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Article

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The Identification of the Clinical Candidate (*R*)-(1-(4-fluorophenyl)-6-((1-methyl-1H-pyrazol-4-yl)sulfonyl)-4,4a,5,6,7,8-hexahydro-1H-pyrazolo[3,4-g]isoquinolin-4a-yl)(4-(trifluoromethyl)pyridin-2-yl)methanone (CORT125134):– A Selective Glucocorticoid Receptor (GR) Antagonist.

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Abstract

The non-selective glucocorticoid receptor (GR) antagonist, mifepristone, has been approved in the USA for the treatment of selected patients with Cushing's syndrome. Whilst this drug is highly effective, lack of selectivity for GR leads to unwanted side effects in some patients. Optimization of the previously described fused azadecalin series of selective GR antagonists led to the identification of CORT125134, which is currently being evaluated in a Phase 2 clinical study in patients with Cushing's syndrome.

Introduction

The glucocorticoid receptor (GR) is a ligand-activated transcription factor and a member of the nuclear receptor superfamily. The GR is widely expressed, and is present in nearly all cell types

and tissues. The essential role played by the GR is confirmed by the observation that mice with targeted disruption of the GR do not survive postpartum due to a number of defects[1]. The GR mediates a breadth of biological processes, including inflammation, gluconeogenesis, immunity, cardiovascular function, bone metabolism, brain function and homeostasis/development, predominantly through transcriptional mechanisms. In the absence of ligand, the GR resides in the cytoplasm and associates with chaperone proteins, including hsp90 and hsp70. Receptor ligand binding (cortisol in humans and higher mammals, corticosterone in rodents) causes a conformational change in the GR, leading to its dissociation from the chaperones and translocation of the ligand-bound receptor to the nucleus[2,3]. Once in the nucleus, the GR regulates gene transcription by both activating and repressing mechanisms[4]. Analogous to other nuclear hormone receptors, the GR serves as an assembly point for transcription coregulators that can directly modify chromatin structure and/or impact the activity of the gene transcription apparatus. The GR can function either as a monomer or as a homo-dimer. Mechanisms by which the GR modulates gene expression include direct binding of the dimer to glucocorticoid response elements (GREs) in the promoter or enhancer region of genes, and binding of the monomer to other transcription factors such as nuclear factor-kappa B (NF-kB) and activator protein 1 (AP-1), through protein-protein interactions. Ligand structure, deoxyribonucleic acid (DNA) sequence, cellular transcription factor composition and regulatory inputs all contribute to gene-specific regulation[5-8].

In healthy individuals, cortisol, the natural ligand for GR, is secreted from the cortical cells of the adrenal glands under the control of adrenocorticotropic hormone (ACTH). Endogenous Cushing's syndrome is a rare multisystem disorder that results from overproduction of cortisol. In both adults and children, Cushing's syndrome is most commonly caused by an ACTH-

secreting pituitary tumor (Cushing's disease). Other forms of Cushing's syndrome result from autonomous production of cortisol from adrenal cortical tumors or overproduction of ACTH from non-pituitary tumors[9,10].

The only curative treatment for Cushing's Syndrome is resection of the tumor that is the source of the excess ACTH or cortisol. Pharmacological treatment is not curative in Cushing's syndrome, but it serves to control the disease after unsuccessful surgery[11]. It may also be used to lower cortisol activity to improve a patient's condition prior to surgery. Pharmacological treatment may be employed as an interim therapy under specific circumstances, such as in patients who are waiting for their radiotherapy to be effective[12].

Currently, there are two United States (US) Food and Drug Administration (FDA)-approved medical therapies for the treatment of endogenous Cushing's syndrome. The first is mifepristone (Figure 1), a non-selective GR antagonist, which has been approved for use in selected adult patients with endogenous Cushing's syndrome who have type 2 diabetes mellitus or glucose intolerance and have failed surgery or are not candidates for surgery. The second is pasireotide, a somatostatin receptor agonist, which has been approved for the treatment of adult patients with Cushing's disease (a sub-set of Cushing's syndrome) for whom pituitary surgery is not an option or has not been curative.

As noted above, Cushing's syndrome is caused by excessive cortisol activity. Excess cortisol activity leads to a plethora of severe symptoms, including the typical body habitus of patients with Cushing's syndrome, as well as diabetes mellitus, hypertension, dermatologic manifestations and psychiatric disturbances. Mifepristone is effective in reducing the clinical impact of excessive cortisol activity, and improving the patients' overall medical condition[13]. Its role in endogenous Cushing´s syndrome includes adjunct therapy following radiation treatment,

and in cases where a patient cannot safely undergo surgery or has experienced failure of surgery. Mifepristone does not decrease cortisol production; it acts by blocking the interaction of cortisol with the GR.

Although mifepristone is very effective, the lack of selectivity for GR has certain disadvantages. Due to its high affinity for the progesterone receptor (PR), mifepristone causes termination of pregnancy, and endometrial thickening or irregular vaginal bleeding in some patients. Our objective was to identify a selective GR antagonist that would provide all the beneficial effects of mifepristone, but would not cause the side effects associated with PR antagonism.

We have previously described the discovery and optimization of a series of selective GR antagonists, based on a fused azadecalin template[14,15]. In our most recent publication[15], we reported the identification of compounds such as CORT113176 **1**, which possess a heteroaryl ketone substituent at the ring junction position, Figure 1. Compound **1** demonstrated modest efficacy in a rat model of olanzapine induced weight gain and also in a rat model of exogenous Cushing's syndrome. In addition, Vendruscolo *et al.*[16] have reported that **1** reduced alcohol intake in rats made dependent on alcohol, and Pineau *et al.*[17] have reported the efficacy of **1** in a rat model of Alzheimer's disease. Further investigation of the heteroaryl ketone series provided compounds such as the previously described compound **33**[15]**,** designated compound **2** herein, with reduced activity in a manual patch clamp hERG assay, good bioavailability in rats, and efficacy in our rat model of exogenous Cushing's syndrome. Although both compounds **1** and **2** demonstrated efficacy in our rat model of exogenous Cushing's syndrome, neither were as effective as mifepristone and we hoped to improve on their activity by the design and synthesis of additional analogues. The structures of these compounds, and the non-selective GR antagonist

mifepristone are shown in Figure 1. We now wish to report further optimization of this series of compounds, and the identification of two clinical candidates, **7** and **12**.

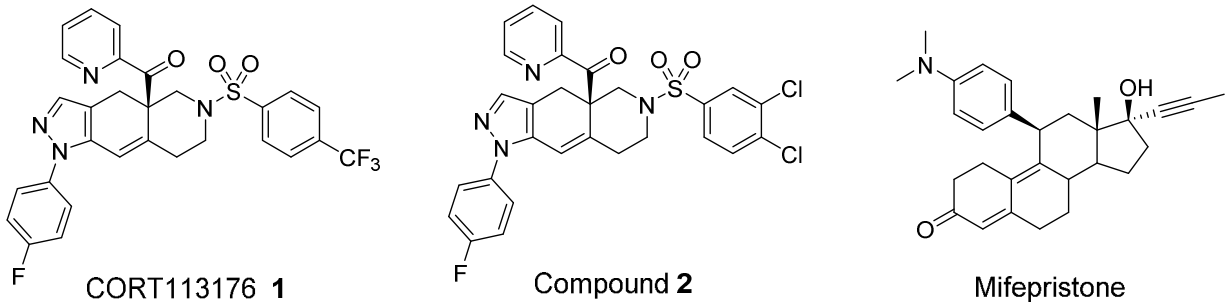


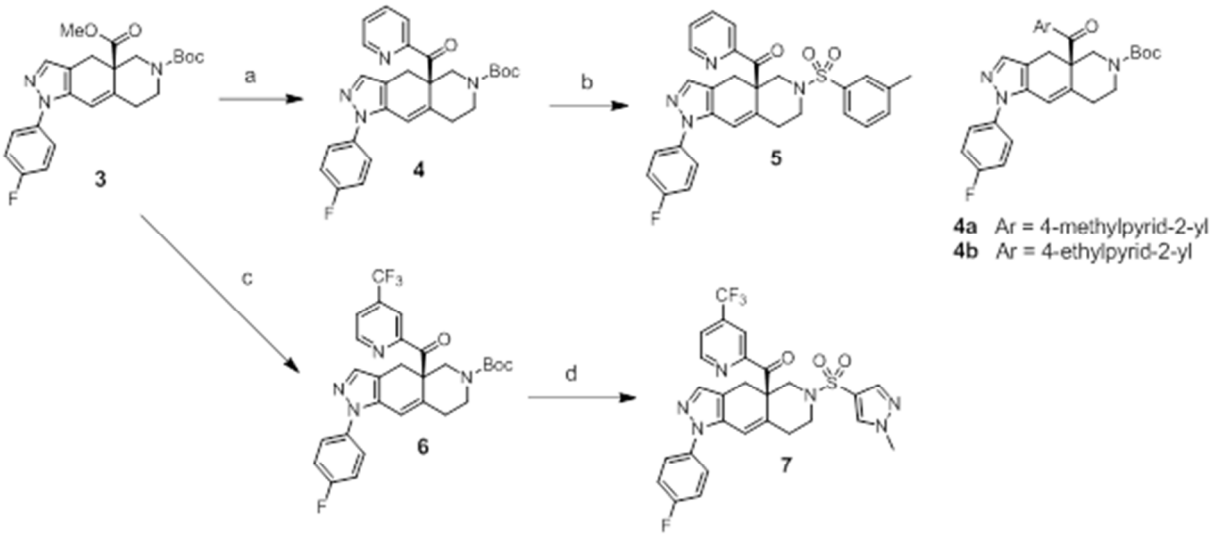
Figure 1. Structures of compounds **1**, **2** and mifepristone

Chemistry

All the compounds described herein were synthesised from the enantiopure azadecalin ester **3**[14] by two principal routes, described in Schemes 1-2. The first route is exemplified in Scheme 1 by the conversion of **3** to the keto-sulphonamide **5** via the Boc-protected ketone intermediate **4**. It was found that low temperature addition of aryllithium reagents to ester **3** generally proceeded only as far as the ketone (eg. **4**, Scheme 1), perhaps due to the steric hindrance afforded by the adjacent quaternary carbon centre. Two additional Boc-ketone intermediates **4a,b** were similarly prepared and readily converted to several different sulphonamides described in Tables 1 and 2. A complication arose with the addition of the aryllithium reagent derived from 2-bromo-4-trifluoromethyl pyridine, which gave rise to the production of an inseparable by-product thought to be derived from loss of the entire ketone substituent at the ring junction. Since the synthesis of the para-trifluoromethyl substituted pyridyl ketone intermediate **6** was important to this programme, improved conditions were developed involving aryl Grignard addition to the ester **3**, which afforded a mixture of ketone and hemiketal products, easily driven to clean ketone product

6 by *in situ* acidic hydrolysis. Isolation of the hemiketal intermediate suggests that double addition of the Grignard in this case is thwarted by stabilization of the initial tetrahedral intermediate, perhaps due to magnesium ion chelation to the adjacent pyridyl nitrogen atom. Again, ketone intermediate **6** was progressed to give a number of different sulphonamides such as the methyl pyrazole analogue **7** shown in Scheme 1.

Scheme 1. Synthesis of keto-sulphonamides[a]

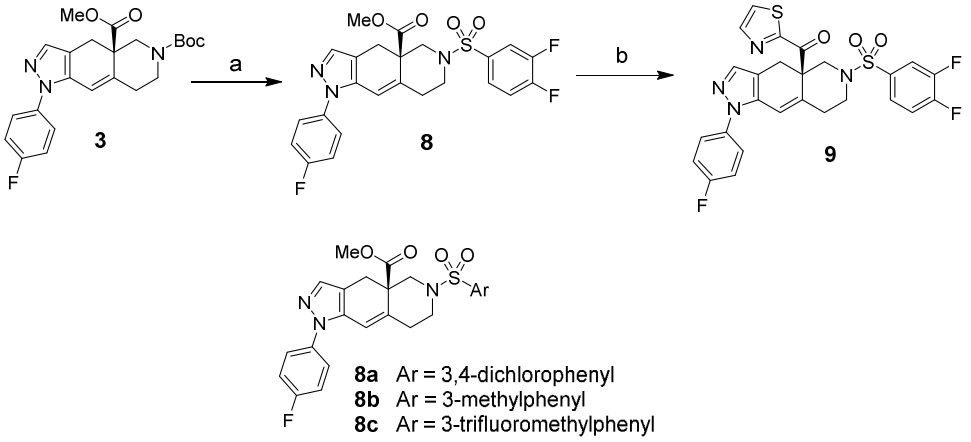


[a]Reagents and conditions: (a) 2-bromopyridine, n-BuLi, THF, -78 °C, 45 min, 53%; (b) (i) TFA, DCM, rt, 1 h; (ii) 3-methylbenzene-1-sulfonyl chloride, Hunig's base, DCM, rt, 0.5 h, 38%; (c) (i) isopropylmagnesium chloride, 2-bromo-4-(trifluoromethyl)pyridine, ether/THF, 0 °C → rt, 2 h; (ii) aq HCl, MeCN, rt, 30 min, 84%; (d) (i) TFA, DCM, rt, 1.5 h; (ii) 1-methyl-1H-pyrazole-4-sulfonyl chloride, K_2CO_3, DCM/water, rt, 20 min, 73%.

In the second preparative route, the order of steps was reversed, as illustrated in Scheme 2, by the synthesis of keto-sulphonamide **9** via sulphonamide ester **8**, easily prepared from Boc-ester **3**.

Again, mono-addition of aryllithium reagents to give the desired ketones generally occurred with negligible over-addition to tertiary alcohol by-products. Three alternative sulphonamides **8a-c** were also used to prepare some of the keto-sulphonamides listed in Tables 1 and 2.

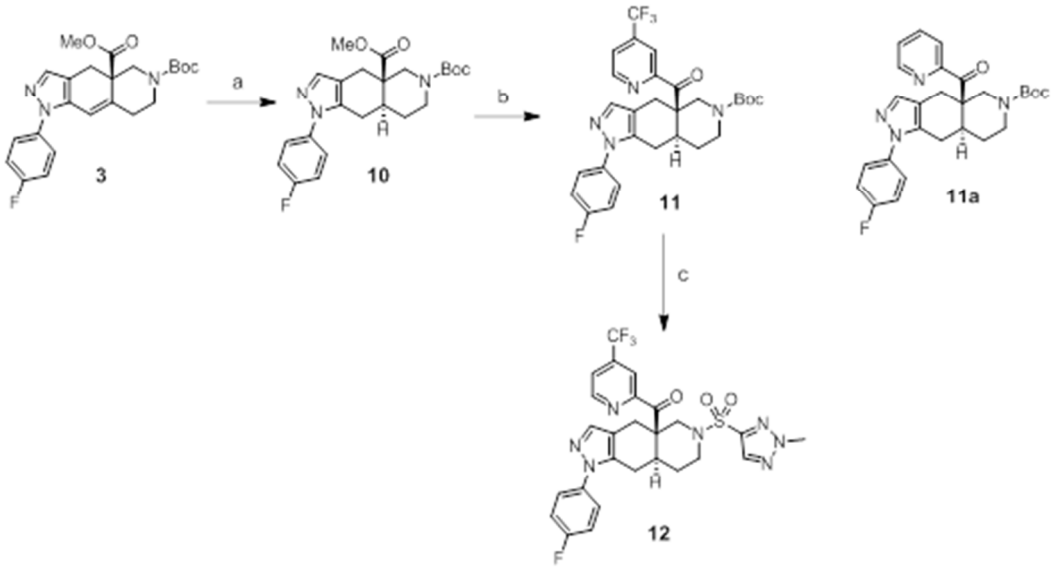
Scheme 2. Alternative synthesis of keto-sulphonamides[a]



[a]Reagents and conditions: (a) (i) HCl, dioxane, rt, 45 min; (ii) 3,4-difluorobenzene-1-sulfonyl chloride, Hunig's base, DCM, rt, 15 min, 92%; (b) 2-bromothiazole, n-BuLi, diethyl ether, -78 °C, 45 min, 36%.

The core-reduced analogues of Table 3 were synthesized by a variant of the route shown in Scheme 1. Hydrogenation of ester **3** occurred with essentially complete diastereoselectivity to afford the *trans* azadecalin intermediate **10** shown in Scheme 3. This ester reacted with aryllithium or aryl Grignard reagents to give ketones such as **11** or **11a**, which were deprotected and treated with a variety of sulphonyl chlorides to give keto-sulphonamides such as **12**, as shown in Scheme 3. The sense of diastereoselection shown by hydrogen addition to **3** was determined by evaluation of the X-ray crystal structure of keto-sulphonamide **12**, which clearly shows the *trans* azadecalin ring geometry **(**Figure 2).

Scheme 3. Synthesis of reduced core analogues[a]



[a]Reagents and conditions: (a) H_2, Pd/C, 55 °C, 45 min, H-cube, 1 mL/min, 99%; (b) 2-bromo-4-(trifluoromethyl)pyridine, isopropylmagnesium bromide, toluene, 0 °C → rt, 18 h, 45%; (i) TFA, DCM, rt, 45 min; (ii) 2-methyl-2H-1,2,3-triazole-4-sulfonyl chloride, Hunig's base, DCM, rt, 2 h, 72%.

