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2-Benzenesulfonyl-8a-benzyl-hexahydro-2H-isoquinolin-6-ones as selective glucocorticoid receptor antagonists

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Abstract—The 2-azadecalin ring system was evaluated as a scaffold for the preparation of glucocorticoid receptor (GR) antagonists. High affinity, selective GR antagonists were discovered based on a hypothetical binding mode related to the steroidal GR antagonist RU-43044. 2-Benzenesulfonyl substituted 8a-benzyl-hexahydro-2H-isoquinolin-6-ones exemplified by (***R***)-**37** had low nanomolar affinity for GR with moderate functional activity (200 nM) in a reporter gene assay. These compounds were devoid of affinity for other steroidal receptors (ER, AR, MR, and PR). Analogues based on an alternative putative binding mode (CP-like) were found to be inactive.

Mifepristone (RU-486)[1–3] is an antagonist at progesterone (PR) and glucocorticoid (GR) receptors and has recently been shown to be an effective treatment for psychotic major depression (PMD).[4–6] The etiology of this condition has been associated with abnormally high levels of cortisol [7,8]; hence, the efficacy of mifepristone in the treatment of PMD is ascribed to GR antagonism.[6] Our goal was to discover a 'second generation' drug which would be a potent and selective GR antagonist. There has also been considerable interest in the development of selective GR antagonists for other indications,[9] including treatment of diabetes,[10,11] obesity,[12,13] endogenous depression,[14] Alzheimer's disease,[15] neuropathic pain,[16] and Cushing's disease.[17]

In addition to mifepristone, the related steroid RU-43044,[2,3] which is selective for GR over PR, and the recently disclosed potent and selective antagonists CP-409069[18] and CP-472555[19] provided structural leads for further design. We decided to explore the benzyl-substituted 2-azadecalin (octa- and decahydro-isoquinoline) ring system as this presented an attractive scaffold to probe GR receptor binding. With appropriate relative

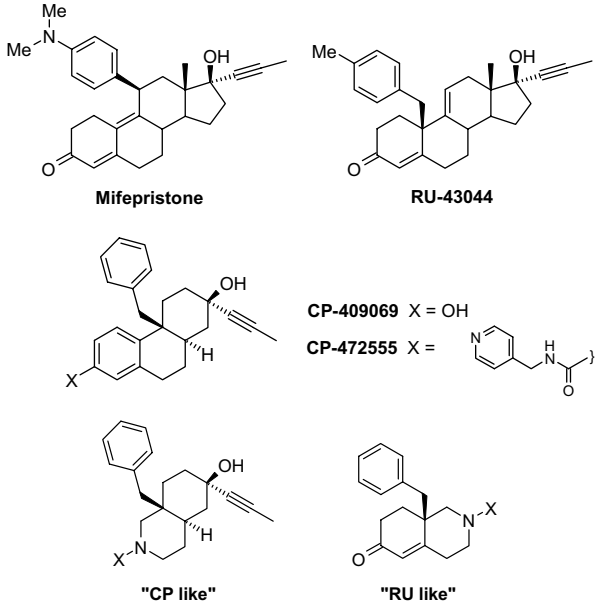

Figure 1. Potential GR-binding modes of substituted azadecalins.

Keywords: Glucocorticoid receptor (GR) antagonists; Azadecalin.
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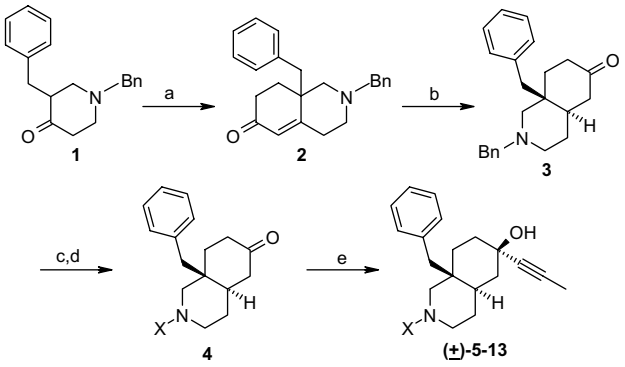
and absolute stereochemistry, the benzyl-2-azadecalin system can be represented in either a 'CP-like' binding mode or an 'RU-like' binding mode with nitrogen substituents X providing auxiliary binding groups (Fig. 1).

