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RESEARCH ARTICLE

Synthesis, biological evaluation and QSAR studies of some new thioether–ester crown ethers

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New thioether–ester crown ethers have been synthesized starting from dithiodibenzoyl chloride and different β,β′-dihydroxydithioethers. The synthetic compounds were screened for their antibacterial and antifungal activity on *Klebsiella pneumoniae*, *Staphilococcus aureus*, *Pseudomanas aeruginosa* and *Candida albicans*. The macrocyclic thioether–esters **6a–i** were effective inhibitors against *Klebsiella pneumoniae* with MIC value in the range of 25–400 μg/mL. The qualitative structure activity relationship (QSAR) calculations (Moriguchi octanol–water partition coefficient (logP), polar surface area (PSA), hydrophilic factor (Hy), Ghose–Crippen molar refractivity (MR), unsaturation index (Ui) and 99 descriptors of WHIM-3D/QSAR (weighted holistic invariant molecular) of thioether compounds **6a–j** were also studied. The results confirm the capability of the proposed approach to give predictive models for MIC values of *K. pneumoniae*. The structures of the synthetic compounds were confirmed by elemental analysis, ^{1}H NMR and MS spectral studies.

Keywords: *Klebsiella pneumoniae*; Thioether–ester crown ethers; Dihydroxydithioethers; Dithiodibenzoyl chloride; MIC; QSAR

1. Introduction

β,β′-Dihydroxydithioethers with two α,α′-substituents have been recently synthesized [1, 2]. The two secondary β,β′-dihydroxy groups make these compounds useful reagents for the synthesis of new thiacrown ethers possessing various sidearms [3, 4]. Biological activities of such sidearmed crownethers have been reported [3]. Antibacterial evaluations of β,β′-dihydroxydithioethers **3a–j** and their corresponding thiacrown ethers **7a–j** have been recently studied [5]. Among the synthetic compounds **3a–j** and **7a–j**, only **7e** and **7f** showed significant activities against *Straphylococcuse aureus* and *Pseudomanas aeruginosa* with MIC values of 525 and 265 μM (100 and 200 μg/mL) [5]. Antibacterial and antifungal activities of some dithiodiphenyl derivatives such as compound **8** are reported in an early literature [6]. A new series of substituted nitrophenyl alkyl disulfides have been recently reported as effective

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antifungal agents [7, 8]. In this paper, we describe the synthesis of new thioether–ester crown ethers **6a-j** from dithiodibenzoyl chloride **5** and corresponding β,β′-dihydroxydithioethers **3a-j**, from which their antibacterial and antifungal activities are also investigated and qualitative structure activity relationship (QSAR) study of these new compounds to propose key futures of this class of antibacterial agents.

2. Results

2.1 *Synthesis*

The β,β′-dihydroxydithioether **3a** and the mixture of two diastreomrers [1] of its derivatives **3b-j** were prepared by reaction of two mole equivalents of oxiranes **1a–j** with dimercaptoehane **2** in the presence of saturated aqueous solution of potassium carbonate (figure 1) [2]. Treatment of dihydroxy compounds **3a–j** with elemental potassium in dry benzene under reflux led to the formation of corresponding dialkoxy salts. Which were directly reacted with dithiodibenzoyl chloride **5** in the presence of triethylamine as catalyst [9]. Purification by column chromatography (silica gel 60, 230–400) afforded 7, 14-disubstituted 7, 8, 10, 11, 13, 14-hexahydro-5*H*,16*H*-dibenzo[*l*,*p*][1, 10, 4, 7, 14, 15] dioxatetrathiacyclooctadecine-5,16-diones **6a-i** and 1, 2, 3, 4, 4a, 6, 7, 8a, 9, 10, 11, 12, 12a, 26a-tetradecahydro-14*H*,25*H*-tetrabenzo[*b*,*h*,*l*,*p*] [1, 10, 4, 7, 14, 15]dioxatetrathiacyclooctadecine-14,25-dione **6j**.

