Bioorganic & Medicinal Chemistry Letters xxx (2014) xxx–xxx

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

The discovery of potent and selective non-steroidal glucocorticoid receptor modulators, suitable for inhalation

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ARTICLE INFO

Article history:
Received 4 February 2014
Revised 21 March 2014
Accepted 24 March 2014
Available online xxxx

Keywords:
Glucocorticoid receptor
Non-steroidal selective glucocorticoid receptor modulators
Inhalation
Indazoles

ABSTRACT

We report the discovery of highly potent and selective non-steroidal glucocorticoid receptor modulators with PK properties suitable for inhalation. A high throughput screen of the AstraZeneca compound collection identified sulfonamide **3** as a potent non-steroidal glucocorticoid receptor ligand. Further optimization of this lead generated indazoles **30** and **48** that were progressed to characterization in in vivo models. X-ray crystallography was used to gain further insight into the binding mode of selected ligands.

Glucocorticoids represent the most potent anti-inflammatory drugs available today and allow successful treatment of several chronic inflammatory and autoimmune diseases. This includes the treatment of respiratory diseases, such as asthma and chronic obstructive pulmonary disease (COPD), where inhaled glucocorticoids (IGCs) alone or in combination with bronchodilators are the mainstay of clinical therapy. However, there is still a large unmet clinical need in both of these diseases.[1]

Glucocorticoids exert their function through binding to the glucocorticoid receptor (GR). Following ligand binding the cytoplasmic receptor translocates to the nucleus, where it regulates gene transcription by both activating and repressive mechanisms. In analogy with other nuclear hormone receptors, the GR serves as an assembly point for transcription coregulators that can directly modify chromatin structure and/or impact the activity of the gene transcription apparatus.[2] Modulation of receptor activity with non-steroidal ligands, through differential coregulator recruitment can be envisioned as a route to develop GR ligands with improved efficacy and/or safety compared to conventional steroids. This vision is supported by related work in the field of non-steroidal ligands acting on the estrogen and androgen receptors.[3]

During the last decade non-steroidal GR ligands have been identified by large number of organizations.[4] Two examples of compounds reaching clinical studies for topical and oral administration respectively are Mapracorat (**1**) and PF-04171327 (**2**) in Figure 1.[5] Furthermore, the development of novel non-steroidal GR agonists has been facilitated by increased understanding of the structural biology of GR.[6]

We initiated a search for inhaled GR modulators for the treatment of respiratory diseases. A high throughput screen of the AstraZeneca compound collection using a competitive human GR fluorescence polarization binding assay identified the sulfonamide **3** as a potent ligand (Fig. 2). This compound was attractive as it could be synthesized in one step from commercially available starting materials. Further profiling of functional cellular activity using a reporter gene assay system, wherein gene transrepression (TR) activity was determined in Chago K1 cells stably transfected with a construct containing several TRE sites (AP-1 pathway) preceding a Lac Z reporter, revealed the compound to be a functional antagonist. An initial key objective was therefore to introduce functional agonism in this series.

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http://dx.doi.org/10.1016/j.bmcl.2014.03.070
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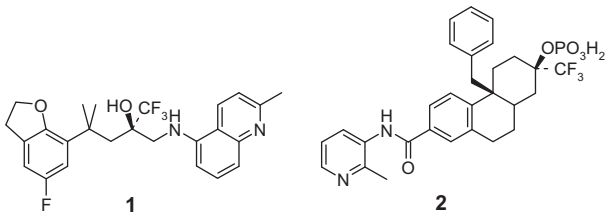


Figure 1. Mapracorat **1** and PF-04171327 **2**.

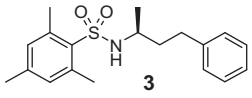
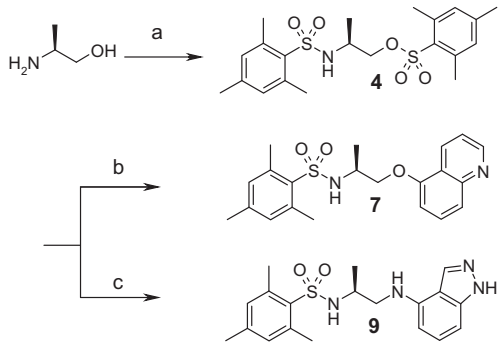


Figure 2. HTS hit **3**.

