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An International Journal for Rapid Communication of Synthetic Organic Chemistry

ISSN: 0039-7911 (Print) 1532-2432 (Online) Journal homepage: http://www.tandfonline.com/loi/lsyc20

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To cite this article: C. P. Kaushik, Raj Luxmi, Mukesh Kumar, Dharmendra Singh, Krishan Kumar & Ashima Pahwa (2019): One-pot facile synthesis, crystal structure and antifungal activity of 1,2,3-triazoles bridged with amine-amide functionalities, Synthetic Communications, DOI: 10.1080/00397911.2018.1544371

To link to this article: https://doi.org/10.1080/00397911.2018.1544371

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https://doi.org/10.1080/00397911.2018.1544371

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One-pot facile synthesis, crystal structure and antifungal activity of 1,2,3-triazoles bridged with amine-amide functionalities

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ABSTRACT

A library of twenty five 1,2,3-triazoles bridged with amine-amide functionalities have been synthesized from reaction of *N*-substituted(prop-2-yn-1-yl)amines **(2a–2e)**, 2-bromo-*N*-arylacetamides **(4a–4e)** and sodium azide through copper(I)-catalyzed alkyne-azide cycloaddition. The synthesized compounds were characterized by using FTIR, ^{1}H NMR, ^{13}C NMR, and HRMS techniques. The structures of synthesized **5a** (CCDC 1569245) and **5h** (CCDC 1569249) were also confirmed by X-ray crystallography. Antifungal evaluation of newly synthesized triazoles was carried out against – *Candida albicans* and *Aspergillus niger*. Biological screening of synthesized 1,2,3-triazoles revealed moderate to good antifungal activity against tested strains.

GRAPHICAL ABSTRACT

ARTICLE HISTORY
Received 19 September 2018

KEYWORDS
Antifungal activity; click synthesis; X-ray crystallography; 1,4-disubstituted 1,2,3-triazoles

Introduction

The continuous escalation in microbial infections has emerged as a threat to human beings throughout the world.[1] A number of antimicrobials have been discovered so far to combat microbial diseases. In spite of this, cases with microbial resistance against the present drugs are increasing steadily. In this regard, nitrogen heterocycles attracted the attention of researchers due to drugs like rufinamide, pyrazinamide, isoniazid, rifampicin etc., possess N-heterocyclic ring system. Nitrogen-containing heterocycles exhibited a wide range of biological activities,[2,3] among these heterocycles, significant emphasis has been given to the triazole nucleus, on account of pharmacological activities like antidiabetic,[4] anticonvulsant,[5] antimicrobial,[6–9] antitrypanosomal,[10,11] antimalarial,[12–14] anti-HIV,[15,16] anticancer,[17–20] antitubercular,[21–23] anti-inflammatory,[24,25] antiallergic,[26] antioxidant,[27–29] etc.

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Supplemental data for this article can be accessed on the publisher's website.

Huisgen's 1,3-dipolar alkyne-azide cycloaddition reaction[30] was traditionally used for accessing substituted 1,2,3-triazoles. This classical reaction of alkyne-azide lacks selectivity yielding both 1,4 and 1,5 disubstituted 1,2,3 triazoles. Owing to this, Cu (I) catalyzed 1,3-dipolar cycloaddition,[31,32] between azides and terminal alkynes, came out as an effective method for the selective synthesis of 1,4-disubstituted 1,2,3-triazoles, nailed as one of the important examples of the "click" reaction. Major advantage of click chemistry protocol is product selectivity with high yield under milder reaction conditions.

Thereby, keeping the above factors, we herein report the synthesis of amine-amide disubstituted 1,2,3-triazoles from *N*-substituted(prop-2-yn-1yl)amines and 2-azido-*N*-arylacetamides (synthesized *in situ* from the reaction of 2-bromo-*N*-arylacetamides and sodium azide) using click chemistry approach. Structural elucidation of all the triazole derivatives was carried out by using FTIR, ^{1}H NMR, ^{13}C NMR, and HRMS techniques. Further, structure of the compounds of **5a** (CCDC 1569245) and **5h** (CCDC 1569249) were also confirmed through single crystal X-ray crystallography. The synthesized triazoles were evaluated for *in vitro* antifungal activity against – *Candida albicans* and *Aspergillus niger* by the serial dilution method.

