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1*H*-Pyrazolo[3,4-*g*]hexahydro-isoquinolines as selective glucocorticoid receptor antagonists with high functional activity

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Abstract—Addition of the 4-fluorophenylpyrazole group to the previously described 2-azadecalin glucocorticoid receptor (GR) antagonist **1** resulted in significantly enhanced functional activity. SAR of the bridgehead substituent indicated that whereas groups as small as methyl afforded high GR binding, GR functional activity was enhanced by larger groups such as benzyl, substituted ethers, and aminoalkyl derivatives. GR antagonists with binding and functional activity comparable to mifepristone were discovered (e.g., **52**: GR binding K_i 0.7 nM; GR reporter gene functional K_i 0.6 nM) and found to be highly selective over other steroid receptors. Analogues **43** and **45** had >50% oral bioavailability in the dog.

Although potential therapeutic indications for glucocorticoid receptor (GR) antagonists have been identified,[1] the need for selective agents remains. Recent progress toward this goal has been reviewed.[1] The standard GR antagonist mifepristone (RU-486)[3] is a potent progesterone receptor (PR) antagonist which places significant restraints on its clinical utility. Our interest in the development of a follow-on compound to mifepristone for the treatment of psychotic major depression (PMD)[4] led to our discovery of selective GR antagonists exemplified by the 2-azadecalinone **1** which have high affinity for GR and modest GR functional antagonist activity.[2] These compounds are structurally related to the steroid RU-43044, which is selective for GR but lacks oral bioavailability.[3b,c] Herein we report that fusion of the phenylpyrazolo group to the azadecalin ring system (Fig. 1) leads to GR antagonists with significantly increased functional activity and somewhat divergent SAR from the previous series. The introduction of the pyrazolo ring onto the azadecalin scaffold was based on the presence of this structural feature in the potent GR agonist fluorocortivazol.[5] Others have utilized this strategy for the preparation of selective GR partial agonists based on the decalin ring system.[6]

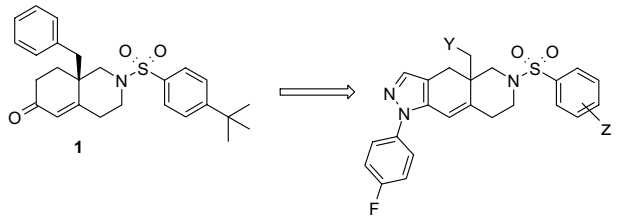

Figure 1. From enone series to fused pyrazoles.

Formylation of homochiral enone **1**[2] followed by reaction with 4-fluorophenylhydrazine furnished the 1*H*-pyrazolo[3,4-*g*]hexahydroisoquinoline **3** (Scheme 1). The regiochemistry of formylation and arylpyrazole formation is consistent with that observed in steroidal A-ring enone systems[5] and hexahydro-2(3H)-naphthalenones.[6,7] Benzyl-protected amine **5** was similarly prepared in racemic form from enone **4**.[2] N-debenzylation of **5** followed by derivatization afforded compounds (±)-**6**–**21** (Scheme 2 and Table 1).

Keywords: Glucocorticoid receptor (GR) antagonist; Pyrazolo-fused azadecalins.
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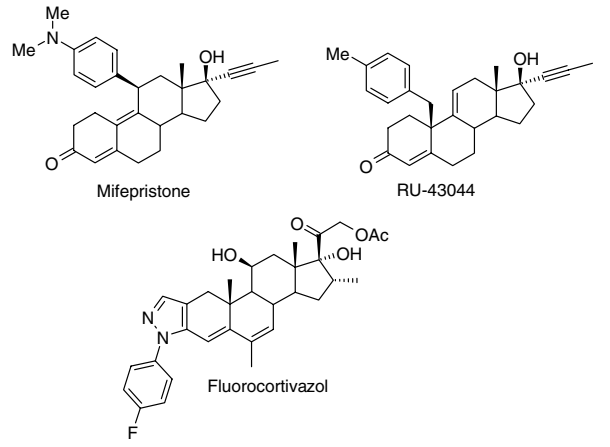
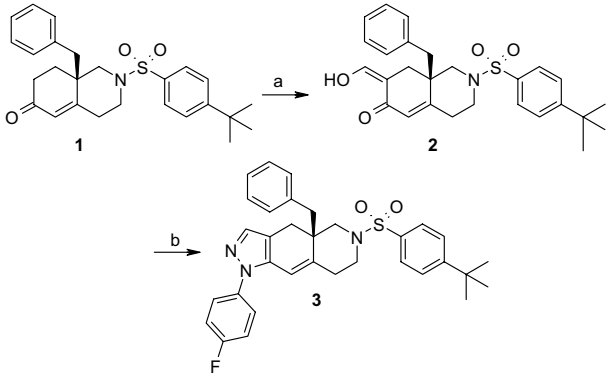


