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Regioselective synthesis, characterization and antimicrobial evaluation of amide–ether-linked 1,4-disubstituted 1,2,3-triazoles

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Abstract: Regioselective synthesis of some amide–ether-linked 1,4-disubstituted 1,2,3-triazoles was realized *via* the copper(I)-catalyzed click reaction of 1-(prop-2-ynyloxy)naphthalene, 2-(prop-2-ynyloxy)naphthalene and 1,4-bis-(prop-2-ynyloxy)benzene with 2-azido-*N*-substituted acetamides. The synthesized compounds were characterized by spectral techniques *viz*. FT-IR, ^{1}H-NMR, ^{13}C-NMR, HRMS and evaluated for their *in vitro* antimicrobial activity against *Bacillus subtilis*, *Staphylococcus* aureus (Gram-positive bacteria), *Pseudomonas aeruginosa*, *Escherichia coli* (Gram-negative bacteria), *Candida albicans* and *Aspergillus brasiliensis* (fungi). Among the synthesized 1,4-disubstituted 1,2,3-triazoles, compound **13d** displayed excellent antibacterial potential, while, compounds **7d** and **13d** appeared as potent fungicidal agents against the tested microbial strains. The docking simulation of the broad spectrum microbicidal disubstituted 1,2,3-triazole **13d** into the active site of *E. coli* type II topoisomerase, DNA gyrase B enzyme was also investigated.

Keywords: click reaction; disubstituted 1,2,3-triazoles; antibacterial activity; antifungal activity.

INTRODUCTION

N-heterocyclic compounds play important roles in human health owing to their presence in many life saving medicines.[1–4] Among these heterocycles, substituted 1,2,3-triazoles have received much attention because of their leading role as antimicrobial,[5–7] antiviral,[8] antitumor,[9–11] antitubercular,[12–14] antitrypanosomal,[15] antiplasmodial,[16,17] anti-HIV,[18,19] anti-allergic,[20,21] analgesic,[22] CNS depressant,[23] anticonvulsant[24] and antihypertensive[25] agents in pharmaceuticals. The 1,4-disubstituted 1,2,3-triazoles are peptidomimetic in nature,[26] and can act

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as both hydrogen bond donor and acceptor,[19] which help in binding the biologically active sites of enzymes of targeted microorganisms.

The copper(I)-catalyzed 1,3-diploar cycloaddition[27] reported by Sharpless[28] and Meldal,[29] also acknowledged as one of the premier click reaction, is the best method for the regioselective synthesis of 1,4-disubstituted 1,2,3-triazoles.[30] Diverse libraries of pharmacologically active, disubstituted 1,2,3-triazoles could be synthesized by using different azides and terminal alkynes[31] *via* this click reaction.[32,33] Additionally, the impacts of these triazoles are also reported in the form of ionic receptors,[34] cyclic peptides,[35] triazolophanes,[36] dendrimers,[37] liquid crystals,[38] nanotubes[39] and peptidomimetics.[40]

Therefore, based on the widespread applications of triazoles, our research has been focused on the regioselective synthesis and biological evaluation of 1,4--disubstituted 1,2,3-triazoles for the development of new potent antimicrobials. Previously, 1,4-disubstituted 1,2,3-triazoles[41–48] having remarkable antimicrobial potential were synthesized.[41–48] In continuation of these studies on 1,2,3--triazoles, various amide–ether-linked 1,4-disubstituted 1,2,3-triazoles (**7a**–**e**, **10a–e**, and **13a**, **b**, **d** and **e**) were synthesized *via* the copper(I)-catalyzed click reaction of 1-(prop-2-ynyloxy)naphthalene (**3**), 2-(prop-2-ynyloxy)naphthalene (**9**) or 1,4-bis(prop-2-ynyloxy)benzene (**12**) with 2-azido-*N*-substituted acetamides. To the best of our knowledge, all the fourteen synthesized 1,4-disubstituted 1,2,3-triazoles are new. The synthesized triazoles were characterized by spectroscopic techniques, *i.e.*, FT-IR, ^{1}H-NMR, ^{13}C-NMR, HRMS, and evaluated for their antimicrobial activities against *Bacillus subtilis*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Escherichia coli*, *Candida albicans* and *Aspergillus niger*. Furthermore, to study the mechanism of action and binding modes with biological targets, docking simulation of the synthesized compound 2,2′-[1,4-phenylenebis(oxymethylene-1*H*-1,2,3-triazole-4,1-diyl)]bis[*N*-(4-nitrophenyl)acetamide] (**13d**) against *E. coli* type II topoisomerase, DNA gyrase B enzyme was performed.

EXPERIMENTAL

General

The chemicals were purchased from Sigma–Aldrich, Hi-Media, Alfa–Aesar and used without further purification. Melting points of the target compounds were recorded in °C by application of the open capillary method and are uncorrected. The IR spectra were recorded on a Shimazdu IR Affinity-I FT-IR spectrophotometer using KBr pellets and the values are given in cm^{-1}. The NMR spectra were recorded at 400 (^{1}H) and 100 (^{13}C) MHz on a commercial Bruker Avance II instrument, in deuterated dimethyl sulphoxide-d_6 (DMSO-d_6) using tetramethylsilane (TMS) as an internal standard (chemical shift in δ, ppm). Coupling constant (J) values are given in Hz. The high resolution mass spectra were recorded on a Waters Micromass Q-Tof Micro (ESI) spectrophotometer. The completion of reactions and the purity of the compounds were analyzed by thin layer chromatography (TLC) using readymade silica gel plates (SIL G/UV$_{254}$, Alugram) and visualized under an ultraviolet lamp.

