How to Cite:
Mazyed, H. A., Razzaq, A. S., Hussein, G. H., & Nahi, R. J. (2022). Synthesis and anti-diabetic activity evaluation of new 1,2,3-triazole derivatives incorporating 2-pyrazoline ring. *International Journal of Health Sciences*, *6*(S4), 7299–7307.
https://doi.org/10.53730/ijhs.v6nS4.10171

Synthesis and anti-diabetic activity evaluation of new 1,2,3-triazole derivatives incorporating 2-pyrazoline ring

Hawraa A. Mazyed
Department of Chemistry, College of Science, AL-Muthanna University, Iraq

Ali S. Razzaq
College of Pharmacy, AL-Muthanna University, Iraq

Ghina H. Hussein
Ministry of Education, Directorate of Education Al-Muthanna, Iraq

Riyadh J. Nahi
College of Medicine/AL-Muthanna University, Iraq
Corresponding author email: riyadhnahi@mu.edu.iq

***Abstract*---**In the present work, a new series of compounds containing 1,2,3-triazole and 2-pyrazoline moieties in the same matrix was synthesized via a multistep synthetic route. The synthesized compounds were characterized by FT-IR, ^{1}HNMR and ^{13}C NMR spectra. The target compounds and their precursors were screened *in vitro* for their α-amylases inhibitory activity. The preliminary activity results revealed that all the tested compounds displayed an inhibition activity ranged from moderate to high depending on their structures and concentrations compared to ascorbose as a standard drug.

***Keywords*---**heterocyclic compounds, 1,2,3-triazole, pyrazolines, furan ring.

Introduction

Nitrogen-containing heterocycles represent a main pharmacophore system in a wide range of pharmaceutical materials [1]. The influences of the nitrogen atom on the reactivity heterocyclic compounds target medication pharmacokinetics and metabolism are affected by interactions between nitrogen atoms and several target inhibitors [2]. An important example of nitrogen-containing heterocycles is triazole and pyrazole rings. 1,2,3-Triazole ring system is an aromatic five-membered heterocycle containing three adjacent nitrogen atoms as one of two

Manuscript submitted: 9 March 2022, Manuscript revised: 18 May 2022, Accepted for publication: 27 June 2022

isomeric structures with the molecular formula $C_2N_3H_3$ [3]. Synthetically, 1,3-dipolar cycloaddition reaction of azides with alkynes or activated alkenes is the common strategy to synthesize of 1,2,3-triazole derivatives [4]. 1,2,3-Triazole ring system could form hydrogen bonds, dipole–dipole bonds and Van der Waals forces interactions with various biomolecules such as enzymes, proteins, nucleic acids and other receptors [5]. Thus, compounds containing 1,2,3-triazole ring system have been used as agents for different biological activities such as antimicrobial [6], anticancer [7], antioxidant [8], antiviral [9] and antidiabetic [10]. 2-Pyrazzoline ring system is one of three partially reduced forms of pyrazole ring system with two adjacent nitrogen atoms and one endocyclic double bond incorporated in five-membered heterocycle carries a π-excessive heterocycle, as seen in pyrrole at position 1 and pyridine at positions [11][12]. 2-Pyrazzoline ring system can be synthesized by various methods, however, Claisen-Schmidt reaction which is followed by cyclization step with hydrazine hydrate under the appropriate conditions is the common method choice [13]. Biologically, compounds containing 2-pyrazoline structure have particularly interesting therapeutic properties such as antimicrobial [14], antidiabetic [15] antifungal [16] and anticancer [17]. As the study of bioactive molecule containing nitrogen atoms is one of the most important fields of the medicinal chemistry, it is interested to combination of 1,2,3-triazole and 2-pyrazoline rings in the same matrix as an attempt to produce new bioactive multi-site compounds towards the development of new drugs.

Experimental Section

The FT-IR spectra were recorded on a Shimadzu FT-IR 8400 spectrometer in KBr discs. NMR spectra were acquired using Inova NMR spectrometer (500 MHz for ^{1}HNMR spectra and 125 MHz for ^{13}CNMR spectra) and the chemical shifts (δ) are given in ppm. The absorbance was recorded using UV-1650 Shimadzu Spectrophotometer.

