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Microwave-Assisted Synthesis of 5-Substituted 3-Amino-1,2,4-triazoles from Aminoguanidine Bicarbonate and Carboxylic Acids

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Abstract: The effect of the molar ratio between reagents, reaction time and temperature on the yield of 5-substituted 3-amino-1,2,4-triazoles obtained by the direct condensation of carboxylic acids with aminoguanidine bicarbonate under acid catalysis conditions was studied. As a result, a general green straightforward synthesis of the title compounds bearing aliphatic substituents or a phenyl ring was developed using sealed reaction vials under controlled microwave synthesis conditions that are suitable for the application of volatile starting carboxylic acids. Our straightforward synthetic method proposed in this work increases the synthetic accessibility of these widely used building blocks and therefore is able to significantly expand the structural diversity of compounds containing a triazole moiety for the needs of drug discovery.

Keywords: aminoguanidine; 3-amino-1,2,4-triazoles; carboxylic acids; microwave-assisted synthesis

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1. Introduction

Among five-membered heterocycles, 1,2,4-triazole can be described as one of the most important pharmacophores. It is bioisosteric to the amide bond and thus can be used in rational drug design for the creation of metabolically stable analogs of biologically active peptides. The compounds with this ring are known to reveal multidirectional biological activity [1]. This characteristic has been determined through a large body of studies on triazole derivatives that showcased their considerable antifungal [2], antibacterial [3], antitubercular [4] and anticancer properties [5], as well as other types of activities [6–9]. This potential drew considerable attention to 1,2,4-triazoles, particularly over the past few decades, especially because these compounds have found applications beyond the drug discovery field, also in material science [10–14].

Notably, a 3-Amino-1,2,4-triazole core possesses four nonequivalent nucleophilic reaction centers. Regardless of its virtually ambiguous reactivity, 3-amino-1,2,4-triazole is applied widely in organic synthesis as a building block for introducing the triazole moiety into the desired molecule. Its molecular weight is only 84 Da, which leaves some room for loading it with various substituents while remaining within the permissible limits imposed on molecular diversity by the Lipinski rule of five (molecular weight of potential drug candidate should be not greater than 500 Da). Therefore, this synthetic strategy has high relevance and importance, especially for diversity-oriented synthesis and medicinal chemistry [15]. In general, 3-amino-1,2,4-triazole may act as a mononucleophile, an 1,3- or an 1,1-binucleophile (Figure 1) depending on the nature of the electrophile and the applied reaction conditions. Nevertheless, numerous publications show the high selectivity of its transformations in many types of reactions with various electrophiles [16].

Strong interest in 3-amino-1,2,4-triazole derivatives in recent years can be highlighted by its use in multicomponent reactions [17], including modified Biginelli [18] and isocyanide-based [19] condensations.

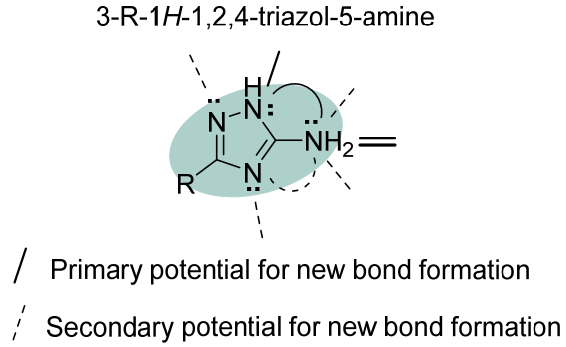


Figure 1. Schematic reactivity profile of 5-R-3-amino-1,2,4-triazoles (3-R-1*H*-1,2,4-triazol-5-amine) towards electrophiles: The potential formation of novel bonds as a result of reaction is shown for major (with solid lines) and for minor or unusual (with dashed lines) reaction directions. Their ability to form Schiff bases upon reaction with aldehydes and their synthetic equivalents is presented with a bold double bond [20].

Moreover, numerous studies have described substituted 3-amino-1,2,4-triazoles (Figure 2) as exhibiting various biological activities [21–25]. Amitrol is a non-selective systemic herbicide broadly used for weed control in agriculture. The EPA revoked approval for Amitrol's use in food products due to its carcinogenic effects observed in animal studies. Due to its high solubility in water, it can cause contamination of drinking water, resulting in leakage and contamination of groundwater and surface water, which can lead to contamination of drinking water and agricultural foods. The World Health Organization has determined the maximum limit of amitrol in drinking water to be 1 μgL^{-1} [21]. The related compound has potent anticonvulsant activity [ED_{50} = 1.4 (1.0–2.2) mg/Kg] compared to diazepam (Sigma) [ED_{50} = 1.2 (0.5–1.9) mg/Kg] [22]. Related triazoles showed dose-dependent activity in the aortic ring tissue model of angiogenesis, highlighting the potential benefit of methionine aminopeptidase-2 ($MetAP_2$) inhibitors as anticancer agents [23]. Loxtidine, a selectively acting histamine H2-antagonist, causes a much longer-lasting inhibition of gastric acid secretion in rats and dogs. Both the insurmountable blockade and the long duration of action are due to the prolonged but gradually reversible occupation of the affected receptors [24]. JNJ-39393406 was suggested for add-on therapy to antipsychotics. This positive allosteric modulator of the $\alpha 7$ receptor shows promising potential as a treatment for schizophrenia, as demonstrated in the Phase I trials and a proof-of-mechanism study. However, while it demonstrates favorable safety and pharmacokinetic profiles, its efficacy in addressing the core deficits of schizophrenia warrants further investigation in larger clinical trials [25].

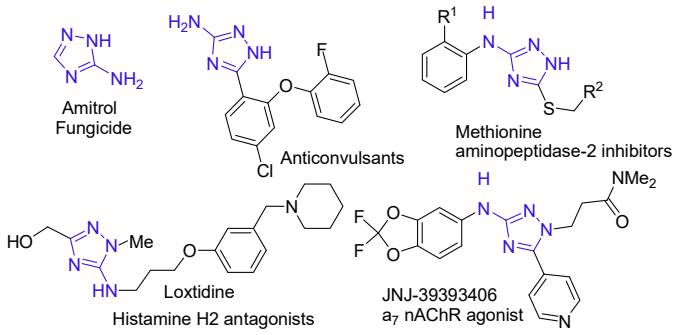


Figure 2. Bioactive representatives of 3-amino-1,2,4-triazoles.

Recent studies have also explored the anticorrosion properties of 3-amino-1,2,4-triazoles [26–28]. These compounds are of interest for their potential application in the creation of energetic materials [29] and have been investigated as fluorescence probes for trace analyses of silymarin, a natural product [30].

It is interesting that more than 11,000 reactions using parent 3-amino-1,2,4-triazole as a reactant are currently described in the literature in 1748 sources (Figure 3), according to CAS SciFinder^n [31]. This fact demonstrates the great utility of this small building block. Contrarily, there are more than an order of magnitude fewer examples described with the use of 5-alkyl substituted derivatives of 3-amino-1,2,4-triazole, which is reflected in the numbers of the reactions and the references (compare R = H and R = Ak in Figure 3A,B). Moreover, the 5-alkyl derivatives are represented mainly with a methyl substituent (compare R = Ak and R = Me in Figure 3A,B), perhaps because the latest is commercially available. For cyclic substituents R, a similar situation is observed, with the vast majority of examples being represented by R = Ph. Therefore, a considerable gap exists between the utility of the parent 3-amino-1,2,4-triazole and its 5-R-derivatives as building blocks, with the structural variability being somewhat limited. This limitation can, at least partially, be attributed to the limited availability of substituted derivatives.

