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α-Methyltryptamine sulfonamide derivatives as novel glucocorticoid receptor ligands

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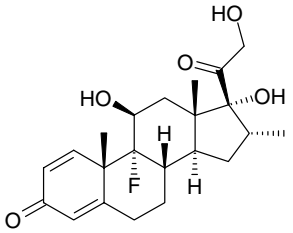
Abstract—α-Methyltryptamine sulfonamides were identified as human glucocorticoid receptor (hGR) ligands in an ultra high throughput screening (UHTS) campaign. Described will be the hit-to-lead activities, including parallel and single point analog synthesis to map the scaffold. Ligands were identified that exhibited 30 nM binding to hGR. The SAR and selectivity of these compounds will be discussed.

Glucocorticoid receptor modulators are among the most widely prescribed drugs (Fig. 1). Indications for agonists include rheumatoid arthritis, bronchial asthma, and severe psoriasis.[1] Antagonists have the potential to be used to treat a multitude of disorders, including diabetes and obesity.[2] However, the use of steroidal glucocorticoid receptor modulators in chronic disease treatment can result in the occurrence of serious side-effects, such as skin thinning, osteoporosis, hypotension, and shock.[3] The discovery of novel classes of non-steroidal agents that interact with the human glucocorticoid receptor (hGR) in the role of agonists[4] or antagonists[5] may lead to the identification of novel therapeutics with diminished side-effects.



Dexamethasone (Dex)
hGR Binding: 0.0034 μM

Figure 1. Marketed hGR modulator.

To this end, we embarked on an ultra high throughput screening (uHTS) campaign to identify novel, non-steroidal hGR ligands.[6] Due to the reported biological consequences of human nuclear receptor activity,[7] a counterscreen against the human progesterone receptor (hPR) was run to indicate preliminary selectivity. α-Methyltryptamine sulfonamide **1a** was identified and displayed binding affinities of 0.70 μM against hGR and greater than 2.0 μM against hPR (Fig. 2). These findings compelled us to more thoroughly examine this series, with the goals of increasing potency and selectivity.

To explore the effects of phenyl sulfonamide substitution, a parallel synthesis array was employed, coupling racemic α-methyl tryptamine with 88 sulfonyl chlorides under basic conditions[8] to rapidly access a variety of sulfonamide analogs. The SAR of mono-substituted

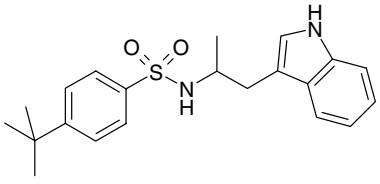


Figure 2. Methyltryptamine sulfonamide uHTS hit.

Keywords: Glucocorticoid receptor; Non-steroidal; Human nuclear receptor.
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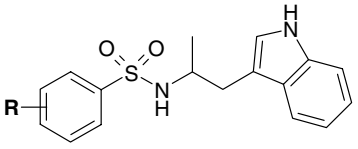
phenyl sulfonamides is displayed in Table 1. Unsubstituted phenyl sulfonamide, **1b**, was shown to have no binding affinity to hGR up to 10 μM. Substitution with lipophilic substituents at the 4-position led to an increase in binding potency compared to **1b** (compounds **1c**, **1d**, and **1e**). Substituting with chloro, **1h**, or phenyl, **1j**, at the 4-position provided compounds that were 2.1 and 2.6 μM, respectively. A 3-position methyl substituent, **1l**, demonstrated no binding, while substituting with a chloro at the same position, **1 m**, gave an affinity of 4.1 μM. 2-Chlorophenyl sulfonamide, **1n**, exhibited a binding potency of 4.1 μM. Of the limited number of polar groups surveyed (**1f**, **1g**, **1i**, **1k**, and **1o**), substitution with a moderately polar functionality at the 2, 3, and 4 positions did not lead to compounds exhibiting binding potency of less than 10 μM.

