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Letters

(*S*)-*N*-{3-[1-Cyclopropyl-1-(2,4-difluoro-phenyl)-ethyl]-1*H*-indol-7-yl}-methanesulfonamide: A Potent, Nonsteroidal, Functional Antagonist of the Mineralocorticoid Receptor

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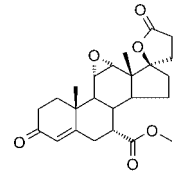
Abstract: A novel, potent series of indole analogs were recently developed as MR antagonists, culminating in **14**. This compound represents the first MR antagonist in this class of molecules, exhibiting picomolar binding affinity and in vivo blood pressure lowering at pharmaceutically relevant doses.

The mineralocorticoid receptor (MR[a]) is a member of the super family of nuclear receptors and is structurally related to those recognizing steroidal ligands. Also included in this receptor subclass are the androgen receptor (AR), glucocorticoid receptor (GR), estrogen receptor (ER), and the progesterone receptor (PR). Although MR binds cortisol and corticosterone with high affinity, aldosterone is generally recognized as the primary endogeneous ligand. Aldosterone action has long been implicated in sodium transport, impacting blood pressure, urinary protein excretion, and potassium levels.[1]

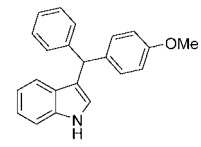
Results of the RALES trial (Randomized Aldactone Evaluation Study) demonstrated that the published MR antagonist spironolactone, added to standard therapy, reduced mortality due to all causes by 30% as well as reduced hospitalizations and improved cardiac function in patients with severe heart failure.[2] These results demonstrated the clinical potential of an aldosterone antagonist acting via the mineralocorticoid receptor as a reasonable therapeutic target. As such, spironolactone therapy is limited due to lack of specificity and unwanted endocrine side effects (gynecomastia, hyperkalemia, menstrual irregularities).[3] Indeed, eplerenone, **1**, also acts as a mineralocorticoid receptor antagonist and is used to treat numerous patients for hypertension and congestive heart failure.

Drug therapies targeting the renin-angiotensin-aldosterone system (RAAS) have established success in treating congestive heart failure through vaso dilatory effects of inhibiting angiotensin-converting enzyme (ACE), downregulating systemic angiotensin II, and circulating aldosterone. However, a phenomenon termed "aldosterone escape" limits the utility of ACE inhibitors, as aldosterone levels normalize over time.[4] Direct antagonism of aldosterone may provide a better alternative or minimally an adjunct therapy.

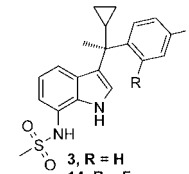
The mineralocorticoid receptor represents an intriguing target with extensive clinical validation in treating hypertension and congestive heart failure, although not without its challenges as the hyperkalemic, events are yet to be well understood. Clearly, a clinical need for drug therapies that address the mechanistic root of CHF and hypertension are valued. Given the current limitations in standard of care, a potent, selective, small molecule MR antagonist may provide clinicians with a valuable tool in the arsenal for treating hypertension and CHF.



Eplerenone, **1**



2



3, R = H
14, R = F

The goal at the outset of the project was to develop a novel series of potent and selective, nonsteroidal, MR antagonists based on the indole scaffold. Published indole analog **2** was revealed as a weak binder through screening efforts of our proprietary in-house collection (data not shown).[5] Through exhaustive exploration of the side chain SAR, the geminal

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[a]Abbreviations: MR, mineralocorticoid receptor; AR, androgen receptor; GR, glucocorticoid receptor; ER, estrogen receptor; PR, progesterone receptor; RAAS, renin-angiotensin-aldosterone system; ACE, angiotensin converting enzyme; CHF, congestive heart failure; SAR, structure–activity relationship; HPLC, high pressure liquid chromatography; po, post oral; qd, quaque die; mpk, milligram per kilogram; MAP, mean arterial pressure; sc, subcutaneous.

