Novel Multi-coded Molecular Recognition Motifs for Fully Extended Programmed Molecular Self-Assembly

Thesis Submitted towards the Partial fulfillment of

BS-MS dual degree programme

By

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Under the guidance of

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CERTIFICATE

This is to certify that this dissertation entitled "**Novel Multi-coded Molecular Recognition Motifs for Fully Extended Programmed Molecular Self Assembly**" towards the partial fulfilment of the BS-MS dual degree programme at the Indian Institute of Science Education and Research, Pune represents original research carried out by **Aditi Jakhar**, IISER Pune under the supervision of **Dr. G.J. Sanjayan**, Scientist – Organic Chemistry Division, NCL Pune during the academic year 2013-2014.

Date:

Place:

Dr. G.J. Sanjayan
Scientist – Organic Chemistry Division
National Chemical Laboratory, Pune

DECLARATION

I hereby declare that the matter embodied in the report entitled "**Novel Multi-coded Molecular Recognition Motifs for Fully Extended Programmed Molecular Self Assembly**" are the results of the investigations carried out by me at the Organic Chemistry Division, NCL Pune, under the supervision of Dr. G.J. Sanjayan and the same has not been submitted elsewhere for any other degree.

Date:

Aditi Jakhar

Place: BS-MS Dual Degree Program, IISER Pune

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Aditi Jakhar

Contents

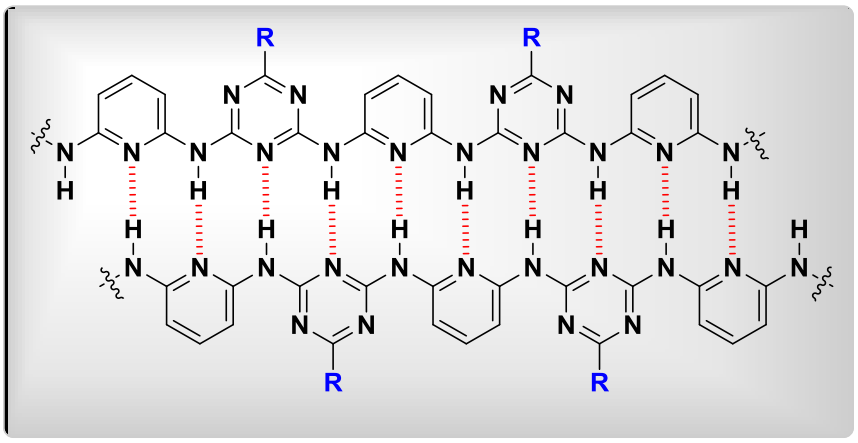
Abbreviations

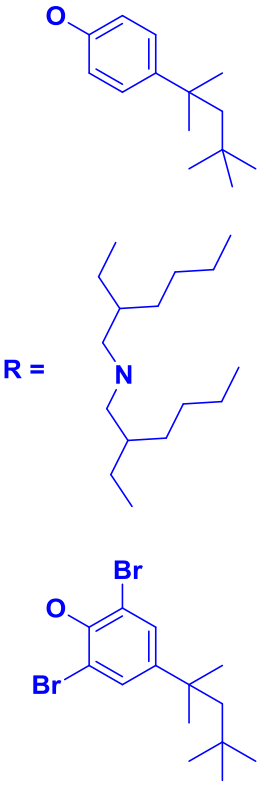
TLC	Thin Layer Chromatography
NMR	Nuclear Magnetic Resonance
HRMS	High Resolution Mass Spectrometry
ESI-MS	Electron spray Ionization mass spectrometry
J	Coupling Constant
Hz	Hertz
MHz	MegaHertz
DIPEA	N, N-diisopropylethylamine
DMF	N, N-dimethylformamide
NMP	*N*-Methyl-2-pyrrolidone
m-CPBA	meta-Chloroperoxybenzoic acid
mg	Milligram
MALDI-TOF	Matrix-assisted laser desorption/ionization-Time of flight
g	Gram
h	hour
LiHMDS	Lithium bis(trimethylsilyl)amide
LDA	Lithium diisopropylamide
min	minutes
M	Molar
mL	Millilitre
mmol	milli mole
THF	Tetrahydrofuran
TFA	Trifluoroacetic acid

Abstract

A synthetic pathway for the synthesis of multi-coded molecular recognition motifs anticipated to exhibit fully extended programmed molecular self-assembly was developed. These systems may find applications in the development of designer peptides (for e.g. artificial sheets). While synthesizing these motifs, various valuable intermediates were successfully achieved through a series of nucleophilic substitution reactions, which featured pre-organized self-complimentary H-bonding between alternating acceptor (A) and donor (D) sites. During the course of this study, a novel synthetic protocol has also been developed to realize conjugation of aminopyridines with 1,3,5-triazine core.

Graphical Abstract





Supramolecular chemistry is referred to as the chemistry beyond molecules or the chemistry of molecular assemblies and the intermolecular bond, which was developed over the last forty years. The concept and the term of supramolecular chemistry were introduced in 1978 by Jean Marie Lehn.[1,2]

Supramolecular chemistry can be broadly classified into two broad areas: (1) *supermolecules*: well-defined, discrete oligomeric species that result from intermolecular association of a few components [a receptor and its substrate(s)] (2) *supramolecular assemblies*: polymolecular entities that result from the spontaneous association of a large unidentified number of components into a specific phase having more or less well defined microscopic characteristics depending on its nature (such as films, membranes, micelles, mesomorphic phase, solid state structures, etc.).

Non covalent forces play the primary role in the organization of molecules in supramolecular assemblies. Among them, some of the interactions which play a major role are π-π stacking, Van der Waals forces, ion-dipole, dipole-dipole, dipole-induced-dipole and hydrogen bonding.

Among them, hydrogen bonding plays the most important role in the formation of a wide range of supramolecular assemblies. The ubiquitous nature of hydrogen bonding and its three important characteristics: strength, directionality and specificity make it unique in comparison with other types of non-covalent interactions, as they generally lack in at least one of these characteristics. Directionality is one widely accepted aspect of hydrogen bonding. It is the directionality in hydrogen bonding that develops from an anisotropic intermolecular potential, that does not force the angle D–H···A away from linearity, where D is the donor and A is the acceptor and separates it from the more general van der Waals forces and other secondary electrostatic interactions, which are likely to be isotropic and may force the angle D-H···A away from linearity. Recognition may occur in a highly specific manner, due to the presence of partial charges that give rise to intermolecular interactions. A

partially electronegative species or atoms will selectively attract a partially electropositive species or atoms i.e. the partial charges act as electrostatic map. The proper alignment which gives the interaction a high degree of selectivity in terms of binding, increases the specificity of the interaction.[3] (Fig 1)

Fig 1*: Hydrogen bonding between the acceptor (A) and the hydrogen atom of the donor (D). The directionality of the (head-on or end-on binding, not side-on binding) electrostatic surface dictates the directionality of the hydrogen bonding which is not observed on the right resulting from an acute bond angle and where there is no contact with the electrostatic potential area of interaction (shown in red in potential map).*

Multipoint hydrogen-bonding motifs are the backbone of recognition processes in biology and are increasingly featuring in the design of multifunctional materials and supramolecular polymers.[4-9] To build up a supramolecular architecture, two or more hydrogen bonding subunits are required whose disposition determines the final structure. When two subunits are incorporated into a single group, it will then possess two recognition faces, double faced H-bonding recognition units. If the faces are same or different the units are *homotopic* or *heterotopic*; when they are complimentary, the unit is self-complimentary and may be termed as *plerotopic*. Each recognition motif may have one, two, three, four, etc. hydrogen bonding donor (**D**) or acceptor (**A**) centers. The stability and selectivity of the association depends on the nature and position of the centers.[10] In the formation of hydrogen bonded complexes, Jorgensen suggested that secondary hydrogen bond interactions contribute significantly to complex stability. For systems containing four hydrogen bonds, the pattern AAAA-DDDD (where all the secondary interactions are attractive, K_{dim} = 3.9 x 10^8 M^{-1}) is believed to result in the most stable complexes and the least stable one is DADA-ADAD (where all the secondary interactions are repulsive, K_{dim} = 3.1 x 10^2 M^{-1}).[11]

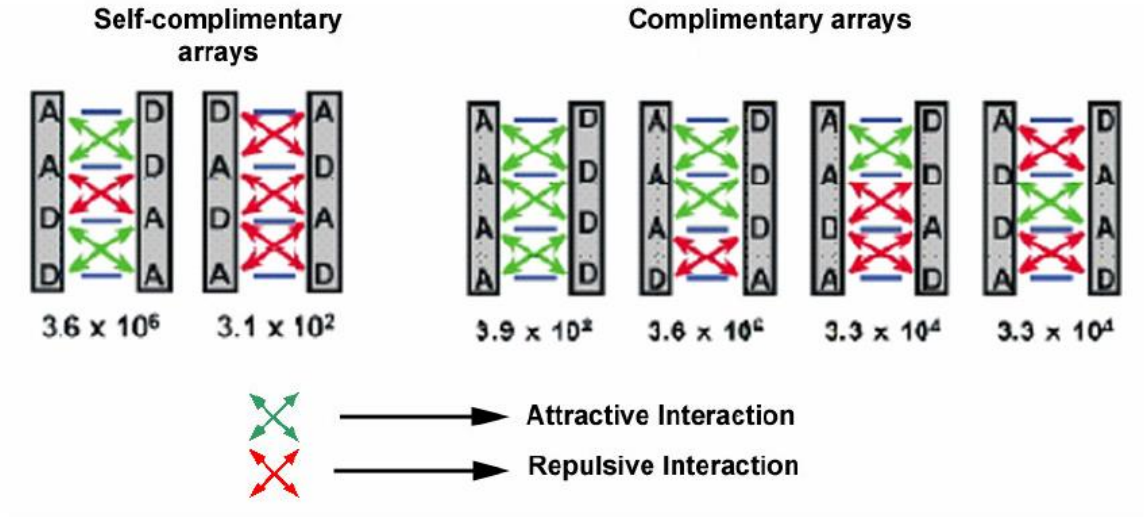


Fig 2*: Complimentary and self-complimentary arrangements in a quadruple H-bonded system*.

But in most of the cases, there are deviations from the calculated values. For example, quadruple DADA H-bonded duplexes **A** and **B** based on diamino triazine reported by Meijer *et al*[12] differ in their stability, though they are held together by identical arrays. (Fig. 3)

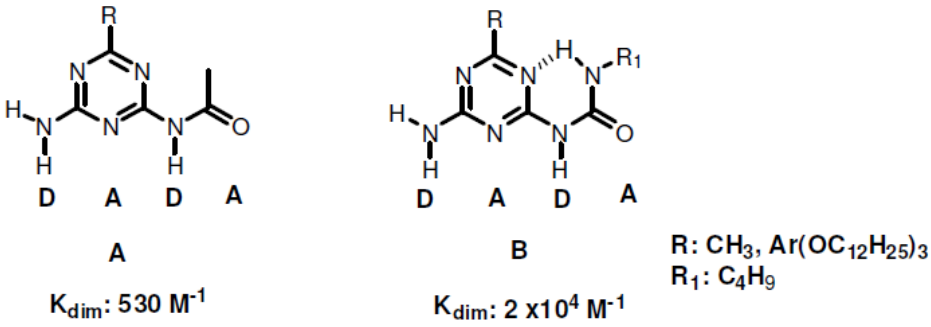


Fig 3: *Deviation from stability rules based on secondary interactions.*

Therefore, the design and synthesis of molecular duplexes with diversely positioned H-bonding acceptor (A) and donor (D) codes have emerged as an interesting area of research in the supramolecular synthesis. Amongst these, some of the noteworthy examples are H-bonded duplexes using multiple H-bonds ranging from doubly H-bonded to duplexes which bind with six H-bonds.[12,13] (Fig 4)

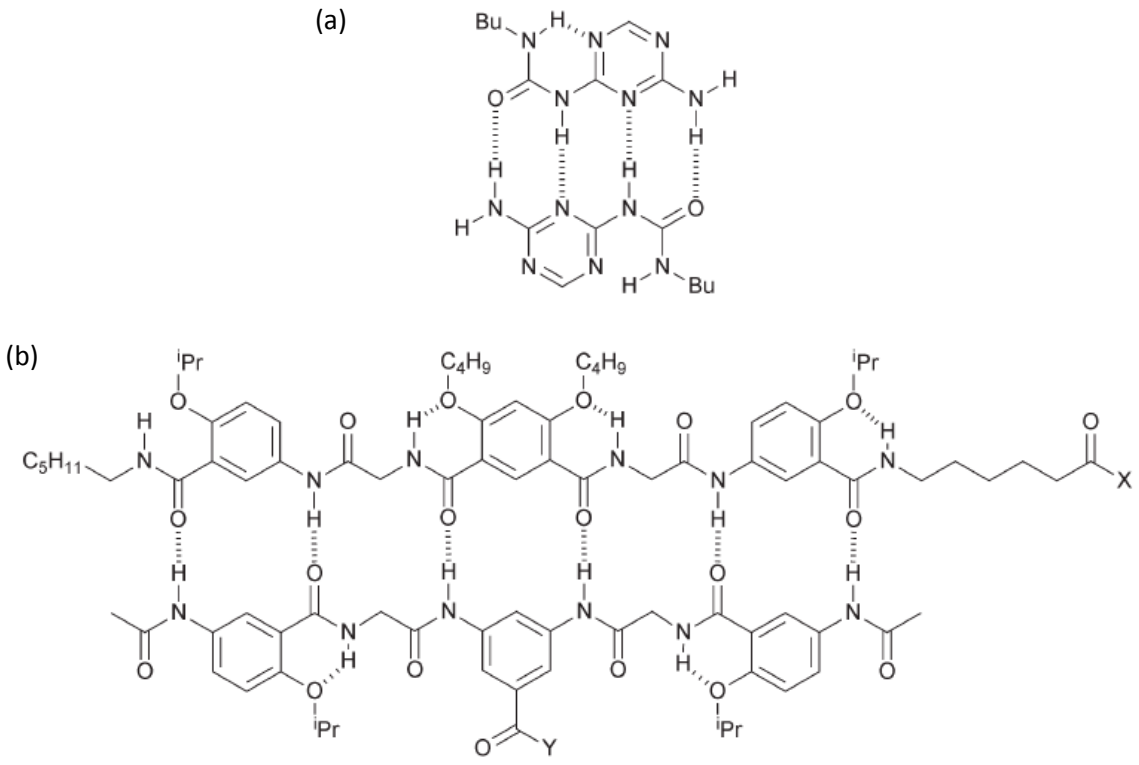


***Fig 4**: Examples for H-bonded duplexes.*

By introducing arrays of donor (D) and acceptor sites (A), the strength and selectivity of hydrogen bonds can be increased, which directly influences the stability and overall shape of the self-assembled ensembles. The design and synthesis of linear arrays of hydrogen-bonds that exhibit well-defined molecular recognition behavior is a constant challenge in supramolecular chemistry.

Aims and Objectives

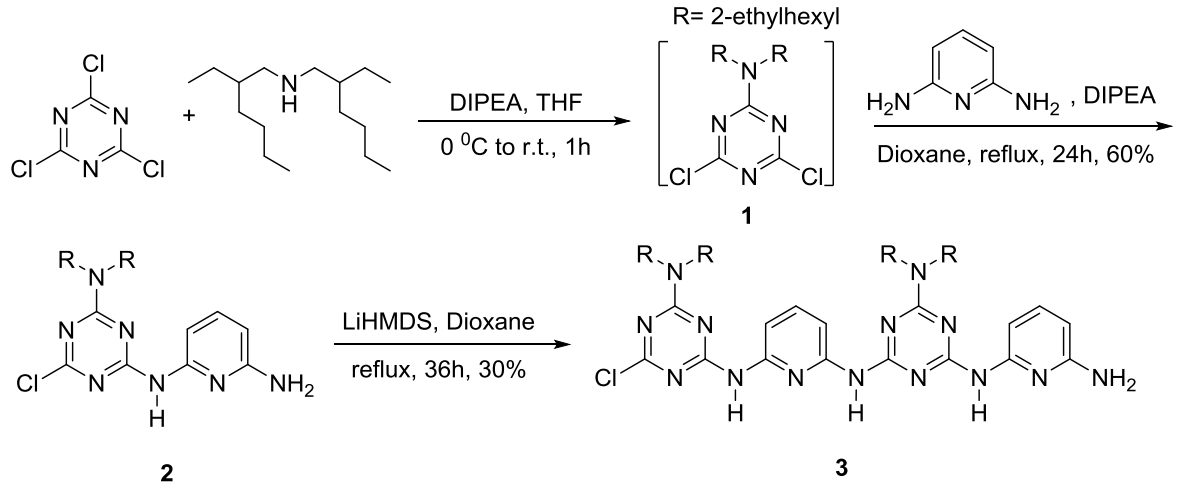
Our major objective was the development of fully extended programmed self-assembling systems embedded with multi-coded recognition motifs which can be expected to show ADAD-DADA type of intermolecular hydrogen bonding. Such systems are expected to undergo duplex formation with enormous strength and thus may find application in the development of designer peptides (e.g. artificial sheets).

The presence of hydrogen bonding acceptor (A) groups in 1,3,5-triazine and the presence of hydrogen bonding donor (D) and acceptor (A) groups in 2,6-diaminopyridine encouraged us to build systems, which feature these two as the basic building blocks. We decided to decorate 1,3,5-triazine with bulky substituent groups, so as to prevent any stacking interactions which may arise and cause solubility issues. Also, the substituent group was planned to be linked by either amine or ether linkage which was expected to improve the reactivity of the system due to their electronegative nature.

