Electronic Supplementary Material (ESI) for New Journal of Chemistry.

Synthesis and antibacterial activity of some novel Piperazinophanes with intra annular ester functionality

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Supporting Information

Content

General Considerations S-1

General Procedure S-2

Synthesises of precyclophanes and Piperazinophanes along with spectral data.....S-3

NMR and Mass spectrum of precyclophanes and Piperazinophanes.....S-4

Antibacterial activity assay.....S-5

Molecular docking of piperazinophanes.....S-6

GENERAL CONSIDERATIONS:

All the melting points were determined by using Toshniwal melting point apparatus by open capillary tube method and were uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on Bruker 300 MHz spectrometer with 75 MHz for ^{13}C nucleus. The chemical shifts are reported in ppm (δ) with TMS as internal standard and coupling constant (*J*) are expressed in Hz. MALDI-TOF mass spectrum on Voyager-DE PRO mass spectrometer using α-cyano-4-hydroxycinnamic acid (α-CHCA) matrix and EI-MS spectra on JEOL DX-303 mass spectrometer. The FAB-MS spectra were recorded on a JEOL SX 102/DA-6000 mass spectrometer using a *p*-nitrobenzyl alcohol (NBA) matrix. Elemental analyses were performed on a Perkin-Elmer 240B elemental analyzer. Glass plates coated with silica gel-G (ACME) of about 0.25 mm thickness were used for TLC and visualized with iodine. Column chromatography was carried out with silica gel (ACME, 100-200 mesh). The organic extracts of crude products were dried over anhydrous magnesium sulphate or sodium sulphate.

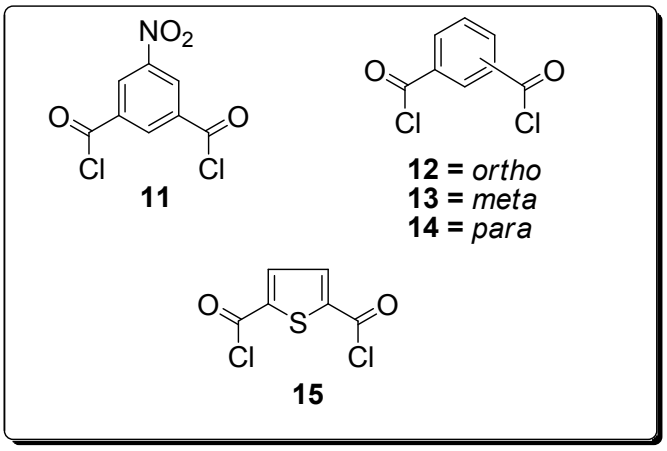
General procedure (A) for Steglich Esterification for the synthesis of precyclophane diynes (« two steps » acylation)

To a solution of propargyl alcohol (2.2equiv.) and DMAP (3 equiv.) in dry CH_2Cl_2 (100 ml) was added slowly at 0°C the appropriate acyl chloride (1equiv.).The solution was purged with nitrogen and stirred at room temperature for 24 h. The reaction was quenched with saturated aqueous sodium bicarbonate solution and the aqueous layer was extracted with CH_2Cl_2 (3x100ml).The combined organic layers were washed with brine (2x100 ml), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The residue obtained was purified by column chromatography with the indicated eluent to afford the desired precyclophane diynes.

General procedure for the synthesis of cyclophane by Mannich reaction (Procedure B)

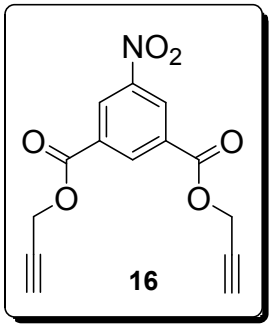
A mixture of precyclophane diyne (0.2 g, 3.98 mmol), piperazine (0.04 g, 3.98 mmol), and formaldehyde (0.02 g, 7.96 mmol) from 37-41% formalin solution and CuCl (0.04 g, 3.98 mmol) in dioxane (30ml) was refluxed under nitrogen atmosphere at 90^{o}C for 2h. After the completion of the reaction, the solvent was removed under reduced pressure and the residue was extracted with $CHCl_3$ (3x100ml), washed with water (2x 100 ml), brine (150 ml) and dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The residue obtained was purified by column chromatography with the indicated eluent to afford the desired cyclophane.

1. **Preparation of diacid chlorides:**



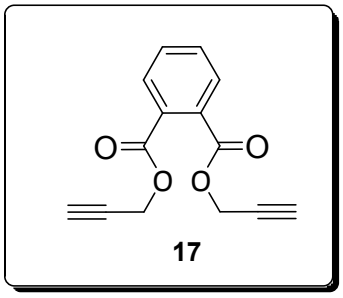
The diacid chlorides **11, 12, 13, 14, and 15** were prepared from corresponding dicarboxylic acid, as reported earlier from our laboratory.[1]

Diprop-2-ynyl 5-nitroisophthalate 16:



Following the general procedure A, the precyclophane nitro ester diyne **16** was obtained as brown crystalline solid from the dichloride **11** (3.0 g, 12 mmol) and propargyl alcohol (1.64 g, 26.72 mmol). Yield 76%; Mp. 146 ^{o}C: ^{1}H NMR: (300 MHz, $CDCl_3$): δ_H 2.59 (t, 2H, J = 2.1 Hz); 5.02 (d, 4H, J = 1.8 Hz); 9.03 (s, 1H); 9.08 (s, 2H). ^{13}C NMR: (75 MHz, $CDCl_3$): δ_C 53.5, 76.0, 76.7, 128.7, 131.9, 136.0, 148.6, 162.8 (ESI-MS) *m/z* 287 [M^+]. Elemental Anal. Calcd for $C_{14}H_9NO_6$: C, 58.54; H, 3.16, ; N, 4.88%. Found: C, 58.51; H, 3.16; N, 4.84%.

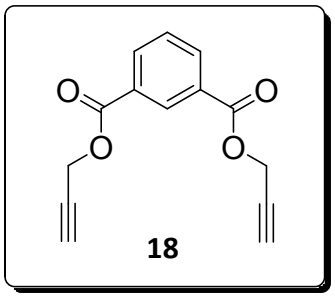
Diprop-2-ynyl phthalate 17:



17

Following the general procedure A, the precyclophane ester diyne **17** was obtained as dark brown liquid from the dichloride **12** (3.0 g, 14.8 mmol) and propargyl alcohol **21** (3.31 g, 32.51 mmol). Yield 80%; ^{1}H NMR: (300 MHz, $CDCl_3$): δ_H 2.48 (t, 2H, J = 2.1 Hz); 4.83 (d, 4H, J = 2.4 Hz); 7.45-7.48 (m, 2H); 7.64-7.67 (m, 2H); ^{13}C NMR: (75 MHz, $CDCl_3$): δ_C 53.2, 75.6, 76.8, 129.1, 131.1, 131.5, 166.4 (ESI-MS) *m/z* 242 [M^+]. Elemental Anal. Calcd for $C_{14}H_{10}O_4$: C, 69.42; H, 4.16 %. Found: C, 68.33; H, 4.15%.

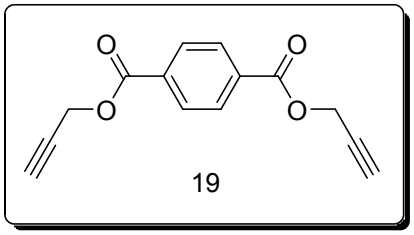
Diprop-2-ynyl isophthalate 18:



18

Following the general procedure A, the precyclophane ester diyne **18** was obtained as white solid from the dichloride **12** (3.0 g, 14.8 mmol) and propargyl alcohol **21** (3.31 g, 32.51 mmol). Yield 82%; Mp.104 ^{o}C : ^{1}H NMR: (300 MHz, $CDCl_3$): δ_H 2.55 (t, 2H, J = 2.1 Hz); 4.96 (d, 4H, J = 2.1 Hz); 7.57 (t, 1H, J = 7.8 Hz); 8.28 (d, 2H, J = 7.8 Hz); 8.74 (s, 1H). ^{13}C NMR: (75 MHz, $CDCl_3$): δ_C 52.8, 75.3, 76.6, 128.8, 130.0, 131.1, 134.4, 164.9. (ESI-MS) *m/z* 242 [M^+]. Elemental Anal. Calcd for $C_{14}H_{10}O_4$: C, 69.42; H, 4.16 %. Found: C, 69.40; H, 4.12%.

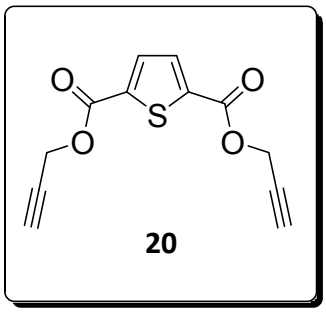
Diprop-2-ynyl terephthalate 19:



19

Following the general procedure A, the precyclophane ester diyne **19** was obtained as dirty white solid from the dichloride **14** (3.0 g, 14.8 mmol) and propargyl alcohol **21** (3.31 g, 32.51 mmol).Yield 78%; Mp. 106-112 ^{o}C: ^{1}H NMR: (300 MHz, $CDCl_3$): δ_H 2.55 (t, 2H, *J* = 2.1 Hz); 4.95 (d, 4H, *J* = 2.4 Hz); 8.13 (d, 4H, *J* = 10.5 Hz). ^{13}C NMR: (75 MHz, $CDCl_3$): δ_C 52.8, 75.4, 76.6, 129.8, 133.5, 164.8. (ESI-MS) *m/z* 242 [M^+]. Elemental Anal. Calcd for $C_{14}H_{10}O_4$: C, 69.42; H, 4.16 %. Found: C, 69.41; H, 4.10%.

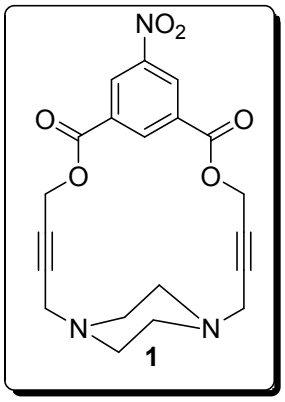
Diprop-2-ynyl thiophene -2,5-dicarboxylate 20:



20

Following the general procedure A, the precyclophane ester diyne **20** was obtained as white solid from the dichloride **12** (3.0 g, 14.4 mmol) and propargyl alcohol **21** (3.31 g, 31.57 mmol). Yield 70 %; Mp.72 ^{o}C : ^{1}H NMR: (300 MHz, $CDCl_3$): δ_H 2.54 (t, 2H, *J* = 2.1 Hz); 4.92 (d, 4H, *J* = 1.5 Hz); 7.79 (s, 2H). ^{13}C NMR: (75 MHz, $CDCl_3$): δ_C 53.1, 75.6, 76.9, 133.7, 138.4, 160.6 (ESI-MS) *m/z* 248 [M^+]. Elemental Anal. Calcd for $C_{12}H_8O_4S$: C, 58.06; H, 3.25; S, 12.92%. Found: C, 58.01; H, 3.19; S, 12.89 %.

