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# Synthesis and Molecular Docking Studies of New 1,2,3-Triazole Derivatives Bearing Cyclohexa-2,4-Dienone for Potential Antivirus Activity

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**Abstract:** In this study, many new 1,4-disubstituted-1,2,3-triazole derivatives with a cyclohexa-2,4-dienone ring system are synthesized and their molecular docking analysis is conducted. Under basic circumstances, a series of 1,4-disubstituted-1,2,3-triazole derivatives 3a-e were reacted with ethyl acetoacetate to produce the target compounds 4a-e. FT-IR, $^{1}$H-NMR, and $^{13}$C-NMR spectroscopies were used to identify compounds 4a–e. The resulting compounds 4a–e were tested on two chosen proteins, 7dpp and 8cx9, as possible antiviral agents using in-silico molecular docking simulations. Comparing the newly synthesized compounds 4a–e to three popular antiviral drugs, the results showed that all of them had a strong binding affinity with the target proteins.

**Keyword:** 1, 2, 3-triazole, chalcones, heterocyclic chemicals, and molecular docking cyclohexa-2,4-dienone

## Introduction

Viral diseases are still a global public health concern, thus, attempts are continuing to discover new, effective and safe drugs to treat this diseases [1]. Reviews have indicated that heterocyclic structures especially that rich with nitrogen atoms have shown an effective activity against viruses [2][3]. Towards this aim, the ring system of 1,2,3-triazoles occupies a significant interest for medicinal chemists due to its unique structural properties such as a versatile synthetic tool, a good linker, a good potential pharmacophore for different medicinal applications [4][5]. Structurally, The 1,2,3-triazole ring system is one of two isomers of the five-membered heterocycle with the chemical formula $C_2N_3H_2$ [6]. In this planar heterocyclic structure, one of the three nitrogen atoms is a pyrrole type and the other two are pyridine types and all five atoms are in $sp^2$ hybrid with six π-electrons which are delocalized around the ring to introduce an aromatic structure [7]. Additionally, the 1,2,3-triazole ring structure displays good stability under hydrolytic, oxidative and reductive conditions and mimics different functional groups such as amide, ester, carboxylic acid, olefin, etc. resulting optimal bioisosteres for the synthesis of new compounds [8] [9]. Consequently, the structure of 1,2,3-triazole demonstrates a capacity for engaging in non-covalent interactions with a diverse array of receptors, including enzymes, proteins, and hydrogen bonds, hydrophobic contacts, van der Waals forces, π-π stacking interactions, and dipole-dipole interactions, among other processes, in nucleic acids [10][11]. Because of this, substances with a 1,2,3-triazole ring structure have a wide variety of biological functions [12][13]. Although new highly regioselective synthetic methodologies used for 1,2,3-triazole synthesis have been recently developedTo create a 1,4-disubstituted-1,2,3-triazole ring system, organic azides are frequently cycloadditionally reacted with alkynes or activated alkenes under various conditions [14]. Molecular docking has become an integral computational tool in drug discovery, providing insights into drug-receptor binding affinities, interaction modes, and thermodynamic properties [15][16]. The strength, stability, and energy profile of complexes (binding affinity, binding constant, and binding free energy) may all be predicted using information gleaned from the preferred orientation of bound molecules [17]. Molecular docking has gained popularity as a method for estimating the approximate binding characteristics of small molecules (drug candidates) and predicting the binding orientation of these molecules to their biomolecular target (such as a protein, carbohydrate, or nucleic acid). Through structure-based drug development, this generates the raw data required to logically design new medications with increased specificity and efficacy [18]. In this study, we presented new derivatives of 1,2,3-triazoles connected to cyclohexa-2,4-dienone and molecular docking study as antivirus agents.

