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Discovery of SAR184841, a potent and long-lasting inhibitor of 11β-hydroxysteroid dehydrogenase type 1, active in a physiopathological animal model of T2D

Olivier Venier [a,*], Cécile Pascal [a], Alain Braun [a], Claudie Namane [a], Patrick Mougenot [a], Olivier Crespin [a], François Pacquet [a], Cécile Mougenot [a], Catherine Monseau [a], Bénédicte Onofri [a], Rommel Dadji-Faïhun [a], Céline Leger [a], Majdi Ben-Hassine [a], Thao Van-Pham [a], Jean-Luc Ragot [a], Christophe Philippo [a], Géraldine Farjot [a], Lionel Noah [a], Karima Maniani [a], Asma Boutarfa [a], Eric Nicolaï [a,*], Etienne Guillot [a], Marie-Pierre Pruniaux [a], Stefan Güssregen [b], Christian Engel [b], Anne-Laure Coutant [c], Beatriz de Miguel [d], Antonio Castro [d]

[a] Sanofi R&D, 1 Avenue Pierre Brossolette, 91385 Chilly-Mazarin, France
[b] Sanofi Deutschland GmbH, Industriepark Hoechst, 65926 Frankfurt am Main, Germany
[c] Sanofi R&D, 371 Rue du Professeur Joseph Blayac, 34184 Montpellier, France
[d] Sanofi R&D, Avenida de Leganés 62, 28925 Alcorcón, Madrid, Spain

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ABSTRACT

Starting from 11β-HSD1 inhibitors that were active ex vivo but with Cyp 3A4 liability, we obtained a new series of adamantane ureas displaying potent inhibition of both human and rodent 11β-HSD1 enzymes, devoid of Cyp 3A4 interactions, and rationally designed to provide long-lasting inhibition in target tissues. Final optimizations lead to SAR184841 with good oral pharmacokinetic properties showing in vivo activity and improvement of metabolic parameters in a physiopathological model of type 2 diabetes.

11β-Hydroxy steroid dehydrogenase type 1 (11β-HSD1) converts the biologically inactive glucocorticoids, cortisone (in man) and 11-dehydrocorticosterone (in rodents), into their biologically active metabolites, respectively, cortisol and corticosterone, which are known to act as functional antagonists of insulin in several target organs and tissues such as the liver, muscle, and adipose tissue (Fig. 1).[1] There is evidence for an excess of cortisol in tissues being a primary driver of insulin resistance and a critical point for disease intervention.[2] Liver- or adipose tissue-specific overexpression of 11β-HSD1 in transgenic mice produces a phenotype closely resembling human type 2 diabetes mellitus.[3] Reduction of intracellular corticosterone levels in rodents as a result of pharmacological inhibition of 11β-HSD1 reverses manifestations of altered metabolic parameters including ectopic fat storage, diabetes, dyslipidemia and atherosclerosis.[4] Both 11β-HSD1 expression and activity are up-regulated in the adipose tissue of obese, insulin-resistant or diabetic humans.[5] Inhibition of 11β-HSD1 therefore offers potential as a novel therapy to lower intracellular cortisol concentrations and thereby enhance insulin sensitivity and hepatic lipid catabolism in type 2 diabetes, obesity, and hyperlipidemia. Two isoforms of 11β-HSD produced from distinct genes are known: 11β-HSD1 is primarily expressed in the liver and adipose tissue, the other isoform, 11β-HSD2, is located mainly in the kidney.[6] 11β-HSD2 converts active glucocorticoids (such as cortisol and corticosterone) into inactive cortisone or 11-dehydrocorticosterone. Any potential drug aimed at inhibiting 11β-HSD1 should therefore be selective for this isoform since inhibition of 11β-HSD2 may result in side effects such as sodium retention, hypokaliemia, and hypertension.[7]

In the last decade, extensive research by the pharmaceutical industry and academic groups allowed the identification of several classes of 11β-HSD1 inhibitors, which have been comprehensively

* Corresponding authors.
E-mail address: olivier.venier@sanofi-aventis.com (O. Venier).

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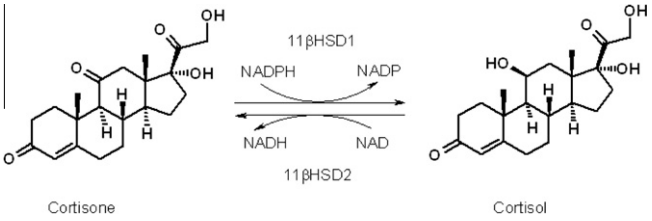
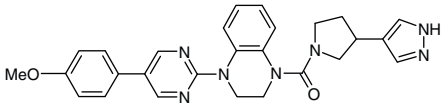


Figure 1. Interconversion of cortisone and cortisol by 11β-HSD1 and 11β-HSD2 enzymes.

