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Synthesis of annulated pyridines as inhibitors of aldosterone synthase (CYP11B2)†

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A series of cyclopenta[c]pyridine aldosterone synthase (AS) inhibitors were conveniently accessed using batch or continuous flow Kondrat'eva reactions. Preparation of the analogous cyclohexa[c]pyridines led to the identification of a potent and more selective AS inhibitor. The structure-activity-relationship (SAR) in this new series was rationalized using binding mode models in the crystal structure of AS.

Aldosterone, a steroid hormone belonging to the mineralocorticoid family, is part of the Renin-Angiotensin-Aldosterone System (RAAS),[1] which is a pathway that has been targeted by many important drugs, including angiotensin II receptor blockers (ARBs), angiotensin-converting-enzyme (ACE) inhibitors, renin inhibitors,[2] and mineralocorticoid receptor (MR) blockers.[3] Unfortunately, while several of these drugs block the action of aldosterone and show an impressive increase in survival in post infarct patients, their prolonged use can also result in massive up-regulation of aldosterone levels by compensatory mechanisms[4] and aldosterone escape.[5] This is a particular concern considering that substantial evidence exists suggesting a pathological role of aldosterone *via* non-MR-mediated pathways.[6] Consequently, the inhibition of aldosterone synthesis may prove to be a superior therapeutic approach to treating hypertension.[7,8]

Aldosterone is synthesized from cholesterol through a linear cascade of reactions mainly catalyzed by enzymes of the cytochrome P450 family.[9,10] The last three steps in this sequence are mediated by aldosterone synthase (CYP11B2), an enzyme that is mainly present in adrenal gland zona glomerulosa cells and to a lower extent in other tissues and is exclusively involved in the synthesis of aldosterone.[10,11] CYP11B2 is therefore considered to be a suitable target for the development of selective aldosterone synthesis inhibitors, although targeting this enzyme presents certain challenges. Specifically, human CYP11B2 shows a high sequence identity (~93%) to cortisol synthase (CYP11B1, 11β-hydroxylase), an enzyme that is critical for the synthesis of cortisol and mainly located in the zona fasciculata/reticularis.[12] In addition, the difference between human and rodent CYP11B2 enzymes is high. For instance, rat and human CYP11B2 display an overall sequence identity of only 68%,[12] thus further complicating the development of aldosterone synthase inhibitors with comparable potency on both species.

Recently, the outcome of the clinical trial of imidazole-type inhibitor LCI699 (**1**, Fig. 1), an orally active CYP11B2 inhibitor, in patients with primary aldosteronism (PA) has been

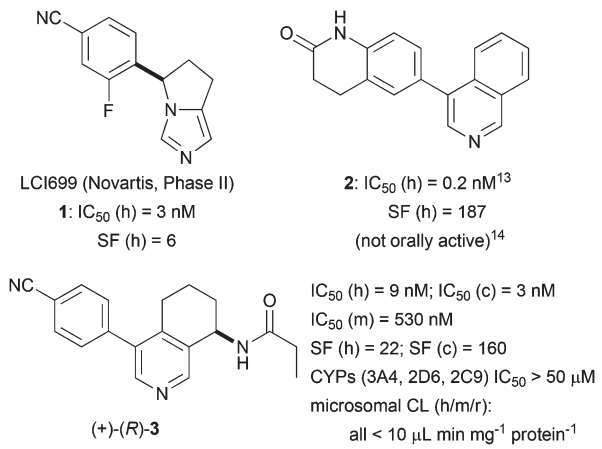

Fig. 1 Structures of aldosterone synthase inhibitors **1**–**3**. *In vitro* aldosterone synthase inhibition was tested in renal leiomyoblastoma cells, ectopically expressing human (h), cynomolgus monkey (c) or mouse (m) CYP11B2 or CYP11B1. The selectivity factor (SF) = IC_{50} (hCYP11B2)/IC_{50} (hCYP11B1).

