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Novel Synthesis of the Hexahydroimidazo[1,5b]isoquinoline Scaffold: Application to the Synthesis of Glucocorticoid Receptor Modulators†

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The first stereoselective synthesis of the hexahydroimidazo[1,5b]isoquinoline (HHII) scaffold as a surrogate for the steroidal A-B ring system is described. The structure−activity relationships of the analogs derived from this scaffold show that the basic imidazole moiety is tolerated by the glucocorticoid receptor (GR) in terms of binding affinity, although the partial agonist activity in the transrepressive assays depends on the substitution pattern on the B-ring. More importantly, most compounds in the HHII series bearing a tertiary alcohol moiety on the B-ring are either inactive or significantly less active in inducing GR-mediated transactivation, thus displaying a "dissociated" pharmacology in vitro.

Introduction

The glucocorticoid receptor (GR[a]) is a member of the nuclear hormone receptor superfamily and a member of the class 1 steroid hormone family of transcription factors. Glucocorticoids that interact with GR have been used for over 50 years to treat inflammatory diseases. A number of studies have shown that glucocorticoids exert their anti-inflammatory activity via the inhibition of the transcription factors NF-κB and AP-1.[1] This inhibition is termed transrepression. It has been shown that the primary mechanism for inhibition of these transcription factors is via a direct physical interaction of the GR monomer that alters the transcription factor complex and inhibits the ability of NF-κB and activator protein-1 (AP-1) to stimulate transcription.[2] Other mechanisms such as sequestration of coactivators by GR have also been proposed.[3,4]

While transrepressive mechanisms contribute to the anti-inflammatory activity of glucocorticoids, the interaction of a glucocorticoid with GR can also lead to the induction and transcription of certain genes such as tyrosine amino transferase (TAT). This induction of transcription is termed transactivation. Unlike transrepression, transactivation appears to require dimerization of GR and binding to consensus sequences termed as glucocorticoid response element (GRE).

Studies employing transgenic GR dimerization defective mice that cannot bind DNA have shown that the transactivation (DNA binding) activities of GR could be separated or dissociated from the transrepressive (non-DNA binding) effect of GR. These studies also suggest that many of the side effects related to glucocorticoid therapy are due to the ability of GR to induce transcription of various genes involved in metabolism, whereas transrepression, which does not require DNA binding, leads to suppression of inflammation.[5,6] These studies suggested the potential of designing GR ligands that would maintain the anti-inflammatory properties associated with transrepression and reduce the side effects associated with transactivation, thereby improving the therapeutic index of this important class of anti-inflammatory drugs.[7]

Based on this observation a number of reports have appeared in the open and patent literature[8,9] describing the in vitro and in vivo characterization of "dissociated glucocorticoids", also referred to as "selective glucocorticoid agonists." In 2004, Ali et al .[10] and Scanlan et al.[11] reported the synthesis and SAR of pyrazolo[3,2-*c*] analogs (**3**) as partial agonists in various in vitro functional assays of transactivation and transrepression for hGR alpha (Figure 1). Both groups (i) removed the C and D rings of fluorocortivazol (**2**) while maintaining the key hydroxyl group meant to mimic the C-11 hydroxyl group of glucocorticoids and (ii) retained the 4-fluorophenylpyrazole moiety, first identified by Hirschmann et al.[12] as an excellent surrogate for the 3-keto group of dexamethasone (**1**) or 16α-methylcortisol, with enhanced anti-inflammatory activity.

Although a few other heterocycles have been prepared as a replacement for the pyrazole moiety of fluorocortivazol,[13] to the best of our knowledge, the isosteric and isoelectronic replacement of the pyrazole group with an imidazole has not been reported in over four decades of steroid research. One reason could be that most of the heterocyclic surrogates for the 3-keto group of steroids are made from either commercially available Wieland-Mischer ketone or from functionalized 2-formyl-substituted steroids. The presence of a nitrogen atom at the ring junction necessitated a completely new synthesis of the hexahydroimidazo[1,5b]isoquinoline (hereafter, HHII, see **4**, Figure 1) scaffold. This paper reports the first stereoselective synthesis of the HHII ring system as a replacement for the A-B ring of the glucocorticoid scaffold, wherein the pyrazole moiety in the Scanlan/Merck chemotype is replaced by an imidazole ring. We also report the consequences of replacing the neutral pyrazole ring with a basic imidazole moiety (predicted $pK_{BH^+} \sim 6.4$) on the SAR of these compounds and their potential to function as GR modulators.

†Dedicated to Dr. A. V. Rama Rao on the occasion of his 75th birthday.

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[a] Abbreviations: HHII, hexahydroimidazo[1,5b]isoquinoline; GR, glucocorticoid receptor; TAT, tyrosine amino transferase; GRE, glucocorticoid response element; AP-1, Activator Protein-1; ELAM, Endothelial Leukocyte Adhesion Molecule.

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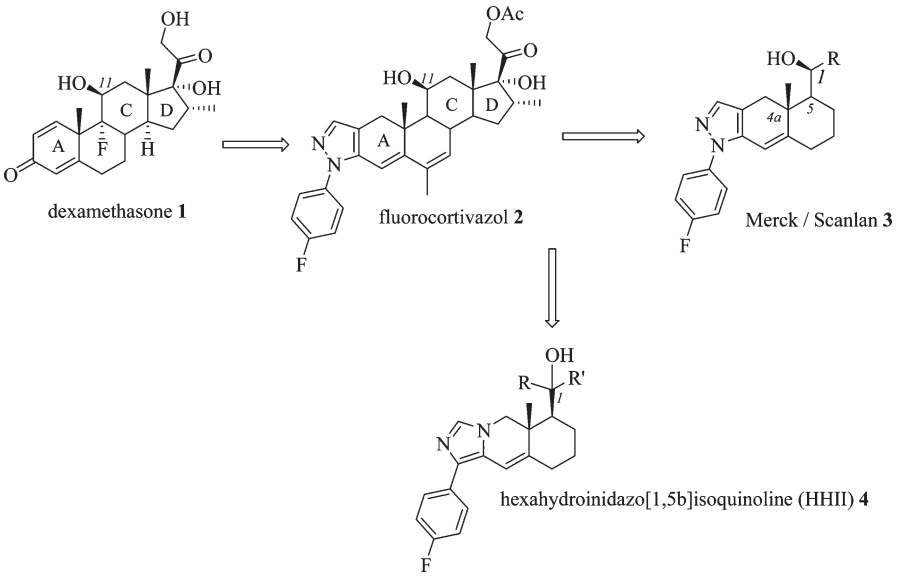
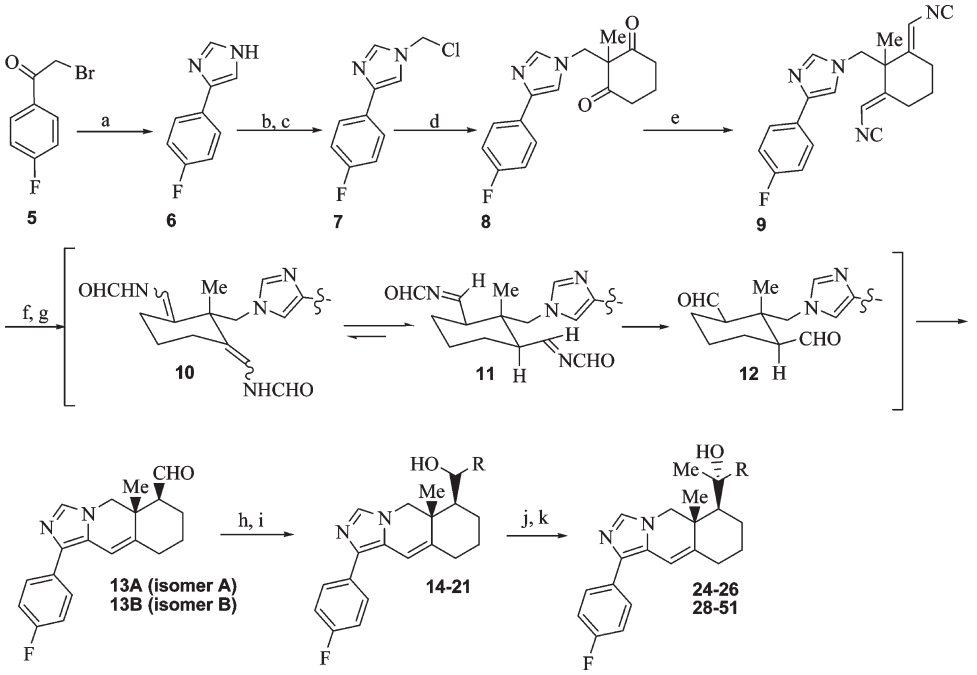


Figure 1. Evolution of the hexahydroimidazo[1,5b]isoquinoline scaffold.

Scheme 1[a]

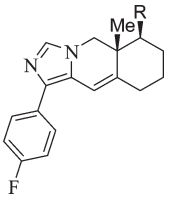


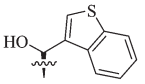
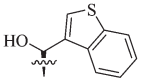
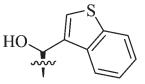
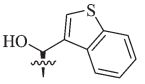
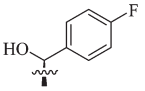
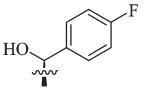
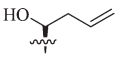
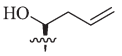
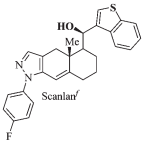
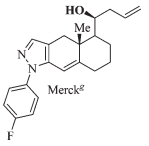
[a] Reagents and conditions: (a) $HCONH_2$, 170 °C, 43%; (b) HCHO, EtOH, RT, 96%; (c) $SOCl_2$, CH_2Cl_2, 100%; (d) 2-methylcyclohexane-1,3-dione, LiI, DBU, THF, RT to 60 °C, 60%; (e) $(EtO)_2P(O)CH_2NC$, *n*-BuLi, −50 °C to RT; (f), NaOAc, AcOH, H_2O, 170 °C, microwave, 30 min, 55% over steps e and f; (g) Chiralpak-AD column, CO_2, MeOH; (h), RMgBr or RLi; (i) silica gel column chromatography for separation of diasteromers; (j) Dess-Martin periodane, pyridine, CH_2Cl_2; (k) MeMgBr, THF.

Chemistry. Although a number of approaches were tried to synthesize this novel ring system, the optimized protocol is outlined in Scheme 1. Reaction of 2-bromo-1-(4-fluorophenyl)ethanone (**5**) with formamide led to 4-(4-fluorophenyl)-1*H*-imidazole (**6**) in good yield. Hydroxymethylation followed by chlorination with thionyl chloride afforded the chloromethyl derivative (**7**). After considerable amount of experimentation, treatment of the chloromethyl derivative (**7**) with 2-methyl-1,3-cyclohexanedione in the presence of DBU and LiI[14] gave us the desired C-alkylated product (**8**) in 60% isolated yield.

