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FULL PAPER

Synthesis of new heterocyclic derivatives from 2-furyl methanethiol and study their applications

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In this research, cyclic compounds derived from 2- furfural mercaptan (oxazole, triazoles) were synthesized, and their biological efficacy was measured and compared with standard drugs. Also, their effectiveness as anti-oxidant was measured and compared with ascorbic acid as a standard substance. Some of the synthesized compounds were deduced with good efficacy.

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KEYWORDS

Heterocyclic, 2-furyl methanethiol, ascorbic, triazole.

Introduction

Triazoles are the class of heterocyclic compounds which are under study since many years. The five membered triazole ring exists in two isomeric forms i.e., 1, 2, 3-triazole and 1, 2, 4-triazole [1] (Figure 1).

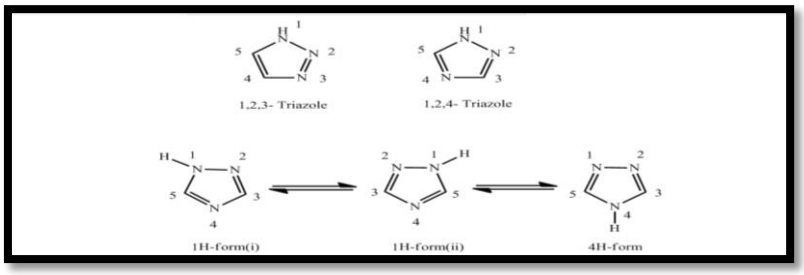


FIGURE 1 Five membered triazole ring isomers

1,2,4-Triazole may exist in equilibrium between three forms:1H form (i), 1H-form(ii) and 4H-form [2]. The calculated energy differences in azole tautomer supports preference for the 1 Hover 4H tautomer. Similarly, the usual tautomeric preference for triazolines over hydroxy triazoles and aminothiazoles over triazolinones is supported based on thermochemical evidence. 1,2,4-Triazole derivatives have received much attention due to their versatile biological properties including antibacterial, antifungal, anti- convulsant, anti-inflammatory, anticancer, and antiproliferative properties. 1,2,4-Triazole nucleus has been incorporated into a wide variety of therapeutically interesting molecules to transform them into better drugs [3,4] anti-microbial, [5] anti-fungal, [6] anti-depressant [7].

Oxadiazoles are five membered rings compound with three hetero atoms (one O atom and two N atoms). The oxadiazole ring has four isomers [8,9].

1,3,4-Oxadiazole is the most thermally stable isomer which has attracted special attention. This is primarily due to the large number of uses in many divers' areas. The stability of 1,3,4-oxadiazole enhanced by alkyl and aryl substitution on positions 2 and 5, the

aryl- substituted of 1,3,4-oxadiazole are less sensitive to acid than alkyl-substituted. It has been established that the susceptibility to hydrolysis increases with increasing solubility as shown in Figure 1 [10]:

Oxadiazoles are five membered rings compound with three hetero atoms (one O atom and two N atoms). The oxadiazole ring has four isomers [8,11], as shown in Figure 2.

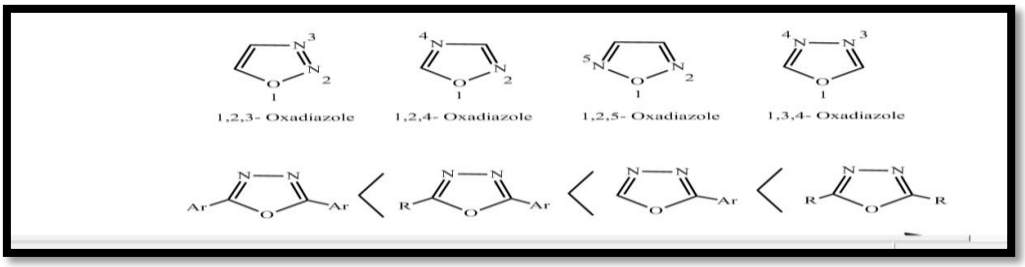


FIGURE 2 The oxadiazole ring has four isomers

1,3,4-Oxadiazole is the most thermally stable isomer which has attracted special attention, which is primarily due to the large number of uses in many divers' areas. The stability of 1,3,4-oxadiazole enhanced by alkyl and aryl substitution on positions 2 and 5, the aryl- substituted of 1,3,4-oxadiazole are less sensitive to acid than alkyl-substituted. It has been established that the susceptibility to hydrolysis increases with increasing solubility as shown in Figure 3 [11]:

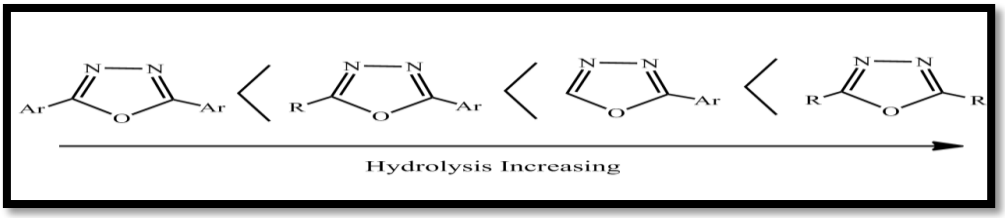


FIGURE 3 The stability of 1,3,4-oxadiazole enhanced by alkyl and aryl substitution on positions 2 and 5

The 1,3,4-Oxadiazoles have been reported to be biologically versatile compounds having bactericidal, fungicidal, herbicidal, analgesic, hypoglycemic, anti-inflammatory and tranquilizing agents. Moreover, various 1,3,4-oxadiazoles are suitable for uses in photography, scintillation materials, dye industry, corrosion inhibitors and as thermal stabilizers for rigged polyvinyl chloride [12].

Oxadiazole like all other compounds containing (-NH-CH=X moiety where X is O, N or S) exist in two tautomeric forms [13] anti-fungal [14], anti-bacterial [15], anti-oxidant [16].

Experimental work

All the materials were supplied from Merk and BDH chemical company. Melting points used electrothermal melting point apparatus, UK. FTIR spectra were used on SHIMADZU FT.IR-8400S infrared, Department of Chemistry, College of Science, University of Baghdad. 1H-NMR spectroscopy operated at 500 MHZ with tetramethyl silane as internal standard. Measurements were made on chemistry department, Tehran University, Iran.

Preparation of 2- Furfural Thiol(A1): -

A mixture of 7.6 g of thiourea in 15 mL of water, was dissolved in 11.5 mL of 11 N hydrochloric acid, by light heating. After the mixture was cooled to room temperature, 8.68 mL 10 g of furfural alcohol was added and the reaction temperature was kept below 55 c^{o} for 2h. Then the greenish solution was left over night. The product solution was neutralized by

50% alkaline solution from NaOH then steam distillation was used to separate 2-furfural mercaptan. The yield was 64% (Note: The steam was processed by a steamer).

