Journal of the Serbian Chemical Society
JSCS-info@shd.org.rs • www.shd.org.rs/JSCS
J. Serb. Chem. Soc. *82* (3) 241–251 (2017) UDC 547.772.2+547.791:542.913:615.281–188
JSCS–4962 *Original scientific paper*

Synthesis of novel pyrazoline-based bis(1,2,3-triazole) scaffolds *via* click chemistry

KOTHURI KIRAN[1,2], DONGAMANTI ASHOK[1]*, BODDU ANANDA RAO[1], MADDERLA SARASIJA[1] and ALAPATI SRINIVAS RAO[3]

[1]*Green and Medicinal Chemistry Laboratory, Department of Chemistry, Osmania University, Hyderabad, 500007, Telangana, India,* [2]*Department of Chemistry, JNTU-H, Hyderabad, Telangana, 500 085, India and* [3]*Vagdevi InnoScience Private Ltd., 5-A/8, IDA Nacharam, Hyderabad, 500 076, Telangana, India*

(Received 16 February, revised 4 September, accepted 16 September 2016)

Abstract: A series of novel bis(1,2,3-triazoles) derivatives **7a**–**m** were synthesized by the 1,3-dipolar cycloaddition (click-reaction) of 1-methyl-3,5-bis(2--(prop-2-yn-1-yloxy)phenyl)-4,5-dihydro-1*H*-pyrazole (**5**) with various aralkyl azides **6a**–**m** in the presence of sodium ascorbate and copper sulphate with good yields. The required precursor **5** was synthesized by reacting (*E*)-1,3--bis(2-hydroxyphenyl)prop-2-en-1-one (**3**) with methylhydrazine hydrate *via* 2,2′-(1-methyl-4,5-dihydro-1*H*-pyrazole-3,5-diyl)diphenol **4**, followed by reaction with propargyl bromide. The homogeneity of all the newly synthesized compounds was checked by TLC. The IR, NMR, mass spectral data and elemental analysis were in accord with the assigned structure. The title compounds were evaluated for their antibacterial activity against various bacterial strains, *i.e.*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus* and *Bacillus subtilis*; compounds **7f**–**7h** and **7j** were found to be moderately active against the bacteria, when compared with that of the standard drug. Furthermore, the same library of compounds was evaluated for their antioxidant activity using the nitric oxide radical scavenging activity. The results of the study showed that compounds **7e**–**7h** and **7k–7m** showed good radical scavenging activity.

Keywords: click chemistry; chalcones; 1,2,3-triazoles; pyrazolines; antibacterial.

INTRODUCTION

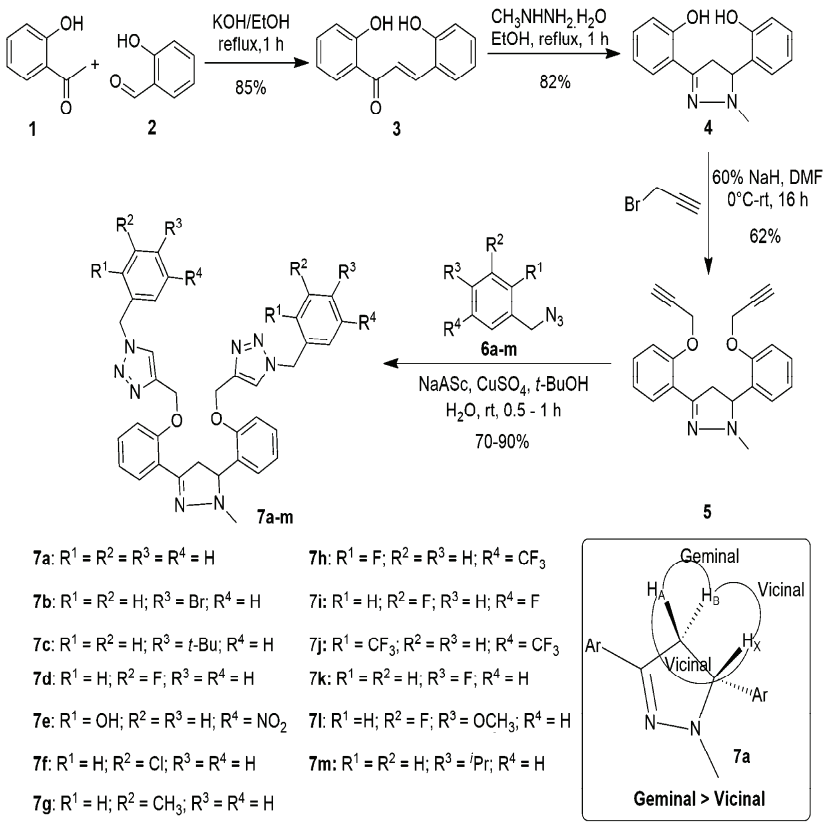
Five-membered heterocyclic compounds occupy a distinctive place in the realm of natural and synthetic organic chemistry. 1,2,3-Triazoles have received great attention due to their contribution in pharmaceutical drugs, regardless of their scarcity in nature. In this respect, various approaches for the preparation of

