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Non-steroidal glucocorticoid agonists—The discovery of aryl pyrazoles as A-ring mimetics

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Dedicated to Margaret Clackers on her retirement from GSK.

Abstract—Starting from an established series of non-steroidal glucocorticoid receptor (GR) agonists, a large array was designed where a metabolically labile benzoxazinone moiety was replaced. Initial hits bound to GR but lacked agonist activity. Following two further iterations, potent GR agonists were discovered with **20D1E1** having NFκB agonism pIC_{50} 8.8 (103%). Other analogues such as **23D1E1** display a dissociated profile (NFκB pIC_{50} 8.1 (103%), MMTV pEC_{50} 7.02 (36%)). The tetrahydronaphthalene moiety can also be replaced with substituted aryls such as **24E1** and **25E1**.

Glucocorticoid agonists have been used for many years as anti-inflammatory agents for treating a whole spectrum of conditions including asthma and rheumatoid arthritis.[1] Fluticasone propionate **1** is commonly used as a safe and effective inhaled treatment for asthma. In contrast, dexamethasone **2** and prednisolone **3** are commonly prescribed oral treatments for rheumatoid arthritis. Other interesting steroids include the agonist cortivazol **4** which features an embedded arylpyrazole motif and the antagonist mifepristone **5**—RU486—which is often used as a standard glucocorticoid antagonist. About 10 million prescriptions are written each year for oral glucocorticoid agonists in the USA alone and it is estimated that well over 50% of patients with rheumatoid arthritis are treated more or less continuously with glucocorticoid agonists.[2] Overall, the market size for all uses of glucocorticoids is estimated as $10 billion per year.[3] However, prolonged use of orally administered glucocorticoid agonists in the treatment of chronic conditions is blighted by serious and unpleasant side-effects including amongst many others glucose intolerance, muscle wasting, skin thinning and osteoporosis.[3]

As a consequence of these side-effects, there has recently been considerable interest in a hypothesis of selective glucocorticoid agonism where the beneficial anti-inflammatory effects are postulated to derive from transrepression (TR) pathways and may be separated from the side-effects derived from transactivation (TA) pathways.[4] Compounds which display selectivity for transrepression over transactivation are often referred to as dissociated agonists. Lucid descriptions of the molecular basis for these pathways have been described in detail elsewhere.[2–4] Recent publications have described non-steroidal structures which are dissociated glucocorticoid receptor (GR) agonists which feature TR/TA selectivity[5–10] and GR antagonists.[11]

At GSK, we are interested in GR agonists as anti-inflammatory agents and have recently described non-steroidal GR modulators designed by using an agreement docking method.[12,13] These modulators exemplified by **6a**, **6b** and **7**, are potent binders to GR with **7** being a sub-micromolar partial agonist. We were subsequently able to convert these analogues into potent agonists of GR possessing indications of

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dissociation—that is selectivity for transrepression over transactivation—through the discovery of an 'agonist trigger'.[13] In **8a**, **8b** and **8c**, the agonist triggers are the methyl, the cyclopentyl and 1-ethylpropyl R^1 groups, respectively. Compounds such as **8b** and **8c** are GR agonists with similar potency to dexamethasone with activity in a mouse delayed hypersensitivity model after topical treatment.[13]

All the tetrahydronaphthalene compounds described so far feature the 5-aminobenzoxazinone moiety which, from modelling studies, acts as the steroidal A-ring mimetic.[12,13] Whilst many of these compounds are both potent and TR/TA efficacy selective, the reactivity of the benzoxazinone moiety severely limits the chemistry that can be performed elsewhere in the molecule. Further, in vitro studies with rat and human liver microsomes indicate that this group is readily metabolized and thus for use as an oral therapy requires replacing. We were also interested in exploring the structure activity relationships (SAR) of benzoxazinone replacements with readouts of transrepression and transactivation (Fig. 1).

Our syntheses of **6**–**8** involved a two-step process—coupling a tetrahydronaphthalene–pyruvic acid to the aminobenzoxazine followed by reaction of the pyruvamide carbonyl with trimethylsilyltrifluoromethane.[12,13] These two steps are often capricious and low yielding and were unsuitable for our intended preparation of large arrays of potential benzoxazine replacements. We therefore decided to work instead with the 'reverse' amides or sulfonamides where the carbonyl group is switched to the other side of the nitrogen (Scheme 1) as the formation of amides and sulfonamides in array formats should then be straightforward.

