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Imidazopyridyl compounds as aldosterone synthase inhibitors

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ABSTRACT

The inhibition of aldosterone synthase (CYP11B2) may be an effective treatment of hypertension and heart failure, among other ailments. Previously reported benzimidazole CYP11B2 inhibitors led the way for bioisosteric imidazopyridines that are both potent and selective over CYP11B1.

Aldosterone is a principal mineralocorticoid that promotes increased blood pressure, inflammation, fibrosis, and organ damage.[1–4] The final steps of its biosynthesis are catalyzed by a single mitochondrial cytochrome P450 enzyme aldosterone synthase (CYP11B2), found predominantly in zona glomerulosa cells of the adrenal gland.[5,6] Inhibition of CYP11B2 should lower plasma aldosterone levels, potentially providing an effective treatment for a variety of ailments, including hypertension, heart failure, and chronic kidney disease.

A great design challenge to advance a CYP11B2 inhibitor in the clinic is to maintain its high selectivity against other CYPs, in particular cortisol synthase CYP11B1, which share >93% homology with CYP11B2. CYP11B1 catalyzes the biosynthesis of cortisol, and inhibition of CYP11B1 can result in impaired stress response and altered glucose metabolism. Selectivity against other steroidogenic CYPs, such as CYPs 17, 19, and 21, is crucial as well, since they regulate the production of androgens and estrogens.

A host of small molecule CYP11B2 inhibitors have been reported.[7,8,12] Among them, LCI-699 has been shown to lower aldosterone levels and blood pressure in the clinic, providing the proof-of-concept for the therapeutic target. At the same time, undesired dose-limiting impairment of cortisol response was also observed, presumably due to the inhibition of CYP11B1.[9–11]

The results from LCI-699 highlight the need to discover CYP11B2 inhibitors that are both potent and selective against CYP11B1 for clinical development. Our discovery of the benzimidazole series[13] has led us to further explore the isosteric equivalents of the heterocycle. We are pleased to find that the imiadzopyridine analog **2** offers good potency on CYP11B2 while maintaining similar selectivity against CYP11B1 as the initial benzimidazole lead **1** (Fig. 1).[14]

The preparation of the imidazopyridines is illustrated with the synthesis of compound **2** (Scheme 1).[14] 5-Fluoropyridin-2-amine was treated with neat ethyl bromoacetate, and the resultant intermediate **2a** was heated in phosphorus oxychloride to afford the corresponding 2-chloro-6-fluoroimidazo[1,2-*a*]pyridine **2b** after careful quenching and isolation. The intermediate **2b** was halogenated at the 3-position with *N*-iodosuccinimide to yield 2-chloro-6-fluoro-3-iodoimidazo[1,2-*a*]pyridine **2c**. Two iterative Suzuki couplings of **2c**, first with cyclopropylboronic acid and the corresponding pyridineboronic acid pinacol ester, afforded the desired compound **2**.

As of the compounds reported in Table 1, compound **3** was prepared by employing methylboronic acid instead of cyclopropylboronic acid in step d. Compound **4** was prepared directly from **2b** and the corresponding boronate ester. Chlorination of compound **4**

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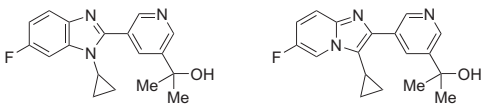
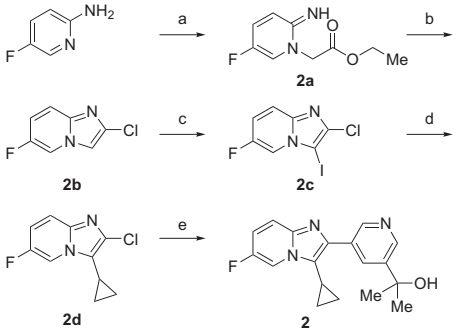


1
CYP11B2 IC_{50} = 1.4 nM
CYP11B1 IC_{50} = 100 nM
CYP11B1/B2 = 75

2
CYP11B2 IC_{50} = 13 nM
CYP11B1 IC_{50} = 830 nM
CYP11B1/B2 = 63

Fig. 1. Comparison of the benzimidazole lead **1** and the imidazopyridine lead **2**.



