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Trends in NMR Structural Elucidation Of Polycyclic Cages, Namely: Adamantane, Pentacycloundecane and Trishomocubane

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ABSTRACT
Advances in Nuclear Magnetic Resonance (NMR) spectroscopy is a cornerstone in structure elucidation of polycyclic 'cage' scaffolds. Due to the compactness of these compounds, much overlap, as well as unique through-space and bond NMR interactions are frequently observed. This review serves as a guide for the NMR elucidation of future derivatives by providing some of the typical and relevant aspects of the characteristic trends, substituent patterns and chemical shift behaviour for the identification of the polycyclic structures, namely adamantane, pentacycloundecane and trishomocubane derivatives.

KEYWORDS
adamantane, NMR elucidation, pentacycloundecane, polycyclic compounds, trishomocubane

1. Introduction

The chemistry of polycyclic 'cage' scaffolds has fascinated organic chemists for over six decades.[1-8] These compounds include adamantane, pentacycloundecane, trishomocubane, pentacyclodecane, cubane, basketane (Figure 1).

These molecules have played a significant role in synthetic, theoretical and medicinal chemistry. The effect of the unusual cage geometries on chemical reactivity,[9] and more importantly, its role in pharmacological profiles have been and still are investigated. Application of these compounds in drug discovery stems from the polycyclic cage compounds ability to increase drug lipophilicity[10], thus serving as a transport aid to carry such drug pharmacophores across cellular membranes, including the blood-brain barrier (BBB) and the central nervous system (CNS).[8, 11-16] Furthermore, polycyclic cage based compounds have been reported to possess antifungal/antibacterial,[17-18] anti-tuberculosis[19-23] and anti-viral properties.[24-28] Research on the chemistry and medicinal applications of this class of polycyclic cage derivatives is ongoing.[9, 29-32]

In terms of their chemistry, these cage moieties exhibit unique features such as strained bonds/angles due to their rigid nature. The result is broad overlapping of ^{1}H NMR resonances for long-range proton-proton interactions due to through-space effects, geminal/vicinal proton-proton coupling and long-range proton-proton interactions, making the spectral data assignments quite challenging.[31,33] Over the years, with advances in NMR spectroscopy, there has been much progress in the elucidation of these types of compounds, which has been vital in contributing to a better understanding of the chemistry of these fascinating molecules. However, despite the great importance of polycyclic cage compounds, a review of these important NMR spectroscopic data for cage compounds highlighting general trends and unusual observations appears to be absent in literature. Accordingly, this review summarises the ^{1}H and ^{13}C NMR data of 20 adamantane, 69 pentacycloundecane and 8 trishomocubane derivatives in the bid to establish tendencies; this will be a useful tool for future structural elucidation of these classes of polycyclic compounds. Herein we provide an account on the progress in the NMR elucidation using two-dimensional NMR techniques for the most commonly reported polycyclic cage families, namely: adamantane, pentacycloundecane and trishomocubane.

2. Discussion

The NMR data are arranged into seven tables and three figures to enable easy interpretation of the collated data and as a guide for the elucidation of newer derivatives. There are a few cases where more than one reference for the NMR data of the same compound are documented. Here we used the data that best described the NMR elucidation or pattern. Information on the references, solvents, and magnetic field strength in which the NMR data were obtained for each compound are provided in Table 1.

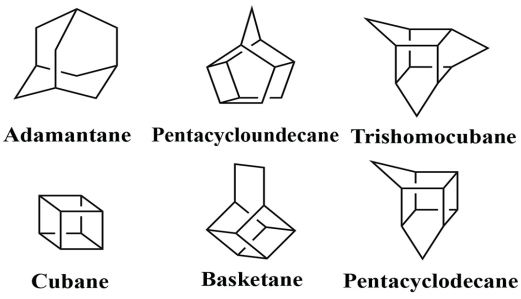

Figure 1. Representative polycyclic cages

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Table 1 Solvent, magnetic field strength and literature references for ^{1}H and ^{13}C NMR data of reported adamantane, pentacycloundecane and trishomocubane derivatives.

Compound #	Solvent/MHz	Ref. ^{1}H	Solvent/MHz	Ref. ^{13}C	Compound #	Solvent/MHz	Ref. ^{1}H	Solvent/MHz	Ref. ^{13}C
1	$CDCl_3$/400	35	$CDCl_3$/100	35	**39**	CD_3OD/400	45	CD_3OD/100	45
2	$CDCl_3$/600	35	$CDCl_3$/150	35	**40**	$(CD_3)_2SO$/400	46	$(CD_3)_2SO$/100	46
3	$CDCl_3$/400	35	$CDCl_3$/100	35	**41**	CD_3OD/600	46	CD_3OD/150	46
4	$CDCl_3$/600	35	$CDCl_3$/150	35	**42**	CD_3OD/400	46	CD_3OD/100	46
5	$CDCl_3$/400	35	$CDCl_3$/100	35	**43**	CD_3OD/400	46	CD_3OD/100	46
6	$CDCl_3$/600	35	$CDCl_3$/150	35	**44**	$(CD_3)_2SO$/400	46	$(CD_3)_2SO$/100	46
7	$(CD_3)_2SO$/400	36	$(CD_3)_2SO$/100	36	**45**	$CDCl_3$/400	47	$CDCl_3$/100	47
8a	$CDCl_3$/300	37	$CDCl_3$/75	37	**46**	$CDCl_3$/400	47	$CDCl_3$/100	47
8b	$CDCl_3$/300	37	$CDCl_3$/75	37	**47**	CD_3OD/400	47	CD_3OD/100	47
9a–9k *(syn)*	CDCl3/300MHz	38	CDCl3/75MHz	38	**48**	$(CD_3)_2SO$/600	48	$(CD_3)_2SO$/150	48
9a–9k *(anti)*	CDCl3/300MHz	38	CDCl3/75MHz	38	**49**	$(CD_3)_2SO$/400	48	$(CD_3)_2SO$/100	48
10a	$CDCl_3$/400	39-40	$CDCl_3$/100	39-40	**50**	$(CD_3)_2SO$/600	48	$(CD_3)_2SO$/150	48
10b	$CDCl_3$/600	40	$CDCl_3$/150/175	40	**51**	$(CD_3)_2SO$/400	48	$(CD_3)_2SO$/100	48
10c	$CDCl_3$/600	40	$CDCl_3$/150/175	40	**52**	$(CD_3)_2SO$/600	48	$(CD_3)_2SO$/150	48
10d	$CDCl_3$/600	40	$CDCl_3$/150/175	40	**53**	$(CD_3)_2SO$/600	48	$(CD_3)_2SO$/150	48
10e	$CDCl_3$/600	40	$CDCl_3$/150/175	40	**54**	$(CD_3)_2SO$/400	48	$(CD_3)_2SO$/100	48
10f	$CDCl_3$/600	40	$CDCl_3$/150/175	40	**55**	$(CD_3)_2SO$/400	48	$(CD_3)_2SO$/100	48
10g	$CDCl_3$/600	40	$CDCl_3$/150/175	40	**56**	$CDCl_3$/400	39	$CDCl_3$/100	39
11	$CDCl_3$/400	39	$CDCl_3$/100	39	**57**	$(CD_3)_2SO$/400	45	$(CD_3)_2SO$/100	45
12	$CDCl_3$/400	39	$CDCl_3$/100	39	**58**	$CDCl_3$/400	45	$CDCl_3$/100	45
13	$CDCl_3$/400	41	$CDCl_3$/100	41	**59**	CD_3OD/400	45	CD_3OD/100	45
14	$CDCl_3$/400	41	$CDCl_3$/100	41	**60**	$CDCl_3$/400	49	$CDCl_3$/100	49
15	$CDCl_3$/400	42	$CDCl_3$/100	42	**61**	$CDCl_3$/400	49	$CDCl_3$/100	49
16	$CDCl_3$/400	42	$CDCl_3$/100	42	**62**	$CDCl_3$/400	49	$CDCl_3$/100	49
17	$CDCl_3$/400	42	$CDCl_3$/100	42	**63**	$(CD_3)_2SO$/500	50	$(CD_3)_2SO$/125	50
18	$CDCl_3$/400	42	$CDCl_3$/100	42	**64**	$CDCl_3$/500	50	$CDCl_3$/125	50
19	$CDCl_3$/400	42	$CDCl_3$/100	42	**65**	CD_3OD/600	51	CD_3OD/150	51
20	$CDCl_3$/400	42	$CDCl_3$/100	42	**66**	CD_3OD/600	51	CD_3OD/150	51
21	$CDCl_3$/600	43	$CDCl_3$/150	43	**67**	$CDCl_3$/500	52	$CDCl_3$/125	52
22	$CDCl_3$/600	43	$CDCl_3$/150	43	**68**	$CDCl_3$/400	53	$CDCl_3$/100	53
23	$CDCl_3$/600	43	$CDCl_3$/150	43	**69**	$CDCl_3$/300	54	$CDCl_3$/75	54
24	D_2O/400	43	D_2O/100	43	**70**	$CDCl_3$/600	54	$CDCl_3$/125	54
25	$CDCl_3$/600	43	$CDCl_3$/150	43	**71**	$CDCl_3$/600	54	$CDCl_3$/125	54
26	$CDCl_3$/600	43	$CDCl_3$/150	43	**72**	$CDCl_3$/400	55	$CDCl_3$/100	55
27	$CDCl_3$/400	44	$CDCl_3$/100	44	**73**	$(CD_3)_2SO$/400	56	$(CD_3)_2SO$/100	56
28	$CDCl_3$/600	45	$CDCl_3$/150	45	**74**	$CDCl_3$/400	56	$CDCl_3$/100	56
29	$CDCl_3$/400	45	$CDCl_3$/100	45	**75**	$CDCl_3$/400	56	$CDCl_3$/100	56
30	$CDCl_3$/400	44	$CDCl_3$/100	44	**76**	$CDCl_3$/400	57	$CDCl_3$/100	57
31	$CDCl_3$/400	41	$CDCl_3$/100	41	**77**	$CDCl_3$/400	57	$CDCl_3$/100	57
32	$CDCl_3$/400	41	$CDCl_3$/100	41	**78**	$CDCl_3$/400	57	$CDCl_3$/100	57
33	D_2O/400	43	D_2O/100	43	**79**	$(CD_3)_2SO$/600	36	$(CD_3)_2SO$/100	36
34	D_2O/400	43	$^{43}D_2O$/100	43	**80**	$CDCl_3$/400	57	$CDCl_3$/100	57
35	$CDCl_3$/400	44	$CDCl_3$/100	44	**77**	$CDCl_3$/400	57	$CDCl_3$/100	57
36	$CDCl_3$/400	44	$CDCl_3$/100	44	**78**	$CDCl_3$/400	57	$CDCl_3$/100	57
37	$CDCl_3$/400	45	$CDCl_3$/100	45	**79**	$(CD_3)_2SO$/600	36	$(CD_3)_2SO$/100	36
38	$CDCl_3$/400	45	$CDCl_3$/100	45	**80**	$CDCl_3$/400	57	$CDCl_3$/100	57