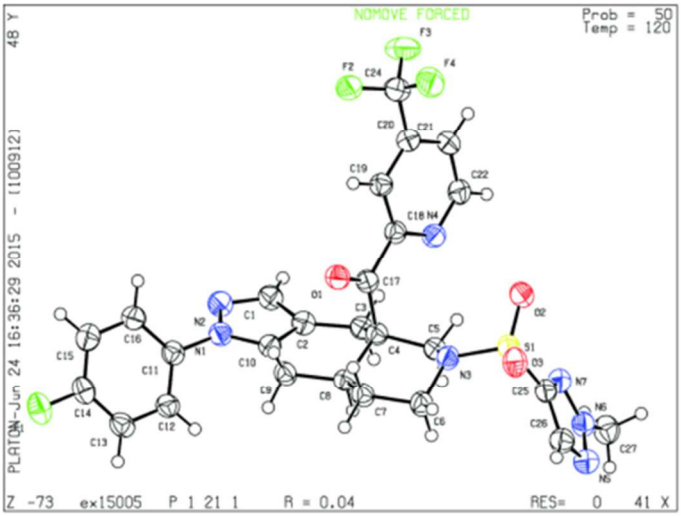
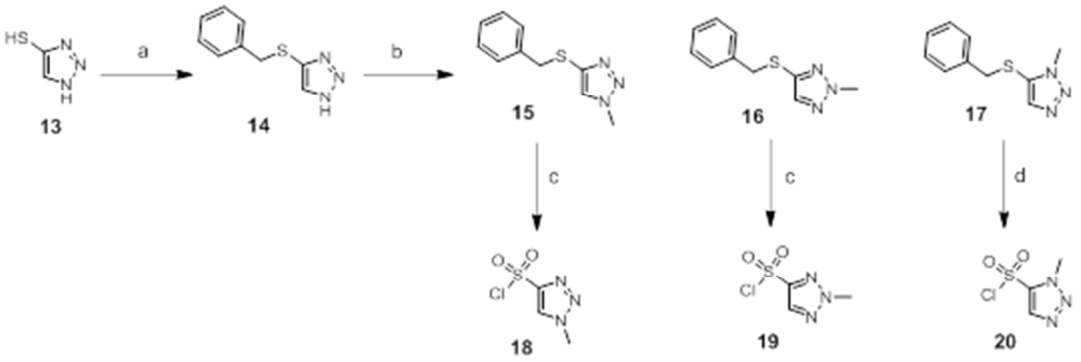


Figure 2. Crystal structure of **12**

Most of the sulphonyl chlorides required to make the sulphonamides described in Tables 1, 2 and 5 were commercially available, with the exception of the triazoles **18-20**. These were synthesized by the route shown in Scheme 4. Benzylation of triazole thiol **13** followed by methylation afforded a mixture of methyl triazole regioisomers **15-17** which were readily separable by column chromatography. Oxidative debenzylation with *N*-chlorosuccinimide or chlorine then gave the three sulphonyl chlorides **18-20**. The regiochemistry of the 2,4-isomer **19** was readily assigned with the aid of the crystal structure of the derived keto-sulphonamide product **12** shown in Figure 2. The 1,4-isomer **18** and the 1,5-isomer **20** were assigned through comparison of the ^{1}H NMR spectra of the precursor sulphides **15** and **17** with those previously reported[18,19].

Scheme 4. Synthesis of triazole sulphonyl chlorides[a]



[a]Reagents and conditions: (a) BnBr, EtOH, 0 °C → rt, 20 min, 87%; (b) MeI, K_2CO_3, DMF, 0 °C → rt, 1 h, 22% (**15**) / 40% (**16**) / 20% (**17**); (c) NCS, AcOH/water, rt, 2 h, 64% (**18**) / 82% (**19**); (d) Cl_2, DCM/water, 0 °C, 5 min, 90%.

Results and Discussion

All compounds were tested for their affinity to GR using a fluorescence polarization (FP) assay. Functional activity was assessed in the human HepG2 cell line. The GR agonist, dexamethasone,

induces the activity of the enzyme tyrosine amino transferase (TAT). GR antagonism is readily determined by measuring the ability of the test compounds to inhibit the effect of dexamethasone. The minimum significant ratio in this assay was 2.2 at the 95% confidence level, so potency differences of 2.2 fold can be detected. For key compounds, competitive antagonism was confirmed by Schild analysis. GR agonism of the test compounds is assessed by testing the compounds in the absence of dexamethasone and measuring any induction in TAT activity. Full details of both assays are provided in the Experimental section.

The next step in our investigation of this very promising series of compounds was the incorporation of a substituent on the heteroaryl ketone. Although our compounds have excellent potency in our binding assay and standard functional GR antagonist assay, most of them are not quite as potent as mifepristone. As can been seen in Figure 3, the heteroaryl ketone substituent in **1** does not fully occupy the space filled by the dimethylanilinophenyl group in mifepristone. We wanted to determine whether we could obtain additional functional potency by the inclusion of a larger heteroaryl ketone group, by adding a substituent to the heteroaryl ring. An overlay of **1** (blue) and mifepristone (pink) is shown in Figure 3, which depicts the GR active site (green except for helix 12 in red). The GR and mifepristone structure comes from PDB 3H52, chain c. A minimised conformer of **1** was placed onto mifepristone using an RMS fitting procedure. The conformer of **1** was generated with Spartan software using the conformer distribution option and then minimised using MMFF94. The inclusion of a methyl substituent on the pyridyl or thiazolyl ring was investigated. We were encouraged to find that a methyl substituent para to the nitrogen often provided a modest increase in potency (see for example compound **5** compared to compound **21**; **26** vs **27**; **28** vs **29**; **32** vs **33**). A comparison of some pairs of compounds, with and without a methyl substituent, is provided in Table 1. However, the inclusion of the methyl

group meta to the pyridyl nitrogen was not advantageous (for example see compound **22**). In the thiazole series, the position of the methyl group also made a significant difference, with 5-methyl providing an enhancement in potency (compound **37**), but a 3-methyl being detrimental (compound **38**). In the pyridyl series we also investigated ethyl substitution (compound **34**), and found that this was beneficial.

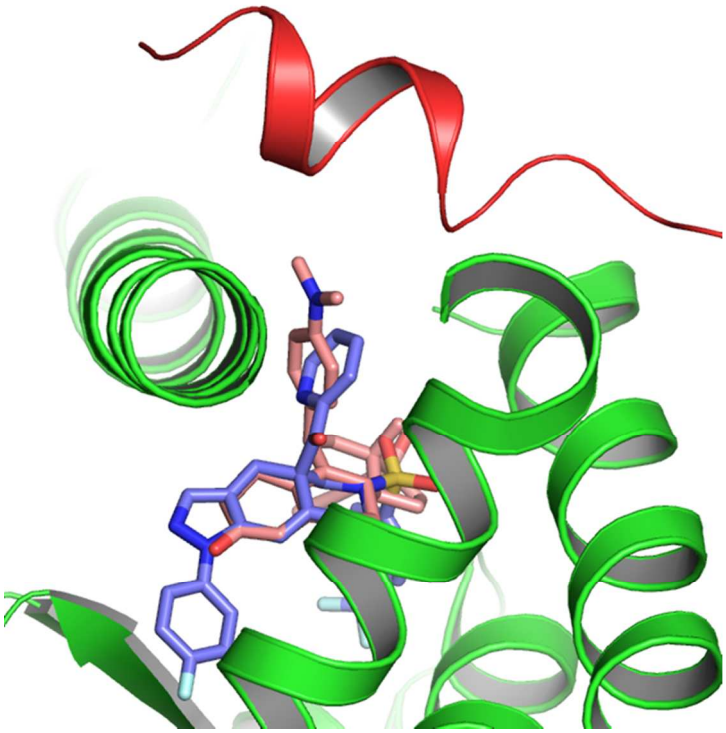
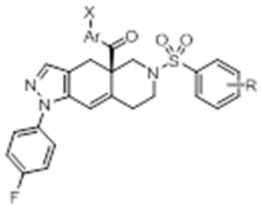


Figure 3. Overlay of **1** and mifepristone

Table 1. Effect of Substitution on the Heteroaryl Ketone Group



Compound	R	Ar	X	FP Ki (nM)	HepG2 TAT Ki (nM)	C_{max} (ng/mL)	AUC (ng.h/mL)
mifepristone	NA	NA	NA	0.09	3.0	nt	nt
1	p-CF_3	2-pyridyl	H	0.28	12	nt	nt
5	m-CH_3	2-pyridyl	H	0.14	6.8	31	83
21	m-CH_3	2-pyridyl	4-CH_3	0.08	3.3	11	44
22	m-CH_3	2-pyridyl	5-CH_3	0.14	7.5	nt	nt
23	m-CH_3	2-pyridyl	6-CH_3	0.20	14	nt	nt
24	m,p-di F	2-pyridyl	H	0.22	7.5	215	974
25	m,p-di F	2-pyridyl	4-CH_3	0.14	5.7	113	421
26	m,m-di F	2-pyridyl	H	0.12	9.2	72	143
27	m,m-di F	2-pyridyl	4-CH_3	0.14	4.3	nt	nt
28	m-CF_3	2-pyridyl	H	0.1	14	nt	nt
29	m-CF_3	2-pyridyl	4-CH_3	0.21	5.1	nt	nt
30	m-F,p-CF_3	2-pyridyl	H	0.29	11	125	726
31	m-F,p-CF_3	2-pyridyl	4-CH_3	0.42	7.5	48	173
32	m-CN	2-pyridyl	H	0.14	15	140	239

33	m-CN	2-pyridyl	4-CH_3	0.15	4.5	70	217
34	m-CN	2-pyridyl	4-CH_2CH_3	0.19	1.7	nt	nt
35	m-CN	2-pyridyl	4-CF_3	0.32	4.8	20	49
36	m-CF_3	2-thiazole	H	0.48	17	103	446
37	m-CF_3	2-thiazole	5-CH_3	0.29	10	nt	nt
38	m-CF_3	2-thiazole	3-CH_3	0.88	63	nt	nt
9	m,p-di F	2-thiazole	H	0.23	37	nt	nt
39	m,p-di F	2-thiazole	5-CH_3	1.3	7.4	30	135
40	m,p-di Cl	2-thiazole	H	0.59	16	197	1,222
41	m,p-di F	2-thiazole	5-CH_3	0.32	7.4	30	135

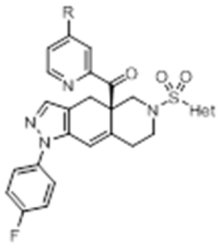
NA = not applicable; nt = not tested

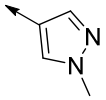
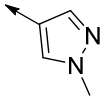
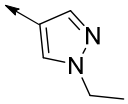
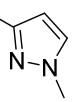
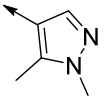
Encouraged by the improved potency of several of the methylated analogues, we conducted some cassette PK studies in rats. We included three test compounds and a reference compound in each cassette, and administered a total oral dose of 12mg/kg (3mg/kg for each compound) by oral gavage. The additional methyl substituent appeared to have a detrimental effect on plasma concentrations, since several compounds provided low C_{max} and AUC when compared to the corresponding compounds lacking the methyl group, see Table 1. For example, the methyl analogues **25**, **31** and **33** all provided lower C_{max} and AUC than the corresponding unsubstituted compounds **24**, **30** and **32**. We considered that the additional methyl group may have been subject to metabolism, thus explaining the reduced plasma concentrations in analogues

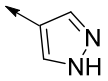
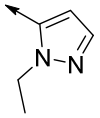
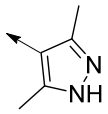
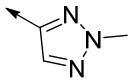
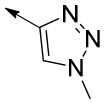
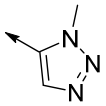
incorporating this group. On this basis, replacement of methyl by trifluoromethyl was expected to provide higher plasma concentrations, but we were concerned by the already higher than ideal lipophilicity and molecular weight of our compounds. This concern was confirmed by the low C_{max} and very low AUC observed with compound **35**. The corresponding unsubstituted pyridyl analogue, compound **32**, exhibited considerably better exposure, see Table 1.

In an effort to reduce lipophilicity and molecular weight, we investigated the replacement of the substituted phenyl sulphonamide by a heteroaryl sulphonamide, but we found that these compounds were typically not sufficiently potent in the HepG2 TAT assay. A representative compound, **42**, is included in Table 2. It occurred to us that the combination of a heteroaryl sulphonamide (to reduce lipophilicity and molecular weight) with a trifluoromethyl substituted pyridyl ketone (to provide improved potency compared with the unsubstituted pyridyl) at the ring junction might provide an acceptable balance of physicochemical properties and potency. As illustrated in Table 2, this expectation proved to be justified, and we identified a number of compounds with acceptable potency (for example compounds **7**, **43**, **44**, 45, **46**, **48**, **50** and **51**). Various substituted pyrazole and triazole sulphonamides provided good GR antagonist potency, although some interesting SAR emerged related to the position of methyl groups on the pyrazole sulphonamides. For example, whereas N-alkylation (compare compound **7** with compound **47**) was well tolerated, it appeared that C-alkylation was often detrimental (compare compound **49** with compound **47**). We were also very gratified to discover that the incorporation of the trifluoromethyl substituent on the pyridyl ketone did not have any negative consequences from a PK perspective. In contrast, the addition of this group appeared to be beneficial, compare compounds **42** and **7**.

Table 2. Heteroaryl sulphonamides



Compound	R	Het	HepG2 TAT Ki nM	C_{max} ng/mL	AUC ng.h/mL
42	H		28	150	780
7	CF_3		7.2	262	1219
43	CF_3		4.6	126	701
44	CF_3		6.6	291	863
45	CF_3		11	239	967
46	CF_3		12	110	283

47	CF_3		7.6	nt	nt
48	CF_3		10	nt	nt
49	CF_3		69	nt	nt
50	CF_3		3.1	255	860
51	CF_3		9.7	91.5	450
52	CF_3		31	nt	nt

Having identified a number of compounds with the required potency in the HepG2 TAT assay and encouraging plasma levels in the rat cassette PK studies, we selected several compounds for additional pharmacokinetic profiling. Good plasma levels in the cassette PK studies generally

correlated with good plasma levels and high bioavailability in single compound i.v./p.o. rat PK studies, using an oral dose of 5mg/kg and an i.v. dose of 1mg/kg. We also evaluated the PK profile of several of the most promising compounds in i.v./p.o. PK studies in monkeys, using an oral dose of 20mg/kg and an i.v. dose of 1mg/kg. Unfortunately, good bioavailability in rats did not always translate into good bioavailability in monkeys, as shown in Table 3. Compound **7** was the only compound with a good PK profile in monkeys. Even minor changes to the structure of the compound, such as moving the position of a nitrogen in the pyrazole ring, had a detrimental effect (compare compound **7** with compound **45**).

Table 3. Oral PK data for selected compounds

Compound	**Rat**			**Monkey**		
	C_{max} ng/mL	**AUC ng.h/mL**	**%F**	**C_{max} ng/mL**	**AUC ng.h/mL**	**%F**
7	297	1550	89	1140	11663	88
44	510	986	68	nt	nt	nt
45	528	1561	62	16	217.4	~1
48	511	1527	52	20.8	193	1.5

For i.v. dosing in both species the compounds were formulated in 10% DMSO, 45% PEG 400 and 45% propylene glycol.

For oral dosing in rats, the compounds were formulated in 10% DMSO and 0.5% methylcellulose in water.

For oral dosing in monkeys, the compounds were formulated in 10% DMSO, 0.1% Tween 80, 0.5% hydroxypropylmethylcellulose in water.

Compound **7** was the clearly the most promising compound in this series, and it was selected for full profiling. Selectivity for GR over the progesterone receptor, androgen receptor and estrogen receptor was assessed in radioligand binding assays, and no affinity (< 10% inhibition of radioligand binding) for the other receptors was detected at a concentration of 1μM whereas 100% inhibition was measured in an analogous GR binding assay. GR antagonism was measured in primary hepatocytes from several species, including human, rat, dog and monkey. Dexamethasone increases the activity of TAT in primary hepatocytes, and the ability of compound **7** to prevent this effect was determined. In addition, GR agonism was assessed by testing the compound in the absence of dexamethasone and measuring TAT activity. Whereas Compound 7 demonstrated full antagonism and no agonism in human and monkey hepatocytes, the compound acted predominantly as a GR agonist in dog hepatocytes, with only modest antagonism observed. There was also evidence for incomplete antagonism, and partial agonism at high (10μM) concentrations in rat hepatocytes. These data are provided in Table 4. GR antagonism was also assessed in human peripheral blood mononuclear cells by testing the ability of compound **7** to prevent the dexamethasone-induced inhibition of LPS stimulated production of tumour necrosis factor alpha (TNFα) (data not shown). Compound **7** was selective for GR over a standard panel of diverse receptors, enzymes and channels (data not shown).

Table 4. TAT assay data for compound **7** in primary hepatocytes from several species

Parameter	Human	Monkey	Rat	Dog
Antagonist K_i (nM)	81.2	210	12	>10,000
Maximum % antagonism	100	99	54.2	31%
Agonist EC_{50} (nM)	N/A	N/A	>10,000	>10,000
Maximum % agonism	0	0	22	80

In vivo efficacy was assessed in a rat model of exogenous Cushing's syndrome as described previously[15]. A dose of 30mg/kg compound **7** administered orally twice a day significantly inhibited effects on plasma insulin and completely prevented the cortisone induced increase in plasma glucose, as shown in Figure 4. Similar effects were achieved with a lower dose, 7.5mg/kg twice a day. Mifepristone at a dose of 30mg/kg was included for comparison. The results obtained with compound **7** were superior to those reported previously with compound **1**[15], and similar to results obtained with mifepristone in the same experiment.

