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Discovery of a potent series of non-steroidal non α-trifluoromethyl carbinol glucocorticoid receptor agonists with reduced lipophilicity

Hawa Diallo [a,*], Davina C. Angell [a], Heather A. Barnett [b], Keith Biggadike [b], Diane M. Coe [b], Tony W. J. Cooper [b], Andy Craven [b], James R. Gray [a], David House [b], Torquil I. Jack [a], Steve P. Keeling [b], Simon J. F. Macdonald [b], Iain M. McLay [c], Samuel Oliver [a], Simon J. Taylor [a], Iain J. Uings [a], Natalie Wellaway [b]

[a] Epinova Discovery Performance Unit, Immuno-Inflammation CEDD, GlaxoSmithKline Medicines Research Center, Stevenage, Hertfordshire SG1 2NY, United Kingdom
[b] Medicinal Chemistry, Respiratory Center of Excellence for Drug Discovery (CEDD), GlaxoSmithKline Medicines Research Center, Stevenage, Hertfordshire SG1 2NY, United Kingdom
[c] Computational and Structural Chemistry, Molecular Discovery Research, GlaxoSmithKline Medicines Research Center, Stevenage, Hertfordshire SG1 2NY, United Kingdom

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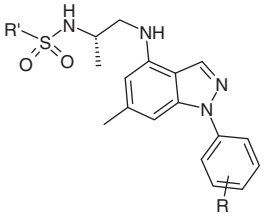
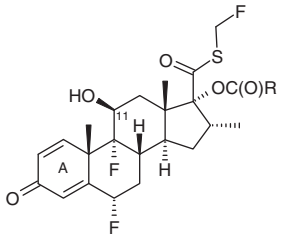
ABSTRACT

A novel series of indazole non-steroidal glucocorticoid receptor agonist has been discovered. This series features a sulfonamide central core and *meta* amides which interact with the extended ligand binding domain. This series has produced some of the most potent and least lipophilic agonists of which we are aware such as **20a** (NFκB pIC_{50} 8.3 (100%), *c* log *P* 1.9). Certain analogues in this series also display evidence for modulated pharmacology.

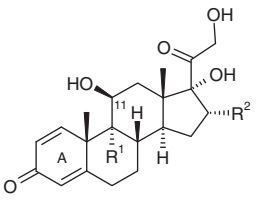


Inflammatory diseases such as asthma, allergic rhinitis, chronic obstructive pulmonary disease (COPD) and rheumatoid arthritis have been treated for many years with glucocorticoid agonists.[1] While mild and moderate asthma and allergic rhinitis can be effectively treated with inhaled or intranasally administered glucocorticoids, for example fluticasone propionate **1** and fluticasone furoate **2**, more severe asthma and rheumatoid arthritis are treated with oral glucocorticoids, such as dexamethasone **3** and prednisolone **4** (Fig. 1). However, when oral glucocorticoids are administered over a long period of time, the beneficial effects are overshadowed by side effects such as glucose intolerance, muscle wasting, skin thinning and osteoporosis.[2]

The activity of glucocorticoids is a consequence of binding of the ligand to the glucocorticoid receptor (GR) located within the cytoplasm and subsequent translocation of the receptor-ligand complex to the nucleus. The receptor-ligand complex regulates gene transcription via transcriptional activation (TA) or transcriptional repression (TR). It was suggested that the side effects observed with synthetic glucocorticoids are mainly associated with transactivation and the beneficial anti-inflammatory effects were



1 R = Et
Fluticasone propionate (FP)
2 R = 2-furoyl
Fluticasone furoate (FF)



3 R^1 = F, R^2 = Me
Dexamethasone
4 R^1 = H, R^2 = H
Prednisolone

Figure 1. Steroidal glucocorticoid agonists.

* Corresponding author. Tel.: +44 0 1438762545; fax: +44 0 1438768232.
E-mail address: hawa.x.diallo@gsk.com (H. Diallo).

