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An efficient click synthesis of chalcones derivatized with two 1-(2-quinolon-4-yl)-1,2,3-triazoles

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Abstract: Chalcones derivatized with 1-(2-quinolonyl)-1,2,3-triazoles were synthesized by reaction of 4-azido-2-quinolones with 1-phenyl-3-(4-propargyloxyphenyl) prop-2-en-1-one, or by aldol reaction of 4-{[1-(2-oxo-1,2-dihydroquinolin-4-yl)-1*H*-1,2,3-triazol-4-yl]methoxy} benzaldehydes with acetophenone. Whereas, chalcones bearing two 1-(2-quinolonyl)-1,2,3-triazoles were synthesized by reaction of 1,3-bis(4-propargyloxyphenyl) prop-2-en-1-one with 4-azido-2-quinolones, or by aldol condensation between 4-{4-[(4-acetylphenoxy)methyl]-1*H*-1,2,3-triazol-1-yl}quinolin-2(1*H*)-ones and 4-{[1-(2-oxo-1,2-dihydroquinolin-4-yl)-1*H*-1,2,3-triazol-4-yl]methoxy} benzaldehydes.

Keywords: aldol condensation; bis(2-quinolonyl)-bis-1,2,3-triazoles; chalcones.

1 Introduction

Chalcones have found success as commercial drugs for the treatment of some digestive system diseases and some are being clinically assayed for the treatment of cancer, cardiovascular diseases, and viral infections [1]. Some chalcones have shown activity against cardiovascular disease [2] and tumor promotion [3] since they decrease the inflammation signaling pathways in affected cells [3]. The induction of apoptosis by chalcones usually consists of mitochondrial pathways, down-regulation of anti-apoptotic proteins, and/or death receptor pathways [4–6]. Chalcones may also cause apoptosis through generation of reactive oxygen species (ROS) [7], despite being known as antioxidant molecules. Strong reactivity with thiol groups in living organisms would stimulate the pro-oxidant activity of chalcones due to the induction of a series of reactions with hydroxyl radicals in living cells, or by reducing the antioxidant mechanisms, such as the glutathione content [7]. Furthermore, some chalcones exhibited a potent renoprotective effect, when they evaluated for any renoprotective effects on cisplatin-treated cultured kidney cells (LLC-PK1) [8].

A quinoline moiety is present in many classes of natural products of biologically active compounds [9]. Several of them have been clinically used as antifungal, antibacterial, and antiprotozoic drugs [9], as well as antituberculotic agents [10]. Some quinoline-based compounds have also revealed antineoplastic, antiasthmatic, and antiplatelet activity [11, 12]. A series of compounds derived from 8-hydroxyquinoline and styrylquinoline derivatives have recently synthesized as potential HIV-1 integrase inhibitors [13, 14].

Aly et al. reported on the promise of 3,3′-methylenebis[4-hydroxyquinolin-2(1*H*)-ones] as anti-Covid-19 agents [15]. Also a series of 6-substituted 4-[2-(4-substituted-benzylidene)-hydrazinyl]quinolin-2(1H)-one derivatives was synthesized [16]. The target compounds were evaluated for their *in vitro* cytotoxic activity against 60 cancer cell lines. The most active compounds were further examined against the most sensitive leukemia RPMI-8226 and healthy cell lines [16]. In addition, we reported on the synthesis of new quinolin-2-one/pyrazole hybrids and their anti-apoptotic activity [17].

1,2,3-Triazoles have attracted considerable interest due to their ease of synthesis and diverse medicinal properties [18, 19]. The large dipole moment of this heterocycle

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imparts to it hydrogen bond–forming ability which could sometimes be desirable for better binding into the cavities of biomolecules [20]. The 1,2,3-triazole moiety is extensively used to develop libraries of compounds effective against cancer cells [21]. The aforementioned findings encouraged us to design and synthesize five bioactive sites in one molecule (Figure 1), utilizing click chemistry.

2 Results and discussion

Our synthetic protocol (Scheme 1) began with the preparation of 4-hydroxy-2-quinolinones **1a**–**e** according to the literature [22, 23]. 4-Hydroxy-2-quinolinones **1a**–**e** were treated with $POCl_3$ to give 2,4-dichloroquinolines **2a**–**d** and 4-chloro-2-quinolinone (**2e**) (R^1 = Me) [24]. Compounds **2a**–**d** were subjected to refluxing acetic acid-water to obtain 4-chloro-2-quinolinones **3a**–**d** [24]. Finally, either compounds **2e** or **3a**–**d** were subjected to sodium azide to produce 4-azidoquinolin-2(1*H*)-ones **4a**–**e** [25].

The alkyne fragments, compounds **6a**,**b**, were synthesized in very good yields from 3-(4-hydroxyphenyl)-1-phenylprop-2-en-1-one (**5a**) or 1,3-bis(4-hydroxy-phenyl) prop-2-en-1-one (**5b**) with propargyl bromide (Scheme 1) [26, 27]. Then, copper(I)-catalyzed azide-alkyne [3+2] dipolar cycloaddition reaction (CuAAC) [28] afforded the target hybrids **7a**–**d**, in good to excellent yields (**Method A**) depending on the concentration of the catalyst (Scheme 2). Also, our target compounds **7a**–**d** were synthesized, in very good yields, *via* the reaction of 4-{[1-(2-oxo-1,2-dihydroquinolin-4-yl)-1*H*-1,2,3-triazol-4-yl]methoxy}benzaldehydes **8a**–**d** [29] with acetophenone (**9**) **Method B** (Scheme 2). All the synthesized compounds were characterized using NMR spectroscopy (^{1}H, ^{13}C, and 2D), elemental analysis, and mass spectrometry. They were in good agreement with the assigned structures.

