TOWARD SYNTHESIS OF A MACROCYCLIC HYBRID AROMATIC PENTAMER

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TOWARD SYNTHESIS OF A MACROCYCLIC HYBRID

AROMATIC PENTAMER

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DECLARATION

I hereby declare that the thesis is my original work and it has been written by me in its entirety.

I have duly acknowledged all the sources of information which have been used in the thesis.

This thesis has also not been submitted for any degree in any university previously.

Sun Xiaonan 04/08/2014

ACKNOWLEDGEMENT

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Summary

In summary, we have designed and attempted to synthesize a hybrid pentamer with cation-binding ability that might differ from those of other closely related hybrid pentamers containing an interior cavity decorated by different functional groups. The synthetic route of the hybrid pentamer was long and time-consuming, and I have only been able to synthesize an acyclic pentamer that nevertheless can undergo an intramolecular ring-closing reaction to afford the desired circular pentamer for which the cation-binding study will then be carried out.

Based on the results obtained, some potential areas for further investigation are proposed. One area is to investigate the ion-binding capacity of the short acyclic oligomers rather than circularly folded pentamers. Secondly, the selective recognition of amine and ammonium guests should be studied since the oxygen atom from pyridone group might serve as a good H-bond acceptor and thus might be able to strongly interact with amines and ammoniums of various types.

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1.Introduction

1.1 Background

Ion-receptor chemistry has been attracting great interest during the last decades[1]. Due to the diversity of the configuration of monomers, different synthetic hosts may contain one or more different functional groups such as amide[2], pyrrole[2], or urea[3] groups. Monomers can incorporate in supramolecular skeletons whose length and configuration can be various according to the number and functional groups of the monomers. They usually target the efficiency of natural receptors5acting as recognition receptors, ion channels and catalyst.

1.1.1 Molecular recognition

Molecular recognition refers to the specific interaction between two or more molecules. The interactions are divided into two main categories. One is direct interaction including non-covalent bonding such as hydrogen bonding, metal coordination, hydrophobic forces[4-5], van der Waals forces, π-π stacking, halogen bonding, electrostatic[6] effects. The other one is indirect interaction, for example, in solution some solvent can also play a significant role in driving molecular recognition [7]. Both the host and guest involved in molecular recognition contribute to molecular complementarity[8-9].

In supramolecular systems, it has been reported that supramolecular can be designed artificially to exhibit molecular recognition. Crown ethers, one of the earliest supramolecular systems, are capable of selectively binding specific cations. Since then numerous artificial systems have been designed and synthesized for different applications. Chemists are still studying in the complexity of molecular recognition.

1.1.2 Macrocyclic receptor for metal ions

It is reported that Ghadiri et al. synthesized cyclic peptides with flat conformation containing even number of alternating D and L amino acids[10]. Their pore size is adjustable by changing the number of the monomers in the cyclic molecular. A one-step macrocyclic reaction was described by Gong et al.[11] in 2008. In this study, it used 4, 6-dimethoxy-1, 3-phenylenediamine that was treated with appropriate diacid chloride. From fig 1.1 we can see that for macrocyclization its precursor oligomers were pre-organized by the three-center H-bonds while its backbone skeleton was also rigidified by the three-center H-bonds. The cavity was large (~8Å across), and it was hydrophilic because of the six convergent aligned oxygens. It could bind hydrated cations through metal-oxygen interatomic interactions.
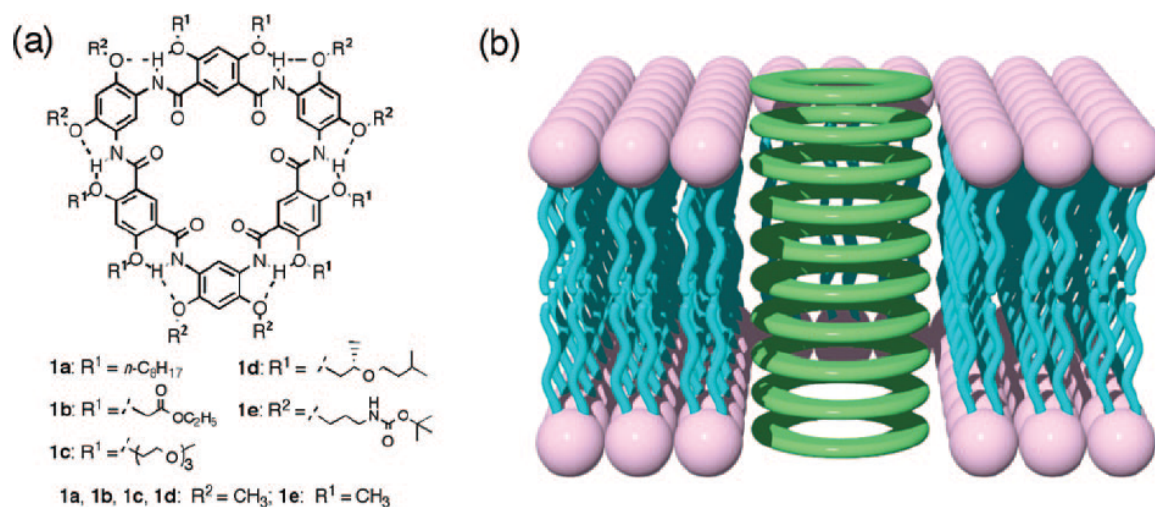

Figure 1.1 (a) Chemical structure of macrocycles. (b) Macrocycles assembling anistropically into a tubular structure that acts as a transmembrane channel or pore in the hydrophobic environment of a lipd bilayer.

A set of structurally well-defined cyclic pentamers built by methoxyl benzene, fluorobenzene or pyridone monomers had been designed and synthesized by Zeng's group as shown in Fig. 1.2.[12-13] As we can see that all the pentamers are intramolecularly H-bonded and highly rigid. The 2D packing of the single crystal of this pentamer b was examined by X-ray diffraction and we found that it was the mathematically predicted densest all-pentagon packing lattice by $c5$-symmetric fluoropentamers[13].
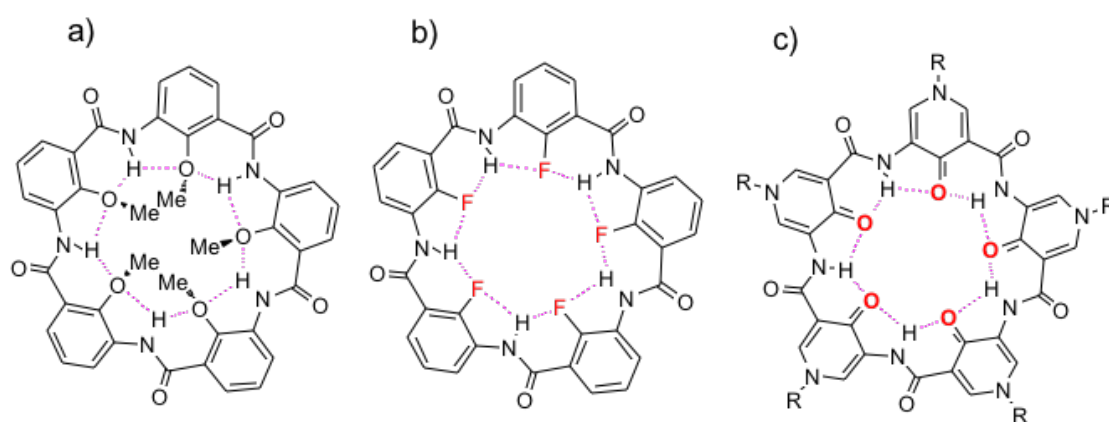

Figure 1.2 Structures of a series of intramolecular H-bounded, highly rigid and structurally well-defined circular pentamer composed of methoxyl benzene (a), fluorobenzene (b) and pyridone (c) building blocks folded pentamers.

