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SYNTHESIS OF HETEROMACROCYCLES CONTAINING 2-IMINO-5-MERCAPTO-2,3-DIHYDRO-1,3,4-THIADIAZOLES AS A SUBUNIT

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Abstract– Macrocycles containing two 2-imino-5-mercapto-2,3-dihydro-1,3,4-thiadiazole subunits linked to the 3- and 5-positions of the heterocycle unit were prepared by regiospecific alkylation of 5-amino-2,3-dihydro-1,3,4-thiadizole-2-thione and 2-acetylamino-5-alkylthio-1,3,4-thiadizoles, respectively. The structures of the macrocycles were established from ^{1}H and ^{13}C NMR, IR, MS spectrometries and elemental analyses. Moreover, the structure of the macrocycle 1,5-[5,5'-(1,3-phenylenedimethylenedithio)bis(2,3-dihydro-2-acetylimino-1,3,4-thiadiazol-2-yl)]-3-oxapentane (**4b**) was supported by X-Ray crystallography.

INTRODUCTION

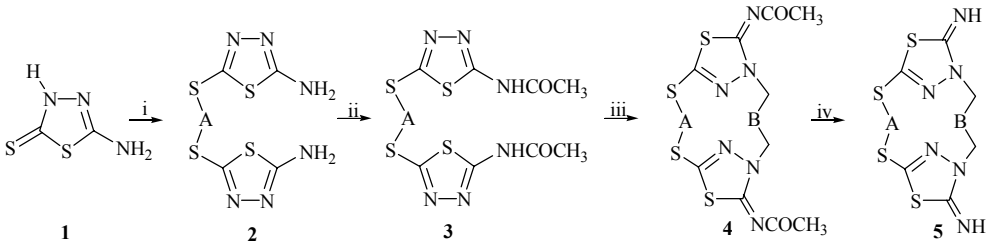
Since the discovery of crown ether, much work has been directed toward the synthesis of new macrocyclic ligands, and the systematic determination of the selectivity of these ligands and the stability of complexes formed with both metal and organic cations.[1-4] To enhance the selectivity of the ligands and the stability of the complexes, various changes in the crown ether structure have been attempted,[1-4] including the replacement of ligand polyether oxygen atoms by sulfur or nitrogen atoms and the insertion

of aromatic or heterocyclic rings into the macroring. Heterocyclic groups provide not only rigidity but also soft donor atoms to form complexes.[5-10] Polydentate macrocyclic compounds containing heterocyclic rings as a subunit possess a variety of interesting properties.[5-10] Consequently, many macrocycles have been synthesized and studied, including heterocyclic rings such as pyridine,[5] bipyridine,[6] triazole,[7] pyrazole,[8] thiophene,[9] and quinoxaline.[10] Although 1,3,4-thiadiazoles have received attention as a sulfur donor subunit,[11] very little is known about the incorporation of heterocyclic compounds into macrocyclic compounds.[12-13] As part of our systematic efforts aimed at the synthesis of new macrocyclic ligands fused with 1,3,4-thiadiazoles,[14] we report our attempt to synthesize novel macrocycles that incorporate 2-imino-5-mercapto-3*H*-2,3-dihydro-1,3,4-thiadizoles. The 2-imino-5-mercapto-2,3-dihydro-1,3,4-thiadizole ring is an interesting subunit, which has an NH group that can form efficient hydrogen bonds, since molecular recognition most commonly occurs through hydrogen bonding.

RESULTS AND DISCUSSION

We reported the synthesis and tautomeric behavior of 5-amino-2,3-dihydro-1,3,4-thiadizole-2-thione (**1**) and its derivatives.[15] Among four possible tautomers, **1** is believed to exist as a stable thione form based on spectroscopic results and *ab initio* calculations.[15] Compound (**1)** is regiospecifically *S*-alkylated under basic conditions, to give 5-amino-2-alkylthio-1,3,4-thiadiazole as 5-alkoxy-2,3-dihydro-1,3,4-thiadiazole-2-thione.[16] In addition, 5-substituted 2-acylamino-1,3,4-thiadiazoles (**3**) are also regiospecifically alkylated at the N(3) position under basic conditions, and yield a single 3-alkylated *endo*-product.[17] Utilizing these reactions, macrocycles containing two 2-imino-5-mercapto-2,3-dihydro-1,3,4-thiadizole subunits linked to the 3- and 5-positions of the heterocyclic unit were prepared from **1**, as shown in Scheme 1.

The reaction of **1** with an appropriate α,ω-dibromoalkane in the presence of KOH in ethanol gave the *S*-alkylated dimer (**2)**. The formation of **2** was confirmed by well-defined ^{1}H and ^{13}C NMR spectra. In **2b**, the NH of compound (**1)** was replaced by a SCH_2 signal at 3.22 and 33.7 ppm in the ^{1}H and ^{13}C NMR spectra, respectively. In the ^{13}C NMR, the thione part of **1** (181.0 ppm) typically changed to the thio group of **2b** (150.0 ppm).



2a, 3a; A = CH_2CH_2
2b, **3b**; A = $(CH_2CH_2)_2O$
2c, **3c**; A = $(CH_2CH_2OCH_2)_2$
2d, **3d**; A = *o*-xylenyl
2e, **3e**; A = *m*-xylenyl
2f, **3f**; A = *p*-xylenyl

4a, 5a; A = CH_2CH_2, B = *o*-phenylene
4b, 5b; A = $(CH_2CH_2)_2O$, B = *m*-phenylene
5c; A = $(CH_2CH_2)_2O$, B = *o*-phenylene
5d; A = $(CH_2CH_2)_2O$, B = *p*-phenylene
4e; A = $(CH_2CH_2OCH_2)_2$, B = *m*-phenylene
4f; A = $(CH_2CH_2OCH_2)_2$, B = *p*-phenylene
4g, **5g**; A = *o*-xylenyl, B = *o*-phenylene
4h, **5h**; A = *p*-xylenyl, B = *p*-phenylene
4i; A= *m*-xylenyl, B = *m*-phenylene
4j; A= *o*-xylenyl, B = *m*-phenylene

Scheme 1. Reagents and conditions: i, α,ω-dibromoalkane, KOH, EtOH, reflux, ii; acetyl chloride, pyridine, rt; iii, α,ω-dibromoalkane, KOH, EtOH, reflux; iv, HCl, MeOH or dioxane.