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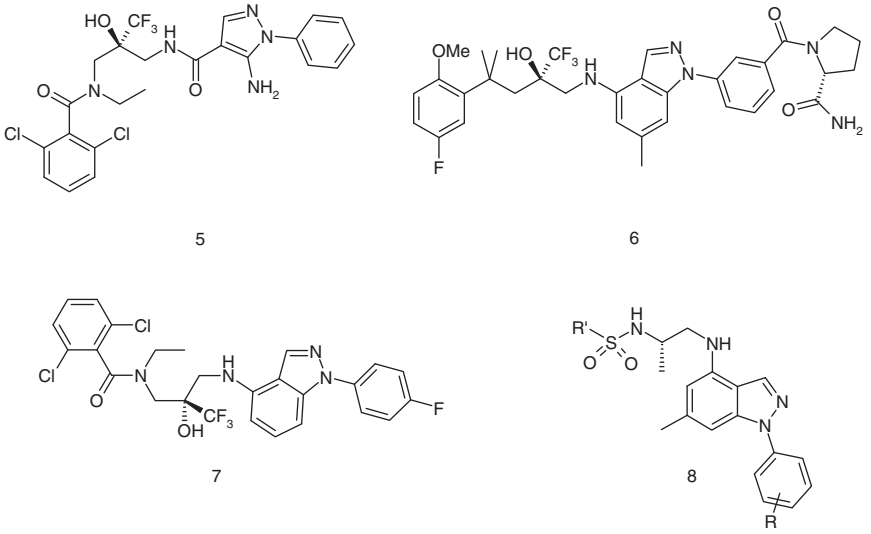
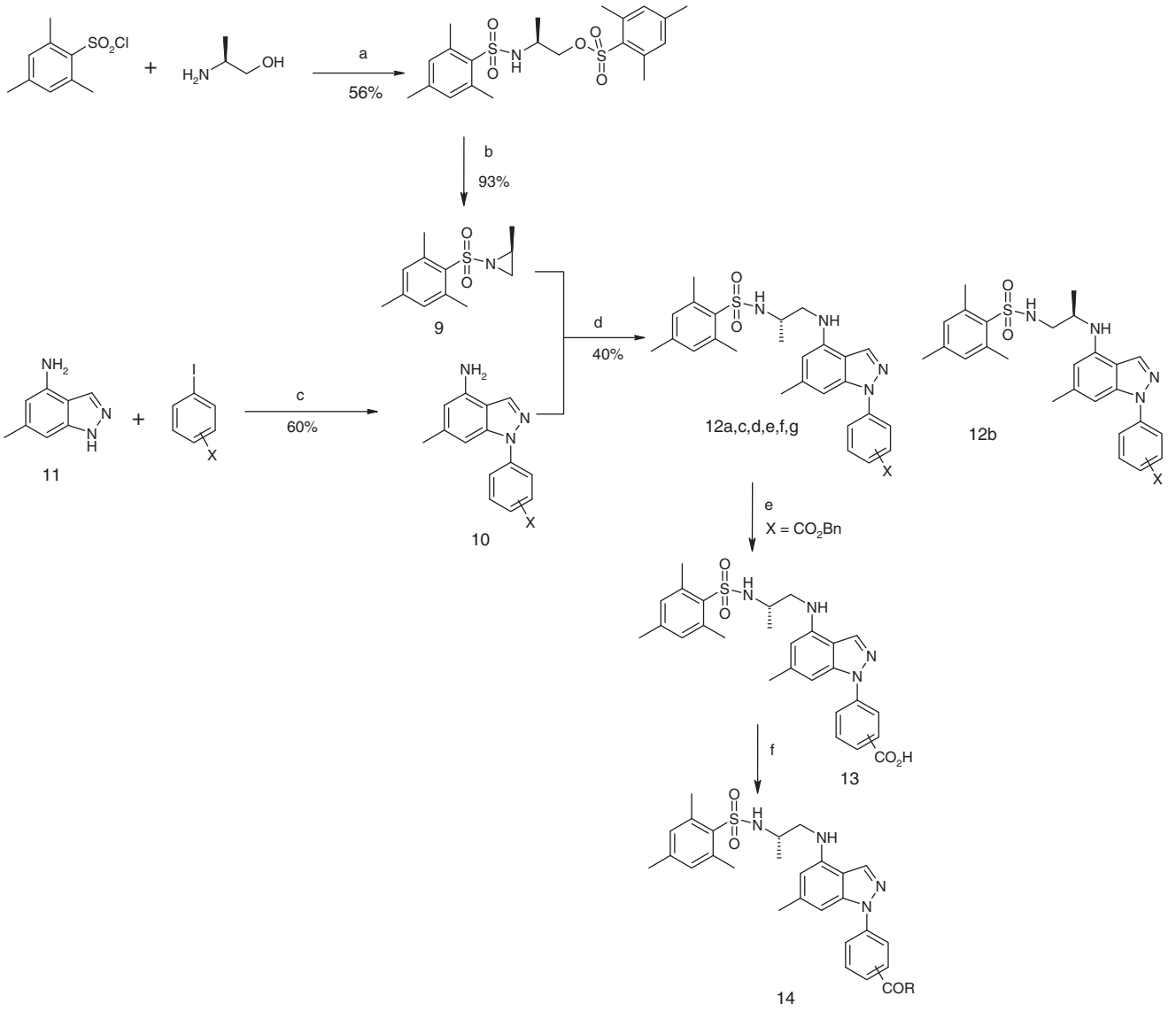


Figure 2. Aryl pyrazole and aryl indazole based GR agonists.



