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**Discovery of Novel Inhibitors of Human  
11 $\beta$ -Hydroxysteroid Dehydrogenase Type 1**

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## **Abstract**

11 $\beta$ -Hydroxysteroid dehydrogenases (11 $\beta$ -HSDs) are key enzymes regulating the pre-receptor metabolism of glucocorticoid hormones, which play essential roles in various vital physiological processes. The modulation of 11 $\beta$ -HSD type 1 activity with selective inhibitors has beneficial effects on various conditions including insulin resistance, dyslipidemia and obesity. Therefore, inhibition of tissue-specific glucocorticoid action by regulating 11 $\beta$ -HSD1 constitutes a promising treatment for metabolic and cardiovascular diseases. Here we report the discovery of a series of novel adamantyl carboxamides as selective inhibitors of human 11 $\beta$ -HSD1 in HEK-293 cells transfected with the HSD11B1 gene. Compounds **9** and **14** show inhibitory activity against 11 $\beta$ -HSD1 with IC<sub>50</sub> values in 100 nM range. Docking studies with the potent compound **8** into the crystal structure of human 11 $\beta$ -HSD1 (1XU9) reveals how the molecule may interact with the enzyme and cofactor.

*Keywords:* Hydroxysteroid dehydrogenase; 11 $\beta$ -HSD1; Inhibitors; Adamantane; Diabetes; Obesity

## **1. Introduction**

Glucocorticoid hormones play essential roles in various vital physiological processes, including regulation of carbohydrate, lipid and bone metabolism, modulation of inflammatory responses and stress. It has been indicated that excessive glucocorticoid action in many aspects is associated with insulin and leptin resistance, leading to the development of obesity, type 2 diabetes and metabolic syndrome (Oppermann, 2006). Glucocorticoid actions depend on both the binding to glucocorticoid receptors (GRs) and the pre-receptor metabolism of the ligand cortisol and its precursor cortisone. It is well known that the pre-receptor metabolism process is mediated by 11 $\beta$ -HSDs, which are microsomal enzymes from the short-chain dehydrogenases/reductases

superfamily. Currently, two different 11 $\beta$ -HSD isozymes (11 $\beta$ -HSD1 and 11 $\beta$ -HSD2) have been reported in humans (Tomlinson et al., 2004). The 11 $\beta$ -HSD1 isoform, highly expressed in liver and adipose tissue, converts cortisone to the active glucocorticoid cortisol, therefore locally amplifying the glucocorticoid action in specific tissues (Fig. 1). Clinical data suggest that inhibition of 11 $\beta$ -HSD1 with a non-selective inhibitor increases hepatic insulin sensitivity along with decreased glucose production (Walker et al., 1995). It is also shown that the modulation of 11 $\beta$ -HSD1 activity with selective inhibitors has beneficial effects on various conditions including insulin resistance, dyslipidemia and obesity (Hermanowski-Vosatka et al., 2005). Recently, the positive proof-of-concept results from a 28-day phase IIa clinical trial with the potent 11 $\beta$ -HSD1 inhibitor INCB013739 were reported by Incyte. It is indicated that treatment of type 2 diabetes mellitus patients with INCB013739 for 28 days significantly improved hepatic and peripheral insulin sensitivity and reduced fasting plasma glucose, plasma low density lipoprotein- and total-cholesterol levels (Hawkins et al, 2008). Therefore, inhibition of tissue-specific glucocorticoid action by regulating 11 $\beta$ -HSD1 constitutes a promising treatment for metabolic and cardiovascular diseases (Hughes et al, 2008; Su et al., 2008).

**(Insert Figure 1)**

To discover new inhibitors of 11 $\beta$ -HSD1 an ongoing project in our group involves the structure based drug design of novel compounds and evaluation of their inhibitory activity against human 11 $\beta$ -HSD1. Our previous studies indicated that some aryl sulphonamide and aryl carboxamide derivative possess moderate inhibitory activity on purified human 11 $\beta$ -HSD1. Compounds **1** and **2** (Fig. 2) exhibited inhibition of human hepatic microsomal 11 $\beta$ -HSD1 with IC<sub>50</sub> values in the low micromolar range (Su et al., 2006; Vicker et al 2007). It is important to have an array of structural types of 11 $\beta$ -HSD1 inhibitors as the physicochemical properties of the

compounds will determine tissue distribution, HPA effects, and ultimately clinical utility. Here we report the discovery and the structure-activity relationships of some adamantyl carboxamide compounds as novel, potent and selective inhibitors of 11 $\beta$ -HSD1 in a HEK-293 cell line.

