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Discovery of selective glucocorticoid receptor modulator MK-5932

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ABSTRACT

A series of partial agonists of the Glucocorticoid Receptor were prepared targeting reduced transactivation activity, while maintaining significant transrepression activity. Incorporation of an *ortho*-aryl amide produced compounds with the desired in vitro profile. Bioreactors consisting of Suspension cultures of Sf21 cells co expressing a CYP3A4 and NADPH-cytochrome P450 oxireductase were used to prepare the major metabolites of these compounds and revealed that oxidative N-dealkylation provided a pathway for formation of metabolites that were more agonistic than the parent partial agonists. Oxidative N-dealkylation was blocked in a new series of compounds, however oxidation alone was capable of producing full agonist metabolites. Incorporation of an *ortho*-primary amide and utilization of fluorine to modulate agonism afforded partial agonist MK-5932. Synthesis of the major metabolites of MK-5932 using bioreactor technology revealed that no significant GR-active metabolites were formed. Orally administered MK-5932 displayed anti-inflammatory efficacy in a Rat Oxazolone-induced chronic dermatitis model, while sparing plasma insulin.

1. Introduction

Glucocorticoids are some of the most commonly prescribed drugs for the treatment of inflammatory and immunological disorders such as asthma[1] and rheumatoid arthritis.[2] Unfortunately, chronic use of these therapeutic agents carries significant risks in the form of the accompanying serious, sometimes irreversible side effects.[3] These include, but are not limited to, osteoporosis,[4] diabetes,[5] glaucoma,[6] and muscle atrophy.[7,8] Efforts to discover novel ways to minimize these undesirable side effects while maintaining the desired anti-inflammatory activity are ongoing. One of the earliest advances toward this goal was the design of new ligands that offer improved selectivity for the glucocorticoid receptor (GR) over other nuclear hormone receptors such as the Mineralocorticoid Receptor (MR), however GR mediated side effects still remained a problem.[9] Topical[10] and inhaled[11] delivery of Glucocorticoids has provided a means for reducing their systemic side effects, thus increasing the therapeutic window for drugs administered by this route. However, not all diseases are amenable to topical or inhaled routes of administration. A novel approach to safely treating inflammatory diseases with Glucocorticoids would be the use of so-termed selective glucocorticoid receptor modulators (SEGRM's). A SEGRM is a molecule designed to activate only a subset of the functions induced by the endogenous ligand in hope of retaining the desired anti-inflammatory benefits, while reducing the undesirable side effects.[12]

In order to formulate an appropriate target in vitro profile for a SEGRM, the current state of glucocorticoid (GC) biology needs to be considered. The GR resides in the cytoplasm in an inactive form associated with various heat shock proteins and other chaperones.[13] GR ligands, after passing through the plasma membrane, bind to the GR resulting in formation of an activated ligand/receptor complex. This activated complex dissociates from some, but not all, of the associated proteins and translocates into the cell nucleus.[14] In its homodimeric form,[15] the activated GR-ligand complex can positively regulate target genes by binding to specific DNA binding sites, referred to as positive glucocorticoid responsive elements (GRE's).[16] This process, termed transactivation, results in the synthesis of both anti-inflammatory proteins, such as Lipocortin-1[17], along with regulator proteins, such as tyrosine aminotransferase (TAT)[18] and phosphoenolpyruvate carboxykinase (PEPCK)[19] which are enzymes involved in gluconeogenesis. Transactivation is thought to play a minor role in eliciting the desired anti-inflammatory action of Glucocorticoids and a more important role in producing the numerous side effects of these drugs. The negative regulation of target genes by the GR is more complicated and can occur through multiple mechanisms. For example, the activated

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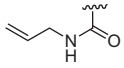
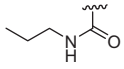
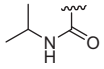
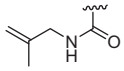
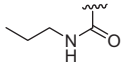
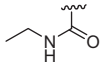
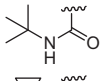
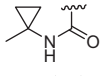
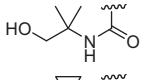
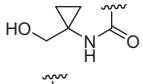
GR-ligand complex can bind to negative GRE's and possibly interfere with the binding of transcription factors, leading to repression of transcription, as has been documented for the regulation of osteocalcin.[20,21] Alternatively, the activated GR-ligand monomer can interact directly (i.e., protein–protein interaction) with transcription factors such as AP-1[22] or NF-κB[23] that are involved in regulating the expression of pro-inflammatory cytokines and inflammatory mediators such as interleukin-1 (IL-1) and tumor necrosis factor-α (TNF-α). This pathway, termed transrepression, does not require binding of the GR to DNA and is thought to play a major role in producing the desired anti-inflammatory activity of Glucocorticoids. The concept that transactivation and transrepression are mechanistically separable has been probed by mutation of the GR in the DNA binding domain. This prevents transactivation, without altering transrepression of AP-1.[24] Accordingly, compounds that exhibit reduced transactivation activity, while maintaining significant transrepression activity, may retain the desired anti-inflammatory activity of current glucocorticoids, with a reduced propensity to induce one or more of the undesirable side effects associated with these compounds.[25] Efforts toward developing such SEGRM's are ongoing, and some promising in vitro and in vivo data has been reported, however clinical proof-of-concept in patients has yet to be achieved.[26]

Our efforts in this area were inspired by reports describing the discovery of C,D-ring truncated analogues of Fluorocortivazol as non-steroidal dissociating GR ligands, shown in Figure 1. It was hypothesized that the steroidal C- and D-rings could be effectively mimicked by incorporation of an appropriate aryl group such as in **2**, or arylethyl group such as in **3**.[27,28] We began our efforts with an analysis of an overlay of compounds such as **3** with the crystal structure of dexamethasone in the human GR ligand binding domain.[29] This revealed that although a simple arylethyl group is an effective mimic of the hydrophobic component of the steroidal C,D-rings, key hydrogen bonding interactions, between the polar functional groups on the D-ring of dexamethasone and residues Q642 and T739, were not being made by compounds such as **3**. Thus, the starting point for our Medicinal Chemistry efforts was to incorporate a substituent capable of hydrogen bonding on the right hand side aryl ring of **3** to potentially rediscover the hydrogen bonding interactions which were lost during the truncation of **1** to afford **3**.

2. Chemistry

Synthesis of our target molecules was designed to enable late stage incorporation of substituted phenethyl substituents via a Sonagashira/Hydrogenation protocol. Synthesis of the Sonagashira precursor was carried out as detailed in Scheme 1. Addition of lithium TMS-acetylide to the Hajos-Parrish Ketone[30] afforded tertiary alcohol **4**. Low temperature formylation of **4**, followed by silyl deprotection of the acetylene produced the desired β-ketoaldehyde **5**. Treatment of crude **5** with *p*-fluororphenylhydrazine hydrochloride and NaOAc in acetic acid afforded the desired indazole acetylene **6**.

Table 1
Compounds described in Scheme 2

Compound	R_1	R_2	R_3	R_4	R_5
7a, **8a**	CO_2Me	H	H	H	H
7b, **8b**	H	CO_2Et	H	H	H
7c, **8c**	H	H	CO_2Me	H	H
7d, **8d**	CO_2Me	F	H	H	H
7e, **8e**	CO_2Me	H	F	H	H
7f, **8f**	CO_2Me	H	H	F	H
9a	CO_2H	H	H	H	H
9b	H	CO_2H	H	H	H
9c	H	H	CO_2H	H	H
9d	CO_2H	F	H	H	H
9e	CO_2H	H	F	H	H
9f	CO_2H	H	H	F	H
10a		H	H	H	H
10b	H		H	H	H
10c	H	H		H	H
10d		H	H	H	H
10e		H	H	H	H
10f		H	H	H	H
10g		F	H	H	H
10h		F	H	H	H
10i		H	H	H	H
10j		H	H	H	H
10k		H	H	H	H
10l		F	H	H	H
10m		H	H	H	H
10n		F	H	H	H
10o		F	H	H	H
10p		H	F	H	H
10q		H	H	F	H
10r		H	H	H	F

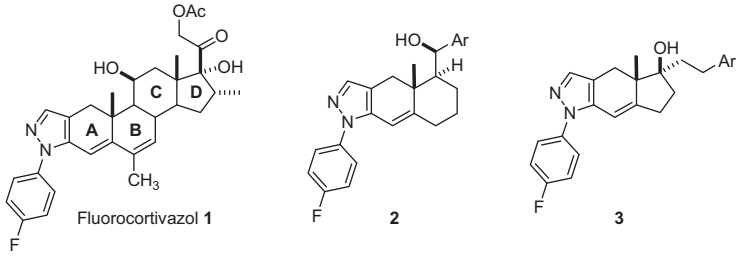
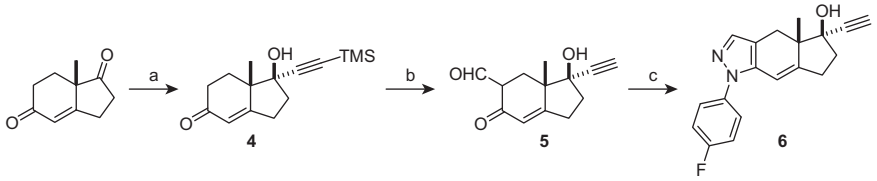
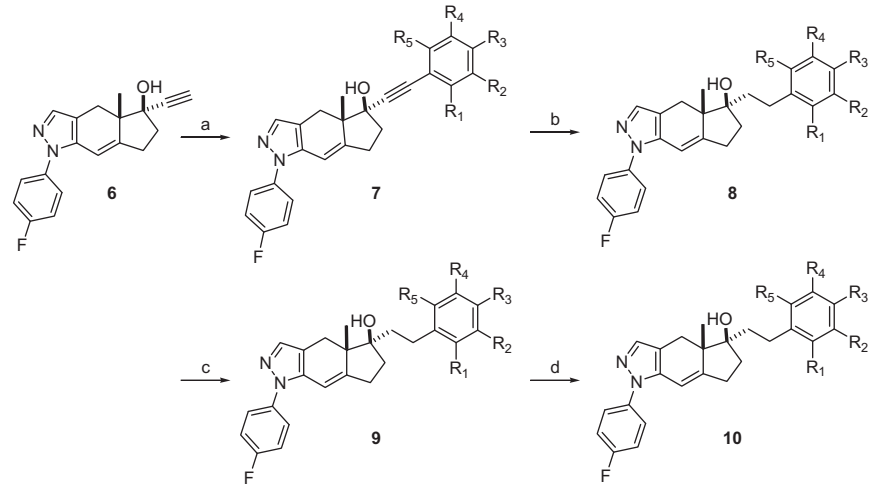


Figure 1. Fluorocortivazol **1** and truncated analogues **2** and **3**.



Scheme 1. Reagents and conditions: (a) ^{n}BuLi, TMS-acetylene, THF, −78 °C, 80% (b) (i) LDA, ethyl formate, THF,−78 °C; (ii) K_2CO_3, MeOH, rt, 75%; (c) *p*-fluorophenylhydrazine·HCl, NaOAc, HOAc, rt, 94%.



Scheme 2. Reagents and conditions: (a) 2% $(PPh_3)_2PdCl_2$, 2% CuI, ArX, $^{i}Pr_2NH$, THF, 80 °C; (b) 10% Pd/C, H_2 balloon, rt; (c) 1 M NaOH, EtOH, 100 °C; (d) R^3NH_2, HATU, $^{i}Pr_2NEt$, DMF, rt.

