

Synthesis, Characterization and Antioxidant Evaluation of Some Tetrazole Derivatives

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Abstract: The present study introduces the synthesis of two series of tetrazole derivatives. Firstly, monosubstituted S_1 was prepared by the reaction of ethyl 4-aminobenzoate with an amount of sodium azide and triethyl orthoformate in hot glacial acetic acid. Then, ethyl 4-(1H-tetrazol-1-yl) benzoate S_1 was treated with a solution of hydrazine hydrate to prepare acetohydrazide S_2 . After that, tetrazole derivatives S_3 - S_4 were prepared via the reaction of acetohydrazide S_2 with various aromatic aldehydes. Secondly, compound 1,5-disubstituted tetrazole S_5 was prepared from the reaction of aryl isothiocyanate with sodium azide in water presence. Then alkylation to compound S_5 was made with ethyl chloroacetate to produce S_6 . In the next step, S_6 was reacted with hydrazine hydrate to get acetohydrazide S_7 . Moreover, the produced S_7 was reacted with some aromatic aldehydes for the synthesis of S_8 - S_{10} . The structures of synthesized compounds were confirmed by the different available spectral methods, i.e., FTIR, $^1\text{H-NMR}$ and $^{13}\text{C-NMR}$ spectroscopy. The antioxidant activity of the synthesized compounds was evaluated by the use of 2,2-diphenyl-1-picrylhydrazyl. The results showed that compound S_{10} has the highest value as radical scavenging among the synthesized compounds.

Keywords: 1,5-disubstituted tetrazole; mono substituted tetrazole; antioxidants

■ INTRODUCTION

Tetrazoles are poly-aza-heterocyclic compounds with a five-membered ring of four nitrogen atoms and one carbon atom. These compounds have never been seen in nature. The simplest type is 1-*H* tetrazole with the chemical formula CH_2N_4 . This compound is a solid material with white to light yellow color crystals and a faint odor. It is soluble in water and alcohol solvents [1].

Tetrazole derivatives have highly beneficial pharmacological and biological properties. They have been reported to exhibit a wide range of biological activities [2] such as analgesic activity [3-4], antifungal [5-8], antimicrobial [1,9-10], anti-inflammatory [8,11], antiviral [12], antihypertensive [13], anticancer [2,14-15], and anti-HIV [16]. The utility of the tetrazole ring in the applications of medicinal chemistry is due to its isosteric properties. The compound of 1,5-disubstituted tetrazole was used as isosteres for the *cis*-amide bond in long peptides. These substituents have shown similar sorts of pharmacological actions [17].

Antioxidants are natural or manufactured chemicals that can interact with free radicals and stop or significantly affect their reactions in the chain before crucial molecules are damaged. They have the ability to engage with free radicals before damaging important molecules and hence interrupting their chain reactions [18-19]. Antioxidants can be categorized in accordance with their mode of movement as radical scavengers, chelators of metallic ions concerned with catalyzing lipid oxidation, or oxygen scavengers. These oxygen scavengers react with an oxygen atom in closed systems. One of the familiar methods for the evaluation of antioxidants is the DPPH method of radical scavenging. This method can be applied to estimate the antioxidant capacity. The target compounds were compared with ascorbic acid as a reference compound [20].

■ EXPERIMENTAL SECTION

Materials

The chemicals used are ethyl *p*-aminobenzoate, triethyl orthoformate, sodium azide, ethyl chloroacetate,

ammonium acetate, 2-furaldehyde, and phenylisothiocyanate from Sigma Aldrich. Ethanol, ethyl acetate, *n*-hexane, *p*-chlorobenzaldehyde, chloroform, and methanol were obtained from Alpha Chemika while hydrazine hydrate 80% was purchased from Scharlau.

Instrumentation

Melting points of the solid chemicals were determined in an open capillary tube by using SMP3 and were uncorrected. Reactions performed in the present study were followed by thin layer chromatography (TLC) using eluents (methanol:chloroform) (1:9), (ethyl acetate:hexane) (4:6) and iodine vapor for the visualization of formed TLC spots. The synthesized compounds were characterized by the technology of FTIR spectra using a KBr disc on Perkin Elmer, tensor 27 (Bruker). The FTIR device is from Shimadzu Company with a range of (400–4000) cm^{-1} . In the characterization, $^1\text{H-NMR}$ and $^{13}\text{C-NMR}$ spectra were used; they were listed on a Bruker-DRX system AL 500 MHz spectrometer with internal standard TMS. The tests of $^1\text{H-NMR}$ and $^{13}\text{C-NMR}$ spectrum were performed at the Higher School of Chemistry/Sharif University, Tehran University, Iran.

Procedure

Synthesis of ethyl 4-(1H-tetrazole-1-yl)benzoate (S₁)

To synthesize the title compound, a quantity of 1.65 g (0.01 mol) of *p*-amino ethyl benzoate was dissolved in a mixture of 25 mL of glacial acetic acid, 0.65 g (0.01 mol) of sodium azide, and 2 mL (0.012 mol) of triethyl orthoformate. The mixture was heated under reflux. The progress of the reaction was monitored by TLC (hexane:ethyl acetate 7:3). After the completion of the reaction, the mixture was poured into crushed ice. The

formed and precipitated solid materials were filtered and then washed with water and recrystallized from methanol solvent. The physical properties of the synthesized compound are shown in Table 1 [7,21-22].