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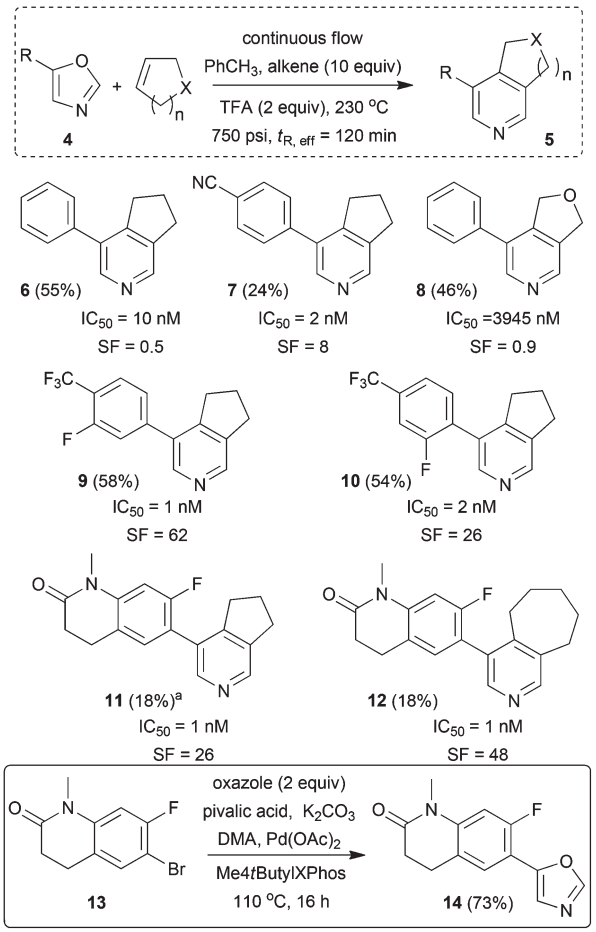
reported.[8,15] This study revealed that administration of LCI699 at doses of up to 1.0 mg b.i.d. safely inhibited CYP11B2 in patients with PA and resulted in significantly reduced levels of aldosterone in both plasma and urine, and consequently the rapid correction of hypokalemia and a modest decrease in blood pressure.[9] However, due to the low selectivity of LCI699 for CYP11B2 over CYP11B1, partial inhibition of cortisol synthesis resulted in dose-dependent increases in both plasma adrenocorticotropic hormone (ACTH) and 11-deoxycortisol (the biosynthetic precursor to cortisol).[8] Very recently, Novartis published an inhibitor with 100-fold selectivity over CYP11B1, that reduced plasma and urinary aldosterone in healthy volunteers and had no concomitant effect on cortisol, 11-deoxycortisol, or ACTH in humans.[16] These clinical data provide support for the inhibition of CYP11B2 as a means to lower inappropriately high aldosterone levels and the use of aldosterone synthase inhibitors as leads for the treatment of hypertension and renal disorders. However, the identification of aldosterone synthase inhibitors with high levels of selectivity for CYP11B2 over CYP11B1 is critical in advancing this therapeutic approach. Towards this goal, several groups have reported pyridine,[17] imidazole,[18] and isoquinoline[13,14] inhibitors of CYP11B2 (*e.g.*, **2**).

We have recently reported that the acylated amino tetrahydroisoquinoline (+)-(*R*)-**3** is a potent inhibitor of human and cynomolgus monkey aldosterone synthase and is remarkably selective for CYP11B2 over CYP11B1 (selectivity factor (SF) = 160) in the latter species (Fig. 1).[19] The tetrahydroisoquinoline (+)-(*R*)-**3** was made available following a 6-step sequence of reactions that also provided access to various analogues.[19] Notably, tetrahydroisoquinoline (+)-(*R*)-**3** significantly lowered aldosterone plasma levels in a dose-dependent manner in mice, rat and cynomolgus monkeys, and protected kidney structure and function in a ZSF1 rat model of chronic kidney disease.[19] Here we describe our efforts aimed at identifying further optimized CYP11B2 inhibitors with an improved selectivity profile and suitability for proof-of-concept studies in translational animal models of hyper-aldosteronism.

