

Supplementary Material

Total synthesis of the four stereoisomers of cyclo(L-Trp-L-Arg) raises uncertainty of the structures of the natural products and invalidates their promising antimicrobial activities

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Table S6. Comparison of ¹³C NMR chemical shifts reported for CDP 3 (**2**) with corresponding shifts observed for **5a** (cyclo(L-Trp-L-Arg)) in either DMSO-*d*₆ or CD₃OD and calculated values of mean absolute error (MAE).

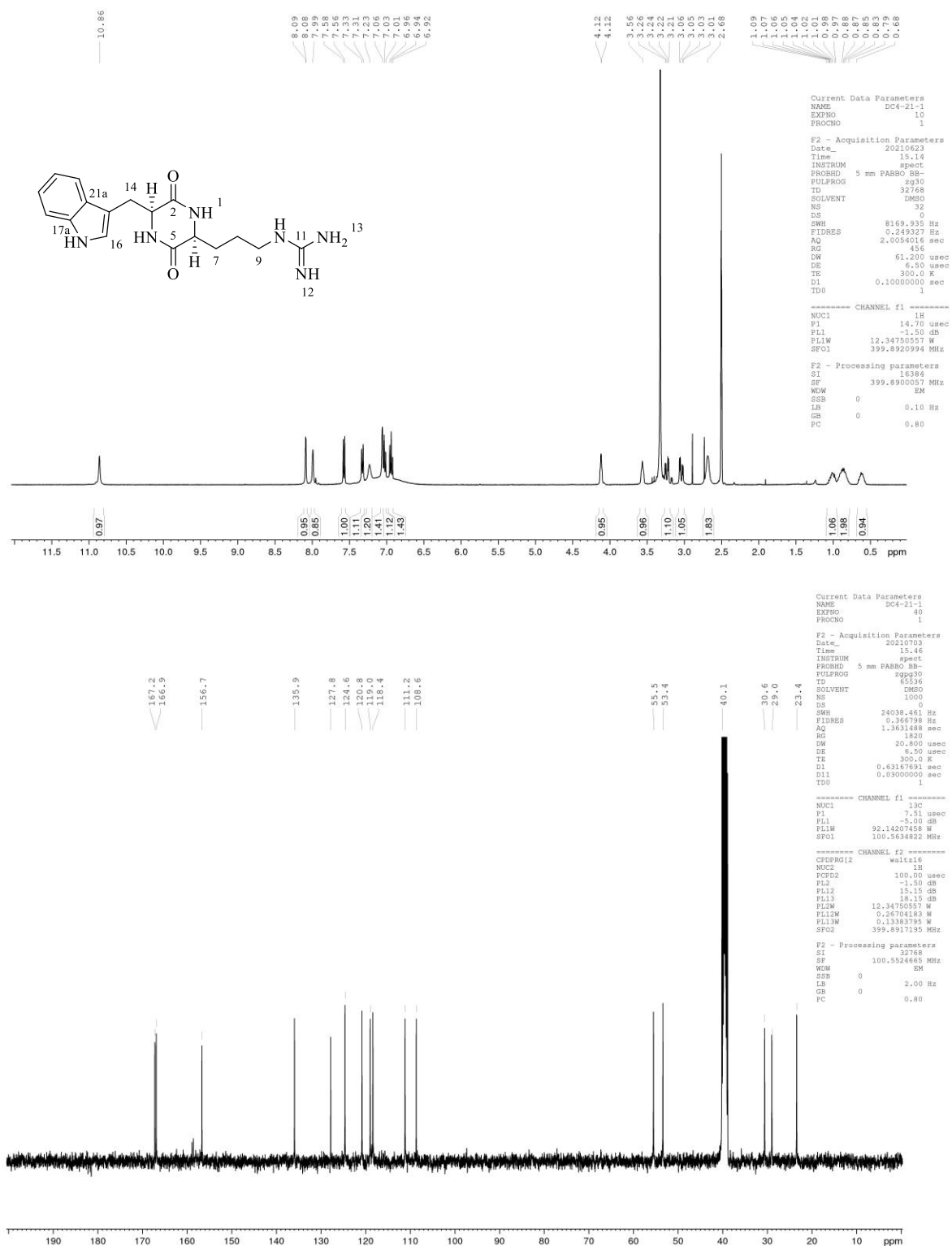


Figure S1. ¹H and ¹³C NMR data (DMSO-d₆) for cyclo(L-Trp-L-Arg) (5a).