Synthesis of compound 1a-e: Compounds 1a-e and their precursors were prepared previously as described in the literatures [18] [19].
Synthesis of compounds 2a-e: To the required compound of compounds 1a-e (10.0 mmole) in an aqueous solution of sodium hydroxide (10.0 ml, 40% v/v), furfural (0.82 ml, 10.0 mmol) in ethanol (25.0 ml) was added. The resulted mixture was then stirred at room temperature for 24 before being acidified with an aqueous solution of HCl (50% v/v). The formed solid product was collected under vacuum filtration, washed with water, recrystallized from ethanol and dried to give the target compound.

Synthesis of 3-(furan-2-yl)-1-(5-methyl-1-phenyl-1H-1,2,3-triazol-4-yl)prop-2-en-1-one (2a): It was prepared by using compound 1a (2.01 g); Yield (2.5 g, 89.5%) as a pale yellow powder. FT-IR (KBr disc, cm^{-1}), 3147 (sp^2-CH, alipha.), 3068 (-CH, Ar), 1662 (C=O), 1597 (C=C, triazolyl), 1556 (C=C, Ar), 1448 (-N=N-). ^{1}H-NMR (500 MHz, DMSO-d_6): δ= 2.59 (s, 3H, CH_3), 6.71 (d, 1H, J=5.0 Hz, –CH= of chalcone moiety), 7.12 (d, 1H, J=5.0 Hz, –CH= furan ring), 7.51-7.94 (8H, m, Ar-H, , –CH= of chalcone moiety and the rest of furan protons).

Synthesis of 1-(1-(4-chlorophenyl)-5-methyl-1H-1,2,3-triazol-4-yl)-3-(furan-2-yl)prop-2-en-1-one (2b): It was prepared by using compound 1b (2.35 g); Yield (2.4

g, 76%) as a white powder. FT-IR (KBr disc, cm^{-1}), 3101 (sp^2-CH, alipha.), 3059 (-CH, Ar), 1660 (C=O), 1600 (C=C, alipha.), 1556 (C=C, Ar), 1460 (-N=N-, triazolyl). ^{1}H-NMR (500 MHz, DMSO-d_6): δ= 2.60 (s, 3H, CH_3), 6.71 (d, 1H, J=6.5 Hz, –CH=CH of Chalcone moirty), 7.13 (d, 1H, J=6.5 Hz, –CH= of furan ring), 7.68 - 7.94 (m, 7H, Ar-H, –CH= of chalcone moiety and the rest of furan protons).

Synthesis of 1-(1-(4-bromophenyl)-5-methyl-1H-1,2,3-triazol-4-yl)-3-(furan-2-yl)prop-2-en-1-one (2c): It was prepared by using compound 1c (2.80 g); Yield (2.5 g, 69 %) as a pale yellow powder. FT-IR (KBr disc, cm^{-1}), 3111 (sp^2-CH, alipha.), 3059 (-CH, Ar), 1660 (C=O), 1599 (C=C, alipha.), 1548 (C=C, Ar). ^{1}H-NMR (500 MHz, DMSO-d_6): δ= 2.60 (s, 3H, CH_3), 6.71 (d, 1H, J=6.5 Hz, –CH=CH– of chalcone moiety), 7.12 (d, 1H, J=6.5 Hz, –CH= of furan ring), 7.60-7.94 (m, 7H, Ar-H–CH= of chalcone moiety and the rest of furan protons).

Synthesis of 3-(furan-2-yl)-1-(5-methyl-1-(4-nitrophenyl)-1H-1,2,3-triazol-4-yl)prop-2-en-1-one (2d): It was prepared by using compound 1c (2.46 g); Yield (2.7 g, 83%) as a pale yellow powder. FT-IR (KBr disc, cm^{-1}), 3117 (sp^2-CH, alipha.), 3003 (-CH, Ar), 1658 (C=O), 1595 (C=C, alipha.), 1554 (C=C, Ar). ^{1}H-NMR (500 MHz, DMSO-d_6): δ= 2.68 (s, 3H, CH_3), 6.72 (d, 1H, J=6.5 Hz, –CH=CH–), 7.14 (d, 1H, J=6.5 Hz, –CH=), 7.66 -8.49 (m, 7H, Ar-H and furan protons).