The required primary amines **13** were prepared by two methods depending upon the R^1 substituent (Scheme 2). Where the R^1 substituent is methyl or ethyl, the starting point was the known dinitrile **9**. The methyl or ethyl groups were introduced by conjugate addition to give **10** (R^1 = Me or Et). Conversion of the nitrile into the methyl ester **11** (R^1 = Me or Et) was achieved using standard conditions in a three-step sequence of hydrolysis, decarboxylation and alkylation. Optimal conversion of **11** (R^1 = Me or Et) into the trifluoromethyl ketone **12** (R^1 = Me or Et) was achieved using fluoroform and potassium hexamethyldisilazide in DMF with careful temperature control (−10 °C for several days) being the key to obtaining high yields. Subsequent conversion into the amine **13a**–**c** was carried out with neat trimethylsilylcyanide and catalytic fluoride followed by reduction with lithium aluminium hydride at which point the two diastereomers can be separated.

The synthesis of the analogue where R^1 is cyclopentyl featured a palladium cascade reaction with the known iodo-aryl olefin **14**[13] and tributyl[1-(trifluoromethyl)ethenyl]stanne. This allowed introduction of the sterically demanding cyclopentyl group.[13] Ozonolysis gave the trifluoromethyl ketone **12** (R^1 = cyclopentyl) which was converted as described above into **13d**.

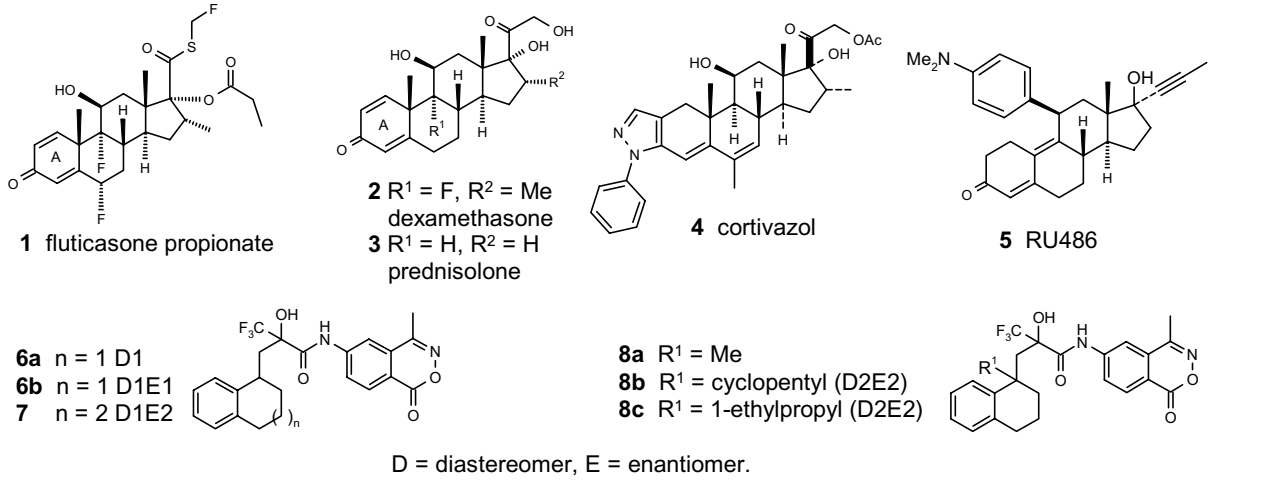
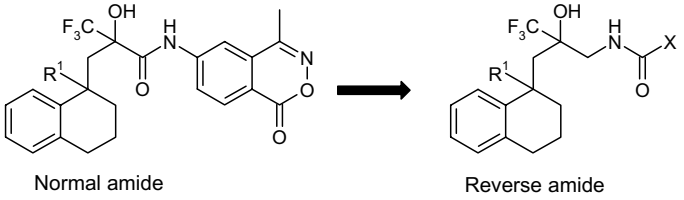
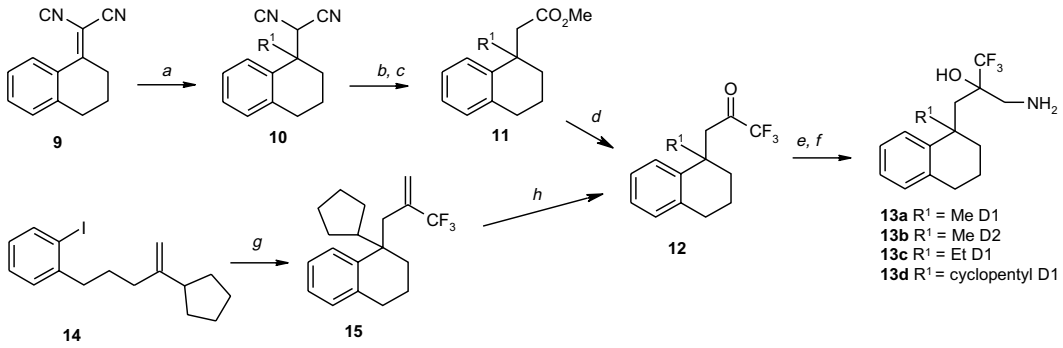