Attempts to convert the 1,3-diketone (**8**) to the 1,3-diformyl compound or its equivalent either failed entirely (e.g., $MeOCH_2SiMe_3$/*t*-BuLi or $MeOCH_2P(O)Ph_2$/LDA or $N_2CHSiMe_3$/LDA) or gave the desired product in very low yield (e.g., $Ph_3P^+CH_2OMeCl^-$/*t*-BuOK), probably due to the sterically hindered nature of the diketone. It is reported in the literature that diethyl isocyanomethylphosphonate is a useful reagent for the one carbon homologation of hindered aldehydes and ketones.[15,16] The reaction proceeds via an intermediate isocyanide, which on acidic hydrolysis affords the one carbon homologated aldehyde. In the event, reaction

Table 1. In Vitro GR Binding and Functional Activity for Secondary Alcohols

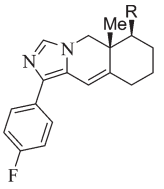


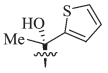
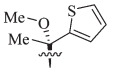
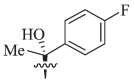
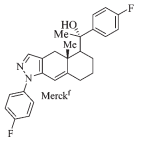
Compound #	Structure	Comment[a]	GR Binding (Ki, nM)[b]	AP-1 (EC50) nM, (Emax)[c]	ELAM (EC50), (Emax) nM[d]
Dexamethasone			1.2	2.5 (100)	1.1 (100)
14		From isomer A Diasteromer 1	134 ± 6	1018 (42)[e]	920 (60)[e]
15		From isomer A Diasteromer 2	> 1150	>2500, >5000	>5000
16		From isomer B Diasteromer 1	7 ± 2	181 (42)[e]	910 (56)[e]
17		From isomer B Diasteromer 2	36 ± 2	>5000	>5000
18		From isomer B Diasteromer 1	25 ± 15	>5000	>5000
19		From isomer B Diasteromer 2	21 ± 13	272 (35)[e]	243 (49)[e]
20		From isomer B Diasteromer 1	8 ± 0.4	>2500	>5000
21		From isomer B Diasteromer 2	9	>2500	>5000
22			1.8 ± 0.3	1.8 (71)[f]	
23			3.9	hIL-6; 9.3 (83)[g]	

[a] See Experimental Section for retention times of isomers A and B. [b] Values are mean of at least two experiments done in triplicate. A value where the standard deviation is not shown is from a single experiment. [c] Activator protein-1 (AP-1) assay in human A549 lung epithelial cell line. Experiments were run in duplicate. [d] Endothelial leukocyte adhesion molecule (ELAM) assay in human A549 lung epithelial cell line. Experiments were run in duplicate. [e] Efficacy represented as a percentage of the maximal response of dexamethasone. [f] See ref 11. [g] See ref 10.

of the 1,3-diketone (**8**) with diethyl isocyanomethylphosphonate gave the intermediate α,β-unsaturated isocyanide (**9**), which was subjected to acidic hydrolysis employing sodium acetate/acetic acid/water under microwave irradiation conditions, at 170 °C. This led to the formation of the desired tricyclic hexahydroimidazo[1,5b]isoquinoline (HHII) compound (**13**) in 55% overall yield from the diketone (**8**) as a single diastereomer. As outlined in Scheme 1, we believe that hydration of the isocyanide group leads to the formation of the intermediate *N*-formylenamine (**10**, characterized by LCMS), which isomerizes to the *N*-formylimine (**11**) via an enamine-imine tautomeric equilibrium that places the bulky 4-(4-fluorophenyl)-1*H*-imidazolylmethylene and *N*-formylimine groups in an equatorial position around the cyclohexane ring. Subsequent hydrolysis leads to the formation of the dialdehyde intermediate (**12**), which undergoes intramolecular ring closure at the more electron rich 5-position of the imidazole ring, to yield compound (**13**) as a single diastereomer with the desired relative stereochemistry at the quaternary carbon bearing the methyl group and the adjacent carbon atom anchoring the formyl moiety (vide infra). Compound (**13**) was resolved into its individual enantiomers using a Chiralpak-AD column and each enantiomer was individually converted into the corresponding secondary alcohols using Grignard or organolithium reagents. The secondary alcohols were obtained as a mixture of diastereomers (approximate ratio of 1:1 in most cases) that could easily be separated by silica gel flash column chromatography. The slower eluting enantiomeric aldehyde (isomer B)

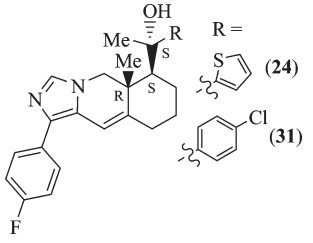
Table 2. In Vitro GR Binding and Functional Activity for Tertiary Alcohol Derivatives



Compound #	Structure	GR Binding (Ki, nM)[a]	AP-1[a,b] EC50 (nM)[a]	AP-1[a,b] % Dex[e]	ELAM[a,c] EC50 (nM)[a]	ELAM[a,c] % Dex.[e]	NP-1 agonist[d] EC50 (nM)[a]	NP-1 agonist[d] % Dex.[e]
Dexamethasone		1.2	2.5	100	1.1	100	4.5	100
24		2 ± 0.2	52 ± 19	55	41 ± 8.5	53	>10000	
25		33	>5000		>5000		>10000	
26		2 ± 0.3	20 ± 11	61	44 ± 24	64	723 ± 231	16
27		2.5	hIL-6 2.2	102			TAT 57 nM	79

[a] Values are mean of at least two experiments done in triplicate. A value where the standard deviation is not shown is from a single experiment. [b] Activator protein-1 (AP-1) assay in human A549 lung epithelial cell line. Experiments were run in duplicate. [c] Endothelial leukocyte adhesion molecule (ELAM) assay in human A549 lung epithelial cell line. Experiments were run in duplicate. [d] GR tranactivation assay (agonist mode) in the NP-1 HeLa cell line. [e] Efficacy represented as a percentage of the maximal response of dexamethasone. [f] See ref 10.

was used for further synthetic transformations, because the secondary alcohols obtained from this enantiomer were more potent than the corresponding analogs from the faster eluting aldehyde (isomer A). Oxidation of the secondary alcohols to the ketone, followed by addition of methylmagnesium bromide, afforded the tertiary alcohols (**28**−**51**), mostly as single diastereomers. The absolute stereochemistry of the tertiary alcohols was established by single crystal X-ray analysis of compounds **24** and **31**, employing the anomalous scattering method.[17]

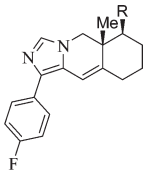


Biological Assays. Compounds were initially measured for their binding affinity to GRα in a competition based fluorescence polarization assay. Partially purified GRα protein was mixed with a fluorescently tagged dexamethasone as a ligand in the presence of test compounds. Compounds that displayed potent GR binding were then evaluated in the functional transrepression and transactivation assays. Compounds underwent an assessment of their ability to repress transcription using two cell-based reporter assays. In one assay, a stable clone of the human lung epithelial cell line A549, which contains a concatemer of five AP-1 response elements controlling a luciferase reporter, was used to measure transrepression. In the presence of test compounds, the ability of the compounds to block activation of the AP-1 reporter by phorbol myristate acetate (PMA) for 6 h is measured. In a second assay (ELAM, endothelial leukocyte adhesion molecule) that also utilizes a stable version of the A549 cell line, a 400 bp portion of the E-selectin gene promoter region is used to control a luciferase reporter. In the presence of test compounds, the ability of the compounds to block activation of the E-selectin reporter by IL-1β for 6 h is measured. This assay is primarily NFκB dependent. The direct transcriptional activation by GR in response to bound ligand was measured using a cell based reporter assay in the agonist mode. The NP-1 HeLa cell line contains a GR chimera that activates the GAL4-luciferase reporter.[18] In the agonist mode, the ability of the bound compounds to directly activate the GR chimera is measured. Data for transrepression (AP-1 and ELAM) and transactivation (NP-1) for representative compounds is shown in Tables 1−3.

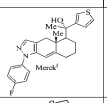
Results and Discussion

Structure−activity relationships for the hexahydroimidazo-[1,5b]isoquinoline (HHII) based GR modulators are outlined in Tables 1−3. Table 1 shows the GR binding and functional data for a series of secondary alcohols derived from aldehydes **13A** and **13B**. Greater GR binding potency was demonstrated with compounds derived from enantiomer **13B** in comparison to **13A** (compare **14** and **15** against **16** and **17**). However, there was less of a stereochemical bias in terms of GR binding for compounds within a diastereomeric set (compare **18** with **19** and compare **20** with **21**). Although, the GR binding affinities for the HHII compounds in the secondary alcohol series

Table 3. In Vitro GR Binding and Functional Activity for Tertiary Alcohols



Compound #	Structure	GR Binding (Ki, nM)[a]	AP-1[a,b]		ELAM[a,c]		NP-1 agonist[d]	
			EC50 (nM)[a]	% Dex.[e]	EC50 (nM)[a]	% Dex.[e]	EC50 (nM)[a]	% Dex.[e]
Dexamethasone		1.2	2.5	100	1.1	100	4.5	100
28		1 ± 0.8	16 ± 8.9	48	61 ± 25	66	>5000	
29		2 ± 0.7	25 ± 0.7	59	31 ± 14	53	920	10
30		2.5 ± 0.4	9.5 ± 0.7	65	99 ± 16	62	1130	19
31		2 ± 0.9	7.5 ± 0.7	59	19 ± 2	67	697 ± 137	35
32		1 ± 0.3	18 ± 1.3	49	31 ± 1.4	55	>10000	
33		2.5 ± 1	59	30	105 ± 79	49	>10000	
34		31 ± 6	280	58	398	45	>10000	
35		2 ± 0.8	573	52	930	68	>5000	
36		2 ± 1.4	324	51	2750 ± 537	68	>10000	
37		2 ± 0.4	29	77	30 ± 21	75	380	26
38		1.5 ± 0.1	28 ± 4	70	18 ± 2	68	272	47
39		4 ± 0.2	11 ± 7.5	86	11 ± 1	93	253 ± 51	59
40		1	5	61	37	68	>10000	

Compound #	Structure	GR Binding (Ki, nM)[a]	AP-1[a,b]		ELAM[a,c]		NP-1 agonist[d]	
			EC50 (nM)[a]	% Dex.[e]	EC50 (nM)[a]	% Dex.[e]	EC50 (nM)[a]	% Dex.[e]
Dexamethasone		1.2	2.5	100	1.1	100	4.5	100
41		0.8	IL-6 1	%dex 97			hTAT 36	%dex 69
42		3 ± 0.8	110 ± 70	73	92 ± 51	68	572 ± 11	18
43		4.3	57	79	79	90	>5000	
44		7.9	34	56	130	84	1130	19
45		47	>5000		>5000		>10000	
46		11 ± 0.0	227	77	121 ± 78	65	760 ± 170	63
47		2.6	37 ± 12	51	49	71	>5000	
48		3.1	2	62	33	77	470	30
49		2 ± 0.4	57 ± 1.2	66	48 ± 20	74	>1000	
50		5.2	31	44	ND	ND	>10000	
51		9 ± 0.7	132	75	133 ± 6.4	84	876	26

[a] Values are mean of at least two experiments done in triplicate. A value where the standard deviation is not shown is from a single experiment. ND = not determined. [b] Activator protein-1 (AP-1) assay in human A549 lung epithelial cell line. Experiments were run in duplicate. [c] Endothelial leukocyte adhesion molecule (ELAM) assay in human A549 lung epithelial cell line. Experiments were run in duplicate. [d] GR tranactivation assay (agonist mode) in the NP-1 HeLa cell line. [e] Efficacy represented as a percentage of the maximal response of dexamethasone. [f] See ref 10.

compared favorably with those reported by the Merck and Scanlan groups, the lack of functional activity in the transrepression assays was disappointing, because the corresponding compounds in the pyrazole series are reportedly partial agonists in the AP-1 and IL-6 transrepression assays (compare compounds **16** with **22** and **20** with **23** in Table 1).

