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Original article

Ultrasound-assisted synthesis of novel 1,2,3-triazoles coupled diaryl sulfone moieties by the CuAAC reaction, and biological evaluation of them as antioxidant and antimicrobial agents

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ABSTRACT

A series of 1,2,3-triazoles coupled diaryl sulfone containing compounds were synthesized by the copper-catalyzed azide-alkyne 1,3-dipolar cycloaddition (CuAAC) reaction in benign solvents under ultrasound irradiation. *In situ* formation of azides from α-bromoketones together with the CuAAC reaction in one pot allowed safe handling and good availability of azides for the development of a small library of compounds. The sonication reduced reaction time and increased yields compared to otherwise same conditions. All synthesized compounds were evaluated for antibacterial, antifungal and antioxidant activities. Compounds **3b**, **6b** and **9e**–**9g** were found to be the most potent antifungal agents with minimal inhibitory concentration (MIC) at 25 μg/mL; moreover other compounds revealed good to moderate antimicrobial activity. Compound **8e** showed an excellent antioxidant activity using a DPPH free radical scavenging assay.

1. Introduction

Antimicrobial agents are fundamental medicines for human and animal health and welfare, and are considered “miracle drugs” to treat infections caused by bacteria, fungi, parasites, and viruses. The discovery of different types of microorganisms explained the main reasons for infection diseases [1,2]. According to the World Health Organization (WHO) the infections caused by resistant microorganisms often fail to respond to conventional treatment, resulting in prolonged illness and greater risk of death. About 440 000 new cases of multidrug-resistant tuberculosis (MDR-TB) emerge annually, causing at least 150 000 deaths. In addition, a high percentage of hospital-acquired infections are caused by highly resistant bacteria such as methicillin-resistant *Staphylococcus aureus* (MRSA) [3,4]. The antioxidants that scavenge reactive oxygen species (ROS) may be of efficient value in preventing the onset and propagation of oxidative diseases such as autoimmune diseases, cardiovascular diseases and neurovascular diseases. A balance between ROS and antioxidants is necessary for proper physiological function [5]. These health risks encourage the development and modification of antioxidants and antimicrobial drugs by the design and synthesis of new chemical compounds with high efficiency, low toxicity and broad spectrum.

The importance of sulfones in medicinal chemistry is well recognized. In particular, organosulfone derivatives have been used as drugs due to their high potential as antibacterial, antifungal, anti-nociceptive and anti-inflammatory agents such as Lasix, Aquazide h, and Sulfadimidine (Fig. 1) [6–14]. Furthermore, the diaryl sulfone function was found a potent antimicrobial agent [15]. Some well-known medicines are available in the market, for example Dapsone [16] and Promine [17]; as shown in Fig. 1. Noticeably, the combination of a diaryl sulfone ring system with various types of heterocyclic analogues has shown significant biological activities [18–22].

The 1,2,3-triazole unit has received great interest and special attention because of its wide and extensive medicinal applications, such as antibacterial [23], antifungicidal [24], antiviral [25],

Abbreviations list: CuAAC, Copper-catalyzed azide-alkyne 1,3-dipolar cycloaddition; MIC, Minimal inhibitory concentration; PEG, Poly(ethylene glycol); DPPH, 2,2-diphenyl-1-picrylhydrazyl.

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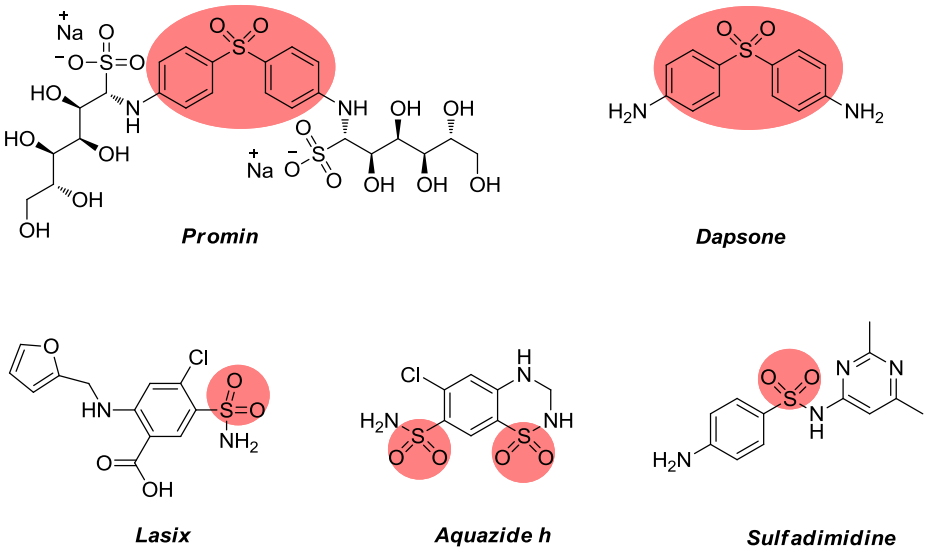


Fig. 1. Examples of drugs molecules containing the diaryl sulfone moiety or sulfonyl groups.

antioxidant [26] or anti-inflammatory agents [27]. 1,4-Disubstituted 1,2,3-triazoles are obtainable in high yields by the copper-catalyzed azide-alkyne 1,3-dipolar cycloaddition (CuAAC) reaction often used in the click chemistry concept which play an efficient role in drug discovery applications. This reaction proceeds with great efficiency and selectivity in aqueous media [28,29].

The above mentioned facts encouraged us to continue our exploration of diaryl sulfone derivatives [30–32], in the pursuit of novel compounds with antimicrobial or antioxidant activities with the potential of becoming new drugs. Combining the activities of the diaryl sulfone group and the 1,2,3-triazole we have designed and synthesized mono and bis-1,2,3-triazole derivatives of the diaryl sulfone scaffold, as outlined in Fig. 2, by installing triple bonds on the scaffold and clicking on new groups while forming 1,2,3-triazoles with the CuAAC reaction. Synthesis under ultrasound irradiation was compared to silent conditions at the same temperature to explore the effect of sonication on the reactions. All synthesized compounds were evaluated for their antioxidant, antibacterial and antifungal activities, and also their minimum inhibitory concentration (MIC).

2. Results and discussion

2.1. Chemistry

The synthesis work is outlined in Scheme 1. *Route A* is a stepwise approach that allow click coupling of two different azides for more diversity, while *route B* saves one step by first introducing both alkynes and then form both triazoles simultaneously from the same azide. The first step in the construction of our scaffold were the preparation of the key aryl sulfone intermediates **2a,b** containing a terminal alkyne by ultrasound mediated Barbier-type propargylation of the corresponding carbonyl compounds **1a,b** [30]. Propargyl bromide in dry THF in the presence of Zinc, and the Lewis acid $ZnBr_2$ as an additive, afforded the homopropargylic alcohol with high yields and regioselectivity above 99%. Times and yields of the reactions under both ultrasound irradiation and silent conditions are tabulated in Table 1. Ultrasound irradiation improved the yield and decreased the reaction time compared to the silent conditions.

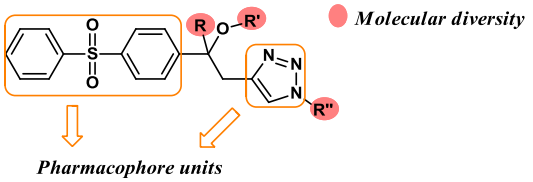
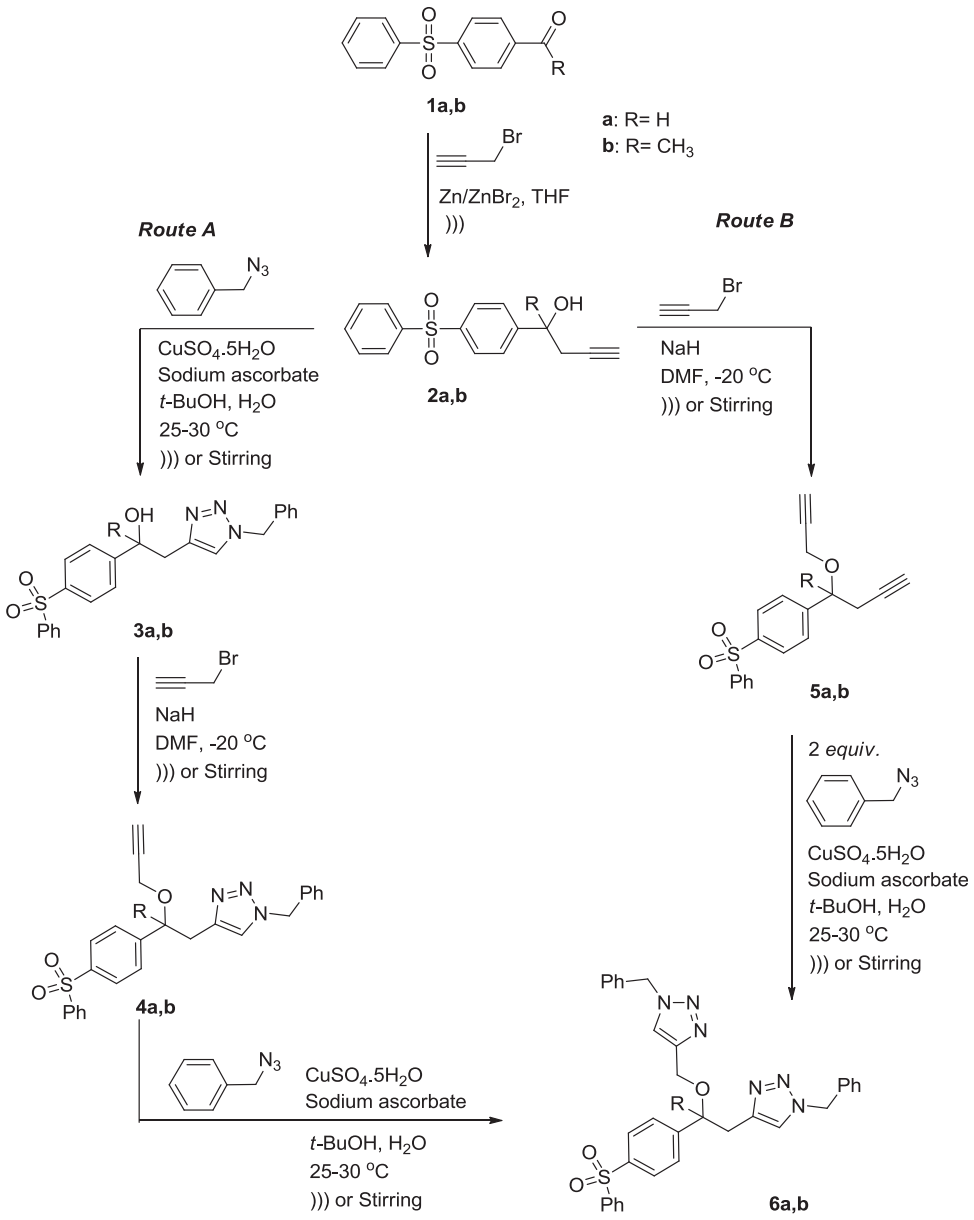