Figure 1. Steroidal (**1**–**5**) agonists and antagonist and non-steroidal glucorticoid agonists (**6**–**8**).



Scheme 1. Structures of the "normal amide" and "reverse amide".



Scheme 2. Reagents and conditions: (a) MeMgBr or EtMgBr, CuI, THF, reflux; (b) KOH, ethylene glycol, reflux; (c) MeI, K_2CO_3, Me_2CO, reflux; (d) $KN(SiMe_3)_2$, CHF_3, DMF, −10 °C; (e) Me_3SiCN, CsF (catalytic), neat, rt; (f) $LiAlH_4$, THF, reflux; (g) $Bu_3SnC(CF_3)CH_2$, $Pd(OAc)_2$, CuI, Ph_3P, DMF, 110 °C; (h) O_3, MeOH, −70 °C to rt, then Me_2S.

Acylation or sulfonylation of the amines **13** was achieved by coupling the acids with HATU (*O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate) and diisopropylethylamine in DMF or the sulfonyl chloride, diisopropylethylamine in dichloromethane, respectively, followed by automated mass directed reverse phase HPLC. In the preparation of a large array, around 200 acids and sulfonyl chlorides were coupled to both racemic diastereomers **13a** and **13b**.

The monomers for the array were selected in a three-step procedure. The first step identified a large set of monomers (carboxylic acids and sulfonyl chlorides) which were compatible with the chemistry and readily available from reliable suppliers. The second step involved elaborating, in silico, all products generated through reaction of these monomers with the amines **13a/13b** and then eliminating all virtual compounds which were outside the following limits: molecular weight > 600, *c*log *P* > 6 and 2–5 H-bond donors or acceptors. The values for molecular weight and *c*log*P* were higher than those usually adopted for such work. However, in this study the primary objective was to identify a benzoxazine replacement, and the decision was made to relax the molecular weight and *c*log *P* criteria as part of this search. The third step applied the elaborated virtual compounds to a 3D pharmacophore filter derived from the 'agreement docking' model reported previously.[12,13] Derivation of this pharmacophore filter is described below in some detail.

The previously reported agreement docking model proposed that compounds such as **8a** bind into the glucocorticoid receptor with the benzoxazine making the interactions seen for the steroidal A-ring (H-bonding to Arg611 and Gln570), the tertiary alcohol making the interactions seen for the steroidal 11β hydroxyl (H-bonding to Asn564) and the substituted phenyl ring dipping into the pocket utilized by the 17α steroidal groups. The folded conformation seen in the model (Fig. 2) provided the bulk necessary to fill the receptor and the trifluoromethyl group was believed to not only increase the H-bonding characteristics of the tertiary alcohol, but also to make good hydrophobic interactions.

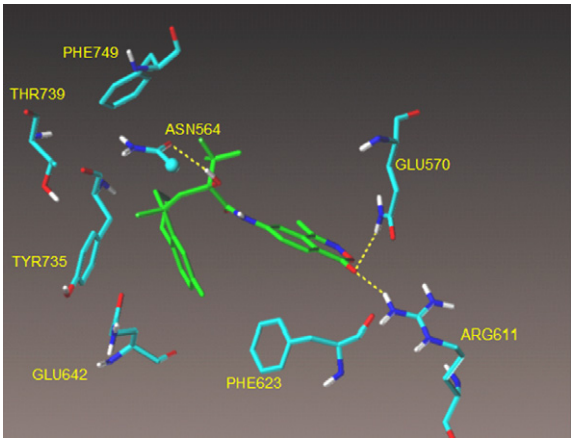


Figure 2. Modelling of **8a** (in green) in relation to key residues in the active site of GR (in turquoise). Dotted yellow lines represent H-bond interactions.