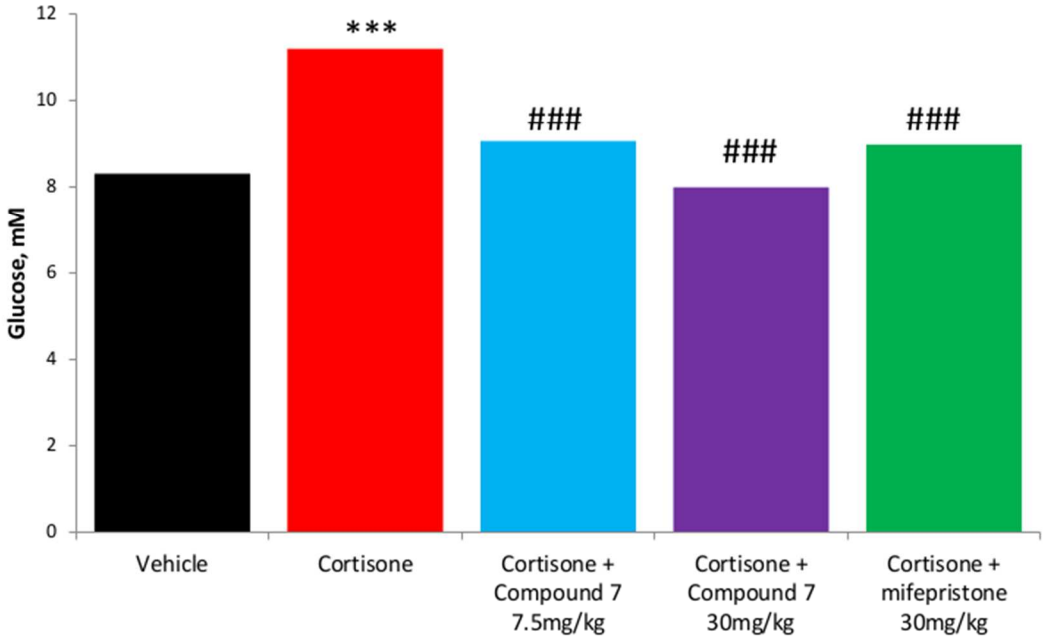


Figure 4. Effects of Compound **7** in the cortisone model of exogenous Cushing's syndrome

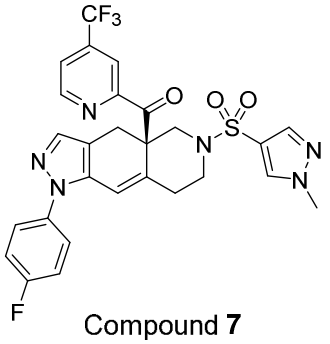
*** denotes $p < 0.001$ compared with vehicle treated mice.
denotes $p < 0.001$ compared with cortisone treated mice.

Compound **7** was found to have high plasma protein binding in rats, monkeys and humans, with 99.7, 98.9 and 99.5% binding respectively. Significant inhibition of CYP3A4 and CYP2C8 was observed, with modest inhibition of other CYPs as shown in Table 5. This CYP inhibition was not time dependent. CYP induction studies carried out in cryopreserved human hepatocytes indicated no induction of CYP1A2, CYP2B6 or CYP3A4.

Table 5. CYP Inhibition of Compound **7**

CYP	**1A2**	**2B6**	**2C8**	**2C9**	**2C19**	**2D6**	**3A4**	**3A5**
IC_{50} (μM)	>10	>10	0.21	2	8	9	1.3	4.9

Compound **7** (CORT125134[20], see Figure 5 for chemical structure) was selected for pre-clinical development and subjected to the usual panel of toxicology and safety pharmacology studies. We have completed a Phase I study in healthy human volunteers. In addition to the usual assessment of safety, tolerability and pharmacokinetics, we also included an assessment of pharmacological effect. This was achieved by the administration of the GR agonist, prednisone, and assessing the ability of **7** to counteract the effects of prednisone on a variety of GR mediated parameters. The results obtained in this Phase I clinical study will be published elsewhere[21]. A Phase 2 study in patients with endogenous Cushing's syndrome is currently in progress in the USA and Europe.



Compound **7**

Figure 5 Chemical structure of **7**

Having identified compound **7** as our first clinical candidate, we next turned our attention to the identification of a back-up compound. A potential minor concern with compound **7** was the presence of the carbon-carbon double bond in the central ring of the fused azadecalin scaffold, since we observed some propensity for this double bond to migrate to the adjacent six membered ring under certain conditions. In order to avoid this possibility, we opted to prepare compounds in which the double bond had been reduced. In general, reduction of the double bond resulted in decreased potency in the HepG2 TAT assay. For example, the reduced analogue of compound **7** (compound **54**) had a Ki of 34 nM, compared with 7.2 nM for compound **7**. As shown in Figure 6, reduction of the double bond affected the conformation of the tricyclic ring system, and altered the position of the key substituents, relative to the unsaturated analogues. Numerous other pairs of compounds (e.g. compound **28** compared to compound **53**; **44** vs **55** and **50** vs **12**) show the same trend, as shown in Table 6.

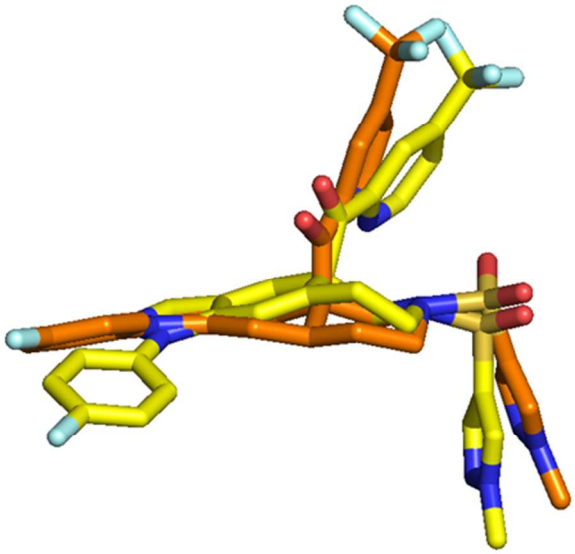
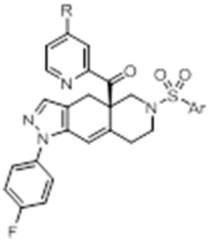
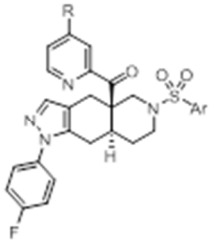


Figure 6. Overlay of Compounds **7** and **12**

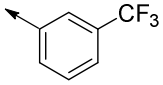
Table 6. Reduced Core Compounds

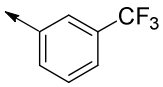
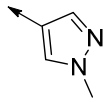
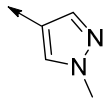
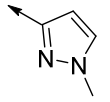
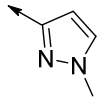
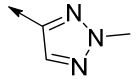
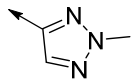
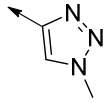
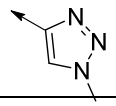


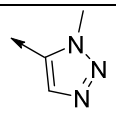
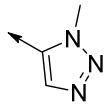
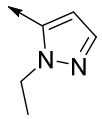
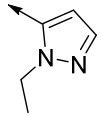
A



B

Compound	**A or B**	**R**	**Ar**	**HepG2 TAT Ki (nM)**
28	A	H		14

53	B	H		44
7	A	CF_3		7.2
54	B	CF_3		34
44	A	CF_3		6.6
55	B	CF_3		24
50	A	CF_3		3.1
12	B	CF_3		12
51	A	CF_3		9.7
56	B	CF_3		60

52	A	CF_3		31
57	B	CF_3		120
48	A	CF_3		10
58	B	CF_3		68

Compound **12** was one of the most potent compounds identified in the reduced core series, so we decided to obtain additional information to determine whether this sub-series provided any benefit over the original compounds. We were very gratified to discover that compound **12** provided excellent plasma levels in rats after oral dosing, higher than any other compound we tested. Following the administration of a 5mg/kg oral dose, the C_{max} was 1255 ng/mL and the

AUC was 9418 ng.h/mL. Bioavailability was 100%. Compound **12** (CORT125281[22]) was selected for further profiling and will be the subject of a later publication.

Conclusions

By further optimization of our fused azadecalin series of selective GR antagonists, we have identified the clinical candidate compound 7. This compound combines excellent potency, selectivity and oral bioavailability in several species with acceptable physicochemical properties. *In vivo* efficacy has been demonstrated in a relevant animal model. We have obtained proof of GR antagonism in human subjects in a Phase I study in healthy subjects, and the evaluation of the compound in patients with Cushing's syndrome is currently in progress. Although mifepristone is a very effective in the treatment of selected patients with Cushing's syndrome, the use of this compound is limited by side effects which result from its affinity for the progesterone receptor. There are also political issues in some countries concerning the use of the "abortion pill" which will be avoided by the development of a compound lacking affinity for the progesterone receptor. By removing affinity for the progesterone receptor, compound **7** provides a significant benefit over mifepristone.

Experimental Section

Chemistry All starting materials and reagents were either commercially available or their synthesis had been previously described in the literature. All purchased chemicals and solvents were used without further purification. All reactions involving air or moisture sensitive reagents were performed under an inert atmosphere. Hydrogenations were performed on a Thales H-cube flow reactor under the conditions stated. Silica gel chromatography was done using the appropriate size prepacked silica filled cartridges (230-400 mesh, 40-63 μm). NMR spectra were

acquired on a Bruker Avance III spectrometer at 400 MHz with chemical shifts reported in ppm relative to residual undeuterated solvent as reference. Reactions were monitored by silica gel F_{254} TLC plates with UV visualisation at 254 nm or by LCMS. LCMS analyses to determine purities and associated mass ions were performed using an Agilent Infinity 1260 LC 6120 quadrupole mass spectrometer with positive and negative ion electrospray and ELS / UV @ 254nm detection using an Agilent Zorbax Extend C18, Rapid Resolution HT 1.8 micron C18 30 x 4.6 mm column and a 2.5 mL / minute flow rate with a 4 minute run time. High resolution masses (HRMS) were determined on a Waters Xevo G2-XS QTOF mass spectrometer. Preparative reverse phase HPLC was performed using UV detection at 215 and 254 nm with a Waters X-Select Prep-C18, 5 µm, 19x50 mm column eluting with a H_2O-MeCN gradient containing 0.1% v/v formic acid over 10 min. All final compounds had an HPLC purity of 95% or better. All chemical names have been generated using CambridgeSoft ENotebook 12.0.

(*R*)-tert-butyl 1-(4-fluorophenyl)-4a-picolinoyl-4a,5,7,8-tetrahydro-1H-pyrazolo[3,4-g]isoquinoline-6(4H)-carboxylate (4). 2-bromopyridine (23.6 ml, 243 mmol) in dry THF (180 mL) was added to n-butyllithium (99 ml, 249 mmol) in dry THF (100 mL) at -78 °C. The reaction mixture was stirred at -78 °C for 45 min. A solution of (*R*)-6-tert-butyl 4a-methyl 1-(4-fluorophenyl)-4a,5,7,8-tetrahydro-1H-pyrazolo[3,4-g]isoquinoline-4a,6(4H)-dicarboxylate **3**[15](34.0 g, 80 mmol) in dry THF (280 mL) was added dropwise over 30 min, and the reaction mixture was stirred for 45 min at -78 °C. Water (400 mL) was added and the reaction mixture was stirred at RT for 10 min. The aqueous phase was extracted with ethyl acetate (2 x 400 mL). The combined organic phases were washed with brine (400 mL), dried ($MgSO_4$), and solvent removed to give an orange oil. The crude product was purified by chromatography on silica (330

g column, 10-60% ethyl acetate/isohexane) to afford 20.5 g (53%) of **4** as a pale yellow solid. LC/MS m/z 475 $(M+H)^+$.

(*R*)-tert-butyl 1-(4-fluorophenyl)-4a-(4-methylpicolinoyl)-4a,5,7,8-tetrahydro-1H-pyrazolo[3,4-g]isoquinoline-6(4H)-carboxylate (4a). Compound **4a** was prepared using the same procedure as described for the synthesis of **4** by substituting 2-bromo-4-methylpyridine for 2-bromopyridine. LC/MS m/z 489 $(M+H)^+$.

(*R*)-tert-butyl 4a-(4-ethylpicolinoyl)-1-(4-fluorophenyl)-4a,5,7,8-tetrahydro-1H-pyrazolo[3,4-g]isoquinoline-6(4H)-carboxylate (4b). Compound **4b** was prepared using the same procedure as described for the synthesis of **4** by substituting 2-bromo-4-ethylpyridine for 2-bromopyridine. LC/MS m/z 503 $(M+H)^+$.

(*R*)-(1-(4-fluorophenyl)-6-(m-tolylsulfonyl)-4,4a,5,6,7,8-hexahydro-1H-pyrazolo[3,4-g]isoquinolin-4a-yl)(pyridin-2-yl)methanone (5). A solution of (*R*)-tert-butyl 1-(4-fluorophenyl)-4a-picolinoyl-4a,5,7,8-tetrahydro-1H-pyrazolo[3,4-g]isoquinoline-6(4H)-carboxylate **4** (0.2 g, 0.42 mmol) in 20% TFA/DCM (6 mL) was stirred at RT for 1 h. Solvent was removed *in vacuo*, azeotroping twice with toluene, to give a dark orange oil. This was dissolved in DCM (6 mL) and 3-methylbenzene-1-sulfonyl chloride (0.073 mL, 0.504 mmol) and di-isopropylethylamine (0.367 ml, 2.10 mmol) were added. The reaction mixture was stirred at RT for 0.5 h, before solvent was removed *in vacuo*. The crude product was purified by chromatography on silica (12 g column, 0-40% Ethyl acetate/isohexane) and by preparative HPLC to afford 88 mg (38%) of **5** as a pale yellow solid. LC/MS m/z 529 $(M+H)^+$; ^{1}H NMR ($CDCl_3$): δ 8.66 (1H, ddd, J = 4.7, 1.7, 0.8 Hz), 7.91-7.89 (1H, m), 7.84 (1H, dt, J = 7.4, 1.7 Hz),

7.50-7.40 (5H, m), 7.36-7.34 (2H, m), 7.29 (1H, s), 7.19-7.13 (2H, m), 6.47 (1H, d, J = 2.1 Hz), 5.51 (1H, dd, J = 12.4, 2.1 Hz), 4.31 (1H, d, J = 16.9 Hz), 3.84-3.80 (1H, m), 2.92-2.78 (2H, m), 2.68 (1H, d, J = 12.4 Hz), 2.49-2.40 (5H, m).

(*R*)-tert-butyl 1-(4-fluorophenyl)-4a-(4-(trifluoromethyl)picolinoyl)-4a,5,7,8-tetrahydro-1H-pyrazolo[3,4-g]isoquinoline-6(4H)-carboxylate (6). Isopropylmagnesium chloride (2M in THF, 35.1 ml, 70.2 mmol) was added to dry ether (100 mL) cooled to 0 °C. A solution of 2-bromo-4-(trifluoromethyl)pyridine (15.9 g, 70.2 mmol) in dry ether (50 mL) was then added over 20 min. The resulting dark coloured suspension was stirred at 0°C for 50 min, then (*R*)-6-tert-butyl 4a-methyl 1-(4-fluorophenyl)-4a,5,7,8-tetrahydro-1H-pyrazolo[3,4-g]isoquinoline-4a,6(4H)-dicarboxylate **3**[23] (10.0 g, 23.4 mmol) was added as a solution in dry ether:THF (4:1, total volume 100 mL) dropwise over 30 min. The reaction was stirred at 0°C for 15 min, then at RT for 2 h. The reaction was re-cooled to 0°C, and quenched by the dropwise addition of ice-cold water (40 mL) and then diluted further with water (120 mL). The layers were then separated, and the aqueous layer extracted with Ethyl acetate (3 x 150 mL). The combined organic extractions were washed with brine (150 mL) and dried over $MgSO_4$, and solvent removed *in vacuo* to give a brown oil. This was diluted with acetonitrile (100 mL) and aqueous HCl (1M, 23.4 mL, 23.4 mmol) and the resulting solution stirred at RT for 30 min. The reaction mixture was diluted with ethyl acetate (300 mL) and washed sequentially with brine (100 mL), saturated aqueous $NaHCO_3$ (100 mL) and brine again (100 mL). The organic layer was then dried over $MgSO_4$ and solvent removed *in vacuo*. The crude product was purified by chromatography on silica (220 g column, 0-60% ethyl acetate/isohexane) to afford 10.9 g (84%) of **6** as a pale yellow solid. LC/MS m/z 543 $(M+H)^+$.

