ACS Medicinal Chemistry Letters

Letter

pubs.acs.org/acsmedchemlett

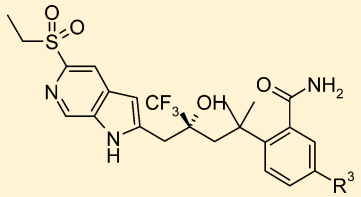
Optimization of Drug-Like Properties of Nonsteroidal Glucocorticoid Mimetics and Identification of a Clinical Candidate

Christian Harcken,* Doris Riether, Pingrong Liu, Hossein Razavi, Usha Patel, Thomas Lee, Todd Bosanac, Yancey Ward, Mark Ralph, Zhidong Chen, Donald Souza, Richard M. Nelson, Alison Kukulka, Tazmeen N. Fadra-Khan, Ljiljana Zuvela-Jelaska, Mita Patel, David S. Thomson, and Gerald H. Nabozny

Department of Medicinal Chemistry and Department of Immunology and Inflammation, Boehringer Ingelheim Pharmaceuticals, Inc., 900 Ridgebury Road, Ridgefield, Connecticut 06877, United States

Supporting Information

ABSTRACT: A series of nonsteroidal "dissociated" glucocorticoid receptor agonists was optimized for drug-like properties such as cytochrome P450 inhibition, metabolic stability, aqueous solubility, and hERG ion channel inhibition. This effort culminated in the identification of the clinical candidate compound (*R*)-**39**.



(*R*)-**38** R^3 = H
(*R*)-**39** R^3 = F

KEYWORDS: *Glucocorticoid mimetics, nonsteroidal glucocorticoids, glucocorticoid-induced osteoporosis, azaindoles, anti-inflammatory agents, drug-like properties*

Cortisol and the related cortisone and corticosterone are steroid hormones that are referred to as glucocorticoids (GCs) and bind to the glucocorticoid receptor (GR), which belongs to a large family of transcription factors, the superfamily of nuclear hormone receptors. GCs play an important role in the regulation of the immune system and therefore are widely used in the treatment of inflammatory and immune diseases such as rheumatoid arthritis, asthma, allergy, and sepsis.[1] Synthetic GCs, which differ from cortisol in their pharmacokinetics and pharmacodynamics, have been created with dexamethasone (**1**) and prednisolone (**2**) (Figure 1) being among the most extensively used anti-inflammatory agents. However, because of harmful dose-limiting side effects and the occurrence of glucocorticoid resistance, the use of these drugs is limited. Side effects include weight gain, hypertension, muscle weakness, skin thinning, diabetes, and the most troublesome

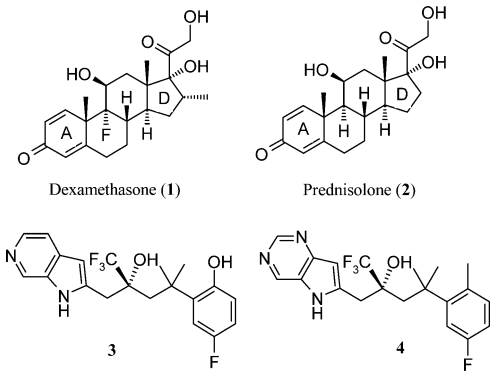


Figure 1. Glucocorticoid receptor agonists.

GC-induced osteoporosis leading to a weakening of the trabecular bone, which causes a significant increase in the risk of spine, hip, and rib fracture.[2,3]

Upon binding of GCs to GR, a conformational change is provoked leading to the release of GR from the chaperone complexes and unmasking of nuclear localization signals followed by translocation of the GR–ligand complex to the nucleus.[4,5] There, it is thought to directly and indirectly induce the expression of a few hundred genes, which is largely cell-type specific. The precise molecular mechanism is highly complex and, despite an impressive amount of research, still only partially understood. However, a simplistic hypothesis, which is based on a series of experiments,[6,7] has become broadly accepted among researchers aiming at GCs with reduced side effects. This hypothesis attributes the anti-inflammatory effects of GCs to the inhibition of gene transcription, referred to as transrepression, while making the activation of transcription, called transactivation, responsible for the majority of side effects. Mechanistically it was rationalized that transrepression involves the GR–ligand complex indirectly in the transcription process through its interaction in a monomeric form with transcription factors such as NF-κB and AP-1 resulting in the down-regulation of key cytokine inflammatory mediators such as TNF-α, IL-1, IL-2, and IL-6. The transactivation pathway directly involves homodimers of GR recognizing GR response elements (GREs) on the DNA resulting in the transcription of genes.[8] While this hypothesis is experimentally poorly