We then decided to explore tertiary alcohols at the C-1 position of the HHII scaffold, since the corresponding pyrazolo[3,2-c] analogs in the Merck series of GR modulators displayed a significant boost in activity in the in vitro transrepression assays. We were mindful, however, that this increase in transrepressive activity was reportedly accompanied by an increase in transactivation, thereby decreasing the potential of these compounds to function as dissociated GR agonists (see compound **27**, Table 2).

The initial compounds made in the tertiary alcohol series of the HHII chemotype showed significant improvement in GR binding potency relative to the corresponding secondary alcohols as well as displaying partial agonist profiles in the AP-1 and ELAM transrepression assays (compare compound **19**, Table 1 with compound **26** in Table 2). More importantly, compounds **24** and **26** (Table 2) did not show any significant functional activity in the NP-1 transactivation assay. A significant loss of GR binding affinity was recorded in the case of methyl ether **25**, along with a complete loss of cellular functional activity (transrepression and transactivation). This was not unanticipated, because the C-11 OH group of glucocorticoids (including deacylcortivazol), which corresponds to the C-1 hydroxyl of the HHII chemotypes, forms an important H-bond with Asn564 on helix 3 of the GR ligand binding domain.[19] The dissociated nature of compounds **24** and **26**, in the in vitro transactivation and transrepression assays prompted us to extensively explore the SAR around the tertiary alcohol series of the HHII chemotype.

Table 3 outlines the GR binding and functional activities in the AP-1, ELAM, and NP-1 assays for a set of tertiary alcohols.

Most of the analogs in the phenyl series (compounds **28**−**33**) were partial agonists in the transrepression assays and, as noted earlier, were inactive or displayed significantly lower activity in the NP-1 transactivation assay. The pyridyl regioisomers although of similar potency in the GR binding assay to the phenyl analogs were either inactive or significantly less active in the transrepression AP-1 and ELAM assays (compare compound **28** with **34**−**36**). The lack of functional activity with the pyridyl regioisomers in relation to the phenyl analog **28** may suggest the inability of the pyridyl regioisomers to engage helix-12 of the GR ligand binding domain to attain the agonist conformation.[20,21] The 2-thienyl analogs **37**−**39** showed GR binding and functional activity similar to the phenyl analogs. It is of interest to note that subtle changes in functionality lead to significant changes in potency in the functional assays for transrepression and transactivation (compare **28** and **31** in the phenyl series and **24** and **39** in the 2-thienyl series). The 3-thienyl analog **40** had significant potency in the GR binding and transrepression assays and like the 2-thienyl analog **24** was inactive in the NP-1 transactivation assay. As expected, the functional potency of the 2-thiazolyl analog **42** in transrepression assays was better than the pyridyl regioisomers but significantly lower than that of the thienyl analogs. A number of alkyl and cycloaklyl analogs were also synthesized (analogs **43**−**51**), and most of them displayed partial agonist profiles in the transrepression AP-1 and ELAM assays without significant activity in the NP-1 transactivation assay.

Although a head-to-head comparison of the tertiary alcohol analogs in the HHII and pyrazolo[3,2-*c*] series in the transrepression and transactivation assays is not possible, because, of the different functional assays employed, it is clear that the compounds display similar binding affinity and either show a partial agonist profile or are inactive in the transactivation functional assays (for example, compare compound **40** with **41** in Table 3).

The compounds listed in Tables 2 and 3 were tested for selectivity against the androgen receptor (AR), progesterone receptor (PR), and, in some cases, against the mineralocorticoid (MR) receptor. Almost all the analogs displayed excellent selectivity against the AR and MR receptors (IC_{50}s > 4000 nM for AR in the binding assay and 30−50% inhibition at 10 μM against MR in an antagonist mode functional assay, and no activity at 10 μM in an agonist mode assay). The PR binding activity varied between 100 and > 1000 nM, depending on the analog tested. For example, compound **31** has a K_i of 133 nM, while **43** has a K_i of 1810 nM in the PR binding assay.[22] A number of analogs listed in Tables 2 and 3 were also tested in in vitro profiling assays for metabolic stability and their ability to inhibit cytochrome P450. Unfortunately, most of the compounds exhibited moderate to poor stability when incubated in vitro with human and mouse liver microsomes[23] and so were not advanced for detailed in vivo evaluation.

Conclusion

The first synthesis of the hexahydroimidazo[1,5b]isoquinoline ring system as an abbreviated steroid scaffold is described. The replacement of the neutral pyrazole ring with a basic imidazole moiety is tolerated by the glucocorticoid receptor in terms of binding and the functional activity of tertiary alcohols in the transrepression assays is significantly superior to that of the secondary alcohols. More importantly, these analogs were either inactive or displayed significantly lower activity in the NP-1 transactivation assay and therefore by definition are "dissociated" in vitro. However, improvements in in vitro and in vivo pharmacokinetic properties are needed to evaluate these compounds in preclinical models for anti-inflammatory activity (for example, mouse or rat adjuvant-induced arthritis models) and side effects (for example, impact on glucose metabolism) before making the conclusion about the ability of these compounds to function as "dissociated" glucocorticoids in vivo.

Experimental Section

All procedures were carried out under a nitrogen atmosphere unless otherwise indicated using anhydrous solvents purchased from commercial sources without further purification. Reactions requiring anhydrous solvents were performed in glassware, which was dried using a heat gun and placed under a nitrogen atmosphere. Column chromatography was performed on silica gel using the solvent systems indicated. Solvent systems are reported as v/v percent ratios. All reactions were monitored by TLC using EM science, 0.25 mm, precoated silica gel plates or by LC/MS. Yields refer to chromatographically and spectroscopically pure compounds, except as otherwise noted. Proton NMR spectra were recorded on a Bruker 400 MHz or a Joel 500 MHz NMR spectrometer. Chemical shifts are reported in δ values relative to tetramethylsilane. Electrospray ionization (ESI) mass spectra were obtained on a Waters Micromass LC/MS single quadrupole mass spectrometer. The purity of the final products was determined by HPLC, using the following method for each compound: column YMC S5 CombiScreen ODS column 4.6 × 50 mm; solvent A = water 90%/MeOH 10%/H_3PO_4 0.2%; solvent B = MeOH 90%/water 10%/H_3PO_4 0.2%; flow rate 4 mL/min, λ = 220 nm; run time = 5 min. Most final products had a purity of ≥95%. For final products whose purity is <95%, the percent purity is specified is at the end of the description of its synthesis.

General Procedure for the Synthesis of Hexahydroimidazo-[1,5b]isoquinoline Core and Secondary Alcohols Outlined in Table 1 (4-Fluorophenyl)((5a*R*,6*S*)-1-(4-fluorophenyl)-5a-methyl-5,5a,6,7, 8,9-hexahydroimidazo[1,5-*b*]isoquinolin-6-yl)methanol (18, 19). (a) A mixture of 2-bromo-1-(4-fluorophenyl)ethanone (10.9 g, 50 mmol) and formamide (14 mL, 350 mmol) was stirred at 170 °C under nitrogen for 4 h. The reaction mixture was cooled and diluted with ethyl acetate (40 mL). Saturated aqueous sodium bicarbonate solution (50 mL) was added with caution to the reaction mixture at 0 °C. The aqueous layer was separated and extracted with ethyl acetate (2 × 40 mL). The combined organic solutions were washed with water (30 mL) and brine (30 mL), dried (Na_2SO_4), and concentrated. Silica gel flash chromatography (10−100% ethyl acetate in hexanes) gave 4-(4-fluorophenyl)-1*H*-imidazole (**6**; 3.46 g, 21 mmol, 43% yield, 95% purity) as a solid. LC/MS = 163.1 $(M + H)^+$; ^{1}H NMR (400 MHz, chloroform-*d*) δ ppm 8.07 (1H, s), 7.72 (2H, dd, J = 8.8 and 5.3 Hz), 7.32 (1H, s), 7.10 (2H, t, J = 8.8 Hz).

(b) To a stirred solution of 4-(4-fluorophenyl)-1*H*-imidazole (10 g, 62 mmol) in 95% ethanol (25 mL) was added aqueous formaldehyde solution (37%, 9 mL) slowly. The reaction mixture was stirred at RT for 1 h before water (25 mL) was added. The reaction mixture was stirred at RT for an additional 3 h. The solid that separated from solution was filtered, washed with aqueous ethanol solution, and dried to give (4-(4-fluorophenyl)-1*H*-imidazol-1-yl)methanol (11.4 g, 59 mmol, 96% yield) as a solid. ^{1}H NMR (400 MHz, MeOD) δ ppm 7.68−7.74 (3H, m), 7.40 (1H, s), 7.10 (2H, t, J = 8.9 Hz), 4.65 (2H, s).

(c) To a stirred solution of thionyl chloride (18 mL) in anhydrous methylene chloride (180 mL) was added (4-(4-fluorophenyl)-1*H*-imidazol-1-yl)methanol (11.4 g, 59 mmol) portionwise at RT under nitrogen. The reaction mixture was stirred at RT for 3.5 h before anhydrous toluene (90 mL) was added.

The mixture was stirred at RT for 30 min. Concentration under reduced pressure gave 1-(chloromethyl)-4-(4-fluorophenyl)-1*H*-imidazole hydrochloride (**7**; 14.5 g, 59 mmol, 100% yield) as a solid. MS found: $(M + H)^+ = 211.3$. The solid was sufficiently pure to be used for the next step without further purification.

