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Structure-based design of 7-azaindole-pyrrolidine amides as inhibitors of 11β-hydroxysteroid dehydrogenase type I

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ABSTRACT

Indole-pyrrolidines were identified as inhibitors of 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1) by high-throughput screening. Optimisation of the initial hit through structure-based design led to 7-azaindole-derivatives, with the best analogues displaying single digit nanomolar IC_{50} potency. The modeling hypotheses were confirmed by solving the X-ray co-crystal structure of one of the lead compounds. These compounds were selective against 11β-hydroxysteroid dehydrogenase type 2 (selectivity ratio >200) and exhibited good inhibition of 11β-HSD1 (IC_{50} < 1 μM) in a cellular model (3T3L1 adipocytes)

Hydroxysteroid dehydrogenases regulate steroid hormone receptors.[1] Among these, the isoform 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2) inactivates active glucocorticoids (such as cortisol in human and corticosterone in rodents) to cortisone or 11-dehydrocorticosterone.[2] On the other hand, the 11β-HSD1 isoform activates inert precursors (cortisone in human, 11-dehydrocorticosterone in rodents) to active glucocorticoids by 11-oxoreductase activity in liver, adipose tissue, brain, skeletal muscle, vascular smooth muscle cells and other organs.[3] The isoform 2 (11β-HSD2) expression is limited to tissues that express the mineralocorticoid receptor, such as kidney, gut and placenta.[4]

Several in vivo studies have exemplified the importance of these converting enzymes. In particular, 11β-HSD1 knockout mice were shown to resist hyperglycemia and to have increased hepatic insulin sensitivity.[5] Furthermore, 11β-HSD1 overexpression in mice resulted in development of visceral adiposity, hyperglycemia and insulin resistance.[6] In parallel, 11β-HSD2 overexpression improved glucose tolerance and insulin sensitivity.[7]

As administration of 11β-HSD1 inhibitors is expected to decrease the level of cortisol and other 11β-hydroxysteroids in target tissues, 11β-HSD1 is a potential target for treating numerous disorders that may be improved by reduction of glucocorticoid action including the metabolic syndrome. Selectivity against the 11β-HSD2 isoform is expected to be crucial as inhibition of 11β-HSD2 is associated with serious side effects, such as hypertension.[8] Many efforts towards the discovery and development of 11β-HSD1 inhibitors have been carried out, and led to the discovery of several chemical classes, that could be mainly grouped (based on the fragment interacting with the catalytic residues) into amides, ureas & carbamates, azoles & simple heteroaryls, sulfones & sulfonamides, thiazolones, and lactams[9,10] and references within. We report herein a new class of inhibitors based on a 7-azaindole-pyrrolidine amide scaffold.

Compound **1** was identified as an initial hit by high-throughput screening (Fig. 1), with moderate potency on human isolated 11β-HSD1 (IC_{50} of 780 nM), and a Binding Efficiency Index (BEI) of 18.3.[11] The BEI index was consistently considered to identify and focus our optimisation program on chemical functionalities carrying the strongest binding contributions. For comparison purpose, a decent HTS hit (molecular weight of 350 Da, potency of 10 μM) would exhibit a BEI of 17.1 while the BEI of a valuable lead (molecular weight of 350 Da, potency of 10 nM) would reach 22.9.

Interestingly, compound **1** was based on an original indole-pyrrolidine scaffold, so far not reported as an 11β-HSD1 inhibitor.[9] Extensive usage of public[10] and in-house crystallographic information was made in a structure-based drug design effort in order to improve the potency of the initial hit, and analogues were synthesised according to Scheme 1.

Docking of the hit **1** was performed in the human 11β-HSD1–adamantane sulfone co-crystal structure (PDB code 2ILT),[12] using

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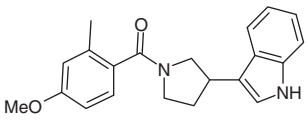
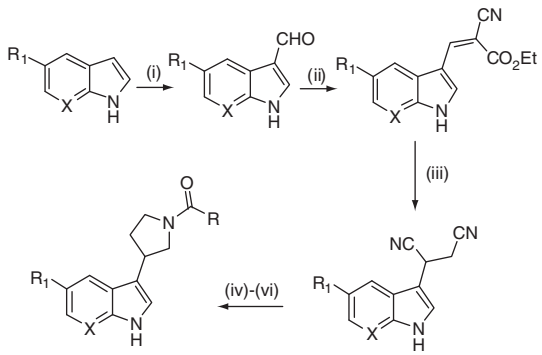


1

IC_{50} = 780 nM
BEI = 18.3

Figure 1. Initial hit discovered by HTS.