Analytical and spectral data of the synthesized compounds are given in Supplementary material to this paper.

*General procedure for the synthesis of terminal alkynes **3**, **9** and **12***

The terminal alkynes **3**, **9** and **12** were synthesized[49] by reacting *α*-naphthol (**1**)/*β*-naphthol (**8**)/hydroquinone (**11**, 1.0 mmol) with propargyl bromide (**2**, 1.5/1.5/2.5 mole ratio, respectively) in the presence of potassium carbonate (3.0/3.0/5.0 mole ratio, respectively) in dry dimethylformamide under continuous stirring for 5–8 h at 35–45 °C (Schemes 1–3). After completion of reaction, 2 M HCl solution was added into the reaction mixture, the content stirred for 5–10 min and then the product was extracted with ethyl acetate (3×50 mL). The organic layer was washed with saturated brine solution, dried using anhydrous sodium sulfate, filtered and evaporated to obtain the desired ether-linked terminal alkynes.

*General procedure for the synthesis of 2-bromo-*N*-substituted acetamides **6a**–**e***

2-Bromo-*N*-substituted acetamides **6a**–**e** were synthesized[48,50] by the dropwise addition of bromoacetyl bromides (**5**, 1.2 mmol) to aromatic amines **4a**–**e** (1.0 mmol) in 15 mL dry dichloromethane under continuous stirring at 0–15 °C for 4–6 h using triethylamine (3.0 mmol) as base (Scheme 1). After completion of the reaction, 50 mL of dichloromethane was added to the reaction mixture, the contents were stirred and then poured into a separating funnel. The organic layer was washed with 2 M HCl, followed by saturated aqueous sodium bicarbonate solution and finally with brine solution. The organic layer was dried using anhydrous sodium sulfate, filtered and evaporated to obtain the desired products.

*General procedure for the synthesis of amide–ether-linked 1,4-disubstituted 1,2,3-triazoles **7a**–**e**, **10a**–**e** and **13a**, **b**, **d** and **e***

For the synthesis[51] of amide–ether-linked 1,4-disubstituted 1,2,3-triazoles, an aqueous solution of sodium azide (3.0/5.0 mole ratio) was added to a solution of 1.0/2.0 mole ratio of 2-bromo-*N*-substituted acetamides **6a**–**e** and dimethylformamide under stirring at 50–65 °C. Then, terminal alkynes **3**, **9** and **12** (1.0 mmol) were added followed by addition of copper sulfate pentahydrate (1.0/2.0 mole ratio) and sodium ascorbate (1.0/2.0 mole ratio). The reaction mixture was stirred for 6–12 h at the same temperature (Schemes 1–3). After completion of the reaction, cold water was added to the reaction mixture and the precipitated solid was filtered off and washed with aqueous ammonia solution followed by water. The crude product was purified by washing with ethyl acetate and dried under vacuum to afford the desired 1,4--disubstituted 1,2,3-triazoles (**7a**–**e**, **10a**–**e** and **13a**, **b**, **d** and **e**) in good yield.

Antibacterial activity

The synthesized amide–ether-linked 1,4-disubstituted 1,2,3-triazoles **7a**–**e**, **10a**–**e** and **13a**, **b**, **d** and **e** were evaluated for their *in vitro* antibacterial potential against Gram-positive bacteria, *i.e.*, *Bacillus subtilis* (MTCC 441) and *Staphylococcus aureus* (MTCC 7443), and Gram-negative bacteria, *i.e.*, *Pseudomonas aeruginosa* (MTCC 424) and *Escherichia coli* (MTCC 1652), by the two-fold serial dilution method[52] using stock solutions of 2000 and 400 μg mL^{-1}. DMSO was employed as the solvent control. Dilutions of the test compounds were prepared in double strength nutrient broth. One mL nutrient broth was taken in each of nine test tubes. To the first test tube, 1.0 mL of test solution (2000 μg mL^{-1}) was added aseptically to obtain a concentration of 1000 μg mL^{-1}. From this dilution, the other concentrations were prepared by the serial dilution method to obtain final concentrations of 500 and 250 μg mL^{-1}. From the second stock solution, 1.0 mL of test solution (400 μg mL^{-1}) was taken in fourth test tube, to prepare a concentration of 200 μg mL^{-1}. From this concentration (200 μg mL^{-1}), the

other dilutions were prepared by serial dilution to obtain final concentrations of 100, 50, 25, 12.5 and 6.25 μg mL^{-1} in test-tube numbers five to nine. All the test tubes were aseptically inoculated with 0.1 mL (100 μL) of the desired bacterial strain taken in sterile saline solution. The inoculated test samples were then incubated at 37±1 °C for 24 h (in case of *B. subtilis*, *S. aureus* and *P. aeruginosa*) and 48 h (in the case of *E. coli*) in a B.O.D. incubator and the results were recorded in terms of the minimum inhibitory concentrations (*MIC*) expressed in μmol mL^{-1}. Ciprofloxacin was used as the standard drug, which was tested under similar experimental conditions for comparison with the synthesized compounds. To check the effect of solvent on bacterial growth, a control test was performed with test medium supplemented with dimethyl sulfoxide at the same dilutions as those used in the experiments.

