

Optimization of Hydroxybenzothiazoles as Novel Potent and Selective Inhibitors of 17 β -HSD1

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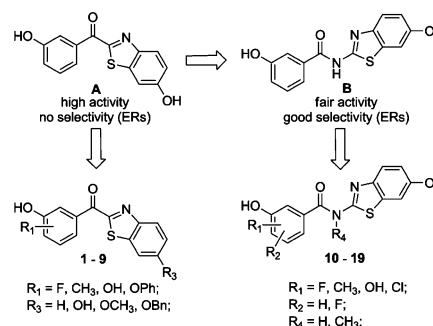
S Supporting Information

ABSTRACT: 17 β -HSD1 is a novel target for the treatment of estrogen-dependent diseases, as it catalyzes intracellular estradiol formation. Starting from two recently described compounds, highly active and selective inhibitors were developed. Benzoyl **6** and benzamide **17** are the most selective compounds toward 17 β -HSD2 described so far. They also showed a promising profile regarding activity in T47-D cells, selectivity toward ER α and ER β , inhibition of hepatic CYP enzymes, metabolic stability, and inhibition of marmoset 17 β -HSD1 and 17 β -HSD2.

INTRODUCTION

For the treatment of steroid hormone-dependent diseases biosynthesis inhibitors blocking hormone formation in the corresponding endocrine gland provide an excellent strategy as demonstrated by the use of CYP19 inhibitors for the treatment of breast cancer (BC).¹ Three further cytochrome P450 (CYP) enzymes are presently in the focus of drug development: CYP17,² CYP11B2,³ and CYP11B1⁴ for the treatment of prostate cancer, congestive heart failure and myocardial fibrosis, and Cushing's syndrome, respectively. As these therapeutic options result in systemic reductions of steroid hormone levels that often are associated with side effects, a softer option could be the inhibition of hormone activation in the diseased cell. For the treatment of benign prostatic hyperplasia, this strategy has already been proven to be successful with inhibitors of 5 α -reductase.⁵ More recently 17 β -hydroxysteroid dehydrogenase 1 (17 β -HSD1) came into the focus of interest as a novel therapeutic target for the treatment of estrogen dependent diseases like BC and endometriosis.⁶ 17 β -HSD1 catalyzes the conversion of the weakly active estrone (E1) to the highly active estradiol (E2) and is overexpressed in some BC tissues.⁶ Efficacy of 17 β -HSD1 inhibitors against human breast cancer cell lines has already been reported in vitro and in nude mice.⁷ Besides some approaches to develop steroidal inhibitors,⁸ there have also been attempts by us and other groups to develop nonsteroidal inhibitors that should be advantageous with respect to side effects.⁹ Recently we reported on two new 17 β -HSD1 inhibitors with different activity/selectivity profiles, the 1,3-benzothiazol-2-ylphenylmethanone **A** and the *N*-(1,3-benzothiazol-2-yl)benzamide **B** (Chart 1).¹⁰ Here we report on the structure optimization of these two lead compounds with regard to 17 β -HSD1 inhibitory activity and selectivity toward 17 β -HSD2 (the enzyme catalyzing the reverse reaction) and the estrogen receptors (ERs) α and β . For selected compounds, 17 β -HSD1 inhibition in human T47-D breast cancer cells, inhibition of 17 β -HSD1 and 17 β -HSD2 from *Callithrix jacchus* (marmoset, animal model for endometriosis¹¹), of human hepatic CYP enzymes, and metabolic stability were determined.

