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The discovery of potent inhibitors of aldosterone synthase that exhibit selectivity over 11-β-hydroxylase

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ABSTRACT

Aldosterone, the final component of the renin–angiotensin–aldosterone system, plays an important role in the pathophysiology of hypertension and congestive heart failure. Aldosterone synthase (CYP11B2) catalyzes the last three steps of aldosterone biosynthesis, and as such appears to be a target for the treatment of these disorders. A sulfonamide–imidazole scaffold has proven to be a potent inhibitor of CYP11B2. Furthermore, this scaffold can achieve high levels of selectivity for CYP11B2 over CYP11B1, a key enzyme in the biosynthesis of cortisol.

The renin–angiotensin–aldosterone system (RAAS) is a key regulator of blood pressure and extracellular volume. Aldosterone, the final component of the RAAS, is a potent mineralocorticoid. Elevated aldosterone levels play an important role in the pathophysiology of hypertension and congestive heart failure.[1] As such, aldosterone has attracted much attention from both the pharmaceutical and clinical communities. Until recently, the majority of this effort has focused on mineralocorticoid receptor (MR) antagonists, such as spironolactone and eplerenone.[2,3] However, current evidence indicates that the deleterious effects of elevated aldosterone levels are not solely mediated by the MR and that non-genomic effects may play a critical role.[4,5] Therefore, directly inhibiting the synthesis of aldosterone may prove advantageous.[6]

The final three steps of aldosterone biosynthesis are catalyzed by a single cytochrome P450 enzyme, CYP11B2, which is expressed in *zona glomerulosa* cells of the adrenal gland.[7] Importantly, fadrozole, an inhibitor of CYP11B2, has been shown to reduce aldosterone levels in humans.[8] Fadrozole was initially developed as an aromatase (CYP19) inhibitor, but it was later discovered that the *R*-enantiomer of fadrozole (FAD286, Fig. 1) is a potent aldosterone synthase inhibitor.[9]

Subsequent studies have shown that FAD286 is also an inhibitor of 11-β-hydroxylase (CYP11B1). CYP11B1 is also expressed in the adrenal gland and catalyzes the last step in the biosynthesis of cortisol, the primary glucocorticoid.[7] Cortisol mediates the stress response affecting energy mobilization and the immune system. Therefore, a selective CYP11B2 inhibitor may be desirable. FAD286 exhibits IC_{50} values of 1.6 and 9.9 nM in recombinant human CYP11B2 and CYP11B1 enzyme assays, respectively.[10] This small degree of selectivity is not surprising, considering that the amino acid sequences of these two enzymes are 95% identical in the coding regions.[11] Homology models of the two enzymes

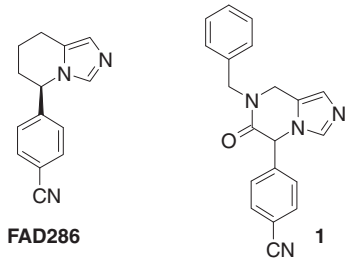

Figure 1. The *R*-enantiomer of fadrozole (FAD286) and a representative analog from the lactam series (**1**).

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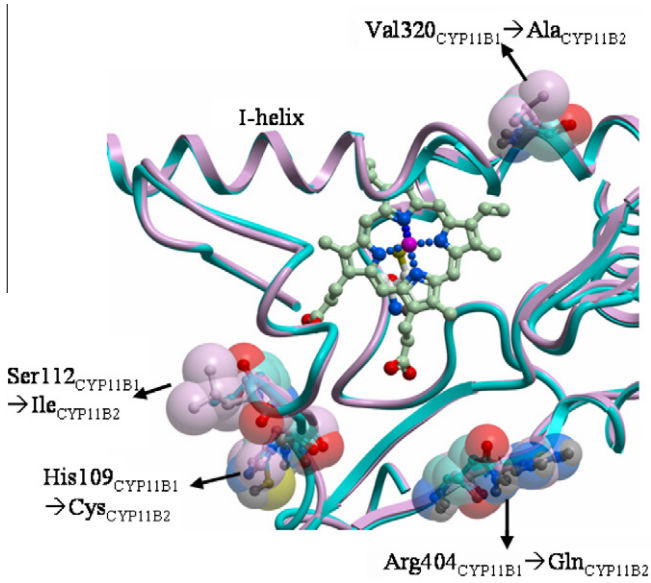


Figure 2. Homology models of CYP11B1 (pink) and CYP11B2 (cyan). Active sites depicted; residues that lie within 10 Å of heme, and are different between CYP11B1 and CYP11B2, are labeled.