FTIR (ν_{max} cm^{-1} , KBr): 3135 (C-H of tetrazole ring), 3086 (C-H aromatic), 2989, 2940, 2960, 2874 (CH aliphatic), 1707 (C=O ester), 1608 (C=N), 1516, 1459 (C=C aromatic), 1461 (N=N), 1207 (C-O), 992, 956 (C-H bending out plane) Fig. S1. $^1\text{H-NMR}$ (500 MHz, DMSO-*d*₆, δ/ppm): 10.23 (s, 1H, CH=N of tetrazole ring), 8.20 (d, *J* = 8.5 Hz, 2H), 8.10 (d, *J* = 8.5 Hz, 2H, aromatic protons), 4.36 (q, *J* = 7.1 Hz, 2H, OCH₂), 1.35 (t, *J* = 7.1 Hz, 3H, CH₃) Fig. S2. $^{13}\text{C-NMR}$ (125 MHz, DMSO-*d*₆, δ/ppm): 164.95 (C=O ester), 142.63 (C=N tetrazole ring), 137.32, 131.30, 130.90, 121.09 (aromatic carbons), 61.57 (OCH₂), 14.42 (CH₃) Fig. S3.

Synthesis of ethyl 4-(1H-tetrazol-1-yl)benzohydrazide (S₂)

A quantity of 0.218 g (0.001 mol) of compound S₁ was mixed with 0.1 mL (0.002 mol) of hydrazine hydrate 80% in ethanol. The mixture was heated under reflux for 3 h. The progress of the reaction was monitored by using TLC with ethyl acetate and hexane as eluent with a ratio of 3:7. After the completion of the reaction, the components were left to cool. The formed solid product was filtered and recrystallized from the ethanol. Table 1 illustrates the physical properties of C₂ [22].

FTIR (ν_{max} cm^{-1} , KBr): 3297, 3256 (NH-NH₂), 1656 (C=O amide), 1611 (C=N), 1586, 1515 (C=C aromatic), 1465 (N=N), 988, 966 (C-H bending Out of plane) Fig. S4. $^1\text{H-NMR}$ (500 MHz, DMSO-*d*₆, δ/ppm): 10.17 (s, 1H, CH=N of tetrazole ring), 10.00 (s, 1H, CONH), 8.07 (d, *J* = 8.6 Hz, 2H, aromatic protons), 8.02 (d, *J* = 8.5 Hz,

Table 1. Experimental data for synthesized of mono and 1,5-disubstituted tetrazole derivatives

Compound no.	Molecular formula	Color	M.wt g/mol	Yield %	m.p °C
S ₁	C ₁₀ H ₁₀ N ₄ O ₂	Pale yellow	218.21	70.0	140–142
S ₃	C ₁₃ H ₁₀ N ₆ OS	Gray	298.32	69.0	223–225
S ₄	C ₁₅ H ₁₁ BrN ₆ O	White	371.19	79.4	248–250
S ₅	C ₇ H ₆ N ₄ S	White	178.21	74.0	139–141
S ₈	C ₁₆ H ₁₃ ClN ₆ OS	White	372.83	69.9	206–208
S ₉	C ₁₄ H ₁₂ N ₆ OS ₂	Light grey	344.41	82.0	246–248
S ₁₀	C ₁₄ H ₁₂ N ₆ O ₂ S	Light yellow	328.35	85.0	178–179

2H, aromatic protons) 4.59 (s, 2H, NH₂) Fig. S5. ¹³C-NMR (125 MHz, DMSO-*d*₆, δ/ppm): 164.94 (C=O amide), 142.81 (C=N tetrazole ring), 135.93, 134.55, 129.22, 121.27 (aromatic carbons) Fig. S6.

General procedure for synthesis S₃, S₄

A mixture of S₂ 0.204 g (0.001 mol) was reacted with 0.001 mol of appropriate aldehyde (2-thiophenecarboxy aldehyde, 4-bromobenzaldehyde). A quantity of 2–3 drops of glacial acetic acid was added to the reactants. Then the components were mixed in 25 mL of absolute ethanol. The mixture was heated under reflux. The progress of the reaction was monitored by TLC using eluent (methanol:chloroform 1:9). The formed solid crystals were filtered, dried and then purified by using the appropriate solvent. Table 1 illustrates the physical properties of the prepared compounds [23-25].

4-(1H-tetrazol-1-yl)-N'-(thiophen-2-ylmethylidene) benzohydrazide (S₃). FTIR (ν_{max} cm⁻¹, KBr) 3298 (NH), 3129 (C-H stretch band of tetrazole ring), 3104 (C-H of aromatic), 2900, 2992 (C-H aliphatic), 1656 (C=O amide), 1603 (C=N) 1544, 1509 (C=C aromatic), 1273 (C-O) Fig. S7. ¹H-NMR (500 MHz, DMSO-*d*₆, δ/ppm): 12 (s, 1H, CONH), 10.23 (s, 1H, CH=N of tetrazole ring), 8.69 (s, 1H, azomethane), 8.16 (d, *J* = 7.5 Hz, 2H, aromatic protons), 8.11 (d, *J* = 7.5 Hz, 2H, aromatic protons), (7.70 (s, 1H), 7.51 (s, 1H), 7.16 (s, 1H), thiophene ring) Fig. S8. ¹³C-NMR (125 MHz, DMSO-*d*₆, δ/ppm): 162.16, 143.94, 142.89, 136.41, 131.80, 129.97, 129.72, 139.41, 131.80, 128.41, 124.52, 121.35 Fig. S9.

