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Synthesis and biological evaluation of quinoline-triazole and quinolone-triazole conjugates

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Abstract: One-pot synthesis of novel quinoline- and quinolone-substituted 1,2,3-triazoles has been performed from the key intermediates, quinoline- and quinolone-substituted propargyl derivatives **1**–**3** (48%–88% yields). The antioxidant properties of the newly synthesized compounds, **1a**–**1c**, **2a**–**2c**, and **3a**–**3c**, were evaluated by monitoring DPPH (2,2-diphenyl-1-picrylhydrazyl) radical scavenging abilities, metal chelating effects, and reducing power. The scavenging effects of compounds on the free radical decreased in the order of **3b** > **3a** > **1b** and were found to be 36.3%, 34.9%, and 27.6% at the concentration of 500 μg/mL, respectively. All of the compounds showed low chelating capacity. Furthermore, the antibacterial activity was studied against gram-positive and gram-negative bacteria and the DNA binding ability of the compounds was evaluated with calf thymus DNA using agarose gel electrophoresis.

Key words: Quinoline, quinolone, triazole, antioxidant, antibacterial

1. Introduction

Triazole-containing compounds possess important pharmacological activities including antimicrobial,[1] anticancer,[2] antidepressant,[3] antiinflammatory,[4] anticonvulsant,[5] anti-HIV,[6] and antifungal[7] activities. A triazole derivative has a moderate dipole character, hydrogen bonding capability, rigidity, and remarkable metabolic stability. The Huisgen 1,3-dipolar cycloadditions of azides and alkynes yielding 1,4-disubstituted 1,2,3-triazoles are regioselective.[8] One-pot multicomponent synthesis of 1,4-disubstituted 1,2,3-triazoles has received much attention because it not only minimizes the time and the cost of the synthesis, but also avoids the isolation of potentially toxic and explosive organic azides formed in situ.[9,10]

On the other hand, quinoline derivatives are known to show diverse biological properties such as antioxidant, antibiotic, cardiovascular, antiplatelet, anticancer (Figure 1), antimicrobial, receptor antagonist, and protein kinase inhibition.[11–17]

Quinolones are among the most widely prescribed antimicrobial agents, such as norfloxacin (Figure 1), since they are generally well tolerated with an excellent safety profile, favorable pharmacokinetic characteristics, and broad antibacterial spectrum against genitourinary infections and common respiratory tract pathogens.[18–20]

Molecular conjugation has been known for the rational design of new biologically active entities by fusion of compounds and/or pharmacophoric units recognized and derived from known bioactive molecules.[21]

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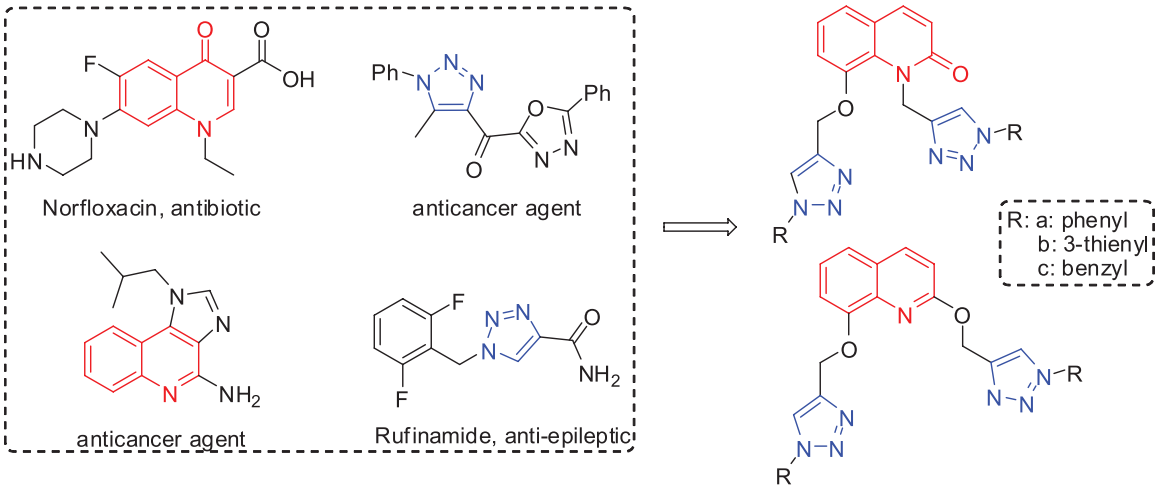


Figure 1. Design of novel conjugate compounds.

Inspired by the biological profiles of 1,2,3-triazole derivatives and the quinoline nucleus, together with their increasing importance in the pharmaceutical field, here we aimed to synthesize quinoline-based mono- and bis-triazole derivatives to obtain certain new chemical entities with two active pharmacophores in a single molecular framework for intensified biological activities. We also incorporated a triazole fragment into the N-1 position of quinolones and changed different substituents on the triazole ring to generate a novel class of quinolone-triazole systems (Figure 1).

