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Discovery of novel oxazolidinedione derivatives as potent and selective mineralocorticoid receptor antagonists

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ABSTRACT

Novel oxazolidinedione analogs were discovered as potent and selective mineralocorticoid receptor (MR) antagonists. Structure–activity relationship (SAR) studies were focused on improving the potency and microsomal stability. Selected compounds demonstrated excellent MR activity, reasonable nuclear hormone receptor selectivity, and acceptable rat pharmacokinetics.

The mineralocorticoid receptor (MR) is a nuclear hormone receptor that regulates the expression of multiple genes involved in cardiovascular disease and electrolyte homeostasis. MR is activated by aldosterone, which increases blood pressure through its effects on natriuresis, with potential additional effects on the brain, heart and vasculature.[1] In visceral tissues, such as the kidney and the gut, MR regulates sodium retention, potassium excretion and water balance in response to aldosterone. Resistant hypertensive patients frequently suffer from increased aldosterone levels, often termed as 'aldosterone breakthrough', as a result of increases in serum potassium or residual subtype I receptor activity of angiotensin II (AT1R).[2] Hyperaldosteronism and aldosterone breakthrough typically cause elevated blood pressure and congestive heart failure (CHF), as well as enhanced MR activity. Hence, direct antagonism of MR has a strong biological rational for treating hypertension and CHF.

Other receptors in the same receptor subclass are androgen receptor (AR), glucocorticoid receptor (GR), estrogen receptor (ER), and the progesterone receptor (PR). It should be noted that both cortisol and corticosterone bind MR, and aldosterone is generally considered as the major endogenous ligand for MR with high affinity.[3] Due to the distinct functions of each nuclear hormone receptor, it is imperative to develop selective MR antagonists to minimize potential side effects as a result of interaction with other nuclear hormone receptors.

Despite significant therapeutic advances in the treatment of hypertension and heart failure, the current standard of care is suboptimal and there is a clear unmet medical need for additional pharmacological interventions. Eplerenone and spironolactone are two MR antagonists that are efficacious in treating cardiovascular disease, particularly hypertension and heart failure.[4] Moreover, multiple studies have shown that treatment with spironolactone or eplerenone significantly lower systolic blood pressure in hypertensive patients.[5] In spite of their therapeutic utility, there remain issues to overcome for both eplerenone and spironolactone. For example, spironolactone elicits unwanted side effects such as gynecomastia and menstrual irregularities due to its AR and PR activity.[6] Conversely, eplerenone is more selective against other nuclear hormone receptors, but it lacks good MR potency relative to spironolactone and requires b.i.d. dosing.[7] As such, we have embarked on a discovery program to identify efficacious and safe MR antagonists that possess the efficacy of spironolactone and selectivity of eplerenone. Herein we report preliminary results on the discovery of oxazolidinedione derivatives as a class of novel, non-steroidal, and potent MR antagonists.[8]

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An in-house high-throughput screening identified compound **1a** with modest MR activity in the human MR NH Pro assay (IC_{50} = 6 μM). This assay is a commercially available PathHunter™ protein–protein interaction assay that measures the ability of compounds to antagonize full-length human MR binding to a coactivator peptide.[9] In this assay, the average IC_{50} for spironolactone and eplerenone is 11 nM and 244 nM, respectively. Hit **1a** possesses at least four distinct subgroups as colored in Figure 1. The optimization strategy is to establish SAR with each of the four subgroups, namely, R^1–R^3 and the oxazolidinedione core, as summarized in Tables 1–4.

Prior to the optimization of R^1 region in **1a** (Table 1), the influence of the absolute configuration of **1a** on MR antagonism was found to be critical with the enantiomer of **1a** being essentially inactive (IC_{50} >40 μM). In addition, 3-OMe substitution of the benzyl group (**1b**) improved the MR activity by sixfold compared to **1a**. The next discovery was that the methyl group present in the R^3 region markedly enhanced the activity against MR (**1c** vs **1b** and **1g** vs **1f**). With this embedded methyl group in the R^3 region, various substitution of the benzyl group were explored (**1h–1o** are shown as a subset), however, none exhibited superior activity to **1g**. On the other hand, the presence of the methyl group in the R^1 region of **1j** and **1k** did not present advantages over compound **1i** in terms of activity. Fused bicyclic aryl or heteroaryl methyl amine-derived amides, in general, led to reduced MR activity (**1p**, **1jj**, **1kk** and **1ll**), except in the case of **1mm**. The incorporation of monocyclic heteroaryls one or two carbons away from the amide group, as shown by **1dd–1ii** and **1nn–1qq**, respectively, resulted in poor MR activity. The size variation of cycloalkyl groups adjacent to amide gave MR activities within a few-fold of fluctuation (**1x–1z**). The addition of a terminal phenyl group to cyclobutyl or cyclopropyl improved potency as shown by **1aa–1cc**. Lastly, aniline analogs **(1q–1w)** provided modest to good potency.

Table 2 summarizes the efforts to optimize the R^2 region. The removal of the benzyl group in this region resulted in a complete loss of activity against MR (**2a** vs **1a**). The binding pocket of R^2 appeared to be non-polar as hetereoaryl analogs (**2b–2d**, **2l and 2m)** led to significant loss of activity. In addition, the size of the binding pocket may be small; larger fused bicyclic groups (**2k**, **2l** and **2m**), or chlorine substitution (**2h–2j**) were associated with at least eightfold decrease in MR potency. Lastly, the only acceptable substitution on the benzyl group appeared to be fluorine (**2e–2g**) despite the loss of four to sixfold potency.

