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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 ^{1}H, ^{13}C-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

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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 oxalylchloride in DCM and following addition of amine 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 moiety, which are known biologically active heterocycles [21,22].

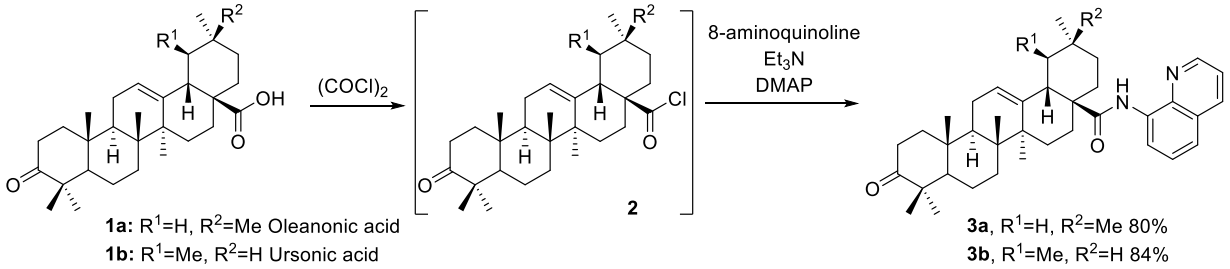
On the other hand, oxidation of the hydroxyl group to ketone can significantly improve several biological properties of triterpenoic acids. Thus, ursonic acid is more efficient towards a wide spectrum of biological targets than ursolic acid [23]. Nevertheless, amides of ursonic and oleanonic acid have 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.

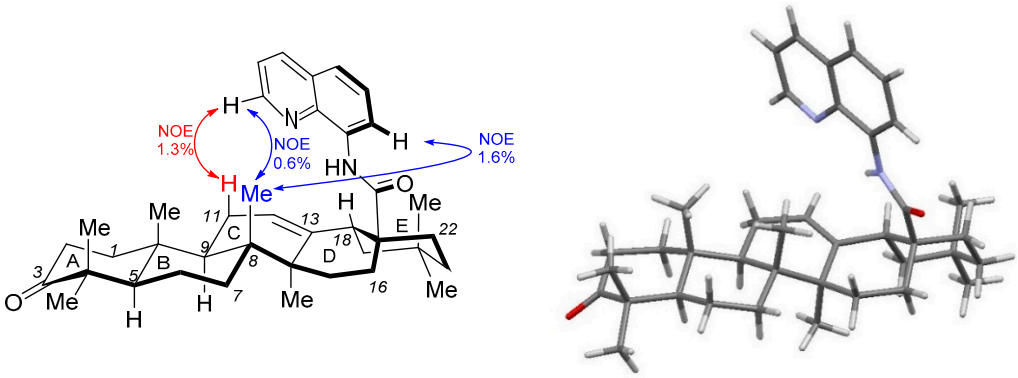
2. Results and Discussion

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).



Scheme 1. Synthesis of target compounds **3a** and **3b**.

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 oleane aliphatic polycycles. However, the location of the heteroaromatic part differs by a torsion angle C18A-C17A-C28A-N9A′, which is −12.37(2)° for conformation I and −4.53(2) ° for conformation II. For both conformers, the planar quinoline moiety is situated almost perpendicularly (80–83°) 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 H_3C-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 H_3C-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 H_3C-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)[25] and triterpenoid-derived quinoline amides (amide NH signal) [20].



(**A**) (**B**)

Figure 1. Comparison of NOE effects observed in solution (**A**) and molecular structure obtained by single-crystal X-ray analysis (**B**) of compound **3a**.

