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Novel glucocorticoids containing a 6,5-bicyclic core fused to a pyrazole ring: Synthesis, in vitro profile, molecular modeling studies, and in vivo experiments

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Abstract—Chemistry was developed to synthesize the title series of compounds. The ability of these novel ligands to bind to the glucocorticoid receptor was investigated. These compounds were also tested in a series of functional assays and some were found to display the profile of a dissociated glucocorticoid. The SAR of the 6,5-bicyclic series differed markedly from the previously reported 6,6-series. Molecular modeling studies were employed to understand the conformational differences between the two series of compounds, which may explain their divergent activity. Two compounds were profiled in vivo and shown to reduce inflammation in a mouse model. An active metabolite is suspected in one case.

Treatment of inflammatory disease remains a serious medical challenge. Although a variety of pharmaceutical agents are available to treat inflammation, none are ideal and the search continues for new methods to combat this affliction. Glucocorticoids (e.g., dexamethasone and prednisolone) constitute one of the most powerful and effective classes of agents for treating inflammation. However, these drugs suffer from serious side effects.[1–4]

Glucocorticoids (GCs) target the glucocorticoid receptor (GR), which is a nuclear hormone receptor. Upon binding to a GC ligand, GR undergoes a conformational change and translocates to the nucleus of the cell. In this active state, GR can suppress pro-inflammatory cytokines, such as IL-6 and TNF-α, leading to relief from inflammation.[1–4] However, the activated GR also upregulates a number of cellular processes that produce undesired side effects. This is particularly true when GCs are administered systemically over prolonged periods of time. Such extended treatment with artificially high levels of GCs leads to a situation mimicking Cushing's syndrome (endogenous corticoid excess) with complications including muscle wasting, osteoporosis, and hyperglycemia due to increased gluconeogenesis.[5]

Both the desired anti-inflammatory effects and the undesired side effects of GCs are mediated via GR. However, recent scientific evidence indicates that anti-inflammatory processes are mediated through a GR–GC *monomer* interacting directly with proinflammatory transcription factors including AP-1 and NF-κB. This process is termed *transrepression*. In contrast, side-effects

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Keywords: Glucocorticoid; Dissociation; Transrepression; Transactivation; Inflammation.

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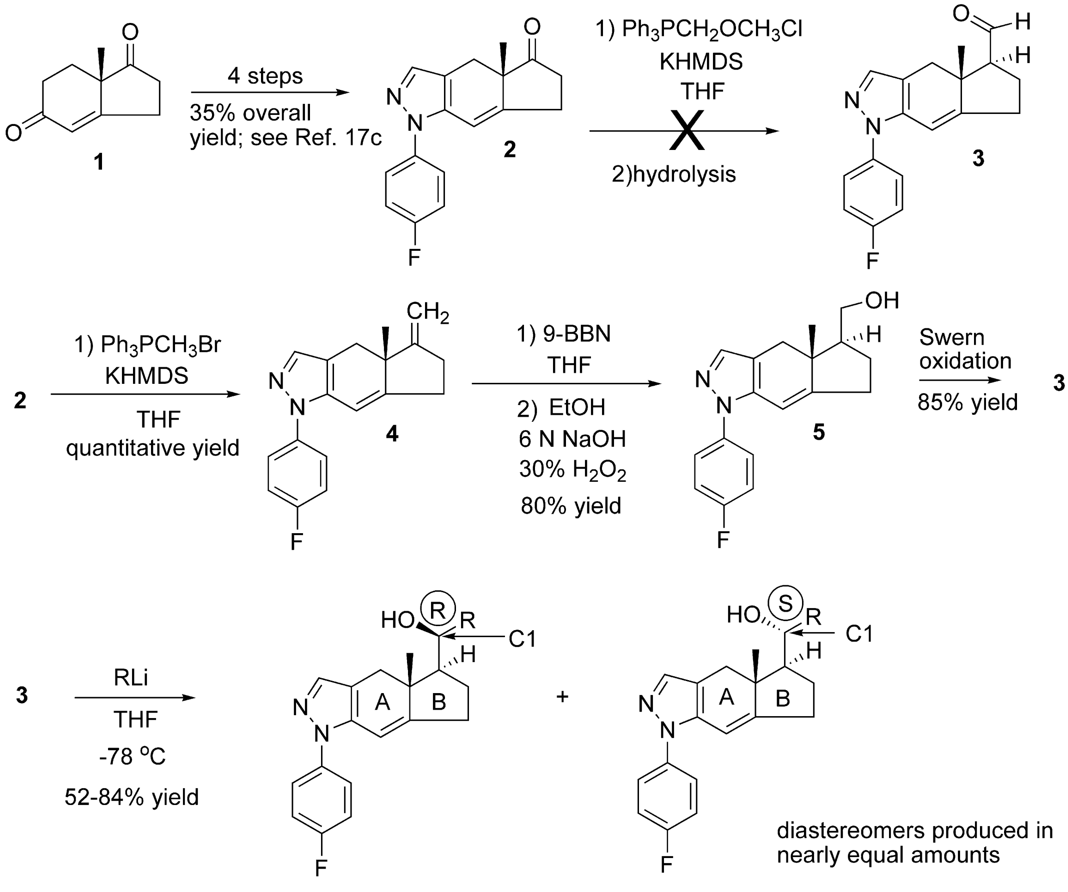
apparently result from a GR–GC *dimer* binding to DNA and upregulating certain metabolic genes, which is known as *transactivation*.[6–15] This hypothesis regarding the dual nature of GR has allowed scientists to entertain the possibility that a ‘dissociated’ GC could be developed.[16] A GC that favors the monomeric GR–GC complex over the dimeric state could retain the desired anti-inflammatory effects of GCs while eliminating side effects. The discovery of such a dissociated GC has been the goal of our research program.