As depicted in Scheme 1, we have recently reported[20] a continuous flow inverse-electron-demand Kondrat'eva reaction[21] and applied this process to the rapid synthesis of several annulated pyridines. Considering that these annulated pyridines (*e.g.*, **6–10**) are produced in a single step from commercially available starting materials and bear clear structural resemblance to established aldosterone synthase inhibitors (*e.g.*, **2** and (+)-(*R*)-**3**, Fig. 1), we endeavored to expand the scope of this convenient process for the production of new inhibitors of hCYP11B2. Towards this goal, biological testing of the readily available annulated pyridines **6–10** revealed that these compounds were indeed potent inhibitors of hCYP11B2, and that the 3-fluoro and 2-fluoro-4-trifluomethylphenyl analogues **9** and **10** displayed selectivity for hCYP11B2 over hCYP11B1 that inspired further efforts in this area. The 1-methyl-3,4-dihydroquinolin-2-one side-chain, originally introduced by the Hartmann group, confers particularly high potency and selectivity for CYP11B2.[13] To further explore the influence of this aryl



Scheme 1 Application of the inverse electron demand Kondrat'eva reaction to the synthesis of annulated pyridines **6–12** (yields reported in parentheses). [a]Compound **11** was prepared in a microwave reactor, see ESI† for details. IC_{50} values were measured against hCYP11B2 and are the mean value of ≥3 experiments with a standard deviation <25%. The selectivity factor (SF) = IC_{50} (hCYP11B2)/IC_{50} (hCYP11B1).

appendage on activity and selectivity, the *N*-methyl dihydroquinolinone **14** was prepared directly from the C–H arylation[22] of oxazole and reacted[20] with cyclopentene or cycloheptene to produce the annulated pyridines **11** and **12**, respectively. Both of these later compounds proved to be potent inhibitors of hCYP11B2, with selectivity comparable to the corresponding cyclopenta[*c*]pyridines **9** and **10**. Moreover, the 2- or 3-fluoro-4-trifluoromethylphenyl analogues also displayed improved selectivity for hCYP11B2/hCYP11B1 when compared to the annulated pyridine **7** (SF = 8), which incorporates the 4-cyanophenyl function found in the lead candidate (+)-(*R*)-**3**.[19] Unfortunately, the physicochemical and metabolic properties of these lipophilic annulated pyridines were not optimal. For example, the cyclopenta[*c*]pyridine **9** has an aqueous solubility of only 1.0 μg mL^{-1} (Lysa assay[23]) and high clearance in both human and rat microsomes (CL = 300 and 164 μL min^{-1} mg^{-1} protein). Moreover, the log *D* value for **9** could not be measured due to compound precipitation.[24] However, passive permeability as measured by the Pampa assay[25]