* Corresponding author. E-mail: ashokdou@gmail.com
doi: 10.2298/JSC160216076A

these privileged structures with drug-like properties have been developed using various synthetic strategies. Medicinally, 1,2,3-triazole derivatives have been shown to possess a wide range of diverse, interesting biological properties, such as, anti-HIV,[1] antimalarial,[2] anti-epileptic,[3] anti-allergic,[4] antileishmanial,[5] anti-cancer,[6,7] anti-inflammatory,[8] antitubercular,[9,10] antidiabetic,[11] antifungal,[12–14] antiviral[15,16] and antibacterial.[17,18] 1,2,3-Triazole derivatives are revealed in prominent pharmaceutical drugs, such as, carboxyamidotriazole, cefatrizine and tazobactam.

Pyrazolines are a significant class of heterocyclic compounds comprising two nitrogen atoms in a five-membered ring. Pyrazoline derivatives are the electron rich nitrogen heterocycles that play an essential role in various biological activities. These heterocyclic compounds occur widely in the environment, in the form of alkaloids, vitamins, pigments and as constituents of plant and animal cells. Considerable attention has been focused on pyrazolines and substituted pyrazolines because of their inspiring biological activities. Pyrazolines constitute an interesting class of heterocycles due to their synthetic versatility and effective biological activities, such as anticancer,[19] antioxidant,[20] antibacterial,[21] antifungal,[22] antidepressant,[23–25] anti-inflammatory,[26] anticonvulsant,[27] antitumor[28] and analgesic[29] properties. As far as the different pyrazoline isomers are concerned, 2-pyrazoline derivatives became the most frequently studied pyrazoline. Various methods are used for the preparation of 2-pyrazolines. Reaction of α,β-unsaturated ketones with substituted hydrazines seems to be the most popular procedure for the synthesis of 2-pyrazolines.

As mentioned, 2-pyrazolines and 1,2,3-triazole derivatives possess valuable bioactivities, which stimulated the preparation of their various derivatives. Recently, much consideration has been paid toward the synthesis and pharmacological evaluation of triazoles, and bis-triazoles, as potent HIV-1 protease inhibitors[30,31] and size-specific ligands for mRNA hairpin loops,[32] respectively. Some derivatives containing a triazole and pyrazoline moiety were synthesized and investigated for their potential antidepressant activities.[33] According to these studies, a system combining two biolabile components, 2-pyrazoline and 1,2,3--triazole, were synthesized and their potential antibacterial and antioxidant effects investigated. Bearing in mind the tremendous biological potency of bis(1,2,3--triazoles) with pyrazoline, the endeavour was the synthesis of pharmacologically active molecules, and then their evaluation for antibacterial and antioxidant activities. In this regard, our research group has focused on the design, synthesis of 1,2,3-triazoles and pyrazolines, thereby contributing to research[34,35] on these biologically important heterocycles. In the current study, the aim was to obtain new compounds containing both pyrazolines and 1,2,3-triazole rings in the same structure, *via* the click reactions shown in Schemes 1 and 2.



Scheme 1. Synthesis route to bis(1,2,3-triazole) derivatives.

EXPERIMENTAL

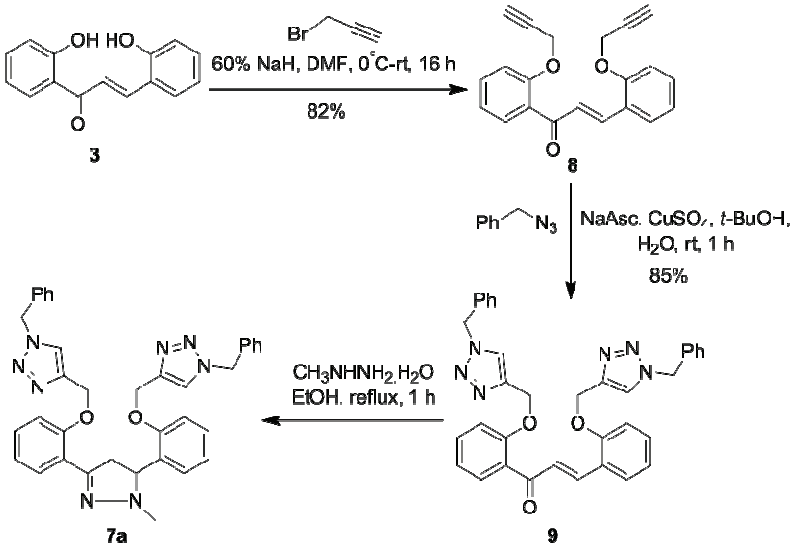
Melting points were determined by the open capillary method using an electrical melting point apparatus and are uncorrected. The IR spectra were recorded as KBr pellets on a Shimadzu FT-IR-8400s spectrophotometer. The ^{1}H-NMR (400 MHz) and ^{13}C-NMR (100 MHz) spectra were recorded on a Bruker DPX 400 spectrophotometer using tetramethylsilane (TMS) as the internal standard, with DMSO-d_6 and $CDCl_3$ as solvents. The mass spectra were recorded on a GCMS-QP 1000 EX mass spectrometer. Thin layer chromatography (TLC) was performed to check the purity of the compounds, the spot being located under UV light and iodine vapours.