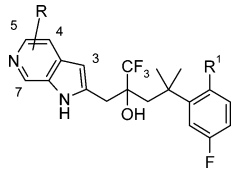
Received: September 24, 2014
Accepted: November 17, 2014
Published: November 20, 2014

Table 1. Profile of Previous Leads

compd	GR IC_{50} [nM][a]	IL-6 IC_{50} [nM] and max. eff. [%][a,b]	MMTV and OC max. eff.[b]	CYP 1A2, 2D6, 2C9, 2C19, 3A4 IC_{50} [μM]	HLM (%Q_h), rat PK $t_{1/2}$	thermodyn. sol pH 6.8 [μg/mL]	patch clamp hERG channel IC_{50} [μM]
3	2	4 (93%)	10%/68%	nd[c]/nd[c]/2/0.2/0.9	47/2 h	10	4.5
4	4	13 (72%)	0%/32%	30/4/10/1/0.1	89/1 h	9	3.8

[a]IC_{50} values are the mean of at least two values, each determined from duplicate 11-point concentration response curves. [b]Maximum efficacy at the highest tested concentration compared to dexamethasone, defined at 100%; maximum concentration tested is 2 μM. [c]Not determined.

Table 2. Substitution on Azaindoles



compd (R^1 = Me)	R	GR IC_{50} [nM][a]	PR IC_{50} [nM][a]	IL-6 IC_{50} [nM] and max. eff. [%][a,b]	CYP3A4 IC_{50} [μM]	HLM (%Q_h)
8	H	10	1900	38 (89%)	0.1	76
9	3-Me	9	240	5 (93%)	0.1	72
10	4-Me	11	1100	59 (91%)	2	81
11	5-Me	22	>2000	170 (71%)	0.6	78
12 (R^1 = OMe)	5,7-Me_2	510	>2000	>2000	0.2	93
13	5-Phe	26	>2000	2 (96%)	3	53
14	5-NH_2	7	1000	37 (91%)	0.5	66
15	5-NMe_2	10	>2000	38 (87%)	0.6	39
16	5-OiPr	10	>2000	3 (96%)	0.3	73
17	5-(4-morpholinyl)	3	>2000	3 (94%)	0.01	31
18	5-$CONH_2$	7	1700	300 (54%)	2	93
19 (R^1 = OMe)	5-SO_2Me	28	>2000	>2000 (40%)	2	91

[a]IC_{50} values are the mean of at least two values, each determined from duplicate 11-point concentration response curves. [b]Maximum efficacy at the highest tested concentration compared to dexamethasone, defined at 100%; maximum concentration tested is 2 μM.

supported and partially even contradicted,[9] it served as an appealing working model for drug discovery programs over the past decade.[10] Several companies have invested intense research in the quest of identifying functionally selective, so-called "dissociated" synthetic glucocorticoids with the goal of offering a therapeutic advantage over currently marketed GCs.[11−13]

We have previously disclosed the identification of non-steroidal GC mimetics,[14,15] including a series of trifluoromethylcarbinol derived compounds.[16−19] Therein we described the identification and profile of azaindole compounds such as **3** and **4** that have demonstrated excellent nuclear receptor selectivity (specifically over the progesterone and mineralocorticoid receptors), potent GR agonism (as indicated by their *in vitro* suppression of IL-1 induced IL-6 production in human foreskin fibroblasts), and excellent *in vivo* activity in chronic disease models (indicated by their inhibition of collagen-induced arthritis in mouse) (Figure 1). We described compounds exemplified by **3**, which showed reduced transactivation (as indicated *in vitro* by their reduced potency and reduced maximum efficacy in an MMTV-promoter transfected HeLa cell) and reduced incidence of metabolic side effects upon chronic dosing *in vivo* (as indicated by reduced increase in body fat, reduced triglyceride, and reduced insulin levels compared to equi-efficacious doses of prednisolone in healthy mice). Compounds exemplified by **4** showed reduced activation of a bone relevant dissociation marker (such as suppression of vitamin D stimulated osteocalcin production in MG-63 osteosarcoma cells) and reduced bone loss compared to traditional GCs upon chronic dosing in healthy mice *in vivo* (indicated by a reduced decrease in femur cortical thickness by microCT compared to prednisolone). However, to enable the evaluation of compounds with such dissociation clinically, a compound with drug-like properties suitable for clinical testing had to be identified. The optimization effort toward our clinical candidate (***R***)-**39** is reported in this letter.