reviewed.[8] These included sulfonamides such as BVT.2733 or PF-915275,[9,10] thiazolones such as AMG221,[11] and amide derivatives such as AZD4017 (Fig. 2).[12]

Several compounds have reached clinical development phases, the most advanced being INCB-13739 which completed phase 2 as add-on therapy on top of metformin, and showed positive effects on end point criteria at the dosage of 200 mg in a 12 week study (HbA1C (−0.6%), fasting plasma glucose (−24 mg/dl) and HOMA-IR (−24%)).[13] Other companies, for example, Vitae pharmaceuticals, BMS, Roche, Pfizer and Lilly are also currently undergoing early clinical development with 11β-HSD1 inhibitors. However, some compounds have been discontinued: PF-915275 for formulation issues,[14] BVT-3498 and BVT-83370 for unknown reasons,[15] MK-0916 and MK-0736 for insufficient activity in a 12 weeks clinical trial.[16] Potential explanations for these failures were proposed: (i) an unsuitable tissue distribution with insufficient activity in fat relative to liver and (ii) a short a duration of action in target tissues. Furthermore, several classes of 11β-HSD1 inhibitors displayed limited activity on rodent enzymes,[8,9,12] making it difficult to assess them in appropriate animal models for optimal drug candidate selection. In metabolic disease pathogenesis, 11β-HSD1 activity is upregulated in adipose tissue and liver, thus inhibition in both tissues is considered to be a prerequisite for producing significant therapeutic benefits.[8b] Therefore, in order to identify new drug candidates with an optimal PK/PD profile we focused our efforts on compounds displaying inhibition of both human and rodent enzymes, thus allowing early ex vivo testing in rodents. Furthermore, we optimized the SAR to obtain compounds with high levels of inhibition and long durations of action in both liver and fat tissues, to ensure sufficient reduction of local cortisol levels, with the objective of a once daily oral administration.



1

h11βHSD1 IC_{50}= 43nM
m11βHSD1 IC_{50}= 49nM
r11βHSD1 IC_{50}= 600nM
h11βHSD2 IC_{50}>10.000nM

Ex-vivo inh. at 30mpk 2h post dosing
Liver 90%
Fat 70%

Cyp 3A4 Inh. IC_{50}< 300nM

We have previously described a new class of human and mouse 11β-HSD1 inhibitors containing the quinoxaline urea core. In our prior report[17] compound **1** was shown to be a potent and selective inhibitor of 11β-HSD1, which inhibited 11β-HSD1 activity ex vivo in liver and adipose tissue. However, further profiling in drug metabolism studies showed that compound **1** was a potent inhibitor of Cyp 3A4 metabolic activity, exhibiting an IC_{50} below 300 nM. Our strategy to reduce the interaction with Cyp 3A4 consisted in replacing the pyrrolidine pyrazole moiety with different groups reported recognize the 11β-HSD1 enzymatic cleft. In

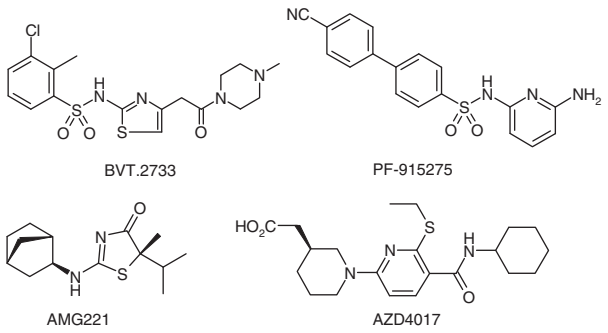


Figure 2. Representative 11β-HSD1 inhibitors.

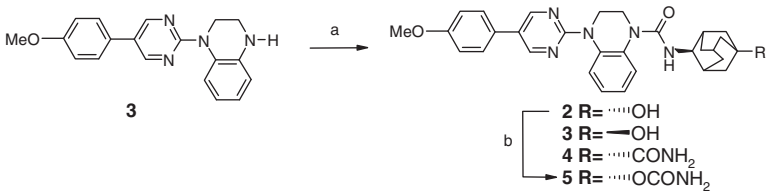
particular, we focused our efforts on the adamantane motif. This group has often been reported in 11β-HSD1 inhibitors as a good pharmacophore to address the lipophilic cofactor pocket of the enzyme and appeared to be a good alternative to increase the duration of action by increasing the overall lipophilicity.[18] Moreover the substitution of an adamantyl moiety with a polar group (hydroxyl, amide, carboxylic acid, etc.) can provide additional interaction points with the cofactor and enable modulation of metabolic stability.[19] To assess the relevance of this strategy in the quinoxaline urea series and determine which kind of polar group is favoured, we prepared a first set of compounds (**2**–**5**) as described in Scheme 1.