X = CH, N

Scheme 1. Reagents and conditions: (i) 1,3-hexamethylenetetramine (HMTA), AcOH, reflux, 3 h; (ii) NC-CH_2-CO_2CH_3, piperidine, EtOH, 0 °C to rt, 5 h; (iii) KCN, EtOH, 80 °C, 2.5 h; (iv) AcOH, H_2SO_4, 120 °C, 1.5 h; (v) $LiAlH_4$, THF, 0 °C–70 °C, 18 h; (vi) RCO_2H, EDC, HOBt, Et_3N, DMF, rt, 18 h.

the program GOLD 4.0.[13] The docking suggested that the amide carbonyl moiety could establish two hydrogen bonds with the hydroxyl groups of catalytic residues Ser170 and Tyr183 (Fig. 2) (all 11β-HSD1 co-crystallized inhibitors but the sulfonamides display at least one of these two hydrogen bonds[10]).

Another hydrogen bond was observed between the nitrogen of the indole and the backbone of Thr124. The influence of this interaction on the potency was assessed. First of all, according to the postulated binding mode, the *N*-alkylated derivative **2** could not establish this interaction, and was indeed confirmed experimentally to be less active (Table 1). Furthermore, modulation of the indolic hydrogen acidic character was expected to tune the strength of the hydrogen bond and had indeed an impact on the potency: electron donating substitutions such as 5-methoxy (compound **3**) were detrimental while electron withdrawing groups such as fluorine (compound **4**) increased dramatically the potency, underlining the strong contribution of the Thr124 hydrogen bond.

A similar influence of the fluorine insertion was observed with a tolyl group in the R_2 position (compounds **7** and **8**). Based on public and proprietary structural information,[11,12] we explored the introduction of a conformationally restricted phenyl acetamide group with the intention of establishing an additional interaction with the aromatic ring of Tyr177. The resulting compound **9** and its 5-fluoroindole analog **10** showed encouraging IC_{50} values of 530 nM and 430 nM respectively, in agreement with our expectations and in-line with the docking-generated binding mode (compound **9**, Fig. 3). Compounds **5** to **10** were synthesised to explore the influence of R_2 on the activity. The introduction of a cyclohexyl was detrimental (compound **5**). Inserting a fluorine atom on the indole ring (compound **6**) did improve the potency as already observed with the fluoro analogue **4** of compound **1**, but not to the same extent.

In parallel, further analysis of the binding mode led to suggest the introduction of an additional nitrogen atom on the indole. This