Scheme 1. Reagents and conditions: (a) pyridine; (b) K_2CO_3, DMF; (c) CuI, K_3PO_4, (1*R*,2*R*)-1,2-cyclohexanediamine, dioxane, 110 °C; (d) NMP, 150 °C, microwave; (e) H_2, 10% Pd/C; (f) amine, HATU, DIPEA, DMF.

mainly associated with transrepression.[3] Consequently novel GR ligands showing selectivity for TR over TA may show similar anti-inflammatory effects to the current therapies while having a markedly better side-effect profile. This TR/TA hypothesis supported much of the work being undertaken in the field.[4] However, more recently, evidence has emerged to indicate that this may be an over simplification with examples of compounds displaying TR/TA selectivity in vitro (e.g., RU24848) still showing unwanted side effects in vivo.[5]

Our efforts in the design of non-steroidal GR agonists (e.g., **5**–**7**) containing either an aminopyrazole moiety or indazole group as 'A' ring mimetics have recently been disclosed (Fig. 2).[6–8] We have also published X-ray crystal structures of the non-steroidal ligands **5** and **6** within the GR ligand binding domain, which show the disruption of the conserved steroidal A ring charged clamp region with the generation of an extended binding pocket.[9,10] A common feature of our previous efforts has been the presence of an α-trifluoromethyl tertiary alcohol; the X-ray crystal structure of **5** and **6** confirmed that this hydroxyl group mimics the steroidal 11-OH and forms a key hydrogen bond with Asn564 in the active site.

The α-trifluoromethyl tertiary alcohol motif is not always critical for activity as investigations into the modification of the trifluoromethyl group in non-steroidal glucocorticoids have been published showing GR binding potency can be maintained when replaced with either cyclohexylmethyl or benzyl analogues.[11] Furthermore α-methyltryptamine sulfonamide derivatives which do not feature a tertiary alcohol have been reported with GR binding potency.[12] In this Letter we wish to disclose our efforts in the development of a novel series of indazole based GR agonists **8** which utilise the extended ligand binding domain and contain an alternative central core structure containing a sulfonamide linker.

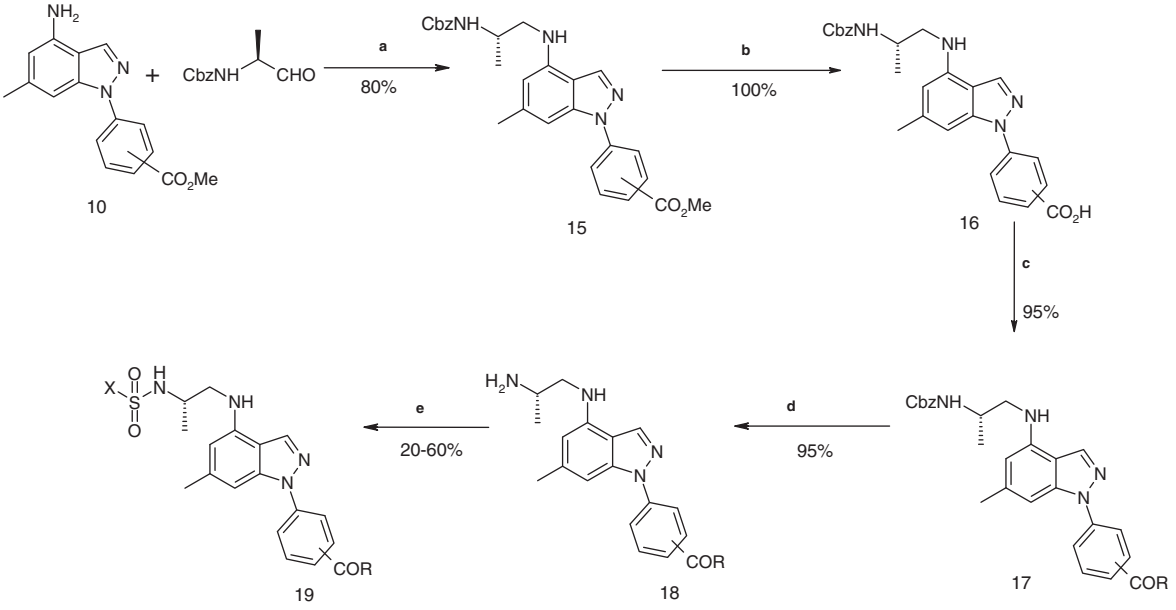
The key step in the synthesis of the initial compounds was the opening of the aziridine **9** by an aryl-aminoindazole **10** under microwave irradiation at 150 °C (Scheme 1). The aziridine intermediate **9** was prepared in two steps from (2*S*)-alaninol via *bis*-sulfonylation followed by ring closure under basic conditions. The aryl-aminoindazoles **10** were prepared separately by arylation of the indazole **11** using copper catalysis in the presence of (1*R*,2*R*)-1,2-cyclohexanediamine.[13] The aziridine opening reaction was partially selective affording a mixture of regioisomers (**12a/12b** 3:1); the individual isomers **12a** and **12b** were obtained by preparative HPLC. When X = CO_2Bn, removal of the benzyl group by hydrogenolysis afforded the acid **13**. The target amides **14** were then synthesised by amide coupling using HATU as a coupling reagent.