As shown in Table 1, replacement of pyrrolidine pyrazole by *trans* 4-amino adamantan-1-ol is well tolerated leading to potent activities on both human and mouse enzymes and lower potency on the rat enzyme.[20] Moreover, compound **2** does not inhibit Cyp 3A4, indicating that pyrrolidine pyrazole was the main contributor to the Cyp interaction in compound **1**. ADME data for compound **2** are also favourable, with moderate metabolic lability and good estimated intestinal permeability. Moving from *trans* to *cis* 4-amino adamantan-1-ol in compound **3** leads to a dramatic loss of potency. Replacement of the hydroxyl group by a primary amide gave rise to compound **4** with equipotent inhibition in human and mouse enzymes and a similar ADME profile. On the other hand, transformation of the alcohol function into a primary carbamate, while also well tolerated, lead to a decrease in metabolic stability.

The Cyp 3A4 issue solved, we evaluated compound **2** in the ex vivo assay which is pivotal in our search for long-lasting 11β-HSD1 inhibitors.[23] At 10 mg/kg per os, compound **2** displayed only moderate inhibition after 2 h in the liver (inh. = 40%) and subcutaneous fat (inh. = 30%).

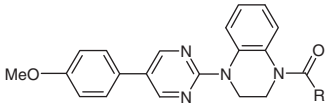
Other modulations were evaluated to improve the ex vivo activity, and the replacement of 4-methoxyphenyl group by a methyl sulphonylpiperazine moiety led to a family of compounds showing increased inhibition levels and duration, up to 16 h post dosing (see Table 2). The synthetic routes for preparing compounds **6**–**9** are shown in Schemes 2–4.

The direct replacement of the 4-methoxyphenyl in compound **2** by 4-methylsulfonylpiperazine gave derivative **6** with a good balance in activity between human and rodent enzymes. Its ADME profile was favourable for in vivo testing with acceptable metabolic stability and good estimated intestinal permeability when in presence of the P-gp inhibitor elacridar. The fact of being a P-gp substrate was not considered detrimental for in vivo activity,[25] since compound **6** showed some activity in the liver after 16 h in the ex vivo assay. The pyridine derivative **7** was as active as its pyrimidine analog in the enzymatic assay, but displayed a better activity in the liver ex vivo assay and interestingly also a significant



Scheme 1. Synthesis of inhibitors (**2–5**). Reagents and conditions: (a) trisphosgene,[21] DIPEA, CH_2Cl_2 then 4-amino adamantan-1-ol (**2**, 19% & **3**, 31% or *trans* 4-amino adamantan-1-carboxamide (**4**, 59%); (b) (1) Trichloroacetyl isocyanate, CH_2Cl_2, (2) K_2CO_3, MeOH, 50 °C, (**5**, 55%).[22]

Table 1
Replacement of the pyrrolidine pyrazole moiety: compounds **2–5**



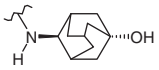
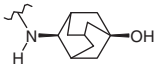
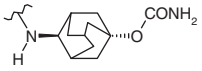
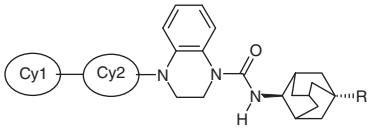
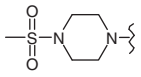
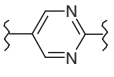
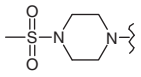
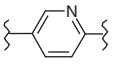
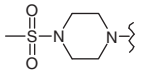
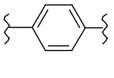
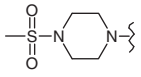
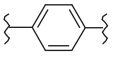
Compd	R	11β-HSD1 IC_{50} (nM) *h*/*m*/*r*	% Metabolic lability *h*/*m*/*r*	Caco2 permeability (10^{-7} cm s^{-1})	CYP 3A4 inh. IC_{50} (μM)
2		5/15/110	41/21/33	248	>10
3		1400/ND/ND	ND	ND	ND
4		18/36/70	49/27/32	182	>10
5		9/5/100	89/96/70	ND	>10

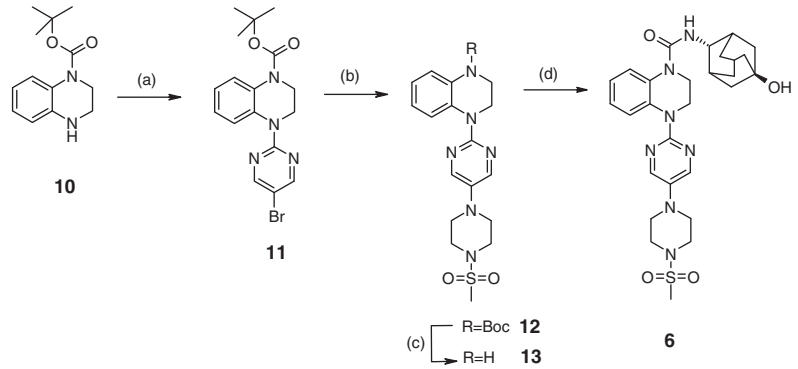
Table 2
Modulation of aryl/heterocycle group: compounds **6–9**



