Synthesis of azacrown sulfonamides via ring closing metathesis and their evaluation in lithium ion selective electrodes

Yehia A. Ibrahim*, Haider Behbehani, Elizabeth John, Nadia M. Shuaib and Adel F. Shoukry

Chemistry Department, Faculty of Science, Kuwait University, P.O. Box 5969, Safat 13060, Kuwait
E-mail: yehiaai@kuc01.kuniv.edu.kw

Dedicated to Professor Nouria A. Al-Awadi on the occasion of her 55th birthyear, for her scientific achievements and on the occasion of her appointment as Vice-President for Academic Affairs, Kuwait University

Abstract
New diazapolyoxa macrocyclic ditosylates with 17–28-membered rings were synthesized by the application of the RCM technique to suitable $\alpha,\omega$-dienes. These compounds were employed as neutral carriers in Li$^+$-selective electrodes. The electrodes exhibited nearly Nernstian responses with relatively high selectivity for lithium over other inorganic cations.

Keywords: Ring closing metathesis, $\alpha,\omega$-dienes, azacrown ethers, crown-sulfonamides, ion-selective electrodes, lithium, PVC membrane

Introduction
Efficient synthetic approaches to macrocyclic heterocyclic compounds have recently been developed using the RCM methodology.$^1$ In the present work we applied our previously developed reaction sequence,$^{2-4}$ using the RCM technique, for the macrocyclization step to prepare a number of macrocyclic diazacrown ditosylates with varying ring sizes, in order to investigate their behavior in Li$^+$ ion-selective electrodes.

Lithium is an important element in biological systems. It has been found to be effective in preventing recurring bouts of depression and elation. However, it is toxic in relatively high concentrations. Therefore, it is important to maintain its concentration in the blood within the range of 0.5-1.5 mM. Lithium is present in human, animal and plant tissues in small amounts.$^{5-8}$ Early lithium ion-selective electrodes were based on amide group type ionophores.$^{9-13}$ Lithium ions were determined in undiluted serum using cyclohexyl diamides based electrodes which had
a selectivity of 80:1 for lithium over sodium ions. A series of diamides based on pyridine, furan and dioxanone backbones, which have higher selectivity for lithium over sodium were prepared. In the present study, coated silver/silver chloride electrodes were prepared based on the following ionophores: 2c, 2d, 4c, 4d, 3c, 3d, 5c, 5d, 6d and 7d as Li⁺-neutral carriers (Scheme 1).
Results and Discussion

Scheme 1 illustrates our synthetic routes starting from the appropriate readily available bistosylamides 1a-e which were converted via their potassium salts into the corresponding 1,ω-dienes 2, 4, 6 upon treatment with allyloxyethyl tosylate, allyl bromide or o-allyloxybenzyl chloride. RCM of these dienes proceeded under mild condition using 1-5 mol% of Grubbs’ catalyst I in CH₂Cl₂ to give excellent yields of the corresponding macrocyclic products 3, 5 and 7 respectively as an E/Z mixture in a ratio determined from their ¹H NMR spectra as shown in Table 1 (cf. Experimental section for E and Z isomer assignments).

Table 1. Catalyst%, yields and E/Z ratios of macrocycles 3a-e, 5b,d and 7d

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Mol% catalyst/substrate</th>
<th>Yield (%)</th>
<th>Product E:Z ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2a</td>
<td>1.5</td>
<td>80</td>
<td>3a 1.8:1</td>
</tr>
<tr>
<td>2</td>
<td>2b</td>
<td>1</td>
<td>86</td>
<td>3b 2:1</td>
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<tr>
<td>3</td>
<td>2c</td>
<td>1</td>
<td>80</td>
<td>3c 2:1</td>
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<td>4</td>
<td>2d</td>
<td>5</td>
<td>60</td>
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<tr>
<td>5</td>
<td>2e</td>
<td>5</td>
<td>95</td>
<td>3e 3:1</td>
</tr>
<tr>
<td>6</td>
<td>4c</td>
<td>1</td>
<td>75</td>
<td>5b 1.8:1</td>
</tr>
<tr>
<td>7</td>
<td>4d</td>
<td>3</td>
<td>85</td>
<td>5d 1:1</td>
</tr>
<tr>
<td>8</td>
<td>6d</td>
<td>5</td>
<td>82</td>
<td>7d 1.7:1</td>
</tr>
</tbody>
</table>

The prepared compounds were investigated as neutral carriers for Li⁺ ion-selective electrodes. The selectivity coefficients of the electrodes towards different cationic species (Mⁿ⁺) were determined by the matched potential method (MPM).¹⁴ According to this method the selectivity coefficient was measured by determining the activity ratio of the primary ion (Li⁺) and the interfering ion (Mⁿ⁺) that gives the same potential change when added to a reference Li⁺ solution. Thus, we measured the change in potential upon changing the lithium ion activity, then the interfering ion was added to an identical reference solution until the same potential change was obtained.

The matched potential method was applied to calculate the selectivity coefficients for the electrodes where Mⁿ⁺ is K⁺, Na⁺, Ca²⁺, Ni²⁺, Cu²⁺, Cd²⁺, Co²⁺, Mn²⁺, Zn²⁺, Mg²⁺ and Pb²⁺. The results revealed that all electrodes showed highest values of selectivity coefficients for lithium ion (Li⁺) towards (Cd²⁺) followed by (Na⁺) in the case of electrodes 2c, 3c, 3d, 4d, 6 and 7. As for Cd²⁺, the order of decrease of interference was 3c=7>3d=4c>2c>4d>6d. The higher selectivity coefficients (less selectivity) of compounds 3c and 7 than the other compounds with respect to Cd²⁺ is most probably due to the ring closing system.
Table 2. Logarithmic values of selectivity coefficients for various lithium ion (Li\(^{+}\)) selective electrodes