A series of methoxyl benzene-based foldamers were synthesized by Li et al. Alkali metal ions were bonded to the oxygen atoms of methoxyl group, thereby increasing the effective molarity of the hydroxide ion, which indicated that the rate of hydrolysis was accelerated when alkali metal hydroxides existed[14]. As can be seen from Fig. 1.3, the selectivity of hydrolysis of methoxyl ether *ortho* terminal was resulted from the electron-withdrawing inductive effect of the nitro groups. The hydrolysis rates of longer foldamers were faster than those of the shorter ones because they can bind alkali metal ions more efficiently. However, the rates were reduced when extra amount of alkali metal salts were added as a result of the
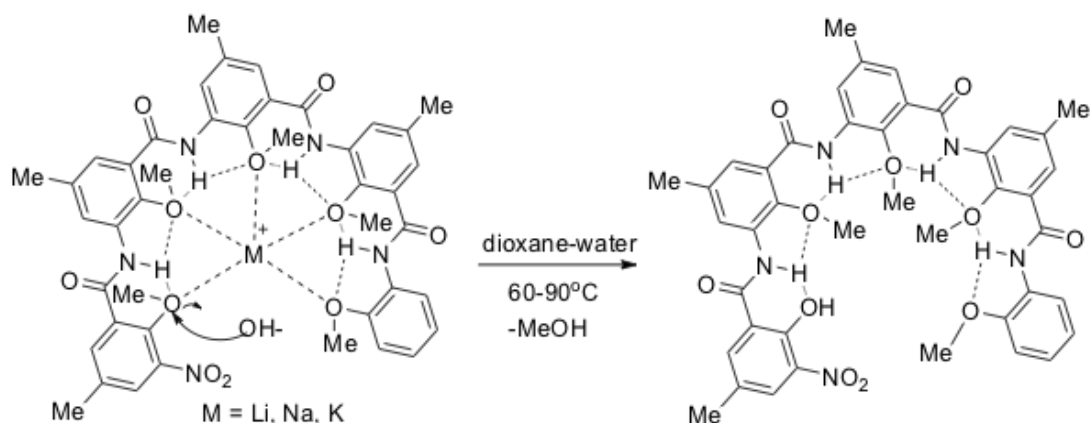
binding competition.

Figure 1.3 Accelerated and selective hydrolysis of methoxy ethers ortho to a NO_2 group.

1.2 Aim of Study

We designed a pentamer approach toward the patterned recognition of metal ions. The designed pentamer are expected to be useful as synthetic receptors for molecular recognition because they have the directionality and strength of hydrogen bonding, synthetic facility, high structural diversity and adaptability. In this regard, the aim of this study was to design and synthesize a new class of cyclic pentamer with tunable cation-binding cavities and to determine their metal binding affinity and selectivity.

## 2. Experimental Section

2.1 Design principle

Ion binding affinity rely on a number of factors such as, (i) shape and preorganization within the host molecule, (ii) the size-match of the host cavity to the guest, (iii) cation charge and type, and (iv) donor atom charge and type. This molecule contains interior cavity that are decorated by electron rich O- and F-atoms and thus are able to bind

metal ions.

2.2 Synthetic Schemes

All the chemicals were purchased from commercial suppliers and used as received unless otherwise noted. All the water in experiments was distilled water. The organic solutions from all water extractions were dried over anhydrous Na_2SO_4 for a minimum of 15 minutes before further step. All the reactions were tested by silica gel thin-layer chromatography (TLC, 0.25 mm thickness, 60F-254, E. Merck). Chemical yields refer to pure isolated substances. Mass spectra of products were obtained from Finnigan MAT95XL-T and Micromass VG7035. ^{1}H NMR spectra were from Bruker ACF-300 (300 MHz) or AVF500 spectrometers (500 MHz). The solvent signal of $CDCl_3$ was referenced at $\delta = 7.26$. Coupling constants (J values) are reported in Hertz (Hz). ^{1}H NMR data are recorded in the order: chemical shift value, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad), number of protons that gave rise to the signal and coupling constant, where applicable. [13]C spectra are proton-decoupled and recorded on Bruker ACF300 (300 MHz) and ACF500 spectrometers (500 MHz). The solvent, $CDCl_3$, was referenced at $\delta = 77$ ppm and DMSO-d_6 was referenced at $\delta = 39.5$. $CDCl_3$ (99.8%-Deuterated) and DMSO-d_6 (99.8%-Deuterated) was purchased from Aldrich and used without further purification. UV-vis absorption and fluorescence spectra were recorded on a Shimadzu UV-1700 spectrometer and a RF-5301 fluorometer respectively.

Scheme 2.1 Synthesis of trimer **1j**
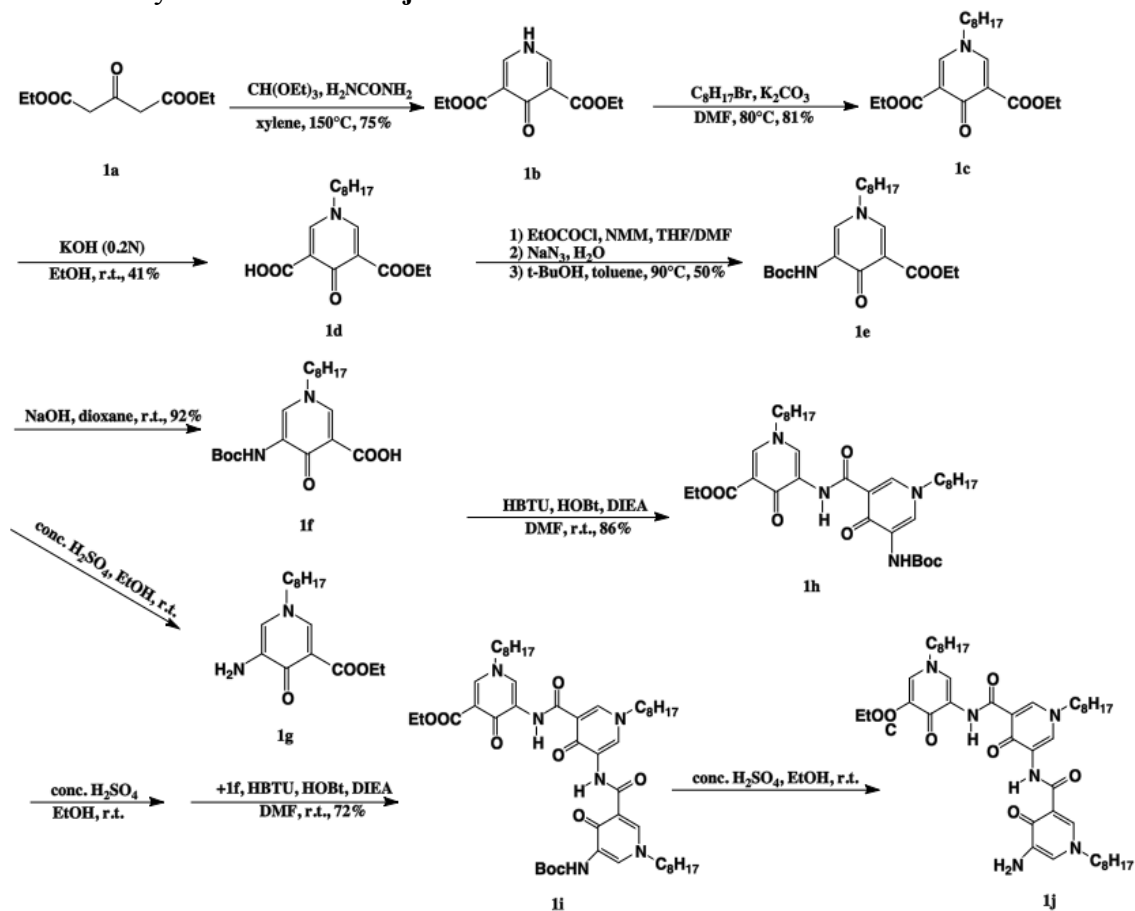
Following the elaboration of the synthetic routes for the efficient preparation of various monomeric building blocks (**1l**, and **1m**), a series of oligoamides (**1h**, **1i** and **1j**) were prepared according to **Scheme 2.1**.

After 4 hours of reflux, a yellow precipitate **1b** was formed. The formed ethanol was removed and reflux for another 1 hour to ensure the reaction was complete. The precipitate was filtered and washed thoroughly with CH_2Cl_2 to remove excessive starting materials and impurities. Product 1b was used directly for the next step reactions without further purification.

Attempted mono hydrolysis of **1c** by varying the ratio of base in ethanol at varying temperatures from 0 ^{o}C to room temperature led to a mixture of two products detected by TLC (starting material **1c**, mono acid **1d** and diacid). By varying the concentration of base,

the hydrolysis conditions using 0.2 M of KOH and slow addition was finally singled out with the chemical yield up to 50 %.

HBTU-mediated step-wise amide coupling method was used for the synthesis of trimer **1i**. The reaction condition was very mild, simply involving mixing the acid and amine with HBTU and HOBt in DMF at room temperature and stirring the solution for 24 hours. Under this condition, a clean reaction producing only **1h** and **1i** were obtained.

