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Discovery of acylurea isosteres of 2-acylaminothiadiazole in the azaxanthene series of glucocorticoid receptor agonists

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ABSTRACT

Acylureas and acyclic imides are found to be excellent isosteres for 2-acylamino-1,3,4-thiadiazole in the azaxanthene-based series of glucocorticoid receptor (GR) agonists. The results reported herein show that primary acylureas maintain high affinity and selectivity for GR while providing improved CYP450 inhibition and pharmacokinetic profile over 2-acylamino-1,3,4-thiadiazoles. General methods for synthesis of a variety of acylureas and acyclic imides from a carboxylic acid were utilized and are described.

Agonists of the glucocorticoid receptor (GR), such as dexamethasone (dex) **1** and prednisolone (pred) **2**, have found broad utility in autoimmune and inflammatory diseases for over sixty years.[1] However, the unparalleled efficacy of these glucocorticoids (GCs), all of which are steroids, is countered by a host of side effects such as glucose intolerance (diabetes), muscle wasting, skin thinning, and osteoporosis.[2] In addition, cross-reactivity of steroids with other members of nuclear hormone receptors (NHRs), such as progesterone receptor (PR), androgen receptor (AR), and mineralocorticoid receptor (MR), can provoke off-target pharmacology.[3] Glucocorticoids provide anti-inflammatory efficacy through the transcriptional repression (transrepression, TR) of pro-inflammatory transcription factors such as AP-1 and NFκB, while side effects are induced through the transactivation (TA) of genes bearing GC response elements in their promoter regions. Ligands which modulate GR function in a pathway-selective manner ('dissociated agonists'), maintaining TR while minimizing TA, would be expected to maintain the clinical efficacy of traditional GR agonists, while providing a relatively improved side effect profile.[4] Growing evidence suggests that ligands which completely dissociate these pathways may not be expected to meet this idealized clinical profile. For example, as various gene products which are subject to GR-dependent TA contribute to the anti-inflammatory and immunosuppressive properties of GCs, complete dissociation may be expected to provide GR modulators of sub-optimal efficacy in treating autoimmune disease.[5]

In our effort to identify selective and dissociated non-steroidal GR agonists, we started from dihydro-ethanoanthracene carboxamides such as compound **3**, which displaying a promising dissociated profile in discrimination between TR and TA activities.[6a] We demonstrated in a subsequent report that several conformational constraints of this system were unnecessary for potent receptor binding, as uncyclized diphenylpropionamides (e.g., **4**) and xanthenes (e.g., **5**) maintained high GR binding affinity and agonist activity.[6b] Recently, we reported that introduction of a pyridine nitrogen to the xanthene core of **5** and arylation adjacent to the pyridine nitrogen to 2-aryl-5*H*-chromeno[2,3-*b*]pyridine (azaxanthene) could not only address metabolic liabilities associated with phenols **4** and **5**, but also provided selective GR ligands which display a broad range of pharmacologic profiles.[7] Among them, two close benzamide analogs (**6** and **7**, BMS-776532 and BMS-791826, respectively) have been found to maintain distinct levels of partial agonist efficacy, displaying anti-inflammatory activity comparable to that of prednisolone (**2**), a known full GR agonist.[7] Both compounds were reported to display non-linear pharmacokinetics, with systemic exposures increasing after oral dosing in a greater than dose proportional manner.[7] We subsequently determined

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0960-894X/

that this behavior can be attributed to potent CYP450 inhibition, with concentrations of **6** and **7** exceeding K_m for the isoform responsible for the metabolism of these compounds (saturable clearance) at relatively low doses (unpublished results). Therefore, work was initiated to identify a developable GR compound which would avoid the liabilities associated with both **6** and **7** while maintaining their promising pharmacological profiles (see Fig. 1).

