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Antidiabetic activity of *N*-(6-substituted-1,3-benzothiazol-2-yl)benzenesulfonamides☆

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Abstract—*N*-(6-Substituted-1,3-benzothiazol-2-yl)benzenesulfonamide derivatives **1**–**8** were synthesized and evaluated for their in vivo antidiabetic activity in a non-insulin-dependent diabetes mellitus rat model. Several compounds synthesized showed significant lowering of plasma glucose level in this model. As a possible mode of action, the compounds were in vitro evaluated as 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1) inhibitors. The most active compounds (**3** and **4**) were docked into the crystal structure of 11β-HSD1. Docking results indicate potential hydrogen bond interactions with catalytic amino acid residues.

Diabetes mellitus is characterized by chronic hyperglycemia and belongs to a group of metabolic disorders with multiple etiologies. Non-insulin-dependent diabetes mellitus (NIDDM) is very common and may result from insulin resistance, inadequate secretion of insulin, hepatic glucose overproduction or glucose intolerance.[1]

Recent estimates from the year 2000 indicate that there are 171 million people in the world with diabetes and this is projected to increase to 366 million by 2030.[1] Diabetes may eventually cause microvascular damage in key tissues leading to conditions such as retinopathy, nephropathy, and neuropathy. It is associated with reduced life expectancy, significant morbidity due to specific diabetes-related microvascular complications, increased risk of macrovascular complications (ischemic heart disease, stroke, and peripheral vascular disease), and diminished quality of life.[2]

The American Diabetes Association (ADA) has estimated the national cost of diabetes in the USA for 2002 to be US $132 billion, increasing to US $192 billion in 2020.[2]

There is thus a growing need for effective therapies to achieve optimal glycemic control in the management of diabetes. Orally administered antihyperglycemic agents (OHAs) can be used either alone or in combination with other OHAs or insulin.[3] The number of available OHAs has increased significantly in the last decade, however, current therapies to reduce plasma glucose levels have inherent problems including compliance, ineffectiveness, and the occurrence of hypoglycemic episodes. Accordingly, there is a need for more effective, orally administered agents, particularly ones that normalize both glucose and insulin levels.[4]

Glucocorticoids (GCs) are potent functional antagonists of insulin action, and promote gluconeogenesis in the

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liver, potentially leading to raised blood glucose concentrations in diabetes.[5] At the tissue level the access of active GCs to its receptors is governed by 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1).[6] This enzyme, which is mainly expressed in liver and adipose tissue, catalyzes the conversion of inactive cortisone into the active hormone cortisol (in rodents 11-dehydrocorticosterone to corticosterone).[7]

Several lines of evidence have implicated GCs and 11β-HSD1 activity in the etiology and/or maintenance of NIDDM and metabolic syndrome. Consequently, it is thought that selective inhibition of 11β-HSD1 may provide a means of treating diabetes and other aspects of the metabolic syndrome.[8]

In recent years considerable activity in the pharmaceutical industry has led to the discovery of several chemical classes of 11β-HSD1 inhibitors. Many patent applications explain the intense interest in this field.[9] Numerous examples of non-steroidal inhibitors have been disclosed; these include thiazole based compounds (**I**),[10] sulfonamides (**II**),[11] adamantanyl triazoles and carboxamides among others (Fig. 1).[8,9,12,13]

Compounds **I** and **II** belong to the arylsulfonamido (benzo)thiazoles class of 11β-HSD1 inhibitors.[10,11] We choose these scaffolds as starting point to design the compounds prepared in this work.

Our first consideration was to move sulfonamide moiety and its substituents from *meta* to *para* position (see Fig. 1). The second one was to mimic compound **I** which had a 2-aminothiazole skeleton.

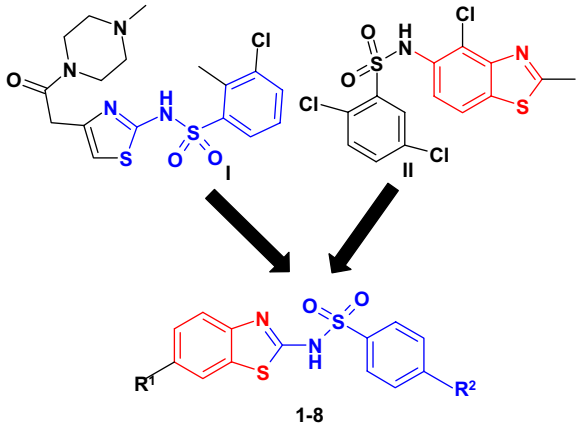


Figure 1. Selected 11β-HSD1 inhibitors and drug design of *N*-(6-substituted-1,3-benzothiazol-2-yl)benzenesulfonamides **1**–**8**.