Antifungal activity

The *in vitro* antifungal evaluation of the 1,4-disubstituted 1,2,3-triazoles **7a**–**e**, **10a**–**e** and **13a**, **b**, **d** and **e** was performed against two fungal strains, *i.e.*, *Candida albicans* (MTCC 227) and *Aspergillus brasiliensis* (MTCC 1344), by the two fold serial dilution method[52] using stock solutions of 2000 and 400 μg mL^{-1} of the compounds. Sabouraud dextrose broth was used as the fungal culture media and DMSO as the solvent control. One mL of freshly prepared sterile culture media was added aseptically in each test tube followed by serial dilution with synthesized compounds to prepare concentrations of 1000, 500, 250, 200, 100, 50, 25, 12.5 and 6.25 μg mL^{-1}. Furthermore, these dilutions of the triazole compounds were inoculated with 0.1 mL of a suspension of the respective microorganism contained in sterilized saline solution. Then the samples of the compounds loaded with microorganisms were incubated at 25±1 °C for two days in case of *C. albicans* and for seven days in case of *A. niger*. Fluconazole, an antifungal triazole, was also screened under similar experimental conditions for comparison of its activity with the respective activity of the target compounds. The results of antifungal activity assay were recorded in terms of the *MIC* value expressed in μmol mL^{-1}.

Computational details

The docking procedure[47] chosen in the present study was in accordance with the procedure reported by Kaushik *et al.* in 2016. The structures of the compounds, sketched with Marvin Sketch 5.10, were optimized and cleaned with gradient optimization.[53] The X-ray crystallographic structure of *E. coli* DNA gyrase B along with co-crystallized ligand CBN (PDB ID: 1KZN) was obtained from the Brookhaven Protein Databank (/http://www.rcsb.org/pdb). Preparation of the protein was accomplished with UCSF Chimera 1.9.[54] Incomplete side chains were completed with the Dunbrack rotamer library[55] and Gasteiger charges were assigned with Antechamber.[56] The structures of the ligands and proteins were transformed into pdbqt format with the aid of AutoDock tools.[57]

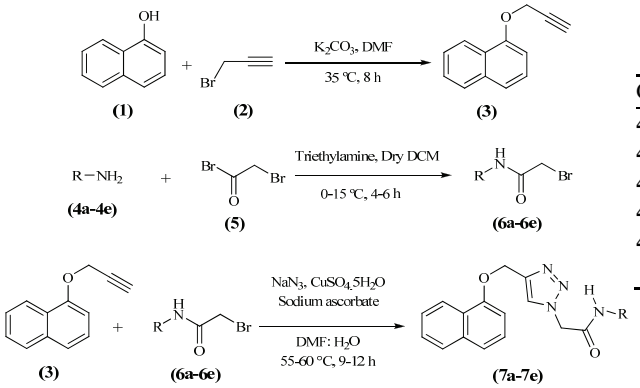
Docking simulations were carried out by AutoDock Vina program. The Vina search space taken was center_x = 19.7572768649, center_y = 30.6958566405, center_z = 36.3020605554, size_x = 25.0, size_y = 24.2096062606 and size_z = 21.3564769495. The exhaustiveness for docking was set to be 8.

Validation of docking protocols was made by means of reported crystal structures of protein–ligand complexes. Protocols selected for the AutoDock Vina docking studies could realistically mimic the X-ray structure as the root-mean square deviation (*RMSD*) between the conformations of the CBN from the X-ray crystal structure and that from AutoDock Vina was less than 2Å. These protocols were used for docking of the compound under study into the active site of DNA gyrase B.

RESULTS

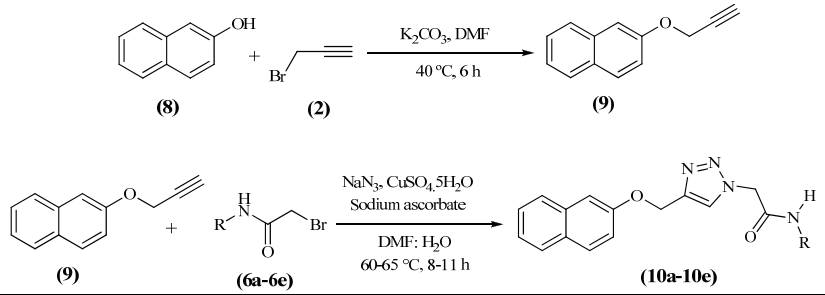
Chemistry

The amide–ether-linked 1,4-disubstituted 1,2,3-triazoles **7a**–**e**, **10a**–**e** and **13a**, **b**, **d** and **e** were synthesized[51] *via* the Cu(I)-catalyzed click reaction of 1-(prop-2-ynyloxy)naphthalene (**3**), 2-(prop-2-ynyloxy)naphthalene (**9**) or 1,4-bis(prop-2-ynyloxy)benzene (**12**) with 2-azido-*N*-substituted acetamides as outlined in Schemes 1–3. 2-Azido-*N*-substituted acetamides were prepared *in situ* by the reaction of sodium azide with the corresponding 2-bromo-*N*-substituted acetamides **6a**–**e**.



