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SYNTHESIS, CHARACTERIZATION IN SILICO AND IN VITRO STUDY OF NEW 1,2,3- TRIAZOLE DERIVATIVES AS ANTIOXIDANT AGENTS

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Abstract: *By the region-selective, a click one-pot reaction a series of new 1,2,3-triazole derivatives were successfully synthesized and evaluated in vitro as antioxidant agents. The molecular structures of synthesized derivatives were characterized using spectral analysis (IR, ^{1}H NMR, and ^{13}C NMR) in addition to elements analysis (C.H.N). The products obtained were investigated in vitro for their antioxidant activity. The results of the DPPH test revealed that 1,2,3-triazole derivatives possess a good selectivity index to capture free radicals. It was found among these compounds that the* ***5a, 5c*** *and* ***5d*** *exhibited potent levels of activity with inhibition percentages of 82.25, 80.42, and 75.36%, respectively compared to that of standard ascorbic acid. In addition, the molecular docking study confirmed the biological activity results of the tested compounds and determined their interactions nature with the active site of the protein.*

Keyword: *1,2,3-triazole, click chemistry, antioxidant, molecular docking, diazotization reaction.*
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Introduction

Oxidative stress is one of the most complex processes that occur in biological systems because of an imbalance between the production of oxidants, such as reactive oxygen species, and the ability to eliminate these oxidants by antioxidant systems [1]. Oxidants are unstable active molecules with one or more of unpaired electrons, e.g., hydroxyl radical OH^{-}, superoxide ion O^{2-}, and hydrogen peroxide H_2O_2, and are known as free radicals that are by-products of enzymatic reactions [2]. Among the effects, it was found that free radicals can interact with proteins, nucleic acids, lipids, and carbohydrates, and thus affect their structure and function. These effects can damage the cells and lead to different pathologies including early aging, atherosclerosis, cancer, and Alzheimer's disease, etc.[3,4]. Antioxidants are active molecules that affect on deactivating or eliminating free radicals by mechanism allowing reduction the oxidative stress and prevention of cellular damage, thus they contribute greatly to maintaining human health [5,6]. It was also found that the overproduction of oxidants in the biological system depletes the antioxidants in the body and thus increases the risk of disease, for this reason, exogenous antioxidants were used to compensate of the lack and protect the body from diseases [7]. Natural and synthetic chemical compounds, e.g., vitamins C, phenolic compounds, and some minerals (Se and Zn), etc., are one of the most important sources of exogenous antioxidants that can be obtained through medicines or nutritional supplements [8]. 1,2,3-triazole and their derivatives are one of the important synthetic compounds in nitrogen-containing, heterocyclic systems, characterized by a range of biological activities and low toxicity parameters [9-11]. Next to their antioxidant activity [12], triazole derivatives exhibited a broad spectrum of biological activities, such as antibacterial [13], anti-fungal [14], anti-inflammatory [15], anti- HIV [16,17], anti-Alzheimer [18], anti-cancer [19,20], and other pharmacological activities [21,22].

Besides, they are used in the industrial field as excellent anti-corrosion agents in acidic environments [23, 24]. In this work, we synthesized a number of 1, 2, 3-triazole derivatives and their activity evaluation in vitro and in silico as antioxidant agents.

Experimental part

General information

Melting points are uncorrected and were measured on SMP apparatus (Gallenkamp). IR spectra were measured with IR spectrophotometer (BRUKER). NMR measurements (^{1}H NMR, ^{13}C NMR) were recorded on Bruker AMX 400 and 100 instruments using TMS as a reference and DMSO-d_6 as a solvent. Microelements (C.H.N.) were measured using Vario Elemental Analyzer 3000 (Shimadzu, Japan). Analyses TLC were carried out on Merck 60 F254. The chemicals were supplied from commercial sources and utilized as received without further purification.

Synthesis

General procedure for preparation of azide compounds 2a-b [23]

One of the aniline compounds (5mmol), anthranilic acid **1a** (0.69gm) or 4-nitroaniline **1b** (0.685gm) was individually dissolved with sodium nitrite $NaNO_2$ (6mmol, 0.2gm) in an acidic solution (10%HCl) and stirred for 30 min at 0°C. Then, the solution of NaN3 (5mmol, 0.326gm in 5 mL water) was gradually added and again stirred for another 1h. Following the completion of the reaction (check by TLC), the solution was treated with 5%NaOH (10mL) and then extracted with chloroform. The organic liquid obtained was dried with Na_2SO_4 and then concentrated to a solid by a vacuum. The final products were recrystallized from absolute ethanol.