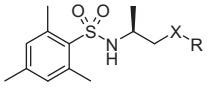
As a first step to improve the synthetic scope, a heteroatom was introduced in the benzylic position in compound **3** to allow parallel chemistry to be used in expansion of the series. A study of the activity of various aryl ethers and anilines was then initiated, using a synthetic route that enabled preparation of ethers (entries **5**–**8**) and amines (entries **9**–**14**) as single enantiomers and exemplified by the synthesis of compounds **7** and **9** in Scheme 1.

Compounds were tested for GR binding and cellular activity in the TR reporter gene assay. For several compounds, affinity to the receptor was retained or improved compared to compound **3** (Table 1). Interestingly, the attachment position to the heterocyclics exhibited a steep SAR. For example, the quinoline (**10**) linked through the 5-position has an affinity to GR of 75 nM whereas affinity is completely abolished for the 6-linked quinoline derivative (**11**). This observation is supported by modeling studies in which the elongated ligand binding pocket in the receptor strictly dictates conditions for the width of compounds. From Table 1 it is also clear that the positioning of aromatic heteroatoms plays an important role for functional activity. While the 5-isoquinoline (**6**) is more potent than the 5-quinoline (**7**) in the binding assay, only the 5-quinoline is an agonist in the cellular TR assay. This can be understood from the perspective that modeling studies place the heterocyclic ring in the same region of the ligand binding pocket as the A and B rings of conventional steroids. For optimal interactions to the receptor, the heteroatom of the heterocyclic ring must emulate the 3-keto oxygen of steroids to pick up key interactions with Arg611, Glu570 and a conserved water molecule.[7] These interactions between helices 3 and 5 of GR have been shown to be critical drivers for agonism.[8]



Scheme 1. Reagents and conditions: (a) 2-mesitylenesulfonyl chloride (2.1 equiv), pyridine, rt, 16 h; (b) 5-hydroxyquinoline (1.7 equiv), DMF, $CsCO_3$, rt, 16 h; (c) 4-aminoindazole, NMP, 130 °C, 2 h.

Table 1
GR binding and activity in TRE reporter gene assay for selected compounds



Compd	X	R	GR[a] IC_{50} (nM)	TR agonistic mode[a]	
				IC_{50} (μM)	Eff.[b] (%)
3	C	Phenyl	55	NA	–
5	O	2,6-Dimethylphenyl	85	NT	–
6	O	5-Isoquinoline	18	NA	–
7	O	5-Quinoline	240	0.96	71
8	O	4-Indole	23	NA	–
9	N	4-Indazole	42	0.76	57
10	N	5-Quinoline	75	1.8	88
11	N	6-Quinoline	10,000	NA	–
12	N	6-Isoquinoline	10,000	NA	–
13	N		18	1.1	59
14	N		160	2.2	56

NT: not tested. NA: not active (<50% inhibition) at 10 μM.
[a] Values are means of at least two experiments.
[b] % Of dexamethasone at 10^{-6} M.

Next, the sulfonamide substituent was explored using a route exemplified for the synthesis of the quinoline (**20**) and isoquinoline (**26**) ethers in Scheme 2.

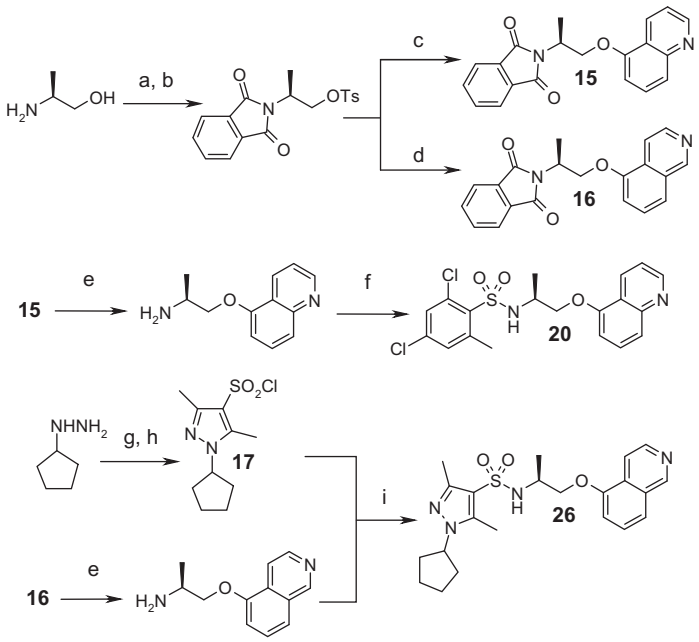
A range of sulfonamides of different sizes were examined, exemplified by compounds **18**–**27** in Table 2. All substituted phenyl sulfonamides (entries **18**–**25**) showed inferior GR binding compared to the corresponding mesityl sulfonamides. Modeling places these substituents in an area corresponding to the steroid D-ring 17α position and the data confirm the critical role of this pocket for binding affinity. The fact that the potent 1,2-diazoles (entries **26** and **27**) are much larger than the original mesityl also illustrates the tendency for flexibility in this region of the receptor, as previously reported.[9] Since the 1,2-diazoles also exhibited a decrease in lipophilicity (log*D* for matched pairs **6** and **26**, were 4.1 and 3.5, respectively), they were selected for further investigations together with the more potent mesityl congener.