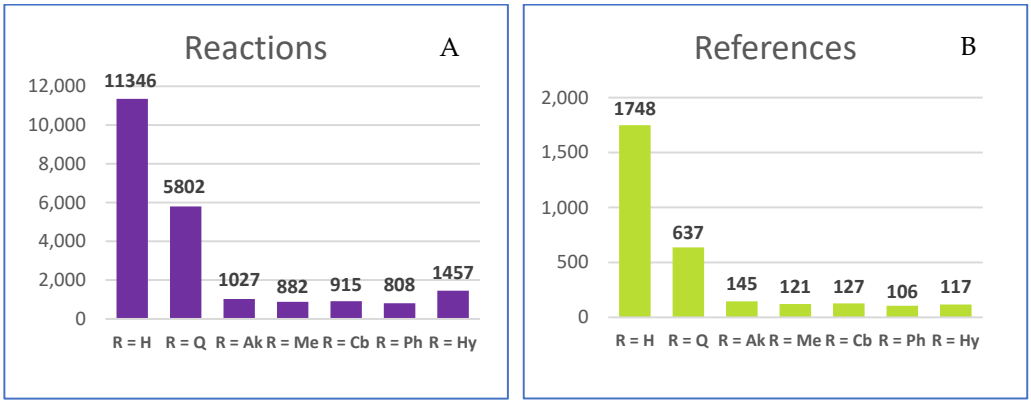


Figure 3. Reaction search results, where 3-R-1*H*-1,2,4-triazol-5-amine (see Figure 1 for its structure) was used as a starting reactant (**A**) and the numbers of literature courses, where these reactions are described (**B**). Here, the designations of the variable substituents are used as in the search engine: Q—any atom except C or H, Ak—any carbon chain, Cb—any carbon cycle, Hy—any heterocycle. Data according to CAS SciFinder^n [31], as of 11.01.2024.

In our research program, we also use 3-amino-1,2,4-triazole [32–36] and its 5-substituted derivatives [37] as starting materials for multicomponent synthesis of different heterocycles. This determines our interest in expanding the synthetic availability of these building blocks. Thus, considering the general importance of these compounds, our aim here was to develop a straightforward and general protocol for their synthesis and assess their laboratory scalability.

Over the last few years, numerous synthetic approaches toward 3-amino-1,2,4-triazoles have been reported in the literature (Table 1). A commonly used method is represented by a reaction of carboxylic acid chlorides with corresponding aminoguanidines to produce N-acyl aminoguanidine derivatives that, upon heating, undergo the ring closure [38]. An efficient procedure for the synthesis of 5-substituted 3-amino-1,2,4-triazoles involves a one-pot reaction of thiourea, dimethyl sulfate and various hydrazides [39]. Another way is through a synthetic method for polysubstituted amino-1,2,4-triazoles via the formation of unsymmetrically substituted thioureas followed by their one-pot S-alkylation with 1,3-propane sultone and condensation with various hydrazides, leading to the desired 1,2,4-triazoles [40]. An elegant approach was suggested for the synthesis of N-substituted 3-(5-amino-1*H*-1,2,4-triazol-3-yl) propanamides via acylation of aminoguanidine hydrochloride with succinic anhydride, followed by a recyclization of the obtained N-guanidinosuccinimide with an

amine under microwave irradiation to form a 1,2,4-triazole ring [41]. Another novel two-step one-pot approach to 3-amino-1,2,4-triazoles consists of the interaction of cyanamide with hydroxylamine followed by an iron (III) chloride catalyzed reaction with various alkyl and arylnitriles [42].

Table 1. Synthetic approaches toward 3-amino-1,2,4-triazoles.

Entry	Starting Material	Conditions	Yields (%)	Reference
1	Carboxylic acid chloride	Aminoguanidine, reflux, 4–6 h or MW 100 W, 2.5–3 h, in water	92–98	[38]
2	Benzohydrazide	Thiourea, dimethyl sulfate, water, 50 °C, 15–20 h	83–95	[39]
3	Unsymmetrically substituted thiourea	1,3-Propane sultone, 16 h; NEt_3, 30 min; hydrazide, 100 °C, 16 h	15–55	[40]
4	Aminoguanidine hydrochloride	Succinic anhydride; amine, MW, 180 °C, 15 min	48–88	[41]
5	Cyanamide	Hydroxylamine, 100 °C, 12 h; iron (III) chloride, nitriles, 100 °C, 12 h	59–94	[42]

Ideally, one would aim to minimize the number of synthetic stages and avoid the use of such hazardous and air-unstable reagents as acyl chlorides, being able to exchange them into much "greener" synthetic equivalents, carboxylic acids. Also, due to the wide commercial availability of diverse carboxylic acids, and since aminoguanidine hydrochloride is about 10 times more expensive than aminoguanidine bicarbonate (the prices were compared in Eur per mol for Germany, according to available packages on www.sigmaaldrich.com), we were interested in developing a straightforward synthetic method for 3-amino-1,2,4-triazoles starting from carboxylic acids and aminoguanidine bicarbonate.

We were also encouraged by such a possibility due to previously published work by Chernyshov's group [43] where the desired triazoles were obtained by heating a mixture of aminoguanidine bicarbonate and pyridinecarboxylic acids by up to 185 °C in the presence of HCl solution in an open vial. However, this method is largely restricted by the application of not volatile carboxylic acid since its procedure includes heating the reaction mixture at high temperatures in an open vessel that is accompanied with evaporation of all the volatile components. Therefore, it is not applicable for small aliphatic acids, as well as for benzoic acid and many of its derivatives, due to their sublimation ability under high temperatures. In this work, we plan to solve this issue by using a microwave-assisted synthesis technique applying sealed vials. Since we plan to use these building blocks in our ongoing research, we are interested in the possibility of laboratory scaling up of such a synthetic method. A recent work also suggests a straightforward microwave-assisted method for the synthesis of polymethylene-bridged bis (1,2,4-triazol-3-amines) in a closed vial under microwave irradiation starting from dicarboxylic acids and aminoguanidine chloride in an aqueous medium [44].

2. Materials and Methods

The NMR spectra of compounds **4a**–**g** were recorded on a Bruker, Avance III-500 Plus spectrometer (500 MHz for ^{1}H and 125 MHz for ^{13}C, solvent DMSO-d_6, internal standard TMS). ^{13}C NMR spectra were registered in the APT mode. IR spectra were measured on a Shimadzu IR Prestige-21 Fourier spectrometer using the ATR mode with a single ATR accessory (prism material diamond), and elemental analyses were performed on a vario MACRO cube CHNS elemental analyzer. Melting points were determined on a WRS-1B Digital Melting-point apparatus and were measured as "not corrected". Analytical samples were taken directly from the final products and used without additional purification. Small-scale microwave experiments were carried out using a monomode Anton Paar Monowave 300 microwave reactor (2.45 GHz) for the optimization experiments and microwave synthesis of compounds **4a**–**h**. The reaction temperature was monitored

by an external IR sensor. The pressure inside the sealed vials was also controlled with an external pressure sensor to ensure the safe pressure level. All the small-scale reactions were carried out using sealed microwave process vials G10 (10 mL). For the scale-up synthesis of **4a** we used a sealed 100 mL vial in a multimode Anton Paar Multiwave 5000 microwave reactor operating with internal temperature and pressure sensors. In both cases, after the completion of the set reaction time, the vial was cooled to 50 °C by air jet cooling. Aminoguanidine hydrocarbonate with the main substance content of not less than 98% (Alfa Aesar), carboxylic acids with the main substance content of not less than 99% (Sigma Aldrich), and the rest of the reagents of chemically pure grade were used. All reagents and solvents were purchased from commercial suppliers and used without further purification. The copies of NMR spectra for compounds **4a**, **4b**, **4d**, and **4f** can be found in Supplementary Materials.

