

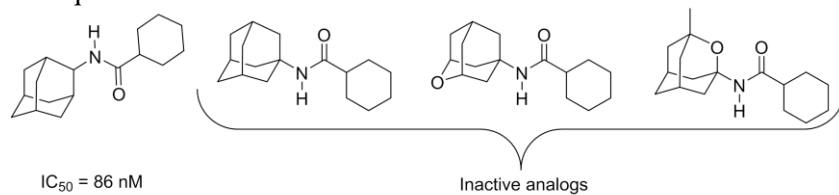
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Novel 11 β -HSD1 inhibitors: C-1 vs C2-substitution and effect of the introduction of an oxygen atom in the adamantane scaffold

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Novel 11 β -HSD1 inhibitors: C-1 vs C-2 substitution and effect of the introduction of an oxygen atom in the adamantane scaffold

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ABSTRACT

The adamantane scaffold is found in several marketed drugs and in many investigational 11 β -HSD1 inhibitors. Interestingly, all the clinically approved adamantane derivatives are C-1 substituted. We demonstrate that, in a series of paired adamantane isomers, substitution of the adamantane in C-2 is preferred over the substitution at C-1 and is necessary for potency at human 11 β -HSD1. Furthermore, the introduction of an oxygen atom in the hydrocarbon scaffold of adamantane is deleterious to 11 β -HSD1 inhibition. Molecular modeling studies provide a basis to rationalize these features.

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Adamantane is a very common building block in medicinal chemistry.¹ So far, seven adamantane derivatives have been introduced in clinical use for a variety of diseases and molecular targets (Figure 1) and hundreds of derivatives have been tested against different targets.

Interestingly, the rapid inspection of the structures of the adamantane derivatives shown in Figure 1 reveals as a general trend that the polycyclic scaffold is substituted at the C-1 position. Of note, the anti-influenza A activity of amantadine is significantly higher than that of its isomer, 2-aminoadamantane.²

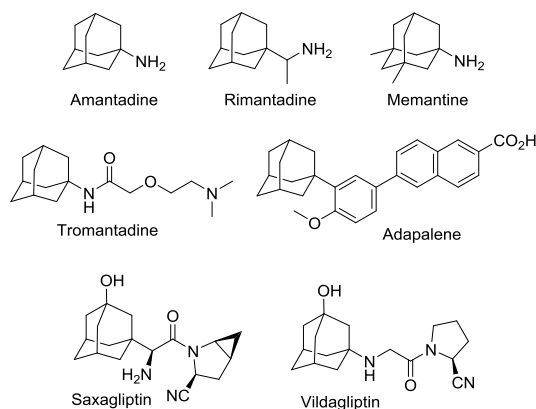


Figure 1. Clinically-approved adamantane derivatives. Amantadine, rimantadine and tromantadine are anti-virals, the first two are M2 channel blockers and are anti-Influenza drugs, and tromantadine inhibits herpes virus simplex replication; memantine is a NMDA receptor antagonist used in the treatment of Alzheimer's disease; adapalene inhibits keratinocyte differentiation and proliferation and is used for the treatment of acne; and saxagliptin and vildagliptin are DPP-IV inhibitors used to treat type 2 diabetes.

In recent years, more than 25 pharmaceutical companies have been working on the synthesis of 11 β -hydroxysteroid dehydrogenase type 1 (11 β -HSD1) inhibitors, as a potential new candidates for the treatment of type II diabetes and metabolic syndrome.³ On the one hand, contrary to the aforementioned trend observed in clinically approved adamantanes, most of the 11 β -HSD1 inhibitors evaluated are 2-adamantyl substituted derivatives (Figure 2).^{4,5} However, for these derivatives no comparison between the activities of compounds substituted at the C-1 and C-2 positions is available. On the other hand, a potential advantage of positioning the substituent at the 1-position is that one of the metabolically labile positions of the adamantane would be blocked. Also, for any given substituent, the theoretical clogP value of the 1-substituted analog is usually lower than that of the 2-substituted derivative.⁶

The synthesis and pharmacological evaluation of a series of 1-adamantyl amide 11 β -HSD1 inhibitors has been previously reported by Webster *et al.*⁷ Of note, inhibitors **1** and **2** were found

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to be equipotent compounds (Figure 3). Later, Xia *et al.* reported that the C-2 substituted amide **3** was 20 times more potent than its 1-isomer, **4** (Figure 3).⁸

Taking into account these seemingly contradictory results and the scarcity of data on 1-substituted adamantane derivatives evaluated as 11 β -HSD1 inhibitors,⁵ we decided to synthesize a small series of 1- and 2-adamantyl derivatives featuring fragments of proven inhibitors of 11 β -HSD1 in order to compare their pharmacological behaviour.

