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Discovery of orally available tetrahydroquinoline-based glucocorticoid receptor agonists

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ABSTRACT

A series of tetrahydroquinoline derivatives were synthesized and profiled for their ability to act as glucocorticoid receptor selective modulators. Structure–activity relationships of the tetrahydroquinoline B-ring lead to the discovery of orally available GR-selective agonists with high in vivo activity.

Glucocorticoids (GCs) such as prednisolone **1** and dexamethasone **2** (Fig. 1) are effective treatments for the signs and symptoms of inflammation.[1,2] However severe side-effects associated with chronic GC treatment, which include osteoporosis and hyperglycemia, can limit long-term use.[3] The glucocorticoid receptor (GR) is a member of the nuclear receptor superfamily that includes steroid hormone receptors androgen (AR), estrogen (ER), mineralocorticoid (MR) and progesterone (PR).[4] Upon ligand binding, GR is able to modulate gene transcription by directly binding to specific DNA sequences within genes. Such transcriptional activation (TA) is thought to be important for the regulation of glucose homeostasis in the liver and may be responsible for several side-effects associated with chronic GC use.[5,6] Alternatively, the receptor can directly repress transcription by modulating the activity of inflammatory mediators including NFκB and AP-1, the basis for the beneficial anti-inflammatory activity of GCs. Identifying GCs that are able to separate transrepression (TR) from transactivation (TA) is an active area of interest.[7–13]

We have previously disclosed a series of tetrahydroquinoline-based non-steroidal glucocorticoid receptor agonists.[14] Preliminary optimization of both the C-6 aryl group and tetrahydroquinoline A-ring lead to compound **3**, a non-steroidal GC agonist which was highly selective for GR and demonstrated in vitro activity similar to prednisolone (Fig. 1).

A liability of compound **3** that rendered it unsuitable for in vivo profiling was poor hepatic microsomal stability. Compound **3** underwent rapid metabolism upon incubation with both human (HLM) or rat liver microsomes (RLM) exhibiting a short half life of <5 min.[15] Here-in we describe SAR studies focused on the B-ring of **3** in an effort to improve microsomal stability while retaining high TR activity and GR selectivity. Such studies would help

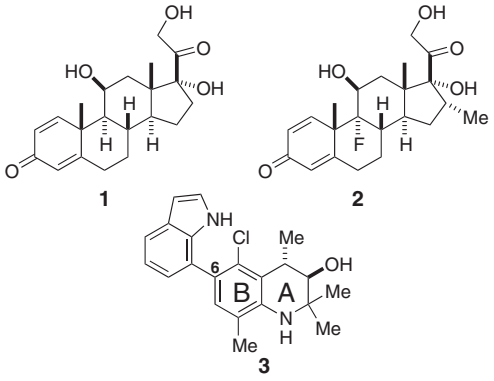

Figure 1. Steroidal and tetrahydroquinoline-based glucocorticoids.

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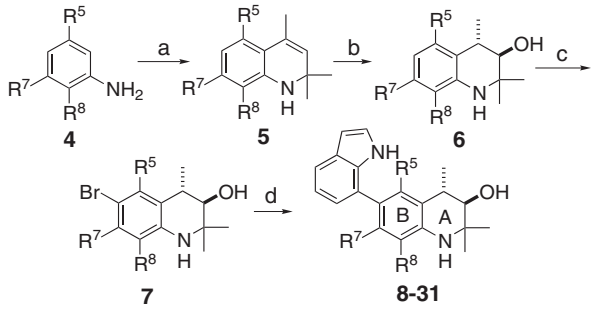


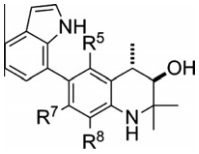
Scheme 1. Representative synthetic route. Reagents and conditions: (a) Iodine, acetone, 120 °C, sealed tube, 15 h; (b) BH_3-THF, THF, then KOH, H_2O_2; (c) NBS, $CHCl_3$; (d) $Pd(PPh_3)_4$, 1*H*-indol-7-ylboronic acid, 2:1 PhMe/EtOH, 2 N Na_2CO_3, 100 °C, 15 h.

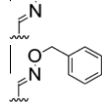
evaluate the suitability of the tetrahydroquinoline-based scaffold for further SAR investigation and to aid profiling of representative analogs in vivo.

The GR-mediated activity of the compounds was evaluated in a number of biological assays. GR binding was determined using a radiolabeled dexamethasone competitive binding assay with baculovirus-expressed GR.[16] Direct TA by GR was measured in a cotransfection (CTF) assay using an MMTV:luciferase reporter.[17] TR activity was determined using a CTF E-selectin[18] repression assay in HepG2 cells to determine repression of transcriptional activation mediated by NFκB or AP-1.[15] Compounds were also profiled in an IL-6 ELISA assay[12] to determine inflammatory cytokine repression in primary neonatal human dermal fibroblast (NHDF) cells as a further measurement of TR activity.

