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Research Article

Synthesis and Docking Studies of the Novel *N*-(2,2-Di(1H-pyrrol-2-yl)ethyl)adamantane-1-carboxamide, a Potential 11β-HSD1 Inhibitor

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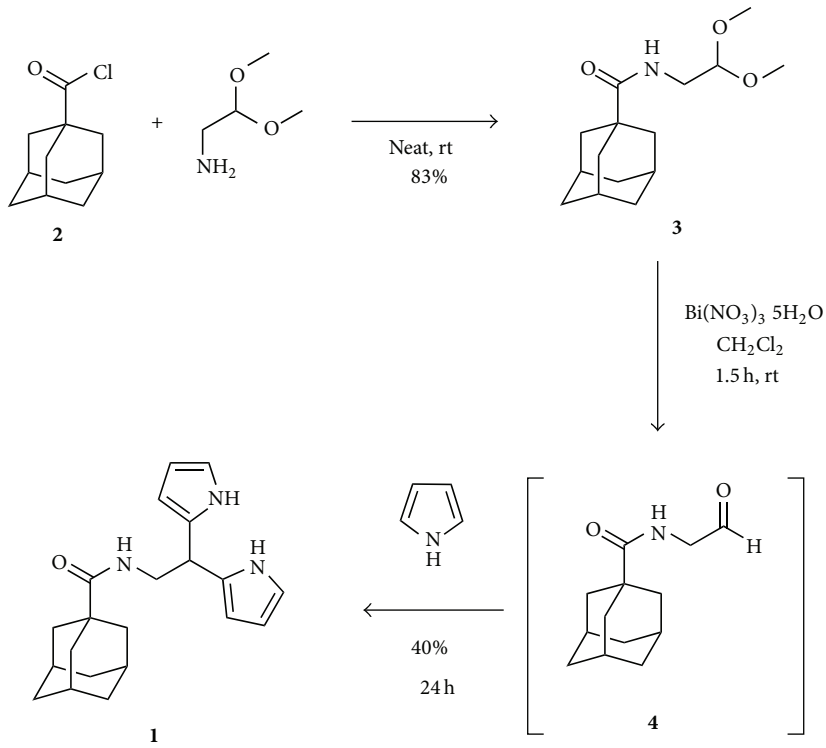
The synthesis of the novel 1-adamantyl-(*N*-*meso*-dipyrrolylmethylene)-carboxamide is described, providing a three-step, two-pot reaction. Docking studies with 11β-HSD1 revealed favorable binding interactions with the enzyme.

1. Introduction

The intracellular levels of glucocorticoids, a class of steroid hormones that bind to the glucocorticoid receptor, are regulated by two isoforms of the 11β-hydroxysteroid dehydrogenase enzymes type 1 (11β-HSD1) and type 2 (11β-HSD2) [1–4]. 11β-HSD1 functions in humans as an NADPH-dependent reductase that converts cortisone to the active glucocorticoid cortisol. 11β-HSD2 catalyzes the reverse reaction and modulates the 11β-HSD1 activity [5]. Selective inhibitors of 11β-HSD2 are expected to benefit a variety of metabolic disorders, including insulin resistance, dyslipidemia, and obesity. 2-Amino-*N*-(adamant-2-yl) acetamide was found to act, in a mouse model, as a potent and selective 11-β-hydroxysteroid dehydrogenase (HSD) inhibitor [6]. The compound lowered body weight, insulin levels, fasting glucose levels, triglycerides, and cholesterol in diet-induced obese mice. Since this discovery, a series of adamantyl derivatives (adamantane carboxamides) were synthesized and shown to have cellular activity and tissue penetration properties [7]. Supramolecular recognition is essential in material science, sensors, and nanosponges, among other applications. It is also nearly impossible to understand molecular mechanisms of action in biological systems without considering supramolecular recognition. Among the compounds that display excellent supramolecular recognition properties are the pyrrole derivatives, which typically form hydrogen bonds with anions. Compounds bearing pyrrole-like porphyrinoids [8], 4,4-difluoro-4-bora-3a,4a-diaza-s-indacenes (BODIPY-based systems) [9, 10], and calixpyrroles have played an important role in the recognition of anions [11]. Pyrrole derivatives have been extensively explored in medicinal chemistry studies of DNA groove binders [12], cytotoxic agents [13], DNA intercalators [14], and anti-inflammatory agents [15], to mention a few. This 5-member heterocycle has been used as a bioisosteric replacement moiety for pyrazoles and amides [16]. Dipyrroles are synthetically versatile and reactive, and they engage in molecular recognition [11]. On the other hand, the adamantyl group is present in compounds in current clinical use and in many more compounds that are in development as potential therapeutics [17].

