Communication

Synthesis of 8-Aminoquinoline Amides of Ursonic and Oleanonic Acid

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Abstract: 8-Aminoquinoline amides of 3-oxo-olean-12-en-28-oic acid and 3-oxo-urs-12-en-28-oic acid were obtained and characterized by ¹H, ¹³C-NMR and single crystal X-ray analysis. The used triterpenoic acids are oxidized forms of naturally occurring oleanolic acid and ursolic acids. Such types of derivatives are known for their anticancer and antiviral activities. On the other hand, 8-aminoquinoline amides are frequently used for transition metal complexation that is applicable for both C-H activation processes and biological activity studies.

Keywords: triterpenoids; oleanolic acid; ursolic acid; 8-aminoquinoline amides

1. Introduction

Many naturally occurring pentacyclic triterpenoids are known as important secondary metabolites, which exhibit significant biological activities. The most representative compounds of this family are oleanolic, ursolic and betulinic acids, which are present in many medicinal plants [1,2]. These triterpenoic acids show remarkable antitumor [3–6], antidiabetic [7,8], anti-inflammatory [9,10] and antiviral [11] properties. Oleanolic and ursolic acids’ structure contains two functional groups that can be easily modified: hydroxyl group at C(3) and carboxyl group at C(28). A possible option of further functionalization of the carboxylic moiety is amidation. In the last few decades, several dozen new ursolic and oleanolic acid amides containing alkyl, aromatic and heteroaromatic moieties have been reported [12–19]. Typically, synthesis of secondary amides of triterpenoic acids is based on the conversion of triterpenoic acid to corresponding acyl chloride in the presence of base (e.g., triethylamine).

Czuk’s group discovered few triterpenoic acid 4-aminoisoquinoline and 5-aminoquinoline amide derivatives, which exhibit high cytotoxicity for human tumor cell lines, but remain significantly less cytotoxic for the mouse fibroblasts NIH 3T3 [20]. Such a high selectivity can be explained by the presence of isoquinoline and quinoline moieties, which are known biologically active heterocycles [21,22].

On the other hand, oxidation of the hydroxyl group to ketone can significantly improve several biological properties of triterpenoic acids. Thus, ursonic acid is more efficient towards a wide spectrum of biological targets than ursolic acid [23]. Nevertheless, amides of ursonic and oleanonic acid have not been widely studied. Wang’s group reported several aniline amides of ursonic acid as potential apoptosis inhibitors [24].

Hence, we decided to assemble novel ursonic and oleanonic acid 8-aminoquinoline amides. This arrangement of the quinoline ring could improve not only biological applications of triterpenoid derivatives, but also could become a directing auxiliary and open up new potential opportunities for functionalization of unreactive sites at the triterpenoid core [25]. The placement of 8-aminoquinoline amide moiety in these compounds is highly
favorable also for formation of stable complexes with transition metals; thereby, it may increase the biological and synthetic application of target molecules.

2. Results and Discussion

The hydroxyl group at C(3) of triterpenoic acid can be easily converted to ketone using selective oxidants such as Jones reagent, Dess–Martin periodinane or pyridinium chlorochromate (PCC). For that purpose, PCC was chosen due to the mild reaction conditions and the most convenient purification procedure. The obtained ketoacids [26] 1a and 1b were converted into corresponding acyl chlorides 2 by a treatment with oxalyl chloride. After full conversion of the starting material (HPLC analysis), oxalyl chloride excess was removed from the reaction mixture by full evaporation. Further addition of freshly prepared triterpenoic acid chloride to a cooled solution of 8-aminoquinoline, triethylamine and DMAP led to the formation of the desired products 3a and 3b with yields of 80% and 84%, respectively (Scheme 1).

