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Synthesis of *Bis*-Amides Employing a Plant-Derived Triterpenoid as Component in the Ugi Reaction †

Fidel Rodríguez-López [1], Hugo A. García-Gutiérrez [1,*] and Rocío Gámez-Montaño [2,*]

[1] Instituto de Investigaciones Químico Biológicas, Universidad Michoacana de San Nicolás de Hidalgo, Edificio B-1, Cd. Universitaria, Morelia 58030, Mexico
[2] Departamento de Química, Universidad de Guanajuato, Noria Alta S/N, Col. Noria Alta, Guanajuato 36050, Mexico
* Correspondence: hgarcia@umich.mx (H.A.G.-G.); rociogm@ugto.mx (R.G.-M.); Tel.: +52-43-326-5788 (H.A.G.-G.); +52-473-732-0006 (ext. 8191) (R.G.-M.)
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Abstract: Herein we describe the synthesis of a series of four novel triterpenoid-derived *bis*-amides, employing masticadienonic acid from *Pistacia mexicana* as a carboxylic acid component in the Ugi reaction. Products were obtained via a facile and efficient one-pot procedure under mild green conditions, with moderate yields (29–58%). The stereo-electronic nature of the aldehyde component influenced the reaction yields.

Keywords: Ugi reaction (U-4CR); isocyanide-based multicomponent reactions (I-MCR); *bis*-amide; triterpenoid

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1. Introduction

Multicomponent reactions (MCRs) are important strategies in modern organic chemistry, where multiple components react together to form a multi-functionalized and complex product, in which all or nearly all of the atoms of the reactants are present [1,2]. These reactions stand out for their many advantages over the traditional multi-step synthesis, such as the high degree of atom economy and bond-formation efficiency in the final product, as well as their simple procedures, the availability of the reactants used in them, and their short working time [2,3].

Since the discovery of the Ugi four-component reactions by Ivar Ugi in 1959, the isocyanide-based multicomponent reactions (IMCRs) have been among the most prominent and most studied groups of MCRs [4]. This reaction involves a carbonyl compound, such as aldehydes or ketones, primary amines, carboxylic acids and isocyanides, to provide easy access to peptide-like structures known as *bis*-amides [5,6].

Ugi reaction is a fairly flexible strategy, allowing the use of a diversity of functional groups, which leads to a wide variety of linear bis-amides [4]. In recent years, this reaction has been used for the synthesis of diverse libraries of compounds with a potential biological activity, using natural products as components, mainly steroids [7]. However, there are a few reports that prove the effectiveness of this methodology for the derivatization of triterpenoids and their semi-synthetic functionalized derivatives [8,9].

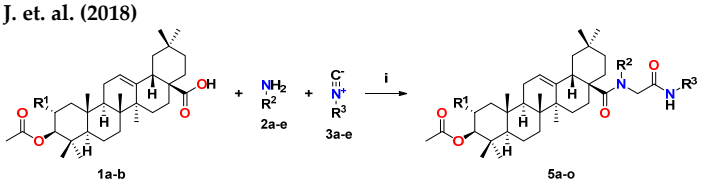
Triterpenoids are an important group of naturally occurring compounds, which are mainly isolated from higher plants [10,11]. These compounds have been extensively studied due to their potential use as antibacterial, antiviral, anti-inflammatory, and antineoplastic agents, the latter being one of the most studied properties of triterpenoids, since it could constitute an alternative treatment for cancer [12–14].

Only two reports, depicted in Scheme 1, describe the use of triterpenes as components in the Ugi reaction, showing that the natural functionality of these compounds can be

exploited for the synthesis of diverse libraries of compounds that incorporate both the bis-amide scaffold, as well as the triterpenoid moiety, which proved to be good cytotoxic agents when evaluated in vitro in various cancer cell lines [8,9].