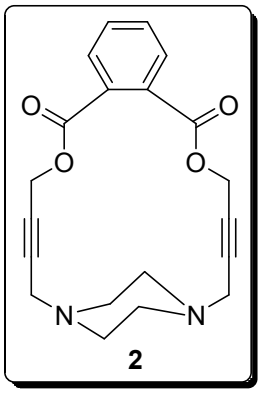
Cyclophane ester 1:



1

Following the general procedure B, the cyclophane ester **1** was obtained as brown solid from the precyclophane ester diyne **16** (0.5 g, 1.74 mmol), piperazine (0.14 g, 1.74 mmol), formaldehyde (0.1046 g, 3.48 mmol) from 37-41% formalin solution and CuCl (0.17 g, 1.74 mmol). Yield 32%; Mp.186 ^{o}C: ^{1}H NMR: (300 MHz, $CDCl_3$): δ_H 2.78 (s, 8H); 3.37(s, 4H); 4.99 (s, 4H); 8.92 (s, 1H); 9.08 (s, 2H). ^{13}C NMR: (75 MHz, $CDCl_3$): δ_C 46.6, 51.4, 55.2, 78.2, 84.7, 128.9, 132.3, 134.9, 148.6, 163.4. (ESI-MS) *m/z* 397 [M^+]. Elemental Anal. Calcd for $C_{20}H_{19}N_3O_6$: C, 60.45; H, 4.82; N, 10.57%. Found: C, 60.39; H, 4.80; N, 10.27 %.

Cyclophane ester 2:

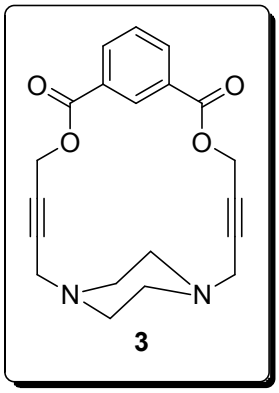


2

Following the general procedure B, the cyclophane ester **2** was obtained as white solid from the precyclophane ester diyne **17** (0.5 g, 2.06 mmol), piperazine (0.17 g, 2.06 mmol), formaldehyde (0.12 g, 3.99 mmol) from 37-41% formalin solution and CuCl (0.20 g, 2.06 mmol). Yield 26%; Mp.171 ^{o}C: ^{1}H NMR: (300 MHz, $CDCl_3$): δ_H 2.72 (s, 8H); 3.71 (s, 4H); 4.72 (s, 4H); 7.58 (s, 2H); 7.75 (s, 2H). ^{13}C NMR: (75 MHz, $CDCl_3$): δ_C 46.9, 51.6, 53.6, 79.2, 82.1, 129.1, 131.4, 166.7 (ESI-MS) *m/z* 352 [M^+]. Elemental

Anal. Calcd for $C_{20}H_{20}N_2O_4$: C, 68.17; H, 5.72; N, 7.95%. Found: C, 68.08; H, 5.70; N, 7.95%.

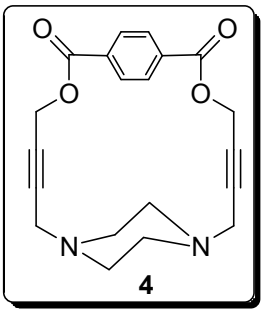
Cyclophane ester 3:



3

Following the general procedure B, the cyclophane ester **3** was obtained as white solid from the precyclophane ester diyne **18** (0.5 g, 2.06 mmol), piperazine (0.17 g, 2.06 mmol), formaldehyde (0.12 g, 3.99 mmol) from 37-41% formalin solution and CuCl (0.20 g, 2.06 mmol). Yield 33%; Mp.204 ^{o}C: ^{1}H NMR: (300 MHz, $CDCl_3$): δ_H 2.99 (s, 8H); 3.46 (s, 4H); 4.94 (s, 4H); 7.60 (t, 1H, J = 7.8 Hz); 8.29 (d, 2H, J = 7.8 Hz); 8.64 (s, 1H). ^{13}C NMR: (75 MHz, $CDCl_3$): δ_C 46.3, 50.6, 54.1, 77.2, 84.0, 128.9, 130.0, 130.2, 134.7, 165.1 (ESI-MS) *m/z* 352 [M^+]. Elemental Anal. Calcd for $C_{20}H_{20}N_2O_4$: C, 68.17; H, 5.72; N, 7.95%. Found: C, 68.08; H, 5.70; N, 7.95%.

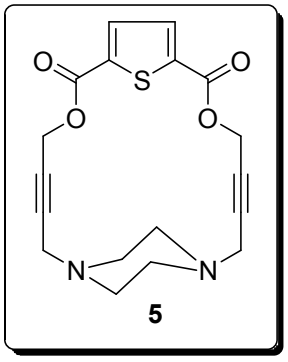
Cyclophane ester 4:



4

Following the general procedure B, the cyclophane ester **4** was obtained as white solid from the precyclophane ester diyne **19** (0.5 g, 2.06 mmol), piperazine (0.17 g, 2.06 mmol), formaldehyde (0.12 g, 3.99 mmol) from 37-41% formalin solution and CuCl (0.20 g, 2.06 mmol). Yield 35%; Mp.136 ^{o}C: ^{1}H NMR: (300 MHz, $CDCl_3$): δ_H 2.65 (s, 8H); 3.33 (s, 4H); 4.90 (s, 4H); 8.07 (s, 4H). ^{13}C NMR: (75 MHz, $CDCl_3$): δ_C 46.9, 51.5, 53.2, 77.2, 84.0, 129.8, 133.7, 165.0. (ESI-MS) *m/z* 352 [M^+]. Elemental Anal. Calcd for $C_{20}H_{20}N_2O_4$: C, 68.17; H, 5.72; N, 7.95%. Found: C, 68.08; H, 5.70; N, 7.95%.

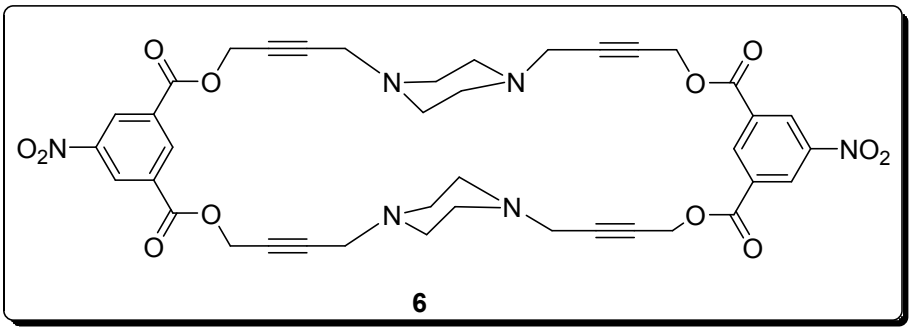
Cyclophane ester 5:



5

Following the general procedure B, the cyclophane ester **5** was obtained as pale yellow powder from the precyclophane diyne **20** (0.5 g, 0.85 mmol), piperazine (0.07 g, 0.85 mmol), formaldehyde (0.05 g, 1.70 mmol) from 37-41% formalin solution and CuCl (0.08 g, 0.85 mmol). Yield 30%; Mp. 242 ^{o}C : ^{1}H NMR: (300 MHz, $CDCl_3$): δ_H 2.81 (s, 8H); 3.37 (s, 4H); 4.87 (s, 4H); 7.78 (s, 2H). ^{13}C NMR: (75 MHz, $CDCl_3$): δ_C 46.7, 51.7, 54.4, 77.2, 81.0, 133.2, 138.2, 160.2. (ESI-MS) *m/z* 358 [M^+]. Elemental Anal. Calcd for $C_{32}H_{30}N_4O_3S_2$: C, 65.95; H, 5.19; N, 9.61%. Found: C, 66.01; H, 5.26; N, 9.67%.

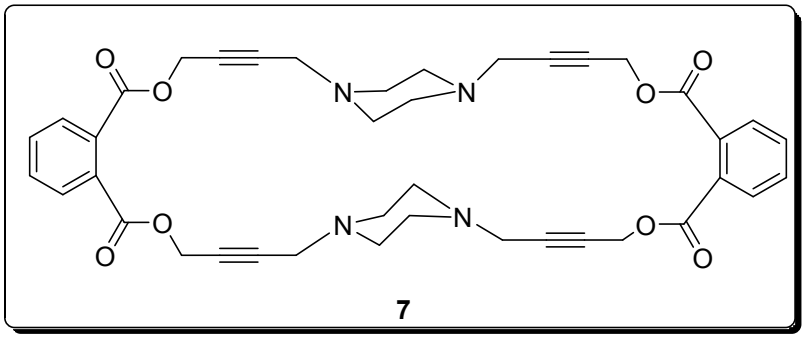
Cyclophane ester 6:



6

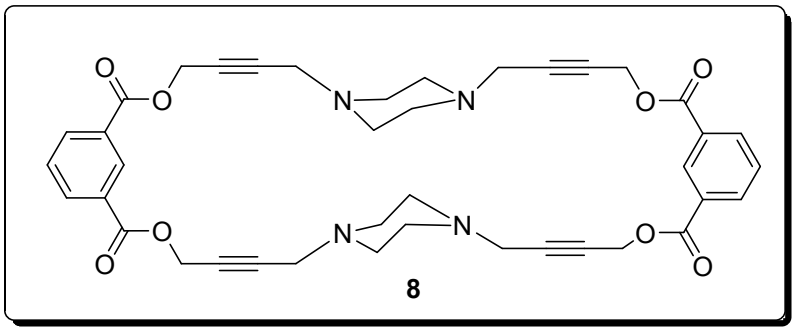
Following the general procedure B, the cyclophane ester **6** was obtained as brown solid from the precyclophane ester diyne **16** (0.5 g, 1.74 mmol), piperazine (0.14 g, 1.74 mmol), formaldehyde (0.1046 g, 3.48 mmol) from 37-41% formalin solution and CuCl (0.17 g, 1.74 mmol). Yield 23%; Mp.156 ^{o}C: ^{1}H NMR: (300 MHz, $CDCl_3$): δ_H 2.80 (s, 16H); 3.45 (s, 8H); 5.04 (s, 8H); 8.99 (s, 2H); 9.06 (s, 4H). ^{13}C NMR: (75 MHz, $CDCl_3$): δ_C 46.9, 51.6, 54.0, 78.7, 82.7, 128.6, 132.1, 136.1, 148.5, 163.0. (ESI-MS) *m/z* 794 [M^+]. Elemental Anal. Calcd for $C_{40}H_{38}N_6O_{12}$: C, 60.45; H, 4.82; N, 10.57 %. Found: C, 60.39; H, 4.81; N, 10.47%.

