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Comparison of synthetic routes for fully substituted (1*H*-1,2,3-triazol-4-yl)acetic acids

Nazariy Pokhodylo[a*]**, Roman Savka**[a] **and Mykola Obushak**[a]

[a]*Department of Organic Chemistry, Ivan Franko National University of Lviv, Kyryla i Mefodiya St. 6, Lviv 79005, Ukraine*

C H R O N I C L E	A B S T R A C T
	The new fully substituted (1*H*-1,2,3-triazol-4-yl)acetic acids were synthesized from available precursors (1*H*-1,2,3-triazol-4-yl)ethanones and 1*H*-1,2,3-triazole-4-carboxylic acids, which are easily prepared by the Dimroth reaction from azides and 1,3-dicarbonyl compounds. The practical methods of homologization (the Arndt–Eistert reaction and homologization as a result of nucleophilic substitution by cyanide anion) and the Willgerodt-Kindler reaction were compared. The Willgerodt-Kindler method starting from (5-methyl-1*H*-1,2,3-triazol-4-yl)ethanones was selected as the most convenient method for the synthesis of 2-(1-aryl-5-methyl-1*H*-1,2,3-triazol-4-yl)acetic acids, which are promising building blocks for drug discovery. Additionally, (1*H*-1,2,3-triazol-4-yl)ethanones were studied for the synthesis of alcohols, amines and in the Johnson–Corey–Chaykovsky reaction.

1. Introduction

The 1*H*-1,2,3-triazoles functionalized in position 4 are well-known building blocks for construction of diversity of triazole derivatives for drug discovery and material sciences.[1] The progress of 4-functionalized fully substituted triazoles (mostly 4-carboxylic acids or 4-keto derivatives) is caused by a convenient and efficient Dimroth reaction, which allows a wide variation of substituents.[2–6] Another approach to 4-functionalized triazoles is the [3+2] cycloaddition reaction of EWG-functionalized acetylenes with organic azides, which can also be performed in regioselective manner without catalyst due to significant charge separation in alkyne, currently being DFT computationally studied.[7] However, the triazole functional groups' transformations, especially non-isohypsic reactions (with a change in the oxidation level of carbon atoms), remain poorly studied. Among such reactions, (1*H*-1,2,3-triazol-4-yl)ethanones and 1*H*-1,2,3-triazole-4-carboxylic acids are commonly researched. For example, it was found that 4-acetyltriazoles had significant C–H activity and easily allowed aldol condensation reactions for the synthesis of chalcones containing the triazole moiety. A number of 1,2,3-triazole chalcones have been tested for antimicrobial activity[8] and studied as transglutaminase inhibitors.[9] Moreover, such chalcones were used as starting reagents for the synthesis of (1*H*-1,2,3-triazol-4-yl)pyridines by the Michael tandem cyclization,[10] 1,2,3-triazol-4-ylpyrazoles[11] and their derivatives for screening antimicrobial activity,[12] and 1,2,3-triazolylhydro-pyrimidine-2-thiones,[13] which were
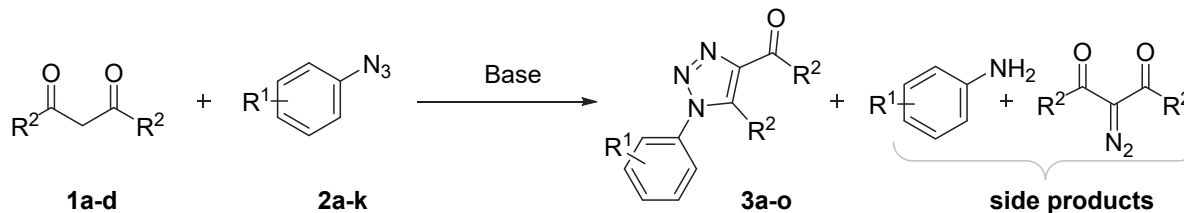
evaluated as antibacterial agents. Recently, chalcones were used in the KF-Al₂O₃-catalyzed tandem nucleophilic attachment of cyanide ion generated from activated acetonitriles, which made it possible to synthesize a series of 2-aryl-4-(1-aryl-5-methyl-1*H*-1,2,3-triazol-4-yl)butyronitriles.[14] We have shown that such chalcones could be used in the thionation-hetero-Diels-Alder domino-reactions yielding 3,4-dihydro-2*H*-thiopyrans and thiopyrano[3,4-*c*]chromenones.[15] In addition, it was found that the starting 1-[1-aryl-5-methyl-1,2,3-triazol-4-yl]ethanones were convenient reagents in the synthesis of quinoline derivatives by the Pfitzinger reaction.[16] Another important class of triazoles widely used nowadays is triazole-4-carboxylic acids and their derivatives (esters or acid chlorides). For examples, unique ethyl 1-aryl-5-formyl-1*H*-1,2,3-triazole-4-carboxylates were used to provide access to insufficiently studied 1-aryl-1,5-dihydro-4*H*-[1,2,3]triazolo[4,5-d]pyridazin-4-ones.[17] The reaction of 1*H*-1,2,3-triazole-4-carboxylic acid chlorides with tryptamine and the following Bischler-Napieralski cyclization is a convenient route to 1-(1*H*-1,2,3-triazol-4-yl)-3*H*-β-carbolines.[18] The 1-aryl-1*H*-1,2,3-triazole-4-carbonyl chlorides were studied in one-pot Boulton–Katritzky rearrangement with 3-amino-5-methylisoxazole and KSCN leading to 1,2,4-thiadiazole derivatives.[19] In addition, diversity of isomeric (1*H*-1,2,3-triazol-4-yl)-1,3,4-oxadiazoles or 1,2,4-oxadiazoles were synthesized by the reaction of 1,2,3-triazole-4-carbonyl chlorides with the corresponding substituted 1*H*-tetrazoles or *N*-hydroxyamides.[20] Lastly, the ligands for lanthanide ions (Pr³⁺, Sm³⁺, Nd³⁺, Yb³⁺, Eu³⁺ and Tb³⁺) were prepared by the acylation of pyrazoline-5-one derivatives[21] or 1-(2-hydroxy-5-methylphenyl)ethanone with the following Baker–Venkataraman rearrangement with 1*H*-1,2,3-triazole-4-carboxylic acid chlorides for studying the luminescence properties of their complexes.[22] In this regard, homologization of 1*H*-1,2,3-triazole-4-carboxylic acids is a matter of utmost interest. It should be noted that, as opposed to the 1-substituted (1*H*-1,2,3-triazol-4-yl)acetic acids, the synthetic approaches to fully substituted ones remain unstudied. The 1-substituted (1*H*-1,2,3-triazol-4-yl)acetic acids can be obtained by the reaction of ethyl-4,4-dichloro-3-{[(4-methylphenyl)sulfonyl]hydrazono}butanoate with amines in the presence of *N*-ethyl-*N*,*N*-diisopropylamine as the base[23] or CuAAC reaction of azides with 3-butynoic acid.[24] At the latter reaction, the azides were prepared from benzyl bromides in one-pot.[25] In addition, a regioselective intramolecular reaction of the dipolar cyclic addition of azides and asymmetric alkynes containing the acetic acid fragment was developed.[26] Noteworthy that compounds containing the (1*H*-1,2,3-triazol-4-yl)acetic acid fragment have been studied as squalene synthase inhibitors.[27]

2. Results and Discussion

In this work, we have compared alternative approaches to the synthesis of fully substituted (1*H*-1,2,3-triazol-4-yl)acetic acids from easily available (1,2,3-triazol-4-yl)carboxylic acids and ketones. The starting ketones were obtained by the reaction of β-diketones (acetylacetone **1a**, dipivaloylmethane **1b**, dibenzoylmethane **1c** and dimedone **1d**) with arylazides **2a–m** (see **Scheme 1, Table 1**). By optimizing the reaction conditions, it was found that the highest yields of the target triazoles **3** in case of acetylacetone **1a** in the reaction with aryl azides with electron-donating substituents were observed during the reaction at room temperature and with the use of sodium methylate as a main catalyst. In contrast, in case of azides with electron-withdrawing substituents, triethylamine (weaker base) was used. This led to increase in the reaction time, however, the formation of side and tarry products of the reaction mixture was not observed. In case of dipivaloylmethane **1b** and dibenzoylmethane **1c**, the reaction was slow at room temperature. The highest yields of compounds **3l-n** were obtained by boiling the reagents in methanol with sodium methylate. The effective K₂CO₃/DMSO system, previously used for selective preparation of 1*H*-1,2,3-triazole-4-carboxylic acids,[28] was studied in the reaction of phenyl azide with dimedone. It was found that the reaction proceeded at room temperature with good yields. Additionally, no strong correlations between azide reactivity and substituents constants were observed indicating that there may be different reaction mechanisms, the implementation of which is influenced by a number of factors, such as solvent, base, enolization degree of ketoester as mentioned earlier.[2] The optimized techniques allowed to obtain substituted high-yield triazoles **3** for their further use as reagents. It should be noted that as an alternative method of the synthesis of (1,5-diphenyl-1*H*-1,2,3-triazol-4-yl)(phenyl)methanone **3m**, the oxidative [3+2] cyclic addition of phenyl azide to chalcone in

an aqueous medium with TEMPO was recently proposed.[29] Cyclic ketones, such as dimedone and cyclohexanedione, can be used to annulate the triazole ring, but their use is limited due to the side processes of diazo transfer observed when using strong base catalysts.[18] However, application of mild bases, such as triethylamine in catalytic amounts,[30] anhydrous magnesium carbonate,[31] 1,1,3,3-tetramethylguanidine (TMG)[32] or DBU,[33] allowed to obtain 1*H*-benzo[*d*][1,2,3]triazole-4(5*H*)-ones in high yields. Furthermore, such compounds could be prepared via the Regits diazo transfer reaction of tosylazide with 1-anilino-5,5-dimethyl-3-oxocyclohex-1-ene.[34]