N'-(4-bromobenzylidene)-4-(1H-tetrazol-1-yl) benzohydrazide (S₄). FTIR (ν_{max} cm⁻¹, KBr) 3214 (NH), 3118 (C-H stretch of tetrazole ring) 3047 (C-H aromatic ring), 2839, 2893, 2939 (C-H aliphatic) 1662 (C=O), 1535, 1593 (C=C aromatic), 1276 (C-O) Fig. S10. ¹H-NMR (500 MHz, DMSO-*d*₆, δ/ppm): 12.11 (s, 1H, CONH), 10.23 (s, 1H, CH=N of Tetrazole ring), 8.46 (s, 1H, azomethane), 8.18 (d, *J* = 8.6 Hz, 2H, aromatic protons), 8.12 (d, *J* = 8.5 Hz, 2H, aromatic protons), 7.70 (d, *J* = 8.6 Hz, 3H, aromatic protons), 7.51 (s, 1H, aromatic protons) Fig. S11.

Synthesis of 1-phenyl-1H-tetrazole-5-thiol (S₅)

To synthesize S₅, a mixture of 100 mL of water, 6.75 g (0.05 mol) of phenyl isothiocyanate and 4.875 g

(0.075 mol) of sodium azide was heated under reflux for 4 h. After the reflux, the mixture was cooled to room temperature and then filtered and extracted with 25 mL of ether to remove unreacted phenyl isothiocyanate. The water phase of the mixture was treated with hydrochloric acid to pH 3. Solid crystals with white color were precipitated. The crystals were then washed with water, filtered, dried, and recrystallized from ethanol [26-27].

FTIR (ν_{max} cm⁻¹, KBr) 3044 (C-H stretching of aromatic ring) 2893, 2968 (C-H stretching of aliphatic), 2550 weak band (S-H), 1587, 1501 (C=C), of aromatic rings and 1455 (N=N), of tetrazole ring, 1283 medium (C-N) stretching of tetrazole ring Fig. S12.

Synthesis of ethyl [(1-phenyl-1H-tetrazol-5-yl)sulfanyl] acetate (S₆)

To prepare S₆, a mixture of compound S₅ (2.7 g, 0.015 mol) and sodium ethanoate (1.23 g, 0.015 mol) was diluted in 50 mL of ethanol. The prepared mixture was added to a mixture of ethyl chloroacetate (1.92 mL, 0.018 mol) in 10 mL of ethanol by using a dropping funnel with continuous stirring. The resulting mixture was heated under reflux for 10 h. After the reaction was performed, the components were poured into the ice bath. The obtained solid crystals were collected, washed, and recrystallized from ethanol. Table 1 shows the physical properties of the synthesized compounds [27-28].

FTIR (ν_{max} cm⁻¹, KBr): 1743 (carbonyl of ester), 1635 (azomethine of tetrazole ring), 1496–1589 (C=C of phenyl ring) Fig. S13. ¹H-NMR (500 MHz, DMSO-*d*₆, δ/ppm): 7.68–7.61 (m, 5H, aromatic proton) 4.29 (s, 2H, SCH₂), 4.13 (q, *J* = 7.1 Hz, 2H, OCH₂), 1.18 (t, *J* = 7.1 Hz, 3H, CH₂CH₃) Fig. S14. ¹³C-NMR (125 MHz, DMSO-*d*₆, δ/ppm): 167.94 (C=O), (154.07) C=N of tetrazole ring, 133.44, 131.08, 130.52, 124.73 (aromatic carbons), 62.07 (O-CH₂), 35.22 (S-CH₂), 14.43 (CH₃) Fig. S15.

Synthesis of 2-[(1-phenyl-1H-tetrazole-5-yl)sulfanyl] acetohydrazide (S₇)

A mixture of compound S₆ (2.5 g, 0.01 mol) and 80% hydrazine hydrate (1 mL, 0.02 mol) in 20 mL of ethanol was prepared. The mixture was stirred at room temperature. The formed precipitate was filtered,

washed, dried, and recrystallized from ethanol. Table 1 shows the physical properties of the prepared compounds [3,27,29-30]. FTIR (ν_{\max} cm^{-1} , KBr) 3296, 3345, 3218 (NH, NH₂), 1686 (C=O of amide) Fig. S16. ¹H-NMR (500 MHz, DMSO-*d*₆, δ/ppm): 7.65–7.75 (m, 5H, aromatic protons), 9.41 (s, 1H, CONH), 4.09 (s, 2H, CH₂), 4.32 (s, 2H, NH₂) Fig. S17. ¹³C-NMR (125 MHz, DMSO-*d*₆, δ/ppm): 165 (C=O amide), 124, 130, 131, 133 (aromatic carbons), 154 (C-H of tetrazole ring), 35.52 (S-CH₂) Fig. S18.

