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Synthesis and NMR elucidation of novel penta-cycloundecane amine derivatives as potential antituberculosis agents

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The synthesis and NMR elucidation of five novel penta-cycloundecane amine derivatives are reported. These compounds are potential antituberculosis agents. The ^{1}H and ^{13}C spectra showed major overlapping of methine signals of the cage skeleton making it extremely difficult to elucidate these compounds. The overlapping occurs as a result of the additions made to the carbonyl carbon (C-8/C-11) of the cage. The two-dimensional NMR technique proved to be a useful tool in overcoming this problem. All compounds reported are *meso* compounds thereby not only simplifying the NMR structure elucidation, but also making it indeed possible.

Supporting information may be found in the online version of this article.

Keywords: NMR; ^{1}H NMR; ^{13}C NMR; 2D NMR; antituberculosis; PCU-diamine

Introduction

Over the years, the chemistry of polycyclic 'cage' compounds has been of major interest to organic chemists.[1–4] Our group has utilized two-dimensional (2D) NMR spectroscopy to study the structure of the cage skeleton in relation to its side 'arms.'[5–8] As part of a program to utilize NMR spectroscopy as a vital tool in the elucidation of penta-cycloundecane (PCU) derivatives, the NMR elucidation of five PCU amine derivatives (**1**–**5**) is reported herein (Fig. 1).

Many authors have reported the difficulty encountered with NMR elucidation of cage compounds;[1,7,9–11] however, the availability of 2D NMR techniques have helped a great deal in overcoming these difficulties. The rigid structure of the cage skeleton is known to exhibit through space effects, geminal and vicinal proton–proton couplings and long-range proton–proton interactions that result into broad overlapping resonances. The reported novel PCU-diamine compounds **1**–**5** are currently being investigated as potential antituberculosis agents. Polycyclic 'cage' compounds (including adamantane and PCU) are known for their highly lipophilic nature, which has been explored as transport medium to carry drugs through lipid-rich cell membranes such as the blood–brain barrier (BBB) and the central nervous system.[3,12–14] It also helps to prolong the activity of the drug in the body by reducing the biodegradation of such drugs.[15,16]

The PCU derivatives above were based on research findings by Bogatcheva *et al*.[17] and Tangallapally *et al*.[18,19] Bogatcheva *et al*. reported new cyclic diamine compounds with promising activity against *Mycobacterium tuberculosis* (M-TB). They have used commercially available diamine derivatives to synthesize a diverse library of 5000 compounds that were tested for antituberculosis activities; this project led to the discovery of SQ 775, an adamantane derivative.

Tangallapally *et al*.[18,19] also reported the discovery of a new class of nitrofuranamide compounds with excellent antituberculosis activity. These compounds gave promising *in vitro* activity but this could not be duplicated with the *in vivo* analysis. It was believed to undergo proteolysis. The introduction of a rigid bicyclic tetradhydroisoquinoline moiety **7** showed improved *in vivo* activity. It is hoped that the introduction of a polycyclic 'cage' compounds (such as PCU) to similar TB active side chains may enhance the *in vivo* activity against M-TB of the resulting compounds as well.

Synthesis of the PCU derivatives

The PCU ditosylate **8** is obtained as described in literature.[20] 2-(Aminomethyl) pyridine **9** and ethanolamine **10** was reacted with benzaldehyde **11** via reductive amination to afford *N*-benzyl-*N*-(2-methylpyridine) **12**[21] and *N*-benzyl ethanolamine **13** (Scheme 1). The PCU ditosylate **8** was reacted with *N*-benzyl-*N*-(2-methylpyridine) **12** under reflux conditions and under nitrogen to afford *N*-benzyl-*N*-(2-methylpyridine) PCU **14**. *N*-Benzyl-*N*-(2-methylpyridine) PCU **14** was deprotected using 10% Pd/C to afford 2-(aminomethyl) pyridine PCU **1**.

N-Benzyl ethanolamine **13** was refluxed with PCU ditosylate **8** under nitrogen atmosphere to afford *N*-benzyl ethanolamine PCU **2** (Scheme 2).

PCU ditosylate **8** was reacted with excess homopiperazine in dry dichloromethane (DCM) with high dilution to afford PCU

