Novel Synthesis of 1,2,4-Triazolophanes and 1,3,4-Oxadiazolophanes: A Dieckmann Condensation Approach

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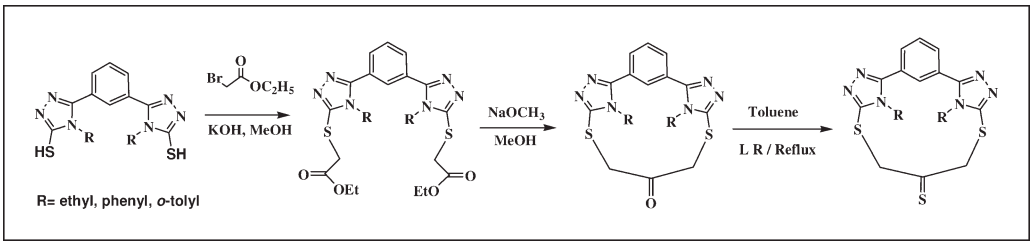

The Dieckmann condensation has been used for the first time for the syntheses of novel 1,2,4-triazolophanes and 1,3,4-oxadiazolophanes. The bis-1,3,4-oxadiazol-2-thiols **1a** and **1b** were reacted with ethyl bromoacetate to give the diesters **2a** and **2b**. Diesters **2a** and **2b** were treated under dry conditions with sodium methoxide in methanol to afford desired symmetrical 1,3,4-oxadiazolophanes **3a** and **3b**. Similarly, diesters of macrocycle precursors containing 1,2,4-triazole moiety, that is, **6a**, **6b**, **10**, **13a**, **13b**, and **13c** were synthesized from **5a**, **5b**, **9**, **12a**, **12b**, and **12c**, respectively. Dieckmann condensation of these diesters afforded symmetrical ketones **7a**, **7b**, **11**, **14a**, **14b**, and **14c**. Extrusion of CO_2 was observed after *in situ* hydrolysis of the conventional Dieckmann product during neutralization by dilute mineral acids to afford highly symmetrical ketone in good yields. Further, the ketones **14a**, **14b**, and **14c** were converted into their respective thiones by the reaction with Lawesson's reagent. All the products were synthesized with good yields, and structures were confirmed by various spectroscopic tools and elemental analyses.

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INTRODUCTION

A progressive interest has been directed in the last few years to the chemistry of crown ethers containing heterocyclic rings on the periphery of the macrocyclic system. These macrocycles were found to exhibit interesting host–guest complexation characteristics [1,2] and biochemical properties [3]. Incorporation of heterocyclic moieties within the cavity of the macrocyclic rings not only provides rigidity but also helps to participate in complexation through their soft donor atoms. Macrocyclic ethers with pyridine and other nitrogen containing heterocyclic subunits were reported to form strong and selective interactions with various charged and neutral guest molecules [4–7]. In a recent communication, we have reported the synthesis of various novel aminotriazolophanes [8] and thiatriazolophanes with various 1,2,4-triazole macrocyclic precursors [9].

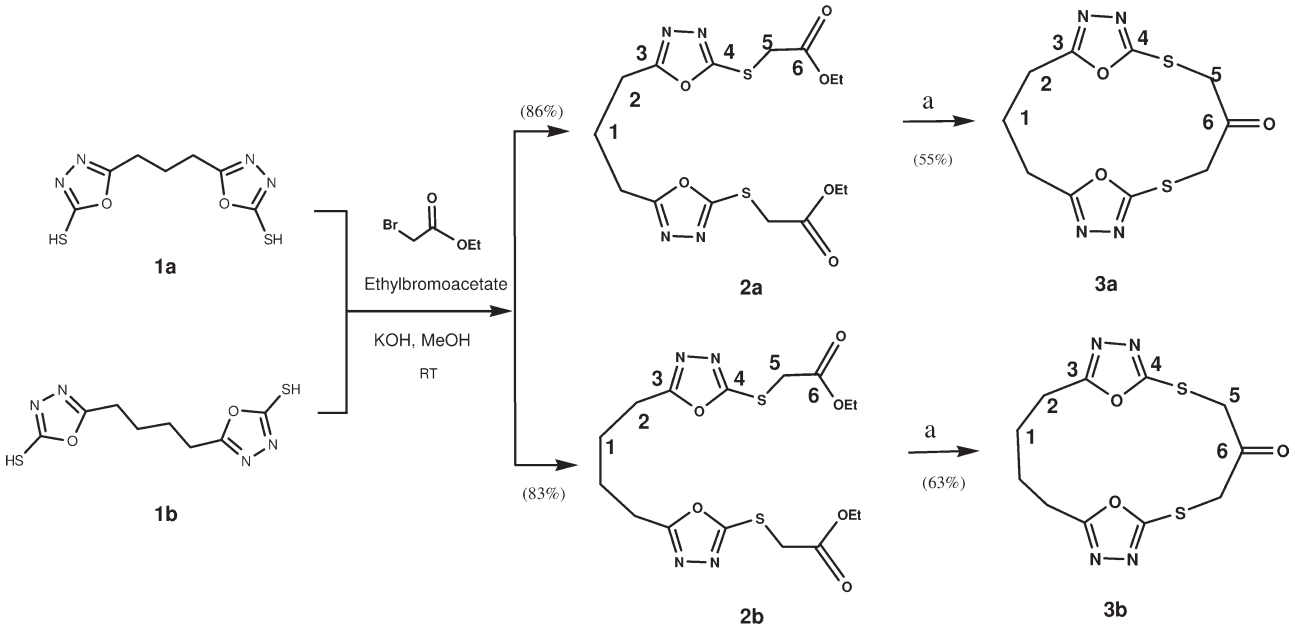
Intramolecular diester cyclization to give cyclic β-Keto esters is commonly known as the Dieckmann condensation [10]. An enormous number of examples for the construction of carbon systems with varying ring size using this reaction have been reported [11–24]. Some of the recent reports focus on the synthesis of pulvinones [25], indolizidines [26], mycophenloic acid [27], and rutaecarpine [28].

We now report for the first time the synthetic applications of Dieckmann condensation for the construction of macrocyclic ethers.

The reaction is most successful for the synthesis of five-, six-, and seven-membered rings, whereas it either failed or resulted in very poor yields for 9- to 12-membered rings [29]. In case of forming 13-membered or larger ring systems by Dieckmann condensation, because of the probability of intermolecular reactions when the esters are reacted under usual dilutions, the ring closure is generally carried out according to high dilution techniques [30].