Moreover, considering that very few heteroadamantanes have been biologically tested as 11 β -HSD1 inhibitors,⁹ we also evaluated some 1- and 5-substituted 2-oxadamantanes. The introduction of an oxygen atom in the scaffold increases the polar surface area and decreases the overall lipophilicity. Thus, if potency is retained, the lipophilic ligand efficiency, which is one of the most significant parameters that normalizes potency relative to lipophilicity, would increase.¹⁰

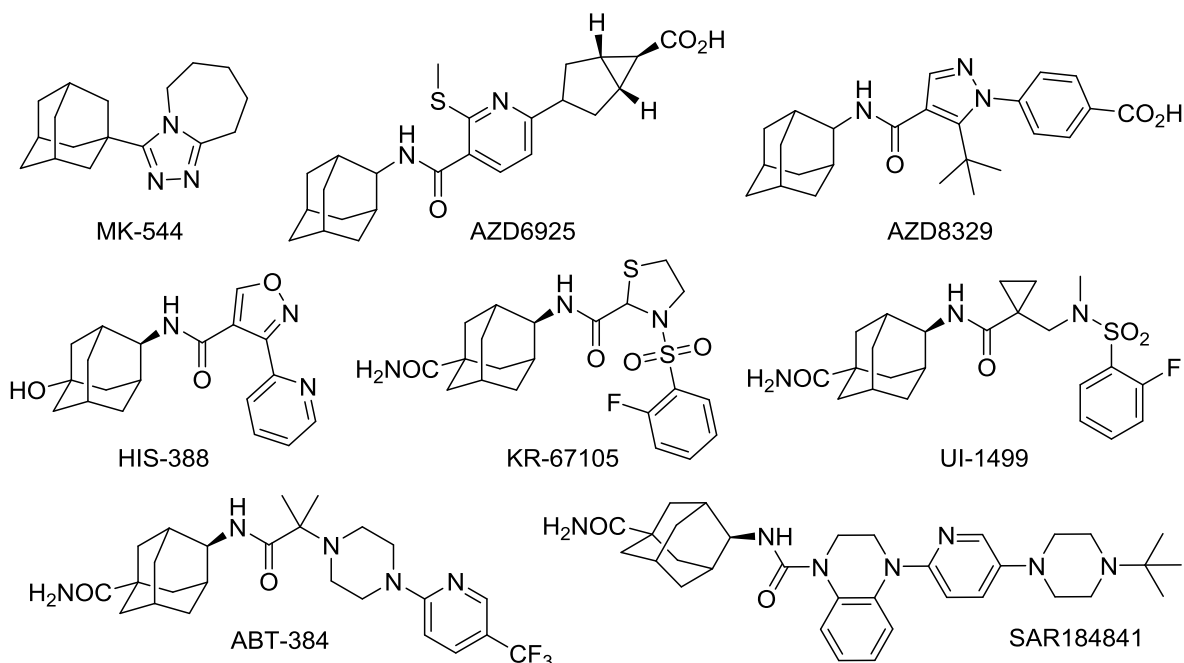


Figure 2. Selected adamantyl-based 11 β -HSD1 inhibitors.

Figure 3. Structures of 11 β -HSD1 inhibitors 1-4.

We started from known urea **5**, an 11 β -HSD1 inhibitor reported by Vitae.¹¹ In our microsomal assay, **5** was shown to be a submicromolar inhibitor of the human 11 β -HSD1 enzyme (IC_{50} = 0.87 μ M). Table 1 shows the structures and the percentage of inhibition of human 11 β -HSD1 at 10 μ M of the novel compounds. The IC_{50} value of the more potent derivatives is also included.