<table>
<thead>
<tr>
<th>Electrode</th>
<th>K(^+)</th>
<th>Na(^+)</th>
<th>Ca(^{2+})</th>
<th>Ni(^{2+})</th>
<th>Cu(^{2+})</th>
<th>Cd(^{2+})</th>
<th>Co(^{2+})</th>
<th>Mn(^{2+})</th>
<th>Zn(^{2+})</th>
<th>Mg(^{2+})</th>
<th>Pb(^{2+})</th>
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<tbody>
<tr>
<td>No ionophore</td>
<td>-1.6</td>
<td>-1.08</td>
<td>-1.7</td>
<td>-2.2</td>
<td>-1.32</td>
<td>-0.6</td>
<td>-2.5</td>
<td>-2.06</td>
<td>-1.64</td>
<td>-2.62</td>
<td>-1.53</td>
</tr>
<tr>
<td>2c</td>
<td>-1.55</td>
<td>-1</td>
<td>-1.77</td>
<td>-2.41</td>
<td>-1.48</td>
<td>-0.81</td>
<td>-2.85</td>
<td>-2.64</td>
<td>-1.82</td>
<td>-2.62</td>
<td>-1.44</td>
</tr>
<tr>
<td>2d</td>
<td>-1.65</td>
<td>-1.4</td>
<td>-1.9</td>
<td>-2.6</td>
<td>-1.08</td>
<td>-2.3</td>
<td>-2.5</td>
<td>-3.17</td>
<td>-2.2</td>
<td>-1.4</td>
<td></td>
</tr>
<tr>
<td>3c</td>
<td>-1.7</td>
<td>-1.14</td>
<td>-1.68</td>
<td>-2.18</td>
<td>-1.41</td>
<td>-0.79</td>
<td>-2.66</td>
<td>-2.52</td>
<td>-1.78</td>
<td>-2.79</td>
<td>-1.64</td>
</tr>
<tr>
<td>3d</td>
<td>-1.63</td>
<td>-1.07</td>
<td>-1.44</td>
<td>-2.16</td>
<td>-1.49</td>
<td>-0.8</td>
<td>-2.71</td>
<td>-2.2</td>
<td>-1.9</td>
<td>-2.71</td>
<td>-1.38</td>
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<tr>
<td>4c</td>
<td>-1.7</td>
<td>-0.92</td>
<td>-1.77</td>
<td>-2.03</td>
<td>-1.37</td>
<td>-0.8</td>
<td>-2.28</td>
<td>-2.38</td>
<td>-1.72</td>
<td>-2.07</td>
<td>-1.25</td>
</tr>
<tr>
<td>4d</td>
<td>-1.72</td>
<td>-1</td>
<td>-2.08</td>
<td>-2.26</td>
<td>-1.54</td>
<td>-0.9</td>
<td>-2.51</td>
<td>-2.37</td>
<td>-1.79</td>
<td>-3.15</td>
<td>-1.41</td>
</tr>
<tr>
<td>5c</td>
<td>-1.85</td>
<td>-1.24</td>
<td>-2.33</td>
<td>-2.14</td>
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<td>-1.93</td>
<td>-2.18</td>
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<td>-0.91</td>
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<td>7d</td>
<td>-1.93</td>
<td>-1.28</td>
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<td>-2.35</td>
<td>-1.58</td>
<td>-0.79</td>
<td>-2.83</td>
<td>-2.61</td>
<td>-1.88</td>
<td>-2.55</td>
<td>-1.2</td>
</tr>
</tbody>
</table>

In general, it is clear from the results given in Table 2 that the investigated compounds exhibit reasonable selectivity towards Li\(^{+}\) cations. It is also noticeable that other univalent metal cations (Na\(^{+}\) and K\(^{+}\)) interfere more than divalent species (with the exception of Cd\(^{2+}\)).

Experimental Section

All melting points are uncorrected. IR spectra were recorded in KBr disks using a Perkin Elmer System 2000 FT-IR spectrophotometer. \(^{1}\)H and \(^{13}\)C NMR spectra were recorded on a Bruker DPX 400, 400 MHz super-conducting NMR spectrometer. Mass spectra were measured on a VG Auto-spec-Q (high resolution, high performance, tri-sector GC/MS/MS) and with LCMS using Agilent 1100 series LC/MSD with an API-ES/APCI ionization mode. Microanalyses were performed on a LECO CH NS-932 Elemental Analyzer. The starting bis tosylamides 1a-e were prepared by reacting the appropriate bisamines, readily synthesizable as reported,\(^{15}\) with tosyl chloride in pyridine. These bis tosyl derivatives 1a-e are reported but without complete identification.\(^{16-18}\) Poly(vinylchloride) of high molecular weight, tetrahydrofuran (THF), and potassium tetrakis-(4-chlorophenyl)borate (KTPClPB), tris(2-ethylhexyl)phosphate (TEHP), were obtained from Aldrich. Solutions of metal salts in the chloride form (Aldrich) were prepared in deionized water.

Potential measurements

All the measurements were carried out using a 713 pH-mv meter (Metrohm, Swiss), and a Titrator 665 Dosimat (Metrohm, Swiss). The electrochemical system was as follows:

Ag|AgCl|KCl (sat’d)|3.0 M KNO\(_3\)|sample solution|membrane|AgCl|Ag
Electrode preparation
All electrodes were prepared as previously described. Pure silver rods of 10 cm length and 5.0 mm diameter, purchased from Goodfellow Cambridge LTD, England, were insulated by tight polyethylene tubes leaving 2 cm at one end for connection and 1 mm at the other end to be coated anodically with AgCl. Membrane solution was prepared by dissolving 18.00 mg of the ionophore, 139 mg of PVC, 139 mg of plasticizer (tris-2-ethylhexylphosphate, TEHP), and 1.42 mg potassium tetrakis(4-chlorophenyl) borate (KTpClPB) in 500 µL tetrahydrofuran (THF).