The hybridization of both structures led to the title compounds reported in this paper. The design was also based on the biological activity predictions made by the computer software PASS® (prediction of activity spectra for substances).[14,15] This software illustrates the predicted activity spectrum of a compound as probable activity (P_a) and probable inactivity (P_i) with the accuracy of prediction reported to be as high as 85%.[16]

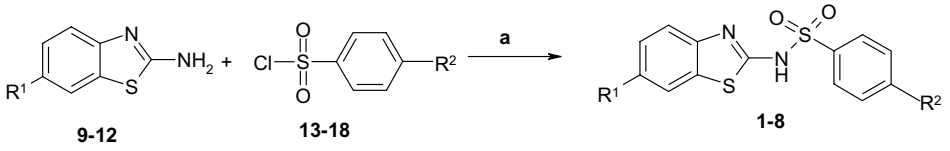
Here, we report the synthesis of *N*-(6-substituted-1,3-benzothiazol-2-yl)benzenesulfonamide derivatives, their in vitro inhibition of 11β-HSD1, and their in vivo antidiabetic activity in streptozotocin (STZ)–nicotinamide induced diabetic rat model.

Compounds **1**–**8** were synthesized from 2-amino-6-substituted benzothiazoles **9**–**12**, via a coupling reaction with arylsulfonyl chlorides **13**–**18**, in the presence of a catalytic amount of 4-dimethylaminopyridine and triethylamine. Title compounds were recovered with 34–90% yields (Scheme 1, Table 1).[17] Compounds were purified by recrystallization or by column chromatography. Compounds **4**, **5**, **7**, and **8** showed the best yields; they contain electron-withdrawing groups *para* to phenyl sulfonamide group (–NO_2, –Cl), while compounds **1**–**3** and **6**, which have electron-donating groups (–CH_3, –OCH_3, and –$NHCOCH_3$) at this position, had the lowest yields.

The chemical structures of the synthesized compounds were confirmed on the basis of their spectral data (NMR and mass spectra), and their purity ascertained by microanalysis. The elemental analysis was within ±0.4% of the theoretical values.[18] Physical constants of the title compounds are shown in Table 1.

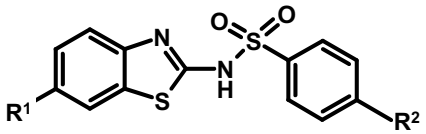
In the nuclear magnetic resonance spectra (^{1}H NMR; δ ppm), the signals of the respective protons of the compounds were verified on the basis of their chemical shifts, multiplicities, and coupling constants. The aromatic region of the ^{1}H NMR spectrum contained an ABX pattern signals ranging from δ 6.94–6.99 (dd, J_{meta} = 2.2–2.6; J_{ortho} = 8.8 Hz), 7.18–7.23 (d, J_{ortho} = 8.8 Hz), and 7.41–7.60 (d, J_{meta} = 2.2–2.6 Hz) attributable to H-5, H-4, and H-7, of the benzothiazole 6-substituted structure, respectively.

A preliminary in vitro compound screen to identify inhibitors of human 11β-HSD1 was performed on a selection of compounds. Inhibition of 11β-HSD1 was determined using a human embryonic kidney (HEK293) cell-based assay (Table 1).[8,19] Compounds **3** and **4** were the most active derivatives of the series and showed 38–53% inhibition at 10 μM, respectively.



Scheme 1. Reagents and conditions: (a) 4-dimethylaminopyridine (cat.), CH_2Cl_2, triethylamine, 40 °C.

Table 1. Physicochemical data, in vitro % inhibition of human 11β-HSD1, and predictive values of biological activities calculated for derivatives **1**–**8**



Compound	R^1	R^2	MW	Mp (°C)	Unoptimized yield (%)	% of inhibition 11β-HSD1 @ 10 μM (HEK 293 cells)	Antiobesity effect		Antidiabetic effect	
							P_a	P_i	P_a	P_i
1	$-NO_2$	$-OCH_3$	365	187.1–189.3	33.8	25.61	0.845	0.006	0.631	0.007
2	$-NO_2$	$-NHCOCH_3$	392	230.2–233.1	53.3	7.69	0.809	0.006	0.595	0.007
3	$-OCH_3$	–H	320	252.9–253.2	39.4	37.63	0.889	0.005	0.716	0.006
4	$-OCH_3$	$-NO_2$	365	236.9–238.2	66.1	53.32	0.833	0.006	0.654	0.007
5	$-OCH_2CH_3$	$-NO_2$	379	247.9–248.9	71.2	15.54	0.817	0.044	0.651	0.007
6	$-OCH_2CH_3$	$-CH_3$	348	228.4–230.3	47.1	16.43	0.858	0.006	0.687	0.007
7	$-CH_3$	–Cl	338	265.6–266.9	85.9	27.21	0.872	0.006	0.697	0.006
8	$-CH_3$	$-NO_2$	349	226.3–227.5	90.1	11.09	0.835	0.006	0.653	0.007

Both compounds have a methoxy group attached at position 5 of the benzothiazole ring. The remaining compounds displayed low levels of inhibition, suggesting low affinity for 11β-HSD1 or poor cellular penetration.

In order to gain an insight into the binding mode of title compounds, **3** and **4** were docked into the ligand-binding pocket of one subunit of human 11β-HSD1 (PDB entry 2BEL).[20] Docking was performed with the program Genetic Optimization for Ligand Docking (GOLD) 3.2.[21] Figure 2 shows the top-ranked binding mode predicted for **4**. Figure 3 depicts the corresponding amino acid residues at 4.5 Å in a 2D interaction map generated with the program Molecular Operating Environment 2007.09 (MOE).[22] In this binding model amino acid residues Tyr177, Pro178, Val180, and Ile 230 form the binding pocket for the benzothiazole ring. The binding pocket of the benzenesulfonamide moiety is formed by the nicotinamide ring of the cofactor and amino acid residues Ile121, Thr122, Thr124, Ser170, Tyr183, and Thr222. An oxygen atom of the sulfonamide group forms a hydrogen bond with the hydroxyl groups of the catalytic residues Ser170 and Tyr183 (Figs. 2 and 3).