We tried several substituents, out of which only two gave desired results: Bis(2-ethylhexyl)amine and 4-tertiary-octylphenol. The long alkyl chain of Bis(2-ethylhexyl)amine successfully disrupted the stacking interactions, thus improving the solubility of our substrates and the nitrogen present, increased the reactivity of cyanuric chloride. In 4-tertiary-octylphenol, the presence of the phenyl ring gave us the opportunity to make further substitutions and further increase the reactivity of substituted cyanuric chloride. Also, the long alkyl chain attached to the phenyl ring helped in improving solubility of the duplex assembly. The ether linkage was also expected to play an important role in increasing the reactivity of the substituted cyanuric chloride.

First, bis(2-ethylhexyl)amine was substituted on commercially available cyanuric chloride to improve the solubility profile and reactivity of further substrates. **1** was obtained *in situ* by reacting cyanuric chloride with bis(2-ethylhexyl)amine in presence of DIPEA. Then, commercially available 2,6-diaminopyridine was added in a 1:1 ratio in presence of DIPEA and refluxed in dioxane to obtain **2** in 60% yield. **2** was subjected to dimerization in presence of strong base LiHMDS and was refluxed in dioxane to give **3** in 30% yield (Scheme 1). LiHMDS gave a cleaner reaction in comparison with LDA.

Scheme 1**: Synthesis of Compound **3



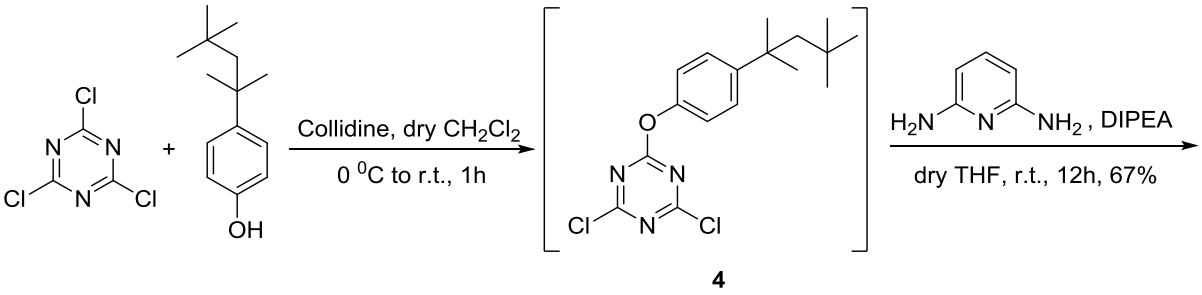
3 was confirmed by ^{1}H and ^{13}C NMR spectral analysis. The secondary N-H chemical shifts were observed at 12.74 ppm and 7.78 ppm as broad peaks, while the primary N-H chemical shift was observed at 5.23 ppm. m/z peaks were found to match the calculated values for $(M+Na)^{+}$ and $(2M+Na)^{+}$ at 909.56 and 1797.37. The presence of $(2M+Na)^{+}$ peak showed that **3** had undergone duplex formation. Further coupling of **3** with itself or with 2,6-diaminopyridine failed under harsh conditions and in the presence of strong bases as **3** is very stable and does not react further.

Since further oligomerization of **3** failed, we decided to change the substituted group on cyanuric chloride to ether to further improve the reactivity of our building blocks. First, (±) borneol and (±) menthol were tried as the substituted groups but due to the

very unstable nature of (±) borneol and (±) menthol substituted cyanuric chloride substrates respectively, they were not pursued further.

Hence, 4-tertiary-octylphenol was chosen to be the substituted group on cyanuric chloride due to the relative stability of 4-tertiary-octylphenol substituted cyanuric chloride and also the presence of alkyl and aryl parts in 4-tertiary-octylphenol which were expected to improve the the solubility profile and reactivity of further substrates.

Scheme 2**: Synthesis of Compound **5



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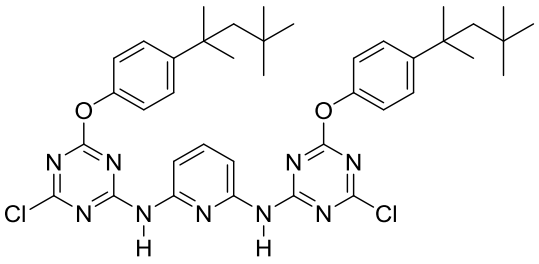


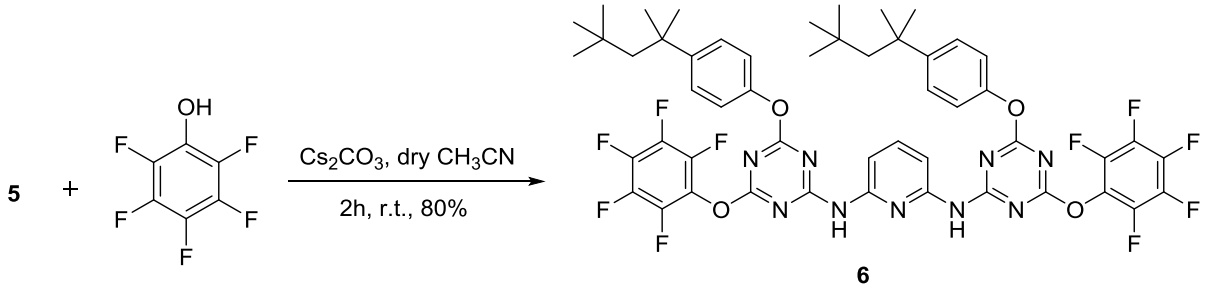
5

First, **4** was obtained *in situ* by reacting cyanuric chloride with 4-tertiary-octylphenol in presence of collidine. Then, 2,6-diaminopyridine was added in a 1:3 ratio in presence of DIPEA and stirred at room temperature to obtain **5** in 67% yield (Scheme 2). **5** was confirmed by ^{1}H and ^{13}C NMR spectral analysis. The secondary N-H chemical shift was observed at 9.54 ppm as a broad peak. m/z peak was found at 744.37 which matched the calculated value for $(M+1)^+$. No 2M peak was observed.

Further coupling of **5** with 2,6-diaminopyridine failed even under harsh conditions, so the chloro groups on both the sides of **5** were substituted by good leaving group, pentafluorophenol to aid in further coupling. For this purpose, **6** was synthesized by

reacting **5** with commercially available pentafluorophenol in 1:3 ratio in presence of Cs_2CO_3, to obtain 80% yield (Scheme 3). **6** was confirmed by ^{1}H and ^{13}C NMR spectral analysis.

Scheme 3**: Synthesis of Compound **6

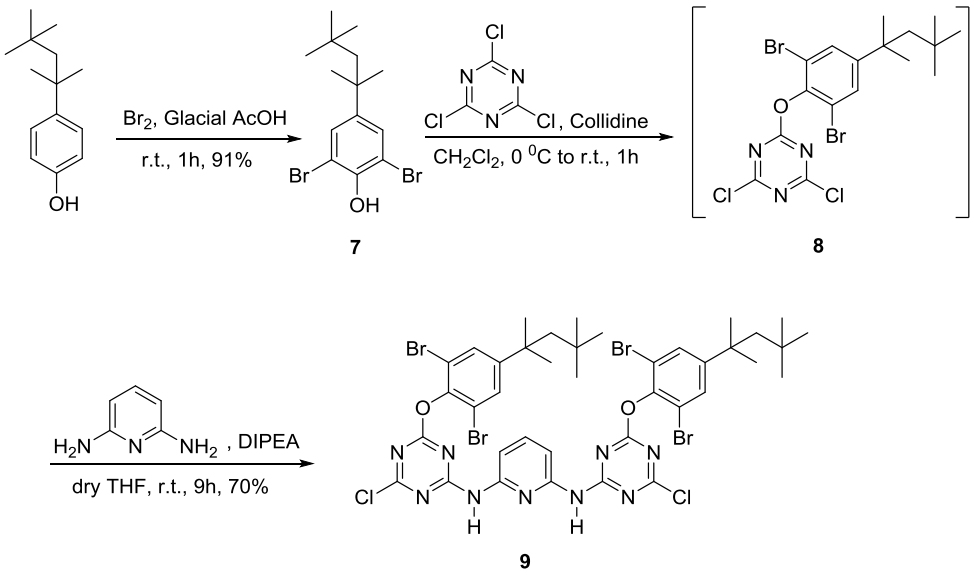


6

The secondary N-H chemical shift was observed at 9.08 ppm as a broad peak. m/z peak was observed at 1040.3655 and matched the calculated value for $(M+1)^{+}$. No 2M peak was observed.

Substitution of pentafluorophenol in **6** by 2,6-diaminopyridine failed even under harsh conditions. So, the reactivity of **5** was improved by synthesizing its brominated analogue (**9**), to aid in further coupling. Direct bromination of **5** was tried by NBS but it gave very low yield (15%), so step wise bromination was done, by first brominating 4-tertiary-octylphenol. **7** was obtained by reacting 4-tertiary-octylphenol with bromine in presence of glacial acetic acid in 91% yield. It was further reacted with cyanuric chloride in presence of collidine to obtain **8**, the brominated analogue of **4** *in situ*. Then, 2,6-diaminopyridine was added in a 1:3 ratio, in presence of DIPEA to obtain **9** in 70% yield (Scheme 4). **5** was confirmed by ^{1}H and ^{13}C NMR spectral analysis. The secondary N-H chemical shift was observed at 10.02 ppm as a broad peak. m/z peak was observed at 1061.6650 which match the calculated value for $(M+1)^{+}$. No 2M peak was observed.

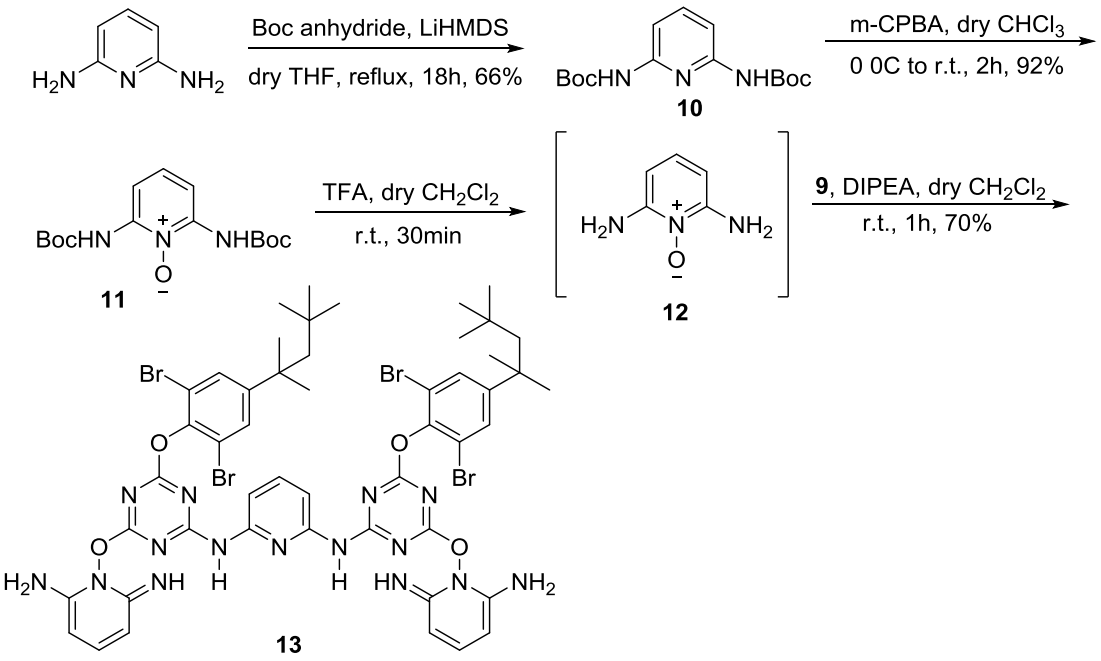
Scheme 4**: Synthesis of Compound **9



Further coupling of **9** with 2,6-diaminopyridine failed even under harsh conditions, so we decided to improve the reactivity of 2,6-diaminopyridine by preparing its N-oxide (**12**). Direct preparation of N-oxide was tried without any protection of the –NH2 groups but it failed. So, the $–NH_2$ groups were first protected with acetyl groups, then the N-oxide was prepared by m-CPBA and then deacylation was done without affecting the N-oxide but it gave a very low yield (2%).

The protecting group was then changed to Boc, to obtain **12**. First, the $–NH_2$ groups were protected with Di-*tert*-butyl dicarbonate in presence of LiHMDS to give **10** in 66% yield, which was further reacted with m-CPBA to give **11** in 92% yield. **11** was confirmed by ^{1}H and ^{13}C NMR spectral analysis. The large downfield chemical shift of secondary N-H to 9.17 ppm from 7.90 ppm (in case of **10**), confirmed the N-oxidation. Boc deprotection was done by TFA, and then DIPEA was added to synthesize **12** *in situ*. **9** was added in presence of DIPEA to give **13** in 70% yield (Scheme 5).

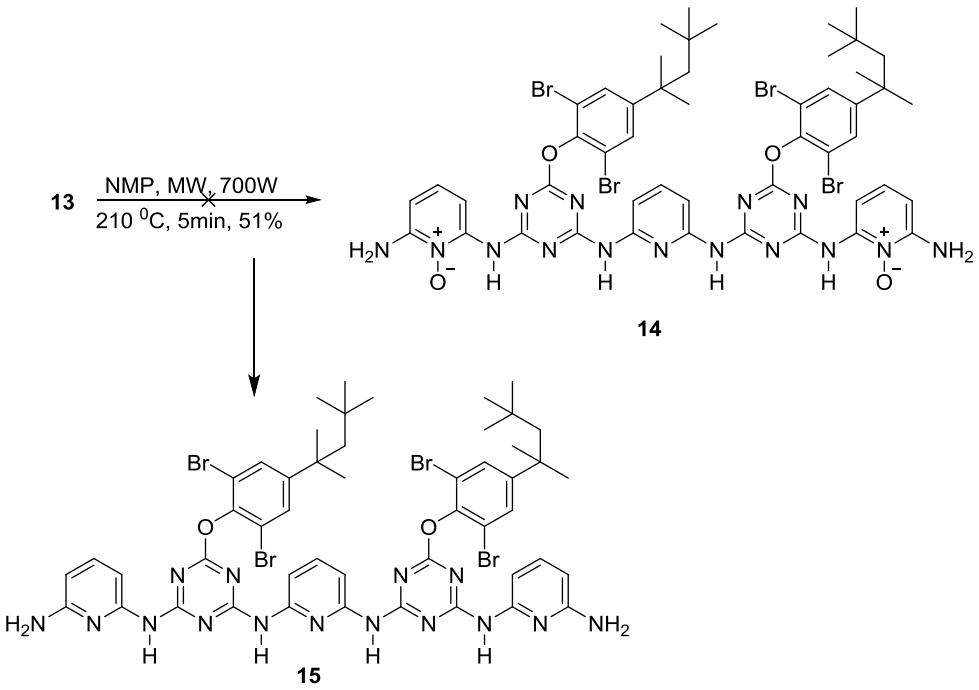
Scheme 5**: Synthesis of Compound **13



13 was confirmed by ^{1}H and ^{13}C NMR spectral analysis. Two sets of N-H chemical shifts were observed in the ^{1}H NMR spectrum. The secondary N-H protons showed a chemical shift of 10.52 ppm and the imine N-H protons showed a chemical shift of 10.04 ppm. The primary N-H protons showed a chemical shift of 6.94 ppm. m/z peak was observed at 1273.6968 and matched the calculated value for $(M+K+1)^{+}$.

13 was then subjected to microwave irradiation at 700W for 5 min in presence of NMP to obtain a rearranged production **15**, which had also undergone deoxygenation in 51% yield (Scheme 6). Our expected product was **14** but surprisingly deoxygenation is happening along with rearrangement in the same step. **15** was confirmed by ^{1}H and ^{13}C NMR spectral analysis. The secondary N-H protons showed two broad peaks at chemical shifts of 9.76 ppm and 9.62 ppm. The primary N-H protons showed a chemical shift of 5.74 ppm. m/z peak was observed at 1205.6931 and matched the calculated value for M^{+}. No 2M peak was observed.

Scheme 6**: Synthesis of Compound **15



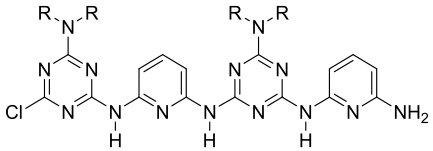
Mass-spectral analytical studies were done to study the self assembling properties of the synthesized compounds. In the case of compound **3**, which has bis(2-ethylhexyl)amine as the substituent group and a molecular weight of 886.83, ESI-MS analysis was done and $(M+Na)^+$ and $(2M+Na)^+$ peaks were observed at m/z 909.56 and 1797.37 respectively. The presence of $(2M+Na)^+$ peak suggests that dimer formation has occurred and the compound exists in a duplex assembly. MALDI-TOF spectral analysis was done for compounds **5**, **9** and **15**. For compound **5**, $(M+H)^+$ peak was observed at m/z 744.1253 and no 2M peak was observed which suggests that dimer or duplex assembly formation might not have taken place. For compound **9**, $(M+H)^+$ peak was observed at m/z 1061.665 and no 2M peak was observed. For compound **15**, M and M+2 peaks were observed at m/z 1205.6931 and 1207.6887 respectively and no 2M peak was observed.