Synthesis of 3-(furan-2-yl)-1-(1-(4-methoxyphenyl)-5-methyl-1H-1,2,3-triazol-4-yl)prop-2-en-1-one (2e): It was prepared by using compound 1d (2.31 g); Yield (2.1 g, 67 %) as a pale yellow powder. FT-IR (KBr disc, cm^{-1}), 3119 (sp^2-CH=, alipha.), 3040 (-CH, Ar), 2839 (CH, alipha.), 1656 (C=O), 1604 (C=C, alipha.), 1554 (C=C, Ar), 1039 (C-O). ^{1}H-NMR (500 MHz, DMSO-d_6): δ= 2.56 (s, 3H, CH_3), 3.83 (3H, s, -OCH_3), 6.71 (d, 1H, J=6.5 Hz, CH=CH of chalcone moiety), 7.12-7.94 (m, 7H, Ar-H, furan protons, CH=CH of chalcone moiety).

General procedure for the synthesis of compounds 3a-e: A mixture of the required compound of compounds 2a-e (5.0 mmol) and hydrazine hydrate (0.65 ml, 20.0 mmol) in ethanol (25 ml) was refluxed for 7.0 hrs. The reaction mixture was then cooled into room temperature before being placed in a crashed ice bath for 30 minutes. The formed solid product was filtered washed with ether, recrystallized from ethanol and dried to give the target compound.

Synthesis of 4-(5-(furan-2-yl)-4,5-dihydro-1H-pyrazol-3-yl)-5-methyl-1-phenyl-1H-1,2,3-triazole (3a): It was prepared by using compound 2a (1.39 g); Yield (1.2 g, 81%) as a pale yellow powder. FT-IR (KBr disc, cm^{-1}), 3277 (-NH), 3109 (Ar, -CH), 2918 (Alipha. Sp^3-CH), 1504 (Ar, C=C). ^{1}H-NMR (500 MHz, DMSO-d_6): δ= 2.53 (s, 3H, CH_3), 3.25-3.45 (q, 2H, J=10.0 Hz, -CH_2 of pyrazole ring), 4.72 (t, 1H, -CH of pyrazole ring), 6.37-6.41 (m, 2H, =HC-CH= of furan ring), 7.63-7.64 (6H, m, Ar-H and =CH-O of furan ring). ^{13}C-NMR (125 MHz, DMSO-d_6): 10.37, 38.8, 56.0, 106.5, 110.8, 125.6, 130.1, 132.2, 136.1, 139.2, 139.2, 142.8, 144.2, 155.3.

1-(4-chlorophenyl)-4-(5-(furan-2-yl)-4,5-dihydro-1H-pyrazol-3-yl)-5-methyl-1H-1,2,3-triazole (3b): It was prepared by using compound 2b (1.56 g); Yield (1.3 g, 79%) as a pale yellow powder. FT-IR (KBr disc, cm^{-1}), 3331 (-NH), 3103 (Ar, -CH), 2970 (Alipha. Sp^3-CH), 1502 (Ar, C=C). ^{1}H-NMR (500 MHz, DMSO-d_6): δ= 2.51 (s, 3H, CH_3), 3.23-3.45 (q, J=5.0 Hz, 2H, -CH_2 of pyrazole ring), 4.87 (t, 1H, -CH of pyrazole ring), 6.38-6.42 (m, 2H, =HC-CH= of furan ring), 7.58-7.71 (m, 5H, Ar-H and =CH-O of furan ring). ^{13}C-NMR (125 MHz, DMSO-d_6): 10.3, 38.8, 56.0, 106.5, 110.8, 127.4, 130.1, 132.3, 134.7, 134.8, 139.3, 142.8, 144.2, 155.3.