(d) To a stirred solution of 2-methylcyclohexane-1,3-dione (10 g, 79 mmol), lithium iodide (26 g, 194 mmol) in anhydrous THF (300 mL) cooled in a water bath was added 1,8-diazabicyclo[5.4.0]-7-undecene (14 mL, 94 mmol) dropwise under nitrogen. The reaction mixture was stirred at RT for 40 min before 1-(chloromethyl)-4-(4-fluorophenyl)-1*H*-imidazole hydrochloride (9.8 g, 40 mmol) was added in one portion. The reaction mixture was stirred at RT for 3 h and at 60 °C for 2 h. After the mixture was cooled, water (250 mL) and heptane (250 mL) were added. The aqueous layer was separated and extracted with ethyl acetate (2 × 250 mL). The combined organic solutions were washed with 16% aqueous potassium carbonate solution (3 × 50 mL), dried (Na_2SO_4), and concentrated. Silica gel flash chromatography (20−100% ethyl acetate in hexanes) gave 2-((4-(4-fluorophenyl)-1*H*-imidazol-1-yl)methyl)-2-methylcyclohexane-1,3-dione (**8**; 7.1 g, 24 mmol, 60% yield, 93% purity) as a solid. LC/MS = 301.4 $(M+H)^+$; ^{1}H NMR (400 MHz, chloroform-*d*) δ ppm 7.70 (2H, dd, J = 8.6 and 5.1 Hz), 7.47 (1H, s), 7.06 (1H, s), 7.05 (2H, t, J = 8.6 Hz), 4.44 (2H, s), 2.67−2.78 (2H, m), 2.46 (2H, ddd, J = 17.04, 6.4, and 4.58 Hz), 1.96−2.07 (1H, m), 1.48−1.62 (1H, m), 1.37 (3H, s).

(e) To a stirred solution of diethyl isocyanomethylphosphonate (6.0 mL, 37 mmol) in anhydrous THF (160 mL) was added butyl lithium solution (1.6 M in hexanes, 23 mL, 37 mmol) dropwise at −50 to −60 °C under argon. The mixture was stirred at the same temperature for 30 min before a solution of 2-((4-(4-fluorophenyl)-1*H*-imidazol-1-yl)methyl)-2-methylcyclohexane-1,3-dione (4.5 g in 30 mL of anhydrous THF, 15 mmol) was added dropwise at −50 to −60 °C. The reaction mixture was stirred at the same temperature for 30 min and at RT for 2 h, concentrated under reduced pressure, dissolved in some ethyl acetate, and filtered through a silica gel pad, which was then rinsed with ethyl acetate. The filtrate was concentrated under reduced pressure to give a solid that was used in the next step without further purification.

(f) One quarter of the above solid was mixed with sodium acetate (1.5 g), acetic acid (4 mL), and water (4 mL). The mixture was heated at 170 °C in a microwave reactor (Emrys Optimizer, Personal Chemistry) under nitrogen for 30 min. The above microwave reaction was repeated three times. The four microwave reaction mixtures were combined and concentrated under reduced pressure to remove solvents. The residue was diluted with water (40 mL) and ethyl acetate (80 mL) and made basic using potassium carbonate and sodium bicarbonate solid at 0 °C. The aqueous layer was separated and extracted with ethyl acetate (3 × 30 mL). The combined organic solutions were dried (Na_2SO_4) and concentrated. Silica gel flash chromatography (30−100% ethyl acetate in hexanes) gave 1-(4-fluorophenyl)-5a-methyl-5,5a,6,7,8,9-hexahydroimidazo[1,5-*b*]isoquinoline-6-carbaldehyde **13A** and **13B** (2.55 g, 8.2 mmol, 55% yield over two steps, 95% purity) as a solid. LCMS = 311.2 $(M + H)^+$. ^{1}H NMR (400 MHz, chloroform-*d*) δ ppm 9.77 (1H, d, J = 1.5 Hz), 7.68 (2H, dd, J = 9.2 and 5.6 Hz), 7.52 (1H, s), 7.10 (2H, t, J = 8.9 Hz), 6.47 (1H, d, J = 2.0 Hz), 4.49 (1H, d, J = 12.2 Hz), 3.80 (1H, d, J = 12.7 Hz), 2.36−2.51 (2H, m), 2.31 (1H, ddd, J = 13.1, 3.4, and 1.3 Hz), 2.13 (1H, ddd, J = 13.4, 3.4, and 1.5 Hz), 2.01−2.09 (1H, m), 1.82 (1H, qd, J = 13.1 and 3.3 Hz), 1.42−1.57 (1H, m), 1.17 (3H, s).

(g) 1-(4-Fluorophenyl)-5a-methyl-5,5a,6,7,8,9-hexahydroimidazo[1,5-*b*]isoquinoline-6-carbaldehyde **13A** and **13B** were resolved into its enantiomers using a Chiralpak-AD column [conditions: ChiralpakAD-H (3 × 25 cm) CO_2/MeOH 68/32, 70 mL/min, at 35 °C and 100 bars at 220 nm; sample: 2.5 g in 22.5 mL of chloroform and IPA (1/1), loading 1.5 cm^3/16.2 min]; retention time for **13A**: 5.40 min; retention time for **13B**: 8.18 min. Enantiomers **13A** and **13B** were used to synthesize the secondary alcohols shown in Table 1. Enantiomer **13B** was used to synthesize the tertiary alcohol analogues shown in Tables 2 and 3 using the following representative procedures.

(h) (4-Fluorophenyl)((5a*R*,6*S*)-1-(4-fluorophenyl)-5a-methyl-5,5a,6,7,8,9-hexahydroimidazo[1,5-*b*]isoquinolin-6-yl)methanol (**18**, **19**): To a stirred solution of (5a*R*,6*S*)-1-(4-fluorophenyl)-5a-methyl-5,5a,6,7,8,9-hexahydroimidazo[1,5-*b*]isoquinoline-6-carbaldehyde (35 mg, 0.11 mmol) in anhydrous THF (1 mL) was added 4-fluorophenymagnesium bromide solution (1 M in THF, 0.6 mL, 0.6 mmol) dropwise at 0 °C under nitrogen. The reaction mixture was stirred at 0 °C for 40 min and at RT for 40 min before being quenched with saturated aqueous ammonium chloride solution (1 mL). The reaction mixture was extracted with ethyl acetate (2 × 2 mL), dried (Na_2SO_4), and concentrated. Prep HPLC purification (YMC S5 20 × 100 mm, 10 min run; solvent A: 10% MeOH/90% H_2O/0.1% TFA; solvent B: 90% MeOH/10% H_2O/0.1% TFA) gave **18** as the faster eluting isomer followed by **19**, which were characterized as their TFA salts. Analytical data for **18** (7 mg, 0.013 mmol, 12% yield, 97% purity). LCMS = 407.4 $(M+1)^+$. ^{1}H NMR (400 MHz, MeOD) δ ppm 8.88 (1H, s), 7.66 (2H, dd, J = 8.9 and 5.3 Hz), 7.42 (2H, dd, J = 8.6 and 5.6 Hz), 7.31 (2H, t, J = 8.6 Hz), 7.08 (2H, t, J = 8.6 Hz), 6.45 (1H, s), 5.06 (1H, s), 4.85 (1H, d, J = 13.2 Hz), 4.11 (1H, d, J = 12.7 Hz), 2.46−2.52 (2H, m), 1.85−1.92 (1H, m), 1.79 (1H, td, J = 12.5 and 3.1 Hz), 1.69−1.75 (1H, m), 1.63 (1H, dd, J = 13.0 and 2.8 Hz), 1.37 (3H, s), 1.16−1.29 (1H, m); Analytical data for **19** (6 mg, 0.012 mmol, 11% yield, 94% purity). LCMS = 407.4 $(M+1)^+$. ^{1}H NMR (400 MHz, MeOD) δ ppm 8.98 (1H, s), 7.67 (2H, dd, J = 8.6 and 5.1 Hz), 7.40 (2H, dd, J = 8.6 and 5.6 Hz), 7.32 (2H, t, J = 8.6 Hz), 7.09 (2H, t, J = 8.9 Hz), 6.51 (1H, d, J = 2.0 Hz), 5.54 (1H, d, J = 13.7 Hz), 4.58 (1H, d, J = 10.2 Hz), 4.08 (1H, d, J = 13.7 Hz), 2.35−2.55 (2H, m), 1.83−1.93 (1H, m), 1.70−1.79 (1H, m), 1.34 (3H, s), 1.19−1.30 (2H, m), 1.10−1.17 (1H, m).

A mixture of the secondary alcohols **18** and **19** (41 mg, 0.79 mmol, 72% yield) was also obtained during prep HPLC.

The following compounds were prepared in the similar fashion.

Benzo[*b*]thiophen-3-yl(1-(4-fluorophenyl)-5a-methyl-5,5a,6,7,8,9-hexahydroimidazo[1,5-*b*]isoquinolin-6-yl)methanol (14): 7 mg, 0.016 mmol, 12% yield, 90% purity. LCMS = 445.3 $(M+1)^+$. ^{1}H NMR (400 MHz, chloroform-*d*) δ ppm 8.01−8.08 (1H, m), 7.88−7.94 (1H, m), 7.69 (2H, dd, J = 8.9 and 5.3 Hz), 7.50 (1H, s), 7.38−7.42 (2H, m), 7.37 (1H, s), 7.09 (2H, t, J = 8.9 Hz), 6.46 (1H, d, J = 2.0 Hz), 5.15 (1H, d, J = 12.7 Hz), 5.06 (1H, d, J = 10.2 Hz), 3.88 (1H, d, J = 13.2 Hz), 2.17−2.42 (3H, m), 1.64−1.72 (1H, m), 1.29 (3H, s), 1.17−1.23 (3H, m).

Benzo[*b*]thiophen-3-yl(1-(4-fluorophenyl)-5a-methyl-5,5a,6,7,8,9-hexahydroimidazo[1,5-*b*]isoquinolin-6-yl)methanol (15): 4 mg, 0.009 mmol, 7% yield, 90% purity. LCMS = 445.3 $(M+1)^+$. ^{1}H NMR (400 MHz, chloroform-*d*) δ ppm 7.90 (1H, d, J = 7.6 Hz), 7.64−7.78 (4H, m), 7.48 (1H, s), 7.35−7.46 (2H, m), 7.10 (2H, t, J = 8.9 Hz), 6.39 (1H, d, J = 1.0 Hz), 5.47 (1H, s), 4.53 (1H, d, J = 11.7 Hz), 3.90 (1H, d, J = 11.7 Hz), 2.33−2.49 (2H, m), 1.73−1.93 (4H, m), 1.34 (3H, s), 1.19−1.32 (1H, m).