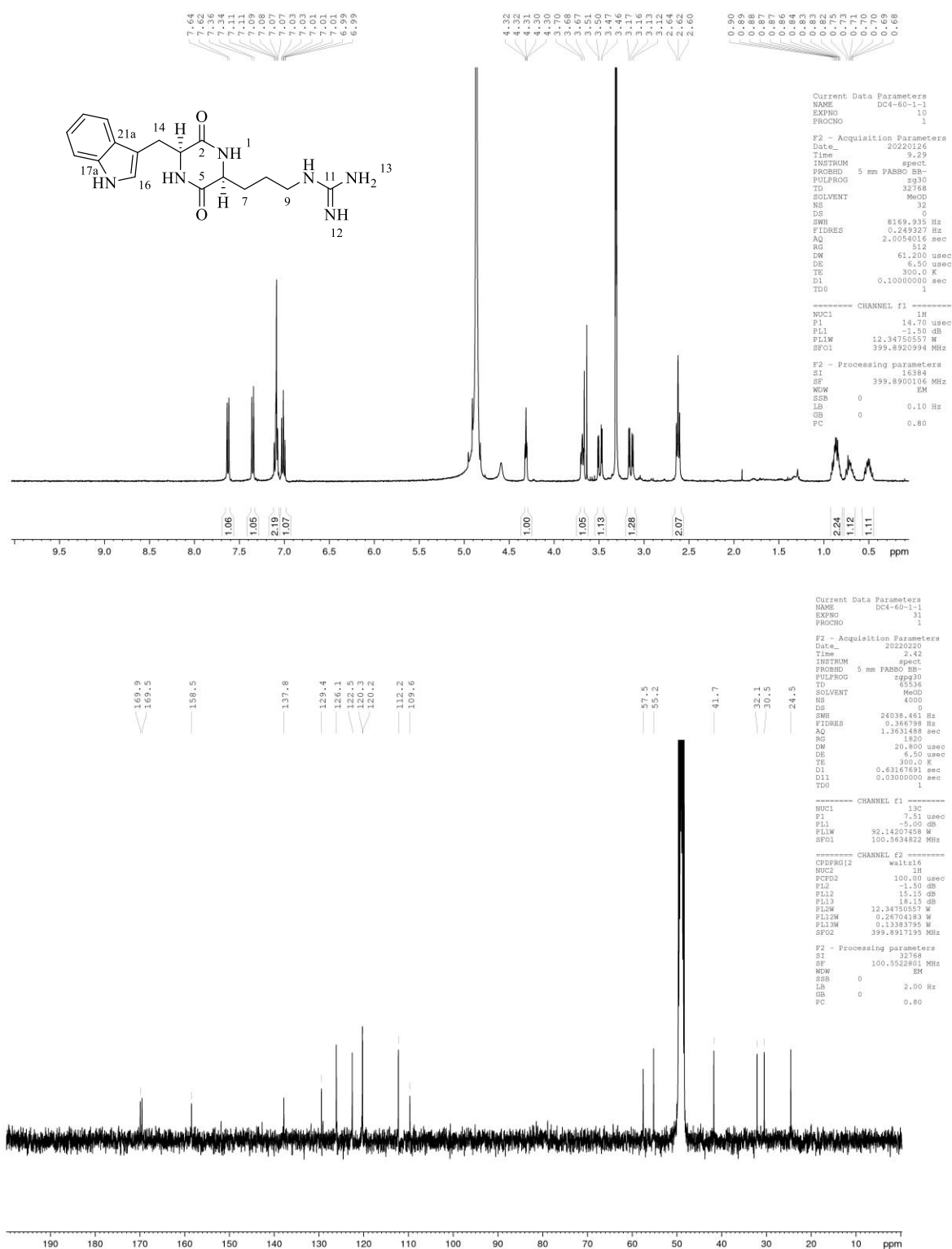


Figure S2. ^1H and ^{13}C NMR data (CD_3OD) for cyclo(L-Trp-L-Arg) (5a).