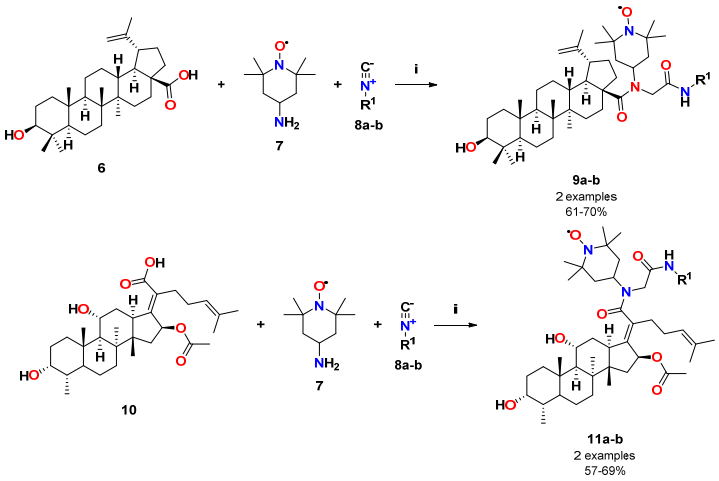
PREVIOUS WORK

Wiemann, J. et. al. (2018)



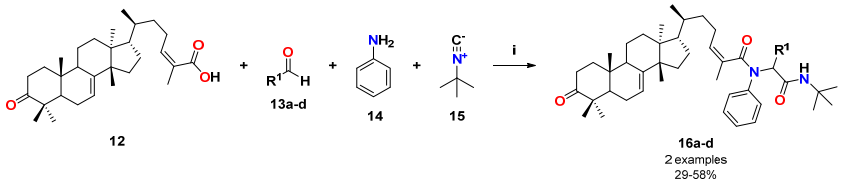
R^1: H, acetoxy
R^2: 2-propenyl, 3-furanyl-methyl, benzyl, butyl, isopropyl
R^3: *tert*-butyl, benzyl, isopropyl, *n*-butyl, 2-methoxy-2-oxoethyl
(i) paraformaldehyde (**4**), MeOH, r.t., 7-12 d

Sultani, H. et. al. (2021)



R^1: *tert*-butyl, 2,4,4-trimethoxybutyl
(i) paraformaldehyde (**4**), MeOH, r.t., 20 h

THIS WORK



R^1: 4-nitrophenyl, 4-chlorophenyl, *n*-hexyl, *E*-styryl
(i) formaldehyde (**4**, 30% v/v in water), EtOH, r.t., 24 h

Scheme 1. Reports of Ugi reactions with triterpenoids as components [8,9].

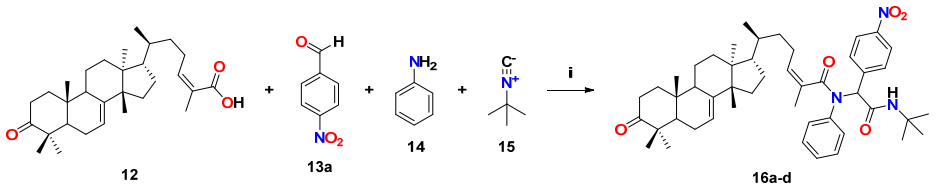
Since there are a few reports of the use of triterpenoids in the Ugi reaction, in the present work the synthesis of *bis*-amides derived from masticadienonic acid, a triterpenoid isolated from *Pistacia mexicana*, was proposed. This compound is interesting because it has an α,β-unsaturated carboxylic acid function, which is not sterically hindered.

2. Results and Discussion

In the present work, we describe the use of a triterpenoid isolated from a plant source as a component in the Ugi multicomponent reaction, for the synthesis of a small library of novel triterpenoid-derived *bis*-amides.

Masticadienonic acid (**12**) was isolated from the hexanic extracts of fruits and stems of *Pistacia mexicana*, as previously described. Then, it was used for the optimization of the Ugi reaction, employing 4-nitrobenzaldehide (**13a**), aniline (**14**), and *tert*-butyl isocyanide (**15**) as the other components, aiming to synthesize the target molecule (**16a**) (Table 1).

Table 1. Screening conditions for the synthesis of the molecule (**16a**).