**(Insert Figure 2)**

## **2. Methods**

### **2.1 Synthesis of target compounds (3-14)**

Compounds **3-14** were synthesized from 1-adamantyl carbonyl chloride or 1-adamantyl acetic acid through an amide coupling reaction with various amines under standard conditions (Vicker et al., 2006). Melting points were determined using a Stanford Research Systems Optimelt and are uncorrected. <sup>1</sup>H NMR spectra were recorded with a JEOL Delta 270 spectrometer and chemical shifts are reported in parts per million (ppm,  $\delta$ ) relative to tetramethylsilane (TMS) as an internal standard. LC/MS spectra were obtained on a Waters Micromass ZQ with Atmospheric Pressure Chemical Ionization (APCI). High resolution mass spectra were recorded on a Bruker MicroTOF with Electrospray Ionisation (ESI). HPLC analyses were performed on a Waters Millennium 32 instrument equipped with a Waters 996 PDA detector, using a Symmetry C18 reverse phase column (4.6 x 150 mm) eluting with 10% H<sub>2</sub>O/MeCN.

General method A: To a solution of 1-adamantyl carbonyl chloride (0.26 mmol) in dichloromethane (DCM, 5 mL) was added triethylamine (0.1 mL), followed by the corresponding amine (0.25 mmol). The reaction mixture was stirred at ambient temperature under nitrogen overnight. Polymer supported trisamine (4.1 mmol/g, 100 mg) was added; the mixture was stirred at room temperature for 2 h, filtered and concentrated *in vacuo* to give the crude product. Purification by flash chromatography gave the adamantyl carboxamide.

General method B: To a solution of the 1-adamantane acetic acid (0.5 mmol) in DCM (8 mL) were added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDCI, 0.6 mmol), 4-(dimethylamino) pyridine (DMAP, 10 mg) and triethylamine (0.1 mL) at room temperature. After stirring for 0.5 h, the corresponding amine (0.5 mmol) was added to the reaction mixture. After 12 h the mixture was partitioned between DCM and brine and the organic layer was washed with brine, dried over MgSO<sub>4</sub> and concentrated *in vacuo*. The crude product was purified with flash chromatography to give the adamantyl acetamide.

**(Insert Scheme 1)**

***N*-(4-Chloro-2-methyl-1,3-benzothiazol-5-yl)adamantane-1-carboxamide (3).** The compound was prepared using general method A to give a white solid in 53% yield. mp 183.5-185.5 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.78 (6H, m), 2.03 (6H, d, *J* = 3.0 Hz), 2.12 (3H, s), 2.86 (3H, s), 7.68 (1H, d, *J* = 8.9 Hz), 8.12 (1H, s) and 8.50 (1H, d, *J* = 8.9 Hz); LC/MS (APCI) *m/z* 361 (M+H)<sup>+</sup>; HRMS (FAB) calcd. for C<sub>19</sub>H<sub>22</sub>ClN<sub>2</sub>OS (M+H)<sup>+</sup> 361.1141, found 361.1147; HPLC *t<sub>R</sub>* 3.90 min (>99%).

***N*-[2-(Thiophen-2-yl)ethyl]adamantane-1-carboxamide (4).** The compound was prepared using general method A to give a white solid in 78% yield. mp 123-126 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.69 (6H, m), 1.80 (6H, d, *J* = 2.8 Hz), 2.01 (3H, s), 3.01 (2H, t, *J* = 5.9 Hz), 3.49 (2H, q, *J* = 6.1 Hz), 5.73 (1H, broad), 6.81 (1H, m), 6.95 (1H, dd, *J* = 5.1, 1.0 Hz) and 7.16 (1H, dd, *J* = 5.2, 1.2 Hz); LC/MS (APCI) *m/z* 290 (M+H)<sup>+</sup>; HRMS (ESI) calcd. for C<sub>17</sub>H<sub>24</sub>NOS (M+H)<sup>+</sup> 290.1579, found 290.1576; HPLC *t<sub>R</sub>* 2.65 min (>99%).

***N*-(Thiophen-2-ylmethyl)adamantane-1-carboxamide (5).** The compound was prepared using general method A to give a white solid in 87% yield. mp 155-155.5 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.70 (6H, m), 1.86 (6H, d, *J* = 3.0 Hz), 2.03 (3H, s), 4.60 (2H, d, *J* = 5.6 Hz), 5.88 (1H, broad), 6.93

(2H, m) and 7.21 (1H, dd,  $J = 3.0, 1.0$  Hz); LC/MS (APCI)  $m/z$  276 (M+H)<sup>+</sup>; HRMS (ESI) calcd. for C<sub>16</sub>H<sub>22</sub>NOS (M+H)<sup>+</sup> 276.1422, found 276.1422; HPLC  $t_R$  2.52 min (>99%).