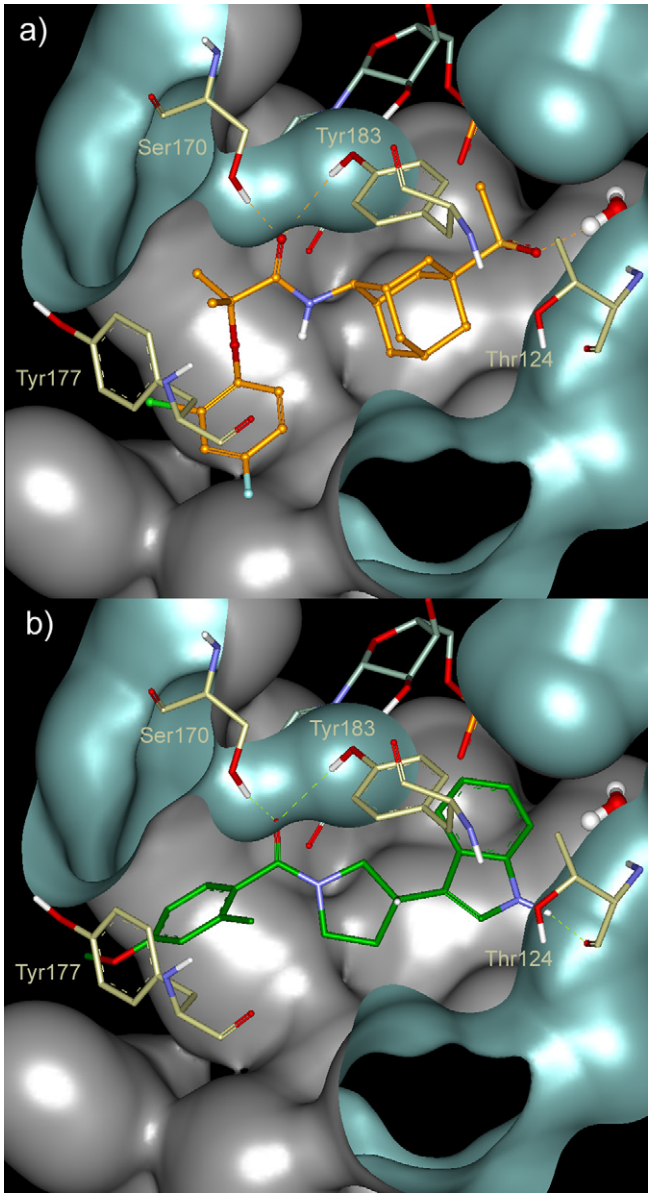


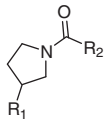
Figure 2. Steroid substrate binding site of human 11β-HSD1 (PDB code 2ILT) with (a) the adamantane sulfone compound from the experimental structure and (b) docked compound **1**; for the sake of clarity, only Tyr177, Thr124 and catalytic residues Ser170 and Tyr183, and only polar and chiral hydrogen atoms and only (*S*)-enantiomer[15] have been displayed; colour coding by atom is as follows: oxygen in red, nitrogen in blue, hydrogen in white, sulfur in yellow, phosphorus in orange; carbon atoms are coloured in orange for the experimental ligand (a), in dark green for compound **1** (b), in light yellow for the protein and in light blue for the NADP(H) cofactor (protonation state not determined in the X-ray structure). The population size and number of operations per docking were set to auto with a maximum search efficiency (200%). Water molecules 4285 and 4288 were set to toggle and spin, and a maximum of 20 poses per ligand was set, using the Chemscore scoring function.[14]

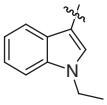
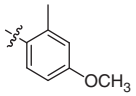
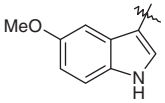
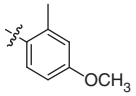
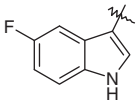
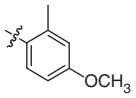
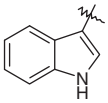
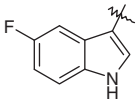
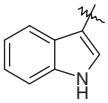
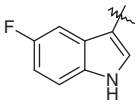
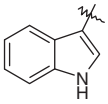
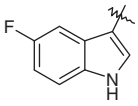
could improve potency by enabling the azaindole moiety to create a second hydrogen bond with a conserved water molecule. With that prospect in mind, new analogues were docked and synthesised (Scheme 2).

Compound **11** (Table 2), the azaindole analogue of indole **7**, reached an improved potency of 360 nM which was consistent with the additional azaindole–water molecule hydrogen bond observed in docking studies (Fig. 4).

IC50 values supported separately both structure-based modifications hypotheses (improvement of the interaction with Tyr177

Table 1
First round of optimisation around indole-pyrrolidines



Compounds	R_1	R_2	h 11β-HSD1 IC_{50}[a], nM (% inhibition @ 1 μM)	BEI[b]
2			nd (28)	–
3			nd (0)	–
4			100	19.9
5			nd (0)	–
6			1300	18.7
7			nd (70)	–
8			800	18.9
9			530	19.0
10			430	18.3

[a] 11β-HSD1 enzyme activity was assessed in 30 mM Hepes buffer, pH 7.4, containing 1 mM EDTA, 1 mM G-6P, and a substrate mixture cortisone/NADPH (200 nM/200 μM). Reaction was initiated by addition of 3 μg of human recombinant 11β-HSD1 expressed in *Escherichia Coli* and terminated with addition of 18β-glycyrrhetinic acid stop solution after 150 min incubation at 37 °C. Determinations of cortisol levels were monitored by HTRF assay (Cisbio International).
[b] Binding Efficiency Index = pKi or pIC50/Molecular Weight (kDa), pIC50 was used in this study.

through insertion of conformationally restricted phenyl acetamide, and addition of a nitrogen atom to the indole ring): compounds **9–10** and **11,** respectively bearing the corresponding modifications, exhibited improved potencies over the initial hit. The combination of these two modifications resulted in a dramatic improvement in potency with compounds **12** and **13** displaying IC_{50} values of 25 and 50 nM (Table 2). Docking of **13** nicely supported all previous hypotheses regarding interactions within the binding site (Figs. 5, S1, S2).

