REVIEW ARTICLE

Synthesis and *In-Vitro* Antioxidant Activity Study of Some New Azoles Derivatives as Sulfa Drugs

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ABSTRACT

In the current work, new azole derivatives were synthesized as sulfa drugs. The key starting material 4-(4-(ethoxycarbonyl)-5-methyl-1H-1,2,3-triazol-1-yl)benzene sulfonic acid 1a was synthesized via 1,3-diplar cycloaddition of 4-azidobenzene sulfonic acid with ethyl acetoacetate in the presence of trimethylamine. Followed by reaction with hydrazine hydrate to give the corresponding hydrazide derivative 1b that was cyclized in the presence of carbon disulfide and potassium hydroxide (KOH) to construct the target 1,3,4-oxadiazole ring system 1c. In addition, compound 1b was reacted with phenylthioisocyanate to give compound 1d that was cyclized in the presence of basic and acidic conditions to construct 1,2,4-triazole 1e and 1,3,4-thiadiazole 1f ring systems, respectively. Moreover, the radicals scavenging ability of all the synthesized compounds against 2,2-Diphenyl-1-picrylhydrazyl (DPPH) radicals was tested *in vitro* to investigate their antioxidant activity. Results revealed that the most synthesized compounds have a promising scavenging property.

Keywords: Antioxidant Activity, DPPH, Heterocyclic Chemistry, Oxadiazole, Sulfonic acid, Sulfa drugs, Thiadiazole, Triazole.

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INTRODUCTION

Heterocyclic compoundsplay a vital role in the design and synthesis of drugs due to their ability to act as biomimetic and pharmacophoresof the most therapeutic agents.[1] A common relevant known group is the azole drugs identified by containing an azole ring system in their structures.[2,3] The azole structure is a five-membered heterocycle with at least two heteroatoms,one of which must be a nitrogen atom.[4,5] Structurally, azole structure is comprisedin different heterocycles such as 1,3,4-oxadiazole,[6] 1,3,4-thiadiazole,[7] 1,2,3-triazole,[8] 1,2,4-triazole,[9] and other rings.Biologically, compounds containing azole structure have been considered a scaffold of choice in developingnew therapeutic agents to gainnew medicinal and pharmaceutical applications.[9,10-13] On the other hand, salt formation with pharmaceutically acceptable counter-ions is a required condition for optimizingthe drug properties.[14] Thus, introducing acidic or basic functional groups such as sulfonic acid groups into the structure of drugs provides this feature and can improve the desired biological, chemical, and physical properties.[15] Generally, compounds containing sulfonic acidgroups are known as organosulfur compounds (also called sulfonic acids) and are consideredanalogs of carboxylicacids with much stronger acidic properties[16] Manypharmaceutical drugsare prepared and used as benzenesulfonatesaltssuch asbesilatesorbesylates as sulfa drugs.[17] Furthermore, drugs containing the sulfonic acid grouphave a goodability tobind proteins.[18] In addition, compounds containing the sulfonic acid group displayed good antioxidant properties[19] or were used as standard antioxidants such as ABTS.[20] Moreover, the most antibacterial sulfa drugs are sulfonic acid derivatives.[21] Currently, as azoles occupy an important position in medicinal chemistry due to their various biological activities, it is interested in combination different azole structures with the sulfonic acid group in the same structure to present new potential sulfa drags.

EXPERIMENTAL PART

General Information: All solvents and starting materials were purchased from commercial suppliers in high purity and were used without further purification. Fourier transform infrared spectroscopy (FTIR) spectra were recorded on an FTIR–8400S plus spectrometer operating from (4000–400 cm^{-1}) as a KBr disc. ^{1}HNMR and ^{13}C-NMR spectra were recorded at 500 MHz and 125 MHz, respectively, on the Inova spectrometer. The mass spectra (MS) were recorded using MS Model: 5973 Network Mass Selective Detector, with Ion source: Electron Impact (EI) 70eV.

