Formation of Substituted 1, 2, 4- triazole and evaluation of antifungal activities with ADMET study

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Abstract

A series of 1,2,4-triazole derivatives were synthesized from ethyl 4-hydroxybenzoate with various substituents, and the data came from spectroscopy, infrared spectroscopy (FT-IR), nuclear magnetic resonance (1H NMR),(13C NMR) resonance. The compounds' identities were determined using mass spectrometry. The compounds' antifungal efficacy was tested on two types of plant fungi, and the results show that some of them are involved in promising activities, which were also studied using the computer for the prepared compounds. (B3, B4 ,B5)

Keywords: *triazole, derivatives, ADMET, Rhizoctonia solani, Fusarium spp.*

INTRODUCTION

For decades, fungicides have been widely used to control fungal-caused plant diseases that threaten human health and crop production. Seed rot is caused by a fungus group that includes Fusarium, Rhizoctonia, and Sclerotium species, and it infects plants at the seedling stage. These pathogens have the ability to infect a wide range of plants. Because they live in wet soils, seedling pathogens frequently cause damping-off symptoms [1, 2]. Triazole compounds have been widely used to prevent and control fungal diseases of many crops (fruits, vegetables, nuts, grains, and seeds) since the 1980s, quickly spreading throughout the European market and becoming the most effective type of fungicide. Triazole compounds are significant due to their high antifungal activity, low resistance risk, and long-term stability in soil and water. Their strategy is based on preventing fungal ergosterol biosynthesis as well as steroid demethylation [3]. Triazole derivatives have a wide range of biological effects [4].antibacterial [5], fungicidal [6, 7], antiviral [8], antiproliferative [9, 10], antioxidant [11,12] cytotoxic and antitumor [13], antileishmanial [14], anti-tubercular [15], anti-inflammatory and analgesic [16], anticonvulsant [17], anti-obesity [18], antimalarial [19], and anticancer [20] properties. Antifungal medications include fluconazole, itraconazole, voriconazole, and ketoconazole. Nazole is a triazole derivative that has been approved for use as an antifungal agent. [21,22].

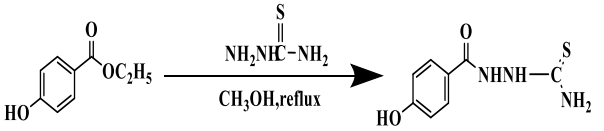
Experimental

All starting materials and solvents were obtained from BDH and Sigma Alderch and

were used without further modification or purification.All starting materials and solvents were obtained from BDH and Sigma-Aldrich Companies and were used without modification or purification. Melting points were determined uncorrected in an open capillary tube .The FT-IR Spectrophotometer, Shimadzu IR -8400s spectrometer was used to record FT-IR infrared spectra. The 1H NMR and 13C NMR spectra were obtained using a 400 MHz Brucker Biospin GmbH. Chemical shifts are reported as values in parts per million (ppm) using DMSO-d6 as a solvent while mass spectroscopy was recorded .Predictions on a GC-Shimadzu QP-2010 plus,The completion of the reactions was checked by TLC using hexane and ethyl acetate (6:4), ethanol and cyclohexane (4:1), ethyl acetate and petroleum ether (5:5) and iodine vapors as a detecting reagent, ADMET and in-silico predictions the proposed compounds' structures are converted into a Simplified Molecular-Input Line-Entry system using the admetsar 2.0 site. (SMILE).The same site then submitted chemical compounds like AlogP, H-Bond Acceptor, H-Bond Donor, Rotatable Bonds, Molecular Weight, and Applicability Domain to predict pharmacokinetics in silico.Using the same tool, human oral bioavailability and intestinal absorption were also predicted.

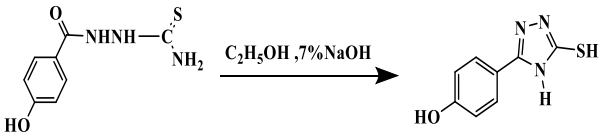
1: Synthesis of (4-hydroxybenzoyl) hydrazine-1-carbothioamide (B1)

Ethyl 4-hydroxybenzoate (0.01mol, 1.6618 g) was dissolved in methanol (30 mL), and then thiosemicarbazide (0.01mol, 0.9114 g) was dissolved in (30 mL) of methanol. The reaction mixture was heated under a reflux flow for 8 hours, then allowed to cool, after which the resulting precipitate was collected to be re-purified from absolute ethanol [23].