In an effort to synthesize dipyrromethane derivatives that could act as anion recognizers with biological activity, we prepared a novel *N*-(2,2-di(1H-pyrrol-2-yl)ethyl)adamantane-1-carboxamide **1** (Figure 4) as a structural analog of 2-amino-*N*-(adamant-2-yl) acetamide inhibitors of the 11β-HSD. A docking analysis suggested the formation of a favorable interaction with the enzyme 11β-HSD1.



Scheme 1: Synthesis of compound **1**.

2. Results and Discussion

2.1. Synthesis. The synthesis of compound **1** is illustrated in Scheme 1. First, adamantanoyl chloride **2** reacted with acetaldehyde dimethyl aminoacetal without a solvent at room temperature to give the acetal **3** with an 83% yield after column purification. Deprotection of the aldehyde was not as easy as expected for typical acetals; in fact, deprotection failed in protic acidic media, probably due to the presence of the carboxamide. $Bi(NO_3)_3{\cdot}5H_2O$ salt has been described as an efficient catalyst for the chemoselective deprotection of dimethylacetal to afford the corresponding aldehyde in high yield [18].

Although the reaction gave the corresponding aldehyde **4** after 2 h of reaction, the compound was unstable and underwent decomposition during an attempt to purify. Faced with the difficulty of purifying compound **4**, we decided to carry out the reaction in situ once the aldehyde had been obtained. The success of this reaction required the identification of the best possible conditions. To this end, we followed the appearance of the product over time using ^{1}H NMR spectroscopy. Figure 1 shows that the aldehyde definitely appeared after 1 h of the reaction, and at 1.5 h, the acetal had completely reacted. Contrary to expectations, after 2 h, compound **4** began to react to again give the acetal **3**. After 24 h, the reversibility of the reaction was apparent.

One possible explanation for the reversibility is that $Bi(NO_3)_3{\cdot}5H_2O$ liberated nitric acid, as has been observed in the condensation of acetone with pyrrole in the presence of a bismuth nitrate catalyst [19].

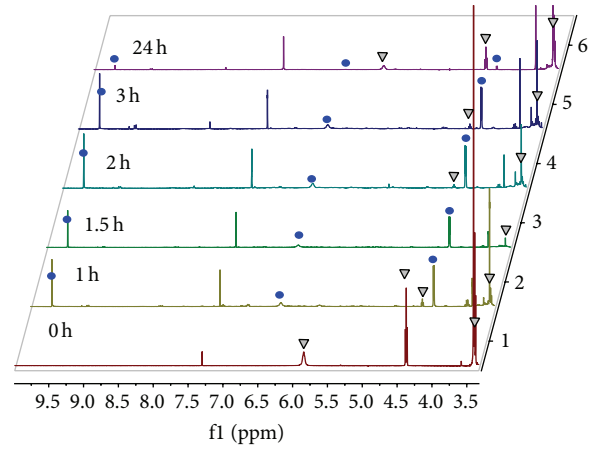


Figure 1: ^{1}H NMR spectra in $CDCl_3$ of the crude reaction of **3** with $Bi(NO_3)_3$ at different reaction times. The triangles indicate the signals associated with compound **3**, and the circles indicate the corresponding aldehyde signals.

Once the aldehyde deprotection reaction had been optimized (with a 1.5 h acetal reaction time), the pyrrane condensation was carried out in the same reaction mixture by adding pyrrole in excess. The addition of another catalyst was unnecessary because pyrrole has been observed to react with carbonyls to give dipyrroles when catalyzed by a bismuth salt [20]. Compound **1** was obtained in a 40% yield after chromatographic purification. The final