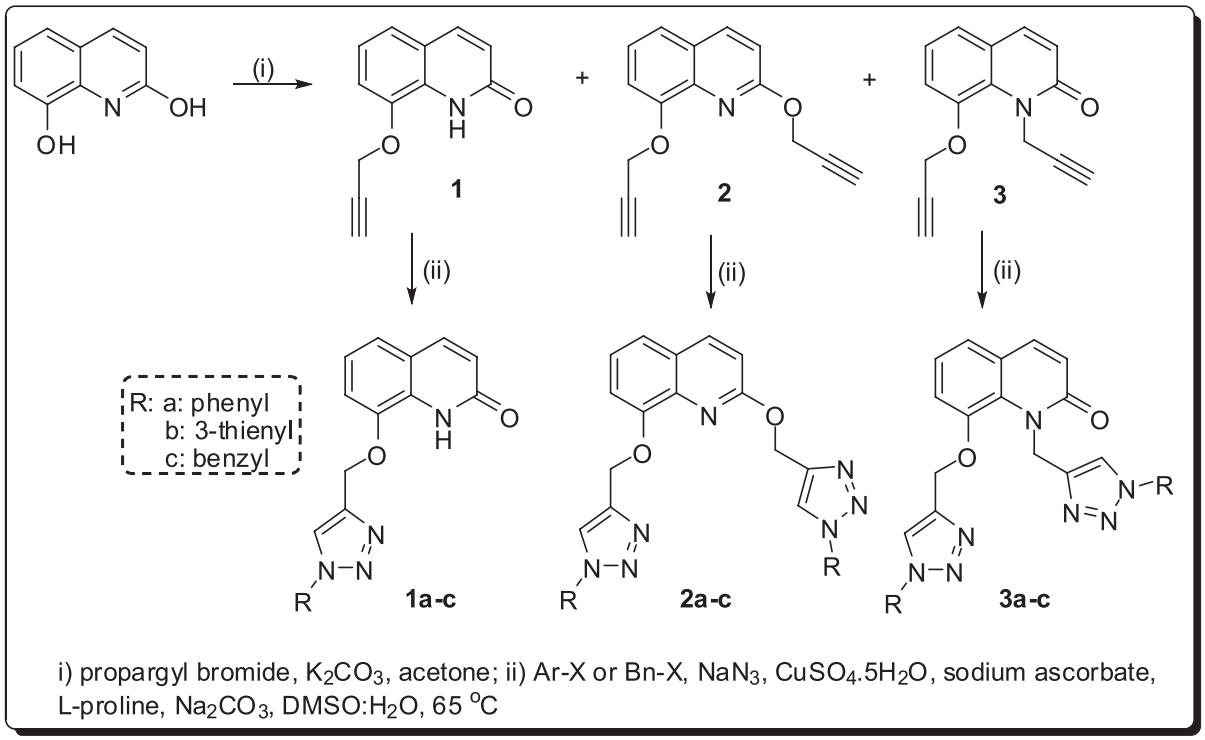
2. Results and discussion

2.1. Chemistry

The quinoline-based propargyl derivatives **1**–**3**, which were used as templates for the construction of triazole scaffolds, were synthesized by the addition of propargyl bromide to commercially available quinoline-2,8-diol (Scheme). Mono and bis O-propargylated quinoline derivatives **1** and **2** and also O,N-propargylated quinolone derivative **3** were obtained from propargylation reaction of quinoline-2,8-diol with K_2CO_3.

Terminal acetylenes on quinoline derivatives **1**–**3** make them valuable candidates for one-pot synthesis of the target triazole structures. The classical copper(I)-catalyzed azide-alkyne cycloaddition (CuAAC) reaction has been generally considered as the most striking method for regioselective synthesis of 1,4-disubstituted 1,2,3-triazoles, which was independently discovered by the groups of Sharpless and Meldal.[22] An alternative and efficient method based upon Lewis base-promoted CuI-catalyzed coupling for regioselective one-pot synthesis of 1,4-disubstituted 1,2,3-triazoles was reported.[23–25] Aliphatic and aromatic azides can easily be generated from the corresponding halides as intermediates used in a one-pot method and converted into the desired triazole derivatives without isolation. The operational simplicity of this method makes it attractive for a wide variety of applications. Initially, 8-(prop-2-ynyloxy)quinolin-2-(1H)-one, **1**, was employed in a one-pot, two-step procedure[23] by reaction with sodium azide and a halide under the action of 20% mol L-proline, 20% mol Na_2CO_3, 10% mol sodium ascorbate, and 10% mol $CuSO_4$ in DMSO/H_2O (Scheme). The role of Na_2CO_3 is to convert Lewis base L-proline to its sodium salt, which catalyzes the reaction. Various aromatic and benzylic halides were reacted under the optimized conditions and finally novel 1,4-disubstituted 1,2,3-triazole derivatives **1a**–**1c** were obtained in good yields (60%–88%) (Table). Next, 2,8-bis(prop-2-ynyloxy)quinoline, **2**,

was subjected to one-pot synthesis under the same conditions and quinoline-substituted bis triazole derivatives **2a**–**2c** were isolated with good results (Table).



Scheme. Synthesis of target triazole derivatives.

The successful synthesis of quinoline-substituted triazole derivatives **1a**–**1c** and **2a**–**2c** prompted us to investigate the construction of quinolone-substituted triazole compounds from 1-(prop-2-ynyl)-8-(prop-2-ynyloxy)quinolin-2(1H)-one, **3**. One-pot triazole reactions afforded quinolone-triazole conjugates **3a**–**3c** in moderate to good yields (48%–82%) (Table).

All synthesized compounds were characterized by ^{1}H and ^{13}C NMR spectroscopy. In the ^{1}H NMR spectrum of compound **1**, a broad singlet at 9.34 ppm shows the NH proton, and the triplet signal at 2.57 ppm belongs to the acetylenic proton. In the ^{13}C NMR spectrum, carbonyl resonates at 161.9 ppm and two peaks at 77.5 and 76.7 ppm indicate acetylenic carbons. In the ^{1}H NMR spectrum of triazole **1a**, the disappearance of the peak belonging to the acetylenic proton and the formation of a new signal at 8.43 ppm indicate the formation of a triazole ring. Also in the ^{13}C NMR spectrum, two acetylenic carbon peaks resonating at 77.5 and 76.7 ppm disappeared while two new olefinic carbon peaks were observed.

2.2. Antioxidant activity

2.2.1. DPPH Assay

Free radicals and reactive oxygen species that are continuously produced in cells are important factors for tissue damage in living organisms.[26] DPPH (2,2-diphenyl-1-picrylhydrazyl) is a steady free radical commonly used for the investigation of organic and inorganic samples that have potential antioxidant capability. Figure 2 shows that the percentage scavenging capabilities of the compounds increased from 4.09% to 28.71%, from 5.14% to

Table. Result of the one-pot synthesis of triazole derivatives.

