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Article

Uncatalyzed addition and cyclization of TsN_3 to 1,1-enediamines: an effective green route to highly functionalized 1,2,3-triazole compounds

Chang-Long Yang[1], Yu-Hao Zhang[1], Quan-Xing Zi[1], Jun Lin[1,*] and Sheng-Jiao Yan[1,*]

[1] Key Laboratory of Medicinal Chemistry for Natural Resources (Yunnan University), Ministry of Education, School of Chemical Science and Technology, Yunnan University, Kunming, 650091, P. R. China.
Emails: linjun@ynu.edu.cn; yansj@ynu.edu.cn.

Abstract: Novel 1,2,3-triazole compounds **3–4** were synthesised *via* the regioselective addition and cyclization reaction of 1,1-enediamines (EDAMs) **1** with *p*-methylbenzenesulfonyl azide (TsN_3) **2** in 1,4-dioxane at refluxing for 5 hours. As a result, 1,2,3-triazoles **3–4** can be easily and efficiently obtained via catalyst-free click chemistry. The reactions have some advantages such as metal-free catalyst, excellent yield, inexpensive raw materials, and convenient final treatment.

Keywords: 1,2,3-Triazole; 1,1-Enediamines; Addition and cyclization; Click chemistry

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1. Introduction

1,2,3-Triazole compounds exhibit various biological activities, such as anti-tumor [1-3], anti-virus [4], anti-tuberculosis [5], anti-bacterial [6], anti-fungal [7], anti-convulsion [8], anti-inflammatory, anti- allergy [9] and others [10-12]. The 1,2,3-triazole skeleton usually contains that of synthesized drugs, for example, an anti-epileptic agent (**rufinamide**), anti-bacterial drug (**tazobactum**), heat shock protein 90 (Hsp90) inhibitor (**SST0287CL1**) [13], carbonic anhydrase inhibitor (compound **A**) [14], anti-influenza A agents (compound **B**) [15], et al [16].

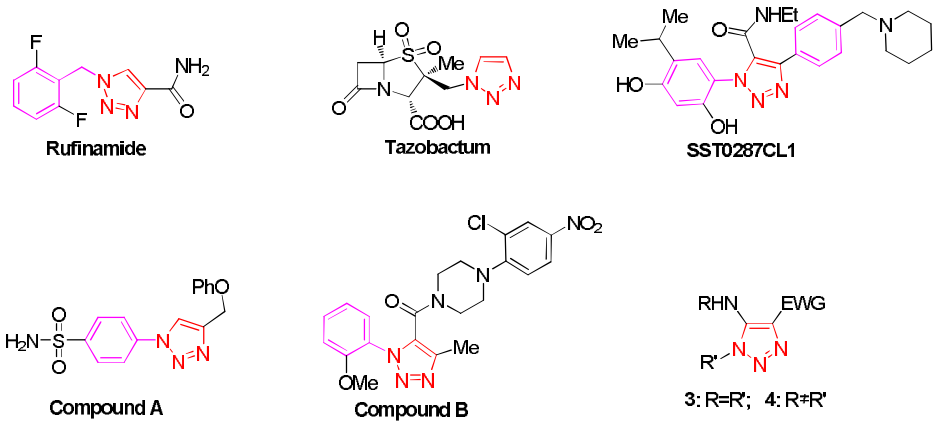

Figure 1. Biologically active 1,2,3-triazoles and the target compounds.

At the same time, 1,2,3-triazole compounds are important building blocks for the synthesis of other *N*-containing heterocycles [17-20]. Therefore, there has been great interest in the synthesis of 1,2,3-triazole compounds in the fields of organic and pharmaceutical chemistry. Thus far, the synthesis methods of 1,2,3-triazole compounds have been extensively reported [21-36]. Among

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them, the click chemical reaction of alkyne and azide in the catalysis of copper salts (CuAAC) or other metal salts is the main method for synthesis of 1,2,3-triazole compounds [21-31]. Azide compounds such as benzene sulfonyl azide, substituted benzene sulfonyl azide, trimethyl silicate, aryl azide, and sodium azide can be used as substrates for this CuAAC click reaction to synthesize 1,2,3-triazoles [3]. Except for the classic synthetic method, there are some methods including using aldehyde/ketone [32-33], α,β-unsaturated ketones [34-35], and enaminones [36] as the building blocks that react with all types of azide compounds to construct 1,2,3-triazole compounds.

1,1-Enediamines (EDAMs) are fascinating and versatile building blocks that are widely used to synthesize various heterocyclic compounds [37-52]. Many of these compounds have a wide range of biological activities, such as antitumor [53-55], pesticide [56-58], and others.

There has been sufficient study to determine the building blocks that will effectively construct the 1,2,3-triazoles by addition and cyclization reaction, especially the met-catalyst click chemistry reaction. However, the molecular diversity of potential pharmacological activities of highly functionalized 1,2,3-triazoles, especially the fully-substituted 1,2,3-triazoles, is very limited. Consequently, it is very important and highly desirable to utilize the building blocks of 1,1-enediamines (EDAMs) to construct fully-substituted 1,2,3-triazoles with potential pharmacological activities by un-catalyzed click chemistry reaction rather than the classic copper(I)-catalyzed azide-alkyne cycloaddition CuAAC reaction. Here, we use EDAMs **1** reacted with *p*-methylbenzenesulfonyl azide (TsN_3) **2** in 1,4-dioxane at refluxing for 5 hours to synthesize the 1,2,3-triazoles **3–4**.

2. Results and Discussion

Initially, 1-phenyl-3,3-bis(phenylamino)prop-2-en-1-one **1d** and TsN_3 **2** were selected as substrates to test the model reaction for optimal reaction conditions. Fortunately, the target compound **3d** was obtained in 70% yield as EDAM **1d** reacted with TsN_3 in dimethylformamide (DMF) (15 mL) at 110°C for 5 h (Table 1, entry 1). Then, various solvents including 1,4-dioxane, acetonitrile, dichloromethane (DCM), and ethanol were screened at refluxing for 5 hours (Table 1, entries 2–5). The results showed that 1,4-dioxane was the best solvent for obtaining the target compound with 85% yield (Table 1, entry 2). Based on the optimal solvent, Cu(I) or Cu(II) was selected as the catalysts for this reaction. The results showed that the Cu(I/II) catalysts did not increase the yield of **3d** (Table 1, entries 6–9). Finally, after careful screening, the results showed that the optimal reaction time is approximately 5 hours. The optimal conditions were 1,4-dioxane as solvent, and refluxing for 5 h without any catalyst (Table 1, entry 2).

After we obtained the optimized reaction conditions, we explored the scope and limitations of the addition and cyclization reaction involving various EDAMs **1** (EDAMs bearing different aromatic groups) with TsN_3 (Table 2, entries 1–15) in 1,4-dioxane. The results showed that this reaction proceeds smoothly with optimal conditions, and we obtained a series of products **3a–3o** in good yields (Table 2, entries 1–15). We found that R was the electron withdrawing group, and it was more reactive than the electron-donating groups or neutral groups (Table 2, entry 3 *vs.* 1–2; 5 *vs.* 4; 12 *vs.* 11, 15 *vs.* 13–14). We also found that the length of the side chain also impacted upon the yield. In general, Benzyl or substituted-Benzyl is very favourable for the yield; however, phenylethyl or substituted phenylethyl results in lower yields (Table 2, entry 4 *vs.* 7 *vs.* 14; 5 *vs.* 8).

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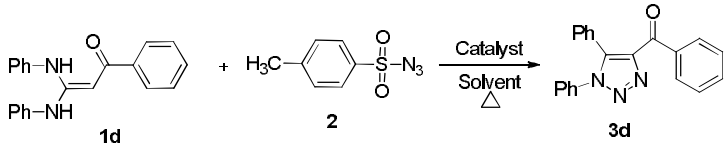
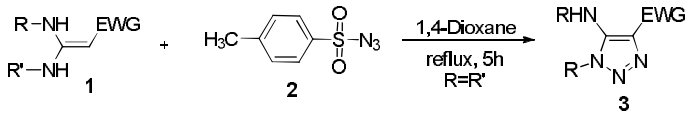
Table 1. Screening optimum reaction conditions for the model reaction[a].



Entry	Solvent	Catalyst	T (°C)	Time (h)	Yield (%)[b]
1	DMF	–	110	5	70
2	**1,4-Dioxane**	**–**	**reflux**	**5**	**85**
3	CH_3CN		reflux	5	80.
4	DCM		reflux	5	81
5	EtOH		reflux	5	75
6	1,4-Dioxane	CuI	reflux	5	80
7	1,4-Dioxane	CuCl	reflux	5	76
8	1,4-Dioxane	$ZnCl_2$	reflux	5	73
9	1,4-Dioxane	$CuSO_4$	reflux	5	66
10	1,4-Dioxane	–	reflux	4	83
11	1,4-Dioxane	–	reflux	6	84
12	1,4-Dioxane	–	reflux	8	80

[a] Reactions were performed with EDAM **1d** (0.8 mmol), TsN_3 **2** (1.0 mmol), and the solvent (15.0 mL). [b] Isolated yields based on **1d**.