With the ultimate goal of incorporating a small alkyl amide as the hydrogen bonding substituent, our general synthetic approach is outlined in Scheme 2. The appropriate aryl halides were coupled with **6** to afford acetylenes **7a–q**. Subsequent hydrogenation afforded the desired phenethyl esters **8a–q**, which were readily hydrolyzed to afford acids **9a–q**. The desired targets were obtained via HATU coupling of acids **9a**–**q** with appropriate amines to afford amides **10a**–**q** (Table 1).[31]

3. Results

Compounds **10a**–**c**, shown in Figure 2, were evaluated for GR activity in a binding assay and transcriptional activity was evaluated using the glucocorticoid induced TNF-α repression assay and Glucocorticoid regulation and modulation of MMTV assay to afford a measure of transrepression and transactivation activity, respectively. It is evident from the data in Table 2 for compounds **10a–c** that the preferred position for a hydrogen bonding substituent is the *ortho* position with respect to the phenethyl linker.

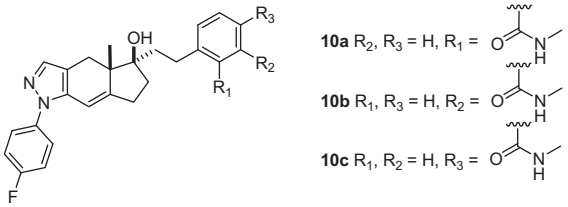


Figure 2. Regioisomeric arylamides **10a**–**c**.

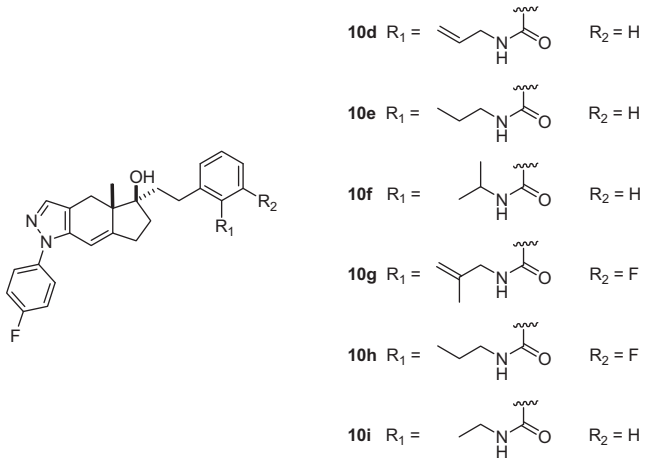


Figure 3. Arylamides **10d**–**i**.

Table 2
In vitro data for regioisomeric aryl amides

Compound	GRBind[32] K_i (nM)	TNF-α repression[33]		MMTV (A549)[34]		MMTV (HeLa)[35]	
		IP (nM)	E_{max} (%dex)	IP (nM)	E_{max} (%dex)	IP (nM)	E_{max} (%dex)
10a	2	263	50	193	49	317	48
10b	15	nd	<10	nd	<10	nd	<10
10c	155	nd	12	nd	<10	nd	<10

Table 3
Binding and transcriptional data for *ortho*-arylamides **10d–i**

Compound	GRBind[32] K_i (nM)	TNF-α repression[33]		MMTV (A549)[34]		MMTV (HeLa)[35]	
		IP (nM)	E_{max} (%dex)	IP (nM)	E_{max} (%dex)	IP (nM)	E_{max} (%dex)
10d	1	123	62	62	37	93	21
10e	2	127	50	81	29	85	17
10f	4	170	62	60	48	83	30
10g	<1	119	67	95	24	132	16
10h	<1	30	72	26	25	43	17
10i	2	88	65	39	51	107	38

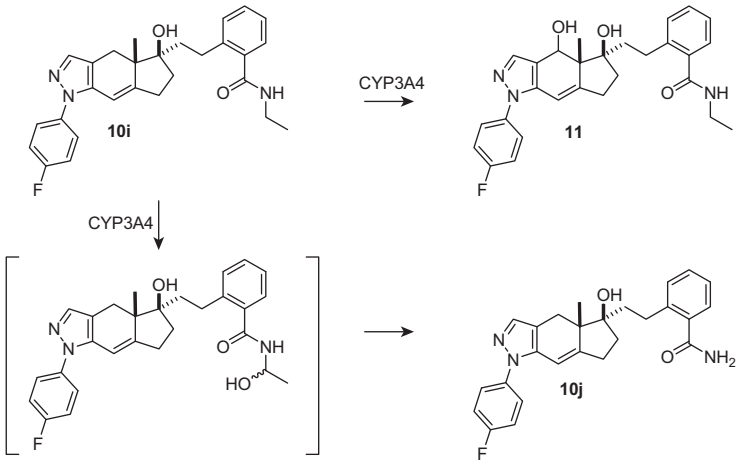


Figure 4. Major metabolites of **10i**.

Table 4
In vitro data for **10i** and metabolites **10j** and **11**

Compound	GRBind[32] K_i (nM)	TNF-α repression[33]		MMTV (A549)[34]		MMTV (HeLa)[35]	
		IP (nM)	E_{max} (%dex)	IP (nM)	E_{max} (%dex)	IP (nM)	E_{max} (%dex)
10i	2	88	65	39	51	107	38
10j	2	56	82	61	60	130	66
11	40	958	34	1564	20	1325	6

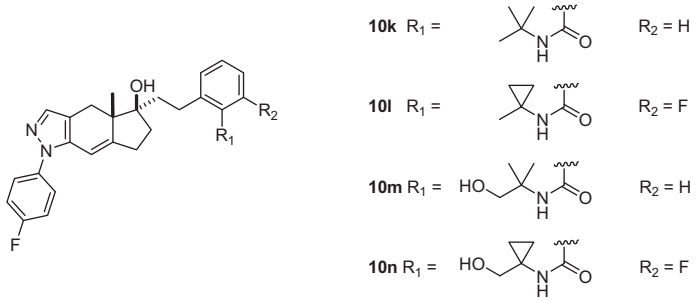
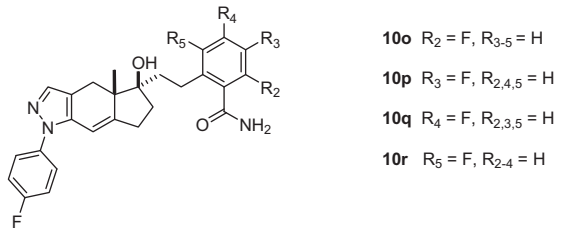


Figure 5. Arylamides **10k–n**.

Table 5
Compounds incapable of oxidative N-dealkylation

Compound	GRBind[32] K_i (nM)	TNF-α repression[33]		MMTV (A549)[34]		MMTV (HeLa)[35]	
		IP (nM)	E_{max} (%dex)	IP (nM)	E_{max} (%dex)	IP (nM)	E_{max} (%dex)
10k	10	246	79	212	23	108	14
10l	<1	20	81	32	41	27	33
10m	1	26	88	33	83	30	71
10n	3	24	96	23	104	35	79



10o R_2 = F, $R_{3\text{-}5}$ = H

10p R_3 = F, $R_{2,4,5}$ = H

10q R_4 = F, $R_{2,3,5}$ = H

10r R_5 = F, $R_{2\text{-}4}$ = H

Figure 6. Arylamides **10o–r**.

Encouraged by this result we prepared the series of compounds, shown in Figure 3, containing an *ortho*-arylamide substituent. Pleasingly, a number of compounds were generated that displayed reduced activity in the transactivation assay, while maintaining potency and activity in the transrepression assay as shown in Table 3.

Of particular concern moving forward was the potential for compounds to undergo metabolic transformations in an in vivo setting and produce metabolites that displayed GR activity. As we sought partial agonists of the GR, active metabolites that behave as antagonists could block the desired anti-inflammatory activity of the parent molecule. On the contrary, metabolites that behave as full agonists could erode any potential separation of anti-inflammatory activity from adverse effects that might be characteristic of the parent partial agonist. Accordingly, we sought a method to generate sufficient quantities of metabolites to enable structural elucidation in addition to testing for GR activity in our in vitro assays. The synthesis of milligram quantities of P450-generated metabolites has been accomplished by employing so termed 'bioreactors' consisting of a suspension culture of Sf21 insect cells, co-infected with baculovirus containing the cDNA for a single cytochrome P450, and NADPH-cytochrome P450 oxireductase.[36] We chose to evaluate the metabolic profile of compound **10i** in a CYP3A4 bioreactor system. The metabolic profile of **10i** is outlined in Figure 4. Cytochrome P450 mediated hydroxylation at the 4-position affords **11**, a compound with much weaker binding affinity than the parent and very little transcriptional activity. However, oxidative N-dealkylation of the aryl amide moiety afforded the primary amide **10j**, a compound that exhibits a higher level of agonism than the parent. Thus, oxidative N-dealkylation provides a mechanism for generation of metabolites more agonistic than the parent molecule, and renders compounds capable of this transformation unsuitable for further development. This was exemplified when **10i** was dosed at 20 mpk in a Rat Oxazolone-induced chronic dermatitis model.[37] Compound **10i** achieved exposure of 75 μM h, however GR active compound **10j** was also present at an exposure of 50 μM h thereby confounding interpretation of the in vivo result. Consistent in vivo results could not be obtained with compound **10i** possibly due to the presence of metabolite **10j**. Metabolite **10j** was independently tested in the Rat Oxazolone-induced chronic dermatitis model and at doses of 5 and 25 mpk and achieved exposures of 134 and 199 μM h, respectively. While **10j**

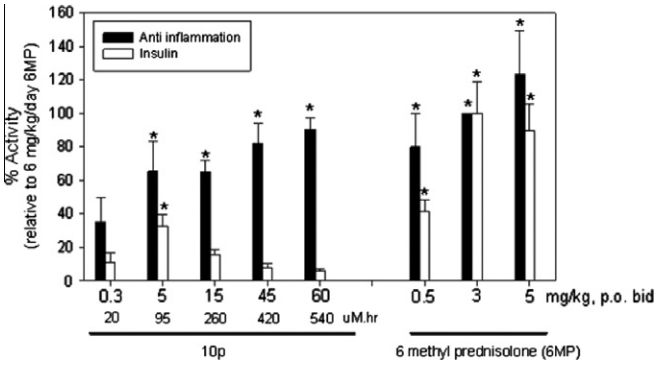


Figure 7. In vivo activity of **10p** in the Rat Oxazolone-induced chronic dermatitis model.