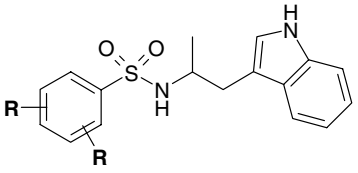
Introduction of a second substituent on the phenyl sulfonamide led to the identification of more potent ligands (Table 2). 2,3-Dichlorophenyl sulfonamide **2b** demonstrated equivalent potency to the original hit **2a**, while 3,4-dichloro or 3,5-dichloro combinations (**2d** and **2e**) were less potent analogs. 2,4-Dichlorophenyl sulfonamide **2f** demonstrated a modest 3-fold increase in binding affinity over **2a**, while 2,6-dichlorophenyl sulfonamide **2g** was 0.24 μM (6-fold increase). This indicates an additive effect for these positions. Compounds **2c** and **2h** demonstrate that methyl is interchangeable with chloro in this manifold.

Table 1. Mono-substituted phenyl sulfonamides



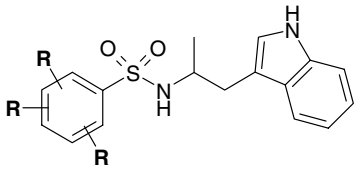
Compound **1**	R	hGR IC_{50} (μM)
b	H	>10
c	4-Me	5.7
d	4-*n*-Pr	1.6
e	4-*i*-Pr	0.75
f	4-OMe	>10
g	4-NO_2	>10
h	4-Cl	2.1
i	4-NHC(O)Me	>10
j	4-Ph	2.6
k	3-CN	>10
l	3-Me	>10
m	3-Cl	4.1
n	2-Cl	4.1
o	2-NO_2	>10

Table 2. Di-substituted phenyl sulfonamides



Compound **2**	R	hGR IC_{50} (μM)
a	2,5-Cl_2	1.3
b	2,3-Cl_2	1.2
c	2-Me-3-Cl	0.82
d	3,4-Cl_2	6.9
e	3,5-Cl_2	4.6
f	2,4-Cl_2	0.48
g	2,6-Cl_2	0.24
h	2-Me-6-Cl	0.28

Table 3. Tri-substituted phenyl sulfonamides



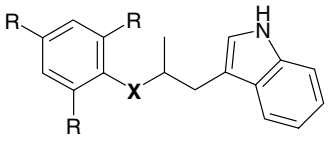
Compound **3**	R	hGR IC_{50} (μM)
a	2,5-F_2-4-Br	3.6
b	2,5-Me_2-4-Cl	1.8
c	3,5-Cl_2-2-OH	>10
d	2,3,4-Cl_3	1.9
e	2,4,5-Cl_3	0.99
f	2,4,6-Cl_3	0.064
g	2,4,6-Me_3	0.040
h	2,4,6-*i*-Pr_3	0.067

The study of tri-substituted phenyl sulfonamides provided ligands with improved binding affinity and a further preferred substituent pattern (Table 3). 2,3,4- and 2,4,5-tri-substituted sulfonamides exhibited micromolar potency (compounds **3a**, **3b**, **3d**, and **3e**) and hydroxy substitution at the *ortho* position was not tolerated. However, when the 2, 4, and 6 positions were substituted with non-polar groups (alkyl or halogen), the binding affinity increased to less than 0.10 μM (compounds **3f** and **3g**). These results indicate that the phenyl sulfonamide is situated in a large lipophilic pocket as 2,4,6-tri-*iso*-propylphenyl sulfonamide **3h** binds at 0.067 μM.

We next explored the substitution and replacement of the sulfonamide moiety to probe its role as linker and interactive functionality. The 2,4,6-tri-substituted pattern was locked while modulating the linkage to the tryptamine portion of the molecule (Table 4). Methylation of the sulfonamide nitrogen, compound **4a**,[9] led to a 20-fold loss of binding potency. Replacement of the sulfonamide also proved detrimental. Amide and urea replacements (**4b**[10] and **4c**[11]) did not exhibit binding affinity up to the highest concentrations tested. Similarly, replacing the sulfonamide with a methylene amine, **4d**,[12] resulted in a dramatic loss of potency.