Synthesis of 4-(4-(ethoxycarbonyl)-5-methyl-1H-1,2,3-triazol-1-yl) benzenesulfonic acid 1a: A mixture of 4-azido-

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benzenesulfonic acid (3.0 g, 15 mmoles), ethyl acetoacetate (3.8 mL, 30 mmoles), triethylamine (4.18 mL, 30.0 mmoles) and dimethylformamide (DMF) (20 mL) was stirred at 50°C for overnight. The formed solid product was collected under vacuum filtration, washed with ether and dried to give the target compound 1a (4.2 g, 89%). FTIR (KBr disc, cm^{-1}); 3437 (OH, SO3H), 3072 (Ar-H), 2983 and 2943 (CH-aliph), 1716 (C=O), 1605 (C=C, Ar), 1508 (N=N). ^{1}H-NMR (500 MHz, DMSO-d6): δ= 1.35 (t, J= 5.9 Hz, 3H, CH3), 2.56 (s, 3H, CH3), 4.37 (q, J= 5.9 Hz, 2H, CH_2), 7.9-8.4 (m, 4H, Ar-H). ^{13}C-NMR (125 MHz, DMSO-d6): δ= 10.2, 14.1, 61.8, 125.4, 126.1, 127.3, 135.5, 136.2, 139.8, 147.5, 161.8.

Synthesis of 4-(4-(hydrazinecarbonyl)-5-methyl-1H-1,2,3-triazol-1-yl) benzenesulfonic acid 1b: A mixture of compound 1a (3.0 g, 9.6 mmole), hydrazine hydrate (15.0 mL, 60%) and ethanol (25 mL) was refluxed for 5.0 hours. The reaction mixture was placed in an crashed ice path and the separated white solid product was filtered off and dried to obtain the target compounds 1b (2.4 g, 86%). FTIR (KBr disc, cm^{-1}); 3444 (-OH), 3343 and 3321 (NH_2), 3220 (NH), 1681 (C=O), 1595 (C=C, Ar) and 1495 (N=N,1,2,3-triazole ring). ^{1}H-NMR (500 MHz, DMSO-d6): δ= 2.54 (s, 3H, CH3), 3.6 (s, br., 1H, OH), 4.54 (s, br, 2H, NH_2), 7.6-7.9 (m, 4H, Ar-H), 9.7 (s, 1H, -NH). ^{13}C-NMR (125 MHz, DMSO-d6): δ= 9.7, 125.3, 127.4, 135.0, 136.0, 138.6, 149.4, 160.8.

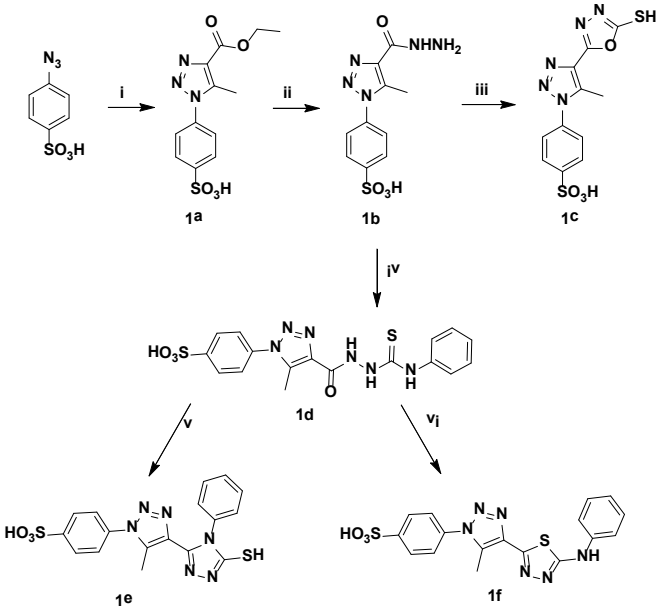
Synthesis of 4-(4-(5-mercapto-1,3,4-oxadiazol-2-yl)-5-methyl-1H-1,2,3-triazol-1-yl)benzene sulfonic acid 1c: A mixture of compound 1b (2.0 g, 6.0 mmoles), potassium hydroxide (1.4 g, 24.9 mmol) carbon disulfide (1.5 mL, 24.9 mmole) in absolute ethanol (50 mL) was refluxed for overnight. The reaction mixture was cooled into room temperature, diluted with water and acidified by concentrated hydrochloric acid until pH= 5. The precipitate formed was filtered, washed with water, dried to give the target compound 1c (1.5 g, 68%). FT-IR (KBr disc, cm^{-1}); 3448 (OH, SO_3H), 1595 (-C=C-, Ar), 1524 (C=N), 1497 (N=N, 1,2,3-triazole ring). ^{1}H-NMR (500 MHz, DMSO-d6): δ = 2.54 (s, 3H, CH_3), 4.54 (br, 1H, NH), 7.5-7.9 (m, 4H, Ar-H), 14.9 (br., 1H, S-OH). ^{13}C-NMR (125 MHz, DMSO-d6): δ= 10.7, 125.3, 127.4, 135.8, 136.8, 138.0, 149.0, 158.4 160.8. HRMS-EI^+ (m/z): Calc. for C11H9N5O4S2=339.1, Found=339.4.