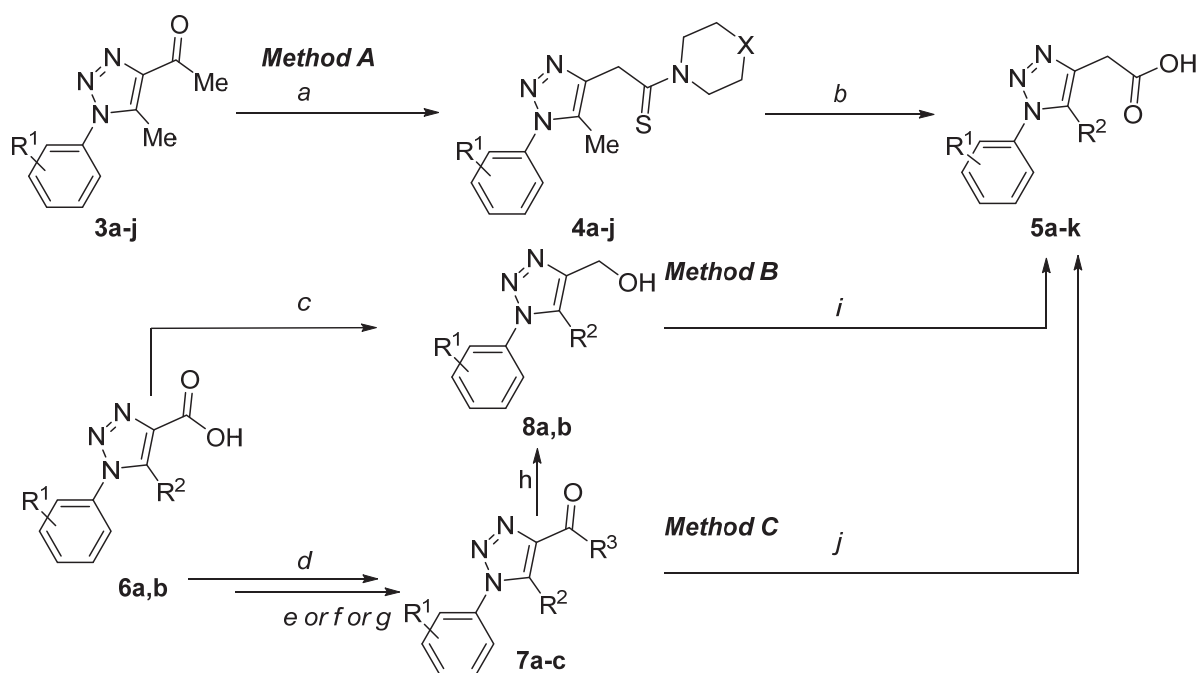**Scheme 1.** Synthesis of 1-(1-aryl-5-methyl-1,2,3-triazol-4-yl)ethanones **3a-o**.

Table 1. Synthesis of 1-(1-aryl-5-methyl-1,2,3-triazol-4-yl)ethanones **3a-o**.

Entry	β-Diketone (1)	Azide R¹ (2)	Hammett constants (R¹)	Base	t, °C	Time, h	Triazole R² (3)	Yields, %[4]
1.	acac[1] (**a**)	H (**2a**)	0.00	Et₃N	60	24	Me (**3a**)	83
2.	acac (**a**)	3-Me (**2b**)	-0.07	Et₃N	60	24	Me (**3b**)	78
3.	acac (**a**)	2-F (**2c**)	0.24	Et₃N	20	72	Me (**3c**)	85
4.	acac (**a**)	4-F (**2d**)	0.06	Et₃N	60	3	Me (**3d**)	92
5.	acac (**a**)	2-Cl (**2e**)	0.20	Et₃N	20	96	Me (**3e**)	70
6.	acac (**a**)	3-Cl (**2f**)	0.37	MeONa	20	48	Me (**3f**)	74
7.	acac (**a**)	4-Cl (**2g**)	0.23	MeONa	20	12	Me (**3g**)	77
8.	acac (**a**)	4-MeO (**2h**)	-0.27	MeONa	20	48	Me (**3h**)	81
9.	acac (**a**)	3-CF₃ (**2i**)	0.43	Et₃N	20	12	Me (**3i**)	89
10.	acac (**a**)	2,5-Cl₂ (**2j**)	0.20; 0.37	Et₃N	20	96	Me (**3j**)	72
11.	acac (**a**)	3-Cl-4-MeO (**2k**)	0.37; -0.27	MeONa	20	48	Me (**3k**)	79
12.	dpm[2] (**b**)	4-Me (**2l**)	-0.17	MeONa	65	1	*t*Bu (**3l**)	88
13.	dbm (**c**)	H (**2a**)	0.00	MeONa	65	1	*t*Bu (**3m**)	92
14.	dbm[3] (**c**)	4-Me (**2l**)	-0.17	MeONa	65	1	Ph (**3n**)	94
15.	dimedone (**d**)	H (**2a**)	0.00	K₂CO₃	20	12	-(CH₂C(CH₃)₂CH₂)₂- (**3o**)	72

[1] acac – acetylacetone; [2] dpm – dipivaloyl methane; [3] dbm – dibenzoyl methane₄; [4] isolated yield

The 1-[1-aryl-5-methyl-1,2,3-triazol-4-yl]ethanones were studied under conditions of the Willgerodt-Kindler reaction for (1*H*-1,2,3-triazol-4-yl)acetic acids synthesis (**Scheme 2**, **Table 2**). It was found that regardless of the substituent in the aryl moiety, thiomorpholides were formed with high yields. However, the hydrolysis of thiomorpholides was difficult in case of some of the substituents requiring prolonged heating. This made it possible to obtain a number of novel (5-methyl-1-aryl-1*H*-1,2,3-triazol-4-yl)acetic acids in good yields. As an alternative route to (1*H*-1,2,3-triazol-4-yl)acetic acids preparation, a multistep synthesis starting from triazole-4-carboxylic acids was proposed. Diversity of triazole-4-carboxylic acids was previously synthesized by the reaction of aryl azides from β-ketoesters.[17-21, 28] The 1*H*-1,2,3-triazole-4-carboxylic acids **6** were converted to (1*H*-1,2,3-triazol-4-yl)methanols via direct reduction or after carbonyl activation through ester or amide. It was found that the reaction of borane, generated by the action of iodine on sodium boron hydride, in tetrahydrofuran in case of 1*H*-1,2,3-triazole-4-carboxylic acid **6a** with a methyl substituent in position 5 occurred with formation of the corresponding alcohol **8** in good yields. The (5-methyl-1-phenyl-1*H*-1,2,3-triazol-4-yl) methanol **8a** was also synthesized from *N*-isopropylanilide **7a** via reduction with lithium aluminium hydride (LAH). Instead, in case of the phenyl substituent, the target alcohol was isolated in low yields due to steric hindering and low solubility of acid. In this regard, acid was quantitatively converted to methyl ester, which was reduced to alcohol with the action of LAH. Mesylation of alcohols **8** with the following nitrile incorporation by the potassium cyanide and hydrolysis led to the target 1*H*-1,2,3-triazol-4-yl)acetic acids **5**. Finally, the Arndt–Eistert synthesis was evaluated for preparation of acid **5k**. The 1,5-diphenyl-1*H*-1,2,3-triazole-4-carboxylic acid **6b** was converted to the corresponding chloride and by acylation of diazomethane yielded diazoketone **7c**. By the Arndt–Eistert rearrangement,

it was converted to the corresponding amide and hydrolysed to give the target acid **5k**. However, the overall yield of the compound was lower than in case of alternative route to this acid via alcohols **8b**. The summarized data of all attempts and paths is presented in **Table 2**.

