DESIGN AND SYNTHESIS OF SQUARAMIDE-BASED MOLECULAR MACHINES

By

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Approval page

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ABSTRACT

DESIGN AND SYNTHESIS OF SQUARAMIDE-BASED MOLECULAR MACHINES

BY

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Advisor: Professor Rajeev S. Muthyala

Artificial molecular machines are sought after in a wide variety of fields. They are useful in the construction of nanodevices (molecular valves, brakes, nanocars, rotors and ratchets), for ion transport and also for optical data storage. In an effort to develop new ion-transport and drug delivery strategies we became interested in designing molecular machines based on amide derivatives of squaric acid (squaramides). In this study, we first determined that secondary diaryl squaramides, which exist in the extended *ZZ* conformation, are excellent neutral receptors for biologically important anions such as chloride, carboxylate, and dihydrogen monophosphate. Next, we envisioned a molecular valve approach to regulate anion binding to squaramides via changes in the external environment (for example, a change in solvent polarity). We reasoned that in non-polar solvents, intramolecular hydrogen bonding between the carbonyl groups and the squaramide NHs would block anion binding (OFF state) while in a polar solvent disruption of intramolecular hydrogen bonding and reorientation of the carbonyl allows anion binding (ON state). Using ortho benzoyl substituted squaramides, we successfully

applied the molecular valve approach to chloride binding. We subsequently studied the generality of the molecular valve approach with other ortho substituents such as secondary and tertiary amides, esters, and nitro groups. We found that the success of the molecular valve approach depends on whether, in a given solvent, intramolecular hydrogen bonding is stronger or weaker relative to intermolecular hydrogen bonding with chloride ion. A significant effort was also spent on developing tertiary squaramide-based molecular machines for drug delivery. Initial studies revealed that simple (for example, N, N'-dimethyl derivatives) tertiary diaryl squaramide exhibited a preference for folded *EE* conformation regardless of solvent polarity. For our goal of transforming these squaramides to functional molecular machines, we decided to exploit the hydrophobic effect. In non-polar solvents we anticipated that the tertiary squaramides would exhibit a preference for *EE* conformation while in aqueous medium we reasoned that the conformation would switch to *ZZ* driven by the hydrophobic effect. However we soon experienced major synthetic challenges. The literature procedures for the synthesis of these tertiary diaryl squaramides routinely resulted in low yields with significant squaraine impurities. We therefore developed a novel copper-based method to synthesize symmetrical tertiary diaryl squaramides. Importantly, this method also enabled synthesis of unsymmetrical tertiary diaryl squaramides. Syntheses, conformational preferences, and our attempts at developing hydrophobically driven molecular machines will also be discussed in this dissertation.

Dedicated to my Beloved Parents

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Firstly, I would like to express my sincere thanks and gratitude to my mentor, Prof. Rajeev S. Muthyala. His ever-willing support, guidance, and constant encouragement enabled successful completion of my doctoral study. I also thank him for introducing me to exciting avenues of supramolecular chemistry.

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My sincere thanks to Mahesh Saqcena for his help in correcting my thesis. I would like to extend my thanks to my colleagues Maciej E. Domaradzki, Niala Bhagirath, and Jorge Ubillus for their ambience and cooperation. I extend my heartfelt thanks to my friends Sattanathan, Rajesh, Mahesh, Jeyavel, and Mahendran for their continued support and guidance throughout my doctoral study. Expressing gratitude towards all my teachers would be an understatement who always inspired me at various times to bring out the very best from me. Last but not the least, I am grateful to my parents, my brothers, and all my friends for their support, love, and guidance.

Vijayakumar Ramalingam

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LIST OF ABBREVATIONS

NMR	Nuclear Magnetic Resonance
HRMS	High Resolution Mass Spectroscopy
DMSO	Dimethylsulfoxide
DMSO-d_6	Deuterated dimethylsulfoxide
DMF	Dimethylformamide
Et_3N	Triethylamine
MeOH	Methanol
EtOH	Ethanol
TLC	Thin Layer Chromatography
Cs_2CO_3	Cesium Carbonate
K_2CO_3	Potassium Carbonate
Na_2CO_3	Sodium Carbonate
K_3PO_4	Potassium Phosphate
TBAF	*n*-Tetrabutylammonium fluoride
CH_3CN	Acetonitrile

$CHCl_3$	Chloroform
$CDCl_3$	Chloroform-*d*
TBAA	*n*-Tetrabutylammonium Acetate
TBA	*n*-Tetrabutylammonium
UV-Vis	Ultraviolet spectroscopy
K_a	Binding constant
λ	wavelength
abs	absorbance
max	maximum
nm	nanometer
AcO-	acetate
$H_2PO_4^-$	dihydrogen monophosphate
CuTc	copper (I) thiophene carboxylate
CuI	copper iodide
Cu_2O	copper oxide
$CuSO_4$	Copper sulphate
TFA	Trifluoroacetic acid
D_2O	Deuterium oxide
J	coupling constant
s	Singlet
d	Doublet
t	Triplet
q	Quartet

quint	Quintet
m	Multiplet
br	Broad
Hz	Hertz
Mp	Melting point

Chapter 1

Aryl squaramides as a novel anion receptors

1.1 Introduction

The serendipitous discovery of crown-ether[1] coordination of alkali metals by Charles J. Pedersen spurred advancement of the field of ion recognition. Initial research in the area concentrated mainly on cation recognition but the importance of anion recognition was also quickly recognized. In fact, anion recognition was reported as early as 1967 by Simmons and coworkers[2].

Unlike cations, anion recognition is complicated in several ways. For instance, anionic species are larger in size than isoelectronic cations and solvation free energies of anions are considerably larger than cations. Anions also vary widely in shape. For example, halides are spherical in shape whereas acetate is Y-shaped. Despite these technical obstacles, recognition of receptors for environmentally and biologically relevant anions[3] such as chloride, phosphate, and acetate is of interest for several reasons. For instance, chloride recognition can be of potential use in the cure for cystic fibrosis[4], a disease caused by chloride channel dysfunction. Anion-sensing based approaches are also useful in detecting and scavenging phosphates and nitrates, the principal ingredients in fertilizers[5]. Anion sensing can also be useful in detection and remediation of pertechnate[6], a byproduct obtained from nuclear fuel waste processing units.

Anion recognition is primarily achieved using either electrostatic or hydrogen bonding interactions. Several anion binding proteins[7] such as phosphate binding proteins (PBP) and sulphate binding proteins (SPB) are known to function through hydrogen

bonding. Some of the common anion binding scaffolds which exploit hydrogen bonding as a mode of recognition include ureas[8a], thioureas[8], porphyrins[9], isophthalimides[10], and sapphyrins[11]. We are interested in exploring aryl squaramides as novel anion receptors.

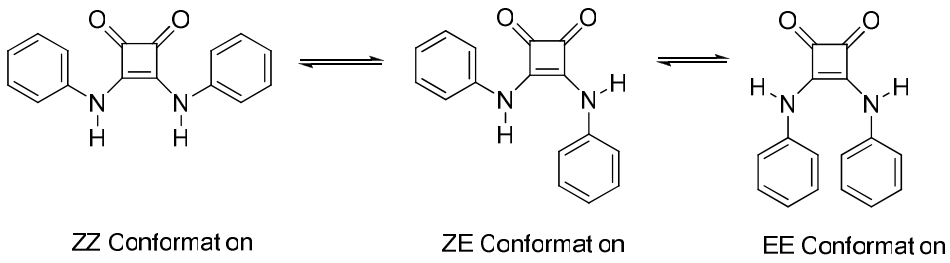


Figure 1.1: Possible conformations of secondary diphenyl squaramide **1**

Secondary diphenyl squaramides are unique, cyclic cross-conjugated vinylogous diamides. Earlier studies on the conformational preference of secondary diphenyl squaramides in our laboratory showed that they exist in *ZZ* conformation[12]. In this conformation, squaramides are ideally preorganized for anion binding. However, reported studies on anion binding to squaramides deal primarily with charged dialkyl[13] derivatives, in which non-directional electrostatic forces[14] are exploited for recognition.

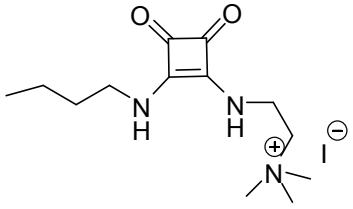


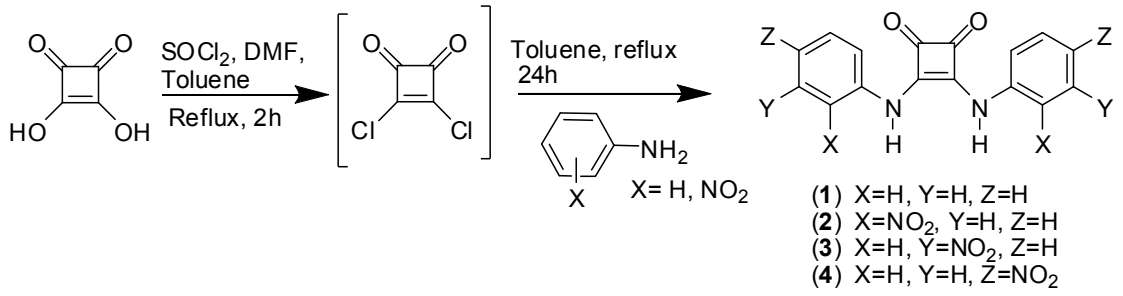
Figure 1.2: Example of a charged secondary dialkyl squaramide[17]

There is no information on the anion binding properties of neutral diaryl squaramides. In connection with our ongoing interest in developing squaramide-based molecular machines, our goal was to first investigate the mode of interaction of different anions with diaryl squaramides. Described below are our studies beginning with acetate ion.

1.2 Synthesis of diaryl squaramides

Squaryl dichloride was obtained by acylation of squaric acid (Scheme 1.1). This reactive squaryl dichloride was not isolated but quenched with the corresponding aniline derivative to synthesis diphenyl squaramide derivatives (**1-4**). The chromogenic[3b] nitro substituent was introduced into the aromatic ring to possibly increase the hydrogen bonding ability of squaramide NH.

Scheme 1.1: Synthesis of diaryl squaramide



1.3 Interaction of diaryl squaramides with acetate

1.3.1 Acetate interaction with 3, 4-bis (phenyl amino) cyclobut-3-ene-1, 2-dione (1)

Preliminary studies on acetate binding to squaramide **1** in DMSO were conducted using ^{1}H NMR. DMSO was used since the squaramide **1** is insoluble in non-polar solvents such as chloroform and toluene. Tetrabutylammonium acetate (TBAA) was used as the acetate ion source. Comparison of uncomplexed ^{1}H NMR spectra of squaramide **1** with acetate-complexed spectra suggested the acetate binding property of

the squaramide **1**. The downfield shift of the aromatic ortho proton (H_1) was consistent with the hydrogen bonding effects that have been associated with the aryl C-H and N-H interaction with anions[15] (Figure 1.3).

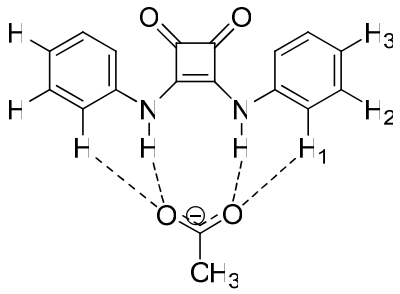


Figure 1.3: Possible binding mode of squaramide **1** with acetate

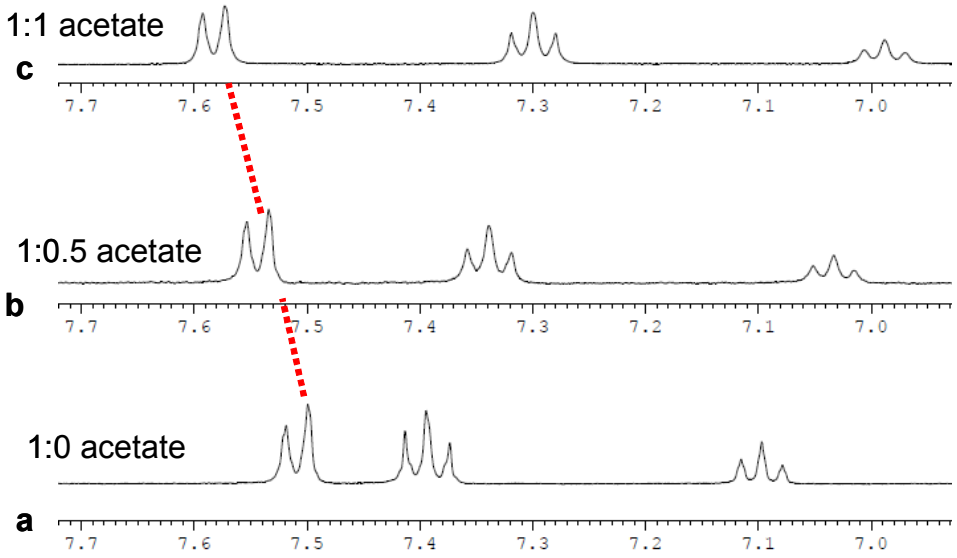


Figure 1.4: a) Uncomplexed ^{1}H NMR spectrum (aromatic region) of squaramide **1.** b) Squaramide **1:** acetate in 1:0.5 molar stoichoimetry. c) Squaramide **1:** acetate in 1:1 molar stoichoimetry.

The binding constant in 0.2 % (v/v) DMSO in acetonitrile was determined by UV-Vis spectroscopy. The addition of DMSO to acetonitrile solvent is necessary for solubility reasons. The host (squaramide **1**) concentration was maintained at $1x10^{-5}$ M and titrated with the guest (acetate) concentration ranging from $1x10^{-6}$ M to $1x10^{-4}$ M. A bathochromic shift of 9-10 nm was observed. This shift is indicative of acetate hydrogen bonding to squaramide[16] **1**. The binding constant K_a, as determined by nonlinear curve fitting method, was found to be $3.3 \pm 0.5 \times 10^5$ M^{-1}.

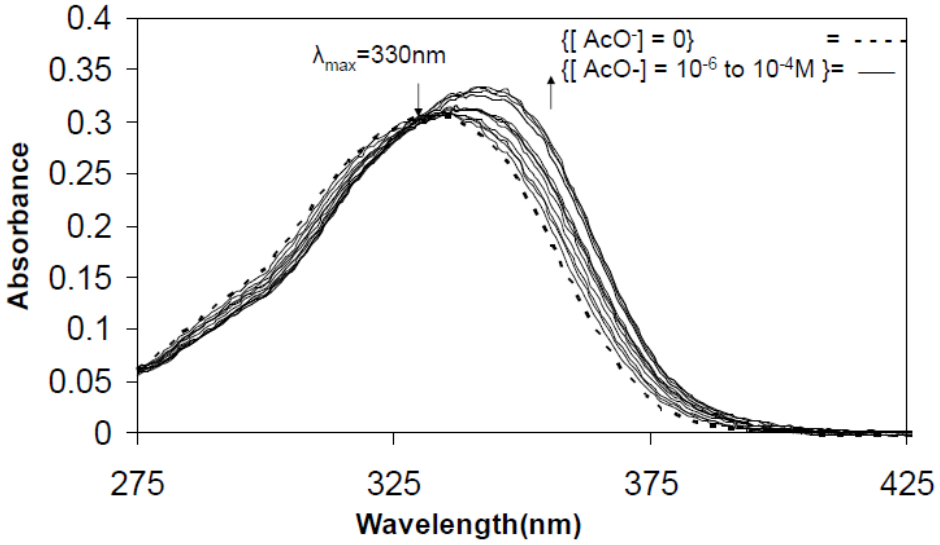


Figure 1.5: UV-Vis spectrum of acetate titration with squaramide **1** in 0.2% DMSO in acetonitrile.

At this point, our next goal was to increase the binding strength of diphenyl squaramide to acetate. The chromogenic nitro derivatives **(2-4)** were envisioned to be suitable candidates for this purpose since we anticipated that the electron withdrawing nature of the nitro group would increase the hydrogen donor ability of the squaramide NHs.

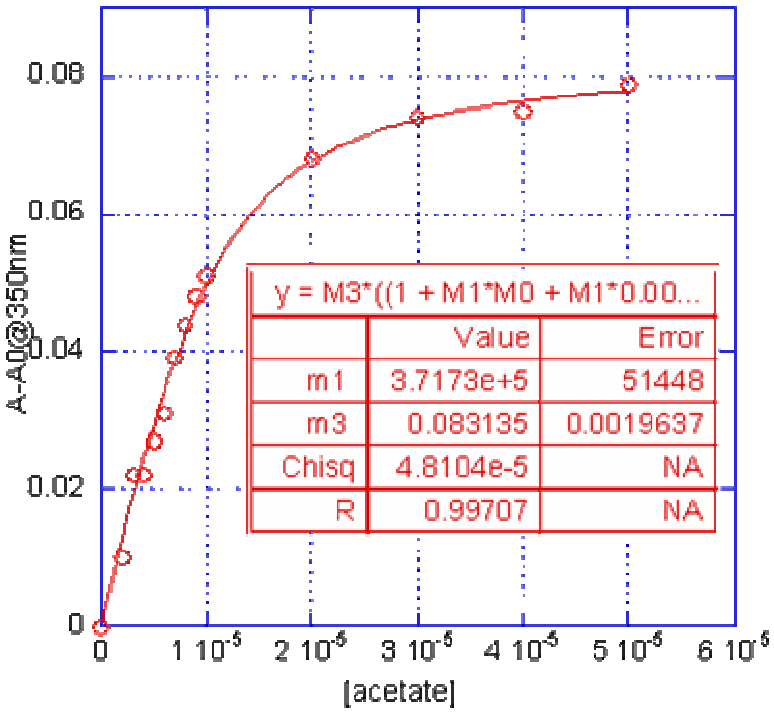


Figure 1.6: Binding isotherm of acetate binding interaction with squaramide **1** as monitored by UV-Vis spectroscopy. The binding constant was calculated using Kalediagraph and the equation[24], Δ abs = Δ abs maximum $(1+K_a\,[Host] + K_a\,[CH_3COO^-])-((1+ K_a\,[Host] + K_a\,[CH_3COO^-])^{2} - 4K_a^{2}\,[Host]\,[CH_3COO^-]^{0.5}/ 2\,K_a\,[CH_3COO^-]$.

1.3.2 Acetate interaction with 3, 4-bis (2-nitrophenylamino) cyclobut-3-ene-1, 2-dione (2)

Secondary aryl squaramides are usually insoluble in non-polar solvents such as chloroform or toluene. However, nitrosquaramide **2** is soluble in both the non-polar solvents mentioned above. This unusual solubility likely arises from the ability of the nitro group to intramolecularly hydrogen[17] bond with the squaramide NH (Figure 1.7) thereby reducing self-aggregation. UV-Vis spectrum of squaramide **2** upon titration with TBA acetate in acetonitrile showed a bathochromic shift of 80-85 nm and clear color

change observed by naked eye. This large red shift and the drastic color change from yellow-orange to violet were suggestive of NH deprotonation[18] in squaramide **2**. Similar bathochromic shift and color change was also observed by titration of squaramide **2** with tetramethylammonium hydroxide anion.

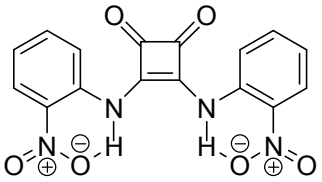


Figure 1.7: Intramolecular hydrogen bonding in squaramide **2**.

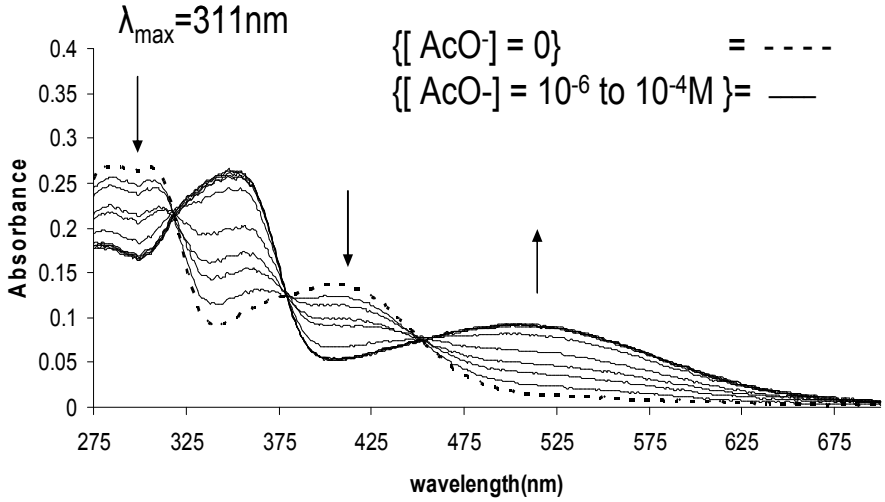


Figure 1.8: UV-Vis spectrum of acetate titration with squaramide **2** in acetonitrile

1.3.3 Acetate interaction with 3, 4-bis (3-nitrophenylamino) cyclobut-3-ene-1, 2-dione (3)

UV-Vis spectrum of meta nitro squaramide **3** with TBA acetate in acetonitrile exhibited a 17-20 nm bathochromic shifts

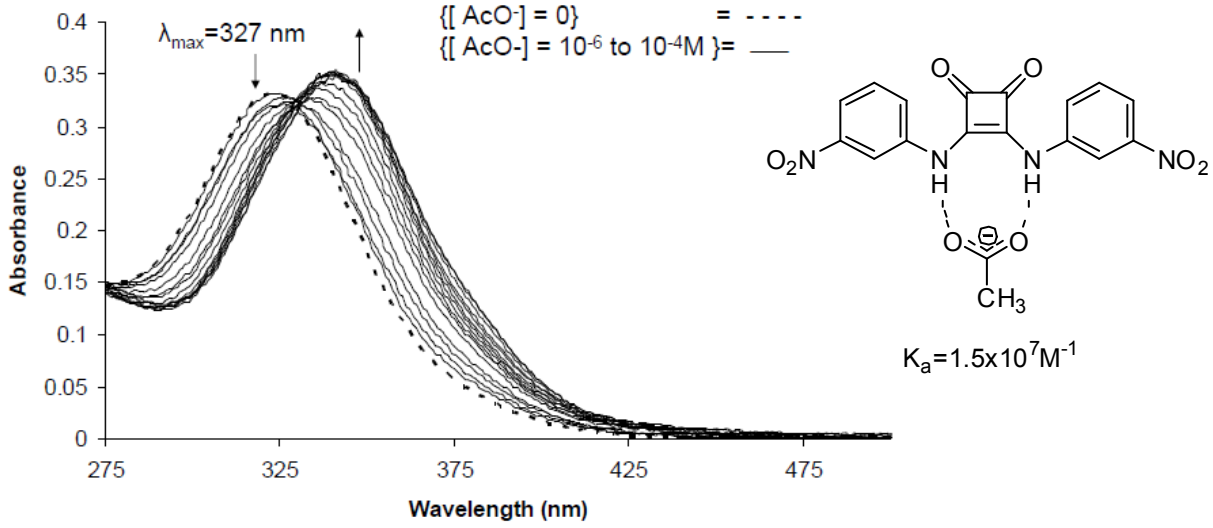


Figure 1.9: UV-Vis spectrum of acetate binding interaction with squaramide **3** in acetonitrile.

This was a clear indication of formation of a hydrogen bonding complex with squaramide **3** (Figure 1.9). The nitro group in the meta position in squaramide **3** decreases the acidity of the squaramide NH compared to orthonitro squaramide **2** (Note that it was not possible to compare acetate K_a values with **1** since different solvents were used). This may explain why only hydrogen bonding species were formed but no deprotonation occurred. Unlike squaramide **2**, however, no visual color changes were observed upon acetate addition in acetonitrile.

1.3.4. Acetate interaction with 3, 4-bis (4-nitrophenylamino) cyclobut-3-ene-1, 2-dione (4)

The p-nitrophenyl squaramide **4** was highly insoluble in non-polar solvents and only sparingly soluble in DMSO. UV-Vis titration of squaramide **4** with TBA acetate in acetonitrile showed an interesting trend in that both the hydrogen bonded species and deprotonated species were observed. As the concentration of TBA acetate increases, the hydrogen bonded species (λ_{max} = 412 nm) is depleted and the deprotonated species (λ_{max} = 495 nm) predominated[19].

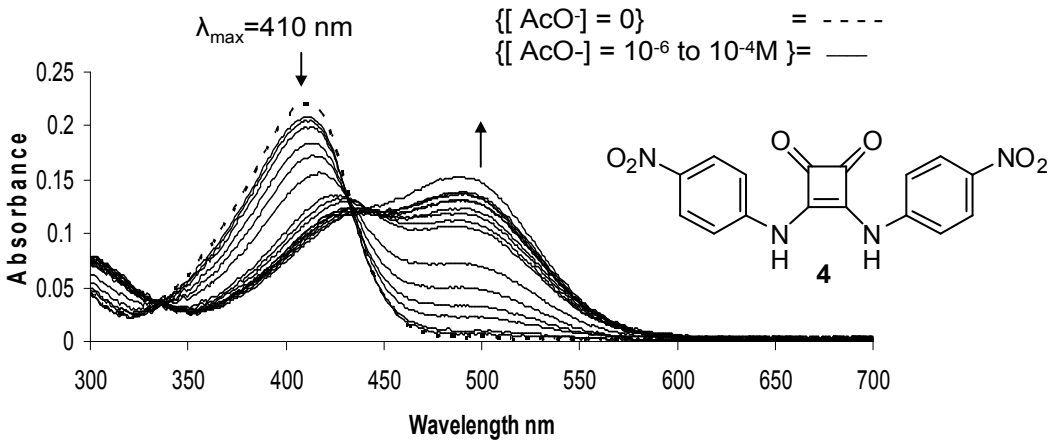


Figure 1.10: UV-Vis spectrum of acetate binding with squaramide **4** in acetonitrile.

1.4 Summary

1.4.1 Acetate binding with diaryl squaramides

The interaction of diaryl squaramide with TBA acetate revealed that the diphenyl squaramide **1** and meta nitro squaramide **3** were identified as excellent acetate anion receptors. Our experimental observations showed that the position of nitro group is very crucial in determining whether hydrogen-bonding or deprotonation species will

predominate upon acetate addition. Due to its superior solubility of diphenyl squaramide **1** in DMSO compared to the nitro squaramide **3**, this was used for further binding studies with other anions such as halides and dihydrogen monophosphate.

1.4.2 Interaction of diphenyl squaramide with halides

Addition of fluoride[23] ion to diphenyl squaramide **1** resulted in deprotonation, indicated by the disappearance of squaramide NH peak and also the upfield shift in the aromatic protons.

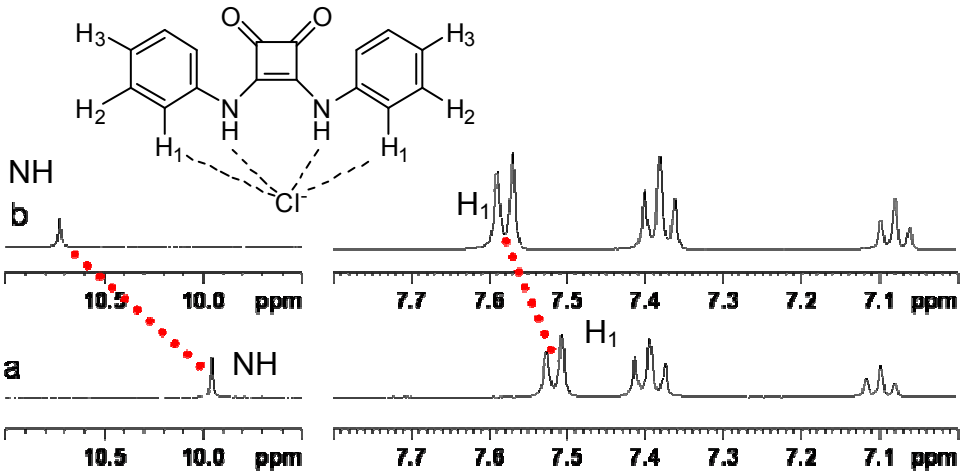


Figure 1.11: a) ^{1}H NMR spectra of diphenyl squaramide **1** in DMSO-d_6. b) Diphenyl squaramide **1**+ Cl^- (1:1) in DMSO-d_6.

In contrast, chloride showed strong hydrogen bonding indicated by downfield shift in the squaramide NH and also distinguishable changes in the chemical shifts of the aromatic protons (Figure 1.11). The chloride binding constant to diphenyl squaramide **1** was determined by ^{1}H NMR in DMSO and was found to be 405 ± 20 M^{-1}, using nonlinear least squares fitting methods.

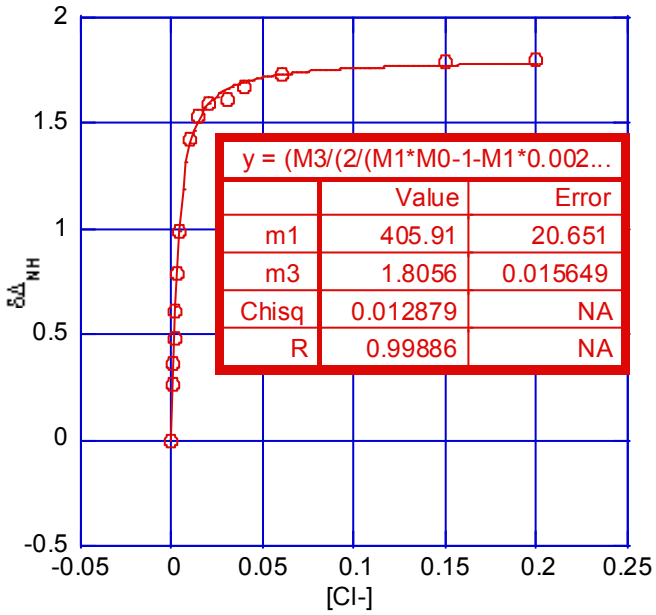


Figure 1.12: Binding isotherm curve for squaramide **1** titration with chloride (m1=K_a)

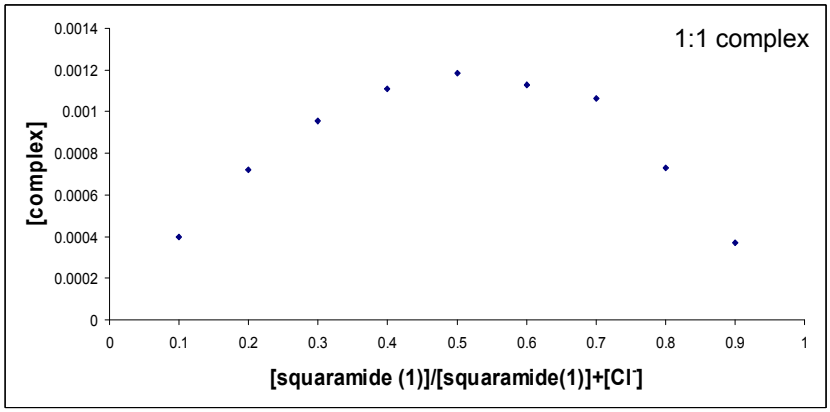


Figure 1.13: Job's plot of squaramide **1** titration with chloride

From a Job's plot the stoichiometry of the chloride complex was found to be 1:1. Squaramide **1** showed highest selectivity for chloride binding amongst the halides. Bromide and iodide showed very weak binding to squaramide **1** in DMSO. This high K_a

value for chloride, even in polar competitive solvents DMSO, is advantageous since very few neutral anion scaffolds exhibit strong chloride binding in polar solvents.

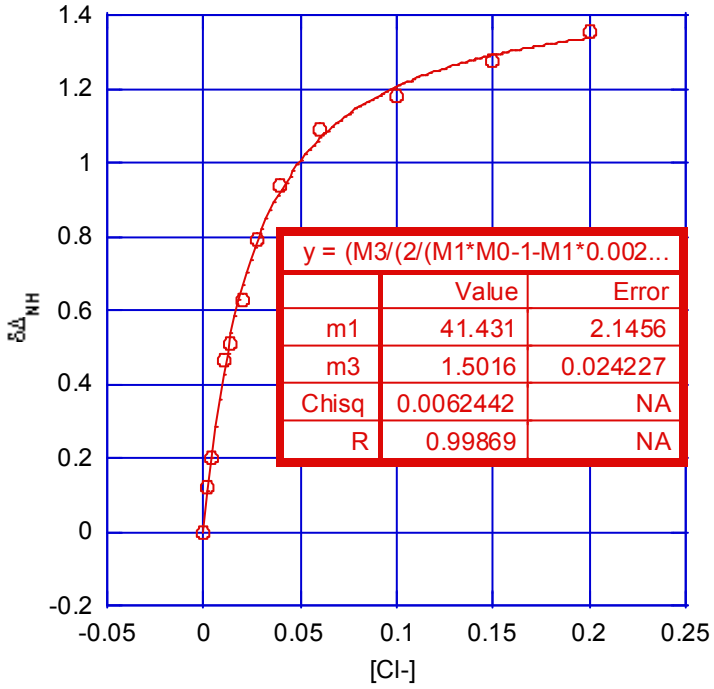
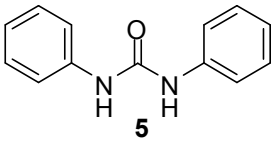
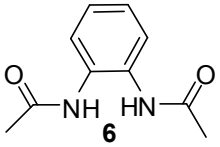
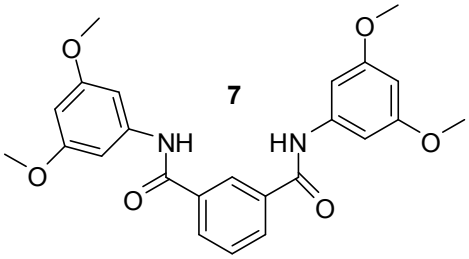
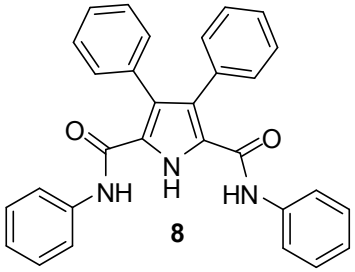
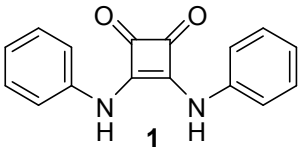


Figure 1.14: Binding isotherm graph of 1, 3-bis (2-nitrophenyl) urea with TBA chloride in DMSO.

The high K_a value is likely due to the strong hydrogen bond donating ability of diphenyl squaramides and the size complementarity between the chloride ion and the squaramide binding site. We compared the strength of chloride binding to squaramide **1**, with other scaffolds in DMSO solvent. Diphenylurea, which also has two hydrogen bond donors, was chosen first for the comparison. A survey of existing literature showed that the chloride binding constant[20] for diphenylurea in DMSO is ~ 40 M^{-1}. This indicated that the binding affinity of squaramide **1** to chloride is approximately 10 times higher than that of diphenyl urea.

Table 1.1: Chloride binding scaffold in DMSO

entry	Chloride binding scaffold	K_a in DMSO M^{-1}
1	 **5**	31[a](41[b])
2	 **6**	13[c]
3	 **7**	20[c]
4	 **8**	12[c]
5	 **1**	405[b]

[a] See reference 20. [b] Experimental obtained by ^{1}H NMR . [c] See reference 21.

To calibrate our results with the literature binding data, we repeated the binding experiments for diphenyl urea with chloride and determined a K_a value of 41 ± 2 M^{-1} (Figure 1.14) which is excellent agreement with the value reported in the literature[20]. Comparing other chloride binding scaffolds[21] also revealed that squaramide **1** is a

stronger chloride receptor (Table 1.1) in DMSO. Additionally, diphenyl squaramides are relatively easier to synthesize and if appended with proper substituents can serve as a powerful chloride receptors.

1.4.3 Interaction of diphenyl squaramide with dihydrogen mono phosphate

Having established the squaramide binding ability to spherical halides, we were interested in the binding of biologically relevant anions. One such anion is dihydrogen monophosphate[22]. This freely available tetrahedral anion was found to interact with diphenyl squaramide **1.**

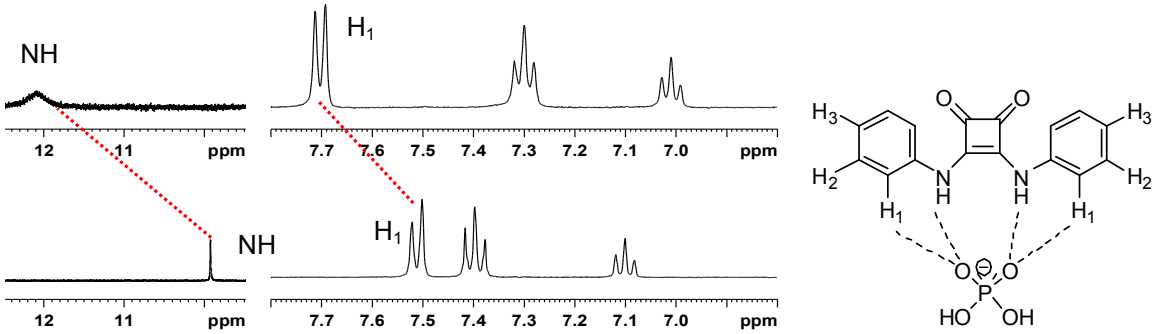


Figure 1.15: a) ^{1}H NMR spectra of diphenyl squaramide **1** in DMSO-d_6. b) Diphenyl squaramide + $H_2PO_4^-$ (1:1) in DMSO-d_6.

^{1}H NMR spectra showed strong evidence of $H_2PO_4^-$ binding to squaramide **1** through hydrogen bonding (Figure 1.15). Binding constant of dihydrogen monophosphate with squaramide **1** was determined by the plot of chemical shift change in CH (ortho proton) versus the concentration of tetrabutylammonium dihydrogen monophosphate (Figure 1.16) and was found to be $7.0 \pm 1 \times 10^3$ M^{-1}. The difference in the δ_{CH} peak was used for binding constant determination since squaramide NH peak disappeared after the addition

of 1:2 equivalents of $H_2PO_4^-$ to squaramide. A Job's plot indicated a 1:1 binding stoichiometry.

To further confirm the phosphate binding property to squaramide **1** by an additional spectroscopic technique, UV-Vis methods were used. A bathochromic shift of approximately 17 nm was observed upon dihydrogen monophosphate addition to squaramide **1**. This observed red shift clearly indicated the formation of hydrogen bonded complex. The binding constant was determined by plotting TBA dihydrogen monophosphate concentration versus absorbance at 370 nm in DMSO and was found to be $8.0 \pm 0.8 \times 10^3$ M^{-1} (obtained as average of two independent experiments).

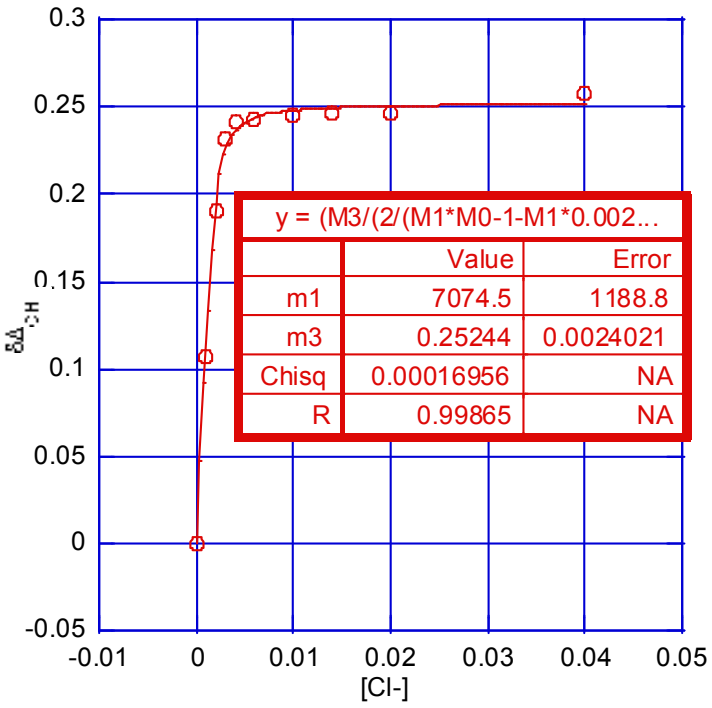


Figure 1.16: Binding isotherm curve for squaramide **1** titration with $H_2PO_4^-$

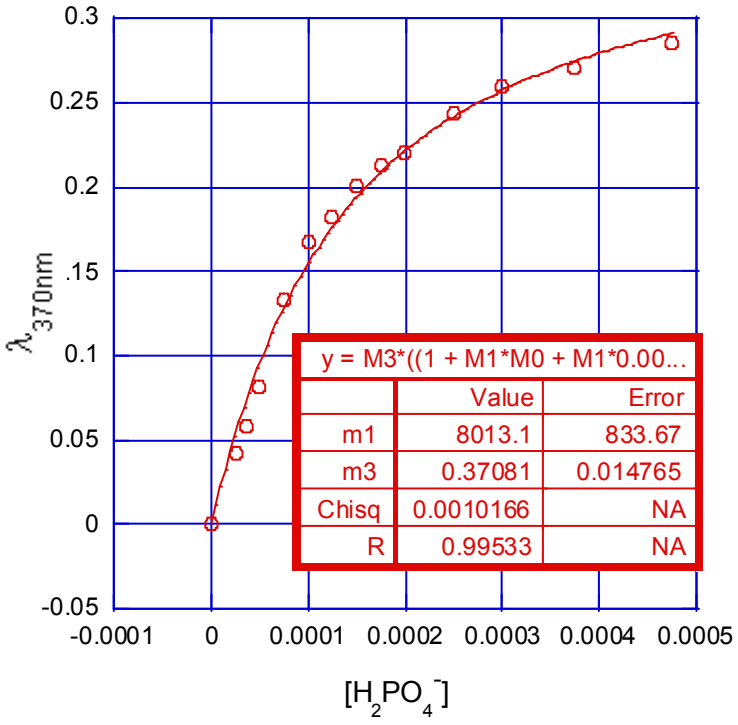


Figure 1.17: Binding isotherm curve for squaramide **1** titration with $H_2PO_4^-$

Therefore, determination of the binding constant of dihydrogen monophosphate to squaramide **1** by two independent approaches, namely UV-Vis and ^{1}H NMR, yielded similar values. Interestingly, the strength of dihydrogen monophosphate binding to squaramide **1** in DMSO was much greater than the chloride binding.

1.4.4 Interaction of N^{15} labeled diphenyl squaramide with $H_2PO_4^-$

The strong binding of $H_2PO_4^-$ with diphenyl squaramide suggested two possible modes of interaction; hydrogen bonding with the squaramide NHs or hydrogen bonding with the cyclobutenedione carbonyls. To differentiate between these two possibilities, the ^{15}N labeled derivative of diphenyl squaramide **1** was used (the compound was synthesized by Dr. R. Muthyala).

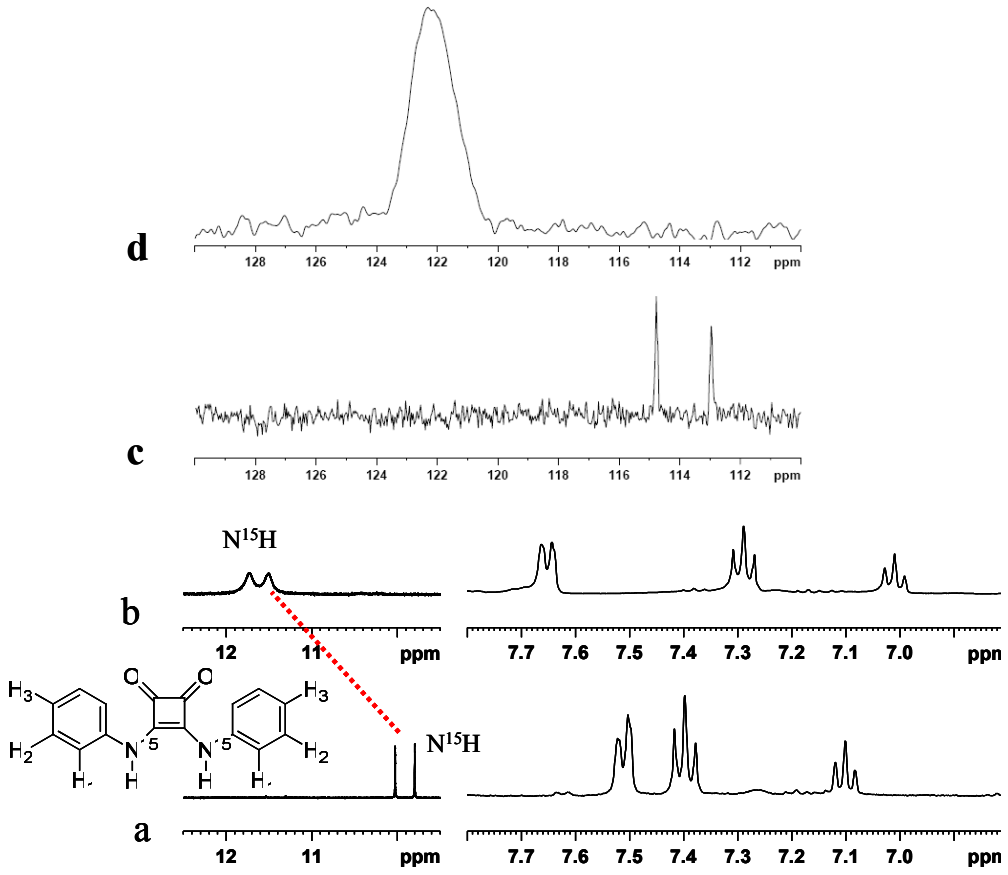


Figure 1.18: a) ^{1}H NMR spectra of N^{15} labeled diphenyl squaramide in DMSO-d_6. b) ^{1}H NMR spectra of N^{15} labeled diphenyl squaramide + $H_2PO_4^-$ (1:1) in DMSO-d_6. c) ^{15}N NMR spectra of N^{15} labeled diphenyl squaramide in DMSO-d_6. d) ^{15}N NMR spectra of N^{15} labeled diphenyl squaramide + $H_2PO_4^-$(1:1) in DMSO-d_6.

^{1}H and ^{15}N NMR spectra of this N^{15} label squaramide showed a doublet splitting pattern for the NH signal (J_{NH} = 94 Hz) (Figure 1.18). Interaction of $H_2PO_4^-$ with this squaramide in 1:1 ratio by ^{1}H NMR resulted in the downfield shift of the NH doublet peak which further suggested that the mode of interaction is hydrogen bonding with the squaramide NHs and not through the cyclobutene dione carbonyls (Figure 1.19).

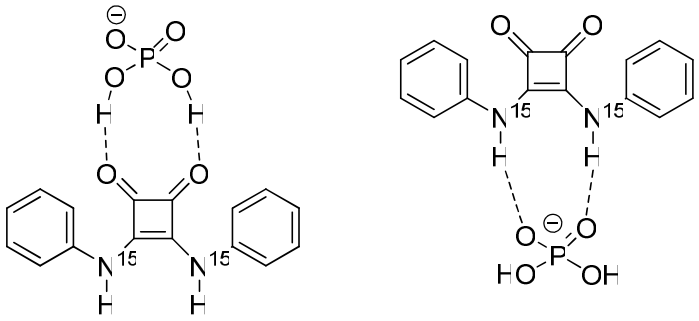


Figure 1.19: Two possible mode's of $H_2PO_4^-$ interaction with N^{15} labeled diphenyl squaramide.

Table 1.2: Squaramide **1** binding (using ^{1}H NMR and UV-vis spectroscopic methods) with various anions

entry	anions	Diphenyl squaramide(**1**) K_a M^{-1} in DMSO	
		^{1}H NMR	UV-Vis
1	F^-	Deprotonation	Deprotonation
2	Cl^-	405	ND[a]
3	Br^-	12	ND[a]
4	I^-	ND[a]	ND[a]
5	CH_3COO^-	NC[b]	371730[c]
6	$H_2PO_4^-$	7074	8013

[a] Not detected. [b] Experiment not conducted. [c] In acetonitrile.

Table 1.2 summarizes the squaramide **1** binding constants to various anions, as determined both by UV-Vis and ^{1}H NMR. Squaramide NHs serve as excellent hydrogen bond donors for spherically shaped, Y-shaped and tetrahedral-shaped anions. Chloride binding to squaramide **1** is stronger than the other halides. Fluoride addition to squaramide **1** resulted only in deprotonation of squaramide NH as opposed to hydrogen bonding. Both bromide and iodide showed very weak binding to the squaramide **1**. Binding of the tetrahedral-shaped $H_2PO_4^-$ to squaramide was confirmed by both UV-Vis and ^{1}H NMR studies. It is noteworthy to mention that diphenyl squaramide has the

ability to bind chloride and dihydrogen monophosphate even in competitive polar solvents such as DMSO.

1.5 Conclusions

We identified diaryl squaramides as excellent neutral anion receptors. The binding of biologically important anions such as chloride, acetate, and dihydrogen monophosphate to diaryl squaramide was studied. Our studies suggest that squaramides can be potentially used as anion receptors even in a polar environment. Studies on nitro substituted diaryl squaramide revealed that position of nitro substituents plays an important role in determining whether anion binding through hydrogen bonding or deprotonation occurs. Insolubility of diphenyl squaramide in non-polar limited the binding studies to only in polar solvent (DMSO). In the next chapter, knowledge of the anion binding properties of diaryl squaramides will be used in the design of functional molecular machines.

1.6 Experimental data

All the glassware was oven dried at 110 ^{o}C and cooled under nitrogen. All reactions were performed under a nitrogen atmosphere unless otherwise specified. Melting points was recorded using Mel-Temp apparatus and are uncorrected. Toluene was distilled over calcium hydride before use. Tetrabutylammonium salts were used as purchased. HPLC grade acetonitrile and DMSO were used for all UV-Vis studies. ^{1}H and ^{13}C NMR are recorded using at 400 MHz and 100 MHz respectively. Chemical shifts are reported in δ ppm and the coupling constants are reported in hertz. The residual solvent peak was used as the internal reference.

1.6.1 UV titration procedure:

A solution of the squaramide (host) (5×10^{-5} M) in acetonitrile was titrated with the solution of the tetrabutylammonium salt (guest) (5×10^{-6} to 5×10^{-4} M). Binding constant was determined by using the equation[24] below.

UV equation: Δ abs= Δ abs $_{maximum}$ $(1+K_a$ [Squaramide] + K_a [Anion])-$((1+ K_a$ [Squaramide] + K_a [Anion]) ^{2} - $4K_a^2$ [Squaramide] [Anion] $^{0.5}$/ 2 K_a [Anion]

Δ abs $_{(maximum)}$ = maximum absorbance

K_a = Binding constant.

[Squaramide]= concentration of squaramide under study.

[Anion] = concentration of tetrabutylammonium salt

1.6.2 ^{1}H NMR titration procedure:

A solution of the squaramide (host) (2×10^{-3} M) in DMSO was titrated with the solution of the tetrabutylammonium salt (guest) (5×10^{-4} to 2×10^{-1} M). Binding constant was determined by using the equation[25] below.

NMR equation:

Y= A $_{max}$/(2/ K_a [Anion]-1- K_a [Squaramide]+((1- K_a [Anion]+K_a[Squaramide])^2 + $4K_a$[Anion])$^{0.5}$)+1)).

Y= chemical shift

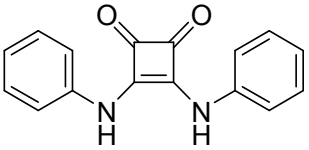
A max = Maximum chemical shift (in this case, NH proton shift).

K_a = Binding constant

[Squaramide]= concentration of squaramide under study.

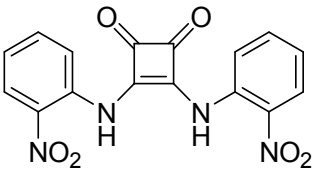
[Anion] = concentration of tetrabutylammonium salt

1.6.3 3, 4-bis (phenylamino) cyclobut-3-ene-1, 2-dione (1)



To a solution of squaric acid (114 mg, 1 mmol) in dry toluene (2 ml), thionyl chloride (238 mg, 2 mmol) and DMF (trace quantity) were added at room temperature. Reaction temperature was increased to 90 ^{o}C and maintained for 2 hours. The reaction mixture allowed to attain room temperature and concentrated to get an oily residue. This residue was diluted with dry toluene followed by addition of aniline (372 mg, 4 mmol). Reaction temperature was increased and the mixture was held at reflux for 16 hours and then cooled and filtered at 60 ^{o}C to get title compound in 75% yield as pale white solid. ^{1}H NMR (400 MHz, DMSO-d_6): 9.89 (s, 2H), 7.50 (d, 2H, *J* = 7.6), 7.39 (t, 2H, *J* = 7.6), 7.09 (t, 2H, *J* = 7.2). ^{13}C NMR (100 MHz, DMSO-d_6): 181.5, 165.6, 138.4, 129.3, 123.28, 118.44. Mp: >250 ^{o}C

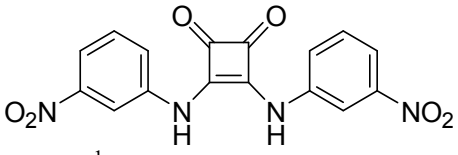
1.6.4 3, 4-bis (2-nitrophenylamino) cyclobut-3-ene-1, 2-dione (2)



To a solution of squaric acid (114 mg, 1 mmol) in dry toluene (2 ml), thionyl chloride (238 mg, 2 mmol) and DMF (trace quantity) were added at room temperature. Reaction temperature was raised to 90 ^{o}C and maintained for 2 hours, and then allowed to attain room temperature and concentrated to get an oily residue. This residue was diluted with dry toluene followed by addition of 2-nitro aniline (492 mg, 4 mmol). The reaction temperature was increased and the mixture was held at reflux for 16 hours, allowed to reach room temperature and filtered to get reddish orange solid. Column purified in dichloromethane to get title compound in 65% yield. ^{1}H NMR (400 MHz, DMSO-d_6): 10.73 (s, 2H), 8.16 (d, 2H, *J* = 8.0), 7.78 (t, 2H, *J* = 8), 7.58 (d, 2H, *J* = 8) 7.38 (t, 2H, *J* =

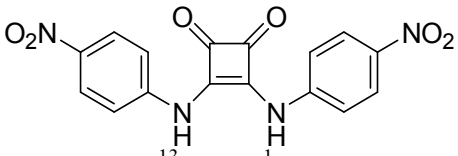
7.6). ^{13}C NMR (100 MHz, DMSO-d$_6$): 183.6, 166.3, 139.4, 134.8, 132.0, 125.5, 125.1, 124.8. Mp: 216-218 ^{o}C.

1.6.5 3, 4-bis (3-nitrophenylamino) cyclobut-3-ene-1, 2-dione (3)



Similar to the procedure **1** using m-nitroaniline (492 mg, 4 mmol). Pale yellow solid obtained in 25% yield. ^{1}H NMR (400 MHz, DMSO-d$_6$): 8.38 (s, 2H), 7.89 (d, 2H, J = 8), 7.79 (d, 2H, J = 8), 7.63 (d, 2H, J = 8). ^{13}C NMR (100 MHz, CD_3CN): 182.5, 165.8, 149.0, 139.6, 130.5, 124.7, 118.1, 113.4. HRMS calculated for $C_{16}H_{10}N_4O_6$ (M-1) 353.0600 Found 353.0534. Mp: >250 ^{o}C.

1.6.6 3, 4-bis (4-nitrophenylamino) cyclobut-3-ene-1, 2-dione (4)



Similar to the procedure **1** using p-nitroaniline Orange-yellow solid obtained in 20% yield. Due to insolubility ^{13}C and ^{1}H NMR were recorded at 80 ^{o}C. ^{1}H NMR (400 MHz, DMSO- d$_6$): 8.14 (d, 4H, J = 7.2), 7.72(d, 4H, J = 6.8). ^{13}C NMR (100MHz, DMSO-d$_6$): 183.3, 168.1, 147.2, 142.2, 125.6, 119.1. HRMS calculated for $C_{16}H_{10}N_4O_6$ (M-1) 353.0600 Found 353.0529. Mp: >250 ^{o}C

1.7 NMR spectra

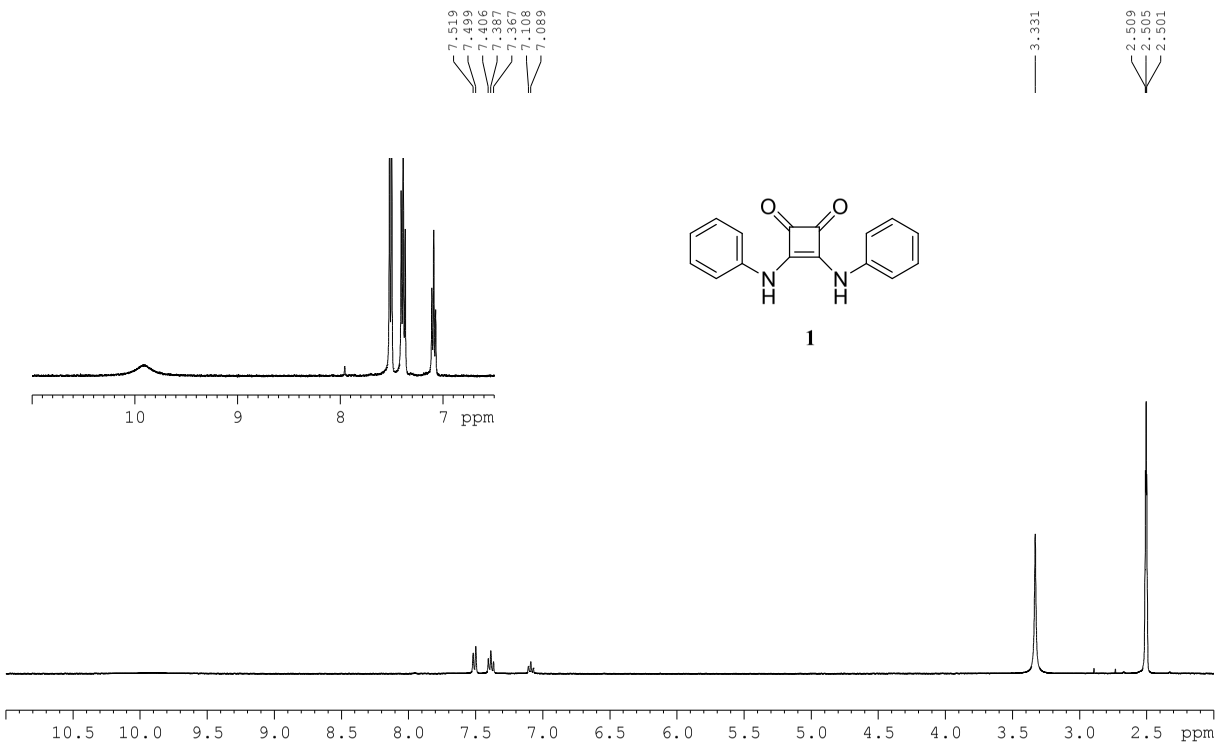


Figure 1.20: ^{1}H NMR (400 MHz) spectrum of 3, 4(phenyl amino) cyclobut-3-ene-1, 2-dione (**1**) in DMSO-d_6.

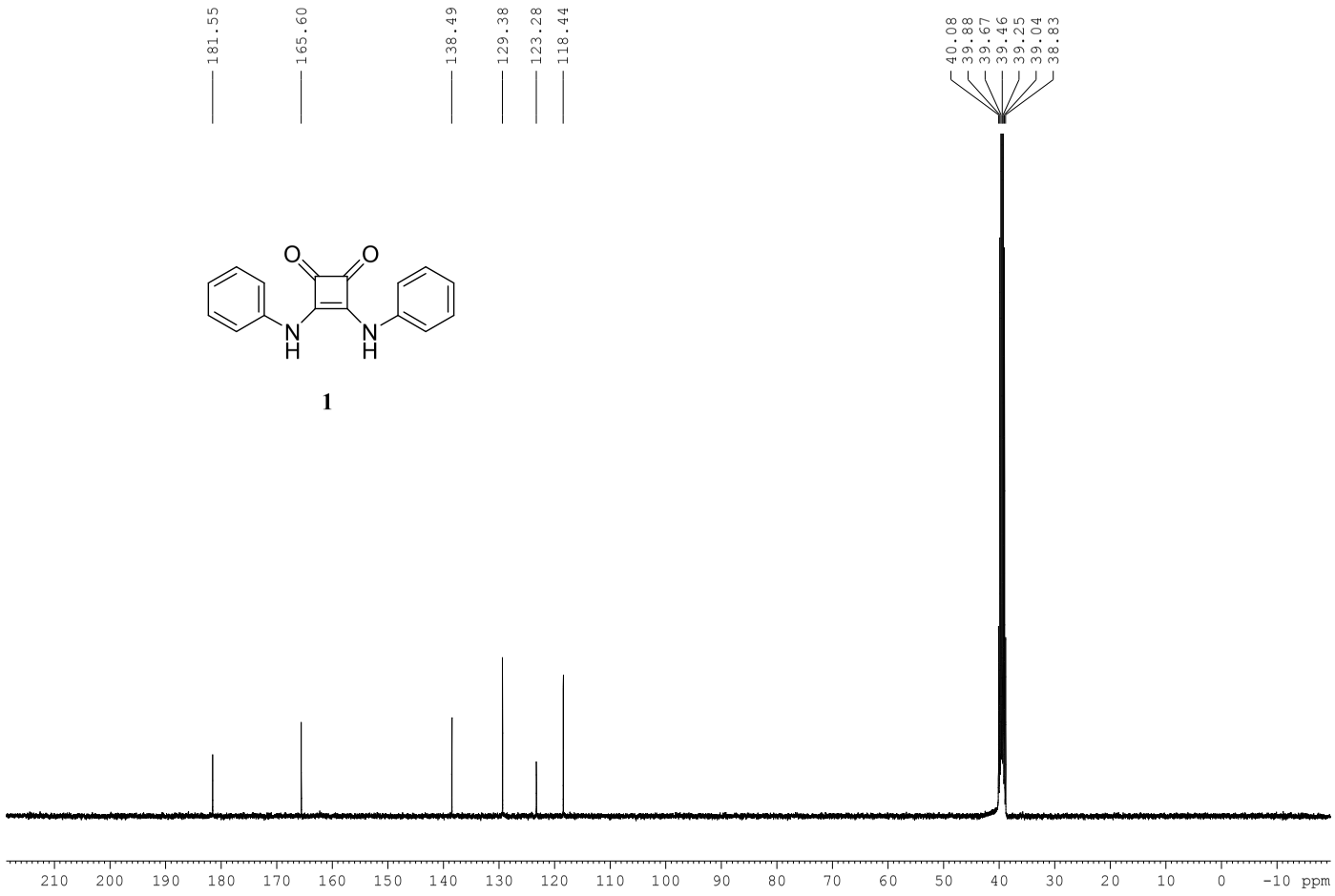


Figure 1.21: ^{13}C NMR (100 MHz) spectrum of 3, 4(phenyl amino) cyclobut-3-ene-1, 2-dione **1** in DMSO-d_6

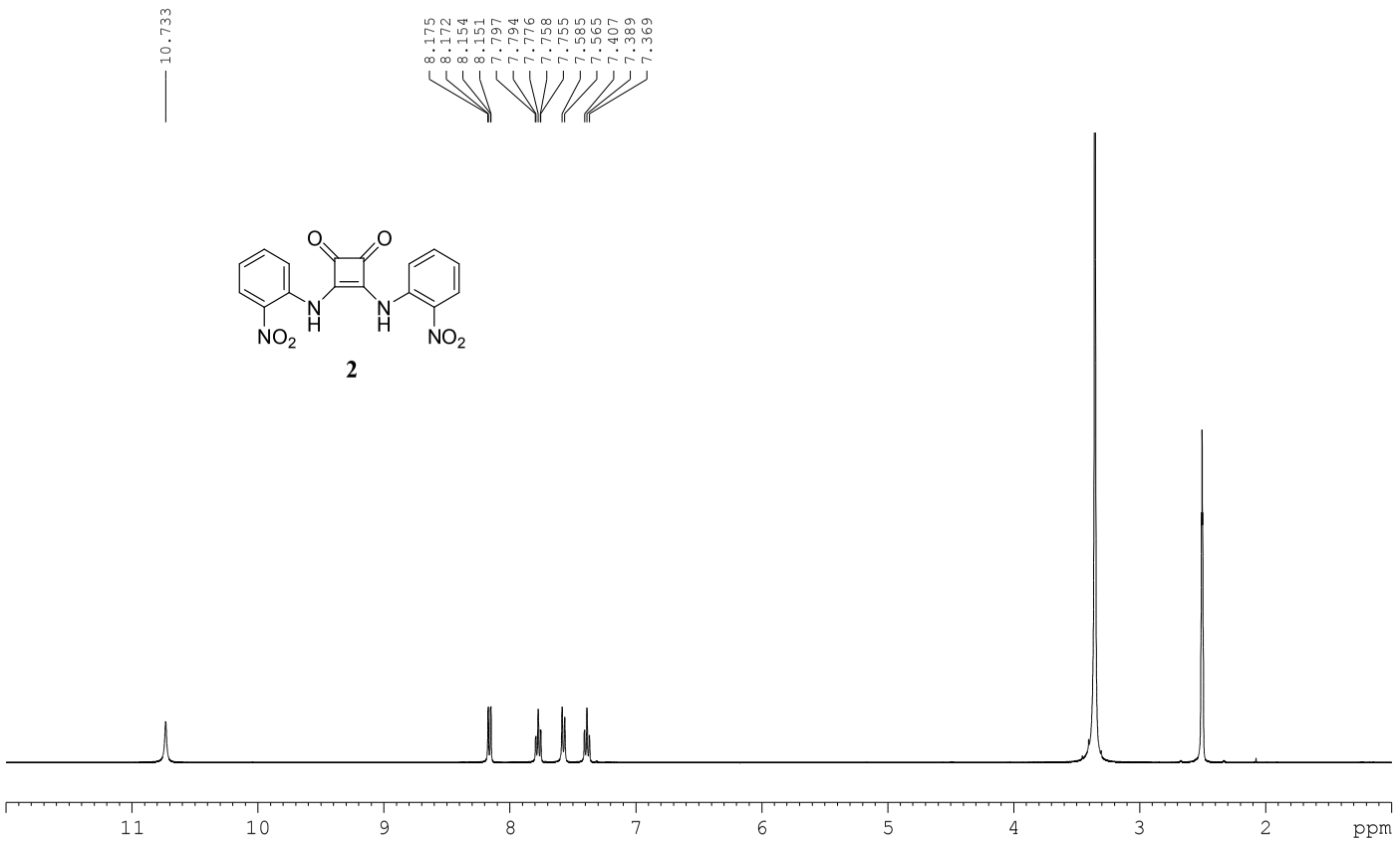


Figure 1.22: ^{1}H NMR (400 MHz) spectrum of 3, 4(2-nitro phenyl amino) cyclobut-3-ene-1, 2-dione **2** in DMSO-d_6

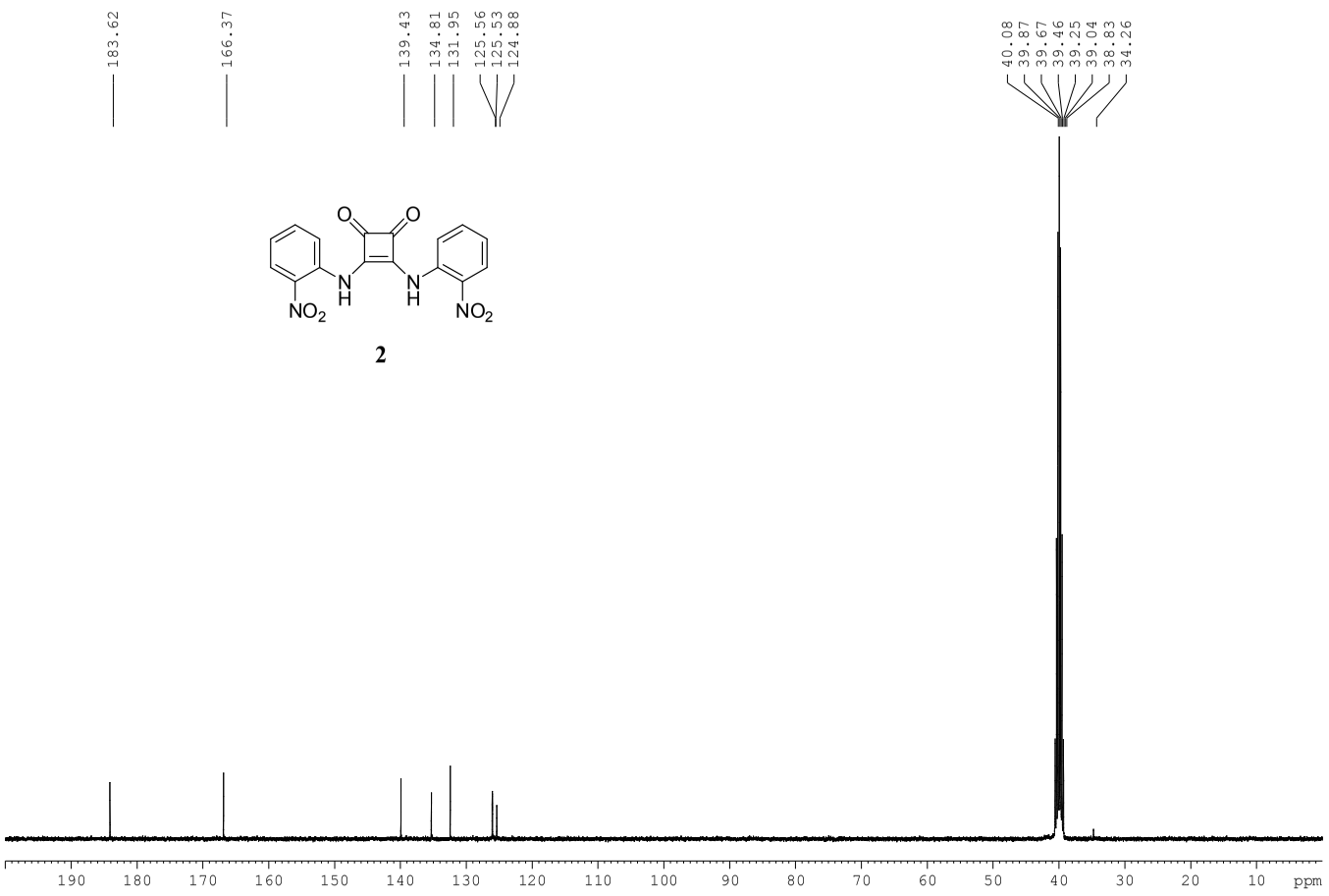


Figure 1.23: ^{13}C NMR (100 MHz) spectrum of 3, 4(2-nitro phenyl amino) cyclobut-3-ene-1, 2-dione **2** in DMSO-d_6

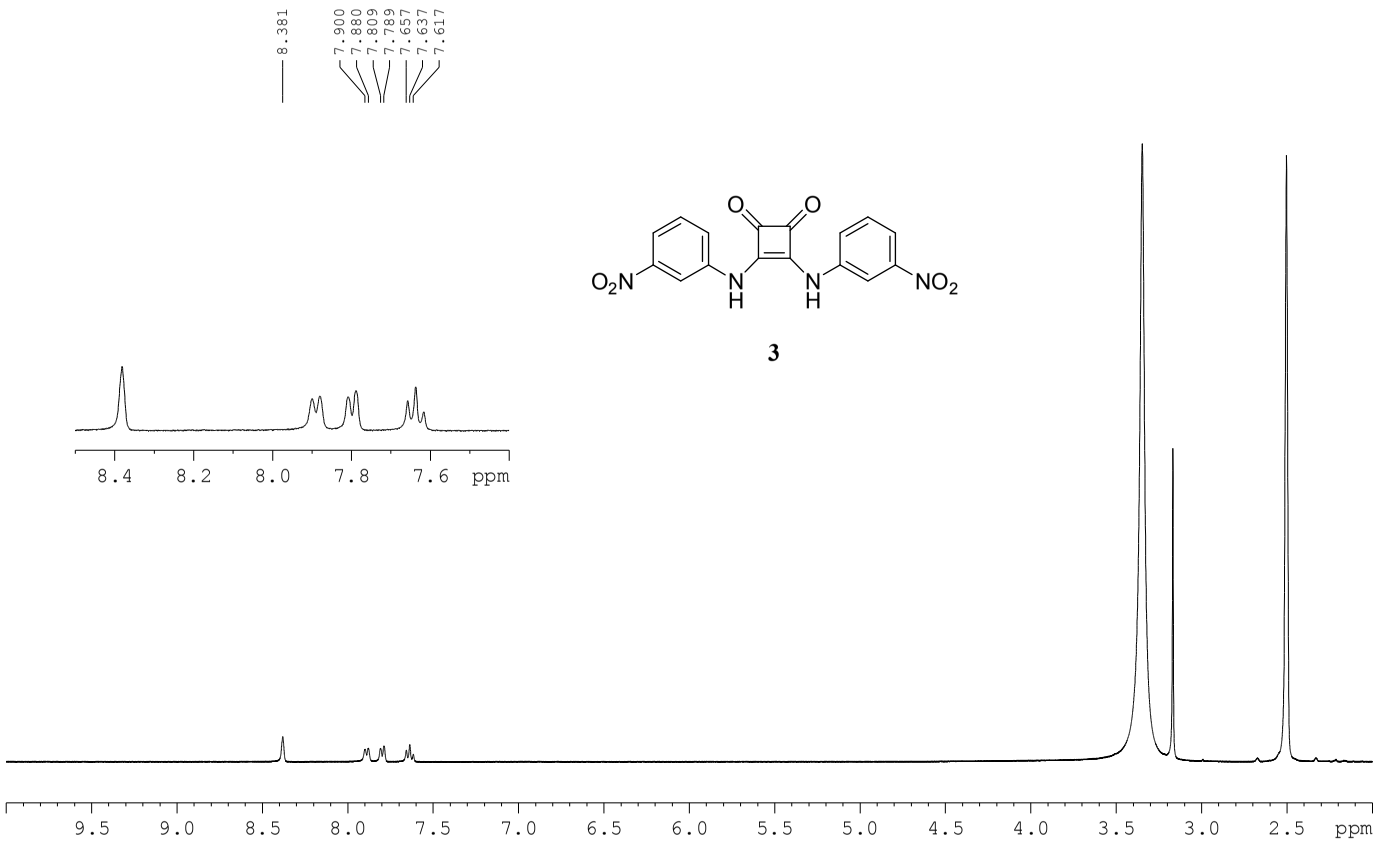


Figure 1.24: ^{1}H NMR (400 MHz) spectrum of 3, 4(3-nitro phenyl amino) cyclobut-3-ene-1, 2-dione (**3**) in DMSO-d_6

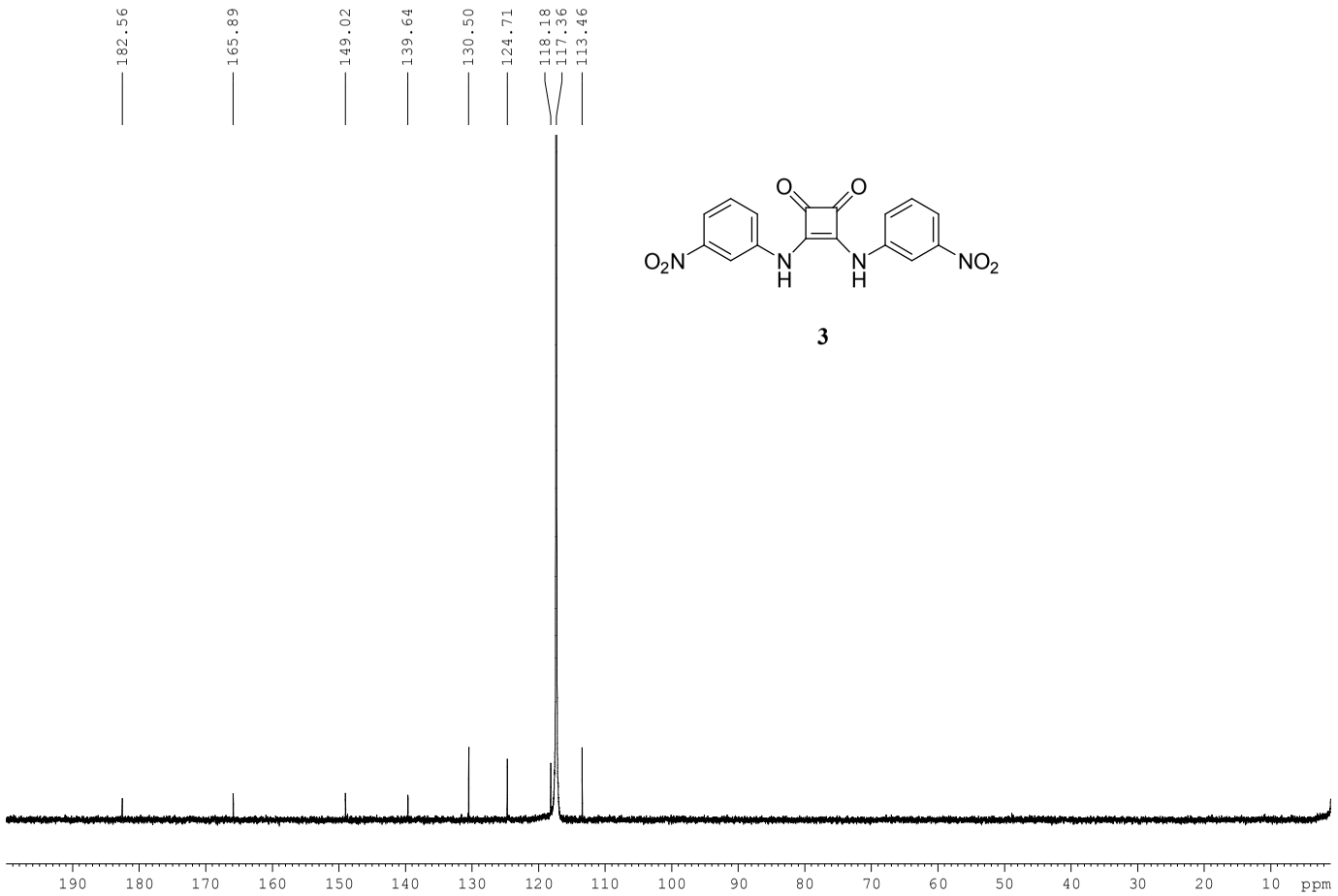


Figure 1.25: ^{13}C NMR (100 MHz) spectrum of 3, 4(3-nitro phenyl amino) cyclobut-3-ene-1, 2-dione (**3)** in acetonitrile-d_3

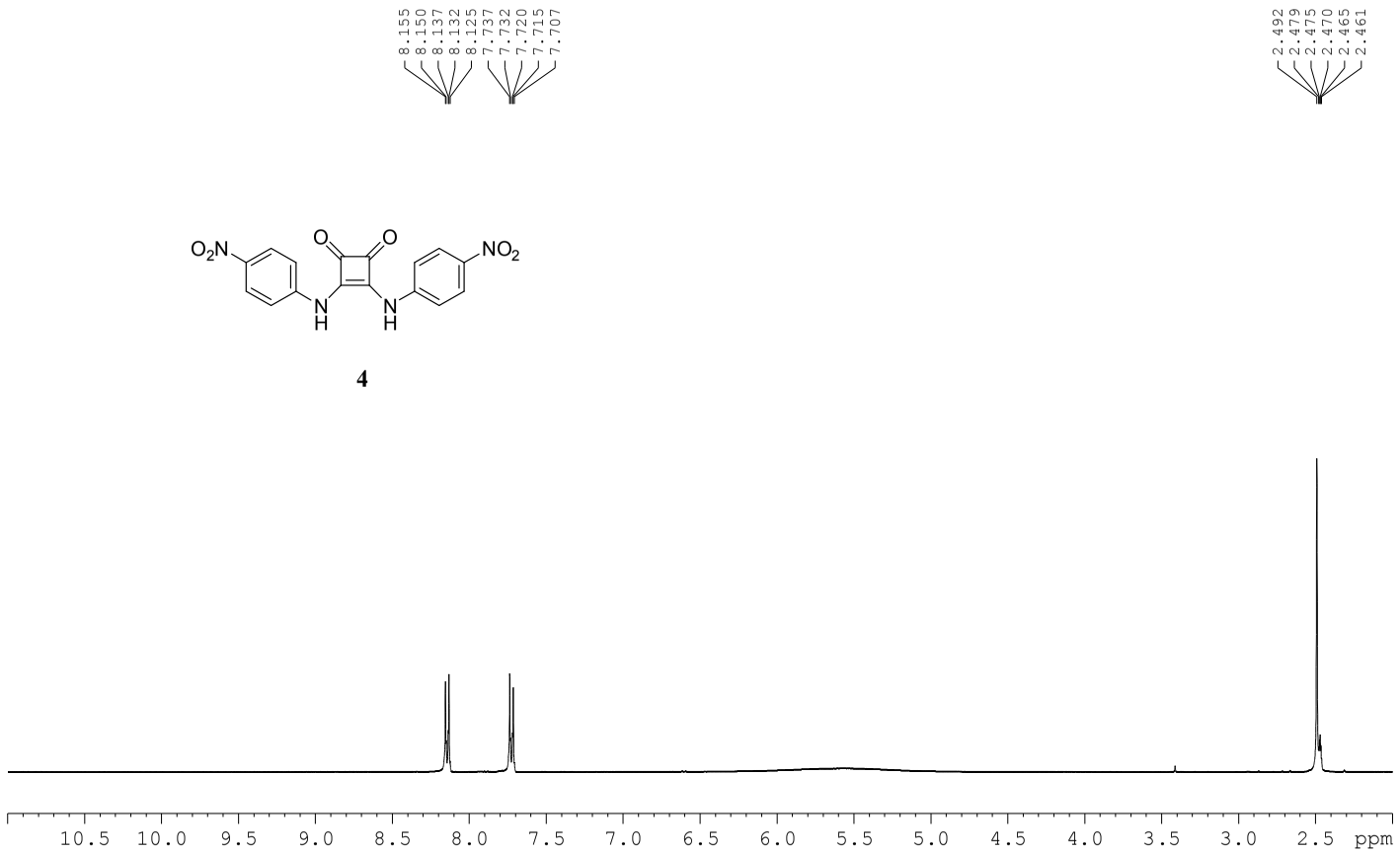


Figure 1.26: ^{1}H NMR (400 MHz) spectrum of 3, 4(4-nitro phenyl amino) cyclobut-3-ene-1, 2-dione (**4**) in DMSO-d_6

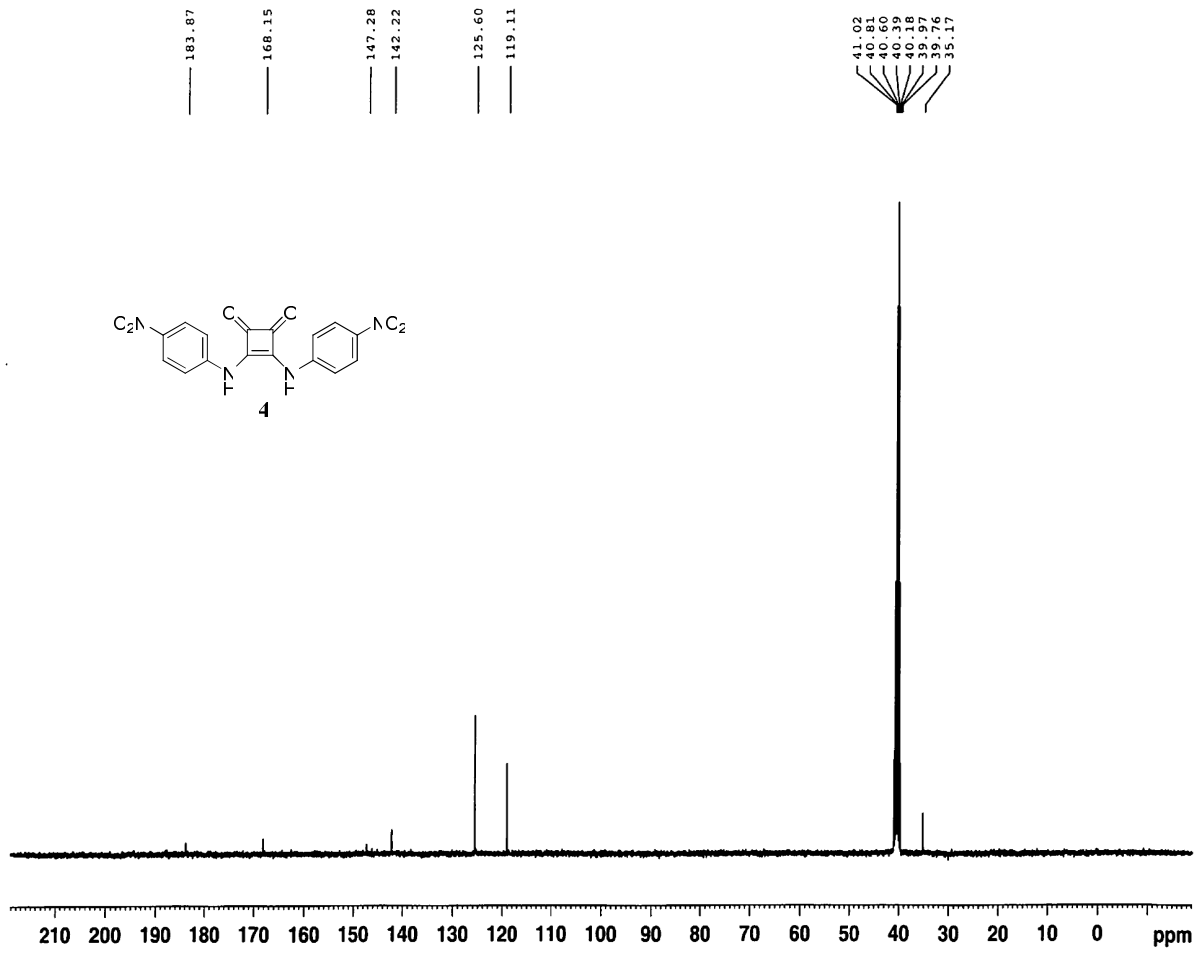


Figure 1.27: ^{13}C NMR (100 MHz) spectrum of 3, 4(4-nitro phenyl amino) cyclobut-3-ene-1, 2-dione **(4)** in DMSO-d6 @ 80^{o}C

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Chapter 2

Chloride Binding Squaramide-Based Molecular Machines

2.1 Introduction

Chloride ions play a vital role in controlling and modulating critical cellular functions[1-2] like acid-base balance, chloride-bicarbonate exchange mechanisms, modulating blood pH, neurotransmission, maintaining electrochemical gradient across the cell, and homeostasis. In our body, chloride [3] levels are maintained at the macro level by the kidneys and at the cellular level by the specific ion transporters and channels. The importance of dynamic regulation of chloride levels is underscored by the fact that a mutation in CFTR gene[4] (cystic fibrosis transmembrane conductance regulator, encoding for chloride ion channel) leads to cystic fibrosis, one of the most common life-shortening childhood-onset disease. Thus, in the event of a defective ion channel, a surrogate ion transporter[4] could be of therapeutic significance.