Benzo[*b*]thiophen-3-yl(1-(4-fluorophenyl)-5a-methyl-5,5a,6,7,8,9-hexahydroimidazo[1,5-*b*]isoquinolin-6-yl)methanol (16): 8 mg, 0.018 mmol, 14% yield, 90% purity. LCMS = 445.3 $(M+1)^+$. ^{1}H NMR (400 MHz, chloroform-*d*) δ ppm 8.02−8.07 (1H, m), 7.88−7.93 (1H, m), 7.69 (2H, dd, J = 8.9 and 5.3 Hz), 7.46 (1H, s), 7.38−7.43 (2H, m), 7.36 (1H, s), 7.08 (2H, t, J = 8.6 Hz), 6.46 (1H, d, J = 1.5 Hz), 5.14 (1H, d, J = 13.2 Hz), 5.06 (1H, d, J = 10.2 Hz), 3.87 (1H, d, J = 13.2 Hz), 2.17−2.41 (3H, m), 1.64−1.71 (1H, m), 1.28 (3H, s), 1.17−1.23 (3H, m).

Benzo[*b*]thiophen-3-yl(1-(4-fluorophenyl)-5a-methyl-5,5a,6,7,8,9-hexahydroimidazo[1,5-*b*]isoquinolin-6-yl)methanol (17): 4 mg, 0.009 mmol, 7% yield, 90% purity. LCMS = 445.3 $(M+1)^+$. ^{1}H NMR (400 MHz, chloroform-*d*) δ ppm 7.90 (1H, d, J = 8.1 Hz), 7.64−7.75 (4H, m), 7.48 (1H, s), 7.35−7.45 (2H, m), 7.10 (2H, t, J = 8.6 Hz), 6.38 (1H, s), 5.46 (1H, s), 4.51 (1H, d, J = 12.2 Hz),

3.89 (1H, d, J = 11.7 Hz), 2.34−2.45 (2H, m), 1.76−1.93 (4H, m), 1.34 (3H, s), 1.19−1.32 (1H, m).

1-(1-(4-Fluorophenyl)-5a-methyl-5,5a,6,7,8,9-hexahydroimidazo-[1,5-*b*]isoquinolin-6-yl)but-3-en-1-ol as a TFA salt (20): 6 mg, 0.013 mmol, 13% yield, 98% purity. LCMS = 353.4 $(M+1)^+$. ^{1}H NMR (400 MHz, MeOD) δ ppm 8.88 (1H, s), 7.65 (2H, dd, J = 8.6 and 5.1 Hz), 7.31 (2H, t, J = 8.9 Hz), 6.44 (1H, d, J = 1.5 Hz), 5.81−5.93 (1H, m), 5.08−5.17 (2H, m), 4.65 (1H, d, J = 12.7 Hz), 3.90 (1H, t, J = 7.1 Hz), 3.80 (1H, d, J = 13.2 Hz), 2.45−2.57 (2H, m), 2.40 (1H, dt, J = 13.7 and 6.9 Hz), 2.21−2.31 (1H, m), 1.95−2.03 (1H, m), 1.68−1.85 (2H, m), 1.58−1.64 (1H, m), 1.36−1.50 (1H, m), 1.24 (3H, s).

1-(1-(4-Fluorophenyl)-5a-methyl-5,5a,6,7,8,9-hexahydroimidazo-[1,5-*b*]isoquinolin-6-yl)but-3-en-1-ol as a TFA salt (21): 6 mg, 0.013 mmol, 13% yield, 93% purity. LCMS = 353.4 $(M+1)^+$. ^{1}H NMR (400 MHz, MeOD) δ ppm 8.93 (1H, s), 7.65 (2H, dd, J = 8.6 and 5.1 Hz), 7.31 (2H, t, J = 8.6 Hz), 6.48 (1H, d, J = 2.0 Hz), 5.90−6.02 (1H, m), 5.29 (1H, d, J = 13.7 Hz), 5.09−5.18 (2H, m), 3.89 (1H, d, J = 13.7 Hz), 3.70−3.77 (1H, m), 2.37−2.56 (3H, m), 2.27 (1H, ddd, J = 14.5, 7.6, and 7.4 Hz), 1.83−1.97 (2H, m), 1.59−1.67 (1H, m), 1.31−1.45 (2H, m), 1.21 (3H, s).

Representative Examples for the Synthesis of Tertiary Alcohols Outlined in Tables 2 and 3. (*S*)-1-(4-Fluorophenyl)-1-((5a*R*,6*S*)-1-(4-fluorophenyl)-5a-methyl-5,5a,6,7,8,9-hexahydroimidazo[1,5-*b*]-isoquinolin-6-yl)ethanol (26). Step A: A TFA salt of (4-fluorophenyl)-((5a*R*,6*S*)-1-(4-fluorophenyl)-5a-methyl-5,5a,6,7,8,9-hexahydroimidazo[1,5-*b*]isoquinolin-6-yl)methanol (**18** and **19**; 40 mg, 0.79 mmol) was neutralized with saturated aqueous sodium bicarbonate solution and extracted with ethyl acetate. The ethyl acetate extract was dried (Na_2SO_4) and concentrated. A total of 32 mg (0.079 mmol) of the secondary alcohol was dissolved in anhydrous methylene chloride (2 mL). *N*-Methylmorpholine oxide (37 mg, 0.32 mmol) was added and the contents stirred at 0 °C for 5 min before tetrapropylammonium perruthenate (6 mg, 0.016 mmol) was added. The reaction mixture was stirred at 0 °C for 30 min and at RT for 2 h. Silica gel flash chromatography of the reaction mixture (10−100% ethyl acetate in hexanes) gave (4-fluorophenyl)-((5a*R*,6*S*)-1-(4-fluorophenyl)-5a-methyl-5,5a,6,7,8,9-hexahydroimidazo[1,5-*b*]isoquinolin-6-yl)methanone (24 mg, 0.059 mmol, 75% yield) as a glassy solid. LCMS = 405.4 $(M+1)^+$. ^{1}H NMR (400 MHz, chloroform-*d*) δ ppm 7.97 (2H, dd, J = 8.9 and 5.3 Hz), 7.66 (2H, dd, J = 8.9 and 5.3 Hz), 7.28 (1H, s), 7.18 (2H, t, J = 8.6 Hz), 7.09 (2H, t, J = 8.6 Hz), 6.46 (1H, d, J = 1.5 Hz), 3.82 (1H, d, J = 12.3 Hz), 3.69 (1H, d, J = 12.3 Hz), 3.50 (1H, dd, J = 12.5 and 3.3 Hz), 2.41−2.57 (2H, m), 1.96−2.09 (2H, m), 1.82−1.90 (1H, m), 1.51−1.64 (1H, m), 1.31 (3H, s).

Step B: To a stirred solution of (4-fluorophenyl)((5a*R*,6*S*)-1-(4-fluorophenyl)-5a-methyl-5,5a,6,7,8,9-hexahydroimidazo-[1,5-*b*]isoquinolin-6-yl)methanone (step A, 24 mg, 0.059 mmol) in anhydrous THF (1 mL) was added methylmagnesium bromide (3 M in diethyl ether, 0.15 mL, 0.45 mmol) dropwise at −78 °C under argon. The reaction mixture was then stirred at RT for 4 h before being quenched with saturated aqueous ammonium chloride solution (2 mL) at 0 °C. The reaction mixture was extracted with ethyl acetate (3 × 2 mL), dried (Na_2SO_4), and concentrated. The residue that was obtained was purified by prep HPLC (YMC S5 20 × 100 mm, 10 min run, solvent A: 10% MeOH/90% H_2O/0.1% TFA; solvent B: 90% MeOH/10% H_2O/0.1% TFA) to yield (*S*)-1-(4-fluorophenyl)-1-((5a*R*,6*S*)-1-(4-fluorophenyl)-5a-methyl-5,5a,6,7,8,9-hexahydroimidazo-[1,5-*b*]isoquinolin-6-yl)ethanol (**26**; 15 mg 0.028 mmol, 95% purity, 47% yield) as a TFA salt. LCMS = 421.4 $(M+1)^+$. ^{1}H NMR (400 MHz, MeOD) δ ppm 8.84 (1H, s), 7.61−7.67 (2H, m), 7.55−7.61 (2H, m), 7.31 (2H, t, J = 8.6 Hz), 7.06 (2H, t, J = 8.9 Hz), 6.43 (1H, s), 5.27 (1H, d, J = 13.7 Hz), 4.13 (1H, d, J = 13.7 Hz), 2.43−2.50 (2H, m), 1.96 (1H, dd, J = 12.2 and 3.6 Hz), 1.83 (1H, dt, J = 12.2 and 3.6 Hz), 1.69 (3H, s), 1.55−1.67 (2H, m), 1.42 (3H, s), 1.11−1.28 (1H, m).

(*S*)-1-((5a*R*,6*S*)-1-(4-Fluorophenyl)-5a-methyl-5,5a,6,7,8,9-hexahydroimidazo[1,5-*b*]isoquinolin-6-yl)-1-(thiophen-2-yl)ethanol (24). Step A: To a stirred solution of (5a*R*,6*S*)-1-(4-fluorophenyl)-5a-methyl-5,5a,6,7,8,9-hexahydroimidazo[1,5-*b*]isoquinoline-6-carbaldehyde (isomer **13B**, 90 mg, 0.29 mmol) in anhydrous THF (2.5 mL) was added thiophen-2-ylmagnesium bromide solution (1 M in THF, 1.5 mL, 1.5 mmol) dropwise at 0 °C under nitrogen. The reaction mixture was stirred at 0 °C for 30 min and at RT for 30 min before being quenched with saturated aqueous ammonium chloride solution (3 mL). The reaction mixture was extracted with ethyl acetate (3 × 2 mL), dried (Na_2SO_4), filtered through a silica gel pad, and concentrated. The crude secondary alcohol mixture was used for the next step without further purification.

Step B: The secondary alcohol obtained in step A was dissolved in anhydrous methylene chloride (2 mL). Pyridine (0.07 mL, 0.87 mmol) and Dess-Martin periodinane (185 mg, 0.44 mmol) were added sequentially at RT. The reaction mixture was stirred at RT for 1 h before being quenched by the slow addition of saturated aqueous sodium bicarbonate solution (5 mL) and saturated aqueous sodium thiosulphate solution (3 mL). The reaction mixture was stirred at RT for 30 min and the aqueous layer was separated and extracted with methylene chloride (3 × 2 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated. Silica gel flash chromatography (20−100% ethyl acetate in hexanes) gave ((5a*R*,6*S*)-1-(4-fluorophenyl)-5a-methyl-5,5a,6,7,8,9-hexahydroimidazo[1,5-*b*]isoquinolin-6-yl)(thiophen-2-yl)methanone, which was used as such for the subsequent step without further purification.

