Synthesis and evaluation of β-hydroxytriazoles and related compounds as antitubercular agents

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A new series of β-hydroxytriazoles were synthesized and evaluated as *Mycobacterium tuberculosis* inhibitors. Our strategy implied the synthesis of alkyne precursors through a Barbier reaction between benzaldehydes and propargyl bromide followed by click chemistry to afford substituted β-hydroxyl benzyltriazoles. These compounds are also key intermediates either for oxidation reactions leading to α,β-diketotriazoles or for elimination reactions affording styryl triazoles. Evaluation of all new compounds for *in vitro* antitubercular activity against *Mycobacterium tuberculosis* H37Rv resulted in compounds with MIC up to 7 μM.

Introduction

Tuberculosis (TB) is a highly contagious bacterial disease. It remains with malaria and AIDS, one of the biggest causes of death worldwide. For illustration, around 2 million deaths occur each year as a result of this disease [1]. Tuberculosis is caused by *Mycobacterium tuberculosis* (*Mtb*), and current chemotherapeutic treatments are based on the use of antibiotics, the most important are: isoniazid (INH), rifampicin, pyrazinamide, ethambutol and streptomycin. Their efficiency was severely compromised by the emergence of multi- and extensively drug-resistant tuberculosis [2]. In the last 10 years, the research on *M. tuberculosis* has progressed with the genome unrevealed, facilitating the discovery of new targets [3]. Nevertheless, there is an urgent need for new anti-TB drug candidates.

Azole derivatives showed high potency as antimycobacterial drugs [4]. Among them, econazole was very promising to replace the most potent frontline antitubercular drugs namely rifampicin and isoniazid [5]. Recently, different groups reported the synthesis of 1*H*-1,2,3-triazoles derived from econazole as antitubercular agents [6-7]. Among them, nine hydroxyl-triazoles were evaluated and particularly one compound bearing a *n*-butyl substituent at position 4 of the triazole (Figure 1, middle) showed the best activity with a MIC of 25 μM. Our group also reported the synthesis of triazole derivatives and their evaluation as *M.tb* inhibitors [8-11]. Among them, several compounds showed interesting MIC values when tested against *M.tb* and *M.tb* antibiotic-resistant strains.

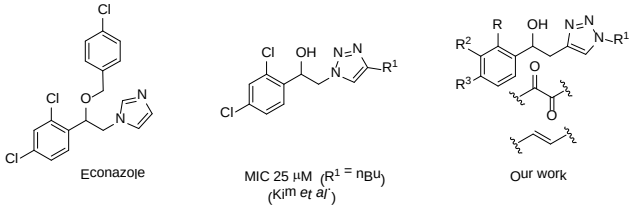


Figure 1. Left: Econazole. Middle: Hydroxyl-triazoles tested on *Mycobacterium tuberculosis* H37Rv strain (Kim *et al*., 2012); Right: Our work: β-hydroxytriazole and related scaffolds with modifications on indicated sites (R, R^1, R^2 and R^3)

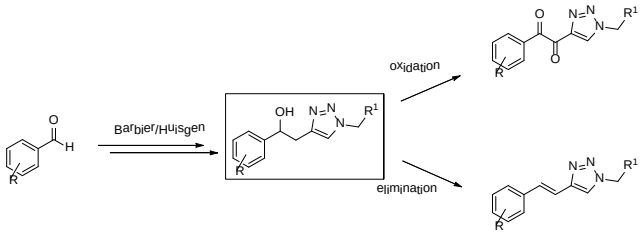
In continuation of our research on the synthesis of biologically active heterocycles against tuberculosis [8,10-12], we wish to report the synthesis and the evaluation of a wide range of β-hydroxytriazole derivatives against *M.tb* H37Rv (Figure 1, right). This work also described the antitubercular activities of a new series of α,β-diketotriazoles and styryl triazoles synthesized conveniently from the corresponding β-hydroxytriazoles.

Results and discussion

Chemistry

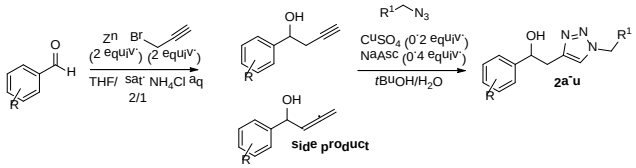
As shown in Scheme 1, β-hydroxytriazoles are synthesized in two steps from commercially available benzaldehydes according to a two-step procedure. α,β-Diketotriazoles and styryltriazoles could be obtained accordingly by oxidation or elimination of the β-hydroxytriazoles.

It has to be noted that this method is more convenient for obtaining α,β-diketotriazoles, the number of commercially available benzaldehydes being significantly higher than that of phenyl acetic acid derivatives [9].



Scheme 1 Strategy for the synthesis of the desired β-hydroxytriazoles, precursors of α,β-ketotriazoles and styryl derivatives.

Adopting this synthetic strategy, the first step was the Barbier condensation of propargyl bromide with different commercial benzaldehydes in the presence of zinc in a solution of THF/NH_4Cl (2/1) (Scheme 2). However, the alkyne product was always accompanied, even after flash chromatography purification, by a side product identified as the corresponding ketene (<5% after purification). The triazole intermediates were then readily available by copper-catalyzed alkyne-azide cycloaddition reaction (CuAAC) [13-14]. The results are shown in Table 1. The yields remained good regardless of the different alkyl or benzyl groups bearing various electron-donating or electron-withdrawing substituents.



Scheme 2 General synthesis of the triazole alcohols.

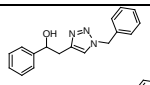
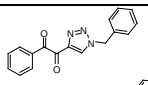
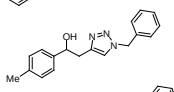
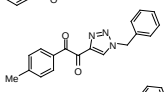
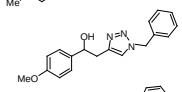
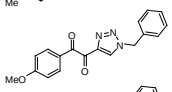
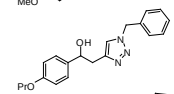
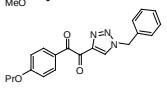
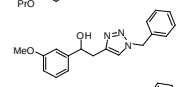
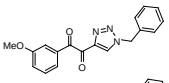
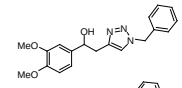
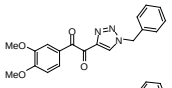
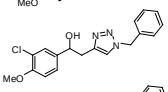
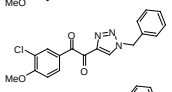
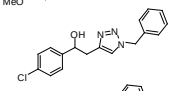
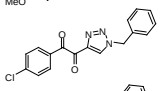
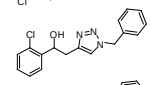
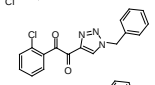
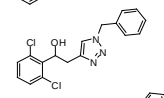
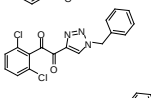
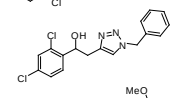
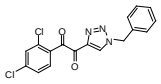
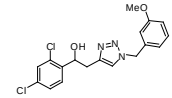
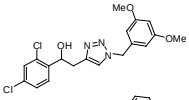
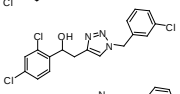
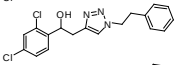
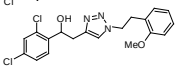
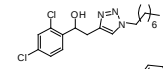
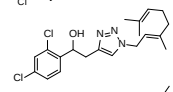
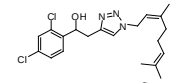
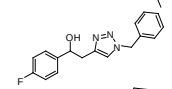
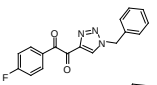
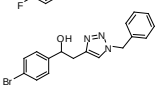
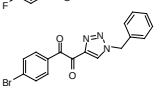
In the case of the synthesis of compounds **2r** and **2s**, the corresponding azides were obtained from commercially available *Z* and *E* mixture of geranyl bromide (20% *Z* isomer by ^{1}H NMR). Then "click" products **2r** and **2s** were isolated with both stereochemistries *Z* and *E*, separable by flash chromatography.