To conclude, the compound having bis(2-ethylhexyl)amine as the substituent group is showing signs for the formation of a duplex assembly whereas the compounds having 4-tertiaryoctylphenol as the substituent group are not showing any signs of a duplex assembly formation.

- Unless otherwise stated, all the chemicals and reagents were obtained commercially.
- Dry solvents and reagents were prepared using the standard procedures.
- ^{1}HNMR, ^{13}CNMR and DEPT spectra were recorded on Ac 200 MHz, AV 400 MHz, Jeol-400 MHz and DRX-500 MHz Bruker NMR spectrometers using tetramethylsilane (TMS) as an integral standard. Chemical shifts have been expressed in ppm units downfield from TMS and peak multiplicities as singlet (s), doublet (d), multiplet (m) and broad singlet (bs).
- ESI HRMS data were recorded on Waters Synapt G2 spectrometer.
- All reactions were monitored by Thin Layer Chromatography (TLC) on precoated 0.25 mm E-Merck silica gel plates ($60F_{254}$) with UV-light, I_2, ninhydrin or bromo cresol solution as the developing reagents in concerned cases.
- All reactions were carried out under nitrogen atmosphere.
- All evaporations were carried out under reduced pressure on Buchi rotatory evaporator below 40 ^{o}C unless otherwise specified.
- Silica gel (230-400) mesh was used for column chromatography.

Synthesis of N2-(6-aminopyridin-2-yl)-N4-(6-((4-(bis(2-ethylhexyl)amino)-6-chloro-1,3,5-triazin-2-yl)amino)pyridin-2-yl)-N6,N6-bis(2-ethylhexyl)-1,3,5-triazine-2,4,6-triamine (3): A stirred solution of cyanuric chloride (5g, 25.77mmol) in 50 ml of dry THF was kept at -5 ^{o}C for 15 min. A solution of bis(2-ethylhexyl)amine (7.78 ml, 25.77mmol), DIPEA (5.37 ml, 30.92mmol) and dry THF (10 ml) was added drop wise to the above stirred solution at -5 ^{o}C. The reaction mixture was left to come down to room temperature and was stirred for 1 hour.

R= 2-ethylhexyl

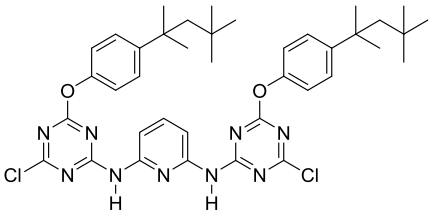


To this reaction mixture, a solution of 2,6-diaminopyridine (2.81g, 25.77mmol) dissolved in dry dioxane (100 ml) was added drop wise. DIPEA (22.44 ml, 128.8mmol) was then added drop wise to this stirred reaction mixture at room temperature. The reaction mixture was then refluxed at 120 ^{o}C for 24h. The reaction mixture was diluted with ethyl acetate (2 x100mL) and was extracted with water (2x100mL). The organic layer was dried over anhydrous sodium sulphate solution after washing it with brine and concentrated in *vacuum.* The resulting crude was purified by silica gel column chromatography using petroleum ether- ethyl acetate (3:1) as the mobile phase to obtain **2** (7.3g, 60%) as a yellowish viscous liquid.

2 (4g, 8.48mmol) was dissolved in dioxane (100 ml) and kept at -78 ^{o}C for 15 min. Then a solution of LiHMDS (25.4 ml, 25.44mmol) in 1M THF was added drop wise to the above stirred solution at -78 ^{o}C. The reaction mixture was then refluxed at 120 ^{o}C for 36h. The reaction mixture was diluted with ethyl acetate (2 x100mL) and was extracted with water (2x100mL). The organic layer was dried over anhydrous sodium sulphate solution after washing it with brine and concentrated in *vacuum.* The resulting crude was purified by silica gel column chromatography using petroleum ether- ethyl acetate (1:3) as the mobile phase to obtain **3** (2.254g, 30%) as a white solid. Characterisation data: ^{1}H NMR (500.13 MHz, Chloroform-*d*): δ 0.87 (d, *J* = 7.3 Hz, 24H), 1.25 (bs, 32H), 1.78 (m, 4H), 3.3-3.7 (m, 8H), 5.25 (bs, 2H),

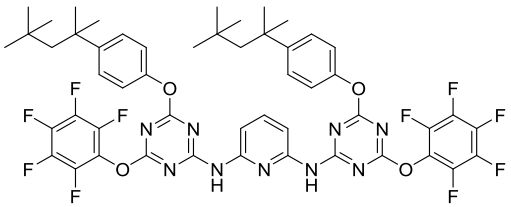
6.17 (d, *J* = 8.2 Hz, 4H), 7.35 (t, *J* = 7.9x(2) Hz, 2H), 7.78 (bs, 2H), 12.75 (bs, 1H); ^{13}C NMR (125.76 MHz, Chloroform-*d*): δ 10.68, 10.78, 14.08, 23.12, 23.62 28.66, 30.33, 31.92, 37.05, 37.35, 49.86, 50.07 76.81, 77.06, 7.31, 100.71, 102.66, 140.02, 150.86, 156.02, 157.18, 165.67; ESI-MS: m/z calculated for $C_{48}H_{79}ClN_{14}Na$: 909.63; Found: 909.56.

Synthesis of N2,N6-bis(4-chloro-6-(4-(2,4,4-trimethylpentan-2-yl)phenoxy)-1,3,5-triazin-2-yl)pyridine-2,6-diamine (5): To a stirred solution of 4-tertiary-octylphenol (5.1g, 24.71mmol) in dry CH_2Cl_2 (100 ml), collidine (3.3 ml, 24.71mmol) was added drop wise. This stirred solution was kept at room temperature for 5 min and then at 0 ^{0}C for 15 min. Then cyanuric chloride (5g, 27.17mmol) was added to the above stirred solution at 0 ^{0}C and the reaction mixture was kept at 0 ^{0}C for 15 min. The reaction mixture was left to come down to room temperature and stirred for 1h.



To this reaction mixture, a solution of 2,6-diaminopyridine (0.9g, 8.24mmol) dissolved in dry THF (40 ml) was added drop wise. DIPEA (7.17 ml, 41.2mmol) was then added drop wise to this stirred reaction mixture at room temperature. The reaction mixture was then stirred at room temperature for 12h. The reaction mixture was diluted with CH_2Cl_2 (2x100mL) and was extracted with water (2x100mL). The organic layer was dried over anhydrous sodium sulphate solution after washing it with brine and concentrated in *vacuum.* The resulting crude was purified by silica gel column chromatography using petroleum ether- ethyl acetate (95:5) as the mobile phase to obtain **5** (4.1g, 67%) as a white solid. Characterisation data: ^{1}H NMR (400.13 MHz, Chloroform-*d*): δ 0.76 (s, 18H), 1.41 (s, 12H), 1.77 (s, 4H), 7.09 (d, *J* = 8.6 Hz, 4H), 7.41 (d, *J* = 7.8 Hz, 5H), 7.7 (bs, 2H), 9.5 (bs, 2H); ^{13}C NMR (100.61 MHz, Chloroform-*d*): δ 29.70, 31.68, 31.86, 32.41, 38.52, 56.97, 110.89, 120.61, 127.19, 140.27, 148.43, 149.09, 149.22, 164.91, 171.89; MALDI-TOF: m/z calculated for $C_{39}H_{47}Cl_2N_9O_2$+1: 744.3217; Found: 744.1235.

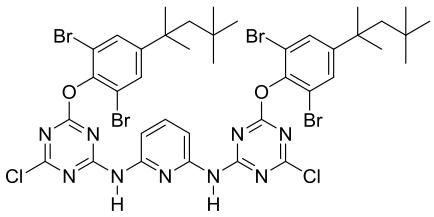
Synthesis of N2,N6-bis(4-(perfluorophenoxy)-6-(4-(2,4,4-trimethylpentan-2-yl)phenoxy)-1,3,5-triazin-2-yl)pyridine-2,6-diamine (6): To a stirred solution of pentafluorophenol (1g, 5.37mmol) in dry acetonitrile (50mL), Cs_2CO_3 (1.75g, 5.37mmol) was added at room temperature and was stirred for 15 min. To the above stirred solution, **5** (1g, 1.345mmol) was added and the reaction mixture was stirred at room temperature for 2h.



The reaction mixture was diluted with CH_2Cl_2 (3x30mL) and was extracted with water (3x30mL). The organic layer was dried over anhydrous sodium sulphate solution after washing it with brine and concentrated in vacuum. The resulting crude was purified by silica gel column chromatography using petroleum ether- ethyl acetate (7:3) as the mobile phase to obtain 4 (1.12g, 80%) as a white solid. Characterisation data: ^{1}H NMR (400.13 MHz, Chloroform-d): δ 0.76 (s, 18H), 1.41 (s, 12H), 1.78 (s, 4H), 7.06 (bs, 4H), 7.39 (bs, 5H), 7.6 (bs, 2H), 9.1 (bs, 2H); ^{13}C NMR (100.61 MHz, Chloroform-d): δ 29.70, 30.33, 31.60, 31.77, 32.35, 38.45, 56.91, 76.68, 77.00, 77.32, 110.41, 120.56, 126.95, 140.18, 148.37, 149.20, 166.29; HRMS (Waters Synapt G2): m/z calculated for $C_{51}H_{47}F_{10}N_9O_4$+1: 1040.3612; Found: 1040.3655.

Synthesis of N2,N6-bis(4-chloro-6-(2,6-dibromo-4-(2,4,4-trimethylpentan-2-yl)phenoxy)-1,3,5-triazin-2-yl)pyridine-2,6-diamine (9): To the stirred solution of 4-tertiary-octylphenol (5g, 24.225mmol) in glacial acetic acid (100 mL), Br_2 (6.25 mL, 121.125mmol) was added at room temperature. The reaction mixture was stirred at room temperature for 1h. $NaHSO_3$ (2g) was added at 0 ^{0}C to quench the excess of bromine. The reaction mixture was diluted with CH2Cl2 (3x100mL) and was extracted with water (3x100mL). The organic layer was dried over anhydrous sodium sulphate solution after washing it with brine and concentrated in vacuum. The resulting crude was purified by silica gel column chromatography using petroleum ether- ethyl acetate (95:5) as the mobile phase to obtain **7** (7.94g, 91%) as a white

solid. Characterisation data: 1H NMR (200.13 MHz, Chloroform-d): δ 0.75 (s, 9H), 1.32 (s, 6H), 1.68 (s, 2H), 5.74 (s, 1H), 7.42 (s, 2H).

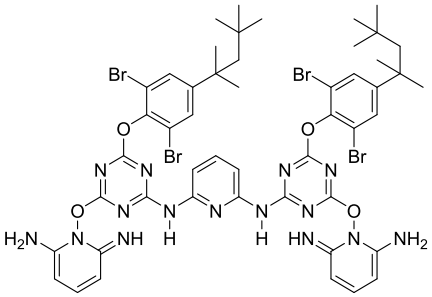


To the stirred solution of **7** (6g, 16.48mmol) in CH_2Cl_2 (100 mL), collidine (2.42 mL, 16.48mmol) was added drop wise at room temperature. This stirred solution was stirred at room temperature for 5 min and then at 0 ^{0}C for 15 min. Then cyanuric chloride (3.4g, 18.12mmol) was added to the above stirred solution at 0 ^{0}C and the reaction mixture was then kept at 0 ^{0}C for 15 min. The reaction mixture was left to come down to room temperature and stirred for 1h.

To this reaction mixture, a solution of 2,6-diaminopyridine (0.6g, 5.46mmol) dissolved in dry THF (30 ml) was added drop wise. DIPEA (4.8 mL, 27.3mmol) was then added drop wise to this stirred reaction mixture at room temperature. The reaction mixture was then stirred at room temperature for 9h. The reaction mixture was diluted with CH_2Cl_2 (2x150mL) and was extracted with water (2x150mL). The organic layer was dried over anhydrous sodium sulphate solution after washing it with brine and concentrated in *vacuum.* The resulting crude was purified by silica gel column chromatography using petroleum ether- ethyl acetate (9:1) as the mobile phase to obtain **9** (4.05g, 70%) as a pale yellow solid. Characterisation data: ^{1}H NMR (200.13 MHz, Chloroform-*d*): δ 0.80 (s, 18H), 1.40 (s, 12H), 1.75 (s, 4H), 7.37 (s, 1H), 7.43 (s, 1H), 7.58 (s, 5H), 9.5 (bs, 2H); ^{13}C NMR (100.61 MHz, Chloroform-*d*): δ 29.92, 31.30, 31.94, 32.50, 38.88, 56.81, 111.18, 116.71, 130.42, 144.09, 148.94, 151.95, 165.03, 172.19; MALDI-TOF: m/z calculated for $C_{39}H_{43}Br_4Cl_2N_9O_2$+1: 1061.3523 ; Found: 1061.6650.

Synthesis of N2,N6-bis(4-((6-amino-2-iminopyridin-1(2H)-yl)oxy)-6-(2,6-dibromo-4-(2,4,4-trimethylpentan-2-yl)phenoxy)-1,3,5-triazin-2-yl)pyridine-2,6-diamine (13): To a stirred solution of 2,6-diaminopyridine (5g, 45.8mmol) in dry THF (50 mL), LiHMDS (150 mL, 183.25 mmol) solution in 1M THF was added drop wise

at 0 ^{0}C and kept for 15 min. To the above stirred solution, Di-*tert*-butyl dicarbonate (31.57 mL, 137.4 mmol) was added drop wise at 0 ^{0}C. The reaction mixture was then stirred at 0 ^{0}C for 15 min, then it was refluxed in THF for 18 h. . The reaction mixture was diluted with ethyl acetate (2x100mL) and was extracted with water (2x100mL). The organic layer was dried over anhydrous sodium sulphate solution after washing it with brine and concentrated in *vacuum.* The resulting crude was purified by silica gel column chromatography using petroleum ether- ethyl acetate (95:5) as the mobile phase to obtain **10** (9.35g, 66%) as a white solid. Characterisation data: ^{1}H NMR (200.13 MHz, Chloroform-*d*): δ 1.52 (s, 18H), 7.59 (m, 3H), 7.7 - 7.9 (bs, 2H)

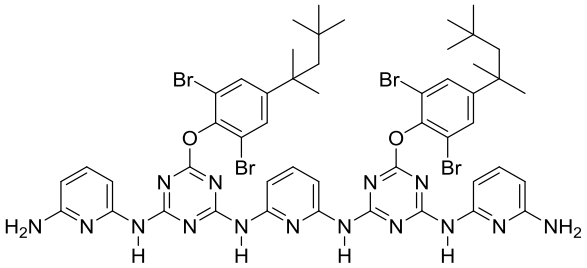


To a stirred solution of **10** (8g, 25.86 mmol) in dry chloroform (150 mL), m-CPBA (9g, 52.15 mmol) was added at 0 ^{0}C. The reaction mixture was stirred at 0 ^{0}C for 15 min and then stirred at room temperature for 2 h. The reaction mixture was diluted with CH_2Cl_2 (2x150mL) and was extracted with saturated NaHCO3 solution (2x150mL). The organic layer was dried over anhydrous sodium sulphate solution and concentrated in *vacuum.* The resulting crude was purified by silica gel column chromatography using petroleum ether- ethyl acetate (4:1) as the mobile phase to obtain **11** (7.74g, 92%) as a white solid. Characterisation data: ^{1}H NMR (400.13 MHz, Chloroform-*d*): δ 1.55 (s, 18H), 7.29 (s, 1H), 7.75 (d, *J* = 8.6 Hz, 2H), 9.16 (s, 2H); ^{13}C NMR (100.61 MHz, Chloroform-*d*): δ 28.12, 82.23, 104.77, 128.76, 142.86, 151.38.

To a stirred solution of **11** (2g, 6.148 mmol) in dry CH_2Cl_2 (100 mL), TFA (4 mL, 18.44 mmol) was added drop wise at room temperature and the reaction mixture was stirred at room temperature for 30 min. Then the above reaction mixture was kept at 0 ^{0}C and DIPEA (6.98 mL, 20.49 mmol) was added drop wise at 0 ^{0}C and stirred for 15 min. To the above stirred solution, **9** (2.17g, 2.05 mmol) was added and the reaction mixture was stirred at room temperature for 1 h. The reaction mixture

was diluted with CH_2Cl_2 (2x100mL) and was extracted with water (2x100mL). The organic layer was dried over anhydrous sodium sulphate solution after washing it with brine and concentrated in *vacuum.* The resulting crude was purified by silica gel column chromatography using ethyl acetate - methanol (95:5) as the mobile phase to obtain **13** (1.78g, 70%) as a white solid. Characterisation data: ^{1}H NMR (400.13 MHz, DMSO-d6): δ 0.76 (s, 18H), 1.38 (s, 12 H), 1.76 (s, 4H), 6.47 (d, *J* = 8.1 Hz, 2H), 6.94 (bs, 6H), 7.45 (bs, 4H), 7.76 (s, 5H), 10.04 (bs, 2H), 10.52 (bs, 2H) ; ^{13}C NMR (100.61 MHz, DMSO-d6): 30.96, 31.64, 32.13, 38.61, 55.82, 101.74, 116.74, 130.26, 141.47, 143.91, 149.09, 149.90, 151.47, 163.93, 169.35; MALDI-TOF m/z calculated for $C_{49}H_{55}Br_4N_{15}O_4K$+1: 1273.1312; Found: 1273.6968.