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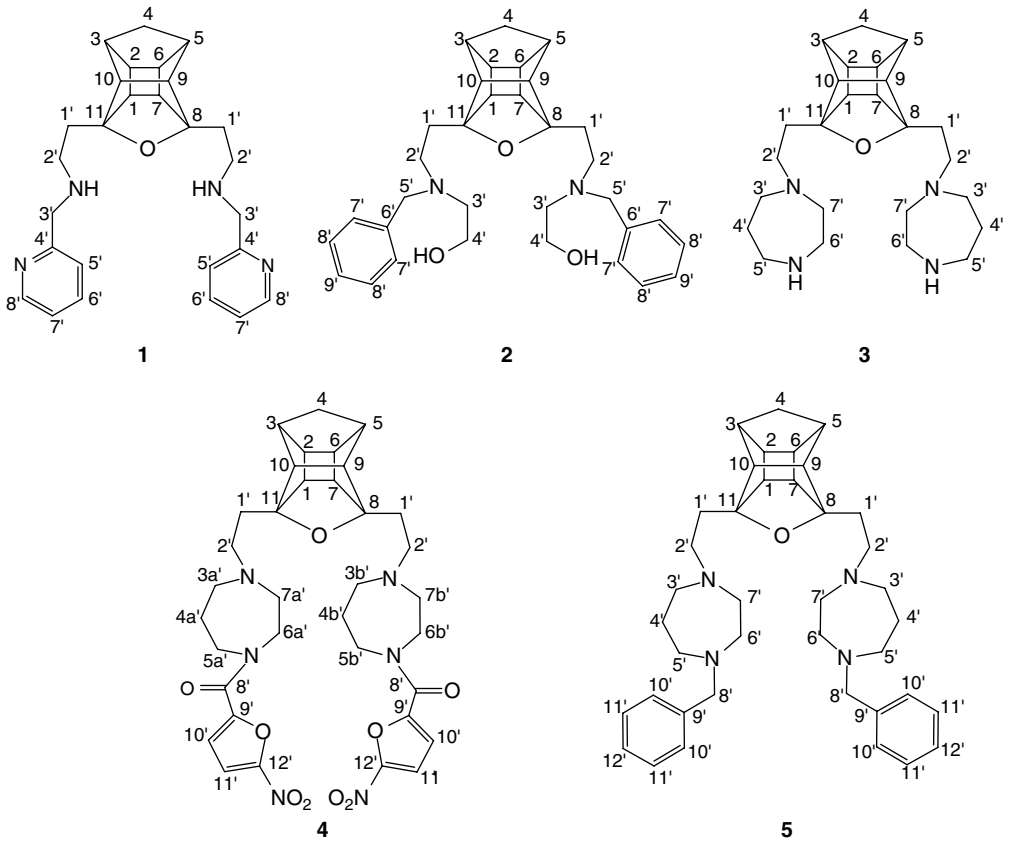
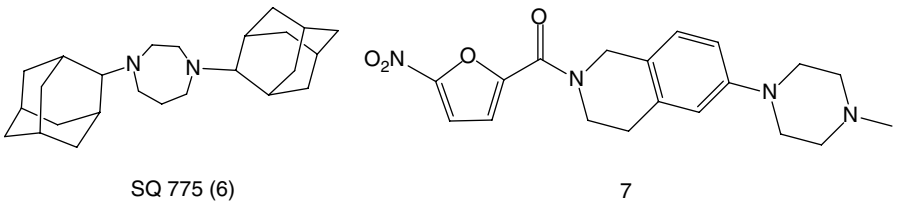


Figure 1. NMR elucidation of five PCU amine derivatives (**1**–**5**).



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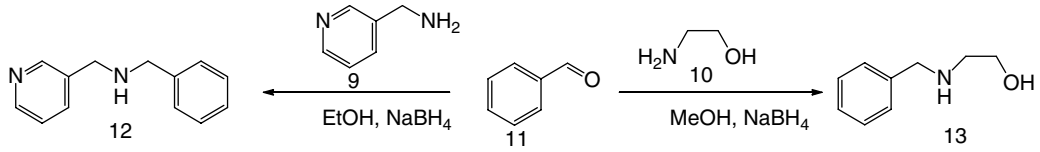
homopiperazine **3**. PCU homopiperazine **3** was reacted with 5-nitrofuran-2-carbonyl chloride to afford 5-nitrofuran-2-carbonyl homopiperazine PCU **2**.[22] The PCU ditosylate **8** was reacted with *N*-benzyl homopiperazine to afford *N*-benzyl homopiperazine PCU **5** (Scheme 3).

Results and Discussions

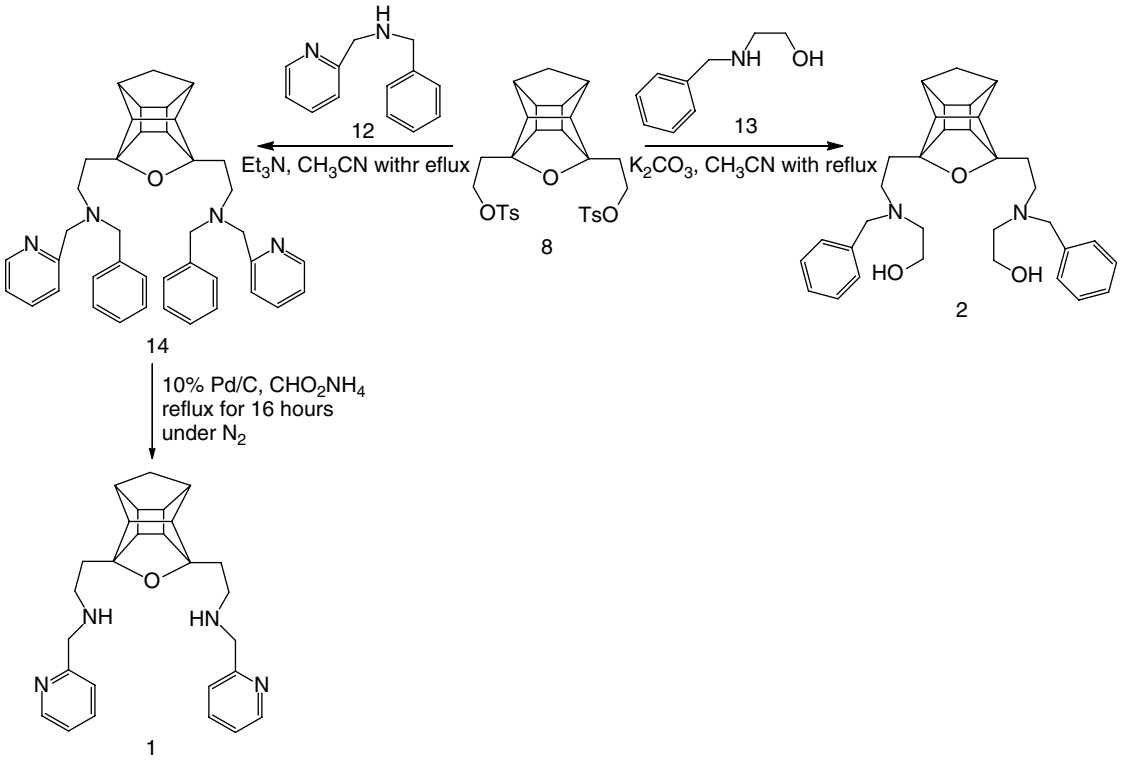
Compounds **1**–**5** are *meso* compounds that simplify their NMR spectra since all groups on the cage, except the methylene group at C-4, exits as pairs. The methylene protons H-4 are geminal protons that are observed as AB spin resonances at approximately δ 1.50 and δ 1.80.[5–8,20,23]