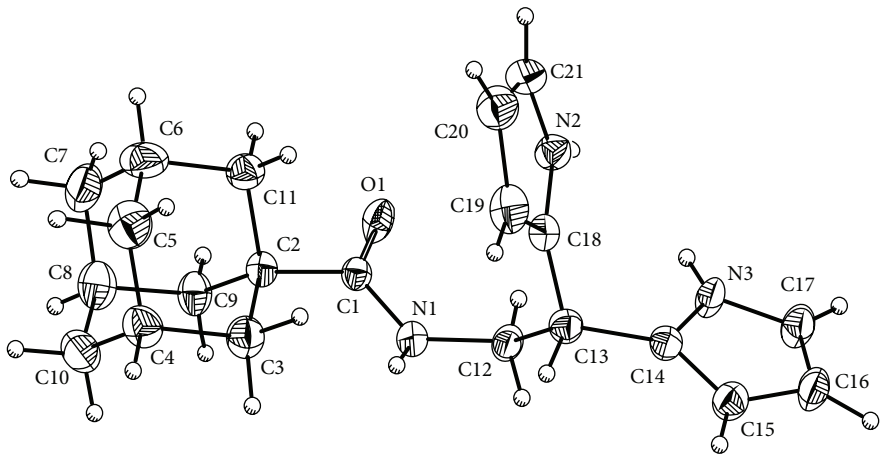


Figure 2: X-ray crystal structure of **1** (ORTEP, the displacement ellipsoids are scaled to the 50% probability level).

confirmation of the structure assignment of 1-adamantyl-(*N-meso*-dipyrrolylmethylene)-carboxamide came from single-crystal X-ray analysis. The single crystal was obtained from dichloromethane. The crystal structure of **1** is shown in Figure 2.

2.2. Docking Studies. The minimum energy of the ligand was calculated using DFT calculations using the hybrid orbital B3LYP with the 3-21G bases sets (Gaussian 98) [21]. The torsional degrees of freedom, Gasteiger atomic partial charges, and polar hydrogen selection were assigned in the AutoDockTools 1.5.6. [22]. The complete protein sequence (accession code P28845, available from the http://www.uniprot.org/ database) was aligned with the crystallized protein structure obtained from the Protein Data Bank using the protein BLAST (http://blast.ncbi.nlm.nih.gov/) by selecting a sequence crystal in the presence of the inhibitor 2-(2-chloro-4-fluorophenoxy)-2-methyl-*N*-[(1*R*,2*S*,3*S*,5*S*,7*S*)-5-(methyl sulfonyl)-2-adamantyl]propanamide (NN1) (Code PDB: 2ILT). The merged protein nonpolar hydrogen atoms and the Kollman charges were assigned in AutoDockTools 1.5.6. The ligand was docked initially in a directed matter into the catalytic site of the enzyme centered in the grid box around the residue TYR 183, reported in the uniprot database as the active site of the enzyme (grid box 60 × 60 × 60 Å). A blind docking study was carried out with an expanded box (120 × 120 × 120 Å) by locating the center of the box over the midpoint of the protein. In both cases, the grid spacing was 0.375 Å. The docking runs were separated using a Lamarckian hybrid genetic algorithm with an initial population of 100 randomly selected individuals and a maximum number of 1 × 107 energy evaluations. The RMSD values were obtained using PyMOL, and the interactions were visualized using the Discovery Studio 3.5 Client and PyMOL Molecular Graphics System, version 1.5.0.4. [23].

Compound **1** was oriented toward the hydrophobic pocket by exploiting the NN1 adamantyl carboxamide 11β-HSD1 inhibitors (Figure 3(a)). The compound interacted with the amino acids Ser 170 and TYR 183 through hydrogen bonds with the active site, as shown in Figures 3(c) and 3(d).

Table 1: Binding energy and kI for compounds **1** and NN1 toward the 11β-HSD1 active site calculated from the docking studies.

Compound	Binding energy (ΔG)	kI (nM)
1	−9.68	80.64
NN1	−10.4	23.97

Figure 3(b) shows the superimposition of compound **1** (in yellow) and NN1 (Green), giving an RMSD of 1.162 Å after docking. The interaction energy is listed in Table 1.

3. Experimental Section

3.1. Materials. Nuclear magnetic resonance spectra were recorded on a Varian Gemini 200 and Mercury 400. ^{1}H NMR spectra were recorded at 200 and 400 MHz and are reported as follows: chemical shift in ppm relative to TMS as an internal standard (for spectra obtained in $CDCl_3$), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, and m = multiplet or overlap of nonequivalent resonances). ^{13}C NMR spectra were recorded at 100 MHz, chemical shift in ppm relative to TMS from the solvent signal ($CDCl_3$ δ 77.0 ppm).

