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Synthesis of Some New Macrocyclic Diamides Based on Dibenzosulfide as N-Pivot Lariat Ethers

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ABSTRACT

Background: 18-memberd ring of tri-aza dibenzo sulfide (TTD) and dibenzo sulfoxide (TSD) macrocyclic diamides showed the oxidative radical forming ability and further strengthened the documentation of their cytotoxicity effects through lipids, proteins and DNA oxidation damages. With this in mind, our group synthesized some novel macrocyclic base on TTD diamides and a podand ***Methods*:** Novel aza macrocyclic diamides were synthesized based on dibenzosulfide using of diester method as N-pivot Lariat ethers from the michael reaction and nucleophilic attack to epoxide ring as a key strategy of corresponding Diamide with acrylonitrile, epoxy-styrene and 1, 2-epoxypropane at reflux in dichloromethane in good overall yields. In addition, a podand was synthesized based on dibenzosulfoxide with epichlorohydrin at reflux in methanol. ***Results*:** The structures of these compounds were confirmed using IR, ^{1}H NMR and ^{13}C NMR spectroscopy. ***Conclusion*:** The presence of additional oxygen atom considerably increases its hydrogen binding capacity and this property can improve biological and complexation characteristics of primary 18-Membered-ring tri-aza Macrocyclic diamide (TTD).

Introduction

Macrocyclic diamides are valuable intermediates for the preparation of aza crown compounds and more complicated ligands such as cryptands and cryptohemispherands that can be functionalized by additional ligating centers including chromogenic and proton-ionizable groups.[1] Macrocyclic diamides and corresponding aza crown compounds have gained a great deal of attention due to their wide application in biology, microanalysis, enzyme mimics, medical and industrial uses.[2]

There are different ways for synthesis of aza crown ether compounds i.e.[3]

- high-dilution method,
- high-pressure approaches,
- template,
- diester method,
- Richman-Atkins method and
- crab-like method

Using of diester method (Figure1) allow the reaction take place under normal conditions without using of high dilution –techniques.[4]

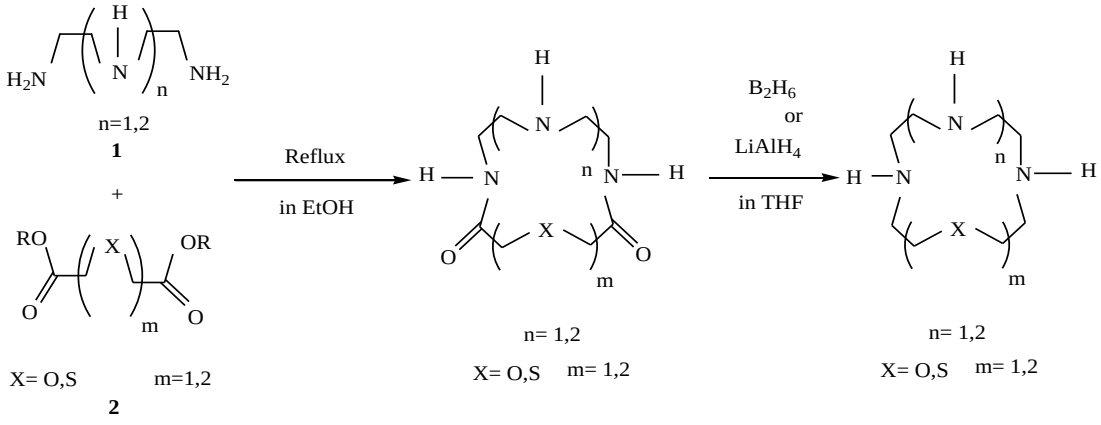

Figure 1. Diesters method, activated carboxylic acid derivatives have also been used for the preparation of macrocyclic diamides in excellent yields under normal conditions reaction.

