

Article

Synthesis and Characterization of New Functionalized 1,2,3-Triazole-Based Acetaminophen Derivatives via Click Chemistry from Expired Commercial Acetaminophen Tablets

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Abstract: We hereby describe an efficient method for the preparation of a series of new 1-substituted 1,2,3-triazole-based acetaminophen derivatives through a clean, good-yielding, simple, and expeditious procedure based on the *O*-propargylation reaction of the acetaminophen (APAP) obtained from expired commercial tablets and the CuBr(PPh₃)₃-catalyzed Huisgen reaction between *O*-propargylated APAP and diverse organoazides prepared from commercially available anilines as available starting reagents. An interesting nitric oxide-releasing 1,2,3-triazole hybrid of APAP was also obtained easily using the developed method. The structures of the designed hybrid compounds, which are expected to be pharmacologically active, were characterized by FT-IR, ¹H-, and ¹³C-NMR and are reported for the first time. According to the in-silico ADMET prediction studies performed in this work and literature analysis, these hybrids are interesting models in search of new pharmacological nontoxic agents endowed with anti-inflammatory and anticancer properties.

Keywords: acetaminophen; 1,4-disubstituted 1,2,3-triazoles; molecular hybrids; azide-alkyne cycloaddition; Huisgen reaction; Cu(PPh₃)₃Br catalyst; click chemistry



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1. Introduction

Acetaminophen (APAP, paracetamol, 4-hydroxyacetanilide, or *N*-acetyl-*p*-aminophenol) is a popular medicament commonly used to treat pain and reduce high body fever. It is typically applied to relieve mild pain such as headache and toothache, and it is a preferred alternative to aspirin, particularly for patients who cannot tolerate aspirin [1–5]. It is safe to take, and side effects are scarce in most people that consume APAP regularly [6,7]. However, its use is one of the most common causes of poisoning worldwide, and its environmental presence has a hazardous impact on non-target organisms [8]. APAP blocks prostaglandin synthesis from arachidonic acid by inhibiting the enzymes cyclooxygenase (COX)-1 and -2 [9], while its metabolite (N-acylphenolamine, AM404) acts by activating TRPV1 receptors, which mediate the anticonvulsant action of APAP [10,11]. It also inhibits prostaglandin synthesis by scavenging peroxynitrite, an activator of COX [12,13]. Thus, APAP possesses antipyretic and moderate analgesic properties. However, it demonstrated a narrow therapeutic window, weak anti-inflammatory activity, and potential hepatotoxic actions [14].

As a consequence, research on new APAP derivatives is an active area of drug development [15–26]. According to current reports, a structural modification of the *N*-acetyl-*p*-aminophenol skeleton can improve, reduce, or even change the enzymatic activities of a drug and, thus, the pharmacological properties including cytotoxicity. Among these studies, APAP-conjugated pharmacophores (A–D) (Figure 1) are very promising lead compounds in APAP-based drug research and development [27–30]. These so-called hybrid molecules or multi-targeted compounds that contain pharmacophore moieties of two or more bioactive molecules play an important role in the modulation of multiple biological

targets exhibiting pharmacodynamic effects [31–34]. Particularly, NO-acetaminophen (nitroparacetamol, APAP-ONO₂, NCX-701) (**A**), a nitric oxide (NO)-releasing derivative of APAP, showed considerable anti-inflammatory activity and has been shown to be much more potent as an analgesic and much less toxic to the liver than its parent drug [35,36].

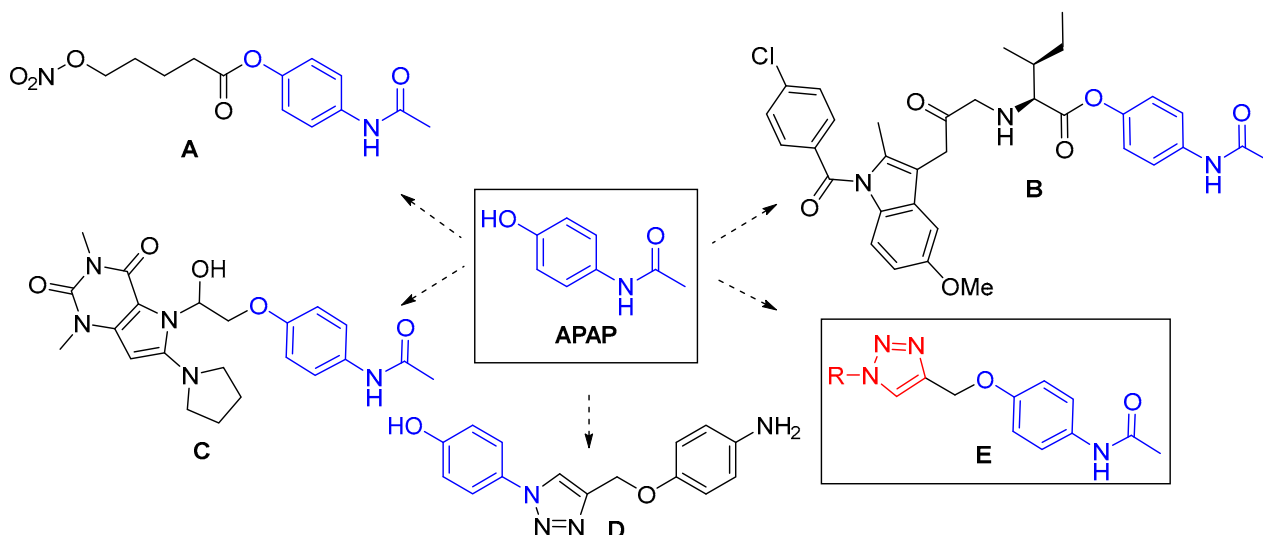


Figure 1. Structure of acetaminophen (APAP), its hybrid compounds (**A–D**) exhibiting more anti-inflammatory activity than the parent APAP (**A–C**) and bronchodilator effect than theophylline drug (**D**), and the designed 1,2,3-triazole-based acetaminophen derivatives (**E**).