Synthesis of 4-(5-methyl-4-(2-(phenylcarbamothioyl) hydrazinecarbonyl)-1H-1,2,3-triazol-1-yl) benzenesulfonic acid 1d: A mixture of the compound 1b (2.0 g, 6.73 mmole) and phenyl isothiocyanate (0.8 mL, 6.73 mmole) was refluxed in ethanol (50 mL) for 10 hours. The reaction mixture was allowed to cool to room temperature. The resulted white precipitate was collected under filtration and dried to give the target thiosemicarbazone derivative 1d (2.7 g, 93%). FT-IR (KBr disc, cm^{-1}); 3470-3213 (OH, SO3H and 3NH groups, overlapped), 3052 (C–H, Ar), 2984 (C–H aliph), 1674 (C=O, CONH), 1595 (C=C, Ar), 1495 (N=N, 1,2,3-triazole ring). ^{1}H-NMR (500 MHz, DMSO-d6): δ= 2.56 (s, 3H, CH3), 7.12-7.87 (m, 9H, Ar-H), 9.75 (s, 2H, -NHCSNH-), 10.60 (s, 1H, O=C-NH-NH). HRMS-EI^+ (m/z): Calc. for C17H16N6O4S2=432, Found= 433.0.

Synthesis of 4-(4-(5-mercapto-4-phenyl-4H-1,2,4-triazol-3-yl)-5-methyl-1H-1,2,3-triazol-1-yl) benzenesulfonic acid 1e: A mixture of compound 1d (2.0 g, 4.3 mmole) and an aqueous solution (25 mL) of sodium hydroxide (10% w/v, 10.0 mL) was refluxed for 4.0 h. The reaction mixture was allowed to cool and then adjusted to pH 5.5–6.0 with a dilute solution of HCl. The crude product was filtered off, washed with water (3x25 mL) to give the target compound 1e in a good yield (1.4 g, 73.6%). FT-IR (KBr disc, cm^{-1}); 3470-3213 (OH, SO3H and NH group overlapped), 3095 (Ar-H), 2974 (CH-aliph), 1595 (C=C, Ar) and 1495 (N=N, 1,2,3-triazole ring). ^{1}H-NMR (500 MHz, DMSO-d6): δ= 2.56 (s, 3H, CH3), 7.1-8.4 (m, 9H, Ar-H), 13.3 (s, 1H, SH). ^{13}C-NMR (125 MHz, DMSO-d6): δ= 10.0, 125.5, 126.5, 129.1, 129.3, 129.6, 133.0, 135.0, 136.6, 140.6, 143.8, 148.2, 169.0. HRMS-EI^+ (m/z): Calc. for C17H16N6O4S2=414.06, Found= 414.3.