1-(4-bromophenyl)-4-(5-(furan-2-yl)-4,5-dihydro-1H-pyrazol-3-yl)-5-methyl-1H-1,2,3-triazole (3c): It was prepared by using compound 2c (1.79 g); Yield (1.5 g, 80%) as a white powder. FT-IR (KBr disc, cm^{-1}), 3331 (-NH), 3076 (Ar, -CH), 2922 (Alipha. Sp^3-CH), 1496 (Ar, C=C). ^{1}H-NMR (500 MHz, DMSO-d_6): δ=2.51 (s, 3H, CH_3), 3.22 and 3.44 (q, 2H, J=10 Hz, -CH_2 of pyrazole ring), 4.86 (1H, triplet, -CH of pyrazole ring), 6.36-6.41 (m, 2H, =HC-CH= of furan ring), 7.58 -7.88 (m, 5H, Ar-H and =CH-O of furan ring). ^{13}C-NMR (125 MHz, DMSO-d_6): 10.3, 38.8, 56.0, 106.5, 110.3, 123.3, 127.6, 132.3, 133.2, 135.3, 139.3, 142.8. 144.2, 155.3.

4-(5-(furan-2-yl)-4,5-dihydro-1H-pyrazol-3-yl)-5-methyl-1-(4-nitrophenyl)-1H-1,2,3-triazole (3d): It was prepared by using compound 2d (1.62 g); Yield (1.3 g, 76%) as a yellow powder. FT-IR (KBr disc, cm^{-1}), 3356 (-NH), 3082 (Ar, -CH), 2920 (Alipha. Sp^3-CH), 1521 (Ar, C=C). ^{1}H-NMR (500 MHz, DMSO-d_6): δ= 2.60 (s, 3H, CH_3), 3.23 and 3.45 (q, 2H, J=15.0 Hz, -CH_2 of pyrazole ring), 4.88 (t, 1H, -CH of pyrazole ring), 6.38-8.50 (m,7H, Ar-H and furan ring). ^{13}C-NMR (125 MHz, DMSO-d_6): 10.5, 38.7, 56.1, 106.5, 110.4, 125.5, 126.4, 132.5, 139.83, 140.9, 142.9, 143.9, 148.03, 155.3.

4-(5-(furan-2-yl)-4,5-dihydro-1H-pyrazol-3-yl)-1-(4-methoxyphenyl)-5-methyl-1H-1,2,3-triazole (3e): It was prepared by using compound 2e (1.54 g); Yield (1.2 g, 74%) as a pale yellow. FT-IR (KBr disc, cm^{-1}), 3319 (-NH), 3018 (Ar, -CH), 2966 (Alipha. Sp^3-CH), 1518 (Ar, C=C). ^{1}H-NMR (500 MHz, DMSO-d_6): δ= 2.46 (s, 3H, CH_3), 3.24 and 3.45 (q, 2H, J=15.0 Hz, -CH_2 of pyrazole ring), 3.68 (s, 3H, -OCH_3), 4.85 (t, 1H, -CH of pyrazole ring), 6.37-7.63 (m, 7H, Ar-H and furan moiety). ^{13}C-NMR (125 MHz, DMSO-d_6): 10.27, 38.83, 56.06, 60.3. 106.5, 110.8, 115.1, 127.1, 129.0, 132.2, 138.9, 142.8, 144.5, 155.4.

