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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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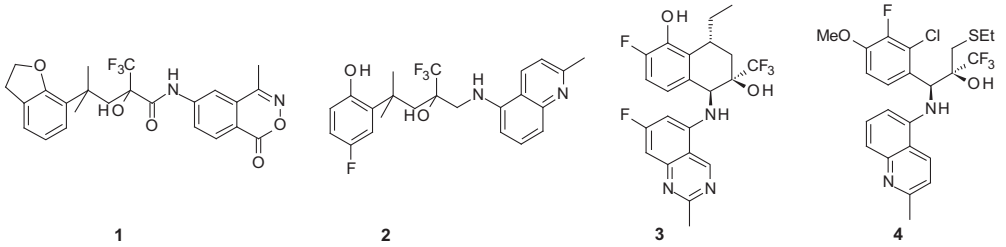
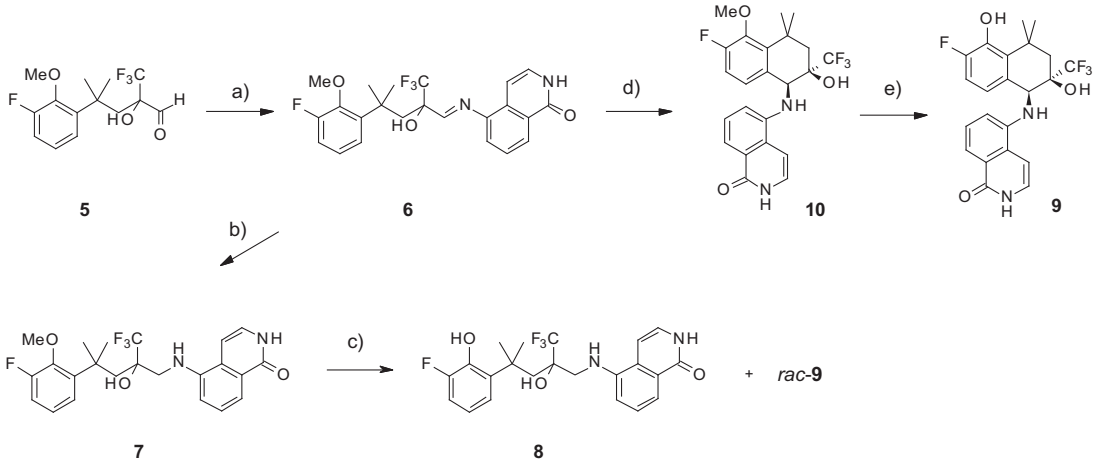


Scheme 1. Overview of the structural evolution of selective glucocorticoid receptor agonist lead structures.



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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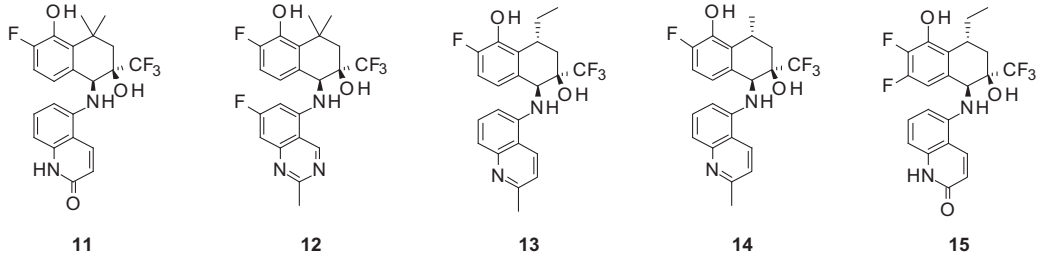


Scheme 3. Tetrahydronaphthalene synthesized for and investigated in this study.

dissociated profile in the recombinant assays comparable to that e.g. of linear **8**. On the contrary, **12** showed a stronger agonistic profile in the transactivation assay than dexamethasone. A handle to increase the dissociation bias towards transrepression came with substituting the geminal dimethyl group with an (*S*)-monoethyl group. Now, both the respective fluoroquinazoline **3** and the methylquinoline **13** showed a better potency and efficacy in the transrepression vs. the transactivation assays comparable to the linear benchmark compounds **2** and **8**. A simple (*S*)-methyl substituent as in **14** reduces potency. The quinolone analog **15**, with *vic* difluoro pattern at the phenol moiety showed a remarkable profile as partial agonist in transrepression and partial antagonist in transactivation and thus is the most dissociated compound in this series.[12,13]

