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Identification of spirooxindole and dibenzoxazepine motifs as potent mineralocorticoid receptor antagonists

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ABSTRACT

Mineralocorticoid receptor (MR) antagonists continue to be a prevalent area of research in the pharmaceutical industry. Herein we report the discovery of various spirooxindole and dibenzoxazepine constructs as potent MR antagonists. SAR analysis of our spirooxindole hit led to highly potent compounds containing polar solubilizing groups, which interact with the helix-11 region of the MR ligand binding domain (LBD). Various dibenzoxazepine moieties were also prepared in an effort to replace a known dibenzoxepane system which interacts with the hydrophobic region of the MR LBD. In addition, an X-ray crystal structure was obtained from a highly potent compound which was shown to exhibit both partial agonist and antagonist modes of action against MR.

1. Introduction

The mineralocorticoid receptor (MR), one of the 48 members of the nuclear hormone receptor (NHR) superfamily, is responsible for regulating gene expression. Aberrant activation of MR leads to a variety of medical conditions such as cardiovascular disease, chronic kidney disease and hypertension. Discovered over 50 years ago, aldosterone is considered the major endogenous ligand for MR. Thus, elevated levels of aldosterone ultimately cause an increase in blood pressure through the inhibition of natriuresis leading to elevated levels of sodium in the blood.[1,2]

MR is part of an NHR subfamily commonly referred to as the estrogen receptor-like family which consists of estrogen (ER), glucocorticoid (GR), progesterone (PR) and androgen (AR) receptors. The ligand binding domains (LBDs) of GR and AR are structurally homologous to the LBD of MR. These high structural homologies present a challenge in developing motifs that selectively bind to MR in the LBD in order to circumvent any potential side effects resulting from other estrogen receptor-like interactions.

To date, only two steroidal MR antagonists, spironolactone (**1**) and eplerenone (**2**), are marketed as drugs and used for the treatment of heart failure and hypertension (Fig. 1). Discovered over 50 years ago and still a widely used medicine, spironolactone suffers from a lack of selective binding to MR leading to a variety of unwanted side effects such as gynecomastia/feminization in men and menstrual irregularities in women. The more current MR antagonist, eplerenone, also known by its trade name Inspra®, was brought to market by Pfizer in 2002. Although this newer steroidal medicine does possess good selectivity to the MR LBD, it suffers from a lack of potency and is therefore taken orally twice daily. There is a clear unmet medical need for new MR antagonists without harmful side effects due to poor selectivity while maintaining high levels of potency for better dosing regimens and patient compliance.[3]

A variety of non-steroidal MR antagonists have been disclosed in the patent and journal literature over the past ten years (Fig. 2).[4] The first crystal structure of a nonsteroidal MR antagonist (**4b**) in the MR LBD was elucidated just three years ago by a team from Takeda.[4b] Other chemotypes have also been disclosed including compound **3b** from Eli Lilly[4c] as well as compounds **5** and **6** which were discovered by Dainippon Sumitomo[4d] and Novartis,[4e] respectively. In addition, Bayer's BAY-94-8862, also known as Finerenone (**6b**), is currently in clinical trials as an MR antagonist for the treatment of heart failure.[4i] Of the several structural motifs in the literature possessing MR antagonist activity, we were particularly drawn to compounds **3**–**6** as a starting point for our efforts. Utilizing Contour®, our structure-based design platform,[4h] as a molecular modeling tool, our goal

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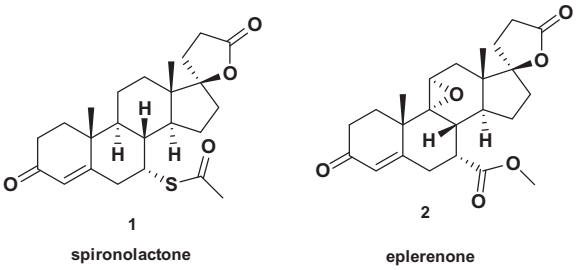

Figure 1. Marketed MR antagonist drugs.

for this project was to develop novel, potent and selective nonsteroidal MR antagonists.

When Vitae initiated the MR project, there were ten liganded MR structures in the PDB (Protein Data Bank), all of which were steroid ligands that bound very similarly to MR.[5] However, in the structure of the S810L mutant of MR with bound spironolactone (PDB code, 2OAX),[5d] the Met-852 sidechain swings away, creating a new pocket to accommodate the thioester sidechain of spironolactone. We hypothesized that this new pocket could be useful for optimizing off-target selectivity. Therefore, 2OAX was used to model various molecular designs. First, we docked two known non-steroidal MR antagonists from the literature: compound **3a**[4f] and **4a**[4a] (Fig. 2).