The SAR for the R^3 area is depicted in Table 3. First, the phenyl group in the R^3 region of analog **1g** contributed significantly to its activity against MR. The absence of this group caused a ~10-fold loss of activity (**3a** vs **1g**). Second, the chirality of the stereogenic center in this region is important for biological activity against MR. For example, diastereomer **3b** is 10-fold less active than **1g**. Fluoro- and chloro-substitution (**3c** and **3d**, respectively) maintained excellent activity. Cyclohexyl analog **3e** was the most potent MR antagonist that we found for this series with an IC_{50} of 14 nM. By introducing a ring fused to the phenyl group, indanyl and tetrahydronaphthyl derivatives rendered IC_{50} of 33 and 170 nM, respectively. Interestingly, **3h**, a one-carbon homolog of **1g**, was much less active than **1g**. A heterocyclic analog (**3i**), or pyridyl replacement of the phenyl of **1g** led to more than 50-fold loss of MR potency. The combination of fluoro- and chloro-substituted phenyl groups resulted in **3j**, which displayed modest activity against MR.

The oxazolidinedione core was also a subject of modification (Table 4). Almost all core modifications, as shown by analogs

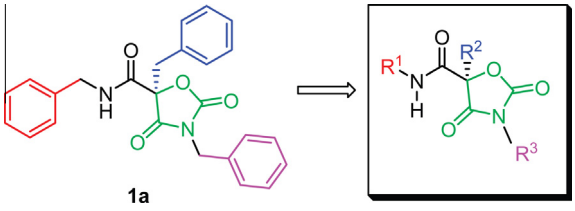
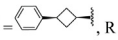
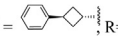
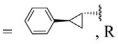
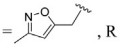
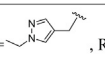
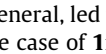
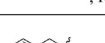
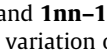
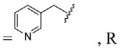
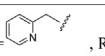
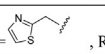
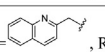
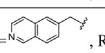
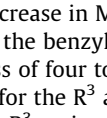


Figure 1. Pharmacophore of the oxazolidinedione series.

Table 1
In vitro SAR of R^1 moiety in the human MR NH Pro assay[a]

Compds	IC_{50} (μM)	Compds	IC_{50} (μM)
R^1 = Bn, R = H (**1a**)	6.0	R^1 = 3-F-phenyl R = Me (**1v**)	0.30
Enantiomer of **1a**	>40	R^1 = 4-CN-phenyl R = Me (**1w**)	0.10
R^1 = 3-OMe-benzyl R = H (**1b**)	1.0	R^1 = Cyclohexyl, R = Me (**1x**)	4.0
R^1 = 3-OMe-benzyl R = Me (**1c**)	0.3	R^1 = Cyclobuty,l R = Me (**1y**)	1.2
R^1 = 4-OMe-benzyl R = Me (**1d**)	1.0	R^1 = Cyclopropyl, R = Me (**1z**)	2.0
R^1 = 2-OMe-benzyl R = Me (**1e**)	0.5	R^1 =  , R = Me (**1aa**)	0.65
R^1 = 3,5-diOMe-benzyl R = H (**1f**)	3.0	R^1 =  , R= Me (**1bb**)	0.19
R^1 = 3,5-diOMe-benzyl R = Me (**1g**)	0.054	R^1 =  , R = Me (**1cc**)	0.25
R^1 = 4-Cl-benzyl R = Me (**1h**)	0.20	R_1 =  , R = Me (**1dd**)	3.0
R^1 = 3-Cl-benzyl R = Me (**1i**)	0.28	R^1 =  , R = Me (**1ee**)	>10
R^1 =  R = Me (**1j**)	0.40	R^1 =  , R = Me (**1ff**)	>40
R^1 =  R = Me (**1k**)	2.6	R^1 =  , R = Me (**1gg**)	13
R^1 = 4-CF_3-benzyl R = Me (**1l**)	0.57	R^1 =  , R = Me (**1hh**)	16
R^1 = 3-CF_3-benzyl R = Me (**1m**)	0.50	R^1 =  , R = H (**1ii**)	>40
R^1 = 4-SO_2Me-benzyl R = Me (**1n**)	>10	R^1 =  , R = Me (**1jj**)	2.5
R^1 = 3-SO_2Me-benzyl R = Me (**1o**)	3.0	R^1 =  , R = Me (**1kk**)	1.5
R^1 = 2-Naphthyl R = Me (**1p**)	0.6	R^1 =  , R = Me (**1ll**)	3.0
 R_1 = Phenyl (**1q**)	0.27	R^1 =  , R = Me (**1mm**)	0.3
R^1 = 4-Cl-phenyl (**1r**)	0.18	R^1 =  , R = Me (**1nn**)	4.0
R^1 = 3-Cl-phenyl R = Me (**1s**)	2.0	R^1 =  , R = Me (**1oo**)	15
R^1 = 2-Cl-phenyl R = Me (**1t**)	1.0	R^1 =  , R = Me (**1pp**)	>40
R^1 = 4-F-phenyl R = Me (**1u**)	0.10	R^1 =  , R = Me (**1qq**)	>40

[a] Values are based on the average of two experiments, each in 10-point titrations.