Electrode Construction
Two 25 µL aliquots of the membrane solution were carefully deposited on the silver-silver chloride electrode surface. The second aliquot was deposited after the first aliquot had almost dried. The tip was left to stand for 24 h to allow the THF solvent to evaporate, and then it was soaked in 0.1 M of lithium chloride solution (LiCl) for 24 h before use.

Compounds 1a-e
General Procedure. To an ice cold solution of the appropriate bisamine dihydrochloride (10 mmol) in dry pyridine, was added p-toluenesulfonyl chloride (21 mmol). The mixture was stirred at 0 ºC for 4 h and then kept overnight in the fridge. The precipitate obtained after addition of cold water was collected and crystallized from EtOH/CHCl₃.

**Compound 1a.** Yield 78%, mp 189–190 ºC, LCMS; m/z 553 (M + 1). IR: 3434, 3273, 1599, 1501, 1401, 1342, 1246, 1165, 1115, 1091, 918, 746, 673, 564. ¹H NMR (CDCl₃): δ 7.62 (d, 4H, J 8.2), 7.55 (dd, 2H, J 7.9, 1.2), 7.15 (d, 4H, J 8.2), 7.12 ( dt, 2H, J 7.4, 1.2), 6.99 (t, 2H, J 7.6), 6.96 (s, 2H, NH), 6.80 (d, 2H, J 7.9), 4.07 (s, 4H, CH₂), 2.32 (s, 6H, CH₃). Anal. calcd. for C₂₈H₂₈N₂O₆S₂ (552.6): C 60.85; H 5.11; N 5.07%; S 11.6. Found: C 60.67; H 4.89; N 5.28; S 11.26%.

**Compound 1b.** Yield 68%, mp 249–250 ºC (lit. 16, mp 228-230 ºC), LCMS; m/z 567 (M + 1). IR: 3277, 2950, 2890, 1598, 1501, 1474, 1400, 1336, 1290, 1252, 1163, 1112, 1094, 1052, 919, 814, 753, 672, 564, 543. ¹H NMR (CDCl₃): δ 7.61 (d, 4H, J 8.1), 7.55 (d, 2H, J 8.2), 7.08 (d, 6H, J 7.3), 6.96 (t, 2H, J 7.6), 6.93 (s, 2H, NH), 6.77 (d, 2H, J 8.1), 3.94 (t, 4H, J 5.4, CH₂), 2.29 (s, 6H, CH₃), 2.09 (q, 2H, J 5.7, CH₂). Anal. calcd. for C₂₉H₃₀N₂O₆S₂ (566.7): C 61.47; H 5.34; N 4.94; S 11.32%. Found: C 61.31; H 5.76; N 5.48; S 11.39%.

**Compound 1c.** Yield (89%), mp 163–164 ºC, LCMS; m/z 597 (M + 1). IR: 3277, 2950, 2890, 1598, 1501, 1474, 1400, 1336, 1290, 1252, 1163, 1112, 1094, 1052, 919, 814, 750, 680, 565, 543. ¹H NMR (CDCl₃): δ 7.65 (d, 4H, J 7.1), 7.56-7.52 (m, 4H), 7.09 (d, 4H, J 7.2), 7.04-7.00 (m, 2H), 6.95-6.96 (m, 2H), 6.86 (d, 2H, J 7.7), 4.09 (s, 4H), 3.82 (s, 4H), 2.26 (s, 6H, CH₃). Anal. calcd. for C₂₈H₃₀N₂O₆S₂ (596.7): C 60.39; H 5.41; N 4.94; S 11.32%. Found: C 60.05; H 5.86; N 5.05; S 11.39%.

**Compound 1d.** Yield (60%), mp 119 ºC, LCMS; m/z 641 (M + 1). IR: 3251, 3063, 2926, 2877, 1599, 1498, 1455, 1410, 1337, 1290, 1262, 1162, 1131, 1114, 1094, 1042, 936, 909, 746, 681,
568. $^1$H NMR (CDCl$_3$): $\delta$ 7.68 (d, 4H, J 8.2), 7.57 (s, 2H, NH), 7.54 (dd, 2H, J 7.9, 1.5), 7.16 (d, 4H, J 8.1), 7.00 (dt, 2H, J 7.7, 1.6), 6.93 (dt, 2H, J 7.6, 1), 6.80 (dd, 2H, J 8, 1.1), 3.99-3.96 (m, 4H), 3.84 (s, 4H), 3.76-3.75 (m, 4H), 2.33 (s, 6H, CH$_3$). Anal. calcd. for C$_{32}$H$_{36}$N$_2$O$_8$S$_2$ (640.8): C 59.98; H 5.66; N 4.37; S 10.01%. Found: C 59.83; H 6.11; N 4.54; S 10.25%.

**Compound 1e.** Yield (50%), mp 146–147 ºC, LCMS; m/z 629 (M + 1). IR: 3557, 3258, 2922, 1598, 1498, 1405, 1335, 1252, 1163, 1112, 1092, 1000, 910, 812, 751, 672, 570, 539. $^1$H NMR (CDCl$_3$): $\delta$ 7.61 (d, 4H, J 8.2), 7.55 (dd, 2H, J 7.9, 1.6), 7.42-7.40 (m, 2H), 7.22-7.20 (m, 2H), 7.16 (d, 4H, J 8.1), 7.04-7.00 (m, 4H), 6.95 (dt, 2H, J 7.6, 1.1), 6.74 (dd, 2H, J 7.5, 0.9), 4.89 (s, 4H, CH$_2$), 2.36 (s, 6H, CH$_3$). Anal. calcd. for C$_{34}$H$_{32}$N$_2$O$_6$S$_2$ (628.7): C 64.95; H 5.13; N 4.46; S 10.20%. Found: C 64.75; H 5.49; N 4.80; S 9.58%.