Reagents: a) S, morpholine or 1-methylpiperazine; b) KOH, EtOH, H_2O; c) $NaBH_4$, I_2, THF d) $SOCl_2$; e) N-isopropylaniline; f) MeOH; g) CH_2N_2, MTBE; h) LAH, THF; i) MsCl, Et_3N, KCN, KOH, EtOH; j) $AgNO_3$, aq. NH_3, dioxane, KOH, EtOH.
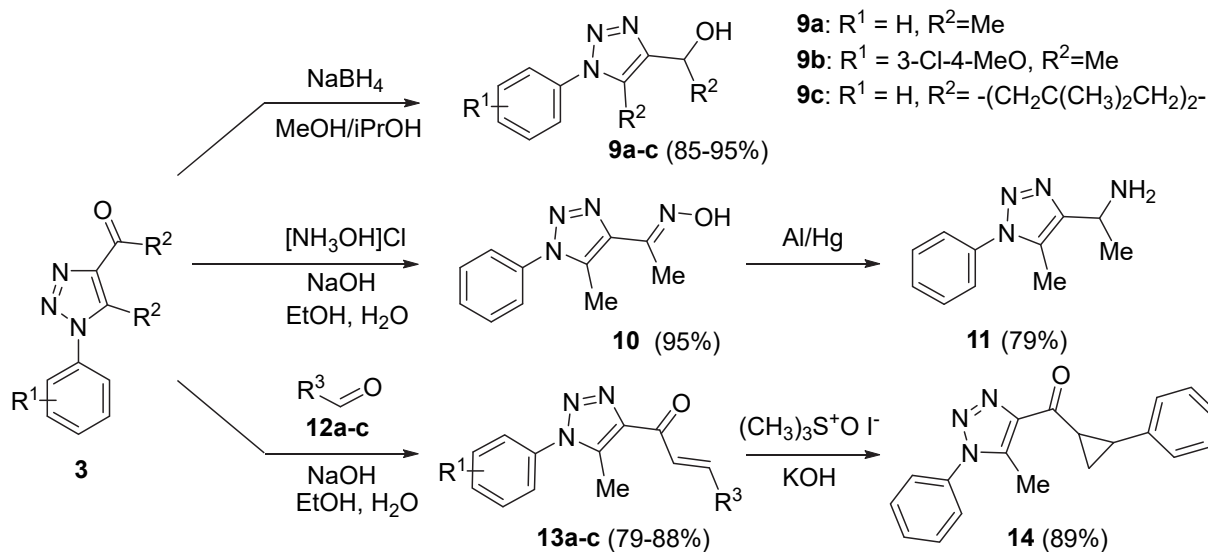
Scheme 2. Synthesis of (5- R^2-1-aryl-1H-1,2,3-triazol-4-yl) acetic acids **5a-k**.

Table 2. Synthesis of (5- R^2-1-aryl-1H-1,2,3-triazol-4-yl) acetic acids **5a-k**.

Entry	R^1	R^2	*Method*	Intermediates	(Triazol-4-yl) acetic acids	Yields, %
1.	H	Me	*A*	**4a**[16] (78%)	**5a**[16]	61%
2.	H	Me	*B*	**7a** R^3 =iPrNPh (91%) **8a** (84%)	**5a**	54%
3.	3-Me	Me	*A*	**4b** X=O (75%)	**5b**	70%
4.	2-F	Me	*A*	**4c** X=O (88%)	**5c**	73%
5.	4-F	Me	*A*	**4d** X=O (83%)	**5d**	79%
6.	2-Cl	Me	*A*	**4e** X=O (81%)	**5e**	64%
7.	3-Cl	Me	*A*	**4f** X=O (85%)	**5f**	72%
8.	4-Cl	Me	*A*	**4g** X=NMe (71%)	**5g**[16]	74%
9.	4-MeO	Me	*A*	**4h** X=O (73%)	**5h**	67%
10.	3-CF_3	Me	*A*	**4i** X=O (90%)	**5i**	84%
11.	2,5-Cl_2	Me	*A*	**4j** X=O (78%)	**5j**	69%
12.	H	Ph	*B*	**7b** R^3 =OMe (100%); **8b** (95%)	**5k**	62%
13.	H	Ph	*C*	**7c** R^3 =CHN_2	**5k**	23%

Recently, a number of 1,5-disubstituted-1,2,3-triazole alcohols containing the sulfonamide group have been shown to have inhibitory activity for human carbonises I, II, IV and IX.[35] The obtained ketones **3** are easily reduced by sodium borohydride to alcohols **9a-c**, which are attractive low molecular weight compounds for medicinal chemistry (**Scheme 3**). Ketone **3** can also be converted to amines **11** via oxime **10** prepared by boiling with hydroxylamine hydrochloride in the presence of an equivalent amount of NaOH for 1 hour and reduction with aluminium amalgam. It is of note that there are only a few examples of the preparation of oximes of (5-methyl-1H-1,2,3-triazol-4-yl)ethanone, which were subsequently used to synthesize compounds for screening for insecticidal and fungicidal

activity.[36] The main use of ketones **3** is the synthesis of chalcones **13**. The corresponding ketone **3** easy reacted with aldehyde **12** in the presence of 10% sodium hydroxide solution at room temperature leading to the formation of chalcones **13a-c** in high yield. We found that chalcone **13a** selectively yielded cyclopropane **14** by the Johnson–Corey–Chaykovsky reaction with trimethylsulfoxone iodide. On the contrary, chalcone **13b** containing the phenol moiety gave a complex mixture in the reaction. It also should be noted that starting ketone **3a** does not react with (dimethyloxosulfaniumyl)methanide generated *in situ* and the formation of the epoxy ring was not observed. Finally, we tested the Wolff–Kishner reduction to convert carbonyl into the methylene group. Previously, reduction of the keto group to methylene was used in 4-benzoyl-1*H*-1,2,3-triazole for the synthesis of benzyltriazoles, which were studied as potassium channel activators.[37] We used ketone **3a** in the same protocol; in our case, the target 4-ethyl-5-methyl-1-phenyl-1*H*-1,2,3-triazole was not found.

9a: R^1 = H, R^2=Me
9b: R^1 = 3-Cl-4-MeO, R^2=Me
9c: R^1 = H, R^2= -(CH$_2$C(CH$_3$)$_2$CH$_2$)$_2$-

13a: R^1 = H, R^3 = Ph; **13b**: R^1 = H, R^3 = 2-hydroxyphenyl; **13c**: R^1 = 3-Cl-4-MeO, R^3 = 2-styryl

Scheme 3.

3. Conclusions

Thus, (1*H*-1,2,3-triazol-4-yl)acetic acids as attractive building blocks were prepared by the Willgerodt-Kindler reaction in high yields. The yields were higher than the results obtained by alternative paths starting from 1*H*-1,2,3-triazole-4-carboxylic acids. Furthermore, (5-methyl-1*H*-1,2,3-triazol-4-yl)ethanones were shown to be suitable reagents for the synthesis of alcohols, amines and cyclopropane derivatives, which can be used for the synthesis of drug-like compounds.

Acknowledgements

4. Experimental

4.1. Instruments

^{1}H and ^{13}C NMR spectra were recorded on Varian Unity Plus 400 (400 and 101 MHz, respectively) and Bruker 170 Avance 500 (500 and 126 MHz, respectively) spectrometers in DMSO-d$_6$ solutions using TMS or the deuterated solvent as internal reference. IR spectra were measured using Thermo Scientific Nicolet iS 10 FT-IR spectrometer. Mass spectral analyses were performed using an Agilent

1100 series LC/MSD with API-ES/APCI mode (200 eV). Elemental analyses were accomplished using a Carlo Erba 1106 instrument. Melting points were determined on a Boetius melting point apparatus.

4.2. Experimental procedure and physical data for compounds

Synthesis of 1-(1-aryl-5-methyl-1,2,3-triazol-4-yl)ethanones 3a-o. To the equimolar mixture of *β*-diketone (0.01 mol) and arylazide (0.01 mol) in methanol (10 mL, for diketones **2a-c**) or DMSO (5mL; for diketone **2d**) base catalysis (1eq. of Et$_3$N or NaOMe; 2eq. of K$_2$CO$_3$) was added. The mixture was vigorously stirred at room temperature or under reflux until all starting azide disappeared (monitoring by TLC). The refluxed mixture was cooled and the resulting crystals were then filtered off and washed with cold methanol on the filter. In case of K$_2$CO$_3$/DMSO system, the mixture was diluted with 15 mL of water. The sediment was filtered off. The crude products could be additionally purified by recrystallization from ethanol to furnish the compound **3** with above 95% purity as a white solid.

1-(5-Methyl-1-phenyl-1*H*-1,2,3-triazol-4-yl)ethanone (3a).[16] This compound was prepared by the heating under reflux using Et$_3$N as base catalysis. White crystals, yield 83%.

1-(5-Methyl-1-m-tolyl-1*H*-1,2,3-triazol-4-yl)ethanone (3b).[16] This compound was prepared by the heating under reflux using Et$_3$N as base catalysis. White crystals, yield 78%.

1-(1-(2-Fluorophenyl)-5-methyl-1*H*-1,2,3-triazol-4-yl)ethanone (3c). This compound was prepared at room temperature using Et$_3$N as base catalysis. White crystals, yield 85%; mp 81–82°C. IR: 1676 (C=O), 1516, 1417, 1282, 1246, 952, 767 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d$_6$), δ, ppm: 2.41 s (3H, CH$_3$) 2.63 s (3H, CH$_3$CO), 7.50 t (1H, H$^4_{Ar}$, J 7.5 Hz), 7.61 t (1H , H$^5_{Ar}$, J 9.3 Hz), 7.68–7.79 m (2H, H$_{Ar}$); ^{13}C NMR (101 MHz, DMSO-d$_6$), δ, ppm: 9.73 (CH$_3$), 28.22 (CH$_3$), 117.74 d (CH$^3_{Ar}$, ^{2}J$_{C-F}$ 19.0 Hz), 123.06 d (CH$^1_{Ar}$, ^{2}J$_{C-F}$ = 11.9 Hz), 126.38 (CH$^5_{Ar}$), 129.64 (CH$^4_{Ar}$), 133.83 d (CH$^6_{Ar}$, ^{3}J$_{C-F}$ = 8.0 Hz), 139.74 (C$^5_{Triazole}$), 143.13 (C$^4_{Triazole}$), 156.42 d (C$^2_{Ar}$, ^{1}J$_{C-F}$ 251.7 Hz), 193.80 (C=O); LC-MS (CI), *m/z*: 220 [M+H]$^+$; Found,%: C 60.21; H, 4.49; N, 19.11. C$_{11}$H$_{10}$FN$_3$O. Calculated,%: C 60.27; H 4.60; N, 19.17.