The oxidation of the alcohol derivatives was also investigated to afford α,β-diketotriazoles in one step. A quick check in the literature showed that the conversion of 1,2-diphenylethanol derivatives to the corresponding diketone compound was not fully exploited. Indeed, a few examples showed the formation of benzil analogues through this pathway. In 2011, Urgoitia *et al*. used two palladacycles in the presence of molecular oxygen in PEG-400, a sustainable reaction media [15]. With a different substrate, diketone product could be obtained also when either MnO_2 or $Pd(OAc)_2$ was employed as the oxidant [16]. In a different way, 4,7-di-*tert*-butyl-acenaphthen-1-ol was oxidized to diketone in the presence of SeO_2 (13.5 equiv.) in dioxane under reflux [17].

We used alcohol **2a** as a model compound to examine the feasibility of a fully complete oxidation reaction to obtain α,β-diketotriazoles. The results are described in Table 2.

While oxidants like PCC, MnO_2, Döering reagent, CuI/TBHP afforded the desired product only in low or very low yields, 2-iodoxybenzoic acid (IBX) was found to allow the complete conversion of the starting alcohol compound within 2 h (Table 2). The α,β-diketo-derivative was isolated in 64% yield (table 2, entry 5).

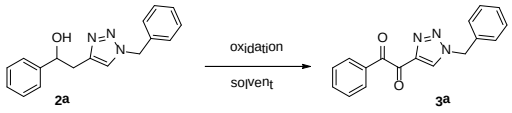
Table 1 Synthesis of triazoles.

	Alcohols	Yield (%)		Diketones	Yield (%)
2a		70	**3a**		65
2b		62	**3b**		78
2c		64	**3c**		35
2d		40	**3d**		35
2e		71	**3e**		26
2f		75	**3f**		Mixture
2g		70	**3g**		49
2h		71	**3h**		61
2i		76	**3i**		82
2j		53	**3j**		83
2k		67	**3k**		74
2l		58	**3l**	Not performed	---
2m		68	**3m**	Not performed	---
2n		55	**3n**	Not performed	---
2o		80	**3o**	Not performed	---
2p		86	**3p**	Not performed	---
2q		65	**3q**	Not performed	---
2r		27	**3r**	Not performed	---
2s		17	**3s**	Not performed	---
2t		72	**3t**		50
2u		78	**3u**		67

A higher amount of IBX did not permit to increase the yield of the reaction (entry 7), while, changing the solvent for DMSO led to a much lower yield (28%) (entry 6). The generation of IBX *in situ* with 2-iodobenzoic acid (2IBA, 0.6 eq) and oxone (2.4 eq) afforded the oxidation product in 65% (entry 9).

Finally, decreasing the quantity of reactants or lowering the temperature is detrimental to the yield, even after 20 h (entries 8, 10). With this method in hand (entry 9), several β-alcohols were oxidized allowing the obtention of the corresponding α,β-diketotriazoles in good yields as shown in Table 1. However, in the presence of alkoxy substituents on the aromatic moiety, the reaction led to the desired diketo compounds **3c**-**3e** and **3g** in poor yields. Furthermore, the product **3f** bearing 3,4-dimethoxy substituents was not observed.

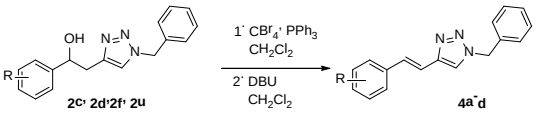
Table 2 Screening of reaction conditions for the oxidation to α,β-diketotriazole.

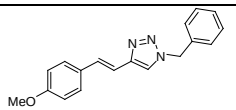
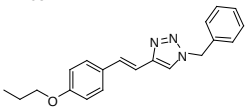
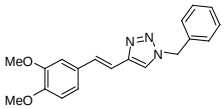
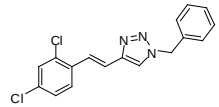
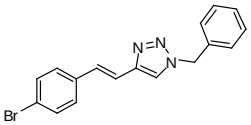


Entry	Oxidant	Solvent	Conditions	Yield (%)
1	PCC (2 eq)	CH_2Cl_2	RT, 4 h	23
2	MnO_2 (6 eq)	CH_3CN	Reflux, 7 h	18
3	Doering	CH_3CN	Reflux, 3 h	6
4	CuI (0.1 eq), TBHP (2 * 4 eq)	CH_3CN	Reflux, 20 h	12
5	IBX (1.5 eq)	CH_3CN	70°C, 20 h	64
6	IBX (1.5 eq)	DMSO	70°C, 20 h	28
7	IBX (3 eq)	CH_3CN	70°C, 20 h	60
8	2IBA (0.3 eq) + oxone (1.2 eq)	CH_3CN/H_2O (2/1)	70°C, 7 h	30
9	2IBA (0.6 eq) + oxone (2.4 eq)	CH_3CN/H_2O (2/1)	70°C, 3 h	65
10	2IBA (0.6 eq) + oxone (2.4 eq)	CH_3CN/H_2O (2/1)	50°C, 20 h	53

Styryl triazole derivatives are scaffolds possessing various biological properties. For example, they were evaluated as potential ligands for angiogenic growth factors FGF-1, FGF-2 and VEGF [18] but also as candidates for β-amyloid (Aβ) plaque imaging [19]. The synthesis of styryl derivatives **4a-e** was performed in two steps from the corresponding alcohol as shown in Table 3. Formation of the bromide derivative combining triphenyl phosphine and carbon tetrabromide with **2**, followed by an elimination step using DBU at room temperature afforded **4a-4e** in good yields.

Table 3 Synthesis of styryl derivatives.



Compounds	Yield (%)[a]
4a 	37
4b 	82
4c 	25
4d 	52
4e 	73

The assignment of *E* stereochemistry for all styryl compounds was based on the $J_{CH=CH}$ coupling constant of 16-17 Hz.

Biology

Bacterial growth experiments against M. tuberculosis H37Rv strain

The minimal inhibitory concentration (MIC) values (μg/mL and μM) of all of the synthesized compounds and one standard antitubercular drug (Isoniazid) were determined in triplicate and are shown in Table 4.

Looking first to the results of triazole alcohol systems we evaluated the influence of the substitution on the aromatic ring of the benzyl hydroxyl frame. Among the alkyl or alkoxy substituents the best activity was observed for the compound bearing a *p*-propoxy one (**2d**) with a MIC of 14 μM. Halogenation of the aromatic ring leads to compounds with activities depending on the positioning of the halogen. Thus when only the positions 4 (**2h, 2t, 2u**) or 2 (**2i**) or 2,6 (**2j**) of the aromatic ring are halogenated, the activity is weak whatever the halogen. In fact, compounds bearing a 2,4 dichloro substitution on the aromatic ring presented the best inhibitory activities. This indicates the strong influence of the 2,4-dichloro substitution on the MIC activities of all compounds tested, the best inhibitor in this series showing a MIC of 7.2 μM (**2k**).

Upon examining the different systems attached to the nitrogen atom of the triazole frame, we can notice that any substitution on the benzylic frame is detrimental to the activity. This is also the case for compound **2q** bearing a lipophilic C-8 chain. Finally, the best result was obtained for compound **2s**, bearing the *Z*-geranyl chain. It is noteworthy to point out that the *E*-geranyl analogue is much less active. All these results indicate the fine tuning and the great susceptibility upon activity for any substitution on the nitrogen atom of the triazole frame. Considering the diketo compounds, we can observe that substitution pattern is not as crucial as before.

Table 4 Compounds tested as inhibitory agents of *M. tuberculosis* growth.