The ^{1}H NMR spectrum of compound **1** shows geminal PCU bridge methylene protons resonances at 1.49 and 1.84 ppm (*d*, $J = 10.28$ Hz) that were assigned to H-4a and H-4s, respectively. The COSY and NOESY spectra show a correlation of H-4a (H-4s) with a signal at 2.33 ppm that was attributed to H-3/H-5 since these protons show correlation with two other methine protons that should be H-2/H-6 and H-9/H-10. However, only H-2/H-6 shows correlation with H-1/H-7 confirming that the resonance at 2.56 ppm belongs to H-2/H-6. Through elimination it is clear that H-9/H-10 is registered at 2.46 ppm, while H-1/H-7 registers at 2.48 ppm. The NOESY spectrum also shows correlation of H-4a with H-2/H-6, while H-4s correlates with H-9/H-10. The HMBC and NOESY spectra are vital tools in understanding how the cage proton interacts/correlate with the 'arms' attached to the cage. The HMBC spectrum shows correlation of C-9/C-10 with H-1′ (2.02 ppm) and H-4a (1.49 ppm), while C-8/C-11 shows correlation with H-2′ (2.78 ppm) and H-1′ (2.02 ppm). The HMBC spectrum also shows correlation of H-3′ (3.89 ppm) with C-2′ (46.1 ppm), C-5′ (122.2 ppm) and C-4′ (159.3 ppm), a quaternary carbon. C-4′ shows HMBC correlation to H-3′ and two other aromatic protons that were assigned to H-5′ (7.30) and H-6′ (δ 7.61). The COSY spectrum shows a correlation of H-5′ (δ 7.30) with H-6′ (δ 7.61 ppm) and H-7′ (7.13 ppm).

The remaining aromatic proton was assigned to H-8′ (8.52 ppm). The coupling constants of the pyridine rings assisted to conform the assignment; pyridine rings give typical coupling constants of 5 and 8 Hz,[24] suggesting that the protons with one coupling constant are H-5′ and H-8′, while the ones with two coupling constants are H-6′ and H-7′.



Scheme 1. Synthesis of compound **12** and **13** via reductive amination.



Scheme 2. Synthetic route for compounds **1** and **2**.

The NOESY spectrum shows a correlation H-9/H-10 with H-1′ at 2.02 ppm. H-1′ also shows both NOESY and COSY correlations with H-2′ at 2.78 ppm. The methylene protons H-3′ (3.89 ppm) also show NOESY correlation with H-1′ (2.02 ppm), H-2′ (2.78 ppm) and H-5′ (7.30 ppm), respectively. Further verification was carried out using the HSQC spectrum. The NMR assignments for 2-(aminomethyl) pyridine PCU **1** are as presented in Table 1.

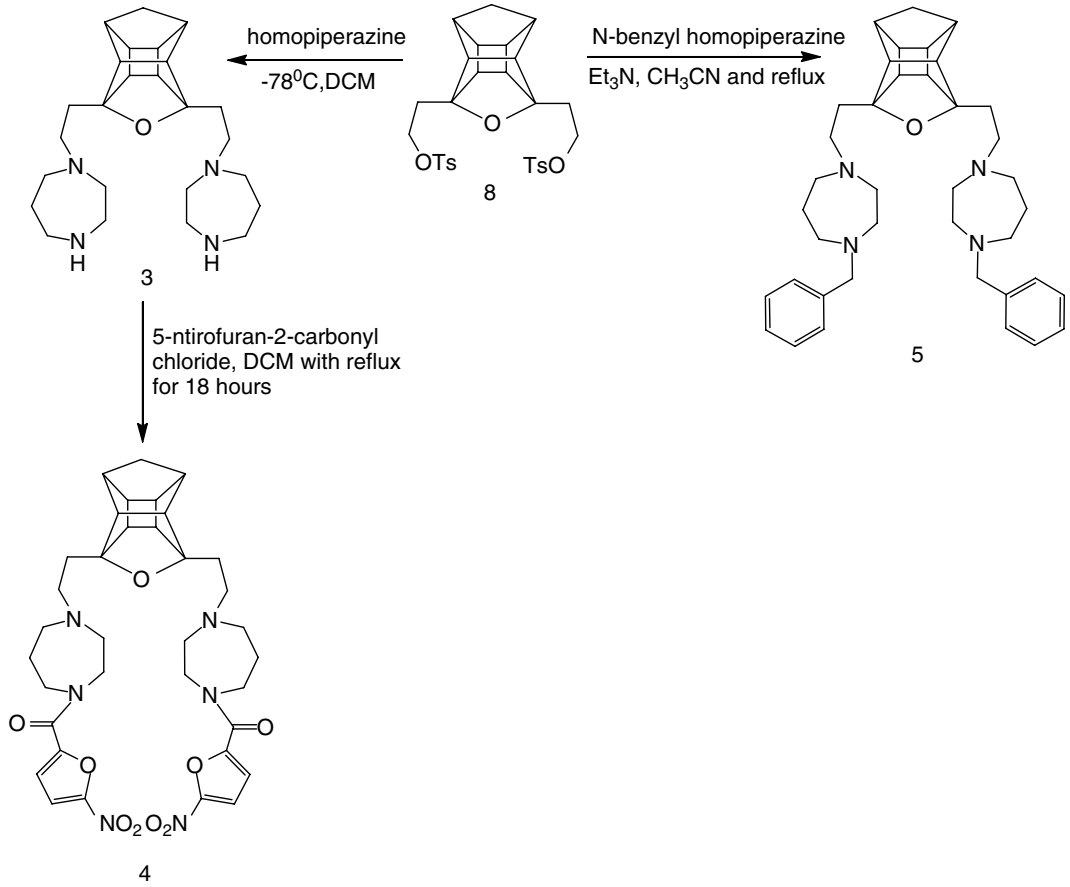
The same methodology used in *N*-(2-methylpyridine) PCU (**1**) was used to elucidate the cage carbons/protons of the rest of the compounds. Details of that will be omitted in the discussion below.