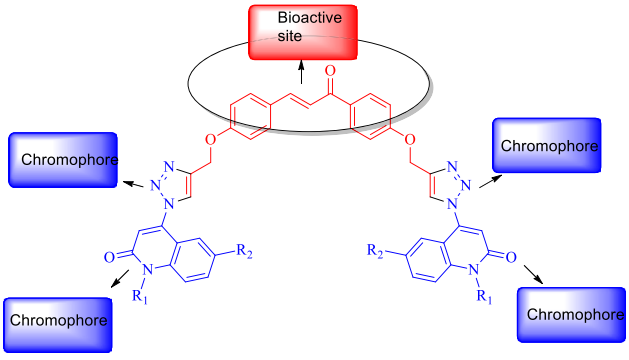
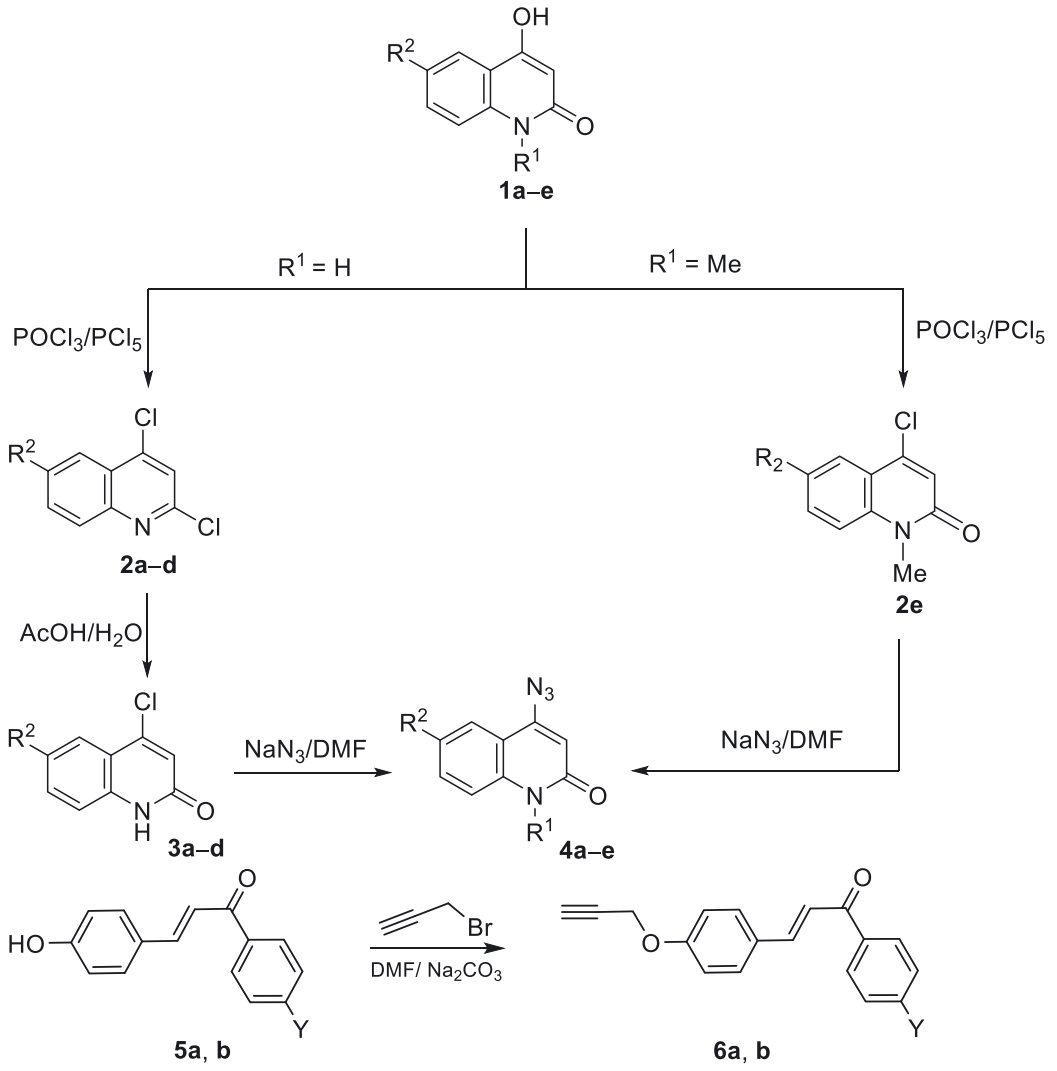


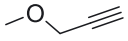
Figure 1: General structure of chalcones derivatized with two quinolonyl-1,2,3-triazoles.

All products **7a**–**d** were formed by combination of 4-azido-2-quinolinones **1a**–**d** with chalcone **6a** in the molar ratio of 1:1 without any elimination. All click reactions gave a single regioisomer, as evidenced by a single set of NMR signals. The assigned structure of compound **7a**, for example, appears in Figure 2; its NMR data appear in the Section 3, and the full 2D correlations are shown in Table 1. The NMR spectra of **7a** consist of two coupling networks, joined by the triazole ring. The carbon atom C-a is distinctive at δ_C = 189.1 ppm. C-a gives HMBC correlation to two protons with a large mutual coupling (J = 15.5 Hz), assigned as H-b and H-c in some order, and to a 2H doublet at δ_H = 8.15 ppm, assigned as H-*o*. H-*o* gives HSQC correlation with its attached carbon at δ_C = 128.4 ppm, and COSY correlation with a 2H doublet at δ_H = 7.57 ppm, assigned as H-*m*. H-*m*, and H-*o* give HMBC correlation with a carbon at δ_C = 131.9 ppm, assigned as C-*p*; H-*m* alone gives HMBC correlation with a carbon at δ_C = 137.8 ppm, assigned as C-*i*.

The ^{1}H doublets at δ_H = 7.84 and 7.75 ppm give HSQC correlation with their attached carbons at δ_C = 119.9 and 143.8 ppm, respectively. The carbon at δ_C = 143.8 ppm gives HMBC correlation with a 2H doublet at δ_H = 7.91 ppm, assigned as H-*o*′. If one assumes this to be a three-bond correlation, it yields the assignments of C-c (δ_C = 143.8 ppm), C-b (δ_C = 119.9 ppm), H-c (δ_H = 7.75 ppm), and H-b (δ_H = 7.84 ppm). Consistent with these assignments, C-b does not correlate with any aromatic proton. H-*o*′ gives HSQC correlation with its attached carbon at δ_C = 130.8 ppm and COSY correlation with a 2H doublet at δ_H = 7.21 ppm, assigned as H-*m*′. H-*m*′ gives HSQC correlation with its attached carbon at δ_C = 115.2 ppm. The carbon at δ_C = 127.8 ppm is assigned as C-*i*′ by analogy with compound **6b**. H-*o*′ give HMBC correlation with a carbon at δ_C = 160.0 ppm, assigned as C-*p*′. C-*p*′ gives HMBC correlation with a 2H singlet at δ_H = 5.39 ppm, assigned as H-4a; its attached carbon resonates at δ_C = 61.0 ppm. H-4a gives HMBC correlation with a carbon at δ_C = 143.0 ppm, assigned as C-4. C-4 gives HMBC correlation with a 1H singlet at δ_H = 8.90 ppm, assigned as H-5; its attached carbon resonates at δ_C = 126.7 ppm. H-5 gives HMBC correlation with a nitrogen at δ_N = 247.3 ppm, assigned as N-1. N-1 also gives HMBC correlation with a 1H singlet at δ_H = 6.86 ppm, assigned as H-8; its attached carbon appears at δ_C = 117.8 ppm. H-8 also gives HMBC correlation with a nitrogen at δ_N = 152.3 ppm, assigned as N-6, and with carbons at δ_C = 143.6 and 114.4 ppm, assigned on chemical-shift grounds as C-9 and C-9a, respectively.