Synthesis of N2,N2'-(pyridine-2,6-diyl)bis(N4-(6-aminopyridin-2-yl)-6-(2,6-dibromo-4-(2,4,4-trimethylpentan-2-yl)phenoxy)-1,3,5-triazine-2,4-diamine) (15):

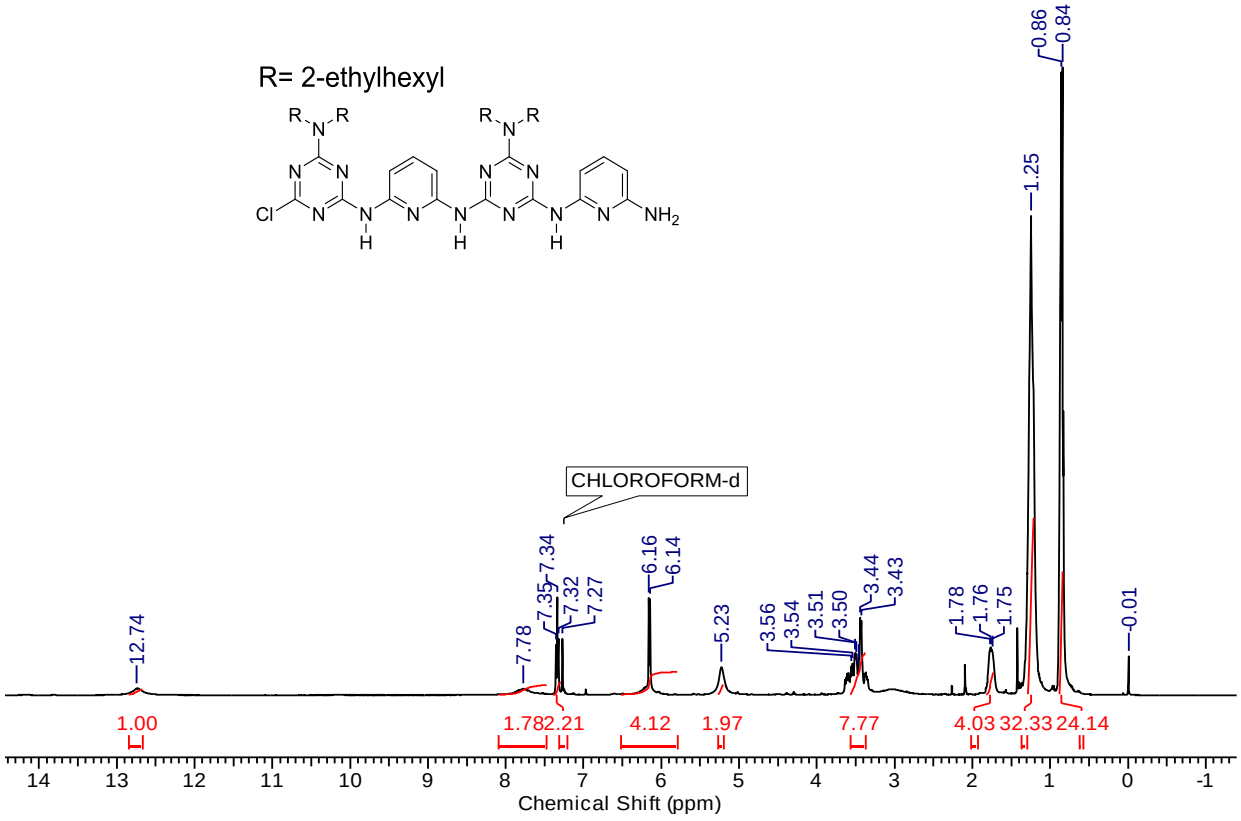


To a stirred solution of NMP (10 mL), 13 (0.5g, 0.404 mmol) was added and the reaction mixture was exposed to microwave irradiation at 700W and refluxed for 5 min. The reaction mixture was diluted with ethyl acetate (3x30mL) and was extracted with water (3x50mL). The organic layer was dried over anhydrous sodium sulphate solution after washing it with brine and concentrated in vacuum. The resulting crude was purified by silica gel column chromatography using pet ether – ethyl acetate (2:3) as the mobile phase to obtain **15** (0.248g, 51%) as a white solid. Characterisation data: ^{1}H NMR (400.13 MHz, DMSO-d6): δ 0.77 (s, 18H), 1.38 (s, 12H), 1.76 (s, 4H), 5.74 (bs, 4H), 6.13 (d, J= 7.8 Hz, 2H), 7.14 (bs, 4H), 7.4 (bs, 2H), 7.74 (s, 5H), 9.62 (bs, 2H), 9.76 (bs, 2H); ^{13}C NMR (100.61 MHz, DMSO-d6): 30.98, 31.67, 32.14, 55.77, 69.76, 116.93, 130.13, 144.14, 149.98, 150.02, 151.22, 158.42, 164.83, 169.09; MALDI-TOF m/z calculated for $C_{49}H_{55}Br_4N_{15}O_2$: 1205.70; Found: 1205.6931.

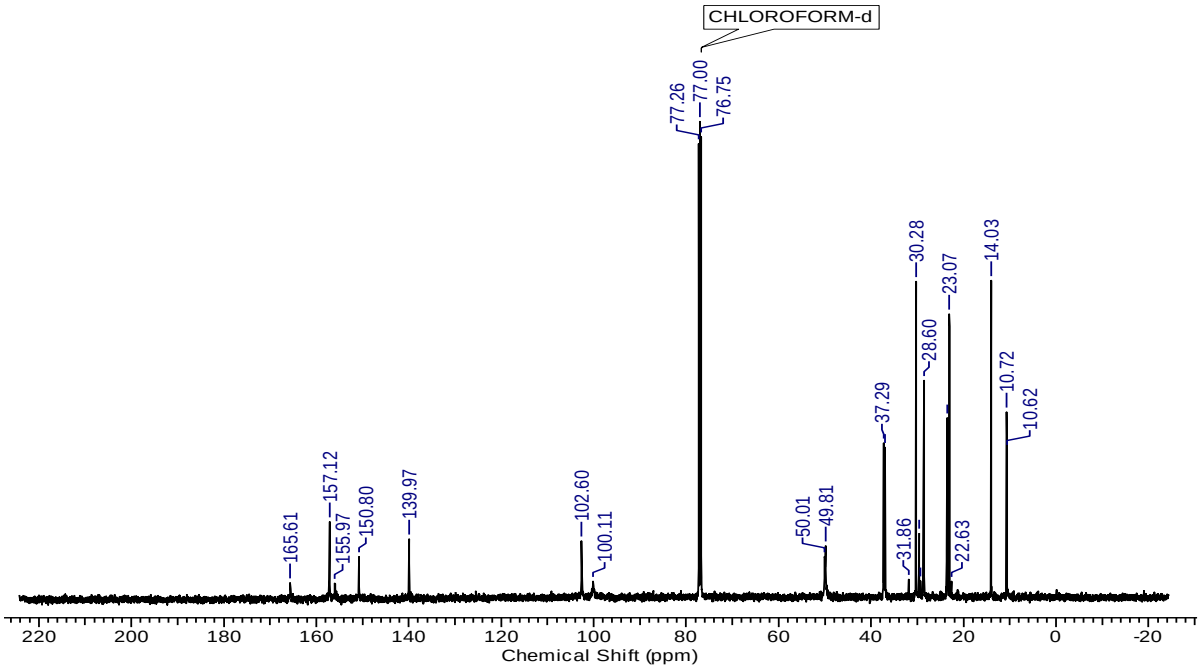
Conclusion

In conclusion, this brief study has opened up ways to realize the objective of developing multi-coded self-assembling motifs containing alternating 1,3,5-triazine and 2,6-diaminopyridine building blocks. These self-assembling motifs will be valuable intermediates for the formation of a fully extended programmed molecular self-assembly. These intermediates feature pre-organized alternate acceptor (A) and donor (D) sites in the form of N and N-H codes, respectively. Due to the presence of these acceptor and donor sites, these intermediates have the potential to form self-complimentary H-bonded duplexes. During the course of this study, we also came up with a novel reaction in which rearrangement and deoxygenation happen in one step, resulting in a multi-coded recognition motif which has alternate arrangement of 5 acceptor sites (N) and 6 donor sites (N-H).

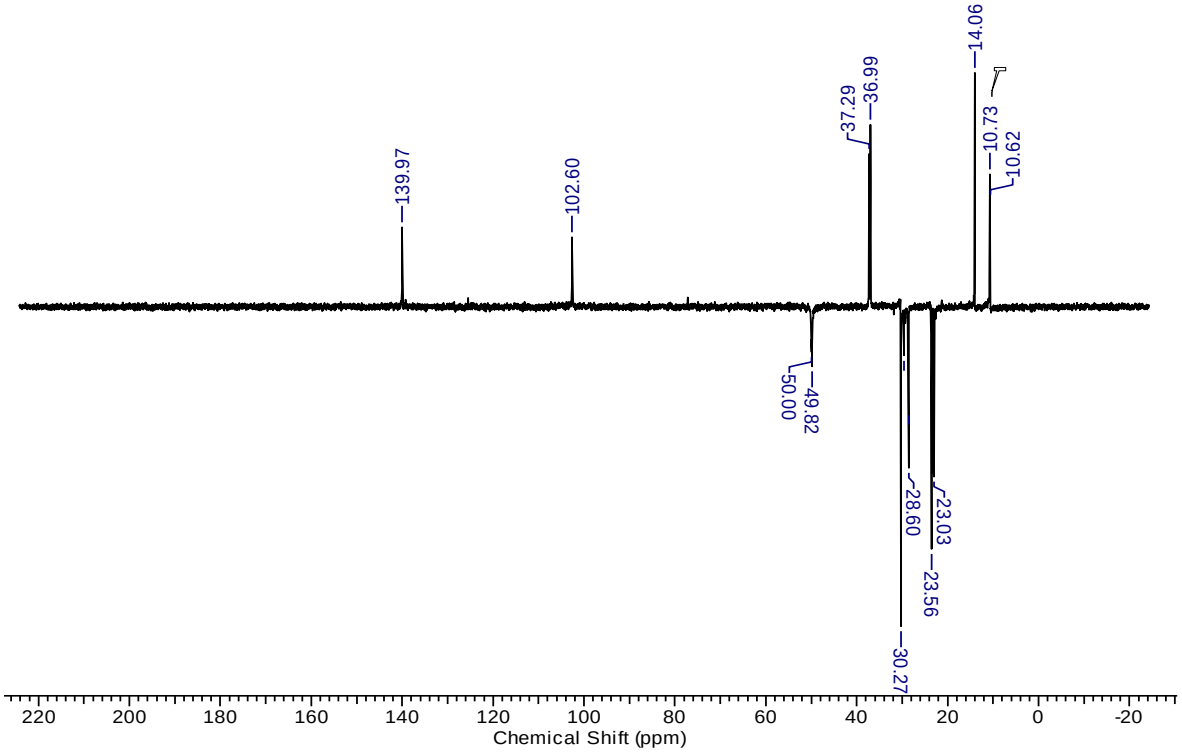
^{1}H NMR Spectrum (500.13MHz, $CDCl_3$) of Compound **3**



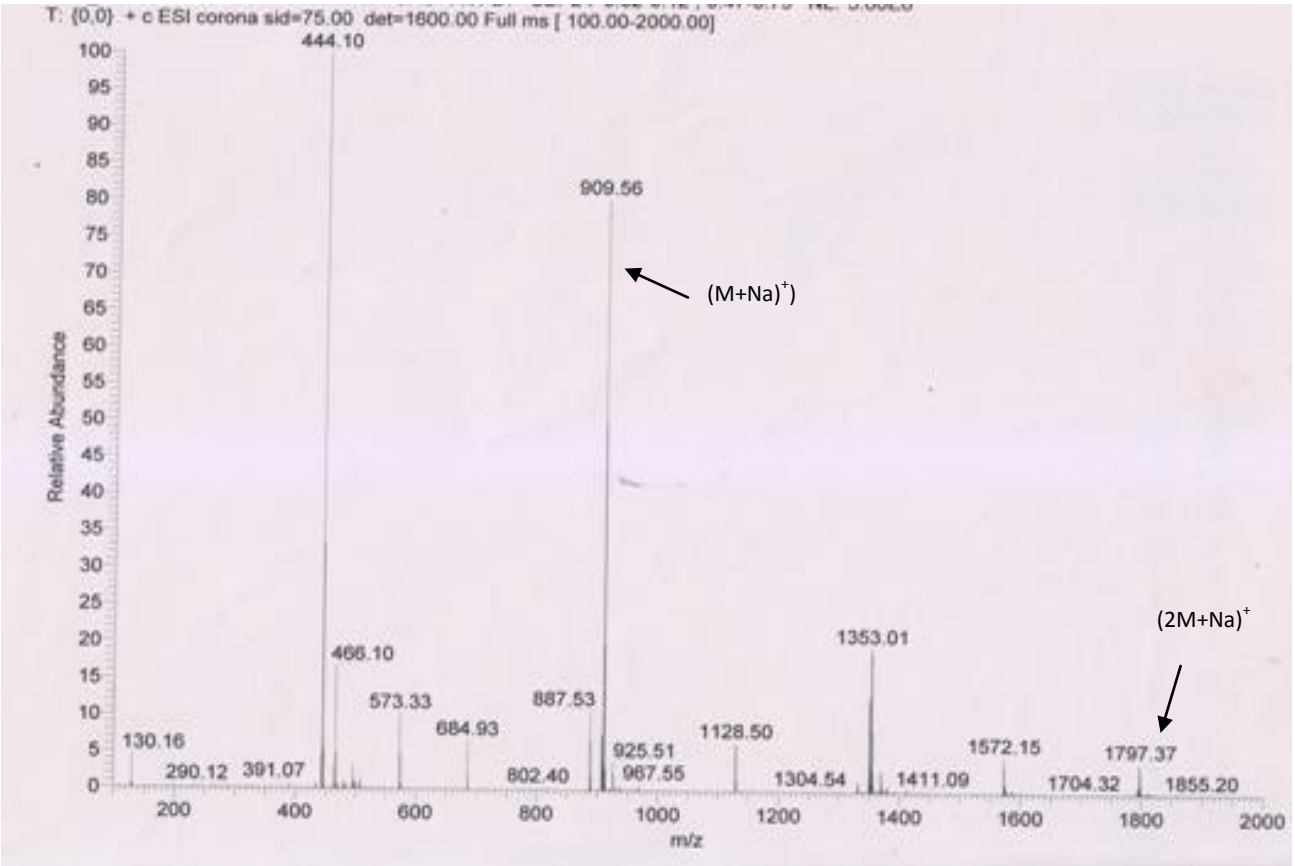
^{13}C NMR Spectrum (125.76MHz, $CDCl_3$) of Compound **3**



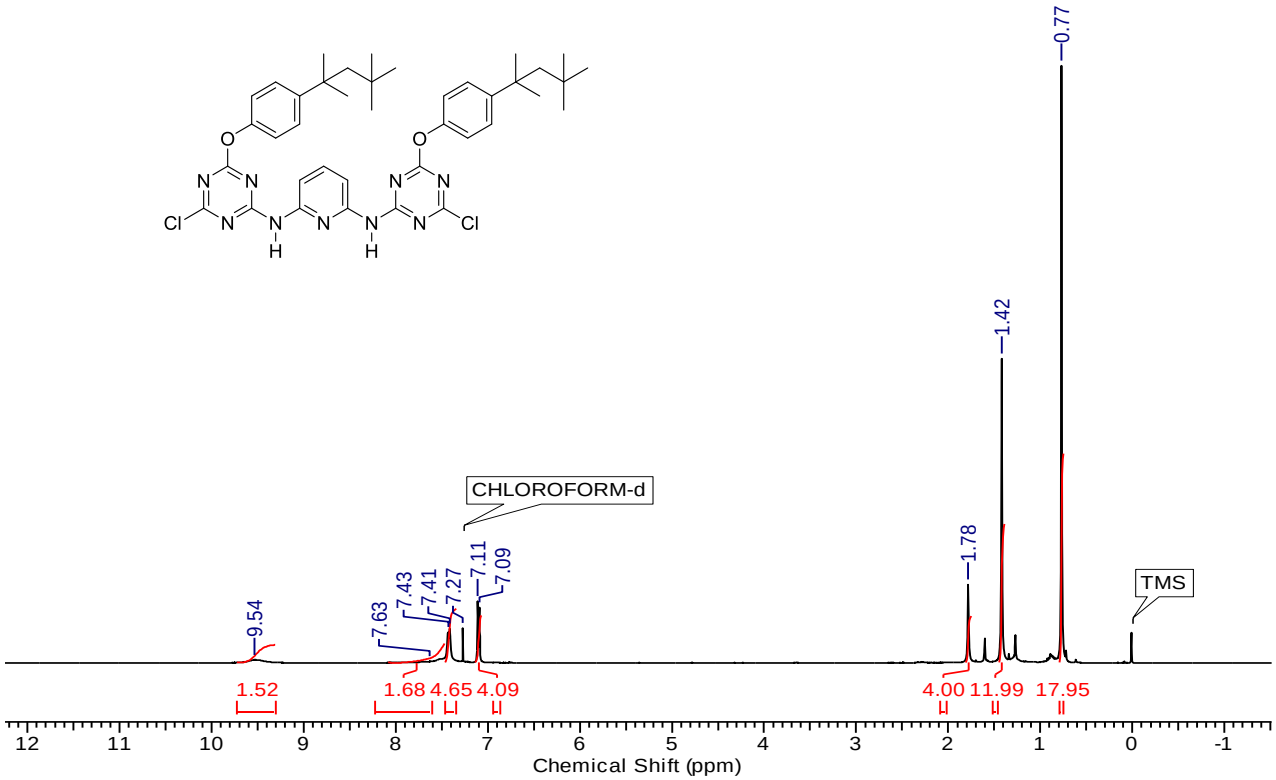
DEPT NMR Spectrum (125.76MHz, $CDCl_3$) of Compound **3**