2-azidobenzoc acid 2a: white crystals, yeild79%, m.p165-167. IR (KBr,cm^{-1}): *v* 3354 (OH), 3274,3157 (NH_2), 3025(C-H), 2214 (N≡N), 1732 (C=O). ^{1}H NMR (DMSO-*d6*, ppm): δ 10.74 (s,1H,OH), 7.92-7.38(d,4H,H-Ar). ^{13}C NMR (DMSO-*d6*, ppm): δ 161.41 (C=O), 129.51-122.93 (C-arom.). Anal. calculated for $C_7H_5N_3O_2$: C, 51.34; H, 3.09; N, 25.76. Found; C, 52.05; H, 3.28; N, 25.92.

1-azido-4-nitrobenzene 2b: yellow crystals, yeild 87%, m.p 132-134. IR (KBr,cm^{-1}): *v* 3032(C-H), 2126 (N≡N), 1585, 1328 (NO_2), . ^{1}H NMR (DMSO-*d6*, ppm): δ 7.92-7.48(d,4H,H-arom.). ^{13}C NMR (DMSO-*d6*, ppm): δ 145.12(C-N_3), 141.23 (C-NO_2), 121.34, 123.65 (C-arom.). Anal. calculated for $C_6H_4N_4O_2$: C, 43.91; H, 2.46; N, 34.14. Found; C, 43.35; H, 2.18; N, 33.72.

General method for synthesis of propargyl derivatives 3a and 3b [25].

Potassium carbonate (0.552 g, 4mmol), was dissolved with one of the derivatives 3a–d (2mmol) in 30 mL of acetone and stirred for 15 min, and then propargyl bromide (2 mmol) was slowly added to the mixture and refluxed for 15–18 h until finish of the reaction (check by TLC). The solution was diluted with H_2O and then extracted with dichloromethane. The organic liquid was dried with anhydrous Na_2SO_4 and the solvent was evaporated with vacuum. Products obtained were purified on short column of SiO_2 using methanol– chloroform as eluent.

N-(4-(prop-2-yn-1-yloxy)phenyl)acetamide 3a: white crystals, yeild 74%, m.p 187-185. IR (KBr,cm^{-1}): *v* 3126(N-H), 2115 (C≡C), 1689(C=O). ^{1}H-NMR(DMSO-*d6*,ppm): δ 9.45(s,1H, NH), 7.50-6.67(d,4H,H-arom.), 4.74(s,2H,CH_2), 3.53(s,1H,$H_{acetylene}$), 2.08(t,8H,Me). ^{13}C-NMR (DMSO-*d6*, ppm): δ 168.3(C=O), 153.5(C-O), 133.6-115.3(C-arom.), 79.3, 78.5(C≡C), 56.0(C-O), 46.7(CH_2), 24.2(CH_3). Anal. calculated for $C_{11}H_{11}NO_2$: C, 69.83; H, 5.86; N, 7.40. Found; C, 68.75; H, 5.41; N, 7.05.

1-((4-chlorophenyl)(phenyl)methyl)-4-(prop-2-yn-1-yl)piperazine 3b: yellow crystals, yeild 78%, m.p 117-115. IR (KBr,cm^{-1}): *v* 2111(C≡C), 835(C-Cl). ^{1}H-NMR(DMSO-*d6*,ppm): δ 7.73-7.23(d,9H,H-arom.), 5.25(s,1H,$H_{tertiary}$, 4.65(s,2H,CH_2), 3.45(s,1H,$H_{acetylene}$), 2.08-1.96 (t,8H,$CH_{2piprazine}$). ^{13}C-NMR (DMSO-*d6*, ppm): δ 135.1-118.6(C-arom.), 79.5(C-tertiary), 76.3, 70.8(C≡C), 52.7, 51.4(C-piprazine), 47.9(CH_2). Anal. calculated for $C_{20}H_{21}ClN_2$: C, 73.95; H, 6.52; N, 8.62. Found; C, 72.66; H, 5.98; N, 8.11.