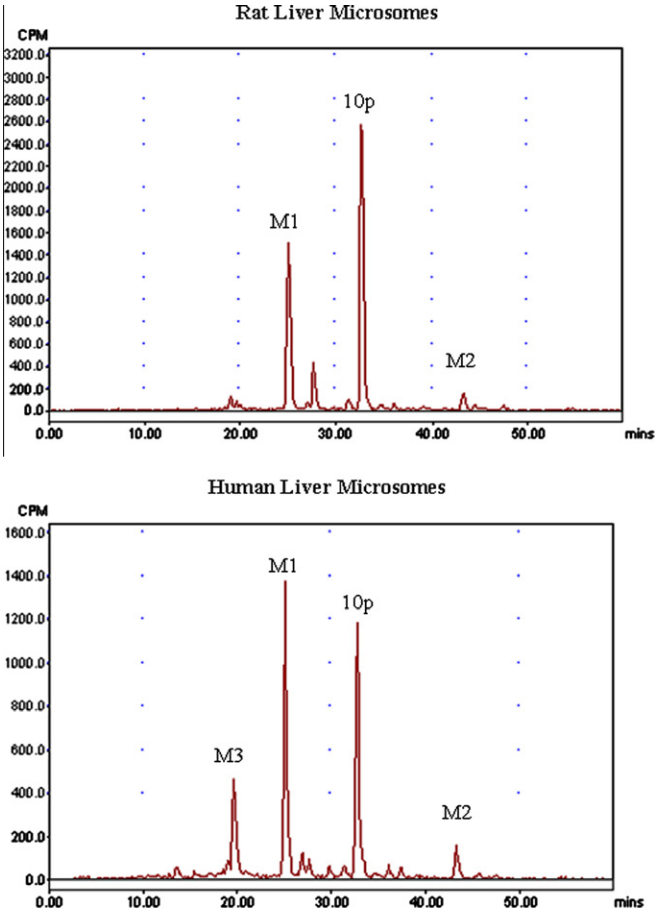
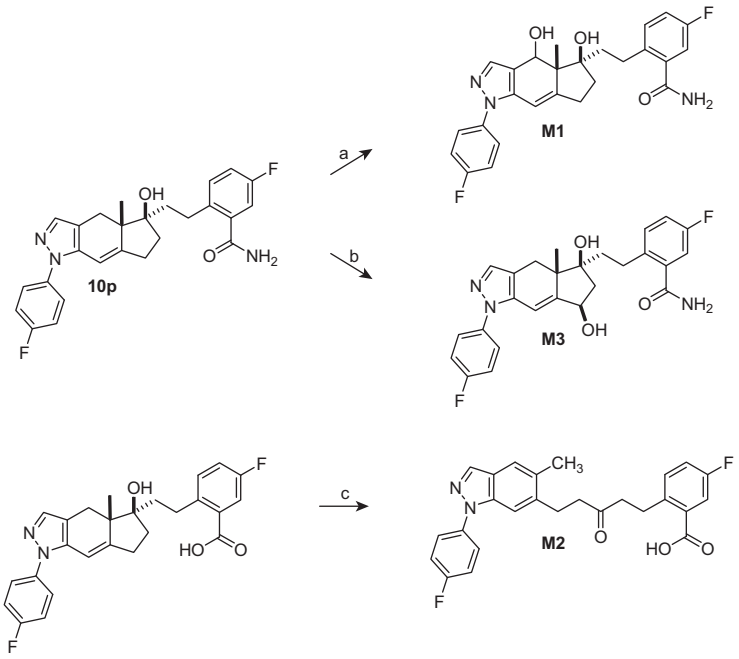


Figure 8. LC–MS traces from in vitro metabolic profiling of **10m** in the rat and human liver microsomes.

Table 6
Modulation of agonism by fluorine incorporation

Compound	GRBind[32]	TNF-α repression[33]		MMTV (A549)[34]		MMTV (HeLa)[35]	
		IP (nM)	E_{max} (%dex)	IP (nM)	E_{max} (%dex)	IP (nM)	E_{max} (%dex)
10j	2	56	82	61	60	130	66
10o	<1	10	84	9	75	11	58
10p	3	131	73	186	35	153	23
10q	<1	89	70	36	120	58	47
10r	<1	3	90	6	82	7	89



Scheme 3. Reagents and conditions: (a) CYP3A4 bioreactor; (b) (i) SeO2, dioxane, 50 °C, 65%; (ii) Dess–Martin, CH_2Cl_2, rt, 94%; (iii) $NaBH_4$, EtOH, 0 °C, 41%. (c) DDQ, HOAc, rt, quant.

Table 7
In vitro profiles of key metabolites of **MK-5932**

Compound	GRBind[32]	TNF-α repression[33]		MMTV (A549)[34]		MMTV (HeLa)[35]	
		IP (nM)	E_{max} (%dex)	IP (nM)	E_{max} (%dex)	IP (nM)	E_{max} (%dex)
MK-5932	3	131	73	186	35	153	23
M1	58	nd	6	nd	<5	nd	<5
M2	>400	nd	<5	nd	<5	nd	<5
M3	>400	nd	<5	nd	<5	nd	<5

displayed significant anti-inflammatory activity, the compound also produced significant effects on plasma insulin at both doses, confirming its ability to interfere with our ability to interpret the in vivo effects of **10i** (Table 4).

In order to minimize the risk of active metabolite generation a series of compounds incapable of undergoing the undesirable oxidative N-dealkylation were prepared as shown in Figure 5. As shown in Table 5, compounds **10k** and **10l** possessed an in vitro profile which we envisioned would afford separation of anti-inflammatory activity from adverse effects in an in vivo setting. When compound **10l** was evaluated at a dose of 15 mpk in the Rat Oxazolone-induced chronic dermatitis model an exposure of 64 μM h was achieved. However, much to our dismay full agonist metabolite **10n** was also detected at an exposure of 3.8 μM h making the overall in vivo readout difficult to interpret.

Guided by the above results it seemed that it was not plausible to have a functional group in the *ortho*-position of the aryl moiety that was capable of undergoing metabolic oxidation. With this in mind we sought a compound containing a primary amide in the *ortho*-position that exhibited the desired dissociation profile. It was reasoned that introduction of a fluorine into the appropriate position of the RHS aryl ring of **10j** may perturb the receptor enough to afford a compound of the desired profile. Accordingly, compounds **10k–n** in Figure 6 were synthesized and gratifyingly compound **10p** afforded a promising in vitro profile, as shown in Table 6, that prompted us to further evaluate it in an in vivo setting.

Compound **10p** was evaluated in the Rat Oxazolone-induced chronic dermatitis model[37] as depicted below in Figure 7. Following oral administration (90:10 PEG400/H_2O) it was shown that **10p** was capable of producing an anti-inflammatory response similar to that produced by 6MP. Interestingly, it was shown that although retaining significant anti-inflammatory activity, **10p** produced no dose responsive effects on plasma insulin. This is in direct contrast to 6MP which significantly elevated plasma insulin levels.

Although encouraged by this result we wanted to examine the potential of **10p** to produce active metabolites as this could significantly affect the compound's ability to retain the observed SEGRM activity when moving across species. In order to evaluate this potential, liver microsome incubations were carried out on radiolabelled **10p**, the results of which are presented in Figure 8.

One major metabolite **M1**, and a minor metabolite **M2**, were present in both rat and human microsome incubations. Of particular concern was metabolite **M3** which was present in human but not rat incubations. Thus it was important for us to establish the identity and in vitro profile of **M1**, **M2**, and particularly of **M3** whose GR activity may not have been captured in our rat in vivo model. The identity of **M1**, **M2**, and **M3** were established by a combination of human P450 bioreactor incubations and chemical synthesis as outlined in Scheme 3.

Metabolite **M1** was isolated from a CYP3A4 bioreactor incubation, and was shown to be a C4-hydroxylated species, similar to what was observed for **10i**. Metabolites **M2** and **M3** were prepared by chemical synthesis. The in vitro data for **M1**, **M2**, and **M3** is shown in Table 7.

Pleasingly none of the observed in vitro metabolites displayed any significant activity in the GR transcriptional assays. In addition to this, aside from metabolites **M1**, **M2**, and **M3**, no significant levels of additional circulating metabolites were observed in vivo in rats. These observations pave the way for evaluation of **10p**, now designated **MK-5932**, in advanced studies to validate the SEGRM hypothesis. Further results pertaining to the Biological activity of **MK-5932** will be reported in due course.

4. Conclusion

A series of *ortho*-amide containing compounds were prepared that offered promising in vitro profiles. Bioreactor guided optimization of the structures to minimize formation of active metabolites led to incorporation of a primary amide as metabolically tolerable functionality. Incorporation of fluorine to modulate agonism produced **MK-5932**, an orally efficacious SEGRM capable of producing significant anti-inflammatory activity, while producing no effects on plasma insulin levels in the Rat Oxazolone-induced chronic dermatitis model.

5. Experimental

5.1. Chemistry

All commercially available reagents and solvents were used without further purification unless otherwise stated. Automated flash chromatography was performed on an Isco CombiFlash® Companion™ using Redisep® disposable flash cartridges with peak detection at 254 nm. Reverse phase purification was accomplished using a Gilson 215 liquid handler equipped with Gemini C18 column (20 × 100 mm or 30 × 100 mm I.D., 5 μm) with a 0.1% TFA in water/acetonitrile gradient. Peak collection was triggered by UV detection at 215 or 254 nm. ^{1}H NMR spectra were recorded on a Unity Inova 500 instrument operating at 500 MHz with tetramethylsilane or residual protiated solvent used as a reference. Analytical LC was performed on a Waters 2695 separations module (YMC Pro C18 column, 50 × 3 mm I.D., S-5 μM, 12 nm particle size); 0.05% TFA in water/acetonitrile gradient; UV detection @ 215 and 254 nm). Low resolution mass spectra were recorded using a Waters Micromass ZQ with electrospray ionization. High resolution mass spectra were recorded using electrospray ionization (ESI) on a 7T Fourier transform ion cyclotron resonance (FTICR) mass spectrometer. Unless otherwise noted, all reactions were conducted in flame dried glassware.

5.1.1. (1*S*,7a*S*)-1-Hydroxy-7a-methyl-1-[(trimethylsilyl)ethynyl]-1,2,3,6,7,7a-hexahydro-5*H*-inden-5-one (4)

A 2.5 M solution of ^{n}BuLi (27.4 mL, 68.5 mmol) in hexanes was added dropwise to a solution of trimethylsilylacetylene (9.48 mL, 68.5 mmol) in THF (90 mL) at −78 °C. The resulting solution was stirred at −78 °C for 30 min, then a solution of Hajos-Parrish Ketone (1–1, 7.5 g, 45.7 mmol) in THF (90 mL) was added and the resulting solution stirred at −78 °C for 30 min. The reaction was quenched with saturated aqueous KH_2PO_4 and the crude product extracted with EtOAc (×3). The combined organic extracts were dried over anhydrous $MgSO_4$ and the solvent removed in vacuo. Purification by flash chromatography on 120 g of silica, eluting with a gradient of 0–55% EtOAc in hexanes afforded 9.54 g, 80% of **4** as a white solid. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 5.80 (t, J = 2.0 Hz, 1H), 2.70 (ddd, J = 19.5, 9.0, 2.2 Hz, 1H), 2.40–2.60 (m, 4H), 2.24 (m, 2H), 1.85 (m, 1H), 1.21 (s, 3H), 0.11 (s, 9H). MS (ESI): m/z = 263.25 (MH^+), 100% pure by LC–MS.