***N*-Methyl-*N*-[2-(thiophen-2-yl)ethyl]adamantane-1-carboxamide (6).** The compound was prepared using general method A to give a white solid in 60% yield. mp 95-99 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  1.67 (6H, m), 2.00 (9H, broad), 3.02 (3H, s), 3.06-3.09 (2H, m), 3.61 (2H, t,  $J = 7.4$  Hz), 6.81-6.82 (1H, m), 6.92 (1H, dd,  $J = 3.2, 5.0$  Hz), 7.13 (1H, dd,  $J = 1.0, 5.0$  Hz); LC/MS (APCI)  $m/z$  304 (M+H)<sup>+</sup>; HRMS (ESI) calcd. for C<sub>18</sub>H<sub>26</sub>NOS (M+H)<sup>+</sup> 304.1735, found 304.1718; HPLC  $t_R$  3.22 min (98%).

***N*-Methyl-*N*-(thiophen-2-ylmethyl)adamantane-1-carboxamide (7).** The compound was prepared using general method A. Colourless thick oil was obtained in 81% yield. <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  1.71 (6H, m), 2.03 (9H, s), 3.07 (3H, s), 4.73 (2H, s), 6.90-6.95 (2H, m) and 7.21 (1H, dd,  $J = 4.4, 1.7$  Hz); LC/MS (APCI)  $m/z$  290 (M+H)<sup>+</sup>; HRMS (ESI) calcd. for C<sub>17</sub>H<sub>24</sub>NOS (M+H)<sup>+</sup> 290.1579, found 290.1575; HPLC  $t_R$  3.89 min (97%).

**2-Adamantan-1-yl-*N*-methyl-*N*-thiophen-2-ylmethyl-acetamide (8).** The compound was prepared using general method B to give a in 68% yield. mp 107-109 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  1.62-1.77 (12H, m), 2.00 (3H, broad), 2.19 (2H, s), 3.00 (3H, s), 4.52 (2H, s), 6.95 (2H, m) and 7.23 (1H, dd,  $J = 5.0, 1.3$  Hz); LC/MS (APCI)  $m/z$  304 (M+H)<sup>+</sup>; HRMS (ESI) calcd. for C<sub>18</sub>H<sub>26</sub>NOS (M+H)<sup>+</sup> 304.1735, found 304.1726; HPLC  $t_R$  4.04 min (>99 %).

***N*-Methyl-*N*-(thiophen-3-ylmethyl)adamantane-1-carboxamide (9).** The compound was prepared using general method A to give a colourless oil in 86% yield. <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  1.70 (6H, s), 2.03 (9H, s), 3.00 (3H, s), 4.63 (2H, s), 6.95 (1H, dd,  $J = 4.9, 1.2$  Hz), 7.05 (1H, dd,  $J = 3.0, 1.2$  Hz) and 7.27 (1H, dd,  $J = 4.9, 3.0$  Hz); LC/MS (APCI)  $m/z$  290 (M+H)<sup>+</sup>; HRMS (ESI) calcd. for C<sub>17</sub>H<sub>23</sub>NOS (M+H)<sup>+</sup> 290.1579, found 290.1566; HPLC  $t_R$  6.87 min (>99 %).

**2-(Adamantan-1-yl)-*N*-methyl-*N*-(thiophen-3-ylmethyl)acetamide (10).** The compound was prepared using general method B to give a white solid in 49% yield. mp 69-71 °C; <sup>1</sup>H NMR

(CDCl<sub>3</sub>) signals from rotamers in 2:1 ratio  $\delta$  1.55-1.75 (12H, m), 1.95 (3H, broad), 2.16 (2H, s), 2.95 (3H, s), 4.57 (2H, s), 7.02 (1H, m), 7.11 (1H, m) and 7.26 (1H, m);  $\delta$  1.55-1.75 (12H, m), 1.95 (3H, broad), 2.19 (2H, s), 2.92 (3H, s), 4.54 (2H, s), 6.91 (1H, m), 7.02 (1H, m) and 7.33 (1H, m); LC/MS (APCI)  $m/z$  304 (M+H)<sup>+</sup>; HRMS (ESI) calcd. for C<sub>18</sub>H<sub>26</sub>NOS (M+H)<sup>+</sup> 304.1735, found 304.1718; HPLC  $t_R$  2.90 min (>99 %).

**5-(Adamantan-1-ylcarbonyl)-4H,5H,6H,7H-thieno[3,2-c]pyridine (11).** The compound was prepared using general method A to give a white solid in 33% yield. mp 141-143 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  1.72 (6H, s), 2.02 (9H, s), 2.88 (2H, t,  $J$  = 4.6 Hz), 3.94 (2H, t,  $J$  = 4.5 Hz), 4.69 (2H, s), 6.79 (1H, d,  $J$  = 5.2 Hz) and 7.11 (1H, d,  $J$  = 5.2 Hz); LC/MS (APCI)  $m/z$  302 (M+H)<sup>+</sup>; HRMS (ESI) calcd. for C<sub>18</sub>H<sub>24</sub>NOS (M+H)<sup>+</sup> 302.1579, found 302.1573; HPLC  $t_R$  3.24 min (>99 %).