3. Materials and Methods

Dichloromethane for the reactions was dried over CaH_2 and freshly distilled prior to use. All purchased chemicals (Angene, Fluorochem, Hadfield, UK) were used as received. All reactions were followed by TLC on E. Merck Kieselgel 60 F_{254} (Merck & Co., Inc., Kenilworth, NJ, USA) and visualized by using UV lamp. Column chromatography was performed on silica gel (60 Å, 40–63 μm, UPAG-AG). ^{1}H and ^{13}C-NMR spectra were recorded on a Bruker Avance 500 MHz (Bruker Corporation, Billerica, MA, USA), in $CDCl_3$ at 25 °C. Chemical shift (δ) values are reported in ppm. The residual solvent peaks are used as an internal reference ($CDCl_3$ 7.26 ppm for ^{1}H-NMR, $CDCl_3$ 77.16 ppm for ^{13}C-NMR), s (singlet), d (doublet), t (triplet), m (multiplet); *J* in hertz.

To a solution of known ketocarboxylic acid[26] **1a** or **1b** (1.300 g, 2.86 mmol, 1 eq.) in anhydrous DCM (14 mL), oxalyl chloride (0.370 mL, 4.29 mmol, 1.5 eq.) was added dropwise at 0–5 °C and stirred for 10 min. The resulting 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, 3.72 mmol, 1.3 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 Na_2SO_4. 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. R_f = 0.42 (Hex/EtOAc 4:1). ^{1}H-NMR (500 MHz, $CDCl_3$) δ 10.37 (s, 1H, H-N), 8.85 (dd, ^3J = 7.7 Hz, ^4J = 1.7 Hz, 1H, H-C(7′)), 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(4′)), 7.52 (dd, ^3J = 8.3, 7.7 Hz, 1H, H-C(6′)), 7.47 (dd, ^3J = 8.3 Hz, ^4J = 1.7 Hz, 1H, H-C(5′)), 7.45 (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 (ddd, ^2J = 15.9 Hz, ^3J = 11.1, 7.3 Hz, 1H, H_a-C(2)), 2.34 (ddd, ^2J = 15.9 Hz, ^3J = 6.8, 3.7 Hz, 1H, H_b-C(2)), 2.16 (td, ^2J = 13.5 Hz,^3J = 3.7 Hz, 1H, H_a-C(16)), 1.97 (m, 2H, H_2-C(11)), 1.92–1.79 (m, 5H, H_b-C(16), H_a-C(1), H_a-C(19), H_2C(22)), 1.74 (ddd, ^2J = 14.1 Hz, ^3J = 13.3, 4.2 Hz, 1H, H_a-C(15)), 1.66 (dd, ^3J = 9.0, 8.6 Hz, 1H, H-C(9)), 1.52–1.23 (m, 9H, H-C(5),H_2C(7), H_b-C(1), H_2-C(6), H_b-C(19), H_2C(21)), 1.22 (s, 3H, H_3-C(27)), 1.13 (ddd, ^2J = 14.1 Hz, ^3J = 6.7,

3.7 Hz, 1H, H_b-C(15)), 1.04 (s, 3H, H_3-C(23)), 0.99 (s, 3H, H_3-C(29)), 0.96 (s, 3H, H_3-C(30)), 0.95 (s, 3H, H_3-C(24)), 0.85 (s, 3H, H_3-C(25), 0.54 (s, 3H, H_3-C(26)). ^{13}C-NMR (125.6 MHz, $CDCl_3$) δ 217.71 (C3), 176.95(O=C-NH), 147.84(C2′) 143.25 (C13), 139.02(C8a′), 136.23 (C4′), 134.94 C(8′), 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 (C2), 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 C(11), 21.40 (C24), 19.47 (C6), 16.23 (C26), 15.00 (C25). IR (FTIR): 3436 (s), 3333 (s), 2942 (s), 2863 (m), 1702 (s), 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 $[C_{39}H_{52}N_2O_2+H]^+$ 581.4107; found 581.4116.

