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Mineralocorticoid receptor antagonists: Identification of heterocyclic amide replacements in the oxazolidinedione series

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ABSTRACT

Novel potent and selective mineralocorticoid receptor antagonists were identified, utilizing heterocyclic amide replacements in the oxazolidinedione series. Structure–activity relationship (SAR) efforts focused on improving lipophilic ligand efficiency (LLE) while maintaining nuclear hormone receptor selectivity and reasonable pharmacokinetic profiles.

The mineralocorticoid receptor (MR) is a member of the nuclear hormone receptor (NHR) super-family and regulates gene expression involved in cardiovascular disease.[1] The natural endogenous hormone aldosterone activates MR leading to chronic kidney disease, hypertension and congestive heart failure via electrolyte imbalance.[2] The only two marketed MR antagonists are the steroids spironolactone and eplerenone, which have demonstrated positive effects in the treatment of patients with the aforementioned conditions (Fig. 1).[3] However, selectivity for MR versus other members in the NHR super-family (members include: androgen receptor (AR), estrogen receptor (ER), glucocorticoid receptor (GR), and progesterone receptor (PR)) is essential to avoid undesired side effects. Spironolactone, for example, has sex hormone related side effects (gynecomastia and menstrual irregularities) due to AR and PR activity.[4] In contrast, eplerenone is very selective for MR versus the other NHR members, but at the price of reduced MR potency and b.i.d dosing.[5]

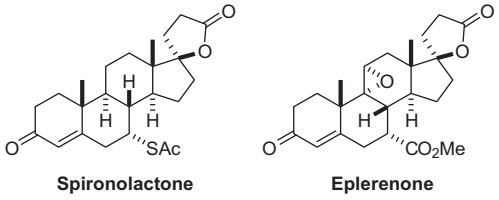

Figure 1. Marketed steroidal MR antagonists.

Due to the limitations of the steroid MR antagonists, we[6] and others[7] have initiated discovery programs targeting non-steroidal MR antagonists. Herein we report our continuing investigation of a novel oxazolidinedione (ODO) class of potent MR antagonists, focusing on efforts toward the discovery of heterocyclic replacements for the amide moiety in compound **1** (Fig. 2). Compound **1** was identified through an in-house high-throughput screen utilizing a commercial PathHunter™ assay[8] and demonstrated modest MR potency (IC_{50} = 6 μM).[9]

As previously disclosed,[10] initial efforts focused on amide substitution and identification of N-3 substitution, with appropriate

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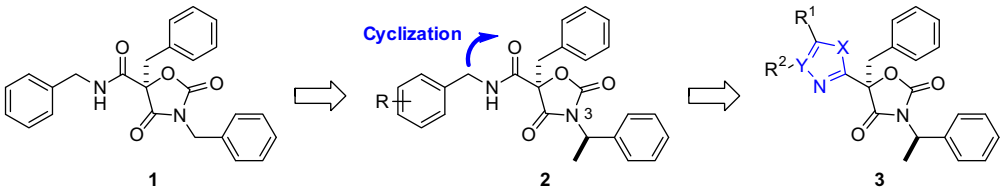
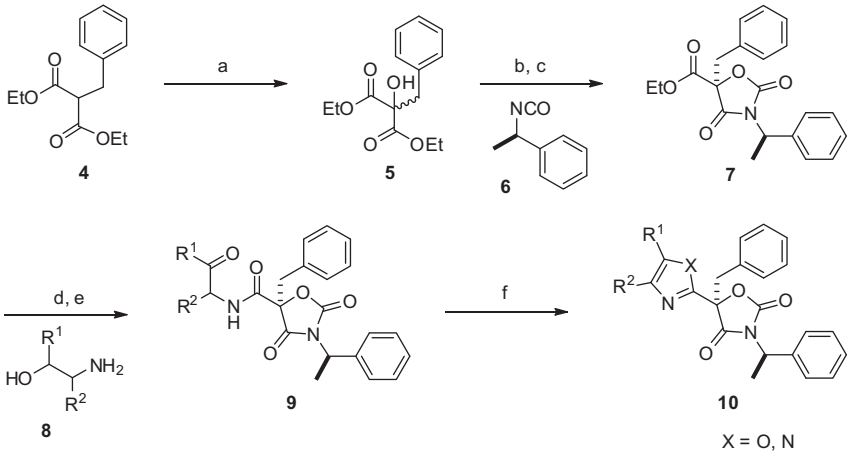


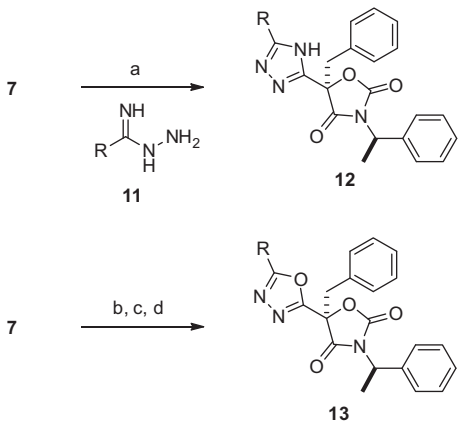
Figure 2. Evolution of ODO class MR antagonists.