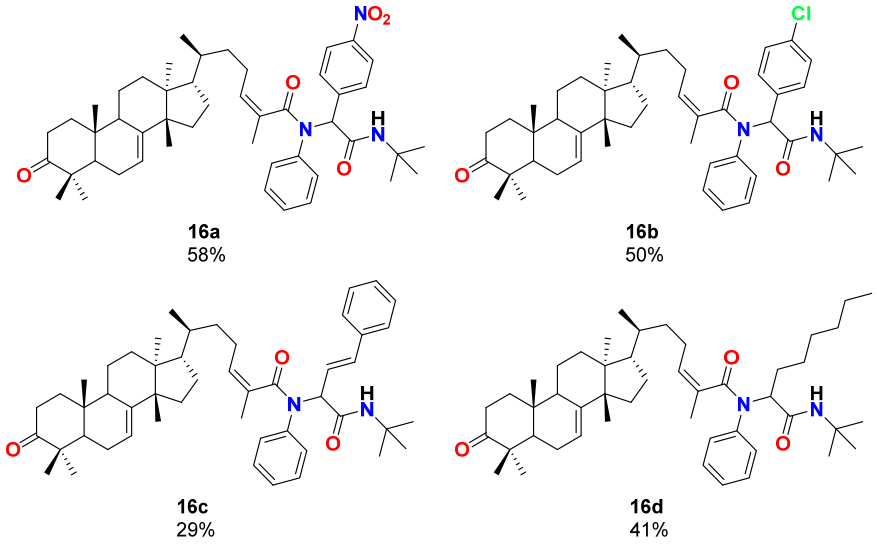
Entry	Solvent	Temperature	Time	Yield
1	MeOH	r.t.	24 h	25%
2	EtOH	r.t.	24 h	58%
3	H_2O	r.t.	24 h	—
4	—	r.t.	24 h	—

In a first attempt, methanol was used as solvent for the reaction. The thin-layer chromatography (TLC) analysis for this experiment showed the formation of a product; however, the presence of several side products was also noted. After purification by column chromatography, the desired product was obtained in a low yield, possibly due to the aforementioned solubility of (**12**) in the solvent used.

For a second experiment, ethanol was chosen to perform the reaction, since (**12**) has better solubility in this solvent. In the TLC analysis, the formation of the desired product was observed, and it was also noted that fewer side products were formed. After the corresponding purification, (**16a**) was isolated in a moderate yield.

Finally, two more experiments were carried out, one with water as solvent and one that was solvent-free, as greener alternatives for this procedure. These efforts were not satisfactory, as no product was identified in the TLC analysis.

In Scheme 2, a series of *bis*-amides (**16a–d**) is depicted, which was synthesized under the optimized conditions (Table 1, entry 2). The effect of the stereo-electronic nature of the carbonyl component was evaluated, employing both activated and deactivated aromatic, aliphatic, and α,β-unsaturated aldehydes. Finally, products were obtained in low to moderate yields (29–58%).



Scheme 2. Scope of the aldehyde component.

3. Experimental Section

3.1. General Information, Instrumentation, and Chemicals

^{1}H and ^{13}C NMR spectra were acquired using Varian Mercury Plus 400 (400 and 100 MHz, respectively). The solvent used for NMR spectroscopy was deuterated chloroform ($CDCl_3$). Chemical shifts (δ) are given in ppm relative to tetramethylsilane (TMS). Coupling constants are reported in Hertz (Hz). Multiplicities of the signals are reported using standard abbreviations: singlet (s), doublet (d), triplet (t), quartet (q), and multiplet (m). NMR spectra were analyzed using MestReNova software version 12.0.0-20080. Reaction progress was monitored by thin-layer chromatography (TLC) on pre-coated silica gel F254 aluminum sheets, and the spots were visualized under UV light at 254 nm or using ceric ammonium sulphate stain under heating. Column chromatography was performed using silica gel (230–400 mesh) as stationary phase. Mixtures of hexanes and ethyl acetate were used as mobile phase for column chromatography and in TLC for reaction progress monitoring and measuring retention factors (R_f). All reagents were purchased from Sigma Aldrich and were used without further purification.

3.2. General Procedure

Masticadienonic acid (**12**, 0.11 mmol, 1.0 equiv.), aldehyde (**13a–d**, 0.11 mmol, 1 equiv.), aniline (**14**, 0.11 mmol, 1.0 equiv.) and tert-butyl isocyanide (**15**, 0.11 mmol, 1.0 equiv.) were dissolved in ethanol (0.44 mL, 0.25 M), and placed in a sealed vial with a magnetic stir bar. The mixture was stirred at room temperature for 24 h. Then, solvent was removed, and the crude was purified by column chromatography using silica gel and a mixture of 15% ethyl acetate in hexanes, to afford the corresponding *bis*-amides (**16a–d**).