Preparation of ethyl 2-((furan-2-yl methyl) thio) acetate(A2): -

A volume of 5.25 mL of 2- furfural mercaptan in 45 mL of DMF and 6 mL of trimethylamine were mixed for 20 minutes, then 4.5 mL of ethyl chloroacetate was added gradually to the mixture for half an hour at room temperature, creating a white precipitate. The reaction was heated for a period of 14 hours at a temperature from (60 to 65 °C). The reaction mixture was poured over ice and sodium bicarbonate was added followed by separating funnel. The organic layer was dried. b.p 220; yield 90% IR (KBr): 1732(C=O), C-H "o.o.p"738; 1HNMR (ppm):1.15 (t, 3H, CH_3), 3.05(s, 2H, SCH_2CO), 3.95 (s, 2H, furan-CH_2), 4.2(q, 2H, CH_2-CH3), 6.25-7.45(m, CH aromatic) [17].

Preparation of 2-((furan-2-yl methyl) thio) acetohydrazide(A3): -

A mixture of 2 g of ethyl 2 - ((furan-2-yl methyl) thio) acetate in 25 mL methanol, and 10 mL of 99% hydrazine hydride was stirred for 24 hours at room temperature. The mixture was poured into a ceramic eyelid to evaporate the excess methanol and hydrazine. The product was purified by fractional distillations. b.p 105 yield 82% IR (KBr) in cm^{-1} :3313 and 3211(NH), 1664(C=O), C-H "o.o.p"740, 1HNMR (ppm): 3.75 (s, 2H, CH_2-S), 3.75(s, 2H, furan-CH_2), 6.1-7.6 (m,CH aromatic), 3.05 (2H,NH_2) 7.8(s,1H,NH)[18].

Synthesis of 2-(2-((furan-2-yl methyl) thio) acetyl) hydrazine-1-carbothioamide (A4) and 2-(2-((furan-2-yl methyl) thio) acetyl) hydrazine-1-carboxamide (A5): -

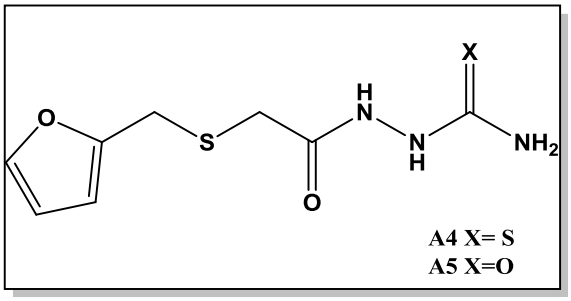


FIGURE 4 Synthesis of 2-(2-((furan-2-yl methyl) thio) acetyl) hydrazine-1-carbothioamide (A4) and 2-(2-((furan-2-yl methyl) thio) acetyl) hydrazine-1-carboxamide (A5)

To a solution of ethyl 2-((furan-2-yl methyl) thio) acetate(A2), 12.5 mmol of (thiosimscarbazide)/(simecarbazide) in dioxane (30 mL) were added with a few drops of piperidine as catalyst. The reaction mixture was reflexed for 10 hours and then allowed to cool. The solid precipitate was filtered off, washed with ethanol and finally recrystallized from ethanol [19] (Figure 4).

2-(2-((furan-2-yl methyl) thio) acetyl) hydrazine-1-carbothioamide (A4)

Yield (84%), light brown crystals, m.p. 162-166 °C (ethanol). IR (KBr) in cm^{-1},3473 and 3262 (NH_2), 3178 (NH), 1643 (C=O), 1164 (C=S)

2-(2-((furan-2-yl methyl) thio) acetyl) hydrazine-1-carboxamide (A5)

Yield (89%), light brown crystals, m.p. 212-216°C (ethanol). IR (KBr) in cm^{-1}, 3431 and 3309 (NH_2),3253 (NH), 1687 and 1650 (C=O).

Synthesis of 5-(((furan-2-yl methyl) thio) methyl)-2,4-dihydro-3H-1,2,4-triazole-3-thione (A6), 5-(((furan-2-yl methyl) thio) methyl)-2,4-dihydro-3H-1,2,4-triazol-3-one (A7): -

A suspension of the 2-(2-((furan-2-yl methyl) thio) acetyl) hydrazine-1-carbothioamide (A4)/2-(2-((furan-2-ylmethyl) thio) acetyl)

hydrazine-1-carboxamide (A5) (12.5 mmol) in alcoholic potassium hydroxide solution (10 mL, 7%) was heated under reflux for 3h. The reaction mixture was allowed to cool and was then adjusted to PH 6 with 10% HCl. The formed precipitate was filtered off, washed with water, dried, and finally recrystallized using ethanol [19].

5-(((furan-2-yl methyl) thio) methyl)-2,4-dihydro-3H-1,2,4-triazole-3-thione (A6): -

Yield (81%), light brown crystals, m.p. 183-186°C (ethanol). IR (KBr) in cm^{-1}, 3461 (NH), 1600 (C=N),1134 (C=S).
1HNMR (ppm); D_2O as a solvent, 3.29 (s, 2H, S-CH_2-triazole ring), 3.95 (s, 2H, furan ring-CH_2-S),6.12-8.54 (m, 3H, aromatic H), 12,06 and 13.9 (s, 2H, N-H).
13CNMR (ppm) D_2O as a solvent, 22.69 (S-CH_2-triazole ring), 38.3 (furan-CH_2-S),
104.87-153.7 (aromatic C), 159.5 (C=N in triazole ring), 175 (C=S).

5-(((furan-2-yl methyl) thio) methyl)-2,4-dihydro-3H-1,2,4-triazol-3-one (A7)

Yield (79%), light brown crystals, m.p. 167-171°C (ethanol). IR (KBr) in cm^{-1}, 3483 (NH), 1629 (C=O), 1604 (C=N).
1HNMR (ppm); D_2O as a solvent, 3.75 (s, 2H, S-CH_2-triazole ring), 3.95 (s, 2H, furan ring-CH_2-S),6.23-7.29 (m, 3H, aromatic H), 6.2 and 10.1 (s, 2H, N-H).
13CNMR (ppm) D_2O as a solvent, 22.39 (S-CH_2-triazole ring), 36.5 (furan-CH_2-S),
108.7-150.1 (aromatic C), 153.7 (C=N in triazole ring), 159.1 (C=O).

Synthesis of 2-(((furan-2-yl methyl) thio) methyl)-5-Aryl-1,3,4-oxadiazole (A8-A10): -

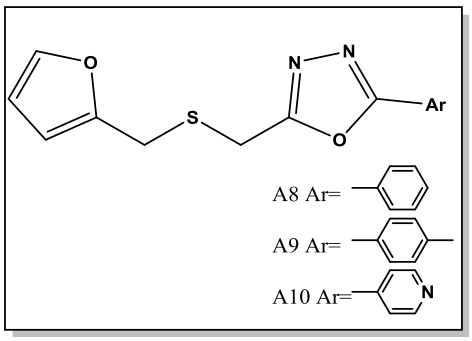


FIGURE 5 Synthesis of 2-(((furan-2-yl methyl) thio) methyl)-5-Aryl-1,3,4-oxadiazole (A8-A10)

A mixture of (12.5 mmol) from 2-((furan-2-yl methyl) thio) acetohydrazide (A3) and an appropriate different aromatic acid (12.5 mmol) was refluxed in $POCl_3$ (2.5 mL) for 8 h. The r-eaction mixture was cooled, poured on to crushed ice and made basic with $NaHCO_3$ solution. The precipitate was filtered off, dried, and recrystallized using ethanol [20] (Figure 5).