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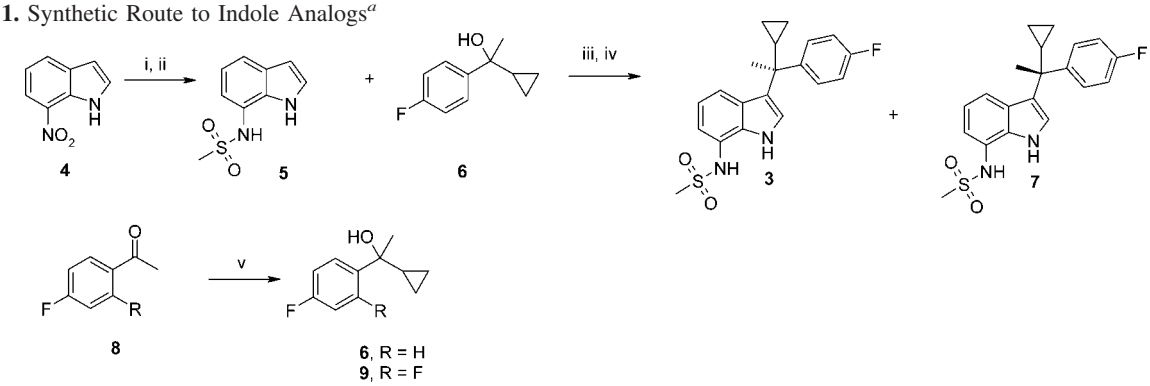
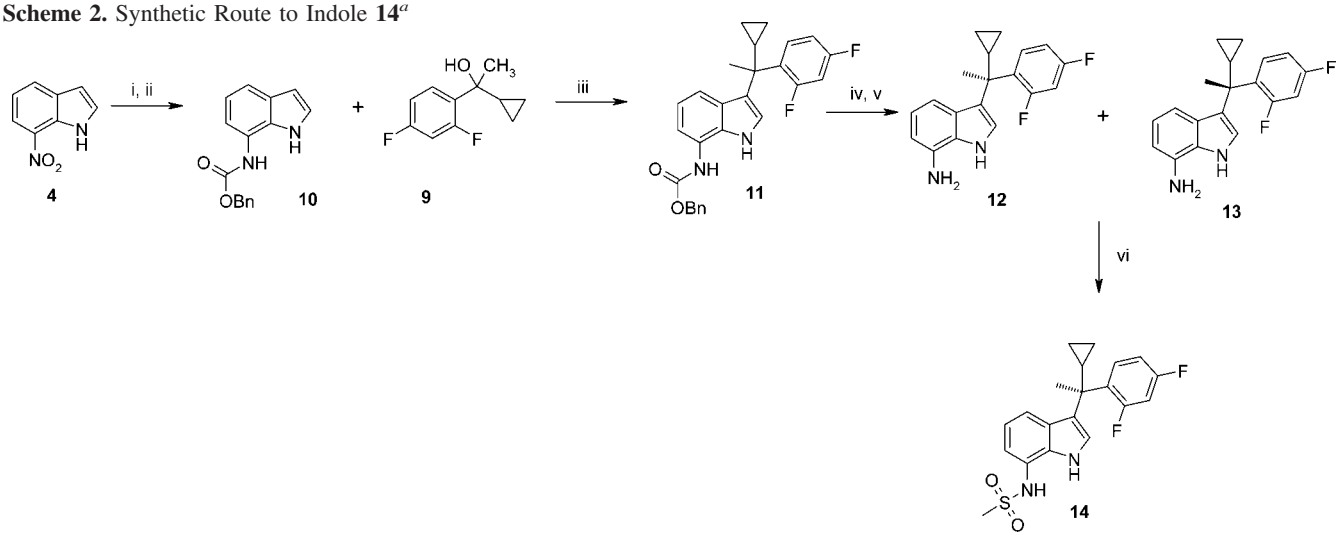
Scheme 1. Synthetic Route to Indole Analogs[a]



[a] Reagents and conditions: (i) H_2, 10% Pd/C, rt, 5 h; (ii) mesyl chloride, TEA, DCM, rt, overnight; (iii) TFA, DCM, rt; (iv) chiral chromatography; (v) cyclopropyl MgBr, THF, rt−45 °C.