Scheme 2.2 Synthesis of monomer **1p**
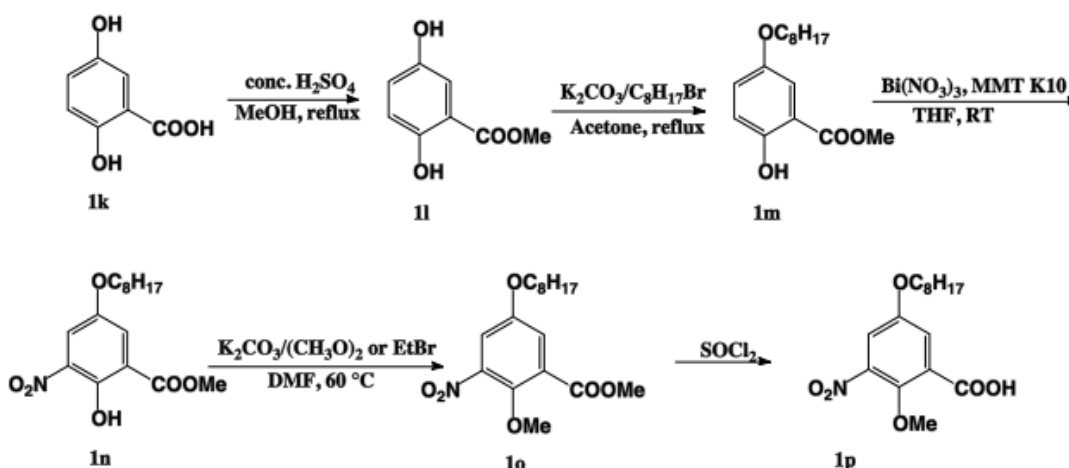
All these reactions were simple to carry out, and recrystallization of the curde product with methanol lead to a high yield up to ~ 80%.

Scheme 2.3 Synthesis of monomer **1f**
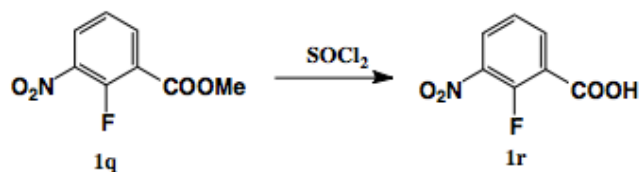
Scheme 2.4 Synthesis of pentamer **1t**
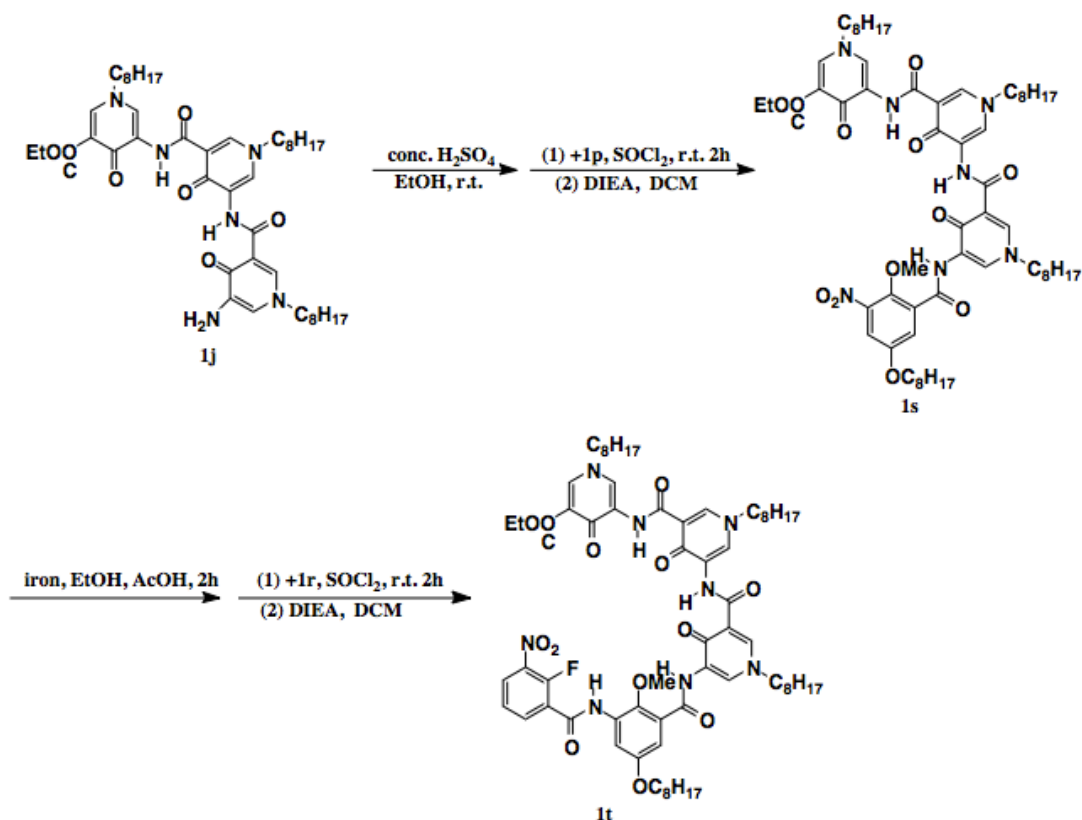
Scheme 2.4 showed the synthesis route of the benzene-pyridone hybrid oligomers. The acyclic tetramer **1s** and pentamer **1t** were synthesized by reacting *in situ* generated monomeric acid chloride (conditions: $SOCl_2$, reflux for 2 hours) with amino-terminated trimer. The nitro group of acyclic tetramer was reduced by iron powder and the ester was hydrolyzed with 1 M KOH aqueous solution subsequently. Once again it was proved to be a successful coupling method for the benzene-pyridone hybrid oligomers synthesis.

3. Results and Discussion

3.1 Synthesis of Pentamer

Diethyl 4-oxo-1,4-dihydropyridine-3,5-dicarboxylate (**1b**)
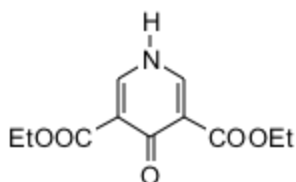
A mixture of diethyl 1,3-acetonedicarboxylate (**1a**, 0.20 mol, 40.0 mL), purchased from Sigma-Aldrich Company, triethyl orthoformate (0.40 mol, 60.0 mL) and urea (0.30 mol, 18.0 g) in 100 mL of xylene was heated to reflux for 4 hours. After all the urea was dissolved and light yellow precipitate formed, the formed ethanol was removed in vacuo, then the reaction mixture was allowed to reflux for another 1 hour. After cooling, the precipitate was filtered and washed with dichloromethane (3 × 50.0 mL), dried under reduced pressure to give the pure compound **1b**. Yield: 35.9 g, 75%. 1H NMR (500 MHz, DMSO-d6) δ 11.18 (s, 1H), 8.19 (s, 2H), 4.18 (q, J = 7.3Hz, 4H), 1.25 (t, J = 7.3Hz, 6H).

Diethyl 1-octyl-4-oxo-1, 4-dihydropyridine-3, 5-dicarboxylate (**1c**)
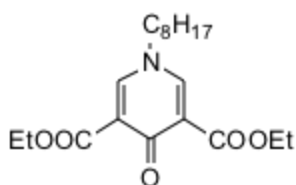
Compound **1b** (71.7 g, 300 mmol) was dissolved in DMF (750 mL) and then anhydrous potassium hydroxide (62.7 g, 450 mmol) and 1-bromo-octane (61.8 mL, 360 mmol) were added. The mixture was stirred at 80 °C for 12 hours. Then the solvent was removed by filtration in *vacuo* leaving the residual mixture. The mixture was first dissolved in CH_2Cl_2 (900 mL), then washed with water to remove residual DMF, and dehydrated by anhydrous sodium sulfate. The crude product was purified by column (MeOH/CH_2Cl_2 = 1/100) after CH_2Cl_2 was removed in *vacuo*. The pure product **1i** was a pale yellow oil. Yield: 60.9 g, 85%. ^{1}H NMR (300 MHz,

CDCl$_3$) δ 7.97 (s, 2H), 4.27 (q, J = 7.1 Hz, 4H), 3.82 (t, J = 7.3 Hz, 2H), 1.82-1.68 (m, 2H), 1.35-1.10 (m, 16H), 0.82 (t, J = 6.5 Hz, 3H). ^{13}C NMR (75 MHz, CDCl$_3$) δ 171.0, 164.6, 144.5, 122.8, 61.1, 57.8, 31.4, 30.4, 28.7, 28.7, 25.8, 22.3, 14.0, 13.8. HRMS-ESI: calculated for [M+Na]$^{+}$ (C$_{19}$H$_{29}$O$_5$N$_1$Na)：m/z 374.1938, found: m/z 374.1929.

