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1,1-Dioxo-5,6-dihydro-[4,1,2]oxathiazines, a novel class of 11ß-HSD1 inhibitors for the treatment of diabetes

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ABSTRACT

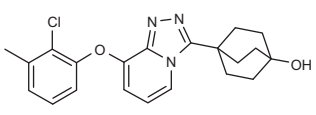
Racemic *cis*-1,1-dioxo-5,6-dihydro-[4,1,2]oxathiazine derivative **4a** was isolated as an impurity in a sample of a hit from a HTS campaign on 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1). After separation by chiral chromatography the **4a**-*S*, **8a**-*R* enantiomer of compound **4a** was identified as the true, potent enzyme inhibitor. The cocrystal structure of **4a** with human and murine 11ß-HSD1 revealed the unique binding mode of the oxathiazine series. SAR elucidation and optimization in regard to metabolic stability led to monocyclic tetramethyloxathiazines as exemplified by compound **21g**.

The enzyme 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1) is highly expressed in human liver and adipose tissue and uses NADPH as cofactor for the intracellular conversion of cortisone to the biologically active cortisol.[1] Cortisol is a key regulator of metabolic processes by modulating tissue-specific gene expression through activation of the glucocorticoid receptor. In the liver, cortisol induces the expression of genes responsible for gluconeogenesis and glycogenolysis resulting in an increased hepatic glucose output. Promotion of preadipocyte differentiation to mature adipocytes by cortisol causes hyperplasia of the adipose tissue.[2] Thus, selective inhibition of this enzyme offers the potential as a novel treatment for type 2 diabetes and hyperlipidemia by controlling the local tissue-specific cortisone/cortisol levels.

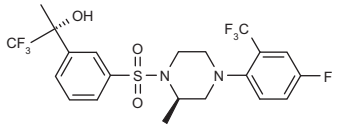
Many pharmaceutical companies are engaged in the search for orally available 11β-HSD1 inhibitors for the treatment of type 2 diabetes.[3a–f] Most of the published structures of 11β-HSD1 inhibitor classes feature a moiety with an H-bond acceptor functionality (acids,[4a] amides,[4b–f] lactams,[4g,h] ureas[4i] and carbamates[4j]) flanked by bulky lipophilic residues such as adamantyl or bicyclooctanyl residues. The carbonyl function in these compounds occupies the position of the reducible ketofunction of the substrate cortisone and is involved in a similar hydrogen bonding network in the active site as shown by several X-ray structures with the human 11β-HSD1.[3f,4c–f,5a,b,7a,b]

The sp^2-nitrogen of inhibitors with heteroaromatic groups such as pyridine[5c,d] or triazole[5e] can also take on this role. Depending on their substitution pattern, 2-aminothiazolones[5f,g] exhibit alternative binding modes in the active site due to tautomerism.

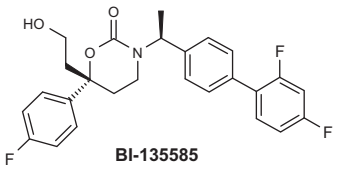
Several compounds (BMS-770767,[6a] HSD-016,[6b] BI-135585,[4j] BMS-816336, LY2523199, RG-4929) have been reported to have been evaluated in Phase I and II clinical trials for their ability to reduce glucose levels and HbA1c in diabetic patients. The published structures of the clinical candidates are shown below



BMS-770767



HSD-016



BI-135585

In our endeavour to find new oral treatments for type 2 diabetes, we recently reported the identification of a new class of potent and selective inhibitors of 11β-HSD1 (pyrrolidine-pyrazole ureas

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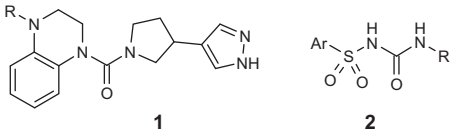
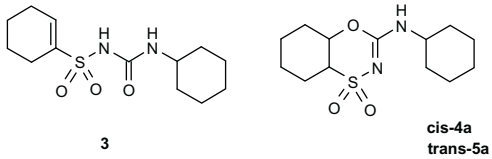
1) and their subsequent optimization in regard to ADME profile and ex vivo activity in target tissues.[7a,b]

A second series was found from the high-throughput screening campaign on 11β-HSD1. This series originated from former synthetic efforts in the area of KATP-blocking sulfonylureas, which are now well-established antidiabetic drugs.[8] The sulfonylureas of the general structure **2** had only weak blocking activities of the KATP channel (IC_{50} >1 μM).