2.1. Adamantane

Adamantane, a naturally occurring substance, was first isolated in 1933 from petroleum fractions.[5-6, 34] The synthesis of adamantane was first reported in 1941[30] with subsequent reports aimed at improving the reaction yield.[6] Although scientists have focused extensively on the synthesis[6] and pharmacological importance of adamantane and its derivatives, great strides have been made recently in the attempt to elucidate adamantane scaffolds when compared to the early 1970s.

From literature, a general trend was observed in the elucidation of monosubstituted (positions 1 or 2) adamantane compounds (**1–6**) (Figure 2). Free rotation along the C-1 or C-2 (of the adamantane scaffold) with the substituent (X = N, O etc.) amplifies the plane of symmetry of the adamantyl moiety. For instance, for substituents at position 1 of the adamantane group (compounds **5** and **6**), the following carbon groups are equivalent: C-2/C-8/C-9 (CH_2), CH-4/C-6/C-10 (CH_2) and C-3/C-5/C-7 (CH). Signals C-1/C-3 (CH), C-8/C-10 (CH_2), C-4/C-9 (CH_2), C-5 (CH), C-6 (CH_2) and C-7 (CH) are equivalent for substituents at position 2 (compounds **1–4**) (see Table 2). The presence of a plane of symmetry on the adamantane moiety further simplifies the structural elucidation of these compounds. However, overlapping in the proton spectrum due to the symmetry and subtle differences of the often diastereotopic carbon skeleton of these derivatives still appears to sometimes obscure some assignments.

Compounds **1–4**,reported by Onajole *et al.*[35], have the most de-shielded proton assigned to H-2, followed by H-4b/9b, H-1/3,

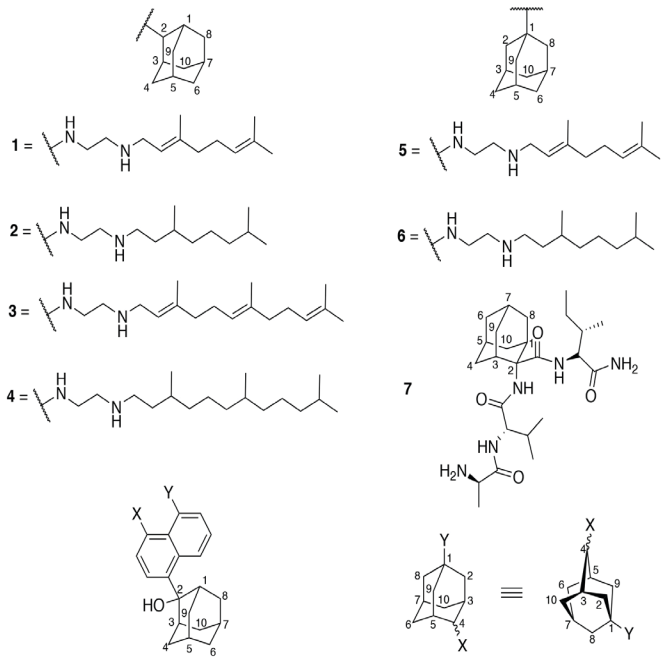

Figure 2 Structures of reported adamantane derivatives **1–9**[35-37]

H-8b/10b or H-7, H-5, H-6/8a/10a and H-4a/9a, consecutively. The de-shielding effect is expected due to the close proximity of the electronegative nitrogen atom.

Makatini *et al.*,[36] reported di-substituents of compound **7** on C-2 with peptide linkages de-shielding the resonances of the neighbouring protons (Table 2), e.g. H-1/3 have chemical shifts around 2.66–2.74 ppm as compared to **1–6**. Another di-substituted adamantane derivatives, **8a** and **8b**,[37] with naphthyl and hydroxyl groups attached to C-2 displayed neighbouring protons resonating in the lower field than normal occurrence, e.g. H-1 resonate at 2.48–2.54 ppm. This shift is attributed to the field-effect induced by the π-electron system and the steric hindrance of the bulk naphthyl group due to restricted rotation about the C-2 of adamantane and C-1′ of the substituent.[37] Moreover, 1D and 2D NMR techniques at different temperatures, as well as computational density functional theory (DFT) studies and single X-ray analysis for **8a**, were used by Jelena *et al.*[37] to investigate the anomaly in the conformations of **8a** and of **8b**. Low-temperature NMR spectra ($CDCl_3$; ^1H and ^{13}C) of compounds, **8a** and **8b** at 223 K showed well-resolved proton and carbon signals for both compounds accounting for fourteen chemically inequivalent aliphatic proton atoms and ten inequivalent carbon atoms, all belonging to the adamantane moiety. It is noteworthy, that low temperatures reduced the interconversion of **8a** and **8b** between their non-symmetrical conformations. However, this is not observed in the fast exchange (i.e. at room temperature) as only six different ^{13}C chemical shifts corresponding to C5, C6, C7 and the diastereotopic atom pairs (C1, C3), (C4, C9) and (C8, C10) respectively and only eight signals were recorded for the protons (Table 3).

The methylene protons in the adamantane moiety are diastereotopic as a result of rigidity in the molecule, making these protons nonequivalent, therefore, exhibiting spin-spin

Table 2 ^1H NMR data for adamantane derivatives (chemical shift)

H	**1**[35]	**2**[35]	**3**[35]	**4**[35]	**5**[35]	**6**[35]	**7**[36]	**8a**[37]	**8b**[37]
1	1.77	1.78	1.83	1.81	–	–	2.66–2.74	2.48	2.54
2	2.64	2.63	2.67	2.66	1.58	1.55	–		
3	1.77	1.78	1.83	1.81	1.99	1.96	2.66–2.74	3.2	3.26
4							1.52–1.71/ 1.89–2.74		
4a	1.41	1.43	1.47	1.45	1.56–1.61	1.48–1.57		1.68	1.69
4b	1.89	1.91	1.93	1.93	–	–		2.55	2.57
5	1.68	1.7	1.74	1.72	1.99	1.96	2.66–2.74	1.94	1.96
6	1.62	1.64	1.68	1.66	1.56–1.61	1.48–1.57	1.52–1.71/ 1.89–2.74		
6a								1.73	1.74
6b								1.67	1.68
7	1.74	1.76	1.81	1.78	1.99	1.96	2.66–2.74	1.78	1.79
8							1.52–1.71/ 1.89–2.74		
8a	1.62	1.64	1.68	1.66	1.58	1.55		1.94	1.9
8b	1.75	1.76	1.81	1.79	–	–		2.42	2.46
9							1.52–1.71/ 1.89–2.74		
9a	1.41	1.43	1.47	1.45	1.58	1.55		1.75	1.77
9b	1.89	1.91	1.93	1.93	–	–		2.58	2.6
10							1.52–1.71/ 1.89–2.74		
10a	1.62	1.64	1.68	1.66	1.56–1.61	1.48–1.57		1.5	1.51
10b	1.75	1.75	1.81	1.79	–	–		1.15	1.12

interactions. The protons (Ha) axial to each of the cyclohexyl rings show signals appearing at a lower frequency than the equatorial protons (Hb) due to the through-space effect. This effect is observed for compounds **1–4** as well as **8a** and **8b**. NOESY/ROESY interactions of Ha/Hb with neighbouring protons were used to distinguish between these two protons resulting from their orientation in space. Studies have shown that a class of 1,4-disubstituted adamantane derivatives (**9a–9k**) (Figure 2) containing electron-withdrawing groups at both positions C-1 and C-4 resulted in increased chemical shifts of adjacent protons.[38] This substituent pattern causes the resonances of the flanking carbons of the *cis*-isomers to be relatively closer together than the *anti*-isomers. These compounds, **9a–9k**, show large discrepancies in both proton and carbon resonance signals from the other classes stated above. In the carbon-13 spectra, compounds **1–4** with substituent attached to C-2 recorded the most de-shielded signal for C-2, followed by either C-6 or C-8/10, C-1/3, C-4/9, C-7, and C-5 consecutively, in decreasing order of chemical shift with C-5 being the most shielded (Table 3). The following class of compounds, **5**, **6**, **7**, including **8a** and **8b** isomers, displayed a definite pattern of chemical shifts of carbon-13 signals for each class as observed in their carbon spectra. The *syn*-isomers of compounds **9** registered C-1, C-8, C-2/9, C-4, C-6/10, in order of decreasing frequency except for **9f** and **9g** (**9k**), where the order of C-2/9 and C-4 (C-8 and C-2/9) are reversed, while the *anti*-isomers recorded C-1, through C-2/9, C-8, C-4, C-3/5, C-7, to C-6/10 in a definite order of decreasing chemical shift except for **9i** and **9k** with each displaying a different pattern. The combined effect of the 1,4-disubstitutents on the adamantane skeleton causes the signals of C-2, 9 and C-6, 10 to be fairly close together in the *syn*-isomers while they are further apart in the *anti*-isomers.