## Experimental Part

### Instruments and Chemicals

All solvents and chemicals were obtained from readily available sources and utilized exactly as specified. At AL-Muthanna University's College of Science, A Shimadzu FTIR 8400 spectrometer was used to record the FTIR spectra on KBr disks. At

Basrah University's College of Pure Science, With DMSO-d6 as the solvent, $^{1}$H-NMR and $^{13}$C-NMR spectra were acquired at 400 MHz and 101 MHz using a state-of-the-art spectrometer. The literature states that we have already produced chemicals 3a–e in our laboratory [19][20][21].

**The general process for creating compounds 4a–e**

For 10 hours, a combination of ethyl acetoacetate (5.00 mmol) and a suitable derivative of chalcones 3a-e (5.00 mmol) in ethanol (60%, 25 mL) with an aqueous potassium hydroxide solution (5.00 mL, 40%) was refluxed. An aqueous solution of HCl was used to acidify the reaction mixture after it had been partially evaporated using a rotary evaporator. As shown below, the target products 4a–e were obtained by vacuum filtering the solid precipitate and then triturating it with ether.

**4-(4-(4-(ethoxycarbonyl)-5-oxo-4,5-dihydro-[1,1'-biphenyl]-3-yl)-5-methyl-1H-1,2,3-triazol-1-yl)benzenesulfonic acid 4a:** It was made with 1.2 g of compound 3a; the yield was 1.15 g, or 95.8%, as dark powder. FT-IR (KBr disc, cm-1), 2922. (sp3 aliphatic, C-H), 3074. (Ar-H), 3452. (OH, sulfonyl), C=O in 1714, C=O in 1678, C=O in 1641, C=C in 1599, C=C in 1558, 1504 (-N=N), C=O in 1126, and C-S in 1037. According to 1H NMR at 400 MHz and DMSO-d6, δ(ppm) = 2.20 (t, J=4.0 Hz, 3H, CH3), 2.32 (s, 3H, CH3), 3.45 (s, 1H, COCHCO), 3.72 (q, J=4.0 Hz, 2H), and 7.37-7.8 (m,,11H, Ar-H, 2(C=CH)). (101 MHz, DMSO-d6) 13C NMR δ = 10.20, 28.13, 51.20, 72.69, 113.4, 124.2, 124.7, 125.4, 127.3, 128.9, 131.2, 135.3, 135.6, 136.6, 138.2, 138.8, 143.4, 151.6, 163.0, and 193.9.

**4-(4-(4-(ethoxycarbonyl)-4'-nitro-5-oxo-4,5-dihydro-[1,1'-biphenyl]-3-yl)-5-methyl-1H-1,2,3-triazol-1-yl)benzenesulfonic acid 4b:** It was made with compound 3b (1.2 g); the yield was a pale yellow powder (1.12 g, 93.33%). FT-IR (KBr disc, cm-1),3455 (OH, sulfonyl),3078. (Ar-H),2922 (sp3 aliphatic, C-H),1713 (C=O),1686 (C=O),1639 (C=C),1598 (C=C),1559 (Ar, C=C),1519 (-N=N),1079 (C-O),1519, and 1348 (NO2). On the basis of $^{1}$H-NMR (400 MHz, DMSO-d6), δ(ppm) = 2.20 (t, J=4.0 Hz, 3H, CH3), 2.32 (s, 3H, CH3), 3.71 (s, 1H, COCHCO), 5.00 (q, J=4.0 Hz, 2H, CH2), 7.37-8.26 (m,10H, 8(Ar-H), 2(C=CH)). (101 MHz, DMSO-d6) 13C NMR δ = 10.19, 28.12, 51.19, 72.68, 113.4, 124.2, 127.3, 128.9, 129.4, 131.1, 135.3, 135.6, 138.2, 143.4, 145.4, 147.4, 150.2, 153.9, 163.0, 193.9.

