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ORIGINAL PAPER

Synthesis, antimicrobial activity, and QSAR studies of amide-ester linked 1,4-disubstituted 1,2,3-triazoles

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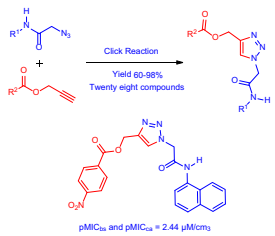
Abstract Synthesis of some amide-ester linked 1,4-disubstituted 1,2,3-triazoles was carried out by employing copper(I)-catalyzed 1,3-dipolar cycloaddition of 2-azido-*N*-substituted acetamides and benzoic acid prop-2-ynyl esters. All the synthesized 28 1,4-disubstituted 1,2,3-triazoles are new. The synthesized triazoles were characterized by IR, ^{1}H NMR, ^{13}C NMR, HRMS and evaluated for their antimicrobial activity against *Staphylococcus aureus*, *Bacillus subtilis*, *Escherichia coli*, *Candida albicans*, and *Aspergillus niger*. Compounds displaying potent antimicrobial activity against each of these microorganisms were found. Quantitative structure activity relationship studies for the synthesized compounds were also carried out to check the effect of various substituents in parent compound on antimicrobial activity.

Graphical abstract



Keywords Heterocycles · 1,4-Disubstituted 1,2,3-triazoles · Cycloaddition · Antibacterial · Antifungal · QSAR

Introduction

In the present scenario, the 1,2,3-triazoles have gained much attention owing to their numerous applications in various fields like pharmaceutical [1], agrochemical [2], polymer [3], and material science [4]. 1,2,3-Triazole derivatives possess diverse biological activities as antiviral [5], antimicrobial [6–11], antibiotic [12], antiprotozoal [13], antitubercular [14], anti-HIV [15], antimalarial [16], anticancer [17], and anti-inflammatory [18] agents. 1,3-Dipolar cycloaddition reaction of organic azides to terminal alkynes was first time scientifically studied by Huisgen in twentieth century leading to the formation of 1,4- and 1,5-disubstituted 1,2,3-triazoles [19]. This area of research was limited before Sharpless [20] and Meldal [21], who independently discovered that the reaction of terminal alkynes with organic azides using copper(I) as catalyst leads to product in 1,4-regioselective fashion. This reaction

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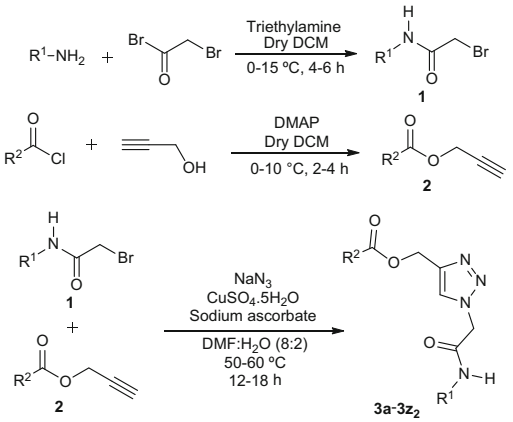
with salient features like higher yield, good selectivity, simple reaction conditions, and versatile chemical transformations, increased the interest of researchers and was termed as one of the important click reaction. Moreover, the use of click reaction have also been reported in the literature for the construction of ionic receptors [22], dendrimers [23], clusters [24], triazolophanes [25], glycopeptides [26], nanotubes [27], cyclic peptides [28], peptidomimetics [29], and liquid crystals [30]. In the recent years, quantitative structure activity relationship (QSAR) has received importance in the field of medicinal chemistry being a predictive tool for preliminary evaluation of the activity of chemical compounds using computer-aided models. QSAR techniques have increased the probability of success with reduced time and low cost involvement in drug discovery process [31]. So, keeping these views in mind, we have used copper(I)-catalyzed click reaction to synthesize a series of 1,4-disubstituted 1,2,3-triazoles **3a**–**3z$_2$** containing amide-ester linkages from benzoic acid prop-2-ynyl esters and 2-azido-*N*-substituted acetamides which were formed in situ by reaction of 2-bromo-*N*-substituted acetamides with sodium azide. All the synthesized 1,4-disubstituted 1,2,3-triazoles are found to be new compounds. The synthesized compounds were characterized by various spectroscopic techniques like IR, ^{1}H NMR, ^{13}C NMR, HRMS and evaluated for their antibacterial and antifungal activity. To observe the effect of various molecular descriptors/parameters on antimicrobial activity, QSAR studies of all synthesized compounds were also carried out. QSAR models are mathematical equations which construct a relationship between chemical structures and their biological activities as a linear regression model of the form $y = Xb + e$. This equation may be used to describe a set of predictor variables (X) with a predicted variable (y) by means of a regression vector (b) [32].

Results and discussion

Chemistry

The synthetic strategy of the target compounds is given in Scheme 1. 2-Bromo-*N*-substituted acetamides **1** were prepared reacting various aromatic amines with bromoacetyl bromide in dry dichloromethane at 0–15 °C using triethylamine as base, while benzoic acid prop-2-ynyl esters **2** were synthesized by reacting corresponding benzoyl chlorides with propargyl alcohol in dry dichloromethane at 0–10 °C in the presence of *N*,*N*-dimethylaminopyridine. Finally, 1,4-disubstituted 1,2,3-triazoles **3a**–**3z$_2$** containing amide-ester linkages were synthesized by reacting 2-bromo-*N*-substituted acetamides **1** and benzoic acid prop-2-ynyl esters **2** in dimethylformamide:water in the presence of sodium azide, copper sulfate pentahydrate and sodium ascorbate with stirring of 12–18 h at 50–60 °C (Scheme 1). The synthesized triazole compounds were characterized by IR, ^{1}H NMR, ^{13}C NMR, and high resolution mass spectrometry. The formation of triazole compounds were confirmed by the presence of absorption bands in the region at 3304–3217 cm^{-1} (N–H str., amide),

Scheme 1



Compound	R^1	R^2
3a	C_6H_5-	*p*-CH_3-C_6H_4-
3b	C_6H_5-	*p*-CH_3O-C_6H_4-
3c	C_6H_5-	*p*-NO_2-C_6H_4-
3d	C_6H_5-	*p*-F-C_6H_4-
3e	*p*-CH_3-C_6H_4-	*p*-CH_3-C_6H_4-
3f	*p*-CH_3-C_6H_4-	*p*-CH_3O-C_6H_4-
3g	*p*-CH_3-C_6H_4-	*p*-NO_2-C_6H_4-
3h	*p*-CH_3-C_6H_4-	*p*-F-C_6H_4-
3i	*p*-CH_3O-C_6H_4-	*p*-CH_3-C_6H_4-
3j	*p*-CH_3O-C_6H_4-	*p*-CH_3O-C_6H_4-
3k	*p*-CH_3O-C_6H_4-	*p*-NO_2-C_6H_4-
3l	*p*-CH_3O-C_6H_4-	*p*-F-C_6H_4-
3m	*p*-F-C_6H_4-	*p*-CH_3-C_6H_4-
3n	*p*-F-C_6H_4-	*p*-CH_3O-C_6H_4-
3o	*p*-F-C_6H_4-	*p*-NO_2-C_6H_4-
3p	*p*-F-C_6H_4-	*p*-F-C_6H_4-
3q	*p*-Br-C_6H_4-	*p*-CH_3-C_6H_4-
3r	*p*-Br-C_6H_4-	*p*-CH_3O-C_6H_4-
3s	*p*-Br-C_6H_4-	*p*-NO_2-C_6H_4-
3t	*p*-Br-C_6H_4-	*p*-F-C_6H_4-
3u	*p*-NO_2-C_6H_4-	*p*-CH_3-C_6H_4-
3v	*p*-NO_2-C_6H_4-	*p*-CH_3O-C_6H_4-
3w	*p*-NO_2-C_6H_4-	*p*-NO_2-C_6H_4-
3x	*p*-NO_2-C_6H_4-	*p*-F-C_6H_4-
3y	α-Naphthyl	*p*-CH_3-C_6H_4-
3z	α-Naphthyl	*p*-CH_3O-C_6H_4-
3z$_1$	α-Naphthyl	*p*-NO_2-C_6H_4-
3z$_2$	α-Naphthyl	*p*-F-C_6H_4-

Table 1 Antimicrobial activity data (pMIC in μM/cm^3) of synthesized compounds **3a–3z$_2$**

Compound	$pMIC_{sa}$	$pMIC_{bs}$	$pMIC_{ec}$	$pMIC_{ca}$	$pMIC_{an}$	$pMIC_{ab}$	$pMIC_{af}$	$pMIC_{am}$
3a	1.45	1.45	1.45	1.45	1.45	1.45[a]	1.45	1.45
3b	1.47	1.47	2.07	1.47	1.47	1.67	1.47	1.59
3c	2.09	2.09	1.48	1.48	1.48	1.89[a]	1.48[b]	1.73
3d	1.45	1.45	1.45	2.05	2.36	1.45	2.21[a]	1.75
3e	1.16	2.07	1.46	2.37	1.46	1.57	1.92[a]	1.71
3f	1.48	1.48	2.39	1.48	1.48	1.78	1.48	1.66
3g	2.10	1.50	1.50	1.50	1.50	1.70	1.50	1.62
3h	2.07	1.47	1.47	1.47	2.37	1.67[b]	1.92[a]	1.77
3i	1.48	1.48	1.48	1.48	1.48	1.48[b]	1.48	1.48
3j	1.50	1.50	2.10	1.50	1.50	1.70	1.50	1.62
3k	1.52	2.42	1.52	2.12	1.52	1.82[a]	1.82[b]	1.82
3l	1.49	1.49	1.49	1.49	1.49	1.49	1.49	1.49
3m	2.37	1.47	1.47	1.47	1.47	1.77	1.47	1.65
3n	1.49	1.49	1.49	1.19	1.49	1.49[b]	1.34[a]	1.43
3o	1.50	1.50	1.50	2.11	1.50	1.50	1.81[b]	1.62
3p	2.38	1.47	1.47	1.47	1.47	1.78[a]	1.47	1.65
3q	1.54	2.14	1.54	1.54	2.14	1.74	1.84[b]	1.78
3r	1.55	1.55	1.55	1.55	1.55	1.55	1.55	1.55
3s	1.27	1.57	2.17	1.57	1.57	1.67	1.57	1.63
3t	1.54	1.54	1.54	2.44	1.54	1.54	1.99[a]	1.72
3u	1.50	1.50	1.50	1.50	1.50	1.50[a]	1.50	1.50
3v	2.12	2.42	1.52	1.52	1.52	2.02[a]	1.52	1.82
3w	1.53	1.53	1.53	1.53	1.53	1.53	1.53	1.53
3x	2.11	1.50	1.50	2.41	2.11	1.71	2.26[a]	1.93
3y	1.51	1.51	2.41	1.51	1.51	1.81[b]	1.51	1.69
3z	1.52	1.52	1.22	1.52	1.52	1.42[a]	1.52	1.46
3z$_1$	1.54	2.44	1.54	2.44	1.54	1.84	1.99[a]	1.90
3z$_2$	1.51	1.51	1.51	1.51	1.51	1.51[b]	1.51	1.51
Norfloxacin	2.61	2.61	2.61	–	–	–	–	–
Fluconazole	–	–	–	2.64	2.64	–	–	–
SD	0.33	0.33	0.30	0.36	0.27	0.16	0.25	0.14