**Synthesis of compounds 2a-e, 4c, 4d and 6**

**General procedure A.** A mixture of the appropriate bistosylamide 1a-e (10 mmol), allyloxyethyl tosylate, allyl bromide or o-allyloxybenzyl chloride (20 mmol) and anhydrous K$_2$CO$_3$ (5.52 g, 40 mmol) was stirred in dry DMF (5 mL) at 100 ºC for 16 h. Crushed ice was added to the mixture and the precipitate was collected, washed with KOH solution (10%) and with water several times and then extracted with DCM, dried over Na$_2$SO$_4$ and evaporated to give 2a-e, 4c, 4d and 6 respectively.

**General procedure B.** To a solution of KOH (10 mmol) in methanol (15 mL) was added each of 1a-e (10 mmol). The mixture was then stirred at room temperature for 15 min and the solvent was then removed in vacuo. To the remaining potassium salt was added DMF (2 mL) and allyloxyethyl tosylate, allyl bromide or o-allyloxybenzyl chloride (20 mmol). The reaction mixture was then heated under reflux for 5 min. The mixture was cooled, diluted with water (20 mL) and extracted with DCM, washed with cold water several times, dried over anhydrous Na$_2$SO$_4$ and evaporated to give 2a-e, 4c, 4d and 6 respectively.

**Compound 2a.** Yield 58% (A), 31% (B); colorless crystals (EtOH), mp 125-126 ºC, R$_f$=0.8 (DCM/pet. ether 40-60/EtOAc 6:4:2). LCMS; m/z 721 (M + 1). IR: 3071, 2889, 2857, 1596, 1498, 1479, 1456, 1345, 1285, 1257, 1164, 1102, 1067, 1049, 916, 818, 799, 750, 712, 696, 655. $^1$H NMR (CDCl$_3$): $\delta$ 7.59 (d, 4H, J 8.1), 7.35 (dt, 2H, J 8.2, 1.5), 7.26 (dd, 4H, J 7.8, 1.5), 7.22 (d, 2H, J 8.1), 6.98 (dt, 2H, J 7.7, 0.9), 6.78 (d, 2H, J 7.6), 5.78 (m, 2H, -CH=), 5.17 (dd, 2H, J 17.3, 1.5, CH$_2$=CH), 5.12 (dd, 2H, J 10.4, 1.2, CH$_2$CH=), 3.87 (d, 4H, J 5.5, OCH$_2$CH=), 3.73 (m, 4H, CH$_2$), 3.59 (s, 4H, CH$_2$), 3.49 (t, 4H, J 6.2, CH$_2$), 2.36 (s, 6H, CH$_3$). $^{13}$C NMR (CDCl$_3$): $\delta$ 155.4, 142.8, 137.9, 134.5, 129.8, 129.1, 127.6, 121.2, 116.9, 112.6, 71.8, 68.3, 68.1, 65.7, 49.3, 21.4%. Anal. calcd. for C$_{38}$H$_{44}$N$_2$O$_8$S$_2$ (720.9): C 63.31; H 6.15; N 3.89; S 8.90. Found: C 63.28; H 6.00; N 4.29; S 8.72%.

**Compound 2b.** Yield 93% (A), 73% (B); colorless crystals (EtOH), mp 136-137 ºC, R$_f$=0.9 (DCM/pet. ether 40-60/EtOAc 6:4:2). LCMS; m/z 735 (M + 1). IR: 3441, 2942, 2884, 1596, 1496, 1454, 1344, 1280, 1250, 1163, 1117, 1089, 1064, 916, 820, 749. $^1$H NMR (CDCl$_3$): $\delta$ 7.61
(d, 4H, J 8.1), 7.29 (dt, 2H, J 8, 1.5), 7.24 (d, 4H, J 8.1), 7.16 (dd, 2H, J 7.7, 1.4), 6.90 (m, 4H), 5.78 (m, 2H, CH=), 5.15 (dd, 2H, J 17.3, 1.3, CH2=CH), 5.11 (d, 2H, J 10.8, CH2=CH), 3.85 (d, 4H, J 5.4, OCH2CH=), 3.90-3.65 (br, 8H), 3.48 (t, 4H, J 6.3), 2.41 (s, 6H, CH3), 1.61 (br, 2H). 

13C NMR (CDCl3): δ 155.9, 142.8, 137.7, 134.5, 132.5, 129.5, 129.1, 127.6, 127.1, 120.6, 116.9, 112.6, 71.8, 68.3, 64.4, 49.3, 28.5, 21.5. Anal. calcd. for C39H46N2O8S2 (734.9): C 63.74; H 6.31; N 3.81; S 8.73%. Found: C 63.44; H 6.72; N 4.02; S 8.85%.

**Compound 2c.** Yield 50% (A), 40% (B); colorless crystals (EtOAc/pet. ether 40-60), mp 87-88 °C, Rf=0.4 (DCM/pet. ether 40-60/EtOAc 6:4:2). LCMS; m/z 765 (M + 1). IR: 3068, 3015, 2925, 2871, 1597, 1496, 1453, 1337, 1284, 1158, 1139, 1118, 1086, 809, 757, 717, 658. 1H NMR (CDCl3): δ 7.61 (d, 4H, J 8), 7.24 (m, 8H), 6.94 (t, 2H, J 7.6), 6.84 (d, 2H, J 8.2), 5.80 (m, 2H, CH=), 5.17 (d, 2H, J 17.2, CH2=CH), 5.11 (d, 2H, J 10.4, CH2=CH), 3.88 (d, 4H, J 5.6, CH2), 3.70-3.87 (m, 8H), 3.50 (t, 4H, J 6.4, CH3), 3.45 (t, 4H, J 4.5, CH2), 2.42 (s, 6H, CH3). 13C NMR (CDCl3): δ 155.7, 142.8, 137.8, 134.5, 132.9, 129.7, 127.9, 127.7, 127.2, 120.8, 116.8, 112.7, 71.8, 69.2, 68.3, 67.2, 49.2, 21.5. Anal. calcd. for C40H48N2O8S2 (764.9): C 62.81; H 6.32; N 3.66; S 8.38%. Found: C 62.68; H 6.08; N 4.15; S 8.09%.