2-(((furan-2-yl methyl) thio) methyl)-5-phenyl-1,3,4-oxadiazole (A8): -

Yield (81%), light brown crystals, m.p. 245-250°C (ethanol). IR (KBr) in cm^{-1}, 1670 (C=N), 1207 (C-O).
1HNMR (ppm); DMSO-d6 as solvent, 3.9 (s, 2H, S-CH_2-oxadiazole ring), 3.97 (s, 2H, furan ring-CH_2-S), 4.71 (s,1H, S-CH=oxadiazole ring) tautomerism,6.06 (s,1H, NH), 6.11-7.98 (m, 8H, aromatic H).
13CNMR (ppm) DMSO-d6 as solvent, 28.6 (furan-CH2-S), 30.45 (S-CH_2-oxadiazole ring), 106.4-152 (aromatic C), 163.7 and 164.5 (C=N in oxadiazole ring).

2-(((furan-2-yl methyl)thio)methyl)-5-(p-tolyl)-1,3,4-oxadiazole (A9): -

Yield (93%), light brown powder, m.p. 210-214 °C (ethanol). IR (KBr) in cm^{-1}, 1666 (C=N), 1172 (C-O).
1HNMR (ppm); DMSO-d6 as solvent, 2.35 (s, 3H, CH_3-phenelyene), 3.56 (s, 2H, S-CH_2-

oxadiazole ring), 4.39 (s, 2H, furan ring-CH_2-S), 4.6 (s,1H, S-CH=oxadiazole ring) tautomerism,6.3 (s,1H, NH), 6.17-8.2 (m, 7H, aromatic H).

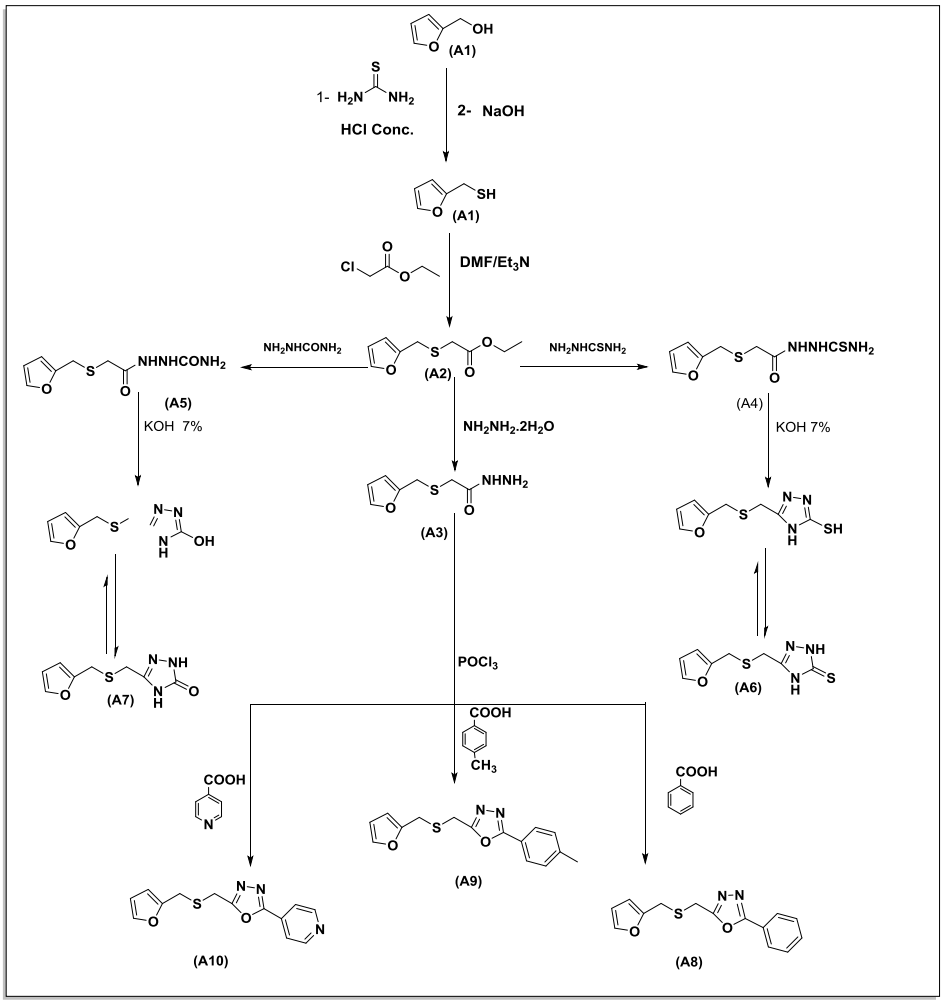
13CNMR (ppm) DMSO-d6 as a solvent,22.1(CH3-phenylene), 28.21 (furan-CH_2-S), 34.39 (S-CH_2-oxadiazole ring), 106.4-145 (aromatic C), 163.4 and 164.5 (C=N in oxadiazole ring).

2-(((furan-2-yl methyl) thio) methyl)-5-(pyridin-4-yl)-1,3,4-oxadiazole (A10): -

Yield (79%), brown crystals, m.p. 188-192°C (ethanol). IR (KBr) in cm^{-1}, 1679 (C=N), 1182 (C-O).

1HNMR (ppm); DMSO-d6 as a solvent, 3.74 (s, 2H, S-CH_2-oxadiazole ring), 3.91 (s, 2H, furan ring-CH_2-S), 6.12-8.75 (m, 7H, aromatic H).

13CNMR (ppm) DMSO-d6 as 30.4 (furan-CH_2-S), 35.5 (S-CH_2-oxadiazole ring), 107.1-152 (aromatic C), 161.4 and 164.4 (C=N in oxadiazole ring).

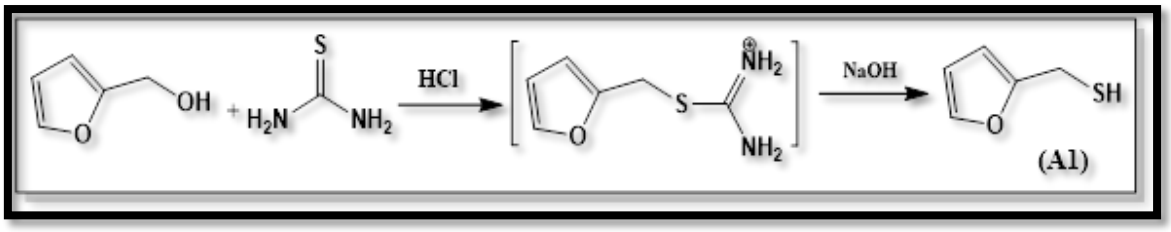


SCHEME 1 2-(((Furan-2-yl methyl) thio) methyl)-5-(pyridin-4-yl)-1,3,4-oxadiazole (A10)