**N-(Furan-2-ylmethyl)-N-methyladamantane-1-carboxamide (12).** The compound was prepared using general method A to give a white solid in 95% yield. mp 53.5-54.5 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  1.70 (6H, s), 2.02 (9H, s), 3.06 (3H, s), 4.59 (2H, s), 6.19 (1H, dd,  $J$  = 3.2, 0.7 Hz), 6.31 (1H, dd,  $J$  = 3.2, 1.7 Hz) and 7.33 (1H, dd,  $J$  = 1.7, 0.7 Hz); LC/MS (APCI)  $m/z$  274 (M+H)<sup>+</sup>; HRMS (ESI) calcd. for C<sub>17</sub>H<sub>24</sub>NO<sub>2</sub> (M+H)<sup>+</sup> 274.1807, found 274.1794; HPLC  $t_R$  6.14 min (>99 %).

**N-[(1-Methyl-1H-pyrrol-2-yl)methyl]adamantane-1-carboxamide (13).** The compound was prepared using general method A to give a white solid in 76% yield. mp xxx; <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  1.58-1.75 (6H, m), 1.83 (6H, d,  $J$  = 2.8 Hz), 2.02 (3H, broad), 3.53 (3H, s), 4.42 (2H, d,  $J$  = 5.2 Hz), 5.60 (1H, broad), 6.05 (2H, d,  $J$  = 2.2 Hz) and 6.65 (1H, t,  $J$  = 2.2 Hz); LC/MS (APCI)  $m/z$  271 (M-H)<sup>+</sup>; HRMS (ESI) calcd. for C<sub>17</sub>H<sub>24</sub>N<sub>2</sub>NaO (M+Na)<sup>+</sup> 295.1786, found 295.1768; HPLC  $t_R$  2.67 min (>99%).

**N-Methyl-N-[(1-methyl-1H-pyrrol-2-yl)methyl]adamantane-1-carboxamide (14 XDS04112, STX2133).** The compound was prepared using general method A to give a white solid in 87% yield. mp 104-105.5 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  1.76 (6H, s), 2.02 (9H, s), 3.02 (3H, s), 3.50 (3H, s),



4.61 (2H, s), 6.03 (2H, d,  $J = 2.3$  Hz) and 6.58 (1H, t,  $J = 2.2$  Hz); LC/MS (APCI)  $m/z$  287 (M+H)<sup>+</sup>; HRMS (ESI) calcd. for C<sub>18</sub>H<sub>27</sub>N<sub>2</sub>O (M+H)<sup>+</sup> 287.2123, found 287.2108; HPLC  $t_R$  6.58 min (>99 %).

## **2.2. 11 $\beta$ -HSD1 Scintillation Proximity Assay (SPA) Protocol: Human Cell Based Assay**

Untransfected HEK-293 cells lack endogenous 11 $\beta$ -HSD1 activity and this cell line has been shown to be a suitable system for evaluating 11 $\beta$ -HSD1 activity after being transfected with the plasmid for expression of 11 $\beta$ -HSD1 or 11 $\beta$ -HSD2 (Schweizer et al., 2003). The high-throughput cell-based assays were conducted on the human 11 $\beta$ -HSD1 transfected HEK-293 cell line with an SPA (Vicker et al., 2006). The activity of 11 $\beta$ -HSD1 is measured in whole HEK-293 cells stably transfected with the HSD11B1 gene using modified literature protocols (Schweizer et al., 2003). Cells are incubated in 96-well microplates in the presence of tritiated substrate. Enzyme activity is determined by measuring the amount of tritiated product by SPA. Assay plates contain internal high and low controls to allow calculation of percentage inhibition. Each well of a 96-well culture plate is seeded with HEK293/HSD11B1 cells in 100  $\mu$ L medium. When the cells are 80% confluent the medium is removed from each well. Then 100  $\mu$ L fresh, serum-free medium containing <sup>3</sup>H-cortisone and test compound in 1% DMSO is added to each well, including control wells. High control wells do not contain compound, while low controls do not contain cells. The plate is incubated at 37 °C for the required time period, after which, 50  $\mu$ L of media is removed from each well and transferred to a microplate containing 100  $\mu$ L of a pre-incubated mixture of anti-cortisol antibody and SPA bead (Fig.3). The mixture is incubated with gentle shaking until equilibrium is reached, before transferring to a scintillation counter to establish the enzyme activity in each sample.