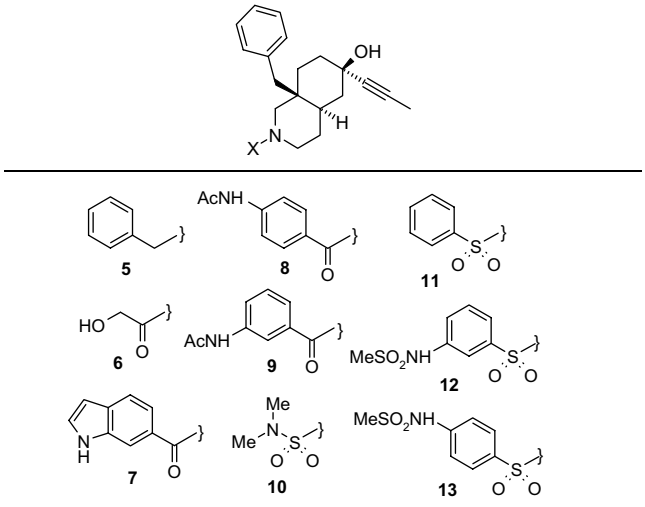
Racemic hexahydro-2,8a-dibenzylisoquinolinone **2** was prepared by Robinson annelation of piperidone **1**[20] as described for the synthesis of the corresponding 8a-methyl analogue[21] (Scheme 1). Lithium/ammonia reduction afforded the *trans*-octahydroisoquinolinone **3** which was converted to various analogues **4** by deprotection and standard N-substitution reactions. Treatment of compounds **4** with butynyl magnesium bromide furnished racemic target compounds **5**–**13** (Table 1) which were obtained as a major diastereomer with the indicated relative stereochemistry. In some cases the minor diastereomer was also isolated by column chromatography.[22]

Compounds **14**–**50** (Tables 2–4), including those substituted on the 8a-benzyl group (Y = OMe, F, Br, NO_2), were readily available by N-debenzylation of enone **2**



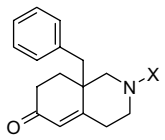
Scheme 1. Reagents and conditions: (a) methylvinyl ketone, NaOMe, MeOH, rt; (b) Li, NH_3; (c) H_2, $Pd(OH)_2/C$, AcOH (d) **5**: benzyl bromide, NaH, THF; **8**–**13**: acyl or sulfonyl chloride, NEt_3, CH_2Cl_2; (e) butynyl magnesium bromide, THF.

Table 1. Compounds **5**–**13**[a]



[a] All compounds are racemic.

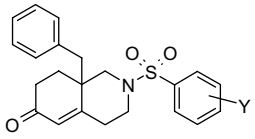
Table 2. GR-binding affinity for compounds **14**–**23**[a]



Compound	X	GR-binding K_i (nM)[b]
14	C(O)-phenyl	>10,000
15	C(O)-*n*-butyl	>10,000
16	C(O)NH-phenyl	>10,000
17	$S(O_2)$-phenyl	225
18	$S(O_2)$-*n*-butyl	>10,000
19	$S(O_2)$-NH-phenyl	1200
20	4-MeO-phenyl	>5000
21	Benzyl	3700
22	4-MeO-benzyl	2250
23	CH_2-(4)-pyridyl	>10,000

[a] All compounds are racemic.
[b] Values are means of two experiments.

