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Design and synthesis of aryl sulfonamide-based nonsteroidal mineralocorticoid receptor antagonists

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ABSTRACT

Hit-to-lead medicinal chemistry efforts are described starting from a screening hit **1**, leading to a new class of aryl sulfonamide-based MR antagonist, exemplified by **17**, that possesses favourable MR binding affinity, selectivity profile against closely related NHRs, physicochemical properties and metabolic stability.

The mineralocorticoid receptor (MR) belongs to the nuclear hormone receptor (NHR) super-family and is a ligand-dependent transcription factor.[1,2] Activation of MR by excessive levels of the steroid hormone aldosterone causes harmful effects in cardiovascular and renal systems such as hypertension, congestive heart failure and chronic kidney disease.[3,4] The blockade of MR has been shown to be beneficial for the treatment of conditions above in the clinical settings, as demonstrated by two marketed steroidal MR antagonists, spironolactone and eplerenone (Fig. 1). There has been extensive research activities on identification of next generation MR antagonists that mitigate limitations associated with the currently available steroid-based agents, such as sex hormone related side effects (for spironolactone) and hyperkalemia. As such, a significant effort has been devoted to the nonsteroidal class for next generation MR antagonists. This has been largely driven by the hypothesis that structural distinctions from the marketed steroidal agents, with high selectivity over other NHRs, might mitigate known risks.[5–9] In fact, preclinical data from the nonsteroidal MR antagonists indicates that the mitigation of hyperkalemia might be possible.[10,11] Among nonsteroidal MR antagonists reported in peer-reviewed literature, BAY 94-8862 (Bayer)[7] is reported to be in phase II clinical trials (Fig. 1).

As part of our discovery program for next generation nonsteroidal MR antagonists, we desired a small, polar molecule that could serve as a novel advanced lead.[12] Desirable attributes for such a lead include a neutral ionization state that could influence the PK and safety profile relative to that of the PF-3882845, a previously disclosed pyrazoline-based acidic MR antagonist (Fig. 1).[13] Recent analysis on physicochemical property space of MR chemical matter suggests the possibility of operating within the drug-like, high

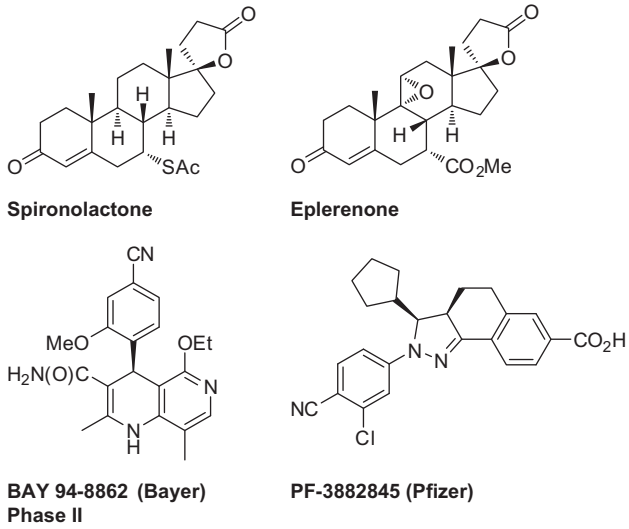

Figure 1. Marketed steroidal MR antagonists and selected published nonsteroidal MR antagonists.

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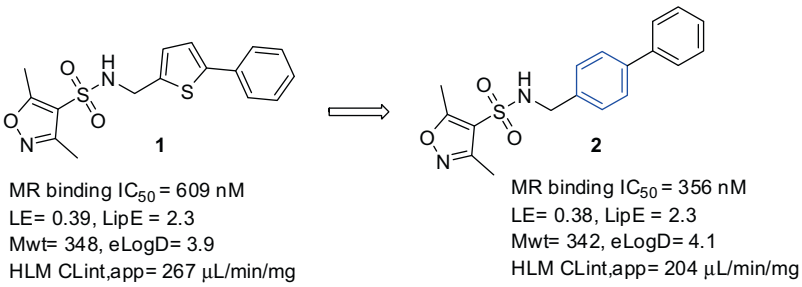
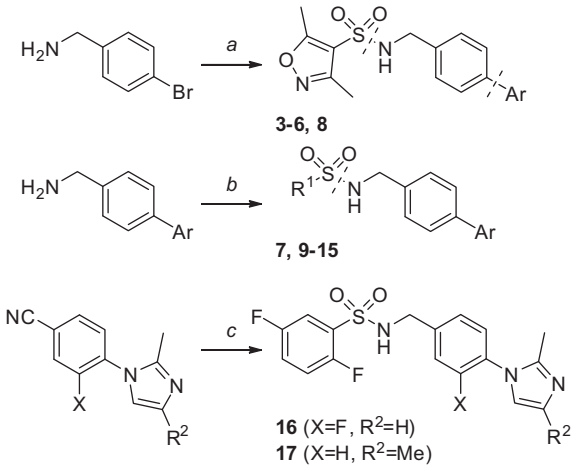


Figure 2. Genesis of aryl sulfonamide-based MR antagonists.