(*R*)-(1-(4-fluorophenyl)-6-((1-methyl-1H-pyrazol-4-yl)sulfonyl)-4,4a,5,6,7,8-hexahydro-1H-pyrazolo[3,4-g]isoquinolin-4a-yl)(4-(trifluoromethyl)pyridin-2-yl)methanone (7). To a solution of (*R*)-tert-butyl 1-(4-fluorophenyl)-4a-(4-(trifluoromethyl)picolinoyl)-4a,5,7,8-tetrahydro-1H-pyrazolo[3,4-g]isoquinoline-6(4H)-carboxylate **6** (9.59 g, 17.7 mmol) in DCM (80 mL) was added TFA (27.2 mL, 354 mmol) dropwise over 20 min, and the resulting dark coloured solution stirred at RT for 1.5 h. The reaction mixture was diluted with toluene (30 mL) and solvent removed *in vacuo*. The dark brown residue was then azeotroped with toluene (3 x 30 mL). The resulting brown gum was diluted with DCM (80 mL) and water (80 mL) and potassium carbonate (12.2 g, 88 mmol) added to the biphasic mixture portionwise over 10 min. 1-methyl-1H-pyrazole-4-sulfonyl chloride (3.51 g, 19.4 mmol) was then added portionwise to the reaction mixture, and the resulting biphasic solution was stirred at RT for 20 min. The reaction mixture was diluted with water (200 mL) and the layers separated. The aqueous layer was extracted with DCM (2 x 100 mL) and the combined organic extractions washed with brine (200 mL) and dried over $MgSO_4$. The solvent was removed to give a thick brown oil, which was purified by chromatography on silica (220 g column, load in DCM, 0-70% ethyl acetate/isohexane) to afford 7.66 g (73%) of **7** as a pale orange solid. HRMS calculated for $C_{27}H_{22}F_4N_6O_3S$ [$(M+H)^+$], 587.1483; found, 587.1483; ^{1}H NMR ($CDCl_3$): δ 8.87 (1H, d, J = 5.0 Hz), 8.16-8.15 (1H, m), 7.72-7.70 (1H, m), 7.69-7.66 (2H, m), 7.47-7.42 (2H, m), 7.30 (1H, s), 7.21-7.14 (2H, m), 6.51 (1H, d, J = 2.1 Hz), 5.44 (1H, dd, J = 12.0, 2.1 Hz), 4.21 (1H, d, J = 16.9 Hz), 3.93 (3H, s), 3.80-3.76 (1H, m), 2.94 (1H, J = 16.9 Hz), 2.88-2.79 (1H, m), 2.66 (1H, d, J = 12.1 Hz), 2.53-2.48 (1H, m), 2.43 (1H, ddd, J = 12.6, 10.5, 3.5 Hz); ^{13}C NMR ($CDCl_3$): δ 197.65 (s), 161.75 (d, J = 247 Hz), 153.91 (s), 148.80 (s), 139.88 (q, J = 35 Hz), 138.86 (s), 138.22 (s),

137.23 (s), 136.68 (s), 135.35 (d, J = 3 Hz), 131.87 (s), 125.60 (d, J = 8 Hz), 122.41 (q, J = 273 Hz), 122.36 (m), 120.30 (m), 117.85 (s), 116.23 (d, J = 23 Hz), 114.49 (s), 112.61 (s), 55.18 (s), 55.01 (s), 46.77 (s), 39.64 (s), 32.14 (s), 28.08 (s).

(*R*)-methyl 6-((3,4-difluorophenyl)sulfonyl)-1-(4-fluorophenyl)-4,4a,5,6,7,8-hexahydro-1H-pyrazolo[3,4-g]isoquinoline-4a-carboxylate (8). (*R*)-6-tert-butyl 4a-methyl 1-(4-fluorophenyl)-4a,5,7,8-tetrahydro-1H-pyrazolo[3,4-g]isoquinoline-4a,6(4H)-dicarboxylate **3**[23] (2.0 g, 4.68 mmol) was added to a solution of HCl in dioxane (4 M, 23.4 mL, 94 mmol) and the reaction mixture stirred at RT for 45 mins. Solvent was then removed *in vacuo* to give an orange solid, which was dissolved in DCM (80 mL) and diisopropylethylamine (4.09 ml, 23.4 mmol). 3,4-Difluorobenzene-1-sulfonyl chloride (0.63 mL, 4.68 mmol) was added and the reaction mixture stirred at RT for 15 mins. Water (20 mL) and DCM (20 mL) were added and the phases were separated. The organic phase was washed with brine (10 mL), dried ($MgSO_4$) and solvent removed *in vacuo* to give 2.2 g (92%) of **8** as a pale yellow solid. LC/MS m/z 504 $(M+H)^+$.

(*R*)-methyl 6-((3,4-dichlorophenyl)sulfonyl)-1-(4-fluorophenyl)-4,4a,5,6,7,8-hexahydro-1H-pyrazolo[3,4-g]isoquinoline-4a-carboxylate (8a). Compound **8a** was prepared using the same procedure as described for the synthesis of **8** by substituting 3,4-dichlorobenzene-1-sulfonyl chloride for 3,4-difluorobenzene-1-sulfonyl chloride. LC/MS m/z 536 $(M+H)^+$.

(*R*)-methyl 1-(4-fluorophenyl)-6-(m-tolylsulfonyl)-4,4a,5,6,7,8-hexahydro-1H-pyrazolo[3,4-g]isoquinoline-4a-carboxylate (8b). Compound **8b** was prepared using the same procedure as described for the synthesis of **8** by substituting 3-methylbenzene-1-sulfonyl chloride for 3,4-difluorobenzene-1-sulfonyl chloride. LC/MS m/z 482 $(M+H)^+$.

(*R*)-methyl 1-(4-fluorophenyl)-6-((3-(trifluoromethyl)phenyl)sulfonyl)-4,4a,5,6,7,8-hexahydro-1H-pyrazolo[3,4-g]isoquinoline-4a-carboxylate (8c). Compound **8c** was prepared using the same procedure as described for the synthesis of **8** by substituting 3-(trifluoromethyl)benzene-1-sulfonyl chloride for 3,4-difluorobenzene-1-sulfonyl chloride. LC/MS m/z 536 $(M+H)^+$.

(*R*)-(6-((3,4-difluorophenyl)sulfonyl)-1-(4-fluorophenyl)-4,4a,5,6,7,8-hexahydro-1H-pyrazolo[3,4-g]isoquinolin-4a-yl)(thiazol-2-yl)methanone (9). A solution of 2-bromothiazole (164 µl, 1.82 mmol) in dry diethyl ether (4 mL) was added to a solution of n-butyllithium (2.5 M in hexanes, 745 µl, 1.862 mmol) in dry diethyl ether (2 mL) at -78°C. The reaction mixture was stirred at -78°C for 45 min. A solution of (*R*)-methyl 6-((3,4-difluorophenyl)sulfonyl)-1-(4-fluorophenyl)-4,4a,5,6,7,8-hexahydro-1H-pyrazolo[3,4-g]isoquinoline-4a-carboxylate **8** (300 mg, 0.596 mmol) in dry diethyl ether (5 mL) was added dropwise and the reaction mixture was stirred for 45 min at -78°C. Water (10 mL) was added and the reaction mixture was stirred at RT for 10 min. The aqueous phase was extracted with ethyl acetate (2 x 10 mL), the combined organic phases were washed with brine (10 mL), dried ($MgSO_4$), and solvent removed *in vacuo* to give a brown oil. The crude product was purified by chromatography on silica (4 g column, 10-50% ethyl acetate/isohexane) to afford 120 mg (36%) of **9** as a pale yellow solid. LC/MS m/z 557 $(M+H)^+$; ^{1}H NMR ($CDCl_3$): δ 8.02 (1H, d, J = 3.1 Hz), 7.68 (1H, d, J = 3.1 Hz), 7.55 - 7.47 (2H, m), 7.45 - 7.40 (2H, m), 7.29 (1H, s), 7.27 - 7.21 (1H, m), 7.20 - 7.13 (2H, m), 6.54 (1H, d, J = 2.2 Hz), 5.47 (1H, dd, J = 12.4, 2.0 Hz), 4.19 (1H, d, J = 16.8 Hz), 3.93 - 3.86 (1H, m), 2.93 - 2.79 (3H, m), 2.63 - 2.52 (2H, m).

(4a*R*,8a*S*)-6-tert-butyl 4a-methyl 1-(4-fluorophenyl)-4a,5,7,8,8a,9-hexahydro-1H-pyrazolo[3,4-g]isoquinoline-4a,6(4H)-dicarboxylate (10). A solution of (*R*)-6-tert-butyl 4a-methyl 1-(4-fluorophenyl)-4a,5,7,8-tetrahydro-1H-pyrazolo[3,4-g]isoquinoline-4a,6(4H)-dicarboxylate **3**[23] (2.0 g, 4.68 mmol) in methanol (80 mL) was hydrogenated in an H-cube (10% Pd/C, 30x4 mm, Full hydrogen, 55 °C, 1 mL/min). Solvent was removed *in vacuo* to give 2.0 g (99%) of **10** as an off-white solid. LC/MS m/z 430 $(M+H)^+$; ^{1}H NMR ($CDCl_3$): δ 7.49-7.40 (3H, m), 7.17-7.10 (2H, m), 4.74-4.58 (1H, br m), 4.39-4.10 (2H, br m), 3.61 (3H, s), 3.28-3.01 (2H, br m), 2.88-2.52 (3H, br m), 2.40-2.12 (2H, br m), 1.91-1.79 (1H, m), 1.45 (9H, s).

(4a*R*,8a*S*)-tert-butyl 1-(4-fluorophenyl)-4a-(4-(trifluoromethyl)picolinoyl)-4a,5,7,8,8a,9-hexahydro-1H-pyrazolo[3,4-g]isoquinoline-6(4H)-carboxylate (11). To a solution of (4a*R*,8a*S*)-6-tert-butyl 4a-methyl 1-(4-fluorophenyl)-4a,5,7,8,8a,9-hexahydro-1H-pyrazolo[3,4-g]isoquinoline-4a,6(4H)-dicarboxylate **10** (450 mg, 1.05 mmol) in dry toluene (4 mL) was added isopropylmagnesium bromide (2.9 M in 2-methyltetrahydrofuran, 903 µL, 2.62 mmol) followed by 2-bromo-4-(trifluoromethyl)pyridine (233 µL, 1.89 mmol) at 0°C. The reaction mixture was allowed to warm to RT and stirred for 18 h. Water (5 mL) and DCM (5 mL) were added, and the organic phase separated and solvent evaporated *in vacuo*. The crude product was purified by chromatography on silica (12 g column, load in DCM, 0-40% ethyl acetate/isohexane) to afford 275 mg (45%) of **11** as a pale orange solid. LC/MS m/z 545 $(M+H)^+$.

(4a*R*,8a*S*)-tert-butyl 1-(4-fluorophenyl)-4a-picolinoyl-4a,5,7,8,8a,9-hexahydro-1H-pyrazolo[3,4-g]isoquinoline-6(4H)-carboxylate (11a). A solution of 2-bromopyridine (0.83 ml, 8.52 mmol) in dry THF (6 mL) was added to a solution of n-butyllithium (2.5 M in hexanes, 3.49

mL, 8.73 mmol) in dry THF (4 mL) at -78 °C. The reaction mixture was stirred at -78°C for 45 min. A solution of (4a*R*,8a*S*)-6-tert-butyl 4a-methyl 1-(4-fluorophenyl)-4a,5,7,8,8a,9-hexahydro-1H-pyrazolo[3,4-g]isoquinoline-4a,6(4H)-dicarboxylate **10** (1.2 g, 2.79 mmol) in dry THF (10 mL) was added dropwise and the reaction mixture was stirred for 45 min at -78°C. Water (12 mL) was added and the reaction mixture was stirred at RT for 10 min. The aqueous phase was extracted with ethyl acetate (2 x 12 mL). The combined organic phases were washed with brine (12 mL), dried ($MgSO_4$), and solvent removed *in vacuo* to give an orange oil. The crude product was purified by chromatography on silica (40 g column, 10-70% ethyl acetate/isohexane) to afford 609 mg (43%) of **11a** as a pale yellow solid. LC/MS m/z 477 $(M+H)^+$.

((4a*R*,8a*S*)-1-(4-fluorophenyl)-6-((2-methyl-2H-1,2,3-triazol-4-yl)sulfonyl)-4,4a,5,6,7,8,8a,9-octahydro-1H-pyrazolo[3,4-g]isoquinolin-4a-yl)(4-(trifluoromethyl)pyridin-2-yl)methanone (12). (4a*R*,8a*S*)-*tert*-butyl 1-(4-fluorophenyl)-4a-(4-(trifluoromethyl)picolinoyl)-4a,5,7,8,8a,9-hexahydro-1H-pyrazolo[3,4-g]isoquinoline-6(4H)-carboxylate **11** (2 g, 3.67 mmol) was stirred in 20% TFA/DCM (200 mL) at RT for 45 min. Solvent was removed *in vacuo* and the residue was azeotroped with toluene (3 x 30 mL), then dissolved in DCM (150 mL). Diisopropylethylamine (3.21 mL, 18.4 mmol) and 2-methyl-2H-1,2,3-triazole-4-sulfonyl chloride **19** (0.667 g, 3.67 mmol) were added, and the reaction mixture stirred at RT for 2 h, before solvent was removed *in vacuo*. The crude product was purified by chromatography on silica (40 g column, load in DCM, 0-75% ethyl acetate/isohexane) to afford 1.58 g (72%) of **12** as a white solid. HRMS calculated for $C_{26}H_{24}F_4N_7O_3S$ $[(M+H)^+]$, 590.1592; found, 590.1592;^{1}H NMR ($CDCl_3$): δ8.86 (1H, d, J = 5.0 Hz), 8.10 (1H, s), 7.81 (1H, s), 7.70 - 7.62 (1H, m), 7.52 - 7.44 (2H, m), 7.33 (1H, s), 7.20 - 7.11 (2H, m), 5.64 (1H, dd, J = 12.5, 2.0 Hz), 4.26 (3H, s), 4.25 (1H, d, J = 16.2 Hz), 4.02 - 3.90

(1H, m), 3.44 (1H, dd, J = 16.2, 10.8 Hz), 2.73 (1H, dd, J = 16.2, 5.9 Hz), 2.67 - 2.53 (3H, m), 2.43 (1H, qd, J = 13.2, 5.0 Hz), 1.88 - 1.75 (2H, m); ^{13}C NMR (DMSO-d_6): δ 200.47 (s), 160.45 (d, J = 244 Hz), 154.61 (s), 149.76 (s), 143.29 (s), 138.14 (s), 138.06 (q, J = 34 Hz), 137.33 (s), 136.13 (d, J = 3 Hz), 135.12 (s), 124.39 (d, J = 9 Hz), 122.55 (q, J = 4 Hz), 122.52 (q, J = 273 Hz), 118.72 (q, J = 4 Hz), 116.08 (d, J = 23 Hz), 113.97 (s), 54.35 (s), 49.99 (s), 46.74 (s), 42.59 (s), 40.04 (s), 28.07 (s), 27.63 (s), 27.04 (s).

4-(benzylthio)-1H-1,2,3-triazole (14). Benzyl bromide (11.8 ml, 99 mmol) was added dropwise to a solution of sodium 1H-1,2,3-triazole-4-thiolate **13** (12.2 g, 99 mmol) in ethanol (100 mL) at 0°C. The reaction mixture was allowed to warm to RT and stirred for 20 mins. The reaction was diluted with ethyl acetate (100 mL) and washed with water (100 mL), brine (100 mL) and dried (Na_2SO_4). Solvent was removed *in vacuo* to give 16.9 g (87%) of **14** as a white solid. LC/MS m/z 192 $(M+H)^+$; ^{1}H NMR ($CDCl_3$): δ 9.72 (1H, v br s), 7.47 (1H, s), 7.30 - 7.21 (5H, m), 4.12 (2H, s).

4-(benzylthio)-1-methyl-1H-1,2,3-triazole (15), 4-(benzylthio)-2-methyl-2H-1,2,3-triazole (16), and 5-(benzylthio)-1-methyl-1H-1,2,3-triazole (17). Iodomethane (2.41 mL, 38.7 mmol) was added dropwise to a mixture of 4-(benzylthio)-1H-1,2,3-triazole **14** (3.7 g, 19.3 mmol) and potassium carbonate (5.88 g, 42.6 mmol) in DMF (40 mL) at 0°C. The reaction was then allowed to warm to RT and stirred for 1 hour. Water (40 mL) and ethyl acetate (40 mL) were added and the organic phase was separated and washed sequentially with water (2 x 40 mL) and brine (40 mL), and dried (Na_2SO_4) before solvent was removed *in vacuo* to give a yellow oil. The crude product was purified by chromatography on silica (80 g column, 0-100% Ethyl

acetate/isohexane) to afford first 1.61 g (40%) of **16** as a colourless oil, LC/MS m/z 206 $(M+H)^+$; ^{1}H NMR (DMSO-d6): δ7.68 (1H, s), 7.35 - 7.19 (5H, m), 4.18 (2H, s), 4.11 (3H, s); followed by 816 mg (20%) of **17** as a pale yellow oil, LC/MS m/z 206 $(M+H)^+$; ^{1}H NMR (DMSO-d6): δ7.71 (1H, s), 7.36 - 7.23 (3H, m), 7.22 - 7.14 (2H, m), 4.09 (2H, s), 3.73 (3H, s); and finally 883 mg (22%) of **15** as a pale yellow oil, LC/MS m/z 206 $(M+H)^+$; ^{1}H NMR (DMSO-d6): δ8.02 (1H, s), 7.34 - 7.19 (5H, m), 4.12 (2H, s), 4.00 (3H, s).