Table 3. GR-binding affinity for substituted sulfonamides **24**–**45**[a]



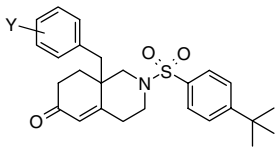
Compound	Y	GR-binding K_i (nM)[b]
17	H	225
24	2-CN	1000
25	2-CF_3	4450
26	3-NO_2	3000
27	4-NO_2	1250
28	4-F	800
29	3-OMe	196
30	4-OMe	216
31	3,4-$(OMe)_2$	1300
32	2,5-$(OMe)_2$	>10,000
33	4-OPh	163
34	3-Cl	432
35	4-Cl	193
36	4-Me	99
37	4-*tert*-Butyl	14
(***R***)-**37**		4
(***S***)-**37**		>10,000
38	4-Phenyl	55
39	2-$NHSO_2Me$	1950
40	3-$NHSO_2Me$	2100
41	4-$NHSO_2Me$	950
42	4-SO_2Me	137
43	4-NHCOMe	750
44	4-NMe_2	113
45	4-(Morpholin-4-yl)	64

[a] All compounds are racemic unless otherwise noted.
[b] Values are means of two experiments.

and subsequent derivatization (Scheme 2). Conversion of the bromo (**49**) and nitro (**50**) compounds to analogues **51**–**59** (Table 4) was accomplished using standard transformations.[23]

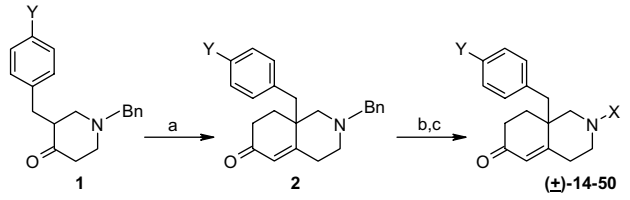
The enantiomers of **37** (Table 3) and **47** (Table 4) were separated by chiral column chromatography. An asym-

Table 4. GR-binding affinity and functional activity for **37** and aryl derivatives **46–59**[a]



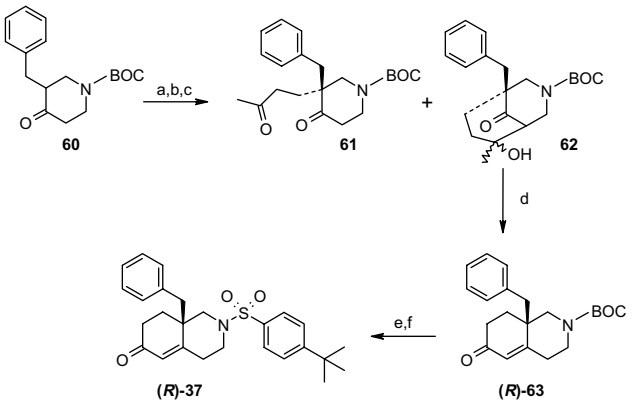
Compound	Y	GR-binding K_i (nM)[b]	GR Functional K_i (nM)[b]
37	H	14	>1000
(***R***)-**37**		4	200
46	3-OMe	76	nt[c]
47	4-OMe	6	230
(***R***)-**47**		4	200
48	4-F	5	>1000
49	4-Br	9	200
50	4-NO_2	45	nt
51	4-CN	65	nt
52	4-NH_2	99	nt
53	4-NMe_2	15	>1000
54	4-$NHSO_2Me$	13	>1000
55	4-NHCOMe	56	>1000
56	4-$NHSO_2NMe_2$	13	323
57	4-(Pyrid-4-yl)	2	180
58	4-(Piperidin-1-yl)	9	>1000
59	4-(Morpholin-4-yl)	10	400
Mifepristone		0.4	1.2
CP-409069		0.6	4

[a] All compounds are racemic unless otherwise noted.
[b] Values are means of two experiments.
[c] Not tested.