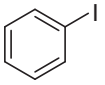
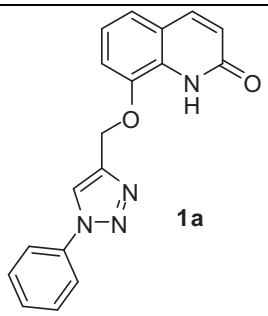
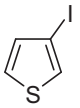
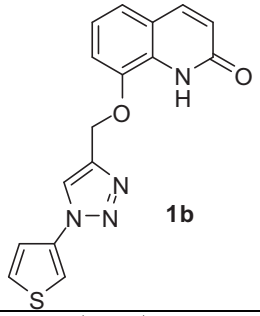
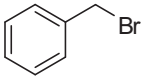
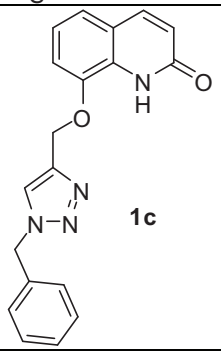
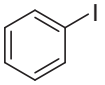
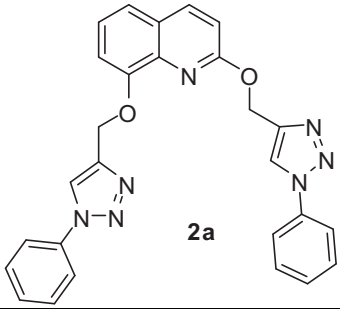
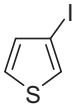
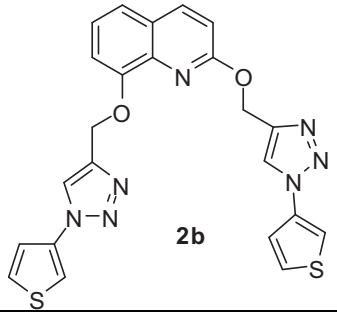
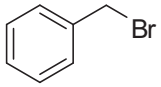
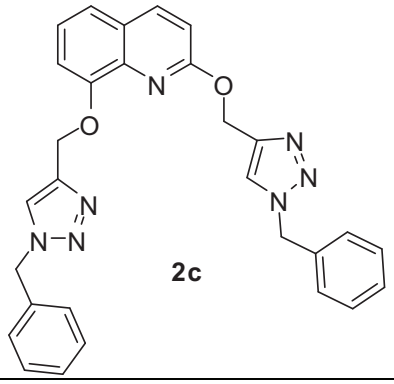
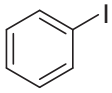
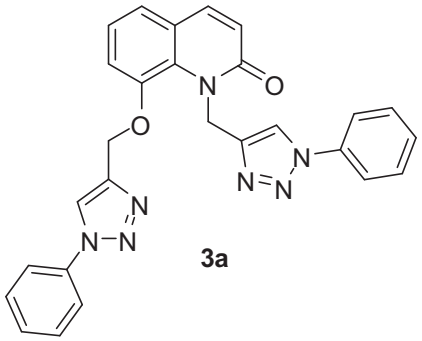
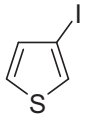
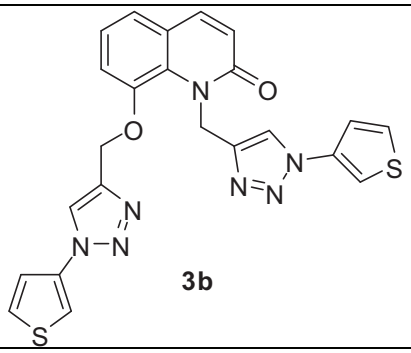
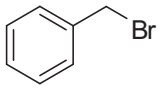
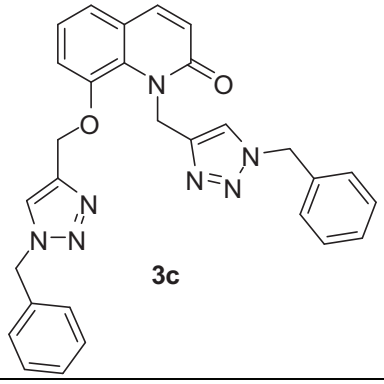
Entry	Ar-propargyl	R-X and Bn-X	Product	Yield (%)
1	1		 **1a**	82
2	1		 **1b**	60
3	1		 **1c**	76
4	2		 **2a**	80
5	2		 **2b**	72

Table. Contunied.

Entry	Ar-propargyl	R-X and Bn-X	Product	Yield (%)
6	2		 **2c**	75
7	3		 **3a**	88
8	3		 **3b**	60
9	3		 **3c**	48

32.59%, and from 8.54% to 36.33% with the increase in concentration of 25–500 μg/mL for **1b**, **3a**, and **3b**, respectively. Other derivatives exhibited weak activities. Trolox was used as a standard and showed higher scavenging capacity than the present compounds at all concentrations.

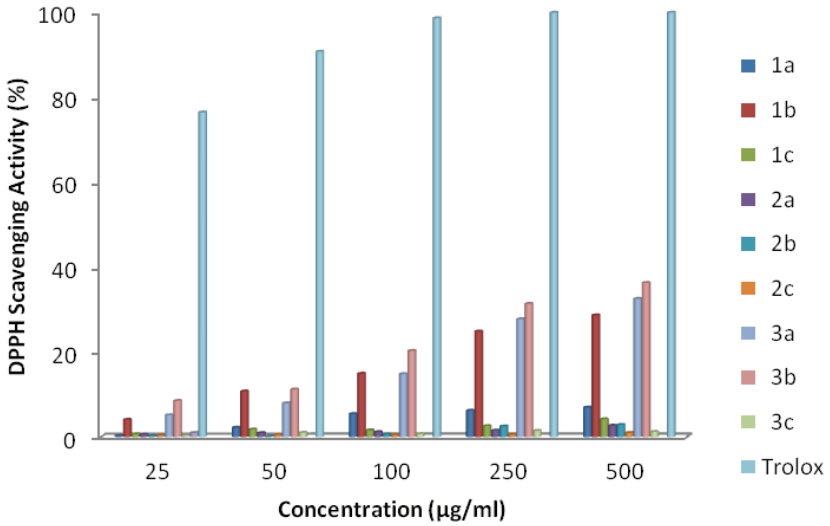


Figure 2. Radical scavenging activities of the compounds.