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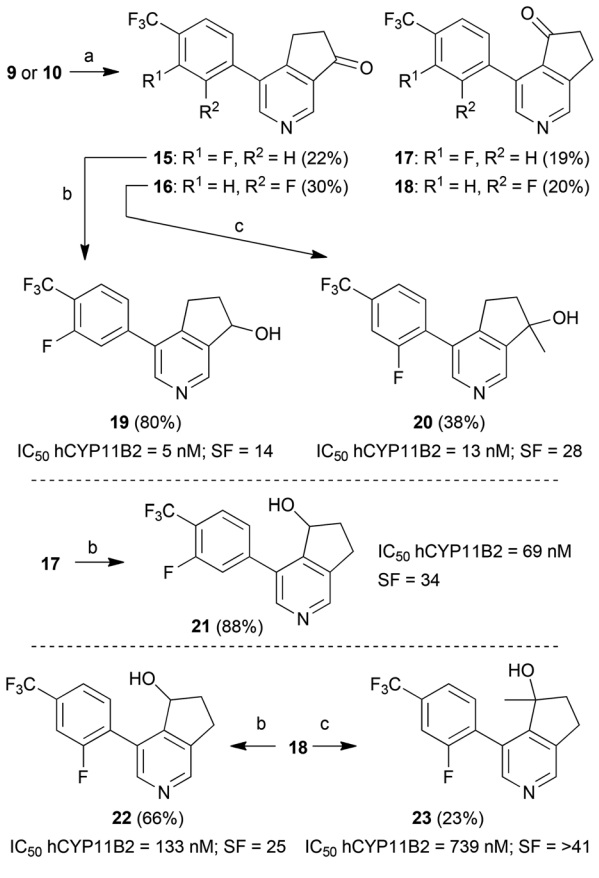
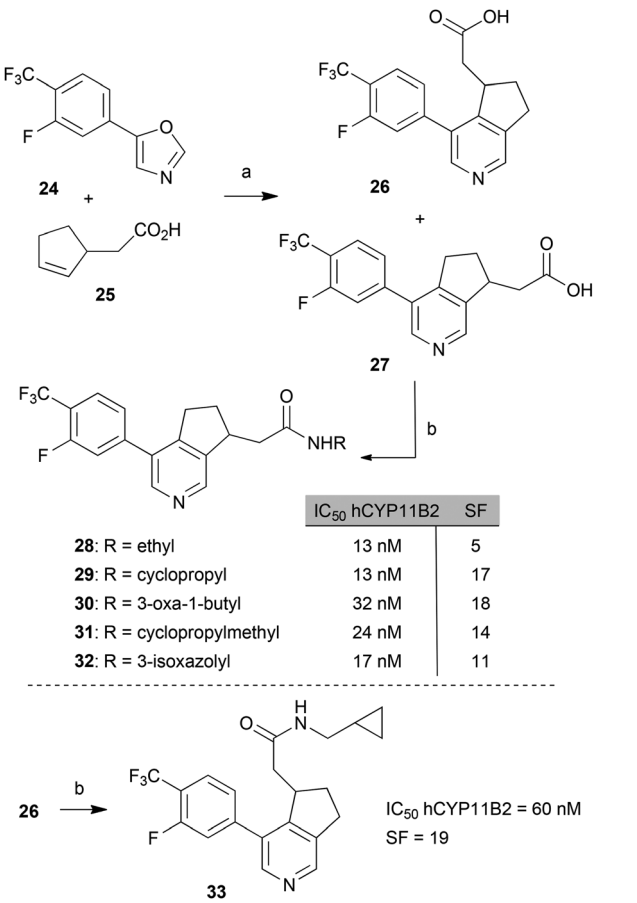
(Pe = 1.09 × 10^{-6} cm s^{-1}) as well as cytochrome P450 (CYP) inhibition data for this compound (CYP3A4, CYP2D6, and CYP2C9: all >45 μM) were encouraging.

In order to reduce lipophilicity and increase aqueous solubility of the most promising aldosterone synthase inhibitors (*i.e.*, **9** and **10**), we investigated the incorporation of an alcohol function onto the saturated annulated ring. Toward this goal, pyridylic oxidation[26] gave the regioisomeric ketones **15–18** in modest yield (~50%).[27,28] Reduction of the carbonyl function with $NaBH_4$ or 1,2-addition of methyl lithium then afforded a small collection of pyridylic alcohols **19–23**. As summarized in Scheme 2, introduction of an alcohol function at the 7-position had little effect on potency or selectivity (*e.g.*, **19**: IC_{50} = 5 nM, SF = 14). Conversely, the corresponding 5-hydroxycyclopenta[*c*]pyridines **21–23** were less active (*e.g.*, **23**: IC_{50} = 739 nM, SF > 41). Gratifyingly, the physicochemical and metabolic profile of the 7-hydroxy cyclopenta[*c*]pyridine **19** was improved considerably when compared to the parent compound **9**. For example, the pyridin-7-ol **19** has a measureable log *D* value of 3.54, enhanced solubility (46.0 μg mL^{-1}), passive permeability (Pe = 4.44 × 10^{-6} cm s^{-1}), improved clearance (hCL/rCL = 10/36 μL min^{-1} mg^{-1} protein) and a clean CYP profile (CYP3A4, CYP2D6 and CYP2C9: all >50 μM). The tertiary alcohol **20** demonstrated similar CYP11B2 inhibitory activity (IC_{50} = 13 nM, SF = 28) and a promising physicochemical and metabolic profile (log *D* = 3.63, solubility = 317 μg mL^{-1}, hCL/rCL = 10/10 μL min^{-1} mg^{-1} protein, CYP3A4, CYP2D6, and CYP2C9: all >50 μM). Interestingly, despite the slightly increased lipophilicity of the tertiary alcohol **20**, this compound demonstrated solubility similar to that of alcohol **19** and reduced microsomal turnover (rat microsomes).