$pMIC_{sa}$, $pMIC_{bs}$, $pMIC_{ec}$, $pMIC_{ca}$ and $pMIC_{an} = -\log$ MIC in μM/cm^3 against different microorganisms. i.e. *Staphylococcus aureus*, *Bacillus subtilis*, *Escherichia coli*, *Candida albicans and Aspergillus niger*, respectively

SD means standard deviation

[a] Test set; [b] outliers

3170–3120 cm^{-1} (C–H, str., triazole ring), 1722–1691 cm^{-1} (C=O str., ester), and 1699–1656 cm^{-1} (C=O str., amide) in IR spectra. The presence of characteristic singlet in the region at $\delta = 5.32$–5.52 (OCH_2), 5.40–5.60 (NCH_2), 8.26–8.38 (CH triazole), 10.35–11.12 (NH amide) ppm in ^{1}H NMR spectra and peaks in the region at $\delta = 52.6$–52.8 (NCH_2), 58.1–59.7 (OCH_2), 127.0–127.4 (C-5 triazole ring), 141.6–142.3 (C-4 triazole ring), 164.1–164.9 (C=O ester), 165.0–165.9 (C=O amide) ppm in ^{13}C NMR spectra also confirmed the formation of target compounds. The results obtained from high resolution mass spectral analysis were found in accordance to the calculated values.

Antibacterial activity

All the synthesized 1,4-disubstituted 1,2,3-triazoles **3a–3z$_2$** were screened for in vitro antibacterial activity against *Staphylococcus aureus* (MTCC 1430), *Bacillus subtilis* (MTCC 2423), and *Escherichia coli* (MTCC 739). The antibacterial potency of the compounds was compared with standard drug, norfloxacin. The minimum inhibitory concentration (MIC) values are given in Table 1.

The results obtained from antibacterial studies revealed that the compounds **3a–3z$_2$** showed moderate to good activities against tested bacterial strains. Compounds **3m** and **3p** ($pMIC_{sa} = 2.37$ and 2.38 μM/cm^3, respectively)

were found to possess good potential against *S. aureus*, whereas, compounds **3k**, **3v**, and **3z$_1$** ($pMIC_{bs}$ = 2.42, 2.42, and 2.44 μM/cm^3, respectively) displayed better activity against *B. subtilis*. In case of *E. coli*, compounds **3f** and **3y** ($pMIC_{ec}$ = 2.39 and 2.41 μM/cm^3, respectively) emerged as potent antibacterial agents.

Antifungal activity

The in vitro antifungal activity of the 1,4-disubstituted 1,2,3-triazoles **3a–3z$_2$** were examined against two fungal strains viz. *Candida albicans* (MTCC 854) and *Aspergillus niger* (MTCC 282). Fluconazole was used as standard drug. The MIC values of the synthesized triazoles and the standard drug are furnished in Table 1.

Antifungal activity results indicated that most of the synthesized compounds exhibited moderate to good activities against tested fungal strains. Compounds **3e**, **3t**, **3x**, and **3z$_1$** ($pMIC_{ca}$ = 2.37, 2.44, 2.41, and 2.44 μM/cm^3, respectively) displayed remarkable antifungal activity against *C. albicans*; compounds **3d** and **3h** ($pMIC_{an}$ = 2.36 and 2.37 μM/cm^3, respectively) appeared as potential antifungal agents against *A. niger*.

In general, antimicrobial activity results reflected that the compound **3z$_1$** as a potent antimicrobial agent ($pMIC_{bs}$ and $pMIC_{ca}$ = 2.44 μM/cm^3), having antimicrobial efficacy comparable to standard drugs, norfloxacin (pMIC = 2.61 μM/cm^3) and fluconazole (pMIC = 2.64 μM/cm^3), respectively.

Structure activity relationship studies

From the above antimicrobial activity results, the following structure activity relationship can be drawn:

1. Presence of electron withdrawing groups, i.e., nitro on benzoate moiety in triazoles containing either phenyl (**3c**) or toluyl (**3g**) groups at nitrogen atom of amide linkage improved the antibacterial activity against *S. aureus*; the presence of methoxy (**3v**) and flouro (**3x**) groups on benzoate moiety in the compounds having *p*-nitrophenyl at nitrogen of amide bond also increased the bactericidal activity. Moreover, the triazoles containing methyl (**3m**) and fluoro (**3p**) groups on benzoate moiety with *p*-fluorophenyl at nitrogen of amide bond also displayed good antibacterial efficiency against *S. aureus*.
2. Triazoles with electron withdrawing group, i.e., nitro on benzoate moiety containing phenyl (**3c**), *p*-methoxyphenyl (**3k**), and naphthyl (**3z$_1$**) groups on nitrogen atom of amide linkage exhibited potent antibacterial activity against *B. subtilis*; compound (**3v**) containing electron donating group, i.e., methoxy on benzoate moiety and electron withdrawing group like nitro on amino phenyl moiety also appeared as potent antibacterial agent against *B. subtilis*.
3. Presence of electron donating groups on benzoate moiety improved the antibacterial activity against *E. coli* in the triazoles having phenyl (**3b**), toluyl (**3f**), *p*-methoxyphenyl (**3j**), and naphthyl (**3y**) moieties linked at nitrogen atom of amide bond. However, compound **3s** possessing electron withdrawing group on benzoate moiety with bromo at amino phenyl moiety also proved as good antibacterial agents against *E. coli*.
4. The triazoles having *p*-flourobenzoate moiety with R^1 representing phenyl (**3d**), *p*-bromophenyl (**3t**), and *p*-nitrophenyl (**3x**) exhibited better antifungal potency against *C. albicans*; compounds having electron withdrawing group, i.e., nitro on benzoate moiety with *p*-methoxyphenyl (**3k**), *p*-flourophenyl (**3o**), and naphthyl (**3z$_1$**) groups on nitrogen of amide bond appeared as potent fungicidal agents. Furthermore, compound **3e** containing electron donating group, i.e., methyl on both

Table 2 QSAR descriptors used in the study

S. no.	QSAR descriptor	Type
1	log *P*	Lipophilic
2	Zero order molecular connectivity index ($^0\chi$)	Topological
3	First order molecular connectivity index ($^1\chi$)	Topological
4	Second order molecular connectivity index ($^2\chi$)	Topological
5	Valence zero order molecular connectivity index ($^0\chi^v$)	Topological
6	Valence first order molecular connectivity index ($^1\chi^v$)	Topological
7	Valence second order molecular connectivity index ($^2\chi^v$)	Topological
8	Kier's alpha first order shape index ($\kappa\alpha_1$)	Topological
9	Kier's alpha second order shape index ($\kappa\alpha_2$)	Topological
10	Kier's first order shape index (κ_1)	Topological
11	Randic topological index	Topological
12	Balaban topological index	Topological
13	Wiener's topological index	Topological
14	Kier's second order shape index (κ_2)	Topological
15	Ionization potential	Electronic
16	Dipole moment (μ)	Electronic
17	Energy of highest occupied molecular orbital (HOMO)	Electronic
18	Energy of lowest unoccupied molecular orbital (LUMO)	Electronic
19	Total energy (Te)	Electronic
20	Nuclear energy (Nu. E)	Electronic
21	Molar refractivity (MR)	Steric

Table 3 Values of selected descriptors used in the present study

Compound	log *P*	MR	$^{0}\chi$	$^{0}\chi^{v}$	*R*	Te	HOMO	μ
3a	3.15	97.90	18.36	14.25	12.60	−4466.28	−8.96	4.29
3b	2.43	99.32	19.06	14.66	13.14	−4786.29	−8.97	4.43
3c	2.63	100.18	19.93	14.52	13.51	−5141.17	−9.08	4.18
3d	2.82	93.07	18.36	13.63	12.60	−4781.81	−9.03	1.45
3e	3.61	102.94	19.23	15.18	12.99	−4622.15	−8.76	3.94
3f	2.89	104.36	19.93	15.59	13.53	−4942.16	−8.78	4.09
3g	3.10	105.22	20.80	15.44	13.90	−5297.04	−8.88	4.43
3h	3.29	98.11	19.23	14.55	12.99	−4937.68	−8.82	1.91
3i	2.89	104.36	19.93	15.59	13.53	−4942.12	−8.57	4.12
3j	2.17	105.78	20.64	15.99	14.07	−5262.14	−8.57	4.35
3k	2.38	106.64	21.51	15.85	14.44	−5617.01	−8.67	3.51
3l	2.57	99.53	19.93	14.96	13.53	−5257.65	−8.61	1.90
3m	3.29	98.11	19.23	14.55	12.99	−4937.68	−8.95	5.80
3n	2.57	99.53	19.93	14.96	13.53	−5257.70	−8.97	5.16
3o	2.77	100.40	20.80	14.82	13.90	−5612.57	−9.07	3.33
3p	2.96	93.29	19.23	13.93	12.99	−5253.21	−9.00	3.39
3q	3.94	105.52	19.23	16.18	12.99	−4805.89	−9.05	5.36
3r	3.22	106.94	19.93	16.59	13.53	−5125.91	−9.05	5.33
3s	3.43	107.80	20.80	16.44	13.90	−5480.78	−9.15	3.53
3t	3.61	100.69	19.23	15.55	12.99	−5121.41	−9.07	3.08
3u	3.10	105.22	20.80	15.44	13.90	−5297.17	−9.77	10.14
3v	2.38	106.64	21.51	15.85	14.44	−5617.18	−9.64	9.65
3w	2.59	107.50	22.38	15.70	14.81	−5972.05	−9.88	4.67
3x	2.77	100.40	20.80	14.82	13.90	−5612.69	−9.79	7.81
3y	4.15	114.35	20.92	16.41	14.58	−5005.51	−8.94	5.70
3z	3.43	115.77	21.63	16.82	15.12	−5325.51	−8.98	6.96
3z$_1$	3.64	116.63	22.50	16.67	15.49	−5680.40	−9.07	8.94
3z$_2$	3.82	109.52	20.92	15.79	14.58	−5321.03	−9.00	6.23

benzoate and amino phenyl moieties displayed good fungicidal action against *C. albicans*.