4-(5-methyl-4-(5-(phenylamino)-1,3,4-thiadiazol-2-yl)-1H-1,2,3-triazol-1-yl) benzene sulfonic acid 1f: A mixture of compound 1d (2.0 g, 4.3 mmole) and concentrated sulphuric acid (10 mL) was refluxed for half an hour and kept at room temperature for 24 h. The content was poured into cold water and neutralized with diluted sodium carbonate solution. The solid product was isolated and crystallized from ethanol to obtain the target compounds 1f in moderate yield (1.1g, 53%): FT-IR (KBr disc, cm^{-1}); 3424 (S-OH), 3337 (NH), 1600 (C=C, Ar), 1560 (C=N, 1,3,4-thiadiazole ring), 1498 (N=N, 1,2,3-triazole ring). ^{1}H-NMR (500 MHz, DMSO-d6): δ = 2.63 (s, 3H, CH3), 6.9-7.9 (m, 9H, Ar-H). ^{13}C-NMR (125 MHz, DMSO-d6): δ= 10.27, 118.5, 119.1, 122.5, 1223.8, 129.1, 129.3, 133.0, 135.0, 137.6, 139.6, 140.8, 149.2, 150.8, 164.0. HRMS-EI^+ (m/z): Calc. for C17H14N6O3S2= 414.06, Found = 414.0.

Antioxidant Assay: The radical scavenging activity of the synthesized compounds 1a-f was investigated against the stable free radicals of 1,1-diphenyl-2-picrylhydrazyl (DPPH) by spectrophotometric method. Practically, the tested compounds were prepared in methanol with five concentrations (12.5, 25, 50, 100, and 200 µg/mL). A methanolic DPPH (1.0 mL, 0.1 mM) solution was then added to a solution of the tested compounds 1a-f (1.0 mL) for each concentration. The resulted solution was incubated for 30 minutes in the dark at 37°C. and the absorbance was measured at 517 nm using UV-1650 Shimadzu Spectrophotometer. The absorbance of solutions the DPPH radical without antioxidant and ascorbic acid in methanol was also measured as a control and a positive reference, respectively. All measurements were performed in triplicate, and the capability of radical scavenging activity (RSA) % of the target compounds was calculated by the equation: *RSA* % = ; where is the absorbance of control solution (DPPH without test sample), and is the absorbance of the sample (DPPH + tested sample). A calibration curve was plotted with %DPPH scavenged versus standard antioxidant ascorbic acid (AA) concentration. Additionally, the IC50 values of the synthesized compounds 1a-f and AA (as standard) were determined. The value of IC50 means that the concentration



Scheme 1: i) Ethyl acetoacetate, E_3N, DMF; ii) Hydrazine hydrate, Ethanol; iii) CS_2, KOH, Ethanol; iv) Phenylthioisocyanate, Ethanol; v) NaOH; vi) conc. H_2SO_4.

of the sample will scavenge 50% of DPPH free radicals. The concentrations versus inhibition percentages of the synthesized compounds were plotted, and the values of IC50 were calculated.

RESULTS AND DISCUSSION

Chemistry: The synthetic pathway that was employed for the synthesis of the titled compounds is outlined in Scheme 1.