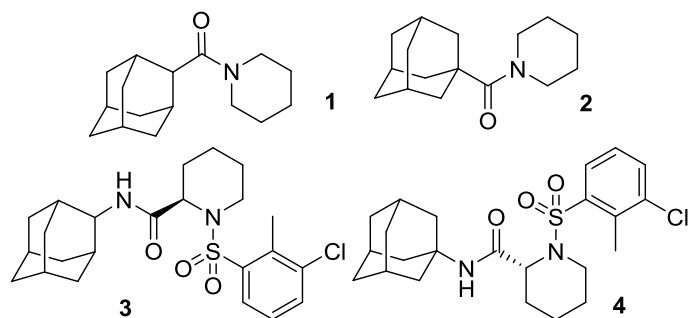
All the compounds were synthesized in medium to high yields using standard chemistry from four known amines: amantadine (1-aminoadamantane), 2-aminoadamantane, 5-amino-2-oxadamantane,¹² and 3-methyl-2-oxadamantane-1-amine¹³ (see details in Supplementary Material). Briefly, the reaction of amantadine with 1-piperidinecarbonyl chloride in dichloromethane in the presence of triethylamine furnished, after column chromatography, urea **6** in 31% yield.¹⁴ In the same way, starting from the known 3-methyl-2-oxadamantane-1-amine, urea **7** was obtained in 34% yield. We also synthesized amides **8** and **9** in high yields, by reaction of amantadine with 3,5-dichloro-4-aminobenzoic acid or cyclohexanecarboxylic acid, respectively.¹⁵

Surprisingly, in our microsomal assay ureas **6** and **7** and amide **8** did not inhibit the human 11 β -HSD1 enzyme. Under the same conditions, amide **9** only inhibited 20% the enzyme activity. Oxadamantanes **10** and **11** were also very poor inhibitors.

Taking into account the aforementioned results and that the corresponding C-2 isomers of **8** and **9** had not been previously tested, we synthesized both amides from 2-aminoadamantane. By way of contrast with the lack of inhibitory activity of their C-1 isomers, amides **12** and **13** displayed potent, nanomolar inhibition. Also, in agreement with the previous trend observed in going from ureas **6** and **7** to their corresponding amides **9** and **10**, the novel amide **12** was more potent than our previous hit **5**. It was noteworthy that ring contraction from **12** to **14** led to a less potent inhibitor.

Overall, for the three pairs of isomers evaluated here, substitution in position 2 of the adamantyl scaffold consistently leads to more potent inhibitory activity of human 11 β -HSD1.

The introduction of an oxygen atom in the adamantane does not improve the activity within the series of the C-1 substituted derivatives. As Ye *et al.* found, within a series of 2,2-disubstituted adamantanes, that the corresponding oxadamantane analogs performed poorly,^{9b} we have not evaluated oxadamantane derivatives with the amino group attached to a methylene group of the polycyclic ring.¹⁶



In order to rationalize these results we combined docking studies with molecular dynamics simulations to examine the structural integrity of the binding of compounds **5**, **6**, and **12**. Let us note that the inhibitory activities of **5** and **6**, which only differ in the substitution at positions C1 and C2, vary from 87% (**5**) to 3% (**6**). On the other hand, compound **12** involves the replacement of the piperidine moiety present in **5** by the cyclohexyl one in **12**, leading to a moderate increase of the inhibitory activity from 87% (**5**) to 100% (**12**).

Compounds were docked in the binding cavity of human 11 β -HSD1 using Glide.¹⁷ In all cases the best scored poses mimicked the binding mode of PF-877423 (Figure S1 in Supporting Information), which is a potent adamantyl-based inhibitor against the human enzyme ($K_i = 1.4$ nM).¹⁸ Thus, all the compounds retained the hydrogen bond formed between the carbonyl oxygen of the amide/urea moiety with the hydroxyl group of Ser170 and the adamantyl cage filled a common site in the binding pocket.

Table 1. Structures and human 11 β -HSD1 inhibitory activities of compounds **5-14**.