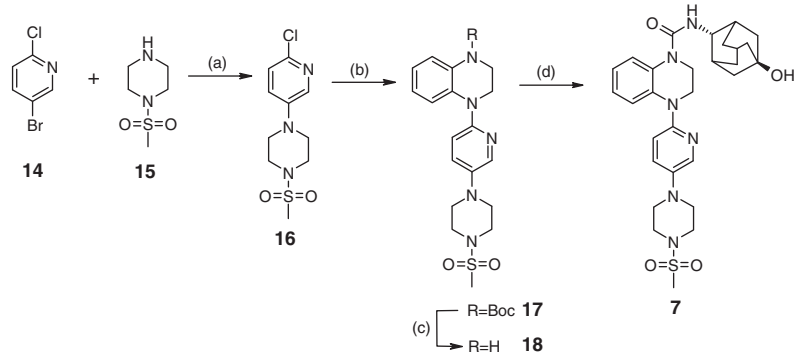
Compd	Cy1	Cy2	R	11β-HSD1 IC_{50} (nM) *h*/*m*/*r*	% Metabolic lability *h*/*m*/*r*	Caco2 permeability (10^{-7} cm s^{-1})	CYP 3A4 inh. IC_{50} (μM)	Mice ex vivo (30 mg/kg) %inh. 16 h post dosing
6			OH	14/1/28	9/18/24	7/109[a]	>10	Liver 30% Sc Fat 0%
7			OH	22/2/16	12/18/19	79	>30	Liver 55% Sc Fat 40%
8			OH	50/1/114	2/9/17	194	>10	Liver 80% Sc Fat 55%
9			$CONH_2$	6/5/24	3/22/26	30	>10	Liver 55% Sc Fat 30%

ND: not determined.
[a] Plus elacridar.

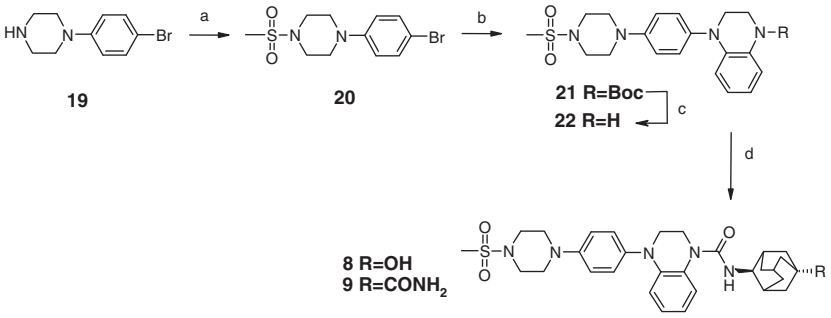
inhibition of 11β-HSD1 activity in fat tissues for the first time in the series. Replacement of the pyridine by a phenyl ring gave compound **8** without losing the inhibitory activity on the enzyme in human and mouse assays, but decreased the inhibitory effect on the rat enzyme. However the replacement of the hydroxyl moiety by a carboxamide group, for example, compound **9** enabled a



Scheme 2. Synthesis of inhibitor **6**. Reagents and conditions: (a) BuLi, THF, 2-chloro-5-bromo-pyrimidine 14%; (b) **15**, NaO*t*Bu, Pd_2dba_3, *S*-Phos, toluene, 100 °C, 70%;[24] (c) HCl 4 M dioxane, 84%; (d) trisphosgene, TEA, DMF then *trans* 4-aminoadamantan-1-ol, 50%.



Scheme 3. Synthesis of inhibitor **7**. Reagents and conditions: (a) NaO*t*Bu, Pd_2dba_3, *S*-Phos, toluene, 100 °C, 76%; (b) Boc-quinoxaline, NaO*t*Bu, Pd_2dba_3, *S*-Phos, toluene, 100 °C, 77%; (c) HCl 4 M dioxane, 80%; (d) trisphosgene, TEA, CH_2Cl_2 then *trans* 4-aminoadamantan-1-ol, 44%.



Scheme 4. Synthesis of inhibitors **8** & **9**. Reagents and conditions: (a) $MeSO_2Cl$, TEA, CH_2Cl_2, 94%; (b) Boc-quinoxaline, NaO*t*Bu, $Pd(OAc)_2$, $P(tBu)_3$, *o*-xylene, 150 °C, 70%; (c) HCl 4 M dioxane, 100%; (d) trisphosgene, TEA, DMF then *trans* 4-aminoadamantan-1-ol (**8**, 71%) or phosgene, TEA, DMF *trans* 4-aminoadamantan-1-carboxamide (**9**, 74%).

return to good inhibition of rat 11β-HSD1. Both compounds **8** and **9** displayed good ADME profiles and long-lasting activity in the ex vivo assay with a level of inhibition similar to pyridine **7**. Finally, no Cyp 3A4 inhibition was observed within this set of molecules.

