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Discovery of novel non-steroidal reverse indole mineralocorticoid receptor antagonists

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ABSTRACT

Reported herein are a series of reverse indoles that represent novel non-steroidal mineralocorticoid receptor (MR) antagonists. The key structure–activity relationships (SAR) are presented below. This reverse indole series is exemplified by a compound that demonstrated efficacy in an acute natriuresis rodent model comparable to marketed MR antagonists, spironolactone and eplerenone.

Mineralocorticoid receptor antagonists (MRA) have traditionally been prescribed as hypotensive drugs that were intended to blunt the potential for aldosterone escape as a means of greater control over of the RAAS signaling pathway.[1] The first generation MRA, spironolactone, demonstrated good efficacy, but was beset with adverse effects (AE), such as gynocomastia and impotence in male patients.[2] The observed AE profile was attributed to a lack of nuclear hormone receptor selectivity, which was overcome with the approval of eplerenone in 2002.[3]

Recent clinical trials involving both spironolactone and eplerenone have demonstrated a strong link between MR antagonism and positive outcome benefits to heart failure patients, albeit with an elevated risk of hyperkalemia that is believed to be mechanism-related.[4] The observed benefits to mortality, cardiovascular adverse events and hospitalization were independent of a hypotensive effect long presumed to be the primary benefit of an MRA.

Over the past decade, a number of reports have detailed efforts to identify a next generation, non-steroidal MRA.[5,6] Reported herein are the background rationale and discovery of a potent and selective reverse indole MRA class that has demonstrated acute PD efficacy (Fig. 1).

Initial efforts sought to expand on the SAR established around a number of efficient central scaffolds.[7] For example, qualitative analysis of literature examples featuring 3,7-disubstituted indole and 4,7-disubstituted benzoxazine scaffolds, e.g., suggested that the analogous display of key functional groups from N1 and C4 of an indole central scaffold could be successful.[8] Further, alkylation at the indole N1-position facilitated the synthesis of more structurally diverse pendant hydrophobic functionality, which would, subsequently, enable SAR refinement.

To this end, the SAR derived from an initial basis set of compounds **1**–**7**,[9] supported the aforementioned hypothesis that the 'reverse indole' scaffold could yield MR antagonists of high lipophilic ligand efficiency (LLE), as well as providing evidence that a second hydrogen bond donor was not required for activity. The initial array of MRAs also revealed subtle but potentially significant determinants of activity, as seen from the improved activity for compounds **5**–**6**, which contain a conformational-directing *ortho*-Cl atom. Lastly, the loss in activity observed for biaryl compound, **7**, suggests a steric limit to the binding pocket.

Having established preliminary aryl ring SAR, the next goal involved gaining a similar understanding with respect to indole

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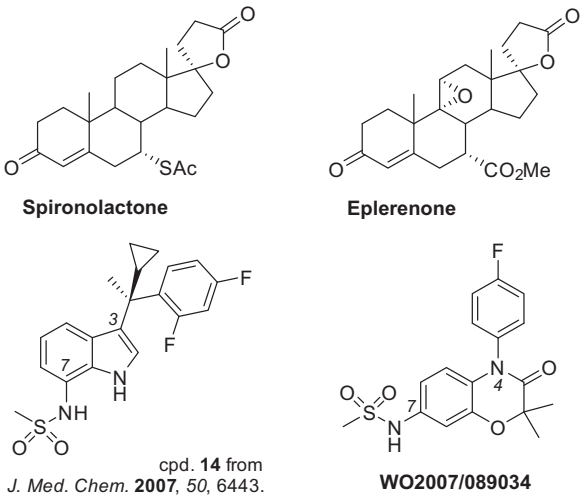


Figure 1. Known mineralocorticoid receptor antagonists.