Step C: To a stirred solution of the above ((5a*R*,6*S*)-1-(4-fluorophenyl)-5a-methyl-5,5a,6,7,8,9-hexahydroimidazo[1,5-*b*]-isoquinolin-6-yl)(thiophen-2-yl)methanone (step B) in anhydrous THF (4 mL) was added methylmagnesium bromide solution (3 M in diethyl ether, 2 mL, 6 mmol) dropwise at −78 °C under argon. The reaction mixture was then stirred at RT for 2.5 h before saturated aqueous ammonium chloride solution (6 mL) was added slowly with water bath cooling. The reaction mixture was extracted with ethyl acetate (3 × 5 mL), dried (Na_2SO_4), and concentrated. Silica gel flash chromatography (10−100% ethyl acetate in hexanes) gave (*S*)-1-((5a*R*,6*S*)-1-(4-fluorophenyl)-5a-methyl-5,5a,6,7,8,9-hexahydroimidazo-[1,5-*b*]isoquinolin-6-yl)-1-(thiophen-2-yl)ethanol (58 mg, 0.14 mmol, 49% yield over three steps, 99% purity) as a solid. MS found: $(M+H)^+$ = 409.2; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.73 (2H, dd, J = 8.90 and 5.34 Hz), 7.58 (1H, s), 7.29 (m, under solvent peak), 7.12 (2H, t, J = 8.90 Hz), 7.00−7.02 (1H, m), 6.96−6.99 (1H, m), 6.42 (1H, s), 4.99 (1H, d, J = 13.22 Hz), 3.88 (1H, d, J = 13.23 Hz), 2.41 (2H, m), 2.16 (1H, s), 2.12 (1H, dd, J = 12.21 and 3.56 Hz), 1.82 (3H, s), 1.63−1.69 (1H, m), 1.59 (1H, dt, J = 13.23 and 3.05 Hz), 1.34 (3H, s), 1.22−1.31 (1H, m).

The following compounds were prepared in a similar fashion. In some cases, the compounds were further purified by crystallization from ethyl acetate and heptanes.

(*S*)-1-((5a*R*,6*S*)-1-(4-fluorophenyl)-5a-methyl-5,5a,6,7,8,9-hexahydroimidazo[1,5-*b*]isoquinolin-6-yl)-1-phenylethanol (28): 5 mg, 0.012 mmol, 25% yield, 95% purity. LCMS = 403.2 $(M+1)^+$. ^{1}H NMR ^{1}H NMR (500 MHz, chloroform-*d*) δ ppm 7.69 (2H, dd, J = 8.8 and 5.5 Hz), 7.50−7.54 (2H, m), 7.36−7.41 (3H, m), 7.29−7.34 (1H, m), 7.09 (2H, t, J = 8.7 Hz), 6.37 (1H, s), 4.62 (1H, d, J = 13.2 Hz), 3.75 (1H, d, J = 13.2 Hz), 2.33−2.42 (2H, m), 1.97 (1H, dd, J = 11.7 and 4.0 Hz), 1.76−1.83 (1H, m), 1.73 (3H, s), 1.53−1.66 (2H, m), 1.32 (3H, s), 1.13−1.30 (1H, m).

(*S*)-1-((5a*R*,6*S*)-1-(4-Fluorophenyl)-5a-methyl-5,5a,6,7,8,9-hexahydroimidazo[1,5-*b*]isoquinolin-6-yl)-1-*o*-tolylethanol (29): 14 mg, 0.034 mmol, 76% yield, 90% purity. LCMS = 417.2 $(M+1)^+$. ^{1}H NMR (400 MHz, chloroform-*d*) δ ppm 7.68 (2H, dd, J = 8.9 and 5.3 Hz), 7.40−7.45 (1H, m), 7.33 (1H, s), 7.14−7.26 (3H, m), 7.09 (2H, t, J = 8.6 Hz), 6.39 (1H, s), 4.73 (1H, d, J = 13.2 Hz), 3.87 (1H, d, J = 12.7 Hz), 2.63 (3H, s), 2.33−2.41 (2H, m), 2.17−2.27 (2H, m), 1.82 (3H, s), 1.74−1.87 (1H, m), 1.55−1.64 (2H, m), 1.34 (3H, s), 1.13−1.25 (1H, m).

(*S*)-1-((5a*R*,6*S*)-1-(4-Fluorophenyl)-5a-methyl-5,5a,6,7,8,9-hexahydroimidazo[1,5-*b*]isoquinolin-6-yl)-1-*m*-tolylethanol (30): 11 mg, 0.026 mmol, 58% yield, 96% purity. LCMS = 417.2 $(M+1)^+$. ^{1}H NMR (400 MHz, chloroform-*d*) δ ppm 7.74 (2H, dd, J = 8.9 and 5.3 Hz), 7.23−7.33 (4H, m), 7.10−7.17 (3H, m), 6.36 (1H, s), 4.68 (1H, d, J = 13.2 Hz), 3.84 (1H, d, J = 13.2 Hz), 2.40 (3H, s), 2.35−2.42 (4H, m), 1.96 (1H, dd, J = 11.7 and 4.1 Hz), 1.71 (3H, s), 1.52−1.86 (2H, m), 1.34 (3H, s), 1.17−1.30 (1H, m).

(*S*)-1-(4-Chlorophenyl)-1-((5a*R*,6*S*)-1-(4-fluorophenyl)-5a-methyl-5,5a,6,7,8,9-hexahydroimidazo[1,5-*b*]isoquinolin-6-yl)ethanol (31): 49 mg, 0.11 mmol, 43% yield, 99% purity. LCMS = 437.1 $(M+1)^+$. ^{1}H NMR (400 MHz, chloroform-*d*) δ ppm 7.71 (2H, dd, J = 8.9 and 5.3 Hz), 7.54 (1H, br s), 7.45 (2H, d, J = 8.7 Hz), 7.34 (2H, d, J = 8.6 Hz), 7.11 (2H, t, J = 8.9 Hz), 6.38 (1H, s), 4.84 (1H, d, J = 13.2 Hz), 3.83 (1H, d, J = 12.7 Hz), 2.34−2.40 (2H, m), 1.88−1.94 (1H, m), 1.79 (1H, dt, J = 12.7 and 3.6 Hz), 1.76 (1H, s), 1.72 (3H, s), 1.49−1.58 (2H, m), 1.33 (3H, s), 1.10−1.21 (1H, m).

3-((*S*)-1-((5a*R*,6*S*)-1-(4-fluorophenyl)-5a-methyl-5,5a,6,7,8,9-hexahydroimidazo[1,5-*b*]isoquinolin-6-yl)-1-hydroxyethyl)benzonitrile (32): 9 mg, 0.017 mmol, 37% yield, 95% purity. LCMS = 428.3 $(M+1)^+$. ^{1}H NMR (400 MHz, MeOD) δ ppm 8.87 (1H, s), 7.95 (1H, s), 7.90 (1H, d, J = 8.1 Hz), 7.61−7.68 (3H, m), 7.54 (1H, t, J = 7.8 Hz), 7.31 (2H, t, J = 8.8 Hz), 6.44 (1H, s), 5.33 (1H, d, J = 13.6 Hz), 4.16 (1H, d, J = 13.6 Hz), 2.44−2.51 (2H, m), 1.95 (1H, dd, J = 12.3 and 3.3 Hz), 1.83 (1H, dt, J = 12.7 and 3.7 Hz), 1.72 (3H, s), 1.63−1.76 (1H, m), 1.54 (1H, dd, J = 13.8 and 3.3 Hz), 1.44 (3H, s), 1.10−1.26 (1H, m).

4-((*S*)-1-((5a*R*,6*S*)-1-(4-fluorophenyl)-5a-methyl-5,5a,6,7,8,9-hexahydroimidazo[1,5-*b*]isoquinolin-6-yl)-1-hydroxyethyl)benzonitrile (33): 4 mg, 0.007 mmol, 16% yield, 94% purity. LCMS = 428.1 $(M+1)^+$. ^{1}H NMR (400 MHz, MeOD) δ ppm 8.84 (1H, s), 7.78 (2H, d, J = 8.6 Hz), 7.72 (2H, d, J = 8.6 Hz), 7.64 (2H, dd, J = 8.8 and 5.0 Hz), 7.31 (2H, t, J = 8.7 Hz), 6.44 (1H, s), 5.26 (1H, d, J = 13.8 Hz), 4.12 (1H, d, J = 13.8 Hz), 2.48 (2H, dd, J = 8.2 and 3.4 Hz), 1.97 (1H, dd, J = 12.6 and 3.3 Hz), 1.83 (1H, dt, J = 12.6 and 3.7 Hz), 1.72 (3H, s), 1.65−1.77 (1H, m), 1.52−1.60 (1H, m), 1.43 (3H, s), 1.11−1.22 (1H, m).

(*S*)-1-((5a*R*,6*S*)-1-(4-Fluorophenyl)-5a-methyl-5,5a,6,7,8,9-hexahydroimidazo[1,5-*b*]isoquinolin-6-yl)-1-(pyridin-2-yl)ethanol, 2 TFA salt (34): 13 mg, 0.021 mmol, 46% yield, 90% purity. LCMS = 404.1 $(M+1)^+$. ^{1}H NMR (400 MHz, MeOD) δ ppm 8.91 (1H, s), 8.79 (1H, dd, J = 5.7 and 1.1 Hz), 8.52 (1H, td, J = 8.0 and 1.6 Hz), 8.17 (1H, d, J = 8.3 Hz), 7.92−7.97 (1H, m), 7.65 (2H, dd, J = 8.9 and 5.2 Hz), 7.31 (2H, t, J = 8.8 Hz), 6.47 (1H, s), 5.11 (1H, d, J = 13.6 Hz), 4.15 (1H, d, J = 13.6 Hz), 2.48−2.54 (2H, m), 2.08 (1H, dd, J = 12.5 and 3.1 Hz), 1.86 (3H, s), 1.76−1.91 (2H, m), 1.56−1.64 (1H, m), 1.45 (3H, s), 1.21−1.33 (1H, m).

(*S*)-1-((5a*R*,6*S*)-1-(4-Fluorophenyl)-5a-methyl-5,5a,6,7,8,9-hexahydroimidazo[1,5-*b*]isoquinolin-6-yl)-1-(pyridin-3-yl)ethanol, 2 TFA salt (35): 22 mg, 0.035 mmol, 77% yield, 95% purity. LCMS = 404.1 $(M+1)^+$. ^{1}H NMR (400 MHz, MeOD) δ ppm 9.06 (1H, d, J = 1.8 Hz), 9.00 (1H, s), 8.81 (1H, dt, J = 8.3 and 1.6 Hz), 8.79 (1H, d, J = 5.5 Hz), 8.07 (1H, dd, J = 8.3 and 5.8 Hz), 7.66 (2H, dd, J = 8.9 and 5.2 Hz), 7.31 (2H, t, J = 8.8 Hz), 6.47 (1H, s), 5.52 (1H, d, J = 13.6 Hz), 4.24 (1H, d, J = 13.8 Hz), 2.46−2.54 (2H, m), 1.98 (1H, dd, J = 12.5 and 2.9 Hz), 1.83 (3H, s), 1.66−1.90 (2H, m), 1.46 (3H, s), 1.40−1.49 (1H, m), 1.12−1.26 (1H, m).