Assignment of the quinoline is straightforward except for the benzene ring. Assignments in this ring follow from an HMBC correlation between C-13a (δ_C = 139.4 ppm) and H-12 (δ_H = 7.65 ppm).

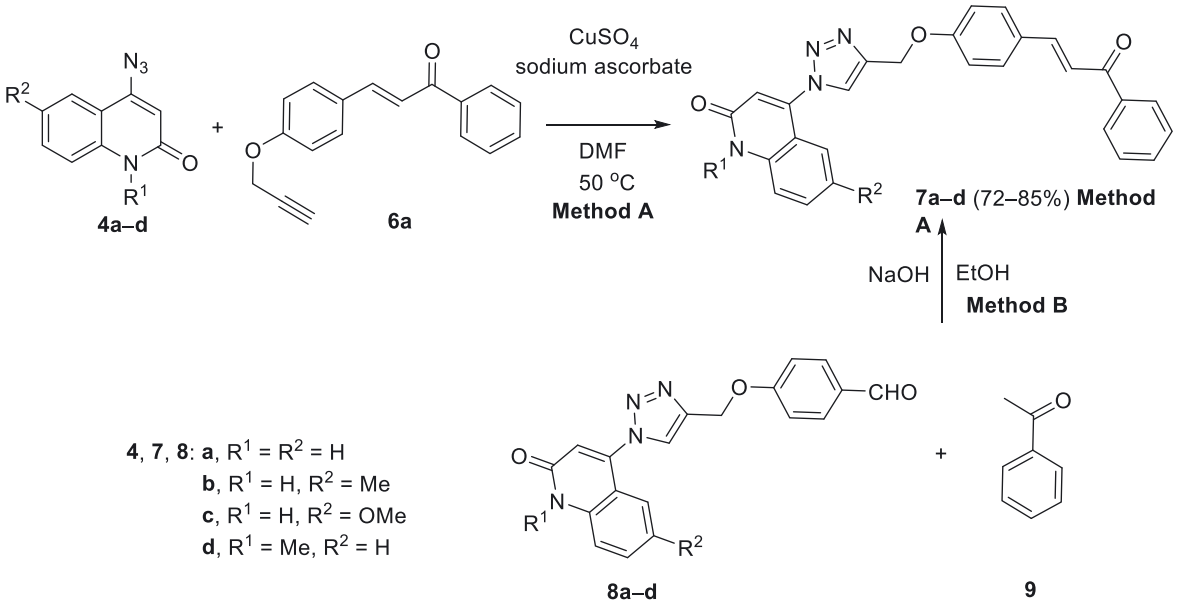


1, 4: **a**, $R^1 = R^2 = H$; **b**, $R^1 = H$, $R^2 = Me$; **c**, $R^1 = H$, $R^2 = OMe$; **d**, $R^1 = Me$, $R^2 = H$; **e**, $R^1 = H$, $R^2 = Cl$;
5: **a**, X = H; **b**, X = OH
6: **a**, Y = H, **b**, Y = 

Scheme 1: Synthesis of target compounds **4a–e** and alkynes **6a, b**.

The regiochemical assignment of the 1,4-disubstituted-1,2,3-triazole ring is based on analogy with compound **8e** (Figure 3), in which N-3 is detected; it has a distinctive downfield chemical shift (δ_N = 358.1 ppm) – as does N-2, in other compounds – and gives HMBC correlation with H-4a [29]. Throughout our series of 4-(1,2,3-triazolo)quinolin-2(1*H*)-ones (18 compounds; ref. [29]. and current work), N-6 and N-1 resonate in the ranges δ_N = 152.5–146.9 and 250.3–246.7 ppm, respectively.

Similarly, we prepared doubly derivatized chalcones by interaction between (*E*)-1,3-bis[4-(prop-2-yn-1-yloxy) phenyl]prop-2-en-1-one (**6b**) and 4-azidoquinolin-2(1*H*)-ones **4a–d** in the presence of CuAAC to obtain 1,2,3-triazoles **10a–d** in 73–81 yield (**Method A**). The 1,2,3-triazoles **10a–d** were also synthesized by the reactions of aldehydes **8a–d** with 4-{4-[(4-acetylphenoxy)-methyl]-1*H*-1,2,3-triazol-1-yl}-quinolin-2(1*H*)-ones **11a–d** in basic medium (**Method B**) as shown in Scheme 3. To confirm our results, NMR (^{1}H, ^{13}C, ^{1}H–^{1}H COSY, HMBC, HSQC, and ^{15}N) in addition to elemental analysis and mass spectrometry were performed for all the obtained products. As an example of this series, we chose compound **10b**



Scheme 2: Reaction of 4-azido-2-quinolinones **1a–d** with chalcone **6a**.

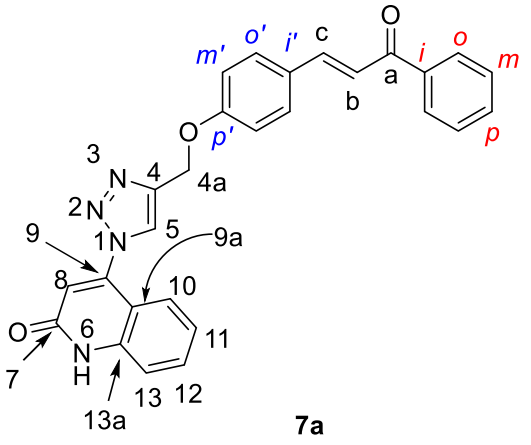


Figure 2: Assigned structure of compound **7a**.

(Figure 4). The NMR data appear in the Experimental Section; full 2D correlations are shown in Table 2. The stoichiometry of one chalcone per two triazoloquinolinones follows from ^{1}H NMR integration for H-b and H-c *vs* the other signals in the aromatic region, and the appearance of two signals for H-5 and 5′, H-4a and 4a′, C-5 and 5′, C-4a and 4a′, and C-4 and 4′. H-4a and 4a′ give HMBC correlation with C-*p* and *p*′, respectively. The other correlations are straightforward, and the coupling constant of 15.4 Hz between H-b and H-c shows that the chalcone C=C bond has *trans* stereochemistry.

We investigated the relationship among the reaction time, yield of products and concentration of Cu catalyst. We found that as a result of increasing the concentration of Cu catalyst, the required reaction time decreased whereas the yields of products increased. We propose that due to the reaction of $CuSO_4$ with sodium ascorbate to form Cu^+ which is responsible for reversible removal of an acidic proton from the terminal alkyne, so during the reaction with 5 mol% $CuSO_4$ we would add more sodium ascorbate to conserve the concentration of Cu^+, but when we arrived at 15 mol% of our catalyst, we found that the reaction needed no more sodium ascorbate and went to completeness in a short time (Table 3).