Results and discussion

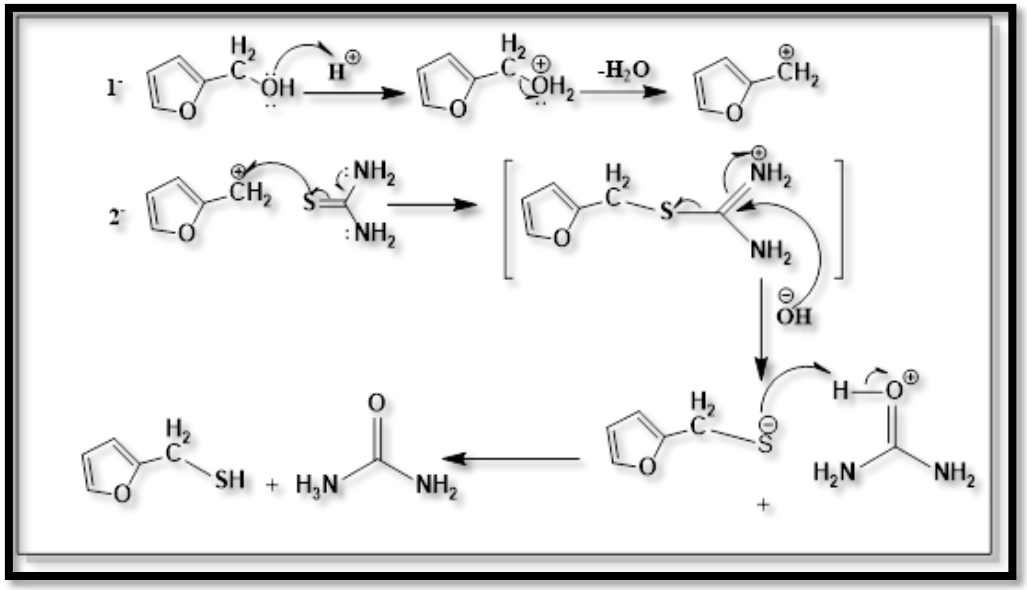
Synthesis of furfuryl mercaptan(A1)

Furfural mercaptan was prepared by addition of furfuryl alcohol to solution of thiourea in concentrated hydrochloric acid. Then concentrated sodium hydroxide solution was added to release furfural mercaptan. Synthesis of the sequence of these compounds is shown below in Equation (1). These compounds were characterized by their physical properties, FT-IR,^{1}H-NMR,^{13}C-NMR spectra and T.L.C. test.



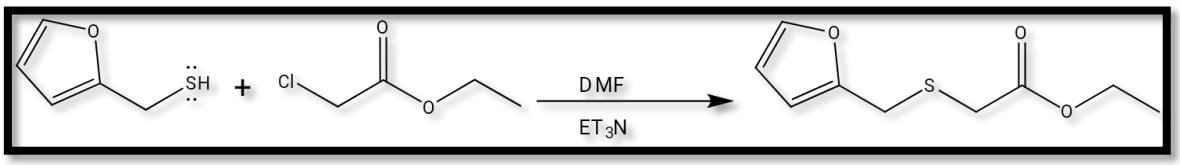
EQUATION 1 Furfural mercaptan synthesis

The mechanism of this reaction involved protonation of hydroxyl group from furfuryl alcohol and oxonium ion was produced, water molecule was removed and carbocation was produced. Thiourea attacked the carbocation to produce 2-(furan-2-yl methyl) isothiouronium ion then hydrolysis by alkaline solution to release furan-2-yl methanethiolate ion, then furan-2-yl methanethiolate attacked hydronium ion to form furfural mercaptan, as shown in Scheme 2.



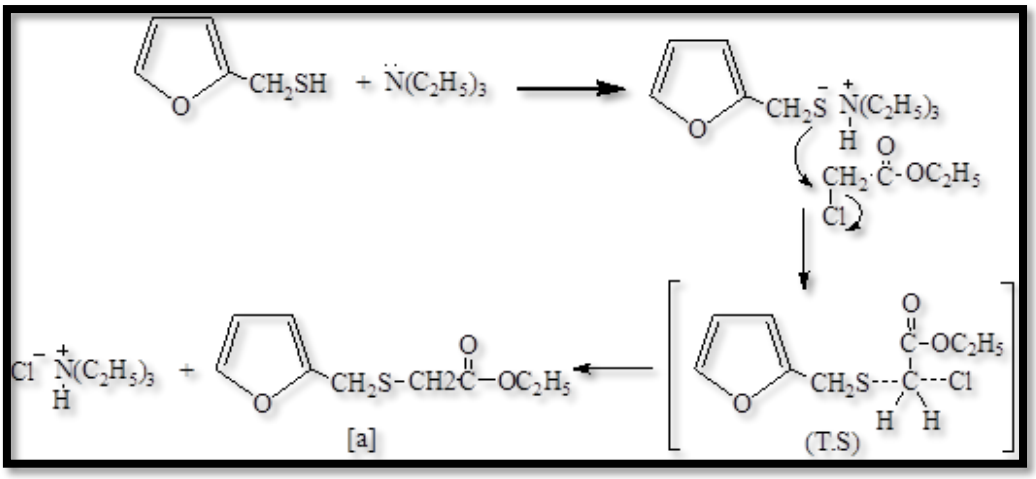
SCHEME 2 The mechanism of furfural mercaptan synthesis

Synthesis of ethyl 2-((furan-2-yl methyl) thio) acetate (A2): -



EQUATION 2 Synthesis of ethyl 2-((furan-2-yl methyl) thio) acetate

The mechanism of this reaction involved the halo-group in ethyl chloroacetate was good leaving group and sulfur compound was a good nucleophile, thus this reaction was a typical nucleophilic substitution reaction of thiol group with good leaving halo-group where the halo group could be replaced easily with thio compound according to the SN_2[18] mechanism as shown in Scheme 3.



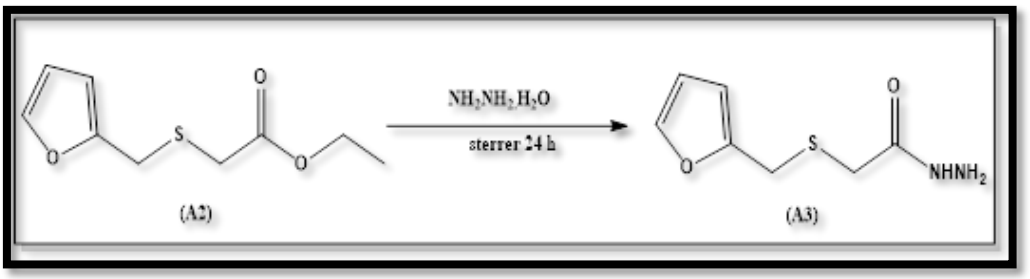
SCHEME 3 The mechanism of Synthesis of ethyl 2-((furan-2-yl methyl) thio) acetate

FT-IR spectral data of compound (A2) showed the appearance of characteristic absorption bands at (1731) cm^{-1} belonging to ν (C=O) of ester group [2] and disappearance of the absorption for ν(S-H) group.