An alternative route was developed to avoid the poorly selective aziridine ring opening reaction: reductive amination of the methyl ester protected aminoindazole **10** with *N*-(*S*)-(benzyloxycarbonyl)alaninal resulted in the orthogonally protected intermediate **15** (Scheme 2). This intermediate was initially used in the synthesis of analogues containing a variety of sulfonyl substituents. Hydrolysis of the ester gave the carboxylic acid **16** and subsequent amide formation yielded the protected amine **17**. The amine was deprotected by hydrogenolysis to give the intermediate **18** which was sulfonylated with a variety of sulfonyl chlorides to give the sulfonamides **19**.

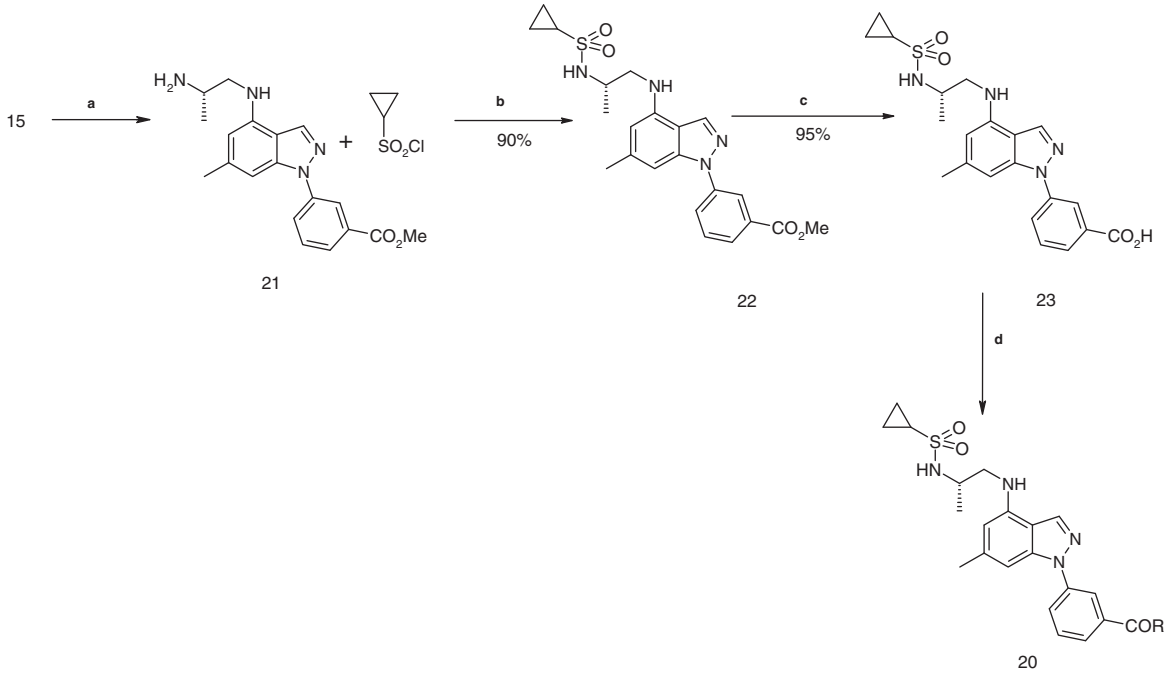
Intermediate **15** was used in the preparation of a further iteration of amides **20** with a preferred cyclopropyl sulfonyl group (Scheme 3). Removal of the CBZ protecting group resulted in the amino ester **21** which was reacted with cyclopropylsulfonyl chloride to give the sulfonamide **22**. An array of amides was prepared using standard conditions after hydrolysis of the ester group.