In summary, two new series of (1,2,3-triaz-ol-1-yl)quinolin-2(1*H*)-ones and bis(4,1-phenylene)bis(oxy)bis(-methylene)bis(1*H*-1,2,3-triazole-4,1-diyl)bis(*N*-methyl-quinoline-2(1*H*)-ones) were synthesized *via* onepot of click reaction. The yields are varied from very good to excellent.

3 Experimental

3.1 General information

All reagents were used as purchased from Merck. The progress of all reactions was monitored with thin-layer chromatography (TLC) on Merck alumina-backed TLC plates and visualized under UV light. Spectra were measured in DMSO-d_6 on a Bruker AV-400 spectrometer (400 MHz for ^{1}H, 100 MHz for ^{13}C, and 40.54 MHz for ^{15}N) in the Department of Chemistry, Florida Institute of Technology. ^{15}N signals were observed indirectly, *via* HSQC and HMBC experiments. Chemical shifts are expressed in δ (ppm) versus internal tetramethylsilane (TMS; $\delta = 0$ ppm) for ^{1}H and ^{13}C, and external liquid ammonia ($\delta = 0$ ppm) for ^{15}N. Correlations were established using ^{1}H–^{1}H COSY, and ^{1}H–^{13}C, and ^{1}H–^{15}N HSQC and HMBC experiments. Splitting patterns are denoted as follows: singlet (s), doublet (d), multiplet (m), triplet (t), quartet (q),

Table 1: Spectral data of compound **7a**.

^{1}H NMR	^{1}H–^{1}H COSY	Assignment
12.28 (s; 1H)	6.86	NH
8.90 (s; 1H)	5.39	H-5
8.15 (d, *J* = 7.5; 2H)	7.57	H-*o*
7.91 (d, *J* = 8.5; 2H)	7.21	H-*o′*
7.84 (d, *J* = 15.6; 1H)	7.75	H-b
7.75 (d, *J* = 15.5; 1H)	7.84	H-c
7.65 (dd, *J* = 7.0, 7.0; 1H)	7.48, 7.25	H-12
7.63 (t, *J* = 7.4; 1H)	7.75	H-*p*
7.57 (dd, *J* = 7.4, 7.4; 2H)	8.15, 7.63	H-*m*
7.48 (d, *J* = 8.1; 1H)	7.25	H-13
7.46 (d, *J* = 8.0; 1H)	7.25	H-10
7.25 (dd, *J* = 7.4, 7.4; 1H)	7.65, 7.46	H-11
7.21 (d, *J* = 8.5; 2H)	7.91	H-*m′*
6.86 (s; 1H)		H-8
5.39 (s; 2H)		H-4a

^{15}N NMR	^{1}H–^{15}N HSQC	^{1}H–^{15}N HMBC	Assignment
247.3		8.90, 6.86	NH
152.3	12.28	7.46, 6.86	N-1

^{13}C NMR	HSQC	HMBC	Assignment
189.1		8.15, 7.84, 7.75	C-a
161.0			C-7
160.0		7.91, 5.39	C-*p′*
143.8	7.75	7.91	C-c
143.6		7.46, 6.86	C-9
143.0		8.90, 5.39	C-4
139.4		7.65, 5.39	C-13a
137.8		7.57	C-*i*
132.9	7.65	7.46	C-12
131.9	7.63	8.15	C-*p*
130.8	7.91	7.91, 7.75	C-*o′*
128.7	7.57	7.57	C-*m*
128.4	8.15	8.15, 7.84, 7.63	C-*o*
127.8			C-*i′*
126.7	8.90	8.90, 5.39	C-5
123.9	7.46	7.65	C-10
122.6	7.25	7.65, 7.48	C-11
119.9	7.84	7.75	C-b
117.8	6.86	6.86	C-8
115.9	7.48	7.25	C-13
115.2	7.21	7.91	C-*m′*
114.4		7.47, 6.86	C-9a
61.0	5.39	5.39	C-4a

doublet of doublets (dd), doublet of triplets (dt), triplet of doublets (td), and doublet of quartet (dq). Melting points were determined with Stuart melting point instrument. Mass spectra were recorded on a Finnigan Fab 70 eV, Al-Azhar University, Egypt. Elemental analyses were carried out on a Perkin device at the Microanalytical Institute of Organic Chemistry, Karlsruhe University, Germany.

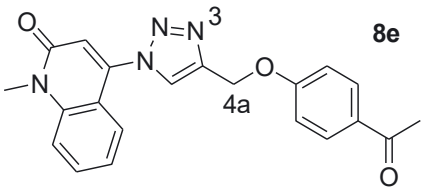


Figure 3: Structure of compound **8e**.

3.2 Starting materials

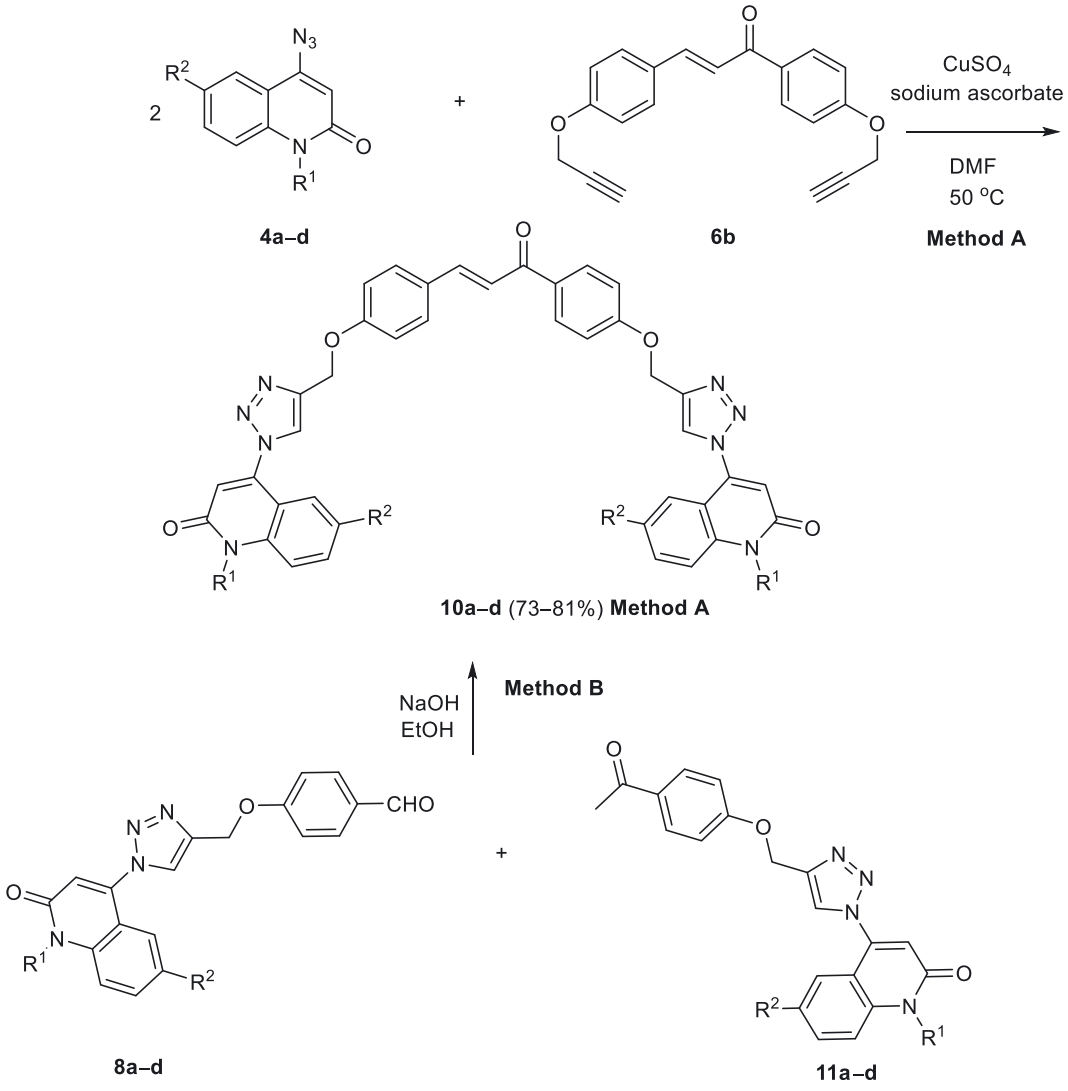
4-Azidoquinolin-2(1*H*)-ones **4a**–**d** were prepared according to the literature [22–26]. (*E*)-1-phenyl-3-[4-(prop-2-yn-1-yloxy)phenyl]prop-2-en-1-one (**6a**) was prepared according to the literature [26] and (*E*)-1,3-bis [4-(prop-2-yn-1-yloxy)phenyl]prop-2-en-1-one (**6b**) was prepared according to the literature [27]. Compounds 4-{[1-(2-oxo-1,2-dihydroquinolin-4-yl)-1*H*-1,2,3-triazol-4-yl]methoxy}benzaldehydes **8a**–**d** were previously prepared according to literature reports [29].