^{1}HNMR spectrum of compound (A2) showed a triplet signal at δ= (1.3) ppm due to (-C<u>H</u>$_3$) protons, quartet signal at δ= (4.2) ppm due to (-O-C<u>H</u>$_2$) protons, signal at δ= (3.25) ppm due to (S-C<u>H</u>$_2$-C=O) protons, signal at δ= (3.86) ppm due to (-C<u>H</u>$_2$-S) protons, signals at δ= (6.05-7.24) ppm due to (CH aromatic ring) protons.

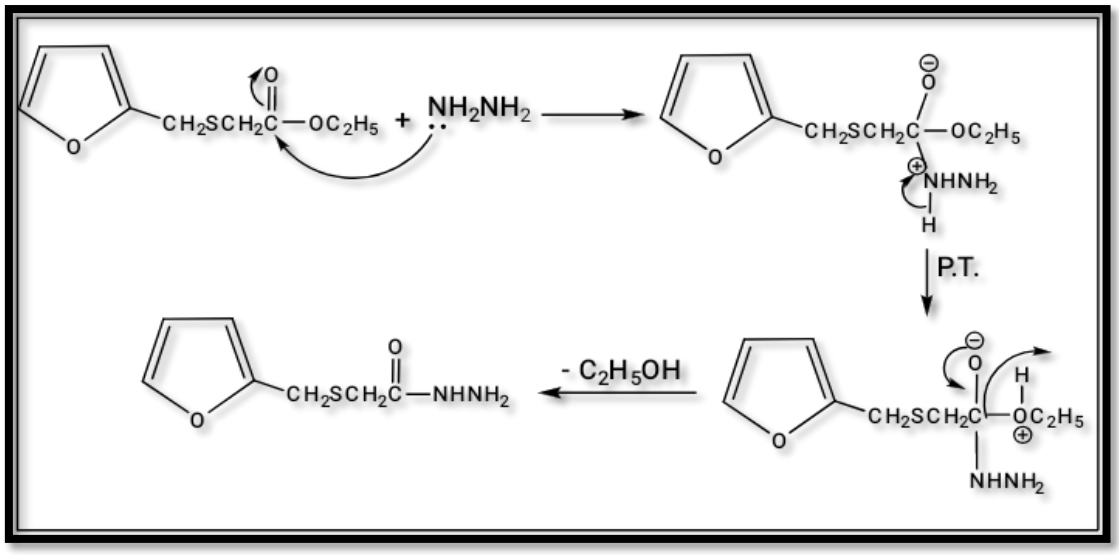
Synthesis of 2- (furfuryl thiol) acetohydrazide (A3): -

This part involved conversion of the prepared ester derivative (A2) to the corresponding acetohydrazide (A3), by the reaction of compound (A2) with hydrazine hydrate (99%) in absolute ethanol by stirring at room temperature as indicated in Equation (3) to give the compound (A3).



EQUATION 3 Synthesis of 2- (furfuryl thiol) acetohydrazide

This reaction was proceeded by a nucleophilic substitution reaction in which the nucleophile ethoxy group was displaced by the stronger nucleophile (NHNH2) as indicated in Scheme 4.



SCHEME 4 The mechanism of Synthesis of 2- (furfuryl thiol) acetohydrazide

FT-IR spectrum of compound (A3) showed the appearance of the characteristic absorption bands at ν (3313 and 3278) cm^{-1}belonging to ν(NH_2), characteristic absorption band at (1664) cm^{-1} due to ν(C=O) amid and disappearance of the absorption band due to ν(C=O) ester and absorption band at (2951-2931) cm^{-1} belonging to ν(C-H) aliphatic.

^{1}HNMR spectrum of the compound (12) (A3) showed a singlet signal at δ= (3.65) ppm due to (-N$\underline{H}_2$), signals at δ= (3.25) ppm due to (S-C$\underline{H}_2$-C=O) protons, signal at δ= (3.86) ppm due to (furan ring-C$\underline{H}_2$-S) protons, signals at δ= (6.1-7.3) ppm due to (C$\underline{H}$ aromatic ring) protons, and singlet signal at δ= (7.88) ppm due to (-N$\underline{H}$) proton.

Synthesis of 5-(((furan-2-yl methyl) thio) methyl)-2,4-dihydro-3H-1,2,4-triazole-3-thione (A6) and 5-(((furan-2-yl methyl) thio) methyl)-2,4-dihydro-3H-1,2,4-triazol-3-one (A7): -

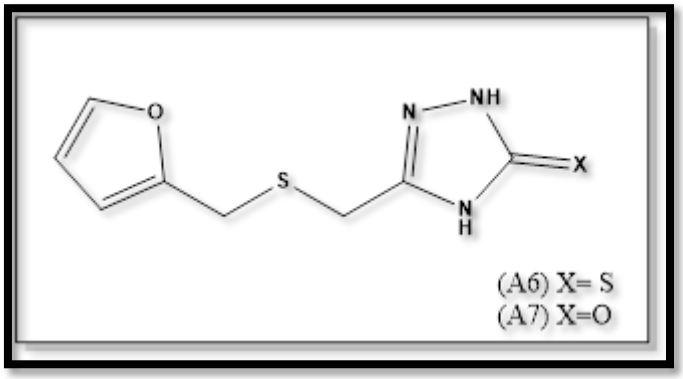
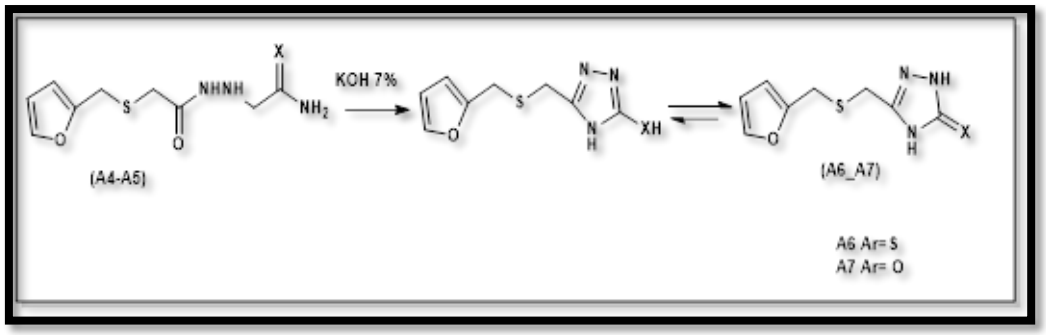
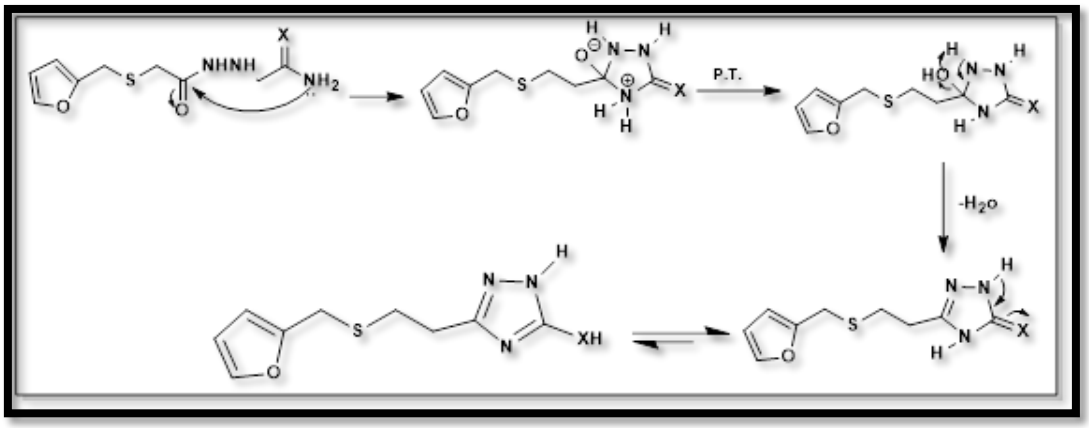