To obtain the target macrocycles containing two 2-imino-5-mercapto-3*H*-2,3-dihydro-1,3,4-thiadizole subunits from compound (**2)**, a cyclization, *N*,*N*-bisalkylation of **2** should be taken place at the N(3) position of the 1,3,4-thiadiazole ring using the corresponding α,ω-dibromoalkane. The 5-substituted 2-amino-1,3,4-thiadiazoles (**2**) were known as ambient compounds; thus its alkylation yielded isomeric mixture of *exo*- (2-position of NH_2) and *endo*- (N(3) position) *N*-alkylated products.[18] However, the alkylation of 5-substituted 2-acylamino-1,3,4-thiadiazoles was reported to quantitatively and regiospecifically take place at N(3) position (*endo*-product) under basic conditions.[17] For the regiospecific alkyaltion at N(3) position of **2,** the regiospecific alkylation of 5-substituted 2-acylamino-1,3,4-thiadiazoles was utilized even if acetylation and deacetylation were required. Thus, acetylation of the amino group of **2** (7.2-7.3 ppm) was performed. This took place at the NH_2 (*endo*-product), as seen in the spectroscopic data, as in the acylation of 2-amino-5-alkylthio-1,3,4-thiadiazoles.[17] For **3b**, the NH_2 of compound (**2b)** was replaced by typical $NHCOCH_3$ signals appearing at 12.48, 2.16, and 169.8, and at

23.4 ppm in the ^{1}H and ^{13}C NMR spectra, respectively. In the ^{13}C NMR spectrum, the chemical shifts of the C(2) and C(5) in the 1,3,4-thiadiazole of **2b** (150.0 and 169.5 ppm) typically changed to those of **3a** (159.5 and 159.8 ppm), as seen in 2-amino-5-alkylthio-1,3,4-thiadizole and 2-acylamino-5-alkylthio-1,3,4-thiadiazole. In addition, a diagnostic carbonyl band was seen in the IR spectrum at 1701 cm^{-1} and in the ^{13}C NMR spectrum at 169.8 ppm. As expected, the cyclization, *N*,*N*-bisalkylation between acetylated compound (**3)** and the appropriate α,ω-dibromoalkane proceeded regiospecifically at the position 3 nitrogen (*endo*-product), as in 5-substituted 2-acylamino-1,3,4-thiadiazoles.[17] The structures of the macrocycles were firmly established by ^{1}H and ^{13}C NMR, IR, MS, and elemental analyses. The successful macrocyclization of **3b** to **4b** was supported by evidence of *N*-alkylation, provided by the appearance of a NCH_2 group replacing the NH at 5.43 and 54.3 ppm in the ^{1}H and ^{13}C NMR spectra, respectively. *N*-Alkylation at the 3 position was clearly proved by the ^{13}C NMR spectrum; the chemical shifts of C(2) and C(5) in 1,3,4-thiadiazole and the carbonyl carbon of **4b** appeared at 156.0, 165.7, and 181.3 ppm. The chemical shift change between **3a** and **4a** is exactly the same as the change between 2-cetylamino-5-alkylthio-1,3,4-thiadiazole and 2-acetylimno-3-alkyl-5-alkylthio-2,3-dihydro-1,3,4-thiadiazole.[17] In addition to this evidence, a strong imido band at 1630 cm^{-1} was seen in the IR spectrum, representing a shift to a shorter wave number than the amide (1701 cm^{-1}) of **3a**. Moreover, the structure of macrocycle (**4b)** was proven by X-Ray crystallography, as shown in Figure 1. Finally, the hydrolysis of heterocycle (**4)** to produce the target heteromacrocycles containing 2-imino-5-mercapto-2,3-dihydro-1,3,4-thiadiazoles as subunits was performed under acid conditions. The structure of the final macrocycle (**5)** was verified by the appearance an acidic NH and the disappearance of CH_3CO. For **5b**, an NH is seen at 10.33 ppm and the acidic character of the NH is further evidence demonstrating regiospecific alkylation at the N(3) position of compound (**3)**. If the alkylation takes place at the amino group, the hydrogen cannot appear at a much lower field in the NMR and the methylene hydrogen and NH should be coupled. Finally, the synthesis of macrocycle (**5)** was more efficiently achieved with good yield *via N*,*N*-bisalkylation of **3** with the appropriate α,ω-dibromoalkane and consecutive hydrolysis of macrocycle (**4)** *in situ* by prolongation of the reaction time in KOH-EtOH basic conditions.

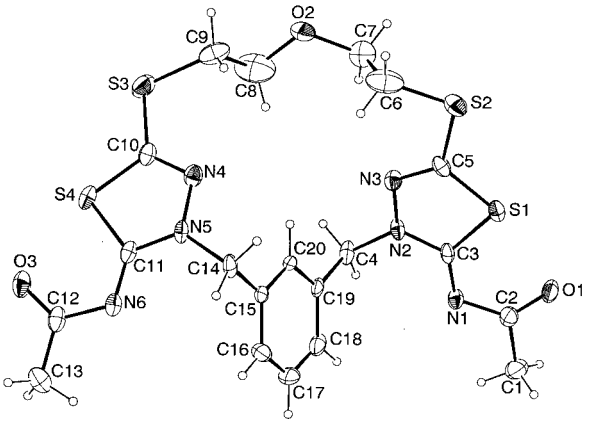


Figure 1. The molecular structure of macrocycle (**4b)**, showing the atomic numbering used for the crystallographic analysis.