The HMBC spectrum for PCU (**2**) shows correlation of C-8/C-11 (95.1 ppm) with H-1′ (1.96 ppm), while the fully substituted aromatic carbon C-6′ shows HMBC correlation to a methylene proton at 3.61 ppm and the phenyl hydrogen register at 7.28 ppm (H-7′ and H-8′); the signal at 3.61 ppm was assigned to H-5′. The COSY spectrum shows correlation of H-1′ (1.96 ppm) with a signal at 2.58 ppm that was assigned to H-2′. A COSY correlation was also observed between 3.54 and 2.63 ppm, the former signal was assigned to H-4′ since it is bonded to an oxygen atom that could contribute to its high frequency while the latter was assigned to H-3′.

The H-5′ protons show HMBC correlation to C-2′ (49.6 ppm), C-3′ (55.0 ppm), C-7′ (129.0 ppm) and C-6′ (139.0 ppm); through elimination the resonance at 127.1 ppm was assigned to C-9′ (H-8′/C-8′ is known – see above). Also evident from the HMBC spectrum is the correlation of H-3′ (2.63 ppm) with C-2′ (49.6 ppm), C-4′ (58.6 ppm) and C-5′ (58.4 ppm). The NOESY spectrum shows correlations of H-1′ (1.96 ppm) with H-9/H-10 (2.30 ppm), H-2′ (2.58 ppm), H-3′ (2.63 ppm) and H-5′ (3.61 ppm), while H-4′ shows NOESY correlations with H-3′ (2.63 ppm). The NOESY spectrum also shows correlation of H-5′ (3.61 ppm) with H-3′ (2.63 ppm) and the phenyl protons at 7.28 ppm.

All the phenyl hydrogen appear as a single resonance at 7.28 ppm as expected[25], while their carbon resonances were assigned based on their chemical environment and their HMBC correlation stated above. The assignments are presented in Table 1.

The homopiperazine moiety on the cage arm for **3** is not totally symmetrical and each methylene proton signal is expected to appear differently with regard to H-3′, H-5′, H-6′ and H-7′. However, C-4′ is expected to be distinct because C-3′, C-5′, C-6′ and C-7′ are all directly bonded to a nitrogen atom with the exception of C-4′ which is only bonded to two carbon atoms. The ^{1}H NMR spectrum shows a methylene proton appearing at a lower frequency (1.70 ppm) which was assigned to H-4′. The assignment was confirmed by a COSY correlation between H-4′ (1.70 ppm) and two signals in the region 2.64 and 2.88 ppm, which should be H-3′ and H-5′. The signal at 2.64 ppm was assigned to H-3′, while 2.88 ppm was assigned to H-5′ since H-3′ is experiencing a more



Scheme 3. Synthetic route for compounds **3**, **4** and **5**.

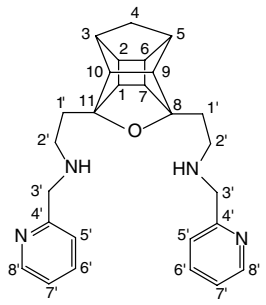
electron-rich environment due to the inductive effect exercised by C-2′. H-6′ (2.86 ppm) shows COSY correlation with H-7′ (2.61 ppm). Another COSY correlation is observed between H-1′ (1.93 ppm) and H-2′ at 2.50 ppm. Also, the NOESY spectrum shows interaction of H-1′ (1.93 ppm) with H-7′ (2.61 ppm), H-2′ (2.50 ppm) and H-9/10 (2.42 ppm). A NOESY interaction of H-4′ (1.70 ppm) with H-3′ (2.64 ppm) and H-5′ (2.88 ppm) is also observed. The HMBC spectrum shows correlation of H-4′ (1.70 ppm) with C-5′ (47.1 ppm) and C-3′ (54.6 ppm), while C-7′ (57.9 ppm) shows correlation with H-6′ (2.86 ppm). The HMBC spectrum also shows correlation of C-3′ (54.6 ppm) with H-4′ (1.70 ppm) and H-5′ (2.88 ppm). The assignments were further confirmed using the HSQC spectrum and the NMR data are presented in Table 2.

The ^{1}H NMR spectrum of PCU **4** shows two high-frequency peaks at regions 3.84–3.85 and 3.72–3.77 ppm regions representing two methylene protons each. It was expected that the cage arms bearing the homopiperazine moiety would be identical. However, based on the number of signals observed on the ^{1}H and ^{13}C spectra, it is clear that a conformational effect was again observed as reported before for other bi-dentate PCU analogous.[6,8] A total of two signals for each carbon on the homopiperazine moiety was observed on the ^{13}C, HMBC and HSQC spectra, this effect is caused by the restricted/hindered rotation of the amide group.[25,26] The methylene protons *cis* to the carboxamide oxygen will appear at a higher frequency compared to the *trans*-methylene protons due to a through space deshielding effect from the carbonyl oxygen atom.[24] Since H-5a′, H-5b′, H-6a′ and H-6b′ are all in close proximity of an amide group they will appear at a higher frequency. As indicated above H-5a′ and H-6b′ (3.86 and 3.84 ppm) will experience a through space deshielding effect from the carboxamide oxygen and they will therefore appear at a higher frequency, in comparison to H-6a′ and H-5b′ (3.73 and 3.75 ppm) that are *trans* to the carboxamide oxygen. The same effect is transferred in a reduced form to H-3a′, H-3b′, H-7a′ and H-7b′.