Table 2. Substrate scope and synthesis of 1,2,3-triazole compounds **3a–3o**[a]



Entry	EWG	R	Product	Yield (%)[b]
1	*p*-MeC_6H_4CO	*p*-$MeOC_6H_4$	**3a**	82
2	*p*-MeC_6H_4CO	C_6H_5	**3b**	84
3	*p*-MeC_6H_4CO	*p*-ClC_6H_4	**3c**	86
4	C_6H_5CO	C_6H_5	**3d**	85
5	C_6H_5CO	*p*-FC_6H_4	**3e**	89
6	*p*-MeC_6H_4CO	*p*-$FC_6H_4CH_2$	**3f**	89
7	C_6H_5CO	$C_6H_5CH_2$	**3g**	87
8	C_6H_5CO	*p*-$FC_6H_4CH_2$	**3h**	90
9	*p*-ClC_6H_4CO	*p*-$ClC_6H_4CH_2$	**3i**	87
10	*p*-FC_6H_4CO	*p*-$MeC_6H_4CH_2$	**3j**	80
11	*o*-ClC_6H_4CO	*p*-$MeC_6H_4CH_2$	**3k**	83
12	*o*-ClC_6H_4CO	*p*-$FC_6H_4CH_2$	**3l**	92
13	C_6H_5CO	*p*-$MeOC_6H_4CH_2CH_2$	**3m**	79
14	C_6H_5CO	$C_6H_5CH_2CH_2$	**3n**	82
15	C_6H_5CO	*p*-$ClC_6H_4CH_2CH_2$	**3o**	84

[a] Reagents and conditions: EDAMs **1** (0.8 mmol), TsN_3 **2** (1.0 mmol), 1,4-dioxane (15.0 mL). [b] Isolated yield based on EDAMs **1**.

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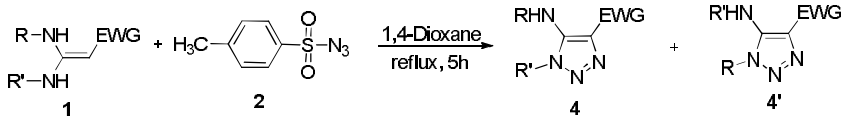
Based onthe results, we conclude that the different substitute EDAMs can react with TsN_3 under standard conditions.

In order to research the regioselectiveness of the addition and cyclization reaction, different substitute EDAMs (R ≠ R') were used in this reaction. The results demonstrated that this reaction exhibits good regioselectiveness, and we obtained the major products **4** with moderate yield and the minor product **4'** with very low yield (Table 3, entries 1–7).

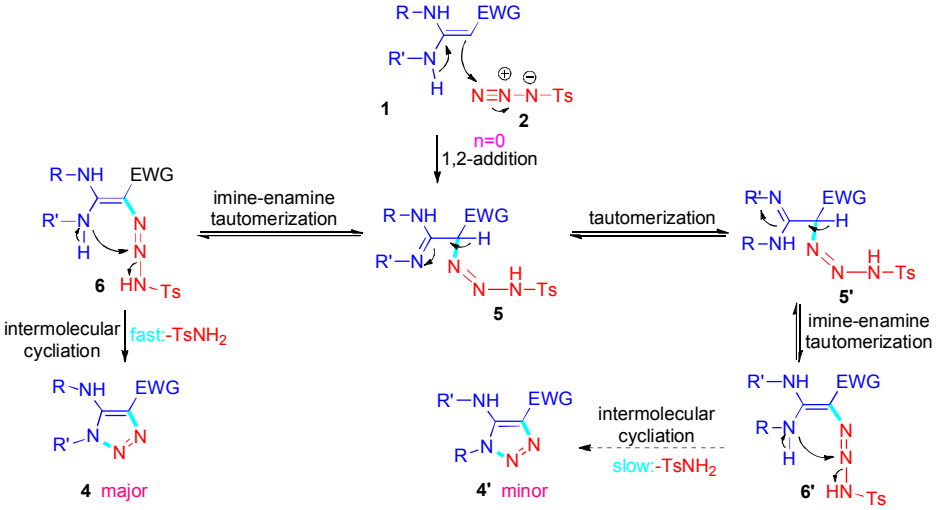
Table 3. Substrate scope and synthesis of 1,2,3-triazole compounds **4** &**4'**[a-b].



Entry	EWG	R	R′	R′	**4**/Yield	**4'**/Yield
1	*p*-MeC_6H_4CO	C_6H_5	$C_6H_5CH_2$		**4a**/62%	**4a'**/25%
2	*p*-MeC_6H_4CO	*p*-FC_6H_4	$C_6H_5CH_2$		**4b**/78%	–
3	*p*-MeC_6H_4CO	C_6H_5	*p*-$ClC_6H_4CH_2CH_2$		**4c**/70%	–
4	C_6H_5CO	*p*-ClC_6H_4	*p*-$MeOC_6H_4CH_2CH_2$		**4d**/55%	**4d'**/30%
5	*p*-ClC_6H_4CO	C_6H_5	*p*-$ClC_6H_4CH_2$		**4e**/82%	–
6	*p*-ClC_6H_4CO	*p*-ClC_6H_4	$C_6H_5CH_2CH_2$		**4f**/75%	–
7	*p*-ClC_6H_4CO	*p*-ClC_6H_4	*m*-$FC_6H_4CH_2CH_2$		**4g**/62%	**4g'**/24%

[a] Reagents and conditions: EDAMs **1** (0.8 mmol), TsN_3 **2** (1.0 mmol), 1,4-dioxane (15.0 mL). [b] Isolated yield based on EDAMs **1**.

According to the results, we obtained the major products **4** and the minor products **4'**. The proposed mechanism is shown in Scheme 1. Firstly, EDAMs **1** react with TsN_3 and transform to intermediate **5** *via* the 1,2-addition reaction. Secondly, the intermediates **5** formed the intermediates **5'** through tautomerization. Thereafter, there are two routes. In route A, intermediate **5** is used to obtain intermediate **6** through an imine-enamine tautomerization. Next, the intermediate **6** obtained the final major products **4** *via* an intermolecular cyclization reaction and loss of one molecule, $TsNH_2$. This step is the crucial step, and with this step, the amino group of intermediate **6** is more highly reactive than that of intermediate **6'**. As a result, we can obtain the major products of **4**, not compounds **4'**.



Scheme 1. Proposed mechanism for construction of 1,2,3-triazoles **4** &**4'**.

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3. Experimental Section

3.1. General Information and Materials

All compounds were fully characterized by spectroscopic data. The NMR spectra were recorded on a Bruker DRX500 (^{1}H: 500 MHz, ^{13}C: 125 MHz) or DRX600 (^{1}H: 600 MHz, ^{13}C: 150 MHz), chemical shifts (δ) are expressed in ppm, and J values are given in Hz, deuterated DMSO-d_6 and $CDCl_3$ were used as solvent. IR spectra were recorded on a FT-IR Thermo Nicolet Avatar 360 using KBr pellet. The reactions were monitored by thin layer chromatography (TLC) using silica gel GF_{254}. The melting points were determined on XT-4A melting point apparatus and are uncorrected. HRMs were performed on an Agilent LC/Msd TOF instrument.

All chemicals and solvents were used as received without further purification unless otherwise stated. Compounds **1** were obtained according to the literature [37-41].

3.2. General procedure for prepared 1,2,3-triazoles 3–4.

EDAMs **1** (0.8 mmol), 4-methylbenzenesulfonyl azide **2** (1.0 mmol), and 1,4-dioxane (15 mL) were charged into a 25-mL round-bottom flask. The mixture was refluxed for approximately 5 h and then monitored by thin-layer chromatography (TLC) until the HKA **1** substrate was completely consumed. After the completion of the reaction, the crude products were purified by column chromatography (petroleum ether/EtOAc=20:1), and a series of compounds **3–4** with 55–92% yield was obtained.

(1-(4-Methoxyphenyl)-5-((4-methoxyphenyl)amino)-1H-1,2, 3-triazol-4-yl)(p-tolyl)methanone ***3a***. White solid; Mp 166–167°C; IR (KBr): 3414, 1601, 1573, 1423, 1227, 923, 752 cm^{-1}; ^{1}H NMR (600 MHz, DMSO-d_6): δ = 2.43 (s, 3H, CH_3), 3.61 (s, 3H, OCH_3), 3.73 (s, 3H, OCH_3), 6.57 (d, J = 8.8 Hz 2H, ArH), 6.81–6.86 (m, 4H, ArH), 7.26 (d, J = 8.8 Hz 2H, ArH), 7.41 (d, J = 8.0 Hz, 2H, ArH), 8.29 (d, J = 8.0 Hz, 2H, ArH), 9.19 (br, 1H, NH); ^{13}C NMR (150 MHz, DMSO-d_6): δ = 21.7, 55.7, 56.0, 114.1, 114.5, 123.8, 126.7, 128.8, 129.4, 130.4, 131.2, 131.7, 135.1, 143.4, 145.0, 156.2, 159.8, 185.0; HRMS (TOF ES$^+$): m/z calcd for $C_{24}H_{23}N_4O_3$ [M+H]$^+$, 415.1765; found, 415.1763.