Efforts were then focused on the aromatic interactions with Tyr177. Several groups were introduced to tune the orientation of the aryl group (Table 2) while halogens as electron withdrawing groups were added on the phenyl acetamide (compounds **14**–**17**). Substitutions on the phenyl acetamide group led to single digit nanomolar IC_{50} values (Table 2), presumably due to increased lipophilic interactions in the pocket and favorable electrostatic interaction between the electron-rich Tyr177 π system and electron-depleted π system of the phenyl moiety.[16] Following the same idea, introduction of an electron rich oxygen atom between the orientating group and the phenyl (compound **18**) led to a 15 fold potency decrease compared to the phenyl acetamide equivalent **12**. However activity was greatly improved with the para-fluoro analog compound **19** (25 nM IC_{50}). The nature of the orientating group seemed not to be crucial since *gem*-dimethyl, cyclopropane and cyclobutane derivatives led to similar potencies (compounds **15**–**17**).

Furthermore, addition of a cyclopropane ring to the pyrrolidine ring to potentially improve its metabolic stability did not alter the activity (compounds **20** and **21**).

Several further modifications were attempted to investigate substitutions on the 7-azaindole group (Table 3). The 2-methyl analogues **22–24** were in the same range of potency as the unsubstituted 7-azaindoles **14** and **16**. However, a fluorine insertion on position 5 of the azaindole ring system (compound **25**) was clearly detrimental for inhibition, with a 30 fold decrease in potency, unlike the 5-fluoro substitution of the indole ring (Table 1,

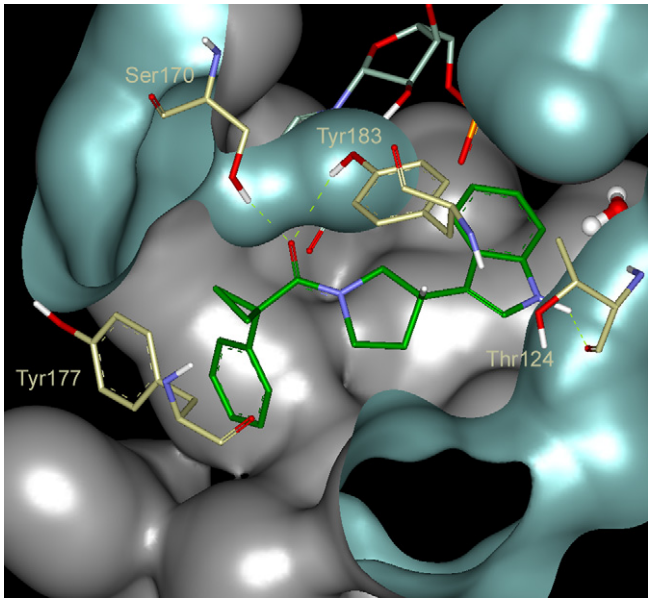
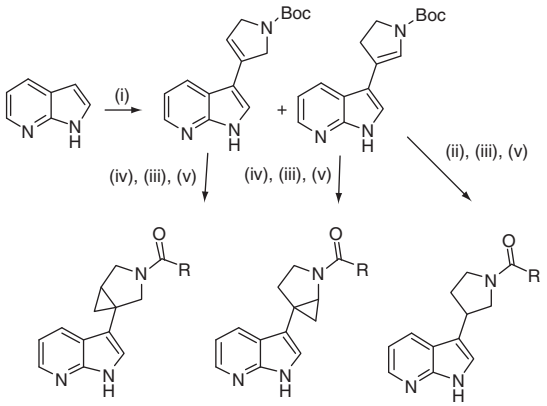
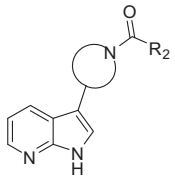