In an effort to emulate the phenyl-pyrazole A-ring substituents in steroid derivatives, such as in cortivazole, a series of 1-aryl-1*H*-indazoles were synthesised.[10] Indazoles **30**–**42** and **47**–**52** (Table 3) were prepared as exemplified by the synthesis of compounds **30** and **47** (Scheme 3).[11] The O, C, S and SO_2 linked 1-aryl-1*H*-indazoles **29**, **43**–**45** and the CF_3 branched indazole ether **46**, were synthesized by different routes.[12]

Many compounds showed excellent potency in the binding and TR assays. The activity of compounds in primary cells were studied in human peripheral blood mononuclear cells (hPBMCs), where the release of tumor necrosis factor-α (TNF-α) in response to lipopolysaccharide (LPS) stimulation was used to test the anti-inflammatory effects. As can be seen from data in Table 3, several of the compounds were confirmed to be potent agonists in this assay.

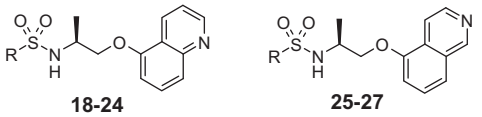
Functional agonism is driven by a well defined structural state of the receptor, where coactivators can be recruited to the binding surface outlined by helix 3, 4 and 12 (Fig. 3).[7] To better understand the molecular details of the conformations induced by the sulfonamides, we determined the X-ray structure of the GR ligand binding domain (LBD) in complex with compound **30**.[13]

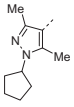
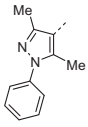
The structure revealed that the compound makes multiple interactions to helix 3, stabilizing it in an agonistic conformation (Fig. 4A). Specifically the nitrogen of the sulfonamide linker makes a direct interaction to the O_δ atom of Asn564. In addition, one of



Scheme 2. Reagents and conditions: (a) phthalic anhydride, toluene, DIEA, reflux, Dean–Stark, 2 h; (b) TsCl, pyridine, rt, 16 h; (c) 5-hydroxyquinoline (1.1 equiv), DMF, $CsCO_3$, 100 °C, 2 h; (d) 5-hydroxyisoquinoline (1.1 equiv), DMF, $CsCO_3$, 100 °C, 2 h; (e) NH_2NH_2 H_2O, EtOH, reflux, 2 h; (f) 2,4-dichloro-6-methylbenzenesulfonyl chloride (1.2 equiv), pyridine, rt, 16 h; (g) 2,4-pentanedione, DIEA, EtOH, reflux, 48 h; (h) HSO_3Cl, CH_2Cl_2, 0 °C, 1 h, then reflux 2 h, then $SOCl_2$, reflux, 2 h; (i) pyridine, rt, 16 h.

Table 2
GR binding and activity in TR reporter gene assay for selected compounds



Compd	R	GR[a] IC_{50} (nM)	TRE[a]	
			IC_{50} (μM)	Eff.[b] (%)
18	2,4-Dimethylphenyl	1600	NT	—
19	2,4,6-Trichlorophenyl	80	2.4	64
20	2,4-Dichloro-6-methylphenyl	220	NA	—
21	2-Methoxyphenyl	>10,000	NT	—
22	3-Cyanophenyl	1800	NT	—
23	2-Cyanophenyl	>10,000	NT	—
24	Phenyl	>10,000	NT	—
25	2,4-Dimethylphenyl	410	NT	—
26		32	NA	—
27		97	NA	—

NT: not tested. NA: not active (<50% inhibition) at 10 μM.
[a] Values are means of at least two experiments.
[b] % Of dexamethasone 10^{-6} M.