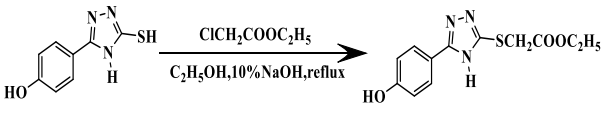
2: Synthesis of 4-(5-mercpto-4H-1, 2, 4-triazol-3-yl) phenol (B2)

The B1 (0.007mol, 1.477 g) was dissolved in (15 mL) of absolute ethanol. The mixture was refluxed for (3-4) hours with (12 ml) of a 7% aqueous sodium hydroxide solution. After the end of the reaction, it was left to cool, and after that, the filtrate was acidified using dilute hydrochloride acid. The precipitate was filtered and washed several times with water. and recrystallization from absolute ethanol [24].



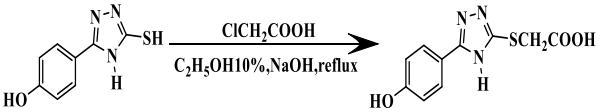
3: Synthesis of ethyl 2-((5- (4-hydroxyphenyl)-4H-1, 2, 4-triazol-3-yl) thio) acetate (B3)

After dissolving the B2 (0.01 mol,1.93 g) in(25 mL) of absolute ethanol and stirring with (5mL) of a 10% aqueous sodium hydroxide solution, and adding the ethyl chloroacetate (0.01 mol,1.070 mL) dissolved in (5mL)of absolute ethanol The mixture was refluxed for three hours. The solution, after it had cooled, was acidified with concentrated hydrochloric acid. The precipitate was filtered and crystallized from 50% absolute ethanol [25].



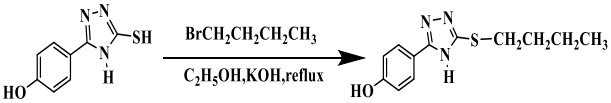
4: Synthesis of 2-((5-(4-hydroxyphenyl)-4H-1,2,4-triazol-3-yl) thio) acetic acid.(B4)

After dissolving the B2 (0.005 mol, 0.965 g) in (20 mL)of absolute ethanol and stirring with (10mL) of 10% aqueous sodium hydroxide solution, and then adding the chloroacetic acid (0.005 mol, 0.472 g) dissolved in (5 mL)of absolute ethanol, the mixture was refluxed for three hours. The solution, after it had cooled, was acidified with concentrated hydrochloric acid. The precipitate was filtered and crystallized from absolute ethanol [26].



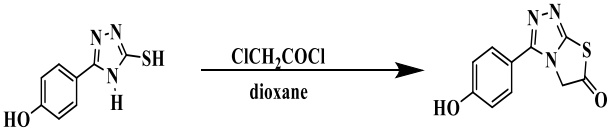
5: Synthesis of 4-(5-(butylthio)-4H-1, 2, 4-triazol-3-yl) phenol. (B5)

After dissolving the B2 (0.002 mol, 0.386 g) in (15 mL) of absolute ethanol, it was placed in a round-bottom flask (50 mL) with (0.002mol,0.1122 g) Potassium hydroxide, and after continuous stirring, (0.002 mol, 0.215mL) butyl bromide dissolved in (5 ml) absolute ethanol The solution after it had cooled then collected the precipitate and recrystallization from absolute ethanol [27].



6: Synthesis of 3-(4-hydroxyphenyl) thiazolo [2,3-c][1,2,4]triazole-6(5H)-one .(B6)

A mixture B2 (0.004 mol, 0.772 g) and chloroacetyl chloride (0.004 mol, 0.318 mL) in dry dioxins (10 mL) was left to stand at room temperature over night. The precipitated solid was separated and recrystallized from benzene. [28]



Antifungal activity testing

The fungi used in the study were obtained from the Department of Plant Protection Research, the Department of Agricultural Research, Rhizoctonia solani, and Fusarium spp, and the isolates were activated at 25 °C for 5 days for both fungi. Potato dextrose agar media were made by dissolving 39 g per liter of distilled water. The compounds were prepared as a stock solution at 100 ppm using distilled water as a solvent, and the required concentrations (75, 50, and 25 ppm) were prepared by diluting the stock solution with the same solvent. Petri plates, pipettes, spoons, test tubes, needles, media, distilled water, and a cork borer were sterilized in an autoclave at 121°C and 15 psi for 15 minutes. Was poured into (9cm) diameter sterile glass dishes, and compound concentrations (100, 75, 50, and 25 ppm) and medium were added in three replicates for each concentration. (100, 75, 50, and 25 ppm) Only one dish was tested for fungi as a first control, and a plate with 1 mL/L beltanol pesticide was added as a second comparison. It was allowed to harden before being inoculated by inserting the divided colony through a cork puncture in the center of the dish, and it was then transferred to a 25-degree Celsius incubator for 5 days. [29] The percentage of mycelial growth inhibition was calculated by using a millimeter scale and calculating the fungus's growth diameter, followed by calculating the : (%) mycelial growth inhibition= A–B /A × 100 where, A = Colony growth of the fungal control plate. B= Colony growth of the fungal in treated plate.