1 **2**

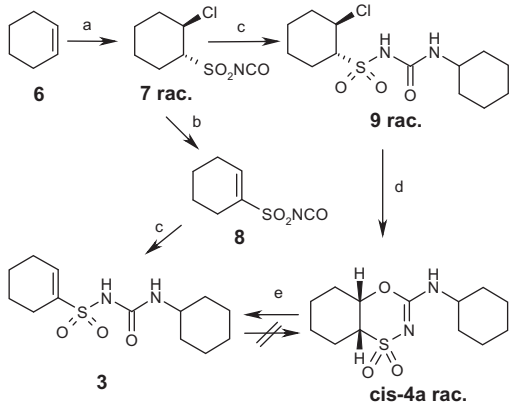
During evaluation of this hit series, the sulfonylurea **3** was more active (IC_{50} = 117 nM) than the corresponding cyclohexyl or phenyl compound in the screening assay with human 11ß-HSD1. The activity was measured from a DMSO stock solution from the compound library. Purity check of the original, solid batch showed that the sample had only a purity of 65%. After purification by column chromatography the pure compound **3** inhibited human 11β-HSD1 with an IC_{50} of only 2.2 μM.



3 cis-4a trans-5a

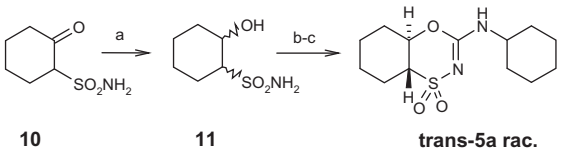
We started a hunt for the 'highly active impurity' which often has been a frustrating activity in drug discovery. However, in this case the original batch was found to contain a sufficient amount of a defined, stable compound. It had the same molecular weight as the sulfonylurea **3** and was separable from **3** by column chromatography. To our delight, the isolated compound had an IC_{50} of 31 nM against human 11β-HSD1, which explained the screening result with the original impure batch of **3**. NMR-studies indicated that the molecule contained no double bond, but had the bicyclic structure **4a** with an oxathiazine scaffold and a *cis*-ring conjunction. For an unequivocal proof of structure we prepared the *cis*- and *trans*-isomers **4a** and **5a** in racemic form by independent routes.

Chlorosulfonylisocyanate, discovered at Hoechst AG in Frankfurt in the mid fifties, has a fascinating chemistry.[9] It adds to olefins to give β-lactams after hydrolysis. However, in the presence of radical initiators such as AIBN, the reaction with olefins, for example cyclohexene, yields 2-chloroalkylsulfonylisocyanates such as **7**. Vinylsulfonylisocyanate **8**, obtained by elimination of HCl with a tertiary amine, reacts with primary amines to yield the corresponding sulfonylureas such as **3**[10] (Scheme 1). On the other hand, we were able to add first cyclohexylamine to the sulfonylisocyanate **7** and then realized an intramolecular cyclisation under basic conditions to racemic **4a**. However, only a low yield was obtained due to the characteristics of consecutive reactions (**9** to **4a** to **3**). High temperature was necessary to initiate the cyclisation of **9** to **4a**. The progress of the reaction could be followed by the formation of a precipitate of compound **4a**. But then subsequent elimination to the more soluble **3** occured. Longer reaction times led to the complete degradation of the desired product **4a** to the compound **3**. The route explains also the observation that the *cis*-isomer **4a** was obtained as single isomer due to a *trans*-addition in the radical step and a S_N2-mechanism in the cyclisation step. On the other hand, we were not able to convert **3** back to **4a** under various conditions. For the synthesis of the *trans*-isomer, racemic 2-oxo-cyclohexyl-