5. The triazoles possessing flouro group on benzoate moiety with R^1 representing phenyl (**3d**), *p*-toluyl (**3h**), *p*-nitrophenyl (**3x**) appeared as effective antifungals against *A. niger*; compound **3q** containing electron donating group on benzoate moiety with bromo on amino phenyl moiety also appeared as good antifungal agent against *A. niger*.

QSAR studies

Quantitative structure activity relationship (QSAR) is a predictive tool for preliminary evaluation of the activity of compounds through computer-aided models. To identify the substituent effect on the antimicrobial activity, QSAR studies were undertaken, by employing the linear free energy relationship (LFER) model [33]. The biological activity data determined as MIC values were first transformed into pMIC values (i.e. −log MIC) and used as dependent variables in QSAR study as given in Table 1. The different molecular descriptors selected for the present study are listed in Table 2.

Molecular descriptors (independent variables) like log of octanol–water partition coefficient (log *P*), molar refractivity (MR), Kier's molecular connectivity ($^{0}\chi$, $^{0}\chi^{v}$, $^{1}\chi$, $^{1}\chi^{v}$, $^{2}\chi$, $^{2}\chi^{v}$) and shape (κ_1, $\kappa\alpha_1$, $\kappa\alpha_2$, $\kappa\alpha_3$), topological indices, Randic topological index (*R*), Balaban topological index (*J*), Wiener topological index (*W*), total energy (Te), energies of highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO), dipole moment (μ) and electronic energy (Ele. *E*) were calculated for the synthesized triazoles **3a–3z$_2$** and the values of selected descriptors are presented in Table 3.

Our previous studies in the field of QSAR [32, 34] indicated that the multi-target QSAR (mt-QSAR) models are better than one target QSAR (ot-QSAR) models in describing the antimicrobial activity. According to the ot-

QSAR models, a person should apply five different equations with different errors to predict the activity of a new compound against five microbial species. The application of ot-QSAR models, which are generally seen in the whole literature, however, were not practical when we had to predict each compound results for more than one target. In those cases we had to develop one ot-QSAR for each target.

However, very recently the interest has been increased in the development of multi-target QSAR (mt-QSAR) models. As opposed to ot-QSAR, the mt-QSAR model is a single equation that considers the nature of molecular descriptors which are common and essential for describing the antibacterial and antifungal activity [35–38].

In this study, we attempted to develop two types of mt-QSAR models viz. mt-QSAR model for describing antibacterial activity of synthesized compounds **3a**–**3z$_2$** against *S. aureus*, *B. subtilis*, and *E. coli* as well as mt-QSAR model for describing antifungal activity of synthesized compounds against *C. albicans* and *A. niger* by calculating their average antibacterial and antifungal activity values which are presented in Table 1. The standard drugs norfloxacin and fluconazole were not included in model generation because of dissimilarity in structure with synthesized compounds.

The data set of 28 triazoles **3a**–**3z$_2$** was divided into training set and test sets. Different compounds were taken in the test set on random selection basis. Compounds **3a**, **3c**, **3k**, **3p**, **3u**, **3v**, and **3z** were taken in test set for antibacterial activity whereas compounds **3d**, **3e**, **3h**, **3n**, **3t**, **3x**, and **3z$_1$** were taken in test set for antifungal activity. Different outliers were identified in case of antibacterial (**3h**, **3i**, **3n**, **3y**, and **3z$_2$**) and antifungal (**3c**, **3k**, **3o**, and **3q**) activities and the QSAR models have been developed after removal of these outliers. In multivariate statistics, it is common to define three types of outliers [39].

1. *X*/*Y* Relation outliers are substances for which the relationship between the descriptors (*X* variables) and the dependent variables (*Y* variables) is not the same as in the (rest of the) training data.
2. *X* Outliers are substances whose molecular descriptors do not lie in the same range as the (rest of the) training data.
3. *Y* Outliers are only defined for training or test samples. They are substances for which the reference value of response is invalid.

As there was no difference in the activity (Table 1) as well as the molecular descriptor range (Table 3) of these outliers when compared to other synthesized 1,4-disubstituted 1,2,3-triazoles indicated the fact that these outliers belong to the category of *Y* outliers (substances for which the reference value of response is invalid).

The average antifungal activity values were correlated with the molecular descriptors of synthesized compounds (Table 4). In general, high colinearity ($r > 0.5$) was observed between different parameters. The high interrelationship was observed between topological parameters, zero order molecular connectivity index ($^0\chi$) and Randic index (R) ($r = 0.946$), and low interrelationship was observed between electronic parameter, energy of highest occupied molecular orbital (HOMO) and lipophilic parameter, log P ($r = 0.039$). Correlation matrix for antibacterial activity of synthesized compounds with their molecular descriptors is given in Table 5.

From the correlation matrix (Table 4), it was observed that topological parameter, valance zero order molecular connectivity index ($^0\chi^v$) was found to be dominating descriptor for antifungal activity of the synthesized compounds (Eq. 1).

MLR-mt-QSAR model for antifungal activity

$$\mathrm{pMIC_{af}} = 0.024\,{}^0\chi^v - 3.71 \times 10^{-5}\,\mathrm{Te} + 0.934$$
$$n = 17,\ r = 0.896,\ q^2 = 0.715,\ s = 0.015,\ F = 28.49 \quad (1)$$

Here and thereafter, n number of data points, r correlation coefficient, q^2 cross validated r^2 obtained by leave one out

Table 4 Correlation matrix for antifungal activity of synthesized compounds

	$\mathrm{pMIC_{af}}$	log P	MR	$^0\chi$	$^0\chi^v$	R	Te	HOMO	μ
$\mathrm{pMIC_{af}}$	1.000								
log P	0.213	1.000							
MR	0.666	0.442	1.000						
$^0\chi$	0.694	0.058	0.771	1.000					
$^0\chi^v$	0.815	0.298	0.926	0.707	1.000				
R	0.629	0.209	0.881	0.946	0.768	1.000			
Te	−0.676	0.173	−0.383	−0.856	−0.415	−0.699	1.000		
HOMO	−0.376	0.039	−0.175	−0.515	−0.101	−0.356	0.588	1.000	
μ	0.185	0.129	0.394	0.413	0.287	0.414	−0.233	−0.641	1.000

Table 5 Correlation matrix for antibacterial activity of synthesized compounds

	$pMIC_{ab}$	log *P*	MR	$^{0}\chi$	$^{0}\chi^{v}$	*R*	Te	HOMO	μ
$pMIC_{ab}$	1.000								
log *P*	0.259	1.000							
MR	0.506	0.328	1.000						
$^{0}\chi$	0.260	−0.117	0.751	1.000					
$^{0}\chi^{v}$	0.399	0.395	0.904	0.532	1.000				
R	0.321	−0.128	0.790	0.978	0.549	1.000			
Te	−0.006	0.230	−0.480	−0.907	−0.331	−0.847	1.000		
HOMO	0.063	−0.001	−0.104	−0.443	−0.009	−0.345	0.597	1.000	
μ	0.730	0.267	0.598	0.518	0.430	0.561	−0.344	−0.392	1.000

method, *s* standard error of the estimate, and *F* Fischer statistics.

The developed QSAR model for antifungal activity (Eq. 1) indicated that there is a positive correlation between $^{0}\chi^{v}$ and antifungal activity of the synthesized compounds. Hence, antifungal activities of synthesized compounds will increase with increase in their $^{0}\chi^{v}$ values (Tables 1 and 3). In case of Te, the antifungal activity of synthesized compounds will decrease with increase in their Te values as its coefficient is negative.

The molecular connectivity index, an adjacency based topological index proposed by Randic is denoted by χ and is defined as sum over all the edges (*ij*) as per following:

$$\chi = \sum_{i=1}^{n} \left(V_i V_j\right)^{-1/2}$$

where V_i and V_j are the degrees of adjacent vertices *i* and *j* and *n* is the number of vertices in a hydrogen suppressed molecular structure [40]. The topological index, χ signifies the degree of branching, connectivity of atoms and unsaturation in the molecule which accounts for variation in activity [41]. In QSAR, the total energy plays important role. Total energy of a molecular system is the sum of the total electronic energy, and the energy of internuclear repulsion [41].

The developed QSAR model (Eq. 1) was cross validated by q^2 value ($q^2 = 0.715$) obtained by leave one out (LOO) method. The value of q^2 more than 0.5 indicated that the model developed is a valid one. According to the recommendations of Golbraikh and Tropsha, the only way to estimate the true predictive power of a model is to test their ability to predict accurately the biological activities of compounds. As the observed and predicted values are close to each other (Table 6), the mt-QSAR model for antifungal activity (Eq. 1) is a valid one [42].

In case of antibacterial activity, electronic parameter, dipole moment (μ, Table 5) was found most dominant in expressing antibacterial activity of the synthesized compounds. So, QSAR model for antibacterial activity (Eq. 2) was developed using μ.

MLR-mt-QSAR model for antibacterial activity

$$pMIC_{ab} = 0.139\ HOMO + 0.056\mu + 2.65$$
$$n = 16,\ r = 0.822,\ q^2 = 0.580,\ s = 0.073,\ F = 13.59 \quad (2)$$

Antibacterial activity of the synthesized compounds is also positively correlated with their μ and HOMO values which mean that antibacterial activity of the synthesized compounds will increase with increase in their μ and HOMO values (Tables 1, 3).

The importance of dipole moment in modulating antibacterial activity of 1,4-disubstituted 1,2,3-triazole bacterial targets may be due to the presence of carbonyl group ($C^{\delta+}=O^{\delta-}$) where permanent polarization is seen due to electronegativity difference between the atoms. This permanent polarization may results in a dipole–dipole interaction with antibacterial target [43].

According to the FMO concept, the HOMO and LUMO of a molecule play important roles in intermolecular interactions. Extending the concept to binding in drug-receptor systems, the major contribution to binding involves the interaction between the HOMO of the drug with the LUMO of the receptor and that between LUMO of the drug with the HOMO of the receptor. The extents of these stabilizing interactions are inversely related to the energy gap between the interacting orbitals [44].