Results and Discussion

A new series of 1, 2, 4-triazole derivatives (B3to B6) were synthesized and yielded good results. All physical parameters and mass spectrum values in the Table (1).The prepared compounds were identified by spectrophotometric measurements, infrared spectrometers, 1H NMR and 13C NMR, the values are shown in the tables (2, 3, 4,).

Table (1): lists some of the physical properties and yield percentages and m/z for compounds (B1-B6)

Comp. Symbol	M.F	M.w	m.p.°C	Yield (%)	Color	R_f Value	m/z
B_1	$C_8H_9N_3O2S$	211	178-180	74	colorless	0.6	-
B_2	$C_8H_7N_3OS$	193	198-200	70	colorless	0.58	-
B_3	$C_{12}H_{13}N_3O_3S$	279	150-152	50	colorless	0.51	279
B_4	$C_{10}H_9N_3O_3S$	251	238-240	52	colorless	0.73	251
B_5	$C_{12}H_{15}N_3OS$	249	198-200	40	Colorless	0.49	249
B_6	$C_{10}H_7N_3O_2S$	233	115-118	55	Colorless	0.54	233

Table (2): Absorption values the (FT-IR) spectrum of compounds (B1-B6)

Comp. symbol	O-Hst. cm^{-1}	N-Hst. cm^{-1}	C-Hst. (Ar.)cm^{-1}	C-Hst. (al.)cm^{-1}	C=Ost. cm^{-1}	C=Cst. cm^{-1}	Other group
B_1	3169	3308 3255 3357	3030	-	1641	1529 -1574	C=S 1156 C-N 1277
B_2	3173	3356 3256	-	-	-	1595	S-H 2564.02 C=N1686 C-N 1275
B_3	3199	3260 3323	3033	2945 2902	1716	-	C-N1329 C-S 669
B_4	3310	3260	3034	2988 2971	1682	1554.98	C=N1595 C-N 1250 C-S 692
B_5	3167	3253	-	2978 2903	-	1614.90	C=N 1640 C-Hben1400-1449 C-N1225
B_6	3191	-	-	2978.5 2816	1667	-	C=N1640 C-N 1280 C-S 705

Table (3): Chemical shift values (1H NMR) of compounds (B2 –B5)

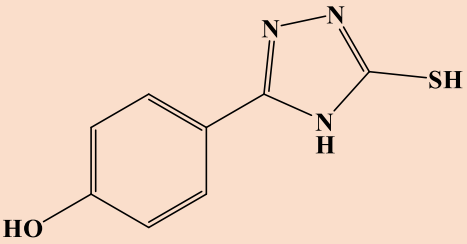
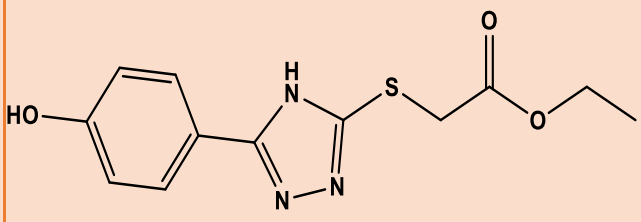
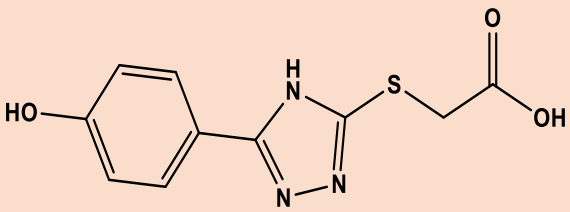
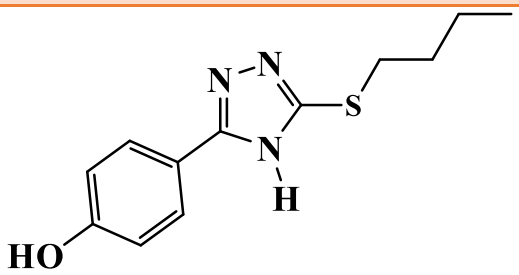
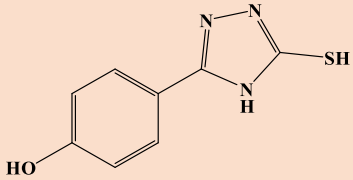
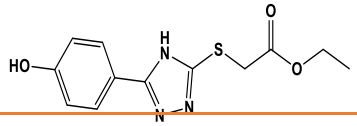
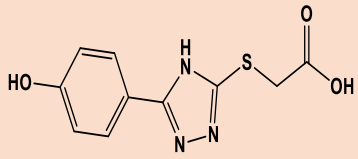
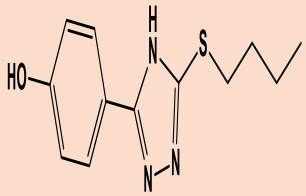
Comp. symbol	Structure	Chemical Shift(ppm)	No. of Protons	Type of signle	group
B_2		7.02-8.04	4	d,d	Ar. protons
		10.09	1	s	OH-
		11.53	1	s	NH-
		13.59	1	s	SH-
B_3		1.10-1.13	3	t	-CH_3
		3.98	2	s	CH_2-C=O
		4.02-4.06	2	m	O-CH_2
		7.09-7.95	4	d,d	Ar. protons
		9.84	1	s	-OH
		11.69	1	s	-NH
B_4		3.98	2	s	CH_2-C=O
		7.28-8.04	4	d,d	Ar. protons
		10.22	1	s	-OH
		11.18	1	s	-NH
		12.62	1	s	OHCarbox.
B_5		0.83-0.86	3	t	-CH_3
		1.27-1.34	2	m	-CH_2
		1.58-1.63	2	m	-CH_2
		3.00-3.03	2	t	S-CH_2
		6.91-7.84	4	d,d	Ar. protons
		9.75	1	s	-OH
		11.43	1	s	-NH