Synthesis of acyl hydrazones (S₈-S₁₀)

To a solution of hydrazide S₆ (0.25 g, 0.001 mol) dissolved in 25 mL of ethanol with various aromatic aldehyde (0.001 mol) (4-chlorobenzaldehyde, 2-thiophenecarboxaldehyde, furfural) respectively, after that add few drops of glacial acetic acid the mixture was refluxed for 24 h. After completion of the reaction, the mixture was left to cool to room temperature Table 1 shows the physical properties of the synthesized compound [31-33].

N'-(4-chlorobenzylidene)-2-[(1-phenyl-1H-tetrazol-5-yl)sulfanyl]acetohydrazide (S₈). FTIR (ν_{\max} cm^{-1} , KBr): 3183 (N-H), 3098 (C-H aromatic), 2932, 2988 (C-H aliphatic), 1675 (C=O amide), 1604 (C=N), 1413, 1490 (C=C phenyl), 1419, 1388 (N=N of tetrazole ring) Fig. S19. ¹H-NMR (500 MHz, DMSO-*d*₆, δ/ppm): 11.84 (CONH, OH tautomeric), 8.03 (s, 1H, CH=N), 7.72 (d, *J* = 8.1 Hz, 2H, aromatic protons), 7.68 (d, *J* = 9.6 Hz, 2H, aromatic protons), 7.53–7.49 (m, 5H, phenyl ring), 4.73 (s, 2H, -SCH₂), 4.30 (s, 1H, CONH) Fig. S20. ¹³C-NMR (125 MHz, DMSO-*d*₆, δ/ppm): 168.31 (C=O), 163.20 (C=N) of tetrazole ring, 146.49 (CH=N), 143.39, 134.97, 133.52, 133.25, 131.09, 130.52, 129.38, 129.35, 129.24, 129.01 (aromatic carbons), 36.51 (S-CH₂) Fig. S21.

2-[(1-phenyl-1H-tetrazol-5-yl)sulfanyl]-N'-(thiophen-3-ylmethylidene)acetohydrazide (S₉). FTIR (ν_{\max} cm^{-1} , KBr): 3166 (NH), 3008, 3062 (C-H aromatic), 2939 (C-H aliphatic), 1661 (C=O amide), 1559 (C=N), 1537, 1458, 1498 (C=C aromatic) Fig. S22. ¹H-NMR (500 MHz, DMSO-*d*₆, δ/ppm): 11.76 (s, 1H, OH) tautomeric, 8.22 (s, 1H, CH=N), 7.69 (s, 5H, aromatic protons), 7.45–7.48 (s, 2H, aromatic protons), 7.13 (s, 1H, aromatic proton), 4.64 (s, 2H, S-CH₂), 4.28 (s, 1H, CONH) Fig. S23. ¹³C-NMR (125 MHz, DMSO-*d*₆,

δ/ppm): 167.89 (C=O amide), 162.96 (C=N tetrazole), 154.64 carbon of (CH=N), 133.54, 131.38, 131.13, 139.83, 130.55, 129.67, 129.27, 128.44, 124.92 (aromatic carbons), 36.41 (S-CH₂) Fig. S24.

N'-(E-furan-2-ylmethylidene)-2-[(1-phenyl-1H-tetrazol-5-yl)sulfanyl]acetohydrazide (S₁₀). FTIR (ν_{\max} cm^{-1} , KBr): 3167 (NH), 3067 (C-H aromatic), 2939 (C-H aliphatic), 1662 (C=O amide), 1593 (C=N), 1496 (C=C) Fig. S25. ¹H-NMR (500 MHz, DMSO-*d*₆, δ/ppm): 11.74 (s, 1H, CONH, OH tautomeric), 7.92 (s, 1H, CH=N), 7.84 (s, 1H, furan ring), 7.69 (s, 5H, aromatic protons), 6.93 (s, 1H, furan ring), 6.63 (s, 1H, furan ring), 4.66 (s, 2H, SCH₂), 4.28 (s, 1H, CONH) Fig. S26. ¹³C-NMR (125 MHz, DMSO-*d*₆, δ/ppm): 168.10 (C=O amide), 163.05 (tetrazole ring), 154.59 (CH=N), 49.28, 145.70, 114.67, 112.67, 135.00, 133.65, 131.31, 130.57, 124.95 (aromatic carbons), 36.66 (S-CH₂) Fig. S27.