The molecular structure of compound 3a was unambiguously established by single-crystal X-ray diffraction analysis (Figure 1). The X-ray analysis revealed two possible conformations of compound 3b in its solid state. They both exhibit previously known geometry of ursane and oleanic polycycles. However, the location of the heteroaromatic part differs by a torsion angle C18A-C17A-C28A-N9A’, which is $-12.37^\circ$ for conformation I and $-4.53^\circ$ for conformation II. For both conformers, the planar quinoline moiety is situated almost perpendicularly ($80^\circ-83^\circ$) against the least squares of the aliphatic polycyclic skeleton (C/D cycles). X-ray analysis of product 3a also showed that 8-aminoquinoline amide moiety occupies conformation, which can affect the NMR chemical shift of protons at C(11) and methyl group protons at C(8) due to anisotropic shielding by the aromatic system. Indeed, further solution NMR studies showed that H-C(11) and H3-C(8) are shielded if compared with starting materials 1a,b that do not contain such an aromatic system. On the other hand, H-C(12) is deshielded as it points nearly perpendicularly to H-C(11). Such an average conformation in the solution is proved also by both 2D-NOESY (mixing time 300 ms) and 1D-NOE interactions that clearly indicate the trough–space interaction of the indicated aromatic system and H-C(11) and H2-C-C(8) (Figure 1). This was further supported by 1D-NOEDIFF spectra as the relative values of the observed NOE effects correlate with the intensity of cross peaks in the 2D-NOESY spectrum (Figure 1A). Thus, the 1D-NOEDIFF spectrum was acquired with presaturation at 8.81 ppm for H-C(2') (6 s, 50 dB; on-resonance) and 4.50 ppm (off-resonance reference), and the intensity difference for the H-C(11) signal at 1.97 ppm was calculated as 1.3%. Next, the presaturation at 0.54 ppm for H3-C-C(8) (8 s, 40 dB; on-resonance) and 4.50 ppm (off-resonance reference) revealed intensity differences for the H-C(2') signal at 8.81 ppm (0.6%) and the H-C(7') signal at 8.85 ppm (1.6%). In addition to that, the 8-aminoquinoline substituent shows typical chemical shifts for both the Daugulis-directing group (heteroaromatic signals) and triterpenoid-derived quinoline amides (amide NH signal) [20].
was removed under reduced pressure. Crude product was purified by column chromatography (eluent 20% DCM/hexanes → 100% DCM) to obtain pure triterpenoic acid 100% DCM (14 mL), oxalyl chloride (0.370 mL, 4.29 mmol, 1.5 eq.) was added dropwise at 0–5 °C. The resulting reaction mixture was quenched with 2% aqueous hydrochloric acid (50 mL). Organic layer was separated and washed with 2% aqueous hydrochloric acid (2 × 50 mL), brine (40 mL) and dried over anhydrous Na2SO4. Then, it was filtered and the solvent was removed under reduced pressure. The obtained residue was dissolved in anhydrous DCM (14 mL), and then it was added dropwise to a solution of 8-aminoquinoline (0.452 mmol, 1.3 eq.), DMAP (0.003 g, 0.029 mmol, 0.01 eq.) and triethylamine (0.516 mL, 3.14 mmol, 1 eq.) in anhydrous DCM (14 mL) at 0–5 °C. The resulting reaction mixture was allowed to warm up to room temperature and left stirring for 2 h. The solvent and the residual oxalyl chloride were removed under reduced pressure. The obtained residue was dissolved in anhydrous DCM (14 mL) and then it was added dropwise to a solution of 8-aminoquinoline (0.452 g, 3.14 mmol, 1 eq.), DMAP (0.003 g, 0.029 mmol, 0.01 eq.) and triethylamine (0.516 mL, 3.14 mmol, 1 eq.) in anhydrous DCM (14 mL) at 0–5 °C. The resulting reaction mixture was allowed to warm up to room temperature and stirred overnight.

The reaction mixture was quenched with 2% aqueous hydrochloric acid (50 mL). Organic layer was separated and washed with 2% aqueous hydrochloric acid (2 × 50 mL), brine (40 mL) and dried over anhydrous Na2SO4. Then, it was filtered and the solvent was removed under reduced pressure. Crude product was purified by column chromatography (eluent 20% DCM/hexanes → 100% DCM) to obtain pure triterpenoic acid 8-aminoquinoline amides 3a and 3b.