Table (4): Chemical shift values (13C NMR) for compunds((B2- B5)

Comp. symbol	Structure	Chemical Shift (δ ppm)	group
B_2		116.22-124.33-128.63	Ar. Carbons
		144.31-144.63	-C- Hetero ring
		145.48	C-OH
B_3		15.81	CH_3
		59.71	-CH_2-

		144.31-145.48	-C- Hetero ring
		116.22- 124.33- 128.63-14. 63	Ar. carbons
		168.54	C=O
B_4		36.30	-CH2-C=O
		144.31-144.32	-C- Hetero ring
		116.34- 124.39- 129.44-144.55	Ar. Carbons
		176.56	COOH. Carbons
B_5		14.48	$-CH_3$
		20.66-30.53-32.42	$-CH_2$-ring
		144.31-145.48	C- Hetero.
		116.22- 124.33-28.63-144.63	Ar. Carbons

Evaluation of antifungal Activity

The results of the statistical analysis showed that the compounds on the Rhizoctonia solani fungi B3, B5, and B4 at a concentration of 100 ppm, respectively, were 80%, 76.11%, and 69.4%, and there were highly significant differences between them and the fungicide used for comparison, which gave an inhibition rate of 100%, while the compound B6 did not give an inhibition rate and for all concentrations, the percentage was 0%. At a concentration of 75 ppm, compound B5 showed an inhibition rate of 72.22% and compound B4 a rate of 60.56%.and B3 69.15% There are significant differences between them and the pesticide beltanol. At a concentration of 50 ppm, the compound showed B3 69.63%, B4 58.33%, and B5 70.81%, and there are significant differences between the pesticide used and the concentration of 25 ppm gave the compound B370%, B4 51.67%, and B5 61.11%, and there are significant differences between them and the pesticide used. As for the effect of the compounds on the Fusarium fungus, compound B3 had a 100% inhibition rate for all concentrations (100, 75, 50, and 25 ppm), and there were no significant differences between them and the comparable fungicide, which gave a 100% inhibition rate, while compounds B4 and B5 gave an inhibition rate of 88.89% for all concentrations, and there were no significant differences between them, but there were significant differences between them and the pesticide used for comparison. The compound for B6 gave the highest inhibition rate of 83.33% at a concentration of 25 ppm, 72.22% at a concentration of 50 ppm, 68.04 % at a concentration of 75 ppm, and 65.22% at a concentration of 100 ppm. There are significant differences between them as concentrations, as well as with the used pesticide For comparison ,as shown in the table (5,6) and figures (1-3) [30-34].

Table (5): The inhibition and colony dimeter for compounds on the Rhizoctonia solani

Treatments	**Concentration**							
	25ppm		**50ppm**		**75ppm**		**100ppm**	
	CD	PGI	CD	PGI	CD	PGI	CD	PGI
B_3	2.70	70.00	2.73	69.63	2.78	69.15	2.75	69.44

B_4	4.35	51.67	3.75	58.33	3.55	60.56	1.80	80.00
B_5	3.50	61.11	2.63	70.81	2.50	72.22	2.15	76.11
B_6	9.00	0.00	9.00	0.00	9.00	0.00	9.00	0.00
Beltanol	0.00							
Control	9.00							
LSD 5%	Treatments		concentration					
	0.54**	**6.10****		**1.69****				