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

*Synthesis of (*E*)-1,3-bis(2-hydroxyphenyl)prop-2-en-1-one (**3**)*[36,37]

To a vigorously stirred solution of 2-hydroxy acetophenone (25 g, 184 mmol) and Salicylaldehyde (22.4 g, 184 mmol) in ethanol (200 mL), KOH (30.92 g, 551 mmol) was added in small portions over 1 h at 0 °C. The reaction mixture was stirred at room temperature for 2 h and refluxed for 1 h. After completion of the reaction and cooling to room temperature, the mixture was poured into ice-cold water, neutralized with concentrated HCl and stirred for 1 h.

The precipitated solid was filtered off, washed with water and dried under vacuum to afford pure chalcone **3**.



Scheme 2. Synthesis route to 1,2,3-triazole derivatives *via* bis-propargyl chalcone.

*Synthesis of 2,2′-(1-methyl-4,5-dihydro-1*H*-pyrazole-3,5-diyl)diphenol (**4**)*

To a stirred solution of (*E*)-1,3-bis(2-hydroxyphenyl)prop-2-en-1-one (**3**, 10 g, 41.7 mmol) in ethanol (50 mL) was added methylhydrazine hydrate (2.3 g, 50.0 mmol) at 0 °C. Later the temperature was raised to room conditions and the mixture refluxed for 1 h. The solvent was evaporated under reduced pressure and the obtained residual syrup was purified by column chromatography (100–200 mesh), eluted with ethyl acetate:hexane (3:2 volume ratio) to obtain compound **4**.

*Synthesis of 1-methyl-3,5-bis[2-(prop-2-ynyloxy)phenyl]-4,5-dihydro-1*H*-pyrazole (**5**)*

To a stirred solution of 60 % NaH (2.2 g, 56.0 mmol) in dry DMF (40 mL) at 0 °C was added drop wise a solution of 2,2′-(1-methyl-4,5-dihydro-1*H*-pyrazole-3,5-diyl)diphenol (**4**, 5.0 g, 18.6 mmol) in DMF (10 mL) over a period of 30 min, and stirred for 1 h at room temperature. Later, propargyl bromide (8.3 mL, 56 mmol, 80 % in toluene) was added at 0 °C and stirred for 16 h at room temperature. After completion of the reaction, the mixture was cooled to 0 °C and quenched by the addition of ice water (50 mL), extracted twice with ethyl acetate, washed with brine solution, dried over anhydrous Na_2SO_4 and evaporated under vacuum. The obtained syrup was purified by column chromatography (100–200 mesh), eluted with ethyl acetate:hexane (1:19 volume ratio) to obtain compound **5**.

*Synthesis of (2E)-1,3-bis[2-(prop-2-ynyloxy)phenyl]prop-2-en-1-one (**8**)*

To a stirred solution of 60 % NaH (0.25 g, 6.25 mmol) in dry DMF (10 mL) was added a solution of (*E*)-1,3-bis(2-hydroxyphenyl)prop-2-en-1-one (**3**, 0.5 g, 2.08 mmol) in DMF (3 mL) dropwise over 15 min at 0 °C. The reaction mixture was stirred at room temperature for 1 h, cooled to 0 °C and propargyl bromide (0.93 mL, 6.25 mmol, 80 % in toluene) added. The mixture was stirred at room temperature for 16 h and later cooled to 0 °C, quenched with ice

water (20 mL), extracted twice with ethyl acetate, washed with brine solution, dried over anhydrous Na_2SO_4 and evaporated. The obtained crude product was purified by column chromatography (100–200 mesh), eluted with ethyl acetate:hexane (1:19 volume ratio) to afford pure compound **8**.

*Synthesis of (2*E*)-1,3-bis({2-[(1-benzyl-1*H*-1,2,3-triazol-4-yl)methoxy]phenyl})prop-2-en-1--one (**9**)*

A solution of (2*E*)-1,3-bis[2-(prop-2-ynyloxy)phenyl]prop-2-en-1-one (**8**, 0.2 g, 0.63 mmol) and benzyl azide **6a** (0.17 g, 1.26 mmol) dissolved in *t*-BuOH:H_2O (5 mL, 1:1 volume ratio) was treated with sodium L-ascorbate (0.025 g, 0.126 mmol) and copper sulphate (0.014 g, 0.063 mmol), stirred at room temperature for 1 h. After completion of the reaction, the mixture was diluted with water, extracted with ethyl acetate, washed with brine solution, dried over anhydrous Na_2SO_4 and evaporated. The crude was purified by column chromatography (100–200 mesh), eluted with ethyl acetate:hexane (1:4 volume ratio) to afford pure product **9**.