3-Oxo-olean-12-en-28-oic acid 8-aminoquinoline amide 3a. Yield of 80% (1.321 g) as a white amorphous solid. Single crystals of amide 3a, which are suitable for X-ray analysis, were obtained by slow evaporation from DCM/hexane’s mixture with m.p. 238–239 °C. Rf = 0.42 (Hex/EtOAc 4:1). 1H-NMR (500 MHz, CDCl3) δ 10.37 (s, 1H, H-N), 8.85 (dd, 3J = 7.7 Hz, 4J = 1.7 Hz, 1H, H-C(1′′′)), 8.81 (dd, 3J = 4.2 Hz, 4J = 1.7 Hz, 1H,H-C(2′′)), 8.15 (dd, 3J = 8.2 Hz, 4J = 1.7 Hz, 1H, H-C(3′′′)), 7.52 (dd, 3J = 8.3, 7.7 Hz, 1H, H-C(1′′′′)), 7.47 (dd, 3J = 8.2 Hz, 3J = 4.2 Hz, 1H, H-C(3′′)), 5.73 (t, 3J = 3.7 Hz, 1H, H-C(12)), 3.01 (dd, 3J = 12.9 Hz, 4J = 3.7 Hz, 1H, H-C(18)), 2.50 (dd, 3J = 15.9 Hz, 3J = 11.1, 7.3 Hz, 1H, Hα-C(2)), 2.34 (dd, 3J = 15.9 Hz, 3J = 6.8, 3.7 Hz, 1H, Hβ-C(2)), 2.16 (td, 3J = 13.5 Hz, 3J = 3.7 Hz, 1H, Hα-C(16)), 1.97 (m, 2H, H2-C(11)), 1.92–1.79 (m, 5H, Hα-C(16), Hβ-C(1)), Hα-C(19), H2-C(22)), 1.74 (ddd, 3J = 14.1 Hz, 3J = 3.3, 4.2 Hz, 1H, Hα-C(15)), 1.66 (dd, 3J = 9.0, 8.6 Hz, 1H, H-C(9)), 1.52–1.23 (m, 9H, H-C(5), H2-C(7), Hα-C(1), H2-C(6), Hb-C(19), H2-C(21)), 1.22 (s, 3H, H3-C(27)), 1.13 (ddd, 3J = 14.1 Hz, 3J = 6.7, 3J = 15 Hz, which are suitable for X-ray analysis, were obtained by slow evaporation from DCM/hexane’s mixture with m.p. 238–239 °C. Rf = 0.42 (Hex/EtOAc 4:1). 1H-NMR (500 MHz, CDCl3) δ 10.37 (s, 1H, H-N), 8.85 (dd, 3J = 7.7 Hz, 4J = 1.7 Hz, 1H, H-C(1′′′)), 8.81 (dd, 3J = 4.2 Hz, 4J = 1.7 Hz, 1H,H-C(2′′)), 8.15 (dd, 3J = 8.2 Hz, 4J = 1.7 Hz, 1H, H-C(3′′′)), 7.52 (dd, 3J = 8.3, 7.7 Hz, 1H, H-C(1′′′′)), 7.47 (dd, 3J = 8.2 Hz, 3J = 4.2 Hz, 1H, H-C(3′′)), 5.73 (t, 3J = 3.7 Hz, 1H, H-C(12)), 3.01 (dd, 3J = 12.9 Hz, 4J = 3.7 Hz, 1H, H-C(18)), 2.50 (dd, 3J = 15.9 Hz, 3J = 11.1, 7.3 Hz, 1H, Hα-C(2)), 2.34 (dd, 3J = 15.9 Hz, 3J = 6.8, 3.7 Hz, 1H, Hβ-C(2)), 2.16 (td, 3J = 13.5 Hz, 3J = 3.7 Hz, 1H, Hα-C(16)), 1.97 (m, 2H, H2-C(11)), 1.92–1.79 (m, 5H, Hα-C(16), Hβ-C(1)), Hα-C(19), H2-C(22)), 1.74 (ddd, 3J = 14.1 Hz, 3J = 3.3, 4.2 Hz, 1H, Hα-C(15)), 1.66 (dd, 3J = 9.0, 8.6 Hz, 1H, H-C(9)), 1.52–1.23 (m, 9H, H-C(5), H2-C(7), Hα-C(1), H2-C(6), Hb-C(19), H2-C(21)), 1.22 (s, 3H, H3-C(27)), 1.13 (ddd, 3J = 14.1 Hz, 3J = 6.7,
3.7 Hz, 1H, H5-C(15)), 1.04 (s, 3H, H3-C(23)), 0.99 (s, 3H, H2-C(29)), 0.96 (s, 3H, H2-C(30)), 0.95 (s, 3H, H3-C(24)), 0.85 (s, 3H, H2-C(25)), 0.54 (s, 3H, H3-C(26)). 13C-NMR (125.6 MHz, CDCl3) δ 217.71 (C3), 176.95 (O=C-NH), 147.84 (C2′), 143.25 (C13), 139.02 (C8a′), 136.23 (C4′), 134.94 (C8′), 127.98 (C4a′), 127.56 (C6′), 123.87 (C12), 121.44 (C3′), 121.13 (C5′), 116.38 (C7′), 55.25 (C5), 48.13 (C17), 47.42 (C4), 46.89 (C9), 46.77 (C19), 42.27 (C18), 41.98 (C14), 39.43 (C8), 39.19 (C1), 36.63 (C10), 34.32 (C21), 34.15 (C22), 33.11 (C30), 32.97 (C22), 31.96 (C7), 30.81 (C20), 27.58 (C15), 26.40 (C23), 25.88 (C27), 24.15 (C16), 23.70 (C29), 23.61 (C11), 21.40 (C24), 19.47 (C6), 16.23 (C26), 15.00 (C25). IR (FTIR): 3436 (s), 3333 (s), 2942 (s), 2863 (m), 1703 (w), 1673 (s), 1532 (s), 1487 (m), 1462 (m), 1424 (m), 1384 (m), 1326 (m), 1261 (w), 1164 (m), 1074 (w), 999 (w), 826 (m), 792 (m), 771 (w), 678 (w) cm⁻¹. HRMS (ESI): m/z calcd. for [C₉H₅N₂O₂⁺H]+ 581.4107; found 581.4116.