(*S*)-1-((5a*R*,6*S*)-1-(4-Fluorophenyl)-5a-methyl-5,5a,6,7,8,9-hexahydroimidazo[1,5-*b*]isoquinolin-6-yl)-1-(pyridin-4-yl)ethanol, 2 TFA salt (36): 20 mg, 0.032 mmol, 70% yield, 90% purity. LCMS = 404.1 $(M+1)^+$. ^{1}H NMR (400 MHz, MeOD) δ ppm 8.97 (1H, s), 8.83 (2H, d, J = 6.8 Hz), 8.28 (2H, d, J = 6.8 Hz), 7.65 (2H, dd, J = 8.8 and 5.0 Hz), 7.31 (2H, t, J = 8.8 Hz), 6.47 (1H, s), 5.39 (1H, d, J = 13.8 Hz), 4.17 (1H, d, J = 13.8 Hz), 2.47−2.54 (2H, m), 2.00 (1H, dd, J = 12.3 and 3.3 Hz), 1.81 (3H, s), 1.71−1.90 (2H, m), 1.50 (1H, dd, J = 13.3 and 3.3 Hz), 1.46 (3H, s), 1.15−1.27 (1H, m).

(*S*)-1-((5a*R*,6*S*)-1-(4-Fluorophenyl)-5a-methyl-5,5a,6,7,8,9-hexahydroimidazo[1,5-*b*]isoquinolin-6-yl)-1-(3-methylthiophen-2-yl)-ethanol (37): 11 mg, 0.026 mmol, 58% yield, 95% purity. LCMS = 423.2 $(M+1)^+$. ^{1}H NMR (400 MHz, chloroform-*d*) δ ppm 7.68 (2H, dd, J = 8.9 and 5.3 Hz), 7.34 (1H, s), 7.05−7.12 (3H, m), 6.82 (1H, d, J = 5.1 Hz), 6.40 (1H, s), 4.73 (1H, d, J = 13.2 Hz), 3.81 (1H, d, J = 12.7 Hz), 2.38 (3H, s), 2.33−2.44 (2H, m), 2.28 (1H, s), 2.21 (1H, dd, J = 12.5 and 3.3 Hz), 1.81 (3H, s), 1.72−1.88 (2H, m), 1.61 (1H, qd, J = 12.8 and 3.3 Hz), 1.31 (3H, s), 1.18−1.28 (1H, m).

(*S*)-1-((5a*R*,6*S*)-1-(4-Fluorophenyl)-5a-methyl-5,5a,6,7,8,9-hexahydroimidazo[1,5-*b*]isoquinolin-6-yl)-1-(5-methylthiophen-2-yl)-ethanol (38): 13 mg, 0.031 mmol, 69% yield, 93% purity. LCMS = 423.1 $(M+1)^+$. ^{1}H NMR (400 MHz, chloroform-*d*) δ ppm 7.70 (2H, dd, J = 8.6 and 5.6 Hz), 7.46 (1H, s), 7.09 (2H, t, J = 8.6 Hz), 6.76 (1H, d, J = 3.6 Hz), 6.58 (1H, dd, J = 3.3 and 1.3 Hz), 6.40 (1H, s), 5.01 (1H, d, J = 13.2 Hz), 3.83 (1H, d, J = 13.2 Hz), 2.47 (3H, s), 2.34−2.42 (2H, m), 2.05−2.11 (2H, m), 1.80 (1H, dt, J = 12.5 and 3.7 Hz), 1.75 (3H, s), 1.59−1.68 (1H, m), 1.51 (1H, qd, J = 12.8 and 3.3 Hz), 1.30 (3H, s), 1.21−1.28 (1H, m).

(*S*)-1-(5-Chlorothiophen-2-yl)-1-((5a*R*,6*S*)-1-(4-fluorophenyl)-5a-methyl-5,5a,6,7,8,9-hexahydroimidazo[1,5-*b*]isoquinolin-6-yl)-ethanol (39): 12 mg, 0.027 mmol, 60% yield, 94% purity. LCMS = 443.1 $(M+1)^+$. ^{1}H NMR (400 MHz, chloroform-*d*) δ ppm 7.67 (2H, dd, J = 8.9 and 5.3 Hz), 7.41 (1H, s), 7.08 (2H, t, J = 8.6 Hz), 6.70−6.77 (2H, m), 6.40 (1H, s), 5.00 (1H, d, J = 13.2 Hz), 3.80 (1H, d, J = 13.2 Hz), 2.72 (1H, br s), 2.30−2.41 (2H, m), 1.88−2.03 (1H, m), 1.81 (1H, dt, J = 12.6 and 3.4 Hz), 1.72 (3H, s), 1.43−1.68 (2H, m), 1.29 (3H, s), 1.16−1.27 (1H, m).

(*S*)-1-((5a*R*,6*S*)-1-(4-Fluorophenyl)-5a-methyl-5,5a,6,7,8,9-hexahydroimidazo[1,5-*b*]isoquinolin-6-yl)-1-(thiophen-3-yl)ethanol (40): 8 mg, 0.02 mmol, 56% yield, 98% purity. LCMS = 409.3 $(M+1)^+$. ^{1}H NMR (400 MHz, chloroform-*d*) δ ppm 7.70 (2H, dd, J = 8.9 and 5.3 Hz), 7.45 (1H, s), 7.33 (1H, dd, J = 5.1 and 3.1 Hz), 7.20 (1H, dd, J = 3.1 and 1.5 Hz), 7.15 (1H, dd, J = 5.1 and 1.5 Hz), 7.10 (2H, t, J = 8.6 Hz), 6.39 (1H, s), 4.73 (1H, d, J = 13.2 Hz), 3.77 (1H, d, J = 13.2 Hz), 2.35−2.41 (2H, m), 1.98 (1H, dd, J = 11.7 and 4.1 Hz), 1.77−1.85 (2H, m), 1.73 (3H, s), 1.50−1.66 (2H, m), 1.31 (3H, s), 1.15−1.29 (1H, m).

(*S*)-1-((5a*R*,6*S*)-1-(4-Fluorophenyl)-5a-methyl-5,5a,6,7,8,9-hexahydroimidazo[1,5-*b*]isoquinolin-6-yl)-1-(thiazol-2-yl)ethanol (42): 12 mg, 0.029 mmol, 50% yield, 90% purity. LCMS = 410.1 $(M+1)^+$. ^{1}H NMR (400 MHz, chloroform-*d*) δ ppm 7.72 (1H, d, J = 3.3 Hz), 7.63−7.69 (2H, m), 7.35 (1H, s), 7.34 (1H, d, J = 3.0 Hz), 7.08 (2H, t, J = 8.8 Hz), 6.38 (1H, s), 4.52 (1H, d, J = 13.1 Hz), 3.72 (1H, d, J = 13.1 Hz), 2.36−2.42 (2H, m), 2.15 (1H, dd, J = 12.5 and 2.9 Hz), 1.82−1.94 (2H, m), 1.80 (3H, s), 1.58−1.75 (2H, m), 1.32 (3H, s), 1.19−1.30 (1H, m).

(*R*)-2-((5a*R*,6*S*)-1-(4-Fluorophenyl)-5a-methyl-5,5a,6,7,8,9-hexahydroimidazo[1,5-*b*]isoquinolin-6-yl)pent-4-en-2-ol (43): 1.4 mg, 0.0038 mmol, 6% yield, 96% purity. LCMS = 367.4 $(M+1)^+$. ^{1}H NMR (400 MHz, chloroform-*d*) δ ppm 7.70 (2H, dd, J = 8.6 and 5.6 Hz), 7.52 (1H, s), 7.10 (2H, t, J = 8.6 Hz), 6.40 (1H, s), 5.84−5.96 (1H, m), 5.31 (1H, dd, J = 10.2 and 2.0 Hz), 5.21 (1H, d, J = 16.3 Hz), 5.10 (1H, d, J = 13.2 Hz), 3.71 (1H, d, J = 13.7 Hz), 2.56 (1H, dd, J = 13.2 and 8.6 Hz), 2.35−2.45 (2H, m), 2.31 (1H, dd, J = 13.2 and 6.6 Hz), 1.88−1.98 (1H, m), 1.72−1.82 (2H, m), 1.50−1.63 (1H, m), 1.33−1.43 (1H, m), 1.31 (3H, s), 1.25 (3H, s), 1.17−1.26 (1H, m).

(*R*)-2-((5a*R*,6*S*)-1-(4-Fluorophenyl)-5a-methyl-5,5a,6,7,8,9-hexahydroimidazo[1,5-*b*]isoquinolin-6-yl)hexan-2-ol (44): 3 mg, 0.0078 mmol, 17% yield, 90% purity. LCMS = 383.2 $(M+1)^+$. ^{1}H NMR (400 MHz, chloroform-*d*) δ ppm 7.69 (2H, dd, J = 8.6 and 5.6 Hz), 7.47 (1H, s), 7.09 (2H, t, J = 8.6 Hz), 6.39 (1H, s), 4.99 (1H, d, J = 13.2 Hz), 3.76 (1H, d, J = 13.2 Hz), 2.38 (2H, d, J = 6.1 Hz), 1.31 (3H, s), 1.23 (3H, s), 1.18−1.96 (12H, m), 0.95 (3H, t, J = 6.9 Hz).

(*R*)-2-((5a*R*,6*S*)-1-(4-Fluorophenyl)-5a-methyl-5,5a,6,7,8,9-hexahydroimidazo[1,5-*b*]isoquinolin-6-yl)-4-phenylbutan-2-ol (45): 3.8 mg, 0.0088 mmol, 20% yield, 96% purity. LCMS = 431.2 $(M+1)^+$. ^{1}H NMR (400 MHz, chloroform-*d*) δ ppm 7.70 (2H, dd, J = 8.9 and 5.3 Hz), 7.50 (1H, s), 7.29−7.35 (2H, m), 7.19−7.25 (3H, m), 7.09 (2H, t, J = 8.6 Hz), 6.39 (1H, s), 5.03 (1H, d, J = 13.2 Hz), 3.79 (1H,

d, J = 13.2 Hz), 2.80 (1H, td, J = 12.6 and 4.8 Hz), 2.64 (1H, td, J = 12.6 and 4.8 Hz), 2.27−2.44 (2H, m), 2.15 (1H, td, J = 13.0 and 5.1 Hz), 1.85−1.95 (1H, m), 1.67−1.84 (3H, m), 1.49−1.62 (2H, m), 1.44 (3H, s), 1.32−1.47 (1H, m), 1.23 (3H, s).