Before the establishment of an in vivo assay, we obtained predictive values concerning biological activities by comparing the chemical structures of the compounds designed (**1**–**8**), with structures or substructures of more than 46,000 well-known biologically active drugs included in the database of PASS®.[14–16,24] The results of the prediction are presented as estimates of the probability P_a, or improbability P_i, which indicates that the compounds are active or inactive according PASS® calculations. For P_a values >0.7, the corresponding compound is very likely to reveal this activity in experiments, but in this case, the chance of the compound being a close analogue of a known pharmaceutical agent is also high. For P_a values between 0.5 and 0.7, the compound is likely to reveal this activity in experiments but the compound may exhibit less similar-

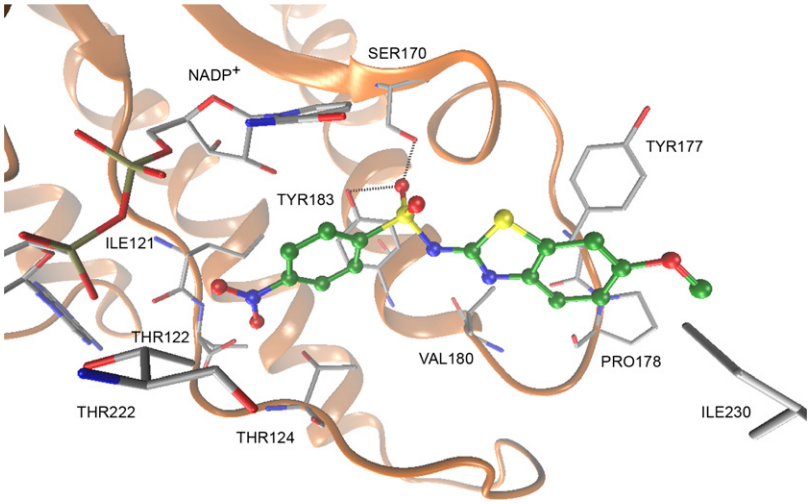


Figure 2. Binding model of **4** into the binding pocket of 11β-HSD1. Cofactor and amino acid residues within 4.5 Å of **4** are labeled. Hydrogen bonds are displayed as black dashes. Figure created with the program VMD 1.8.6.[23]

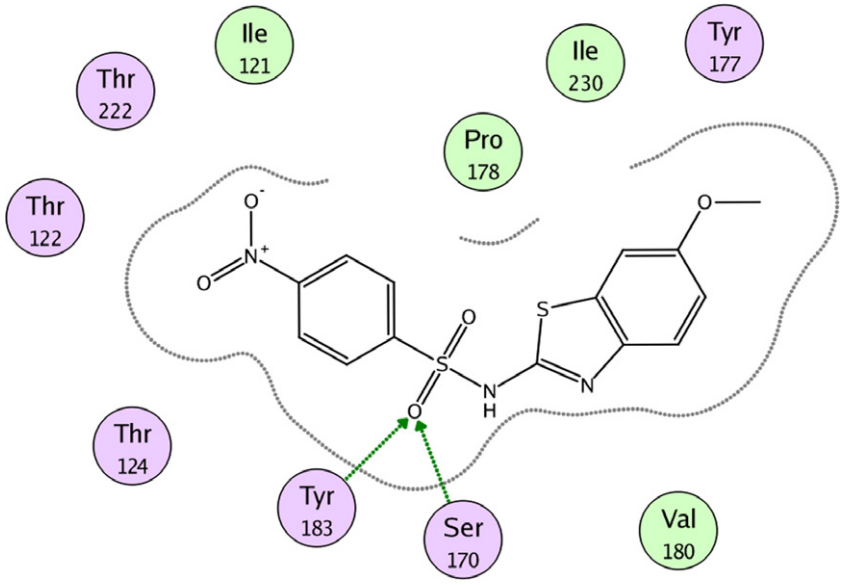


Figure 3. 2D interaction map of **4** docked into the 11β-HSD1 binding pocket (amino acid residues at 4.5 Å of the ligand are shown).

ity to known pharmaceutical agents. For P_a values <0.5, the compound is unlikely to reveal biological activity in experiments, but if the presence of this activity is confirmed in experiments, the compound may be a new biologically active chemical entity.[25]

Results presented in Table 1 describe two biological activities taken from PASS® software: antiobesity and antidiabetic effects. P_a values estimated for antiobesity activity were ranging between 0.80 and 0.88. These results indicated that designed compounds exhibited chemical structures similar to known antiobesity drugs, and are likely to reveal this activity. P_a-estimated antidiabetic activity values were determined to be ranged between 0.59 and 0.71, which also indicates that chemical structures of compounds **1**–**8** exhibited levels of similarity to those of known antidiabetic drugs.