The proposed binding modes based on the molecular modeling for these two compounds are shown in Figures 3 and 4. These binding modes appeared to be consistent with the binding mode of tanaproget with the progesterone receptor (PR) as revealed in the crystal structure (PDB code, 1ZUC).[6] If the proposed binding modes for compounds **3a** and **4a** are correct, one can imagine hybrid

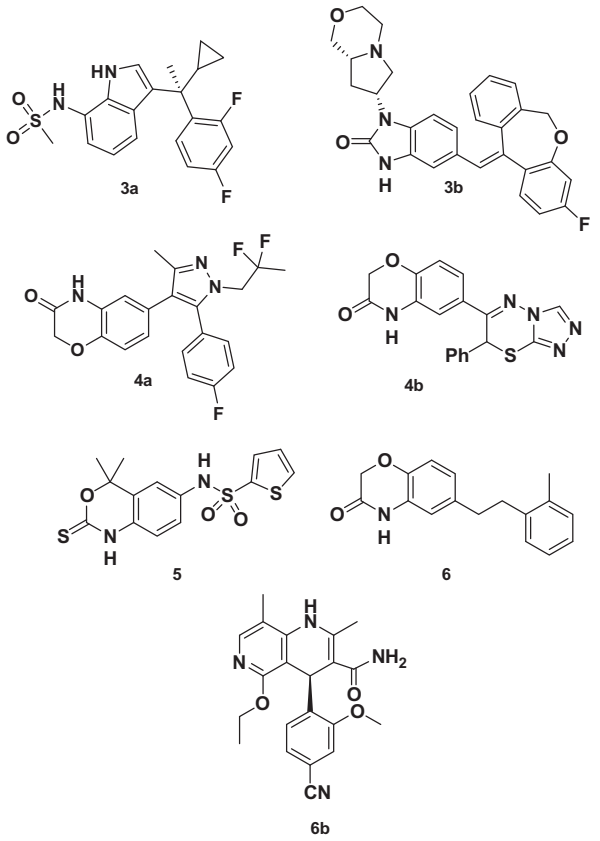

Figure 2. MR antagonists from literature and patents.

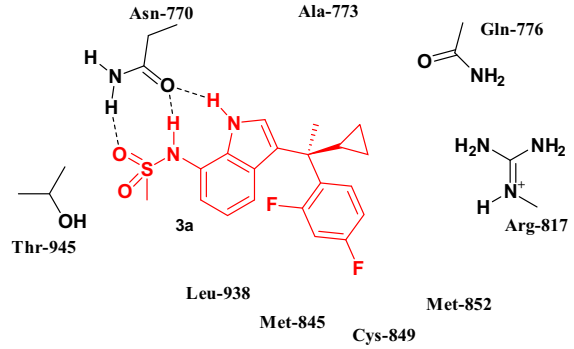

Figure 3. The proposed binding mode for compound **3a**.

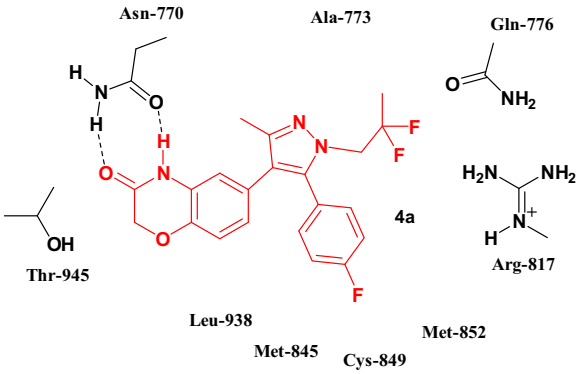

Figure 4. The proposed binding mode for compound **4a**.

structures **3c** and **4c** (Fig. 5) as potential ligands for MR. To test this hypothesis, compound **4c** was synthesized and was found to bind to MR with a K_i of 390 nM and showed inhibition of MR activity in a cellular Gal4 assay (IC_{50} = 889 nM), suggesting the validity of our proposed binding model. Moreover, the binding mode of **4a** was subsequently confirmed crystallographically by Takeda.[4b,g]

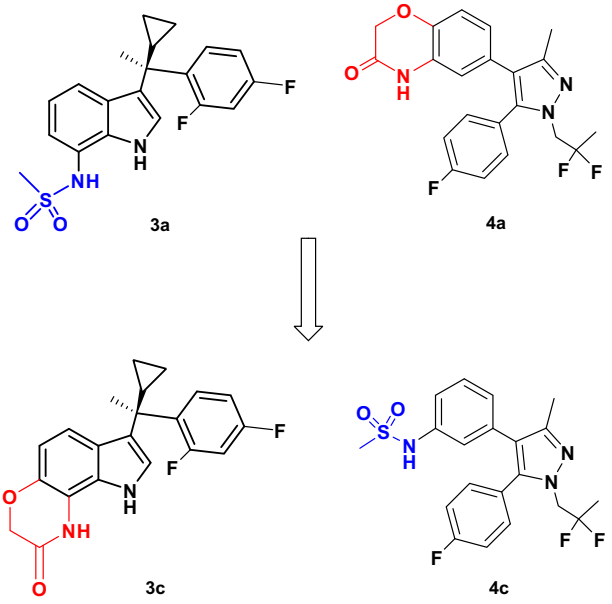

Figure 5. Hybrid structures **3c** and **4c**.