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ORIGINAL PAPER

Efficient synthesis, antitubercular and antimicrobial evaluation of 1,4-disubstituted 1,2,3-triazoles with amide functionality

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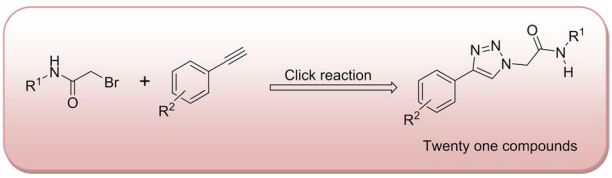
Abstract

A series of 21 amide linked 1,4-disubstituted-1,2,3-triazoles were achieved via one-pot synthesis through Cu(I) catalyzed click reaction between terminal alkynes and 2-azido-*N*-substituted acetamides. Newly formed triazoles were characterized by various spectroscopic techniques (FT-IR, ^{1}H NMR, ^{13}C NMR spectroscopy, and HRMS) and investigated for in vitro antitubercular evaluation against bacteria, i.e., *Mycobacterium tuberculosis* and antimicrobial evaluation against *Bacillus subtilis*, *Staphylococcus epidermidis*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Candida albicans*, and *Aspergillus niger*. Some of the synthesized triazole derivatives were found to exhibit moderate inhibitory activity against the tested antitubercular strain, whereas one compound displayed a significant inhibitory activity against most of the tested microbial strains.

Graphical abstract



Keywords Click reaction · Heterocycles · 1,4-Disubstituted · 1,2,3-Triazoles · Alkynes · One-pot synthesis · Biological activity

Introduction

Tuberculosis is one of the highly contagious and major challenging diseases around the world. *Mycobacterium tuberculosis*, etiologic agent of tuberculosis, led to the death of large number of people for more than five millennia. Despite availability of useful vaccine bacille Calmette–Guerin (BCG) and effective chemotherapy, still, tuberculosis has become leading cause of mortality. Infectious diseases caused by microorganisms have also been increasing threat to public health. Use of conventional antibiotics has now become ineffective due to increasing resistance in strains against them. Emergence of multi-drug resistant strains against tuberculosis and microbial infections has become an alarming issue that drew attention of medicinal researchers to develop new drug profile for their effective treatment. In this perspective, triazoles have proved to be potent antitubercular and antimicrobial agents due to extensive therapeutic importance [1, 2].

Triazoles, a significant class of nitrogen containing heterocycles, are attractive structural motifs which displayed versatility in diverse fields such as material sciences, synthetic organic chemistry, and drug discovery [3–5]. Triazole derivatives have been widely utilized in industries as dyestuffs, agrochemicals, optical brighteners, photostabilizers,

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corrosion inhibitors [6, 7], etc. In spite of these industrial applications, 1,2,3-triazole scaffolds emerged as imperative pharmacophore owing to their prevalent biological properties like antiviral [8], antimicrobial [9, 10], antiHIV [11], antiproliferative [12], antimalarial [13, 14], anticancer [15], antiallergic [16], anticonvulsant [17], antioxidant [18], antitubercular [19], etc.

In past, plethora of methods have been developed for synthesis of 1,2,3-triazoles for different purposes [20]. Most established strategy for the synthesis of disubstituted 1,2,3-triazoles from azides and terminal alkynes was introduced by Huisgen [21]. This conventional approach affords formation of both 1,4- and 1,5-disubstituted triazoles at elevated temperature. To conquer the problem of poor regioselectivity, Sharpless [22] and Meldal [23] in 2002 invented Cu(I) catalyzed click reaction of terminal alkynes and azides to generate 1,4-disubstituted 1,2,3-triazoles only. However, this experimentally simple and highly regioselective approach appears to possess enormous scope in many other areas like bioconjugation [24], polymer chemistry [25], peptidomimetics [26], and supramolecular chemistry [27].

Prompted by the above considerations and as an extension of our previous work on synthesis of biologically active 1,4-disubstituted 1,2,3-triazoles [28–31], we, herein, reported the synthesis, and antitubercular and antimicrobial potential of amide linked 1,4-disubstituted 1,2,3-triazoles via Cu(I) catalyzed click reaction between terminal alkynes and 2-azido-*N*-substituted acetamides. All the synthesized triazoles were well characterized by the spectroscopic techniques FT-IR, ^{1}H NMR, ^{13}C NMR spectroscopy, and HRMS, and also assessed for in vitro antitubercular potential against *Mycobacterium tuberculosis*; antimicrobial potential against *Bacillus subtilis*, *Staphylococcus epidermidis*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Candida albicans*, and *Aspergillus niger*.

Results and discussion

Chemistry

Synthetic strategy for preparation of *N*-aryl-2-(4-substituted-1*H*-1,2,3-triazol-1-yl)acetamides **4a**–**4u** is given in Scheme 1. 2-Bromo-*N*-substituted acetamides **2a**–**2g** [32] were synthesized by reacting aromatic amines **1a**–**1g** with bromoacetyl bromide in the presence of base potassium carbonate in dichloromethane. Afterwards, target 1,4-disubstituted 1,2,3-triazoles **4a**–**4u** with amide functionality were obtained by one-pot synthesis through click reaction between commercially available terminal alkynes **3a**–**3c** and 2-azido-*N*-substituted acetamides (which were attained in situ by reaction of 2-bromo-*N*-substituted acetamides **2a**–**2g** and sodium azide) by utilizing catalytic amount of copper sulfate pentahydrate and sodium ascorbate in *N*,*N*-dimethylformamide to lead desired products **4a**–**4u** in good yield.

Structures of newly synthesized triazole derivatives **4a**–**4u** were explicated by different spectral techniques, i.e., FT-IR, ^{1}H NMR, ^{13}C NMR spectroscopy, and HRMS. FT-IR spectra of synthesized compounds confirmed the formation of triazoles due to appearance of absorption bands in the region of 3211–3308 cm^{-1} (N–H, str., amide), 3123-3185 cm^{-1} (C–H, str., triazole ring), and 1666–1703 cm^{-1} (>C=O str. amide). In ^{1}H NMR spectra, singlet resonated in the region at $\delta = 8.54$–8.76 and 10.39–11.18 ppm due to triazolyl proton and N–H proton, respectively. Moreover, in ^{13}C NMR spectra, signals displayed in region at $\delta = 145.6$–146.8, 123.0–124.3, and 164.0–165.8 ppm designated to C_4, C_5 of triazole ring and carbonyl carbon of amide linkage. Furthermore, the results obtained from high-resolution mass spectral analysis were found in accordance to their calculated values.

Antitubercular activity

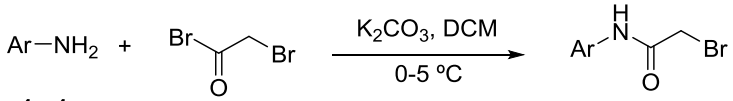
All synthesized triazole derivatives **4a**–**4u** were screened for in vitro antitubercular activity against bacterial strain *M. tuberculosis* H_{37}RV (MTCC 200) by Lowenstein–Jensen (L. J.) slope method. Isoniazid was used as a standard drug. Results were recorded in terms of minimum inhibitory concentration (μmol/cm^3). As reflected from Table 1, some of synthesized triazole derivatives were found to display noteworthy antitubercular activity against strain used for experimentation. Compound **4a** possessed good antitubercular potential in comparison to the standard drug. It has been deduced that compound **4c** (0.1933 μmol/cm^3), **4l** (0.1530 μmol/cm^3), **4q** (0.1831 μmol/cm^3), and **4t** (0.1333 μmol/cm^3) also showed moderate inhibitory activity against tested bacterial strain.

