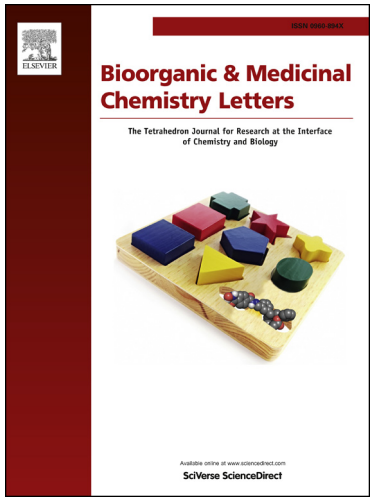

Heterocyclic glucocorticoid receptor modulators with a 2,2-dimethyl-3-phenyl-N-(thiazol or thiadiazol-2-yl)propanamide core

Hai-Yun Xiao, Dauh-Rurng Wu, James E. Sheppeck II, Sium F. Habte, Mark D. Cunningham, John E. Somerville, Joel C. Barrish, Steven G. Nadler, T.G. Murali Dhar

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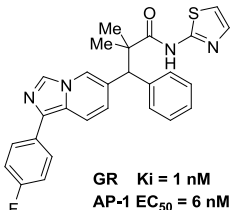

GR Ki = 1 nM
AP-1 EC_{50} = 6 nM

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ABSTRACT

A series of heterocyclic glucocorticoid receptor (GR) modulators with 2,2-dimethyl-3-phenyl-N-(thiazol or thiadiazol-2-yl)propanamide core are described. Structure-activity relationships suggest a combination of H-bond acceptor and a 4-fluorophenyl moiety as being important structural components contributing to the glucocorticoid receptor binding and functional activity for this series of GR modulators.

The glucocorticoid receptor (GR) is a member of the steroid family of nuclear hormone receptors that is involved in modulating a variety of immunological and metabolic signaling pathways upon glucocorticoid binding. The effective immunosuppressive and anti-inflammatory effects of glucocorticoids like prednisone is unfortunately often accompanied by significant adverse effects like osteoporosis, metabolic and cardiovascular disease on long term usage. Given the recent advances in understanding the mechanisms of glucocorticoid receptor action, there has been a significant effort in academia and industry to selectively target the beneficial anti-inflammatory effects (transrepression) over the adverse effects attributed to transactivation of certain genes using "dissociated" steroids and non-steroidal glucocorticoid receptor agonists.[1]

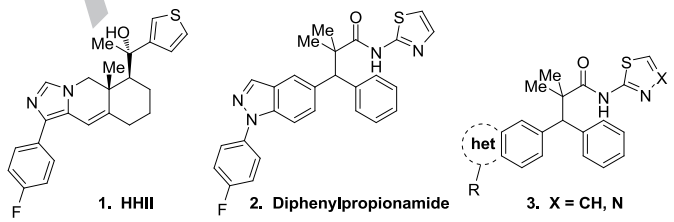
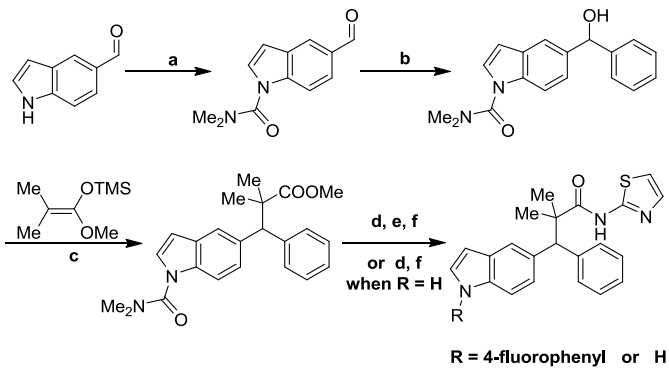