In accordance with these findings, we could obtain the product in usual dilution condition in all cases. In continuation [31–35] of our research interest in synthesizing novel macrocyclic crown ethers containing heterocyclic subunits, we now report here the synthesis of 1,2,4-triazolophanes and 1,3,4-oxadiazolophanes using Dieckmann condensation. To our knowledge, this is the first report on the macrocyclic ring closure using Dieckmann condensation for the synthesis of 1,2,4-triazolophanes and 1,3,4-oxadiazolophanes.

Scheme 1. Synthesis of 1,3,4-oxadiazolophanes.



Further, the carbonyl groups of these macrocycles so synthesized were converted into thione by treating with Lawesson's reagent as per the reported methods [36].

RESULTS AND DISCUSSION

In the present investigation, we have carried out the Dieckmann cyclization of the diesters (e.g., **2a**) using sodium methoxide as a base in dry methanol, under moderate to high dilution conditions with high speed stirring in nitrogen atmosphere. The 1,2,4-oxadiazole [34] macrocycle precursors, for example, **1a** and **1b** were treated with potassium hydroxide in methanol. The salt generated *in situ* was treated with ethylbromoacetate to afford the diesters, for example, **2a** and **2b**. Diesters **2a** and **2b** were then subjected to Dieckmann condensation using metal alkoxides, that is, sodium methoxide in methanol at room temperature under nitrogen atmosphere. The shift in the carbonyl peak in the IR spectrum of the compounds **3a** and **3b** suggested the conversion of the diester into cyclic ketone (Scheme 1). The ^{1}H and ^{13}C NMR spectra, HRMS, and elemental analyses of the compounds are in agreement with the proposed structures.

Monoketones (**3a**, **3b**) and diketone (**4**; Fig. 1) were collected and identified. However, increasing the dilution avoided formation of dimmer/diketone. As it was not a part of our research interest, no attempt was made to isolate and characterize any diketones, triketones, or polymeric products except (**4**), its structure was later confirmed by ^{1}H NMR, ^{13}C NMR, HRMS, and elemental analyses.

The steps from ester to carbalkoxyketone involve the use of a strong base, a base, which acts practically irreversibly for best results, but since the hydrolysis and decarboxylation steps may not require strong acid treatment; the latter feature directed the hydrolysis followed by decarboxylation to afford the symmetrical ketone instead of conventional β-ketoesters [11].

The *N,N*-disubstituted 1,2,4-triazole macrocycle precursors **5a** and **5b** [9] were similarly treated with potassium hydroxide and ethylbromoroacetate to afford the diesters **6a** and **6b**. Subsequent exposure of the diesters, **6a** and **6b**, to Dieckmann condensation conditions afforded the triazolophanes **7a** and **7b** (Scheme 2) with 60–63% yield.

In another approach, 4-phenyl-5-(2′-hydroxyphenyl)-3-mercapto-1,2,4-triazole (**8**) was synthesized as per the known procedure [37]. Reaction of **8** with 1,3-dibromo-propane (2:1 mol ratio) in methanol afforded 1,3-bis[4-phenyl-5(2′-hydroxyphenyl)-1,2,4-

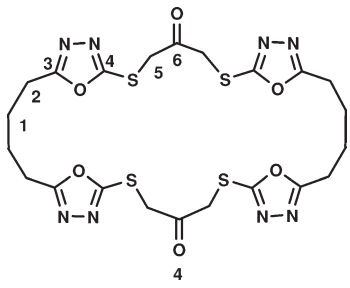
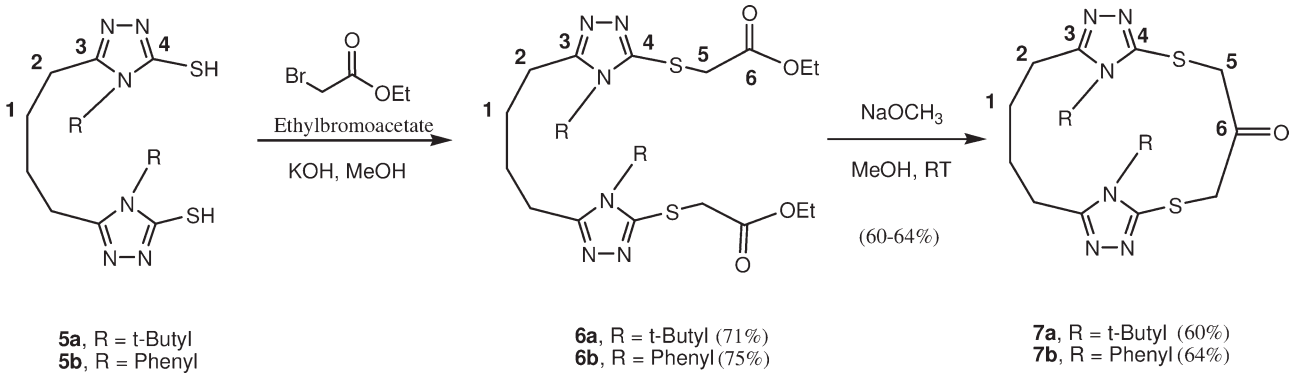


Figure 1. Diketone **4**.

Scheme 2. Synthesis of triazolophanes through Dieckmann condensation.



triazol-3-yl]mercaptopropane (**9**). Further, diester **10** was obtained by reaction of compound **9** with ethylbromoacetate. Dieckmann cyclization of diester **10** afforded symmetrical ketone **11** in 46% yields (Scheme 3).

