ISSN 1070-4280, Russian Journal of Organic Chemistry, 2020, Vol. 56, No. 4, pp. 698–705. © Pleiades Publishing, Ltd., 2020.

Synthesis of Some Azamacrocycles Bearing 1,2,4-Oxadiazole and 1,2,3-Triazole Moieties

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Received November 9, 2019; revised February 19, 2020; accepted February 20, 2020

Abstract—A tetraazacrown ether, 4,9-di(prop-2-yn-1-yl)-1,4,9,12-tetraazacyclohexadecane-2,11-dione, bearing propargyl groups on two nitrogens was synthesized starting from 1,4,9,12-tetraazacyclohexadecane-2,11-dione and subjected to 1,3-cycloaddition reaction with 5-(azidomethyl)-3-(4-R-phenyl)-1,2,4-oxadiazoles which were prepared by acylation of the corresponding *para*-substituted benzamidoximes with chloroacetyl chloride, followed by azidation. In this way, a series of azacrown ethers bearing 1,2,4-oxadiazole and 1,2,3-triazole rings were successfully obtained, and their structure elucidation was performed by means of spectral/physical data.

Keywords: azacrown ether, azide, amidoxime, 1,2,4-oxadiazole, 1,2,3-triazole

DOI: 10.1134/S1070428020040193

Polycyclic ethers or crown ethers have first been reported by Pedersen [1–3] who was awarded by Noble Prize in 1987 and died just two years later in 1989. Over the subsequent decades there has been continuing and increasing interest in the synthesis of various types of crown compounds, including nitrogen- and sulfur-containing ones [4–9]. This type of macrocycles has been shown to form complexes with alkali, alkaline earth, and heavy metal cations. These complexation properties make azacrowns interesting to researchers in many areas [10–12]. Azacrowns have also found remarkable uses as synthetic receptors in molecular recognition processes and, in some cases, their anion complexation properties are quite similar to those in certain biological systems [13]. Their enhanced complexing ability for ammonium salts and transition metal ions were reported. On the other hand, azacrowns are important intermediates for the synthesis of cryptands (from diazacrowns), nitrogen-pivot lariat crown ethers, and other species requiring one or two nitrogens in the macrocycle [14–20].

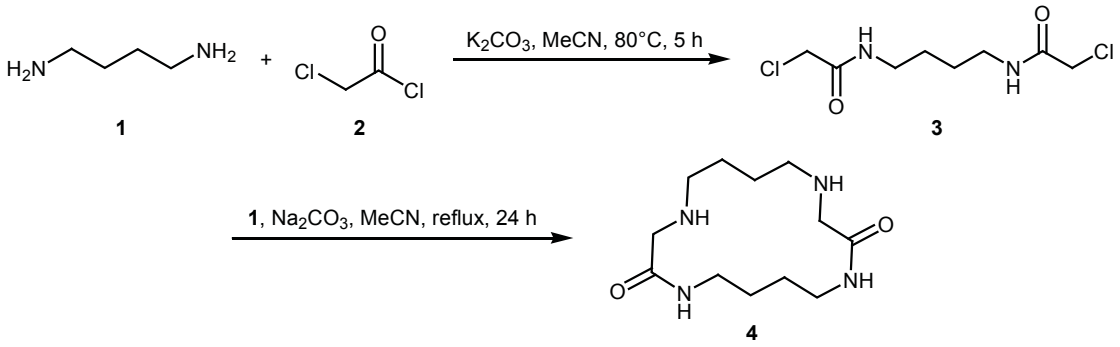
In addition, there are a number of interesting uses of azacrowns as catalysts in nucleophilic substitution and oxidation reactions, in the design of chromogenic reagents that are sensitive to alkali and alkaline earth metal cations, and as light emitting materials [21–23]. Furthermore, heterocyclic compounds containing a 1,2,4-oxadiazole or 1,2,3-triazole ring have been reported to exhibit various biological activities [24–31].

Taking into account the above considerations and importance of azamacrocyclic compounds in different areas, we were inspired to synthesize a series of azacrown ethers carrying 1,2,4-oxadiazole moiety and to carry out their 1,3-dipolar cycloaddition reactions.

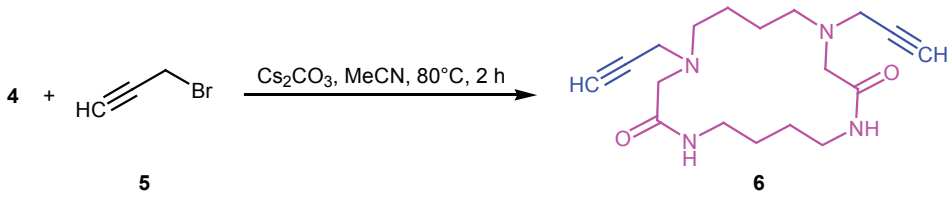
Initially, azacrown **4** was synthesized from butane-1,4-diamine and chloroacetyl chloride according to modified literature procedures (Scheme 1). The structures of **3** and **4** were confirmed by spectral and physical data. Azacrown **4** was then substituted at the secondary amine nitrogens with propargyl bromide **5** to give azacrown **6** (Scheme 2). The structure of **6** was confirmed by spectral and physical data. Most characteristic IR bands arose from acetylenic stretching vibrations around 2100 cm^{-1} along with the carbonyl and NH bands. In the ^{13}C NMR spectrum of **6**, the acetylenic carbons resonated at δ_C 78.16 and 73.40 ppm, and the carbonyl carbon signal appeared at δ_C 170.82 ppm.