Cyclophane ester 7:



Following the general procedure B, the cyclophane ester **7** was obtained as brown solid from the precyclophane ester diyne **17** (0.5 g, 2.06 mmol), piperazine (0.17 g, 2.06 mmol), formaldehyde (0.12 g, 3.99 mmol) from 37-41% formalin solution and CuCl (0.20 g, 2.06 mmol). Yield 28%; Mp.204 ^{o}C: ^{1}H NMR: (300 MHz, $CDCl_3$): δ_H 2.80 (s, 16H); 3.46 (s, 8H); 4.95 (s, 8H); 7.58 (s, 4H); 7.76 (s, 4H).^{13}C NMR: (75 MHz, $CDCl_3$): δ_C 46.8, 51.3, 53.6, 79.6, 81.7, 129.9, 131.3, 166.6. (ESI-MS) *m/z* 704 [M^+]. Elemental Anal. Calcd for $C_{40}H_{40}N_4O_8$: C, 68.17; H, 5.72; N, 7.95%. Found: C, 68.11; H, 5.70; N, 7.94%.

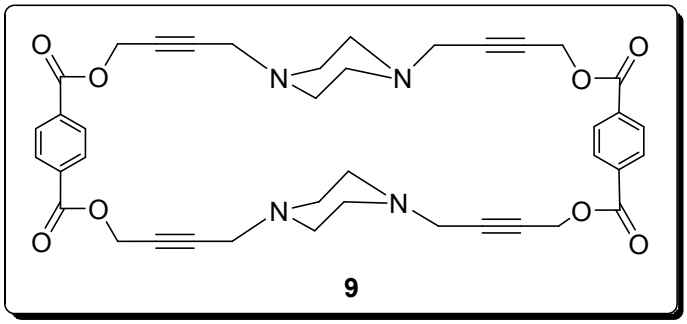
Cyclophane ester 8:



8

Following the general procedure B, the cyclophane ester **8** was obtained as white solid from the precyclophane ester diyne **18** (0.5 g, 2.06 mmol), piperazine (0.17 g, 2.06 mmol), formaldehyde (0.12 g, 3.99 mmol) from 37-41% formalin solution and CuCl (0.20 g, 2.06 mmol). Yield 30 %; Mp.172 ^{o}C: ^{1}H NMR: (300 MHz, $CDCl_3$): δ_H 2.84 (s, 16H); 3.39 (s, 8H); 4.95 (s, 8H J= 13.5 Hz); 7.59 (t, 2H, *J* = 7.5 Hz); 8.28 (d, 4H, *J* = 7.2 Hz); 8.66 (s, 2H). ^{13}C NMR: (75 MHz, $CDCl_3$): δ_C 46.6, 51.2, 54.2, 79.2, 84.0, 128.8, 130.1, 130.2, 134.7, 165.3 (ESI-MS) *m/z* 704 [M^+]. Elemental Anal. Calcd for $C_{40}H_{40}N_4O_8$: C, 68.17; H, 5.72; N, 7.95%. Found: C, 68.08; H, 5.70; N, 7.95%.

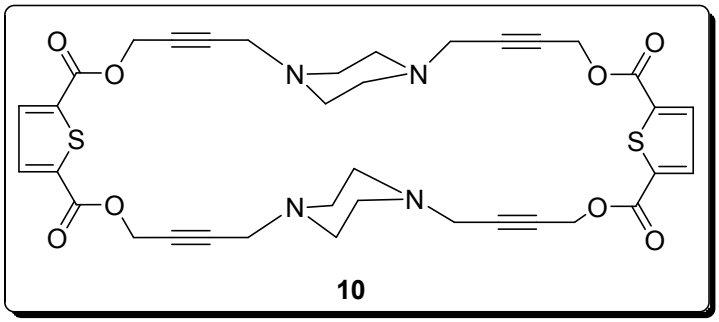
Cyclophane ester 9:



9

Following the general procedure B, the cyclophane ester **9** was obtained as white solid from the precyclophane ester diyne **19** (0.5 g, 2.06 mmol), piperazine (0.17 g, 2.06 mmol), formaldehyde (0.12 g, 3.99 mmol) from 37-41% formalin solution and CuCl (0.20 g, 2.06 mmol). Yield 32%; Mp.92 ^{o}C: ^{1}H NMR: (300 MHz, $CDCl_3$): δ_H 2.70 (s, 16H); 3.40 (s, 8H); 4.97 (s, 8H); 8.13 (s, 8H). ^{13}C NMR: (75 MHz, $CDCl_3$): δ_C 47.0, 51.6, 53.3, 79.2, 82.0, 129.8, 133.5, 165.0. (ESI-MS) *m/z* 704 [M^+]. Elemental Anal. Calcd for $C_{40}H_{40}N_4O_8$: C, 68.17; H, 5.72; N, 7.95%. Found: C, 68.08; H, 5.70; N, 7.95%.

Cyclophane ester 10:



10

Following the general procedure B, the cyclophane ester **10** was obtained as pale yellow powder from the precyclophane thiophenyl diyne **20** (0.5 g, 0.85 mmol), piperazine (0.07 g, 0.85 mmol), formaldehyde (0.05 g, 1.70 mmol) from 37-41% formalin solution and CuCl (0.08 g, 0.85 mmol). Yield 30%; Mp. 298 ^{o}C: ^{1}H NMR: (300 MHz, $CDCl_3$): δ_H 2.92 (s, 16H); 3.42 (s, 8H); 4.88 (s, 8H); 7.79 (s, 4H). ^{13}C NMR: (75 MHz, $CDCl_3$): δ_C 46.6, 51.3, 53.6, 79.6, 80.0, 133.3, 138.2, 160.0. (ESI-MS) *m/z* 716 [M^+]. Elemental Anal. Calcd for $C_{32}H_{30}N_4O_3S_2$: C, 65.95; H, 5.19; N, 9.61%. Found: C, 66.01; H, 5.26; N, 9.67%.

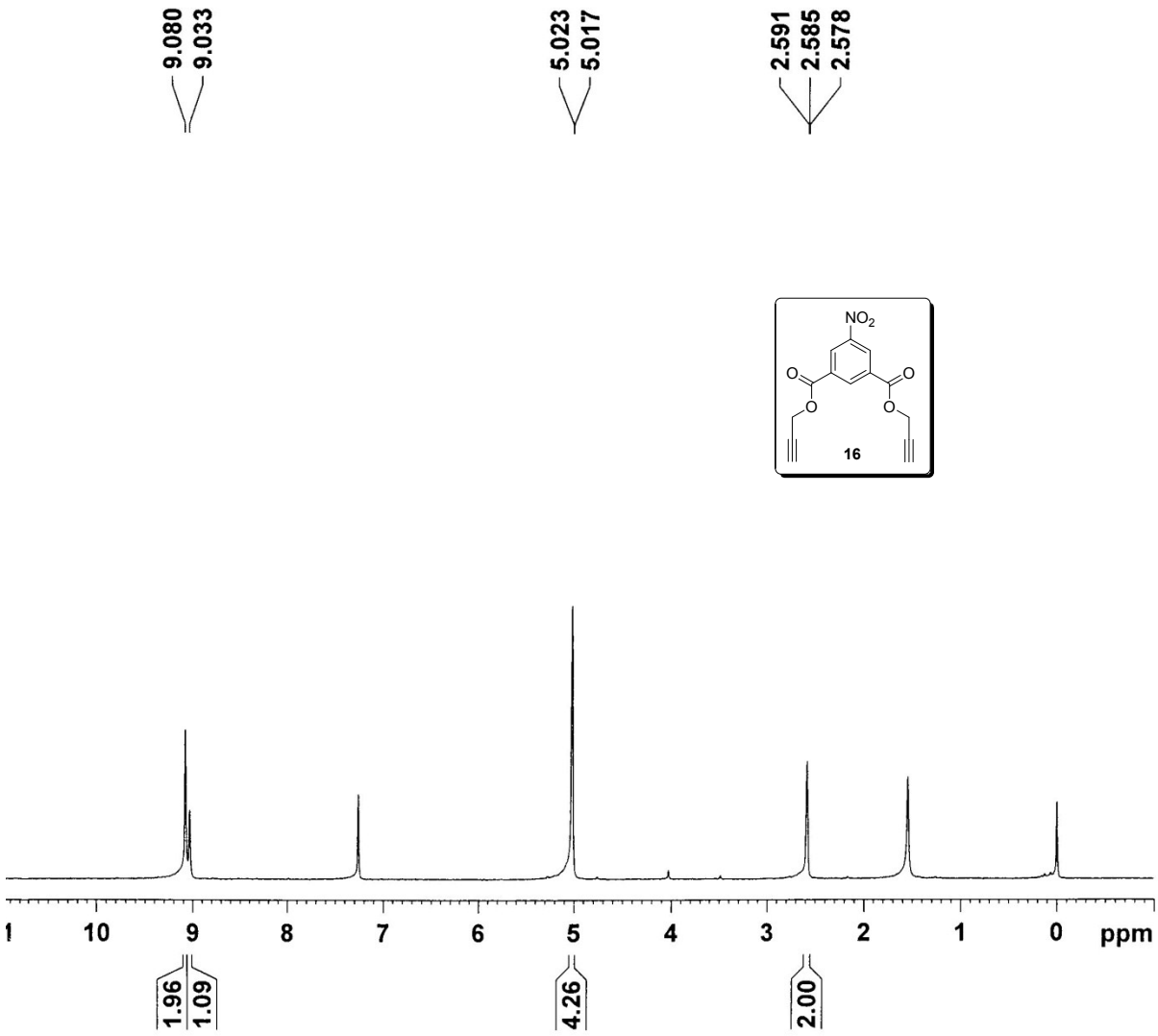


Figure 1: ^{1}H NMR spectrum (300MHz, $CDCl_3$) of diprop-2-ynyl 5-nitroisophthalate 16