2.2 *Biological evaluations*

Antibacterial activities of thioether–ester crown ethers **6a–j** were evaluated. The MIC values– i.e. the lowest concentration of a drug that prevents growth of a particular pathogen [10]–of **6a–j** against two gram negative strains of bacteria, *P. aeruginosa* and *Klebsiella pneumoniae*, a gram positive *S. aureus* methicillin resistant and a kind of yeast *Candida albicans*, were measured. Four isolated strains of the mentioned pathogens from different organs of the patients at the Microbiological Laboratory of Ghaem Hospital of Medical University of Mashhad-Iran were tested. Oxacillin (for *S. aureus*), Gentamycin (for *P. aeruginosa* and *K. pneumoniae*) and Clotrimazole (for *C. albicans*) were used as positive control in all tests, and their MIC values were expressed in micrometer. The synthetic compounds **6a–j**, were only effective on the *K. pneumoniae* with MIC values between 63 and 884 μM (25–400 μg/mL) except **6j** which it showed no effective response at concentration >400 μg/mL. These results were compared with Gentamycin activity using the standard MIC values of 16 μg/mL respectively (table 1).

2.3 *Structure optimization*

Structures **6a–j** were simulated in chem3D professional; Cambridge software [11]. For optimizing, output files were minimized under semi-empirical PM3 method (convergence limit = 0.01; Iteration limit = 50; RMS gradient = 0.05 kcal/mol; Polak–Ribiere optimizer algorithm) in HyperChem7.5 [12].

2.4 *QSAR studies*

QSAR studies were performed for optimized compounds **6a–j** in DRAGON 2.1 [13]. In this study, Moriguchi octanol–water partition coefficient (logP) [14], polar surface area (PSA) [15], hydrophilic factor (Hy) [16], Ghose–Crippen molar refractivity (MR) [17], unsaturation index