Results of antitubercular screening inferred that compounds possessing nitro group on anilide ring found to display a better inhibitory activity in comparison to compounds substituted with methoxy group on anilide ring. Among synthesized compounds substituted with halogen moiety, compound having both fluoro and bromo groups was found to behave as good antitubercular agent.

Antimicrobial activity

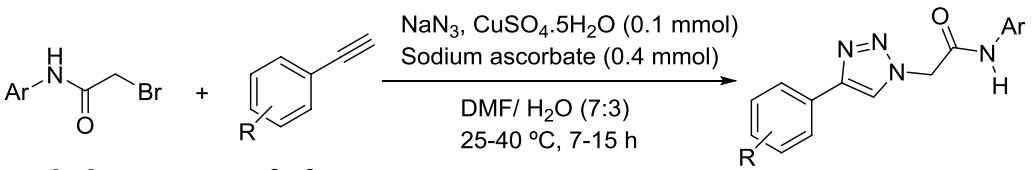
All newly synthesized triazole derivatives **4a**–**4u** were assessed for in vitro antimicrobial evaluation against *B. subtilis* (MTCC 441), *S. epidermidis* (MTCC 6880) (Gram-positive bacteria), *E. coli* (MTCC 1652), *P. aeruginosa* (MTCC 424) (Gram-negative bacteria), and *C. albicans* (MTCC 183), and *A. niger* (MTCC 8189) (fungi) by serial dilution technique [33]. Ciprofloxacin and fluconazole were

Scheme 1



1a-1g **2a-2g**

1a, **2a**: Ar = C_6H_5 **1b**, **2b**: Ar = 4-$CH_3OC_6H_4$
1c, **2c**: Ar = 4-$NO_2C_6H_4$ **1d**, **2d**: Ar = 4-FC_6H_4
1e, **2e**: Ar= 4-ClC_6H_4 **1f, 2f**: Ar = 4-BrC_6H_4
1g, **2g**: Ar = α-Naphthyl



2a-2g **3a-3c** **4a-4u**

3a: R = H
3b: R = 4-CH_3
3c: R= 3-F

Compound	Ar	R	Yield /%
4a	C_6H_5	H	82
4b	4-$CH_3OC_6H_4$	H	88
4c	4-$NO_2C_6H_4$	H	81
4d	4-FC_6H_4	H	85
4e	4-ClC_6H_4	H	86
4f	4-BrC_6H_4	H	78
4g	α-Naphthyl	H	88
4h	C_6H_5	4-CH_3	83
4i	4-$CH_3OC_6H_4$	4-CH_3	81
4j	4-$NO_2C_6H_4$	4-CH_3	87
4k	4-FC_6H_4	4-CH_3	80
4l	4-ClC_6H_4	4-CH_3	86
4m	4-BrC_6H_4	4-CH_3	85
4n	α-Naphthyl	4-CH_3	78
4o	C_6H_5	3-F	80
4p	4-$CH_3OC_6H_4$	3-F	77
4q	4-$NO_2C_6H_4$	3-F	88
4r	4-FC_6H_4	3-F	79
4s	4-ClC_6H_4	3-F	75
4t	4-BrC_6H_4	3-F	85
4u	α-Naphthyl	3-F	87

used as standard drugs against bacteria and fungi, respectively. Results were recorded in terms of MIC (minimum inhibitory concentration) which was expressed in μmol/cm^3.

It can be revealed from antibacterial screening data (Table 2) that most of the synthesized triazoles exhibited moderate-to-good antibacterial activity against tested bacterial strains. Among all the synthesized triazole derivatives, compound **4r** found to exhibit a significant antibacterial activity against all the bacterial strains. Compound **4g** (MIC 0.0190 μmol/cm^3), **4k** (MIC 0.0201 μmol/cm^3), and **4r** (MIC 0.0199 μmol/cm^3) against *B. subtilis*; **4c** (MIC 0.0193 μmol/cm^3), **4q** (MIC 0.0183 μmol/cm^3),

Table 1 In vitro antitubercular activity of 1,4-disubstituted 1,2,3-triazoles **4a–4u**

Compound	Minimum inhibitory concentration (MIC/μmol cm^{-3})
	M. tuberculosis $H_{37}RV$
4a	0.0898
4b	0.3243
4c	0.1933
4d	0.3375
4e	0.7994
4f	0.6999
4g	1.5227
4k	0.8552
4i	3.1021
4j	1.4822
4k	0.2014
4l	0.1530
4m	0.2694
4n	0.3651
4o	1.6875
4p	0.7661
4q	0.1831
4r	0.7954
4s	0.3023
4t	0.1333
4u	0.2887
Isoniazid	0.0015

Table 2 In vitro antibacterial activity of 1,4-disubstituted 1,2,3-triazoles **4a–4u**

Compound	Minimum inhibitory concentration (MIC/μmol cm^{-3})			
	Gram-positive bacteria		Gram-negative bacteria	
	B. subtilis	*S. epidermidis*	*E. coli*	*P. aeruginosa*
4a	0.0898	0.0449	0.0898	0.1797
4b	0.1622	0.0405	0.0811	0.0811
4c	0.0387	0.0193	0.0387	0.0387
4d	0.0422	0.0422	0.0211	0.0211
4e	0.0799	0.0799	0.0799	0.0400
4f	0.0350	0.0350	0.0175	0.0350
4g	0.0190	0.0761	0.0381	0.0381
4h	0.0428	0.0428	0.0855	0.0855
4i	0.0388	0.0776	0.0776	0.0776
4j	0.0371	0.0371	0.0371	0.0371
4k	0.0201	0.0403	0.0806	0.0806
4l	0.1530	0.3060	0.1530	0.3060
4m	0.0673	0.0337	0.0337	0.0168
4n	0.0730	0.0365	0.1460	0.1460
4o	0.0844	0.0420	0.0420	0.0420
4p	0.0383	0.0383	0.0383	0.0383
4q	0.0366	0.0183	0.0183	0.0366
4r	0.0199	0.0199	0.0199	0.0199
4s	0.0378	0.0378	0.0378	0.0378
4t	0.0333	0.0167	0.0333	0.0333
4u	0.0361	0.0722	0.0361	0.0361
Ciprofloxacin	0.0189	0.0189	0.0189	0.0189

4r (MIC 0.0199 μmol/cm^3), and **4t** (MIC 0.0167 μmol/cm^3) against *S. epidermidis*; **4d** (MIC 0.0211 μmol/cm^3), **4f** (MIC 0.0175 μmol/cm^3), **4q** (MIC 0.0183 μmol/cm^3), and **4r** (MIC 0.0199 μmol/cm^3) against *E. coli*; **4d** (MIC 0.0211 μmol/cm^3), **4 m** (MIC 0.0168 μmol/cm^3), and **4r** (MIC 0.0199 μmol/cm^3) against *P. aeruginosa* displayed activity comparable to standard drug.