2.2.2. Metal chelating assay

Fe^{2+} induces the production of oxyradicals and lipid peroxidation; thus, reduction of its concentration prevents oxidative damage.[27] To better evaluate the antioxidant potential of the synthesized compounds, their chelating capacities were estimated against Fe^{2+}. As can be seen from Figure 3, chelating activities of samples were not increased prominently with the increasing concentration. The maximum chelating activity was found to be 16.2% for **2c** at a concentration of 500 μg/mL. EDTA was used as a standard and showed better activity than all the sample solutions.

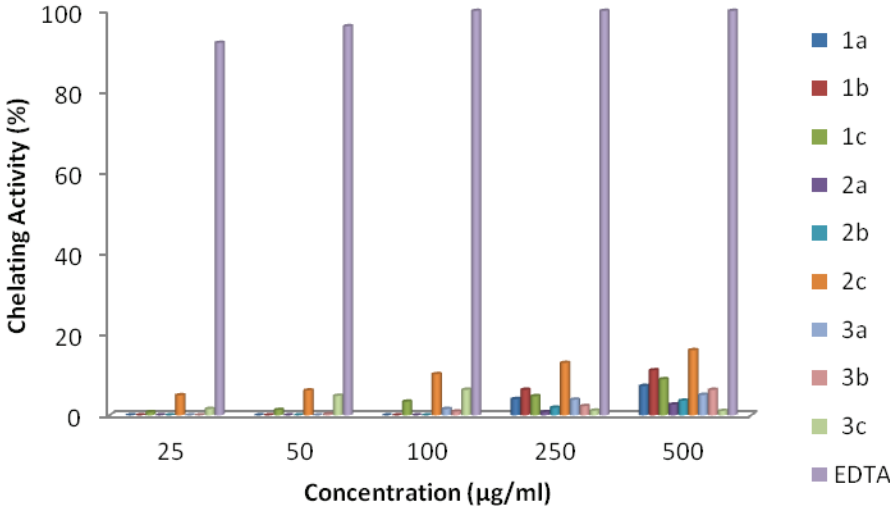


Figure 3. Metal chelating activity of compounds.

2.2.3. Reducing power assay

In this study, reducing power assay was based on the reduction of Fe^{3+}/ferricyanide compound to the ferrous form in the presence of antioxidants. The amount of Fe^{2+} can be indicated by the formation of Perls' Prussian blue at 700 nm.[28] The reducing power of the compounds and α-tocopherol on ferrous ions increased with

increasing concentrations (Figure 4). According to these results, the most active derivative was **2c** with an absorbance value of 0.487 at 500 μg/mL concentration, followed by **2b** with 0.442, **1b** with 0.378, and **1a** with 0.319, while the reference α-tocopherol exhibited 0.713 absorbance value.

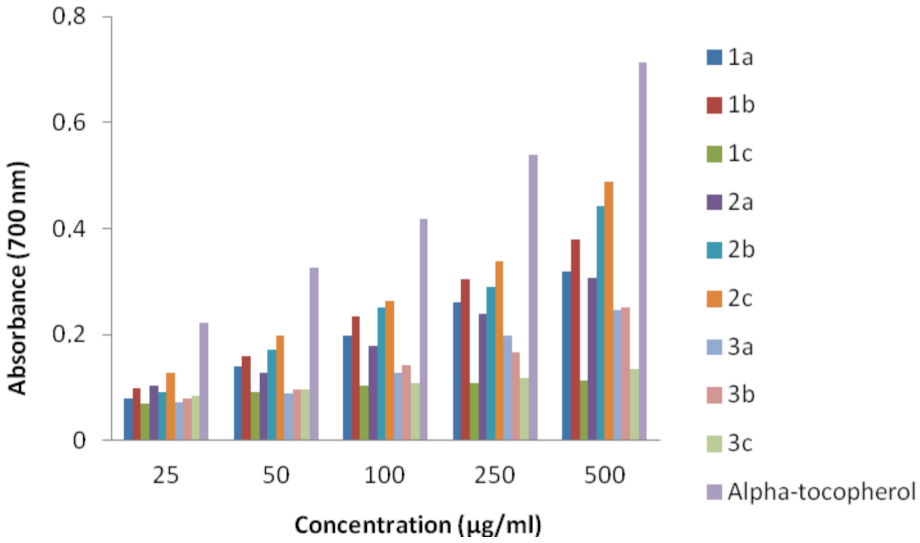


Figure 4. Reducing power of compounds.

2.3. Antibacterial activity

All the compounds were tested for their antibacterial activity by using a disk diffusion method against three gram-positive bacteria (*Enterococcus hirae*, *Staphylococcus aureus*, and *Bacillus cereus*) and three gram-negative bacteria (*Legionella pneumophila*, *Escherichia coli*, *and Pseudomonas aeruginosa*). Among them all (500 μg/mL), **2c** and **1b** showed weak antibacterial activities (7 mm) against *B. cereus*. Streptomycin and tetracycline showed 14-mm and 20-mm inhibition zones against the same bacterium, respectively. The other derivatives did not show any antibacterial activity against the studied bacteria.

2.4. DNA binding activity

Mixtures of calf thymus DNA (CT-DNA) with triazole compounds and CT-DNA alone were then loaded onto 0.8% agarose gel. Intercalative or electrostatic binding interactions decrease the movement of DNA in agarose gel electrophoresis.[29] Upon running the gel electrophoresis, CT-DNA mixed with triazoles moved from the well as the control (CT-DNA alone) did, and they did not reduce the mobility of DNA (Figure 5). This result demonstrated that the compounds did not show binding activity to DNA.