3-Aryl-5-(azidomethyl)-1,2,4-oxadiazoles **7a**–**7h** were synthesized according to the previously reported procedure [26] starting from aryl-substituted 5-(chloromethyl)oxadiazoles which were easily prepared by the action of chloroacetyl chloride on aryl-substituted monoamidoximes in refluxing benzene (Scheme 3). Azacrown **6** with acetylenic side chains was then subjected to 1,3-dipolar cycloaddition with azidooxadiazoles **7a**–**7h** to yield mixtures of mono- and bis-cycloadducts **8a**–**8h** and **9a**–**9h** in a regioselective

Scheme 1.



Scheme 2.

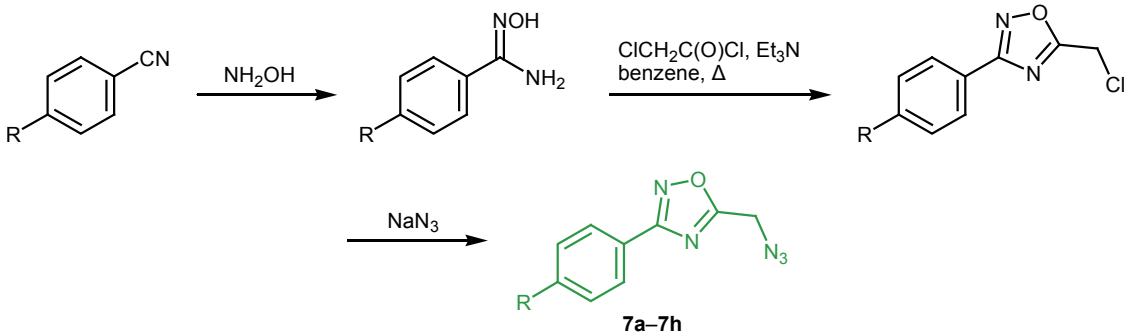


manner (Scheme 4). The products can be easily separated and purified by flash column chromatography.

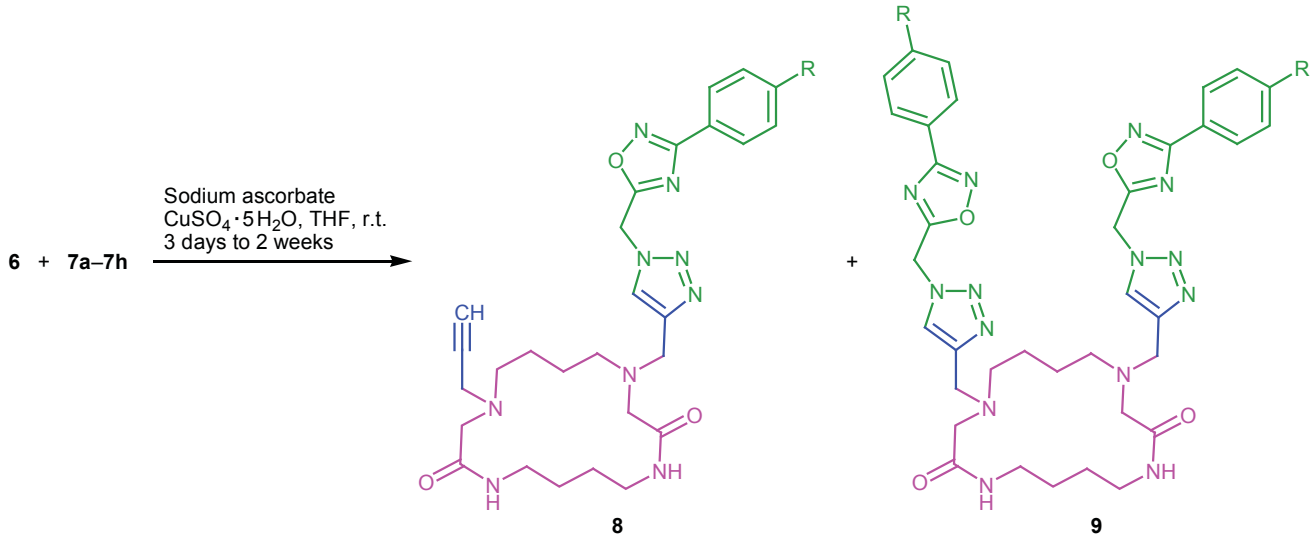
Despite variation of the reactant molar ratio and "click chemistry" catalyst in order to obtain only disubstituted cycloadducts, the reaction ended up each time to give a mixture of **8** and **9**. Their structures were identified on the basis of spectral and physical data. The IR spectra of **8a**–**8h** showed basically carbonyl, NH, and C≡C stretching bands. In the ^{1}H NMR spectra, the triazole =CH proton resonated at around δ 7.78 ppm as a singlet, the NHC=O signal appeared as a singlet at δ 5.91 ppm, and the signal of methylene protons on the bridging carbon atom between the oxadiazole and triazole rings was also a singlet at δ 5.27 ppm. In addition, we observed acetylenic proton signal at δ 2.20 ppm. The ^{13}C NMR signals were basically those of carbonyl carbons around δ_C 172 ppm, iminic carbons of the oxadiazole rings in the range δ_C 171–167 ppm, and acetylenic carbons at δ_C 78 (**C**≡CH) and 73 ppm (C≡**C**H). Due to symmetrical structure of bis-cycloadducts **9**, less number of both proton and carbon NMR signals can be observed. In addition, no acetylenic stretching vibration band was present in their IR spectra. Exact mass measurements also confirmed the assigned structures. Analysis of the obtained data led us to conclude that the cycloaddition occurred through a more energetically favored cyclic transition state leading to 1,4-substituted triazole derivatives rather than 1,5-regioisomers. These results coincide with the previous literature findings which have been observed in the cycloadditions of organic azides with terminal acetylenic dipolarophiles [32–36].