Results clearly illustrated that compounds possessing electron withdrawing nitro group on anilide rings exhibited a better bactericidal activity in comparison to compounds with electron-donating methoxy group. In most of cases, compounds with 4-bromo substituents on anilide ring displayed a better inhibitory activity in comparison to compounds with the other halogen groups.

Results of antifungal screening (Table 3) clearly give a picture that some of triazole derivatives showed promising antifungal activity against tested fungal strains. Among the synthesized triazoles, compounds **4d** and **4k** exhibited a better antifungal potency against both the fungal strains used. Compounds **4d** (MIC 0.0211 μmol/cm^3), **4f** (MIC 0.0175 μmol/cm^3), and **4k** (MIC 0.0201 μmol/cm^3) against *C. albicans*; **4d** (MIC 0.0211 μmol/cm^3), **4j** (MIC 0.0185 μmol/cm^3), **4k**(MIC 0.0201 μmol/cm^3), and **4r** (MIC 0.0199 μmol/cm^3) against *A. niger* demonstrated appreciable antifungal activity. It is appreciable that some of molecules like **4q**, **4t** against *S. epidermidis*; **4f**, **4q** against *E. coli*; **4m** against *P. aeruginosa* displayed a better activity in comparison to the standard drug used.

It can be analyzed from antifungal screening that triazoles with electron withdrawing nitro group on anilide ring displayed considerable improvement in antifungal activity as compared to electron-donating methoxy group. In case of *A. niger*, triazoles with 4-fluorophenyl moiety found to possess a better fungicidal activity than triazole derivatives having other halogens. It is evident from results that compounds **4f**, **4k** against *C. albicans*, and **4j**, **4k**, **4r** against *A. niger* were found to exhibit a better inhibitory activity in comparison to standard drug used.

Conclusion

In summary, synthesis of a series of *N*-aryl-2-(4-substituted-1*H*-1,2,3-triazol-1-yl)acetamides **4a–4u** were achieved via one-pot Cu(I) catalyzed click reaction between terminal alkynes and 2-azido-*N*-substituted acetamides. Synthesized

Table 3 In vitro antifungal activity of 1,4-disubstituted 1,2,3-triazoles **4a–4u**

Compound	Minimum inhibitory concentration (MIC/μmol cm^{-3})	
	C. albicans	*A. niger*
4a	0.0898	0.0898
4b	0.0811	0.0405
4c	0.0387	0.0387
4d	0.0211	0.0211
4e	0.0400	0.0400
4f	0.0175	0.0350
4g	0.0381	0.0381
4h	0.0428	0.0428
4i	0.0388	0.0388
4j	0.0371	0.0185
4k	0.0201	0.0201
4l	0.0765	0.0383
4m	0.0373	0.0373
4n	0.0365	0.0730
4o	0.0422	0.0422
4p	0.0766	0.0766
4q	0.0366	0.0366
4r	0.0398	0.0199
4s	0.0378	0.0378
4t	0.0333	0.0333
4u	0.0361	0.1444
Fluconazole	0.0204	0.0204

triazole derivatives were evaluated for in vitro antitubercular potential against *Mycobacterium tuberculosis* and antimicrobial potential against *Bacillus subtilis*, *Staphylococcus epidermidis*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Candida albicans*, and *Aspergillus niger*. Compound **4a** overall displayed appreciating antitubercular activity against *M. tuberculosis*. Compounds **4d** and **4k** emerged as potent antifungal agent than the other triazole derivatives, while compound **4r** showed noteworthy microbicidal activity against most of the tested strains used.

Experimental

All reagents and solvents used in the present work were commercially available grade and used as received without further purification. Nutrient broth and Sabouraud dextrose broth used in antimicrobial activity were purchased from Hi-Media, Mumbai. Melting points of the synthesized compounds were recorded on an Electrothermal Melting Point apparatus. The FT-IR absorption spectra were scanned on IR AFFINITY-I FT-IR (SHIMAZDU) spectrometer using potassium bromide (KBr) powder and wave numbers are noted in cm^{-1}. Nuclear magnetic resonance spectra (^{1}H and ^{13}C) were recorded on a 400 MHz BrukerAvance-III spectrometer operating at 400 MHz and 100 MHz, respectively, in DMSO-d_6. Chemical shifts (δ) are observed in parts per million (ppm). Coupling constant (J) values were stated in Hertz (Hz). High-resolution mass spectra (HRMS) were scanned on Waters Micromass Q-Tof Micro (ESI) spectrometer. Values were represented in *m/z*. Ready-made silica gel plates (SIL G/UV254, ALUGRAM) were used for thin-layer chromatography (TLC) and spots were visualized under ultraviolet lamp.

General procedure for the synthesis of *N*-aryl-2-(4-substituted-1*H*-1,2,3-triazol-1-yl)-acetamides 4a-4u

Synthesis of 2-bromo-*N*-substituted acetamides **2a**–**2g** [32] was carried out by dissolving aromatic amines (1.0 mmol) **1a**–**1g** in 8–15 cm^3 dichloromethane, followed by addition of potassium carbonate (1.5 mmol) as base and stirred the solution. Afterwards, bromoacetyl bromide (1.2 mmol) was added dropwise to above stirred solution at 0–5 °C and continued stirring for 15 min. When reaction was completed, ice cold water was added, and solid product was precipitated, filtered, and dried.

For the synthesis of *N*-aryl-2-(4-substituted-1*H*-1,2,3-triazol-1-yl)acetamides **4a**–**4u**, aqueous solution of sodium azide (3.0 mmol) was added to 2-bromo-*N*-substituted acetamides **2a**–**2g** (1.0 mmol) in 7–14 cm^3 *N*,*N*-dimethylformamide at 25–40 °C and stirred solution for 1 h. Afterwards, terminal alkynes **3a**–**3c** (1.0 mmol) were added to above solution, followed by the addition of copper sulfate pentahydrate (0.1 mmol) and sodium ascorbate (0.4 mmol) and continued stirred the reaction contents at the same temperature for 7–15 h. Progress of reaction was monitored by TLC at regular intervals. As the reaction was completed, ice cold water was added to reaction mixture; solid residues were precipitated, collected by filtration, and washed with ammonia solution. Crude precipitates were then purified by washing with ethyl acetate and dried by applying vacuum to afford target 1,4-disubstituted 1,2,3-triazoles **4a**–**4u** in good yield.

***N*-Phenyl-2-(4-phenyl-1*H*-1,2,3-triazol-1-yl)acetamide (4a, $C_{16}H_{14}N_4O$)** White solid; yield: 82%; m.p.: 250–254 °C; FT-IR (KBr): $\bar{V}$ = 3267 (N–H str.), 3134 (C–H str., triazole ring), 3065 (C–H str., aromatic ring), 2934 (C–H str., aliphatic), 1672 (C=O str., amide), 1599, 1547 (C=C str., aromatic ring) cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 5.42 (s, 2H, NCH_2), 7.10 (t, 1H, Ar–H, J = 8.0 Hz), 7.33–7.37 (m, 3H, Ar–H), 7.47 (t, 2H, Ar–H, J = 8.0 Hz), 7.63 (d, 2H, Ar–H, J = 8.0 Hz), 7.90 (d, 2H, Ar–H, J = 8.0 Hz), 8.62 (s, 1H, C–H triazole), 10.55 (s, 1H, N–H amide) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 52.7, 119.7, 123.4 (C_5

triazole), 124.2, 125.6, 128.3, 129.4, 131.2, 138.9, 146.7 (C_4 triazole), 164.5 (C=O amide) ppm; HRMS: *m/z* calculated for $C_{16}H_{14}N_4O$ ($[M+H]^+$) 279.1201, found 279.1249.