Scheme 2. Synthetic Route to Indole **14**[a]



[a] Reagents and conditions: (i) H_2, 10% Pd/C, 5 h; (ii) $BnCO_2Cl$, Na_2CO_3, H_2O/MeOH, 0 °C, 30 min; (iii) TFA, DCM, rt, overnight; (iv) H_2, 10% Pd/C, 40 °C, overnight; (v) chiral separation; (vi) mesyl chloride, TEA, DCM, rt, 1.5 h.

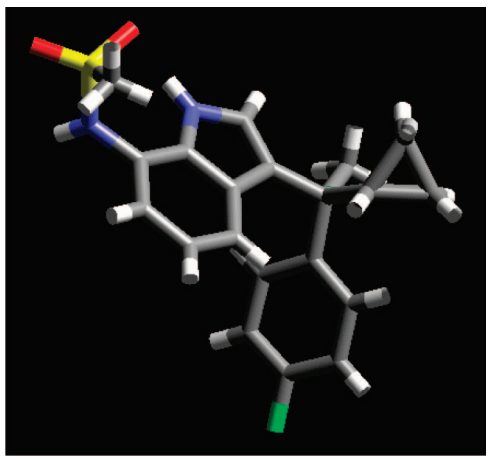


Figure 1. Crystal structure of **3**.

dialkyl substitution was discovered. The effect was 2-fold, offering an enhanced in vitro profile, while introducing novel composition. The full SAR of the indole series will be presented in a future publication and is beyond the scope of this initial communication, however, key elements of the SAR progression are worth noting. First, optimization of the series uncovered the propensity for a proton donor in the seven position of the indole nucleus, specifically, a methane sulfonamide. Second,

Table 1. In Vitro Binding, Functional and Selectivity Comparison of MR Antagonists[a]

cmpd	hMR K_i	hMR K_b	hGR K_i	hAR K_i	hPR K_i	hER K_i
14	0.494	19	8.9	700.1	162.9	>1100
R-enantiomer	2.25	66				
3	1.56	38.2	167	849	137	>1100
7	7.5	115	387	590	313	>1100
1	124	189	1758	8892	29424	>1100
spironolactone	2.323	17.7	32.6	39.4	399.7	>1100

[a] In nanomolar, nM.

definition of the dialkyl SAR revealed a sterically limited, hydrophobic pocket, with the methyl/cyclopropyl motif offering the best combination of synthetic accessibility, in vitro and in vivo activity, with a clear preference for the *S*-enantiomer. Phenyl substitution showed an interesting pharmacophore in going from the monofluorinated analog **3** to the difluoro analog; a 3-fold increase with in vitro binding was obtained. This trend translated into the functional assay as well as in vivo, affording the highly optimized analog **14**.[7]

Compounds in this series were prepared according to Scheme 1, utilizing multigram quantities of the advanced intermediate **5**.[7] The 7-methanesulfonamide indole was prepared by hydrogenation of the commercial nitro indole **4**, followed by mesylation, to give **5** in 91.3% overall yield. Ketones **8** were reacted with the appropriate Grignard to afford the tertiary carbinol. In the key coupling step, the carbinol was condensed with the

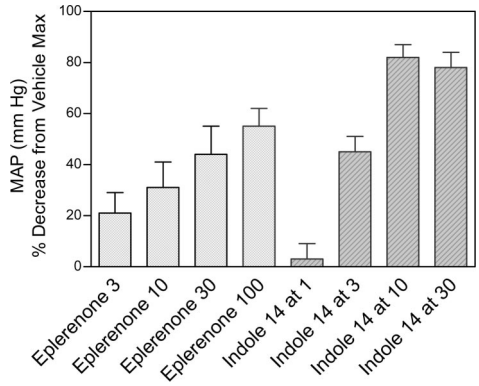


Figure 2. Reduction in aldosterone-induced (0.75 ug/hr, s.c.) hypertension by mineralocorticoid antagonists (1–100 mg/kg/day, po × 14 days).

