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Discovery of new selective glucocorticoid receptor agonist leads

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ABSTRACT

We report on the discovery of two new lead series for the development of glucocorticoid receptor agonists. Firstly, the discovery of tetrahydronaphthalenes led to metabolically stable and dissociated compounds. Their binding mode to the glucocorticoid receptor could be elucidated through an X-ray structure. Closer inspection into the reaction path and analyses of side products revealed a new amino alcohol series also addressing the glucocorticoid receptor and demonstrating strong anti-inflammatory activity *in vitro*.

For more than 60 years, glucocorticoids (GCs) have been used to treat severe inflammatory conditions,[1] such as asthma,[2] rheumatoid arthritis,[3] eye and skin diseases (atopic dermatitis, contact eczema, and psoriasis).[4] Since long-term and high-dose treatment with orally applied GCs can cause serious adverse effects, e.g. osteoporosis, diabetes, Cushing's syndrome, glaucoma, and muscle atrophy, the last 2 decades have seen tremendous efforts to better understand the mode of action of GCs on a molecular level and in using this knowledge to devise efficacious and safer GCs. The concept that beneficial, anti-inflammatory effects are exerted through the transrepression pathway, while side-effects are triggered through the transactivation activity of GCs served as a valuable hypothesis in the quest for novel GCs. Briefly, this concept maintains that the monomeric GC-bound glucocorticoid receptor abrogates transcription of pro-inflammatory gene products (transrepression),[5] whereas a dimeric GC-GR complex promotes *inter alia* expression of enzymes involved in catabolic processes (transactivation). This rationale showed a way forward to increase the therapeutic window of GCs by identifying compounds that act as full agonists in the transrepression pathway, yet affect the transactivation pathway to a minor extent as partial agonists or even as antagonists.[6] This hypothesis is indeed quite simplistic and, consequently, has been refined to reflect the complexity of GC and glucocorticoid receptor (GR) biology.[7] Nevertheless, it served as a valuable paradigm for the identification of novel, non-steroidal GR agonists, and led to new selective GR (transrepression) agonists (SEGRAs).[8–10]

Based on our discovery of novel selective glucocorticoid receptor agonists (SEGRAs) such as quinoline **2** by replacing the benzoxazinone moiety of the original lead **1** yielded compounds with considerable selectivity against other nuclear hormone receptors (Scheme 1).[8] In an effort to systematically explore the structure activity relationship around quinoline **2**, particularly with the aim to identify compounds for oral application, we discovered cyclic analogs, exemplified by tetrahydronaphthalene **3,** as potent and metabolically stable SEGRAs. Through careful inspection of the synthetic pathways, we concomitantly discovered super-potent glucocorticoid agonists like amino alcohol **4**. Our approach towards these novel SEGRA chemotypes is outlined in this paper.

Our strategy to render the quinolines of type **2** more stable entailed *inter alia* reduction of lipophilicity by replacing the quinoline with more polar heterocycles as well as modification of the substitution pattern of the fluorophenol moiety. Along these lines, when synthesizing isoquinolone **8** from imine **6** through a sequence of reductive amination and methyl ether cleavage under

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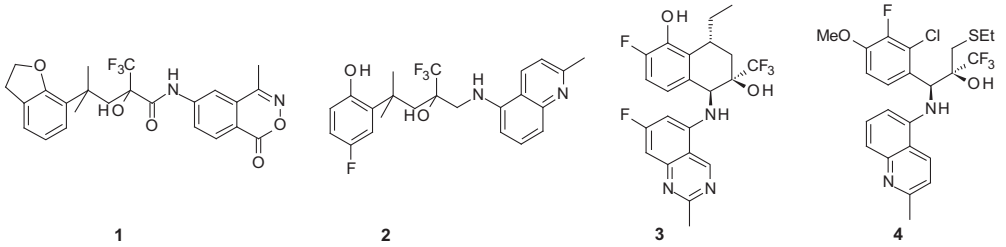
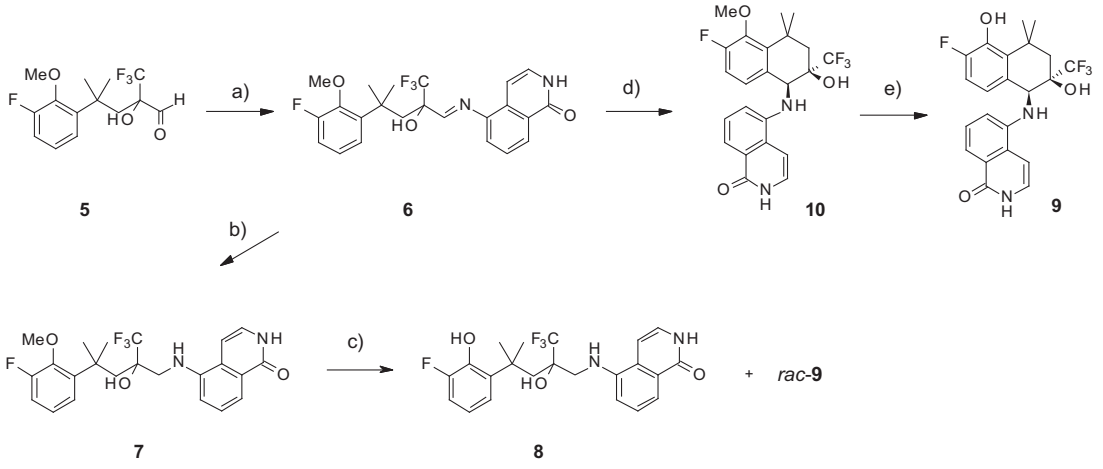