The signals for the proton and carbon resonances fall within a similar region for equivalent positions for this class compounds with the same substituent pattern as displayed in Tables 2 and 3. The electron-withdrawing groups on either C-1, C-2 or C-4 have the effect of shifting the resonance signals of the adjacent protons towards the higher frequency region. So far,

Table 3. ^{13}C NMR data for adamantane derivatives (chemical shift)

Atom	**1**[35]	**2**[35]	**3**[35]	**4**[35]	**5**[35]	**6**[35]	**7**[36]	**8a**[37]	**8b**[37]	Atom	**1**[35]	**2**[35]	**3**[35]	**4**[35]	**5**[35]	**6**[35]	**7**[36]	**8a**[37]	**8b**[37]
1	31.8	32.1	32.3	32.1	50.2	50.7	31.2	37.8	37.8	7	27.6	27.8	27.8	27.8	29.7	29.5	31.2	27.2	27.1
2	61.7	61.8	61.9	61.8	42.8	42.7	63.6	77.7	78.0	8							32.2/33.3	36.3	36.3
3	31.8	32.1	32.3	32.1	29.7	29.5	31.2	36.1	36.1	8a	37.4	37.5	37.6	37.5	42.8	42.5			
4							32.2/33.3	32.5	32.5	8b	37.4	37.5	37.6	37.5	–	–			
4a	31.1	31.3	31.3	31.3	36.8	36.6				9							32.2/33.3	33.7	33.8
4b	31.1	31.3	31.3	31.3	–	–				9a	31.1	31.3	31.3	31.3	42.8	42.5			
5	27.4	27.6	27.6	27.6	29.7	29.5	31.2	26.5	26.5	9b	31.1	31.3	31.3	31.3	–	–			
6	37.7	37.9	27.6	37.9	36.8	36.6	32.2/33.3	37.4	37.4	10							32.2/33.3	33.9	33.8
6a										10a	37.4	37.5	37.6	37.5	36.8	36.6			
6b										10b	37.4	37.5	37.6	37.5	–	–			

Atom	**9a**[38] *(syn)*	**9a**[38] *(anti)*	**9b**[38] *(syn)*	**9b**[38] *(anti)*	**9c**[38] *(syn)*	**9c**[38] *(anti)*	**9d**[38] *(syn)*	**9d**[38] *(anti)*	**9f**[38] *(syn)*	**9f**[38] *(anti)*	9g[38] *(syn)*	9g[38] *(anti)*	9h[38] *(syn)*	9h[38] *(anti)*	9i[38] *(syn)*	9i[38] *(anti)*	9k[38] *(syn)*	9k[38] *(anti)*
1	68.03	67.61	68.6	68.29	68.15	67.91	65.65	65.28	67.89	67.7	79.69	79.47	68.01	68.17	66.61	66.43	67.46	67.58
2	41.67	48.37	41.73	48.65	41.86	48.45	43.44	50.07	39.27	45.93	37.15	42.05	39.46	46.13	40.72	43.76	41.33	45.18
3	35.24	34.66	35.24	34.78	34.76	34.21	35.61	35.18	34.35	33.67	34.47	33.79	34.47	33.76	32.84	32.60	31.98	31.64
4	39.03	39.24	38.50		40.74	41.08	40.77	41.08	39.44	39.72	39.63	39.80	39.07	39.23	35.29	35.56	47.88	48.22
5	35.24	34.66	35.24	34.78	34.76	34.21	35.61	35.18	34.35	33.67	34.47	33.79	34.47	33.76	32.84	32.6	31.98	31.64
6	36.53	29.43	36.64	29.52	36.61	29.64	36.61	29.68	37.00	29.84	35.23	30.03	37.29	29.98	34.81	31.43	36.24	31.90
7	30.97	30.98	31.23	31.15	31.27	31.05	32.17	31.95	29.97	30.01	30.10	30.15	30.39	30.80	28.84	29.12	29.71	29.58
8	47.99	47.99	48.02	48.10	48.01	48.01	49.63	49.61	45.62	45.53	41.67	41.50	45.79	45.63	43.91	44.30	44.68	44.90
9	41.67	48.37	41.73	48.65	41.86	48.45	43.44	50.07	39.27	45.93	37.15	42.05	39.46	46.13	40.72	43.76	41.33	45.18
10	36.53	29.43	36.64	29.52	36.61	29.64	36.61	29.68	37.00	29.84	35.23	30.03	37.29	29.98	34.81	31.43	36.24	31.90

aromatic rings attached to an adamantane cage is expected to cause a large de-shielding effect of the adjacent proton resonances as compared to carbonyl, amino, hydroxyl, and other electron-withdrawing groups. The ^{13}C Attach Proton Test (APT), Heteronuclear Single Quantum Coherence (HSQC), and Heteronuclear Multiple Bond Correlation (HMBC) spectra served as useful tools in resolving the overlapping signals of the proton and carbon signals observed mainly for the unsymmetrical derivatives.

2.2. Pentacycloundecane

The synthesis of the Cookson's dione, which is the starting material for all pentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane (PCU) derivatives, was first reported in 1964.[4] It was not until 1993 that Cadd *et al.*[33] published the complete NMR assignment of the compound using ^{1}H and ^{13}C NMR spectra. Although 1D NMR was found to be useful in the elucidation of various polycyclic cage compounds, 2D NMR proved to be a more effective tool for the PCU elucidation due to the geminal/vicinal proton-proton couplings along with long-range proton-proton interactions and the prevalence of overlapping of proton and carbon signals. The elucidation of PCU compounds becomes fairly straightforward for compounds with a plane of symmetry, therefore, making all of the atoms except for the protons on C-4 (H-4a and H-4s) to appear in pairs: H-1/H-7, H-2/H-6, H-3/H-5, H-9/H-10, determined from the ^{1}H-NMR data. It has been confirmed that the geminal protons at C-4 resonating as a pair of doublets display an AB spin-spin interaction around 1.5 and 1.8 ppm with a coupling constant of approximately 10 Hz.[48, 58] Hence, Correlation Spectroscopy (COSY), Nuclear Overhauser Effect Spectroscopy (NOESY) and Rotating frame Overhause Effect Spectroscopy (ROESY) interactions of H-4a (H-4s) with H-3/5 and H-2/6 (H-9/10), respectively, have been established as a starting point for the structural elucidation of PCU cage derivatives. In addition, HMBC, NOESY, and ROESY techniques are useful in determining the side "arm" with respect to the cage moiety.[48]

Kenwright *et al.*,[40] reported a series of compounds, **10a–10g** (Figure 3), where the protons in the 2 and 6 positions of the four-membered ring have the highest shift in frequency of all the methine protons in unsubstituted PCU derivatives. However, the chemical shift of position 2 appears de-shielded when position 1 is substituted by an alkyl or methoxy group. At least in most cases, it reduces to a frequency lower than any one of the bridgehead protons at position 3 or 5. H-6 is always the most de-shielded proton (Table 4) when there is no substituent attached to position 7, while H-2, H-3, or H-5 follow at the next highest frequency, but the order depends on the position and type of substituent at H-9 or H-10. A significant shift in the proton signal of H-9/H-10 is found in the derivatives where alkyl substituent is attached to either C-9 or C-10 than when alkyl substituent is attached to other positions and in unsubstituted PCU derivatives.

Generally, electron-withdrawing groups such as methoxy at C-1 and/or C-2 cause adjacent proton signals to be de-shielded but has no marked effect on protons farther away from the substituent. Furthermore, it is generally observed that the relative shifts in the signals of the methine protons are opposite to the trend for the carbon signals. Hence, the proton with the highest chemical shift value has its corresponding carbon appearing at the lowest frequency.