EXPERIMENTAL

All melting points were determined on an electrically heated Thomas-Hoover capillary melting point apparatus and were uncorrected. The IR spectra were recorded on a Jasco Report-100 spectrophotometer. The ^{1}H and ^{13}C NMR spectra were obtained using a Bruker ARX-400 spectrometer at 400 MHz and 100 MHz respectively with tetramethylsilane as the internal reference. Elemental analyses were carried out on an EA 1110 (CE Instrument). NMR measurements and elemental analyses were performed at the Central Research Facilities of Chungnam National University. EIMS, HRMS and FABHRMS spectra were obtained on a VG Trio-1000 GC/MS spectrometer, a JEOL JEM-SX 102A spectrometer and a JEOL-JMS HX-100/110A spectrometer, respectively at Korea Basic Science Institute, Taeduk, Taejon. The progresses of reaction and purity of products were traced with TLC.

5-Amino-2,3-dihydro-1,3,4-thiadiazole-2-thione (**1**)was prepared as previously reported.[15]

General procedure for the synthesis of α,ω-bis[(5-amino-1,3,4-thiadiazol-2-yl)thio]alkane (2)

α,ω-Dibromoalkane (5.8 mmol) was added to a solution of compound (**1)** (1.4 g, 10.6 mmol) dissolved in EtOH (50 mL)-KOH (0.63 g, 11.23 mmol). The resulting mixture was heated under reflux until the compound (**1)** was disappeared on TLC. The solvent was evaporated under reduced pressure to leave a solid residue, which was washed with water. The crude product was recrystallized from the appropriate solvent.

1,2-Bis[(5-amino-1,3,4-thiadiazol-2-yl)thio]ethane (2a): Yield 78 %, mp 249-253 ℃ (H_2O), R_f 0.19

(*n*-Hexane : Ethyl acetate : Ethanol (5 : 3 : 1)). υ_{max} (KBr)/cm^{-1}: 3350, 3100, 1640, 1500, 1420, 1140; δ_H (400 MHz, DMSO-d_6): 7.33 (br, 4H, NH_2), 3.36 (s, 4H, CH_2); δ_C (100 MHz, DMSO-d_6): 169.7 (C=N), 148.9 (C-S), 33.9 (SCH_2).

1,5-Bis[(5-amino-1,3,4-thiadiazol-2-yl)thio]-3-oxapentane (2b): Yield 72%, mp 159-160 °C (H_2O), R_f 0.1 (*n*-Hexane : Ethyl acetate : Ethanol (5 : 3 : 1)). υ_{max} (KBr)/cm^{-1}: 3350, 3150, 1640, 1520, 1120; δ_H (400 MHz, DMSO-d_6): 7.27 (br, 4H, NH_2), 3.66 (t, J = 6.4 Hz, 4H, OCH_2), 3.22 (t, J = 6.4 Hz, 4H, SCH_2); δ_C (100 MHz, DMSO-d_6): 169.5 (C=N), 150.0 (C-S), 68.7 (OCH_2), 33.7 (SCH_2).

1,8-Bis[(5-amino-1,3,4-thiadiazol-2-yl)thio]-3,6-dioxaoctane (2c): Yield 68%, mp 160-162 °C (H_2O), R_f 0.09 (*n*-Hexane : Ethyl acetate : Ethanol (5 : 3 : 1)). υ_{max} (KBr)/cm^{-1}: 3290, 3110, 2950, 2870, 1630, 1510, 1140, 1110; δ_H (400 MHz, DMSO-d_6): 7.24 (br, 4H, NH_2), 3.60 (t, J = 5.6 Hz, 4H, OCH_2), 3.29 (s, 4H, OCH_2), 3.22 (t, J = 5.6 Hz, 4H, SCH_2); δ_C (100 MHz, DMSO-d_6): 169.5 (C=N), 150.1 (C-S), 69.6 (OCH_2), 68.9 (OCH_2), 33.8 (SCH_2).

α,α'-Bis[(5-amino-1,3,4-thiadiazol-2-yl)thio]-*o*-xylene (2d): Yield 83%, mp 207-208 °C (MeOH), R_f 0.18 (*n*-Hexane : Ethyl acetate : Ethanol (5 : 3 : 1)). υ_{max} (KBr)/cm^{-1}: 3300, 3150, 1620, 1520, 1440, 1060; δ_H (400 MHz, DMSO-d_6): 7.33-7.23 (m, 8H, NH_2 + C_6H_4), 4.42 (s, 4H, CH_2); δ_C (100 MHz, DMSO-d_6): 170.1 (C=N), 149.0 (C-S), 135.2, 130.7, 128.0 (C_6H_4), 36.0 (SCH_2). *Anal*. Calcd for $C_{12}H_{12}N_6S_4$: C, 39.11; H, 3.28; N, 22.80. Found: C, 39.07; H, 3.54; N, 22.49.