Cpds	MIC (μg/ml)/(μM)	Cpds	MIC (μg/ml)/(μM)
2a	>40/>135.4	**3a**	40/130.1
2b	10/32.3	**3b**	40/124.5
2c	>40/>122.9	**3c**	5/15.6
2d	5/14.1	**3d**	40/109.4
2e	>40/>122.9	**3e**	40/118.5
2f	40/112.5	**3f**	---
2g	40/111.7	**3g**	20/53.8
2h	>40/>121.3	**3h**	40/117.0
2i	20/60.64	**3i**	20/60.64
2j	40/109.8	**3j**	20/53.1
2k	2.5/7.2	**3k**	5/13.9
2l	>20/>52.9	**3l**	---
2m	20/49	**3m**	4/9.5[a]
2n	20/52.3	**3n**	---
2o	20/51	**3o**	5/13.4[a]
2p	20/55.2	**3p**	---
2q	20/54	**3q**	32/80.7[a]
2r	5/12.7	**3r**	---
2s	>20/>50.7	**3s**	---
2t	40/127.6	**3t**	40/123.0
2u	20/53.4	**3u**	40/103.5
isoniazid	0.05/0.4		

[a.] Reference [11]

In fact, the benzylic moiety can afford substituents on the aromatic ring such as methoxy, 2,4-dichloro, but also substituents on

the *N*-1 position of the triazole such as substituted benzylic, phenylethyl and still maintain good inhibitory activity. In that respect, the diketo compounds can afford more flexibility concerning the substitution on both sides of the triazole ring than the corresponding triazolo alcohol derivatives.

Table 5 Activities of the styryl derivatives.

Cpds	MIC (μg/ml)/(μM)
4a	40/112.2
4b	10/28.9
4c	>40/>125.2
4d	>40/>118.5
4e	>40/>130.1

The styryl triazole derivatives were also evaluated. The results showed that they are not good inhibitors of *M. tuberculosis* excepted for compound **4b** with a MIC of 29 μM, bearing the *n*-propoxy substituent on the aromatic ring. It is also noteworthy to point out that the 2,4-dichloro compound is not active while the corresponding hydroxyl and diketo analogue possess good MIC values.

Cytotoxicities of some selected compounds

Finally, the cytotoxicity of three different compounds was evaluated on two human cell lines, the colon cancer cell line HCT116 and the fibroblast cell line GM637 (Table 6). The two alcohols **2d** and **2k** are not cytotoxic when tested at 100 μM. For comparison with **2k**, the diketo and the styryl derivatives **3k** and **4b** have no cytotoxicity below 50 μM.

Table 6 Cytotoxicities of compounds **2d**, **2k** and **3k.**

Cpds	IC_{50} (μM) HCT116 strain	IC_{50} (μM) GM637H strain
2d	>100	>100
2k	>100	>100
3k	>50	>50
4b	$50 < IC_{50} < 100$	$50 < IC_{50} < 100$

Conclusions

In summary, the synthesis of a new series of β-hydroxytriazole, α,β-diketotriazole and styryl derivatives and their evaluation as antitubercular inhibitors are reported. Additionally, a convenient method to afford α,β-diketotriazoles from β-hydroxytriazoles was developed in which the key step was the double oxidation of the benzylic moieties using IBX generated *in situ* as oxidant. The antimicrobial activities against *M. tuberculosis* H37Rv of all compounds showed selective trends on the substitution patterns of the triazole ring for the benzylic compounds and to a much lesser extent to the diketo ones. Several derivatives displayed promising MIC values in the range of 7-15 μM with best one (**2k**) at 7.2 μM.

Experimental section/Computational details

Material

All chemicals were obtained from Aldrich or Acros Organics and used without further purification. Nuclear magnetic resonance spectra were recorded on a Bruker AC 300 spectrometer (^{1}H and ^{13}C NMR). Mass spectrometry (MS) data were obtained on a ThermoQuest TSQ 7000 spectrometer, high-resolution mass spectra (HRMS) were performed on a ThermoFinnigan MAT 95 XL spectrometer using electrospray ionization

(ESI) methods. IR spectra were recorded on a Perkin Elmer 1725.

Synthesis and characterizations

Synthesis of 1-phenylbut-3-yn-1-ol derivatives:

Zinc (9.4 mmol, 2 eq) was added to a solution of benzaldehyde (4.7 mmol, 1 eq) and propargyl bromide (9.4 mmol, 2 eq) in a mixture (2/1) of THF and a solution of saturated aqueous NH_4Cl. The reaction was stirred vigorously at room temperature for 5 h. Then the reaction mixture was diluted with AcOEt and washed with H_2O. The solvent was dried with $MgSO_4$, filtered and evaporated under reduced pressure. The desired product was purified on a silica gel column by flash chromatography. These compounds are known for most of them and the spectroscopic data match those reported (1-phenylbut-3-yn-1-ol (**1a**, 60%) [20], 1-(4-methylphenyl)but-3-yn-1-ol (**1b**, 66%) [21], 1-(4-methoxyphenyl)but-3-yn-1-ol (**1c**, 48%) [20], 1-(3-methoxyphenyl)but-3-yn-1-ol (**1d**, 60%) [20], 1-(3,4-dimethoxyphenyl)but-3-yn-1-ol (**1f**, 41%) [22], 1-(4-chloropheny)but-3-yn-1-ol (**1h**, 75%) [20], 1-(2-chloropheny)but-3-yn-1-ol (**1i**, 24%) [20], 1-(2,6-dichlorophenyl)but-3-yn-1-ol (**1j**, 74%) [23], 1-(2,4-dichlorophenyl)but-3-yn-1-ol (**1k**, 88%) [20], 1-(4-fluorophenyl)but-3-yn-1-ol (**1t**, 23%) [21], 1-(4-bromophenyl)but-3-yn-1-ol (**1u**, 78%) [23]. The synthesized products were used as such for the next reaction (presence of α-allenol <5-10% by ^1H NMR).

1-(4-Propoxyphenyl)but-3-yn-1-ol (**1e**).

Yield: 57%. ^1H NMR ($CDCl_3$) δ 7.26 (d, *J* = 8.4 Hz, 2H); 6.86 (d, *J* = 8.7 Hz, 2H); 4.78 (t, *J* = 6.3 Hz, 1H); 3.90 (t, *J* = 6.6 Hz, 2H); 2.62 (m, 2H); 2.04 (t, *J* = 2.6 Hz, 1H); 1.79 (m, 2H); 1.03 (t, *J* = 7.4 Hz, 3H).

1-*(3-Chloro-4-methoxyphenyl)but-3-yn-1-ol* (**1g**).

Yield: 61%. ^1H NMR ($CDCl_3$) δ 7.33 (d, *J* = 2.2 Hz, 1H); 7.16 (dd, *J* = 8.5 Hz, 2.1 Hz, 1H); 6.84 (d, *J* = 8.5 Hz, 1H); 4.71 (t, *J* = 6.3 Hz, 1H); 3.83 (s, 3H); 2.99 (br s, 1H); 2.53 (dd, *J* = 6.4 Hz, 2.6 Hz, 2H); 2.04 (t, *J* = 2.6 Hz, 1H).

Procedure for the synthesis of triazole derivatives:

$CuSO_4$ (0.2 equiv) and sodium ascorbate (0.4 equiv) were added to a solution of alkyne (0.7 mmol, 1 eq) and azide (0.84 mmol, 1.2 eq) in *t*BuOH/H_2O (1/1) at room temperature. Then the reaction mixture was diluted with AcOEt and washed with H_2O. The solvent was dried with $MgSO_4$, filtered and evaporated under reduced pressure. The desired product was purified on a silica gel column by flash chromatography.

*2-(1-Benzyl-1H-1,2,3-triazol-4-yl)-1-phenylethanol (***2a***).*

White powder. Yield 70%. M.p. 104 °C. M.p.:102 °C. IR (neat, ν/cm^{-1}) 3238; 3119; 1551; 1454; 1425; ^1H NMR ($CDCl_3$) δ 7.12-7.31 (m, 11H); 5.38 (d, *J* = 14.9 Hz, 1H); 5.32 (d, *J* = 14.9 Hz, 1H); 4.96 (t, *J* = 6.3 Hz, 1H); 3.95 (br s, 1H); 3.03 (d, *J* = 6.3 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 145.0; 143.5; 134.6; 128.8; 128.4; 128.1; 127.7; 127.2; 125.6; 122.1; 72.8; 53.7; 35.3; HRMS: (DCI/CH_4, m/z) calc. for $C_{17}H_{18}N_3O$:280.1450. Found: 280.1444.

