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Adamantane sulfone and sulfonamide 11-β-HSD1 Inhibitors

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Abstract—Potent and selective adamantane sulfone and sulfonamide inhibitors of 11-β-HSD-1 have been discovered. Selected compounds from these series have robust pharmacokinetic profiles and strongly inhibit liver, fat, and brain HSD1 for extended periods after oral dosing.

Recently, selective inhibitors of 11-β-hydroxysteroid dehydrogenase (11-β-HSD1) have been studied as a potential treatment for metabolic disease.[1] Interest in this target has been heightened by the results obtained during the analysis of genetically altered rodents and inhibitor pharmacology.[2] Particularly notable amongst these experiments are those conducted in adipose 11-β-HSD1 overexpressing mice, whose enzyme expression mimics that seen in obese humans.[3] The phenotype of these mice is strikingly similar to the human metabolic syndrome where the mice have visceral obesity and hyperphagia that is exacerbated by a high fat diet. The mice also are insulin resistant, hyperlipidemic, and hypertensive. 11-β-HSD1 knockout mice have also been generated and are resistant to obesity or stress induced hyperglycemia and have improved insulin sensitivity and glucose tolerance.[4] Additionally, the animals have an interesting lipid profile (decreased triglyceride and increased HDL) and resist diabetes and weight gain, despite consuming more calories. These mice also show reduced age-related learning impairment. Inhibitors from different chemical series have also been effective in rodent models of diabetes, obesity, and learning. Amongst the most studied compounds reported to date are the nonselective steroidal 11-β-HSD1 and 2 inhibitor carbenoxolone (**1**)[5] and the 11-β-HSD1 selective inhibitors BVT.2733 **2**[6] and 544 **3**[7] (Fig. 1).

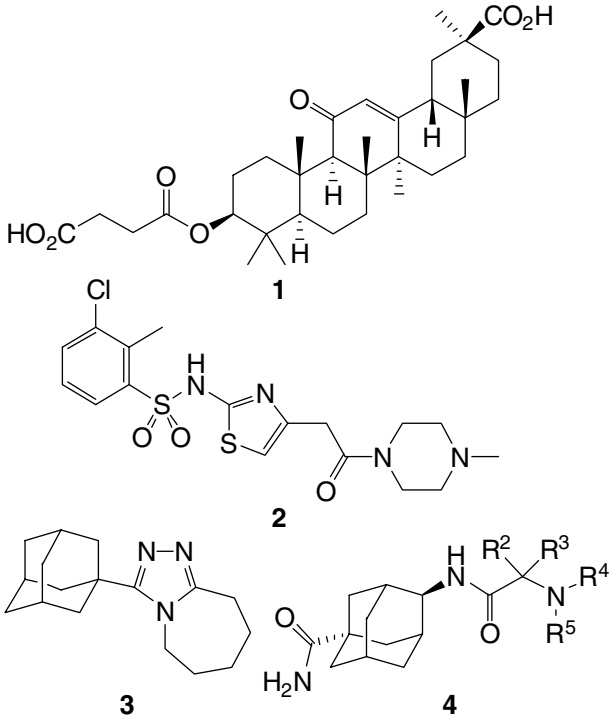

Figure 1. 11-β-HSD1 inhibitors. The steroidal 11-β-HSD2 unselective inhibitor carbenoxolone (**1**) and the selective nonsteroidal inhibitors BVT.2733 **2**, 544 **3**, and adamantane amide **4**.

Keywords: 11-β-HSD-1; HSD1; 11-β-Hydroxysteroid dehydrogenase; HSD1 inhibitor; Adamantane; Sulfone; Sulfonamide.
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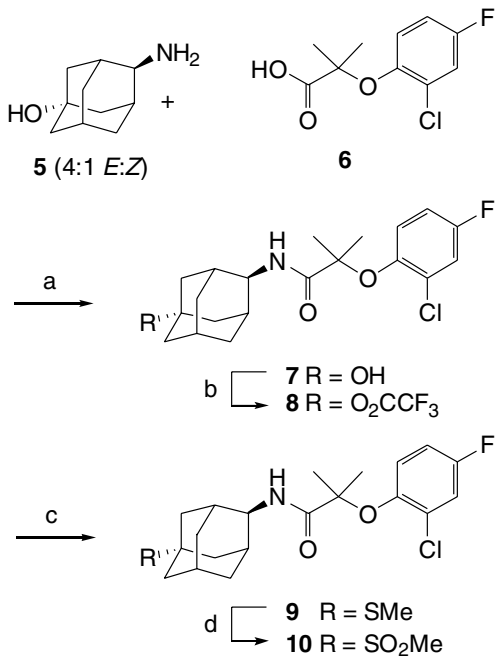