Results and discussion

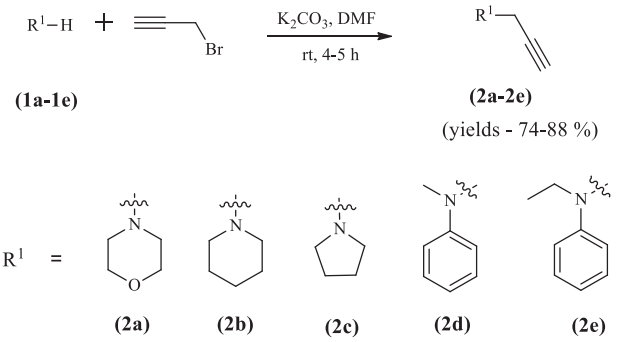
Chemistry

The synthetic route for preparation of target compounds **(5a–5y)** is given in Scheme 3. The terminal alkynes i.e. *N*-substituted(prop-2-yn-1yl)amines **(2a–2e)** were synthesized from reaction of secondary amines **(1a–1e)** and propargyl bromide at room temperature for 4–5 h in dimethylformamide solvent using potassium carbonate as a base (Scheme 1). 2-Bromo-*N*-arylacetamides **(4a–4e)** were synthesized from the reaction of aromatic amine **(3a–3e)** with bromoacetyl bromide in the presence of potassium carbonate in dichloromethane at 0–5 °C for 15–20 min (Scheme 2). In the last step for the synthesis of amine-amide linked 1,4-disubsituted 1,2,3-triazoles **(5a–5y)**, *N*-substituted(prop-2-yn-1yl)amines **(2a–2e)** were reacted to 2-bromo-*N*-arylacetamides **(4a–4e),** sodium azide at 25-40 °C for 6–10 h in the presence of copper sulfate pentahydrate and sodium ascorbate in dimethylformamide.

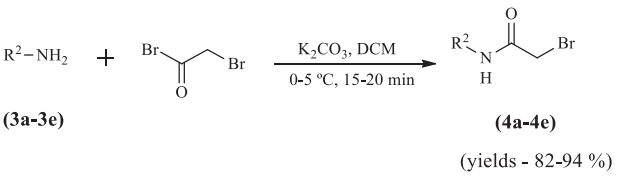
The structures of synthesized compounds were supported by FTIR, ^{1}H NMR, ^{13}C NMR spectroscopy and HRMS data. In FTIR spectra, absorption frequencies at 3294–3260 cm^{-1} were corresponding to N–H stretching of amide group. Absorption bands at 3172–3132 cm^{-1} and 3098–3047 cm^{-1} corresponds to C–H str. of triazole and aromatic ring, respectively. Band at 1720–1670 cm^{-1} was corresponding to C = O stretching of amide group.

^{1}H NMR showed singlets at δ 11.08–10.30 for amide proton and at δ 8.04–7.95 for triazolyl proton whereas, the singlets at δ 5.52–5.24 and at δ 4.62–3.52 were observed for methylene protons of NCH_2CO and NCH_2 moiety, respectively.

^{13}C NMR signals for carbonyl carbon of amide group appeared in range of δ 165.9–164.2. Whereas, signals for C-4 and C-5 of triazole ring appeared in region δ 145.2–143.3 and δ 126.1–124.9, respectively. Further, HRMS data of all the compounds confirmed the assigned structures.



Scheme 1. Synthesis of N-substituted(prop-2-yn-1yl)amines (**2a–2e**).



Compound	R^2
4a	C_6H_5
4b	4-$CH_3OC_6H_4$
4c	4-FC_6H_4
4d	4-$NO_2C_6H_4$
4e	α-$C_{10}H_7$ (α-naphthyl)

Scheme 2. Synthesis of 2-Bromo-N-arylacetamides (**4a–4e**).