Several recent papers from these laboratories have described a novel GC platform consisting of a truncated steroid (A and B rings) with an appended *p*-fluorophenyl pyrazole.[17–19] The *p*-fluorophenyl pyrazole provides specificity for GR over other steroid receptors. Substituents on the B-ring were tuned to modulate transrepression and transactivation activities and attempt to dissociate the two parameters. Examples have been reported in which the B-ring was substituted with an aryl or heteroaryl group and a hydroxyl moiety.[17a] In these cases, the A,B-ring system was a classical steroid 6,6-ring system (6,6-system). More recently, ketal substituents were examined on the B-ring.[17c] In addition to the traditional 6-membered B-ring, a 5-membered B-ring was also explored. In this work, a general trend appeared in which compounds with a 5-membered B-ring had better activity in the transrepression assays than those with a 6-membered B-ring.[17c] However, binding and, more importantly, functional activity in the transactivation assay were similar. Based on this general trend of improved transrepression activity for compounds containing a 5-membered B-ring, an exploration of this core structure was undertaken with hydroxy-aromatic and heteroaromatic substituents on the B-ring. It was also believed that compounds with a 5-membered B-ring should have better pharmacokinetic properties as there are fewer sites available for metabolism in the smaller ring. Hydroxy-aromatic and heteroaromatic substituents have now been examined in the 6,5-system and the findings are reported in this Letter.

The synthesis of these novel GCs is outlined in Scheme 1. An initial attempt was made to adopt the route used for synthesis of the 6,6-system to our 6,5-platform. This strategy worked well for conversion of the known Hajos-Parrish ketone (**1**) to intermediate **2**, which contains the requisite *p*-fluorophenyl pyrazole. At this point in the synthesis, an attempt was made to convert ketone **2** to aldehyde **3** as had been done previously for the 6,6-template.[17a] However, the transformation was problematic. Conversion to an enol-ether intermediate via a Wittig reaction and hydrolysis to the aldehyde proceeded in poor yield. Furthermore, equilibration of the diastereomeric mixture of aldehyde products to the desired *S*-configuration at the newly formed stereocenter was unsatisfactory. Therefore, an alternative protocol



Scheme 1. Synthesis of glucocorticoids with 6,5-ring system.

was employed.[20] Conversion of **2** to alkene **4** using a Wittig reaction was quantitative. Hydroboration proceeded cleanly with a selectivity of ~25:1 to give **5**, which was oxidized to **3** in good yield via a Swern reaction.