Fig. 2. The designed bioactive scaffold has three variable parts, while containing 1,2,3-triazole and diaryl sulfone as a main backbone.

Next, we investigated the scope and the generality of the CuAAC reaction [33]. The commercially available benzyl azide was applied on alkynes **2a,b**, and later **4a,b** and **5a,b**, affording excellent yields of 1,4-disubstituted 1,2,3-triazoles (**3a,b** and **6a,b**) under both ultrasound irradiation and silent conditions (Scheme 1).

The synthesis of monotriazoles **3a,b** involved the click reaction between propargyl alcohol **2a,b** and benzyl azide by copper sulfate and sodium ascorbate at 25–30 °C in *tert*-butanol:water 2:1 under ultrasound irradiation compared to simple stirring [33] (Table 2). Along *Route A* in Scheme 1 the hydroxyl group in aryl sulfones **3a,b** was propargylated with propargyl bromide in dry DMF and sodium hydride (NaH) at −20 °C under sonication or stirring, affording the O-propargylated isomer **4a,b** in high yields (Table 3) with no trace of allene formation. The O-propargylated products were reacted with benzyl azide using the click conditions as described in the experimental section, to form bis-triazoles **6a,b** in excellent yields in short time. Along *route B*, outlined in Scheme 1, hydroxyalkynes **2a,b** were first propargylated (Table 3) to bisalkynes **5a,b**, before reaction with two equivalents of azide under ultrasound irradiation gave bis-triazoles **6a,b** in better yields than by silent conditions. It is clear from the results listed in Table 2, that the 1,3-dipolar cycloaddition reaction performed better under ultrasound irradiation. While the reactions under silent conditions needed 1–4 h for completion with yields between 76% and 85%, ultrasound irradiation gave yields between 86% and 97% after just 20–30 min.

To further expand the novel 1,2,3-triazole series a variety of α-azido ketones was desired. However, it has been reported that the 1,3-dipolar cycloaddition of α-azido ketones with alkynes were difficult because α-azido ketones are often unstable to heat and light. In addition isolation and purification of the α-azido ketones were difficult due to incomplete conversion [34]. Therefore, *in situ* preparation would provide an efficient way to handle them safely. Multicomponent reactions (MCRs) have significant advantages in



Scheme 1. Synthesis of mono and bis-1,2,3-triazoles by stepwise introduction of alkyne followed by the CuACC reaction (*Route A*) for increased diversity, or simultaneous bis-1,2,3-triazole formation (*Route B*) for increased efficiency.

the synthesis of drug libraries by efficient introduction of molecular complexity with good atom economy [35].

As part of our program aimed to use green chemistry tools in organic synthesis [30–32], we decided to develop a one-pot synthesis of 1,4-disubstituted 1,2,3-triazoles from α-bromoketones, sodium azide, and alkynes. The model reaction, as shown in Table 4, was performed in the presence of different types of solvents, copper sulfate and sodium ascorbate at 25–30 °C under ultrasound irradiation to find optimum conditions.

The best results were obtained when using H_2O/*t*-BuOH (3:1) as an efficient medium for the one-pot synthesis of 1,4-disubstituted 1,2,3-triazoles (Table 4, entry 9).

Table 1
Synthesis of homopropargyl alcohols **2a,b** by the Barbier-type reaction (Scheme 1).

Entry	Starting material	Product	Ultrasound irradiation		Stirring conditions	
			Time (h)	Yield (%)	Time (h)	Yield (%)
1	**1a**	**2a**	1	89	12	73
2	**1b**	**2b**	1.5	80	12	70

Table 2
Synthesis of 1,2,3-triazoles **3a,b**; **6a,b** by the CuAAC reaction (Scheme 1).

Entry	Starting material	Product	Ultrasound irradiation		Stirring conditions	
			Time (min)	Yield (%)	Time (h)	Yield (%)
1	**2a**	**3a**	20	97	1	85
2	**2b**	**3b**	20	91	1	76
3	**4a**	**6a**	30	95	2	80
4	**4b**	**6b**	30	93	2	81
5	**5a**	**6a**	30	90	4	79
6	**5b**	**6b**	30	86	4	78

Table 3
Synthesis of alkynes **4a,b** and bis-alkynes **5a,b** by propargylation of the corresponding alcohols (Scheme 1).

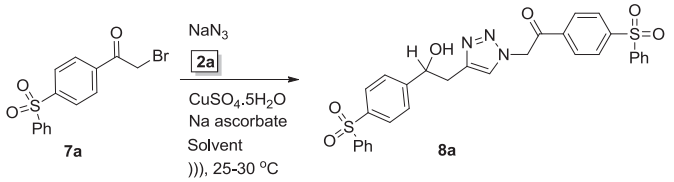
Entry	Starting material	Product	Ultrasound irradiation		Stirring conditions	
			Time (min)	Yield (%)	Time (h)	Yield (%)
1	**2a**	**5a**	30	99	2	90
2	**2b**	**5b**	30	90	2	85
3	**3a**	**4a**	30	80	2	70
4	**3b**	**4b**	30	78	2	66

A plausible mechanism for the formation of 1,2,3-triazoles is initial formation of the α-azido ketone as an intermediate, as was observed when reacting equimolar quantities of α-halo ketone derivative **7a** with sodium azide without alkyne **2a** under identical conditions. Subsequently, 1,3-dipolar cycloaddition of α-azido ketone and terminal alkyne **2a** afforded the desired product **8a.** In general, we found that the new solvent system, H_2O/*t*-BuOH (3:1) afforded keto 1,2,3-triazoles in good yield within a short time compared to the other solvents.

With the optimized conditions in hand, we prepared a range of mono and bis-keto triazoles containing aryl sulphone groups *via* the one-pot click reaction as shown in Tables 5 and 6.

All compounds were purified by silica gel column chromatography and were fully characterized by IR, ^{1}H nuclear magnetic resonance (NMR), ^{13}C NMR and high-resolution mass spectral (HRMS) analyses. Furthermore, the structures **9a–c; 9e–g** were confirmed by elemental analysis (see experimental section). For example The IR spectrum of **8d** displayed a strong band at about 1701 cm^{-1} indicating the presence of a ketone group. The ^{1}H NMR spectra of **8d** showed a distinct singlet signal at δ 7.76 ppm for triazolyl C5–H proton. ^{13}C NMR also displayed two distinct signals at δ 124.9 ppm and δ 192.3 ppm corresponding to the triazolyl C5 and the carbonyl carbon respectively. The mass spectrum of this compound exhibits the molecular ion peak at m/z = 470 $[M+Na]^+$, which is in agreement with the calculated mass. As outlined in Table 5, the one-pot three component synthesis of 1,2,3-triazoles carried out under ultrasonic irradiation gave excellent yields and shorter reaction times compared to the silent reaction. For example, the product **8d** took about 3 h for completion under silent conditions and the yield of the product was 84%. In comparison, under ultrasonic irradiation, the reaction time was 30 min and the yield 95%.

Table 4
Effect of solvents on the one-pot synthesis of keto 1,2,3-triazoles from *in situ* formed azides.[a]



Entry	Solvent	Time (h)	Yield[b] (%)
1	DMSO	12	None
2	DMF	12	None
3	*t*-BuOH	12	None
4	H_2O	12	10
5	PEG[c]	12	8
6	PEG/H_2O (1:1)	12	25
7	H_2O/*t*-BuOH (1:1)	12	33
8	H_2O/*t*-BuOH (2:1)	5	60
9	H_2O/*t*-BuOH (3:1)	1	90

[a] Reaction conditions: **7a** (1.0 equiv.), NaN_3 (1.2 equiv.), **2a** (1.0 equiv.), $CuSO_4 \cdot 5H_2O$ (0.1 equiv.) and Na ascorbate (0.3 equiv.).
[b] Isolated yields.
[c] PEG = Poly(ethylene glycol), average mol wt = 200.