Compounds **1**–**7** were evaluated for in vivo antidiabetic activity using a STZ–nicotinamide rat model of diabetes.[26] Glibenclamide was taken as positive control.[27] The antidiabetic activity of compounds **1**–**7** was deter-

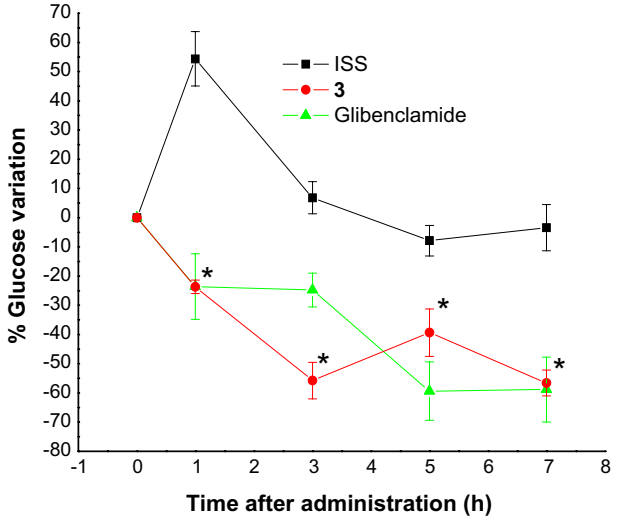


Figure 4. Effect of a single **3** administration (100 mg/kg; intragastric, $n = 5$) in streptozotocin–nicotinamide rat model of diabetes. ISS, isotonic saline solution. $^{*}p < 0.05$ versus ISS group.

Table 2. In vivo antidiabetic activity of compounds **1**–**7** at 100 mg/kg dose

Compound	Blood glucose-lowering profile (mg/dL)				% of change of glucose over control			
	1 h	3 h	5 h	7 h	1 h	3 h	5 h	7 h
1	−22.7 ± 4.4**	−42.2 ± 5.1*	−27.0 ± 8.0*	−32.4 ± 7.7*	**77.1****	49	19.1	29
2	17.2 ± 6.8*	18.6 ± 5.2	−11.9 ± 7.1	−33.4 ± 4.3*	37.2	11.8	4	30
3	−23.7 ± 2.3**	−55.8 ± 6.2*	−39.4 ± 8.1*	−56.6 ± 4.5*	**78.1****	62.9	31.5	53.2
4	−15.3 ± 5.2**	−35.7 ± 5.5*	−26.0 ± 10.0	−31.2 ± 10.1*	69.7	42.5	18.1	27.8
5	−0.2 ± 11.7**	−42.0 ± 8.8*	−59.6 ± 7.8*	−26.4 ± 6.5*	54.6	48.8	51.7	23
6	−27.2 ± 9.0**	−20.7 ± 10.5*	−32.9 ± 5.0*	−35.0 ± 6.6*	**81.6****	39.7	25	31.6
7	20.4 ± 5.0*	−29.3 ± 7.5*	−20.1 ± 11.2	−24.8 ± 9.6	34	36.1	12.2	21.4
Glibenclamide	−23.6 ± 9.2**	−24.8 ± 5.6*	−59.4 ± 10.1*	−58.8 ± 11.1*	78	32.6	51.5	55.4
ISS (Control)	54.4 ± 9.3	6.8 ± 5.5	−7.9 ± 5.2	−3.4 ± 7.9	0	0	0	0

Values represent means ± SEM. ($n = 5$). $^{*}p < 0.05$; $^{**}p < 0.01$ as compared to untreated group.
The negative value (−) indicates a decrease in glycemia compared with time 0.
ISS, isotonic saline solution.

Table 3. Rule of five properties calculated for **1**– **8**

Compound	MW	*mi*log*P*	H bond donors	H bond acceptors	TPSA (Å^2)	Volume (Å^3)	Violations
Rule	<500	<5	<5	<10	<140		<1
1	365	3.62 ± 0.94	1	8	114.11	278.71	0
2	392	2.67 ± 0.94	2	9	133.983	301.11	0
3	320	3.29 ± 0.92	1	5	68.295	255.37	0
4	365	3.49 ± 0.93	1	8	114.119	278.71	0
5	379	4.02 ± 0.93	1	8	114.119	295.51	0
6	348	4.28 ± 0.92	1	5	68.295	288.74	0
7	338	4.69. ± 0.66	1	4	59.061	259.93	0
8	349	4.03. ± 0.63	1	7	104.885	269.72	0

mined at 100 mg/kg dose. Among the seven screened compounds, six of them (**1**, **3**–**7**) demonstrated good glucose-lowering activity ranging from 40 to 60 mg/dL in this model of NIDDM (Table 2).[28]

The most pronounced effect was observed during the first hour of post-intragastric administration of tested compounds. The percentage of variation of glucose increased from 34% to 81%, compared with untreated animals.

The antidiabetic activity of the screened compounds revealed that unsubstituted position 4 of the benzenesulfonamide (compound **3**) reduced elevated blood sugar levels in the range of 32–78%. The effect was consistent during the seven hours of experiment (Fig. 4). Compound **3**, the most active derivative, showed sugar-lowering activity profile comparable to standard drug glibenclamide (78% of change of glucose over control). Compound **6**, with a methyl group attached to the position 4 of benzenesulfonamide, also showed a good sugar-lowering profile (25–81%). Substitution at *para* position with nitro group (compound **4**) showed moderate changes of glucose levels compared with control, ranging from 18% to 69%, while compound **2**, with *p*-acetamide group resulted in either reduction or a complete loss of antihyperglycemic activity. Noteworthy, **2** showed the lowest percentage of inhibition of 11β-HSD1 (Table 1).