Considering the improved properties of the alcohols **19** and **20**, we endeavored to access additional 7-functionalized cyclopenta[*c*]pyridines. Exploiting the inverse-electron-demand Kondrat'eva reaction,[20] 2-cyclopentene-1-acetic acid (**25**) was reacted with oxazole **24** at high temperatures to provide the regioisomeric cyclopenta[*c*]pyridines **26** and **27**



Scheme 2 Synthesis and hCYP11B2 inhibitory activity of the hydroxylated annulated cyclopenta[*c*]pyridines **19–23**. The selectivity factor (SF) = IC_{50} (CYP11B2)/IC_{50} (CYP11B1). Conditions: (a) dirhodium(II)tetrakis-(caprolactam), TBHP, $NaHCO_3$, CH_2Cl_2, rt, 48 h; (b) $NaBH_4$, MeOH, 0 °C; (c) MeLi, LiCl, Et_2O, 0 °C to rt, 2 h. TBHP = *tert*-butyl hydroperoxide.



Scheme 3 Synthesis and hCYP11B2 inhibitory activity of the amides **28–33**. The selectivity factor (SF) = IC_{50} (CYP11B2)/IC_{50} (CYP11B1). Conditions: (a) TFA, 200 °C, microwave reactor, 10 h (34%, *ca*. 1 : 1 mixture of **26** and **27** separated by MPLC); (b) RNH_2, HATU, DIEA, DMF, rt, 16 h (amides **28–33** purified by preparative HPLC). Yields for compounds **28–33** after preparative HPLC purification: **28** (30%); **29** (21%); **30** (25%); **31** (34%); **32** (19%); **33** (20%). TFA = trifluoroacetic acid, HATU = 1-[bis(dimethylamino)-methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxid hexafluorophosphate, DIEA = diisopropyl ethylamine, DMF = dimethylformamide.

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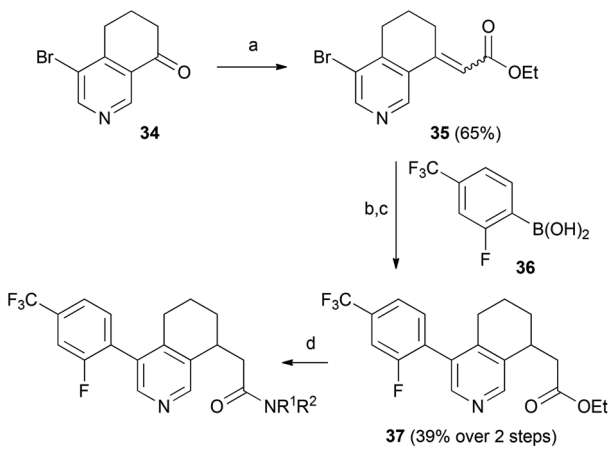
(Scheme 3).[29,30] Notably, due to the involatile nature of 2-cyclopentene-1-acetic acid **25**, this reaction could be performed in a microwave reactor. Standard amide formation followed by preparative HPLC then afforded the amides **28–32**, which were thus accessed in only 2 steps from oxazole **24**. For comparison purposes, the regioisomeric amide **33** was also isolated following coupling of the mixture of cyclopenta[*c*]pyridines **26** and **27** with (aminomethyl)cyclopropane. As indicated in Scheme 3, the amides **28–32** were all potent inhibitors of hCYP11B2 and showed modest selectivity (SF ~ 5–18) over hCYP11B1. As expected, the regioisomeric amide **33** proved to be a less potent inhibitor of hCYP11B2.