**(Insert Figure 3)**

### 3. Molecular Modelling

The crystal structure of one subunit of human 11 $\beta$ -HSD1 (IXU9) from the Protein Data Bank was used in docking studies with the cofactor NADP<sup>+</sup> present (Hosfield et al., 2005; Berman et al., 2000). The docking studies of compound **8** were performed with GOLD, version 3.1.1. Fifteen docks were performed and the GOLDScore fitness function was used to rank the docked conformations. The top three highest ranked docks were virtually identical with the top scored dock. A similar study was also performed with the substrate; the docked conformations are depicted in figure 4 below. The key residues involved in catalysis, Ser170 and Tyr183 in the active site, together with the cofactor are shown. It can be seen that the substrate and inhibitor dock in similar positions with the 11-keto carbonyl of cortisone and the carbonyl of the carboxamide in close proximity to the hydroxyl of Tyr183 and the *pro* (*S*) hydrogen of the cofactor which is transferred during the substrate reduction. The distance between the oxygen of Tyr183 and the 11-keto carbonyl of cortisone and the carboxamide carbonyl are  $\sim 2.8$  Å and 2.3 Å respectively. The adamantyl moiety is buried deep in the binding pocket forming favourable hydrophobic interactions with the side chains of Thr124, Ala223 and Ile121, whereas the thiophenyl ring stays close to the opening of the pocket, and interacts with the side chain of Leu126, Tyr177 and Val180. Clearly the inhibitor fits very well into the substrate pocket of the active site.

**(Insert Figure 4a and 4b)**

### 4. Results and Discussion

Our previous studies indicated that some aryl sulphonamide and aryl carboxamide derivatives possess moderate inhibitory activity on purified human 11 $\beta$ -HSD1. Compounds **1** and **2** (Fig. 2) exhibited inhibition of human hepatic microsomal 11 $\beta$ -HSD1 with IC<sub>50</sub> values in the

low micromolar range (Su et al., 2006; Vicker et al 2007). However, these compounds showed only < 50% inhibition at 10  $\mu$ M concentration when tested in HEK-293 cells transfected with human 11 $\beta$ -HSD1. The highly hydrophobic adamantyl carboxamide moiety was used to replace the aryl carboxamide or sulphonamide group in these molecules which led to a slightly increased activity. Compound **3** exhibited inhibitory activity on the HEK-293 cell line with an IC<sub>50</sub> value of 5280 nM, which provided a springboard for further optimisation. The replacement of the substituted benzothiazole ring in **3** with a 2-thiophenyl group attached to a flexible two-carbon tether gave **4** with an IC<sub>50</sub> value of 679 nM, an 8-fold increase of activity. Further modification of **4** with the linker reduced by one methylene unit or *N*-methylation generated compound **5** or **6** with 1.5-fold improvement of activity. The combination of these modifications gave **7** with an IC<sub>50</sub> of 229 nM, a further 3-fold increase of potency over **4**. Introducing a methylene unit between the adamantyl moiety and the carbonyl group gave **8** with no improvement in activity over **7**. The cyclised compound **11** with limited flexibility in the linker lost activity by 2-fold in comparison with **7**. On the other hand, replacing the 2-thiophenyl group in **7** with a 3-thiophenyl group resulted in compound **9** with an IC<sub>50</sub> of 125 nM, an increase of activity by 2-fold; whereas its analogue **10** with an extra methylene unit between the adamantyl and carbonyl group only showed an IC<sub>50</sub> of 350 nM. The substitution of the 2-thiophenyl group in **7** with a furanyl group retained the activity at the same level; whereas the substitution with *N*-methylpyrrole gave the most potent compound **14** in the series with an IC<sub>50</sub> of 113 nM. The effect of *N*-methylation of the carboxamide group is significant when comparing **14** with **13**, improving the potency by 15-fold. The most potent inhibitor **14** is ~50 fold more active than the initial lead compound **3**. These novel inhibitors are also selective over 11 $\beta$ -HSD2. Compounds **5** and **7** exhibited moderate metabolic stability on human liver microsomes. Furthermore, they do not inhibit the key CYP's 1A2, 3A4BQ, 2D6, 2C9, 2C19 and have IC<sub>50</sub> values of ~ 10  $\mu$ M for the inhibition of CYP

3A4BFC. Compound **5** was also tested on apical to basolateral transport across CaCo2 (TC7) monolayers; the result showed a high Papp rank indicating good permeability.