Synthesis of compounds **4a**–**h** (General method for a small scale synthesis): A mixture of 1.36 g (0.01 mol) of aminoguanidine hydrocarbonate (compound **1**), 1.25 mL (0.015 mol) of a 37% solution of HCl, was mixed under agitation for 1 h, water was evaporated, and thus 1.3 g dry solid (compound **2**) was collected and mixed with organic acid **3** (0.012 mol) in a G10 microwave process vial. The mixture was irradiated at 180 °C for 3 h in the monomode Anton Paar Monowave 300 microwave reactor. The resulting melt was cooled and neutralized with 10% water solution of NaOH to achieve pH 8, and the solvent was evaporated in vacuum and crystalized from 5 mL of ethyl acetate. Compounds **4a**–**h** were obtained in the form of white solids and further characterized without additional purification. 5-Subsituted 1,2,4-triazoles (**4a**–**g**) were synthesized without the use of the solvent, with the exception of **4h** where *i*-PrOH was used as solvent since benzoic acid (**3h**) is solid.

Synthesis of compound **4a**, scaling-up: A mixture of 13.6 g (0.1 mol) of aminoguanidine hydrocarbonate (compound **1**) and 12.5 mL (0.15 mol) of a 37% solution of HCl was mixed under agitation for 2 h. Water was evaporated, and thus 13 g dry solid (compound **2**) was collected and mixed with propionic acid **3a** (0.12 mol, 8.89 g) in a 100 mL microwave process vial. The mixture was irradiated at 180 °C for 3 h in a multimode Anton Paar Multiwave 5000 microwave reactor. The resulting melt was cooled and neutralized with a 10% water solution of NaOH to achieve pH 8, and the solvent was evaporated in a vacuum and crystalized from 50 mL of ethyl acetate. In this way, compound **4a** was successfully obtained with 87% yield by direct scaling up the small scale synthesis.

3-Amino-5-ethyl-1,2,4-triazole (**4a**): Previously described [45]. Yield 86% (87% for the scale-up procedure), mp 132–134 °C. IR (ATR), ν (cm^{-1}): 3425, 3329, 3232, 2978, 2939, 2831, 2792, 2719, 2654, 1627, 1581, 1543, 1462, 1427, 1392, 1292, 1064, 968, 840, 802. ^{1}H NMR spectrum, δ, ppm: 1.14 t (*J* = 7.5 Hz, 3H, CH_3), 2.44 q (*J* = 8.3 Hz, 2H, CH_2), 5.66 br. (2H, NH_2), 11.86 br. (1H, NH) (Figure 4). ^{13}C NMR spectrum, δ, ppm: 12.28 (CH_3), 20.70 (CH_2), 153.41 (C-3 of triazole), 161.18 (C-5 of triazole). Found (%): C 42.72, H 7.18, N 49.84; $C_4H_8N_4$. Calculated (%): C 42.84, H 7.14, N 49.96.

3-Amino-5-propyl-1,2,4-triazole (**4b**): Previously described [40]. Yield 83%, mp 142–145 °C. IR (ATR), ν (cm^{-1}): 3410, 3321, 3213, 2958, 2931, 2870, 2839, 2781, 2650, 1620, 1546, 1481, 1462, 1404, 1342, 1265, 1080, 1056, 1033, 898, 759. ^{1}H NMR spectrum, δ, ppm: 0.88 t (*J* = 7.5 Hz, 3H, CH_3, **A** and **B**), 1.59 m (2H, CH_2, **A** and **B**), 2.38 br. (2H, CH_2, **A**), 3.48 br. (2H, CH_2, **B**), 5.20 (2H, NH_2, **B**) and 5.73 br. (2H, NH_2, **A**), 11.59 br. (1H, NH, **A**) and 12.29 br. (1H, NH, **B**) Two tautomers exist in the ratio **A**:**B** = 3:1, see (Figure 5). ^{13}C NMR spectrum, δ, ppm: 13.66 (CH_3), 20.86 (CH_2), 34.60 (CH_2), 162.45 (C-3 of triazole), 164.52 (C-5 of triazole). Found (%): C 47.54, H 7.88, N 45.04; $C_5H_{10}N_4$. Calculated (%): C 47.60, H 7.99, N 44.41.

3-Amino-5-butyl-1,2,4-triazole (**4c**): Previously described [46]. Yield 85%, mp 123–125 °C. IR (ATR), ν (cm^{-1}): 3448, 3325, 3228, 3167, 2962, 2931, 2858, 1681, 1631, 1573, 1543, 1465, 1450, 1427, 1396, 1319, 1238, 1064, 1006, 848, 736. ^{1}H NMR spectrum, δ, ppm: 0.87 t (*J* = 7.5 Hz, 3H, CH_3), 1.29 m (2H, CH_2), 1.56 m (2H, CH_2), 2.42 m (2H, CH_2), 5.61 br. (2H, NH_2). ^{13}C NMR spectrum, δ, ppm: 13.59 (CH_3), 21.67 (CH_2), 26.86 (CH_2), 29.65 (CH_2),

158.65 (C-3 of triazole), 161.96 (C-5 of triazole). Found (%): C 50.98, H 8.82, N 39.53; $C_6H_{12}N_4$. Calculated (%): C 51.41, H 8.63, N 39.97.

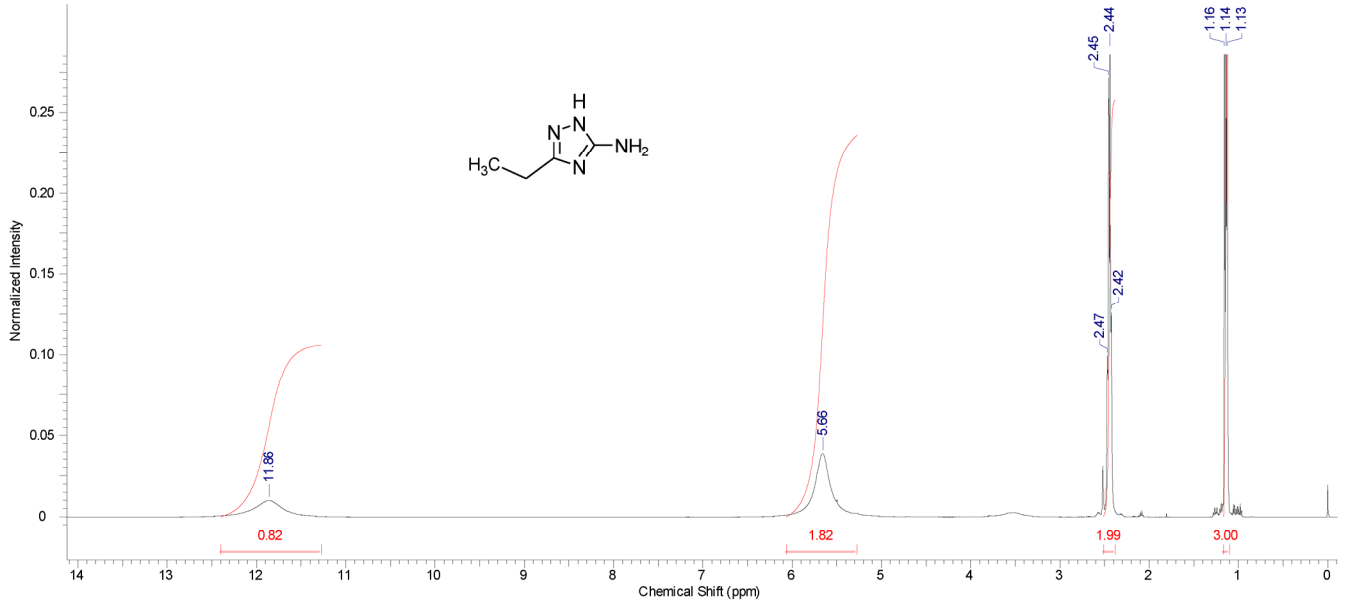


Figure 4. ^{1}H NMR Spectrum of compound **4a** showing only one set of proton signals.