In summary, we have demonstrated a practical method to construct some novel azacrown ethers carrying acetylenic side chain and their 1,3-dipolar cycloaddition to a series of 1,2,4-oxadiazoles carrying azidomethyl group. Thus, we have successfully obtained macroazacyclic compounds carrying both

Scheme 3.



Scheme 4.



R = H (**a**), Me (**b**), F (**c**), Cl (**d**), Br (**e**), NO_2 (**f**), MeO (**g**), MeS (**h**).

R	H	Me	F	Cl	Br	NO_2	MeO	MeS
Yield of **8**, %	25	44	30	30	38	35	36	38
Yield of **9**, %	73	53	61	42	56	41	46	41

1,2,4-oxadiazole and triazole rings on the same molecule and established their structures by physical and spectroscopic methods.

EXPERIMENTAL

Reagents were purchased from commercial sources and used as received. Melting points were measured in capillary tubes on a Meltemp apparatus and are uncorrected. The ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ on Jeol and Varian spectrometers operating at 400 (^{1}H) and 100 MHz (^{13}C); the chemical shifts were determined relative to the residual proton and carbon signals of the solvent ($CHCl_3$, δ 7.26 ppm; $CDCl_3$, δ_C 77.20 ppm). The IR spectra were recorded in KBr on a Shimadzu S8000 spectrometer. HRMS measurements were performed on Waters Synapt and Agilent Technologies 6224 spectrometers using the ionization modes specified. Routine TLC analyses were carried out on pre-coated silica gel plates with fluorescent indicator. Flash column chromatography was performed on silica gel (230–400 mesh ASTM). A rotary TLC apparatus (Chromatotron) was utilized for further separation and purifications. Stain solutions of potassium permanganate and iodine were used for visualization of TLC spots.

***N*,*N*′-(Butane-1,4-diyl)bis(2-chloroacetamide) (3)** [37, 38]**.** A 500-mL three-necked round-bottomed flask equipped with a magnetic stirrer, cooling bath, internal thermometer, and dropping funnel was charged with a solution of 1,4-diaminobutane (10.0 g, 0.113 mol) in methylene chloride (100 mL). Distilled water (80 mL) and potassium carbonate (31.6 g, 0.222 mol) were added to the solution with stirring, the mixture was ice-cooled, and chloroacetyl chloride (24.5 mL, 0.222 mol) was added over a period of 60–90 min, maintaining the temperature below 10°C. The mixture was then allowed to warm up to room temperature, and the precipitate was filtered off. It was taken into 150 mL of water, the mixture was vigorously stirred for 2 h, and the product was filtered off and dried overnight in a vacuum oven at 60°C. Yield 19.84 g (74%), white solid, mp 132–133°C. IR spectrum (KBr), ν, cm^{-1}: 3321, 2939, 2928, 1643, 1610, 1550, 1504, 1454. ^{1}H NMR spectrum, δ, ppm: 8.18 s (2H), 3.99 s (4H), 3.04 d (4H, J = 2.2 Hz), 1.37 s (4H). ^{13}C NMR spectrum, δ_C, ppm: 165.96, 42.61, 39.32, 26.69. Mass spectrum (ESI$^+$): m/z 264 $[M + H]^+$.

1,4,9,12-Tetraazacyclohexadecane-2,11-dione (4) [39, 40]**.** Compound **3** (5.0 g, 0.02 mol) and 1,4-butanediamine (1.83 g, 0.021 mol) were mixed in acetonitrile (100 mL) under nitrogen, and sodium carbonate (48.51 g, 0.46 mol) was added in portions with mechanical stirring. The mixture was further stirred at 80°C for 24 h. When the reaction was complete (TLC), the mixture was filtered, the filtrate was evaporated

under reduced pressure, and the residue was purified by column chromatography on silica gel (CH_2Cl_2/MeOH, 3:1). Yield 1.161 g (21%), white solid, mp 141–142°C, R_f 0.25 (CH_2Cl_2/MeOH, 5:2). IR spectrum (KBr), ν, cm^{-1}: 3356, 3321, 3267, 2943, 2874, 1643, 1539, 1442, 1242, 1153, 848. ^1H NMR spectrum, δ, ppm: 7.40 s (2H), 3.37–3.28 m (4H), 3.23 s (4H), 2.60 t (4H, J = 6.5 Hz), 1.63–1.48 m (10H). ^{13}C NMR spectrum, δ_C, ppm: 171.94, 52.89, 50.12, 37.77, 27.75, 27.52. Mass spectrum (ESI^+): m/z 257 $[M + H]^+$.

1,12-Di(prop-2-yn-1-yl)-1,4,9,12-tetraazacyclohexadecane-2,11-dione (6) [41]**.** 1,4,9,12-Tetraazacyclohexadecane-2,11-dione (**4**, 519 mg, 2.025 mmol) was dissolved in acetonitrile (30 mL), cesium carbonate (2.836 g, 8.71 mmol), propargyl bromide (0.721 mL, 8.096 mmol), and 4Å molecular sieves were added in succession, and the mixture was stirred under reflux for 2.5 h. After the reaction was complete (TLC), the mixture was filtered, and the precipitate was washed with acetonitrile. The solvent was evaporated under reduced pressure, and the residue was purified by flash column chromatography (EtOAc/MeOH, 5:1). Yield 362 mg (54%), white solid, mp 164–165°C. IR spectrum (KBr), ν, cm^{-1}: 3344, 3308, 3273, 3232, 2939, 2868, 2818, 2096, 1647, 1529, 1464, 1334, 1280, 1124. ^1H NMR spectrum, δ, ppm: 7.20 br.s (2H), 3.35 s (4H), 3.29 s (4H), 3.10 s (4H), 2.53 s (4H), 2.20 s (2H), 1.53 s (4H), 1.44 s (4H). ^{13}C NMR spectrum, δ_C, ppm: 170.82, 78.16, 73.40, 58.42, 54.90, 44.71, 37.96, 27.85, 26.06. Mass spectrum (ESI^+): m/z 333 $[M + H]^+$.