*2-(1-Benzyl-1H-1,2,3-triazol-4-yl)-1-p-tolylethanol (***2b***).*

White powder. Yield 62%. M.p.: 105 °C. IR (neat, ν/cm^{-1}) 3150; 2921; 1606; 1558; 1497; 1452; ^1H NMR ($CDCl_3$) δ 7.34 (m, 3H); 7.19 (m, 5H); 7.09 (d, *J* = 7.9 Hz, 2H); 5.47 (d, *J* =

14.9 Hz, 1H); 5.41 (d, *J* = 14.9 Hz, 1H); 4.97 (t, *J* = 6.3 Hz, 1H); 3.39 (br s, 1H); 3.05 (d, *J* = 6.3 Hz, 2H); 2.31 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 145.2; 140.6; 137.0; 134.6; 128.93; 128.90; 128.5; 127.8; 125.6; 122.0; 72.9; 53.9; 35.4; 21.0; HRMS: (DCI/CH_4, m/z) calc. for $C_{18}H_{20}N_3O$: 294.1606. Found: 294.1609.

*2-(1-Benzyl-1H-1,2,3-triazol-4-yl)-1-(4-methoxyphenyl)ethanol (***2c***).*

White powder. Yield 64%. M.p.: 92 °C. IR (neat, ν/cm^{-1}) 3126; 1610; 1584; 1510; 1248; ^{1}H NMR ($CDCl_3$) δ 7.32 (m, 3H); 7.22 (d, *J* = 8.7 Hz, 2H); 7.17 (m, 3H); 6.81 (d, *J* = 8.6 Hz, 2H); 5.43 (d, *J* = 8.6 Hz, 2H); 5.46 (d, *J* = 15.1 Hz, 1H); 5.4 (d, *J* = 15.1 Hz, 1H); 4.96 (br s, 1H); 3.76 (s, 3H); 3.56 (br s, 1H); 3.03 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 158.8; 135.8 (br.); 134.7; 128.9; 128.5; 127.8; 126.9; 113.6; 72.7; 55.1; 53.9; 35.4; HRMS: (DCI/CH_4, m/z) calc. for $C_{18}H_{20}N_3O_2$: 310.1556. Found: 310.1556.

*2-(1-Benzyl-1H-1,2,3-triazol-4-yl)-1-(4-propoxyphenyl)ethanol (***2d***).*

White powder. Yield 40%. M.p.: 99 °C. IR (neat, ν/cm^{-1}): 3215; 3215; 2919; 1609; 1509; 1242; ^{1}H NMR ($CDCl_3$) δ 7.35 (m, 3H); 7.23 (m, 5H); 6.83 (d, *J* = 8.7 Hz, 2H); 5.48 (s, 2H); 4.99 (t, *J* = 6.1 Hz, 1H); 3.90 (t, *J* = 6.6 Hz, 2H); 3.06 (d, *J* = 6.2 Hz, 2H); 1.80 (m, 2H+1H); 1.03 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 158.5; 145.3; 135.5; 134.7; 129.0; 128.6; 127.9; 126.9; 122.0; 114.3; 72.8; 69.4; 54.0; 35.4; 22.5; 10.5; HRMS: (DCI/CH_4, m/z) calc. for $C_{20}H_{24}N_3O_2$: 338.1869. Found: 338.1879.

*2-(1-Benzyl-1H-1,2,3-triazol-4-yl)-1-(3-methoxyphenyl)ethanol (***2e***).*

White powder. Yield 71%. M.p. 73 °C. IR (neat, ν/cm^{-1}) 3343; 3124; 1611; 15861493; 1432; 1266; ^{1}H NMR ($CDCl_3$) δ 7.32 (m, 3H); 7.19 (m, 4H); 6.89 (d, *J* = 2.1 Hz, 1H); 6.86 (d, *J* = 7.6 Hz, 1H); 6.76 (dd, *J* = 8.1 Hz, 2.7 Hz, 1H); 5.44 (d, *J* = 15.0 Hz, 1H); 5.38 (d, *J* = 15.0 Hz, 1H); 4.96 (t, *J* = 6.3 Hz, 1H); 3.73 (s, 3H); 3.38 (br s, 1H); 3.04 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 159.5; 145.3; 145.0; 134.6; 129.2; 128.9; 128.5; 127.8; 122.1; 118.0; 113.0; 11.0; 72.9; 55.0; 53.8; 35.3; HRMS: (DCI/CH_4, m/z) calc. for $C_{18}H_{20}N_3O_2$: 310.1556. Found: 310.1549.

*1-(1-Benzyl-1H-1,2,3-triazol-4-yl)-2-(3,4-dimethoxyphenyl)ethanol (***2f***).*

Brown gum. Yield 75%. IR (neat, ν/cm^{-1}) 2935; 2835; 1593; 1516; 1455; 1263; 1138; ^{1}H NMR ($CDCl_3$) δ 7.35 (m, 3H); 7.21 (m, 3H); 6.91 (s, 1H); 6.84 (d, *J* = 8.3 Hz, 1H); 6.77 (d, *J* = 8.2 Hz, 1H); 5.49 (d, *J* = 15.0 Hz, 1H); 5.44 (d, *J* = 15.0 Hz, 1H); 4.98 (br s, 1H); 3.84 (s, 3H); 3.83 (s, 3H); 3.06 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 148.9; 148.3; 136.8; 136.3; 136.2; 134.6; 129.0; 128.7; 127.9; 117.9; 110.8; 108.9; 73.0; 55.84; 55.77; 54.0; 35.5; HRMS: (DCI/CH_4, m/z) calc. for $C_{19}H_{21}N_3O_3$: 339.1583. Found: 339.1586.

*2-(1-Benzyl-1H-1,2,3-triazol-4-yl)-1-(3-chloro-4-methoxyphenyl)ethanol (***2g***).*

White powder. Yield 70%. M.p.: 118 °C. IR (neat, ν/cm^{-1}) 3218; 1605; 1551; 1498; 1457; 1260; ^{1}H NMR ($CDCl_3$) δ 7.09-7.35 (m, 8H); 6.78 (d, *J* = 8.3 Hz, 2H); 5.42 (d, *J* = 15.6 Hz, 1H); 5.37 (d, *J* = 15.6 Hz, 1H); 4.91 (br s, 1H); 3.81 (s, 3H); 2.98 (br s, 2H); ^{13}C NMR ($CDCl_3$) δ 153.9; 137.2; 137.1; 136.9; 134.5; 128.9; 128.5; 127.7; 127.6; 125.1; 121.9; 111.6; 72.0; 56.0; 53.9; 35.2; HRMS: (DCI/CH_4, m/z) calc. for $C_{18}H_{19}N_3O_2Cl$: 344.1166. Found: 344.1173.

*2-(1-Benzyl-1H-1,2,3-triazol-4-yl)-1-(4-chlorophenyl)ethanol (***2h***).*

White powder. Yield 71%. M.p.: 115 °C. IR (neat, ν/cm^{-1}) 3207; 2929; 1552; 1456; 1435; ^{1}H NMR ($CDCl_3$) δ 7.33 (m, 3H); 7.19 (m, 4H); 7.15 (m, 3H); 5.43 (d, *J* = 14.9 Hz, 1H); 5.37 (d,

J = 14.9 Hz, 1H); 4.97 (t, *J* = 6.1 Hz, 1H); 4.02 (br s, 1H); 3.00 (d, *J* = 6.2 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 144.7; 142.1; 134.5; 132.8; 128.9; 128.6; 128.2; 127.8; 127.1; 72.2; 53.9; 35.2; HRMS: (DCI/CH_4, m/z) calc. for $C_{17}H_{17}N_3OCl$: 314.1060. Found: 314.1045.