1-(1-(4-Fluorophenyl)-5-methyl-1*H*-1,2,3-triazol-4-yl)ethanone (3d).[38] This compound was prepared by the heating under reflux using Et$_3$N as base catalysis. White crystals, yield 92%.

1-(1-(2-Chlorophenyl)-5-methyl-1*H*-1,2,3-triazol-4-yl)ethanone (3e).[10] This compound was prepared at room temperature using Et$_3$N as base catalysis. White crystals, yield 70%.

1-(1-3-Chlorophenyl)-5-methyl-1*H*-1,2,3-triazol-4-yl)ethanone (3f).[10] This compound was prepared at room temperature using MeONa as base catalysis. White crystals, yield 74%.

1-(1-(4-Chlorophenyl) -5-methyl-1*H*-1,2,3-triazol-4-yl)ethanone (3g).[16] This compound was prepared at room temperature using MeONa as base catalysis. White crystals, yield 77%.

1-(1-(4-Methoxyphenyl)-5-methyl-1*H*-1,2,3-triazol-4-yl)ethanone (3h).[10] This compound was prepared at room temperature using MeONa as base catalysis. White crystals, yield 81%.

1-(5-Methyl-1-(3-(trifluoromethyl)phenyl)-1*H*-1,2,3-triazol-4-yl)ethanone (3i). This compound was prepared at room temperature using Et$_3$N as base catalysis. White crystals, yield 89%; mp 45–46°C; IR: 1679 (C=O), 1525, 955 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d$_6$), δ, ppm: 2.54 s (3H, CH$_3$), 2.64 s (3H, CH$_3$CO), 7.90 t (1H, H$^5_{Ar}$, J 7.7 Hz), 7.97–8.05 m (2H, H$_{Ar}$), 8.09 s (1H, H$^2_{Ar}$); LC-MS (CI), *m/z*: 270 [M+H]$^+$; Found,%: C 53.59; H, 3.72; N, 15.76. C$_{12}$H$_{10}$F$_3$N$_3$O. Calculated,%: C 53.54; H, 3.74; N, 15.61.

1-(1-(2,5-Dichlorophenyl)-5-methyl-1*H*-1,2,3-triazol-4-yl)ethanone (3j).[10] This compound was prepared at room temperature using Et$_3$N as base catalysis. White crystals, yield 72%.

1-(1-(3-Chloro-4-methoxyphenyl)-5-methyl-1*H*-1,2,3-triazol-4-yl)ethanone (3k). This compound was prepared at room temperature using MeONa as base catalysis. White crystals, yield 79%; mp 112–113°C; IR: 1682 (C=O), 1537, 1275, 952 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d$_6$), δ, ppm: 2.48 s (3H, CH$_3$), 2.62 s (3H, CH$_3$CO), 3.96 s (3H, CH$_3$O), 7.38 d (1H, H$^5_{Ar}$, J 8.8 Hz), 7.60 d (1H, H$^6_{Ar}$, J 8.5 Hz), 7.80 s (1H, H$^2_{Ar}$); LC-MS (CI), *m/z*: 266 [M+H]$^+$; Found,%: C 54.00; H, 4.42; N, 16.09. C$_{12}$H$_{12}$ClN$_3$O$_2$. Calculated,%: C 54.25; H, 4.55; N 15.82.

1-(5-tert-Butyl-1-p-tolyl-1*H*-1,2,3-triazol-4-yl)-2,2-dimethylpropan-1-one (3l). This compound was prepared by the heating under reflux using MeONa as base catalysis. White crystals, yield 88%; mp 78–79°C; IR: 1678 (C=O), 1514, 1412, 1210, 945, 820 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d$_6$), δ, ppm: 1.14 s (9H, t-Bu), 1.35 s (9H, t-Bu), 2.42 s (3H, CH$_3$), 7.39 d (2H, H$^{3,5}_{Ar}$, J 7.8 Hz), 7.44 d (2H,

H^{2,6}$_{Ar}$, J 7.8 Hz); LC-MS (CI), *m/z*: 300 [M+H]$^+$; Found,%: C 72.12; H, 8.38; N, 13.90. C$_{18}$H$_{25}$N$_3$O. Calculated,%: C 72.21; H, 8.42; N, 14.03.

(1,5-Diphenyl-1*H*-1,2,3-triazol-4-yl)(phenyl)methanone (3m).[17] This compound was prepared by the heating under reflux using MeONa as base catalysis. White crystals, yield 92%.

Phenyl(5-phenyl-1-p-tolyl-1*H*-1,2,3-triazol-4-yl)methanone (3n). This compound was prepared by the heating under reflux using MeONa as base catalysis. White crystals, yield 94%, mp 190–191°C; IR: 1652 (C=O), 1511, 1446, 1222, 919, 692 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d$_6$), δ, ppm: 2.39 s (3H, CH$_3$), 7.21 d (2H, H^{3,5}$_{Ar}$, J 8.8 Hz), 7.25 d (2H, H^{2,6}$_{Ar}$, J 8.8 Hz), 7.28–7.42 m (5H, H$_{Ph}$), 7.52 t (2H, H^{3,5}$_{Ph}$, J 7.6 Hz), 7.63 m (1H, H^4$_{Ph}$), 8.17 d (2H, H^{2,6}$_{Ph}$, J 7.2 Hz); LC-MS (CI), *m/z*: 340 [M+H]$^+$; Found,%: C 77.75; H, 4.96; N, 12.43. C$_{22}$H$_{17}$N$_3$O. Calculated,%: C 77.86; H, 5.05; N, 12.38.

6,6-Dimethyl-1-phenyl-6,7-dihydro-1*H*-benzo[*d*][1,2,3]triazole-4(5*H*)-one (3o).[33] This compound was prepared at room temperature using K$_2$CO$_3$ as base catalysis. White crystals, yield 72%; mp 154-155°C; ^{1}H NMR (400 MHz, DMSO-d$_6$), δ, ppm: 0.98 s (6H, CH$_3$), 2.18 s (1H, CH$_2$), 2.31 m (1H, CH$_2$), 2.99 s (2H, CH$_2$), 7.53–7.92 m (5H, H$_{Ph}$); LC-MS (CI), *m/z*: 242 [M+H]$^+$; Found,%: C 69.74; H 6.29; N, 17.47. C$_{14}$H$_{15}$N$_3$O. Calculated,%: C 69.69; H 6.27; N, 17.41.

Synthesis of [5-methyl-1-aryl-1*H*-1,2,3-triazol-4-yl]-1-(morpholin-4-yl)ethanthiones 4a-j (Wilgerodt-Kindler reaction). The mixture of ketone **3** (0.01 mol), sulphur .64 g (0.02 mol) and amine (0.02 mol) was heated for 5 h at 135°C (oil bath temperature). The warm mixture was carefully poured into 50 mL of hot ethanol and triturated for crystallization. The mixture was left overnight in the refrigerator; the product was filtered off, washed with a little cold ethanol and air-dried.

2-(5-Methyl-1-phenyl-1*H*-1,2,3-triazol-4-yl)-1-morpholinoethane-1-thione   (4a).[16]   Prepared previously. White solid, yield 78%.

2-(5-Methyl-1-m-tolyl-1*H*-1,2,3-triazol-4-yl)-1-morpholinoethanethione (4b). White solid, yield 75%; mp 107–108°C; IR: 1462, 1438 (C=S), 1274, 1109, 1030, 785 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d$_6$), δ, ppm: 2.34 s (3H, CH$_3$), 2.41 s (3H, CH$_3$), 3.66 s (4H, CH$_2$), 4.06 s (2H, CH$_2$) , 4.22 s (2H, CH$_2$), 4.32 s (2H, CH$_2$), 7.31–7.43 m (3H, H$_{Ph}$), 7.49 t (1H, H^5$_{Ph}$, J 7.5 Hz); LC-MS (CI), *m/z*: 317 [M+H]$^+$; Found,%: C 60.77; H 6.30; N, 17.76. C$_{16}$H$_{20}$N$_4$OS. Calculated,%: C 60.73; H, 6.37; N, 17.71.