4-({1-[(3-Phenyl-1,2,4-oxadiazol-5-yl)methyl]-1*H*-1,2,3-triazol-4-yl}methyl)-9-(prop-2-yn-1-yl)-1,4,9,12-tetraazacyclohexadecane-2,11-dione (8a) and 4,9-bis({1-[(3-phenyl-1,2,4-oxadiazol-5-yl)-methyl]-1*H*-1,2,3-triazol-4-yl}methyl)-1,4,9,12-tetraazacyclohexadecane-2,11-dione (9a). Copper(II) sulfate pentahydrate (13.7 mg, 0.055 mmol) was added with stirring to a solution of 5-(azidomethyl)-3-phenyl-1,2,4-oxadiazole (**7a**, 55 mg, 0.274 mmol) and azacrown alkyne **6** (50 mg, 0.150 mmol) in THF (25 mL). Sodium ascorbate (27.1 mg, 0.137 mmol) was then added in portions over a period of 10 min, and the mixture was stirred for 3 days to 2 weeks at room temperature. The solvent was evaporated, and the crude material was purified by flash column chromatography (EtOAc/MeOH, 6:1) to give **8a** and **9a**.

Compound **8a**. Yield 20 mg (25%), yellow oil, R_f 0.489 (EtOAc/MeOH, 5:1). IR spectrum (KBr), ν, cm^{-1}: 3344, 3302, 3136, 3070, 2935, 2862, 2380, 1638, 1600, 1527, 1446, 1350, 1276, 1114. ^1H NMR spectrum, δ, ppm: 8.01 d (2H, J = 9.6 Hz), 7.78 s (1H), 7.56–7.40 m (4H), 7.31–7.26 m (1H), 5.91 s (2H), 5.27 s (1H), 3.82 s (2H), 3.35 s (1H), 3.26 d (4H, J = 14.8 Hz), 3.34 d (1H, J = 1.6 Hz), 3.26 d (2H, J = 14.8 Hz), 3.09 d (2H, J = 5.6 Hz), 2.62–2.46 d.t (2H, J = 24.4, 6.8, 6.4 Hz), 2.19 br.s (1H), 1.57–1.35 m (8H). ^{13}C NMR spectrum, δ_C, ppm: 172.32, 171.14, 171.09, 168.95, 145.36, 131.85, 129.09, 128.92, 127.60, 125.82, 123.54, 78.19, 73.39, 58.45, 58.36, 58.31, 55.73, 54.98, 50.55, 45.33, 44.76, 38.12, 38.03, 27.60, 26.14, 25.93. HRMS (ESI-TOF): m/z 534.2920 $[M + H]^+$. $C_{27}H_{36}N_9O_3$. Calculated: M + H 534.2941.

Compound (**9a**). Yield 100 mg (73%), yellow oil, R_f 0.378 (EtOAc/MeOH, 5:1). IR spectrum (KBr), ν, cm^{-1}: 3348, 3136, 3055, 2939, 2862, 2831, 1662, 1600, 1527, 1446, 1350, 1269, 1114. ^1H NMR spectrum, δ, ppm: 8.00–7.93 m (4H), 7.82 s (2H), 7.52–7.37 m (8H), 5.89 s (4H), 3.76 s (4H), 3.19 s (4H), 3.05 s (4H), 2.49 s (4H), 1.49 d (8H, J = 6.7 Hz). ^{13}C NMR spectrum, δ_C, ppm: 172.47, 171.37, 168.86, 145.52, 131.83, 129.41, 129.07, 128.88, 127.54, 125.80, 123.71, 58.50, 55.79, 50.52, 45.32, 38.12, 27.32, 26.03. HRMS (ESI-TOF): m/z 735.3581 $[M + H]^+$. $C_{36}H_{43}N_{14}O_4$. Calculated: M + H 735.3592.

Compounds **8b**–**8h** and **9b**–**9h** were synthesized in a similar way.

4-[(1-{[3-(4-Methylphenyl)-1,2,4-oxadiazol-5-yl]-methyl}-1*H*-1,2,3-triazol-4-yl)methyl]-9-(prop-2-yn-1-yl)-1,4,9,12-tetraazacyclohexadecane-2,11-dione (8b). Yield 30 mg (44%), white solid, mp 146–147°C, R_f 0.480 (EtOAc/MeOH, 5:1). IR spectrum (KBr), ν, cm^{-1}: 3348, 3302, 3140, 3051, 2935, 2862, 1662, 1597, 1531, 1450, 1269, 1230. ^1H NMR spectrum, δ, ppm: 7.90–7.86 m (2H), 7.77 s (1H), 7.25 d.d (4H, J = 4.4, 3.5 Hz), 5.89 d (2H, J = 1.0 Hz), 3.81 s (2H), 3.33 d (2H, J = 9.4 Hz), 3.31–3.20 m (4H), 3.09 d (4H, J = 6.0 Hz), 2.54 d.d (2H, J = 13.2, 6.8 Hz), 2.49 t (2H, J = 6.4 Hz), 2.38 s (3H), 2.18 d (1H, J = 1.4 Hz), 1.53 s (4H), 1.47 d.d (4H, J = 18.9, 8.7 Hz). ^{13}C NMR spectrum, δ_C, ppm: 171.97, 168.86, 142.19, 129.67, 127.42, 122.91, 77.98, 73.31, 61.75, 58.31, 55.55, 54.80, 50.52, 45.27, 44.58, 38.00, 27.48, 25.70, 21.58. Mass spectrum (ESI^+): m/z 548 $[M + H]^+$. HRMS (ESI-TOF): m/z 548.3099 $[M + H]^+$. $C_{28}H_{38}N_9O_3$. Calculated: M + H 548.3089.