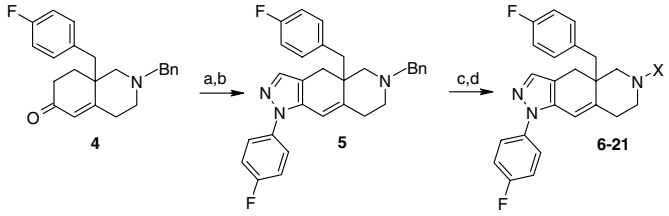


Scheme 1. Reagents and conditions: (a) HCO_2Et, NaH, toluene; (b) 4-fluorophenylhydrazine hydrochloride, AcOH, NaOAc, rt.

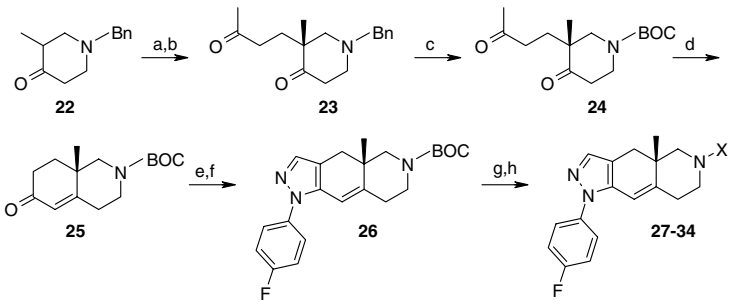
Analogues containing an angular methyl substituent were prepared as shown in Scheme 3. The (3*R*)-piperidone **23**[8a] was prepared by chiral imine mediated Michael addition as previously described.[8] The benzyl group was switched to Boc by hydrogenolysis and treatment with di-*tert*-butyl dicarbonate to facilitate N-deprotection later in the synthetic sequence. Cyclization of the resulting Boc-protected diketone **24** gave enone **25**. Formylation of **25** was accomplished by conversion to the enolate with LDA followed by reaction with 2,2,2-trifluoroethyl formate,[9] a sequence that was more convenient and higher yielding than the traditional NaH/ethyl formate procedure used in Schemes 1 and 2. As previously noted for Wieland–Miescher ketone derivatives,[6a] the regiochemistry of the two formylation procedures is the same. Sulfonamides **27**–**34** (Table 2) were subsequently prepared in standard fashion from aryl pyrazole **26**.

Bridgehead ether derivatives **41**–**57** were prepared commencing from the known homochiral enone **35**[10] by the reaction sequence shown in Scheme 4. Intermediate alcohols **38**–**40** were also converted to amine analogues **61**–**79** via reductive amination of the aldehydes **58**–**60** (Scheme 5).[11]