We suspected that the metabolic liability of **6** and **7** may reside within the 2-acylamino-1,3,4-thiadiazole moiety. The X-ray co-crystal structure of GR ligand-binding domain (LBD) bound indazole 2-acyl-1,3,4-aminothiadiazole ligand was useful in our efforts to identify surrogates for this functionality.[8a] It revealed that Asn564 and Gln642 play a role in binding through a three-centered hydrogen bond network to the 2-acyl-1,3,4-aminothiadiazole moiety as shown in the left panel of Figure 2. Specifically, Asn564 engages in two H-bonds, one to the amide NH and another to one nitrogen of the thiadiazole, while Gln642 forms an additional H-bond with the amide carbonyl oxygen. These interactions effectively mimic the engagement of both residues within the steroidal C-11 β hydroxyl and D ring C-17 substituents of **1** and **2**.[9] We envisioned that both acyclic imide and acylurea structures could mimic the three-centered hydrogen bond network of thiazole and thiadiazole amide ligands. Docking the acyclic acylurea into the published crystal structure fit very well in the GR LBD pocket as shown in the right panel of Figure 2. Herein we report our results on synthesis and biological characterization of the acyclic imide and acylurea GR ligands.

The synthesis of a series of acyclic imides is outlined in Scheme 1. The preparation of 5*H*-chromeno[2,3-*b*]pyridine carboxylic acid **8a** has been described before.[7] Suzuki–Miyaura coupling of **8a**,**b** with aryl boronate provided 2-aryl-5*H*-chromeno[2,3-*b*]pyridine carboxylic acid **9.** Following the method of Andrus et al.,[10] activation of the acid **9** with carbodiimide followed by treatment with pentafluorophenol gives an activated pentafluorophenyl ester **10**. Condensation of ester **10** with an amide anion, which is separately generated from treatment of an alkyl or cycloalkyl amide with an appropriately strong base such as sodium hexamethyl-disilazide gives acyclic imides **12** in 65% yield. Alternatively, the acyclic imides can also be synthesized in the following two step sequence. The carboxylic acid **8** was first converted into a primary amide **11**, which was treated with sodium hexamethyldisilazide to generate an amide anion, and then condensation with an acyl chloride gives imides **13**∼**18** in 66–70% yield (Scheme 1).

The synthesis of *N*-methyl acylurea is outlined in Scheme 2. The acid **8** was converted into a primary amide **19**, using HATU as an activation reagent, diisopropylethyl amine as a base and ammonium chloride as an ammonium source. Condensation of **19** with methyl carbamoyl chloride in the presence of sodium hexamethyldisilazide or sodium hydride gives *N*-methyl acylurea compound **20** in 80% yield.

The structure of the *N*-methyl acylurea **20** was confirmed by an X-ray crystal structure (Fig. 3). In the similar manner, the synthesis of *N*,*N*-dimethyl acylurea **21** can be achieved as shown in Scheme 3. Arylation of **20** provided **22**.

Another approach for preparation of secondary acylureas is shown in Scheme 4. Condensation of **11** with isocyanate in an inert solvent such as toluene, at 90°C gives compounds **23**–**25** in 65–82% yields.

One method for synthesis of primary acylureas involved cleavage of the *para*-methoxy benzyl (PMB) protected secondary acylurea **25** with neat trifluoroacetic acid (TFA), or 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) to provide the primary acylurea **26** in an excellent yield (Scheme 5).

The primary acylurea can also be prepared according to the method of Xiao et al.[11] Therefore, conversion of carboxylic acid **8** to an acylcyanamide **28** was effected using BOP as an activation agent, in the presence of diisopropylethyl amine and cyanamide. The acylcyanamide **28** proved to be stable in the subsequent Suzuki coupling reaction. Thus, condensation with aryl boronate, in the presence of tetrakis catalyst and potassium phosphate tribasic solution, gives the 2-aryl-5*H*-chromeno[2,3-*b*]pyridine acylcyanamide **29**. The acyl-cyanamide **30** can be hydrolyzed to primary acylurea **30** under strongly acidic conditions. Thus, treatment with 4 N HCl in water provided the useful acid intermediate **30** in 86% yield. The primary acylureas bearing different benzamides **31**–**36** were readily prepared by condensation of **30** with various amines as shown in Scheme 6.