In vitro α-Amylase Inhibition Assay

The synthesized compounds 2a-e and 3a-e have been screened as antidiabetic agents against alpha amylase enzyme using. The α-amylase inhibition assay was performed using the 3,5-dinitrosalicylic acid (DNSA) method that was described in the literature [20]. All the target compounds and ascorbase as standard antidiabetic agent were prepared in a buffer solution of ((Na_2HPO_4/ NaH_2PO_4 (0.02 M), NaCl (0.006 M) at pH 6.9) with three concentrations; 50, 100 and 150 μg/mL. A solution of α-amylase (200 μL, 2.0 units/mL) was mixed with 200 μL of the tested compounds and incubated for 10 min at 30 °C, followed by addition of an aqueous solution of starch (200 μL, 1.0% w/v). The resulting solution was incubated for 3.0 min before being terminated by the addition of DNSA reagent with heating it in a water bath at 85–90 °C for 10 minutes. The mixture was then cooled to room temperature and diluted with 5.0 mL of distilled water. For each solution, the absorbance was then measured at 540 nm using a UV-Visible spectrometer. The control with 100% enzyme activity was prepared by replacing the synthesized compounds with 200 μL of buffer solution. A control was prepared using the same procedure replacing the tested compound with distilled

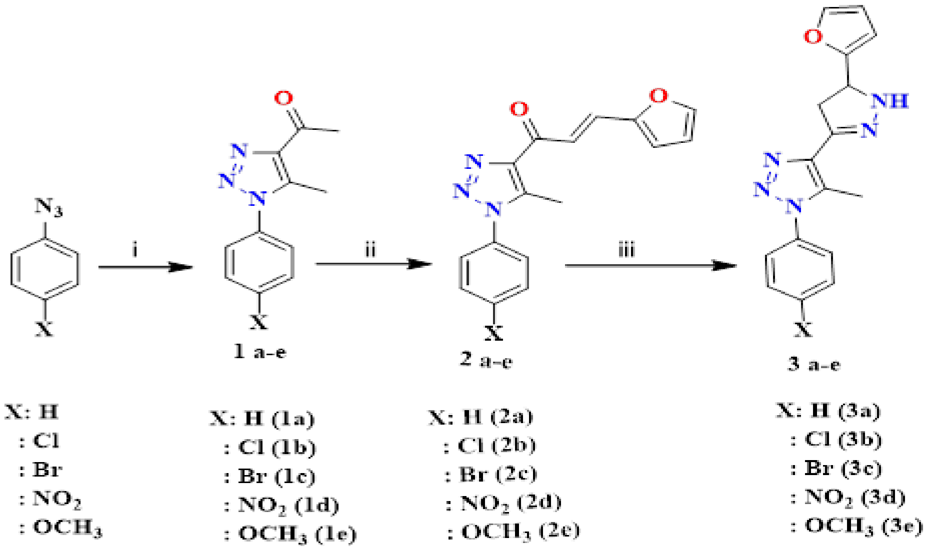
water. The α-amylase inhibitory activity was expressed as percent inhibition and was calculated using the equation given below:
a-amylase inhibition % =

Where is the absorbance of control solution without test sample and is the absorbance of the tested compound.

Results and Discussion

Chemistry

The synthesis of the titled compounds was performed by a multistep reaction as shown in Scheme 1. The key intermediates phenyl azide were used as building blocks to construct 1,2,3-triaozle ring system to the target compounds via 1,3-cycloaddition reaction with acetylacetone in the presence of triethylamine. In the current work, a series of *p*-substituted 1-(5-methyl-1-phenyl-1H-1,2,3-triazol-4-yl)ethanone derivatives 1a–e was synthesized to investigate the effects of a structural variation of the substituent group on the α-amylase inhibitory activity of the target compounds. Compounds 1a–e were then condensed with furfural via Claisen-Schmidt reaction conditions. Herein, using furfural is to introduce furan ring to the target compounds as an additional heterocyclic structure combined with 1,2,3-treiazole and pyrazoline rings in the same matrix. This reaction was achieved in ethanolic sodium hydroxide solution (30%, w/v) at room temperature to give the corresponding chalcones 2a-e. The structure of compounds 2a-d and 3a-d was confirmed by FT-IR, ^{1}H-NMR spectra. FT-IR spectra of compounds 2a-d mainly showed shifting characteristic absorption band of carbonyl group C=O to 1662-1656 cm^{-1}. In addition, ^{1}H-NMR exhibited new two doublets singles at 6.70-6.72 ppm and 7.64-7.68 ppm that is imputed for (HC=CH) protons of chalcones.