To build our understanding of the binding characteristics of tetrahydronaphthalenes, we determined the X-ray structure of GR ligand binding domain in complex with compound **15**.[14] The structure confirmed that compound **15** makes several key interactions that will drive the functional profile (Fig. 1). The quinolone moiety occupies the same volume as the A and B rings of classical steroidal glucocorticoids,[15] with the amide making direct interactions to both gatekeeper residues Gln570 and Arg611, thus stabilizing the helix 3–helix 5 interface. The interaction in between helices 3 and 5 is an important agonist trigger across the steroid receptor family.[16] Looking at the 1,2,3,4-tetrahydronaphthalene, the 2-hydroxyl makes a direct interaction to the O^{δ} of Asn564 on H3. As Asn564 is central for the stabilization of the loop in between helices 11 and 12,[17] this interaction will likely influence receptor activation by keeping helix 12 in the active conformation. In addition, the 5-hydroxyl makes a direct interaction to Gln642 on helix 7. While the androgen receptor also has a glutamine residue in the corresponding sequence position ($Gln783^{AR}$), structural differences between the two receptors place $Gln783^{AR}$ further away from the ligand.[18] As such, Gln642 is unique to GR in this position and has been shown to be a key component for the evolution of the hormone selectivity profile of the receptor.[19] Looking at the overall compound **15** pose within the ligand binding pocket, it is interesting to note that the tetrahydronaphthalene ring is placed perpendicular to the quinolone. This enables the ligand to access the junction in between helices 3, 7 and 11 through a novel, more direct, vector compared to the steroidal 17α vector. Many of the most potent GR ligands extend into this sub pocket, and the plasticity in this region has been associated with the ligand entry trajectory.[20]

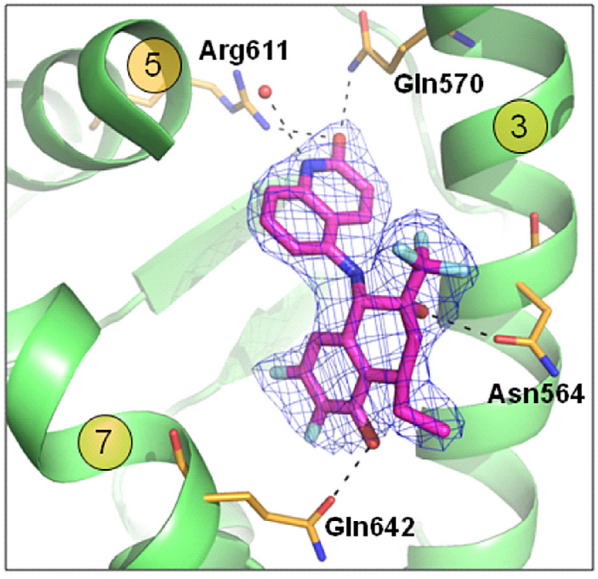


Fig. 1. Refined 2mFo-DFc electron density of GR ligand binding domain in complex with compound **16**. The dotted lines represent putative hydrogen bonds.

Due to its potency and efficacy in the THP-1 assay, metabolic stability in human liver microsomes, reduced lipohilicity compared to **13** and a clean profile in the binding assays towards steroid receptors, we were initially interested in investigating compound **3** in *in vivo* studies. The *in vivo* pharmacokinetic profile in adult, male rats (Table 2) showed moderate blood clearance and an oral bioavailability of 59%, thus allowing for oral administration.

We demonstrated *in vivo* efficacy in two anti-inflammatory rat models (Table 3). Upon oral treatment, compound **3** significantly inhibited the inflammation induced either by croton oil in Wistar rats[21] or trimellitic anhydride (TMA) in Brown Norway rats[22] taking reduction of ear edema formation as endpoint. The maximum effect[23] of the tetrahydronaphthalene **3** at 30 mg/kg proved to be stronger than that of prednisolone along with a markedly lower ED_{50}.

Hence, we devised a robust and stereoselective synthesis providing sufficient amounts of material for broad biological profiling (Scheme 4). The synthesis started with coupling boronic acid **16** to 2-bromo-1-butene followed by a stereoselective ene-reaction with ethyl trifluromethylpyruvate employing a chiral Lewis acid catalyst.[24] As we could not reduce the enantiomerically enriched (R)-hydroxyl ester **18** with diisobutylaluminum hydride, we took recourse to lithium aluminum hydride and were delighted to obtain the aldehyde as main product. We assume that this untypical outcome is influenced by the α-2-trifluoromethyl substituent. Hydrogenation of the E/Z double bond over palladium delivered the aldehyde **19** as a 1:1.2 mixture with its epimer. Separation of the aldehyde diastereomers was followed by imine formation (**20**) and cyclization under Lewis acid catalysis. With the Et, CF_3, and NHHet group occupying an equatorial position, the reaction is considered to be driven thermodynamically.

For a more detailed exploration of the reaction mechanism leading to tetrahydronaphthalenes, we examined the cyclization of imine **21** which harbors a bulky bromo-substituent expected to hinder cyclization due to steric encumbrance (Scheme 5). Upon treatment of imine **21** with Lewis acid we obtained a rearrangement product, amino alcohol **22**, in addition to the tetrahydronaphthalene **23**.