The model was used to prepare a 3D pharmacophoric query which, it was hoped, would be suitable to screen compounds for compatibility with the receptor site. The query can be seen graphically (Fig. 3). **8a** is shown in the conformation derived from the docking model (Fig. 3a) and also with the placement of H-bond acceptor query points (light green), H-bond donor query points (purple), aromatic ring query points (orange) and a hydrophobic point (light blue) (Fig. 3b). The sizes of the spheres indicate the tolerances that are allowed for a compound to be classed as successfully fitting the query. Standard tolerances of 1.5 Å were used for the two central groups, but the aromatic ring and H-bond acceptor groups were provided with larger tolerances to reflect the additional mobility of the protein residues in these regions. The conformational database of elaborated compounds was built within Catalyst (Accelrys Inc.) using the 'best' conformer generation options and searching was subsequently performed using the 'best' search option.

The three steps of the selection procedure provided the following monomer numbers: Step 1, 20,000 monomers, Step 2, 1000 monomers and Step 3, 200 monomers. The H-bonding filter limits for Step 2 incorporated the knowledge that the amine monomer would bring with

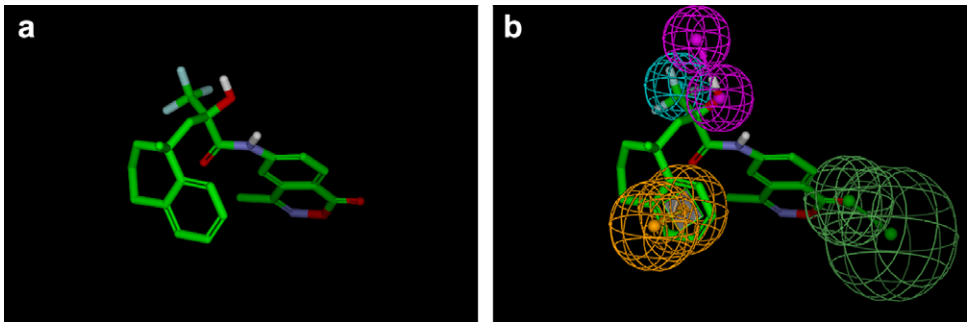


Figure 3. (a) **8a** in the conformation derived from the docking model and (b) the derived pharmacophore query (see text for details).

it one H-bond acceptor and two H-bond donors and that there was a requirement, arising from the 3D constraints, for a H-bond acceptor atom to exist in each of the selected acid/sulfonyl chloride monomers. These monomers were used for the array synthesis and the compounds screened in cellular agonist and GR binding assays. Several compounds with binding activity were identified.

One of the 200 compounds selected using this process is **17** (shown with RR stereochemistry in Fig. 4). This compound was later found to show good GR binding affinity and can be seen fitted to the 3D Query (Fig. 4a), and superimposed with **8a** using this fitting to the pharmacophore (Fig. 4b).

GR binding assay. The compounds were tested for their ability to bind to GR using competition experiments with fluorescent-labelled dexamethasone.[12] The tight binding limit of the assay is about pIC_{50} 8.5.

GR NFκB functional agonist assay (transrepression). A functional GR agonist assay was carried out using human A549 lung epithelial cells.[13] This assay allows determination of the ability of compounds to repress transcription (i.e., transpression). Efficacy is expressed as a percentage of the dexamethasone response.

GR MMTV functional assay (transactivation). Human A549 lung epithelial cells engineered from the mouse mammary tumour virus were used as previously described.[13] 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.