Antioxidants activity

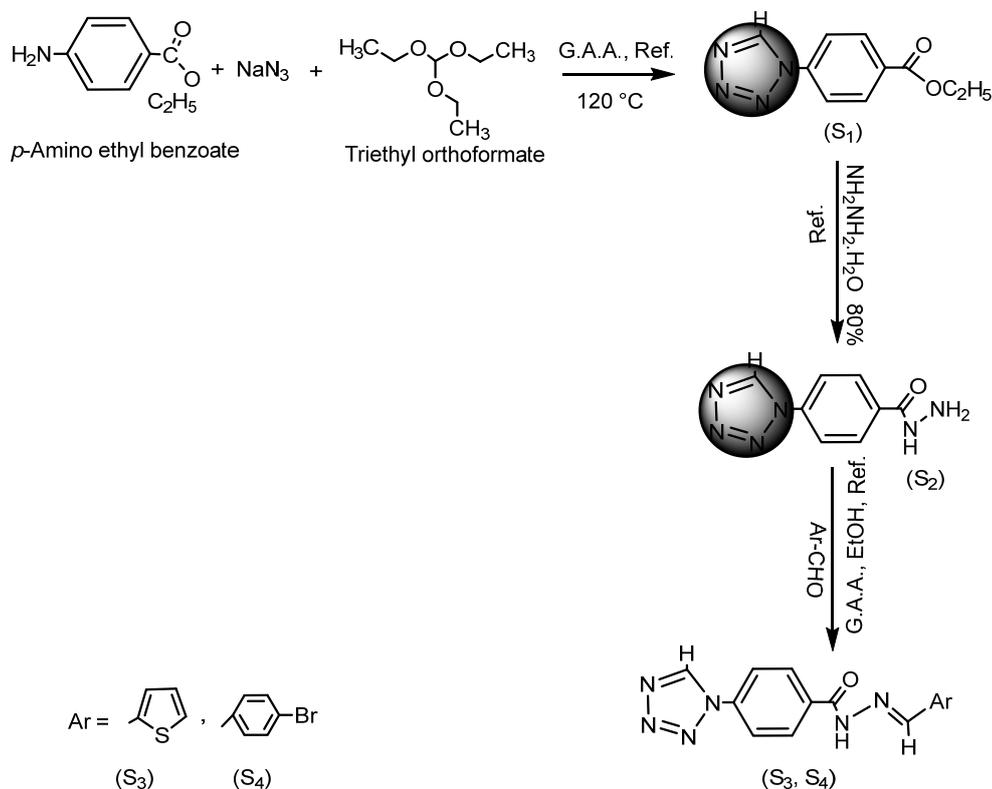
For fast evaluation of antioxidant activity, the radical scavenging model of DPPH radicals is widely used. Solutions of the synthesized compounds (S₃-S₉) were used at various concentrations (1000, 500, 250, and 100 $\mu\text{g}/\text{mL}$) [20] in the solvent methanol:DMSO (4:1). To prepare the DPPH solution, 40 mg was taken and dissolved in 100 mL of solvent (methanol: DMSO). Samples were kept in a dark place for 2 h. Later tested spectrophotometrically against DPPH. In contrast, assessing the decrease in DPPH absorbance at 517 nm. As a result of DPPH scavenging, the absorbance of the mixture dropped after the color conversion. The percent of inhibition of free radical generation from DPPH was calculated by using the following formula [22].

$$\text{Inhibition (\%)} = \frac{A_{\text{control}} - A_{\text{sample}}}{A_{\text{control}}} \times 100$$

where A_{control} : Absorbance of DPPH + solvent (MeOH:DMSO) and A_{sample} : Absorbance of DPPH + sample

RESULTS AND DISCUSSION

In the present study, two types of tetrazole derivatives were synthesized. Monosubstituted tetrazole (Scheme 1) was synthesized from the reaction of primary amines with sodium azide and triethyl orthoformate in



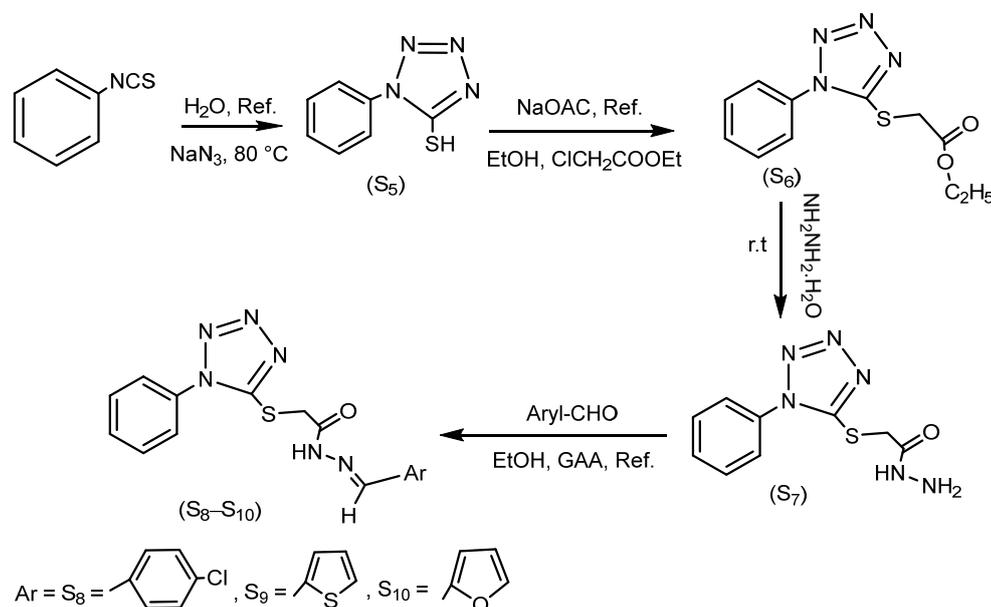
Scheme 1. Synthesis of monosubstituted tetrazole derivative

hot glacial acetic acid. The product was obtained in good yield, as shown in Table 1. The results of the FTIR spectrum displayed that compound S_1 has a sharp medium band at 3135 cm^{-1} , which is attributed to the stretching vibration of C-H of the tetrazole ring. The strong band at 1707 cm^{-1} is attributed to the stretching vibration of the carbonyl of ester. The $^1\text{H-NMR}$ data show that the azomethine group of tetrazole ring at 10.23 ppm, while protons of the ethoxy group at 4.36 ppm, ethylene group at 1.35 ppm. The $^{13}\text{C-NMR}$ analysis displays important signals at 164.95 ppm, which belong to the carbon of carbonyl ester, 142 ppm of (C=N) of tetrazole ring.