The validity of QSAR model for antibacterial activity (Eq. 2) is indicated by its high q^2 value (0.580) as well as the low residual values (Table 6). The developed models (Eqs. 1, 2) were also able to predict the activity of test sets. The high residual values observed in case of outliers justified their removal while developing QSAR models.

Table 6 Observed, predicted and residual antibacterial and antifungal activities of the synthesized compounds obtained by developed QSAR models (Eqs. 1, 2)

Compound	$pMIC_{ab}$			$pMIC_{af}$		
	Obs.	Pre.	Res.	Obs.	Pre.	Res.
3a	1.45	1.44	0.01	1.45	1.44	0.01
3b	1.67	1.46	0.21	1.47	1.46	0.01
3c	1.89	1.47	0.42	1.48	1.47	0.01
3d	1.45	1.44	0.01	2.21	1.44	0.77
3e	1.57	1.47	0.10	1.92	1.47	0.45
3f	1.78	1.49	0.29	1.48	1.49	−0.01
3g	1.70	1.50	0.20	1.50	1.50	0.00
3h	1.67	1.47	0.20	1.92	1.47	0.45
3i	1.48	1.49	−0.01	1.48	1.49	−0.01
3j	1.70	1.51	0.19	1.50	1.51	−0.01
3k	1.82	1.52	0.30	1.82	1.52	0.30
3l	1.49	1.49	0.00	1.49	1.49	0.00
3m	1.77	1.47	0.30	1.47	1.47	0.00
3n	1.49	1.49	0.00	1.34	1.49	−0.15
3o	1.50	1.50	0.00	1.81	1.50	0.31
3p	1.78	1.46	0.32	1.47	1.46	0.01
3q	1.74	1.50	0.24	1.84	1.50	0.34
3r	1.55	1.52	0.03	1.55	1.52	0.03
3s	1.67	1.53	0.14	1.57	1.53	0.04
3t	1.54	1.50	0.04	1.99	1.50	0.49
3u	1.50	1.50	0.00	1.50	1.50	0.00
3v	2.02	1.52	0.50	1.52	1.52	0.00
3w	1.53	1.53	0.00	1.53	1.53	0.00
3x	1.71	1.50	0.21	2.26	1.50	0.76
3y	1.81	1.51	0.30	1.51	1.51	0.00
3z	1.42	1.54	−0.12	1.52	1.54	−0.02
$3z_1$	1.84	1.54	0.30	1.99	1.54	0.45
$3z_2$	1.51	1.51	0.00	1.51	1.51	0.00

It was observed from mt-QSAR models (Eqs. 1, 2) that the antibacterial and antifungal activities of the synthesized 1,4-disubstituted 1,2,3-triazoles were governed by electronic parameter, dipole moment (μ) and topological parameter, valence zero order molecular connectivity index ($^0\chi^v$), respectively.

Generally for QSAR studies, the biological activities of compounds should span 2–3 orders of magnitude. But in this study the range of antimicrobial activities of the synthesized compounds is within one order of magnitude. This is in accordance with results suggested by Bajaj et al. [45] who stated that the reliability of the QSAR model lies in its predictive ability even though the activity data are in the narrow range. When biological activity data lies in the narrow range, the presence of minimum standard deviation of the biological activity justifies its use in QSAR studies [46]. The minimum standard deviation (Table 1) observed in the antimicrobial activity data justifies its use in QSAR studies.

Conclusion

A series of amide-ester linked 1,4-disubstituted 1,2,3-triazoles **3a**–**$3z_2$** was synthesized through an easy Cu(I)-catalyzed click reaction of 2-azido-*N*-substituted acetamides with benzoic acid prop-2-ynyl esters and evaluated for their in vitro antimicrobial activity against *S. aureus*, *B. subtilis*, *E. coli*, *C. albicans*, and *A. niger*. Compounds **3m**, **3p** against *S. aureus*, compounds **3k**, **3v**, **$3z_1$** against *B. subtilis*, and compounds **3f**, **3y** against *E. coli* showed antibacterial activity comparable to standard drug, norfloxacin. The compounds **3e**, **3t**, **3x**, **$3z_1$** against *C. albicans*

and compounds **3d**, **3h** against *A. niger* displayed potent antifungal activity like reference drug, fluconazole. Remaining synthesized triazole compounds have moderate to good antimicrobial activity. The QSAR studies were carried out to predict the relationship between various physicochemical parameters and antimicrobial activity of 1,4-disubstituted 1,2,3-triazoles **3a–3z$_2$** which indicated the importance of dipole moment (μ) and zero order molecular connectivity index ($^0\chi^v$) in describing the antibacterial and antifungal activities of the synthesized compounds, respectively.

Experimental

All the chemicals were purchased from commercial suppliers and used without further purification. Melting points of the target compounds were recorded in °C by applying open capillary method and are corrected. The IR spectra were recorded on Shimazdu IR Affinity-I FT-IR spectrophotometer using potassium bromide powder and values are given in cm^{-1}. The ^{1}H NMR spectra were recorded on Bruker Avance II 400 MHz spectrometer and ^{13}C NMR on Bruker Avance II 400 at 100 MHz, in deuterated dimethylsulfoxide using tetramethylsilane (TMS) as an internal standard (chemical shift in δ, ppm). Coupling constant (J) values are given in Hertz (Hz). High resolution mass spectra were recorded on Waters Micromass Q-Tof Micro (ESI) spectrometer. The completion of reactions and the purity of the compounds were analyzed by thin layer chromatography (TLC) using readymade silica gel plates (SIL G/UV254, ALUGRAM) and visualized under ultraviolet lamp.

*General procedure for the synthesis of 1,4-disubstituted 1,2,3-triazoles **3a–3z$_2$***

2-Bromo-*N*-substituted acetamides **1** were synthesized by drop-wise addition of bromoacetyl bromides (1.2 mmol) to aromatic amines (1.0 mmol) in dry dichloromethane with continuous stirring at 0–15 °C for 4–6 h using triethylamine (3.0 mmol) as base [47]. For the synthesis of benzoic acid prop-2-ynyl esters **2** [7, 8, 11], the benzoyl chlorides (1.0 mmol) were added to the stirred solution of propargyl alcohol (1.2 mmol) in dry dichloromethane at 0–10 °C for 2–4 h in the presence of *N*,*N*-dimethylaminopyridine (1.0 mmol). Finally, in the last step, to a solution of 2-bromo-*N*-substituted acetamides **1** (1.0 mmol) and benzoic acid prop-2-ynyl esters **2** (1.0 mmol) in dimethylformamide:water (8:2) was added sodium azide (3.0 mmol) with stirring at 50–60 °C. Then copper sulfate pentahydrate (0.1 mmol) and sodium ascorbate (0.4 mmol) were added to the above reaction mixture and stirring was continued for 12–18 h. After completion of the reaction, ice cold water was added to the reaction mixture, then filtered the precipitated solid and washed with aqueous ammonia solution followed by water. To remove traces of reactants and other impurities, crude product was washed with ethyl acetate, dried under vacuum to afford the desired 1,4-disubstituted 1,2,3-triazoles **3a–3z$_2$** in good yields.

[1-[2-Oxo-2-(phenylamino)ethyl]-1H-1,2,3-triazol-4-yl]methyl 4-methylbenzoate (**3a**, $C_{19}H_{18}N_4O_3$)
Light yellow solid; yield: 81 %; m.p.: 206–210 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.38 (s, 3H, CH_3), 5.37 (s, 2H, OCH_2), 5.42 (s, 2H, NCH_2), 7.09 (t, J = 8.0 Hz, 1H, Ar–H), 7.32–7.35 (m, 4H, Ar–H), 7.59 (d, J = 8.0 Hz, 2H, Ar–H), 7.87 (d, J = 8.0 Hz, 2H, Ar–H), 8.29 (s, 1H, C–H triazole), 10.49 (s, 1H, N–H amide) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 21.6, 52.7, 58.2, 119.7, 124.2, 127.1 (C-5 triazole), 129.4, 129.8, 138.9, 142.2 (C-4 triazole), 144.3, 164.6 (C=O ester), 165.9 (C=O amide) ppm; FT-IR (KBr): $\bar{\nu}$ = 3257 (N–H str., amide), 3143 (C–H str., triazole ring), 3066, 1712 (C=O str., ester), 1672 (C=O str., amide), 1605, 1550, 1444, 1282, 1105 cm^{-1}; HRMS: *m/z* for $C_{19}H_{18}N_4O_3$ 349.13126 ([M+H]$^+$).

[1-[2-Oxo-2-(phenylamino)ethyl]-1H-1,2,3-triazol-4-yl]methyl 4-methoxybenzoate (**3b**, $C_{19}H_{18}N_4O_4$)
White solid; yield: 75 %; m.p.: 176–180 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.83 (s, 3H, OCH_3), 5.34 (s, 2H, OCH_2), 5.44 (s, 2H, NCH_2), 7.05 (d, J = 8.0 Hz, 2H, Ar–H), 7.09 (t, J = 8.0 Hz, 1H, Ar–H), 7.34 (d, J = 8.0 Hz, 2H, Ar–H), 7.59 (d, J = 8.0 Hz, 2H, Ar–H), 7.93 (d, J = 8.0 Hz, 2H, Ar–H), 8.26 (s, 1H, C–H triazole), 10.50 (s, 1H, N–H amide) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 52.7, 56.0, 58.1, 114.6, 119.7, 122.0, 124.2, 127.0 (C-5 triazole), 129.4, 131.8, 138.9, 142.3 (C-4 triazole), 163.8, 164.3 (C=O ester), 165.9 (C=O amide) ppm; FT-IR (KBr): $\bar{\nu}$ = 3278 (N–H str., amide), 3134 (C–H str., triazole ring), 3068, 1707 (C=O str., ester), 1668 (C=O str., amide), 1606, 1544, 1448, 1269, 1107, 1033 cm^{-1}; HRMS: *m/z* for $C_{19}H_{18}N_4O_4$ 367.13058 ([M+H]$^+$).