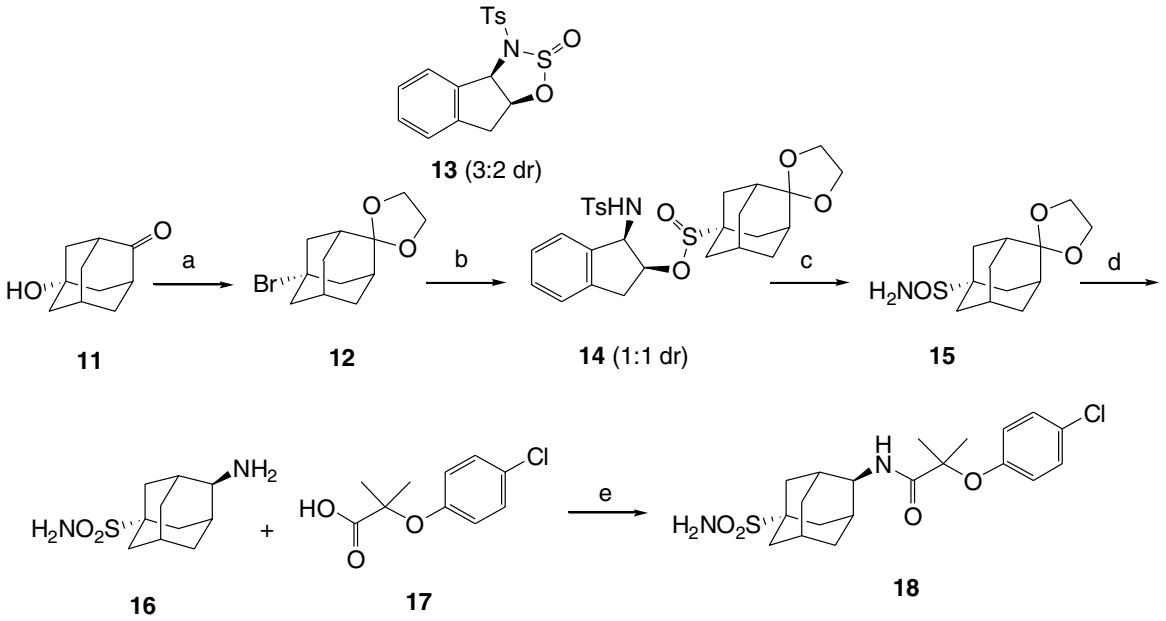
Scheme 1. Reagents and conditions: (a) TBTU, DMF, rt, 12 h, 70%; (b) $(CF_3CO)_2O$, TFA, 80 °C, 1 h; (c) NaSMe, CF_3CO_2H, 115 °C, 12 h, 83% (two steps); (d) $NaBO_3{\cdot}4H_2O$, CH_3CO_2H, rt, 1.25 h, 97%.

Our efforts to identify potent and selective inhibitors of 11-β-HSD1 have centered upon the optimization of a series of 2-adamantylamino amides.[8] Initially, these compounds were chosen for further study due to their permeability, which we hoped would give them the ability to penetrate and inhibit 11-β-HSD1 in fat.

However, the metabolic stability of adamantane is frequently poor and is best improved in this series by the judicious placement of charged groups on the adamantane. These groups tend to reduce permeability (and often potency). During our optimization, we sought to strike a balance between permeability and metabolic stability. A 1-carboxamido adamantane substituent (e.g., amides **4**) worked well in vitro, but it suffered cleavage in vivo and led us to explore the sulfone and sulfonamide analogs reported herein. We have also been interested in tissue selective inhibitors with different durations of action. Long-acting compounds that potently inhibit liver, fat, and brain 11-β-HSD1 offer a starting point for finding compounds with selective exposure profiles.