The promising inhibitory activity of the 6,7-dihydro-5*H*-cyclopenta[*c*]pyridines **28–32** prompted us to explore the analogous series of cyclohexa[*c*]pyridines, which possess a tetrahydroisoquinoline core similar to that of the reported aldosterone synthase inhibitor (+)-(*R*)-**3**. We have reported previously a significantly reduced yield for the inverse electron demand Kondrat'eva reaction involving cyclohexene,[20] and elected instead to prepare this series of compounds following a linear sequence of reactions that initiated with the bromopyridine **34** (Scheme 4).[19] Appending the appropriate carboxymethyl group involved a Horner–Wadsworth–Emmons reaction, which afforded a 3 : 2 mixture of *E* : *Z* alkenes **35**. Considering the similar inhibitory activity of compounds bearing a 3-fluoro or 2-fluoro-4-trifluoromethylphenyl group (see above), we elected to couple only 2-fluoro-4-trifluoromethylphenyl boronic acid (**36**) to the bromopyridines **35**, which provided the corresponding enoate. Hydrogenation afforded the ester **37** that was subsequently reacted with a small collection of primary or secondary amines afforded the amides **38–42**. As highlighted in Scheme 4, within this series of amides the *N*,*N*-dimethylacetamide **42** (IC_{50} = 32 nM, SF = 96) and *N*-methylacetamide **38** (IC_{50} = 11 nM, SF = 95) proved to be both the most potent and selective inhibitors of hCYP11B2 and the former compound was selected for chiral separation. The isolated enantiomers of **42** displayed significantly different affinities for the hCYP11B2 receptor, with the (+)-enantiomer (IC_{50} = 36 nM, SF = 42) being ~4-fold more potent than the (−)-enantiomer (IC_{50} = 133 nM, SF = 69). The log *D* value for (+)-**42** was measured to be 3.63 and the solubility was found to be 191 μg mL^{-1}. Passive permeability of this compound was high (Pe = 3.12 × 10^{-6} cm s^{-1}), the CYP profile was clean (CYP3A4, CYP2D6 and CYP2C9: all >50 μM) and clearance in both human and rat microsomes (hCL/rCL = 10/61 μL min^{-1} mg^{-1} protein) was much improved over the unfunctionalized annulated pyridine **10** (Scheme 1).

In order to better rationalize the structure activity relationships among these annulated pyridines, we modeled representative ligands into the recently solved X-ray crystal structure of hCYP11B2 with the bound 4-chloro-3-fluorophenyl analogue of compound (+)-(*R*)-**3**.[19] As depicted in Fig. 2, there is good spatial overlap between the cyclohexa[*c*]pyridine **42** and the anaologue of this previously reported inhibitor (+)-(*R*)-**3**. Both compounds have a close contact of the pyridine nitrogen atom to the heme iron. Additionally, both the propanamide appendage of this (+)-(*R*)-**3** analogue and the *N*,*N*-dimethylacetamide of **42** are preferentially oriented perpendicular to the tetra-



	IC_{50} hCYP11B2	SF
38: R^1 = methyl, R^2 = H	11 nM	95
39: R^1 = cyclopropyl, R^2 = H	37 nM	12
40: R^1 = cyclopropylmethyl, R^2 = H	71 nM	25
41: R^1 = 3-oxa-1-butyl, R^2 = H	222 nM	23
42: R^1 = R^2 = methyl	32 nM	96

Scheme 4 Synthesis and hCYP11B2 inhibitory activity of the amides **38** – **42**. The selectivity factor (SF) = IC_{50} (CYP11B2)/IC_{50} (CYP11B1). Conditions: (a) (i) ethyl 2-(diethoxyphosphoryl)acetate, NaHMDS, THF, −50 °C to 0 °C, 1 h; (ii) **34**, reflux, 4 h (*ca.* 3 : 2 mixture of *E* : *Z* isomers); (b) **36**, $Pd(PPh_3)_4$, Na_2CO_3, EtOH : H_2O (6 : 1), 85 °C, microwave reactor, 6 h; (c) H_2 (3 bar), 10% Pd/C, MeOH, rt, 16 h; (d) NHR^1R^2, $Al(CH_3)_3$, THF, microwave reactor, 120 °C, 1 h (yields over two steps: **38** (95%); **39** (67%); **40** (89%); **41** (59%); **42** (89%)). NaHMDS = sodium bis(trimethylsilyl)amide.