Chart 1. Compounds A and B and Synthesized Compounds

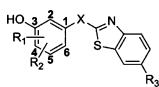


RESULTS

Chemistry. The synthesis of **1–9** started from 1,3-benzothiazol-2-ylamine or 1,3-benzothiazole. **1–3** and **5–7** were prepared in a four-step synthesis previously described¹⁰ (steps a–d in Scheme 1). **4** was synthesized in three steps starting with the nucleophilic addition of **4iii** to 4-fluoro-3-methoxybenzaldehyde. For **8**, **8iiii** and **8iii** were synthesized and coupled via nucleophilic addition. Oxidation of the resulting alcohol and ether cleavage of the silanyl ether using tetra-*n*-butylammonium fluoride (TBAF) gave the final compound. **9** was synthesized by coupling **1iii** and **9iiii**, followed by oxidation, cleavage with TBAF, boronic acid–phenol cross-coupling reaction mediated by copper(II) acetate, and cleavage of the two methoxy groups with boron tribromide (BBr₃). **10–18** were prepared via two steps as described¹⁰ (steps a and b in Scheme 2): (a) amide coupling between 6-methoxy-1,3-benzothiazol-2-ylamine and the corresponding benzoyl chloride and (b) ether cleavage. **19** was synthesized by *N*-methylation of **11i** with methyl iodide and sodium hydride in DMF and subsequent ether cleavage.

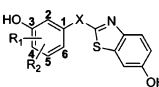
Received: August 18, 2011

Published: January 26, 2012

Table 1. 17 β -HSD1 Inhibitory Activities and Selectivities of Compounds 1–19


compd	X	R ₁	R ₂	R ₃	IC ₅₀ (nM) ^{e,f}		SF ^{d,f}
					HSD1 ^a	HSD2 ^b	
A	CO	H	H	OH	44	1035	24
1		2-F	H	OH	5	83	17
2		4-F	H	OH	13	121	9
3		4-F	H	OCH ₃	38	59	2
4		4-F	H	H	136	104	1
5		6-F	H	OH	13	1416	109
6		4-CH ₃	H	OH	27	4003	148
7		6-OH	H	OH	78	1538	20
8		4-CH ₃	H	OBn	ni	ni	nd
9		4-OPh	H	OH	863	1457	2
B	CONH	H	H	OH	243	9264	38
10		2-F	H	OH	29	1224	42
11		4-F	H	OH	171	1480	9
12		6-F	H	OH	112	3804	34
13		4-CH ₃	H	OH	ni	nd	nd
14		5-OH	H	OH	3000 ^e	nd	nd
15		6-OH	H	OH	ni	nd	nd
16		2-Cl	6-F	OH	221	469	2
17		2-F	6-F	OH	13	1774	136
18		2-F	4-F	OH	99	541	5
19	CONCH ₃	4-F	H	OH	667 ^e	2704 ^e	4

^aHuman placenta, cytosolic fraction, substrate [³H]E1 + E1 [500 nM], cofactor NADH [500 μM]. ^bHuman placenta, microsomal fraction, substrate [³H]E2 + E2 [500 nM], cofactor NAD⁺ [1500 μM]. ^cMean values of three determinations, standard deviation less than 10%. ^dSelectivity factor: IC₅₀(17 β -HSD2)/IC₅₀(17 β -HSD1). ^eCalculated with LOGIT transformation. ^fnd: not determined. ni: no inhibition (less than 10% inhibition at 1 μM).

Table 2. Binding Affinities for the ER α and ER β , 17 β -HSD1 Inhibitory Activity in T47-D Cells, and Inhibition of *Callithrix jacchus* 17 β -HSD1 and 17 β -HSD2 by Selected Compounds


compd	X	R ₁	R ₂	RBA (%) ^b		IC ₅₀ (nM), ^c T47-D	% inhibition		
				ER α ^a	ER β ^a		calHSD1 ^d		calHSD2, ^e
						5 nM		50 nM	50 nM
A	CO	H	H	<10	<1				
1		2-F	H	0.1	<0.1				
2		4-F	H	<1	<1	11	80		34
5		6-F	H	<0.1	0.1				
6		4-CH ₃	H	<0.1	<0.1	258		83	40
7		6-OH	H	<0.1	<0.1	365 ^f			
B	CONH	H	H	<0.1	<0.1	245			
10		2-F	H	<0.1	<0.1	73 ^g	67		48
12		6-F	H	<0.1	<0.1	152 ^g			
17		2-F	6-F	<0.1	<0.1	37 ^g	87		51