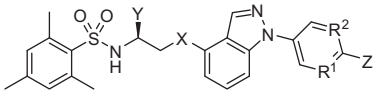
the sulfone oxygens is located within hydrogen bonding distance to a putative water molecule, which is ideally placed to make further interactions to both Thr739 and the N_δ atom of Asn564. Interactions to Asn564 are of particular importance as the N_δ atom makes a further hydrogen bond to the backbone carbonyl group of Glu748, in the loop between helices 11 and 12, thus stabilizing this region and directly contributing to agonism.[14]

Adjacent to Asn564, the backbone carbonyl of Leu563 is within hydrogen bonding distance of the amine linker at the indazole 4 position (Fig. 4A). The importance of this interaction is emphasized by ether congener **29**, which lacks a donor at this position and has no activity in the hPBMC assay (compared to 14 nM for **30**). Interestingly, compound **46** illustrates that the hPBMC activity can be recovered if a trifluoromethyl is introduced adjacent to the sulfonamide nitrogen. It is plausible that the introduction of the electron withdrawing group strengthens the ability of the sulfonamide nitrogen to donate its hydrogen to Asn564.

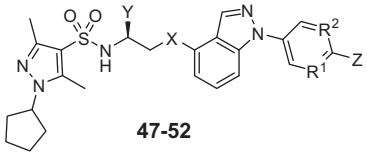
Beyond the sulfonamide, the mesitylene tail enters hydrophobic volume where helices 3, 7 and 11 meet (Fig. 4B). As predicted, this volume overlaps with the 17α substituent that can be found in most highly potent steroid ligands. Compounds like **48**, with a large 17α substituent, highlight the tendency for flexibility of this region. It is interesting to note that none of the natural ligands for the steroid receptors extend into this volume. The intrinsic plasticity of the receptor in this volume is likely coupled to the mechanism of ligand entry into and exit from the ligand binding domain.[15] At the other end of compound **30**, the indazole fragment makes a putative interaction to the N_ε atom of Gln570 (Fig. 4A). The gatekeeper residues, Gln570 and Arg611, are arranged in the open conformation to accommodate the *p*-fluorophenyl motif.[16] This motif acts as a hydrophobic link between helices 3 and 5 at the core of the receptor and makes a strong contribution to the functional agonism observed for compounds with similar moieties.[8,17]

This analysis indicates that the sulfonamide template makes distinct interactions to the receptor relative to conventional steroid ligands.[7] Taken together with the fact that steroids are based upon a more rigid scaffold, we hypothesized the sulfonamides would induce a distinct structural state leading to a unique protein–protein interaction pattern. To investigate this further, we measured the binding of the GR LBD to various coregulator peptides in the presence of compounds **30** and **48** using surface plasma resonance measurements.[18] Figure 5 shows that the sulfonamides **30** and **48** have a different profile relative to the steroids dexamethasone and fluticasone propionate.

Table 3
GR binding, activity in TR reporter gene assay and in PBMCs for selected compounds