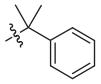
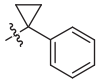
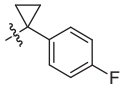
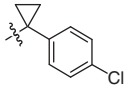
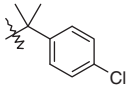
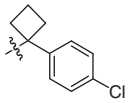
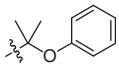
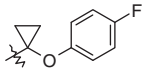
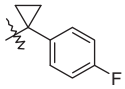
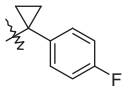
Figure 3. Steroid substrate binding site of human 11β-HSD1 (PDB code 2ILT) with docked compound **9** ((*S*)-enantiomer represented); displayed details and colour coding by atoms are identical to Figure 2b.



Scheme 2. Reagents and conditions: (i) *N*-Boc-pyrrolidin-3-one, KOH, MeOH, H_2O, 75 °C, 18 h (ii) HCO_2NH_4, 10% $Pd(OH)_2/C$, EtOH, reflux, 1 h; (iii) HCl/MeOH, rt, 12 h; (iv) $ZnEt_2$, CH_2I_2, DCM, 0 °C ->rt, 18 h; (v) RCO_2H, EDC, HOBt, TEA, DMF, rt, 18 h.

Table 2
Azaindole-pyrrolidines derivatives



Compounds	Spacer	R_2	h 11β-HSD1 IC_{50}[a], nM	BEI[b]
11			360	21.1
12			25	22.8
13			50	22.0
14			17	22.2
15			4	22.9
16			10	21.8
17			7	21.4
18			370	18.4
19			25	20.8
20			46	20.3
21			25	21

[a] h 11β-HSD1 experimental protocol as described in Table 1.
[b] BEI as described in Table 1.

compounds **6**, **8** and **10**). This difference could be attributed to a negative contribution of the 5-fluoro substituent on the pyridine-water interaction in the case of the 7-azaindole. The importance of this interaction was further illustrated with the 6-azaindole derivative **26** which displayed almost one log loss of potency (43 nM IC_{50}).

The ternary complex structure of a racemic mixture of compound **22**, NADP(H) and a humanised murine 11β-HSD1 was obtained by X-ray crystallography[17] (the protonation state of NADP was not determinable in the structure). The final model contains eight molecules in the asymmetric unit that form four homodimers. The overall structure of the active site mutant does not differ significantly when compared to the murine wild type one.[18] Compound **22** is bound to the steroid binding site of 11β-HSD1 and is also in contact with NADP(H). The active site amino acids and both enantiomers of **22** are well defined in the electron density map, sharing a similar binding mode and orientation in the active site (Fig. S3). Figure 6 shows the binding site of the humanised murine 11β-HSD1 (6 point mutations) with the initial Fo-Fc electron density map of the (*S*)-enantiomer of **22** at 2.5σ superimposed. The compound forms two hydrogen bonds to the side chain hydroxyl groups of residues Ser170 and Tyr183. Another hydrogen bond is established between the indolic nitrogen of the ligand and the main chain carbonyl oxygen atom of Thr124. A further hydrophilic contact was observed in four of the eight monomers to the main chain amide nitrogen atom of Thr124 via a water molecule conserved in other co-crystal structures. The azaindole methyl forms hydrophobic contacts with Leu126 hydrophobic side chain. The pyridine ring is involved in a π–π aromatic stacking interaction with the phenyl moiety of Tyr177, close to the solvent exposed area of the protein dimer interface. Overall, the crystal structure confirmed the binding modes observed during the dockings and used in the compound optimisation program.

Compounds **13** and **16** were selected for further characterization and preliminary results are presented herein (Table 4). These compounds were selective against 11β-HSD2 (selectivity ratio >200). We hypothesised that the increased potency observed with