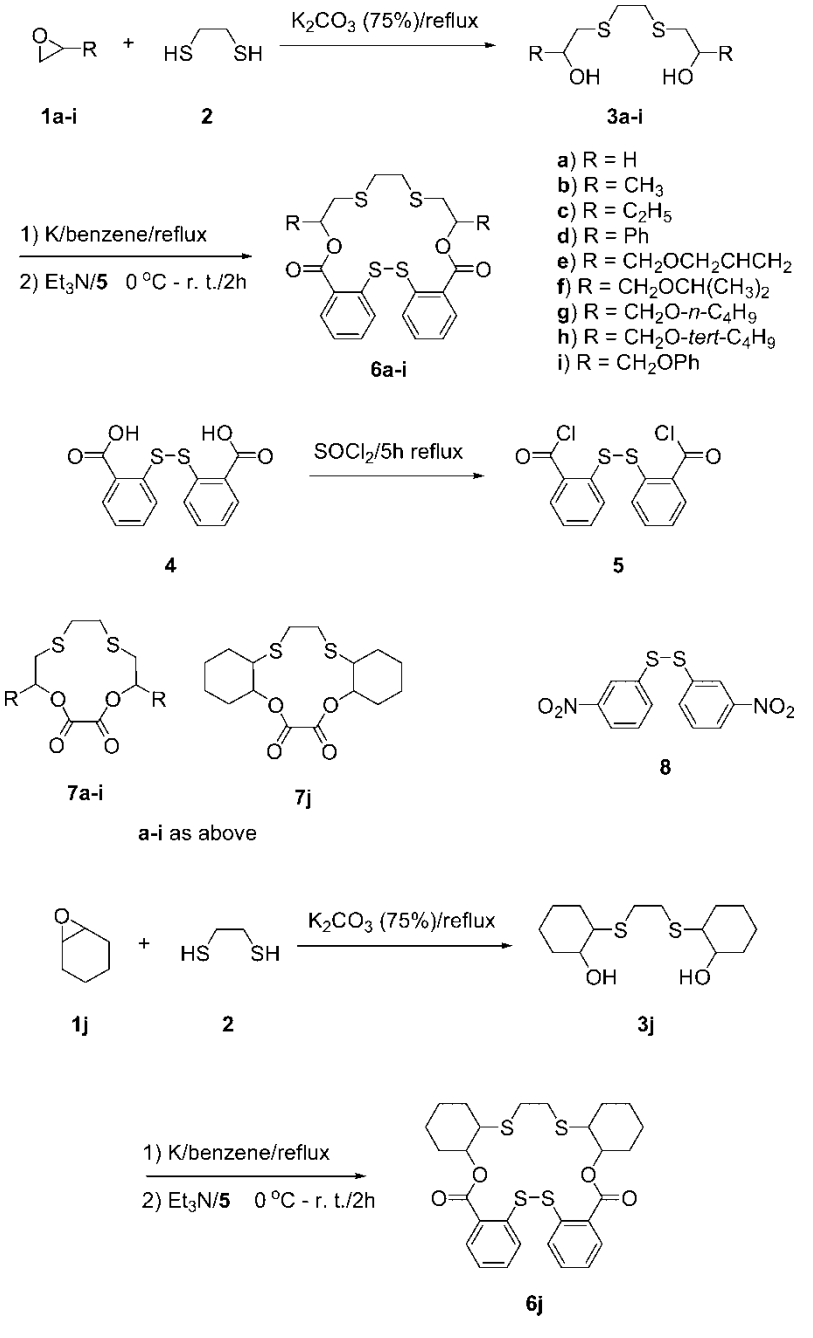

Figure 1. The general procedure for the synthesis of compounds **6a–j**.

(Ui) [16] and 99 descriptors of WHIM-3D/QSAR (weighted holistic invariant molecular) [18] were determined. Some of the calculations are outlined in table 2.

The QSARs of these molecules were analyzed by multiple regression analysis (MRA) in order to predict the lead optimization in this set of compounds.

Table 1. The MIC values of compounds **6a–j** against mentioned microorganism at μM unit. The sign (–), indicates no effective response at more than 400 μg/mL concentration.

Compound	*S. aureus*	*P. aeruginosa*	*K. pneumomniae*	*C. albicans*
6a	–	–	884	–
6b	–	–	208	–
6c	–	–	263	–
6d	–	–	793	–
6e	–	–	63	–
6f	–	–	84	–
6g	–	–	126	–
6h	–	–	80	–
6i	–	–	105	–
6j	–	–	–	–

Table 2. Data obtained from QSAR analyses (logP: Moriguchi octanol–water partition coefficient, PSA: polar surface area).

Compound	logP	L_2m	PSA
6a	4.463	4.978	153.8
6b	4.905	6.451	153.8
6c	5.331	5.911	153.8
6d	6.476	7.200	153.8
6e	4.433	8.656	172.3
6f	4.582	7.128	172.3
6g	4.771	6.597	172.3
6h	4.771	8.071	172.3
6i	5.085	7.470	172.3
6j	6.142	6.979	153.8

3. Discussion

The ring opening of the starting oxiranes **1b–i** was regionspecific by nucleophilic attack on the terminal carbon atoms affording a secondary diols. Compounds **3b–j** were obtained as a mixture of isomeric diastereomers. Their spectral data were perfectly consistent with literature data [1, 2].

Accordingly, compounds **6b–j** were obtained as a mixture of diastereomers, but the two stereogenic centers within the molecule are far from each other so they could not be discerned by ^{1}H NMR technique. Their ^{1}H NMR spectrum showed a sharp singlet for the two methylene groups of the dimercaptoethane moiety. This is not the case for compound **6j** for which a multiplet was observed for these methylene groups [5]. This may be explained if one assumes that the ring opening of cyclohexene oxide **1j** gave exclusively *trans*- diols which were formed as an equimolar mixture of *meso*- and *threo*- stereoisomers [1, 2].

The *S. aureus* methicillin resistant, *P. aeruginosa* and *K. pneumonia* have become a major nosocomial pathogen in community, long-term care facilities and tertiary care hospitals [19–21]. Compounds **6a–i** exhibited moderate to weak antibacterial activities only against *K. pneumoniae* pathogens in comparison with Gentamycin. These activities are possibly rooted in the *ortho*-carbonyl disulfide moiety in the chemical structure of **6a–i**. The key role of disulfide linkage for antifungal activity has been proved in previously published works [6, 8]. The biological activity potential of the *ortho*-carbonyl disulfide of desired macrocycles is strongly affected by the characteristics of their side arms such as lipophilic and steric factors. Doing QSAR studies can rationalize these effects and finally a broad range of MIC values.