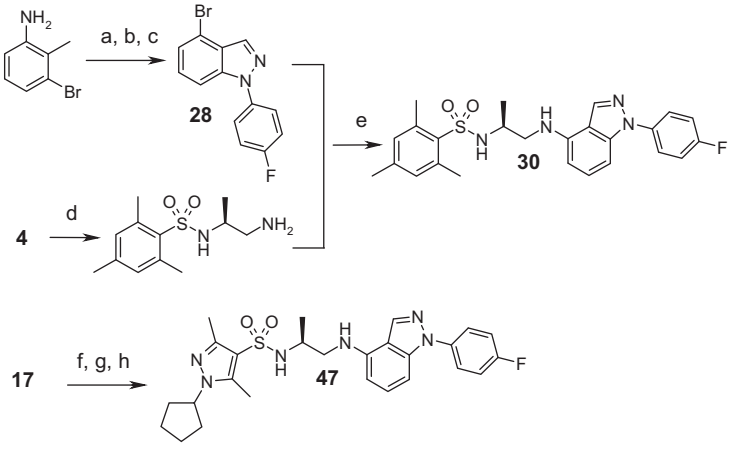
29-46



47-52

Compd	X	Y	R^1	R^2	Z	GR IC_{50}[a] (nM)	TR IC_{50}[a] (nM)		hPBMC IC_{50}[a] (nM)	
							IC_{50}	Eff.[b] (%)	IC_{50}	Eff. (%)
29	O	Me	C	C	F	5.2	60	93	NA	–
30	NH	Me	C	C	F	4.9	1.5	89	14	73
31	NH	Me	N	C	F	2.3	2.3	91	23	62
32	NH	Me	C-Me	C	H	3.8	6.6	84	8.8	55
33	NH	Me	C	C	H	3.5	1.5	88	1.6	82
34	NH	Me	N	N	H	5.3	6.9	67	8.1	63
35	NH	Me	N	C	H	5.6	2.6	94	2.0	84
36	NH	Me	C	C	Cl	3.4	3.7	99	13	72
37	NH	Me	C-Me	C	F	4.1	14	77	23	69
38	NH	Me	C	C	Me	3.9	4.5	85	12	58
39	NH	*i*Pr	C	C	F	35	12	83	2.1	61
40	NH	Me	C–F	C	H	4.0	6.1	80	28	69
41	NH	Me	C-OMe	C	H	6.9	41	62	NT	–
42	NH	Me	C	C	OMe	5.4	NT	–	NT	–
43	CH_2	Me	C	C	F	4.6	23	76	12	37
44[c]	S	Me	C	C	F	7.7	NA	–	NT	–
45[c]	SO_2	Me	C	C	F	795	NT	–	NT	–
46[c]	O	CF_3	C	C	F	3.8	14	73	36	76
47	NH	Me	C	C	F	3.8	9.7	87	NT	–
48	NH	Me	N	C	F	3.0	7.2	88	14	60
49	NH	Me	C	C	OCF_3	12	NT	–	NT	–
50	NH	Me	C	C	CN	4.7	16	87	13	68
51	NH	Me	N	N	H	5.7	43	76	NA	–
52	NH	Me	N	N	OMe	23	NT	–	NT	–

NT: not tested. NA: not active (<50% inhibition) at 10 μM.
[a] Values are means of at least two experiments.
[b] % Of dexamethasone 10^{-6} M.
[c] Racemic mixture.



Scheme 3. Reagents and conditions: (a) HCl, H_2O, rt, 1 h, then $NaNO_2$, H_2O, −5 °C, 25 min, then HBF_4; (b) KOAc, 18-crown-6, CH_2Cl_2, rt, 1 h; (c) 4-fluorobenzeneboronic acid, $Cu(OAc)_2$, pyridine, CH_2Cl_2, rt, 16 h; (d) NH_3 (aq), MeCN, rt, 2 h; (e) BINAP, $Pd(dba)_3$, toluene, NaOtBu, Microwave (300 W, 110 °C, 15 min; (f) L-alaninamide hydrochloride, pyridine, DIEA, rt, 16 h; (g) borane-THF, THF, rt, 16 h; (h) **28**, BINAP, $Pd(dba)_3$, toluene, NaOtBu, microwave (300 W, 110 °C, 15 min).

Guided by above results compounds **30** and **48** were selected for further characterization in vitro and in vivo. To measure steroid hormone receptor selectivity, the compounds were profiled in progesterone, mineralcorticoid, androgen and estrogen (ERα and ERβ) receptor binding assays. Both compounds showed little affinity to any of the receptors tested and selectivity over progesterone and mineralcorticoid receptors are improved compared to reference inhaled steroidal glucocorticoids.[19] Release of TNFα from LPS stimulated rat PBMCs was used to establish anti-inflammatory effects of compounds in rat and ensure species cross over in in vivo pharmacodynamic models. Analysis of physicochemical and in vitro PK properties (Table 4) indicated both compounds could be regarded as suitable for inhalation and with properties similar to reference IGCs. This included high hepatic clearance that was sought to ensure minimal systemic exposure of active ligand.

The metabolism and metabolites were investigated in vitro using human liver microsomes and human hepatocytes. A major metabolic pathway was observed to be N-dealkylation via oxida-

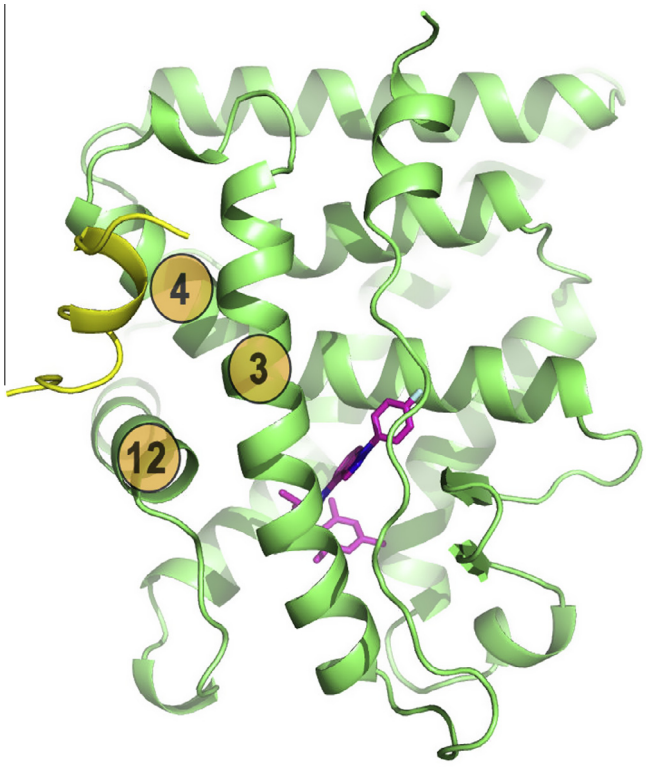


Figure 3. The global arrangement of GR in complex with **30**. The Tif-2 coactivator peptide (yellow) binds in the groove outlined by helices 3, 4 and 12.