**4-(4-(4'-bromo-4-(ethoxycarbonyl)-5-oxo-4,5-dihydro-[1,1'-biphenyl]-3-yl)-5-methyl-1H-1,2,3-triazol-1-yl)benzenesulfonic acid 4c:** Compound 3c (1.2 g) was used in its preparation, yielding a yellow powder (1.08 g, 90.00%). FT-IR (KBr disc, cm-1), 3457 (OH, sulfonyl), 3036 (Ar-H), 2982 (sp3 aliphatic, C-H), 1719 (C=O), 1686 (C=O), 1638 (C=C), 1599 (C=C), 1555 (Ar, C=C), 1501 (-N=N), 1073 (C-O), 1038 (C-S), and 5805 (C-Br). $^{1}$H NMR (400 MHz, DMSO-d6): δ(ppm) = 2.18 (t, J=4.0 Hz, 3H, CH3), 2.31 (s, 3H, CH3), 3.71 (q, J =4.0 Hz, 2H, CH2), 4.92 (s, 1H, C=OCHCO), 6.59-7.8 (m,10H, 8(Ar-H), 2(C=CH)). δ = 10.17, 28.10, 51.17, 72.66, 113.7, 124.2, 125.3, 127.3, 128.9, 129.4, 131.1, 135.2, 135.6, 138.1, 138.8, 143.3, 145.3, 153.80, 163.0, 193.9, 13C NMR (101 MHz, DMSO-d6).

**4-(4-(4'-chloro-4-(ethoxycarbonyl)-5-oxo-4,5-dihydro-[1,1'-biphenyl]-3-yl)-5-methyl-1H-1,2,3-triazol-1-yl)benzenesulfonic acid 4d:** It was made from compound 3d (1.2 g), yellow powder, m.p. 360–362 °C, and Yield (1.1 g, 91.6%). FT-IR (KBr disc, cm-1), 3452. (OH, sulfonyl), 3018. (Ar-H), 2924. (sp3 aliphatic, C-H), 1718. (C=O), 1683. (C=O), 1639. (C=C), 1600. (C=C), 1554. (Ar, C=C), 1504, 1191.75 (C-O), 1037.74 (C-S), 844.85 (C-Cl). On the basis of $^{1}$H NMR (400 MHz, DMSO-d6), δ(ppm)= 2.19 (t, J=4.0 Hz, 3H, CH3), 2.32 (s, 3H, CH3), 3.46 (s, 1H, COCHCO), 3.71 (q, J=4.0 Hz, 2H, CH2), 7.35–8.25 (m,10H, 8(Ar-H), 2(C=CH)). (101 MHz, DMSO-d6) 13C NMR δ = 10.20, 28.13, 51.20, 72.69, 113.4, 124.2, 125.4, 127.4, 129.5, 131.2, 135.3, 135.57, 136.62, 138.22, 138.74, 140.04, 143.37, 151.6, 163.0, 193.9.

**4-(4-(4-(ethoxycarbonyl)-4'-methoxy-5-oxo-4,5-dihydro-[1,1'-biphenyl]-3-yl)-5-methyl-1H-1,2,3-triazol-1-yl)benzenesulfonic acid 4e:** It was made from compound 3e (1.2 g); the yield was 0.8 g, or 66.66%, as a reddish-brown powder. (OH, sulfonyl), 3446. (KBr disc, cm-1), 3007 (Ar-H), 2939 (sp3 aliphatic, C-H), 1718 (C=O), 1687 (C=O), 1635 (C=C), 1600. (C=C), 1554. (Ar, C=C), 1508. (-N=N), 1126. (C-O), 1039 (C-S). At 400 MHz and DMSO-d6, $^{1}$H-NMR: δ(ppm) = 2.19 (t, J=4.0 Hz, 3H, CH3), 2.32 (s, 3H, CH3), and 2.54 (s, 3H, OCH3) 7.55-8.25 (m,10H, 8(Ar-H), 2(C=CH)), 3.46 (s, 1H, C=OCHC=O), 3.23 (q, J=4.0 Hz, 2H, CH2), and 3.46 (s, 1H). The 13C NMR (101 MHz, DMSO-d6) δ = 10.17, 28.10, 51.17, 67.27, 72.68, 113.4, 119.4, 119.4, 124.2, 125.3, 128.9, 129.4, 135.2, 135.6, 138.1, 138.8, 143.3, 145.3, 151.6, 153.9, 163.0, and 193.9 data.