Scheme 1. Reagents and conditions for preparation of compound **2**: (a) ethyl bromoacetate, neat, room temperature; (b) phosphorous oxychloride, neat, 110 °C; (c) *N*-iodosuccinimide, MeCN, room temperature; (d) *c*-PrB(OH)$_2$, Pd(PPh$_3$)$_2$(OAc)$_2$ (0.1 equiv), Cs_2CO_3, THF, 100 °C; (e) 5-(1-hydroxy-1-methylethyl) pyridine-3-boronic acid pinacol ester, Pd(OAc)$_2$ (0.1 equiv), S-Phos (0.2 equiv), K_3PO_4, THF, 100 °C.

by *N*-chlorosuccinimide afforded compound **5** The precursor for compound **6** (**6d**) was prepared through lithiation of intermediate **2c** (Scheme 2).

Our investigation focused on improving selectivity over CYP11B1 and to bring forward a suitable candidate for *in vivo* studies. In the benzimidazole series, N-substitution was found to exert a substantial effect on CYP11B2 inhibition, with optimal activity limited to a small cyclopropyl-containing group.[13] Here in the imidazopyridine series, we observed a similar SAR pattern (Table 1).

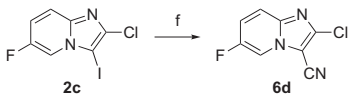
Poor activity was observed when the corresponding C-3 position of the imidazopyridine is unsubstituted (compound **4**). Both the methyl group (compound **3**) and the chloro group (compound **5**) give compounds that are more potent than the corresponding cyclopropyl compound at CYP11B2 but less selective against CYP11B1. The pseudohalide cyano group leads to a less potent and less selective compound (compound **6**).

Prior work in the benzimidazole series has established that substitution at the 2- or the 6-position of the pyridine is not tolerated by CYP11B2.[13] With the cyclopropyl group confirmed as the optimal one balancing potency at CYP11B2 and selectivity against CYP11B1, we proceeded to examine the effect of different substituents R^2 on the pyridine (Table 2). Compounds **7**–**17** were synthesized similarly as compound **2**, with the appropriate boronate ester used in the second Suzuki coupling.

Compounds **7** and **8**, bearing a tertiary alcohol with one of the methyl groups replaced by a trifluoromethyl group, show similar activity on CYP11B2 with similar levels of selectivity against CYP11B1 as compound **2**. The carboxylate ester group improves the CYP11B2 activity while decreasing the CYP11B1 activity (compound **9**), resulting in a highly selective compound, but it does not offer enough metabolic stability to go forward. Electron-withdrawing groups such as fluoro or trifluoromethyl (compounds **10**, **12**) have little effect on either the CYP11B2 activity or CYP11B1 selectivity, while the cyano group (compound **11**) leads to some erosion of CYP11B2 activity. Groups such as methoxy, methyl or phenyl improve the CYP11B2 activity and CYP11B1 selectivity slightly (compounds **13**–**15**). Finally, replacing the entire pyridine with isoquinoline gives a potent CYP11B2 inhibitor with similar selectivity as compound **2** against CYP11B1 (compound **17**).

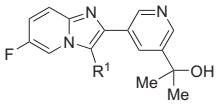
We then sought to investigate the effect of different R^4 and R^5 on the imidazopyridine. We investigated two series, one with the pyridine bearing a tertiary alcohol at the 5-position of the pyridine (Table 3) and another with the pyridine bearing a 5-fluoro group (Table 4). In the 5-tertiary alcohol series, when the fluorine is moved from the 6-position to the 7-position (compound **18**), reduction in potency at CYP11B2 and selectivity against CYP11B1 was observed. Replacing the fluoro with a cyano group at the 6-position results in little change in potency and selectivity (compound **19**).

In the 5-fluoro series, moving the halogen from the 6-position to the 7-position has a similar effect in loss of potency at CYP11B2 (compound **20**). Replacing the fluoro with a chloro group generates a compound with a similar profile (compound **21**). By introducing an extra halogen at the 7-position (R^5), we obtained a compound with better potency at CYP11B2 while maintaining similar selectivity at CYP11B1 (compound **22**). Incorporating additional alkyl



Scheme 2. Reagents and conditions for preparation of intermediate **6d**: (f) *n*-butyllithium, THF, −78 °C, 5 min; *p*-toluenesulfonyl cyanide.

Table 1
Effect of R^1 substitution on CYP11B2/CYP11B1 inhibition.[a]



Compound	R^1	hCYP11B2 (IC_{50}, nM)	hCYP11B1 (IC_{50}, nM)	B1/B2[b]
2	Cyclopropyl	13	830	63
3	Me	1.2	37	31
4	H	52	880	17
5	Cl	1.2	33	27
6	CN	23	600	27

[a] All IC_{50}'s reported in this table correspond to n ⩾ 2, reported as their geometric mean.
[b] Ratio of hCYP11B1 IC_{50}/hCYP11B2 IC_{50}.