Figure 1. Heterocycle based GR modulators

We recently reported on a series of hexahydroimidazo[1,5b]isoquinoline (HHII) (**1**)[2a] derived GR modulators and pyrazolodiphenylpropionamide-based GR agonists (**2**)[2b] where the basic imidazole ring of the HHII scaffold and the pyrazole ring of **2** served as replacements for the A-B ring of the steroid scaffold (Figure 1). This report describes the synthesis heterocyclic GR modulators (**3**) employing novel approaches and the SAR, which is rationalized based on the X-ray co-crystal structure of a pyrazole based diphenylpropionamide GR agonist and deacylcortivazol, with the glucocorticoid receptor ligand binding domain (GR-LBD).

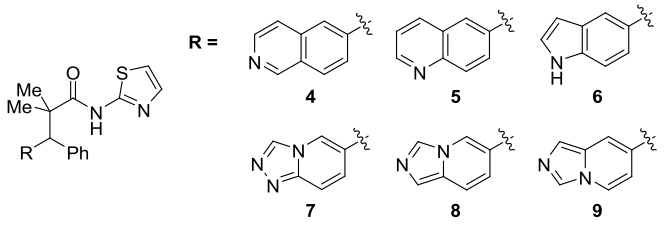
Representative synthetic pathways utilized in the preparation of these heterocycles is outlined in Schemes 1-3. The key step in these reactions is a variation of the Mukaiyama aldol reaction i.e. the addition of silylketene acetal of methyl isobutyrate under Lewis acid conditions to a highly electrophilic bisbenzylic alcohol.



Scheme 1. Reagents and conditions: (a) Me_2NCOCl, NaH, DMF, 97%; (b) PhMgBr, THF, 100%; (c) CH_2Cl_2, $BF_3.OEt_2$, 97%, (d) NaOH, MeOH, DMSO, 91%; (e) 1-bromo-4-fluorobenzene, CuI, trans-cyclohexane-1,2-diamine, K_2CO_3, Bu_4NI, dioxane, 56%; (f) 2-aminothiazole, HATU, $EtNPr^i_2$, DMF, 22-75%.

We previously reported on in vitro assays to characterize GR binding, transrepression (AP-1) and transactivation (Gal4-reporter).[11] Table 1 outlines GR binding data for the six heterocycles examined.

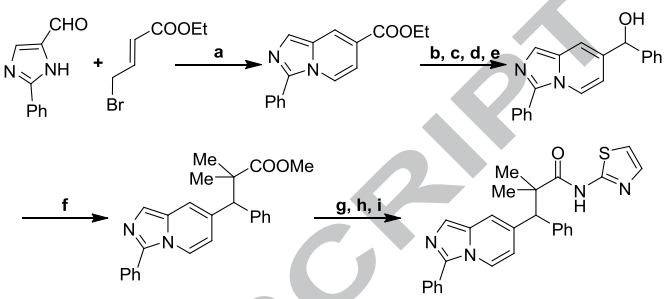
Table 1. SAR around the heterocyclic core[a]



Compd No.	GR Ki, (nM)	AP-1 repression EC_{50}, (nM)	(eff % dex)[b]
Dexamethasone	1.1	2.5	(100)
4	15	>10000	
5	85	>10000	
6	7	230	(61)
7	169	>10000	
8	13	>10000	
9	18	1200	(39)

[a] Values are means of at least two experiments done in triplicate. [b] Efficacy represented as a percentage of the maximal response of dexamethasone (100%). %dex is not reported where <5%.