General procedure for synthesis of 1,2,3-triazole 5a-d derivatives [26]

A mixture of one of the azido compounds **2a-b** (2mmol), one of alkynes **3a-b** (2mmol), sodium ascorbate, aqueous copper sulfate $CuSO_4.5H_2O$ as a catalyst were dissolved in 30 mL of DMF/H_2O (2:1) and refluxed for 14–18h at 60°C, and then was monitored by TLC until the end of the reaction. The reaction mixture was cooled to room temperature and treated with brine solution. Next step, a solution was extracted with chloroform and the product obtained was dried with anhydrous Na_2SO_4 and vacuumed to evaporation of the solvent. Products obtained were purified on short column of SiO_2 using methanol–dichloromethane as eluent.

N-(4-((1-(4-nitrophenyl)-1H-1,2,3-triazol-4-yl)methoxy)phenyl)acetamide 5a: white crystals, yield;76%, m.p.;186-184. IR (KBr,cm^{-1}): *v* 3369(N-H), 1696 (C=O), 1625 (N=N), 1609 (C=$C_{triazole}$), 1515, 1318 (NO_2). ^{1}H-NMR (DMSO-*d6*, ppm): δ 9.48(s,1H,NH), 8.12 (s,1H, H-$5_{triazole}$), 7.95-6.60(d,8H,Ar-H), 4.70 (s,2H,CH_2), 2.72(s,3H, CH_3). ^{13}C-NMR (DMSO-*d6*, ppm): δ 167.6(C=O), 156.3 (C-O), 139.8(C-$4_{triazole}$), 113.2(C-$5_{triazole}$), 137.5-119.4 (C-arom.), 63.8 (CH_2), 24.4 (CH_3). Anal. calculated for $C_{17}H_{15}N_5O_4$: C, 57.79; H, 4.28; N, 19.82. Found; C, 56.31; H, 3.88; N, 18.92.

1-((4-chlorophenyl)(phenyl)methyl)-4-((1-(4-nitrophenyl)-1H-1,2,3-triazol-4-yl)methyl)piperazine 5b: yellow crystals, yield;61%, m.p.;214-212. IR (KBr,cm^{-1}): *v* 1637 (N=N), 1588 (C=$C_{triazole}$), 1510, 1345 (NO_2), 864(C-Cl). ^{1}H-NMR (DMSO-*d6*, ppm): δ 8.26 (s,1H, H-$5_{triazole}$), 7.98-6.72(d,13H,Ar-H), 3.87 (s,1H,CH), 3.37(s,2H, CH_2), 2.85-2.80 (t,8H,$CH_{2piprazine}$). ^{13}C-NMR (DMSO-*d6*, ppm): δ 139.1-124.2 (C-arom.), 118.5(C-$4_{triazole}$), 116.8(C-$5_{triazole}$), 79.4(C-tertiary), 58.8 (CH_2) 57.3, 55.8(C-piprazine). Anal. calculated for $C_{26}H_{25}ClN_6O_2$: C, 63.87; H, 5.15; N, 17.19. Found; C, 62.67; H, 4.73; N, 16.65.

2-(4-((4-acetamidophenoxy)methyl)-1H-1,2,3-triazol-1-yl)benzoic acid 5c: dark brown crystals, yield;68%, m.p.;151-149. IR (KBr,cm^{-1}): *v* 3416(OH), 3235(N-H), 1736,1668 (C=O), 1612 (N=N).1459, 1571(C=C), 1722, 1687(C=O), 1625(N=N). ^{1}H-NMR (DMSO-*d6*, ppm): δ 12.89(s,1H,OH), 9.85(s,1H,NH), 7.96 (s,1H, H-$5_{triazole}$), 7.78-6.76(d,8H,Ar-H), 5.16 (s,2H,CH_2), 2.50(s,3H, CH_3). ^{13}C-NMR (DMSO-*d6*, ppm): δ 168.3, 166,2(C=O), 154.2 (C-O), 144.7(C-$4_{triazole}$), 118.5(C-$5_{triazole}$), 132.9-121.2 (C-arom.), 76.3 (CH_2), 24.6 (CH_3). Anal. calculated for $C_{18}H_{16}N_4O_4$: C, 61.36; H, 4.58; N, 15.90. Found; C, 60.42; H, 4.06; N, 15.11.