Scheme 2. Reagents and conditions: (a) methylvinyl ketone, NaOME, MeOH, rt; (b) $ClCO_2CHClCH_3$, dichloroethane, reflux; MeOH, reflux; (c) **14–19**: isocyanate, or acyl or sulfonyl chloride, NEt_3, CH_2Cl_2; **20**: 4-MeO-phenylboronic acid, $Cu(OAc)_2$, Et_3N, CH_2Cl_2; **22–23**: 4-MeO-benzyl bromide or 4-picolyl bromide, NaH, THF.

metric synthesis of (***R***)-**37** was subsequently developed based on the chiral imine Michael addition protocol used for the enantioselective synthesis of quaternary centers,[24] including enantiomers of the 8a-methyl analogue corresponding to enone **2**[21] (Scheme 3). Conversion of BOC-protected 2-benzyl-4-piperidone **60**[25] to the imine with (*R*)-(α)-methylbenzylamine followed by reaction with methylvinyl ketone in toluene afforded a separable mixture of Michael adduct **61** and Michael-aldol adduct **62** in a ratio of ca. 2:1. Base treatment of **62** gave enone (***R***)-**63** with 96–98% ee, albeit in low (10–20%) overall yield from **60**.[26] The stereochemical assignment for (***R***)-**63** is based on the absolute stereochemistry observed in the directly analogous octalone[24] and hexahydroisoquinolinone[21] examples. Removal of the BOC-group with TFA and subsequent sulfonylation afforded (***R***)-**37** (96–98% ee by chiral HPLC).[27,28]



Scheme 3. Reagents and conditions: (a) (*R*)-α-methylbenzylamine, toluene, reflux; (b) methylvinyl ketone, toluene, 6 days; (c) AcOH, H_2O; (d) NaOMe, MeOH, 75 °C; (e) TFA; (f) 4-(*t*)-butylbenzenesulfonyl chloride, NEt_3, CH_2Cl_2.

Affinity for GR was determined by ligand binding measuring displacement of [^{3}H]dexamethasone from recombinant baculovirus derived human GR.[18] Functional activity at human GR was determined in SW1353/MMTV-5 cells transfected with a plasmid encoding firefly luciferase located behind a glucocorticoid response element (GRE).[18] GR antagonist activity was measured as inhibition of dexamethasone induced luciferase expression. Selected compounds were tested for GR agonist activity by performing the assay in the absence of dexamethasone. Selectivity over the estrogen (ERα), androgen (AR), mineralocorticoid (MR), and progesterone (PR) receptors was determined by ligand binding assays.[29]

Compounds **5–13** (Table 1), which were based on the hypothetical 'CP-like' GR-binding mode, were remarkable in their lack of affinity for the receptor. None of these compounds, as well as a number of related analogues (not shown), inhibited 50% binding of radiolabeled dexamethasone at a concentration of 10 micromolar. The diastereomers of **5–13**, obtained as minor products and which are epimeric at the tertiary alcohol center, were similarly inactive. The high affinity of CP-472555 and related compounds indicates that the GR tolerates fairly large groups in the 'A-ring' portion of these molecules.[19] The lack of affinity of the substituted 2-azadecalins **5–13** demonstrates that the N-substituents apparently do not allow binding to GR in a similar manner.

Results for initial compounds based on the 'RU-like' binding mode were similarly disappointing with the exception of the benzenesulfonamide derivative **17** which had weak GR binding with a K_i of 225 nM (Table 2). The related alkylsulfonamide **18** was essentially devoid of binding affinity. The binding observed for **17** prompted the synthesis of a series of substituted benzenesulfonamides (Table 3). A trend toward increased binding for large, and generally lipophilic, *para*-substituents was observed with the racemic 4-(*tert*-butyl)-benzenesulfonamide **37** having the highest binding affinity (14 nM). Binding affinity was enantiospecific,

with (***R***)-**37** having a K_i of 4 nM. The active enantiomer is therefore in the same absolute stereochemical series as the A–B ring system of RU-43044.

Substituted benzyl derivatives of lead compound **37** were then evaluated (Table 4). We concentrated on *para*-substitution, partly on the basis of the higher affinity of 4-methoxy analogue **47** (6 nM) compared to 3-methoxy compound **46** (76 nM), and because the *para*-position is highly tolerant of substitution in mifepristone.[30] GR-binding affinity was retained with a variety of *para*-substituents including the 4-pyridyl derivative **57** with a K_i of 2 nM. Perhaps not surprisingly this compound showed significant Cyp inhibition (2C9: 76%: 2C19: 61%: 2D6: 44% at 1 μM), an activity not shown by other analogues including **37** and **47**.