As seen previously in the 6,6-series, aryl and heteroaryl lithium reagents added smoothly to aldehyde **3** providing secondary alcohol products. However, the stereochemical outcome of the addition reaction differed greatly between the 6,5- and 6,6-series. Whereas additions to the 6,6-aldehyde had provided the *R*-diastereomer (β-hydroxyl) almost exclusively, additions to the 6,5-aldehyde gave nearly equal amounts of the *R* and *S* isomers at the newly formed stereocenter. The selectivity in the addition was never better than 2:1 and often closer to 1:1. The diastereomers were separated by either silica gel chromatography or chiral HPLC in more challenging cases.[21]

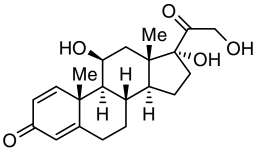
Following synthesis, the capacity of these novel GC ligands to bind GR was tested by measuring their ability to displace radiolabeled dexamethasone. The GCs were then further evaluated in a series of in vitro assays.[22] In order to determine the extent to which the GCs were dissociated, markers for transrepression (TR) and transactivation (TA) were measured in both mouse and human cell lines.[23] In the human A549 lung carcinoma cell line, repression of the inflammatory cytokine interleukin-6 (IL-6) relative to a dexamethasone control was measured.[24] IL-6 was also used to evaluate TR in a mouse cell line. To discern the TA activity of these compounds, tyrosine amino transferase (TAT) activity was measured in human cells. TAT is a hepatic gene known to be upregulated by GCs.[25] In mouse cell lines, TA was analyzed by investigating the levels of glutamine synthetase, an enzyme associated with protein metabolism in muscle.[26]

The investigation of GC ligands containing the 6,5-A,B-ring system began with the synthesis of compounds containing monocyclic substituents at the C1 position that had shown potency in the 6,6-system; *p*-fluorophenyl and thiophene rings were evaluated. The in vitro data for these compounds are shown in Table 1, with results from previously reported compounds in the 6,6-series included for comparison.[17] Striking differences in the activity of the two series were apparent. The 6,5-*p*-fluorophenyl analogs (**8** and **9**) bound much more weakly to GR than their 6,6-system counterparts (**6** and **7**), displacing less than 65% of [^{3}H]dexamethasone in our binding assay. While compound **6** was a moderately potent, well-dissociated, benchmark compound for our program, its counterpart, compound **8**, displayed almost no functional activity in both mouse and human cell lines. Compound **9** was more active but still fairly weak, particularly in the mouse assays, and was not deemed to be of interest, especially in light of the weak GR binding that was observed. The results obtained for the thiophene substituent were also unsatisfying. Diastereomers **11** and **12** bound to GR with reasonable affinity and had promising, dissociated profiles in the human cell lines with >75% of dexamethasone's activity in TR and very little TA. Unfortunately, the thiophene substituents in the 6,5-series did not display the balanced mouse/human profile seen in the 6,6-series (i.e., compound **10**). Compounds **11** and **12** had almost no activity in the mouse cell lines and therefore could not be evaluated in an in vivo mouse model of inflammation.

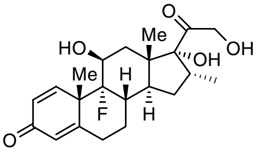
Having obtained disappointing results with monocyclic substituents in the 6,5-series, attention was turned to bicyclic substituents at C1, which had displayed favorable profiles in the 6,6-series (Table 2). The benzothiophene ring system had been one of the best substituents in the 6,6-series, and investigation of the 6,5-series was begun with this moiety. Whereas a connection to either the 2- or the 3-position of the benzothiophene ring had yielded active GR ligands in the 6,6-series (compounds **13**, **16**, and **17**), a striking difference between the two points of attachment was observed in the 6,5-series. Forming a linkage between the B-ring and the 2-position of the benzothiophene ring led to compounds that were functionally inactive (compounds **14** and **15**). However, attachment of the benzothiophene at the 3-position led to a large improvement in potency and functional activity; these were the first GCs observed in the 6,5-series with >50% of dexamethasone's activity in both the mouse and human TR assays. Compound **18**, bearing an *R* configuration at the hydroxyl center, had similar potency to compound **19** (*S* hydroxyl) in the GR binding assay and the two compounds had comparable EC_{50}'s in the mouse and human IL-6 TR assays. However, when their efficacy was measured relative to dexamethasone, compound **18** was found to have a larger window of dissociation. Compound **18** achieved >70% of dexamethasone's activity in both TR assays, and <35% of dexamethasone's activity in the two TA assays. Compound **19** had >90% TR relative to dexamethasone, but also nearly 60% TA in both mouse and human species. Thus, the trend previously observed for GCs, in which compounds with the strongest functional activity showed little dissociation, was continued.[17] Having obtained promising results for the benzothiophene diastereomers, exploration continued of bicyclic ring systems. A naphthyl substituent yielded similar results: attachment at the 2-position was not tolerated, leading to complete loss of functional activity (compounds **20** and **21**), while linkage to C1 of the naphthyl ring led to a pair of potent diastereomers (compounds **22** and **23**). As in the benzothiophene series, although both **22** and **23** bound to GR with near equal affinity, the diastereomer with an *S* configuration at the hydroxyl center (**23**) showed greater functional activity, but a smaller window of dissociation. Finally, a benzofuran moiety was investigated, although in this case only attachment at the 3-position was undertaken. Again, both diastereomers showed strong binding affinity for GR and good functional activity. Interestingly, in this case, the diastereomer with an *S* configuration at the hydroxyl center (**25**) had a larger window of dissociation, particularly in the assays using human cell lines.