3.3. Spectral Data

3.3.1. *N*-(2-(*tert*-butylamino)-1-(4-nitrophenyl)-2-oxoethyl)-*N*-phenyl-3-oxotirucalla-7,24*Z*-dien-26-amide (**16a**)

Yellow oil; R_f = 0.31 (20% ethyl acetate in hexanes): ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ 8.04 (m, 2H), 7.41 (m, 2H), 7.20 (m, 2H), 7.17 (m, 1H), 7.05 (m, 2H), 6.20 (bs, 1H), 6.02 (s, 1H), 5.31 (dd, *J* = 6.1, 3.2 Hz, 1H), 5.06 (d, *J* = 1.8 Hz, 1H), 2.76 (td, *J* = 14.5, 5.4 Hz, 1H), 2.59 (m, 1H), 2.45 (m, 1H), 2.28 (dt, *J* = 14.1, 3.8, 1H), 2.25 (m, 1H), 2.10 (m, 2H), 1.99 (m, 2H), 1.98 (m, 1H), 1.81 (m, 2H), 1.73 (t, *J* = 8.7 Hz, 1H), 1.65 (m, 1H), 1.64 (d, *J* = 1.5 Hz, 3H), 1.56 (m, 2H), 1.53 (m, 2H), 1.49 (m, 1H), 1.48 (m, 2H), 1.48 (m, 1H), 1.40 (m, 1H), 1.38 (s, 9H),1.28 (m, 1H), 1.14 (m, 1H), 1.12 (s, 3H), 1.05 (s, 3H), 1.01 (s, 3H), 1.01 (s, 3H), 0.89 (d, *J* = 6.2 Hz, 3H), 0.81 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 217.2, 173.1, 167.9, 147.7, 146.1, 142.0, 139.3, 132.1, 131.3, 131.1, 129.5, 128.8, 128.6, 123.4, 118.1, 65.1, 53.2, 52.5, 52.0, 51.4, 48.6, 48.1, 43.7, 38.7, 36.3, 36.2, 35.4, 35.2, 35.1, 34.2, 33.8, 28.8, 28.4, 27.6, 27.5, 24.7, 24.5, 22.2, 21.8, 20.9, 18.5, 13.0.

3.3.2. *N*-(2-(*tert*-butylamino)-1-(4-chlorophenyl)-2-oxoethyl)-*N*-phenyl-3-oxotirucalla-7,24*Z*-dien-26-amide (**16b**)

Colorless oil; R_f = 0.39 (20% ethyl acetate in hexanes): ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ 7.18 (m, 2H), 7.16 (m, 1H), 7.14 (m, 2H), 7.12 (m, 2H), 7.05 (m, 2H), 5.95 (bs, 1H), 5.89 (s, 1H), 5.30 (m, 2H), 5.01 (m, 2H), 2.77 (td, *J* = 14.5, 5.4 Hz, 1H), 2.58 (m, 1H), 2.45 (m, 1H), 2.29 (dt, *J* = 14.1, 3.8, 1H), 2.24 (m, 1H), 2.10 (m, 2H), 1.99 (m, 2H), 1.98 (m, 1H), 1.82 (m, 1H), 1.73 (t, *J* = 8.7 Hz, 1H), 1.65 (m, 1H), 1.63 (d, *J* = 1.4 Hz, 3H), 1.55 (m, 2H), 1.53 (m, 2H), 1.50 (m, 1H), 1.48 (m, 2H), 1.47 (m, 1H), 1.40 (m, 1H), 1.35 (s, 9H), 1.29 (m, 1H), 1.14 (m, 1H), 1.11 (s, 3H), 1.06 (s, 3H), 1.01 (s, 3H), 1.00 (s, 3H), 0.89 (d, *J* = 6.2 Hz, 3H), 0.80 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 217.2, 172.8, 168.5, 146.2, 139.7, 134.5, 133.4, 131.8, 131.7, 131.5, 129.8, 128.6, 128.5, 128.3, 118.0, 64.8, 53.2, 53.2, 52.5, 51.8, 51.4, 48.7, 48.1, 43.7, 38.7, 36.3, 36.2, 35.4, 35.2, 34.2, 33.8, 28.8, 28.4, 27.6, 27.4, 24.7, 24.5, 22.2, 21.8, 21.0, 18.5, 13.0.