***N*-(4-Methoxyphenyl)-2-(4-phenyl-1*H*-1,2,3-triazol-1-yl)-acetamide (4b, $C_{17}H_{16}N_4O_2$)** White solid; yield: 88%; m.p.: 228–232 °C; FT-IR (KBr): $\bar{V}=3277$ (N–H str.), 3163 (C–H str., triazole ring), 3084 (C–H str., aromatic ring), 2951 (C–H str., aliphatic), 1668 (C=O str., amide), 1605, 1547, 1464 (C=C str., aromatic ring), 1244 (C–O asym. str., ether), 1032 (C–O sym. str., ether) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): $\delta=3.73$ (s, 3H, OCH_3), 5.37 (s, 2H, NCH_2), 6.93 (d, 2H, Ar–H, $J=8.0$ Hz), 7.35 (t, 1H, Ar–H, $J=8.0$ Hz), 7.47 (t, 2H, Ar–H, $J=8.0$ Hz), 7.53 (d, 2H, Ar–H, $J=8.0$ Hz), 7.89 (d, 2H, Ar–H, $J=8.0$ Hz), 8.61 (s, 1H, C–H triazole), 10.40 (s, 1H, N–H amide) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): $\delta=52.8$, 55.3, 114.5, 121.2, 123.4 (C_5 triazole), 125.6, 128.3, 129.4, 131.2, 132.0, 146.6 (C_4 triazole), 156.1, 164.1 (C=O amide) ppm; HRMS: *m/z* calculated for $C_{17}H_{16}N_4O_2$ ($[M+H]^+$) 309.1307, found 309.1350.

***N*-(4-Nitrophenyl)-2-(4-phenyl-1*H*-1,2,3-triazol-1-yl)acetamide (4c, $C_{16}H_{13}N_5O_3$)** White solid; yield: 81%; m.p.: 264–268 °C; FT-IR (KBr): $\bar{V}=3302$ (N–H str.), 3160 (C–H str., triazole ring), 3064 (C–H str., aromatic ring), 2935 (C–H str., aliphatic), 1703 (C=O str., amide), 1616, 1599, 1568 (C=C str., aromatic ring), 1504 (N–O asym. str., NO_2), 1344 (N–O sym. str., NO_2) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): $\delta=5.53$ (s, 2H, NCH_2), 7.39 (t, 1H, Ar–H, $J=8.0$ Hz), 7.50 (t, 2H, Ar–H, $J=8.0$ Hz), 7.88–7.93 (m, 4H, Ar–H), 8.30 (d, 2H, Ar–H, $J=8.0$ Hz), 8.65 (s, 1H, C–H triazole), 11.18 (s, 1H, N–H amide) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): $\delta=52.8$, 119.6, 123.5 (C_5 triazole), 125.6, 128.4, 129.3, 131.1, 143.0, 144.9, 146.8 (C_4 triazole), 165.8 (C=O amide) ppm; HRMS: *m/z* calculated for $C_{16}H_{13}N_5O_3$ ($[M+H]^+$) 324.1052, found 324.1096.

***N*-(4-Fluorophenyl)-2-(4-phenyl-1*H*-1,2,3-triazol-1-yl)acetamide (4d, $C_{16}H_{13}FN_4O$)** White solid; yield: 85%; m.p.: 246–250 °C; FT-IR (KBr): $\bar{V}=3283$ (N–H str.), 3135 (C–H str., triazole ring), 3086 (C–H str., aromatic ring), 2938 (C–H str., aliphatic), 1670 (C=O str., amide), 1616, 1558 (C=C str., aromatic ring) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): $\delta=5.40$ (s, 2H, NCH_2), 7.18–7.22 (m, 2H, Ar–H), 7.35 (t, 1H, Ar–H, $J=8.0$ Hz), 7.47 (t, 2H, Ar–H, $J=8.0$ Hz), 7.62–7.64 (m, 2H, Ar–H), 7.89 (d, 2H, Ar–H, $J=8.0$ Hz), 8.62 (s, 1H, C–H triazole), 10.61 (s, 1H, N–H amide) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): $\delta=52.8$, 116.0 (d, 2C, Ar–C, $J=22.0$ Hz), 121.6 (d, 2C, Ar–C, $J=8.0$ Hz), 123.5 (C_5 triazole), 125.6, 128.3, 129.4, 131.2, 135.3 (d, 2C, Ar–C, $J=3.0$ Hz), 146.7 (C_4 triazole), 158.7 (d, 1C, Ar–C, $J=239.0$ Hz), 164.6 (C=O amide) ppm; HRMS: *m/z* calculated for $C_{16}H_{13}FN_4O$ ($[M+H]^+$) 297.1107, found 297.1152.

***N*-(4-Chlorophenyl)-2-(4-phenyl-1*H*-1,2,3-triazol-1-yl)acetamide (4e, $C_{16}H_{13}ClN_4O$)** White solid; yield: 86%; m.p.: 258–262 °C; FT-IR (KBr): $\bar{V}=3263$ (N–H str.), 3123 (C–H str., triazole ring), 3076 (C–H str., aromatic ring), 2941 (C–H str., aliphatic), 1674 (C=O str., amide), 1607, 1543, 1493 (C=C str., aromatic ring) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): $\delta=5.42$ (s, 2H, NCH_2), 7.33–7.48 (m, 5H, Ar–H), 7.65 (d, 2H, Ar–H, $J=8.0$ Hz), 7.89 (d, 2H, Ar–H, $J=8.0$ Hz), 8.62 (s, 1H, C-H triazole), 10.68 (s, 1H, N–H amide) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): $\delta=52.8$, 121.3, 123.5 (C_5 triazole), 125.6, 127.9, 128.3, 129.3, 129.4, 131.2, 137.8, 146.7 (C_4 triazole), 164.9 (C=O amide) ppm; HRMS: *m/z* calculated for $C_{16}H_{13}ClN_4O$ ($[M+H]^+$) 313.0856 (^{35}Cl), 315.0827 (^{37}Cl), found 313.1152 (^{35}Cl), 315.1083 (^{35}Cl).