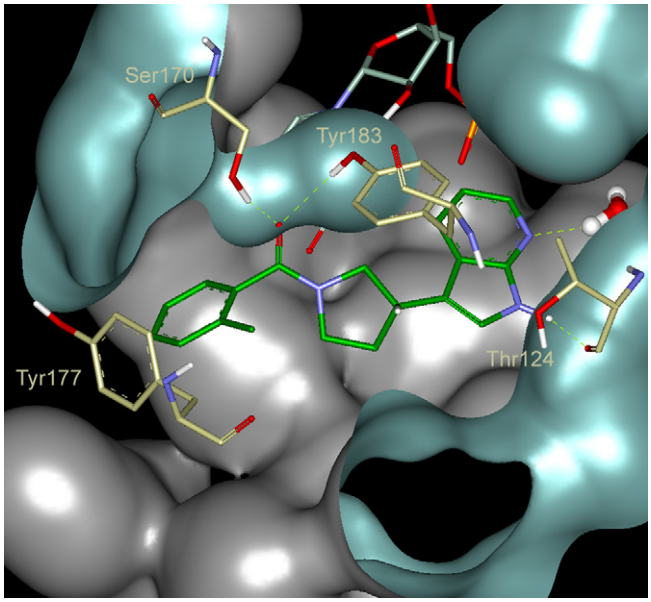


Figure 4. Steroid substrate binding site of human 11β-HSD1 (PDB code 2ILT) with docked compound **11** ((*S*)-enantiomer represented); displayed details and colour coding by atoms are identical to Figure 2b.

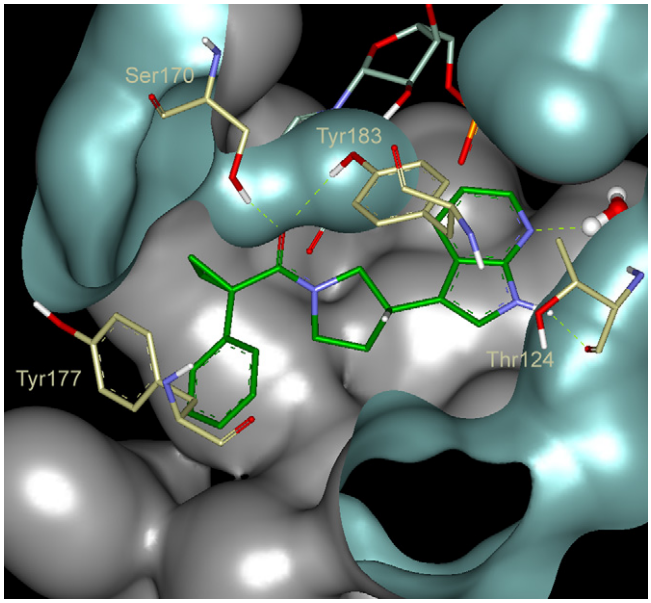


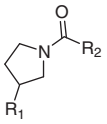
Figure 5. Steroid substrate binding site of human 11β-HSD1 (PDB code 2ILT) with docked compound **13** ((*S*)-enantiomer represented); displayed details and colour coding by atoms are identical to Figure 2b.

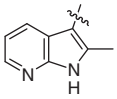
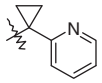
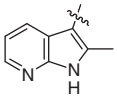
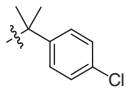
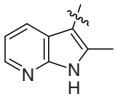
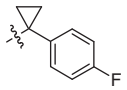
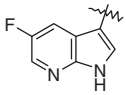
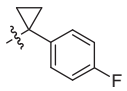
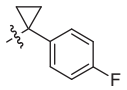
13 and **16** on the human enzyme compared to the mouse one could be attributed to the increased lipophilic and optimised aromatic interactions with Tyr177 in human[19], that is mutated in a non aromatic Gln residue in the mouse enzyme. Furthermore, compound **13** displayed good inhibition on mouse 11β-HSD1 (IC_{50} of 362 nM) in a cellular model (3T3L1 adipocytes), but suffered from a poor PK profile.

The clearance (CL) was higher than the hepatic blood flow in the mouse, suggesting very quick metabolism, supported also by the very low recovery of unchanged drug in feces (RF results). Clearance was improved with compound **16** but remained disappointing.

In conclusion, we have reported a new, original and promising class of 11β-HSD1 inhibitors based on a 7-azaindole-pyrrolidine scaffold. The most active compounds were obtained with aromatic cylopropane carboxamides inducing a strong lipophilic and π–π interaction with Tyr177, and single digit nanomolar IC_{50} was achieved. These compounds were selective against 11β-HSD2 and showed moderate inhibition of mouse 11β-HSD1

Table 3
Variation of the azaindole moiety



Compounds	R_1	R_2	h 11β-HSD1 IC_{50}[a], nM	BEI[b]
22			19	22.3
23			12	20.7
24			5	22.7
25			439	17.3
26			43	21.1

[a] h 11β-HSD1 experimental protocol as described in Table 1.
[b] BEI as described in Table 1.