1-methyl-1H-1,2,3-triazole-4-sulfonyl chloride (18). N-chlorosuccinimide (2.60 g, 19.5 mmol) was added to a solution of 4-(benzylthio)-1-methyl-1H-1,2,3-triazole **15** (1.0 g, 4.87 mmol) in acetic acid (26 mL) and water (13 mL) and the mixture stirred at RT for 2 h. Water (40 mL) was added and the mixture was extracted with ethyl acetate (40 mL). The organic phase was washed sequentially with a saturated aqueous sodium hydrogen carbonate solution (3 x 40 mL) and brine (40 mL), then dried ($MgSO_4$), and solvent removed *in vacuo* to give 810 mg of **18** (64%) as a colourless oil, which was used without further purification. LC/MS (quenched into a solution of morpholine in methanol) m/z 233, $(M+H+morpholine)^+$; ^{1}H NMR ($CDCl_3$): δ8.22 (1H, s), 4.25 (3H, s).

2-methyl-2H-1,2,3-triazole-4-sulfonyl chloride (19). N-chlorosuccinimide (3.38 g, 25.3 mmol) was added to a solution of 4-(benzylthio)-2-methyl-2H-1,2,3-triazole **16** (1.30 g, 6.33 mmol) in acetic acid (32 mL) and water (16 mL) and the mixture stirred at RT for 1 h. Water (40 mL) was added and the mixture was extracted with ethyl acetate (40 mL). The organic phase was washed sequentially with a saturated aqueous sodium hydrogen carbonate solution (40 mL) and brine (40 mL), then dried ($MgSO_4$), and solvent removed *in vacuo* to give 1.35 g of **19** (82%) as a pale yellow oil, which was used without further purification. LC/MS (quenched into a solution of

morpholine in methanol) m/z 233, $(M+H+morpholine)^+$; ^1H NMR ($CDCl_3$): δ8.11 (1H, s), 4.36 (3H, s).

1-methyl-1H-1,2,3-triazole-5-sulfonyl chloride (20). Chlorine gas was bubbled through a solution of 5-(benzylthio)-1-methyl-1H-1,2,3-triazole **17** (200 mg, 0.974 mmol) in dichloromethane (15 mL) and water (3 mL) for 2 min at 0°C, then the reaction mixture was stirred at 0°C for a further 5 min. Water (10 mL) was added and the mixture was extracted with dichloromethane (10 mL). The separated organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo* to give 317 mg of **20** (90%) as a colourless oil, which was used without further purification. LC/MS (quenched into a solution of morpholine in methanol) m/z 233, $(M+H+morpholine)^+$; ^1H NMR ($CDCl_3$): δ8.27 (1H, s), 4.40 (3H, s).

(*R*)-(1-(4-fluorophenyl)-6-(m-tolylsulfonyl)-4,4a,5,6,7,8-hexahydro-1H-pyrazolo[3,4-g]isoquinolin-4a-yl)(4-methylpyridin-2-yl)methanone (21). Compound **21** was prepared using the same procedure as described for the synthesis of **9** by treating (*R*)-methyl 1-(4-fluorophenyl)-6-(m-tolylsulfonyl)-4,4a,5,6,7,8-hexahydro-1H-pyrazolo[3,4-g]isoquinoline-4a-carboxylate **8b** with 2-bromo-4-methylpyridine/n-butyllithium. LC/MS m/z 543 $(M+H)^+$; ^1H NMR ($CDCl_3$): δ8.50 (1H, dd, J = 3.9, 0.4 Hz), 7.71 (1H, m), 7.51-7.48 (2H, m), 7.45-7.40 (2H, m), 7.35-7.33 (2H, m), 7.28-7.26 (2H, m), 7.18-7.12 (2H, m), 6.46 (1H, d, J = 2.1 Hz), 5.53 (1H, dd, J = 12.2, 2.1 Hz), 4.30 (1H, d, J = 16.9 Hz), 3.84-3.80 (1H, m), 2.90-2.77 (2H, m), 2.69 (1H, d, J = 12.3 Hz), 2.48-2.42 (2H, m), 2.40 (3H, s), 2.39 (3H, s).

(*R*)-(1-(4-fluorophenyl)-6-(m-tolylsulfonyl)-4,4a,5,6,7,8-hexahydro-1H-pyrazolo[3,4-g]isoquinolin-4a-yl)(5-methylpyridin-2-yl)methanone (22). Compound **22** was prepared using the same procedure as described for the synthesis of **9** by treating (*R*)-methyl 1-(4-fluorophenyl)-

6-(m-tolylsulfonyl)-4,4a,5,6,7,8-hexahydro-1H-pyrazolo[3,4-g]isoquinoline-4a-carboxylate **8b** with 2-bromo-5-methylpyridine/n-butyllithium. LC/MS m/z 543 $(M+H)^+$; ^1H NMR ($CDCl_3$): δ 8.46 (1H, m), 7.82 (1H, d, J = 8.0 Hz), 7.61 (1H, ddd, J = 8.0, 2.3, 0.9 Hz), 7.51-7.48 (2H, m), 7.45-7.40 (2H, m), 7.35-7.33 (2H, m), 7.27 (1H, s), 7.18-7.12 (2H, m), 6.46 (1H, d, J = 2.1 Hz), 5.57 (1H, dd, J = 12.2, 2.1 Hz), 4.29 (1H, d, J = 16.9 Hz), 3.84-3.79 (1H, m), 2.90-2.78 (2H, m), 2.70 (1H, d, J = 12.0 Hz), 2.48-2.39 (8H, m).

(*R*)-(1-(4-fluorophenyl)-6-(m-tolylsulfonyl)-4,4a,5,6,7,8-hexahydro-1H-pyrazolo[3,4-g]isoquinolin-4a-yl)(6-methylpyridin-2-yl)methanone (23). Compound **23** was prepared using the same procedure as described for the synthesis of **9** by treating (*R*)-methyl 1-(4-fluorophenyl)-6-(m-tolylsulfonyl)-4,4a,5,6,7,8-hexahydro-1H-pyrazolo[3,4-g]isoquinoline-4a-carboxylate **8b** with 2-bromo-6-methylpyridine/n-butyllithium. LC/MS m/z 543 $(M+H)^+$; ^1H NMR ($CDCl_3$): δ 7.72 - 7.68 (2H, m), 7.42 - 7.36 (4H, m), 7.34 - 7.30 (4H, m), 7.18 - 7.13 (2H, m), 6.45 (1H, d, J = 2.0 Hz), 5.55 (1H, dd, J = 12.2, 2.0 Hz), 4.19 (1H, d, J = 17.0 Hz), 3.84 - 3.80 (1H, m), 2.87 (1H, d, J = 17.0 Hz), 2.83 - 2.73 (1H, m), 2.71 (1H, d, J = 12.2 Hz), 2.62 (3H, s), 2.54 - 2.42 (2H, m), 2.39 (3H, s).

(*R*)-(6-((3,4-difluorophenyl)sulfonyl)-1-(4-fluorophenyl)-4,4a,5,6,7,8-hexahydro-1H-pyrazolo[3,4-g]isoquinolin-4a-yl)(pyridin-2-yl)methanone (24). Compound **24** was prepared using the same procedure as described for the synthesis of **5** by treating (*R*)-tert-butyl 1-(4-fluorophenyl)-4a-picolinoyl-4a,5,7,8-tetrahydro-1H-pyrazolo[3,4-g]isoquinoline-6(4H)-carboxylate **4** with HCl (4M in dioxane) followed by 3,4-difluorobenzene-1-sulfonyl chloride. LC/MS m/z 551 $(M+H)^+$; ^1H NMR ($CDCl_3$): δ 8.63 (1H, ddd, J = 4.8, 1.7, 1.0 Hz), 7.88 (1H, ddd, J = 7.9, 1.7, 1.0 Hz), 7.84 (1H, dt, J = 7.3, 1.7 Hz), 7.52-7.40 (5H, m), 7.28 (1H, s), 7.24-

7.22 (1H, m), 7.20-7.13 (2H, m), 6.49 (1H, d, J = 2.1 Hz), 5.53 (1H, dd, J = 12.2, 2.0 Hz), 4.28 (1H, d, J = 16.9 Hz), 3.88-3.83 (1H, m), 2.91-2.78 (3H, m), 2.59-2.48 (2H, m).

(*R*)-(6-((3,4-difluorophenyl)sulfonyl)-1-(4-fluorophenyl)-4,4a,5,6,7,8-hexahydro-1H-pyrazolo[3,4-g]isoquinolin-4a-yl)(4-methylpyridin-2-yl)methanone (25). Compound **25** was prepared using the same procedure as described for the synthesis of **5** by treating (*R*)-tert-butyl 1-(4-fluorophenyl)-4a-(4-methylpicolinoyl)-4a,5,7,8-tetrahydro-1H-pyrazolo[3,4-g]isoquinoline-6(4H)-carboxylate **4a** with HCl (4M in dioxane) followed by 3,4- difluorobenzene-1-sulfonyl chloride. LC/MS m/z 565 $(M+H)^+$; ^1H NMR ($CDCl_3$): δ 8.46 (1H, dd, J = 5.0, 0.5 Hz), 7.68 (1H, m), 7.50-7.40 (4H, m), 7.29-7.26 (2H, m), 7.24-7.13 (3H, m), 6.48 (1H, d, J = 2.1 Hz), 5.55 (1H, dd, J = 12.4, 2.1 Hz), 4.27 (1H, d, J = 16.9 Hz), 3.89-3.84 (1H, m), 2.88-2.78 (3H, m), 2.62-2.56 (1H, m), 2.53-2.48 (1H, m), 2.40 (3H, s).

(*R*)-(6-((3,5-difluorophenyl)sulfonyl)-1-(4-fluorophenyl)-4,4a,5,6,7,8-hexahydro-1H-pyrazolo[3,4-g]isoquinolin-4a-yl)(pyridin-2-yl)methanone (26). Compound **26** was prepared using the same procedure as described for the synthesis of **5** by treating (*R*)-tert-butyl 1-(4-fluorophenyl)-4a-picolinoyl-4a,5,7,8-tetrahydro-1H-pyrazolo[3,4-g]isoquinoline-6(4H)-carboxylate **4** with HCl (4M in dioxane) followed by 3,5-difluorobenzene-1-sulfonyl chloride. LC/MS m/z 551 $(M+H)^+$; ^1H NMR ($CDCl_3$): δ 8.67 (1H, ddd, J = 4.7, 1.7, 0.8 Hz), 7.88 (1H, ddd, J = 7.9, 1.5, 1.0 Hz), 7.84 (1H, dt, J = 7.3, 1.7 Hz), 7.48 (1H, ddd, J = 7.4, 4.7, 1.5Hz), 7.46-7.41 (2H, m), 7.29 (1H, s), 7.22-7.13 (4H, m), 6.98 (1H, tt, J = 8.5, 2.3 Hz), 6.49 (1H, d, J = 2.1 Hz), 5.56 (1H, dd, J = 12.3, 2.1 Hz), 4.28 (1H, d, J = 16.9 Hz), 3.87-3.82 (1H, m), 2.92-2.78 (3H, m), 2.62-2.55 (1H, m), 2.53-2.48 (1H, m).

(*R*)-(6-((3,5-difluorophenyl)sulfonyl)-1-(4-fluorophenyl)-4,4a,5,6,7,8-hexahydro-1H-pyrazolo[3,4-g]isoquinolin-4a-yl)(4-methylpyridin-2-yl)methanone (27). Compound **27** was prepared using the same procedure as described for the synthesis of **5** by treating (*R*)-tert-butyl 1-(4-fluorophenyl)-4a-(4-methylpicolinoyl)-4a,5,7,8-tetrahydro-1H-pyrazolo[3,4-g]isoquinoline-6(4H)-carboxylate **4a** with HCl (4M in dioxane) followed by 3,5- difluorobenzene-1-sulfonyl chloride. LC/MS m/z 565 $(M+H)^+$; ^{1}H NMR ($CDCl_3$): δ8.51 (1H, br. d, J = 4.9 Hz), 7.72 - 7.69 (1H, m), 7.46 - 7.41 (2H, m), 7.32 - 7.27 (2H, m), 7.20 - 7.13 (4H, m), 6.97 (1H, tt, J = 8.5, 2.3 Hz), 6.49 (1H, d, J = 2.1 Hz), 5.61 (1H, dd, J = 12.3, 2.1 Hz), 4.29 (1H, d, J = 16.9 Hz), 3.85 (1H, ddt, J = 8.4, 3.9, 2.1 Hz), 2.90 - 2.77 (3H, m), 2.63 - 2.57 (1H, m), 2.50 (1H, br. dt, J = 14.9, 2.0 Hz), 2.41 (3H, s).

(*R*)-(1-(4-fluorophenyl)-6-((3-(trifluoromethyl)phenyl)sulfonyl)-4,4a,5,6,7,8-hexahydro-1H-pyrazolo[3,4-g]isoquinolin-4a-yl)(pyridin-2-yl)methanone (28). Compound **28** was prepared using the same procedure as described for the synthesis of **5** by treating (*R*)-tert-butyl 1-(4-fluorophenyl)-4a-picolinoyl-4a,5,7,8-tetrahydro-1H-pyrazolo[3,4-g]isoquinoline-6(4H)-carboxylate **4** with TFA/DCM followed by 3-(trifluoromethyl)benzene-1-sulfonyl chloride. LC/MS m/z 583 $(M+H)^+$; ^{1}H NMR ($CDCl_3$): δ8.65-8.64 (1H, m), 7.94 (1H, m), 7.89-7.78 (4H, m), 7.63-7.59 (1H, m), 7.47 (1H, ddd, J = 7.3, 4.8, 1.5 Hz), 7.44-7.40 (2H, m), 7.28 (1H, s), 7.19-7.13 (2H, m), 6.48 (1H, d, J = 2.2 Hz), 5.56 (1H, dd, J = 12.4, 2.2 Hz), 4.26 (1H, d, J = 16.9 Hz), 3.89-3.85 (1H, m), 2.91-2.79 (3H, m), 2.58-2.48 (2H, m).

(*R*)-(1-(4-fluorophenyl)-6-((3-(trifluoromethyl)phenyl)sulfonyl)-4,4a,5,6,7,8-hexahydro-1H-pyrazolo[3,4-g]isoquinolin-4a-yl)(4-methylpyridin-2-yl)methanone (29). Compound **29** was prepared using the same procedure as described for the synthesis of **5** by treating (*R*)-tert-butyl 1-(4-fluorophenyl)-4a-(4-methylpicolinoyl)-4a,5,7,8-tetrahydro-1H-pyrazolo[3,4-g]isoquinoline-

6(4H)-carboxylate **4a** with HCl (4M in dioxane) followed by 3-(trifluoromethyl)benzene-1-sulfonyl chloride. LC/MS m/z 597 $(M+H)^+$; ^1H NMR ($CDCl_3$): δ 8.49 (1H, dd, J = 4.9, 0.38 Hz), 8.00 - 7.88 (2H, m), 7.80 - 7.78 (1H, m), 7.71 - 7.68 (1H, m), 7.61 (1H, t, J = 7.8 Hz), 7.46 - 7.39 (2H, m), 7.29 - 7.27 (2H, m), 7.19 - 7.13 (2H, m), 6.48 (1H, d, J = 2.0 Hz), 5.61 (1H, dd, J = 12.3, 2.0 Hz), 4.27 (1H, d, J = 16.9 Hz), 3.91 - 3.81 (1H, m), 2.92 - 2.78 (3H, m), 2.62 - 2.49 (2H, m), 2.40 (3H, s).

(*R*)-(6-((3-fluoro-4-(trifluoromethyl)phenyl)sulfonyl)-1-(4-fluorophenyl)-4,4a,5,6,7,8-hexahydro-1H-pyrazolo[3,4-g]isoquinolin-4a-yl)(pyridin-2-yl)methanone (30). Compound **30** was prepared using the same procedure as described for the synthesis of **5** by treating (*R*)-tert-butyl 1-(4-fluorophenyl)-4a-picolinoyl-4a,5,7,8-tetrahydro-1H-pyrazolo[3,4-g]isoquinoline-6(4H)-carboxylate **4** with HCl (4M in dioxane) followed by 3-fluoro-4-(trifluoromethyl)benzene-1-sulfonyl chloride. LC/MS m/z 601 $(M+H)^+$; ^1H NMR ($CDCl_3$): δ 8.64 (1H, ddd, J = 4.9, 1.5, 1.1 Hz), 7.87-7.81 (2H, m), 7.71-7.67 (1H, m), 7.57 (1H, br d, J = 8.2 Hz), 7.51-7.47 (2H, m), 7.45-7.40 (2H, m), 7.28 (1H, s), 7.19-7.13 (2H, m), 6.50 (1H, d, J = 2.0 Hz), 5.59 (1H, dd, J = 12.4, 2.0 Hz), 4.25 (1H, d, J = 16.9 Hz), 3.92-3.87 (1H, m), 2.91-2.80 (3H, m), 2.67-2.61 (1H, m), 2.55-2.51 (1H, m).