An asymmetric keto-ketal, **11**, reported by Kruger *et al.*,[39] recorded H-2 as the most de-shielded signal, followed next by H-3 and H-6 in decreasing order of frequency. At the same time, H-9 was registered as the most shielded signal among the methine protons. PCU ether with symmetrical substituents at positions 8 and 11 recorded the most de-shielded signal for H-2/6 of all the methine protons for **12–44** (Table 4). The next set of de-shielded signals is recorded for H-1/7 and H-9/10 consecutively, while the reverse is true for only 13, but H-3/5 immediately follows H-1/7 in decreasing order of chemical shift for **41–44**. However, **27** and **31** are the only compounds where H-1/7 was recorded as the most de-shielded proton and followed next by H-9/10 and H-2/6 accordingly. The chiral side arm substituent of compound **27** induced diastereomeric character to the cage moiety. As a result of this effect, the cage protons are nonequivalent, thus making its elucidation challenging. Also, in compound **35**, the diastereomeric effect

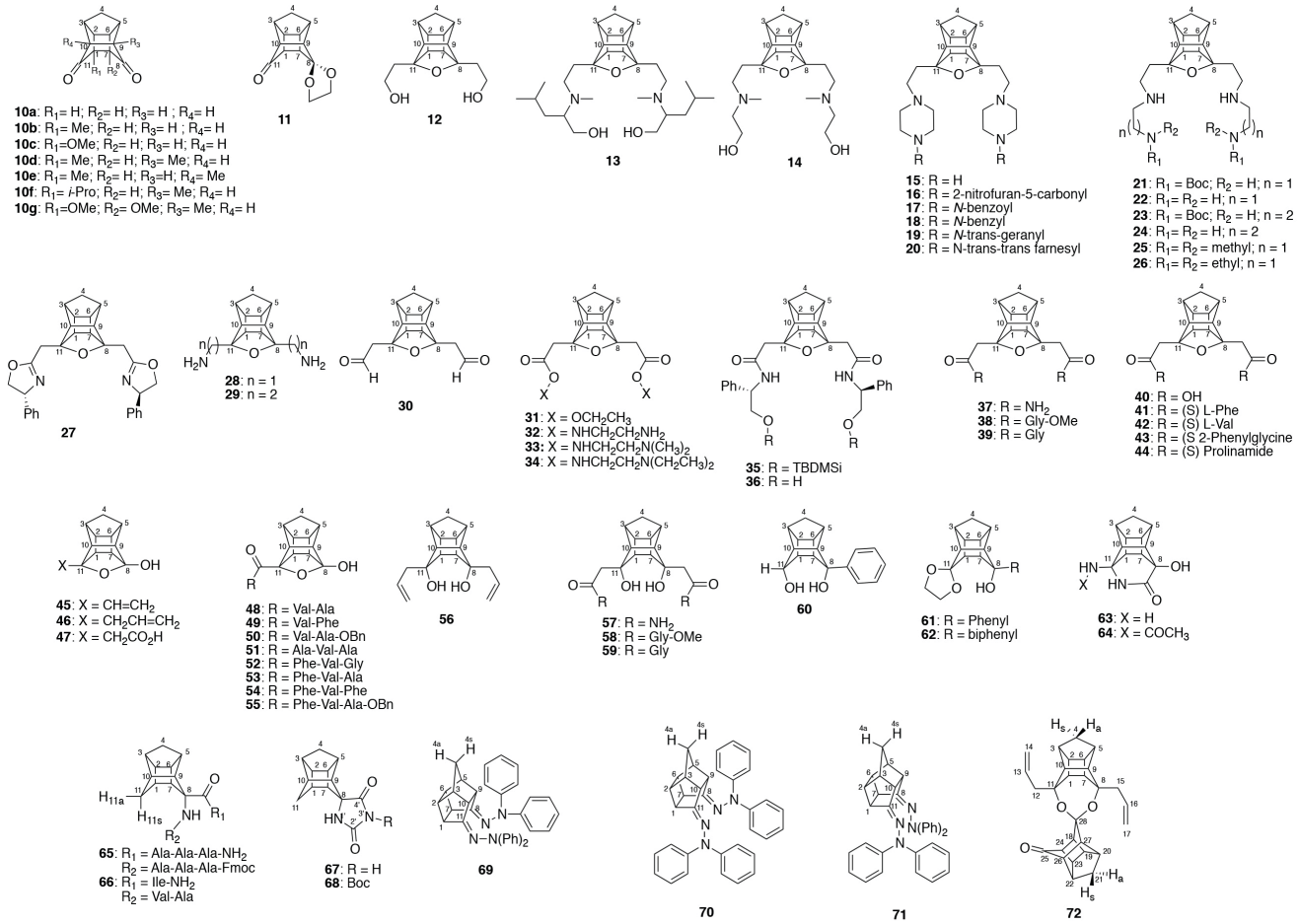

Figure 3: Structures of reported PCU derivatives **10–72**[39-55]

Table 4 ^{1}H NMR data for pentacycloundecane derivatives (chemical shift and coupling constant)

Atom	**10a**[40]	**10b**[40]	**10c**[40]	**10d**[40]	**10e**[40]	**10f**[40]	**10g**[40]	**11**[39]	**12**[39]	**13**[41]
H1	2.79							2.63	2.61	2.5
H2	3.15	2.79	3.09	2.76	2.70	2.85	3.22	2.94	3.75	2.58
H3	2.91	2.85	2.96	2.84	2.38	2.73	2.92	2.8	2.41	2.35
H4a	1.86	1.88	1.95	1.84	1.79	1.81	1.93	1.56	1.52	1.5
H4s	2.03	2.03	2.04	2.08	2.04	2.04	2.10	1.85	1.88	1.85
H5	2.91	2.91	2.93	2.49	2.84	2.43	2.53	2.58	2.41	2.35
H6	3.15	3.14	3.26	3.09	3.06	2.94	3.22	2.78	3.75	2.58
H7	2.79	2.36	2.88	2.41	2.28	2.55		2.55	2.61	2.5
H8										
H9	2.68	2.66	2.71		2.09			2.43	2.57	2.47
H10	2.68	2.72	2.64	2.2		2.1	2.14	2.47	2.57	2.47
H11										

Atom	**14**[41]	**15**[42]	**16**[42]	**17**[42]	**18**[42]	**19**[42]	**20**[42]	**21**[43]	**22**[43]	**23**[43]
H1	2.49	2.47	2.53	2.48	2.48	2.51	2.46	2.47	2.47	2.33
H2	2.58	2.6	2.61	2.59	2.57	2.6	2.57	2.57	2.57	2.43
H3	2.36	2.38	2.38	2.36	2.35	2.38	2.35	2.34	2.34	2.2
H4a	1.50, 10.4 Hz	1.52, 10.1 Hz	1.52, 10.2 Hz	1.50, 10.3 Hz	1.48, 10.3 Hz	1.51	1.48	1.49, 10.4 Hz	1.48, 10.4 Hz	1.35, 10.3 Hz
H4s	1.85, 10.4 Hz	1.87, 10.1 Hz	1.87, 10.2 Hz	1.85, 10.3 Hz	1.84, 10.3 Hz	1.87	1.84	1.85, 10.3 Hz	1.84, 10.3 Hz	1.70, 10.3 Hz
H5	2.36	2.38	2.38	2.36	2.35	2.38	2.35	2.34	2.34	2.2
H6	2.58	2.6	2.61	2.59	2.57	2.6	2.57	2.57	2.57	2.43
H7	2.49	2.47	2.53	2.48	2.48	2.51	2.46	2.47	2.47	2.33
H8										
H9	2.47	2.45	2.51	2.47	2.43	2.44	2.43	2.46	2.45	2.31
H10	2.47	2.45	2.51	2.47	2.43	2.44	2.43	2.46	2.45	2.31
H11										

Table 4 (continued) ^{1}H NMR data for pentacycloundecane derivatives (chemical shift and coupling constant)

Atom	**24**[43]	**25**[43]	**26**[43]	**27**[44]	**28**[45]	**29**[45]	**30**[44]	**31**[41]	**32**[41]	**33**[43]
H1	2.69	2.65	2.65	2.82	2.58	2.41	2.68	2.73	2.53	2.57
H2	2.73	2.69	2.68	2.64	2.6	2.5	2.71	2.61	2.56	2.59
H3	2.52	2.48	2.47	2.41	2.37	2.27	2.5	2.38	2.33	2.4
H4a	1.6, 10.6 Hz	1.55, 10.5 Hz	1.55, 7.0 Hz	1.51, 10.5 Hz	1.52, 10.4 Hz	1.42, 10.4 Hz	1.59, 10.5 Hz	1.47, 10.4 Hz	1.40, 10.6 Hz	1.49, 10.6 Hz
H4s	1.97, 10.6 Hz	1.93, 10.5 Hz	1.93, 7.0 Hz	1.90, 10.5 Hz	1.82, 10.4 Hz	1.78, 10.4 Hz	1.93, 10.5 Hz	1.83, 10.4Jz	1.75, 10.6 Hz	1.83, 10.6 Hz
H5	2.52	2.48	2.47	2.41	2.37	2.27	2.5	2.38	2.33	2.4
H6	2.73	2.69	2.68	2.64	2.6	2.5	2.71	2.61	2.56	2.59
H7	2.69	2.65	2.65	2.82	2.58	2.41	2.68	2.73	2.53	2.57
H8										
H9	2.67	2.63	2.63	2.75	2.57	2.39	2.64	2.64	2.45	2.54
H10	2.67	2.63	2.63	2.75	2.57	2.39	2.64	2.64	2.45	2.54
H11										

Atom	**34**[43]	**35**[44]	**36**[44]	**37**[45]	**38**[45]	**39**[45]	**40**[46]	**41**[46]	**42**[46]	**43**[46]
H1	2.59	2.87	2.73	2.59	2.65	2.77	2.58	2.09/2.11	2.55	2.37
H2	2.61	2.87	2.73	2.57	2.62	2.74	2.47	2.48	2.62	2.51
H3	2.42	2.56	2.45	2.39	2.43	2.5	2.36	2.26/2.30	2.49/2.55	2.43
H4a	1.50, 10.6 Hz	1.65, 10.5 Hz	1.55, 10.5 Hz	1.47, 10.5 Hz	1.49, 10.5 Hz	1.59, 10.4 Hz	1.02, 10.4 Hz	1.04, 10.6 Hz	1.18, 10.8 Hz	1.10, 10.8 Hz
H4s	1.85, 10.6 Hz	1.98, 10.5 Hz	1.90, 10.5 Hz	1.82, 10.5 Hz	1.85, 10.5 Hz	1.97, 10.4 Hz	1.49, 10.4 Hz	1.39, 10.5 Hz	1.60, 10.7 Hz	1.50, 10.7 Hz
H5	2.42	2.56	2.45	2.39	2.43	2.5	2.36	2.26/2.30	2.49/2.55	2.43
H6	2.61	2.87	2.73	2.57	2.62	2.74	2.47	2.48	2.62	2.51
H7	2.59	2.87	2.73	2.59	2.65	2.77	2.58	2.09/2.11	2.55	2.37
H8										
H9	2.56	2.87	2.73	2.58	2.62	2.73		1.67/1.89	2.33/2.40	2.15
H10	2.56	2.87	2.73	2.58	2.62	2.73		1.67/1.89	2.33/2.40	2.15
H11										