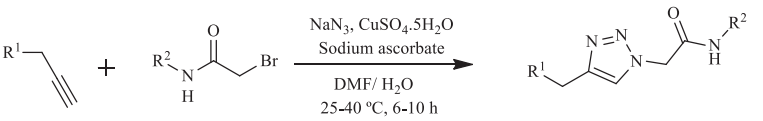
X-ray crystallographic study

Single crystals of 2-(4-(Morpholinomethyl)-1*H*-1,2,3-triazol-1-yl)-*N*-phenylacetamide **(5a)** (Table 1, Figure 1) and *N*-(4-fluorophenyl)-2-(4-(piperidin-1-ylmethyl)-1*H*-1,2,3-triazol-1-yl)acetamide **(5h)** (Table 2, Figure 2) were grown in ethyl acetate using the slow evaporation technique. Single crystal data for compounds **5a** and **5h** has been deposited in the Cambridge Crystallographic Data Center and assigned to the CCDC 1569245 and CCDC 1569249, respectively, which is available online at www.ccdc.cam.ac.uk/conts/retrieving.html.

Antifungal activity

In vitro antifungal activity of the synthesized compounds **(5a–5y)** was carried out against two fungal strains – *Candida albicans* (MTCC 227) and *Aspergillus niger* (MTCC 282) by the standard serial dilution method. Fluconazole was used as standard drug and minimum inhibitory concentrations (MIC in μmol/mL) were recorded and presented in Table 3.

Results indicated that some of the synthesized compounds possess significant activity. The compound **5d** (MIC, 0.0361 μmol/mL), **5e** (MIC, 0.0356 μmol/mL), **5n** (MIC,

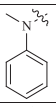
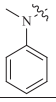
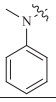
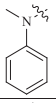
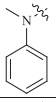
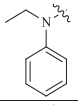
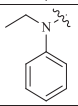
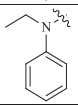
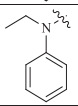
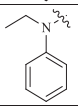


(2a-2e) **(4a-4e)** **(5a-5y)**

Compound	R^1	R^2	Reaction Time (h)	Yield %
5a		C_6H_5	7	92
5b		4-$CH_3OC_6H_4$	9	88
5c		4-FC_6H_4	7	91
5d		4-$NO_2C_6H_4$	6	88
5e		α-$C_{10}H_7$ (α-naphthyl)	10	90
5f		C_6H_5	9	92
5g		4-$CH_3OC_6H_4$	7	88
5h		4-FC_6H_4	8	82
5i		4-$NO_2C_6H_4$	6	86
5j		α-$C_{10}H_7$	10	90
5k		C_6H_5	9	86
5l		4-$CH_3OC_6H_4$	9	90
5m		4-FC_6H_4	8	82
5n		4-$NO_2C_6H_4$	7	88
5o		α-$C_{10}H_7$	9	84

Scheme 3. Synthesis of amine-amide linked 1,4-disubstituted 1,2,3-triazoles

0.0378 µmol/mL), **5o** (MIC, 0.0373 µmol/mL), **5t** (MIC, 0.0336 µmol/mL) and **5 y** (MIC, 0.0324 µmol/mL) showed good activity against *C. albicans*. Whereas, in case of

5p		C_6H_5	7	88
5q		4-$CH_3OC_6H_4$	9	90
5r		4-FC_6H_4	7	86
5s		4-$NO_2C_6H_4$	6	82
5t		α-$C_{10}H_7$	8	88
5u		C_6H_5	8	76
5v		4-$CH_3OC_6H_4$	9	82
5w		4-FC_6H_4	8	86
5x		4-$NO_2C_6H_4$	6	81
5y		α-$C_{10}H_7$	8	78

Scheme 3. Continued.

A. niger compounds **5e** (MIC, 0.0178 µmol/mL), **5i** (MIC, 0.0181 µmol/mL), and **5n** (MIC, 0.0189 µmol/mL) showed appreciable activity.