tion in the α-methylene position leading compound cleavage and formation of several fragments, including 4-aminoindazoles.[21] Generally, compounds in this series showed little CYP P450 inhibition and among the more interesting compounds CYP inhibition was low. Furthermore, the risk of cytochrome P450 related drug-drug interactions for inhaled drugs is reduced because of the low doses typically administered, leading to low systemic exposure.

Compounds were further characterized in vivo in pharmacokinetic models. Compound **48** was administrated iv and as predicted from in vitro data, in vivo clearance was high. The lung concentrations and blood PK after instillation by *intra tracheal* route were determined for compounds **30** and **48**. A key driver for lung retention of neutral compounds is the rate of dissolution, which is linked to solubility. Compound **30** is more lipophilic and less soluble than

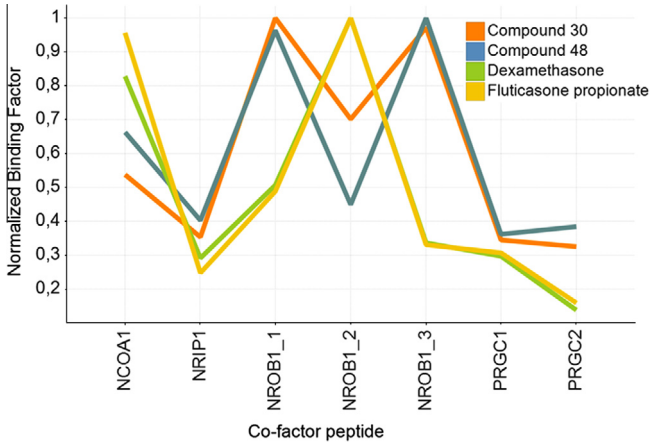


Figure 5. The binding of various coregulator peptides to the GR LBD in complex with compounds **30**, compound **48**, dexamethasone and fluticasone propionate.

compound **48**. From Figure 6 it can be seen that compound **30** has high lung tissue retention, about 50% of the dose remain in the lung 24 h after dosing. In contrast, the more polar compound **48** rapidly disappeared from the lung tissue with only minor amounts of the dose remaining in the lung 4 h after dosing. In a separate study the blood concentration–time curves after *i.t.* instillation of both compounds were determined. The result is in line with the results from the study of lung tissue levels, showing more rapid systemic absorption for compound **48** resulting in higher Cmax compared to compound **30** (Fig. 7).

The efficacy of compound **30** was evaluated in a rat LPS model of acute inflammation.[22] In this model compound **30** was instilled intratracheally 2 h prior to challenge with LPS, and experiments terminated 4 h after challenge. The end points measured in this model were total number of leukocytes in the broncho-alveolar lavage (BAL) fluids, and increase in lung weight (edema).

Compound **30** at doses of 30 and 100 μg/kg significantly inhibited inflammatory cell influx in animals treated with LPS, by 90% and 85%, respectively. The compound also inhibited lung edema in a dose-dependent manner. Fluticasone propionate dosed at same doses as compound **30** was used as reference (Figs. 8 and 9).

Cigarette smoke is the main risk factor for developing chronic obstructive pulmonary disease (COPD) in humans. Using a mouse model of inflammation, female Balb/C mice were exposed to cigarette smoke twice daily for four days to induce a local inflammatory response in the lung, reflected by an increase in the number