APAP-triazole conjugated pharmacophore **D** also displayed more potent anti-inflammatory activity along with analgesic and antipyretic properties than APAP, while its hepatotoxic side effects were found to be less significant than its parent skeleton [27]. In general, the molecular scaffold of the 1,2,3-triazole has special and different physicochemical properties such as an amide bond, mimicry (amide bioisostere), poor basicity, metabolic stability, and the ability to participate as a hydrogen-bond acceptor, which could be favorable in binding biomolecular targets and increasing solubility [37–40]. Moreover, the 1,2,3-triazole ring is a good linker and valuable structural platform [41,42] possessing a broad spectrum of pharmacological activities such as anti-inflammatory, anticancer, antioxidant, antitubercular, anticonvulsant, antibacterial activity, etc. [43–47].

Due to their marked and diverse pharmacological properties, there are several methods described in the literature for the synthesis of 1,2,3-triazoles [48,49]; however, the [3 + 2] cycloaddition [50] of an azide to the triple bond of acetylenes (Huisgen reaction [51]) is the most important, versatile, and popular route despite the lack of regioselectivity [52]. This is due to the use of copper catalysts in the Huisgen reaction, i.e., copper (I)-catalyzed azide-alkyne cycloaddition (CuAAC), which was discovered independently by two research groups: Sharpless, Folkin, and colleagues [53] and Meldal, Tornøe, and co-workers [54] in 2002. It is noteworthy that CuAAC is regioselective, allowing the preparation of isomeric 1,4-disubstituted 1,2,3-triazoles [53,54].

The CuAAC reaction has become an excellent reaction for organic synthesis and represents the classic example of click chemistry [55]. Numerous Cu-catalytic systems have been reported for the CuAAC reaction, but the most widely used methodology is based on a CuSO₄/sodium ascorbate (NaAsC) system in a solvent mixture of water and alcohol (Sharpless–Folkin protocol) [53]. This combination of CuSO₄/NaAsC (reducing agent) is used as a precatalyst system, which generated the Cu(I) species in situ. This system is extremely efficient, but it is essentially limited to water-tolerant substrates. Alternatively, copper(I) salts (iodide, bromide, chloride, and acetate) and their mixed catalytic systems can be used in acetonitrile as a co-solvent within the protecting ligands for the Cu(I) centers from oxidation (Meldal–Tornøe protocol) [54]. In this sense, the bromotris(triphenylphosphine)

copper(I) complex $\text{CuBr}(\text{PPh}_3)_3$ was found to be an organic solvent-soluble, air-stable, and efficient catalyst, whose preparation is very easy and inexpensive, for the clean and quick preparation of diverse 1,4-disubstituted 1,2,3-triazoles [56,57].

From a green chemistry perspective, the use of expired drug components, i.e., pharmaceutical waste, as starting materials for the organic synthesis and medicinal chemistry of new active pharmaceutical ingredients (APIs) is an important but underdeveloped principle of sustainable chemistry [58]. The generation of expired or unused drug constituents has caused the discharge of chemicals into the environment and, thereby, leads to the spreading of pollution, which has already occurred on the surface, ground, and in sewage. To solve these environmental and health problems, it is believed that recycling expired or unused drugs will recover the active principles of drugs in their pure forms, which can later be reformulated into new drug products [59–61].

Considering the above-stated features, and as a continuation of our efforts in the study on the catalyzed 1,3-dipolar cycloaddition reactions towards new potentially bioactive triazole-based heterocyclic molecules [62–66], we designed, synthesized, and characterized new functionalized 1,2,3-triazole (TA)-based acetaminophen derivatives using expired acetaminophen pills as the starting material.

Therefore, in this work, we describe a practical method for the synthesis of the title compounds through a common strategy based on the CuAAC reaction of *O*-propargyl-APAP and diverse aryl- and alkyl azides using the 1 mol% $\text{CuBr}(\text{PPh}_3)_3$ complex as an air-stable catalyst in a solvent mixture of *tert*-BuOH: H_2O (1:1) at room temperature for a period of 9–13 h. In addition, the developed method allowed us to obtain a new nitric oxide-releasing 1,2,3- TA hybrid of APAP. Finally, prepared 1,2,3-triazole-based APAP derivatives were subjected to *in silico* ADMET analysis (Molinspiration online platform and OSIRIS property explorer), evaluating certain physicochemical properties (Lipinski descriptors), drug-likeness and drug-score parameters, and toxicity risks.

2. Materials and Methods

2.1. Materials and Instruments

All work-up and purification procedures were carried out with reagent-grade solvents (purchased from Aldrich and Merck, St. Louis, MO, USA) in the air. Thin-layer chromatography (TLC) was performed using Silufol UV254 plates (0.25 mm), exposed in a UV light chamber of 254 nm. The melting points (uncorrected) were measured using the Fisher-Johns melting point apparatus.