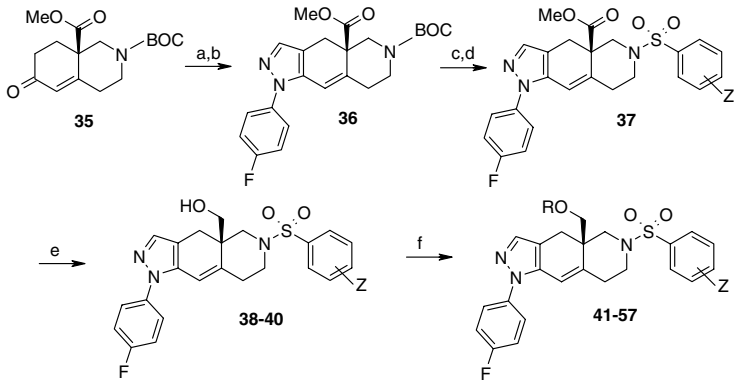
Ligand binding was used to determine GR affinity by measurement of [^{3}H]dexamethasone displacement from recombinant baculovirus derived human GR.[12] Functional GR antagonist activity was measured as inhibition of dexamethasone induced luciferase expression in SW1353/MMTV-5 cells transfected with a plasmid encoding firefly luciferase located behind a glucocorticoid response element (GRE).[12] GR agonist activity



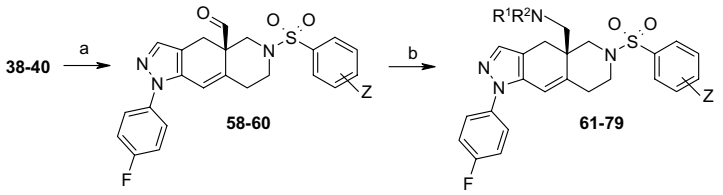
Scheme 2. Reagents and conditions: (a) HCO_2Et, NaH, toluene; (b) 4-fluorophenyl hydrazine hydrochloride, AcOH, NaOAc, rt; (c) $ClCO_2CHClCH_3$, dichloroethane, reflux; MeOH, reflux; (d) **6**–**15**: sulfonyl chloride, NEt_3, CH_2Cl_2; **16**: phenylboronic acid, $Cu(OAc)_2$, Et_3N, CH_2Cl_2; **17**–**20**: benzyl bromide or 2,3, or 4-picolyl bromide, NaH, THF; **21**: benzoyl chloride, Et_3N, CH_2Cl_2.



Scheme 3. Reagents and conditions: (a) (*R*)-α-methylbenzylamine, toluene, reflux; (b) methylvinyl ketone, THF, 50 °C; (c) H_2, Pd/C, EtOH, BOC_2O; (d) NaOMe, MeOH; (e) LDA, Et_2O, −78 °C; $HCO_2CH_2CF_3$; (f) 4-fluorophenyl hydrazine hydrochloride, AcOH, NaOAc, rt; (g) 20% TFA/CH_2Cl_2; (h) RSO_2Cl, diisopropylethylamine, CH_2Cl_2.



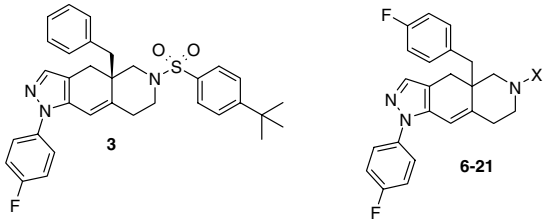
Scheme 4. Reagents and conditions: (a) LDA, Et_2O, −78 °C; $HCO_2CH_2CF_3$; (b) 4-fluorophenyl hydrazine hydrochloride, AcOH, NaOAc, rt; (c) 20% TFA/CH_2Cl_2; (d) $ArSO_2Cl$, diisopropylethylamine, CH_2Cl_2; (e) DIBAL-H, CH_2Cl_2, −78 °C to rt; (f) NaH, THF, RBr or RI, rt-reflux.