5.1.2. (3*R*,3a*S*)-3-Ethynyl-3-hydroxy-3a-methyl-6-oxo-2,3,3a,4,5,6-hexahydro-1*H*-indene-5-carbaldehyde (5)

A 1.5 M solution of lithium diisopropylamide mono(tetrahydrofuran) in cyclohexane (121 mL, 182 mmol) was added to a solution of **4** (9.54 g, 36.4 mmol) in THF (400 mL) at −78 °C and the resulting solution stirred at this temperature for 1 h to afford a thick suspension. Methyl formate (22.6 mL, 364 mmol) was added dropwise over about 15 min and the resulting suspension stirred at −78 °C for 5 h. The reaction was quenched at −78 °C with 1 M aqueous HCl solution and the aqueous layer checked to ensure it was acidic. The crude product was extracted with EtOAc (×3) and the combined organic extracts were dried over anhydrous $MgSO_4$ and the solvent removed in vacuo to afford crude the crude product, MS (ESI): m/z = 291.18 (MH^+), 78% pure by LC–MS, that was used directly in the next step without purification. Removal of the TMS-group was accomplished by adding K_2CO_3 (5.03 g, 72.8 mmol) to a solution of the crude material in MeOH (300 mL), and stirring the resulting suspension stirred at ambient temperature for 90 min. The MeOH was removed in vacuo and 1 M aqueous HCl was added to the residue and the crude product extracted with EtOAc (×3). The combined organic extracts were dried over anhydrous $MgSO_4$ and the solvent removed in vacuo. Purification by flash chromatography on 330 g of silica, eluting with a gradient of 0–70% EtOAc in hexanes afforded 5.94 g, 75% of **5** as a tan solid. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.38 (s, 1H), 5.89 (t, J = 1.95 Hz, 1H), 3.15 (d, J = 13.9 Hz, 1H), 2.69 (s, 1H), 2.58–2.75 (m, 2H), 2.20–2.33 (m, 3H), 1.87 (s, OH), 1.14 (s, 3H). MS (ESI): m/z = 219.25 (MH^+), 100% pure by LC–MS.

5.1.3. (4a*S*,5*R*)-5-Ethynyl-1-(4-fluorophenyl)-4a-methyl-1,4,4a,5,6,7-hexahydrocyclopenta[*f*]indazol-5-ol (6)

NaOAc (41.3 g, 504 mmol) was added to a solution of **5** (100 g, 458 mmol) and 4-fluorophenylhydrazine hydrochloride (**1**–**5**) (82 g, 504 mmol) in acetic acid (916 mL) and the resulting suspension stirred at ambient temperature for 1 h. The reaction was quenched slowly (caution CO_2 evolution) with saturated aqueous $NaHCO_3$ solution and the crude product extracted with EtOAc (×3). The combined organic extracts were dried over anhydrous $MgSO_4$ and the solvent removed in vacuo. Purification by flash chromatography on 1.5 kg of silica, eluting with a gradient of 0–100% EtOAc in hexanes afforded 133 g, 94% of **6** as a tan solid. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.45 (m, 2H), 7.43 (s, 1H), 7.15 (M, 2H), 6.18 (m, 1H), 3.35 (d, J = 15.4 Hz, 1H), 2.70 (s, 1H), 2.62 (d, J = 15.6 Hz, 1H), 2.54–2.62 (m, 2H), 2.23–2.32 (m, 2H), 1.73 (s, OH), 1.14 (s, 3H). MS (ESI): m/z = 309.2 (MH^+), 100% pure by LC–MS.

5.1.4. General procedure for the synthesis of acetylenes 7a–g

Diisopropylamine (1.0 equiv) was added to a solution of **6** (1.0 equiv), aryl halide (1.2 equiv), bis(triphenylphosphine)palladium(II) chloride (2 mol %), and CuI (2 mol %) in anhydrous THF (0.25 M) at ambient temperature. The resulting solution was stirred at 80 °C for 1 h, then diluted with diethyl ether, filtered through a pad of celite, and the solvent removed in vacuo. Purification by flash chromatography on silica, eluting with a gradient of 0–100% EtOAc in hexanes afforded the desired products.

5.1.4.1. Methyl 2-{[(4a*S*,5*R*)-1-(4-fluorophenyl)-5-hydroxy-4a-methyl-1,4,4a,5,6,7-hexahydrocyclopenta[*f*]indazol-5-yl]ethynyl}benzoate (7a). 91% Yield; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.91 (dd, J = 7.8, 1.2 Hz, 1H), 7.43 (s, 1H), 7.41–7.49 (m, 5H), 7.35 (td, J = 7.8, 1.5 Hz, 2H), 6.20 (t, J = 2.0 Hz, 1H), 3.84 (s, 3H), 3.43 (d, J = 15.6 Hz, 1H), 2.77 (s, OH), 2.72 (d, J = 15.4 Hz, 1H), 2.65–2.69 (m, 2H), 2.05–2.45 (m, 2H), 1.21 (s, 3H); MS (ESI): m/z = 443.14 (MH^+), 100% pure by LC–MS.

5.1.4.2. Ethyl 3-{[(4a*S*,5*R*)-1-(4-fluorophenyl)-5-hydroxy-4a-methyl-1,4,4a,5,6,7-hexahydrocyclopenta[*f*]indazol-5-yl]ethynyl}benzoate (7b). 91% Yield; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.05 (m, 1H), 7.97 (m, 1H), 7.56 (dt, J = 7.8, 1.5 Hz, 1H), 7.45 (s, 1H), 7.45–7.48 (m, 2H), 7.37 (t, J = 7.8 Hz, 1H), 7.15 (m, 2H), 6.21 (m, 1H), 4.37 (q, J = 7.1 z, 2H), 3.41 (d, J = 15.4 Hz, 1H), 2.71 (d, J = 15.4 Hz, 1H), 2.62–2.68 (m, 2H), 2.32–2.44 (m, 2H), 2.28 (s, OH), 1.39 (t, J = 7.1 Hz, 3H), 1.19 (s, 3H); MS (ESI): m/z = 457.15 (MH^+), 100% pure by LC–MS.

5.1.4.3. Methyl 4-{[(4a*S*,5*R*)-1-(4-fluorophenyl)-5-hydroxy-4a-methyl-1,4,4a,5,6,7-hexahydrocyclopenta[*f*]indazol-5-yl]ethynyl}benzoate (7c). 98% Yield; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.95 (m, 2H), 7.45 (s, 1H), 7.43–7.48 (m, 4H), 7.15 (t, J = 8.5 Hz, 2H), 6.21 (m, 1H), 3.91 (s, 3H), 3.39 (d, J = 15.4 Hz, 1H), 2.71 (d, J = 15.4 Hz, 1H), 2.58–2.70 (m, 2H), 2.35–2.42 (m, 2H), 2.33 (s, OH), 1.19 (s, 3H); MS (ESI): m/z = 443.14 (MH^+), 100% pure by LC–MS.

5.1.4.4. Methyl 2-fluoro-6-{[(4a*S*,5*R*)-1-(4-fluorophenyl)-5-hydroxy-4a-methyl-1,4,4a,5,6,7-hexahydrocyclopenta[*f*]indazol-5-yl]ethynyl}benzoate (7d). 90% Yield; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.44–7.46 (m, 1H), 7.43 (s, 1H), 7.31–7.36 (m, 1H), 7.33 (m, 1H), 7.24 (dd, J = 7.8, 0.8 Hz, 1H), 7.15 (m, 2H), 7.08 (td, J = 8.8, 1.0 Hz, 1H), 6.20 (t, J = 2.0 Hz, 1H), 3.80 (s, 3H), 3.33 (d, J = 15.4 Hz, 1H), 2.69 (d, J = 15.4 Hz, 1H), 2.61–2.66 (m, 2H), 2.55 (s, OH), 2.34–2.37 (m, 2H), 1.18 (s, 3H); MS (ESI): m/z = 461.15 (MH^+); 100% pure by LC–MS.

5.1.4.5. Methyl 5-fluoro-2-{[(4a*S*,5*R*)-1-(4-fluorophenyl)-5-hydroxy-4a-methyl-1,4,4a,5,6,7-hexahydrocyclopenta[*f*]indazol-5-yl]ethynyl}benzoate (7e). 100% Yield; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.61 (m, 1H), 7.42–7.47 (m, 4H), 7.11–7.16 (m, 3H), 6.19 (m, 1H), 3.84 (s, 3H), 3.41 (d, J = 15.4 Hz, 1H), 2.71 (d, J = 15.4 Hz, 1H), 2.64–2.68 (m, 2H), 2.35–2.42 (, 2H), 1.20 (s, 3H); MS (ESI): m/z = 461.16 (MH^+); 100% pure by LC–MS.

5.1.4.6. Methyl 4-fluoro-2-{[(4a*S*,5*R*)-1-(4-fluorophenyl)-5-hydroxy-4a-methyl-1,4,4a,5,6,7-hexahydrocyclopenta[*f*]indazol-5-yl]ethynyl}benzoate (7f). 92% Yield; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.95 (dd, J = 8.8, 5.9 Hz, 1H), 7.46 (dd, J = 9.0, 4.9 z, 2H), 7.43 (s, 1H), 7.13–7.26 (m, 3H), 7.04 (dd, J = 8.3, 2.7 Hz, 1H), 6.21 (m, 1H), 3.84 (s, 3H), 3.39 (d, J = 15.4 Hz, 1H), 2.82 (s, OH), 2.72 (d, J = 15.4 Hz, 1H), 2.65–2.68 (m, 2H), 2.41–2.42 (m, 2H), 1.20 (s, 3H); MS (ESI): m/z = 461.16 (MH^+); 100% pure by LC–MS.

5.1.5. General procedure for the synthesis of compounds 8a–g

10% Pd/C (0.4 equiv of Pd) was added to a solution of **7a–g** (1 equiv) in EtOAc (128 mL) at ambient temperature and the flask evacuated and backfilled with hydrogen. The resulting suspension was stirred at ambient temperature under a balloon of hydrogen for the indicated time, filtered through a pad of celite and the solvent removed in vacuo to afford the desired products, used without further purification.

5.1.5.1. Methyl 2-{2-[(4a*S*,5*R*)-1-(4-fluorophenyl)-5-hydroxy-4a-methyl-1,4,4a,5,6,7-hexahydrocyclopenta[*f*]indazol-5-yl]ethyl}benzoate (8a). 99% Yield; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.95 (d, J = 8.1 Hz, 2H), 7.43–7.46 (m, 2H), 7.40 (s, 1H), 7.26–7.28 (m, 2H), 6.19 (m, 1H), 3.90 (s, 3H), 2.89–2.96 (m, 1H), 2.88 (d, J = 15.4 Hz, 1H), 2.76–2.82 (m, 1H), 2.59–2.65 (m, 1H), 2.46 (d, J = 15.1 Hz, 1H), 2.30–2.38 (m, 1H), 2.15–2.20 (m, 1H), 1.94–2.00 (m, 1H), 1.84–1.90 (m, 1H), 1.72–1.78 (m, 1H), 1.16 (s, 3H); MS (ESI): m/z = 447.16 (MH^+), 100% pure by LC–MS.

5.1.5.2. Ethyl 3-{2-[(4a*S*,5*S*)-1-(4-fluorophenyl)-5-hydroxy-4a-methyl-1,4,4a,5,6,7-hexahydrocyclopenta[*f*]indazol-5-yl]ethyl}benzoate (8b). 91% Yield; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.88 (s, 1H), 7.86 (d, J = 7.6 Hz, 1H), 7.43–7.47 (m, 2H), 7.40 (m, 2H), 7.34 (t, J = 7.6 Hz, 1H), 7.14 (m, 2H), 6.19 (m, 1H), 4.37 (q, J = 7.1 Hz, 1H), 2.89–2.95 (m, 1H), 2.88 (d, J = 15.1 Hz, 1H), 2.76–2.82 (m, 1H), 2.59–2.65 (m, 1H), 2.45 (d, J = 15.1 Hz, 1H), 2.32–2.40 (m, 1H), 2.16–2.21 (m, 1H), 1.94–2.01 (m, 1H), 1.84–1.90 (m, 1H), 1.39 (q, J = 7.1 Hz, 3H), 1.16 (s, 3H); MS (ESI): m/z = 461.20 (MH^+), 96% pure by LC–MS.