Having synthesized compounds with a range of monocyclic and bicyclic hydroxy-aromatic and heteroaromatic substituents in the 6,5-series, it was evident that the

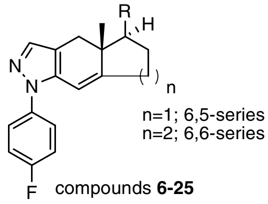
Table 1. Binding of GCs with monocyclic aromatic substiuents at C1 to GR; transrepression and transactivation in mouse and human cell lines



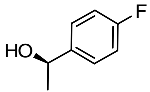
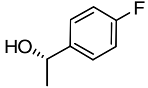
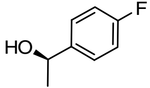
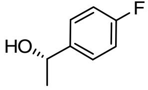
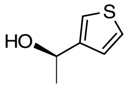
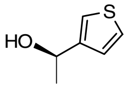
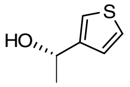
prednisolone



dexamethasone



compounds **6-25**

Compound	*n*	R	GR[a]	hIL-6[b]		hTAT[c]		mIL-6[d]		mGS[e]	
			IC_{50} (nM)	EC_{50} (nM)	%dex	EC_{50} (nM)	%dex	EC_{50} (nM)	%dex	EC_{50} (nM)	%dex
Prednisolone	—	—	13.8	4.5	102	24	82	5.7	95	3.4	89
6	2		5.3	9.7	67	nd	25	22	74	nd	31
7	2		10.4	16.5	48	nd	15	6.5	70	nd	23
8	1		17.4*	nd	26	nd	3	nd	19	nt	nt
9	1		12.0*	6	58	nd	7	392	62	nd	21
10	2		5.1	1.0	81	nd	28	23	74	nd	21
11	1		8.0	21	77	nd	17	145	44	nd	19
12	1		28	2.1	80	nd	7	ia	ia	nt	nt

nd, not determined; EC_{50} values were not determined in cases where %dex ⩽ 35%. ia, inactive; %dex <10%. nt, not tested. ∗, Inflection point rather than IC_{50}. At the maximum dose tested (10 μM) for these two compounds only 55–65% of [^{3}H]dexamethasone was displaced from GR; >90% of [^{3}H]dexamethasone was displaced in the binding assay for all other compounds reported here.

[a] Binding to hGRα receptor determined by displacement of [^{3}H]dexamethasone.

[b] Human IL-6 assay in A549 lung carcinoma cell line.

[c] Activity in human tyrosine amino transferase (TAT) assay in HepG2 cells.

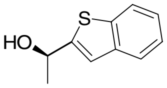
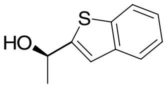
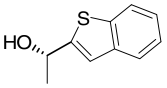
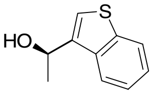
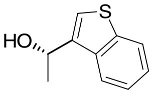
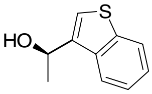
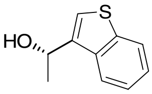
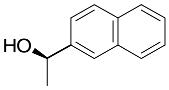
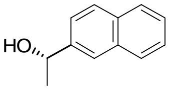
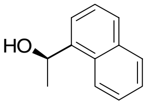
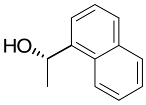
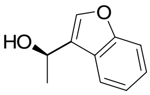
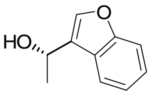
[d] Mouse IL-6 assay in peritoneal exudate cells harvested from C57Bl/6 mice.