2.2. Biological activities

2.2.1. Antimicrobial activity

The antimicrobial activities of all the synthesized triazole linked diaryl sulfone derivatives were tested by the presence or absence of inhibition zones and zone diameter against ten microbial strains: Four Gram-positive bacteria (*S. aureus* ATCC 29213, *Bacillus subtilis* ATCC 663, *Bacillus megaterium* ATCC 9885 and *Sarcina lutea*); three Gram-negative bacteria (*Klebsiella pneumonia* ATCC 13883, *Pseudomonas aeruginosa* ATCC 2795 and *Escherichia coli* 25922); two yeasts (*Candida albicans* NRRL Y-477 and *Saccharomyces cerevisae*) and one fungi (*Aspergillus niger*). The results from the evaluation of antimicrobial effects are summarized in Table 7. The compounds were compared with the standard antibacterial drug Ciprofloxacin and the yeast/antifungal drug Clotrimazole.

It was found that compounds **3a,b**; **6a,b**; **8a–8h**; **9a–9h** showed variable antibacterial activity against Gram-positive and Gram-negative bacteria. For example, compound **3a** showed a zone inhibition of 19 mm against *S. aureus* ATCC 29213 and compounds **3a**; **8b–8d**; **9a,9b** displayed zone inhibitions in the range of 19–20 mm against *S. lutea*. Other compounds showed moderate to poor inhibition against both Gram-positive and Gram-negative bacteria.

The Minimum inhibitory concentration (MIC) of all compounds was also screened as listed in Table 8. All tested compounds showed high MICs, ranging from 50 to 200 μg/mL, against Gram-positive and Gram-negative bacteria compared to the standard drug Ciprofloxacin. Unfortunately, none of the tested compound presented any significant activity against yeast.

Antifungal activity was screened against *A. niger*. The compounds showed good to excellent antifungal activities against the strain, comparable to the standard drug Clotrimazole as shown in Table 7.

Compounds **3b**, **6b**, **8d**, **8e**, **8h**, **9b** and **9d–g** showed the highest zone inhibition against *A. niger* in the range 32–34 mm. The MICs of the new compounds against this pathological strain are tabulated in Table 8. Compounds **3b**, **6b** and **9e–g** were found most effective against the fungal strain with the lowest MIC of 25 μg/mL, similar to Clotrimazole.

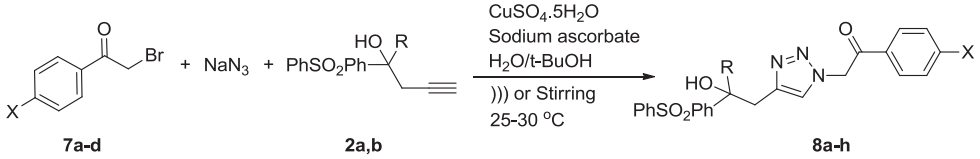
2.2.2. Structure–activity relationships

The results of the antimicrobial screening revealed that the backbone built from ketone **1b** (R = Me in Fig. 2), had consistently better antifungal activity than molecules based on the aldehyde **1a** against *A. niger*, and some are as potent as standard drugs. The modifications added to the hydroxyl group through the ether link at R′ (**6** compared to **3**, and **9** compared to **8**), with a benzyl group or keto benzene derivatives as R″, reduced the activity of the less active compounds but had little impact when R = Me. In addition we found that replacement of the *para*-hydrogen of keto benzene **9h** by phenylsulfonyl, fluoro and bromo functions, as in **9e–g** respectively, increased the antimicrobial activity.

2.2.3. Antioxidant activity

The antioxidant activity of all synthesized compounds were measured against 2,2-diphenyl-1-picrylhydrazyl (DPPH) free radical. The DPPH procedure is one of the most effective methods for evaluating the concentration of radical scavenging materials active by a chain-breaking mechanism [36]. DPPH radical scavenging activity evaluation is a rapid and convenient assay for screening the antioxidant activities of products. Table 9

Table 5
One-pot synthesis of triazoles **8a**–**h**.



Entry	Starting material	X	R	Product	Ultrasound irradiation		Stirring conditions	
					Time (min)	Yield (%)	Time (h)	Yield (%)
1	**7a**	SO_2Ph	H	**8a**	60	90	4	80
2	**7b**	F	H	**8b**	30	96	3	83
3	**7c**	Br	H	**8c**	30	94	3	85
4	**7d**	H	H	**8d**	30	95	3	84
5	**7a**	SO_2Ph	Me	**8e**	60	89	4	79
6	**7b**	F	Me	**8f**	30	94	3	81
7	**7c**	Br	Me	**8g**	30	91	3	80
8	**7d**	H	Me	**8h**	30	92	3	81

summarizes the radical scavenging activities of all compounds, compared to the synthetic antioxidant 4-((1-(4-Methoxyphenyl)-1H-1,2,3-triazol-4-yl)- methoxy)aniline (BHT). It has been reported that the aryl sulfone moiety enhance the antioxidant activity through enhanced expression of antioxidant genes, and this new class of powerful antioxidants might be a potent treatment for Parkinson's disease [37,38]. Several compounds showed an excellent free radical scavenging activity. Compound **8e**, with R′ = H and R″ containing another diaryl sulfone moiety, was the strongest radical scavenger with an IC_{50} value of 20 μg/mL. Moreover compound **8a** showed an excellent radical scavenging activity with IC_{50} at 74 μg/mL. Compounds **9h**, **9c**, **9f** and **9d** also showed very good scavenging activities with IC_{50} at 125, 150, 150 and 175 μg/mL, respectively. The other compounds also showed scavenging activity, but demanded higher concentrations of the compounds.

3. Conclusion

We have synthesized a series of 1,2,3-triazoles linked to an diaryl sulfone moiety exploiting the click chemistry properties of the CuAAC-reaction in aqueous *tert*-butanol under ultrasound irradiation compared to silent conditions. It was observed that ultrasound irradiation improved the yields and decreased the reaction times. All new compounds were characterized by IR, ^1H NMR, ^{13}C NMR and HRMS analysis. All synthesized compounds were screened for antibacterial, antifungal and antioxidant activities. Compounds **3b**; **6b** and **9e**–**g** were found to be the most effective against fungal strains. Other compounds revealed good to moderate antimicrobial activity. In addition, the antioxidant activity of all compounds was measured using the DPPH free radical assay. Compound **8e** was more potent than the standard antioxidant BHT.

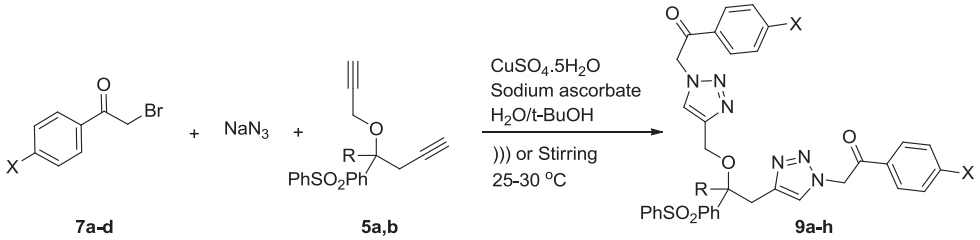
4. Experimental

4.1. Chemistry

4.1.1. General

All chemicals used in this work were purchased from Fluka, VWR or Merck and were used without purification. Melting points were determined on a Bibby Sterilin ltd electrothermal melting

Table 6
One-pot synthesis of bistriazoles **9a**–**h**.



Entry	Starting material	X	R	Product	Ultrasound irradiation		Stirring conditions	
					Time (min)	Yield (%)	Time (h)	Yield (%)
1	**7a**	SO_2Ph	H	**9a**	45	85	4	76
2	**7b**	F	H	**9b**	45	90	3	80
3	**7c**	Br	H	**9c**	45	89	3	87
4	**7d**	H	H	**9d**	45	88	3	78
5	**7a**	SO_2Ph	Me	**9e**	60	83	4	75
6	**7b**	F	Me	**9f**	45	88	3	79
7	**7c**	Br	Me	**9g**	45	85	3	74
8	**7d**	H	Me	**9h**	45	86	3	75

Table 7
Antimicrobial activity expressed as inhibition diameter zones in millimeters (mm) of novel triazoles against the pathological strains based on well diffusion assay.[a]

Entry	*Gram-positive bacteria*				*Gram-negative bacteria*			*Yeast*		*fungi*
	S. aureus ATCC 29213	*B. subtilis* ATCC 6633	*B. megaterium* ATCC 9885	*S. lutea*	*K. pneumoniae* ATCC 13883	*P. aeruginosa* ATCC 27953	*E. coli* ATCC 25922	*C. albicans* NRRL Y-477	*S. cerevisae*	*A. niger*
3a	19	17	14	20	23	20	19	19	17	30
3b	22	16	17	23	24	23	22	19	16	32
6a	14	15	14	17	17	18	19	18	18	30
6b	14	14	17	17	15	19	18	16	14	34
8a	17	20	15	22	19	17	17	15	16	28
8b	14	19	17	20	15	19	14	13	N.A.	32
8c	22	14	19	20	24	25	22	20	17	30
8d	14	19	N.A.	20	22	20	17	12	N.A.	29
8e	N.A.[b]	N.A.	17	14	18	15	19	15	17	32
8f	17	19	17	21	19	22	19	15	N.A.	32
8g	17	17	N.A.	N.A.	19	19	17	15	14	20
8h	18	19	15	22	13	19	14	15	14	32
9a	17	14	N.A.	19	13	14	N.A.	14	N.A.	20
9b	26	19	17	20	16	15	14	22	19	32
9c	17	17	20	22	N.A.	N.A.	17	21	20	20
9d	24	17	20	24	15	23	20	23	22	20
9e	14	14	22	25	19	19	17	15	14	34
9f	27	15	17	26	26	27	25	N.A.	15	34
9g	24	14	23	24	26	26	24	15	14	32
9h	N.A.	16	17	17	23	19	21	15	16	28
Ciprofloxacin	20	22	24	20	25	24	23	N.A.	N.A.	N.A.
Clotrimazole	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.	30	31	33