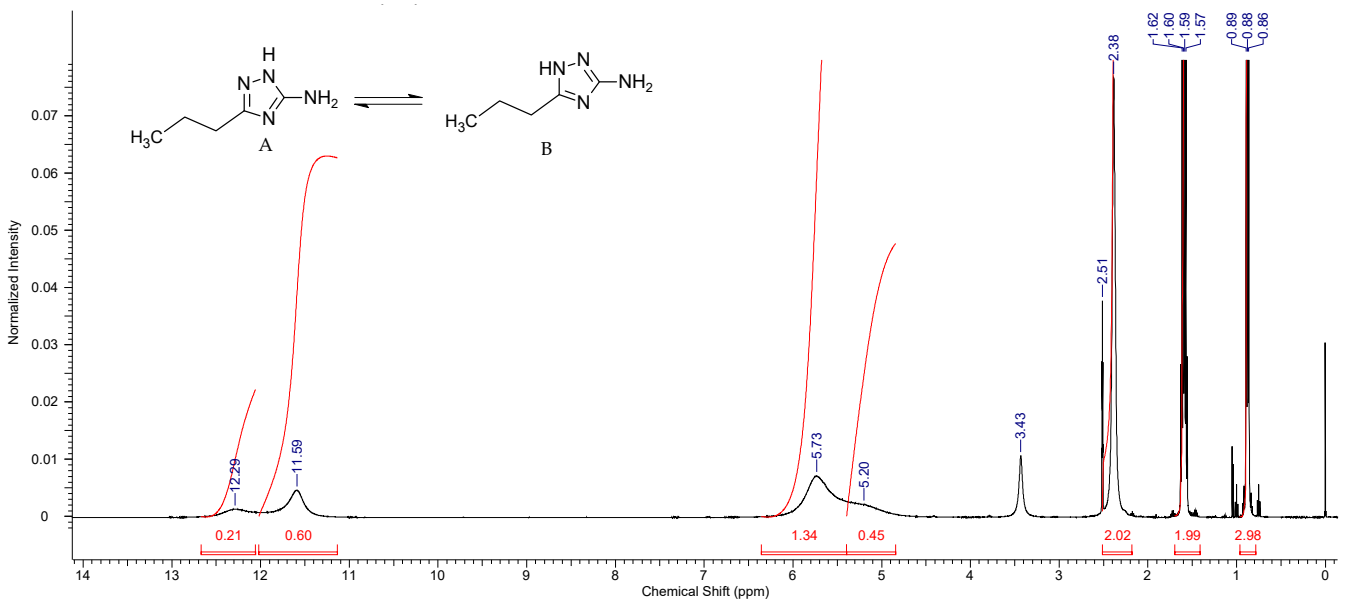


Figure 5. ^{1}H NMR Spectrum of compound **4b** showing formation of two tautomers **A** and **B**.

3-Amino-5-*iso*-butyl-1,2,4-triazole (**4d**): Yield 76%, mp 125–127 °C. IR (ATR), ν (cm^{-1}): 3309, 3163, 2962, 2927, 2873, 1681, 1635, 1589, 1539, 1458, 1395, 1377, 1338, 1311, 1261, 1087, 1014, 960, 798, 744, 677. ^{1}H NMR spectrum, δ, ppm: 1.03 d (*J* = 5 Hz, 3H, CH_3), 1.14 d (*J* = 5 Hz, 3H, CH_3), 2.22 m (1H, CH), 2.52 m (2H, CH_2), 5.58 br. (2H, NH_2). ^{13}C NMR spectrum, δ, ppm: 11.45 (CH_3), 11.63 (CH_3), 19.98 (CH), 28.28 (CH_2), 158.38 (C-3 of triazole), 158.77 (C-5 of triazole). Found (%): C 51.87, H 8.98, N 40.25; $C_6H_{12}N_4$. Calculated (%): C 51.41, H 8.63, N 39.97.

3-Amino-5-*tert*-butyl-1,2,4-triazole (**4e**): Previously described [47]. Yield 72%, mp 120–122 °C. IR (ATR), ν (cm^{-1}): 3298, 3136, 2966, 2931, 2858, 1666, 1627, 1589, 1504, 1450, 1384, 1319, 1265, 1165, 1114, 1037, 987, 952, 810, 759, 594. ^{1}H NMR spectrum, δ, ppm: 1.21 s (9H, CH_3), 5.59 br. (2H, NH_2), 11.11 br. (1H, NH). ^{13}C NMR spectrum, δ, ppm: 29.20

(3 × CH_3), 31.91 (CH), 158.77 (C-3 of triazole), 166.02 (C-5 of triazole). Found (%): C 50.81, H 8.51, N 39.35; $C_6H_{12}N_4$. Calculated (%): C 51.41, H 8.63, N 39.97.

3-Amino-5-*cyclo*-butyl-1,2,4-triazole (**4f**): Yield 70%, mp 173–174 °C. IR (ATR), ν (cm^{-1}): 3414, 3321, 3213, 2970, 2939, 2858, 2781, 2704, 2638, 1620, 1543, 1469, 1411, 1342, 1303, 1249, 1080, 991, 914, 902, 763, 748. ^{1}H NMR spectrum, δ, ppm: 1.83 m (1H, CH_2), 1.92 m (1H, CH_2), 2.18 m (4H, CH_2), 3.34 m (1H, CH), 5.67 br. (2H, NH_2), 11.90 br. (1H, NH). ^{13}C NMR spectrum, δ, ppm: 18.11 (CH_2), 27.36 (2×CH_2), 39.24 (CH), 158.97 (C-3 of triazole), 162.43 (C-5 of triazole). Found (%): C 51.88, H 7.03, N 39.97; $C_6H_{10}N_4$. Calculated (%): C 52.16, H 7.29, N 40.55.

3-Amino-5-pentyl-1,2,4-triazole (**4g**): Previously described [46]. Yield 85%, mp 129–131 °C. IR (ATR), ν (cm^{-1}): 3410, 3321, 3213, 3143, 2954, 2920, 2854, 2785, 2723, 2692, 2654, 1620, 1546, 1481, 1404, 1342, 1269, 1087, 1057, 899, 760. ^{1}H NMR spectrum, δ, ppm: 0.85 t (*J* = 7.5 Hz, 3H, CH_3), 1.27 m (4H, 2XCH_2), 1.57 m (2H, CH_2), 2.40 m (2H, CH_2), 5.55 br. (2H, NH_2), 11.75 br. (1H, NH). ^{13}C NMR spectrum, δ, ppm: 13.83 (CH_3), 21.82 (CH_2), 27.21 (CH_2), 30.84 (CH_2), 152.21 (C-3 of triazole), 161.06 (C-5 of triazole). Found (%): C 54.13, H 8.96, N 35.97; $C_7H_{14}N_4$. Calculated (%): C 54.52, H 9.15, N 36.33.