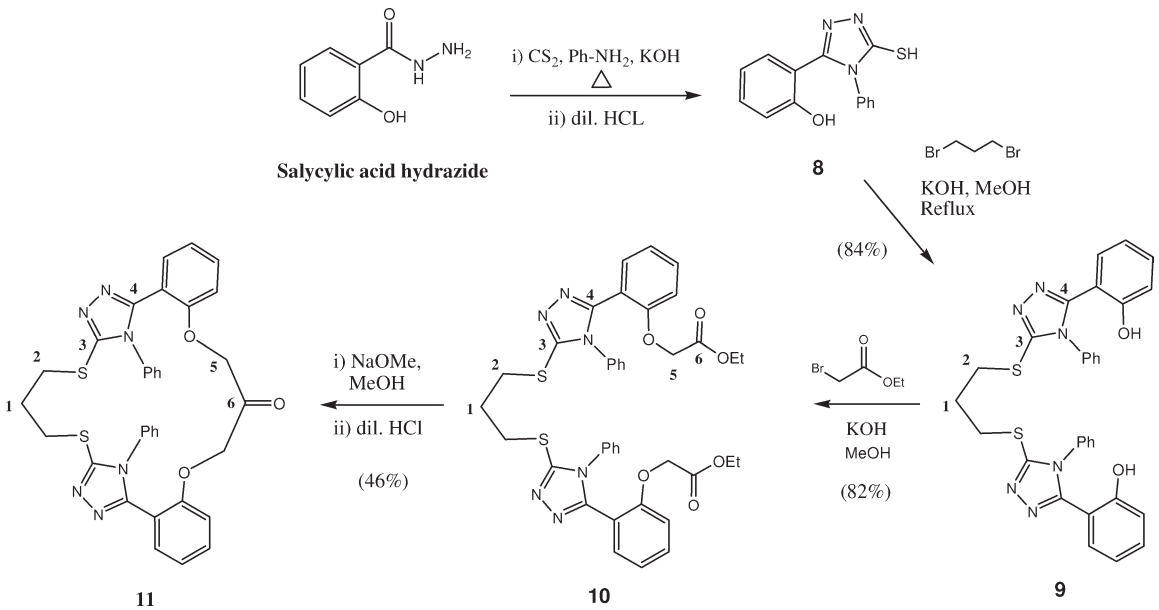
The scope of the Dieckmann condensation was further explored with compounds, **12a**, **12b**, and **12c** [9], which on reaction with ethylbromoacetate afforded respective diesters **13a**, **13b**, and **13c**. Dieckmann condensation of these diesters resulted symmetrical ketones **14a, 14b**, and **14c** in good yields (Scheme 4), further these ketones were reacted with Lawesson's reagent in refluxing toluene to achieve thionation of the ketone macrocycles (Scheme 5). The absence of the characteristic carbonyl peak in the IR and carbonyl carbon in ^{13}C NMR, finally mass spectrum confirmed the structures of the compound **14a**, **14b**, and **14c**. We were also successful in using microwave irradiation technique to facilitate the thionation reaction in some cases of the synthesized compounds; and the structures were confirmed through mix melting point and CO-IR.

In conclusion, we were successful in using the Dieckmann condensation reaction for the synthesis of macrocyclic aza crown ethers containing 1,2,4-triazole and 1,3,4-oxadiazole units. This report also highlights the synthesis of heterophanes containing 10 or more members in good yields.

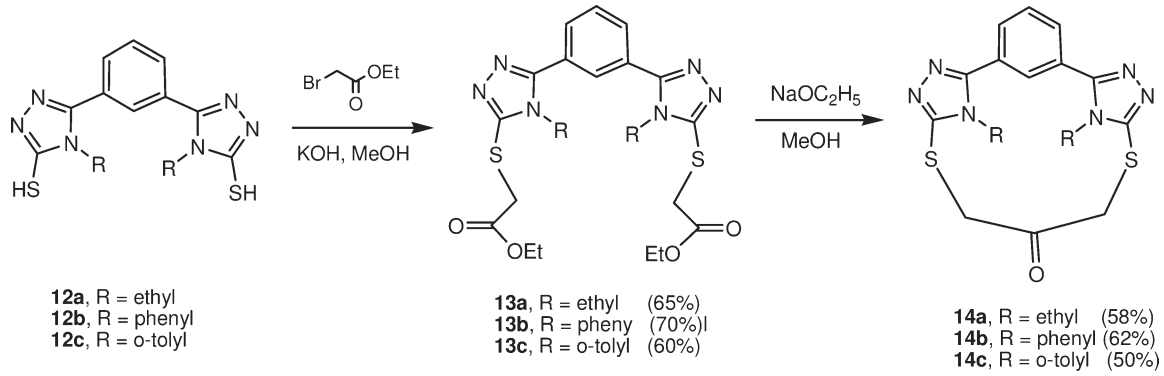
EXPERIMENTAL

General experimental procedures. All chemicals were obtained from E-Merck and Qualigens. Solvents were purified according to reported methods. The progress of the reactions was followed with TLC using silica gel SILG/UV 254 plates. Chromatography was carried on a column over silica gel 60, 0.063–0.200mm (70–230 mesh ASTM). IR spectra were run on a Perkin Elmer 257-FTIR 1600 spectrophotometer using potassium bromide (KBr) discs. The ^{1}H and ^{13}C NMR (300 MHz) were run on a Jeol AL-300 spectrometer (δ in ppm, *J* in

Scheme 3. Synthesis of lariat triazolophanes ethers via Dieckmann condensation.



Scheme 4. Conversion of the crown precursor to macrocycle through Dieckmann condensation.



12a, R = ethyl
12b, R = phenyl
12c, R = o-tolyl

13a, R = ethyl (65%)
13b, R = pheny (70%)l
13c, R = o-tolyl (60%)

14a, R = ethyl (58%)
14b, R = phenyl (62%)
14c, R = o-tolyl (50%)

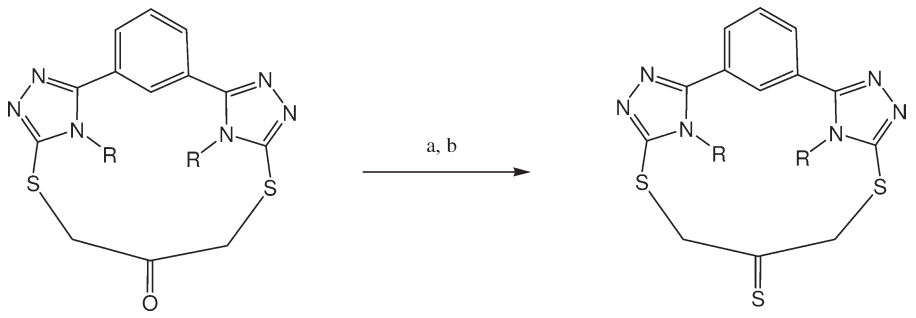
Hz). Mass spectra were recorded on a Shimadzu GCMS-QP 2010. The C, H, N, S analysis of the compounds were carried out at UICT, Analytical Chemistry Department, Mumbai and are in agreement with the theoretical values. Melting points were taken in open capillaries and are uncorrected.