[1-[2-Oxo-2-(phenylamino)ethyl]-1H-1,2,3-triazol-4-yl]methyl 4-nitrobenzoate (**3c**, $C_{18}H_{15}N_5O_5$)
Light yellow solid; yield: 64 %; m.p.: 206–210 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 5.40 (s, 2H, OCH_2), 5.50 (s, 2H, NCH_2), 7.09 (t, J = 8.0 Hz, 1H, Ar–H), 7.32 (d, J = 8.0 Hz, 2H, Ar–H), 7.60 (d, J = 8.0 Hz, 2H, Ar–H), 8.20 (d, J = 8.0 Hz, 2H, Ar–H), 8.27 (s, 1H, C–H triazole), 8.35 (d, J = 8.0 Hz, 2H, Ar–H), 10.66 (s, 1H, N–H amide) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 52.7, 59.2, 119.7, 124.2, 124.4, 127.3 (C-5 triazole), 129.4, 131.2, 135.2, 138.9, 141.6 (C-4 triazole), 150.8, 164.6 (C=O ester), 165.9 (C=O amide) ppm; FT-IR (KBr):

$\overline{v}$ = 3251 (N–H str., amide), 3149 (C–H str., triazole ring), 3082, 1720 (C=O str., ester), 1699 (C=O str., amide), 1604, 1556, 1519, 1442, 1350, 1269, 1099 cm^{-1}; HRMS: *m/z* for $C_{18}H_{15}N_5O_5$ 382.11374 ($[M+H]^+$).

[1-[2-Oxo-2-(phenylamino)ethyl]-1H-1,2,3-triazol-4-yl]methyl 4-fluorobenzoate (**3d**, $C_{18}H_{15}FN_4O_3$)
White solid; yield: 72 %; m.p.: 188–192 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 5.34 (s, 2H, OCH_2), 5.44 (s, 2H, NCH_2), 7.09 (t, *J* = 8.0 Hz, 1H, Ar–H), 7.34 (d, *J* = 8.0 Hz, 2H, Ar–H), 7.36 (d, *J* = 8.0 Hz, 2H, Ar–H), 7.59 (d, *J* = 8.0 Hz, 2H, Ar–H), 8.04 (d, *J* = 8.0 Hz, 2H, Ar–H), 8.29 (s, 1H, C–H triazole), 10.40 (s, 1H, N–H amide) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 52.6, 58.5, 116.6, 119.7, 124.2, 126.4, 127.1 (C-5 triazole), 129.4, 132.6, 138.9, 142.2 (C-4 triazole), 164.3 (C=O ester), 165.0, 165.9 (C=O amide) ppm; FT-IR (KBr): $\overline{v}$ = 3278 (N–H str., amide), 3136 (C–H str., triazole ring), 3064, 1716 (C=O str., ester), 1678 (C=O str., amide), 1604, 1548, 1444, 1276, 1151, 1109 cm^{-1}; HRMS: *m/z* for $C_{18}H_{15}FN_4O_3$ 355.11443 ($[M+H]^+$).

[1-[2-Oxo-2-(p-tolylamino)ethyl]-1H-1,2,3-triazol-4-yl]methyl 4-methylbenzoate (**3e**, $C_{20}H_{20}N_4O_3$)
White solid; yield: 68 %; m.p.: 234–238 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.25 (s, 3H, CH_3), 2.38 (s, 3H, CH_3), 5.34 (s, 2H, OCH_2), 5.42 (s, 2H, NCH_2), 7.13 (d, *J* = 8.0 Hz, 2H, Ar–H), 7.34 (d, *J* = 8.0 Hz, 2H, Ar–H), 7.47 (d, *J* = 8.0 Hz, 2H, Ar–H), 7.87 (d, *J* = 8.0 Hz, 2H, Ar–H), 8.28 (s, 1H, C–H triazole), 10.40 (s, 1H, N–H amide) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 20.9, 21.6, 52.6, 58.2, 119.7, 127.1 (C-5 triazole), 129.8, 133.2, 136.4, 142.2 (C-4 triazole), 144.3, 164.3 (C=O ester), 165.9 (C=O amide) ppm; FT-IR (KBr): $\overline{v}$ = 3253 (N–H str., amide), 3140 (C–H str., triazole ring), 3064, 1699 (C=O str., ester), 1668 (C=O str., amide), 1548, 1438, 1278, 1105 cm^{-1}; HRMS: *m/z* for $C_{20}H_{20}N_4O_3$ 365.16000 ($[M+H]^+$).

[1-[2-Oxo-2-(p-tolylamino)ethyl]-1H-1,2,3-triazol-4-yl]methyl 4-methoxybenzoate (**3f**, $C_{20}H_{20}N_4O_4$)
White solid; yield: 78 %; m.p.: 230–234 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.26 (s, 3H, CH_3), 3.83 (s, 3H, OCH_3), 5.34 (s, 2H, OCH_2), 5.40 (s, 2H, NCH_2), 7.05 (d, *J* = 8.0 Hz, 2H, Ar–H), 7.13 (d, *J* = 8.0 Hz, 2H, Ar–H), 7.47 (d, *J* = 8.0 Hz, 2H, Ar–H), 7.93 (d, *J* = 8.0 Hz, 2H, Ar–H), 8.26 (s, 1H, C–H triazole), 10.40 (s, 1H, N–H amide) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 20.9, 52.6, 56.0, 58.1, 114.6, 119.7, 122, 127.0 (C-5 triazole), 129.8, 131.8, 133.2, 136.4, 142.3 (C-4 triazole), 163.8, 164.3 (C=O ester), 165.6 (C=O amide) ppm; FT-IR (KBr): $\overline{v}$ = 3251 (N–H str., amide), 3140 (C–H str., triazole ring), 3066, 1693 (C=O str., ester), 1668 (C=O str., amide), 1606, 1546, 1273, 1103 cm^{-1}; HRMS: *m/z* for $C_{20}H_{20}N_4O_4$ 381.15515 ($[M+H]^+$).

[1-[2-Oxo-2-(p-tolylamino)ethyl]-1H-1,2,3-triazol-4-yl]methyl 4-nitrobenzoate (**3g**, $C_{19}H_{17}N_5O_5$)
White solid; yield: 68 %; m.p.: 244–248 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.26 (s, 3H, CH_3), 5.35 (s, 2H, OCH_2), 5.50 (s, 2H, NCH_2), 7.13 (d, *J* = 8.0 Hz, 2H, Ar–H), 7.47 (d, *J* = 8.0 Hz, 2H, Ar–H), 8.20 (d, *J* = 8.0 Hz, 2H, Ar–H), 8.32 (s, 1H, C–H triazole), 8.35 (d, *J* = 8.0 Hz, 2H, Ar–H), 10.41 (s, 1H, N–H amide) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 20.9, 52.7, 59.2, 119.7, 124.2, 127.3 (C-5 triazole), 129.8, 131.2, 133.2, 135.2, 136.3, 141.6 (C-4 triazole), 150.8, 164.5 (C=O ester), 165.9 (C=O amide) ppm; FT-IR (KBr): $\overline{v}$ = 3251 (N–H str., amide), 3120 (C–H str., triazole ring), 3076, 1718 (C=O str., ester), 1658 (C=O str., amide), 1531, 1354, 1273, 1103 cm^{-1}; HRMS: *m/z* for $C_{19}H_{17}N_5O_5$ 396.12949 ($[M+H]^+$).

[1-[2-Oxo-2-(p-tolylamino)ethyl]-1H-1,2,3-triazol-4-yl]methyl 4-fluorobenzoate (**3h**, $C_{19}H_{17}FN_4O_3$)
Light green solid; yield: 62 %; m.p.: 206–210 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.26 (s, 3H, CH_3), 5.34 (s, 2H, OCH_2), 5.44 (s, 2H, NCH_2), 7.13 (d, *J* = 8.0 Hz, 2H, Ar–H), 7.36 (d, *J* = 16.0 Hz, 2H, Ar–H), 7.46 (d, *J* = 8.0 Hz, 2H, Ar–H), 8.04 (d, *J* = 16.0 Hz, 2H, Ar–H), 8.29 (s, 1H, C–H triazole), 10.40 (s, 1H, N–H amide) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 20.9, 52.6, 58.2, 116.3, 119.7, 126.4, 127.1 (C-5 triazole), 129.8, 132.6, 133.2, 136.3, 142.0 (C-4 triazole), 164.3 (C=O ester), 165.0, 165.9 (C=O amide) ppm; FT-IR (KBr): $\overline{v}$ = 3278 (N–H str., amide), 3132 (C–H str., triazole ring), 3064, 1716 (C=O str., ester), 1678 (C=O str., amide), 1606, 1546, 1278, 1151, 1103 cm^{-1}; HRMS: *m/z* for $C_{19}H_{17}FN_4O_3$ 369.13495 ($[M+H]^+$).

[1-[2-(4-Methoxyphenylamino)-2-oxoethyl]-1H-1,2,3-triazol-4-yl]methyl 4-methylbenzoate (**3i**, $C_{20}H_{20}N_4O_4$)
White solid; yield: 90 %; m.p.: 218–222 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.38 (s, 3H, CH_3), 3.72 (s, 3H, OCH_3), 5.32 (s, 2H, OCH_2), 5.42 (s, 2H, NCH_2), 6.91 (d, *J* = 8.0 Hz, 2H, Ar–H), 7.34 (d, *J* = 8.0 Hz, 2H, Ar–H), 7.50 (d, *J* = 8.0 Hz, 2H, Ar–H), 7.87 (d, *J* = 8.0 Hz, 2H, Ar–H), 8.27 (s, 1H, C–H triazole), 10.35 (s, 1H, N–H amide) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 21.6, 52.6, 55.6, 58.2, 114.5, 121.2, 127.1 (C-5 triazole), 129.8, 132.0, 142.2 (C-4 triazole), 144.3, 156.0, 164.3 (C=O ester), 165.9 (C=O amide) ppm; FT-IR (KBr): $\overline{v}$ = 3248 (N–H str., amide), 3138 (C–H str., triazole ring), 3064, 1699 (C=O str., ester), 1664 (C=O str., amide), 1610, 1550, 1450, 1267, 1103 cm^{-1}; HRMS: *m/z* for $C_{20}H_{20}N_4O_4$ 381.15867 ($[M+H]^+$).