The data from the initial *para*-fluoro indazoles **12a** (X = F) and **12b** (X = F) were very encouraging and demonstrated the potential of the new sulfonamide linker. Both compounds demonstrated good GR binding, were potent in the NFκB functional assay of transrepression (**12a** pIC_{50} 8.9 (101% max): **12b** pIC_{50} 8.2 (95% max)) but did not show any TR efficacy selectivity (**12a** MMTV pIC_{50} 8.4 (96% max): **12b** MMTV pIC_{50} 7.3 (119% max)) (Table 1). The regioisomer with the methyl substituent adjacent to the sulfonamide motif **12a** was more potent and had a profile comparable to the indazole **7** containing the α-trifluoromethyl carbinol motif (NFκB pIC_{50} 10.1 (100% max)) and effort was, therefore, focused on this isomer.

Superimposition of the structure of the sulfonamide **12a** (green) on the crystal structure of the aryl pyrazole **5** (orange) suggests the sulfonamide may act in a similar manner to the trifluoromethylcarbinol forming a hydrogen bond between the NH of the sulfonamide to Asn564 and the coincidence of the α-methylgroup of



Scheme 2. Reagents and conditions: (a) $NaBH(OAc)_3$, acetic acid, DCM; (b) 2 N NaOH, MeOH; (c) amine, HATU, DIPEA, DMF; (d) NH_4CO_2H, Pd/C, EtOH; (e) sulfonylchloride, DIPEA, DCM.



Scheme 3. Reagents and conditions: (a) NH_4CO_2H, Pd/C, EtOH; (b) DIPEA, DCM; (c) 2 N NaOH, MeOH; (d) amine, HATU, DIPEA, DMF.

Table 1
Comparison of profile of sulfonamides **12a** and **12b** with dexamethasone and indazole **7**

Compound	GR[a] binding pIC_{50}	NFκB[b] pIC_{50} (% max)	MMTV[c] agonism pIC_{50} (% max)
3	7.9 ± 0.21	9.0 ± 0.2 (102)	8.4 ± 0.26 (99)
7	7.8	10.1 ± 0.13 (100)	9.5 ± 0.14 (122)
12a	7.8 ± 0.09	8.9 ± 0.21 (101)	8.4 ± 0.04 (96)
12b	7.9	8.2 (95)	7.3 ± 0.12 (119)

[a] GR binding assay: the compounds were tested for their ability to bind to GR using competition experiments with fluorescent-labelled dexamethasone. The tight binding limit of the assay is about pIC_{50} 8.5.
[b] GR NFκB Functional agonist assay (transrepression): a functional GR agonist assay was carried out using human A549 lung epithelial cells. This assay allows determination of the ability of compounds to repress transcription (i.e., transrepression). Efficacy is expressed as a percentage of the dexamethasone response.
[c] GR MMTV Functional assay (transactivation): human A549 lung epithelial cells engineered from the mouse mammary tumour virus were used. Whilst the standards dexamethasone **2** and prednisolone **3** have comparable efficacy in the NFκB transrepression agonist assay and the MMTV transactivation agonist assay, they are more potent in the NFκB assay by about 0.4–0.6 pIC_{50} units.

the sulfonamide **12a** and the trifluoromethyl group (Fig. 3). The trimethylphenyl group (of **12a**) and dichlorophenyl group (of **5**) sit in different places in the receptor with the Gln642 residue moving to accommodate the two positions. The indazole and pyrazole systems can both make similar H-bond interactions with Gln570.

The effects of simple substitution of the indazole *N*-1 phenyl ring on the biological activity were next investigated (Table 2). Both simple electron donating and withdrawing groups were tolerated (**12d**–**12f** R = OMe, CN, SO_2Me); the compounds showed good GR binding (pIC_{50} 7.5–7.8) and were active in the functional NFκB assay. Whilst the fluoro analogue **12a** showed no TR/TA selectivity the corresponding methoxy **12d** and cyano **12e** analogues showed a reduction in the maximum effect observed in the MMTV TA assay indicating the possibility of introducing TR/TA efficacy selectivity in this series. For small substituents the *para* position was preferred with the corresponding *meta* analogues showing a reduction in potency (**12a** NFκB pIC_{50} 8.9 (101%) vs **12c** pIC_{50} 8.1 (96%), **12d** NFκB pIC_{50} 7.9 (88%) vs **12g** pIC_{50} 7.3 (88%)). All the analogues described herein were 10 to 100 fold selective for GR with respect to PR (data not shown) and more than 100 fold selective over AR (data not shown) in binding and agonist assays.