Synthesis of 1,3-bis[(5-carbethoxymethylmercapto)-1,3,4-oxadiazol-2-yl]propane (2a). 1,3-Bis(5-mercapto-1,3,4-oxadiazol-2-yl)propane (2.58 g, 10 mmol) and KOH (1.12 g, 20 mmol) in 20 mL of methanol were mixed together at 0°C. To the slurry thus obtained, ethyl bromoacetate (3.34 g, 20 mmol) was added portion wise over a period of 20–30 min at 0°C. The reaction workup was carried out by addition of water and subsequent extraction with dichloromethane. The organic layer was washed with 2% NaOH solution, aqueous NH_4Cl, distilled water, and finally was dried over sodium sulphate and concentrated. The product thus obtained was sufficiently pure to be used without further purification. m.p. 90–92°C, Yield: 86%. IR (KBr, cm^{-1}): 2964.3, 2920.1, 1752.6, 1584.4, 1495.3, 1302.2, 1153.8, and 1025.4. ^{1}H NMR ($CDCl_3$) : δ 1.31 (*t*, 6H, J = 6.5 Hz, 2x —OCH_2CH_3), 1.98 (quintet, 2H, J = 6.5 Hz, H1), 2.98 (t, 4H, J = 6.5 Hz, H2), 4.16 (s, 4H, H5) and 4.29 (q, 4H, J = 6.5 Hz, —OCH_2). ^{13}C NMR ($CDCl_3$): 14.06 (2x —OCH_2CH_3), 20.54 (C1), 22.16 (C2), 32.04 (C5), 62.11 (2x —O—CH_2), 154.78 (C3), 164.19 (C4), and 168.12 ppm (C6). MS (DI): M^+ at m/z 416. The other main fragmentation peaks were at m/z 387, 358, 300, 341, and 94. Anal. (calcd./found in %) for $C_{15}H_{20}N_4O_6S_2$: C, 43.2/43.5; H, 4.84/4.63; N, 13.45/13.53; S, 15.40/15.60.

A similar protocol was used for the syntheses of other diesters namely **2b**, **6a**, **6b**, **10**, **13a**, **13b**, and **13c**.

Synthesis of 2,6-dithia-1,7(2,5)-1,3,4-oxadiazola-cyclodecaphane-4-one (3a). The diester of 1,4-bis[(5-carbethoxymethylmercapto)-1,3,4-oxadiazol-2-yl]butane (4.58 g, 10 mmol) was stirred with sodium methoxide (0.54 g, 10 mmol) in dry methanol (100 mL) under anhydrous conditions for 6 h. The reaction mixture was then poured onto crushed ice and acidified with dil. hydrochloric acid. The colorless solid was filtered, washed with water, and dried. Compound was further purified by column chromatography using ethyl acetate:hexane (8:2). m.p. 163–165°C. Yield: 55%. HRMS: Found M^+ 298.3408; $C_{10}H_{10}N_4O_3S_2$ requires 298.3414. IR (KBr, cm^{-1}): 2934.9, 1721.9, 1585.3, 1491.4, 1262.7, and 1170.8. ^{1}H NMR ($CDCl_3$): δ 1.87 (quintet, 2H, J = 7.0 Hz, H1), 2.93 (t, 4H, J = 7.0 Hz, H2), 4.09 (s, 4H, H5). ^{13}C NMR ($CDCl_3$): 25.59 (C1), 34.67 (C2), 53.56 (C5), 161.30 (C3), 165.72 (C4), and 170.60 ppm (C6). MS (DI): M^+ at *m/z* 398. The other main fragmentation peaks were at *m/z* 242, 126 and 94. Anal. (calcd./found in %) for $C_{10}H_{10}N_4O_3S_2$: C, 40.3/40.5; H, 3.38/3.52; N, 18.78/18.58; S, 21.49/21.58.

Scheme 5. Thionation by Lawesson's reagent.



14a, R= ethyl
14b, R= phenyl
14c, R= o-tolyl

15a, R= ethyl (50%)
15b, R= pheny (49%)
15c, R= o-tolyl (45%)

a) MW, b) Lawesson's reagent, Reflux, Tolune

Similar protocol was used for the synthesis of **3b**, **7a**, **7b**, **11**, **14a**, **14b**, and **14c**.

Synthesis of 1,4-bis[(5-carbethoxymethylmercapto)-1,3,4-oxadiazol-2-yl] butane (2b). m.p. 156–127°C, Yield 83%. IR (KBr, cm^{-1}): 2987.2, 2919.5, 1765.4, 1584.2, 1495.9, 1302.4, 1153.1, and 1025.8. ^{1}H NMR ($CDCl_3$) : δ 1.29 (t, 6H, J = 6.0 Hz, 2x —OCH_2CH_3), 1.89 (quintet, 4H, J = 6.0 Hz, H1), 2.87 (t, 4H, J = 6.0 Hz, H2) and 4.19 (s, 4H, H5) and 4.23 (q, 4H, J = 6.0 Hz, 2x —OCH_2). ^{13}C NMR ($CDCl_3$): 8.82 (2x —OCH_2CH_3), 19.65 (C1), 20.16 (C2), 29.14 (C5), 57.13 (2x —OCH_2), 157.69 (C3), 162.19 (C4), and 162.32 (C6) ppm. MS (DI): M^+ at *m/z* 430. The other main fragmentation peaks were at *m/z* 385, 341, 356, 140, and 108. Anal. (calcd./found in %) for $C_{16}H_{22}N_4O_6S_2$: C, 44.64/44.5; H, 5.15/5.26; N, 13.0/13.11; S, 14.90/14.77.

Synthesis of 2,6-dithia-1,7(2,5)-1,3,4-oxadiazola-cyclo undecaphane-4-one (3b). m.p. 180–182°C, Yield 63%. HRMS: Found M^+ 312.3674; $C_{11}H_{12}N_4O_3S_2$ requires 312.3680. IR (KBr, cm^{-1}): 2934.9, 1728.9, 1585.3, 1491.4, 1262.7, and 1170.8. ^{1}H NMR (CD_3OD): δ 1.87 (quintet, 4H, J = 6.0 Hz, H1), 2.93 (t, 4H, J = 6.0 Hz, H2), 4.18 (s, 4H, H5). ^{13}C NMR (CD_3OD): 25.59 (C1), 34.67 (C2), 53.56 (C5), 165.35 (C3), 169.72 (C4), and 170.64 (C6) ppm. MS (DI): M^+ at *m/z* 312. The other main fragmentation peaks were at *m/z* 256, 140, and 108. Anal. (calcd./found in %) for $C_{11}H_{12}N_4O_3S_2$: C, 42.3/42.5; H, 3.87/3.62; N, 17.94/17.78; S, 20.53/20.29.