Scheme 5. Reagents and conditions: (a) DMSO, $COCl_2$, TEA, −45 °C; (b) R^1R^2NH, $NaBH(OAc)_3$, dichloroethane.

could be measured in the same assay in the absence of dexamethasone. Standard ligand binding assays were used to measure selectivity over other steroid receptors (ER, AR, MR, and PR).[13]

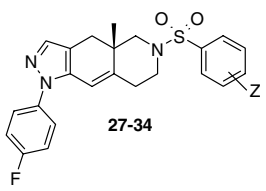
Table 1. GR binding affinity and functional activity for **3**, **6**–**21**[a]

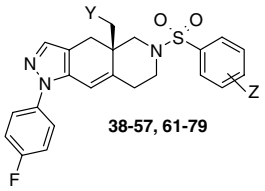


Compound	X	GR Binding K_i (nM)[b]	GR Functional K_i (nM)[b]
3		1.4	4.7
6	$S(O_2)$-4-(*t*-butyl)-phenyl	1.3	14
7	$S(O_2)$-phenyl	2.2	36
8	$S(O_2)$-4-Me-phenyl	1.5	17
9	$S(O_2)$-4-F-phenyl	1.4	26
10	$S(O_2)$-4-(morpholin-4-yl)-phenyl	1.3	11
11	$S(O_2)$Me	13	>1000
12	$S(O_2)$-*n*-butyl	12	>1000
13	$S(O_2)$-2-(*t*-butyl)-pyrid-5-yl	4.5	343
14	$S(O_2)$-morpholin-4-yl	26	>1000
15	$S(O_2)$-NH-phenyl	3	68
16	Phenyl	15	438
17	Benzyl	2.5	245
18	CH_2-pyrid-2-yl	18	390
19	CH_2-pyrid-3-yl	22	>1000
20	CH_2-pyrid-4-yl	41	>1000
21	C(O)-phenyl	>1000	
1		4	200
Mifepristone		0.4	1.2

[a] Compounds **6**–**21** are racemic.
[b] Values are means of two experiments.

Table 2. GR binding affinity and functional activity for **27**–**34**, **38**–**57**, and **61**–**79**[a]





Compound	Y	Z	GR Binding K_i (nM)[b]	GR Functional K_i (nM)[b]
27		2-Me	22	nt
28		4-Me	2.3	96
29		4-*t*-Bu	1.2	53
30		2-F	34	nt
31		4-F	9	293
32		4-OMe	3.7	178
33		4-CF_3	3.4	78
34		4-NH_2	17	>1000
38	OH	H	10	nt
39	OH	4-*t*-Bu	1.6	47
40	OH	4-F	8.6	184
41	OCH_3	H	1.0	20
42	OCH_3	4-Me	0.5	5.7
43	OCH_3	4-F	1.4	33
44	OCH_3	4-*t*-Bu	0.8	7.7
45	OCH_3	4-CF_3	0.8	28
46	OCH_2CH_3	4-*t*-Bu	0.8	1.9
47	OCH_2CH_3	4-CF_3	0.9	6.8
48	$OCH_2CH_2CH_3$	4-CF_3	0.9	9.0
49	OCH_2CH_2OMe	H	0.5	2.9
50	OCH_2CH_2OMe	4-Me	0.3	1.2
51	OCH_2CH_2OMe	4-F	0.6	5.2
52	OCH_2CH_2OMe	4-*t*-Bu	0.7	0.6
53	OCH_2CH_2OH	4-*t*-Bu	0.8	8.7
54	$OCH_2CH_2CH_2OMe$	4-*t*-Bu	0.8	1.6
55	OCH_2CH_2CN	4-*t*-Bu	0.8	5.1
56	OCH_2CH_2(pyrrolidin-1-yl)	4-*t*-Bu	12	201
57	OCH_2CH_2(piperidin-1-yl)	4-*t*-Bu	8.6	77
61	NHEt	4-*t*-Bu	2.4	16
62	NH-*i*-Pr	4-*t*-Bu	2.1	17
63	NH-allyl	4-*t*-Bu	0.9	11
64	NMe_2	H	1.1	10
65	NMe_2	4-F	2.6	29
66	NMe_2	4-*t*-Bu	1.2	6.9
67	NEt_2	4-*t*-Bu	1.7	14
68	$NHCH_2CH_2OH$	4-*t*-Bu	2.8	28
69	$NHCH_2CH_2OMe$	4-*t*-Bu	1.0	3.1
70	$NHCH_2CH_2NMe_2$	4-*t*-Bu	3.8	60
71	Azetidin-1-yl	4-*t*-Bu	1.4	11
72	Pyrrolidin-1-yl	H	1.5	4.9
73	Pyrrolidin-1-yl	4-F	1.6	8.0
74	Pyrrolidin-1-yl	4-*t*-Bu	1.1	3.4
75	Piperidin-1-yl	H	0.8	5.8
76	Piperidin-1-yl	4-*t*-Bu	1.6	5.8
77	Morpholin-1-yl	H	0.6	18
78	Morpholin-1-yl	4-*t*-Bu	0.9	7.1
79	4-Methylpiperazin-1-yl	4-*t*Bu	6.7	85
Mifepristone			0.4	1.2