We then investigated the substitution effects of α-substitution (**R2**) to the sulfonamide nitrogen to probe the nature of this position (Table 5). Deletion of the methyl group (**5a**) resulted in complete loss of binding affinity. Ethyl substitution was tolerated, **5b**[13], while substitution with polar functionality was not. Methylene hydroxy **5c**[14] or esters **5d** and **5e**[15] exhibited a lack of binding potency up to 2.0 μM. The stereochemical orientation

Table 4. Sulfonamide substitution and replacement



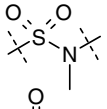
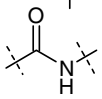
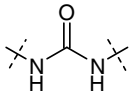
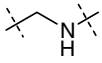
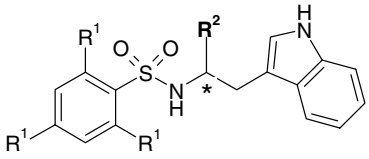
Compound **4**	X	R	hGR IC_{50} (μM)
a		Me	1.3
b		Me	>2.0
c		Cl	>2.0
d		Me	>2.0

Table 5. Study of tryptamine chain substitution



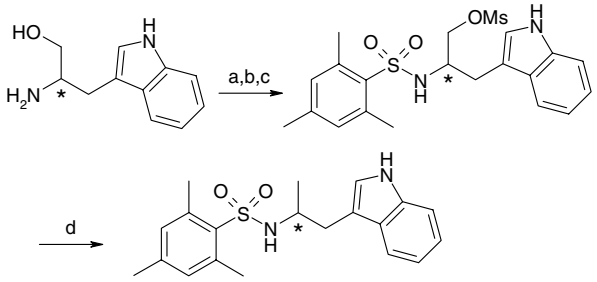
Compound **5**	R^1	R^2	hGR IC_{50} (μM)
a	Me	H	>2.0
b	Cl	Et	0.064
c	Me	CH_2OH	>2.0
d	Me	(*R*)-COOMe	>2.0
e	Me	(*S*)-COOMe	>2.0
f[a]	Me	Me*	>2.0
g[b]	Me	Me*	0.029

[a] (*R*)-configuration.
[b] (*S*)-configuration.

of the tryptamine substituent proved to be of consequence. Racemic methyltryptamine sulfonamide **3g** was subjected to resolution on a chiral HPLC column (Chiracel OD) to provide enantiomeric pairs **5f/5g**.[16]

These enantiomers illustrate that there is a stereochemical component to the binding affinity of this series. One enantiomer binds at 0.029 μM while the other demonstrates no binding at the highest concentration tested. Stereoisomers **5f** and **5g** were independently synthesized to reveal the absolute configuration of the active enantiomer, starting from enantiopure D- or L-tryptophanol (Scheme 1). It was found that the compound with the (*S*)-configuration, **5g**, was the enantiomer demonstrating potent binding (Fig. 3).[17]

A brief study of the effect of indole substitution on binding affinity is presented in Table 6.[18] The isomeric, 2-substituted indole **6a** did not demonstrate binding affinity at the highest concentration tested. Methylation



Scheme 1. Synthesis of enantiomeric pair **5f/5g**. Reagents and Conditions: (a) TMSCN, TEA, CH_2Cl_2, rt, 16 h; (b) Mesitylene sulfonyl chloride, TEA, CH_2Cl_2, rt, 16 h; (c) MsCl, TEA, CH_2Cl_2, rt, 16 h; (d) $LiBHEt_3$, THF, 40 ° C, 16 h.

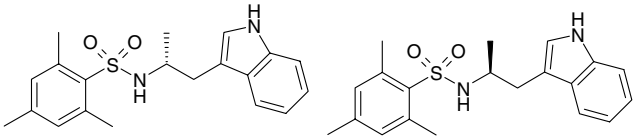
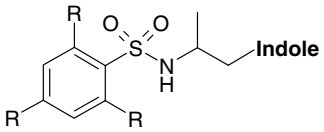


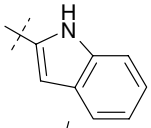
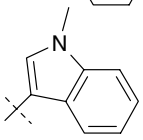
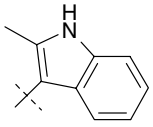
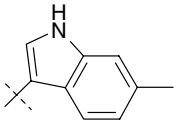
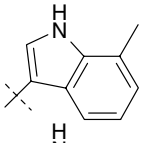
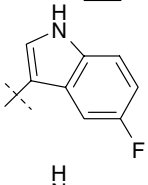
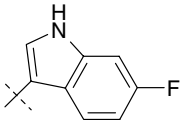
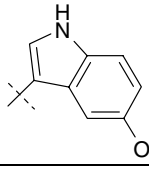
Figure 3. Enantiomers of **3g**.