6 **7 rac.** **9 rac.** **8** **3** **cis-4a rac.**

Scheme 1. Synthesis of racemic oxathiazine *cis*-**4a**. Reagents and conditions: (a) $ClSO_2NCO$, AIBN, CCl_4, 85 °C, 6 h, 70–90% (crude); (b) tributylamine, benzene, 40 °C; (c) cyclohexylamine, diisopropylethylamine, CH_2Cl_2, 0 °C, 1 h; 51%; (d) NaOH, dioxane, 100 °C, ~1 h, 10% (precipitate); (e) NaOH, dioxane, 100 °C, ~1 h (dissolution of precipitate).



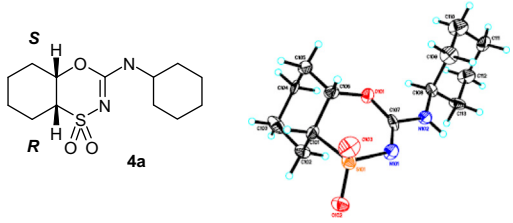
10 **11** **trans-5a rac.**

Scheme 2. Synthesis of racemic oxathiazine *trans*-**5a**. Reagents and conditions: (a) BH_3 Me_2S, THF, quant; (b) KOtBu, NMP, rt; then cyclohexylisothiocyanate, 10 min; (c) NBS, rt, 2 h, separation of *cis*- and *trans*-diastereomers, 50% (from **11**).

sulfonamide[11] **10** was reduced to a mixture of diastereomers **11** (*trans*/*cis*-ratio: 63/37). Addition of cyclohexylisothiocyanate and subsequent cyclisation by *N*-bromosuccinimide gave the pure, racemic trans-isomer **5a** after purification (Scheme 2).

Next, we separated the two diastereomeric pairs by chiral chromatography, one *cis*-diastereomer was much more active than the other diastereomers (Table 1).

We determined the absolute configuration (**4a**-*S*, **8a**-*R*) of the most active *cis*-enantiomer **4a** by X-ray crystallography.



4a

For crystallization studies with the human and mouse 11ß-HSD1 enzyme we used the racemic mixture of **4a**. The structures were solved at a resolution of 1.96 Å (R-factor 16.8%, R-free 20.3%) for the human enzyme and 2.21 Å (R-factor 16.7%, R-free 21.0%) for

Table 1
Activity of pure diastereomers

Diastereomer	IC_{50} (μM)		
	Human	Mouse	Rat
A/*cis*-**4a**	0.024	0.328	0.246
B/*cis*-**4a**	0.575		
C/*trans*-**5a**	0.197	0.572	1.140
D/*trans*-**5a**	0.655		