**Compounds 2d.** Yield 71% (A), 60% (B); colorless oil, purified by column chromatography (DCM/pet. ether 40-60), Rf=0.6 (EtOAc/pet. ether 40-60, 2:1). LCMS; m/z 809 (M + 1). IR: 3068, 3015, 2925, 2871, 1597, 1496, 1451, 1345, 1287, 1254, 1163, 1118, 1092, 1073, 929, 816, 755, 711, 657. 1H NMR (CDCl3): δ 7.60 (d, 4H, J 8.1), 7.27 (m, 4H), 7.23 (d, 4H, J 8.1), 6.94 (t, 2H, J 7.5), 6.82 (m, 2H), 5.80 (m, 2H, CH=), 5.18 (d, 2H, J 7.4, 1.3, CH2=CH), 5.12 (d, 2H, J 10.3, CH2=CH), 3.89 (d, 4H, J 5.5, OCH2CH=), 3.83 (br, 8H), 3.59 (s, 4H), 3.52 (t, 4H, J 6.3), 3.43 (t, 4H, J 4.6), 2.41 (s, 6H, CH3). 13C NMR (CDCl3): δ 155.5, 142.7, 137.7, 134.5, 133.1, 129.7, 129.1, 127.6 (2C), 120.8, 116.9, 112.4, 71.8, 70.7, 69.0, 68.4, 67.0, 49.1, 21.5. Anal. calcd. for C42H52N2O10S2 (809.02): C 62.36; H 6.48; N 3.46; S 7.93%. Found: C 62.08; H 6.44; N 3.87; S 7.70%.

**Compound 2e.** Yield 57% (A), 20% (B); colorless oil, purified by column chromatography (DCM/pet. ether 40-60/EtOAc), Rf=0.9 (DCM/pet. ether 40-60/EtOAc 6:4:2). LCMS; m/z 797 (M + 1). IR: 3068, 3028, 2925, 2865, 1596, 1497, 1344, 1163, 1091, 755, 656, 579. 1H NMR (CDCl3): δ 7.58 (d, 4H, J 8), 7.31 (m, 4H), 7.22 (m, 4H), 7.09 (d, 4H, J 7.8), 7.03 (d, 2H, J 8.2), 6.95 (t, 2H, J 7.5), 5.78 (m, 2H), 5.14 (d, 2H, J 18.2, CH2=CH), 5.10 (d, 2H, J 11.4, CH2=CH), 4.91 (br s, 4H), 3.84 (d, 4H, J 5.1, OCH2CH=), 3.80 (br, 4H), 3.51 (t, 4H, J 6.1, CH3), 2.31 (s, 6H, CH3). 13C NMR (CDCl3): δ 155.7, 142.7, 137.5, 134.4, 134.0, 132.5, 129.8, 129.1, 128.2, 128.1, 127.4, 127.3, 120.9, 116.8, 113.1, 71.7, 68.2, 67.6, 49.4, 22.4. Anal. calcd. for C44H48N2O10S2 (797.0): C 66.31; H 6.07; N 3.51; S 8.05%. Found: C 66.08; H 6.04; N 3.80; S 7.88%.

**Compound 2c.** Yield 63% (A), 96% (B); colorless crystals (EtOH), mp 125-126 °C, Rf=0.9 (DCM/pet. ether 40-60/EtOAc 6:4:2). LCMS; m/z 677 (M + 1). IR: 3069, 3037, 2944, 2883, 1597, 1495, 1451, 1334, 1286, 1257, 1165, 1144, 1117, 1094, 1071, 1056, 951, 928, 866, 817, 797, 750, 721, 665, 579, 549. 1H NMR (CDCl3): δ 7.62 (d, 4H, J 7.8), 7.27 (t, 2H, J 7.8), 7.26 (d, 4H, J 7.8), 7.19 (d, 2H, J 7.8), 6.93 (t, 2H, J 7.6), 6.82 (d, 2H, J 8.2), 5.75 (m, 2H, CH=CH2),
5.06 (d, 2H, J 17, CH=CH), 4.97 (d, 2H, J 10, CH=CH), 4.22 (d, 4H, J 4.2), 3.86 (br, 4H), 3.51 (t, 4H, J 4.3), 2.43 (s, 6H, CH₃). ¹³C NMR (CDCl₃): δ 155.9, 142.8, 137.7, 133.5, 132.8, 129.6, 129.1, 127.6, 126.9, 120.8, 118.2, 112.6, 69.3, 67.3, 52.6, 21.5. Anal. calcd. for C₃₆H₄₀N₂O₇S₂ (676.9): C 63.88; H 5.96; N 4.14; S 9.47%. Found: C 63.92; H 6.01; N 4.40; S 9.28%.