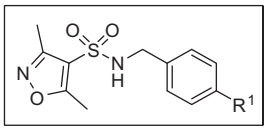
Scheme 1. Synthesis of aryl sulfonamide-based MR antagonists. Reagents and conditions: (a) (1) 3,5-Dimethyl-1,2-isoxazole-4-sulfonyl chloride, DIPEA, DCM-DMF or DCM, 30 °C or rt, (2) Ar-B(OH)$_2$ (for **3**–**6**) or 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine-3-carbonitrile (for **8**), Pd(PPh$_3$)$_4$, Na$_2$CO$_3$, DME-H$_2$O, 100 °C or 130 °C; (b) R^{1}SO$_2$Cl, K$_2$CO$_3$, DIPEA, DCM, 30 °C (for **10**), R^{1}SO$_2$Cl, pyridine, THF, rt (for **11**–**14**) or R^{1}SO$_2$Cl, DMAP, TEA, DCM or DCE, 50 °C (for **7**, **9** and **15**); (c) H$_2$ (15 psi), Raney Ni, MeOH-NH$_3$ aq, followed by 2,5-difluorobenzenesulfonyl chloride (1.2 equiv), TEA (1.3 equiv), DMF, 0 °C to rt, 24% (for **16**), 16% (for **17**).

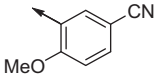
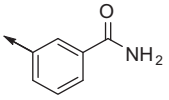
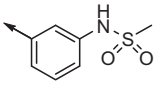
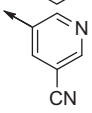
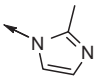
probability safety space (cLog*P* <3, TPSA >75).[14,5] Herein we describe the hit-to-lead effort starting from the aryl sulfonamide-based MR antagonist **1**.

High throughput screening of the Pfizer compound collection using a MR luciferase reporter antagonist assay and the subsequent verification in a filter binding assay with ^{3}H-aldosterone yielded 3,5-dimethyl isoxazole sulfonamide hit **1** (Fig. 2).[15] Subsequent file mining using a MR filter binding assay revealed that the central thiophene ring could be replaced by a phenyl ring leading to a marginal improvement in MR binding affinity (compound **2**,[16] Fig. 2). While **1** and **2** showed good ligand efficiency (LE),[17] their lipophilic efficiency (LipE)[18–20] was relatively low due to the combination of high Log*D* and modest binding affinity. The high Log*D* is likely responsible for the high turnover in human liver microsomes (HLM). Despite these deficiencies, it was envisaged that the large inherent chemical space accessible through high throughput parallel-chemistry may allow for efficient improvement of LipE and metabolic stability. Thus, **2** was selected as a starting point for the optimization effort with the initial goal to identify the advanced lead that balance MR potency and metabolic stability by optimizing LipE.

Synthesis of aryl sulfonamide-based MR antagonists **3**–**17** is described in Scheme 1. Most of the analogue syntheses in this series were driven through parallel chemistry, with two general methods employed for a rapid development of SAR of both the aryl sulfonamide group and the terminal aryl ring. The single step

Table 1
SAR of the distal aryl ring (R^1) based on compound **2**



Compd	R^1	MR binding IC$_{50}$ ± SD[a] (nM)	LipE[b]	*e*Log*D*[22]	HLM CL$_{int,app}$ (μL/min/mg)
2		356 ± 166	2.3	4.1	203
3		40 ± 11	4.1	3.3	N.D.[c]
4		45 ± 15	4.1	3.2	198
5		2029 ± 1137	3.3	2.4	N.D.[c]
6		1393 ± 263	3.0	2.9	39
7[d]		1530 ± 180	3.4	2.4	86
8		1974 ± 829	3.8	1.9	25
9[d]		4698 ± 1835	3.8	1.5	17

[a] Values are arithmetic means of at least two experiments. See note 15 for details.
[b] LipE = pIC_{50}−*e*Log*D*.
[c] N.D. = Not determined.
[d] Tested as trifluoroacetic acid salts.

sulfonylamidation protocol took advantage of available primary amines to test a range of biaryl scaffolds, and served as a complementary approach to the two-step sequence. The two-step sulfonylamidation–Suzuki coupling sequence starting from 1-(4-bromophenyl)methanamine allowed for examination of a diverse set of substituted (hetero)aryl groups with the additional flexibility to change the other two regions of the molecule (arylsulfonamide group and the central Ph ring) if needed.[16] Compounds **16** and **17** were synthesized via singleton mode by the two-step nitrile reduction–sulfonylamidation sequence starting from the corresponding benzonitrile intermediates.[21]

The initial tactic employed for the simultaneous improvement of LipE and metabolic stability of the screening hit **2** was centered