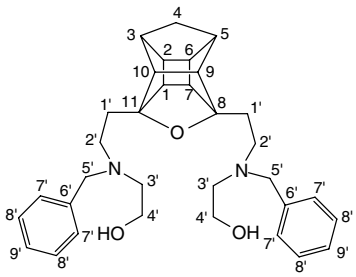
The nature of this conformational effect was studied using a temperature-dependent NMR study. The ^{1}H NMR spectrum recorded at 101 °C gave a single peak at 3.69 ppm suggesting that the two peak regions observed at 3.84–3.85 and 3.72–3.77 ppm shifted to 3.69 ppm due to the applied temperature. This implies that the energy barrier to the rotation about the C–N bond has been broken with the arms now moving faster than the NMR time scale to become a single peak as described in literature.[24,25]

A similar pattern observed in PCU homopiperazine **3** where H-4′ of the homopiperazine methylene appeared at a lower frequency was expected with regard to compound **4**. Owing to the conformational effect observed for **4**, two methylene protons belonging to the homopiperazine moiety were observed at region 1.98 and δ 2.03 ppm. Using the COSY and NOESY spectra, the former signal 1.98 ppm (H-4b′) shows correlation with protons at 2.68 and 3.73 ppm (H-3b′ and H-5b′) while the latter signal 2.03 ppm (H-4a′) shows correlation with protons at 2.69 and 3.86 ppm (H-3a′ and H-5a′). The COSY and NOESY spectra also show correlation of 2.80 ppm with 3.75 ppm, while 2.88 ppm correlates with 3.84 ppm. Having explained the correlation of the three carbon side of homopiperazine moiety of each cage 'arm' and how the amide bond affects the orientation of these carbon,

Table 1. NMR data[a] for PCU derivatives **1** and **2**



1



2

2 (Aminomethyl) pyridine PCU (**1**)				*N*-benzyl ethanolamine PCU (**2**)			
Atom	δ^1H^b	*J* (Hz)	$\delta^{13}C^b$	Atom	δ^1H^b	*J* (Hz)	$\delta^{13}C^b$
1/7	2.48	–	47.9	1/7	2.33	–	47.7
2/6	2.56	–	41.5	2/6	2.49	–	41.4
3/5	2.33	–	44.2	3/5	2.25	–	44.1
4a	1.49	10.28	43.5	4a	1.44	10.28	43.4
4s	1.84	10.32	43.5	4s	1.77	10.32	43.4
8	–	–	95.4	8	–	–	95.1
9/10	2.46	–	58.5	9/10	2.30	–	58.4
11	–	–	95.4	11	–	–	95.1
1′	2.02	7.28	32.5	1′	1.96	7.32, 7.36	29.3
2′	2.78	–	46.1	2′	2.58	–	49.6
3′	3.89	–	55.1	3′	2.63	–	55.0
4′	–	–	159.3	4′	3.54	4.60, 4.72	58.6
5′	7.30	7.72	122.2	5′	3.61	–	58.4
6′	7.61	7.48, 7.56	136.5	6′	–	–	139.0
7′	7.13	5.24, 6.8	120.0	7′	7.28	–	129.0
8′	8.52	4.16	149.2	8′	7.28	–	128.3
–	–	–	–	9′	7.28		127.1

[a] 400 MHz for ^1H and 100 MHz for ^{13}C.
[b] Solvent $CDCl_3$.

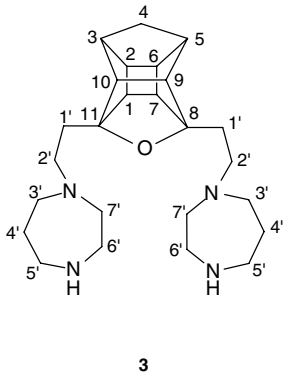
2.80 ppm was assigned to H-7a′, 2.88 ppm to H-7b′, 3.75 ppm to H-6a′ and 3.84 ppm to H-6b′. The NOESY spectrum shows correlation of H-1′ with H-3/5 and H-9/10 while H-4a′ shows correlation to H-7a′ and H-7b′. Also evident from the NOESY spectrum is the correlation of H-3a′ with H-4a′ and H-5a′, while H-3b′ shows interaction with H-4b′ and H-5b′. The HMBC spectrum shows correlation of C-4a′ (28.7 ppm) and C-3a′ (54.4 ppm) to H-5a′ (3.86 ppm), while C-4b′ (27.0 ppm) and C-3b′ (54.8 ppm) shows correlation to H-5b′ (3.73 ppm). The carbonyl carbon, C-8′ (157.9 ppm), shows HMBC correlation with H-5a′ (3.86 ppm), H-6a′ (3.75 ppm), H-5b′ (3.73 ppm) and H-6b′ (3.84 ppm).

The quaternary carbons on the nitro furan group were assigned based on the conjugative effect of the nitro group and the carbonyl group on the carbons to which they are attached. C-12′ is directly bonded to a nitro group and this is expected to appear at a higher frequency when compared to C-9′ which is bonded to a carbonyl carbon. On the basis of this information 149.1 and 151.2 ppm were assigned to C-9′ and C-12′, respectively. The assignment of the furan protons (7.19 and 7.35 ppm) was based on their chemical environment, both alkene protons have conjugated bond with both a carbonyl and a nitro group; the nitro group causing a greater deshielding effect.[25] The signals at 7.19 and 7.35 ppm were therefore assigned to H-10′ and H-11′, respectively. Both quaternary carbons (C-9′ and C-12′) show HMBC correlations with H-10′ (7.19 ppm) and H-11′ (7.35 ppm). The assignments of all signals are presented in Table 2.