A representative adamantane sulfone synthesis is shown in Scheme 1. A 4:1 *E*:*Z* mixture of 5-hydroxy-2-adamantamine **5**, obtained from reductive amination of 5-hydroxy-2-adamantanone, is coupled to carboxylic acids like ether **6**.[8] These ethers are easily prepared from the corresponding phenols using 1,1,1-trichloro-2-methylpropan-2-ol under precedented reaction conditions.[9] The tertiary alcohol was then converted to the corresponding trifluoroacetate **8**, which underwent a substitution reaction when treated with NaSMe in trifluoroacetic acid. The oxidation of the resultant sulfide **9** provided sulfone **10** in excellent yield. These steps were scaled up effectively, all proceeding in the yields quoted when run on scales greater than 10 g.

We were also interested in the corresponding sulfonamides, like **18**, which proved more difficult to prepare (Scheme 2). Although adamantane sulfonyl chlorides are readily prepared, they do not couple effectively with amines. Senanayake and coworkers developed chemistry able to overcome this problem in less functionalized systems and we adopted their approach.[10] For these analogs, 2-hydroxy-5-adamantanone **11** was converted into bromoketal **12**. Insertion, employing Rieke zinc,



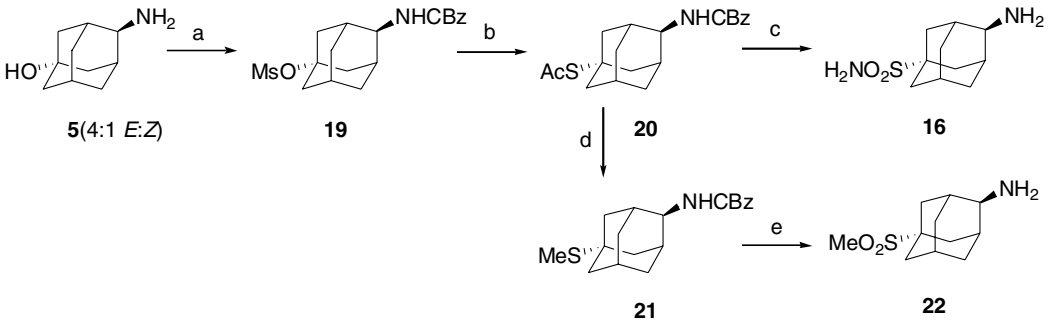
Scheme 2. Reagents and conditions: (a) 48% HBr, H_2O, 100 °C, 12 h, 49%; $HOCH_2CH_2OH$, cat. *p*-TsOH, PhH, 80 °C, 4 h, 98%; (b) Rieke zinc, THF, rt, 48 h; **14**, THF, −50 °C, 12 h, 34%; (c) $LiNH_2$, $Fe(NO_3)_3{\cdot}9H_2O$, THF, −45 → −78 °C, 2 h, 72%; (d) OsO_4, NMO, THF, rt, 12 h; 1 M HCl, H_2O, THF, 60 °C, 12 h, 81%; H_2, NH_3, Pd/C, MeOH, rt, 48 h, 65%; (e) TBTU, *i*-Pr_2NEt, DMF, rt, 12 h, 65%.

provided the corresponding adamantyl zinc reagent that coupled with the 1,2,3-oxathiazolidine-2-oxides **13** (3:2 dr) to provide sulfinate esters **14** (1:1 dr). Treatment with lithium amide then provided sulfinamides **15**, which underwent oxidation, deprotection, and reductive amination to provide aminosulfonamide **16**. This intermediate allowed for the preparation of a wide variety of inhibitors. For instance, coupling with acid **17** led to the potent 11-β-HSD1 inhibitor amide **18**.

Due to the expense and difficulties encountered in scaling up these reactions a more efficient protocol was sought (Scheme 3). The 4:1 *E*:*Z* mixture of 5-hydroxy-2-adamantamine **5** was protected and the diastereomers chromatographically separated. After mesylation provided **19**, the corresponding thioacetate **20** was prepared by heating in thioacetic acid. This intermediate was efficiently converted to the key sulfonamide intermediate **16** by removal of the acetate group. This was followed by reaction of the thiol with chloramine, oxidation to the sulfonamide, and finally by deprotection. Alternatively, the thioacetate **20** could be converted to a key sulfone intermediate **22** by cleavage/alkylation with methyl iodide, oxidation to the sulfone, and hydrogenolytic deprotection.