(1-Phenyl-5-(phenylamino)-1H-1,2,3-triazol-4-yl)(p-tolyl)-methanone ***3b***. White solid; Mp 138–139°C; IR (KBr): 3417, 1618, 1561, 1421, 1239, 929, 755 cm^{-1}; ^{1}H NMR (600 MHz, DMSO-d_6): δ = 2.43 (s, 3H, CH_3), 6.78–6.84 (m, 3H, ArH), 7.00 (t, J = 15.8 Hz, 2H, ArH), 7.36–7.42 (m, 5H, ArH), 7.47–7.49 (m, 2H, ArH), 8.25 (d, J = 8.2 Hz, 2H, ArH), 9.24 (br, 1H, NH); ^{13}C NMR (150 MHz, DMSO-d_6): δ = 21.7, 119.7, 122.9, 124.6, 129.0, 129.5, 129.6, 130.5, 133.3, 135.0, 140.0, 143.2, 143.7, 185.2; HRMS (TOF ES$^+$): m/z calcd for $C_{22}H_{19}N_4O$ [M+H]$^+$, 355.1553; found, 355.1548.

(1-(4-Chlorophenyl)-5-((4-chlorophenyl)amino)-1H-1,2,3-triazol-4-yl)-(p-tolyl)methanone ***3c***. White solid; Mp 173–175°C; IR (KBr): 3424, 1603, 1571, 1426, 1239, 926, 771 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 2.42 (s, 3H, CH_3), 6.85 (d, J = 9.0 Hz, 2H, ArH), 7.08 (d, J = 9.0 Hz 2H, ArH), 7.39 (d, J = 8.0 Hz 2H, ArH), 7.54 (s, 4H, ArH), 8.20 (d, J = 8.0 Hz, 2H, ArH), 9.32 (br, 1H, NH); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 21.7, 121.0, 126.4, 126.7, 128.8, 129.0, 129.4, 129.8, 130.5, 133.7, 134.4, 134.5, 134.9, 139.5, 142.7, 143.7, 185.0; HRMS (TOF ES$^+$): m/z calcd for $C_{22}H_{17}Cl_2N_4O$ [M+H]$^+$, 423.0774; found, 423.0771.

Phenyl(1-phenyl-5-(phenylamino)-1H-1,2,3-triazol-4-yl)-methanone ***3d***. Yellow solid; Mp135–136°C; IR (KBr): 3424, 1625, 1514, 1423, 1237, 935, 712 cm^{-1}; ^{1}H NMR (600 MHz, DMSO-d_6): δ = 6.79-6.85 (m, 3H, ArH), 7.00–7.02 (m, 2H, ArH), 7.36–7.41 (m, 3H, ArH), 7.47–7.49 (m, 2H, ArH), 7.59–7.61 (m, 2H, ArH), 7.67–7.70 (m, 1H, ArH), 8.31 (d, J = 7.1 Hz, 2H, ArH), 9.28 (br, 1H, NH); ^{13}C NMR (150 MHz, DMSO-d_6): δ = 119.9, 123.0, 124.7, 128.8, 128.9,

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129.6, 130.3, 130.3, 133.2, 133.2, 135.8, 137.6, 139.9, 143.4, 185.6; HRMS (TOF ES$^+$): *m/z* calcd for $C_{21}H_{17}N_4O$ $[M+H]^+$, 341.1397; found, 341.1395.

4.2.5 (1-(4-Fluorophenyl)-5-((4-fluorophenyl)amino)-1H-1,2,3-triazol-4-yl)-(phenyl)methanone ***3e***. Yellow solid; Mp 142–143°C; IR (KBr): 3443, 1625, 1519, 1427, 1221, 926, 739 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 6.87 (t, *J* = 17.5 Hz, 2H, ArH), 6.92–6.95 (m, 2H, ArH), 7.24 (d, *J* = 17.5 Hz, 2H, ArH), 7.47–7.50 (m, 2H, ArH), 7.60 (t, *J* = 15.5 Hz, 2H, ArH), 7.68 (t, *J* = 15.0 Hz, 1H, ArH), 8.32 (d, *J* = 7.0 Hz, 2H, ArH), 9.34 (br, 1H, NH); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 115.3 (d, *J* = 38.8 Hz), 116.4 (d, *J* = 23.8 Hz), 123.4 (d, *J* = 32.5 Hz), 127.7 (d, *J* = 10.0 Hz), 128.8, 130.3, 132.0, 132.2 (d, *J* = 2.5 Hz), 133.1, 135.7, 137.7, 144.3, 158.8 (d, *J* = 238.8 Hz), 162.4 (d, *J* = 246.3 Hz), 185.5; HRMS (TOF ES$^+$): *m/z* calcd for $C_{21}H_{15}F_2N_4O$ $[M+H]^+$, 377.1208; found, 377.1208.

(1-(4-Fluorobenzyl)-5-((4-fluorobenzyl)amino)-1H-1,2,3-triazol-4-yl)(p-tolyl)methanone ***3f***. White solid; Mp 115–116°C; IR (KBr): 3440, 1606, 1574, 1436, 1233, 948, 764 cm^{-1}; ^{1}H NMR (600 MHz, DMSO-d_6): δ = 2.39 (s, 3H, CH_3), 4.58 (d, *J* = 6.8 Hz, 2H, $NHCH_2$), 5.57 (s, 2H, NCH_2), 7.04–7.07 (m, 2H, ArH), 7.12–7.15 (m, 2H, ArH), 7.20–7.22 (m, 4H, ArH), 7.32 (d, *J* = 8.0 Hz, 2H, ArH), 7.74 (t, *J* = 8.0 Hz, 1H, NH), 8.01 (d, *J* = 13.3 Hz, 2H, ArH); ^{13}C NMR (150 MHz, DMSO-d_6): δ = 21.6, 46.7, 49.7, 115.6 (d, *J* = 21.0 Hz), 116.1 (d, *J* = 22.5 Hz), 129.2, 129.4 (d, *J* = 4.5 Hz), 129.5 (d, *J* = 3.0 Hz), 130.2, 130.4, 132.4, 135.3 (d, *J* = 3.0 Hz), 135.6, 143.0, 147.4, 161.2 (d, *J* = 63.0 Hz), 162.8 (d, *J* = 64.5 Hz), 185.5; HRMS (TOF ES$^+$): *m/z* calcd for $C_{24}H_{21}F_2N_4O$ $[M+H]^+$, 419.1678; found, 419.1679.

(1-Benzyl-5-(benzylamino)-1H-1,2,3-triazol-4-yl)(phenyl)-methanone ***3g***. Yellow solid; Mp 88–89°C; IR (KBr): 3439, 1627, 1517, 1420, 1172, 943, 738 cm^{-1}; ^{1}H NMR (600 MHz, DMSO-d_6): δ = 4.64 (d, *J* = 6.6 Hz, 2H, $NHCH_2$), 5.62 (s, 2H, NCH_2), 7.15 (d, *J* = 7.0 Hz, 2H, ArH), 7.19 (d, *J* = 7.3 Hz, 2H, ArH), 7.24–7.29 (m, 3H, ArH), 7.37–7.43 (m, 3H, ArH), 7.55 (t, *J* = 15.3 Hz, 2H, ArH), 7.62–7.65 (m, 1H, ArH), 7.85 (t, *J* = 13.3 Hz, 1H, NH), 8.13 (t, *J* = 8.4 Hz, 2H, ArH); ^{13}C NMR (150 MHz, DMSO-d_6): δ= 47.3, 50.5, 127.1, 127.4, 127.7, 128.4, 128.6, 129.0, 129.3, 130.0, 130.2, 132.6, 136.3, 138.3, 139.1, 147.8, 185.8; HRMS (TOF ES$^+$): *m/z* calcd for $C_{23}H_{21}N_4O$ $[M+H]^+$, 367.1710; found, 367.1712.

(1-(4-Fluorobenzyl)-5-((4-fluorobenzyl)amino)-1H-1,2,3-triazol-4-yl)(p henyl)methanone ***3h***. Yellow solid; Mp 77–78°C; IR (KBr): 3439, 1622, 1512, 1433, 1176, 951, 765 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 4.61 (d, *J* = 6.5 Hz, 2H, $NHCH_2$), 5.60 (s, 2H, NCH_2), 7.03–7.07 (m, 2H, ArH), 7.13–7.16 (m, 2H, ArH), 7.20 (d, *J* = 7.0 Hz, 4H, ArH), 7.52 (t, *J* = 15.5 Hz, 2H, ArH), 7.60 (t, *J* = 14.5 Hz, 1H, ArH), 7.74 (t, *J* = 14.5 Hz, 1H, NH), 8.06 (d, *J* = 7.5 Hz, 2H, ArH); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 46.7, 49.7, 115.6 (d, *J* = 21.3 Hz), 116.1 (d, *J* = 22.5 Hz), 128.5, 129.4 (d, *J* = 2.5 Hz), 129.5 (d, *J* = 2.5 Hz), 130.1, 132.3 (d, *J* = 2.5 Hz), 132.6, 135.3 (d, *J* = 3.8 Hz), 137.6, 138.3, 147.4, 161.0 (d, *J* = 52.5 Hz), 163.0 (d, *J* = 53.8 Hz), 185.9; HRMS (TOF ES$^+$): *m/z* calcd for $C_{23}H_{19}F_2N_4O$ $[M+H]^+$, 405.1521; found, 405.1521.