Atom	**44**[46]	**45**[47]	**46**[47]	**47**[47]	**48**[48]	**49**[48]	**50**[48]	**51**[48]	**52**[48]	**53**[48]
H1	2.67	2.76	2.58	2.81	2.75	2.77	2.72	2.76	2.73	2.73
H2	2.52	2.67	2.59	2.66	2.66	2.65	2.58	2.63	2.59	2.59
H3	2.42	2.51	2.42	2.5	2.52	2.51	2.45	2.47	2.44	2.46
H4a	1.04, 10.6 Hz	1.57, 10.4 Hz	1.52, 10.8 Hz	1.56, 10.4 Hz	1.47, d, 10.4 Hz	1.47, d 10.1 Hz	1.47, d 9.3 Hz	1.48, d 10.2 Hz	1.44, d 0.2 Hz	1.45, d 10.1 Hz
H4s	1.48, 10.5 Hz	1.91, 10.4 Hz	1.85, 10.8 Hz	1.90, 10.4 Hz	1.82/1.84,[a] d, 6.0 Hz	1.83, d 10.1 Hz	1.82,[b] t 9.3 Hz	1.83, d 10.2 Hz	1.79/1.80,[a] d, 6.1 Hz	1.79/1.80,[a] d, 6.1 Hz
H5	2.42	2.65	2.61	2.58	2.46	2.49	2.44	2.47	2.45	2.45
H6	2.52	2.78	2.74	2.74	2.68	2.66	2.64	2.65	2.65	2.67
H7	2.67	2.61	2.62	2.56	2.48	2.51	2.47	2.44	2.44	2.42
H8		-	-	-						
H9	2.1	2.62	2.59-2.62	2.57	2.52	2.55	2.49	2.47	2.47	2.48
H10	2.1	2.75	2.59-2.62	2.75	2.71	2.69	2.66	2.65	2.65	2.65
H11		-	-	-						

Atom	**54**[48]	**55**[48]	**56**[39]	**57**[45]	**58**[45]	**59**[45]	**60**[49]	**61**[49]	**62**[49]	**63**[50]
H1	2.71	2.72	2.44	2.41	2.46	2.6	2.86	2.68	2.71	2.268
H2	2.57	2.58	2.45	2.48	2.49	2.64	2.56	2.66	2.69	2.549
H3	2.43	2.45	2.36	2.4	2.38	2.56	2.35	2.62	2.66	2.569
H4a	1.44, d 10.2 Hz	1.44, d 10.1 Hz	1.07	1.05, 10.5 Hz	1.06, 10.8 Hz	1.20, 10.7 Hz	0.99, 10.8 Hz	1.08, 11.0 Hz	1.10, 10.8 Hz	1.336, 10.5 Hz
H4s	1.78, 10.2 Hz	1.79, 10.1 Hz	1.5	1.50, 10.5 Hz	1.52, 10.8 Hz	1.65, 10.7 Hz	1.51, 10.8 Hz	1.51, 11.0 Hz	1.54, 10.8 Hz	1.660, 10.5 Hz
H5	2.43	2.44	2.36	2.4	2.38	2.56	1.79	1.81	1.91	2.645
H6	2.66	2.64	2.45	2.48	2.49	2.64	2.58	2.6	2.64	2.723
H7	2.46	2.45	2.44	2.41	2.46	2.6	3.12	3.16	3.19	2.282
H8							5.10 (8-OH)			
H9	2.45	2.5	2.15	2.19	2.31	2.37	2.55	2.63	2.69	2.097
H10	2.66	2.64	2.15	2.19	2.31	2.37	2.59	2.33	2.35	2.066
H11							3.81, 1.62 (11-OH)			

[a] Two separate resonances potentially due to a side-chain conformational effect
[b] Due to the coalescence of the pair of doublets, the signal appears as a triplet

Table 4 (continued) ^{1}H NMR data for pentacycloundecane derivatives (chemical shift and coupling constant)

Atom	**64**[50]	**65**[51]	**66**[51]	**67**[52]	**68**[53]	**69**[54]	**70**[54]	**71**[54]	**72**[55]
H1	2.966	2.73	2.75	2.838	2.85	3.37–3.41	2.75–2.78	2.40–2.46	2.33
H2	2.628	2.62	2.62	2.652	2.66	2.81–2.85	2.55–2.62	2.60–2.64	2.52
H3	2.535	2.26	2.3	2.273	2.33	2.19–2.23	2.49–2.53	2.55–2.59	2.27
H4a	1.489, 10.4 Hz	1.23, 10.35 Hz	1.26, 10.5 Hz	1.243, 10.8 Hz	1.23, 10.91 Hz	1.32 (d, 11.15 Hz)	1.42 (d, 10.84 Hz)	1.47 (d, 10.89 Hz)	1.15, 10.7 Hz
H4s	1.788, 10.4 Hz	1.71, 10.35 Hz	1.72, 10.5 Hz	1.64, 10.8 Hz	1.66, 10.91 Hz	1.37 (d, 11.15 Hz)	1.64 (d, 10.84 Hz)	1.90 (d, 10.89 Hz)	1.57
H5	2.878	2.57	2.15	2.989	2.98	2.19–2.23	2.33–2.36	2.55–2.59	2.27
H6	2.91	2.57	2.64	2.752, q, 7.1 Hz	2.77	2.81–2.85	2.68–2.73	2.60–2.64	2.52
H7	2.535	3.28	3.33	2.591, t, 6.6 Hz	2.6	3.37–3.41	2.86–2.90	2.40–2.46	2.53
H8									
H9	2.333	2.85	2.84	2.324	2.33	2.55–2.58	2.90–2.94	3.18–3.24	2.21
H10	2.794	2.46	2.47	2.528	2.53	2.55–2.58	2.78–2.81	3.18–3.24	2.31
H11		0.96 (11a)/ 2.06 (11s), 13.0 Hz	1.04(11a)/ 2.10 (11s), 12.8 Hz	1.267 (11a), dt, 8.4, 3.4 Hz/ 1.450 (11s), d, 13.7 Hz	1.28 (11a, 12.5 Hz)/ 1.40 (11s, 12.5 Hz)				

(induced by the chirality on the side arms) causes all the cage carbon signals to display a split pattern. High-temperature NMR experiments of **35** (333, 393 and 423 K) revealed that the C-1/7, C-9/10, and C-8/11 signals remained split even at the highest tested temperature (423 K) with the exception of C-4, an achiral methylene carbon, thus further confirming the diastereomeric effect experienced by these carbon atoms. This observed interaction illustrated a conformation of **35**, where one of the "arms" is positioned in front of the cage moiety while the other is at the back. As previously reported for related chiral PCU ligands,[41-44, 48, 55, 59] the presence of heteroatoms on the side arms at close proximity to the cage induces a through-space de-shielding effect, which results in non-equivalence of atoms on the cage and that of the "arm" as observed in the ^{13}C spectrum.

H-3/5 was registered as the most shielded proton of all the methine protons for the symmetrically substituted PCU ether at positions 8 and 11, except for **41–44**, where H-9/10 was recorded as the lowest frequency. The chemical shift of the carbon signals of compounds **12–44** follows a definite trend by decreasing from C-8/11 through C-9/10, C-1/7, C-3/5, C-4 to C-2/6. However, **31**, **32** and **40–44** show deviation from this regular pattern, where C-4 was registered as the lowest carbon frequency while C-2/6 takes the position of C-4, and that observed for **32** is given as follows, C-8/11, through C-9/10, C-1/7, C-2/6, C-3/5, to C-4. It is noteworthy that equivalent carbons resonate within a similar range of frequency. The electron-withdrawing effect induced by the oxo bridge of the ether functional group holding C-8 and C-11 together has an intense effect on these carbons; hence, they were recorded as the most de-shielded. Since C-1/7 and C-9/10 are both adjacent to the ether group, C-1/7 is expected to be the next de-shielded because it is enclosed in a four-membered ring inducing strain effect. However, C-9/10 was recorded as the second most de-shielded carbon due to the high stretching strain exerted by the oxo bridge of the ether. This evidence is supported by single X-ray diffraction of certain PCU derivatives indicating shorter bond length for C9-C10 than normal value expected due to the stretching strain induced by the oxo bridge holding the cage "mouth" together by C8 and C11.[60]

For the ether monosubstituted hydroxyl group at position 8, with position 11 substituted by an alkene functionality (**45** and **46**), methylene carboxylic acid (**47**) and the carbonyl group of peptide linkage (**48–55**), H-1 signal was attributed to the highest frequency, followed by H-10 and/or H-6. However, **45** and **46** registered the highest chemical shift value for H-6, followed by H-1 and H-10, and H-10 and H-1, respectively. The highest ppm was attributed to H-1 due to the electron-withdrawing effect induced by the carbonyl group attached to position 11. At the same time, there is little effect due to the alkene functionality compared to the carbonyl. H-3, H-5, and H-7 were recorded as the lowest frequency for **45–47**, **48–50/54–55** and **51–53**. H-3 and H-5 are farther away from the electron-withdrawing groups, hence experience little or no effect from these groups. This class of compounds exhibited a general pattern of carbon chemical shift decreasing from C-8, C-11, C-10, C-9, C-1, C-7 to C-3. The lowest frequency was registered for C-6 except for **45** and **46**, which recorded the lowest chemical shift for C-2. Simultaneously, the remaining two carbons, C-4 and C-5, show a very slight difference in ppm with C-4 slightly higher than C-5 or vice versa (see Table 5). C-8 was recorded as the most de-shielded carbon due to the hydroxyl group directly attached to