Table 1 shows the drug-like properties of previously identified and described compounds **3** and **4**. Clearly, the compounds are at high risk of drug−drug interactions due to their potent cytochrome P450 (CYP) inhibition across multiple isoforms. Preliminary dose projections showed a potential for high clinical dose requirements due to their overall high clearance and low bioavailability.[18] The safety margins of these compounds are limited due to potent inhibition of the human ether-a-go-go potassium channel (hERG channel), which is involved in cardiac repolarization. Lastly, the aqueous solubility of these compounds is low, potentially contributing to low bioavailability and complicating clinical formulation development.

The 6-azaindole moiety had previously been identified as a preferred steroid A-ring mimetic that allowed combining the desired dissociated biological profile with acceptable PK properties.[16] However, it was assumed that this moiety is also primarily responsible for the potent CYP inhibition and hERG channel inhibition observed. The effect of substitution on the azaindole ring system had not been examined previously. It was hypothesized that substitution could have an effect on the ability of the azaindoles to function as a nucleophilic ligand for CYP enzymes. A limited exploration of substitution on the A-ring mimetic had been undertaken on the related indole[17] and diazaindole[18] ring systems; however, no significant trends with

dx.doi.org/10.1021/ml500387y | ACS Med. Chem. Lett. 2014, 5, 1318−1323

regard to reducing CYP inhibition had been observed. A more systematic investigation was called for.

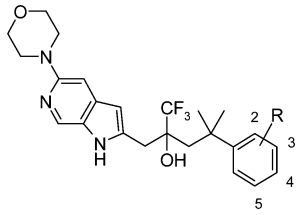
All analogues with modified substitution on the azaindole were prepared in combination with the 2-methyl-5-fluorophenyl D-ring mimetic (except in two cases where the approximately equivalent 2-methoxy-5-fluorophenyl moiety was used). Substitution in the 3-position of the azaindole as in **9** reduced NR selectivity (PR selectivity factor was approximately 25-fold) compared to the comparator **8** (Table 2). Small substitution in the 4-position such as methyl in **10** appeared tolerated and demonstrated some reduction in CYP3A4 inhibition. Larger substituents in the 4-position were not tolerated (data not shown).

Small substituents in the 5-position led to a significant reduction in agonist potency (IL-6 IC_{50} 170 nM in **11**). Additional 7-substitution abolished even the GR binding affinity (GR IC_{50} 510 nM in **12**). Furthermore, flanking of the nucleophilic azaindole nitrogen with methyl groups on both sides as in **12** provided very little improvement in the CYP profile.

Large substituents in the 5-position exemplified by phenyl-substituted **13** were well tolerated. Compounds with large A-ring substitution are presumed to access an induced A-ring pocket;[21] they typically show steroid-like potency (IL-6 IC_{50} 2 nM for **13** vs 1 nM for dexamethasone), full agonist activity (96% vs 100% for dexamethasone), and little or no dissociation. With this opportunity for substitution in the 5-position we planned to assess the impact of electron donating and electron withdrawing groups (EWG) and further test the tolerance for polar substituents based on our overall goal to address not only the CYP and hERG channel inhibition, but also to increase metabolic stability and increase solubility. Small electron donor groups like amino in **14** or dimethylamino in **15** maintained a similar profile compared to the unsubstituted azaindole. Increased potency was achieved by substitution with a larger donor group such as isopropoxy in **16** or 4-morpholinyl in **17**. None of these compounds show sufficient reduction of CYP inhibition; however, it was noted that these donor-substituted azaindole compounds typically showed improved metabolic stability. Electron-withdrawing groups like carboxamido in **18** or methylsulfonyl in **19** diminish the nucleophilicity of the azaindole nitrogen the most and result in a significantly improved CYP profile (CYP3A4 IC_{50} 18 μM for **18**); however, these compounds lose most of their GR agonist activity. None of the substitutions on the azaindole ring system appeared to be helpful in reducing CYP3A4 inhibition while maintaining an overall acceptable profile. The hERG channel inhibition and solubility profile of these compounds was not improved significantly either (e.g., **13** hERG channel IC_{50} 3.8 μM; **17** solubility 5.3 μg/mL at pH 6.8). Therefore, we turned next to an exploration of substitution on the D-ring mimetic phenyl ring.