(1-(4-Chlorobenzyl)-5-((4-chlorobenzyl)amino)-1H-1,2,3-triazol-4-yl)(4-chlorophenyl)methanone ***3i***. Yellow solid; Mp 120–121°C; IR (KBr): 3450, 1622, 1514, 1412, 1212, 950, 766 cm^{-1}; ^{1}H NMR (600 MHz, DMSO-d_6): δ = 4.62 (d, *J* = 6.7 Hz, 2H, $NHCH_2$), 5.58 (s, 2H, NCH_2), 7.09 (d, *J* = 8.4 Hz, 2H, ArH), 7.13 (d, *J* = 8.5 Hz, 2H, ArH), 7.26 (d, *J* = 8.4 Hz, 2H, ArH), 7.42 (d, *J* = 8.5 Hz, 2H, ArH), 7.59 (t, *J* = 11.3 Hz, 2H, ArH), 7.84 (t, *J* = 13.3 Hz, 1H, NH), 8.10 (t, *J* = 8.6 Hz, 2H, ArH); ^{13}C NMR (150 MHz, DMSO-d_6): δ = 46.7, 49.7, 128.7, 128.8, 129.1, 129.2, 129.2, 129.9, 132.1, 132.2, 133.1, 135.1, 137.0, 137.6, 138.2, 147.5, 184.3; HRMS (TOF ES$^+$): *m/z* calcd for $C_{23}H_{18}Cl_3N_4O$ $[M+H]^+$, 471.0541; found, 471.0534.

(4-Fluorophenyl)(1-(4-methylbenzyl)-5-((4-methylbenzyl)-amino)-1H-1,2,3-triazol-4-yl)methanone ***3j***. White solid; Mp 108–110°C; IR (KBr): 3450, 1624, 1598, 1518, 1154, 932, 775 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$): δ= 2.33 (s, 3H, CH_3), 2.35 (s, 3H, CH_3), 4.40 (d, *J* = 6.8 Hz, 2H, $NHCH_2$), 5.42 (s, 2H, NCH_2), 6.98 (d, *J* = 7.9 Hz, 2H, ArH), 7.04 (d, *J* = 7.9 Hz, 2H, ArH), 7.13–7.25 (m, 6H, ArH), 8.00 (t, *J* = 13.1 Hz, 1H, NH), 8.56–8.58 (m, 2H, ArH); ^{13}C NMR (150 MHz, $CDCl_3$): δ= 21.1, 21.1, 47.5, 51.6, 115.2(d, *J* = 21.0 Hz), 126.0, 126.3, 129.7 (d, *J* = 12.0 Hz), 130.0, 132.8, 132.9 (d, *J* = 9.0 Hz), 133.7, 135.0, 137.7, 138.1, 148.8, 164.6, 166.3, 184.7; HRMS (TOF ES$^+$): *m/z* calcd for $C_{25}H_{24}FN_4O$ $[M+H]^+$, 415.1929; found, 415.1929.

(2-Chlorophenyl)(1-(4-methylbenzyl)-5-((4-methylbenzyl)-amino)-1H-1,2,3-triazol-4-yl)methanone ***3k***. Yellow solid; Mp 126–128°C; IR (KBr): 3398, 1632, 1589, 1438, 1210, 933, 756 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 2.26 (s,

3H, CH_3), 2.30 (s, 3H, CH_3), 4.73 (d, *J* = 6.5 Hz, 2H, $NHCH_2$), 5.48 (s, 2H, NCH_2), 7.04–7.09 (m, 6H, ArH), 7.17 (d, *J* = 7.5 Hz, 2H, ArH), 7.38–7.43 (m, 2H, ArH), 7.46–7.52 (m, 2H, ArH), 7.65 (t, *J* = 13.0 Hz, 1H, NH); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 21.1, 21.1, 47.4, 49.8, 127.2, 127.4, 127.6, 129.4, 129.8, 129.9, 130.4, 130.5, 131.4, 133.1, 136.5,136.8, 137.6, 140.2, 146.7, 186.3; HRMS (TOF ES$^+$): *m/z* calcd for $C_{25}H_{24}ClN_4O$ $[M+H]^+$, 431.1633; found, 431.1632.

(2-Chlorophenyl)(1-(4-fluorobenzyl)-5-((4-fluorobenzyl)-amino)-1H-1,2,3-triazol-4-yl)methanone ***3l***. Yellow solid; Mp 102–103°C; IR (KBr): 3443, 1624, 1570, 1423, 1236, 925, 733 cm^{-1}; ^{1}H NMR (600 MHz, DMSO-d_6): δ = 4.79 (d, *J* = 6.8 Hz, 2H, $NHCH_2$), 5.52 (s, 2H, NCH_2), 7.08 (t, *J* = 17.6 Hz, 2H, ArH), 7.16–7.21 (m, 6H, ArH), 7.36–7.37 (m, 1H, ArH), 7.40–7.43 (m, 1H, ArH), 7.47–7.51 (m, 2H, ArH), 7.73 (t, *J* = 13.2 Hz, 1H, NH); ^{13}C NMR (150 MHz, DMSO-d_6): δ = 47.0, 49.1, 115.5 (d, *J* = 21.0 Hz), 116.0 (d, *J* = 21.0 Hz), 127.2, 129.6 (d, *J* = 9.0 Hz), 129.7 (d, *J* = 9.0 Hz), 129.7, 129.9, 130.4, 130.4, 132.1 (d, *J* = 1.5 Hz), 135.7 (d, *J* = 3.0 Hz), 140.3, 146.4, 161.2 (d, *J* = 63.0 Hz), 162.8 (d, *J* = 66.0 Hz), 186.3; HRMS (TOF ES$^+$): *m/z* calcd for $C_{23}H_{18}ClF_2N_4O$ $[M+H]^+$, 429.1132; found, 439.1128.

(1-(4-Methoxyphenethyl)-5-((4-methoxyphenethyl)amino)-1H-1,2,3-tri-azol-4-yl)(phenyl)methanone ***3m***. Yellow solid; Mp 76–78°C; IR (KBr): 3448, 1611, 1512, 1419, 1178, 961, 739 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 2.72 (t, *J* = 14.0 Hz, 2H, CH_2), 3.02 (t, *J* = 14.0 Hz, 2H, CH_2), 3.62 (m, 2H, $NHCH_2$), 3.69 (s, 3H, OCH_3), 3.71 (s, 3H, OCH_3), 4.47 (t, *J* = 15.0 Hz, 2H, NCH_2), 6.81–6.86 (m, 4H, ArH), 7.10–7.14 (m, 5H, ArH), 7.53 (t, *J* = 15.0 Hz, 2H, ArH), 7.60 (t, *J* = 7.5 Hz, 1H, NH), 8.1 (t, *J* = 8.5 Hz, 2H, ArH); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 34.2, 35.3, 45.8, 48.8, 55.4, 55.4, 114.3, 114.3, 128.5, 129.5, 129.8, 130.2, 130.2, 130.3, 130.8, 132.5, 138.4, 147.7, 158.3, 158.5, 185.6; HRMS (TOF ES$^+$): *m/z* calcd for $C_{27}H_{29}N_4O_3$ $[M+H]^+$, 457.2234; found, 457.2241.

(1-Phenethyl-5-(phenethylamino)-1H-1,2,3-triazol-4-yl)-(phenyl)metha none ***3n***. Yellow solid; Mp 85–87°C; IR (KBr): 3399, 1624, 1517, 1427, 1177, 921, 741 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 2.80 (t, *J* = 14.5 Hz, 2H, CH_2), 3.10 (t, *J* = 14.5 Hz, 2H, CH_2), 3.65–3.70 (m, 2H, $NHCH_2$), 4.52 (t, *J* = 15.0 Hz, 2H, NCH_2), 7.20–7.30 (m, 11H, ArH), 7.53 (t, *J* = 15.0 Hz, 2H, ArH), 7.61 (t, *J* = 14.5 Hz, 1H, NH), 8.12 (d, *J* = 7.0 Hz, 2H, ArH); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 35.1, 36.2, 45.6, 48.56, 126.8, 127.1, 128.5, 128.8, 128.9, 129.2, 129.3, 129.5, 130.3, 132.5, 138.0, 138.5, 139.0, 147.6, 185.7; HRMS (TOF ES$^+$): *m/z* calcd for $C_{25}H_{25}N_4O$ $[M+H]^+$, 397.2023; found, 397.2021.