Scheme 1. Overview of the structural evolution of selective glucocorticoid receptor agonist lead structures.



Scheme 2. (a) 5-Aminoisoquinolone, HOAc, rt, 74.4%; (b) $NaBH(OAc)_3$, HOAc, dichloroethane, rt, 68.4%; (c) BBr_3 (1 M in CH_2Cl_2), rt, 51.2% of **8**, 16.5% of **9**; (d) $TiCl_4$ (1 M in CH_2Cl_2), CH_2Cl_2, −20 °C – rt, 63.2%; chiral HPLC separation (Chiralpak AD 20 μM, solvents hexane/ethanol/diethylamine); (e) BBr_3 (1 M in CH_2Cl_2), rt, 96.3%.

Lewis acidic conditions we also obtained a cyclized congener, the tetrahydronaphthalene **9**, apparently stemming from **6** not completely consumed in the reduction step (Scheme 2). In a more targeted approach cyclization was effectively catalyzed by titanium tetrachloride yielding **10** followed by ether cleavage with boron tribromide to **9**. We only isolated the diastereomer in which hydroxyl and the substituted amino adopt a *cis* configuration leaving both amino and trifluoromethyl groups in equatorial positions.

Although the racemic linear congener **8** binds to GR with higher affinity, transrepression data both in recombinant and primary assays indicate that tetrahydronaphthalene **9** displays equal anti-inflammatory activity after separation of enantiomers (Table 1). Gratifyingly, clearance by liver microsome proved to be reduced for the cyclic compound (Table 1) which prompted us to further explore this template as illustrated with six further analogs entailing modification of the gem-dimethyl part of the tetrahydronaphthalene core and introducing isoquinolone surrogates.[11]

Replacing the isoquinolone with a quinolone and fluoroquinazoline moiety led to **11** and **12** respectively (Scheme 3). Along with isoquinolone **9** all three tetrahydronaphthalenes did not display a

Table 1
Anti-inflammatory and immunomodulatory (transrepression) and transactivation activity in recombinant cell assays[12]; anti-inflammatory activity in THP-1 monocyte assays[13]; binding profile against nuclear hormone receptors[13]; stability in human liver microsomes.

Cmpd	Transrepression/ transfected HeLa, LUC readout		Transactivation/ transfected HeLa, LUC readout		Transrepression/ monocyte inhibition of IL-8 production		Binding towards nuclear hormone receptors				Stability in human liver microsomes
	pIC_{50}	Max. efficacy [%][a]	pEC_{50}	Max. efficacy [%][a]	pIC_{50}	Max. efficacy [%][a]	GR pIC_{50}	PR pIC_{50}	MR pIC_{50}	AR pIC_{50}	% recovery after 30′
DEX[b]	8.8	100	8.1	100	8.6	100	7.9	<6.0	<6.0	<6.0	ND[c]
2	8.3	97	7.9	88	8.3	97	8.2	<6.0	<6.0	<6.0	31
8[d]	8.4	82	7.6	63	8.4	82	8.6	6.7	<6.0	<6.0	13
9	8.2	84	7.9	81	8.2	84	7.7	6.1	<6.0	6.5	48
11	7.8	68	7.6	71	7.8	68	7.8	6.1	<6.0	6.1	ND
12	7.4	93	6.8	120	7.4	93	6.9	<6.0	<6.0	<6.0	ND
3	8.2	88	7.6	73	8.2	88	6.9	<6.0	<6.0	<6.0	98
13	8.3	86	7.9	72	8.3	86	7.9	6.1	<6.0	<6.0	86
14	7.7	79	7.4	57	7.7	79	7.8	<6.0	<6.0	<6.0	ND
15	8.2	78	8.0	29	8.2	78	7.2	<6.0	<6.0	<6.0	ND
22[d]	7.7	87	6.8	115	7.7	87	7.2	6.2	<6.0	<6.0	ND
4	9.8	91	9.2	87	9.8	91	7.5	6.1	<6.0	<6.0	ND

[a] Maximal efficacy response is normalized maximum efficacy of dexamethasone (= 100%).
[b] DEX: Dexamethasone.
[c] ND: not determined.
[d] Data given for the racemate.

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