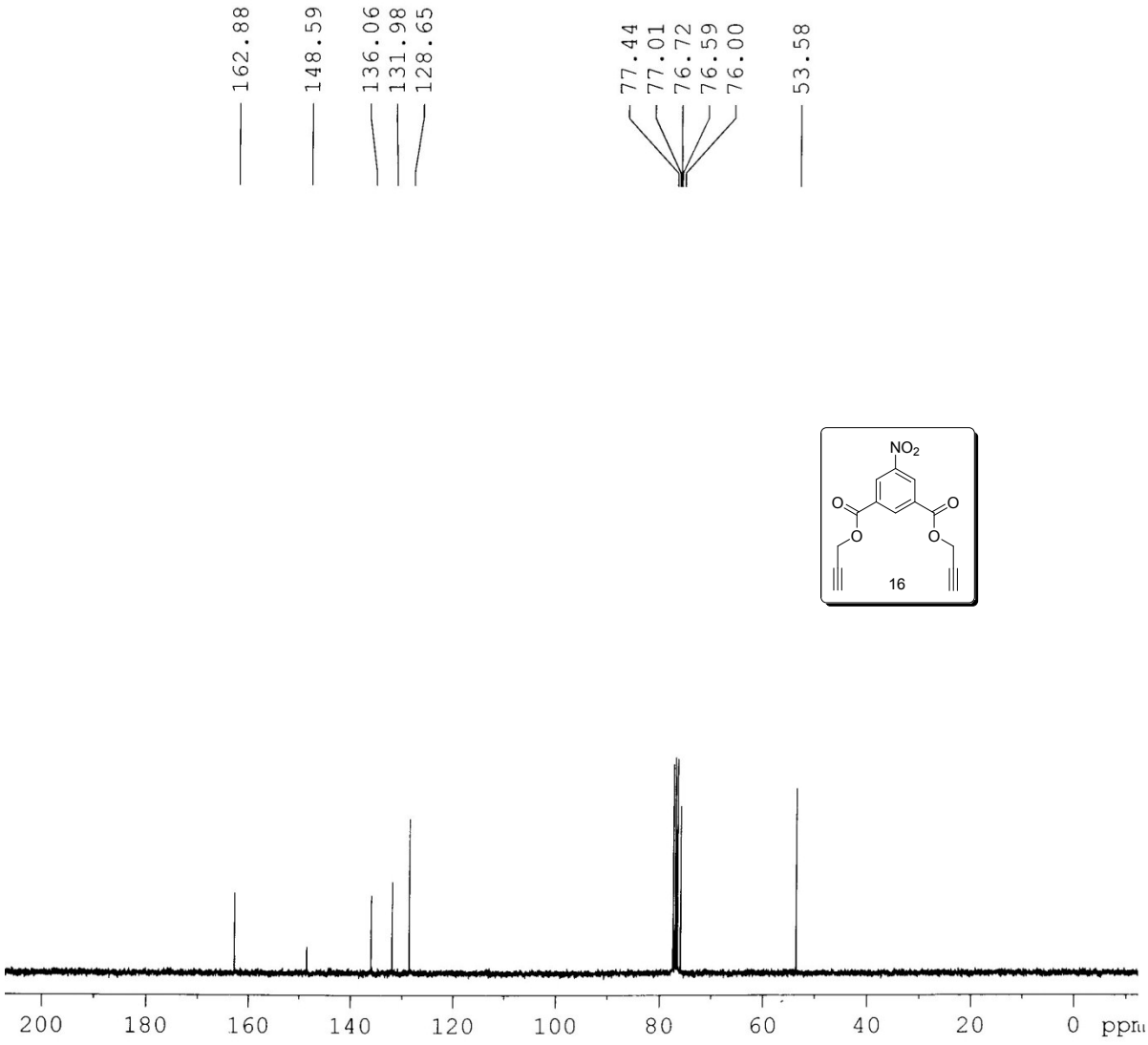
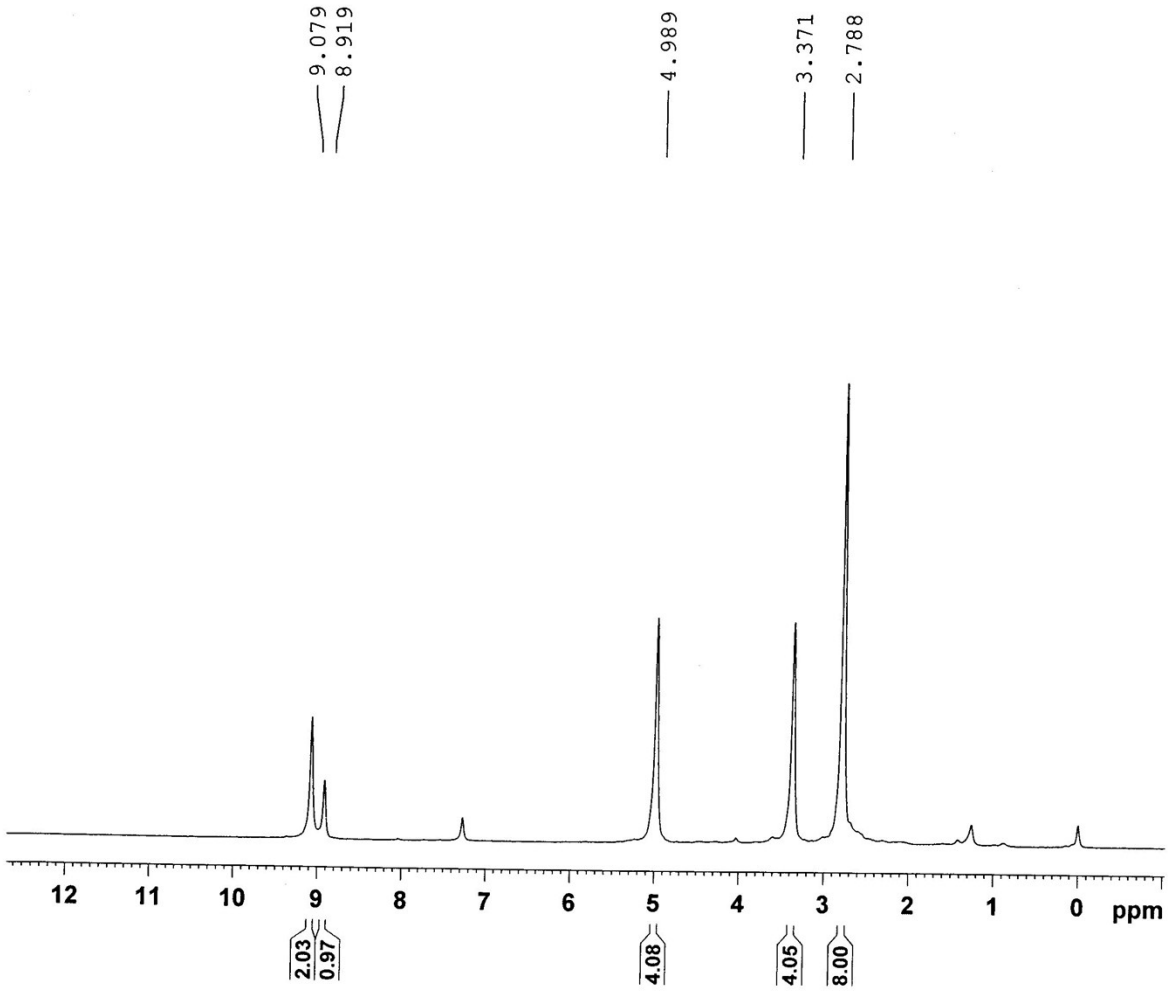


Figure 2: ^{13}C NMR spectrum (75MHz, $CDCl_3$) of diprop-2-ynyl 5-nitroisophthalate 16