From the above result, it was observed, that compounds having naphthyl moiety exhibited better activity in comparison to phenyl moiety. The results also supported the fact that the presence of morpholine contributed to better antimicrobial efficacy as compared to piperidine against the tested stains.

Conclusion

In present work, we have synthesized a library of twenty five 1,2,3-triazole having amine-amide functionalities through one pot three-component reaction of *N*-substituted(prop-2-yn-1-yl)amines, 2-bromo-*N*-arylacetamides, sodium azide in the presence of copper sulfate pentahydrate and sodium ascorbate. Further, for confirmation of structures, X-ray crystallography of synthesized **5a** (CCDC 1569245) and **5h** (CCDC

Table 1. Crystal data and structure refinement for 2-(4-(Morpholinomethyl)-1*H*-1,2,3-triazol-1-yl)-*N*-phenylacetamide (**5a**).

Property	Data
Empirical formula	$C_{15}H_{19}N_5O_2$
Formula weight	301.35
Temperature/K	293
Crystal system	Orthorhombic
Space group	$Pca2_1$
a/Å	9.8849(7)
b/Å	9.5292(7)
c/Å	32.354(2)
$\alpha/^\circ$ $\beta/^\circ$ $\gamma/^\circ$	90, 90, 90
Volume/Å^3	3047.6(4)
Z	8
ρ_{calc} g/cm^3	1.314
μ/mm^{-1}	0.744
F(000)	1280.0
Crystal size/mm^3	$0.284 \times 0.116 \times 0.067$
Radiation	CuKα ($\lambda = 1.54184$)
2Θ range for data collection/$^\circ$	9.28 to 146.696
Index ranges	$-11 \leq h \leq 10$, $-10 \leq k \leq 8$, $-39 \leq l \leq 36$
Reflections collected	6955
Independent reflections	3939 [$R_{int} = 0.0656$, $R_{sigma} = 0.0690$]
Data/restraints/parameters	3939/1/397
Goodness-of-fit on F^2	1.022
Final R indexes [I>=2σ (I)]	$R_1 = 0.0697$, $wR_2 = 0.1656$
Final R indexes [all data]	$R_1 = 0.1217$, $wR_2 = 0.2177$
Largest diff. peak/hole / e Å^{-3}	0.36/−0.29
Flack parameter	−0.4(9)

1569249) was also carried out. All the triazoles were evaluated for *in vitro* antifungal activity. The preliminary structure-activity relationship analysis suggested that the presence of Naphthyl ring enhanced antifungal activities of these compounds in comparison to the phenyl ring. Triazole derivatives having morpholine moiety showed better antimicrobial activity as compared to derivatives having piperidine moiety.

Experimental section

Material and methods

The chemicals used in the synthesis were purchased from Alfa-Aesar, Sigma-Aldrich and used without further purification. Thin layer chromatography was used to monitor the progress of the reactions and visualized by UV light. Melting points were determined by the open capillary method and are uncorrected. IR spectra were recorded on a SHIMADZU AFFINITY-I FT-IR spectrophotometer (Shimadzu Corporation, Nishinokyo-Kuwabaracho Nakagyo-Ku, Kyoto 604-8511, Japan) using KBr powder and the values are expressed in cm^{-1}. The ^{1}H NMR and ^{13}C NMR spectra of the synthesized compounds were recorded at 400 MHz and 100 MHz, respectively, using Bruker Avance II 400 MHz NMR spectrometer (Bruker Biospin International AG, Aegeristrasse 52, CH-6301 Zug (Switzerland)) in DMSO-d_6 solvent, and the chemical shifts were expressed in δ and coupling constants (J) in Hz. Splitting patterns were indicated as s: singlet, d: doublet, t: triplet, q: quartet, m: multiplet. HRMS were obtained using Waters Micromass Q-Tof Micro (ESI) spectrophotometer and values were quoted in m/z.

Table 2. Crystal data and structure refinement for *N*-(4-fluorophenyl)-2-(4-(piperidin-1-ylmethyl)-1*H*-1,2,3-triazol-1-yl)acetamide (**5h**).