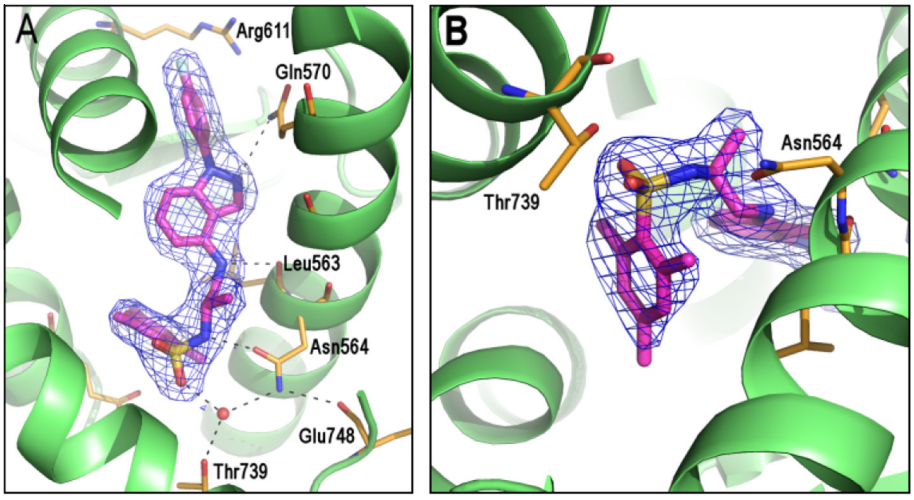


Figure 4. (A) Refined 2mFo-DFc electron density of GR in complex with **30**. The dotted lines represent putative hydrogen bonds. (B) Detailed view of the mesitylene tail.

Table 4
Physical Chemical properties and in vitro/vivo profile of **30** and **48**

	30	**48**
MR/PR/AR IC_{50}[a] (μM)	>1/0.77/>1	>5/4.5/>1
ERα/ERβ IC_{50}[a] (μM)	>5/>5	>5/>5
Rat PBMC IC_{50} (nM/% efficacy)	0.9/87	4.5/83
Log*D*7.4	4.1	3.7
Solubility[b] (μM)	<0.2/<0.43	1.5/22
Hu PPB Fu% (fraction unbound%)	<0.003	0.005
Rat Mics[c]/Heps Cl_{int}[d]	>200/13	>200/33
Hu Mics[c]/Hu Heps Cl_{int}[d]	78/18	>200/47
CYP2D6, CYP1A2 CYP2C19 IC_{50}	>20 μM	>20 μM
CYP3A4 IC_{50}	10 μM	22 μM
CYP2C9 IC_{50}	7.9 μM	17 μM
hERG[20] (μM)	NA	8.7
Rat (iv) PK Cl/$t_{½}$/Vds[e]	NT	78/6.4/15

NA: not active (<25% inhibition) at 50 μM.
[a] MR assay in SPA format and PR, AR, ERα and ERβ assays in FP format.
[b] Thermodynamic solubility of crystalline/amorphous compound in 0.1 M phosphate buffer pH 7.4 at 25 °C for 24 h.
[c] Microsome metabolism intrinsic clearance Cl_{int} (μL/min/mg).
[d] Hepatocyte metabolism intrinsic clearance Cl_{int} (μL/min/10^6 cells).
[e] Blood PK after iv administration; Cl (mL/min/kg), $t_{½}$ (h), Vss (L/kg).

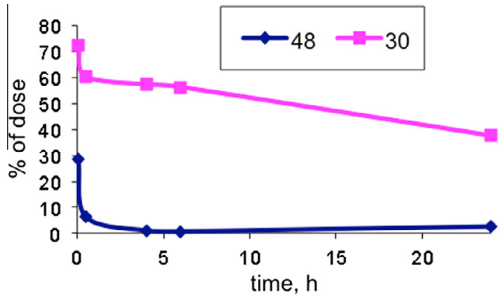


Figure 6. Lung tissue levels of compound **30** and compound **48** after *i.t.* administration to the lung.

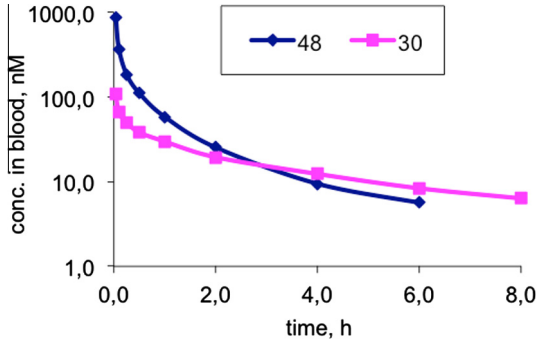


Figure 7. Blood levels of compound **30** and compound **48** after *i.t.* administration of 2 μmol/kg to the lung.

of neutrophils in BAL fluid.[23] Compound **30** was tested in the mouse cigarette smoke model. Mice were exposed to cigarette smoke for 50 min, twice daily, for four days. Animals were pretreated with compound **30**, 30 min prior to the first cigarette smoke exposure on each day (4 days treatment in total). 24 h after last exposure mice were terminated and the number of neutrophils in the BAL fluids determined.

Compound **30** significantly inhibited neutrophil influx into BAL fluid of mice exposed to cigarette smoke for four days at a dose of 30 μg/kg (Fig. 10). Fluticasone propionate and budesonide was used as references in this study.