Unlike cation carriers, there are very few naturally available anion carriers. Prodigiosins[11] (**9**), which function as co-transporters of proton and chloride (**10**) are the only noteworthy examples. Therefore, the recognition of anionic species by synthetic receptors is a fast growing area of supramolecular chemistry[5]. For instance, a synthetic prodigiosin mimic was synthesized by Gale *et al*. containing amidopyrrole[12] (**11**) demonstrating enhanced H^+/Cl^- co-transport. Davis *et al.* showed that synthetic sterols[13](**12**) (termed "cholapods") can effectively transport chloride ions across liposomal membranes. However, incorporation of a binding and release mechanism has

thus far not been incorporated into a synthetic chloride ion receptor. Such a gated receptor has potential applications ranging from biology[9] to materials science.[10]

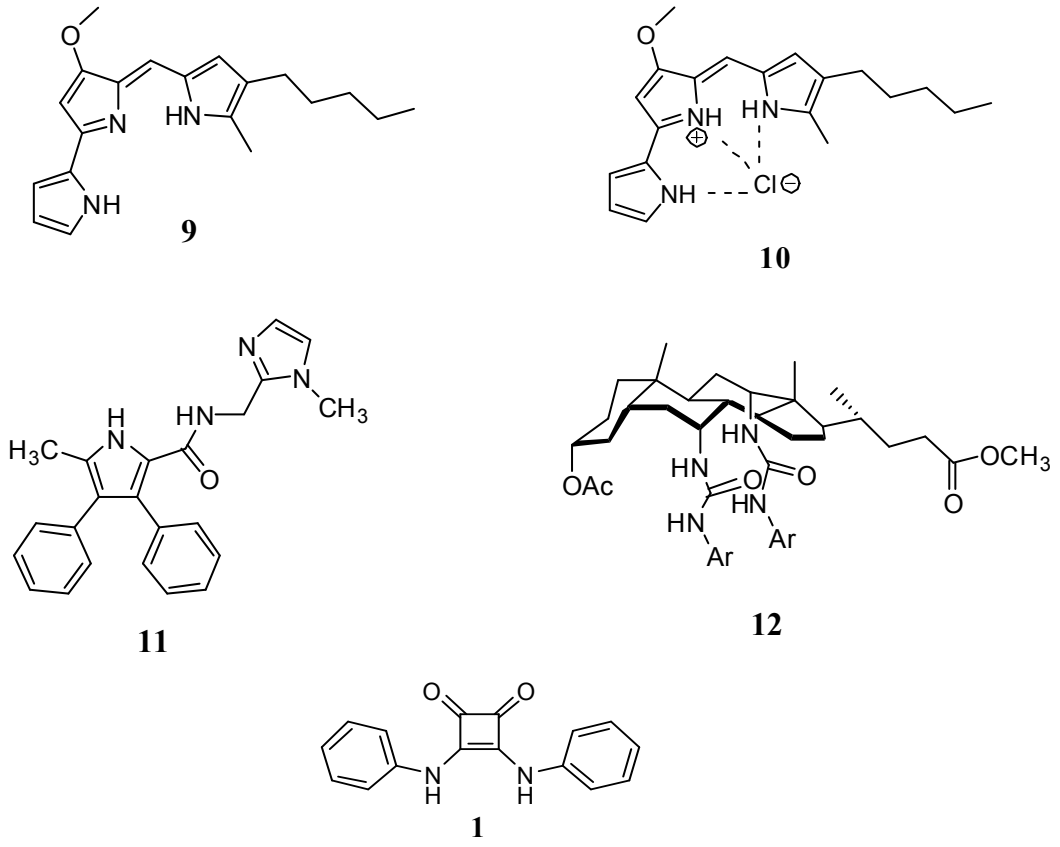


Figure 2.1: Chloride anion transporters

We have found that diphenyl squaramides **1** are promising new receptors which can bind chloride strongly (Chapter 1). In this chapter, we will evaluate the sensitivity of chloride binding to squaramides as a function of the environment as mimicked by different solvents.

2.2 Proposed molecular valve approach

From our studies on diaryl squaramides as anion receptors, we know that diphenyl squaramides are very good chloride receptors and that they exist predominantly in the *ZZ* conformation[14].

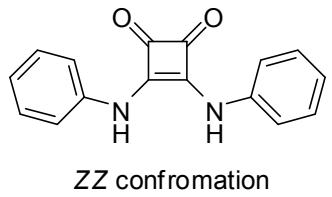


Figure 2.2: Diphenyl squaramide **1**

To regulate chloride binding, we decided to exploit ortho carbonyl groups, which can intramolecularly hydrogen bond with the NH group, as valves. We hypothesized that in non-polar solvents the intramolecular hydrogen bonding between the NH and C=O will be strong so that the anion binding will be turned "OFF" (Figure 2.4). In polar solvents, disruption of NH--O=C hydrogen bond followed by rotation of carbonyl groups would unlock the anion binding site ("ON" mode). Thus, our molecular valve approach will not only lead to binding of chloride to squaramide but also in the controlled-release of chloride, which could be exploited for drug delivery by mimicking the natural anion transporters.

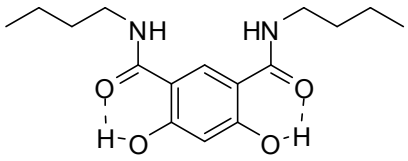


Figure 2.3: Isophthalamide scaffold for chloride binding

This proposal is complementary to the work of Santacroce *et al*., in isopthalamide[7] derivatives, in which intramolecular hydrogen bonding was exploited to preorganize the binding cavity.

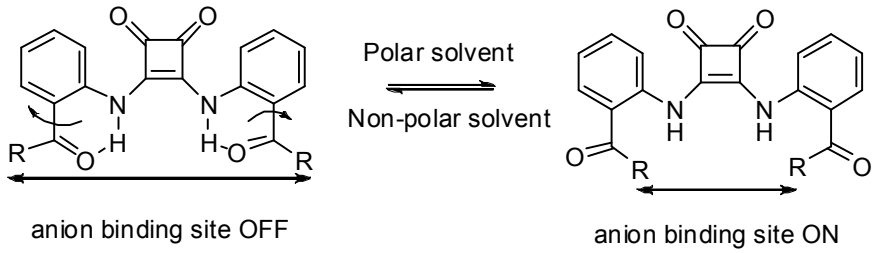


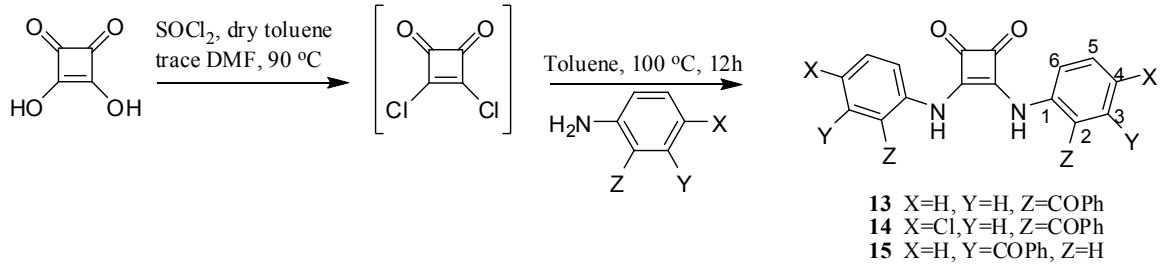
Figure 2.4: Solvent induced changes in benzoyl squaramides

2.3 Results and Discussion

2.3.1 Synthesis of squaramides and evidence of conformational preference

Symmetrical squaramides capable of anion binding, with concomitant molecular switching, were prepared starting from squaric acid[15] (scheme **2.1)**. The reactive squaryl dichloride was quenched with 2-aminobenzophenone derivatives to obtain corresponding crude squaramides **(13-15).** Squaramides were purified (by Mr. Maceij E. Domaradzki) by column chromatography, followed by repeated recrystallization to obtain pure squaramides.

Scheme 2.1:



^{1}H NMR spectra of squaramides **(13-15)** clearly show the conformational preference to be *ZZ* since the H_6 proton is most deshielded amongst the aromatic protons due to its proximity to the cyclobutenedione carbonyls.

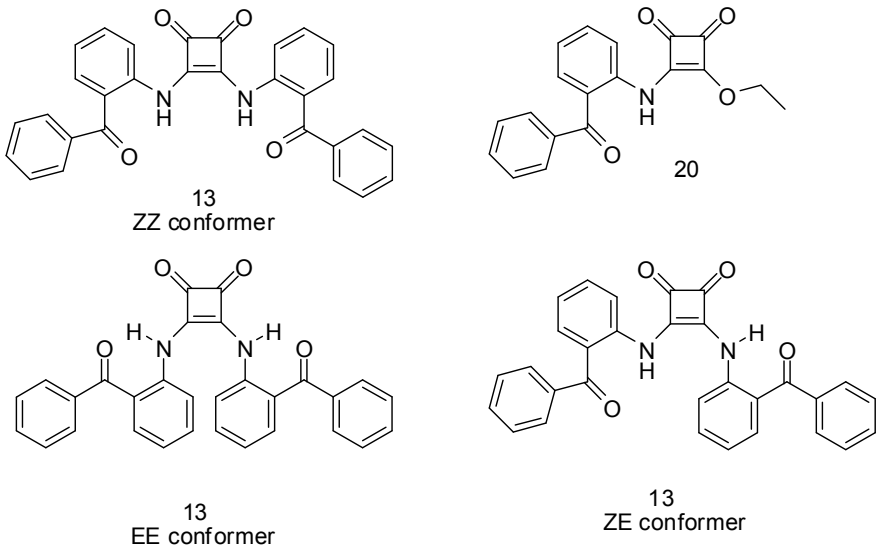


Figure 2.5: Conformational preference of ortho-carbonyl squaramide

Furthermore, in case of ortho-carbonyl squaramides **(13** and **14)**, the *ZZ* conformation is stabilized by strong intramolecular hydrogen bonding between the squaramide NH and the benzoyl carbonyl group. The *EZ* conformation was excluded since ^{1}H NMR did not have different sets of signals for aromatic protons, and the *EE* conformer was excluded because there was no upfield shift due to π-π interaction of co-facial[14] aromatic rings when compared to the ^{1}H NMR of monoester squaramide **20**. X-ray crystal structure analysis (conducted by Dr. Victor Young of the University of Minnesota) of **14** also revealed that *ZZ* conformation is the preferred conformation. This analysis showed clearly strong intramolecular hydrogen bonding between squaramide NH and the benzophenone carbonyl. The intramolecular hydrogen bond distance between squaramide NH and carbonyl is 1.94 Å (N2-H-O4). This intramolecular hydrogen bond distance

value is similar to the literature values[25]. A weak C-H··O interaction between squaramide carbonyl and $CHCl_3$ was also observed (section 2.8.7 for crystal data and structure refinement).

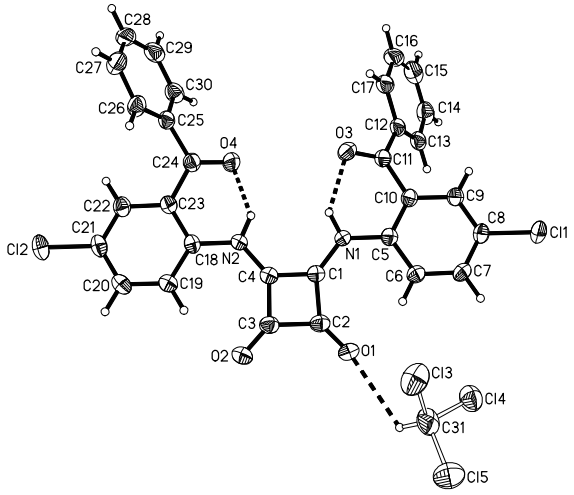


Figure 2.6: X-ray crystal structure of squaramide **14** (chloroform solvated) showing *ZZ* conformation

2.3.2 Intramolecular hydrogen bonding in squaramides:

In the solution state, strong intramolecular hydrogen bonding in the ortho squaramide **13**, (Figure 2.7) between the carbonyl functionality of the ortho benzoyl group and the NH, was supported by the 2.2 ppm downfield shift of NH peak (11.4 ppm) compared to the meta isomer **15** (9.2 ppm) in chloroform. Similarly in the ^{13}C NMR spectrum of squaramide **13** the carbonyl carbon was deshielded by about 4 ppm when compared to squaramide **15.** The sharpness of the NH peak in the ^{1}H NMR spectrum of 13, relative to 15, also suggested intramolecular hydrogen bonding. The solution IR spectra in chloroform further supported strong intramolecular hydrogen bonding. For example, the

benzoyl carbonyl signals for squaramide **13** and **14** appear at 1641 cm^{-1} and 1644 cm^{-1} respectively, which are at lower frequencies compared to squaramide **15** (1660 cm^{-1}).

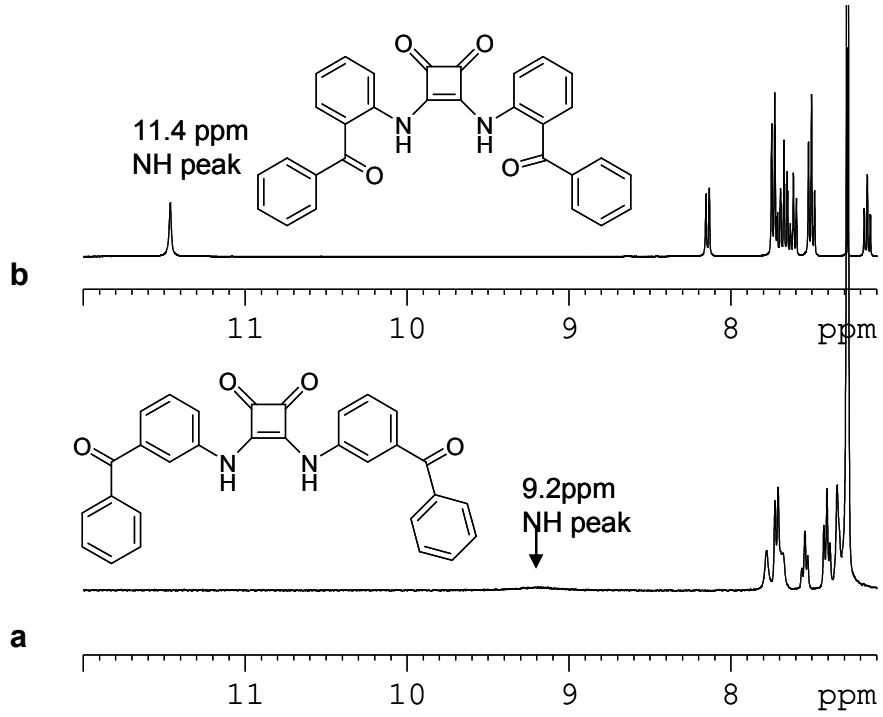


Figure 2.7: a) ^{1}H NMR spectrum of squaramide **15,** aromatic region in $CDCl_3$. b) ^{1}H NMR spectrum of squaramide **13,** aromatic region in $CDCl_3$

2.3.3 Interaction of squaramides with chloride ion

The ^{1}H NMR binding studies of squaramide **13** with tetrabutylammonium chloride (TBA-Cl) were performed in non-polar (chloroform) and polar solvents (acetonitrile and DMSO). In chloroform, chloride did not bind (no spectral changes were observed in NMR or UV-Vis) due to the strong intramolecular hydrogen bonding which prevented the anion binding to squaramide-NH (Figure 2.8). In acetonitrile, addition of chloride led to a downfield shift in the NH peak indicative of binding. However, in DMSO, no binding was observed possibly due to solvent competition with the anion for the binding

site or due to strong solvation of the anion. The possibility of a nucleophilic chloride attack at the benzoyl carbonyl carbon of squaramide **13** was ruled out since the carbonyl peaks in the ^{13}C NMR spectra were intact with chloride titration.

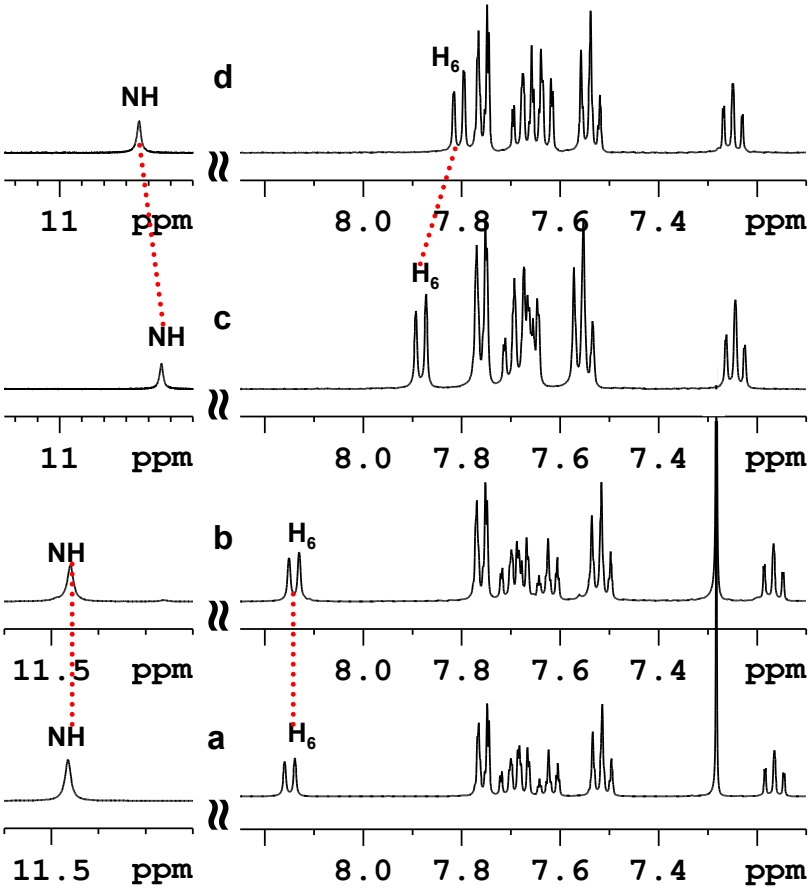


Figure 2.8: a) ^{1}H NMR spectrum of squaramide **13** (2 mM) in $CDCl_3$. b) Squaramide **13** with TBA Cl^- 1:1 (2 mM) in $CDCl_3$ c) ^{1}H NMR spectrum of squaramide **13** (2mM) in CH_3CN d) ^{1}H NMR spectrum of squaramide **13** with TBA Cl- 1:1(2 mM) in CH_3CN.

To exclude the possibility of aggregation, the ^{1}H NMR spectra of uncomplexed squaramides (**13** and **14)** were recorded from 0.5 mM to 5.0 mM, both in chloroform and acetonitrile. Only minor changes (< 0.01 ppm) in the ^{1}H NMR spectra were observed. Among the halides only chloride showed selective binding to the ortho carbonyl squaramides **13** and **14**. Bromide and iodide did not cause any spectral changes in ^{1}H

NMR (Figure 2.40). With fluoride, deprotonation of squaramide NH was observed as a 77 nm bathochromic shift suggested NH deprotonation (The fluoride-induced shift was nearly identical to the one obtained upon addition of OH^- anion).

2.4 Binding studies

2.4.1 Binding of squaramide 13 with chloride

There were no noticeable changes in the UV-Vis spectra upon titration of squaramide **13** with tetrabutylammonium chloride. Therefore, ^1H NMR was used to determine binding constant[17]. A plot of $\Delta\delta$ of the NH peak versus chloride concentration was used to determine the binding constant, which was found to be 84 $\pm$ 8 M^{-1} (Figure 2.9) in acetonitrile. A non–linear curve fitting method (using Kaleidagraph) was used to generate the binding isotherm curve. Job's plot[16] showed the stoichiometry of the complex to be 1:1 (Figure 2.10).

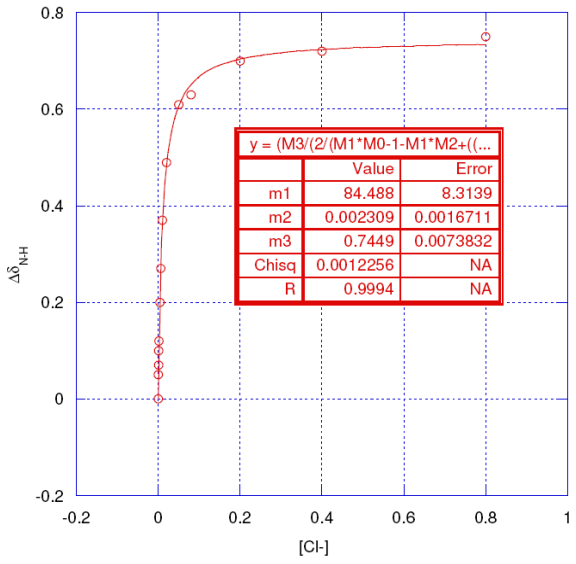


Figure 2.9: Binding isotherm curve of squaramide **13** with chloride. Binding constant was calculated from the curve using Kalediagraph and the equation[25]. $Y= A_{max}/(2/ K_a [Anion]-1- K_a [Squaramide]+((1- K_a [Anion]+Ka[Squaramide])^2 + 4K_a[Anion])^{0.5})+1))$, wherein Y is the chemical shift and K_a is the binding constant.

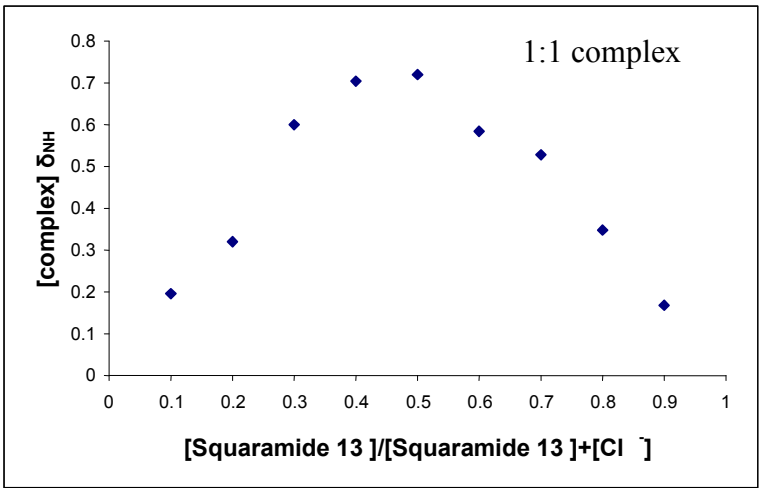


Figure 2.10: Job's plot of squaramide **13** with chloride titration.

2.4.2 Titration of Squaramide 14 with chloride

Squaramide **14** also showed no observable changes in UV-Vis spectroscopy upon titration with TBA-Cl in both acetonitrile and chloroform.

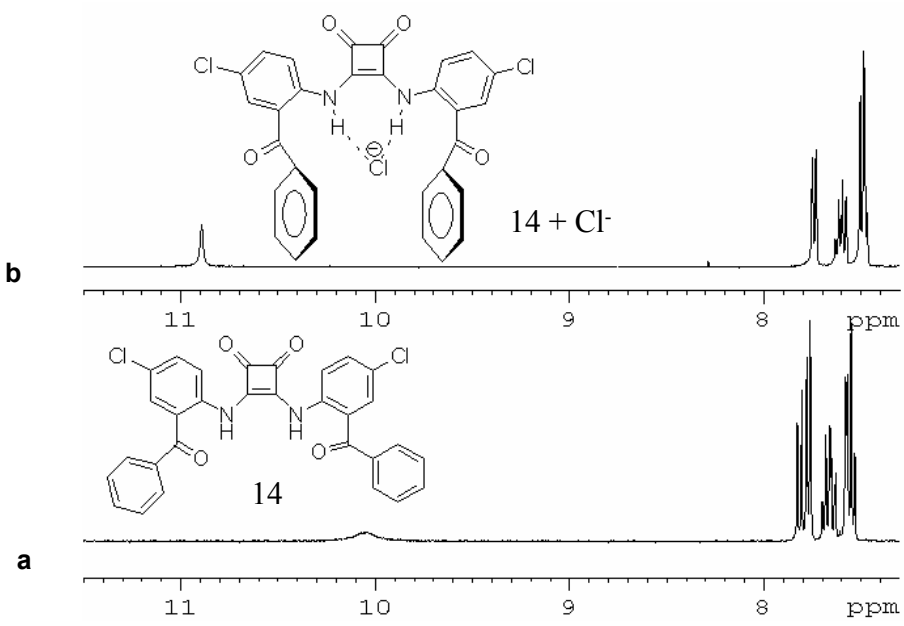


Figure 2.11: a) ^{1}H NMR spectrum squaramide **14** in acetonitrile. b) ^{1}H NMR spectrum squaramide **14** with TBA Cl- (1:1) 2mM in acetonitrile.

Thus ^{1}H NMR was used for determination of the binding constant. No change was observed in the ^{1}H NMR spectra of squaramide **14** upon chloride titration in chloroform. However, in acetonitrile a 0.7 ppm downfield chemical shift was observed for squaramide NH proton upon chloride addition. Binding constant was determined using ^{1}H NMR by titration of TBA chloride with squaramide **14** and was found to be 517±34 M^{-1}, which is approximately six times greater than squaramide **13.** This increase in the binding constant is likely due to the presence of electron withdrawing chloride in the para position. Job's plot indicated a 1:1 binding stoichiometry for the complex (Figure 2.13). Thus squaramides **13** and **14** behave in a very similar manner showing solvent dependent chloride binding.

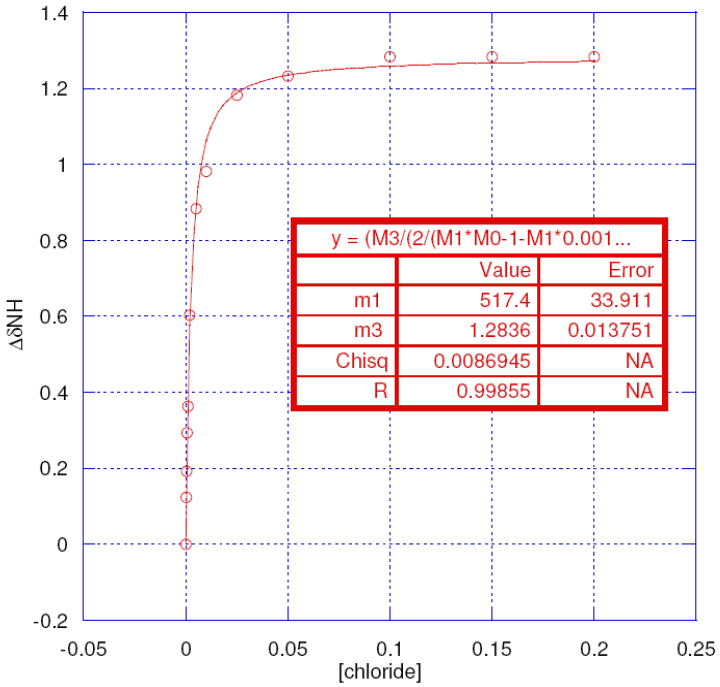


Figure 2.12: Binding isotherm curve of squaramide **14** with chloride. Binding constant was calculated from the curve using KalediaGraph and the equation $Y= A_{max}/(2/ K_a [Anion]-1- K_a [Squaramide]+((1- K_a [Anion]+K_a[Squaramide])^2 + 4K_a[Anion])^{0.5})+1))$, wherein Y is the chemical shift and K_a is the binding constant.

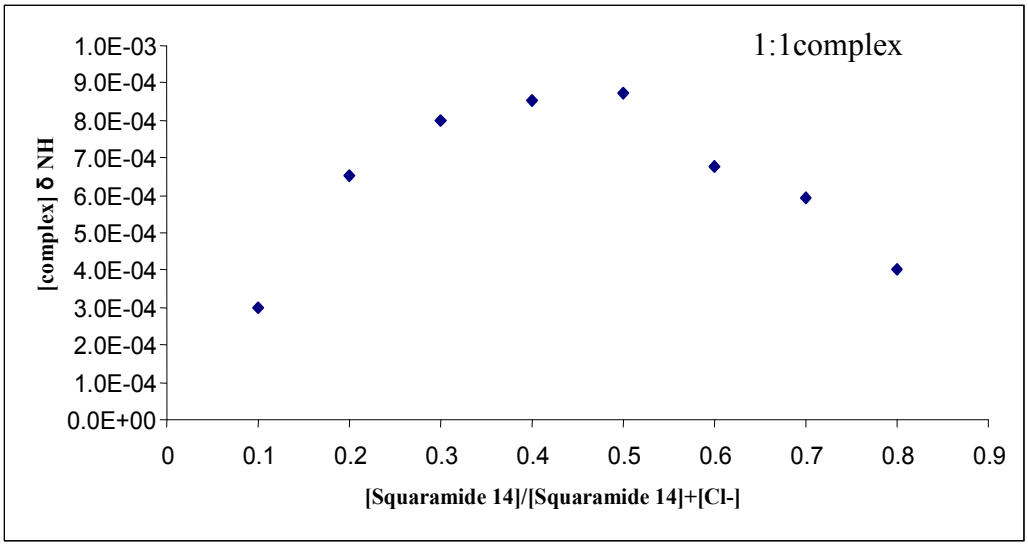
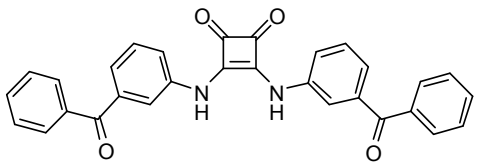


Figure 2.13: Job's plot of squaramide **14** with chloride anion.

2.4.3 Titration of Squaramide 15 with chloride

Squaramide **15**, in which there is no intramolecular hydrogen bonding between squaramide NH and the carbonyl oxygen (by virtue of its distance), was synthesized as a control compound. Unlike the ortho carbonyl squaramides **13** and **14**, distinct spectral changes were observed in UV-Vis spectroscopy upon chloride titration. ^{1}H NMR spectrum of squaramide **15** titration with chloride also showed a large downfield shift in the NH peak indicating strong binding. This shift was indicative of chloride hydrogen bonding with squaramide NH.



15

Figure 2.14: Squaramide **15**, no intramolecular hydrogen bonding possible (solvent-independent binding).

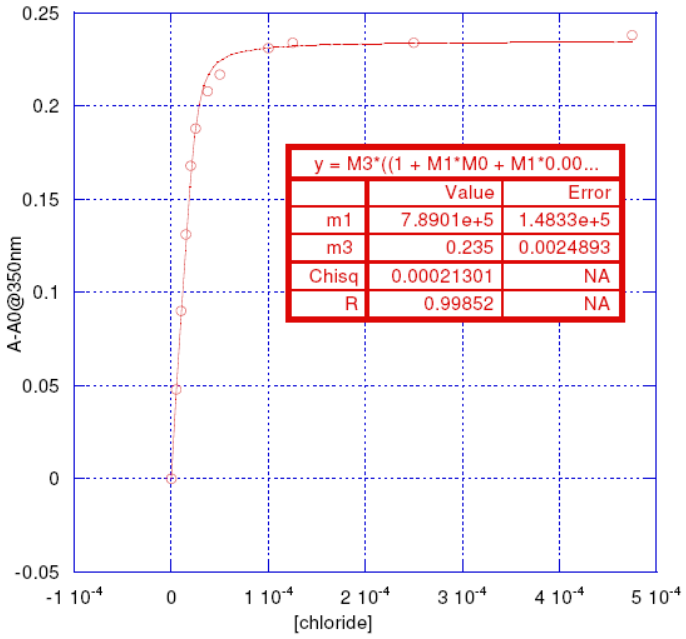


Figure 2.15: Binding isotherm curve of squaramide **15** with chloride anion in chloroform. The binding constant was calculated from the curve using Kalediagraph and the equation Δ abs= Δ abs maximum (1+K_a [Host] + K_a [Cl]-)-((1+ K_a [Host] + K_a [Cl-]) ^{2} - 4K_a^2 [Host] [Cl-] 0.5/ 2 K_a [Cl-].

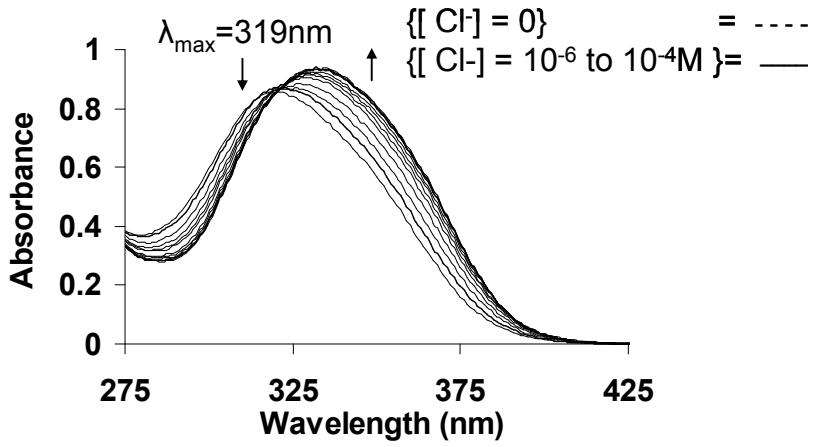


Figure 2.16: UV-Vis spectrum of squaramide **15** (2.5 X 10^{-5} M) with chloride anion in acetonitrile

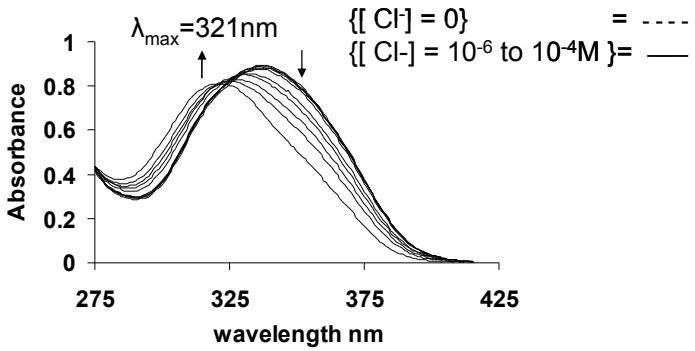


Figure 2.17: UV-Vis spectrum of squaramide **15** (2.5 X 10^{-5} M) with chloride anion in chloroform

To exclude the possibility of aggregation, UV-Vis spectroscopy[18] was used to determine binding constant of squaramide **15.** Binding constants in chloroform and acetonitrile were found to be 7.89 x 10^5 M^{-1} and 4.14 x 10^5 M^{-1} respectively (Figures 2.15 and 2.18), indicating that solvent polarity plays no role in chloride binding for the meta isomer. This result also suggests that the solvation of tetrabutylammonium chloride in chloroform and acetonitrile may be similar. Table **2.1** summarizes the solvent polarity dependent binding of chloride to squaramides **13** and **14** and solvent independent binding of **15**.

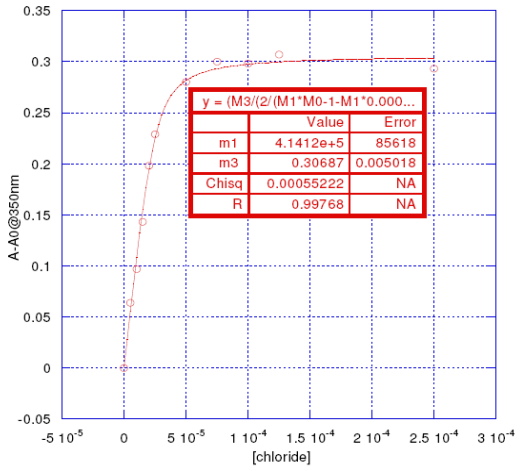
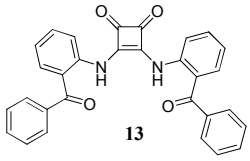
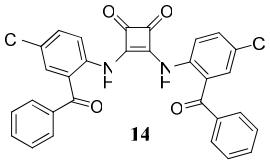
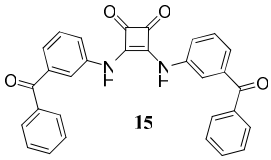


Figure 2.18: Binding isotherm curve of squaramide **15** with chloride anion in acetonitrile.

Table 2.1: Association constants, Ka, of squaramides:

entry	squaramide	chloride binding constant	
		chloroform	acetonitrile
1	 **13**	ND [c]	(84 M^{-1})[a]
2	 **14**	ND [c]	(514 M^{-1})[a]
3	 **15**	(7.89 x 10^5 M^{-1}) [b]	(4.14 x 10^5 M^{-1}) [b]

[a] Determined by ^{1}H NMR. [b] Determined by UV-Vis spectroscopy. [c]ND not detected.

2.5 Evidence for disruption of intramolecular hydrogen bonding

^{1}H NMR spectra of uncomplexed squaramide **13** were recorded in solvents of varying dielectric constants. A plot of dielectric constants versus the δ NH peak of squaramide **13** was linear—increasing solvent polarity led to an upfield shift.

Table 2.2: Solvent dependent squaramide NH changes in ^{1}H NMR

entry	Solvent	Dielectric constant	Squaramide **13** NH Peak in ppm
1	Toluene	2.4	11.38
2	Chloroform	4.8	11.49
3	Methylene chloride	9	11.33
4	Acetonitrile	37.5	10.54
5	DMSO	46.7	10.21

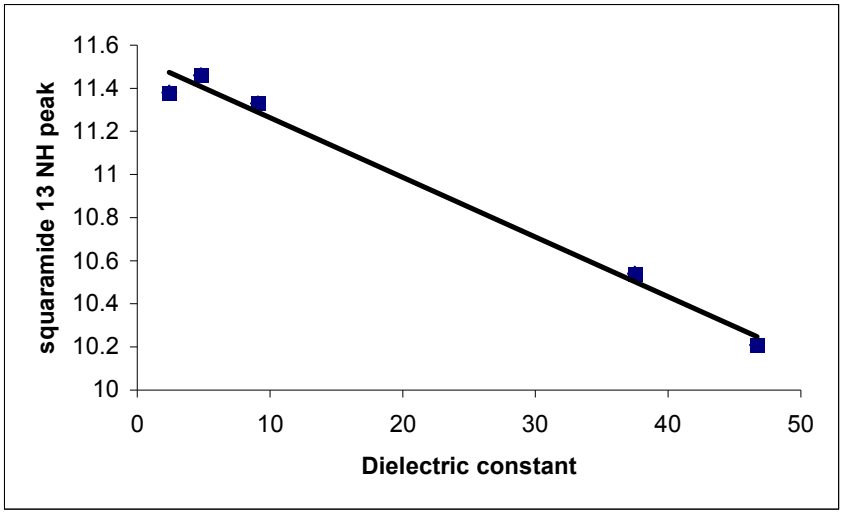
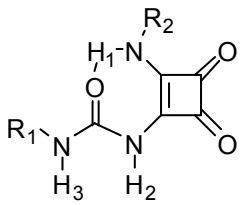


Figure 2.19: Correlation of NH peak vs dielectric constant of solvent

This suggests that as we increase the solvent polarity, weakening or disruption of intramolecular hydrogen bonding occurs. With squaramide **15** (control compound with no intramolecular hydrogen bonding) no clear trend was observed. Disruption of intra and intermolecular hydrogen bonding by polar solvents, such as acetonitrile, in carbamoyl squaramide[19] **18** was also demonstrated by Davis *et al*. In their study they describe upfield shifts, similar to those observed by us, in the intramolecularly hydrogen bonded squaramide NH peak (H_1) upon increasing the solvent polarity. The H_1 peak of squaramides **18** shifted 0.7 ppm with a change in solvent from $CHCl_3$ to CH_3CN.



18

Figure 2.20: Carbamoyl squaramide monomer **18**.

2.6 Requirements of ortho carbonyl squaramide for chloride binding:

To assess the relative contributions of weakened intramolecular hydrogen bonding and/or a requirement of carbonyl reorientation to chloride binding, squaramides **16** and **17** were prepared.

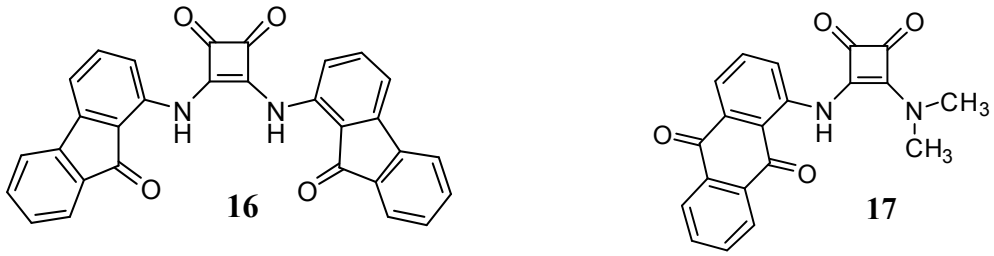


Figure 2.21: Squaramides **16** and **17**

In squaramide **16,** increase in the distance between the squaramide NH and the fluorenone carbonyl group decreases the strength of intramolecular hydrogen bonding[20] whereas in squaramide **17** the intramolecular hydrogen bonding is strengthened as indicated by ^{1}H NMR data (Table **2.3)**. A literature survey of similar compound (Figure 2.22) also suggested the weak intramolecular hydrogen bonding in fluorenone **16a** compared to anthraquinone derivative **17a**. The distance between the H1 and O1 bond in **16a** is 2.21Å whereas in **17a,** the distance decreased by 0.3 Å as calculated by molecular mechanics[20].

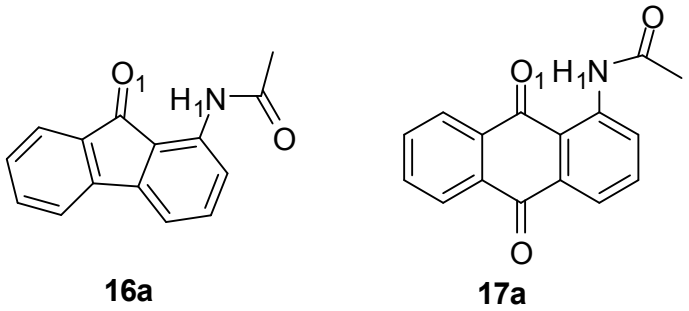


Figure 2.22: N-acetyl fluorenone and anthraquinone.

Table 2.3: Use of δNH as a measure of intramolecular hydrogen bonding

entry	ortho carbonyl squaramide	^{1}HNMR NH peak in $CDCl_3$
1	**13**	11.4
2	**14**	11.3
3	**16**	10.4
4	**17**	12.5

The ^{1}H NMR spectra of squaramide **16** with chloride anion in $CDCl_3$ showed no binding. This suggests that the weakening of intramolecular hydrogen bonding alone is not adequate, and that the reorientation of carbonyl group is important for chloride binding. Attempts to record the ^{1}H NMR spectrum of squaramide **16** in CD_3CN failed due to its insolubility.

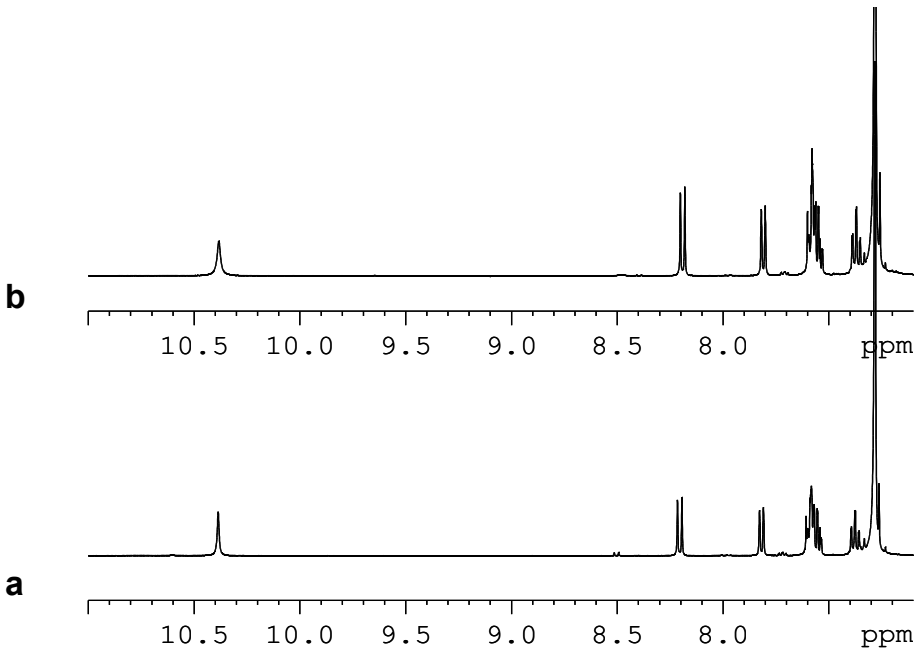


Figure 2.23: a) ^{1}H NMR spectrum, aromatic region of squaramide **16** in $CDCl_3$. b) ^{1}H NMR spectrum aromatic region of squaramide **16** in $CDCl_3$ with TBA chloride (1:1) 2 mM in $CDCl_3$.

Computational studies (in collaboration with Dr. Seogjoo Jang) of squaramide **13** were performed to understand the structural differences between the uncomplexed and the chloride-bound squaramide. The DFT calculations (B3LYP 6-31+G (d,p) showed that chloride binding leads to an increase in the hydrogen distance (C=O···HN) from 1.76 Å to 2.48 Å (Figure 2.24). Reorientation of the benzoyl carbonyl group away from the squaramide NH was also clearly evident. The hydrogen bond angle[21] of squaramide **13** was found to be 140°. Furthermore, in the chloride bound form, the calculated[22] N···Cl distance is 3.1 Å which is close to the experimentally obtained value in other chloride complexes[22]. Therefore, computational and experimental data showed that the carbonyl groups function as reversible molecular valves to open and close the chloride-binding cavity in response to changes in solvent polarity.

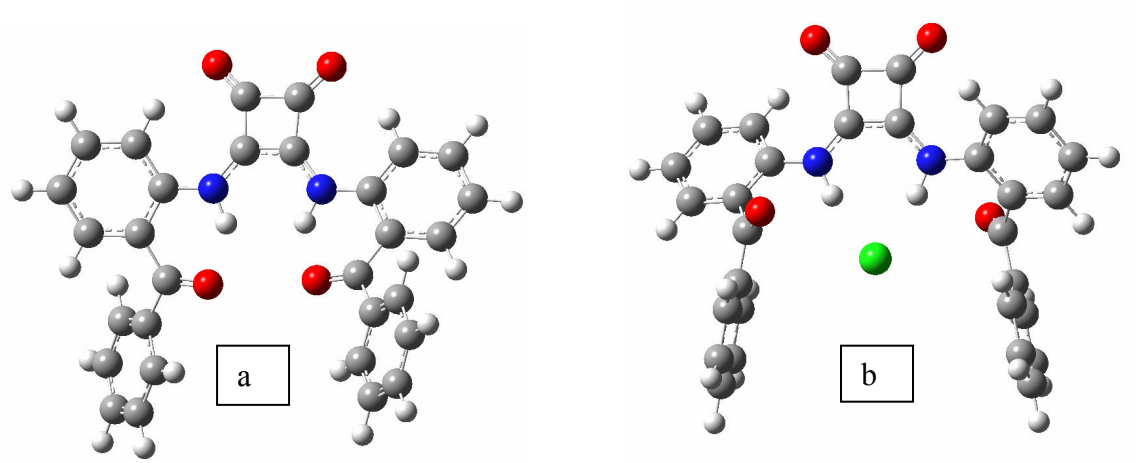


Figure 2.24: Gaussian optimized structure using B3LYP 6-31+G (d,p) a) Uncomplexed squaramide **13** b) chloride anion complexed squaramide **13.**

2.7 Conclusions

A combined solvent and chloride-induced conformational switching in ortho carbonyl squaramides was demonstrated. The results presented here provide the first documented

evidence that ortho carbonyl squaramide derivatives can be employed as molecular valves for chloride binding and release. Selective chloride binding among the halide was shown by aryl squaramides. Furthermore, the anion binding affinity can be manipulated by incorporating electron withdrawing groups as seen in squaramide **14** where stronger binding was observed compared to squaramide **13**. Binding and release of chloride in polar and non-polar solvents respectively serves as a new model in designing efficient anion receptors. These "smart" squaramides could find potential therapeutic applications constructs serving as surrogate anion carriers.

2.8 Experimental section

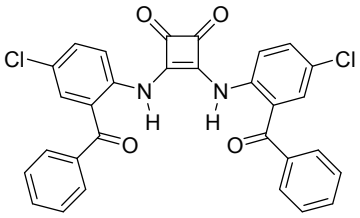
All reactions were performed under nitrogen atmosphere unless otherwise specified. All glassware was oven-dried at 110 ^{o}C and cooled under nitrogen. Melting points were recorded using a Mel-Temp apparatus and are uncorrected. All tetrabutylammonium salts were purchased from commercial sources and were used without further purification. HPLC grade acetonitrile and chloroform were used for all UV-Vis studies. The K_a values were determined using either ^{1}H NMR or UV-vis spectroscopy. The binding isotherms were generated by titrating the appropriate squaramides with tetrabutylammonium chloride such that the guest to host ratio ranged from 0-400 equivalents. The binding constant (K_a) was then determined using a nonlinear least squares regression method. For the Job plots, equimolar solutions (2 mM each) of the squaramide and the tetrabutylammonium chloride were mixed in different volume ratios so that the mole fraction of the squaramide ranged from 1 to 0.1 in increments of 0.1. The ^{1}H and ^{13}C NMR were recorded at 400 MHz and 100 MHz, respectively. The chemical shifts are reported in δ ppm using the residual solvent peak (7.28 ppm for

$CDCl_3$ and 2.50 ppm for d_6-DMSO) as the internal reference. Coupling constants are reported in hertz. HRMS were collected at the CUNY Mass Spectrometry Facility at Hunter College. X-Ray crystal structure solution and data collection was performed by Dr. Victor G. Young, Jr. at the X-Ray Crystallographic Laboratory of the Department of Chemistry at the University of Minnesota. All calculations were performed using Pentium computers using the current SHELXTL suite of programs.

2.8.1 Preparation of 3, 4-bis (2-benzoyl phenyl amino) cyclobut-3-ene-1, 2-dione (13)

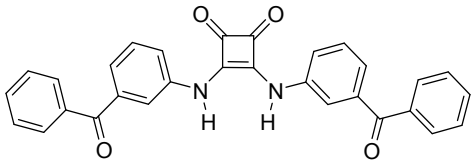
To a stirring solution of squaric acid (114 mg, 1 mmol) in dry toluene, thionyl chloride (238 mg, 2 mmol) and DMF (20 μL) were added at room temperature under nitrogen atmosphere. Reaction temperature was then increased to 95 ^oC (oil bath temperature) and maintained for 2hours. Reaction mixture was allowed to attain room temperature and concentrated to obtain an oily residue which was dissolved in dry toluene (2 ml). To this, a solution of 2-aminobenzophenone (788 mg, 4 mmol) in toluene (10 ml) was added at room temperature. The reaction mixture was held at refluxed for 24h. The precipitated solids were filtered and washed with methanol (50 ml) and recrystallized twice from acetonitrile to obtain compound (**13)** in 60% yield. ^1H NMR ($CDCl_3$): 11.46 (s, 2H), 8.14 (d, 2H, *J* = 8.4), 7.73 (d, 4H, *J* = 6.8), 7.72-7.59 (m 6H), 7.50 (t, 4H, *J* = 7.2), 7.16 (t, 2H, *J* = 8Hz). ^{13}C NMR ($CDCl_3$): 199.9, 183.3, 166.32, 140.4, 138.3, 135.0, 134.3, 132.4, 129.8, 128.3, 1213, 122.4, and 120.9. UV-Vis (CH_3CN) (λ_{max}, ε) (383 nm), (1.9 x 10^4 M^{-1} cm^{-1}), (313 nm), (2.1 x 10^4 M^{-1} cm^{-1}). IR in chloroform 1795 (four membered ring carbonyl) and 1640 cm^{-1}. HRMS calculated for $C_{30}H_{20}N_2O_4$ (M+1) = 473.1495 found 473.1492. Mpt: 223-224 °C.

2.8.2 Preparation of 3, 4-bis (2-benzoyl 4-chloro phenyl amino) cyclobut-3-ene-1, 2-dione (14)



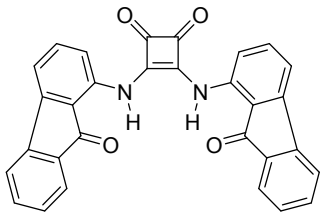
Orange-yellow solid obtained in 60% yield. ^{1}H NMR ($CDCl_3$): 11.30 (s, 2H), 8.12 (d, 2H, J = 8.4Hz), 7.72(d, 4H, J = 6.8), 7.67-7.61 (m, 6H), 7.53 (t, 4H, J = 8.0). ^{13}C NMR ($CDCl_3$): 198.8, 183.0, 166.0, 138.8, 137.5, 134.8, 133.4, 133.0, 129.8, 128.6, 128.1, 123.4, 122.57. UV-Vis (CH_3CN) (λ_{max}, ε) 388 nm (1.8 x 10^4 $M^{-1}cm^{-1}$), 319 nm (2.4 x 10^4 $M^{-1}cm^{-1}$), IR in chloroform 1795 (four membered ring carbonyl) and 1643 cm^{-1}, HRMS calculated for $C_{30}H_{18}Cl_2N_2O_4$ (M^+) = 540.0643 found 540.0646. Mpt. 248-250 °C

2.8.3 Preparation of 3, 4-bis (3-benzoyl phenyl amino) cyclobut-3-ene-1, 2-dione (15)



Pale yellow solid obtained in 45% yield. ^{1}H NMR (CD_3CN): 8.38 (s, 2H), 7.82 (d, 4H, J = 8.0), 7.75 (s, 2H,), 7.67 (m, 4H,), 7.55 (m, 8H). ^{13}C NMR (CD_3CN): 195.2, 1813, 165.4, 138.3, 138.2, 136.8, 132.3, 129.5, 129.1, 128.0, 124.9, 1213 and 119.8. UV-Vis (CH_3CN) (λ_{max}, ε) (320nm) (3.2 x 10^4 $M^{-1}cm^{-1}$). IR in chloroform 1793cm^{-1}(four membered ring carbonyl) and 1662 cm^{-1}. HRMS calculated for $C_{30}H_{20}N_2O_4$ (M^+) = 472.1423 found 472.1432. Mpt.170-172 °C

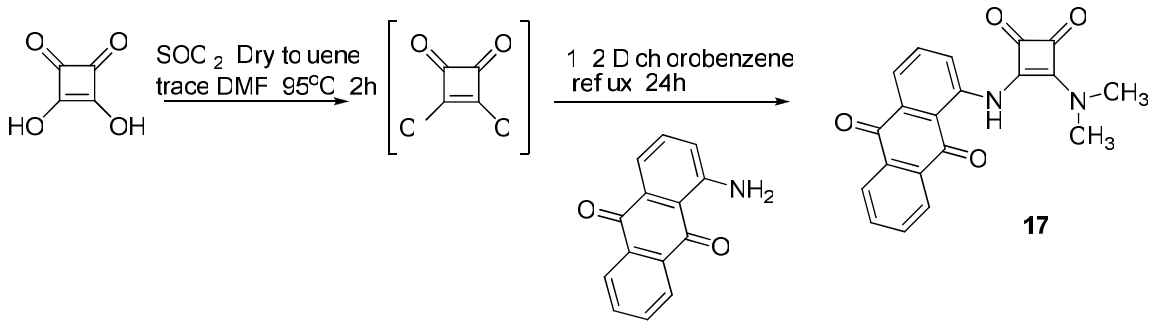
2.8.4 Preparation of 3, 4-bis (9-oxo-9H-fluoren-1-ylamino) cyclobut-3-ene-1, 2-dione (16)



1, 2-dichlorobenzene was used as solvent. Reaction temperature was maintained at 145 ^{o}C for 24h. Reddish brown

solid obtained in 53% yield. ^{1}H NMR (DMSO-d_6): 10.62 (s, 2H), 7.84 (d, 2H, J = 8.2), 7.65-7.56 (m, 8H), 7.40(m, 4H). ^{13}C NMR (DMSO-d_6): 191.4, 184.2, 166.7, 144.7, 143.4, 136.9, 136.8, 135.5, 133.8, 130.1, 124.1, 123.2, 121.8, 120.8 and 117.2. HRMS calculated for $C_{30}H_{16}N_2O_4$ (M^+) = 468.1110 found 468.1122. Mp> 250 ^{o}C.

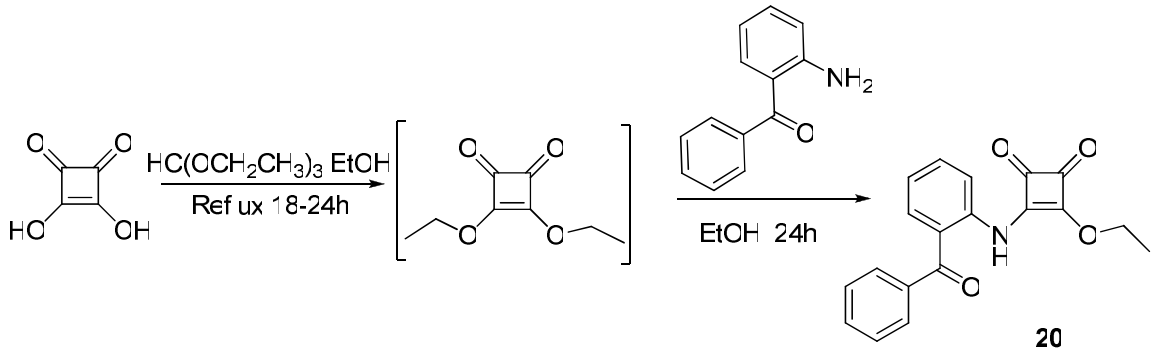
2.8.5 Preparation 1-(2-(dimethylamino)-3, 4-dioxocyclobut-1-enylamino) anthracene-9, 10-dione (17)



To a stirring solution of squaric acid (114 mg, 1 mmol) in dry toluene, thionyl chloride (238 mg, 2 mmol) and DMF (20 µL) were added at room temperature under nitrogen atmosphere. Reaction temperature was then increased to 95 ^{o}C (oil bath temperature) and maintained for 2hr. Reaction mixture was allowed to attain room temperature and concentrated to obtain an oily residue which was dissolved in dry toluene (2 ml). A solution of 2-aminoanthraquinone (446 mg, 2 mmol) in 1, 2 dichlorobenzene (10 ml) was dissolved in a separate round-bottom flask and added drop-wise to prepared squaryl dichloride at room temperature. Upon complete addition, the reaction mixture was refluxed for 24h. Column purified (2% methanol in methylene chloride) to obtain compound **17** in 7% yield. ^{1}H NMR ($CDCl_3$): 12.5 (s, 1H), 8.91(d, 1H, J = 7.6), 8.38 (dd, 1H, J = 6.8, 2.4), 8.31 (dd, 1H, J = 7.2, 2.4), 8.06 (d, 1H, J = 7.6), 7.82 (m, 3H), 3.59 (s,

6H). ^{13}C NMR ($CDCl_3$): 186.4, 183.0, 182.5, 170.8, 169.2, 141.3, 135.6, 134.4, 134.3, 134.2, 133.9, 1315, 127.5, 127.0, 126.7, 1213, 117.1, 39.7. HRMS calculated for $C_{20}H_{14}N_2O_4$ (M^+) = 346.0953 found 346.0972, Mpt. >250 °C

2.8.6 3-ethoxy-4-(2-benzoyl phenyl amino) cyclobut-3-ene-1, 2-dione (20)



Squaric acid (114 mg, 1 mmol) was stirred with ethanol (3 ml) in a 25 ml RB flask under nitrogen atmosphere for 30 minutes, and then triethylorthoformate (0.4 ml) was added. The reaction mixture was refluxed for 24 hours to obtain diethyl squarate which was subsequently quenched with 2-aminobenzophenone (197 mg, 1 mmol). Reaction mixture was stirred for overnight at room temperature. The obtained solid was filtered and column chromatographed (30% ethyl acetate in hexane) to get pale yellow solid in 50 % yield. ^1H NMR (400 MHz, $CDCl_3$): 11.18 (s, 1H), 8.1(d, 1H, J = 8), 7.73 (d, 2H, J = 7.2), 7.65 (m, 3H,), 7.53 (t, 2H, J = 7.6), 7.15 (t, 1H, J = 8), 4.9 (q, 2H, J = 7.2) 1.54 (t, 3H, J = 8.2). ^{13}C NMR (100 MHz, $CDCl_3$): 199.7, 186.5, 185.0, 180.3, 170.2, 140.1, 138.2, 134.2, 1313, 129.8, 128.4, 1213, 122.4, 120.5, 70.7, 15.8. Mpt. 159-161 ^{o}C.