*General procedure for the synthesis of compounds (**6a**–**m**)*[36-46]

A solution of aralkyl bromide (3 mmol) in dry DMF (5 mL) at 0 °C was treated with sodium azide (3.5 mmol) and stirred at room temperature for 16 h. The reaction mixture was quenched by adding ice water, extracted with diethyl ether, washed with brine, dried over anhydrous Na_2SO_4 and evaporated at below 40 °C to give **6a**–**m**. The compounds **6a**–**m** were not characterized and were treated immediately with compound **5** without further purification to obtain the compounds **7a**–**m**.

*General procedure for the synthesis of compounds (**7a**–**m**)*

A solution of 1-methyl-3,5-bis[2-(prop-2-ynyloxy)phenyl]-4,5-dihydro-1*H*-pyrazole (**5**, 0.29 mmol) and aralkyl azide (**6a**–**m**, 0.58 mmol) dissolved in *t*-BuOH:H_2O (1:1 volume ratio) was treated with sodium L-ascorbate (0.058 mmol) and copper sulphate (0.029 mmol) and stirred at room temperature for 0.5–1 h. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was diluted with water, extracted with ethyl acetate, washed with brine, dried over anhydrous Na_2SO_4 and evaporated. The crude was purified by column chromatography (100–200 mesh), eluted with ethyl acetate:hexane (7:3 volume ratio) to afford compounds **7a**–**m**.

Biological activity

Antibacterial assay. The *in vitro* antibacterial studies against the test organisms were realised by the agar well diffusion method.[38] Nutrient broth (NB) plates were swabbed with 24 h old broth culture (100 mL) of the test bacteria. Using a sterile cork borer, wells (6 mm) were made into each Petri plates. Different concentrations of the test samples dissolved in DMSO were added into the wells by using sterile pipettes. Gentamicin was used as the standard antibiotic for the antibacterial activity. The plates were incubated at 37 °C for 24 h. After the incubation, the diameter of zone of inhibition of each well was measured. Duplicates were maintained and the average values were calculated for eventual antibacterial activity. The broth dilution test was used to determine minimum inhibitory concentration (*MIC*) of the above-mentioned samples.[39] Freshly prepared nutrient broth was used as the diluent. The 24 h old culture of the test bacteria *Escherichia coli, Pseudomonas aeruginosa, Staphylococcus aureus and Bacillus subtilis* were diluted 100 fold in nutrient broth (100 µL bacterial cultures in 10 mL NB). Increasing concentrations of the test samples were added to the test tubes containing the bacterial cultures. All the tubes were incubated at 37 °C for 24 h. The tubes were examined for visible turbidity and using NB as a control. The lowest concentration that inhibited visible growth of the tested organisms was recorded as the *MIC*.

Antioxidant activity

Nitric oxide radical scavenging activity. The scavenging effect on nitric oxide was measured according to the method of Marcocci[40] *et al.* with a little modification.[41] Briefly, 4 mL of a drug solution was added (in a test tube) to 1 mL of sodium nitroprusside (SNP) solution (25 mM) and the tubes incubated at 29 °C for 2 h. A 2 mL aliquot of the incubation solution was diluted with 1.2 mL Griess reagent (1 % sulphanilamide in 5 % H_3PO_4 and 0.1 % *N*-1-naphthylethylenediamine dihydrochloride). The absorbance of the chromophore that was formed during diazotization of the nitrite with sulphanilamide and subsequent coupling with *N*-1-naphthylethylenediamine dihydrochloride was immediately read at 550 nm and the concentration determined from a standard curve ($y = mx+c$) of sodium nitrite salt treated in the same way with Griess reagent. Inhibition of nitrite formation by the drug or the standard plant antioxidant (vitamin C) was calculated relative to the control:

$$\text{Inhibition, \%} = 100(A_{\text{control}} - A_{\text{test}})/A_{\text{control}}$$

where A_{test} is the absorbance of the control reaction mixture excluding the test compound/drug solution and A_{control} is the absorbance of the test compounds/drug solution.