2-(4-((4-((4-chlorophenyl)(phenyl)methyl)piperazin-1-yl)methyl)-1H-1,2,3-triazol-1-yl)benzoic acid 5d: orange crystals, yield;65%, m.p.;228-226. IR (KBr,cm^{-1}): *v* 3337(OH), 1747 (C=O), 1631 (N=N), 1495 (C=$C_{triaz.}$), 829(C-Cl). ^{1}H-NMR (DMSO-*d6*, ppm): δ 11.75(s,1H,OH), 8.22 (s,1H, H-$5_{triazole}$), 8.10-6.78(d,13H,Ar-H), 4.70 (s,1H,CH), 3.40(s,2H, CH_2), 2.79-2.75 (t,8H,$CH_{2piprazine}$). ^{13}C-NMR (DMSO-*d6*, ppm): δ 168.7 (C=O), 139.8-119.6 (C-arom.), 119.1(C-$4_{triazole}$), 115.3(C-$5_{triazole}$), 79.0(C-tertiary), 59.7 (CH_2) 58.4, 57.9(C-piprazine). Anal. calculated for $C_{27}H_{26}ClN_5O_2$: C, 66.46; H, 5.37; N, 14.35. Found; C, 65.42; H, 4.96; N, 13.76.

Antioxidant Screening Assay [27]

The antioxidant activity of derivatives **5a–d** was screened using the DPPH (1,1-diphenyl-2-picryl hydrazyl) assay to determine the radical scavenging potential of under-study compounds. Briefly, a solution of DPPH (60μM in 2ml of ethanol) was added to a solution of the tested compound at 12.5, 25, 50, 100, 250, and 500μM concentrations. Following the addition and homogenizing, the mixture was incubated in the dark for 30 min. The absorbance of the sample was determined at wavelength 515nm on a UV/Vis spectrophotometer "Amersham Biospectro". The same steps were applied with ascorbic acid for comparison, as all results obtained were utilized to calculate the percentage of inhibition according to the following formula:

Antioxidant effect as % = [(Ac−As) ÷Ac] × 100

where A_C = the control absorbance, while A_S = the sample absorbance.

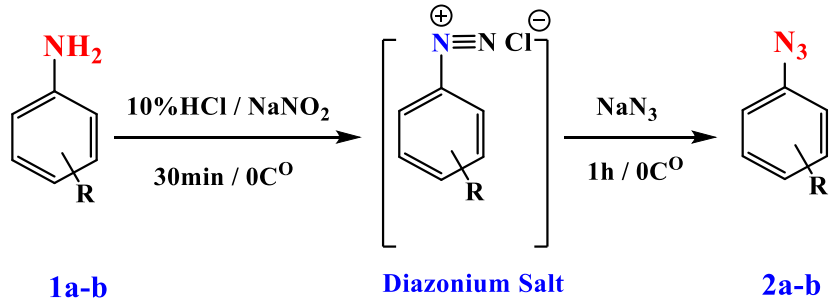
Docking study analysis [28]

Four compounds with good antioxidant activity underwent molecular docking studies to identify the potential binding with the protein of cytochrome c peroxidase enzyme (PDB: 2X08) obtained from the protein data bank. The

compounds were structured and converted to PBD format and then used as ligands. Autodock 4.2.6 program was employed to calculate the binding energy of the ligand with the protein pocket (2X08). Discovery studio software was utilized to set the receptor and visualize the binding modes that occur theoretically by 2D and 3D interaction poses.

Results and Discussion

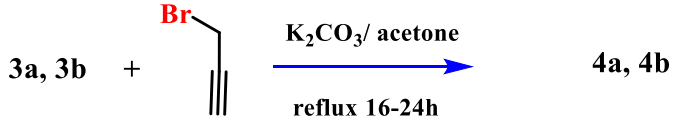
By the diazotization reaction, the azide compounds **2a** and **2b** were individually synthesized from anthranilic acid **1**a and 4-nitroaniline **1b**, respectively in an acidic medium (10%HCl) containing sodium nitrite and sodium azide and at 0℃, as shown in Scheme 1.