4,9-Bis[(1-{[3-(4-methylphenyl)-1,2,4-oxadiazol-5-yl]methyl}-1*H*-1,2,3-triazol-4-yl)methyl]-1,4,9,12-tetraazacyclohexadecane-2,11-dione (9b). Yield 50 mg (53%), yellow oil, R_f 0.375 (EtOAc/MeOH, 5:1). IR spectrum (KBr), ν, cm^{-1}: 3348, 3136, 2939,

2862, 1658, 1597, 1531, 1481, 1454, 1411, 1346, 1273, 1226. ^{1}H NMR spectrum, δ, ppm: 7.87 d (4H, *J* = 7.6 Hz), 7.80 s (2H), 7.50 t (2H, *J* = 5.2 Hz), 7.26–7.24 m (4H), 5.88 s (4H), 3.78 s (4H), 3.23 s (4H), 3.07 s (4H), 2.51 s (4H), 2.37 s (6H), 1.52 d (8H, *J* = 10.7 Hz). ^{13}C NMR spectrum, δ_C, ppm: 172.03, 168.83, 142.16, 130.85, 127.40, 122.92, 58.44, 55.40, 50.55, 45.27, 38.09, 27.24, 25.83, 21.55. Mass spectrum (ESI$^+$): *m*/*z* 763 [*M* + H]$^+$. HRMS (ESI-TOF): *m*/*z* 763.3916 [*M* + H]$^+$. $C_{38}H_{47}N_{14}O_4$. Calculated: *M* + H 763.3905.

4-[(1-{[3-(4-Fluorophenyl)-1,2,4-oxadiazol-5-yl]-methyl}-1*H*-1,2,3-triazol-4-yl)methyl]-9-(prop-2-yn-1-yl)-1,4,9,12-tetraazacyclohexadecane-2,11-dione (8c). Yield 25 mg (30%), yellow oil, R_f 0.405 (EtOAc/MeOH, 5:1). IR spectrum (KBr), ν, cm^{-1}: 3348, 3302, 3140, 2858, 1662, 1585, 1531, 1481, 1450, 1419, 1342, 1226. ^{1}H NMR spectrum, δ, ppm: 8.06–7.98 d.d (2H, *J* = 8.0, 5.6 Hz), 7.77 s (1H), 7.46 br.s (1H), 7.26 d (1H, *J* = 6.4 Hz), 7.18–7.11 t (2H, *J* = 8.0 Hz), 5.91 s (2H), 3.80 s (2H), 3.35 s (2H), 3.25 d (4H, *J* = 9.2 Hz), 3.09 s (4H), 2.63–2.44 d.t (4H, *J* = 16.0, 12.0, 5.6 Hz), 2.19 s (1H), 1.61–1.38 m (8H). ^{13}C NMR spectrum, δ_C, ppm: 172.46, 171.13, 168.13, 164.91 d (C–F, *J* = 251.3 Hz), 145.40, 129.90, 129.81, 123.54, 122.09, 122.06, 116.47, 116.25, 78.21, 73.39, 58.47, 58.32, 55.73, 55.06, 45.29, 44.84, 38.12, 38.04, 27.61, 27.58, 26.12, 25.96. HRMS (ESI-TOF): *m*/*z* 552.2827 [*M* + H]$^+$. $C_{27}H_{35}FN_9O_3$. Calculated: *M* + H 552.2847.

4,9-Bis[(1-{[3-(4-fluorophenyl)-1,2,4-oxadiazol-5-yl]methyl}-1*H*-1,2,3-triazol-4-yl)methyl]-1,4,9,12-tetraazacyclohexadecane-2,11-dione (9c). Yield 70 mg (61%), white solid, R_f 0.262 (EtOAc/MeOH, 5:1). IR spectrum (KBr), ν, cm^{-1}: 3348, 3140, 3055, 2939, 2862, 2831, 1666, 1597, 1566,1527, 1469, 1408, 1342, 1265. ^{1}H NMR spectrum, δ, ppm: 8.04–7.95 m (4H), 7.82 d (2H, *J* = 14.6 Hz), 7.53–7.44 m (2H), 7.12 t (4H, *J* = 8.2 Hz), 5.90 s (4H), 3.76 d (4H, *J* = 15.2 Hz), 3.21 s (4H), 3.04 d (4H, *J* = 15.1 Hz), 2.51 s (4H), 1.52 s (8H). ^{13}C NMR spectrum, δ_C, ppm: 172.53, 171.36, 168.08, 164.87 d (C–F, (*J* = 251.3 Hz), 145.58, 129.86, 129.77, 123.62, 122.07, 122.03, 116.44, 116.22, 60.49, 58.51, 55.87, 50.54, 45.28, 38.13, 27.35, 26.07. HRMS (ESI-TOF): *m*/*z* 771. 3391 [*M* + H]$^+$. $C_{36}H_{41}F_2N_{14}O_4$. Calculated: *M* + H 771.3401.