α,α'-Bis[(5-amino-1,3,4-thiadiazol-2-yl)thio]-*m*-xylene (2e): Yield 93%, mp 202-205 °C (MeOH), R_f 0.13 (*n*-Hexane : Ethyl acetate : Ethanol (5 : 3 : 1)). υ_{max} (KBr)/cm^{-1}: 3250, 3100, 1620, 1500, 1120, 1060, 800, 700; δ_H (400 MHz, DMSO-d_6): 7.35 (br, 4H, NH_2), 7.27-7.23 (m, 4H, C_6H_4), 4.29 (s, 4H, CH_2); δ_C (100 MHz, DMSO-d_6): 169.9 (C=N), 149.4 (C-S), 137.3, 129.5, 128.6, 128.1 (C_6H_4), 38.3 (SCH_2). FABHRMS Calcd for $C_{12}H_{13}N_6S_4$ 369.0085; found 369.0082

α,α'-Bis[(5-amino-1,3,4-thiadiazol-2-yl)thio]-*p*-xylene (2f): Yield 96%, mp 263-265 °C (DMF), R_f 0.16 (*n*-Hexane : Ethyl acetate : Ethanol (5 : 3 : 1)). IR (KBr)/cm^{-1}: 3266, 3112, 2955, 1623, 1519, 1064; δ_H (400 MHz, DMSO-d_6): 7.29 (s, 4H, C_6H_4), 7.25 (br, 4H, NH_2), 4.27 (s, 4H, CH_2); δ_C (100 MHz, DMSO-d_6): 169.9 (C=N), 148.9 (C-S), 136.3, 129.1 (C_6H_4), 38.1 (SCH_2). FABHRMS Calcd for

$C_{12}H_{13}N_6S_4$ 369.0085; found 369.0084. *Anal*. Calcd for $C_{12}H_{12}N_6S_4$: C, 39.11; H, 3.28; N, 22.80. Found: C, 39.43; H, 3.80; N, 22.91.

General procedure for the synthesis of α,ω-bis[(5-acetylamino-1,3,4-thiadiazol-2-yl)thio]alkane (3)

To a solution of compound (**2)** (1.3 mmol) in pyridine (20 mL) was added acetyl chloride (0.23 mL, 3.12 mmol) in one portion. The resulting mixture was stirred at rt until the compound (**2)** was disappeared on TLC. The solvent evaporated under reduced pressure to leave a solid residue, which was washed with water. The crude product was recrystallized from the appropriate solvents.

1,2-Bis[(5-acetylamino-1,3,4-thiadiazol-2-yl)thio]ethane (3a): Yield 86%, mp 317-319℃ (EtOH : DMF (1 : 1)). υ_{max} (KBr)/cm^{-1}: 3200, 3050, 2900, 2800, 1700 (C=O), 1580, 1380, 1320; δ_H (400 MHz; DMSO-d_6): 12.57(br, 2H, NH), 3.57(s, 4H, CH_2), 2.16(s, 6H, CH_3); δ_C (100 MHz; DMSO-d_6): 169.9(C=O), 160.1(C=N), 158.5(C-S), 34.4(SCH_2), 24.2(CH_3).

1,5-bis[(5-acetylamino-1,3,4-thiadiazol-2-yl)thio]-3-oxapentane (3b): Yield 76%, mp 222-225 ℃ (H_2O : EtOH = 1 : 7), R_f 0.27 (*n*-Hexane : Ethyl acetate : Ethanol (5 : 3 : 1)). υ_{max} (KBr)/cm^{-1}: 3163, 3046, 2912, 2706, 1701 (C=O), 1561, 1367, 1306; δ_H (400 MHz, DMSO-d_6): 12.48 (br, 2H, NH), 3.72 (t, J = 6.4 Hz, 4H, CH_2), 3.38 (t, J = 6.4 Hz, 4H, SCH_2) 2.16(s, 6H, CH_3); δ_C (100 MHz, DMSO-d_6): 169.8 (C=O), 159.8 (C=N), 159.5 (C-S), 69.8 (OCH_2), 34.3 (SCH_2), 23.4 (CH_3).

1,8-bis[(5-acetylamino-1,3,4-thiadiazol-2-yl)thio]-3,6-dioxaoctane (3c): Yield 90%, mp 215-217 ℃ (H_2O : EtOH = 1 : 7), R_f 0.21 (*n*-Hexane : Ethyl acetate : Ethanol (5 : 3 : 1)). υ_{max} (KBr)/cm^{-1}: 3263, 3159, 3043, 2903, 2784, 1695 (C=O), 1560, 1373; δ_H (400 MHz, DMSO-d_6): 12.53 (br, 2H, NH), 3.71 (t, J = 5.6 Hz, 4H, OCH_2), 3.55 (s, 4H, OCH_2), 3.38 (t, J = 5.6 Hz, 4H, SCH_2), 2.17 (s, 6H, CH_3); δ_C (100 MHz, DMSO-d_6): 168.7 (C=O), 158.6 (C=N), 158.5 (C-S), 69.6 (OCH_2), 68.8 (OCH_2), 33.2 (SCH_2), 22.3 (CH_3).

α,α'-Bis[(5-acetylamino-1,3,4-thiadiazol-2-yl)thio]-*o*-xylene (3d): Yield 89%, mp 293-295℃ (H_2O : DMF = 1 : 1), R_f 0.43 (*n*-Hexane : Ethyl acetate : Ethanol (5 : 3 : 1)). υ_{max} (KBr)/cm^{-1}: 3200, 3100, 2950, 2800, 1720 (C=O), 1580, 1400, 1320; δ_H (400 MHz, DMSO-d_6): 12.52 (br, 2H, NH), 7.41-7.25 (m, 4H, C_6H_4), 4.61 (s, 4H, CH_2), 2.16(s, 6H, CH_3); δ_C (100 MHz, DMSO-d_6): 169.8 (C=O), 160.2 (C=N), 158.6

(C-S), 136.1, 131.9, 129.4 (C_6H_4), 36.3 (SCH_2), 23.4 (CH_3). *Anal*. Calcd for $C_{16}H_{16}N_6O_2S_4$: C, 42.46; H, 3.56; N, 18.57. Found: C, 42.17; H, 3.72; N, 18.52.