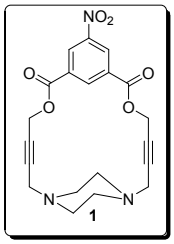


Figure 3: ^{1}H NMR spectrum (300MHz, $CDCl_3$) of Cyclophane ester 1

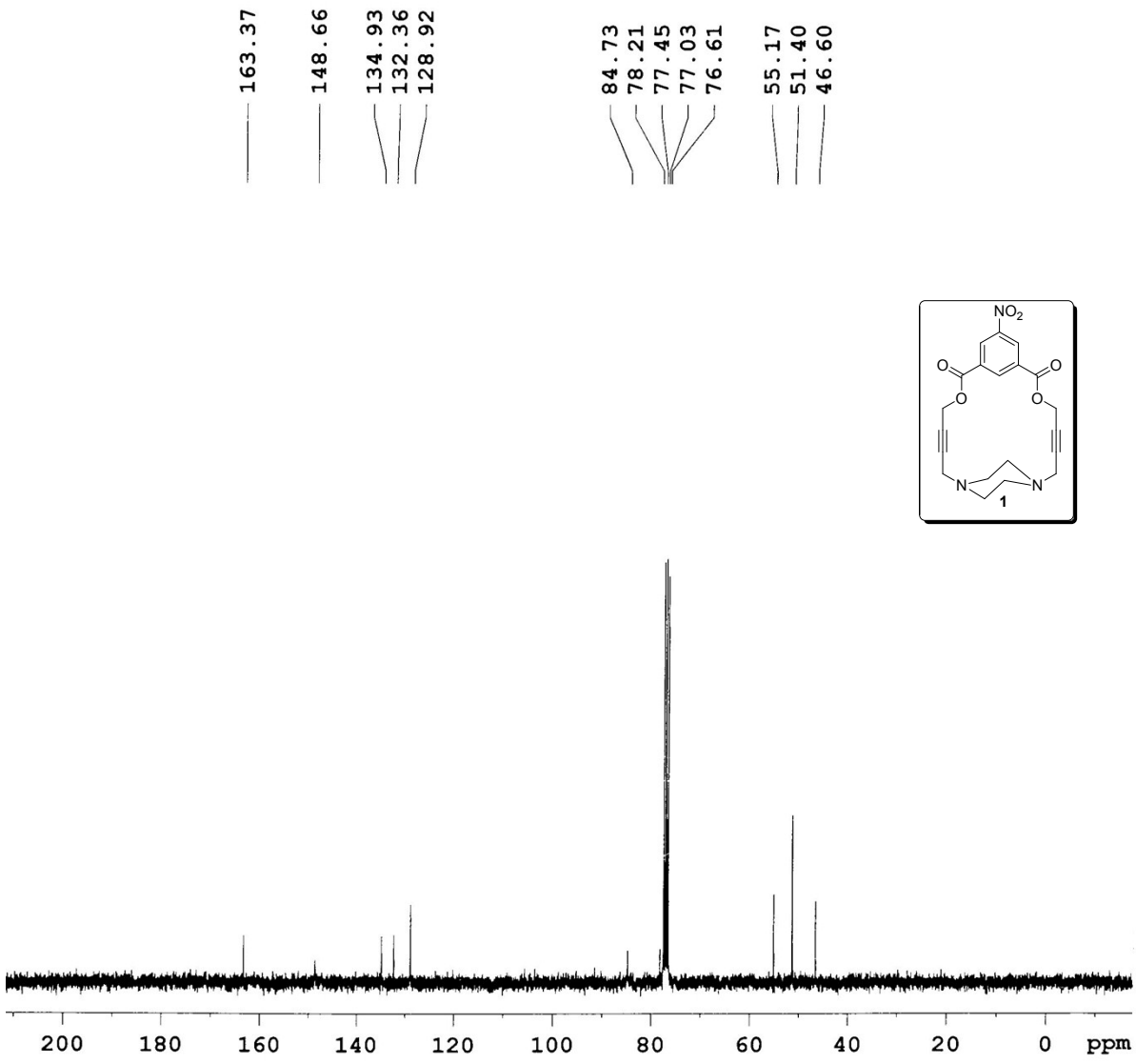


Figure 4: ^{13}C NMR spectrum (75MHz, $CDCl_3$) of Cyclophane ester 1

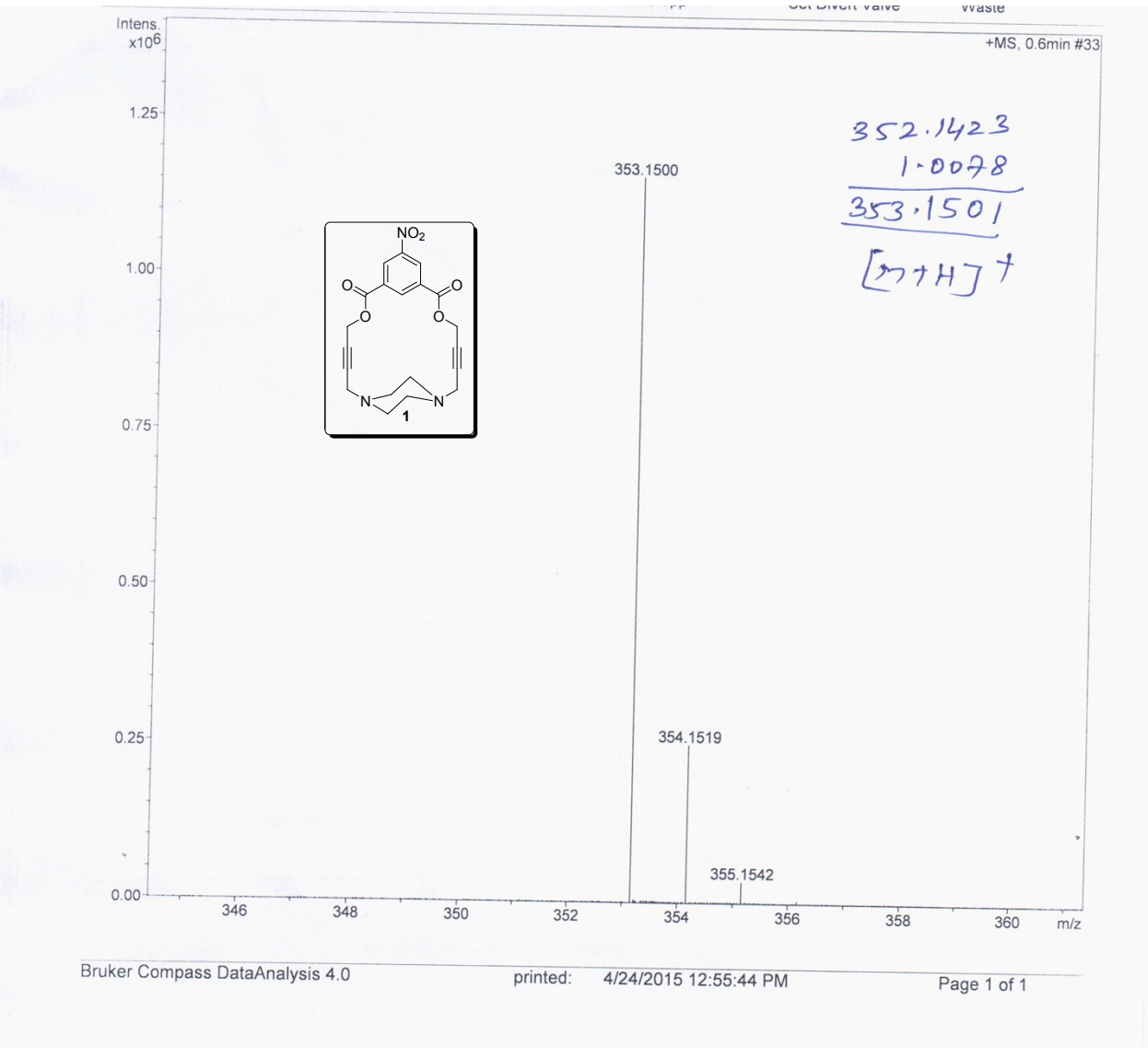