A limited structure−actvity relationship (SAR) study of D-ring substitution had been performed previously using the unsubstituted 6-azaindole;[16] however, to allow for greater flexibility with regard to potency as well as metabolic stability, more drastic changes on the D-Ring were examined using the potent and metabolically stable 5-morpholinyl substituted 6-azaindole. Some historic D-ring mimetics were re-examined: The unsubstituted phenyl comparator **20** showed good agonist efficacy (Table 3). 3-Fluoro substitution as in **21** had little to no effect, whereas 4-fluoro substitution in **22** reduced agonist potency and efficacy. The 2-methoxy-5-fluorophenyl D-ring

Table 3. 5-(4-Morpholinyl)-6-azaindoles



compd	R	GR IC_{50} [nM][a]	IL-6 IC_{50} [nM] and max. eff. [%][a,b]	CYP3A4 IC_{50} [μM]	HLM (%Q_h)
20	H	8	17 (90%)	0.1	33
21	3-F	9	18 (89%)	0.1	29
22	4-F	14	48 (64%)	0.1	nd[c]
23	2-OMe-5-F	2	2 (95%)	0.2	47
24	3-OH	24	53 (80%)	4	68
25	2-$CONH_2$	19	4 (95%)	3	36
26	2-SO_2Me	10	2 (95%)	0.01	62
27	2-SO_2NH_2	21	7 (95%)	0.5	67
28	3-$CONH_2$	46	56 (82%)	2	60
29	3-SO_2Me	62	60 (81%)	0.7	65
30	3-SO_2NH_2	170	>2000 (37%)	2	52

[a]IC_{50} values are the mean of at least two values, each determined from duplicate 11-point concentration response curves. [b]Maximum efficacy at the highest tested concentration compared to dexamethasone, defined at 100%; maximum concentration tested is 2 μM. [c]Not determined.

mimetic in **23** had previously been demonstrated to be approximately equivalent to the standard 2-methyl-5-fluorophenyl group. It was known that phenolic hydroxyl groups are tolerated in the 2-position (see **3** in Table 1); however, a hydroxyl group in the 3-position as in **24** caused a significant reduction of the maximum agonist efficacy. Despite this fact, we were eager to test alternative polar substituents of different electronic nature in an effort to address key liabilities. This effort paid off as EWG-substitution in the 2-position with hydrogen donor/acceptor properties such as carboxamido in **25**, methylsulfonyl in **26**, and sulfonylamido in **27** were very well tolerated and provided compounds as potent and efficacious as the 2-methoxy-5-fluorophenyl and 2-methyl-5-fluorophenyl analogue discussed above. These EWG-substituted D-ring mimetics are in fact more potent and efficacious than those standard moieties which only becomes apparent in combination with weaker A-ring mimetics (see below). The same EWG-substitution in the 3-position of the D-ring mimetic such as in **28**, **29**, and **30** resulted in reduced potency and efficacy in good agreement with the SAR understanding.

It was noted that the improved metabolic stability of the donor-substituted azaindoles was maintained. All compounds in Table 3 (with the exception of **23**) showed good NR selectivity with a PR and MR IC_{50} > 2000 nM. As expected, additional polar substituents helped reduce hERG channel inhibition and improve aqueous solubility (e.g., **26** hERG channel IC_{50} 20 μM; **29** solubility 47 μg/mL at pH 6.8). Most importantly, the CYP3A4 inhibition IC_{50} values for all compounds in Table 3 were ranging from 0.01 to 4 μM. Despite the absence of any obvious CYP3A4 inhibition SAR trends, this supported the further investigation of the series.

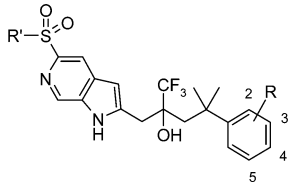
After this exploration of substitution on A-ring and D-ring mimetic moieties it became apparent that substituents in both positions have a major impact on CYP3A4 inhibition and metabolic stability but also hERG channel inhibition and

dx.doi.org/10.1021/ml500387y | ACS Med. Chem. Lett. 2014, 5, 1318−1323

solubility. However, it was not obvious whether any combination of residues could achieve the desired balance of all parameters. From various combination molecules that were made, the combination of the A-ring mimetics with weak agonist potency (but the best CYP inhibition profile) with the most potent (but also most CYP3A4 inhibiting) D-ring mimetics showed some promise. Specifically, the 5-EWG substituted 6-azaindoles (such as **18** and **19** in Table 2) as A-ring mimetics were combined with 2-EWG substituted phenyl D-ring mimetics (such as **25** and **26** in Table 3).