The in vitro assays used to characterize biological activities of the GR ligands including nuclear receptor binding, transrepression in an A549 cell line [AP-1 and E-selectin (NFκB dependent)], and transactivation in GAL-4 reporter in a HeLa cell line [NP-1 agonist assay] have been previously reported.[7]

GR binding and functional activity for acyclic imides and acylureas are summarized in Table 1. The 2-acylamino-1,3,4-thiadiazole of **6** (GR K_i = 1.9 nM)[7] was simply replaced with an acyclic imide to get compound **13** (GR K_i = 69.4 nM). A significant loss of of GR binding affinity and functional activities were observed. While it is not a trend when the left hand amide was modified. The acyclic imide compounds **14** and **15**, both of which are bearing a different amide, do show good GR binding affinity and functional activities in both transrepression and transactivation assays (Table 1). The GR selectivity over PR is also affected by the left hand amide. Among three methyl imides **13**–**15**, the morpholine amide **15** showed the least PR selectivity. However, the PR selectivity can be improved by varying the methyl imide with others, such as imides **16**–**18**. It is also noted that SAR of the acyclic imides is very sensitive. The imides **16**–**18** showed weaker human whole blood (*h*WB) activity, which is consistent with their weak transactivation activity. The major issue for further development the imide series is hydrolytic instability of acyclic imides in low pH. Under acidic conditions, the acyclic imide can be readily hydrolyzed back to a primary amide.

The relatively weak GR binding affinity of the *N*,*N*-dimethyl acylurea compound **21** was improved by removing one methyl group to *N*-monomethyl acylurea **22**. This can be rationalized based on what is likely a requirement for a cyclic hydrogen bond between the terminal *NH* and the carbonyl oxygen adjacent to the quaternary carbon, maintaining the acylurea in the most productive *trans* conformation. Accordingly, the GR binding affinity of **22** increased more than 10-fold relative to **21**. Like compound **22**, other secondary acylureas **23-25** also exhibited potent GR binding affinity and transrepression activity (AP-1 and E-selectin).

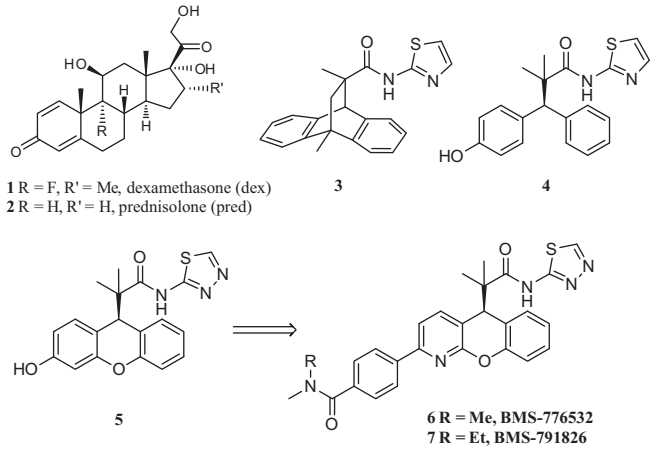


Figure 1. Synthetic glucocorticoid agonists.