[1-[2-(4-Methoxyphenylamino)-2-oxoethyl]-1H-1,2,3-triazol-4-yl]methyl 4-methoxybenzoate (**3j**, $C_{20}H_{20}N_4O_5$)
White solid; yield: 78 %; m.p.: 188–192 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.72 (s, 3H, OCH_3), 3.83 (s,

3H, OCH_3), 5.32 (s, 2H, OCH_2), 5.40 (s, 2H, NCH_2), 6.91 (d, $J = 8.0$ Hz, 2H, Ar–H), 7.05 (d, $J = 8.0$ Hz, 2H, Ar–H), 7.50 (d, $J = 8.0$ Hz, 2H, Ar–H), 7.93 (d, $J = 8.0$ Hz, 2H, Ar–H), 8.27 (s, 1H, C–H triazole), 10.35 (s, 1H, N–H amide) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 52.6$, 55.6, 56.0, 58.1, 114.6, 121.2, 122.0, 127.0 (C-5 triazole), 131.8, 132.0, 142.3 (C-4 triazole), 156.0, 163.8, 164.1 (C=O ester), 165.6 (C=O amide) ppm; FT-IR (KBr): $\overline{v} = 3277$ (N–H str., amide), 3136 (C–H str., triazole ring), 3060, 1691 (C=O str., ester), 1676 (C=O str., amide), 1606, 1548, 1263, 1107 cm^{-1}; HRMS: *m/z* for $C_{20}H_{20}N_4O_5$ 397.14987 ([M+H]$^+$).

[1-[2-(4-Methoxyphenylamino)-2-oxoethyl]-1H-1,2,3-triazol-4-yl]methyl 4-nitrobenzoate (**3k**, $C_{19}H_{17}N_5O_6$)
White solid; yield: 65 %; m.p.: 196–200 °C; ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 3.72$ (s, 3H, OCH_3), 5.32 (s, 2H, OCH_2), 5.50 (s, 2H, NCH_2), 6.91 (d, $J = 8.0$ Hz, 2H, Ar–H), 7.50 (d, $J = 8.0$ Hz, 2H, Ar–H), 8.20 (d, $J = 8.0$ Hz, 2H, Ar–H), 8.32 (s, 1H, C–H triazole), 8.35 (d, $J = 8.0$ Hz, 2H, Ar–H), 10.35 (s, 1H, N–H amide) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 52.6$, 55.6, 59.2, 114.5, 121.2, 124.4, 127.3 (C-5 triazole), 131.2, 132.0, 135.2, 141.6 (C-4 triazole), 150.8, 156.0, 164.5 (C=O ester), 165.6 (C=O amide) ppm; FT-IR (KBr): $\overline{v} = 3230$ (N–H str., amide), 3120 (C–H str., triazole ring), 3066, 1716 (C=O str., ester), 1656 (C=O str., amide), 1602, 1527, 1456, 1352, 1269, 1103 cm^{-1}; HRMS: *m/z* for $C_{19}H_{17}N_5O_6$ 412.12063 ([M+H]$^+$).

[1-[2-(4-Methoxyphenylamino)-2-oxoethyl]-1H-1,2,3-triazol-4-yl]methyl 4-fluorobenzoate (**3l**, $C_{19}H_{17}FN_4O_4$)
White solid; yield: 80 %; m.p.: 208–212 °C; ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 3.72$ (s, 3H, OCH_3), 5.32 (s, 2H, OCH_2), 5.44 (s, 2H, NCH_2), 6.91 (d, $J = 8.0$ Hz, 2H, Ar–H), 7.36 (d, $J = 16.0$ Hz, 2H, Ar–H), 7.49 (d, $J = 8.0$ Hz, 2H, Ar–H), 8.04 (d, $J = 16.0$ Hz, 2H, Ar–H), 8.29 (s, 1H, C–H triazole), 10.35 (s, 1H, N–H amide) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 52.6$, 55.6, 58.5, 114.5, 116.3, 121.2, 126.5, 127.1 (C-5 triazole), 132.0, 132.6, 142.0 (C-4 triazole), 156.0, 164.4 (C=O ester), 165.0, 165.9 (C=O amide) ppm; FT-IR (KBr): $\overline{v} = 3277$ (N–H str., amide), 3136 (C–H str., triazole ring), 1716 (C=O str., ester), 1678 (C=O str., amide), 1604, 1548, 1280, 1148, 1111 cm^{-1}; HRMS: *m/z* for $C_{19}H_{17}FN_4O_4$ 383.11694 ([M+H]$^+$).

[1-[2-(4-Fluorophenylamino)-2-oxoethyl]-1H-1,2,3-triazol-4-yl]methyl 4-methylbenzoate
(**3m**, $C_{19}H_{17}FN_4O_3$)
White solid; yield: 76 %; m.p.: 230–234 °C; ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 2.38$ (s, 3H, CH_3), 5.36 (s, 2H, OCH_2), 5.42 (s, 2H, NCH_2), 7.18 (d, $J = 8.0$ Hz, 2H, Ar–H), 7.33 (d, $J = 8.0$ Hz, 2H, Ar–H), 7.60 (d, $J = 8.0$ Hz, 2H, Ar–H), 7.87 (d, $J = 8.0$ Hz, 2H, Ar–H), 8.29 (s, 1H, C–H triazole), 10.56 (s, 1H, N–H amide) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 21.6$, 52.6, 58.2, 115.9, 116.1, 121.5, 127.1 (C-5 triazole), 129.8, 135.2, 142.2 (C-4 triazole), 144.3, 157.5, 159.9, 164.6 (C=O ester), 165.9 (C=O amide) ppm; FT-IR (KBr): $\overline{v} = 3253$ (N–H str., amide), 3151 (C–H str., triazole ring), 3070, 1703 (C=O str., ester), 1672 (C=O str., amide), 1604, 1558, 1510, 1274, 1158, 1101 cm^{-1}; HRMS: *m/z* for $C_{19}H_{17}FN_4O_3$ 367.12173 ([M+H]$^+$).

[1-[2-(4-Fluorophenylamino)-2-oxoethyl]-1H-1,2,3-triazol-4-yl]methyl 4-methoxybenzoate
(**3n**, $C_{19}H_{17}FN_4O_4$)
Light green solid; yield: 78 %; m.p.: 212–216 °C; ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 3.83$ (s, 3H, OCH_3), 5.34 (s, 2H, OCH_2), 5.41 (s, 2H, NCH_2), 7.05 (d, $J = 8.0$ Hz, 2H, Ar–H), 7.18 (d, $J = 8.0$ Hz, 2H, Ar–H), 7.60 (d, $J = 8.0$ Hz, 2H, Ar–H), 7.93 (d, $J = 8.0$ Hz, 2H, Ar–H), 8.27 (s, 1H, C–H triazole), 10.55 (s, 1H, N–H amide) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 52.6$, 56.0, 58.1, 114.6, 115.9, 121.5, 122.0, 127.0 (C-5 triazole), 131.8, 135.2, 142.3 (C-4 triazole), 159.9, 163.8, 164.3 (C=O ester), 165.8 (C=O amide) ppm; FT-IR (KBr): $\overline{v} = 3248$ (N–H str., amide), 3155 (C–H str., triazole ring), 3072, 1703 (C=O str., ester), 1683 (C=O str., amide), 1608, 1556, 1269, 1101 cm^{-1}; HRMS: *m/z* for $C_{19}H_{17}FN_4O_4$ 385.12134 ([M+H]$^+$).

[1-[2-(4-Fluorophenylamino)-2-oxoethyl]-1H-1,2,3-triazol-4-yl]methyl 4-nitrobenzoate (**3o**, $C_{18}H_{14}FN_5O_5$)
White solid; yield: 77 %; m.p.: 214–218 °C; ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 5.38$ (s, 2H, OCH_2), 5.50 (s, 2H, NCH_2), 7.17 (d, $J = 8.0$ Hz, 2H, Ar–H), 7.61 (d, $J = 8.0$ Hz, 2H, Ar–H), 8.20 (d, $J = 8.0$ Hz, 2H, Ar–H), 8.33 (s, 1H, C–H triazole), 8.35 (d, $J = 8.0$ Hz, 2H, Ar–H), 10.64 (s, 1H, N–H amide) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 52.6$, 59.2, 115.9, 121.4, 124.4, 127.3 (C-5 triazole), 131.2, 135.2, 141.7 (C-4 triazole), 150.8, 157.5, 159.9, 164.5 (C=O ester), 165.9 (C=O amide) ppm; FT-IR (KBr): $\overline{v} = 3217$ (N–H str., amide), 3153 (C–H str., triazole ring), 3066, 1714 (C=O str., ester), 1668 (C=O str., amide), 1618, 1560, 1516, 1352, 1271, 1105 cm^{-1}; HRMS: *m/z* for $C_{18}H_{14}FN_5O_5$ 400.10425 ([M+H]$^+$).

[1-[2-(4-Fluorophenylamino)-2-oxoethyl]-1H-1,2,3-triazol-4-yl]methyl 4-fluorobenzoate
(**3p**, $C_{18}H_{14}F_2N_4O_3$)
Light greenish solid; yield: 68 %; m.p.: 206–210 °C; ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 5.34$ (s, 2H, OCH_2), 5.44 (s, 2H, NCH_2), 7.18 (d, $J = 8.0$ Hz, 2H, Ar–H), 7.36 (d, $J = 8.0$ Hz, 2H, Ar–H), 7.61 (d, $J = 8.0$ Hz, 2H, Ar–

H), 8.04 (d, $J = 8.0$ Hz, 2H, Ar–H), 8.29 (s, 1H, C–H triazole), 10.40 (s, 1H, N–H amide) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 52.6$, 58.5, 115.9, 121.5, 126.4, 127.1 (C-5 triazole), 132.7, 135.2, 142.2 (C-4 triazole), 159.9, 164.3 (C=O ester), 165.0, 165.9 (C=O amide) ppm; FT-IR (KBr): $\overline{v} = 3280$ (N–H str., amide), 3140 (C–H str., triazole ring), 3055, 1714 (C=O str., ester), 1676 (C=O str., amide), 1606, 1550, 1278, 1101 cm^{-1}; HRMS: *m/z* for $C_{18}H_{14}F_2N_4O_3$ 373.10470 ([M+H]$^+$).

[1-[2-(4-Bromophenylamino)-2-oxoethyl]-1H-1,2,3-triazol-4-yl]methyl 4-methylbenzoate
(**3q**, $C_{19}H_{17}BrN_4O_3$)
White solid; yield: 72 %; m.p.: 230–234 °C; ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 2.38$ (s, 3H, CH_3), 5.36 (s, 2H, OCH_2), 5.42 (s, 2H, NCH_2), 7.33 (d, $J = 8.0$ Hz, 2H, Ar–H), 7.52 (d, $J = 8.0$ Hz, 2H, Ar–H), 7.56 (d, $J = 8.0$ Hz, 2H, Ar–H), 7.87 (d, $J = 8.0$ Hz, 2H, Ar–H), 8.29 (s, 1H, C–H triazole), 10.64 (s, 1H, N–H amide) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 21.6$, 52.6, 58.1, 121.6, 127.1 (C-5 triazole), 129.8, 132.2, 138.2, 142.2 (C-4 triazole), 144.3, 164.6 (C=O ester), 165.6 (C=O amide) ppm; FT-IR (KBr): $\overline{v} = 3246$ (N–H str., amide), 3143 (C–H str., triazole ring), 3051, 1703 (C=O str., ester), 1674 (C=O str., amide), 1606, 1546, 1274, 1103 cm^{-1}; HRMS: *m/z* for $C_{19}H_{17}BrN_4O_3$ 429.06156 ([M+H]$^+$).