RESULTS AND DISCUSSION

Chemistry

The route for the synthesis of the title compounds **7a**–**m** is outlined in Scheme 1. Initially, the title compound **7a** was synthesised as shown in Scheme 2, when conversion of compound **9** (triazole derivative) to the *N*-substituted dihydro pyrazole derivative **7a** was obtained in very low yield making the purification difficult. The bis-propargyl derivative **8** was obtained in 82 % yield from the corresponding chalcone derivative on treatment with NaH and DMF. The bis-propargyl derivative **8** was converted to the bis triazole derivatives **9** *via* copper-catalyzed click reaction with the aralkyl azides in 85 % yield. The bis-triazole derivatives **9** were treated with methylhydrazine hydrate in ethanol at reflux temperature. Finally, the target compound **7a** was obtained in very low yield. Due to the low yield obtained following Scheme 2, Scheme 1 was approached, whereby the target compounds were isolated in good yields. The precursor **5** was synthesized by reacting (*E*)-1,3-bis(2-hydroxyphenyl)prop-2-en-1-one (**3**) with methylhydrazine hydrate *via* 2,2′-(1-methyl-4,5-dihydro-1*H*-pyrazole-3,5-diyl)diphenol (**4**)**,** followed by reaction with propargyl bromide. The structures of newly synthesized compounds **7a**–**m** were characterized by IR, ^{1}H-NMR, ^{13}C-NMR, mass and CHNS spectral analysis. Except the aralkyl azides **6h**, **6j**, all the other aralkyl azides **6a,**[42] **6b**,[43] **6c**,[44] **6d**,[45] **6e**,[46] **6f**,[47] **6g**,[48] **6i**,[49] **6k**,[50] **6l**[51] and **6m**[44] are known in the literature. After isolation, the aralkyl azides were treated immediately with compound **5** without further purification to obtain compounds **7a**–**m**.

The IR, ^{1}H-NMR, ^{13}C-NMR and mass spectra for the synthesised compounds are given in the Supplementary material to this paper.

The elucidation of the structure of pyrazoline ring protons is usually realised by ^{1}H-NMR spectroscopy. In the ^{1}H-NMR spectrum, the signals of the res-

pective protons of the pyrazoline ring are verified based on their chemical shifts, multiplicities, and coupling constants. The formation of a pyrazoline ring was confirmed by the presence of an ABX system in the ^{1}H-NMR due to geminal––vicinal coupling between protons H_A, H_B and H_X. The H_A and H_B protons appeared as a doublet of doublet due to geminal and vicinal coupling as shown in Scheme 1, bottom inset (compound **7a**). These H_A and H_B differ in their coupling with H_X and hence, they are anisogamous. H_A, which appeared as a doublet of doublet at δ 2.67 ppm, is the proton *cis* to H_X and geminal to H_B (J_{AB} = 16.8 Hz, J_{AX} = 14.8 Hz). H_B is the proton *trans* and vicinal to H_X and appeared as a doublet of doublet at δ 3.52 ppm (J_{BA} = 16.8 Hz, J_{BX} = 9.6 Hz). Moreover, H_X appeared as doublet of doublet at δ 4.24 ppm (J_{XA} = 14.8, J_{XB} = 9.6 Hz).[30,52] All the other signals from NMR spectra are in agreement with the proposed structures.

Antibacterial activity

The newly synthesized compounds **7a**–**m** were screened *in vitro* for their antibacterial activity against *Escherichia coli* (ATCC 11229) and *Pseudomonas aeruginosa* (ATCC 27853), as examples of Gram-negative bacteria, and *Staphylococcus aureus* (ATCC 6538) and *Bacillus subtilis* (ATCC 6633), as examples of Gram-positive bacteria. Agar well-diffusion method was used to assay the antibacterial activity against test strains on Mueller–Hinton agar plates. Gentamicin was employed as a standard antibacterial drug. The results obtained as minimum inhibitory concentration (*MIC*) in μg mL^{-1} and measurements are presented in Table I.

TABLE I. Antibacterial activity (*MIC* / μg mL^{-1}) of the newly synthesized compounds **7a**–**m**

Compound	Bacteria			
	Gram-negative		Gram-positive	
	E. coli	*P. aeruginosa*	*S. aureus*	*B. subtilis*
7a	25	12.5	25	12.5
7b	12.5	25	6.25	12.5
7c	25	25	25	12.5
7d	25	50	25	50
7e	25	50	50	25
7f	12.5	6.25	12.5	12.5
7g	6.25	6.25	6.25	6.25
7h	6.25	12.5	6.25	6.25
7i	25	50	12.5	12.5
7j	12.5	12.5	25	12.5
7k	12.5	50	25	12.5
7l	25	25	25	50
7m	12.5	50	25	12.5
Gentamicin	3.125	3.125	3.125	3.125

Investigation of the antibacterial efficiency of the synthesized compounds revealed that most of the tested compounds displayed variable inhibitory effects on the growth of the tested Gram-negative and Gram-positive bacterial strains. It is evident from Table I, that compound **7g** exhibited the highest antibacterial effect, but was less potent than gentamicin in inhibiting the growth of *E. coli*, *P. aeruginosa*, *S. aureus* and *B. subtilis* (*MIC* = 6.25 μg/mL). Next to **7g**, compounds **7f** and **7h** (6.25–12.5 μg mL^{-1}) and **7j** (6.25–25 μg mL^{-1}) were found less potent as compared to the control drug gentamicin. It was envisaged from the analysis of the antibacterial activity results that the presence of methyl-, chloro- and triflouromethyl-substituted derivatives had a moderate effect in determining the antibacterial activity and the exhibited antimicrobial potency.