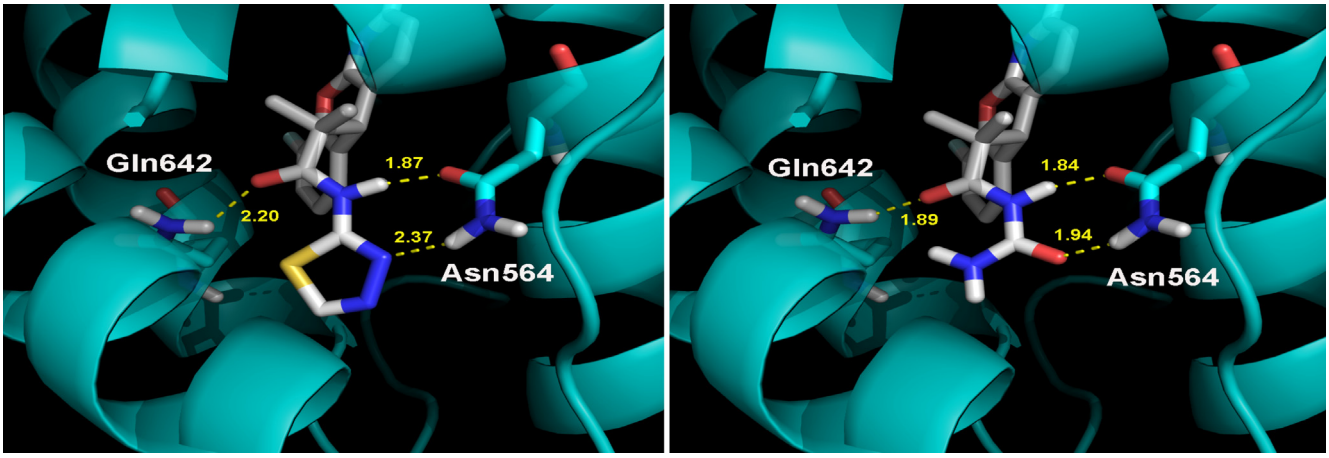
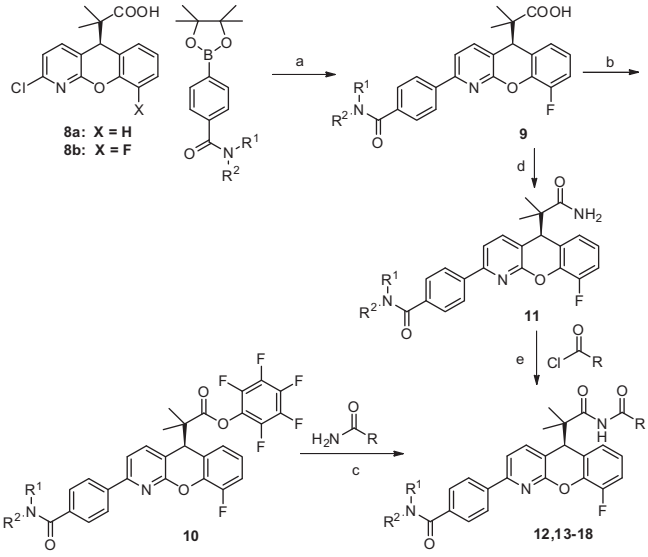
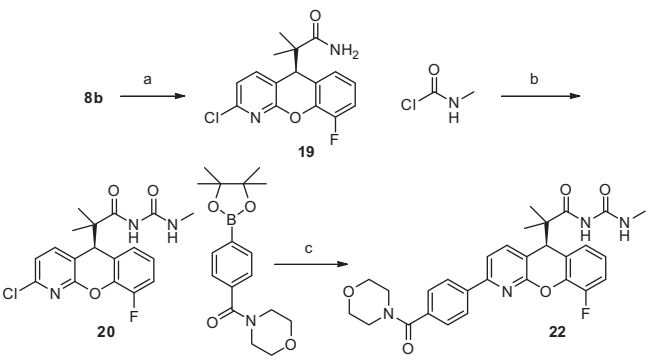


Figure 2. (Left) Azaxanthene 2-acylaminothiadiazole model based on published co-crystal structure of indazole 2-acylaminothiadiazole ligand (Ref. 8a: Sheppeck et al. *BMCL*, **2013**, *23*, 5442). (Right) Acyclic imide/acylurea modeled to mimic three-centered hydrogen bond network of thiazole and thiadiazole amide ligands.



Scheme 1. Acyclic imides synthesis. Reagents and conditions: (a) $Pd(PPh_3)_4$, DMF, K_3PO_4 (2 M), 90 °C, 92%; (b) pentafluorophenol, DCC, DMF, room temperature; (c) NaHMDS, THF, 0 °C, 65% for 2 steps; (d) NH_4Cl, HATU, DIEA, DMF, room temperature, 90%; (e) NaHMDS, THF, 0 °C, 66–70%.



Scheme 2. *N*-Methyl acylurea synthesis. Reagents and conditions: (a) NH_4Cl, HATU, DIEA, DMF, room temperature, 5 h, 85%; (b) $NaHSi(TMS)_2$ (1.5 equiv) or NaH, THF, 80%; (c) $Pd(PPh_3)_4$, DMF, K_3PO_4 (2M), 90 °C, 62%.