**Computational Methodology**:

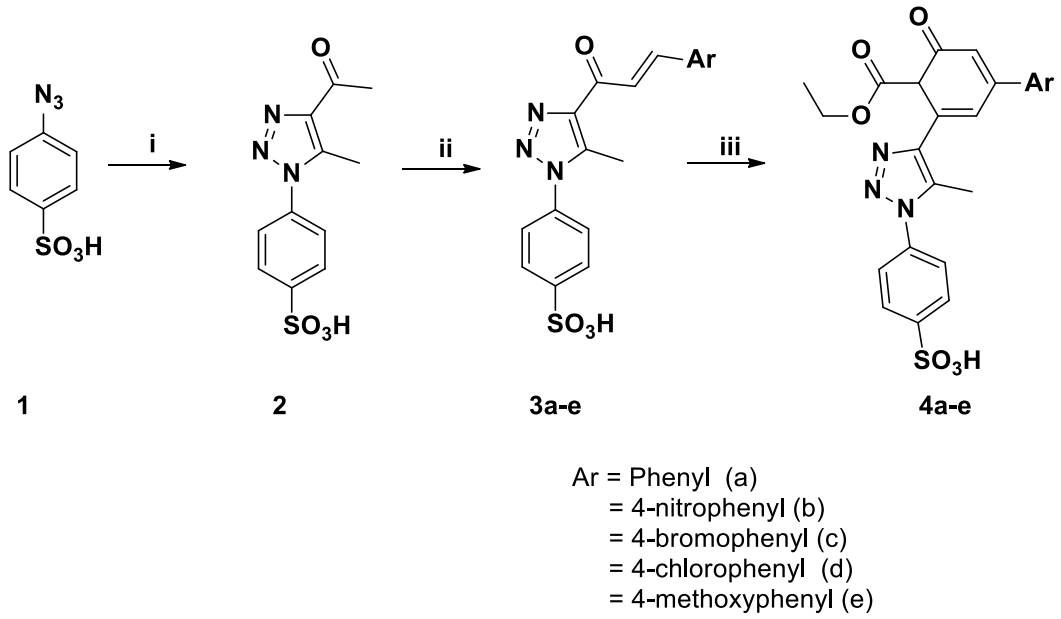
***Simulation studies using molecular docking*:** The study used the Molecular Operating Environment software version 2015.10 to carry out molecular docking investigations, which required building the ligand and protein structures according to the procedure that was described in the literatures [21]. To create the 3D structures of the target compounds 4a–e, the Chemdraw program was used. The proteases generated by SARS-CoV-2 PLpro (PDB ID: 8cx9) and SARS-CoV-2 3CL (PDB ID: 7dpp)

According to the Protein Data Bank (PDB), three-dimensional crystal structures were acquired in PDB format. [22]. The target proteins' metal ions or H2O molecules were eliminated as undesirable substances. with PyRx version 0.8, which operates with the Auto Dock Vina setup, the molecular docking was carried out [23]. The ligands (compounds 4a–e) and the protein were imported separately into the PyRx virtual screening program. The produced chemicals (ligands) have rotational torsions, while the protease proteins were fixed. Additionally, the protease protein's core was used to construct the box's size, and all dockings used an exhaustiveness value of 20 Ao. The ligands with the highest binding affinities were chosen to analyze the inter-residue interaction. The interaction between the ligand and the protein was shown by the PyMOL tool application program.

**Results and Discussion**

***Chemistry***

In the current study five 1,2,3-triazole derivatives **4a-e** were successfully synthesized and characterized as shown in Scheme 1.