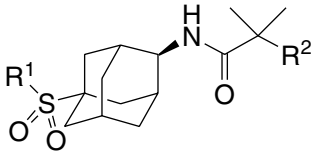
Compounds were assayed in human and mouse HSD1 (h- and m-HSD1) and HSD2 assays that assessed the ability of a compound to inhibit the interconversion between cortisone and cortisol.[8] A cellular assay in HEK cells overexpressing h-HSD1 was also employed. Mouse liver microsomes were utilized as an initial screening system for metabolic stability.

Sulfone **10** has excellent potency against h- and m-HSD1 and good selectivity over h- and m-HSD2 (Table 1). The compound also has moderate cellular potency and metabolic stability. Increasing the size of the sulfone group typically decreased potency, although moderately potent compounds such as **23**–**25** were found. Monosub-



Scheme 3. Reagents and conditions: (a) CbzCl, Na_2CO_3, THF, rt, 12 h, 76% (pure *E*); MsCl, Et_3N, CH_2Cl_2, 0 °C → rt, 12 h; (b) AcSH, 70 °C, 12 h; CbzCl, Na_2CO_3, THF, rt, 12 h, 75% (three steps); (c) MeSNa, MeOH, rt, 1 h; NH_4OH, NaOCl, Et_3N, THF, H_2O, 0 °C → rt, 1 h; MCPBA, EtOH, H_2O, rt, 12 h, 48% (three steps); H_2, Pd/C, MeOH, rt, 12 h, 100%; (d) NaOMe, MeI, MeOH, rt, 12 h; (e) OsO_4, NMO, THF, rt, 2 h, 83% (two steps); H_2, Pd/C, MeOH, EtOAc, rt, 12 h, 100%.

Table 1. Human and mouse 11-β-HSD-1 and 11-β-HSD-2 assay results for compounds **10** and **23**–**31**



Compound	R^1	R^2	h-HSD1 K_i[a] (nM)	h-HSD2 IC_{50}[a] (nM)	m-HSD1 K_i[a] (nM)	m-HSD2 IC_{50}[a] (nM)	h-HSD1 HEK IC_{50}[a] (nM)	% remaining MLM[b]
10	Me	2-Cl, 4-F phenoxy	7	26,000	4	>100,000	98	57
23	Et	2-Cl, 4-F phenoxy	26	15,000	7	>100,000	450	ND
24	CH_2CONH_2	2-Cl, 4-F phenoxy	8	3300	4	>100,000	300	59
25	$(CH_2)_3$-morpholine	2-Cl, 4-F phenoxy	110	15,000	38	87,000	500	<1
26	Me	2-Cl phenoxy	5	5400	2	>100,000	120	ND
27	Me	3-Cl phenoxy	8	17,000	10	>100,000	530	7
28	Me	4-Cl phenoxy	7	65,000	8	>100,000	410	70
20	Me	2-CF_3 phenoxy	7	>100,000	3	>100,000	120	ND
30	Me	2-OMe, 4-F phenoxy	20	>100,000	7	>100,000	690	ND
31	Me	2-F, 4-Cl phenoxy	11	21,000	8	>100,000	210	63

[a] Values are means of at least two experiments (ND, not determined).
[b] Percent remaining after a 30 min incubation with mouse liver microsomes (ND, not determined).

stitution of the phenyl ether with small electron-withdrawing groups maintained potency as in **26**–**29** and substituents in the 4 position had the greatest effect upon metabolic stability, suggesting this is a site of metabolism. Disubstituted analogs such as **10**, **30**, and **31** were also potent and selective.

An X-ray crystal structure of sulfone **10** bound to h-HSD1 was obtained (pdb code 2ILT). This structure indicates that the inhibitor binds to the steroid binding site with its central amide interacting with the residues responsible for substrate ketone reduction (Fig. 2).