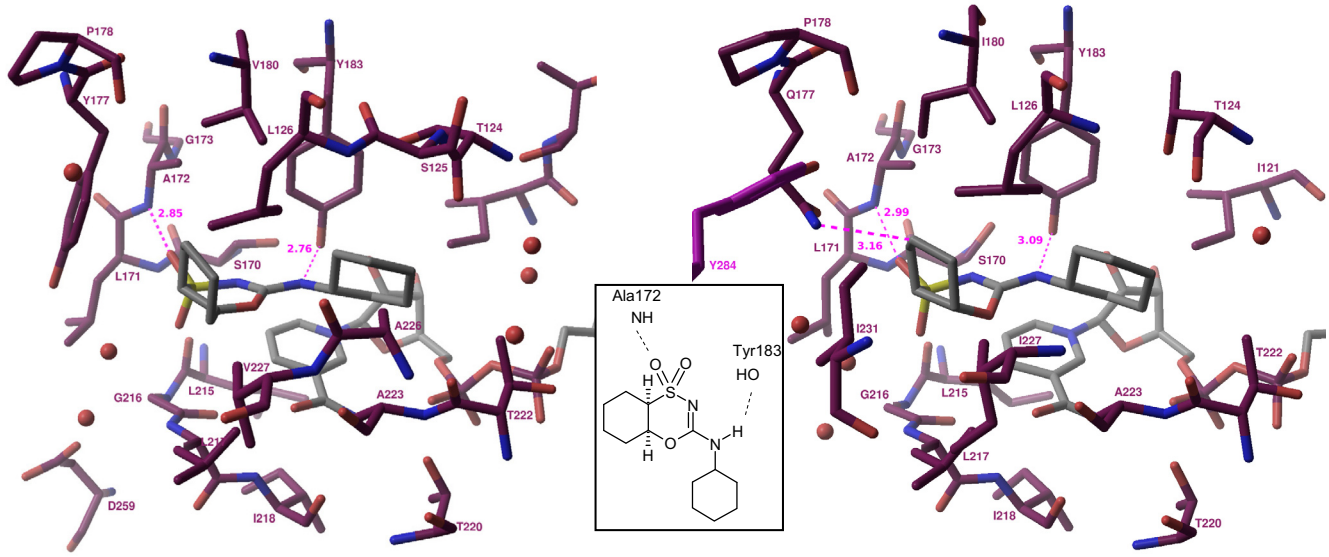
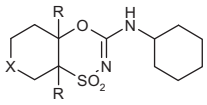


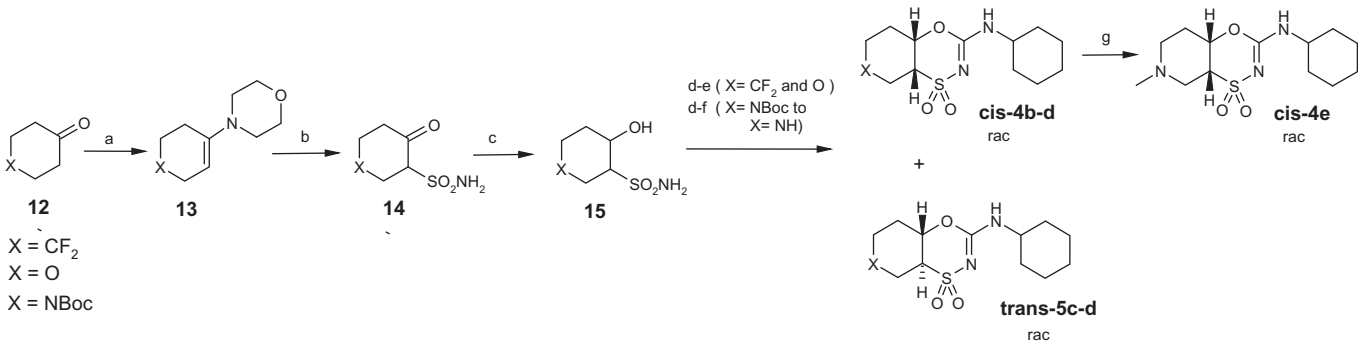
Figure 1. Active site of human (**1a**) and murine (**1b**) 11ß-HSD1 in complex with ligand **4a**.

Table 2
SAR around racemic **4** and **5**



Compd	X	R	Human IC_{50} (μM)
cis-**4a**	CH_2	H	0.031
cis-**4b**	CF_2	H	0.234
cis-**4c**	O	H	1.220
trans-**5c**	O	H	0.799
cis-**4d**	NH	H	>2.250
trans-**5d**	NH	H	>2.250
cis-**4e**	NMe	H	>2.250
cis-**16**	CH_2	Me	0.018