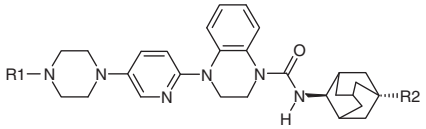
Compound **7** was considered as a good lead for further optimization due to its overall favourable profile with well balanced enzymatic activity on human and rodent enzymes, acceptable ADME parameters and significant ex vivo activity in target tissues 16 h after treatment. Moreover, the pyridine ring could give opportunities to improve the intrinsic solubility or to form solubilising salts.[26] In consequence, the final modulations shown in Table 3 were made on the *N*-pyridylquinoxaline scaffold.

The synthesis of compounds **23**–**28** is depicted in Schemes 5–7.

In the final optimization step, we focused the chemical modulations on the two far ends of the scaffold. This allowed a fine tuning of the physicochemical properties, in order to obtain a well balanced inhibition profile in liver and fat tissues. All compounds were assayed ex vivo for enzymatic inhibition in the liver and fat tissues 16 h after single oral administration at lower dose, for example, 3 mg/kg, in order to identify candidates for in vivo evaluation in a physiopathological model.

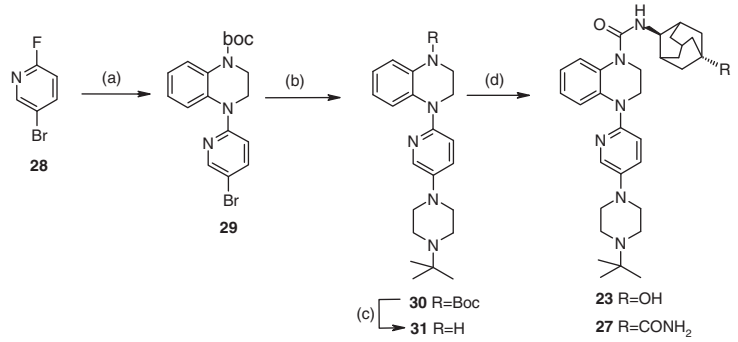
Replacement of the methylsulfonyl group by a *t*-butyl group led to *t*-butylpiperazine **23**, which displayed similar in vitro enzymatic inhibition profile, ADME parameters and ex vivo activity to compound **7**. This result reflects the fact that the piperazine substitution is very tolerant in terms of chemical structure modulation and supports the hypothesis of the absence of critical interactions between this part of the molecule and the 11β-HSD1 protein (see below). The acetamide **24** was also found to be potent in enzymatic assays, but despite an acceptable ADME profile, did not show any

Table 3
Modulation of piperazine & adamantyl substitution: compounds **23–28**

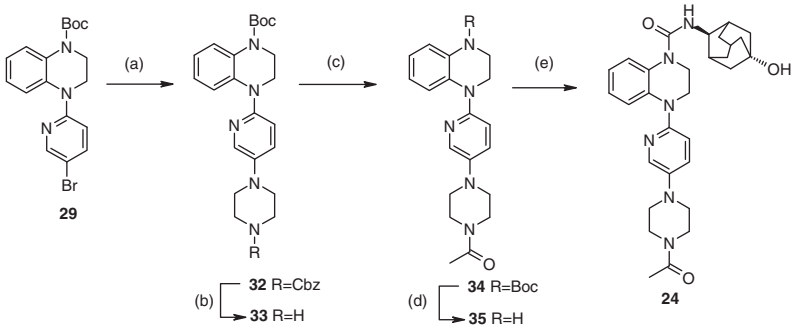


Compd	R1	R2	11β-HSD1 IC_{50} (nM) *h*/*m*/*r*	% Metabolic lability *h*/*m*/*r*	Caco2 permeability (10^{-7} cm s^{-1})	CYP 3A4 inh. IC_{50} (μM)	Mice ex vivo (30 mg/kg) %inh. 16 h post dosing
7		OH	19/9/25	18/19/12	79	>30	Liver 47% Sc Fat 20%
23		OH	9/8/18	14/6/20	34	ND	Liver 55% Sc Fat 20%
24		OH	11/11/65	5/14/18	10/141[a]	>30	Liver 0% Sc Fat 0%
25		OH	9/21/21	9/22/23	98	>10	Liver 65% Sc Fat 40%
26		$CONH_2$	4/6/7	2/13/15	3/97[a]	>30	Liver 72% Sc Fat 60%
27		$CONH_2$	4/8/9	1/18/31	4/144[a]	>30	Liver 75% Sc Fat 50%

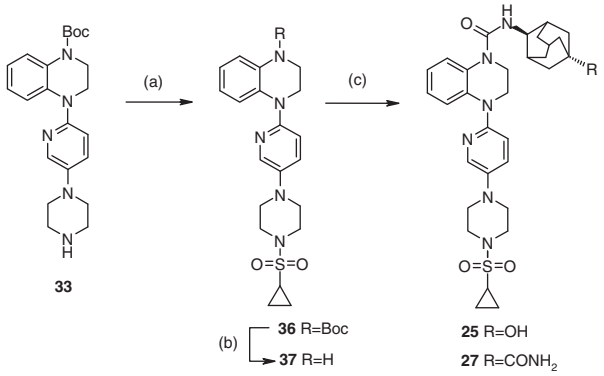
ND: not determined.
[a] Plus elacridar.