^aHuman recombinant protein, incubation with 10 nM [³H]E2 and inhibitor for 1 h. ^bRBA: relative binding affinity in percent (E2 = 100%), mean value of three determinations, standard deviation less than 10%. ^cMean value of three determinations, standard deviation less than 10%; ^dMarmoset placenta, cytosolic fraction, substrate [³H]E1 + E1 [500 nM], cofactor NADH [500 μM]. ^eMarmoset placenta, microsomal fraction, substrate [³H]E2 + E2 [500 nM], cofactor NAD⁺ [1500 μM]. ^fStandard deviation less than 15%. ^gCalculated with LOGIT transformation at 50 nM inhibitor.

inhibition of 17 β -HSD2 and affinity to the ERs. Thus, **6** shows the highest selectivity toward 17 β -HSD2 described so far (SF = 148). In the amide series introduction of fluorine in the 4-position (**11**) led to a decrease in selectivity toward 17 β -HSD2, as observed for **2** in the ketone series, while introducing a fluorine in the 2-position (**10**) and the 6-position (**12**) did not

alter selectivity. The difluoro-substituted **17** showed the best selectivity in this series toward 17 β -HSD2 and the ERs with values similar to those of **6**. To summarize, we have discovered two highly potent 17 β -HSD1 inhibitors that are the most selective compounds described so far. Compounds **6** and **17** also show very good intracellular activity and high potency

toward the marmoset target enzyme ($IC_{50} < 50$ nM in the case of **6** and $IC_{50} < 5$ nM in the case of **17**). Recently published sequence alignment studies¹³ showed that human and marmoset 17 β -HSD1 share high homology (80% identity and 85% similarity). Interestingly, among the seven human 17 β -HSD1 amino acid residues (S142, N152, Y155, Y218, H221, R258, and E282) described¹⁰ as potential interaction partners of **A** and **B**, only one amino acid variation was observed in the *Callithrix jacchus* enzyme: E282N. Similar binding modes in the marmoset enzyme as described for the two classes in human 17 β -HSD1 can be postulated. In summary **6** and **17** should be suitable candidates that after optimization could be evaluated in a marmoset model of endometriosis.

EXPERIMENTAL SECTION

Chemistry. General. Chemical names follow IUPAC nomenclature. Starting materials were purchased and used without purification. ¹H and ¹³C NMR spectra were measured on a Bruker AM500 spectrometer (500 MHz), and mass spectra (ESI) were recorded on a MSQ electro mass spectrometer (ThermoFisher). The purity for final compounds was $\geq 95\%$ and was determined by HPLC-MS (see SI).

The following compounds were prepared according to previously described procedures: 6-methoxy-1,3-benzothiazole (**1iii**),¹⁴ 6-hydroxy-1,3-benzothiazole (**8iiii**),¹⁴ [3-(*tert*-butyldimethylsilyloxy)-4-methyl]benzaldehyde (**8iii**),¹⁵ 3-methoxy-4-(*tert*-butyldimethylsilyloxy)benzaldehyde (**9iiii**).¹⁶ Synthetic details and characterization of compounds can be found in SI. Method A involves formation of methanols, method B amide formation, method C oxidation with SIBX, method D ether cleavage with PyHCl, and method E ether cleavage with BBr₃. **6ii**, **17i**, **6i**, **6**, and **17** are presented as examples.

(6-Methoxy-1,3-benzothiazol-2-yl)(4-methyl-3-methoxyphenyl)methanol (6ii). **6ii** was prepared by reaction of 6-methoxy-1,3-benzothiazole (**1iii**) (0.25 g, 1.5 mmol), *n*-BuLi (0.61 mL, 1.5 mmol), and 4-methyl-3-methoxybenzaldehyde (0.18 g, 1.2 mmol) according to method A. The product was purified by CC (hexane/ethyl acetate, 60:40): yield, 89% (0.42 g).