Scheme 1. Synthesis of oxazole and imidazole ODO MR antagonists. Reagents and conditions: (a) CsF, DMF, Air, 40 °C, 3 days, 71%; (b) NaOH, 4 Å ms, THF, 0 °C, 5 min. then **6**, 0 °C to rt, 4 h, 46%; (c) Chiral SFC (AD column); (d) **8**, EtOH, 70 °C, 2 h; (e) DMP, DCM, rt, 30 min. 40–82% over two steps; (f) oxazole: I_2, PPh_3, TEA, 5 min, then **9**, DCM, 1 h or imidazole: NH_4OAc, AcOH, 100 °C, 40 h, 25–90% over two steps.

R stereochemistry, to identify MR antagonists **2**. We envisioned cyclization of the amide moiety would afford novel antagonists (**3**), with improved physicochemical, ADME, and safety profiles by attempting to improve the lipophilic ligand efficiency (LLE).[11]

The synthesis of oxazole and imidazole MR antagonists is depicted in Scheme 1.[12] Diethyl malonate derivative **4** was oxidized by treatment with cesium fluoride in the presence of air to afford racemic hydroxymalonate **5**. The hydroxymalonate was converted to enantiopure oxazolidinedione **7** by first condensation with chiral isocyanate **6** in the presence of sodium hydroxide followed by purification via chiral supercritical fluid chromatography (SFC). Treatment of key intermediate **7** with substituted hydroxylethyl amines **8**, provided cyclization precursors **9** after oxidation of the alcohol with Dess–Martin periodinane. The final oxazole targets



Scheme 2. Synthesis of triazole and oxadiazole ODO MR antagonists. Reagents and conditions: (a) **11**, DIEA, EtOH, 70 °C, 1 h, 30–75%; (b) anhydrous hydrazine, MeOH, sonication, 1 h; (c) RCOOH, DIEA, HATU, DCM, rt, 1.5 h; (d) I_2, PPh_3, TEA, 5 min, then product from step c, DCM, 1 h, 40–90% over three steps.

10 were prepared by adding intermediates **9** to a freshly prepared solution of iodine, triphenylphosphine and triethylamine. Alternatively, treatment of intermediates **9** with ammonium acetate in hot acetic acid afforded imidazoles **10**.

Highlighted in Scheme 2 is the synthesis of triazole and oxadiazole MR antagonists. The 1,3,4-triazole derivatives **12** were synthesized in a single step from key intermediate **7** by heating with amino-hydrazides in ethanol. 1,3,4-Oxadiazoles **13** were prepared in three steps from **7** by first acyl-hydrazide formation using anhydrous hydrazine, followed by amide bond generation using a variety of acids. Finally, cyclization utilizing the procedure for synthesizing the oxazoles (addition of the product from the previous step to a freshly prepared solution of iodine, triphenylphosphine and triethylamine) provided 1,3,4-oxadiazoles **13**.

Our initial focus was to identify heterocyclic amide replacements (Table 1) to simultaneously improve not only liver microsome (LM) stability but also LLE with respect to the previously disclosed 3,5-dimethoxy benzyl amide analog (IC_{50} = 54 nM; LLE = 2.54; *c*log*P* = 4.73; H, R LM% at 1 μM incubation after 0.5 h = 0, 0).[6d] While oxazole region-isomers **10a** and **10b** had a significant loss in potency and LLE, gratifyingly, each compound demonstrated an increase in microsomal stability when compared to the amide analog. We could improve the intrinsic potency and LLE by making the benzyl substitution (**10c**); however, not surprisingly this came at the expense of the microsomal stability. Switching to phenyl imidazole **10d** improved the intrinsic potency and LLE, while showing similar LM stability compared to the oxazoles; however, benzyl substituted imidazole **10e** had a similar profile to oxazole **10c**. Addition of the 3,5-dimethoxy phenyl substitution (**10f**) significantly improved the intrinsic potency and LLE with respect to the other cyclized analogs, while maintaining some of the microsomal stability improvements gained from cyclization. Unfortunately, the oxazoles and imidazoles did not achieve our goal of improved LLE compared to their respective amide analogs.