Synthesis of 2,6,13,17-tetrathia-1,7,12,15(2,5)-1,3,4-oxadiazola-cyclodocosane-4,15-dione (4). m.p. <300°C, Yield 13%. HRMS: Found M^+ 624.7352; $C_{22}H_{24}N_8O_6S_4$ requires 624.7360. IR (KBr, cm^{-1}): 2961.5, 1734.2, 1603.1, 1516.3, 1285.8, and 1182.6. ^{1}H NMR (DMSO-d_6): δ 1.66 (quintet, 8H, J = 6.0 Hz, H1), 2.68 (t, 8H, J = 6.0 Hz, H2), 4.12 (s, 8H, H5). ^{13}C NMR (DMSO-d_6): 29.62 (C1), 34.63 (C2), 56.18 (C5), 166.12 (C3), 169.96 (C4), and 180.23 (C6) ppm. Anal. (calcd./found in %) for $C_{22}H_{24}N_8O_6S_4$: C, 42.3/42.6; H, 3.87/3.59; N, 17.94/17.83; S, 20.53/20.33.

Synthesis of 1,4-bis(5-mercapto-4-t-butyl-1,2,4-triazol-3-yl)butane (5a). m.p. 213–215°C, Yield 70%. IR (KBr, cm^{-1}): 2920.9, 1520.9, 1491.4, 1262.7, and 1170.8. ^{1}H NMR (DMSO-d_6): δ 1.77 (quintet, 4H, J = 6.75 Hz, H1), 1.84 (s, 18H, 2x —$C(CH_3)_3$), 2.92 (t, 4H, J = 6.75 Hz, H2) and 13.13 (s, 2H, S*H*). ^{13}C NMR (DMSO-d_6): 26.72 (C1), 28.98 (2x —$C(CH_3)_3$), 29.85 (C2), 61.72 (2x N—$C(CH_3)_3$), 152.85 (C3), and 152.46 (C4) ppm. MS (DI): M^+ at *m/z* 368. The other main fragmentation peaks were at *m/z* 312, 256, 115, 142, and 128. Anal. (calcd./found in %) for $C_{16}H_{28}N_6S_2$: C, 52.14/52.28; H, 7.66/7.52; N, 22.18/22.28; S, 17.40/17.51.

Synthesis of 4-bis [4-t-butyl-5-(carbethoxy methylmercapto)-1,2,4-triazol-3-yl] butane (6a). m.p. 178–180°C, Yield 71%. IR (KBr, cm^{-1}): 2947.3, 1770.5, 1557.2, 1502.7, 1307.5, 1173.9, 1218.4, and 1029.4. ^{1}H NMR ($CDCl_3$) : δ 1.27 (t, 6H, J = 6.5 Hz, 2x —OCH_2CH_3), 1.73 (s, 18H, 2x —$C(CH_3)_3$), 2.09 (quintet, 4H, J = 6.5Hz, H1), 2.93 (t, 4H, J = 6.5 Hz, H2), 4.12 (s, 4H, H5) and 4.18 (quartet, 4H, J = 6.5 Hz, 2x —OCH_2). ^{13}C NMR ($CDCl_3$): 14.02 (2x —OCH_2CH_3), 27.59 (C1), 29.75 (2x —$C(CH_3)_3$), 30.62 (C2), 36.04 (C5), 58.84 (2x N—$C(CH_3)_3$), 61.72 (2x —OCH_2), 149.36 (C3), 155.85 (C4), and 168.61 (C6) ppm. MS (DI): M^+ at *m/z* 540. The other main fragmentation peaks were at *m/z* 426, 282, 190, 136, and 110. Anal. (calcd./found in %) for $C_{24}H_{40}N_6O_4S_2$: C, 53.31/53.20; H, 7.46/7.68; N, 15.54/15.88; S, 11.86/11.58.

Synthesis of 4-bis[4-phenyl-5-(carbethoxy methylmercapto)-1,2,4-triazol-3-yl] butane (6b). m.p. 137–139°C, Yield: 75%. IR (KBr, cm^{-1}): 3136.3, 2957.2, 1769.8, 1620.4, 1502.3, 1334.1, and 1228.4. ^{1}H NMR ($CDCl_3$) : δ 1.16 (t, 6H, J = 7 Hz, —OCH_2CH_3), 2.14 (quintet, 4H, J = 7 Hz, H1), 2.93 (t, 4H, J = 7 Hz, H2), 4.15 (s, 4H, H5), 4.31 (quartet, 4H, J = 7 Hz, 2x —OCH_2) and 6.79, 7.23, and 7.52 (m, 10H, Aromatic *H*). ^{13}C NMR ($CDCl_3$): 15.12 (2 x —OCH_2CH_3), 29.12 (C1), 32.32 (C2), 37.13 (C5), 63.12 (2x —OCH_2), 129.11, 132.43, 134.22, and 136.23 (4, Aromatic *C*), 147.24 (C3), 154.35 (C4), and 170.01 (C6) ppm. MS (DI): M^+ at *m/z* 580. The other main fragmentation peaks were at *m/z* 406, 272, 138, and 110. Anal. (calcd./found in %) for $C_{28}H_{32}N_6O_4S_2$: C, 57.91/57.8; H, 5.55/5.37; N, 14.47/14.58; S, 11.0/11.21.

Synthesis of 1^4,6^4-di-t-butyl-2,6-dithia-1,7(3,5)-1,2,4-triazola-cycloundecaphane-4-one (7a). m.p. 153–155°C, Yield 60%. HRMS: Found M^+ 422.6108; $C_{19}H_{30}N_6OS_2$ requires 422.6111. IR (KBr, cm^{-1}): 2933.6, 2836.2, 1727.4, 1502.2, 1378.0, 1194.2, and 1293.5. ^{1}H NMR ($CDCl_3$): δ 1.75 (s, 18H, 2x —$C(CH_3)_3$), 1.90 (quintet, 4H, J = 7 Hz, H1), 2.98 (t, 4H, J = 7 Hz, H2) and 4.15 (s, 4H, H5). ^{13}C NMR ($CDCl_3$): 28.41 (C1), 29.79 (C2), 35.67 (2x —$C(CH_3)_3$), 55.45 (C5), 59.0 (2 x —$C(CH_3)_3$), 157.50 (C3), 163.01 (C4), and 170.40 (C6) ppm. MS (DI): M^+ at *m/z* 422. The other main fragmentation peaks were at *m/z* 308, 252, 136, and 110. Anal. (calcd./found in %) for $C_{19}H_{30}N_6OS_2$: C, 54.0/54.11; H, 17.16/17.29; N, 19.89/19.68; S, 5.17/5.31.