2,6-Difluoro-3-methoxy-N-(6-methoxy-1,3-benzothiazol-2-yl)benzamide (17i). **17i** was prepared by reaction of 6-methoxy-1,3-benzothiazol-2-ylamine (0.3 g, 1.79 mmol) and 2,6-difluoro-3-methoxybenzoyl chloride (0.4 g, 1.79 mmol) according to method B. The product was purified by CC (dichloromethane/methanol, 95:05): yield, 29% (0.18 g).

(4-Methyl-3-methoxyphenyl)(6-methoxy-1,3-benzothiazol-2-yl)methanone (6i). **6i** was prepared by reaction of **6ii** (0.33 g, 1.03 mmol) and 2-iodoxybenzoic acid (0.58 g, 2.06 mmol) according to method C. The product was purified by CC (hexane/ethyl acetate, 85:15): yield, quantitative (0.33 g).

(4-Methyl-3-hydroxyphenyl)(6-hydroxy-1,3-benzothiazol-2-yl)methanone (6). **6** was prepared by reaction of **6i** (0.33 g, 1.05 mmol) and pyridinium hydrochloride (12.13 g, 105 mmol) according to method D. The product was purified by preparative HPLC: yield, 42% (0.12 g). ¹H NMR (CD₃COCD₃): 2.32 (s, 3H), 7.21 (dd, *J* = 8.8 Hz, *J* = 2.4 Hz, 1H), 7.32 (d, *J* = 7.6 Hz, 1H), 7.55 (d, *J* = 2.1 Hz, 1H), 8.02 (d, *J* = 1.5 Hz, 1H), 8.06 (d, *J* = 8.8 Hz, 1H), 8.10 (dd, *J* = 7.6 Hz, *J* = 1.5 Hz, 1H), 8.70 (s, 1H), 9.22 (s, 1H). ¹³C NMR (CD₃COCD₃): 17.1, 107.9, 113.8, 117.7, 117.7, 119.0, 124.3, 127.8, 132.1, 135.5, 140.3, 142.7, 156.7, 159.3, 185.2. MS (ESI): 287.0 (M + H)⁺.

2,6-Difluoro-3-hydroxy-N-(6-hydroxy-1,3-benzothiazol-2-yl)benzamide (17). **17** was prepared by reaction of **17i** (0.18 g, 0.51 mmol) and boron tribromide (5.1 mmol) according to method E. The product was purified by CC (dichloromethane/methanol, 90:10): yield, 30% (0.05 g). ¹H NMR (CD₃SOCD₃): 6.97–7.01 (m, 2H), 7.17–7.22 (m, 1H), 7.41 (d, *J* = 2.5 Hz, 1H), 7.59 (d, *J* = 8.2 Hz, 1H). ¹³C NMR (CD₃SOCD₃): 107.2, 112.2, 112.3, 116.4, 120.6, 120.7, 122.7, 134.4, 142.6, 142.7, 142.7, 142.8, 143.3, 147.9, 147.9, 151.9, 151.9, 155.3, 155.6, 159.8, 167.1. MS (ESI): 323.1 (M + H)⁺.

Biological Methods. See SI.

ASSOCIATED CONTENT

Supporting Information

Synthetic procedures, characterization, and HPLC purities of intermediates and final compounds and all biological assays. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Author Contributions

The manuscript was written with contributions of all authors. All authors have given approval to the final version.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

We thank Mrs. Henn and Ludwig for performing the biological tests, Drs. Zapp and Boettcher for NMR and MS analytics, and Professor Einspanier for supplying marmoset placenta.

ABBREVIATIONS USED

BC, breast cancer; 17 β -HSD1, 17 β -hydroxysteroid dehydrogenase type 1; 17 β -HSD2, 17 β -hydroxysteroid dehydrogenase type 2; E1, estrone; E2, 17 β -estradiol; EDD, estrogen-dependent disease; ER, estrogen receptor; SF, selectivity factor; RBA, relative binding affinity; CC, column chromatography

ADDITIONAL NOTE

For the sake of clarity, IUPAC nomenclature is not strictly followed except for the experimental part where the correct IUPAC names are given.

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