$	12	270
35	$R_6 = F$, $R_5 = Me$	14	150
36	$R_6 = Cl$, $R_5 = Me$	36	nd
37	$R_6 = Br$, $R_5 = Me$	96	580
38	$R_6 = CN$, $R_5 = Me$	60	nd
39	$R_6 = Me$, $R_5 = Me$	48	810
40	$R_6 = OMe$, $R_5 = Me$	690	nd
41	$R_6 = CF_3$, $R_5 = Me$	220	nd
42	$R_7 = F$, $R_5 = Me$	42	260
43	$R_7 = Cl$, $R_5 = Me$	230	nd
44	$R_7 = Br$, $R_5 = Me$	910	nd
45	$R_7 = OMe$, $R_5 = Me$	250	450
46	$R_7 = OCF_3$, $R_5 = Me$	220	nd
47	$R_7 = Me$, $R_5 = Me$	110	700
48	$R_7 = CF_3$, $R_5 = Me$	130	nd
49	$R_7 = CN$, $R_5 = Me$	570	nd
50	$R_7 = Br$, $R_5 = Me$	9100	nd
51	$R_7 = CO_2Me$, $R_5 = Me$	25,000	nd
52	$R_8 = F$, $R_5 = Me$	47	240
53	$R_8 = Cl$, $R_5 = Me$	17	300
54	$R_8 = Me$, $R_5 = Me$	58	1100
55	$R_8 = OMe$, $R_5 = Me$	100	160
56	$R_8 = CF_3$, $R_5 = Me$	370	nd
57	$R_8 = CO_2H$, $R_5 = Me$	1000	nd
58	$R_8 = CO_2Me$, $R_5 = Me$	470	nd
59	$R_8 = CO_2H$, $R_5 = Me$	1000	nd
60	$R_8 =$ *O*-allyl, $R_5 = Me$	13	340
61	$R_5 = Me$, $R_6 = F$, $R_8 = F$	15	100

[a] Values are means of two experiments (nd = not determined).

(140×), h-MR (700×), h-AR (50×), h-ER_a, and h-ER_b (1700×), and h-TR_α and h-TR_β (1700×).

In order to assess the in vivo potential of this class of GR selective modulators, rat liver microsomal metabolism



Scheme 4. Rat pharmacokinetics of sulfonamide **4** (5 mpk dose).

and rat oral/iv pharmacokinetic data was obtained. In rat liver microsomes, sulfonamide **4** was rapidly metabolized with a half-life of 8 min. The primary metabolic event was N-debenzylation as determined by HPLC/MS coinjection of an authentic sample of *N*-(3-benzylamino-2-methyl-phenyl)-methanesulfonamide. In Sprague–Dawley rats, the GR modulator **4** had a short iv half-life ($t = 2.0$ h) and high iv clearance (1.6 L/h kg) consistent with rapid metabolism (Scheme 4). Oral bioavailability was less than 5%.

In summary, a novel and potent series of selective GR modulators related to *N*-{3-[benzyl-(4-chloro-2-fluoro-benzyl)-amino]-2-methyl-phenyl}-methanesulfonamide **19** was discovered. These compounds undergo rapid metabolic decomposition leading to poor pharmacokinetics. In order for them to have in vivo utility, potentially through inhibition of the expression of key enzymes that regulate hepatic glucose production, the metabolic stability of this series will need to be improved. The successful realization of this goal will be reported in a future publication.

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