The first combination of the methylsulfonyl azaindole with the 2-carboxamidophenyl D-ring mimetic **31** provided a breakthrough (Table 4): The compound showed acceptable

Table 4. 5-(Alkylsulfonyl)-6-azaindoles



compd	R	R′	GR IC_{50} [nM][a]	IL-6 IC_{50} [nM] and max. eff. [%][a, b]	CYP3A4 IC_{50} [μM]	HLM (%Q_h)
31	2-$CONH_2$	Me	140	80 (86%)	>30	27
32	2-CONHMe	Me	>2000	nd[c]	nd[c]	nd[c]
33	2-SO_2Me	Me	34	27 (91%)	>30	93
34	2-SO_2NH_2	Me	180	200 (77%)	15	65
35	2-$CONH_2$-4-F	Me	120	59 (90%)	3	47
36	2-$CONH_2$-4-Cl	Me	40	19 (93%)	15	23
37	2-$CONH_2$-4-Me	Me	110	45 (92%)	6	72
38	2-$CONH_2$	Et	370	100 (86%)	14	66
39	2-$CONH_2$-4-F	Et	70	46 (88%)	26	29
40	2-$CONH_2$-4-F	iPr	370	570 (66%)	4	11
41		Me	260	>2000 (21%)	2	93

[a]IC_{50} values are the mean of at least two values, each determined from duplicate 11-point concentration response curves. [b]Maximum efficacy at the highest tested concentration compared to dexamethasone, defined at 100%; maximum concentration tested is 2 μM. [c]Not determined.

agonist potency and efficacy (IL-6 IC_{50} 80 nM with 86% max. efficacy) while not showing any CYP3A4 inhibition up to 30 μM and good metabolic stability (27% Q_h). It is assumed that the high polar surface area plays a key role in reducing the affinity to CYP enzymes as an inhibitor and as a metabolic substrate beyond what would have been expected if the properties of the A-ring and D-ring moieties had simply been additive. Curiously, these compounds with high polar surface area on both ends of the molecule show somewhat diminished GR binding (e.g., GR IC_{50} 140 nM vs IL-6 IC_{50} 80 nM for **31**). Available space in the 2-position on the D-ring mimetic is strictly limited: The methylamide **32** loses all GR activity. The bis-methylsulfone **33** shows a similar improvement in the CYP profile but is rapidly metabolized. The sulfonamide **34** loses additional potency. Next, an additional D-ring substitution was investigated to fine-tune the profile. An additional 4-fluoro substituent in **35** maintained the profile of **31**, an additional chloro substitution in **36** increased the maximum efficacy, the compound lost the dissociated profile (data not shown), and an additional methyl group in **37** started to erode the metabolic stability. The size of the A-ring sulfone was varied next. The ethylsulfones **38** and **39** maintain potency, while with further increased size, exemplified here by the isopropylsulfone **40** or the conformationally restrained cyclic sulfone **41**, a significant loss of potency is caused.

All compounds in Table 4 show good NR selectivity with PR and MR IC_{50} values > 2000 nM and no detectable inhibition at that highest tested concentration.

Compounds **38** and **39** showed the best overall profile and were selected for further studies. Both compounds were resynthesized as pure enantiomers using a combination of the racemic route described in the Supporting Information and the previously published general asymmetric synthesis for this scaffold.[22] **(*R*)-38** and **(*R*)-39** were isolated with >99% *ee*. A highly optimized, large-scale enantiopure synthesis of **(*R*)-39** was published recently.[23] The pure enantiomers showed an approximately 2-fold improved potency against GR compared to the racemic mixtures as expected (Table 5). The maximum transrepression efficacy remained at 87% and 88%, respectively, which translated into a desirable dissociation profile with maximum effects at 2 μM of 27% and 33% for the MMTV reporter gene assay (vs dexamethasone at 100%) and 44% and 39% for osteocalcin production (vs dexamethasone at 100%), respectively. Both compounds showed significantly reduced inhibition of CYP activity across isoforms (measured as inhibition of conversion of reference drug substrates in microsomes). The metabolic stability of **(*R*)-39** is higher than for **(*R*)-38**; however, their *in vivo* PK profile is similar with rat PK half-lives of 5.8 and 4.2 h, respectively. The thermodynamic equilibrium solubility of the most stable polymorph of the compounds was still low with 10 and 5 μg/mL, respectively; however, formulations with acceptable dissolution rates and preclinical bioavailability were identified for **(*R*)-39**. Lastly, the increased polar surface area of the molecules resulted in reduced affinity to the hERG ion channel (IC_{50} > 30 μM).