Infrared spectra (FT-IR) were taken on an FT-IR Nicolet™ iS50 spectrophotometer, and the wavenumbers of the absorption peaks were listed in cm^{-1} . ^1H NMR spectra were recorded on a Bruker Avance-400 (400 MHz) spectrometer. Chemical shifts were reported in ppm with the solvent resonance as the internal standard (CDCl_3 : δ 7.26 ppm; DMSO-d_6 : δ 2.50 ppm). Data were reported as follows: Chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, and m = multiplet), coupling constants (Hz), and integration. ^{13}C NMR spectra were recorded on a Bruker Avance-400 (400 MHz) spectrometer with complete proton decoupling. Chemical shifts are reported in ppm from solvent resonance as the internal standard (CDCl_3 : δ 77.00 ppm; DMSO-d_6 : δ 40.45 ppm). Elemental analyses were performed on a PerkinElmer 2400 Series II analyzer and were within ± 0.4 of theoretical values.

Eighteen tablets of the commercial acetaminophen brand 500 g-Genfar® (10.13 g) with an expiration date of 25 December 2018 were obtained at the blue point of reception of the University Wellness department at the Industrial University of Santander and then were pulverized, treated with a CH_2Cl_2 :MeOH (3:1) mixture, stirred vigorously at rt for 24 h, and filtered to obtain a white crystalline solid whose characteristics (Mp, R_f) correspond to the *N*-(4-hydroxyphenyl)acetamide (acetaminophen, paracetamol) (see Supplementary Materials).

2.2. General Procedure for the Synthesis of 1,2,3-Triazole-Based APAP Derivatives 5a–f

In a 20 mL flask, alkyne **3** (1 mmol, 189 mg) and the $\text{CuBr(PPh}_3)_3$ catalyst (1 mol%) dissolved in a 4 mL *tert*-BuOH: H_2O mixture (1:1) were added at room temperature and the reaction mixture was stirred for 30 min. Then, the corresponding azide **4a–f** (1.3 mmol) was slowly added, and the reaction was allowed to continue until TLC monitoring showed that the precursors had been completely consumed. The formed products **5a–f** were precipitated with cold water, filtered, washed with methanol, recrystallized, and characterized as stable solid substances (see Supplementary Materials).

2.3. Spectroscopic Characterization

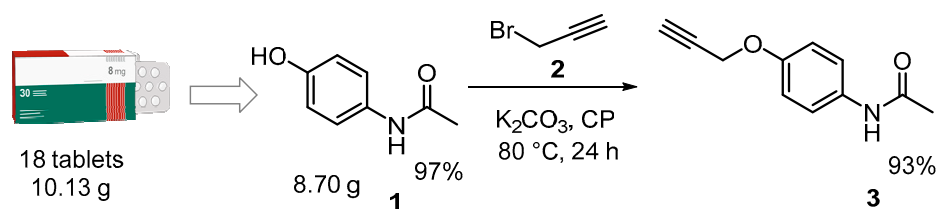
N-(4-((1-(3-hydroxypropyl)-1*H*-1,2,3-triazol-4-yl)methoxy)phenyl)acetamide (**5a**): 270 mg (93%). Gray solid, $R_f = 0.20$ (ethyl acetate). Mp = 156–160 °C. IR (ATR, $\nu_{\text{max}}/\text{cm}^{-1}$): 3376 ($\nu(\text{N-H})$ amide and (O-H)), 2920 and 2842 ($\nu_{\text{Ar}}(\text{C-H})$), 1675 ($\nu(\text{C=O})$ amide), 1576–1393 ($\nu_{\text{Ar}}(\text{C=C})$), 1226 ($\nu(\text{C-N})$), 863–759 ($\gamma_{\text{Ar}}(\text{C-H})$). ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.79 (1H, s, -NH), 8.19 (1H, s, 12-CH), 7.48 (2H, d, $J = 8.2$ Hz, 3- and 3'- H_{Ar}), 6.96 (2H, d, $J = 8.2$ Hz, 2- and 2'- H_{Ar}), 5.08 (2H, s, 7- CH_2), 4.68 (1H, t, $J = 5.1$ Hz, 15- CH_2OH), 4.42 (2H, t, $J = 7.0$ Hz, 13- CH_2), 1.98 (7H, m, 14- CH_2 , 15- CH_2 and 6- CH_3). ^{13}C NMR (101 MHz, DMSO-d_6) δ (ppm): 167.8 (-C=O), 153.8 ($\text{C}_{\text{Ar}}\text{-O}$), 142.7 ($\text{C}_{\text{Ar}}\text{-NH-C=O}$), 132.8 (=C_{Triazole}- $\text{CH}_2\text{-O}$), 124.5 (=C-N_{Triazole}), 120.5 (2 $\text{C}_{\text{Ar}}\text{-C}_{\text{Ar}}\text{-O}$), 114.7 (2 $\text{C}_{\text{Ar}}\text{-C}_{\text{Ar}}\text{-NH}$), 61.3 (-O- $\text{CH}_2\text{-}$), 57.4 (- $\text{CH}_2\text{-CH}_2\text{-OH}$), 46.7 (N- $\text{CH}_2\text{-CH}_2\text{-}$), 32.9 (N- $\text{CH}_2\text{-CH}_2\text{-}$), 23.8 ($\text{H}_3\text{C-CO-}$). Anal. calcd. for $\text{C}_{14}\text{H}_{18}\text{N}_4\text{O}_3$ (MW = 290.32 g/mol): C, 57.92; H, 6.25; N, 19.30%. Found: C, 68.35; H, 5.26; N, 8.15%.