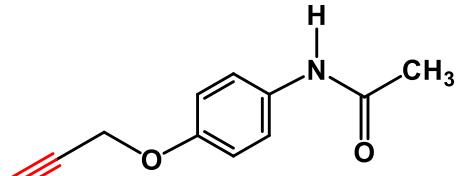
where R = 1a: 2-COOH, 1b: 4-NO_2

Scheme 1. Experimental steps for synthesis of compounds (2a, 2b)

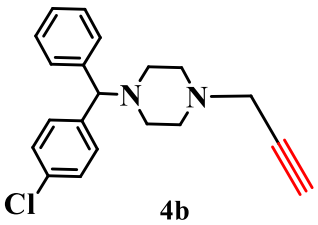
In the second step, the alkyne derivatives **4a** and **4b** were synthesized through reaction propargyl bromide with N-(4-hydroxyphenyl)acetamide **3a**, 1-((4-chlorophenyl)(phenyl)methyl) piperazine **3b**, individually in the presence of potassium carbonate and acetone as solvent as shown in Scheme 2.



Where



4a



4b

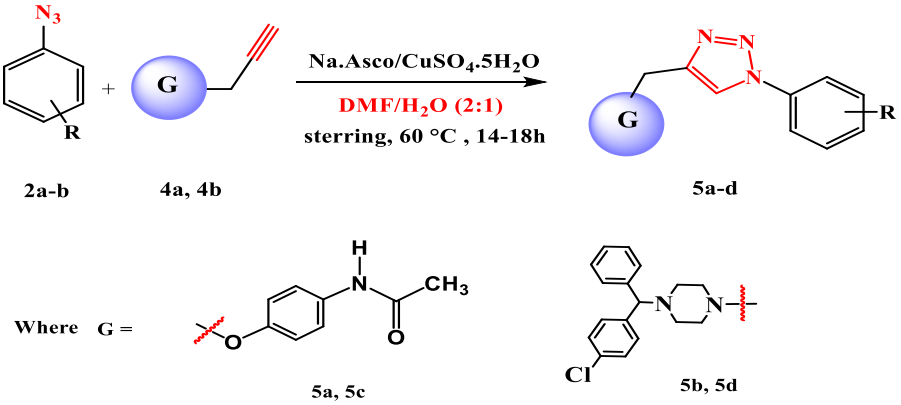
Scheme 2. Experimental steps for synthesis of compounds (4a, 4b)

In the next step and by the region-selective click reaction, 1,2,3-triazole derivatives **5a-d** were synthesized from reaction of the azide derivatives **2a, 2b** with different alkynes **4a** and **4b** using sodium ascorbate and hydrated copper sulfate as catalytic agents. This reaction occurs according to the cyclo-addition 1,3-dipolar mechanism that leads to the formation of 5-membered hetero-cycles, as shown in scheme 3. The structures of all newly synthesized derivatives were determined utilizing different spectroscopic methods (IR, 1H-NMR, 13C-NMR) in addition to micro-elements analysis. The data of spectral and micro-elements analysis were included in the experimental section.

Biological activity

Antioxidant activity study

The antioxidant activities of under-study compounds **5a-d** were evaluated in vitro using DPPH assay, and the ascorbic acid was used as a reference. The radicals scavenging test depends on a mechanism that make it possible to reduce the DPPH radical solution by a hydrogen donor antioxidant which leads to the formation of the non-radical form of DPPH-H. Generally, the results revealed that tested compounds showed potent activity as antioxidants.



Scheme 3. Experimental steps for synthesis of compounds (5-d)

Moreover, compounds **5a, 5c** and **5d** have the most potent levels of activity as compared to that of standard ascorbic acid at all the used concentrations, while the activity of compound **5b** was less effective than with increased concentration. At a concentration 500µM, it was found that the percentage inhibition of compounds **5a, 5c** and **5d** potency of 82.25, 80.42 and 75.36%, respectively as shown in Table 1. In addition, our results indicated that some of synthesized compounds possess structural properties that help in capturing free radicals; this was confirmed in a molecular docking study.

Table 1. Results of DPPH assay of compounds 5a-d at wavelength 515nm and concentration 500µM.