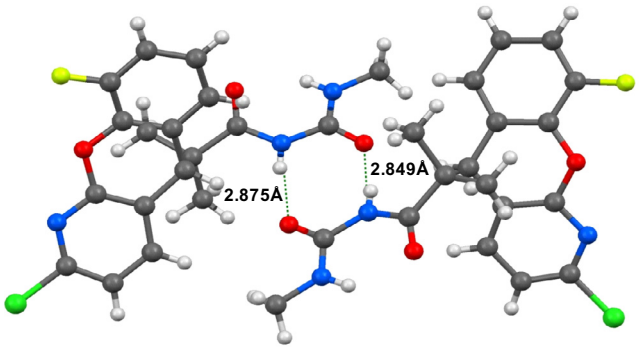
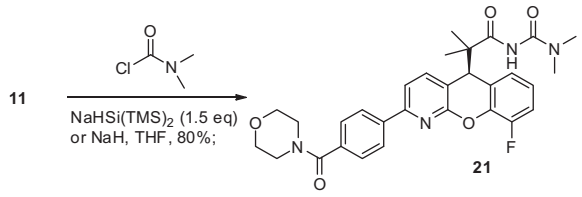
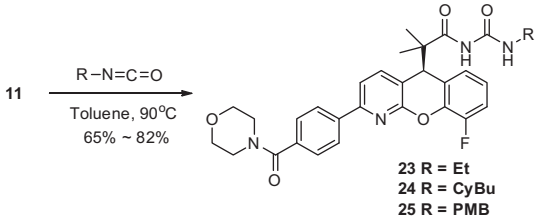


Figure 3. X-ray structure of *N*-methyl acylurea **20**.



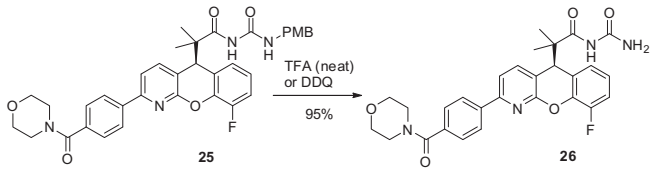
Scheme 3. *N*,*N*-Dimethyl acylurea synthesis.



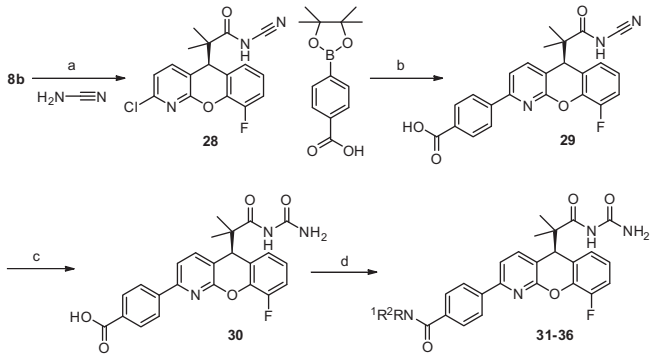
Scheme 4. Secondary acylurea synthesis.

However, neither *N*,*N*-dimethylacylurea **21** nor secondary acylureas **22-25** had good human whole blood activity (Table 1).

Gratifyingly, primary acylurea **26**, showed very good GR binding affinity (GR K_i = 2.1 nM) and potent functional activity in both AP-1 (EC_{50} = 2.1 nM) and E-selectin (EC_{50} = 1.2 nM) assays. More importantly, the human whole blood activity of **26** (*h*WB EC_{50} = 20 nM) increased dramatically to become as efficacious as dex (100% of dex) but with weaker NP-1 transactivation activity (74% of dex).



Scheme 5. Primary acylurea synthesis, a general method.



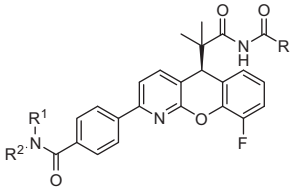
Scheme 6. Primary acylurea synthesis, an improved method. Reagents and conditions: (a) BOP, DIEA, DMF, 80 °C, 12 h, 80%; (b) $Pd(PPh_3)_4$, DMF, K_3PO_4 (2 M), 90 °C, 4 h, 65%; (c) 4 N HCl, dioxane, 60 °C, 2 h, 86%; (d) amine, BOP, DIEA, DMF, room temperature, 2 h, 80–90%.