3.3 General procedure for the formation of compounds 7a–d and 10a–d

Method A: In a 100 ml round bottom flask, to a solution of terminal alkynes **6a**,**b** (1.1 mmol) in 20 ml DMF, then (15 mmol%) $CuSO_4{\cdot}5H_2O$ and (0.024 g,15 mmol%) sodium ascorbate were added. The reaction mixture was stirred for 20 min at room temperature until it changes to a yellowish green color. Then, 4-azido compounds **4a**–**d** (1.0 mmol) were added to the mixture. The reaction mixture was allowed to stir at 50 °C for 4 h, and another portion of sodium ascorbate (0.079 g, 0.4 mmol) and 0.024 g (15 mmol%) of $CuSO_4{\cdot}5H_2O$ were added. The reaction mixture was monitored with TLC. After completion, the mixture was poured in a beaker containing 100 g ice, diluted with H_2O, and the obtained products **7a**–**d** and **10a**–**d** were extracted by filtration and washed several times with ethanol.

Method B: In 100 ml round bottom flask (1 mmol) of acetophenone (**9**) and **11a**–**d** suspended in 50 ml ethanol and 1.5 ml of 80% NaOH with stirring until the dissolved mixture and a white solid was formed. Then **8a**–**d** (1 mmol) was added in one portion with stirring. Stirring was continued for 6 h and the reaction was monitored with TLC. After completion, the mixture was poured in a beaker containing 100 g of ice. The obtained products **7a**–**d** and **10a**–**d** were extracted by filtration and washed several times with ethanol.

3.3.1 (*E*)-4-(4-{[4-(3-Oxo-3-phenylprop-1-en-1-yl)phenoxy]methyl}-1*H*-1,2,3-triaz-ol-1-yl)quinolin-2(1*H*)-one (7a): Colorless powder, yield: 0.349 g (78%), m. p. 222–224 °C. – ^{1}H NMR: δ_H = 12.28 (s, 1H, H-6), 8.90 (s, 1H, H-5), 8.15 (d, *J* = 7.5 Hz, 2H, H-*o*), 7.91 (d, *J* = 8.5 Hz, 2H, H-*o′*), 7.84 (d, *J* = 15.6 Hz, 1H, H-b), 7.75 (d, *J* = 15.5 Hz, 1H, H-c), 7.65 (dd, *J* = 7.0, 7.0 Hz, 1H, H-12), 7.63 (t, *J* = 7.4 Hz, 1H, H-*p*), 7.57 (dd, *J* = 7.4, 7.4 Hz, 2H, H-*m*), 7.48 (m, 1H, H-13), 7.46 (m, 1H, H-10), 7.25 (dd, *J* = 7.4, 7.4 Hz, 1H, H-11), 7.21 (d, *J* = 8.5 Hz, 2H, H-*m′*), 6.86 (s, 1H, H-8), 5.39 (s, 2H, H-4a). – ^{13}C NMR: δ_C = 189.1 (C-a), 161.0 (C-7), 160.0 (C-*p′*), 143.8 (C-c), 143.6 (C-9), 143.0 (C-4), 139.4 (C-13a), 137.8 (C-*i*),



4, **8**, **10**, **11**: **a**, $R^1 = R^2 = H$; **b**, $R^1 = H$, $R^2 = Me$; **c**, $R^1 = H$, $R^2 = OMe$; **d**, $R^1 = Me$, $R^2 = H$

Scheme 3: Synthesis of compounds **10a–d**.

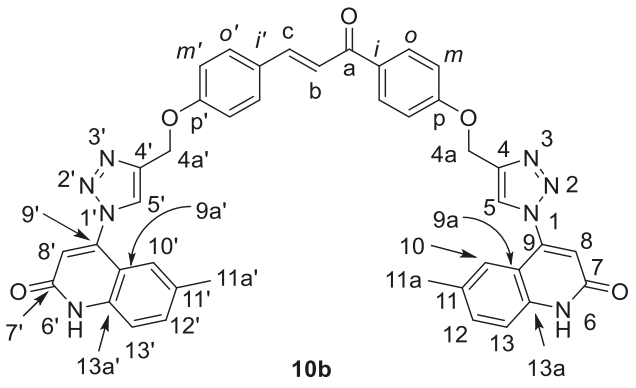


Figure 4: Assigned structure of compound **10b**.

132.9 (C-12), 131.9 (C-*p*), 130.8 (C-*o′*), 128.7 (C-*m*), 128.4 (C-*o*), 127.8 (C-*i′*), 126.7 (C-5), 123.9 (C-10), 122.6 (C-11), 119.9 (C-b), 117.8 (C-8), 115.9 (C-13), 115.2 (C-*m′*), 114.4 (C-9a), 61.0 (C-4a). – ^{15}N NMR: $\delta_N = 247.3$ (N-1), 152.3 (N-6). – MS: *m*/*z* (%) = 448 (35) $[M]^+$. – $C_{27}H_{20}N_4O_3$: Calcd. C 72.31, H 4.49, N 12.49; found C 72.44, H 4.36, N 12.40.