**Compound 4d.** Yield 50% (A), 83% (B); brown oil (EtOAc/pet. ether 40-60), Rₜ=0.6 (EtOAc/pet. ether 40-60, 2:1). LCMS; m/z 721 (M + 1). IR: 3069, 3025, 2927, 2876, 1597, 1496, 1451, 1344, 1287, 1257, 1163, 1118, 1093, 1061, 929, 815, 754, 712, 665, 578, 551.¹H NMR (CDCl₃): δ 7.59 (d, 4H, J 8.1), 7.24 (m, 8H), 6.93 (t, 2H, J 7.5), 6.78 (d, 2H, J 8.1), 5.76 (m, 2H, -CH=CH₂), 5.09 (dd, 2H, J 17.0, J 0.7, -CH=CH₂), 4.98 (d, 2H, J 10.1, -CH=CH₂), 4.23 (br, 4H), 3.82 (br, 4H), 3.61 (s, 4H), 3.43 (t, 4H, J 4.5), 2.42 (s, 6H, CH₃). ¹³C NMR (CDCl₃): δ 155.6, 142.8, 137.6, 133.6, 133.2, 129.6, 129.1, 127.6, 126.6, 120.6, 118.2, 112.2, 70.7, 69, 67, 52.4, 21.5. Anal. calcd. for C₃₈H₄₄N₂O₈S₂ (720.9): C 63.31; H 6.15; N 3.89; S 8.90%. Found: C 62.99; H 6.21; N 4.11; S 8.62%.

**Compound 6d.** Yield 56% (A), 54% (B); colorless crystals (EtOH), Rₜ=0.9 (DCM/pet. ether 40-60/EtOAc 6:4:2). MS; m/z 932 (M'). IR: 3434, 3073, 2922, 2873, 1599, 1496, 1453, 1341, 1286, 1253, 1161, 1119, 1094, 1044, 754, 658, 573, 554.¹H NMR (CDCl₃): δ 7.61 (d, 4H, J 8.0), 7.44 (d, 2H, J 7.4), 7.22 (d, 4H, J 8.0), 7.17-7.07 (m, 6H), 6.84 (t, 2H, J 7.4), 6.78 (t, 2H, J 7.6), 6.70 (d, 4H, J 8.2), 5.88 (m, 2H, -CH=CH₂), 5.30 (dd, 2H, J 17.3, 1.0, -CH=CH₂), 5.19 (dd, 2H, J 10.8, 1.0, -CH=CH₂), 4.88 (br, 4H), 4.35 (d, 4H, J 4.6), 3.76 (br s, 4H), 3.67 (s, 4H), 3.47 (t, 4H, J 5.1), 2.41 (s, 6H, CH₃). ¹³C NMR (CDCl₃): δ 156.4, 155.8, 142.5, 138.0, 133.4, 133.0, 130.7, 129.3, 129.0, 128.6, 127.7, 127.2, 125.3, 120.4 (two overlapped CH), 116.8, 112.0, 111.3, 70.8, 69.1, 68.7, 66.9, 48.3, 21.5. Anal. calcd. for C₅₂H₅₆N₂O₁₀S₂ (933.1): C 66.93; H 6.05; N 3.00; S 6.87%. Found: C 66.22; H 6.01; N 3.19; S 6.34%.

**General procedures for RCM**

To a solution of each of 2a-e, 4c,d, 6 (2 mmol) in DCM (10 ml), Grubbs’ catalyst I (1-5%) was added. The reaction mixture was heated under reflux for 2 h, the solvent was removed in vacuo and the product was crystallized from the appropriate solvent or purified by column chromatography.

**Compound 3a.** Yield 0.6 g (80%); colorless crystals (EtOH), mp 127-128 °C, Rₜ=0.6 (DCM/pet. ether 40-60/EtOAc 6:4:2). LCMS; m/z 693 (M + 1). IR: 3066, 3024, 2926, 2869, 1596, 1496, 1451, 1346, 1283, 1254, 1215, 1163, 1122, 1091, 1073, 816, 756, 656, 577, 554.¹H NMR (CDCl₃) E-isomer: δ 7.59 (m, 4H), 7.38 (m, 2H), 7.28 (m, 4H), 7.09 (d, 2H, J 8.2), 6.94-6.99 (m, 4H), 5.26 (s, 2H, CH=), 3.74 (s, 4H), 3.50-4.20 (br m, 8H), 3.35 (t, 4H, J 6.4), 2.45 (s, 6H, CH₃).¹³C NMR (CDCl₃) E-isomer: δ 157, 143.1, 136.7, 131.1, 129.8, 129.3, 129.2, 127.8, 127.7, 121.2, 114.4, 70.6, 68.1, 67.1, 49.9, 21.5.¹H NMR (CDCl₃) Z-isomer: δ 7.59 (m, 4H), 7.38 (m, 2H), 7.28 (m, 4H), 7.16 (d, 2H, J 8.8), 6.94-6.99 (m, 2H), 6.83 (d, 2H, J 8), 5.47 (t, 2H, J 3.6, CH=), 3.84 (s, 4H), 3.50-4.20 (br m, 8H), 3.46 (t, 4H, J 6.6), 2.47 (s, 6H, CH₃).¹³C NMR
(CDCl₃) Z-isomer: δ 155.9, 142.9, 137.4, 132.3, 129.9, 129.4, 129.3, 127.9, 127.7, 121.3, 113.1, 67.9, 67.0, 65.9, 49.1, 21.5. Anal. calcd. for C₃₆H₄₀N₂O₈S₂ (692.8): C 62.41; H 5.82; N 4.04; S 9.26%. Found: C 62.21; H 5.76; N 4.27; S 8.96%.

**Compound 3b.** Yield 0.6 g (86%); colorless crystals (EtOH/DCM), mp 242-243 °C, R₆=0.6 (DCM/pet. ether 40-60/EtOAc 6:4:2). LCMS; m/z 707 (M + 1). IR: 3064, 3023, 2926, 2870, 1596, 1497, 1453, 1342, 1280, 1256, 1163, 1124, 1092, 1060, 969, 818, 754, 713, 657, 575, 553. ¹H NMR (CDCl₃) E-isomer: δ 7.58 (d, 4H, J 8.2), 7.31 (dt, 2H, J 8.8, 1.4), 7.27 (d, 4H, J 8.2), 7.11 (dd, 2H, J 7.7, 1.3), 6.91 (t, 2H, J 7.5), 6.87 (d, 2H, J 8.3), 4.93 (s, 2H, CH=), 3.80 (br, 4H), 3.68 (t, 4H, J 5.7), 3.60 (s, 4H), 3.33 (s, 4H), 2.44 (s, 6H, CH₃), 1.62 (q, 2H, J 5.8). ¹³C NMR (CDCl₃) E-isomer: δ 156.5, 142.9, 136.9, 131.9, 129.7, 129.2, 129.1, 127.6, 126.9, 120.6, 112.2, 70.4, 67, 63.5, 49.5, 28.1, 21.5. Anal. calcd. for C₃₇H₄₂N₂O₈S₂ (706.9): C 62.88; H 5.94; N 3.96; S 9.06%. Found: C 62.40; H 6.42; N 4.12; S 9.06%.