[e] Mouse glutamine synthetase (GS) assay in C2C12 cells.

SAR was much tighter than in the 6,6-series. The trend observed in the ketal work did not follow in the hydroxyl series. Rather than seeing improved transrepression upon moving from the 6,6- to the 6,5-core, many compounds bearing the same substituents had very little activity, although a select few had the desired profile. In an attempt to better understand these results, molecular modeling was employed. To explore the structural impact of B ring size on activity, we chose to study the conformational preferences for a subset of compounds that exhibited disparate activity profiles, the fluorophenyls and the 2- or 3-benzothiophenes. The compounds with an *R* configuration at the hydroxyl group, **6**, **8**, **13**, **14**, **16**, and **18**, were studied first. The two benzothiophenes, **16** and **18**, were then compared to their analogs, **17** and **19**, which have an *S* configuration at the hydroxyl group. Two hundred conformations were generated for each of the compounds using an implementation of distance geometry, which incorporates the theory and algorithm as previously described.[27] Each set of conformers was then energy minimized using MMFFs with a distance-dependent dielectric of 2*r* without explicit solvent.[28] Alignment of all the compounds onto the pyrazole moiety common to each provides the basis for our discussion.

The presence of the axial methyl at what would correspond to the C10 position in the steroid core forces the pendant aromatics to position the lowest energy conformers on the opposite face of the tricyclic system; the α face using the steroid frame of reference. In all of the 6,6-systems, the most stable orientation of the pendant aromatic is one in which the aromatic is most removed from the axial methyl; ∼160° angle on the dihedral defined by the four atoms starting at the C10 position and ending with the aromatic. Conversely, in the

Table 2. Binding of GCs with bicyclic aromatic substiuents at C1 to GR; transrepression and transactivation in mouse and human cell lines

Compound	*n*	R	GR[a]	hIL-6[b]		hTAT[c]		mIL-6[d]		mGS[e]	
			IC_{50} (nM)	EC_{50} (nM)	%dex	EC_{50} (nM)	%dex	EC_{50} (nM)	%dex	EC_{50} (nM)	%dex
Prednisolone	—	—	13.8	4.5	102	24	82	5.7	95	3.4	89
13	2		29.1	19	66	nd	22	42	66	1209	41
14	1		69.1	nd	34	ia	ia	nd	22	ia	ia
15	1		689	ia	ia	ia	ia	ia	ia	nd	nd
16	2		5.1	18	86	nd	21	54	78	nd	33
17	2		1.5	6	94	356	43	11	99	3	100
18	1		2.1	5	71	nd	29	16	73	nd	33
19	1		3.1	10	92	675	62	14	92	36	58
20	1		86	nd	14	ia	ia	ia	ia	ia	ia
21	1		198	nd	13	ia	ia	ia	ia	ia	ia
22	1		5	48	80	nd	28	46	78	68	36
23	1		6.4	33	87	703	65	32	88	94	71
24	1		2.3	3	83	1624	57	13	83	39	88
25	1		3.9	5	78	1315	21	33	81	92	56

nd, not determined; EC_{50} values were not determined in cases where %dex $\leqslant$ 35%. ia, inactive; %dex <10%. nt, not tested. At the maximum dose tested (10 μM) for these two compounds only 55–65% of [^{3}H]dexamethasone was displaced from GR; >90% of [^{3}H]dexamethasone was displaced in the binding assay for all other compounds reported here.

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[d] Mouse IL-6 assay in peritoneal exudate cells harvested from C57Bl/6 mice.

[e] Mouse glutamine synthetase (GS) assay in C2C12 cells.

6,5-systems (except for compound **19** which maps to the 6,6-system in this instance), the energetically favored position of the aromatic is proximate to the axial methyl at ~65° angle along the same dihedral as above. In the case of the *p*-fluorophenyl compounds **6** and **8** and the 2-benzothiophenes **13** and **14**, the difference in energy between the lowest energy conformer and the next higher group is ~1.5 kcal/mol with a barrier to rotation between the two of the order of 2–4 kcal/mol.[29] For the 3-benzothiophenes **16** and **18**, the difference between the