(1-(4-Chlorophenethyl)-5-((4-chlorophenethyl)amino)-1H -1,2,3-triazol-4-yl)(phenyl) methanone ***3o***. Yellow solid; Mp 99–100°C; IR (KBr): 3442, 1618, 1584, 1424, 1175, 958, 742 cm^{-1}; ^{1}H NMR (600 MHz, DMSO-d_6): δ = 2.78 (t, *J* = 12.7 Hz, 2H, CH_2), 3.08 (t, *J* = 12.8 Hz, 2H, CH_2), 3.67 (d, *J* = 6.2 Hz, 2H, $NHCH_2$), 4.50 (t, *J* = 13.2 Hz, 2H, NCH_2), 7.11 (s, 1H, ArH), 7.21 (s, 4H, ArH), 7.30-7.35 (m, 4H, ArH), 7.52 (t, *J* = 14.2 Hz, 2H, ArH), 7.60 (t, *J* = 14.2 Hz, 1H, NH), 8.08 (d, *J* = 7.3 Hz, 2H, ArH); ^{13}C NMR (150 MHz, DMSO-d_6): δ = 34.2, 35.4, 45.4, 48.2, 128.5, 128.7, 128.8, 129.6, 130.3, 131.1, 131.2, 131.5, 131.8, 132.5, 137.0, 138.1, 138.5, 147.6, 185.7; HRMS (TOF ES$^+$): *m/z* calcd for $C_{25}H_{23}Cl_2N_4O$ $[M+H]^+$, 465.1243; found, 465.1245.

(1-Benzyl-5-(phenylamino)-1H-1,2,3-triazol-4-yl)(p-tolyl)-methanone ***4a***. Yellow solid; Mp 91–92°C; IR (KBr): 3415, 1614, 1571, 1426, 1261, 921, 739 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 2.40 (s, 3H, CH_3), 5.45 (s, 2H, NCH_2), 6.80 (d, *J* = 8.0 Hz, 2H, ArH), 6.93 (t, *J* = 13.5 Hz, 1H, ArH), 7.06 (d, *J* = 6.0 Hz, 2H, ArH), 7.20 (t, *J* = 14.5 Hz, 2H, ArH), 7.30 (d, *J* = 6.5 Hz, 3H, ArH), 7.35 (d, *J* = 8.0 Hz, 2H, ArH), 8.10 (d, *J* = 7.5 Hz, 2H, ArH), 8.86 (br, 1H, NH); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 21.7, 51.01, 118.3, 122.3, 127.8, 128.4, 129.1, 129.3, 129.4, 130.5, 134.6, 135.1, 135.5, 141.7, 142.3, 143.5, 185.0; HRMS (TOF ES$^+$): *m/z* calcd for $C_{23}H_{21}N_4O$ $[M+H]^+$, 369.1710; found, 369.1715.

(5-(Benzylamino)-1-phenyl-1H-1,2,3-triazol-4-yl)(p-tolyl) -methanone ***4a'***. Yellow solid; Mp 121–122°C; IR (KBr): 3442, 1618, 1574, 1440, 1223, 924, 724 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 2.41 (s, 3H, CH_3), 4.19 (d, *J* = 6.5 Hz, 2H, $NHCH_2$), 6.89 (d, *J* = 6.0 Hz, 2H, ArH), 7.20 (d, *J* = 6.5 Hz, 3H, ArH), 7.38 (d, *J* = 6.0 Hz, 2H, ArH), 7.46 (d, *J* = 7.5 Hz, 2H, ArH), 7.53–7.61 (m, 3H, ArH), 8.20 (t, *J* = 13.0 Hz, 1H, NH), 8.26 (d, *J* = 8.0 Hz, 2H, ArH); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 21.7, 47.3, 127.0, 127.1, 127.7, 128.9, 129.2, 129.3, 129.8, 130.3, 130.5, 135.2, 136.0, 138.6, 143.2, 148.5, 185.2; HRMS (TOF ES$^+$): *m/z* calcd for $C_{23}H_{21}N_4O$ $[M+H]^+$, 369.1710; found, 369.1708.

(1-Benzyl-5-((4-fluorophenyl)amino)-1H-1,2,3-triazol-4-yl)(p-tolyl) methanone ***4b***. Yellow solid; Mp 114–116°C; IR (KBr): 3442, 1618, 1510, 1436, 1217, 920, 726 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 2.40 (s, 3H, CH_3), 5.45 (s, 2H, NCH_2), 6.83 (s, 2H, ArH), 7.02–7.05 (m, 4H, ArH), 7.30 (d, *J* = 7.5 Hz, 3H, ArH), 7.35 (d, *J* = 8.0 Hz, 2H, ArH), 8.10

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(d, J = 8.0 Hz, 2H, ArH), 8.91 (br, 1H, NH); ^{13}C NMR (125 MHz, DMSO-d_6): δ= 21.7, 50.9, 115.9 (d, J = 22.5 Hz), 120.6 (d, J = 8.8 Hz), 127.7, 128.4, 129.1, 129.3, 130.5, 134.0, 135.1, 135.5, 137.8, 142.8, 143.5, 158.1 (d, J = 236.25 Hz), 184.9; HRMS (TOF ES$^+$): m/z calcd for $C_{23}H_{20}FN_4O$ [M+H]$^+$, 387.1616; found, 387.1614.

(1-(4-Chlorophenethyl)-5-(phenylamino)-1H-1,2,3-triazol-4-yl)(p-tolyl)-methanone ***4c***. White solid; Mp 158–159°C; IR (KBr): 3339, 1634, 1512, 1420, 1234, 947, 788 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 2.40 (s, J = 14.5 Hz, 3H, CH_3), 3.07 (t, J = 14.5 Hz, 2H, CH_2), 4.40 (t, J = 14.5 Hz, 2H, NCH_2), 6.77 (d, J = 14.5 Hz, 2H, ArH), 6.92 (t, J = 14.5 Hz, 1H, ArH), 7.07 (d, J = 14.5 Hz, 2H, ArH), 7.25–7.28 (m, 4H, ArH), 7.34 (d, J = 14.5 Hz, 2H, ArH), 8.06 (d, J = 14.5 Hz, 2H, ArH), 8.80 (br, 1H, NH); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 21.7, 33.9, 48.7, 118.0, 122.1, 128.8, 129.3, 129.5, 130.5, 131.0, 131.8, 134.5, 135.0, 136.8, 141.8, 142.1, 143.6, 185.0; HRMS (TOF ES$^+$): m/z calcd for $C_{24}H_{22}ClN_4O$ [M+H]$^+$, 417.1477; found, 417.1472.

(5-((4-Chlorophenyl)amino)-1-(4-methoxyphenethyl)-1H-1,2,3-triazol-4-yl)(phenyl) methanone ***4d***. White solid; Mp 144–145°C; IR (KBr): 3439, 1614, 1572, 1425, 1234, 936, 779 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 3.05 (t, J = 14.5 Hz, 2H, CH_2), 3.67 (s, 3H, OCH_3), 4.43 (t, J = 14.5 Hz, 2H, NCH_2), 6.70 (d, J = 14.5 Hz, 2H, ArH), 6.76 (d, J = 14.5 Hz, 2H, ArH), 7.00 (d, J = 14.5 Hz, 2H, ArH), 7.54 (t, J = 14.5 Hz, 2H, ArH), 7.63 (d, J = 14.5 Hz, 1H, ArH), 8.09 (d, J = 14.5 Hz, 2H, ArH), 8.91 (s, 1H, NH); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 34.1, 49.0, 55.4, 114.3, 118.9, 125.1, 128.7, 129.1, 129.5, 130.1, 130.3, 133.1, 134.7, 137.7, 141.1, 141.5, 158.5, 185.2; HRMS (TOF ES$^+$): m/z calcd for $C_{24}H_{22}ClN_4O$ [M+H]$^+$, 433.1426; found, 433.1421.

(1-(4-Chlorophenyl)-5-((4-methoxyphenethyl)amino)-1H-1,2,3-triazol-4-yl)(phenyl) methanone ***4d'***. Yellow solid; Mp 131–133°C; IR (KBr): 3426, 1623, 1513, 1439, 1212, 990, 773 cm^{-1}; ^{1}H NMR (600 MHz, DMSO-d_6): δ = 2.51 (t, J = 14.6 Hz, 2H, CH_2), 3.11–3.14 (m, 2H, $NHCH_2$), 3.68 (s, 3H, OCH_3), 6.76 (d, J = 8.6 Hz, 2H, ArH), 6.86 (d, J = 8.5 Hz, 2H, ArH), 7.57–7.59 (m, 2H, ArH), 7.64–7.67 (m, 1H, ArH), 7.71–7.77 (m, 5H, ArH), 8.27 (d, J = 8.2 Hz, 2H, ArH); ^{13}C NMR (150 MHz, DMSO-d_6): δ = 35.3, 45.7, 55.4, 114.2, 128.7, 129.0, 130.0, 130.1, 130.1, 130.3, 132.8, 135.2, 135.3, 137.9, 148.8, 158.3, 185.4; HRMS (TOF ES$^+$): m/z calcd for $C_{24}H_{22}ClN_4O$ [M+H]$^+$, 433.1426; found, 433.1420.