Comparing the calculated 1D/QSAR and WHIM-3D/QSAR (66 directional WHIM and 33 global WHIM) data of **6a–i** with MIC values, showed that there is a linear relationship between lipophilicity (logP), 2ed component size directional WHIM index (L_2m) and logMIC (figure 2a and b). L_2m is a directional descriptor that confirms the importance of molecular size to predict MIC of this class of compounds. The results showed that decreasing of logP and L_2m respectively correlate with decreasing and increasing of tendency of these armed thioether–ester crown ethers in inhibiting of *K. pneumonia* growth (figure 2a and b). The data in table 2 also showed compounds with more PSA *i.e.* **6e–i**, gave the best resulting MIC values.

However this study is a beginning for synthesis and evaluation of a new generation of antibacterial agents. Although compounds **6a–i** are each as a mixture of diastreomers [1, 2], if one can obtain a diastereomerically pure sample of any of these compounds, the MIC value of a pure diastereomer might be less or more than of what we expected.

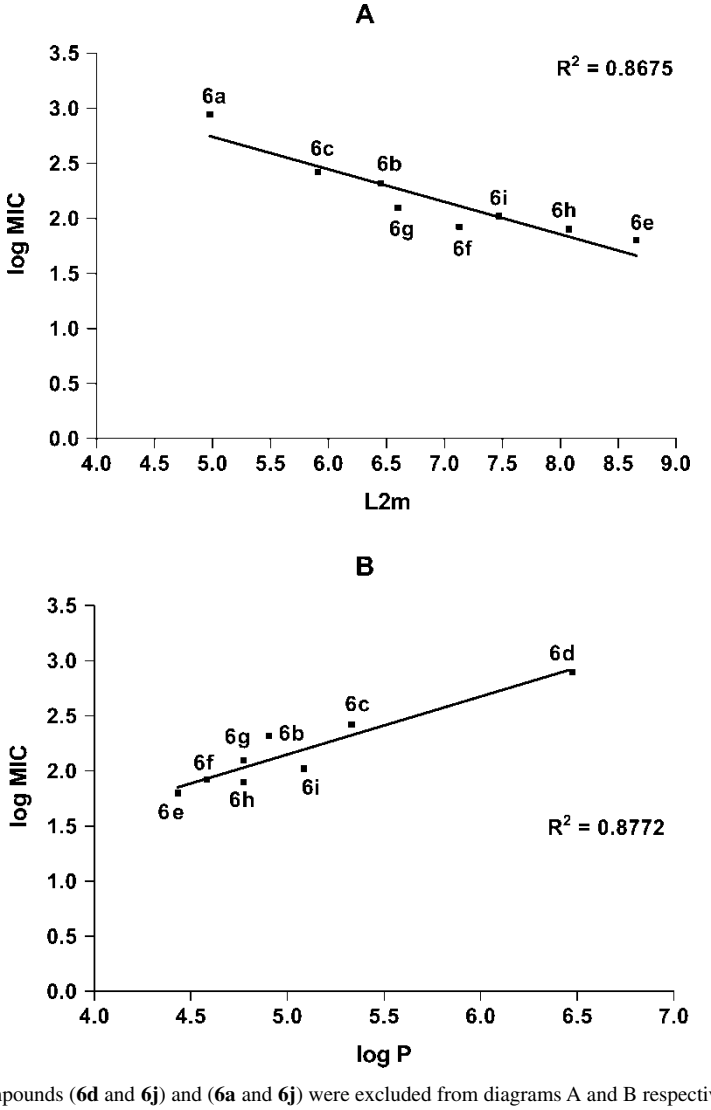

Figure 2. Compounds (**6d** and **6j**) and (**6a** and **6j**) were excluded from diagrams A and B respectively because of high deviation.

4. Conclusion

The aim of this study was to develop an efficient synthetic approach to construct various 7, 14-disubstituted thioether–ester crown ethers and to screen for possible antibacterial activities. The efficient synthetic approach disclosed herein had led to quick output of a series of 7, 8, 10, 11, 13, 14-hexahydro-5*H*,16*H*-dibenzo[*l*,*p*][1, 10, 4, 7, 14, 15] dioxatetrathiacyclooctadecine-5,16-diones for the evaluation of antibacterial activities of these compounds which indicated that **6a–i** are inhibitors for *K. pneumonia*.