2.5. Conclusions

In summary, we have described the design and synthesis of novel hybrid compounds between a heteroaryl ring (quinoline and quinolone) and a triazole scaffold. The key intermediates, mono and bis O-propargylated quinoline **1** and **2** and O,N-propargylated quinolone derivatives, are synthesized from quinoline-2,8-diol. Propargyl skeletons are reacted with aromatic and benzylic halides and sodium azide via a CuI/L-proline-catalyzed one-pot synthesis method, and novel quinoline-triazoles **1a**–**1c** and **2a**–**2c** and quinolone-triazoles **3a**–**3c** are

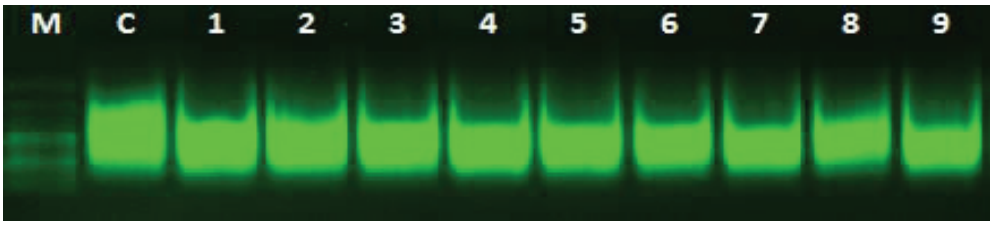


Figure 5. DNA binding of newly synthesized compounds. Lane M, DNA marker; Lane C, control, CT-DNA; Lane 1, CT-DNA + 500 μg/mL of **1a**; Lane 2, CT-DNA + 500 μg/mL of **1b**; Lane 3, CT-DNA + 500 μg/mL of **1c**; Lane 4, CT-DNA + 500 μg/mL of **2a**; Lane 5, CT-DNA + 500 μg/mL of **2b**; Lane 6, CT-DNA + 500 μg/mL of **2c**; Lane 7, CT-DNA + 500 μg/mL of **3a**; Lane 8, CT-DNA + 500 μg/mL of **3b**; Lane 9, CT-DNA + 500 μg/mL of **3c.**

constructed without isolation of potentially unstable organic azide intermediates. Three methods, namely radical scavenging, metal chelating, and reducing power assays, were used to define the antioxidant capacities of the compounds. In addition, antibacterial properties and DNA binding activities of the compounds were studied. According to the results, the highest chelating ability and reducing power were obtained for **2c** and it was seen that **3b** showed maximum DPPH scavenging activity. The compounds did not show any binding activity to DNA.

3. Experimental

3.1. General

All experiments were carried out in predried glassware an inert atmosphere of argon. All the chemicals used in the biologic assay studies were purchased from Sigma (Sigma-Aldrich GmbH, Steinheim, Germany). The blank antimicrobial test disks were obtained from Oxoid (7.0 mm, Oxoid Ltd, Basingstoke, UK). ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ on an Agilent NMR spectrometer (400 MHz) and the chemical shifts are expressed in ppm relative to $CDCl_3$ (δ 7.26 and 77.0 for ^{1}H and ^{13}C NMR, respectively) as the internal standard. FTIR spectra were recorded on a Thermo Scientific Nicolet with attenuated total reflectance (ATR). LC/MS-MS spectra were recorded on a Thermo Scientific Q Exactive instrument. Melting point was measured by a Stuart SMP3 instrument.

Flash column chromatography was performed using thick-walled glass columns and silica gel (60-mesh; Merck). The reactions were monitored by thin-layer chromatography (TLC) using Merck 0.2-mm silica gel 60 F254 analytical aluminum plates, visualized by UV light. All extracts were dried over anhydrous magnesium sulfate and solutions were concentrated under reduced pressure using a rotary evaporator.

3.2. General procedure for the synthesis of compounds 1–3

K_2CO_3 was added to a solution of quinoline-2,8-diol (1,6 g, 10 mmol) in dry acetone (50 mL). The solution was refluxed for 30 min. After cooling, propargyl bromide (20 mmol) was added dropwise. The mixture was refluxed overnight. The reaction mixture was filtered and the filtrate was concentrated in vacuum. Crude product was purified by flash column chromatography using ethyl acetate/ hexane (1:2) as the eluent to give compounds **1**–**3**.

3.2.1. 8-(Prop-2-ynyloxy)quinolin-2-(1H)-one, 1

Light yellow solid (0.80 g, 40% yield); mp 148–150 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.34 (bs, NH), 7.69 (dd, J= 2.1 and 9.6 Hz, 1H), 7.18–7.06 (m, 3H), 6.64 (dd, J= 1.7 and 9.6 Hz, 1H), 4.82 (dd, J= 1 .4 and 2.4 Hz, 2H), 2.57 (t, J= 2.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 161.9, 143.3, 140.3, 128.8, 122.7, 122.0, 120.6, 120.2, 111.9, 77.5, 76.7, 56.8. IR (ATR): 1644 (C=O), 2359 (C≡C), 3006 (C-H), 3154 (C≡C-H), 3254 (N-H) cm^{-1}. MS:m/z (%) = 200 (40), 101 (100), 87 (32), 79 (86), 73 (28). LC-MS/MS. Anal. Calcd. for $C_{12}H_9NO_2$ $[M+H]^+$: m/z 200.07061. Found: m/z200.07124.