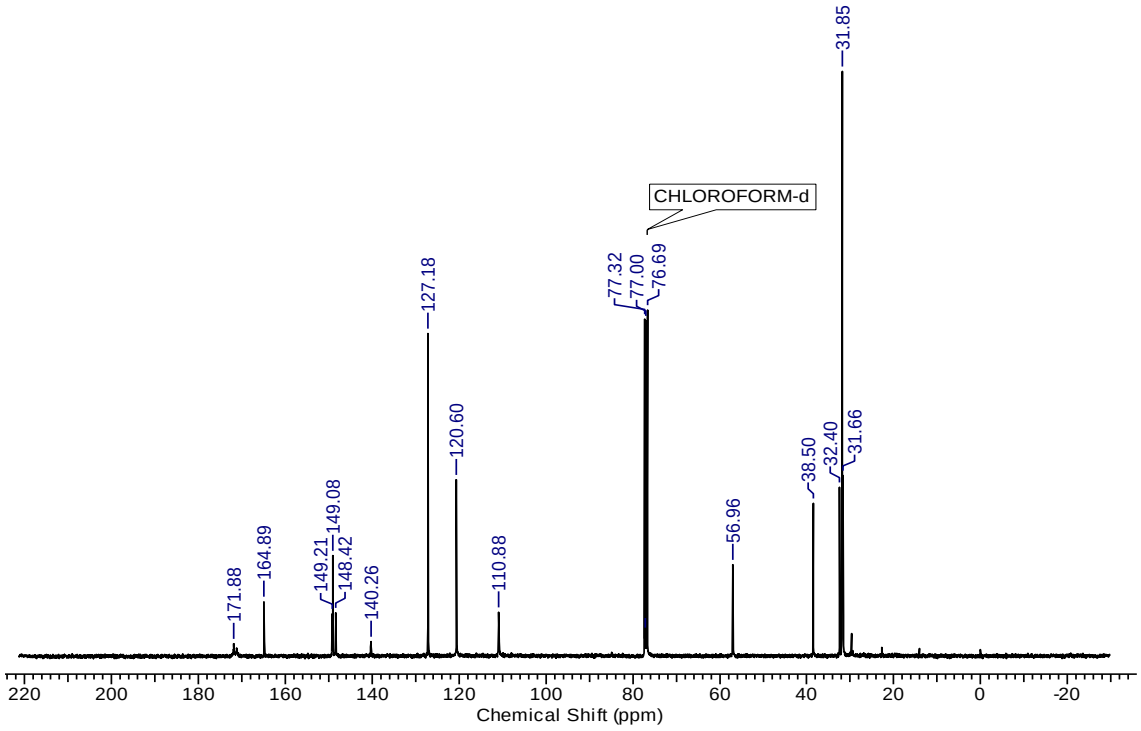
ESI-MS for Compound **3**



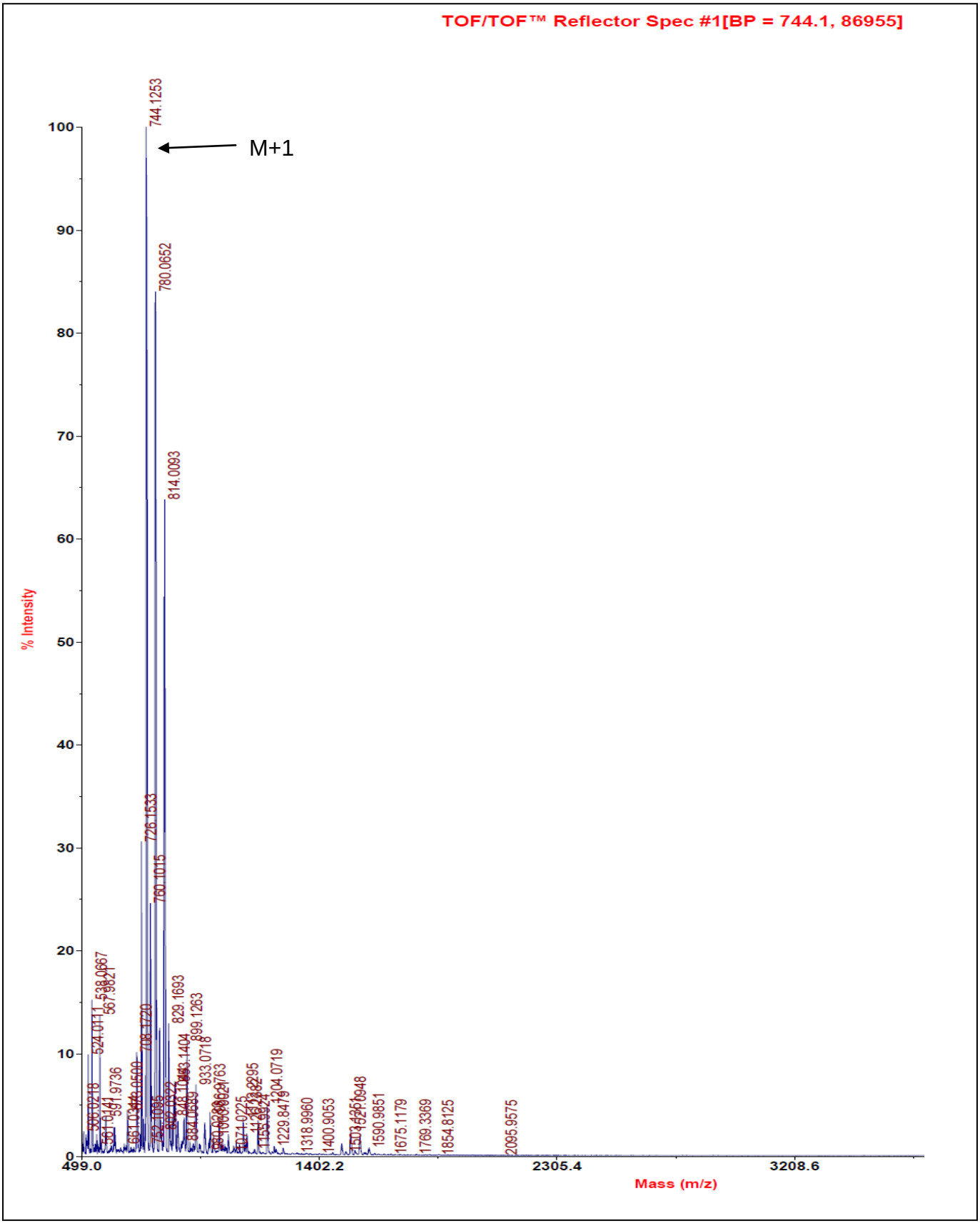
^{1}H NMR Spectrum (400.13MHz, $CDCl_3$) of Compound **5**



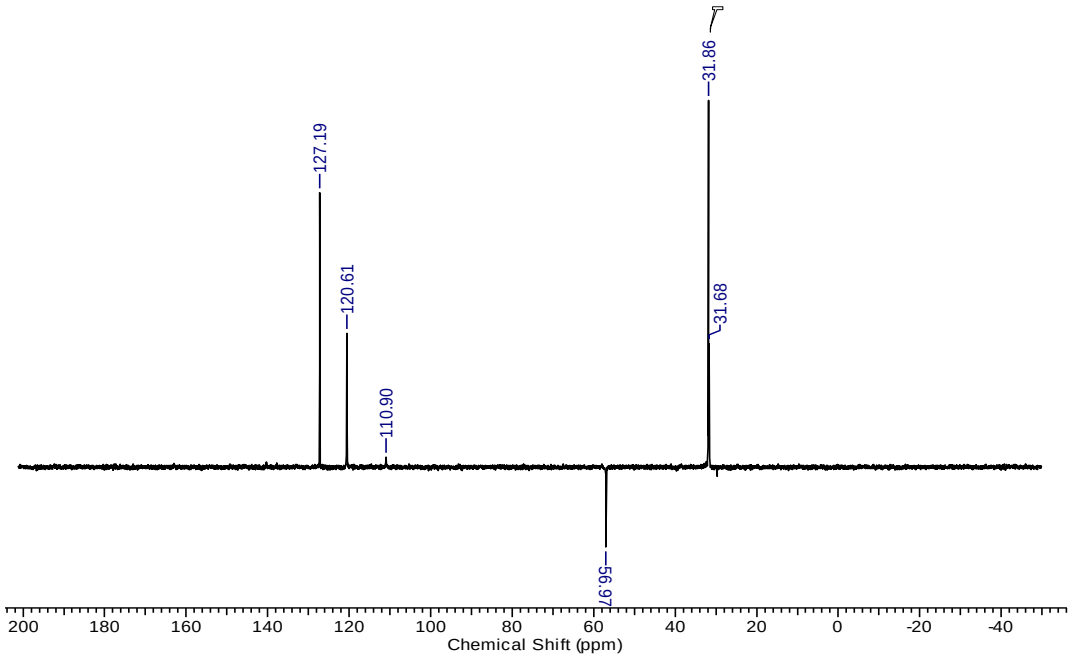
^{13}C NMR Spectrum (100.61MHz, CDCl3) of Compound **5**



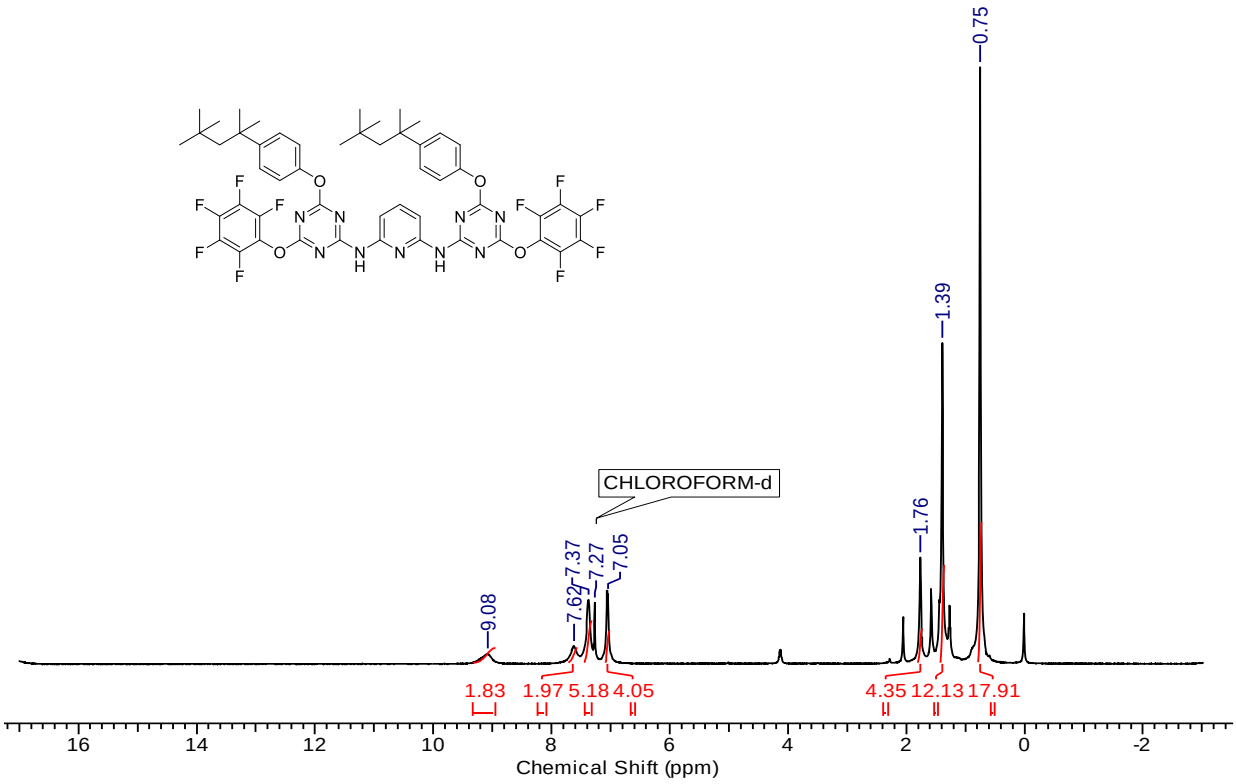
MALDI-TOF of Compound **5**



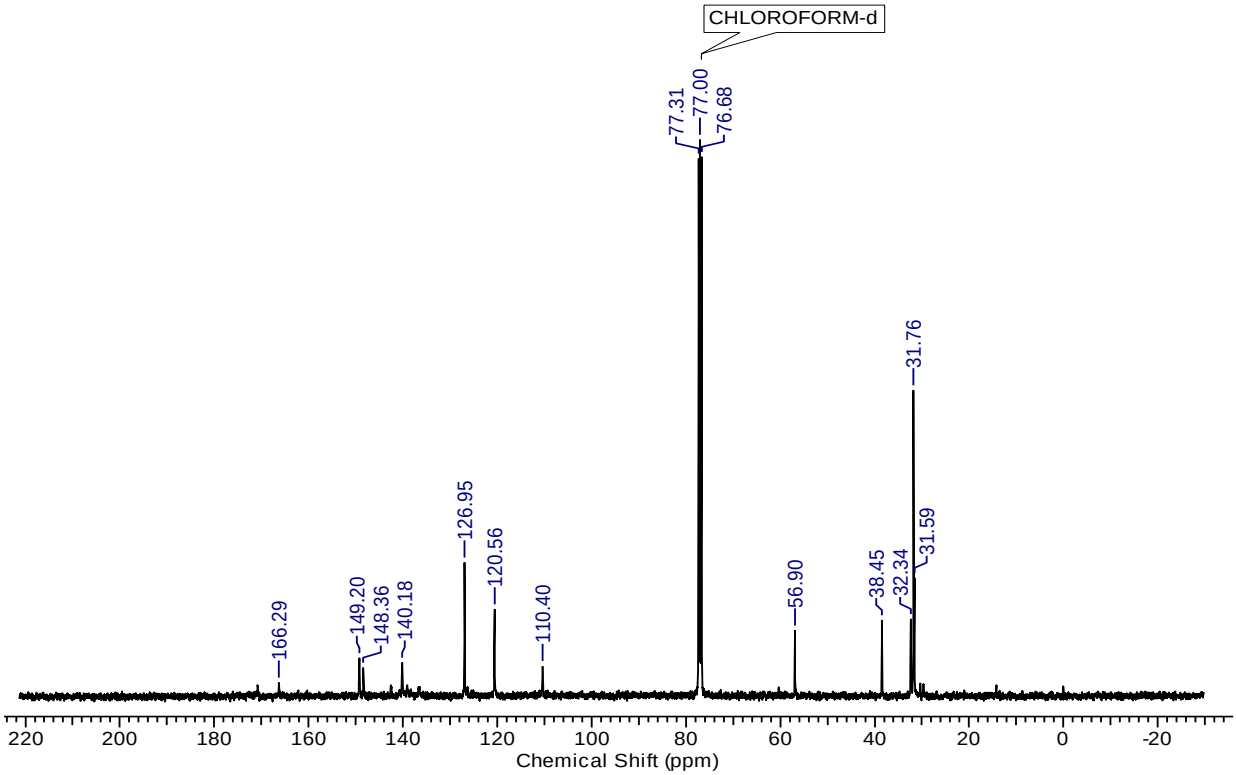
DEPT NMR Spectrum (100.61MHz, $CDCl_3$) of Compound **5**



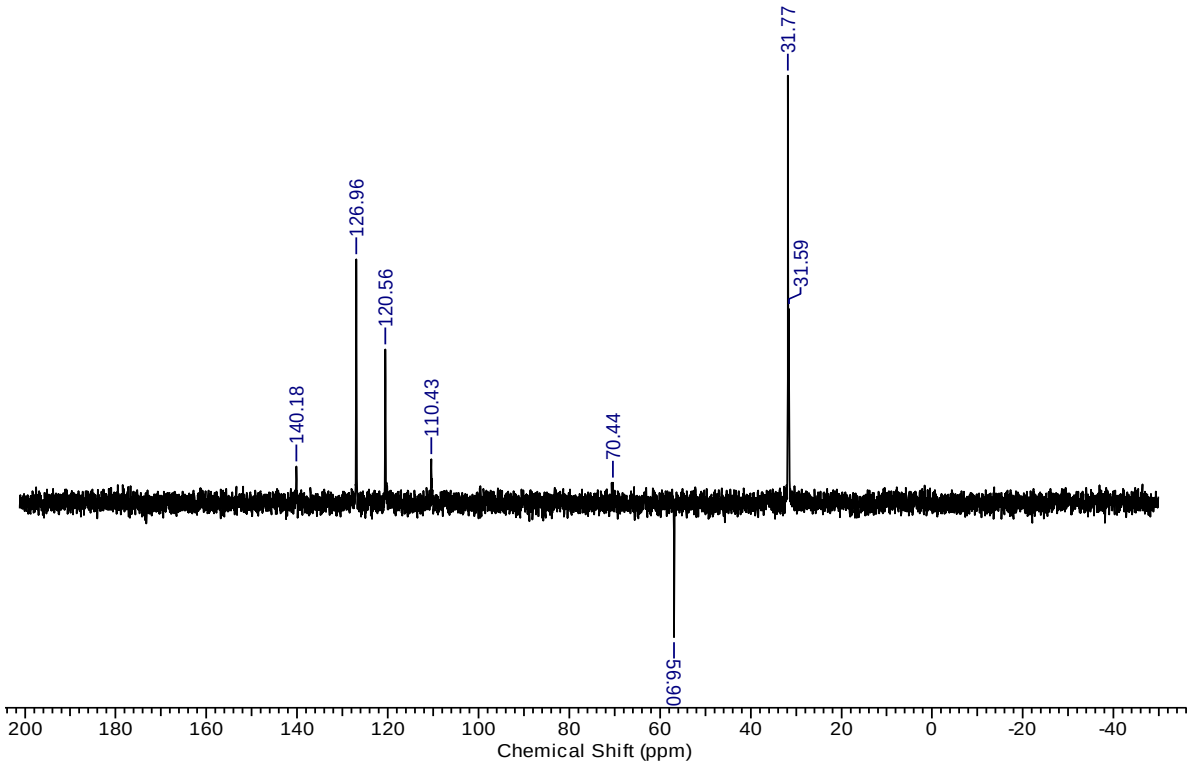
^{1}H NMR Spectrum (400.13MHz, CDCl3) of Compound **6**