Reagents and solvents were of the highest quality available and used as received. TLC was performed on silica gel plates visualized with a UV lamp at 254 nm. Flash chromatography was performed on Aldrich silica gel (70–230 mesh).

*3.2. Synthesis of N-(2,2-Dimethoxyethyl)adamantane-1-carboxamide **3**.* Aminoacetaldehyde dimethyl acetal (1.5 mL) was dropped to 1-adamantanecarbonyl chloride (0.3 g, 1.5 mmol) at ambient temperature. The precipitated was washed with distilled water (3 × 10 mL). The crude reaction mixture was diluted with EtOAc (10 mL) and extracted with water (3 × 10 mL). The combined organic layers were dried with Na_2SO_4, filtered, and concentrated in vacuo. Purification by column chromatography (silica gel 70–230 mesh, hexane : EtOAc 6 : 4) afforded the title compound **3** (0.34 g, 83%) as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.82–1.62 (m, 6H), 1.85 (d, J = 2.7 Hz, 6H), 2.06 (d, J = 9.6 Hz, 3H), 3.53–3.24 (m, 8H),

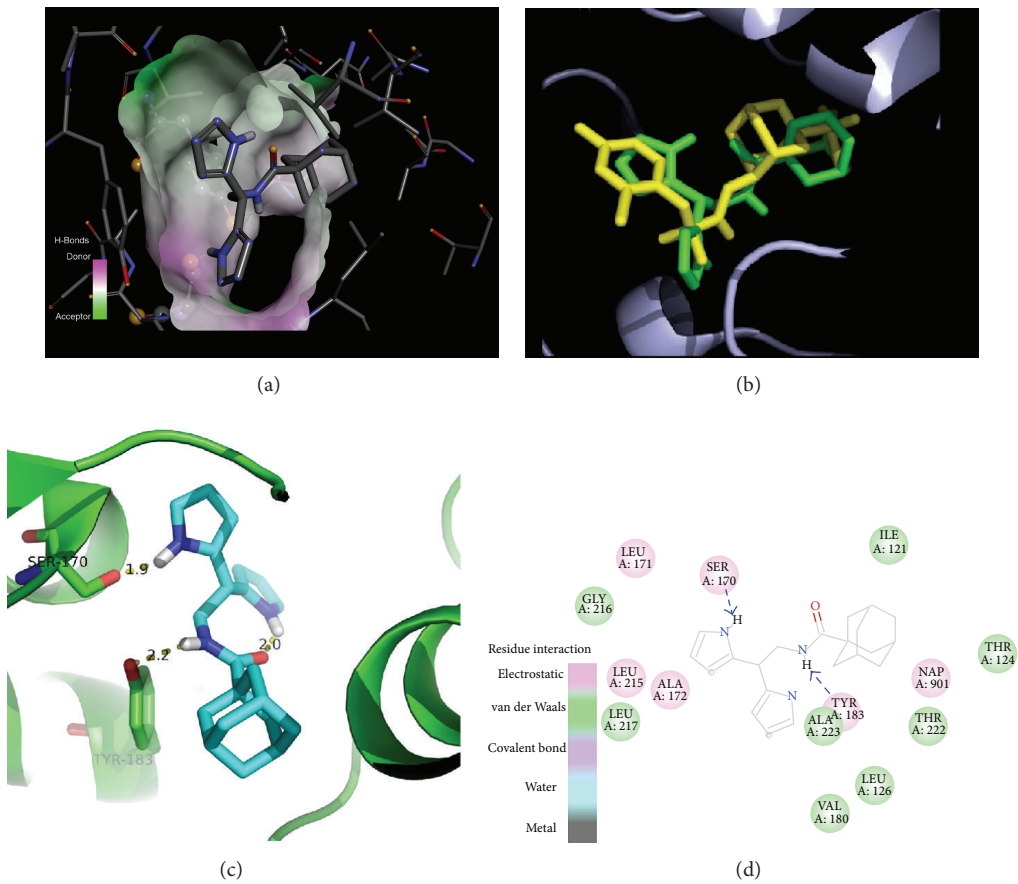


Figure 3: (a) Compound **1** docked in the active site. (b) Comparison of compound **1** and 2-(2-chloro-4-fluorophenoxy)-2-methyl-*N*-[(1*R*,2*S*,3*S*,5*S*,7*S*)-5-(methylsulfonyl)-2-adamantyl]propanamide after docking. (c) Hydrogen bonding interactions between compound **1** and the amino acid residues Ser 170 an TYR 183. (d) Binding pocket of compound **1**.