4-[(1-{[3-(4-Chlorophenyl)-1,2,4-oxadiazol-5-yl]-methyl}-1*H*-1,2,3-triazol-4-yl)methyl]-9-(prop-2-yn-1-yl)-1,4,9,12-tetraazacyclohexadecane-2,11-dione (8d). Yield 30 mg (30%), yellow oil, R_f 0.420 (EtOAc/MeOH, 5:1). IR spectrum (KBr), ν, cm^{-1}: 3348, 3302, 3136, 3055, 2935, 2862, 1662, 1597, 1527, 1465, 1408, 1384, 1342, 1265. ^{1}H NMR spectrum, δ, ppm: 7.98–7.93 d.d (2H, *J* = 8.4, 1.2 Hz), 7.76 s (1H), 7.47–7.41 d.d (3H, *J* = 8.4, 1.2 Hz), 7.29–7.26 m (1H), 5.91 s (2H), 3.81 s (2H), 3.40–3.01 m (5H), 2.60–2.48 d.t (4H, *J* = 20.8, 12.0, 5.6 Hz), 2.21–2.16 m (2H), 1.90–1.65 br.s (4H), 1.60–1.15 m (8H). ^{13}C NMR spectrum, δ_C, ppm: 172.63, 171.39, 168.13, 145.62, 138.04, 129.42, 128.88, 124.30, 123.60, 78.23, 73.37, 58.49, 58.42, 55.73, 55.11, 54.93, 50.46, 45.28, 44.88, 44.73, 38.13, 38.04, 37.98, 29.78, 27.85, 27.63, 27.58, 26.13, 26.09, 25.99. HRMS (ESI-TOF): *m*/*z* 568.2539 [*M* + H]$^+$. $C_{27}H_{35}ClN_9O_3$. Calculated: *M* + H 568.2551.

4,9-Bis[(1-{[3-(4-chlorophenyl)-1,2,4-oxadiazol-5-yl]methyl}-1*H*-1,2,3-triazol-4-yl)methyl]-1,4,9,12-tetraazacyclohexadecane-2,11-dione (9d). Yield 60 mg (42%), yellow oil, R_f 0.320 (EtOAc/MeOH, 5:1). IR spectrum (KBr), ν, cm^{-1}: 3348, 3136, 2928, 2854, 1658, 1597, 1570, 1527, 1465, 1408, 1342, 1265. ^{1}H NMR spectrum, δ, ppm: 7.95–7.89 m (4H), 7.80 s (2H), 7.51–7.45 br.t (2H, *J* = 5.6 Hz), 7.44–7.38 d.d (4H, *J* = 8.8, 2.4 Hz), 5.89 s (4H), 3.77 s (4H), 3.21 br.s (4H), 3.05 br.s (4H), 2.50 br.s (4H), 1.21 br.s (8H). ^{13}C NMR spectrum, δ_C, ppm: 172.63, 171.39, 168.13, 145.62, 138.04, 129.42, 128.88, 124.30, 123.60, 58.52, 55.89, 50.56, 45.28, 38.15, 31.99, 30.36, 29.77, 29.73, 29.69, 29.58, 29.43, 29.23, 27.35, 26.08. HRMS (ESI-TOF): *m*/*z* 803.2804 [*M* + H]$^+$. $C_{36}H_{41}Cl_2N_{14}O_4$. Calculated: *M* + H 803.2812.

4-[(1-{[3-(4-Bromophenyl)-1,2,4-oxadiazol-5-yl]-methyl}-1*H*-1,2,3-triazol-4-yl)methyl]-9-(prop-2-yn-1-yl)-1,4,9,12-tetraazacyclohexadecane-2,11-dione (8e). Yield 35 mg (38%), yellow oil, R_f 0.410 (EtOAc/MeOH, 5:1). IR spectrum (KBr), ν, cm^{-1}: 3425, 3360, 3302, 3055, 2935, 2866, 1666, 1597, 1527, 1469, 1423, 1404, 1342, 1265. ^{1}H NMR spectrum, δ, ppm: 7.91–7.87 d (2H, *J* = 8.4 Hz), 7.76 br.s (1H), 7.62–7.58 d (2H, *J* = 8.4 Hz), 7.45 br.s (1H), 7.28–7.22 m (1H), 5.91 s (2H), 3.82 s (2H), 3.57 s (1H), 3.36 s (1H), 3.27 d (4H, *J* = 16.0 Hz), 3.09 s (4H), 2.61–2.48 d.t (4H, *J* = 22.8, 16.4, 6.4 Hz), 1.70 br.s (6H), 1.60–1.40 m (4H). ^{13}C NMR spectrum, δ_C, ppm: 172.46, 171.12, 167.99, 132.42, 132.23, 129.09, 126.52, 124.77, 123.47, 78.04, 74.10, 58.49, 58.34, 55.29, 50.48, 45.29, 44.88, 38.13, 38.04, 27.64, 27.58, 26.11, 25.98. HRMS (ESI-TOF): *m*/*z* 612.2026 [*M* + H]$^+$. $C_{27}H_{35}BrN_9O_3$. Calculated: *M* + H 612.2046.