5-(ethoxycarbonyl)-1-octyl-4-oxo-1,4-dihydropyridine-3-carboxylic acid (**1d**)

Compound **1c** (52.8 g, 150.0 mmol) was dissolved in ethanol (450 mL) and then 0.2 M potassium hydroxide (750 mL, 150.0 mmol) was added dropwise and slowly. The mixture was stirred at room temperature overnight. The ethanol was removed in *vacuo* after being neutralized by 1M HCl (210.0 mL). The mixture was filtered to obtain crude product that was dried in the oven later. The crude product **1d** was purified by column (MeOH/CH$_2$Cl$_2$ = 1/100) to obtain a white solid. Yield: 26.93 g, 51%. ^{1}H NMR (300 MHz, CDCl$_3$) δ15.25 (s, 1H), 8.54 (d, J = 2.4 Hz, 1H), 8.30 (d, J = 2.4 Hz, 1H), 4.38 (q, J = 7.1 Hz, 2H), 4.05 (t, J = 7.4 Hz, 2H), 1.95 – 1.75 (m, 2H), 1.38 (t, J = 7.1 Hz, 3H)., 1.34 – 1.19 (m, 10H), 0.85 (t, J = 6.8 Hz, 3H). ^{13}C NMR (75 MHz, CDCl$_3$) δ 176.2, 165.6, 163.0, 146.5, 145.6, 121.1, 119.4, 61.8, 59.0, 31.5, 30.6, 28.8, 28.8, 25.9, 22.4, 14.1, 13.9. HRMS-ESI: calculated for [M+Na]$^{+}$ (C$_{17}$H$_{25}$O$_5$N$_1$Na)：m/z 346.1625, found: m/z 346.1615.
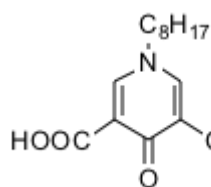
Ethyl5-(tert-butoxycarbonylamino)-1-octyl-4-oxo-1,4-dihydropyridine-3-carboxylate (**1e**)

Compound **1d** (19.38 g, 60.0 mmol) was dissolved in THF/DMF (150.0 mL/90.0 mL) in a round bottom flask with a balloon installing on top of
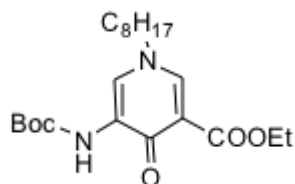
it. 4-methylmorpholin (7.20 mL, 72.0 mmol) and ethyl chloroformate (7.20 mL, 72 mmol) were injected to the cooled solution after it was cooled to 0 ºC in an ice bath. The mixture was stirred for 25 minutes. Then sodium azide (5.85 g, 90.0 mmol) dissolved in as little amount of water as possible was injected into it and stirred for 30 minutes. After THF was removed in *vacuo* at 28 ºC, the mixture was first dissolved in CH_2Cl_2 (540 mL), then washed with water to remove residual THF/DMF, and dehydrated by anhydrous sodium sulfate. After CH_2Cl_2 was removed in *vacuo*, the residue was dissolved in tolene (300 mL), with *t*-butanol (8.28 mL, 90 mmol). The solution was stirred at 90ºC for 30 hours. The crude product was obtained after removing toluene in *vacuo*, and then was purified by column (EA/*n*-hexane = 1/3) to give the pure white solid product **1e**. Yield: 9.32 g, 48%. ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.29 (s, 1H), 8.07 (d, *J* = 2.3 Hz, 1H), 7.94 (s, 1H), 4.36 (q, *J* = 7.1 Hz, 2H), 3.84 (t, *J* = 7.4 Hz, 2H), 1.87 – 1.77 (m, 2H), 1.50 (s, 9H), 1.38 (t, *J* = 7.1 Hz, 3H), 1.33 – 1.23 (m, 10H), 0.87 (t, *J* = 6.9 Hz, 3H). ^{13}C NMR (125 MHz, CDCl$_3$) δ 167.1, 165.2, 152.9, 141.5, 133.2, 123.0, 113.4, 81.0, 60.9, 58.8, 31.6, 30.6, 28.9, 28.9, 28.2, 26.1, 22.5, 14.3, 14.0. HRMS-ESI: calculated for $[M+Na]^+$ (C$_{21}$H$_{34}$O$_5$N$_2$Na)：*m/z* 417.2360, found: *m/z* 417.2353.

5-(tert-butoxycarbonylamino)-1-octyl-4-oxo-1,4-dihydropyridine-3-carboxylic acid (**1f**)
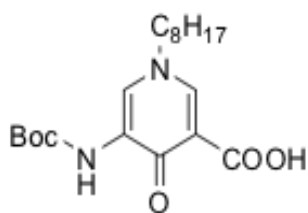
Compound **1e** (6.3 g, 16.00 mmol) was dissolved in dioxane/H$_2$O (80.0 mL/20.0 mL) with 1.0 M Sodium hydroxide (32.0 mL, 32.0 mmol) being added. The mixture was stirred at room temperature for 10 hours. Water (200 mL) was added to give precipitation,

and then it was neutralized by 40.0 mL 1M AcOH. The crude product was obtained after

filtration and then dissolved in 300 mL CH_2Cl_2, washed with water to remove dioxane and

dried over anhydrous Na_2SO_4 to give a pure brown solid product **1f**. Yield: 5.67 g, 90%. ^{1}H

NMR (500 MHz, $CDCl_3$) δ 14.94 (s, 1H), 8.56 (s, 1H), 8.32 (d, J = 2.2 Hz, 1H), 7.65 (s, 1H),

7.26 (s, 1H), 3.97 (t, J = 7.4 Hz, 2H), 2.00 – 1.80 (m, 2H), 1.56 (s, 9H), 1.39 – 1.20 (m, 10H),

0.88 (t, J = 6.9 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.7, 166.3, 152.4, 140.4, 131.8,

125.7, 112.7, 81.9, 59.7, 31.5, 30.7, 28.9, 28.8, 28.1, 26.1, 22.5, 13.9. HRMS-ESI: calculated

for $[M+Na]^+$ ($C_{19}H_{30}O_5N_2Na$): m/z 389.2074, found: m/z 389.2032.

Ethyl5-(5-(tert-butoxycarbonylamino)-1-octyl-4-oxo-1,4-dihydropyridine

-3-carboxamido)-1-octyl-4-oxo-1,4-dihydropyridine-3-carboxylate (**1h**)
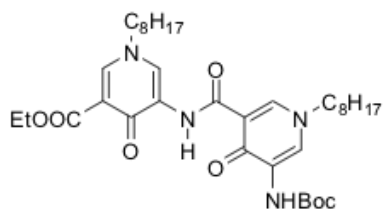
Compound **1e** (3.94 g, 10.00 mmol) was dissolved in

ethanol (140.0 mL) with concentrated sulphuric acid (10.00

mL) being added slowly. The solution was neutralized by

saturated aquous solution of sodium bicarbonate after being stirred at room temperature for

12 hours. Then the product was extracted with CH_2Cl_2 (4 × 120.0 mL). All the DCM

solution was collected and combined, and then dehydrated by anhydrous Na_2SO_4 to obtain

the pure product 1g, which would be directly brought into use in the next step. Compound 1f

(3.66 g, 10.00 mmol), compound 1g (10.00 mmol), HBTU (4.26 g, 11.0 mmol) and HOBt

(1.46 g, 11.0 mmol) were dissolved in DMF (60.0 mL), and then DIEA (3.62 mL, 20.0 mmol)

was added, which was stirred at room temperature for 24 hours. Then DMF was removed in

vacuo and the residue was dissolved in CH_2Cl_2 (400 mL), washed with water (3 × 300 mL)

to remove residual DMF and then the DCM solution dehydrated by Na_2SO_4 to obtain the

crude product, which was purified by column (MeOH/CH_2Cl_2 = 1/100) to obtain the pure

white product **1h**. Yield: 6.97 g, 88%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 12.90 (s, 1H), 8.85 (d,

J = 2.3 Hz, 1H), 8.33 (s, 1H), 8.25 (d, J = 2.2 Hz, 1H), 8.07 (d, J = 2.3 Hz, 1H), 8.03 (s, 1H),

4.33 (q, J = 7.1 Hz, 2H), 3.89 (t, J = 7.3 Hz, 2H), 3.83 (t, J = 7.3 Hz, 2H), 1.85 − 1.75 (m,

4H), 1.47 (d, J = 3.6 Hz, 11H), 1.35 (t, J = 7.1 Hz, 3H), 1.31 − 1.19 (m, 20H), 0.83 (t, J = 6.8

Hz, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.9, 167.6, 165.8, 163.2, 152.7, 142.2, 139.7,

133.6, 132.5, 126.0, 123.5, 114.8, 114.6, 80.9, 60.8, 59.0, 58.5, 38.4, 31.5, 31.5, 30.5, 30.4,

28.9, 28.84, 28.83, 28.1, 28.07, 26.1, 22.4 14.2, 13.8. HRMS-ESI: calculated for [M+Na]$^{+}$

($C_{35}H_{54}O_7N_4Na$)：*m/z* 665.3885, found: *m/z* 665.3869.