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The development of lariat ethers began at the conceptual stage in the mid-1970 s. The pivot group can be attached to either the macroring carbon or nitrogen atoms. Some of the carbon- and nitrogen-pivot lariat crown ethers exhibited increased cation binding abilities over the parent crown ethers, probably by further ligation of the cation by the side arm donor atoms.Collision with a sidearm might also occur but the fact that a larger number of donor groups are present in the macroring in a preorganized fashion suggested that ring collision would be more productive. In second step, a conformational change was expected in which the extended sidearm would desolvated and then reaches over the macrocycle to secure the ring-bound cation.[5]

Since monomacrocycles show higher binding rates (cation capture and release rates) than do the bicyclic cryptands, it was exhibited fast complexation with a variety of transition and heavy metals, molecular ions, and natural molecules and decomplexation rates, that is they would be dynamic cation binders. The lariat ethers are designed with a normal crown macro-ring augmented by a Lewis basic donor group attached by a flexible side chain.[6] The term "lariat ethers" refers to a crown ethers or similar macrocyclic derivatives with one or more podand side arms to enhance the cation complexing ability. Originally, the sidearm was expected to contain one or more Lewis basic donor groups (as Figure 2).[7]

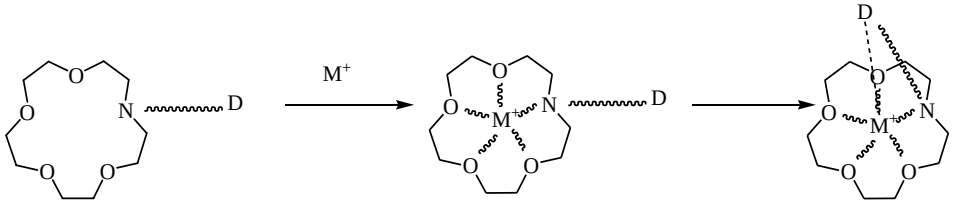

Figure 2. The term "Lariat ethers

It was anticipated that the sidearm and macroring would cooperate in binding a cation and that this interaction would result in three-dimensional (enveloping) complexation while retaining rapid binding kinetics. This will increase the binding strength of the ligand toward the metal ions.[8]

The amide group, so generously used by nature in a variety of antibiotic ionophores [9] has acquired a special status in the design of receptors because it displays dual (O or N and NH) lighting character, higher negative charge on oxygen than for ether and ester groups, and geometrical rigidity.[10]

In addition, amide-based macrocycles for selective recognition of metal cations and organic molecules typically adopt reorganization of their binding sites through hydrogen bonding or configurationally rigidity around the amide carbon-nitrogen bond.[11] In other words, these compounds structurally possess a hydrophilic cavity surrounded by a hydrophobic ring and are characterized by having a different number of ethylene oxide units and amide groups.[12]

The latter may be attached at many elements (which we call pivot atoms) but to date; only carbon and nitrogen have been so utilized (Figure 3).[13]

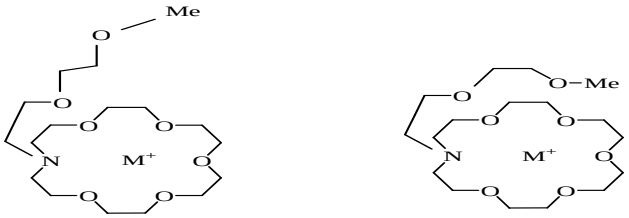

Figure 3. The nitrogen-pivots are quite flexible, and invertible nitrogen serves as a donor within the macroring and the sidearm point of attachment.

In biological studies these macrocycles such as tri-aza macrocyclic diamides[14] (Figure 4, compound 4´) and (Figure5, compound 4´) showed inhibitory effects in some biological transformations i.e. the role of oxidative stress in V79 cell culture as a model of mammalian cells in a range of doses (0.5–8 mM) and what were assessed the effects of these substances on ROS level, cellular viability, apoptosis events, activity of antioxidant enzymes including superoxide dismutase (SOD), glutathione peroxidase (GPX), catalase (CAT), and on some macromolecules' oxidative damage end-products: malondialdehyde (MDA), dityrosine, and 8-hydroxy-deoxyguanosine (8 OH-dG) that were assessed by spectrometry and HPLC methods. [12] Also they were revealed cytotoxicity effects on cell culture particularly at doses >1 mM after 24-h incubation, there is an increasing interest in their biochemical stability and cytotoxicity effects. [12]