3.3.2 (*E*)-6-Methyl-4-(4-{[4-(3-oxo-3-phenylprop-1-en-1-yl)phenoxy]methyl}-1*H*-1,2,3-triazol-1-yl)quinolin-2(1*H*)-one (7b): Colorless powder, yield: 0.370 g (80%), m. p. 246–248 °C. – ^{1}H NMR: $\delta_H = 12.22$ (s, 1H, NH), 8.89 (s, 1H, H-5), 8.15 (d, $J = 7.4$ Hz, 2H, H-*o*), 7.90 (d, $J = 8.1$ Hz, 2H, H-*o′*), 7.84 (d, $J = 15.6$ Hz, 1H, H-b), 7.75 (d, $J = 15.5$ Hz, 1H, H-c), 7.66 (t, $J = 7.0$ Hz, 1H, H-*p*), 7.57 (dd, $J = 7.3$, 7.3 Hz, 2H, H-*m*), 7.47 (bd, $J = 7.9$ Hz, 1H, H-12), 7.38 (bd, $J = 7.9$ Hz, 1H, H-13), 7.22 ("d", 3H, H-m′, 10), 6.82 (s, 1H, H-8), 5.39 (s, 2H, H-4a), 2.29 (s, 3H, H-11a). – ^{13}C NMR: $\delta_C = 189.0$ (C-a), 160.8 (C-7), 160.0 (C-*p′*), 143.8 (C-c), 143.4 (C-9), 142.9

Table 2: Spectral data of compound **10b**.

^{1}H NMR	^{1}H–^{1}H COSY		Assignment
12.22 (s; 2H)			NH-6,6′
8.90 (s; 1H)			H-5,5′
8.89 (s; 1H)			H-5′,5
8.21 (d, *J* = 8.5; 2H)	7.28		H-*o*
7.91 (d, *J* = 8.6; 2H)	7.21		H-*o*′
7.87 (d, *J* = 15.4; 1H)	7.72		H-b
7.72 (d, *J* = 15.4; 1H)	7.87		H-c
7.49 (d, *J* = 8.3; 2H)	7.39, 7.21		H-12,12′
7.39 (d, *J* = 8.4; 2H)	7.49		H-13,13′
7.28 (d, *J* = 8.4; 2H)	8.21		H-*m*
7.21 (m; 4H)	7.91, 7.49, 2.30		H-*m*′,10,10′
6.82 (s; 2H)			H-8,8′
5.45 (s; 2H)			H-4a′
5.39 (s; 2H)			H-4a
2.30 (s; 6H)	7.21		H-11a,11a′
^{15}N NMR	**^{1}H–^{15}N HSQC**	**^{1}H–^{15}N HMBC**	**Assignment**
247.6		8.90, 8.89, 6.82	N-1,1′
152.0	12.22	6.82	N-6,6′
^{15}C NMR	**HSQC**	**HMBC**	**Assignment**
187.3		8.21, 7.91, 7.87, 7.72	C-a
161.7, 160.8		8.21, 7.72, 7.28, 5.39	C-*p*,7,7′
159.9		7.91, 7.21, 5.45	C-*p*
143.4		7.21, 6.82	C-9,9′
143.05		7.91	C-c
142.9, 142.8		8.90, 8.89, 5.45, 5.39	C-4,4′
137.5		7.49, 7.21	C-13a,13a′
133.2	7.49	7.21	C-12,12′
131.8		8.21, 7.39, 2.30	C-11,11′
131.1		7.28	C-*i*
130.8	8.21	8.21, 7.72	C-*o*
130.7	7.91	7.91	C-*o*′
127.9		7.87, 7.21	C-*i*′
126.8, 126.7	8.90, 8.89	8.90, 8.89, 5.45, 5.39	C-5,5′
123.1	7.21	7.49, 2.30	C-10,10′
119.8	7.87		C-b
117.8	6.82	6.82	C-8,8′
115.9	7.39		C-13,13′
115.2	7.21		C-*m*′
114.8	7.28		C-*m*
114.4		7.39, 6.82	C-9a,9a′
61.1	5.45		C-4a′
61.0	5.39		C-4a
20.5	2.30	7.49, 7.21, 2.30	C-11a,11a′

Table 3: Relationship between concentration of the Cu catalyst and the reaction time for compounds **10a–d**.

Compounds	Conc. (mol%)	Temp. (°C)	Time (h)	Yield (%)
10a–d	5	50	48	60–70
	10	50	24	65–70
	15	50	4	72–85

(C-4), 137.8 (C-*i*), 137.5 (C-13a), 133.2 (C-12), 132.9 (C-*p*), 131.7 (C-11), 130.8 (C-*o*′), 128.7 (C-*m*), 128.4 (C-*o*), 127.8 (C-*i*′), 126.7 (C-5), 123.1 (C-10), 119.9 (C-b), 117.8 (C-8), 115.9 (C-13), 115.2 (C-*m*′), 114.4 (C-9a), 61.0 (C-4a), 20.5 (C-11a). – ^{15}N NMR: δ_N = 247.5 (N-1), 151.9 (N-6). – MS: *m*/*z* (%) = 462 (17) $[M]^+$. – $C_{28}H_{22}N_4O_3$: Calcd. C 72.71, H 4.79, N 12.11; found C 72.66, H 4.88, N 11.95.

3.3.3 (*E*)-6-Methoxy-4-(4-{[4-(3-oxo-3-phenylprop-1-en-1-yl) phenoxy]methyl}-1*H*-1,2,3-triazol-1-yl)quinolin-2(1*H*)-one (7c): Colorless powder, yield: 0.405 g (85%), m. p. 230–232 °C. – ^{1}H NMR: δ_H = 12.19 (s, 1H, H-6), 8.93 (s, 1H, H-5), 8.15 (d, *J* = 7.4 Hz, 2H, H-*o*), 7.90 (d, *J* = 8.0 Hz, 2H, H-*o*′), 7.84 (d, *J* = 15.6 Hz, 1H, H-b), 7.75 (d, *J* = 15.5 Hz, 1H, H-c), 7.66 (t, *J* = 6.9 Hz, 1H, H-*p*), 7.57 (dd, *J* = 7.2, 7.1 Hz, 2H, H-*m*), 7.44 (bd, *J* = 8.5 Hz, 1H, H-13), 7.34 (bd, *J* = 7.5 Hz, 1H, H-12), 7.21 (d, *J* = 8.0 Hz, 2H, H-*m*′), 6.91 (s, 1H, H-10), 6.86 (s, 1H, H-8), 5.40 (s, 2H, H-4a), 3.68 (s, 3H, H-11b). – ^{13}C NMR: δ_C = 189.04 (C-a), 160.5 (C-7), 160.0 (C-*p*′), 154.5 (C-11), 143.8 (C-c), 143.0 (C-4,9), 137.8 (C-*i*), 134.1 (C-13a), 132.9 (C-*p*), 130.8 (C-*o*′), 128.7 (C-*m*), 128.4 (C-*o*), 127.8 (C-*i*′), 126.7 (C-5), 121.0 (C-12), 119.9 (C-b), 118.0 (C-8), 117.4 (C-13), 115.2 (C-*m*′), 114.9 (C-9a), 105.6 (C-10), 61.0 (C-4a), 55.4 (C-11b). – ^{15}N NMR: δ_N = 247.9 (N-1), 151.0 (N-6). – MS: *m*/*z* (%) = 479 (18) $[M+1]^+$, 478 (40) $[M]^+$. – $C_{28}H_{22}N_4O_4$: Calcd. C 70.28, H 4.63, N 11.71; found C 70.33, H 4.80, N 11.88.