3.3.3. *N*-((*E*)-1-(*tert*-butylamino)-1-oxo-4-phenylbut-3-en-2-yl)-*N*-phenyl-3-oxotirucalla-7,24*Z*-dien-26-amide (**16c**)

Yellow oil; R_f = 0.20 (25% ethyl acetate in hexanes): ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ 7.36 (m, 2H), 6.88 (m, 2H), 6.08 (dt, *J* = 7.5, 1.2 Hz, 1H), 6.01 (bs, 1H), 5.99 (d, *J* = 2.9 Hz, 1H), 5.30 (dd, *J* = 6.1, 3.4 Hz, 1H), 3.80 (s, 3H), 2.74 (td, *J* = 14.5, 5.4 Hz, 1H), 2.59 (m, 1H), 2.44 (m, 1H), 2.28 (dt, *J* = 14.1, 3.8, 1H), 2.25 (m, 1H), 2.11 (m, 2H), 1.98 (m, 1H), 1.99 (m, 1H), 1.97 (d, *J* = 1.5 Hz, 3H), 1.81 (m, 1H), 1.73 (t, *J* = 8.7 Hz, 1H), 1.65 (m, 1H), 1.56 (m, 2H), 1.55 (m, 2H), 1.49 (m, 1H), 1.48 (m, 2H), 1.48 (m, 1H), 1.41 (m, 1H), 1.36 (s, 9H), 1.28 (m, 1H), 1.15 (m, 1H), 1.12 (s, 3H), 1.05 (s, 3H), 1.01 (s, 3H), 0.99 (s, 3H), 0.89 (d, *J* = 6.2 Hz, 3H), 0.81 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 217.3, 172.9, 162.0, 146.2, 143.5, 136.3, 129.8, 129.4, 129.1, 128.9, 128.8, 128.5, 127.7, 127.0, 126.4, 121.1, 117.9, 64.6, 58.5, 53.1, 52.5, 51.3, 48.6, 48.1, 43.7, 38.7, 36.2, 36.0, 35.2, 35.1, 34.2, 33.8, 28.9, 28.4, 27.6, 27.0, 25.5, 24.7, 24.5, 22.2, 21.8, 21.0, 18.5, 13.0.

3.3.4. *N*-(1-(*tert*-butylamino)-1-oxooctan-2-yl)-*N*-phenyl-3-oxotirucalla-7,24*Z*-dien-26-amide (**16d**)

Colorless oil; R_f = 0.30 (15% ethyl acetate in hexanes): ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ 7.33 (m, 2H), 7.28 (m, 1H), 7.24 (m, 2H), 6.02 (bs, 1H), 5.30 (dd, *J* = 6.0, 3.2 Hz, 1H), 5.13 (dd, *J* = 6.02, 0.9 Hz, 1H), 5.03 (dt, *J* = 7.6, 1.6 Hz, 1H), 2.77 (td, *J* = 14.5, 5.4 Hz, 1H), 2.59 (m, 1H), 2.45 (m, 1H), 2.28 (dt, *J* = 14.1, 3.8, 1H), 2.25 (m, 1H), 2.10 (m, 2H), 1.99 (m, 2H), 1.97 (m, 1H), 1.82 (m, 1H), 1.76 (m, 2H), 1.73 (t, *J* = 8.7 Hz, 1H), 1.68 (d, *J* = 1.6 Hz, 3H), 1.64 (m, 1H), 1.56 (m, 2H), 1.53 (m, 2H), 1.49 (m, 1H), 1.48 (m, 2H), 1.48 (m, 1H), 1.47 (m, 2H), 1.40 (m, 1H), 1.37 (s, 9H), 1.31 (m, 2H), 1.29 (m, 2H), 1.28 (m, 1H), 1.26 (m, 2H), 1.16 (m, 1H), 1.11 (s, 3H), 1.05 (s, 3H), 1.01 (s, 3H), 1.00 (s, 3H), 0.89 (d, *J* = 6.2 Hz, 3H), 0.88 (t, *J* = 6.7 Hz, 3H) 0.81 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 216.9, 172.5, 168.0, 145.1, 142.0, 132.0, 130.7, 129.4, 127.9, 126.9, 117.4, 60.2, 52.8, 52.3, 51.5, 48.2, 47.5, 43.5, 38.5, 36.4, 36.1, 35.6, 34.9, 34.8, 33.9, 33.5, 31.7, 31.5, 28.8, 28.6, 28.1, 27.4, 26.8, 24.6, 24.5, 24.3, 22.3, 21.9, 21.8, 20.7, 18.4, 18.3, 14.0, 12.7.