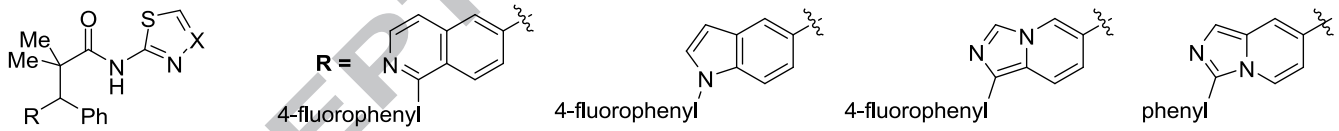
As is evident from the table isoquinoline (**4**), and the two isomeric imidazopyridines (**8**, **9**) are potent binders of GR. The potency of quinoline (**5**) in the GR binding assay is significantly lower compared to the isoquinoline (**4**). This was not completely unexpected since the X-ray co-crystal structure of a pyrazole based diphenylpropionamide GR agonist with the ligand binding domain (LBD) of GR[2b] clearly indicates an important H-bonding interaction of the nitrogen atom with Arg611 residue on helix 5. It is possible that the trajectory of the nitrogen atom in case of the quinoline does not allow it to effectively engage in a H-bonding interaction with Arg611. The GR binding potency of indole (**6**) is probably due to the interaction of the indole NH with Gln570 on helix 3 of the GR LBD. Although **4**, **6**, **8** and **9** were potent in the GR binding assay, significant improvements in functional potency (as evidenced by the lack of significant activity in the AP-1 assay) was needed for the compounds to be evaluated further.



Scheme 2. Reagents and conditions: (a) DMF, K_2CO_3, 85°C, 16 h, 29%; (b) NaOH, EtOH, 92%; (c) MeO(Me)NH-HCl, EDCI, $EtNPr^i_2$, HOBt, MeCN, 100%; (d) PhMgBr, THF, 77%; (e) $NaBH_4$, THF, EtOH, 100%; (f) $Me_2C{=}C(OMe)OSiMe_3$, $BF_3.OEt_2$, CH_2Cl_2, 78%; (g) LiOH, H_2O, dioxane, 95%; (h) chiral separation using CHIRALPAK® AD-H column; (i) 2-aminothiazole, HATU, $EtNPr^i_2$, DMF, 90-94%

As was originally described by Hirshman et. al,[3] incorporation of a 4-fluorophenyl moiety at the N-1 position of a pyrazole- (which serves as an A-ring mimic of steroids), significantly improves the functional potency relative to the des-fluorophenyl analog. In the reported X-ray co-crystal structure of deacylcortivazol with GR LBD,[4] key interactions include the engagement of pyrazole N-2 with Gln570 and the significant expansion of the GR binding pocket to accommodate the arylpyrazole moiety.

Table 2. Phenyl substituted heterocycles[a]



X = CH; 10 **X = N; 11** **X = CH; 12** **X = CH; 13** **X = N; 14** **X = CH; 15** **X = N; 16**

Compd No.	GR Ki, (nM)	AP-1 repression EC_{50}, (nM)	(eff % dex)[b]	GAL 4 reporter EC_{50} (nM)	(eff % dex)[b]
Dexamethasone	1.1	2.5	(100)	4.2	(100)
10	285	>10000			
11	196	>10000			
12	13	220	(60)		
13	3	16	(66)	103	(74)
13 enantiomer1	4	>5000		>10000	
13 enantiomer2	1	6	(73)	60	(69)
14	3	36	(68)	262	(66)
14 enantiomer1	6	1200	(24	>10000	
14 enantiomer2	2	24	(72)	118	(65)
15	5	60	(70)	360	(32)
15 enantiomer1	11	>2500		>10000	
15 enantiomer2	2	23	(67)	147	(51)
16	3	899	(66)	2000	(30)
16 enantiomer1	5	1122	(34)	>10000	
16 enantiomer2	1	254	(61)	613	(43)