Product	11 β -hHSD1 inhibition at 10 μ M ^a	11 β -hHSD1 IC ₅₀ (nM) ^a
5	87	873
6	3	ND
7	0	ND
8	0	ND
9	20	ND
10	9	ND
11	9	ND

12		100	86
13		86	74
14		76	520

11 β -HSD1 inhibition was determined in mixed sex, Human Liver Microsomes (Celsis In-vitro Technologies) by measuring the conversion of ³H-cortisone to ³H-cortisol in a cortisol-Scintillation Proximity Assay. Percentage inhibition was determined relative to a no inhibitor control.

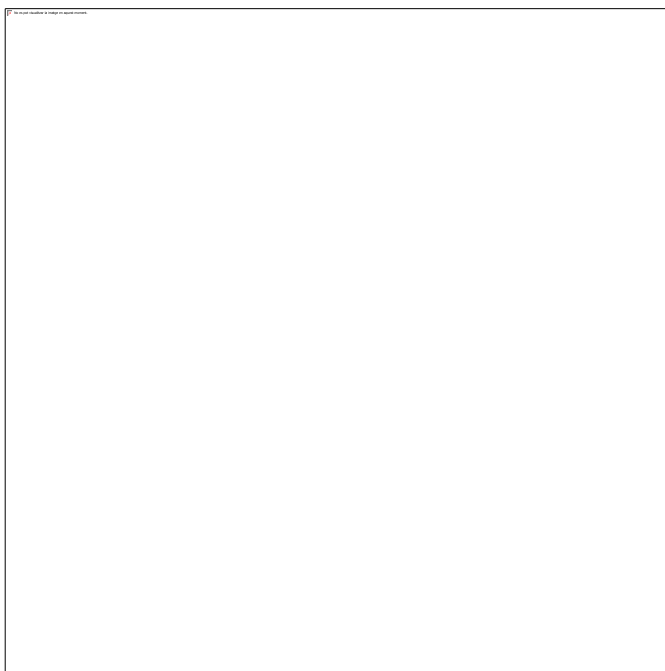


Figure 4. Last snapshot of a representative molecular dynamics simulation for the complexes between human 11 β -HSD1 and compounds PF-877423 (top left), **6** (top right), **12** (bottom left) and **5** (bottom right). In all cases residues Tyr183 and Ser170, the NADP cofactor and the ligand are represented as sticks and only the polar hydrogens are shown. The shape of the binding cavity is shown as a white contour.

Three independent 50 ns MD simulations were run for each ligand-receptor complex, and additional runs were performed for the complex with PF-877423, which was used as a reference system. All the simulations were stable except that of the complex with the C1-substituted compound **6**, since the ligand was released from the binding site in one simulation. Upon exclusion of this latter trajectory, the root-mean square deviation (RMSD) profiles were similar in all cases. Thus, the RMSD of the protein backbone varied from 1.5 to 2.2 Å, whereas the residues in the binding site showed a larger RMSD (2.5-3.7 Å) due to the enhanced flexibility of the loops that enclose the binding pocket.

The hydrogen bond formed between the inhibitor and the hydroxyl group of Ser170 was retained in all cases (average distance of 2.8 Å). Often, an additional hydrogen bond with the hydroxyl unit of Tyr183 was transiently formed. Nevertheless, compound **6** consistently showed a higher root-mean square fluctuation (1.4 Å) compared to inhibitors **5** and **12** (RMSF of 0.8

Å), suggesting a poorer fit of the hydrophobic cage in the binding cavity due to the change in the substitution pattern from position C1 in **6** to position C2 in **5** and **12**. This reflects the larger steric hindrance of the adamantyl cage with the NADP nicotinamide ring arising from the C1-substitution, because C2-derived compounds are found to adopt a configuration where the C2-H unit is primarily oriented toward the nicotinamide ring (Figure 4)

Finally, the moderate increase in the inhibitory activity of compound **12** relative to **5** may be ascribed to the enhanced hydrophobicity afforded by the cyclohexane unit, as noted in their respective clogP values of 4.5 and 3.6, determined from quantum mechanical IEF/MST continuum solvation calculations.¹⁹ This trend agrees with similar findings reported for series of structurally related compounds.²⁰

In conclusion, bearing in mind the aforementioned pharmacological results, it is clear that for potent 11 β -HSD1 inhibitory activity, 2-substituted adamantanes are preferred over their corresponding 1-substituted counterpart. Also, the introduction of an oxygen atom in the polycyclic scaffold did not improve the activity (compare **9** vs **10** and **11**).