4,9-Bis[(1-{[3-(4-bromophenyl)-1,2,4-oxadiazol-5-yl]methyl}-1*H*-1,2,3-triazol-4-yl)methyl]-1,4,9,12-tetraazacyclohexadecane-2,11-dione (9e). Yield 75 mg (56%), yellow oil, R_f 0.273 (EtOAc/MeOH, 5:1). IR spectrum (KBr), ν, cm^{-1}: 3348, 3140, 3055,

2939, 2862, 2831, 1666, 1597, 1566, 1527, 1469, 1408, 1342, 1265. ^{1}H NMR spectrum, δ, ppm: 7.89–7.85 m (4H), 7.79 s (2H), 7.59 d.d (4H, *J* = 11.1, 3.4 Hz), 7.49 t (2H, *J* = 5.3 Hz), 5.91 s (4H), 3.80 s (4H), 3.24 s (4H), 3.08 s (4H), 2.53 s (4H), 1.53 d (8H, *J* = 9.6 Hz). ^{13}C NMR spectrum, δ_C, ppm: 172.59, 171.32, 168.26, 132.41, 129.06, 126.52, 124.75, 123.52, 58.54, 55.89, 50.62, 45.28, 38.17, 27.36, 26.08. HRMS (ESI-TOF): *m*/*z* 891.1828 $[M + H]^+$. $C_{36}H_{41}Br_2N_{14}O_4$. Calculated: *M* + H 891.1802.

4-[(1-{[3-(4-Nitrophenyl)-1,2,4-oxadiazol-5-yl]methyl}-1*H*-1,2,3-triazol-4-yl)methyl]-9-(prop-2-yn-1-yl)-1,4,9,12-tetraazacyclohexadecane-2,11-dione (8f). Yield 45 mg (35%), yellow oil, R_f 0.522 (EtOAc/MeOH, 5:1). IR spectrum (KBr), ν, cm^{-1}: 3448, 3302, 3140, 3101, 2939, 2862, 1662, 1612, 1531, 1450, 1415, 1342, 1292. ^{1}H NMR spectrum, δ, ppm: 8.31 d (2H, *J* = 8.9 Hz), 8.20 d.d (2H, *J* = 7.3, 6.7 Hz), 7.79 s (1H), 7.41 t (1H, *J* = 5.2 Hz), 7.29–7.25 m (1H), 5.96 s (2H), 3.81 s (2H), 3.35 d (2H, *J* = 1.7 Hz), 3.32–3.20 m (4H), 3.06 d (4H, *J* = 12.5 Hz), 2.53 d.t (4H, *J* = 13.1, 5.9 Hz), 2.19 s (1H), 1.53 s (4H), 1.52–1.43 m (4H). ^{13}C NMR spectrum, δ_C, ppm: 173.37, 171.22, 171.15, 170.92, 167.41, 149.78, 145.51, 131.68, 128.67, 124.31, 123.64, 78.25, 73.38, 58.51, 58.29, 50.29, 45.24, 45.00, 38.13, 38.04, 27.64, 27.49, 26.07. HRMS (ESI-TOF): *m*/*z* 579.2771 $[M + H]^+$. $C_{27}H_{35}N_{10}O_5$. Calculated: *M* + H 579.2792.

4,9-Bis[(1-{[3-(4-nitrophenyl)-1,2,4-oxadiazol-5-yl]methyl}-1*H*-1,2,3-triazol-4-yl)methyl]-1,4,9,12-tetraazacyclohexadecane-2,11-dione (9f). Yield 75 mg (41%), yellow solid, mp 133–134°C, R_f 0.370 (EtOAc/MeOH, 5:1). IR spectrum (KBr), ν, cm^{-1}: 3348, 3136, 2928, 2854, 1658, 1597, 1570, 1527, 1465, 1408, 1342, 1265. ^{1}H NMR spectrum, δ, ppm: 8.29 d (4H, *J* = 8.0 Hz), 8.18 d (4H, *J* = 8.4 Hz), 7.82 s (2H), 7.48 t (2H, *J* = 5.2 Hz), 5.96 s (4H), 3.81 s (4H), 3.21 br.s (4H), 3.06 s (4H), 2.53 s (4H), 1.53 br.s (8H). ^{13}C NMR spectrum, δ_C, ppm: 173.36, 171.38, 167.39, 149.76, 145.62, 131.65, 128.65, 124.30, 123.65, 58.48, 55.98, 50.54, 45.25, 38.16, 27.37, 26.09. HRMS (ESI-TOF): *m*/*z* 825.3261 $[M + H]^+$. $C_{36}H_{41}N_{16}O_8$. Calculated: *M* + H 825.3293.

4-[(1-{[3-(4-Methoxyphenyl)-1,2,4-oxadiazol-5-yl]methyl}-1*H*-1,2,3-triazol-4-yl)methyl]-9-(prop-2-yn-1-yl)-1,4,9,12-tetraazacyclohexadecane-2,11-dione (8g). Yield 30 mg (36%), white solid, mp 124–125°C, R_f 0.300 (EtOAc/MeOH, 5:1). IR spectrum (KBr), ν, cm^{-1}: 3441, 3348, 3302, 3136, 3059, 2939, 2839, 1662, 1573, 1531, 1481, 1423, 1346, 1257. ^{1}H NMR spectrum, δ, ppm: 7.95–7.92 m (2H), 7.76 s (1H), 7.48 t (1H, *J* = 5.3 Hz), 7.25 t (1H, *J* = 4.3 Hz), 6.96–6.93 m (2H), 5.88 s (2H), 3.82 t (3H, *J* = 3.3 Hz), 3.80 s (2H), 3.34 d (2H, *J* = 1.2 Hz), 3.26 d (4H, *J* = 14.7 Hz), 3.08 d (4H, *J* = 3.1 Hz), 2.52 d.t (4H, *J* = 13.0, 6.0 Hz), 2.18 d (1H, *J* = 0.9 Hz), 1.53 s (4H), 1.50–1.43 m (4H). ^{13}C NMR spectrum, δ_C, ppm: 172.01, 171.19, 168.62, 162.39, 145.37, 129.26, 123.51, 118.19, 114.47, 78.19, 72.87, 58.47, 55.76, 54.96, 53.55, 50.54, 45.32, 44.72, 38.10, 38.01, 27.63, 26.18, 25.93. HRMS (ESI-TOF): *m*/*z* 564.3041 $[M + H]^+$. $C_{28}H_{38}N_9O_4$. Calculated: *M* + H 564.3047.