α,α'-Bis[(5-acetylamino-1,3,4-thiadiazol-2-yl)thio]-*m*-xylene (3e): Yield 79.7%, mp 282-285 ℃ (H_2O : DMF = 1 : 1), R_f 0.28 (*n*-Hexane : Ethyl acetate : Ethanol (5 : 3 : 1)). υ_{max} (KBr)/cm^{-1}: 3150, 2900, 2800, 1700 (C=O), 1560, 1380, 1300; δ_H (400 MHz, DMSO-d_6): 12.52 (br, 2H, NH), 7.41-7.29 (m, 4H, C_6H_4), 4.45 (s, 4H, CH_2), 2.17 (s, 6H, CH_3); δ_C (100 MHz, DMSO-d_6): 169.8 (C=O), 160.1 (C=N), 158.8 (C-S), 138.1, 130.7, 130.0, 129.4 (C_6H_4), 38.5 (SCH_2), 23.4 (CH_3). *Anal*. Calcd for $C_{16}H_{16}N_6O_2S_4$: C, 42.46; H, 3.56; N, 18.57. Found: C, 42.16; H, 3.89; N, 18.66.

α,α'-Bis[(5-acetylamino-1,3,4-thiadiazol-2-yl)thio]-*p*-xylene (3f): Yield 86.6%, mp 304-305 ℃ (H_2O : DMF = 1 : 1), R_f 0.5 (*n*-Hexane : Ethyl acetate : Ethanol (5 : 3 : 1)). υ_{max} (KBr)/cm^{-1}: 3160, 3040, 2916, 2786, 1696, 1562, 1307, 1048; δ_H (400 MHz, DMSO-d_6): 12.54 (br, 2H, NH), 7.36 (s, 4H, C_6H_4), 4.46 (s, 4H, CH_2), 2.17 (s, 6H, CH_3); δ_C (100 MHz, DMSO-d_6): 169.8 (C=O), 160.0 (C=N), 158.9 (C-S), 137.2, 130.3 (C_6H_4), 38.3 (SCH_2), 23.4 (CH_3). *Anal*. Calcd for $C_{16}H_{16}N_6O_2S_4$: C, 42.46; H, 3.56; N, 18.57. Found: C, 42.31; H, 3.82; N, 18.37.

General procedure for the synthesis of acetylated macrocycles (4)

α,ω-Dibromoalkane (1 mmol) was added to a solution of compound (**3)** (1 mmol) dissolved in EtOH (40 mL)-KOH (0.15 g, 2.6 mmol). The resulting mixture was heated under reflux until the compound (**3)** was disappeared on TLC. The solvent was evaporated under reduced pressure to leave a solid residue, which was washed with water. The crude product was recrystallized from the appropriate solvent.

1,2-[5,5'-(1,2-Pheylenemethylenethio)bis(2-acetylimino-2,3-dihydro-1,3,4-thiadiazol-3-yl)]ethane (4a): Yield 34%, mp 290-292℃ (acetone : *n*-hexane = 1 : 1), R_f 0.75 (THF : *n*-Hexane (10 : 9)). υ_{max} (KBr)/cm^{-1}: 3050, 3000, 1620 (C=O), 1520, 1480, 1400, 1300, 1000, 760; δ_H (400 MHz, $CDCl_3$): 7.52-7.25 (m, 4H, C_6H_4), 5.69 (s, 4H, NCH_2), 3.38 (s, 4H, SCH_2), 2.39(s, 6H, CH_3); δ_C (100 MHz, $CDCl_3$): 180.7 (C=O), 165.8 (C=N), 153.8 (C-S), 134.2, 130.5, 129.1 (C_6H_4), 49.5 (NCH_2), 31.3 (SCH_2), 26.7(CH_3); EIMS (*m/z*) 478 (M^+). FABHRMS Calcd for $C_{18}H_{19}N_6O_2S_4$ 479.0452; found 479.0453.

Anal. Calcd for $C_{18}H_{18}N_6O_2S_4$: C, 45.17; H, 3.79; N, 17.56; S, 26.79. Found: C, 45.09; H, 3.76; N, 18.13; S, 26.60.

1,5-[5,5'-(1,3-Phenylenedimethylenedithio)bis(2-acetylimino-2,3-dihydro-1,3,4-thiadiazol-3-yl)]-3-oxapentane (4b): Yield 9.3%, mp 199-201℃ (THF : EtOH = 1 : 1), R_f 0.68 (*n*-Hexane : Ethyl acetate : Ethanol (5 : 3 : 1)). υ_{max} (KBr)/cm^{-1}: 2910, 2880, 1630 (C=O) , 1610, 1510, 1380, 1290, 1120; δ_H (400 MHz, $CDCl_3$): 7.40-7.28 (m, 4H, C_6H_4), 5.43 (s, 4H, NCH_2), 3.75 (t, J = 6.4 Hz, 4H, OCH_2), 3.20 (t, J = 6.4 Hz, 4H, SCH_2), 2.33 (s, 6H, CH_3); δ_C (100 MHz, $CDCl_3$): 181.3 (C=O), 165.7 (C=N), 156.0 (C-S), 136.6, 130.1, 129.8, 129.4 (C_6H_4), 69.0 (OCH_2), 54.3 (NCH_2), 31.8 (SCH_2), 27.3 (CH_3); EIMS (*m/z*): 522 (M^+). FABHRMS Calcd for $C_{20}H_{23}N_6O_3S_4$ 523.0715; found 523.0713. *Anal*. Calcd for $C_{20}H_{22}N_6O_3S_4$: C, 45.96; H, 4.24; N, 16.08; S, 24.54. Found: C, 45.88; H, 4.26; N, 16.02; S, 23.93.