Table (6): The inhibition and colony dimeter for compounds on the fusarium spp

	Concentration							
Treatments	**25(ppm)**		**50(ppm)**		**75(ppm)**		**100(ppm)**	
	CD	PGI%	CD	PGI%	CD	PGI%	CD	PGI%
B_3	0.00	100.00	0.00	100.00	0.00	100.00	0.00	100.00
B_4	1.00	88.89	1.00	88.89	1.00	88.89	1.00	88.89
B_5	1.00	88.89	1.00	88.89	1.00	88.89	1.00	88.89
B_6	1.50	83.33	2.50	72.22	2.88	68.04	3.13	65.22
Beltanol	0.00							
Control	9.00							
LSD 5%	Treatments		concentration					
	0.24**	**2.76****		**0.77****				

Figure (1): Antifungal activity of prepared compound (B4) against Rhizoctonia solani

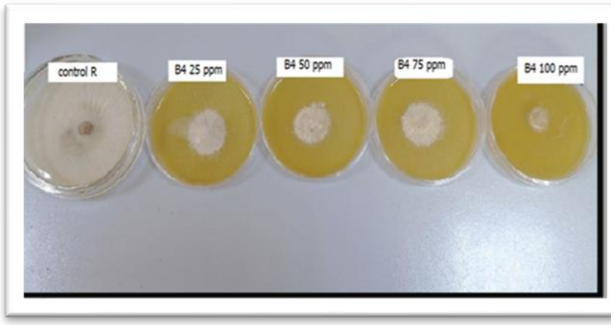


Figure (2): Antifungal activity of prepared compound (B4) against Fusarium spp

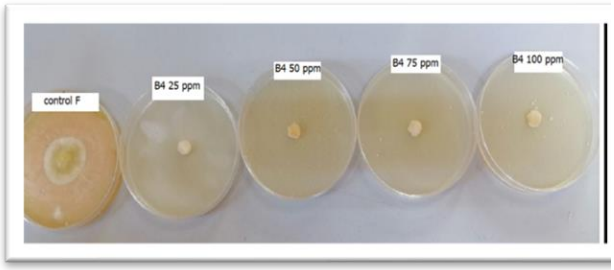
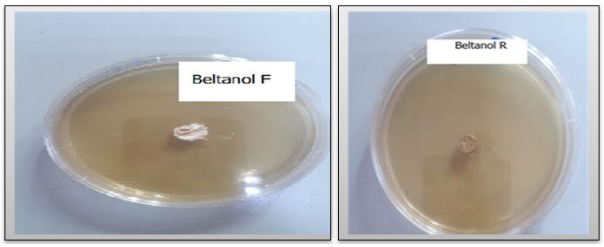


Figure (3): Antifungal activity of Beltanol pesticide against Fusarium spp and Rhizoctonia solani



In-silico & ADMET Prediction Models

Computer-aided by in silico software, which relates to the most well-known biological terms, in vivo and in vitro, Absorption, distribution, metabolism, excretion, and toxicity are the five criteria that make up ADMET for the compound. Molecular Mass: The molecular masses of pharmaceutical drugs must not exceed 500 daltons under Lipinski's rule. All prepared triazole derivatives comply with B3-B5 values between (249.34 and

279.32). Lipophilicity (Octanol/water split coefficient): In a two-stage octanol/water system, the octanol/water fraction (log P) illustrates the proportion of a material's concentration in the octanol to that material's concentration in the aqueous portion. Lipophilic chemicals own a plus log P, while hydrophilic chemicals own a minus log P. According to Lipinski's rule, log P should not overtake 5. Positive log values were found for all of the tiazole derivatives tested, indicating that they are lipophilic (B3, B4, and B5 at 1.8, 1.35, and 3.07, respectively). The total number of donor bonds (H-BD) in the nitrogen-hydrogen and oxygen-hydrogen media should be less than 5. The values 6,5,4 for the (B3,B4,B5)respectively Just as the total number of acceptor hydrogen bonds (H-BA) in an oxygen-nitrogen medium should not exceed 10, The values for compound B3,B4,B5. At (2,3,2) respectively An additional rule indicates that the rotatable bonds (RB) are less than 10 and values 5, 4 and 5 for compounds B3, B4, B5 respectively. Bioavailability refers to the mean and extent of accessibility of the active pharmaceutical ingredient (API) within the target site. The bioavailability of a compound, triazole B3-B5, ranged from 70% to 72%. Human intestinal absorption (HIA) is the one of the most pertinent lineaments of ADMET The HIA accounts for all of the triazoles compounds B3-B5 99.46%, 99.37%,99.57% : The aqueous solubility of compounds(logS)for compounds (B3,B4,B5)-3.264,-,2.805and-2.761