the murine enzyme. The compound is unambiguously defined in both cases. In the crystal structure we found exclusively the **4a**-*S*, **8a**-*R* enantiomer of compound **4a** bound to the steroid binding site of 11β-HSD1 (Fig. 1a and b). Compound **4a** binds in an identical fashion to the steroid binding site of the human and the murine enzyme. The cyclohexyl-NH interacts with the key active site residue Tyr183 involved in substrate ketone reduction. The second active site residue, Ser170, is not directly interacting with the inhibitor. One of the sulfonyl oxygen atoms forms an anchoring hydrogen bond to the main chain nitrogen of Ala172, the second sulfonyl oxygen forms a water-mediated hydrogen bond to the protein. The cyclohexylamine ring is in chair conformation and points into a buried, water-filled pocket formed by the cofactor NADPH and the protein stretches Ile121-Thr126 and Thr222-Val227. The fairly small cyclohexyl moiety does not completely fill the buried pocket, indicating the possibility to include bulkier or bridged ring systems in this position. The bicyclic oxathiazine ring is oriented towards a solvent access channel to the binding pocket, offering a possibility to extend the compound into this water-filled channel. Only the **4a**-*S*, **8a**-*R* enantiomer of compound **4a** can bind in this particular binding mode to 11β-HSD1. Without adjustment of the binding mode or surrounding protein residues the second *cis*-enantiomer and the *trans*-isomers clash with the protein. The annellated cyclohexyl moiety points towards residue 177. This residue is one of the main differences between human and murine 11β-HSD1, featuring a tyrosine side chain in the human enzyme and a glutamine in the murine enzyme. For Tyr177 of human 11β-HSD1 we observe electron density for two alternate tyrosine side chain conformations within the same crystal structure, indicating a certain flexibility of the human enzyme in this region. The side chain is in a typical van-der-Waals distance to the inhibitor. In contrast, Gln177 in



Scheme 3. Synthesis of oxathiazines **4b–e** and **5c–d**. Reagents and conditions: (a) morpholine, toluene, reflux, 5 h, 91–100%; (b) $ClSO_2NH_2$, diisopropylethylamine, THF, −40 °C to rt, 16–81%; (c) $NaBH_4$, MeOH, 42–64%; (d) KOtBu, DMF or NMP, rt, 5 min; then cyclohexylisothiocyanate, 5 min; (e) NBS, rt, 5 min; separation of diastereomers, 12–36% (from **15**); (f) TFA, CH_2Cl_2, rt, 15 min, quant.; (g) paraformaldehyde, $Na(CN)BH_3$, AcOH, THF, rt, 16 h, 59%.

the murine 11β-HSD1 is found in a clearly defined single conformation. This conformation places the glutamine side chain considerably closer to the inhibitor. The suboptimal distance between ligand and protein at this position is contributing to the 40-fold lower in vitro activity on the murine enyzme.

A concern with the oxathiazine core structure was the chemical stability as well as the stability in plasma. However, under acidic and neutral conditions compound **4a** was stable. Studies in plasma with compound **4a** also showed no significant degradation of compound **4a**.

To assess the ability of our compounds for inhibition of 11β-HSD1 in target tissues, especially liver and adipose tissue, we established a pharmacodynamic assay.[7a,7b] Our goal was to increase human and rodent activity and obtain sufficient metabolic stability for in vivo studies.

Firstly, we carried out some modifications in the annellated cyclohexyl ring of the oxathiazine core structure (Table 2). Introduction of heteroatoms (O, N) or a CF_2 group in position **7** of the oxathiazine core (X = CF_2, O, N, NMe; compounds **4b**–**e** and **5b**–**d**), using the chemistry developed for the *trans*-isomer (Scheme 3), led to considerable loss of activity. However, replacing the hydrogens at the bridging carbons by methyl groups (compound **16**, synthesis in Scheme 4) is possible with slight improvement of the activity on the human 11β-HSD1.

For rapid SAR evaluation in regard to the cycloalkylamine part, the racemic *cis*-derivatives **4f**–**w** were obtained by the same route as described in Scheme 1 despite moderate yields (Table 3). Increasing the ring size from five to eight led to an improvement of activity against the human and rodent 11β-HSD1, but also to an increase in metabolic lability. Thus, we prepared compounds with monocyclic (4-dimethylcyclohexyl, 3,3,5,5-tetramethylcyclohexyl), bicyclic (bicyclo[3.3.0]- or bicyclo[2.2.2]octanyl) and tricyclic (adamantyl, noradamantyl) ring systems, but the most potent and lipophilic ones such as **4l**, **4q**, **4t** or **4w** showed high metabolic lability.