Interestingly, a good agreement was found between predicted probabilities (P_a) of antiobesity and antidiabetic effect, and experimental in vivo antidiabetic activities. The predicted probabilities showed the following rank order: **3** > **7** > **6** > **4** > **8** > **5** > **1** > **2** (Table 1). Compound **3**, with the highest value of P_a, was the most active in the in vivo antidiabetic effect, while compound **2**, with the lowest value of P_a was practically inactive in the in vivo model.

The benzothiazoles prepared in this work have physical properties compatible with reasonable pharmacokinetics and drug availability. It is important to note that compounds **3** and **6** (the in vivo most active compounds) possess the same total polar surface area (TPSA = 68.295 Å^2), while inactive compound **2**, has a TPSA value of 133.983 Å^2. These compounds are fully compatible with Lipinski's rule of five,[29] which should allow for the development of additional antidiabetic analogues (Table 3). Their advantages include: (i) physical properties known to be compatible with desirable pharmacokinetic (low molecular weight, favorable *C*log*P*, favorable hydrogen bond-donating and accepting capabilities), (ii) simple synthetic access and thus low production costs, and (iii) polar groups improving the likelihood of reasonable solubility.

In conclusion, a series of *N*-(6-substituted-1,3-benzothiazol-2-yl)benzenesulfonamides were synthesized through a short synthetic route. Compounds **3** and **4** showed moderate inhibitory activity of 11β-HSD1 in an in vitro cell-based assay. Docking calculations suggest that these compounds may form hydrogen-bonding interactions with the catalytic residues of 11β-HSD1. We also demonstrated that most of the title compounds showed good in vivo antidiabetic activity in a model of NIDDM and have the potential to be developed further. The study has also shown an increased probability of compounds to be biologically active if they are selected on the basis of PASS prediction. The high bioactivity of compounds **3**, **4**, and **6** makes them a suitable lead to develop new chemical entities for potential use in the treatment of NIDDM.

Acknowledgments

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References and notes

1. Wild, S.; Roglic, G.; Green, A.; Sicree, R.; King, H. *Diabetes Care* **2004**, *27*, 1047.
2. Hogan, P.; Dall, T.; Nikolov, P. *Diabetes Care* **2003**, *26*, 917.
3. Krentz, A.; Bailey, C. *Drugs* **2005**, *65*, 385.
4. Sarabu, R.; Tilley, J. *Ann. Rep. Med. Chem.* **2005**, *40*, 167.