**Scheme 1: (i) Et,N, DMF, aectylacetone; (ii) ethyl acetoacetate, NaOH(aq), HCl; (iii) an appropriate aldehyde, NaOH(aq), HCl.**

Compounds **3a-e** have been previously prepared and characterized in our lab as mentioned above. Interestingly, compounds **3a-e** introduce the sulfonic acid group (-$SO_3H$), which is a crucial tool for enhancing the target compounds' water solubility that is required in medicinal applications and by the same time, it presents the chalcone structure which is considered an important scaffold in the organic synthesis. Because chalcones have a reactive α,β-unsaturated carbonyl group, they can react in a variety of ways, such as attacking the carbonyl group (1,2-addition) or interacting with the α-carbon (1,4-conjugate addition) to create compounds, particularly cyclic structures. The current work is aimed to combine 1,2,3-triaozle ring with cyclohexa-2,4-dienone ring system. Firstly, it was looked at factors, including reaction temperature, reaction time, and the base utilized as a catalyst, in order to achieve this goal at optimum conditions. By monitoring the reaction by TLC technique, With strong yields and high purity, it was possible to determine the ideal conditions for producing the targeted compounds 4a–e in a straightforward work-up. Structure of target compounds 4a–e were confirmed using FT-IR, 1H-NMR, and 13C-NMR spectra. The carbonyl group of chlacones 3a-e's distinctive absorption band at 1660-1668 cm-1 largely vanishes, according to FT-IR spectra. New absorption bands appear at 1713-1419 cm-1 and 1678-1683 cm-1, respectively, which may be attributed to the carbonyl group of the ester function group attached to the ring and the carbonyl group incorporated into the cyclohexa-2,4-dienone ring system. Other main functional groups such as $SO_3H$, Ar-C=C C=N and N=N displayed their absorption band at the expected frequencies. $^1$H-NMR spectra of compound 4a-e indicated the absence of the signal of protons of α, β-unsaturated ketone group of compounds **3a-e** [21]. This absence is linked to the emergence of the triplet peak at 2.18–2.19 ppm and the quartet peak at 3.2–5.0 ppm, which are associated with the CH3 and CH2 groups, respectively of ester group that is connected to the formed cyclohexa-2,4-dienone ring system. Moreover, singlet peak appeared at 3.45-4.92 ppm can be imputed to proton of the COCHCOO that incorporated into cyclohexa-2,4-dienone, in addition, the integral calculations show correctly that the protons of (C=CHCO and C=CH-C=) of cyclohexa-2,4-dienone ring system and phenyl groups were observed as overlapped peaks in the 7.75-8.25 ppm region. In

addition, the $^{13}$C-NMR spectra of compounds **3a-e** show two new signals at belong to -$CH_3$ and -$CH_2$ of ester that is bound cyclohexa-2,4-dienone ring system at 28.12-28.13 and 51-17-51.20 ppm, respectively associated the disappearance of the disappearance the peaks belong to the carbon atom of chalcone structure at their chemical shifts.

**Molecular Docking Analysis**

The most potential protein targets of drugs were theoretically estimated using molecular docking screenings to the target of viruses. Using PyRx software, the potential antiviral activity of the synthesized compounds 4a–e against two specific proteins (7dpp and 8cx9) was examined in terms of binding affinity and docking interactions in comparison to three chosen standard antivirals; X77 [24] and N3[25] and Remdesivir,[26]. In general, All of the synthesized compounds 4a–e had a promising binding affinity with the 7dpp and 8cx9 pdb protein active sites in comparison to the binding affinity of the chosen standard antivirals (X77, N3 Remdesivir), as indicated in Tables 1 and 2. Interestingly, all the synthesized compounds **4a-e** showed binding affinity values higher than those recorded for the standard drugs X77 and Remdesivir. However, N3 drug displayed slightly higher binding affinity value that those recorded for compounds **4a-e** with both tested protein. Importantly, among compounds **4a-e**, compound **4e** that substituted with methoxy group exhibited the strongest binding affinity value with 7dpp protein as shown in Table 1. On the other hand, compound **4d** that substituted with chloro group displayed the highest binding affinity value with 8cx9 pdb protein as shown in Table 2.