Ethyl5-(5-(5-(tert-butoxycarbonylamino)-1-octyl-4-oxo-1,4-dihydro

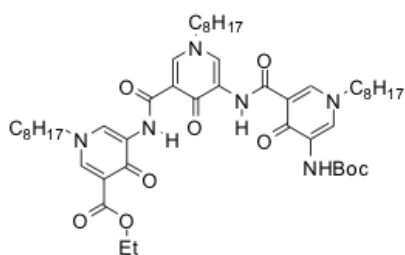pyridine-3-carboxamido)-1-octyl-4-oxo-1,4-dihydropyridine-3-carboxamido)-1-octyl-4-oxo-

1,4-dihydropyridine-3-carboxylate (**1i**)

Compound **1h** (4.5 g, 7.0 mmol) was dissolved in ethanol/CH_2Cl_2 (100.0 mL/20.0 mL) with concentrated sulphuric acid (8.00 mL) being added slowly. After the solution was stirred at room temperature for 12 hours, it

was neutralized by saturated aquous solution of $NaHCO_3$, and then the product was extracted

with CH_2Cl_2 (4 × 100.0 mL). All the DCM solution was collected and combined, and then

dried by anhydrous Na_2SO_4 to obtain the pure dimer amine **1h'**, which would be directly

used in the next step. Compound **1f** (3.66 g, 7.0 mmol), dimer amine **1h'** (7.0 mmol), HBTU

(2.94 g, 7.60 mmol) and HOBt (1.0 g, 7.60 mmol) were dissolved in DMF (50.0 mL), with

DIEA (2.54 mL, 14.00 mmol) being added. The solution was stirred at room temperature for

24 hours. The DMF was removed in *vacuo* before the residual mixture was dissolved in

CH_2Cl_2 (400 mL), washed with water (3 × 300 mL) to remove residual DMF, and dried by

Na_2SO_4 to obtain the crude product, which was purified by column (MeOH/CH_2Cl_2 = 1/50)

to yield the pure white product **1p**. Yield: 4.69 g, 75%. ^1H NMR (500 MHz, CDCl$_3$) δ 13.07

(s, 1H), 12.96 (s, 1H), 8.96 (d, J = 2.3 Hz, 1H), 8.90 (d, J = 2.3 Hz, 1H), 8.37 (s, 1H), 8.32 (d,

J = 2.3 Hz, 1H), 8.27 (d, J = 2.3 Hz, 1H), 8.10 (d, J = 2.4 Hz, 1H), 8.04 (s, 1H), 4.42 (q, J =

7.1 Hz, 2H), 3.92 (dd, J = 13.2, 6.8 Hz, 5H), 3.84 (t, J = 7.3 Hz, 2H), 1.90 – 1.81 (m, 6H),

1.54 (s, 9H), 1.40 (t, J = 7.1 Hz, 3H), 1.34 – 1.21 (m, 30H), 0.90 – 0.88 (m, 9H). ^{13}C NMR

(125 MHz, CDCl$_3$) δ 169.0, 167.9, 167.4, 166.0, 163.6, 163.5, 152.9, 142.3, 140.4, 139.7,

133.7, 132.8, 132.5, 126.8, 126.4, 123.5, 115.7, 114.8, 114.4, 81.0, 60.8, 59.2, 59.0, 58.5,

31.6, 31.6, 30.6, 30.6, 30.5, 28.9, 28.9, 28.2, 27.9, 26.1, 22.5, 14.5, 13.9. HRMS-ESI:

calculated for $[M+Na]^+$ (C$_{49}$H$_{74}$O$_9$N$_6$Na)：*m/z* 913.5409, found: *m/z* 913.5409.

Methyl 2,5-dihydroxybenzoate (**1l**)
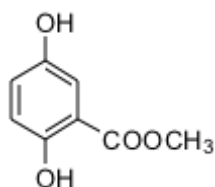
2,5-dihydroxybenzoic acid (**1k**)(9.24 g, 60.0 mmol) was dissolved in

MeOH (120.0 mL), with concentrated H_2SO_4 (10.00 mL) being added

slowly. After the mixed solution was heated under reflux for 48 hours,

the solvent was removed in *vacuo* and the residue was dissolved in

CH_2Cl_2 (200 mL), washed with water (2 × 100.0 mL) and died by anhydrous Na_2SO_4. The

pure light brown product **1l** was obtained after DCM was removed. Yield: 8.78 g, 95%. ^1H

NMR (300 MHz, CDCl$_3$) δ 10.33 (s, 1H), 7.28 (d, J = 3.1 Hz, 1H), 7.01 (d, J = 8.9 Hz, 1H), 6.88 (d, J = 8.9 Hz, 1H), 4.76 (s, 1H), 3.93 (s, 3H). ^{13}C NMR (75 MHz, CDCl$_3$) δ 170.8, 156.1, 148.5, 124., 119., 115.5, 112.8, 53.0. HRMS-ESI: calculated for $^{2+}$ (C$_8$H$_8$O$_4$): m/z 167.0344 found: m/z 167.0343.

Methyl 2-hydroxy-5-(octyloxy)benzoate (**1m**)

1l (4.02 g, 24.0 mmol) was dissolved in anhydrous acetone (90 mL), with anhydrous potassium carbonate (6.00 g, 43.5 mmol) and 1-bromooctane (4.14 mL, 24.00 mmol) being added. After the mixed solution was heated under reflux for 48 hours, it was filtered and the residual solvent was removed in *vacuo*. The filtered product was dissolved in CH$_2$Cl$_2$ (120.0 mL), washed with water (3 × 30.0 mL) to remove residual acetone and dried by anhydrous Na$_2$SO$_4$. The crude product, after DCM having been removed, was recrystallized from MeOH to give pure light yellow product **1m**. Yield: 2.89 g, 72%. ^{1}H NMR (300 MHz, CDCl$_3$) δ 10.35 (s, 1H), 7.29 (d, J = 3.1 Hz, 1H), 7.08 (d, J = 9.0 Hz, 1H), 6.90 (d, J = 9.0 Hz, 1H), 3.95 (s, 3H), 3.88 (m, 2H), 1.76 (m, 2H), 1.42 (m, 2H), 1.25 (m, 8H), 0.89 (m, 3H). ^{13}C NMR (75 MHz, CDCl$_3$) δ 171.0, 156.6, 152.2, 125.2, 119.1, 113.5, 112.5, 69.5, 52.9, 32.4, 30.0, 29.9, 29.9, 26.7, 23.3, 14.7. HRMS-EI: calculated for $^{2+}$ (C$_{16}$H$_{24}$O$_4$): m/z 280.1675 found: m/z 280.1677.
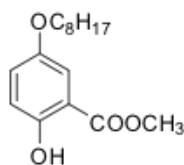
Methyl 2-hydroxy-3-nitro-5-(octyloxy)benzoate (**1n**)
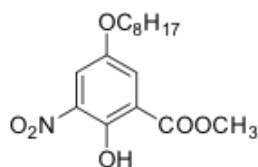
1m (1.4 g, 5.00 mmol) and Montmorillonite K10 (2.50 g) were added to a suspension of bismuth nitrate (1.95 g, 5.00 mmol) in

THF (50.0 mL). The mixture was stirred at room temperature for 24 hours and then was filtered to obtain a solid. Residual solvent was removed from the solid in *vacuo* and then the solid was dissolved in DCM. The DCM solution was washed with 1M HCl (1 × 250.0 mL), water (2 × 250.0 mL) and dried by anhydrous Na_2SO_4. The crude product was obtained after DCM was removed, which was recrystallized from MeOH to give pure yellow solid **1n**. Yield: 0.85 g, 61%. ^{1}H 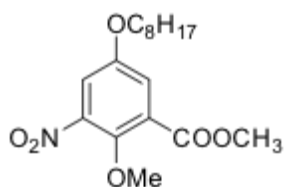NMR (300 MHz, CDCl$_3$) δ 11.44 (s, 1H), 7.72 (d, J = 3.3 Hz, 1H), 7.69 (d, J = 3.1 Hz, 1H), 4.00 (s, 3H), 3.96 (m, 2H), 1.79 (m, 2H), 1.31 (m, 2H), 1.29 (m, 8H), 0.89 (m, 3H). ^{13}C NMR (75 MHz, CDCl$_3$) δ 169.3, 150.9, 150.3, 138.1, 122.9, 117.6, 116.8, 69.9, 53.7, 32.4, 29.8, 29.8, 29.6, 26.5, 23.2, 14.6. HRMS-ESI: calculated for $^{2+}$ ($C_{16}H_{23}NO_6$): *m/z* 324.1447 found: *m/z* 324.1461.