Antioxidant activity

The antioxidant activity of the synthesized compounds **7a**–**m** were evaluated *in vitro* by the nitric oxide radical scavenging assay.[40,41] The results were compared with that of the standard antioxidant ascorbic acid. Most of the compounds tested significantly inhibited nitric oxide radical levels compared to the standard antioxidant used in the study (Table II). As could be seen in Table II, compounds **7e**–**h** and **7k**–**m** exhibited strong scavenging effects on the nitric oxide stable radical, with respective IC_{50} values of 2.50±0.65, 2.50±0.60, 2.50±0.24, 2.50±0.76, 2.50±0.37, 2.43±0.41 and 2.47±0.38 μg mL^{-1}.

These values were lower than the positive controls in the study (AA with 5.35±0.67 μg/mL), indicating that compounds with hydroxyl, nitro, chloro, methyl, fluoro, trifluoromethyl, methoxy and isopropyl substituents were found to be the most potent antioxidant agents towards nitric oxide. The remaining compounds showed moderate activity.

TABLE II. Antioxidant activity (IC_{50} / μg mL^{-1}) of the synthesized compounds **7a**–**m** against nitric oxide; values are the means of three replicates±*SD*. A lower IC_{50} value indicates better scavenging activity

Compound	Value
7a	2.53±0.25
7b	2.51±0.42
7c	2.52±0.24
7d	2.52±0.11
7e	2.50±0.65
7f	2.50±0.60
7g	2.50±0.24
7h	2.50±0.76
7i	2.51±0.29
7j	2.55±0.40
7k	2.50±0.37
7l	2.43±0.41
7m	2.47±0.38
Ascorbic acid	5.35±0.67

CONCLUSIONS

In conclusion, a novel series of bis(1,2,3-triazole) derivatives were successfully synthesized through copper-catalyzed Huisgen [3+2] cycloaddition of various aralkyl azides with bis -propargyl pyrazoline **5** in good to excellent yields. Furthermore, this synthesis approach provided a structural framework that could be explored further in the development of new 1,2,3-triazole derivatives from 2-pyrazolines moieties. It is believed that the procedural simplicity, the efficiency, and the easy accessibility of the reaction partners give access to an array of heterocyclic frameworks. In this study, new hybrid molecules consisting of biologically important 1,2,3-triazole derivatives from 2-pyrazolines pharmacophores were synthesized and their antibacterial and antioxidant activities determined. Amongst the synthesized compounds, **7f**–**h** and **7j** showed the moderate antibacterial activity against the tested bacterial strains. The radical scavenging activities of the synthesized compounds also showed that the compounds **7e**–**h** and **7k–m** exhibited potent IC_{50} values. The experimental results of this study will likely provide a new basis for the design of interesting pyrazoline-based bis(1,2,3-triazoles), and further studies, including the design of new analogues of the heterocyclic moiety, are in progress.

SUPPLEMENTARY MATERIAL

Analytical and spectral data for the synthesized compounds are available electronically at the pages of journal website: http://www.shd.org.rs/JSCS/, or from the corresponding authors on request.

Acknowledgements. The authors are thankful to the Head of Department of Chemistry, Osmania University and JNTU-H Hyderabad for their valuable support.

ИЗВОД

СИНТЕЗА „КЛИК" РЕАКЦИЈОМ НОВИХ ДЕРИВАТА ПИРАЗОЛИНА КОЈИ САДРЖЕ 1,2,3-ТРИАЗОЛСКИ ПРСТЕН

KOTHURI KIRAN[1,2], DONGAMANTI ASHOK[1], BODDU ANANDA RAO[1], MADDERLA SARASIJA[1] и ALAPATI SRINIVAS RAO[3]

[1]*Green and Medicinal Chemistry Laboratory, Department of Chemistry, Osmania University, Hyderabad, 500007, Telangana, India,* [2]*Department of Chemistry, JNTU-H, Hyderabad, Telangana, 500 085, India и* [3]*Vagdevi InnoScience Private Ltd., 5-A/8, IDA Nacharam, Hyderabad, 500 076, Telangana, India*

Извршена је синтеза серије бис(1,2,3-триазола) **7a**–**m** реакцијом 1,3-диполарне циклоадиције („клик" реакција), 1-метил-3,5-бис[2-(проп-2-инил-окси)фенил]-4,5-дихидро-1*H*-пиразола **5** са арил-азидима **6a**–**m** у присуству натријум-аскорбата и бакар-сулфата, у врло добром приносу. Неопходан прекурсор **5** добијен је у реакцији (*E*)-1,3-бис(2-хидроксифенил)проп-2-ен-1-она (**3**) са метил-хидразином хидратом преко 2,2′-(1-метил-4,5-дихидро-1*H*-пиразол-3,5-диил)дифенола (**4**), после реакције са пропаргил-бромидом. Чистоћа свих нових деривата потврђена је танкослојном хроматографијом. Структура једињења је потврђена IR и NMR спектроскопијом, масеном спектрометријом и елементалном анализом. Испитана је антибактеријска активност синтетисаних деривата према *Escherichia coli, Pseudomonas aeruginosa, Staphylococcus*

aureus и *Bacillus subtilis*. Једињења **7f**–**h** и **7j** показала су умерену антибактеријску активност у поређењу са стандардима. Осим тога, испитивањем антиоксидативне активности у присуству азот-моноксида испитивана једињења показују способност везивања слободних радикала. Деривати **7e**–**h** и **7k**–**m** показују добру активност.