3.3.4 (*E*)-1-Methyl-4-(4-{[4-(3-oxo-3-phenylprop-1-en-1-yl)phenoxy] methyl}-1*H*-1,2,3-triazol-1-yl)quinolin-2(1*H*)-one (7d): Colorless powder, yield: 0.334 g (72%), m. p. 210–212 °C. – ^{1}H NMR: δ_H = 8.89 (s, 1H, H-5), 8.15 (d, *J* = 7.4 Hz, 2H, H-*o*), 7.91 (d, *J* = 8.2 Hz, 2H, H-*o*′), 7.84 (d, *J* = 15.5 Hz, 1H, H-b), 7.74 (d, *J* = 15.4 Hz, 1H, H-c), 7.64 (dd, *J* = 7.0, 7.0 Hz, 1H, H-12), 7.62 (t, *J* = 7.3 Hz, 1H, H-*p*), 7.56 (dd, *J* = 7.3, 7.3 Hz, 1H, H-m), 7.46 (m, 1H, H-13), 7.46 (m, 1H, H-10), 7.25 (dd, *J* = 7.0, 7.0 Hz, 1H, H-11), 7.21 (d, *J* = 8.4 Hz, 2H, H-m′), 6.84 (s, 1H, H-8), 5.39 (s, 2H, H-4a), 2.21 (s, 3H, H-6a). – ^{13}C NMR: δ_C = 189.0 (C-a), 160.9 (C-7), 160.0 (C-*p*′), 143.8 (C-c), 143.5 (C-9), 142.9 (C-4), 139.4 (C-13a), 137.5 (C-*i*), 132.9 (C-12), 131.9 (C-*p*), 130.8 (C-o′), 128.3 (C-*m*), 128.3 (C-*o*), 127.8 (C-*i*′), 126.7 (C-5), 123.9 (C-10), 122.6 (C-11), 119.9 (C-b), 117.8 (C-8), 115.9 (C-13), 115.9 (C-m), 114.4 (C-9a), 61.0 (C-4a), 22.1 (C-6a). – $C_{28}H_{22}N_4O_3$: Calcd. C 72.71, H 4.79, N 12.11; found C 72.79, H 4.65, N 12.20.

3.3.5 (*E*)-4,4′-[({[(3-Oxoprop-1-ene-1,3-diyl)bis(4,1-phenylene)] bis(oxy)}bis(methylene))-bis(1*H*-1,2,3-triazole-4,1-diyl)] bis(quinoline-2(1*H*)-one) (10a): Yellowish green powder, yield: 0.540 g (78%), m. p. 260–262 °C. – ^{1}H NMR: δ_H = 12.28 (s, 2H, 2NH), 8.91 (s, 1H, H-5,5′), 8.90 (s, 1H, H-5′,5), 8.21 (d, *J* = 8.4 Hz, 2H, H-*o*), 7.96 (s, 1H, DMF), 7.90 (d, *J* = 8.8 Hz, 2H, H-*o*′), 7.87 (d, *J* = 16.9 Hz, 1H, H-b), 7.72 (d, *J* = 15.4 Hz, 2H, H-c), 7.65 (dd, *J* = 7.5, 7.5 Hz, 2H, H-12,12′), 7.48 (d, *J* = 8.2 Hz, 2H, H-10,10′), 7.46 (d, *J* = 8.1 Hz, 2H, H-13,13′), 7.25 (m, 4H, H-*m*,*m*′,11,11′), 6.87 (s, 2H, H-8,8′), 5.44 (s, 2H, H-4a′), 5.39 (s, 2H, H-4a), 2.90 (s, 3H, DMF), 2.74 (s, 3H, DMF). – ^{13}C NMR: δ_C = 187.3 (C-a), 162.3 (DMF), 161.8, 161.0 (C-*p*,7,7′), 159.9 (C-*p*′), 143.6 (C-9,9′), 143.0

(C-c), 142.8 (C-4,4′), 139.4 (C-13a,13a′), 131.9 (C-12,12′), 131.1 (C-*i*), 130.8 (C-*o*), 130.7 (C-*o′*), 128.0 (C-*i′*), 126.8, 126.7 (C-5,5′), 123.9 (C-10,10′), 122.6 (C-11,11′), 119.8 (C-b), 117.7 (C-8,8′), 116.0 (C-13,13′), 115.2 (C-*m′*), 114.8 (C-*m*), 114.4 (C-9a,9a′), 61.1 (C-4a′), 61.0 (C-4a),. – ^{15}N NMR: δ_N = 247.5 (N-1,1′). – MS: *m*/*z* (%) = 688 (16). – $C_{39}H_{28}N_8O_5$: Calcd. C 68.02, H 4.10, N 16.27; found C 68.12, H 3.97, N 16.35.