Methyl 2-methoxy-3-nitro-5-(octyloxy)benzoate (**1o**)

Anhydrous K_2CO_3 (8.00 g, 50.0 mmol) and iodomethane (1.5 mL, 24.0 mmol) were added into a DMF (60.0 mL) solution of **1n** (6.5 g, 20.0 mmol). The mixture was heated at 60 ^{o}C for 4 hours. CH$_2$Cl$_2$ (200 mL) was then added and the reaction mixture was filtered. The solvent was removed in *vacuo* and the residue was dissolved in CH$_2$Cl$_2$ (200 mL), washed with water (3 × 100.0 mL) and dried over anhydrous Na_2SO_4. Removal of CH$_2$Cl$_2$ gave the crude product, which was recrystallized from MeOH to give pure product **1o** as a yellow solid. Yield: 4.88 g, 75%. ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.52 (d, J = 3.3 Hz, 1H), 7.40 (d, J = 3.1 Hz, 1H), 3.93 (m, 2H), 3.92 (s, 3H), 3.61 (s, 3H), 1.77 (m, 2H), 1.43 (m, 2H), 1.27 (m, 8H), 0.86 (m, 3H). ^{13}C NMR (75 MHz, CDCl$_3$) δ 166.0, 150.5, 149.9, 134.4, 121.3, 115.1, 114.6, 68.9,

54.8, 51.5, 31.8, 29.6, 29.37, 28.9, 25.9, 22.8, 14.0. HRMS-ESI: calculated for [2+] (C$_{17}$H$_{25}$NO$_6$): *m/z* 339.1682 found: *m/z* 339.1691.

2-methoxy-3-nitro-5-(octyloxy)benzoic acid (**1p**)
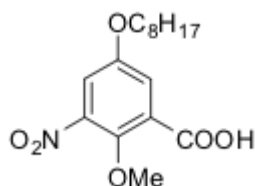
1M NaOH (34.0 mL, 34.0 mmol) was added into a solution of hot MeOH (60.0 mL) with 1o (5.60 g, 16.60 mmol). The mixture was refluxed for 1 hour and then quenched with water (200 mL). The aqueous layer was neutralized by addition of 1M HCl (50.0 mL). The precipitated crude product was collected by filtration, which was recrystallized from MeOH to give a yellow solid **1p**. Yield: 4.48 g, 80%. ^{1}H NMR (300 MHz, CDCl$_3$) δ 13.67 (s, 1H), 7.65 (d, *J* = 3.2 Hz, 1H), 7.53 (d, *J* = 3.1 Hz, 1H), 3.92 (m, 2H), 3.59 (s, 3H), 1.70 (m, 2H), 1.40 (m, 2H), 1.19 (m, 8H), 0.79 (m, 3H). ^{13}C NMR (125 MHz, CDCl$_3$) δ 165.4, 154.9, 146.4, 144.7, 125.8, 122.1, 116.0, 69.4, 64.7, 31.7, 29.2, 29.1, 28.8, 25.8, 22.6, 14.0. HRMS-EI: calculated for [2+] (C$_{16}$H$_{23}$NO$_6$): *m/z* 324.1447 found: *m/z* 324.1453.

1,4-dihydropyridine-3-carboxamido)-1-octyl-4-oxo-1,4-dihydropyridine-3-carboxamido)-1-octyl-4-oxo-1,4-dihydropyridine-3-carboxamido)-1-octyl-4-oxo-1,4-dihydropyridine-3-carboxylate (**1s**)
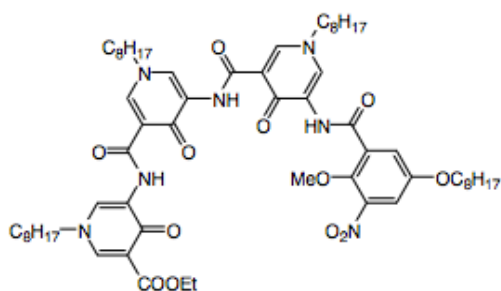
Concentrated H$_2$SO$_4$ (8.00 mL) was added into in an ethanol/CH$_2$Cl$_2$ (100.0 mL/20.0 mL) solution of compound **1r** (1.78 g, 2.00 mmol). The solution was stirred at room temperature for 12 hours. The product

was extracted with CH_2Cl_2 (3 × 100.0 mL) after being neutralized using saturated aqueous solution. Collection and combination of the DCM solution and dryness over sodium sulfate anhydrous would give the pure trimer amine **1j**, which was directly used in the next step. A solution of 1o (1.36 g, 4.00 mmol) in $SOCl_2$ (8.00 mL) was refluxed for 2 hours to obtain **1p**. After removing $SOCl_2$, the **1p** (4.00 mmol) and DIEA (1.36 mL, 8.00 mmol) in dry CH_2Cl_2 (120.0 mL) were combined with the residue **1j**, which was proceeding for 24 hours. After being washed with HCl solution and extracted by DCM, the organic layer (DCM) was dried over Na_2SO_4. The crude product was purified by column chromatography on silica gel (MeOH/CH_2Cl_2) to give pure white solid 1s. Yield: 2.16 g, 70%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 12.88 (s, 1H), 12.88 (s, 1H), 12.63 (s, 1H), 10.85 (s, 1H), 9.01 (d, J = 1.9 Hz, 1H), 8.99 (d, J = 1.9 Hz, 1H), 8.90 (d, J = 2.2 Hz, 1H), 8.36 (d, J = 1.8 Hz, 1H), 8.33 (d, J = 2.0 Hz, 1H), 8.12 (d, J = 2.2 Hz, 1H), 7.80 (d, J = 3.3 Hz, 1H), 7.47 (d, J = 3.2 Hz, 1H), 4.41 (q, J = 7.1 Hz, 2H), 4.18 (s, 3H), 4.06 – 3.98 (m, 4H), 3.94 (t, J = 7.2 Hz, 2H), 3.86 (t, J = 7.3 Hz, 2H), 1.95 – 1.75 (m, 10H), 1.46 – 1.39 (m, 5H), 1.38 – 1.16 (m, 47H), 0.90 – 0.84 (m, 13H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.85, 168.51, 167.58, 165.99, 163.45, 163.20, 162.12, 154.58, 145.51, 144.80, 142.45, 141.24, 140.61, 133.68, 132.66, 131.87, 128.91, 127.37, 126.48, 120.76, 115.83, 115.56, 114.92, 114.81, 69.17, 64.71, 61.12, 59.28, 59.08, 58.64, 50.76, 31.74, 31.62, 30.68, 30.63, 30.58, 29.23, 29.16, 28.97, 28.96, 26.17, 25.86, 22.60, 22.52, 14.38, 14.04, 13.99. HRMS-EI: calculated for [2]+ ($C_{60}H_{87}N_7O_{12}$): m/z 1097.6413 found: m/z 1097.6417.

Ethyl

5-(5-(5-(3-(2-fluoro-3-nitrobenzamido)-2-methoxy-5-(octyloxy)benzamido)-1-octyl-4-oxo-1 ,4-dihydropyridine-3-carboxamido)-1-octyl-4-oxo-1,4-dihydropyridine-3-carboxamido)-1-oc tyl-4-oxo-1,4-dihydropyridine-3-carboxylate (**1t**)
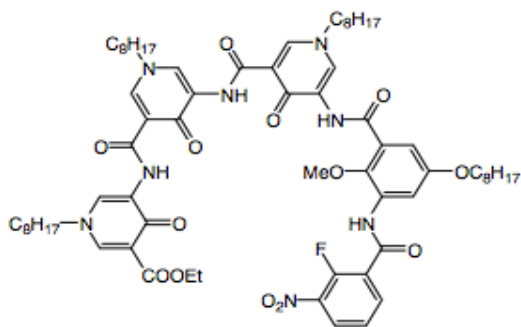

Acetate acid (2.00 mL) was added to an EtOH (40.0 mL) solution with 1s (2.2 g, 2.00 mmol) and iron (0.74 g, 10.00 mmol) in. The solution was refluxed for 2 hours. After cooling, the solvent was evaporated in *vacuo*. The residue was dissolved with DCM, which was then washed with water and Brine. The DCM solution was dried over Na_2SO_4. Removal of the DCM gave the amine product **1s'**, which was brought into use for the next step reaction. A solution of 1q (0.8 g, 4.00 mmol) in $SOCl_2$ (8.00 mL) was heated under reflux for 2 hours to obtain acid product **1r**. After removal of $SOCl_2$, the amine product **1s'**, DIEA (1.36 mL, 8.00 mmol) and residual **1r** was added into dry CH_2Cl_2 (40.0 mL), which was proceeding for 12 hours. After washed with 1 M HCl solution, the organic solution was dried over Na_2SO_4. The residue, after removing the solvent, was purified by flash column chromatography on silica gel (MeOH/CH_2Cl_2) to give the product **1t**. Yield: 2.1 g, 60%.^{13}C NMR (126 MHz, CDCl$_3$) δ 168.32, 168.16, 167.65, 163.66, 162.92, 162.75, 161.75, 155.28, 152.16, 143.20, 141.96, 140.81, 140.40, 135.98, 133.11, 132.66, 132.39, 132.09, 128.03, 127.74, 127.13, 126.33, 115.31, 115.06, 113.71, 113.70, 113.59, 111.23, 68.42, 63.07, 60.19, 59.32, 59.13, 58.70, 31.70, 31.51, 30.63, 30.55, 30.50, 29.27, 29.18, 29.14, 28.88, 26.08, 25.93, 22.53, 22.41, 14.13, 13.96, 13.88. HRMS-EI:

calculated for [2]+ (C67H91FN8O13): m/z 1234.6690 found: m/z 1234.6693.