Synthesis of 1^4,6^4-di-phenyl-2,6-dithia-1,7(3,5)-1,2,4-triazola-cycloundecaphane-4-one (7b). m.p. 187–189°C, Yield 64%. HRMS: Found M^+ 462.5906; $C_{23}H_{22}N_6OS_2$ requires 462.5904. IR (KBr, cm^{-1}): 3134.5, 2973.6, 1732.4, 1510.2, 1378.0, 1194.2, and 1293.5. ^{1}H NMR ($CDCl_3$): δ 2.11 (quintet, 4H, J = 7 Hz, H1), 2.92 (t, 4H, J = 7 Hz, H2), 4.21 (s, 4H, H5) and 6.87, 7.12, and 7.46 (m, 10H, Aromatic *H*). ^{13}C NMR ($CDCl_3$): 28.41 (C1), 29.79 (C2), 53.95 (C5), 129.16, 131.58, 133.29, and 136. 23 (4, Aromatic *C*), 154.63 (C3), 163.01 (C4), and 171.32 (C6) ppm. MS (DI): M^+ at *m/z* 462. The other main fragmentation peaks were at *m/z* 406, 138, and 110. Anal. (calcd./found in %) for $C_{23}H_{22}N_6OS_2$: C, 59.72/59.5; H, 4.79/4.59; N, 18.17/18.33; S, 13.86/13.55.

Synthesis of 1,3-bis[4-phenyl-5(2′-hydroxyphenyl)-1,2,4-triazol-3-yl]mercaptopropane (9). m.p. 166–168°C, Yield: 75%. IR (KBr, cm^{-1}): 3068.6, 2946.0, 1621.3, 1565.3, 1502.4, 1334.3, and 1228.5. ^{1}H NMR ($CDCl_3$) : δ 2.34 (quintet, 2H, J = 6.5 Hz, H1), 3.78 (t, 4H, J = 6.5 Hz, H2), 6.58–7.53(m, 18H, Aromatic *H*) and 11.12 (s, 2H, 2x —OH, D_2O-exchangeable). ^{13}C NMR ($CDCl_3$): 30.32 (C1), 34.16 (C2), 112.28, 113.23, 114.83, 116.43, 117.93, 119.45, 122.41, 126.34, 34.43, and 155.23(10, Aromatic *C*), 151.62(C3), 153.53 (C4) ppm. MS (DI): M^+ at *m/z* 578. The other main fragmentation peaks were at *m/z* 311, 269, 134, and 91. Anal. (calcd./found in %) for $C_{31}H_{26}N_6O_2S_2$: C, 64.34/64.5; H, 4.53/4.32; N, 14.52/14.70; S, 11.08/11.32.

Synthesis of 1,3-bis[{5-(4-phenyl-2′-carbethoxy phenyl)-1,2,4-triazol-3-yl }mercapto]propane (10). m.p. 144–146°C, Yield: 82%. IR (KBr, cm^{-1}): 3109.6, 2937.8, 1766.9, 1609.7, 1366.4, and 1241.8. ^{1}H NMR ($CDCl_3$) : δ 1.21 (t, 6H, J = 6.5 Hz, 2x —OCH_2CH_3), 2.26 (quintet, 2H, J = 6.5 Hz, H1), 3.41 (t, 4H, J = 6.5 Hz, H2), 4.16 (quartet, 4H, J = 6.5 Hz, 2x —OCH_2), 4.14(s, 4H, H5) and 6.58–7.53(m, 18H, Aromatic *H*). ^{13}C NMR ($CDCl_3$): 14.12 (2x —OCH_2CH_3), 29.12 (C1), 32.17

(C2), 61.42 (2x —O*C*H$_2$CH$_3$), 65.59(C5), 112.28, 116.42, 118.39, 120.42, 122.13, 124.42, 125.53, 132.12, 134.43, and 155.53 (10, Aromatic *C*), 151.62(C3), 153.53 (C4), and 168.28 (C6) ppm. MS (DI): M$^+$ at *m/z* 750. The other main fragmentation peaks were at *m/z* 576, 311, 269, 134, and 91. Anal. (calcd./found in %) for $C_{39}H_{38}N_6O_6S_2$: C, 62.28/72.5; H, 5.10/5.28; N, 11.19/11.31; S, 8.54/8.34.

Synthesis of 1,9-Dibenzena-2,8-(3,5)-1,2,4-triazola-10,14-dioxa-3,7-dithia-2^4,8^4-diphenyl-12-oxo-cyclotetradecaphane (11). m.p. 172–174°C, Yield: 46%. HRMS: Found M$^+$ 632.7536; $C_{34}H_{28}N_6O_3S_2$ requires 632.7545. IR (KBr, cm^{-1}): 3057.4, 2954.0, 1723.7, 1555.3, 1511.1, 1331.1, and 1222.4. ^{1}H NMR ($CDCl_3$): δ 2.26 (quintet, 2H, J = 6.5 Hz, H1), 3.41 (t, 4H, J = 6.5 Hz, H2), 4.54(s, 4H, H5) and 6.57–7.64(m, 18H, Aromatic *H*). ^{13}C NMR ($CDCl_3$): 29.12 (C1), 32.10 (C2), 70.09(C5), 112.28, 125.43, 126.84, 127.33, 128.53, 129.42, 132.32, 134.43, and 155.53 (9, Aromatic *C*), 151.62(C3), 153.53 (C4), and 173.10(C6) ppm. MS (DI): M$^+$ at *m/z* 632. The other main fragmentation peaks were at *m/z* 576, 311, 269, 134, and 91. Anal. (calcd./found in %) for $C_{34}H_{28}N_6O_3S_2$: C, 64.54/64.36; H, 4.46/4.20; N, 13.28/13.50; S, 10.13/10.34.

Synthesis of 1,3-bis (4-ethyl-5-mercapto-1,2,4-triazol-3-yl) benzene (12a). m.p. 170–170°C, Yield 74%. IR (KBr, cm^{-1}): 3100.0, 2933.1, 1623.6, 1545.9, 1501.6, 1277.9, and 1145.9. ^{1}H NMR (DMSO-d_6): δ 1.51 (t, 6H, J = 7.0 Hz, 2x —N—CH$_2$C*H*$_3$), 3.78 (quintet, 4H, J = 7.0 Hz, 2x N—C*H*$_2$), 7.44, 7.78, and 8.16 (m, 4H, Aromatic *H*) and 14.08 (s, 2H, —SH, D_2O exchangeable). ^{13}C NMR (DMSO-d_6): 16.37 (2x —N—CH$_2$*C*H$_3$), 38.97 (2x —N—*C*H$_2$), 125.14, 126.99, 129.32, and138.83 (4, Aromatic *C*), 150.22 (2x N—*C*=N) and 166.97 (2x S—*C*=N) ppm. MS (DI): M$^+$ at *m/z* 332. The other main fragmentation peaks were at *m/z* 303, 274, 216, 130, and 91. Anal. (calcd./found in %) for $C_{14}H_{16}N_6S_2$: C, 50.58/50.34; H, 4.85/4.59; N, 25.28/25.39; S, 19.29/19.49.