(Примљено 16. фебруара, ревидирано 4. септембра, прихваћено 16. септембра 2016)

REFERENCES

1. M. J. Giffin, H. Heaslet, A. Brik, Y. C. Lin, G. Cauvi, C. H. Wong, D. E. McRee, J. H. Elder, C. D. Stout, B. E. Torbett, *J. Med. Chem*. **51** (2008) 6263
2. E. M. Guantai, K. Ncokazi, T. J. Egan, J. Gut, P. J. Rosenthal, P. J. Smith, K. Chibale, *Bioorg. Med. Chem*. **18** (2010) 8243
3. S. Palhagen, R. Canger, O. Henriksen, J. A. V. Parys, M. E. Riviere, M. A. Karolchyk, *Epilepsy Res.* **43** (2001) 115
4. D. R. Buckle, C. J. M. Rockell, H. Smith, B. A. Spicer, *J. Med. Chem*. **27** (1984) 223
5. S. A. Bakunov, S. M. Bakunova, T. Wenzler, M. Ghebru, K. A. Werbovetz, R. Brun, R. R. Tidwell, *J. Med. Chem.* **53** (2010) 254
6. E. C. Kohn, C. C. Felder, W. Jacobs, K. A. Holmes, A. Day, R. Freer, L. A. Liotta, *Cancer Res*. **54** (1994) 935
7. J. L. Yu, Q. P. Wu, Q. S. Zhang, Y. H. Liu, Y. Z. Li, Z. M., Zhou, *Bioorg. Med. Chem. Lett*. **20** (2010) 240
8. S. Syed, M. M. Alam, N. Mulakayala, C. Mulakayala, G. Vanaja, A. M. Kalle, P. R. Reddanna, M. S. Alam, *Eur. J. Med. Chem.* **49** (2012) 324
9. C. Gill, G. Jadhav, M. Shaikh, R. Kale, A. Ghawalkar, D. Nagargoje, M. Shiradkar, *Bioorg. Med. Chem. Lett.* **18** (2008) 6244
10. R. P. Tripathi, A. K. Yadav, A. Arya, S. S. Bisht, V. Chaturvedi,; S. K. Sinha, *Eur. J. Med. Chem.* **45** (2010) 14
11. E. Bokor, T. Docsa, V. Gergely, L. Somsak, *Bioorg. Med. Chem.* **18** (2010) 1171
12. N. G. Aher, V. S. Pore, N. N. Mishra, A. Kumar, P. K. Shukla, A. Sharma, M. K. Bhat, *Bioorg. Med. Chem. Lett.* **19** (2009) 759
13. J. N. Sangshetti, R. R. Nagawade, D. B. Shinde, *Bioorg. Med. Chem. Lett.* **19** (2009) 3564
14. J. N. Sangshetti, A. R. Chabukswar, D. B. Shinde, *Bioorg. Med. Chem. Lett.* **20** (2010) 742
15. L. Zhou, A. Adel, M. Korn, R. Burda, J. Balzarini, E. Clercq, E. R. Kern, P. F. Torrence, *Antiviral Chem. Chemother.* (2005) 375
16. A. Sh. El-Etrawy, A. A. H. Abdel-Rahman, *Chem. Heterocycl. Compd. (N.Y., NY. U.S.)* **46** (2010) 1105
17. B. S. Holla, M. Mahalinga, M. S. Karthikeyan, B. Poojary, P. M. Akberali, N. S. Kumari, *Eur. J. Med. Chem.* **40** (2005) 1173
18. K. D. Thomas, A. V. Adhikari, N. S. Shetty, *Eur. J. Med. Chem.* **45** (2010) 3803
19. K. S. Nimavat, K. H. Popat, H. S. Joshi, *Indian J. Heterocycl. Chem.* **12** (2003) 225
20. P. Venkatesh, K. Hari, Prasath, S. Sharfudeen, V. Soumya, V. Spandana, J. Priyanka, *J. Pharm. Res.* **5** (2012) 2875
21. Y. H. Seham, *Molecules*. **18** (2013) 2683
22. H. S. Shailesh, S. P. Pankaj, *Chem. Sci. Trans.* **1** (2012) 632
23. E. Palaska, M. Aytemir, İ. T. Uzbay, D. Erol, *Eur. J. Med. Chem.* **36** (2001) 539
24. R. Y. Prasad, L. A. Rao, L. Prasoona, K. Murali, R. P. Kumar, *Bioorg. Med. Chem. Lett.* **15** (2005) 5030
25. E. Palaska, D. Erol, R. Demirdamar, *Eur. J. Med. Chem.* **31** (1996) 43