Table 2 summarizes the comparison of primary acylurea **26** with the corresponding 2-acylaminothiadiazole **27**. Overall, both primary acylurea **26** and azole azide compound **27** not only have similar GR binding affinity and other NHRs selectivity, but also share similar functional activities in AP-1 repression assay and *h*WB LPS/THF activity. The NP-1 transactivation activity of acylurea **26** was found to be somewhat higher than that of **27**. Most importantly, primary acylurea **26** showed improved CYP450 inhibition, particularly against isoform 3A4, and metabolic stability. The half life of **26** upon incubation with human liver microsomes was found to be about four times longer than that of **27** (Table 2). Clearly, the issue of the relatively low PR selectivity relies on the morpholine amides of compounds **26** and **27**. Since the leading compound **7**, which bearing a *N*-methylethyl amide, possesses more than 1000-fold selectivity of PR/GR.

With the goals of both improving selectivity over PR and weakening transactivation activity, structure activity relationships around the pendant aryl ring were undertaken (Table 3). We first explored different benzamides. Not surprisingly (cf., **14** vs **15**), the results showed that pyrrolidine amides **32** and **33** displayed improved PR selectivity over corresponding morpholine amides **26** and **31**. We also found that PR affinity decreased for des-fluoro compounds, such as **31** and **33**. By removing the fluorine from the C-8 of the azaxanthene ring, the PR potency decreased about 4-fold. The 3*S*-fluoro-pyrollidine acylurea compound **34** showed no PR binding affinity (PR K_i >33330 nM).

At this point, we turned our attention to explore SAR to attenuate transactivation activity of the primary acylureas, since all of these primary acylureas displayed higher level of NP-1 transactivation activity compared against corresponding 2-acylamino-1,3,4-thiadiazoles. We previously reported that a desirable activity profile of a 'dissociated' GR agonist is one with good partial agonist activity in assays for transrepression, while showing some level of transactivation to achieve anti-inflammatory efficacy paralleling that of steroidal full GR agonists. NP-1 agonism efficacy in the range of 50–65% relative to dex (100%) provided useful efficacy both in whole blood and animal inflammatory models. We found that if the pendant phenyl was replaced with a 5-pyridinyl group, the primary acylureas **35** and **36** did show favorably attenuated NP-1 transactivation activity (53% and 55% of dex for **35** and **36**,

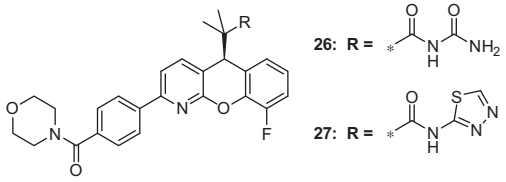
Table 1
Acyclic imide and acylurea replacement for azole amide[a]



Compd	Structure		GR binding[a]	PR binding[a]	AP-1 repression[b]		E-selectin repression[b]		NP-1 agonism[c]		*h*WB LPS/TNF	
	R	NR^1R^2	K_i (nM)	K_i (nM)	EC_{50} (nM)	%dex[d]	EC_{50} (nM)	%dex[d]	EC_{50} (nM)	%dex[d]	EC_{50} (nM)	%dex[d]
Dex			1.2	778	2.5	100	1.1	100	4.5	100	6.9	100
6			1.9	1529	33.2	70	33.8	63	242	32	830	83
7			1.6	1829	17.7	79	6.89	77	98.5	57	379	91
13	Me	NMe_2	69.4	12380	212.6	110	109.1	72	1046	55	1892	103
14	Me	Pyrrolidine	2.5	12380	5.1	100	3.6	89	27	67	218	96
15	Me	Morpholine	5.9	268	5	91	3.2	90	14	76	88	99
16	iPr	Morpholine	12.9	5043	23.7	61	74.8	61	1043	14	389	81
17	CyPr	Morpholine	8.5	2040	18.4	76	17.6	62	177	67	418	68
18	CyBu	Morpholine	8.7	5337	17.5	73	32.8	56	586	6	2378	72
21	NMe_2	Morpholine	110.5	10630	907	72	203.2	56	8912	55	–	–
22	NHMe	Morpholine	6.9	1168	10.7	77	16.1	66	302	67	1035	89
23	NHEt	Morpholine	5.7	2909	34.2	80	36.4	61	241	86	2143	88
24	NHcyBu	Morpholine	8.7	5337	17.5	73	32.8	56	676	87	2378	72
25	NHPMB	Morpholine	7.4	623	243.6	46	148.8	52	10530	–	–	–
26	NH_2	Morpholine	2.1	52.8	2.1	89	1.2	90	5.5	74	20.3	100

[a] Values are means of two or more experiments performed in triplicate.
[b] Activation protein (AP-1) and E-selectin assays were performed in an A549 lung epithelial line.
[c] GR transactivation NP-1 assay (run in agonist mode) was performed in the HeLa cell line.
[d] Efficacy represented as percentage of the maximal response of dexamethasone (100%).