In addition, in complex action studies, they revealed high selectivity towards heavy metal ions such as Ag^{+}, Co^{2+}, Hg^{2+} and Cd^{2+} in the presence of other ions.[13, 15, 16] Also, dibenzosulfide and dibenzosulfoxide can be used as important hosts in host- guest chemistry.[15, 16]

With this in mind, our group is continued previous researches[16] (Figure 4) toward the synthesis of new

dibenzosulfide and dibenzosulfoxide[17] macrocyclic compounds as lariat ethers and Podand.

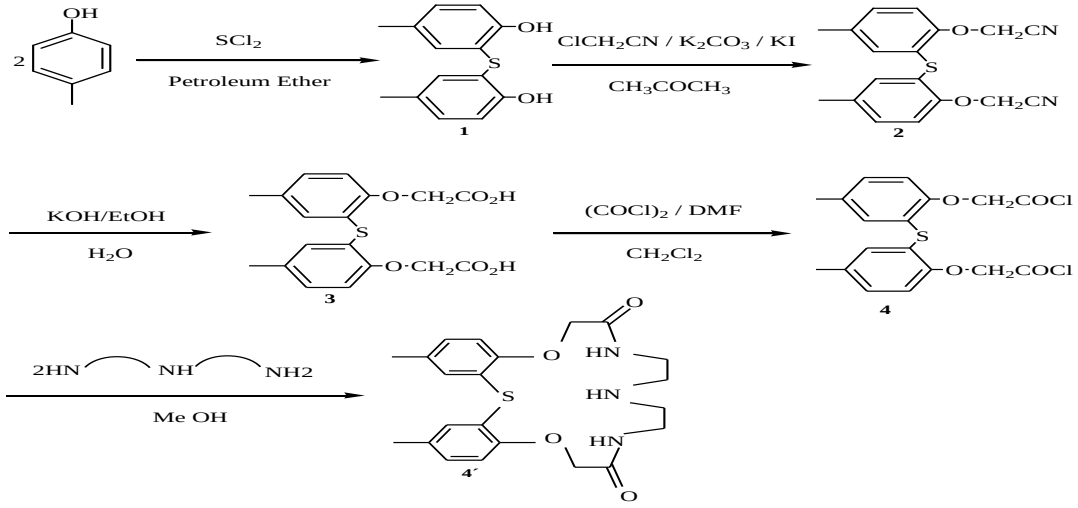

Figure 4. TTD based on dibenzosulfide

Materials and Methods

Chemistry

All reactions were carried out in an efficient hood. The starting materials were purchased from E. Merck, Darmstadt and Fluka Chemie AG CH-9470 Buchs chemical companies. Column chromatography and preparative thin laryer chromatography were performed on silicagel 60 (0.04-0.063 mm) and silicagel 60 P F 254, respectively. All of reagent- grade and absolute methanol were of the highest purity available and used as received .KI, K_2CO_3, Fe $(NO_3)_3$ and Cu $(NO_3)_2$ Supplied from Fluka. The melting points were measured with an Electrothermal Engineering LTD 9100 apparatus. IR spectra were measured on a FT-IR Bruker Perkin- Elmer model 543. The ^{1}H NMR and ^{13}C NMR spectra were obtained using Spectrospin/Avance 400 MHz, $CDCl_3$, 125 MHz, $CDCl_3$, 100 MHz, CDCl3) (FT-NMR, Bruker BRUKER AVANCE DRE 400 MHz and BRUKER AVANCE DPX 100 MHz spectrometers.