**Table 1: Molecular Docking data of compounds 4a-e with 7 dpp protein.**

| No. | Subs. | S-Score | Interactions | Receptor | Distance | E (Kcal/Mol) |
|---|---|---|---|---|---|---|
| 4a | Phenyl | -6.748 | H-donor | GLN192 | 2.88 | -6.2 |
| | | | H-acceptor | GLN192 | 3.12 | -0.9 |
| | | | H-acceptor | THR190 | 3.09 | -2.2 |
| | | | H-acceptor | GLN192 | 3.35 | -1.2 |
| 4b | $NO_2$ | -6.597 | H-donor | THR26 | 2.91 | -7.6 |
| | | | H-acceptor | THR26 | 3.10 | -3.1 |
| | | | H-acceptor | GLN189 | 3.36 | -1.0 |
| 4c | Br | -6.462 | H-donor | GLU166 | 2.70 | -10.4 |
| | | | H-Pi | HIS41 | 4.25 | -0.8 |
| 4d | Cl | -6.650 | H-donor | THR190 | 2.89 | -3.7 |
| | | | H-acceptor | GLY143 | 3.28 | -1.7 |
| | | | H-acceptor | GLN189 | 3.29 | -0.9 |
| 4e | $CH_3O$ | -7.166 | H-donor | GLU166 | 2.80 | -11.7 |
| X77 (standard drug) | | -5.43 | | | | |
| N3 (standard drug) | | -7.497 | | | | |
| Remdesivir (standard drug) | | -6.25 | | | | |

**Table 2: Molecular Docking data of compounds 4a-e with 8cx9 pdb protein.**

| No. | Subs. | S-score | Interactions | Receptor | Distance | E (Kcal/Mol) |
|---|---|---|---|---|---|---|
| **4a** | Phenyl | -5.645 | H-donor | LEU162 | 2.90 | -4.6 |
| | | | H-acceptor | TYR264 | 3.22 | -1.9 |
| | | | Pi-H | ASN267 | 4.49 | -0.6 |

| | | | | | | |
|---|---|---|---|---|---|---|
| **4b** | $NO_2$ | -5.623 | H-acceptor | ARG166 | 3.05 | -2.3 |
| | | | Pi-H | GLN269 | 4.76 | -0.7 |
| **4c** | Br | -5.763 | H-donor | Try59 | 2.85 | -4.9 |
| **4d** | Cl | -5.937 | H-donor | LEU162 | 2.92 | -4.5 |
| | | | H-acceptor | TYR264 | 3.39 | -1.0 |
| | | | Pi-H | ASN267 | 4.44 | -0.6 |
| **4e** | $CH_3O$ | -5.813 | H-donor | GLN221 | 2.95 | -4.1 |
| | | | H-acceptor | THR66 | 3.19 | -3.7 |
| X77 (standard drug) | | -4.86 | | | | |
| N3(standard drug) | | -6.963 | | | | |
| Remdesivir (standard drug) | | -3.76 | | | | |

**Conclusions**

In conclusion, the present study has effectively joined 1,2,3-triazole, cyclohexa-2,4-dienone and sulfonic acid moieties into the same matrix as potential antivirus agents. It has successfully the reaction of the synthesized chalcones **3a-f** with ethyl acetoacetate was effectively used to construct the target cyclohexa-2,4-dienone ring system to result the desired compounds **4a-f** in an easy and sufficient route with excellent yields and high purity. According to molecular docking research, the produced derivatives 4a–e showed a strong propensity for binding to the tested proteins' active sites. Additionally, the target compounds' binding affinities were demonstrated to be higher than those of two widely utilized antivirals. Surprisingly, these substances may make good medications as antiviral medicines.