Table 5 ^{13}C NMR data for Pentacycloundecane derivatives (chemical shift)

Atom	**10a**[40]	**10b**[40]	**10c**[40]	**10d**[40]	**10e**[40]	**10f**[40]	**10g**[40]	**11**[39]	**12**[39]	**13**[41]
C1	43.8	48.4	82.0	48.1	47.7	56.4	83.4 or 83.5	42.3	47.6	47.9
C2	38.7	45.0	43.3	44.3	43.9	40.2	41.1 or 41.2	41.5	41.4	41.6
C3	44.6	43.7	43.9	44.0	49.5	44.0	43.8	45.8	44.1	44.2
C4	40.5	40.9	41.9	39.5	39.9	39.7	41.3	38.7	43.5	43.5
C5	44.6	44.5	43.8	50.0	44.6	50.1	49.4	42.9	44.1	44.2
C6	38.7	36.2	34.6	34.9	35.5	35.5	41.1 or 41.2	36.3	41.4	41.6
C7	43.8	50.3	48.5	49.8	50.0	45.7	83.4 or 83.5	41.3	47.6	47.9
C8	212.1	212.2	209.6	213.9	212.4	214.6	211.0	215.4	96.4	95.0
C9	54.7	54.5	54.7	58.2	62.0	59.7	54.8	50.7	58.2	58.6
C10	54.7	54.7	50.8	61.4	58.4	63.3	58.5	53	58.2	58.6
C11	212.1	212.8	210.6	213.0	214.5	212.9	209.4	113.9	96.4	95.0

Table 5 (continued) ^{13}C NMR data for Pentacycloundecane derivatives (chemical shift)

Atom	**14**[41]	**15**[42]	**16**[42]	**17**[42]	**18**[42]	**19**[42]	**20**[42]	**21**[43]	**22**[43]	**23**[43]
C1	47.9	48	48.1	48	48	48.0	48.0	47.8	47.9	47.8
C2	41.6	41.8	41.8	41.8	41.8	41.8	41.8	41.5	41.6	41.5
C3	44.3	44.5	44.5	44.4	44.5	44.5	44.5	44.2	44.3	44.1
C4	43.4	43.4	43.5	43.5	43.4	43.4	43.4	43.5	43.5	43.4
C5	44.3	44.5	44.5	44.4	44.5	44.5	44.5	44.2	44.3	44.1
C6	41.6	41.8	41.8	41.8	41.8	41.8	41.8	41.5	41.6	41.5
C7	47.9	48	48.1	48	48	48.0	48.0	47.8	47.9	47.8
C8	95	94.9	94.8	94.7	94.8	94.9	94.9	95.6	95.4	95.2
C9	58.7	58.8	58.8	58.8	58.8	58.8	58.8	58.4	58.6	58.5
C10	58.7	58.8	58.8	58.8	58.8	58.8	58.8	58.4	58.6	58.5
C11	95	94.9	94.8	94.7	94.8	94.9	94.9	95.6	95.4	95.2

Atom	**24**[43]	**25**[43]	**26**[43]	**27**[44]	**28**[45]	**29**[45]	**30**[44]	**31**[41]	**32**[41]	**33**[43]
C1	47.3	47.2	47.2	48.67/48.58	45.9	47.7	48.57	48.5	47.5	48.3
C2	41.2	41.1	41.1	41.86/41.84	41.5	41.3	41.62	43.3	44.3	41.5
C3	44.1	44	44.1	44.64/44.61	41.5	44	44.16	44.5	43.9	44.1
C4	43.0	43	43	43.55	43.4	43.4	43.45	41.8	43.2	43.4
C5	44.1	44	44.1	44.64/44.61	41.5	44	44.16	44.5	43.9	44.1
C6	41.2	41.1	41.1	41.86/41.84	41.5	41.3	41.62	43.3	44.3	41.5
C7	47.3	47.2	47.2	48.67/48.58	45.9	47.7	48.57	48.5	47.5	48.3
C8	94.9	94.9	94.8	93.71/93.69	97.4	95.3	92.77	92.8	93.6	93.8
C9	57.9	57.9	57.9	59.26/59.16	56.4	58.3	59.21	59.2	58.4	58.6
C10	57.9	57.9	57.9	59.26/59.16	56.4	58.3	59.21	59.2	58.4	58.6
C11	94.9	94.9	94.8	93.71/93.69	97.4	95.3	92.77	92.8	93.6	93.8

Atom	**34**[43]	**35**[44]	**36**[44]	**37**[45]	**38**[45]	**39**[45]	**40**[46]	**41**[46]	**42**[46]	**43**[46]
C1	48.2	48.83/47.82	48.63/48.01	48	48.1	49.5	42.2	44.5/44.8	44.3	45.7
C2	41.4	41.50/41.44	41.54/41.39	41.3	41.4	42.8	38.8	39.4/39.7	40.6/40.7	40.6
C3	44.1	44.28/44.19	44.12/44.00	43.9	44	45.6	43.8	43.2/43.8	45.7	44.4
C4	43.4	43.35	43.48	43.3	43.4	44.3	33.4	33.9	34.8	34.8
C5	44.1	44.28/44.19	44.12/44.00	43.9	44	45.6	43.8	43.2/43.8	45.7	44.4
C6	41.4	41.50/41.44	41.54/41.39	41.3	41.4	42.8	38.8	39.4/39.7	40.6/40.7	40.6
C7	48.2	48.83/47.82	48.63/48.01	48	48.1	49.5	42.2	44.5/44.8	44.3	45.7
C8	93.9	94.21/94.16	94.14	93.6	94	95.2	76.4	77.2/77.8	78.5/78.6	78.7
C9	58.5	59.11/58.06	59.05/58.40	58.4	58.6	59.9	49.9	49.1/49.4	50.7/50.9	50.8
C10	58.5	59.11/58.06	59.05/58.40	58.4	58.6	59.9	49.9	49.1/49.4	50.7/50.9	50.8
C11	93.9	94.21/94.16	94.14	93.6	94	95.2	76.4	77.2/77.8	78.5/78.6	78.7

Atom	**44**[46]	**45**[47]	**46**[47]	**47**[47]	**48**[48]	**49**[48]	**50**[48]	**51**[48]	**52**[48]	**53**[48]
C1	42	49.39	48.03	49.52	48.9	48.7	48.2	48.4	48.1	48.2
C2	38.5	42.12	41.93	43.34	42.2	42.1	42.2	42.2	42.1	42.1
C3	43.9	45.36	45.2	46.38	46.1	46	46.2	46.1	46.2	46.1
C4	33.5	43.55	43.5	44.05	42.8	42.8	42.8	42.8	42.8	42.8
C5	43.9	43.96	44.03	45.14	42.7	42.7	42.8	42.7	42.7	42.7
C6	38.5	42.25	42.3	42.99	41.1	40.9	41	41	40.9	40.9
C7	42	47.92	47.75	48.49	46.3	46.2	46.4	46.3	46.2	46.3
C8	77.8	118.48	118.16	119.13	118.2	118.1	118.2	118.2	118.1	118.1
C9	50.3	57.74	58.13/58.17	58.78	56.2	56.4	56.2	56.2	56.1	56.1
C10	50.3	59.17	58.13/58.17	59.8	58.6	58.5	57.9	58.2	57.9	58.2
C11	77.8	91.84	91.46	89.89	89.8	89.6	89.7	89.5	89.6	89.5

Atom	**54**[48]	**55**[48]	**56**[39]	**57**[45]	**58**[45]	**59**[45]	**60**[49]	**61**[49]	**62**[49]	**63**[50]
C1	48.1	48.2	42.8	42.5	42.9	44.4	38.9	39.26	39.31	45.90
C2	42	42.1	40	38.9	39.3	40.7	39.01	39.42	39.48	40.30
C3	46	46.1	44	43.8	44.3	45.8	44.3	52.91	52.9	45.59
C4	42.8	42.8	33.9	33.5	34	34.8	34.11	34.58	34.63	36.58
C5	42.7	42.8	44	43.8	44.3	45.8	46.69	44.93	44.59	45.26
C6	41	41	40	38.9	39.3	40.7	41.52	40.68	40.71	41.43
C7	46.3	46.4	42.8	42.5	42.9	44.4	41.5	41.7	41.79	44.96
C8	118.1	118.2	72.2	76.6	77.3	78.6	79.4	78.7	78.62	79.86
C9	56.1	56.2	49.1	49.3	49.5	51	51.31	45.6	45.61	52.33
C10	58.2	57.9	49.1	49.3	49.5	51	46.7	47.5	47.55	53.78
C11	89.5	89.6	77.2	76.6	77.3	78.6	71.92	115.5	115.51	73.58

Table 5 (continued) ^{13}C NMR data for Pentacycloundecane derivatives (chemical shift)