Synthesis of 1,3-bis[4-ethyl-5-carbethoxymethyl mercapto-1,2,4-triazol-3-yl]benzene (13a). m.p. 78–80°C, Yield 65%. IR (KBr, cm^{-1}): 2982.8, 2933.6, 1761.6, 1648.8, 1467.7, 1305.3, and 1174.2. ^{1}H NMR ($CDCl_3$): δ 1.29 (t, 6H, J = 6.5 Hz, 2x —N—CH$_2$C*H*$_3$), 1.38 (t, 6H, J = 6.5 Hz, 2x —O—CH$_2$C*H*$_3$), 4.13 (q, 4H, J = 6.5 Hz, 2x —N—C*H*$_2$), 4.19 (s, 4H, 2x —S—C*H*$_2$), 4.24 (q, 4H, J = 6.5 Hz, 2x —O—C*H*$_2$), 7.64, 7.70, and 7.85 (4, Aromatic *H*). ^{13}C NMR ($CDCl_3$): 13.23 (2x —N—CH$_2$*C*H$_3$), 15.98 (2x —O—CH$_2$*C*H$_3$), 35.10 (2x —S—*C*H$_2$), 40.05 (2x —N—*C*H$_2$), 62.20 (2x —O—*C*H$_2$), 127.36, 128.43, 128.53, and 136.12 (4, Aromatic *C*), 150.00 (2x —N—*C*=N), 154.55 (2x —S—*C*=N) and 167.35 (2x —*C*=O) ppm. MS (DI): M$^+$ at *m/z* 536. The other main fragmentation peaks were at *m/z* 303, 274, 216, 130, and 91. Anal. (calcd./found in %) for $C_{24}H_{36}N_6O_4S_2$: C, 53.71/53.5; H, 6.76/6.60; N, 15.66/15.46; S, 11.95/11.86.

Synthesis of 1,3-bis[4-phenyl-5-carbethoxymethyl mercapto-1,2,4-triazol-3-yl]benzene (13b). m.p. 160–162°C, Yield 70%. IR (KBr, cm^{-1}): 2979.3, 2904.5, 1769.8, 1641.8, and 1595.4. ^{1}H NMR (DMSO-d_6): δ 1.28 (t, 6H, J = 7.0 Hz, 2x —OCH$_2$C*H*$_3$) 4.09 (q, 2H, J = 7.0 Hz, 2x —O—C*H*$_2$) 4.23 (s, 2x S—C*H*$_2$) and 7.29–7.58 (m, 14H, Aromatic *H*). ^{13}C NMR (DMSO-d_6): 14.05 (2x —OCH$_2$*C*H$_3$), 33.88 (2x S—*C*H$_2$), 61.31 (2x —O—*C*H$_2$), 126.94, 128.34, 128.98, 129.43, 130.43, 132.33, 132.98, and 133.31 (8, Aromatic *C*), 151.41 (2x —N—*C*=N), 153.57 (2x —S—*C*=N) and 168.02 (2x *C*=O) ppm. MS (DI): M$^+$ at *m/z* 600. The other main fragmentation peaks were at *m/z* 513, 426, 0394, 216, 130, and 91. Anal. (calcd./found in %) for $C_{30}H_{28}N_6O_4S_2$: C, 59.98/59.77; H, 4.70/4.56; N, 13.99/13.73; S, 10.68/10.51.

Synthesis of 1,3-bis[4-(2′-methylphenyl)-5-carbethoxy methylmercapto-1,2,4-triazol-3-yl]benzene (13c). m.p. 165–167°C, Yield 60%. IR (KBr, cm^{-1}): 3429.5, 2971.8, 1742.5, and 1437.3. ^{1}H NMR (DMSO-d_6): δ 1.51 (t, 6H, 2x —OCH$_2$—C*H*$_3$), 1.85(s, 6H, 2x Ar—C*H*$_3$), 3.45 (s, 4H, 2x —S—C*H*$_2$) and 7.24–7.65 (m, 12H, Aromatic *H*). ^{13}C NMR (DMSO-d_6): 13.79 (2x —OCH$_2$—*C*H$_3$) 17.01 (2x Ar—*C*H$_3$), 33.49 (2x —S—*C*H$_2$), 52.62(2x —O*C*H$_2$), 125.98, 126.32, 126.98, 127.44, 128.33, 128.87, 129.32, 130.33, 132.39, and 135.38 (10, Aromatic *C*), 147.60 (2x —N—*C*=N), 153.73 (2x —S—*C*=N), and 167.79 (*C*=O) ppm. MS (DI): M$^+$ at *m/z* 628. The other main fragmentation peaks were at *m/z* 542, 306, 216, 150, 128, and 91. Anal. (calcd./found in %) for $C_{32}H_{32}N_6O_4S_2$: C, 61.13/61.33; H, 5.13/5.31; N, 13.37/13.52; S, 10.20/10.58.

Synthesis of 2(1,3)-benzena-1^4,3^4-diethyl-4,8-dithia-(1,3)(3,5)-1,2,4-triazola-cyclooctaphane-6-one (14a). m.p. 215–217°C, Yield 58%. HRMS: Found M$^+$ 386.4926; $C_{17}H_{18}N_6OS_2$ requires 386.4944. IR (KBr, cm^{-1}): 3429.5, 2971.4, 1742.9, and 1437.5. ^{1}H NMR (DMSO-d_6): δ 1.23 (t, 6H, J = 7.5 Hz, 2x —N—CH$_2$C*H*$_3$), 3.74 (s, 4H, 2x —S—C*H*$_2$), 4.06 (q, 4H, J = 7.5 Hz, 2x —N—C*H*$_2$) and 7.78, 7.83, and 7.87 (m, 4H, Aromatic *H*). ^{13}C NMR (DMSO-d_6): 15.32 (2x —N—CH$_2$*C*H$_3$), 35.25 (2x —S—*C*H$_2$), 40.21 (2x —N—*C*H$_2$), 126.14, 127.74, 129.34, and 130. 57 (4, Aromatic *C*), 145.84 (2x —N—*C*=N), 154.68 (2x —S—*C*=N) and 169.99 (*C*=O) ppm. MS (DI): M+ at *m/z* 386. The other major fragments were located at *m/z* 330, 158, 130, and 91. Anal. (calcd./found in %) for $C_{17}H_{18}N_6OS_2$: C, 52.83/52.53; H, 4.69/4.56; N, 21.74/21.62; S, 16.59/16.78.