The FTIR spectrum of S_2 shows new bands at 3297 and 3256 cm^{-1} belonging to NH and NH_2 , and also appearing a new band at 1656 cm^{-1} attributed to the stretching vibration of the carbonyl group. The $^1\text{H-NMR}$ of S_2 demonstrate that the azomethane group of tetrazole ring gives a signal at 10.17 ppm (CONH) at 10 ppm. The $^{13}\text{C-NMR}$ gives signals at 164 ppm due to carbonyl amide and 142 ppm of imine (C=N) of tetrazole ring.

Compounds S_3 and S_4 were synthesized by the reaction between hydrazide S_2 with various aromatic aldehydes. The FTIR spectrum of compound S_3 demonstrates vibration at 3298 cm^{-1} belonging to NH and disappeared bands refer to the stretching vibration of NH_2 . The stretching vibration of the C=N band occurs at 1603 cm^{-1} . Meanwhile, the FTIR of compound S_4 illustrates the appearance of a band at 3214 cm^{-1} belonging to NH and a strong band at 1608 cm^{-1} , and this belongs to the band C=N. The $^1\text{H-NMR}$ of compounds S_3 and S_4 shows the appearance of signals at 12 and 12.11 ppm due to the appearance CONH group. The azomethine CH=N of tetrazole ring at 10.23 ppm. Moreover, signals at 8.46 and 8.69 ppm attributed to azomethine CH=N. $^{13}\text{C-NMR}$ of compound S_3 shows the signal at 162.16 ppm (C=O), 143.94 carbon of tetrazole ring, 142.89 refer to CH=N.

Another type of tetrazole derivative is 1,5-disubstituted tetrazole (Scheme 2). These compounds were obtained from the cyclization reaction of aryl isothiocyanate with sodium azide in water. The FTIR



spectrum of S_5 exhibits a characteristic band that resonates at 3044 cm^{-1} regions corresponding to C-H aromatic. The appearance of new weak absorption at 2550 cm^{-1} refers to the frequency of the thiol group [34].

The FTIR spectrum of S_6 has illustrated bands at 1743 cm^{-1} due to the stretching vibration of carbonyl of ester, 1635 cm^{-1} attributed to stretching vibration of imine of tetrazole ring. The $^1\text{H-NMR}$ shows signals at 4.13 ppm, which belong to the methylene group (CH_2CH_2), while S- CH_2 protons are found at 4.29 ppm. The $^{13}\text{C-NMR}$ shows a signal at 167 ppm due to the carbon of C=O ester and other signals at 14 and 62 ppm to the carbon of methyl and methylene, respectively.

The FTIR of compound C_7 appeared in new bands at 3345 , 3296 , and 3218 cm^{-1} ; this is attributed to NH and NH_2 , sharp strong band at 1686 and 1660 cm^{-1} due to imine (C=N) of tetrazole. The $^1\text{H-NMR}$ spectrum of S_7 observed signals at 7.65 – 7.69 ppm attributed to the proton of the aromatic ring, and the presence singlet signal at 9.41 ppm due to proton CONH, singlet signal at 4.09 ppm belong to the CH_2 group, and signal at 4.32 ppm due to NH_2 . The $^{13}\text{C-NMR}$ of compound S_7 shows a signal at 165 ppm attributed to the carbonyl of amide 35.52 ppm due to S- CH_2 .

FTIR of S_8 was characterized by the availability of new NH stretch bands at 3183 and 1604 cm^{-1} refers to the stretching vibration of imine group C=N. Moreover, for compound S_9 , FTIR shows NH at 3166 cm^{-1} and a strong absorption at 1559 cm^{-1} due to the stretching vibration of C=N. For compound S_{10} , the FTIR spectra show clear bands at 3141 and 3177 cm^{-1} belonging to stretching vibration N-H, strong band intensity at 1663 cm^{-1} due to the stretching of carbonyl amide. Appearing medium band at 1542 cm^{-1} due to stretching vibration of C=N. The $^1\text{H-NMR}$ spectra of compounds S_8 – S_{10} show the appearance of signals at 11.74 – 11.84 ppm and this belongs to CONH due to OH tautomeric as well as signals at 4.63, 4.73 ppm due to SCH_2 . The $^{13}\text{C-NMR}$ spectrum of compounds S_8 – S_{10} by appearance signals at 167.89 – 168.13 ppm due to carbonyl of amide. On the other hand, the signals at 162.96 – 163.20 ppm demonstrated the carbon of tetrazole ring. Additionally, signals at 36.41 – 36.66 ppm are attributed to (S- CH_2). Finally, the investigation of antioxidant activity revealed that the synthesized compounds showed antioxidant activity. Compound S_{10} had the highest value as radical scavenging among the synthesized compounds in the present study as shown in Table 2.