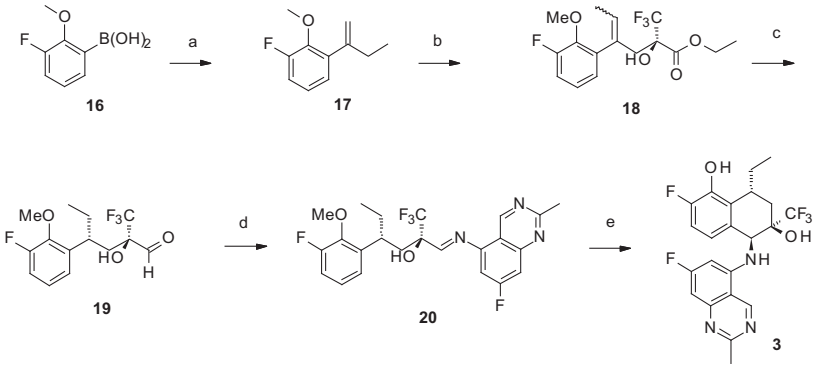
Table 2
Physicochemical and pharmacokinetic properties (rat) of compound **3.**

Cmpd	Sol[a] [mg/L]	logP	CL_b [L/h/kg]	V_{ss} [L/kg]	$t_{1/2}$ [h]	F [%]
3	26	4	1.6	11	5.8	59

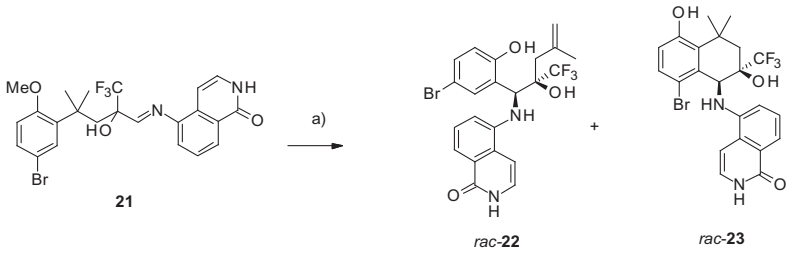
CL_b, V_{ss} and $t_{1/2}$ determined after 1.25 mg/kg bolus i.v.; F determined after 10 mg/kg in microcrystalline suspension.
[a] thermodynamic solubility in 0.1 M phosphate buffer pH 7.4 at 25 °C.

Table 3
ED_{50} values and maximum effects of compound **3** and the reference prednisolone given as mean values ± standard deviations of n experiments. For calculation of mean ED_{50} values and maximum effects, inhibition of edema as the major parameter of anti-inflammatory activity has been used.

Cmpd	ED_{50} [mg/kg]		Max. effect @ 30 mg/kg [%]	
	3	Prednisolone	**3**	Prednisolone
Croton oil (n = 3)	1.4 ± 0.9	15.7 ± 2.4	124 ± 13	55 ± 10
TMA (n = 2)	1.3 ± 0.0	6.7 ± 5.8	107 ± 8	83 ± 11



Scheme 4. (a) 2-Bromo-1-butene, 1 mol% $Pd(PPh_3)_4$, toluene, 1-propanol, 120 °C, 5 h, 50%; (b) trifluoropyruvate, 5 mol% Cu[(4S,4S)-bis-(4-phenyl-2-oxazolin-2-yl)propane $(H_2O)_2$]$((SbF_6)2$, CH_2Cl_2, 93%, E/Z ratio 2:1, E: 9% ee, Z: 58% ee; (c) 1. $LiAlH_4$, diethyl ether, −15 °C, 73%; 2. H_2, Pd/C, methanol, acetic acid, 76%, RR/SR ratio 1:1.2; (d) 7-fluoro-2-methylquinazolin-5-amine, $Ti(OtBu)_4$, toluene, quant. (e) BBr_3, CH_2Cl_2, −40 °C to 0 °C, 40%; chiral HPLC separation (Chiracel OD-H 5μ).



Scheme 5. (a) BBr_3 (1 M in CH_2Cl_2), rt, 50%, **22/23** ratio 1.8:1.

It is tempting to speculate about the reaction mechanism leading either to a rearrangement or cyclization. We assume one central five-membered transition state that either rearranges into the tetrahydronaphthalene (Scheme 6, path A) or reacts to a terminal alkene under re-establishment of the aromatic ring as a driving force (path B). Clearly, this reaction deserves more scrutiny to verify this hypothesis.