[1-[2-(4-Bromophenylamino)-2-oxoethyl]-1H-1,2,3-triazol-4-yl]methyl 4-methoxybenzoate (**3r**, $C_{19}H_{17}BrN_4O_4$)
White solid; yield: 70 %; m.p.: 226–230 °C; ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 3.83$ (s, 3H, OCH_3), 5.36 (s, 2H, OCH_2), 5.40 (s, 2H, NCH_2), 7.05 (d, $J = 8.0$ Hz, 2H, Ar–H), 7.51–7.57 (m, 4H, Ar–H), 7.93 (d, $J = 8.0$ Hz, 2H, Ar–H), 8.27 (s, 1H, C–H triazole), 10.64 (s, 1H, N–H amide) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 52.7$, 56.0, 58.1, 114.6, 121.6, 122.0, 127.0 (C-5 triazole), 131.8, 132.2, 138.2, 142.3 (C-4 triazole), 163.8, 164.9 (C=O ester), 165.6 (C=O amide) ppm; FT-IR (KBr): $\overline{v} = 3277$ (N–H str., amide), 3136 (C–H str., triazole ring), 3066, 1708 (C=O str., ester), 1681 (C=O str., amide), 1604, 1539, 1485, 1267, 1105 cm^{-1}; HRMS: *m/z* for $C_{19}H_{17}BrN_4O_4$ 445.05141 ([M+H]$^+$).

[1-[2-(4-Bromophenylamino)-2-oxoethyl]-1H-1,2,3-triazol-4-yl]methyl 4-nitrobenzoate (**3s**, $C_{18}H_{14}BrN_5O_5$)
Light yellowish solid; yield: 76 %; m.p.: 228–232 °C; ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 5.38$ (s, 2H, OCH_2), 5.50 (s, 2H, NCH_2), 7.52 (d, $J = 8.0$ Hz, 2H, Ar–H), 7.56 (d, $J = 8.0$ Hz, 2H, Ar–H), 8.20 (d, $J = 8.0$ Hz, 2H, Ar–H), 8.35 (d, $J = 8.0$ Hz, 2H, Ar–H), 8.33 (s, 1H, C–H triazole), 10.64 (s, 1H, N–H amide) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 52.7$, 59.7, 121.6, 124.4, 127.3 (C-5 triazole), 131.2, 132.2, 135.2, 138.2, 141.7 (C-4 triazole), 150.8, 164.5 (C=O ester), 165.6 (C=O amide) ppm; FT-IR (KBr): $\overline{v} = 3246$ (N–H str., amide), 3170 (C–H str., triazole ring), 3047, 1714 (C=O str., ester), 1686 (C=O str., amide), 1600, 1533, 1278, 1112 cm^{-1}; HRMS: *m/z* for $C_{18}H_{14}BrN_5O_5$ 458.03157 ([M+H]$^+$).

[1-[2-(4-Bromophenylamino)-2-oxoethyl]-1H-1,2,3-triazol-4-yl]methyl 4-fluorobenzoate
(**3t**, $C_{18}H_{14}BrFN_4O_3$)
Light green solid; yield: 79 %; m.p.: 224–228 °C; ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 5.37$ (s, 2H, OCH_2), 5.44 (s, 2H, NCH_2), 7.36 (d, $J = 8.0$ Hz, 2H, Ar–H), 7.52 (d, $J = 8.0$ Hz, 2H, Ar–H), 7.56 (d, $J = 8.0$ Hz, 2H, Ar–H), 8.04 (d, $J = 8.0$ Hz, 2H, Ar–H), 8.29 (s, 1H, C–H triazole), 10.66 (s, 1H, N–H amide) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 52.7, 58.5, 115.9, 116.6, 121.6, 126.5, 127.1$ (C-5 triazole), 132.2, 132.7, 138.2, 142.1 (C-4 triazole), 164.8 (C=O ester), 165.0 (C=O amide) ppm; FT-IR (KBr): $\overline{v} = 3275$ (N–H str., amide), 3128 (C–H str., triazole ring), 1714 (C=O str., ester), 1680 (C=O str., amide), 1602, 1543, 1278, 1103 cm^{-1}; HRMS: *m/z* for $C_{18}H_{14}BrFN_4O_3$ 433.03168 ([M+H]$^+$).

[1-[2-(4-Nitrophenylamino)-2-oxoethyl]-1H-1,2,3-triazol-4-yl]methyl 4-methylbenzoate (**3u**, $C_{19}H_{17}N_5O_5$)
Yellow solid; yield: 96 %; m.p.: 226–230 °C; ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 2.37$ (s, 3H, CH_3), 5.43 (s, 2H, OCH_2), 5.47 (s, 2H, NCH_2), 7.33 (d, $J = 8.0$ Hz, 2H, Ar–H), 7.84 (d, $J = 8.0$ Hz, 2H, Ar–H), 7.86 (d, $J = 12.0$ Hz, 2H, Ar–H), 8.24 (d, $J = 12.0$ Hz, 2H, Ar–H), 8.31 (s, 1H, C–H triazole), 11.10 (s, 1H, N–H amide) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 21.6$, 52.8, 58.2, 119.5, 125.6, 127.1 (C-5 triazole), 129.7, 129.8, 142.3 (C-4 triazole), 143.1, 144.3, 145.0, 164.5 (C=O ester), 165.9 (C=O amide) ppm; FT-IR (KBr): $\overline{v} = 3219$ (N–H str., amide), 3153 (C–H str., triazole ring), 3078, 1710 (C=O str., ester), 1683 (C=O str., amide), 1556, 1512, 1348, 1271, 1103 cm^{-1}; HRMS: *m/z* for $C_{19}H_{17}N_5O_5$ 396.13101 ([M+H]$^+$).

[1-[2-(4-Nitrophenylamino)-2-oxoethyl]-1H-1,2,3-triazol-4-yl]methyl 4-methoxybenzoate
(**3v**, $C_{19}H_{17}N_5O_6$)
Light yellow solid; yield: 98 %; m.p.: 234–238 °C; ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 3.83$ (s, 3H, OCH_3), 5.37 (s, 2H, OCH_2), 5.41 (s, 2H, NCH_2), 7.05 (d, $J = 8.0$ Hz, 2H, Ar–H), 7.86 (d, $J = 8.0$ Hz, 2H, Ar–H), 7.93 (d, $J = 8.0$ Hz, 2H, Ar–H), 8.25 (d, $J = 8.0$ Hz, 2H, Ar–H), 8.28 (s, 1H, C–H triazole), 11.11 (s, 1H N–H, amide) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 52.8$, 56.0, 58.1, 114.6, 119.5, 122.0, 126.5, 127.1 (C-5 triazole), 131.8, 142.3 (C-4 triazole), 143.1, 145.0, 163.8, 164.9 (C=O ester), 165.9 (C=O amide) ppm; FT-IR (KBr): $\overline{v} = 3253$ (N–H str., amide), 3155 (C–H str., triazole ring), 3082, 1708 (C=O str., ester), 1681 (C=O str., amide), 1604,

1556, 1506, 1348, 1265, 1103 cm^{-1}; HRMS: *m/z* for $C_{19}H_{17}N_5O_6$ 412.12053 ($[M+H]^+$).

[1-[2-(4-Nitrophenylamino)-2-oxoethyl]-1H-1,2,3-triazol-4-yl]methyl-4-nitrobenzoate (**3w**, $C_{18}H_{14}N_6O_7$)
Light yellow solid; yield: 80 %; m.p.: 224–228 °C; ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 5.48$ (s, 2H, OCH_2), 5.51 (s, 2H, NCH_2), 7.83 (d, $J = 8.0$ Hz, 2H, Ar–H), 8.19 (d, $J = 8.0$ Hz, 2H, Ar–H), 8.24 (d, $J = 8.0$ Hz, 2H, Ar–H), 8.29 (s, 1H, C–H triazole), 8.35 (d, $J = 8.0$ Hz, 2H, Ar–H), 11.12 (s, 1H, N–H amide) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 52.8$, 59.2, 119.5, 124.4, 125.6, 127.3 (C-5 triazole), 131.2, 135.2, 141.8 (C-4 triazole), 143.1, 145.0, 150.8, 164.5 (C=O ester), 165.8 (C=O amide) ppm; FT-IR (KBr): $\overline{\nu} = 3222$ (N–H str., amide), 3155 (C–H str., triazole ring), 3049, 1722 (C=O str., ester), 1685 (C=O str., amide), 1587, 1516, 1342, 1269, 1103 cm^{-1}; HRMS: *m/z* for $C_{18}H_{14}N_6O_7$ 425.08582 ($[M+H]^+$).

[1-[2-(4-Nitrophenylamino)-2-oxoethyl]-1H-1,2,3-triazol-4-yl]methyl 4-fluorobenzoate (**3x**, $C_{18}H_{14}FN_5O_5$)
White solid; yield: 60 %; m.p.: 230–234 °C; ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 5.44$ (s, 2H, OCH_2), 5.49 (s, 2H, NCH_2), 7.36 (d, $J = 8.8$ Hz, 2H, Ar–H), 7.87 (d, $J = 8.8$ Hz, 2H, Ar–H), 8.03 (d, $J = 8.8$ Hz, 2H, Ar–H), 8.24 (d, $J = 8.8$ Hz, 2H, Ar–H), 8.32 (s, 1H, C–H triazole), 11.11 (s, 1H, N–H amide) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 52.8$, 58.5, 116.5, 119.5, 125.5, 126.4, 127.1 (C-5 triazole), 132.7, 142.1 (C-4 triazole), 143.0, 145.1, 164.4 (C=O ester), 165.0, 165.8 (C=O amide) ppm; FT-IR (KBr): $\overline{\nu} = 3217$ (N–H str., amide), 3159 (C–H str., triazole ring), 3051, 1708 (C=O str., ester), 1687 (C=O str., amide), 1602, 1573, 1508, 1344, 1278, 1112 cm^{-1}; HRMS: *m/z* for $C_{18}H_{14}FN_5O_5$ 398.09097 ($[M+H]^+$).