3-Amino-5-phenyl-1,2,4-triazole (4h): Previously described [46]. Yield 85%, mp 185–187 °C. IR (ATR), ν (cm^{-1}): 3360, 3321, 3078, 2978, 2935, 2862, 2800, 2758, 1666, 1604, 1558, 1489, 1419, 1350, 1311, 1211, 1157, 1107, 1049, 1002, 837, 686. ^{1}H NMR spectrum, δ, ppm: 6.12 br. (2H, NH_2), 7.32–8.02 m (5H, aromatic H), 12.60 br. (1H, NH). ^{13}C NMR spectrum, δ, ppm: 125.33 (aromatic CH), 128.39 (aromatic CH), 128.46 (aromatic CH), 129.24 (aromatic CH), 131.06 (aromatic C), 132.67 (aromatic CH), 157.60 (C-3 of triazole), 158.14 (C-5 of triazole). Found (%): C 59.27, H 4.85, N 34.26; $C_8H_8N_4$. Calculated (%): C 59.99, H 5.03, N 34.98.

3. Results and Discussion

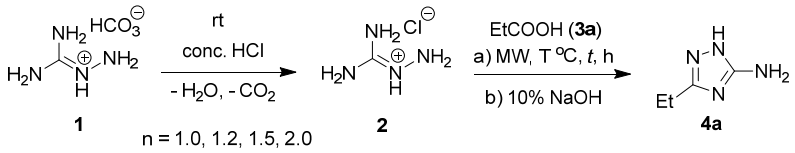
We started our experiments by using initial representative propionic acid (**3a**). In the first stage, aminoguanidine carbonate (**1**) was neutralized by aqueous hydrogen chloride, acid **3a** was added to a vial, and the sealed vial was heated at 180 °C for several hours; however, the isolated yields of **4a** were negligible. Application of higher temperatures slightly incised the isolated yields. Additionally,, the yields were still limited to 20–25% almost independently on the increased reaction temperature and time. Such reaction behavior is typical for equilibrium processes, and in this case, and further increasing the temperature and reaction time will not increase the product yield. The increasing temperature also resulted in the rise of the internal pressure to an unsafe level, perhaps due to the elimination of the residual carbon dioxide left dissolved in the reaction mixture after the neutralization step.

Two molecules of water are formed during both the initial acylation and the final cyclization steps. Due to the use of volatile starting carboxylic acids, it was impossible to eliminate the water from the reaction mixture during the process by using an open reactor. Thus, to minimize the water content in the reaction mixture and to shift the equilibrium to the products' side, after the aminoguanidine bicarbonate neutralization step, the water was removed in vacuum and the obtained hydrochloride **2** was dried in a drying oven at 45 °C in air. This stage also made negligible the undesired process of the additional pressure increase inside the vial due to residual carbon dioxide. It should be noted here that the neutralization stage can be easily omitted by the immediate use of more expensive aminoguanidine hydrochloride as starting material.

For the condensation the initial solid reagent **2** (1.0 mmol) and liquid propionic acid **3a** (1.2 mmol) were heated under microwaves in a sealed vial. It was observed that the amounts of hydrochloric acid left form the neutralization step, which influenced significantly the isolated yields (compare Entry 2 and Entry 4, Table 2) and thus required additional optimization, as well as reaction temperature and time of the interaction. Since aqueous phase is removed before the condensation, we can assume that some amount of HCl, additional to 1:1 stichometry of salt **2**, can remain in the solid residue due to the

partial formation of aminoguanidine dihydrochloride. Thus, we observe the effect of this additional amount of acid in the reaction medium on the final product yield (Table 2). This salt has been previously described in the literature [48].

Table 2. Optimization of reaction conditions.

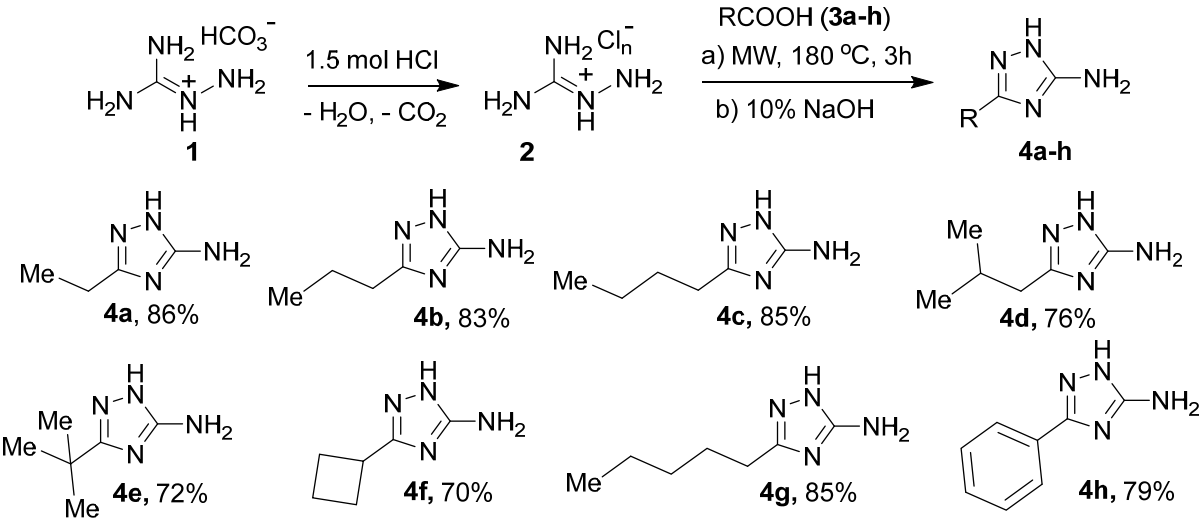


Entry	Amount of HCl, mmol (*n*)	T °C/t, h	Yield [1] (%)
1	1.0	180/2	48
2	1.0	180/4	70
3	1.2	180/2	53
4	1.2	180/4	75
5	1.5	180/2	73
6	1.5	180/4	86
7	1.5	180/3	86
8	2.0	180/2	52
9	2.0	180/4	66
10	1.5	170/3	62
11	1.5	190/3	76
12	1.5	200/3	70

[1] The isolated product yields of **4a**.

As one can see from Table 2, the maximal isolated yield is achieved through the use of 1.5 equiv of HCl under microwave heating at 180 °C for 3 h (Entry 7). For the isolation, the resulting reaction mixture was neutralization with 10% water solution of NaOH to achieve pH 8. The solvent was evaporated in a vacuum, and the pure product was extracted from the solid residue by hot ethyl acetate.

With the use of this procedure, we were able to synthesize a row of 5-substituted 3-amino-1,2,4-triazoles (**4a**–**g**) without any changing in the procedure, with the exception of **4h,** where *i*-PrOH was used as a solvent since benzoic acid (**3h**) is solid (Scheme 1). The synthesis of 2-methylpropyl (**4d**) and cyclobutyl (**4f**) derivatives has not been previously described in the literature; however, their use as building blocks is known [49,50].