Synthesis of bis [(2-hydroxy-5-methyl) phenyl] solfuxide (1´)

To mixture of dichloromethane (200 ml), anhydrous aluminium chloride (25 g, 0.187 mol) and Paracresol (19.34 ml, 20 g, 0.185 mol), was added thionyl chloride (6.75ml, 11g, 0.0925 mol) and stirred in ice water bath (in fifteen minutes) and recrystallized with ethanol solvent. Yield: 17 g (85%); White Crystals; mp= 192-194 $^{\circ}$C; R_f = 0.2 Methanol/Ethyl acetate (1:3). IR νmax (KBr)/cm^{-1}: 3065 (O-H), 2987, 2918, 2858, 1608 (CH_3), 1587, 1504 (C=C, Ar), 1453, 1411, 1357, 1286 (C-O), 1261, 1225, 1201, 1135, 1055 (S=O), 945, 879, 824, 781, 755, 709, 681, 565, 524, 488, 465, 437, 414. ^{1}H NMR (400 MHz, $CDCl_3$): δ= 2.26 (s, 6 H), 6.81-6.83 (d, JJ= 6 Hz, 2 H), 7.04 (s, 2 H), 7.14-7.16 (d, JJ= 6 HZ, 2 H), 8.63 (Broad, O-H).

Synthesis of 2, 2´- sulfinyl -bis [-(4 - methyl) phenol] sulfide (2´)

To mixture of compound (1) (5 g, 0.1 mol), and acetic acid anhydrous (60 ml), was added zinc dust (5g) and refluxed in solvent boiling point (in 24hours) and recrystallized with toluene solvent. Yield: 4.70 g (94%); Colorless Crystals or Pale Yellow Crystals; mp= 114-115 $^{\circ}$C. R_f = 0.6 Ethyl acetate /Petroleum ether (2:1). IR νmax (KBr)/cm^{-1}: 3400-3200 (O-H), 3040, 3010, 2920, 1900, 1880, 1760-1900 (Ar), 1580 (C=C), 1500, 1480, 1475 (C=C), 1400, 1360, 1375 (CH_3), 1280, 1230, 1140, 1060, 940, 880, 820, 760. ^{1}H NMR (500 MHz, $CDCl_3$): δ =2.4 (s, 6 H), 6.1 (Broad, O-H), 6.8-7.2 (m, 6 H Ar).

Synthesis of 2, 2´- sulfinyl bismethyl [(4-methyl) phenoxyacetate] or methylation diester (3´)

To mixture of compound (2) (7.5 g, 0.03 mol), methyl chloroacetate (6.45ml, 0.07 mol), acetone (100 ml), and potassium carbonate (15 g) was added potassium iodide (0.5 g) and refluxed in 60 $^{\circ}$C (in 24hours) and recrystallized with methanol or methanol/ water solvent. Yield: 7.13 g (95%); Solid White Cotton; mp= 100 $^{\circ}$C; R_f = 0.4 Ethyl acetate/Petroleum ether (5:1). IR νmax (KBr)/cm^{-1}: 2960, 2940, 1760 (C=O), 1480, 1440, 1280, 1250, 1200 (C-O), 1150, 1080, 990, 800. ^{1}H NMR (500 MHz, $CDCl_3$): δ =2.2 (s, 6 H), 3.7 (s, 6 H), 4.65 (s, 4 H), 6.8-7.2 (m, 6 H Ar).

Synthesis of 7, 10, 13- tree aza-1- thia- 4, 16- dioxa, 2, 3 ,17 ,18-dibenzo- 20, 24- dimethyl- cycloocatdecan-6, 14- dione (4´)

To mixture of methanol (60 ml), and compound (3) (3 g, 0.00769) was added diethylenetriamine (0.84 ml, 0.00773 mol) and refluxed in solvent boiling point (in 24hours) and recrystallized with methanol. Yield: 1.5 g (50%); White Crystals; mp= 220-222 $^{\circ}$C. R_f = 0.4