(*R*)-(6-((3-fluoro-4-(trifluoromethyl)phenyl)sulfonyl)-1-(4-fluorophenyl)-4,4a,5,6,7,8-hexahydro-1H-pyrazolo[3,4-g]isoquinolin-4a-yl)(4-methylpyridin-2-yl)methanone (31). Compound **31** was prepared using the same procedure as described for the synthesis of **5** by treating (*R*)-tert-butyl 1-(4-fluorophenyl)-4a-(4-methylpicolinoyl)-4a,5,7,8-tetrahydro-1H-pyrazolo[3,4-g]isoquinoline-6(4H)-carboxylate **4a** with HCl (4M in dioxane) followed by 3-fluoro-4-(trifluoromethyl)benzene-1-sulfonyl chloride. LC/MS m/z 615 $(M+H)^+$; ^1H NMR ($CDCl_3$): δ 8.47 (1H, dd, J = 4.9, 0.3 Hz), 7.69-7.65 (2H, m), 7.58-7.56 (1H, m), 7.48 (1H, br d,

J = 9.4 Hz), 7.45-7.40 (2H, m), 7.28 (1H, ddd, J = 4.9, 1.6, 0.7 Hz), 7.26 (1H, s), 7.19-7.13 (2H, m), 6.49 (1H, d, J = 2.0 Hz), 5.64 (1H, dd, J = 12.5, 2.0 Hz), 4.23 (1H, d, J = 16.9 Hz), 3.92-3.88 (1H, m), 2.91-2.80 (3H, m), 2.69-2.63 (1H, m), 2.55-2.50 (1H, m), 2.39 (3H, s).

(*R*)-3-((1-(4-fluorophenyl)-4a-picolinoyl-4a,5,7,8-tetrahydro-1H-pyrazolo[3,4-g]isoquinolin-6(4H)-yl)sulfonyl)benzonitrile (32). Compound **32** was prepared using the same procedure as described for the synthesis of **5** by treating (*R*)-tert-butyl 1-(4-fluorophenyl)-4a-picolinoyl-4a,5,7,8-tetrahydro-1H-pyrazolo[3,4-g]isoquinoline-6(4H)-carboxylate **4** with HCl (4M in dioxane) followed by 3-cyanobenzene-1-sulfonyl chloride. LC/MS m/z 540 $(M+H)^+$; ^{1}H NMR ($CDCl_3$): δ 8.68 - 8.66 (1H, m), 7.93 - 7.78 (5H, m), 7.60 (1H, td, J = 7.8, 0.6 Hz), 7.50 (1H, ddd, J = 6.8, 4.8, 2.2 Hz), 7.45 - 7.39 (2H, m), 7.28 (1H, m), 7.19 - 7.13 (2H, m), 6.50 (1H, d, J = 2.1 Hz), 5.60 (1H, dd, J = 12.4, 2.1 Hz), 4.26 (1H, d, J = 16.9 Hz), 3.92 - 3.83 (1H, m), 2.90 - 2.78 (3H, m), 2.58 - 2.49 (2H, m).

(*R*)-3-((1-(4-fluorophenyl)-4a-(4-methylpicolinoyl)-4a,5,7,8-tetrahydro-1H-pyrazolo[3,4-g]isoquinolin-6(4H)-yl)sulfonyl)benzonitrile (33). Compound **33** was prepared using the same procedure as described for the synthesis of **5** by treating (*R*)-tert-butyl 1-(4-fluorophenyl)-4a-(4-methylpicolinoyl)-4a,5,7,8-tetrahydro-1H-pyrazolo[3,4-g]isoquinoline-6(4H)-carboxylate **4a** with HCl (4M in dioxane) followed by 3-cyanobenzene-1-sulfonyl chloride. LC/MS m/z 554 $(M+H)^+$; ^{1}H NMR ($CDCl_3$): δ 8.50 (1H, br. d, J = 4.9 Hz), 7.93 - 7.91 (2H, m), 7.79 (1H, dt, J = 7.8, 1.3 Hz), 7.69 - 7.68 (1H, m), 7.63 - 7.58 (1H, m), 7.44 - 7.41 (2H, m), 7.30 (1H, ddd, J = 4.9, 1.7, 0.7 Hz), 7.27 (1H, s), 7.19 - 7.13 (2H, m), 6.49 (1H, d, J = 2.0 Hz), 5.64 (1H, dd, J = 12.4, 2.0 Hz), 4.25 (1H, d, J = 16.9 Hz), 3.89 (1H, ddt, J = 8.5, 3.9, 2.0 Hz), 2.85 - 2.79 (3H, m), 2.63 - 2.50 (2H, m), 2.41 (3H, s).

(*R*)-3-((4a-(4-ethylpicolinoyl)-1-(4-fluorophenyl)-4a,5,7,8-tetrahydro-1H-pyrazolo[3,4-g]isoquinolin-6(4H)-yl)sulfonyl)benzonitrile (34). Compound **34** was prepared using the same procedure as described for the synthesis of **5** by treating (*R*)-tert-butyl 4a-(4-ethylpicolinoyl)-1-(4-fluorophenyl)-4a,5,7,8-tetrahydro-1H-pyrazolo[3,4-g]isoquinoline-6(4H)-carboxylate **4b** with HCl (4M in dioxane) followed by 3-cyanobenzene-1-sulfonyl chloride. LC/MS m/z 568 $(M+H)^+$; ^{1}H NMR ($CDCl_3$): δ 8.53 (1H, dd, J = 4.9, 0.5 Hz), 7.95 (1H, m), 7.91 (1H, ddd, J = 7.9, 1.9, 1.2 Hz), 7.78 (1H, ddd, J = 7.9, 1.2, 0.3 Hz), 7.71-7.70 (1H, m), 7.59 (1H, dt, J = 7.9, 0.5 Hz), 7.45-7.40 (2H, m),7.33-7.32 (1H, m), 7.27 (1H, s), 7.19-7.13 (2H, m), 6.49 (1H, d, J = 2.0 Hz), 5.64 (1H, dd, J = 12.3, 2.0 Hz), 4.25 (1H, d, J = 16.9 Hz), 3.91-3.86 (1H, m), 2.88-2.80 (3H, m), 2.71 (2H, q, J = 7.7 Hz), 2.63-2.50 (2H, m), 1.27 (3H, t, J = 7.7 Hz).

(*R*)-3-((1-(4-fluorophenyl)-4a-(4-(trifluoromethyl)picolinoyl)-4a,5,7,8-tetrahydro-1H-pyrazolo[3,4-g]isoquinolin-6(4H)-yl)sulfonyl)benzonitrile (35). Compound **35** was prepared using the same procedure as described for the synthesis of **5** by treating (*R*)-tert-butyl 1-(4-fluorophenyl)-4a-(4-(trifluoromethyl)picolinoyl)-4a,5,7,8-tetrahydro-1H-pyrazolo[3,4-g]isoquinoline-6(4H)-carboxylate **6** with HCl (4M in dioxane) followed by 3-cyanobenzene-1-sulfonyl chloride. LC/MS m/z 608 $(M+H)^+$; ^{1}H NMR ($CDCl_3$): δ 8.90 (1H, d, J = 5.0 Hz), 8.13 (1H, m), 7.98 (1H, m), 7.91-7.89 (1H, m), 7.84-7.81 (1H, m), 7.74 (1H, dd, J = 5.0, 0.9 Hz), 7.65-7.61 (1H, m), 7.45-7.40 (2H, m), 7.29 (1H, s), 7.20-7.14 (2H, m), 6.51 (1H, d, J = 2.0 Hz), 5.53 (1H, dd, J = 12.3, 2.0 Hz), 4.18 (1H, d, J = 16.9 Hz), 3.91-3.87 (1H, m), 2.90 (1H, d, J = 16.9 Hz), 2.88-2.77 (2H, m), 2.58-2.51 (2H, m).

(*R*)-(1-(4-fluorophenyl)-6-((3-(trifluoromethyl)phenyl)sulfonyl)-4,4a,5,6,7,8-hexahydro-1H-pyrazolo[3,4-g]isoquinolin-4a-yl)(thiazol-2-yl)methanone (36). Compound **36** was prepared

using the same procedure as described for the synthesis of **9** by treating (*R*)-methyl 1-(4-fluorophenyl)-6-((3-(trifluoromethyl)phenyl)sulfonyl)-4,4a,5,6,7,8-hexahydro-1H-pyrazolo[3,4-g]isoquinoline-4a-carboxylate **8c** with 2-bromothiazole/n-butyllithium. LC/MS m/z 589 $(M+H)^+$; ^{1}H NMR ($CDCl_3$): δ 8.04 (1H, d, J = 3.1 Hz), 7.97 (1H, s), 7.90 (1H, d, J = 7.9 Hz), 7.81 (1H, d, J = 7.9 Hz), 7.70 - 7.59 (2H, m), 7.46 - 7.39 (2H, m), 7.30 (1H, s), 7.13 - 7.19 (2H, m), 6.53 (1H, d, J = 2.2 Hz), 5.54 (1H, dd, J = 12.4, 2.0 Hz), 4.21 (1H, d, J = 16.8 Hz), 3.93 - 3.89 (1H, m), 2.95 - 2.84 (2H, m), 2.80(1H, d, J = 12.5 Hz), 2.61 - 2.52 (2H, m).

(*R*)-(1-(4-fluorophenyl)-6-((3-(trifluoromethyl)phenyl)sulfonyl)-4,4a,5,6,7,8-hexahydro-1H-pyrazolo[3,4-g]isoquinolin-4a-yl)(5-methylthiazol-2-yl)methanone (37). Compound **37** was prepared using the same procedure as described for the synthesis of **9** by treating (*R*)-methyl 1-(4-fluorophenyl)-6-((3-(trifluoromethyl)phenyl)sulfonyl)-4,4a,5,6,7,8-hexahydro-1H-pyrazolo[3,4-g]isoquinoline-4a-carboxylate **8c** with 2-bromo-5-methylthiazole/n-butyllithium. LC/MS m/z 603 $(M+H)^+$; ^{1}H NMR ($CDCl_3$): δ 7.98 (1H, s), 7.91 (1H, br. d, J = 7.9 Hz), 7.84 - 7.80 (1H, m), 7.68 - 7.61 (2H, m), 7.46 - 7.39 (2H, m), 7.29 (1H, s), 7.20 - 7.12 (2H, m), 6.51 (1H, d, J = 2.1 Hz), 5.54 (1H, dd, J = 12.4, 2.1 Hz), 4.17 (1H, d, J = 16.7 Hz), 3.93 - 3.89 (1H, m), 2.95 - 2.77 (3H, m), 2.60 - 2.49 (5H, m).

(*R*)-(1-(4-fluorophenyl)-6-((3-(trifluoromethyl)phenyl)sulfonyl)-4,4a,5,6,7,8-hexahydro-1H-pyrazolo[3,4-g]isoquinolin-4a-yl)(4-methylthiazol-2-yl)methanone (38). Compound **38** was prepared using the same procedure as described for the synthesis of **9** by treating (*R*)-methyl 1-(4-fluorophenyl)-6-((3-(trifluoromethyl)phenyl)sulfonyl)-4,4a,5,6,7,8-hexahydro-1H-pyrazolo[3,4-g]isoquinoline-4a-carboxylate **8c** with 2-bromo-4-methylthiazole/n-butyllithium. LC/MS m/z 603 $(M+H)^+$; ^{1}H NMR ($CDCl_3$): δ 7.96 (1H, s), 7.88 (1H, d, J = 7.9 Hz), 7.80 (1H,

d, J = 7.9 Hz), 7.62 (1H, t, J = 7.9 Hz), 7.42 (2H, ddt, J = 8.1, 5.6, 2.8 Hz), 7.30 (1H, s), 7.21 (1H, d, J = 0.9 Hz), 7.20 - 7.12 (2H, m), 6.52 (1H, d, J = 2.2 Hz), 5.56 (1H, dd, J = 12.4, 2.2 Hz), 4.18 (1H, d, J = 16.8 Hz), 3.95 - 3.88 (1H, m), 2.91 - 2.80 (3H, m), 2.63 - 2.50 (5H, m).

(*R*)-(6-((3,4-difluorophenyl)sulfonyl)-1-(4-fluorophenyl)-4,4a,5,6,7,8-hexahydro-1H-pyrazolo[3,4-g]isoquinolin-4a-yl)(5-methylthiazol-2-yl)methanone (39). Compound **39** was prepared using the same procedure as described for the synthesis of **9** by treating (*R*)-methyl 6-((3,4-difluorophenyl)sulfonyl)-1-(4-fluorophenyl)-4,4a,5,6,7,8-hexahydro-1H-pyrazolo[3,4-g]isoquinoline-4a-carboxylate **8** with 2-bromo-5-methylthiazole/n-butyllithium. LC/MS m/z 571 $(M+H)^+$; ^{1}H NMR ($CDCl_3$): δ 7.63 (1H, m), 7.54-7.49 (2H, m), 7.45-7.40 (2H, m), 7.29 (1H, s), 7.27-7.21 (1H, m), 7.19-7.13 (2H, m), 6.52 (1H, d, J = 2.0 Hz), 5.44 (1H, dd, J = 12.4, 2.0 Hz), 4.15 (1H, d, J = 16.9 Hz), 3.93-3.89 (1H, m), 2.91-2.80 (3H, m), 2.64-2.52 (5H, m).

(*R*)-(6-((3,4-dichlorophenyl)sulfonyl)-1-(4-fluorophenyl)-4,4a,5,6,7,8-hexahydro-1H-pyrazolo[3,4-g]isoquinolin-4a-yl)(thiazol-2-yl)methanone (40). Compound **40** was prepared using the same procedure as described for the synthesis of **9** by treating (*R*)-methyl 6-((3,4-dichlorophenyl)sulfonyl)-1-(4-fluorophenyl)-4,4a,5,6,7,8-hexahydro-1H-pyrazolo[3,4-g]isoquinoline-4a-carboxylate **8a** with 2-bromothiazole/n-butyllithium. LC/MS m/z 589 $(M+H)^+$; ^{1}H NMR ($CDCl_3$): δ 8.00 (1H, d, J = 3.0 Hz), 7.77 (1H, dd, J = 1.8, 0.9 Hz), 7.67 (1H, d, J = 3.0 Hz), 7.54-7.48 (2H, m), 7.45-7.40 (2H, m), 7.29 (1H, s), 7.20-7.14 (2H, m), 6.54 (1H, d, J = 2.1 Hz), 5.46 (1H, dd, J = 12.6, 2.0 Hz), 4.18 (1H, d, J = 16.9 Hz), 3.94-3.90 (1H, m), 2.92-2.84 (3H, m), 2.66-2.54 (2H, m).

(*R*)-(6-((3,4-dichlorophenyl)sulfonyl)-1-(4-fluorophenyl)-4,4a,5,6,7,8-hexahydro-1H-pyrazolo[3,4-g]isoquinolin-4a-yl)(5-methylthiazol-2-yl)methanone (41). Compound **41** was

prepared using the same procedure as described for the synthesis of **9** by treating (*R*)-methyl 6-((3,4-dichlorophenyl)sulfonyl)-1-(4-fluorophenyl)-4,4a,5,6,7,8-hexahydro-1H-pyrazolo[3,4-g]isoquinoline-4a-carboxylate **8a** with 2-bromo-5-methylthiazole/n-butyllithium. LC/MS m/z 603 $(M+H)^+$; ^1H NMR ($CDCl_3$): δ 7.77 (1H, d, J = 1.9 Hz), 7.60 (1H, d, J = 1.0 Hz), 7.56 - 7.48 (2H, m), 7.45 - 7.40 (2H, m), 7.28 (1H, s), 7.21 - 7.13 (2H, m), 6.53 (1H, d, J = 2.1 Hz), 5.45 (1H, dd, J = 12.5, 2.1 Hz), 4.13 (1H, d, J = 16.6 Hz), 3.94 (1H, ddt, J = 8.5, 3.9, 2.0 Hz), 2.93 - 2.84 (3H, m), 2.68 - 2.61 (1H, m), 2.57 (3H, d, J = 1.0 Hz), 2.58 - 2.52 (1H, m).

(*R*)-(1-(4-fluorophenyl)-6-((1-methyl-1H-pyrazol-4-yl)sulfonyl)-4,4a,5,6,7,8-hexahydro-1H-pyrazolo[3,4-g]isoquinolin-4a-yl)(pyridin-2-yl)methanone (42). Compound **42** was prepared using the same procedure as described for the synthesis of **5** by treating (*R*)-tert-butyl 1-(4-fluorophenyl)-4a-picolinoyl-4a,5,7,8-tetrahydro-1H-pyrazolo[3,4-g]isoquinoline-6(4H)-carboxylate **4** with TFA/DCM followed by 1-methyl-1H-pyrazole-4-sulfonyl chloride. LC/MS m/z 519 $(M+H)^+$; ^1H NMR ($CDCl_3$): δ 8.66 (1H, ddd, J = 4.7, 1.7, 0.8 Hz), 7.91-7.89 (1H, m), 7.84 (1H, dt, J = 7.6, 1.8 Hz), 7.68-7.65 (2H, m), 7.49-7.42 (3H, m), 7.30 (1H, s), 7.20-7.14 (2H, m), 6.49 (1H, d, J = 2.1 Hz), 5.46 (1H, dd, J = 12.2, 2.1 Hz), 4.31 (1H, d, J = 16.9 Hz), 3.91 (3H, s), 3.80-3.76 (1H, m), 2.91 (1H, d, J = 16.9 Hz), 2.88-2.79 (1H, m), 2.68 (1H, d, J = 12.2 Hz), 2.50-2.41 (2H, m).