Compound	R
4a; **6a**; **7a**	C_6H_5
4b; **6b**; **7b**	4-$CH_3OC_6H_4$
4c; **6c**; **7c**	4-BrC_6H_4
4d; 6**d**; **7d**	4-$NO_2C_6H_4$
4e; **6e**; **7e**	α-$C_{10}H_7$ (α-naphthyl)

Scheme 1. Synthesis of amide–ether-linked 1,4-disubstituted 1,2,3-triazoles **7a**–**e**.

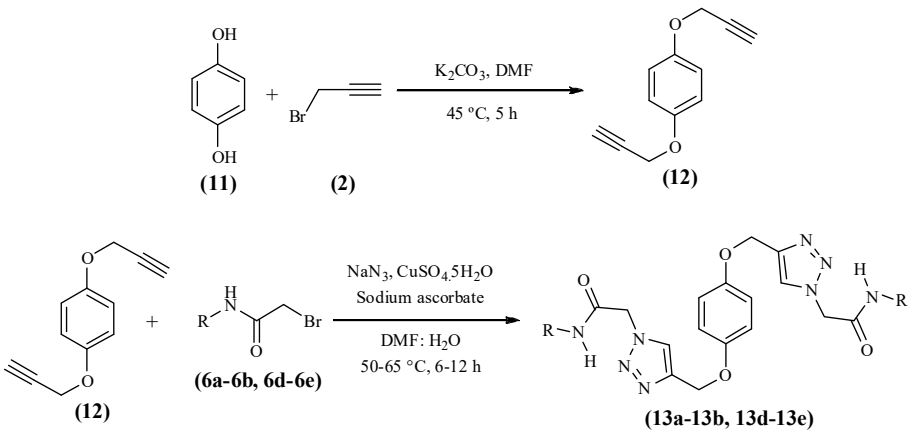


Compound	R
6a; **10a**	C_6H_5
6b; **10b**	4-$CH_3OC_6H_4$
6c; **10c**	4-BrC_6H_4
6d; **10d**	4-$NO_2C_6H_4$
6e; **10e**	α-$C_{10}H_7$ (α-naphthyl)

Scheme 2. Synthesis of amide–ether-linked 1,4-disubstituted 1,2,3-triazoles **10a**–**e**.

1-(Prop-2-ynyloxy)naphthalene (**3**), 2-(prop-2-ynyloxy)naphthalene (**9**) and 1,4-bis(prop-2-ynyloxy)benzene (**12**) were synthesized[49] by reacting α-naphthol

(**1**), *β*-naphthol (**8**) or hydroquinone (**11**), respectively, with propargyl bromide (**2**) in the presence of potassium carbonate using dimethylformamide as solvent (Schemes 1–3).



Compound	R
6a; **13a**	C_6H_5
6b; **13b**	4-$CH_3OC_6H_4$
6d; **13d**	4-$NO_2C_6H_4$
6e; **13e**	α-$C_{10}H_7$ (α-naphthyl)

Scheme 3. Synthesis of amide–ether-linked 1,4-disubstituted 1,2,3-bistriazoles **13a**, **b**, **d** and **e**.

2-Bromo-*N*-substituted acetamides **6a**–**e** were synthesized[48,50] by treating various aromatic amines (**4a**–**e**) with bromoacetyl bromide (**5**) in dry dichloromethane using triethylamine as base (Scheme 1).

The ether linked terminal alkynes, *i.e.*, 1-(prop-2-ynyloxy)naphthalene (**3**), 2-(prop-2-ynyloxy)naphthalene (**9**) and 1,4-bis(prop-2-ynyloxy)benzene (**12**), were then reacted with 2-bromo-*N*-substituted acetamides **6a**–**e** in the presence of sodium azide, copper sulfate pentahydrate and sodium ascorbate in dimethylformamide–water to afford 1,4-disubstituted 1,2,3-triazoles **7a**–**e** (Scheme 1), **10a**–**e** (Scheme 2) and **13a**, **b**, **d** and **e** (Scheme 3), respectively.[51]

The synthesized 1,4-disubstituted 1,2,3-triazoles (**7a**–**e**, **10a**–**e, 13a**, **b**, **d** and **e**) were characterized by spectroscopic techniques such as FT-IR, ^{1}H-NMR, ^{13}C--NMR and high resolution mass spectrometry. The formation of compounds was confirmed by the presence of absorption bands in the region 3317–3251 cm^{-1} (N–H str., amide), 3165–3124 cm^{-1} (C–H str., triazole ring) and 1705–1662 cm^{-1} (C=O str., amide) in the FT-IR spectra. The presence of characteristic singlet in the δ regions 5.08–5.42 ppm (OCH_2), 5.31–5.60 ppm (NCH_2), 8.24–8.44 ppm (C–H triazole) and 10.36–11.14 ppm (N–H amide) in the ^{1}H-NMR spectra, as

well as the peaks in ^{13}C-NMR spectra at δ 52.5–52.8 ppm (NCH_2), 61.2–62.1 ppm (OCH_2), 126.6–126.9 ppm (C5 triazole ring), 142.8–143.2 ppm (C4 triazole ring) and 164.1–165.9 ppm (C=O amide) also confirmed the formation of the target compounds. The results obtained from high resolution mass spectral analysis were in accordance with calculated values.

Antibacterial activity

All the synthesized amide–ether-linked 1,4-disubstituted 1,2,3-triazoles (**7a**––**e**, **10a**–**e, 13a**, **b**, **d** and **e**) were examined for their antibacterial activity against four bacterial strains, *B. subtilis* (MTCC 441), *S. aureus* (MTCC 7443), *P. aeruginosa* (MTCC 424) and *E. coli* (MTCC 1652) using the serial dilution method.[52] The antibacterial potentials of the compounds were compared with the reference drug, ciprofloxacin, and the *MIC* values were recorded in μmol mL^{-1} as given in Table I.