2-(1-(2-Fluorophenyl)-5-methyl-1*H*-1,2,3-triazol-4-yl)-1-morpholinoethanethione   (4c). White solid, yield 88%; mp 124–125°C; IR: 1441 (C=S), 1265, 1104, 1025 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d$_6$), δ, ppm: 2.23 s (3H, CH$_3$), 3.53–3.77 m (4H, CH$_2$), 3.96–4.14 m (2H, CH$_2$), 4.18–4.30 m (2H, CH$_2$), 4.35 s (2H, CH$_2$), 7.46 m (1H, H^5$_{Ar}$, J 7.5 Hz), 7.58 m (1H, H^4$_{Ar}$, J 9.3 Hz), 7.63–7.79 m (2H, H$_{Ar}$); ^{13}C NMR (101 MHz, DMSO-d$_6$), δ, ppm: 8.72 (CH$_3$), 50.61 (CH$_2$), 51.73 (2xCH$_2$N), 66.43 (CH$_2$O), 66.69 (CH$_2$O), 117.67 d (CH^3$_{Ar}$, ^{2}J$_{C-F}$ 19.3 Hz), 126.29 d (CH^6$_{Ar}$, ^{3}J$_{C-F}$ 2.5 Hz), 129.57 (2xCH^{4,5}Ar), 133.18 d (C^1$_{Ar}$, ^{2}J$_{C-F}$ 8.0 Hz), 134.04 (C^5$_{Triazole}$), 140.27 (C^4$_{Triazole}$), 156.39 d (CH^2$_{Ar}$, ^{1}J$_{C-F}$ 251.1 Hz), 197.55 (C=S); LC-MS (CI), *m/z*: 321 [M+H]$^+$; Found,%: C 56.15; H, 5.41; N, 17.44. C$_{15}$H$_{17}$FN$_4$OS. Calculated,%: C 56.23; H 5.35; N, 17.49.

2-(1-(4-Fluorophenyl)-5-methyl-1*H*-1,2,3-triazol-4-yl)-1-morpholinoethanethione   (4d). White solid, yield 83%, mp 124–125°C; IR: 1437 (C=S), 1219, 1114, 1031, 886 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d$_6$), δ, ppm: 2.33 s (3H, CH$_3$), 3.66 br.s (4H, CH$_2$), 4.06 br.s (2H, CH$_2$), 4.22 br.s (2H, CH$_2$), 4.33 s (2H, CH$_2$), 7.45 t (2H, H^{3,5}$_{Ar}$, J 8.4 Hz), 7.65 dd (2H, H^{3,5}$_{Ar}$, J 8.4, 4.8 Hz); LC-MS (CI), *m/z*: 321 [M+H]$^+$; Found,%: C 56.33; H, 5.39; N, 17.39. C$_{15}$H$_{17}$FN$_4$OS. Calculated,%: C 56.23; H 5.35; N, 17.49.

2-(1-(2-Chlorophenyl)-5-methyl-1*H*-1,2,3-triazol-4-yl)-1-morpholinoethanethione   (4e). White solid, yield 81%; mp 136–137°C; IR: 1438 (C=S), 1108, 1030, 860 cm^{-1}; 1H NMR (400 MHz, DMSO-d$_6$), δ, ppm: 2.16 s (3H, CH$_3$), 3.55–3.71 m (4H, CH$_2$), 4.03 br.s (2H, CH$_2$), 4.23 br.s (2H, CH$_2$), 4.36 s (2H, CH$_2$), 7.58-7.71 m (3H, H^{3,5}$_{Ar}$), 7.79 d (1H, H^{6}Ar, J 7.8 Hz); LC-MS (CI), *m/z*: 337 [M+H]$^+$; Found,%: C 53.41; H, 5.13; N, 16.74. C$_{15}$H$_{17}$ClN$_4$OS. Calculated,%: C 53.49; H, 5.09; N, 16.63.

2-(1-(3-Chlorophenyl)-5-methyl-1*H*-1,2,3-triazol-4-yl)-1-morpholinoethanethione   (4f). White solid, yield 85%; mp 96–97°C; IR: 1432 (C=S), 1111, 1028, 896 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d$_6$), δ, ppm: 2.37 s (3H, CH$_3$), 3.66 br.s (4H, CH$_2$), 4.05 br.s (2H, CH$_2$), 4.22 br.s. (2H, CH$_2$), 4.34 s (2H, CH$_2$), 7.58–7.68 m (3H, H$_{Ar}$), 7.77 s (1H, H^2$_{Ar}$); LC-MS (CI), *m/z*: 337 [M+H]$^+$; Found,%: C 53.57; H, 5.18; N, 16.52. C$_{15}$H$_{17}$ClN$_4$OS. Calculated,%: C 53.49; H, 5.09; N, 16.63.

2-(1-(4-Chlorophenyl)-5-methyl-1*H*-1,2,3-triazol-4-yl)-1-(4-methylpiperazin-1-yl)ethanedione (4g). White solid, yield 71%; mp 154–155°C; IR: 1496, 1462 (C=S), 1315, 1047, 1033, 998, 825 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d$_6$), δ, ppm: 2.19 (s, 3H), 2.36 s (3H, CH$_3$), 2.38 br.s (4H, CH$_2$), 4.03 br.s (2H, CH$_2$), 4.21 br.s (2H, CH$_2$), 4.32 s (2H, CH$_2$), 7.64 d (2H, H^{3,5}$_{Ar}$, J 8.3 Hz), 7.68 d (2H, H^{2,6}$_{Ar}$, J 7.9 Hz); LC-MS (CI), *m/z*: 350 [M+H]$^+$; Found,%: C 54.99; H, 5.73; N, 20.14. C$_{16}$H$_{20}$ClN$_5$S. Calculated,%: C 54.92; H, 5.76; N, 20.02.

2-(1-(4-Methoxyphenyl)-5-methyl-1*H*-1,2,3-triazol-4-yl)-1-morpholinoethanethione (4h). White solid, yield 73%; mp 129–130°C; IR: 1436 (C=S), 1283, 1104, 1032 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d$_6$), δ, ppm: 2.30 s (3H, CH$_3$), 3.66 s (4H, CH$_2$), 3.84 s (3H, CH$_3$O), 4.07 br.s (2H, CH$_2$), 4.22 br.s (2H, CH$_2$), 4.32 s (2H, CH$_2$), 7.13 d (2H, H^{2,6}$_{Ar}$, J 8.7 Hz), 7.49 d (2H, H^{3,5}$_{Ar}$, J 8.7 Hz); LC-MS (CI), *m/z*: 333 [M+H]$^+$; Found,%: C 57.91; H 6.15; N, 16.81. C$_{16}$H$_{20}$N$_4$O$_2$S. Calculated,%: C 57.81; H, 6.06; N, 16.85.

2-(5-Methyl-1-(3-(trifluoromethyl)phenyl)-1*H*-1,2,3-triazol-4-yl)-1-morpholinoethanethione (4i). White solid, yield 90%; mp 99–100°C; IR: 1433 (C=S), 1195, 1105, 1033 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d$_6$), δ, ppm: 2.39 s (3H, CH$_3$), 3.67 br.s (4H, CH$_2$), 4.06 br.s (4H, CH$_2$), 4.22 br.s (2H, CH$_2$), 4.35 s (2H, CH$_2$), 7.87 d (1H, H^4$_{Ar}$, J 7.4 Hz), 7.92–7.99 m (2H, H$_{Ar}$), 8.01 s (1H, H^2$_{Ar}$); LC-MS (CI), *m/z*: 371 [M+H]$^+$; Found,%: C 51.79; H, 4.75; N, 15.22. C$_{16}$H$_{17}$F$_3$N$_4$OS. Calculated,%: C 51.88; H 4.63; N, 15.13.

2-(1-(2,5-Dichlorophenyl)-5-methyl-1*H*-1,2,3-triazol-4-yl-1-morpholinoethanethionate (4j). White solid, yield 78%; mp 124–125°C; IR: 1437 (C=S), 1110, 1032, 842, 794 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d$_6$), δ, ppm: 2.19 s (3H, CH$_3$), 3.53–3.70 (4H, CH$_2$), 4.02 br.s (2H, CH$_2$), 4.22 br.s (2H, CH$_2$), 4.36 s (2H, CH$_2$), 7.78 dd (1H, H^4$_{Ar}$, J 8.7, 1.7 Hz), 7.84 d (1H, H^3$_{Ar}$, J 8.7 Hz), 7.91 (1H, H^6$_{Ar}$, J 1.6 Hz); LC-MS (CI), *m/z*: 371 [M+H]$^+$; Found,%: C 48.59; H, 4.40; N, 15.14. C$_{15}$H$_{16}$Cl$_2$N$_4$OS. Calculated,%: C 48.52; H, 4.34; N, 15.09.

Synthesis of (5-methyl-1-aryl-1*H*-1,2,3-triazol-4-yl) acetic acids 5 (*Method A*). The crude thiomorpholide **4** (0.01 mol) was added to a mixture of KOH solution (8 g of 50% aqueous solution) and ethanol 14 mL (if the solution is not homogeneous, ethanol is added to complete homogenization). The mixture was boiled for 6–12 h, then poured into water and acidified. The solution was cooled, the precipitate formed was filtered off. The acid was recrystallized from aqueous ethanol.

2-(5-Methyl-1-phenyl-1*H*-1,2,3-triazol-4-yl)acetic acid (5a).[16] Prepared previously. White solid, yield 61%.