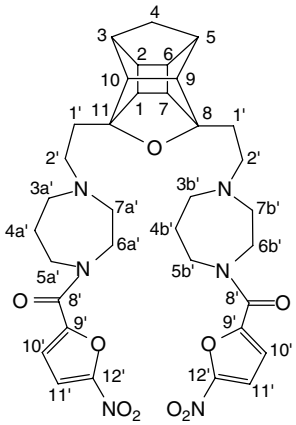
Following the same methodology and pattern used in elucidating compounds **3** and **4** (both homopiperazine-based compounds), compound **5** was also elucidated. It is quite clear that the conformational effect as observed for PCU-**4** is not observed here. As expected, one of the methylene protons (H-4′) on the homopiperazine moiety appears at a lower frequency of 1.77 ppm. This resonance shows a COSY and NOESY correlation with 2.73 and 2.67 ppm. On the basis of the chemical environment, the peak at 2.73 ppm was assigned to H-5′ and the signal at 2.67 ppm was assigned to H-3′. Resonances of H-6′ and H-7′ could not be assigned because of overlapping of signals.

The overlap of C-3′, C-5′, C-6′ and C-7′ (homopiperazine carbons) made it difficult to assign the specific resonances. However, the separate orientation of the H-4′ and C-4′ made it possible to assign the proton signals using its correlation with 3′ and 5′ from the COSY, NOESY and HMBC spectra. This enabled the assignment of H-3′ (2.67 ppm) and H-5′ (2.73 ppm). The position of H-6′ and H-7′ (overlapping) was observed between 2.66 and 2.68 ppm due to a NOESY interaction with H-8′. The carbons for C-3′, C-5′,

Table 2. NMR data[a] for PCU derivatives **3** and **4**



3



4

PCU homopiperazine (**3**)				5-Nitrofuran-2-carbonyl homopiperazine PCU (**4**)			
Atom	δ^1H^b	*J* (Hz)	$\delta^{13}C^b$	Atom	δ^1H^b	*J* (Hz)	$\delta^{13}C^b$
1/7	2.44	–	47.9	1/7	2.48	–	48.0
2/6	2.54	–	41.7	2/6	2.60	–	41.8
3/5	2.32	–	44.4	3/5	2.37	–	44.4
4a	1.45	10.28	43.3	4a	1.52	10.16	43.4
4s	1.81	10.24	43.3	4s	1.84	10.24	43.4
8	–	–	94.8	8	–	–	94.7
9/10	2.42	–	58.7	9/10	2.46	–	58.8
11	–	–	94.8	11	–	–	94.7
1′	1.93	7.84, 7.88	30.3	1′	2.00	–	30.4
2′	2.50	–	54.5	2′	2.59	–	54.3
3′	2.64	–	54.6	3a′	2.69	–	54.4
4′	1.70	5.40, 5.44	30.1	3b′	2.68	–	54.8
5′	2.88	–	47.1	4a′	2.03	–	28.7
6′	2.86	–	48.6	4b′	1.98	–	27.0
7′	2.61	–	57.9	5a′	3.86	–	48.8
–	–	–	–	5b′	3.73	–	46.2
–	–	–	–	6a′	3.75	–	47.3
–	–	–	–	6b′	3.84	–	47.9
–	–	–	–	7a′	2.80	–	54.9
–	–	–	–	7b′	2.88	–	56.7
–	–	–	–	8′	–	–	157.9
–	–	–	–	9′	–	–	149.1
–	–	–	–	10′	7.19	3.6	117.8
–	–	–	–	11′	7.35	3.6	111.7
–	–	–	–	12′	–	–	151.2

[a] 400 MHz for ^1H and 100 MHz for ^{13}C.
[b] Solvent $CDCl_3$.

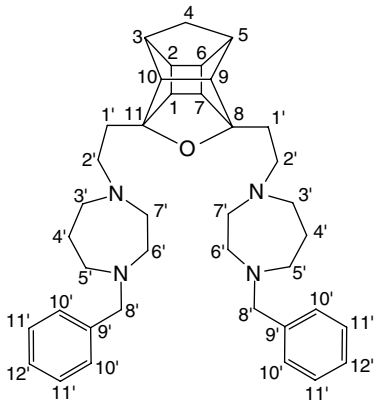
C-6′ and C-7′ are observed between 54.1 and 55.1 ppm (HSQC spectrum).

The HMBC spectrum shows correlation of H-8′ (3.60 ppm) with a homopiperazine carbon (either C-5′ or/and C-6′), a phenyl carbon at 128.8 ppm and a quaternary carbon at 139.5 ppm, the former was assigned to C-10′, while the latter was assigned to C-9′, respectively. The signals at 128.1 and 126.7 ppm were assigned to C-11′ and C-12′, respectively, based on their chemical environment. The NOESY spectrum shows interaction of H-1′ (1.96 ppm) with H-3′ (2.67 ppm), H-2′ (2.55 ppm) and H-9/10 (2.45 ppm). All the phenyl hydrogens appear as a multiplet signal (7.19–7.32 ppm) which is expected,[25] while their carbon resonances were assigned based on their chemical environment and their HMBC correlations stated above. The assignments are presented in Table 3.

Conclusion

The NMR elucidation of five novel PCU derivatives was successfully carried out. The 2D NMR spectroscopy proved to be a crucial tool

Table 3. NMR data[a] for PCU derivatives **5**



5

N-benzyl homopiperazine PCU (**5**)

Atom	δ^1H[b]	*J* (Hz)	δ^{13}C[b]
1/7	2.48	–	47.9
2/6	2.58	–	41.7
3/5	2.35	–	44.4
4a	1.48	10.28	43.3
4s	1.84	10.32	43.3
8	–	–	94.8
9/10	2.45	–	58.8
11	–	–	94.8
1′	1.96	7.96, 8.08	30.3
2′	2.55	–	54.1–55.1
3′	2.67	–	54.1–55.1
4′	1.77	5.72, 5.80	27.5
5′	2.73	–	54.1–55.1
6′	2.66–2.68	–	54.1–55.1
7′	2.66–2.68	–	54.1–55.1
8′	3.60	–	62.7
9′	–	–	139.5
10′	7.19–7.32	–	128.8
11′	7.19–7.32	–	128.1
12′	7.19–7.32	–	126.7

[a] 400 MHz for ^{1}H and 100 MHz for ^{13}C.
[b] Solvent $CDCl_3$.

in structural elucidation of compounds with major overlapping of protons. The compounds reported are all *meso* compounds. As observed before, large side-arm groups attached to the PCU cage exhibit conformational effects.