TABLE I. Antibacterial activity of 1,4-disubstituted 1,2,3-triazoles **7a**–**e**, **10a**–**e**, **13a**, **b**, **d** and **e** in terms of their *MIC* values in μmol mL^{-1}

Compound	Gram-positive bacteria		Gram-negative bacteria	
	B. subtilis (MTCC 441)	*S. aureus* (MTCC 7443)	*P. aeruginosa* (MTCC 424)	*E. coli* (MTCC 1652)
7a	0.2790	0.2790	0.2790	0.5581
7b	0.6436	0.5149	0.6436	0.6436
7c	2.2870	0.5717	0.5717	1.1435
7d	0.0620	0.1239	0.0620	0.2479
7e	0.6121	0.4897	0.2448	0.4897
10a	0.1395	0.2790	0.1395	0.5581
10b	0.2575	0.5149	0.5149	0.2575
10c	1.1434	0.4574	1.1434	0.4574
10d	0.0310	0.1239	0.0620	0.1239
10e	0.4897	0.2448	0.2448	0.2448
13a	0.0928	0.0928	0.3714	0.1857
13b	0.1671	0.3341	0.4176	0.1671
13d	0.0199	0.0398	0.0199	0.0398
13e	0.3914	0.3914	0.3132	0.3914
Ciprofloxacin	0.0377	0.1509	0.0377	0.0754

A perusal of the antibacterial activity data revealed that the synthesized triazoles displayed moderate to good activity against the tested bacterial strains. In case of *B. subtilis*, compounds **10d** and **13d** exhibited excellent antibacterial activity, while compound **7d** displayed moderate activity. Likewise, compounds **7d**, **10d** and **13a** and **d** showed good bactericidal potency against *S. aureus*, whereas **7a** and **10a** and **e** exhibited moderate inhibitory activity. The growth of *P. aeruginosa* was considerably suppressed by compounds **7d**, **10d** and **13d**;

however, in case of *E. coli*, only compound **13d** appeared as a potent antibacterial agent, while compounds **10d** and **13b** displayed moderate activity.

Antifungal activity

The 1,4-disubstituted 1,2,3-triazoles **7a**–**e**, **10a**–**e, 13a**, **b**, **d** and **e** were examined for their antifungal activity against two fungal strains, *C. albicans* (MTCC 227) and *A. brasiliensis* (MTCC 1344) using the serial dilution method.[52] Fluconazole was used as the reference compound. The results were recorded in terms of their *MIC* values in μmol mL^{-1}, as given in Table II.

TABLE II. Antifungal activity of 1,4-disubstituted 1,2,3-triazoles **7a**–**e**, **10a**–**e**, **13a**, **b**, **d** and **e** in terms of their *MIC* values in μmol mL^{-1}

Compound	*C. albicans* (MTCC 227)	*A. brasiliensis* (MTCC 1344)
7a	0.0698	0.0349
7b	0.6436	0.5149
7c	0.4574	0.2287
7d	0.0310	0.0620
7e	1.2242	0.6121
10a	0.0698	0.1395
10b	0.5149	0.2575
10c	0.2287	0.2287
10d	0.0620	0.0310
10e	0.6121	0.4897
13a	0.0464	0.0928
13b	0.0835	0.0835
13d	0.0199	0.0795
13e	0.0783	0.1566
Fluconazole	0.0408	0.0816

The antifungal activity data showed that the synthesized compounds exhibited moderate to good activity against tested fungal strains. In case of *C. albicans*, compounds **7d** and **13a** and **d** appeared as good antifungal agent, while compounds **7a**, **10a** and **d** and **13b** and **e** displayed moderate inhibition effects. Moreover, compounds **7a** and **d**, **10d** and **13b** and **d** displayed good fungicidal potency against *A. brasiliensis*.

From the above results, it was observed that in most of the cases, the presence of a nitro group at the *p*-position of the anilide ring improved the antimicrobial potency, whereas, the presence of a methoxy/bromo group on the anilide ring decreased the antimicrobial potency of the synthesized triazoles compared to the activities of the parent compounds.

Docking studies

E. coli type II topoisomerase, DNA gyrase B enzyme was previously used as a target for envisaging the antimicrobial potential of compounds containing a tri-

azole moiety.[47] In order to determine the binding orientation and characteristics of compound **13d**, docking simulations in the active site of the *E. coli* type II topoisomerase, DNA gyrase B enzyme were performed. The protein was taken from the RCSB Protein Data Bank (PDB ID: 1KZN) and the docking studies were realized with Autodock Vina docking software.[58] The highest ranking binding orientation of compound **13d** in the binding site of the protein is shown in Fig. 1. Hydrogen bond interactions were created between **13d** and active site residues, *i.e.*, Val118 and Asn46. Asn46 formed hydrogen bonds with one oxygen atom of the nitro group (H···O distance = 3.044 Å) and the ethereal oxygen atom (H···O distance = 3.132 Å).