Classification of compounds can be according to solubility values (Log S); Compounds with 0 and higher solubility value are highly soluble, those in the range of −2 to 0 are very soluble, those in the range of −4 to −2 are soluble, those range of -6 to -4 moderately soluble, if less than −6 are poorly soluble and insoluble if the value less than -10. Plasma protein binding defines the degree of binding of a drug to plasma proteins .the values 78.9%,80.9% and87.2% for the compounds (B3,B4,B5)respectively It determines the degree of drug binding to plasma proteins. Protein binding can be measured in different ways, eg. Balanced dialysis (reference method), ultrafiltration, Ultra Centrifugation. The main plasma proteins that bind antibiotics are serum albumin and α1-acid glycoprotein. The term acute oral toxicity is often used in relation to the ability to kill and to determine the lethal dose, 50. The values ranged from 2.173, 2.063 and 1.921 for the values B3, B4, B5, respectively [35-41].

Conclusion

A number of 1,2,4-triazole derivatives have been synthesized and produced in high yields. based on melting point range, infrared spectral values, 1H NMR,13CNMR and mass spectrometric data. It has been tested for antifungal efficacy against Rhizoctonia solani and Fusarium spp. when compared to the common pesticide beltanol and the computerized study In-silico for the five indicators: absorption, distribution, metabolism, excretion, and toxicity. Showed good indicators.

Reference

1 - Häfker, N.S., Andreatta, G., Manzotti, A., Falciatore, A., Raible, F. and Tessmar-Raible, K., 2023. Rhythms and clocks in marine organisms. Annual Review of Marine Science, 15, pp.509-538.

2- Devi, R.K., Ganesan, M., Chen, T.W., Chen, S.M., Rasheed, R.A., Al-Onazi, W.A., Elshikh, M.S., Liu, X. and Yu, J., 2023. Hexagonal nanosheets of pyrrochlore-type lanthanum stannate for sensitive detection of chlorinated

pesticide in food and environmental samples. Food Chemistry, 404, p.134516.

3-Hergueta-Castillo, M.E., López-Rodríguez, E., López-Ruiz, R., Romero-González, R. and Frenich, A.G., 2022.Targeted and untargeted analysis of triazole fungicides and their metabolites in fruits and vegetables by UHPLC-orbitrap-MS2. Food Chemistry, 368, p.130860.

4- Ding, Y., Zhang, L., Yang, S., Li, Z. and Wang, P.Y., 2021.Synthesis, Antimicrobial Activity, and Molecular Docking of Benzoic Hydrazide or Amide Derivatives Containing a 1, 2, 3‐Triazole Group as Potential SDH Inhibitors .Chinese Journal of Chemistry, 39(5), pp.1319-1330.

5- Li, J. and Zhang, J., 2022. The Antibacterial Activity of 1, 2, 3-triazole-and 1, 2, 4-Triazole-containing Hybrids against Staphylococcus aureus: An Updated Review (2020-Present). Current Topics in Medicinal Chemistry, 22(1), pp.41-63.

6-Othmène,Y.B.,Monceaux, K., Belhadef, A., Karoui, A., Salem, I.B., Boussabbeh, M., Abid-Essefi, S. and Lemaire, C., 2022.Triazole fungicide tebuconazole induces apoptosis through ROS-mediated endoplasmic reticulum stress pathway. Environmental Toxicology and Pharmacology, p.103919.

7- Li, C., Fan, S., Zhang, Y., Zhang, X., Luo, J. and Liu, C., 2022. Toxicity, bioactivity of triazole fungicide metconazole and its effect on mycotoxin production by Fusarium verticillioides: new perspective from an enantiomeric level. Science of The Total Environment, 828, p.154432.

8-de Alencar, D.M., Gonçalves, J., Vieira, A., Cerqueira, S.A., Sebastião, C., Leitão, M.I.P., Francescato, G., Antenori, P., Soares, H. and Petronilho, A., 2021.Development of Triazoles and Triazolium Salts Based on AZT and Their Anti-Viral Activity against HIV-1.Molecules, 26(21), p.6720.

9- Mustafa, M., Abdelhamid, D., Abdelhafez, E.M., Ibrahim, M.A., Gamal-Eldeen, A.M. and Aly, O.M., 2017. Synthesis, antiproliferative, anti-tubulin activity,and docking study of new 1, 2, 4-triazoles as potential combretastatin analogues.European journal of medicinal chemistry, 141, pp.293-305.