3.2.2. 2,8-Bis(prop-2-ynyloxy)quinoline, 2

White solid (0.54 g, 23% yield); mp 115–117 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.00 (d, J= 8.8 Hz, 1H), 7.41 (dd, J= 1.6 and 7.8 Hz, 1H), 7.34–7.26 (m, 2H), 6.98 (d, J= 8.8 Hz, 1H), 5.19 (d, J= 2.5 Hz, 2H), 5.05 (d, J= 2.4 Hz, 2H), 2.53 (t, J= 2.4 Hz, 1H), 2.52 (t, J= 2.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 159.9, 151.9, 139.3, 138.3, 126.7, 124.2, 121.6, 114.9, 113.1, 79.2, 79.0, 75.7, 74.4, 58.1, 53.6. IR (ATR): 2120 (C≡C), 2950 (C-H), 3282, and 3292 (C≡C-H) cm^{-1}. MS:m/z (%) = 238 (100), 221 (13), 101 (14), 79 (14). LC-MS/MS. Anal. Calcd. for $C_{15}H_{11}NO_2$ $[M+H]^+$: m/z238.08626. Found: m/z238.08694.

3.2.3. 1-(Prop-2-ynyl)-8-(prop-2-ynyloxy)quinolin-2(1H)-one, 3

Yellow solid (0.83 g, 35% yield); mp 123–125 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.61 (d, J= 9.4 Hz, 1H), 7.29 (dd, J= 3.2 and 6.3 Hz, 1H), 7.19–7.18 (m, 2H), 6.69 (d, J= 9.4 Hz, 1H), 5.41 (d, J= 2.4 Hz, 2H), 4.85 (d, J= 2.4 Hz, 2H), 2.58 (t, J= 2.4 Hz, 1H), 2.20 (t, J= 2.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 162.6, 146.1, 139.8, 130.1, 123.2, 123.0, 122.9, 121.8, 116.3, 80.4, 78.0, 76.4, 70.6, 58.4, 36.3. IR (ATR): 1644 (C=O), 2359 (C≡C), 2972 (C-H), 3235 and 3276 (C≡C-H) cm^{-1}. MS:m/z (%) = 238 (100), 101 (8), 79 (18), 74 (9). LC-MS/MS. Anal. Calcd. for $C_{15}H_{11}NO_2$ $[M+H]^+$: m/z238.08626. Found: m/z238.08693.

3.3. General procedure for one-pot synthesis of 1,4-disubstituted 1,2,3-triazole derivatives 1a–1c, 2a–2c, and 3a–3c

A mixture of an aromatic or benzylic halide (1 mmol), quinoline-propargyl compound (for **1a**–**1c** 1 mmol and for **2a**–**2c** and **3a**–**3c** 0.5 mmol), L-proline (24 mg, 0.2 mmol), Na_2CO_3 (24 mg, 0.2 mmol), NaN_3 (65 mg, 1 mmol), sodium ascorbate (20 mg, 0.1 mmol), DMSO/H_2O (18:2, 2.0 mL), and $CuSO_4 \cdot 5H_2O$ solution (1 M, 0.05 mL) in a 20-mL scintillation vial was stirred overnight at 70 °C. The crude mixture was poured into cold dilute NH_4OH solution (30 mL) and extracted with ethyl acetate (4 × 20 mL). The collected organic layer was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The crude product was purified by flash column chromatography using mixtures of ethyl acetate and hexane.

3.3.1. 8-((1-Phenyl-1H-1,2,3-triazol-4-yl)methoxy)quinolin-2(1H)-one, 1a

White solid (0.26 g, 82% yield); mp 200–202 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.87 (bs, NH), 8.43 (s, 1H), 7.76 (d, J= 7.5 Hz, 2H), 7.71 (d, J= 9.2 Hz, 1H), 7.52–7.41 (m, 3H), 7.21–7.11 (m, 3H), 6.55 (d, J= 9.5 Hz, 1H), 5.44 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 162.2, 144.2, 143.9, 140.6, 136.9, 129.8, 128.9, 128.6, 122.3, 121.8, 120.6, 120.3, 120.2, 111.7, 62.9. IR (ATR): 1471 (C=N triazole), 1660 (C=O), 3098 (C≡C-H), 3200

(N-H) cm^{-1}. MS:m/z (%) = 319 (97), 221 (14), 193 (50), 183 (34), 169 (40), 155 (32). LC-MS/MS. Anal. Calcd. for $C_{18}H_{14}N_4O_2$ $[M+H]^+$: m/z319.11895. Found: m/z319.11935.

3.3.2. 8-((1-(Thiophen-3-yl)-1H-1,2,3-triazol-4-yl)methoxy)quinolin-2-(1H)-one, 1b

White solid (0.19 g, 60% yield); mp 192–194 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.37 (bs, NH), 8.16 (s, 1H), 7.45 (d, J= 9.6 Hz, 1H), 7.62 (dd, J= 1.7 and 3.0 Hz, 1H), 7.50–7.46 (m, 2H), 7.22–7.13 (m, 3H), 6.64 (d, J= 9.6 Hz, 1H), 5.44 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 162.0, 144.1, 143.3, 140.4, 135.6, 128.6, 127.4, 122.6, 122.3, 121.8, 120.8, 120.3, 120.2, 114.7, 111.6, 62.6. IR (ATR): 1474 (C=N triazole), 1650 (C=O), 3110 (C-H), 3180 (N-H) cm^{-1}. MS:m/z (%) = 347 (97), 344 (62), 193 (100), 141 (82), 131 (45). LC-MS/MS. Anal. Calcd. for $C_{16}H_{12}N_4O_2S$ $[M+Na]^+$: m/z347.05732. Found: m/z347.05807.

3.3.3. 8-((1-Benzyl-1H-1,2,3-triazol-4-yl)methoxy)quinolin-2-(1H)-one, 1c

White solid (0.25 g, 76% yield); mp 180–182 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.31 (bs, NH), 7.70–7.67 (m, 2H), 7.40–7.34 (m, 3H), 7.30–7.28 (m, 2H), 7.16–7.09 (m, 3H), 6.58 (d, J= 9.6 Hz, 1H), 5.55 (s, 2H), 5.30 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 162.0, 144.1, 143.3, 140.4, 134.2, 129.2, 128.9, 128.6, 128.2, 123.1, 122.5, 122.2, 120.2, 120.1, 111.6, 62.7, 54.3. IR (ATR): 1476 (C=N triazole), 1648 (C=O), 3096 (C-H), 3138 (N-H) cm^{-1}. MS:m/z (%) = 333 (45), 296 (100), 281 (16), 155 (13). LC-MS/MS. Anal. Calcd. for $C_{19}H_{16}N_4O_2$ $[M+H]^+$: m/z333.13460. Found: m/z333.13538.