(*R*)-(6-((1-ethyl-1H-pyrazol-4-yl)sulfonyl)-1-(4-fluorophenyl)-4,4a,5,6,7,8-hexahydro-1H-pyrazolo[3,4-g]isoquinolin-4a-yl)(4-(trifluoromethyl)pyridin-2-yl)methanone (43). Compound **43** was prepared using the same procedure as described for the synthesis of **7** by treating (*R*)-tert-butyl 1-(4-fluorophenyl)-4a-(4-(trifluoromethyl)picolinoyl)-4a,5,7,8-tetrahydro-1H-pyrazolo[3,4-g]isoquinoline-6(4H)-carboxylate **6** with HCl/Dioxane followed by 1-ethyl-1H-pyrazole-4-sulfonyl chloride. LC/MS m/z 601 $(M+H)^+$; ^1H NMR ($CDCl_3$): δ 8.88-8.87 (1H,

m), 8.15 (1H, m), 7.71-7.69 (2H, m), 7.67 (1H, d, J = 0.6 Hz), 7.47-7.42 (2H, m), 7.30 (1H, s), 7.20-7.14 (2H, m), 6.51 (1H, d, J = 2.0 Hz), 5.44 (1H, dd, J = 12.0, 2.0 Hz), 4.22-4.16 (3H, m), 3.80-3.76 (1H, m), 2.94 (1H, d, J = 16.9 Hz), 2.88-2.79 (1H, m), 2.67 (1H, d, J = 12.3 Hz), 2.52-2.40 (2H, m), 1.51 (3H, t, J = 7.3 Hz).

(*R*)-(1-(4-fluorophenyl)-6-((1-methyl-1H-pyrazol-3-yl)sulfonyl)-4,4a,5,6,7,8-hexahydro-1H-pyrazolo[3,4-g]isoquinolin-4a-yl)(4-(trifluoromethyl)pyridin-2-yl)methanone (44). Compound **44** was prepared using the same procedure as described for the synthesis of **7** by treating (*R*)-tert-butyl 1-(4-fluorophenyl)-4a-(4-(trifluoromethyl)picolinoyl)-4a,5,7,8-tetrahydro-1H-pyrazolo[3,4-g]isoquinoline-6(4H)-carboxylate **6** with HCl/Dioxane followed by 1-methyl-1H-pyrazole-3-sulfonyl chloride. LC/MS m/z 587 $(M+H)^+$; ^{1}H NMR ($CDCl_3$): δ 8.89 (1H, d, J = 5.0 Hz), 8.14 (1H, m), 7.70-7.68 (1H, m), 7.47-7.42 (2H, m), 7.39 (1H, d, J = 2.3 Hz), 7.31 (1H, s), 7.21-7.15 (2H, m), 6.57 (1H, d, J = 2.2 Hz), 6.52 (1H, d, J = 2.1 Hz), 5.56 (1H, dd, J = 12.6, 2.1 Hz), 4.24 (1H, d, J = 16.9 Hz), 3.96 (3H, s), 3.89-3.85 (1H, m), 2.96 (1H, d, J = 16.9 Hz), 2.93 (1H, d, J = 12.4 Hz), 2.88-2.79 (1H, m), 2.68-2.61 (1H, m), 2.51-2.47 (1H, m).

(*R*)-(1-(4-fluorophenyl)-6-((1-methyl-1H-pyrazol-5-yl)sulfonyl)-4,4a,5,6,7,8-hexahydro-1H-pyrazolo[3,4-g]isoquinolin-4a-yl)(4-(trifluoromethyl)pyridin-2-yl)methanone (45). Compound **45** was prepared using the same procedure as described for the synthesis of **7** by treating (*R*)-tert-butyl 1-(4-fluorophenyl)-4a-(4-(trifluoromethyl)picolinoyl)-4a,5,7,8-tetrahydro-1H-pyrazolo[3,4-g]isoquinoline-6(4H)-carboxylate **6** with HCl/Dioxane followed by 1-methyl-1H-pyrazole-5-sulfonyl chloride. LC/MS m/z 587 $(M+H)^+$; ^{1}H NMR ($CDCl_3$): δ 8.81 (1H, d, J = 4.9 Hz), 8.12 (1H, m), 7.70-7.69 (1H, m), 7.47-7.41 (2H, m), 7.35 (1H, d, J = 2.1 Hz), 7.28 (1H, s), 7.21-7.15 (2H, m), 6.62 (1H, d, J = 2.1 Hz), 6.54 (1H, d, J = 2.0 Hz), 5.50 (1H, dd, J = 12.4,

2.0 Hz), 4.18 (1H, d, J = 16.9 Hz), 3.95 (3H, s), 3.94-3.90 (1H, m), 3.02 (1H, d, J = 12.6 Hz), 2.92 (1H, d, J = 16.9 Hz), 2.86-2.74 (2H, m), 2.60-2.55 (1H, m).

(*R*)-(6-((1,5-dimethyl-1H-pyrazol-4-yl)sulfonyl)-1-(4-fluorophenyl)-4,4a,5,6,7,8-hexahydro-1H-pyrazolo[3,4-g]isoquinolin-4a-yl)(4-(trifluoromethyl)pyridin-2-yl)methanone (46). Compound **46** was prepared using the same procedure as described for the synthesis of **7** by treating (*R*)-tert-butyl 1-(4-fluorophenyl)-4a-(4-(trifluoromethyl)picolinoyl)-4a,5,7,8-tetrahydro-1H-pyrazolo[3,4-g]isoquinoline-6(4H)-carboxylate **6** with HCl/Dioxane followed by 1,5-dimethyl-1H-pyrazole-4-sulfonyl chloride. LC/MS m/z 601 $(M+H)^+$; ^{1}H NMR ($CDCl_3$): δ 8.84 (1H, d, J = 4.9 Hz), 8.13 (1H, br s), 7.69 (1H, dd, J = 4.9, 1.0 Hz), 7.61 (1H, s), 7.47-7.41 (2H, m), 7.28 (1H, s), 7.20-7.14 (2H, m), 6.51 (1H, d, J = 2.0 Hz), 5.46 (1H, dd, J = 12.3, 1.9 Hz), 4.16 (1H, d, J = 16.9 Hz), 3.85-3.79 (1H, m), 3.71 (3H, s), 2.92 (1H, d, J = 16.9 Hz), 2.87-2.76 (2H, m), 2.58-2.50 (2H, m), 2.34 (3H, s).

(R)-(6-((1H-pyrazol-4-yl)sulfonyl)-1-(4-fluorophenyl)-4,4a,5,6,7,8-hexahydro-1H-pyrazolo[3,4-g]isoquinolin-4a-yl)(4-(trifluoromethyl)pyridin-2-yl)methanone (47). Compound **47** was prepared using the same procedure as described for the synthesis of **7** by treating (*R*)-tert-butyl 1-(4-fluorophenyl)-4a-(4-(trifluoromethyl)picolinoyl)-4a,5,7,8-tetrahydro-1H-pyrazolo[3,4-g]isoquinoline-6(4H)-carboxylate **6** with HCl/Dioxane followed by 1H-pyrazole-4-sulfonyl chloride. LC/MS m/z 573 $(M+H)^+$; ^{1}H NMR ($CDCl_3$): δ 11.0 (1H, br s), 8.86 (1H, d, J = 4.9 Hz), 8.15 (1H, m), 7.83 (2H, s), 7.71-7.69 (1H, m), 7.46-7.41 (2H, m), 7.31 (1H, s), 7.20-7.14 (2H, m), 6.50 (1H, d, J = 2.0 Hz), 5.44 (1H, dd, J = 12.1, 2.0 Hz), 4.20 (1H, d, J = 16.9 Hz), 3.82-3.78 (1H, m), 2.92 (1H, d, J = 16.9 Hz), 2.87-2.78 (1H, m), 2.67 (1H, d, J = 12.2 Hz), 2.52-2.40 (2H, m).

(*R*)-(6-((1-ethyl-1H-pyrazol-5-yl)sulfonyl)-1-(4-fluorophenyl)-4,4a,5,6,7,8-hexahydro-1H-pyrazolo[3,4-g]isoquinolin-4a-yl)(4-(trifluoromethyl)pyridin-2-yl)methanone (48). Compound **48** was prepared using the same procedure as described for the synthesis of **7** by treating (*R*)-tert-butyl 1-(4-fluorophenyl)-4a-(4-(trifluoromethyl)picolinoyl)-4a,5,7,8-tetrahydro-1H-pyrazolo[3,4-g]isoquinoline-6(4H)-carboxylate **6** with HCl/Dioxane followed by 1-ethyl-1H-pyrazole-5-sulfonyl chloride. LC/MS m/z 601 $(M+H)^+$; ^{1}H NMR ($CDCl_3$): δ 8.81 (1H, d, J = 4.9 Hz), 8.13 (1H, m), 7.71-7.69 (1H, m), 7.47-7.42 (2H, m), 7.40 (1H, d, J = 2.0 Hz), 7.28 (1H, s), 7.21-7.15 (2H, m), 6.59 (1H, d, J = 2.0 Hz), 6.55 (1H, d, J = 1.6 Hz), 5.52 (1H, dd, J = 12.6, 2.0 Hz), 4.35-4.23 (2H, m), 4.18 (1H, d, J = 16.9 Hz), 3.92-3.87 (1H, m), 3.02 (1H, d, J = 12.8 Hz), 2.92 (1H, d, J = 16.9 Hz), 2.89-2.74 (2H, m), 2.59-2.55 (1H, m), 1.40 (3H, t, J = 7.3 Hz).

(*R*)-(6-((3,5-dimethyl-1H-pyrazol-4-yl)sulfonyl)-1-(4-fluorophenyl)-4,4a,5,6,7,8-hexahydro-1H-pyrazolo[3,4-g]isoquinolin-4a-yl)(4-(trifluoromethyl)pyridin-2-yl)methanone (49). Compound **49** was prepared using the same procedure as described for the synthesis of **7** by treating (*R*)-tert-butyl 1-(4-fluorophenyl)-4a-(4-(trifluoromethyl)picolinoyl)-4a,5,7,8-tetrahydro-1H-pyrazolo[3,4-g]isoquinoline-6(4H)-carboxylate **6** with HCl/Dioxane followed by 3,5-dimethyl-1H-pyrazole-4-sulfonyl chloride. LC/MS m/z 601 $(M+H)^+$; ^{1}H NMR ($CDCl_3$): δ 8.79 (1H, d, J = 4.9 Hz), 8.12 (1H, m), 7.67 (1H, dd, J = 4.9, 1.0 Hz), 7.47-7.42 (2H, m), 7.27 (1H, s), 7.21-7.15 (2H, m), 6.53 (1H, d, J = 2.1 Hz), 5.42 (1H, dd, J = 12.3, 2.0 Hz), 4.19 (1H, d, J = 16.9 Hz), 3.87-3.83 (1H, m), 2.93 (1H, d, J = 16.9 Hz), 2.91 (1H, d, J = 12.8 Hz), 2.85-2.80 (1H, m), 2.72-2.76 (1H, m), 2.56-2.52 (1H, m), 2.32 (6H, s).

(*R*)-(1-(4-fluorophenyl)-6-((2-methyl-2H-1,2,3-triazol-4-yl)sulfonyl)-4,4a,5,6,7,8-hexahydro-1H-pyrazolo[3,4-g]isoquinolin-4a-yl)(4-(trifluoromethyl)pyridin-2-yl)methanone (50). Compound **50** was prepared using the same procedure as described for the synthesis of **7** by

treating (*R*)-tert-butyl 1-(4-fluorophenyl)-4a-(4-(trifluoromethyl)picolinoyl)-4a,5,7,8-tetrahydro-1H-pyrazolo[3,4-g]isoquinoline-6(4H)-carboxylate **6** with HCl/Dioxane followed by 2-methyl-2H-1,2,3-triazole-4-sulfonyl chloride **19**. LC/MS m/z 588 $(M+H)^+$; ^1H NMR ($CDCl_3$): δ 8.89 (1H, dt, J = 5.0, 0.8 Hz), 8.15 - 8.13 (1H, m), 7.81 (1H, s), 7.70 (1H, ddd, J = 5.1, 1.7, 0.8 Hz), 7.48 - 7.42 (2H, m), 7.30 (1H, s), 7.22 - 7.13 (2H, m), 6.54 (1H, d, J = 2.2 Hz), 5.59 (1H, dd, J = 12.7, 2.2 Hz), 4.25 (3H, s), 4.22 (1H, d, J = 17.0 Hz), 3.90 (1H, ddt, J = 10.6, 6.0, 2.0 Hz), 2.99 (1H, d, J = 12.7 Hz), 2.95 (1H, d, J = 17.0 Hz), 2.84 (1H, tdd, J = 12.7, 5.9, 3.0 Hz), 2.74 - 2.67 (1H, m), 2.52 (1H, br. dt, J = 14.6, 2.7 Hz).

(*R*)-(1-(4-fluorophenyl)-6-((1-methyl-1H-1,2,3-triazol-4-yl)sulfonyl)-4,4a,5,6,7,8-hexahydro-1H-pyrazolo[3,4-g]isoquinolin-4a-yl)(4-(trifluoromethyl)pyridin-2-yl)methanone (51). Compound **51** was prepared using the same procedure as described for the synthesis of **7** by treating (*R*)-tert-butyl 1-(4-fluorophenyl)-4a-(4-(trifluoromethyl)picolinoyl)-4a,5,7,8-tetrahydro-1H-pyrazolo[3,4-g]isoquinoline-6(4H)-carboxylate **6** with HCl/Dioxane followed by 1-methyl-1H-1,2,3-triazole-4-sulfonyl chloride **18**. LC/MS m/z 588 $(M+H)^+$; ^1H NMR ($CDCl_3$): δ 8.87 (1H, d, J = 4.9 Hz), 8.15 (1H, m), 7.89 (1H, s), 7.70-7.69 (1H, m), 7.48-7.43 (2H, m), 7.31 (1H, s), 7.21-7.15 (2H, m), 6.54 (1H, s), 5.61 (1H, dd, J = 12.5, 2.0 Hz), 4.23 (1H, d, J = 16.9 Hz), 4.15 (3H, s), 3.95-3.87 (1H, m), 3.14 (1H, d, J = 12.5 Hz), 2.96 (1H, d, J = 16.9 Hz), 2.88-2.78 (2H, m), 2.57-2.48 (1H, m).

(*R*)-(1-(4-fluorophenyl)-6-((1-methyl-1H-1,2,3-triazol-5-yl)sulfonyl)-4,4a,5,6,7,8-hexahydro-1H-pyrazolo[3,4-g]isoquinolin-4a-yl)(4-(trifluoromethyl)pyridin-2-yl)methanone (52). Compound **52** was prepared using the same procedure as described for the synthesis of **7** by treating (*R*)-tert-butyl 1-(4-fluorophenyl)-4a-(4-(trifluoromethyl)picolinoyl)-4a,5,7,8-tetrahydro-1H-pyrazolo[3,4-g]isoquinoline-6(4H)-carboxylate **6** with HCl/Dioxane followed by 1-methyl-

1H-1,2,3-triazole-5-sulfonyl chloride **20**. LC/MS m/z 588 $(M+H)^+$; ^1H NMR ($CDCl_3$): δ 8.80 (1H, d, J = 4.9 Hz), 8.11 (1H, m), 7.91 (1H, s), 7.73-7.71 (1H, m), 7.47-7.41 (2H, m), 7.28 (1H, s), 7.21-7.16 (2H, m), 6.56 (1H, s), 5.51 (1H, dd, J = 12.7, 2.1 Hz), 4.13 (1H, d, J = 16.9 Hz), 4.11 (3H, s), 4.01-3.93 (1H, m), 3.09 (1H, d, J = 12.7 Hz), 2.92 (1H, d, J = 16.9 Hz), 2.87-2.81 (2H, m), 2.65-2.60 (1H, m).

((4a*R*,8a*S*)-1-(4-fluorophenyl)-6-((3-(trifluoromethyl)phenyl)sulfonyl)-4,4a,5,6,7,8,8a,9-octahydro-1H-pyrazolo[3,4-g]isoquinolin-4a-yl)(pyridin-2-yl)methanone (53). Compound **53** was prepared using the same procedure as described for the synthesis of **12** by treating (4a*R*,8a*S*)-tert-butyl 1-(4-fluorophenyl)-4a-picolinoyl-4a,5,7,8,8a,9-hexahydro-1H-pyrazolo[3,4-g]isoquinoline-6(4H)-carboxylate **11a** with HCl/Dioxane followed by 3-(trifluoromethyl)benzene-1-sulfonyl chloride. LC/MS m/z 585 $(M+H)^+$; ^1H NMR ($CDCl_3$): δ 8.66 - 8.61 (1H, m), 7.94 (1H, s), 7.88 (1H, br. d, J = 7.9 Hz), 7.84 - 7.77 (3H, m), 7.61 (1H, t, J = 7.8 Hz), 7.53 - 7.41 (3H, m), 7.33 (1H, s), 7.21 - 7.11 (2H, m), 5.66 (1H, dd, J = 12.2, 2.1 Hz), 4.31 (1H, d, J = 16.2 Hz), 4.03 - 3.91 (1H, m), 3.43 (1H, dd, J = 16.2, 11.2 Hz), 2.71 (1H, dd, J = 16.2, 5.9 Hz), 2.62 - 2.35 (4H, m), 1.85 - 1.68 (2H, m).