3-Oxo-urs-12-en-28-oic acid 8-aminoquinoline amide **3b**. Yield of 84% (1.385 g) as a white amorphous solid. R_f = 0.40 (Hex/EtOAc 4:1). ^{1}H-NMR (500 MHz, $CDCl_3$) δ 10.30 (s, 1H,N-H), 8.85 (dd, ^3J = 7.7 Hz, ^4J = 1.5 Hz, 1H,H-C(7′)), 8.82 (dd, ^3J = 4.0 Hz, ^4J = 1.5 Hz, 1H, H-C(2′)), 8.15 (dd, ^3J = 8.2 Hz, ^4J = 1.5 Hz, 1H, H-C(4′)), 7.53 (dd,^3J = 8.1, 7.7 Hz, 1H, H-C(6′)), 7.49 (dd ^3J = 8.1 Hz, ^4J = 1.5 Hz, 1H, H-C(5′), 7.47 (dd, ^3J = 8.2, 4.0 Hz, 1H, H-C(3′)), 5.70 (t, ^3J = 3.8 Hz, 1H, H-C(12)), 2.51 (ddd, ^2J = 15.9 Hz ^3J = 10.9, 7.3 Hz, 1H, H_a-C(2)), 2.41–2.34 (m, 2H, H_b-C(2), H-C(18)), 2.17 (td, ^2J = 13.7 Hz, ^3J = 4.3 Hz, 1H, H_a-C(16)), 2.09–1.81 (m, 6H, H_a-C(1), H_a-C(15), H_b-C(16), H_2C-(11), H_a-C(22)), 1.70 (ddd, ^2J = 13.8 Hz, ^3J = 13.5, 4.1 Hz, 1H, H_b-C(22)), 1.67–1.26 (m, 10H, H_b-C(1), H-C(5), H_2-C(6), H_2-C(7), H_2-C(21), H-C(19), H-C(9)), 1.18 (s, 3H, H_3-C(27)), 1.17–1.08 (m, 2H, H_b-C(15), H-C(20)), 1.07 (s, 3H, H_3-C(23)), 1.03 (s, 3H, H_3-C(30)), 1.01 (s, 3H, H_3-C(29)), 0.97 (s, 3H, H_3-C(24)), 0.83 (s, 3H, H_3-C(25)), 0.54 (s, 3H, H_3-C(26)). ^{13}C-NMR (125.6 MHz, $CDCl_3$) δ 217.65(C_3), 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), 2868 (s), 1705 (s), 1668 (s), 1526 (s), 1486 (s), 1458 (m), 1424 (m), 1383 (s), 1324 (m), 826 (m), 792 (m), 671(w), 663 (w) cm^{-1}. HRMS (ESI): *m/z* calcd. for $[C_{39}H_{52}N_2O_2+H]^+$ 581.4107; found 581.4124.

Single-crystal diffraction data for oleanolic derivative **3a** were collected on an XtaLAB Synergy-S Dualflex diffractometer (Rigaku Corporation, Tokyo, Japan) equipped with a HyPix6000 detector and micro-focus-sealed X-ray tube using Cu K_α 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 ω-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 (See the Supplementary Materials). 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 CB2 1EZ, UK; Fax: +44-1223-336033; E-mail: deposit@ccdc.cam.ac.uk). Crystal data for compound **3a** ($C_{39}H_{52}N_2O_2$; M = 580.83 g/mol): monoclinic, space group $P2_1$ (no. 4), a = 7.3438(1) Å, b = 25.6051(3) Å, c = 17.3123(3) Å, β = 100.256(1) °, V = 3203.37(8) $Å^3$, Z = 4, T = 150.0(2) K, μ(CuKα) = 0.56 mm^{-1}, D_{calc} = 1.204 g/cm^3, 30,249 reflections measured ($5.2° \leq 2\Theta \leq 153.2°$), 10,724 unique ($R_{int}$ = 0.042, R_{sigma} = 0.044) which were used in all calculations. The final R_1 was 0.035 ($I > 2\sigma(I)$) and wR_2 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 ^{1}H-NMR and ^{13}C-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: ^{1}H-NMR spectrum of **3a**; Figure S2: ^{13}C-NMR spectrum of **3a**; Figure S3: IR spectrum of **3a**; Figure S4: Mass spectrum of **3a**; Figure S5: ^{1}H-NMR spectrum of **3b**; Figure S6: ^{13}C-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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References