5. Alberts, P.; Engblom, L.; Edling, N.; Forsgren, M.; Klingstrom, G.; Larsson, C.; Ronquist-Nii, Y.; Ohman, B.; Abrahmsen, L. *Diabetologia* **2002**, *45*, 1528.
6. Seckl, J. R.; Chapman, K. E. *Eur. J. Biochem.* **1997**, *249*, 361.
7. Seckl, J. R.; Walker, B. R. *Endocrinology* **2001**, *142*, 1371.
8. Webster, S. P.; Ward, P.; Binnie, M.; Craigie, E.; McConnell, K. M. M.; Sooy, K.; Vinter, A.; Seckl, J. R.; Walker, B. R. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 2838.
9. (a) Wamil, M.; Seckl, J. R. *Drug Discovery Today* **2007**, *12*, 504; (b) Wang, M. *Curr. Opin. Invest. Drugs* **2006**, *7*, 319; (c) Fotsch, C.; Askew, B. C.; Chen, J. J. *Expert Opin. Ther. Patents* **2005**, *15*, 289; (d) Webster, S. P.; Pallin, T. D. *Expert Opin. Ther. Patents* **2007**, *17*, 1407.
10. Barf, T.; Vallgarda, J.; Emond, R.; Haggstrom, C.; Kurz, G.; Nygren, A.; Larwood, V.; Mosialou, E.; Axelsson, K.; Olsson, R.; Engblom, L.; Edling, N.; Ronquist-Nii, Y.; Ohman, B.; Alberts, P.; Abrahmsen, L. *J. Med. Chem.* **2002**, *45*, 3813.
11. Su, X.; Vicker, N.; Ganeshapillai, D.; Smith, A.; Purohit, A.; Reed, M. J.; Potter, B. V. *Mol. Cell Endocrinol.* **2006**, *248*, 214.
12. Olson, S.; Aster, S. D.; Brown, K.; Carbin, L.; Graham, D. W.; Hermanowski-Vosatka, A.; LeGrand, C. B.; Mundt, S. S.; Robbins, M. A.; Schaeffer, J. M.; Slossberg, L. H.; Szymonifka, M. J.; Thieringer, R.; Wright, S. D.; Balkovec, J. M. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 4359.
13. Boyle, C. D.; Kowalski, T. J.; Zhang, L. . L. *Ann. Rep. Med. Chem.* **2006**, *41*, 127.
14. Stepanchikova, A. V.; Lagunin, A. A.; Filimonov, D. A.; Poroikov, V. V. *Curr. Med. Chem.* **2003**, *10*, 225.
15. Poroikov, V. V.; Filimonov, D. A.; Borodina, Y. V.; Lagunin, A. A.; Kos, A. . *J. Chem. Inf. Comput. Sci.* **2000**, *40*, 1349.
16. Poroikov, V. V.; Filimonov, D. A. *J. Comput. Aided Mol. Des.* **2002**, *16*, 819.
17. General method of synthesis of derivatives **1**–**8** . To a solution of 2-amino-6-substituted benzothiazole (0.0030 mol) in dichloromethane (10 mL) were added triethylamine (1.1 equiv), and a catalytic amount of 4-dimethylaminopyridine (DMAP). After stirring at room temperature for 15 min, a solution of 4-substituted-benzenesulfonyl chloride (0.0033 mol, 1.1 equiv) in 5 mL of dichloromethane was added droopingly. The reaction mixture was stirred at 40 °C under nitrogen atmosphere for 6–10 h. After complete conversion as indicated by TLC, the solvent was removed in vacuo, the residue was neutralized with saturated $NaHCO_3$ solution, and the aqueous layer was extracted with ethyl acetate (3× 15 mL), washed with water (3× 20 mL), and dried over anhydrous Na_2SO_4. The solvent was evaporated in vacuo and the precipitated solids were recrystallized from an appropriate solvent or purified by column chromatography.
18. 4-Methoxy-*N*-(6-nitro-1,3-benzothiazol-2-yl)benzene sulfonamide (**1**). Yellow solid. Mp 187.1–189.3 °C. ^{1}H NMR (200 MHz, DMSO-d_6): δ 3.80 (s, 3H, CH_3O), 7.08 (d, 2H, H-3′, H-5′, J = 8.0), 7.80 (d, 2H, H2′, H6′, J = 8.4), 8.21 (sa, 2H, H-4, H-5), 8.81 (s, 1H, H-7) ppm. ^{13}C NMR (50.28 MHz, DMSO-d_6): δ 55.65 (CH_3), 114.27 (C-3′, C-5′), 119.15 (C-7), 123.15 (C-5), 126.30 (C-4), 126.97 (C-7a), 127.99 (C-2′, C-6′), 133.12 (C-1′), 138.96 (C-6), 142.81 (C-3a), 162.28 (C-4′), 167.75 (C-2) ppm; MS (FAB^+): m/z 366 $(M+H)^+$; Anal. Calcd for $C_{14}H_{11}N_3O^5S_2$: C, 46.02; H, 3.03; N, 11.50. Found: C, 46.49; H, 3.83; N, 10.94.