Methanol/ Ethyl acetate (3:1). IR νmax (KBr)/cm^{-1}: 3420 (NH Amin), 3380 (NH Amide), 3360, 3040, 2940, 2880, 1686, 1680, 1676 (C=O), 1570, 1537 (NH Amide), 1490, 1280, 1250, 1210, 1080, 1050, 830, 800, 770, 680, 590, 560, 438. ^{1}HNMR (500 MHz, $CDCl_3$): δ =2.25 (s, 6 H), 2.78-2.8 (m, 4 H), 3.39-3.4 (m, 4 H), 4.6 (s, 4 H), 6.82-6.83 (d, JJ=8.29 HZ, 2 H), 6.91 (s, 2 H), 7.09-7. (d, JJ=8.17 HZ, 2 H), 7.48 (s, 2 H), 7.48 (broad) . ^{13}C NMR (125 MHz, $CDCl_3$): δ =168.27, 153.58, 132.61, 132.51, 129.7, 122.19, 112.29, 67.88, 49.33, 39.25, 20.97. MS: *m/z* (%) = 429 [M^+], 430 [M+1] $^+$, 431 [M+2] $^+$, 386, 360, 316, 303, 257, 241, 228, 180, 178, 164, 151, 121, 108, 105, 91, 85, 84, 56, 49, 43, 30.

Synthesis of N-cyano ethyl (7, 10, 13- three aza-1-thia- 4, 16- dioxa, 2, 3 ,17 ,18- dibenzo- 20, 24-dimethyl- cyclooctadecan-6, 14- dione) (5)

To mixture of compound (4´) (0.24g, 0.55 mmol), three ethyl amin (2.37 ml, 0.017 mol) and dichloromethane (25 ml), was added acrylonitrile (1.19 ml, 18.15 mmol) and refluxed in solvent boiling point (in 24hours). After complexation of the reaction (by TLC), the mixture was cooled in room temperature, and washed with alkali solution (10%) and water, then recystallized from n-Hexane / Chloroform. Yield 0.19 g (80%); White Crystals; mp= 150-152 ºC. R_f= 0.33 Methanol/ Ethyl acetate (5:1). IR νmax (KBr)/cm-1: 3386, 2987, 2906, 2468, 1629, 1475, 1401, 1361, 1254, 1220, 1181, 1159, 1102, 1078, 1014, 942, 899, 806, 748, 660, 627, 558, 530. 1H NMR (400 MHz, CDCl3): δ =1.42-1.45 (m, 2 H) , 2.22 (s, 6 H), 2.75-2.77 (m, 4 H), 3.35-3.39 (m, 4 H), 3.57-3.58 (m, 2 H), 4.56 (s, 4 H), 6.78-6.88 (d, 2 H), 7.45 (Broad, 2 H), 6.88 (s, 2 H), 7.05-7.07 (d, 2 H). ^{13}CNMR (100 MHz, CDCl3): δ= 166.91, 152.18, 131.22, 131.13, 126.56, 124.53, 120.80, 111.23, 66.82, 51.94, 47.88, 37.79, 19.51, 7.02.

Synthesis of 1- hydroxy-1- phenyl Ethyl (7, 10, 13-threeaza-1-thia-4, 16-dioxa, 2, 3, 17, 18- Dibenzo-20, 24-dimethyl- cyclooctadecan-6, 14- Dione) -2-hydroxyl-2- phenyl ethyl (6)

To mixture of compound (4´) (0.58 mmol, 0.25g) ferric nitrate (5.3mmol, 1.88g) in dichloromethane (25 ml) was added styrene oxide (0.48mmol, 0.05 g) and stirred at room temperature (in 24 hours). After complex action of the reaction (TLC), the mixture was filtered by funnel and washed with acidic solution (10%) and water. The compound was recrystalized from Chloroform. Yield: 0.1 g (40%); Pale yellow Crystals; mp= 128 _130 ºC. R_f = 0.28 Methanol/ Ethyl acetate (3:1). IR νmax (KBr)/cm^{-1}: 3670-3100 (O-H), 3422, 3100, 3069, 3029, 2926, 2855, 1727, 1683, 1564, 1525, 1492, 1457, 1430, 1364, 1325, 1289, 1247, 1199, 1169, 1104, 1066, 1048, 894, 805, 750, 728, 674, 555, 528, 427. 1HNMR (400 MHz, CDCl3): δ=2.30 (m, 2 H), 2.31(s, 6H), 3.52-3.65 (m, O-H, 1 H), 6.83-7.43 (m, Ar), 7.43(s, 1H). ^{13}CNMR (100 MHz, CDCl3): δ= 167.16, 153.66, 150.01, 131.98, 131.89, 130.51, 130.11, 129.89, 112.25, 111.43, 107.16, 67.01, 52.36, 46.52, 46.08, 37.0, 35.76, 19.52, 19.43.