1,8-[5,5'-(1,3-Pheylenemethylenedithio)bis(2-acetylimino-2,3-dihydro-1,3,4-thiadiazol-3-yl)]-3,6-dioxaoctane (4e): Yield 9.2%, mp 172-175℃ (acetone), R_f 0.58 (*n*-Hexane : Ethyl acetate : Ethanol (5 : 3 : 1)). υ_{max} (KBr)/cm^{-1} 2890, 1620 (C=O), 1510, 1470, 1380, 1280, 1100; δ_H (400 MHz DMSO-d_6): 7.38 (m, 4H, C_6H_4), 5.44 (s, 4H, NCH_2), 3.55 (t, J = 5.6 Hz, 4H, OCH_2), 3.46 (s, 4H, OCH_2), 3.22 (t, J = 5.6 Hz, 4H, SCH_2), 2.17 (s, 6H, CH_3); δ_C (100 MHz, DMSO-d_6): 180.4 (C=O), 165.5 (C=N), 156.5 (C-S), 137.3, 130.2, 129.1, 127.3 (C_6H_4), 70.6 (OCH_2), 69.7 (OCH_2), 54.1 (NCH_2), 33.2 (SCH_2), 27.6 (CH_3); EIMS (*m/z*): 566 (M^+). FABHRMS Calcd for $C_{22}H_{27}N_6O_4S_4$ 567.0977; found 567.0972.

1,8'-[5,5'-(1,4-Phenylenemethylenedithio)bis(2-acetylimino-2,3-dihydro-1,3,4-thiadiazol-3-yl)]-3,6-dioxaoctane (4f): Yield 4.1% (separation by SiO_2 column chromatography, $CHCl_3$: Ethyl acetate : EtOH (10 : 1 : 1) and $CHCl_3$: Ethyl acetate (3 :2)), mp 206-208℃, R_f 0.58 ($CHCl_3$: Ethyl acetate (3 : 2)). υ_{max} (KBr)/cm^{-1}: 2920, 1610 (C=O), 1510, 1470, 1380, 1280, 1110, 1000; δ_H (400 MHz, DMSO-d_6): 7.35 (s, 4H, C_6H_4), 5.45 (s, 4H, NCH_2), 3.60 (t, J = 5.6 Hz, 4H, OCH_2), 3.37 (s, 4H, OCH_2), 3.22 (t, J = 5.6 Hz, 4H, SCH_2), 2.32 (s, 6H, CH_3); δ_C (100 MHz, DMSO-d_6): 181.3 (C=O), 165.9 (C=N), 155.9 (C-S), 136.1, 129.6 (C_6H_4), 70.5, 69.8 (C-O), 53.9 (NCH_2), 32.7 (SCH_2), 27.3 (CH_3); EIMS (*m/z*): 566 (M^+). FABHRMS Calcd for $C_{22}H_{27}N_6O_4S_4$ 567.0977; found 567.0978.

α,α'-[5,5'-(1,2-Phenylenemethylenedithio)bis(2-acetylamino-2,3-dihydro-1,3,4-thiadiazol-3-yl)]-*o*-xylene (4g): Yield 43.8 %, mp 289-291 ℃ (DMF), R_f 0.76 (THF : *n*-hexane = 10 : 9). υ_{max} (KBr)/cm^{-1}: 3100, 3050, 2950, 1620, 1520, 1480, 1380, 1280; δ_H (400 MHz, $CDCl_3$): 7.31-7.25 (m, 8H, C_6H_4), 5.77 (s,

4H, NCH_2), 4.48 (s, 4H, CH_2), 2.33 (s, 6H, CH_3); δ_C (100 MHz, $CDCl_3$): 181.1 (C=O), 165.8 (C=N), 156.1 (C-S), 135.3, 134.3, 131.7, 130.9, 129.7, 129.4 ($2C_6H_4$), 51.7 (NCH_2), 34.5 (SCH_2), 27.3 (CH_3); EIMS (*m/z*): 554 (M^+). *Anal*. Calcd for $C_{24}H_{22}N_6O_2S_4$: C, 51.97; H, 4.00; N, 15.15; S, 23.12. Found: C, 52.11; H, 4.10; N, 15.43; S, 22.37.

α,α'-[5,5'-(1,4-Phenylenemethylenedithio)bis(2-acetylamino-2,3-dihydro-1,3,4-thiadiazol-3-yl)]-*p*-xylene (4h): Yield 50 %, mp 266-270 ºC (DMF), R_f 0.66 (*n*-Hexane : Ethyl acetate : Ethanol (5 : 3 : 1)). υ_{max} (KBr)/cm^{-1}: 2930, 1600 (C=O), 1510, 1380, 1280; δ_H (400 MHz, DMSO-d_6): 7.38 (s, 4H, C_6H_4), 7.07 (s, 4H, C_6H_4), 5.51 (s, 4H, CH_2), 4.30 (s, 4H, SCH_2), 2.22 (s, 6H, CH_3); δ_C (100 MHz, DMSO-d_6): 180.5 (C=O), 165.7 (C=N), 155.5 (C-S), 137.7, 137.0, 130.3, 130.2 ($2C_6H_4$), 53.90 (NCH_2), 35.2 (SCH_2), 27.60 (CH_3); EIMS: 554 (M^+). FABHRMS Calcd for $C_{24}H_{23}N_6O_2S_4$ 555.0765; found 555.0764.