Scheme 5. Synthesis of inhibitors **23** & **27**. Reagents and conditions: (a) BocQuinoxaline, *t*BuOK, NMP, 90%; (b) NaO*t*Bu, Pd_2dba_3, *S*-Phos, toluene, 110 °C, 74%; (c) HCl 4 M dioxane, 100%; (d) phosgene, TEA, CH_2Cl_2 then *trans* 4-aminoadamantan-1-ol, (**23**, 52%) or phosgene, TEA, CH_2Cl_2 then *trans* 4-aminoadamantan-1-carboxamide (**27**, 52%).



Scheme 6. Synthesis of inhibitors **24**. Reagents and conditions: (a) CBz-piperazine, NaO*t*Bu, Pd_2dba_3, *S*-Phos, toluene, 100 °C, 74%; (b) H_2, Pd/C, MeOH, 94%; (c) acetyl chloride, TEA, CH_2Cl_2, 100%; (d) HCl 4 M dioxane, 100%; (e) phosgene, TEA, CH_2Cl_2 then *trans* 4-aminoadamantan-1-ol, 53%.



Scheme 7. Synthesis of inhibitors **25** & **27**. Reagents and conditions: (a) cyclopropylsulfonyl chloride, TEA, CH_2Cl_2, 100%; (b) HCl 4 M dioxane, 97%; (c) triphosgene, TEA, CH_2Cl_2 then *trans* 4-aminoadamantan-1-ol, (**25**, 50%), or trisphosgene, TEA, CH_2Cl_2/DMF then *trans* 4-aminoadamantan-1-carboxamide (**27**, 56%).

inhibition of 11β-HSD1 in the ex vivo assay after 16 h post-dosing. Changing the methyl sulphonamide into cyclopropylsulfonamide led to compound **25** which displayed a nanomolar activity in the in vitro assays, but also a good level of activity ex vivo.

It is worth noting that the two most potent inhibitors in the ex vivo assay, compounds **26** and **27**, bear a primary amide group instead of the hydroxyl group at position 1 of the adamantane ring. Introduction of this carboxamide motif generated single digit nanomolar inhibitors in the enzymatic assays with a very well balanced activity on human and rodent enzymes. These two compounds showed favourable overall ADME profiles and despite being P-gp substrates (with low permeability when tested alone but high permeability in the presence of elacridar) both inhibited 11β-HSD1 activity by more than 50% in target tissues 16 h after 3 mg/kg oral administration making them valid candidates for further in vivo evaluation.[27]

Finally compound **26** (SAR184841) was selected as the best potential candidate for the following reasons: (i) a better ex vivo activity in fat, (ii) a lower molecular weight, and (iii) the presence of a basic group (pK_a = 8.5 for the *t*-butylpiperazine) amenable to salt formation to improve solubility (solubility >2 mg/mL in aqueous buffer up to pH 4.5).

Table 4
Profile of SAR184841

h 11βHSD2 IC_{50} (nM)	h-Erg IC_{50} (nM)	Cyp 3A4 inhibition	Cyp induction	Selectivity (Cerep profile)	In vitro clearance in h. Hep (mL h^{-1} 10^{-6}hep
4000	>10000	None	None	Clean	0.035

Table 5
Pharmacokinetic profile for SAR184841 in rat (3 mg/kg iv & 10 mg/kg po)

C_{max} (ng/mL) in plasma (po)	$AUC_{0\text{-}inf}$ (ng h/mL) in plasma (po)	Tissue/plasma $AUC_{0\text{-}inf}$ ratio liver/adipose/brain (po)	Plasma clearance (L/h/kg)	V_{dss} (L/kg)	$t_{1/2}$ in plasma (po)	*F*%
556	580	224/2.2/0.14	5.2	14	4.4	25