In the current work, 4-azidebenzene sulfonic acid was used as a key starting material for synthesizing the target compounds 1a-f. 4-Azidebenzene sulfonic acid was synthesized according to the work that was described in the literature.[22] Synthesis of 4-azidebenzene sulfonic acid takes advantage that this compound introduces the target sulfonic acid group and azido groups into the target compounds. Specifically, introducing the sulfonic group into the target compounds, 1a-f leads to improved pharmaceutical properties as sulfa drugs, while the azide group will be used as an azide component of the 1,3-dipolar cycloaddition reaction[22] and activated alkenes coming from β-dicarbonyl compounds or malonodinitrile on the other hand, either with recourse to conventional heating or to microwave activation, to afford 1-aryl-1H-1,2,3-triazoles. The mechanism and the regioselectivity of the reactions involving β-dicarbonyl compounds have been theoretically studied using density functional theory (DFT) methods at the B3LYP/6-31G* level: they are domino processes comprising a tautomeric equilibrium of the β-dicarbonyl compounds with their enol forms, a 1,3-dipolar cycloaddition of the enol forms with the aryl azides (high activation energy. Thus, the reaction of 4-azidobenzene sulfonic acid with the ethyl acetoacetate in the presence of trimethylamine as an activation agent according to the procedure described in the literature.[24] This reaction led to the construct 1,2,3-triaozle ring system to give 4-(4-(ethoxycarbonyl)-5-methyl-1H-1,2,3-triazol-1-yl) benzenesulfonic acid 1a in a high yield. Chemical structures of compounds 1a and 1b were following their spectral data. Mainly, FTIR spectrum of compound 1a displayed the absorption bands of the C=O group of ester group and N=N group of triazole ring system at ~1716 cm^{-1} and ~1508 cm^{-1}, respectively. Furthermore, its ^{1}H-NMR spectrum showed peaks at δ = 1.35 and 4.37 belong to protons of the ethyl group of the ester associated with the correct integral belong to protons of methyl group that attached to triazole ring system and phenyl group to indicate that ethyl 5-methyl-1H-1,2,3-triazole-4-carboxylate moiety was constructed. In addition, identification of structure of compound 1a was also supported by ^{13}C-NMR spectrum as mentioned in experimental part. As hydrazide derivatives have been described as starting materials or building blocks for the assembly of several heterocyclic rings, the functional ester group of compound 1a was converted to hydrazide group via refluxing with hydrazine hydrate in ethanol to give the hydrazide derivative 1b in a high yield according to the procedure that was described in the literature.[25] As proof of the proposed structure of compound 1b, its FTIR spectrum displayed shifting of the absorption band of C=O group to ~1681 cm^{-1} along with the appearance of new bands at 3290 cm^{-1} and 3318 cm^{-1} which are attributed to NH and NH_2 functional groups. In addition, its ^{1}H-NMR spectrum was devoid from any signals attributed to protons of ethyl group of ester that were seen in compound 1a; instead, it showed new signals attributed to NH and NH_2 protons at δ 4.54 ppm and 9.7 ppm, respectively to and indicated that the ester group was converted to the hydrazide group. Besides, compound 1b was supported by ^{13}C-NMR and Mass spectra, as mentioned in the experimental part. Along with the compound 1b, the efforts were turned to exploit its hydrazide group to combine the 1,2,3-triaozle ring with 1,3,4-oxadiazole ring system via reaction with carbon disulfide in the presence of potassium hydroxide to give the target 4-(4-(5-mercapto-1,3,4-oxadiazol-2-yl)-5-methyl-1H-1,2,3-triazol-1-yl)benzene sulfonic acid 1c in a good yield. The structure of compound 1c was also confirmed by FTIR, 1H-NMR and mass spectral data, where its FTIR and 1H-NMR spectra were devoid of the absorption bands of C=O, NH, and NH_2 groups that were seen in compound 1b. In addition, the ^{13}C-NMR spectrum of compound 1c displayed signals of carbon atoms of (O-C=N) and S-C=N groups at δ= 158.4 and 160.8 pmm, respectively, to indicate that 1,3,4-oxadiazole ring system being constructed. Furthermore, the mass spectra recorded for compounds 1c indicated that the calculated value corresponding to the ratio m/z has been very close to the measured *m/z*. On the other hand, compound 1b was reacted with phenyl isothiocyanate in boiling ethanol to yield a compound 1d in an excellent yield. This reaction proceeds via a nucleophilic attacking of the NH_2 group of compound 1b towards the thiocarbonyl group of phenyl isothiocyanate. FTIR, NMR, and Mass spectra supported the structure of compound 1d. Mainly, the FTIR spectrum of compound 1d exhibited a new absorption band at 1251 cm^{-1}, corresponding to the stretching vibration of the C=S group associated with C=O at 1674 cm^{-1}. In addition, ^{1}H-NMR spectra