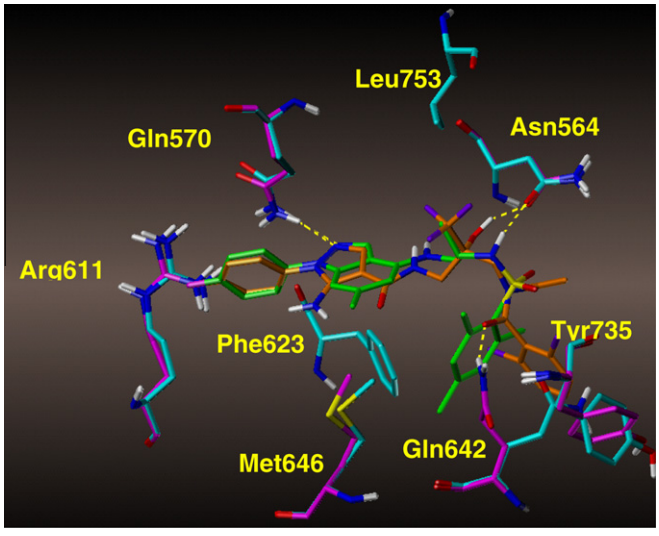


Figure 3. Docking of sulfonamide **12a** (green) on X-ray crystal structure of **5** (orange). GR residues in magenta for **12a** and in cyan for **5**. Both **5** and **12a** make H-bond interaction with Asn564. The indazole (**12a**) and pyrazole (**5**) systems are seen to both make similar H-bond interactions with Gln570.

Table 2
Effects of substituents of terminal phenyl ring[a]

Compound	Isomer	Structure	GR binding pIC_{50}	NFκB pIC_{50} (% max)	MMTV agonism pIC_{50} (% max)
12a	*p*	F	7.8 ± 0.09	8.9 ± 0.21 (101)	8.4 ± 0.04 (96)
12c	*m*	F	7.8 ± 0.16	8.1 ± 0.18 (96)	7.6 ± 0.16 (92)
12d	*p*	OMe	7.8 ± 0.15	7.9 ± 0.21 (88)	7.3 ± 0.17 (63)
12e	*p*	CN	7.8 ± 0.24	8.7 ± 0.16 (94)	8.3 ± 0.07 (68)
12f	*p*	SO_2Me	7.5	8.3 ± 0.11 (90)	7.9 ± 0.02 (81)
12g	*m*	OMe	NT[b]	7.3 ± 0.2 (88)	6.7 ± 0.07 (92)

[a] See Table 1 for assay details.
[b] Not tested.

Table 3
Effects of amide substituents on terminal *N*-phenyl ring[a]

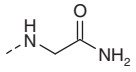
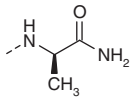
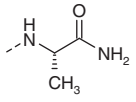
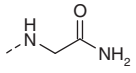
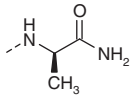
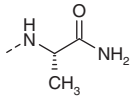
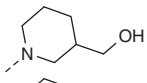
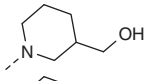
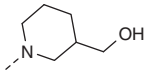
Compound	Isomer	Structure	GR binding pIC_{50}	NFκB pIC_{50} (% max)	MMTV agonism pIC_{50} (% max)
14a	*p*	NHMe	7.7 ± 0.3	8.3 ± 0.17 (78)	6.6 ± 0.52 (119)
14b	*p*	NH*i*Pr	7.9 ± 0.24	8.7 ± 0.02 (87)	8.0 ± 0.27 (89)
14c	*p*		8.1 ± 0.43	8.9 ± 0.02 (82)	8.1 ± 0.16 (79)
14d	*p*		7.8 ± 0.23	8.5 ± 0.08 (83)	7.2 ± 0.05 (89)
14e	*p*		7.6 ± 0.07	8.1 ± 0.02 (79)	6.8 ± 0.25 (110)
14f	*p*		7.5 ± 0.41	8.1 ± 0.34 (80)	7.8 ± 0.11 (38)
14g	*m*	NH*i*Pr	8.2 ± 0.08	9.9 ± 0.01 (97)	9.3 ± 0.03 (129)
14h	*m*		8.1 ± 0.11	9.5 ± 0.1 (95)	8.9 ± 0.22 (127)
14i	*m*		7.9 ± 0.01	9.6 ± 0.01 (93)	8.6 ± 0.13 (110)
14j	*m*		7.8 ± 0.31	9.7 (94)	8.7 ± 0.1 (106)
14k	*m*		8.3	9.3 ± 0.49 (100)	8.8 ± 0.06 (125)

Table 3 (*continued*)

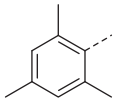
Compound	Isomer	Structure	GR binding pIC_{50}	NFκB pIC_{50} (% max)	MMTV agonism pIC_{50} (% max)
14l	*m*		7.6 ± 0.16	7.7 ± 0.15 (63)	6.6 ± 0.05 (51)
14l1	*m*		7.6 ± 0.06	7.4 ± 0.2 (65)	6.2 ± 0.17 (41)
14l2	*m*		7.8 ± 0.25	7.4 ± 0.2 (68)	6.5 ± 0.01 (37)

[a] See Table 1 for assay details.