Synthesize of 2-hydroxy propyl (7, 10, 13- three aza-1-thia-4, 16-dioxa, 2, 3, 17, dibenzo-20, 24- dim ethyl-cyclooctadecan- 6, 4- dione) - 2- hydroxyl- 3-methyl ethyl (7)

To mixture of compound (4´) (0.53 mmol, 0.23g) and copper (II) nitrate (4.92mmol, 1.72 g) in dichloromethane (25ml) at room temperature, was added 1,2- Propylene oxide (1.53 mmol, 0.03 g) and stirred at room temperature (in 24hours) . Then the reaction mixture was refluxed for 24h. After completion of the reaction (TLC), the mixture was filtered, then washed with acid, solution (10%) and water, dried and evaporated to afford a precipitate that was recrystallized from Chloroform. Yield 0.8 g (35%); Pale Yellow Crystals; mp= 168-170 ºC. R_f = 0.22 Methanol/ Ethyl acetate (3:1). IR νmax (KBr)/cm-1: 3500-3100 (O-H), 3419, 2973, 2947, 2867, 1650, 1472, 1445, 1389, 1310, 1187, 1056, 1026, 1011, 904, 827, 785, 685, 594, 480. ^{1}H NMR (400 MHz , CDCl3): δ= 1.04-1.05(dd,3 H), 1.08 (m, 3 H), 2.02 (s, 6 H), 2.10-2.17 (m, 4 H), 2.178-2.179 (m, 4 H), 3.35 (s, 4 H),6.68-6.70(d, 2 H), 6.87-6.89 (broad , 1H), 6.89 (s, 2 H), 7.04 (d, 2 H), 7.455 (broad, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ= 163.30, 155.20, 133.90, 129.91, 127.35, 119.82, 115.91, 87.20, 75.66, 75.31, 66.82, 62.38, 51.94, 42.22, 28.84, 19.22.

Synthesis of bis [2- (1- oxo - 2, 3- epoxypropan) -5-methyl phenyl] sulfoxide (8)

To a mixture of compound (1´) (1.52 mmol, 0.4g) and potassium iodide (catalyt) in methanol (30ml), was added solution of epichlorohydrin (Chloromethyloxirane) (0.0035 mmol, 0.28 ml), and methanol (5ml) and refluxed in solvent boiling point (in 24hours). Then the reaction mixture was refluxed for 24 h. After completion of the completion of the reaction (TLC) the mixture respectively dried and evaporated to afford a precipitate that was recrystallized from Chloroform. Yield: 0.28 g (70%); Colorless Crystals; mp= 170-172 ºC. R_f = 0.3 Methanol/ Ethyl acetate (3:1) IR νmax (KBr)/cm-1: 3158, 3013, 2920, 2867, 1660, 1600, 1469, 1396, 1245, 1133, 1100, 1020, 961, 881, 822, 788, 748, 701, 678, 635, 596, 513, 481. ^{1}H NMR (400 MHz, CDCl3): δ= 2.23 (d, 4 H), 2.26 (s, 6 H), 2.32 (m, 2 H), 2.33 (ddd, 4 H), 6.87-6.98(m, 2 H), 7.14 (d, 2H), 7.05 (s, 2 H). ^{13}C NMR (100 MHz, CDCl3): δ =152.18, 133.11, 128.96, 122.38, 118.23, 112.42, 68.68, 51.94, 44.03, 19.48**.**

Results and Discussion

In this study, the first, another method was developed to synthesis of TTD using $SOCl_2$ instead of SCl_2 ((Figure5).