GR MMTV antagonist assay. The GR antagonist assay also used human A549 lung epithelial cells stably transfected with the mouse mammary tumour virus (MMTV) luciferase reporter gene. Compounds were tested for their ability to antagonise dexamethasone-induced activation.[13]

All the compounds were screened for GR binding activity with the most potent 10% of binders (those with $pIC_{50} > 6.5$) then being screened for GR agonist activity in an NFκB assay in A549 cells.[13] The amide analogues of **13a** (diastereomer 1) are substantially more active than those derived from **13b** (diastereomer 2) in contrast to the sulfonamide analogues where both diastereomers are active and with diastereomer 2 analogues having superior potency. Although no compounds displayed any GR agonism, three key compounds that emerged were the amide **16D1** (compound **16** diastereomer 1) and sulfonamides **17D1** and **17D2** with binding activities of pIC_{50} of 7.4, 6.8 and 7.5, respectively (Table 1). Separation of **17D2** into its enantiomers confirmed the binding activity of the racemate with **17D2E1** (compound **17** diastereomer 2 enantiomer 1) and **17D2E2** having pIC_{50}'s of 7.3 and 7.5, respectively. Further, **17D2E2** displayed micromolar GR antagonist activity with pIC_{50} 6.5. Binding data from other sulfonamides suggested that the phenyl ring of the pyrazole **17D2** contributes about a 10-fold increase in binding activity (data not shown).

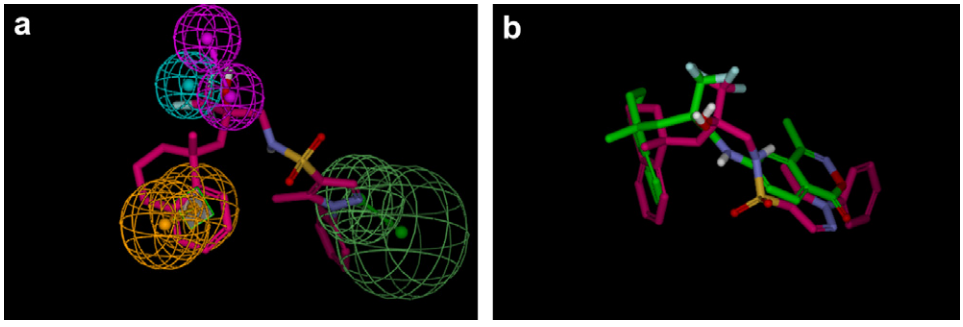
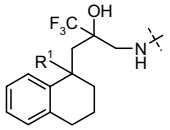
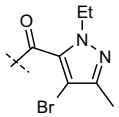
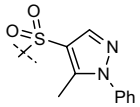
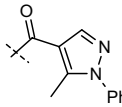
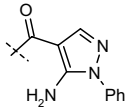
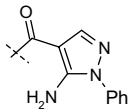
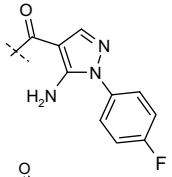
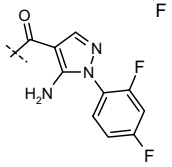


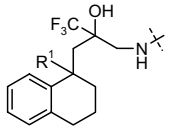
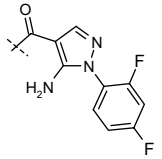
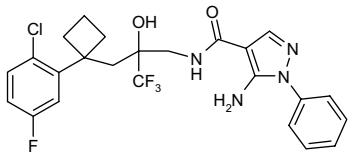
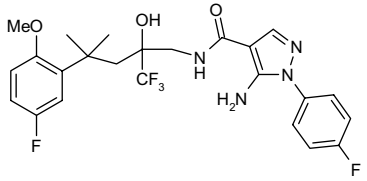
Figure 4. In (a), **17** (with the RR stereochemistry) is shown fitted to the 3D pharmacophore query and in (b), **17** (in magenta) is shown superimposed on **8a** (in green).

Table 1. Selected biological data for standard compounds and compounds that bind to GR

	Structure	R^1	GR binding[a] pIC_{50}	NFκB[a] pIC_{50} (% max)	MMTV[a] agonism pEC_{50} (% max)	MMTV[a] antagonism pIC_{50}
						