Experimental

The NMR data were recorded on a Bruker AVANCE III 400 MHz instrument using 50 mg of sample per 0.5 ml of $CDCl_3$. Infrared (IR) spectra were obtained on a Perkin Elmer Spectrum 100 instrument with an Attenuated Total Reflectance attachment. Mass spectra were obtained using a Waters LCT Premier Time of Flight mass spectrometer. Column chromatography was carried out using silica gel 60. Tetrahydrofuran was freshly distilled before use from a sodium benzophenone ketyl under N_2 atmosphere, while DCM was dried using phosphorus pentoxide before use.

The chemical shifts were referenced to the solvent peak 7.24 ppm for $CDCl_3$ at ambient temperature. The ^{1}H NMR spectrum was recorded at a transmitter frequency of 400.222 MHz (spectral width, 8223.68 Hz; acquisition time, 1.992 s; pulse width, 10 μs; scans, 16; relaxation delay, 1 s). The ^{13}C NMR spectrum was recorded at 100.645 MHz (spectral width, 24038.46 Hz; acquisition time, 1.363 s; pulse width, 8.40 μs; scans, 2400; relaxation delay, 2 s). The 2D experimental data parameters were as follows: 90° pulse width, 10 μs for all spectra; spectral width for ^{1}H, 3067.49 **1**–**5**; spectral width for ^{13}C, 16666.67 for **1**–**5**; number of data points per spectrum, 2048, (COSY) for **1**–**5**, 2048, (NOESY) for **1**–**5**, 4096, (HMBC) for **1**–**5**, 1024 (HSQC) for **1**–**5**; number of time-incremented spectra, 128 (COSY) for **1**–**5**, 256, (NOESY) for **1**–**5**, 128, (HMBC) for **1**–**5**, 256 (HSQC) for **1**–**5**; relaxation delay, 1.34 s (COSY) for **2** and **4**, 1.05 s (COSY) for **3**, 1.43 and 1.36 s (COSY) for **1** and **5**, 2.00, 1.91, 1.63, 1.92 and 1.93 s (NOESY), mixing time, 0.30 s (NOESY) for 1–5, respectively. 1.38, 1.20, 0.64, 1.22 and 1.25 s (HMBC) for **1**–**5**, respectively, 1.47,1.42, 1.5, 1.43 and 1.44 s (HSQC) for **1**–**5**, respectively; spectra acquired in phase-sensitive mode, **1**–**5** (NOESY and HSQC); spectra acquired in absolute value mode, **1**–**5** (COSY and HMBC); gradients used for **1**–**5** (COSY, HSQC and HMBC). All NMR spectra are available as Supporting Information.

(Aminomethyl) pyridine PCU 1

A mixture of 1 g (9.2 mmol) of 2-(aminomethyl) pyridine **9** and 0.98 g (9.2 mmol) of benzaldehyde **11** in 15 ml ethanol was stirred for 1 h at room temperature (RT) under nitrogen atmosphere. The corresponding imine was reduced with solid $NaBH_4$ (0.7 g, 18 mmol) that was added slowly over 30 min, the mixture was further stirred for an additional 30 min, the mixture was then refluxed over night. The mixture was allowed to cool to RT, an additional 15 ml of ethanol was added to the reaction vessel after which 10% HCl was added to quench excess $NaBH_4$. The acidic mixture was basified with 25% NH_4OH solution. The desired product was extracted with DCM (2 × 50 ml), the solution was dried over Na_2SO_4 and concentrated *in vacuo*. The crude product was distilled under vacuum to afford 1.2 g (65%) of *N*-benzyl-*N*-(2-methylpyridine) **12**.

In the next step, a mixture of *N*-benzyl-*N*-(2-methylpyridine) **12** (1.5 g, 7.6 mmol), PCU ditosylate **8** (1.9 g, 3.4 mmol) and Et_3N (710 μl) in CH_3CN (20 ml) was refluxed under nitrogen for 4 days. The reaction was monitored on thin-layer chromatography (TLC), after completion the reaction was filtered and concentrated *in vacuo*. The crude product was purified via column chromatography on silica gel using CH_3Cl : MeOH : NH_4OH (88 : 10 : 2, R_f = 0.8) as eluent to give *N*-benzyl-*N*-(2-methylpyridine) PCU **14** as a yellow oil (1.55 g, 75%). ^{1}H NMR [$CDCl_3$, 400 MHz]: δ_H 1.39 (AB, J_{AB} = 10.2 Hz, 1H), 1.73 (AB, J_{AB} = 10.2 Hz, 1H), 2.01 (t, J = 7.8 Hz, 4H), 2.18–2.58 (m, 8H), 3.61 (s, 2H), 3.72 (s, 2H), 7.10 (t, J = 5.2 Hz, 1H), 7.19–7.33 (m, 5H), 7.52 (d, J = 7.7 Hz, 1H), 7.60 (t, J = 7.5 Hz, 1H), 8.47 (d, J = 4.2 Hz, 1H).