[a] The experiment was carried out in triplicate and the average zone of inhibition was calculated.
[b] N.A. (no activity).

point apparatus and are uncorrected. Sonochemical reactions were carried out in a Branson B1510 DTH ultrasound cleaning bath (50 kHz, 245 W). The synthesis of O-propargylated compounds was carried out by BRANSON Digital Sonifier 250 (230 V, 50/60 Hz) fitted with a microtip at 40% of maximum amplitude. All reactions were monitored by thin layer chromatography using Fluka GF254 silica gel plates with detection under UV light at 254 and 360 nm. IR spectra were recorded from KBr tablets on a Perkin Elmer 2000 FTIR spectrometer. NMR spectra were recorded on a Varian Mercury VX-300 NMR spectrometer at 300.13 and 75.47 MHz, at ambient temperature unless otherwise stated. ^{1}H NMR and ^{13}C NMR spectra were recorded in deuterated chloroform ($CDCl_3$) or dimethyl sulphoxide (DMSO-d_6) using TMS as internal standard. ^{13}C chemical shifts were related to that of the solvent. High resolution Mass spectra (HRMS) were recorded on an ESI-MS Thermo LTQ Orbitrap XL (Infusion 5 μL/min, resolution: 100 000 at *m*/*z* 400, ca. 10 scans/sample averaged). The CHNS elemental analyses were performed on a vario El analyser (microanalytical unit, Cairo University, Giza, Egypt). The diaryl sulfones **1a,b**, and α-bromoketones **7a**–**d** were prepared according to the literature [30,39].

4.1.2. Procedure for sonicated reactions

*4.1.2.1. General procedure for zinc-mediated homopropargyl alcohols **2a,b**.* A mixture of carbonyl compound **1a** or **b** (1.0 mmol, 1.0 equiv)

Table 8
Minimum inhibitory concentration (μg/mL) against the pathological strains based on two folds serial dilution technique.

Entry	*S. aureus* ATCC 29213	*B. subtilis* ATCC 6633	*B. megaterium* ATCC 9885	*S. lutea*	*K. pneumoniae* ATCC 13883	*P. aeruginosa* ATCC 27953	*E. coli* ATCC 25922	*C. albicans* NRRL Y-477	*S. cerevisae*	*A. niger*
3a	200	200	N.A.	200	200	200	200	200	200	50
3b	200	200	200	200	100	200	200	200	200	25
6a	N.A.	N.A.	N.A.	200	200	200	200	200	200	50
6b	N.A.	N.A.	200	200	N.A.	200	200	200	N.A.	25
8a	200	200	N.A.	100	200	200	N.A.	N.A.	200	50
8b	N.A.	200	200	200	N.A.	200	N.A.	N.A.	N.A.	50
8c	200	N.A.	200	200	100	100	200	200	200	50
8d	N.A.	200	N.A.	200	200	200	200	N.A.	N.A.	100
8e	N.A.	N.A.	200	N.A.	200	N.A.	200	N.A.	200	50
8f	200	200	200	200	200	200	200	N.A.	N.A.	50
8g	200	200	N.A.	N.A.	200	200	200	N.A.	N.A.	200
8h	200	200	N.A.	200	N.A.	200	N.A.	N.A.	N.A.	50
9a	200	N.A.	N.A.	200	N.A.	N.A.	N.A.	N.A.	N.A.	100
9b	100	200	200	200	200	N.A.	N.A.	200	200	50
9c	200	200	200	200	N.A.	N.A.	200	200	200	200
9d	100	200	200	100	100	100	200	200	200	200
9e	N.A.	N.A.	200	100	200	200	200	N.A.	N.A.	25
9f	100	N.A.	200	50	100	100	100	N.A.	N.A.	25
9g	100	N.A.	100	100	100	100	100	N.A.	N.A.	**25**
9h	N.A.	N.A.	200	200	200	200	200	N.A.	200	50
Ciprofloxacin	25	25	25	25	25	25	25	N.A.	N.A.	N.A.
Clotrimazole	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.	25	25	25

Table 9
Anti-oxidant activity measured as IC_{50} by the DPPH procedure.

Compounds	IC_{50} (μg/mL)
3a	200
3b	600
6a	500
6b	600
8a	74
8b	275
8c	500
8d	425
8e	20
8f	425
8g	800
8h	600
9a	600
9b	275
9c	150
9d	175
9e	600
9f	150
9g	N.A.
9h	125
BHT	50

in THF (10.0 mL), Zn (197.9 mg, 3.0 mmol, 3.0 equiv) and $ZnBr_2$ (76.5 mg, 0.3 mmol, 0.3 equiv) in a 50 mL Erlenmeyer flask was subjected to ultrasonic irradiation at 25–30 °C while propargyl bromide (356.9 mg, 3.0 mmol, 3.0 equiv) was slowly added dropwise. The reaction was monitored by TLC. After completion of the reaction (Reaction times as shown in Table 1) saturated aqueous $NaHCO_3$ (4.0 mL) was added, and the resulting mixture was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and the solvent removed under reduced pressure. The residue afforded the corresponding homopropargyl alcohols **2a,b**. The products were purified by column chromatography (SiO_2; ethyl acetate/petroleum ether 1:4).

*4.1.2.1.1. 1-(4-(Phenylsulfonyl)phenyl)but-3-yn-1-ol (**2a**).* White solid; mp. 110–112 °C; IR ν_{max} (cm^{-1}): 3289 (OH), 3255 (≡CH), 2118 (C≡C), 1316, 1155 (SO_2); ^1H NMR (DMSO-d_6, 300 MHz) δ 7.95–7.61 (m, 9H), 5.52 (t, J = 4.2 Hz, 1H, D_2O-exchangeable), 4.77 (t, J = 5.4 Hz, 1H), 2.53–2.59 (m, 2H), 2.08 (t, J = 3.9 Hz, 1H); ^{13}C NMR (DMSO-d_6, 75.46 MHz) δ 149.8, 141.1, 139.5, 133.0, 129.2, 126.93, 126.8, 126.6, 80.7, 72.1, 70.0, 28.1; MS (ESI) m/z 309 $[M+Na]^+$. HRMS (ESI) calcd. for $C_{16}H_{14}O_3S$ + Na $[M+Na]^+$, 309.0556; found 309.0556.

*4.1.2.1.2. 2-(4-(Phenylsulfonyl)phenyl)pent-4-yn-2-ol (**2b**).* Pale yellow oil; IR ν_{max} (cm^{-1}): 3503 (OH), 3296 (≡CH), 2119 (C≡C), 1307, 1156 (SO_2); ^1H NMR (DMSO-d_6, 300 MHz) δ 7.97–7.61 (m, 9H), 5.50 (s, 1H, D_2O-exchangeable), 2.70 (d, J = 2.7 Hz, 1H), 2.49 (d, J = 2.4 Hz, 1H), 2.08 (t, J = 1.35 Hz, 1H), 1.48 (s, 3H); ^{13}C NMR ($CDCl_3$, 75.46 MHz) δ 151.9, 141.5, 140.2, 133.2, 129.3, 127.7, 125.9, 79.4, 73.1, 72.4, 34.4, 29.1; MS (ESI) m/z 323 $[M+Na]^+$. HRMS (ESI) calcd. for $C_{17}H_{16}O_3S$ + Na $[M+Na]^+$, 323.0712; found 323.0713.

*4.1.2.2. General procedure for the synthesis of 1,4-disubstituted 1,2,3-triazoles **3a,b**.* A mixture of terminal alkyne **2a** or **b** (1.0 mmol, 1.0 equiv), benzyl azide (133.2 mg, 1.0 mmol, 1.0 equiv), $CuSO_4 \cdot 5H_2O$ (24.9 mg, 0.1 mmol, 0.1 equiv), and sodium ascorbate (59.4 mg, 0.3 mmol, 0.3 equiv) in H_2O (1.0 mL), and *tert*-butanol (2.0 mL) was sonicated at 25–30 °C while monitored by TLC. After the appropriate time (see Table 2), the mixture was extracted with ethyl acetate (4 × 10 mL). The combined organic extracts were washed with H_2O, dried over anhydrous $MgSO_4$, filtered and concentrated in *vacuo*. The crude product was purified by column chromatography (SiO_2; ethyl acetate/petroleum ether 4:1) to obtain the pure product.

*4.1.2.2.1. 2-(1-Benzyl-1H-1,2,3-triazol-4-yl)-1-(4-(phenylsulfonyl)phenyl)ethanol (**3a**).* White solid; mp. 164–166 °C; IR ν_{max} (cm^{-1}): 3246 (OH), 1595 (C=N), 1315, 1153 (SO_2); ^1H NMR (DMSO-d_6, 300 MHz) δ 7.96–7.18 (m, 14H), 7.80 (s, 1H), 5.68 (d, J = 4.5 Hz, 1H, D_2O-exchangeable), 5.52 (s, 2H), 4.91 (t, J = 4.5 Hz, 1H), 2.95 (d, J = 6.3 Hz, 2H); ^{13}C NMR (DMSO-d_6, 75.46 MHz) δ 151.4, 143.8, 141.3, 139.5, 136.3, 133.7, 129.8, 128.7, 128.0, 127.7, 127.3, 127.2, 123.4, 71.3, 52.6, 35.3; MS (ESI) m/z 420 $[M+H]^+$. HRMS (ESI) calcd. for $C_{23}H_{22}N_3O_3S$ $[M+H]^+$, 420.1379; found 420.1379.