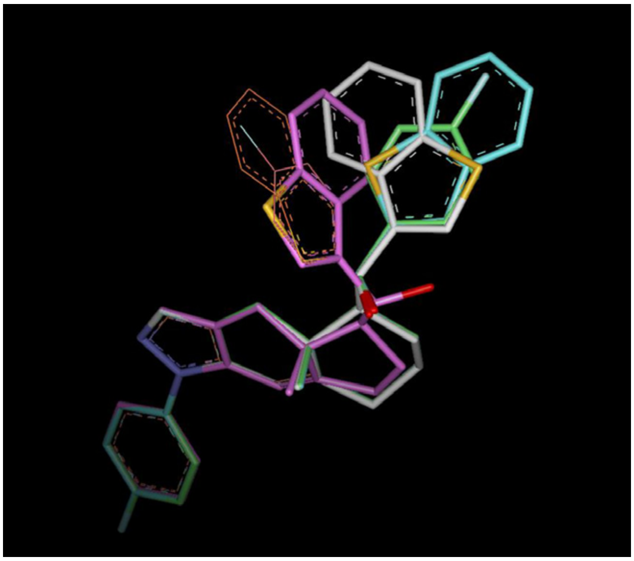

Figure 1. Superposition of the lowest energy conformers representing compounds **6** (light green), **8** (pink), **13** (cyan), **14** (orange), **16** (white), and **18** (purple) aligned to the pyrazole common to each. The compounds with the least activity (**8** and **14**) are depicted in wire.

lowest energy conformer group and the next higher is ~2.5 kcal/mol with a similar rotational barrier to that noted above.

In examining the superposition of the lowest energy conformer for the six compounds with an *R* configuration at the hydroxyl group (depicted in Fig. 1), it becomes clear that one might first correlate activity with the rotation angle about the bond connecting the aromatic to the fused ring system. The compounds that favor placement of the pendant aromatic near the axial methyl group at C10, the 6,5-ring systems, suffer the largest drops in binding and activity. The exception to this is when the compound can extend its aromatic group into the space occupied by the pendant aromatics in the 6,6-system. As shown in Figure 1, compound **18** is capable of this feat and, although not modeled but by extension, compounds **22** and **24** could potentially achieve this as well. The other 'rescue' of potency for the 6,5-system is by inverting chirality of the hydroxyl group from *R* to *S*, which, as noted above, causes the benzothiophene of the 6,5-compound **19** to occupy the region of space coincident with activity as depicted in Figure 2. The inversion of chirality and concomitant potency enhancement in the 6,5-ring system might also apply to compounds **23** and **25**.

Although, as rationalized by molecular modeling, a number of analogs lost activity in moving from the 6,6- to the 6,5-series, some were still quite potent. We decided to profile two of these compounds, **18** and **19**, in vivo. Initial results in a mouse anti-inflammatory model that measures inhibition of LPS-induced TNFα were promising (Table 3).[30] Both compounds were similar to prednisolone in their ability to reduce inflammation, albeit at a higher dose (30 mpk vs 3 mpk). Encouraged by this result, we determined the pharmacokinetic (PK) profile of these two compounds. Surprisingly, the two diastereomers differed markedly in their PK. Dosed intravenously in a mouse, compound **19** had a normalized AUC of 1.7 μM h kg/mg, a clearance (Cl) of 22.3 ml/min/kg, a half-life of 7.8 h, and an oral bioavailability (F) of 34%; the type of strong PK parameters envisioned for this 6,5-series. In contrast, compound **18** had a normalized AUC of only 0.4 μM h kg/mg, an extremely high Cl of 106.8 mL/min/kg, a half-life of 3.1 h, and an *F* of 19%. The relatively poor PK of **18** was quite disappointing as this was a fairly well-dissociated compound in vitro, of great interest to the program. Furthermore, the result of the PK experiment