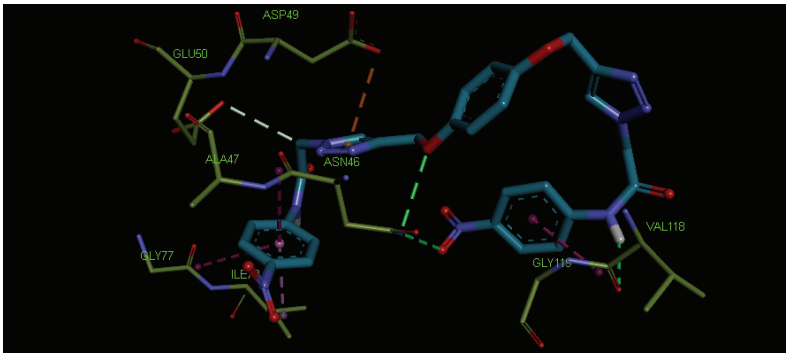


Fig. 1. Docked pose of compound **13d** showing H-bonding, C–H bonding, hydrophobic and electrostatic interactions in active site of *E. coli* type II topoisomerase, DNA gyrase B.

One carbon–hydrogen bond was established with Glu50. One of the triazole rings was involved in electrostatic π–anion interaction with Asp49. One phenyl ring was sandwiched between Gly77, Ile78 and Asn46, Ala47 by hydrophobic π–amide type interactions, while another phenyl ring exhibited the same types of interactions with Val118 and Gly119. These interactions prove that compound **13d** might inhibit the type II topoisomerase, DNA gyrase B enzyme, which could be the probable basis of its antimicrobial action. Docked conformation of compound **13d** along with co-crystallized ligand clorobiocin in ribbon diagrams (secondary structure) of the protein is shown in Fig. 2 and the surface diagram is presented in Fig. 3.

CONCLUSIONS

Regioselective synthesis of amide–ether-linked 1,4-disubstituted 1,2,3-triazoles was performed *via* copper(I) catalyzed click reactions of 1-(prop-2-ynyloxy)naphthalene, 2-(prop-2-ynyloxy)naphthalene of 1,4-bis(prop-2-ynyloxy)benzene with 2-azido-*N*-substituted acetamides. The synthesized triazoles were evaluated *in vitro* for their antimicrobial activity against *B. subtilis*, *S. aureus*, *P. aeruginosa*, *E. coli*, *C. albicans* and *A. brasiliensis*. Compounds **10d** and **13d** against

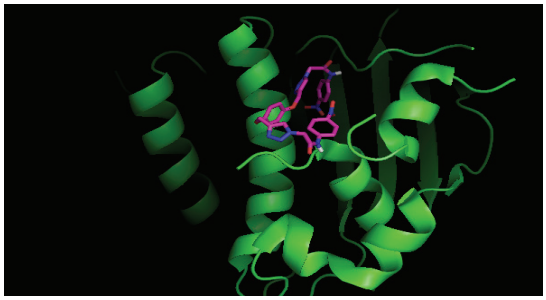


Fig. 2. Secondary structure of *E. coli* type II topoisomerase, DNA gyrase B with docked inhibitor compound **13d**.

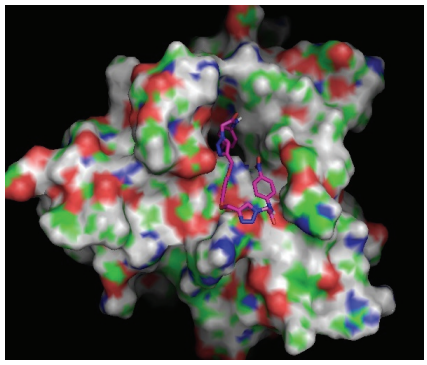


Fig. 3. Surface diagram showing docked molecule **13d** with the enzyme *E. coli* type II topoisomerase, DNA gyrase B.

B. subtilis, **7d**, **10d** and **13a** and **d** against *S. aureus* and **13d** against *P. aeruginosa* and *E. coli* exhibited better antibacterial activity compared to the reference drug. Moreover, compounds **7d** and **13d** appeared as better fungicidal agents against *C. albicans*, while the compounds **7a** and **d**, **10d** and **13d** displayed excellent fungicidal potency against *A. brasiliensis*, comparable to reference drug. In summary, compound **13d** displayed remarkable antimicrobial potential against all tested strains, while compound **7d** also appeared as a potent fungicidal agent. Furthermore, docking of the key microbicidal compound **13d** into the active site of the *E. coli* type II topoisomerase, DNA gyrase B enzyme was also simulated.

SUPPLEMENTARY MATERIAL

Physical and spectral data, together with the NMR spectra of the synthesized compounds, are available electronically at the pages of the journal website: http://www.shd.org.rs/JSCS/, or from the corresponding author on request.