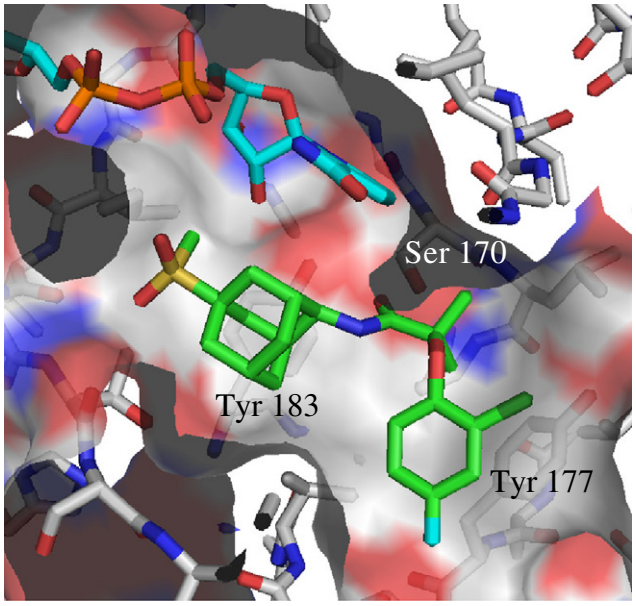


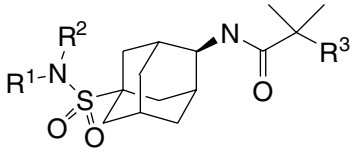
Figure 2. Crystal structure of sulfone **10** bound to h-11-β-HSD1. Atoms are colored according to atom type and the components differ by carbon atom colors: the protein is gray, the NADP+ cofactor is cyan, and compound **16** is green. The protein surface is also colored according to atom type.

The sulfonamides display a similar SAR as the sulfones (Table 2). The parent sulfonamide phenyl ether **32** has good potency against h- and m-HSD1 with good selectivity over h- and m-HSD2. It has modest cellular potency and moderate metabolic stability. Small electron-withdrawing groups on the phenyl ether improve potency as in aryl chlorides **33**, **34**, and **18**. Metabolic stability is similarly high in the 4-substituted analog, again implicating it as a site of metabolism. Mono- or disubstitution of the sulfonamide, as in **35** and **36** respectively, yields modest changes in potency, but dramatically reduces metabolic stability. Acyl sulfonamide **37**, predicted to have good metabolic stability, was unfortunately not potent. Removing the ether oxygen decreased mouse HSD1 potency as in amide **38**. Polysubstituted arenes like **40** and **41** showed some of the best overall profiles, having better metabolic stability than the more cellularly potent monosubstituted analog **39**.

Adamantane sulfone and sulfonamide inhibitors with the best combination of potency, selectivity, and metabolic stability were studied in mouse pharmacokinetic experiments (Table 3). Sulfonamide **40** had a good volume of distribution consistent with tissue penetration and a moderate half-life and clearance. Its bioavailability is moderate but improved upon by sulfonamide **18**, which may undergo enterohepatic recirculation. Sulfone **10** has a similar pharmacokinetic profile and has excellent bioavailability. A study in monkeys also showed a continued trend of excellent bioavailability, longer half-life, lower clearance, and a volume of distribution consistent with tissue penetration.

In order to determine the reason for the improved half-life in monkeys, the metabolic stability of sulfone **10** was

Table 2. Human and mouse 11-β-HSD-1 and 11-β-HSD-2 assay results for compounds **18** and **32**–**41**



Compound	R^1	R^2	R^3	h-HSD1 K_i[a] (nM)	h-HSD2 IC_{50}[a] (nM)	m-HSD1 K_i[a] (nM)	m-HSD2 IC_{50}[a] (nM)	h-HSD1 HEK IC_{50}[a] (nM)	% remaining MLM[b]
32	H	H	Phenoxy	21	59,000	13	>100,000	580	62
33	H	H	2-Cl phenoxy	4	5500	2	>100,000	83	36
34	H	H	3-Cl phenoxy	4	6300	6	>100,000	320	ND
18	H	H	4-Cl phenoxy	5	16,000	5	>100,000	230	96
35	Me	H	4-Cl phenoxy	8	85,000	8	>100,000	620	<1
36	Me	Me	4-Cl phenoxy	14	60,000	21	100,000	560	<1
37	Ac	H	4-Cl phenoxy	170	ND	110	ND	ND	ND
38	H	H	Ph	8	>100,000	210	>100,000	420	ND
39	H	H	2-OCF_3 phenoxy	7	25,000	3	>100,000	54	38
40	H	H	2-Cl, 4-F phenoxy	6	>100,000	3	>100,000	125	61
41	H	H	2,6 Di-Cl, 4-F phenoxy	3	9000	2	>100,000	190	55

[a] Values are means of at least two experiments (ND = not determined).
[b] Percent remaining after a 30 min incubation with mouse liver microsomes (ND, not determined).