***N*-(4-Bromophenyl)-2-(4-phenyl-1*H*-1,2,3-triazol-1-yl)-acetamide (4f, $C_{16}H_{13}BrN_4O$)** White solid; yield: 78%; m.p.: 268–272 °C; FT-IR (KBr): $\bar{V}=3211$ (N–H str.), 3155 (C–H str., triazole ring), 3007 (C–H str., aromatic ring), 2940 (C–H str., aliphatic), 1676 (C=O str., amide), 1609, 1543, 1489 (C=C str., aromatic ring) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): $\delta=5.40$ (s, 2H, NCH_2), 7.35 (t, 1H, Ar–H, $J=8.0$ Hz), 7.47 (t, 2H, Ar–H, $J=8.0$ Hz), 7.53–7.60 (m, 4H, Ar–H), 7.88 (d, 2H, Ar–H, $J=8.0$ Hz), 8.61 (s, 1H, C–H triazole), 10.67 (s, 1H, N–H amide) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): $\delta=52.7$, 115.9, 121.7, 123.5 (C_5 triazole), 125.6, 128.3, 129.4, 131.2, 132.2, 138.2, 146.4 (C_4 triazole), 165.0 (C=O amide) ppm; HRMS: *m/z* calculated for $C_{16}H_{13}BrN_4O$ ($[M+H]^+$) 357.0351 (^{79}Br), 359.0331 (^{81}Br), found 357.0350 (^{79}Br), 359.0322 (^{81}Br).

***N*-(Naphthalen-1-yl)-2-(4-phenyl-1*H*-1,2,3-triazol-1-yl)acetamide (4g, $C_{20}H_{16}N_4O$)** White solid; yield: 88%; m.p.: 260–264 °C; FT-IR (KBr): $\bar{V}=3246$ (N–H str.), 3132 (C–H str., triazole ring), 3049 (C–H str., aromatic ring), 2934 (C–H str., aliphatic), 1666 (C=O str., amide), 1549, 1470 (C=C str., aromatic ring) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): $\delta=5.61$ (s, 2H, NCH_2), 7.35 (t, 1H, Ar–H, $J=8.0$ Hz), 7.45–7.64 (m, 5H, Ar–H), 7.75 (d, 1H, Ar–H, $J=8.0$ Hz), 7.82 (d, 1H, Ar–H, $J=8.0$ Hz), 7.90 (d, 2H, Ar–H, $J=8.0$ Hz), 7.98 (d, 1H, Ar–H, $J=8.0$ Hz), 8.20 (d, 1H, Ar–H, $J=8.0$ Hz), 8.67 (s, 1H, C–H triazole), 10.49 (s, 1H, N–H amide) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): $\delta=52.5$, 122.1, 123.1, 123.6 (C_5 triazole), 125.6, 126.1, 126.2, 126.5, 126.7, 128.0, 128.3, 128.7, 129.4, 131.2, 133.2, 134.2, 146.7 (C_4 triazole), 165.6 (C=O amide) ppm; HRMS: *m/z* calculated for $C_{20}H_{16}N_4O$ ($[M+H]^+$) 329.1358, found 329.1410.

***N*-Phenyl-2-[4-(*p*-tolyl)-1*H*-1,2,3-triazol-1-yl]acetamide (4h, $C_{17}H_{16}N_4O$)** White solid; yield: 83%; m.p.: 262–266 °C;

FT-IR (KBr): $\bar{V}$ = 3269 (N–H str.), 3163 (C–H str., triazole ring), 3094 (C–H str., aromatic ring), 2924 (C–H str., aliphatic), 1676 (C=O str., amide), 1599, 1543, 1499 (C=C str., aromatic ring) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ = 2.30 (s, 3H, CH_3), 5.37 (s, 2H, NCH_2), 7.10 (t, 1H, Ar–H, J = 8.0 Hz), 7.27 (d, 2H, Ar–H, J = 8.0 Hz), 7.34 (t, 2H, Ar–H, J = 8.0 Hz), 7.60 (d, 2H, Ar–H, J = 8.0 Hz), 7.77 (d, 2H, Ar–H, J = 8.0 Hz), 8.54 (s, 1H, C-H triazole), 10.52 (s, 1H, N–H amide) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 21.2, 52.8, 119.7, 123.1 (C_5 triazole), 124.3, 125.5, 128.3, 129.3, 129.9, 137.6, 138.9, 146.7 (C_4 triazole), 164.6 (C=O amide) ppm; HRMS: *m/z* calculated for $C_{17}H_{16}N_4O$ ($[M+H]^+$) 293.1358, found 293.1404.

***N*-(4-Methoxyphenyl)-2-[4-(*p*-tolyl)-1*H*-1,2,3-triazol-1-yl]-acetamide (4i, $C_{18}H_{18}N_4O_2$)** White solid; yield: 81%; m.p.: 250–254 °C; FT-IR (KBr): $\bar{V}$ = 3279 (N–H str.), 3166 (C–H str., triazole ring), 3064 (C–H str., aromatic ring), 2912 (C–H str., aliphatic), 1678 (C=O str., amide), 1607, 1543, 1462 (C=C str., aromatic ring), 1244 (C–O asym. str., ether), 1034 (C–O sym. str., ether) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ = 2.34 (s, 3H, CH_3), 3.73 (s, 3H, OCH_3), 5.35 (s, 2H, NCH_2), 6.92 (d, 2H, Ar–H, J = 8.0 Hz), 7.27 (d, 2H, Ar–H, J = 8.0 Hz), 7.53 (d, 2H, Ar–H, J = 8.0 Hz), 7.77 (d, 2H, Ar–H, J = 8.0 Hz), 8.54 (s, 1H, C-H triazole), 10.39 (s, 1H, N–H amide) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 21.2, 52.7, 55.6, 114.5, 121.3, 123.0 (C_5 triazole), 125.5, 128.4, 129.8, 132.0, 137.5, 146.6 (C_4 triazole), 156.1, 164.1 (C=O amide) ppm; HRMS: *m/z* calculated for $C_{18}H_{18}N_4O_2$ ($[M+H]^+$) 323.1463, found 323.1509.

***N*-(4-Nitrophenyl)-2-[4-(*p*-tolyl)-1*H*-1,2,3-triazol-1-yl]acetamide (4j, $C_{17}H_{15}N_5O_3$)** White solid; yield: 87%; m.p.: 276–280 °C; FT-IR (KBr): $\bar{V}$ = 3277 (N–H str.), 3185 (C–H str., triazole ring), 3064 (C–H str., aromatic ring), 2935 (C–H str., aliphatic), 1701 (C=O str., amide), 1618, 1566, 1468 (C=C str., aromatic ring), 1504 (N–O asym. str., NO_2), 1344 (N–O sym. str., NO_2) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ = 2.34 (s, 3H, CH_3), 5.48 (s, 2H, NCH_2), 7.28 (d, 2H, Ar–H, J = 8.0 Hz), 7.77 (d, 2H, Ar–H, J = 8.0 Hz), 7.86 (d, 2H, Ar–H, J = 8.0 Hz), 8.27 (d, 2H, Ar–H, J = 8.0 Hz), 8.55 (s, 1H, C–H triazole), 11.14 (s, 1H, N–H amide) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 21.2, 52.8, 119.6, 123.0 (C_5 triazole), 125.6, 125.6, 128.2, 123.0, 137.7, 143.1, 145.0, 146.8 (C_4 triazole), 165.8 (C=O amide) ppm; HRMS: *m/z* calculated for $C_{17}H_{15}N_5O_3$ ($[M+H]^+$) 338.1208, found 338.1254.