Figure 5: HRMS mass spectrum of Cyclophane ester 1

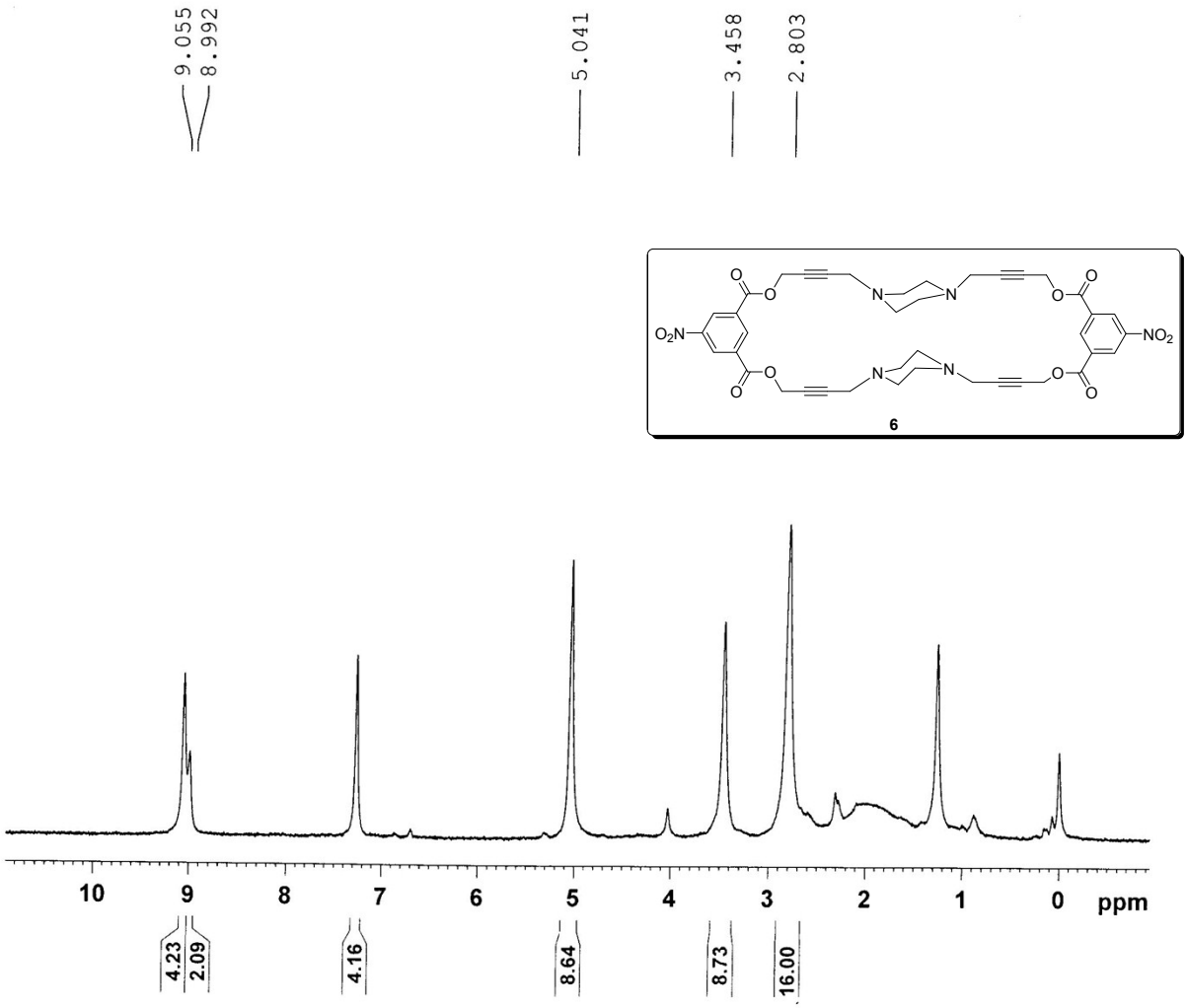


Figure 6: ^{1}H NMR spectrum (300MHz, $CDCl_3$) of Cyclophane ester 6

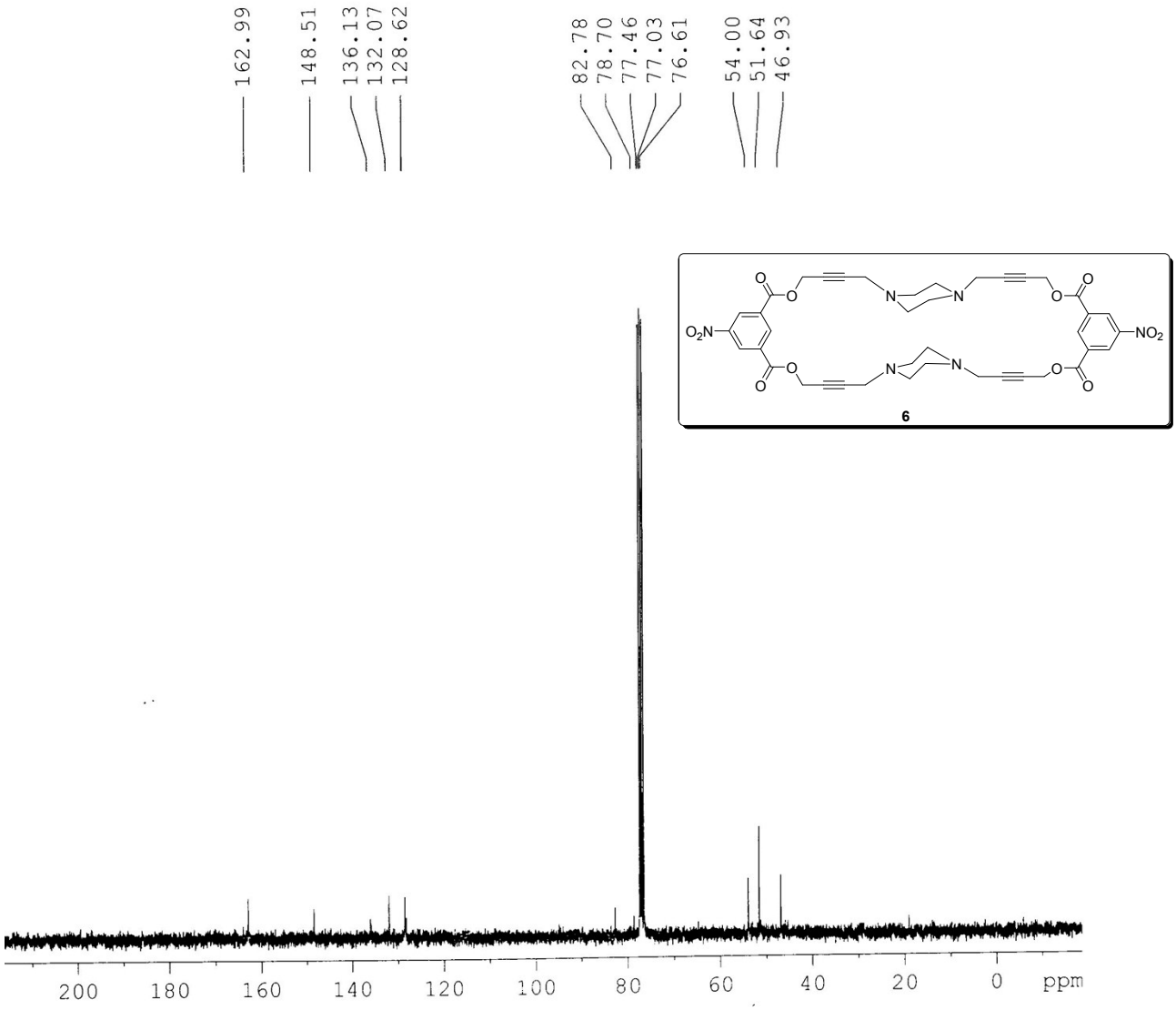