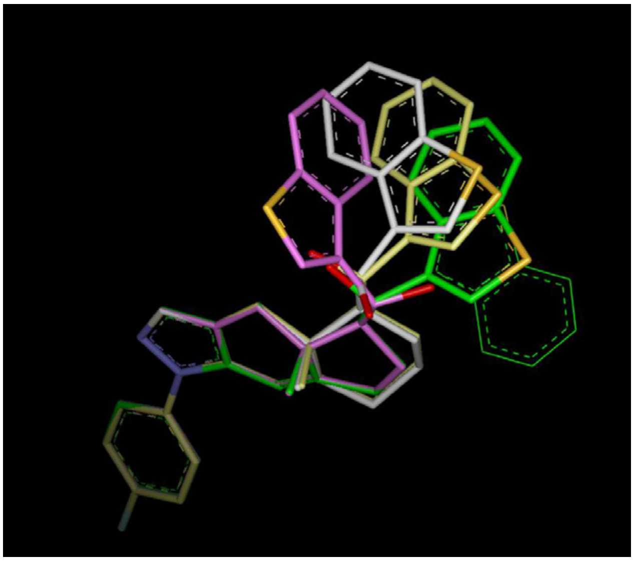

Figure 2. Superposition of the lowest energy conformers for the 6,6- and 6,5-benzothiophene diastereomers. These are the *R* hydroxyl group compounds **16** (white) and **18** (purple) and the *S* hydroxyl group compounds **17** (yellow) and **19** (green). The benzothiophene ring of **19** has two isoenergetic conformers, one of which is shown as wire.

Table 3. In vivo efficacy

Compound (dose)	Absolute inhibition of TNFα (%)	Inhibition of TNFα relative to prednisolone (%)
Prednisolone (3 mpk)	71	100
18 (30 mpk)	80	113
19 (30 mpk)	73	103

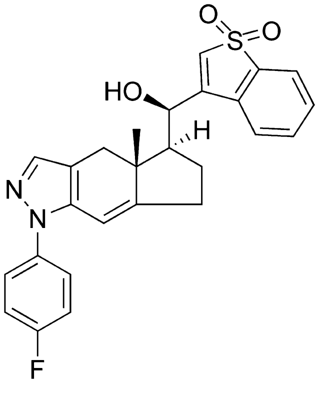

Figure 3. Compound **26.**

with **18** called into question the impressive PD result and raised the suspicion that there might be an active metabolite. Exposure of compound **18** to mouse liver microsomes resulted in rapid formation of a major metabolite with a molecular weight greater than the parent by 32 mass units.[31] Although the identity of this species was not proven, compound **26** (Fig. 3) was hypothesized to be the metabolite. Compound **26** could be prepared in low yield (~15%) by treatment of compound **18** with *m*-CPBA. Compound **26** was profiled in vitro and shown to be very potent and *not dissociated*.[32] This finding highlights yet another difficulty of working in the dissociated glucocorticoid field: due to subtle structural differences between compounds that have a significant window of dissociation and those that do not, one must ensure that not only is a parent compound well dissociated, but that any active metabolites are as well.

In summary, a series of GR ligands containing a 6,5-A,B-ring system with a *p*-fluorophenyl pyrazole appendage and an aromatic or heteroaromatic substituent at the C1 hydroxyl center have been synthesized using newly developed chemistry. These compounds were evaluated in functional in vitro assays and compared to analogous compounds containing a 6,6-A,B-ring system. It was found that monocyclic aromatic or heteroaromatic B-ring substituents lacked potency in our TR and TA assays, particularly in mouse cell lines. Bicyclic ring systems displayed strong activity in both mouse and human cell lines, although the SAR was much tighter than in the 6,6-series, with the point of attachment to the aryl or heteroaryl substituent of critical importance. Molecular modeling was employed to better understand this divergence in activity between the 6,6- and 6,5-systems. Modeling explained the in vitro data nicely with the lowest energy conformation of active compounds displaying the aromatic or heteroaromatic substituent in one region of space and inactive compounds displaying their substituents in another. Interestingly, as in the 6,6-series, a benzothiophene paired with an *R* configuration at the hydroxyl center (compound **18**) gave the best profile, with TR activity more than double that of TA in both mouse and human cell lines. Although this partially dissociated compound was able to suppress inflammation in a mouse PD model, several lines of evidence point to a poorly dissociated metabolite that may account for the strong in vivo activity. This is a cautionary tale for other investigators working in the field. As in the 6,6-series, dissociative properties dropped off in the most potent compounds (i.e., **19** and **23**), and although compounds with similar properties were identified, the 6,5-series does not appear to offer any advantage over the previously explored 6,6-series in terms of a dissociative window.

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32. Data for compound **26**: GR IC$_{50}$ = 2.8 nM, hIL-6 EC$_{50}$ = 2 nM (92% dex), hTAT EC$_{50}$ = 24 nM (77% dex), mIL-6 EC$_{50}$ = 4.8 nM (88% dex), and mGS EC$_{50}$ = 3.3 nM (67% dex). **26** was not prepared in sufficient quantity to be tested in vivo.