A mixture of (1.8 g, 1.7 mmol) *N*-benzyl-*N*-(2-methylpyridine) PCU **14**, ammonium formate (0.54 g, 8.5 mmol) and 150 mg of 10% Pd/C in methanol was refluxed under nitrogen atmosphere for 15 h. The mixture was cooled to RT and filtered under vacuum, the filtrate was then washed with 10% $NaHCO_3$, the mixture dried over Na_2SO_4, concentrated *in vacuo* to afford pure 2 (aminomethyl) pyridine PCU **(1)** as a light yellow oil (CH_3Cl : MeOH : NH_4OH – 88 : 10 : 2, R_f = 0.65; 854 mg, 67%). IR ν_{max}: 3314, 2955, 1665, 1590, 1433 and 753 cm^{-1}, high-resolution mass spectrometry (HRMS) calculated for $C_{27}H_{32}N_4O$ ($M + H^+$) 429.2654, found 429.2667.

N-Benzyl ethanolamine PCU 2

A mixture of *N*-ethanolamine **10** (1.2 g, 20 mmol) and benzaldehyde **11** (2.1 g, 20 mmol) in 20 ml of methanol was stirred at 25 °C under dinitrogen atmosphere for 2 h. The mixture was cooled to 0° using an external ice-salt bath after which $NaBH_4$ (1.5 g, 40 mmol) was added slowly. The mixture was stirred overnight at RT. Excess $NaBH_4$ was quenched by adding 20 ml of 10% HCl, the mixture was basified with 25% NH_4OH and the product was extracted from the mixture with DCM (2 × 30 ml). The solvent was dried over Na_2SO_4 and concentrated *in vacuo* to afford pure *N*-benzyl ethanolamine **13** (2.2 g, 72%). ^{1}H NMR [$CDCl_3$, 400 MHz]: δ_H 2.71 (t, 2H), 3.04 (NH), 3.60 (t, 2H), 3.75 (s, 2H), 7.23–7.33 (m, 5H). ^{13}C NMR ($CDCl_3$): δ_C: 50.6 (t), 53.4 (t), 60.6 (t), 127.0 (d), 128.1 (d), 128.3 (d), 139.6 (s).

A mixture of *N*-benzyl ethanolamine **13** (1.2 g, 7.9 mmol), PCU ditosylate **8** (2 g, 3.6 mmol) and K_2CO_3 (0.745 g, 5.4 mmol) in CH_3CN was refluxed under nitrogen for 4 days. The reaction was monitored on TLC, after completion the reaction was filtered and concentrated *in vacuo*. The crude product was purified via column chromatography on silica gel using CH_3Cl : MeOH : NH_4OH (88 : 10 : 2, R_f = 0.7) as eluent to give *N*-benzyl ethanolamine PCU **2** (1.3 g, 70%). IR ν_{max}: 3371, 2951, 1601, 1452, 1043, 732 and 697 cm^{-1}. HRMS calculated for $C_{33}H_{42}N_2O_3$ ($M + H^+$) 515.3274, found 515.3288.

PCU homopiperazine 3

To a vigorously stirred solution of homopiperazine (2.2 g, 22 mmol) in 400 ml of DCM at −78 °C (dry ice, 2-propanol) under N_2 atmosphere was added dropwise to PCU ditosylate **8** (1.2 g, 2.2 mmol) in 100 ml of DCM over 45 min. The reaction mixture was left to attain RT with stirring for 24 h. The solution was washed with water to remove excess homopiperazine, the organic extract was dried over Na_2SO_4 and concentrated *in vacuo*. The crude residue was purified via column chromatography using CH_3Cl : MeOH : NH_4OH (88 : 10 : 2, R_f = 0.2) to give PCU homopiperazine **3** as a light yellow oil (0.55 g, 62%). IR ν_{max}: broad absorption (N–H) 3386, 2818, 1465, 1108, 927, 918 and 748 cm^{-1}. HRMS calculated for $C_{25}H_{40}N_4O$ ($M + H^+$) 413.3280, found 413.3287.

5-Nitrofuran-2-carbonyl homopiperazine PCU 4

To a stirred mixture of PCU homopiperazine **3** (0.5 g, 1.2 mmol) in 2 ml of DCM and Et_3N (670 µl, 4.8 mmol) under N_2 atmosphere was added freshly prepared 5-nitrofuran-2-carbonyl chloride[27] (0.65 g, 3.6 mmol) in 3 ml of DCM and stirred for 18 h with reflux. The reaction mixture was diluted with 60 ml of ethyl acetate and washed sequentially with (2 × 50 ml) 10% $NaHCO_3$, (2 × 50 ml) water and (2 × 50 ml) brine. The organic layer was removed and dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude residue was purified via column chromatography using CH_3Cl : MeOH : NH_4OH (88 : 10 : 2, R_f = 0.72) to give 5-nitrofuran-2-carbonyl homopiperazine PCU **4** as a brown oil (0.51 g, 61%). IR ν_{max}: 3479, 2951, 2859, 1627, 1530, 1352, 810 and 729 cm^{-1}. HRMS calculated for $C_{35}H_{42}N_6O_9$ ($M + H^+$) 691.3092, found 691.3105.

N-Benzyl homopiperazine PCU 5

A mixture of *N*-benzyl homopiperazine and PCU ditosylate **8** (0.7 g, 3.68 mmol) and triethylamine (350 µl, 2.5 mmol) in CH_3CN was refluxed for 4 days under N_2 atmosphere. The reaction mixture was cooled, filtered and concentrated *in vacuo*. The crude residue was purified via column chromatography on silica gel using CH_3Cl : MeOH : NH_4OH (88 : 10 : 2, R_f = 0.65) as eluents to give *N*-benzyl homopiperazine PCU **5** as a yellow oil (0.84 g, 85%). IR ν_{max}: 2935, 2811, 1452, 1351, 1111, 729 and 695 cm^{-1}. HRMS calculated for $C_{39}H_{52}N_4O$ ($M + H^+$) 593.4219, found 593.4230.

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Supporting information

Supporting information may be found in the online version of this article.

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