All of the spectral data of other compounds can be found in the Supplementary Materials.

3. Results and Discussion

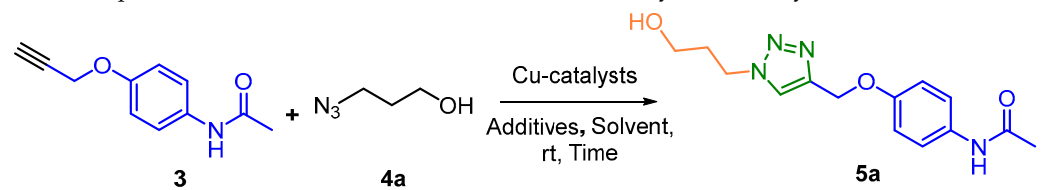
3.1. Chemistry

Performing click chemistry and considering green chemistry principles, the synthesis of the designed 1,2,3-TA-based APAP derivatives was planned in two synthetic steps. The initial step consisted of obtaining and functionalizing APAP **1**, which was carried out by extracting the active ingredient from expired commercial acetaminophen with an extraction yield of 97% and its subsequent *O*-alkylation reaction with propargyl bromide (**2**) to obtain *O*-propargyl-APAP **3** in a basic medium (anhydrous potassium carbonate, K_2CO_3) using propylene carbonate (CP) as a green solvent at 80 °C for a period of 24 h (see, Supplementary Materials) (Scheme 1).



Scheme 1. Preparation of *O*-propargyl-APAP **3**.

The second step was based on the CuAAC reaction of alkyne **3** as a 2π -component and 3-azidopropan-1-ol (**4a**) (i.e., a three-atom 4π -component) selected for the optimization of the [3 + 2]-cycloaddition reaction conditions for the synthesis of hybrid **5a** as model substrates (Table 1). Azide **4a** was obtained following a general protocol for azide preparation from 3-chloro-1-propanol and sodium azide in DMF at 60 °C for a period of 16 h [67]. Initially, we wanted to analyze the effectiveness of the two procedures mentioned above (the Sharpless–Folkin protocol vs. the Meldal–Törnøe protocol) in the reaction model. Thus, the first three experiments were carried out under classical conditions of the Sharpless–Folkin protocol using the Cu(II)-catalyst, CuSO_4 in the presence of reducing additive, NaAsC in an aqueous medium (*tert*-BuOH: H_2O , 1:1) (Table 1, entries 1–3).

Table 1. Optimization of CuAAC reaction conditions for the synthesis of hybrid **5a** ^a.


Entry	Solvent	Catalyst	Additive: mol% NaAsC ^b	Load Catalyst (mol%)	Time (h)	Yield (%) ^c
1	<i>tert</i> -BuOH:H ₂ O 1:1	CuSO ₄ ·5H ₂ O	15	10	18	83
2	<i>tert</i> -BuOH:H ₂ O 1:1	CuSO ₄ ·5H ₂ O	10	5	18	86
3	<i>tert</i> -BuOH:H ₂ O 1:1	CuSO ₄ ·5H ₂ O	1	0.5	13	85
4	<i>tert</i> -BuOH:H ₂ O 1:1	[CuBr(PPh ₃) ₃]	-	5	18	90
5	<i>tert</i> -BuOH:H ₂ O 1:1	[CuBr(PPh ₃) ₃]	-	1	18	92
6	<i>tert</i> -BuOH:H ₂ O 1:1	[CuBr(PPh ₃) ₃]	-	1	12	90
7	<i>tert</i> -BuOH:H ₂ O 1:1	[CuBr(PPh ₃) ₃]	-	1	9	93
8	<i>tert</i> -BuOH:H ₂ O 1:1	[CuBr(PPh ₃) ₃]	-	0.5	11	87
9	CH ₃ CN	[CuBr(PPh ₃) ₃]	-	1	12	73
10	CP	[CuBr(PPh ₃) ₃]	-	1	18	NR ^d

^a Reaction conditions: **3** (1 mmol) and **4a** (1.3 mmol) at rt; ^b NaAsC: sodium ascorbate; ^c Isolated yield after recrystallization (EtOH); ^d NR: no reaction.

With catalyst and additive loads of 15 and 10 mol%, respectively, the desired triazole **5a** was obtained after 18 h of stirring at room temperature (TLC monitoring) in 83% yield (Entry 1). When the respective catalytic and additive loads were reduced to 10 and 5 mol% and then to 5 and 0.1 mol%, yields of **5a** and its reaction times practically did not change (Entries 2 and 3). Thus, this protocol works well, producing the needed triazole molecule in good yields (83–86%).