2	Dexamethasone	—	8.12 ± 0.21	9.00 ± 0.22 (102% ± 6)	8.27 ± 0.23 (102% ± 13)	<6 (7% ± 7)
5	RU486	—	8.16 ± 0.26	<6	<6 (4% ± 1)	7.94 ± 0.20 (100% ± 3)
16D1[c]		Me	7.39 ± 0.29	<6 (15% ± 12)	nt[b]	nt
17D1		Me	6.80 ± 0.18	<6 (16% ± 20)	nt	nt
17D2			7.46 ± 0.16	<6 (32% ± 7)	nt	nt
17D2E1[c]			7.29 ± 0.10	<6 (51% ± 3)	nt	nt
17D2E2			7.52 ± 0.01	<6 (57% ± 3)	<6 (2% ± 0)	6.51 ± 0.23 (67% ± 6)
18D1		Me	8.12 ± 0.21	7.08 ± 0.21 (45% ± 16)	<6 (0% ± 0)	6.22 ± 0.02 (87% ± 1)
18D1E1			8.03 ± 0.16	7.31 ± 0.45 (52% ± 10)	<6 (5% ± 9)	6.03 ± 0.04 (93% ± 1)
19D1E1		Me	8.24 ± 0.09	7.77 ± 0.16 (58% ± 8)	6.74 ± 0.07 (76% ± 6)	nt
19D1E2			8.29 ± 0.08	8.23 ± 0.06 (87% ± 1)	7.74 ± 0.06 (93% ± 17)	nt
20D1E1		Et	8.13 ± 0.27	8.78 ± 0.20 (108% ± 5)	8.25 ± 0.03 (106% ± 11)	nt
21D1E1		Et	7.70 ± 0.54	8.44 ± 0.38 (106% ± 5)	8.11 ± 0.12 (98% ± 12)	nt
21D1E2			8.01 ± 0.28	8.52 ± 0.31 (94% ± 9)	7.97 ± 0.05 (93% ± 14)	nt
22D1E1		Et	8.33 ± 0.14	8.19 ± 0.15 (97% ± 4)	7.84 ± 0.03 (98% ± 2)	<6 (11% ± 1)
22D1E2			8.33 ±0.22	8.35 ± 0.18 (95% ± 2)	7.91 ± 0.01 (99% ± 4)	nt

(*continued on next page*)

Table 1 (*continued*)

	Structure	R^1	GR binding[a] pIC_{50}	NFκB[a] pIC_{50} (% max)	MMTV[a] agonism pEC_{50} (% max)	MMTV[a] antagonism pIC_{50}
						
23D1E1		Cyclo-pentyl	8.02[e]	8.07 ± 0.14 (103% ± 2)	7.02 ± 0.21 (36% ± 2)	6.56 ± 0.07 (93% ± 1)
23D1E2			7.68[e]	7.52 ± 0.24 (82% ± 5)	6.82 ± 0.01 (13% ± 2)	nt
24E1[c,d]		—	8.37[e]	8.43 ± 0.09 (93% ± 3)	7.82 ± 0.05 (104% ± 12)	nt
24E2			8.32[e]	7.88 ± 0.14 (75% ± 4)	7.76 ± 0.07 (103% ± 8)	nt
25E1[c,d]		—	8.26 ± 0.22	9.34 ± 0.21 (105% ± 3)	8.92 ± 0.17 (99% ± 20)	<6 (4% ± 5)
25E2			8.17 ± 0.05	7.75 ± 0.47 (97% ± 6)	7.80 ± 0.10 (70% ± 12)	nt

Notes.

[a] For assay details, see text.

[b] nt, not tested.

[c] AD1 refers to compound A diastereomer 1. Similarly BD2E1 refers to compound B diastereomer 1 enantiomer 2. CE1 refers to compound C, enantiomer 1.

[d] For syntheses of **24** and **25** amines, see Ref. 16.

[e] Value from $n = 1$.

The most promising leads from this initial array were followed up in the search for agonism. In this regard, the commercial availability of pyrazole acids along with their ease of preparation was attractive in comparison to pyrazole sulfonyl chlorides. We therefore selected a diverse follow up set of pyrazole acids where the acid was located at the 2, 3 and 4 positions of the pyrazole for coupling to **13a**. Analogues linked through the 3-position of the pyrazole are inactive in contrast to those linked through the 5-position which are potent binders. However, linking through the 4-position together with phenyl substitution on N1 gave outstanding binding activity and, for the first time, GR agonism. Thus the 5-methylpyrazole **18D1** binds with pIC_{50} 8.1 and is a partial agonist with NFκB pIC_{50} 7.1 (45%). Further profiling in MMTV agonist and antagonist assays showed **18D1** to have no agonist activity ($pEC_{50} < 6$ (0%)) but micromolar antagonist activity (pIC_{50} 6.2 (87%)). The active enantiomer **18D1E1** displays a similar profile to the racemate **18D1**. This dissociated profile between in vitro readouts of transrepression and transactivation is clearly of considerable interest.