*4.1.2.2.2. 1-(1-Benzyl-1H-1,2,3-triazol-4-yl)-2-(4-(phenylsulfonyl)phenyl)propan-2-ol (**3b**).* White solid; mp. 186–188 °C; IR ν_{max} (cm^{-1}): 3496 (OH), 1596 (C=N), 1320, 1151 (SO_2); ^1H NMR (DMSO-d_6, 300 MHz) δ 7.94–7.07 (m, 14H), 7.59 (s, 1H), 5.47 (s, 2H), 5.43 (s, 1H, D_2O-exchangeable), 3.06 (s, 2H), 1.42 (s, 3H); ^{13}C NMR (DMSO-d_6, 75.46 MHz) δ 154.5, 143.0, 141.4, 138.8, 136.4, 133.6, 129.7, 128.6, 127.9, 127.2, 126.9, 126.5, 123.8, 72.8, 52.4, 39.5, 29.4; MS (ESI) m/z 434 $[M+H]^+$. HRMS (ESI) calcd. for $C_{24}H_{24}N_3O_3S$ $[M+H]^+$, 434.1533; found 434.1538.

*4.1.2.3. General procedure for synthesis of O-propargylated aryl sulfone derivatives **4a,b**; **5a,b**.* A suspension of NaH (96.0 mg, 4.0 mmol, 4.0 equiv) in dry DMF (5.0 mL) in a 50 mL Erlenmeyer flask was added a solution of a diaryl sulfone derivative (Compounds **2a,b**; **3a,b**) (1.0 mmol, 1.0 equiv) in dry DMF (10.0 mL) at −20 °C. Then, propargyl bromide (5.0 mmol) was slowly added dropwise to the reaction mixture under sonication. The mixture was irradiated with the Branson digital sonifier 250 (Microtip, 40% maximum amplitude with pulse on = 15.0 s, pulse off = 5.0 s) at −20 °C for a given time (monitored by TLC) as outlined in Table 3, before the mixture was carefully quenched with H_2O (20 mL) and subsequently extracted with ethyl acetate (4 × 10 mL). The combined organic layers were washed with brine and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure, and the crude residue obtained was purified by column chromatography (SiO_2, ethyl acetate/petroleum ether 1:3) to obtain the propargyl ethers **4a,b**; **5a,b**.

*4.1.2.3.1. 1-Benzyl-4-(2-(4-(phenylsulfonyl)phenyl)-2-(prop-2-yn-1-yloxy)ethyl)-1H-1,2,3-triazole (**4a**).* White solid; mp. 118–120 °C; IR ν_{max} (cm^{-1}): 3268 (≡CH), 2128 (C≡C), 1598 (C=N), 1318, 1160 (SO_2), 1210 (C–O–C); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.96–7.20 (m, 14H), 7.42 (s, 1H), 5.47 (s, 2H), 4.86 (t, J = 5.7 Hz, 1H), 4.08 (dd, J = 16.5, 2.4 Hz, 1H), 3.81 (dd, J = 16.5, 2.4 Hz, 1H), 3.19 (dd, J = 15.0, 8.1 Hz, 1H), 3.01 (dd, J = 15.0, 5.4 Hz, 1H), 2.24 (t, J = 1.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75.46 MHz) δ 146.3, 143.9, 141.2, 134.8, 133.3, 129.3, 129.0, 128.6, 127.9, 127.8, 127.7, 127.6, 122.4, 79.1, 78.9, 74.9, 56.3, 54.0, 34.4; MS (ESI) m/z 458 $[M+H]^+$. HRMS (ESI) calcd. for $C_{26}H_{24}N_3O_3S$ $[M+H]^+$, 458.1533; found 458.1535.

*4.1.2.3.2. 1-Benzyl-4-(2-(4-(phenylsulfonyl)phenyl)-2-(prop-2-yn-1-yloxy)propyl)-1H-1,2,3-triazole (**4b**).* White solid; mp. 140–142 °C; IR ν_{max} (cm^{-1}): 3287 (≡CH), 2121 (C≡C), 1676 (C=N), 1307, 1157 (SO_2), 1219 (C–O–C); ^1H NMR (DMSO-d_6, 300 MHz) δ 7.91–7.10 (m, 15H), 5.44 (s, 2H), 3.91 (s, 2H), 3.07 (s, 2H), 2.45 (t, br, 1H), 1.48 (s, 3H); ^{13}C NMR (DMSO-d_6, 75.46 MHz) δ 150.2, 142.0, 141.1, 139.7, 136.2, 133.7, 129.8, 128.7, 127.9, 127.4, 127.3, 127.3, 123.9, 81.0, 79.5, 76.5, 52.5, 51.4, 37.6, 23.4; MS (ESI) m/z 472 $[M+H]^+$. HRMS (ESI) calcd. for $C_{27}H_{26}N_3O_3S$ $[M+H]^+$, 472.1689; found 472.1692.

*4.1.2.3.3. 1-(Phenylsulfonyl)-4-(1-(prop-2-yn-1-yloxy)but-3-yn-1-yl)benzene (**5a**).* Pale yellow oil; IR ν_{max} (cm^{-1}): 3288 (≡CH), 2118 (C≡C), 1307, 1155 (SO_2), 1181 (C–O–C); ^1H NMR (DMSO-d_6, 300 MHz) δ 8.0–7.60 (m, 9H), 4.73 (t, J = 6.0 Hz, 1H), 4.14 (dd, J = 15.9, 2.4 Hz, 1H), 3.98 (dd, J = 16.2, 2.4 Hz, 1H), 3.47 (t, J = 2.4 Hz, 1H), 2.80 (t, J = 2.4 Hz, 1H), 2.64 (m, 2H); ^{13}C NMR (DMSO-d_6,

75.46 MHz) δ 146.0, 141.0, 140.6, 133.8, 129.9, 128.1, 127.4, 80.2, 79.7, 77.7, 77.2, 73.4, 56.0, 26.2; MS (ESI) *m/z* 347 $[M+Na]^+$. HRMS (ESI) calcd. for $C_{19}H_{16}O_3S$ + Na $[M+Na]^+$, 347.0712; found 347.0714.

*4.1.2.3.4. 1-(Phenylsulfonyl)-4-(2-(prop-2-yn-1-yloxy)pent-4-yn-2-yl)benzene (**5b**).* Yellow oil; IR ν_{max} (cm^{-1}): 3291 (≡CH), 2110 (C≡C), 1307, 1156 (SO_2), 1218 (C–O–C); ^1H NMR (DMSO-d_6, 300 MHz) δ 7.80–7.40 (m, 9H), 3.71 (d, *J* = 6.6 Hz, 2H), 3.08 (t, *J* = 6.0 Hz, 1H), 3.02 (s, 2H), 2.89 (t, *J* = 1.8 Hz, 1H), 1.40 (s, 3H); ^{13}C NMR (DMSO-d_6, 75.46 MHz) δ 149.3, 141.0, 140.1, 133.8, 129.8, 127.4, 127.3, 80.7, 80.2, 78.7, 76.6, 73.8, 51.56, 31.45, 23.4; MS (ESI) *m/z* 361 $[M+Na]^+$. HRMS (ESI) calcd. for $C_{20}H_{18}O_3S$ + Na $[M+Na]^+$, 361.0869; found 361.0870.

*4.1.2.4. General procedure for the synthesis of 1,4-disubstituted 1,2,3-bistriazoles **6a,b***

4.1.2.4.1. Route A. In an Erlenmeyer flask, a mixture of O-propargylated diaryl sulfones **4a** or **b** (1.0 mmol, 1.0 equiv), benzyl azide (133.2 mg, 1.0 mmol, 1.0 equiv), $CuSO_4 \cdot 5H_2O$ (24.9 mg, 0.1 mmol, 0.1 equiv), and sodium ascorbate (59.4 mg, 0.3 mmol, 0.3 equiv) in H_2O (1.0 mL), and *tert*-butanol (2.0 mL) was subjected to ultrasonic irradiation at 25–30 °C for an appropriate time as outlined in Table 2(monitored by TLC), and subsequently extracted with ethyl acetate (4 × 10 mL). The combined organic extracts were washed with H_2O, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude compound was purified by column chromatography (SiO_2, ethyl acetate/petroleum ether 4:1) to obtain the pure product.

4.1.2.4.2. Route B. A mixture of the bis-terminal alkyne **5a** or **b** (1.0 mmol), benzyl azide (266.4 mg, 2.0 mmol, 2.0 equiv), $CuSO_4 \cdot 5H_2O$ (49.8 mg, 0.2 mmol, 0.2 equiv), and sodium ascorbate (118.8 mg, 0.6 mmol, 0.6 equiv) in H_2O (1.0 mL), and *tert*-butanol (2.0 mL) was subjected to the same treatment as in *Route A*.

*4.1.2.4.3. 1-Benzyl-4-((2-(1-benzyl-1H-1,2,3-triazol-4-yl)-1-(4-(phenylsulfonyl)phenyl)ethoxy)-methyl)-1H-1,2,3-triazole (**6a**).* White solid; mp. 131–133 °C; IR ν_{max} (cm^{-1}): 1599 (C=N), 1308, 1162 (SO_2), 1220 (C–O–C); ^1H NMR (DMSO-d_6, 300 MHz) δ 8.04 (s, 1H), 7.97–7.11 (m, 19H), 7.73 (s, 1H), 5.53 (s, 2H), 5.48 (s, 2H), 4.83 (t, *J* = 6.6 Hz, 1H), 4.36 (s, 2H), 3.06 (dd, *J* = 14.7, 8.1 Hz, 1H), 2.95 (dd, *J* = 14.4, 6.0 Hz, 1H); ^{13}C NMR (DMSO-d_6, 75.46 MHz) δ 147.4, 143.8, 143.0, 141.1, 140.2, 136.3, 136.0, 133.8, 129.8, 128.8, 128.7, 128.1, 128.0, 127.9, 127.8, 127.5, 127.4, 124.1, 123.4, 79.1, 61.8, 52.7, 52.5, 33.4; MS (ESI) *m/z* 591 $[M+H]^+$. HRMS (ESI) calcd. for $C_{33}H_{31}N_6O_3S$ $[M+H]^+$, 591.2173; found 591.2179.