Figure 7: ^{13}C NMR spectrum (75MHz, $CDCl_3$) of Cyclophane ester 6

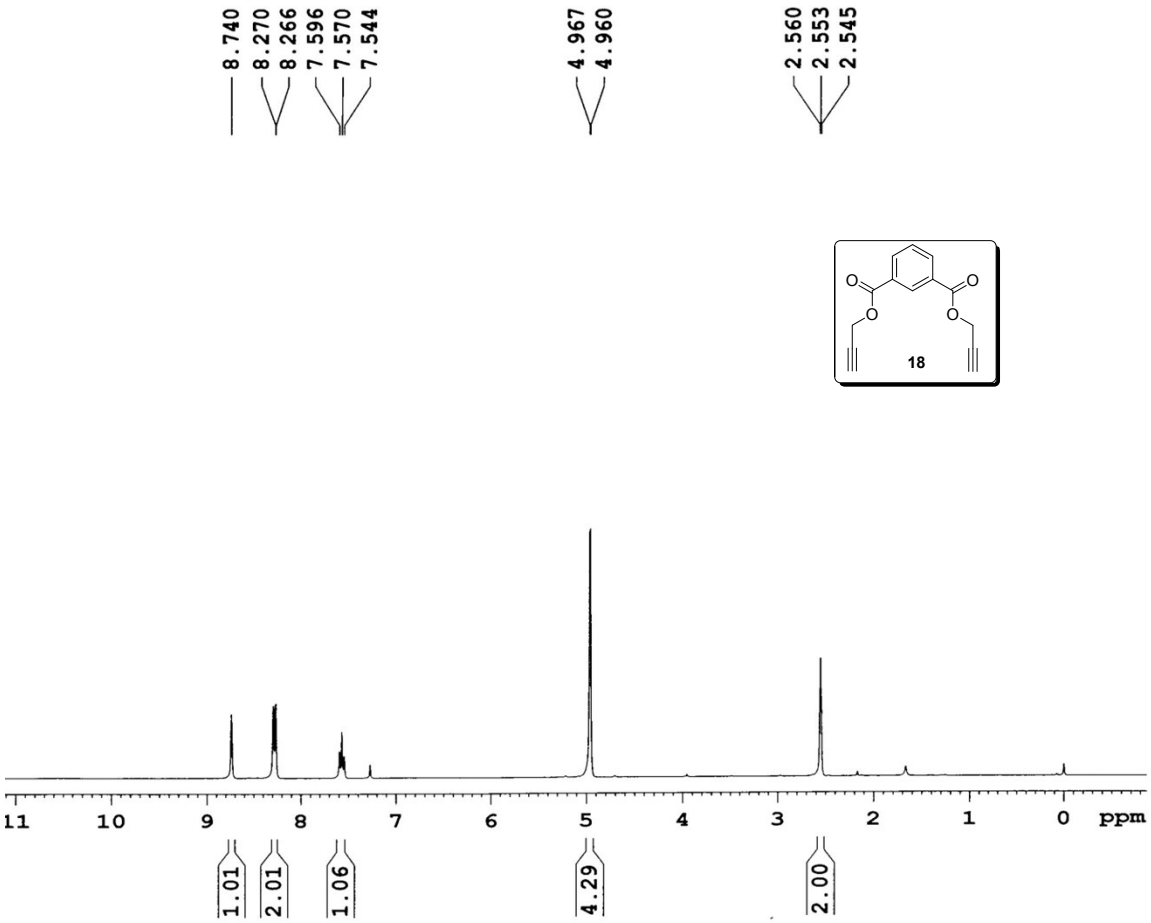


Figure 8: ^{1}H NMR spectrum (300MHz, $CDCl_3$) of diprop-2-ynyl isophthalate 18

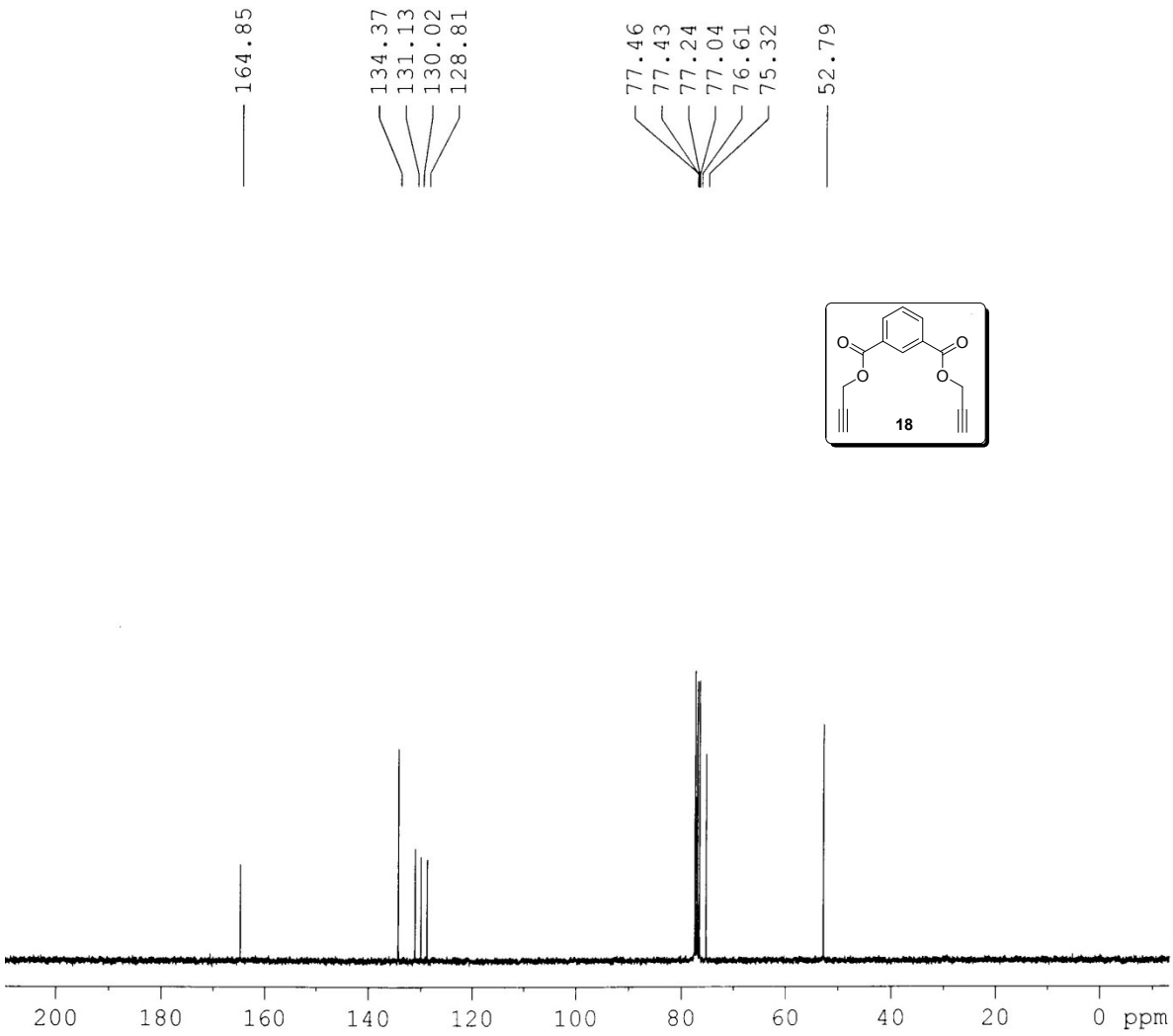
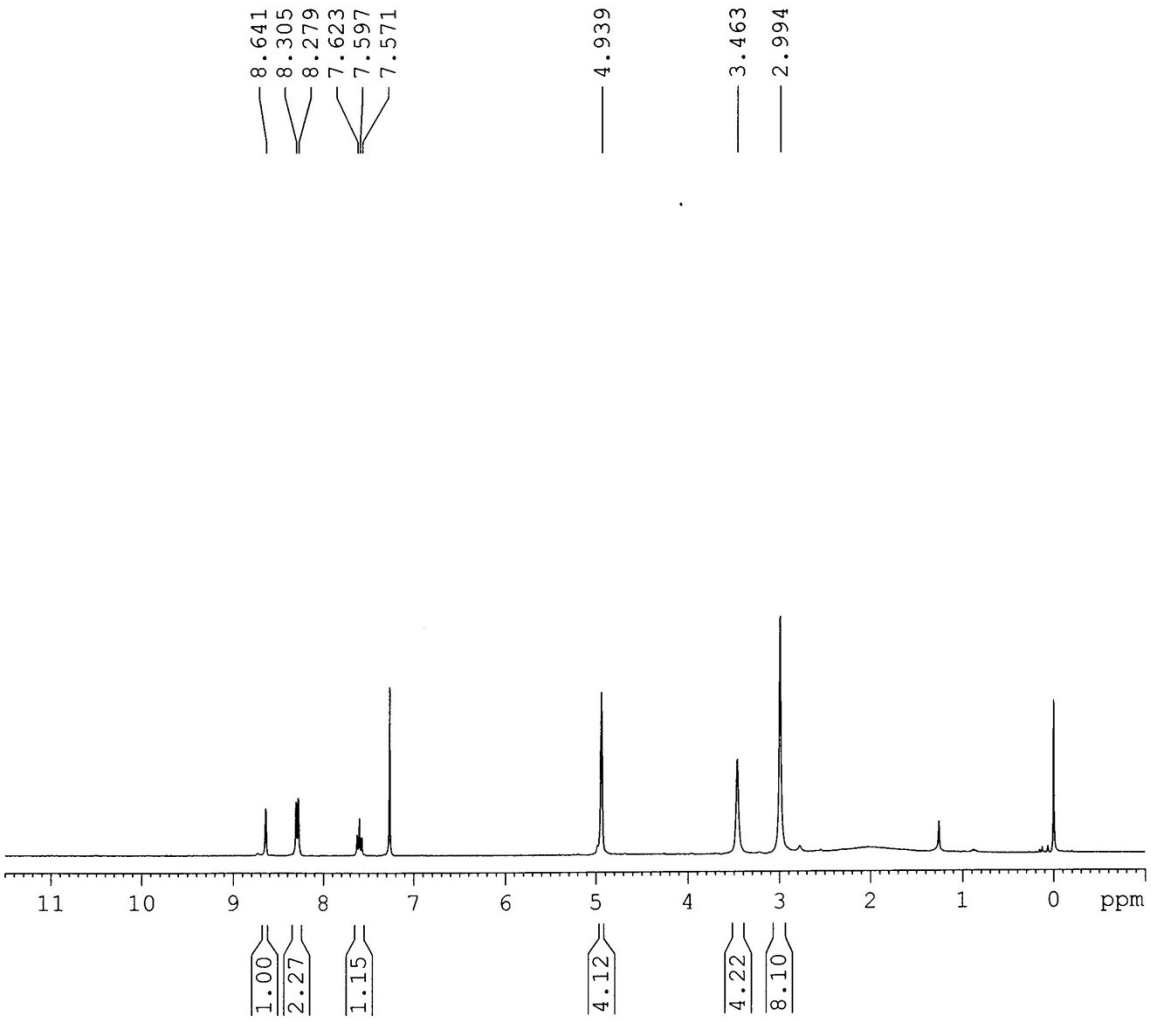