**Compound 3c.** Yield 0.6 g (80%); colorless crystals (EtOH), mp 129-130 °C, R₆=0.4 (DCM/pet. ether 40-60/EtOAc 6:4:2). LCMS; m/z 737 (M + 1). IR: 3420, 2927, 2867, 1597, 1497, 1449, 1345, 1278, 1166, 1138, 1094, 1069, 936, 814, 761, 711, 658, 578, 553. ¹H NMR (CDCl₃) E-isomer: δ 7.61 (two overlapped doublets, 4H, J 8.1), 7.21-7.30 (m, 6H), 7.16 (dd, 2H, J 7.7, 1.3), 6.93 (t, 2H, J 7.4), 6.86 (d, 2H, J 8.2), 5.28 (br, 2H, CH=), 3.89 (s, 3H), 3.77-3.72 (m, 8H), 3.50 (s, 3H), 3.42-3.36 (m, 6H), 2.43 (s, 6H, CH₃). ¹³C NMR (CDCl₃) E-isomer: δ 156.1, 142.9, 137.1, 132.3, 129.6, 129.4, 129.1, 127.7, 127.7, 120.8, 112.7, 70.4, 68.8, 67.4, 67.3, 49.2, 21.5. ¹H NMR (CDCl₃) Z-isomer: δ 7.61 (two overlapped doublets, 4H, J 8.1), 7.21-7.30 (m, 8H), 6.93 (t, 2H, J 7.4), 6.81 (d, 2H, J 8.2), 5.28 (br, 2H, CH=), 3.82 (s, 4H), 3.77-3.72 (m, 8H), 3.42-3.36 (m, 8H), 2.44 (s, 6H, CH₃). ¹³C NMR (CDCl₃) Z-isomer: δ 155.8, 142.8, 137.4, 132.8, 129.6, 129.2, 129.1, 127.3, 127.1, 120.9, 112.4, 69.1, 67.5, 67.3, 65.3, 48.5, 21.5. Anal. calcd. for C₃₈H₄₄N₂O₈S₂ (736.9): C 61.94; H 6.02; N 3.80; S 8.70%. Found: C 61.62; H 5.98; N 3.93; S 8.37%.

**Compound 3d.** Yield 0.47 g (60%); colorless crystals, purified by column chromatography (EtOAc/pet. ether 40-60, 2:1), mp 57-58 °C, R₆=0.6 (EtOAc/pet. ether 40-60, 2:1). LCMS; m/z 781 (M + 1). IR: 3064, 3023, 2926, 2870, 1596, 1496, 1452, 1345, 1286, 1163, 1119, 1072, 755. ¹H NMR (CDCl₃) E-isomer: δ 7.59 (m, 4H), 7.19-7.25 (m, 8H), 6.93 (m, 2H), 6.80 (d, 2H, J 8.1), 5.52 (br s, 2H, CH=), 3.82 (s, 8H, CH₂), 3.75 (t, 4H, J 6.6), 3.58 (s, 4H), 3.48 (t, 8H, J 6.6), 2.42 (s, 6H, CH₃). ¹³C NMR (CDCl₃) E-isomer: δ 155.5, 142.6, 137.7, 134.5, 133.4, 129.7, 129, 127.6, 127, 120.8, 117.1, 112.4, 72.2, 70, 69.3, 67.9, 67, 48.9, 21.4. ¹H NMR (CDCl₃) Z-isomer: δ 7.59 (m, 4H), 7.19-7.25 (m, 8H), 6.93 (m, 2H), 6.80 (d, 2H, J 8.1), 5.44 (t, 2H, J 5.4, CH=), 3.86 (s, 8H), 3.77 (s, 4H), 3.61 (s, 4H), 3.43 (s, 8H), 2.45 (s, 6H, CH₃). Anal. calcd. for C₄₀H₃₈N₂O₁₀S₂ (780.9): C 61.52; H 6.20; N 3.59; S 8.21%. Found: C 61.10; H 6.21; N 3.68; S 7.73%.

**Compound 3e.** Yield 0.7 g (95%); purified by column chromatography (DCM/pet. ether 40-60/EtOAc 6:4:2), colorless crystals (EtOH), mp 100-101 °C, R₆=0.6 (DCM/pet. ether 40-60/EtOAc). LCMS; m/z 769 (M + 1). IR: 3064, 3027, 2923, 2857, 1595, 1496, 1452, 1344, 1162, 1091, 1072, 1001, 756. ¹H NMR (CDCl₃) E and Z isomers: δ 7.61-7.57 (m, 4H, E, Z), 7.26-7.36
(m, 6H, E, Z), 7.17-7.13 (m, 6H, E, Z), 6.96-6.93 (m, 4H, E, Z), 5.35 (t, 2H, J 3.6, CH=, Z), 5.14 (s, 2H, CH=, E), 5.14-5.02 (br, 4H, CH2, E, Z), 3.65 (m, 8H, E, Z), 3.44-3.39 (m, 4H, E, Z), 2.38 (s, 6H, CH3, E, Z). Anal. calcd. for C49H44N2O8S2 (768.9): C 65.64; H 5.77; N 3.64; S 8.34%. Found: C 64.88; H 5.77; N 3.86; S 7.97%.