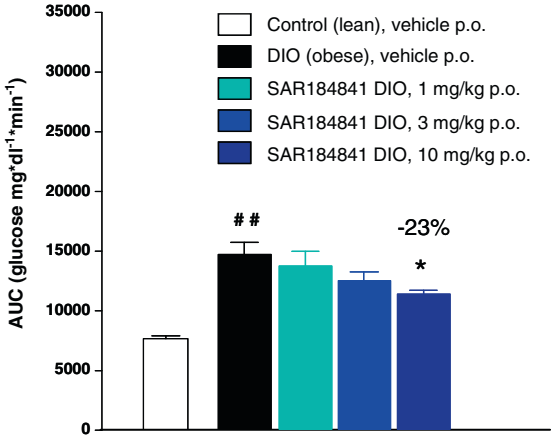


Figure 4. Oral glucose tolerance test (OGTT) performed after the 3rd week of treatment in DIO mice (18 h-fasted animals), treated with SAR184841 (1, 3 or 10 mg/kg/day). AUC: area under the glucose curve (0–60 min post 2 g/kg oral glucose challenge); n = 9–10 animals per group; $^{*}p$ <0.05, versus DIO obese group (Dunnett test); $^{\#\#}p$ <0.01, versus control lean group (Student *t* test).

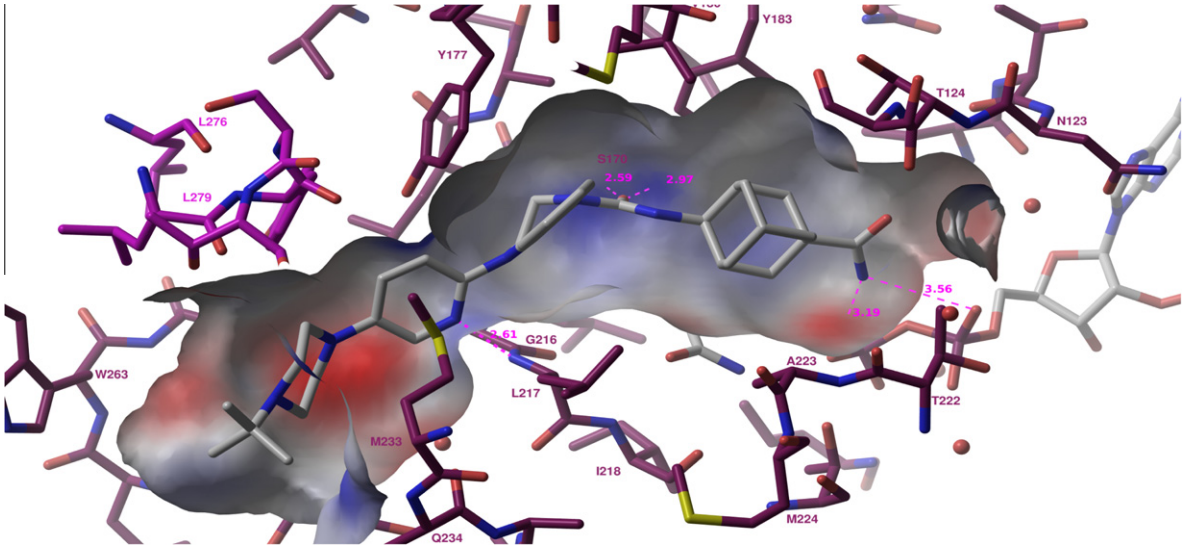


Figure 3. Crystal structure of human 11β-HSD1 in complex with compound **26**.[28]

Table 6
Effect of SAR184841 treatment on metabolic parameters in DIO mice model

Biochemical parameters	Plasma glucose (mg/dL)	Plasma insulin (ng/mL)	Plasma leptin (ng/mL)	Plasma triglycerides (mg/mL)	Plasma cholesterol (mg/dL)	Liver triglycerides (mg/g)
Control lean vehicle	226 ± 7	0.6 ± 0.1	1.0 ± 0.4	27.1 ± 1.3	82.7 ± 3.9	10.6 ± 0.9
DIO obese vehicle	297 ± 15##	3.6 ± 0.2##	22.5 ± 2.4##	36.2 ± 2.1##	154.3 ± 8.6##	210.5 ± 15.4##
SAR184841, 1 mg/kg	263 ± 9	2.8 ± 0.4	14.9 ± 1.4**	33.8 ± 2.9	127.7 ± 5.8*	167.4 ± 15.0
SAR184841, 3 mg/kg	251 ± 19	2.3 ± 0.4*	12.5 ± 0.8**	38.4 ± 1.9	125.1 ± 7.1*	142.8 ± 26.7
SAR184841, 10 mg/kg	224.6 ± 10*	1.9 ± 0.2**	12.5 ± 1.2**	35.0 ± 1.8	123.6 ± 6.4*	129.1 ± 19.4*

* p <0.05, versus DIO obese group (Dunnett test).
** p <0.01, versus DIO obese group (Dunnett test).
p <0.01, versus control lean group (Student test).

We obtained a crystal structure of SAR184841 in complex with human 11β-HSD1 (PDB Code 4HX5). Figure 3 shows a view of SAR184841 bound in the active site.