To explore accessibility to the extended ligand binding domain (as exploited by the prolinamide group in **6**) from this template a set of *para* and *meta* amides were prepared (Table 3). The amides showed good GR binding (pIC_{50} 7.5–8.3). A simple methylamide showed good level of potency (**14a** NFκB pIC_{50} 8.3 (78%)) and several compounds such as *meta iso*propyl and cyclopropyl amides showed very high level of potency (**14g** NFκB pIC_{50} 9.9 (97%) **14h** pIC_{50} 9.5 (95%)). For the *iso*propyl, glycinamide, L-alaninamide and D-alaninamide analogues the *meta* substituted amides were consistently more potent than the corresponding *para* analogues (e.g., R = NH*i*Pr **14b** *para* NFκB pIC_{50} 8.7 (87%) **14g** *meta* NFκB pIC_{50} 9.9 (97%)). Interestingly the *meta* amide of L-alaninamide **14k** was a full agonist in both the TR and TA assays whilst the corresponding *para* analogue **14f** showed much reduced efficacy (38%) in the TA assay. Although less potent, this level of TR/TA selectivity seen with compound **14f** is particularly noteworthy and indicates how small changes can have a dramatic effect on the pharmacological profile. Alternatives to the polar terminal amide were tolerated; formation of an amide from racemic 3-piperidinylmethanol produced **14l** with reduced functional activity in the NFκB assay (pIC_{50} 7.7 (63%)) but interestingly this compound showed reduced activity in the MMTV assay (pIC_{50} 6.6 (51%)). Separation of the diastereoisomeric **14l** into the single isomers (**14l1**, **14l2**) showed that the stereochemistry of the terminal chiral centre had no significant impact on the profile of the compound.

Although the introduction of polar amides into the series resulted in a reduction of lipophilicity (*c* log *P* **14k** 4.7, **12a** 6.9) the alaninamide **14k** showed no oral bioavailability in the rat.[14] The presence of the lipophilic 2,4,6-trimethylbenzene (mesityl) sulfonyl motif was clearly detrimental to the physicochemical properties of the molecule and so in the next iteration we prepared a number of sulfonamides whilst keeping the very potent *iso*propyl amide (as in **14g**) constant (Table 4). Although the methanesulfonamide **19a** showed a 1000 fold reduction in potency with respect to the mesityl sulphonamide (NFκB pIC_{50} 6.7 (67%)), the weak activity indicated the potential for replacement of the aryl group. Slightly larger alkyl sulfonamides such as the propylsulfonamide resulted in increased potency (*n*Pr **19b** NFκB pIC_{50} 7.7 (87%); *i*Pr **19c** NFκB pIC_{50} 8.1 (92%); cycloPr **19d** NFκB pIC_{50} 8.7 (100%)). These compounds were good GR binders and full agonists in both TR and TA assays (e.g., **19c** MMTV pIC_{50} 7.3 (88%); cycloPr **19d** MMTV pIC_{50} 7.9 (110%)). Although the cyclopropyl sulfonamide

Table 4
Alternative sulfonamide groups[a]

Compound	Structure	GR binding pIC_{50}	NFκB pIC_{50} (% max)	MMTV agonism pIC_{50} (% max)
14g		8.2 ± 0.08	9.9 ± 0.01 (97)	9.3 ± 0.03 (129)
19a	Me	6.9 ± 0.05	6.7 ± 0.18 (67)	5.7 ± 0.31 (49)
19b	*n*Pr	7.9 ± 0.04	7.7 ± 0.22 (87)	7.1 ± 0.27 (85)
19c	*i*Pr	7.4	8.1 ± 0.12 (92)	7.3 ± 0.03 (88)
19d	cycloPr	7.8 ± 0.09	8.7 ± 0.27 (100)	7.9 ± 0.21 (110)

[a] See Table 1 for assay details.

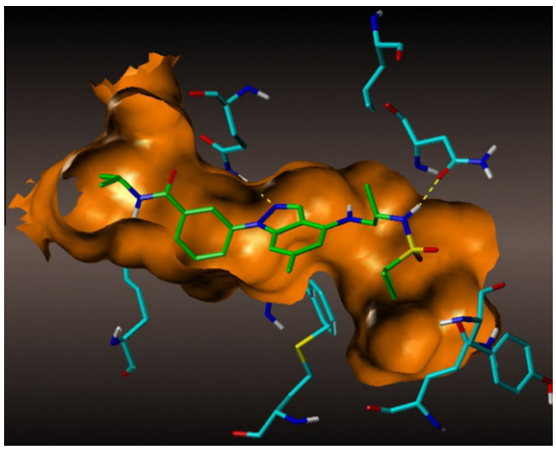
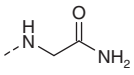
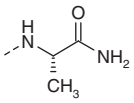
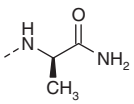
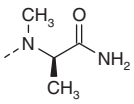
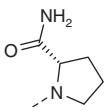
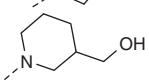