3.3.4. 2,8-Bis((1-phenyl-1H-1,2,3-triazol-4-yl)methoxy)quinoline, 2a

White solid (0.19 g, 80% yield); mp 200–202 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.62 (s, 1H), 8.19 (s, 1H), 8.00 (d, J= 8.8 Hz, 1H), 7.67–7.64 (m, 4H), 7.50–7.31 (m, 9H), 6.98 (d, J= 8.8 Hz, 1H), 5.76 (s, 2H), 5.59 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 160.6, 152.7, 145.0, 144.6, 139.2, 137.8, 137.0, 136.8, 129.8, 129.6, 129.5, 129.4, 128.8, 128.6, 126.5, 124.8, 124.1, 123.8, 121.0, 120.8, 120.6, 120.5, 120.4, 113.6, 111.7, 63.3, 59.2. IR (ATR): 1482 (C=N triazole), 3282 and 3292 (C-H) cm^{-1}. MS:m/z (%) = 476 (63), 397 (98), 353 (20), 260 (22). LC-MS/MS. Anal. Calcd. for $C_{27}H_{21}N_7O_2$ $[M+H]^+$: m/z476.18295. Found: m/z476.18246.

3.3.5. 2,8-Bis((1-(thiophen-3-yl)-1H-1,2,3-triazol-4-yl)methoxy)quinoline, 2b

White solid (0.17 g, 72% yield); mp 195–197 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.53 (s, 1H), 8.17 (s, 1H), 8.10 (dd, J= 1.3 and 3.1 Hz, 1H), 8.00 (d, J= 8.8 Hz, 1H), 7.60 (dd, J= 1.5 and 3.2 Hz, 1H), 7.57–7.56 (m, 1H), 7.49–7.42 (m, 1H), 7.44–7.42 (m, 4H), 7.38–7.35 (m, 3H), 6.97 (d, J= 8.8 Hz, 1H), 5.73 (s, 2H), 5.55 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 160.5, 152.7, 144.4, 144.2, 139.1, 137.7, 131.9, 128.5, 127.3, 127.0, 126.4, 125.5, 124.1, 124.0, 121.5, 120.8, 120.7, 114.3, 114.1, 113.6, 111.6, 63.1, 59.1. IR (ATR): 1474 (C=N triazole), 3110 and 3146 (C-H) cm^{-1}. MS:m/z (%) = 488 (100), 311 (75), 255 (99), 101 (84), 87 (65). LC-MS/MS. Anal. Calcd. for $C_{23}H_{17}N_7O_2S_2$ $[M+H]^+$: m/z488.09579. Found: m/z488.090619.

3.3.6. 2,8-Bis((1-benzyl-1H-1,2,3-triazol-4-yl)methoxy)quinoline, 2c

White solid (0.19 g, 75% yield); mp 146–148 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.01 (s, 1H), 7.94 (d, J= 8.8 Hz, 1H), 7.57 (s, 1H), 7.35–7.36 (m, 5H), 7.25–7.17 (m, 5H), 7.16–7.13 (m, 3H), 6.90 (d, J= 8.8 Hz, 1H),

5.52 (s, 2H), 5.45 (s, 2H), 5.43 (s, 2H), 5.34 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 160.4, 152.6, 144.6, 144.0, 139.0, 137.6, 135.0, 134.3, 129.0, 128.8, 128.8, 128.4, 128.1, 128.0, 126.2, 125.8, 124.0, 122.8, 120.4, 113.5, 111.2, 63.1, 59.1, 54.1, 53.8. IR (ATR): 1481 (C=N triazole), 3088 and 3150 (C-H) cm^{-1}. MS:m/z (%) = 504 (12), 413 (100), 391 (40), 271 (12), 193 (10). LC-MS/MS. Anal. Calcd. for $C_{29}H_{25}N_7O_2$ $[M+H]^+$: m/z504.21425. Found: m/z504.21548.

3.3.7. 8-((1-Phenyl-1H-1,2,3-triazol-4-yl)methoxy)-1-((1-phenyl-1H-1,2,3-triazol-4-yl)methyl)quinolin-2(1H)-one, 3a

White solid (0.21 g, 88% yield); mp 168–169 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.30 (s, 1H), 7.92 (s, 1H), 7.69–7.00 (m, 5H), 7.43–7.32 (m, 7H), 7.15–7.12 (m, 2H), 6.71 (d, J= 9.4 Hz, 1H), 6.03 (s, 2H), 5.44 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 163.5, 147.0, 146.4, 143.7, 140.3, 136.9, 136.8, 130.3, 129.6, 129.5, 128.7, 128.5, 123.2, 123.2, 122.3, 122.2, 121.6, 121.0, 120.3, 120.2, 115.1, 62.6, 42.8. IR (ATR): 1466 (C=N triazole), 1648 (C=O), 2923 and 3087 (C-H) cm^{-1}. MS:m/z (%) = 476 (5), 413 (100), 193 (10), 169 (9), 141 (7). LC-MS/MS. Anal. Calcd. for $C_{27}H_{21}N_7O_2$ $[M+H]^+$: m/z476.18295. Found: m/z476.18359.