1. Yeung, M.F. A review on presence of oleanolic acid in natural products. *Nat. Prod. Med.* **2009**, *2*, 77–290.
2. Ramsay, K.S.; Wafo, P.; Ali, Z.; Khan, A.; Oluyemisi, O.O.; Marasini, B.P.; Khan, I.A.; Bonaventure, N.T.; Choudhary, M.I.; Atta-ur-Rahman. Chemical con-stituents of Stereospermum acuminatissimum and their urease and alpha-chymotrypsin inhibitions. *Fitoterapia* **2012**, *83*, 204–208. [CrossRef] [PubMed]
3. Choi, C.Y.; You, H.J.; Jeong, H.G. Nitric oxide and tumor necrosis factor-a production by oleanolic acid via nuclear factor-kB activation in macrophages. *Biochem. Biophys. Res. Commun.* **2001**, *288*, 49–55. [CrossRef] [PubMed]
4. Yan, S.L.; Huang, C.Y.; Wu, S.T.; Yin, M.C. Oleanolic acid and ursolic acid induce apoptosis in four human liver cancer cell lines. *Toxicol. In Vitro* **2010**, *24*, 842–848. [CrossRef]
5. Mieriņa, I.; Vilskersts, R.; Turks, M. Delivery Systems for Birch-bark Triterpenoids and their derivatives in anticancer research. *Curr. Med. Chem.* **2020**, *27*, 1308–1336. [CrossRef]
6. Lombrea, A.; Scurtu, A.D.; Avram, Z.; Pavel, I.Z.; Turks, M.; Lugiņina, J.; Peipiņš, U.; Dehelean, C.A.; Soica, C.; Danciu, C. Anticancer potential of betulonic acid derivatives. *Int. J. Mol. Sci.* **2021**, *22*, 3676. [CrossRef]
7. Teodoro, T.; Zhang, L.; Alexander, T.; Yue, J.; Vranic, M.; Volchuk, A. Oleanolic acid enhances insulin secretion in pancreatic b-cells. *FEBS Lett.* **2008**, *582*, 1375–1380. [CrossRef]
8. Jang, S.M.; Yee, S.T.; Choi, J.; Choi, M.S.; Do, G.M.; Jeon, S.M.; Yeo, J.; Kim, M.J.; Seo, K.I.; Lee, M.K. Ursolic acid enhances the cellular immune system and pancreatic beta-cell function in streptozotocin-induced diabetic mice fed a high-fat diet. *Int. Immunopharmacol.* **2009**, *9*, 113–119. [CrossRef]
9. Huguet, A.I.; del Carmen Recio, M.; Máñez, S.; Giner, R.M.; Ríos, J.L. Effect of triterpenoids on the inflammation induced by protein kinase C activators, neuronally acting irritants and other agents. *Eur. J. Pharmacol.* **2000**, *410*, 69–81. [CrossRef]
10. Ikeda, Y.; Murakami, A.; Ohigashi, H. Ursolic acid: An anti- and pro-inflammatory triterpenoid. *Mol. Nutr. Food Res.* **2008**, *52*, 26–42. [CrossRef]
11. Kong, L.; Li, S.; Liao, Q.; Zhang, Y.; Sun, R.; Zhu, X.; Zhang, Q.; Wang, J.; Wu, X.; Fang, X.; et al. Oleanolic acid and ursolic acid: Novel hepatitis C virus antivirals that inhibit NS5B activity. *Antivir. Res.* **2013**, *98*, 44–53. [CrossRef] [PubMed]
12. Mlala, S.; Oyedeji, A.O.; Gondwe, M.; Oyedeji, O.O. Ursolic Acid and Its Derivatives as Bioactive Agents. *Molecules* **2019**, *24*, 2751. [CrossRef] [PubMed]
13. Cwynar, B.B. Anilides and Toluidides of 3β-Acetyloleanolic Acid. *Nat. Prod. Commun.* **2012**, *7*, 507–510. [CrossRef]