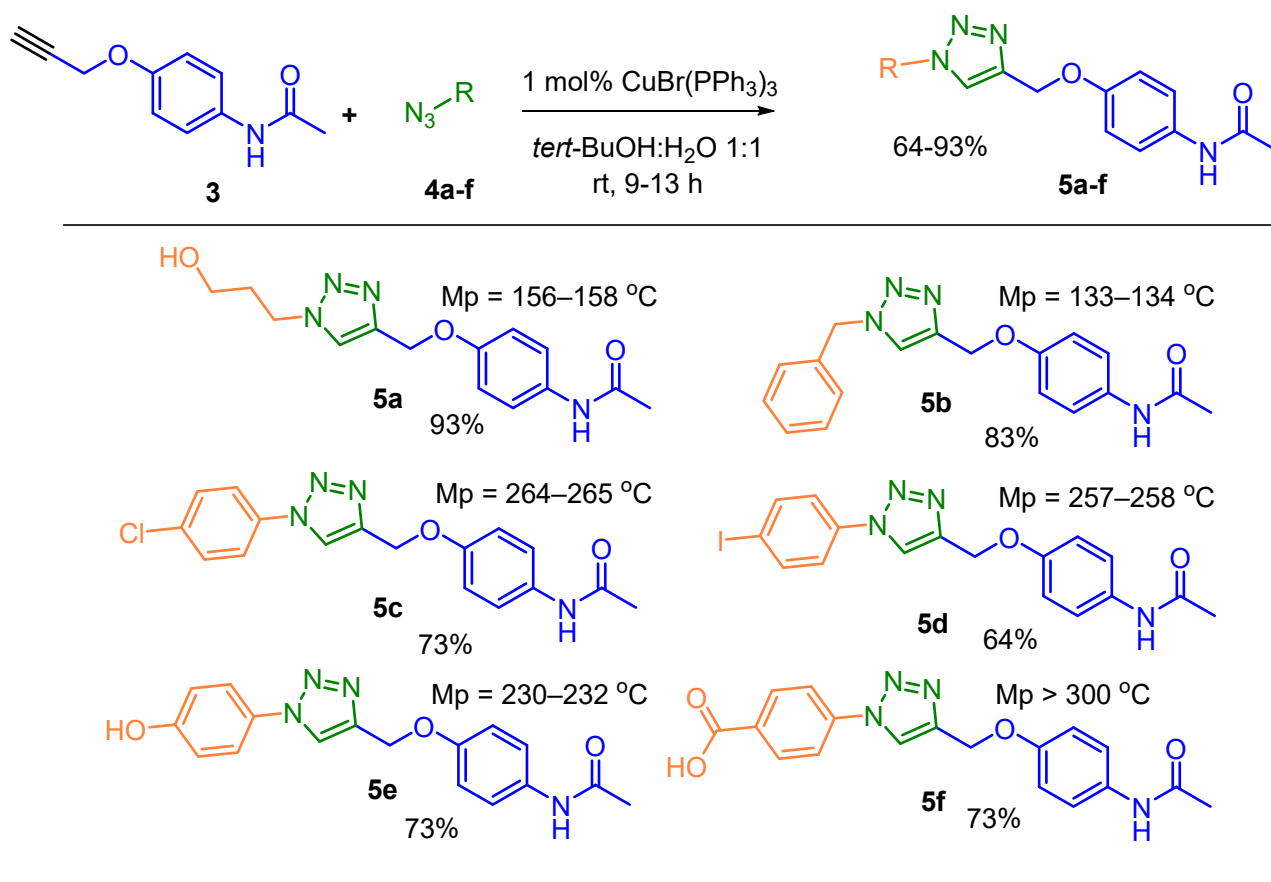
Evaluating the second protocol, our attention was drawn to the influence of the nature of the solvent and the charge of the catalyst. Performing the model reactions of **3** and **4a** with the 5 mol% CuBr(PPh₃)₃ complex in the same reaction medium, we noted the increase in yield product **5a** (90%) in the same reaction time (Entry 4 vs. Entries 2 and 3). The reduction in catalytic load allowed a shorter reaction time, maintaining good yields of the desired triazole (90–93%) (Entries 5–7). Reduction in the charge of up to 0.5 mol% led to a decrease in the product yield and a lengthening of the reaction time (Entry 8 vs. Entry 7). We also tested the organic solvents (MeCN and CP) but in the case of MeCN, the cycloaddition of **3** and **4a** occurred worse than the experiments carried out before (Entry 9), and in the case of CP, there was no product formed (Entry 10).

Analyzing all the pros and cons of the results obtained, we have chosen the most effective 1 mol% CuBr(PPh₃)₃/*tert*-BuOH: H₂O 1:1 system to generate a small series of functionalized 1,2,3-TA-based APAP derivatives **5a–f** from alkyne **3** and freshly prepared diverse organoazides R-N₃ **4a–f** carried out utilizing Filimonov's procedure [68] (Scheme 2).