recorded for compounds 1d showed that all the signals belong to its starting materials combined with the correct integration of protons of compound 1d. Further evidence was gained from a mass spectrum that showed the molecular ion peak at *m/z* 437, which agrees with the molecular weight of compound 1d. As hydrazinecarbothioamides are considered intermediates compounds in the synthetic transformations, compound 1d was used as a precursor to construct 1,2,4-triazole and 1,3,4-thiadiazole rings via cyclization reactions. Subsequently, treatment compound 1d with an aqueous solution of sodium hydroxide under refluxing led to construct 1,2,4-triazole ring system to give 4-(4-(5-mercapto-4-phenyl-4H-1,2,4-triazol-3-yl)-5-methyl-1H-1,2,3-triazol-1-yl)benzene sulfonic acid 1e in a moderate yield. While treatment of compound 1d with concentrated sulphuric acid at room temperature constructed 1,3,4-thiadiazole ring system and afforded the corresponding 4-(5-methyl-4-(5-(phenylamino)-1,3,4-thiadiazol-2-yl)-1H-1,2,3-triazol-1-yl)benzene sulfonic acid 1f in a moderate yield. Their spectral data supported the structure of compounds 1e and 1f. The FT-IR spectrum recorded for compound 1e showed no absorption band was detected about 1674 cm-1 to indicate the absence of the C=O group of hydrazinecarbothioamide 1d. As a result to construct 1,2,4-triazole ring system. Moreover, it was seen that the νS-H vibration band (~2500–2600 cm^{-1}) was absent, and the νC=S vibration band was observed in region 1247–1255 cm^{-1} to indicate that this compound can exist in the latter tautomeric form. Its ^{1}H-NMR showed that all the signals are belonging to its compound 1d combined with the correct integration of protons of compound 1e. Interestingly, its ^{13}C-NMR spectrum showed a signal peak at 169.0 ppm can be imputed to the C-3 of 1,2,4-triazole nucleus, which resonated is characteristic of C=S group to indicate the presence of the thione tautomeric. Besides the main peaks, FT-IR spectra recorded for compound 1f exhibited a new absorption band at 3284 cm^{-1} belongs to the secondary amine associated with absorption bands at 1613 cm^{-1} due to the presence of -C=N- a stretch of thiadiazole ring system. In addition, the absence of the C=O absorptions provided definitive proof for the formation of the new compound. Also, the formation of compound 1f was supported by ^{1}H-NMR, ^{13}C-NMR, and Mass spectra as detailed in the exponential part. In general, the current work highlighted that the target compounds 1a-f were synthesized in an easy, convenient, and efficient synthetic route and were pure enough do not require further purification by common chromatography as proved by total leukocyte count (TLC) test.

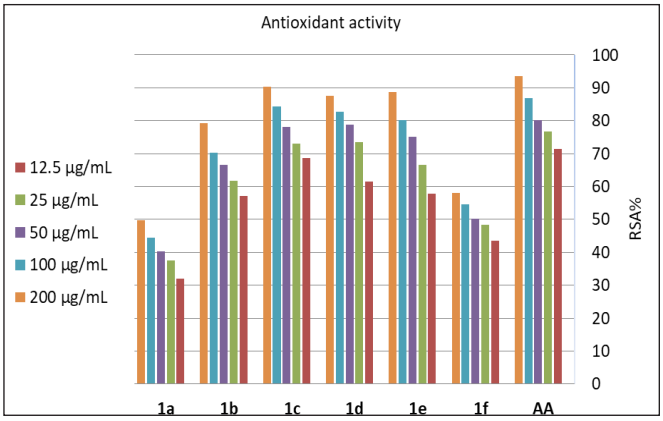


Figure 1: *In vitro* antioxidant activity of the synthesized compounds by using DPPH radicals scavenging assay (where (AA): ascorbic acid as a standard antioxidant).