**Compound 5c.** Yield 0.49 g (75%); colorless crystals (EtOAc/pet. ether 40-60), mp 220-221 °C, Rf=0.6 (DCM/pet. ether 40-60/EtOAc 6:4:2). MS; m/z 648. IR: 3024, 2920, 2872, 1597, 1496, 1451, 1343, 1286, 1259, 1160, 1122, 1092, 1063, 753, 578. 1H NMR (CDCl3) E-isomer: δ 7.52 (m, 4H), 7.31-7.20 (m, 8H), 6.95 (t, 2H, J 7.4), 5.41 (t, 2H, J 5, CH=), 3.1-4.1 (m, 12H), 2.42 (s, 6H, CH3). 13C NMR (CDCl3) E-isomer: δ 156, 142.5, 137.5, 132.4, 129.5, 128.9 (2C), 127.6, 126.6, 120.8, 111.7, 68.7, 66.8, 51.4, 21.4. 1H NMR (CDCl3) Z-isomer: δ 7.52 (m, 4H), 7.31-7.20 (m, 8H), 7.08 (d, 2H, J 7.6), 6.88 (t, 2H, J 8.3), 6.74 (d, 2H, J 8.1), 5.58 (br s, 2H, CH=), 3.1-4.1 (m, 12H), 2.43 (s, 6H, CH3). 13C NMR (CDCl3) Z-isomer: δ 155.3, 142.6, 138.2, 134.6, 129.7, 129.5, 128.9, 127.7, 120.6, 111.6, 67.8, 66.2, 44.3, 21.5. Anal. calcd. for C49H43N2O8S2 (648.8): C 62.94; H 5.59; N 4.32; S 9.88%. Found: C 62.88; H 5.61; N 4.52; S 9.63%.

**Compound 5d.** Yield 0.6 g (85%); colorless crystals (EtOH), mp 184-185 °C, Rf=0.4 (DCM/pet. ether 40-60/EtOAc 6:4:2). MS; m/z 692. IR: 3024, 2920, 2872, 1597, 1496, 1451, 1343, 1286, 1259, 1216, 1161, 1122, 1092, 1064, 937, 888, 814, 751, 693, 658, 579, 553. 1H NMR (CDCl3) E-isomer: δ 7.53 (d, 4H, J 8.1), 7.21-7.26 (m, 6H), 7.00 (dd, 2H, J 7.6, 1.1), 6.86 (t, 2H, J 7.5), 6.72 (d, 2H, J 8.2), 5.41 (s, 2H, CH=), 3.48-4.20 (m, 16H), 2.42 (s, 6H, CH3). 13C NMR (CDCl3) E-isomer: δ 155.9, 142.5, 137.3, 131.8, 129.3, 129.2, 128.9 (2C), 127.5, 120.3, 111.6, 70.4, 69, 66.7, 51.6, 21.3. 1H NMR (CDCl3) Z-isomer: δ 7.53 (d, 4H, J 8.1), 7.21-7.26 (m, 6H), 7.00 (dd, 2H, J 7.6, 1.1), 6.91 (m, 2H), 6.76 (d, 2H, J 8.3), 5.35 (s, 2H, CH=), 3.48-4.20 (m, 16H), 2.42 (s, 6H, CH3). 13C NMR (CDCl3) Z-isomer: δ 155.3, 142.4, 138.1, 133.2, 129.5, 128.3, 127.4, 126.5, 126.4, 120.5, 112.0, 70.7, 68.8, 67.4, 46.4, 21.3. Anal. calcd. for C49H40N2O8S2 (692.8): C 62.41; H 5.82; N 4.04; S 9.26%. Found: C 62.24; H 5.86; N 4.25; S 8.62%.

**Compound 7d.** Yield 0.7 g (82%); colorless crystals (EtOAc/ pet. ether 40-60), mp 192-193 °C, Rf=0.7 (DCM/pet. ether 40-60/EtOAc 6:4:2). LCMS; m/z 905 (M + 1). IR: 3066, 3027, 2926, 2872, 1599, 1495, 1453, 1342, 1286, 1256, 1238, 1220, 1160, 1120, 1092, 753. 1H NMR (CDCl3) E-isomer: δ 7.61 (d, 6H, J 8.2), 7.23-7.08 (m, 10H), 6.98 (t, 2H, J 7.4), 6.82 (t, 2H, J 7.5), 6.71 (d, 2H, J 8.1), 6.62 (d, 2H, J 8.1), 5.70 (s, 2H, CH=), 4.92 (s, 4H), 4.26 (s, 4H), 3.68 (br, 4H), 3.58 (s, 4H), 3.34 (br, 4H), 2.41 (s, 6H, CH3). 1H NMR (CDCl3) Z-isomer: δ 7.62 (d, 6H, J 8.2), 7.23-7.08 (m, 10H), 6.98 (t, 2H, J 7.4), 6.82 (t, 2H, J 7.5), 6.75 (d, 2H, J 8.3), 6.66 (m, 2H), 5.65 (s, 2H, CH=, J 4.4), 4.89 (s, 4H), 4.33 (s, 4H), 3.68 (br, 4H), 3.59 (s, 4H), 3.34 (br, 4H), 2.43 (s, 6H, CH3). 13C NMR (CDCl3) E-isomer: δ 156.3, 155.4, 142.6, 138.2, 133.9, 130.2, 129.4, 129, 128.4, 127.7 (2C), 126.5, 121.1, 120.5, 111.9, 111.8, 70.7, 68.9, 68.1, 67.1, 47.7, 21.5. Anal. calcd. for C50H52N2O10S2 (905.1): C 66.35; H 5.79; N 3.10; S 7.09%. Found: C 66.00; H 5.65; N 3.08; S 6.86%. 

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