Table 2
Comparison of acylurea **26** and 2-acylaminothiadiazole **27**[a]



Compd	**26**	**27**
GR binding K_i, nM	2.1	1.6
PR Binding K_i, nM	52.8	44.9
AR Binding K_i, nM	>50000	>50000
ERα Binding K_i, μM	>75	>75
MR agonist[b]	>5	>5
AP-1 repression $EC_{50,}$ nM (%dex)	2.1 (89)	2.1 (93)
NP-1 agonism $EC_{50,}$ nM (%dex)	5.5 (74)	10.8 (58)
*h*WB LPS/THF $EC_{50,}$ nM (%dex)	20.3 (100)	21.5 (108)
HLM $t_{1/2}$, min	41	9.1
CYP IC50, μM (3A4/2C8/2C9/2C19)	>40/8.9/14/11	0.3/3/7/1.0/1.3

[a] Values are means at least two experiments.
[b] In A549 cell line, EC_{50} (μM)/(%maximal efficacy) determination (aldosterone as a positive control).

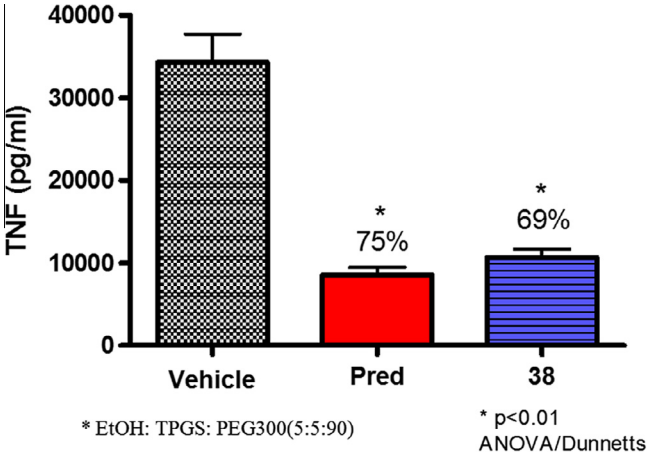
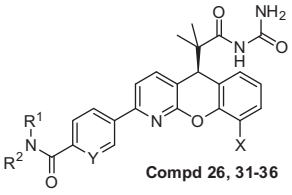


Figure 4. Compound **38** in rat LPS-induced TNFα.

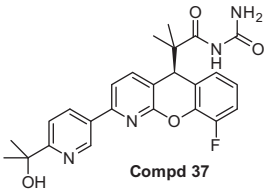
respectively). Potent and efficacious AP-1 and *h*WB activities were maintained. The attached amide group of the pendent pyridine could also be further modified to other groups such as *tert*-carbinol (**37**) and isopropoxyl (**38**). For example, compound **38** did show potent GR binding affinity and functional activity (GR K_i = 0.7 nM, AP-1 EC_{50} = 6.7 nM), selectivity over PR and AR (~450 fold and >7000 fold, respectively), and no potency below 10,000 nM in a in vitro safety assessment panel comprised of GPCR, neurotransmitter transporter, ion channel and enzyme off-targets (data not shown).