N-(4-{[(6-Nitro-1,3-benzothiazol-2-yl)amino]sulfonyl} phenyl)acetamide (**2**). Yellow solid. Mp 230.2–233.1 °C. ^{1}H NMR (200 MHz, DMSO-d_6): δ 2.94 (s, 3H, CH_3CO), 7.84 (d, 2H, H-4, H-5, J = 8.8), 8.52 (s, 1H, NH), 8.69 (s, 4H, H-2′, H-3′, H-5′, H-6′), 9.11 (s, 1H, H-7) ppm. ^{13}C NMR (50.28 MHz, DMSO-d_6): δ 23.91 (CH_3), 116.87 (C-7),116.93 (C-5), 117.71 (C-3′, C-5′), 118.02 (C-4), 121.91 (C-7a), 122.03 (C-2′, C-6′), 131.56 (C-1′), 140.67 (C-4′), 153.64 (C-6), 158.54 (C-3a), 163.31 (CO), 171.75 (C-2) ppm; MS(FAB^+): m/z 393 $(M+H)^+$; Anal. Calcd for $C_{15}H_{12}N_4O_5S_2$: C, 45.91; H, 3.08; N, 14.28. Found: C, 45.91; H, 3.08; N, 14.28.
N-(6-Methoxy-1,3-benzothiazol-2-yl)benzenesulfonamide (**3**). White solid. Mp 252.9–253.2 °C ^{1}H NMR (200 MHz, DMSO-d_6): δ 6.97 (dd, 1H, H-5, J = 8.8, J = 2.2 Hz), 7.20 (d, 1H, H-4, J = 8.8 Hz), 7.45(d, 1H, H-7, J = 2.2 Hz), 7.61–7.44 (m, 3H, H-′, H-4′, H-5′), 7.84 (m, 2H, H-2′, H-6′) ppm. ^{13}C NMR (50.28 MHz, DMSO-d_6): δ 55.71 (CH_3O), 106.90 (C-7), 113.42 (C-5), 114.61 (C-4), 125.62 (C-2′, C-6′), 125.90 (C-7a), 129.12 (C-3′, C-5′), 129.70 (C-4′), 132.21 (C-1′), 142.03 (C-4a), 155.92 (C-6), 166.40 (C-2). MS (FAB^+): m/z 321 $(M+H)^+$; Anal. Calcd for $C_{14}H_{12}N_2O_3S_2$: C, 52.48; H, 3.78; N, 8.74. Found: C, 52.29; H, 3.65; N, 8.98.
N-(6-Methoxy-1,3-benzothiazol-2-yl)-4-nitrobenzenesulfonamide (**4**). Yellow solid. Mp 236.9–238.2 °C. ^{1}H NMR (200 MHz, DMSO-d_6): δ 3.79 (s, 3H, CH_3O), 6.99 (dd, 1H, H-5 J = 8.8, J = 2.2 Hz), 7.23 (d, 1H, H-4, J = 8.8 Hz), 7.47 (d, 1H, H-7, J = 2.2 Hz), 8.08 (d, 2H, H-2′, H-6′, J = 8.4 Hz), 8.36 (d, 2H, H-3′, H-5′, J = 8.8 Hz) ppm; ^{13}C NMR (50.28 MHz, DMSO-d_6) δ 55.71 (CH_3), 106.90 (C-7), 113.81 (C-5), 114.92 (C-4), 124.40 (C-3′, C-5′), 126.04 (C-7a), 127.21 (C-2′, C-6′), 129.70 (C-3a), 147.30 (C-1′), 149.32 (C-4′), 156.21 (C-6), 167.02 (C-2) ppm; MS (FAB^+): m/z 366 $(M+H)^+$; Anal. Calcd for $C_{14}H_{11}N_3O_5S_2$: C, 46.02; H, 3.03; N, 11.50. Found: C, 45.75; H, 2.93; N, 11.77.
N-(6-Ethoxy-1,3-benzothiazol-2-yl)-4-nitrobenzenesulfonamide (**5**). Yellow solid. Mp 247.9–248.9 °C. ^{1}H NMR (200 MHz, DMSO-d_6): δ 1.31 (t, 3H, CH_3), 4.01 (q, 2H, CH_2O), 6.99 (dd, 1H, H-5, J = 8.8, J = 2.6 Hz), 7.23 (d, 1H, H-4, J = 8.8 Hz), 7.47 (d, 1H, H-7, J = 2.2 Hz), 8.11–8.05 (m, 2H, H-2′, H-6′), 8.39–8.33 (m, 2H, H-3′, H-5′) ppm; ^{13}C NMR (50.28 MHz, DMSO-d_6) δ 14.26 (CH_3), 63.42 (CH_2O), 107.18 (C-4), 113.46 (C-7), 124.13 (C-3′, C-5′), 126.86 (C-2′, C-6′), 129.30 (C-5), 147.03 (C-7a), 148.9 (C-6), 155.08 (C-1′), 166.66 (C-4′), 171.93 (C-3a), 172.80 (C-2) ppm; MS (FAB+): m/z 380 $(M+H)^+$; Anal. Calcd for $C_{15}H_{13}N_3O_5S_2$: C, 47.48; H, 3.45; N, 11.08. Found: C, 46.88; H, 3.33; N, 11.26.
N-(6-Ethoxy-1,3-benzothiazol-2-yl)-4-methylbenzene sulfonamide (**6**). Beige solid. Mp 228.4–230.3 °C. ^{1}H NMR (200 MHz, DMSO-d_6): δ 1.30 (t, 3H, CH_3), 2.33 (s, 3H, CH_3O), 3.99 (q, 2H, CH_2O), 6.94 (dd, 1H, H-5, J = 8.8, J = 2.6 Hz), 7.18 (d, 1H, H-4, J = 8.8 Hz), 7.34 (d, 2H, H-3′, H-5′, J = 8.0 Hz), 7.41 (d, 1H, H-7, J = 2.6 Hz), 7.73 (d, 2H, H-3′, H-7′, J = 8.2 Hz) ppm; ^{13}C NMR (50.28 MHz, DMSO-d_6) δ 14.26 (CH_3), 20.63 (CH_3), 63.34 (CH_2), 107.10 (C-7), 113.07 (C-4), 114.60 (C-7a), 125.32 (C-2′, C-6′), 125.53 (C-5), 129.02 (C-3′, C-5′), 130.02 (C-6), 138.80 (C-1′), 142.04 (C-4′), 154.70 (C-3a), 165.80 (C-2) ppm. MS(FAB^+): m/z 349 $(M+H)^+$; Anal. Calcd for $C_{16}H_{16}N_2O_3S_2$: C, 55.15; H, 4.63; N, 8.04. Found: C, 54.20; H, 4.40; N, 8.04.
4-Chloro-*N*-(6-methyl-1,3-benzothiazol-2-yl)benzenesulfonamide (**7**). White solid. Mp 265.6–266.9 °C. ^{1}H NMR (200 MHz, DMSO-d_6): δ 7.19 (s, 1H, H-7), 7.61 (m, 4H, H-2′, H-3′, H-5′, H-6′), 7.86 (m, 2H, H-4, H-5) ppm. ^{13}C NMR (50.28 MHz, DMSO-d_6): δ 20.75 (CH_3), 112.54 (C-7), 122.42 (C-4), 124.69 (C-7a), 127.65 (C-2′, C-6′), 128.13 (C-5), 129.14 (C-3′, C-5′), 133.25 (C-6), 133.85 (C-4′), 137.04 (C-3a), 140.80 (C-1′), 166.91 (C-2) ppm. MS