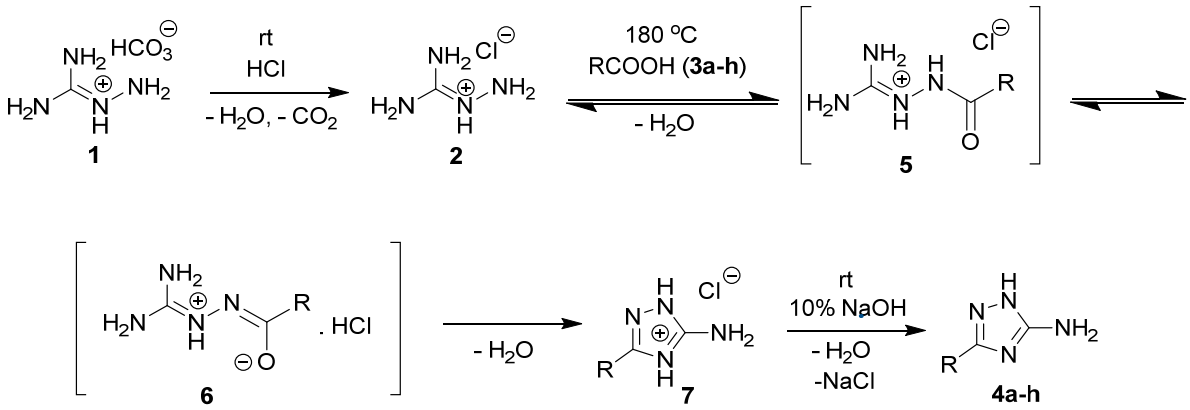


Scheme 1. Isolated yields for various 5-substituted 3-amino-1,2,4-triazoles obtained using **1** (1.0 mmol) and **3** (1.2 mmol) solvent-free for **4a**–**g**; and 2.0 mL of *i*-PrOH for **4h**.

For the pilot scaling-up, we increased the amounts of starting materials by 10 times and used a large multimode Anton Paar Multiwave 5000 reactor with its 100 mL vial. For the tested case of the product **4a** from our first attempt, we succeeded in obtaining a 87% yield of the desired compound, which was 9.7 g of substance from one production cycle. Thus, the laboratory scaling-up of the process was quite achievable, indicating good perspectives for further development of an industrial procedure if necessary.

Spectra ^{1}H and ^{13}C NMR of all the obtained products contained the expected proton and carbon peaks found in their characteristic areas (see, for example, Figure 4). Occasionally, the ^{1}H NMR spectra may contain two ranges of proton signals, as one can see in Figure 5 with the ^{1}H NMR spectrum of *n*-propyl derivative **4b**. This behavior is in good agreement with previous studies on the tautomerism of 3-amino-1,2,4-triazoles, where it was shown that the main tautomers observed in the spectra are forms A and B (Figure 5). The ratio of the integral intensities for the NH and NH_2 proton signals of these forms and their relative position on the ppm scale also correlates well with the previous data [38]. The presence or absence of signals of tautomeric forms and their relative intensity depends on the conditions of NMR spectra measurement and the rate of equilibrium formation between tautomers. However, a more detailed study of this aspect is beyond the scope of the routine characterization of the compounds in this work.

As previously reported [43], the cyclization ability of guanyl hydrazides **5** to aminotriazoles 7 was significantly influenced by the acyl group structure and the acidity of the medium (Scheme 2). The cyclization rate of guanyl hydrazides in the form of free bases appears to be substantially higher than that of salt forms. In this case, the additional amount of acid may slow down the rate of the cyclization step (although perhaps it is required to accelerate the first acylation stage). As a result, the acid-base properties of these intermediates (**5**) can be considered as an additional factor influencing the synthesize of aminotriazoles from guanidine and carboxylic acids.



Scheme 2. Plausible reaction mechanism.

Previous studies have shown that the crucial stage in the synthesis of 3-substituted 5-amino-1,2,4-triazoles from aminoguanidine and carboxylic acids is the one in which guanyl hydrazides are formed. Due to the fact that the guanyl hydrazide (**5**) formation step is acid-catalyzed and reversible, its success is highly dependent on the reaction conditions. In this regard, the following points are important: (i) reaction medium pH $\leq$ 1, (ii) to ensure rapid equilibrium attainment (it is necessary to use a concentrated solution with minimal water content), (iii) the application of an optimized excess of HCl acid as also shown previously [43,51].

Chernyshov's group has presented the guanyl hydrazides of aliphatic carboxylic acids being synthesized as salts by heating the corresponding carboxylic acids with aminoguanidine bicarbonate and concentrated hydrochloric acid by reflux, a process which was followed by distillation of the water and carboxylic acid excess in a vacuum. Attempts to isolate and characterize aliphatic carboxylic acid guanyl hydrazides in the form of free bases

proved unsuccessful. The treatment of salts with aqueous ammonia or sodium hydroxide succeeded by purification resulted in the cyclization of aliphatic carboxylic acid guanyl hydrazides to the corresponding aminotriazoles [43,51,52]. Thus, there are reasons to assume that the most difficult, and the rate determining stage in our process, is the acylation of guanidine to produce **5,** which requires such a high temperature (180 °C), under which both stages with the elimination of water (**2** to **5** and **5** to **7**) can be effectively accomplished. The excessive water is undesirable in the reaction mixture, as it decreases dramatically the reaction yield independently on the increased reaction time and temperature.

As a result of this work, we have presented here an efficient microwave-assisted method for the straightforward synthesis of 3-amino-1,2,4-triazoles directly from volatile aliphatic carboxylic or benzoic acids. The high reaction yields were obtained due to the minimal amount of water in the reaction media and the optimized amount of HCl as a catalyst (1.5 equiv), while the high reaction temperature of 180 °C was achieved using the technology of controlled microwave synthesis in sealed reaction vessels of volumes ranging from 10 to 100 mL. The application of microwaves to accelerate this reaction is well-suited to the process considering the high polarity of the reaction mixture, which enables rapid attainment of the required high temperature in the sealed vessels.

Supplementary Materials: The supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/pr12030573/s1.

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Data Availability Statement: Data are available upon request to the corresponding author.

Conflicts of Interest: The authors declare no conflicts of interest.

References

1. Moulin, A.; Bibian, M.; Blayo, A.-L.; El Habnouni, S.; Martinez, J.; Fehrentz, J.-A. Synthesis of 3,4,5-trisubstituted-1,2,4-triazoles. *Chem. Rev.* **2010**, *110*, 1809–1827. [CrossRef]
2. Kazeminejad, Z.; Marzi, M.; Shiroudi, A.; Kouhpayeh, S.A.; Farjam, M.; Zarenezhad, E. Novel 1,2,4-triazoles as antifungal agents. *BioMed Res. Int.* **2022**, *2022*, 4584846. [CrossRef]
3. Strzelecka, M.; Świątek, P. 1,2,4-Triazoles as important antibacterial agents. *Pharmaceuticals* **2021**, *14*, 224. [CrossRef]
4. Zhang, S.; Xu, Z.; Gao, C.; Ren, Q.-C.; Chang, L.; Lv, Z.-S.; Feng, L.-S. Triazole derivatives and their anti-tubercular activity. *Eur. J. Med. Chem.* **2017**, *138*, 501–513. [CrossRef]
5. Kaur, R.; Ranjan Dwivedi, A.; Kumar, B.; Kumar, V. Recent developments on 1,2,4-triazole nucleus in anticancer compounds: A review. *Anti-Cancer Agents Med. Chem.* **2016**, *16*, 465–489. [CrossRef] [PubMed]
6. Ferreira, V.F.; da Rocha, D.R.; da Silva, F.C.; Ferreira, P.G.; Boechat, N.A.; Magalhães, J.L. Novel 1*H*-1,2,3-, 2*H*-1,2,3-, 1*H*-1,2,4- and 4*H*-1,2,4-triazole derivatives: A patent review (2008–2011). *Expert Opin. Ther. Patents* **2013**, *23*, 319–331. [CrossRef] [PubMed]
7. Zeidler, J.; Baraniak, D.; Ostrowski, T. Bioactive nucleoside analogues possessing selected five-membered azaheterocyclic bases. *Eur. J. Med. Chem.* **2015**, *97*, 409–418. [CrossRef] [PubMed]
8. Ayati, A.; Emami, S.; Foroumadi, A. The importance of triazole scaffold in the development of anticonvulsant agents. *Eur. J. Med. Chem.* **2016**, *109*, 380–392. [CrossRef]
9. Sathyanarayana, R.; Poojary, B. Exploring recent developments on 1,2,4-triazole: Synthesis and biological applications. *J. Chin. Chem. Soc.* **2020**, *67*, 459–477. [CrossRef]
10. Singh, G.; Prem Felix, S. Studies on energetic compounds: 25. An overview of preparation, thermolysis and applications of the salts of 5-nitro-2,4-dihydro-3*H*-1,2,4-triazol-3-one (NTO). *J. Hazard. Mater.* **2002**, *90*, 409–418. [CrossRef]
11. Phadke Swathi, N.; Alva, V.D.P.; Samshuddin, S. A review on 1,2,4-triazole derivatives as corrosion inhibitors. *J. Bio. Tribo. Corros.* **2017**, *3*, 42. [CrossRef]