3.3.6 (*E*)-4,4′-[({[(3-Oxoprop-1-ene-1,3-diyl)bis(4,1-phenylene)]-bis(oxy)}bis(methylene))-bis(1*H*-1,2,3-triazole-4,1-diyl)] bis(6-methylquinoline-2(1*H*)-one) (10b): Yellowish green powder, yield: 0.608 g (79%), m. p. 285–287 °C. – ^{1}H NMR: δ_H = 12.22 (s, 2H, H-6, 6′), 8.90, 8.89 (2 × s, each 1H, H-5,5′), 8.21 (d, *J* = 8.5 Hz, 2H, H-*o*), 7.91 (d, *J* = 8.6 Hz, 2H, H-*o′*), 7.87 (d, *J* = 15.4 Hz, 1H, H-b), 7.72 (d, *J* = 15.4 Hz, 1H, H-c), 7.49 (d, *J* = 8.3 Hz, 2H, H-12, 12′), 7.39 (d, *J* = 8.4 Hz, 2H, H-13, 13′), 7.28 (d, *J* = 8.4 Hz, 2H, H-*m*), 7.21 (m, 4H, H-*m′*, 10, 10′), 6.82 (s, 2H, H-8, 8′), 5.45(s, 2H, H-4a′), 5.39 (s, 2H, H-4a), 2.30 (s, 6H, H-11a, 11a′) – ^{13}C NMR: δ_C = 187.3 (C-a), 161.7, 160.8 (C-*p*, 2, 2′), 159.9 (C-*p′*), 143.4 (C-9, 9′), 143.0 (C-c), 142.9, 142.8 (C-4, 4′), 137.5 (C-13a, 13a′), 133.2 (C-12, 12′), 131.8 (C-11, 11′), 131.1 (C-*i*), 130.8 (C-*o*), 130.7 (C-*o′*), 127.9 (C-*i′*), 126.8, 126.7 (C-5, 5′), 123.1 (C-10, 10′), 119.8 (C-b), 117.8 (C-8, 8′), 115.9 (C-13, 13′), 115.2 (C-*m′*), 114.8 (C-*m*), 114.4 (C-9a, 9a′), 61.1 (C-4a′), 61.0 (C-4a), 20.5 (C-11a, 11a′). – ^{15}N NMR: δ_N = 247.6 (N-1, 1′), 152.0 (N-6, 6′), N-2, 2′, 3, 3′ n/o. – MS: *m*/*z* (%) = 717 (16) $[M+1]^+$, 716 (35) $[M]^+$. – $C_{41}H_{32}N_8O_5$: Calcd. C 68.71, H 4.50, N 15.63; found C 68.66, H 4.61, N 15.49.

3.3.7 (*E*)-4,4′-[({[(3-Oxoprop-1-ene-1,3-diyl)bis(4,1-phenylene)] bis(oxy)}bis(methyl-ene))bis(1*H*-1,2,3-triazole-4,1-diyl)] bis(6-methoxyquinoline-2(1*H*)-one) (10c): Yellowish green powder, yield: 0.606 g (81%), m. p. 226–228 °C. – ^{1}H NMR: δ_H = 12.19 (s, 2H, 2NH), 8.94 (s, 1H, H-5/5′), 8.93 (s, 1H, H-5′/5), 8.19 (d, *J* = 9.1 Hz, 2H, H-*o*), 7.89 (d, *J* = 8.6 Hz, 2H, H-*o′*), 7.83 (m, 1H, H-b), 7.72 (m, 1H, H-c), 7.44 (d, *J* = 9.0 Hz, 2H, H-13, 13′), 7.34 (dd, *J* = 8.9, 2.2 Hz, 1H, H-12, 12′), 7.27 (d, *J* = 8.5 Hz, 2H, H-*m*), 7.20 (d, *J* = 8.4 Hz, 2H, H-*m′*), 6.91 (d, *J* = 1.4 Hz, 2H, H-10, 10′), 6.86 (s, 2H, H-8, 8′), 5.45 (s, 2H, H-4a), 5.40 (s, 2H, H-4a′), 3.68 (s, 6H, H-11b, 11b′). – ^{13}C NMR: δ_C = 187.3 (C-a), 161.7 (C-7, 7′), 160.5 (C-*p*), 159.8 (C-*p′*), 154.5 (C-11), 143.1, 142.9 (C-c, 4, 4′, 9, 9′), 134.1 (C-13a, 13a′), 130.8 (C-*o*), 130.6 (C-*o′*), 127.9 (C-*i′*), 126.65, 126.58 (C-5, 5′), 121.0 (C-12, 12′), 119.9 (C-b), 118.0 (C-8, 8′), 117.4 (C-13, 13′), 114.9 (C-*m*, *m′*, 9a, 9a′), 105.6 (C-10, 10′), 61.1 (C-4a), 61.0 (C-4a′), 55.4 (C-11b, 11b′). – ^{15}N NMR: δ_N = 247.8 (N-1, 1′), 151.1 (N-6, 6′). – *m*/*z* (%) = 748 (14). – $C_{41}H_{32}N_8O_7$: Calcd. C 65.77, H 4.31, N 14.97; found C 65.66, H 4.29, N 15.11.

3.3.8 (*E*)-4,4′-[({[(3-Oxoprop-1-ene-1,3-diyl)bis(4,1-phenylene)] bis(oxy)}bis(methylene)-)bis-(1*H*-1,2,3-triazole-4,1-diyl)]bis-(*N*-methylquinoline-2(1*H*)-one) (10d): Yellowish green powder, yield: 0.520 g (73%), m. p. 205–207 °C. – ^{1}H NMR: δ_H = 8.91 (s,1H, H-5/5′), 8.90 (s, 1H, H-5′/5), 8.21 (d, *J* = 8.6, 2H, H-*o*), 7.91 (d, *J* = 8.8, 2H, H-*o′*), 7.83 (d, *J* = 16.5 Hz, 1H, H-b), 7.79 (dd, *J* = 8.2, 7.0 Hz, 2H, H-12, 12′), 7.74 (d, *J* = 8.2 Hz, 2H, H-13, 13′), 7.73 (d, *J* = 17.8 Hz, 1H, H-c), 7.46 (d, *J* = 8.0 Hz, 2H, H-10, 10′), 7.35 (dd, *J* = 7.5, 7.5 Hz, 2H, H-11, 11′), 7.28 (d, *J* = 8.6 Hz, 2H, H-m), 7.21 (d, *J* = 8.4 Hz, 2H, H-m′), 7.00 (s, 2H, H-8, 8′), 5.45 (s, 2H, H-4a), 5.39 (s, 2H, H-4a′), 3.73 (s, 6H, H-6a, 6a′). – ^{13}C NMR: δ_C = 187.3 (C-a), 161.8 (C-7, 7′), 160.3 (C-*p*), 159.9 (C-*p′*), 143.0 (C-c), 142.8, 142.6 (C-4, 4′, 9, 9′), 140.1 (C-13a, 13a′), 132.3 (C-12, 12′), 131.1 (C-*i*), 130.8 (C-o), 130.7 (C-*o′*), 128.0 (C-*i′*), 127.0, 126.9 (C-5, 5′), 124.4 (C-10, 10′), 122.7 (C-11, 11′), 119.8 (C-b), 117.3 (C-8, 8′), 115.6, 115.5 (C-9a, 9a′, 13, 13′), 115.2 (C-*m′*), 114.8 (C-*m*), 61.1 (C-4a), 61.0 (C-4a′), 29.6 (C-6a, 6a′). – ^{15}N NMR: δ_N = 246.7 (N-1, 1′), 146.9 (N-6, 6′). – MS: *m*/*z* (%) = 716 (24). – $C_{41}H_{32}N_8O_5$: Calcd. C 68.71, H 4.50, N 15.63; found C 68.88, H 4.41, N 15.77.

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