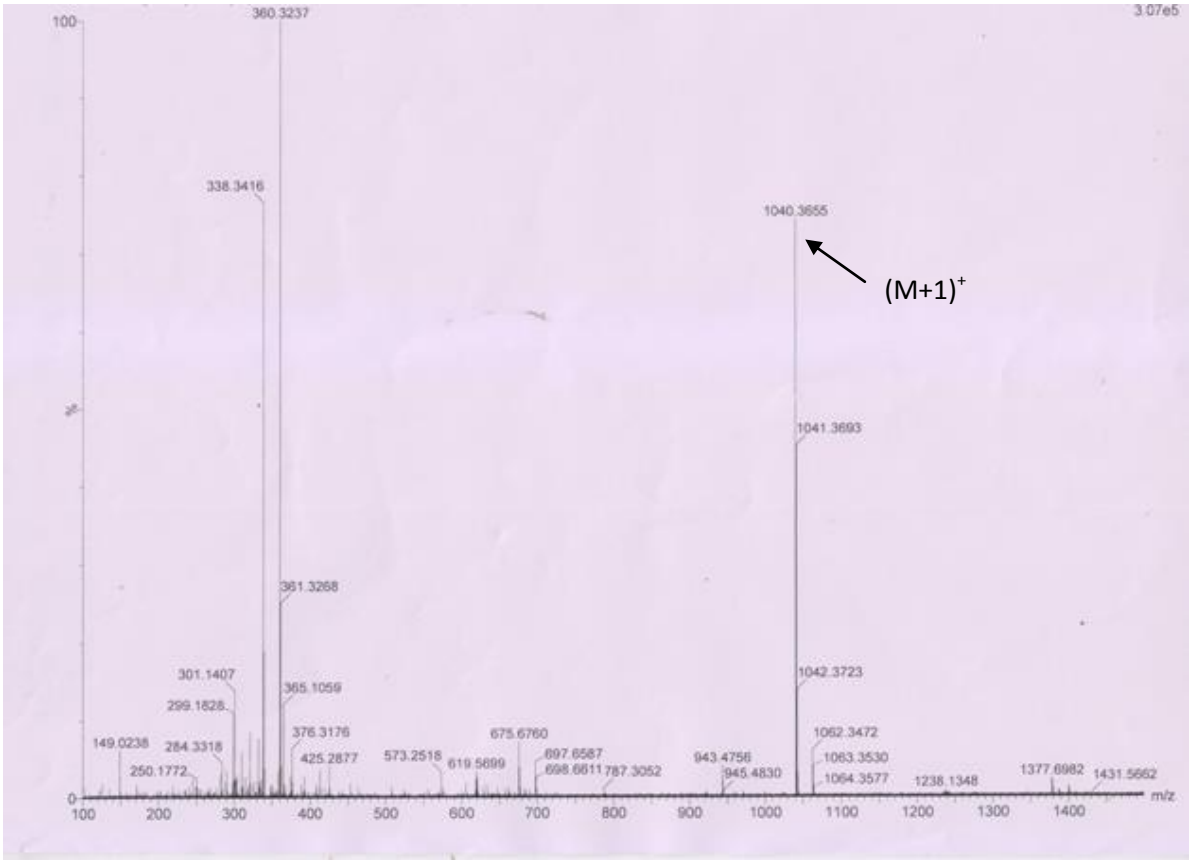
^{13}C NMR Spectrum (100.61MHz, CDCl3) of Compound **6**



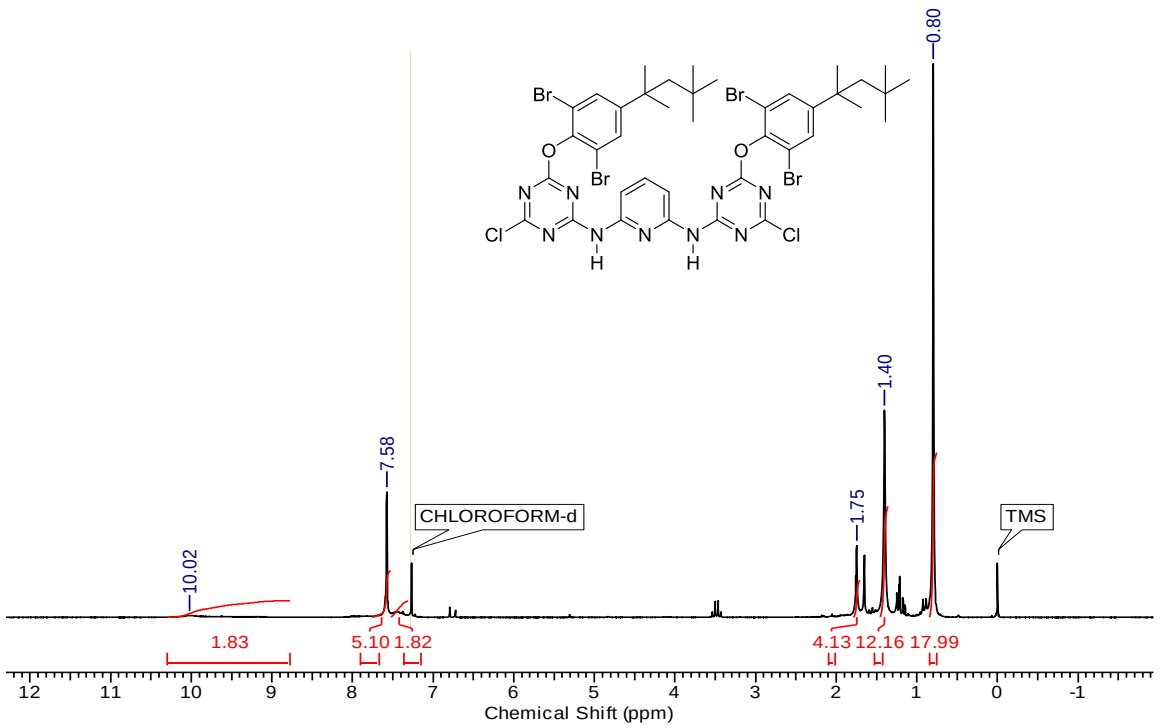
DEPT NMR Spectrum (100.61MHz, $CDCl_3$) of Compound **6**



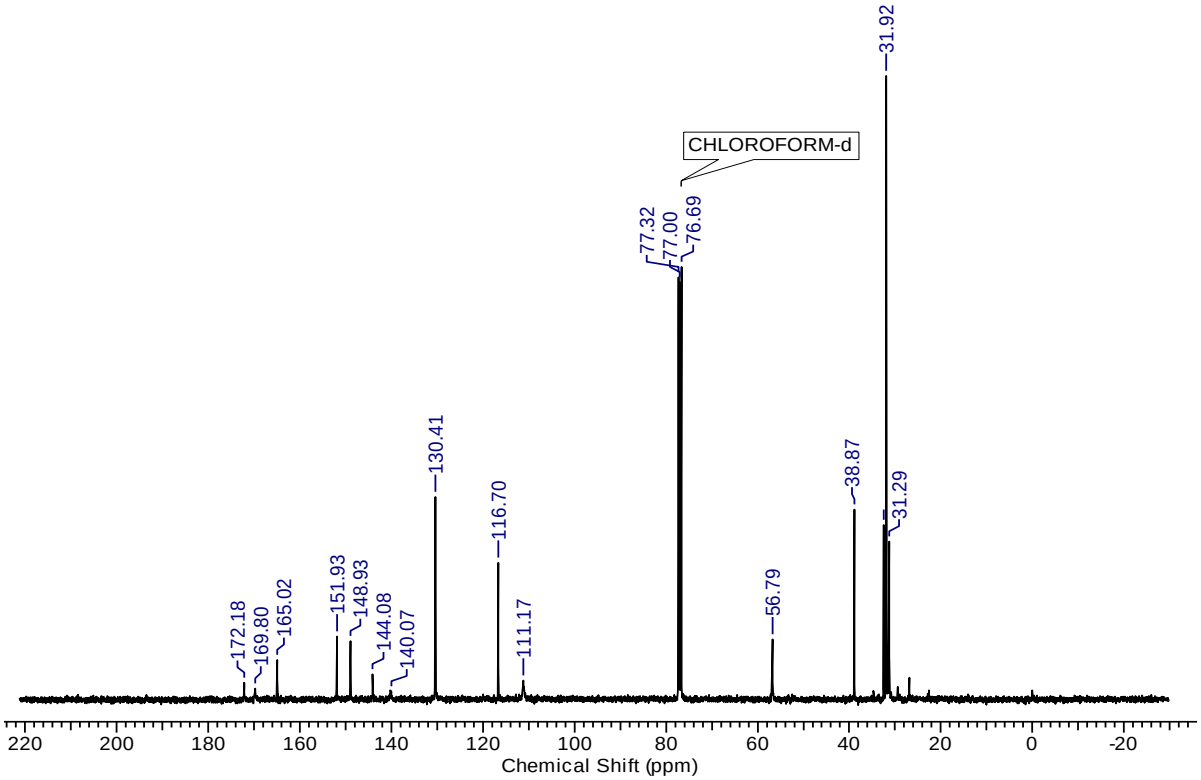
ESI-MS of Compound **6**



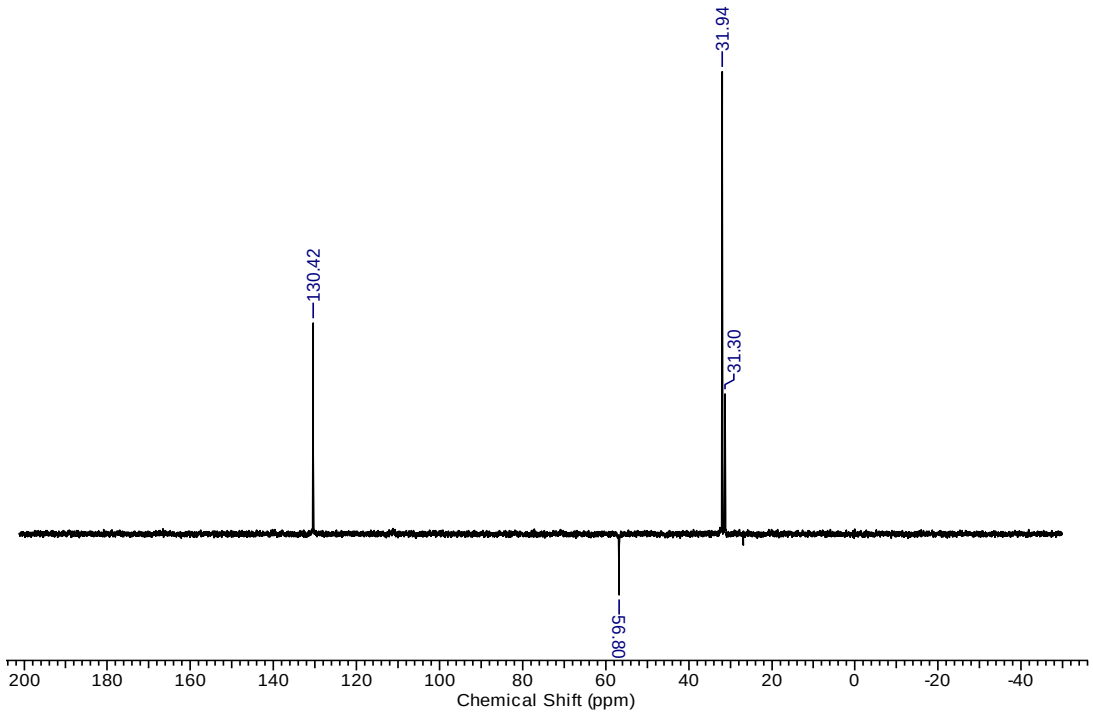
^{1}H NMR Spectrum (400.13MHz, CDCl3) of Compound **9**



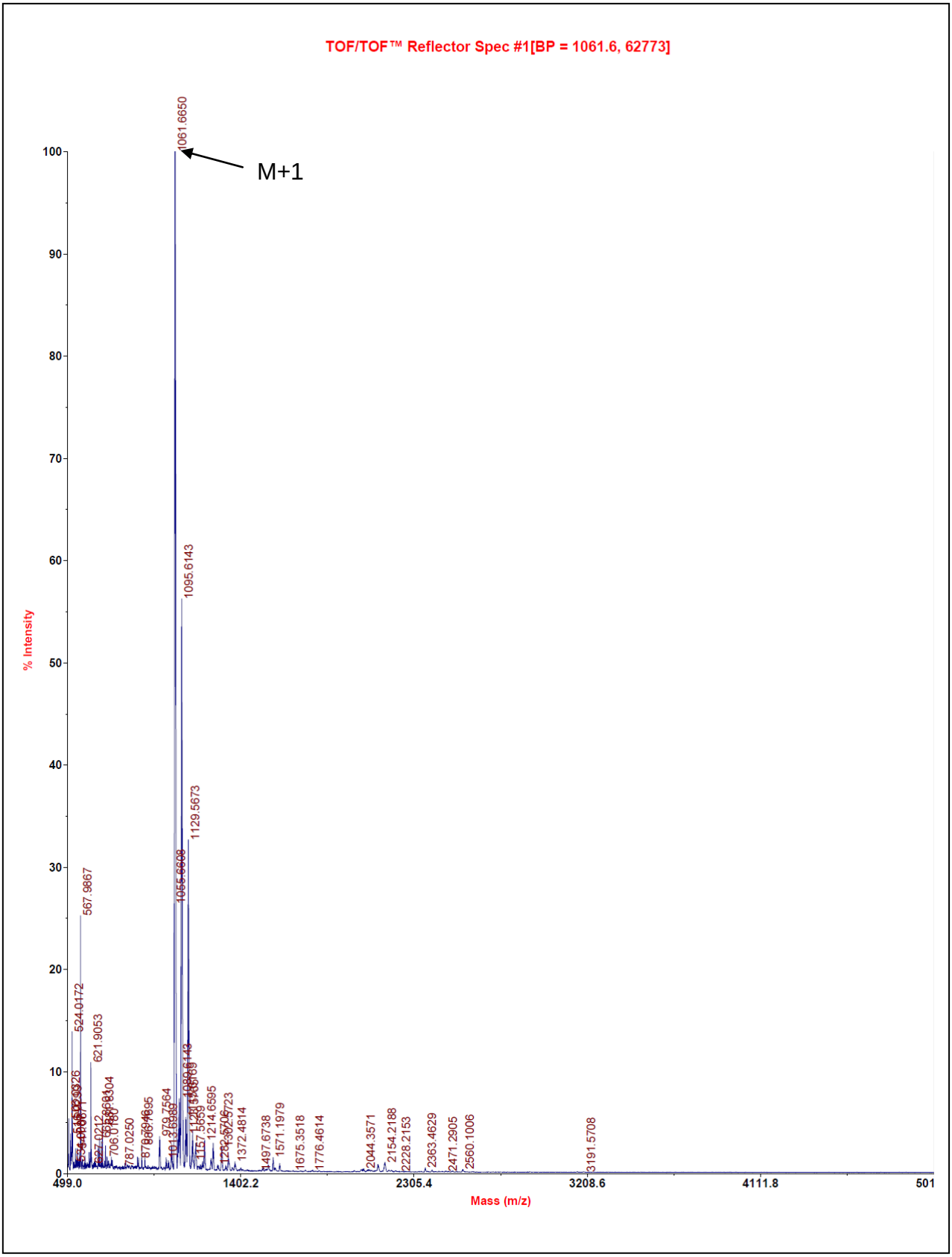
^{13}C NMR Spectrum (100.61MHz, CDCl3) of Compound **9**