12. Naik, A.D.; Dîrtu, M.M.; Railliet, A.P.; Marchand-Brynaert, J.; Garcia, Y. Coordination polymers and metal organic frameworks derived from 1,2 4-triazole amino acid linkers. *Polymers* **2011**, *3*, 1750–1775. [CrossRef]
13. Haasnoot, J.G. Mononuclear, oligonuclear and polynuclear metal coordination compounds with 1,2,4-triazole derivatives as ligands. *Coord. Chem. Rev.* **2000**, *200–202*, 131–185. [CrossRef]
14. Aromí, G.; Barrios, L.A.; Roubeau, O.; Gamez, P. Triazoles and tetrazoles: Prime ligands to generate remarkable coordination materials. *Coord. Chem. Rev.* **2011**, *255*, 485–546. [CrossRef]
15. Nasri, S.; Bayat, M.; Kochia, K. Strategies for synthesis of 1,2,4-triazole-containing scaffolds using 3-amino-1,2,4-triazole. *Mol. Divers.* **2021**, *26*, 717–739. [CrossRef] [PubMed]
16. Chebanov, V.A.; Desenko, S.M. Multicomponent heterocyclization reactions with controlled selectivity (Review). *Chem. Heterocycl. Comp.* **2012**, *48*, 566–583. [CrossRef]
17. Murlykina, M.V.; Morozova, A.D.; Zviagin, I.M.; Sakhno, Y.I.; Desenko, S.M.; Chebanov, V.A. Aminoazole-based Ddiversity-oriented synthesis of heterocycles. *Front. Chem.* **2018**, *6*, 527–569. [CrossRef]
18. Pacetti, M.; Pismataro, M.C.; Felicetti, T.; Giammarino, F.; Bonomini, A.; Tiecco, M.; Bertagnin, C.; Barreca, M.L.; Germani, R.; Cecchetti, V.; et al. Switching the three-component Biginelli-like reaction conditions for the regioselective synthesis of new 2-amino [1,2,4]triazolo[1,5-*a*]pyrimidines. *Org. Biomol. Chem.* **2024**, *22*, 767–783. [CrossRef]
19. Aouali, M.; Mhalla, D.; Allouche, F.; El Kaim, L.; Tounsi, S.; Trigui, M.; Chabchoub, F. Synthesis, antimicrobial and antioxidant activities of imidazotriazoles and new multicomponent reaction toward 5-amino-1-phenyl[1,2,4]triazole derivatives. *Med. Chem. Res.* **2015**, *24*, 2732–2741. [CrossRef]
20. Gümüş, M.K. Green formation of novel pyridinyltriazole-salicylidene Schiff bases. *Curr. Org. Synth.* **2019**, *16*, 309–313. [CrossRef]
21. Çakır, O.; Bakhshpour, M.; Göktürk, I.; Yılmaz, F.; Baysal, Z. Sensitive and selective detection of amitrole based on molecularly imprinted nanosensor. *J. Mol. Recognit.* **2021**, *34*, e2929. [CrossRef]
22. Mahdavi, M.; Akbarzadeh, T.; Sheibani, V.; Abbasi, M.; Firoozpour, L.; Tabatabai, S.A.; Shafiee, A.; Foroumadi, A. Synthesis of two novel 3-amino-5-[4-chloro-2-phenoxyphenyl]-4*H*-1,2,4-triazoles with anticonvulsant activity. *Iran. J. Pharm. Res.* **2010**, *9*, 265–269.
23. Marino, J.P.; Fisher, P.W.; Hofmann, G.A.; Kirkpatrick, R.B.; Janson, C.A.; Johnson, R.K.; Ma, C.; Mattern, M.; Meek, T.D.; Ryan, M.D.; et al. Highly potent inhibitors of methionine aminopeptidase-2 based on a 1,2,4-triazole pharmacophore. *J. Med. Chem.* **2007**, *50*, 3777–3785. [CrossRef]
24. Brittain, R.T.; Jack, D.; Reeves, J.J.; Stables, R. Pharmacological basis for the induction of gastric carcinoid tumours in the rat by loxtidine, an insurmountable histamine H_2-receptor blocking drug. *Br. J. Pharmacol.* **1985**, *85*, 843–847. [CrossRef]
25. Beinat, C.; Banister, S.D.; Herrera, M.; Law, V.; Kassiou, M. The therapeutic potential of α_7 nicotinic acetylcholine receptor (α_7 nAChR) agonists for the treatment of the cognitive deficits associated with schizophrenia. *CNS Drugs* **2015**, *29*, 529–542. [CrossRef]
26. Arkhipushkin, I.A.; Agafonkina, M.O.; Kazansky, L.P.; Kuznetsov, Y.I.; Shikhaliev, K.S. Characterization of adsorption of 5-carboxy-3-amino-1,2,4-triazole towards copper corrosion prevention in neutral media. *Electrochim. Acta* **2019**, *308*, 392–399. [CrossRef]
27. Chirkunov, A.A.; Kuznetsov, Y.I.; Shikhaliev, K.S.; Agafonkina, M.O.; Andreeva, N.P.; Kazansky, L.P.; Potapov, A.Y. Adsorption of 5-alkyl-3-amino-1,2,4-triazoles from aqueous solutions and protection of copper from atmospheric corrosion. *Corros. Sci.* **2018**, *144*, 230–236. [CrossRef]
28. Faisal, M.; Saeed, A.; Shahzad, D.; Abbas, N.; Larik, F.A.; Channar, P.A.; Fattah, T.A.; Khan, D.M.; Shehzadi, S.A. General properties and comparison of the corrosion inhibition efficiencies of the triazole derivatives for mild steel. *Corros. Rev.* **2018**, *36*, 507–545. [CrossRef]
29. Kukuljan, L.; Kranjc, K. 3-(5-Amino-1,2,4-triazole)-1,2,4-oxadiazole: A new biheterocyclic scaffold for the synthesis of energetic materials. *Tetrahedron Lett.* **2019**, *60*, 207–209. [CrossRef]
30. Atia, N.N.; Ali, M.F.B. 3-Amino-5-pyridin-3-yl-1,2,4-triazole, a novel fluorescence probe for trace analysis of silymarin in bulk material, pharmaceutical dosage forms and human plasma: Further insights on reaction mechanism using computational molecular modeling and NMR spectroscopy. *Spectrochim. Acta Part A Mol. Biomol. Spectrosc.* **2018**, *204*, 188–195. [CrossRef]
31. Available online: https://scifinder-n.cas.org/ (accessed on 11 January 2024).
32. Gorobets, N.Y.; Sedash, Y.V.; Ostras, K.S.; Zaremba, O.V.; Shishkina, S.V.; Baumer, V.N.; Shishkin, O.V.; Kovalenko, S.M.; Desenko, S.M.; Van der Eycken, E.V. Unexpected alternative direction of a Biginelli-like multicomponent reaction with 3-amino-1,2,4-triazole as the urea component. *Tetrahedron Lett.* **2010**, *51*, 2095–2098. [CrossRef]
33. Sedash, Y.V.; Gorobets, N.Y.; Chebanov, V.A.; Konovalova, I.S.; Shishkin, O.V.; Desenko, S.M. Dotting the i's in three-component Biginelli-like condensations using 3-amino-1,2,4-triazole as a 1,3-binucleophile. *RSC Adv.* **2012**, *2*, 6719–6728. [CrossRef]
34. Kondratiuk, M.; Gorobets, N.Y.; Sedash, Y.V.; Gümüş, M.K.; Desenko, S.M. 5-(5-Bromo-2-hydroxy-3-methoxyphenyl)-7-methyl-4,5,6,7-tetrahydro[1,2,4]triazolo[1,5-*a*]pyrimidin-7-ol. *Molbank* **2016**, *2016*, M898. [CrossRef]
35. Gümüş, M.K.; Gorobets, N.Y.; Sedash, Y.V.; Shishkina, S.V.; Desenko, S.M. Rapid formation of chemical complexity via a modified Biginelli reaction leading to dihydrofuran-2 (3H)-one spiro-derivatives of triazolo [1,5-*a*] pyrimidine. *Tetrahedron Lett.* **2017**, *58*, 3446–3448. [CrossRef]
36. Komykhov, S.A.; Bondarenko, A.A.; Musatov, V.I.; Diachkov, M.V.; Gorobets, N.Y.; Desenko, S.M. (5*S*,7*R*)-5-Aryl-7-methyl-4,5,6,7-tetrahydro-[1,2,4]triazolo[1,5-*a*]pyrimidin-7-ols as products of three-component condensation. *Chem. Heterocycl. Comp.* **2017**, *53*, 378–380. [CrossRef]