2.8.7 Crystal data and structure refinement for squaramide (14).$CHCl_3$

Identification code	09041a	
Empirical formula	$C_{30.50}H_{18.50}Cl_{3.50}N_2O_4$	
Formula weight	601.05	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 7.4803(8) Å	□ = 97.0370(10)°
	b = 13.4027(14) Å	□ = 95.3740(10)°
	c = 13.7401(14) Å	□ = 104.6630(10)°
Volume	1311.4(2) Å^3	
Z	2	
Density (calculated)	1.522 Mg/m^3	
Absorption coefficient	0.443 mm^{-1}	
F(000)	614	
Crystal color, morphology	Yellow, Block	
Crystal size	0.45 x 0.40 x 0.40 mm^3	
Theta range for data collection	1.51 to 26.37°	
Index ranges	$-9 \le h \le 9, -16 \le k \le 16, 0 \le l \le 17$	
Reflections collected	15222	
Independent reflections	5334 [R(int) = 0.0342]	
Observed reflections	3945	
Completeness to theta = 26.37°	99.4%	
Absorption correction	Multi-scan	
Max. and min. transmission	0.8427 and 0.8256	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	5334 / 0 / 379	
Goodness-of-fit on F^2	1.034	
Final R indices [I>2sigma(I)]	$R1$ = 0.0477, $wR2$ = 0.1078	
R indices (all data)	$R1$ = 0.0723, $wR2$ = 0.1195	
Largest diff. peak and hole	0.611 and -0.354 e.Å^{-3}	

2.8.8 Cartesian coordinates for uncomplexed squaramide (13) and chloride complexed squaramide (13):

B3LYP/6-31G* (d,p) optimized Cartesian coordinates for 13 and its complex with Cl-

Receptor 13: B3LYP/6-31G* (d,p)

Stoichiometry C30H20N2O4

Framework group C1[X (C30H20N2O4)]

Deg. of freedom 162

Full point group C1

Largest Abelian subgroup C1 NOp 1

Largest concise Abelian subgroup C1 NOp 1

Table 2.2 Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	-0.686943	-2.525786	-0.157155
2	6	0	0.686969	-2.525777	0.157101
3	6	0	0.743776	-4.016578	0.176472
4	6	0	-0.743720	-4.016589	-0.176560
5	7	0	-1.528236	-1.476271	-0.305574
6	1	0	-1.181420	-0.530771	-0.100060
7	7	0	1.528240	-1.476252	0.305571
8	1	0	1.181418	-0.530749	0.100077
9	6	0	-1569499	-1.459244	-0.706273
10	6	0	-3.493747	-2.596133	-1.246273
11	6	0	-3.612235	-0.244227	-0.574807
12	6	0	-4.807279	-2.528753	-1.697120

13	1	0	-2.953422	-3.533943	-1.300629
14	6	0	-4.932807	-0.212780	-1.070721
15	6	0	-5.530674	-1.331895	-1.634176
16	1	0	-5.262822	-3.420745	-2.117112
17	1	0	-5.483686	0.719048	-1.026548
18	1	0	-6.544249	-1.276103	-2.017546
19	6	0	1569499	-1.459224	0.706283
20	6	0	3.612230	-0.244202	0.574843
21	6	0	3.493743	-2.596116	1.246282
22	6	0	4.932799	-0.212758	1.070762
23	6	0	4.807265	-2.528732	1.697157
24	1	0	2.953396	-3.533912	1.300682
25	6	0	5.530668	-1.331879	1.634204
26	1	0	5.483689	0.719064	1.026576
27	1	0	5.262817	-3.420734	2.117118
28	1	0	6.544225	-1.276077	2.017621
29	8	0	-1.576582	-4.875387	-0.392018
30	8	0	1.576640	-4.875362	0.391982
31	6	0	-3.012460	0.974655	0.022401
32	8	0	-1.782442	1.104331	0.128533
33	6	0	3.012457	0.974682	-0.022366
34	8	0	1.782439	1.104354	-0.128502
35	6	0	-3.876418	2.093124	0.524646
36	6	0	-3.424823	3.409555	0.333168
37	6	0	-5.052392	1.871079	1.259891
38	6	0	-4.155757	4.485289	0.834232
39	1	0	-2.499637	3.571948	-0.210050
40	6	0	-5.767205	2.949578	1.785259
41	1	0	-5.393718	0.857969	1.446462

42	6	0	-5.327741	4.257300	1.563543
43	1	0	-3.808451	5.500248	0.664978
44	1	0	-6.665197	1467469	2.368176
45	1	0	-5.891651	5.095106	1.963335
46	6	0	3.876415	2.093145	-0.524621
47	6	0	3.424772	3.409574	-0.333238
48	6	0	5.052421	1.871093	-1.259812
49	6	0	4.155695	4.485302	-0.834330
50	1	0	2.499547	3.571968	0.209914
51	6	0	5.767221	2.949584	-1.785215
52	1	0	5.393755	0.857981	-1.446360
53	6	0	5.327721	4.257306	-1.563573
54	1	0	3.808363	5.500261	-0.665131
55	1	0	6.665254	1467469	-2.368069
56	1	0	5.891616	5.095105	-1.963400

Receptor 13 + Cl-: B3LYP/6-31G* (d,p)

Stoichiometry $C_{30}H_{20}ClN_2O_4(1-)$

Framework group C1[X (C30H20ClN2O4)]

Deg. of freedom 165

Full point group C1

Largest Abelian subgroup C1 NOp 1

Largest concise Abelian subgroup C1 NOp 1

Table 2.3 Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z

1	6	0	-0.701543	-2.506022	0.090326
2	6	0	0.701762	-2.505958	-0.090366
3	6	0	0.757067	-3.991244	-0.096959
4	6	0	-0.756711	-3.991310	0.096970
5	7	0	-1.575345	-1.482732	0.124123
6	1	0	-1.167659	-0.536809	-0.040480
7	7	0	1.575467	-1.482599	-0.124198
8	1	0	1.167658	-0.536683	0.040246
9	6	0	-2.912573	-1.525083	0.537018
10	6	0	-3.378308	-2.512559	1.422322
11	6	0	-3.796357	-0.498152	0.121487
12	6	0	-4.687961	-2.480327	1.893917
13	1	0	-1413781	-3.311425	1.726253
14	6	0	-5.095957	-0.462073	0.649422
15	6	0	-5.553943	-1.446774	1.524218
16	1	0	-5.024977	-3.261837	2.569473
17	1	0	-5.765770	0.332735	0.333673
18	1	0	-6.570684	-1.411460	1.904431
19	6	0	2.912714	-1.524882	-0.537054
20	6	0	3.796447	-0.497936	-0.121460
21	6	0	3.378514	-2.512326	-1.422355
22	6	0	5.096068	-0.461804	-0.649335
23	6	0	4.688188	-2.480046	-1.893893
24	1	0	1414018	-3.311201	-1.726333
25	6	0	5.554120	-1.446475	-1.524132
26	1	0	5.765844	0.333017	-0.333540
27	1	0	5.025257	-3.261531	-2.569451
28	1	0	6.570878	-1.411125	-1.904297
29	8	0	-1.620563	-4.845672	0.229721

30	8	0	1.621001	-4.845524	-0.229684
31	6	0	-3.475552	0.438177	-1.016629
32	8	0	-3.073538	-0.008192	-2.083952
33	6	0	3.475581	0.438355	1.016680
34	8	0	3.073488	-0.008055	2.083955
35	6	0	-3.767450	1.902427	-0.862106
36	6	0	-3.990986	1366735	-2.017854
37	6	0	-3.779089	2.531071	0.391104
38	6	0	-4.245322	4.033439	-1.920752
39	1	0	-3.951529	2.169217	-2.981612
40	6	0	-4.017231	3.903486	0.486653
41	1	0	-3.566712	1.952943	1.283821
42	6	0	-4.259103	4.654864	-0.666382
43	1	0	-4.423217	4.617539	-1519791
44	1	0	-4.000777	4.386791	1.459406
45	1	0	-4.446224	5.722941	-0.590245
46	6	0	3.767265	1.902645	0.862141
47	6	0	3.990589	1367020	2.017886
48	6	0	3.778936	2.531249	-0.391088
49	6	0	4.244745	4.033756	1.920763
50	1	0	3.951114	2.169527	2.981656
51	6	0	4.016900	3.903693	-0.486660
52	1	0	3.566722	1.953062	-1.283804
53	6	0	4.258558	4.655142	0.666374
54	1	0	4.422475	4.617910	1519799
55	1	0	4.000472	4.386964	-1.459430
56	1	0	4.445539	5.723243	0.590220
57	17	0	0.000070	1.210501	-0.000078

2.8.9 IR spectra of squaramide 13, 14 and 15

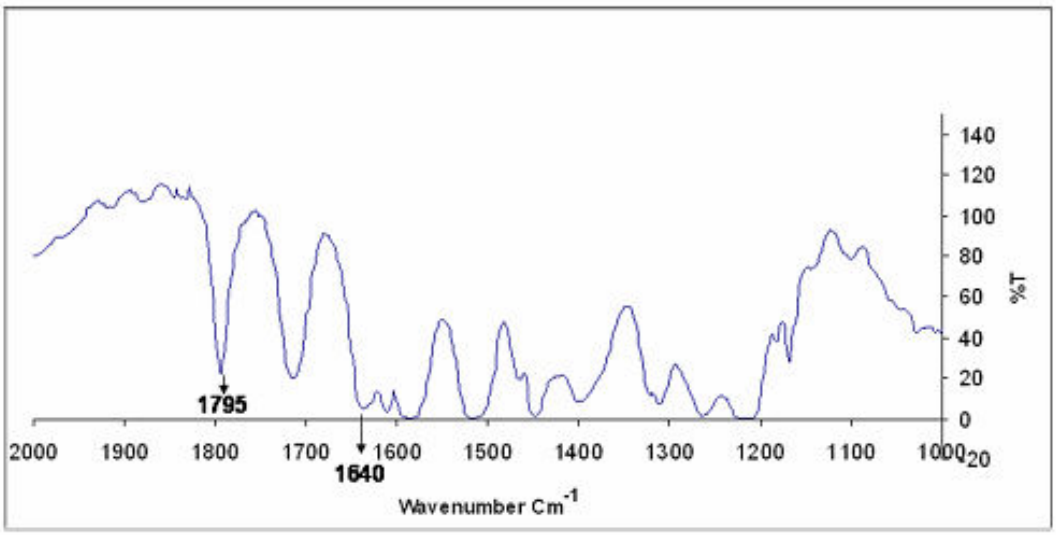


Figure 2.25: IR spectrum of 3, 4 (2-benzoyl phenyl amino) cyclobut-3-ene-1, 2dione (**13**)

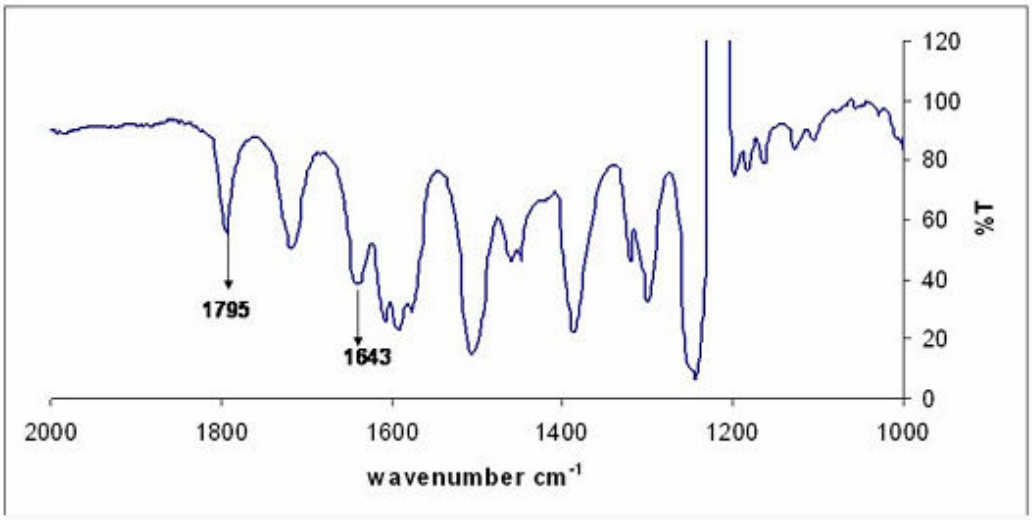


Figure 2.26: IR Spectrum of 3, 4(2-benzoyl 4 chloro phenyl amino) cyclobut-3-ene-1, 2 dione (**14**)

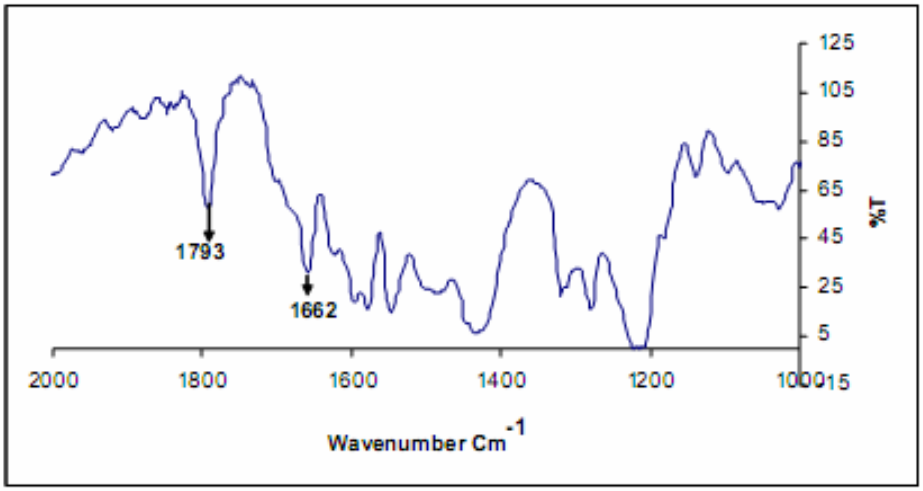


Figure 2.27: IR spectrum of 3, 4 (3-benzoyl phenyl amino) cyclobut-3-ene-1, 2 dione (**15**)

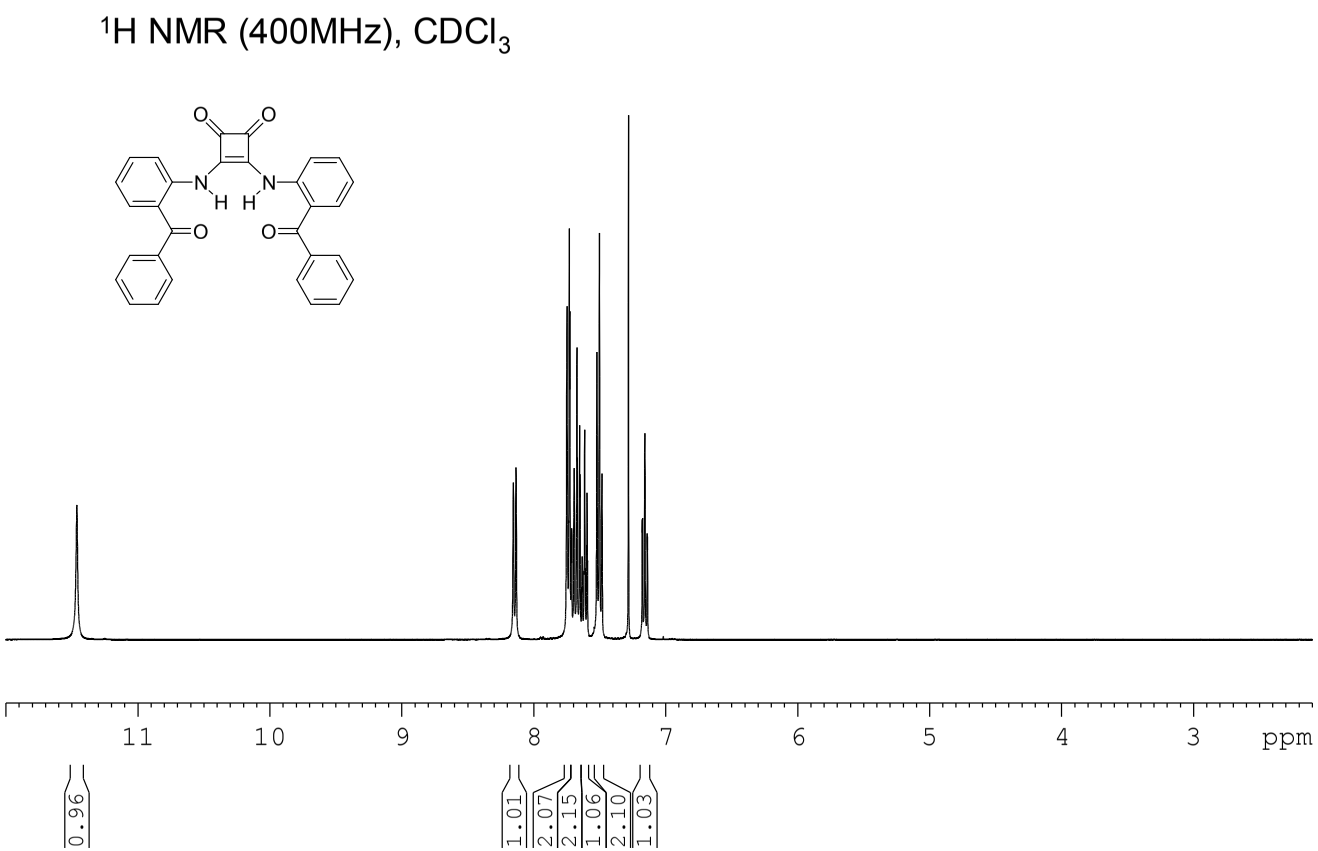


Figure 2.28: ^{1}H NMR spectrum of 3, 4(2-benzoyl phenyl amino) cyclobut-3-ene-1, 2dione (**13)**

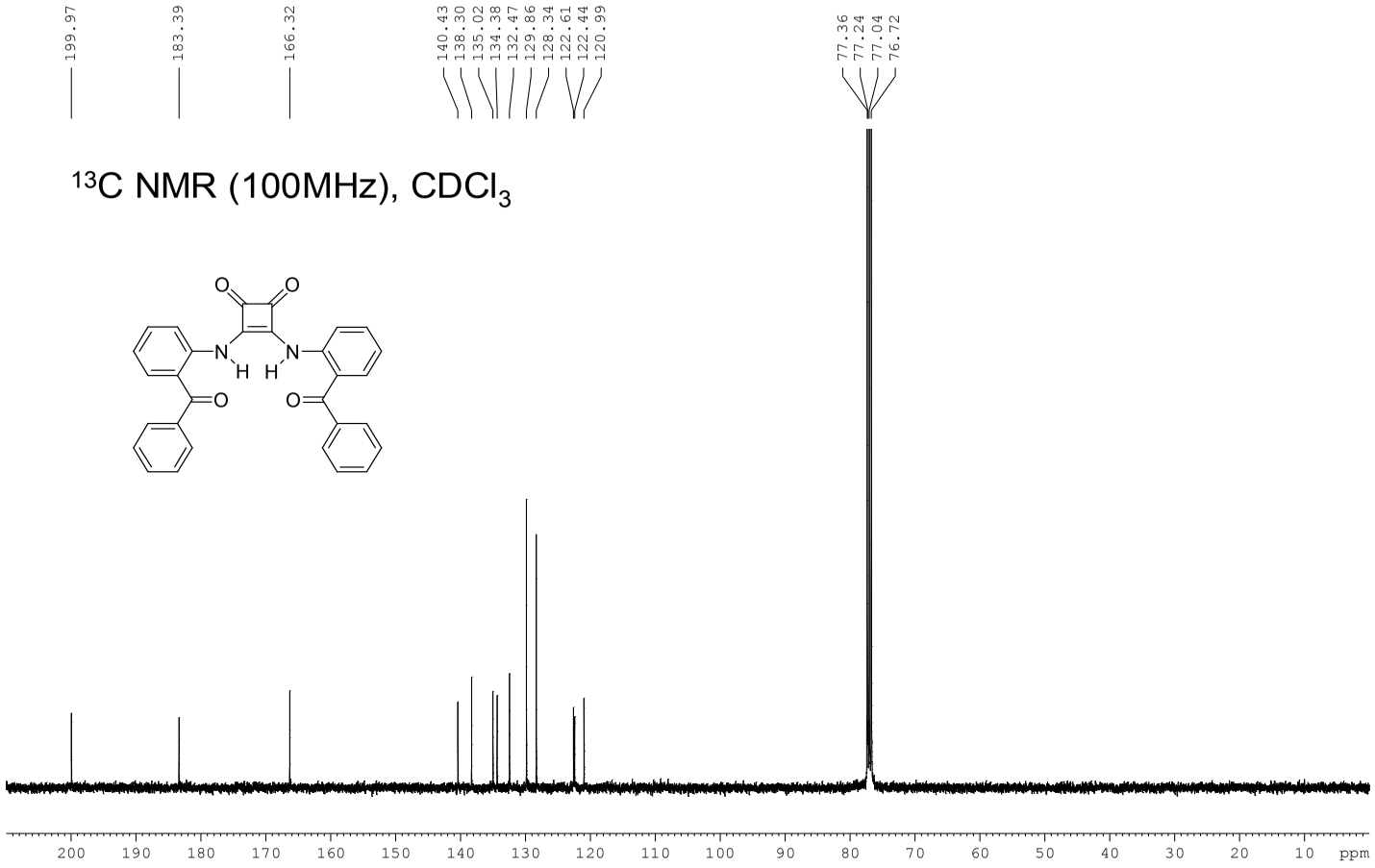


Figure 2.29: ^{13}C NMR spectrum of 3, 4(2-benzoyl phenyl amino) cyclobut-3-ene-1, 2 dione (**13**)

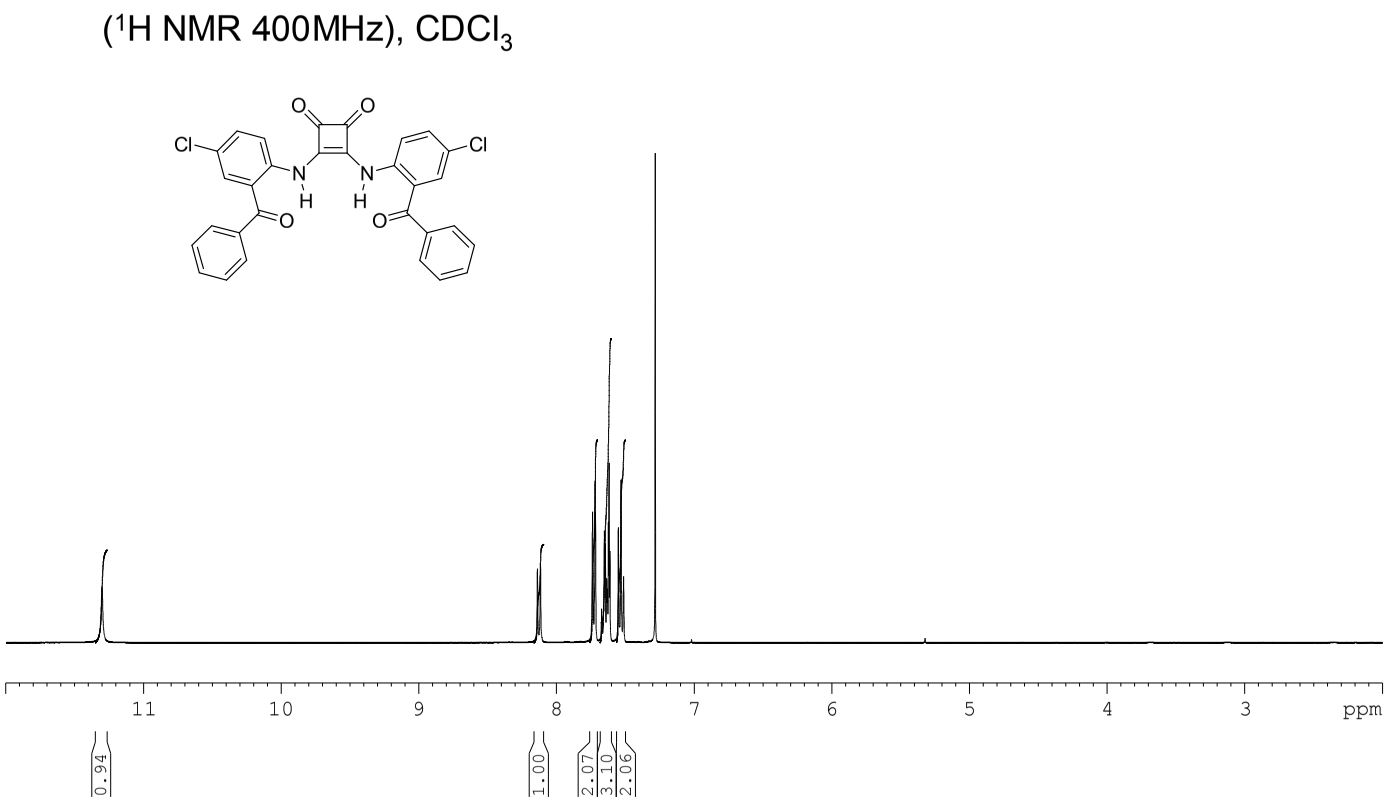


Figure 2.30: ^{1}H NMR spectrum of 3, 4(2-benzoyl 4-chloro phenyl amino) cyclobut-3-ene-1, 2dione (**14**)

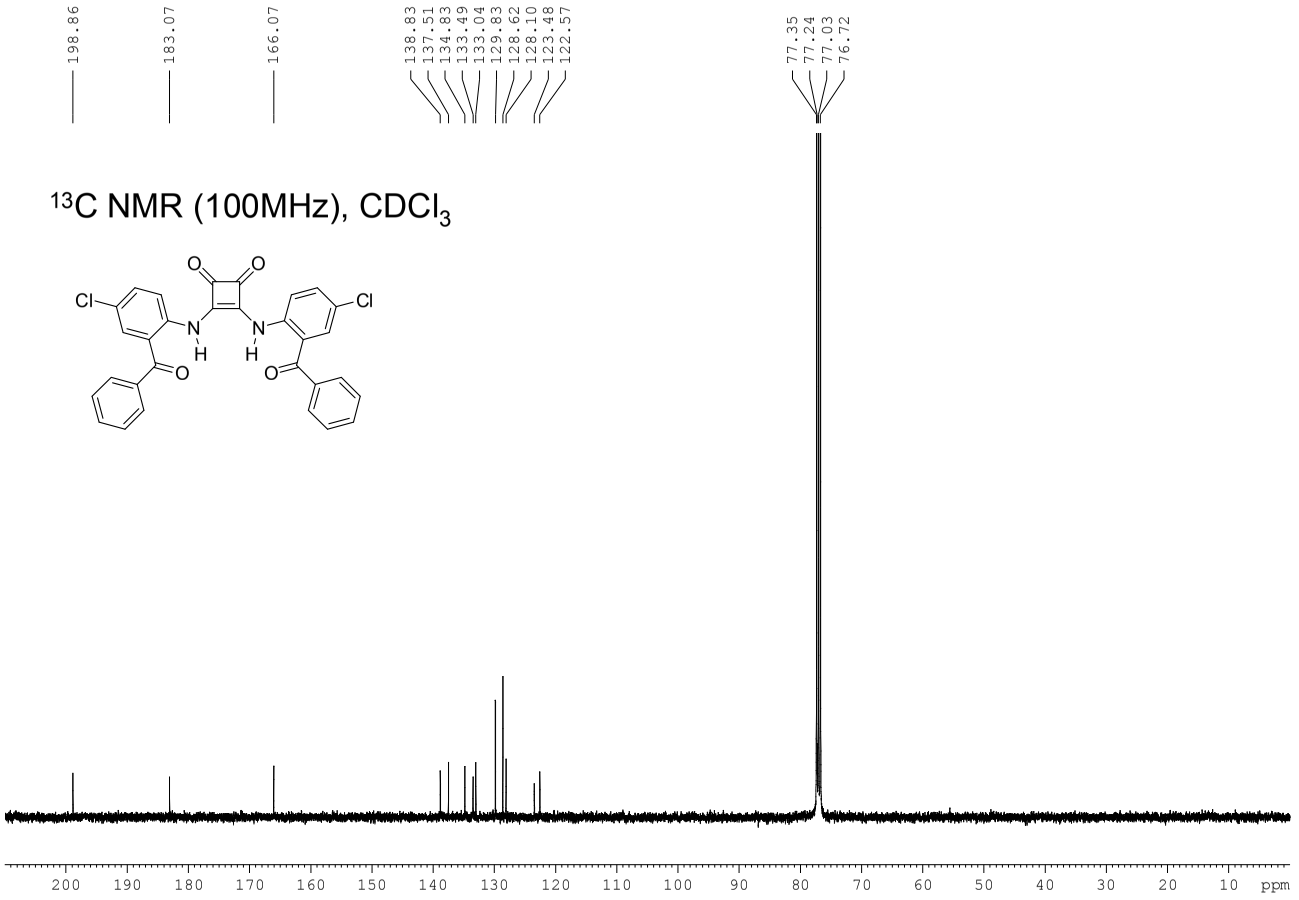


Figure 2.31: ^{13}C NMR spectrum of 3, 4(2-benzoyl 4-chloro phenyl amino) cyclobut-3-ene-1, 2dione (**14**)

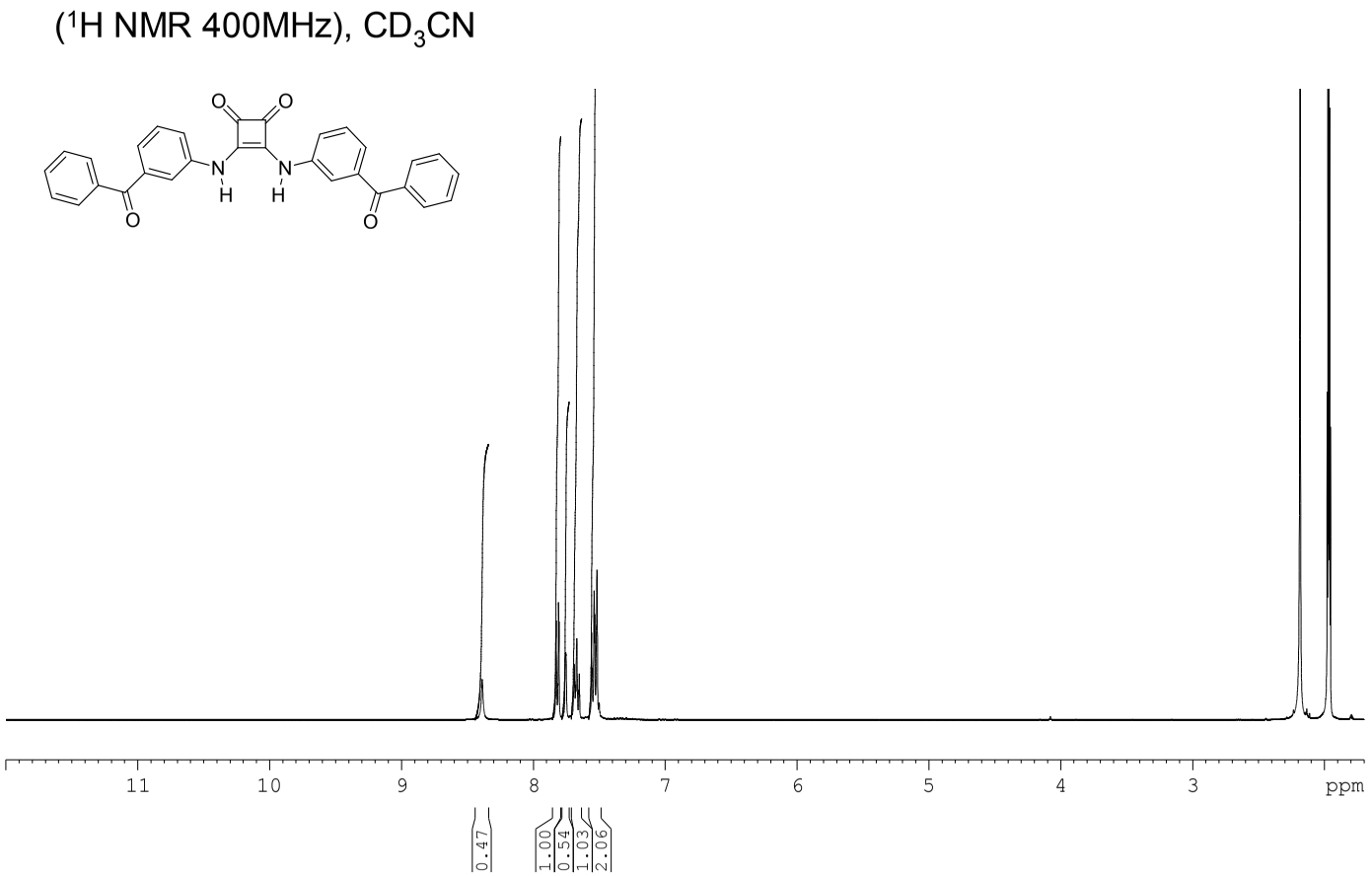


Figure 2.32: ^{1}H NMR spectrum of 3, 4(3-benzoyl phenyl amino) cyclobut-3-ene-1, 2dione (**15**)

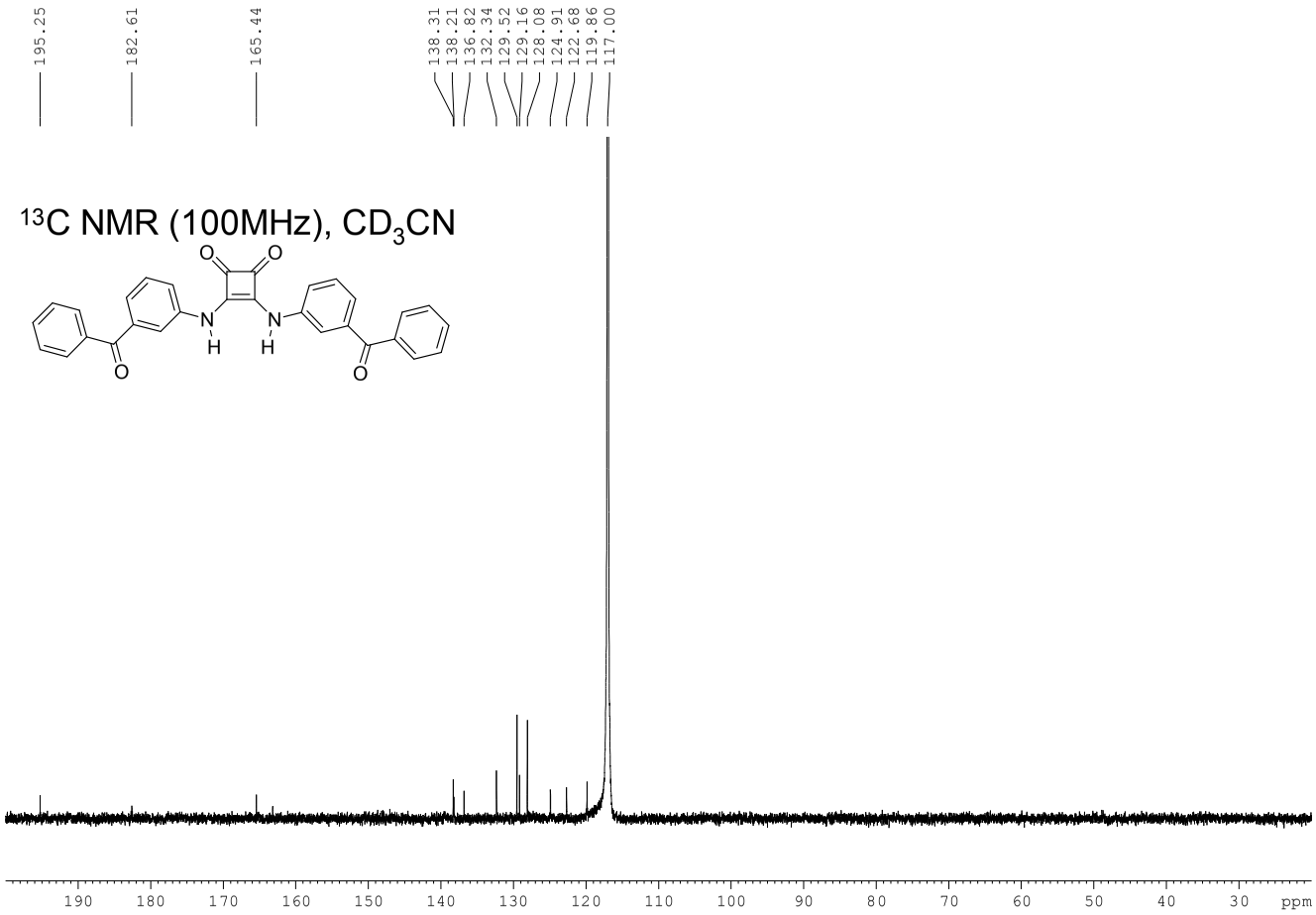


Figure 2.33: ^{13}C NMR spectrum of 3, 4(3-benzoyl phenyl amino) cyclobut-3-ene-1, 2dione (**15**)

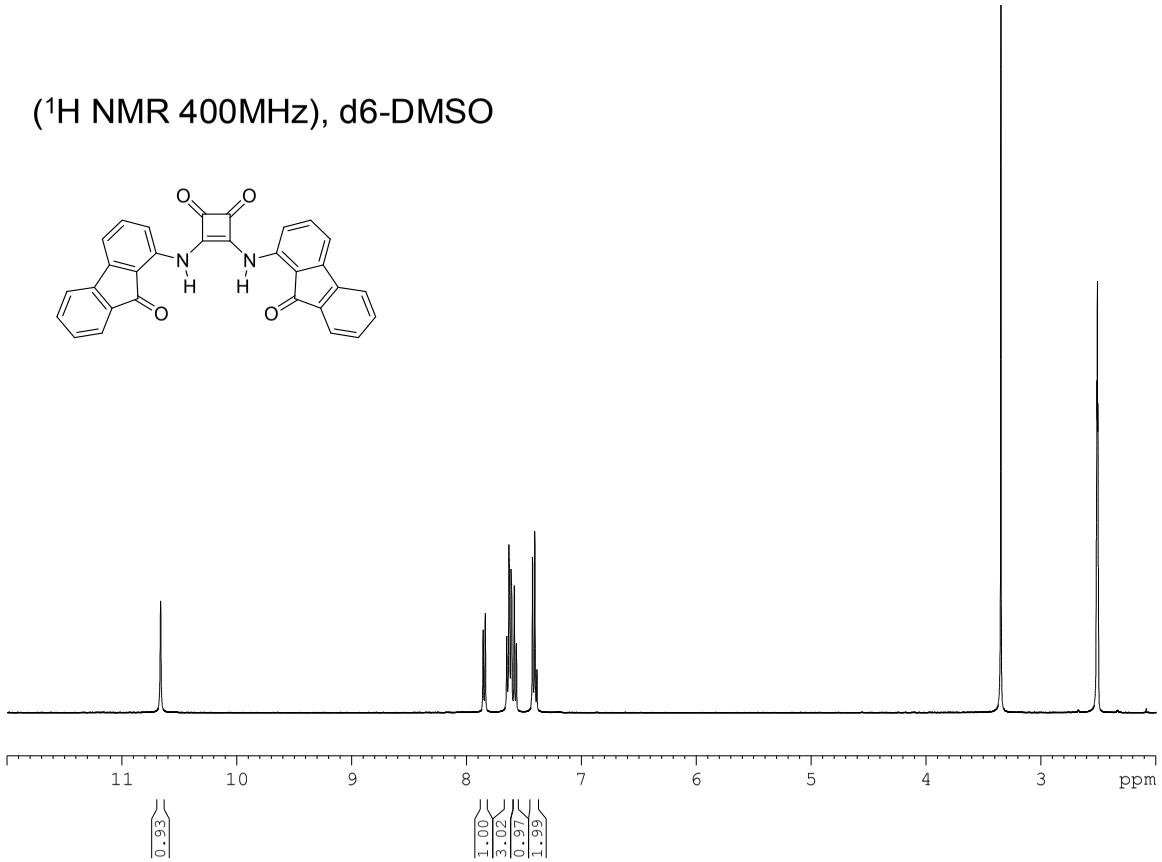


Figure 2.34: ^{1}H NMR spectrum of 3,4-bis(9-oxo-9H-fluoren-1-ylamino)cyclobut-3-ene-1,2-dione (**16**)

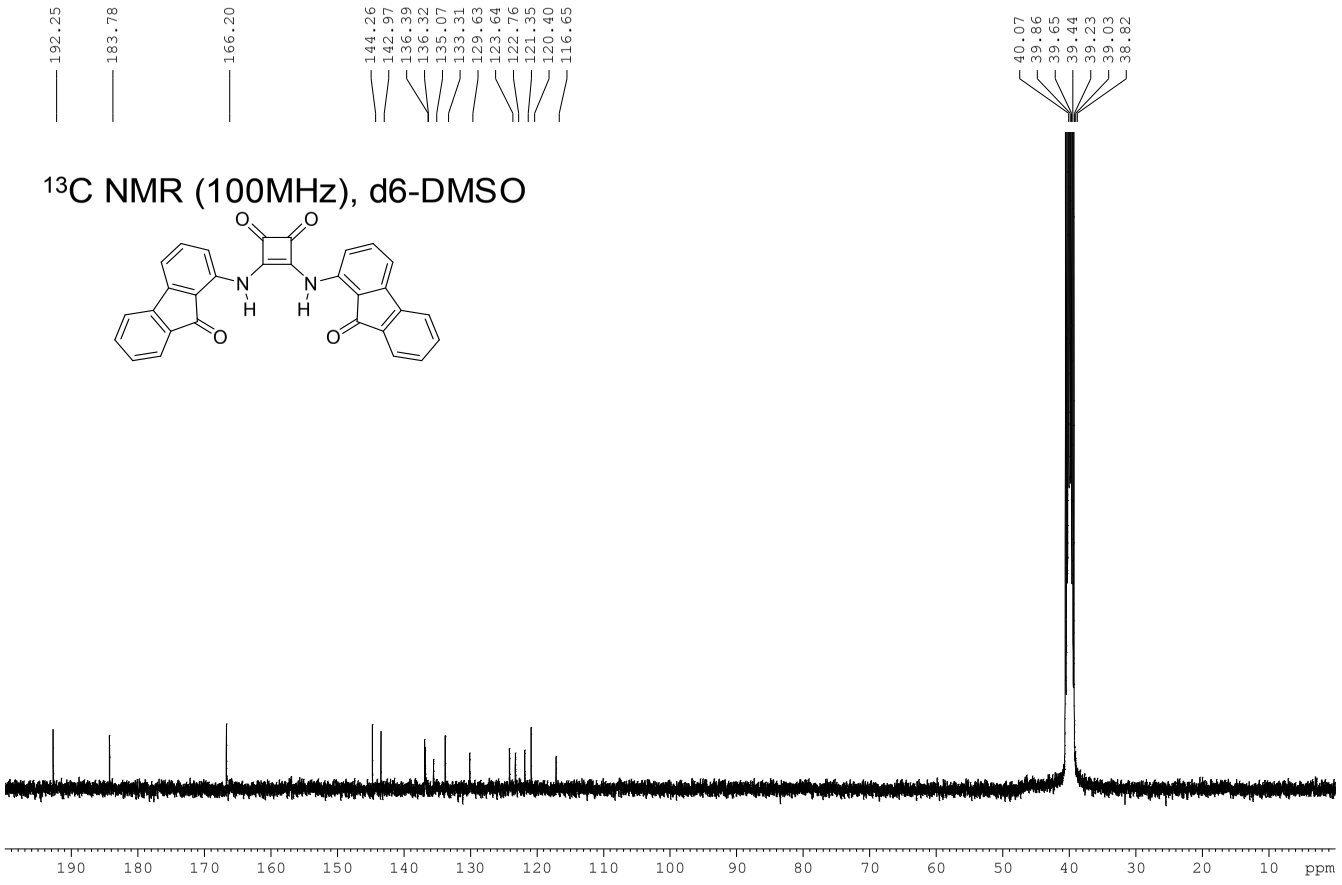


Figure 2.35: ^{13}C NMR spectrum of 3, 4-bis(9-oxo-9H-fluoren-1-ylamino)cyclobut-3-ene-1,2-dione (**16**)

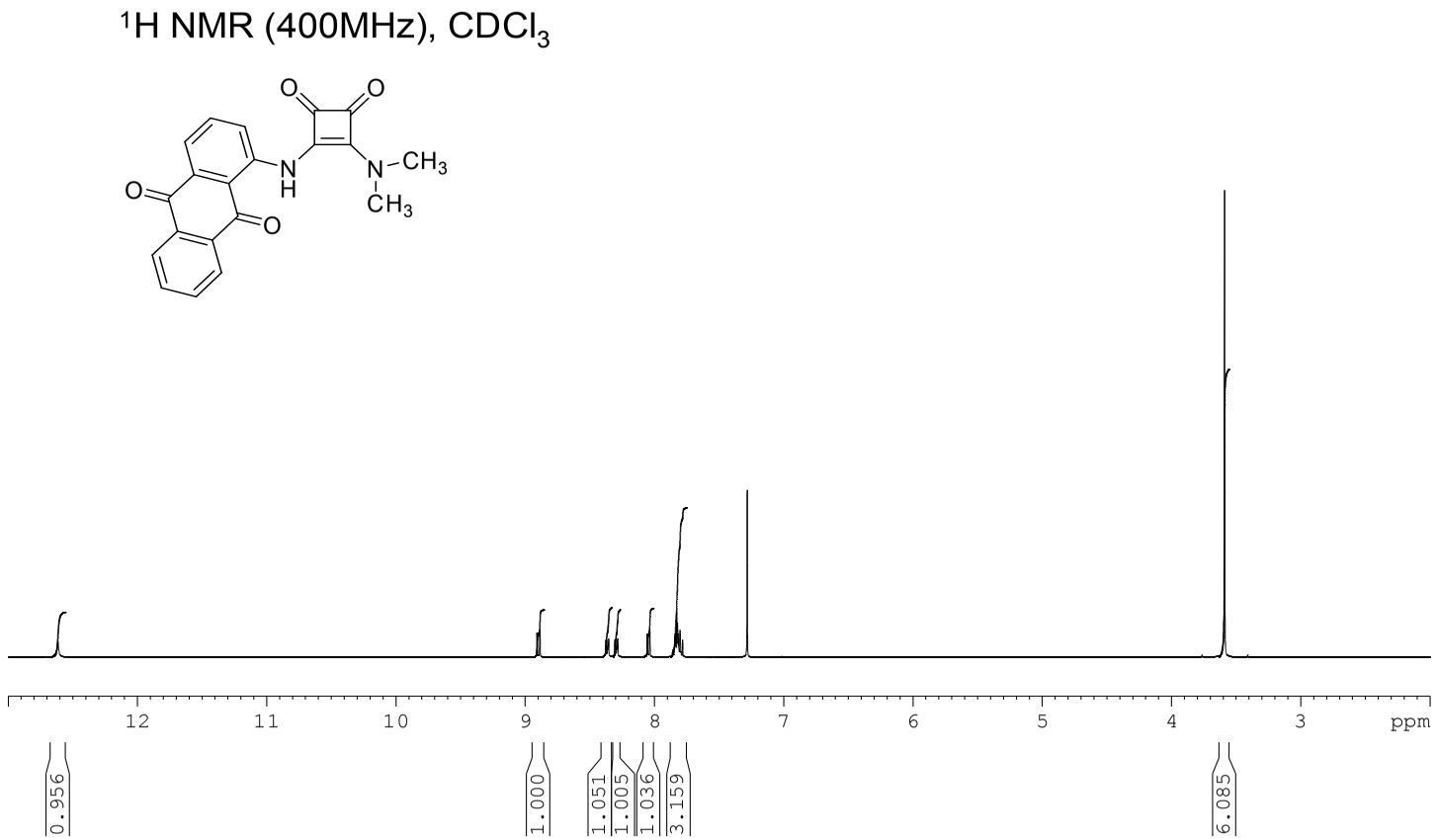


Figure 2.36: ^{1}H NMR spectrum of 1-(2-(dimethylamino)-3,4-dioxocyclobut-1-enylamino)anthracene-9,10-dione (**17**)

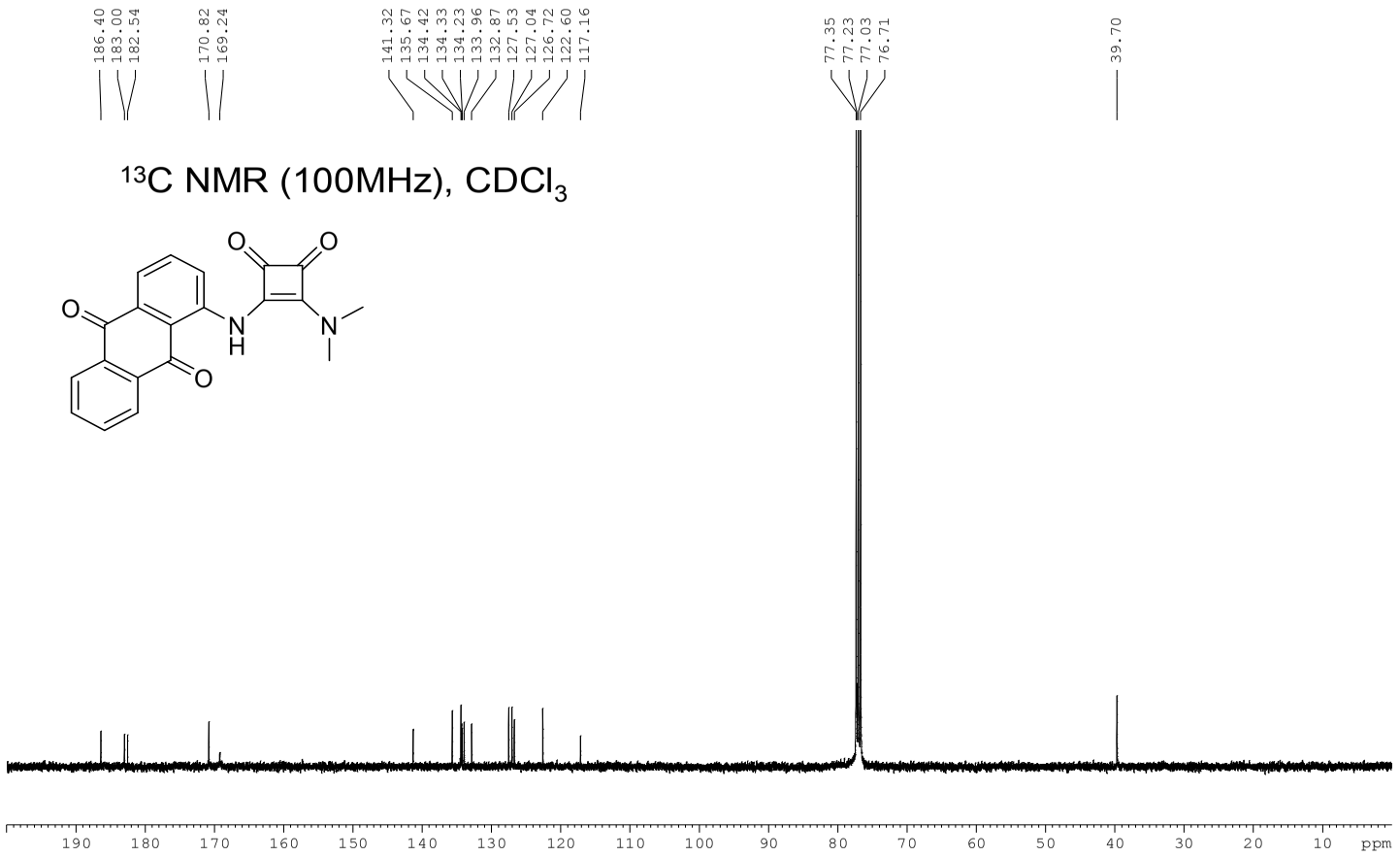


Figure 2.37: ^{1}H NMR spectrum of 1-(2-(dimethylamino)-3, 4-dioxocyclobut-1-enylamino)anthracene-9,10-dione (**17**)

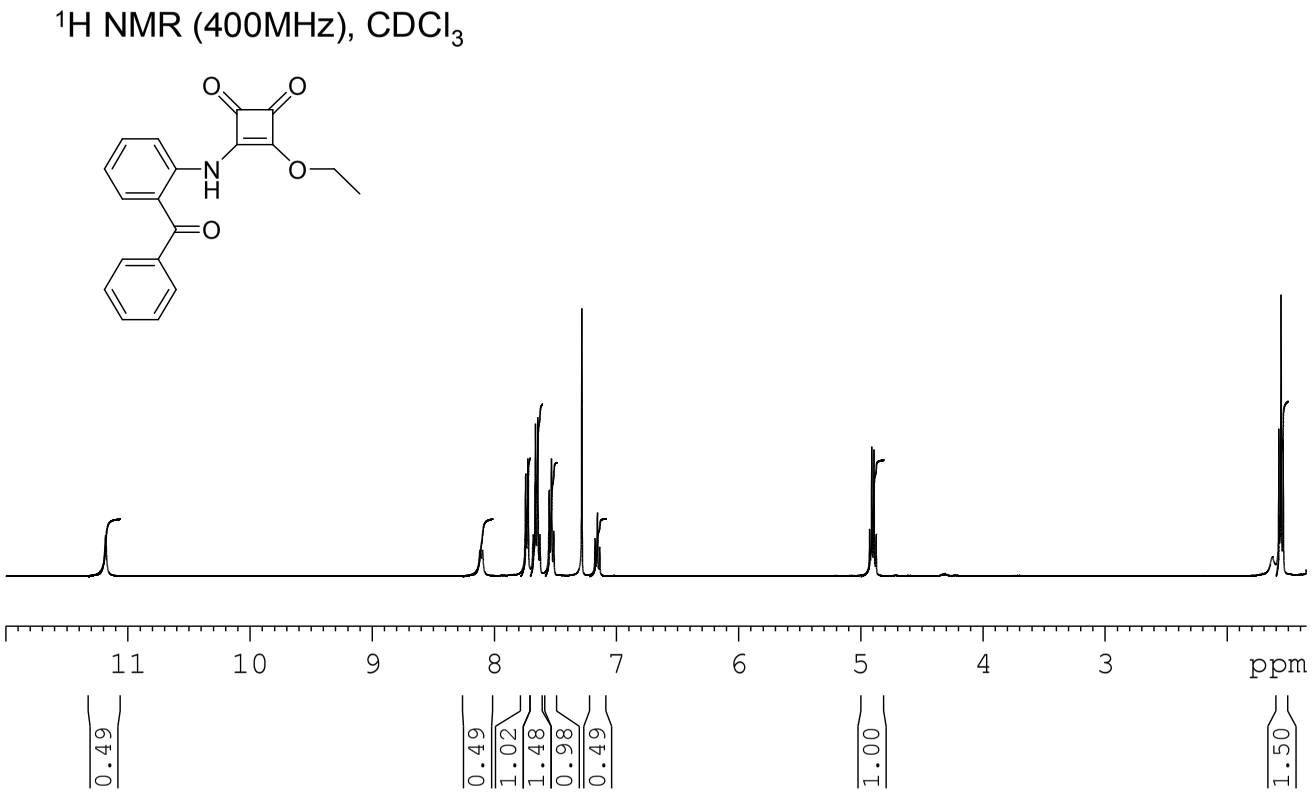


Figure 2.38: ^{1}H NMR spectrum of 3-ethoxy-4-(2-benzoyl phenyl amino) cyclobut-3-ene-1, 2-dione (**20**)

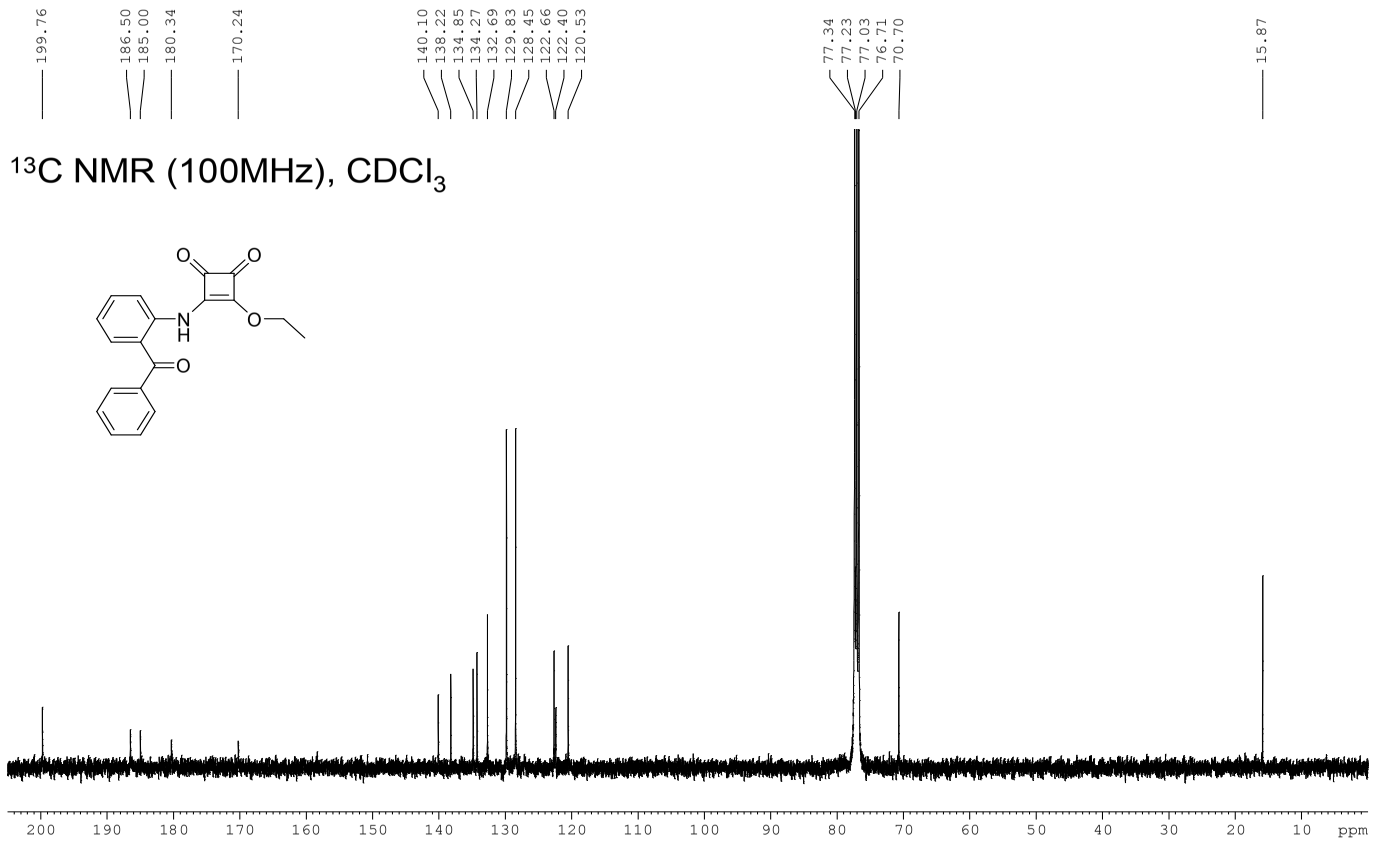


Figure 2.39: ^{13}C NMR spectrum of 3-ethoxy-4-(2-benzoyl phenyl amino) cyclobut-3-ene-1, 2-dione (**20**)

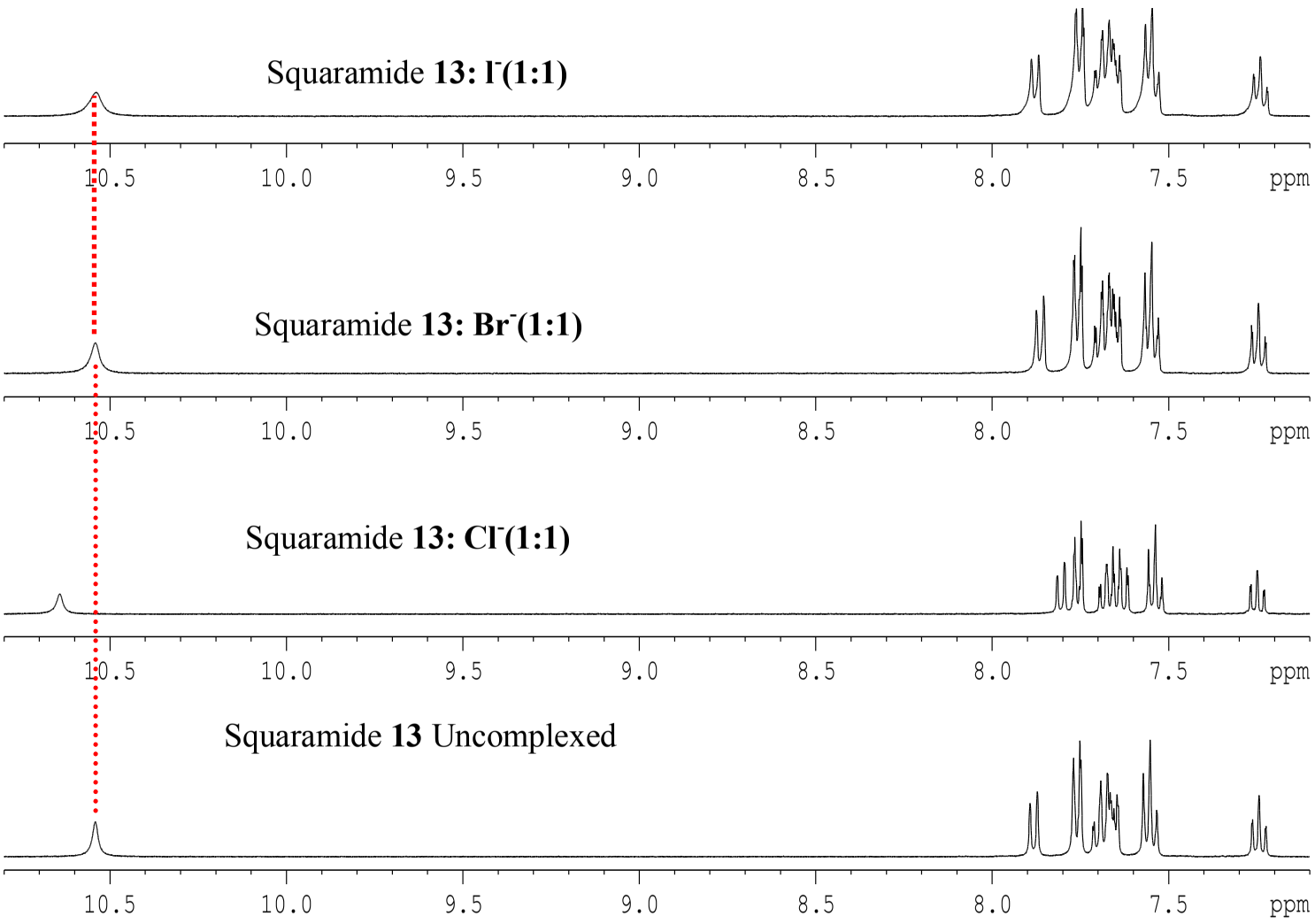


Figure 2.40: Overlay 1H NMR spectra's of squaramide **13** (2mM) with Cl^-, Br^-, and I^- in CD_3CN

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Chapter 3

Development of second generation squaramide-based molecular valves for chloride transport

3.1 Introduction

In the previous chapter, we demonstrated that keto groups can function as molecular valves[2] to regulate chloride binding to squaramides. We then began to explore the generality of this approach with other carbonyl functional groups. We became interested, in particular, with the use of amide carbonyls as valves[1]. We speculated that with the amide functional group even stronger chloride binding would occur through additional hydrogen bonding. We describe below our results.

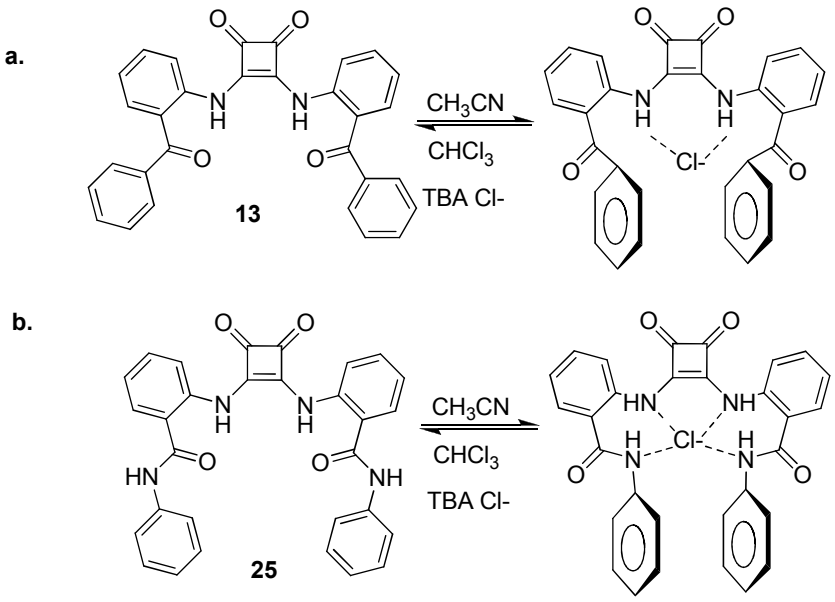


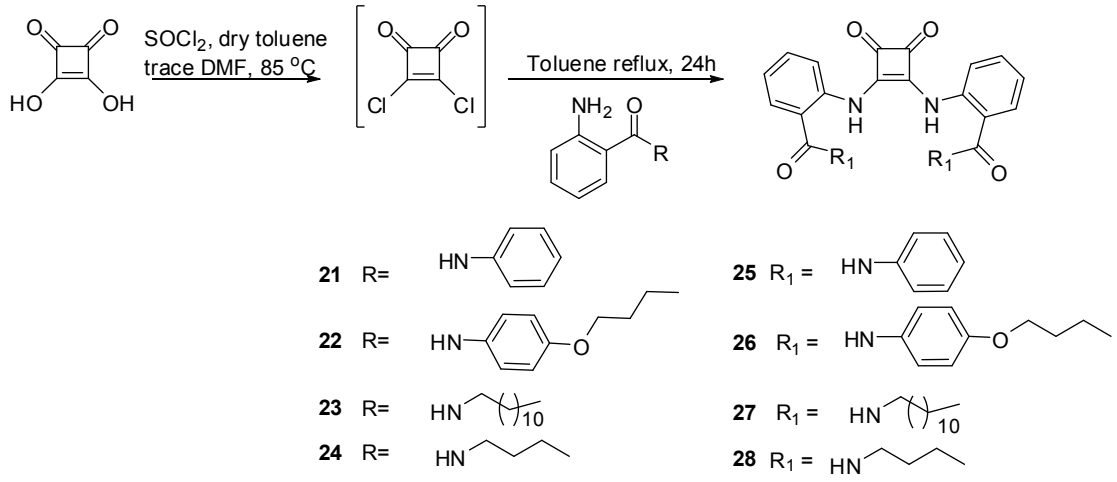
Figure 3.1: a) Keto-squaramide-based molecular valve. b) Proposed stronger chloride binding in amide squaramide (**25)**

3.2 Results

3.2.1 Synthesis

Synthesis of amide derived squaramides **25-28** was achieved by quenching the reactive squaryl dichloride with the corresponding amine derivatives (Scheme 3.1). The 2-amino N-phenyl benzamide and alkyl derivatives **21-24** were synthesized through three different procedures (see the experimental section) reported in the literature[3,4, 5,] .

Scheme 3.1: Synthesis of secondary amide derivatives of squaramide



3.2.2 Secondary amide carbonyl valves

The squaramide derivative **25** was synthesized to study the strength of chloride binding when additional hydrogen bonding sites are available. Due to its insolubility in chloroform, ^{1}H and ^{13}C NMR were recorded in DMSO in which chloride complexation

was not detectable. Limited solubility of squaramide **25** in acetonitrile allowed for the study of chloride binding by ^{1}H NMR.

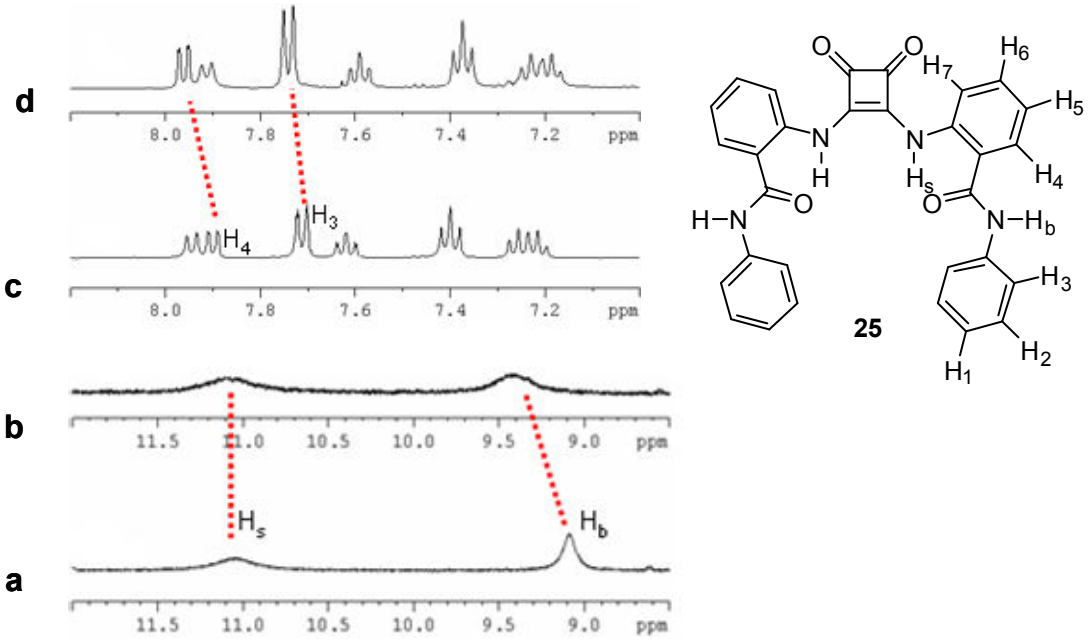


Figure 3.2: a) Squaramide **25** uncomplexed ^{1}H NMR in CD_3CN NH region. b) Squaramide **25** + TBA chloride (1:1) ^{1}H NMR in CD_3CN NH region. c) Squaramide **25** ^{1}H NMR in CD_3CN aromatic region. d) Squaramide **25** + TBA chloride (1:1) ^{1}H NMR in CD_3CN aromatic region.

Comparison of chloride-complexed ^{1}H NMR spectra with uncomplexed spectra revealed no shift in squaramide NH peaks. Instead, surprisingly, downfield shift of the benzamide NH peak and changes in aromatic proton peaks were observed. This was unusual since in acetonitrile perturbation of intramolecular hydrogen bonding was expected to align the four NH groups favorably thereby creating a cavity for anion binding. To further corroborate whether peripheral binding occurs (Figure 3.3), other squaramide derivatives were investigated. In an effort to improve the solubility of the squaramide derivatives in chloroform and acetonitrile, we prepared butyloxy ether derived squaramide **26**.

Unfortunately squaramide **26** was also insoluble in chloroform and only sparingly soluble in acetonitrile. Chloride binding with squaramide **26** was studied by ^{1}H NMR in acetonitrile, which again revealed similar peripheral mode of chloride binding, similar to squaramide **25,** in acetonitrile. We then decided to incorporate the dodecyl group in the amide functionality of the squaramide derivative. The dodecyl squaramide, with enhanced hydrophobicity was completely insoluble in polar solvents such as acetonitrile and DMSO, but soluble in non-polar solvents such as chloroform.

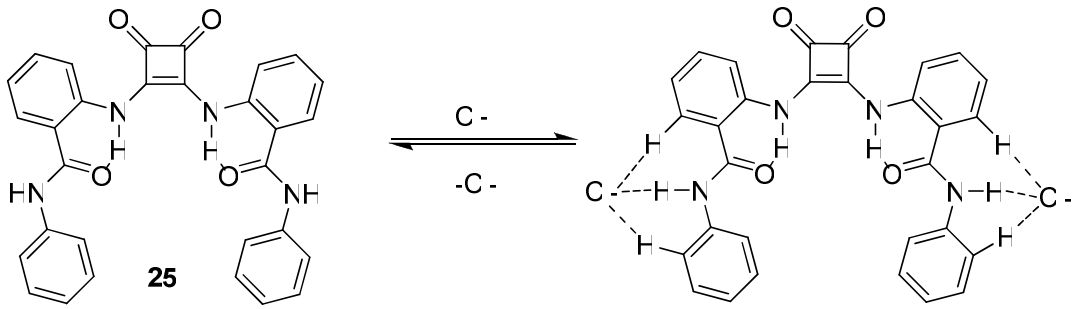


Figure 3.3: Peripheral chloride binding with squaramide **25** in acetonitrile.

Mode of chloride binding of the dodecyl squaramide **27** was studied by ^{1}H NMR in chloroform. Chloride binding was not expected with squaramide **27** in chloroform since intramolecular hydrogen bonding between the squaramide NH and the amide carbonyl blocks the anion binding site. Indeed, we observed no chloride binding with squaramide NH. However, chloride binding with the peripheral benzamide NH was evident. This peripheral mode of chloride binding was also corroborated by nuclear overhauser enhancement spectroscopy (NOESY) experiments in chloroform (see Figure 3.39 on page 123). The binding constant was determined to be 19 ± 0.7 M^{-1}. The observed peripheral chloride binding with squaramide **27** is similar to chloride interactions with squaramide **25** and **26** in acetonitrile.

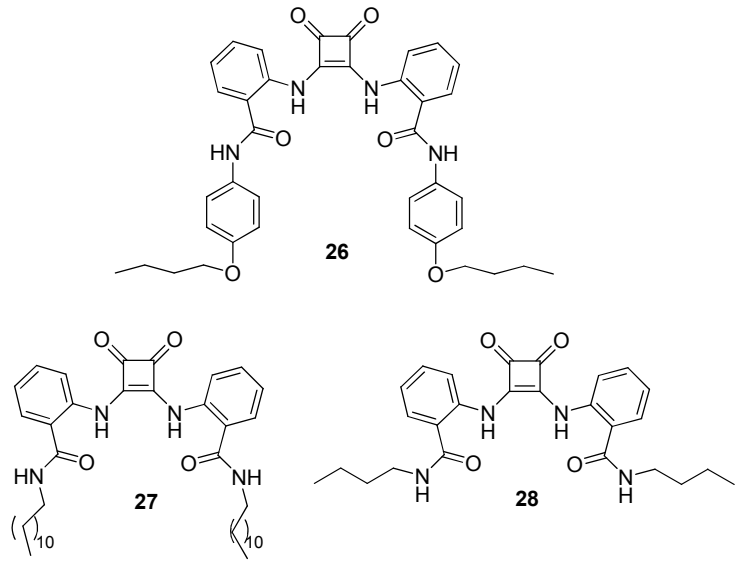


Figure 3.4: Secondary amide derivatives of squaramides.

Squaramide **28**, with shortened carbon chain (from dodecyl to butyl), was predicted to be soluble in both chloroform and acetonitrile; but it was soluble only in a polar solvent such as DMSO.

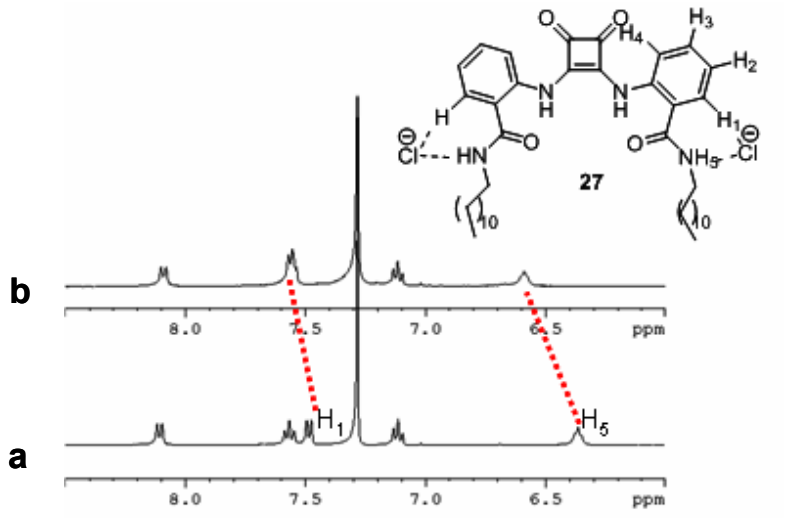


Figure 3.5: Peripheral chloride binding in squaramide **27** a) Squaramide **27** uncomplexed ^{1}H NMR in $CDCl_3$. b) Squaramide **27** + TBA chloride (1:1) ^{1}H NMR in $CDCl_3$.

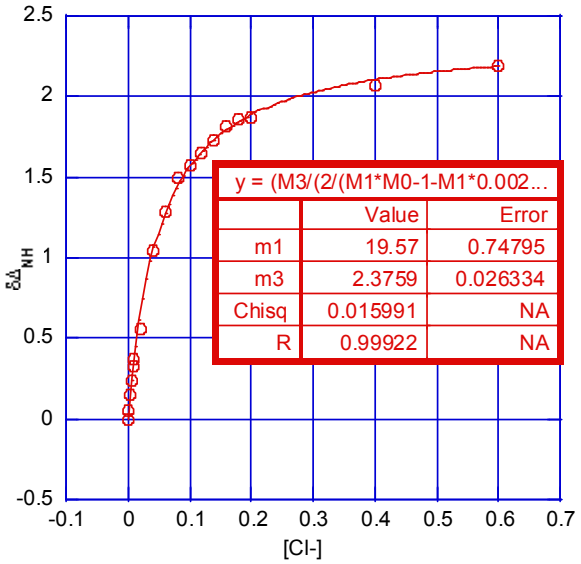


Figure 3.6: Binding isotherm curve for squaramide **27** with chloride in chloroform

Thus, two main problems which we encountered in chloride binding to secondary amide squaramides **25-28** were partial solubility of the squaramides in either chloroform or acetonitrile and the presence of a peripheral chloride binding site.

3.2.3 Tertiary amide carbonyl valves

To overcome the above mentioned problems associated with secondary amide derivatives of squaramide we hypothesized that if we removed the peripheral binding sites in these derivatives, then chloride binding will occur specifically with squaramide NH. Tertiary amide of squaramide **29** with no additional binding site other than the squaramide NH was therefore synthesized to study chloride binding. Squaramide **29** was found to be soluble in both polar acetonitrile and non-polar chloroform, which allowed us to perform the chloride binding studies. Chloride binding to squaramide **29** was studied by ^{1}H NMR

in both chloroform and acetonitrile. The binding constants were found to be 42 and 1008 M^{-1} in chloroform and acetonitrile, respectively.

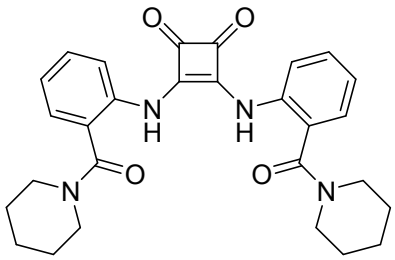


Figure 3.7: Tertiary amide derivative of squaramide (**29)**

These results show that in a polar solvent (acetonitrile) the NH binding site is "OPEN" allowing stronger chloride binding, whereas in a non-polar solvent (chloroform) strong intramolecular hydrogen bonding between the squaramide NH and the carbonyl inhibits chloride binding to squaramide.