5.1.5.3. Methyl 4-{2-[(4a*S*,5*S*)-1-(4-fluorophenyl)-5-hydroxy-4a-methyl-1,4,4a,5,6,7-hexahydrocyclopenta[*f*]indazol-5-yl]ethyl}benzoate (8c). 92% Yield; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.95 (d, J = 8.1 Hz, 2H), 7.43–7.46 (m, 2H), 7.40 (s, 1H), 7.26–7.28 (m, 2H), 7.13–7.16 (m, 2H), 6.19 (m, 1H), 3.90 (s, 3H), 2.89–2.96 (m, 1H), 2.88 (d, J = 15.4 Hz, 1H), 2.76–2.82 (m, 1H), 2.59–2.65 (m, 1H), 2.46 (d, J = 15.1 Hz, 1H), 2.30–2.38 (m, 1H), 2.15–2.20 (m, 1H), 1.94–2.01 (m, 1H), 1.84–1.90 (m, 1H), 1.72–1.78 (m, 1H), 1.16 (s, 3H); MS (ESI): m/z = 447.19 (MH^+), 100% pure by LC–MS.

5.1.5.4. Methyl 2-fluoro-6-{2-[(4a*S*,5*R*)-1-(4-fluorophenyl)-5-hydroxy-4a-methyl-1,4,4a,5,6,7-hexahydrocyclopenta[*f*]indazol-5-yl]ethyl}benzoate (8d). 92% Yield; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.43–7.47 (m, 2H), 7.38 (s, 1H), 7.30–7.34 (m, 1H), 7.12–7.16 (, 2H), 7.03 (d, J = 7.3 Hz, 1H), 6.96 (m, 1H), 6.18 (m, 1H), 3.92 (s, 3H), 2.90–2.96 (m, 1H), 2.82 (d, J = 15.1 Hz, 1H), 2.75–2.80 (m, 1H), 2.58–2.63 (m, 1H), 2.43 (d, J = 15.1 Hz, 1H), 2.32–2.40 (m, 1H), 2.09 ddd, J = 12.9, 8.8, 2.2 Hz, 1H), 1.96 (s, OH), 1.94–2.01 (m, 1H), 1.80–1.86 (m, 1H), 1.72–1.78 (m, 1H), 1.16 (s, 3H); MS (ESI): m/z = 465.17 (MH^+); 93% pure by LC–MS.

5.1.5.5. Methyl 5-fluoro-2-{2-[(4a*S*,5*R*)-1-(4-fluorophenyl)-5-hydroxy-4a-methyl-1,4,4a,5,6,7-hexahydrocyclopenta[*f*]indazol-5-yl]ethyl}benzoate (8e). 95% Yield; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.63 (dd, J = 9.8, 2.9 Hz, 1H), 7.42–7.45 (m, 2H), 7.36 (s, 1H), 7.22 (dd, J = 8.5, 5.6 Hz, 1H), 7.12–7.15 (m, 3H), 6.17 (m, 1H), 3.90 (s, 3H), 3.19–3.24 (m, 1H), 2.90–2.96 (m, 1H), 2.78 (d, J = 15.4 Hz, 1H), 2.58–2.64 (m, 1H), 2.43 (d, J = 15.1 Hz, 1H), 2.36–2.42 (m, 1H), 2.14–2.19 (m, 1H), 2.07 (s, OH), 1.99–2.06 (m, 1H), 1.70–1.80 (m, 2H), 1.81 (s, 3H); MS (ESI): m/z = 465.19 (MH^+); 96% pure by LC–MS.

5.1.5.6. Methyl 4-fluoro-2-{2-[(4a*S*,5*R*)-1-(4-fluorophenyl)-5-hydroxy-4a-methyl-1,4,4a,5,6,7-hexahydrocyclopenta[*f*]indazol-5-yl]ethyl}benzoate (8f). 92% Yield; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.98 (m, 1H), 7.42–7.45 (m, 2H), 7.36 (s, 3H), 7.12–7.16 (m, 2H), 6.92–6.97 (m, 2H), 6.17 (m, 1H), 3.88 (s, 3H), 3.25–3.31 (m, 1H), 2.90–2.96 (m, 1H), 2.78 (d, J = 15.4 Hz, 1H), 2.72 (s, OH), 2.58–2.64 (m, 1H), 2.43 (d, J = 15.4 Hz, 1H), 2.36–2.42 (m, 1H), 2.15 (dd, J = 8.6, 2.0 Hz, 1H), 2.00–2.07 (m, 1H), 1.74–1.83 (m, 2H), 1.18 (s, 3H); MS (ESI): m/z = 465.20 (MH^+); 91% pure by LC–MS.

5.1.6. General procedure for the synthesis of acids 9a–g

A 1 M aqueous solution of NaOH (2.0 equiv) was added to a solution of **8a–g** (1.0 equiv) in EtOH (0.25 M) and the resulting suspension heated at 100 °C for 1 h. The ethanol was removed in vacuo and 1 M aqueous HCl solution was added and the product was extracted with EtOAc (×3). The combined organic extracts were dried over anhydrous $MgSO_4$ and the solvent removed in vacuo to afford the desired products.

5.1.6.1. 2-{2-[(4a*S*,5R)-1-(4-Fluorophenyl)-5-hydroxy-4a-methyl-1,4,4a,5,6,7-hexahydrocyclopenta[*f*]indazol-5-yl]ethyl}benzoic acid (9a). 98% Yield; ^{1}H NMR (CD_3OD, 500 MHz): δ 7.86 (d, J = 7.8 Hz, 1H), 7.42–7.46 (m, 3H), 7.37 (s, 1H), 7.32 (d, J = 7.8 Hz, 1H), 7.23–7.26 (m, 3H), 6.14 (m, 1H), 3.31–3.34 (m, 1H), 2.95 (dd, J = 12.0, 4.6 Hz, 1H), 2.82 (d, J = 15.1 Hz, 1H), 2.48–2.61 (m, 2H), 2.45 (d, J = 15.4 Hz, 1H), 2.21–2.25 (m, 1H), 1.98–2.05 (m, 1H), 1.70–1.80 (m, 2H), 1.13 (s, 3H); MS (ESI): m/z = 433.05 (MH^+), 100% pure by LC–MS.

5.1.6.2. 3-{2-[(4a*S*,5*S*)-1-(4-Fluorophenyl)-5-hydroxy-4a-methyl-1,4,4a,5,6,7-hexahydrocyclopenta[*f*]indazol-5-yl]ethyl}benzoic acid (9b). 97% Yield; ^{1}H NMR (CD_3OD, 500 MHz): δ 7.98 (m, 1H), 7.83(dt, J = 7.8, 1.5 Hz, 1H), 7.44–7.47 (m, 2H), 7.39 (s, 1H), 7.37 (t, J = 7.6 Hz, 2H), 7.23–7.27 (m, 2H), 6.18 (m, 1H), 2.91 (td, J = 12.5, 4.2 Hz, 1H), 2.86 (d, J = 15.6 Hz, 1H), 2.76–2.82 (m, 1H), 2.58–2.63 (m, 1H), 2.48 (d, J = 15.4 Hz, 1H), 2.35–2.44 (m, 1H), 2.13–2.17 (m, 1H), 2.00–2.07 (m, 1H), 1.81–1.86 (m, 1H), 1.69–1.75 (m, 1H), 1.13 (s, 3H); MS (ESI): m/z = 433.20 (MH^+), 97% pure by LC–MS.

5.1.6.3. 4-{2-[(4a*S*,5*S*)-1-(4-fluorophenyl)-5-hydroxy-4a-methyl-1,4,4a,5,6,7-hexahydrocyclopenta[*f*]indazol-5-yl]ethyl}benzoic acid (9c). 67% Yield; ^{1}H NMR (CD_3OD, 500 MHz): δ 7.92 (d, J = 8.1 Hz, 2H), 7.44–7.47 (m, 2H), 7.39 (s, 1H), 7.33 (d, J = 8.1 Hz, 2H), 7.23–7.27 (m, 2H), 6.18 (m, 1H), 2.89–2.95 (m, 1H), 2.85 (d, J = 15.6 Hz, 1H), 2.77–2.82 (m, 1H0, 2.58–2.63 (m, 1H), 2.48 (d, J = 15.4 Hz, 1H), 2.35–2.42 (m, 1H), 2.12–2.16 (m, 1H), 2.02–2.07 (m, 1H), 1.81–1.86 (m, 1H), 1.69–1.75 (m, 1H), 1.14 (s, 3H); MS (ESI): m/z = 433.18 (MH^+), 97% pure by LC–MS.

5.1.6.4. 2-Fluoro-6-{2-[(4a*S*,5*R*)-1-(4-fluorophenyl)-5-hydroxy-4a-methyl-1,4,4a,5,6,7-hexahydrocyclopenta[*f*]indazol-5-yl]ethyl}benzoic acid (9d). 100% Yield; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.38–7.46 (m, 3H), 7.30 (dd, J = 13.7, 7.8 Hz, 1H), 7.13 (t, J = 8.3 Hz, 2H), 7.00 (d, J = 7.6 Hz, 1H), 6.93–6.97 (m, 1H), 6.10 (s, 1H), 3.00–3.05 (m, 1H), 2.79 (d, J = 15.4 Hz, 1H), 2.75–2.80 (, 1H), 2.58 (dd, J = 18.6, 9.3 Hz, 1H), 2.45 (d, J = 15.4 Hz, 1H), 2.31–2.39 (m, 1H), 1.99–2.12 (m, 2H), 1.89–1.94 (m, 1H), 1.74–1.81 (m, 1H); 1.15 (s, 3H); MS (ESI): m/z = 451.14 (MH^+); 94% pure by LC–MS.

5.1.6.5. 5-Fluoro-2-{2-[(4a*S*,5*R*)-1-(4-fluorophenyl)-5-hydroxy-4a-methyl-1,4,4a,5,6,7-hexahydrocyclopenta[*f*]indazol-5-yl]ethyl}benzoic acid (9e). 100% Yield; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.72 (dd, J = 9.3, 2.7 Hz, 1H), 7.43–7.46 (m, 2H), 7.41 (s, 1H), 7.21 (dd, J = 8.6, 5.6 Hz, 1H), 7.12–7.16 (m, 3H), 6.15 (m, 1H), 3.30–3.35 (m, 1H), 2.78–2.85 (m, 1H), 2.79 (d, J = 15.6 Hz, 1H), 2.61 (dd, J = 18.8, 9.8 Hz, 1H), 2.47 (d, J = 15.4 Hz, 1H), 2.33–2.41 (m, 1H), 2.14–2.18 (m, 1H), 2.04–2.11 (m, 1H), 1.78–1.85 (m, 2H), 1.20 (s, 3H); MS (ESI): m/z = 451.18 (MH^+); 94% pure by LC–MS.