Table 3. Pharmacokinetic results for sulfonamides **40** and **18** and sulfone **10**

Compound	Species	Dose (mpk)	iv $t_{1/2}$ (h)[a]	V_{ss} (L/kg)[a]	V_{β} L/kg[a]	iv CLp (L/h/kg)[a]	po AUC (μg h/mL)[a]	F (%)[a]
40	Mouse	10	2.8	2.6	3.5	0.9	7.0	61
18	Mouse	5 iv, 10 oral	1.8	2.1	2.1	0.8	18.3	150
10	Mouse	10	1.0	1.5	1.7	1.1	8.9	100
10	Monkey	2.5	5.1	2.7	3.1	0.4	6.81	109

[a] Values are means obtained from samples taken from three animals.

Table 4. Metabolic stability results for compound **10**

Species	Intrinsic clearance [a] (L/h/kg)	
	Liver microsomes	Hepatocyte
Mouse	6.0	0.2
Monkey	1.5	0.1
Human	1.6	ND

[a] Values are means of three experiments (ND, not determined).

Table 5. Ex vivo study in DIO mice for compounds **10** and **40**

Compound	% inhibition[a]		
	Liver (1, 7, 16 h)	Fat (1, 7, 16 h)	Brain (1, 7, 16 h)
10	95, 95, 89	87, 93, 86	90, 90, 77
40	70, 78, 82	62, 88, 93	29, 48, 73

[a] Values are means from samples taken from two animals.

assessed in mouse and monkey microsomes and hepatocytes (Table 4). The compound shows greater stability in monkey microsomes relative to mouse, which is similar to the trend observed with other adamantanes.[8] Human liver microsomes give a similar metabolic stability to monkey, and little difference was noted in hepatocytes.

To determine the capacity of these compounds to inhibit liver, fat, and brain 11-β-HSD1, the compounds were orally dosed at 30 mpk in DIO mice (Table 5). At several timepoints thereafter (1, 7, and 16 h), the animals were sacrificed, and the ex vivo tissue inhibition assessed relative to vehicle. Sulfone **10** robustly inhibited liver, fat, and brain 11-β-HSD1 up to 16 h post-dose, indicating long and potent coverage in these tissues. Sulfonamide **40** also shows potent and long duration inhibition in liver and fat, although its brain inhibition is initially modest and builds over time. This suggests it may be a good lead to modify to discover inhibitors that work in liver and fat, but fail to penetrate the central nervous system. Such a compound may potentially have greater efficacy and/or fewer side effects due to reduced HPA axis activation.

Novel adamantane sulfone and sulfonamides were discovered that potently and selectively inhibit both human and mouse 11-β-HSD1. Representative members of these two series have mouse pharmacokinetic profiles that make them interesting tool compounds to assess the effects of 11-β-HSD1 inhibition. In particular, sulfone **10** provides potent inhibition in liver, fat, and brain HSD1 up to 16 h post-dose in DIO mice, while sulfonamide **40** gives similar activity with less brain inhibition.