Compound **1u**
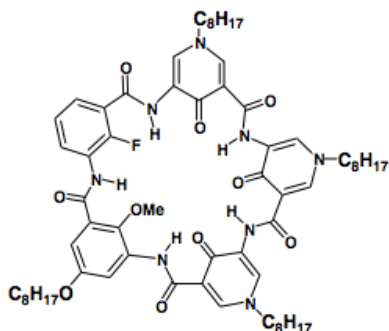
After the solution of **1t** (0.62 g, 0.50 mmol) and iron (0.14 g, 2.50 mmol) in EtOH (50.0 mL) and THF (50.0 mL) was added acetate acid (1.00 mL), it was refluxed for 5 hours. After cooling, the solvent was filtered and evaporated then the residue was dissolved in CH_2Cl_2 (50.0 mL) and washed with water (3 × 100 mL). The collected organic layer was dehydrated over Na_2SO_4. Evaporation of the solvent gave the amine product. Amine product was dissolved in dioxane (50.0 mL), and the 1.00 mL 1M of KOH was added and refluxed for 5 hours. After quenching with water (30.0 ml), the aqueous layer was neutralized by 1.00 mL 1M HCl. The mixture was extracted with CH_2Cl_2 (3 × 50.0 mL). The organic extracts were dehydrated over Na_2SO_4 and concentrated under reduced pressure. BOP (0.66 g, 1.50 mmol) and DIEA (0.26 mL, 2.00 mmol) were added into the solution of the organic extracts in dry CH_2Cl_2 (20.0 mL). The solution was washed with 1M HCl after being stirred at room temperature for 12 hours. After removal of the solvent, the residue was purified by flash column chromatography on silica gel using MeOH/CH_2Cl_2.

4. Conclusions and Future work

In summary, we have designed and synthesized a pentamer with tunable metal binding cavities. However, the synthetic routes of the pentamer were stepwise, which were long and time-consuming processes with low overall yields. To overcome this problem, our group had created a one-pot cyclization, which is a new and promising methodology for synthesizing pentamer.

Based on the results obtained, some potential areas for further investigation are highlighted below. One area of investigation is to study their metal binding affinities based on the fact that the pyridone group enhanced the cation-binding potential. Secondly, the selective recognition of amine and ammonium guests can be studied based on that the oxygen atom on pyridone group should be a good acceptor of hydrogen bound to the various types of amines and ammoniums.

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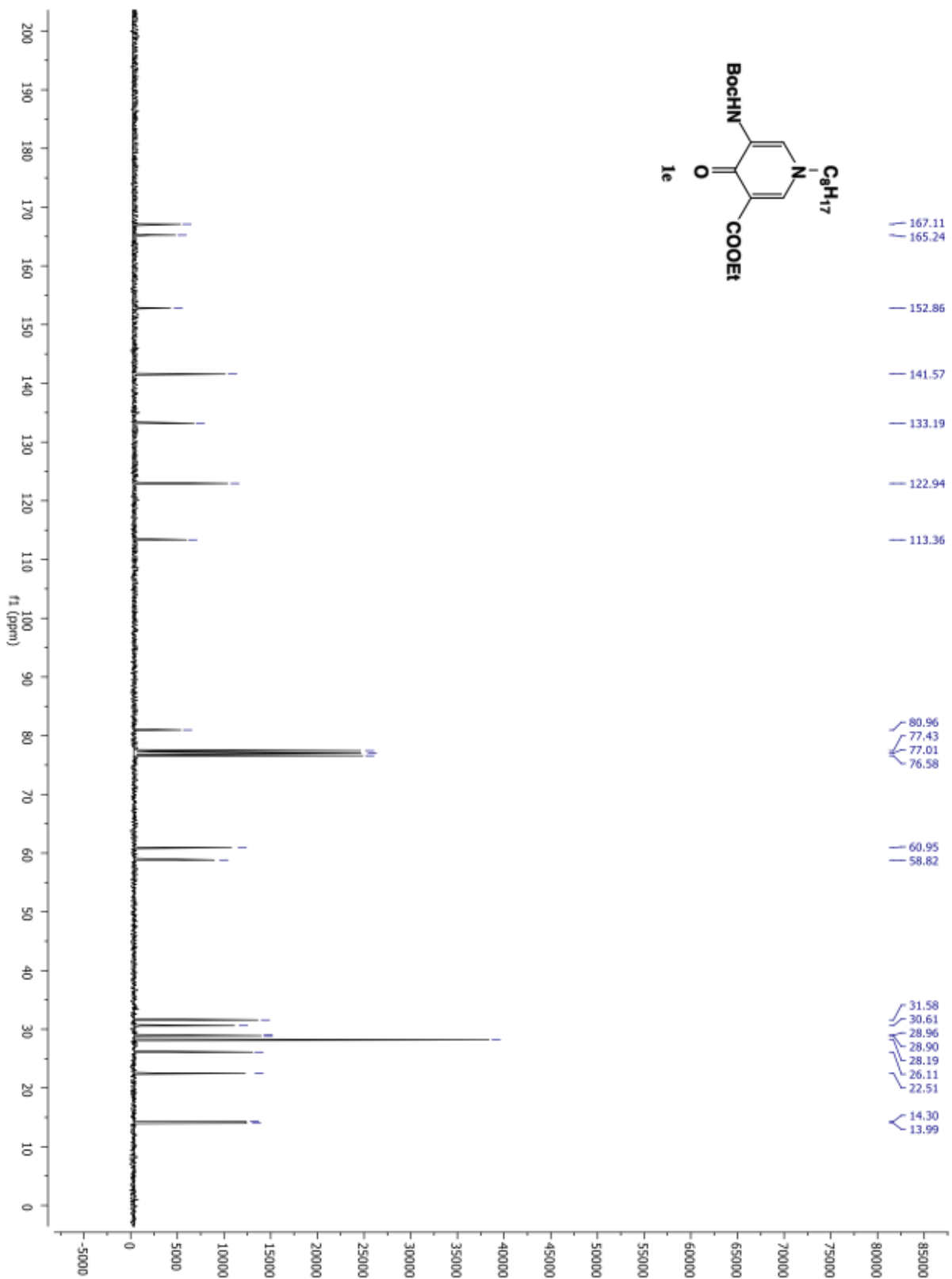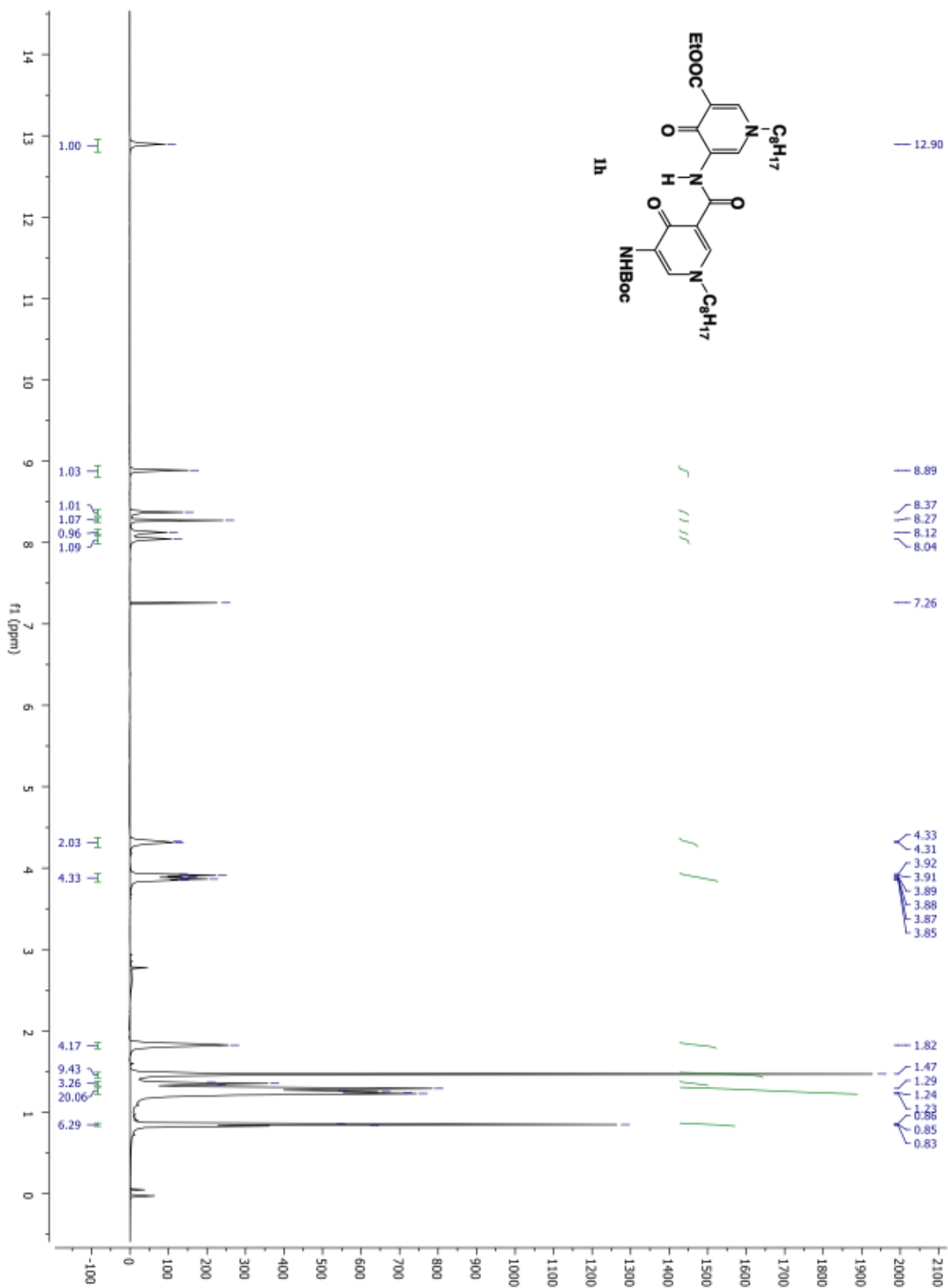1. Sessler, J. L.; Gale, P. A.; Cho, W.-S., *Anion receptor chemistry*. Royal Society of Chemistry: **2006**; Vol. 8.