7-methanesulfonamide indole **5** under acidic conditions, usually trifluoroacetic acid, to give the 3-alkylated indole as a racemic mixture. Chiral separation afforded the individual enantiomers, giving **3** in 95% enantiomeric excess.[9,10]

The racemic mixture of **14** proved to be a very challenging chiral separation on scale. However, by modifying the synthetic route and subjecting the racemic amino indole (**12** and **13**) to an optimized chiral resolution, a significant advancement in separation was achieved.[9,10] This was ultimately a critical step in the prosecution of this molecule. Again, starting with the commercially available 7-nitro indole, **4**, and cyclopropyl phenyl ketone, **8**, analog **14** was prepared in a five-step synthesis, as shown in Scheme 2.[7] In the manner of Scheme 1, the difluorophenyl geminal dialkyl carbinol **9** was condensed with the protected amino indole **10** under acidic conditions to give the 3-alkylated indole **11**. Deprotection followed by chiral resolution of the resultant aniline offered optimal separation, giving the pure *S*-enantiomer **12**. Finally, mesylation and recrystallization gave the final compound **14**. The absolute stereochemistry of **3** was unambiguously determined through single crystal X-ray analysis to be the *S*-enantiomer, as shown in Figure 1. Correlative studies utilizing chiral HPLC and optical rotation identified **14** as also having the *S*-absolute configuration.

The indole series was found to be potent, selective MR antagonists, as exhibited by **3** and **14**. Human MR (hMR) and selectivity binding, as well as functional activity, proceeded as described in the literature.[6,7] Members of this class of compounds showed greater than 10-fold selectivity against related receptors in the steroidal class based on binding presented in Table 1.

In benchmarking against reference compounds, the selectivity profile for **14** is similar and, in some cases, exceeds that of **1**. Most importantly, the AR and PR selectivity window is well above that of **1** and spironolactone, offering a distinct advantage. In the indole examples, the *S*-enantiomer was about 3-fold more potent in either the binding or the functional assays. Simply going from a *para*-fluoro to an *ortho*,*para*-difluoro phenyl, an increase in binding affinity was realized that persists throughout the flowscheme. Analog **14** is a high affinity (MR $K_i = 0.494 \pm 0.23$ nM), functional antagonist ($K_b = 19 \pm 12.8$ nM) with reasonable in vivo efficacy and potency. Most importantly, **14** showed greater binding affinity than **1**, a trend mirrored in the functional and in vivo setting as well.

In salt-loaded, uninephrectomized Sprague–Dawley rats, **14** was more potent than **1** on a dose basis.[8] After 14 days (po, qd), a 3 mpk dose of **14** showed equivalent blood pressure lowering to **1** at 30 mpk, as shown in Figure 2. Interestingly, indole **3** was not active at 3 mpk (data not shown). By adding the *ortho*-fluoro in **14**, the result is a very potent and efficacious compound. Clearly, **14** compares favorably to **1** regarding in vivo potency.

Analog **14** is a potent, selective, orally efficacious antagonist of the mineralocorticoid receptor. The analog based on the indole scaffold is more potent than the marketed drug **1** in a rat model for hypertension and offers a better in vitro selectivity profile than the standard spironolactone. Clinical side effects surrounding the current therapies in the steroidal class of molecules make a small molecule inhibitor a valued strategy for treating hypertension and congestive heart failure. The optimal indole **14** and related analogs may offer clinicians a valuable tool in the fight against these critical disease states.

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Supporting Information Available: Experimental procedures and characterization data for **14** and other indole analogs and a detailed description of in vivo assays. This material is available free of charge via the Internet at http://pubs.acs.org.

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