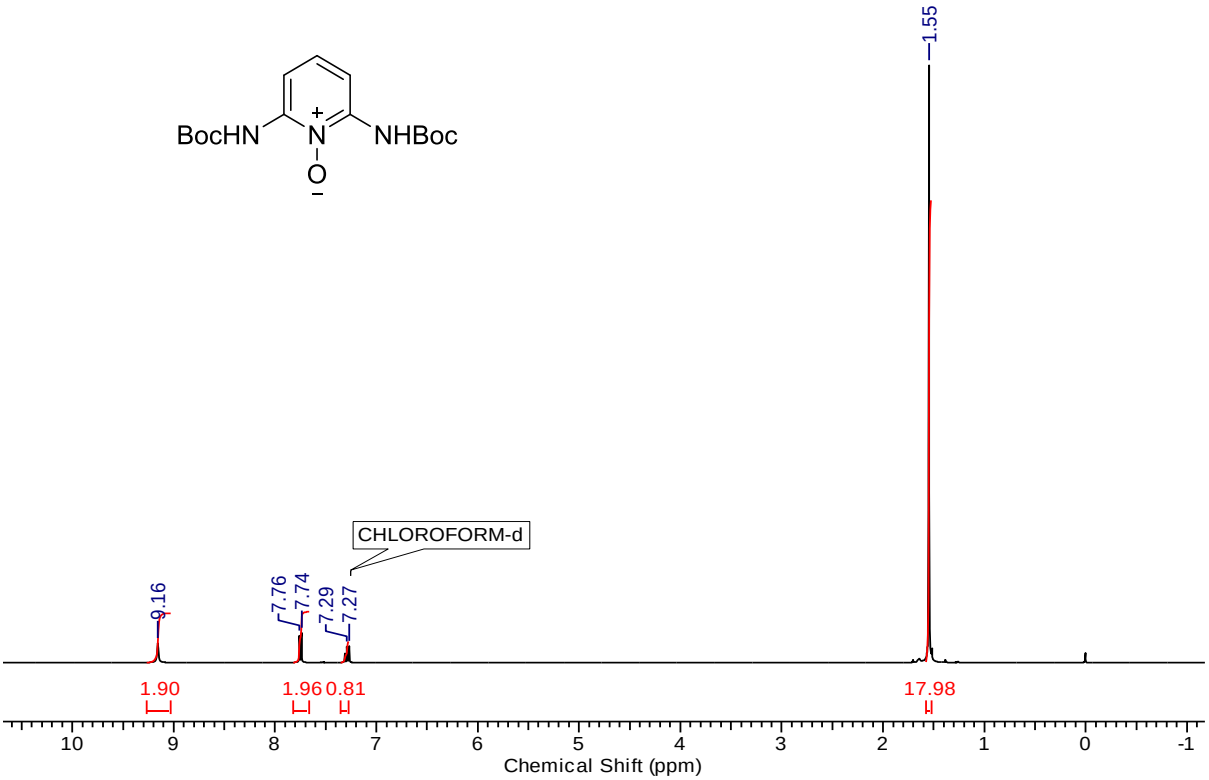
DEPT NMR Spectrum (100.61MHz, $CDCl_3$) of Compound **9**



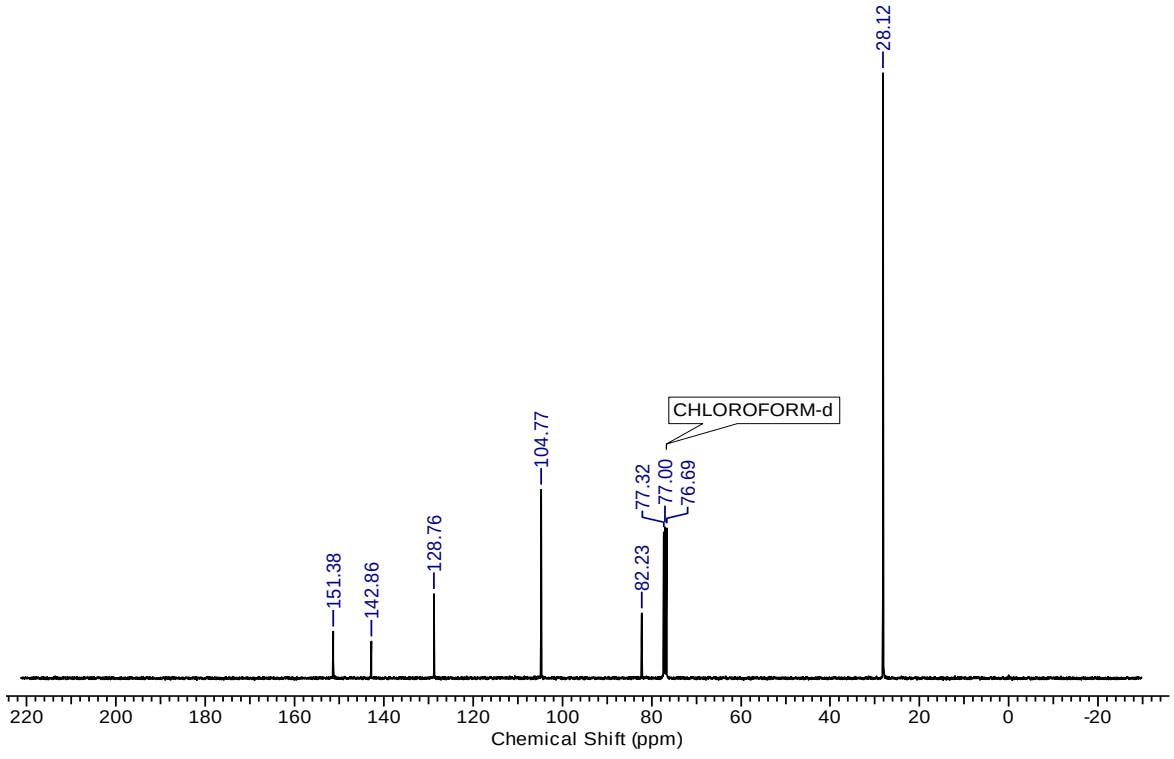
MALDI-TOF of Compound **9**



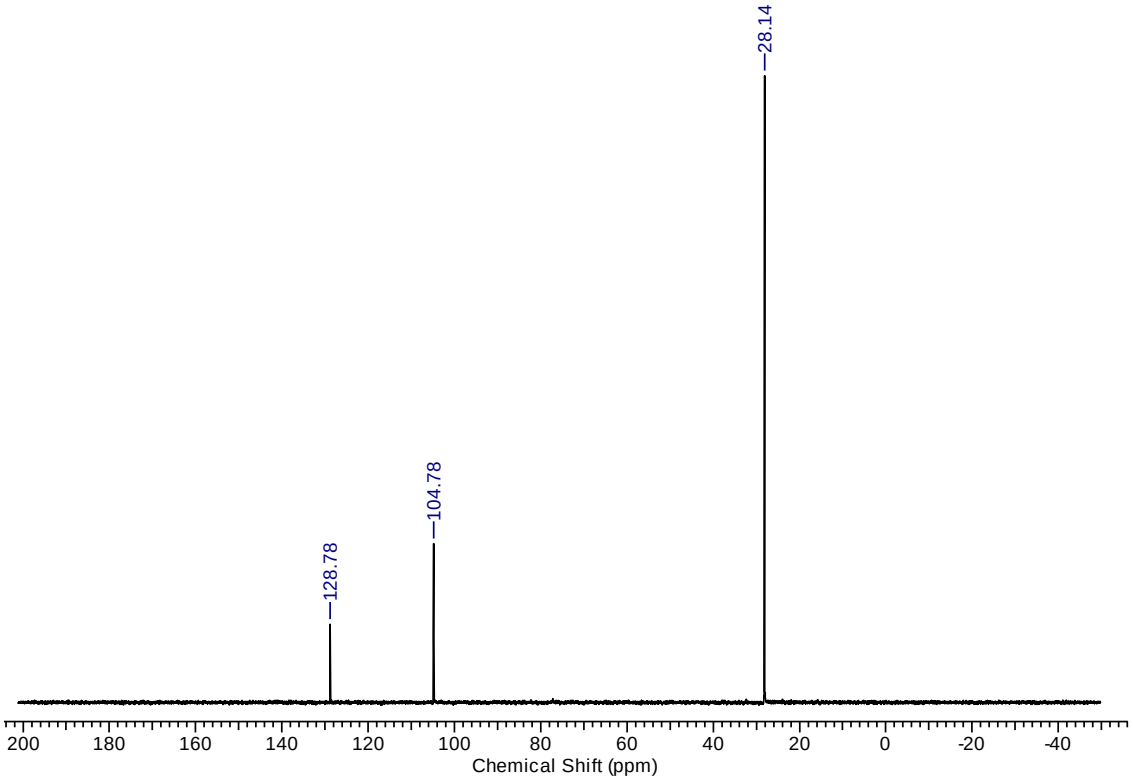
^{1}H NMR Spectrum (400.13MHz, CDCl3) of Compound **11**



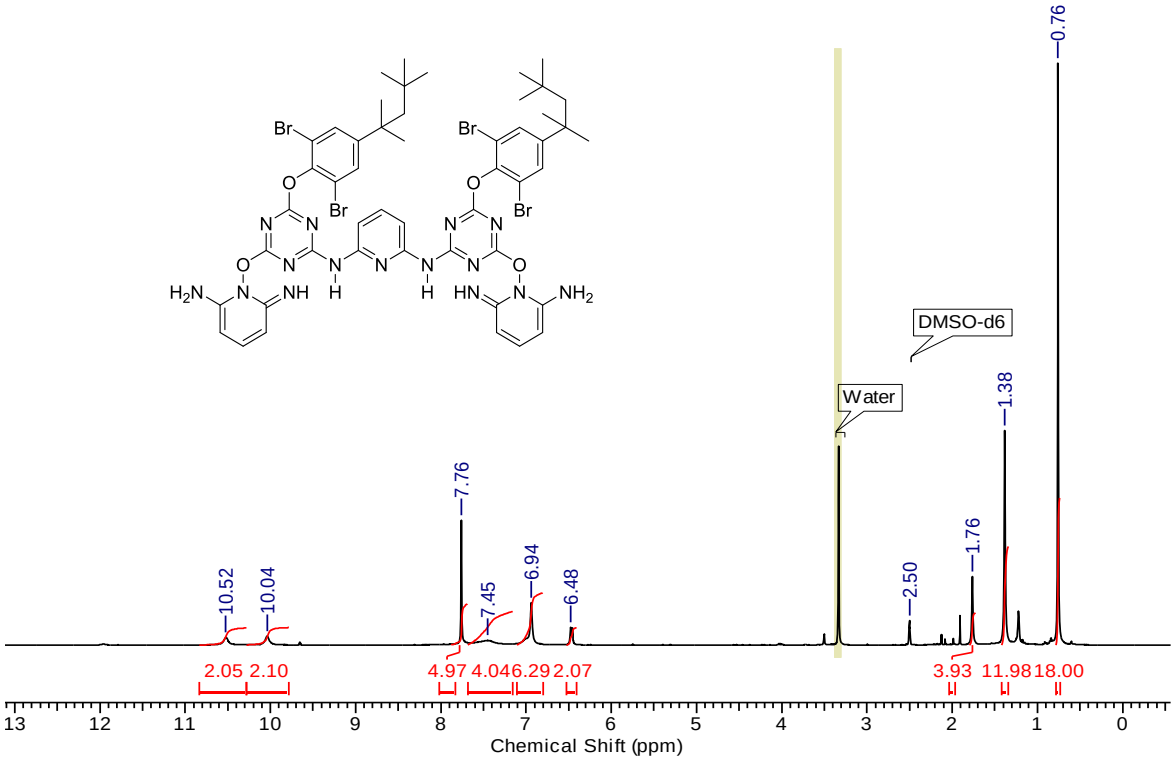
^{13}C NMR Spectrum (100.61MHz, CDCl3) of Compound **11**



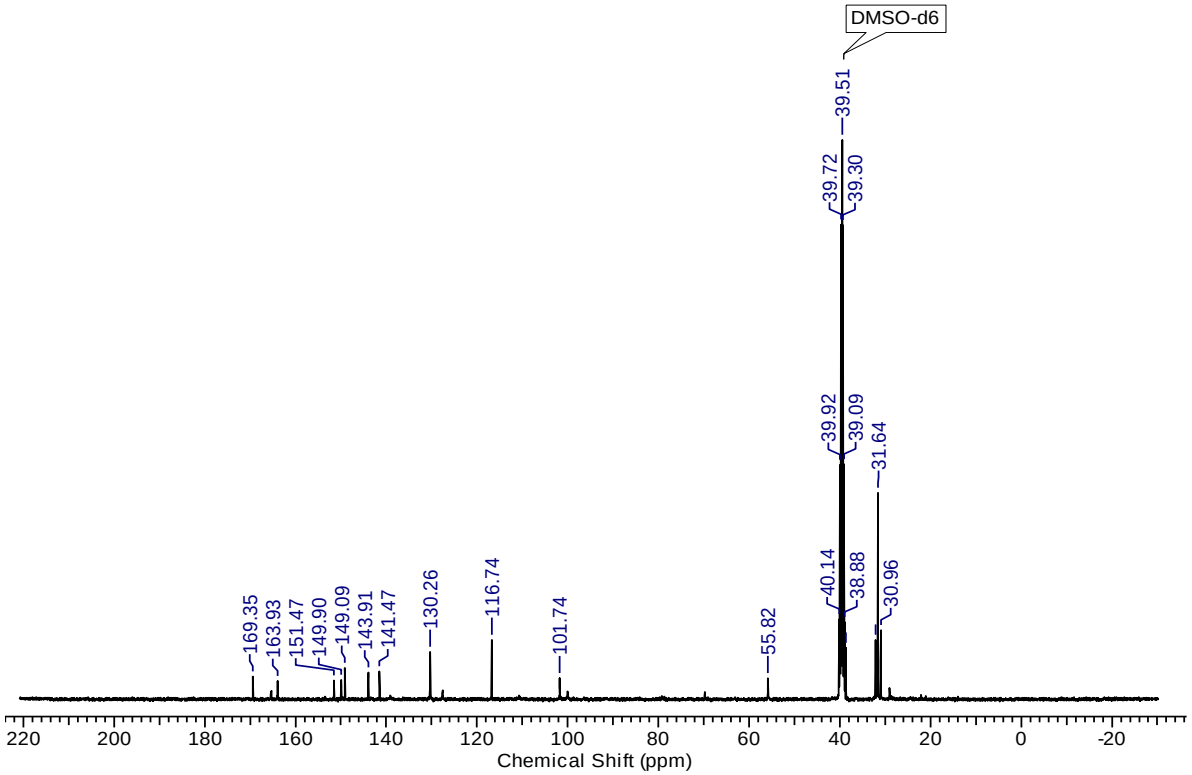
DEPT NMR Spectrum (100.61MHz, $CDCl_3$) of Compound **11**



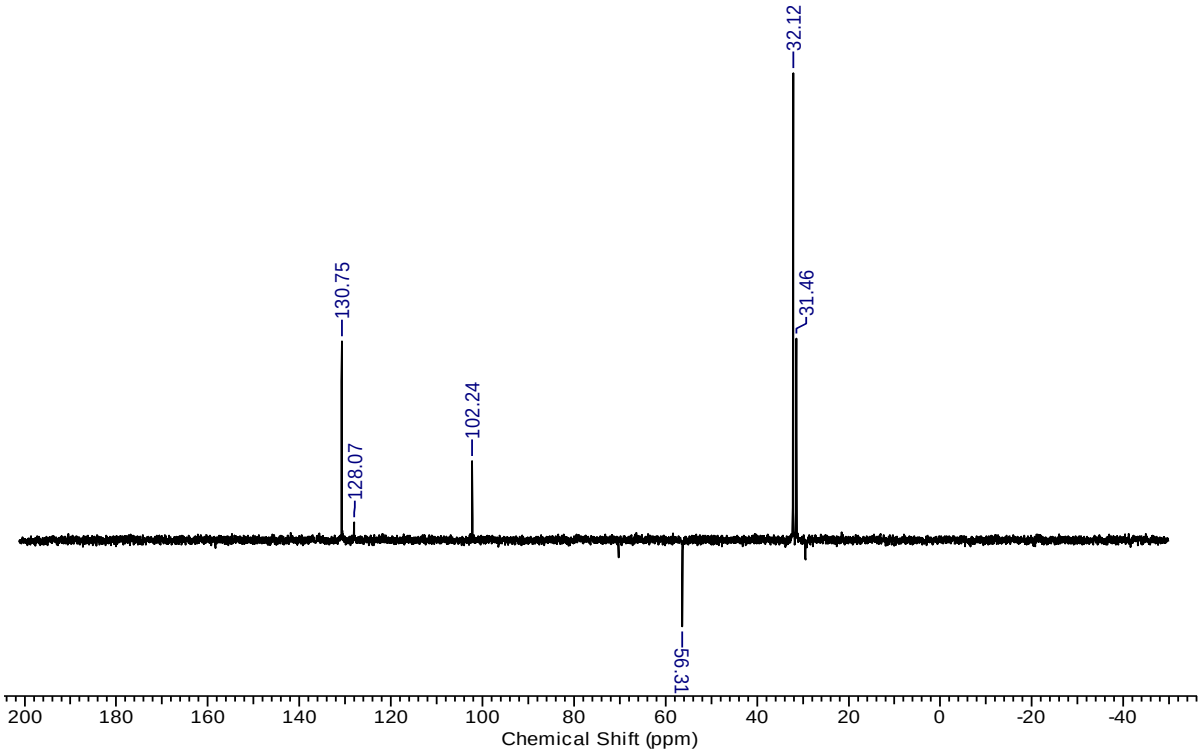
^{1}H NMR Spectrum (400.13MHz, DMSO-d6) of Compound **13**