of the indole nitrogen (**6b**) also led to loss of binding potency, while methyl substitution at the 2-position (**6c**) resulted in 10-fold loss of affinity. Methylation of the indole phenyl ring at the 6-position (**6d**) also adversely affected the binding, while 7-methyl substitution (**6e**) exhibited a 3-fold loss of potency. Fluoroindoles **6d** and **6f** were equipotent to unsubstituted **3g** (0.069 and 0.079 μM, respectively) and 5-methoxy substitution was not tolerated.

Having identified compounds with hGR binding of less than 0.100 μM, the selectivity of these compounds against other human nuclear receptors (hNR) was explored.[19] A select panel of compounds screened against hPR and human mineralcorticoid receptor (hMR) is shown below (Table 7).[20] Compound **1a**, our starting point, demonstrates weak selectivity against the hNR panel. 2,6-Dichlorophenyl sulfonamide, **2g**, shows a 6-fold selectivity over hMR, and no selectivity against hPR, while 2,4-dichloro substitution (**2f**) elicits at least a 4-fold selectivity over hPR and equivalent cross reactivity with hMR. 2,4,6-Trichlorophenyl sulfonamide, **3f** selectively binds to hGR over hPR (8-fold), while selectivity is poor against hMR. 2,4,5-Trichloro substitution (compound **3e**) does not retain hPR selectivity. 2,4,6-Trimethyl derivative **3g** exhibits 35-fold increase of selectivity against hPR, while hMR selectivity increases (7-fold). Finally, tri-*iso*-propylphenyl sulfonamide **3h** exhibited the highest degree of selectivity in the hNR panel. When the stereocenter is resolved, the hMR selectivity is affected. Enantiomer **5f**, the compound lacking hGR potency, retains its hMR cross reactivity, while **5g** is 34-fold selective against hMR. Other changes to the tryptamine chain substitution or modulation of the indole substituent pattern had little effect on the selectivity profile. Based on these data, it appears as though the selectivity profile of these compounds is dependent on steric environment of the phenyl ring as well as orientation of the chiral center.

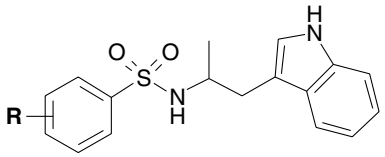
Table 6. Study of indole substitution



Compound **6**	Indole	R	hGR IC_{50} (μM)
a		Me	>2.0
b		Cl	>2.0
c		Cl	0.57
d		Me	0.49
e		Me	0.12
f		Me	0.065
g		Me	0.079
h		Cl	>2.0

In conclusion, a uHTS campaign identified methyltryptamine sulfonamides as novel hGR ligands. Utilizing parallel synthesis, the hGR potency was increased 17-fold. 2,4,6-Tri-substituted phenyl sulfonamides, with alkyl or halogen substituents, were found to be the most potent ligands. The sulfonamide proved to be crucial for hGR binding and the tryptamine chain substituent was required to be lipophilic in nature. Resolution of the α-methyltryptamine moiety revealed an enantiomeric preference with hGR binding affinity residing in one enantiomer. Independent synthesis of each enantiomer identified the (*S*)-configuration as being the preferred stereocenter. The selectivity of the tryptamine sulfonamides was also improved. Placement of sterically demanding groups at the 2, 4, and 6 positions of the sulfonamide provided a hGR selective compound. Therefore, this effort has led to the discovery of a novel, potent, and selective hGR ligand.