(1-(4-Chlorobenzyl)-5-(phenylamino)-1H-1,2,3-triazol-4-yl)(4-chloroph -enyl)methanone ***4e***. White solid; Mp 150–151°C; IR (KBr): 3448, 1619, 1573, 1421, 1230, 934, 764 cm^{-1}; ^{1}H NMR (600 MHz, DMSO-d_6): δ = 5.48 (s, 2H, NCH_2), 6.81 (d, J = 7.7 Hz, 2H, ArH), 6.93 (t, J = 13.1 Hz, 1H, ArH), 7.06 (d, J = 7.8 Hz, 2H, ArH), 7.20 (t, J = 14.1 Hz, 2H, ArH), 7.38 (d, J = 7.5 Hz, 2H, ArH), 7.62 (d, J = 7.7 Hz, 2H, ArH), 8.19 (d, J = 7.7 Hz , 2H, ArH), 8.98 (br, 1H, NH); ^{13}C NMR (150 MHz, DMSO-d_6): δ = 50.3, 118.7, 122.6, 128.9, 129.1, 129.4, 129.7, 132.2, 133.1, 134.0, 134.4, 136.3, 138.1, 141.3, 142.7, 183.9; HRMS (TOF ES$^+$): m/z calcd for $C_{22}H_{17}Cl_2N_4O$ [M+H]$^+$, 423.0774; found, 423.0772.

(4-Chlorophenyl)(5-((4-chlorophenyl)amino)-1-phenethyl-1H-1,2,3-tri-azol-4-yl) methanone ***4f***. Yellow solid; Mp 119–120°C; IR (KBr): 3439, 1620, 1574, 1424, 1235, 944, 767 cm^{-1}; ^{1}H NMR (600 MHz, DMSO-d_6): δ = 3.12 (t, J = 14.3 Hz, 2H, CH_2), 4.47 (t, J = 14.3 Hz, 2H, NCH_2), 6.74 (d, J = 8.7 Hz, 2H, ArH), 7.11 (d, J = 7.6 Hz, 2H, ArH), 7.19 (t, J = 7.6 Hz, 1H, ArH), 7.22–7.24 (m, 4H, ArH), 7.62–7.63 (m, 2H, ArH), 8.14–8.16 (m, 2H, ArH), 8.97 (br, 1H, NH); ^{13}C NMR (150 MHz, DMSO-d_6): δ = 34.8, 48.7, 119.2, 125.4, 127.1, 128.9, 129.1, 129.1, 129.3, 132.2, 134.3, 136.3, 137.7, 138.1, 140.9, 141.8, 183.7; HRMS (TOF ES$^+$): m/z calcd for $C_{23}H_{19}Cl_2N_4O$ [M+H]$^+$, 437.0930; found, 437.0931.

(4-Chlorophenyl)(5-((4-chlorophenyl)amino)-1-(3-fluoro-phenethyl)-1H-1,2,3-triazol-4-yl)methanone ***4g***. White solid; Mp 124–126°C; IR (KBr): 3439, 1624, 1591, 1429, 1220, 938, 770 cm^{-1}; ^{1}H NMR (600 MHz, DMSO-d_6): δ = 3.14 (t, J = 14.5 Hz, 2H, CH_2), 4.50 (t, J = 14.5 Hz, 2H, $NHCH_2$), 6.73 (d, J = 8.8 Hz, 2H, ArH), 6.99 (d, J = 7.0 Hz, 1H, ArH), 7.00–7.01 (m, 2H, ArH), 7.22–7.29 (m, 3H, ArH), 7.62 (d, J = 8.5 Hz, 2H, ArH), 8.15 (d, J = 8.5 Hz 2H, ArH), 8.98 (br, 1H, NH); ^{13}C NMR (150 MHz, DMSO-d_6): δ = 34.4, 48.4, 113.9 (d, J = 21.0 Hz), 115.8 (d, J = 21.0 Hz), 119.2, 125.3, 125.4, 128.9, 129.1, 130.7 (d, J = 7.5 Hz), 132.2, 134.3, 136.3, 138.1, 140.7, 140.9, 141.8, 162.6 (d, J = 243.0 Hz), 183.7; HRMS (TOF ES$^+$): m/z calcd for $C_{23}H_{17}Cl_2FN_4O$ [M+H]$^+$, 455.0836; found, 455.0844.

(4-Chlorophenyl)(1-(4-chlorophenyl)-5-((3-fluoropheneth-yl)amino)-1H-1,2,3-triazol-4-yl)methanone ***4g'***. Yellow solid; Mp 133–134°C; IR (KBr): 3439, 1624, 1571, 1424, 1236, 925, 766 cm^{-1}; ^{1}H NMR (600 MHz, DMSO-d_6): δ = 2.67 (t, J = 14.5 Hz, 2H, CH_2), 3.18–3.22 (m, 2H, $NHCH_2$), 6.75 (d, J = 10.0 Hz, 1H, ArH), 6.80 (d, J = 7.0 Hz, 1H, ArH), 7.00–7.01 (m, 1H, ArH), 7.25 (t, J = 14.3 Hz, 1H, ArH), 7.66 (d, J = 8.5 Hz, 2H, ArH), 7.71–7.75 (m, 4H, ArH), 7.78 (t, J = 13.0 Hz, 1H, NH), 8.32 (d, J = 8.5 Hz, 2H, ArH); ^{13}C NMR (150 MHz, DMSO-d_6): δ = 35.8, 45.1, 113.6 (d,

J = 19.5 Hz), 115.7 (d, J = 21.0 Hz), 125.1, 128.7, 128.9, 129.0, 130.2, 130.6 (d, J = 7.5 Hz), 132.0, 135.1, 135.4, 136.4, 137.8, 141.5 (d, J = 7.5 Hz), 148.8, 162.6 (d, J = 243.0 Hz), 183.8; HRMS (TOF ES$^+$): m/z calcd for $C_{23}H_{17}Cl_2FN_4O$ $[M+H]^+$, 455.0836; found, 455.0831.

4. Conclusions

In summary, conclusion, an environmentally friendly method for concise synthesis of 1,2,3-triazole compounds **3–4** in 1,4-dioxane at reflux with good yields by regioselective reaction has been constructed. Using this procedure, we can easily obtain a series of potentially biologically active 1,2,3-triazole derivatives **3–4** in the absence of any metal catalyst. The advantages of this method are the use of a metal-free catalyst, convenience of operation, short reaction times, excellent yield, inexpensive raw materials, and convenient final treatment. In addition, the generality with respect to the substrate scope, and facile accessibility to the starting materials is also highly appealing. This process has great potential to be applied to parallel synthesis in drug discovery.

Supplementary Materials: The following are available online at www.mdpi.com/link, Figure 1~36.

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Conflicts of Interest:

The authors declare no conflict of interest.

References

1. Zheng, Y.C.; Duan, Y.C.; Ma, J.L.; Xu R.M.; Zi, X.L.; Lv, W.L.; Wang, M.M.; Ye, X.W.; Zhu, S.; Mobley, D.; Zhu, Y.Y.; Wang, J.W.; Li, J.F.; Wang, Z.R.; Zhao, W.; Liu, H.M. Triazole–Dithiocarbamate Based Selective Lysine Specific Demethylase 1 (LSD1) Inactivators Inhibit Gastric Cancer Cell Growth, Invasion, and Migration. *J. Med. Chem.* **2013**, *56*, 8543.
2. Singh, A.; Saha, S.T.; Perumal, S.; Kaur, M.; Kumar, V. Azide–Alkyne Cycloaddition En Route to 1H-1,2,3-Triazole-Tethered Isatin–Ferrocene, Ferrocenylmethoxy–Isatin, and Isatin–Ferrocenylchalcone Conjugates: Synthesis and Antiproliferative Evaluation. *ACS Omega* **2018**, *3*, 1263.
3. Yan, S.J.; Liu, Y.J.; Chen, Y.L.; Liu, L.; Lin, J. An efficient one-pot synthesis of heterocycle-fused 1,2,3-triazole derivatives as anti-cancer agents. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 5225.
4. Verenkar, S.K.V.; Qiu, L.; Zhang, J.; Kankanala, J.; Li, H.G.; Geraghty, R.J.; Wang, Z.Q. 5′-Silylated 3′-1,2,3-triazolyl Thymidine Analogues as Inhibitors of West Nile Virus and Dengue Virus. *J. Med. Chem.* **2015**, *58*, 4016.
5. Boechat, N.; Ferreira, V.F.; Ferreira, S.B.; Ferreiar, M.L.G.; da Silva, F.C.; Bastos, M.M.; Costa, M.S.; Lourenco, M.C.S.; Pinto, A.C.; Krettli, A.U.; Aguiar, A.C.; Teixeira, B.M.; da Silva, N.V.; Martins, P.R.C.; Bezerra, F.A.F.M.; Camilo, A.L.S.; da Silva, G.P.; Costa, C.C.P. Novel 1,2,3-Triazole Derivatives for Use against Mycobacterium tuberculosis H37Rv (ATCC 27294) Strain. *J. Med. Chem.* **2011**, *54*, 5988.
6. Genin, M.J.; Allwine, D.A.; Anderson, D.J.; Barbachyn, M.R.; Emmert, D.E.; Garmon, S.A.; Graber, D.R.; Grega, K.C.; Hester, J.B.; Hutchinson, D.K.; Morris, J.; Reischer, R.J.; Ford, C.W.; Zurenko, G.E.; Hamel, J.C.; Schaadt, R.D.; Stapert, D.; Yagi, B.H. Substituent Effects on the Antibacterial Activity of Nitrogen-Carbon-Linked (Azolylphenyl)oxazolidinones with Expanded Activity Against the Fastidious Gram-Negative Organisms Haemophilus influenzae and Moraxella catarrhalis. *J. Med. Chem.* **2000**, *43*, 953.