5.1.6.6. 4-Fluoro-2-{2-[(4a*S*,5*R*)-1-(4-fluorophenyl)-5-hydroxy-4a-methyl-1,4,4a,5,6,7-hexahydrocyclopenta[*f*]indazol-5-yl]ethyl}benzoic acid (9f). 100% Yield; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.06–8.09 (m, 1H), 7.43–7.46 (m, 2H), 7.41 (s, 1H), 7.15 (t, J = 8.5 hz, 1H), 6.94–6.98 (m, 2H), 6.16 (s, 1H), 3.38–3.43 (m, 1H), 2.80–2.85 (m, 1H), 2.80 (d, J= 15.1 Hz, 1H), 2.59–2.64 (m, 1H), 2.48 (d, J = 15.4 Hz, 1H), 2.34–2.42 (m, 1H), 2.05–2.17 (m, 2H), 1.81–1.90 (m, 2H), 1.21 (s, 3H); MS (ESI): m/z = 451.18 (MH^+); 89% pure by LC–MS.

5.1.7. General procedure for the synthesis of amides 10a–r

PYBOP® TPYBOP (1 equiv) was added to a solution of the appropriate amine (1.5 equiv), Hünig's Base (3.0 equiv) and the appropriate acid (1.0 equiv) in anhydrous DMF (0.20 M) at ambient temperature. The resulting solution was stirred at ambient temperature for 1 h. The DMF was removed in vacuo, water was added and the crude product was extracted with EtOAc (×3). The combined organic extracts were washed with saturated sodium bicarbonate solution, dried over anhydrous $MgSO_4$, filtered and the solvent removed in vacuo. Purification by flash chromatography on silica, eluting with a gradient of 0–100% $CHCl_3$ to 70:20:10 $CHCl_3$/EtOAc/MeOH afforded the following products.

5.1.7.1. 2-{2-[(4a*S*,5*R*)-1-(4-Fluorophenyl)-5-hydroxy-4a-methyl-1,4,4a,5,6,7-hexahydrocyclopenta[*f*]indazol-5-yl]ethyl}-*N*-methylbenzamide (10a). 49% Yield; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.42–7.45 (m, 2H), 7.32–7.36 (m, 2H), 7.35 (s, 1H), 7.20–7.24 (m, 2H), 7.12–7.15 (m, 2H), 6.15 (m, 1H), 5.97 (m, NH), 3.03–3.08 (m, 1H), 2.99 (d, J = 4.9 Hz, 3H), 2.80 (d, J = 15.4 Hz, 1H), 2.71–2.79 (m, 1H), 2.55–2.61 (m, 1H), 2.44 (d, J = 15.4 Hz, 1H), 2.31–2.39 (m, 1H), 2.00–2.08 (m, 2H), 1.91–1.97 (m, 1H), 1.77–1.84 (m, 1H), 1.16 (s, 3H); HRMS: calcd for $C_{27}H_{29}FN_3O_2$ $(MH)^+$ 446.2238, found 446.2237; 100% pure by LC–MS.

5.1.7.2. 3-{2-[(4a*S*,5*S*)-1-(4-Fluorophenyl)-5-hydroxy-4a-methyl-1,4,4a,5,6,7-hexahydrocyclopenta[*f*]indazol-5-yl]ethyl}-*N*-methylbenzamide (10b). 94% Yield; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.65 (s, 1H), 7.51–7.53 (m, 1H), 7.43–7.46 (m, 2H), 7.39 (s, 1H), 7.32–7.33 (m, 2H), 7.14 (t, J = 8.5 Hz, 2H), 6.17 (m, 1H), 6.16 (m, NH), 3.72 (m, 1H), 3.18 (dd, J = 14.9, 7.3 Hz, 1H), 3.00 (d, J = 4.9 Hz, 3H), 2.88–2.94 (m, 1H), 2.87 (d, J = 15.4 Hz, 1H), 2.75–2.80 (m, 1H), 2.58–2.64 (m, 1H), 2.44 (d, J = 15.4 Hz, 1H), 2.31–2.38 (m, 1H), 2.15–2.20 (m, 1H), 1.94–2.01 (m, 1H), 1.84–1.89 (m, 1H), 1.72–1.78 (m, 1H), 1.16 (s, 3H); HRMS: calcd for $C_{27}H_{29}FN_3O_2$ $(MH)^+$ 446.2238, found 446.2248; 91% pure by LC–MS.

5.1.7.3. 4-{2-[(4a*S*,5*S*)-1-(4-Fluorophenyl)-5-hydroxy-4a-methyl-1,4,4a,5,6,7-hexahydrocyclopenta[*f*]indazol-5-yl]ethyl}-*N*-methylbenzamide (10c). 87% Yield; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.67 (d, J = 8.1 Hz, 2H), 7.43–7.45 (m, 2H), 7.40 (s, 1H), 7.24–7.26 (m, 1H), 7.13–7.16 (m, 2H), 6.19 (m, 1H), 6.12 (m, NH), 3.00 (d, J = 4.9 Hz, 3H), 2.89–2.94 (m, 1H), 2.87 (d, J = 15.4 Hz, 1H), 2.86–2.94 (m, 1H), 2.74–2.80 (m, 1H), 2.58–2.64 (m, 1H), 2.46 (d, J = 15.4 Hz, 1H), 2.29–2.37 (m, 1H), 2.14–2.19 (m, 1H), 1.94–2.01 (m, 1H), 1.83–1.89 (m, 1H), 1.71–1.77 (m, 1H), 1.16 (s, 3H); HRMS: calcd for $C_{27}H_{29}FN_3O_2$ $(MH)^+$ 446.2238, found 446.2245; 100% pure by LC–MS.

5.1.7.4. *N*-Allyl-2-{2-[(4a*S*,5*R*)-1-(4-Fluorophenyl)-5-hydroxy-4a-methyl-1,4,4a,5,6,7-hexahydrocyclopenta[*f*]indazol-5-yl]ethyl}benzamide (10d). 48% Yield; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.42–7.46 (m, 2H), 7.39 (d, J = 7.8 Hz, 1H), 7.35 (s, 1H), 7.34–7.37 (m, 1H), 7.21–7.26 (m, 2H), 7.12–7.15 (m, 2H), 6.15 (m, 1H), 6.00 (m, NH), 5.89–5.97 (m, 1H), 5.25–5.29 (m, 1H), 5.18–5.20 (m, 1H), 4.02–4.12 (m, 2H), 3.04–3.09 (m, 1H), 2.80 (d, J = 15.4 Hz, 1H), 2.73–2.78 (m, 1H), 2.55–2.61 (m, 1H), 2.44 (d, J = 15.4 Hz, 1H), 2.31–2.39 (m, 1H), 1.99–2.08 (m, 2H), 1.90–1.95 (m, 1H), 1.78–1.84 (m, 1H), 1.16 (s, 3H); HRMS: calcd for $C_{29}H_{31}FN_3O_2$ $(MH)^+$ 472.2395, found 472.2404; 100% pure by LC–MS.

5.1.7.5. 2-{2-[(4a*S*,5*R*)-1-(4-Fluorophenyl)-5-hydroxy-4a-methyl-1,4,4a,5,6,7-hexahydrocyclopenta[*f*]indazol-5-yl]ethyl}-*N*-propylbenzamide (10e). 92% Yield; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.42–7.45 (m, 2H), 7.32–7.36 (m, 2H), 7.35 (s, 1H),

7.19–7.23 (m, 2H), 7.13 (t, J = 8.5 Hz, 2H), 6.15 (m, 1H), 5.96 (m, NH), 3.38–3.41 (m, 3H), 3.03–3.08 (m, 1H), 2.80 (d, J = 15.4 Hz, 1H), 2.55–2.60 (m, 1H), 2.44 (d, J = 15.4 Hz, 1H), 2.30–2.38 (m, 1H), 1.99–2.06 (m, 2H), 1.90–1.97 (m, 1H), 1.78–1.84 (m, 1H), 1.59–1.66 (m, 3H), 1.16 (s, 3H), 0.98 (t, J = 7.3 Hz, 3H); HRMS: calcd for $C_{29}H_{33}FN_3O_2$ $(MH)^+$ 474.2551, found 474.2548; 100% pure by LC–MS.

5.1.7.6. 2-{2-[(4a*S*,5*R*)-1-(4-Fluorophenyl)-5-hydroxy-4a-methyl-1,4,4a,5,6,7-hexahydrocyclopenta[*f*]indazol-5-yl]ethyl}-*N*-isopropylbenzamide (10f). 76% Yield; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.42–7.45 (m, 2H), 7.35 (s, 1H), 7.32–7.35 (m, 2H), 7.20–7.23 (m, 2H), 7.12–7.15 (m, 2H), 6.15 (m, 1H), 5.73 (d, J = 7.8 Hz, NH), 4.23–4.30 (m, 1H), 3.04–3.09 (m, 1H), 2.81 (d, J = 15.4 Hz, 1H), 2.71–2.77 (m, 1H), 2.55–2.61 (m, 1H), 2.44 (d, J = 15.4 Hz, 1H), 2.31–2.39 (m, 1H), 1.98–2.07 (m, 2H), 1.90–1.95 (m, 1H), 1.78–1.84 (m, 1H), 1.27 (d, J = 6.3 Hz, 3H), 1.25 (d, J = 6.6 Hz, 3H), 1.16 (s, 3H); HRMS: calcd for $C_{29}H_{33}FN_3O_2$ $(MH)^+$ 474.2551, found 474.2565; 100% pure by LC–MS.

5.1.7.7. 2-Fluoro-6-{2-[(4a*S*,5*R*)-1-(4-fluorophenyl)-5-hydroxy-4a-methyl-1,4,4a,5,6,7-hexahydrocyclopenta[*f*]indazol-5-yl]ethyl}-*N*-(2-methylprop-2-en-1-yl)benzamide (10g). 69% Yield; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.42–7.45 (m, 2H), 7.36 (s, 1H), 7.28–7.31 (m, 1H), 7.12–7.15 (m, 2H), 7.03 (d, J = 7.8 Hz, 1H), 6.94–6.97 (m, 1H), 6.15 (s, 1H), 6.06 (m, NH), 4.96 (s, 1H), 4.09 (s, 1H), 4.10 (dd, J = 15.6, 6.3 Hz, 1H), 3.96 (dd, J = 15.9, 5.6 Hz, 1H), 2.95–3.00 (m, 1H), 2.83 (s, OH), 2.80 (d, J = 15.4 Hz, 1H), 2.73–2.78 (m, 1H), 2.55–2.61 (m, 1H), 2.44 (d, J = 15.4 Hz, 1H), 2.31–2.38 (m, 1H), 1.98–2.05 (m, 2H), 1.90–1.95 (m, 1H), 1.81 (s, 3H), 1.76–1.84 (m, 1H), 1.57 (s, 3H); HRMS: calcd for $C_{30}H_{32}F_2N_3O_2$ $(MH)^+$ 504.2457, found 504.2456; 100% pure by LC–MS.