Table 7. NR selectivity of phenyl sulfonamides



Compound	R	hGR IC_{50} (μM)	hPR IC_{50} (μM)	hMR IC_{50} (μM)
Dex	—	0.0034	>2.00	0.033
1a	4-*t*-Bu	0.735	>2.00	1.07
1e	4-*i*-Pr	0.750	1.00	1.40
2f	2,4-Cl_2	0.480	>2.00	0.850
2g	2,6-Cl_2	0.240	0.170	1.60
3e	2,4,5-Cl_3	0.710	0.440	1.00
3f	2,4,6-Cl_3	0.064	0.570	0.130
3g	2,4,6-Me_3	0.040	1.40	0.290
3h	2,4,6-*i*-Pr_3	0.067	>2.00	>2.00
5f	2,4,6-Me_3	>2.00	>2.00	0.520
5g	2,4,6-Me_3	0.029	1.20	1.00

Acknowledgment

We thank Oliver Deeg.

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8. α-Methyltryptamine (780 mg, 4.40 mmol) and triethylamine (1.25 mL, 8.98 mmol) was dissolved in 18 mL CH_2Cl_2. This solution (0.2 mL) was dispensed into 88 wells of a 96-well microtiter plate. To each was added 0.5 mL of a solution of the specified sulfonyl chloride (0.1 mmol) in CH_2Cl_2. The plate was sealed and placed on a shaker for 48 h. The plate was transferred to the automated Gilson 215 SPE instrument where each well was passed through a CH_2Cl_2 pre-washed NH_2/CBA-layered solid-phase extraction cartridge (100 mg sorbent each, Varian Bond-elut). The cartridge was washed with 2× 0.3 mL CH_2Cl_2. The filtrates were concentrated in vacuo and the residues dissolved into 0.5 mL CH_2Cl_2. Fifty microliters of each well was transferred to a collection plate for LC–MS analysis.
9. (a) Compound **3g** was treated with the following conditions: (**a**) DMAP, $(BOC)_2O$, CH_3CN, rt, 16 h; (b) K_2CO_3, MeI, DMF, 50 °C, 16 h; (c) μW, 180 °C, 20 min, repeat 3 times.
10. α-Methyltryptamine was treated with 2 equiv TEA and 2,4,6-tri-methylbenzoyl chloride in CH_2Cl_2 overnight.
11. α-Methyltryptamine was treated with 2,4,6-tri-chlorophenyl isocyanate in THF at 50 °C overnight.
12. α-Methyltryptamine was treated with 1.5 equiv 2,4,6-trimethylbenzaldehyde in $C_2H_4Cl_2$ at 180 °C with μW irradiation for 3 min. To this were added EtOH and 1.5 equiv $NaBH_4$. The mixture was concentrated after 20 min.
13. (a) 3-Indole carboxaldehyde, nitropropane, AcOH, sonication, rt, 4; (b) Nitro olefin, BH_3/THF, TMSCl, rt, 14 h; (c) Crude amine, TEA, sulfonyl chloride, rt, 16 h.
14. (a) α-Methyltryptamine, TMSCN, TEA, CH_2Cl_2, rt, 16 h; (b) Mesitylene sulfonyl chloride, TEA, CH_2Cl_2, rt, 16 h.
15. **5d** and **5e**: tryptophan methyl ester was treated with 2 equiv TEA and mesitylene sulfonyl chloride in CH_2Cl_2 overnight.
16. Racemate **3g** (19.0 mg, 0.05 mmol) was dissolved into 8 mL of a 10% IPA/hexane solution. 2.0 mL of this solution was injected onto an HPLC (column: Chiracel OD 1.0 mm, flowrate: 5 mL/min). **5f** was collected at 30.8 min and **5g** collected at 35.2 min. This cycle was repeated three more times to give 15.0 of **5f** (48% yield) and 15.5 mg of **5g** (50% yield).
17. >95% ee for each enantiomer.
18. General experimental for compounds **6c**–**6h**: (**a**) 3-indole carboxaldehyde, nitroethane, AcOH, sonication, rt, overnight. See Ref. 13.
19. GR, PR, and MR binding assays were performed in a fluorescence polarization format that measures competition for binding to the nuclear receptor, present in lysates of baculovirus-infected insect cells, between a test compound and a fluorescently labeled receptor ligand, or probe. IC_{50} values were determined by fitting the fluorescence polarization signal data to a 4-parameter logistic equation.
20. All compounds in this series are >2.00 μM against human estrogen receptor (hER).