The inhibitor binds with its central amide carbonyl group to the hydroxyl side chains of the key residues Tyr183 and Ser170 responsible for substrate ketone reduction. The adamantyl amide binds in the upper binding pocket formed by the protein stretches Ile121-Leu126 and Thr222-Val227, the Tyr183 side chain and the nicotine amide end of the co-factor NADP(H). The terminal amide group forms hydrogen bonds to the oxygen atom at the pyrophosphate of the co-factor and a water-mediated hydrogen bond to the main chain nitrogen of Thr124. The tetrahydroquinoxaline points toward the solvent access channel. In the monomers with completely resolved ligand the attached pyridyl-piperazine points stick-like into this channel. The pyridyl nitrogen forms a hydrogen bond to the main chain nitrogen of Leu217. We did not observe well defined contacts of the terminal *t*-butylpiperazine to the protein, because the C-terminus of the adjacent monomer forming part of the solvent access channel is not well resolved in these monomers. Residues of mouse 11β-HSD1 with differences in sequence to the human enzyme are not in direct contact with the inhibitor or are located in regions that are typically highly flexible. We postulate that the mixed human/rodent activity can be explained by minor protein adaptations accommodating the ligand.

Further profiling of SAR184841 revealed that the properties of this compound made it suitable for preclinical development. As seen in Table 4, SAR184841 exhibited about 1000-fold selectivity for 11β-HSD1 versus human 11β-HSD2 and presented an IC_{50} over 10 μM for the h-Erg channel. The compound was inactive (IC_{50} >50 μM) in Cyp 3A4 inhibition assays either in a competitive or a non competitive manner. No Cyp inductions were observed and the selectivity profile versus a panel of 120 receptors and enzymes (including glucocorticoid and mineralocorticoid receptors) was excellent.[29] SAR184841 has a low in vitro metabolic clearance in human hepatocytes and was also found negative in an in vitro teratogenicity assay (Fetax) and mutagenicity assay (AmesII).

The pharmacokinetic profile of SAR184841 in rat is presented in Table 5. The compound is characterized by extensive plasma clearance, a very large volume of distribution, a long apparent terminal half-life value and an acceptable oral bioavailability.

The potent and long-lasting effect of SAR184841 was demonstrated in a pharmacodynamic study in mice over 24 h after single oral administration. A 3 mg/kg dosage inhibited over 90% of 11β-HSD1 activity in both liver and fat until 7 h post-dosing, and then 60% of enzyme activity in the liver and 40% of enzyme activity in fat up to 24 h after administration (not shown). The in vivo efficacy of SAR184841 was then investigated in a diet induced obese (DIO) mice model.[30] When administered once daily for 4 weeks at 1, 3 or 10 mg/kg/day, SAR184841 improved several key metabolic parameters monitored in the study (Table 6). Notably, dose-dependent reductions of plasma glucose and plasma insulin were observed. These effects were associated with an improvement of glucose tolerance measured after 3 weeks (Fig. 4, significant decrease of −23% in OGTT AUC at 10 mg/kg). Plasma leptin, and plasma cholesterol were also significantly decreased by SAR184841 at all doses. Liver triglyceride levels, but not plasma triglycerides, were significantly reduced at 10 mg/kg. Whatever the dose, SAR148841 had neither an effect on food intake, nor on body weight of the DIO animals. Plasma levels of SAR18484 at the end of the study (about 22 h after the last administration) were quite low (0 ± 0, 3.8 ± 9.3, and 2.6 ± 1.8 nM, respectively, for dose 1, 3 and 10 mg/kg), reflecting the good clearance of the compound in the body, even after a month-treatment. Finally, liver function biomarkers were not altered by any of the treatment doses after 4-weeks treatment, and HPA axis biomarkers (corticosterone) were not modified by SAR184841 treatment (data not shown).

In conclusion, we found in our series that a substituted adamantyl group is a good bioisoster for a pyrolidine pyrazole moiety, and thus avoids Cyp 3A4 inhibition. Replacement of a pyrimidine ring by a pyridine and introduction of a piperazine group led to increased activity in the ex vivo assay. Finally, fine modulation of piperazine and adamantyl substitution resulted in the discovery of SAR184841. This compound is a potent human/rodent mixed inhibitor of 11β-HSD1, with long lasting activity in target tissues. It showed an improvement of key metabolic endpoints in a physiopathological mouse model of obesity and diabetes after 4 weeks of oral treatment. On the basis of its overall profile, SAR184841 was selected as candidate for clinical development. Further details of these investigations will be reported in due course.

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29. Receptor binding assays performed by Cerep (www.cerep.com).
30. C57Bl/6J mice, 20 week-old, fed a high-fat/high-fructose diet, were treated po with SAR184841 (1, 3 or 10 mg/kg/day in methylcellulose-tween 80 vehicle) during 4 weeks; n = 9–10 animals per group.