Scheme 1. (i) acetylacetone, trimethylamine, DMF, (ii) furfural, eq. NaOH, Ethanol; (iii) Hydrazine hydrate; Ethanol.

Chalcones have a simple privileged scaffold for the discovery of new compounds. Thus, the synthesized chalcones 2a–e were used as intermediates for the combination of 1,2,3-triazole and 2-pyrazoline rings through 1,4-addition of hydrazine hydrate to the α,β-unsaturated carbonyl system, followed by dehydration and rearrangement step to give the final products 3a–e. Thus, treatment of 3-(furan-2-yl)-1-(5-methyl-1-phenyl-1H-1,2,3-triazol-4-yl)prop-2-en-1-one derivatives 2a-e with hydrazine hydrate led to construct 2-pyrazoline ring system to give the final compounds 3a-e. Compounds 3a-e were identified by FT-IR, ^{1}HNMR and ^{13}CNMR spectra. Mainly, FT-IR spectra showed the disappearance the absorption band of carbonyl group (C=O) of chalcone structure at 1662-1656 cm^{-1} associated with the appearance of a new sharp absorption band at region 3277-3356 cm^{-1} belonging to the secondary amine (-NH) group of pyrazoline ring system. ^{1}H-NMR spectra of compounds 3a-e demonstrated the disappearance singles of protons of CH=CH of chalcones besides exhibited doublet-doublet signal at 3.22-3.45 ppm corresponding to the protons at C-4 and triplet at 4.85-4.88 belong to proton of C-5 of the pyrazoline ring system. Moreover, ^{13}CNMR spectra agreed with FT-IR and ^{1}HNMR. In general, the current work highlighted that the target compounds were synthesized in an efficient synthetic pathway.

Determination α-Amylase Inhibition Activity

Diabetes mellitus is increasing in prevalence worldwide, and its complication has grown into a public health problem. It is a condition characterized by both insulin resistance (poor tissue insulin sensitivity) and impaired insulin secretion from pancreatic β-cells [21][22]. The synthesized compounds 2a-e and 3a-e were in vitro tested for their inhibitory potential against α-amylase enzyme. Three concentrations of the tested compounds (50 μg/mL, 100 μg/mL and 200 μg/mL) were used for the assay. In general, all the synthesized derivatives displayed α-amylase inhibitory activities compared to acarbose as a standard agent. For compounds 2a-e, 2b, 2e, 3b and 3e exhibited a good anti α-amylase activity. Compounds 2d and 3d showed appreciable inhibition activity, compounds 2c and 3c with para nitro substitution showed the least inhibitory activity. Compounds 2b and 3b that substituted with chloro group at para position showed the greater inhibition (%) of the α-amylase enzyme, compared to the other compounds with value of 89.54 and 89.5%, respectively at 200 μg/mL. In addition, compounds 2b and 3b displayed a higher % inhibition values even than the standard drug acarbose. Based on the results shown in Table 1 and Figure 1, the present study indicated that compounds 2b, 2e, 3b and 3e could be useful in management of postprandial hyperglycemia.

Table 1: α-amylase inhibition activity of compounds 2a-3e

	α-amylase inhibition%		
Comp. No.	50 μg/mL	100 μg/mL	200 μg/mL
2a	37.67	39.51	42.72
2b	70.43	81.24	89.54
2c	27.92	32.23	40.99
2d	64.14	67.50	73.75
2e	75.49	77.84	86.46

3a	39.00	40.90	49.50
3b	72.33	83.43	89.50
3c	10.04	12.60	16.04
3d	73.87	76.57	80.47
3e	84.59	86.39	85.94
Acarbose	70.46	76.43	84.54