*1-(1-Benzyl-1H-1,2,3-triazol-4-yl)-2-(2-chlorophenyl)ethanol (***2i***).*

White powder. Yield 76%. M.p. 136 °C. IR (neat, ν/cm^{-1}) 3207; 2928; 1552; 1455; ^{1}H NMR ($CDCl_3$) δ 7.53 (dd, *J* = 7.5 Hz, 1.9 Hz, 1H); 7.34 (m, 3H); 7.28 (dd, *J* = 7.6 Hz, 1.6 Hz, 1H); 7.13-7.24 (m, 5H); 5.46 (s, 2H); 5.38 (dd, *J* = 8.2 Hz, 3.1 Hz, 1H); 3.68 (br s, 1H); 3.20 (dd, *J* = 15.1 Hz, 3.2 Hz, 1H); 2.96 (dd, *J* = 15.1 Hz, 8.3 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 145.0; 140.8; 134.5; 131.4; 129.1; 129.0; 128.6; 128.3; 127.9; 127.2; 126.9; 121.9; 69.7; 54.0; 33.2; HRMS: (DCI/CH_4, m/z) calc. for $C_{17}H_{17}N_3OCl$: 314.1060. Found: 314.1049.

*2-(1-Benzyl-1H-1,2,3-triazol-4-yl)-1-(2,6-dichlorophenyl)ethanol (***2j***).*

White powder. Yield 53%. M.p.: 110 °C. IR (neat, ν/cm^{-1}) 3217; 2923; 1560; 1430; ^{1}H NMR ($CDCl_3$) δ 7.34 (m, 3H); 7.20-7.26 (5H); 7.09 (dd, *J* = 8.7 Hz, 7.2 Hz, 1H); 5.70 (br s, 1H); 5.50 (d, *J* = 14.9 Hz, 1H); 5.43 (d, *J* = 14.9 Hz, 1H); 3.54 (dd, *J* = 14.9 Hz, 9.1 Hz, 1H); 3.50 (br s, 1H); 3.21 (dd, *J* = 14.8 Hz, 5.2 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 136.6; 134.7; 134.3; 129.3; 129.02; 128.96; 128.5; 127.9; 71.1; 54.0; 53.4; 31.4; HRMS: (DCI/CH_4, m/z) calc. for $C_{17}H_{16}N_3OCl_2$: 348.0670. Found: 348.0678.

*2-(1-Benzyl-1H-1,2,3-triazol-4-yl)-1-(2,4-dichlorophenyl)ethanol (***2k***).*

White powder. Yield %. M.p.: 132 °C. IR (neat, ν/cm^{-1}) 3172; 2929; 1604; 1588; 1497; 1461; ^{1}H NMR ($CDCl_3$) δ 7.45 (d, *J* = 8.4 Hz, 1H); 7.36 (m, 3H); 7.29 (d, *J* = 2.1 Hz, 1H); 7.15-7.25 (m, 4H); 5.48 (s, 2H); 5.34 (m, 1H); 4.23 (br s, 1H); 3.17 (dd, *J* = 15.0 Hz, 2.3 Hz, 1H); 2.93 (dd, *J* = 15 Hz, 7.9 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 139.4; 134.5; 133.3; 131.9; 129.1; 128.9; 128.8; 128.3; 128.0; 127.2; 69.4; 54.1; 33.0; HRMS: (DCI/CH_4, m/z) calc. for $C_{17}H_{16}N_3OCl_2$: 348.0670. Found: 348.0663.

*1-(2,4-Dichlorophenyl)-2-(1-(3-methoxybenzyl)-1H-1,2,3-triazol-4-yl)ethanol (***2l***).*

Colorless oil. Yield 58%. IR (neat, ν/cm^{-1}) 3214; 2923; 1601; 1493; 1467; 1325; 1261. ^{1}H NMR ($CDCl_3$) δ 7.43 (d, *J* = 8.4 Hz, 1H); 7.28 (m, 2H); 7.20 (s, 1H); 7.16 (dd, *J* = 8.4 Hz, 2.1 Hz, 1H); 6.88 (dd, *J* = 8.3 Hz, 2.4 Hz, 1H); 6.77 (m, 2H); 5.42 (s, 2H); 5.33 (dd, *J* = 8.0 Hz, 3.3 Hz, 1H); 3.77 (s, 3H); 3.16 (dd, *J* = 15.1 Hz, 3.4Hz, 1H); 2.92 (dd, *J* = 15.1 Hz, 8.0 Hz, 1H) ; ^{13}C NMR ($CDCl_3$) δ 160.0; 144.6; 139.4; 135.9; 133.3; 131.9; 130.1; 128.8; 128.3; 127.2; 121.9; 120.1; 113.9; 113.7; 69.3; 55.2; 54.0; 33.1; HRMS: (DCI/CH_4, m/z) calc. for $C_{18}H_{18}N_3O_2Cl_2$: 378.0776. Found: 378.0777.

*1-(2,4-Dichlorophenyl)-2-(1-(3,5-dimethoxybenzyl)-1H-1,2,3-triazol-4-yl)ethanol (***2m***).*

Colorless oil. Yield 68%. IR (neat, ν/cm^{-1}) 3219; 2926; 2839; 1597; 1463; 1354; 1208. ^{1}H NMR ($CDCl_3$) δ 7.46 (d, *J* = 8.4 Hz, 1H); 7.30 (d, *J* = 2.1 Hz, 1H); 7.21 (s, 1H); 7.19 (dd, *J* = 8.5 Hz, 2.1 Hz, 1H); 6.43 (t, *J* = 2.2 Hz, 1H); 6.36 (d, *J* = 2.2 Hz, 2H); 5.40 (s, 2H); 5.35 (dd, *J* = 8.0 Hz, 3.3 Hz, 1H); 3.76 (s, 6H); 3.18 (dd, *J* = 15.1 Hz, 3.2 Hz, 1H); 2.92 (dd, *J* = 15.1 Hz, 7.9 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 161.3; 144.7; 139.4; 136.5; 133.4; 132.0; 128.9; 128.3; 127.2; 121.9; 106.1; 100.2; 69.4; 55.4; 54.2; 33.0; HRMS: (DCI/CH_4, m/z) calc. for $C_{19}H_{20}N_3O_3Cl_2$: 408.0882. Found: 408.0880.

*2-(1-(3-Chlorobenzyl)-1H-1,2,3-triazol-4-yl)-1-(2,4-dichlorophenyl)ethanol (***2n***).*

Colorless oil. Yield 55%. IR (neat, ν/cm^{-1}) 2927; 1580; 1561; 1466; 14321380; 1319; 1223. ^{1}H NMR ($CDCl_3$) δ 7.43 (d, *J* = 8.4 Hz, 1H); 7.30 (m, 3H); 7.23 (s, 1H); 7.19 (m, 2H); 7.08 (dt, *J* = 6.8 Hz, 1.8Hz, 1H); 5.43 (s, 2H); 5.34 (dd, *J* = 7.9 Hz, 3.5 Hz, 1H); 3.57 (brs, 1H); 3.18 (dd, *J* = 15.1 Hz, 3.4 Hz, 1H); 2.95 (dd, *J* = 15.2 Hz, 7.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 144.8; 139.4; 136.4; 134.9; 133.4; 131.9; 130.3; 128.93; 128.87; 128.3; 127.9; 127.2; 126.0; 69.2; 53.3; 33.1; HRMS: (DCI/CH_4, m/z) calc. for $C_{17}H_{15}N_3OCl_3$: 382.0281. Found: 382.0271.

*1-(2,4-Dichlorophenyl)-2-(1-phenethyl-1H-1,2,3-triazol-4-yl)ethanol (***2o***).*

Colorless oil. Yield 80%. IR (neat, ν/cm^{-1}) 3030; 1587; 1559; 1464; 1382; 1215. ^{1}H NMR ($CDCl_3$) δ 7.49 (d, *J* = 8.4 Hz, 1H); 7.20-733 (m, 5H); 7.08 (m, 3H); 5.30 (dd, *J* = 8.2 Hz, 3.0 Hz, 1H); 4.55 (t, *J* = 7.2 Hz, 2H); 3.39 (brs, 1H); 3.18 (t, *J* = 7.1 Hz, 2H); 3.14 (dd, *J* = 15.1 Hz, 3.1 Hz, 1H); 2.88 (dd, *J* = 15.1 Hz, 8.3 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 144.1; 139.5; 136.9; 133.4; 132.0; 128.9; 128.8; 128.6; 128.3; 127.2; 127.1; 122.3; 69.5; 51.6; 36.6; 33.0; 30.9; HRMS: (DCI/CH_4, m/z) calc. for $C_{18}H_{18}N_3OCl_2$: 362.0827. Found: 392.0826.