(*R*)-1-(4-Fluorophenyl)-2-((5a*R*,6*S*)-1-(4-fluorophenyl)-5a-methyl-5,5a,6,7,8,9-hexahydroimidazo[1,5-*b*]isoquinolin-6-yl)propan-2-ol (46): 4.7 mg, 0.0086 mmol, 33% yield, 95% purity. LCMS = 435.4 $(M+1)^+$. ^{1}H NMR (400 MHz, MeOD) δ ppm 8.93 (1H, s), 7.62−7.69 (2H, m), 7.23−7.36 (4H, m), 7.00 (2H, t, J = 8.9 Hz), 6.47 (1H, s), 5.52 (1H, d, J = 14.2 Hz), 4.10 (1H, d, J = 13.7 Hz), 3.12 (1H, d, J = 13.2 Hz), 2.74 (1H, d, J = 13.2 Hz), 2.47−2.59 (2H, m), 1.75−2.06 (4H, m), 1.46 (3H, s), 1.28−1.43 (1H, m), 1.16 (3H, s).

(*R*)-1-Cyclopropyl-1-((5a*R*,6*S*)-1-(4-fluorophenyl)-5a-methyl-5,5a,6,7,8,9-hexahydroimidazo[1,5-*b*]isoquinolin-6-yl)ethanol (47): 4 mg, 0.008 mmol, 24% yield, 90% purity. LCMS = 367.4 $(M+1)^+$. ^{1}H NMR (400 MHz, MeOD) δ ppm 8.91 (1H, s), 7.62−7.67 (2H, m), 7.31 (2H, t, J = 8.6 Hz), 6.44 (1H, s), 5.42 (1H, d, J = 13.7 Hz), 3.93 (1H, d, J = 14.2 Hz), 2.43−2.59 (2H, m), 1.92−2.08 (2H, m), 1.89 (1H, dd, J = 12.7 and 3.1 Hz), 1.59−1.71 (1H, m, J = 12.8, 12.8, 12.7, and 2.8 Hz), 1.38−1.47 (1H, m), 1.33 (3H, s), 1.26 (3H, s), 1.10−1.23 (1H, m), 0.26−0.50 (4H, m).

(*R*)-1-Cyclohexyl-1-((5a*R*,6*S*)-1-(4-fluorophenyl)-5a-methyl-5,5a,6,7,8,9-hexahydroimidazo[1,5-*b*]isoquinolin-6-yl)ethanol (48): 2.6 mg, 0.005 mmol, 11% yield, 90% purity. LCMS = 409.2 $(M+1)^+$. ^{1}H NMR (400 MHz, MeOD) δ ppm 8.93 (1H, s), 7.61−7.67 (2H, m), 7.31 (2H, t, J = 8.9 Hz), 6.43 (1H, s), 5.58 (1H, d, J = 13.7 Hz), 3.87 (1H, d, J = 14.2 Hz), 2.41−2.56 (2H, m), 1.53−2.00 (9H, m), 1.35 (3H, s), 1.27 (3H, s), 1.04−1.41 (7 H, m).

(*R*)-1-((5a*R*,6*S*)-1-(4-Fluorophenyl)-5a-methyl-5,5a,6,7,8,9-hexahydroimidazo[1,5-*b*]isoquinolin-6-yl)-1-(tetrahydro-2*H*-pyran-4-yl)-ethanol (49): 6 mg, 0.01 mmol, 10% yield, 90% purity. LCMS = 411.3 $(M+1)^+$. ^{1}H NMR (400 MHz, MeOD) δ ppm 8.94 (1H, s), 7.61−7.67 (2H, m), 7.31 (2H, t, J = 8.8 Hz), 6.45 (1H, s), 5.57 (1H, d, J = 13.8 Hz), 3.96−4.06 (2H, m), 3.88 (1H, d, J = 13.8 Hz), 3.36−3.45 (2H, m), 2.43−2.55 (2H, m), 1.93 (2H, dd, J = 11.7 and 3.4 Hz), 1.36 (3H, s), 1.30−1.75 (8H, m), 1.29 (3H, s).

(*S*)-1,1,1-Trifluoro-2-((5a*R*,6*S*)-1-(4-fluorophenyl)-5a-methyl-5,5a,6,7,8,9-hexahydroimidazo[1,5-*b*]isoquinolin-6-yl)propan-2-ol (50): 1 mg, 0.002 mmol, 12% yield, 98% purity. LCMS = 395.2 $(M+1)^+$. ^{1}H NMR (400 MHz, MeOD) δ ppm 8.96 (1H, s), 7.64 (2H, dd, J = 8.9 and 5.2 Hz), 7.28−7.34 (2H, m), 6.48 (1H, d, J = 2.0 Hz), 5.56 (1H, d, J = 13.8 Hz), 3.93 (1H, d, J = 13.8 Hz), 2.42−2.58 (2H, m), 2.18 (1H, dd, J = 12.7 and 3.4 Hz), 1.86−1.98 (2H, m), 1.66−1.79 (1H, m), 1.51 (3H, s), 1.37−1.46 (1H, m), 1.36 (3H, s).

(*R*)-2-((5a*R*,6*S*)-1-(4-Fluorophenyl)-5a-methyl-5,5a,6,7,8,9-hexahydroimidazo[1,5-*b*]isoquinolin-6-yl)-4-methylpentan-2-ol (51): 7.8 mg, 0.016 mmol, 23% yield, 98% purity. LCMS = 383.3 $(M+1)^+$. ^{1}H NMR (400 MHz, MeOD) δ ppm 8.91 (1H, s), 7.64 (2H, dd, J = 8.6 and 5.1 Hz), 7.31 (2H, t, J = 8.9 Hz), 6.43 (1H, s), 5.39 (1H, d, J = 13.7 Hz), 4.08 (1H, d, J = 13.7 Hz), 2.43−2.53 (2H, m), 1.83−1.99 (2H, m), 1.56−1.80 (4H, m), 1.39 (2H, dd, J = 14.0 and 3.8 Hz), 1.34 (3H, s), 1.32 (3H, s), 1.05 (3H, d, J = 6.6 Hz), 0.97 (3H, d, J = 6.6 Hz).

(5a*R*,6*S*)-1-(4-Fluorophenyl)-6-((*S*)-1-methoxy-1-(thiophen-2-yl)-ethyl)-5a-methyl-5,5a,6,7,8,9-hexahydroimidazo[1,5-*b*]isoquinoline (25). To a stirred solution of (*S*)-1-((5a*R*,6*S*)-1-(4-fluorophenyl)-5a-methyl-5,5a,6,7,8,9-hexahydroimidazo[1,5-*b*]isoquinolin-6-yl)-1-(thiophen-2-yl)ethanol (**24**; 13 mg, 0.032 mmol) in anhydrous dimethylformamide (0.3 mL) was added sodium hydride (60% oil dispersion, 9 mg, 0.23 mmol) at 0 °C. The reaction mixture was stirred at RT for 40 min before methyl iodide (1 drop) was added. The reaction mixture was stirred at RT for a further 30 min and purified using reverse phase HPLC (YMC S5 20 × 100 mm, 10 min run, solvent A: 10% MeOH/90% H_2O/0.1% TFA; solvent B: 90% MeOH/10% H_2O/0.1% TFA) to yield (5a*R*,6*S*)-1-(4-fluorophenyl)-6-((*S*)-1-methoxy-1-(thiophen-2-yl)ethyl)-5a-methyl-5,5a,6,7,8,9-hexahydroimidazo[1,5-*b*]isoquinoline·TFA salt (15 mg, 0.028 mmol, 87% yield, 96% purity). LCMS = 423.2 $(M+1)^+$. ^{1}H NMR (400 MHz, MeOD) δ ppm 9.00 (1H, s), 7.64−7.71 (2H, m), 7.41 (1H, dd, J = 5.16 and 1.13 Hz), 7.33 (2H, t, J = 8.69 Hz), 7.07 (1H, dd, J = 3.53 and 1.26 Hz), 6.98 (1H, dd, J = 5.04 and 3.53 Hz), 6.48 (1H, s), 5.31 (1H, d, J = 13.85 Hz), 4.23 (1H, d, J = 14.10 Hz), 3.13 (3H, s), 2.47−2.54 (2H, m), 2.20 (1H, dd, J = 12.46 and 2.90 Hz), 1.79−1.86 (1H, m), 1.78 (3H, s), 1.60−1.74 (1H, m, J = 12.97, 12.97, 12.84, and 3.27 Hz), 1.49 (1H, d, J = 13.35 Hz), 1.40 (3H, s), 1.17−1.28 (1H, m).

Receptor Binding Assay. The GR ligand binding assay was conducted in fluorescence polarization format which measures the competition between a test compound and a fluorescently labeled ligand (GS-red) for binding to the full length or ligand binding domain of GRα (Invitrogen, cat#P2893). Compounds were tested in concentrations ranging from 5 μM to 85 pM. IC_{50} values were determined by fitting the fluorescence polarization signal data using a four parameter logistic equation. The K_i values were determined by application of the Cheng-Prusoff equation to the IC_{50} values, where $K_i = IC_{50}/(1 + \text{ligand concentration}/K_d)$ (Cheng, Y.; Prusoff, W. H. Relationship between the inhibition constant (K_i) and the concentration of inhibitor which causes 50% inhibition (IC_{50}) of an enzymatic reaction. *Biochem. Pharmacol.* **1973**, *22*, 3099−3108). The K_d value used for GR was 0.3 nM, as supplied by the assay manufacturer (Invitrogen, cat#P2893). Data shown represent the mean of two or more experiments.

Transrepression Assays. AP-1 activity was measured using an AP-1 response element (5 copies) cloned into a luciferase reporter vector. This reporter is stably transfected into the human A549 lung epithelial cell line. AP-1 activity is induced by addition of phorbol myristate acetate (PMA; 15 ng/mL), and inhibition of induction by compounds is quantitated by measuring decreased luciferase activity. NFκB is measured using a truncated, NFκB dependent, E-selectin promoter (~400 bp) cloned into a luciferase reporter vector. This reporter is stably transfected into the human A549 lung epithelial cell line. NFκB activity is induced using IL-1β (0.5 ng/mL) and inhibition of induction by compounds is quantitated by measuring decreased luciferase activity.

Transactivation Assay. NP-1 activity is measured using a GR ligand binding domain (GR-LBD) chimera cloned into a GAL4 Luciferase reporter system. This reporter system is stably transfected into a HeLa cell line (Webster, N. J. G.; Green, S.; Jin, J. R.; Chambon, P. The hormone-binding domains of the estrogen and glucocorticoid receptors contain an inducible transcription activation function. *Cell* **1988**, *54* (2), 199−207). Response to ligand/compound induced binding is quantitated by measuring luciferase activity. Direct activation of the GR-LBD by compounds can be measured (agonist) as increased luciferase activity, or the ability of compounds to inhibit 10 nM dexamethasone induction can be measured (antagonist) as decreased luciferase activity.

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(17) Crystallographic data (excluding structure factors) for compounds **24** and **31** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 751588 and 751589. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, U.K.; fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk). Compound **24** was crystallized from ethyl acetate and heptane. Compound **31** was crystallized from a solvent mixture comprising ethyl acetate, heptane, methanol, and dichloromethane.
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