Acknowledgments

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References and notes

1. a) Lamoureux, G.; Artavia, G. *Curr. Med. Chem.* **2010**, *17*, 2967. b) Liu, J.; Obando, D.; Liao, V.; Lifa, T.; Codd, R. *Eur. J. Med. Chem.* **2011**, *46*, 1949. c) Wanka, L.; Iqbal, K.; Schreiner, P. R. *Chem. Rev.* **2013**, *113*, 3516.
2. Zoidis, G.; Kolocouris, N.; Foscolos, G. B.; Kolocouris, A.; Fytas, G.; Karayannis, P.; Padalko, E.; Neyts, J.; DeClercq, E. *Antiviral Chem. Chemother.* **2003**, *14*, 153. For another, non-related example, see: Lee, W.-G.; Lee, S.-D.; Cho, J.-H.; Jung, Y.; Kim, J.-H.; Hien, T. T.; Kang, K.-W.; Ko, H.; Kim, Y.-C. *J. Med. Chem.* **2012**, *55*, 3687.
3. a) Scott, J. S.; Chooramun, J., 11 β -Hydroxysteroid Dehydrogenase Type 1 (11 β -HSD1) inhibitors in Development, in: R. M. Jones (Ed.), *New Therapeutic Strategies for Type 2 Diabetes*. Small Molecule Approaches, RSC Drug Discovery Series No. 27, Royal Society of Chemistry, Cambridge, 2012, pp 109–141; b) Gathercole, L. L.; Lavery, G. G.; Morgan, S. A.; Cooper, M. S.; Sinclair, A. J.; Tomlinson, J. W.; Stewart, P. M. *Endocrine Rev.* **2013**, *34*, 525; c) Scott, J. S.; Goldberg, F. W.; Turnbull, A. V. *J. Med. Chem.* **2014**, *57*, 4466.
4. a) 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; b) Sorensen, B.; Rohde, J.; Wang, J.; Fung, S.; Monzon, K.; Chiou, W.; Pan, L.; Deng, X.; Stolarik, D.; Frevort, E. U.; Jacobson, P.; Link, J. T. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 5958; c) Becker, C. L.; Engstrom, K. M.; Kerdesky, F. A.; Tolle, J. C.; Wagaw, S. H.; Wang, W. *Org. Process Res. Dev.* **2008**, *12*, 1114; d) Scott, J. S.; Barton, P.; Bennett, S. N. L.; deSchoolmeester, J.; Godfrey, L.; Kilgour, E.; Mayers, R. M.; Packer, M. J.; Rees, A.; Schofield, P.; Selmi, N.; Swales, J. G.; Whittamore, P. R. *O. Med. Chem. Commun.* **2012**, *3*, 1263; e) Scott, J. S.; deSchoolmeester, J.; Kilgour, E.; Mayers, R. M.; Packer, M. J.; Hargreaves, D.; Gerhardt, S.; Ogg, D. J.; Rees, A.; Selmi, N.; Stocker, A.; Swales, J. G.; Whittamore, P. R. *O. J. Med. Chem.* **2012**, *55*, 10136; f) Venier, O.; Pascal, C.; Braun, A.; Namane, C.; Mougenot, P.; Crespin, O.; Pacquet, F.; Mougenot, C.; Monseau, C.; Onofri, B.; Dadjji-Faihun, R.; Leger, C.; Ben-Hassine, M.; Van-Pham, T.; Ragot, J.-L.; Philippo, C.; Farjot, G.; Noah, L.; Maniani, K.; Boutarfa, A.; Nicolai, E.; Guillot, E.; Pruniaux, M.-P.; Güssregen, S.; Engel, C.; Coutant, A.-L.; de Miguel, B.; Castro, A. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 2414; g) Park, S. B.; Jung, W. H.; Kang, N. S.; Park, J. S.; Bae, G. H.; Kim, H. Y.; Rhee, S. D.; Kang, S. K.; Ahn, J. H.; Jeong, H. G.; Kim, K. Y. *Eur. J. Pharmacol.* **2013**, *721*, 70; h) Okazaki, S.; Takahashi, T.; Iwamura, T.; Nakaki, J.; Sekiya, Y.; Yagi, M.; Kumagai, H.; Sato, M.; Sakami, S.; Nitta, A.; Kawai, K.; Kainoh, M. *J. Pharmacol. Exp. Ther.* **2014**, *351*, 181; i) Byun, S. Y.; Shin, Y. J.; Nam, K. Y.; Hong, S. P.; Ahn, S. K. *Life Sci.* **2015**, *120*, 1.