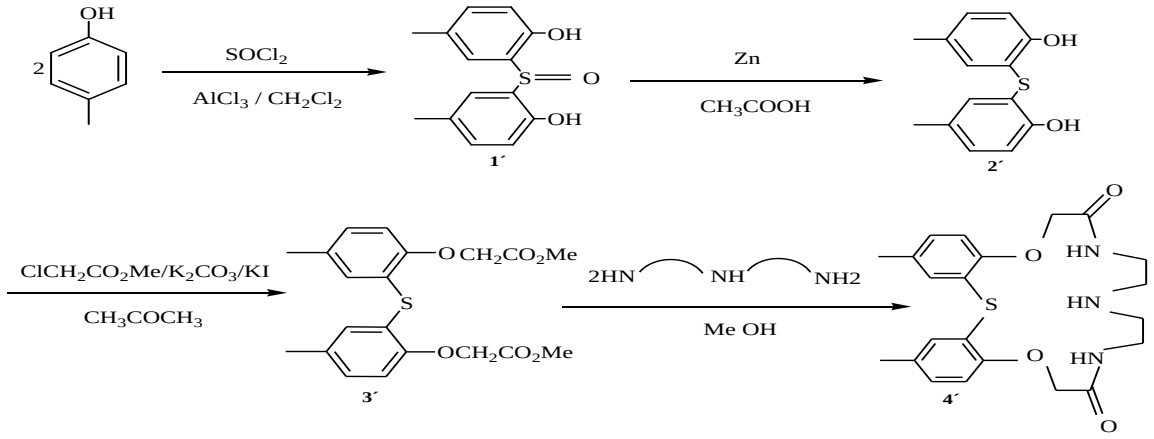

Figure 5. Synthesis of 7, 10, 13- tri aza-1- thia- 4, 16- diox a- 20, 24 - dimethyl-2, 3, 17, 18- Dibenzo- cyclootcadecan-6, 14- dion) (TTD) based on dibenzosulfoxide.