7. Nilkanth, G.A.; Vandana, S.P.; Nripendra, N.M.; Awanit Kumar, K.S.; Praveen, Aanchal Sharma, Manoj, K.B. Synthesis and antifungal activity of 1,2,3-triazole containing fluconazole analogues. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 759.
8. Kelley, J.L.; Koble, C.S.; Davis, R.G.; McLean, E.W.; Soroko, F.E.; Cooper, B.R. l-(Fluorobenzyl)-4-amino -LHr-l,2,3-triazolo[4,5-*c*]pyridines: Synthesis and Anticonvulsant Activity. *J. Med. Chem.* **1995**, *38*, 4131.
9. Wijtmans, M.; de Graaf, C.; de Kloe, G.; Istyastono, E.P.; Smit, J.; Lim, H. Boonnak, R.; Nijmeijer, S.; Smits, R.A.; Jongejan, A.; Zuiderveld, O.; de Esch, I.J.P.; Leurs, R. Triazole Ligands Reveal Distinct Molecular Features That Induce Histamine H4 Receptor Affinity and Subtly Govern H4/H3 Subtype Selectivity. *J. Med. Chem.* **2011**, *54*, 1693.
10. Agalave, S.G.; Maujan, S.R.; Pore, V.S. Click Chemistry : 1,2,3-Trizaoles as Pharmacophores. *Chem. Asian J.* **2011**, *6*, 2696.
11. Micetich, R.G.; Maiti, S.N.; Spevak, P.; Hall, T.W.; Yamabe, S.; Ishida, N.; Tanaka, M.; Yamazaki, T.; Nakai, A.; Ogawa, K. Synthesis and 0-Lactamase Inhibitory Properties of 20-[(l,2,3-Triazol-l-yl)methyl]-2a: -methylpenam-3a-carboxylic Acid 1,1-Dioxide and Related Triazolyl Derivatives. *J. Med. Chem.* **1987**, *30*, 1469.
12. Thomas, K.D.; Adhikari, A.V.; Shetty, N.S. Design, synthesis and antimicrobial activities of some new quinoline derivatives carrying 1,2,3-triazole moiety. *Eur. J. Med. Chem.* **2010**, *45*, 3803.
13. Taddei, M.; Ferrini, S.; Giannotti, L.; Corsi, M.; Manetti, F.; Giannini, G.; Vesci, L.; Milazzo, F.M.; Alloatti, D.; Guglielmi, M.B.; Castorina, M.; Cervoni, M.L.; Barbarino, M.; Fodera,R.; Carollo, V.; Pisano, C.; Armaroli, S.; Cabri, W. Synthesis and Evaluation of New Hsp90 Inhibitors Based on a 1,4,5-Trisubstituted 1,2,3-Triazole Scaffold. *J. Med. Chem.* **2014**, *57*, 2258.
14. Nocentini, A.; Ferraroni, M.; Carta, F.; Ceryso, M.; Gratteri, P.; Lanzi, C.; Masini, E.; Supuran, C.T. Benzenesulfonamides Incorporating Flexible Triazole Moieties Are Highly Effective Carbonic Anhydrase Inhibitors: Synthesis and Kinetic, Crystallographic, Computational, and Intraocular Pressure Lowering Investigations. *J. Med. Chem.* **2016**, *59*, 10692.
15. Cheng, H.M.; Wan, J.T.; Lin, M.I.; Liu, Y.X.; Lu, X.Y.; Liu, J.S.; Xu, Y.; Chen, J.X.; Tu, Z.C.; Cheng, Y.S.E.; Ding, K. Design, Synthesis, and in Vitro Biological Evaluation of 1*H*-1,2,3-Triazole-4-carboxamide Derivatives as New Anti-influenza A Agents Targeting Virus Nucleoprotein. *J. Med. Chem.* **2012**, *55*, 2144.
16. Thirumurugan, P.; Matosiuk, D.; Jozwiak, K. Click Chemistry for Drug Development and Diverse Chemical− Biology Applications. *Chem. Rev.* **2013**, *113*, 4905.
17. Lei, X.Q.; Gao, M.H.; Tang, Y.F. Rh(II)-Catalyzed Transannulation of *N*-Sulfonyl-1,2,3-Triazoles with 2,1-Benzisoxazoles or 1,2-Benzisoxazoles. *Org. Lett.* **2016**, *18*, 4990.
18. Cheng, W.L.; Tang, Y.H.; Xu, Z.F.; Li, C.Y. Synthesis of Multifunctionalized 2-Carbonylpyrrole by RhodiumCatalyzed Transannulation of 1-Sulfonyl-1,2,3-triazole with β-Diketone. *Org. Lett.* **2016**, *18*, 6168.
19. Xu, Z.F.; Dai, H.C.; Shan, L.H.; Li, C.Y. Metal-Free Synthesis of (*E*)-Monofluoroenamine from 1-Sulfonyl-1,2,3-triazole and Et2O·BF3 via Stereospecific Fluorination of *α*-Diazoimine. *Org. Lett.* **2018**, *20*, 1054.
20. Jeon, H.J.; Jung, D.J.; Kim, J.H.; Kim, Y.; Bouffard, J.; Lee, S. From Triazoles to Imidazolines through the Sequential N−H Insertion of *α*-Imino Rhodium−Carbenes into *β*-Enamino Esters/Enamine−Imine Tautomerization/Conjugate Addition Cascade. *J. Org. Chem.* **2014**, 79, 9865.
21. Kacprzak, K.; Skiera, I.; Piasecka, M.; Paryzek, Z. Alkaloids and Isoprenoids Modification by Copper(I)-Catalyzed Huisgen 1,3-Dipolar Cycloaddition (Click Chemistry): Toward New Functions and Molecular Architectures. *Chem. Rev.* **2016**, 116, 5689.
22. Huang, D.Y.; Yan, G.B. Recent Advances in Reactions of Azides.*Adv. Synth. Catal*. **2017**, 359, 1600.
23. Zhao, F.; Chen, Z.; Liu, Y.; Jiang, Y. Palladium-Catalyzed Acylation of Arenes by 1,2,3-Triazole-Directed C-H Activation. *Eur. J. Org. Chem.* **2016**, *36*, 5971.
24. Lauria, A.; Delisi, R.; Mingoia, F.; Terenzi, A.; Martorana, A.; Barone, G.; Almerico, A.M. 1,2,3-Triazole in Heterocyclic Compounds, Endowed with Biological Activity, through 1,3-Dipolar Cycloadditions. *Eur. J. Org. Chem.* **2014**, *16*, 3289.
25. Liu, W.; Li, Y.; Wang, Y.; Kuang, C. Site-Selective Direct Arylation of 1,2,3-Triazole *N*-Oxides. *Eur. J. Org. Chem.* **2013**, *24*, 5272.
26. Liu, T.F.; Gu, L.; Wang, L.; Yi, W.B.; Cai, C. Chemoselective Preparation of Unsymmetrical Bis(1,2,3-triazole) Derivatives and Application in Bis(1,2,3-triazole)-Modified Peptidomimetic Synthesis. *Eur. J. Org. Chem.* **2012**, *34*, 6767.