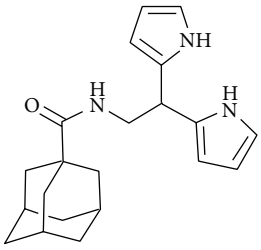


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Figure 4: *N*-(2,2-di(1H-pyrrol-2-yl)ethyl)adamantane-1-carboxamide **1**.

4.37 (t, J = 5.4 Hz, 8H), 5.84 (s, ^{1}H). ^{13}C NMR ($CDCl_3$, 100 MHz): 28, 26.4, 39. 40.5, 40.7, 54.5, 102.7, 178. MS-EI m/z: 255 (M+).

3.3. Synthesis of N-(2,2-Di(1H-pyrrol-2-yl)ethyl)adamantane-1-carboxamide ***1****.* To a solution of compound **3** (200 mg, 0.75 mmol) in CH_2Cl_2, $Bi(NO_3)_3{\cdot}5H_2O$ (90 mg, 0.18 mmol) was added. The solution was stirred at ambient temperature in a round-bottomed flask for 1.5 h. After this period of time, 2 mL of pyrrole was added and stirred for 24 h. The solvent was removed in vacuo. Purification by column chromatography (silica gel 70–230 mesh, hexane : EtOAc 6 : 4) afforded the title compound **1** (0.1 g, 40%) as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.82–1.58 (m, 12H), 1.99 (s, 3H), 3.77 (dd, J = 7.2, 6.1 Hz, 2H), 4.35–4.23 (m, 1H), 5.80 (t, J = 5.5 Hz, 1H), 6.04 (tdd, J = 2.5, 1.6, 0.7 Hz, 2H), 6.16 (dd, J = 5.9, 2.7 Hz, 2H), 6.68 (td, J = 2.7, 1.5 Hz, 2H), 8.63 (s, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): 27.9, 36.3, 38, 38.9, 40.5, 43, 105.8, 108.2, 117.4, 130.5, 178.8 MS-EI m/z: 337 (M + H) HRMS observed 338.2235; estimated 338.2232.

3.4. X-Ray Crystallography. Single-crystal X-ray experiment was performed on a Bruker Smart CCD diffractometer using MoKα radiation (λ = 0.7073 Å). A total of 1321 frames were collected at a scan width of 0.3° and an exposure time of 10 s/frame. These data were processed with the HKL Scalepack software package, provided by the diffractometer manufacturer, by using a narrow-frame integration algorithm. Crystal data were $C_{20}H_{27}N_3O_1{\cdot}C_1H_2Cl_2$, M = 422.18, monoclinic, space group P21/n, a = 10.0410(4) Å, b = 10.0766(2) Å, c = 21.6398(8), β = 94.002(1) Å, V = 2184.2(1) Å^3, Z = 4, ρ = 1.18 mg/mm^3, μ(MoKα) = 0.315 mm^{-1}, total reflections = 16561, unique reflections 5022 (Rint 0.04%), and observed

reflections 3463. The final R indices were $[I > 2\sigma(I)]$ $R1 = 6.9\%$ and $wR2 = 18.2\%$. Largest difference peak and hole, 0.573 and $-0.404\,e \cdot Å^3$. The structure was solved using the Shelx97 software. Structural refinement was carried out by full-matrix least squares on $F2$ using the SHELX97 program. The nonhydrogen atoms were treated anisotropically, and the hydrogen atoms, included in the structure factor calculation, were refined isotropically. Atomic coordinates, bond lengths, bond angles, and anisotropic thermal parameters are in deposit at the Cambridge Crystallographic Data Center. CCDC number 975489 contains the supplementary crystallographic data for this paper available online at http://dx.doi.org/10.1155/2014/294246. These data can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html (or from the CCDC, 12 Union Road, Cambridge, UK).

4. Conclusions

These results suggested that compound **1**, which was easy to synthesize in two steps from an adamantoyl chloride, is a potentially active inhibitor against the 11β-HSD1 compound because of its structural analogy to other active adamantyl compounds and its interactions in silico with the active site.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

Acknowledgments

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