[a] All compounds have the absolute stereochemistry indicated.
[b] Values are means of two experiments.
[c] nt, not tested.

Fusion of the aryl pyrazole group onto enone **1** led to a ca. 40-fold increase in GR functional activity as compound **3** was found to have K_i of 4.7 nM compared to 200 nM for **1**[2] (Table 1). The enantiospecificity of GR binding (and functional activity) of the enone series was conserved as the racemate corresponding to **3** was

Table 3. Pharmacokinetic data for selected compounds

Compound	Species	Dose (mg/kg po)[a]	C_{max} (ng/mL)	AUC (μg/h/mL)	$t_{1/2}$ (h)	F (%)	Brain/plasma ratio
29	Rat	5	199	1.009	2.7	13	0.07
41	Rat	5	23	0.112	3.6	3	0.75
43	Rat	5	106	0.621	2.1	22	1.1
44	Rat	5	94	0.430	2.9	11	0.10
45	Rat	5	163	0.966	3.4	16	0.83
78	Rat	5	75	0.302	2.0	10	0.10
29	Dog	2.5	524	1.684	4.2	26	—
41	Dog	2.5	258	0.894	5.9	20	—
43	Dog	2.5	381	1.676	4.2	54	—
45	Dog	2.5	647	3.638	6.7	58	—

[a] Compounds were administered in 10% DMSO/90% methylcellulose (1% water). $N = 3$ for rat studies and $N = 2$ for dog studies.

of lower activity (binding $K_i = 3.6$ nM, functional K_i 30 = nM). N-substituents were surveyed for the related p-fluorophenyl derivatives **6**–**21** (tested as racemates). The SAR diverged from that of the enone series[2] as other substituents, notably *N*-benzyl, provided high binding affinity (compound **17**); however, *N*-sulfonyl derivatives continued to demonstrate superior functional GR antagonist activity. Whereas aryl sulfonamides again showed the best antagonist profile, the penchant for the p-*tert*-butyl group in the enone series was diminished as evidenced by the functional activity of **7**–**10**.

Having made a rather significant structural change from enone **1** to aryl pyrazole **3**, it was of interest to re-examine the structural requirements of the bridgehead substituent. In the enone series, the bridgehead benzyl group was an apparent key to high GR binding affinity, at least in comparison to the angular methyl compound which was essentially devoid of affinity.[14] During the course of this work, GR partial agonist activity was reported for bridgehead methyl substituted arylpyrazole derivatives in the decalin series.[6] We were thus prompted to prepare compounds **27**–**34** (Table 2). The direct comparators **3** (Table 1) and **29** indicated that the bridgehead benzyl group was not required for GR binding; however, the antagonist activity was enhanced in the benzyl derivative (4.7 nM for **3** vs. 53 nM for **29**). Notably, bridgehead methyl derivative **29** was devoid of GR agonist activity in the functional assay (as was compound **3**).