Compounds	Absorbance of Sample	% Inhibition
5a	**0.178**	**82.25±4.52**
5b	**0.218**	**29.5±1.25**
5c	**0.086**	**80.42±4.14**
5d	**0.112**	**75.36±3.98**
Ascorbic-acid	**0.065**	**85.88±4.72**

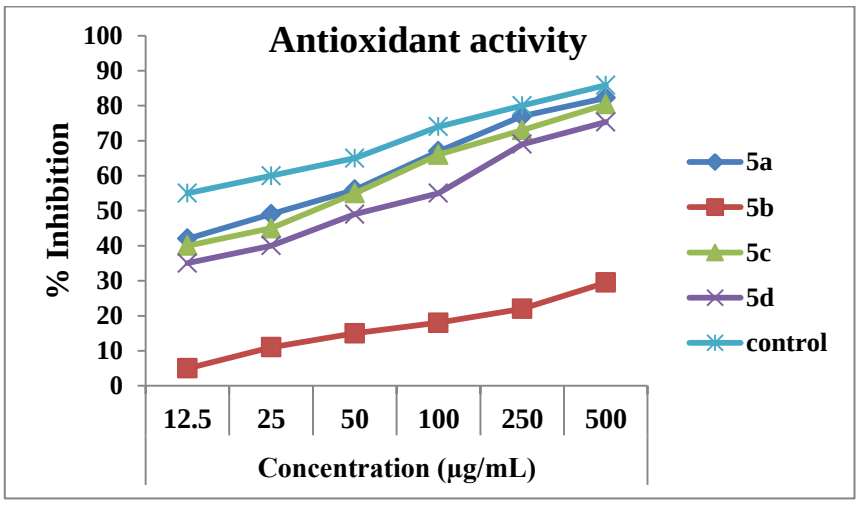


Fig. 1. Antioxidant activity results of compounds 5a-d by DPPH assay.

Molecular Docking study

In silico, a molecular docking study of compounds **5a-d** was performed to identify their antioxidant activity results. The target compounds were docked as ligands with the protein of cytochrome c peroxidase enzyme (PDB: 2X08) and attained favorable conformation. According to the docking calculations, the binding energy of 1,2,3-triazole derivatives **5a–d** were -2.8, 3.7, -4.1 and -3.6 [kcal/mol], respectively. The docking results revealed that 1,2,3-triazole derivatives **5a, 5c,** and **5d** were bound with the active site of the protein selectively and acceptably via different types of interactions such as hydrogen bond, hydrophobic, and electrostatic interactions. A summary of the binding energies and types of interactions is shown in Table 2, while the binding pose of compounds **5a, 5c** and **5d** with the active pocket of the target protein was shown as 2D, 3D representations in Fig. 2, 3 and 4.

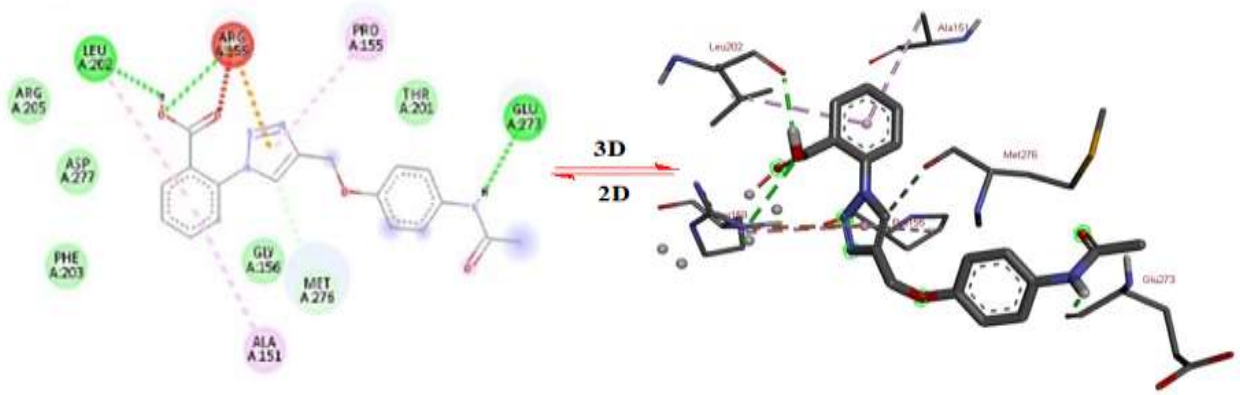


Fig 2. Conformations for 5-a simulations with the active site of cytochrome c peroxidase enzyme