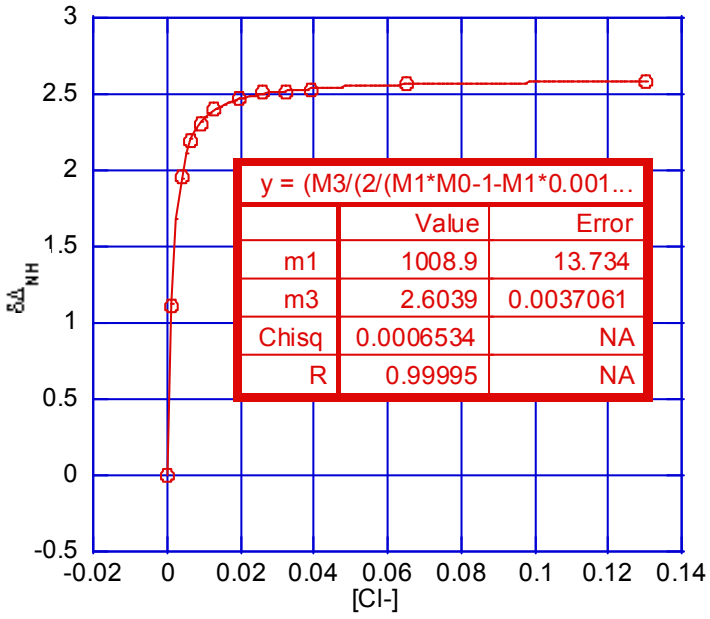


Figure 3.8: Binding isotherm of squaramide **29** with chloride in acetonitrile.

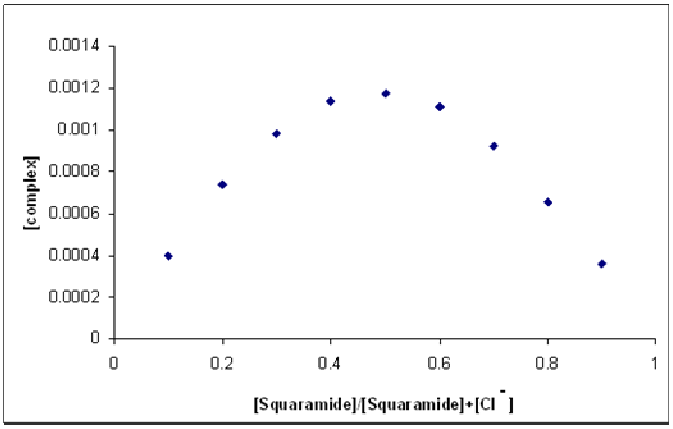
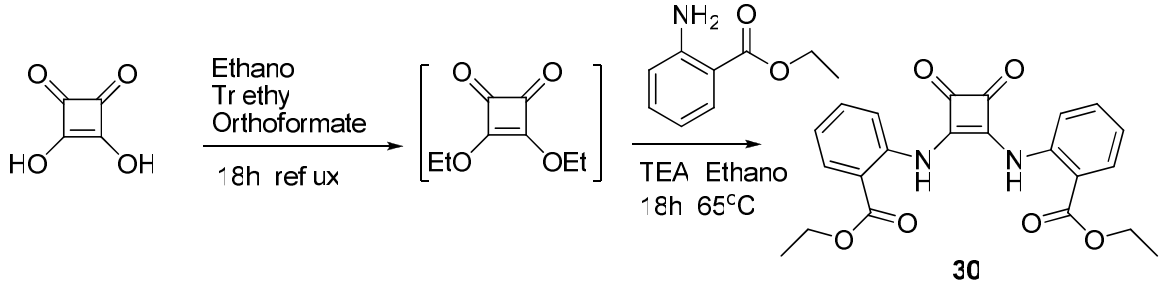


Figure 3.9: Job's plot for squaramide **29** with chloride (1:1 complex)

3.2.4 Ester carbonyl valves

Scheme 3.2:



Ethyl ester squaramide **30** was synthesized by quenching 2-amino ethyl benzoate with diethyl squarate and were purified by column chromatography. Squaramide **30** was soluble both in acetonitrile and chloroform; and therefore ^{1}H NMR was used to characterize chloride binding. No binding of chloride with squaramide **30** was observed in chloroform, whereas in acetonitrile weak binding was observed with a binding constant of 14 ± 1 M^{-1}. The stoichiometry of the chloride complex with squaramide **30** in acetonitrile was found to 1:1 by Job's plot. The absence of chloride binding to squaramide **30** in chloroform was mainly due to the strong intramolecular hydrogen bonding between the squaramide NH and the carbonyl of the ester.

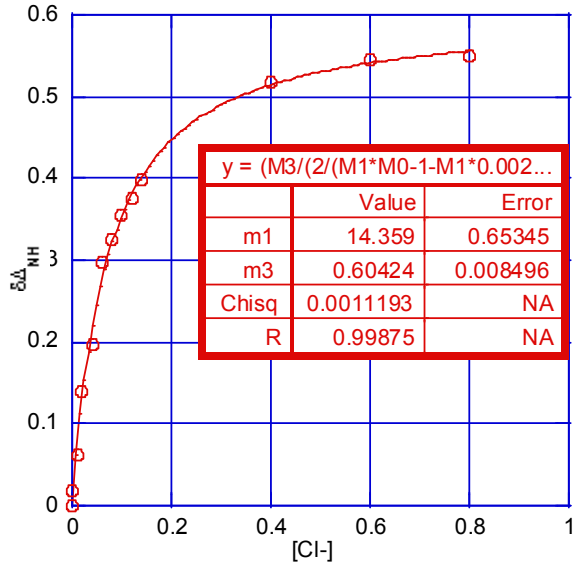


Figure 3.10: Binding isotherm curve for squaramide **30** with chloride in acetonitrile.

A likely explanation of weak binding of chloride to squaramide **30** in acetonitrile maybe the presence of bulky ethyl groups preventing chloride access to the binding pocket.

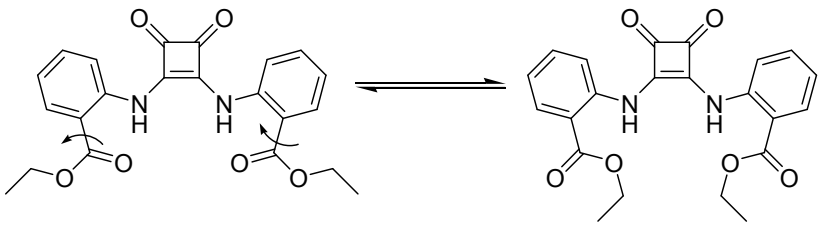


Figure 3.11: Equilibration between the "open" and "closed" forms of ester squaramide

3.2.5 Nitro group-based valves

In ortho- nitro squaramide, **2**, intramolecular hydrogen bonding[6] between one of the oxygen atoms of the nitro group and the squaramide NH improves solubility in non-polar chloroform and polar acetonitrile. The chloride binding to ortho nitro squaramide was

studied by ^{1}H NMR in chloroform and acetonitrile. Binding constant was found to be 220 and 545 M^{-1} in chloroform and acetonitrile, respectively.

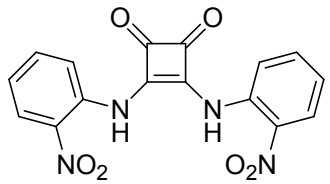


Figure 3.12: ortho nitro squaramide **2**

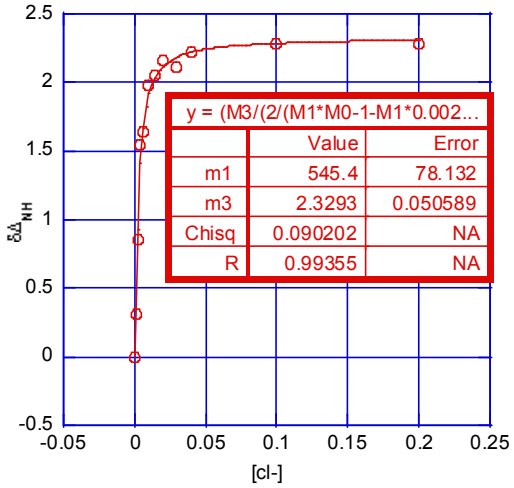


Figure 3.13: Binding isotherm of squaramide **2** with chloride in acetonitrile

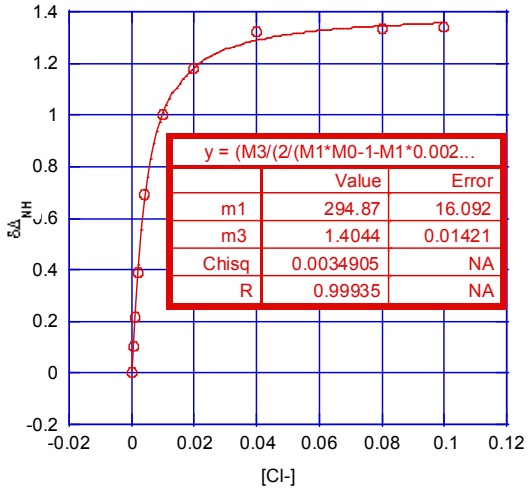


Figure 3.14: Binding isotherm of squaramide **2** with chloride in chloroform

Ortho nitro functional group also shows same interesting trend observed earlier in ketone (**13** and **14**) and the tertiary amidosquaramide (**29**) in that chloride binding was weaker in chloroform compared to acetonitrile.

3.2.6 Ortho dimethyl diphenyl squaramide (31):

Inhibition of chloride binding in the ortho substituted squaramides discussed thus far could be either due to steric hindrance or blocking of the anion binding site by intramolecular hydrogen bonding. To understand the contribution of steric effects in our molecular valve strategy the ortho methyl squaramide **31** was synthesized. Unfortunately, however, due to its insolubility in chloroform and acetonitrile, binding studies were limited to DMSO. The chloride binding constant for **31** was 204 M^{-1} compared to 405 M^{-1} for the unsubstituted diphenyl squaramide in DMSO-d_6. This shows that steric factors (in an ortho substituent) alone cannot be used for effective regulation of anion binding to squaramides. Solvent-polarity dependent intramolecular hydrogen bonding is essential for opening and closing the anion binding site in ortho substituted squaramides.

Figure 3.15: Diphenyl squaramide **1** and ortho dimethyl diphenyl squaramide **31**

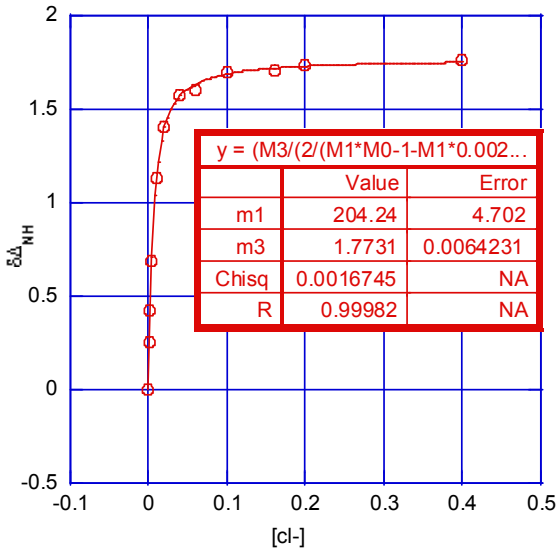
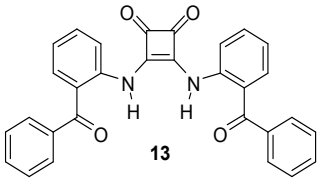
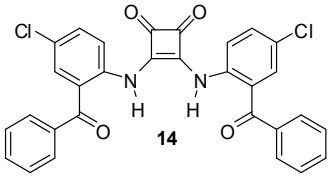
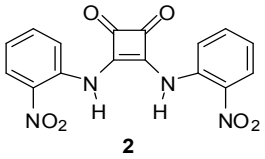
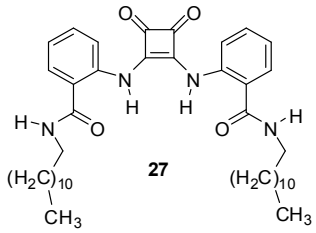
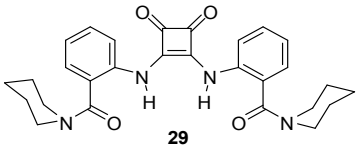
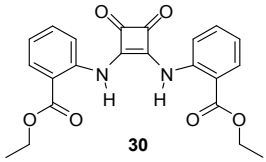


Figure 3.16: Binding isotherm of squaramide **31** with chloride in DMSO.

3.3 Discussion

Of the various ortho-carbonyl squaramides tested for molecular valve approach, only keto-derived orthocarbonyl squaramide proved to be the most promising. Moreover, addition of the electron-withdrawing chloro substituent at the para position of benzoyl squaramide **13** further increased the binding constant by approximately six times. Nitro-squaramide **2** also showed similar trend of solvent-selective chloride binding, but is only weakly solvent selective as compared to keto-squaramides **13** and **14**. The secondary amide squaramides which we initially proposed for stronger binding due to additional hydrogen bonding sites showed no chloride binding to squaramide NH, but instead exhibited peripheral binding to benzamide NH. This problem of peripheral binding was circumvented by tertiary amide squaramide **29** with no peripheral hydrogen bond donors. Tertiary amide squaramide **29** also showed good solvent-selective chloride binding like keto-squaramides **13** and **14**. Ethyl ester squaramide **30** did not show any chloride

Table 3.1: Binding constant values and the NH chemical shift of squaramides

entry	squaramides	$CHCl_3$ K_a M^{-1}	CH_3CN K_a M^{-1}	CH_3CN δ_{NH} in ppm
1	 **13**	ND[a]	84±8	10.54
2	 **14**	ND[a]	515±33	10.01
3	 **2**	294±13	545±78	9.79
4	 **27**	19±0.7	ND[a]	IS[b]
5	 **29**	42±2.5	1008±13	8.71
6	 **30**	ND[a]	7±1	10.95

[a]Not detected. [b]Insoluble in acetonitrile.

binding in chloroform and only weak binding in acetonitrile probably due to steric hindrance caused by the bulky ethyl groups.

The observed trends in Table 3.1 can be correlated to the chemical shifts of the squaramide NHs and therefore to the strength of the intramolecular hydrogen bond[7]. The squaramide δ_{NH} is deshielded in the order: secondary amide > ester > keto > nitro > tertiary amide. Since the deshielding of the NH is a function of the strength of the intramolecular hydrogen our data suggests an increases in the hydrogen bond strength in the order tertiary amide < nitro < keto, < ester < secondary amide[8]. The hydrogen bond is strongest in the secondary amide **27** which is why no disruption was observed in acetonitrile solvent. In the case of the ortho ester squaramide **30** with the second strongest hydrogen bond, weak chloride binding was observed. Only in the case of the keto functionality is a right balance achieved between disruption of the intramolecular hydrogen and chloride binding. By studying compounds with a range of different hydrogen bond strengths we were able to gain insights into the successful application of our molecular valve approach and facilitate future design strategies.

3.4 Conclusions

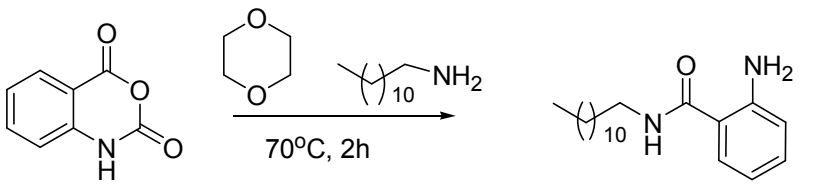
We report here that carbonyl groups in tertiary amide squaramide functions as solvent-sensitive, anion-binding molecular valves. Keto-derived ortho squaramides show more solvent selective chloride binding than the tertiary amide squaramides which make them promising candidates for furthering our molecular valve approach. Solubility of these squaramide pose constrains in designing molecular valves. This concept of novel solvent-selective chloride binding opens up newer possibilities in medicinal chemistry

since it can serve in the treatment of defective ion-channel diseases such as cystic fibrosis.

3.5 Experimental section

All reactions were performed under nitrogen atmosphere unless otherwise specified. All glassware was oven-dried at 110 ^{o}C and cooled under nitrogen. Melting points were recorded using Mel-Temp apparatus and are uncorrected. All tetra butyl ammonium salts were purchased from commercial sources and were used without further purification. HPLC grade acetonitrile and chloroform were used for all UV-Vis studies. ^{1}H and ^{13}C NMR were recorded at 400 MHz and 100 MHz, respectively. The chemical shifts are reported in δ ppm using the residual solvent peak (7.28 ppm for $CDCl_3$ and 2.50 ppm for d_6-DMSO) as the internal reference. Coupling constants are reported in hertz. High resolution mass spectra were collected at the CUNY Mass Spectrometry Facility at Hunter College

3.5.1 Preparation of 2-amino-N-dodecyl-benzamide (23):

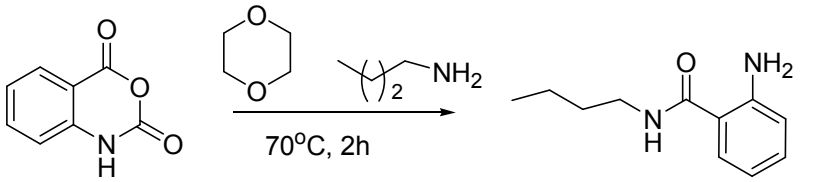


Isatoic anhydride 2-amino-*N*-dodecylbenzamide

To a suspension of isatoic anhydride (815 mg, 5 mmol) in dioxane (8 ml), n-dodecyl amine (2.28 g, 7.5 mmol) dissolved in dioxane (2 ml) were added drop-wise over 15 minutes. Immediate evolution of carbon dioxide was observed. The reaction was

monitored by TLC for completion of starting material, stopped after 12 hours and concentrated to get residue. Recrystallization followed by column chromatography in 2% methanol in methylene chloride to obtain 741mg in 49% yield. ^{1}H NMR ($CDCl_3$): 7.32 (d, 1H, J = 8), 7.22 (t, 1H, J = 7.8), 6.67 (m, 2H), 6.04 (s, 1H), 5.50 (s, 2H,), 3.40 (m, 2H), 1.60 (m, 2H,), 1.33 (m, 18H), 0.90 (t, 3H, J = 7.2). ^{13}C NMR ($CDCl_3$): 169.2, 148.6, 132.1, 126.9, 117.2, 116.6, 116.4, 39.7, 31.9, 29.7, 29.6, 29.6, 29.5, 29.3, 27.0, 22.7, 14.1. HRMS calculated for $C_{19}H_{32}N_2O$ (M^+) = 304.2514 found 304.2515.

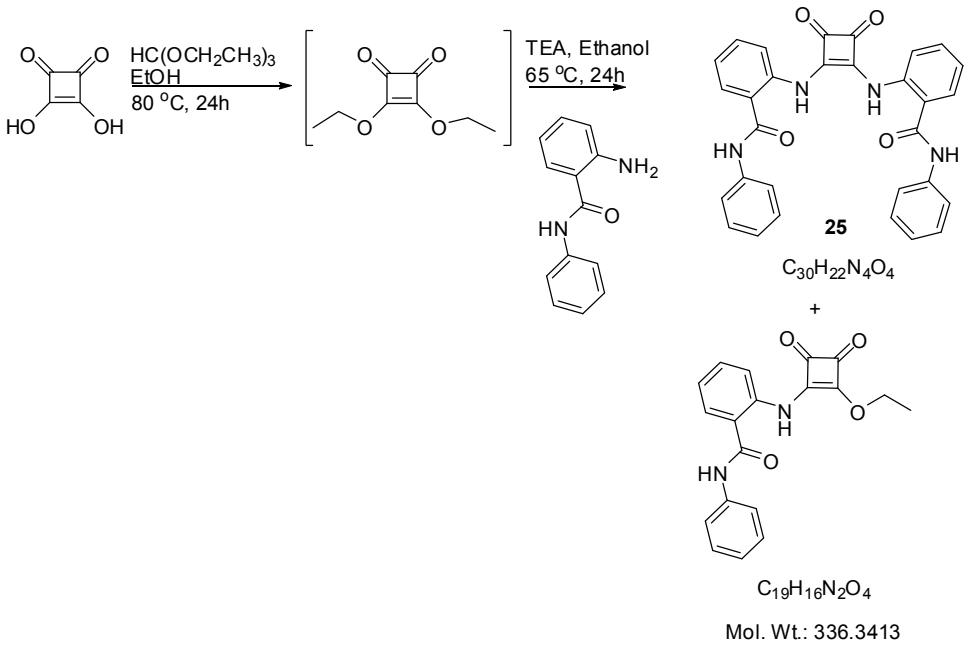
3.5.2 Preparation of 2-amino-N-butyl-benzamide (24):



Isatoic anhydride 2-amino-*N*-dodecylbenzamide

Similar to procedure **23,** n-butyl amine (574 mg, 7.5 mmol). Recrystallization in ether, followed by column chromatography in 2% methanol in methylene chloride to obtain 410 mg in 42% yield. ^{1}H NMR ($CDCl_3$): 7.32 (d, 1H, J = 8), 7.22 (t, 1H, J = 7.8), 6.69 (m, 2H), 6.04 (s, 1H), 5.51 (s, 2H), 3.44(m, 2H), 1.62 (m, 2H), 1.45 (m, 2H), 0.98 (t, 3H, J = 7.2) . ^{13}C NMR ($CDCl_3$): 169.3, 148.6, 132.1, 126.9, 117.2, 116.6, 116.4, 39.4, 31.7, 20.2, 13.8. Reference: *Org Lett*., **2005**, *7*, 5285-8.

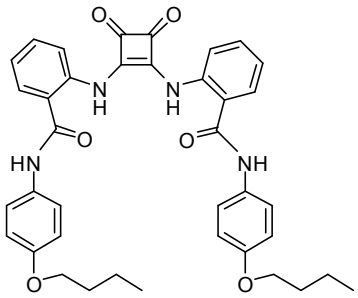
3.5.3 Preparation of 2, 2'-(3, 4-dioxocyclobut-1-ene-1, 2-diyl) bis (azanediyl) bis (N-phenylbenzamide) (25):



To a stirring solution of squaric acid (228 mg, 2 mmol) in ethanol (6 ml), triethylorthoformate (0.83 ml, 2.5 mmol) was added and the reaction temperature increased to 80 ^{o}C and maintained for 24hours. In a separate RB flask N'-phenyl 2-amino benzamide (1060 mg, 5 mmol) was dissolved in ethanol (6 ml) and triethylamine (505 mg, 5 mmol). To this stirring solution, the prepared diethyl squarate was added portion-wise. After complete addition reaction temperature was increased to 65 ^{o}C and maintained for 24hours. Reaction mixture was then allowed to attain room temperature and stirred with 15% Hydrochloric acid (100 ml) solution. Precipitated yellow solid was filtered and washed with water (250 ml) to obtain crude product (600 mg). This crude product was washed with isopropanol 3 times followed by repeated recrystallization in acetonitrile: chloroform (1:1) to yield 3.5 % (29 mg) of the pure squaramide **25**. ^{1}H

NMR (DMSO-d_6):10.54(s, 1H), 10.49 (s, 1H), 7.73 (m, 3H), 7.55(t, 1H, *J* = 8), 7.47 (d, 1H, *J* = 7.8), 7.30 (m, 3H), 7.11(t, 1H, *J* = 8). ^{13}C NMR (DMSO-d_6): δ 183.1, 166.7, 166.2, 139.0, 138.8, 132.1, 131.3, 128.9, 128.5, 125.9, 123.9, 123.2, 120.3. HRMS calculated for $C_{30}H_{22}N_4O_4$ (M^+) = 502.1641 found 502.1655.

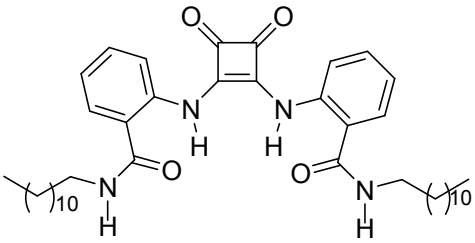
3.5.4 Preparation of 2, 2'-(3, 4-dioxocyclobut-1-ene-1, 2-diyl) bis(azanediyl)bis(N-(4-butoxyphenyl)benzamide) (26):



26

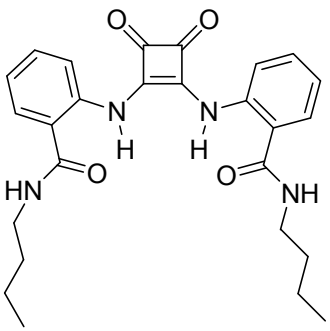
To a stirring solution of squaric acid (114 mg, 1 mmol) in dry toluene, thionyl chloride (238 mg, 2 mmol) and DMF (20 μL) were added at room temperature under nitrogen atmosphere. Reaction temperature was then increased to 95 ^{o}C (oil bath temperature) and maintained for 2hours. Reaction mixture was allow to attain room temperature and concentrated to obtain an oily residue which was dissolved in dry toluene (2 ml). To this, a solution of 2-amino-N-(4-butoxy-phenyl)-benzamide (852 mg, 3 mmol) in toluene (5 ml) were added at room temperature. The reaction mixture was then refluxed for 24hours. Hot filtration of reaction mixture, to obtain 100 mg of pure squaramide **26**. ^{1}H NMR (DMSO-d_6): 10.63 (s, 1H,), 10.41(s, 1H), 7.74 (d, 1H, *J* = 7.8), 7.63 (d, 2H, *J* = 8), 7.53 (m, 2H), 7.27(t, 1H, *J* = 8), 6.89 (d, 2H, *J* = 8). ^{13}C NMR (DMSO-d_6): 183.0, 166.2, 165.7, 155.1, 136.4, 131.7, 128.6, 121.9, 114.2, 67.2, 30.7, 18.7, 13.7 . HRMS calculated for $C_{38}H_{38}N_4O_6$ (M^+) = 646.2791 found 646.2798.

3.5.5 Preparation of 2, 2'-(3, 4-dioxocyclobut-1-ene-1, 2-diyl)bis(azanediyl)bis(N-dodecylbenzamide) (27):



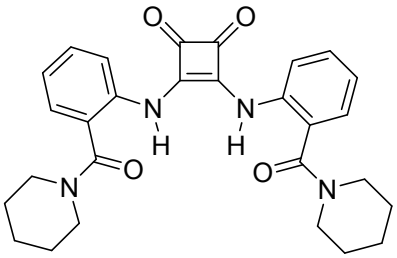
Similar to procedure of squaramide **26**, pale yellow solid obtained in 45% yield. ^{1}H NMR ($CDCl_3$): 11.87 (s, 2H), 8.11(d, 2H, *J* = 8.0), 7.56 (t, 2H, *J* = 8), 7.49 (d, 2H, *J* = 8), 7.11 (t, 2H, *J* = 8), 3.50 (q, 4H, *J* = 6.8), 1.68 (m, 4H), 1.39(m, 42H), 0.90(t, 6H, *J* = 7.8). ^{13}C NMR ($CDCl_3$): 183.1, 168.7, 168.2, 139.7, 133.2, 126.4, 119.1, 40.15, 31.9, 29.6, 29.6, 29.6, 29.4, 29.3, 27.1, 27.7, 14.1. HRMS calculated for $C_{42}H_{62}N_4O_4$ (M^+) = 686.4771 found 687.4768. Mpt. 209-211 ^{o}C

3.5.6 Preparation of 2, 2'-(3, 4-dioxocyclobut-1-ene-1, 2-diyl)bis(azanediyl)bis(N-butylbenzamide) (28):



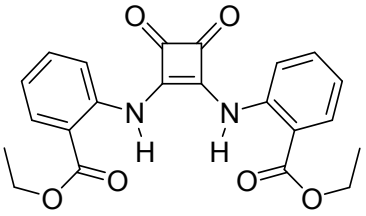
Similar to procedure of squaramide **26** pale yellow solid obtained in 40% yield. ^{1}H NMR (DMSO-d_6): 11.31 (s, 1H), 8.76 (t, 1H, *J* = 8.0), 7.71 (d, 1H, *J* = 7.8), 7.63 (d, 1H, *J* = 8) 7.54 (t, 1H, *J* = 8),7.21 (t, 1H, *J* = 8), 3.29 (m, 2H), 1.54 (m, 2H), 1.35(m, 2H), 0.90 (t, 3H, *J* = 7.8). ^{13}C NMR (DMSO-d_6): 183.1, 167.6, 166.0, 137.5, 131.5, 128.1, 123.1, 122.5, 121.7, 40.8, 30.0, 19.6, 13.6. HRMS calculated for $C_{26}H_{30}N_4O_4$ (M^+) = 462.2267 found 462.2264.

3.5.7 Preparation of 3, 4-bis (2-(piperidine-1-carbonyl) phenylamino) cyclobut-3-ene-1, 2-dione (29):



Pale yellow solid obtained in 35% yield. ^{1}H NMR ($CDCl_3$): 9.32 (s, 2H), 7.55 (d, 2H, J = 8.0), 7.47 (t, 2H, J = 8), 7.25 (d, 2H, J = 8) 7.15 (t, 2H, J = 8), 3.58 (m, 4H), 1.8 (m, 6H). ^{13}C NMR ($CDCl_3$): 183.1, 168.5, 166.1, 135.4, 130.8, 127.4, 125.6, 124.0, 12.5, 24.4, 22.3, 14.0. HRMS calculated for $C_{28}H_{30}N_4O_4$ (M^+) = 486.2267 found (M^+) = 486.2277. Mpt. 232-235 ^{o}C

3.5.8 Preparation of diethyl 2, 2'-(3, 4-dioxocyclobut-1-ene-1, 2-diyl) bis (azanediyl) dibenzoate (30):



Yellow solid obtained in 30% yield. ^{1}H NMR ($CDCl_3$): 11.38 (s, 2H), 8.25 (d, 2H, J = 8), 8.09 (d, 2H, J = 8), 7.65 (t, 2H, J = 7.8), 7.1 (t, 2H, J = 8.0), 4.48 (q, 4H, J = 6.8), 1.47 (t, 6H, J = 7.2) ppm. ^{13}C NMR ($CDCl_3$): 183.1, 168.6, 166.28, 141.0, 135.1, 131.1, 122.8, 119.9, 114.9, 61.8, 14.1. HRMS calculated for $C_{22}H_{20}N_2O_6$ (M+) = 408.4040 found (M+1) 409.1394. Mpt. 176-178 ^{o}C

3.5.9 Preparation of 3, 4-bis (o-tolylamino) cyclobut-3-ene-1, 2-dione (31):

Squaric acid (1.14 mg, 1 mmol) was stirred with ethanol (3 ml) in a 10 ml RB flask under nitrogen atmosphere for 30 minutes, triethylorthoformate (0.4 ml) was then added. The reaction was refluxed for 24 hours to obtain diethyl squarate. The obtained diethyl squarate was cooled to 5-10 ^{0}C followed by the addition of 2-amino

toluene (428 mg, 4 mmol), the reaction was stirred at room temperature for 24 hours. The precipitated solid was filtered and washed with diethyl ether (2 × 100 ml) and dried under vacuum to get title compound in 85% yield. ^{1}H NMR (400 MHz, DMSO-d_6): 9.34 (s, 2H), 7.32 (d, 2H, J = 8) 7.21 (m, 4H), 7.07 (t, 2H, J = 8), 2.35 (s, 6H). ^{13}C NMR (100 MHz, DMSO-d_6): 182.5, 166.4, 136.1, 130.4, 128.6, 126.3, 124.6, 122.3, 17.7 ppm. HRMS calculated for $C_{18}H_{16}N_2O_2$ (M^+) = 292.1211 found (M^+) 292.1212 mp: >250 ^{o}C

3.6 IR and NMR spectra of squaramides

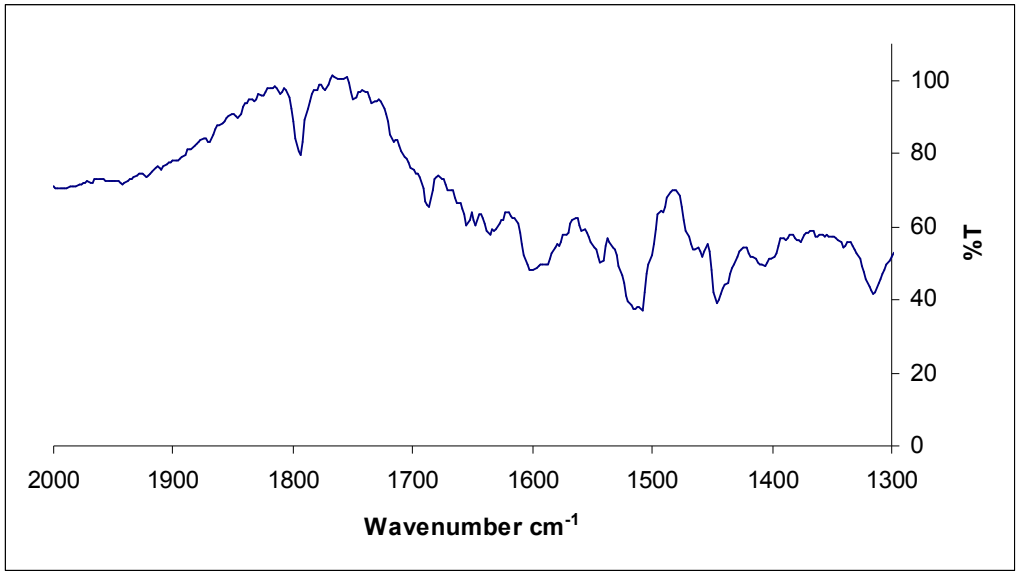


Figure 3.17: IR spectrum of squaramide **27** in chloroform

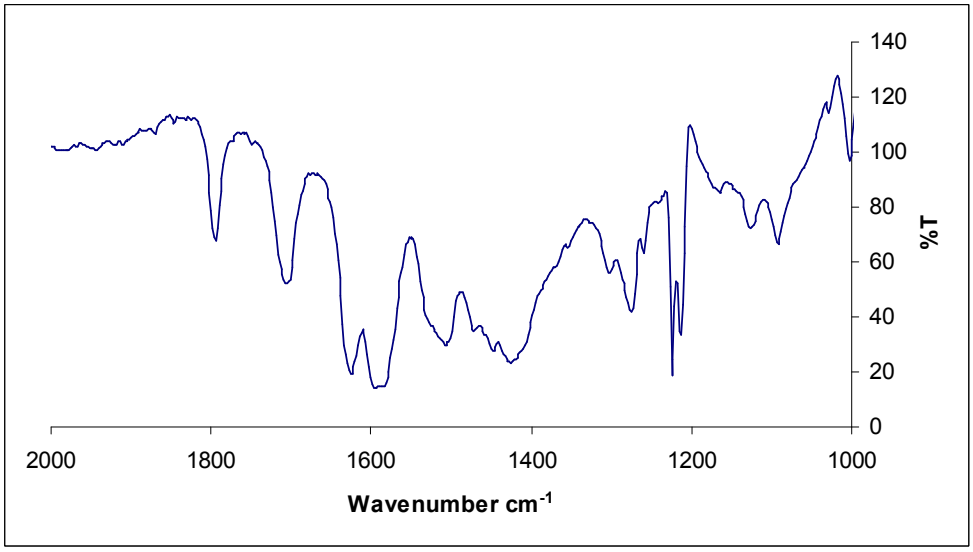


Figure 3.18: IR spectrum of squaramide **29** in chloroform

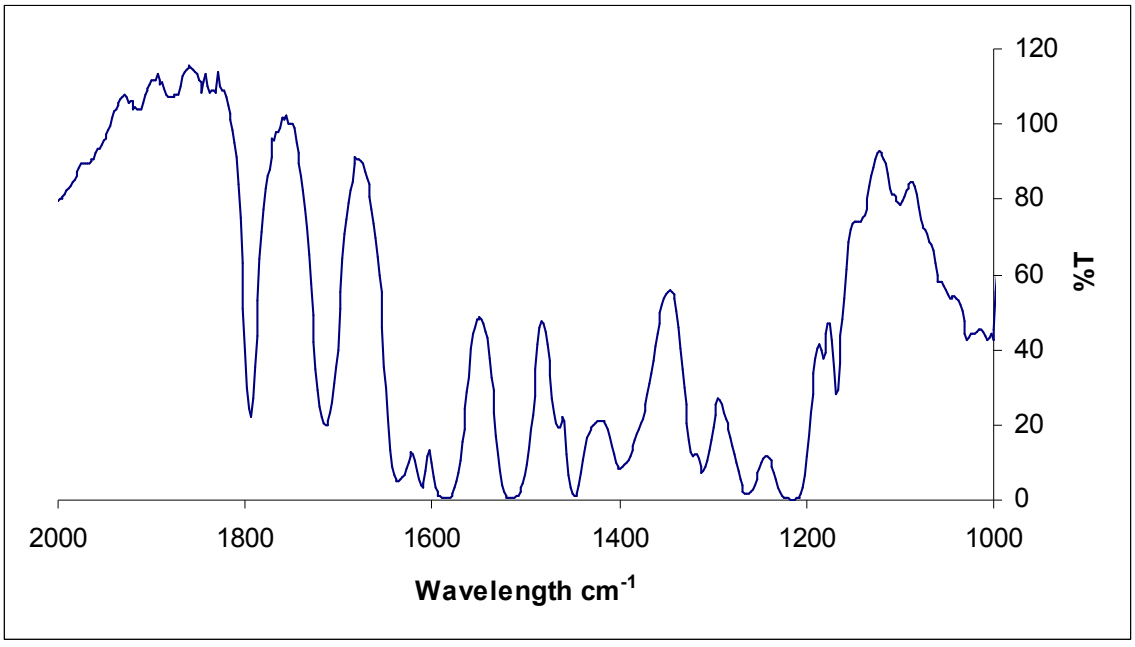


Figure 3.19: IR spectrum of squaramide **30** in chloroform

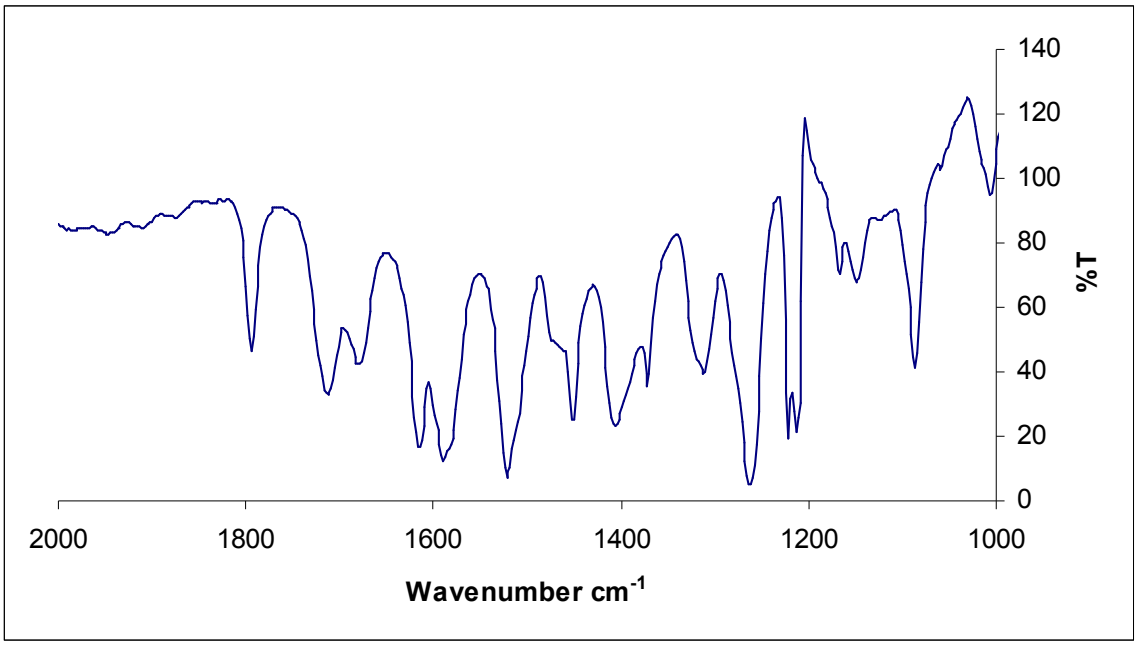


Figure 3.20: IR spectrum of squaramide **2** in chloroform

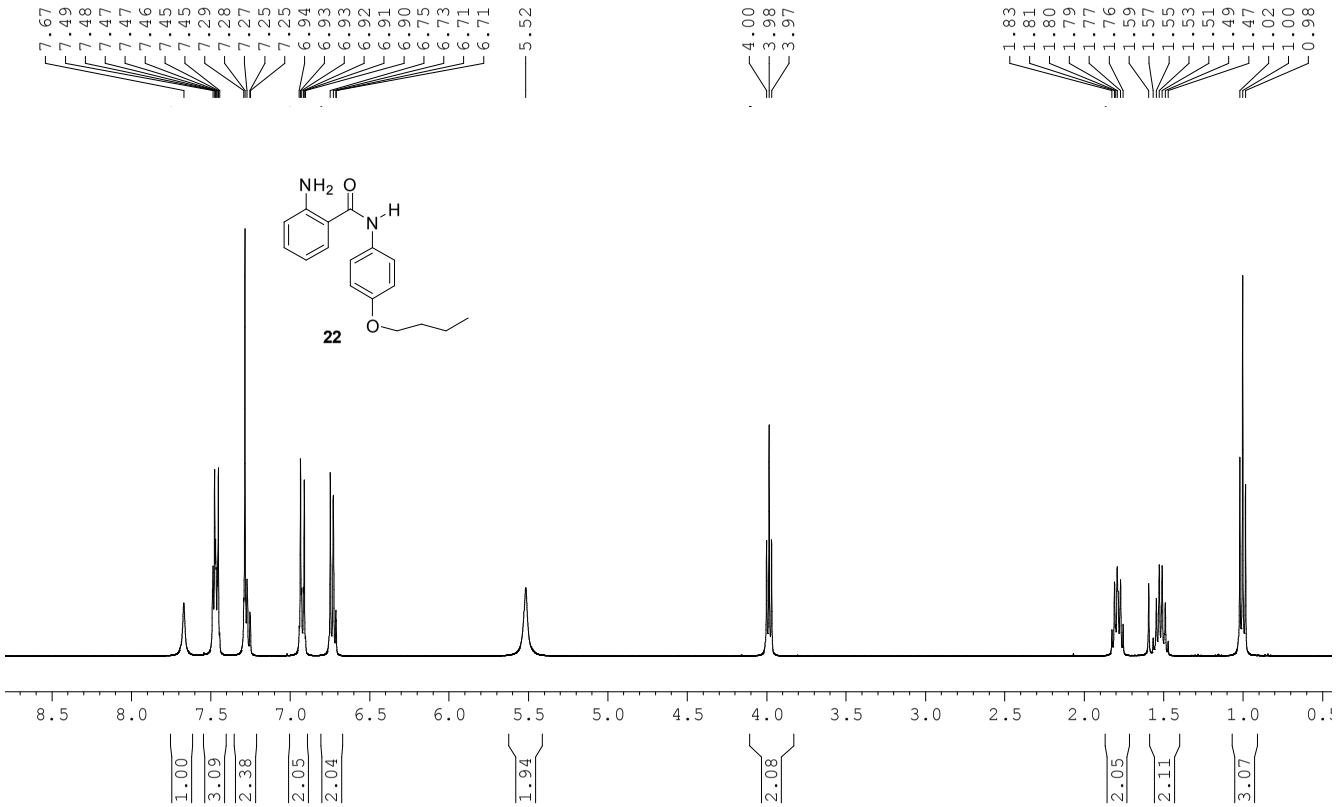


Figure 3.21: ^{1}H NMR spectrum of 2-amino-N-(4-butoxy-phenyl)-benzamide (**22**) in $CDCl_3$

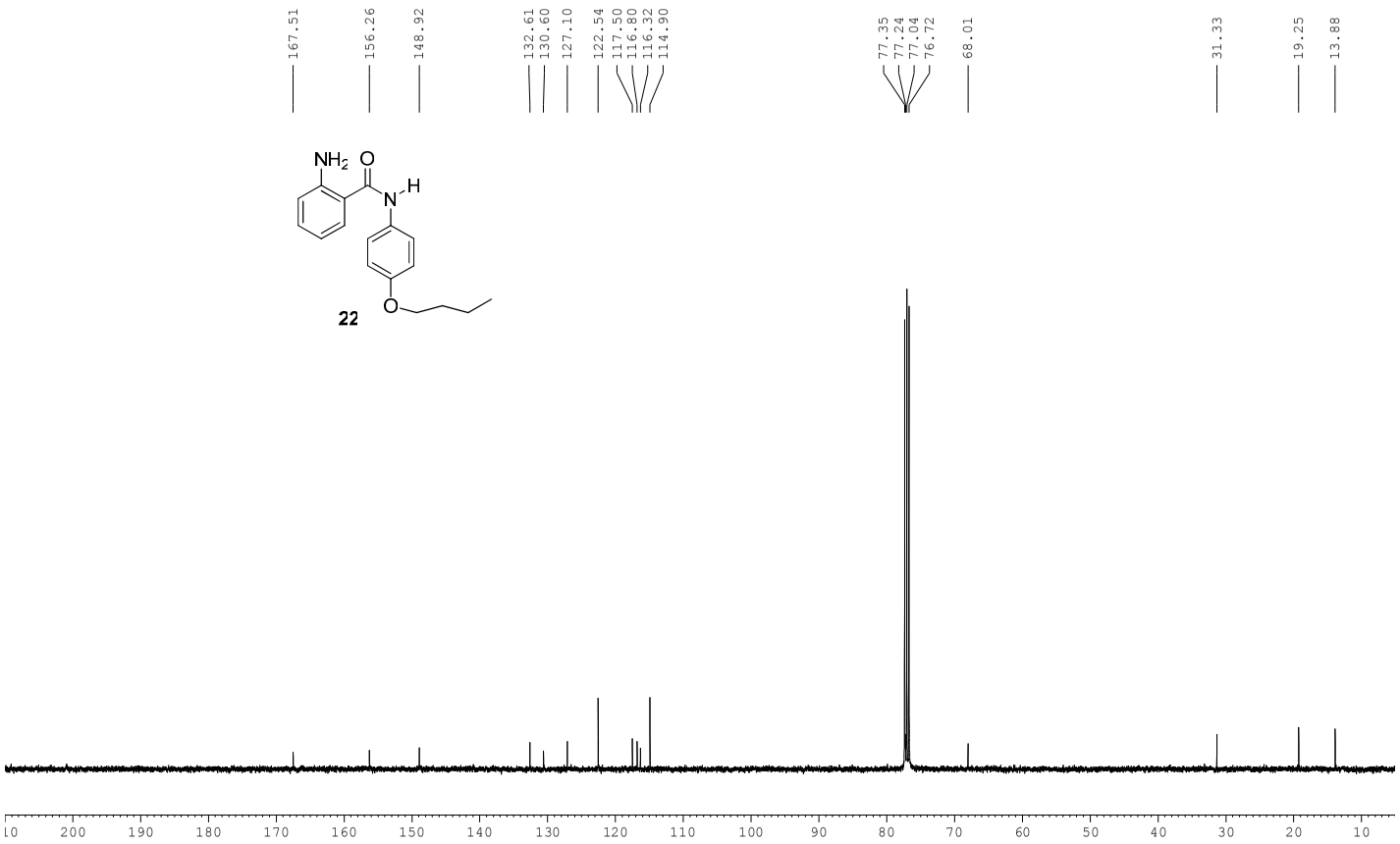


Figure 3.22: ^{13}C NMR spectra of 2-amino-N-(4-butoxy-phenyl)-benzamide (**22)** in $CDCl_3$

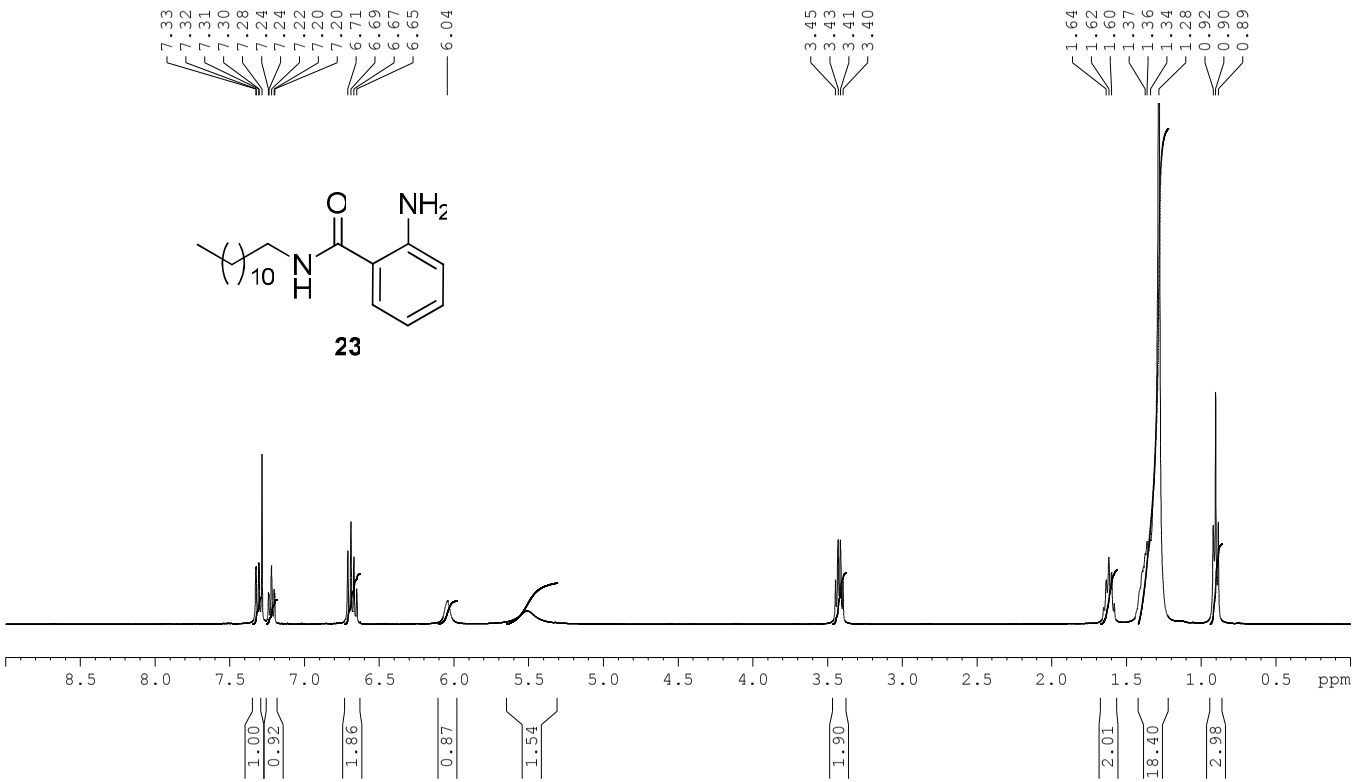


Figure 3.23: ^{1}H NMR spectra of 2-amino-N-dodecyl-benzamide (**23**) in $CDCl_3$

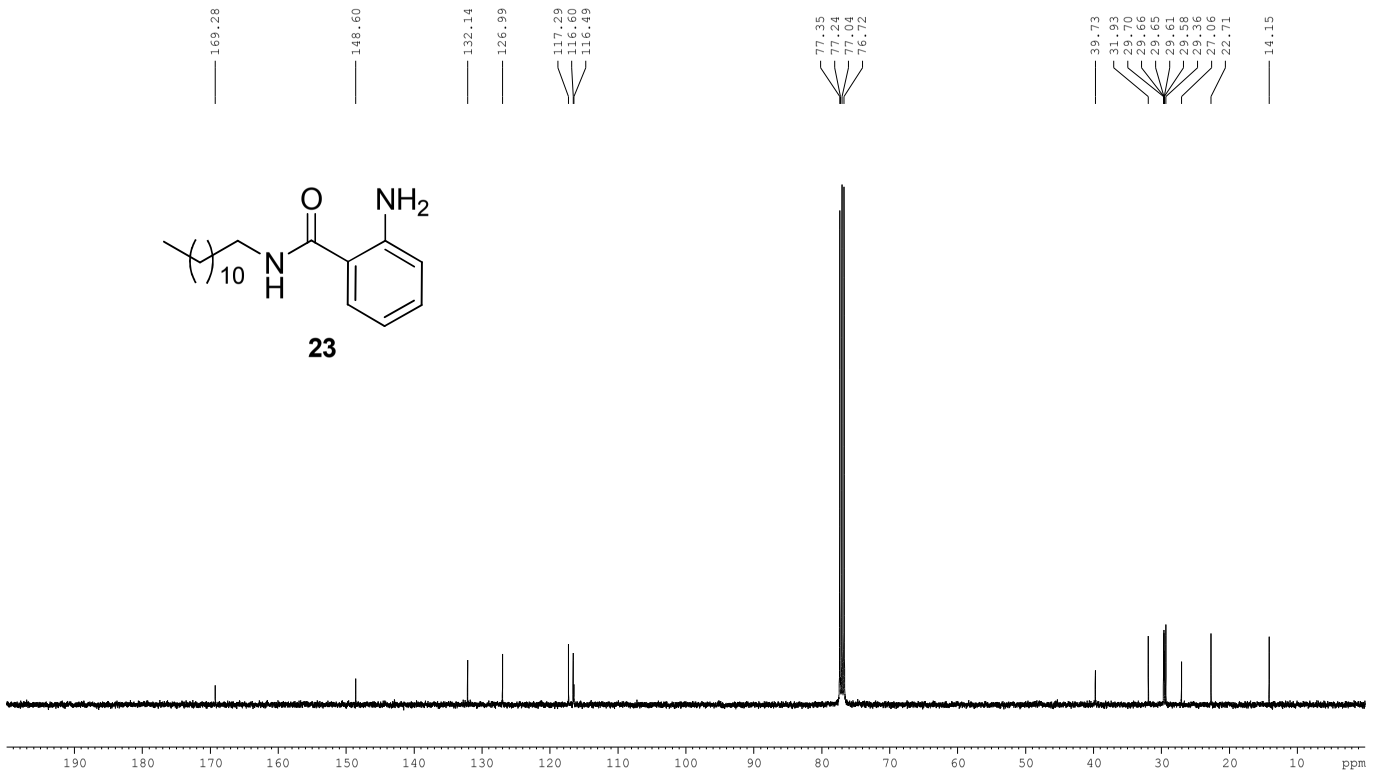


Figure 3.24: ^{13}C NMR spectra of 2-amino-N-dodecyl-benzamide (**23**) in $CDCl_3$

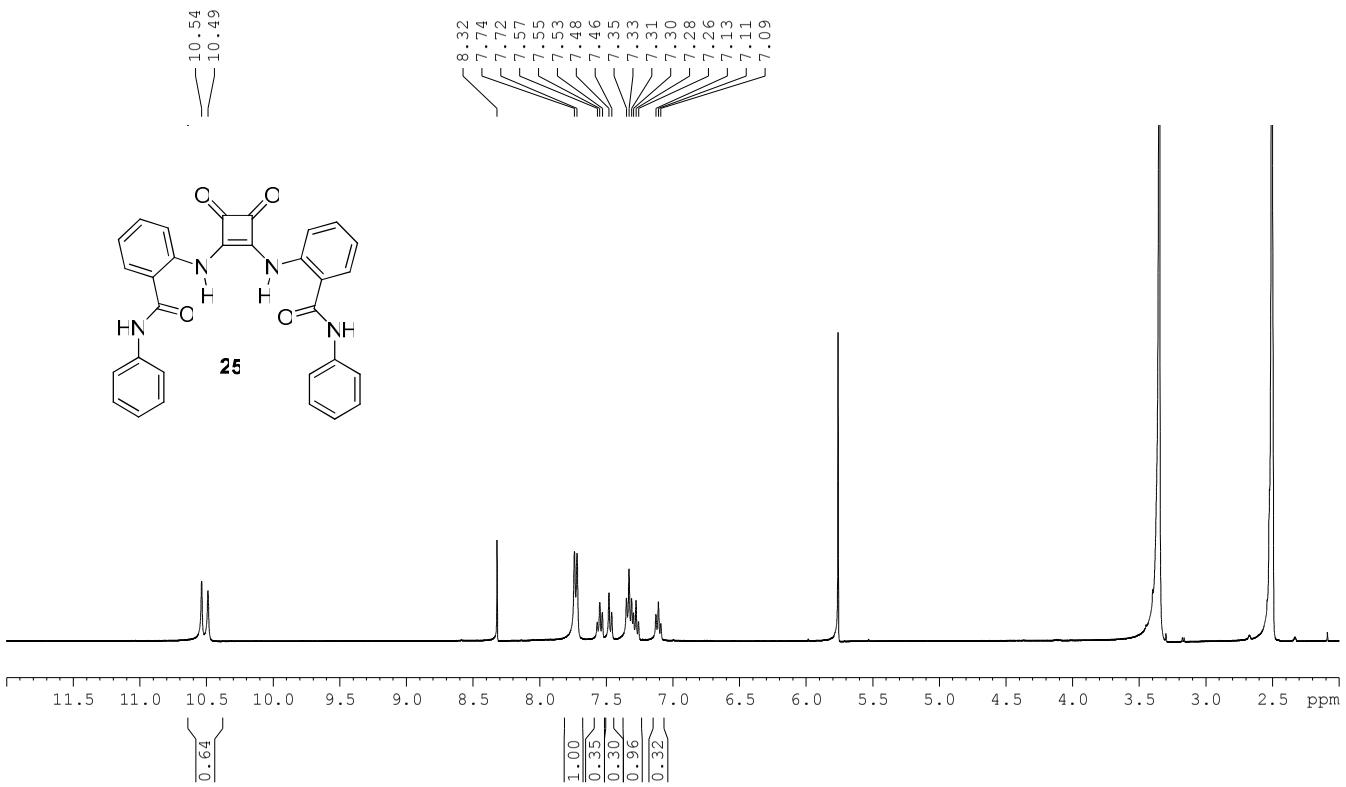


Figure 3.25: ^{1}H NMR spectra of squaramide (**25**) in DMSO-d_6.

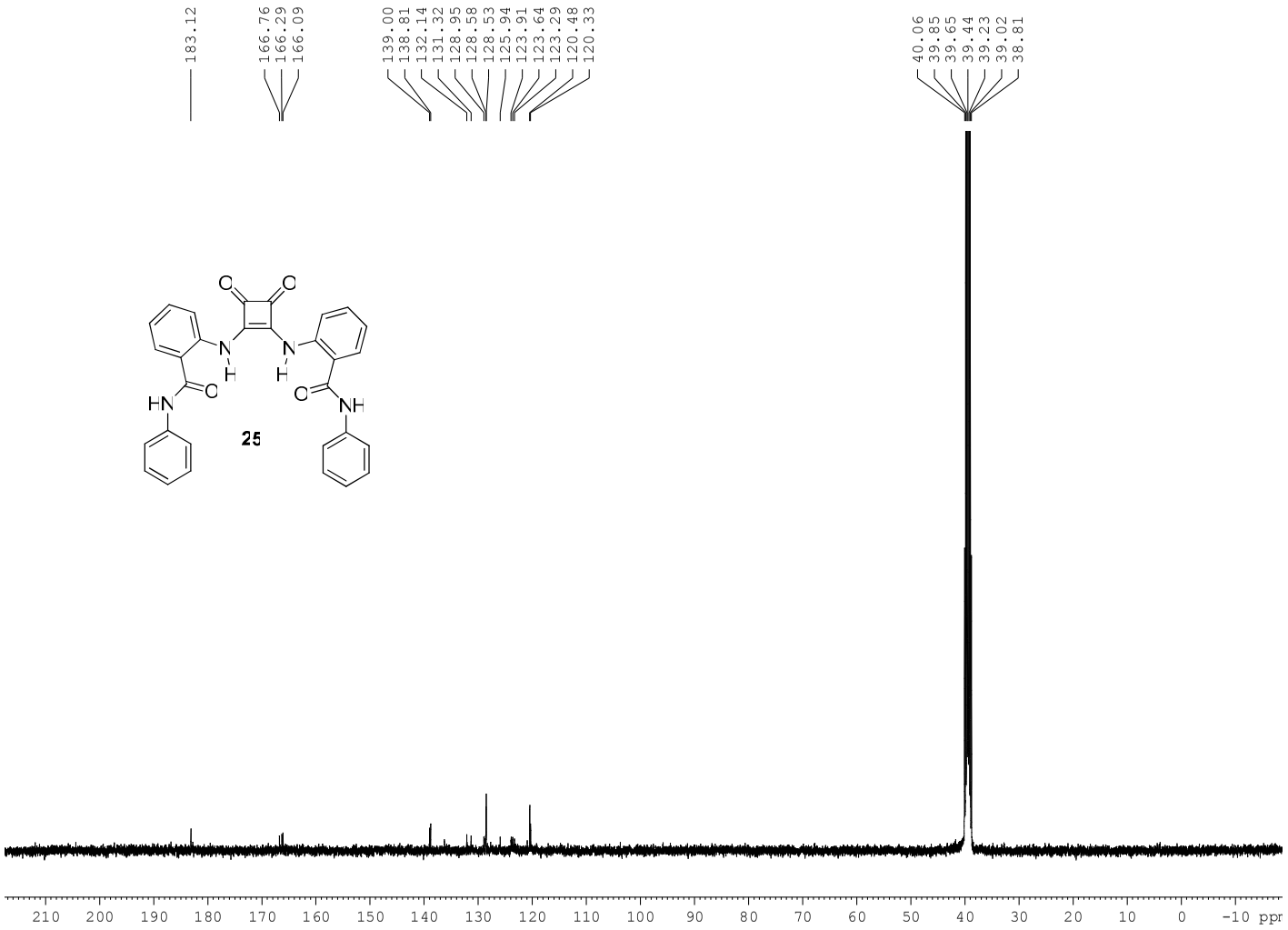


Figure 3.26: ^{13}C NMR spectra of squaramide (**25)** in DMSO-d_6.

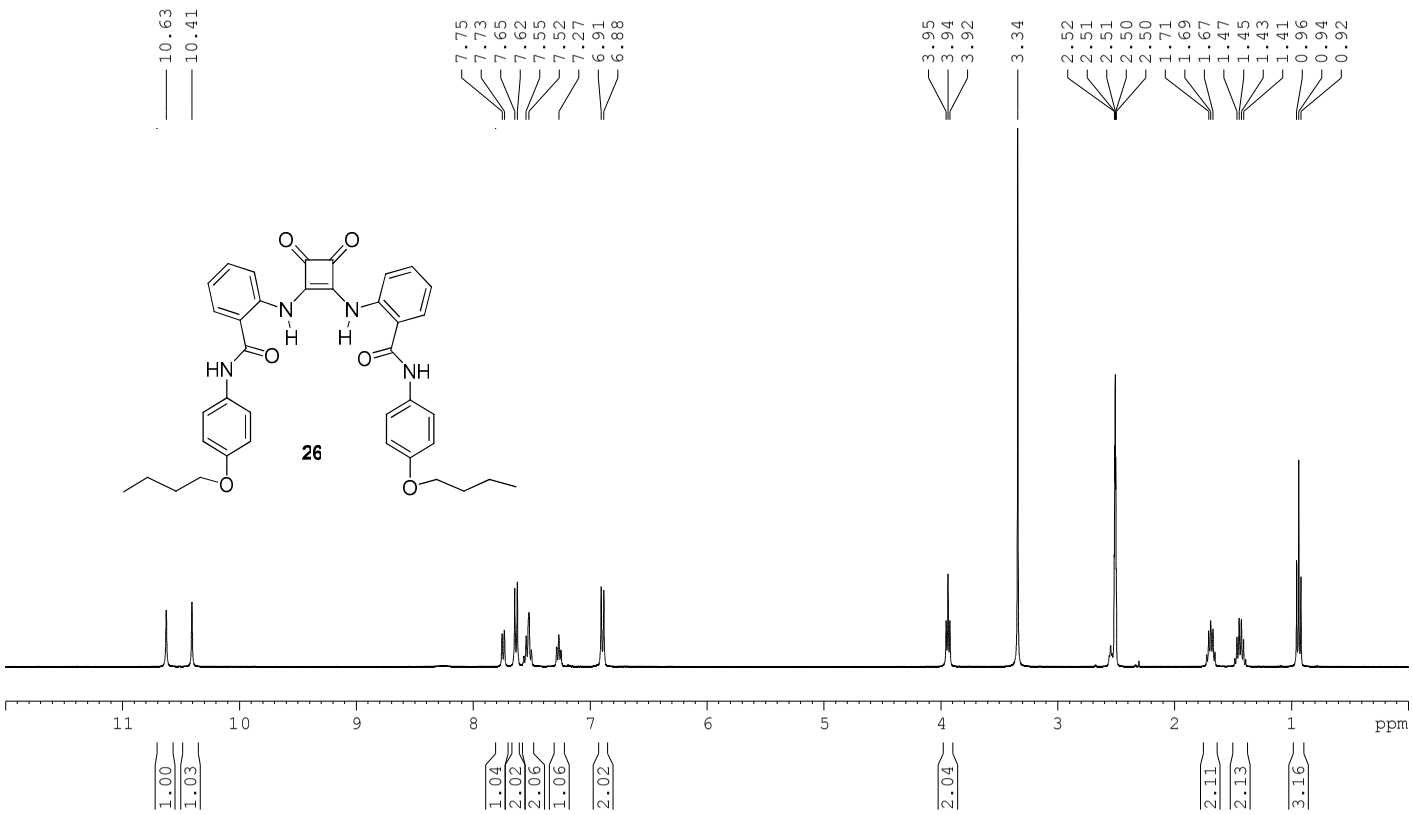


Figure 3.27: ^{1}H NMR spectra of squaramide (**26)** in DMSO-d_6.

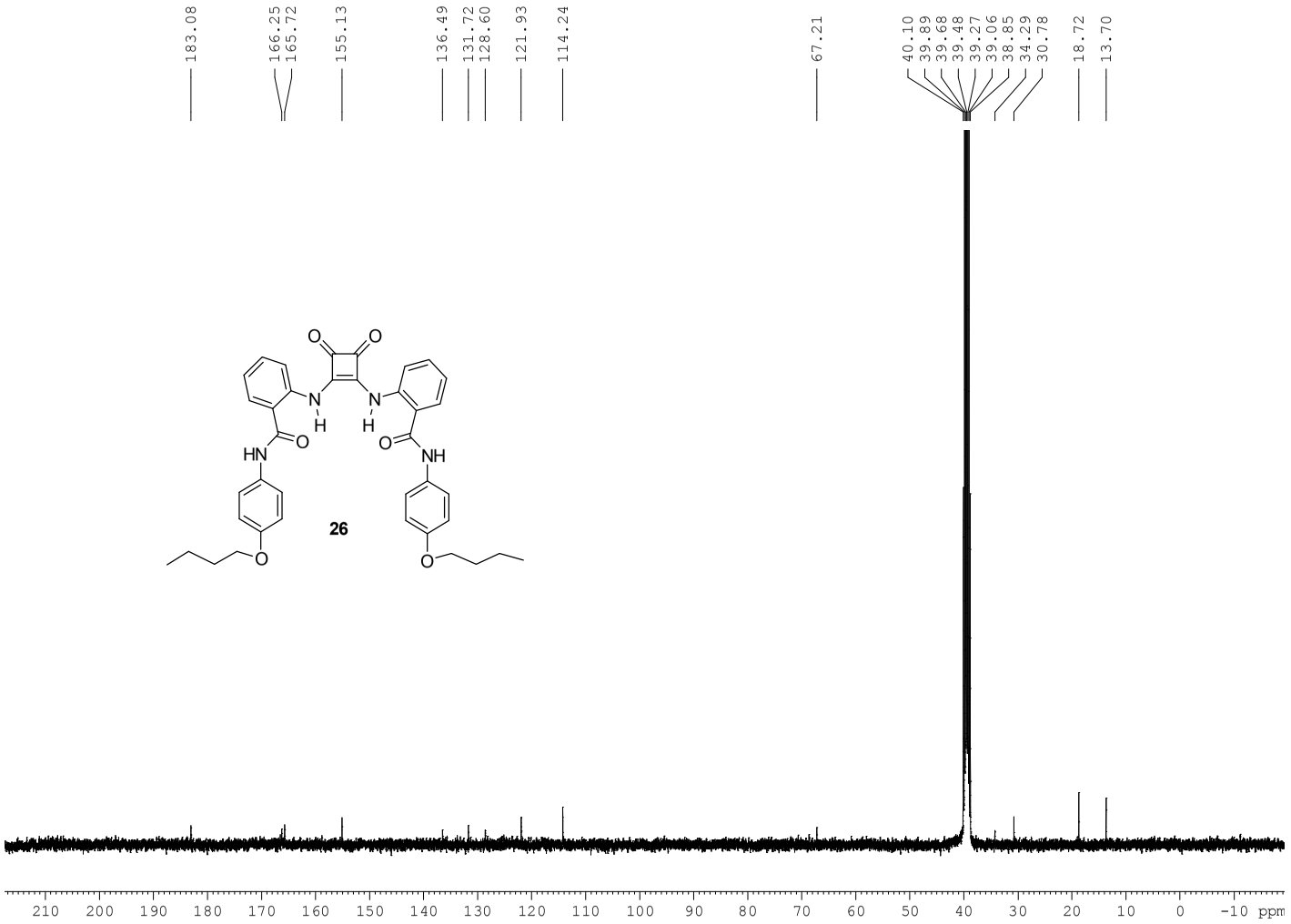


Figure 3.28: ^{13}C NMR spectra of squaramide (**26)** in DMSO-d_6.

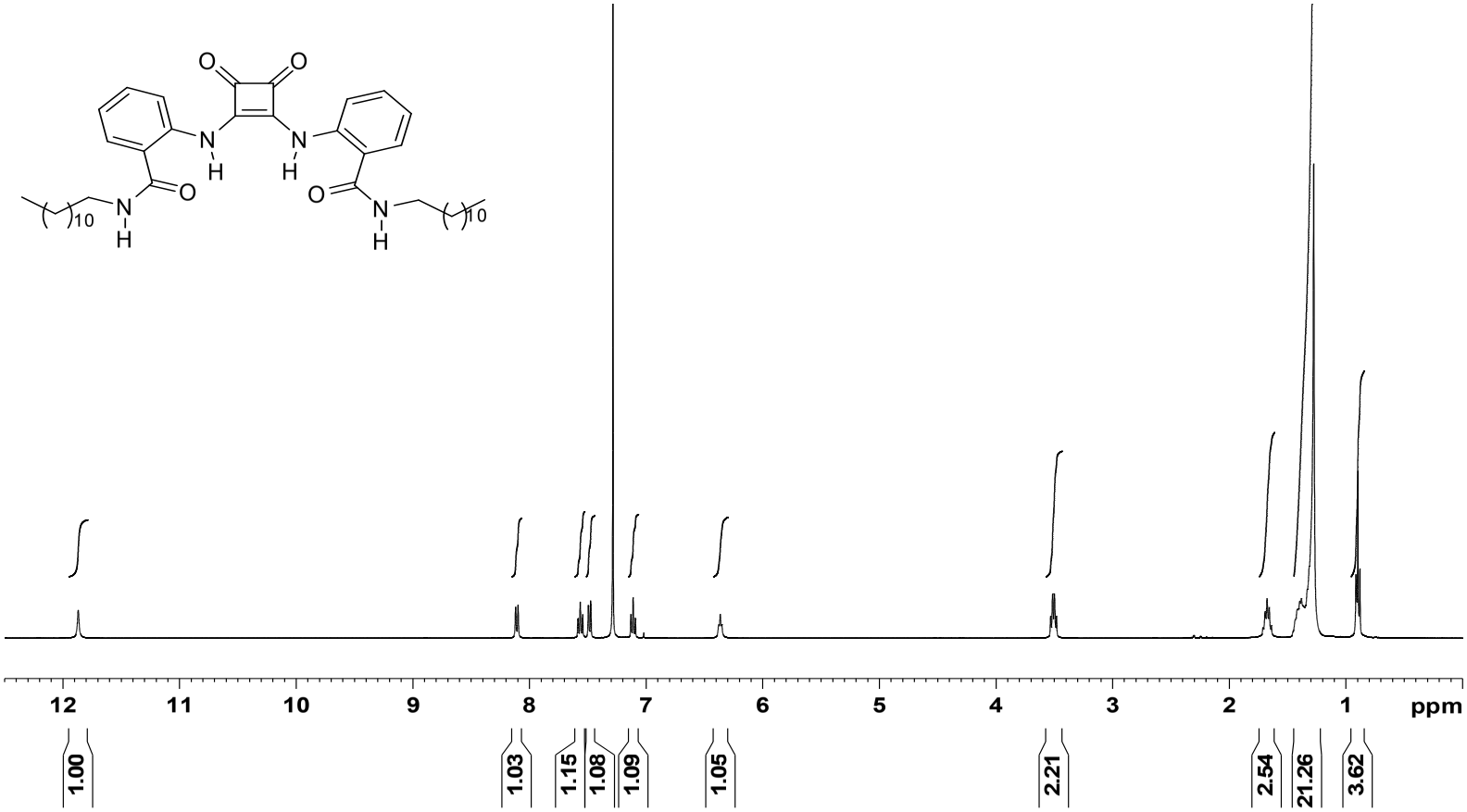


Figure 3.29: ^{1}H NMR spectra of squaramide **(27)** in $CDCl_3$.

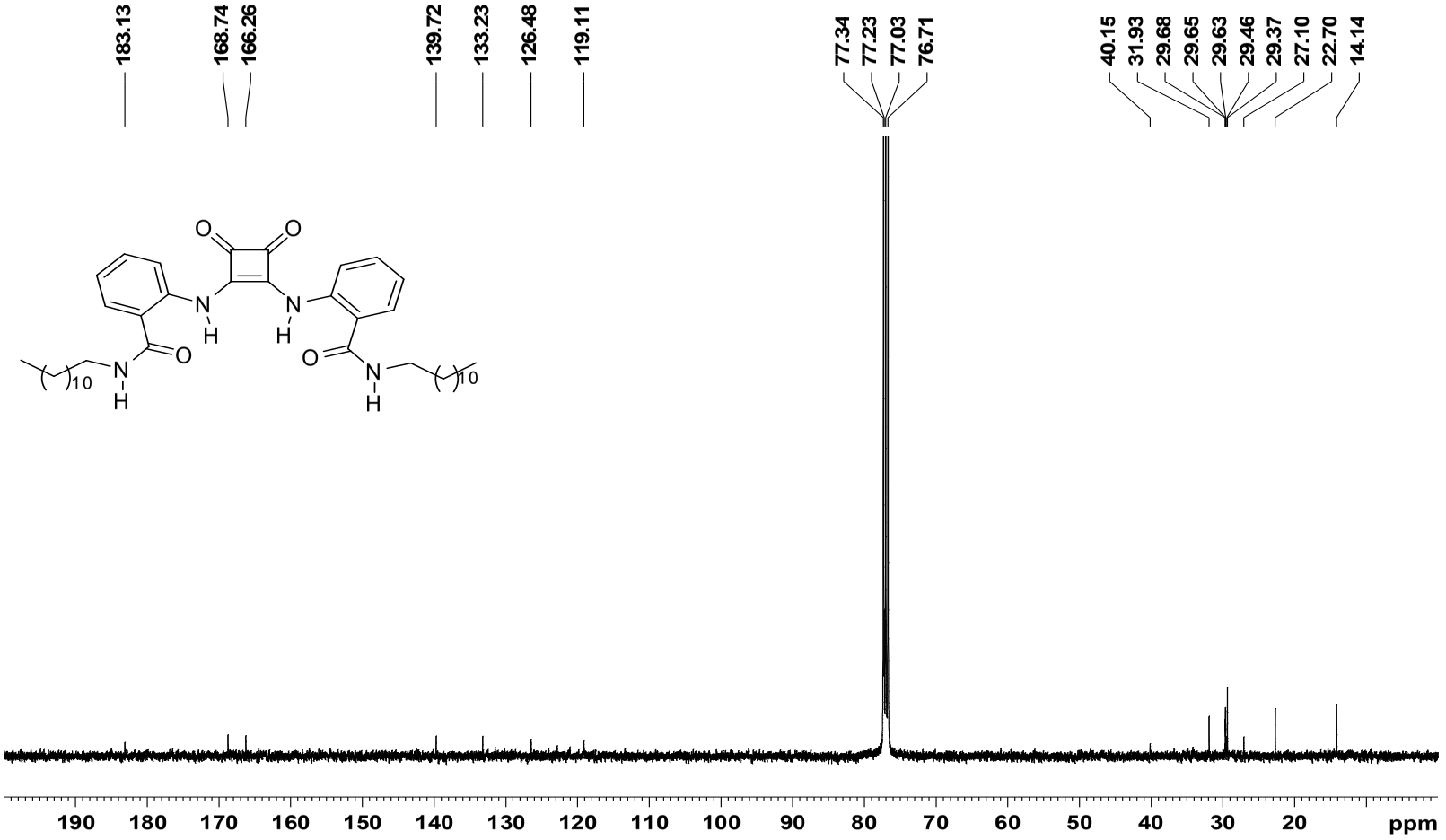


Figure 3.30: ^{13}C NMR spectra of squaramide (**27**) in $CDCl_3$.