We would have discarded the rearranged side-product, but were surprised to observe significant activity in the transrepression assay (cf. **22** in Table 1).[25] Based on this chemotype we devised analogs that were accessible through a very straightforward synthesis allowing variations in the aryl ring substitution pattern, while allowing the exploration of the hydrophobic pocket occupied by the isopropene moiety (Scheme 7). Thus, we arrived at thioether **4**, which was found to be a picomolar active GR agonist in the transrepression assay, but displayed reduced dissociation (Table 1). Its synthesis started with condensation of aminoquinoline **24** with aldehyde **25.** Addition of the anion of trifluoromethyloxiran[26] to imine **26** yielded epoxide **27**, which was opened with thioethanol to yield thioether **4**. This compound served as a lead compound for the identification of highly potent GR agonists[27] for the topical treatment of atopic dermatitis, which will be reported in the future as a separate communication.

In summary, we reported 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, particularly **3**, which eventually demonstrated *in vivo* efficacy and dissociation in animal models upon oral exposure. Careful investigation of reaction mechanisms and product mixtures revealed the amino alcohol series providing pM active agonists, such as **4**, that were further developed into candidates for topical treatment of severe atopic dermatitis.

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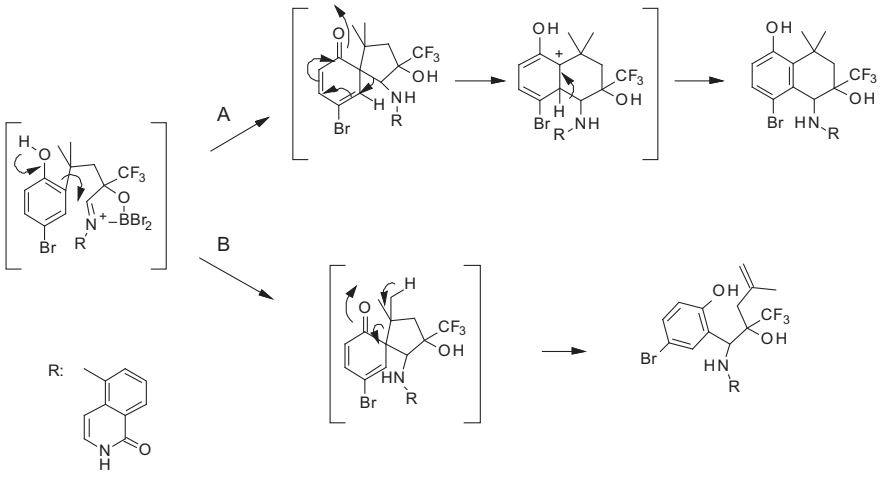
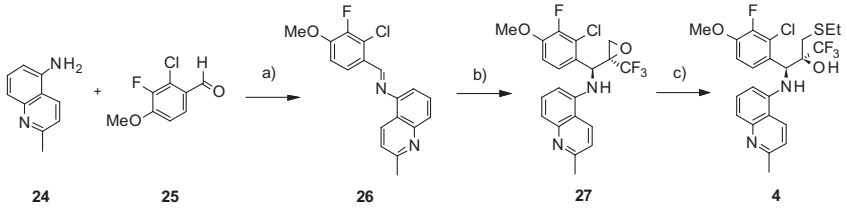


Scheme 6. Potential mechanisms delivering either amino alcohols or tetrahydronaphthalenes.



Scheme 7. (a) Acetic acid, toluene, 4 Å molecular sieves 120 °C, 92%; (b) (*S*)1,1,1-trifluoroepoxypropane, *n*-BuLi, THF, hexane, diethyl ether, −95 °C to −10 °C, 79%, SS/RS ratio 8:1; (c) Cs_2CO_3, CH_3CH_2SH, DMF, 44%.

A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmcl.2016.12.047.

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12. Anti-inflammatory/immunomodulatory activity *in vitro* (transrepression): Inhibition of collagenase promoter activity. HeLa cells stably transfected with a luciferase reporter gene linked to the collagenase promoter were challenged with inflammatory stimulus (12-O-tetradecanoylphorbol-13-acetate (TPA)) in the presence of the reference (dexamethasone) or the test compounds. Transactivation activity *in vitro*: Induction of MMTV promoter activity has been used as surrogate marker for transactivation-mediated side effects. The MMTV promoter was linked to a luciferase reporter gene and HeLa cells were stably transfected with this construct. Cells were incubated with increasing concentrations of reference (dexamethasone) or test compounds.Inhibition of IL-8 production**:** IL-8 synthesis was induced by stimulation of the human promyeloic cell line THP-1 with lipopolysaccharide (LPS). Cells were treated with LPS in the absence or presence of test compounds or reference (dexamethasone).
13. Receptor binding assays. Extracts from Sf9 cells, infected with recombinant baculovirus coding for the human glucocorticoid receptor (GR), progesterone receptor (PR), androgen receptor (AR), or mineralocorticoid receptor (MR) were used for the receptor binding assays. Data were determined in duplicate.
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