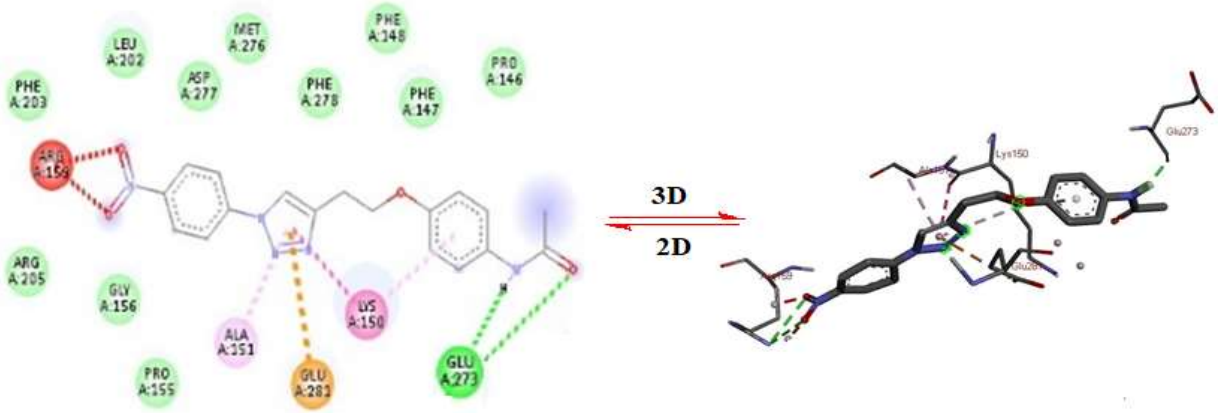


Fig 3. Conformations for 5-c simulations with the active site of cytochrome c peroxidase enzyme

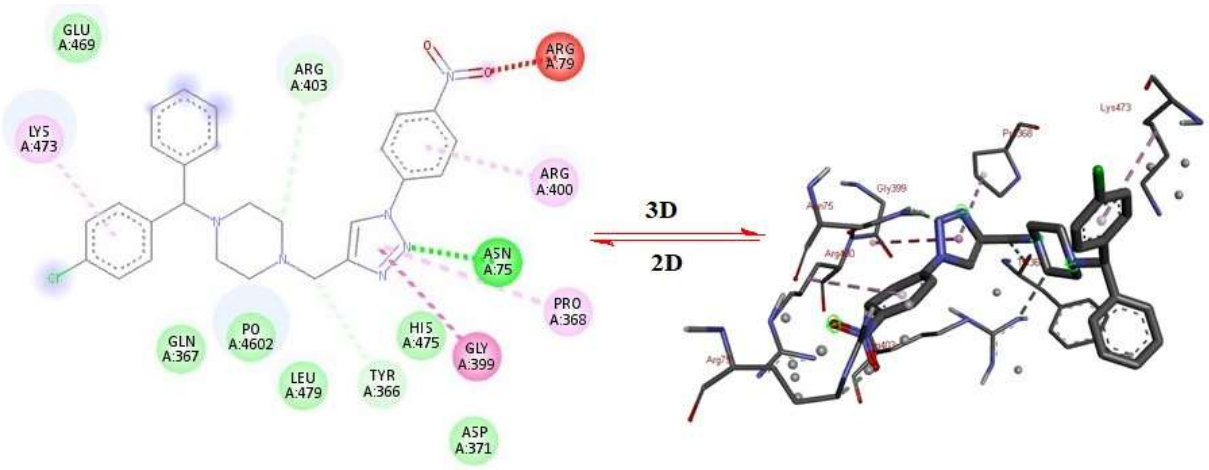


Fig 4. Conformations for 5-d simulations with active site of cytochrome c peroxidase enzyme

Table 2. Docking results, types of interactions and the binding energy of 1,2,3-triazole derivatives with the catalytic site of cytochrome c peroxidase enzyme

Compound	Ligand moiety	Site(A.A)	Interaction	E (kcal/mol)
5a	NH	GLU 273(A)	H- Bond	-2.8
	C=O	GLU 469(A)	H- Bond	
	N=N	GLU 282(A)	Pi-Anion	
		LYS 150(A)	Pi-Amid	
		ALA 351(A)	Pi-Alkyl	
	6-ring	LYS 150(A)	Pi-Alkyl	
		Other	Electrostatic	
5c	NH	GLU 273(A)	H- Bond	-4.1
	OH	LEU 202(A)	H- Bond	
		ARG 259(A)	H- Bond	
	N=N	PRO 155(A)	Pi-Alkyl	
		ARG 259(A)	Pi-Cat ion	
	6-ring	ALA 151(A)	Pi-Alkyl	
		LEU 202(A)	Pi-Alkyl	
		other	Electrostatic	
5d	5-ring	GLY 399(A)	Pi- Amid	-3.6
		PRO 368(A)	Pi-Alkyl	
	N=N	ASN 75(A)	H- Bond	
	6-ring	LYS 473(A)	Pi-Alkyl	
		ARG 400(A)	Pi-Alkyl	
	C-N	ARG 400(A)	C-H-Bond	
		TYR 366(A)	C-H-Bond	
		other	Electrostatic	