4,9-Bis[(1-{[3-(4-methoxyphenyl)-1,2,4-oxadiazol-5-yl]methyl}-1*H*-1,2,3-triazol-4-yl)methyl]-1,4,9,12-tetraazacyclohexadecane-2,11-dione (9g). Yield 54 mg (46%), white solid, mp 191–192°C, R_f 0.180 (EtOAc/MeOH, 5:1). IR spectrum (KBr), ν, cm^{-1}: 3332, 3124, 2935, 2839, 1658, 1612, 1597, 1573, 1527, 1481, 1346, 1303. ^{1}H NMR spectrum, δ, ppm: 7.90 d (4H, *J* = 8.2 Hz), 7.79 s (2H), 7.46 d.d (2H, *J* = 12.7, 7.3 Hz), 6.91 t (4H, *J* = 7.5 Hz), 5.86 s (4H), 3.81 d (6H, *J* = 0.8 Hz), 3.78–3.74 m (4H), 3.21 s (4H), 3.05 s (4H), 2.49 s (4H), 1.50 d (8H, *J* = 11.0 Hz). ^{13}C NMR spectrum, δ_C, ppm: 172.10, 171.33, 168.57, 162.35, 145.57, 129.22, 123.59, 118.18, 114.44, 58.56, 55.78, 55.50, 50.55, 45.31, 38.11, 27.37, 26.07. HRMS (ESI-TOF): *m*/*z* 795.3804 $[M + H]^+$. $C_{38}H_{47}N_{14}O_6$. Calculated: *M* + H 795.3803.

4-{[1-({3-[4-(Methylsulfanyl)phenyl]-1,2,4-oxadiazol-5-yl}methyl)-1*H*-1,2,3-triazol-4-yl]methyl}-9-(prop-2-yn-1-yl)-1,4,9,12-tetraazacyclohexadecane-2,11-dione (8h). Yield 40 mg (38%), yellow oil, R_f 0.522 (EtOAc/MeOH, 5:1). IR spectrum (KBr), ν, cm^{-1}: 3448, 3302, 3136, 3055, 2931, 2858, 1662, 1597, 1527, 1469, 1408, 1346, 1269. ^{1}H NMR spectrum, δ, ppm: 7.91 d (2H, *J* = 8.1 Hz), 7.76 s (1H), 7.47 t (1H, *J* = 5.3 Hz), 7.27 t (3H, *J* = 6.1 Hz), 5.90 s (2H), 3.81 s (2H), 3.35 t (2H, *J* = 3.9 Hz), 3.26 d (4H, *J* = 15.1 Hz), 3.09 d (4H, *J* = 3.7 Hz), 2.59–2.53 m (3H), 2.52–2.46 m (4H), 2.19 d.d (1H, *J* = 2.2, 1.5 Hz), 1.54 s (4H), 1.52–1.42 m (4H). ^{13}C NMR spectrum, δ_C, ppm: 172.29, 171.38, 168.56, 145.61, 143.90, 127.78, 125.79, 123.61, 121.92, 78.22, 73.37, 58.48, 55.74, 55.02, 50.53, 45.32, 44.78, 38.11, 38.03, 27.61, 26.16, 25.96, 15.04. HRMS (ESI-TOF): *m*/*z* 580.2803 $[M + H]^+$. $C_{28}H_{38}N_9O_3S$. Calculated: *M* + H 580.2818.

4,9-Bis{[1-({3-[4-(methylsulfanyl)phenyl]-1,2,4-oxadiazol-5-yl}methyl)-1*H*-1,2,3-triazol-4-yl]methyl}-1,4,9,12-tetraazacyclohexadecane-2,11-dione (9h). Yield 60 mg (41%), white solid, mp 184–185°C, R_f 0.370 (EtOAc/MeOH, 5:1). IR spectrum (KBr), ν, cm^{-1}: 3441, 3147, 2924, 2854, 1647, 1593, 1527, 1465, 1465, 1408, 1384, 1346. ^{1}H NMR spectrum, δ, ppm: 7.86 d (4H, *J* = 8.0 Hz), 7.80 s (2H),

7.48 t (2H, J = 5.5 Hz), 7.27–7.24 m (4H), 5.88 s (4H), 3.76 s (4H), 3.21 s (4H), 3.05 s (4H), 2.49 d.d (10H, J = 11.4, 3.4 Hz), 1.50 d (8H, J = 10.8 Hz). ^{13}C NMR spectrum, δ_C, ppm: 172.29, 171.38, 168.56, 145.61, 143.90, 127.78, 125.79, 123.61, 121.92, 58.56, 55.82, 50.56, 45.31, 38.13, 27.35, 26.07, 15.01. HRMS (ESI-TOF): m/z 827.3316 $[M + H]^+$. $C_{38}H_{47}N_{14}O_4S_2$. Calculated: M + H 827.3346.

FUNDING

This study was performed under financial support by the Directorate of Research Projects Commission, Bolu Abant İzzet Baysal University (BAP grant no. 2013.03.03.624).

CONFLICT OF INTEREST

No conflict of interest is declared by the authors.

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