5.1.7.8. 2-Fluoro-6-{2-[(4a*S*,5*R*)-1-(4-fluorophenyl)-5-hydroxy-4a-methyl-1,4,4a,5,6,7-hexahydrocyclopenta[*f*]indazol-5-yl]ethyl}-*N*-propylbenzamide (10h). 66% Yield; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.42–7.45 (m, 2H), 7.36 (s, 1H), 7.25–7.29 (m, 1H), 7.12–7.15 (m, 2H), 7.02 (d, J = 7.3 Hz, 1H), 6.94 (m, 1H), 6.15 (m, 1H), 5.98 (m, NH), 3.36–3.50 (m, 2H), 2.94–2.99 (m, 1H), 2.91 (s, OH), 2.81 (d, J = 15.4 Hz, 1H), 2.71–2.79 (m, 1H), 2.55–2.61 (m, 1H), 2.44 (d, J = 15.4 Hz, 1H), 2.30–2.38 (m, 1H), 1.98–2.08 (m, 1H), 1.76–1.83 (m, 1H), 1.64 (sextet, J = 7.3 Hz, 2H), 1.23–1.32 (m, 2H), 1.16 (s, 3H), 0.99 (t, J = 7.3 Hz, 3H); HRMS: calcd for $C_{29}H_{32}F_2N_3O_2$ $(MH)^+$ 492.2457, found 492.2456; 100% pure by LC–MS.

5.1.7.9. *N*-Ethyl-2-{2-[(4a*S*,5*R*)-1-(4-fluorophenyl)-5-hydroxy-4a-methyl-1,4,4a,5,6,7-hexahydrocyclopenta[*f*]indazol-5-yl]ethyl}benzamide (10i). 72% Yield; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.43–7.45 (m, 2H), 7.35 (s, 1H), 7.32–7.36 (m, 2H), 7.20–7.26 (m, 2H), 7.12–7.15 (m, 2H), 6.15 (s, 1H), 5.90 (m, NH), 3.45–3.51 (m, 2H), 3.39 (s, OH), 3.04–3.09 (m, 1H), 2.81 (d, J = 15.4 Hz, 1H), 2.71–2.77 (m, 1H), 2.55–2.61 (m, 1H), 2.44 (d, J = 15.4 Hz, 1H), 2.31–2.38 (m, 1H), 1.97–2.07 (m, 2H), 1.91–1.95 (m, 1H), 1.78–1.84 (m, 1H), 1.25 (t, J = 7.3 Hz, 3H), 1.71 (s, 3H); HRMS: calcd for $C_{28}H_{31}FN_3O_2$ $(MH)^+$ 460.2395, found 460.2395; 100% pure by LC–MS.

5.1.7.10. 2-{2-[(4a*S*,5*R*)-1-(4-Fluorophenyl)-5-hydroxy-4a-methyl-1,4,4a,5,6,7-hexahydrocyclopenta[*f*]indazol-5-yl]ethyl}benzamide (10j). 93% Yield; ^{1}H NMR (CD_3OD, 500 MHz): δ 7.43–7.46 (m, 2H), 7.37 (s, 1H), 7.34–7.39 (m, 2H), 7.30 (d, J = 7.6 Hz, 1H), 7.20–7.27 (m, 3H), 6.61 (m, 1H), 2.99–3.07 (m, 1H), 2.88–2.91 (m, 1H), 2.84 (d, J = 15.1 Hz, 1H), 2.55–2.60 (m, 1H), 2.46 (d, J = 15.1 Hz, 1H), 2.41–2.49 (m, 1H), 2.13–2.17 (m, 1H), 1.97–2.04 (m, 1H), 1.73–1.84 (m, 1H), 1.12 (s, 3H); HRMS: calcd for $C_{26}H_{27}FN_3O_2$ $(MH)^+$ 432.2082, found 432.2083; 100% pure by LC–MS.

5.1.7.11. *N*-(*tert*-butyl)-2-{2-[(4a*S*,5*R*)-1-(4-Fluorophenyl)-5-hydroxy-4a-methyl-1,4,4a,5,6,7-hexahydrocyclopenta[*f*]indazol-5-yl]ethyl}benzamide (10k). 97% Yield; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.43–7.45 (m, 2H), 7.35 (s, 1H0, 7.30–7.33 (m, 2H), 7.21 (d, J = 8.1 Hz, 2H), 7.12–7.15 (m, 2H), 6.15 (s, 1H), 5.73 (s, NH), 3.02–3.07 (m, 1H), 2.84 (d, J = 15.4 Hz, 1H), 2.70–2.76 (m, 1H), 2.55–2.60 (m, 1H), 2.45 (d, J = 15.4 Hz, 1H), 2.31–2.39 (m, 1H), 2.00–2.03 (m, 2H), 1.90–1.94 (m, 1H), 1.79–1.85 (m, 1H), 1.47 (s, 9H), 1.17 (s, 3H); HRMS: calcd for $C_{30}H_{35}FN_3O_2$ $(MH)^+$ 488.2708, found 488.2701; 100% pure by LC–MS.

5.1.7.12. 2-{2-[(4a*S*,5*R*)-1-(4-Fluorophenyl)-5-hydroxy-4a-methyl-1,4,4a,5,6,7-hexahydrocyclopenta[*f*]indazol-5-yl]ethyl}-*N*-(1-methylcyclopropyl)benzamide (10l). 63% Yield; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.42–7.45 (m, 2H), 7.36 (s, 1H), 7.23–7.27 (m, 1H), 7.12–7.15 (m, 2H), 7.00 (d, J = 7.6 Hz, 1H), 6.91 (t, J = 8.5 Hz, 1H), 6.24 (s, 1H), 6.16 (m, 1H), 2.91–2.97 (m, 1H), 2.81 (d, J = 15.4 Hz, 1H), 2.68–2.74 (m, 1H), 2.55–2.61 (m, 1H), 2.45 (d, J = 15.1 Hz, 1H), 2.31–2.39 (m, 1H), 1.96–2.05 (m, 2H), 1.89–1.96 (m, 1H), 1.76–1.82 (m, 1H), 1.51 (s, 3H), 1.16 (s, 3H), 0.85–0.91 (m, 2H), 0.71–0.77 (m, 2H); HRMS: calcd for $C_{30}H_{32}F_2N_3O_2$ $(MH)^+$ 504.2457, found 504.2460; 100% pure by LC–MS.

5.1.7.13. 2-{2-[(4a*S*,5*R*)-1-(4-Fluorophenyl)-5-hydroxy-4a-methyl-1,4,4a,5,6,7-hexahydrocyclopenta[*f*]indazol-5-yl]ethyl}-*N*-(2-hydroxy-1,1-dimethylethyl)benzamide (10m). 72% Yield; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.42–7.45 (m, 2H), 7.36 (s, 1H), 7.32–7.34 (m, 2H), 7.20–7.25 (m, 2H), 7.12–7.15 (, 2H), 6.16 (s, 1H), 5.87 (s, 1H), 3.80 (d, J = 11.5 Hz, 1H), 3.72 (d, J = 11.5 Hz, 1H), 3.09–3.13 (m, 1H), 2.81 (d, J = 15.1 Hz, 1H), 2.71–2.79 (m, 1H), 2.56–2.62 (m, 1H), 2.43 (d, J = 15.4 Hz, 1H), 2.33–2.42 (m, 1H), 2.07–2.11 (m, 1H), 1.81–1.84 (m, 2H), 1.41 (m, 6H), 1.15 (s, 3H); HRMS: calcd for $C_{30}H_{35}FN_3O_3$ $(MH)^+$ 504.2657, found 504.2663; 100% pure by LC–MS.

5.1.7.14. 2-{2-[(4a*S*,5*R*)-1-(4-Fluorophenyl)-5-hydroxy-4a-methyl-1,4,4a,5,6,7-hexahydrocyclopenta[*f*]indazol-5-yl]ethyl}-*N*-[1-(hydroxymethyl)cyclopropyl]benzamide (10n). 76% Yield; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.42–7.45 (m, 2H), 7.37 (s, 1H), 7.25–7.29 (m, 1H), 7.14 (t, J = 8.5 Hz, 2H), 7.01 (d, J = 7.6 Hz, 1H), 6.90–6.94 (m, 1H), 6.40 (s, 1H), 6.17 (m, 1H), 3.83 (d, J = 9.3 Hz, 1H), 3.66–3.68 (m, 2H), 3.11 (td, J = 12.5, 3.2 Hz, 1H), 2.81 (d, J = 15.4 Hz, 1H), 2.72 (td, J = 12.5, 5.9 Hz, 1H), 2.58–2.63 (m, 1H), 2.43 (d, J = 15.4 Hz, 1H), 2.32–2.39 (m, 1H), 2.06–2.11 (m, 1H), 1.95–2.02 (m, 1H), 1.85–1.89 (m, 1H), 1.70–1.77 (m, 1H), 1.15 (s, 3H), 0.94 (m, 4H); HRMS: calcd for $C_{30}H_{32}F_2N_3O_3$ $(MH)^+$ 520.2406, found 520.2409; 100% pure by LC–MS.

5.1.7.15. 2-Fluoro-6-{2-[(4a*S*,5*R*)-1-(4-fluorophenyl)-5-hydroxy-4a-methyl-1,4,4a,5,6,7-hexahydrocyclopenta[*f*]indazol-5-yl]ethyl}benzamide (10o). 45% Yield; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.42–7.47 (m, 2H), 7.37 (s, 1H), 7.29–7.33 (m, 1H), 7.12–7.15 (m, 2H), 7.06 (d, J = 8.1 Hz, 1H), 6.95–6.99 (m, 1H), 6.16 (m, 1H), 6.01 (s, NH), 5.89 (s, NH), 3.02–3.07 (m, 1H), 2.79–2.85 (m, 1H), 2.81 (d, J = 15.4 Hz, 1H), 2.60 (s, OH), 2.56–2.62 (m, 1H), 2.44 (d, J = 15.4 Hz, 1H), 2.32–2.41 (m, 1H), 2.06–2.11 (m, 1H), 1.95–2.02 (m, 1H), 1.87–1.91 (m, 1H), 1.78–1.84 (m, 1H), 1.16 (s, 3H); HRMS: calcd for $C_{26}H_{26}F_2N_3O_2$ $(MH)^+$ 450.1988, found 450.1994; 100% pure by LC–MS.

5.1.7.16. 5-Fluoro-2-{2-[(4a*S*,5*R*)-1-(4-fluorophenyl)-5-hydroxy-4a-methyl-1,4,4a,5,6,7-hexahydrocyclopenta[*f*]indazol-5-yl]ethyl}benzamide (10p). 71% Yield; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.42–7.45 (m, 2H), 7.36 (s, 1H), 7.23 (dd, J = 8.5, 5.6 Hz, 1H), 7.17 (dd, J = 8.8, 2.7 Hz, 1H), 7.12–7.15 (m, 1H), 7.08 (td, J = 8.3, 2.7 Hz, 1H), 6.16 (s, 1H), 5.94 (s, NH), 5.78 (s, NH), 3.94 (s, OH), 3.03–3.09 (m, 1H), 2.81 (d, J = 15.4 Hz, 1H), 2.76–2.84 (m, 1H), 2.56–2.62 (m, 1H), 2.43 (d, J = 15.4 Hz, 1H), 2.33–2.41 (m, 1H), 2.06–2.11 (m, 1H), 1.98–2.02 (m, 1H), 1.61–1.88 (m, 2H), 1.15 (s, 3H); HRMS: calcd for $C_{26}H_{26}F_2N_3O_2$ $(MH)^+$ 450.1988, found 450.1998; 100% pure by LC–MS.