5. For some examples of 1-substituted adamantane evaluated as 11 β -HSD1 inhibitors see: a) 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; b) Su, X.; Pradaux-Caggiano, F.; Thomas, M. P.; Szeto, M. W. Y.; Halem, H. A.; Culler, M. D.; Vicker, N.; Potter, B. V. L. *Chem. Med. Chem.* **2010**, *5*, 1026; c) Su, X.; Vicker, N.; Thomas, M. P.; Pradaux-Caggiano, F.; Halem, H. A.; Culler, M. D.; Potter, B. V. L. *Chem. Med. Chem.* **2011**, *6*, 1439; d) Su, X.; Pradaux-Caggiano, F.; Vicker, N.; Thomas, M. P.; Halem, H. A.; Culler, M. D.; Potter, B. V. L. *Chem. Med. Chem.* **2011**, *6*, 1616; e) Wang, H.; Robl, J. A.; Hamann, L. G.; Simpkins, L.; Golla, R.; Li, Y.-X.; Seethala, R.; Zvyaga, T.; Gordon, D. A.; Li, J. J. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 4146; f) Kim, S. H.; Kwon, S. W.; Chu, S. Y.; Lee, J. H.; Narsaiah, B.; Kim, C. H.; Kang, S. K.; Kang, N. S.; Rhee, S. D.; Bae, M. A.; Ahn, S. H.; Ha, D. C.; Kim, K. Y.; Ahn, J. H. *Chem. Pharm. Bull.* **2011**, *59*, 46; g) Su, X.; Halem, H. A.; Thomas, M. P.; Moutrille, C.; Culler, M. D.; Vicker, N.; Potter, B. V. L. *Bioorg. Med. Chem.* **2012**, *20*, 6394.
6. For example, the clogP of amide **2** (2.64) is 1 unit lower than that of amide **1** (3.68). Calculated using BioByte software: *BioLoom 5.0* BioByte Co., Claremont, CA, USA. <http://www.biobyte.com>
7. 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.
8. Xia, G.; Liu, L.; Liu, H.; Yu, J.; Xu, Z.; Chen, Q.; Ma, C.; Li, P.; Xiong, B.; Liu, X.; Shen, J. *Chem. Med. Chem.* **2013**, *8*, 577.
9. a) Yeh, V. S. C.; Kurukulasuriya, R.; Madar, D.; Patel, J. R.; Fung, S.; Monzon, K.; Chiou, W.; Wang, J.; Jacobson, P.; Sham, H. L.; Link, J. T. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 5408; b) Ye, X.-Y.; Chen, S. Y.; Nayeem, A.; Golla, R.; Seethala, R.; Wang, M.; Harper, T.; Slecza, B. G.; He, B.; Gordon, D. A.; Robl, J. A. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 6699.
10. a) Freeman-Cook, K. D.; Hoffman, R. L.; Johnson, T. W. *Future Med. Chem.* **2013**, *5*, 113; b) Murray, C. W.; Erlanson, D. A.; Hopkins, A. L.; Keseru, G. M.; Leeson, P. D.; Rees, D. C.; Reynolds, C. H.; Richmond, N. J. *J. Med. Chem.* **2014**, *57*, 616.
11. Tice, C. M.; Zhao, W.; Xu, Z.; Cacatian, S. T.; Simpson, R. D.; Ye, Y.-J.; Singh, S. B.; McKeever, B. M.; Lindblom, P.; Guo, J.; Krosky, P. M.; Kruk, B. A.; Berbaum, J.; Harrison, R. K.; Johnson, J. J.; Bukhtiyarov, Y.; Panemangalore, R.; Scott, B. B.; Zhao, Y.; Bruno, J. G.; Zhuang, L.; McGeehan, G. M.; He, W.; Claremon, D. A. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 881.
12. Duque, M. D.; Camps, P.; Profire, L.; Montaner, S.; Vázquez, S.; Sureda, F. S.; Mallol, J.; López-Querol, M.; Naesens, L.; De Clercq, E.; Prathalingam, S. R.; Kelly, J. M. *Bioorg. Med. Chem.* **2009**, *17*, 3198.
13. Leiva, R.; Gazzarrini, S.; Esplugas, R.; Moroni, A.; Naesens, L.; Sureda, F. X.; Vázquez, S. *Tetrahedron Lett.* **2015**, *56*, 1272.
14. Urea **6** had been synthesized previously using a Pd-catalyzed carbonylation reaction: Orito, K.; Miyazawa, M.; Nakamura, T.; Horibata, A.; Ushito, H.; Nagasaki, H.; Yuguchi, M.; Yamashita, S.; Yamazaki, T.; Tokuda, M. *J. Org. Chem.* **2006**, *71*, 5951.
15. The *N*-methyl derivative of **8** is reported to be a submicromolar inhibitor of 11 β -HSD1. See, Richards, S.; Sorensen, B.; Jae, H.; Winn, M.; Chen, Y.; Wang, J.; Fung, S.; Monzon, K.; Frevort, E. U.; Jacobson, P.; Sham, H.; Link, J. T. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 6241.
16. For further related 2,2-disubstituted adamantanes that led to the discovery of the clinical candidate BMS-816336 see: a) Ye, X.-Y.; Yoon, D.; Chen, S. Y.; Nayeem, A.; Golla, R.; Seethala, R.; Wang, M.; Harper, T.; Slecza, B. G.; Apedo, A.; Li, Y.-X.; He, B.; Kirby, M.; Gordon, D. A.; Robl, J. A. *Bioorg. Med. Chem. Lett.* **2014**, *24*, 654; b) Ye, X.-Y.; Chen, S. Y.; Wu, S.; Yoon, D. S.; Wang, H.;