2-(5-Methyl-1-m-tolyl-1*H*-1,2,3-triazol-4-yl)acetic acid (5b). White solid, yield 70%; mp 149–150°C; IR: 1717 (C=O), 1496, 997 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d$_6$), δ, ppm: 2.25 s (3H, CH$_3$), 2.40 s (3H, CH$_3$), 3.71 s (2H, CH$_2$), 7.34–7.39 m (2H, H$_{Ar}$), 7.40 s (1H, H^2$_{Ar}$), 7.49 t (1H, H^5$_{Ar}$, J 7.6 Hz), 12.55 br.s (1H, COOH). LC-MS (CI), *m/z*: 232 [M+H]$^+$; Found,%: C 62.41; H, 5.78; N, 18.11. C$_{12}$H$_{13}$N$_3$O$_2$. Calculated,%: C 62.33; H, 5.67; N, 18.17.

2-(1-(2-Fluorophenyl)-5-methyl-1*H*-1,2,3-triazol-4-yl)acetic acid (5c). White solid, yield 73%; mp 147–148°C; IR: 1715 (C=O), 1496, 1257, 1021 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d6), δ, ppm: 2.15 s (3H, CH$_3$), 3.75 s (2H, CH$_2$), 7.45 t (1H, H^5$_{Ar}$, J 7.6 Hz), 7.58 t (1H, H^4$_{Ar}$, J 9.5 Hz), 7.61– 7.71 m (2H, H^{3,6}$_{Ar}$), 12.58 s (1H, COOH); ^{13}C NMR (101 MHz, DMSO-d$_6$), δ, ppm: 8.28 (CH$_3$), 31.59 (CH$_2$), 117.64 d (CH^3$_{Ar}$, ^{2}J$_{C-F}$ 19.3 Hz), 126.27 d (CH^6$_{Ar}$, ^{3}J$_{C-F}$ 3.2) Hz), 129.51 s (2xCH^{4,5}$_{Ar}$), 133.09 d (C^1$_{Ar}$, ^{2}J$_{C-F}$ 7.9 Hz), 133.95 (C^5$_{Triazole}$), 138.95 (C^4$_{Triazole}$), 156.37 d (CH^2$_{Ar}$, ^{1}J$_{C-F}$ 250.8 Hz), 172.11 (O=C–O); LC-MS (CI), *m/z*: 236 [M+H]$^+$; Found,%: C 56.07; H 4.22; N 17.80. C$_{11}$H$_{10}$FN$_3$O$_2$. Calculated,%: C 56.17; H 4.29; N, 17.86.

2-(1-(4-Fluorophenyl)-5-methyl-1*H*-1,2,3-triazol-4-yl)acetic acid (5d). White solid, yield 79%; mp 159–160°C; IR: 1716 (C=O), 1497, 1221, 1125, 1030 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d$_6$), δ, ppm: 2.25 s (3H, CH3), 3.71 s (2H, CH2), 7.46 t (2H, H^{3,5}$_{Ar}$, J 8.6 Hz), 7.66 dd (2H, H^{3,5}$_{Ar}$, J 8.2, 4.9 Hz), 12.53 s (1H, COOH); LC-MS (CI), *m/z*: 236 [M+H]$^+$; Found,%: C 56.22; H, 4.34; N, 17.93. C$_{11}$H$_{10}$FN$_3$O$_2$. Calculated,%: C 56.17; H 4.29; N, 17.86.

2-(1-(2-Chlorophenyl)-5-methyl-1*H*-1,2,3-triazol-4-yl)acetic acid (5e). White solid, yield 64%; mp 204–205°C; IR: 1717 (C=O), 1496, 1315, 1291, 1158, 1144, 997, 825, 771 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d$_6$), δ, ppm: 2.09 s (3H, CH$_3$), s (2H, CH$_2$), 7.56 –7.64 m (2H, H^{3,4}$_{Ar}$), 7.67 t (1H , H^5$_{Ar}$, J 8.2

Hz,), 7.79 d (1H, H^6_{Ar}, J 7.9 Hz), 12.54 s (1H, COOH); LC-MS (CI), *m/z*: 252 [M+H]$^+$; Found,%: C 52.58 H 4.11; N, 16.74; $C_{11}H_{10}ClN_3O_2$. Calculated,%: C 52.50; H 4.01; N, 16.70.

2-(1-(3-Chlorophenyl)-5-methyl-1*H*-1,2,3-triazol-4-yl)acetic acid (5f). White solid, yield 72%; mp 171–172°C; IR: 1722 (C=O), 1492, 1012, 885 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d$_6$), δ, ppm: 2.28 s (3H, CH$_3$), 3.72 s (2H, CH$_2$), 7.57– 7.69 m (3H, H$_{Ar}$), 7.77 s (1H, H$^2_{Ar}$), 12.57 s (1H, COOH); LC-MS (CI), *m/z*: 252 [M+H]$^+$; Found,%: C, 52.43; H, 4.07; Cl, 14.01; N, 16.81. $C_{11}H_{10}ClN_3O_2$. Calculated,%: C, 52.50; H, 4.01; Cl, 14.09; N, 16.70.

2-(1-(4-Chlorophenyl)-5-methyl-1*H*-1,2,3-triazol-4-yl)acetic acid (5g).[16] Prepared previously. White solid, yield 74%.

2-(1-(4-Methoxyphenyl)-5-methyl-1*H*-1,2,3-triazol-4-yl)acetic acid (5h). White solid, yield 67%; mp 199–200°C; IR: 1726 (C=O), 1494, 1281, 1100, 999 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d$_6$), δ, ppm: 2.22 s (3H, CH$_3$), 3.70 s (2H, CH$_2$), 3.84 s (3H, CH$_3$O), 7.13 d (2H, H$^{3,5}_{Ar}$, J 8.7 Hz,), 7.49 d (2H, H$^{2,6}_{Ar}$, J 8.6 Hz), 12.52 s (1H, COOH); LC-MS (CI), *m/z*: 248 [M+H]$^+$; Found,%: C 58.24; H, 5.38; N, 16.92. $C_{12}H_{13}N_3O_3$. Calculated,%: C 58.29; H, 5.30; N, 16.99.

2-(5-Methyl-1-(3-(trifluoromethyl)phenyl)-1*H*-1,2,3-triazol-4-yl)acetic acid (5i). White solid, yield 84%; mp 98–99°C; IR: 1727 (C=O), 1499, 1320, 1119, 1068, 830, 799, 699 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d$_6$), δ, ppm: 2.32 s (3H, CH$_3$), 3.74 s (2H, CH$_2$), 7.81–7.97 m (3H, H$^{3,5}_{Ar}$), 7.99 s (1H, H$^2_{Ar}$), 12.51 s (1H, COOH); LC-MS (CI), *m/z*: 286 [M+H]$^+$; Found,%: C 50.59; H, 3.59; N, 14.71. $C_{12}H_{10}F_3N_3O_2$. Calculated,%: C 50.53; H, 3.53; N, 14.73.

2-(1-(2,5-Dichlorophenyl)-5-methyl-1*H*-1,2,3-triazol-4-yl)acetic acid (5j). White solid, yield 69%; mp 176–177°C; IR: 1719 (C=O), 1496, 996 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d$_6$), δ, ppm: 2.12 s (3H, CH$_3$), 3.73 s (2H, CH$_2$), 7.78 dd (1H, H$^4_{Ar}$, J 8.3, 1.8 Hz) , 7.84 d (1H, H$^3_{Ar}$, J 8.7 Hz,), 7.90 d (1H, H$^6_{Ar}$, J 1.8 Hz), 12.54 s (1H, COOH); LC-MS (CI), *m/z*: 286 [M+H]$^+$; Found,%: C 46.28; H, 3.09; N, 14.75. $C_{11}H_9Cl_2N_3O_2$. Calculated,%: C 46.18; H 3.17; N, 14.69.

N-Isopropyl-5-methyl-N,1-diphenyl-1*H*-1,2,3-triazole-4-carboxamide (7a). To a cooled to 0°C solution of the N-isopropylaniline (1.35 g, 10 mmol) and triethylamine (1.4 mL, 10 mmol) in 50 mL of dioxane with vigorous stirring the 5-methyl-1-phenyl-1*H*-1,2,3-triazole-4-carbonyl chloride[20] (2.21 g, 10 mmol) was added and left for 1 h at room temperature. The mixture was heated under reflux, cooled and diluted with water (50 mL). The solid amide **7a** was washed on filter with saturated NaHCO$_3$ and ice water. White solid, yield 91%; mp 143–144°C; IR: 1679 cm^{-1} (C=O); ^{1}H NMR (400 MHz, DMSO-d$_6$), δ, ppm: 1.20 d (6H, CH$_3$, J 6.7 Hz), 2.42 s (3H, CH$_3$), 4.95–5.09 m (1H, CH), 7.15 d (2H, H$^{2,6}_{Ph}$, J 8.0 Hz), 7.26–7.38 m (3H, H$_{Ph}$), 7.39–7.51 m (2H, H$_{Ph}$), 7.54–7.60 m (3H, H$_{Ph}$); LC-MS (CI), *m/z*: 233 [M+H]$^+$; Found,%: C 71.35; H 6.27; N, 17.44. $C_{19}H_{20}N_4O$. Calculated,%: C 71.23; H 6.29; N, 17.49.