Attempts to block potential metabolic hot spots by a hydroxyl group at these positions improved metabolic stability, but led to considerable loss of activity against human and rodent enzymes, for example in the case of the bicyclo[2.2.2]octanyl derivative **4s**.

Aniline could not replace the cyclohexylamine moiety (compound **4m**), however, the corresponding benzylamine derivative **4o** or cyclohexylmethylamine derivative **4n** showed only a three to fourfold drop in activity compared to **4a**.

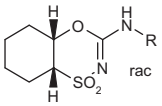
In order to improve metabolic stability, we introduced polar side chains at the alpha-position of the benzyl amine (Table 4). Two methyl groups (**4x**) at the benzylic position diminished the activity against 11β-HSD1, however oxathiazines with chiral amino alcohols showed an increase in activity. A clear SAR was seen for the carbon chain length 1 < 2 > 3 (**17b**, **d**, and **e**) as well as for the chirality at the benzylic center (**17a**–**d**). Compounds with other polar moieties such as an amino (**17f**) or amide residues (**17g**–**h**) were less active. However, metabolic stability was still not satisfactory for the most active **17d**. Metabolite studies with this compound showed that only one metabolite is formed by oxidation of the annellated cyclohexyl ring (data not shown).

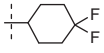
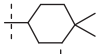
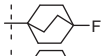
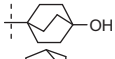
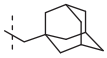
Compound *cis*-**16** (Table 2) with two additional methyl groups at the ring conjunction was quite potent. We wondered if we could remove the annellated cyclohexyl ring. Thus, we synthesized monocyclic tetramethyloxathiazines **21a**–**h** (Scheme 4) reducing the number of stereogenic centers. We used the rich chemistry of chlorosulfonylisocyanate and its derivatives such as **18a**–**b**. Treatment of *N*-chlorosulfonylcarbamates **18a**–**b** with sodium hydride in the presence of olefins[13] such as 1,2-dimethylcyclohexene or 2,3-dimethylbutene gave the corresponding 1,4-cycloadducts **19** or **20a**–**b**, albeit in low yields. Reaction of these cycloadducts with the appropriate amines led to **16** and **21a**–**g**. Treatment of the similarly obtained ester **22** with excess Grignard reagent gave the alcohol **21h**.

We also prepared spiro-oxathiazines **26a**–**d** as depicted in Scheme 5. Deprotonation of the Boc-protected cyclopropylsulfonamide **23**,[14] addition of the appropriate ketone or aldehyde and subsequent removal of the Boc-protecting group gave the ß-hydroxy sulfonamides **24a**–**d**. Addition of cyclohexylisothiocyanate and cyclisation with *N*-bromo-succinimide led to the spiro-oxathiazines **26a**–**d**.

The tetramethyloxathiazine **21a** was more potent than the spiro-oxathiazines **26** against human 11β-HSD1 enyzme (Table 5). The SAR for the corresponding *N*-benzyl-derivatives **21b**–**h** is shown in Table 6. Potency against human 11β-HSD1 is in the range of 4–15 nM, whereas the compounds were less active against the murine enzyme (26–452 nM). Compound **21e** with a chloro-substituent in 2-position showed high activity against

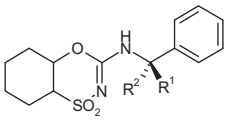
Table 3
SAR of racemic *cis*-oxathiazines **4f**–**w**; variation of ring



Compd	R	IC50 (μM)		Metabolic lability[12] (%)	
		Human	Mouse	Human	Mouse
4f		0.425			
4a		0.031	1.220	18	19
4g		0.022	0.087	45	54
4h		0.013	0.031	79	84
4i		0.671			
4j		0.406			
4k		0.064	0.455	55	55
4l		0.011	0.057	93	97
4m		0.675			
4n		0.080	0.729		
4o[a]		0.104	0.786		
4p		0.008	0.047		
4q[a]		0.016	0.275	94	87
4r		0.024	0.454		
4s		0.065	0.695	12	20
4t[a]		0.004	0.040	91	98
4u		0.063	0.400		
4v		0.027	0.076		
4w		0.004	0.009	83	65

[a] More active enantiomer.