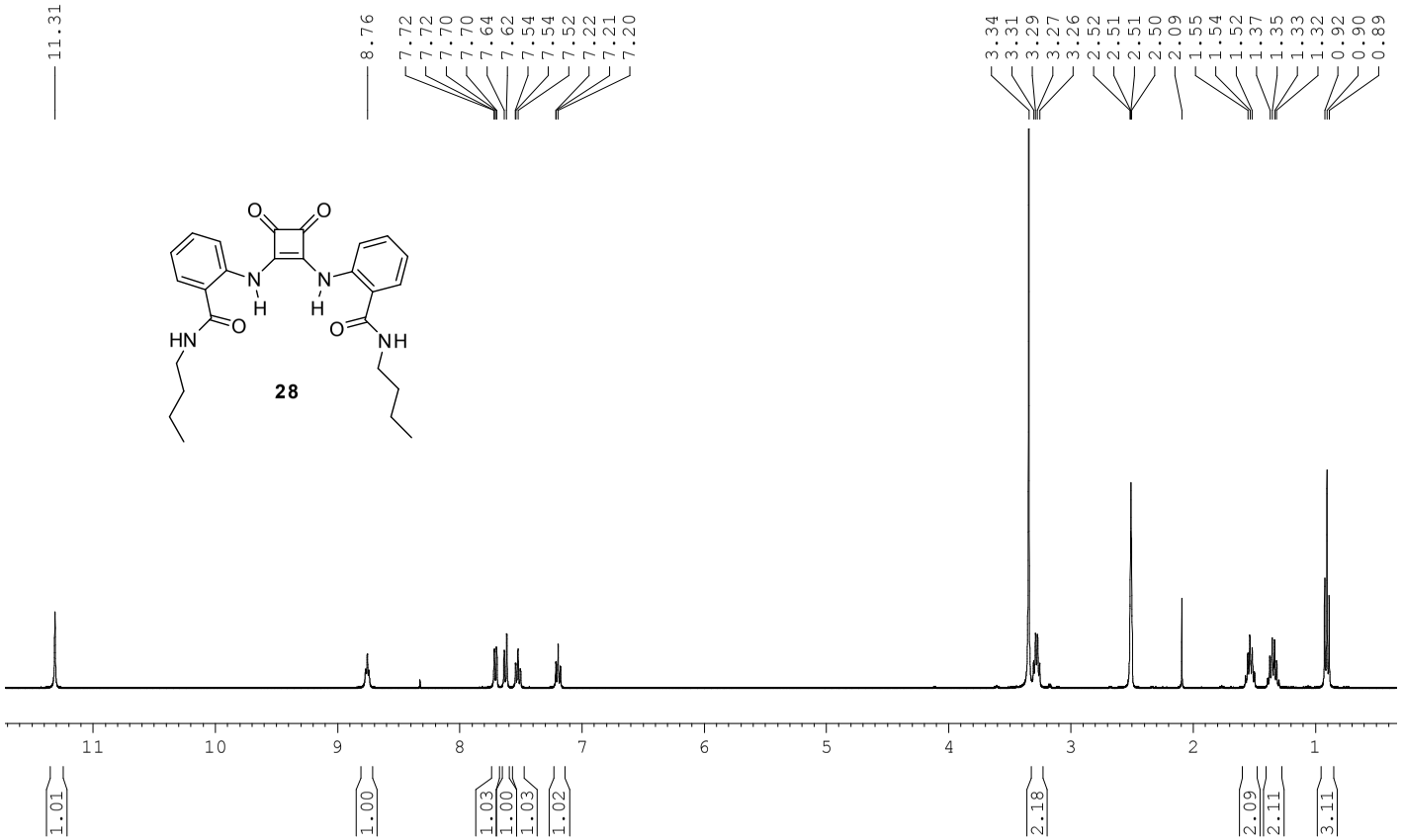


Figure 3.31: ^{1}H NMR spectra of squaramide (**28)** in DMSO-d_6.

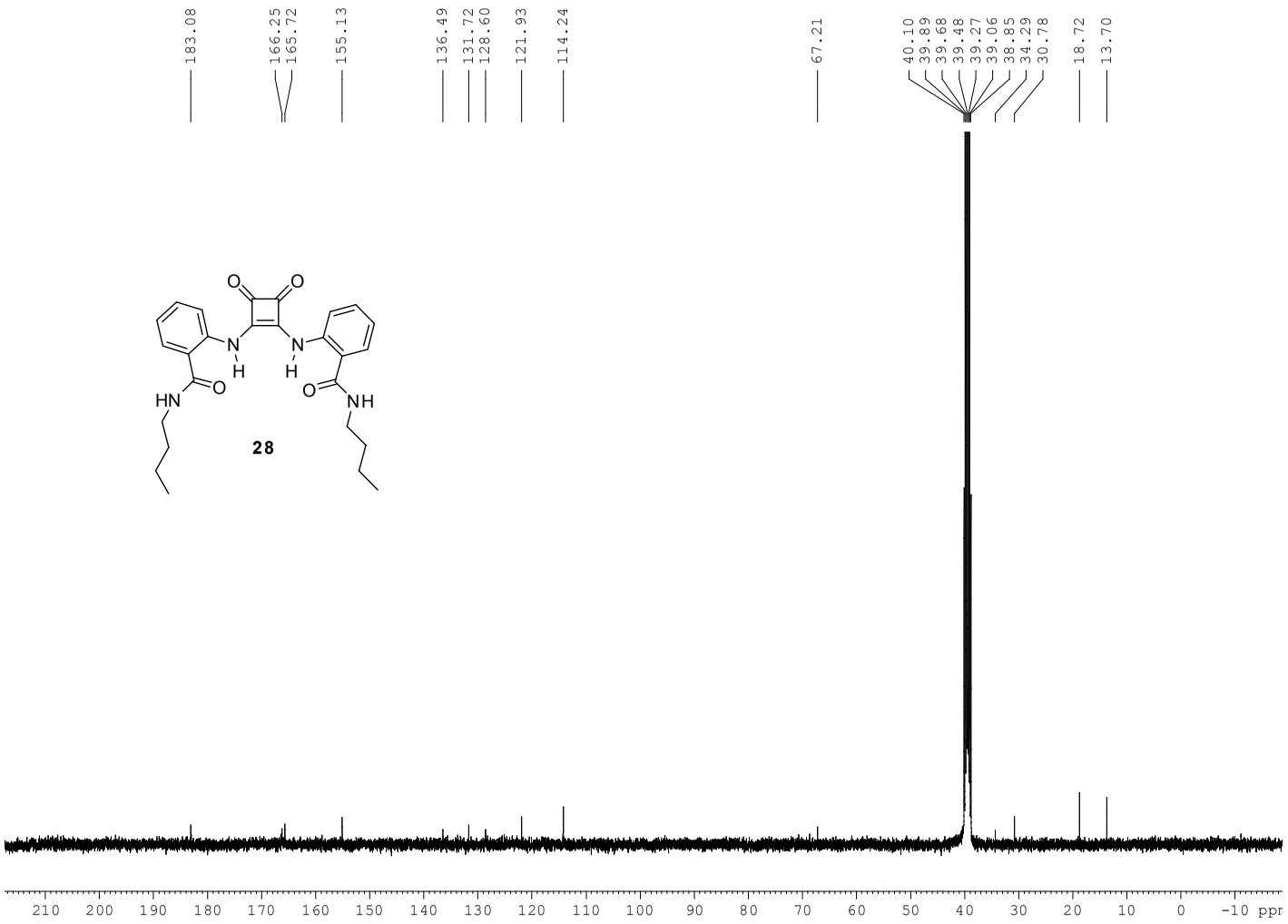


Figure 3.32: ^{13}C NMR spectra of squaramide (**28)** in DMSO-d_6.

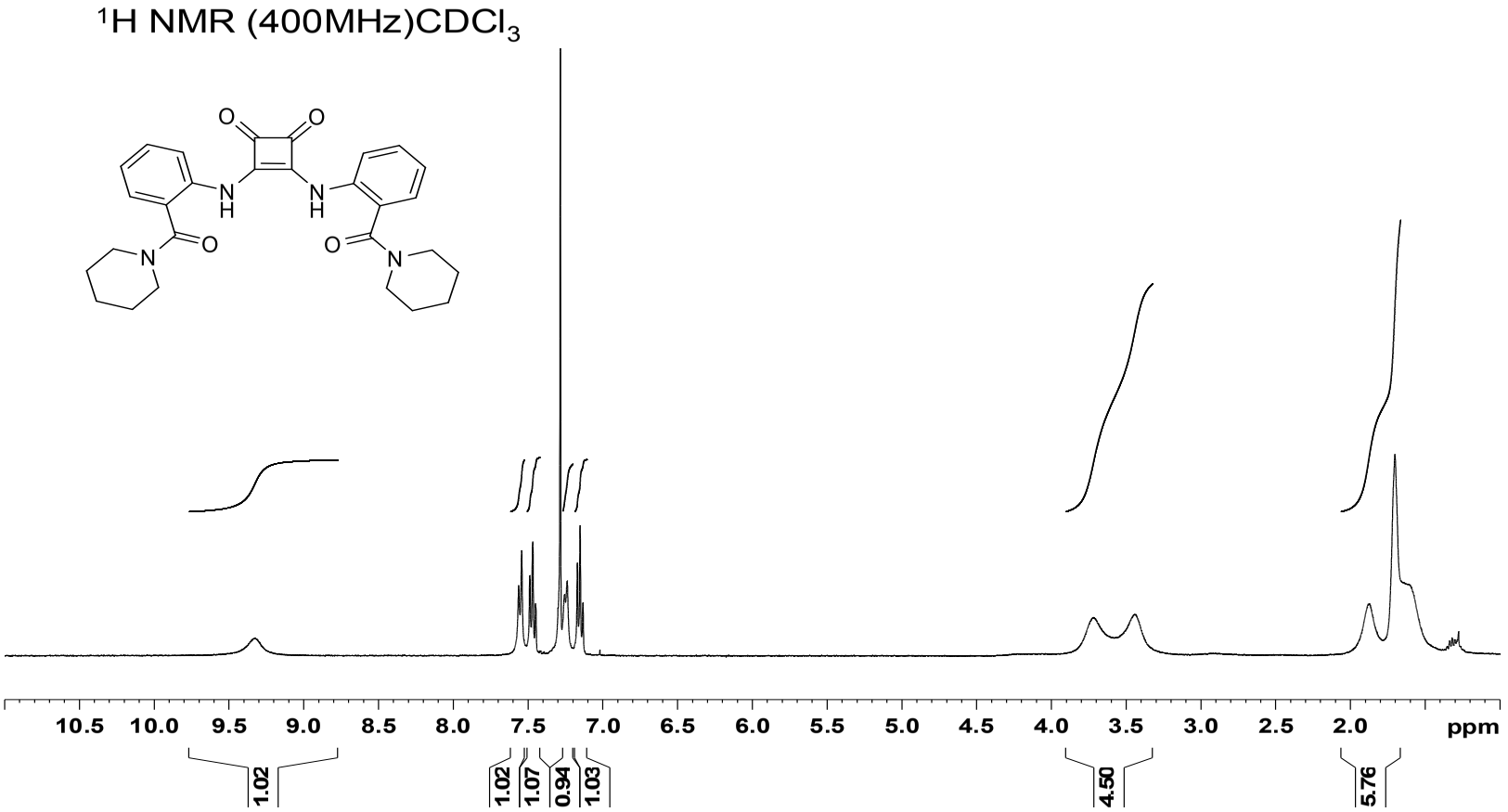


Figure 3.33: [1] H NMR spectra of squaramide (**29)** in $CDCl_3$.

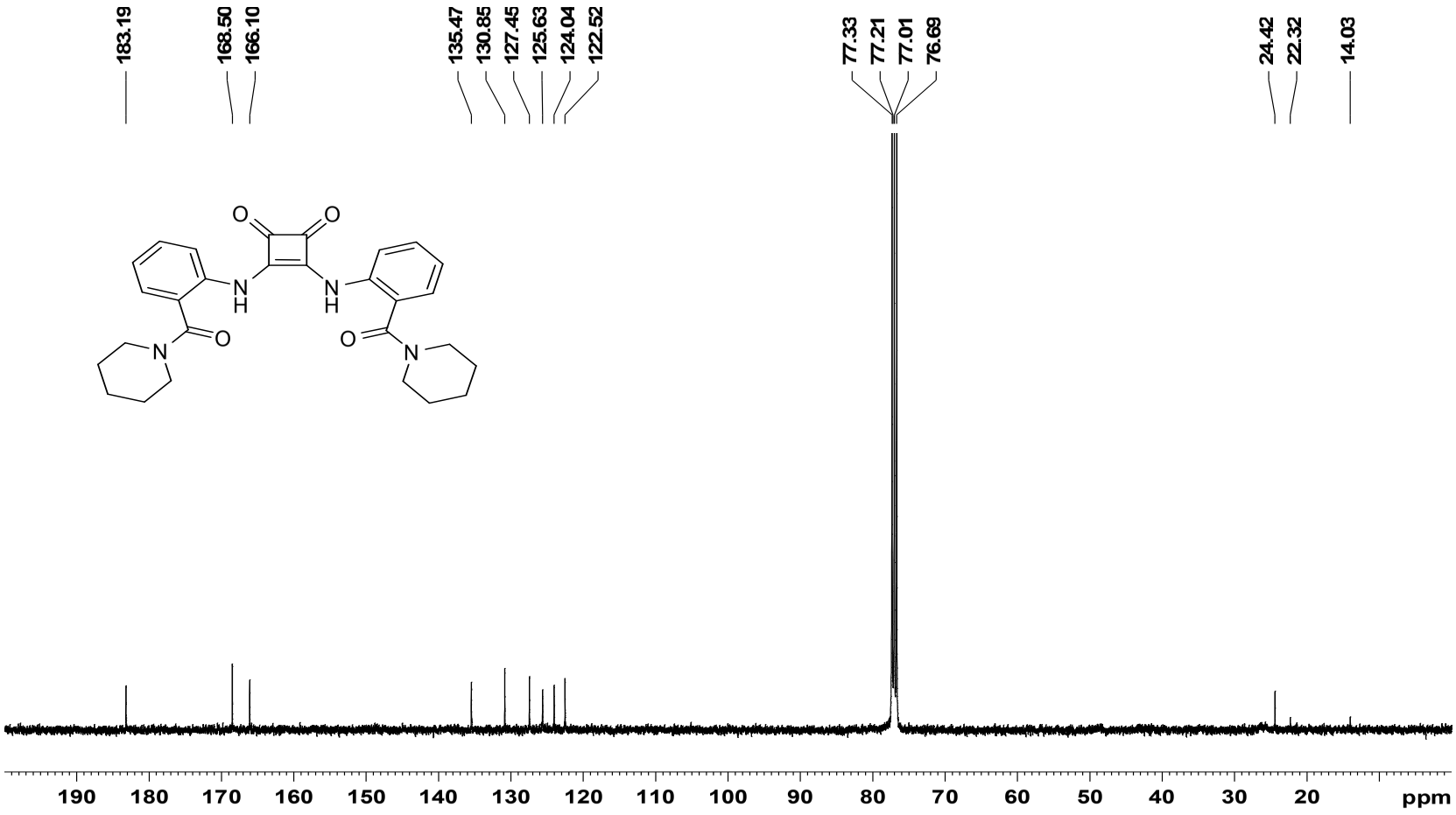


Figure 3.34: ^{13}C NMR spectra of squaramide (**29)** in $CDCl_3$.

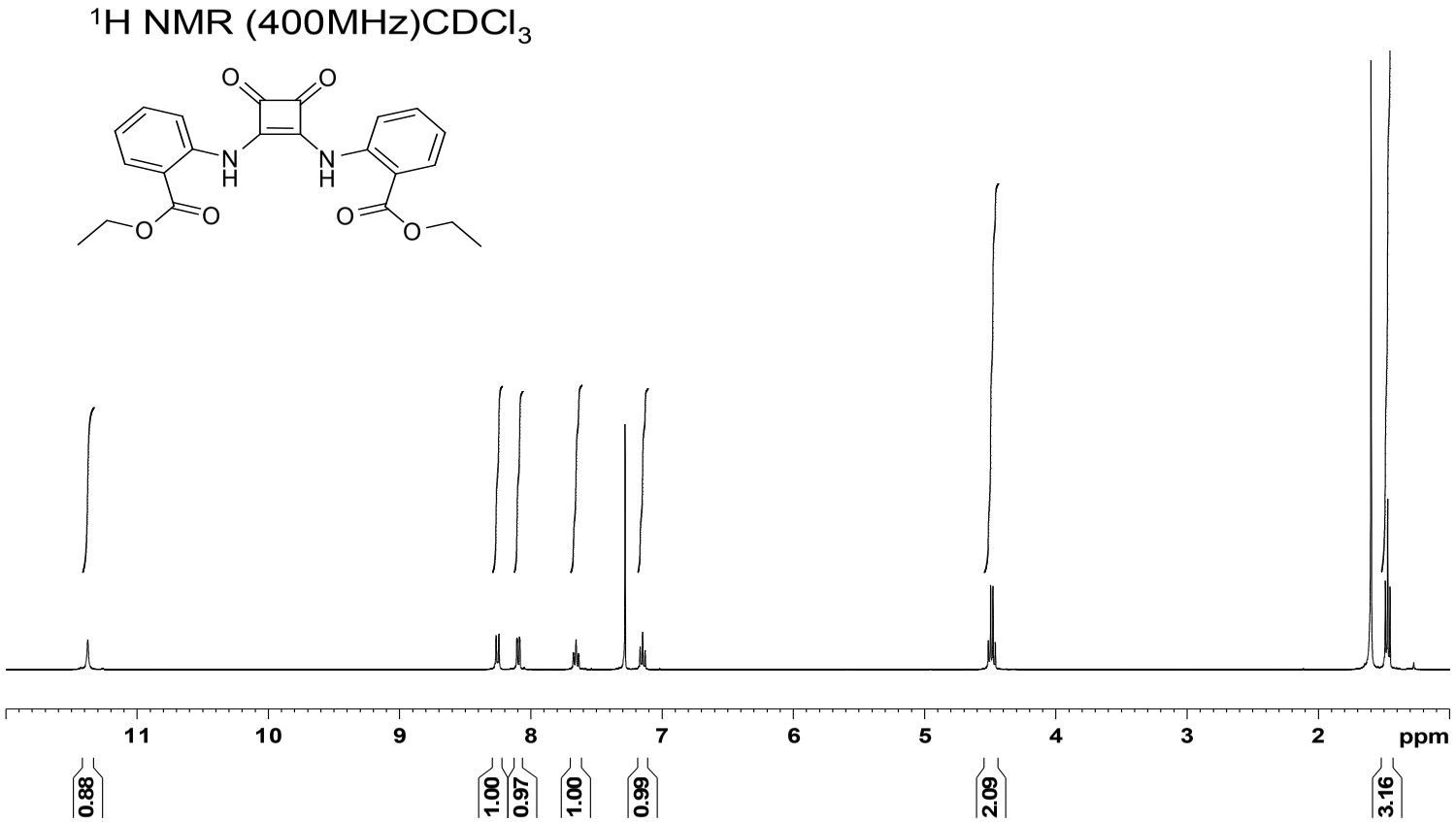


Figure 3.35: [1] H NMR spectra of squaramide (**30)** in $CDCl_3$.

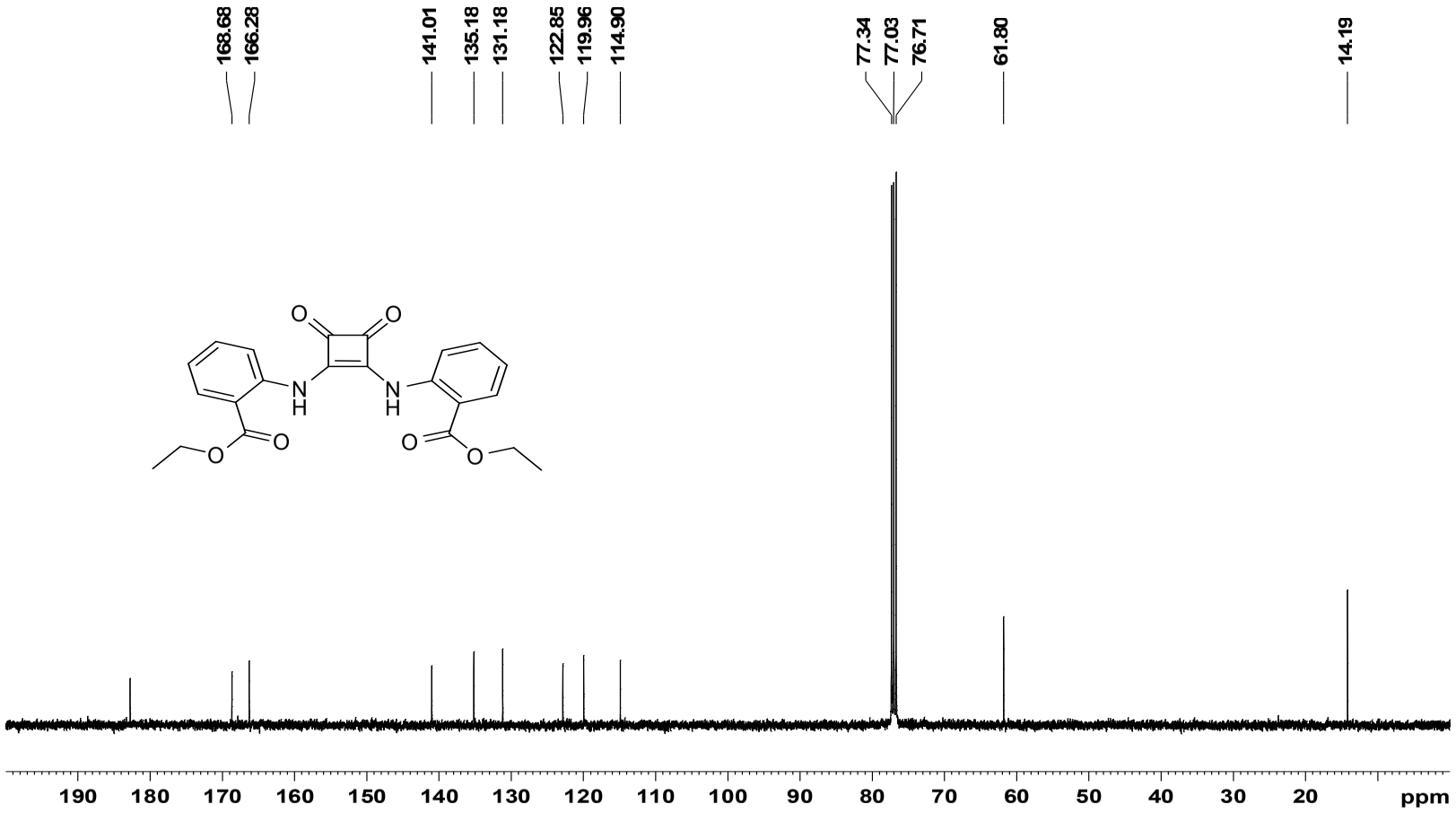


Figure 3.36: ^{13}C NMR spectra of squaramide (**30**) in $CDCl_3$

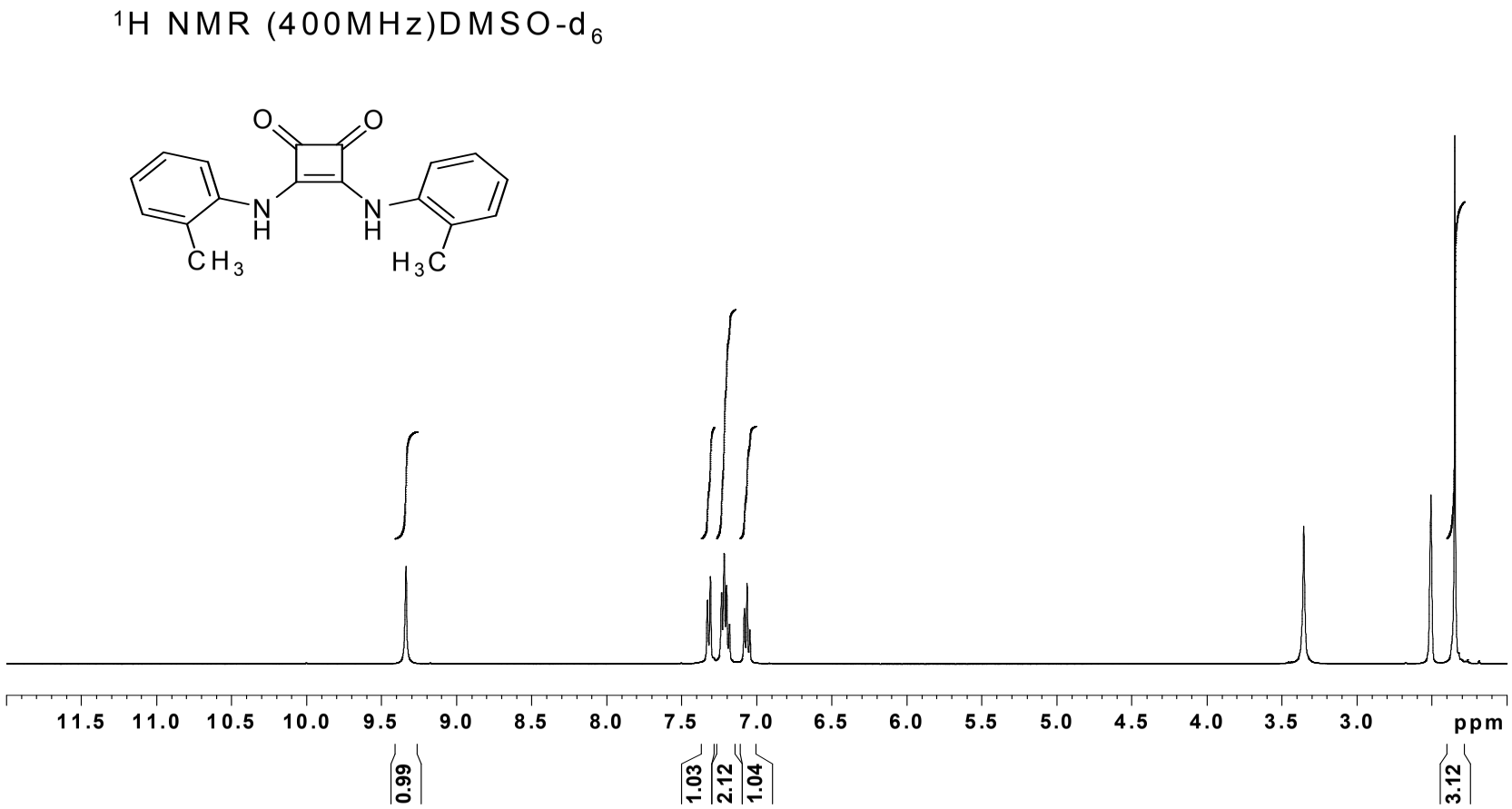


Figure 3.37: [1] H NMR spectra of squaramide (**31)** in DMSO-d_6.

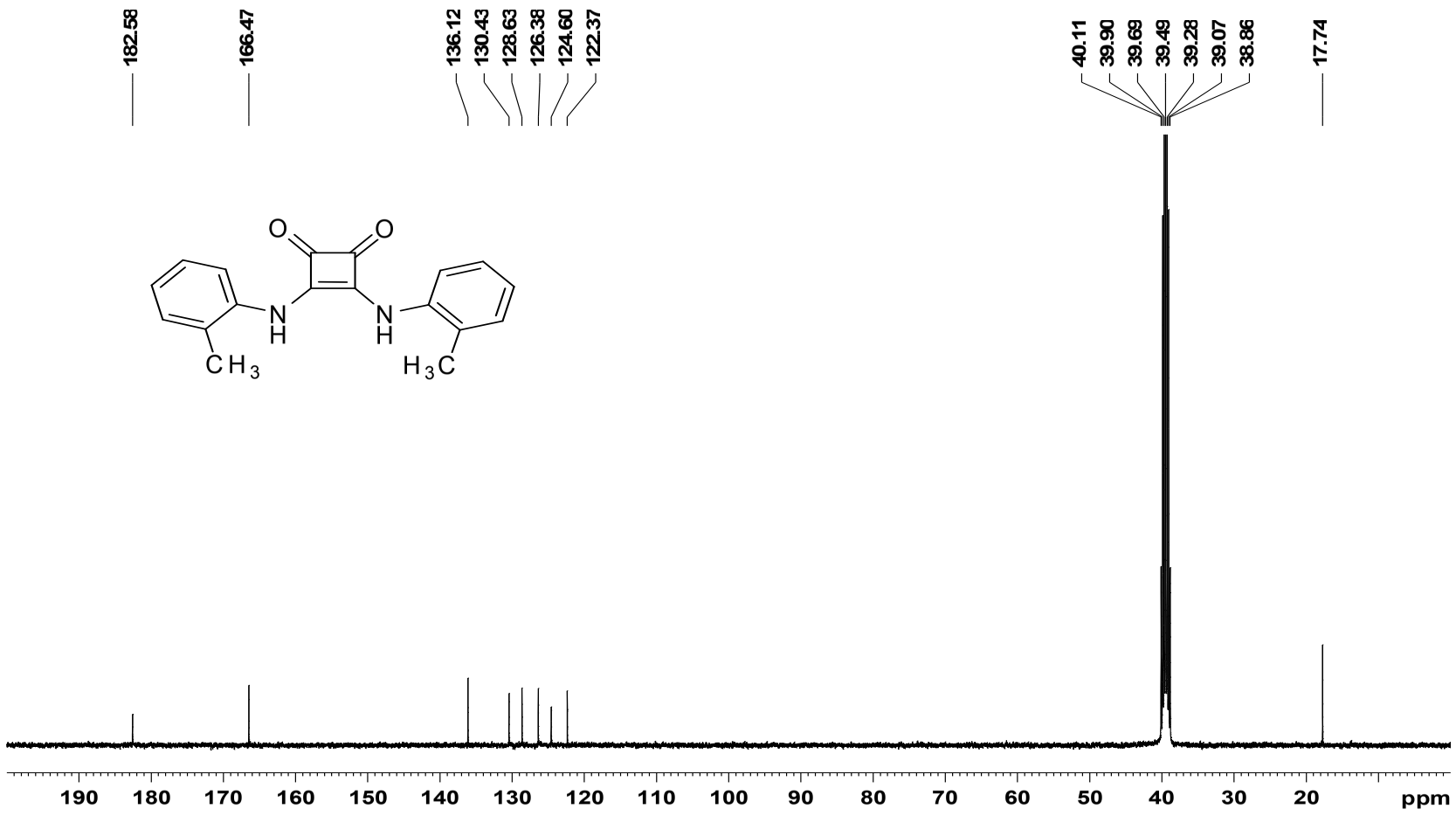


Figure 3.38: ^{13}C NMR spectra of squaramide (**31)** in DMSO-d_6.

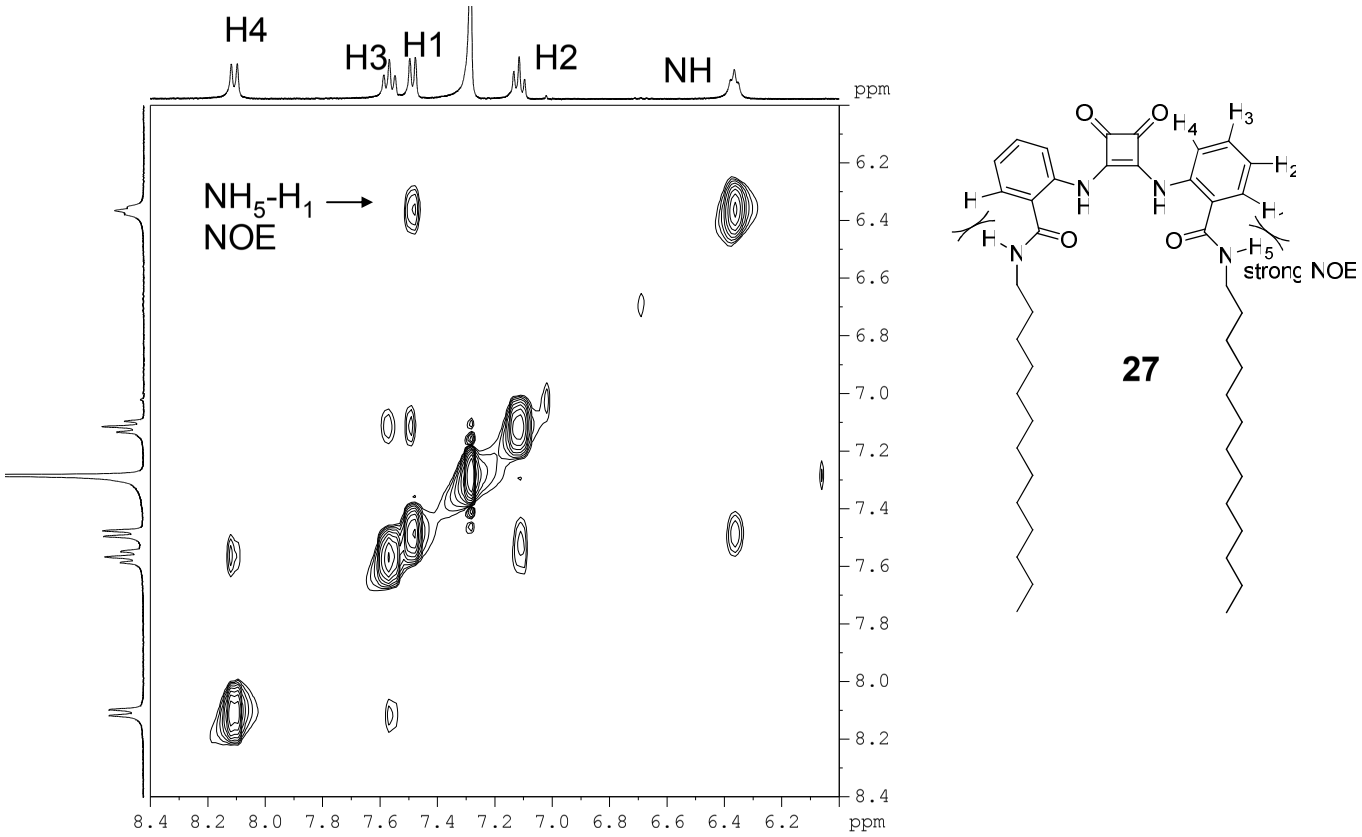


Figure 3.39: 2D NOESY spectra of squaramide **27** in $CDCl_3$

3.7 References:

1. (a) Nguyen, T. D.; Liu, Y.; Saha, S.; Leung, K. C.; Stoddart, J. F.; Zink, J. I. *J Am Chem Soc* **2007**, *129*, 626-34. (b) Nguyen, T. D.; Tseng, H. R.; Celestre, P. C.; Flood, A. H.; Liu, Y.; Stoddart, J. F.; Zink, J. I., *Proc Natl Acad Sci U S A* **2005,** 102, (29), 10029-34. (c)Hernandez, R.; Tseng, H. R.; Wong, J. W.; Stoddart, J. F.; Zink, J. I. *J Am Chem Soc* **2004**, *126*, 3370-1.
2. Ramalingam, V.; Domaradzki, M. E.; Jang, S.; Muthyala, R. S. *Org Lett* **2008,** 10, (15), 3315-8.
3. Liang, Y.; Su, B.; Zhao, J.; Sun W. *Synth. Commun*. **2004**, 34, 3235–2.
4. Huang, X.; Anderson, K. W.; Zim, D.; Jiang, L.; Klapars, A.; Buchwald, S. L. *J Am Chem Soc* **2003**, *125*, 6653-5.
5. Bonne, D.; Dekhane, M.; Zhu, J. *Org Lett* **2005**, *7*, 5285-8.
6. Prohens, R.; Rotger, M C.; Pin˜a, M. N.; Deya`, PM.; Morey, J.; Ballester P.; Costa,A. *Tetrahedron Lett*. **2001**, 42, 4933–6.
7. (a) Etter, M. C. *Acc. Chem. Res*. **1990**, 23, 120-126. (b) Laurence, C.; Berthelot, M. *Perspectives in Drug Discovery and Design*, **2000,** *18* 39–60.
8. Joshi K A.; Patil, D D.; Gejji, S P. *Journal of Molecular Structure: THEOCHEM* **2007**, *813*, 9–19.

Chapter 4

Development of a copper-based method for synthesizing tertiary diaryl squaramides

4.1 Introduction:

Aromatic π-π interactions are one of the most important noncovalent forces due to their wide occurrence ranging from biological science to materials[1]. Although aromatic interactions are weak they dictate how molecules self-assemble such as in DNA base stacking, stabilization of protein structures, crystal packing, and even in recognition of drugs by enzymes[2]. The aromatic interaction between arenes can be broadly classified into three types, namely edge-to- face or T-shaped (A), face-to-face (B), or a parallel-offset geometry (C) [1,3] .

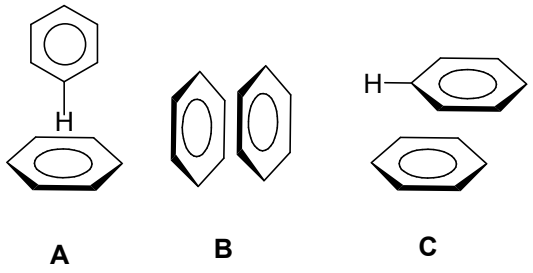
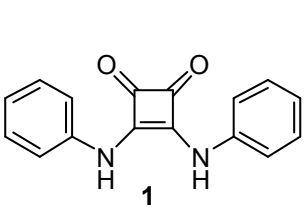


Figure 4.1: Possible aromatic interactions

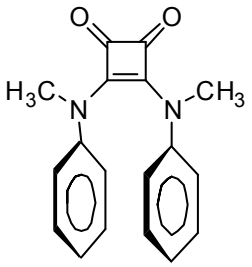
Conformational studies[7] in our laboratory have shown that tertiary diphenyl squaramide **37** exist in folded *EE* conformation. The *EE* conformation in tertiary diphenyl squaramide **37** enforces co-facial arrangement of aryl groups, similar to the corresponding tertiary aryl urea[6] **32**.



1

ZZ conformer

Secondary diaryl squaramide



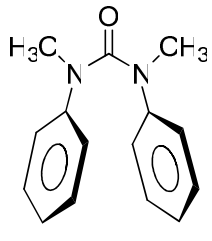
37

EE conformer

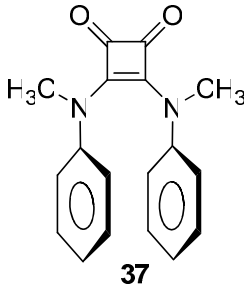
Tertiary diaryl squaramide

Figure 4.2: Conformational preference of secondary and tertiary squaramides

However, unlike urea **32** where the phenyl rings are splayed, the aryl groups in the squaramide **37** are more parallel to each other[7]. In an effort to understand the factors responsible for the conformational preferences of tertiary squaramides for their potential use as molecular machines we needed to prepare a number of symmetrical and unsymmetrical squaramides.



32



37

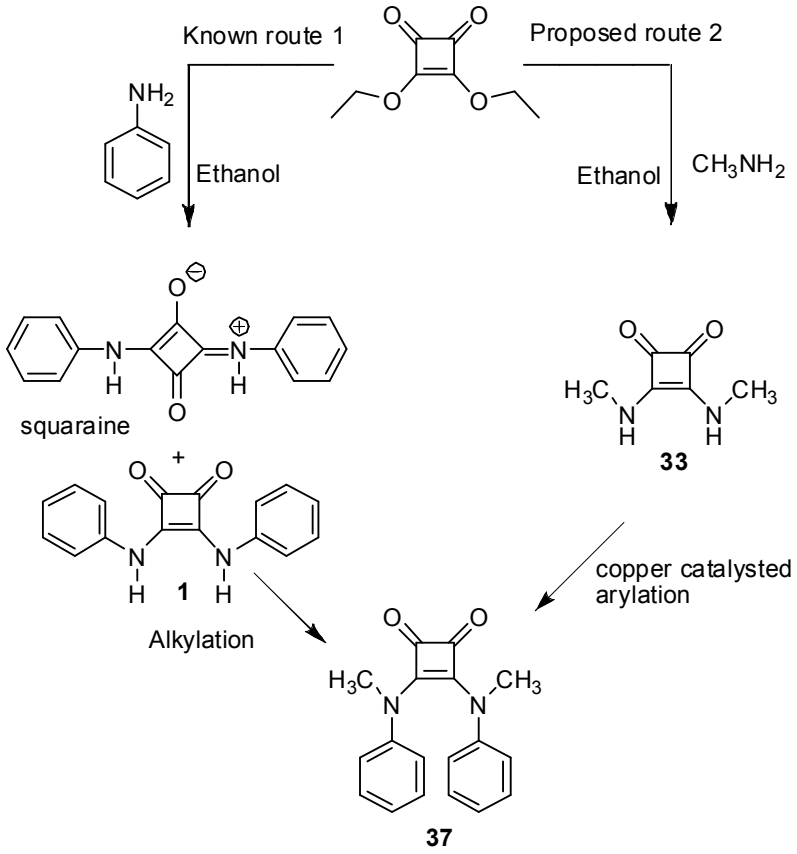
Figure 4.3: Tertiary diaryl urea and squaramide

4.2 Proposed synthesis of tertiary diaryl squaramides:

Generally, synthesis of tertiary diaryl squaramides[8] involves the diamination of diethyl squarate followed by alkylation of the diaryl squaramide (Scheme 4.1). The main

disadvantage of the above mentioned route is the formation of dye material (1, 3-squaraine[9] isomer) along with the 1, 2-squaramide, both of which are insoluble in most of the common organic solvents resulting in purification problems. Since purification at this stage was not feasible due to insolubility of diphenyl squaramide, alkylation was performed to obtain the end product. The crude mixture was subsequently purified by column chromatography to obtain tertiary diaryl squaramide, albeit in low yield.

Scheme 4.1: Synthesis of 3, 4-bis (N-methyl-N-phenyl amino) cyclobut-3-ene-1, 2-dione

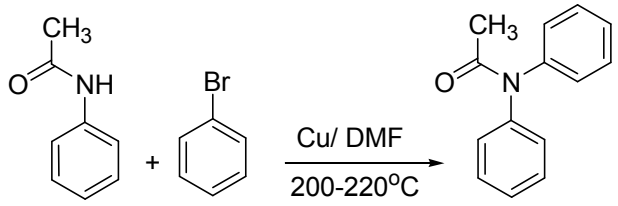


To minimize the formation of squaraine we decided to explore an alternative route, in which diethyl squarate was first quenched with methylamine in ethanol to obtain N, N'-dimethyl squaramide followed by copper-catalyzed C-N bond formation to access tertiary diaryl squaramides (scheme 4.1). In this chapter, the development of a copper-based method for preparing tertiary diaryl squaramides will be discussed.

4.3 Optimization of C-N bond formation reaction:

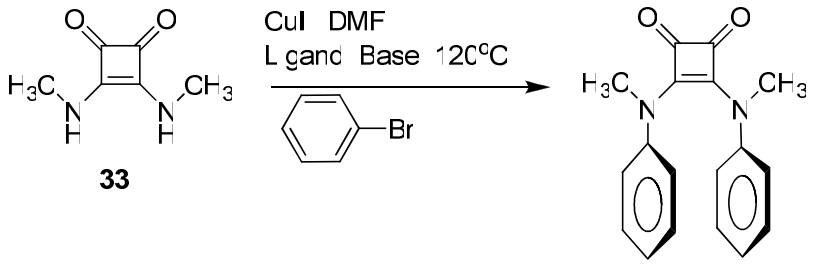
While copper-mediated mono N-arylation of amides[11] is common, examples pertaining to copper-mediated diarylations are rare[12]. Further, there was no precedence for N-arylation of squaramides. Monoarylation of amides was conventionally performed using Goldberg reaction[13] (Scheme 4.2), which requires elevated temperatures. But such a methodology cannot be employed here as squaramides could potentially undergo ring opening at high temperatures.

Scheme 4.2: Goldberg reaction



Recent advances in ligand-assisted[10] Goldberg reactions have significantly decreased reaction temperatures and improved yields. We therefore pursued ligand-assisted, copper-mediated synthesis for preparing tertiary diaryl squaramides. The optimization of ligand, base, solvent and temperature was carried out to achieve the diarylation of squaramide.

4.3.1 Choice and size of the ligand:



33 **37**

Ligands play a pivotal role in decreasing the reaction temperature and also in improving the yield. Vicinal diamine ligands such as N, N'-dimethyl ethylenediamine and cyclohexyl diamine have been commonly used for the copper mediated N-arylation of amides and ureas[10], but these diamine ligands when employed for N-arylation of secondary squaramide resulted in low yields.

Table 4.1: Optimization of N-arylation of secondary squaramide

Entry	Ligand	Base	Temperature °C	CuI:Ligand	**37** Yield (%)
1	--	K_2CO_3	120	1:1	7
2	A	K_2CO_3	120	1:1	17
3	B	K_2CO_3	120	1:1	26
4	C	K_2CO_3	120	1:1	27
5	D	K_2CO_3	120	1:1	<5
6	E	K_2CO_3	120	1:1	45
7	G	K_2CO_3	120	1:1	60
8	F	K_2CO_3	120	1:1	65
9	F	K_2CO_3	120	2:1	30
10	F	K_2CO_3	120	1:2	28
11	F	K_2CO_3	95	1:1	21
12	F	K_2CO_3	140	1:1	<5
13	F	K_3PO_4	120	1:1	0
14	F	Cs_2CO_3	120	1:1	0
15	F	Na_2CO_3	120	1:1	20
16	H	K_2CO_3	120	1:1	60
17	I	K_2CO_3	120	1:1	63
18	J	K_2CO_3	120	1:1	50
19	K	K_2CO_3	120	1:1	31
20	L	K_2CO_3	120	1:1	27

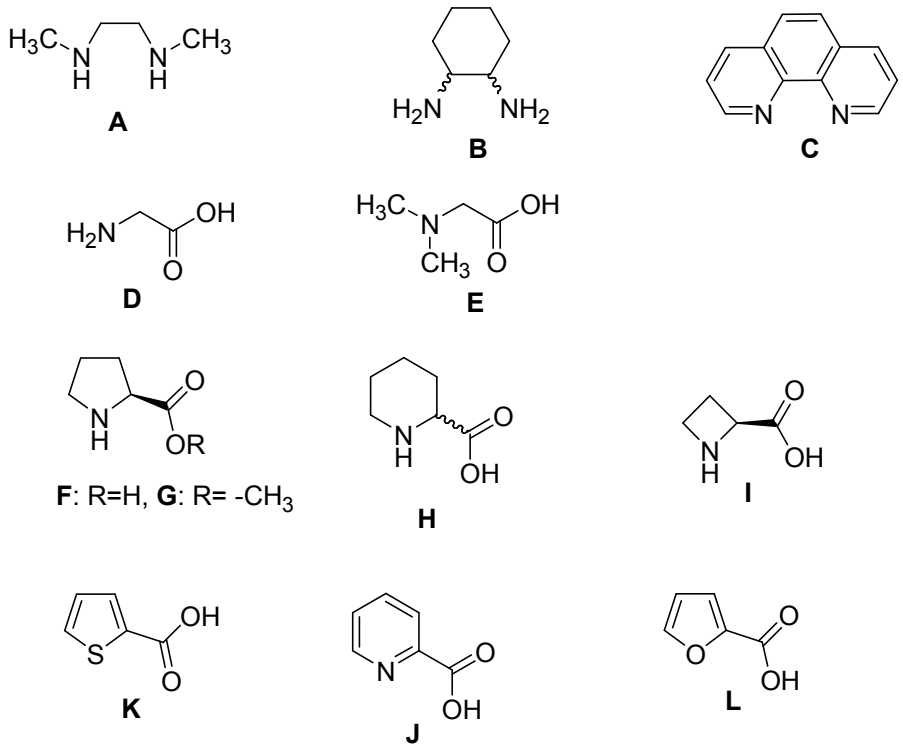


Figure 4.4: Ligands for N-arylation of squaramides

To overcome this problem we examined different types of ligand for the N-arylation of N, N'-dimethyl squaramide **33**. These ligands can be broadly classified as (N, N), (N, O), (S, O), (O, O) on the basis of atoms chelating with copper (Figure 4.4). Except for glycine (**D**), other α-amino acid ligands consistently resulted in good yield. Among the α-amino acid ligands, cyclic secondary α-amino acids proved to be the best ligands for N-arylation of secondary squaramide. Our experiments also indicated that the ring size variation of these cyclic α-amino acids resulted in no significant yield improvement. Therefore L-proline was used as the ligand for tertiary diaryl squaramide synthesis.

4.3. 2 Choice of base and solvent*:*

The strength of the base plays a major role in the N-arylation of squaramide. N-arylation occurs in good yield with insoluble weak bases such as potassium carbonate; however, with an increase in the strength of the base such as potassium phosphate (K_3PO_4) instantaneous deprotonation of dimethyl squaramide **33** NH occurs, likely resulting in formation of various copper amidates[18] (Figure 4.5), leading to termination of the reaction. Studies by Buchwald[11q] *et al* have demonstrated the importance of the rate of deprotonation versus rate of N-arylation. More soluble bases such as cesium carbonate tend to increase the rate of deprotonation, thus leading to undesired multiply ligated species. Thus, a suitable base for N-arylation of squaramide should be weak and insoluble in the organic reaction medium.

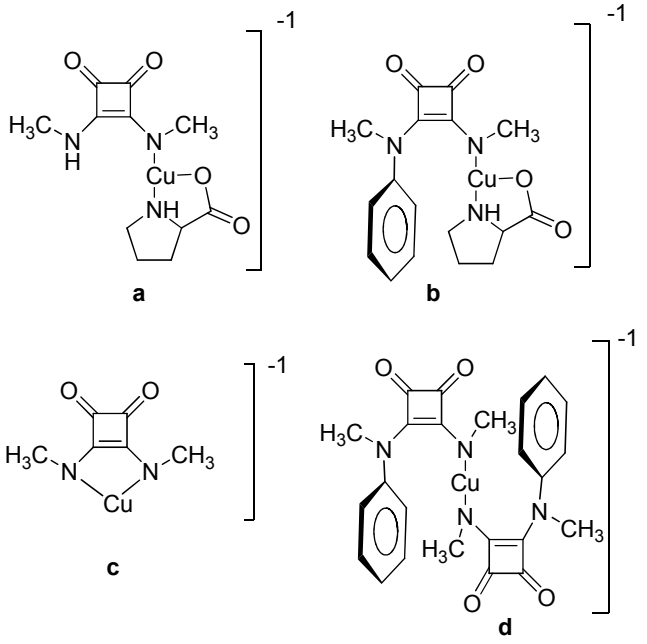


Figure 4.5: Possible copper amidates

Since potassium carbonate met both the criteria it was employed as the base for the N-arylation reactions. The choice of solvents was very limited since N, N' dimethyl

squaramide **33** is insoluble in most of the common organic solvents such as acetone, ethyl acetate, toluene and dioxane. Polar aprotic solvents such as DMF, DMSO and N-methyl pyrrolidine (NMP) were used to perform N-arylation of squaramide. Among these DMF proved to be the most suitable solvent for N-arylation.

Table 4.2: Solvents for squaramide N-arylation**.**

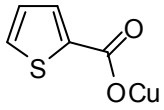
entry	solvent	Disquaramide **37** Yield (%)
1	Toluene	5
2	Dioxane	0
3	DMF	65
4	DMSO	58
5	NMP	54

4.3.3 Copper source and copper/ligand ratio:

Liebeskind's copper (I) thiophene carboxylate (CuTc) (Figure 4.6), a reactive copper catalyst for alkenylation[14] of amide coupling reaction was found to be inefficient for the N-arylation of squaramide **33**. Copper iodide proved to be an efficient catalyst for the N-arylation of squaramide **33.** Recrystallization[15] of crude copper iodide did not improve the yield any further.

Table 4.3: Selection of copper source for squaramide N-arylation

entry	Copper source	Disquaramide **37** Yield (%)
1	Cu_2O	21
2	$CuSO_4$	23
3	CuTC	20
4	CuI	65
5	CuI (recrystallised)	64



CuTc

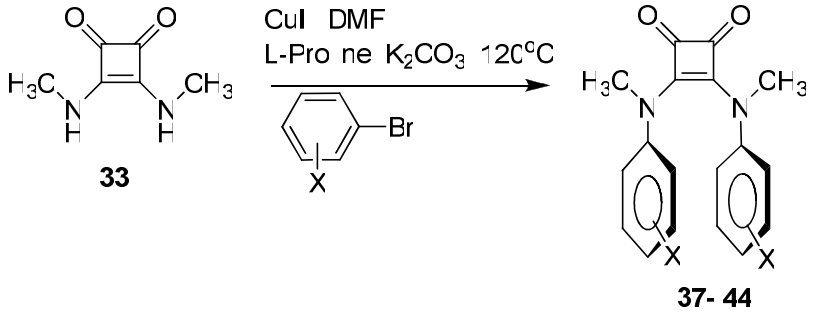
Figure 4.6

Apart from the copper source, variation of copper catalyst to ligand ratio also plays a major role in the yield of N-arylation. A 1:1 copper/ligand ratio was found to be optimal for the N-arylation of dimethyl squaramide **33** (see Table 4.1).

4.3.4 Optimized procedure for N-arylation of squaramide:

From the above results, the general reaction conditions were optimized (entry 8). Copper iodide was the catalyst, potassium carbonate was the most suitable base, L-proline as a ligand gave the best yields in DMF at 120^{o} C for the diarylation of squaramide. Decreasing the reaction temperature resulted in low yield whereas increasing above 140^{o} C resulted in polymeric material. These conditions were then used to study the effect of substitution, ring size and steric effect on the aryl bromide.

4.4 Substituent effects



The effect of substitution on the aryl bromide used in N-arylation of dimethyl squaramide **33** was investigated**.** Comparison of entries 2 and 4 (Table 4.4) shows selectivity for copper insertion into C-Br bonds compared to C-Cl bonds. The decreased yield observed for 2- bromotoluene (entry 3) compared to 4- bromotoluene (entry 4) indicates the importance of steric effects. Electron releasing substituents in aryl bromides resulted in

good yields whereas electron withdrawing groups (entry 6 and 7), led to very low yields. For the latter substituents, the desired tertiary squaramides could be isolated in low yields only when the reaction time was decreased to 3 hr from 18 hr.

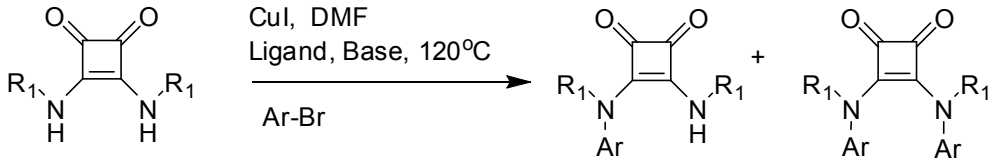
Table 4.4: Substituent effects

Entry	X	Product	Yield (%)
1	H	**37**	65
2	4-Cl	**38**	44
3	2-CH_3	**39**	20
4	4-CH_3	**40**	70
5	4-$N(CH_3)_2$	**41**	55
6	4-CO_2CH_3	**42**	10
7	3-CO_2CH_3	**43**	21
8	4-$CH_2CO_2C_2H_5$	**44**	45
9	4-NO_2	**45**	0

4.5 Effects of N-alkyl group and ring size

The role of steric effects in the N-alkyl substitutent was studied. Linear unbranched N-alkyl group (such as squaramide in **33** and **36**) resulted in diarylation, but branched N-alkyl groups (such as the t-butyl groups or cyclohexyl groups in **34** and **35**) consistently resulted only in monoarylation. Surprisingly, increasing the bulk of N-alkyl group from methyl (**33**) to tertiary butyl (**34**) gave high monoarylation yields. Efforts to achieve diarylation for **34** and **35** by increasing the aryl bromide loading and elevated temperatures were not fruitful. One of the successes of the copper catalyzed N-arylation reaction is the ability to synthesize tertiary squaramides with different aryl ring sizes. While the diphenanthryl squaramide **57** was successfully synthesized, only the monoanthryl **52** and the monopyrenyl **54** squaramides were formed, presumably due to the steric bulk of these larger rings. An effort to prepare the dipyrenyl squaramide **62** by means of microwave[21] reactor also resulted only in monoarylated product.

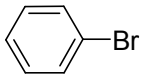
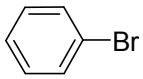
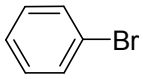
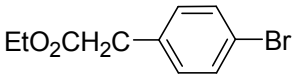
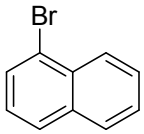
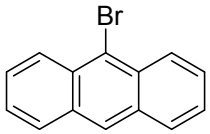
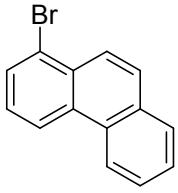
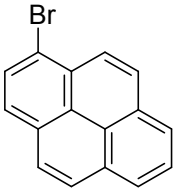
Table 4.5: Effect of N-alkyl group and ring size of aryl bromide



33: R_1 = -CH_3
34: R_1 = -$C(CH_3)_3$
35: R_1 = Cyclohexyl
36: R_1 = n-$C_{12}H_{25}$

Mono **47-54**

Di **55-57, 59-62**

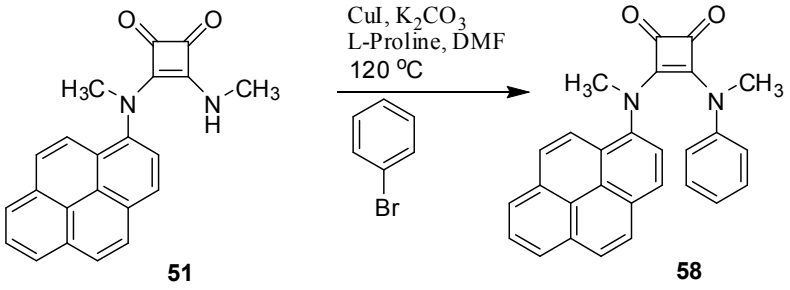
Entry	Secondary squaramide	Ar-Br	Yield (%) Mono + Di
1	**33**		**47**(12)+**37**(65)
2	**34**		**48**(96)+**59**(0)
3	**35**		**49**(85)+**60**(0)
4	**36**		**50**(35)+ **55**(18)
5	**33**		**51**(10)+**56**(35)
6	**33**		**52**(12)+**61**(0)
7	**33**		**53**(30)+**57**(14)
8	**33**		**54**(55)+ **62**(0)

A closer look into the aryl bromides revealed that the number of ring junctions[20] (and therefore the amount of steric hindrance) next to the bromide have an effect on the formation of diarylated squaramide. For example, anthracenyl bromide (entry 6) has two ring junctions on either side of the bromide, thus resulting only in monoarylation of the squaramide **52** compared to the bromophenanthrene which resulted in diarylation.

4.6 Unsymmetrical squaramides:

Unsymmetrical squaramides are conveniently synthesized in a two step process. The first step to effect monoarylation was carried out by temperature (90^{o}C) controlled copper catalyzed N-arylation followed by second N-arylation using a different aryl bromide to obtain the mixed unsymmetrical diaryl squaramides.

Scheme 4.3: Unsymmetrical tertiary aryl squaramide



To check the feasibility of double monoarylation reaction, monopyrene squaramide **54** was allowed to react with bromobenzene using our copper catalyst protocol (Scheme 4.3) which resulted in unsymmetrical squaramide **58** in 51% yield. Thus temperature controlled double monoarylation is advantageous to synthesize a wide range of unsymmetrical squaramides. It is of interest to note, that the cofacial *EE* conformation

was again observed in squaramide **58** with the phenyl ring aromatic protons appearing between 5.5-6.5 ppm in the ^{1}H NMR spectrum due to shielding by the pyrene ring.

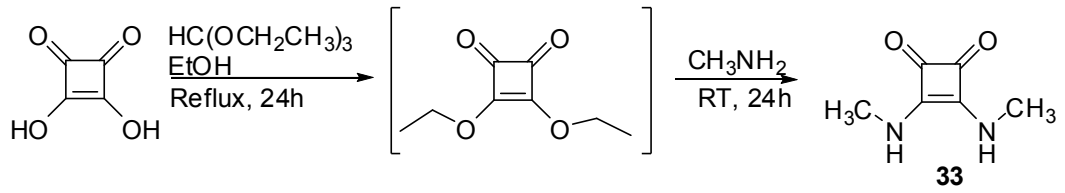
4.7 Conclusions

A new synthesis of tertiary diaryl squaramide via copper-mediated C-N bond formation was developed. This method is attractive as it can be utilized for N-arylation of other sterically congested scaffolds. These tertiary diaryl squaramides with co-facial arene geometry can serve as a platform for providing further insights into π-π stacking interactions. Controlled mono arylation opens up the synthesis of a wide range of unsymmetrical squaramides (for example, donor and acceptor aryl groups) with interesting photophysical properties.

4.8 Experimental section:

All reactions are carried out in oven dried round bottom flask under nitrogen atmosphere. Anhydrous DMF was purchased from Sigma Aldrich and used without further purification. Copper iodide (99.99%) was purchased from Strem chemicals. Silica gel (230-400) mesh was used for column chromatography. ^{1}H and ^{13}C NMR spectra were recorded at 400 and 100 MHz respectively on a Bruker Avance DPX-400 instrument. The spectra are reported in δ ppm referenced to the solvent peak (7.28ppm for $CDCl_3$ and 2.5ppm for DMSO-d_6). Coupling constants are reported in hertz. The melting points are uncorrected and were recorded using a Mel-Temp apparatus. High resolution mass spectra were collected at the CUNY Mass Spectrometry facility and the samples were ionized using electrospray ionization within a mass range of 105Da to 2800Da in both positive and negative modes.

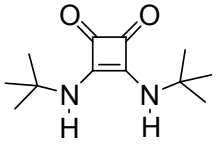
4.8.1 Preparation of 3, 4-bis (methylamino) cyclobut-3-ene-1, 2-dione (33):



Squaric acid (2.28 g, 20 mmol) was stirred with ethanol (30 ml) in a 100 ml RB flask under nitrogen atmosphere for 30 minutes, and then triethylorthoformate (8 ml) was added. The reaction was refluxed for 24 hours to obtain diethyl squarate. The obtained diethyl squarate was cooled to 5-10 ^{o}C followed by the addition of methyl amine in THF 2 M (26 ml). After the complete addition of methyl amine, reaction was stirred at room temperature for 24 h. The precipitated solid was filtered, washed with the diethyl ether (2 x 100 ml) and dried under vacuum to get title compound in 85% yield. ^{1}H NMR (400 MHz, DMSO-d_6): 7.4 (broad, 2 H), 3.1 (s, 6H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): 182.5, 168.3, 30.2. M. pt: >250 ^{o}C.

Reference (33 and 36): Hutchings, M. G.; Ferguson, I, Allen, S.; Zyss, J.; Ledoux, I. *J. Chem. Res., Synop*. **1998**, 5, 244-245.

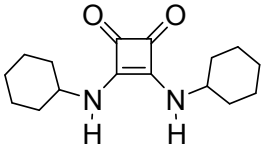
4.8.2 Preparation of 3, 4-bis (tert-butyl amino) cyclobut-3-ene-1, 2-dione (34):



Similar to procedure **33**, using tert-Butyl amine. Pale yellow solid was obtained in 50% yield. ^{1}H NMR (DMSO-d_6): 7.62 (s, 2H), 1.37 (s, 18H). ^{13}C NMR (DMSO-d_6): 180.8, 168.2, 52.2, 30.1.

Reference (34): Schmidt, A. H. *Synthesis* **1980**, 961-993.

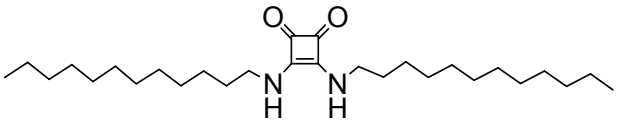
4.8.3 Preparation of 3, 4-bis (cyclohexyl amino) cyclobut-3-ene-1, 2-dione (35):



Similar to procedure **33** using cyclohexyl amine. Pale yellow solid obtained in 70% yield. ^{1}H NMR (DMSO-d_6): 7.32 (b, 2H), 3.76 (s, 2H), 1.89(b, 2H), 1.67 (b, 2H), 1.54 (b, 4H), 1.29(b, 12H,) ppm. ^{13}C NMR (DMSO-d_6): 181.8, 166.9, 51.9, 33.6, 24.7, 23.9.

Reference (35): Frauenhoff, G. R.; Takusagawa, F.; Busch, H. *Inorg Chem* **1992**, 31(19), 4002-7

4.8.4 Preparation of 3, 4-bis (dodecyl amino) cyclobut-3-ene-1, 2-dione (36):

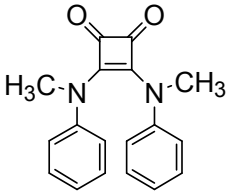


Similar to the procedure **33**, using dodecyl amine. Pale white solid obtained in 82% yield. ^{1}H NMR (Toluene-d_8): 7.88 (broad singlet, 2H), 3.75(broad multiplet, 4H), 1.76(m, 4H), 1.45(m, 4H), 1.32 (broad multiplet, 32H,), 0.90 (t, 6H, J = 6.4Hz). ^{13}C NMR (Toluene-d_8): 183.3, 168.8, 45.2, 32.2, 31.7, 30.09, 30.06, 30.05, 30.02, 29.78, 29.69, 27.0, 22.9, 13.9. M.pt: 172-174^{o}C. **Note**: NMR was recorded at 90 ^{o}C in toluene-d_8

Reference (36): Hutchings, M. G.; Ferguson, I, Allen, S.; Zyss, J.; Ledoux, I. *J. Chem. Res., Synop*. **1998**, 5, 244-245.

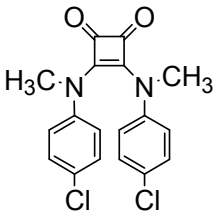
4.9 General Procedure for Diarylation:

4.9.1 Preparation of 3, 4-bis (N-methyl-N-phenyl amino) cyclobut-3-ene-1, 2-dione (37):



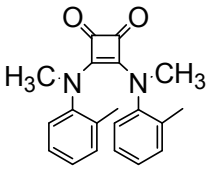
To a 25 ml RB flask, copper iodide (95 mg, 0.5 mmol), L-proline (58 mg, 0.5 mmol), potassium carbonate (345 mg, 3 mmol) and anhydrous DMF (1 ml) were added. The mixture was stirred at room temperature under nitrogen atmosphere for 20 minutes. Bromobenzene (471 mg, 3 mmol) and 3, 4-bis (methyl amino) cyclobut-3-ene-1, 2-dione (140 mg, 1 mmol) were then added and the reaction temperature was increased to 120 ^{o}C and maintained for 18 hours. The reaction mixture was cooled to room temperature, diluted with ethylacetate (15 ml), filtered and concentrated. The residue was chromatographed (2:3 Ethyl acetate / hexane) to yield the title compound in 65% yield. ^{1}H NMR (400 MHz, $CDCl_3$): 7.02(t, 4H, J = 7.6), 6.89 (t, 2H, J = 7.2), 6.61(d, 4H, J = 7.6), 3.70(s, 6H). ^{13}C NMR ($CDCl_3$): 186.7, 167.6, 142.8, 128.7, 125.0, 121.1, 39.1. Mpt 174-175 ^{o}C.