FIGURE 6 Synthesis of 5-(((furan-2-yl methyl) thio) methyl)-2,4-dihydro-3H-1,2,4-triazole-3-thione (A6) and 5-(((furan-2-yl methyl) thio) methyl)-2,4-dihydro-3H-1,2,4-triazol-3-one (A7)

Reaction of the compound (A4) and compound (A5) with alcoholic potassium hydroxide solution (7%) under refluxing condition affected intramolecular cyclization through the loss of H_2O giving the desired thio-triazine derivative and hydroxyl-triazine derivatives respectively as shown in Equation 4 and Scheme 5.



EQUATION 4 Synthesis of 5-(((furan-2-yl methyl) thio) methyl)-2,4-dihydro-3H-1,2,4-triazole-3-(thione/one)



SCHEME 5 mechanism of Synthesis of 5-(((furan-2-yl methyl) thio) methyl)-2,4-dihydro-3H-1,2,4-triazole-3-(thione/one)

FT-IR spectra of the compound A6 showed absorption bands for ν (N-H) at 3461cm^{-1}, ν (C=S) at 1134 cm^{-1}, while FT-IR spectrum of the compound A7 showed absorption bands at 3483 cm^{-1} to ν (N-H), 1629 cm^{-1}due to ν (C=O).

The ^{1}H-NMR spectrum of the compound A5 showed singlet signal at 3.29 ppm for two protons of (S-CH_2-triazole ring), singlet 3.95ppm for two protons of (S-CH2-furan ring), two singlet signals at 12.06 and 13.99 for two protons (NH) group and multi signals at (6.21-8.54ppm) for C-H aromatic. While ^{13}C-NMR spectrum for the same compound showed at 22.6 ppm for methylene group of (S-CH_2-triazole ring), singlet signal at 38.5ppm for methylene group of (furan-CH_2-S), signal at 175.8 ppm for (C=S).

The ^{1}H-NMR spectrum of compound A6 showed singlet signal at 3.75 ppm for two protons of (S-CH_2-triazole ring), singlet 3.95ppm for two protons of (S-CH2-furan ring), two singlet signals at 6.2 and 10.10 for two protons (NH) group and multi signals at (6.23-7.29 ppm) for C-H aromatic. While ^{13}C-NMR spectrum for the same compound showed at 22.4 ppm for methylene group of (S-CH_2-triazole ring), singlet signal at 36.4 ppm for methylene group of (furan-CH_2-S), signal at 159.13.8 ppm for (C=O).

Synthesis of 2-(((furan-2-yl methyl) thio) methyl)-5-Aryl-1,3,4-oxadiazole (A8-A10): -

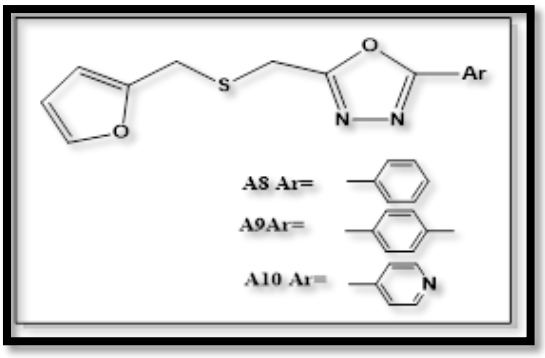
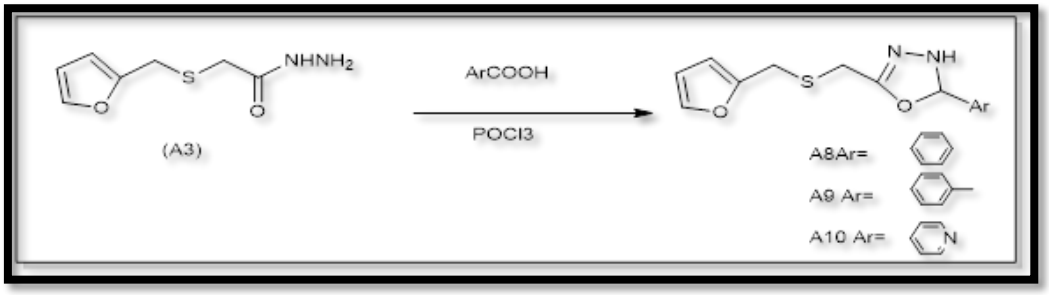


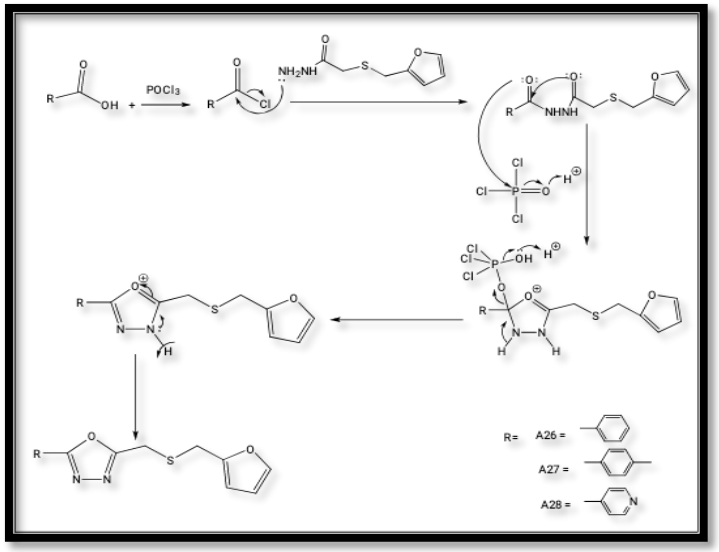
FIGURE 7

Reaction of 2-((furan-2-yl methyl) thio) acetohydrazide (A3) with an appropriate different aromatic acid in $POCl_3$ (2.5 mL) under refluxing condition as shown in Equation 5.



EQUATION 5 Synthesis of 2-(((furan-2-yl methyl) thio) methyl)-5-Aryl-1,3,4-oxadiazole

The first step [3] of this reaction was involved conversion aromatic acid to acid chloride derivatives by $POCl_3$ following nucleophilic attack to carbonyl group which led to intermolecular cyclization to produce oxadiazole derivatives. All mechanism steps in the synthesized compounds are shown in Scheme 6.