4. Conclusions

In the present work, we successfully incorporate a plant-derived triterpenoid as a component in the Ugi reaction for the synthesis of a series of novel bis-amides (**16a–d**), thus broadening the perspectives on the versatility of this methodology.

The synthesized products were obtained using mild reaction conditions and a green solvent, such as ethanol. Moderate yields were observed when activated aromatic and aliphatic aldehydes were employed; however, the experiment where α,β-unsaturated aldehyde was used as a component led to lower yields. This is another example of the effect of the stereo-electronic nature of the components in the final outcome of the Ugi reaction.

Finally, due to the limited number of reports on the field of MCRs with natural products, such as triterpenoids as components, we are encouraged to continue our studies on the Ugi reaction, aiming to make a more complex contribution in the future.

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References

1. Zhu, J.; Wang, Q.; Wang, M.-X. *Multicomponent Reactions in Organic Synthesis*; Wiley-VCH: Weinheim, Germany, 2015; pp. 1–12.
2. Ameta, K.L.; Dandia, A. *Multicomponent Reactions: Synthesis of Bioactive Heterocycles*, 1st ed.; Taylor & Francis: Boca Raton, FL, USA, 2017.
3. Herrera, R.P.; Marques-Lopez, E. *Multicomponent Reactions: Concepts and Applications for Design and Synthesis*; Wiley: Hoboken, NJ, USA, 2015; pp. 1–302.
4. Fouad, M.A.; Abdel-Hamid, H.; Ayoup, M.S. Two Decades of Recent Advances of Ugi Reactions: Synthetic and Pharmaceutical Applications. *RSC Adv.* **2020**, *10*, 42644–42681. [CrossRef]
5. Heravi, M.M.; Zadsirjan, V. *Recent Advances in Applications of Name Reactions in Multicomponent Reactions*; Elsevier: Amsterdam, The Netherlands, 2020; pp. 1–14.
6. El Kaïm, L.; Grimaud, L. Ugi and Passerini Reactions with Carboxylic Acid Surrogates. In *Isocyanide Chemistry*; Wiley: Hoboken, NJ, USA, 2012; pp. 159–194.
7. Reguera, L.; Attorresi, C.I.; Ramírez, J.A.; Rivera, D.G. Steroid Diversification by Multicomponent Reactions. *Beilstein J. Org. Chem.* **2019**, *15*, 1236–1256. [CrossRef]
8. Wiemann, J.; Heller, L.; Csuk, R. An Access to a Library of Novel Triterpene Derivatives with a Promising Pharmacological Potential by Ugi and Passerini Multicomponent Reactions. *Eur. J. Med. Chem.* **2018**, *150*, 176–194. [CrossRef] [PubMed]
9. Sultani, H.N.; Morgan, I.; Hussain, H.; Roos, A.H.; Haeri, H.H.; Kaluđerović, G.N.; Hinderberger, D.; Westermann, B. Access to New Cytotoxic Triterpene and Steroidal Acid-TEMPO Conjugates by Ugi Multicomponent-Reactions. *Int. J. Mol. Sci.* **2021**, *22*, 7125. [CrossRef] [PubMed]
10. Talapatra, S.K.; Talapatra, B. *Chemistry of Natural Products: Stereochemistry, Conformation, Synthesis, Biology and Medicine*; Springer: New York, NY, USA, 2015.
11. Osbourn, A.E.; Lanzotti, V. *Plant-Derived Natural Products: Synthesis, Function and Application*; Springer: New York, NY, USA, 2009.
12. Dzubak, P.; Hajduch, M.; Vydra, D.; Hustova, A.; Kvasnica, M.; Biedermann, D.; Markova, L.; Urban, M.; Sarek, J. Pharmacological Activities of Natural Triterpenoids and Their Therapeutic Implications. *Nat. Prod. Rep.* **2006**, *23*, 394–411. [CrossRef] [PubMed]
13. Chudzik, M.; Korzonek-Szlacheta, I.; Król, W. Triterpenes as Potentially Cytotoxic Compounds. *Molecules* **2015**, *20*, 1610–1625. [CrossRef] [PubMed]
14. Oviedo-Chavez, I.; Ramirez-Apan, T.; Martinez-Vazquez, M. Cytotoxic Activity and Effect on Nitric Oxide Production of Tirucallane-Type Triterpenes. *J. Pharm. Pharmacol.* **2005**, *57*, 1087–1091. [CrossRef] [PubMed]