For unknown reasons, a previously not observed species selectivity (reduced mouse functional transrepression potency assessed as inhibition of TNF-stimulated IL-6 production in mouse RAW cells, **(*R*)-39** IC_{50} 600 nM) of this subseries of compounds precluded a pharmacological evaluation in standard preclinical *in vivo* mouse models. However, the translation of *in vitro* dissociation markers to preclinical *in vivo* parameters in mouse models had been previously established with tool compounds from this series and was expected to apply to these

Table 5. Profile of Enantiopure Preferred Compounds

compd	GR IC_{50} [nM][a]	IL-6 IC_{50} [nM] and max. eff. [%][a,b]	MMTV and OC max. eff.[b]	CYP 1A2, 2D6, 2C9, 2C19, 3A4 IC_{50} [μM]	HLM (%Q_h), rat PK $t_{1/2}$	thermodyn. sol pH 6.8 [μg/mL]	patch clamp hERG channel IC_{50} (μM)
(*R*)-38	95	43 (87%)	27%/44%	>50/>50/12/40/34	69/5.8 h	10	>30
(*R*)-39	55	23 (88%)	33%/39%	>50/41/12/9/8	11/4.2 h	5	>30

[a]IC_{50} values are the mean of at least two values, each determined from duplicate 11-point concentration response curves. [b]Maximum efficacy at the highest tested concentration compared to dexamethasone, defined at 100%; maximum concentration tested is 2 μM.

dx.doi.org/10.1021/ml500387y | *ACS Med. Chem. Lett.* 2014, 5, 1318−1323

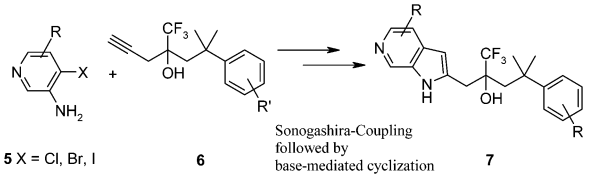
optimized compounds.[18] (*R*)-**39** was tested in a 9-day type II collagen-induced arthritis model in rats at 3, 10, and 30 mg/kg qd po in 30% cremophor to guide human efficacious concentration projections. Animals treated with the low dose (3 mg/kg) of (*R*)-**39** had nonsignificant decreases for all measured histology parameters (ankle inflammation, pannus formation, cartilage damage, and bone resorption). Pannus and bone resorption were near significant (25%, $p = 0.07$). Mid-dose (10 mg/kg) animals had significantly decreased pannus and bone resorption (33%) as well as summed scores (27%), while all parameters were significantly decreased (87−96%) in the high dose (30 mg/kg) group (data not shown). The ED_{50} value for the summed scores was 14 mg/kg. No side effect related parameters were feasible to be evaluated in this shorter duration model.

(*R*)-**39** met all our preclinical criteria and progressed into clinical development. Results from early clinical trials will be reported in due course.

EXPERIMENTAL PROCEDURES

Synthesis. All compounds (except **9**) described herein have been synthesized following the general scheme outlined in previous publications and summarized in Scheme 1:[16,18] A substituted

Scheme 1. Synthesis of Azaindoles



halogenated aminopyridine **5** undergoes a Sonogashira coupling with the alkyne **6**, and the coupling product is cyclized under basic conditions to the azaindoles **7**.[20] The majority of the synthetic effort was spent on generating the required substituted alkynes and substituted pyridines, where required, compounds were modified further after the key coupling/cyclization sequence. Synthetic schemes outlining the synthesis of each individual compound are given in the Supporting Information. All compounds discussed have been synthesized and tested as racemic mixtures unless noted otherwise. It is known that all GR activity in this class of compounds resides in the (*R*)-isomers.[16]

Methods. Assay descriptions can be found in the Supporting Information.

ASSOCIATED CONTENT

Supporting Information

Assay descriptions, compound purity information, analytical data for (*R*)-**38** and (*R*)-**39**, and synthetic schemes detailing the preparation of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

*Tel. 203-778-7924. E-mail christian.harcken@boehringer-ingelheim.com.