*4.1.2.4.4. 1-Benzyl-4-(((1-(1-benzyl-1H-1,2,3-triazol-4-yl)-2-(4-(phenylsulfonyl)phenyl)Propan-2-yl)oxy)methyl)-1H-1,2,3-triazole (**6b**).* White solid; mp. 150–152 °C; IR ν_{max} (cm^{-1}): 1595 (C=N), 1307, 1156 (SO_2), 1219 (C–O–C); ^1H NMR (DMSO-d_6, 300 MHz) δ 7.94–7.10 (m, 21H), 5.48 (s, 2H), 5.43 (s, 2H), 3.06 (s, 2H), 2.07 (s, 2H), 1.42 (s, 3H); ^{13}C NMR ($CDCl_3$, 75.46 MHz) δ 150.1, 145.5, 143.1, 141.4, 140.5, 134.8, 134.5, 133.2, 129.3, 129.1, 129.0, 128.8, 128.6, 128.0, 127.7, 127.6, 127.1, 122.8, 122.1, 79.3, 57.2, 54.1, 53.8, 39.4, 23.1; MS (ESI) *m/z* 605 $[M+H]^+$. HRMS (ESI) calcd. for $C_{34}H_{33}N_6O_3S$ $[M+H]^+$, 605.2329; found 605.2338.

*4.1.2.5. General procedure for the one-pot synthesis of 1,4-disubstituted 1,2,3-monotriazoles **8a–h**.* To a solution of a α-bromoketone (**7a–d**) (1.0 mmol, 1.0 equiv), NaN_3 (78.01 mg, 1.2 mmol, 1.2 equiv), and terminal alkyne **2a** or **b** (1.0 mmol, 1.0 equiv) in H_2O (3.0 mL), and *tert*-butanol (1.0 mL) was added $CuSO_4 \cdot 5H_2O$ (24.9 mg, 0.10 mmol, 0.10 equiv) and sodium ascorbate (59.4 mg, 0.30 mmol, 0.30 equiv). The reaction mixture was sonicated in the water bath of an ultrasonic cleaner at 25–30 °C until the reaction was complete, as indicated by TLC (Reaction times are given in Table 5). Then the organic phase was extracted with dichloromethane (4 × 10 mL). The combined organic extracts were washed with H_2O, dried over anhydrous $MgSO_4$, filtered and concentrated in *vacuo*. The crude product was purified by column chromatography (SiO_2, dichloromethane/methanol 10:1) to obtain the pure product.

*4.1.2.5.1. 2-(4-(2-Hydroxy-2-(4-(phenylsulfonyl)phenyl)ethyl)-1H-1,2,3-triazol-1-yl)-1-(4-(phenyl sulfonyl)phenyl)ethanone (**8a**).* White solid; mp. 221–223 °C; IR ν_{max} (cm^{-1}): 3417 (OH), 1713 (C=O), 1596 (C=N), 1295, 1153 (SO_2); ^1H NMR (DMSO-d_6, 300 MHz) δ 8.23–7.54 (m, 18H), 7.73 (s, 1H), 6.12 (s, 2H), 5.65 (d, *J* = 4.2 Hz, 1H, D_2O-exchangeable), 4.90 (t, *J* = 5.7 Hz, 1H), 2.97 (d, *J* = 6.0 Hz, 2H); ^{13}C NMR (DMSO-d_6, 75.46 MHz) δ 191.8, 151.4, 145.3, 143.4, 141.3, 140.3, 139.5, 137.9, 134.2, 133.6, 129.9, 129.7, 129.5, 127.9, 127.7, 127.3, 124.7, 71.3, 55.9, 35.2; MS (ESI) *m/z* 610 $[M+Na]^+$. HRMS (ESI) calcd. for $C_{30}H_{25}N_3O_6S_2$ + Na $[M+Na]^+$, 610.1077; found 610.1080.

*4.1.2.5.2. 1-(4-Fluorophenyl)-2-(4-(2-hydroxy-2-(4-(phenylsulfonyl)phenyl)ethyl)-1H-1,2,3-triazol-1-yl)ethanone (**8b**).* White solid; mp. 140–142 °C; IR ν_{max} (cm^{-1}): 3452 (OH), 1702 (C=O), 1598 (C=N), 1305, 1153 (SO_2); ^1H NMR (DMSO-d_6, 300 MHz) δ 8.16–7.41 (m, 13H), 7.75 (s, 1H), 6.10 (s, 2H), 5.65 (d, *J* = 4.5 Hz, 1H, D_2O-exchangeable), 4.91 (t, *J* = 5.7 Hz, 1H), 2.98 (d, *J* = 6.3 Hz, 2H); ^{13}C NMR (DMSO-d_6, 75.46 MHz) δ 191.0, 165.5 (d, *J* = 251.1 Hz), 151.4, 143.3, 141.3, 139.5, 133.6, 131.2 (d, *J* = 9.6 Hz), 130.9 (d, *J* = 3.0 Hz), 129.7, 127.3, 124.8, 116.1 (d, *J* = 21.9 Hz), 71.3, 55.6, 35.2; MS (ESI) *m/z* 488 $[M+Na]^+$. HRMS (ESI) calcd for $C_{24}H_{20}FN_3O_4S$ + Na $[M+Na]^+$, 488.1051; found 488.1049.

*4.1.2.5.3. 1-(4-Bromophenyl)-2-(4-(2-hydroxy-2-(4-(phenylsulfonyl)phenyl)ethyl)-1H-1,2,3-triazol-1-yl)ethanone (**8c**).* White solid; mp. 190–192 °C; IR ν_{max} (cm^{-1}): 3420 (OH), 1703 (C=O), 1586 (C=N), 1306, 1154 (SO_2); ^1H NMR (DMSO-d_6, 300 MHz) δ 7.99–7.59 (m, 13H), 7.80 (s, 1H), 6.09 (s, 2H), 5.69 (s broad, 1H, D_2O-exchangeable), 4.94 (broad, 1H), 2.99 (s broad, 2H); ^{13}C NMR (DMSO-d_6, 75.46 MHz) δ 191.6, 151.4, 141.3, 139.4, 137.9, 133.6, 133.2, 132.0, 130.1, 129.7, 128.23, 127.2, 71.23, 55.6, 35.2; MS (ESI) *m/z* 548 $[M+Na]^+$. HRMS (ESI) calcd. for $C_{24}H_{20}BrN_3O_4S$ + Na $[M+Na]^+$, 548.0250; found 548.0252.

*4.1.2.5.4. 2-(4-(2-Hydroxy-2-(4-(phenylsulfonyl)phenyl)ethyl)-1H-1,2,3-triazol-1-yl)-1-phenylethanone (**8d**).* White solid; mp. 160–162 °C; IR ν_{max} (cm^{-1}): 3307 (OH), 1701 (C=O), 1596 (C=N), 1309, 1154 (SO_2); ^1H NMR (DMSO-d_6, 300 MHz) δ 8.06–7.56 (m, 14H), 7.76 (s, 1H), 6.10 (s, 2H), 5.67 (d, *J* = 4.5 Hz, 1H, D_2O-exchangeable), 4.92 (t, *J* = 6.3 Hz, 1H), 2.99 (d, *J* = 6.0 Hz, 2H); ^{13}C NMR (DMSO-d_6, 75.46 MHz) δ 192.3, 151.4, 143.3, 141.3, 139.5, 134.2, 133.6, 129.8, 129.0, 128.2, 127.3, 124.9, 71.4, 55.7, 35.2; MS (ESI) *m/z* 470 $[M+Na]^+$. HRMS (ESI) calcd. for $C_{24}H_{21}N_3O_4S$ + Na $[M+Na]^+$, 470.1142; found 470.1142.

*4.1.2.5.5. 2-(4-(2-Hydroxy-2-(4-(phenylsulfonyl)phenyl)propyl)-1H-1,2,3-triazol-1-yl)-1-(4-(phenylsulfonyl)phenyl)ethanone (**8e**).* White solid; mp. 205–207 °C; IR ν_{max} (cm^{-1}): 3431 (OH), 1710 (C=O), 1595 (C=N), 1307, 1156 (SO_2); ^1H NMR (DMSO-d_6, 300 MHz) δ 8.19–7.58 (m, 19H), 6.08 (s, 2H), 5.45 (s broad, 1H), 3.10 (s, 2H), 1.41 (s, 3H); ^{13}C NMR (DMSO-d_6, 75.46 MHz) δ 191.8, 154.7, 145.2, 141.4, 140.2, 138.8, 137.9, 134.2, 133.6, 129.9, 129.7, 129.4, 127.9, 127.6, 127.2, 126.9, 126.5, 72.7, 55.9, 39.2, 29.2; MS (ESI) *m/z* 624 $[M+Na]^+$. HRMS (ESI) calcd. for $C_{31}H_{27}N_3O_6S_2$ + Na $[M+Na]^+$, 624.1233; found 624.1236.