**(Insert Table 1)**

## **5. Conclusions**

Here we report the discovery of adamantyl carboxamide derivatives as novel potent selective inhibitors of human 11 $\beta$ -HSD1. The target compounds were synthesised through an amide formation reaction and their ability to inhibit human 11 $\beta$ -HSD1 was evaluated on a HEK-293 cell line stably transfected with the HSD11B1 gene. The SAR studies indicate that an adamantyl carboxamide linking to an aromatic system, such as thiophene, furan or N-methyl pyrrole through a methylene unit can lead to potent novel selective inhibitors of 11 $\beta$ -HSD1. N-Methylation of the carboxamide group significantly improves inhibitory activity. Potent compounds **9** and **14** inhibit human 11 $\beta$ -HSD1 with the IC<sub>50</sub> values in 100 nM range, a 50-fold increase over the initial lead compound. Docking studies with compound **8** into the crystal structure of human 11 $\beta$ -HSD1 reveal how the molecule may interact with the enzyme and cofactor. Compounds **7** and **14** show properties as candidates worthy of further preclinical investigation. In addition to being selective over human 11 $\beta$ -HSD2, compounds **7** and **14** are inactive on human 17 $\beta$ -hydroxysteroid dehydrogenase type 1. Furthermore, they are also potent on murine 11 $\beta$ -HSD1 and are currently under *in vivo* evaluation in a C57BL/C mouse model.

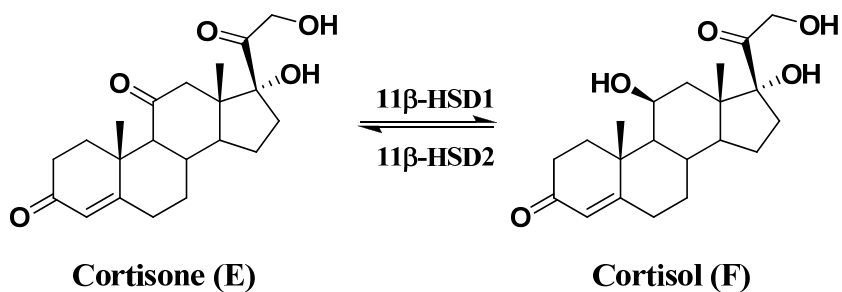
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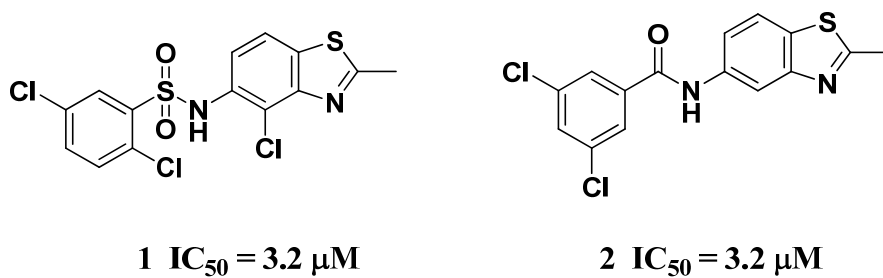
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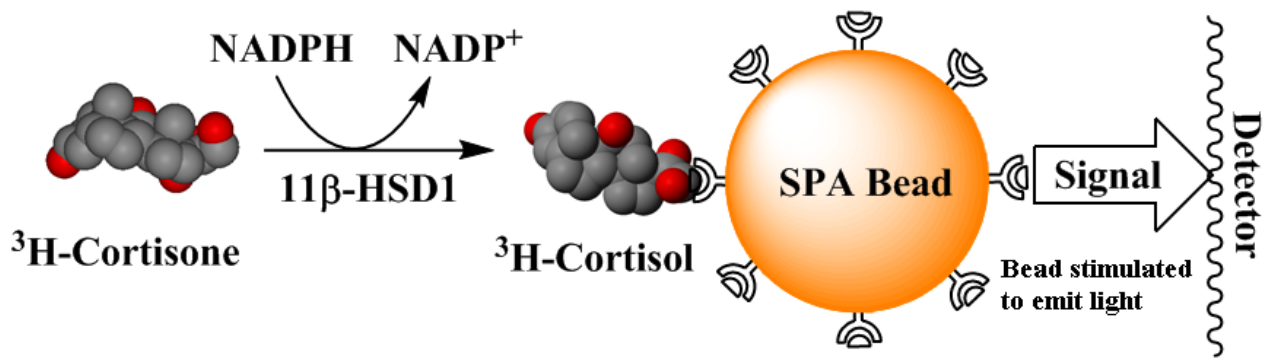
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**Figure 1.** Interconversion of cortisone - cortisol