Antioxidant Assay: The antioxidant is chemical molecules capable of inhibiting the oxidation of another molecule via stopping the free radical chain of reactions by sacrificing their electrons to feed free radicals without becoming free radicals themselves[26] from food engineering to medicine and pharmacy, is of major interest to the scientific community. The present paper is a critical presentation of the most important tests used to determine the antioxidant activity, detection mechanism, applicability, advantages and disadvantages of these methods. Out of the tests based on the transfer of a hydrogen atom, the following were presented: the oxygen radical absorption capacity (ORAC). Although several methods are available to evaluate the antioxidant activity of antioxidant agents, DPPH free radical scavenging activity is the common and fast method.[27] The DPPH free radicals are highly stable and capable of capturing an electron or hydrogen radical from another molecule to become stable. The deep purple color solution of DPPH has a strong absorption at 515–520 nm and turns yellow color in the presence of an antioxidant which reacts with free radicals of DPPH by pairing the nitrogen centered single electron in DPPH with a hydrogen atom or by electronic donation[28] DPPH. Thus, the reduction of DPPH absorption at 517 nm represents the ability of antioxidants to scavenge free radicals. In the current work, the free radical scavenging activity of the synthesized compounds 1a-f was achieved against the stable free radicals of DPPH and compared with ascorbic acid (AA) as a standard antioxidant agent. The antioxidant activity of the synthesized compounds 1a-f was evaluated in five different concentrations (12.5, 25, 50, 100, and 200 µg/mL) of each compound to investigate the minimum active concentration. Based on the experimental results, all the synthesized compounds 1a-f displayed an antioxidant activity against the free radicals of DPPH, as detailed in Figure 1. The highest antioxidant activity among the synthesized compounds was showed by compound 1c with 90% inhibition of radical formation at 200 µg/mL, and the descending order of radical scavenging activity of compounds 1a-f was 1c > 1d > 1e > 1b > 1f > 1a. Interestingly, compounds 1b, 1c, 1d, and 1e have shown a promising inhibition activity of more than 50% at the lowest concentration (12.5 µg/mL) compared with ascorbic acid as a standard antioxidant as summarized in Figure 1.

According to the structure-antioxidant activity relationship, it was found that the antioxidant activity was associated with concentration and the nature of the structure of the tested compounds. At each concertation, maximum DPPH radical scavenging activity was observed in compounds 1c that containing 1,2,3-triazole and 1,3,4-oxadiazole ring combined with benzene sulfonic acid moiety in the same structures and the minimum value was recorded for compound 1a that containing only 1,2,3-triaozle ring system in comparison with

Table 1: IC_{50} values of standard antioxidant, the target compounds **1a-f**.

No. of Comp.	*1a*	*1b*	*1c*	*1d*	*1e*	*1f*	*AA*
IC50 (µg/mL)	199.68	17.29	13.4	14.14	15.8	27.41	12.57

ascorbic acid as a standard antioxidant. Additionally, IC50 values of the synthesized compounds 1a-f and known standards (AA) were also calculated and a low IC50 value indicates high antioxidant activity as shown in Table 1.

These exponential results revealed that the activity level of compound **1c** is greater than another compound under the inverse relationship between IC_{50} value and antioxidant activity. This higher scavenging activity is perhaps due to the presence of thiol group as a hydrogen donating group, thereby increasing the stability of the formed free radical of the synthesized compound.

CONCLUSIONS

In conclusion, a series of azole derivatives containing benzene sulfonic acid moiety were designed and synthesized via an easy, convenient, and efficient synthetic route and evaluated in vitro as an antioxidant agent using DPPH radical scavenger assay. Antioxidant screening results indicate that an interesting DPPH radical scavenging activity was observed with most of the synthesized compounds. In addition, the synthesized compounds can be used for future studies as new antioxidant standard agents and as antibacterial sulfa drugs.

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