Methyl 1,5-diphenyl-1*H*-1,2,3-triazole-4-carboxylate (7b). The 1,5-diphenyl-1*H*-1,2,3-triazole-4-carbonyl chloride (2.84 g, 10 mmol) was added to 25 mL of methanol. The mixture was heated under reflux for 30 min. The methanol was evaporated yielding ester **7b** quantitatively. White solid, mp 154-155°C; IR: 1716 cm^{-1} (C=O); ^{1}H NMR (400 MHz, DMSO-d$_6$), δ, ppm: 7.27-7.48 m (10H, H$_{Ph}$), 3.79 s (3H, CH$_3$O); LC-MS (CI), *m/z*: 280 [M+H]$^+$; Found,%: C, 68.89; H, 4.54; N, 15.14;. $C_{16}H_{13}N_3O_2$. Calculated,%: C, 68.81; H, 4.69; N, 15.05.

(5-Methyl-1-phenyl-1*H*-1,2,3-triazol-4-yl)methanol (8a). To a cooled to 0°C suspension of NaBH$_4$ (1.4 g, 37.8 mmol) in 250 mL THF iodine (4.4 g, 17.3 mmol) was added portion-wise. The mixture was maintained for 10 min after iodine was decoloured and the 5-methyl-1-phenyl-1*H*-1,2,3-triazole-4-carboxylic acid **6a** (2.0 g, 10 mmol) was added in one portion under vigorous stirring and slow heating to reflux. After heating for 5 h the mixture was cooled to room temperature. The conc. HCl (5 mL) and water (10 mL) was slowly added. The mixture was refluxed for 15 min and the solvent evaporated under reduced pressure. To the residue, the 20%-aq. NaOH solution was added to pH~10. Water was extracted with dichloromethane. The solvent was removed to give pure methanol **8a**. White solid, yield 84%; mp 224–225°C; IR: 1283 cm^{-1} (C–O); ^{1}H NMR (400 MHz, DMSO-d$_6$), δ, ppm: 2.31 s (3H, CH$_3$), 4.56 d (2H, CH$_2$, J 5.0 Hz), 5.15 t (1H, OH, J 5.0 Hz). 7.54-7.69 m (5H, H$_{Ph}$); LC-MS (CI), *m/z*: 190 [M+H]$^+$; Found,%: C 63.40; H 5.96; N, 22.29. $C_{10}H_{11}N_3O$. Calculated,%: C 63.48; H, 5.86; N, 22.21.

(1,5-Diphenyl-1*H*-1,2,3-triazol-4-yl)methanol (8b). To the solution of methyl 1,5-diphenyl-1*H*-1,2,3-triazole-4-carboxylate **7b** (1.3 g, 5 mmol) in 25 mL of THF at 0°C with vigorous stirring was added in

portions LAH (0.19 g, 0.05 mol) and left overnight. To cooled to 0°C mixture water (0.19 mL), 10%-aq. NaOH (0.38 mL) and water (0.19 mL) were added dropwise consequently. The mixture was stirred at room temperature for 15 min and filtered through SiO_2. The solvent was evaporated in vacuum yielding methanol **8b**. White solid, yield 95%; mp 128–129°C; ^1H NMR (400 MHz, DMSO-d6), δ, ppm: 4.50 d (2H, CH_2, J 5.4 Hz), 5.21 t (1H, OH, J 5.4 Hz), 7.28– 7.36 m (4H, H_{Ph}), 7.36–7.42 m (3H, H_{Ph}), 7.43–7.49 m (3H, H_{Ph}); LC-MS (CI), *m/z*: 252 $[M+H]^+$; Found,%: C, 71.77; H, 5.29; N, 16.73. $C_{15}H_{13}N_3O$. Calculated,%: C, 71.70; H, 5.21; N, 16.72.

This protocol allowed to obtain methanol **8a** from acid **6a** methyl ester or amide **7a**.

Synthesis of (1*H*-1,2,3-triazol-4-yl)acetic acids 5 (*Method B*). To the solution of corresponding (1*H*-1,2,3-triazol-4-yl)methanol **8** (10 mmol) in methylene chloride (25 mL) and Et_3N (2.0 mL, 14 mmol) at 0°C methane sulfonyl chloride (1.1 mL, 14 mmol) was added dropwise with vigorous stirring. The reaction was left at room temperature for 10 h. The reaction mixture was washed with water and the saturated sodium chloride solution. The organic layer was then dried with sodium sulfate and concentrated to yield methanesulfonate in quantitative yield, which was used without further purification. To the solution of the methanesulfonate in methanol (25 mL), potassium cyanide (1.3 g, 20 mmol) was added. The mixture was heated and water was added dropwise until all salts dissolved. The solution was refluxed for 5 h and KOH (1.7 g, 30 mmol) in water (10 mL) was added. The mixture was additionally refluxed for 3 h. Methanol was removed under reduced pressure and the residue was dissolved in a minimal quantity of water. The solution was extracted with MTBE and carefully acidified. The solid acid **5** was separated by filtration.

2-(5-Methyl-1-phenyl-1*H*-1,2,3-triazol-4-yl)acetic acid 5a. Yield 54%.

2-(1,5-Diphenyl-1*H*-1,2,3-triazol-4-yl)acetic acid 5k. White solid, yield 62%; mp 224–225°C (dec.); IR: 1722 (C=O), 1485, 990 cm^{-1}; ^1H NMR (400 MHz, DMSO-d6), δ, ppm: 3.62 s (2H, CH_2), 7.22–7.28 m (2H, H_{Ph}), 7.29–7.34 m (2H, H_{Ph}), 7.37– 7.42 m (3H, H_{Ph}), 7.42– 7.47 м (3H, H_{Ph}), 12.59 (s, 1H, COO*H*); LC-MS (CI), *m/z*: 280 $[M+H]^+$. Found,%: C, 68.71; H, 4.74; N, 15.13. $C_{16}H_{13}N_3O_2$. Calculated,%: C, 68.81; H, 4.69; N, 15.05.

2-Diazo-1-(1,5-diphenyl-1*H*-1,2,3-triazol-4-yl)ethan-1-one 7c. To the vigorously stirred solution of diazomethane (obtained from 3.8 g nitrosomethylurea and 14 mL 40%-aq. KOH) in MTBE (45 mL) at -10°C, 1,5-diphenyl-1*H*-1,2,3-triazole-4-carbonyl chloride (2.8 g, 10 mmol) was added. The mixture was left overnight and then cooled to -10ºC to filter the formed diazoketone. Light yellow solid, yield 74%; mp 96°C (dec.); IR: 2150 (C=N_2), 1661 (C=O), 1504, 1432, 1211cm^{-1}; ^1H NMR (400 MHz, DMSO-d6), δ, ppm: 6.77 s (1H, C*H*N_2). 7.25–7.54 m (10H, H_{Ph}); LC-MS (CI), *m/z*: 261 $[M+H-N_2]^+$; Found,%: C, 66.47; H, 3.78; N, 24.27. $C_{16}H_{11}N_5O$. Calculated,%: C, 66.43; H, 3.83; N, 24.21.

2-(1,5-Diphenyl-1*H*-1,2,3-triazol-4-yl)acetic acid 5k (*Method C*). The diazoketone **7c** (1.7 g, 5.6 mmol) dissolved in 15 mL of dioxane and gently heated to 70ºC with vigorous stirring. To the mixture, 15%-aq. solution of $AgNO_3$ (1.5 mL) and 7.5 mL of ammonia solution was added. Rapid gas release started. The mixture was refluxed for 3 h and the solvent was evaporated. The residue was dissolved in ethanol (50 mL) and KOH (1.7 g, 30 mmol) was added. The solution was heated under reflux for 5 h. After ethanol was removed, water (15 mL) was added and the solution was washed with MTBE and acidified with conc. HCl. The solid acid was separated by filtration, washed with water and diluted alcohol. Yield 23%.

Synthesis of (5-methyl-1-aryl-1*H*-1,2,3-triazol-4-yl) ethanols 9a-c. To a solution of the corresponding (1,2,3-triazol-4-yl)ethanone **3** (4 mmol) in methanol (20 mL), sodium borohydride (0.15 g; 0.04 mol) was carefully added in small portions. The mixture was refluxed for 2 h. Thereafter, 10 mL of isopropanol was added and the mixture was heated for one more hour. The solvent was removed at reduced pressure. Water (20 mL) was added and solid was filtered off and air-dried. The products were formed pure and did not require additional crystallization.

1-(5-Methyl-1-phenyl-1*H*-1,2,3-triazol-4-yl)ethanol (9a). White solid, yield 89%, mp 117–118°C; IR: 1476, 1283, 995, 790 cm^{-1}; ^1H NMR (400 MHz, DMSO-d6), δ, ppm: 1.52 d (3H, CH_3, J 6.4 Hz), 2.35 s (3H, CH_3), 4.91 m (1H, CH), 5.02 d (1H, OH, J 3.9 Hz), 7.48–7.63 (m, 5H, H_{Ph}); LC-MS (CI), *m/z*: 190 $[M+H]^+$; Found,%: C 65.20; H, 6.30; N, 20.51. $C_{11}H_{13}N_3O$. Calculated,%: C 65.01; H, 6.45; N, 20.68.