3-Oxo-urs-12-en-28-oic acid 8-aminooquiline amide 3b. Yield of 84% (1.385 g) as a white amorphous solid. Rf = 0.40 (Hex/ EtOAc 4:1). 1H-NMR (500 MHz, CDCl3) δ 10.30 (s, 1H, N-H), 8.85 (dd, J = 7.7 Hz, J = 1.5 Hz, 1H, H-C(2)), 8.15 (dd, J = 8.2 Hz, J = 1.5 Hz, 1H, H-C(4′)), 5.53 (dd, J = 8.1, 7.7 Hz, 1H, H-C(5′)), 7.49 (dd, J = 8.1 Hz, J = 1.5 Hz, 1H, H-C(3′)), 4.79 (dd, J = 8.2, 4.0 Hz, 1H, H-C(5′)), 4.27 (dd, J = 3.7 Hz, 1H, H-C(3′)), 3.50 (t, J = 3.8 Hz, 1H, H-C(C12)), 2.51 (dd, J = 15.9 Hz, J = 10.9, 7.3 Hz, 1H, H-C(2)), 4.21–2.34 (m, 2H, H₃-C (2), H-C(18)), 0.56 (s, 3H, H-C(25)). 13C-NMR (125.6 MHz, CDCl3) δ 217.65 (C5), 176.74 (O=C-NH), 147.70 (C1′), 138.94 (C8a′), 137.75 (C13), 136.14 (C4′), 134.89 (C8′), 127.87 (C4a′), 127.46 (C6′), 126.89 (C3′), 121.31 (C12), 120.96 (C5′), 116.31 (C7′), 55.09 (C5), 53.70 (C18), 49.43 (C17), 47.27 (C4), 46.68 (C9), 42.21 (C14), 39.81 (C19), 39.44 (C8), 39.19 (C1), 38.94 (C20), 37.38 (C22), 36.45 (C10), 34.04 (C2), 32.10 (C7), 30.95 (C21), 27.89 (C15), 26.39 (C23), 25.08 (C16), 23.45 (C27), 23.29 (C11), 21.29 (C24), 21.15 (C23), 19.36 (C6), 17.17 (C29), 16.19 (C26), 15.03 (C25). IR (FTIR): 3367 (s), 2927 (s), 2863 (s), 1705 (s), 1668 (s), 1526 (s), 1486 (s), 1473.70 (C134.94 C(8) with a HyPix6000 detector and micro-focus-sealed X-ray tube using Cu Kα radiation (λ = 1.54184 Å). Single crystals were fixed with oil in a nylon loop of a magnetic CryoCap and set on a goniometer head. The samples were cooled down to 150 K, and w-scans were performed with a step size of 0.5°. Data collection and reduction were performed with the CrysAlisPro 1.171.40.35a software (Oxford Diffraction Ltd., Abingdon, UK). Structure solution and refinement were performed with SHELXT and SHELXL software that are parts of the CrysAlisPro and Olex2 suites.