In summary, we have successfully identified a series of highly potent and selective non-steroidal glucocorticoid receptor modulators. These were shown to have activity in pharmacodynamic models including the acute Tobacco Smoke model. Structure studies of receptor–ligand binding provided insight into functional drivers of agonism and cofactor affinity profiles revealed a differential binding mode compared to reference steroidal glucocorticoids. The ligands were shown to have PK properties (high clearance and solubility range) suitable for further optimisation as inhaled GR modulators.

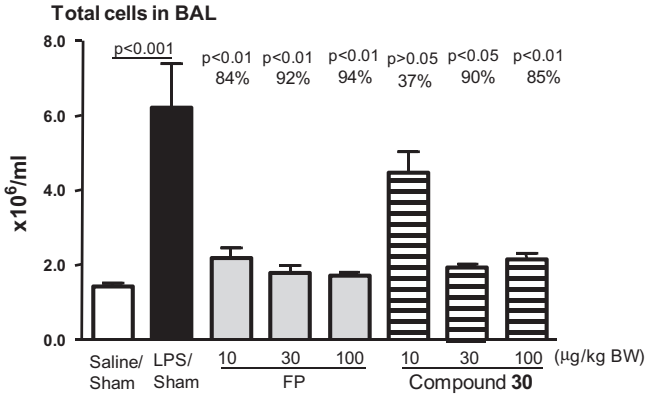


Figure 8. Inhibition of leukocyte influx following *i.t.* administration of compound **30** and fluticasone propionate (FP) in the acute LPS model.

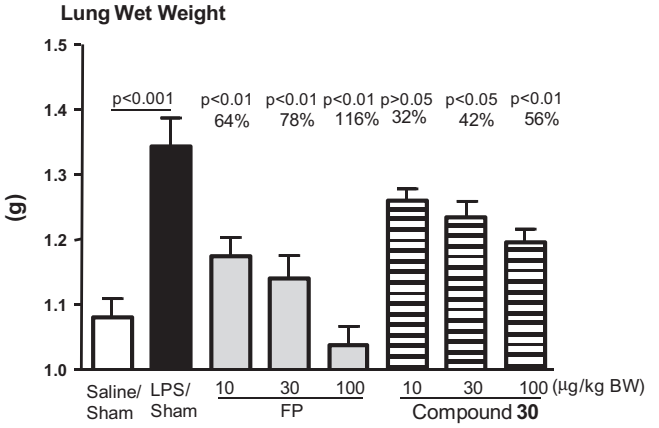


Figure 9. Inhibition of lung edema following *i.t.* administration of compound **30** and fluticasone propionate (FP) in the acute LPS model.

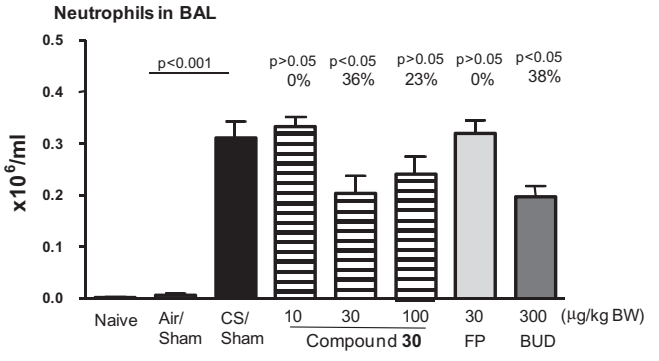


Figure 10. Inhibition of neutrophil influx following *i.t.* administration of compound **30**, fluticasone propionate (FP) and budesonide (BUD) in the acute cigarette smoke model.

Acknowledgments

The authors would like to thank Dr. Göran Carlström for NMR support; Tina Jellesmark Jensen for GR LBD protein expression support; Ann-Helene Jansson and Charlotte Brange for in vivo study support. We also thank Dr. Mark Furber for proofreading this manuscript.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmcl.2014.03.070.

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11. Compound **39** was prepared analogous to compound **30**, but starting from (*S*) 2-amino-3-methyl-1-butanol instead of (*S*) 2-amino-1-propanol.
12. Supplementary material 1: Synthetic schemes of the O, C, S and SO_2 linked 1-aryl-1*H*-indazoles **29**, **43**–**45** and the CF_3 branched indazole ether **46.**
13. The experimental details are described in the attached Supplementary material 2: Materials and Methods: Structure determination. The coordinates for the complex of GR LBD with compound **30** have been deposited in the PDB with accession code 4csj.
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