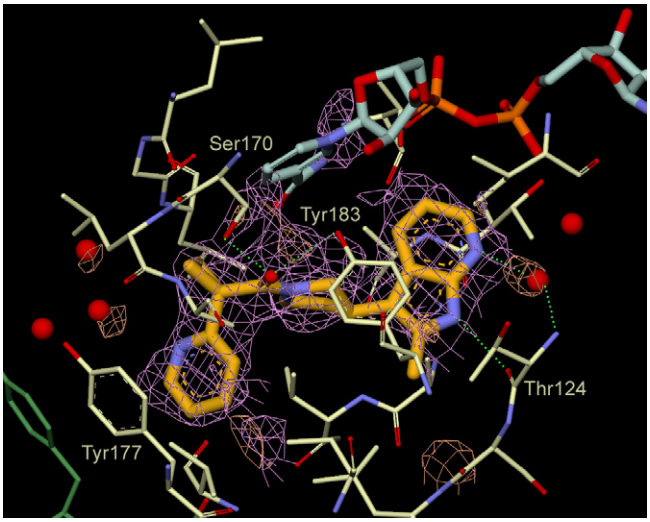


Figure 6. Steroid substrate binding site of humanised murine 11β-HSD1 in complex with compound **22** (PDB code 3GMD) ((*S*)-enantiomer); compound **22** is depicted in heavy sticks, the protein in light sticks and water molecules in large balls; colour coding by atoms is as follows: oxygen in red, nitrogen in blue, sulfur in yellow, phosphorus in orange; carbon atoms are coloured in light orange for compound **22**, in light grey for the chain A of the protein, in green for chain B of the protein and in light blue for the NADP(H) cofactor. Initial ligand Fo-Fc density contoured at 2.5σ is shown in purple and initial water Fo-Fc density contoured at 3σ is shown in brown.

Table 4
Profile of compounds **13** and **16**

Compounds	13	16
h 11β-HSD1 IC50[a]	50	10
m 11 β -HSD1 IC50[a]	230	720
m 11 β -HSD1 3T3L1 cellular IC50[b] (nM)	362	1221
h 11 β -HSD2 IC50[c]	>10 μM	>10 μM
h 11 β -HSD2/ HSD1 IC50 Selectivity ratio	>200	>1000
Plasma $t_{1/2}$[d]	0.2 h	0.3 h
F[d]	<5%	<5%
CL[d]	20.0 L/h/kg	4.0 L/h/kg
Vss[d,e]	5.0 L/kg	1.5 L/kg
RF[d,f]	⩽1%	⩽5%
m SPB[g]	91%	94%

[a] h 11β-HSD1 experimental protocol as described in Table 1; for murine (m) 11β-HSD1, 2.5 μg of microsome fraction from liver (Tebu) was used in the assay.
[b] 3T3L1 cells were differentiated (5 days) in adipocytes and further cultured (4 days) in a 24 well plate format before incubation with test compounds (10-5-10-7 M) for 150 min. Cortisol in the culture supernatant was then measured for 11β-HSD1 activity in HTRF assay (see Table 1).
[c] 11β-HSD2 enzyme activity was assessed in 50 mM Tris buffer, pH 7.8, containing 1 mM MgCl2, 0.5 mM NAD, and 1 μg of human recombinant 11β-HSD2 expressed in *E. Coli*. Reaction was initiated by addition of cortisol 20 nM and terminated with addition of carbenoxolone 10 μM stop solution after 60 min incubation at room temperature. Determinations of cortisol levels were monitored by an HTRF assay (Cisbio International).
[d] Dosed i.v. (0.2 mg/kg) and p.o. (0.5 mg/kg) in male rats in a low dose cocktail study; mean values over 3 rats.
[e] Volume of distribution at steady state.
[f] Recovery of unchanged drug in feces (0–24 h collection).
[g] mouse serum protein binding.

(IC_{50} of 1221 nM) in a cellular model (3T3L1 adipocytes). Further optimisation of this series to improve PK profile will be reported in due course.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmcl.2012.07.070.

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