Conclusions

In the current work, we focused on the synthesis of a series of 1, 2, 3-triazole derivatives by the 3,1-dipole cyclo-addition mechanism and their in vitro evaluation as antioxidants. The results of the test indicated that some synthesized compounds had a good selectivity index as radicals scavenging agents, among those compounds, N-(4-((1-(4-nitrophenyl)-1H-1,2,3-triazol-4-yl)methoxy)phenyl) acetamide showed higher inhibition level with percentage potency of 80.15% as compared to other compounds. In addition, molecular docking simulation confirmed the biological activity results by determining the interactions nature that spontaneously occurs between the compound

and the active site of the protein. Generally, results obtained indicated that some synthesized compounds are able to capture free radicals; this was confirmed in a molecular docking study.

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Conflict of Interest: The authors acknowledge that there is no conflict of interest.

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СИНТЕЗ, ХАРАКТЕРИСТИКА IN SILICO И ИССЛЕДОВАНИЕ IN VITRO НОВЫХ ПРОИЗВОДНЫХ 1,2,3-ТРИАЗОЛА В КАЧЕСТВЕ АНТИОКСИДАНТОВ

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Аннотация: С помощью региоселективной реакции был успешно синтезирован ряд новых производных 1,2,3-триазола. Молекулярную структуру синтезированных производных охарактеризовали с помощью спектрального анализа (ИК, ЯМР 1H и ЯМР 13C), а также элементного анализа. Полученные продукты исследовали in vitro на предмет их антиоксидантной активности. Результаты ДФРГ теста показали, что производные 1,2,3-триазола обладают хорошим показателем селективности по захвату свободных радикалов. Было обнаружено, что соединения 5a, 5c и 5d проявляют высокие уровни активности с процентами ингибирования 82,25, 80,42 и 75,36% соответственно по сравнению с таковым стандартной аскорбиновой кислоты. Кроме того, исследование молекулярного докинга подтвердило результаты биологической активности тестируемых соединений и определило характер их взаимодействия с активным центром белка.
Ключевые слова: 1,2,3-триазол, клик-химия, антиоксидант, молекулярный докинг, реакция диазотирования

ANTİOKSİDANLAR KİMİ 1,2,3-TRİAZOLUN YENİ TÖRƏMƏLƏRİNİN IN VITRO TƏDQİQİ VƏ IN SILICO SİNTEZİ, XARAKTERİSTİKASI

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Xülasə: Regioselektiv reaksiyadan istifadə edərək 1,2,3-triazolun bir sıra yeni törəmələri uğurla sintez edilmişdir. Sintez edilmiş törəmələrin molekulyar strukturu spektral (İQ, 1H NMR və 13C NMR), həmçinin element analizdən istifadə etməklə xarakterizə olunmuşdur. Əldə edilən məhsullar antioksidant kimi tətbiqinə görə in vitro tədqiq edilmişdir. DFPH testinin nəticələri göstərmişdir ki, 1,2,3-triazol törəmələri sərbəst radikalları təmizləmək üçün yaxşı seçiciliyə malikdir. 5a, 5c və 5d birləşmələrinin standart askorbin turşusu ilə müqayisədə müvafiq olaraq 82. 25, 80.42 və 75.36 % inhibitorlaşma faizi ilə yüksək aktivlik nümayiş etdirdiyi aşkar edilmişdir. Bundan əlavə, molekulyar dokinq tədqiqatı nəticəsində birləşmələrin bioloji aktivliyinin olması təsdiqlənmiş və onların zülalın aktiv sahəsi ilə qarşılıqlı təsirinin xarakteri təyin edilmişdir.
Açar sözlər: 1,2,3-triazol, klik kimyası, antioksidant, molekulyar dokinq, diazotlaşma reaksiyası