5. Experimental

^{1}H NMR (500 MHz) spectra were obtained by using a Bruker Avance DRX-500 Fourier transformer spectrometer on sample dissolved in $CDCl_3$. Chemical shifts are reported in ppm (δ) downfield from tetramethylsilane (TMS). Electron impact (EI) mass spectra were recorded on a Varian Match 7A spectrometer. The IR spectra were obtained on a 4300 Shimadzu Fourier transform spectrometer. All chemicals were purchased from Merck and Fluka Co. and used without further purification.

5.1 *Synthesis of dithiodibenzoyl chloride (5)*

Thionyl chloride (100 mL) was added to 2,2′-dithiosalicylic acid **4** (32.0 mmol, 10 g). The mixture was stirred under reflux for 5 h. The thionyl chloride was then evaporated under reduced pressure gave the brown crystalline residue of **5** (10.6 g, 95% yield, mp 441. [9]: 42–44 °C). The purity of **5** was quite sufficient to use it directly for the following synthesis.

5.2 *General procedure for the synthesis of 7,8,10,11,13,14-hexahydro-5H,16H-dibenzo[l,p][1,10,4,7,14,15]dioxatetrathiacyclooctadecine-5,16-diones (6a–j)*

A solution of β,β′-dihydroxydithioether (5.0 mmol) in dry benzene (20 mL) was reacted with elemental potassium (10.0 mmol) under reflux condition. When all potassium disappeared, the reaction mixture was left at room temperature and triethylamine (10.0 mmol) and 2,2′-dithiosalicylic acid chloride **5** were added respectively in one portion. After 2 h stirring, the mixture was washed with water (3 × 20 mL), then acidified with HCl 5% (20 mL) and dried with anhydrous sodium carbonate and concentrated under reduced pressure. The desired compounds were purified by column chromatography (silica gel 60; 230–400, eluent: chloroform). Purity of the compounds was checked on TLC (silica gel 60 F_{254}, dichloromethane–methanol 9:1).

5.3 *General procedure for minimum inhibitory concentration*

The minimum inhibitory concentrations (MICs) of **6a–j** were determined in dilution tube test method, which had been introduced by NCCLS (National Committee for Clinical Laboratory Standards) [21]. For broth dilution methods, in which decreasing concentrations of the antimicrobial agents must be tested, usually a prepared in serial two-fold dilution of a broth medium is placed in tubes which will support the growth of the test microorganism. After sufficient incubation (usually overnight), the tubes are examined for turbidity, indicating growth of the microorganism. The organism will grow in the tube that does not contain enough antimicrobial agents to inhibit growth. The lowest drug concentration of the agent that prevents growth of the

test organism, as detected by lack of visual turbidity (matching the negative growth control), is designated the minimum inhibitory concentration (MIC). A serial dilution of tested compounds (final concentration of 800–25 μg/mL), were added to the test bacteria in Mueller–Hinton broth and were incubated at 37 °C for 18–20 h. Growth was presented in the medium control and was absent from the inoculum control [22].

7,8,10,11,13,14-hexahydro-5H,16H-dibenzo[l,p][1,10,4,7,14,15]dioxatetrathiacycloocta-decine-5,16-dione (6a).
Yellow solid (53%); mp 71 °C; ^{1}HNMR: δ 2.9 (s, 4H, -SCH_2CH_2S-), 3.0 (t, $J = 8$ Hz, 4H, -SCH_2-), 4.5 (t, $J = 8$ Hz, 4H, -$COOCH_2$-), 7.2–8.2 (m, 8H, aromatic H), MS m/z: 452 (M+), 272 (100%), IR: 1718, 1230, 1100 cm^{-1}. (Found: C, 53.15; H, 4.50; S, 28.27. $C_{20}H_{20}O_4S_4$ requires: C, 53.07; H, 4.45; S, 28.34%).