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**References**

[1] S. Muralidar, S. Visaga, and S. Sekaran, 'Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID- 19', Biochimie, vol. 179, pp. 85–100, 2020, doi: https://doi.org/10.1016/j.biochi.2020.09.018.

[2] V. V. Chernyshov, I. I. Popadyuk, O. I. Yarovaya, and N. F. Salakhutdinov, Nitrogen-Containing Heterocyclic Compounds Obtained from Monoterpenes or Their Derivatives: Synthesis and Properties, vol. 380, no. 42. Springer International Publishing, 2022.

[3] L. G. M. and C. M. Ahmad, Gulraiz, Maria Sohail , Muhammad Bilal, Nasir Rasool, Muhammad Usman Qamar, Codrut Ciurea, 'N-Heterocycles as Promising Antiviral Agents: A Comprehensive Overview', molecules, vol. 29, no. 2232, pp. 1–67, 2024, doi: https://doi.org/10.3390/molecules29102232.

[4] K. Bozorov, J. Zhao, and H. A. Aisa, '1,2,3-Triazole-containing hybrids as leads in medicinal chemistry: A recent overview', Bioorganic Med. Chem., vol. 27, no. 16, pp. 3511–3531, 2019.

[5] E. Kabir and M. Uzzaman, 'A review on biological and medicinal impact of heterocyclic compounds', Results Chem., vol. 4, no. 100606, pp. 1–11, 2022, doi: 10.1016/j.rechem.2022.100606.

[6] D. P. Vala, R. M. Vala, and H. M. Patel, 'Versatile Synthetic Platform for 1,2,3-Triazole Chemistry', ACS Omega, vol. 7, no. 42, pp. 36945–36987, 2022, doi: 10.1021/acsomega.2c04883.

[7] S. A. Mohammed M. Matin, Priyanka Matin, Md. Rezaur Rahman, Taibi Ben Hadda, Faisal A. Almalki, Shafi Mahmud, Mohammed M. Ghoneim, Maha Alruwaily, 'Triazoles and Their Derivatives : Chemistry , Synthesis , and Therapeutic

Applications', Front. Mol. Biosci., vol. 9, pp. 1–8, 2022.

[8] D. Coelho, Y. Colas, M. Ethève-Quelquejeu, E. Braud, and L. Iannazzo, 'Halo-1,2,3-triazoles: Valuable Compounds to Access Biologically Relevant Molecules', ChemBioChem, vol. 25, no. 10, pp. 1–14, 2024, doi: 10.1002/cbic.202400150.

[9] M. S. Malik, S. A. Ahmed, I. I. Althagafi, M. A. Ansari, and A. Kamal, 'Application of triazoles as bioisosteres and linkers in the development of microtubule targeting agents', RSC Med. Chem., vol. 11, no. 3, pp. 327–348, 2020, doi: 10.1039/c9md00458k.

[10] M. Marzi, M. Farjam, Z. Kazeminejad, A. Shiroudi, A. Kouhpayeh, and E. Zarenezhad, 'A Recent Overview of 1,2,3-Triazole-Containing Hybrids as Novel Antifungal Agents: Focusing on Synthesis, Mechanism of Action, and Structure-Activity Relationship (SAR)', J. Chem., vol. 2022, p. 7884316, 2022, doi: 10.1155/2022/7884316.

[11] S. J. N. Kerru, L. Gummidi, S. Maddila, K. Kumar Gangu, 'A Review on Recent Advances in Nitrogen-Containing Molecules and Their Biological Applications', Molecules, vol. 25, no. 1909, pp. 1–42, 2020, doi: doi:10.3390/molecules25081909.

[12] H. Y. Guo, Z. A. Chen, Q. K. Shen, and Z. S. Quan, 'Application of triazoles in the structural modification of natural products', J. Enzyme Inhib. Med. Chem., vol. 36, no. 1, pp. 1115–1144, 2021, doi: 10.1080/14756366.2021.1890066.