Figure 4. Docking of the sulfonamide **19d** into the GR binding domain. GR residues for **19d** in cyan.

was 10 fold less potent that the mesityl derivative the replacement of the aryl group had resulted in a significant reduction in the lipophilicity of the compound (**19d** *c log P 3.9* vs **14g** 6.4). Docking of the cyclopropyl analogue **19d** into the active site showed the cyclopropyl group partially occupies the region occupied by the mesityl group of **12a** and the *iso*propylamide group can be seen to project into the extended ligand binding domain colloquially called '*meta*' channel (Fig. 4).

We therefore continued our investigation by re-optimising the *meta*-amides with the cyclopropylsulfonamide left hand side (LHS) (Table 5). Similar SAR was observed for the cyclopropylsulfonamide as had been observed for the mesityl analogues; the glycinamide, L- and D-alaninamide analogues (**20a**, **20b** and **20c**) showed comparable potency to the simple *iso*propyl amide **19d**. The tertiary amide derived from *N*-methyl D-alaninamide **20d** (NFκB pIC_{50} 8.6 (103%)) had similar activity to the D-alaninamide indicating a tertiary amide is tolerated. However when the D-prolinamide **20e** was introduced there was a significant reduction in NFκB potency (pIC_{50} 6.1 (101%)); this observation indicated the divergence of the SAR for the *meta* channel substituents from the previously disclosed series containing the trifluoromethylcarbinol linker.[10] None of these compounds showed any TR/TA selectivity (e.g., **20d** NFκB pIC_{50} 8.6 (103%), MMTV pIC_{50} 7.3 (111%)) with the exception of the piperidinylmethanol **20f**. This compound was less potent than the parent compound with the mesityl LHS **14l** (**20f** NFκB pIC_{50} 6.6 (58%) vs **14l** NFκB pIC_{50} 7.7 (63%)) but showed no activity in the MMTV assay (**20f** MMTV pIC_{50} <5.2). The potency observed was not dependent on the presence of additional polar substituents in the *meta* channel: *N*-methyl D-alaninamide **20d** had comparable potency to the *iso*propyl substituent. Moreover, the combination of the cyclopropyl LHS with *N*-methyl D-alaninamide right hand side (RHS) **20d** reduces the lipophilicity further. So by replacing the mesityl LHS (e.g., **14i**) for a cyclopropyl LHS (e.g., **20a**) and combining with the glycinamide RHS, the lipophilicity has been reduced nearly 1000-fold (*c* log *P* **20a** 1.9 compared with **14i** 4.4) for only a 10-fold loss in agonist activity.

Table 5
Cyclopropylsulfonamide amides[a]

Compound	Structure	GR binding pIC_{50}	NFκB pIC_{50} (% max)	MMTV agonism pIC_{50} (% max)
19d	NH*i*Pr	7.8 ± 0.09	8.7 ± 0.27 (100)	7.9 ± 0.21 (110)
20a		8.1 ± 0.31	8.3 ± 0.11 (100)	6.7 ± 0.09 (95)
20b		7.4 ± 0.09	8.3 ± 0.09 (102)	6.7 ± 0.18 (114)
20c		7.5 ± 0.19	8.5 ± 0.39 (106)	6.9 ± 0.24 (116)
20d		7.5 ± 0.12	8.6 ± 0.21 (103)	7.3 ± 0.24 (111)
20e		6.8	6.1 ± 0.01 (101)	5.4 ± 0.08 (76)
20f		6.9	6.6 ± 0.1 (58)	<5.2

[a] See Table 1 for assay details.

Compound **20a** is one of the most potent and least lipophilic non-steroidal GR agonists of which we are aware. Reducing the lipophilicity of the compounds did not however improve the oral PK, (e.g., **19d** had low bioavailability and **20d** low AUC in the rat) but this work has moved the series into physicochemical space much more compatible with oral activity and drug like properties.

In this Letter we have presented the discovery of a potent tractable series of non-steroidal GR agonists which utilise a novel binding site to allow the reduction of the lipophilicity of the analogues. The presence of a polar substituent in this region of the molecule also provides a further opportunity for manipulation of the pharmacological profile and provides a promising starting point for novel non-steroidal dissociated glucocorticoids with low lipophilicity.

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14. *c* log *P* calculated with Daylight software.