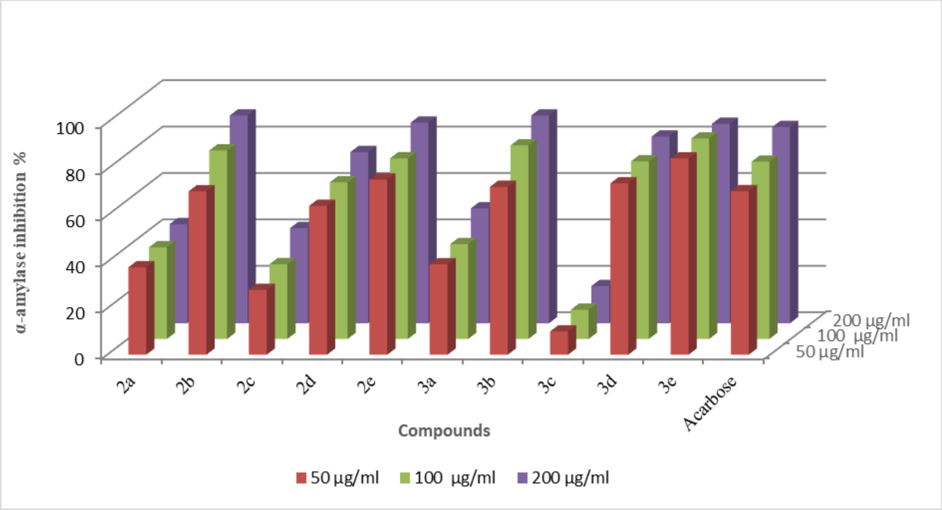


Figure 1: α-amylase inhibition activity of the synthesized compounds 2a-d and 3a-d.

Conclusions

In conclusion, a new series of 1,2,3-triazole derivatives containing pyrozoline and furan rings combined in the same matrix was synthesized using precedent methodologies and evaluated their diabetics inhibitory against α-amylase. The synthesized compounds showed varying degrees of inhibitory activity ranging from weak to high activity depending their structures and concentrations.

Acknowledgment

The authors would like to thank the department of Chemistry/College of Science/AL-Muthanna University for the facilities during this work.

References

1. A. S. Razzaq and R. J. Nahi, 'In vitero , evaluation of antioxidant and antibecterial activities of new 1, 2, 3-Triazole derivatives containing 1,2,3-Triaozle ring', *Syst. Rev. Pharm.*, vol. 12, no. 1, pp. 196–200, 2021.
2. B. Kummari *et al.*, 'Design and synthesis of 1,2,3-triazole-etodolac hybrids as potent anticancer molecules', *RSC Adv.*, vol. 7, no. 38, pp. 23680–23686, 2017.
3. F. Ibraheem, M. Ahmad, U. A. Ashfaq, S. Aslam, Z. A. Khan, and S. Sultan, 'Synthesis, molecular docking and anti-diabetic studies of novel

benzimidazole-pyrazoline hybrid molecules', *Pak. J. Pharm. Sci.*, vol. 33, no. 2, pp. 847–854, 2020.