7,14-dimethyl-7,8,10,11,13,14-hexahydro-5H,16H-dibenzo[l,p][1,10,4,7,14,15]dioxatetra-thiacyclooctadecine-5,16-dione (6b).
Yellow solid (42%); mp 63 °C; ^{1}HNMR: δ 1.5 (d, $J = 6$ Hz, 6H, CH_3-) 2.4–3.1 (m, 4H, -SCH_2-), 2.9 (s, 4H, -SCH_2CH_2S-), 5.3 (m, 2H, -COOCH-), 7.1–8.3 (m, 8H, aromatic H), MS m/z: 480 (M+), 152 (100%), IR: 1722, 1231, 1100 cm^{-1}. (Found: C, 55.08; H, 5.11; S, 26.54. $C_{22}H_{24}O_4S_4$ requires: C, 54.97; H, 5.03; S, 26.68%).

7,14-diethyl-7,8,10,11,13,14-hexahydro-5H,16H-dibenzo[l,p][1,10,4,7,14,15]dioxatetra-thiacyclooctadecine-5,16-dione (6c).
Yellow viscous liquid (44%); ^{1}HNMR: δ 1.06 (t, $J = 8$ Hz, 6H, CH_3-) 1.89 (m, 4H, CH_3CH_2-) 2.64–3.17 (m, 4H, -SCH_2-), 2.90 (s, 4H, -SCH_2CH_2S-), 5.2 (m, 2H, -COOCH-), 7.2–8.3 (m, 8H, aromatic H), MS m/z: 508 (M+), 169 (100%), IR: 1723, 1231, 1100 cm^{-1}. (Found: C, 56.78; H, 5.61; S, 25.02. $C_{24}H_{28}O_4S_4$ requires: C, 56.66; H, 5.55; S, 25.21%).

7,14-diphenyl-7,8,10,11,13,14-hexahydro-5H,16H-dibenzo[l,p][1,10,4,7,14,15]dioxatetra-thiacyclooctadecine-5,16-dione (6d).
Yellow viscous liquid (31%); ^{1}HNMR: δ 2.6–3.2 (m, 4H, -SCH_2-), 2.8 (s, 4H, -SCH_2CH_2S-), 5.7 (m, 2H, -COOCH-), 7.1–8.2 (m, 18H, aromatic H), MS m/z: 604 (M+), 137 (100%), IR: 1727, 1235, 1100 cm^{-1}. (Found: C, 63.78; H, 4.63; S, 21.09. $C_{32}H_{28}O_4S_4$ requires: C, 63.55; H, 4.67; S, 21.21%).

7,14-di[(allyloxy)methyl]-7,8,10,11,13,14-hexahydro-5H,16H-dibenzo[l,p][1,10,4,7,14,15] dioxatetrathiacyclooctadecine-5,16-dione (6e).
Yellow viscous liquid (36%); ^{1}HNMR: δ 2.7–3.1 (m, 4H, -SCH_2-), 2.8 (s, 4H, -SCH_2CH_2S-), 3.8 (d, 4H, $J = 6$ Hz, CH_2 (allyl)), 4.0 (m, 4H, -CH_2O-) 5.1–5.5 (m, 6H, -COOCH- & =CH_2), 5.7–6.1 (m, 2H, -CH=), 7.2–8.2 (m, 8H, aromatic H), MS m/z: 592 (M+), 137 (100%), IR: 1723, 1233, 1100 cm^{-1}. (Found: C, 56.90; H, 5.47; S, 21.49. $C_{28}H_{32}O_6S_4$ requires: C, 56.73; H, 5.44; S, 21.64%).

7,14-di(isopropoxymethyl)-7,8,10,11,13,14-hexahydro-5H,16H-dibenzo[l,p][1,10,4,7, 14,15]dioxatetrathiacyclooctadecine-5,16-dione (6f).
Yellow viscous liquid (30%); ^{1}HNMR: δ 1.2 (d, $J = 6$ Hz, 12H, CH_3-), 2.6–3.1 (m, 4H, -SCH_2-), 2.8 (s, 4H, -SCH_2CH_2S-), 3.4–3.8 (m, 6H, -CH_2O- & CH (isopropyl)), 5.3 (m, 2H, -COOCH), 7.1–8.2 (m, 8H, aromatic H), MS m/z: 596 (M+), 137 (100%), IR: 1724, 1232, 1100 cm^{-1}. (Found: C, 56.50; H, 6.11; S, 21.29. $C_{28}H_{36}O_6S_4$ requires: C, 56.35; H, 6.08; S, 21.49%).