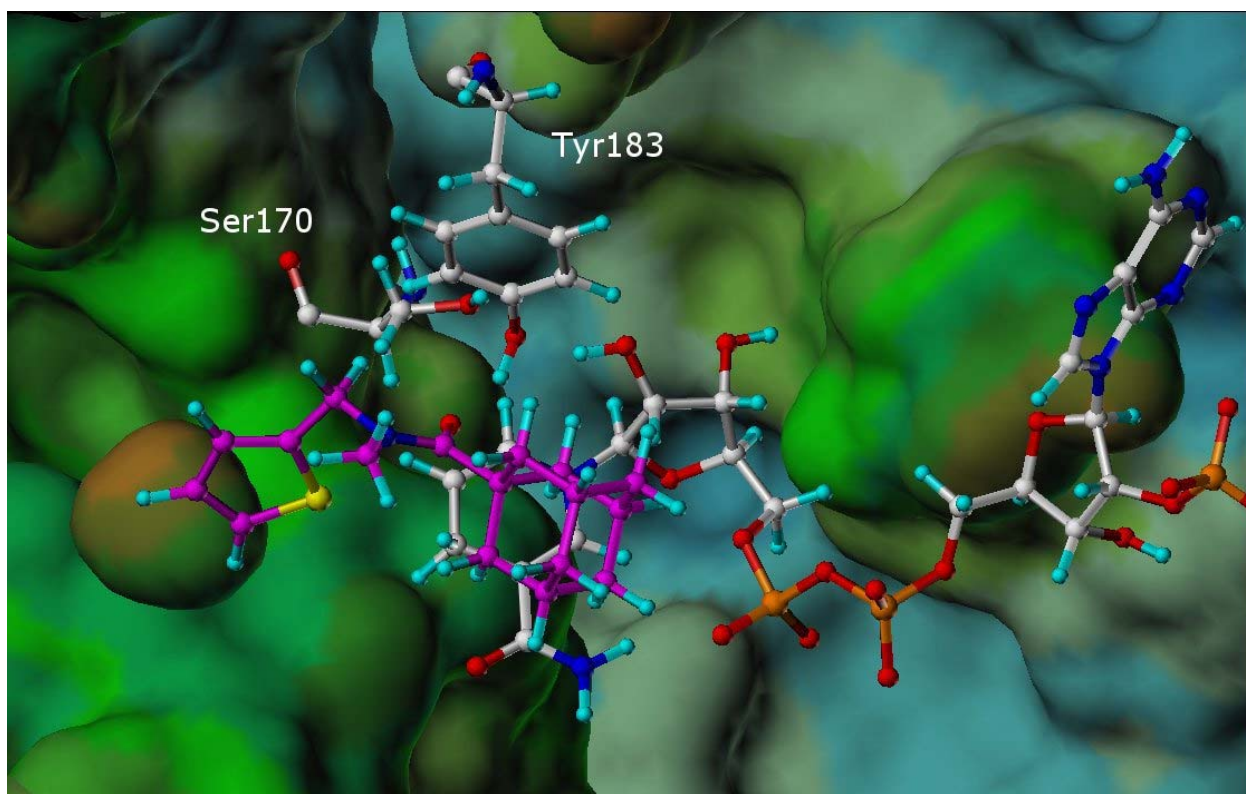


**Figure 2.** Structures of inhibitors of human 11 $\beta$ -HSD1

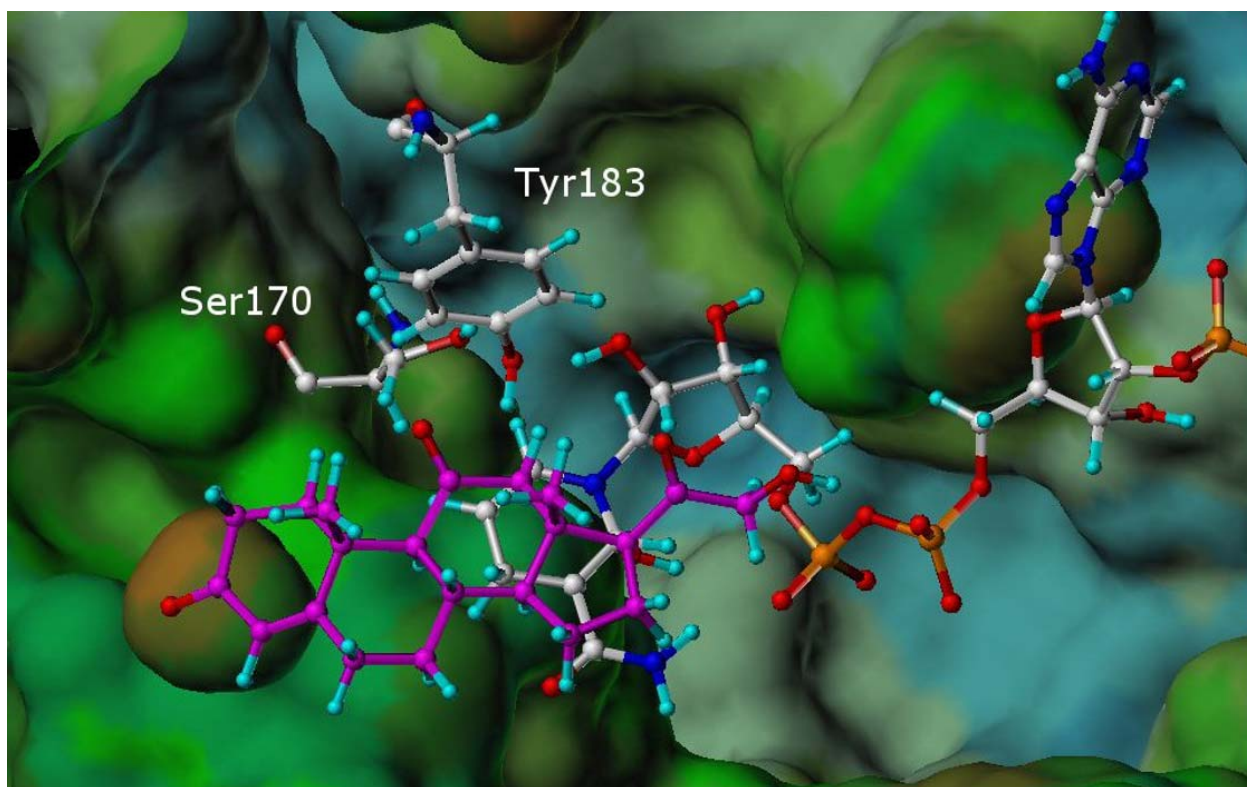


**Figure 3.** 11β-HSD1 Scintillation Proximity Assay (SPA) assay principle

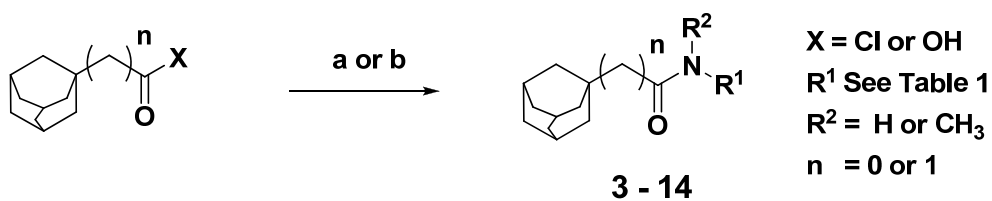




**Figure 4a.** Compound **8** in magenta docked into 1XU9 in the presence of  $\text{NADP}^+$ . The protein surface is colour mapped to show a gradient from amino acid residues that are electron donors in brown, through to hydrophobic areas in green and electron acceptors in blue.



**Figure 4b.** Cortisone in magenta docked into 1XU9 in the presence of NADP<sup>+</sup>. The protein surface is colour mapped to show a gradient from amino acid residues that are electron donors in brown, through to hydrophobic areas in green and electron acceptors in blue.

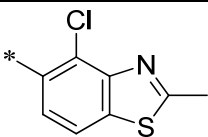
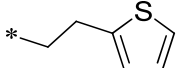
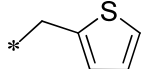
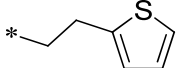