4.9.2 Preparation of 3, 4-bis (N-(4-chlorophenyl)-N-methylamino) cyclobut-3-ene-1, 2-dione (38):



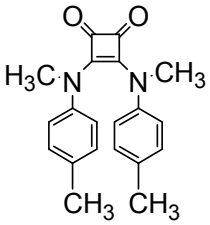
Solid was obtained in 44% yield. ^{1}H NMR (400 MHz, $CDCl_3$): 7.03(d, 4H, J = 8.8), 6.55(d, 4H, J = 8.8), 3.7 (s, 6H). ^{13}C NMR ($CDCl_3$):186.5, 167.3, 141.3, 130.9, 128.7, 122.7, 39.2. HRMS calculated for $C_{18}H_{14}N_2O_2Cl_2$ (M^{+}+1) 361.0501 Found 361.0502. Mpt. >250 ^{o}C

4.9.3 Preparation of 3, 4-bis (N-methyl-N-o-tolyl amino) cyclobut-3-ene-1, 2-dione (39):



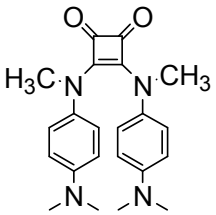
Pale yellow color solid obtained in 20% yield. ^{1}H NMR (400 MHz, $CDCl_3$): 6.96-6.91 (m, 4H), 6.85 (d, 2H), 6.65(d, 2H, *J* = 6.4), 3.64 (s, 6H), 2.21 (s, 6H).Due to interconversion between the syn and anti forms, aromatic signals are broad. ^{13}C NMR ($CDCl_3$): 185.6, 168.7, 142.8, 132.5, 131.5, 127.1, 127.0, 124.8, 40.8, 18.0. HRMS calculated for $C_{20}H_{20}N_2O_2$ (M^++1) 321.1597 Found 321.1600. Mpt. 160-162 ^{o}C

4.9.4 Preparation of 3, 4-bis (N-methyl-N-p-tolyl amino) cyclobut-3-ene-1, 2-dione (40):



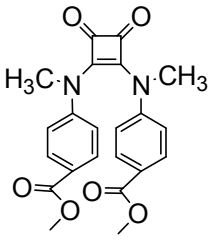
Pale yellow color solid obtained in 70% yield. ^{1}H NMR (400 MHz, $CDCl_3$): 6.80 (d, 4H, *J* = 8), 6.50 (d, 4H, *J* = 8), 3.63 (s, 6H), 2.21(s, 6H) ppm. ^{13}C NMR ($CDCl_3$): 186.4, 167.5, 140.6, 134.9, 129.0, 121.4, 39.3, 20.7. HRMS calculated for $C_{20}H_{20}N_2O_2$ (M^++1) 321.1597. Found 321.1598. Mp: 193-195 ^{o}C

4.9.5 Preparation of 3, 4-bis (N-(4-(dimethyl amino) phenyl)-N-methyl amino) cyclobut-3-ene-1, 2-dione (41):



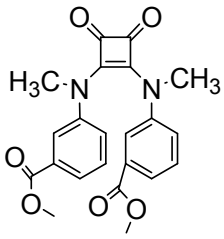
Brown color solid obtained in 55% yield. ^{1}H NMR (400 MHz, $CDCl_3$): 6.54 (d, 4H, *J* = 8.8), 6.3 (d, 4H, *J* = 8.8), 3.60 (s, 6H), 2.89 (s, 12H). ^{13}C NMR ($CDCl_3$): 185.9, 167.2, 148.2, 133.1, 122.7, 112.4, 39.8, 38.6. HRMS calculated for $C_{22}H_{26}N_4O_2$ (M^++1) 379.2128 Found 379.2129. Mpt180-183 ^{o}C

4.9.6 Preparation of 3, 4-bis (N-methyl-N (methyl p-carboxy) phenyl) cyclobut-3-ene-1, 2-dione (42):



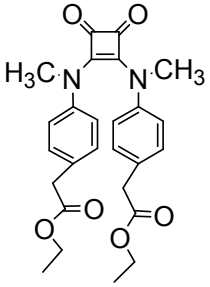
Pale yellow color solid obtained in 10% yield. ^{1}H NMR (400 MHz, $CDCl_3$): 7.69 (d, 4H, *J* = 8.8), 6.67 (d, 4H, *J* = 8.8), 3.90 (s, 6H), 3.76 (s, 6H). ^{13}C NMR ($CDCl_3$): 187.0, 167.7, 165.8, 146.0, 130.3, 126.2, 119.9, 52.1, 38.4. HRMS calculated for $C_{22}H_{20}N_2O_6$ (M^++1) 409.1394 Found 409.1391. Mpt: >250 ^{o}C **Note**: Reaction time was only 3 hours

4.9.7 Preparation of 3, 4-bis (N-methyl-N (methyl m-carboxy) phenyl) cyclobut-3-ene-1, 2-dione (43):



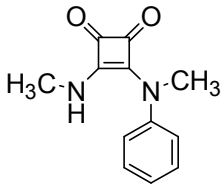
Pale yellow color solid obtained in 21% yield. ^{1}H NMR (400 MHz, $CDCl_3$): 7.45(d, 2H, *J* = 7.6), 7.18(t, 2H, *J* = 4), 7.06 (t, 2H, *J* = 8), 6.80 (d, 2H, *J* = 8), 3.92 (s, 6H), 3.78 (s, 6H). ^{13}C NMR ($CDCl_3$): 186.9, 167.2, 165.8, 142.8, 130.7, 128.9, 125.7, 124.1, 121.7, 52.4, 38.5. HRMS calculated for $C_{22}H_{20}N_2O_6$ (M^++1) 409.1394 Found 409.1391Mp.166-168 ^{o}C Note: Reaction time was only 3 hours

4.9.8 Preparation of 3, 4-bis (N-methyl N (ethyl 4-phenyl acetate) cyclobut-3-ene-1, 2-dione (44):



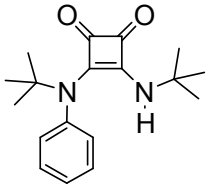
Solid obtained in 45% yield. ^{1}H NMR (400 MHz, $CDCl_3$): 6.91 (d, 4H, *J* = 8.0), 6.53 (d, 4H, J =8.4), 4.19(q, 4H, *J* = 7.2), 3.64 (s, 6H), 3.46 (s, 4H), 1.30 (t, 6H, *J* = 6.8). ^{13}C NMR ($CDCl_3$): 186.5, 171.1, 167.6, 141.7, 131.0, 129.5, 121.5, 60.9, 40.4, 39.2, 14.2. HRMS calculated for $C_{26}H_{28}N_2O_6$ (M^++1) 465.2020. Found 465.2024. Mp: 157-160 ^{o}C

4.9.9 Preparation of 3-(N-methyl-N-phenyl amino)-4-(methyl amino) cyclobut-3-ene-1, 2-dione (47):



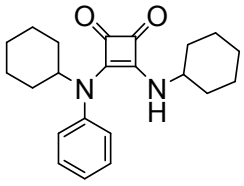
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49(t, 2H, *J* = 7.6), 7.33 (t, 1H, *J* = 7.6), 7.11 (d, 2H, *J* = 7.6), 3.97 (broad, 1H), 3.81(s, 3H), 3.29(s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 184.8, 183.9, 168.2, 164.9, 141.5, 129.8, 126.8, 122.6, 38.8, 31.6. HRMS calculated for $C_{12}H_{12}N_2O_2$ (M^++1) 217.0971. Found 217.0971. Mp: 213-215 ^oC

4.9.10 Preparation of 3-(N-tert-butyl-N-phenyl amino)-4-(tert-butyl amino) cyclobut-3-ene-1, 2-dione (48):



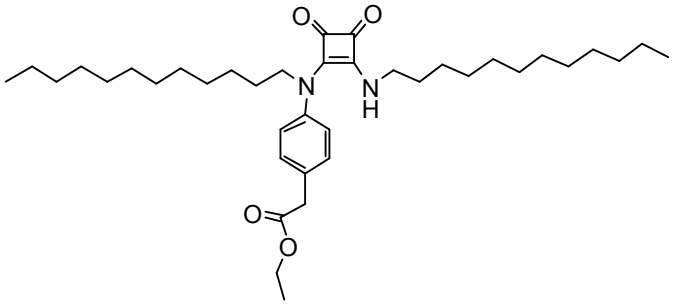
Pale white solid obtained in 95% yield. ^{1}H NMR ($CDCl_3$): δ aromatic signal are broad due to restricted rotation of phenyl 7.48(m, 3H), 7.25(m, 2H) 1.48(s, 9H), 1.09(s, 9H). ^{13}C NMR ($CDCl_3$): 182.6, 181.8, 169.8, 168.2, 140.0, 130.0, 129.0, 129.0, 60.0, 52.8, 30.6, 30.3. HRMS calculated for $C_{18}H_{24}N_2O_2$ (M^++1) 301.1910. Found 301.1915. Mpt. 200-202 ^{o}C

4.9.11 Preparation of 3-(N-cyclohexyl-N-phenyl amino)-4-(cyclohexyl amino) cyclobut-3-ene-1, 2-dione (49):



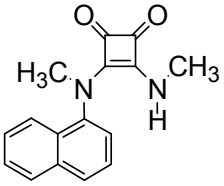
^{1}H NMR ($CDCl_3$): 7.48(d, 2H, *J* = 6.4), 7.23 (t, 2H, *J* = 6), 7.30 (t, 1H, *J* = 8), 4.59(m, 1H), 3.89 (broad singlet, 1H), 3.31(m, 1H), cyclohexyl ring proton 0.82-2.05(m, 20H). ^{13}C NMR ($CDCl_3$): 183.2, 182.7, 167.5, 166.0, 137.3, 129.2, 129.1, 128.9, 60.5, 52.0, 33.9, 32.4, 25.3, 25.0, 24.9, 23.6. HRMS calculated for $C_{22}H_{28}N_2O_2$ (M^++1) 353.2223 Found 353.2227. Mp: 185-188 ^{o}C

4.9.12 Preparation of 3-(N-dodecyl-N-(4-ethylphenylacetate amino)-4-(dodecylamino) cyclobut-3-ene-1, 2-dione (50) :



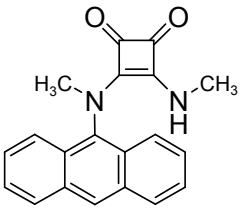
Obtained as a viscous liquid. ^{1}H NMR ($CDCl_3$): 7.35 (d, 2H, *J* = 8.4), 7.07(d, 2H, *J* = 8.4), 4.17 (q, 2H, *J* = 7.2), 4.11 (m, 1H), 3.99 (m, 2H), 3.65 (s, 2H), 3.55 (q, 2H, *J* = 6.4), 1.57 (m, 2H), 1.43 (m, 2H), 1.28 (t, 3H, *J* = 6.8), 1.22 (m, 36H), 0.86 (t, 6H *J* = 6.8). ^{13}C NMR($CDCl_3$): 184.3, 183.2, 170.9, 167.4, 165.0, 138.6, 133.3, 131.8, 130.5, 124.4, 61.1, 51.7, 44.7, 40.5, 31.8, 31.2, 29.6, 29.5, 29.5, 29.5, 29.4, 29.3, 29.3, 29.2, 29.1, 29.0, 26.2, 26.2, 22.6, 14.1. HRMS calculated for $C_{38}H_{62}N_2O_4$ (M^++1) 611.4782 found 611.4783

4.9.13 Preparation of 3-(N-methyl-N-(naphthalen-1-yl) amino)-4-(methyl amino) cyclobut-3-ene-1, 2-dione (51):



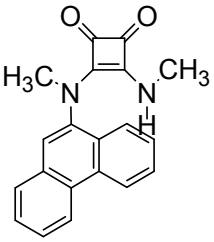
Pale yellow solid was obtained in 10% yield. ^{1}H NMR ($CDCl_3$): 7.99 (d, 1H, *J* = 7.6), 7.96(d, 1H, *J* = 8.0), 7.92 (d, 1H, *J* = 8.8), 7.67 (t, 1H, *J* = 5.6), 7.64 (t, 1H, *J* = 6.8), 7.57 (t, 1H, *J* = 8),7.45 (d, 1H, *J* = 7.6), 3.88 (s, 3H), 3.38 (s, 1H), 2.95 (s, 3H). ^{13}C NMR ($CDCl_3$): 184.1, 183.3, 168.6, 166.8, 137.9, 134.4, 130.1, 129.4, 129.1, 128.9, 128.1, 127.5, 125.3, 124.1, 122.2. HRMS calculated for $C_{16}H_{14}N_2O_2$ (M^++1) 267.1128. Found 267.1125. Mpt: 220-222^{o} C

4.9.14 Preparation of 3-(N-(anthracen-10-yl)-N-methyl amino)-4-(methyl amino) cyclobut-3-ene-1, 2-dione (52):



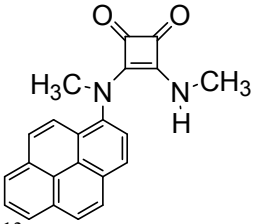
Solid obtained in 10% yield. Temperature was increased to 120°C. ^{1}H NMR ($CDCl_3$): 8.62 (s, 1H), 8.15 (d, 2H, *J* = 8.4), 8.04 (d, 2H, *J* = 8.8), 7.69 (t of d, 2H), 7.63 (t of d, 2H) 3.96 (s, 6H). ^{13}C NMR ($CDCl_3$):183.9, 183.1, 168.9, 167.4, 131.4, 129.2, 128.7, 128.4, 128.0, 126.4, 121.8, 40.5, 31.2. HRMS calculated for $C_{20}H_{16}N_2O_2$ (M^++1) 317.1284. Found 317.1287. Mpt >250° C

4.9.15 Preparation of 3-(N-methyl-N-(phenanthren-9-yl) amino)-4-(methyl amino) cyclobut-3-ene-1,2-dione(53)



Light brown solid was obtained in 20% yield. ^{1}H NMR ($CDCl_3$): 8.82 (d, 1H, *J* = 8.4), 8.75 (d, 1H, *J* = 8.0), 7.98 (t, 1H, *J* = 8.8), 7.78 (multiplet, 5H), 7.74 (s, 1H), 3.9 (s, 3H), 3.7 (b, 1H), 2.95 (s, 3H). ^{13}C NMR ($CDCl_3$): 184.1, 183.3, 168.6, 166.8, 136.5, 131.4, 130.4, 129.0, 128.3, 128.2, 128.1, 127.8, 127.6, 124.9, 123.7, 123.2, 122.8, 40.8, 31.4. HRMS Calculated for $C_{20}H_{16}N_2O_2$ (M^++1) 317.1284 found 317.1283

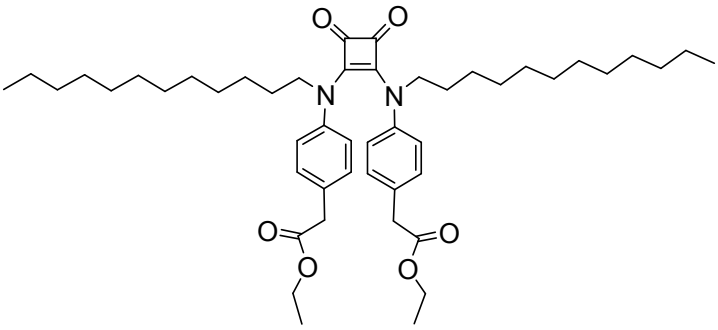
4.9.16 Preparation of 3-(N-methyl-N-(pyren-1-yl) amino)-4-(methyl amino) cyclobut-3-ene-1, 2-dione (54):



Yellow solid was obtained in 55% yield. Temperature was raised to 120 ° C. ^{1}H NMR ($CDCl_3$): 8.33 (d, 1H, *J* = 7.2), 8.28-8.11(m, 7H), 7.94 (d, 1H, *J* = 8), 4.00 (s, 3H), 3.2(broad, 1H), 2.84 (s, 3H) ppm. ^{13}C NMR ($CDCl_3$): 183.3, 168.8, 131.4, 131.1, 130.8, 130.0, 128.9, 127.1, 126.9, 126.5,

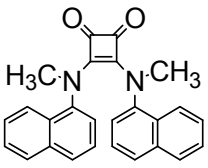
126.4, 125.2, 124.0, 120.6, 41.2, 31.3. HRMS Calculated for $C_{22}H_{16}N_2O_2$ (M^++1) 341.1284. Found 341.1287. Mpt: 188-190 ^oC

4.9.17 Preparation of 3, 4-bis (N-dodecyl-N-4-ethyl phenylacetate amino) cyclobut-3-ene-1, 2-dione (55):



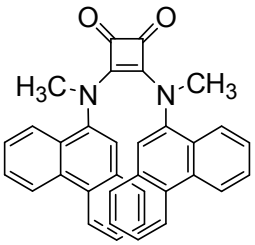
^1H NMR ($CDCl_3$): 6.85 (d, 4H, J = 8.4), 6.40 (d, 4H, J = 8.0), 4.21(q, 4H, J = 7.2), 3.99 (t, 6H), 3.46 (s, 4H), 1.33-1.23 (m, 40H), 1.57(broad, 4H), 0.87(t, 6H, J = 6.8). ^{13}C NMR ($CDCl_3$): δ 186.1, 171.1, 167.5, 140.2, 131.0, 129.3, 122.8, 60.9, 52.7, 40.4, 31.9, 29.9, 29.6, 29.5, 29.3, 29.2, 26.4, 22.6, 14.2, 14.1. HRMS calculated for $C_{48}H_{72}N_2O_6$ (M^++1) 773.5463 found 773.5463.

4.9.18 Preparation of 3, 4-bis (N-methyl-N-(naphthalen-1-yl) amino) cyclobut-3-ene-1, 2-dione (56):



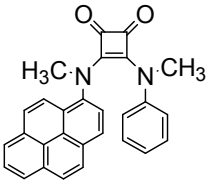
^1H NMR (DMSO-d_6): Broad signals in the aromatic region are observed due to syn and anti mixture at room temperature. So ^1H NMR was taken at 80^oC ^1H NMR: 7.60(d, 2H, J = 7.6), 7.47- 7.35 (m, 6H), 7.15 (d, 2H, J = 8), 6.97(d, 2H, J = 7.6), 6.82(t, 2H, J = 8), 3.46(s, 6H). ^{13}C NMR (DMSO-d_6) at 80 ^oC: 185.5, 169.4, 140.3, 134.1, 128.6, 127.5, 127.0, 126.8, 126.3, 125.6, 123.3, 122.6. HRMS Calculated for $C_{26}H_{20}N_2O_2$ (M^++1) 393.1597. Found 393.1596. Mp: 228-230 ^oC

4.9.19 Preparation of 3, 4-bis (N-methyl-N-(phenanthren-10-yl) amino) cyclobut-3-ene-1, 2-dione (57):



Solid obtained in 7% yield. ^{1}H NMR ($CDCl_3$): mixture of syn and anti isomers. ^{1}H NMR ($CDCl_3$): 8.0 (t, 2H, *J* = 8), 7.94 (d, 2H, *J* = 8), 7.53-7.38 (t, 6H), 7.27-7.19 (m, 2H), 7.11-7.04 (m, 2H), 6.92 (s, 2H), 6.72(t, 2H, *J* = 8), 3.73 (s, 6H). ^{13}C NMR ($CDCl_3$): 185.9, 169.4, 138.3, 131.0, 130.4, 129.2, 128.9, 128.2, 127.8, 127.0 126.8, 126.6, 126.6, 126.5, 126.2, 125.3, 125.0, 124.1, 123.5, 123.3, 122.9, 122.5, 122.2, 122.9, 121.5, 42.0, 41.7. HRMS calculated for $C_{34}H_{24}N_2O_2$ (M^++1) 493.1910. found 493.1913.

4.9.20 Preparation of 3-(N-methyl-N-(pyren-1-yl) amino)-4-(N-methyl-N-phenylamino) cyclobut-3-ene-1, 2-dione (58):



A 25 ml RB flask was charged with copper iodide (95 mg, 0.5 mmol), L-proline (58 mg, 0.5 mmol), potassium carbonate (345 mg, 3 mmol) and anhydrous DMF (1 ml). The mixture was stirred at room temperature under nitrogen atmosphere for 20 minutes. To this, 3-(N-methyl-N-(pyren-1-yl)amino)-4-(methyl amino)cyclobut-3-ene-1,2-dione(340mg, 1 mmol) and bromobenzene (471 mg, 3 mmol) were added and temperature increased to 120 ^{o}C and maintained for 18 hours. The reaction mixture was cooled to room temperature, diluted with ethyl acetate (15 ml), filtered and concentrated. The residue upon column chromatography (2:3 Ethyl acetate / hexane) gave the title compound in 51% yield. ^{1}H NMR ($CDCl_3$): 8.24 (d, 1H, *J* = 8), 8.12-8.06 (m, 5H),7.94 (d, 1H, *J* = 8) 7.86 (t, 1H, *J* = 8), 7.42 (d, 1H, *J* = 8), 6.23 (t, 2H, *J* = 8), 6.13 (d, 2H, *J* = 8), 5.75 (t, 1H, *J* = 7.2), 4.02 (s, 3H), 3.43 (s, 3H). ^{13}C NMR ($CDCl_3$): 186.5, 186.2, 169.9, 167.5, 143.0, 136.8, 130.9,

130.5, 130.4, 128.4, 127.8, 127.8, 126.7, 126.4, 125.8, 125.7, 125.2, 124.9,124.7, 124.1, 123.8, 122.6, 122.0, 120.9. HRMS calculated for $C_{30}H_{25}N_3O_2$ (M^++1) 417.1597 Found 417.1599. Mp: 187-190 ^{o}C.