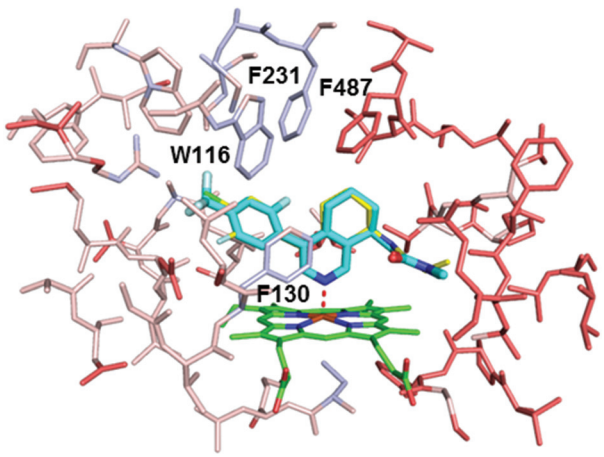


Fig. 2 Model of compound **42** (cyan) in the X-ray structure of hCYP11B2 with the 4-chloro-3-fluorophenyl analogue of (+)-(*R*)-**3** (PDB code: 4ZGX)[19] in yellow. The protein is colored by increasing B-factor on a blue to red color scale with red indicating B-factors >50 $Å^2$. The heme is shown in green. The four amino acid residues that are in close contact (≤4.5 Å) with a potential substituent at C5 of the annulated 6-membered ring system are labeled.

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hydroisoquinoline core to minimize steric strain. These modeling data further suggest that the more potent enantiomer of **42** (*i.e.*, (+)-**42**) should possess an (*R*)-configuration at C8. As discussed above, in general, the 5-substituted cyclopenta[*c*] pyridines (*e.g.*, **21–23** and **33**) are significantly less active than the corresponding 7-substituted isomers. Our binding mode model indicates that C5 appendages point into a hydrophobic pocket formed by the side chains of amino acid residues Trp 116, Phe 130, Phe 231, and Phe 487, while substituents at the 7-position are more exposed to solvent. The small size and necessary desolvation penalty involved with the placement of polar functional groups (*e.g.*, hydroxyl or carbonyl) into this pocket may well be responsible for the diminished inhibitory activity of the C5-substituted compounds. Furthermore, the opposite side of the hCYP11B2 binding pocket (*i.e.*, location of C7 appendages) shows higher crystallographic B-factors, indicating greater intrinsic flexibility and less preorganization. This inherent flexibility in combination with partial solvent exposure may also explain the fact that inhibitory activities varied only slightly amongst the series of 7-functionalized cyclopenta[*c*]pyridines (*e.g.*, **28–32**) and cyclohexa[*c*]-pyridines (*e.g.*, **38–42**).

Conclusions

In conclusion, we have exploited a recent advance in the inverse electron demand Kondrat'eva reaction to prepare a series of 7-substituted 6,7-dihydro-5*H*-cyclopenta[*c*]pyridines and have evaluated their activity as aldosterone inhibitors. These compounds demonstrated promising activity and selectivity over the structurally related hCYP11B1, prompting us to explore the synthesis of the analogous cyclohexa[*c*] pyridines. The tetrahydroisoquinoline **42** proved to be the most selective compound in this latter series and following separation of the enantiomers by chiral HPLC, the (+)-enantiomer was found to be approximately 4-fold more potent than the (−)-enantiomer against aldosterone synthase and twice as selective against the humans enzyme CYP11B2 than our previously reported inhibitor (+)-(*R*)-**3**. In order to rationalize the relationship between structure and CYP11B2 inhibitory activity, binding mode models for representative ligands were constructed using the crystal structure of human CYP11B2 with the structurally close analogue of the known ligand (+)-(*R*)-**3** as a template. Despite some topological differences, the novel aldosterone inhibitor **42** and 4-chloro-3-fluorophenyl tetrahydroisoquinoline analogue (+)-(*R*)-**3** were found to occupy a very similar binding site region with close contact of the pyridine nitrogen atom to the heme iron.

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