(FAB$^+$): *m/z* 339 (M+H)$^+$; Anal. Calcd for $C_{14}H_{11}ClN_2O_2S_2$: C, 49.63; H, 3.27; N, 8.27. Found: C, 49.02; H, 3.13; N, 8.26.

N-(6-methyl-1,3-benzothiazol-2-yl)-4-nitrobenzenesulfonamide (**8**). Beige solid. Mp 226.3–227.5 °C. ^{1}H NMR (200 MHz, DMSO-d_6): δ 2.3 (s, 3H, CH_3), 7.19 (s, 2H, H-4, H-5), 7.60 (s, 1H, H-7), 8.07 (d, 2H, H-2′, H-6′, J = 8.8 Hz), 8.34 (d, 2H, H-3′, H-5′, J = 8.8 Hz) ppm. ^{13}C NMR (50.28 MHz, DMSO-d_6): δ 20.73 (CH_3), 112.80 (C-7), 122.44 (C-4), 124.40 (C-3′, C-5′), 124.92 (C-7a), 127.20 (C-2′, C-6′), 128.20 (C-5), 133.43 (C-6), 134.15 (C-1′), 147.30 (C-3a), 149.30 (C-4′), 167.30 (C-2) ppm; MS (FAB$^+$): *m/z* 350 (M+H)$^+$; Anal. Calcd for $C_{14}H_{11}N_3O_4S_2$: C, 48.13; H, 3.17; N, 12.03. Found: C, 47.38; H, 3.13; N, 12.16.

19. In vitro inhibition 11β-HSD1 assay. In vitro cellular enzyme inhibition was determined using a scintillation proximity assay (SPA).[8] Human 11β-HSD1 enzyme inhibition was assessed in HEK293 cells stably transfected with the full-length human hsd11b1 gene. HEK293 cells were plated in 96-well poly-D-Lys coated flat-bottomed microplates in DMEM containing 1% glutamine, 1% penicillin and streptomycin. Compounds **1**–**8** were added to plates such that the final concentration of DMSO was 1%. Tritiated cortisone was added at a final concentration of 20 nM and the cells incubated at 37 °C in 5% CO_2, 95% O_2 for 2 h. The assay solutions were transferred to a scintillation microplate and mixed with a solution of antimouse YSi SPA beads and anticortisol antibody in assay buffer (50 mM Tris–HCl, pH 7.0; 300 mM NaCl, 1 mM EDTA, 5% glycerol). The plate was incubated for 2 h at room temperature and read on a scintillation counter. The percentage of inhibition was determined relative to a non-inhibited control.
20. Berman, H. M.; Westbrook, J.; Feng, Z.; Gilliland, G.; Bhat, T. N.; Weissig, H.; Shindyalov, I. N.; Bourne, P. E. *Nucleic Acids Res.* **2000**, *28*, 235, Website: http://www.rcsb.org/pdb/home/home.do.
21. Jones, G.; Willett, P.; Glen, R. C.; Leach, A. R.; Taylor, R. *J. Mol. Biol.* **1997**, *267*, 727.
22. Chemical Computing Group Inc., 1255 University Street, Montreal, Quebec, Canada H3B 3X3, 2005. Molecular Operating Environment (MOE). http://www.chemcomp.com.
23. Humphrey, W.; Dalke, A.; Schulten, K. *J. Mol. Graphics* **1996**, *14*, 33.
24. Website: http://www.ibmh.msk.su/PASS.
25. Marwaha, A.; Goelb, R. K.; Mahajana, M. P. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 5251.
26. Masiello, P.; Broca, C.; Gross, R.; Roye, M.; Manteghetti, M.; Hillaire-Buys, D.; Novelli, M.; Ribes, G. *Diabetes* **1998**, *47*, 224.
27. Ortiz-Andrade, R. R.; Rodríguez-López, V.; Garduño-Ramírez, M. L.; Castillo-España, P.; Estrada-Soto, S. *J. Ethnopharmacol.* **2005**, *101*, 37.
28. In vivo antidiabetic assay. Induction of diabetes: streptozotocin (STZ) was dissolved in citrate buffer (pH 4.5) and nicotinamide was dissolved in normal physiological saline. NIDDM was induced in overnight fasted rats by a single intraperitoneal injection of 65 mg/kg streptozotocin, 15 min after the i.p administration of 110 mg/kg of nicotinamide. Hyperglycemia was confirmed by the elevated glucose levels in plasma, determined at 72 h by glucometer. The animals with blood glucose concentration higher 250 mg/dL, were used for the antidiabetic screening.The diabetic animals were divided into groups of five animals each (n = 5). Rats of experimental groups were administered a suspension of the compounds **1**– **7** (prepared in 1% Tween 80) orally (100 mg/kg body weight). Control group animals were also fed with 1% Tween 80. Glibenclamide (5 mg/kg) was used as hypoglycemic reference drug. Blood samples were collected from the caudal vein at 0, 1, 3, 5, and 7 h after vehicle, sample, and drug administration. Blood glucose concentration was estimated by enzymatic glucose oxidase method using a commercial glucometer (Accutrend GCT, Roche®). The percentage variation of glycemia for each group was calculated in relation to initial (0 h) level, according to: % Variation of glycemia=$[(G_x - G_0)/G_0] \times 100$, where G_0 were initial glycemia values and G_x were the glycemia values at +1, +3, +5, and +7 h, respectively. All values were expressed as means ± SEM. Statistical significance was estimated by analysis of variance (ANOVA), $p < 0.05$ and $p < 0.01$ implies significance.
29. Lipinski, C. A.; Lombardo, F.; Dominy, B. W.; Feeney, P. J. *Adv. Drug Delivery Rev.* **1997**, *23*, 3.