((4a*R*,8a*S*)-1-(4-fluorophenyl)-6-((1-methyl-1H-pyrazol-4-yl)sulfonyl)-4,4a,5,6,7,8,8a,9-octahydro-1H-pyrazolo[3,4-g]isoquinolin-4a-yl)(4-(trifluoromethyl)pyridin-2-yl)methanone (54). Compound **54** was prepared using the same procedure as described for the synthesis of **12** by treating (4a*R*,8a*S*)-tert-butyl 1-(4-fluorophenyl)-4a-(4-(trifluoromethyl)picolinoyl)-4a,5,7,8,8a,9-hexahydro-1H-pyrazolo[3,4-g]isoquinoline-6(4H)-carboxylate **11** with TFA/DCM followed by 1-methyl-1H-pyrazole-4-sulfonyl chloride. LC/MS m/z 589 $(M+H)^+$; ^1H NMR ($CDCl_3$): δ 8.84 (1H, d, J = 5.0 Hz), 8.10 (1H, m), 7.66-7.65 (3H, m), 7.50-7.45 (2H, m), 7.33 (1H, s), 7.18-7.12 (2H, m), 5.47 (1H, dd, J = 11.8, 2.0 Hz), 4.22 (1H, d, J = 16.2 Hz), 3.92 (3H,

s), 3.85-3.83 (1H, m), 3.42 (1H, dd, J = 16.5, 11.4 Hz), 2.71 (1H, dd, J = 16.5, 5.8 Hz), 2.60 (1H, d, J = 16.2 Hz), 2.46-2.34 (2H, m), 2.29 (1H, d, J = 12.0 Hz), 1.84-1.70 (2H, m).

((4a*R*,8a*S*)-1-(4-fluorophenyl)-6-((1-methyl-1H-pyrazol-3-yl)sulfonyl)-4,4a,5,6,7,8,8a,9-octahydro-1H-pyrazolo[3,4-g]isoquinolin-4a-yl)(4-(trifluoromethyl)pyridin-2-yl)methanone (55). Compound **55** was prepared using the same procedure as described for the synthesis of **12** by treating (4a*R*,8a*S*)-tert-butyl 1-(4-fluorophenyl)-4a-(4-(trifluoromethyl)picolinoyl)-4a,5,7,8,8a,9-hexahydro-1H-pyrazolo[3,4-g]isoquinoline-6(4H)-carboxylate **11** with TFA/DCM followed by 1-methyl-1H-pyrazole-3-sulfonyl chloride. LC/MS m/z 589 $(M+H)^+$; ^{1}H NMR ($CDCl_3$): δ 8.85 (1H, d, J = 5.0 Hz), 8.10-8.09 (1H, m), 7.65-7.63 (1H, m), 7.50-7.45 (2H, m), 7.38 (1H, d, J = 2.5 Hz), 7.34 (1H, s), 7.18-7.12 (2H, m), 6.55 (1H, d, J = 2.5 Hz), 5.57 (1H, dd, J = 11.8, 2.0 Hz), 4.27 (1H, d, J = 16.2 Hz), 3.97 (3H, s), 3.93-3.89 (1H, m), 3.44 (1H, dd, J = 16.2, 10.9 Hz), 2.71 (1H, dd, J = 16.4, 6.0 Hz), 2.63-2.55 (2H, m), 2.54 (1H, d, J = 12.2 Hz), 2.45-2.34 (1H, m), 1.82-1.74 (2H, m).

((4a*R*,8a*S*)-1-(4-fluorophenyl)-6-((1-methyl-1H-1,2,3-triazol-4-yl)sulfonyl)-4,4a,5,6,7,8,8a,9-octahydro-1H-pyrazolo[3,4-g]isoquinolin-4a-yl)(4-(trifluoromethyl)pyridin-2-yl)methanone (56). Compound **56** was prepared using the same procedure as described for the synthesis of **12** by treating (4a*R*,8a*S*)-tert-butyl 1-(4-fluorophenyl)-4a-(4-(trifluoromethyl)picolinoyl)-4a,5,7,8,8a,9-hexahydro-1H-pyrazolo[3,4-g]isoquinoline-6(4H)-carboxylate **11** with HCl/Dioxane followed by 1-methyl-1H-1,2,3-triazole-4-sulfonyl chloride **18**. LC/MS m/z 590 $(M+H)^+$; ^{1}H NMR ($CDCl_3$): δ8.85 (1H, d, J = 5.0 Hz), 8.11-8.10 (1H, m), 7.88 (1H, s), 7.66-7.65 (1H, m), 7.50-7.45 (2H, m), 7.34 (1H, s), 7.18-7.12 (2H, m), 5.68 (1H, dd, J = 12.6, 2.0 Hz), 4.26 (1H, d, J = 16.4 Hz), 4.15 (3H, s), 3.97-3.92 (1H, m), 3.43 (1H, dd, J = 16.4, 11.1 Hz), 2.78-2.70 (3H, m), 2.63 (1H, d, J = 16.2 Hz), 2.47-2.36 (1H, m), 1.87-1.78 (2H, m).

((4a*R*,8a*S*)-1-(4-fluorophenyl)-6-((1-methyl-1H-1,2,3-triazol-5-yl)sulfonyl)-4,4a,5,6,7,8,8a,9-octahydro-1H-pyrazolo[3,4-g]isoquinolin-4a-yl)(4-(trifluoromethyl)pyridin-2-yl)methanone (57). Compound **57** was prepared using the same procedure as described for the synthesis of **12** by treating (4a*R*,8a*S*)-tert-butyl 1-(4-fluorophenyl)-4a-(4-(trifluoromethyl)picolinoyl)-4a,5,7,8,8a,9-hexahydro-1H-pyrazolo[3,4-g]isoquinoline-6(4H)-carboxylate **11** with HCl/Dioxane followed by 1-methyl-1H-1,2,3-triazole-5-sulfonyl chloride **20**. LC/MS m/z 590 $(M+H)^+$; ^{1}H NMR ($CDCl_3$): δ8.77 (1H, d, J = 5.0 Hz), 8.04 (1H, m), 7.89 (1H, s), 7.69-7.67 (1H, m), 7.48-7.43 (2H, m), 7.28 (1H, s), 7.18-7.12 (2H, m), 5.59 (1H, dd, J = 12.6, 2.0 Hz), 4.12 (1H, d, J = 16.3 Hz), 4.06 (3H, s), 4.06-4.01 (1H, m), 3.35 (1H, dd, J = 16.4, 11.2 Hz), 2.82-2.72 (3H, m), 2.61 (1H, d, J = 16.2 Hz), 2.47-2.36 (1H, qd, J = 13.0, 5.2 Hz), 1.91-1.82 (2H, m).

((4a*R*,8a*S*)-6-((1-ethyl-1H-pyrazol-5-yl)sulfonyl)-1-(4-fluorophenyl)-4,4a,5,6,7,8,8a,9-octahydro-1H-pyrazolo[3,4-g]isoquinolin-4a-yl)(4-(trifluoromethyl)pyridin-2-yl)methanone (58). Compound **58** was prepared using the same procedure as described for the synthesis of **12** by treating (4a*R*,8a*S*)-tert-butyl 1-(4-fluorophenyl)-4a-(4-(trifluoromethyl)picolinoyl)-4a,5,7,8,8a,9-hexahydro-1H-pyrazolo[3,4-g]isoquinoline-6(4H)-carboxylate **11** with HCl/Dioxane followed by 1-ethyl-1H-pyrazole-5-sulfonyl chloride. LC/MS m/z 603 $(M+H)^+$; ^{1}H NMR ($CDCl_3$): δ8.78 (1H, d, J = 5.0 Hz), 8.07 (1H, m), 7.66-7.64 (1H, m), 7.49-7.44 (2H, m), 7.36 (1H, d, J = 2.0 Hz), 7.29 (1H, s), 7.18-7.12 (2H, m), 6.58 (1H, d, J = 2.0 Hz), 5.57 (1H, dd, J = 12.5, 2.0 Hz), 4.32 (3H, m), 3.98-3.94 (1H, m), 3.38 (1H, dd, J = 16.2, 10.8 Hz), 2.76-2.69 (2H, m), 2.66 (1H, d, J = 12.6 Hz), 2.61 (1H, d, J = 16.2 Hz), 2.51-2.40 (1H, m), 1.89-1.80 (2H, m), 1.39 (3H, t, J = 7.2 Hz).

Human GR Fluoresence Polarisation Assay

The concentrations of fluorescent glucocorticoid (Fluormone GS Red; Panvera P2894) ligand (K_d 0.3 ± .01 nM) and GR (Panvera P2812) were chosen so that the polarization signal was approximately 60% of the maximal response (0.5nM Fluormone GS Red and 1nM GR). Maximal response (high polarization) was measured in the presence of 1% (v/v) final DMSO and basal response (low polarization) was measured in the presence of 1μM dexamethasone. The assays were performed in duplicate using increasing concentrations of inhibitor compounds (0 – 100nM), at a final volume of 20μl and 1% (v/v) DMSO. The plates were mixed and incubated for 4 hours at room temperature.

All fluorescence polarization (FP) assays were performed on Perkin Elmer Envision 2104 Multiplate Reader. Corning 3575 384-well, black, non-binding surface, round-bottom, polypropylene micro titre plates were used loaded with 20μL of assay solution per well. For Fluormone GS Red, 535nm excitation and 590nm emission filters were used. The FP assays were performed in ice cold 10mM potassium phosphate (pH7.4), 20mM Na_2MoO_4, 0.1mM EDTA, 3% DMSO (PanVera P2814), 0.1mM stabilizing peptide (PanVera P2815) and 5μM DTT. All aqueous solutions were prepared using deionized water collected from a Millipore water purification system.

FP was determined by measuring the parallel and perpendicular fluorescence intensity ($F_{\parallel}$ and $F_{\perp}$) with respect to the linearly polarized excitation light. The milli fluorescence polarization (mP) is expressed by equation 1.

$$mP = 1000\left(\frac{F_{\parallel} - G(F_{\perp})}{F_{\parallel} + G(F_{\perp})}\right) \quad 1$$

Where $G\ factor\ (G) = (1.07)$

The percentage inhibition of the competitor at each concentration point was determined by using equation 2, and the IC_{50} of an inhibitor was determined from the plot of % inhibition against inhibitor concentration using equation 3.

$$\%\ inhibition = \left(\frac{mP_{max} - mP_{obs}}{mP_{max} - mP_{min}}\right) 100\% \quad (2)$$

$$mP = \frac{mP_{min} + (mP_{max} - mP_{min})}{1 + 10^{\left((\log IC_{50} - x)\ (Hill\ slope)\right)}} \quad (3)$$

Where $x = Log[inhibitor]$, $mP_{min} = 100\%\ inhibition$ and $mP_{max} = 0\%\ inhibition$

Compound IC_{50} values were calculated by plotting compound concentration v % inhibition curve and fitting the data to a 4-parameter, one-site dose-response equation. Compound K_i values were determined from the experimental IC_{50} values using a ligand depletion correction equation

$$K_i = \frac{(L_b) * (IC_{50}) * (K_d)}{(L_0) * (R_0) + L_b * (R_0 - L_0 + L_b - K_d)} \quad (4)$$

Where:

$Equilibrium\ dissociation\ constant\ of\ GS\ red\ ligand\ (K_d) = 0.3nM$

$Concentration\ of\ bound\ ligand\ (L_b) = 0.3nM$

$Total\ ligand\ concentration\ (L_o) = 0.5nM$

$Total\ receptor\ concentration\ (R_o) = 1.0nM$

The minimum significant ratio for this assay is 1.91, with limits of agreement between 0.46 and 1.69.

HepG2 TAT Assay

HepG2 cell lines were purchased from the European Collection of Authenticated Cell Cultures (ECACC 85011430). Cells were cultured in Minimum Essential Medium (MEME; Sigma; M2279) supplemented with 10% (v/v) foetal bovine serum (FBS; Gemini BioProducts), 2mM L-glutamine (Sigma; G7513) and 1% (v/v) non-essential amino acids (NEAA; Sigma; M7145). Cells were cultured at 37ºC in a humidified atmosphere with 5% CO_2.

HepG2 cells were counted and adjusted to a concentration of 1.25 x 10^5 cells/ml in growth media comprising of RPMI-1640 without phenol red, 10% (v/v) charcoal-stripped FBS, 2mM L-glutamine and a 200µl volume (25,000 cells/well) was added into a 96-well, sterile tissue culture plate and incubated at 37ºC, 5% CO_2 for 24 hours.

Growth media was carefully removed and replaced with assay media (RPMI-1640 without phenol red, 2mM L-glutamine + 10µM forskolin). For testing compounds in the antagonist mode, an 8-point half-log compound dilution curve was generated with a final assay concentration range from 10µM to 0.003µM in 0.1% DMSO. Test compounds were pre-incubated with HepG2 cells for 30-minutes at 37ºC, 5% CO_2, before the addition of 100nM dexamethasone challenge and then subsequently incubated for 20 hour (37ºC, 5% CO_2). For testing compounds in the agonist mode, an 8-point half-log compound dilution curve was generated with a final assay concentration range from 10µM to 0.003µM in 0.1% DMSO. HepG2 cells were pre-incubated with assay media containing 0.1% DMSO for 30-minutes at 37ºC, 5% CO_2, before the addition of test compounds and then subsequently incubated for 20 hours (37ºC, 5% CO_2).

HepG2 cells were then lysed with 30µl of cell lysis buffer containing a protease inhibitor cocktail for 15 minutes at 4ºC. 155µl of substrate mixture was then added containing 5.4mM Tyrosine Na salt, 10.8mM alpha ketoglutarate and 0.06mM pyridoxal 5' phosphate in 0.1M potassium phosphate buffer (pH 7.4). After 2 hours incubation at 37ºC, the reaction was terminated by the addition of 15µl of 10M KOH, and the plates incubated for a further 30 minutes at 37ºC. TAT activation was measured by reading the absorbance at lambda 340nm.

IC_{50} values were obtained by fitting percent inhibition of 100nM dexamethasone response versus compound concentration data to a four parameter, one-site dose–response equation. K_i values were calculated using the Cheng and Prusoff (1973) equation. EC_{50} values were obtained by fitting percent activation of basal TAT response versus compound concentration data to a four parameter, one-site dose–response equation. An EC_{50} value of 20nM for dexamethasone (which was measured on numerous occasions) was used to calculate the Ki values of the test compounds.

The assay variance was determined and the calculated minimum significant ratio (MSR) was 2.21 at the 95% confidence level, with the limits of agreement of MSR between 0.45 and 2.21. The overall standard deviation of the assay was <0.2.

Rat Cassette PK Studies

Three male Sprague Dawley CD-1 rats (220-250g, Charles River UK) with implanted jugular vein catheters were dosed by oral gavage with the selected three test compounds and a reference compound, with each compound administered at a dose of 3mg/kg. The compounds were formulated in DMSO:methylcellulose (0.5% in water), 10:90, at a concentration of 2.4mg/mL (0.6mg/mL for each compound) in a dosing volume of 5mL/kg. Serial blood samples were

collected pre-dose and at 0.25, 0.5, 1, 2, 4, 6, 8 and 24 hours post-dose for preparation of plasma and analysis of compound concentrations. Samples were analysed by LC/MS.

Rat i.v./p.o. PK Studies

Five male Sprague Dawley CD-1 rats (220-250g, Charles River UK) with implanted jugular vein catheters were dosed by oral gavage with the selected test compound. The compound was formulated in DMSO:methylcellulose (0.5% in water), 10:90, at a concentration of 1mg/mL for dosing by oral gavage. This provided a dose of 5mg/kg in a dosing volume of 5mL/kg. Serial blood samples were collected pre-dose and at 0.25, 0.5, 1, 2, 4, 6, 8 and 24 hours post-dose for preparation of plasma and analysis of compound concentrations. Three rats were used for i.v. dosing, and the compound was dissolved in DMSO:PEG400:propylene glycol, 10:45:45 and a concentration of 0.5mg/mL. . Serial blood samples were collected pre-dose and at 0.08, 0.25, 0.5, 1, 2, 4, 6, 8 and 24 hours post-dose for preparation of plasma and analysis of compound concentrations. Samples were analysed by LC/MS.

Cortisone-induced Insulin Resistance in Rats

Male Sprague Dawley rats (200-250g) underwent a three day baseline period in which they were dosed daily with vehicle. This procedure has been found to reduce the incidence of stress-induced effects in subsequent studies. Groups of eight rats were administered vehicle, cortisone 21-acetate alone, or cortisone 21-acetate and the appropriate test compound. Test compounds were formulated as a suspension in DMSO:Tween 80: HPMC (0.5%), 10:0.1:89.9 and administered twice a day for six days at the appropriate doses by oral gavage. Cortisone 21-acetate (formulated as a fine suspension in 1% methylcellulose) was administered once a day s.c

at a dose of 30mg/kg. Twenty-four hours after the final dose of cortisone 21-acetate (twelve hours after the final administration of test compound) blood samples were taken from the lateral tail vein for analysis of glucose and insulin. Glucose was measured using a commercial clinical reagent (Thermoelectron Infinity glucose reagent TR15421 and insulin was measured using the Mercodia ultrasensitive rat insulin ELISA. The rats were terminated by carbon dioxide asphyxiation followed by cervical dislocation.

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ABBREVIATIONS

GR = glucocorticoid receptor

GRE = glucocorticoid response element

PR = progesterone receptor

TAT = tyrosine amino transferase

SUPPORTING INFORMATION

Molecular formula strings

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