***N*-(4-Fluorophenyl)-2-[4-(*p*-tolyl)-1*H*-1,2,3-triazol-1-yl]-acetamide (4k, $C_{17}H_{15}FN_4O$)** White solid; yield: 80%; m.p.: 254–258 °C; FT-IR (KBr): $\bar{V}$ = 3283 (N–H str.), 3177 (C–H str., triazole ring), 3065 (C–H str., aromatic ring), 2943 (C–H str., aliphatic), 1676 (C=O str., amide), 1614, 1545, 1466 (C=C str., aromatic ring) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ = 2.34 (s, 3H, CH_3), 5.38 (s, 2H, NCH_2), 7.17–7.22 (m, 2H, Ar–H), 7.27 (d, 2H, Ar–H, J = 8.0 Hz), 7.61–7.65 (m, 2H, Ar–H), 7.77 (d, 2H, Ar–H, J = 8.0 Hz), 8.54 (s, 1H, C–H triazole), 10.59 (s, 1H, N–H amide) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 21.2, 52.7, 116.0 (d, 2C, Ar–C, J = 22.0 Hz), 121.5 (d, 2C, Ar–C, J = 8.0 Hz), 123.0 (C_5 triazole), 125.4, 128.3, 129.9, 135.3 (d, 2C, Ar–C, J = 3.0 Hz), 137.6, 146.7 (C_4 triazole), 158.7 (d, 1C, Ar–C, J = 239.0 Hz), 164.6 (C=O amide) ppm; HRMS: *m/z* calculated for $C_{17}H_{15}FN_4O$ ($[M+H]^+$) 311.1263, found 311.1408.

***N*-(4-Chlorophenyl)-2-[4-(*p*-tolyl)-1*H*-1,2,3-triazol-1-yl]acetamide (4l, $C_{17}H_{15}ClN_4O$)** White solid; yield: 86%; m.p.: 268–272 °C; FT-IR (KBr): $\bar{V}$ = 3269 (N–H str.), 3128 (C–H str., triazole ring), 3074 (C–H str., aromatic ring), 2914 (C–H str., aliphatic), 1670 (C=O str., amide), 1610, 1547, 1493 (C=C str., aromatic ring) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ = 2.34 (s, 3H, CH_3), 5.39 (s, 2H, NCH_2), 7.27 (d, 2H, Ar–H, J = 8.0 Hz), 7.41 (d, 2H, Ar–H, J = 8.0 Hz), 7.64 (d, 2H, Ar–H, J = 8.0 Hz), 7.77 (d, 2H, Ar–H, J = 8.0 Hz), 8.55 (s, 1H, C–H triazole), 10.67 (s, 1H, N–H amide) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 21.2, 52.5, 121.3, 123.1 (C_5 triazole), 125.6, 127.9, 128.4, 129.3, 130.0, 137.6, 137.8, 146.7 (C_4 triazole), 164.9 (C=O amide) ppm; HRMS: *m/z* calculated for $C_{17}H_{15}ClN_4O$ ($[M+H]^+$) 327.1013 (^{35}Cl), 329.0983 (^{37}Cl), found 327.1014 (^{35}Cl), 329.0985 (^{37}Cl).

***N*-(4-Bromophenyl)-2-[4-(*p*-tolyl)-1*H*-1,2,3-triazol-1-yl]-acetamide (4m, $C_{17}H_{15}BrN_4O$)** White solid; yield: 85%; m.p.: 276–280 °C; FT-IR (KBr): $\bar{V}$ = 3265 (N–H str.), 3157 (C–H str., triazole ring), 3071 (C–H str., aromatic ring), 2941 (C–H str., aliphatic), 1676 (C=O str., amide), 1607, 1543, 1491 (C=C str., aromatic ring) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ = 2.34 (s, 3H, CH_3), 5.39 (s, 2H, NCH_2), 7.27 (d, 2H, Ar–H, J = 8.0 Hz), 7.52–7.60 (m, 4H, Ar–H), 7.77 (d, 2H, Ar–H, J = 8.0 Hz), 8.54 (s, 1H, C–H triazole), 10.67 (s, 1H, N–H amide) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 21.3, 52.8, 115.9, 121.7, 123.1 (C_5 triazole), 125.6, 128.4, 130.0, 132.2, 137.6, 138.3, 146.8 (C_4 triazole), 164.7 (C=O amide) ppm; HRMS: *m/z* calculated for $C_{17}H_{15}BrN_4O$ ($[M+H]^+$) 371.0507 (^{79}Br), 373.0487 (^{81}Br), found 371.0509 (^{79}Br), 373.0490 (^{81}Br).

***N*-(Naphthalen-1-yl)-2-[4-(*p*-tolyl)-1*H*-1,2,3-triazol-1-yl]-acetamide (4n, $C_{21}H_{18}N_4O$)** White solid; yield: 78%; m.p.: 266–270 °C; FT-IR (KBr): $\bar{V}$ = 3260 (N–H str.), 3166 (C–H str., triazole ring), 3059 (C–H str., aromatic ring), 2934 (C–H str., aliphatic), 1666 (C=O str., amide), 1549, 1466 (C=C str., aromatic ring) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ = 2.34 (s, 3H, CH_3), 5.59 (s, 2H, NCH_2), 7.28 (d, 2H, Ar–H, J = 8.0 Hz), 7.51–7.64 (m, 3H, Ar–H), 7.74–7.83

(m, 4H, Ar–H), 7.98 (d, 1H, Ar–H, $J = 8.0$ Hz), 8.20 (d, 1H, Ar–H, $J = 8.0$ Hz), 8.60 (s, 1H, C–H triazole), 10.48 (s, 1H, N–H amide) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 21.2$, 52.5, 122.0, 123.1 (C_5 triazole), 123.1, 125.6, 126.0, 126.2, 126.5, 126.7, 128.0, 128.5, 128.7, 129.9, 133.2, 134.2, 137.3, 146.7 (C_4 triazole), 165.6 (C=O amide) ppm; HRMS: *m/z* calculated for $C_{21}H_{18}N_4O$ ($[M+H]^+$) 343.1514, found 343.1562.

2-[4-(3-Fluorophenyl)-1*H*-1,2,3-triazol-1-yl]-*N*-phenylacetamide (4o, $C_{16}H_{13}FN_4O$) White solid; yield: 80%; m.p.: 258–262 °C; FT-IR (KBr): $\bar{V} = 3263$ (N–H str.), 3132 (C–H str., triazole ring), 3069 (C–H str., aromatic ring), 2937 (C–H str., aliphatic), 1668 (C=O str., amide), 1593, 1549, 1485 (C=C str., aromatic ring) cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 5.42$ (s, 2H, NCH_2), 7.10 (t, 1H, Ar–H, $J = 8.0$ Hz), 7.17–7.21 (m, 1H, Ar–H), 7.35 (t, 2H, Ar–H, $J = 8.0$ Hz), 7.49–7.55 (m, 1H, Ar–H), 7.61 (d, 2H, Ar–H, $J = 8.0$ Hz), 7.70–7.76 (m, 2H, Ar–H), 8.70 (s, 1H, C–H triazole), 10.54 (s, 1H, N–H amide) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 52.8$, 112.2 (d, 1C, Ar–C, $J = 23.0$ Hz), 115.0 (d, 1C, Ar–C, $J = 21.0$ Hz), 119.6, 121.6 (d, 1C, Ar–C, $J = 3.0$ Hz), 124.2 (C_5 triazole), 124.3, 129.4, 131.5 (d, 1C, Ar–C, $J = 9.0$ Hz), 133.6 (d, 1C, Ar–C, $J = 9.0$ Hz), 138.8, 145.6 (d, 1C, Ar–C, $J = 3.0$ Hz, C_4 triazole), 163.1 (d, 1C, Ar–C, $J = 241.0$ Hz), 164.5 (C=O amide) ppm; HRMS: *m/z* calculated for $C_{16}H_{13}FN_4O$ ($[M+H]^+$) 297.1107, found 297.1155.