4. H. A. Mazyed and R. J. Nahi, 'Synthesis and antioxidant study of new1,3-oxazepin-4,7-dione and1,2,3-triazole derivatives', *Int. J. Pharm. Res.*, vol. 12, no. 1, pp. 252–259, 2020.
5. H. Wang *et al.*, 'A new series of cytotoxic pyrazoline derivatives as potential anticancer agents that induce cell cycle arrest and apoptosis', *Molecules*, vol. 22, no. 10, 2017.
6. Herman, H., Ardani, I. G. A. I., Aryani, L. N. A., Windiani, I. G. A. T., Adnyana, I. G. N. S., & Setiawati, Y. (2022). Signs and symptoms of depression in children and adolescents with type 1 diabetes mellitus: A case report. *International Journal of Health & Medical Sciences*, *5*(1), 150-153. https://doi.org/10.21744/ijhms.v5n1.1861
7. J. Khawandanah, 'Double or hybrid diabetes: A systematic review on disease prevalence, characteristics and risk factors', *Nutr. Diabetes*, vol. 9, no. 1, pp. 1–9, 2019.
8. J. Mateusz Daśko, Anna Dołęga, Siedzielnik Magdalena, Karol Biernacki, Olga Ciupak and D. S. Rachon, 'Novel 1,2,3-triazole derivatives as mimics of steroidal system—synthesis, crystal structures determination, hirshfeld surfaces analysis and molecular docking', *Molecules*, vol. 26, no. 4059, pp. 1–15, 2021.
9. 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.
10. 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.
11. K. Karrouchi *et al.*, 'Synthesis and pharmacological activities of Pyrazole derivatives: A review', *Molecules*, vol. 23, no. 1, pp. 1–85, 2018.
12. M. M. Heravi and V. Zadsirjan, 'Prescribed drugs containing nitrogen heterocycles: an overview', *RSC Adv.*, vol. 10, no. 72, pp. 44247–44311, 2020.
13. M. Murwih Alidmat, M. Khairuddean, N. Mohammad Norman, A. N. Mohamed Asri, M. H. Mohd Suhaimi, and G. Sharma, 'Synthesis, characterization, docking study and biological evaluation of new chalcone, pyrazoline, and pyrimidine derivatives as potent antimalarial compounds', *Arab. J. Chem.*, vol. 14, no. 9, p. 103304, 2021.
14. M. R. Aouad *et al.*, 'Novel 1,2,3-Triazole Derivatives as Potential Inhibitors against Covid-19 Main Protease: Synthesis, Characterization, Molecular Docking and DFT Studies', *ChemistrySelect*, vol. 6, no. 14, pp. 3468–3486, 2021.
15. P. A. Channar *et al.*, 'Synthesis, conformational studies and NBO analysis of (4-chloro-3,5-dimethyl-1H-pyrazol- 1-yl)(p-tolyl)methanone', *J. Mol. Struct.*, vol. 1191, pp. 152–157, 2019.
16. R. J. Nahi and N. H. Imran, 'Synthesis, Characterization and Thermal Stability Study of New Heterocyclic Compounds Containing 1,2,3-Triazole and 1,3,4-Thiadiazole Rings', *Orient. J. Chem.*, vol. 35, no. 1, pp. 234–240, 2019.
17. R. Kaur *et al.*, '1,2,3-Triazole β-lactam conjugates as antimicrobial agents', *Heliyon*, vol. 6, no. 6, p. e04241, 2020.

18. S. K. Jain and R. Singhal, ‘a Review on Pyrazoline Derivatives As Antimicrobial Agent’, *Int. J. Pharm. Pharm. Sci.*, vol. 12, no. 6, pp. 15–24, 2020.
19. S. Kumar, S. L. Khokra, and A. Yadav, ‘Triazole analogues as potential pharmacological agents: a brief review’, *Futur. J. Pharm. Sci.*, vol. 7, no. 106, pp. 1–22, 2021.
20. S. Y. Hassan, ‘Synthesis, antibacterial and antifungal activity of some new pyrazoline and pyrazole derivatives’, *Molecules*, vol. 18, no. 3, pp. 2683–2711, 2013.
21. Suryasa, I. W., Rodríguez-Gámez, M., & Koldoris, T. (2021). Health and treatment of diabetes mellitus. *International Journal of Health Sciences*, *5*(1), i-v. https://doi.org/10.53730/ijhs.v5n1.2864
22. U. Galicia-Garcia *et al.*, ‘Pathophysiology of type 2 diabetes mellitus’, *Int. J. Mol. Sci.*, vol. 21, no. 17, pp. 1–34, 2020.
23. V. Channa Basappa, V. Hamse Kameshwar, K. Kumara, D. K. Achutha, L. Neratur Krishnappagowda, and A. K. Kariyappa, ‘Design and synthesis of coumarin-triazole hybrids: biocompatible anti-diabetic agents, in silico molecular docking and ADME screening’, *Heliyon*, vol. 6, no. 10, p. e05290, 2020.
24. Z. D. Kifle and E. F. Enyew, ‘Evaluation of In Vivo Antidiabetic, In Vitro α-Amylase Inhibitory, and In Vitro Antioxidant Activity of Leaves Crude Extract and Solvent Fractions of Bersama abyssinica Fresen (Melianthaceae)’, *J. Evidence-Based Integr. Med.*, vol. 25, pp. 1–11, 2020.