The high GR affinity and modest functional antagonist activity of **29** prompted synthesis of other bridgehead derivatives as a means to provide increased polarity and possibly lower molecular weight relative to the highly lipophilic benzyl compound **3** (MW = 555, *c*Log $P = 8.5$). Bridgehead alcohols, ethers, and methylamino derivatives (Table 2) were targeted because of their accessibility from ester **35** which is readily available in enantiomerically pure form.[10] Data in Table 2 indicate that the bridgehead position is highly tolerant to substitution as high GR binding was observed for almost all analogues in both the oxygen (**38**–**57**) and nitrogen linked series (**61**–**79**). Enantiospecificity was again observed, as the racemates of many of these compounds were also evaluated and showed lower GR binding and functional activity (data not shown). Also as previously noted (Table 1), differences in GR functional activity emerged among compounds with similar binding affinity.

Ethers were significantly more active than the alcohol progenitors as GR functional antagonists (e.g. compare alcohol **39** with ethers **44**, **52**–**55**). For direct comparators (i.e., compounds containing the same benzenesulfonamide) there was a trend toward increased GR functional activity with increasing size of the ether group, although the trend was not completely linear (**44** vs **46**, **52**, **54**; **45** vs **47**, **48**). Derivatives with an aminoalkyl group at the bridgehead also showed high GR functional activity with the exception of those that contained more distal polar functionality (**68**, **70**, **79**). The same phenomenon was noted in the ether series where terminal amine-substituted ethyl ethers **56** and **57** showed significantly lower GR functional activity. A similarity between the ether and amine series was that compounds with the highest functional activity contained the methoxyethyl group (**52**: $K_i = 0.6$ nM and **69**: $K_i = 3.1$ nM).

The high selectivity for GR of the enone series[2] was retained in the 4-fluorophenylpyrazoles as none of the analogues in Tables 1 and 2 displaced 50% binding at ER, AR, MR or PR at 10 μM. Many of these compounds are in the same range as mifepristone in GR functional potency and represent a significant advance given the lack of selectivity of the latter over PR (mifepristone PR binding = 1.3 nM).

As a prelude to pharmacodynamic testing, selected compounds were tested for oral bioavailability, initially in the rat with subsequent testing in the dog (Table 3). The whole brain to plasma ratio was also determined in the rat. Bridgehead methoxyethyl ethers and amines showed uniformly low bioavailability in the rat ($F = \leqslant 10\%$).[15] Several of the methyl ethers demonstrated a better profile, notably compounds **43** and **45**, which had reasonable brain/plasma ratios in the rat and respectable bioavailability and $T_{1/2}$ in the dog. Pharmacokinetic properties were significantly better in the dog than in the rat for the four compounds examined. The rat data did not correlate well with in vitro microsomal clearance rates, implying that absorption is the main determinant for bioavailability in this series of compounds. The methoxyethyl ether does appear to be a metabolic liability

however, as compounds with this group showed rapid microsomal clearance across species, most importantly human microsomes.[16] Although based on only three examples (**29**, **44**, **78**), it also appeared that the *tert*-butyl substituent on the benzenesulfonamide was detrimental to brain penetration in the rat, possibly due to the molecular size. It can be noted that the compounds with the best in vivo pharmacokinetic profile (e.g., **43** and **45**) have modest GR functional activity relative to other analogues; hence further optimization of the series is ongoing in an attempt to improve this situation. Results of these efforts, and pharmacodynamic testing, will be reported in due course.