*4.1.2.5.6. 1-(4-Fluorophenyl)-2-(4-(2-hydroxy-2-(4-(phenylsulfonyl)phenyl)propyl)-1H-1,2,3-triazol-1-yl)ethanone (**8f**).* White solid; mp. 183–185 °C; IR ν_{max} (cm^{-1}): 3404 (OH), 1702 (C=O), 1598 (C=N), 1307, 1156 (SO_2); ^1H NMR (DMSO-d_6, 300 MHz) δ 8.13–7.40 (m, 14H), 6.05 (s, 2H), 5.48 (s broad, 1H, D_2O-exchangeable), 3.10 (s, 2H), 1.43 (s, 3H); ^{13}C NMR ($CDCl_3$, 75.46 MHz) δ 188.6, 166.4 (d, *J* = 256.0 Hz), 153.3, 141.4, 139.4, 133.1, 130.8 (d, *J* = 9.6 Hz), 130.2 (d, *J* = 3.0 Hz), 129.2, 127.5, 126.0, 116.3 (d, *J* = 21.9 Hz), 74.1, 55.3, 39.2, 29.8; MS (ESI) *m/z* 502 $[M+Na]^+$. HRMS (ESI) calcd. for $C_{25}H_{22}FN_3O_4S$ + Na $[M+Na]^+$, 502.1207; found 502.1206.

*4.1.2.5.7. 1-(4-Bromophenyl)-2-(4-(2-hydroxy-2-(4-(phenylsulfonyl)phenyl)propyl)-1H-1,2,3-triazol-1-yl)ethanone (**8g**).* White solid; mp. 179–181 °C; IR ν_{max} (cm^{-1}): 3418 (OH), 1702 (C=O), 1586 (C=N), 1307, 1155 (SO_2); ^1H NMR (DMSO-d_6, 300 MHz) δ 7.96–7.59 (m, 14H), 6.04 (s, 2H), 5.45 (s, 1H, D_2O-exchangeable), 3.10 (s, 2H), 1.42 (s, 3H); ^{13}C NMR (DMSO-d_6, 75.46 MHz) δ 191.5, 154.7, 141.3, 138.7, 133.5, 133.2, 131.9, 130.1, 129.7, 127.2, 126.9, 126.5, 72.6, 55.4, 39.2, 29.3; MS (ESI) *m/z* 562 $[M+Na]^+$. HRMS (ESI) calcd. for $C_{25}H_{22}BrN_3O_4S$ + Na $[M+Na]^+$, 562.0407; found 562.0409.

*4.1.2.5.8. 2-(4-(2-Hydroxy-2-(4-(phenylsulfonyl)phenyl)propyl)-1H-1,2,3-triazol-1-yl)-1-phenylethanone (**8h**).* White solid; mp. 140–142 °C; IR ν_{max} (cm^{-1}): 3396 (OH), 1703 (C=O), 1596 (C=N), 1307, 1155 (SO_2); ^1H NMR (DMSO-d_6, 300 MHz) δ 8.05–7.58 (m, 15H), 6.07 (s, 2H), 5.49 (s broad, 1H, D_2O-exchangeable), 3.12 (s, 2H), 1.44 (s, 3H); ^{13}C NMR (DMSO-d_6, 75.46 MHz) δ 192.2, 154.8, 141.4, 138.8, 134.2, 133.6, 129.7, 128.9, 128.1, 127.3, 126.9, 126.6, 72.8, 55.7, 39.5, 29.3; MS (ESI) *m/z* 484 $[M+Na]^+$. HRMS (ESI) calcd for $C_{25}H_{23}N_3O_4S$ + Na $[M+Na]^+$, 484.1301; found 484.1300.

*4.1.2.6. General procedure for the one-pot synthesis of 1,4-disubstituted 1,2,3-bistriazoles **9a**–**h**.* To a solution of a α-bromoketone (**7a**–**d**) (2.0 mmol, 2.0 equiv), NaN_3 (156.02 mg, 2.4 mmol, 2.4 equiv), and bis-terminal alkyne **5a** or **b** (1.0 mmol, 1.0 equiv) in H_2O (3.0 mL), and *tert*-butanol (1.0 mL) was added $CuSO_4 \cdot 5H_2O$ (49.8 mg, 0.20 mmol, 0.20 equiv) and sodium ascorbate (118.8 mg, 0.60 mmol, 0.60 equiv). The reaction mixture was sonicated in the water bath of an ultrasonic cleaner at 25–30 °C until the reaction was complete, as indicated by TLC (Reaction times are given in Table 6). Then the organic phase was extracted with dichloromethane (4 × 10 mL). The combined organic extracts were washed with H_2O, dried over anhydrous $MgSO_4$, filtered and concentrated in *vacuo*. The crude product was purified by column chromatography (SiO_2, dichloromethane/methanol 10:1) to obtain the pure product.

*4.1.2.6.1. 2-(4-((2-(1-(2-Oxo-2-(4-(phenylsulfonyl)phenyl)ethyl)-1H-1,2,3-triazol-4-yl)-1-(4-(phenylsulfonyl)phenyl)ethoxy)methyl)-1H-1,2,3-triazol-1-yl)-1-(4-(phenylsulfonyl)phenyl)ethanone (**9a**).* White solid; mp. 145–147 °C; IR ν_{max} (cm^{-1}): 1709 (C=O), 1596 (C=N), 1307, 1156 (SO_2), 1222 (C–O–C); ^1H NMR (DMSO-d_6, 300 MHz, 50 °C) δ 8.21–7.56 (m broad, 29H), 6.16 (s broad, 2H), 6.11 (s broad, 2H), 4.88 (t broad, 1H), 4.43 (s broad, 2H), 3.06 (d broad, 2H). MS (ESI) *m/z* 927 $[M+H]^+$. HRMS (ESI) calcd. for $C_{47}H_{39}N_6O_9S_3$ $[M+H]^+$, 927.1935; found 927.1925. Anal. calcd. for $C_{47}H_{38}N_6O_9S_3$: C, 60.89; H, 4.13; N, 9.07; S, 10.38%. Found: C, 60.96; H, 4.10; N, 9.10; S, 10.35%.

*4.1.2.6.2. 1-(4-Fluorophenyl)-2-(4-((2-(1-(2-(4-fluorophenyl)-2-oxoethyl)-1H-1,2,3-triazol-4-yl)-1-(4-(phenylsulfonyl)phenyl)ethoxy)methyl)-1H-1,2,3-triazol-1-yl)ethanone (**9b**).* White solid; mp. 202–204 °C; IR ν_{max} (cm^{-1}): 1700 (C=O), 1598 (C=N), 1307, 1156 (SO_2), 1232 (C–O–C); ^1H NMR (DMSO-d_6, 300 MHz, 50 °C) δ 8.09–7.33 (m broad, 19H), 6.09 (s, 2H), 6.04 (s, 2H), 4.96 (t broad, 1H), 4.51 (s broad, 2H), 3.12 (s broad, 2H); ^{13}C NMR (DMSO-d_6, 75.46 MHz, 50 °C) δ 189.9, 189.8, 164.9 (d, J = 251.9 Hz), 164.8 (d, J = 252.0 Hz), 146.7, 140.7, 139.8, 132.8, 130.5 (d, J = 9.5 Hz), 130.4 (d, J = 9.4 Hz), 128.9, 127.2, 126.8, 126.6, 115.3 (d, J = 22.0 Hz), 115.2 (d, J = 21.9 Hz), 78.5, 61.7, 55.1, 55.0, 32.9; MS (ESI) *m/z* 705 $[M+Na]^+$. HRMS (ESI) calcd. for $C_{35}H_{28}F_2N_6O_5S$ + Na $[M+Na]^+$, 705.1702; found 705.1703; Anal. calcd. for $C_{35}H_{28}F_2N_6O_5S$: C, 61.58; H, 4.13; N, 12.31; S, 4.70%. Found: C, 61.66; H, 4.11; N, 12.29; S, 4.67%.

*4.1.2.6.3. 1-(4-Bromophenyl)-2-(4-((2-(1-(2-(4-bromophenyl)-2-oxoethyl)-1H-1,2,3-triazol-4-yl)-1-(4 (phenylsulfonyl)phenyl)ethoxy)methyl)-1H-1,2,3-triazol-1-yl)ethanone (**9c**).* White solid; mp. 200–202 °C; IR ν_{max} (cm^{-1}): 1702 (C=O), 1586 (C=N), 1306, 1154 (SO_2), 1225 (C–O–C); ^1H NMR (DMSO-d_6, 300 MHz, 50 °C) δ 7.93–7.60 (m broad, 19H), 6.10 (s broad, 2H), 6.01 (s broad, 2H), 4.94 (t broad, 1H), 4.50 (s broad, 2H), 3.11 (d broad, 2H). MS (ESI) *m/z* 802 $[M+Na]^+$. HRMS (ESI) calcd. for $C_{35}H_{28}Br_2N_6O_5S$ + Na $[M+Na]^+$, 825.0101; found 825.0109; Anal. calcd. for $C_{35}H_{28}Br_2N_6O_5S$: C, 52.25; H, 3.51; N, 10.45; S, 3.99%. Found: C, 52.20; H, 3.49; N, 10.50; S, 4.05%.

*4.1.2.6.4. 2-(4-((2-(1-(2-Oxo-2-phenylethyl)-1H-1,2,3-triazol-4-yl)-1-(4-(phenylsulfonyl) phenyl)ethoxy)methyl)-1H-1,2,3-triazol-1-yl)-1-phenylethanone (**9d**).* White solid; mp. 180–182 °C; IR ν_{max} (cm^{-1}): 1701 (C=O), 1596 (C=N), 1307, 1154 (SO_2), 1227 (C–O–C); ^1H NMR (DMSO-d_6, 300 MHz, 50 °C) δ 8.02–7.50 (m, 21H), 6.14 (s, 2H), 6.09 (s, 2H), 4.88 (t, J = 6.6 Hz, 1H), 4.49 (d, J = 12.0 Hz, 1H), 4.40 (d, J = 12.0 Hz, 1H), 3.13 (dd, J = 15.0, 7.5 Hz, 1H), 3.04 (dd, J = 15.0, 5.7 Hz, 1H); ^{13}C NMR (DMSO-d_6, 75.46 MHz, 50 °C) δ 191.8, 191.6, 146.9, 143.2, 142.3, 140.6, 139.8, 133.8, 133.7, 133.6, 133.5, 133.3, 129.3, 128.5, 128.4, 127.6, 127.5, 127.1, 126.9, 125.2, 124.2, 78.5, 61.4, 55.3, 55.2, 33.1; MS (ESI) *m/z* 669 $[M+Na]^+$. HRMS (ESI) calcd. for $C_{35}H_{30}N_6O_5S$ + Na $[M+Na]^+$, 669.1891; found 669.1892.