2-[4-(3-Fluorophenyl)-1*H*-1,2,3-triazol-1-yl]-*N*-(4-methoxyphenyl)acetamide (4p, $C_{17}H_{15}FN_4O_2$) White solid; yield: 77%; m.p.: 276-280 °C; FT-IR (KBr): $\bar{V} = 3265$ (N–H str.), 3155 (C–H str., triazole ring), 3007 (C–H str., aromatic ring), 2912 (C–H str., aliphatic), 1672 (C=O str., amide), 1608, 1543, 1489 (C=C str., aromatic ring), 1229 (C–O asym. str., ether), 1076 (C–O sym. str., ether) cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 3.73$ (s, 3H, OCH_3), 5.38 (s, 2H, NCH_2), 6.92 (d, 2H, Ar–H, $J = 8.0$ Hz), 7.16–7.20 (m, 1H, Ar–H), 7.49–7.54 (m, 3H, Ar–H), 7.69–7.76 (m, 2H, Ar–H), 8.69 (s, 1H, C-H triazole), 10.41 (s, 1H, N–H amide) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 53.0$, 55.6, 112.2 (d, 1C, Ar–C, $J = 23.0$ Hz), 114.5, 115.0 (d, 1C, Ar–C, $J = 21.0$ Hz), 121.3, 121.6 (d, 1C, Ar–C, $J = 2.0$ Hz), 124.2 (C_5 triazole), 124.3, 131.5 (d, 1C, Ar–C, $J = 8.0$ Hz), 131.9, 133.6 (d, 1C, Ar–C, $J = 8.0$ Hz), 145.6 (d, 1C, Ar–C, $J = 3.0$ Hz, C_4 triazole), 156.1, 163.1 (d, 1C, Ar–C, $J = 242.0$ Hz), 164.0 (C=O amide) ppm; HRMS: *m/z* calculated for $C_{17}H_{15}FN_4O_2$ ($[M+H]^+$) 327.1213, found 327.1258.

2-[4-(3-Fluorophenyl)-1*H*-1,2,3-triazol-1-yl]-*N*-(4-nitrophenyl)acetamide (4q, $C_{16}H_{12}FN_5O_3$) White solid; yield: 88%; m.p.: 240–244 °C; FT-IR (KBr): $\bar{V} = 3308$ (N–H str.), 3148 (C–H str., triazole ring), 3084 (C–H str., aromatic ring), 2957 (C–H str., aliphatic), 1701 (C=O str., amide), 1616, 1564 (C=C str., aromatic ring), 1501 (N–O asym. str., NO_2), 1342 (N–O sym. str., NO_2) cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 5.51$ (s, 2H, NCH_2), 7.16–7.20 (m, 1H, Ar–H), 7.49–7.54 (m, 1H, Ar–H), 7.69–7.75 (m, 2H, Ar–H), 7.86 (d, 2H, Ar–H, $J = 8.0$ Hz), 8.26 (d, 2H, Ar–H, $J = 8.0$ Hz), 8.70 (s, 1H, C-H triazole), 11.15 (s, 1H, N–H amide) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 52.7$, 112.2 (d, 1C, Ar–C, $J = 23.0$ Hz), 115.0 (d, 1C, Ar–C, $J = 21.0$ Hz), 119.6, 121.7 (d, 1C, Ar–C, $J = 3.0$ Hz), 124.2 (C_5 triazole), 125.6, 131.5 (d, 1C, Ar–C, $J = 9.0$ Hz), 133.5 (d, 1C, Ar–C, $J = 9.0$ Hz), 143.1, 144.9, 145.7 (d, 1C, Ar–C, $J = 3.0$ Hz, C_4 triazole), 163.1 (d, 1C, Ar–C, $J = 242.0$ Hz), 165.7 (C=O amide) ppm; HRMS: *m/z* calculated for $C_{16}H_{12}FN_5O_3$ ($[M+H]^+$) 342.0958, found 342.1000.

***N*-(4-Fluorophenyl)-2-[4-(3-fluorophenyl)-1*H*-1,2,3-triazol-1-yl]acetamide (4r, $C_{16}H_{12}F_2N_4O$)** White solid; yield: 79%; m.p.: 246–250 °C; FT-IR (KBr): $\bar{V} = 3260$ (N–H str.), 3136 (C–H str., triazole ring), 3067 (C–H str., aromatic ring), 2937 (C–H str., aliphatic), 1672 (C=O str., amide), 1614, 1549, 1481 (C=C str., aromatic ring) cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 5.40$ (s, 2H, NCH_2), 7.17–7.22 (m, 3H, Ar–H), 7.49–7.55 (m, 1H, Ar–H), 7.61–7.75 (m, 4H, Ar–H), 8.69 (s, 1H, C–H triazole), 10.61 (s, 1H, N–H amide) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 52.8$, 112.8 (d, 1C, Ar–C, $J = 23.0$ Hz), 115.0 (d, 1C, Ar–C, $J = 21.0$ Hz), 116.0 (d, 2C, Ar–C, $J = 22.0$ Hz), 121.6 (d, 1C, Ar–C, $J = 8.0$ Hz), 121.6 (d, 1C, Ar–C, $J = 3.0$ Hz), 124.2 (C_5 triazole), 131.5 (d, 1C, Ar–C, $J = 8.0$ Hz), 133.5 (d, 1C, Ar–C, $J = 9.0$ Hz), 135.2 (d, 1C, Ar–C, $J = 3.0$ Hz), 145.6 (d, 1C, Ar–C, $J = 2.0$ Hz, C_4 triazole), 158.7 (d, 1C, Ar–C, $J = 239.0$ Hz), 163.1 (d, 1C, Ar–C, $J = 242.0$ Hz), 164.5 (C=O amide) ppm; HRMS: *m/z* calculated for $C_{16}H_{12}F_2N_4O$ ($[M+H]^+$) 315.1013, found 315.1063.