Property	Data
Empirical formula	$C_{16}H_{20}N_5OF$
Formula weight	317.37
Temperature/K	293
Crystal system	Monoclinic
Space group	C2/c
a/Å	34.1018(6)
b/Å	9.53697(18)
c/Å	9.89235(16)
$\alpha/^\circ$, $\beta/^\circ$, $\gamma/^\circ$	90, 90.3176(15), 90
Volume/Å^3	3217.22(10)
Z	8
ρ_{calc}g/cm^3	1.310
μ/mm^{-1}	0.775
F(000)	1344.0
Crystal size/mm^3	$0.3 \times 0.3 \times 0.15$
Radiation	CuKα ($\lambda = 1.54184$)
2Θ range for data collection/$^\circ$	9.63 to 146.224
Index ranges	$-42 \leq h \leq 41$, $-8 \leq k \leq 11$, $-11 \leq l \leq 12$
Reflections collected	11066
Independent reflections	3175 [$R_{int} = 0.0408$, $R_{sigma} = 0.0259$]
Data/restraints/parameters	3175/0/288
Goodness-of-fit on F^2	1.023
Final R indexes [I>=2σ (I)]	$R_1 = 0.0473$, $wR_2 = 0.1255$
Final R indexes [all data]	$R_1 = 0.0513$, $wR_2 = 0.1314$
Largest diff. peak/hole / e Å^{-3}	0.22/−0.23

Table 3. *In vitro* antifungal activity of 1,4-disubstituted 1,2,3-triazoles (5a–5y).

Compound	Minimum Inhibitory Concentration (MIC, μmol/mL). *Candida albicans*	*Aspergillus Niger*
5a	0.0830	0.0415
5b	0.0754	0.0377
5c	0.0782	0.0391
5d	**0.0361**	0.0361
5e	**0.0356**	**0.0178**
5f	0.0836	0.0418
5g	0.0759	0.0379
5h	0.0788	0.0394
5i	0.0726	**0.0181**
5j	0.0716	0.0358
5k	0.0876	0.0438
5l	0.0793	0.0396
5m	0.0824	0.0412
5n	**0.0378**	**0.0189**
5o	**0.0373**	0.0373
5p	0.0778	0.0389
5q	0.0711	0.0356
5r	0.0736	0.0368
5s	0.0682	0.0341
5t	**0.0336**	0.0336
5u	0.0745	0.0373
5v	0.0684	0.0342
5w	0.0708	0.0354
5x	0.0657	0.0328
5y	**0.0324**	0.0324
Fluconazole	0.0408	0.0102

The bold numbers represents the activity of synthesized compound comparable to standard drug used.

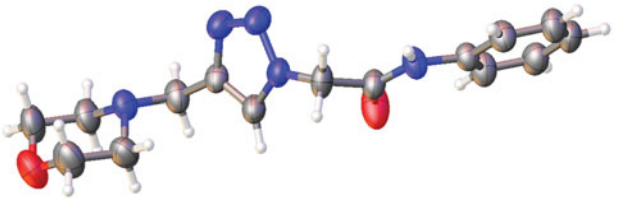


Figure 1. Crystal structure of 2-(4-(Morpholinomethyl)-1H-1,2,3-triazol-1-yl)-N-phenylacetamide (5a).

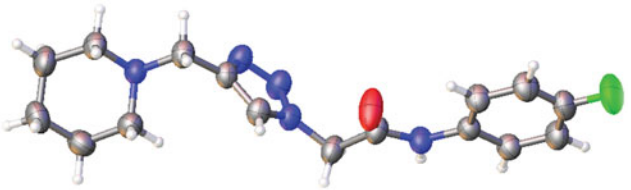


Figure 2. Crystal structure of N-(4-fluorophenyl)-2-(4-(piperidin-1-ylmethyl)-1H-1,2,3-triazol-1-yl)acetamide (5h)

Procedure for the preparation of 2-(4-(morpholinomethyl)-1H-1,2,3-triazol-1-yl)-N-phenylacetamide