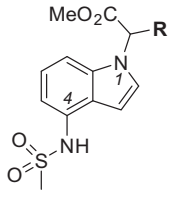
substitution (**8**–**14**). A brief SAR examination revealed two significant findings. First, although replacement of the sulfonamide with a nitrile (**11**) led to a significant improvement in activity, the off-target activity at other NHR precluded its employment. The second finding was that the sulfonamide SAR was also highly sensitive as close homologs (**13**–**14**) resulted in erosion of activity (Tables 1 and 2).

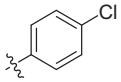
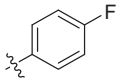
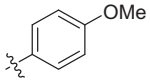
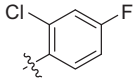
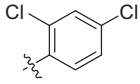
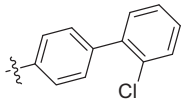
Despite the knowledge gained from probing the indole and aryl ring SAR, the conclusions largely supported what was previously established in the literature. Less well known, however is the SAR governing substitution at the benzylic carbon linking the aforementioned moieties. Further, the reverse indole scaffold readily lent itself to rapid SAR development, and more significantly, unsymmetrical substitution (see Table 3).

The introduction of a methyl substituent to form a quaternary carbon (**15**) applied a common strategy to improve potency by restricting rotation.[10] The functional activity for **15** affirmed this strategy, but expanding the SAR revealed a separate and distinct preference for small compact lipophilic substituents, highlighted by compounds **16**, **18**, and **20**. Extending the hydrophobic surface proved to be deleterious (**17**), and introducing polar functionality in the form of a methoxymethyl group, also had an adverse effect on activity.

Chromatographic separation of the enantiomers from racemic **16**, indicated a clear preference for one stereoisomer (**21**), which was tentatively assigned the *R*-stereochemistry based on correlation studies using Vibrational Circular Dichroism (VCD).[11] Also

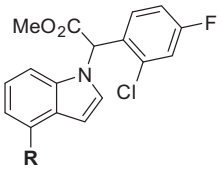
Table 1
In vitro SAR for the pendant phenyl ring, compounds **1**–**7**



Compd[a]	R	hMR NH Pro IC_{50}[b] (nM)	LLE[c]
1	Ph	4000	–
2		1700	1.8
3		10,000	2.1
4		9800	–
5		530	2.9
6		80	3.8
7		3920	1.4

[a] Compounds are racemic.
[b] Values are the average of two 10-pt titrations.
[c] LLE = $pIC_{50} - c\log P$.

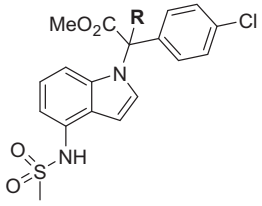
Table 2
In vitro SAR at the indole C4-position, compounds **8**–**14**



Compd[a]	R	hMR NH Pro IC_{50}[b] (nM)	LLE[c]	Other NHR counterscreens
8	H	2700	1.4	
9	F	2310	1.2	
10	Cl	940	1.3	AR_{ag} = 58 nM[d] (76%)
11	CN	200	2.9	GR_{antag} = 0.3 μM[d] AR_{ag} = 9 nM[d] (76%)
12	CO_2Et	4800	1.1	
5	$NHSO_2Me$	530	2.9	GR_{antag} = 3.2 μM[d]
13	$NHC(O)CF_3$	7900	1.4	
14	$NHSO_2CF_3$	2120	2.1	

[a] Compounds are racemic.
[b] Values are the average of two 10-pt titrations.
[c] LLE = $pIC_{50} - c\log P$.
[d] Value is from a single 10-pt titration.

Table 3
In vitro SAR for the α-alkyl substituents, compounds **17**–**22**



Compd[a]	R	hMR NH Pro IC_{50}[b] (nM)	LLE[c]
2	H	1860	1.8
15	Me	200	3.2
16	Et	60	3.4
17	Bn	275	2.3
18	$CH_2{}^cPr$	30	–
19	CH_2OMe	1900	–
20	CH_2CN	70	4.3

[a] Compounds are racemic.
[b] Values are the average of two 10-pt titrations.
[c] LLE = $pIC_{50} - c\log P$.