SCHEME 6 mechanism of Synthesis of 2-(((furan-2-yl methyl) thio) methyl)-5-Aryl-1,3,4-oxadiazole

The FT-IR spectra of the compounds (A26-A28) showed absorption bands for ν(C=N) appearance at (1666-1679) cm^{-1}, ν (C-O-C) (1172-1207) cm^{-1}. All FT-IR spectra also showed the disappearance of ν (C=O) amide absorbance.

The ^{1}H-NMR spectrum of the compound A8 showed, singlet signal at 3.9 ppm for two protons of (S-CH_2-oxadiazole ring), singlet 3.97 for two protons of (CH_2-furan ring), singlet signal at 4.71 ppm for one proton of tautomerism structure (CH=C-NH) group and multi signals at (6.11-7.98ppm) for C-H aromatic, 6.06 (N-H). While ^{13}C-NMR spectrum for the same compound showed 28.6 ppm for methylene group of (S-CH_2-oxsadiazol ring), signal at 30.4 ppm for methylene group of (furan-CH_2-S), 163.7 and 164.5 cm^{-1} for two (C=N) group.

The ^{1}H-NMR spectrum of the compound A9 showed singlet signal at 2.35 for three protons for (CH_3-phenylene). Singlet signal at 3.56 ppm for two protons of (S-CH_2-CO), singlet 4.30 for two protons of (CH_2-furan ring), singlet signal at 4.6 ppm for one proton of tautomerism structure (CH=C-NH) group and multi signals at (6.17-8.2) ppm for C-H aromatic, 6.3 (N-H). While ^{13}C-NMR spectrum for the same compound showed 22.1 CH_3-phenylene at 28.2 ppm for methylene group of (S-CH_2-CO), signal at 34.4 ppm for methylene group of (furan-CH_2-S), 163.5 and 164.5 cm^{-1} for two (C=N) group.

Biological activities: -

a. Anti-bacterial activity: -

The efficacy of some synthesized compounds was measured and compared with some medicines such as ciprofloxacin and amoxicillin against two types of bacteria, one positive for Gram stain (*Staphylococcus aureus*) and negative for Gram stain (*Klebsiella pneumoniae*) by using well diffusion method.

b. Anti-fungal activity

The efficacy of some synthesized compounds was tested for anti-fungal and compared with Metronidazole 500 mg against *Rhizopodium Microspores* by agar well diffusion method with a diameter of 5 mm. It was noticed that the chemical composition for the drug was close to the chemical composition of the prepared compounds whose effectiveness was measured, as the drug contains an imidazole ring as well as a hydroxyl group, while the prepared compounds contained a pyrazoline ring and also a hydroxyl group. This effectiveness is shown in Table 1.

TABLE 1 Biological activity for comp. (A6-A10)

Compound NO.	Staphylococcus aurius Conc.100(mg/mL) Inhibition zone diameter (mm)	Klebsilla pneumoniae Conc. 100 (mg/mL) Inhibition zone diameter (mm)	Rhizosporium Conc.100 (mg/mL) Inhibition zone diameter (mm)
A6	23	16	18
A7	22	18	17
A8	25	18	20
A9	20	18	32*
A10	25	24	17
Amoxicillin 500 mg	15	32	xx
Ciprofloxacin 500 mg	47	47	xx
Metronidazole 500 mg	xx	xx	30

The results showed that the find compounds (A6-A10) were more active than Amoxicillin as slandered drug against *Staphylococcus aureus* and less active against

Klebsiella pneumoniae than Amoxicillin and ciprofloxacin as standard drugs. The results also showed that the compound A10 which has pyridine ring has the highest activity, while A9 showed the other antifungal activity larger than standard drug Metronidazole 500 mg while the other synthesized compounds showed less activities than the same standard drug as shown in Table 1.

c. Anti-oxidant activities

DPPH Radical scavenging activity[21]

- DPPH (1,1-Diphenyl-2-picryl-hydrazyl): DPPH (4 mg) was dissolved in 100 mL of methanol, and the solution was kept protected from light by covering the test tubes with aluminum foil.
- Various concentrations (100, 50, 25,12.5 and 6.25) ppm were prepared from (A4-A10). It was prepared by dissolving 1 milligram of the compound and dissolving it with 10 mL of methanol to prepare 100 ppm, then it was diluted to 50 and 25 ppm……etc.
- Ascorbic acid (vitamin C): Similar concentrations of the plant extract were prepared.

On the basis of the radical scavenging effect of the stable DPPH free radical, the antioxidant function of some selective synthesized compounds (A4-A10), and a normal (vitamin C) were assessed using the following process. In a test tube, 1 mL of the diluted or normal solution (6.25,12.5,25, 50, 100 ppm) was applied to 1 mL of DPPH solution. The absorbance of each solution was measured at 517 nm using a spectrophotometer after 1 hour of incubation at 37°C. Triplicates of all measurements were taken. The following equation was used to determine the potential to scavenge DPPH radicals:

I%= (Abs blank – Abs sample)/ Abs blank x 100.

Some of the newly synthesized compounds showed antioxidant activity against DPPH free radical and gave good scavenging percentage. So, the compounds that gave antioxidant were selected, more tests were performed, and the IC50 value was extracted as shown in the Table 2 below.

TABLE 2 % Scavenging for compounds (A4-A10)

Comp. No.	Conc. (µg/ mL)	Scavenging %
A4	6.25	13,8
	12.5	15.9
	25	19.1
	50	27.5
	100	42.7
A5	6.25	20.5
	12,5	33.4
	25	42.7
	50	71.1
	100	85.3
A6	6.25	11.9
	12.5	13.1
	25	17.5
	50	22.6
	100	36.8
A7	6.25	9.5
	12.5	11.9
	25	12.4
	50	13.6
	100	15.9

	6.25	7.0
	12.5	15.4
A8	25	24
	50	27.6
	100	31.2
	6.25	29.9
	12.5	40.5
A9	25	66.2
	50	73.4
	100	85.2
	6.25	2.1
	12.5	8.6
A10	25	11.6
	50	18.3
	100	24.1
	6.25	30.4
	12.5	85.8
Ascorbic acid	25	95.2
	50	97.7
	100	98.1