10- Wu, M.J., Wu, D.M., Chen, J.B., Zhao, J.F., Gong, L., Gong, Y.X., Li, Y., Yang, X.D. and Zhang, H., 2018.Synthesis and anti-proliferative activity of allogibberic acid derivatives containing 1, 2, 3-triazole pharmacophore. Bioorganic & Medicinal Chemistry Letters, 28(14), pp.2543-2549.

11- Saadaoui, I., Krichen, F., Salah, B.B., Mansour, R.B., Miled, N., Bougatef, A. and Kossentini, M., 2019.Design, synthesis and biological evaluation of Schiff bases of 4-amino-1, 2, 4-triazole derivatives as potent angiotensin converting enzyme inhibitors and antioxidant activities.Journal of Molecular Structure, 1180, pp.344-354.

12-Peng, Z., Wang, G., Zeng, Q.H., Li, Y., Wu, Y., Liu, H., Wang, J.J. and Zhao, Y., 2021.Synthesis, antioxidant and anti-tyrosinase activity of 1, 2, 4-triazole hydrazones as antibrowning agents. Food Chemistry, 341, p.128265

13- Yamada, M., Takahashi, T., Hasegawa, M., Matsumura, M., Ono, K., Fujimoto, R., Kitamura, Y., Murata, Y., Kakusawa, N., Tanaka, M. and Obata, T., 2018. Synthesis, antitumor activity, and cytotoxicity of 4-substituted 1-benzyl-5-diphenylstibano-1H-1,2,3-triazoles.Bioorganic&Medicinal chemistry Letters, 28(2), pp.152-154.

14-Ouellette,W., Jones, S. and Zubieta, J., 2011.Solid state coordination chemistry of metal-1, 2, 4-triazolates and the related metal-4-pyridyltetrazolates.CrystEngComm, 13(14), pp.4457-4485.

15- Cao, Y. and Lu, H., 2021. Advances in the application of 1, 2, 4-triazole-containing hybrids as anti-tuberculosis agents.Future Medicinal Chemistry, 13(23), pp.2107-2124.

16-Azim, T.,Wasim, M., Akhtar, M.S. and Akram, I., 2021.An in vivo evaluation of anti-inflammatory, analgesic and anti-pyretic activities of newly synthesized 1, 2, 4 Triazole derivatives .BMC Complementary Medicine and Therapies, 21(1), pp.1-15.

17-Song, M.X., Huang, Y.S., Zhou, Q.G., Deng, X.Q. and Yao, X.D., 2021.Synthesis of ring-opened derivatives of triazole-containing quinolinones and their antidepressant and anticonvulsant activities. Bioorganic chemistry, 106, p.104505.

18- Xu, M., Peng, Y., Zhu, L., Wang, S., Ji, J. and Rakesh, K.P., 2019. Triazole derivatives as inhibitors of Alzheimer's disease: current developments and structure-activity relationships. European Journal of Medicinal Chemistry, 180, pp.656-672.

19-Ceesay, M.M., Couchman, L., Smith, M., Wade, J., Flanagan, R.J. and Pagliuca, A., 2016.hhb Triazole antifungals used for prophylaxis and treatment of invasive fungal disease in adult haematology patients: trough serum concentrations in relation to outcome.Medical Mycology, 54(7), pp.691-698.

20- Wu, X., Wang, J., Xia, S., Cheng, S. and Shi, Y., 2022. 1, 2, 3-Triazole Derivatives with Anti-breast Cancer Potential.Current Topics in Medicinal Chemistry.

21-Echeverria-Esnal, D.,Martín-Ontiyuelo, C., Navarrete-Rouco, M.E., Barcelo-Vidal, J., Conde-Estévez, D., Carballo, N., De-Antonio Cusco, M., Ferrández, O., Horcajada, J.P. and Grau, S., 2022. Pharmacological management of antifungal agents in pulmonary aspergillosis: an updated review.Expert Review of Anti-infective Therapy, 20(2), pp.179-197.

22- Tanaka, R., Shiraiwa, K., Takano, K., Ogata, M., Honda, S., Yoshida, N., Okuhiro, K., Yoshida, M., Narahara, K., Kai, M. and Tatsuta, R., 2022. High-throughput simultaneous quantification of five azole anti-fungal agents and one active metabolite in human plasma using ultra-high-performance liquid chromatography coupled to tandem mass spectrometry .Clinical Biochemistry, 99, pp.87-96.

23 -Kumari, M., Tahlan, S., Narasimhan, B., Ramasamy, K., Lim, S.M., Shah, S.A.A., Mani, V. and Kakkar, S., 2021. Synthesis and biological evaluation of heterocyclic 1, 2, 4-triazole scaffolds as promising pharmacological agents. BMC chemistry, 15, pp.1-16.