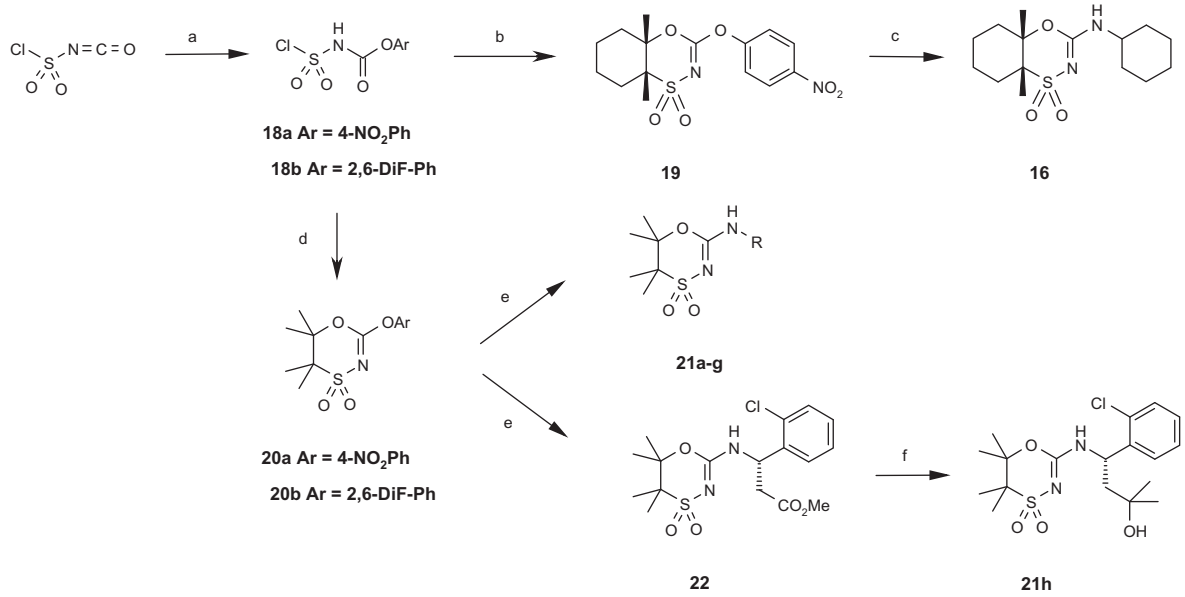
Table 4
SAR of *N*-benzyl-oxathiazines (diastereomeric mixtures of *cis*-oxathiazines)



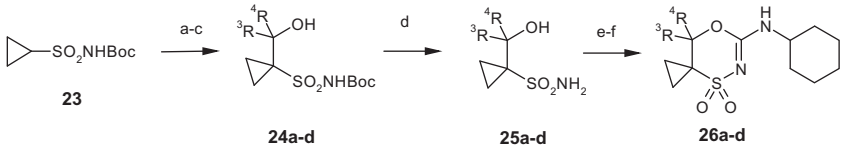
Compd	R^1	R^2	IC_{50} (μM)		Metabolic lability[12] (%)	
			Human	Mouse	Human	Mouse
4o	H	H	0.104	0.786		
4x	Me	Me	0.215	0.444		
17a	$-CH_2OH$	H	>2.250			
17b	H	CH_2OH	0.050	0.152		
17c	$-(CH_2)_2OH$	H	1.480			
17d	H	$-(CH_2)_2OH$	0.011	0.016	77	41
17e	H	$-(CH_2)_3OH$	0.038	0.294	89	78
17f	H	$-(CH_2)_2NH_2$	1.580			
17g	H	$-CH_2CONH_2$	0.334		47	35
17h	H	$-CH_2CONHMe$	0.652			

human and murine enzymes, but lacked metabolic stability in murine microsomes. Compound **21g** with a 4-fluoro-substituent showed good metabolic stability and high potency against human 11β-HSD1, but was considerably less active against the murine enzyme.