Full crystallographic data for compound 3a were deposited with the Cambridge Crystallographic Data Center as a supplementary publication No. CCDC-2159312 (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; Fax: +44-1223-363033; E-mail: deposit@ccdc.cam.ac.uk). Crystal data for compound 3a (C₉H₅N₂O₂; M = 580.83 g/mol): monoclinic, space group P2₁ (no. 4), a = 7.4348(1) Å, b = 25.6051(3) Å, c = 17.3123(3) Å, β = 100.256(1)°, V = 3203.37(8) Å³, Z = 4, T = 150.0(2) K, μ(CuKα) = 0.56 mm⁻¹, Dcalc = 1.204 g/cm³, 30,249 reflections measured (5.2° ≤ 2θ ≤ 153.2°), 10,724 unique (Rint = 0.042, Rsigma = 0.044) which were used in all calculations. The final R₁ was 0.035 (I > 2σ(I)) and wR₂ was 0.090 (all data).
4. Conclusions

Oleanonic acid (3-oxo-olean-12-en-28-oic acid 8-aminoquinoline amide 3a) and ursonic acid (3-oxo-urs-12-en-28-oic acid 8-aminoquinoline amide 3b) were successfully synthesized from the corresponding acyl chlorides and fully characterized by 1H-NMR and 13C-NMR spectroscopy. Combined-solution NOESY spectroscopy and single-crystal X-ray analysis of amide 3a revealed that the aminoquinoline moiety leans over the pentacyclic core and is located closer to the C/D cycles than to the E cycle.

Supplementary Materials: The following supporting information are available online. Figure S1: 1H-NMR spectrum of 3a; Figure S2: 13C-NMR spectrum of 3a; Figure S3: IR spectrum of 3a; Figure S4: Mass spectrum of 3a; Figure S5: 1H-NMR spectrum of 3b; Figure S6: 13C-NMR spectrum of 3b; Figure S7: IR spectrum of 3b; Figure S8: Mass spectrum of 3b. CheckCIF report and *.cif file for compound 3a as separate files.

Author Contributions: V.K. and J.L. conducted synthetic experiments and prepared the manuscript; M.T. brought the idea, managed the research and reviewed the manuscript; A.M. performed and described the X-ray studies. All authors have read and agreed to the published version of the manuscript.

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