24-Ledeti, I.V., Bercean, V.N., Badea, V., Balan, M. and Csunderlik, C., 2010.The Alkylation of 1H-5-mercapto-3-phenyl-1, 2, 4-triazole and 4H-4-amino-5-mercapto-3-phenyl-1, 2, 4-triazole.REVISTA DE CHIMIE, 61(9), pp.833-837.

25 -Haggam, R.A., 2015. Heterocyclization and functionalization of 1, 2-bis-(4-amino-5-mercapto-1, 2, 4-triazol-3-yl) benzene. Research on Chemical Intermediates, 41, pp.1135-1148.

26- Popiołek, Ł., Kosikowska, U., Dobosz, M. and Malm, A., 2012.Synthesis and

antimicrobial properties of new thiosemicarbazide, 1, 2, 4-triazole, and 1, 3, 4-thiadiazole derivatives of sulfanylacetic acid. Phosphorus, Sulfur, and Silicon and the Related Elements, 187(4), pp.468-481

27- Alyahyaoy, H.A., 2019. Synthesis, characterization and antibacterial evaluation of new 1, 2, 4-triazole-3-thiol derivatives. International Journal of Green Pharmacy (IJGP), 13(3).

28- El-Sayed, R., 2006. Synthesis, antibacterial and surface activity of 1, 2, 4-triazole derivatives. Grasas y aceites, 57(2), pp.180-188.

29- Dahal, N. and Shrestha, R.K., 2018. Evaluation of efficacy of fungicides against Fusarium oxysporum f. sp. lentis in vitro at Lamjung, Nepal. Journal of the Institute of Agriculture and Animal Science, 35(1), pp.105-112.

30- da Silva, N.M., Gentz, C.D.B., Reginatto, P., Fernandes, T.H.M., Kaminski, T.F.A., Lopes, W., Quatrin, P.M., Vainstein, M.H., Abegg, M.A., Lopes, M.S. and Fuentefria, A.M., 2021.8-Hydroxyquinoline 1, 2, 3-triazole derivatives with promising and selective antifungal activity. Medical Mycology, 59(5), pp.431-

31- Zhao, P., Deng, Y., Wang, T., Qi, Z., Du, Y., Liu, L. and Ji, M., 2022. Baseline Sensitivity to and Succinate Dehydrogenase Activity and Molecular Docking of Fluxapyroxad and SYP-32497 in Rice Sheath Blight (Rhizoctonia solani AG1-IA) in China. Agronomy, 12(12), p.3075.

32- Ashiq, S., Edwards, S., Watson, A., Blundell, E. and Back, M., 2022. Antifungal effect of brassica tissues on the mycotoxigenic cereal pathogen Fusarium graminearum. Antibiotics, 11(9), p.1249

33- Spolti, P., Del Ponte, E.M., Dong, Y., Cummings, J.A. and Bergstrom, G.C., 2014. Triazole sensitivity in a contemporary population of Fusarium graminearum from New York wheat and competitiveness of a tebuconazole-resistant isolate. Plant disease, 98(5), pp.607-613

34-Vasilchenko, A.V., Poshvina, D.V., Semenov, M.V., Timofeev, V.N., Iashnikov, A.V., Stepanov, A.A., Pervushina, A.N. and Vasilchenko, A.S., 2023. Triazoles and Strobilurin Mixture Affects Soil Microbial Community and Incidences of Wheat Diseases. Plants, 12(3),

35-Longfei G.; Hongbin Y.; Yingchun C.; Lixia S.; Peiwen D.; Weihua L.; Guixia L.; Yun T. (2019). "ADMET-score – a comprehensive scoring function for evaluation of chemical drug-likeness". Med.Chem.Comm., 10(1): 148–157.

36- Leo A.; Hansch C. and Elkins D. (2002) "Partition coefficients and their uses," Chem. Rev., 71(6): 525–616.

37- Davis J. L. (2018) "Pharmacologic Principles," Equine Intern. Med. Fourth Ed., pp. 79–137.

38-Yan A.; Wang Z. and Cai Z. (2008) "Prediction of Human Intestinal Absorption by GA Feature Selection and Support Vector Machine Regression" Int. J. Mol. Sci., 9(10):1961

39-Damiãoa M.; Pasqualotob K.; Pollic M. C. and Parise-Filhoa R. (2014) "To be drug or prodrug: Structure-property exploratory approach regarding oral bioavailability" J. Pharm. Pharm. Sci., 17(4): 532–540.

40- Sorkun M.C.; KhetanA. And Er S. (2019) "AqSolDB, a curated reference set of

aqueous solubility and 2D descriptors for a diverse set of compounds", Scientific Data, 6(143):1-8.

41- Walum E. (1998), "Acute Oral Toxicity", Environmental Health Perspectives, 106(2).