In conclusion, the starting point for a new class of 11β-HSD1 inhibitors was found as an impurity in a hit sample from a HTS campaign on this enzyme. 1,1-Dioxo-5,6-dihydro-[4,1,2]oxa-thiazine derivative 4a was isolated as racemate from the original sample and its structure proven by an independent synthesis. After separation by chiral chromatography the (**4a**-*S*, **8a**-*R*)-enantiomer of **4a** was identified as the true, potent enzyme inhibitor of 11β-HSD1. Co-crystal structures with human and murine enzyme revealed the unique binding mode of the oxathiazine series. Potency could be improved by introduction of bulky bi- and tricycles, however the resulting compounds displayed low metabolic stability. Modifications around the oxathiazine core structure led to potent and metabolically stable tetramethyloxathiazines as illustrated

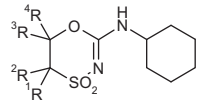


Scheme 4. Synthesis of oxathiazines **16** and **21a–h**. Reagents and conditions: (a) ArOH, CH_2Cl_2, rt, 1.5 h, quant (crude); (b) NaH, THF, −78 °C, then 1,2-dimethylcyclohexene, −78 °C to 35 °C, 30 min, 10%; (c) cyclohexylamine, diisopropylethylamine, CH_2Cl_2, rt, 17%; (d) NaH, THF, −78 °C, then 2,3-dimethylbutene, −78 °C to 35 °C, 30 min, 16–24%; (e) R-NH_2, diisopropylethylamine, CH_2Cl_2, rt, 23–81%; (f) MeMgBr, THF, 18%.



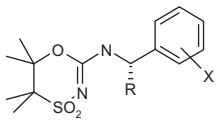
Scheme 5. Synthesis of spiro-oxathiazines **26a–d**. Reagents and conditions: (a) 2 equiv BuLi, THF, −78 °C; (b) R^3-(C=O)-R^4, −78 °C to rt; (c) NH_4Cl, 33–39% (from 23); (d) 1 N HCl, EtOAc, 70 °C, 10 h, 73–83%; (e) KOtBu, NMP, rt, 5 min; then cyclohexylisothiocyanate, 10 min; (f) NBS, rt, 1 h, 13–39% (from **25**).

Table 5
SAR of tetramethyloxathiazine **21a** and spiro-oxathiazines **26a–d**



Compd	R^1, R^2	R^3, R^4	IC_{50} (μM)		Metabolic lability[12] (%)	
			Human	Mouse	Human	Mouse
21a	Me, Me	Me, Me	0.018	0.865	5	9
26a	$-(CH_2)_2-$	Me, Me	0.028	1.620		
26b	$-(CH_2)_2-$	$-(CH_2)_3-$	0.082	0.813		
26c	$-(CH_2)_2-$	$-CH_2-O-CH_2-$	0.139			
26d	$-(CH_2)_2-$	Et, H	0.177	2.510		

Table 6
SAR of tetramethyloxathiazines **21b–h**



Compd	R	X	IC_{50} (μM)		Metabolic lability[12] (%)	
			Human	Mouse	Human	Mouse
21b	Me	H	0.015	0.286		
21c	Me	2-Cl	0.004	0.029		
21d	$-(CH_2)_2OH$	H	0.007	0.232	4	11
21e	$-(CH_2)_2OH$	2-Cl	0.004	0.026	25	52
21f	$-(CH_2)_2OH$	3-CN	0.006	0.110		
21g	$-(CH_2)_2OH$	4-F	0.007	0.199	2	9
21h	$-CH_2-CMe_2OH$	2-Cl	0.010	0.452		

by compound **21g**. Further optimization of this new class of 11β-HSD1 inhibitors will be the subject of upcoming papers.

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