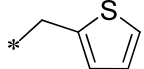
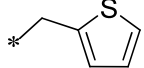
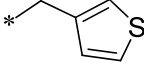
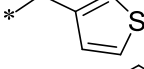
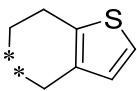
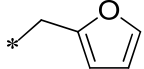
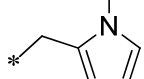
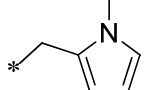


**Scheme 1:** Synthesis of 1-adamantyl carboxamide or acetamide derivatives

*Reagents and Conditions:* a) X=Cl, R<sup>1</sup>R<sup>2</sup>NH, Et<sub>3</sub>N/DCM;

b) X=OH, R<sup>1</sup>R<sup>2</sup>NH, EDCI, DMAP, Et<sub>3</sub>N/DCM

**Table 1. Inhibition of Human 11 $\beta$ -HSD1 in HEK-293 Cells**

Cpd	R <sup>1</sup>	R <sup>2</sup>	n	IC <sub>50</sub> (nM)
3		H	0	5280
4		H	0	679
5		H	0	403
6		CH <sub>3</sub>	0	448
7		CH <sub>3</sub>	0	229
8		CH <sub>3</sub>	1	308
9		CH <sub>3</sub>	0	125
10		CH <sub>3</sub>	1	350
11			0	435
12		CH <sub>3</sub>	0	249
13		H	0	1700
14		CH <sub>3</sub>	0	113

\* indicating the point of attachment.