[13] M. J. Vaishnani et al., 'Biological importance and synthesis of 1,2,3-triazole derivatives: a review', Green Chem. Lett. Rev., vol. 17, no. 1, p. 2307989, 2024, doi: 10.1080/17518253.2024.2307989.

[14] I. Ameziane, E. Hassani, K. Rouzi, A. Ameziane, E. Hassani, and K. Karrouchi, 'Recent Developments Towards the Synthesis of Triazole Derivatives : A Review', vol. 5, pp. 450–471, 2024.

[15] A. M. Dar and S. Mir, 'Molecular Docking: Approaches, Types, Applications and Basic Challenges', J. Anal. Bioanal. Tech., vol. 8, no. 2, pp. 8–10, 2017, doi: 10.4172/2155-9872.1000356.

[16] L. G. Ferreira, R. N. Santos, G. Oliva, and A. D. Andricopulo, 'Molecular Docking and Structure-Based Drug Design Strategies', Molecules, vol. 20, pp. 13384–13421, 2015, doi: 10.3390/molecules200713384.

[17] B. Mukesh and K. Rakesh, 'Molecular docking: a review', Int J Res Ayurveda Pharm, vol. 2, no. 6, pp. 1746–1751, 2011.

[18] I. A. Guedes, C. S. de Magalhães, and L. E. Dardenne, 'Receptor–ligand molecular docking', Biophys. Rev., vol. 6, pp. 75–87, 2014.

[19] Hawraa A. Mazyed and Riyadh J. Nahi, 'Synthesis and Antioxidant Study of new1,3- Oxazepin-4,7-dione and 1,2,3-Triazole derivatives', Int. J. Pharm. Res., vol. 12, no. 1, pp. 252–259, 2020.

[20] H. A. Shaalan and R. J. Nahi, 'Synthesis and In Vitro Antioxidant Activity Study of Some New Azoles Synthesis and In-Vitro Antioxidant Activity Study of Some New Azoles Derivatives as Sulfa Drugs', Int. J. Drug Deliv. Technol., vol. 11, no. 3, pp. 1107–1111, 2021, doi: 10.25258/ijddt.11.3.78.

[21] A. A. Kozan and R. J. Nahi, 'Synthesis and Molecular Docking Studies of New Pyrimidinone ring Containing 1,2,3-Triazole Derivatives', Int. J. Drug Deliv. Technol., vol. 13, no. 3, pp. 1005–1010, 2023, doi: 10.25258/ijddt.13.3.39.

[22] W. Consortium, 'Protein Data Bank : the single global archive for 3D macromolecular structure data', Nucleic Acids Res., vol. 47, pp. 520–528, 2019, doi: 10.1093/nar/gky949.

[23] G. M. Morris et al., 'Software News and Updates AutoDock4 and AutoDockTools4 : Automated Docking with Selective Receptor Flexibility', J. Comput. Chem., vol. 30, no. 16, pp. 2785–2791, 2009, doi: 10.1002/jcc.

[24] J. Prajapati, R. Patel, P. Rao, M. Saraf, R. Rawal, and D. Goswami, 'Perceiving SARS - CoV - 2 Mpro and PLpro dual inhibitors from pool of recognized antiviral compounds of endophytic microbes : an in silico simulation study', Struct. Chem., vol. 33, pp. 1619–1643, 2022, doi: 10.1007/s11224-022-01932-0.

[25] K. Arafet et al., 'Mechanism of inhibition of SARS-CoV-2 MprobyN3peptidyl Michael acceptor explained by QM/MM simulations and design of new derivatives with tunable chemical reactivity', Chem. Sci., vol. 12, no. 4, pp. 1433–1444, 2021, doi: 10.1039/d0sc06195f.

[26] H. Xian et al., 'Remdesivir in Coronavirus Disease 2019 ( COVID - 19 ) treatment : a review of evidence', Infection, vol. 49, no. 3, pp. 401–410, 2021, doi: 10.1007/s15010-020-01557-7.