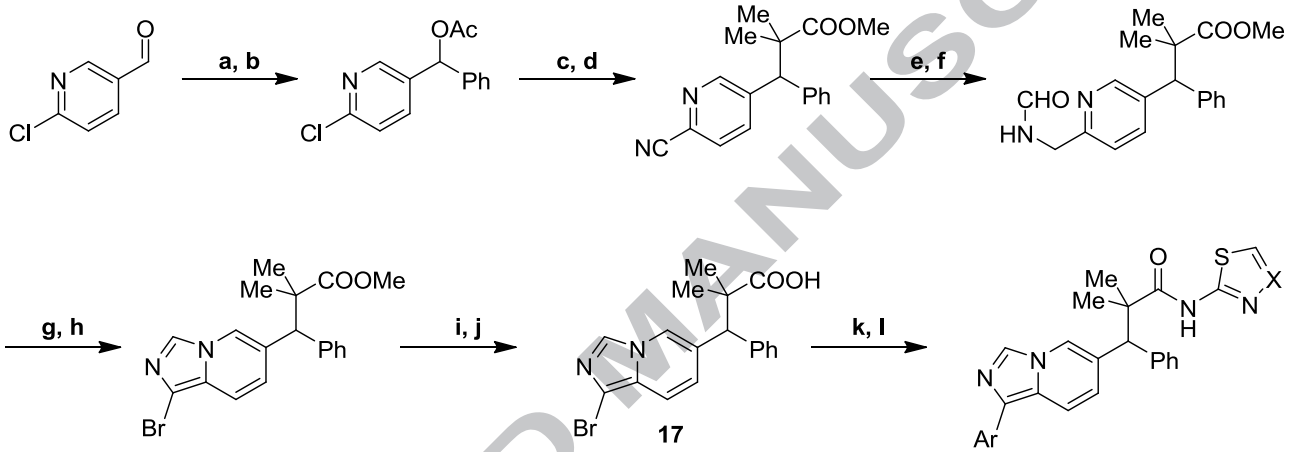
[a] Values are means of at least two experiments done in triplicate. [b] Efficacy represented as a percentage of the maximal response of dexamethasone (100%). %dex is not reported where <5%.

This observation has been taken advantage of by a number of groups who have incorporated 4-fluorophenyl moiety into non-steroidal GR modulators leading to compounds with dissociated profiles. By analogy to what has been described above, we reasoned that incorporating the 4-fluorophenyl moiety to scaffolds **4, 6, 8** and **9** should lead to compounds with improved functional potency.

The synthesis of compound **15** is outlined in Scheme 2 and the GR binding and functional data for the corresponding compounds is shown in Table 2.

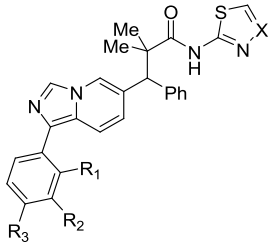
As is clear from Table 2, appending the 4-fluorophenyl moiety to the indole did not lead to significant changes in functional potency, as judged by the activity of the compound in the AP-1 assay (compare compound **12** with **6**). This may be because the lack of a H-bond donor in compound **12** is compensated by the gain in hydrophobic interactions of the 4-fluorophenyl moiety with the "arylpyrazole" pocket of GR. However, the loss of both binding potency for the 4-fluorophenylisoquinoline analog was surprising (compare **10** with **4**). In contrast, however, the imidazopyridines (**13** and **15**) showed significant improvements in functional potency when compared to their des-phenyl or des-fluorophenyl analogs, **8** and **9** respectively, suggesting that the 4-fluorophenyl moiety in the isoquinoline analog **10**, may not have the right trajectory to be accommodated in the "arylpyrazole" pocket of GR.

The enantiomers of compound **15** were prepared from the corresponding acid intermediate (step h, Scheme 2) and their potency in the GR binding and functional assays was established. As Table 2 indicates, both compounds displayed similar potency