α,α'-[5,5'-(1,3-Phenylenemethylenedithio)bis(2-acetylamino-2,3-dihydro-1,3,4-thiadiazol-3-yl)]-*m*-xylene (4i): Yield 54.1%, mp 223-225 ºC (DMF), R_f 0.71 (*n*-Hexane : Ethyl acetate : Ethanol (5 : 3 : 1)). υ_{max} (KBr)/cm^{-1}: 3400, 3150, 2900, 1700, 1600, 1540, 1500, 1365; δ_H (400 MHz, DMSO-d_6): 7.23-7.00 (m, 8H, C_6H_4), 5.37 (s, 4H, CH_2), 4.30 (s, 4H, CH_2), 2.15 (s, 6H, CH_3); δ_C (100 MHz, DMSO-d_6): 180.6 (C=O), 165.5 (C=N), 154.3 (C-S), 137.1, 135.8, 129.1, 128.7, 128.4, 128.3, 128.1, 127.9 ($2C_6H_4$), 53.6 (NCH_2), 37.1 (SCH_2), 26.7 (CH_3); EIMS: 554 (M^+). FABHRMS Calcd for $C_{24}H_{23}N_6O_2S_4$ 555.0765; found 555.0762.

α,α'-[5,5'-(1,2-Phenylenemethylenedithio)bis(2-acetylimino-2,3-dihydro-1,3,4-thiadiazol-3-yl)]-*m*-xylene (4j): Yield 25%, mp 302-304 ºC (DMF), R_f 0.58 (*n*-Hexane : Ethyl acetate : Ethanol (5 : 3 : 1)). υ_{max} (KBr)/cm^{-1} 3303, 2926, 1618 (C=O), 1503, 1380, 1275, 1002, 953; δ_H (400 MHz, $CDCl_3$): 7.45-7.36 (m, 8H, C_6H_4), 5.46 (s, 4H, NCH_2), 4.50 (s, 4H, CH_2), 2.31 (s, 6H, CH_3); δ_C (100 MHz, $CDCl_3$): 219.6 (C=O), 181.2 (C=O), 165.4 (C=N), 155.7 (C-S), 136.3, 134.2, 131.6, 129.8 ($2C_6H_4$), 54.3 (NCH_2), 35.2 (SCH_2), 27.3 (CH_3); EIMS (*m/z*): 554 (M^+). *Anal*. Calcd for $C_{24}H_{22}N_6O_2S_4$: C, 51.96; H, 4.00; N, 15.15; S, 23.12. Found: C, 51.85; H, 3.97; N, 15.22; S, 22.85.

1,2-[5,5'-(1,2-Phenylenemethylenedithio)bis(2-imino-2,3-dihydro-1,3,4-thiadiazol-3-yl)]ethane (5a): hydrolysis of 4a

1,2-[5,5'-(1,2-Pheylenemethylenethio)bis(2-acetylimino-2,3-dihydro-1,3,4-thiadiazol-3-yl)]ethane (**4a**) (0.28 g, 0.59 mmol) was dissolved in MeOH (60 mL)-conc-HCl (0.26 mL, 2.7 mmol). The mixture was heated under reflux for 2.5 h. The reaction mixture was cooled at rt and distilled off solvent under reduce pressure. The resulting solid was recrystallized from water/EtOH (1 : 1) to give of colorless solide (0.13 g, 57%). mp 250 ℃ (decomp), R_f 0.38 (n-hexane : ethyl acetate : EtOH = 5 : 3 : 1), υ_{max} (KBr)/cm^{-1}: 2950, 2850, 2750, 1625, 1560, 1500, 1180, 1040, 740; δ_H (400 MHz, DMSO-d_6): 9.82 (br, 2H, NH), 7.51-7.22 (m, 4H, Ph), 5.15 (s, 4H, NCH_2), 3.21 (s, 4H, CH_2); δ_C (100 MHz, DMSO-d_6): 161.3 (C=N), 141.1 (C-S), 135.5, 130.2, 128.1(Ph), 46.8 (NCH_2), 31.6 (SCH_2).

α,α'-[5,5'-(3-Oxapentane-1,5-dithio)bis(2-imino-3,4-dihydro-1,3,4-thiadiazol-3-yl)]-*m*-xylene (5b): macrocyclization from 3b

1,5-[5,5'-(1,3-Phenylenedimethylenedithio)bis(2-acetylimino-2,3-dihydro-1,3,4-thiadiazol-3-yl)]-3-oxapentane (**3b)** (0.46 g, 1.1 mmol) was dissolved in KOH (0.15 g, 2.68 mmol)-EtOH (80 mL) solution. α,α'-Dibromo-*m*-xylene (0.58 g, 2.2 mmol) was added to the solution in one portion. The reaction mixture was heated under reflux for 24 hr. The reaction mixture was cooled at rt. The resulting solid was collected by filtration and washed with water and *n*-hexane. The crude product was recrystallized from DMF/EtOH (1 : 1) to give of colorless solid (0.27 g, 56%). mp 270 ℃ (decomp), R_f 0.46 (*n*-hexane : ethyl acetate : EtOH = 5 : 3 : 1). υ_{max} (KBr)/cm^{-1} 3421 (NH), 1623, 1571, 1499; δ_H (400 MHz, DMSO-d_6): 10.33 (br, 2H, NH), 7.47-7.34 (m, 4H, Ph), 5.47 (s, 4H, NCH_2), 3.56-3.24 (m, 8H, CH_2CH_2); δ_C (100 MHz, DMSO-d_6): 166.9 (C=N), 154.5 (C-S), 134.5,129.6,129.1 (Ph), 67.4 (OCH_2), 51.3 ($N\underline{C}H_2Ph$), 32.5 (SCH_2); MS (EI): *m/z* 438 (M^+). HRMS Calcd for $C_{16}H_{18}ON_6S_4$ 438.0425; found 438.0423.