Figure 9: ^{13}C NMR spectrum (75MHz, $CDCl_3$) of diprop-2-ynyl isophthalate 18



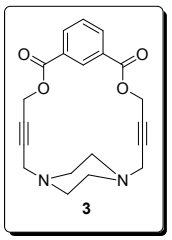


Figure 10: ^{1}H NMR spectrum (300MHz, $CDCl_3$) of Cyclophane ester 3

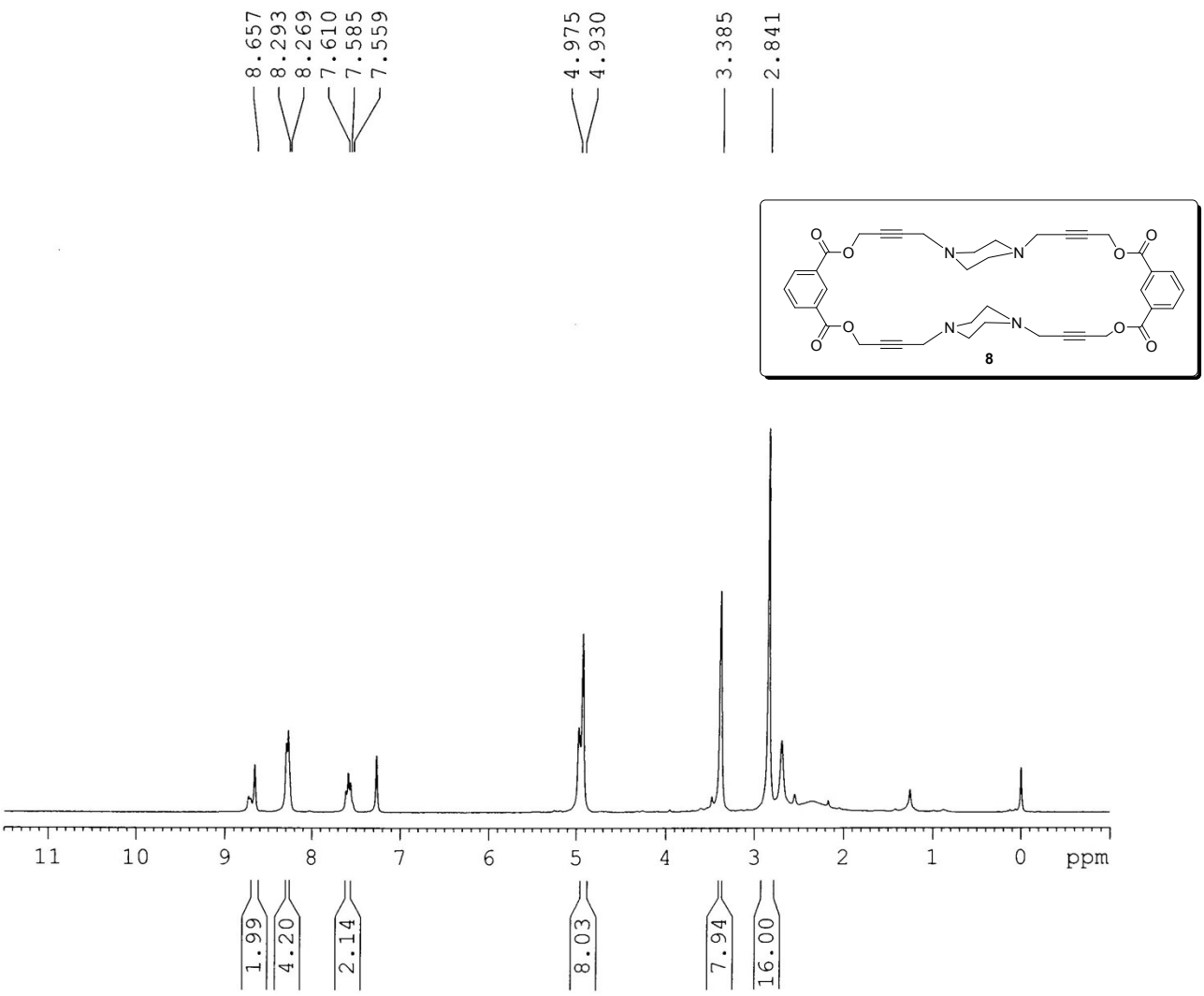


Figure 11: ^{1}H NMR spectrum (300MHz, $CDCl_3$) of Cyclophane ester 8

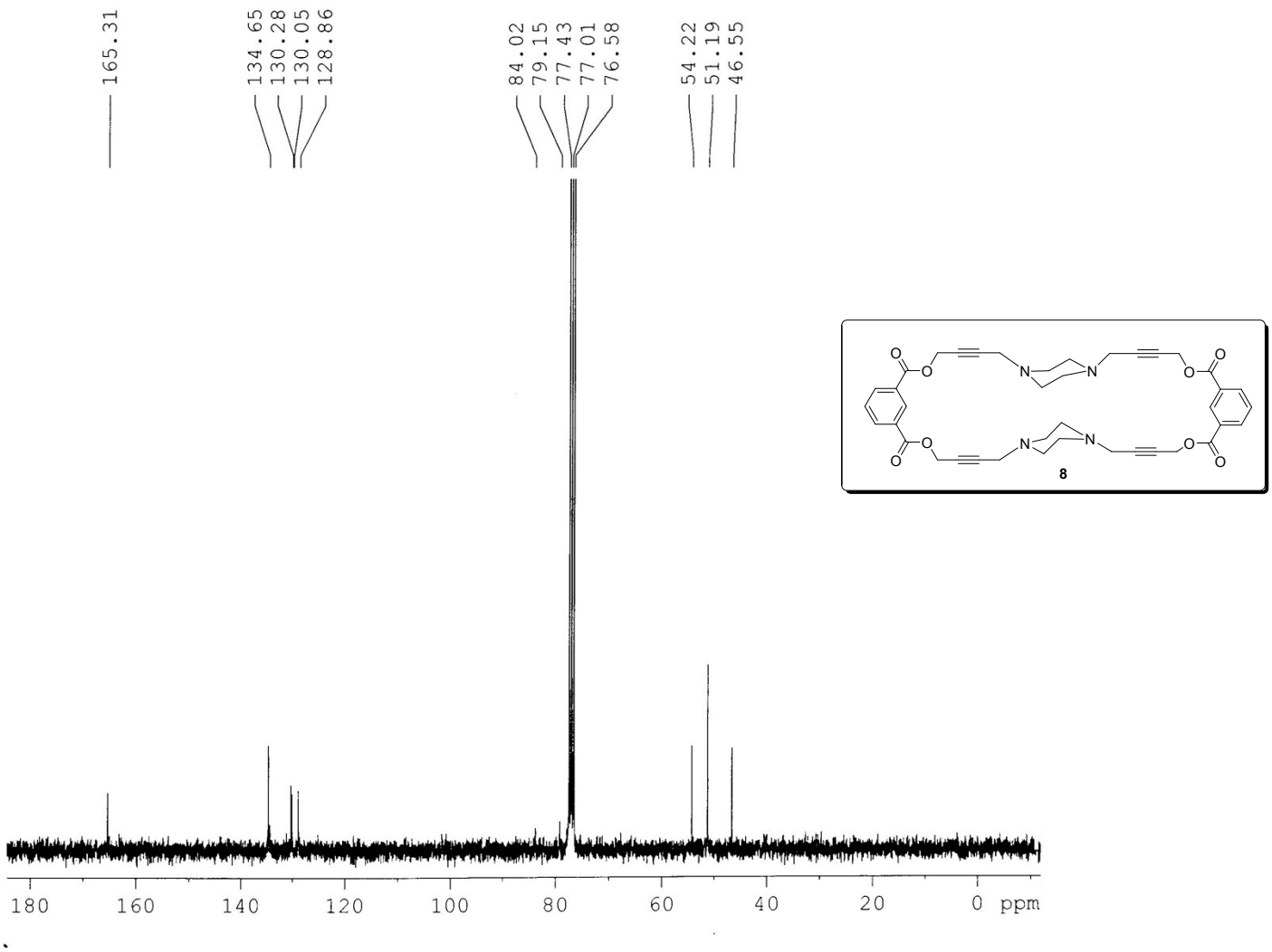


Figure 12: ^{13}C NMR spectrum (75MHz, $CDCl_3$) of Cyclophane ester 8

Antibacterial activity assay:

The emergence of drug resistance against the bacterial pathogens has out spaced the development and delivery of new effective antibacterial drugs. As a result there is a threat to the global health that the currently available therapies will no longer be effective in treating infections due to increasing drug resistance in bacteria. To combat these emergences of drug resistance, discovering of novel antibacterial agents is must. In an attempt to find the compound with effective biological activities, we studied the antibacterial activity of the synthesized piperazinophanes. The antibacterial activity assay was performed by resazurin dye reduction assay. The change of color of the dye from blue to pink indicates that the microbial cells are viable. The enzyme oxido-reductase present inside the bacterial cells converted the resazurin to resorufin which is pink in color. When the color of the dye remains blue then it indicates that there is no activity of viable cells. The test material when added kills the bacterial and fungal cells during incubation. This was determined by the blue or purple color of dye in the respective wells. The pink color formation in the wells even after treating with test compounds or commercial drug indicates the presence of viable cells. Thus the least concentration in which the color remains blue was taken as the MIC value of the respective compound.

Biological activity:

Minimum Inhibitory Concentration

The minimum inhibitory concentrations of the compound against the human pathogens were analyzed by resazurin reduction assay described by Sarkar et al. (2007).

Method to Prepare Resazurin dye solution

The Resazurin dye solution was made by dissolving a 270 mg tablet in 40 mL of sterile distilled water. The instrument vortex mixer was used to ensure that the resazurin solution was well-dissolved and form homogenous solution.

Preparation of the activity plates

The 96 wells plates were prepared under aseptic conditions. A volume of 200µL of compounds (1mg/mL) in 5% (v/v) Di methyl sulfoxide was pipetted into the first row of the 96 wells plate. To all other remaining wells 100µL of nutrient broth was added for the bacterial cells. The serial dilutions were performed using micropipette with sterile pipette tips such that each well had 100µL of the test material in serially descending concentrations. To all these wells 10µL of resazurin dye solution was added. A 10µL of bacterial suspension (5×10^6 cells/mL) was added to each well to achieve a concentration of 5×10^5 cells/mL. The commercial antibiotics streptomycin was used as positive controls in the assay plate. The plates were placed in an incubator at 37 °C for 18–24 h. The colour change was then observed visually. The colour changes from blue to pink or colourless were recorded as reduction of dye by the viable bacteria. The lowest concentration at which no colour change occurred was taken as the MIC value.

Picture of antibacterial activity of the synthesized piperazinophanes 1-7 by resazurin reduction method:

Figure 13

Figure 14

Figure 15

Figure 16

e 18

Figure 19

Figure keys:

C1- control - Compound + dye + without bacteria

C2- control - dye + *Escherichia coli*+ without compound

C3- control - dye + *Klebsiella pneumoniae*+ without compound

C4 -control - dye + *Staphylococcus aureus*+ without compound

C5- control- dye +*Streptococcus pyogens*+ without compound

S1 to S10– Compound + dye + *Escherichia coli*

S1a to S10a – Compound + dye + *Klebsiella pneumoniae*

S1b to S10b – Compound + dye + *Staphylococcus aureus*

S1c to S10c – Compound + dye +*Streptococcus pyogens*

P1 – Streptomycin + dye + *Escherichia coli*

P2– Streptomycin + dye + *Klebsiella pneumoniae*

P3 – Streptomycin + dye + *Staphylococcus aureus*

P4 – Streptomycin + dye +*Streptococcus pyogens*

Figure 13-19 Antibacterial activity of piperazinophanes 1-7 by resazurin reduction method.

Picture of Molecular docking studies:

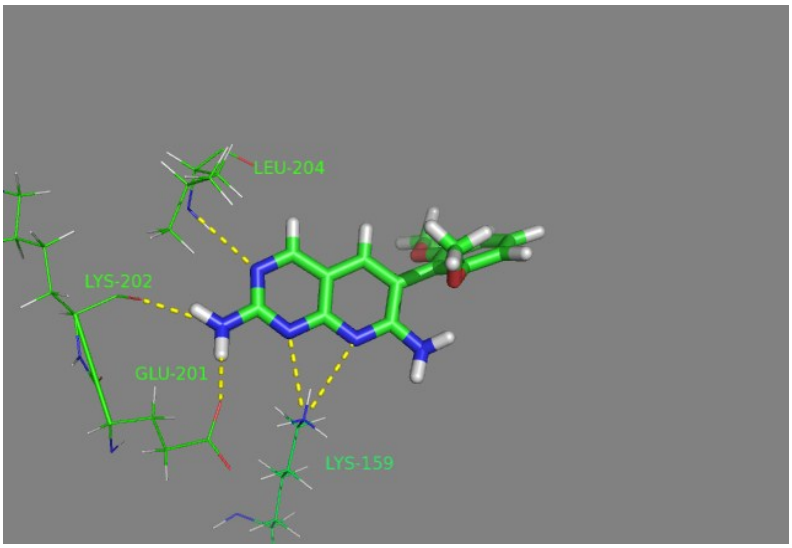


Figure 20: Molecular Docking of Co-ligand in the active pocket of Protein (PDB ID-2V59)

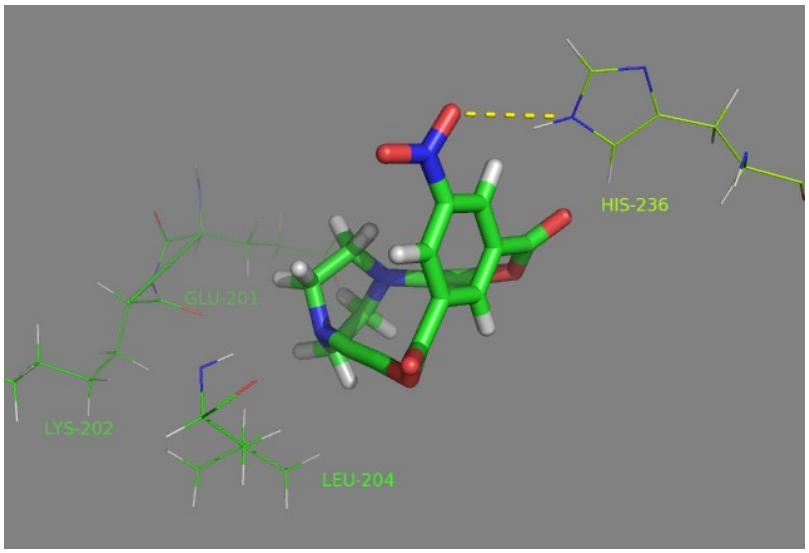


Fig.21-Molecular Docking of compound **S1** in the active pocket of protein (PDB ID-2V59)

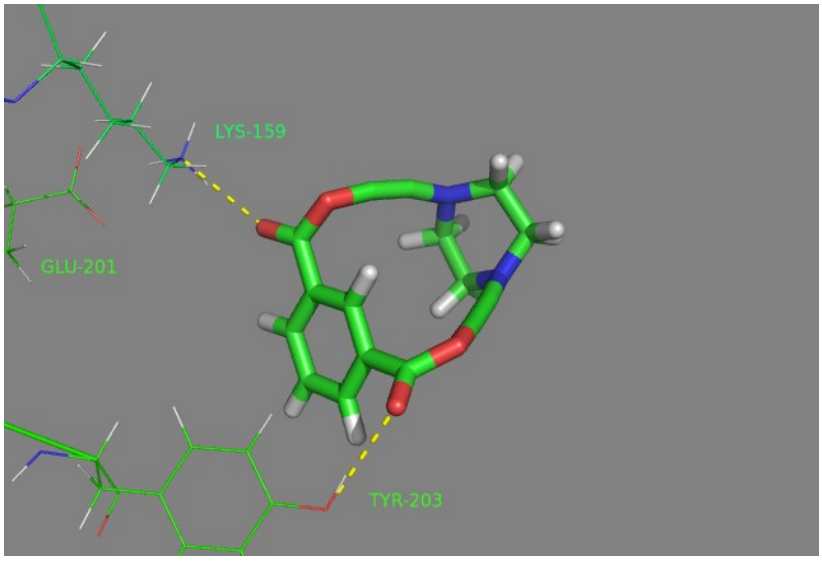


Fig.22- Molecular Docking of Compound **S2** in the active pocket of Protein (PDB ID-2V59)