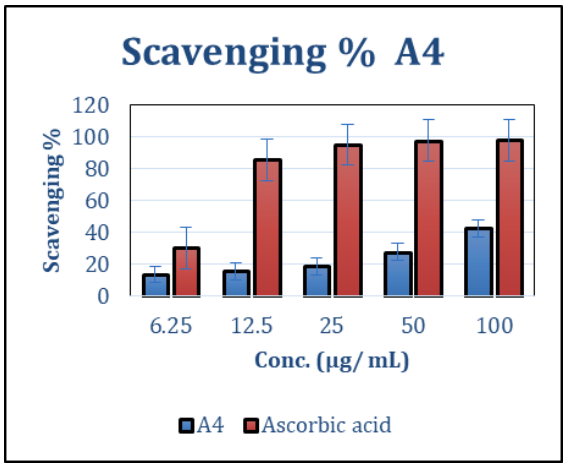


FIGURE 8

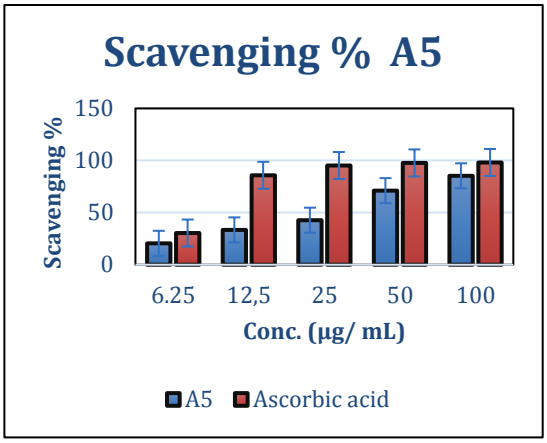


FIGURE 9

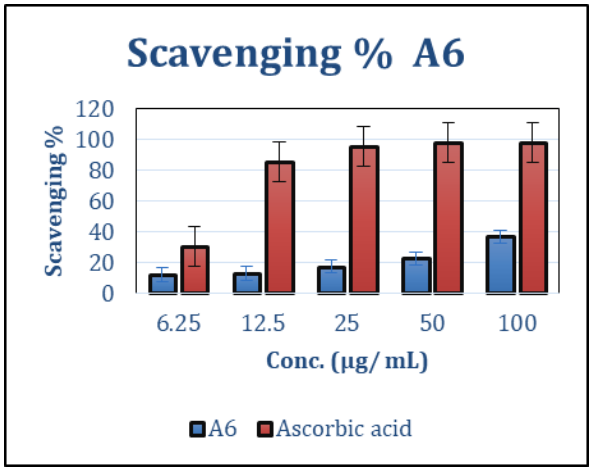


FIGURE 10

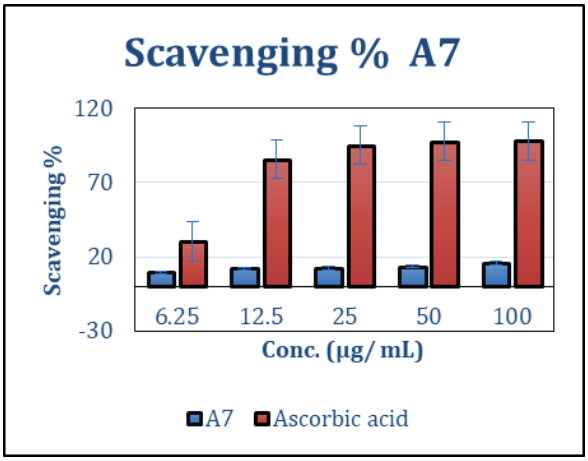


FIGURE 9

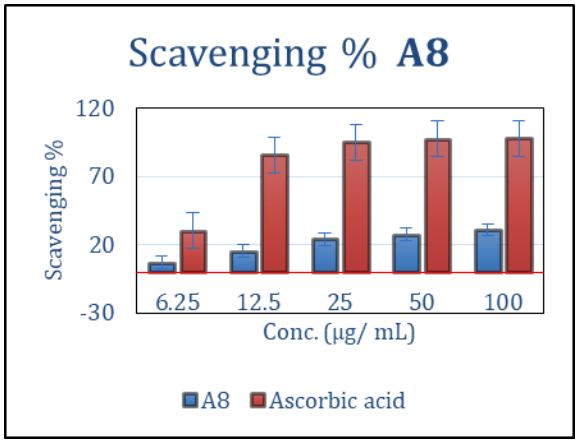


FIGURE 10

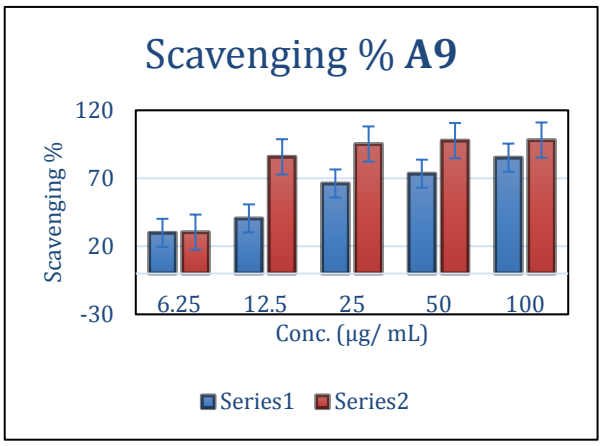


FIGURE 13

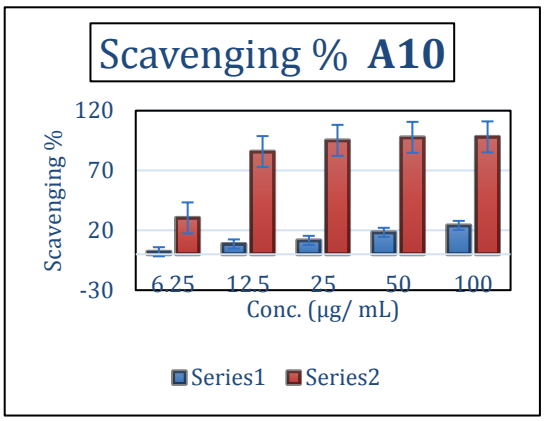


FIGURE 14

FIGURES (8-14) Scavenging % of the prepared compounds A4-A10

The IC50 Value of DPPH Radical Scavenging Activity[22]

The IC50 value was determined to assess the sample concentration required to inhibit 50% of the radical. The higher the antioxidant activity of A9, the lower the IC50 value. The highest antioxidant activity was found in A9 (45,8 ppm), accompanied by ethyl acetate extract (66.12 ppm), and the highest Ic50 was found in A7 (238.9 ppm) (Table 3). Ascorbic acid (36.3 ppm) has an IC50 value of 36.3 ppm.

TABLE 3 IC50 value of DPPH radical scavenging activity

Comp. NO.	Linear Equation	IC50
A4	y = 0.476x	105
A5	y = 1.0284x	48.6
A6	y = 0.4118x	121.4
A7	y = 0.2093x	238.9
A8	y = 0.4006x	124.8
A9	y = 1.0914x	45.8
A10	y = 0.2804x	178.3
Ascorbic acid	y = 1.3767x	36.3

TABLE 4 Antioxidant Activity according to Phongpaichit, 2007

IC50 (µg/mL)	Mark
10-50 µg/mL	Strong Antioxidant Activity
50-100 µg/mL	Intermediate Antioxidant Activity
>100 µg/mL	Weak Antioxidant Activity

Conclusion

The compounds A4 to A10 were prepared, the reaction was controlled using the TLC test, and the compounds were identified using FT-IR, ^{1}HNMR, and ^{13}CNMR. Anti-bacteria, anti-fungi, and antioxidants were among the biological activities tested on them. Some of the prepared compounds were found to have strong efficacy on antifungal, while the others had antibacterial efficacy when compared with standard drugs. The oxidative efficacy of the compounds A9 and A5 was the strongest. Unlike using ascorbic acid as a normal material, the remainder performed poorly as antioxidants.

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