In the next iteration we focussed further on aryl pyrazoles linked through the pyrazole C4 and found that replacement of the 5-methyl group with a 5-amino group leads to about a 10-fold enhancement in NFκB agonist activity with **19D1E2** having a pIC_{50} of 8.2 (87%). In this case, **19D1E2** is also a full agonist in the MMTV agonist assay (pIC_{50} 7.7 (93%)). Remarkably, given the ease with which agonist activity is usually lost, the other enantiomer **19D1E1** is also an agonist although a little less potent and more partial (pIC_{50} 7.8 (58%)). Infra-red spectroscopic analysis of solutions of **19D1** and analogues indicated an H-bonding network between the pyrazole NH_2, the amide carbonyl and the tertiary alcohol. Two conformers were also observed indicating the presence and absence of a π-amide NH interaction (Fig. 5). Ab initio calculations of fragments of **19D1** (in bold in Form A) also indicated that the Form A H-bonding network shown is substantially preferred to that shown by the alternative Form B by 3.4 kcal/mol^{-1}. This analysis suggested that conversion of the six membered H-bonded ring (in blue in Form A) into a covalently bonded ring might provide active compounds and indeed this is the case (details of which will be described elsewhere).[14]

We then explored the effect of fluorine substitution on the aryl ring of the aryl pyrazole. *Para* fluoro or *ortho, para* difluoro substitution either has no effect or slightly reduces the NFκB agonism (compare **20D1E1** with **21D1E1,2** and **22D1E1,2**) and the compounds remain full MMTV agonists.

We have published previously that in the tetrahydronaphthalene series the substituent in the R^1 position can have a profound effect on the potency and TR/TA selectivity.[13] The R^1 = ethyl **20D1E1** analogue of the R^1 = methyl compound **19D1E1/E2** displays a fivefold increase in NFκB agonism with full efficacy (NFκB pIC_{50} 8.78 (108%)) and no selectivity over MMTV agonism (pEC_{50} 8.25 (106%)). Also prepared was the difluoroaryl cyclopentyl analogue **23D1E1** which is less potent as an NFκB agonist (pIC_{50} 8.07 (103%)) but possesses reduced MMTV agonist efficacy (pEC_{50} 7.02 (36%)) and commensurate activity in the MMTV antagonist assay (pIC_{50} 6.56 (93%)) as seen with **8** in the benzoxazinone series.

We have also prepared aryl pyrazole analogues which feature chlorofluoro and methoxyfluoro aryl replacements for the tetrahydronaphthalenes (**24E1,2** and **25E1,2**) and shown that they are also very potent full NFκB agonists.

These aryl pyrazole analogues display outstanding selectivity for GR over other nuclear receptors such as the androgen (AR), progesterone (PR), mineralocorticoid and estrogen receptors with $pIC_{50} < 6$ in binding assays of PR and AR.

Having used the 'agreement model' to identify suitable monomers for the array it was of great interest to return to the model and consider the detailed binding interaction for the phenylpyrazoles. It was noted that cortivazol, a commercial steroidal glucocorticoid agonist **4**, also bears a phenylpyrazole system and modelling was performed using this steroid to assist studies of the phenylpyrazoles arising from this work. Yoshikawa et al. had reported[15] that cortivazol required a shift of Arg611 and Gln570 to enable the additional arylpyrazole moiety to be accommodated within the receptor. This is indeed the case and Figure 6a shows the predicted movements for these residues, with the original positions, as seen in steroidal crystal structures, in white and the final position in light blue. This 'cortivazol' model was then used to place the new derivatives, both the sulfonamide **17** (RR stereochemistry) shown in magenta superimposed along with cortivazol (Fig. 6b),

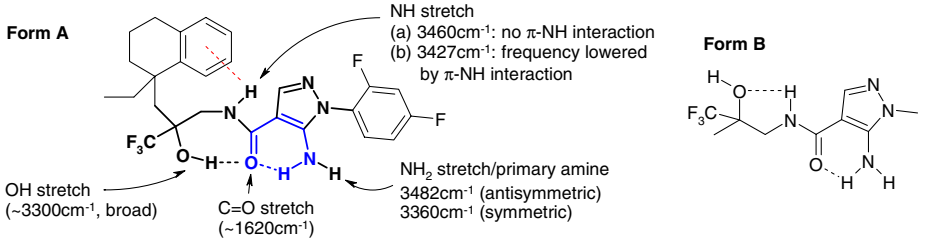


Figure 5. Possible H-bonding networks (Forms A and B). Dotted blue or black lines represent H-bonds. Form A is observed in the infra-red spectrum and is also preferred from ab initio calculations on fragments (the bold part of Form A and Form B).