ИЗВОД

РЕГИОСЕЛЕКТИВНА СИНТЕЗА, КАРАКТЕРИЗАЦИЈА И ИСПИТИВАЊЕ АНТИМИКРОБНЕ АКТИВНОСТИ АМИД–ЕТАР 1,4-ДИСУПСТИТУИСАНИХ 1,2,3-ТРИАЗОЛА

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Извршена је региоселективна синтеза амид–етар 1,4-дисупституисаних 1,2,3-триазола преко бакар(I)-катализоване „клик” реакције 1-(проп-2-инилокси)нафталена, 2-(проп-2-инилокси)нафталена или 1,4-бис(проп-2-инилокси)бензена са 2-азидо-*N*-супституисаним ацетамидима. Синтетисана једињења окарактерисана су FT-IR, ^{1}H-NMR и ^{13}C-NMR спектроскопијама и HRMS масеном спектрометријом и испитана је њихова *in vitro* антимикробна активност према *Bacillus subtilis*, *Staphylococcus aureus* (Грам-пози-

тивне бактерије), *Pseudomonas aeruginosa*, *Escherichia coli* (Грам-негативне бактерије), *Candida albicans* и *Aspergillus brasiliensis* (гљиве). Од синтетисаних дисупституисаних 1,2,3-триазола, једињење **3d** показује изврсну антибактеријску активност, док једињења **7d** и **13d** делују као антифунгални агенси према тестираним микробним сојевима. Рачунарском симулацијом смештања у активно место ензима DNA гираза B из *E. coli* (топоизомераза типа II), испитан је широк опсег антимикробних активности дисупституисаног деривата 1,2,3-триазола **13d**.

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REFERENCES

1. C. H. Zhou, Y. Wang, *Curr. Med. Chem.* **19** (2012) 239
2. C. R. Reddy, M. D. Reddy, B. Srikanth, *Org. Biomol. Chem.* **10** (2012) 4280
3. R. Kumar, M. S. Yar, S. Chaturvedi, A. Srivastava, *Int. J. PharmTech. Res.* **5** (2013) 1844
4. C. R. Reddy, M. D. Reddy, *J. Org. Chem.* **79** (2014) 106
5. B. Garudachari, A. M. Isloor, M. N. Satyanarayana, H. K. Fun, G. Hegde, *Eur. J. Med. Chem.* **74** (2014) 324
6. M. Gaur, M. Goel, L. Sridhar, T. D. S. Ashok, S. Prabhakar, P. Dureja, P. Raghunathan, S. V. Eswaran, *Monatsh. Chem.* **143** (2012) 283
7. M. J. Genin, D. A. Allwine, D. J. Anderson, M. R. Barbachyn, D. E. Emmert, S. A. Garmon, D. R. Graber, *J. Med. Chem.* **43** (2000) 953
8. Y. W. He, C. Z. Dong, J. Y. Zhao, L. L. Ma, Y. H. Li, H. A. Aisa, *Eur. J. Med. Chem.* **76** (2014) 245
9. R. M. Kumbhare, T. L. Dadmal, R. Pamanji, U. B. Kosurkar, L. R. Velatooru, K. Appalanaidu, Y. K. Rao, J. V. Rao, *Med. Chem. Res.* **23** (2014) 4404
10. S. Zhou, H. Liao, M. Liu, G. Feng, B. Fu, R. Li, M. Cheng, Y. Zhao, P. Gong, *Bioorg. Med. Chem.* **22** (2014) 6438
11. G. Raju, R. Srinivas, M. D. Reddy, C. R. Reddy, N. Nagesh, *Nucleosides,. Nucleotides Nucleic Acids* **33** (2014) 489
12. F. Mir, S. Shafi, M. S. Zaman, N. P. Kalia, V. S. Rajput, C. Mulakayala, N. Mulakayala, I. A. Khan, M. S. Alam, *Eur. J. Med. Chem.* **76** (2014) 274
13. T. Yempala, J. P. Sridevi, P. Yogeeswari, D. Sriram, S. Kantevari, *Eur. J. Med. Chem.* **71** (2014) 160
14. D. T. G. Gonzaga, D. R. daRocha, F. C. daSilva, V. F. Ferreira, *Curr. Top. Med. Chem.* **13** (2013) 2850
15. G. G. Junqueira, M. R. Carvalho, P. Andrade, C. D. Lopes, Z. A. Carneiro, R. Sesti-Costa, J. S. Silva, I. Carvalho, *J. Braz. Chem. Soc.* **25** (2014) 1872
16. M. Asif, *Int. J. Adv. Res. Chem. Sci.* **1** (2014) 22
17. G. R. Pereira, G. C. Brandao, L. M. Arantes, H. A. Oliveira, R. C. Paula, M. F. A. Nascimento, F. M. Santos, R. K. Rocha, J. C. D. Lopes, A. B. Oliveira, *Eur. J. Med. Chem.* **73** (2014) 295
18. F. Silva, M. C. B. V. Souza, I. I. P. Frugulhetti, H. C. Castro, S. L. Souza, T. M. Souza, D. Q. Rodrigues, A. M. T. Souza, P. A. Abreu, F. Passamani, C. R. Rodrigues, V. F. Ferreira, *Eur. J. Med. Chem.* **44** (2009) 373
19. M. Whiting, J. Muldoon, Y. C. Lin, S. M. Silverman, W. Lindstron, A. J. Olson, H. C. Kolb, M. G. Finn, K. B. Sharpless, J. H. Elder, V. V. Fokin, *Angew. Chem. Int. Ed.* **45** (2006) 1435
20. S. Pattan, P. Gadhave, V. Tambe, S. Dengale, D. Thakur, S. V. Hiremath, R. V. Shete, P. Deotarse, *Indian J. Chem., B* **51** (2012) 297