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References and notes

1. (a) Fotsch, C.; Askew, B. C.; Chen, J. J. *Expert Opin. Ther. Patents* **2005**, *15*, 289; (b) Barf, T.; Williams, M. *Drugs Future* **2006**, *31*, 231.
2. Walker, B. R.; Seckl, J. R. *Expert Opin. Ther. Targets* **2003**, *7*, 771.
3. (a) Masuzaki, H.; Paterson, J.; Shinyama, H. *Science* **2001**, *294*, 2166; (b) Masuzaki, H.; Yamamoto, H.; Kenyon, C. J.; Elmquist, J. K.; Morton, N. M.; Paterson, J. M.; Shinyama, H.; Sharp, M. G. F.; Fleming, S.; Mullins, J. J.; Seckl, J. R.; Flier, J. S. *J. Clin. Invest.* **2003**, *112*, 83.
4. (a) Kotelevtsev, Y.; Holmes, M. C.; Burchell, A.; Houston, P. M.; Schmoll, D.; Jamieson, P.; Best, R.; Brown, R.; Edwards, C. R. W.; Seckl, J. R.; Mullins, J. J. *Proc. Natl. Acad. Sci. U.S.A.* **1997**, *94*, 14924; (b) Morton, N. M.; Paterson, J. M.; Masuzaki, H.; Holmes, M. C.; Staels, B.; Fievet, C.; Walker, B. R.; Flier, J. S.; Mullins, J. J.; Seckl, J. R. *Diabetes* **2004**, *53*, 931; (c) Morton, N. M.; Holmes, M. C.; Fiévet, C.; Staels, B.; Tailleux, A.; Mullins, J. J.; Seckl, J. R. *J. Biol. Chem.* **2001**, *276*, 41293; (d) Yau, J. L. W.; Noble, J.; Kenyon, C. J.; Hibberd, C.; Kotelevtsev, Y.; Mullins, J. J.; Seckl, J. R. *Proc. Natl. Acad. Sci.* **2001**, *98*, 4716.
5. Sandeep, T. C.; Yau, J. L. W.; MacLullich, A. M. J.; Noble, J.; Deary, I. J.; Walker, B. R.; Seckl, J. R. *Proc. Natl. Acad. Sci.* **2004**, *101*, 6734.
6. (a) Barf, T.; Vallgårda, J.; Emond, R.; Häggström, C.; Kurz, G.; Nygren, A.; Larwood, V.; Mosialou, E.; Axelsson, K.; Olsson, R.; Engblom, L.; Edling, N.; Rönquist-Nil, Y.; Öhman, B.; Alberts, P.; Abrahmsén, L. *J. Med. Chem.* **2002**, *45*, 3813; (b) Alberts, P.; Engblom, L.; Edling, N.; Forsgren, M.; Klingström, G.; Larsson, C.; Rönquist-Nii, Y.; Öhman, B.; Abrahmsèn, L. *Diabetologia* **2002**, *45*, 1528; (c) Alberts, P.; Nilsson, C.; Selén, G.; Engblom, L. O. M.; Edling, N. H. M.; Norling, S.; Klingström, G.; Larsson, C.; Forsgren, M.; Ashkzari, M.; Nils-

son, C. E.; Fiedler, M.; Bergqvist, E.; Öhman, B.; Björkstrand, E.; Abrahmsén, L. B. *Endocrinology* **2003**, *144*, 4755.

7. (a) Olson, S.; Aster, S. D.; Brown, K.; Carbin, L.; Graham, D. W.; Hermanowski-Vosatka, A. H.; LiGrand, 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; (b) Hermanowski-Vosatka.; Balkovec, J. M.; Cheng, K.; Chen, H. Y.; Hernandez, M.; Koo, G. C.; Le Grand, C. B.; Li, Z.; Metzger, J. M.; Mundt, S. S.; Noonan, H.; Nunes, C. N.; Olson, S. H.; Pikounis, B.; Ren, N.; Robertson, N.; Schaeffer, J. M.; Shah, K.; Springer, M. S.; Strack, A. M.; Strowski, M.; Wu, K.; Wu, T.; Xiao, J.; Zhang, B. B.; Wright, S. D.; Thieringer, R. *JEM* **2005**, *202*, 517.
8. Rohde, J. J.; Pliushchev, M. A.; Sorensen, B. K.; Wodka, D.; Shuai, Q.; Wang, J.; Fung, S.; Monzon, K. M.; Chiou, W. J.; Pan, L.; Deng, X.; Chovan, L. E.; Ramaiya, A.; Mullally, M.; Henry, R. F.; Stolarik, D. F.; Imade, H. M.; Marsh, K. C.; Beno, D. W. A.; Fey, T. A.; Droz, B. A.; McDowell, C.; Brune, M. B.; Camp, H. S.; Sham, H. L.; Frevert, E. U.; Jacobson, Link, J. T. *J. Med. Chem.*, manuscript accepted for publication.
9. Deffieux, D.; Fabre, I.; Courseille, C.; Quideau, S. *J. Org. Chem.* **2002**, *67*, 4458.
10. Han, Z.; Krishnamurthy, D.; Grover, P.; Fang, Q. K.; Senanayake, C. H. *J. Am. Chem. Soc.* **2002**, *124*, 7880.