*1-(2,4-Dichlorophenyl)-2-(1-(2-methoxyphenethyl)-1H-1,2,3-triazol-4-yl)ethanol (***2p***).*

Colorless oil. Yield 86%. IR (neat, ν/cm^{-1}) 2937; 2836; 1589; 1496; 1464; 1239. ^{1}H NMR ($CDCl_3$) δ 7.51 (d, *J* = 8.4 Hz, 1H); 7.33 (d, *J* = 2.1 Hz, 1H); 7.23 (m, 2H); 7.07 (s, 1H); 6.80-6.93 (m, 3H); 5.29 (dd, *J* = 8.4 Hz, 3.0 Hz, 1H); 4.55 (t, *J* = 7.1 Hz, 2H); 3.83 (s, 3H); 3.16 (t, J = 7.2 Hz, 2H); 3.15 (dd, *J* = 15.1 Hz, 3.1 Hz, 1H); 2.86 (dd, *J* = 15.1 Hz, 8.4 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 157.4; 144.0; 139.5; 133.3; 132.0; 130.6; 128.9; 128.5; 128.3; 127.2; 125.1; 122.1; 120.6; 110.3; 69.5; 55.2; 49.9; 33.0; 32.0; HRMS: (DCI/CH_4, m/z) calc. for $C_{19}H_{20}N_3O_2Cl_2$: 392.0933. Found: 392.0932.

*1-(2,4-Dichlorophenyl)-2-(1-octyl-1H-1,2,3-triazol-4-yl)ethanol (***2q***).*

Colorless oil. Yield 65%. IR (neat, ν/cm^{-1}) 2954; 2926; 2856; 1589; 1561; 1467; 1380; 1219. ^{1}H NMR ($CDCl_3$) δ 7.51 (d, *J* = 8.4 Hz, 1H); 7.32 (d, *J* = 2.1 Hz, 1H); 7.28 (s, 1H); 7.22 (dd, *J* = 8.4 Hz, 2.1 Hz, 1H); 5.35 (dd, *J* = 8.2 Hz, 3.0 Hz, 1H); 4.30 (t, *J* = 7.2 Hz, 2H); 3.20 (dd, *J* = 15.1 Hz, 3.1 Hz, 1H); 2.93 (dd, *J* = 15.1 Hz, 8.2 Hz, 1H); 1.86 (m, 2H); 1.26 (m, 10H); 0.87 (t, *J* = 6.7 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 144.3; 139.6; 133.4; 132.0; 128.9; 128.4; 127.2; 121.7; 69.5; 50.3; 33.0; 31.7; 30.2; 29.0; 28.9; 26.4; 22.6; 14.0; HRMS: (DCI/CH_4, m/z) calc. for $C_{18}H_{26}N_3OCl_2$: 370.1453. Found: 370.1446.

(*E)-1-(2,4-dichlorophenyl)-2-(1-(3,7-dimethylocta-2,6-dienyl)-1H-1,2,3-triazol-4-yl)ethanol (***2r***).*

Colorless oil. Yield 27%. IR (neat, ν/cm^{-1}) 2921; 2850; 1589; 1562; 1467; 1382; 1221. ^{1}H NMR ($CDCl_3$) δ 7.54 (d, *J* = 8.4 Hz, 1H); 7.33 (d, *J* = 2.1 Hz, 1H); 7.22-7.26 (m, 2H); 5.37 (m, 2H); 5.05 (m, 1H); 4.93 (d, *J* = 7.3 Hz, 2H); 3.20 (dd, *J* = 15.2 Hz, 3.0 Hz, 1H); 2.91 (dd, *J* = 15.1 Hz, 8.2 Hz, 1H); 2.11 (m, 4H); 1.76 (s, 3H); 1.67 (s, 3H); 1.59 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 144.4; 143.5; 139.5; 133.4; 132.2; 132.0; 128.9; 128.4; 127.3; 123.4; 121.2; 116.8; 69.5; 47.9; 39.3; 33.1; 26.0; 25.7; 17.7; 16.4; HRMS: (DCI/CH_4, m/z) calc. for $C_{20}H_{26}N_3OCl_2$: 394.1453. Found: 394.1438.

*(Z)-1-(2,4-dichlorophenyl)-2-(1-(3,7-dimethylocta-2,6-dienyl)-1H-1,2,3-triazol-4-yl)ethanol (***2s***).*

Colorless oil. Yield 17%. IR (neat, ν/cm^{-1}). 2923; 2851; 1590; 1562; 1467; 1380; 1220. ^{1}H

NMR ($CDCl_3$) δ 7.53 (d, *J* = 8.4 Hz, 1H); 7.33 (m, 1H); 7.22-7.27 (m, 2H); 5.36 (m, 2H); 5.11 (m, 1H); 4.91 (d, *J* = 6.9 Hz, 2H); 3.22 (d, *J* = 15.1 Hz, 1H); 2.94 (m, 1H); 2.21 (m, 4H); 1.84 (s, 3H); 1.71 (s, 3H); 1.64 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 144.4; 143.2; 139.6; 133.4; 132.7; 132.0; 128.9; 128.4; 127.3; 123.1; 121.2; 117.7; 69.5; 47.7; 33.1; 32.0; 26.2; 25.7; 23.4; 17.7; HRMS: (DCI/CH_4, m/z) calc. for $C_{20}H_{26}N_3OCl_2$: 394.1453. Found: 394.1447.

*1-(1-Benzyl-1H-1,2,3-triazol-4-yl)-2-(4-fluorophenyl)ethanol (***2t***).*

White powder. Yield 72%. M.p.: 100 °C. IR (neat, ν/cm^{-1}) 3364; 1603; 1557; 1508; 1216; ^1H NMR ($CDCl_3$) δ 7.30 (m, 3H); 7.15 (m, 5H); 6.88 (t, *J* = 8.6 Hz, 2H); 5.39 (d, *J* = 15.1 Hz, 1H); 5.33 (d, *J* = 15.1 Hz, 1H); 4.95 (m, 1H); 4.35 (br s, 1H); 2.98 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 161.7 ($^1J_{C\text{-}F}$ = 245.0 Hz); 139.4; 134.5; 128.8; 128.4; 127.6; 127.3; 127.2; 114.8 ($^2J_{C\text{-}F}$ = 21.3 Hz); 72.1; 53.7; 35.3; HRMS: (DCI/CH_4, m/z) calc. for $C_{17}H_{17}N_3OF$: 298.1356. Found: 298.1360.

*2-(1-Benzyl-1H-1,2,3-triazol-4-yl)-1-(4-bromophenyl)ethanol (***2u***).*

White powder. Yield 78%. M.p.: 116 °C. IR (neat, ν/cm^{-1}) 3422; 1591; 155; 1487; 1454; ^1H NMR ($CDCl_3$) δ 7.34 (m, 5H); 7.15 (m, 5H); 5.44 (d, *J* = 14.9 Hz, 1H); 5.38 (d, *J* = 514.9 Hz, 1H); 4.96 (t, *J* = 6.2 Hz, 1H); 4.03 (br s, 1H); 3.00 (d, *J* = 6.2 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 144.6; 142.6; 134.5; 131.2; 129.0; 128.6; 127.8; 127.4; 122.0; 121.0; 72.3; 53.9; 35.2; HRMS: (DCI/CH_4, m/z) calc. for $C_{17}H_{17}N_3OBr$: 358.0555. Found: 358.0558.

Procedure for the synthesis of α,β-diketotriazole derivatives.