3.3.8. 8-((1-(Thiophen-3-yl)-1H-1,2,3-triazol-4-yl)methoxy)-1-((1-(thiophen-3-yl)-1H-1,2,3-triazol-4-yl)methyl)quinolin-2(1H)-one, 3b

White solid (0.15 g, 60% yield); mp 194–196 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.26 (s, 1H), 7.83 (s, 1H), 7.65 (d, J= 9.4 Hz, 1H), 7.54 (dd, J= 1.3 and 3.1 Hz, 1H), 7.44–7.42 (m, 2H), 7.39–7.34 (m, 4H), 7.19–7.14 (m, 2H), 6.71 (d, J= 9.4 Hz, 1H), 6.02 (s, 2H), 5.42 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 163.6, 146.5, 146.3, 143.3, 140.3, 135.8, 135.7, 135.6, 130.2, 127.1, 123.3, 123.2, 122.7, 122.2, 121.6, 121.5, 120.7, 120.6, 115.1, 114.2, 113.8, 62.6, 42.8. IR (ATR): 1453 (C=N triazole), 1662 (C=O), 2953 and 3087 (C-H) cm^{-1}. MS:m/z (%) = 488 (5), 413 (100), 193 (9), 141 (8). LC-MS/MS. Anal. Calcd. for $C_{23}H_{17}N_7O_2S_2$ $[M+H]^+$: m/z488.09579. Found: m/z488.09726.

3.3.9. 8-((1-Benzyl-1H-1,2,3-triazol-4-yl)methoxy)-1-((1-benzyl-1H-1,2,3-triazol-4-yl)methyl)quinolin-2(1H)-one, 3c

White solid (0.12 g, 48% yield); mp 150–151 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.71 (s, 1H), 7.60 (d, J= 9.4 Hz, 1H), 7.36–7.27 (m, 8H), 7.26–7.23 (m, 2H), 7.17–7.10 (m, 4H), 6.56 (d, J= 9.4 Hz, 1H), 5.83 (s, 2H), 5.47 (s, 2H), 5.36 (s, 2H), 5.23 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 163.5, 146.7, 146.5, 143.4, 140.1, 134.7, 134.6, 130.4, 129.1, 129.0, 128.7, 128.6, 128.1, 127.9, 124.1, 123.1, 123.1, 122.7, 122.0, 121.6, 115.4, 63.2, 54.1, 54.0, 43.0. IR (ATR): 1449 (C=N triazole), 1662 (C=O), 2988 and 3136 (C-H) cm^{-1}. MS:m/z (%) = 504 (12), 413 (100), 271 (19), 193 (8). LC-MS/MS. Anal. Calcd. for $C_{29}H_{25}N_7O_2$ $[M+H]^+$: m/z504.21425. Found: m/z504.21552.

3.4. DPPH assay

DPPH assay was based on the method previously described by Blois.[30] To each compound (25–500 μg/mL) dissolved in DMSO (0.5 mL) 2.0 mL of DPPH radical was added. The solution mixture was left in the dark for 30 min and then the absorbance was measured by a spectrophotometer at 517 nm. DMSO was used as the blank. The percentage of radical scavenging activity was computed by using the following equation:

$$\mathrm{I}\% = (\mathrm{A}_{control} - \mathrm{A}_{sample})/\mathrm{A}_{control} \times 100,$$

where $\mathrm{A}_{control}$ represents the absorbance of the control (alone) and A_{sample} is the absorbance of the test triazole sample. Trolox was used as a positive control.

3.5. Metal chelating assay

The metal chelating assay was measured following the method of Dundar et al.[28] All the compounds prepared (25–500 μg/mL) in DMSO (0.5 mL) were mixed with 1.85 mL of methanol and added to 50 μL of ferrous chloride (2 mmol/L). Reaction started by the addition of ferrozine (5 mmol/L). The solution mixture was left in the dark for 10 min at room temperature and then the absorbance was measured at 562 nm against a blank. EDTA was used as a positive control. The percentage of ferrous ion chelating activity was computed by using the following equation:

$$\text{Chelating ability } (\%) = (\mathrm{A}_{control} - \mathrm{A}_{sample})/\mathrm{A}_{control} \times 100,$$

where $\mathrm{A}_{control}$ represents the absorbance of the control sample and A_{sample} is the absorbance of the test sample or positive control.

3.6. Reducing power

Reducing power capabilities of the synthesized compounds were studied according to the method of Oyaizu.[31] All the compounds were prepared (25–500 μg/mL) in DMSO (0.25 mL), and 0.25 mL of sodium phosphate buffer (200 mM, pH 6.6) and 0.25 mL of potassium ferricyanide (1%) were added and the solution mixture was incubated for 20 min at 50 °C. Then 0.25 mL of trichloroacetic acid (10%) was added, and the solution mixture was centrifuged at 1000 rpm for 10 min. Thereafter, 0.5 mL of sterilized water and 0.2 mL of ferric chloride (0.1%) were mixed with the supernatant (0.5 mL). Finally, at 700 nm the absorbance was measured against a blank. As a positive control, α-tocopherol was used.

3.7. Antibacterial activity

Legionella pneumophila subsp. *pneumophila* (ATCC 33152), *Staphylococcus aureus* (ATCC 6538), *Bacillus cereus*, *Enterococcus hirae* (ATCC 10541), *Pseudomonas aeruginosa* (ATCC 9027), and *Escherichia coli* (ATCC 10536) were used as test microorganisms. In this study, a disk diffusion method was used for the assessment of antibacterial activities of the newly synthesized compounds.[32] Streptomycin (10 μg) and tetracycline (30 μg) were used as positive controls.

3.8. DNA binding activity

The interactions of compounds with CT-DNA were studied by agarose gel electrophoresis. For this purpose, CT-DNA (concentration: 20 μg/mL) diluted with sterile distilled water at a 1:5 ratio and 5 μL of diluted DNA were treated with 500 μg/mL compounds in DMSO (8 μL). The solution mixture was incubated at 37 °C for 4 h in the dark and then 3 μL of DNA loading dye was added. The samples were loaded on 0.8% agarose gel containing 7 μL of 0.05% ethidium bromide. Electrophoresis was performed for 1 h at 80 V in TAE buffer (50 mM Tris base, 50 mM acetic acid, 2 mM EDTA, pH 7.8). The gel was imaged under UV light and photographed.[33]

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