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Appendices

^{1}H and ^{13}C Spectra for Major Compounds in the Thesis

1e

BocHN

O

COOEt

N

C$_8$H$_{17}$

8.30
8.07
7.94

7.26

4.40
4.38
4.36
4.33
3.87
3.85
3.82

1.85
1.83
1.81
1.50
1.39
1.31
0.90
0.88
0.85

1.00
1.06
1.01

2.14

2.20

2.11
9.28
2.88
10.45

3.32

f1(ppm)

174.21
172.30
167.99
165.90
163.32
163.17
152.89
142.53
139.85
134.85
133.66
132.60
126.37
123.84
114.66
81.13
77.33
77.08
76.82
61.09
59.27
58.74
31.66
31.64
30.72
30.63
29.01
28.98
28.96
28.21
26.17
22.56
14.32
14.03

1h

f1 (ppm)

12.88
12.63

10.85

9.01
9.01
9.00
8.99
8.90
8.90
8.37
8.36
8.33
8.32
8.12
8.12
7.80
7.79
7.47
7.47

4.43
4.42
4.41
4.39
4.18
4.04
4.03
4.02
4.01
4.00
3.96
3.94
3.93
3.88
3.86
3.85

1.89
1.88
1.86
1.85
1.81
1.79
1.78
1.45
1.44
1.42
1.41
1.32
1.28
1.27
1.26
1.24
0.89
0.88
0.86
0.86
0.85
0.84

0.95
0.96

0.97

0.96
1.01
0.97

1.03
1.09
0.98
1.01
0.95

1.99
3.00
4.46
2.28
2.14

9.50

5.35
47.01

12.94

190   180   170   160   150   140   130   120   110   100   90   80   70   60   50   40   30   20   10   0
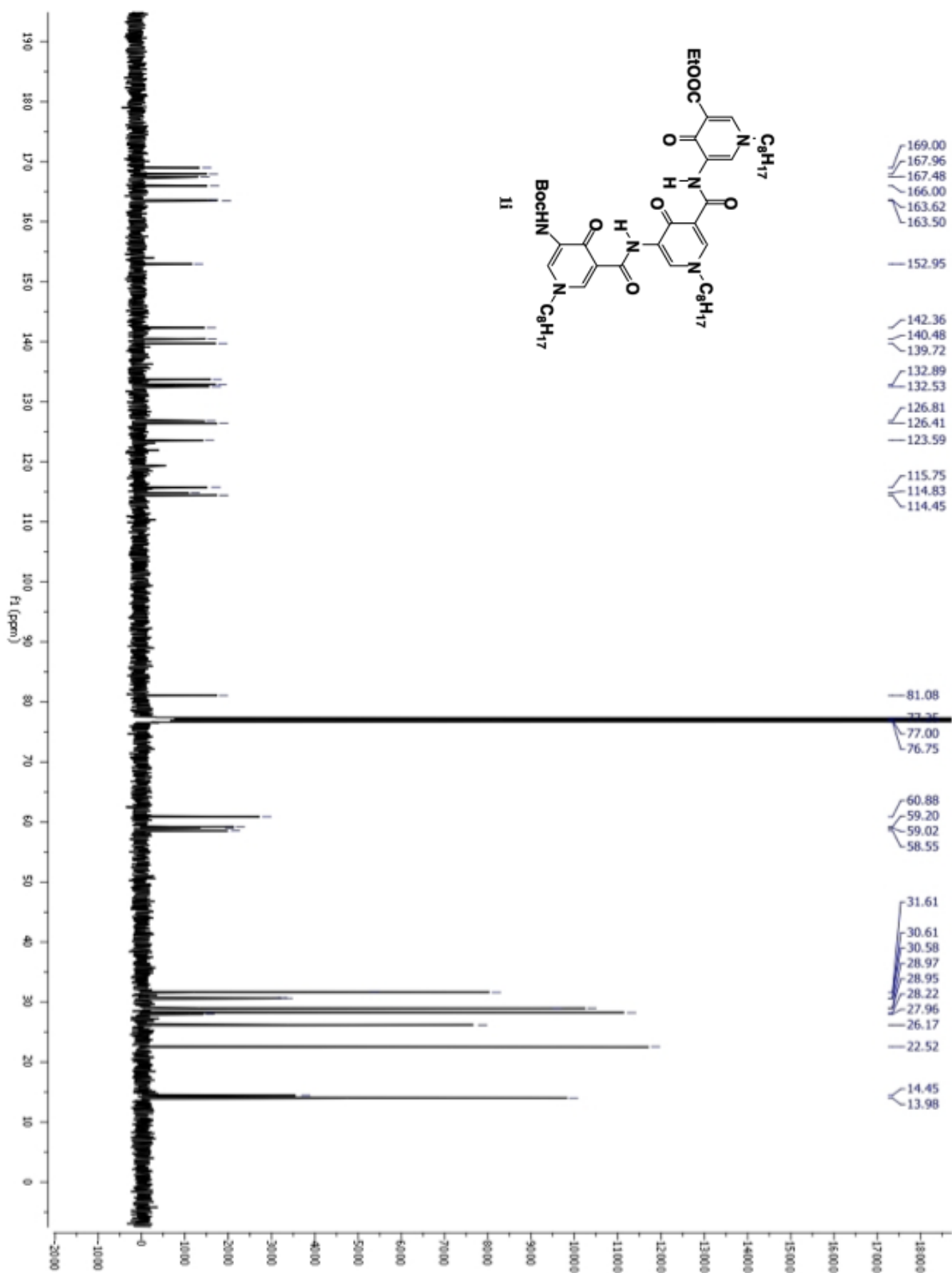
168.85
168.51
167.58
165.99
163.45
163.20
162.12

154.58

145.51
144.80
142.45
141.24
140.61
133.68
132.66
131.87
128.91
127.37
126.48

120.76
115.83
115.56
114.92
114.81

69.17
64.71
61.12
59.28
59.08
58.64

50.76

31.74
31.62
30.68
30.63
30.58
29.65
29.23
29.16
28.97
28.96
26.17
25.86
22.60
22.52

EtO₂C

O

C₈H₁₇

N

O

H
N

O₂N

OC₈H₁₇

1s

OMe

H
N

O

N
C₈H₁₇

O

O

H
N

N

O

C₈H₁₇