14. Shao, J.W.; Dai, Y.C.; Xue, J.P.; Wang, J.C.; Lin, F.P.; Guo, Y.H. In vitro and in vivo anticancer activity evaluation of ursolic acid derivatives. *Eur. J. Med. Chem.* **2011**, *46*, 2652–2661. [CrossRef] [PubMed]
15. Honda, T.; Honda, Y.; Favaloro, F.G., Jr.; Gribble, G.W.; Suh, N.; Place, A.E.; Rendi, M.H.; Sporn, M.B. A novel dicyanotriterpenoid, 2-cyano-3,12-dioxooleana-1,9(11)-dien-28-onitrile, active at picomolar concentrations for inhibition of nitric oxide production. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1027–1030. [CrossRef]
16. Li, J.F.; Zhao, Y.; Cai, M.M.; Li, X.F.; Li, J.X. Synthesis and evaluation of a novel series of heterocyclic oleanolic acid derivatives with anti-osteoclast formation activity. *Eur. J. Med. Chem.* **2009**, *44*, 2796–2806. [CrossRef]
17. Zhu, Y.M.; Shen, J.K.; Wang, H.K.; Cosentino, L.M.; Lee, K.H. Synthesis and anti-HIV activity of oleanolic acid derivatives. *Bioorg. Med. Chem. Lett.* **2011**, *11*, 3115–3118. [CrossRef]
18. Zhang, Y.; Li, J.X.; Zhao, J.; Wang, S.Z.; Pan, Y.; Tanaka, K.; Kadota, S. Synthesis and activity of oleanolic acid derivatives, a novel class of inhibitors of osteoclast formation. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 1629–1632. [CrossRef]
19. Zhang, Y.N.; Zhang, W.; Hong, D.; Shi, L.; Shen, Q.; Li, J.Y.; Li, J.; Hu, L.H. Oleanolic acid and its derivatives: New inhibitor of protein tyrosine phosphatase 1B with cellular activities. *Bioorg. Med. Chem. Lett.* **2008**, *16*, 8697–8705. [CrossRef]
20. Sommerwerk, S.; Heller, L.; Kuhfs, J.; Csuk, R. Selective killing of cancer cells with triterpenoic acid amides-The substantial role of an aromatic moiety alignment. *Eur. J. Med. Chem.* **2016**, *122*, 452–464. [CrossRef]
21. Khan, A.Y.; Gopinatha, S.K. Natural isoquinoline alkaloids: Binding aspects to functional proteins, serum albumins, hemoglobin, and lysozyme. *Biophys. Rev.* **2015**, *7*, 407–420. [CrossRef] [PubMed]
22. Gorka, A.P.; de Dios, A.; Roepe, P.D. Quinoline Drug–Heme Interactions and Implications for Antimalarial Cytostatic versus Cytocidal Activities. *J. Med. Chem.* **2013**, *56*, 5231–5246. [CrossRef] [PubMed]
23. Son, J.; Sang, Y.L. Therapeutic Potential of Ursonic Acid: Comparison with Ursolic Acid. *Biomolecules* **2020**, *10*, 1505. [CrossRef] [PubMed]
24. Huang, R.Z.; Hua, S.X.; Liao, Z.X.; Huang, X.C.; Wang, H.S. Side chain-functionalized aniline-derived ursolic acid derivatives as multidrug resistance reversers that block the nuclear factor-kappa B (NF-κB) pathway and cell proliferation. *Med. Chem. Comm.* **2017**, *8*, 1421–1434. [CrossRef] [PubMed]
25. Zaitsev, V.G.; Shabashov, D.; Daugulis, O. Highly regioselective arylation of sp^3 C-H bonds catalyzed by palladium acetate. *J. Am. Chem. Soc.* **2005**, *127*, 13154–13155. [CrossRef] [PubMed]
26. Wen, X.; Sun, H.; Liu, J.; Cheng, K.; Zhang, P.; Zhang, L.; Hao, J.; Zhang, L.; Ni, P.; Zographos, S.E.; et al. Naturally Occurring Pentacyclic Triterpenes as Inhibitors of Glycogen Phosphorylase: Synthesis, Structure−Activity Relationships, and X-ray Crystallographic Studies. *J. Med. Chem.* **2008**, *51*, 3540–3554. [CrossRef]