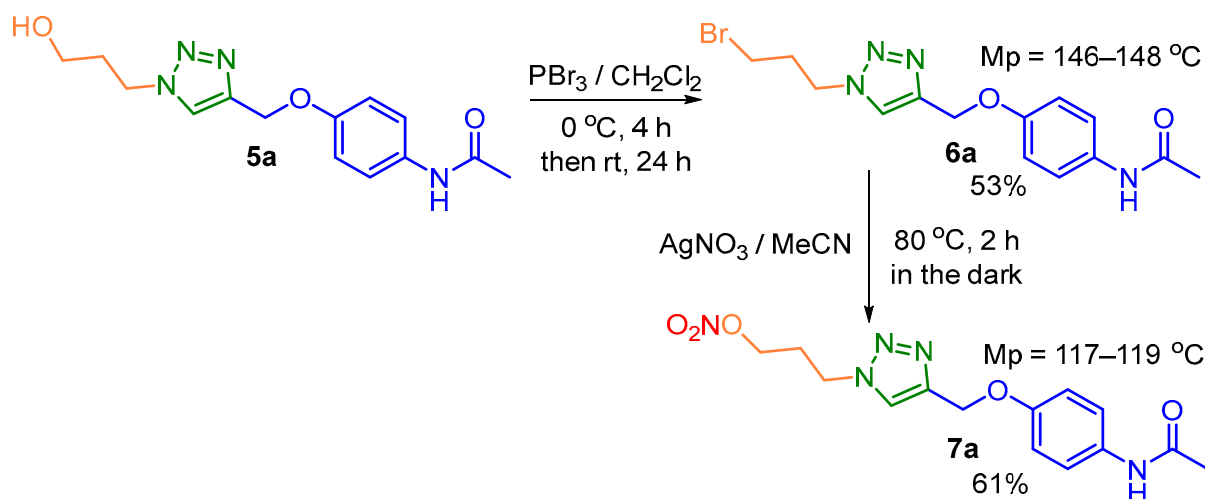
The 1,2,3-TA-based APAP hybrids obtained are not only molecule targets but are also a valuable platform for generating new, more complex compounds. Considering this, hybrid **5a** was transformed into nitrate propyl-triazole-APAP hybrid **7a**, as a stable, yellow solid, via the two steps using the consecutive S_N2 reactions (Scheme 3). Noteworthy, the latter hybrid belongs to nitric oxide-releasing agents (i.e., “hybrid nitrates”), which are explored in clinical trials in a range of indications, including cancer chemoprevention [69–71].

The yields for these click reactions were in the range of 53–93%. The final products **5a–f**, **6a**, and **7a** are new APAP derivatives that became stable powders of different colors (from yellow to red and pink) with well-defined melting points (Schemes 2 and 3). The structures of the designed hybrid compounds were characterized by FT-IR, ¹H-, and ¹³C-NMR spectroscopy. While infrared spectroscopy was used in the first instance to identify characteristic absorption bands of the functional groups present in the different synthesized hybrids, the NMR experiments strongly confirmed their structures. The proton at the C-5 position of the triazole ring of these hybrids appeared as a singlet at δ 7.62–9.02 ppm indicating that the 1,4-regioisomers were obtained (see Supplementary Materials). Taking

derivative **6a** as an example, its $^1\text{H-NMR}$ spectrum amplified in the aromatic region (Figure 2) is discussed below.



Scheme 2. Preparation of functionalized 1,2,3-triazole-based APAP derivatives **5a-f** via the CuAAC reaction.



Scheme 3. Synthesis of nitrate propyl-triazole-APAP hybrid **7a** through simple transformations.

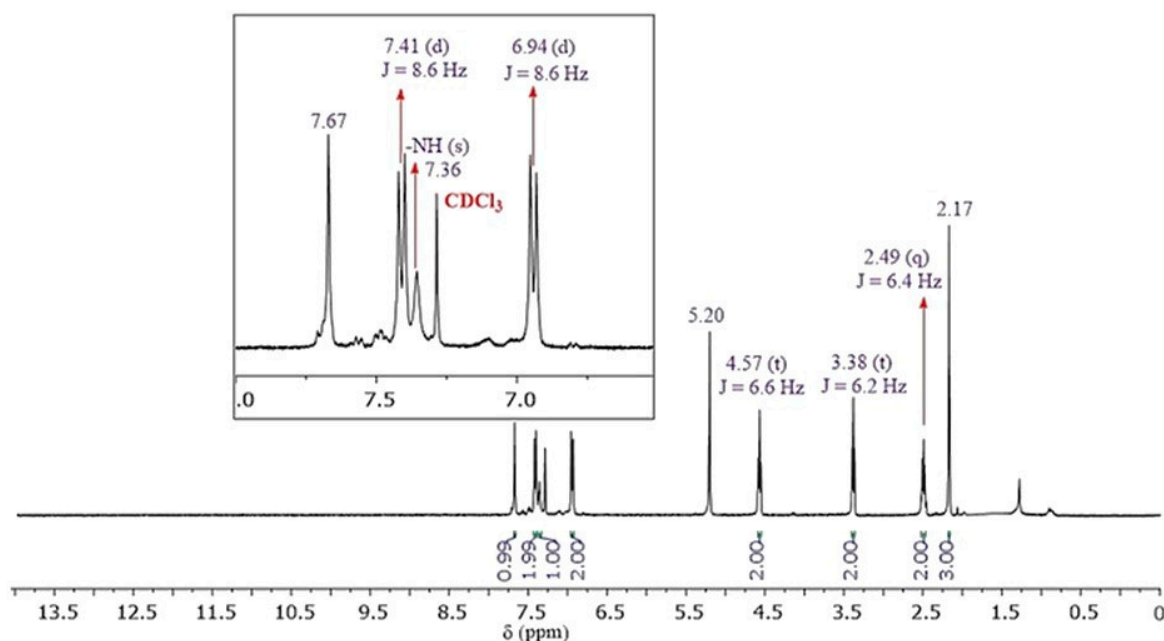


Figure 2. ^1H -NMR of the hybrid **6a** (400 MHz, CDCl_3 , δ , ppm).