21. D. R. Buckle, C. J. M. Rockell, H. Smith, B. A. Spicer, *J. Med. Chem.* **29** (1986) 2262
22. H. A. Saad, N. A. Osman, A. H. Moustafa, *Molecules* **16** (2011) 10187
23. D. Kumudha, R. R, Reddy, T. Kalavathi, *World J. Pharm. Pharm. Sci.* **3** (2014) 728
24. A. Karakurt, M. D. Aytemir, J. P. Stables, M. Ozalp, F. K. Betul, S. Ozbey, S. Dalkara, *Arch. Pharm.* **339** (2006) 513
25. K. A. Ali, E. A. Ragab, T. A. Farghaly, M. M. Abdalla, *Acta Pol. Pharm.* **68** (2011) 237
26. V. D. Bock, D. Speijer, H. Hiemstra, J. H. Maarseveen, *Org. Biomol. Chem.* **5** (2007) 971
27. F. Himo, T. Lovell, R. Hilgraf, V. V. Rostovtsev, L. Noodleman, K. B. Sharpless, V. V. Fokin, *J. Am. Chem. Soc.* **127** (2005) 210
28. V. V. Rostovtsev, L. G. Green, V. V. Fokin, K. B. Sharpless, *Angew. Chem. Int. Ed.* **41** (2002) 2596
29. C. W. Tornøe, C. Charistensen, M. Meldal, *J. Org. Chem.* **67** (2002) 3057
30. A. A. Ali, M. Chetia, D. Sarma, *Tetrahedron Lett.* **57** (2016) 1711
31. C. R. Reddy, R. Ranjan, P. Kumaraswamy, M. D. Reddy, R. Gree, *Curr. Org. Chem.* **18** (2014) 2603
32. A. A. Ali, M. Chetia, P. J. Saikia, D. Sarma, *RSC Adv.* **4** (2014) 64388
33. A. A. Ali, M. Chetia, B. Saikia, P. J. Saikia, D. Sarma, *Tetrahedron Lett.* **56** (2015) 5892
34. A. Kumar, P. S. Pandey, *Org. Lett.* **10** (2008) 165
35. R. A. Turner, A. G. Oliver, R. S. Lokey, *Org. Lett.* **9** (2007) 5011
36. V. Haridas, K. Lal, Y. K. Sharma, S. Upreti, *Org. Lett.* **10** (2008) 1645
37. V. Haridas, K. Lal, Y. K. Sharma, *Tetrahedron Lett.* **48** (2007) 4719
38. S. Balamurugan, G. Y. Yeap, W. A. K. Mahmood, *Liq. Cryst.* **41** (2014) 776
39. W. S. Horne, C. D. Stout, M. R. Ghadiri, *J. Am. Chem. Soc.* **125** (2003) 9372
40. Y. Angell, K. Burgess, *Chem. Soc. Rev.* **36** (2007) 1674
41. K. Lal, A. Kumar, M. S. Pavan, C. P. Kaushik, *Bioorg. Med. Chem. Lett.* **22** (2012) 4353
42. C. P. Kaushik, K. Kumar, S. K. Singh, D. Singh, S. Saini, *Arab. J. Chem.* **9** (2016) 865
43. C. P. Kaushik, K. Lal, A. Kumar, S. Kumar, *Med. Chem. Res.* **23** (2014) 2995
44. K. Lal, C. P. Kaushik, K. Kumar, A. Kumar, A. K. Qazi, A. Hamid, S. Jaglan *Med. Chem. Res.* **23** (2014) 4761
45. C. P. Kaushik, K. Kumar, K. Lal, S. K. Singh, *Chem. Biol. Interface* **4** (2014) 341
46. C. P. Kaushik, K. Kumar, D. Singh, S. K. Singh, D. K. Jindal, R. Luxmi, *Synth. Commun.* **45** (2015) 1977
47. C. P. Kaushik, K. Kumar, K. Lal, B. Narasimhan, A. Kumar, *Monatsh. Chem.* **147** (2016) 817
48. C. P. Kaushik, K. Kumar, B. Narasimhan, D. Singh, P. Kumar, A. Pahwa, *Monatsh. Chem.* **148** (2017) 765
49. G. Chen, Y. Zhou, C. Cai, J. Lu, X. Zhang, *Molecules* **19** (2014) 5674
50. B. J. Henderson, D. J. Carper, T. F. Gonzalez-Cestari, B. Yi, K. Mahasenan, R. E. Pavlovicz, M. L. Dalefield, R. S. Coleman, C. Li, D. B. McKay, *J. Med. Chem.* **54** (2011) 8681
51. R. Berg, B. F. Straub, *Beilstein J. Org. Chem.* **9** (2013) 2715
52. J. G. Cappucino, N. Sherman, *Microbiology, a Laboratory Manual*, 4th ed., Addison Wesley, Longman Inc., Harlow, 1999, p. 263
53. Marvin Sketch 5.10.1, ChemAxon Ltd., 2012, http://www.chemaxon.com
54. E. F. Pettersen, T. D. Goddard, C. C. Huang, G. S. Couch, D. M. Greenblatt, E. C. Meng, T. E. Ferrin, *J. Comput. Chem.* **25** (2004) 1605
55. R. L. Dunbrack, *Curr. Opin. Struct. Biol.* **12** (2002) 431
56. J. Wang, W. Wang, P. A. Kollman, D. A. Case, *J. Mol. Graphics Modell.* **25** (2006) 247

57. AutoDock Tools (version 1.5.6 rc2), Stefano Forte, Molecular Graphics Laboratory, Department of Molecular Biology, The Scripps Research Institute, 2010, http:// //mgltools.scripps.edu
58. O. Trott, A. J. Olson, *J. Comput. Chem.* **31** (2010) 455.