Synthesis of 2(1,3)-benzena-1^4,3^4-diphenyl-4,8-dithia-6-oxo-(1,3)(3,5)-1,2,4-triazola-cyclooctaphane (14b). m.p. 170–172°C, Yield 62%. HRMS: Found M$^+$ 482.5790; $C_{25}H_{18}N_6OS_2$ requires 482.5803. IR (KBr, cm^{-1}): 3059.5, 1734.9, 1641.2, and 1596.8. ^{1}H NMR (DMSO-d_6): δ 4.05 (s, 4H, 2x S—C*H*$_2$) and 7.28–7.78 (m, 14H, Aromatic *H*). ^{13}C NMR (DMSO-d_6): 34.18 (2x —S—*C*H$_2$), 126.96, 127.33, 128.42, 128.98, 130.39, 130.84, 132.39, and 133.33 (8, Aromatic *C*), 151.73 (2x —N—*C*=N), 153.51 (2x —S—*C*=N), and 169.28 (*C*=O) ppm. MS (DI): M+ at *m/z* 482. The other major fragments were located at *m/z* 426, 292, 158, 130, and 91. Anal. (calcd./found in %) for $C_{25}H_{18}N_6OS_2$: C, 62.22/62.33; H, 3.76/3.64; N, 17.41/17.52; S, 13.29/13.50.

Synthesis of 2(1,3)-benzena-1^4,3^4-di(2′-methylphenyl)-4,8-dithia-6-oxo-(1,3)(3,5)-1,2,4-triazola-cyclooctaphane (14c). m.p. 223–225°C, Yield 50%. HRMS: Found M$^+$ 510.6320; $C_{27}H_{22}N_6OS_2$ requires 510.6332. IR (KBr, cm^{-1}): 3490.6, 2928.8, 1723.3, and 1447.9. ^{1}H NMR (DMSO-d_6): δ 1.78 (s, 6H, 2x Ar—C*H*$_3$), 4.10 (s, 4H, 2x —S—C*H*$_2$), 7.25–7.61 (m, 12H, Aromatic *H*). ^{13}C NMR (DMSO-d_6): 16.65 (2x Ar—*C*H$_3$), 33.25 (2x —S—*C*H$_2$), 126.04, 126.63, 127.30, 127.98, 128.68, 129.33, 131.34, 132.49, 133.89, and 135.10 (10, Aromatic *C*), 151.76 (2x —N—*C*=N), 153.22 (2x —S—*C*=N) and 169.17 (*C*=O) ppm. MS (DI): M+ at *m/z* 510. The other major fragments were located at *m/z* 454, 306, 158, 130, and 91. Anal. (calcd./found in %) for $C_{27}H_{22}N_6OS_2$: C, 63.51/63.39; H, 4.34/4.41; N, 16.46/16.52; S, 12.56/12.68.

Synthesis of 2(1,3)-benzena-1^4,3^4-diethyl-4,8-dithia-6-thio-(1,3)(3,5)-1,24-triazola-cyclooctaphan (15a). m.p. 268–270°C, Yield 50%. IR (KBr, cm^{-1}): 2932.5, 1624.9, 1544.5, 1278.5, and 1145.3. ^{1}H NMR (DMSO-d_6): δ 1.17 (t, 6H, J = 7.0 Hz, 2x —N—CH_2—CH_3), 3.34 (s, 4H, 2x —S—CH_2), 4.09 (q, 4H, J = 7.0 Hz, 2x —N—CH_2), 7.79, 7.81, 7.98, and 8.88 (Aromatic *H*). ^{13}C NMR (DMSO-d_6): 13.82 (2x —N—CH_2—*C*H_3), 33.45 (2x —N—*C*H_2), 40.44 (2x —S—*C*H_2), 127.45, 128.34, 129.49, and 131.33 (4 Aromatic *C*), 150.74 (2x —N—*C*=N), 153.45 (2x —S—*C*=N), and 167.41 (*C*=S) ppm. MS (DI): M+ at *m*/*z* 402. The other major fragments were located at *m*/*z* 330, 158, 130, and 91. Anal. (calcd./found in %) for $C_{17}H_{18}N_6S_3$: C, 50.72/50.65; H, 4.51/4.36; N, 20.88/20.67; S, 23.89/23.78.

Synthesis of 2(1,3)-benzena-1^4,3^4-diphenyl-4,8-dithia-6-thio-(1,3)(3,5)-1,24-triazola-cyclooctaphan (15b). m.p. >300°C, Yield 49%. IR (KBr, cm^{-1}): 3169, 2927, 1595, and 1497. ^{1}H NMR (DMSO-d_6): δ 3.48 (s, 4H, 2x S—CH_2), 7.24–7.47 (m, 14H, Aromatic *H*). ^{13}C NMR (DMSO-d_6): 38.68 (2x —S—*C*H_2), 126.22, 126.78, 127.59, 128.39, 128.89, 129.44, 130.33–132.21 (8, Aromatic *C*), 134.14 (2x —N—*C*=N), 149.62 (2x —S—*C*=N), and 168.66 (*C*=S)ppm. MS (DI): M+ at *m*/*z* 498. The other major fragments were located at *m*/*z* 426, 292, 158, and 91. Anal. (calcd./found in %) for $C_{25}H_{18}N_6S_3$: C, 60.22/60.11; H, 3.64/3.56; N, 16.85/16.77; S, 19.29/19.40.

Synthesis of 2(1,3)-benzena-1^4,3^4-di(2′-methylphenyl-4,8-dithia-6-thio-(1,3)(3,5)-1,24-triazola-cyclooctaphan (15c). m.p. 243–245°C, Yield 45%. IR (KBr, cm^{-1}): 3435.6, 2922.5, 1597.2, 1497.8, and 1263.4. ^{1}H NMR (DMSO-d_6): δ 1.98 (s, 6H, 2x Ar—CH_3), 3.82(s, 4H, 2x —S—CH_2), 7.13–7.45 (m, 12H, Aromatic *H*). ^{13}C NMR (DMSO-d_6): 17.73 (2x Ar-*C*H_3), 28.27 (2x —S—*C*H_2), 126.22, 126.55, 127.32, 127.98, 128.48, 128.84, 129.32, 130.29, 131.38, and 133.22 (10, Aromatic *C*), 137.18 (2x —N—*C*=N), 152.34 (2x —S—*C*=N) and 151.32 (*C*=S) ppm. MS (DI): M+ at *m*/*z* 526. The other major fragments were located at *m*/*z* 454, 306, 158, and 91. Anal. (calcd./found in %) for $C_{27}H_{22}N_6S_3$: C, 61.57/61.64; H, 4.21/4.30; N, 15.96/15.88; S, 18.26/18.44.

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