2-Iodobenzoic acid (0.6 equiv), oxone (2.4 equiv) were added to a solution of alcohol (mmol, 1 equiv) in 3 mL of AcCN/H_2O (2/1) at room temperature. The reaction mixture was warmed to reflux and was stirred under air for 20 h. Then the solvent was evaporated under reduced pressure and the residue was dissolved in AcOEt. The organic layer was washed with water (3 x 20 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography.

The compounds **3a**, **3c** and **3k** are known for most of them and the spectroscopic data match those reported.[9]

*1-(1-Benzyl-1H-1,2,3-triazol-4-yl)-2-p-tolylethane-1,2-dione (***3b***).*

White powder. Yield 78%. M.p.: 137 °C. IR (neat, ν/cm^{-1}) 3123; 2920; 1677; 1661; 1604; 1518; 1245; ^1H NMR ($CDCl_3$) δ 8.21 (s, 1H); 7.89 (d, *J* = 8.3 Hz, 2H); 7.38 (m, 3H); 7.26-7.33 (m, 4H); 5.59 (s, 2H); 2.41 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 191.6; 185.7; 146.2; 144.4; 133.3; 130.3; 129.8; 129.6; 129.3; 129.2; 128.4; 128.3; 54.5; 21.9; HRMS: (DCI/CH_4, m/z) calc. for $C_{18}H_{16}N_3O_2$: 306.1243. Found: 306.1244.

1-(1-Benzyl-1*H*-1,2,3-triazol-4-yl)-2-(4-propoxyphenyl)ethane-1,2-dione *(***3d***).*

White powder. Yield %. M.p. 98 °C. IR (neat, ν/cm^{-1}): 3100; 2943; 1675; 1660; 1595; 1567; 1268; ^1H NMR ($CDCl_3$) δ 8.17 (s, 1H); 8.00 (d, *J* = 9.0 Hz, 2H); 7.30-7.42 (m, 5H); 6.95 (d, *J* = 9.0 Hz, 2H); 5.60 (s, 2H); 4.00 (t, *J* = 6.6 Hz, 2H); 1.83 (m, 2H); 1.04 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 190.3; 185.6; 164.7; 144.5; 133.3; 132.8; 129.4; 129.3; 128.4; 125.1; 114.7; 69.9; 54.5; 22.3; 10.4; HRMS: (DCI/CH_4, m/z) calc. for $C_{20}H_{20}N_3O_3$: 350.1505. Found: 315.1496.

*2-(1-Benzyl-1H-1,2,3-triazol-4-yl)-1-(3-methoxyphenyl)ethane-1,2-dione (***3e***).*

White powder. Yield 26%. M.p.: 120 °C. IR (neat, ν/cm^{-1}) 3101; 2939; 1670; 1597; 1517; 1461; 1281; ^{1}H NMR ($CDCl_3$) δ 8.19 (s, 1H); 7.55 (m, 2H); 7.30-7.42 (m, 6H); 7.19 (ddd, J = 8.2 Hz, 2.5 Hz, 1.1 Hz, 1H); 5.60 (m, 2H); 3.84 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 191.9; 185.6; 159.9; 144.5; 133.5; 133.2; 129.9; 129.4; 129.3; 128.4; 128.1; 123.4; 122.0; 113.1; 55.5; 54.6; HRMS: (DCI/CH_4, m/z) calc. for $C_{18}H_{16}N_3O_3$: 322.1192. Found: 322.1184.

*1-(1-Benzyl-1H-1,2,3-triazol-4-yl)-2-(3-chloro-4-methoxyphenyl)ethane-1,2-dione (**3g**).*

White powder. Yield 49%. M.p.: 139 °C. IR (neat, ν/cm^{-1}) 3122; 2926; 1679; 1668; 1593; 1278; ^{1}H NMR ($CDCl_3$) δ 8.22 (s, 1H); 8.05 (d, *J* = 2.1 Hz, 1H); 7.93 (dd, *J* = 8.7 Hz, 2.1 Hz, 1H); 7.29-7.40 (m, 5H); 6.98 (d, *J* = 8.7 Hz, 1H); 5.60 (s, 2H); 3.97 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 189.3; 184.9; 160.2; 144.2; 133.3; 132.0; 131.2; 129.3; 129.2; 128.5; 128.4; 125.8; 123.5; 111.6; 56.5; 54.5; HRMS: (DCI/CH_4, m/z) calc. for $C_{18}H_{15}N_3O_3Cl$: 356.0802. Found: 356.0801.

*1-(1-Benzyl-1H-1,2,3-triazol-4-yl)-2-(4-chlorophenyl)ethane-1,2-dione (**3h**).*

White powder. Yield 61%. M.p.: 123 °C. IR (neat, ν/cm^{-1}) 3119; 2923; 1691; 1674; 1587; 1531; ^{1}H NMR ($CDCl_3$) δ 8.24 (s, 1H); 7.95 (d, *J* = 8.6 Hz, 2H); 7.46 (d, *J* = 8.6 Hz, 2H); 7.39 (m, 3H); 7.31 (m, 2H); 5.60 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 190.5; 184.9; 144.2; 141.6; 133.2; 131.5; 130.6; 129.34; 129.28; 128.42; 128.38; 54.5; HRMS: (DCI/CH_4, m/z) calc. for $C_{17}H_{13}N_3O_2Cl$: 326.0696. Found: 326.0703.

*1-(1-Benzyl-1H-1,2,3-triazol-4-yl)-2-(2-chlorophenyl)ethane-1,2-dione (**3i**).*

White powder. Yield 82%. M.p.: 125 °C. IR (neat, ν/cm^{-1}) 3148; 2922; 1677; 1566; ^{1}H NMR ($CDCl_3$) δ 8.24 (s, 1H); 7.83 (dd, *J* = 8.2 Hz, 2.0 Hz, 1H); 7.52 (m, 1H); 7.30-7.45 (m, 7H); 5.61 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 192.0; 183.5; 143.7; 134.5; 134.0; 133.3; 133.1; 132.0; 130.4; 129.3; 129.2; 128.4; 127.2; 54.5; HRMS: (DCI/CH_4, m/z) calc. for $C_{17}H_{13}N_3O_2Cl$: 326.0710. Found: 326.0710.

*1-(1-Benzyl-1H-1,2,3-triazol-4-yl)-2-(2,6-dichlorophenyl)ethane-1,2-dione (**3j**).*

White powder. Yield 83%. M.p.: 116 °C. IR (neat, ν/cm^{-1}) 3121; 1712; 1690; 1677; 1577; 1430; ^{1}H NMR ($CDCl_3$) δ 8.50 (s, 1H); 7.33-7.42 (m, 8H); 5.65 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 189.7; 178.0; 141.6; 134.6; 133.4; 132.6; 132.2; 130.0; 129.3; 129.2; 128.3; 128.1; 54.5; HRMS: (DCI/CH_4, m/z) calc. for $C_{17}H_{12}N_3O_2Cl_2$: 360.0307. Found: 360.0316.

*1-(1-Benzyl-1H-1,2,3-triazol-4-yl)-2-(4-fluorophenyl)ethane-1,2-dione (**3t**).*

White powder. Yield %. M.p.: 86 °C. IR (neat, ν/cm^{-1}) 3111; 1671; 1595; 1520; 1240; ^{1}H NMR ($CDCl_3$) δ 8.24 (s, 1H); 8.06 (d, *J* = 8.6 Hz, 1H); 8.04 (d, *J* = 8.7 Hz, 1H); 7.33 (m, 5H); 7.16 (t, *J* = 8.5 Hz, 2H); 5.60 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 190.1; 185.1; 166.8 ($^{1}J_{C\text{-}F}$ = 258.4 Hz); 144.2; 133.3; 133.1; 133.0; 129.33; 129.26; 128.7 ($^{3}J_{C\text{-}F}$ = 2.9 Hz); 128.4; 116.2 ($^{2}J_{C\text{-}F}$ = 22.2 Hz); 54.5; HRMS: (DCI/CH_4, m/z) calc. for $C_{17}H_{13}N_3O_2F$: 310.0992. Found: 310.0998.