27. Wan, J.P.; Chao, S.; Liu, Y.Y. Base-Promoted Synthesis of N-Substituted 1,2,3-Triazoles via Enaminone−Azide Cycloaddition Involving Regitz Diazo Transfer. *Org. Lett.* **2016**, *18*, 6034.
28. Wang, W.G.; Wei, F.; Ma, Y.D.; Tung, C.H.; Xu, Z.H. Copper(I)-Catalyzed Three-Component Click/Alkynylation: One-Pot Synthesis of 5-Alkynyl-1,2,3-triazoles. *Org. Lett*. **2016**, *18*, 4158.
29. Goitia, A.; Bengoa, E.G.; Correa, A. Selective C(sp2)−H Halogenation of "Click" 4-Aryl-1,2,3-triazoles. *Org. Lett.* **2017**, *19*, 962.
30. Liao, Y.; Lu, Q.; Chen, G.; Yu, Y.; Li, C.; Huang, X. Rhodium-Catalyzed Azide−Alkyne Cycloaddition of Internal Ynamides: Regioselective Assembly of 5-Amino-Triazoles under Mild Conditions. *ACS Catal.* **2017**, *7*, 7529.
31. Kumar, N.; Ansari, M.Y.; Kant, R.; Kumar, A. Copper-catalyzed decarboxylative regioselective synthesis of 1,5-disubstituted 1,2,3-triazoles. *Chem. Commun.* **2018**, *54*, 2627.
32. Lima, C.G.S.; Ali, A.; van Berkel, S.S.; Westermann, B.; Paixao, M.W. Emerging approaches for the synthesis of triazoles: beyond metal-catalyzed and strain-promoted azide–alkyne cycloaddition. *Chem. Commun.* **2015**, *51*, 10784.
33. Ramasastry, S.S.V. Enamine/Enolate-Mediated Organocatalytic Azide–Carbonyl [3+2] Cycloaddition Reactions for the Synthesis of Densely Functionalized 1,2,3-Triazoles. A*ngew. Chem. Int. Ed*. **2014**, *53*, 14310.
34. Debia, N.P.; Saraiva, M.T.; Martins, B.S.; Beal, R.; Goncalves, P.F.B.; Rodembusch, F.S.; Alves, D.; Lüdtke, D.S. Synthesis of Amino Acid-Derived 1,2,3-Triazoles: Development of a Nontrivial Fluorescent Sensor in Solution for the Enantioselective Sensing of a Carbohydrate and Bovine Serum Albumin Interaction. *J. Org. Chem*. **2018**, 83, 1348.
35. Zhou, X.; Xu, X.H.; Liu, K.; Gao, H.; Wang, W.; Li, W.J. Organocatalytic 1,3-Dipolar Cycloaddition Reaction of *β*-Keto Amides with Azides–Direct Access to 1,4,5-Trisubstituted 1,2,3-Triazole-4-carboxamides. *Eur. J. Org. Chem*. **2016**, *10*, 1886.
36. Wan, J.P.; Chao, S.; Liu, Y.Y. Base-Promoted Synthesis of N-Substituted 1,2,3-Triazoles via Enaminone−Azide Cycloaddition Involving Regitz Diazo Transfer. *Org. Lett.* **2016**, *18*, 6034.
37. da Silva, R.C.; da Silva, G.P.; Sangi, D.P.; de M. Pontes, J.G.; Ferreira, A.G.; Corréa, A.G. and Paixão, M.W. 1,1-Diamino-2-nitroethylenes as excellent hydrogen bond donor organocatalysts in the Michael addition of carbon-based nucleophiles to *β*-nitrostyrenes. *Tetrahedron.* **2013**, *69*, 9007.
38. Mertens, H.; Troschutz, R.; Roth, H.J. Synthese primärer Nitroketenaminale. *Arch. Pharm.* (Weinheim, Ger.) **1986**, *319*, 161.
39. Wang, B.Q.; Zhang, C.H.; Tian, X.X.; Lin, J.; Yan, S.J. Cascade Reaction of Isatins with 1,1-Enediamines: Synthesis of Multisubstituted Quinoline-4-carboxamides. *Org. Lett.* **2018**, *20*, 660.
40. Wang, B.Q.; Luo, Q.; Xiao, Q.; Lin, J.; Yan, S.J. Synthesis of Quinone Methide Substituted Neonicotinoid Derivatives via 1,6-Conjugate Addition of N-Benzyl Nitro Ketene Aminals with para-Quinone Methides Accompanying Oxidation. *ACS Sustainable Chem. Eng*. **2017**, *5*, 8382.
41. Hu, X.M.; Luo, D.Y.; Zi, Q.X.; Lin, J.; Yan, S.J. Diastereoselective Synthesis of Morphan Derivatives by Michael and Hetero-Michael Addition of 1,1-Enediamines to Quinone Monoketals. *ACS Omega* **2018**, *3*, 8.
42. Zhang, C.H.; Huang, R.; Hu, X.M.; Lin, J.; Yan, S.J. Three-Component Site-Selective Synthesis of Highly Substituted 5H-Chromeno-[4,3-*b*]pyridines. *J. Org. Chem.* **2018**, *83*, 4981.
43. Tu, X.J.; Hao, W.J.; Ye, Q.; Wang, S.S.; Jiang, B.; Li, G.G.; Tu, S.J. Four-Component Bicyclization Approaches to Skeletally Diverse Pyrazolo[3,4-*b*]pyridine Derivatives. *J. Org. Chem.* **2014**, *79*, 11110.
44. Liu, T.; Zhu, H.Y.; Luo, D.Y.; Yan, S.J.; Lin, J. A Convenient Synthesis of 3,7′-Bisindole Derivatives. *Molecules* **2016**, *21*, 638.
45. Zeng, C.C.; Liu, F.J.; Ping, D.W.; Hu, L.M.; Cai, Y.L.; Zhong, R.G. One-Pot Electrochemical Synthesis of Fused Indole Derivatives Containing Active Hydroxyl Groups in Aqueous Medium. *J. Org. Chem.* **2009**, *74*, 6386.
46. Zhou, B.; Liu, Z.C.; Qu, W.W.; Yang, R.; Lin, X.R.; Yan, S.J.; Lin, J. An environmentally benign, mild, and catalyst-free reaction of quinones with heterocyclic ketene aminals in ethanol: site-selective synthesis of rarely fused [1,2-**a**]indolone derivatives via an unexpected anti-Nenitzescu strategy. *Green Chem.* **2014**, *16*, 4359.
47. Wang, K.M.; Yan, S.J.; Lin, J. Heterocyclic Ketene Aminals: Scaffolds for Heterocycle Molecular Diversity. *Eur. J. Org. Chem.* **2014**, *6*, 1129.

48. Ma, Y.L.; Wang, K.M.; Huang, R.; Lin, J.; Yan, S.J. An environmentally benign double Michael addition reaction of heterocyclic ketene aminals with quinone monoketals for diastereoselective synthesis of highly functionalized morphan derivatives in water. *Green Chem.* **2017**, *19*, 3574.
49. Li, M.; Shao, P.; Wang, S.W.; Kong, W.; Wen, L.R. Four-Component Cascade Heteroannulation of Heterocyclic Ketene Aminals: Synthesis of Functionalized Tetrahydroimidazo[1,2-*a*]pyridine Derivatives. *J. Org. Chem.* **2012**, *77*, 8956.
50. Wang, L.; Shi, L.X.; Liu, L.; Li, Z.X.; Xu, T.; Hao, W.J.; Li, G.G.; Tu, S.J.; Jiang, B. Synthesis of Diastereoenriched Oxazolo[5,4-*b*]indoles via CatalystFree Multicomponent Bicyclizations . *J. Org. Chem.* **2017**, *82*, 3605.
51. Poomathi, N.; Perumala, P. T.; Ramakrishna, S. An efficient and eco-friendly synthesis of 2-pyridones and functionalized azaxanthone frameworks via indium triflate catalyzed domino reaction. *Green Chem.* **2017**, *19*, 2524.
52. Chen, L.; Huang, R.; Du, X.X.; Yan, S.J.; Lin, J. One-Pot Synthesis of Highly Functionalized Bicyclic Imidazopyridinium Derivatives in Ethanol. *ACS Sustainable Chem. Eng.* **2017**, *5*, 1899.
53. Huang, C.; Yan, S.J.; Zeng, X.H.; Dai, X.Y.; Zhang, Y.; Lin, J. Biological evaluation of polyhalo 1,3-diazaheterocycle fused isoquinolin-1(2*H*)-imine derivatives. *Eur. J. Med. Chem.* **2011**, *46*, 1172.
54. Yu, F.C.; Lin, X.R.; Liu, Z.C.; Zhang, J.H.; Liu, F.F.; Wu, W.; Ma, Y.L.; Qu, W.W.; Yan, S.J.; Lin, J. Beyond the Antagonism: Self-Labeled Xanthone Inhibitors as Modeled "Two-in-One" Drugs in Cancer Therapy. *ACS Omega* **2017**, *2*, 873.
55. Du, X.X.; Huang, R.; Yang, C.L.; Lin, J.; Yan, S.J. Synthesis and evaluation of the antitumor activity of highly functionalised pyridin-2-ones and pyrimidin-4-ones. *RSC Adv.* **2017**, *7*, 40067.
56. Bao, H.B.; Shao, X.; Zhang, Y.; Deng, Y.; Xu, X.; Liu, Z.; Li, Z. Specific Synergist for Neonicotinoid Insecticides: IPPA08, a cisNeonicotinoid Compound with a Unique Oxabridged Substructure. *J. Agric. Food Chem.* **2016**, *64*, 5148.
57. Li, J.; Zhang, S.; Wu, C.; Li, C.; Wang, H.; Wang, W.; Li, Z.; Ye, Q. Stereoselective Degradation and Transformation Products of a Novel Chiral Insecticide, Paichongding, in Flooded Paddy Soil. *J. Agric. Food Chem.* **2016**, *64*, 7423.
58. Kondo, H.; Taguchi, M.; Inoue, Y.; Sakamoto, F.; Tsukamoto, G. Synthesis and antibacterial activity of thiazolo-, oxazolo-, and imidazolo[3,2-*a*][1,8]naphthyridinecarboxylic acids. *J. Med. Chem.* **1990**, *33*, 2012.

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