Atom	**64**[50]	**65**[51]	**66**[51]	**67**[52]	**68**[53]	**69**[54]	**70**[54]	**71**[54]	**72**[55]
C1	44.01	37.9	37.2	35.40	35.9	43.9 (49.1)	38.4 (40.6)	40.4 (41.7)	41.5
C2	39.96	43.0	43.1	41.30	41.5	40.4	41.1	38.1	39.2
C3	43.63	48.2	48.4	46.00	46.5	45.2	44.6	45.2	42.29
C4	37.59	35.3	35.4	33.82	34.3	38.1	38.1	38	35.1
C5	45.61	42.2/45.8	44.7	42.41	42.4	45.2	46	45.2	42.58
C6	42.19	42.2/45.8	43.1	41.19	41.4	40.4	39.9	38.1	39.6
C7	45.21	42.2	40.2	41.40	41.7	43.9 (51.4)	44.0 (49.1)	40.4 (45.4)	40.4
C8	80.31	67.1	67.5	68.52	68.1	169.4	169.5	167.5	84
C9	52.68	48.2	49.2	48.15	49	46.8 (49.6)	47.3 (51.3)	52.3 (55.1)	51.1
C10	51.88	44.1	44.2	42.06	43.2	46.8 (52.1)	52.4 (59.4)	52.3 (59.9)	49.5
C11	74.11	30.1	29.8	28.35	29.5	169.4	162.6	167.5	84.3

this position. The decreasing order of chemical shift ranging from C-10, through C-9, C-1, to C-7 is also supported by the evidence given above for **12–44**, except that there is no plane of symmetry; therefore, each carbon resonates at a different frequency. The unsymmetrical and non-separable diastereomeric nature of compounds **48–55** resulted in complicated ^{1}H NMR and splitting of ^{13}C signals.[48] However, despite the overlapping of signals observed in the proton spectra, 2D NMR spectroscopy proved to be a crucial tool towards the effective structural elucidation of these compounds.

Compounds **56–59** are symmetrically di-substituted at positions 8 and 11 with hydroxyl groups at these positions. These compounds all show similar patterns in chemical shifts, where H-2/6 was registered as the most de-shielded signal, followed by H-1/7 and H-3/5 consecutively, with H-9/10 being the least de-shielded of all the methine protons. The carbon-13 signals here show the following trend of chemical shift in decreasing order, from C-8/11, through C-9/10, C-3/5, C-1/7, C-2/6, to C-4. The hydroxyl groups attached to C-8 and C-11 cause a large de-shielding effect of these carbon signals.

The remaining compounds, **60-72**, lack a plane of symmetry except for compounds **69** and **71** with symmetrical di-substituents at positions 8 and 11. Compounds **69-71** are conformational isomers, while **70** proved to be the most stable isomer in solution. The observed ^{13}C NMR chemical shifts for **69-71** were also calculated using DFT[54] in order to compare the observed ^{13}C shifts with the calculated values to assess the reliability of the computational method. Nuclear shielding was observed for the calculated structures with the aliphatic cage carbons chemical shifts dependent on the orientation of imine nitrogen lone pairs. These shifts were not observed for the experimental spectrum for atoms C-1, C-7 and C-9, C-10; thus, it was attributed to replacing the phenyl groups with vinyl units in the computational model.[54] The calculated results suggested that **70** was energetically more stable, which agrees with the experimentally observed isomeric ratios. Here the shifts in the signals do not follow a regular pattern, while the through-space de-shielding effect plays a significant role in determining the shifts of signals. The carbon signals exhibited a definite pattern for the following pairs of compounds with similar functional groups, **63** and **64**, **65** and **66**, **67** and **68**.

In contrast, the remaining compounds do not follow a specified order of chemical shifts. Conclusively, in most cases, it can be proposed that H-2/6 seems to be the most de-shielded of the methine protons, followed by either H-1/7 or H-9/10 and H-3/5 being the most shielded proton for symmetrically substituted PCU ethers at positions 8 and 11 for **12–44**. The PCU ethers, **45-55**, with mono-substituent at position 11 and a hydroxyl group at position 8, lacking plane of symmetry, have H-1 and C-8 recorded at the highest ppm (for ^{1}H and ^{13}C NMR spectra, respectively). Simultaneously, the most shielded signal is usually registered as H-3 and C-2 or C-6 in most cases and sometimes varies from H-5 to H-7 for ^{1}H NMR. The factors responsible for the shifts in the proton signals of the PCU derivatives include an inductive effect (comprising electron-withdrawing and electron-donating effect), ring strain and through-space de-shielding effect. Through-space de-shielding effect results from the proximity in space of bulky groups (such as carbonyl group, alkene, phenyl ring, etc.) possessing a high density of electrons which may lead to conformational isomers, hence, making elucidation difficult. The inductive effect and ring strain are the major factors responsible for the shifts in carbon frequencies. Corresponding carbons of protons were determined using HSQC and HMBC spectra. Therefore, 2D NMR techniques have been established to show a high level of significance towards the structural elucidation of PCU compounds.

In summary, the PCU family of compounds is quite intriguing, as it can exist in one of three forms (asymmetric, diastereomeric or mesomeric), which then dictate the protocol to be followed on its NMR elucidation. The mesomeric PCU cage becomes chiral upon attachment of a group that breaks the symmetry. In such cases, COSY and NOESY interactions, in particular, are required to supplement the 1D spectra in order to aid the elucidation. Next, the PCU cage can exist as diastereoisomers, i.e. when the side arm substituents are the same yet possess chirality. Here the carbon signals appear as pairs due to diastereomeric splitting. In both cases, the asymmetric and diastereomeric PCU derivatives experience conformational effects induced by the side arms (one arm pointing to the back whilst one arm points to the front of the cage) that influence the NMR spectra (NOESY interactions, splitting of carbons). When the side arms prove to be stable in a specific orientation relative to the cage, these isomers are referred to as configurational isomers. Finally, the PCU cage may have identical achiral side arms resulting in a mesomeric structure. In this instance, all the atoms on the PCU molecule, except for the methylene at the C-4 position, become equivalent resulting in much overlap in both the proton and carbon spectra. The carbon spectra, in particular, are somewhat simplified in these cases as an overlap of the equivalent signals occur. Generally, a convenient starting point in the elucidation of any of the above three forms of PCU is with the geminal bridge methylene protons (H-4) that register as an AB spin system around 1.1 and 1.5 ppm displaying a coupling constant of approximately 10 Hz. Essentially thereafter, the core PCU protons (i.e. H-1 through to H-11) are assigned using mainly COSY and NOESY spectra; the NOESY interactions are particularly important to confirm the cage methine protons with the substituents on the side arms due to the induction of different chemical environments. Typically, the COSY interaction of H-4a/s with H-3/5 is followed by the interaction of H2/6 and its connection with H-1/7. Thereafter,

the H-2/6 interaction with H-9/10 confirms the core handle to further the elucidation. The route to be followed is dependent on whether the arms make the cage asymmetric, diastereomeric (noting that configurational isomers can exist in these cases) or mesomeric.

2.3. Trishomocubane

The most stable of all the pentacycloundecane based cages, namely, the D3-symmetrical trishomocubane, was first reported in 1970.[61] It has become well known for its pharmacological properties.[62-63] There are many publications on the synthesis and reactivity of these derivatives.[1, 62] Herein we highlight only the NMR elucidation reports on this intrinsically chiral, D3 symmetric propeller-shaped cage made up of slightly twisted 5-membered rings (Figure 4). In earlier reports, simple chemical shift values, intensity ratios or only the ^{13}C spectral data were used to characterise these cages since the ^{1}H spectra proved to be very complicated.[61, 63-64] The NMR data was assigned using chemical shift values, double resonance ^{1}H NMR, off-resonance proton decoupled ^{13}C NMR, Heteronuclear Correlation (HETCOR), nuclear overhauser enhanced (NOE) difference spectra, and previously reported data. The starting core structures, trishomocuban-4-ol and trishomocubanone, displayed much overlapping of the methine proton signals in the ^{1}H NMR spectra, which were overcome by adding lanthanide shift (LIS) reagents that resulted in some separation of the signals.[65]

The trishomocubane hydantoin derivatives, **73-77**,[56-57] reveal H-10 as the most de-shielded signal of all the methine protons followed by H-6 and H-9 or H-2 in most cases (Table 6) as evident from the DFT calculations[56]. It shows H-10 being the closest in space to the carbonyl oxygen of the hydantoin group, therefore, experiences the largest through-space de-shielding effect. H-6, H-2, and H-9 are more likely to experience a small through-space de-shielding effect due to the carbonyl group of the t-Boc directly attached to the amide nitrogen of the hydantoin group in **75**.[56] Among the methine protons, the most shielded signals are assigned to H-5 and H-3, with H-5 slightly more shielded than H-3 except for **75**, where H-1 and H-8 are recorded in the lower frequency region with H-1 being more shielded. COSY and NOESY correlations are used to establish the assignments of the methylene protons H-7a (s) and H-11a (s). These geminal protons (H-7a (s) and H-11a (s)) exhibit an AB spin-spin splitting pattern and resonates as a pair of doublets with a coupling constant of approximately 10 Hz.[56] In the C-13 spectra, the most de-shielded signal was assigned to C-4 due to direct attachment to the electron-withdrawing carbonyl and amide nitrogen of the hydantoin ring.[56] C-3 and