A singlet centered at 7.41 ppm corresponding to the hydrogen of the amide function corroborates the IR analysis for this compound (3278 cm^{-1} , $\nu(\text{N-H})$ amide). On the other hand, the signal in the form of a singlet at 7.67 ppm corresponds to the proton at the C-5 position of the triazole ring. In addition, in this region, we found two signals as doublets (d) at 7.41 ppm and 6.94 ppm with vicinal proton–proton coupling constants $^3J_{\text{HH}}$ ($^3J = 8.6\text{ Hz}$) that are consistent with the hydrogens of the benzene ring as an APAP skeleton. Another singlet corresponding to the hydrogens of the linker $3\text{-C}_{\text{Triazole}}\text{-CH}_2\text{-O}$ -fragment is found at 5.20 ppm. Next, at 4.47 ppm and 3.38 ppm, there are two triplets ($^3J = 6.6$ and 6.2 Hz , respectively) that correspond to the hydrogens of the $\text{-CH}_2\text{-CH}_2\text{-N}_{\text{Triazole}}$ fragment. At 2.49 ppm there is a quartet ($^3J = 6.4\text{ Hz}$) that corresponds to the $\text{Br-CH}_2\text{-}$ group and, finally, at 2.17 ppm there is a singlet that belongs to the methyl group in the acetaminophen fragment.

The analysis of its ^{13}C NMR spectrum also indicated the nature of the diverse carbons present in the molecule through their location in the different regions of the spectrum and, in a general way, confirmed its condensed formula, finding all the carbons (see, Supplementary Materials).

3.2. In Silico ADMET Prediction of Physicochemical Properties (Lipinski descriptors) of Prepared Triazole-APAP Hybrids

To estimate the druggability of the APAP hybrids obtained, we complemented the present work by evaluating the potential therapeutic properties of these candidates using different *in silico* tools. In particular, their physicochemical properties, so-called Lipinski descriptors, and toxicity risks were predicted.

First, by using the Molinspiration online platform [72], we calculated the physicochemical properties such as lipophilicity (i.e., the logarithm of the partition coefficient between *n*-octanol and water), molecular weight, hydrogen bond donors and acceptors, rotatable bonds, and topological polar surface area according to Lipinski's rule of five (RO5) [73] (Table 2). Even though this rule does not predict whether a compound is pharmacologically active, it would aid in acquiring a deeper knowledge about the pharmacokinetics including the Absorption, Distribution, Metabolism, and Excretion (ADME) of the molecule under investigation. In this way, researchers or pharmaceuticals screen out the best orally admissible drug-like candidates with good ADME characteristics. Thus, these properties affect the pharmacokinetics and drug-likeness of small molecules.

Table 2. Calculated Lipinski's rule of five parameters ^a for the synthesized molecules.

Comp.	MW ^b	cLogP ^c	HBA ^d	HBD ^e	ROTB ^f	TPSA ^g	n Violations
5a	290.32	0.60	7	2	7	89.28	0
5b	322.37	2.56	6	1	6	69.05	0
5c	342.79	2.92	6	1	5	69.05	0
5d	434.24	3.32	6	1	5	69.05	0
5e	324.34	1.76	7	2	5	89.28	0
5f	352.35	2.15	8	2	6	106.35	0
6a	353.22	1.97	6	1	7	69.05	0
7a	335.32	1.86	10	1	9	124.11	0
APAP	151.16	0.68	3	2	1	49.33	0
APAP-ONO₂	296.28	2.17	8	1	9	110.46	0

^a Lipinski's rule of bioavailability: Molecular weight ≤ 500 Da, lipophilicity assessed by the $\text{cLogP} \leq 5$, number of hydrogen bond donors and acceptors ≤ 5 and ≤ 10 , respectively, number of rotatable bonds ≤ 10 , and topological polar surface area $\leq 140 \text{ \AA}^2$; ^b Molecular Weight (g/mol); ^c Logarithm of the partition coefficient between *n*-octanol and water; ^d Number of hydrogen-bond acceptors; ^e Number of hydrogen-bond donors; ^f Number of rotatable bonds; ^g Polar Surface Area ($\text{\AA}^2$).

The data obtained showed that all the compounds **5a–f**, **6a**, **7a** and the reference molecules (APAP and APAP-ONO₂) (Figure 1) contain high bioavailability properties and fulfill all the parameters established by this rule. It was observed that the hybrids **5b–f**, **6a**, **7a**, and APAP-ONO₂ are more lipophilic molecules possessing cLogP values with a shorter range (1.76–3.32) than compound **5a** and APAP, which showed similar, small lipophilicity ($\text{cLogP} = 0.60$ and 0.68 , respectively). The prediction results of the molecular properties for the compounds **5a–f**, **6a**, and **7a** (Table 2) showed TPSA values between 69 and 124 $\text{\AA}$ confirming their drug-relevant properties. It is interesting to note that the reference molecules, APAP and APAP-ONO₂, exhibited very different lipophilicity and polar surface parameters ($\text{cLogP} = 0.68$ vs. $\text{cLogP} = 2.17$; $\text{TPSA} = 49.33$ vs. $\text{TPSA} = 110.46$, respectively). This difference is due to the presence of the *O*-pentanoylnitrate fragment (NO-acetaminophen), which considerably improved the bioavailability properties of the acetaminophen drug. Noteworthy, both “nitrate hybrids” **7a** and NO-acetaminophen displayed comparable Lipinski descriptors.