- Hong, Z.; Oconnor, S. P.; Li, J.; Li, J.; Walker, S.; Kennedy, L. J.; Apedo, A.; Nayeem, A.; Sheriff, S.; Morin, P.; Camac, D.; Harrity, T.; Zebo, R.; Taylor, J.; Morgan, N.; Ponticiello, R.; Golla, R.; Seethala, R.; Wang, M.; Harper, T.; Slecicka, B. G.; He, B.; Kirby, M.; DiMarco, J.; Scaringe, R.; Hanson, R. L.; Guo, Z.; Li, J.; Sun, J.-H.; Wong, M. K.; Chen, B.-C.; Haque, L.; Leahy, D. K.; Chan, C.; Li, Y.-X.; Zvyaga, T.; Hansen, L.; Patel, C.; Gordon, D. A.; Robl, J. A. Abstracts of the 249th National Meeting of the ACS, 2015, MEDI-25, Chem. Abstr. 2015:477592.
17. Friesner, R.A.; Murphy, R.B.; Repasky, M.P.; Frye, L.L.; Greenwood, J.R.; Halgren, T.A.; Sanschagrin, P.C.; Mainz, D.T. *J. Med. Chem.* **2006**, *49*, 6177.
18. Cheng, H.; Hoffman, J.; Le, P.; Nair, S. K.; Cripps, S.; Matthews, J.; Smith, C.; Yang, M.; Kupchinsky, S.; Dress, K.; Edwards, M.; Cole, B.; Walters, E.; Loh, C.; Ermolieff, J.; Fanjul, A.; Bhat, G. B.; Herrera, J.; Pauly, T.; Hosea, N.; Paderes, G.; Rejto, P. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 2897.
19. a) Curutchet, C.; Orozco, M.; Luque, F. J. *J. Comput. Chem.* **2001**, *22*, 1180; b) Kolar, M.; Fanfril, J.; Lepsik, M.; Fort, F.; Luque, F. J.; Hobza, P. *J. Phys. Chem. B* **2013**, *117*, 5950.
20. Robb, G. R.; Boyd, S.; Davies, C. D.; Dossetter, A. G.; Goldberg, F. W.; Kemmitt, P. D.; Scott, J. S.; Swales, J. G. *Med. Chem. Commun.* **2015**, *6*, 926.

Supplementary Material

Experimental and computational procedures. NMR spectra for all the new compounds.