Compounds within the series were synthesized as depicted in Scheme 1. Skraup reaction[19] of substituted aniline **4** followed by hydroboration-oxidation gave racemic tetrahydroquinoline **6** as a single regioisomer. C-6 bromination followed by Suzuki coupling with 1*H*-indol-7-ylboronic acid gave the desired analogs **8–31**.[20] Starting from a variety of substituted anilines **4** we were able to access analogs with varied B-ring substitution patterns.

Table 1
In vitro assay results for selected glucocorticoid receptor modulators[a]



Compd	R^5	R^7	R^8	GR binding K_i (nM)	GRE activation agonist mode		E-Selectin repression		IL-6 repression	
					EC_{50} (nM)	Eff. (%)	IC_{50} (nM)	Eff. (%)	IC_{50} (nM)	Eff. (%)
1	Prednisolone			5.3 ± 0.3	5.3 ± 0.6	129 ± 6.5	4.1 ± 0.8	100 ± 1.4	23 ± 2.6	97 ± 0.7
3	Cl	H	Me	1.7 ± 0.4	7.1 ± 4.8	144 ± 5.9	1.1 ± 0.2	95 ± 6.8	7.8 ± 1.8	81 ± 2.7
8	H	H	Me	9.0	108 ± 34	161 ± 29	21 ± 13	83 ± 0.1	—	—
9	F	H	Me	2.3 ± 0.3	56 ± 33	123 ± 14	5.9 ± 2.1	88 ± 4.6	7.1 ± 1.1	75 ± 5.4
10	Me	H	Me	1.2 ± 0.2	0.9 ± 0.6	97 ± 11	4.7 ± 2.2	103 ± 2.1	9.3 ± 4.0	97 ± 1.1
11	Et	H	Me	11.7	16 ± 1.0	169 ± 25	15 ± 3.2	93 ± 0.1	—	—
12		H	Me	319	105 ± 45	160 ± 49	11 ± 1.1	82 ± 10	—	—
13		H	Me	6.9	0.4 ± 0.2	120 ± 4.6	1.7 ± 1.1	107 ± 1.8	4.2 ± 2.5	94 ± 3.0
14		H	Me	1.5	0.2 ± 0.1	130 ± 20	0.9 ± 0.4	106 ± 2.3	3.4 ± 1.1	95 ± 2.0
15		H	Me	6.0	34	122	5.5 ± 1.7	95 ± 4.7	3.8	68
16		H	Me	3.5	3.7 ± 1.7	127 ± 3.3	3.1 ± 1.2	94 ± 6.7	14.4	51
17		H	Me	19.6	40 ± 12	152 ± 29	—	—	—	—
18		H	Me	16.6	5.7 ± 0.9	120 ± 1.3	6.5 ± 0.5	95 ± 8.1	16 ± 15	78 ± 14
19	CN	H	Me	1.3	9.6 ± 3.1	173 ± 18	5.3 ± 0.8	96 ± 1.2	16 ± 2.2	64 ± 5.9
20		H	Me	10.4	112 ± 40	168 ± 62	7.8 ± 7.1	84 ± 0.9	—	—
21	H	Cl	Me	1.8	36 ± 17	134 ± 17	21 ± 19	96 ± 3.5	26 ± 9.4	82 ± 4.8
22	H	F	Me	0.9 ± 0.8	40 ± 29	162 ± 29	1.7 ± 0.3	97 ± 1.1	4.1 ± 1.7	64 ± 6.3
23	H	Me	Me	38.3	205 ± 92	165 ± 45	42 ± 19	79 ± 1.1	—	—
24	H	CF_3	Me	106	—	—	—	—	—	—
25	H	$CHCH_2$	Me	3.1	18 ± 0.6	110 ± 12	13 ± 4.2	91 ± 1.4	—	—
26	Cl	H	F	8.0	89 ± 17	126 ± 7.7	17 ± 1.6	86 ± 3.0	14	56
27	H	F	F	2.4	11 ± 4.6	193 ± 49	7.7 ± 1.3	95 ± 1.3	20 ± 0.1	44 ± 2.9
28	F	F	F	5.0	16 ± 10	156 ± 17	3.8 ± 1.0	89 ± 3.8	19 ± 3.1	68 ± 4.6
29	F	F	Cl	1.0	1.3 ± 0.1	139 ± 7.6	3.9 ± 1.3	97 ± 2.8	16 ± 3.0	52 ± 6.6
30	Cl	Cl	H	157	480 ± 0.4	100 ± 8.3	301 ± 38	72 ± 0.1	—	—
31	F	F	H	2.5 ± 1.0	0.6 ± 0.2	138 ± 16	1.5 ± 0.7	100 ± 2.7	11 ± 5.6	90 ± 2.3

[a] EC_{50} and IC_{50} values determined from half-log concentration response curves. Agonist efficacies are represented as the percentage maximal response in comparison to dexamethasone (100%). E-selectin repression efficacies are represented as a percent of maximal inhibition of the response induced by TNFα and IL-1β. IL-6 repression efficacies represent the percent of maximal inhibition of the response induced by IL-1β. Standard errors (SEM) represent the mean value of at least three separate experiments with triplicate determinations. If no SEM is noted, value is from a single determinant. A hyphen (—) = not active and denotes <20% efficacy or potency >1 μM.