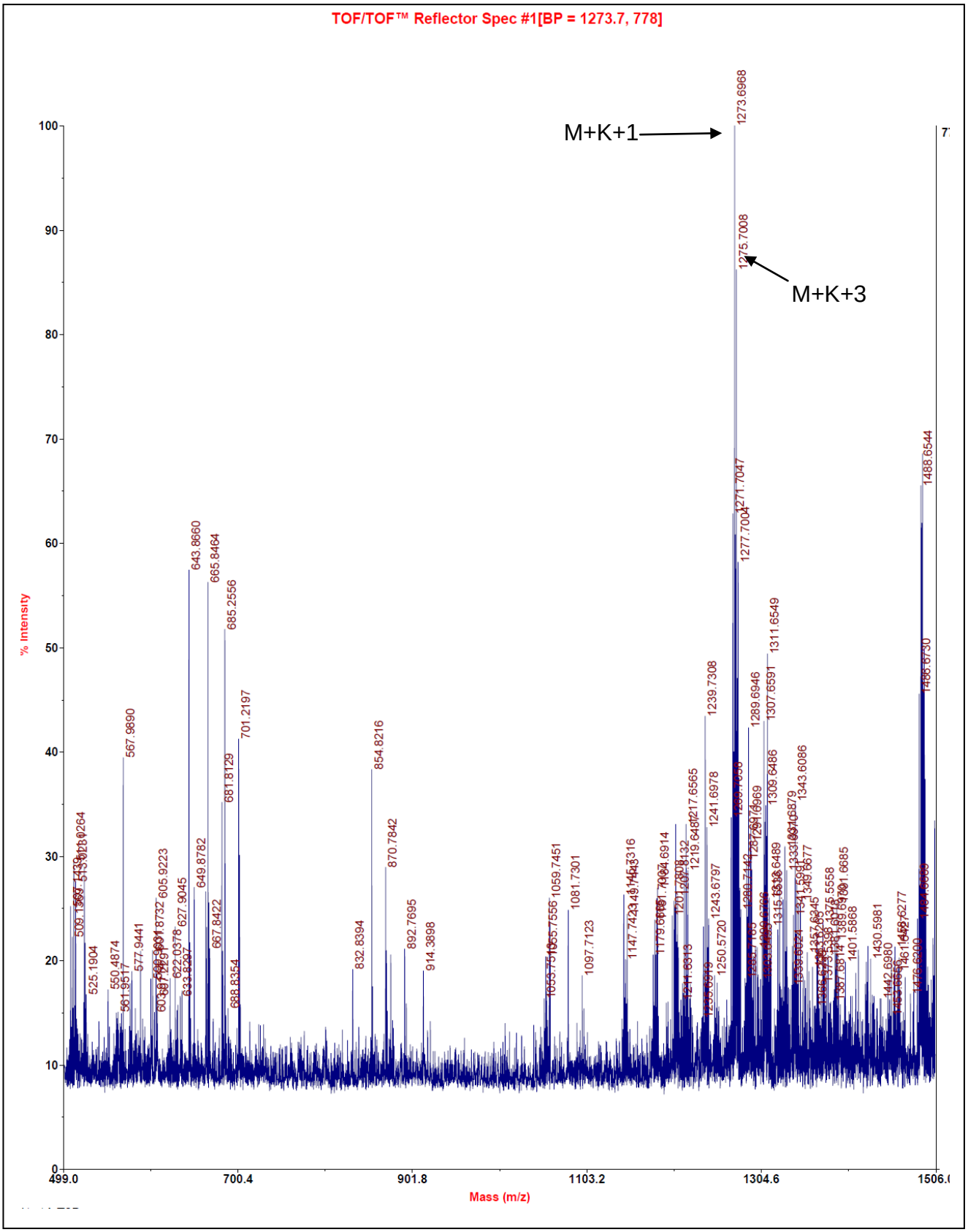
^{13}C NMR Spectrum (100.61MHz, DMSO-d6) of Compound **13**



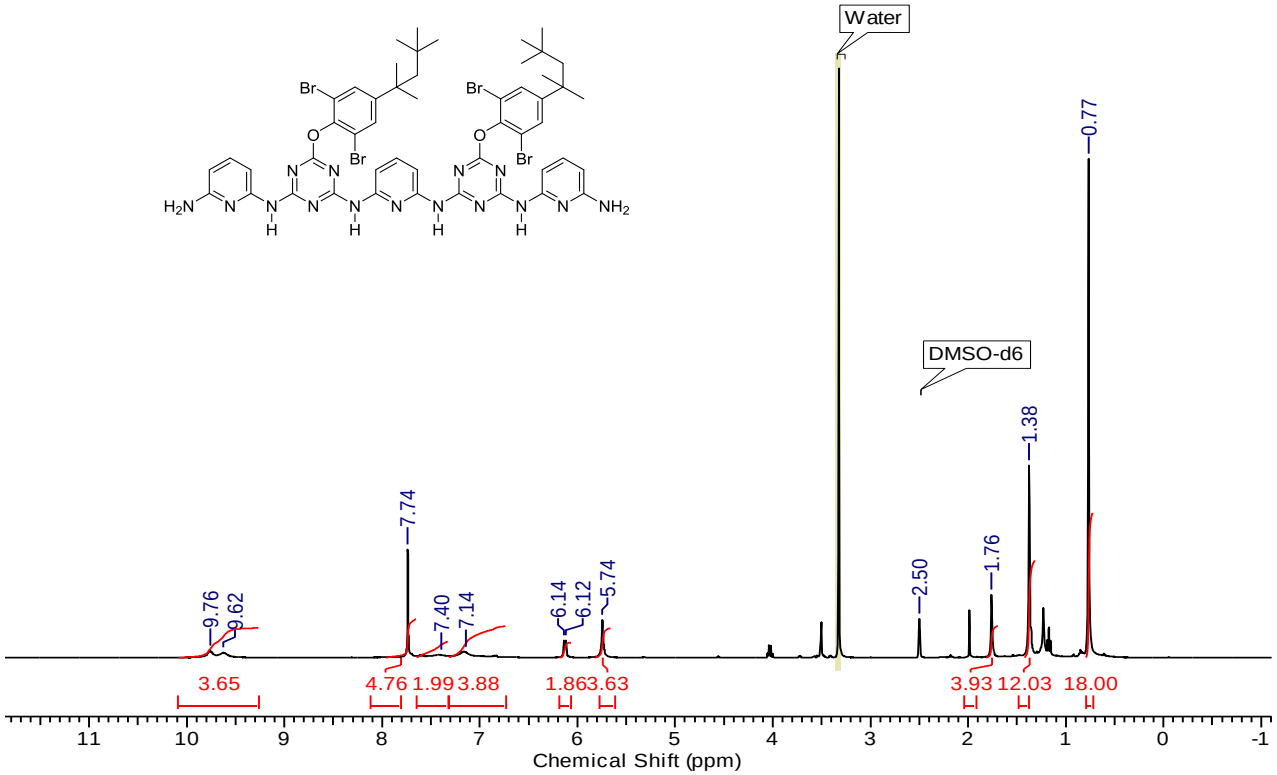
DEPT NMR Spectrum (100.61MHz, DMSO-d6) of Compound **13**



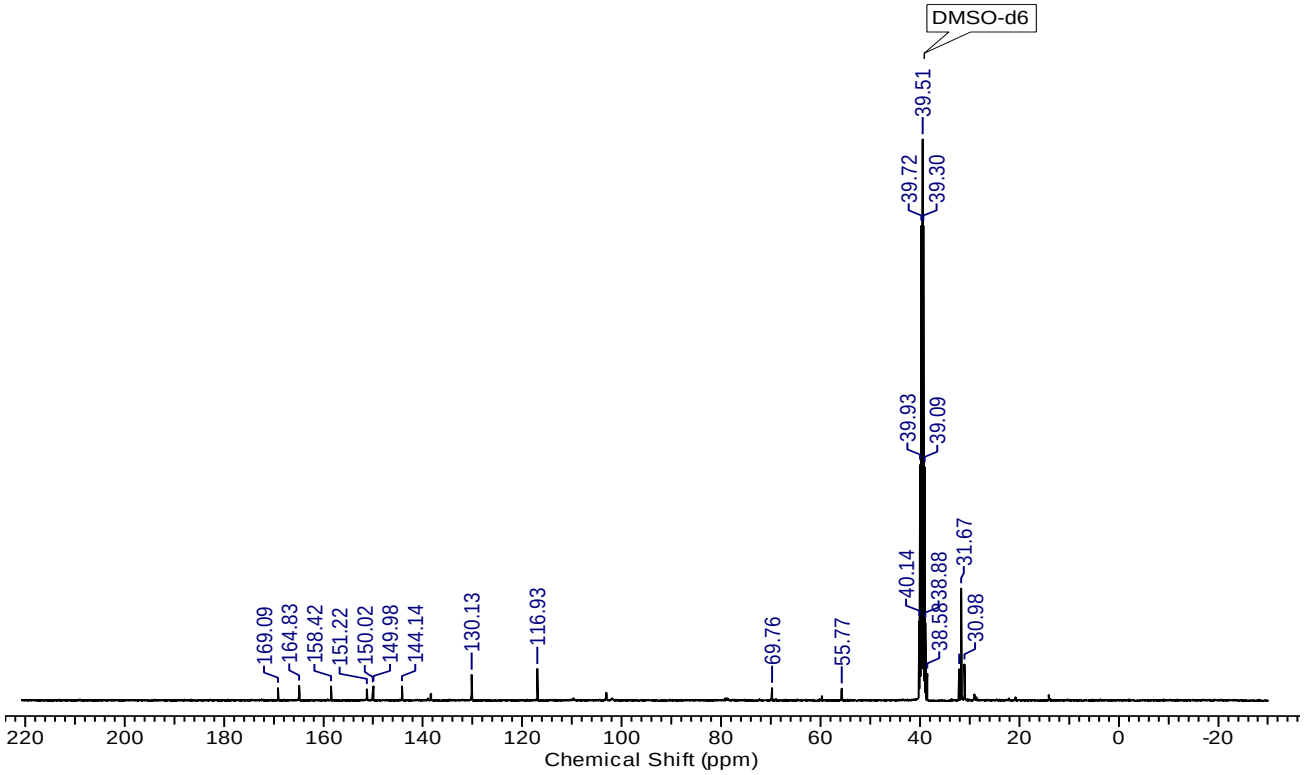
MALDI-TOF of Compound **13**



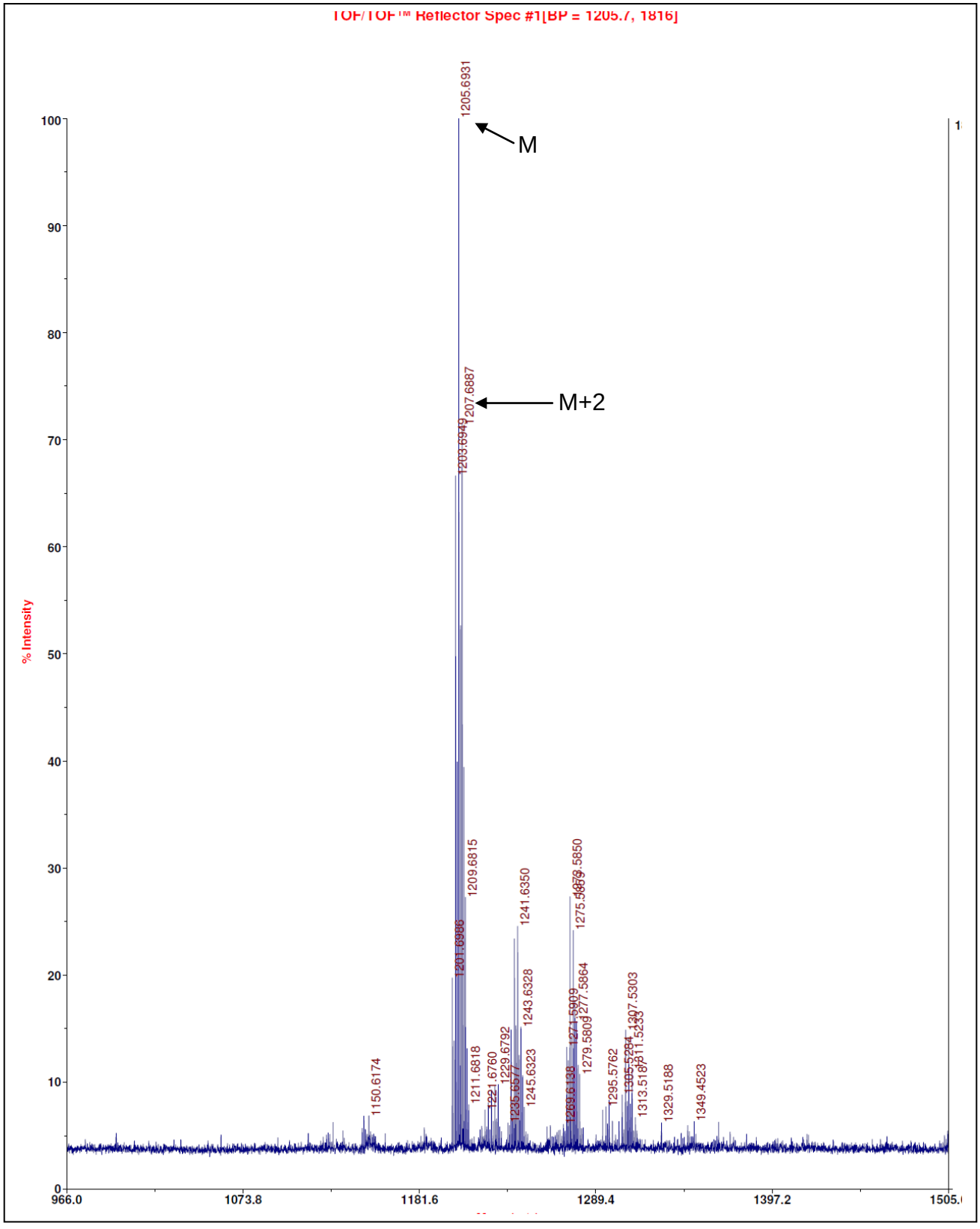
^{1}H NMR Spectrum (400.13MHz, DMSO-d6) of Compound **15**



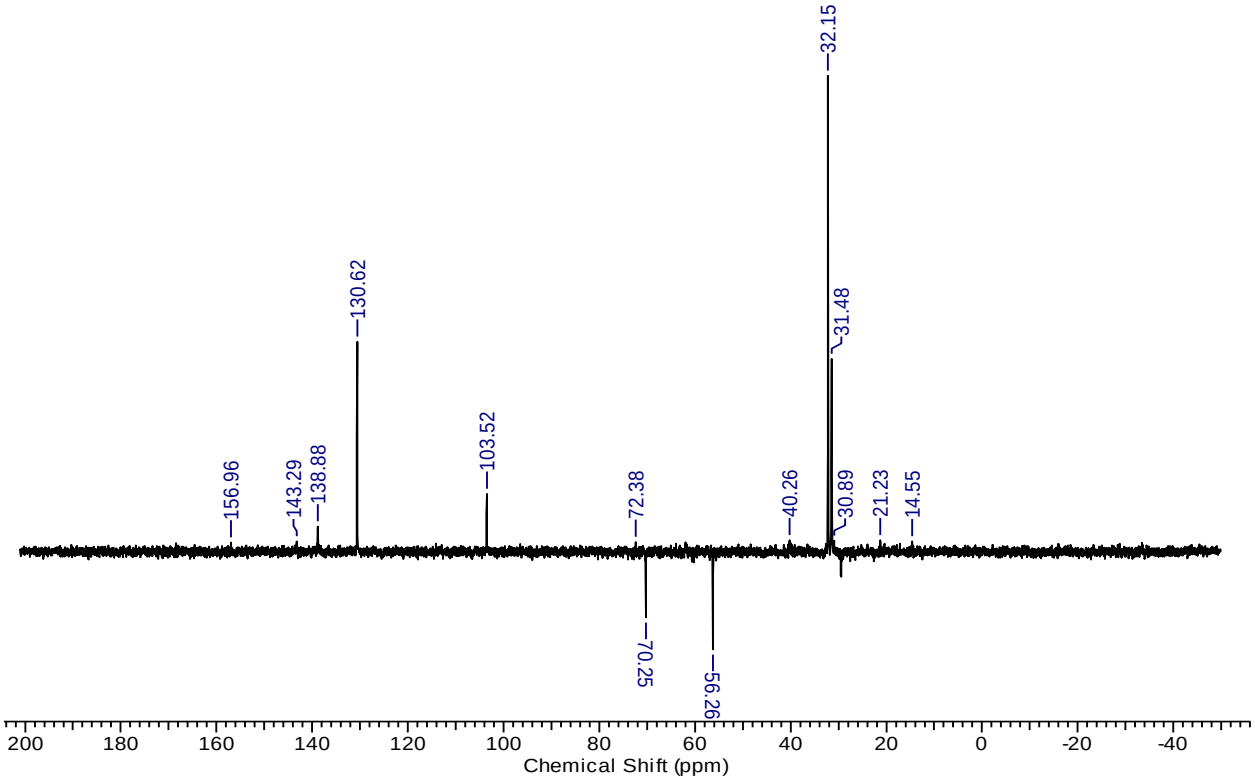
^{13}C NMR Spectrum (100.61MHz, DMSO-d6) of Compound **15**



MALDI-TOF of Compound **15**



DEPT NMR Spectrum (100.61MHz, DMSO-d6) of Compound **15**



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