Representative high affinity ligands were evaluated for GR functional antagonist activity in the SW1353/MMTV-5 reporter gene assay. None of the compounds demonstrated agonist activity and several of them were found to be GR antagonists with moderate activity in the 200 nM K_i range (Table 4). This level of GR antagonist activity was considerably lower than that observed for the standards mifepristone and CP-409069 for which GR binding was much closer to the GR antagonist activity. A similar dissociation between GR binding and functional activity has been reported for other series of non-steroidal GR antagonists.[31] A possible explanation for this discrepancy in our series is lack of cellular penetration. To test this hypothesis, a whole cell GR-binding assay was carried out in SW1353 cells with (***R***)-**47**. This compound demonstrated almost 100-fold lower binding in the whole cell assay (352 nM) compared to the original isolated GR-binding assay (4 nM). Whole cell binding of mifepristone (0.82 nM) and CP-409069 (5.5 nM) was consistent with their more potent GR functional activity.

Selectivity profiling indicated that none of the sulfonamide compounds in Table 4 displaced 50% binding at ERα, AR, MR or PR at 10 μM. Consistent with its reported lack of selectivity for GR over PR,[1–3] mifepristone had a K_i of 1.3 nM at PR. Thus, although compounds from the current series are relatively weak GR functional antagonists, they are nonetheless highly selective over other steroid receptors.

This initial exploration of the 2-azadecalin system produced GR antagonists that appear to bind in the 'RU-like' binding mode, as opposed to the alternative 'CP-like' orientation. Selective, high affinity GR ligands were produced which had moderate GR functional antagonist activity relative to mifepristone or CP-409069. The 2-azadecalin system therefore provides a useful scaffold for further investigation of high affinity antagonists with increased GR functional activity.

Acknowledgment

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22. The stereochemistry of the major diastereomer (diastereomeric ratio ca. 5:1) was assigned on the basis of propensity of this system to add nucleophiles from the α-face. For example, $NaBH_4$ reduction affords predominantly (>80%) the β-alcohol, the stereochemistry of which was rigorously established by NMR.

23. **51**: treatment of **49** with $Zn(CN)_2$ and $Pd(PPh_3)_4$ in DMF/microwave; **52**: treatment of **50** with Fe and NH_4Cl/aq IPA; **53**: treatment of **52** with CH_2O, HCO_2H, EtOH/microwave; **54**–**56**: sulfonylation or acylation of **52**; **57**: Suzuki coupling of **49** with 4-pyridyl boronic acid; **58** and **59**: amination of the tetramethyl[1,3,2]dioxaboran-2-yl derivative of bromo compound **49**.
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25. Available from **1** by hydrogenation (Pd/C) in EtOH containing di-*tert*-butyl dicarbonate.
26. Somewhat unexpectedly, base treatment of the Michael product (**61** and epimer) afforded (***R***)-**63** with a lower ee (ca. 85%).
27. Enantiomeric excess was determined by chiral HPLC analysis using a Chiralpack 1A column.
28. BOC protection was employed in this sequence as the benzyl derivative corresponding to (***R***)-**63** underwent partial (ca. 20%) racemization upon deprotection with ACE-Cl. The mechanism through which partial racemization of the quaternary center occurs is unclear, although one can postulate a reverse Mannich-type process followed by ring closure.
29. Estrogen receptor: [^{3}H]estradiol, Pan Vera 26467A ERα; androgen receptor: [^{3}H]dihydrotesterone, Pan Vera 24938 AR; mineralocorticoid receptor: [^{3}H]aldosterone, Sf9 cells/recombinant MR; progesterone receptor: [^{3}H]progesterone, Pan Vera 24900 PR.
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