5.1.7.17. 4-Fluoro-2-{2-[(4a*S*,5*R*)-1-(4-fluorophenyl)-5-hydroxy-4a-methyl-1,4,4a,5,6,7-hexahydrocyclopenta[*f*]indazol-5-yl]ethyl}benzamide (10q). 86% Yield; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.47 (dd, J = 8.5, 5.7 Hz, 1H), 7.45–7.49 (m, 2H), 7.35 (s, 1H), 7.13 (t, J = 8.4 Hz, 2H), 6.96 (dd, J = 9.6, 2.6 Hz, 1H), 6.91 (td, J = 8.3, 2.6 Hz, 1H), 6.16 (s, 1H), 6.01 (s, 1H), 5.89 (s, 1H), 3.17–3.08 (m, 1H), 2.85–2.78 (m, 2H), 2.59 (dd, J = 18.8, 9.5 Hz, 1H), 2.43 (d, J = 15.3 Hz, 1H), 2.42–2.30 (m, 1H), 2.12–1.94 (m, 2H), 1.91–1.74 (m, 2H), 1.72 (s, 1H), 1.15 (s, 3H); HRMS: calcd for $C_{26}H_{26}F_2N_3O_2$ $(MH)^+$ 450.1988, found 450.1985; 100% pure by LC–MS.

5.1.7.18. 3-Fluoro-2-{2-[(4a*S*,5*R*)-1-(4-fluorophenyl)-5-hydroxy-4a-methyl-1,4,4a,5,6,7-hexahydrocyclopenta[*f*]indazol-5-yl]ethyl}benzamide (10r) was synthesized from acetylene (6) according to the following sequence. *5.1.7.18.1. (4a**S**,5**R**)-5-Ethenyl-1-(4-fluorophenyl)-4a-methyl-1,4,4a,5,6,7-hexahydrocyclopenta[**f**]indazol-5-ol (**12**).* (4a*S*,5*R*)-5-Ethynyl-1-(4-fluorophenyl)-4a-methyl-1,4,4a,5,6,7-hexahydrocyclopenta[*f*]indazol-5-ol (3.00 g, 9.73 mmol) (**6**) and Lindlar Catalyst (414 mg) were dissolved in THF (65 mL). Pyridine (10 mL) was added and the reaction was evacuated and backfilled with hydrogen then stirred at ambient temperature under a balloon of hydrogen for 2 h. The reaction was purged with nitrogen then filtered through Celite and the solvent removed in vacuo. Purification by flash chromatography on Silica, eluting with a gradient of 0–100% EtOAc in hexanes afforded **12** (2.65 g, 88%) as a white solid; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.48–7.42 (m, 2H), 7.38 (s, 1H), 7.18–7.11 (m, 2H), 6.19 (s, 1H), 6.03 (dd, J = 17.3, 11.0 Hz, 1H), 5.33 (d, J = 17.3 Hz, 1H), 5.14 (d, J = 11.0 Hz, 1H), 2.83 (d, J = 15.7 Hz, 1H), 2.68 (dd, J = 19.0, 10.4 Hz, 1H), 2.49–2.38 (m, 2H), 2.26–2.18 (m, 1H), 1.97–1.91 (m, 1H), 1.66 (s, 1H), 1.19 (s, 3H); MS (ESI): m/z = 311.01 (MH^+), 100% pure by LC–MS.

*5.1.7.18.2. (4aS,5S)-1-(4-Fluorophenyl)-4a-methyl-5-[2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)ethyl]-1,4,4a,5,6,7-hexahydrocyclopenta[f]indazol-5-ol (**13**).* Pinacolborane (6.40 mL, 44.1 mmol) was added to a solution of (4a*S*,5*R*)-5-ethenyl-1-(4-fluorophenyl)-4a-methyl-1,4,4a,5,6,7-hexahydrocyclopenta[*f*]indazol-5-ol (**12**) (6.85 g, 22.1 mmol), Chloro(1,5-cyclooctadiene)iridium(I) dimer (222 mg, 0.331 mmol), and Bis(diphenylphosphino)methane (255 mg, 0.662 mmol) in CH_2Cl_2 (88 mL) and the reaction heated at 60 °C for 2 h. The solvent was removed in vacuo and the residue purified by flash chromatography on Silica, eluting with a gradient of 0–100% EtOAc in hexanes to afford **13** (7.22 g, 75%) as a white solid; ^{1}H NMR showed a mixture of Boron species, taken forward as isolated; MS (ESI): m/z = 339.24 ($M-C_6H_{11}O^+$), 100% pure by LC–MS.

*5.1.7.18.3. 3-Fluoro-2-{2-[(4aS,5R)-1-(4-fluorophenyl)-5-hydroxy-4a-methyl-1,4,4a,5,6,7-hexahydrocyclopenta[f]indazol-5-yl]ethyl}benzonitrile (**14**).* (4a*S*,5*S*)-1-(4-Fluorophenyl)-4a-methyl-5-[2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)ethyl]-1,4,4a,5,6,7-hexahydrocyclopenta[*f*]indazol-5-ol (**13**) (200 mg, 0.456 mmol), 2-bromo-3-fluorobenzonitrile (91 mg, 0.456 mmol), 1,1′-bis(di-tert-butylphosphino)ferrocene palladium dichloride (30 mg, 0.046 mmol), and Cs_2CO_3 (446 mg, 1.37 mmol) in degassed toluene(0.9 mL)/water (0.3 mL) were heated at 80 °C for 1 h. The reaction was quenched with water and extracted with EtOAc (×3). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography on Silica, eluting with a gradient of 0–100% EtOAc in hexanes to afford **14** (139 mg, 71%) as a white solid; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.50 (s, 1H), 7.44–7.40 (m, 3H), 7.33–7.25 (m, 2H), 7.17 (t, J = 8.3 Hz, 2H), 6.15 (s, 1H), 3.18 (td, J = 12.7, 4.5 Hz, 1H), 2.97 (td, J = 12.6, 4.8 Hz, 1H), 2.84 (d, J = 15.4 Hz, 1H), 2.65 (dd, J = 19.0, 9.8 Hz, 1H), 2.53–2.42 (m, 2H), 2.34–2.26 (m, 1H), 2.07–1.98 (m, 1H), 1.88–1.80 (m, 1H), 1.75–1.67 (m, 1H), 1.17 (s, 3H), 0.90–0.82 (m, 1H); MS (ESI): m/z = 432.09 (MH^+), 100% pure by LC–MS.

5.1.7.19. 3-Fluoro-2-{2-[(4a*S*,5R)-1-(4-fluorophenyl)-5-hydroxy-4a-methyl-1,4,4a,5,6,7-hexahydrocyclopenta[*f*]indazol-5-yl]ethyl}benzamide (10r). 25% w/v aq NaOH (52 μL) was added to a solution of 3-fluoro-2-{2-[(4a*S*,5*R*)-1-(4-fluorophenyl)-5-hydroxy-4a-methyl-1,4,4a,5,6,7-hexahydrocyclopenta[*f*]indazol-5-yl]ethyl}benzonitrile (**14**) (50 mg, 0.12 mmol) in EtOH (1.8 mL) and the resulting reaction heated at 100 °C in a microwave for 15 min. The reaction was quenched with 1 M HCl and extracted with EtOAc (×3). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by Preparative Reverse Phase HPLC (C-18, 20 × 150 mm, Waters Sunfire) Solvent A (0.1% TFA/water), Solvent B (0.1% TFA/Acetonitrile) 15–85% A/B over 20 min to afford **10r** (26 mg, 50%) as a white solid; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.56 (s, 1H), 7.43 (dd, J = 8.5, 4.6 Hz, 2H), 7.31–7.13 (m, 5H), 6.45 (s, 1H), 6.20 (s, 1H), 6.09 (s, 1), 3.01 (s, 1H), 2.99–2.89 (m, 1H), 2.83 (d, J = 15.3 Hz, 1H), 2.62 (dd, J = 19.1, 9.6 Hz, 1H), 2.53–2.34 (m, 2H), 2.15 (t, J = 10.5 Hz, 1H), 2.09–1.97 (m, 1H), 1.86 (t, J = 7.8 Hz, 2H), 1.16 (s, 3H); HRMS: calcd for $C_{26}H_{26}F_2N_3O_2$ $(MH)^+$ 450.1993, found 450.1993; 100% pure by LC–MS.

5.2. Biological Evaluation

5.2.1. Competition radioligand binding assay

Human full length GR expressed in insect cells from Invitrogen (P2812) was incubated with compounds and 3*H*-dexamethasone at 4 °C overnight before filtration capture of protein and quantitation of bound radioactivity. An excess of unlabelled dexamethasone was used to determine non-specific binding. Data is reported as an average of a minimum of two runs.

5.2.2. TNF-α promoter transrepression assay

U937 cells were stably transfected with a bβ-lactamase reporter construct carrying the human TNF-α promoter (−1083 to +182). Assays were carried out in 5% charcoal-stripped FBS. Reporter gene expression was stimulated by treatment with 1 μg/mL LPS and 50 ng/mL TPA. Cells were treated with compounds for 16 h, and β-lactamase activity was measured using standard methods. Controls were DMSO only and 100 nm dexamethasone. Compound activity is reported as a percentage of the difference between the controls. Data is reported as an average of a minimum of three runs.

5.2.3. MMTV promoter transactivation assay

HeLa or A549 cells were transiently transfected with a luciferase reporter construct carrying the MMTV promoter which contains two glucocorticoid response elements (GREs). Assays were

carried out in 10% charcoal-stripped FBS. Cells were treated with compounds for 16 h and reporter gene activity was measured using standard methods. Compound activity was determined and expressed as for the transrepression assay. Data is reported as an average of a minimum of three runs.

5.2.4. In Vivo inflammation assay

All animal related procedures were approved by the Institutional Animal Care and Use Committee at Merck Research Laboratories, West Point, PA and conform to the Guide for the Care and Use of Laboratory Animals (US National Institutes of Health, National Research Council, 1996). Intact adult (6 month old) female Sprague–Dawley rats are used in the oxazolone (OX) contact dermatitis model. Rats were sensitized on the ventral abdomen with OX on Day 0. On Days 7 and 9, a randomly-selected ear was challenged (same ear each time) with OX; the other was treated with vehicle. Daily treatment begun on Day 7 and continued for **7d** with test compounds at different doses and 6-methlyprednisolone or DEX as positive controls. The animals were sacrificed on Day 14. As part of the necropsy procedures, the rat is weighed and deeply anesthetized in a CO_2 chamber prior to the collection of approximately 5 ml whole blood via cardiac puncture. The rat is then examined for certain signs of death and tissues are dissected in a highly stylized fashion. The following endpoints were evaluated: (a) ear inflammation induced by oxazalone, (b) plasma insulin. All blood samples were collected between 1330 and 1530 h, ~4–5 h after the last compound treatment. Primary data for this assay are left and right ear thickness. Inter-ear thickness difference (etd) is used for the estimating the level of inflammation and effectiveness of the compounds is determined by their ability to reduce the increase the thickness of the inflamed ear. Plasma insulin is also measured. Data are analyzed by ANOVA plus Fishers PLSD post-hoc test to identify intergroup differences. A *P*-value of <0.05 was considered statistically significant.

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Supplementary data

Supplementary data (details describing the preparation and characterization of compounds **11**, **M1**, **M2**, and **M3** along with copies of ^{1}H NMR spectra for all new compounds) associated with this article can be found, in the online version, at doi:10.1016/j.bmc.2011.10.054.

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