[1-[2-(Naphthalen-1-ylamino)-2-oxoethyl]-1H-1,2,3-triazol-4-yl]methyl 4-methylbenzoate (**3y**, $C_{23}H_{20}N_4O_3$)
White solid; yield: 78 %; m.p.: 236–240 °C; ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 2.38$ (s, 3H, CH_3), 5.47 (s, 2H, OCH_2), 5.58 (s, 2H, NCH_2), 7.33 (d, $J = 8.0$ Hz, 2H, Ar–H), 7.52 (d, $J = 8.0$ Hz, 1H, Ar–H), 7.57 (d, $J = 8.0$ Hz, 1H, Ar–H), 7.59 (d, $J = 8.0$ Hz, 1H, Ar–H), 7.72 (d, $J = 8.0$ Hz, 1H, Ar–H), 7.80 (d, $J = 8.0$ Hz, 1H, Ar–H), 7.87 (d, $J = 8.0$ Hz, 2H, Ar–H), 7.96 (d, $J = 8.0$ Hz, 1H, Ar–H), 8.18 (d, $J = 8.0$ Hz, 1H, Ar–H), 8.36 (s, 1H, C–H triazole), 10.48 (s, 1H, N–H amide) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 21.6$, 52.6, 58.2, 122.0, 123.1, 126.0, 126.2, 126.5, 126.7, 127.1 (C-5 triazole), 127.2, 128.0, 128.7, 129.4, 129.8, 133.2, 134.2, 142.2 (C-4 triazole), 144.3, 164.3 (C=O ester), 165.6 (C=O amide) ppm; FT-IR (KBr): $\overline{\nu} = 3253$ (N–H str., amide), 3151 (C–H str., triazole ring), 3047, 1703 (C=O str., ester), 1666 (C=O str., amide), 1608, 1548, 1454, 1267, 1101 cm^{-1}; HRMS: *m/z* for $C_{23}H_{20}N_4O_3$ 401.15076 ($[M+H]^+$).

[1-[2-(Naphthalen-1-ylamino)-2-oxoethyl]-1H-1,2,3-triazol-4-yl]methyl 4-methoxybenzoate (**3z**, $C_{23}H_{20}N_4O_4$)
White solid; yield: 73 %; m.p.: 216–220 °C; ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 3.83$ (s, 3H, OCH_3), 5.41 (s, 2H, OCH_2), 5.58 (s, 2H, NCH_2), 7.05 (d, $J = 8.0$ Hz, Ar–H, 2H), 7.52 (d, $J = 8.0$ Hz, 1H, Ar–H), 7.58 (d, $J = 8.0$ Hz, 1H, Ar–H), 7.59 (d, $J = 8.0$ Hz, 1H, Ar–H), 7.72 (d, $J = 8.0$ Hz, 1H, Ar–H), 7.80 (d, $J = 8.0$ Hz, 1H, Ar–H), 7.92–7.97 (m, 3H, Ar–H), 8.18 (d, $J = 8.0$ Hz, 1H, Ar–H), 8.33 (s, 1H, C–H triazole), 10.49 (s, 1H, N–H amide) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 52.6$, 56.0, 58.1, 114.6, 122.0, 123.1, 126.0, 126.2, 126.5, 126.7, 127.1 (C-5 triazole), 128.0, 128.7, 131.8, 133.2, 134.2, 142.3 (C-4 triazole), 163.8, 164.3 (C=O ester), 165.6 (C=O amide) ppm; FT-IR (KBr): $\overline{\nu} = 3236$ (N–H str., amide), 3161 (C–H str., triazole ring), 3049, 1705 (C=O str., ester), 1680 (C=O str., amide), 1600, 1550, 1454, 1269, 1112 cm^{-1}; HRMS: *m/z* for $C_{23}H_{20}N_4O_4$ 417.15579 ($[M+H]^+$).

[1-[2-(Naphthalen-1-ylamino)-2-oxoethyl]-1H-1,2,3-triazol-4-yl]methyl 4-nitrobenzoate (**3z$_1$**, $C_{22}H_{17}N_5O_5$)
White solid; yield: 78 %; m.p.: 204–208 °C; ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 5.52$ (s, 2H, OCH_2), 5.59 (s, 2H, NCH_2), 7.51 (d, $J = 8.0$ Hz, 1H, Ar–H), 7.57 (d, $J = 8.0$ Hz, 1H, Ar–H), 7.59 (d, $J = 8.0$ Hz, 1H, Ar–H), 7.72 (d, $J = 8.0$ Hz, 1H, Ar–H), 7.80 (d, $J = 8.0$ Hz, 1H, Ar–H), 7.96 (d, $J = 8.0$ Hz, 1H, Ar–H), 8.17 (d, $J = 8.0$ Hz, 1H, Ar–H), 8.20 (d, $J = 8.0$ Hz, 2H, Ar–H), 8.34 (s, 1H, C–H triazole), 8.37 (d, $J = 8.0$ Hz, 2H, Ar–H), 10.47 (s, 1H, N–H amide) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 52.6$, 59.2, 122.0, 123.1, 124.4, 126.0, 126.2, 126.5, 126.7, 127.4 (C-5 triazole), 128.0, 128.7, 131.2, 133.2, 134.2, 135.2, 141.7 (C-4 triazole), 150.8, 164.5 (C=O ester), 165.6 (C=O amide) ppm; FT-IR (KBr): $\overline{\nu} = 3304$ (N–H str., amide), 3155 (C–H str., triazole ring), 3089, 1714 (C=O str., ester), 1670 (C=O str., amide), 1600, 1554, 1525, 1352, 1274, 1112 cm^{-1}; HRMS: *m/z* for $C_{22}H_{17}N_5O_5$ 432.13090 ($[M+H]^+$).

[1-[2-(Naphthalen-1-ylamino)-2-oxoethyl]-1H-1,2,3-triazol-4-yl]methyl 4-fluorobenzoate
(**3z$_2$**, $C_{22}H_{17}FN_4O_3$)
Light green solid; yield: 87 %; m.p.: 220–224 °C; ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 5.45$ (s, 2H, OCH_2), 5.59 (s, 2H, NCH_2), 7.36 (d, $J = 8.0$ Hz, 2H, Ar–H), 7.50 (s, 1H, Ar–H), 7.58–7.59 (m, 2H, Ar–H), 7.72 (d, $J = 8.0$ Hz, 1H, Ar–H), 7.80 (d, $J = 8.0$ Hz, 1H, Ar–H), 7.96 (d, $J = 8.0$ Hz, 1H, Ar–H), 8.04 (d, $J = 8.0$ Hz, 2H, Ar–H), 8.18 (s, 1H, Ar–H), 8.36 (s, 1H, C–H triazole), 10.54 (s, 1H, N–H amide) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 52.6$, 58.6, 116.6, 122.0, 123.1, 126.0, 126.2, 126.5,

126.6, 127.2 (C-5 triazole), 128.0, 128.7, 132.7, 133.2, 134.2, 142.1 (C-4 triazole), 164.4 (C=O ester), 165.0, 165.6 (C=O amide), 166.9 ppm; FT-IR (KBr): $\bar{\nu} = 3253$ (N–H str., amide), 3146 (C–H str., triazole ring), 3032, 1707 (C=O str., ester), 1664 (C=O str., amide), 1600, 1550, 1436, 1273, 1101 cm^{-1}; HRMS: *m/z* for $C_{22}H_{17}FN_4O_3$ 405.13562 ($[M+H]^+$).

Antibacterial activity

All the synthesized 1,4-disubstituted 1,2,3-triazoles **3a–3z$_2$** were screened for in vitro antibacterial activity against two Gram positive bacteria, *S. aureus* (MTCC 1430) and *B. subtilis* (MTCC 2423) and one Gram negative bacteria, *E. coli* (MTCC 739). Dilutions of test and standard compounds were prepared in double strength nutrient broth [48], while dimethylsulfoxide was used as solvent control. The in vitro activities of synthesized triazoles were tested in 1.0 cm^3 nutrient broth (1000 mm^3) taken in each test tube by standard serial dilution method [49]. To the first test tube, 1.0 cm^3 of drug solution (100 μg/cm^3) was added aseptically to get the concentration of 50 μg/cm^3. From this dilution, other concentrations were prepared aseptically by serial dilution technique to get final concentration 25, 12.5, 6.25, 3.12, 1.56, and 0.78 μg/cm^3. All the test tubes were aseptically inoculated by desired bacterial suspension of 0.1 cm^3 (100 mm^3). The samples were incubated at 37 °C for 24 h and the results were recorded in terms of minimum inhibitory concentration (MIC) as depicted in Table 1. To check the effect of solvent on bacterial growth, a control test was performed with test medium supplemented with dimethylsulfoxide at same dilution as used in experiment. The antibacterial potency of the compounds was compared with norfloxacin, taken as reference drug.

Antifungal activity

All synthesized triazoles **3a–3z$_2$** were evaluated for in vitro antifungal activity against two fungal strains viz. *Candida albicans* (MTCC 854) and *A. niger* (MTCC 282) and fluconazole was used as standard drug. Sabouraud dextrose broth [48] was employed as culture media and dimethylsulfoxide as solvent control. A suspension of fungal spores in sterile saline was prepared from 2 to 7 days old culture of fungus growing on sabourauds dextrose broth (2 days for *C. albicans* and 7 days for *A. niger*). The final spore concentration was 100 mm^3/cm^3. The stock solutions of 50 μg/cm^3 of test compounds and standard drug were diluted to get concentrations of 25, 12.5, 6.25, 3.12, 1.56, and 0.78 μg/cm^3. These dilutions were inoculated with suspension of respective microorganism in their culture media and were incubated at 25 °C for 2 days for *C. albicans* and for 7 days in case of *A. niger.* The results of antifungal evaluation are given in terms of minimum inhibitory concentration (MIC) as furnished in Table 1.

QSAR studies

The structures of amide-ester linked 1,4-disubstituted 1,2,3-triazoles **3a–3z$_2$** were first pre-optimized with the molecular mechanics force field (MM^+) procedure included in Hyperchem 6.03 [50] and the resulting geometries are further refined by means of the semiempirical method parametric method-3 (PM3). We chose a gradient norm limit of 0.01 kcal/Å for the geometry optimization. The lowest energy structure was used for each molecule to calculate physicochemical properties using TSAR 3.3 software for Windows [51]. Further, the regression analysis was performed using the SPSS software package [52].

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