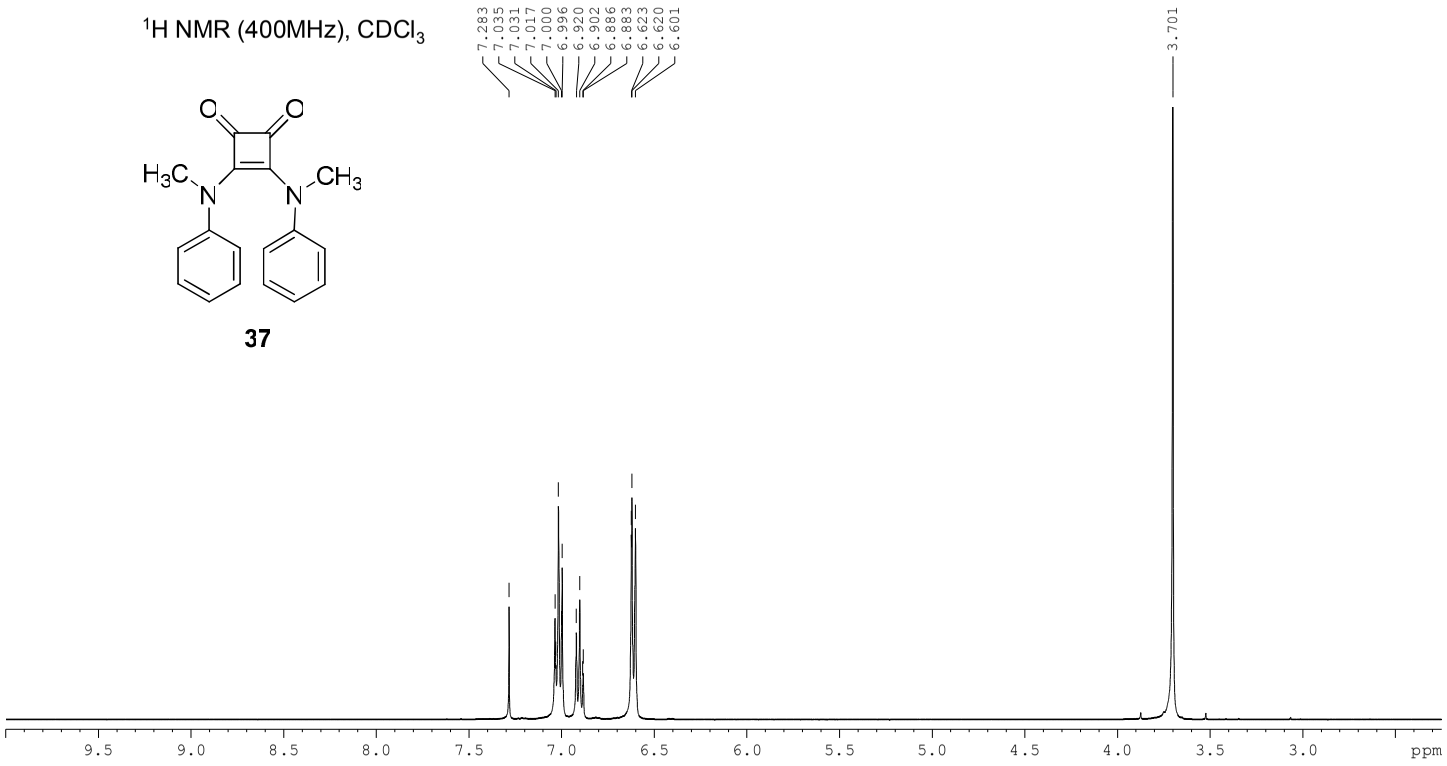


Figure 4.7: ^{1}H NMR spectra of squaramide **37** in $CDCl_3$

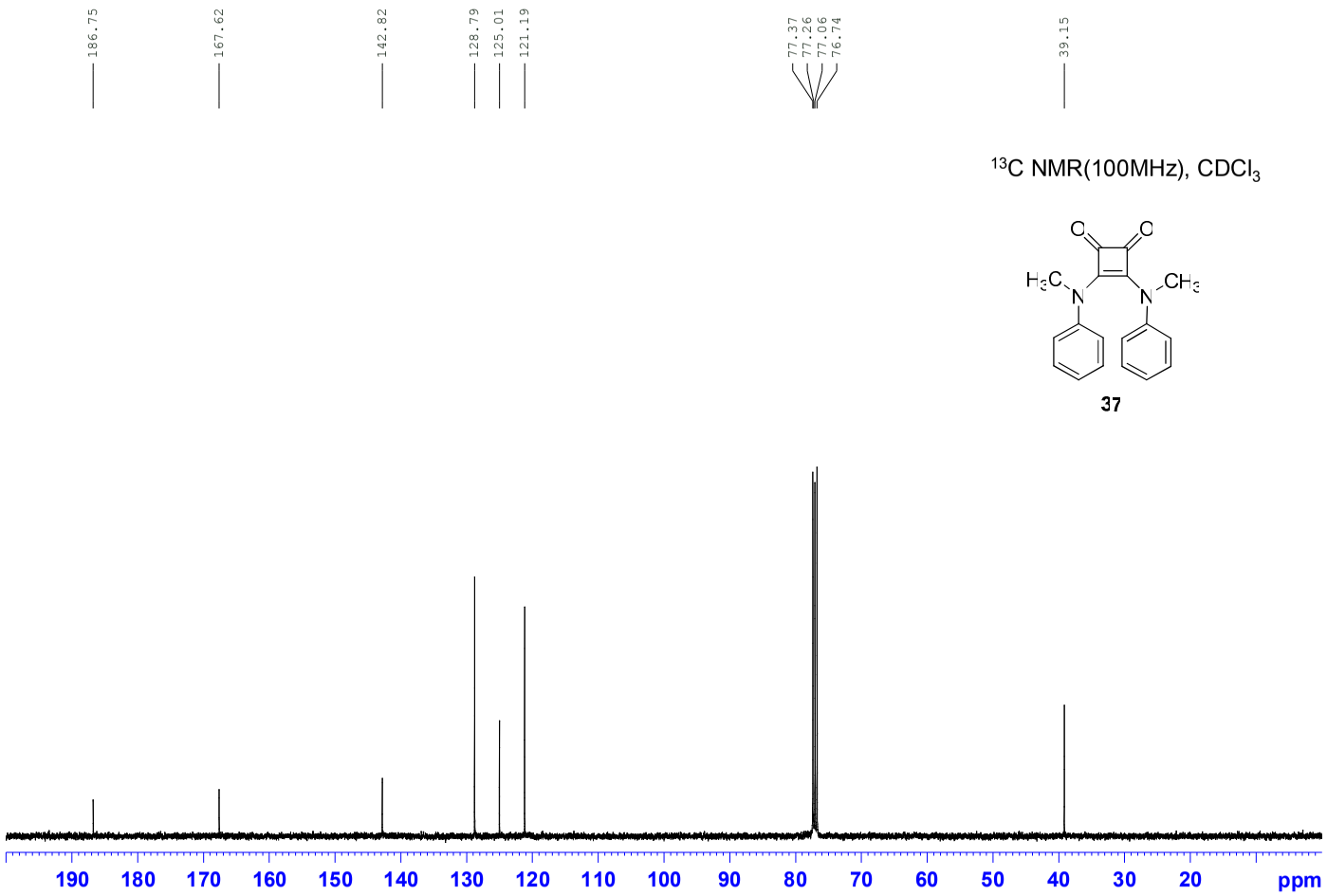


Figure 4.8: ^{13}C NMR spectra of squaramide **37** in $CDCl_3$

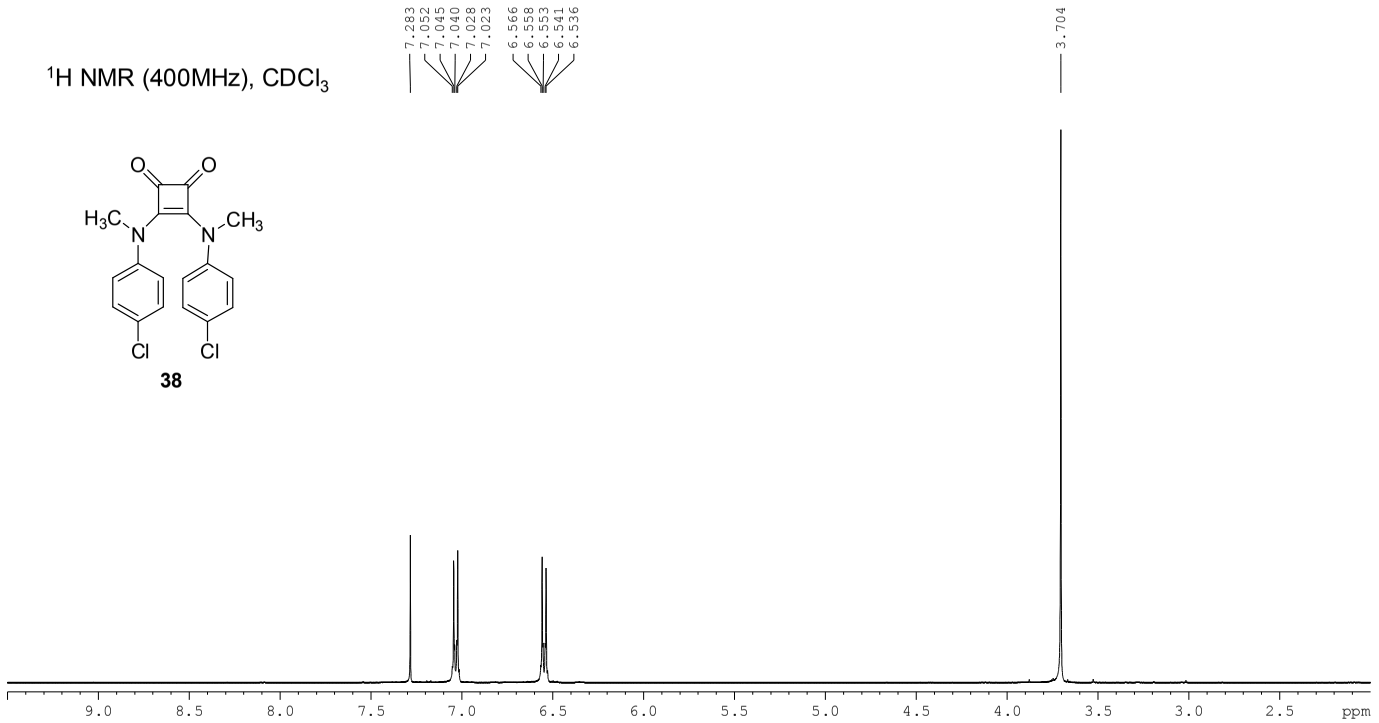


Figure 4.9: ^{1}H NMR spectra of squaramide **38** in $CDCl_3$

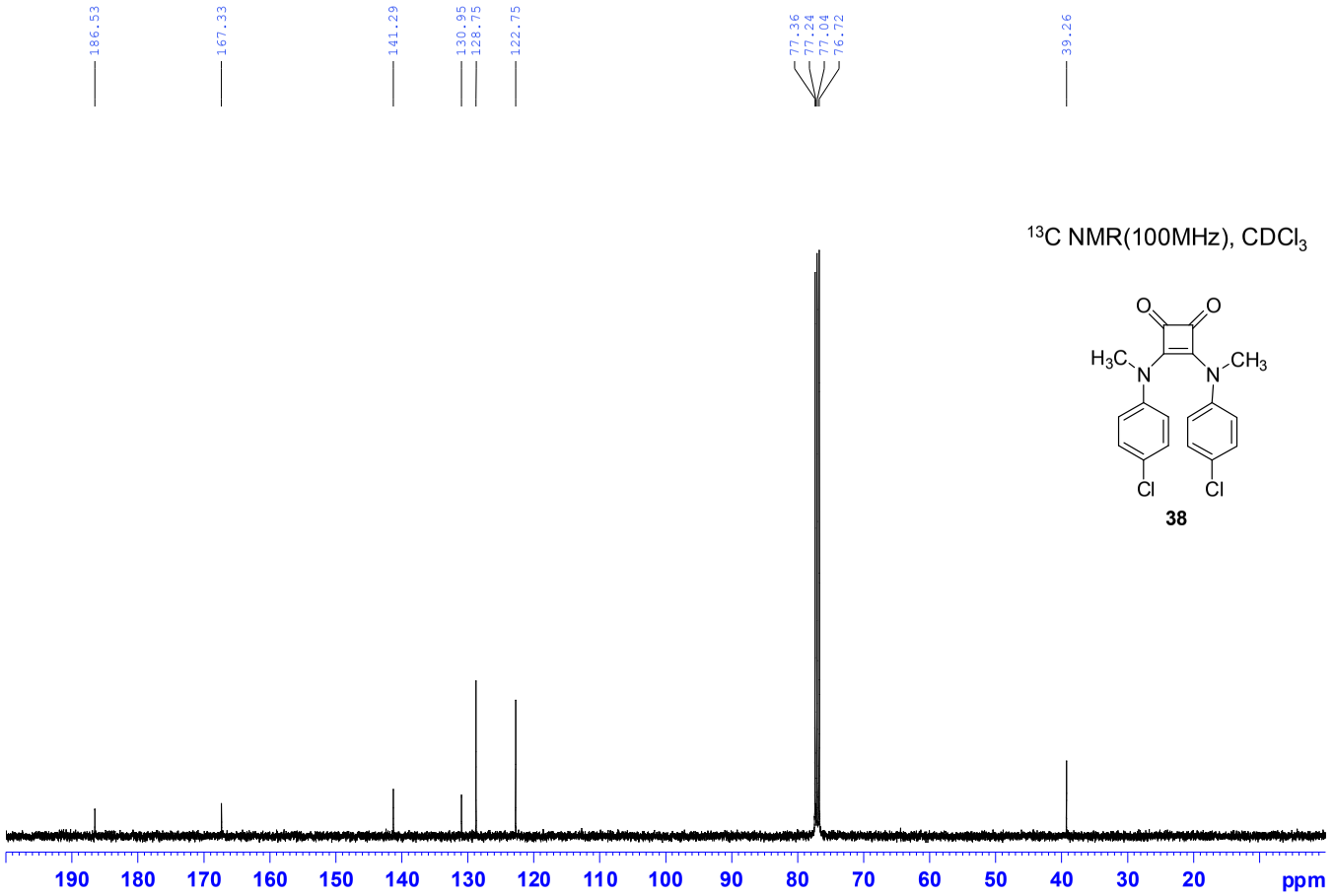


Figure 4.10: ^{13}C NMR spectra of squaramide **38** in $CDCl_3$

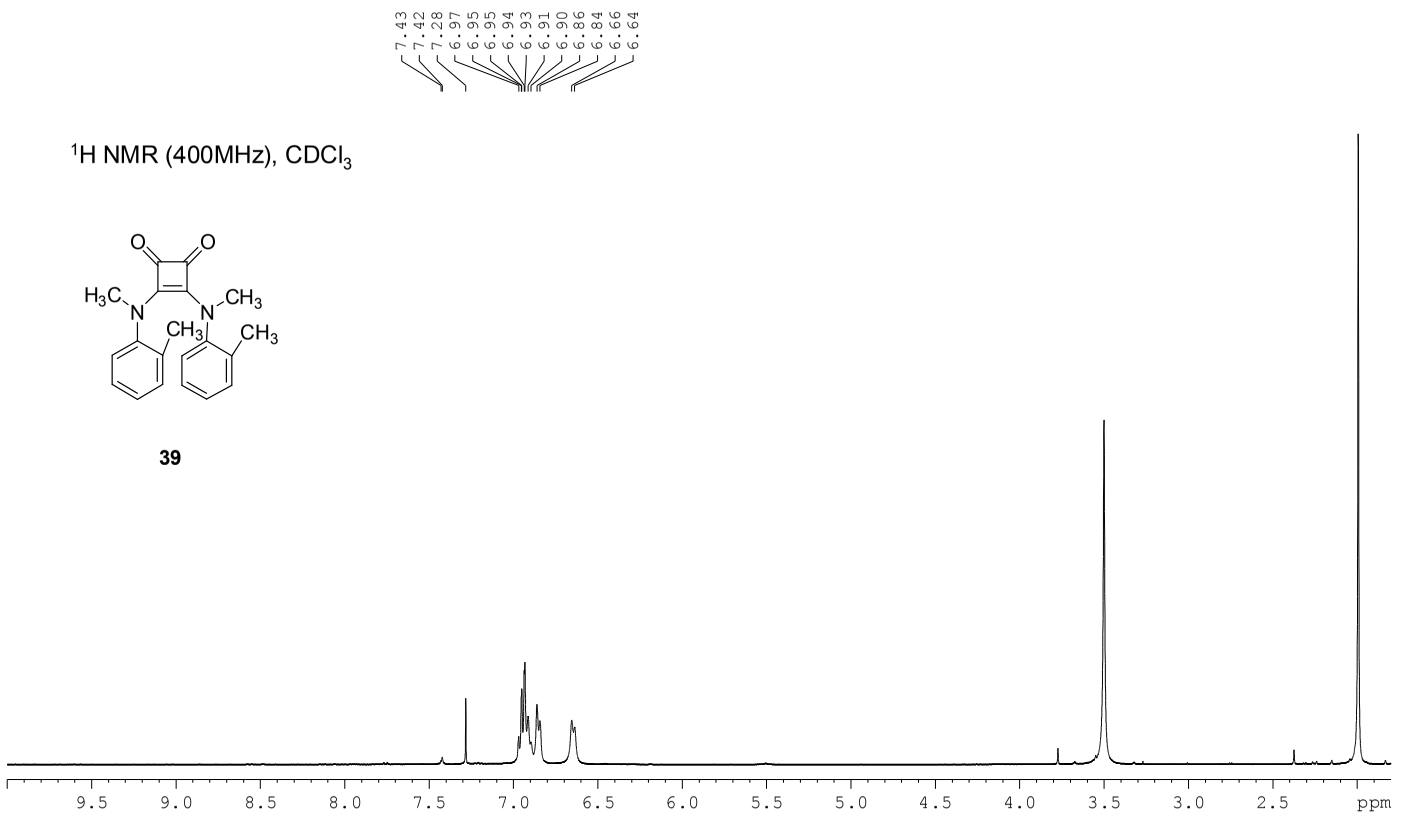


Figure 4.11: ^{1}H NMR spectra of squaramide **39** in $CDCl_3$

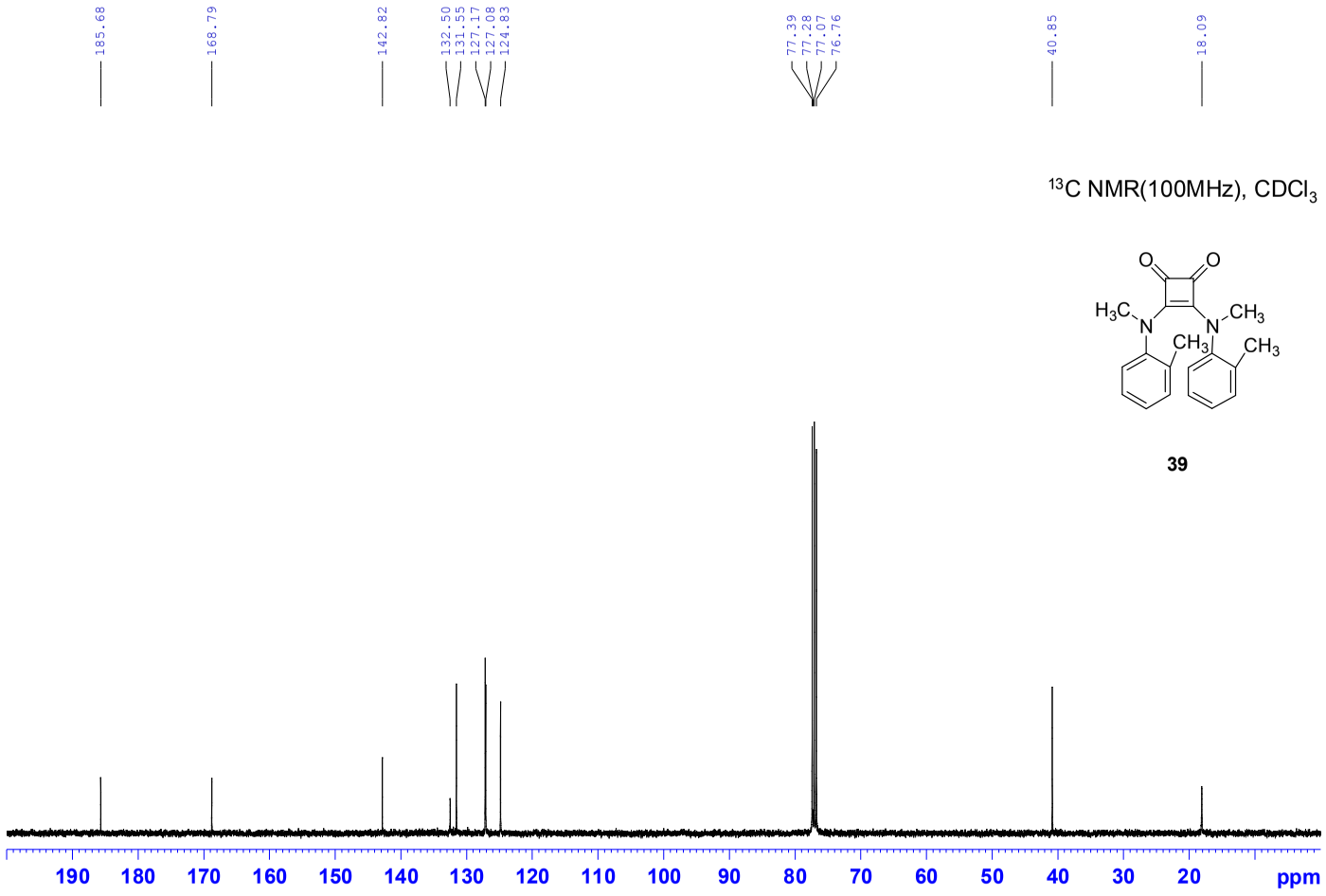


Figure 4.12: ^{13}C NMR spectra of squaramide **39** in $CDCl_3$

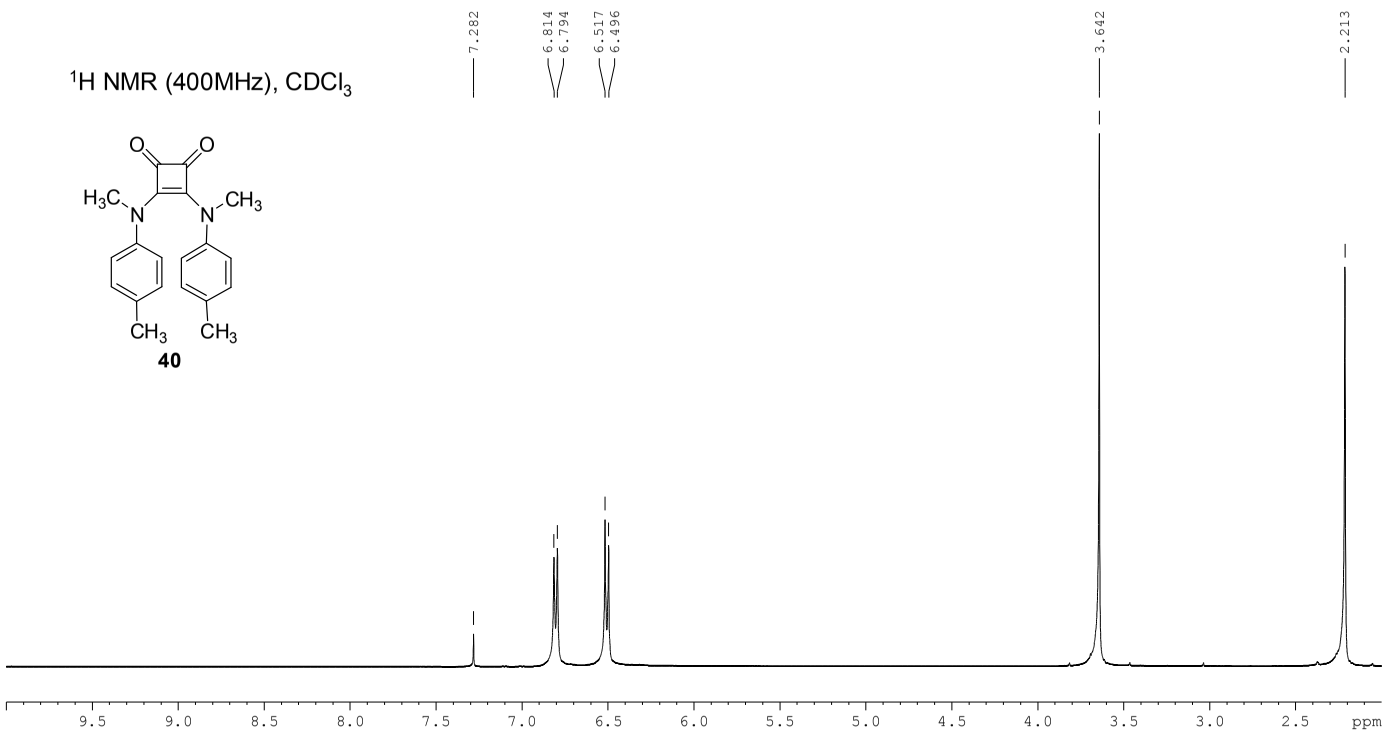


Figure 4.13: ^{1}H NMR spectra of squaramide **40** in $CDCl_3$

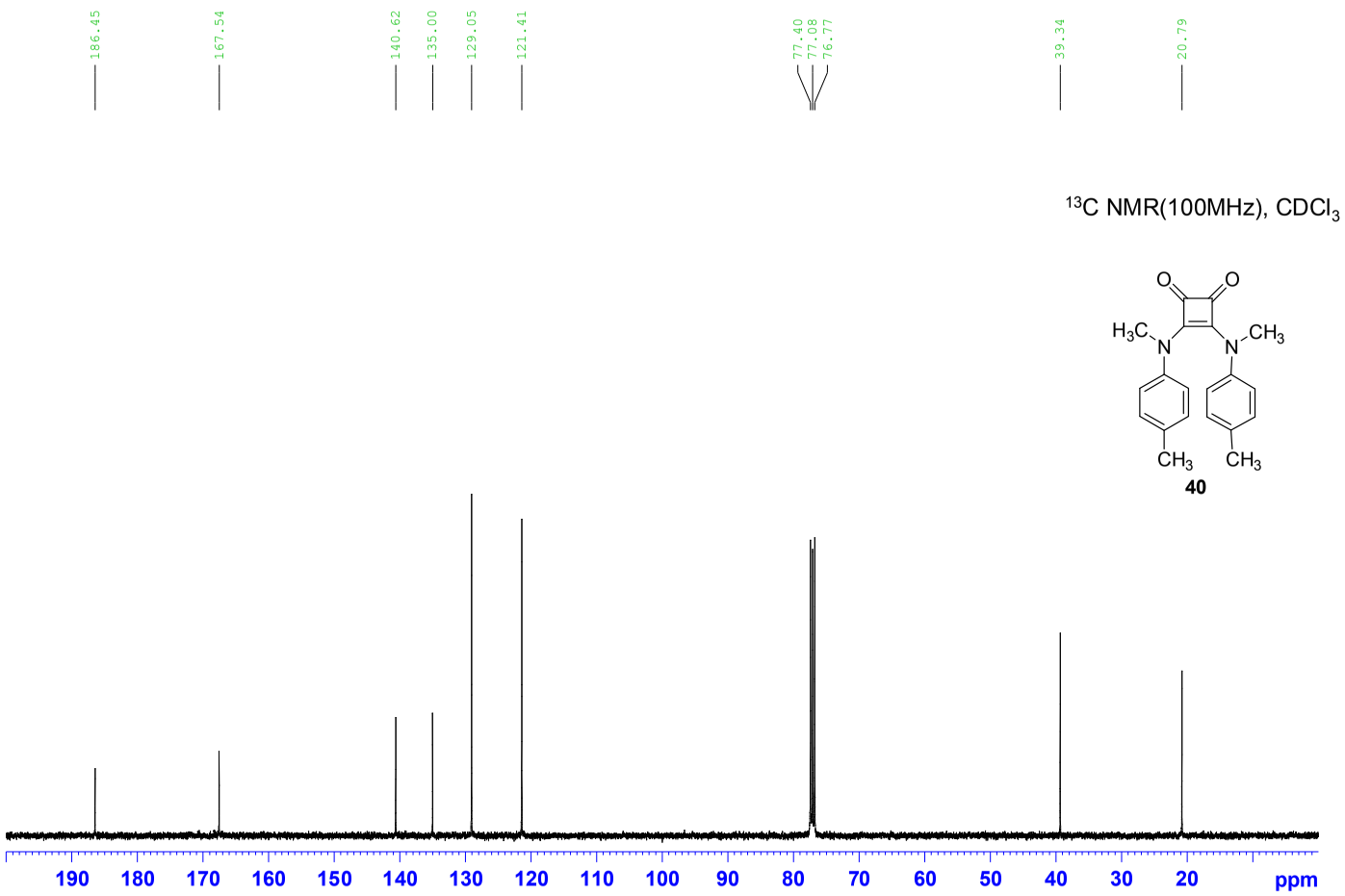


Figure 4.14: ^{13}C NMR spectra of squaramide **40** in $CDCl_3$

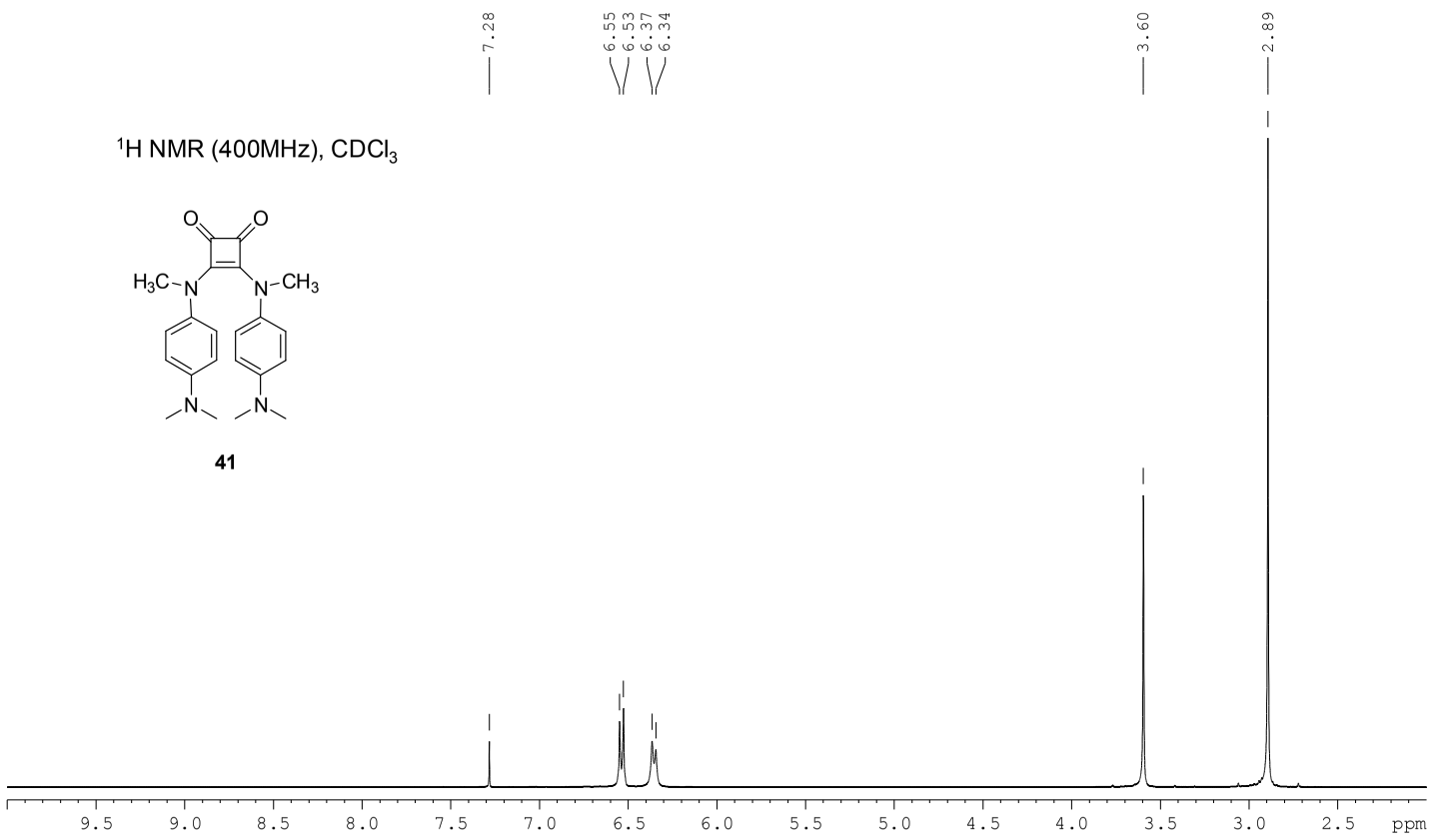


Figure 4.15: ^{1}HNMR spectra of squaramide **41** in $CDCl_3$

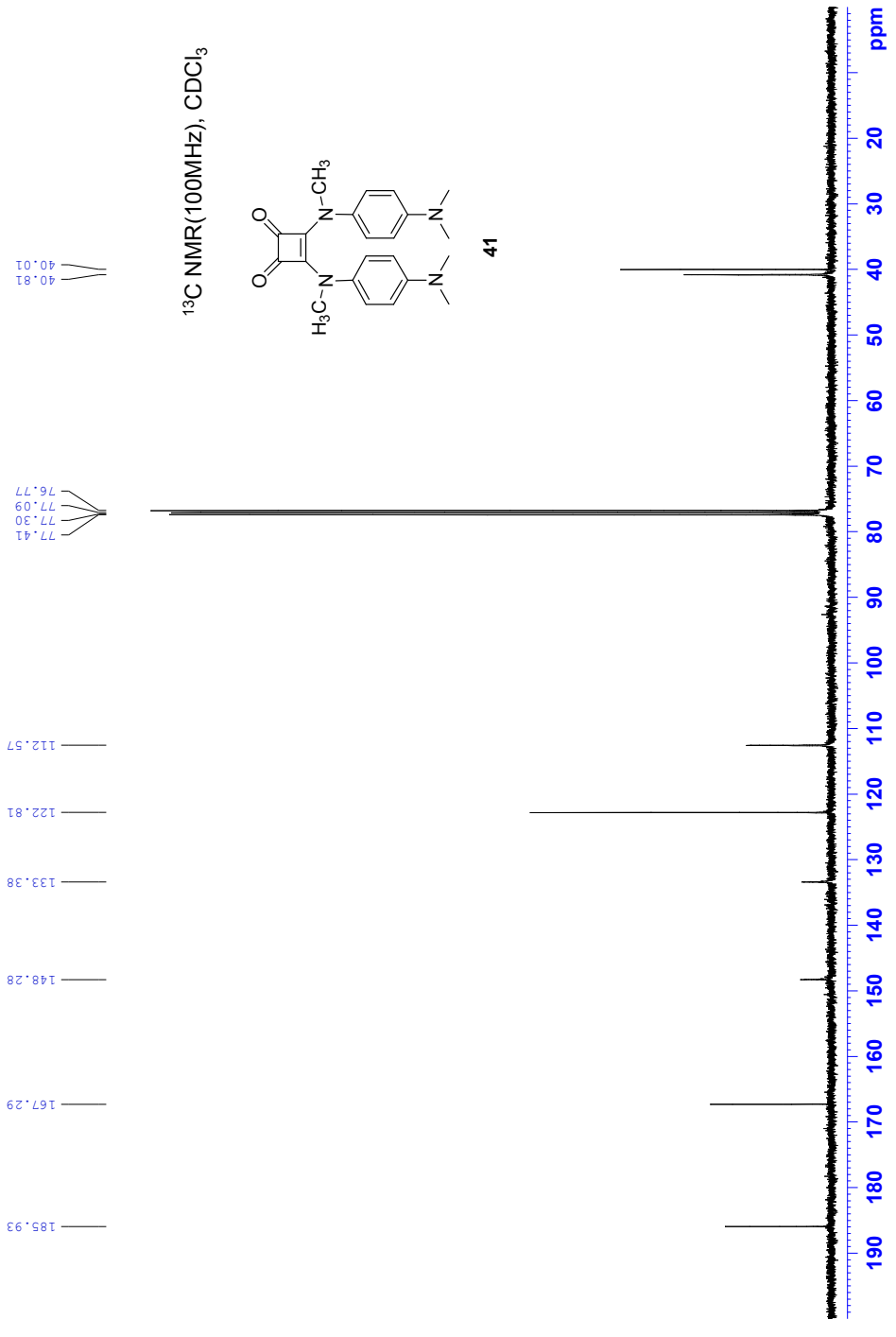


Figure 4.16: ^{13}C NMR spectra of squaramide **41** in $CDCl_3$

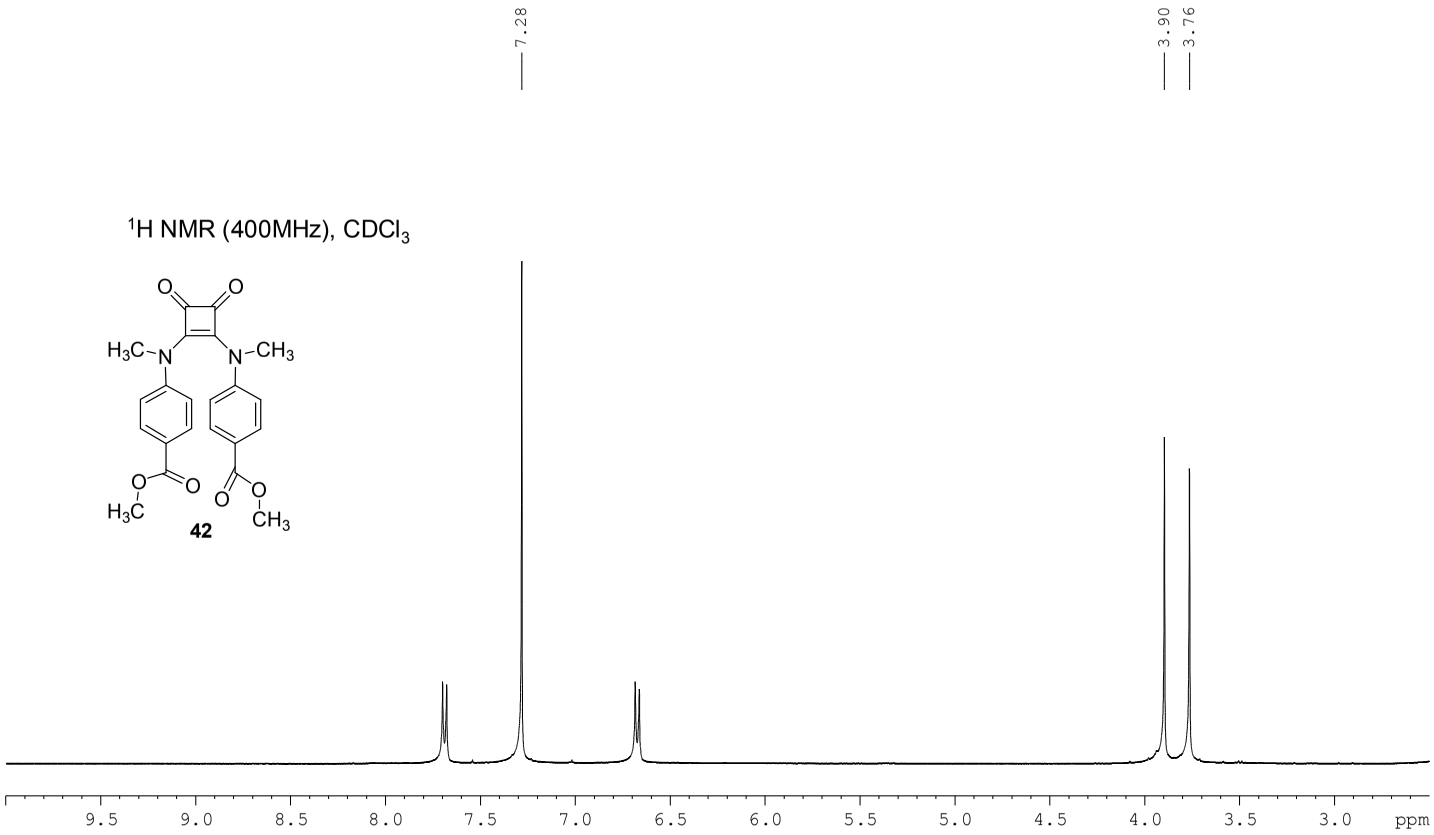


Figure 4.17: ^{1}H NMR spectra of squaramide **42** in $CDCl_3$

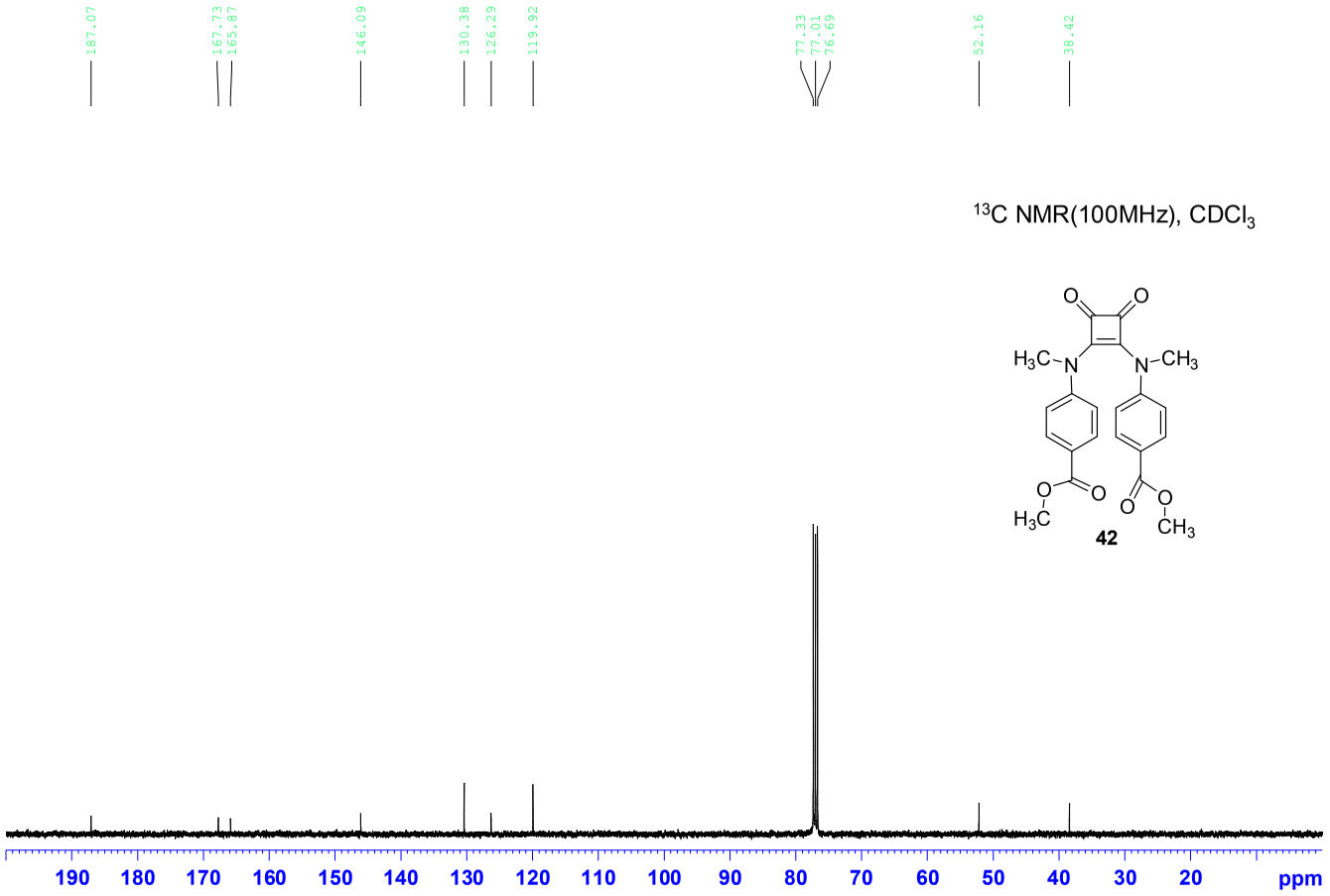


Figure 4.18: ^{13}C NMR spectra of squaramide **42** in $CDCl_3$

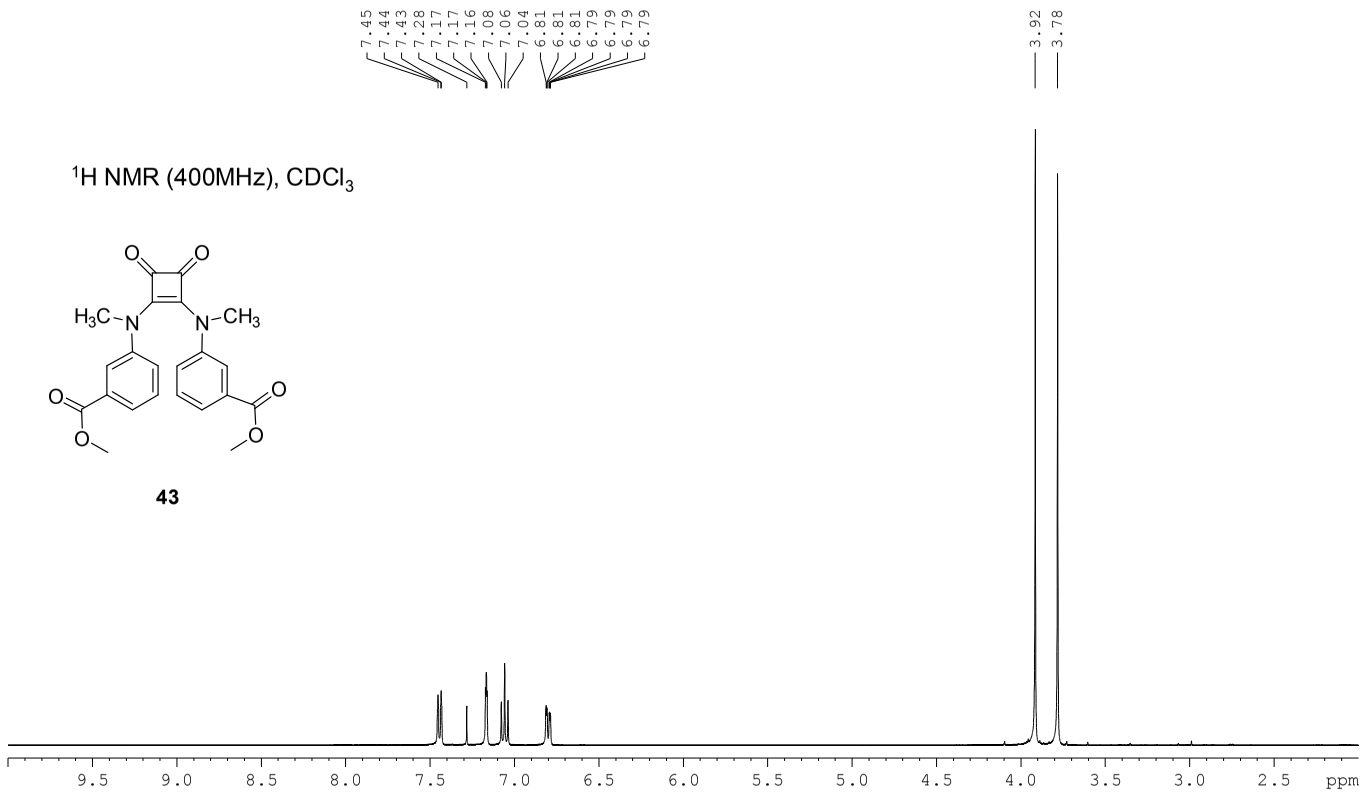


Figure 4.19: ^{1}HNMR spectra of squaramide **43** in $CDCl_3$

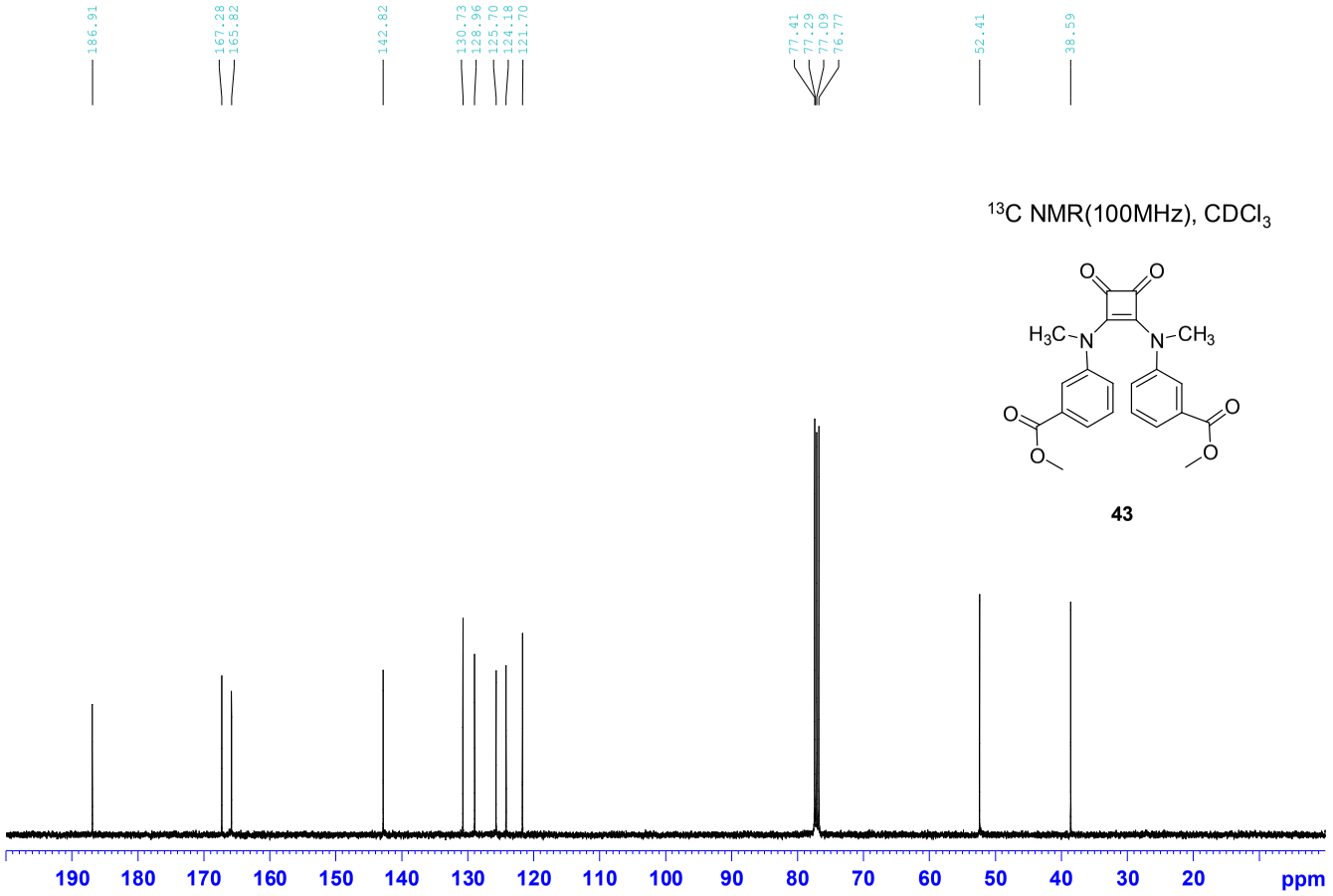


Figure 4.20: ^{13}C NMR spectra of squaramide **43** in $CDCl_3$

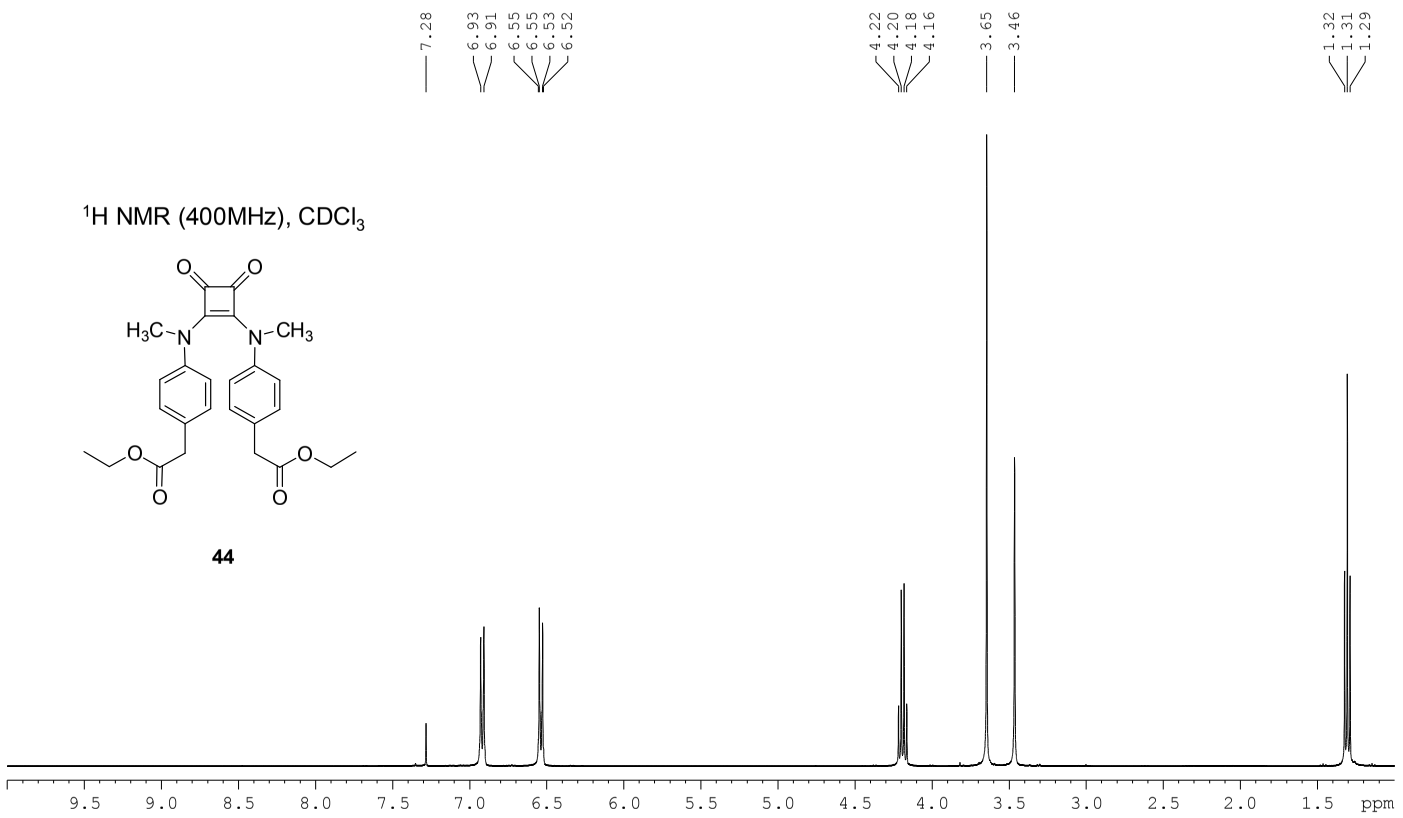


Figure 4.21: ^{1}H NMR spectra of squaramide **44** in $CDCl_3$

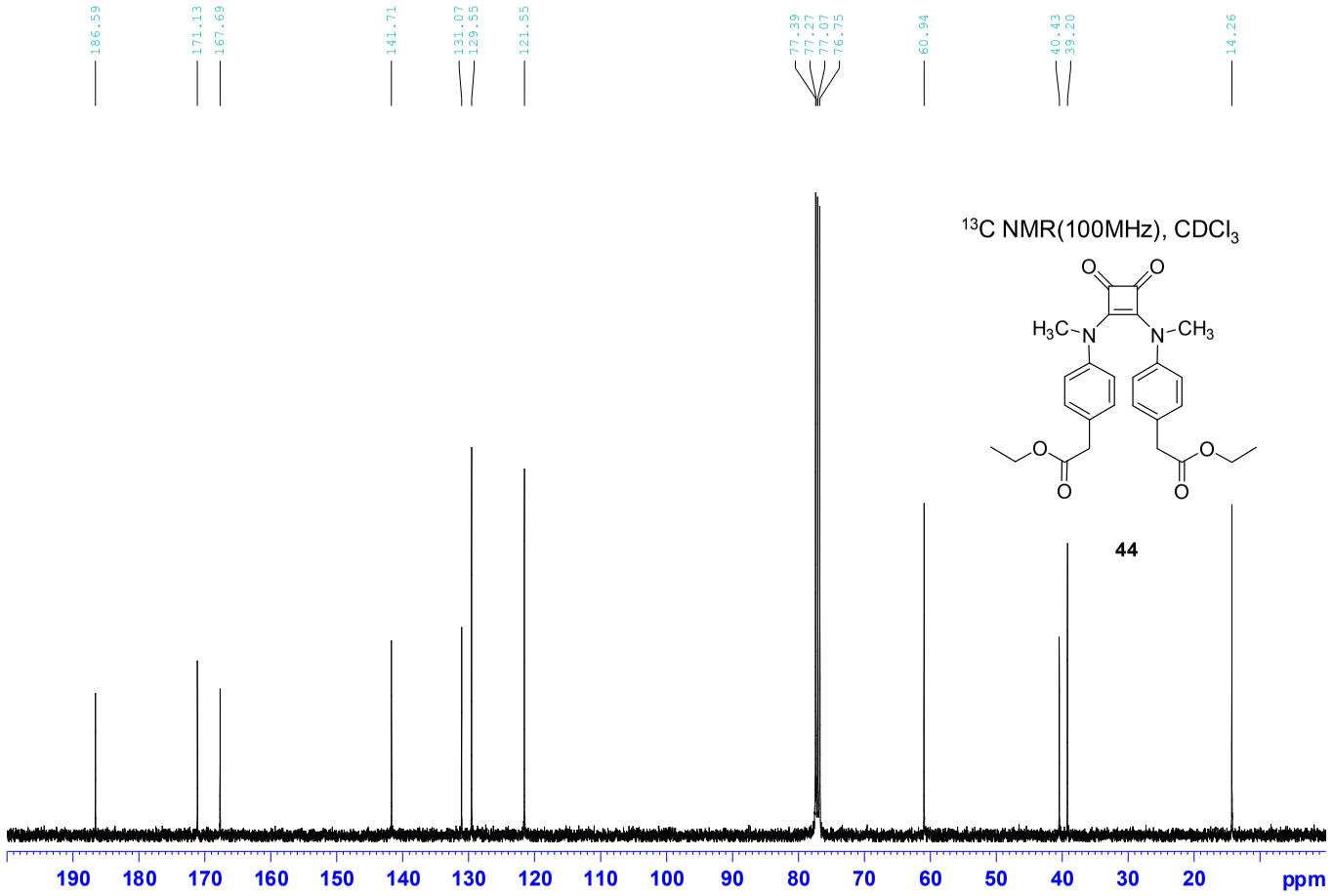


Figure 4.22: ^{13}C NMR spectra of squaramide **44** in $CDCl_3$

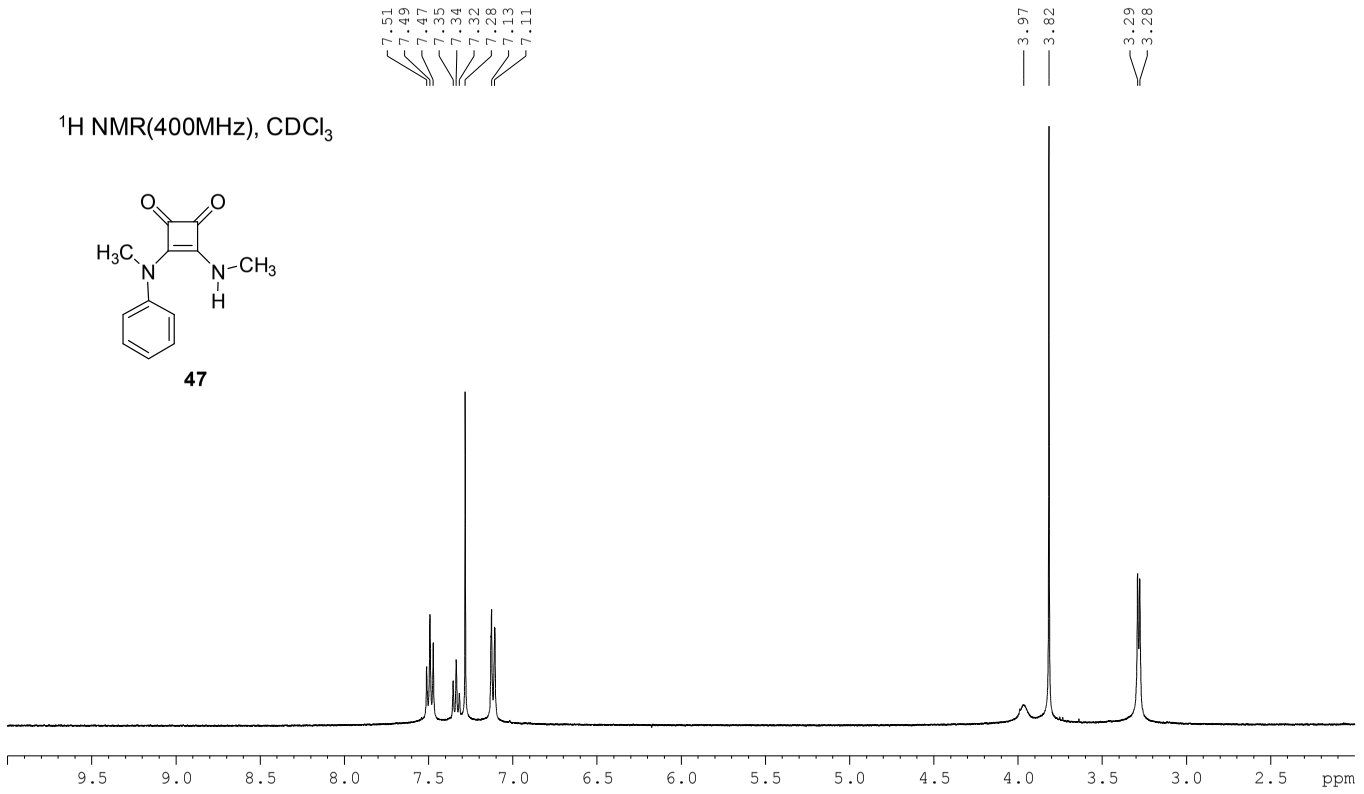


Figure 4.23: ^{1}H NMR spectra of squaramide **47** in $CDCl_3$

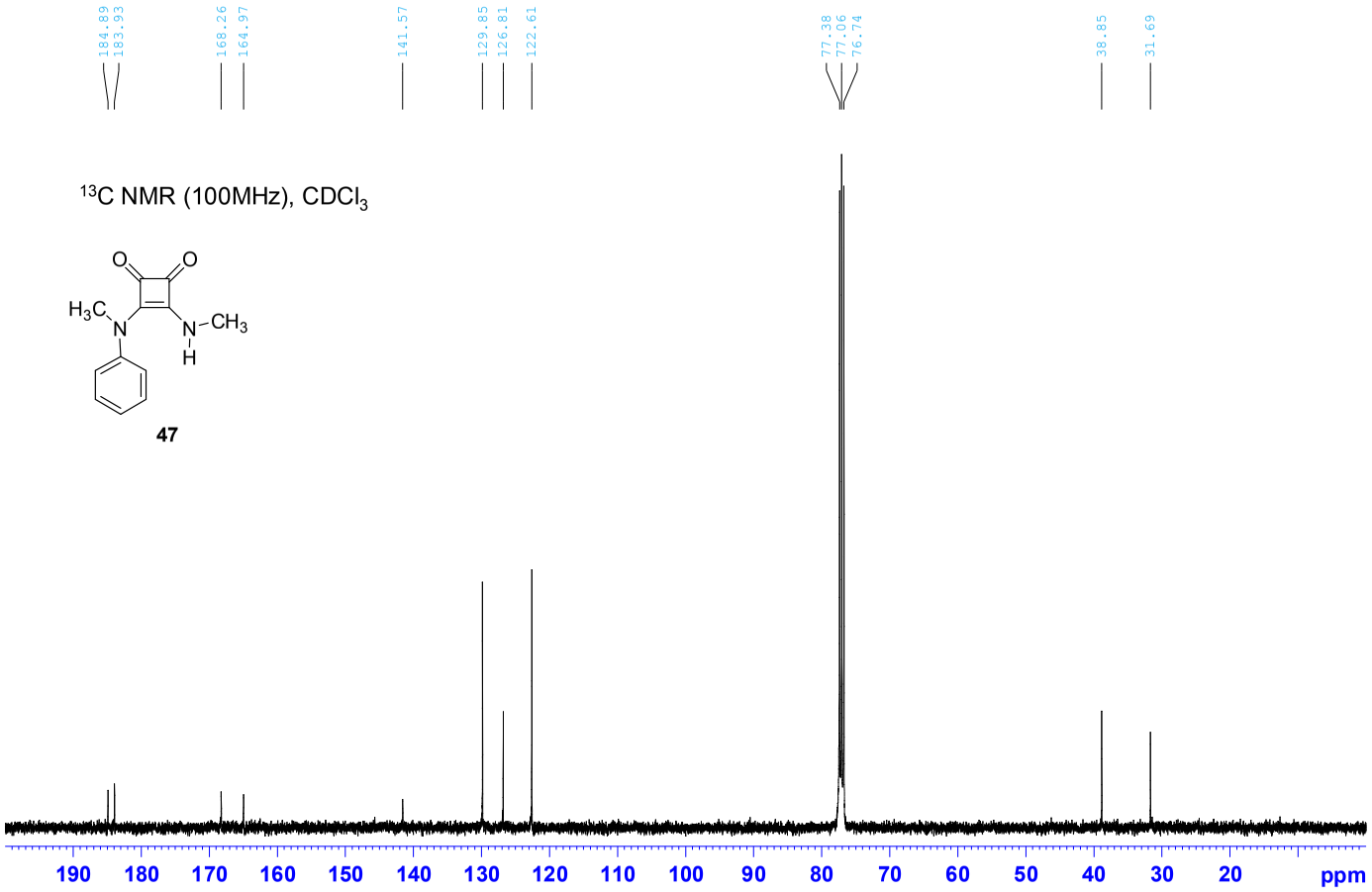


Figure 4.24: ^{13}C NMR spectra of squaramide **47** in $CDCl_3$

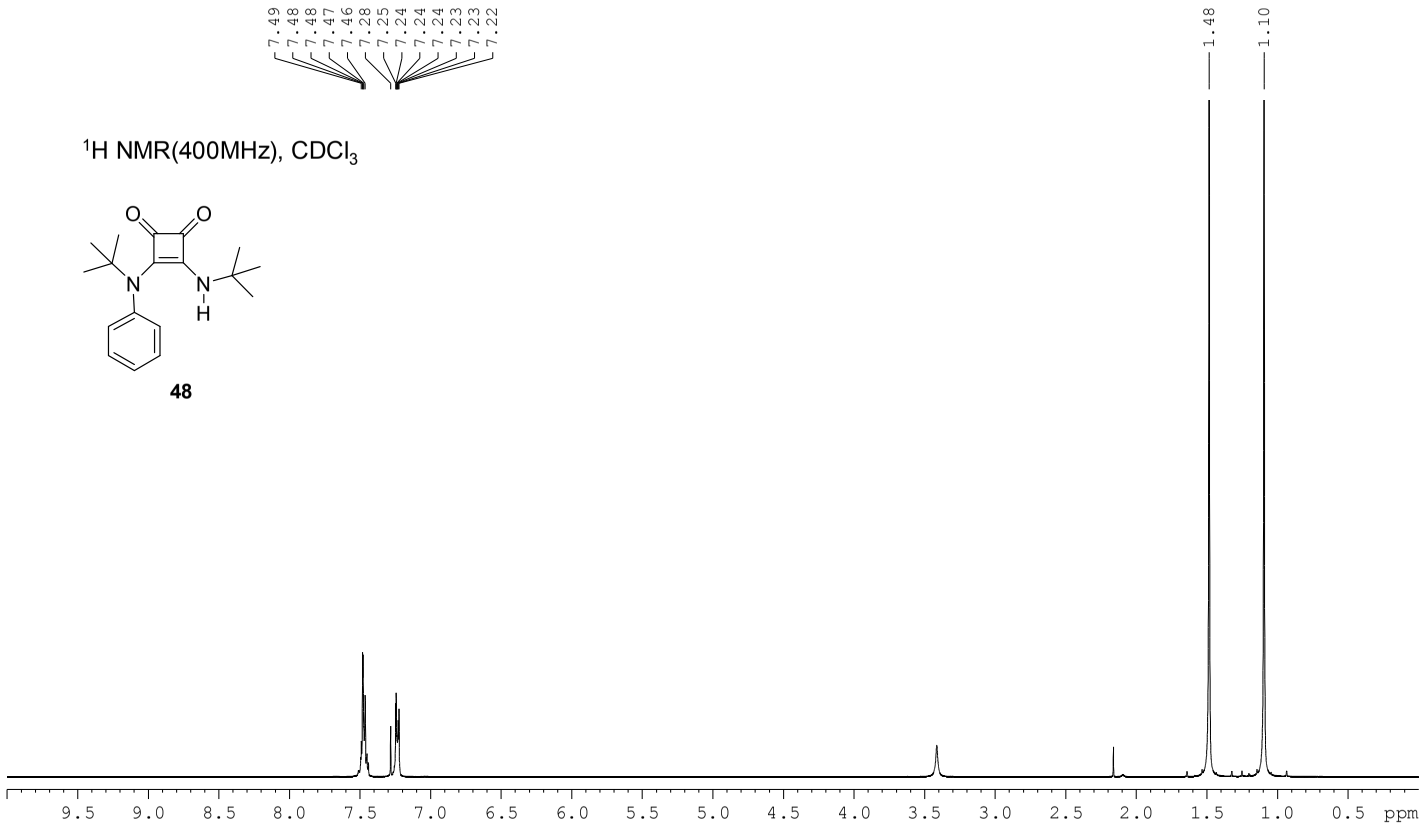


Figure 4.25: ^{1}H NMR spectra of squaramide **48** in $CDCl_3$

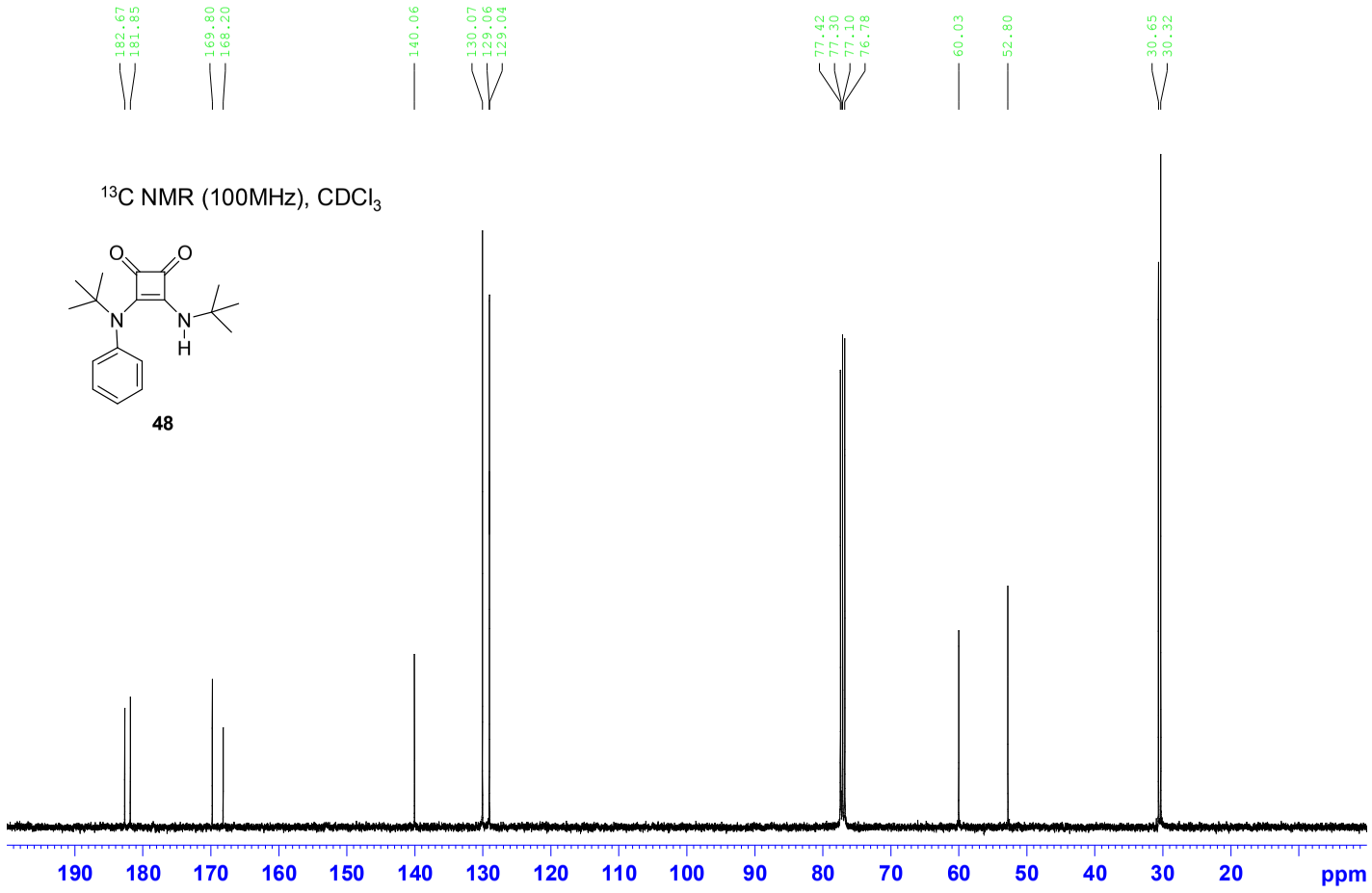


Figure 4.26: ^{13}C NMR spectra of squaramide **48** in $CDCl_3$

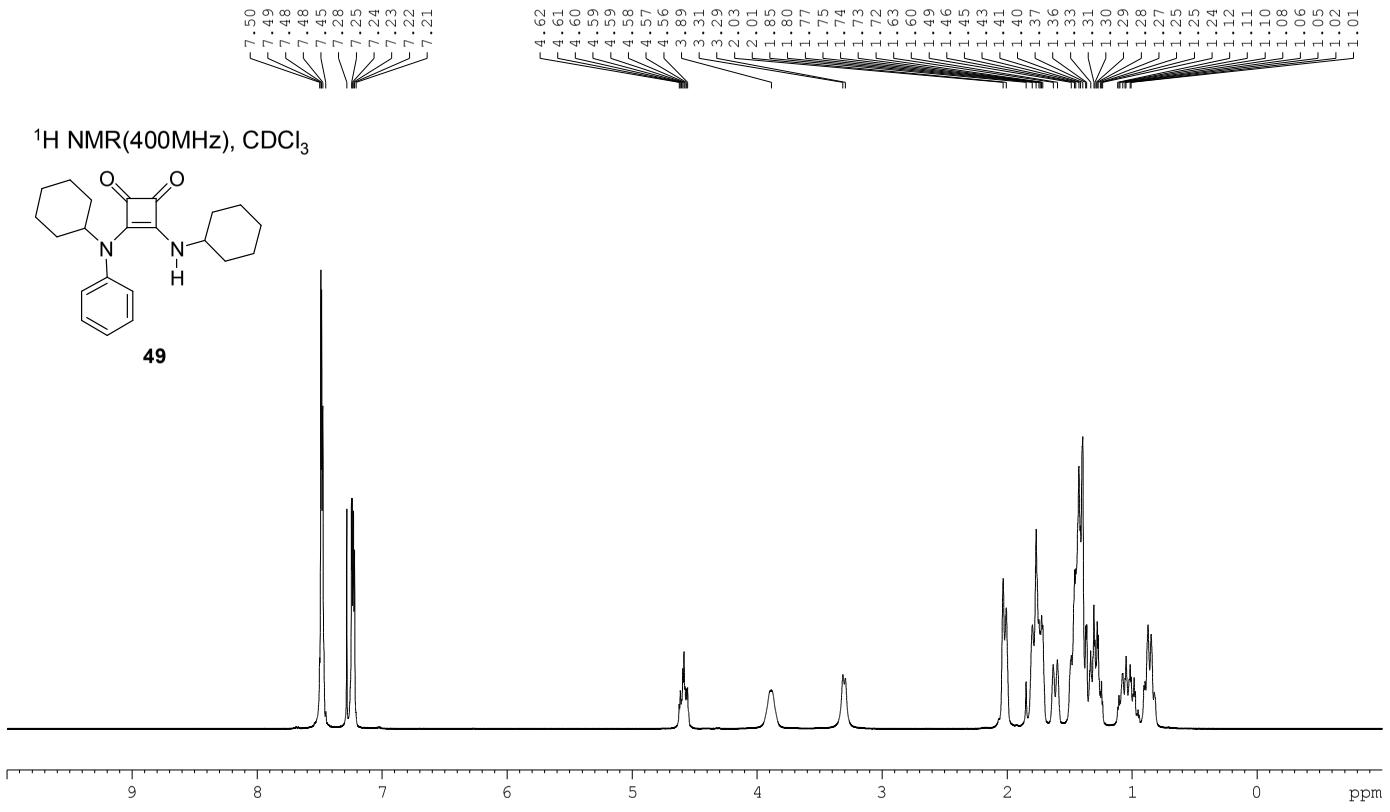


Figure 4.27: ^{1}H NMR spectra of squaramide **49** in $CDCl_3$

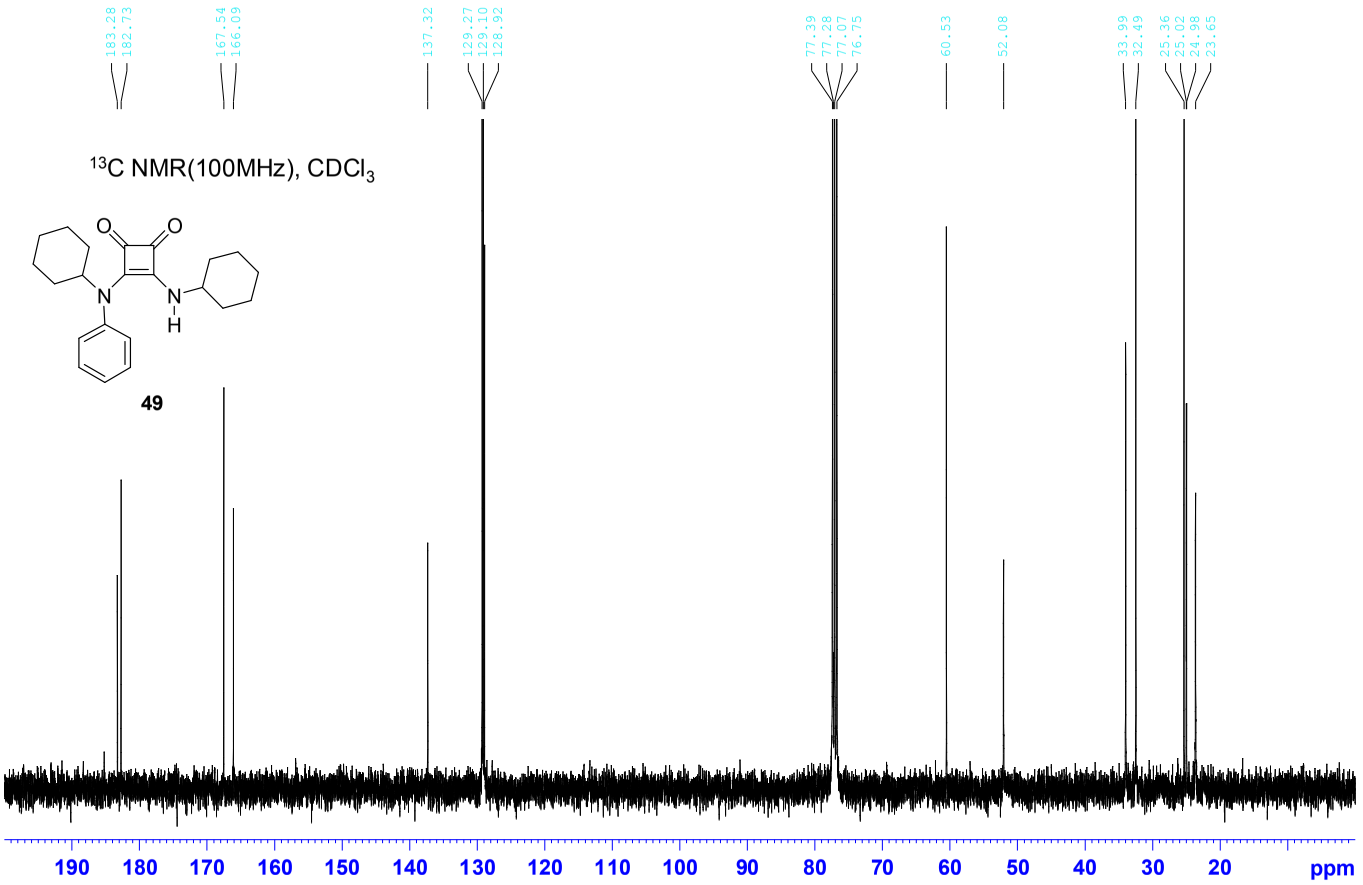


Figure 4.28: ^{13}C NMR spectra of squaramide **49** in $CDCl_3$

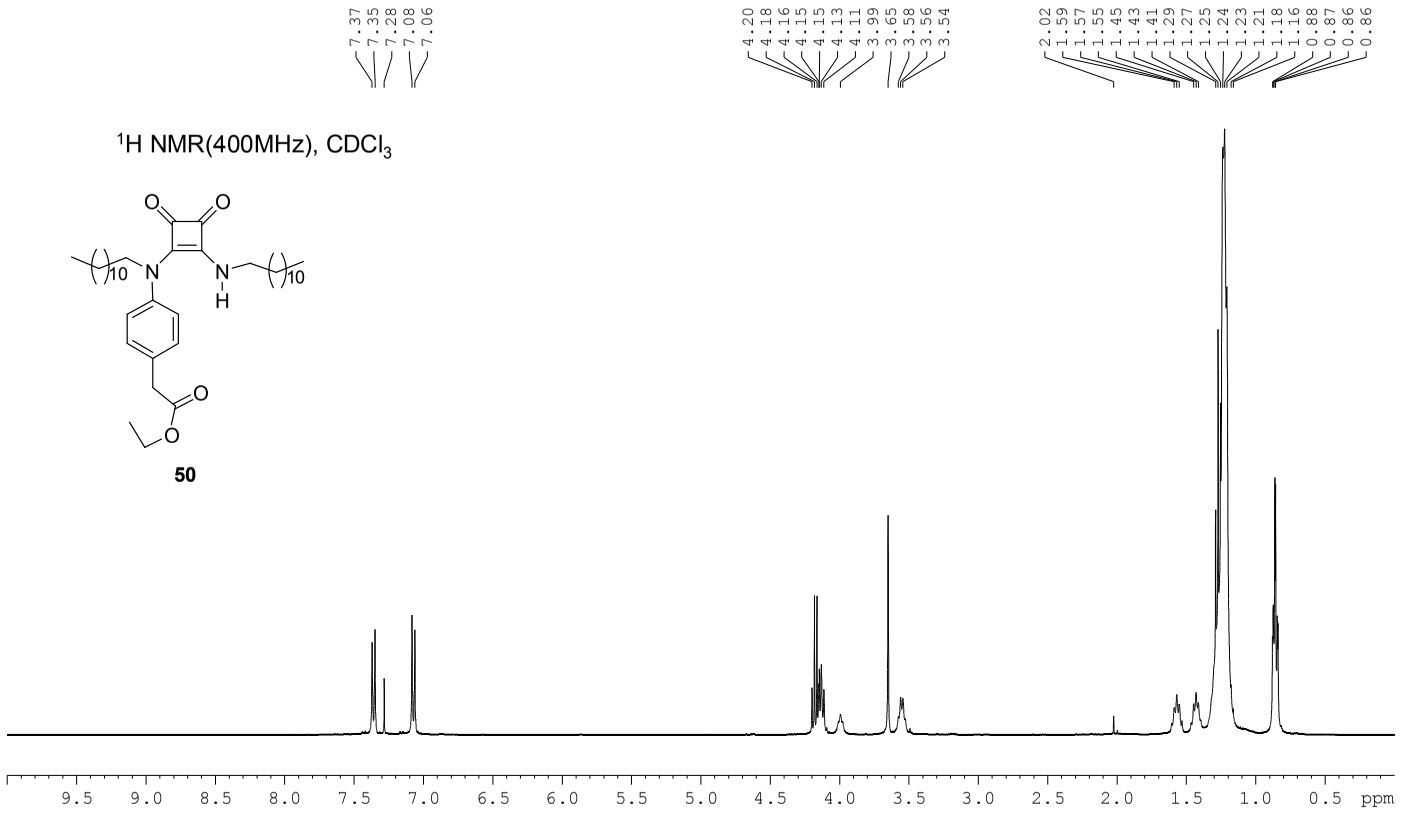


Figure 4.29: ^{1}H NMR spectra of squaramide **50** in $CDCl_3$

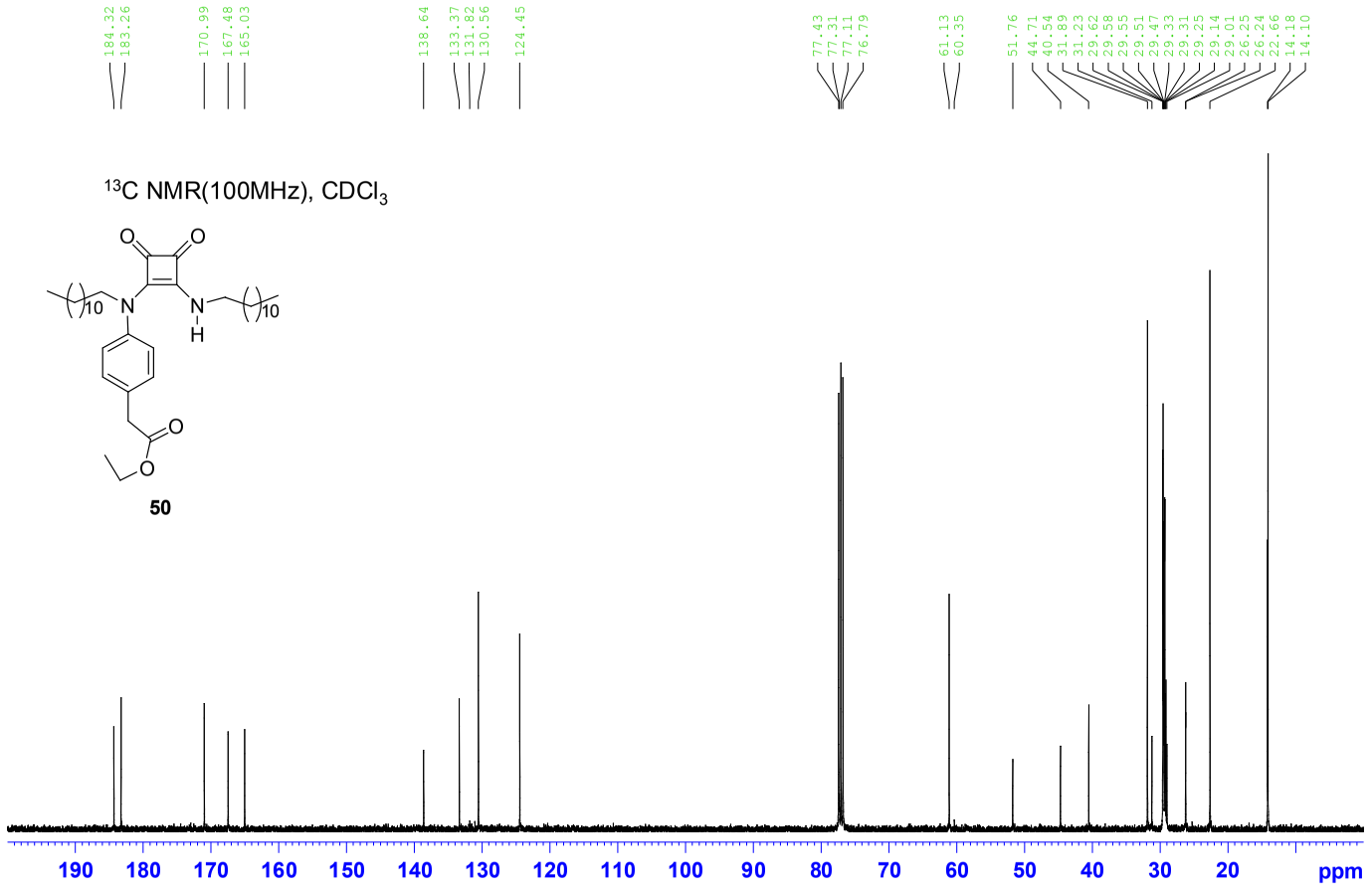


Figure 4.30: ^{13}C NMR spectra of squaramide **50** in $CDCl_3$

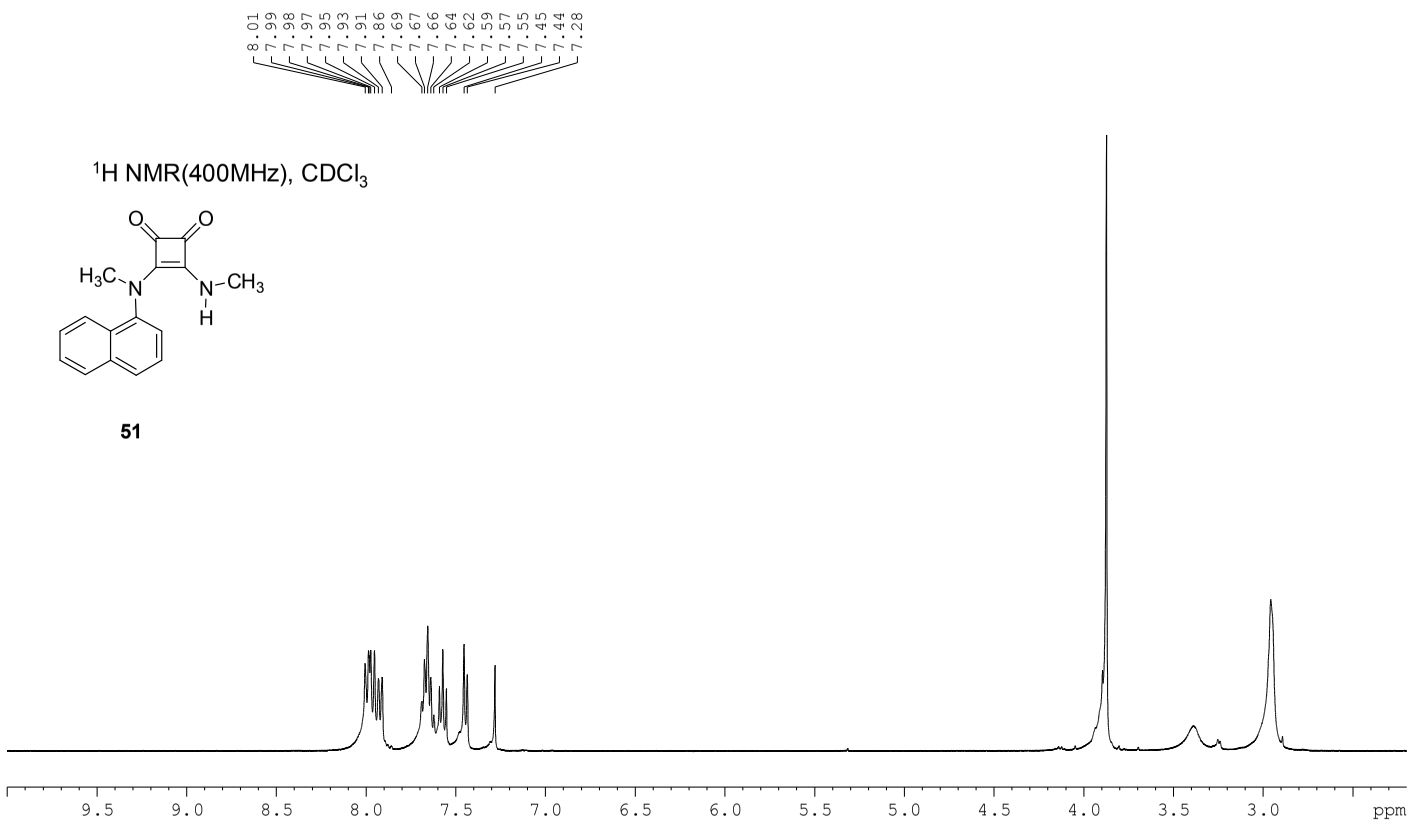


Figure 4.31: ^{1}H NMR spectra of squaramide **51** in $CDCl_3$

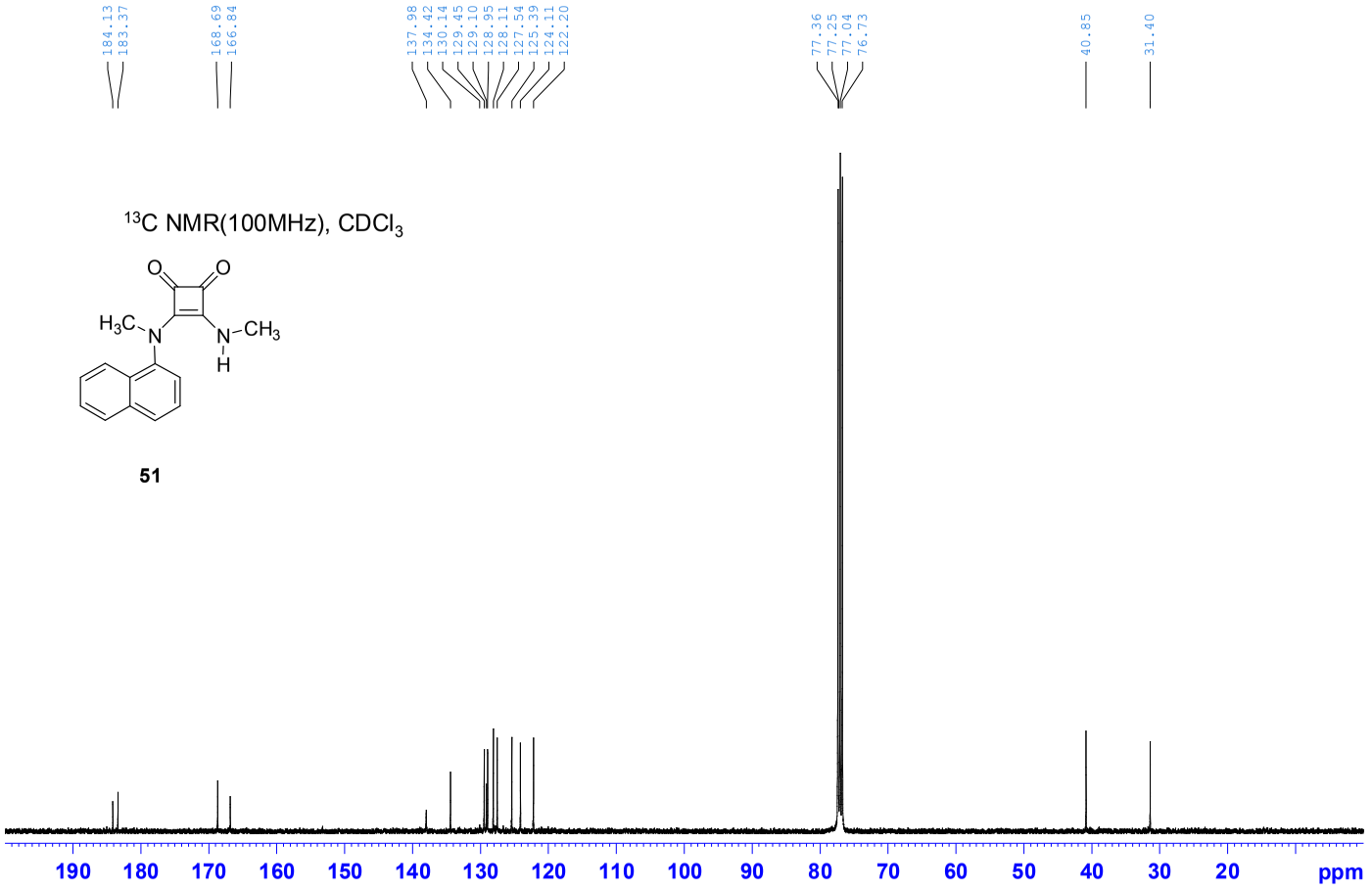


Figure 4.32: ^{13}C NMR spectra of squaramide **51** in $CDCl_3$

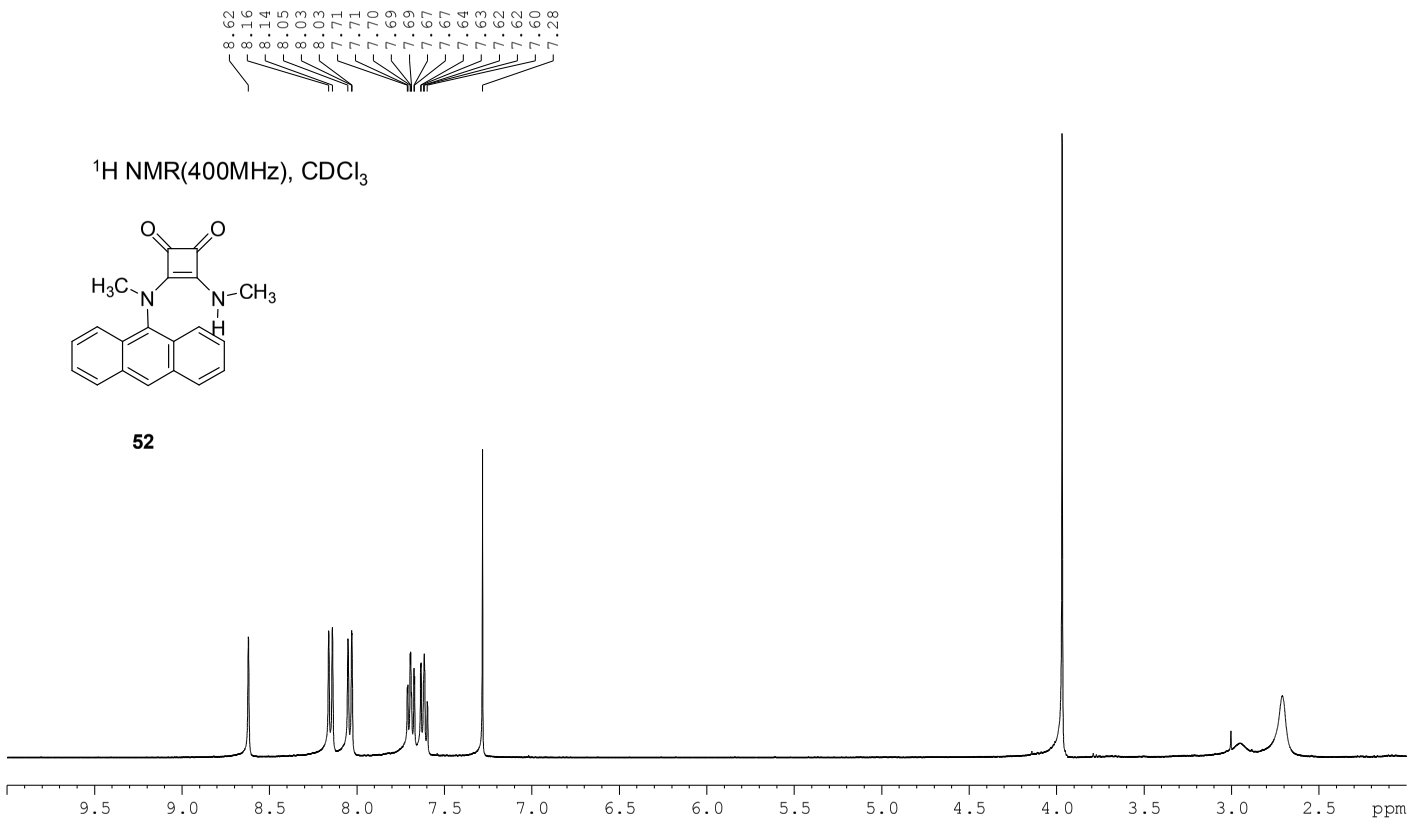


Figure 4.33: ^{1}H NMR spectra of squaramide **52** in $CDCl_3$

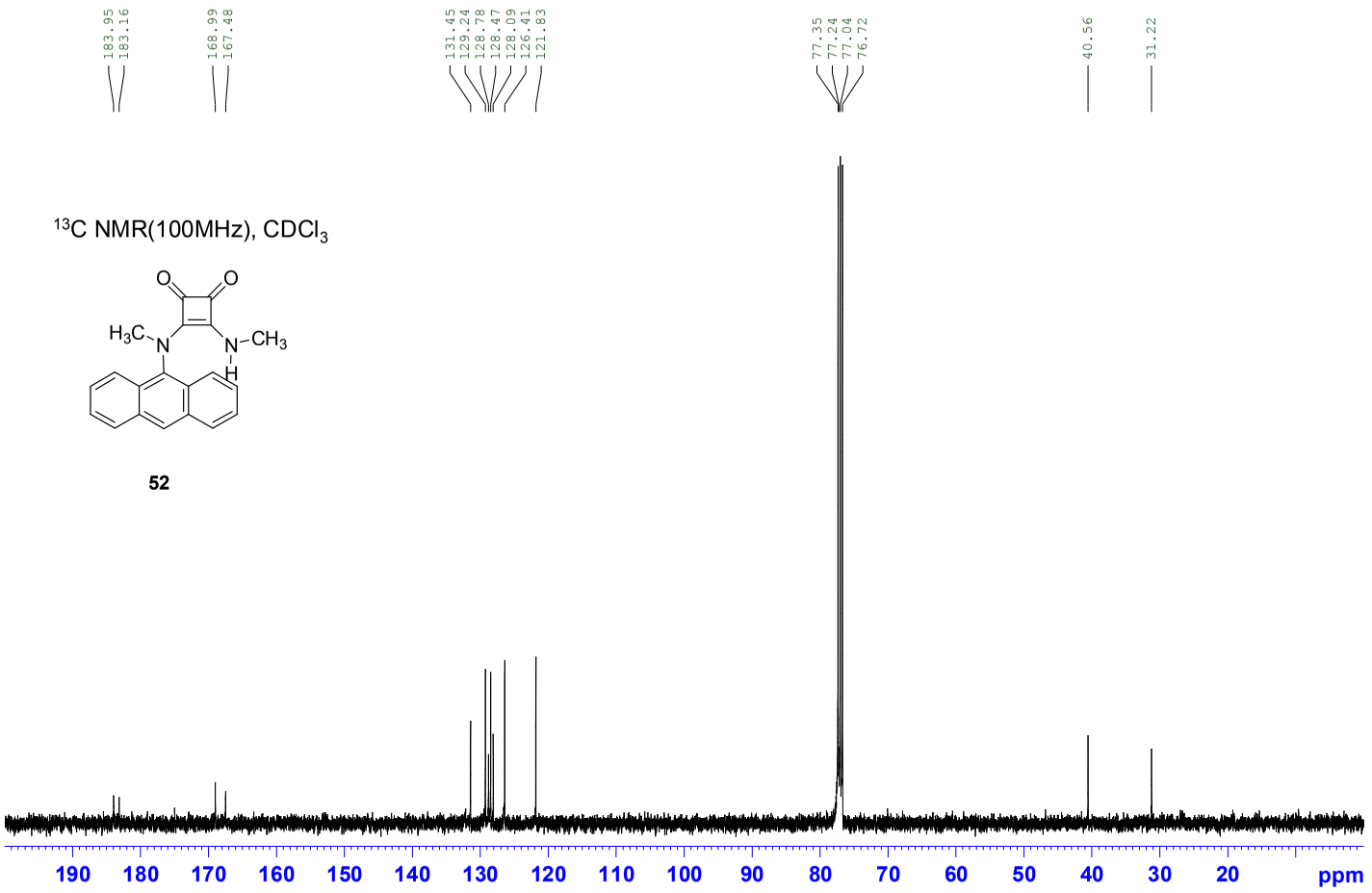


Figure 4.34: ^{1}H NMR spectra of squaramide **52** in $CDCl_3$

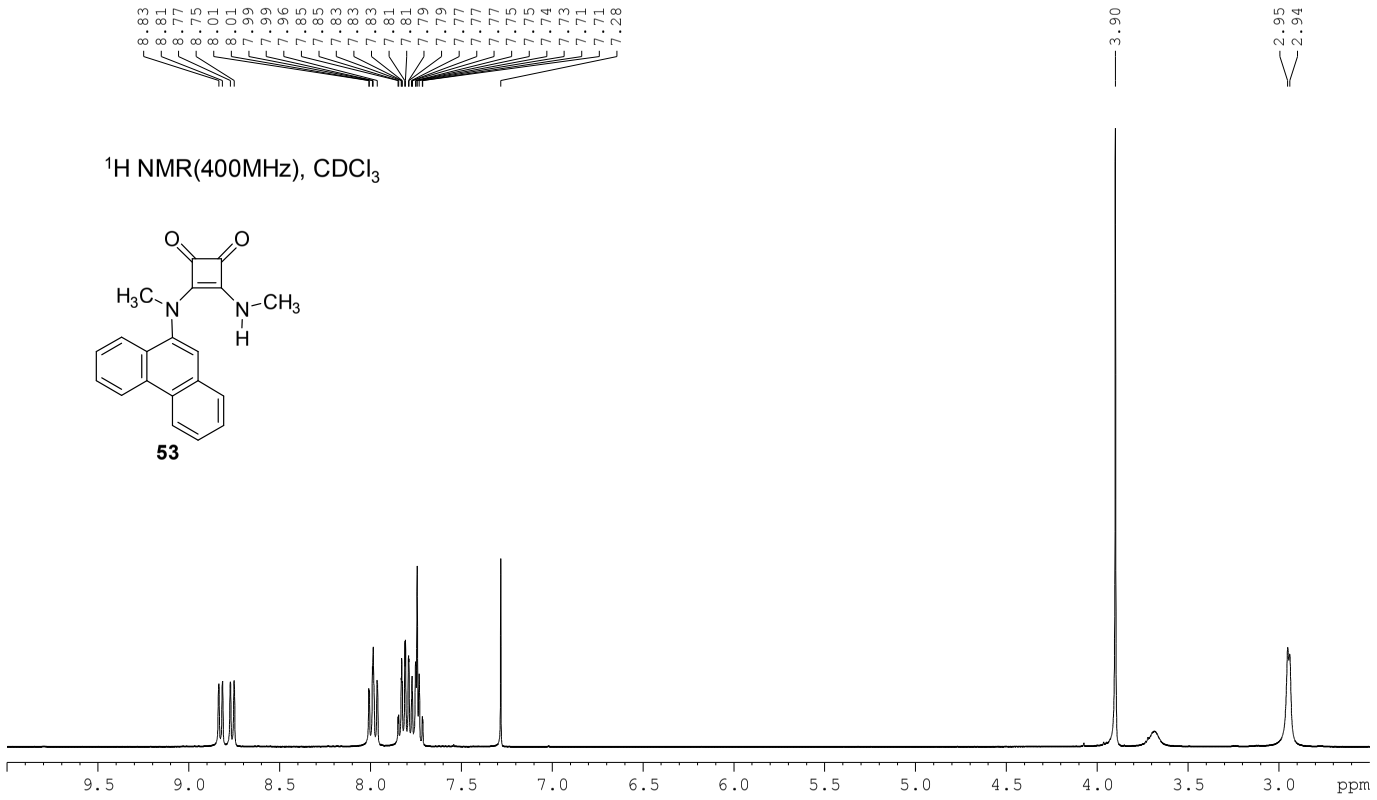


Figure 4.35: ^{1}H NMR spectra of squaramide **53** in $CDCl_3$

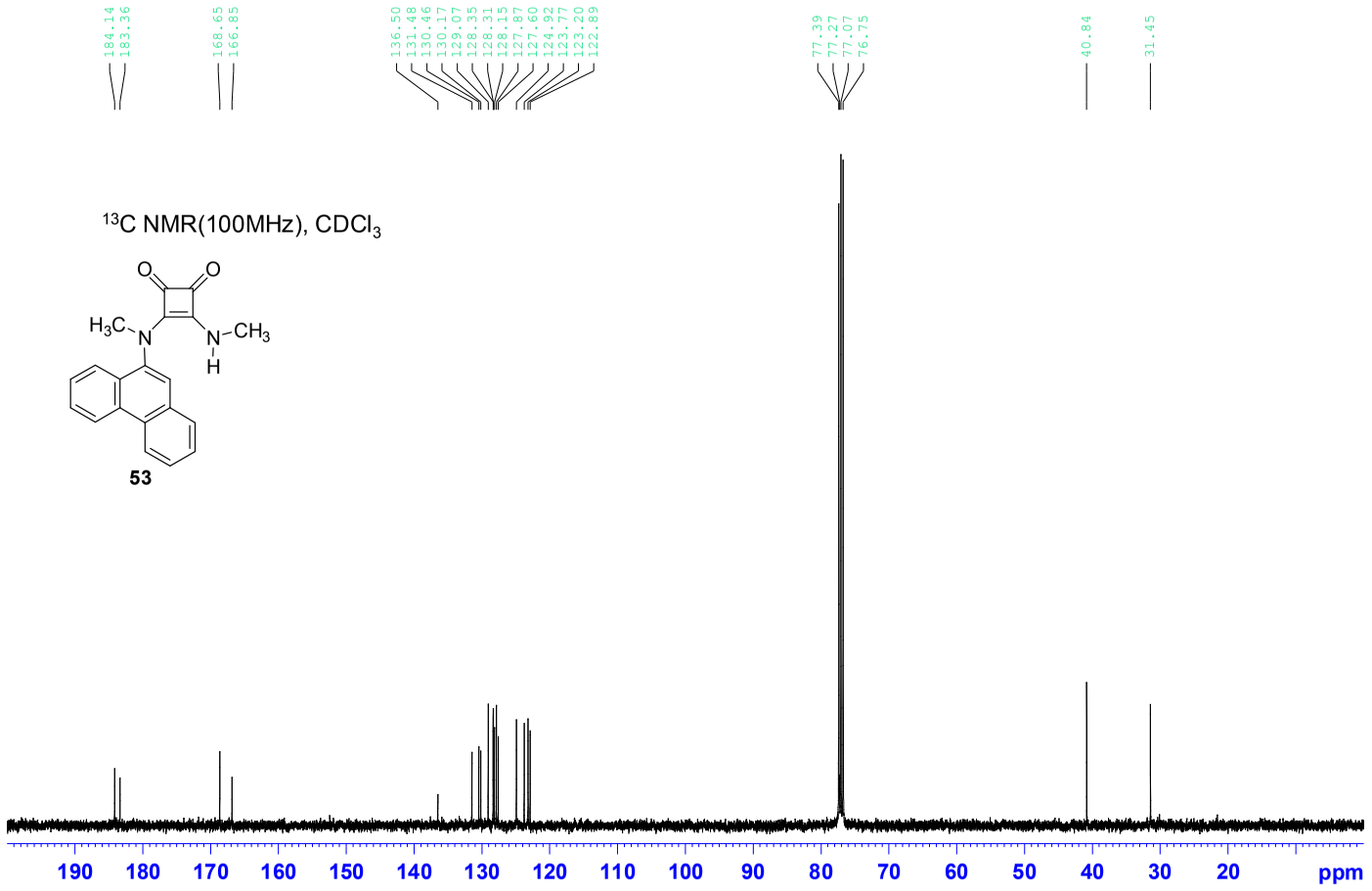


Figure 4.36: ^{13}C NMR spectra of squaramide **53** in $CDCl_3$

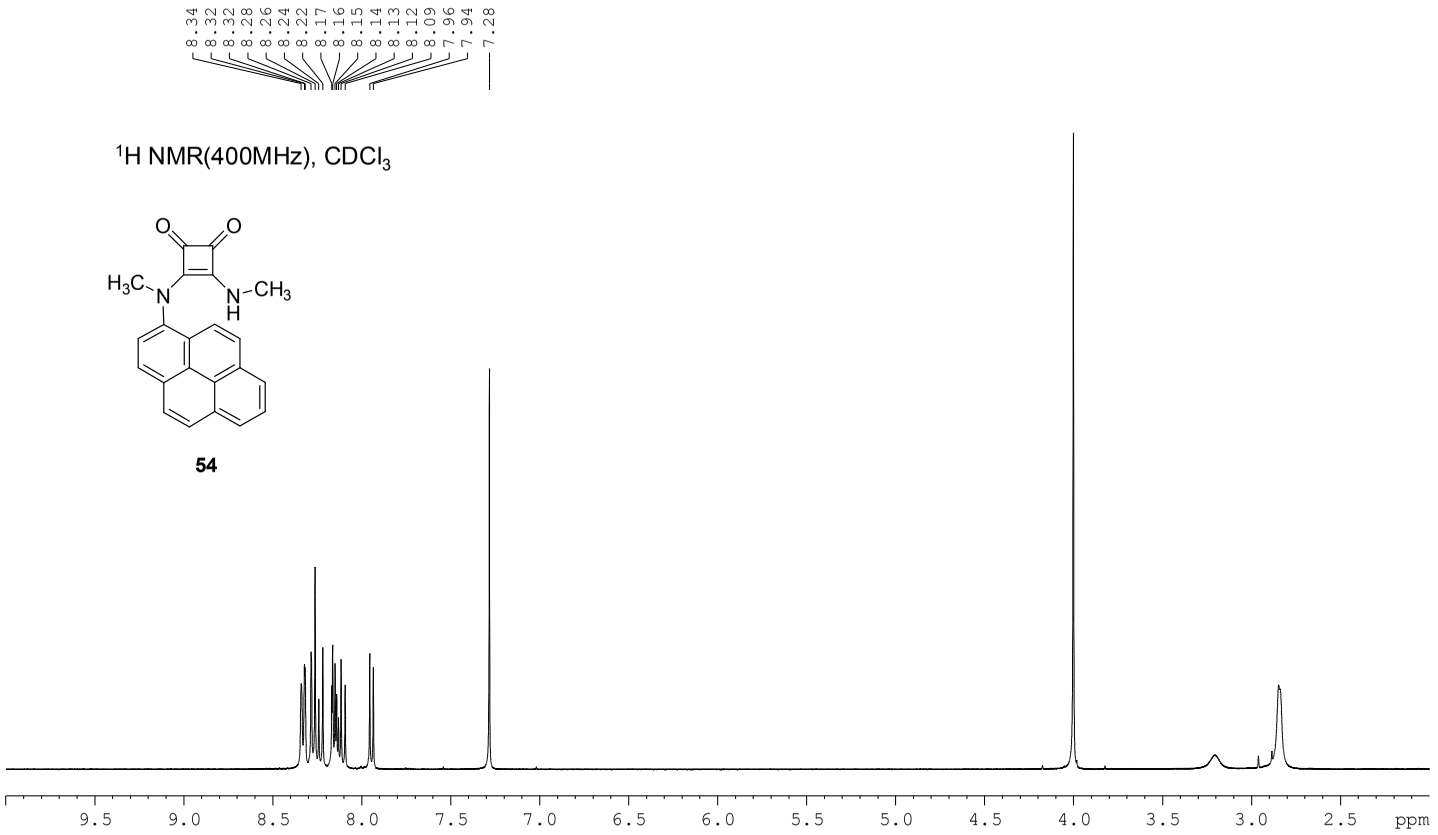


Figure 4.37: ^{1}H NMR spectra of squaramide **54** in $CDCl_3$

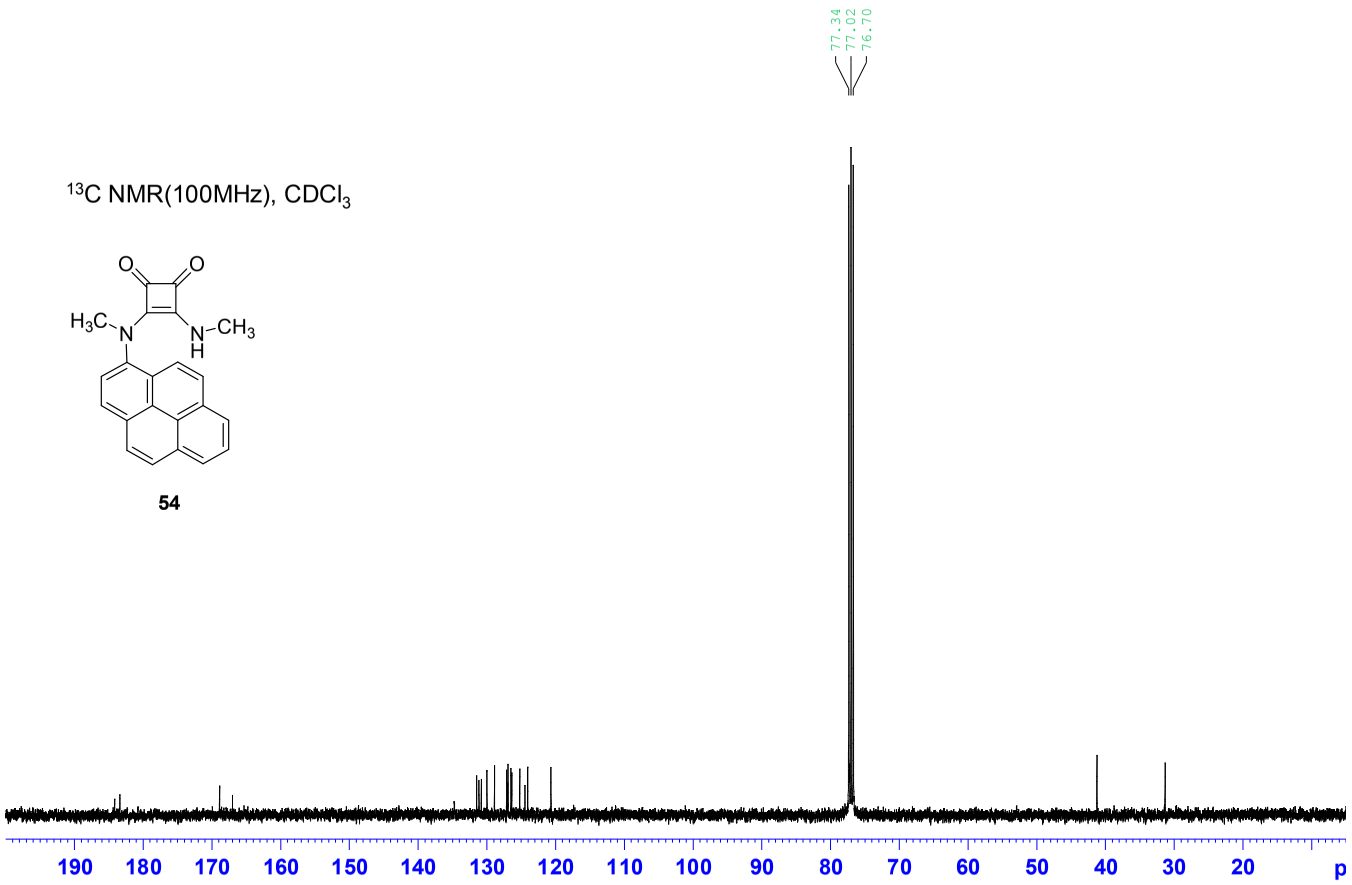


Figure 4.38: ^{13}C NMR spectra of squaramide **54** in $CDCl_3$

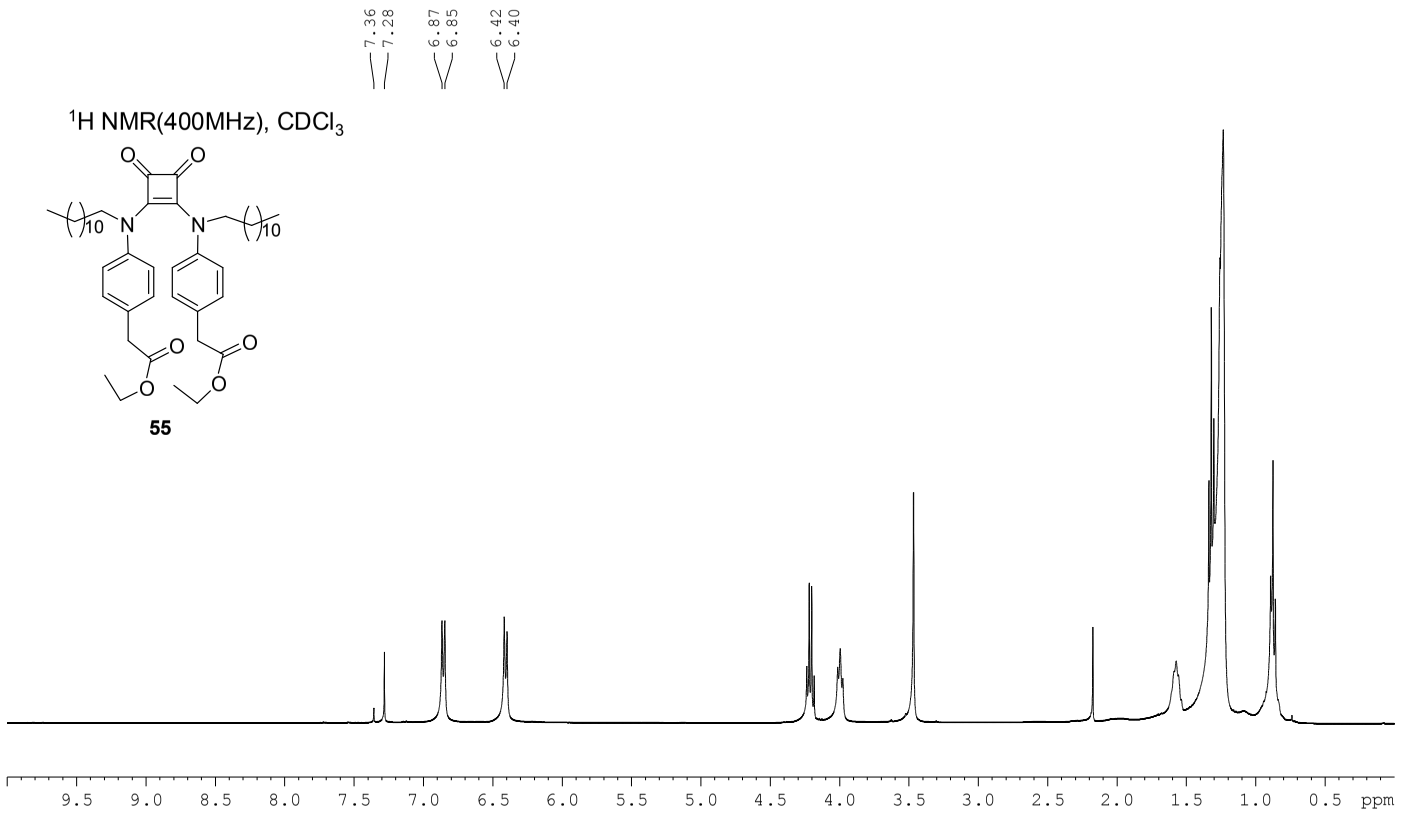


Figure 4.39: ^{1}H NMR spectra of squaramide **55** in $CDCl_3$

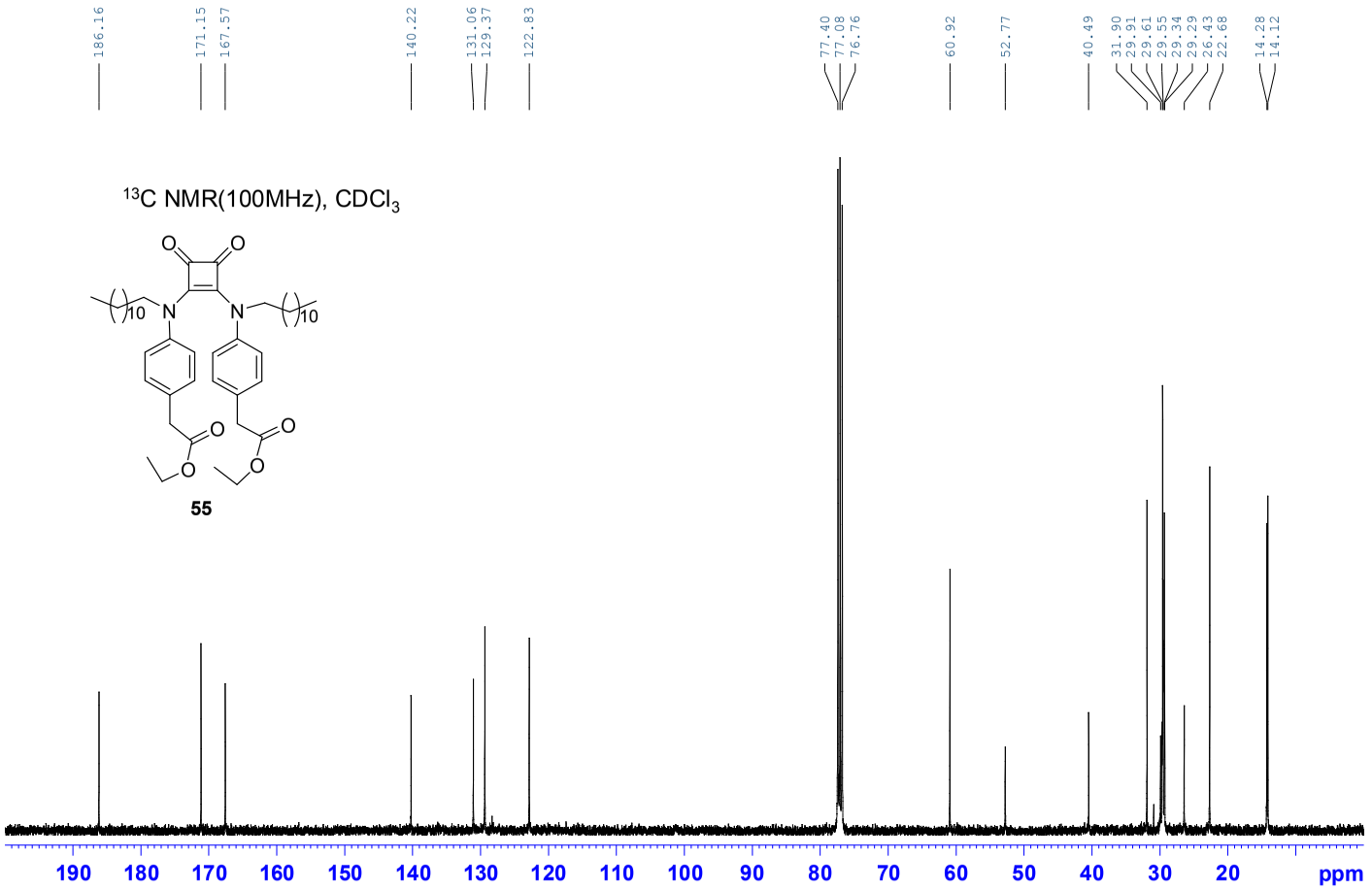


Figure 4.40: ^{13}C NMR spectra of squaramide **55** in $CDCl_3$

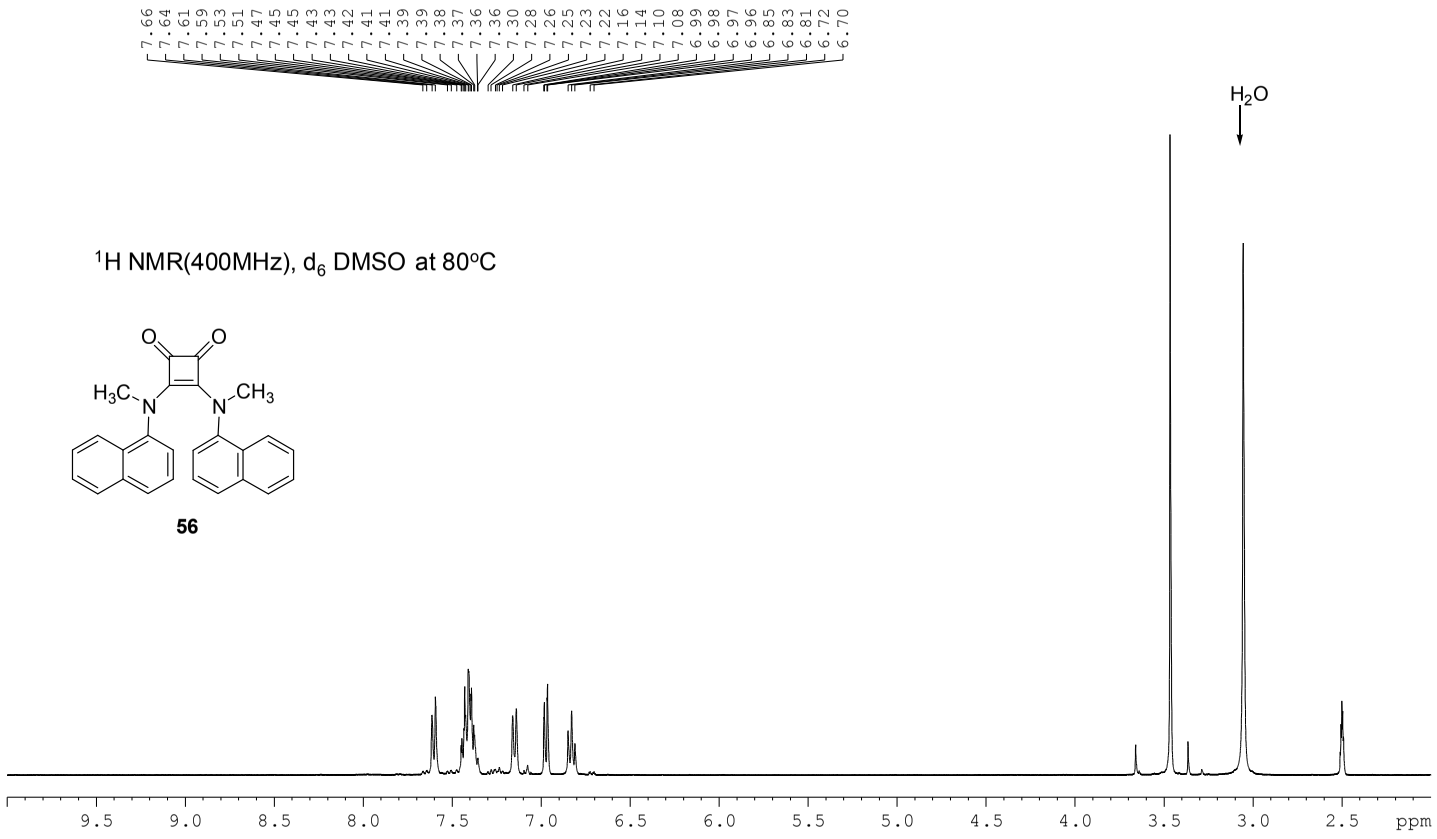


Figure 4.41: ^{1}H NMR spectra of squaramide **56** in $CDCl_3$

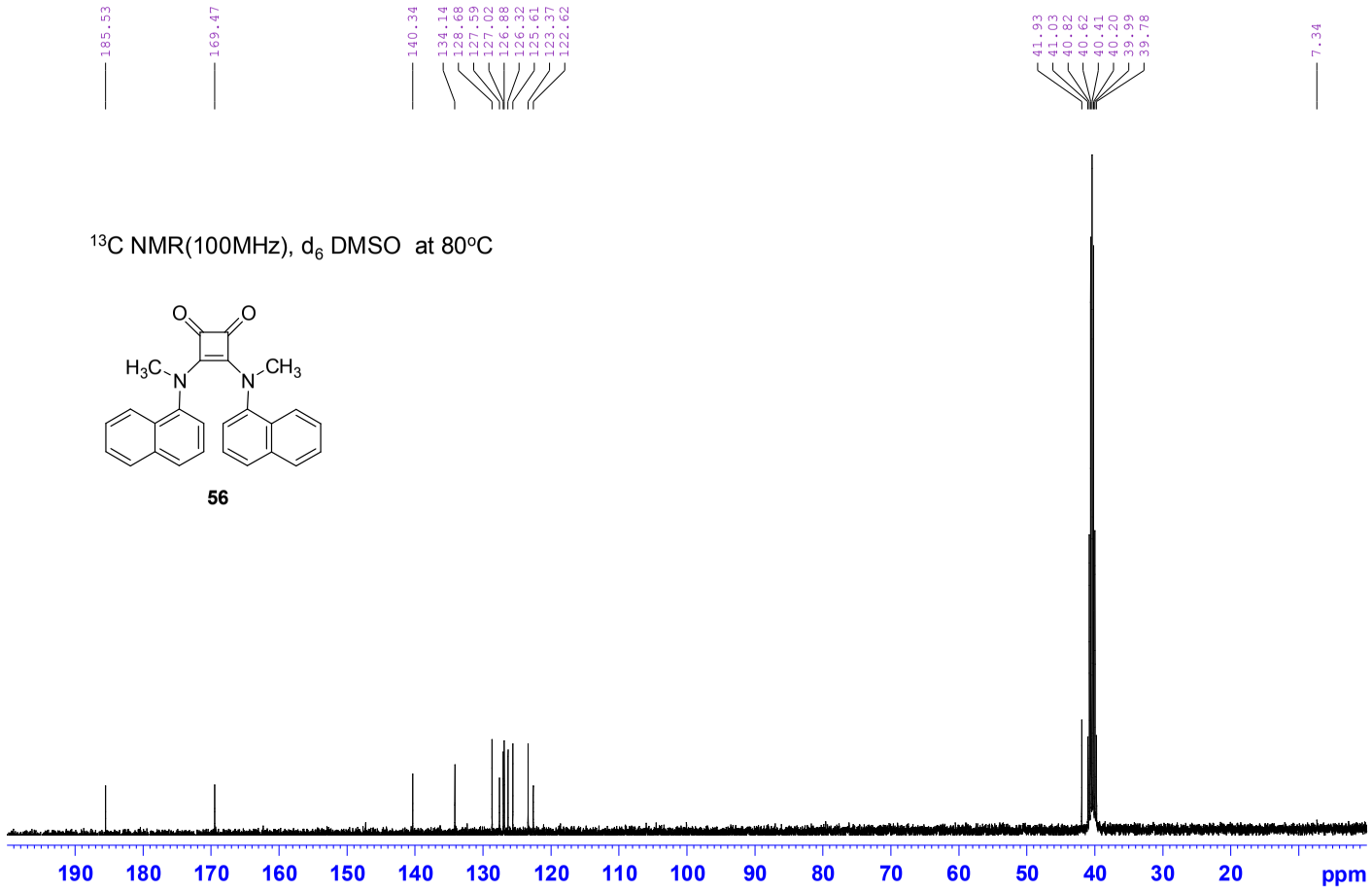


Figure 4.42: ^{13}C NMR spectra of squaramide **56** in $CDCl_3$

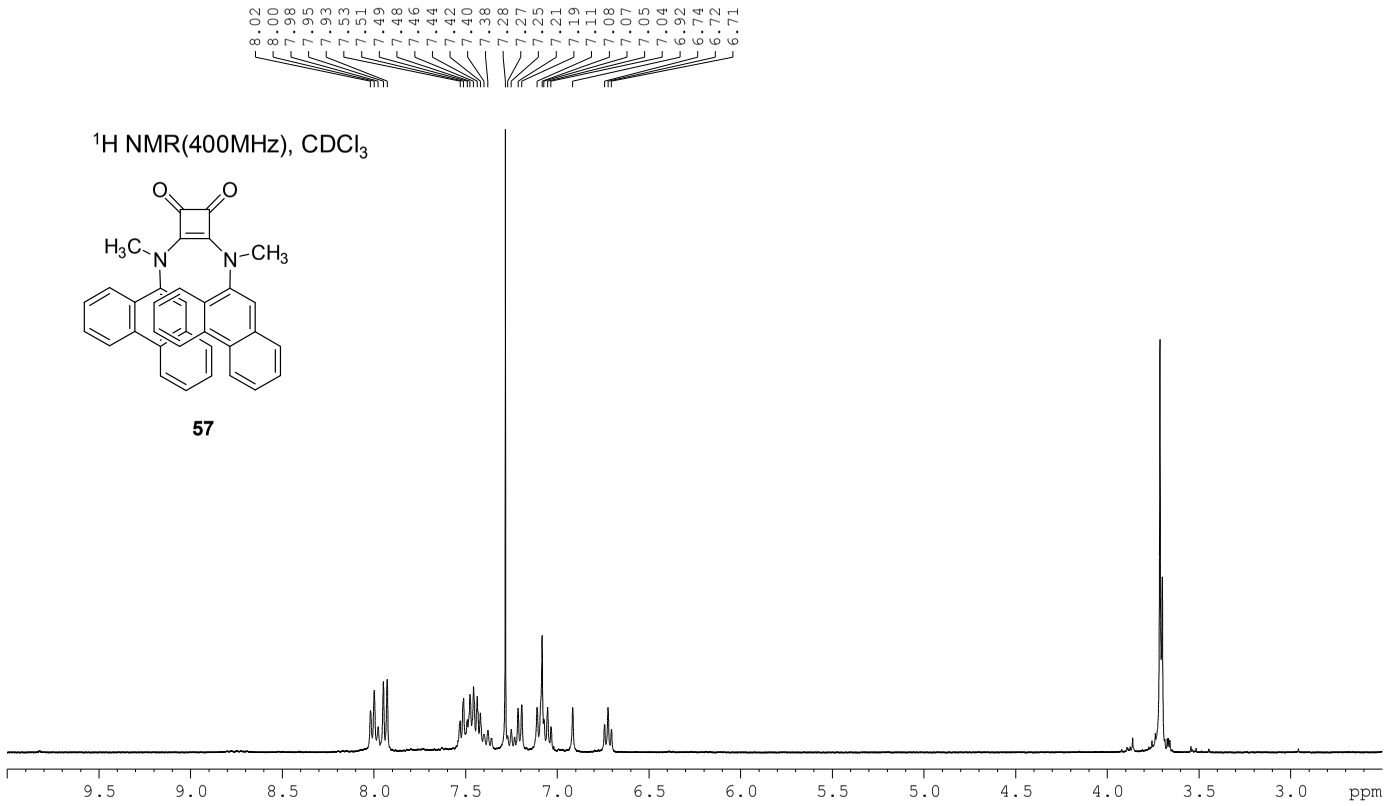


Figure 4.43: ^{1}H NMR spectra of squaramide **57** in $CDCl_3$

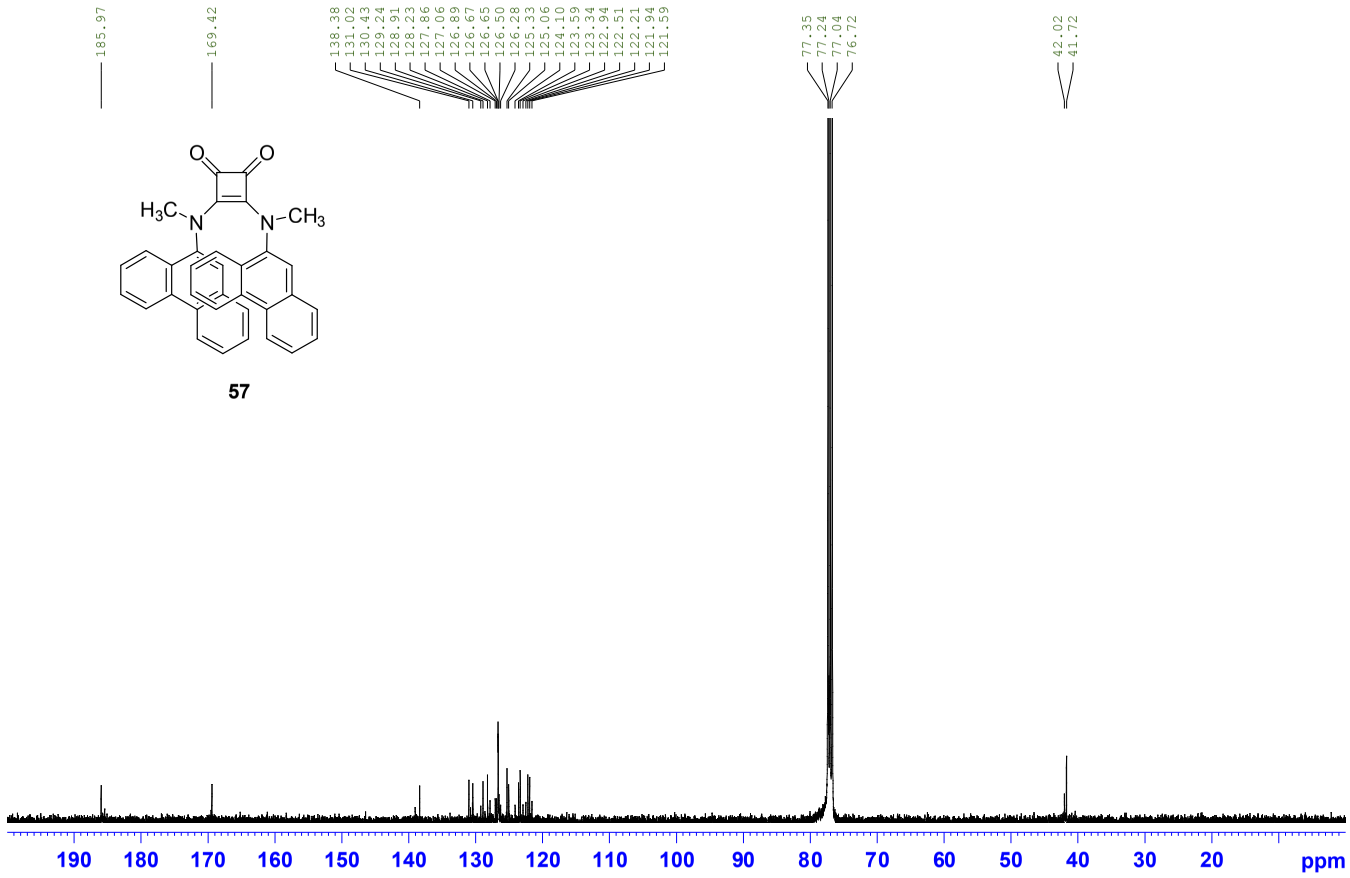


Figure 4.44: ^{13}C NMR spectra of squaramide **57** in $CDCl_3$

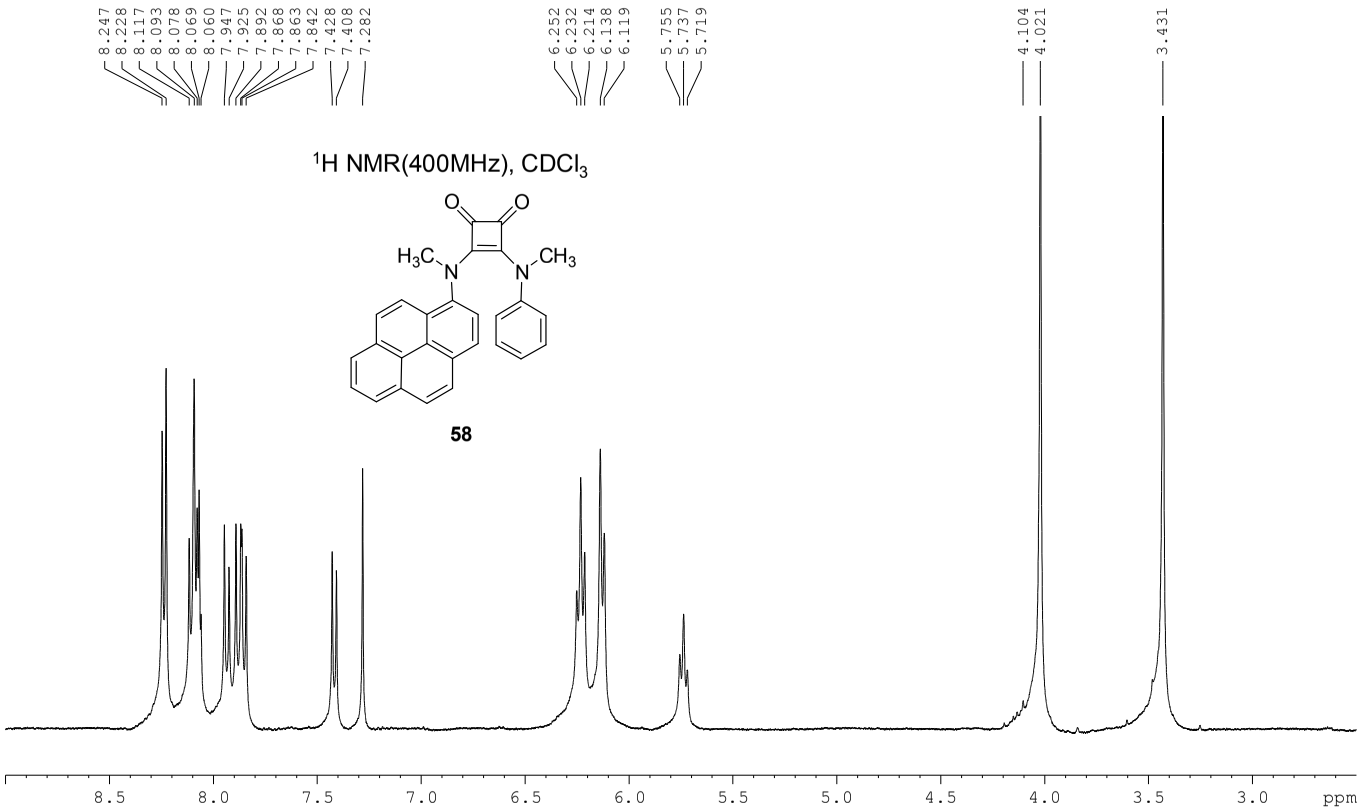


Figure 4.45: ^{1}H NMR spectra of squaramide **58** in $CDCl_3$

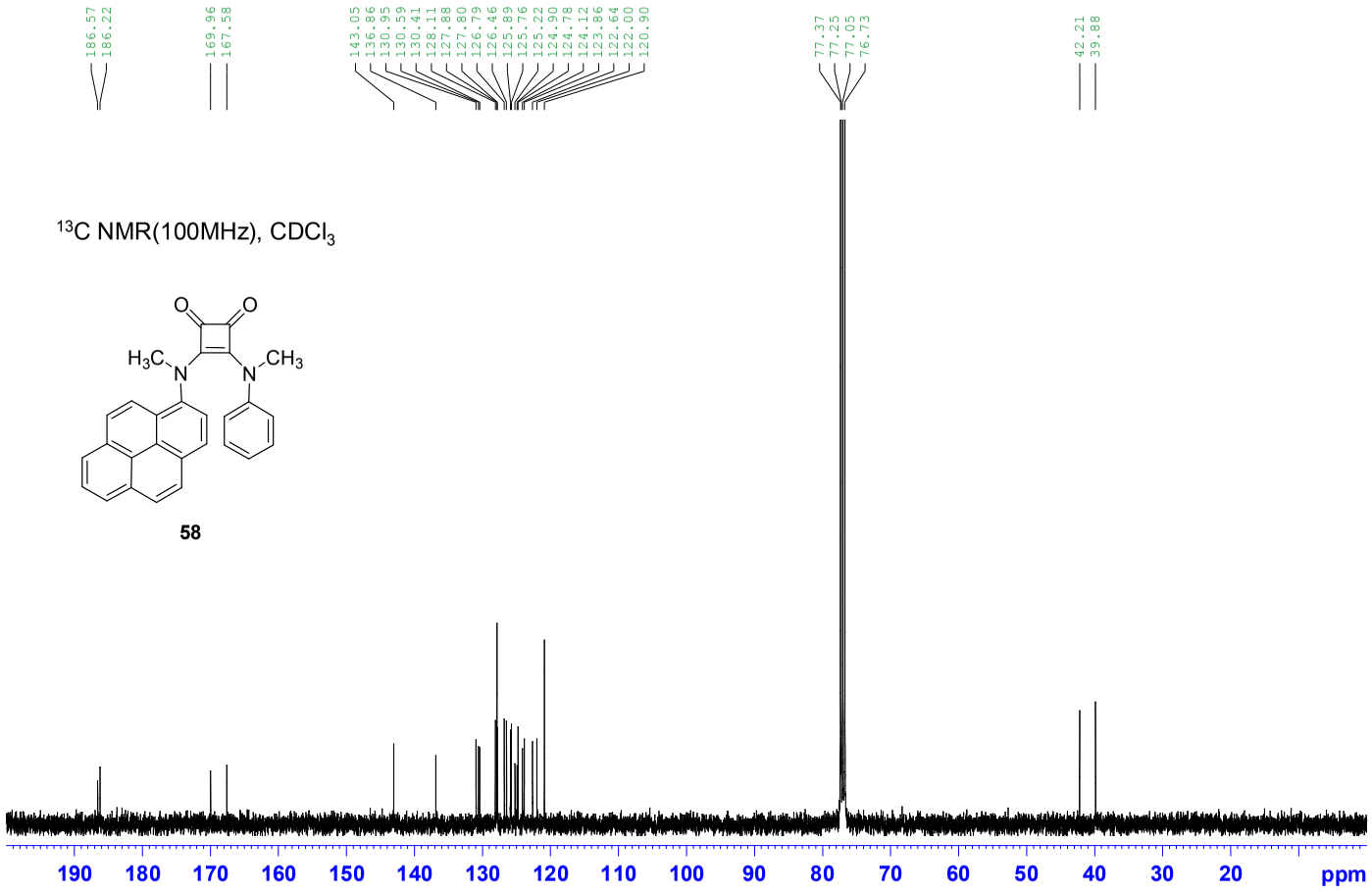


Figure 4.46: ^{13}C NMR spectra of squaramide **58** in $CDCl_3$

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Chapter 5

Attempts toward the use of tertiary diaryl squaramides as molecular switches

5.1 Introduction:

Studies involving small molecules capable of functioning as molecular switches[1] in response to external stimuli are of immense interest. Different stimuli commonly used are: chemical (pH, solvent polarity change), photochemical[2] (photoisomerization) or electrochemical[3] (redox reactions). Conformational switching via amide[4] C-N bond rotation is of particular interest due to its relevance to protein function. For instance, cis–trans isomerization in proline-amide[5] was shown to be responsible for ion channel gating in neurotransmitter receptors.

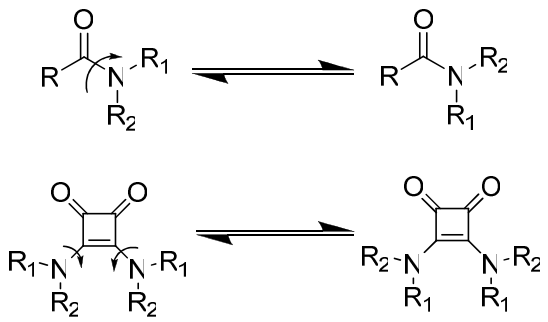


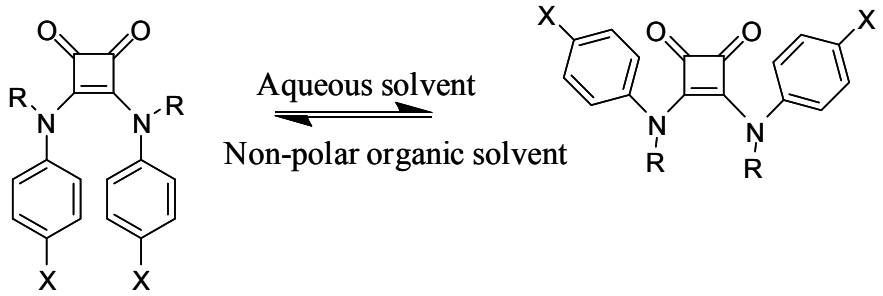
Figure 5.1: Possible conformational isomer in amide and squaramide

Synthetic molecular switches that rely on rotation around amide C-N bond are rare because typical rotational barriers[6] are about 20 kcal/mol owing to the partial double bond character. For tertiary squaramides, the rotational barrier has been shown to be about 16 Kcal/mol[7] – the lower value in squaramides compared to amides is likely due to the presence of cross-conjugation. With this knowledge, we became interested in studying large-amplitude conformational switching in tertiary squaramides (Figure 5.2) using

chemical stimuli such as a change in solvent polarity and metal ion chelation. Our attempts in this direction are described in this chapter.

5.2 Proposed hydrophobically driven molecular switches:

Symmetrical amphiphilic tertiary diaryl squaramides (Figure 5.2) containing both non-polar and polar substituents appended to the tertiary nitrogen were envisioned to function as hydrophobically driven[8] molecular switches. We speculated that in a non-polar organic solvent, the hydrocarbon side chains (R) would be in an extended *EE* conformation with the favorable aryl π-π interactions further stabilizing this conformation. We further anticipated that with a change to an aqueous solvent or apolar organic solvent, such as methanol, the conformation would flip to *ZZ* so that the hydrocarbon side chains will come together to minimize solvent exposure. Thus, we envisaged symmetrical amphiphilic tertiary diaryl squaramides to serve as hydrophobically-driven reversible molecular switches.



EE *ZZ*

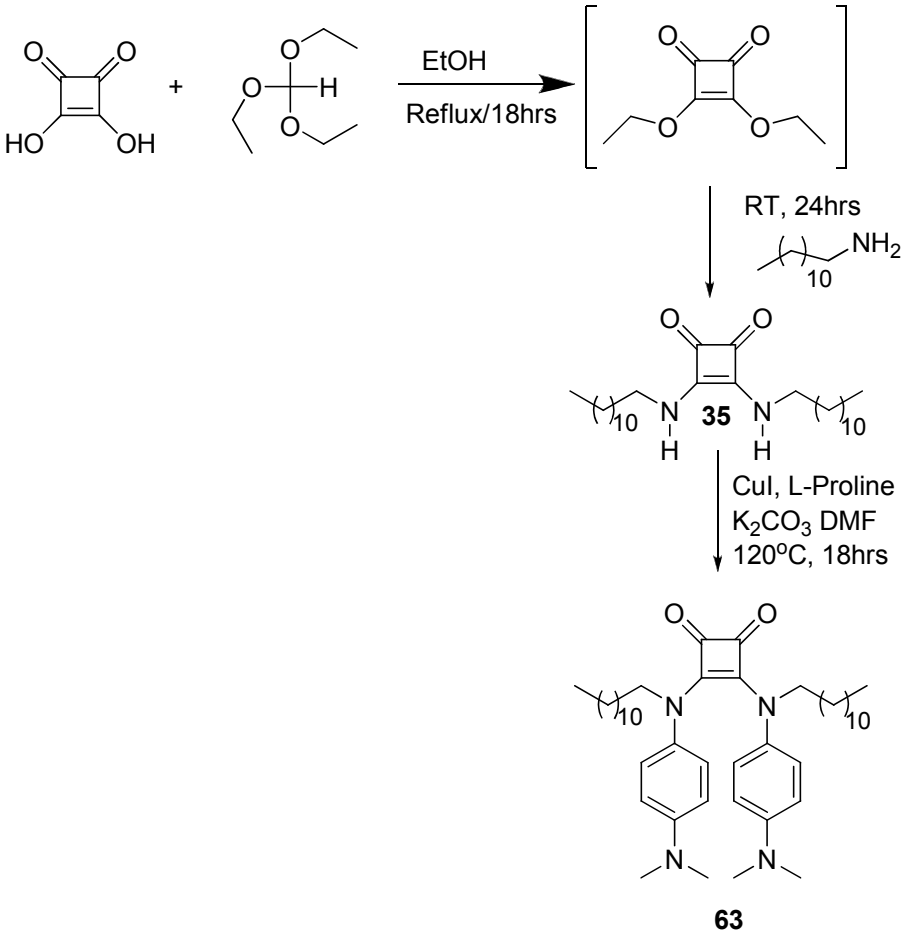
R= Long alkyl chain such as dodecyl chain
X= Charged species such as ammonium salt

Figure 5.2: Proposed hydrophobic driven molecular switch

5.2.1 Synthesis of tertiary diaryl squaramide:

Synthesis of squaramide **63** was achieved by amidation of diethyl squarate followed by treating this secondary squaramide to the copper catalyzed N-arylation protocol developed in our laboratory[10] (Chapter 4). For the initial work, symmetrical amphiphilic tertiary diaryl squaramides, where one of the substituents attached to tertiary nitrogen is polar and the other is non-polar (Scheme 5.1), were designed to function as hydrophobically driven molecular switches.

Scheme 5.1: Synthesis of squaramide **63**



5.2.2 Results and discussion:

Analysis of the conformational preferences of the amphiphilic squaramide was performed using ^{1}H NMR in different solvents. The ^{1}H NMR spectra of squaramide **63** in $CDCl_3$ (non-polar solvent) confirmed that the two phenyl rings are in a co-facial arrangement indicated by the upfield shift of aromatic protons compared to monoaryl tertiary squaramide **66**. Since we speculated that a change in solvent polarity could trigger a conformational switch, we were interested in examining the ^{1}H NMR of **63** in D_2O. Unfortunately, the ^{1}H NMR spectra of **63** or that of it's doubly protonated derivative could not be recorded in D_2O due to its insolubility probably due to the presence of the aliphatic dodecyl chains. To circumvent the problem of insolubility in water, we synthesized squaramide **64** with decreased alkyl chain length (butyl side chain).

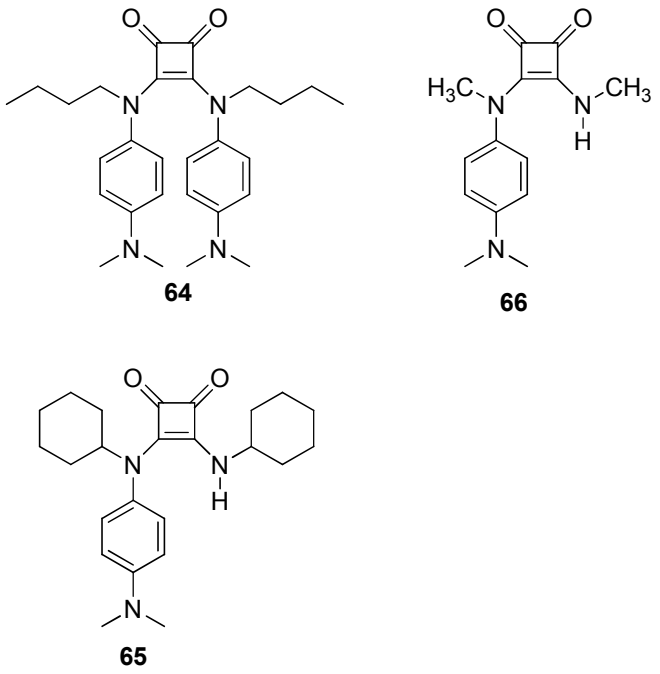


Figure 5.3: Tertiary aryl squaramides for molecular switches