Acknowledgment

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References and notes

1. Mohler, M. L.; He, Y.; Wu, Z.; Hong, S.-S.; Miller, D. D. *Expert Opin. Ther. Patents* **2007**, *17*, 59.
2. Clark, R. D.; Ray, N. C.; Blaney, P.; Crackett, P. H.; Hurley, C.; Williams, K.; Dyke, H. J.; Clark, D. E.; Lockey, P. M.; Devos, R.; Wong, M.; White, A.; Belanoff, J. K. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 5704, Homochiral compounds in the current manuscript have the indicated absolute stereochemistry. Where absolute stereochemistry is not shown, compounds are racemic.
3. (a) Teutsch, G.; Ojasoo, T.; Raynaud, J. P. *J. Steroid Biochem.* **1988**, *31*, 549; (b) Teutsch, G.; Gaillard-Moguilewsky, M.; Lemoine, G.; Nique, F.; Philibert, D. *Biochem. Soc. Trans.* **1991**, *19*, 901; (c) Philibert, D.; Costerousse, G.; Gaillard-Moguilewsky, M.; Nedelec, F.; Tournemine, C.; Teutsch, G. *Front. Horm. Res.* **1991**, *19*, 1.
4. Flores, B. H.; Kenna, H.; Keller, J.; Solvason, H. B.; Schatzberg, A. F. *Neuropsychopharmacology* **2006**, *31*, 628; Nihalani, N. D.; Schwartz, M. L. *Curr. Opin. Invest. Drugs* **2007**, *8*, 563.
5. (a) Fried, J. H.; Mrozik, H.; Arth, G. E.; Bry, T. S.; Steinberg, N. G.; Tishler, M.; Hirschmann, R.; Steelman, S. L. *J. Am. Chem. Soc.* **1963**, *85*, 236; (b) Hirschmann, R.; Steinberg, N. G.; Buchschacher, P.; Fried, J. H.; Kent, G. J.; Tishler, M. *J. Am. Chem. Soc.* **1963**, *85*, 120.
6. (a) Shah, N.; Scanlan, T. S. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 5199; (b) Thompson, C. F.; Quraishi, N.; Ali, A.; Tata, J. R.; Hammond, M. L.; Balkovec, J. M.; Einstein, M.; Ge, L.; Harris, G.; Kelly, T. M.; Mazur, P.; Pandit, S.; Santoro, J.; Sitlani, A.; Wang, C.; Williamson, J.; Miller, D. K.; Yamin, T. D.; Thompson, C. M.; O'Neill, A.; Zaller, D.; Forrest, M. J.; Carballo-Jane, E.; Luell, S. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 2163.
7. Kumar, V.; Bell, M. R.; Wetzel, J. R.; Herrmann, J. L.; McGarry, R.; Schane, H. P.; Winneker, R. C.; Snyder, B. W.; Anzalone, A. J. *J. Med. Chem.* **1993**, *36*, 3278.
8. (a) Barth, M. M.; Binet, J. L.; Thomas, D. M.; de Fornel, D. C.; Samreth, S.; Schuber, F. J.; Renaut, P. P. *J. Med. Chem.* **1996**, *39*, 2302; (b) Pfau, M.; Revial, G.; Guingand, A.; d'Angelo, J. *J. Am. Chem. Soc.* **1985**, *107*, 273, Compound **26** was obtained with an ee of 96% (chiral HPLC analysis) which is consistent with the ee of >95% for diketone **23** reported in Ref. 8a.
9. Zayia, G. H. *Org. Lett.* **1999**, *1*, 989.
10. Christoffers, J.; Scharl, H. *Eur. J. Org. Chem.* **2002**, 1505, The ee of **35** obtained by this procedure was >98% (chiral HPLC analysis) which is consistent with the reported value of 97% ee..
11. The optical purity of final compounds **38**–**57** and **61**–**79** was >98% ee on the basis of the ee of the starting ester **35** (Ref. 10). Intermediate **37** (Z = *tert*-butyl) had an ee of 99% (chiral hplc) confirming that the chiral integrity of the system was maintained.
12. Morgan, B. P.; Swick, A. G.; Hargrove, D. M.; LaFlamme, J. A.; Moynihan, M. S.; Carroll, R. S.; Martin, K. A.; Lee, E.; Decosta, D.; Bordner, J. *J. Med. Chem.* **2002**, *45*, 2417.
13. 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.
14. The bridgehead methyl analogue corresponding to **1** had a K_i of >10 μM in GR binding (unpublished results).
15. Methoxyethyl ethers (rat *F*%): **50** (8), **52** (0), **55** (2); amines: **61** (0), **62** (5), **66** (0), **69** (0), **71** (4), **74** (2).
16. For example, methyl ether **43** showed 57% remaining after a 30 min incubation with human microsomes, compared to 7% remaining for the corresponding methoxyethyl ether **51**.