Then, in order to assess the possible secondary biological properties of the prepared hybrids, a toxicity profile evaluation was performed using the free software OSIRIS property explorer, which computes toxicity risks and drug-relevant properties of compounds, provides results as color-coded features, and exploits the Chou and Jurs algorithm, based on computed atom contribution [74]. Thus, the APAP–triazole hybrids were predicted to have no risk of mutagenic (Mut), tumorigenic (Tum), irritant (Irr), or reproductive (Rep) effects (Table 3). The only exception was the *N*-ethylbromide-triazole-APAP derivative **6a**, which presented a high predisposition to be tumorigenic and to have reproductive effects. By comparing the toxicity risks obtained for molecules **5a**, **6a**, and **7a**, it is concluded that the inclusion of bromine in this series of analogs considerably increased toxicity. Noteworthy, the OSIRIS prediction of APAP indicates that it is mutagenic, tumorigenic, and reproductively harmful, although, in practice, side effects of acetaminophen are rare if taken at appropriate doses.

Moreover, we used the OSIRIS program to predict the compounds' drug-likeness (DL) and drug-score (DS) properties. The first is related to the similarity to drugs (with a score of -10 to 10) and is the qualitative calculation of the chance for a compound to become an oral drug with respect to bioavailability. Its positive value indicates that the compound comprises fragments that are frequently present in commercial drugs. The second (with a numerical value between 0 and 1) combines DL, Log P, MW, and toxicity risks in one convenient value that can be used to judge the compound's overall potential to qualify for a drug. Thus, the value of the drug score is used to judge the compound's overall potential to qualify as a drug candidate. Compounds without predicted toxicity risks and with drug

scores of DS 0.5 and above were considered promising. Table 3 includes these data for synthesized compounds and APAP and APAP-ONO₂ as reference molecules.

Table 3. Toxicity risks and drug-likeness predicted by OSIRIS Property Explorer ^a.

Comp.	Mut ^b	Tum ^c	Irr ^d	Rep ^e	Drug-Likeness	Drug-Score
5a	■	■	■	■	−0.75	0.62
5b	■	■	■	■	1.72	0.78
5c	■	■	■	■	1.06	0.70
5d	■	■	■	■	0.65	0.59
5e	■	■	■	■	0.46	0.72
5f	■	■	■	■	−0.52	0.59
6a	■	■	■	■	−8.16	0.12
7a	■	■	■	■	−0.71	0.59
APAP	■	■	■	■	1.93	0.20
APAP-ONO ₂	■	■	■	■	−8.25	0.45

^a ■ = No risk, ■ = Moderated risk, ■ = High risk; ^b Mutagenicity: Induction of permanent transmissible changes in the structure of the genetic material of cells or organisms; ^c Tumorigenicity: The process by which neoplastic cells grown in tissue culture form tumors; ^d Irritant: Stimulus from the compound that causes irritation; ^e Reproductive effect: Adverse effect of compounds that interferes with the reproductive organs of an organism, such as genitalia and gonads.

The OSIRIS Property Explore software indicated that almost all the molecular hybrids presented high DS values ranging from 0.59 to 0.78 with the exception of compound **6a**. By comparing the DS values obtained for molecules **5a**, **6a**, and **7a**, it is concluded that the inclusion of bromine in this series of analogs not only considerably increased toxicity but also decreased the DS property (0.12), so it could be inferred that the inclusion of this atom in the aliphatic fragment of the triazole-APAP hybrid **6a** also decreased the similarity of the molecule with known drugs.

The *N*-benzyl-triazole-APAP hybrid **5b** showed the best DS parameter (0.78), making it acceptable as a potential drug, while the acetaminophen DS displayed a low value of 0.20, comparable with hybrid **6a**. This difference suggests that its combination with the *N*-substituted triazole fragment in the same molecule could contribute to improving the properties that influence the possibility of being potential drugs. Moreover, all the hybrids synthesized **5a–f** including the *N*-propyl-nitrate-triazole-APAP hybrid **7a** exhibited DS values (0.59–0.78) very close to or higher than that of NO-acetaminophen (0.45), confirming the potential of these compounds to become potential drugs; therefore, other types of substitutions in these molecules should be evaluated in order to increase their value.

4. Conclusions

In conclusion, we have successfully applied an eco-friendly method for obtaining new 1,2,3-triazole-based acetaminophen derivatives through the 1 mol% CuBr(PPh₃)₃/*tert*-BuOH:H₂O 1:1 system from easily accessible starting materials. These new drug hybrids were obtained with good to excellent yields (64–93%) without chromatography column separation using the expired acetaminophen drug, i.e., pharmaceutical waste, as raw material. Taking advantage of the chemical reactivity of hybrid **5a**, a new nitric oxide-releasing *N*-propyl-nitrate-triazole-APAP hybrid **7a** was synthesized in two easy steps with good performance (61%) for the first time.

Based on our observations, most of the new molecules appeared to be stable solids under laboratory conditions. Furthermore, the *in silico* studies indicated the potential of the hybrid compounds due to their interesting physicochemical properties containing high bioavailability levels and fulfilling all parameters established by Lipinski's rule. According to the Osiris platform, almost all of the designed and obtained molecular hybrids did not show any risk of toxicity and presented higher Drug-Score values, ranging from 0.59 to 0.78, than those of reference drugs acetaminophen and NO-acetaminophen. Finally, our study demonstrated that the hybridization of acetaminophen by a 1-substituted 1,2,3-

triazole ring is a valuable approach for the research and development of new agents based on acetaminophen.

Supplementary Materials: The following supporting information can be downloaded at: <https://www.mdpi.com/article/10.3390/reactions4030020/s1>, synthetic procedures FT-IR and NMR.

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