***N*-(4-Chlorophenyl)-2-[4-(3-fluorophenyl)-1*H*-1,2,3-triazol-1-yl]acetamide (4s, $C_{16}H_{12}ClFN_4O$)** White solid; yield: 75%; m.p.: 264–268 °C; FT-IR (KBr): $\bar{V} = 3267$ (N–H str.), 3159 (C–H str., triazole ring), 3078 (C–H str., aromatic ring), 2995 (C–H str., aliphatic), 1676 (C=O str., amide), 1610, 1549, 1489 (C=C str., aromatic ring) cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 5.42$ (s, 2H, NCH_2), 7.16–7.21 (m, 1H, Ar–H), 7.41 (d, 2H, Ar–H, $J = 8.0$ Hz), 7.49–7.54 (m, 1H, Ar–H), 7.64 (d, 2H, Ar–H, $J = 8.0$ Hz), 7.69–7.75 (m, 2H, Ar–H), 8.69 (s, 1H, C–H triazole), 10.69 (s, 1H, N–H amide) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 52.5$, 112.2 (d, 1C, Ar–C, $J = 23.0$ Hz), 115.0 (d, 1C, Ar–C, $J = 21.0$ Hz), 121.3, 121.6 (d, 1C, Ar–C, $J = 3.0$ Hz), 124.2 (C_5 triazole), 127.9, 129.3, 131.5 (d, 1C, Ar–C, $J = 9.0$ Hz), 133.5 (d, 1C, Ar–C, $J = 8.0$ Hz), 137.8, 145.6 (d, 1C, Ar–C, $J = 2.0$ Hz, C_4 triazole), 163.0 (d, 1C, Ar–C,

$J = 247.0$ Hz), 164.7 (C=O amide) ppm; HRMS: *m/z* calculated for $C_{16}H_{12}ClFN_4O$ ($[M + H]^+$) 331.0762 (^{35}Cl), 333.0732 (^{37}Cl), found 331.0766 (^{35}Cl), 333.0736 (^{37}Cl).

***N*-(4-Bromophenyl)-2-[4-(3-fluorophenyl)-1*H*-1,2,3-triazol-1-yl]acetamide (4t, $C_{16}H_{12}BrFN_4O$)** White solid; yield: 85%; m.p.: 250–254 °C; FT-IR (KBr): $\bar{V} = 3254$ (N–H str.), 3132 (C–H str., triazole ring), 3063 (C–H str., aromatic ring), 2941 (C–H str., aliphatic), 1668 (C=O str., amide), 1618, 1549, 1479 (C=C str., aromatic ring) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): $\delta = 5.42$ (s, 2H, NCH_2), 7.16–7.21 (m, 1H, Ar–H), 7.49–7.60 (m, 5H, Ar–H), 7.69–7.75 (m, 2H, Ar–H), 8.69 (s, 1H, C–H triazole), 10.69 (s, 1H, N–H amide) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 52.7$, 112.2 (d, 1C, Ar–C, $J = 23.0$ Hz), 115.0 (d, 1C, Ar–C, $J = 21.0$ Hz), 115.9, 121.7 (d, 1C, Ar–C, $J = 4.0$ Hz), 121.7, 124.2 (C_5 triazole), 131.5 (d, 1C, Ar–C, $J = 8.0$ Hz), 132.2, 133.5 (d, 1C, Ar–C, $J = 8.0$ Hz), 138.2, 145.6 (d, 1C, Ar–C, $J = 3.0$ Hz, C_4 triazole), 163.1 (d, 1C, Ar–C, $J = 242.0$ Hz), 164.8 (C=O amide) ppm; HRMS: *m/z* calculated for $C_{16}H_{12}BrFN_4O$ ($[M + H]^+$) 375.0257 (^{79}Br), 377.0236 (^{81}Br), found 375.0252 (^{79}Br), 377.0232 (^{81}Br).

2-[4-(3-Fluorophenyl)-1*H*-1,2,3-triazol-1-yl]-*N*-(naphthalen-1-yl)acetamide (4u, $C_{20}H_{15}FN_4O$) White solid; yield: 87%; m.p.: 258–262 °C; FT-IR (KBr): $\bar{V} = 3258$ (N–H str.), 3152 (C–H str., triazole ring), 3051 (C–H str., aromatic ring), 2937 (C–H str., aliphatic), 1670 (C=O str., amide), 1553, 1481 (C=C str., aromatic ring) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): $\delta = 5.63$ (s, 2H, NCH_2), 7.16–7.21 (m, 1H, Ar–H), 7.49–7.64 (m, 4H, Ar–H), 7.71–7.83 (m, 4H, Ar–H), 7.97 (d, 1H, Ar–H, $J = 8.0$ Hz), 8.21 (d, 1H, Ar–H, $J = 8.0$ Hz), 8.76 (s, 1H, C–H triazole), 10.55 (s, 1H, N–H amide) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 52.6$, 112.2 (d, 1C, Ar–C, $J = 23.0$ Hz), 115.0 (d, 1C, Ar–C, $J = 21.0$ Hz), 121.7 (d, 1C, Ar–C, $J = 3.0$ Hz), 122.1, 123.1, 124.3 (C_5 triazole), 126.0, 126.2, 126.5, 126.7, 128.0, 128.7, 131.5 (d, 1C, Ar–C, $J = 8.0$ Hz), 133.2, 133.6 (d, 1C, Ar–C, $J = 9.0$ Hz), 134.2, 145.6 (d, 1C, Ar–C, $J = 3.0$ Hz, C_4 triazole), 163.1 (d, 1C, Ar–C, $J = 242.0$ Hz), 165.5 (C=O amide) ppm; HRMS: *m/z* calculated for $C_{20}H_{15}FN_4O$ ($[M + H]^+$) 347.1213, found 347.1307.

General procedure for in vitro antitubercular activity

All synthesized triazole derivatives **4a**–**4u** were evaluated for in vitro antitubercular activity against bacterial strain *M. tuberculosis* $H_{37}RV$ (MTCC 200) by Lowenstein–Jensen (L. J.) slope method in the Microcare Laboratory and TRC, Surat, Gujrat.

Minimum inhibition concentration was used to evaluate the antitubercular activity. Results were expressed in terms of μmol/cm^3 and isoniazid was used as reference drug. Lowenstein–Jensen (L. J.) was used as nutrient medium to grow and dilute the suspension of compounds for the test. Inoculum size for test strain was adjusted to 1 mg/cm^3. DMSO was used as diluent/vehicle to get desired concentration of synthesized compounds to test upon the standard bacterial strain. Each synthesized drug was diluted obtaining 2000 μg/cm^3 concentration, as a stock solution.

Following steps were taken to precede antitubercular activity

Primary screen: in primary screening, 500 μg/cm^3, 250 μg/cm^3, and 125 μg/cm^3 concentrations of the synthesized compounds were taken. The active synthesized compounds found in this primary screening were further tested in a second set of dilution against the tested strain.

Secondary screen: the compounds found active in primary screening were similarly diluted to obtain 100 μg/cm^3, 50 μg/cm^3, 25 μg/cm^3, 12.5 μg/cm^3, 6.250 μg/cm^3, 3.125 μg/cm^3, and 1.562 μg/cm^3 concentrations.

Reading result: the highest dilution showing at least 99% inhibition is taken as MIC. The result of this is much affected by the size of the inoculum. The test mixture should contain 10^8 organism/cm^3.

The standard drugs: the Standard strain *M. tuberculosis*, $H_{37}RV$, was tested with each new batch of medium. The recommended drug concentration was 0.2 mg/cm^3 for isoniazid.

General procedure for in vitro antimicrobial activity

All the synthesized triazole derivatives **4a**–**4u** were examined for their in vitro antimicrobial activity against two Gram-positive bacterial strains, i.e., *B. subtilis* (MTCC 441) and *S. epidermidis* (MTCC 6880), two Gram-negative bacterial strains, i.e., *E. coli* (MTCC 1652) and *P. aeruginosa* (MTCC 424), and two fungal strains, i.e., *C. albicans* (MTCC 183) and *A. niger* (MTCC 8189) by the serial dilution technique [33]. Ciprofloxacin and fluconazole were used as reference drugs against bacteria and fungi, respectively.

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