Table 2. Antioxidant activity for the synthesized compounds by using DPPH

Compound	1000 µg/mL	500 µg/mL	250 µg/mL	100 µg/mL
Ascorbic acid	98.91	98.75	98.66	98.50
S ₃	57.35	55.26	54.13	52.93
S ₄	58.15	56.30	53.57	51.65
S ₈	57.02	53.50	52.61	51.64
S ₉	55.90	54.21	49.88	48.35
S ₁₀	61.84	60.48	51.72	47.71

■ CONCLUSION

In this study, two series of tetrazole derivatives have been synthesized. The first type was prepared from a cyclization reaction of a primary amine with sodium azide with a good yield of 70%. At the same time, the second type was prepared from a cycloaddition reaction [3+2]. The prepared compounds were confirmed via spectral methods FTIR, ¹H-NMR, and ¹³C-NMR. The antioxidant activity of tetrazole derivatives was evaluated with DPPH radical. It was found that compound S₁₀ exhibited the highest free radical scavenging activity in comparison with other compounds.

■ REFERENCES

- [1] Nessim, M.I., Elewa, S.I., and Mohamed, M.G., 2018, Synthesis and study antimicrobial activities of some novel tetrazole derivatives, *Egypt. J. Chem.*, 61 (1), 197–206.
- [2] Bhaskar, V.H., and Mohite, P.B., 2010, Synthesis, characterization and evaluation of anticancer activity of some tetrazole derivatives, *J. Optoelectron. Biomed. Mater.*, 2 (4), 249–259.
- [3] Maruthamuthu, M., Rajam, S., Stella, C.R., Dileepan, A.G.B., and Ranjith, R., 2016, The chemistry and biological significance of imidazole, benzimidazole, benzoxazole, tetrazole and quinazolinone nucleus, *J. Chem. Pharm. Res.*, 8 (5), 505–526.
- [4] Bhaskar, V.H., and Mohite, P.B., 2011, Synthesis analgesic, anti-inflammatory and antimicrobial activities of some 1-[5-(substitutedphenyl)-4,5-dihydro-1H-pyrazol-3-yl]-5-phenyl-1H-tetrazole, *J. Optoelectron. Biomed. Mater.*, 3 (1), 7–16.
- [5] Malik, M.A., Al-Thabaiti, S.A., and Malik, M.A., 2012, Synthesis, structure optimization and antifungal screening of novel tetrazole ring bearing acyl-hydrazones, *Int. J. Mol. Sci.*, 3 (9), 10880–10898.
- [6] Qian, A., Zheng, Y., Wang, R., Wei, J., Cui, Y., Cao, X., and Yang, Y., 2017, Design, synthesis, and structure-activity relationship studies of novel tetrazole antifungal agents with potent activity, broad antifungal spectrum and high selectivity, *Bioorg. Med. Chem. Lett.*, 28 (3), 344–350.
- [7] Vembu, S., Parasuraman, P., and Gopalakrishnan, M., 2014, Design, *in silico* molecular docking studies, synthesis, spectral characterization and *in vitro* antifungal evaluation of 1-(4-(1H-tetrazole-1-yl)phenyl)-3-arylprop-2-en-1-ones, *Pharma Chem.*, 6 (5), 35–44.
- [8] Kaushik, N., Kumar, N., Kumar, A., and Singh, U.K., 2018, Tetrazoles: Synthesis and biological activity, *Immunol., Endocr. Metab. Agents Med. Chem.*, 18 (1), 3–21.
- [9] Özkan, H., and Demirci, H., 2019, Synthesis and antimicrobial and antioxidant activities of sulfonamide derivatives containing tetrazole and oxadiazole rings, *J. Heterocycl. Chem.*, 56 (9), 2528–2535.
- [10] Zhang, H.Z., Gan, L.L., Wang, H., and Zhou, C.H., 2017, New progress inazole compounds as antimicrobial agents, *Mini-Rev. Med. Chem.*, 17 (2), 122–166.
- [11] George, S., Varma, P.S., Suresh, I., and Shanmugapandiyam, P., 2012, Synthesis,