7,14-di(butoxymethyl)-7,8,10,11,13,14-hexahydro-5H,16H-dibenzo[l,p][1,10,4,7,14,15] dioxatetrathiacyclooctadecine-5,16-dione (6g).
Yellow viscous liquid (36%); ^{1}HNMR: δ 0.9 (t, $J = 8$ Hz, 6H, CH_3-), 1.2–1.7 (m, 8H, -CH_2CH_2-) 2.6–3.1 (m, 4H, -SCH_2-), 2.8 (s, 4H, -SCH_2CH_2S-), 3.5 (t, $J = 8$ Hz, 4H, -OCH_2-(butyl)), 3.8 (m, 4H, -CH_2O-), 5.3 (m, 2H, -COOCH), 7.1–8.2 (m, 8H, aromatic H), MS m/z: 624 (M+), 137 (100%), IR: 1722, 1232, 1100 cm^{-1}. (Found: C, 57.78; H, 6.51; S, 20.47. $C_{30}H_{40}O_6S_4$ requires: C, 57.66; H, 6.45; S, 20.53%).

7,14-di(tert-butoxymethyl)-7,8,10,11,13,14-hexahydro-5H,16H-dibenzo[l,p][1,10,4,7, 14,15]dioxatetrathiacyclooctadecine-5,16-dione (6h).
Yellow viscous liquid (38%); ^{1}HNMR: δ 1.2 (s, 18H, -CH_3) 2.7–3.2 (m, 4H, -SCH_2-), 2.9 (s, 4H, -SCH_2CH_2S-), 3.7 (m, 4H, -CH_2O-), 5.3 (m, 2H, -COOCH), 7.1–8.2 (m, 8H, aromatic H), MS m/z: 624 (M+), 137 (100%), IR: 1726, 1233, 1100 cm^{-1}. (Found: C, 57.69; H, 6.61; S, 20.41. $C_{30}H_{40}O_6S_4$ requires: C, 57.66; H, 6.45; S, 20.53%).

7,14-di(phenoxymethyl)-7,8,10,11,13,14-hexahydro-5H,16H-dibenzo[l,p][1,10,4,7,14,15] dioxatetrathiacyclooctadecine-5,16-dione (6i).
Yellow viscous liquid (29%); ^{1}HNMR: δ 2.7–3.2 (m, 4H, -SCH_2-), 2.9 (s, 4H, -SCH_2CH_2S-), 4.4 (m, 4H, -CH_2OPh), 5.5 (m, 2H, -COOCH), 6.8–8.1 (m, 18H, aromatic H), MS m/z: 664 (M+), 137 (100%), IR: 1725, 1236, 1100 cm^{-1}. (Found: C, 61.66; H, 4.81; S, 19.18. $C_{34}H_{32}O_6S_4$ requires: C, 61.42; H, 4.85; S, 19.29%).

1,2,3,4,4a,6,7,8a,9,10,11,12,12a,26a-tetradecahydro-14H,25H-tetrabenzo[b,h,l,p][1,10,4, 7,14,15]dioxatetrathiacyclooctadecine-14,25-dione (6j).
Yellow solid (33%) Mp: 53-55 °C; ^{1}HNMR: δ 1.3–1.6 (m, 8H, -CH_2CH_2-), 1.8 (m, 4H, -CH_2-), 2.1 (m, 4H, -CH_2-), 2.8–3.1 (m, 6H, -SCH- & -SCH_2CH_2S-), 5.1 (m, 2H, CH-OCO), 7.1–8.2 (m, 8H, aromatic H); MS m/z: 560 (M+), 158 (100%), IR: 1722, 1231, 1100 cm^{-1}. (Found: C, 60.04; H, 5.65; S, 22.77. $C_{28}H_{32}O_4S_4$ requires: C, 59.97; H, 5.75; S, 22.87%).

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