26. B. Ramesh, T. Sumana, *E-J. Chem.* **7** (2010) 514
27. Z. Ozdemir, B. H. Kandilici, B. Gumucel, U. Calis, A. A. Bilgin, *Eur. J. Med. Chem*. **42** (2007) 373
28. P. J. Jainey, I. K. Bhat, *J. Young Pharm.* **4** (2012) 82
29. S. Sridhar, Y. Rajendraprasad, *Eur. J. Chem.* **9** (2012) 1810
30. M. Whiting, J. C. Tripp, Y. C. Lin, W. Lindstorm, A. J. Olson, J. H. Elder, K. B. Sharpless, V. V. Fokin, *J. Med. Chem.* **49** (2006) 7697
31. M. Whiting, J. Muldoon, Y. C. Lin, S. M. Silverman, W. Lindstrom, A. J. Olson, H. C. Kolb, M. G. Finn, K. B. Sharples, J. H. Elder, V. V. Fokin, *Angew. Chem. Int. Ed.* **45** (2006) 1435
32. J. R. Thomas, X. Liu, P. J. Hergenrother, *J. Am. Chem. Soc.* **127** (2005) 12434
33. A. K. Zafer, O. Ahmet, Z. G. Turan, D. A. Mehlika, D. C. Ozgur, *Eur. J. Med. Chem.* **45** (2010) 4383
34. D. Ashok, V. H. Rao, P. Sreenivas, *Heterocycl. Commun.* **19** (2013) 363
35. D. Ashok, K. Sudershan, M. Khalilullah, *Green Chem. Lett. Rev.* **5** (2012) 121
36. R. K. Gupta, M. V. George, *Tetrahedron* **31** (1975) 1263
37. C. W. Mai, M. Yaeghoobi, N. Abd-Rahman, Y. B. Kang, M. P. Rao, *Eur. J. Med. Chem*. **77** (2014) 378
38. K. T. Chung, W. R. Thomasson, C. D. Wu-Yuan, *J. Appl. Bacteriol.* **69** (1990) 498
39. J. Bishnu, L. Sunil, S. Anuja, *J. Sci. Eng. Technol.* **5** (2009) 143
40. I. Marcocci, J. J. Marguire, M. T. Droy-lefaiz, *Biochem. Biophys. Res. Commun.* **201** (1994) 748
41. C. S. Alisi, G. O. C. Onyeze, *Afr. J. Biochem. Res.* **2** (2008) 145
42. L. B. de O. Freitas, T. F. Borgati, R. P. de Freitas, A. L. T. G. Ruiz, G. M. Marchetti, J. E. de Carvalho, E. F. F. da Cunha, T. C. Ramalho, R. B. Alves, *Eur. J. Med. Chem.* **84** (2014) 595
43. O. Tosic, J. Mattay, *Eur. J. Org. Chem.* **2** (2011) 371
44. Y. S. Lee, S. M. Park, H. M. Kim, S. K. Park, K. Lee, C. W. Lee, B. H. Kim, *Bioorg. Med. Chem. Lett.* **19** (2009) 4688
45. L. M. Hu, S. L. Zhang, X. Z. He, Z. G. Luo, X. L. Wang, W. Liu, X. M. Qin, *Bioorg. Med. Chem.* **20** (2012) 177
46. Z. P. Demko, K. B. Sharpless, *Org. Lett.* **3** (2001) 4091
47. D. Dou, G. He, Y. Li, Z. Lai, L. Wei, K. R. Alliston, G. H. Lushington, D. M. Eichhorn, W. C. Groutas, *Bioorg. Med. Chem.* **18** (2010) 1093
48. Z. J. Zheng, F. Ye, L. S. Zheng, K. F. Yang, G. Q. Lai, L. W. Xu, *Chem. Eur. J.* **18** (2012) 14094
49. G. Colombano, C. Albani, G. Ottonello, A. Ribeiro, R. Scarpelli, G. Tarozzo, J. Daglian, K.-M. Jung, D. Piomelli, T. Bandiera, *ChemMedChem.* **10** (2015) 380
50. L. Campbell-Verduyn, P. H. Elsinga, L. Mirfeizi, R. A. Dierckx, B. L. Feringa, *Org. Biomol. Chem*. **6** (2008) 3461
51. A. Kamal, S. M. A. Hussaini, S. Faazil, Y. Poornachandra, G. N. Reddy, C. G. Kumar, V. S. Rajput, C. Rani, R. Sharma, I. A. Khan, N. J. Babu, *Bioorg. Med. Chem. Lett.* **23** (2013) 6842
52. M. M. El-Enany, S. E. M. El-Meligie, N. A. Abdou, H. B. El-Nassan, *Orient. J. Chem.* **26** (2010) 1265.