1-(1-(3-Chloro-4-methoxyphenyl)-5-methyl-1*H*-1,2,3-triazol-4-yl)ethanol (9b). White solid, yield 93%; mp 135–136°C; IR: 1497, 1293, 1033, 998, 806, 720 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d$_6$), δ, ppm: 1.51 s (3H, CH$_3$, J 6.8 Hz), 2.32 s (3H, CH$_3$), 3.98 s (3H, CH$_3$O), 4.89 m (1H, CH), 5.01 d (1H, OH, J 3.9 Hz), 7.29 d (1H, H^5$_{Ar}$, J 8.7 Hz), 7.45 dd (1H, H^6$_{Ar}$, J 8.7, 2.0 Hz), 7.55 d (1H, H^2$_{Ar}$, J 2.0 Hz); LC-MS (CI), *m/z*: 268 [M+H]$^+$; Found,%: C 53.68; H, 5.19; N, 15.82. C$_{12}$H$_{14}$ClN$_3$O$_2$. Calculated,%: C 53.84; H, 5.27; N, 15.70.

6,6-Dimethyl-1-phenyl-4,5,6,7-tetrahydro-1*H*-benzo[*d*][1,2,3]triazol-4-ol (9c). White solid, yield 95%; mp 199–200°C; IR: 1464, 1280, 998 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d$_6$), δ, ppm: 0.88 s (3H, CH$_3$). 1.07 s (3H, CH$_3$), 1.46–1.71 s (1H, CH$_2$), 1.84–1.97 s (1H, CH$_2$), 2.69 s (2H, CH$_2$), 4.56–4.92 m (1H, CH), 5.40 s (1H, OH), 7.31–7.99 m (5H, H$_{Ph}$); LC-MS (CI), *m/z*: 244 [M+H]$^+$; Found,%: C 69.03; H, 7.08; N, 17.21. C$_{14}$H$_{17}$N$_3$O. Calculated,%: C 69.11; H, 7.04; N, 17.27.

1-(5-Methyl-1-phenyl-1*H*-1,2,3-triazol-4-yl)ethanone oxime (10). To the solution of (1,2,3-triazol-4-yl)ethanone **3a** (2.0 g, 10 mmol) in ethanol (10 mL), solutions of hydroxylamine hydrochloride (0.76 g, 0.011 mol) in water (5 mL) and sodium hydroxide (0.44 g, 0.011 mol) in water (5 mL) were added. The mixture was refluxed for 2 h. The precipitate was filtered off. White solid, yield 95%; mp 185–186°C; IR: 1692, 1499, 1418, 1260, 976, 920, 759, 694 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d$_6$), δ, ppm: 2.29 s (3H, CH$_3$), 2.43 s (3H, CH$_3$), 7.62 br.s (5H, H$_{Ph}$), 11.33 s (1H, OH). ^{13}C NMR (101 MHz, DMSO-d$_6$), δ, ppm: 11.14 (CH$_3$), 12.65 (CH$_3$), 125.95 (2xCH^{2,6}$_{Ar}$), 130.31 (2xCH^{3,5}$_{Ar}$), 130.38 (CH^4$_{Ar}$), 132.16 (C^5$_{Triazole}$), 136.36 (C^1$_{Ar}$), 141.87 (C^4$_{Triazole}$), 149.70 (C=N); LC-MS (CI), *m/z*: 217 [M+H]$^+$; Found,%: C 61.06; H, 5.52; N, 25.99. C$_{11}$H$_{12}$N$_4$O. Calculated,%: C 61.10; H, 5.59; N, 25.91.

1-(5-Methyl-1-phenyl-1*H*-1,2,3-triazol-4-yl)ethanamine (11). The solution of oxime **10** (1.4 g, 6.3 mmol) in tetrahydrofuran (25 mL) was added dropwise to a stirred suspension of the aluminium amalgam in tetrahydrofuran (15 mL) [prepared according to the following procedure: aluminium turnings (8.00 g, 0.297 mol) washed (10-15 s) with solution of sodium hydroxide (1M, 10mL) resulting in the evolution of hydrogen gas and the solution was decanted; the aluminium washed with water (10 mL); an aqueous solution of mercury (II) chloride (0.5%, 5 mL) was then added to aluminium and allowed to stand for 1-2 min. This procedure was repeated, and the aluminium was washed with water (10 mL), absolute ethanol (10 mL), and dry TBME (10 mL)]. A few drops of water were carefully added to the reaction mixture and the reaction was stored keeping temperature below ca. 50°C by periodically immersing the flask in cool water. After 4 h, the reaction mixture was filtered through SiO$_2$. The solvent was removed under reduced pressure to yield light yellow viscous oil. Yield 79%; IR: 2930, 1484, 1160, 986 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d$_6$), δ, ppm: 1.39 d (3H, CH$_3$, J 6.7 Hz), 1.81 br.s (2H, NH$_2$), 2.31 s (3H, CH$_3$), 4.14 q (1H, CH, J 6.5 Hz), 7.31–7.70 m (5H, H$_{Ph}$); LC-MS (CI), *m/z*: 203 [M+H]$^+$. Found%: C 65.39; H 6.93; N 27.76. C$_{11}$H$_{14}$N$_4$ Calculated,%: C 65.32; H 6.98; N 27.70.

Synthesis of chalcones 13. The corresponding (1,2,3-triazol-4-yl)ethanone **3** (7.5 mmol) dissolved in a minimum amount of ethanol was added to 10% solution of sodium hydroxide cooled to 0°C. Next aldehyde (**12**, 7.5 mmol) was added dropwise and the reaction mixture was left overnight. The precipitate was filtered off, washed with water and recrystallized from an ethanol-DMF mixture.

(E)-1-(5-Methyl-1-phenyl-1*H*-1,2,3-triazol-4-yl)-3-phenylprop-2-en-1-one   (13a).   Prepared previously.[15]

(E)-3-(2-Hydroxyphenyl)-1-(5-methyl-1-phenyl-1*H*-1,2,3-triazol-4-yl)prop-2-en-1-one(13b). White solid, yield 84%; mp 194–195°C; IR: 1664 (C=O), 1611 (C=C), 1493, 1023, 997 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d$_6$), δ, ppm: 2.60 s (3H, CH$_3$), 6.90 t (1H, H^5$_{Ar}$, J 7.2 Hz), 6.97 d (1H, H^6$_{Ar}$, J 6.7 Hz) , 7.29 t (1H, H^4$_{Ar}$, J 7.2 Hz), 7.55–7.77 (m, 7H), 8.02–8.18 m (2H), 10.35 s (1H, OH). LC-MS (CI), *m/z*: 203 [M+H]$^+$. Found,%: C 70.79; H, 5.10; N, 13.91. C$_{18}$H$_{15}$N$_3$O$_2$. Calculated,%: C 70.81; H 4.95; N, 13.76.

(2E,4E)-1-(1-(3-chloro-4-methoxyphenyl)-5-methyl-1*H*-1,2,3-triazol-4-yl)-5-phenylpenta-2,4-dien-1-one (13c). White solid, yield 88%; mp 154–155°C; IR: 1670 (C=O), 1618, 1608 (C=C), 1499, 1281, 990 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d$_6$), δ, ppm: 2.56 s (3H, CH$_3$), 3.97 s (3H, CH$_3$O), 7.25 d (1H, CH =, J 15.5 Hz), 7.32–7.46 m (5H), 7.57 g (1H, CH =, J 14.9 Hz), 7.59–7.74 m (4H), 7.84 s (1H, H^2$_{Ar}$); LC-MS (CI), *m/z*: 380 [M+H]$^+$; Found,%: C 66.52; H 4.70; N, 11.01. C$_{21}$H$_{18}$ClN$_3$O$_2$. Calculated,%: C 66.40; H, 4.78; N, 11.06.

(5-Methyl-1-phenyl-1*H*-1,2,3-triazol-4-yl)(2-phenylcyclopropyl)methanone (14). To a KOH suspension (1.2 g, 20 mmol) in dimethyl sulfoxide (40 mL), trimethylsulfoxonium iodide (5.6 g, 20 mmol) was gradually added and the mixture was stirred for 30 min. Then chalcone (**13a**, 2.5 g, 10 mmol) was added and the mixture was left for 7 h. Stirred for 1 h at 50°C and then a small amount of water was added. The solvent was removed in vacuum. The residue was mixed with water and filtered. The solid was washed with water (100 mL) and the saturated aqueous sodium chloride solution (20 mL) to give the title compound **14**. White solid, yield 89%; mp 81–82°C; IR: 1661 (C=O), 1498, 1420, 1092, 1032, 975, 744, 690 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d$_6$), δ, ppm: 1.65–1.73 td (1H, c-Pr, J 7.5, 4.4 Hz), 1.76–1.83 dt (1H, c-Pr, J 9.8 , 4.7 Hz), 2.55 s (3H, CH$_3$), 2.59–2.66 m (1H, c-Pr), 3.43– 3.51 m (1H, c-Pr), 7.24 t (1H, H$_{Ph}$, J 6.8 Hz), 7.28 d (2H, H$^{2,6}_{Ph}$, J 7.4 Hz), 7.33 t (2H, H$^{3,5}_{Ph}$, J 7.3 Hz), 7.61–7.70 m (5H, H$_{Ph}$); LC-MS (CI), *m/z*: 304 [M+H]$^+$; Found,%: C 75.29; H, 5.72; N, 13.81. C$_{19}$H$_{17}$N$_3$O. Calculated,%: C 75.23; H, 5.65; N, 13.85.

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