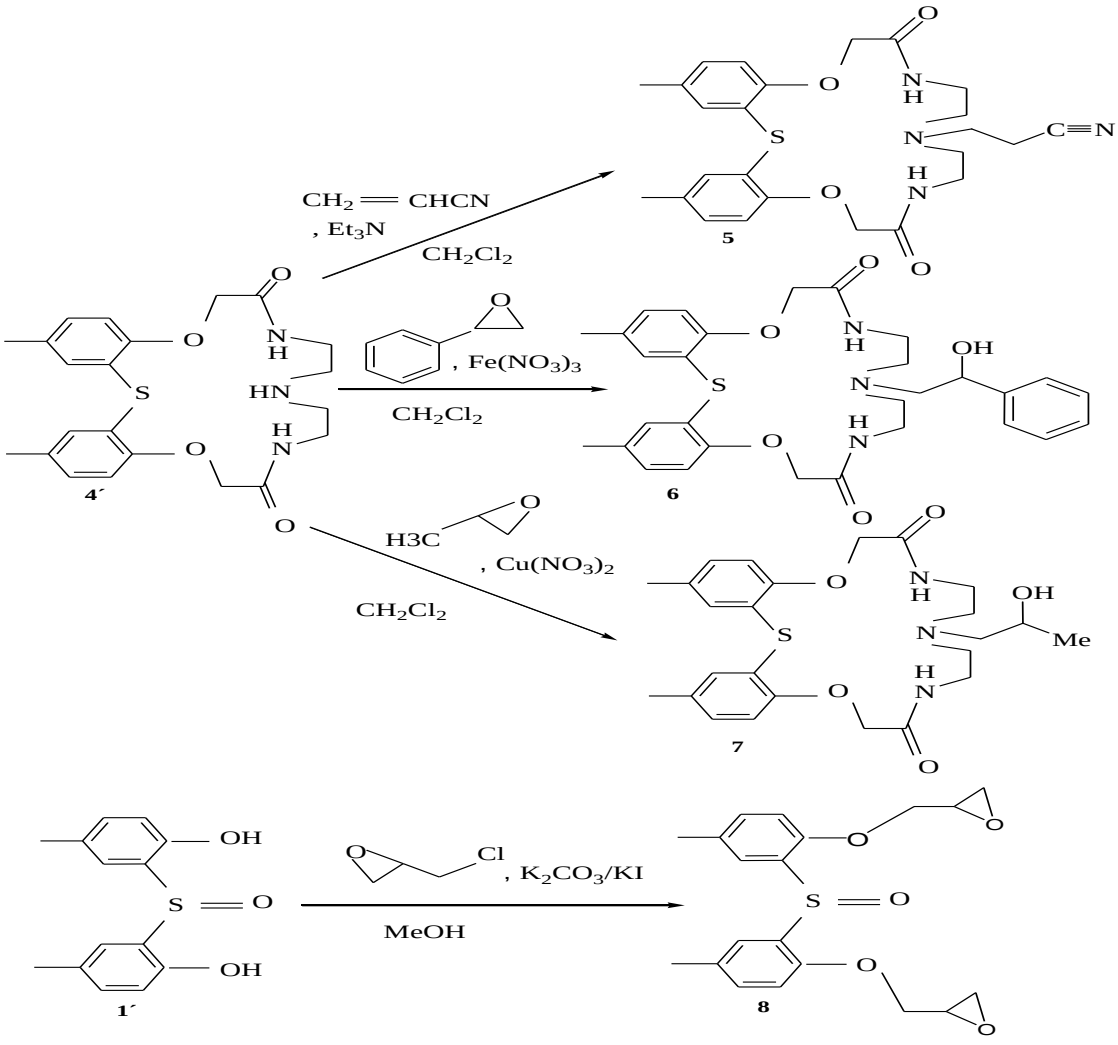

Figure 6. Synthesis of Lariat ethers **5**, **6**, **7** and Podand **8.**

In the next step, new aza macrocycles were synthesized as lariat ethers (compounds 5, 6, 7) and podand (compound 8) via michael reaction [18, 19] and nucleophilic attack to epoxide ring [20], respectively (Figure 6). The details of reactions i.e. solvent, catalyst, time and yields are listed in Table 1. The synthesized new aza macrocyclic compounds could modify the selectivity of 18-Membered-ring.[12] The –CN, –OH or Ph and epoxid groups in 5, 6, 7 and 8 often play a key role in the complexation of various guests in aza

macrocycles. On the other hand, the presences of additional oxygen atom considerably increase its hydrogen binding capacity and these properties can improve biological and complexation characteristics of these compounds.[21]

In addition, open chain molecules are called podand is synthesised based on dibenzosulfoxide as Bisepoxide, which are another group of receptors which can be used as important hosts in host- guest chemistry.[22] Moreover, it could be used as building blocks for the construction of a large number of supramolecular systems.[22]

Table 1. Preparation of 1´, 2´, 3´, 4´ and Synthesis of 5, 6, 7 (Lariat ethers) and 8 (Podand).

Entry	Solvent	Catalyst (mmol)	Time (h)	Yield (%)
1´	CH_2Cl_2	$AlCl_3$	15	85
2´	CH_3COOH	Zn	24	94
3´	CH_3COCH_3	K_2CO_3/KI	24	95
4´	CH_3OH	-	24	50
5	CH_2Cl_2	Et_3N (0.55)	24	80
6	CH_2Cl_2	$Fe(NO_3)_3$ (0.58)	24	40
7	CH_2Cl_2	$Cu(NO_3)_2$ (0.53)	24	35
8	CH_3OH	K_2CO_3/KI (1.52)	24	70

Conclusion

Diesters method as a key strategy for synthesis of TTD was used. The synthesis of 5, 6, 7 and 8 compounds were listed under different reaction conditions. The structures of TTD , Lariat ethers and podand with recognition sites –CN, –OH, Ph and bisepoxid groups are confirmed using IR, ^{1}H NMR , ^{13}C NMR spectroscopy**.**

Conflict of interest

The authors report no conflicts of interest.

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