The starting reactant, 4-(prop-2-yn-1-yl)morpholine **(2a)** was synthesized by drop-wise addition of propargyl bromide (1.2 mmol) to the stirred solution of morpholine **(1a,** 1.0 mmol**)** in dimethylformamide (15 mL) in the presence of potassium carbonate (2.0 mmol), stirring was continued for 4 h at room temperature. After the completion of reaction as indicated by TLC water (20 mL) was added in the reaction mixture. The product was extracted with ethyl acetate (3 × 30 mL) from the reaction mixture. The separated organic layer was evaporated under reduced pressure to get 4-(prop-2-yn-1-yl)morpholine **(2a)**.

For synthesis of 2-bromo-*N*-phenylacetamides **(4a),** to the stirred solution of aniline (**3a–3e,** 1.0 mmol) in dichloromethane (20 mL), 2-bromoacetyl bromide (1.2 mmol) was added in the presence of potassium carbonate at 0–5 °C and stirring of the mixture was continued for 15–20 min at the same temperature. After the completion of reaction dilute hydrochloric acid was added, solid product was precipitated out which was filtered and dried.

Further, to synthesize 2-(4-(Morpholinomethyl)-1*H*-1,2,3-triazol-1-yl)-*N*-phenylacetamide **(5a),** 2-bromo-*N*-phenylacetamides (**4a,** 1.0 mmol) dissolved in dimethylformamide (16 mL), aqueous sodium azide (3.0 mmol) was added and stirring was continued at 25–40 °C for 30 min. To this mixture 4-(prop-2-yn-1yl)morpholine (**2a**, 1.0 mmol), aqueous copper sulfate pentahydrate (0.1 mmol) and sodium ascorbate (0.4 mmol) were added and stirring was continued for 7 h at the same temperature. After completion of reaction, ice cold water was added to reaction mixture, precipitated product was filtered and washed with ammonia solution. Crude product was washed with ethyl acetate (30 mL) and dried under vacuum to get pure product in good yield.

2 -(4-(Morpholinomethyl)-1H-1,2,3-triazol-1-yl)-N-phenylacetamide (5a)

Appearance: white crystalline solid; Yield: 92%; m.p. 186–190 °C; FTIR (KBr): 3276 (N–H str. amide), 3140 (C–H str. triazole), 3098 (C–H str. aromatic ring), 2935 (C–H str., aliphatic), 1686 (C = O str. amide), 1557 (C = C str., aromatic ring) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 10.48 (s, 1 H, N–H amide), 8.02 (s, 1 H, C–H triazole), 7.58 (d, 2 H, J = 8 Hz), 7.34 (t, 2 H, J = 8 Hz), 7.09 (t, 1 H, J = 8 Hz), 5.31 (s, 2H), 3.58-3.51 (m, 6H), 2.40 (4H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 164.7 (C = O amide), 143.3 (C_4 triazole), 138.9, 129.4, 126.0 (C_5 triazole), 124.3, 119.7, 66.6, 53.2, 52.6; HRMS (m/z) calculated for $C_{15}H_{19}N_5O_2$ $[M + H]^+$: 302.1539. Found: 302.1612.

X-ray crystallographic study

Single crystals of $C_{15}H_{19}N_5O_2$ **(5a)** and $C_{16}H_{20}N_5OF$ **(5h)** were selected and determined on a SuperNova, Single source at offset, Titan diffractometer. The crystal was kept at 293 K during data collection. Using Olex2,[33] the structure was solved with the ShelXT[34] structure solution program using Direct Methods and refined with the ShelXL[35] refinement package using Least Squares minimization.

Antifungal activity

The antifungal activity of newly synthesized compounds was assessed *in vitro* against fungal strains – *Candida albicans* (MTCC 227) and *Aspergillus niger* (MTCC 282) as per the serial dilution method.[36] Fluconazole was used as a standard drug for fungal strains. Results were recorded in terms of minimum inhibitory concentration (MIC) expressed in μmol/mL in Table 3.

Acknowledgments

Authors are highly thankful to University Grants Commission, New Delhi for financial assistance.

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