Scheme 3. Reagents and conditions: (a) PhMgBr, THF, 100%; (b) Ac_2O, DMAP, $EtNPr^i_2$, CH_2Cl_2, 92%; (c) $Me_2C{=}C(OMe)OSiMe_3$, $TiCl_4$, CH_2Cl_2, 79%; (d) $Zn(CN)_2$, $PdCl_2$-dppf-CH_2Cl_2, Zn, DMA, 120°C, 2h, 63%; (e) H_2, Pd/C, HCl, MeOH, 2.5h, 98%; (f) HCO_2H, 90°C, 73%; (g) $POCl_3$, PhMe, 115°C, 94%; (h) NBS, MeCN, -10°C then RT, 56%; (i) chiral separation using CHIRALPAK®AD-H column; (j) LiOH, H_2O, dioxane 100%; (k) $ArB(OH)_2$, $PdCl_2$-dppf-CH_2Cl_2, K_3PO_4, DMF, 90°C; (l) 2-aminothiazole or 2-amino-1,3,4-thiadiazole, HATU, $EtNPr^i_2$, DMF, 30-60% combined yield for (k) and (l).

Table 3. Substituted 1-phenylimidazo[1,5-a]pyridine enantiomer 2 analogs[a]



Compd No.	Structure X	R_1	R_2	GR R_3	AP-1 repression Ki, (nM)	EC_{50}, (nM)	(eff % dex)[b]	GAL 4 reporter EC_{50} (nM)	(eff % dex)[b]
Dexamethasone					1.1	2.5	(100)	4.2	(100)
18	CH	H	CN	H	4	225	(30)	>10000	
19	N	H	CN	H	4	1350	(32)	>10000	
20	CH	H	H	CN	4	89	(37)	>10000	
21	N	H	H	CN	2	140	(37)	>10000	
22	N	H	CH_2OH	H	5	>5000		>10000	
23	CH	F	H	F	2	14	(75)	78	(73)
24	N	F	H	F	1	15	(69)	117	(61)
25	CH	H	Cl	F	8	114	(26)	>10000	
26	N	H	Cl	F	5	111	(20)	>10000	

[a] Values are means of at least two experiments done in triplicate. [b] Efficacy represented as a percentage of the maximal response of dexamethasone (100%). %dex is not reported where <5%.

in the GR binding assay, however, enantiomer 2 was significantly more potent in the functional assay than enantiomer 1. A similar trend was noticed for the thiadiazole analogs (**16** enantiomer 1 and 2) and the imidazopyridine isomers (**13** enantiomer 1 and 2 and **14** enantiomer 1 and 2). The absolute configuration of the more active isomer was not established.

Since the binding and functional potencies of the imidazopyridines (**13** and **15**) were similar, we decided to use imidazopyridine (**13**) to further investigate the 4-fluorophenyl SAR because of the accessibility of the key bromo intermediate (**17**, Scheme 3) for Suzuki coupling reactions. The Suzuki coupling reactions were carried out using the homochiral bromo compound (enantiomer 2, step i, Scheme 3) derived from intermediate (**17**), since compounds derived from this intermediate were active in the functional assay as shown in Table 2. Reaction conditions for the Suzuki coupling reaction are shown in Scheme 3 and the GR binding and functional data for the corresponding analogs is shown in Table 3. [5]

In general most compounds were potent in the GR binding assay. However, for the limited number of compounds examined, the fluoro (**13**, **14**, Table 2) and the difluoroanalogs (**23**, **24,** Table 3) had the best functional potency in the AP-1 assay. A significant loss in functional potency (AP-1) was seen with meta substituted (**18**, **19**, **22**) or meta-para disubstituted analogs (**25**, **26**). A small group at the para position appears to be preferred since there is a significant loss in functional potency in the AP-1 assay with the p-cyano analog (**20**, **21**).

In conclusion, a series of novel heterocyclic modulators of glucocorticoid receptor have been identified. SAR suggests that a combination of a H-bond acceptor (probably engaging Gln570 or Arg611) and a 4-fluoropheny substituent is optimal for improving functional potency in the AP-1 transrepression assay. Unfortunately, compounds that were active in the transrepression assay were also potent in the in vitro functional transactivation assay (GAL4 assay) and therefore were not pursued further as non-steroidal GR agonists.

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