37. Gümüş, M.K.; Gorobets, N.Y.; Sedash, Y.V.; Chebanov, V.A.; Desenko, S.M. A modified Biginelli reaction toward oxygen-bridged tetrahydropyrimidines fused with substituted 1,2,4-triazole ring. *Chem. Heterocycl. Comp.* **2017**, *53*, 1261–1267. [CrossRef]
38. Dolzhenko, A.V.; Pastorin, G.; Dolzhenko, A.V.; Chui, W.K. An aqueous medium synthesis and tautomerism study of 3(5)-amino-1,2,4-triazoles. *Tetrahedron Lett.* **2009**, *50*, 2124–2128. [CrossRef]
39. Beyzaei, H.; Khosravi, Z.; Aryan, R.; Ghasemi, B. A green one-pot synthesis of 3(5)-substituted 1,2,4-triazol-5(3)-amines as potential antimicrobial agents. *J. Iran. Chem. Soc.* **2019**, *16*, 2565–2573. [CrossRef]
40. Bogolyubsky, A.V.; Savych, O.; Zhemera, A.V.; Pipko, S.E.; Grishchenko, A.V.; Konovets, A.I.; Doroshchuk, R.O.; Khomenko, D.N.; Brovarets, V.S.; Moroz, Y.S.; et al. Facile one-pot parallel synthesis of 3-amino-1,2,4-triazoles. *ACS Comb. Sci.* **2018**, *20*, 461–466. [CrossRef]
41. Lim, F.P.L.; Tan, L.Y.; Tiekink, E.R.; Dolzhenko, A.V. Synthesis of 3-(5-amino-1*H*-1,2,4-triazol-3-yl) propanamides and their tautomerism. *RSC Adv.* **2018**, *8*, 22351–22360. [CrossRef] [PubMed]
42. Rohand, T.; Mkpenie, V.N.; El Haddad, M.; Marko, I.E. A novel iron-catalyzed one-pot synthesis of 3-amino-1,2,4-triazoles. *J. Heterocycl. Chem.* **2019**, *56*, 690–695. [CrossRef]
43. Chernyshev, V.M.; Tarasova, E.V.; Chernysheva, A.V.; Taranushich, V.A. Synthesis of 3-pyridyl-substituted 5-amino-1,2,4-triazoles from aminoguanidine and pyridinecarboxylic acids. *Russ. J. Appl. Chem.* **2011**, *84*, 1890–1896. [CrossRef]
44. Lim, F.P.L.; Hu, L.M.; Tiekink, E.R.T.; Dolzhenko, A.V. One-pot, microwave-assisted synthesis of polymethylene-bridged bis (1*H*-1,2,4-triazol-5(3)-amines) and their tautomerism. *Tetrahedron Lett.* **2018**, *59*, 3792–3796. [CrossRef]
45. Reilly, J.; Madden, D. The stability of diazonium salts of the triazole series. *J. Chem. Soc.* **1929**, 815–816. [CrossRef]
46. Huang, L.; Ding, J.; Li, M.; Hou, Z.; Geng, Y.; Li, X.; Yu, H. Discovery of [1,2,4]-triazolo [1,5-*a*]pyrimidine-7(4*H*)-one derivatives as positive modulators of GABAA1 receptor with potent anticonvulsant activity and low toxicity. *Eur. J. Med. Chem.* **2020**, *185*, 111824. [CrossRef]
47. Wei, Z.; Zhang, Q.; Tang, M.; Zhang, S.; Zhang, Q. Diversity-Oriented Synthesis of 1,2,4-Triazols, 1,3,4-Thiadiazols, and 1,3,4-Selenadiazoles from N-Tosylhydrazones. *Org. Lett.* **2021**, *23*, 4436–4440. [CrossRef]
48. Gaubert, G.; Bertozzi, F.; Kelly, N.M.; Pawlas, J.; Scully, A.L.; Nash, N.R.; Gardell, L.R.; Lameh, J.; Olsson, R. Discovery of selective nonpeptidergic neuropeptide FF2 receptor agonists. *J. Med. Chem.* **2009**, *52*, 6511–6514. [CrossRef]
49. Bongard, J.; Schmitz, A.L.; Wolf, A.; Zischinsky, G.; Pieren, M.; Schellhorn, B.; Bravo-Rodriguez, K.; Schillinger, J.; Koch, U.; Nussbaumer, P. Chemical validation of DegS as a target for the development of antibiotics with a novel mode of action. *ChemMedChem* **2019**, *14*, 1074–1078. [CrossRef] [PubMed]
50. Lo, M.M.-C.; Chobanian, H.R.; Palyha, O.; Kan, Y.; Kelly, T.M.; Guan, X.-M.; Reitman, M.L.; Dragovic, J.; Lyons, K.A.; Nargund, R.P. Pyridinesulfonylureas and pyridinesulfonamides as selective bombesin receptor subtype-3 (BRS-3) agonists. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 2040–2043. [CrossRef] [PubMed]
51. Astakhov, A.V.; Tarasova, E.V.; Chernysheva, A.V.; Rybakov, V.B.; Starikova, Z.A.; Chernyshev, V.M. Tautomerism and basicity of carboxylic acid guanyl hydrazides (acylaminoguanidines). *Russ. Chem. Bull.* **2021**, *70*, 1509–1522. [CrossRef]
52. Chernyshev, V.M.; Chernysheva, A.V.; Starikova, Z.A. Rearrangement of 2-(2,5-dioxopyrrolidin-1-yl) guanidine: An efficient synthesis and structure of 3-(5-amino-1*H*-1,2,4-triazol-3-yl) propanoic acid and derivatives. *Heterocycles* **2010**, *81*, 2291. [CrossRef]