*2-(1-Benzyl-1H-1,2,3-triazol-4-yl)-1-(4-bromophenyl)ethane-1,2-dione (**3u**).*

Yellow powder. M.p.: 130 °C. Yield %. IR (neat, ν/cm^{-1}) 3131; 2953; 1690; 1671; 1578; 1515; 1245; ^{1}H NMR ($CDCl_3$) δ 8.24 (s, 1H) ; 7.86 (d, *J* = 8.7 Hz, 2H); 7.62 (d, *J* = 8.7 Hz, 2H); 7.29-7.40 (m, 5H); 5.60 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 190.7; 184.8; 144.1; 133.2; 131.4; 131.0; 130.5; 129.3; 129.2; 128.4; 128.3; 54.5;

HRMS: (DCI/CH_4, m/z) calc. for $C_{17}H_{13}N_3O_2Br$: 370.0191. Found: 370.0209.

General procedure for elimination reaction.

A mixture of PPh_3 (1.4 equiv.), CBr_4 (1.25 equiv.) and alcohol (0.3 mmol, 1equiv.) in anhydrous dichloromethane (4 mL) was stirred at room temperature. The progress of the reaction was followed by TLC. The solvent was removed under vacuum and the product was purified by silica gel chromatography using a mixture of petroleum ether/ethyl acetate.

The product was used directly for the next step. DBU (1.5 equiv.) was added in dichloromethane at 4°C and the mixture was stirred at room temperature for 1h. When the reaction was complete by TLC, the mixture was washed with HCl (1N), brine and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to afford the corresponding styryl derivatives.

(*E)-1-Benzyl-4-(4-methoxystyryl)-1H-1,2,3-triazole (***4a***).*

White powder. Yield 37%. M.p.: 183 °C. IR (neat, ν/cm^{-1}) 3107; 3037; 2835; 1606; 1509; 1435; 1260; ^{1}H NMR ($CDCl_3$) δ 7.49 (s, 1H); 7.42 (m, 5H); 7.30 (m, 2H); 7.22 (d, *J* = 16.5 Hz, 1H); 6.92 (d, *J* = 16.4 Hz, 1H); 6.88 (m, 2H); 5.53 (s, 2H); 3.81 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 159.5; 147.0; 134.7; 130.3; 129.5; 129.1; 128.7; 128.0; 127.7; 119.8; 114.6; 114.1; 55.3; 54.1; HRMS: (DCI/CH_4, m/z) calc. for $C_{18}H_{18}N_3O$: 292.1450. Found: 292.1461.

*(E)-1-Benzyl-4-(4-propoxystyryl)-1H-1,2,3-triazole (***4b***).***

White powder. Yield 82%. M.p.: 163°C. IR (neat, ν/cm^{-1}): 3091; 2965; 2878; 1605; 1509; 1253; 1239; ^{1}H NMR ($CDCl_3$) δ 7.45 (s, 1H); 7.37 (m, 5H); 7.29 (m, 2H); 7.21 (d, *J* = 16.5 Hz, 1H); 6.91 (d, *J* = 16.5 Hz, 1H); 6.87 (d, *J* = 8.8 Hz, 2H); 5.53 (s, 2H); 3.93 (t, *J* = 6.6 Hz, 2H); 1.80 (m, 2H); 1.03 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 159.1; 147.0; 134.7; 130.4; 129.3; 129.1; 128.7; 128.0; 127.7; 119.7; 114.7; 114.4; 69.5; 54.1; 22.5; 10.5; HRMS: (DCI/CH_4, m/z) calc. for $C_{20}H_{22}N_3O$: 320.1763. Found: 320.1775.

*(E)-1-Benzyl-4-(3,4-dimethoxystyryl)-1H-1,2,3-triazole (***4c***).*

Yellow powder. Yield 25%. M.p.: 194 °C. IR (neat, ν/cm^{-1}): 3104; 2965; 1599; 1581; 1512; 1264; ^{1}H NMR ($CDCl_3$) δ 7.46 (s, 1H); 7.37 (m, 3H); 7.28 (m, 2H); 7.19 (d, *J* = 16.4 Hz, 1H); 7.02 (d, *J* = 1.9 Hz, 1H); 6.99 (dd, *J* = 8.3 Hz, *J* = 1.9 Hz, 1H); 6.93 (d, *J* = 16.4 Hz, 1H); 6.83 (d, J = 8.2 Hz, 1H); 5.52 (s, 2H); 3.90 (s, 3H); 3.88 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 149.10; 149.07; 146.8; 134.6; 130.4; 129.8; 129.1; 128.7; 128.0; 119.9; 119.8; 114.9; 111.1; 108.5; 55.9; 55.8; 54.1; HRMS: (DCI/CH_4, m/z) calc. for $C_{19}H_{20}N_3O_2$: 322.1556. Found: 322.1566.

(*E)-1-Benzyl-4-(2,4-dichlorostyryl)-1H-1,2,3-triazole (***4d***).*

White powder. Yield 52%. M.p.: 109°C. IR (neat, ν/cm^{-1}): 3099; 2922; 2852; 1554; 1472; 1389; ^{1}H NMR ($CDCl_3$) δ 7.57 (s, 1H); 7.55 (d, *J* = 7.1 Hz, 1H); 7.51 (d, *J* = 15.9 Hz, 1H); 7.38 (m, 3H); 7.31 (m, 2H); 7.22 (dd, *J* = 8.5 Hz, *J* = 2.1 Hz, 1H); 7.05 (d, *J* = 16.5 Hz, 1H); 5.55 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 146.2; 134.5; 133.83; 133.77; 129.6; 129.2; 128.8; 128.1; 127.3; 127.1; 125.5; 120.6; 120.0; 54.2; HRMS: (DCI/CH_4, m/z) calc. for $C_{17}H_{14}N_3Cl_2$: 330.0565. Found: 330.0574.

*(E)-1-benzyl-4-(4-bromostyryl)-1H-1,2,3-triazole (***4e***).*

White powder. Yield 73%. M.p.: 180 °C. IR (neat, ν/cm^{-1}) 3090; 3046; 1605; 1487; 1457;

1223; ^{1}H NMR ($CDCl_3$) δ 7.26-7.48 (m, 10H); 7.21 (d, *J* = 16.5 Hz, 1H); 7.02 (d, *J* = 16.4 Hz, 1H); 5.53 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 146.2; 135.6; 134.5; 131.8; 129.3; 129.1; 128.8; 128.0; 127.9; 121.6; 120.4; 117.3; 54.1; HRMS: (DCI/CH_4, m/z) calc. for $C_{17}H_{15}N_3Br$: 340.0449. Found: 340.0461.

Growth conditions and minimum inhibitory concentration (MIC) determination in M. tuberculosis

H37Rv was used as the reference strain. The strains were grown at 37 °C in Middlebrook 7H9 broth (Difco), supplemented with 0.05% Tween 80, or on solid Middlebrook 7H11 medium (Difco) supplemented with oleic acid-albumin-dextrose-catalase (OADC). MICs for the new compounds were determined by means of the micro-broth dilution method. Dilutions of *M. tuberculosis* wild-type (about 10^5–10^6 cfu/ml) were streaked onto 7H11 solid medium containing a range of drug concentrations (0.25 μg/mL to 40 μg/mL). Plates were incubated at 37 °C for about 21 days and the growth was visually evaluated. The lowest drug dilution at which visible growth failed to occur was taken as the MIC value. Results were expressed as the average of at least three independent determinations.

Cytotoxicities.

Human colon cancer cell line HCT116 (ATCC) and human fibroblasts (GM637 cell line) were cultured in DMEM supplemented with 10% fetal calf serum. For cytotoxicity evaluation, 3000 cells were seeded per well in 96-wells plates and, 24 h later, were treated with concentrations ranging from 100 nM to 50 μM (8 replicates for each). After 4 days of treatment, the cytotoxicity of each compound was measured by using the WST-1 kit (Roche).

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