*4.1.2.6.5. 2-(4-(((1-(1-(2-Oxo-2-(4-(phenylsulfonyl)phenyl)ethyl)-1H-1,2,3-triazol-4-yl)-2-(4-(phenylsulfonyl)phenyl)propan-2-yl)oxy)methyl)-1H-1,2,3-triazol-1-yl)-1-(4-(phenylsulfonyl)phenyl)ethanone (**9e**).* White solid; mp. 220–222 °C; IR ν_{max} (cm^{-1}): 1709 (C=O), 1595 (C=N), 1307, 1156 (SO_2), 1222 (C–O–C); ^1H NMR (DMSO-d_6, 300 MHz, 50 °C) δ 8.21–7.62 (m broad, 29H), 6.12 (s broad, 2H), 6.01 (s broad, 2H), 4.43 (s broad, 2H), 3.09 (s broad, 2H), 1.61 (s broad, 3H); MS (ESI) *m/z* 941 $[M+H]^+$. HRMS (ESI) calcd. for $C_{48}H_{41}N_6O_9S_3$ $[M+H]^+$, 941.2092; found 941.2082; Anal. calcd. for $C_{48}H_{40}N_6O_9S_3$: C, 61.26; H, 4.28; N, 8.93; S, 10.22%. Found: C, 61.19; H, 4.21; N, 9.01; S, 10.25%.

*4.1.2.6.6. 1-(4-Fluorophenyl)-2-(4-(((1-(1-(2-(4-fluorophenyl)-2-oxoethyl)-1H-1,2,3-triazol-4-yl)-2-(4-(phenylsulfonyl)phenyl)propan-2-yl)oxy)methyl)-1H-1,2,3-triazol-1-yl)ethanone (**9f**).* White solid; mp. 210–212 °C; IR ν_{max} (cm^{-1}): 1702 (C=O), 1598 (C=N), 1307, 1157 (SO_2), 1231 (C–O–C); ^1H NMR (DMSO-d_6, 300 MHz, 50 °C) δ 8.09–7.30 (m broad, 19H), 6.18 (s broad, 2H), 6.07 (s broad, 2H), 4.44 (s broad, 2H), 3.34 (s broad, 2H), 1.62 (s broad, 3H); MS (ESI) *m/z* 719 $[M+Na]^+$. HRMS (ESI) calcd. for $C_{36}H_{30}F_2N_6O_5S$ + Na $[M+Na]^+$, 719.1859; found 719.1862; Anal. calcd. for $C_{36}H_{30}F_2N_6O_5S$: C, 62.06; H, 4.34; N, 12.06; S, 4.60%. Found: C, 62.15; H, 4.31; N, 12.03; S, 4.56%.

*4.1.2.6.7. 1-(4-Bromophenyl)-2-(4-(((1-(1-(2-(4-bromophenyl)-2-oxoethyl)-1H-1,2,3-triazol-4-yl)-2-(4-(phenylsulfonyl)phenyl)propan-2-yl)oxy)methyl)-1H-1,2,3-triazol-1-yl)ethanone (**9g**).* White solid; mp. 217–219 °C; IR ν_{max} (cm^{-1}): 1702 (C=O), 1586 (C=N), 1306, 1156 (SO_2), 1224 (C–O–C); ^1H NMR (DMSO-d_6, 300 MHz, 50 °C) δ 7.91–7.61 (m broad, 19H), 6.07 (s broad, 2H), 5.98 (s broad, 2H), 4.48 (s broad, 2H), 3.10 (s broad, 2H), 1.65 (s broad, 3H); MS (ESI) *m/z* 817 $[M+H]^+$. HRMS (ESI) calcd. for $C_{36}H_{31}Br_2N_6O_5S$ $[M+H]^+$, 817.0438; found 817.0432; Anal. calcd. for $C_{36}H_{30}Br_2N_6O_5S$: C, 52.82; H, 3.69; N, 10.27; S, 3.92%. Found: C, 52.91; H, 3.64; N, 10.22; S, 3.97%.

*4.1.2.6.8. 2-(4-(((1-(1-(2-Oxo-2-phenylethyl)-1H-1,2,3-triazol-4-yl)-2-(4-(phenylsulfonyl)phenyl)propan-2-yl)oxy)methyl)-1H-1,2,3-triazol-1-yl)-1-phenylethanone (**9h**).* White solid; mp. 207–209 °C; IR ν_{max} (cm^{-1}): 1702 (C=O), 1596 (C=N), 1307, 1156 (SO_2), 1227 (C–O–C); ^1H NMR (DMSO-d_6, 300 MHz, 50 °C) δ 8.03–7.51 (m, 21H), 6.09 (s, 2H), 5.99 (s, 2H), 4.52 (d, J = 12.0 Hz, 1H), 4.43 (d, J = 12.0 Hz, 1H), 3.27 (s, 2H), 1.64 (s, 3H); ^{13}C NMR (DMSO-d_6, 75.46 MHz, 50 °C) δ 191.9, 191.8, 150.6, 144.3, 141.6, 141.1, 139.5, 134.1, 134.0, 133.8, 133.8, 133.3, 129.4, 128.7, 128.6, 127.8, 127.2, 127.0, 126.9, 125.1, 124.9, 78.7, 56.8, 55.5, 55.3, 37.6, 23.6; MS (ESI) *m/z* 683 $[M+Na]^+$. HRMS (ESI) calcd. for $C_{36}H_{32}N_6O_5S$ + Na $[M+Na]^+$, 683.2047; found 683.2051.

4.1.3. Procedure for silent reactions

All previous reactions were performed with the same reactants at same temperature and same scale as shown above, but without

ultrasound irradiation. The reactions were run under stirring for the appropriate time as indicated by TLC (see Tables 1–6). The products were obtained and purified as described for the reactions under ultrasound.

4.2. Biological testing

4.2.1. Antimicrobial activity

The compounds were individually tested against a panel of gram positive and gram negative bacterial pathogens, yeast and fungi. Antimicrobial tests were carried out by the agar well diffusion method [40] using 100 μL of suspension containing 1×10^8 CFU/mL of pathological tested bacteria and 1×10^6 CFU/mL of yeast and fungi spread on nutrient agar (NA) and Sabouraud dextrose agar (SDA) respectively. After the media had cooled and solidified, wells (10 mm in diameter) were made in the solidified agar and loaded with 100 μL of test compound solution; prepared by dissolving 200 mg of the chemical compound in 1 mL of dimethyl sulfoxide (DMSO). The inculcated plates were then incubated for 24 h at 37 °C for bacteria (48 h at 28 °C for fungi). Negative controls were prepared using DMSO employed for dissolving the tested compound. Ciprofloxacin (50 mg/mL) and Clotrimazole (50 mg/mL) were used as standard for antibacterial and antifungal activity respectively. After incubation time, antimicrobial activity was evaluated by measuring the zone of inhibition against the test organisms and compared with that of the standard. The observed zone of inhibition is presented in Table 7. Antimicrobial activities were expressed as inhibition diameter zones in millimeters (mm). The experiments were carried out in triplicate and the average zone of inhibition was calculated.

4.2.2. Minimum inhibitory concentration (MIC)

The antimicrobial activity of the active compounds (having inhibition zones (IZ) $\geq$ 16 mm) was then evaluated using the two fold serial dilution technique [41]. Two fold serial dilutions of the test compound solutions were prepared using the proper nutrient broth. The final concentrations of the solutions were 200, 100, 50 and 25 μg/mL. Each 5 mL received 0.1 mL of the appropriate inoculum and incubated at 37 °C for 24 h (48 h at 28 °C for fungi). The lowest concentration showing no growth was taken as the minimum inhibitory concentration (MIC). The observed zones of inhibition are presented in Table 8.

4.2.3. Antioxidant activity

4.2.3.1. DPPH free radical scavenging activity. The hydrogen atom or electron donation ability of the corresponding compounds was measured from the bleaching of the purple colored methanolic solution of DPPH. This spectrophotometric assay uses stable radical diphenylpicrylhydrazyl (DPPH) as a reagent. One hundred microliters of various sample concentrations were added to 5 mL of 0.004% methanolic solution of diphenylpicrylhydrazyl (DPPH). After 60 min of incubation in dark, the absorbance was read against a blank at 517 nm. Inhibition free radical DPPH in percent ($I\%$) was calculated as in Eq (1) :

$$I\% = (A_{\text{blank}} - A_{\text{sample}})/(A_{\text{blank}}) \times 100 \quad (1)$$

where A_{blank} is the absorbance of the control reaction (containing all reagents except the test compound), and A_{sample} is the absorbance of the test sample [42,43].

For determination of IC_{50} (The concentration that make 50% inhibition of the DPPH color), different concentrations of the chemical compounds were dissolved in methanol to obtain final concentrations ranging from 50 to 600 μg/mL. An inhibition curve was made against concentration and IC_{50} was determined. All results of antioxidant activity are summarized in Table 9.

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Appendix A. Supplementary data

^{1}H and ^{13}C NMR spectra of all new compounds in this article can be found in the online version at http://dx.doi.org/10.1016/j.ejmech.2014.07.042.

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