Notes

The authors declare no competing financial interest.

ABBREVIATIONS

AP-1, Activator protein 1; CYP, cytochrome P450; EWG, electron-withdrawing group; FBS, fetal bovine serum; GC, glucocorticoid; GR, glucocorticoid receptor; GRE, glucocorticoid response element; hERG, human ether-a-go-go related gene; HLM, human liver microsome; IL-1,2,6, interleukin 1,2,6; MMTV, mouse mammary tumor virus; MR, mineralocorticoid receptor; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; PR, progesterone receptor; Q_h, hepatic blood flow; TA, transactivation; TNF-α, tumor necrosis factor alpha; TR, transrepression

REFERENCES

(1) Buttgereit, F.; Saag, K. G.; Cutolo, M.; da Silva, J. A. P.; Bijlsma, J. W. J. The molecular basis for the effectiveness, toxicity, and resistance to glucocorticoids: focus on the treatment of rheumatoid arthritis. *Scand. J. Rheumatol.* **2005**, *34*, 14−21.

(2) Schäcke, H.; Döcke, W.-D.; Asadullah, K. Mechanisms involved in the side effects of glucocorticoids. *Pharmacol. Ther.* **2002**, *96*, 23−43.

(3) Weinstein, R. S. Glucocorticoid-induced bone disease. *N. Engl. J. Med.* **2011**, *365*, 62−70.

(4) Zhou, J.; Cidlowski, J. A. The human glucocorticoid receptor: One gene, multiple proteins and diverse responses. *Steroids* **2005**, *70*, 407−417.

(5) Adcock, I. M. Molecular mechanisms of glucocorticosteroid actions. *Pulm. Pharmacol. Ther.* **2000**, *13*, 115−126.

(6) Clark, A. R.; Belvisi, M. G. Maps and legends: the quest for dissociated ligands of the glucocorticoid receptor. *Pharmacol. Ther.* **2012**, *134*, 54−67.

(7) Reichardt, H. M.; Tuckermann, J. P.; Gottlicher, M.; Vujic, M.; Weih, F.; Angel, P.; Herrlich, P.; Schütz, G. Repression of inflammatory responses in the absence of DNA binding by the glucocorticoid receptor. *EMBO J.* **2001**, *20*, 7168−7173.

(8) Newton, R.; Holden, N. S. Separating transrepression and transactivation: a distressing divorce for the glucocorticoid receptor? *Mol. Pharmacol.* **2007**, *72*, 799−809.

(9) Clark, A. R.; Belvisi, M. G. Maps and legends: the quest for dissociated ligands of the glucocorticoid receptor. *Pharmacol. Ther.* **2012**, *134*, 54−67.

(10) Buckbinder, L.; Robinson, R. P. The glucocorticoid receptor: molecular mechanism and new therapeutic opportunities. *Curr. Drug Targets: Inflammation Allergy* **2002**, *1*, 127−136.

(11) Razavi, H.; Harcken, C. Non-Steroidal Dissociated Glucocorticoid Receptor Agonists. In *Anti-Inflammatory Drug Discovery*; Levin, J., Laufer, S., Eds.; RSC Publishing: London, U.K., 2012; pp 481−516.

(12) Berlin, M. Recent advances in the advancement of glucocorticoid receptor modulators. *Expert Opin. Ther. Patents* **2010**, *20*, 855−873.

(13) DeBosscher, K. Selective glucocorticoid modulators. *J. Steroid Biochem. Mol. Biol.* **2010**, *120*, 96−104.

(14) Kuzmich, D.; Bentzien, J.; Betageri, R.; DiSalvo, D.; Fadra-Khan, T.; Harcken, C.; Kukulka, A.; Nabozny, G.; Nelson, R.; Pack, E.; Souza, D.; Thomson, D. Function-regulating pharmacophores in a sulfonamide class of glucocorticoid receptor agonists. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 6640−6644.

(15) Regan, J.; Lee, T. W.; Zindell, R. M.; Bekkali, Y.; Bentzien, J.; Gilmore, T.; Hammach, A.; Kirrane, T. M.; Kukulka, A. J.; Kuzmich, D.; Nelson, R. M.; Proudfoot, J. R.; Ralph, M.; Pelletier, J.; Souza, D.; Zuvela-Jelaska, L.; Nabozny, G.; Thomson, D. S. Quinol-4-ones as steroid A-ring mimetics in nonsteroidal dissociated glucocorticoid agonists. *J. Med. Chem.* **2006**, *49*, 7887−7896.