In light of its promising in vitro pharmacologic profile, acylurea **38** was selected for further evaluation. Half lives of **38** upon incubation with human, rat, and dog liver microsomes (1 mg/mL) were determined to be 191 min, 14 min, and 98 min, respectively. Accordingly, moderate clearance (20.8 mL/min/kg) was determined for **38** after a single 1 mg/kg intravenous dose to rats. A bioavailability of 25.7% was determined after a single 10 mg/kg oral dose of a solution of **38** to rats. The pharmacokinetics of **38** was also evaluated in dogs. Clearance with IV dose was low (9.0 mL/min/kg) and consistent with high microsomal stability. High exposures and 82% oral bioavailability was recorded after a single 5 mg/kg oral dose to dogs. In order to evaluate a pharmacodynamic effect of **38** in vivo, generation of TNF-α in LPS-challenged rats was determined. Thus, Lewis male rats received either a single 10 mg/kg oral dose of **38** (Fig. 4), prednisolone (30 mg/kg), or vehicle. Ninety minutes later, the LPS was administered IP, and serum TNF-α was determined after another 90 min. **38** was found to provide nearly equivalent efficacy to prednisolone (69% and 75% inhibition relative to vehicle, respectively). At 3 h post dose, the serum concentration of **38** was determined to be 0.5 μM, equivalent to

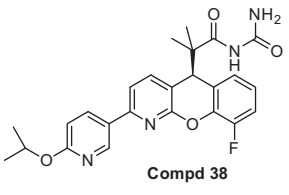
Table 3
Primary acylurea structure–activity relationship[a]



Compd 26, 31-36



Compd 37



Compd 38

Compd	Structure			GR binding	PR binding	AP-1 repression[b]		E-selectin repression[b]		NP-1 agonism[c]		*h*WB LPS/TNF[c]		Metabolic stability
	X	Y	NR^1R^2	K_i (nM)	K_i (nM)	EC_{50} (nM)	%Dex[d]	EC_{50} (nM)	%Dex[d]	EC_{50} (nM)	%Dex[d]	EC_{50} (nM)	%Dex	% remaining (h/r/m)
26	F	CH	Morpholine	2.1	52.8	2.1	89	1.2	90	5.5	74	20.3	100	83/90/80
31	H	CH	Morpholine	1.5	282.2	6.2	111	4.8	90	11	79	3054	98	95/86/75
32	F	CH	Pyrrolidine	0.7	604.1	1.6	90	1.4	88	5.3	98	—	—	89/71/73
33	H	CH	Pyrrolidine	1.9	2322	8.7	95	5.0	94	49.3	87	207	101	78/49/76
34	F	CH	3*S*-F-pyrrolidine	1.2	33330	0.8	104	0.6	90	1.3	94	—	—	56/67/77
35	F	N	Pyrrolidine	2.0	1362	16.5	90	12.2	79	112.6	53	211	99	73/86/86
36	F	N	Morpholine	7.3	22.7	20.3	96	16.3	77	142.9	55	277	93	—/—/—
37				4.0	106.2	21.9	97	14.7	85	107.4	49	199	106	73/83/76
38				0.7	312.5	6.7	82	3.8	79	59.2	54	355	101	97/58/86

[a] Values are means of two or more experiments performed in triplicate.
[b] Activation protein (AP-1) and E-selectin assays were performed in an A549 lung epithelial line.
[c] GR transactivation NP-1 assay (run in agonist mode) was performed in the HeLa cell line.
[d] Efficacy represented as percentage of the maximal response of dexamethasone (100%). %Dex is not reported where <5%.

eight-fold the IC_{50} for inhibition of LPS-induced TNFα in rat whole blood.

In conclusion, acyclic imides and acylureas have been found to serve as excellent isosteres for 2-acylamino-1,3,4-thiadiazole in the azaxanthene series of GR agonists. A structure-based design approach was used in their identification, rationalizing that a network of three key hydrogen bonds to the receptor would be maintained, and SAR favoring primary and secondary (over tertiary) acylureas is consistent with the proposed binding mode. Primary acylureas were found to be particularly potent and efficacious in cellular assays of transrepression and transactivation. Microsomal stability and CYP inhibition profiles of primary acylureas were found to be generally improved relative to 2-acylaminothiadiazoles. SAR to weaken transactivation while maintaining anti-inflammatory activity (cytokine inhibition) in human whole blood was identified, leading to the identification of **38**, a compound with promising pharmacokinetic properties and which proved efficacious in a pharmacodynamic assay in vivo. Ultimately, the utility of partial agonists of GR such as **38** in treating human disease while improving on the safety profile of traditional glucocorticoids remains to be determined.

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