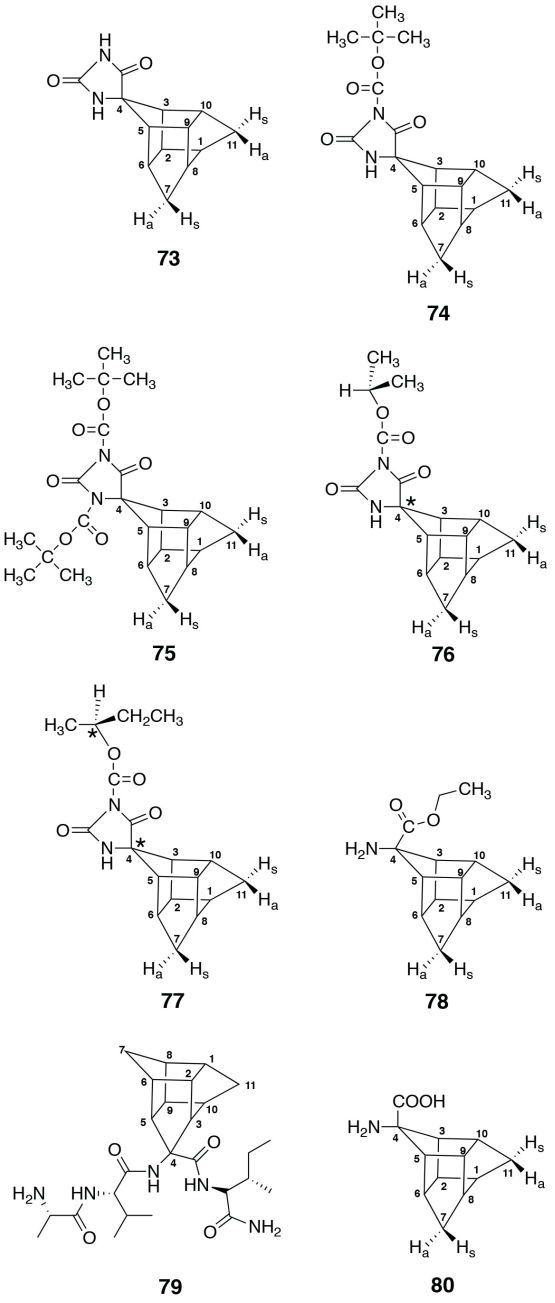

Figure 4 Structures of reported Trishomocubane derivatives **73–80**[36, 56-57]

Table 6: ^{1}H NMR data for trishomocubane derivatives (chemical shift and coupling constant)

atom	**73**[56]	**74**[56]	**75**[56]	**76**[57]	**77**[57]	**78**[57]	**79**[36]	**80**[57]
1	2.1	2.18	2.09–2.13	2.17–2.18	2.17	2.07	2.09	2.07
2	2.18	2.27	2.38–2.40	2.27–2.30	2.28–2.31	2.16–2.18	2.08	2.11–2.15
3	1.97	2.09	2.52–2.53	2.08–2.10	2.09–2.11	1.94	2.58	1.94–1.95
4								
5	1.91	2.08	2.16–2.17	2.07–2.08	2.07–2.09	2.05	2.36	2.05
6	2.45	2.39	2.28	2.44	2.45	2.6	2.01	2.6
7a	1.36–1.39 (10.2 Hz)	1.46–1.49, 10.4 Hz	1.46–1.48, 8.6 Hz	1.45–1.48,10.44 Hz	1.45–1.48, 10.6 Hz	1.39–1.42	1.35, 9.24 Hz	1.39–1.42, 11.7 Hz
7s	1.24–1.27 (10.2 Hz)	1.34–1.37;10.4 Hz	1.30–1.33, 11.5 Hz	1.33–1.36	1.32–1.35	1.3	1.25, 9.84 Hz	1.30, 11.7 Hz
8	2.1	2.19	2.14–2.15	2.17–2.18	2.17	2.09	2.03	2.09
9	2.13	2.33	2.29	2.30–2.33	2.31–2.33	2.04	2.48	2.04
10	2.84	2.95	3.12	2.94	2.95	2.16–2.18	2.07	2.16–2.18
11a	1.36–1.39 (10.2 Hz)	1.46–1.49, 10.4 Hz	1.44–1.46, 8.6 Hz	1.45–1.48,10.44 Hz	1.45–1.48, 10.6 Hz	1.39–1.39	1.31, 10.26 Hz	1.37–1.39, 11.7 Hz
11s	1.19–1.22 (10.2 Hz)	1.26–1.29, 10.4 Hz	1.27–1.30, 11.5 Hz	1.25–1.28, 10.44 Hz	1.26–1.28, 10.6 Hz	1.3	1.23, 10.38 Hz	1.30, 11.7 Hz

C-5 are recorded as the next most de-shielded signals owing to their direct attachment to the most de-shielded carbon, C-4, except in **75** where C-5 is more de-shielded than C-3 (Table 7). The next increased de-shielded signals are attributed to either C-8 or C-1, while the most shielded signals are assigned to C-7 except **75**, which recorded C-11 as the most shielded carbon.[56] Hence, other carbons show variable shifts in signals that do not follow a regular shielding pattern or de-shielding effect.

Compounds **78** and **80**, reported by Govender et. al.,[57] recorded H-6 as the highest ppm signal and consecutively followed by either H-10 or H-2 (Table 6), while the most shielded signal was assigned to both H-7s and H-11s having the same chemical shift. Here, H-10 appears shielded due to the free rotation of the carbonyl functionality obtained upon hydrolysis of the rigid hydantoin ring. The proton chemical shifts of both compounds follow essentially the same order.[57] Compound **79** recorded the most de-shielded and shielded signals for H-3 and H-11s, respectively.[36] The high chemical shift value of H-3 is due to the through-space de-shielding effect of the carbonyl side chain. The authors indicated that there are at least three useful points of entry for the NMR elucidation for the side chains of peptide **79** (AVPI).[36] These are the HMBC interaction of the Ala methyl protons (H-1) with the carbonyl carbon (C-3), the characteristic methyl protons (H-22/H-23) of the Val, and the characteristic ethyl group on Ile. The only quaternary carbon atom (C-4) of compound **79**[36] was assigned to the signal at 69.7 ppm. ROESY interactions were crucial to elucidate the rest of the cage protons for compound **79**.[36] The C-13 spectra for compounds **79** and **80** recorded C-4 as the most de-shielded carbon due to direct attachment to carbonyl functionality and amino group. The next de-shielded carbon was attributed to either C-3 or C-5 due to being directly attached to the most de-shielded carbon, namely, C-4, as given above, similarly for **73–77**. Simultaneously, the most shielded signal could either be assigned to C-7 or C-11 (Table 7).

3. Conclusion

The use of NMR spectroscopy for elucidating large compounds has revolutionised the traditional analytical methods used in many research fields. The data provided by 1D NMR spectroscopy is much simpler to analyse; however, it typically does not provide enough information to fully elucidate these compounds. 2D NMR spectroscopy allows for structure elucidation by determining the proximity and effects of protons on carbons or other protons via bond/space interactions. 2D NMR spectroscopy is especially useful for structural elucidation of similar compounds, as there are typical patterns that can be identified. After analysing a variety of literature, it can be concluded that adamantane, pentacycloundecane, and trishomocubane have unique NMR patterns. For unsubstituted adamantane, the general pattern in ^{13}C-NMR consists of matching shifts for C-8 and C-9, C-3, C-5 and C-7, and C-4, C-6, and C-10. In the ^{1}H-NMR data, there is a plane of symmetry present through H-2, H-5, H-6, and H-7 when a substituent is at position 2. However, when a substituent is at position 1, a plane of symmetry is observed in ^{1}H-NMR data through H-1, H-9, H-5, and H-10. There is a plane of symmetry present in pentacycloundecane when there is a lack of substituents and when there are identical substituents on position C-8 and C-11 (mesomeric). The following hydrogens were found to have identical shifts in ^{1}H-NMR: H-2 and H-6, H-1 and H-7, H-9 and H-10, H-3 and H-5. C-4 has two geminal protons: H-4a and H-4s, which typically differ in chemical shifts and do not appear equivalent. In addition, if the side arm of the cage has a chiral subsitutent, a diastereomeric effect is observed, which results in most of the cage carbon signals to split. When the side substituents are non-chiral but different, the PCU cage then appears asymmetric. Depending on the nature of the side arm, the presence of extended chains/heteroatoms can easily induce a through-space de-shielding effect, which results in nonequivalent atoms on the cage skeleton and the side arm interactions with the core. Trishomocubane, on the other hand, was found to have the following paired hydrogens; H-6 and H-7, H-7s and H-11s, H-1 and H-8, H-11a, and H-7a when substituents are not present on the ring. Although these patterns are most easily observed in unsubstituted compounds, they are still present in some compounds with substituents (mostly in monosubstituted derivatives). However, it is then necessary to consider the structures of the substituents as well because they may cause significant differences in the NMR spectra. Hence, 2D NMR as an elucidation tool has progressively allowed more precise and accurate structure determination of these cage compound structures. It is foreseen in the future that the combination of 2D NMR and computational chemistry will provide more insight into the 3D structure elucidation and interactions of these larger molecules.

Table 7 ^{13}C NMR data for trishomocubane derivatives (chemical shift)

atom	**73**[56]	**74**[56]	**75**[56]	**76**[57]	**77**[57]	**78**	**79**[36]	**80**[57]
1	46.66	46.69	45.93	46.71	46.73		41.8	46.91
2	43.69	42.78	46.23	43.22	43.23		42.7	43.22
3	55.67	56.08	54.03	56.13	56.12, 56.17		52.2	56.2
4	73.48	71.78	76.55	71.92	71.96, 72.00		69.7	69.07
5	54.82	55.12	58.15	55.22	55.21, 55.25		53.4	54.04
6	45.66	45.32	45.27	45.3	45.34		43	44.63
7a	32.95	32.8	33.02	32.78	32.79		32.7	32.68
7s								
8	47.1	46.76	46.11	46.71	46.73		42.1	46.92
9	42.2	43.2	41.94	42.75	41.98		53.1	44.57
10	42.75	41.98	42.91	41.96	42.75		42.7	42.1
11a	33.49	33.16	32.94	33.13	33.15		32	33.6
11s								

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