(16) Riether, D.; Harcken, C.; Razavi, H.; Kuzmich, D.; Gilmore, T.; Bentzien, J.; Pack, E. J., Jr.; Souza, D.; Nelson, R. M.; Kukulka, A.; Fadra, T. N.; Zuvela-Jelaska, L.; Pelletier, J.; Dinallo, R.; Panzenbeck, M.; Torcellini, C.; Nabozny, G. H.; Thomson, D. S. Non-steroidal dissociated glucocorticoid agonists containing azaindoles as steroid A-ring mimetics. *J. Med. Chem.* **2010**, *53*, 6681−6698.

(17) Betageri, R.; Gilmore, T.; Kuzmich, D.; Kirrane, T. M.; Bentzien, J.; Wiedenmeyer, D.; Regan, J.; Kukulka, A. J.; Fadra, T. N.; Nelson, R. M.; Zuvela-Jelaska, L.; Souza, D.; Pelletier, J.; Proudfoot, J.;

Dinallo, R.; Panzenbeck, M.; Torcellini, C.; Lee, H.; Pack, E.; Harcken, C.; Nabozny, G.; Thomson, D. S. Non-steroidal dissociated glucocorticoid agonists: Indoles as A-ring mimetics and function-regulating pharmacophores. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 6842−6851.

(18) Harcken, C.; Riether, D.; Kuzmich, D.; Liu, P.; Betageri, R.; Ralph, M.; Emmanuel, M.; Reeves, J. T.; Berry, A.; Souza, D.; Nelson, R. M.; Kukulka, A.; Fadra, T. N.; Zuvela-Jelaska, L.; Dinallo, R.; Bentzien, J.; Nabozny, G. H.; Thomson, D. S. Identification of highly efficacious glucocorticoid receptor agonists with a potential for reduced clinical bone side effects. *J. Med. Chem.* **2014**, *57*, 1583−1598.

(19) Razavi, H.; Riether, D.; Harcken, C.; Bentzien, J.; Dinallo, R. M.; Souza, D.; Nelson, R. M.; Kukulka, A.; Fadra-Kahn, T. N.; Pack, E. J.; Zuvela-Jelaska, L.; Pelletier, J.; Panzenbeck, M.; Torcellini, C. A.; Proudfoot, J. R.; Nabozny, G. H.; Thomson, D. S. Discovery of a potent and dissociated non-steroidal glucocorticoid receptor agonist containing an alkyl carbinol pharmacophore. *Bioorg. Med. Chem. Lett.* **2014**, *24*, 1934−1940.

(20) Harcken, C.; Ward, Y.; Thomson, D.; Riether, D. A general and efficient synthesis of azaindoles and diazaindoles. *Synlett* **2005**, *20*, 3121−3125.

(21) Suino-Powell, K.; Xu, Y.; Zhang, C.; Tao, Y.-G.; Tolbert, W. D.; Simons, S. S., Jr.; Xu, H. E. Doubling the size of the glucocorticoid receptor ligand binding pocket by deacylcortivazol. *Mol. Cell. Biol.* **2008**, *28*, 1915−1923.

(22) Lee, T. W.; Proudfoot, J. R.; Thomson, D. S. A concise asymmetric route for the synthesis of a novel class of glucocorticoid mimetics containing a trifluoromethyl-substituted alcohol. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 654−657.

(23) Reeves, J. T.; Fandrick, D. R.; Tan, Z.; Song, J. J.; Rodriguez, S.; Qu, B.; Kim, S.; Niemeier, O.; Li, Z.; Byrne, D.; Campbell, S.; Chitroda, A.; DeCroos, P.; Thomas Fachinger, T.; Fuchs, V.; Gonnella, N. C.; Grinberg, N.; Haddad, N.; Jäger, B.; Lee, H.; Lorenz, J. C.; Ma, S.; Narayanan, B. A.; Nummy, L. J.; Premasiri, A.; Roschangar, F.; Sarvestani, M.; Shen, S.; Spinelli, E.; Sun, X.; Varsolona, R. J.; Yee, N.; Brenner, M.; Senanayake, C. H. Development of a large scale asymmetric synthesis of the glucocorticoid agonist BI 653048 BS H3PO4. *J. Org. Chem.* **2013**, *78*, 3616−3635.