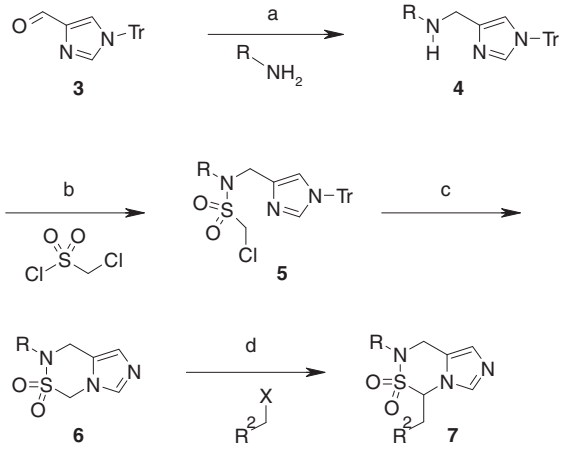
provided further evidence that achieving high levels of selectivity would be challenging.[12] Our modeling indicated that only four residues differed between the two enzymes within 10 Å of the heme, the presumed substrate binding site (Fig. 2).

Having recognized the ability of FAD286 to inhibit CYP11B2, we began a program to discover novel analogs of this compound with improved properties. Early efforts focused on modifying the saturated portion of the fused ring system of fadrozole. One promising series, which contains a lactam moiety exemplified by **1**[13,14] (Fig. 1), was found to have excellent potency against CYP11B2 (IC_{50}: 40 nM).[15] However, compounds from this series were also potent CYP11B1 inhibitors (e.g., IC_{50} = 2 nM for **1**).

The potency of the lactam series led us to explore a bioisosteric sulfonamide series. This Letter describes the development of cyclic sulfonamide analogs with the aim of greatly improving selectivity for CYP11B2 over CYP11B1.

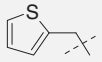
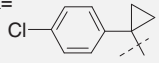
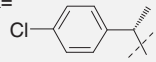
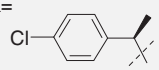
Sulfonamide **2** (Table 1), one of the earliest molecules synthesized in this series, displays modest CYP11B1/CYP11B2 selectivity. However, it is also plagued by poor solubility (<0.5 μM), low metabolic stability in human liver microsomes (HLM, $t_{1/2}$ <5 min),[16] and activity against CYP19 (39% inhibition at 1 μM).[17] In an attempt to improve upon this profile we initially explored the space around the nitrogen of the sulfonamide. From a synthetic perspective this required a four-step sequence starting from commercially available aldehyde **3** (Scheme 1).

A series of reductive aminations with commercially available primary amines permitted access to a diverse array of amino-imidazoles. Sulfonylation of the resulting secondary amines with chloromethanesulfonyl chloride, followed by microwave-mediated cyclization afforded sulfonamides of type **6** in modest yields. Alkylation with the appropriate alkyl halide or epoxide completes the



Scheme 1. Reagents and conditions: (a) $NaBH(OAc)_3$, DCM, rt; (b) DIPEA, DCM, −78 °C; (c) DMF, EtOH, DIPEA (3:1:1), microwave irradiation at 200 °C for 1 h, 10–30% yield for the three steps; (d) KHMDS, THF, −78 °C to rt 10–70%.

Table 1
Exploration of the space around the sulfonamide nitrogen

	hCYP11B2 IC_{50}, (nM) (Ref. 10)	hCYP11B1 IC_{50}, (nM) (Ref. 10)	hCYP19 % Inhib @ 1 μM (Ref. 16)	HLM $t_{1/2}$, (min) (Ref. 15)
2, R = 4-F-Ph-CH_2–	2.5	26.1	39	5
8, R = 4-Cl-Ph-CH_2–	5.2	50.2	51	8
9, R = Ph-CH_2–	18.6	103	14	3.
10, R = 4-CF_3O-Ph-CH_2–	104	544	13	7
11,[19] R = 4-CF_3-Ph-CH_2–	121	566	0	13
12, R = c-C_3H_5–	>1000	930	9	>405
13, R = c-C_3H_5-CH_2–	758	122	19	55
14, R= 	117	55.7	13	2
15, R= 	628	119	71	19
16, R= 	9.4	76.0	56	6
17, R= 	61.7	204	24	5