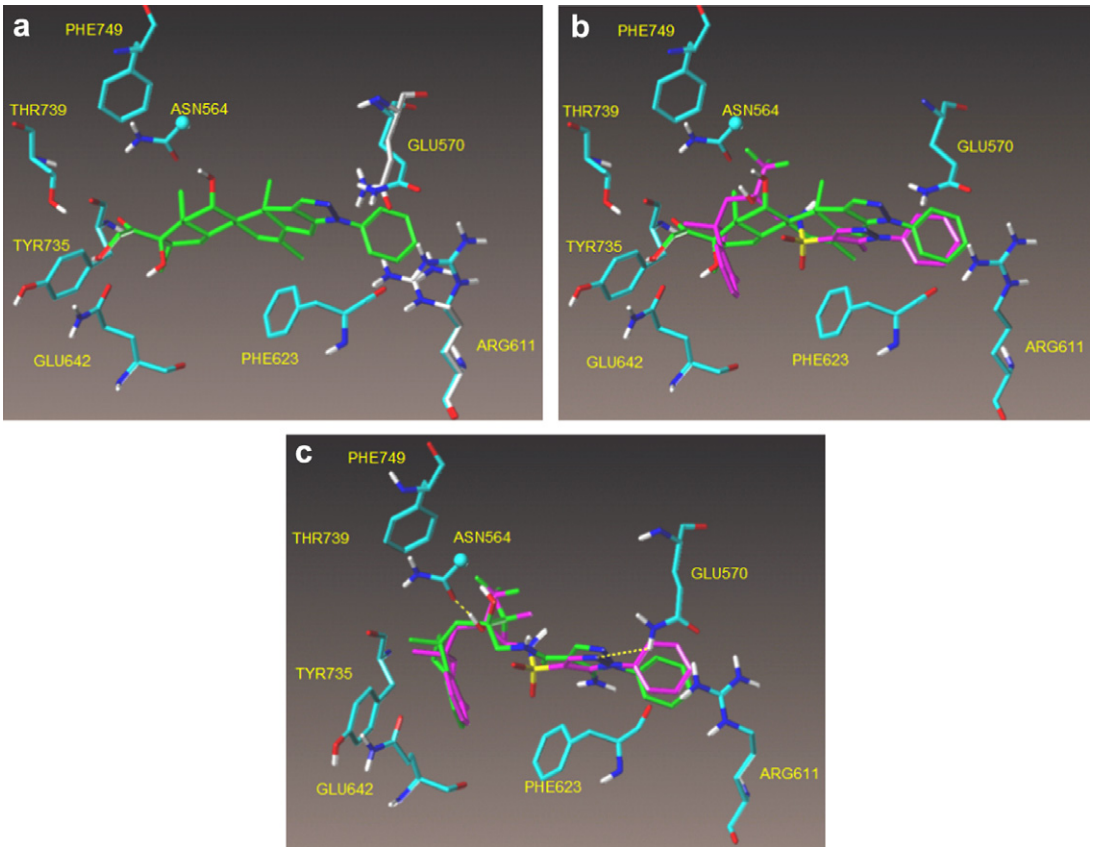


Figure 6. (a) Cortivazol **4** (in green) in the active site of GR. Key residues amino-acid residues are shown (in turquoise) with Glu570 and Arg611 moving to accommodate the aryl ring (see text). (b) The sulfonamide **17** (RR stereochemistry) in magenta superimposed on cortivazol and (c) the amide **19** (RR stereochemistry) in green superimposed on **17**.

and the amide **19** (RR stereochemistry) shown in green superimposed on **17** in magenta (Fig. 6c).

In summary, we have described an iterative approach which has led to the discovery of a series of amide aryl pyrazoles which are potent GR agonists and some of which display TR/TA selectivity. Further developments of this series will be published in due course.

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