As expected, **64** with decreased alkyl chain length was soluble both in $CDCl_3$ and in D_2O with 3%TFA. This permitted us to study the conformation of this squaramide as a function of solvent polarity. Squaramide **66** was used as a control compound. Examination of ^1H NMR spectra of squaramide **64** in both polar and non-polar solvents revealed no significant changes in the ^1H NMR chemical shifts. Instead, only changes possibly attributable to the protonation of the N, N-dimethyl amino group by TFA were observed. We speculated, based on this result, strong π-π interactions between the phenyl groups likely prevented conformational switching in squaramide **64**. Therefore, we focused our attention on preparing mono-aryl substituted squaramide **65.** However, from the work carried out on this compound it is not entirely clear to us if the observed ^1H NMR spectral changes, upon changing solvent from $CDCl_3$ and D_2O with 3% TFA, are due to a conformational switch or ring interconversion of the cyclohexyl group.

5.3 Proposed alkali metal induced molecular switches:

In an alternate approach to utilizing tertiary diaryl squaramide as a molecular switch, we envisioned the use of alkali ion complexation[11] as the chemical stimulus.

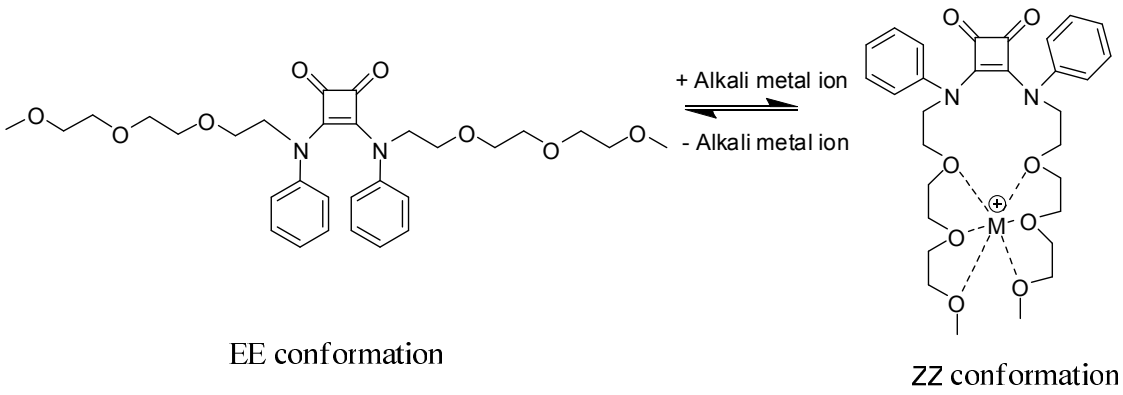


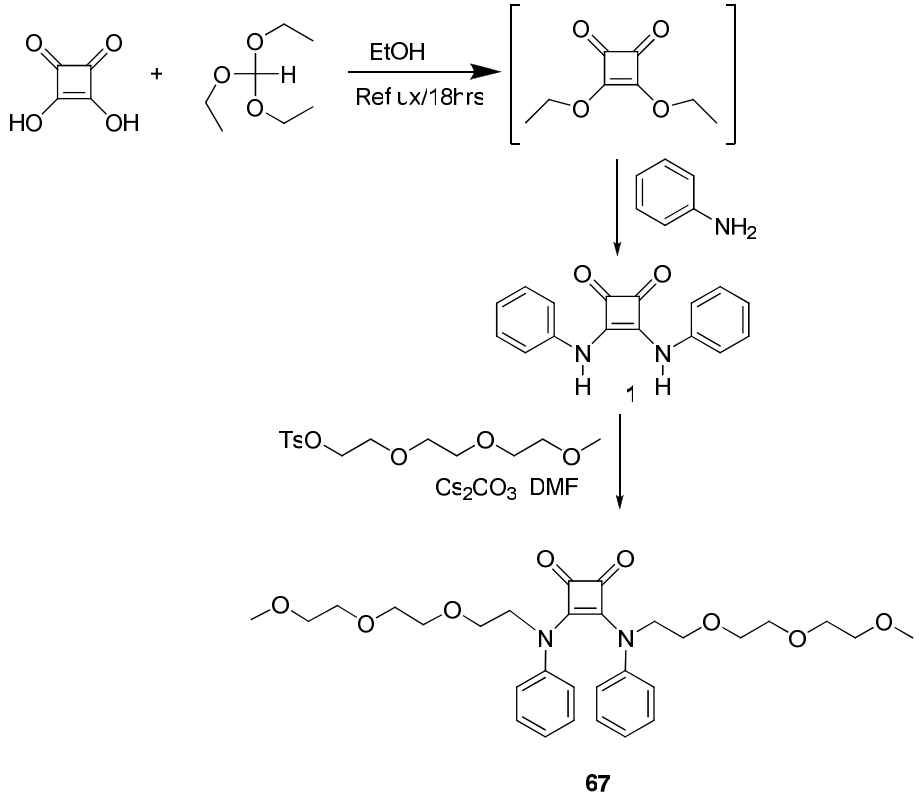
Figure 5.4: Proposed alkali metal induced conformational switch

We postulated that if we appended a polyoxygenated side chain to the tertiary nitrogen atom of the squaramide, we could possibly trigger a conformational switch driven by metal ion complexation. A model compound with proposed molecular switching mechanism is shown in Figure 5.4.

5.3.1 Synthesis of semi-crown ether squaramide (67):

The conventional copper iodide based N-arylation was not pursued since copper might complex with the alkoxy group, limiting its availability to act as catalyst. Therefore, synthesis of semi-crown squaramide was achieved starting from esterification of squaric acid by triethyl orthoformate to obtain diethyl squarate. The diethyl squarate was then treated with aniline to synthesize diphenyl squaramide, which upon alkylation yielded squaramide **67.**

Scheme 5.2: Synthesis of squaramide **67**



5.3.2 Results and discussion:

The ^{1}H NMR spectra of squaramide **67** in acetonitrile revealed that both the phenyl groups are in co-facial arrangement (upfield shift of aromatic protons) with the alkoxy groups in extended state. Since potassium, lithium and cesium ions are well known to complex with crown ethers, we were interested in examining if these cations can drive the conformational switch and form the complex leading to crown ether-like conformation. The ^{1}H NMR spectrum of uncomplexed squaramide **67** when overlayed with the potassium- and cesium-complexed squaramide **67** revealed no difference, indicating the absence of expected molecular switch. However, when lithium was added to squaramide **67**, broadening and chemical shift changes in the aromatic and alkoxy signals were observed in NMR spectrum (Figure 5.5). This broadening could result from the lithium complexation with either alkoxy oxygen or with the cyclobutenedione carbonyls. Future work on addressing these and other issues will be carried out at the University of Minnesota, Rochester in the laboratories of Dr. Rajeev Muthyala.

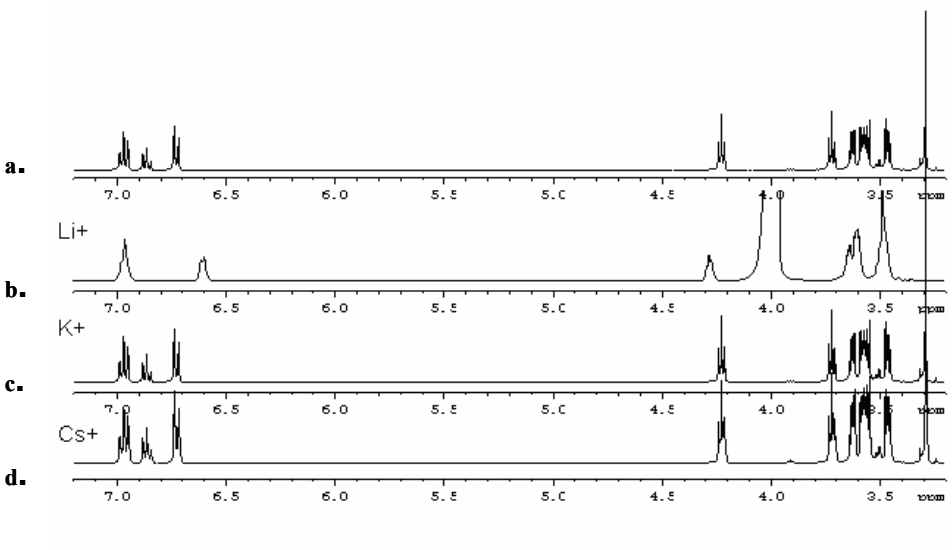


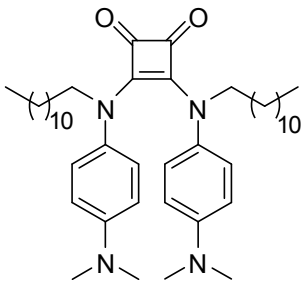
Figure 5.5: ^{1}H NMR Overlay spectrum of semi crown ether squaramide **67** in CD_3CN a) uncomplexed squaramide **67** b) **67** with Li^{+} and c) **67** with K^{+}. c) **67** with Cs^{+}.

5.4 Conclusions:

The copper catalyzed N-arylation of secondary squaramide developed in our laboratory was used to synthesize wide variety of amphiphilic tertiary diaryl squaramides. This simple N-arylation procedure allowed us to explore whether tertiary diaryl squaramides function as hydrophobically driven molecular switches. The experimental data obtained this far showed no evidence of hydrophobically driven molecular switching in tertiary diaryl squaramide with changes in solvent polarity. An alternative metal ion induced conformational switching appears promising but more experiments are needed.

5.5 General procedure for di-N-arylation:

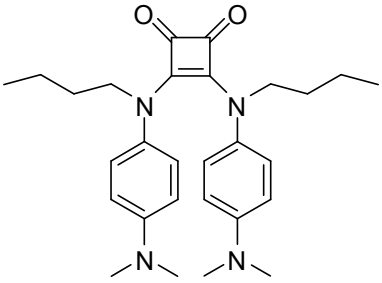
5.5.1 Preparation of 3, 4-bis ((4-(dimethylamino) phenyl) (dodecyl) amino) cyclobut-3-ene-1, 2-dione (63):



To a 25 ml RB flask was added Copper Iodide (95 mg, 0.5mmol), L-proline (58 mg, 0.5 mmol), potassium carbonate (345 mg, 3 mmol) and anhydrous DMF (1 ml). The mixture was stirred at room temperature under nitrogen atmosphere for 20 minutes. 4-bromo-N, N-dimethylaniline (597 mg, 3 mmol) and 3, 4-bis (dodecyl amino) cyclobut-3-ene-1, 2-dione (448 mg, 1 mmol) were then added and the reaction temperature increased to 120 ^{o}C and maintained for 18 hours. The reaction mixture was cooled to room temperature, diluted with ethylacetate (15 ml), filtered and concentrated. The residue was chromatographed (2:3 Ethyl acetate / hexane) to yield the title compound in 50% yield. ^{1}H NMR ($CDCl_3$): 6.41(d, 4H, J = 8.0), 6.30(d, 4H, J = 8.2), 3.94 (t, 4H, J = 7.6), 2.90 (s, 12H), 1.53 (m, 4H), 1.30(m, 36H), 0.88 (t, 6H, J = 7.8). ^{13}C

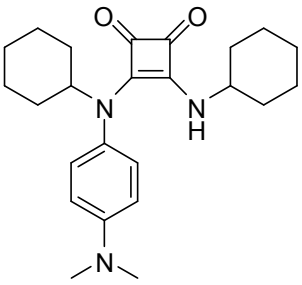
NMR ($CDCl_3$): 185.5, 167.2, 148.2, 131.7, 123.9, 112.4, 53.0, 40.7, 31.9, 29.6, 29.6, 29.5, 29.3, 26.4, 22.6, 14.1..

5.5.2 Preparation of 3, 4-bis (butyl (4-(dimethylamino) phenyl) amino) cyclobut-3-ene-1, 2-dionedione (64):



Similar to the procedure **63**, title compound obtained in 48% yield. ^{1}H NMR ($CDCl_3$): 6.41(d, 4H, *J* = 8.0), 6.30 (d, 4H, *J* = 8.0), 3.39 (t, 4H, *J* = 7.6), 2.89 (s, 12H), 1.51 (m, 4H), 1.33 (m, 4H), 0.88 (t, 6H, *J* = 7.2). ^{13}C NMR ($CDCl_3$): 185.4, 167.3, 148.2, 131.2, 123.9, 112.4, 52.8, 40.7, 31.6, 19.6, 13.8.

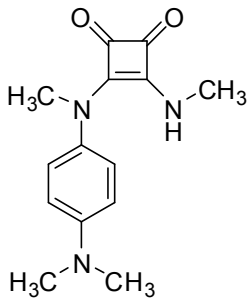
5.5.3 Preparation of 3-(cyclohexyl (4-(dimethylamino)phenyl)amino)-4-(cyclohexylamino) cyclobut-3-ene-1,2-dione (65):



To a 25ml RB flask was added copper Iodide (95 mg, 0.5 mmol), L-proline (58 mg, 0.5 mmol), potassium carbonate (345 mg, 3 mmol) and anhydrous DMF (1 ml). The mixture was stirred at room temperature under nitrogen atmosphere for 20 minutes and 4-bromo-N, N-dimethylaniline (597 mg, 3 mmol) and 3, 4-bis (cyclohexyl amino) cyclobut-3-ene-1, 2-dione (276 mg, 1 mmol) were then added and the reaction temperature increased to 90 ^{o}C and maintained for 18 hours. The reaction mixture was cooled to room temperature, diluted with ethylacetate (15 ml), filtered and concentrated. The residue was chromatographed (2:3 Ethyl acetate / hexane) to yield the title compound in 51% yield. ^{1}H NMR ($CDCl_3$): 7.05(d, 2H, *J* = 8.0), 6.67 (d, 2H, *J* = 7.8),

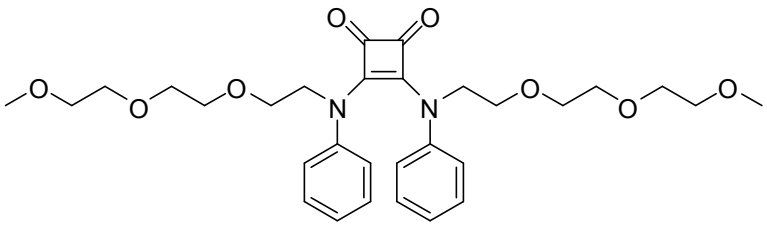
4.5 (m, 1H), 3.9 (m, 1H,), 3.5 (m, 1H), 3.02 (s, 6H,) 1.9-0.98 (m, 20H). ^{13}C NMR ($CDCl_3$):182.7, 182.7, 167.6, 167.1, 150.3, 130.1, 125.1, 111.2, 60.5, 51.6, 40.4, 33.7, 32.3, 25.2, 25.1, 25.0, 23.3. HRMS calculated for $C_{24}H_{33}N_3O_2$ M^+= 395.2572 obtained M^+= 395.2577

5.5.4 Preparation of 3-((4-(dimethylamino) phenyl)(methyl)amino)-4-(methylamino) cyclobut-3-ene-1,2-dione (66):



Similar to procedure **65** title compound obtained in 55% yield. ^1H NMR ($CDCl_3$): 7.05(d, 2H, *J* = 8.0), 6.72 (d, 2H, *J* = 8.0), 3.9 (s, 1H), 3.70 (s, 6H) 3.21(d, 3H, *J* = 3.2), 3.02(s, 3H). ^{13}C NMR ($CDCl_3$): 183.7, 183.7, 168.1, 165.9, 149.5, 130.4, 124.9, 112.3, 70.4, 39.8, 31.5. HRMS calculated for $C_{14}H_{17}N_3O_2$ M^+= 259.1320 obtained M^+= 259.1318

5.5.5 Preparation of 3, 4-bis ((2-(2-(2-methoxyethoxy)ethoxy)ethyl)(phenyl)amino) cyclobut-3-ene-1,2-dione (67):



To a solution of diphenyl squaramide (132 mg, 0.5 mmol) in DMF (1 ml), cesium carbonate (487 mg, 1.5 mmol) and 2-(2-(2-methoxyethoxy)ethoxy)ethyl 4-methylbenzenesulfonate (318 mg, 1 mmol) were added. The residue was chromatographed using 100% ethyl acetate to yield the title compound in 10% yield. ^1H NMR ($CDCl_3$): 6.92 (t, 4H, *J* = 7.6), 6.83 (t,

2H, J = 6.8), 6.61 (d, 4H, J = 7.6), 4.26 (t, 4H, J = 5.2), 3.74-3.54 (m, 24H), 3.38 (s, 6H). ^{13}C NMR ($CDCl_3$): 186.8, 167.6, 142.1, 129.2, 128.5, 127.3, 124.8, 122.2, 71.9, 70.6, 70.6, 70.2, 59.0, 52.2.

5.6 NMR spectra:

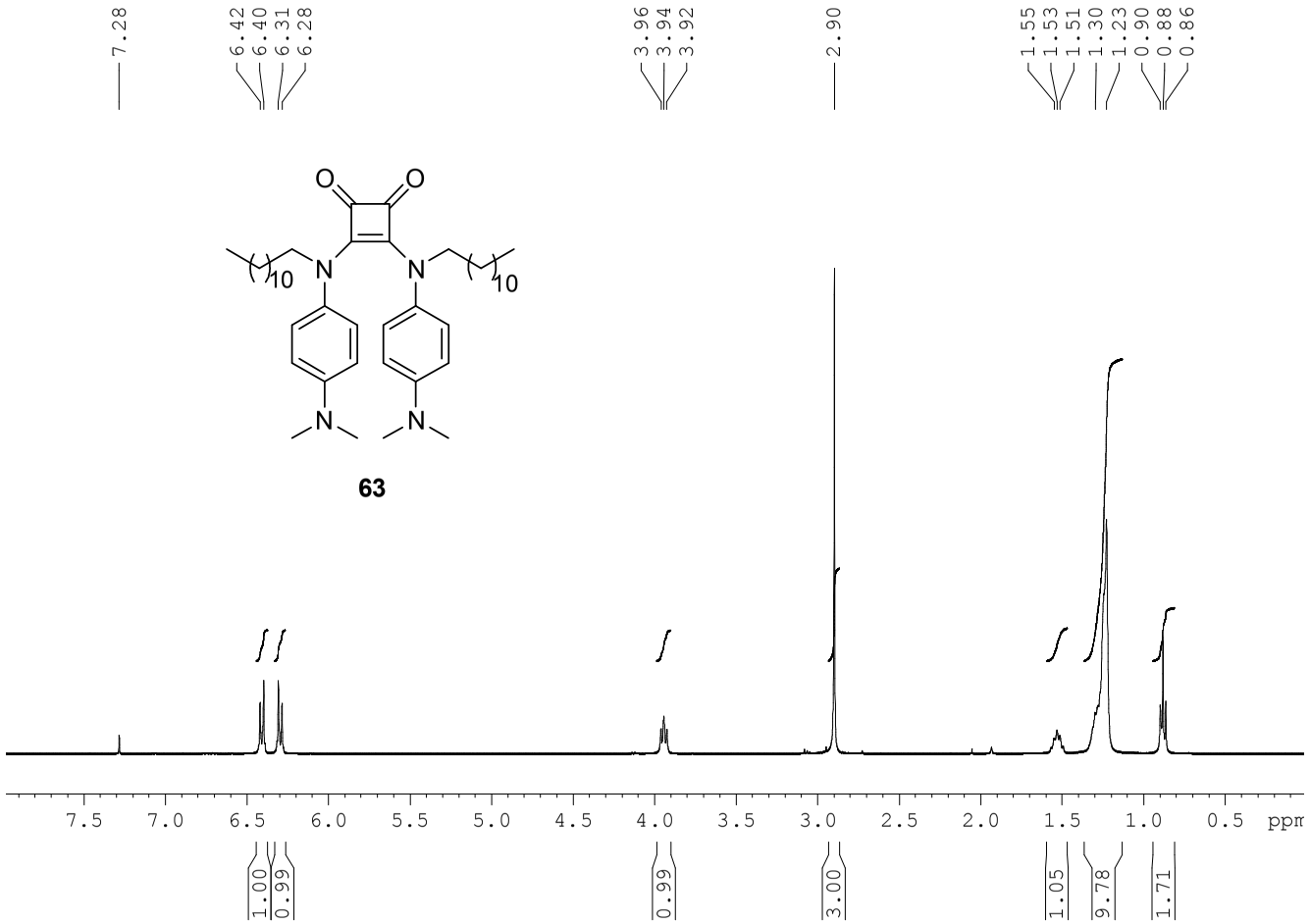


Figure 5.6: ^{1}H NMR spectra of squaramide **63** in $CDCl_3$

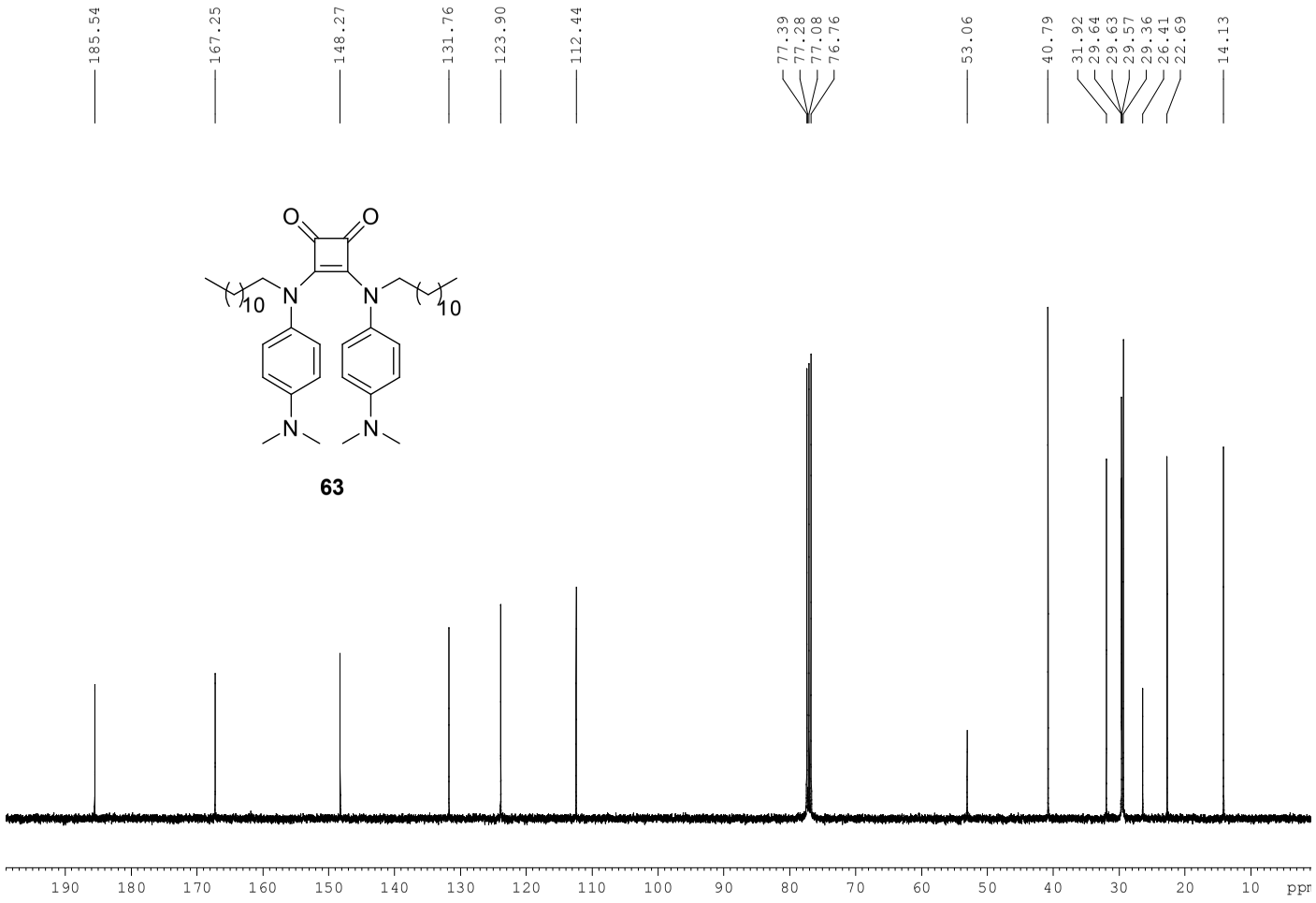


Figure 5.7: ^{13}C NMR spectra of squaramide **63** in $CDCl_3$

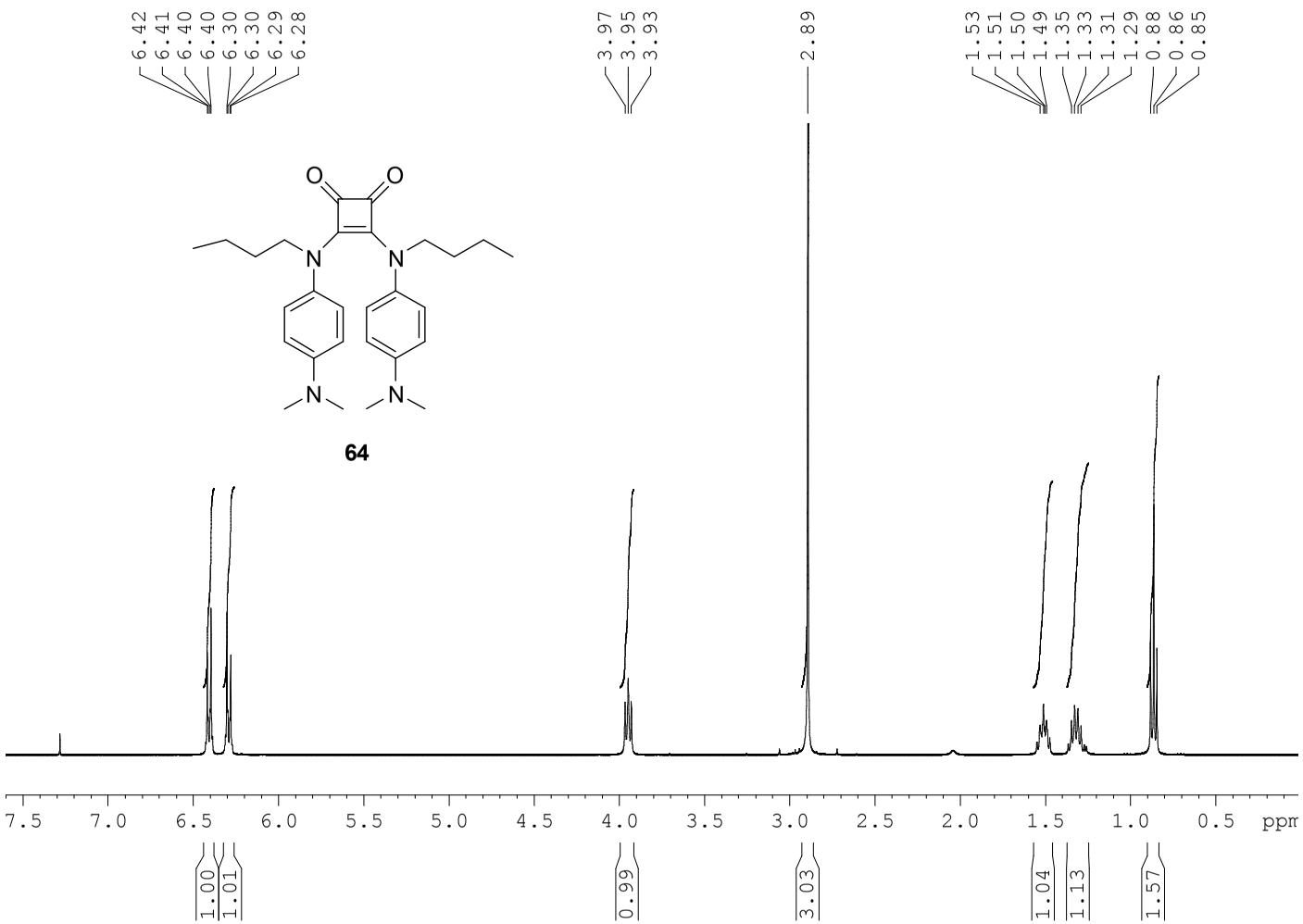


Figure 5.8: ^{1}H NMR spectra of squaramide **64** in $CDCl_3$

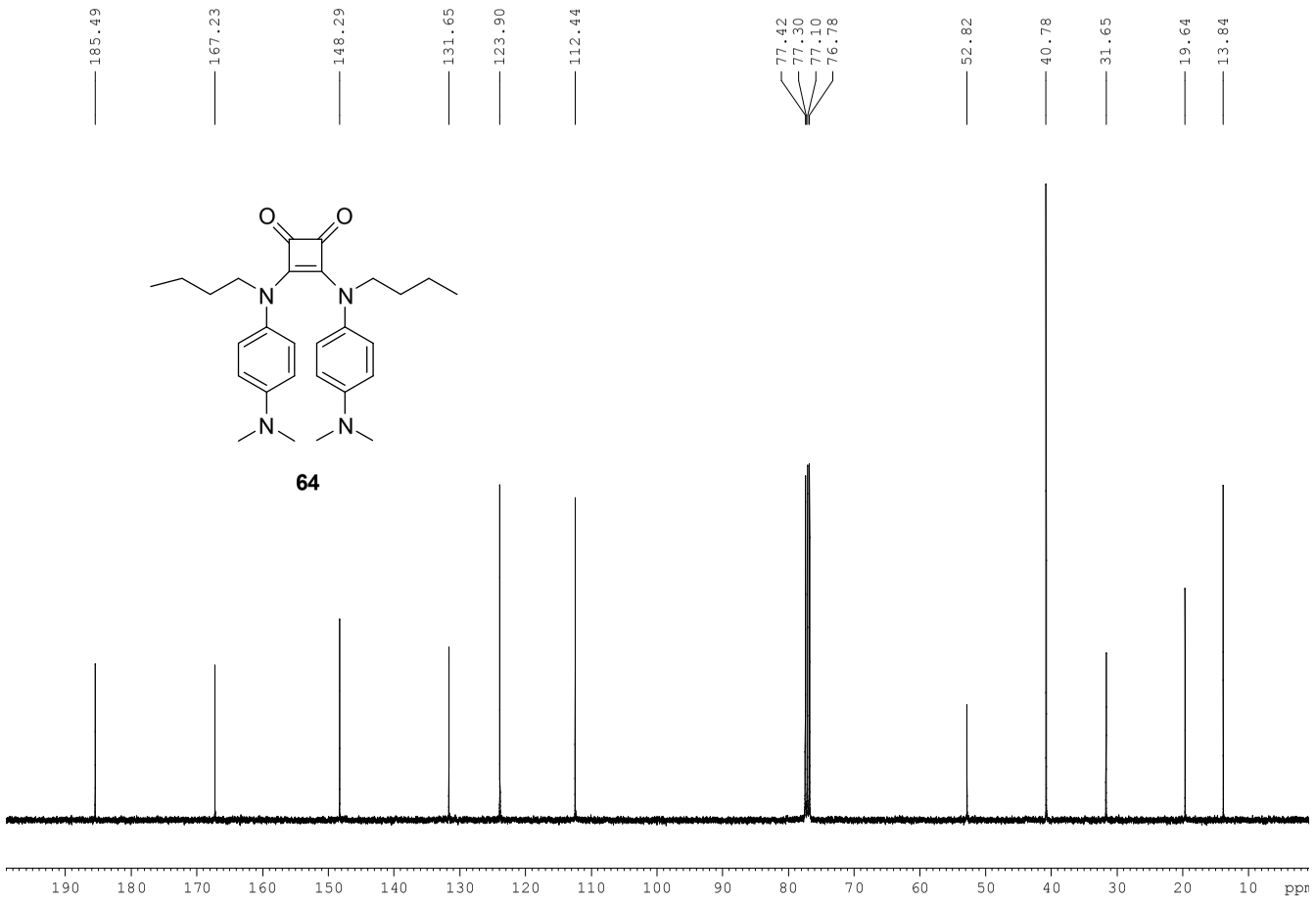


Figure 5.9: ^{13}C NMR spectra of squaramide **64** in $CDCl_3$

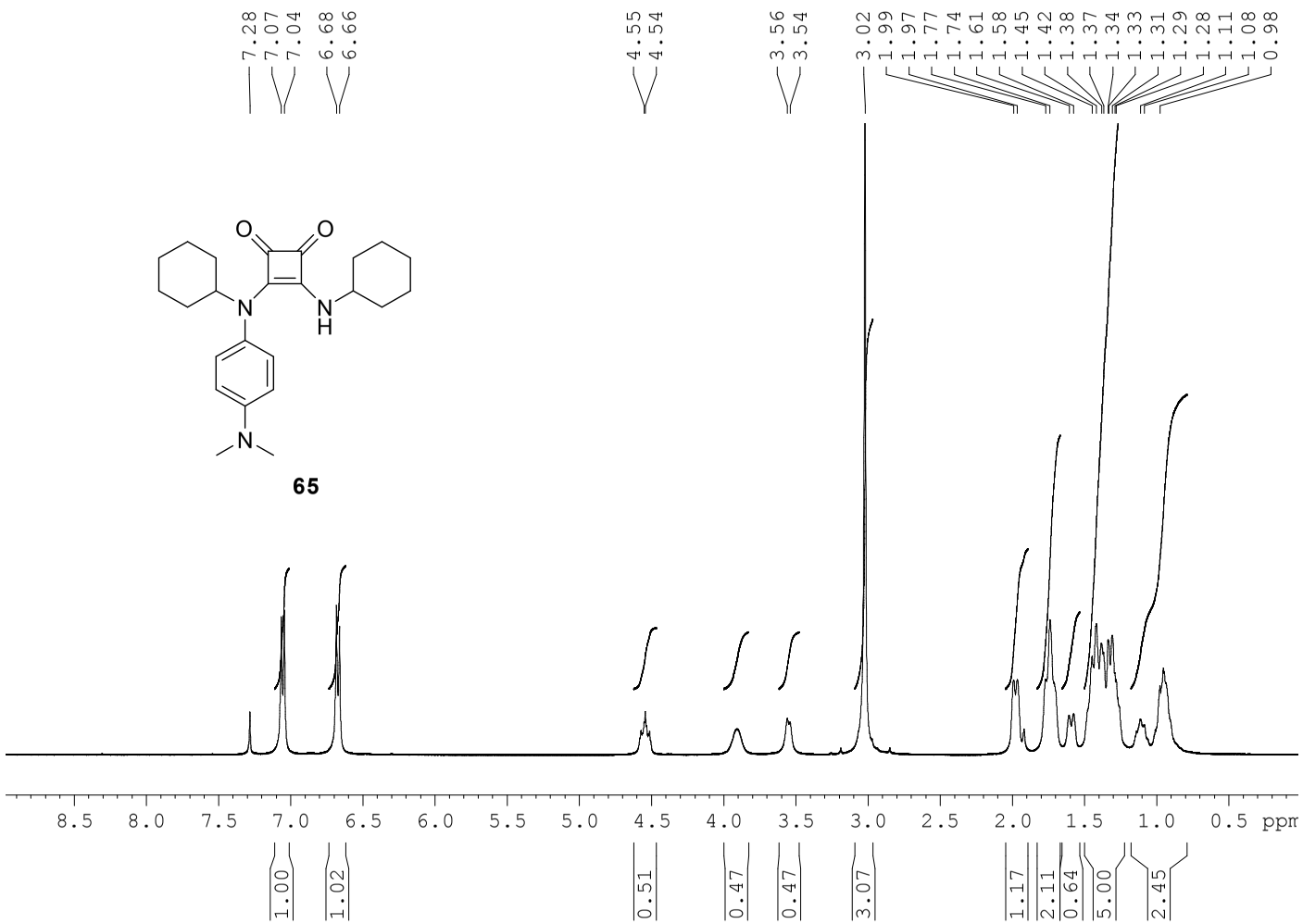


Figure 5.10: ^{1}H NMR spectra of squaramide **65** in $CDCl_3$

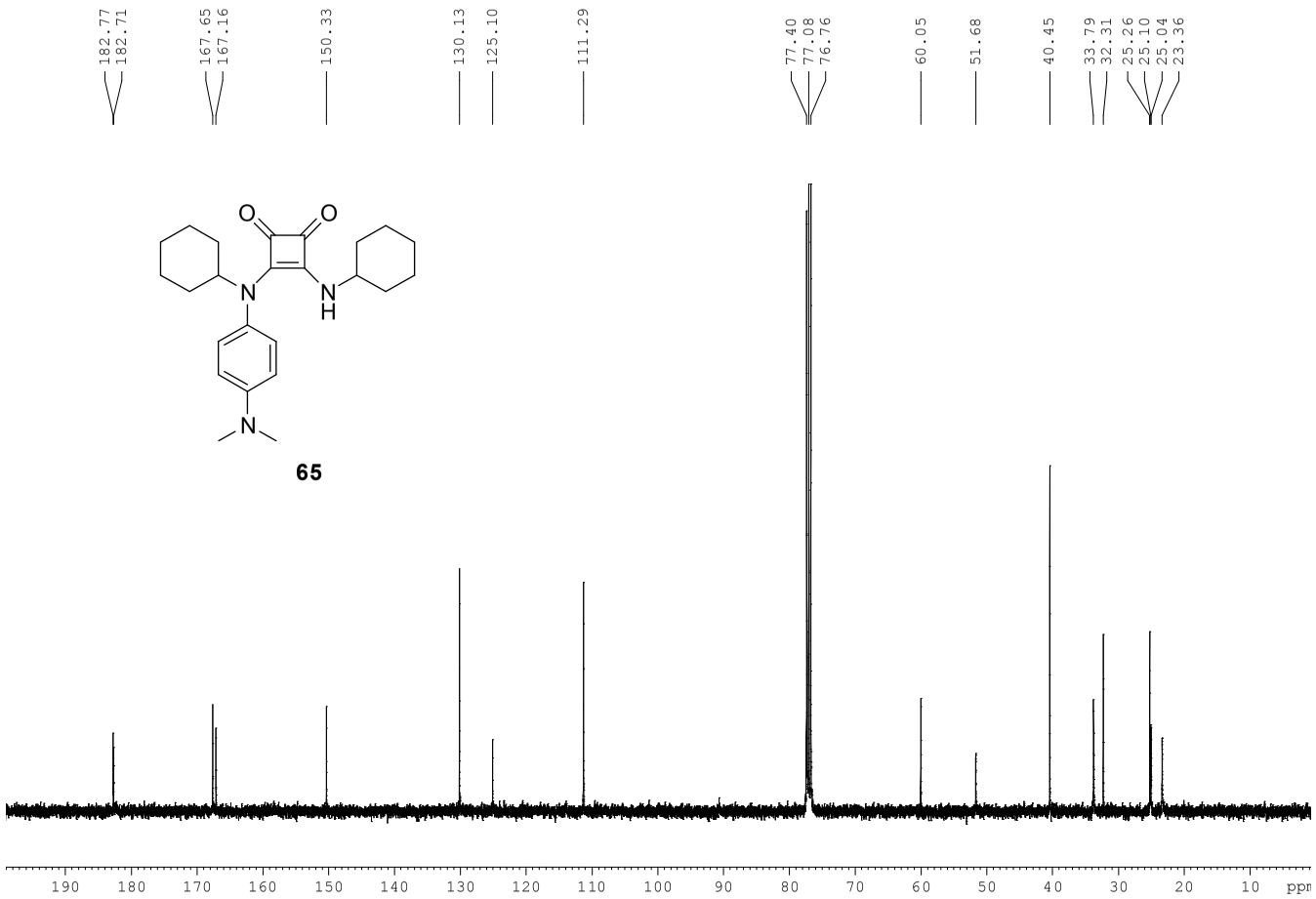


Figure 5.11: ^{13}C NMR spectra of squaramide **65** in $CDCl_3$

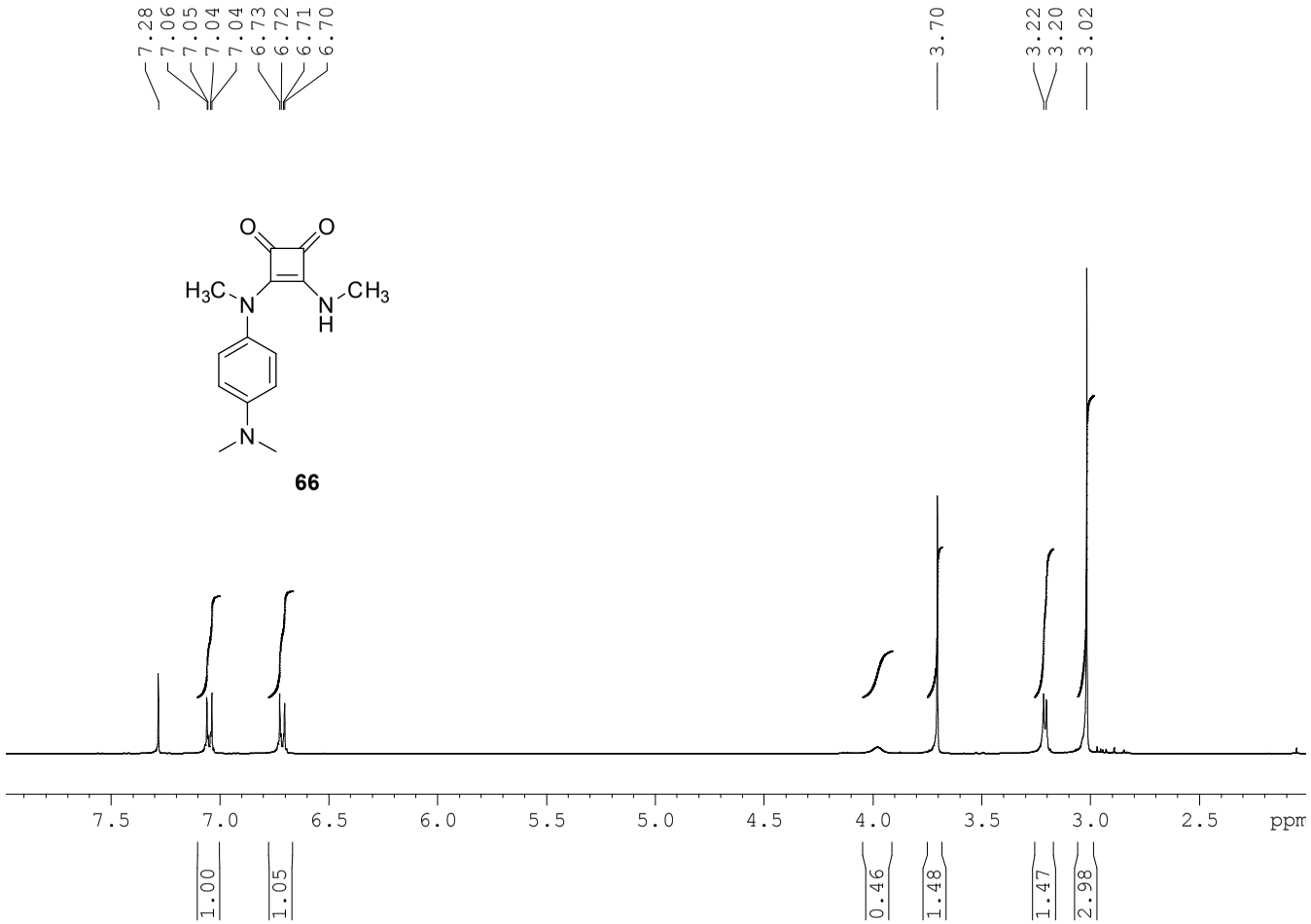


Figure 5.12: ^{1}H NMR spectra of squaramide **66** in $CDCl_3$

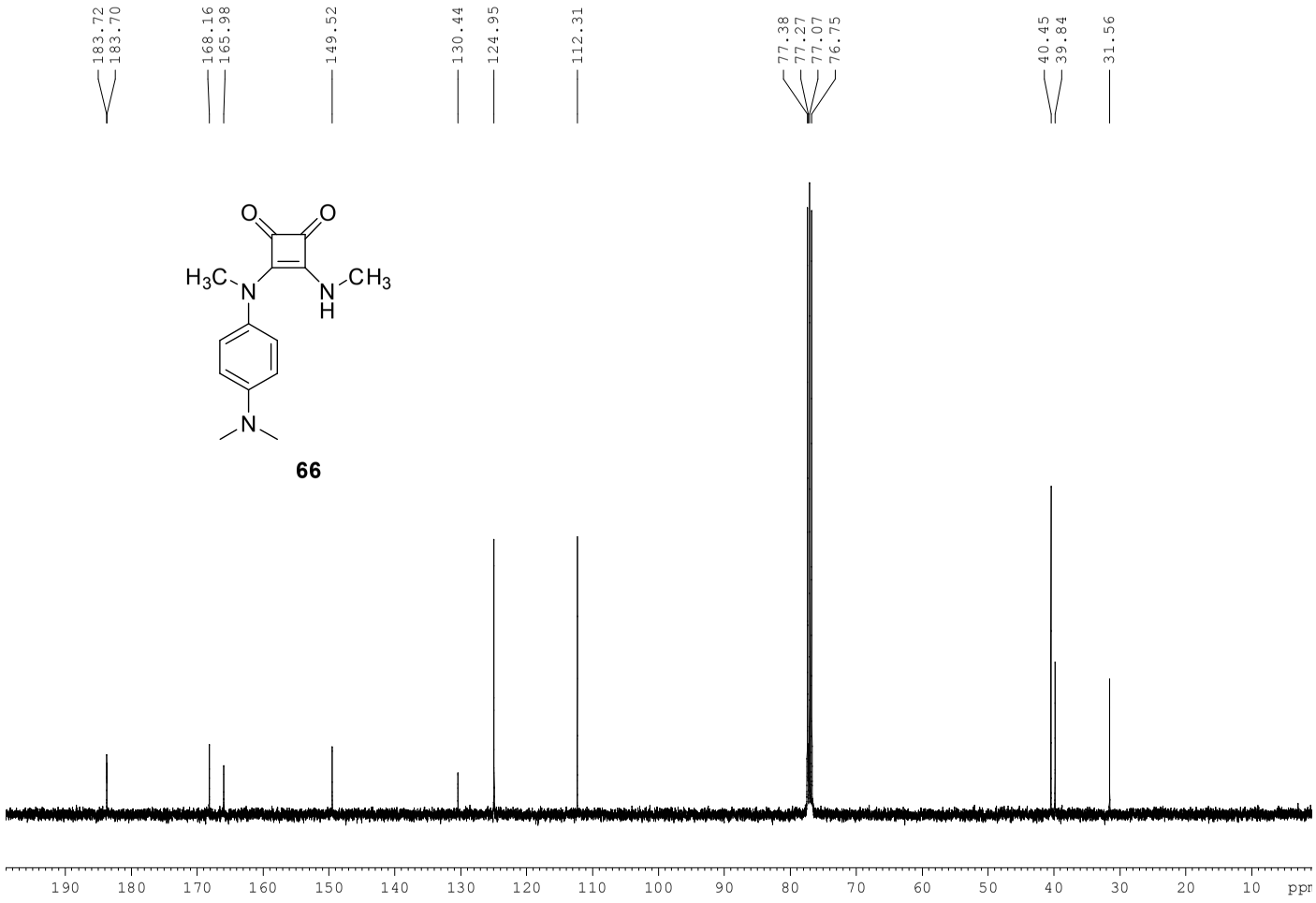


Figure 5.13: ^{13}C NMR spectra of squaramide **66** in $CDCl_3$

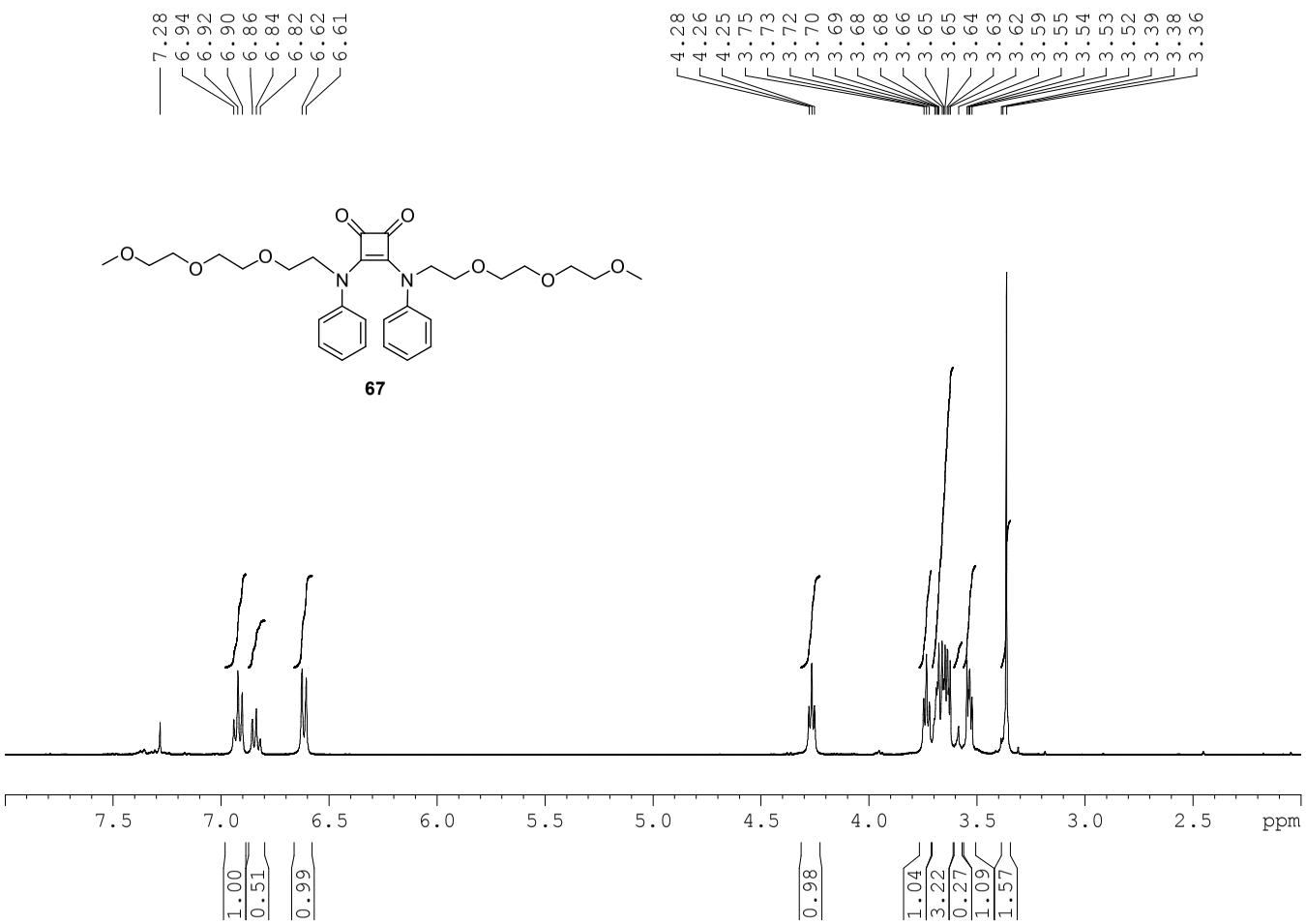


Figure 5.14: ^{1}H NMR spectra of squaramide **67** in $CDCl_3$

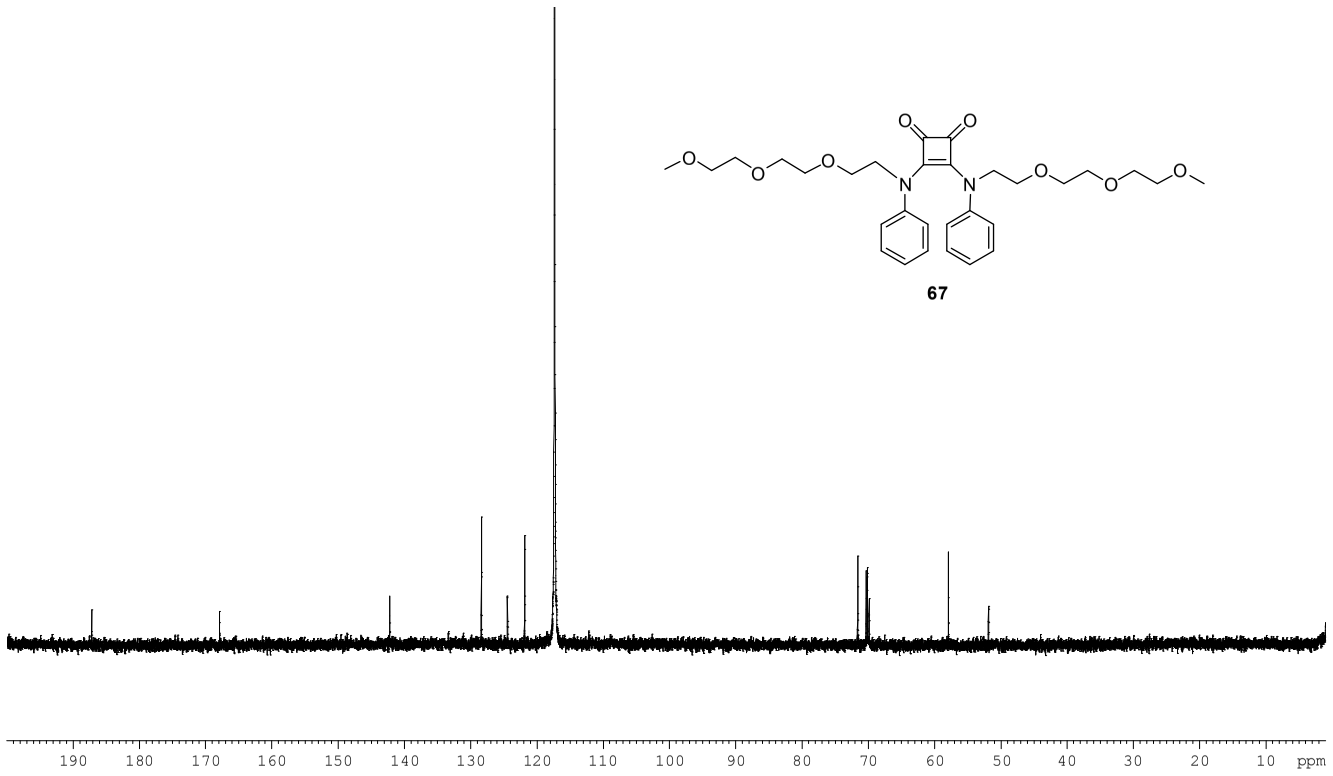


Figure 5.15: ^{13}C NMR spectra of squaramide **67** in CD_3CN

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Chapter 5

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