- antimicrobial and anti-inflammatory activities of 3-(1-substituted phenyl-1*H*-tetrazol-5-yl) pyridine derivatives, *Asian J. Pharm. Clin. Res.*, 5 (4), 81–84.
- [12] Mikolaichuk, O.V., Zarubaev, V.V., Muryleva, A.A., Esaulkova, Y.L., Spasibenko, D.V., Batyrenko, A.A., Korniyakov, I.V., and Trifonov, R.E., 2021, Synthesis, structure, and antiviral properties of novel 2-adamantyl-5-aryl-2*H*-tetrazoles, *Chem. Heterocycl. Compd.*, 57 (4), 442–447.
- [13] Asif, M., 2014, Biological potentials of substituted tetrazole compounds, *Pharm. Methods*, 5 (2), 2–8.
- [14] Zhang, J., Wang, S., Ba, Y., and Xu, Z., 2019, Tetrazole hybrids with potential anticancer activity, *Eur. J. Med. Chem.*, 178, 341–351.
- [15] Popova, E.A., Protas, A.V., and Trifonov, R.E., 2018, Tetrazole derivatives as promising anticancer agents, *Anti-Cancer Agents Med. Chem.*, 17 (14), 1856–1868.
- [16] Samanta, P.K., Biswas, R., Das, T., Nandi, M., Nandi, M., Adhikary, B., Richards, R.M., and Biswas, P., 2019, Mesoporous silica supported samarium as recyclable heterogeneous catalyst for synthesis of 5-substituted tetrazole and 2-substituted benzothiazole, *J. Porous Mater.*, 26 (1), 145–155.
- [17] Kaplancıklı, Z.A., Yurttaş, L., Özdemir, A., Turan-Zitouni, G., Çiftçi, G.A., Yıldırım, Ş.U., and Abu Mohsen, U., 2014, Synthesis and antiproliferative activity of new 1,5-disubstituted tetrazoles bearing hydrazone moiety, *Med. Chem. Res.*, 23 (2), 1067–1075.
- [18] Maleki, A., and Sarvary, A., 2015, Synthesis of tetrazoles via isocyanide-based reactions, *RSC Adv.*, 5 (75), 60938–60955.
- [19] Mohana, K.N., and Kumar, C.B.P., 2013, Synthesis and antioxidant activity of 2-amino-5-methylthiazol derivatives containing 1,3,4-oxadiazole-2-thiol moiety, *Int. Scholarly Res. Not.*, 2013, 620718.
- [20] Kosanić, M., Ranković, B.R., and Dasic, M., 2013, Antioxidant and antimicrobial properties of mushrooms, *Bulg. J. Agric. Sci.*, 19 (5), 1040–1046.
- [21] Gouda, M.A., Al-Ghorbani, M., Helal, M.H., Salem, M.A., and Hanashalshahaby, E.H.A., 2020, Recent progress on the synthetic routes to 1(5)-substituted 1*H*-tetrazoles and its analogs, *Synth. Commun.*, 50 (20), 3017–3043.
- [22] Mekky, A.H., Sayer, A.H., and Abed, H.J., 2019, Synthesis, antioxidant activity of some novel Schiff base derived from ethyl 4-aminobenzoate, *Biochem. Cell. Arch.*, 19 (1), 1247–1256.
- [23] Al-Ajely, M.S., and Yaseen, A.N., 2015, Synthesis and characterization of some new hydrazides and their derivatives, *Ibn Al-Haitham J. Pure Appl. Sci.*, 28 (3), 103–112.
- [24] Alsaheb, S.A., and Dhedan, R.M., 2021, Synthesis and characterization of some tetrazole derivatives and evaluation of their biological activity, *Egypt. J. Chem.*, 64 (6), 2925–2936.
- [25] Al-Bayati, R.I.H., Habib, M.J., and Mekky, A.H., 2015, Synthesis and characterization of new saccharin derivatives, *J. Multidiscip. Curr. Res.*, 3, 61–72.
- [26] Abdul-Nabi, A.S., and Jasim, E.Q., 2014, Synthesis, characterization and study of some tetrazole compounds as new corrosion inhibitors for C-steel in 0.5 M HCl solution, *Int. J. Eng. Res.*, 3 (10), 613–617.
- [27] Mekky, A.H., and Thamir, S.M., 2019, Synthesis, characterisation and antibacterial evaluation of some novel 1-phenyl-1*H*-tetrazole-5-thiol derivatives, *Int. J. Res. Pharm. Sci.*, 10 (2), 1136–1142.
- [28] Herr, R.J., 2002, 5-Substituted-1*H*-tetrazoles as carboxylic acid isosteres: Medicinal chemistry and synthetic methods, *Bioorg. Med. Chem.*, 10 (11), 3379–3393.
- [29] Kadawla, M., Sinha, J., and Verma, P.K., 2018, Microwave assisted synthesis of novel 3-mercapto-4,5-disubstituted 1,2,4-triazole derivatives and evaluation of antimicrobial, antitubercular activity, *Pharma Innovation J.*, 7 (1), 41–47.
- [30] Mekkey, A.H., Malk, F.H., and Kadhim, S.H., 2020, Synthesis and optical studies of the 3,4-dimethoxy benzaldehyde [5-(2-hydroxyphenyl)-1,3,4-oxadiazol-2-yl] hydrazone metal complexes, *Univ. Thi-Qar J. Sci.*, 7 (2), 95–100.
- [31] Arshad, M., Bhat, A.R., Pokharel, S., Kim, J.E., Lee,

- E.J., Athar, F., and Choi, I., 2014, Synthesis, characterization and anticancer screening of some novel piperonyl-tetrazole derivatives, *Eur. J. Med. Chem.*, 71, 229–236.
- [32] Sager, A.G., and Mekky, A.H., 2020, Synthesis and characterization new liquid crystals of Schiff base using microwave radiation, *Drug Invent. Today*, 14 (1), 70–78.
- [33] Mekky, A.H., Mohammad, Z.A.A., and Auribi, S.M., 2012, Synthesis and biological activity of monocyclic spiro azetidine-2-one, *J. Educ. Pure Sci.*, 2 (1), 67–74.
- [34] Butler, R.N., 1977, Recent advances in tetrazole chemistry, *Adv. Heterocycl. Chem.*, 21, 323–435.