α,α'-[5,5'-(3-Oxapentane-1,5-dithio)bis(2-imino-3,4-dihydro-1,3,4-thiadiazol-3-yl)]-*o*-xylene (5c): macrocyclization from 3b

The preparation was followed by the same procedure of **5b**. Yield 32%, mp 250 ℃ (decomp, DMF : EtOH = 1 : 1), R_f 0.48 (*n*-hexane : ethyl acetate : ethanol = 5 : 3 : 1). $\upsilon_{max,}$(KBr)/cm^{-1}: 3420 (NH), 1635,

1569, 1485. δ_H (400 MHz, DMSO-d_6): 10.31(2H, br, NH), 7.43-7.32 (4H, m, Ph), 5.57 (4H, s, CH_2), 3.48-3.17 (8H, m, CH_2CH_2). δ_C (100 MHz, DMSO-d_6): 167.5 (C=N), 154.3 (C-S), 131.8, 129.6, 129.1 (Ph), 67.4 (OCH_2), 51.3 ($N\underline{C}H_2Ph$), 32.5 (SCH_2); EIMS (*m/z*): 438 (M^+, 5.71 %). HRMS Calcd for $C_{16}H_{18}N_6OS_4$ 438.0425; found 438.0429.

α,α'-[5,5'-(3-Oxapentane-1,5-dithio)bis(2-imino-3,4-dihydro-1,3,4-thiadiazol-3-yl)]-*p*-xylene (5d): macrocyclization from 3b

The preparation was followed by the same procedure of **5b**. Yield 68%, mp 270 ºC (decomp, DMF : EtOH = 1 : 1), R_f 0.55 (*n*-hexane : ethyl acetate : ethanol = 5 : 3 : 1). υ_{max} (KBr)/cm^{-1}: 3422(NH), 1628, 1559, 1488. δ_H (400 MHz, DMSO-d_6): 10.23(2H, br, NH), 7.44 (4H, s, Ph), 5.39 (4H, s, CH_2), 3.31-3.14 (8H, m, CH_2CH_2). δ_C (100 MHz, DMSO-d_6): 167.2 (C=N), 153.5 (C-S), 133.9, 129.4 (Ph), 67.8 (OCH_2), 53.1 ($N\underline{C}H_2Ph$), 31.6 (SCH_2); EIMS (*m/z*): 438 (M^+). HRMS Calcd for $C_{16}H_{18}N_6OS_4$ 438.0425; found 438.0417.

α,α'-[5,5'-(1,2-Phenylenemethyledithio)bis(2-imino-2,3-dihydro-1,3,4-thiadiazol-3-yl)]-*o*-xylene (5g): hydrolysis of 4g

The preparation was followed by the same procedure of **5a**. Yield 74%, mp 222-224 ºC (DMF), R_f 0.49 (*n*-hexane : ethyl acetate : ethanol = 5 : 3 : 1). υ_{max} (KBr)/cm^{-1}: 2992, 1627, 1561, 1489. δ_H (400 MHz, DMSO-d_6): 10.25 (2H, br, NH), 7.47-7.42 (4H, m, Ph), 7.34-7.28 (4H, m, Ph), 5.65 (4H, s, NCH_2), 4.53 (4H, s, SCH_2); δ_C (100 MHz, DMSO-d_6): 167.5 (N-C=N), 154.2 (S-C-S), 134.2, 132.2, 130.6, 129.4, 129.2, 128.4 (Ph), 50.7 ($N\underline{C}H_2Ph$), 33.4 ($S\underline{C}H_2Ph$); EIMS (*m/z*): 470 (M^+). HRMS Calcd for $C_{20}H_{18}N_6S_4$ 470.0476; found 470.0472.

α,α'-[5,5'-(1,4-Phenylenemethyledithio)bis(2-imino-2,3-dihydro-1,3,4-thiadiazol-3-yl)]-*p*-xylene (5h): macrocyclization from 3f

The preparation was followed by the same procedure of **5b**. Yield 60%, mp 340 ºC (decomp, DMF), R_f 0.25 (n-hexane : THF = 9 : 10). υ_{max} (KBr)/cm^{-1}: 3462 (NH), 1626, 1507, 1481; δ_H (400 MHz, DMSO-d_6): 10.21 (2H, br, NH), 7.50 (4H, s, Ph), 7.13 (4H, s, Ph), 5.46 (4H, s, CH_2), 4.03 (4H, s, CH_2); δ_C (100 MHz, DMSO-d_6): δ167.1 (C=N), 153.9 (C-S), 136.1, 134.6, 129.3, 129.1(Ph), 52.3 ($N\underline{C}H_2Ph$), 34.9

(S<u>C</u>H_2Ph); EI-MS (m/z): 470 (M^+). HRMS Calcd for $C_{20}H_{18}N_6S_4$ 470.0476; found 470.0472.

X-Ray crystal structure of macrocycle (4b)

Compound (**4b**) was crystallized from slow evaporation of a solution of CH_2Cl_2/toluene (1 : 1). $C_{20}H_{22}N_6O_3S_4$: M.W. 522.68, orthorombic, space group Pccn, a = 15.709(5), b = 20.901(3), c = 14.340(3) Å, α= 90, β= 90, γ= 90°, V = 4708.6(18) $Å^3$, Z =8, Dc = 1.475 g/cm^3, μ= 0.440 mm^{-1}, F(000) = 2176, T = 293 K. The data were collected CAD-4 diffractometer (Enraf-Nonius, 1994) using graphite-mono-chromated Mo-Kα radiation (0.71073 Å). The structure was solved by direct methods (SHELX86)[18] (all non-H atoms), followed by full-matrix least-squares refinement (SHELX97)[19] on F^2. Hydrogen atoms were located from ΔF synthesis and positionally refined. All non–hydrogen atoms were anisotropically refined, leading to a final R_1 and wR_2, 0.0794 and 0.1840 repectively, for 2895 unique reflections and 293 refined parameters. S[F^2] 1.072 and $(\Delta / \sigma)_{max}$ was 0.000. Maximum and minimum features in ΔF synthesis are 0.815 and -0.335 e$Å^{-3}$, respectively.

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