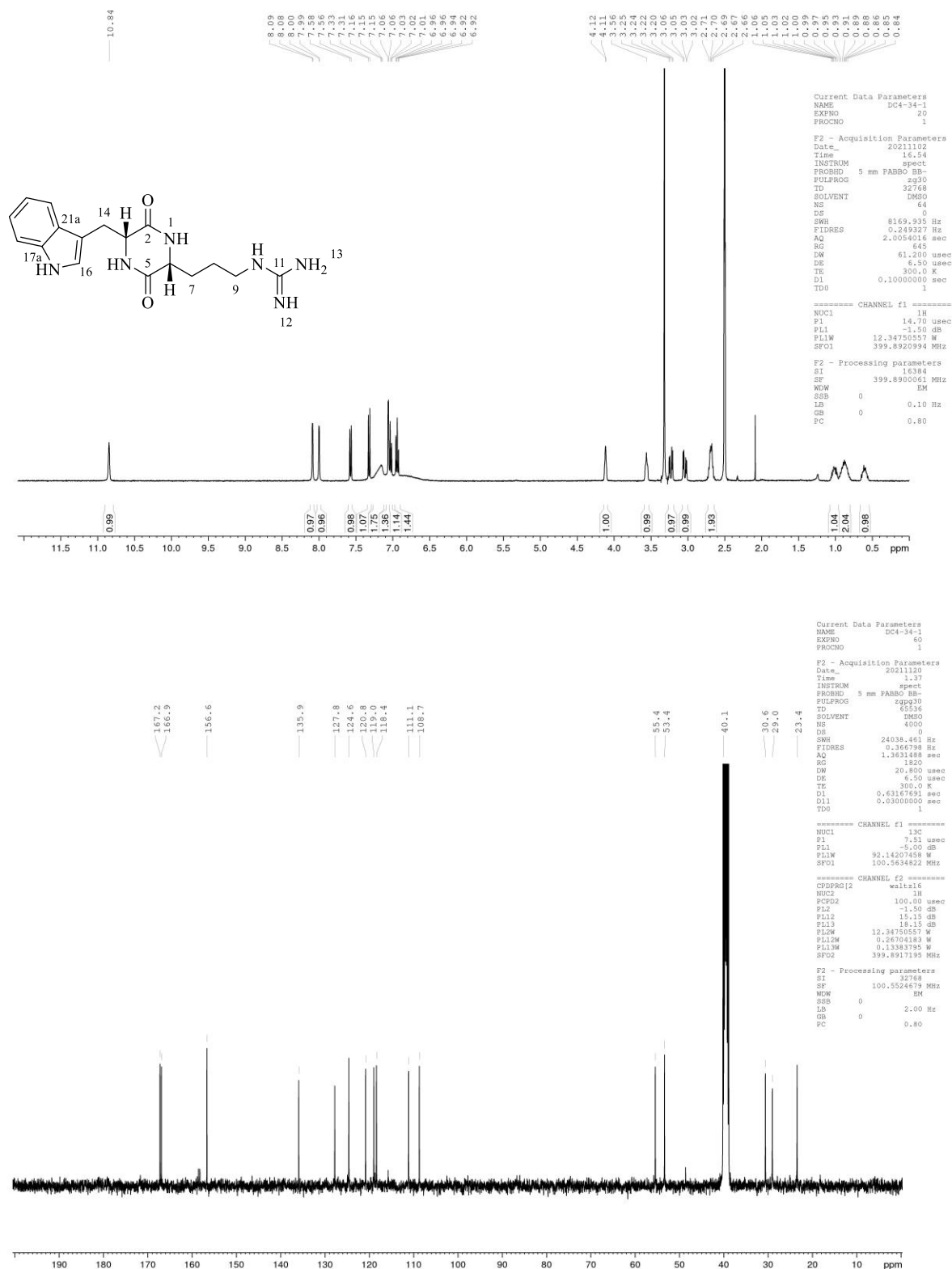


Figure S3. ^1H and ^{13}C NMR data (DMSO- d_6) for cyclo(D-Trp-D-Arg) (5b).

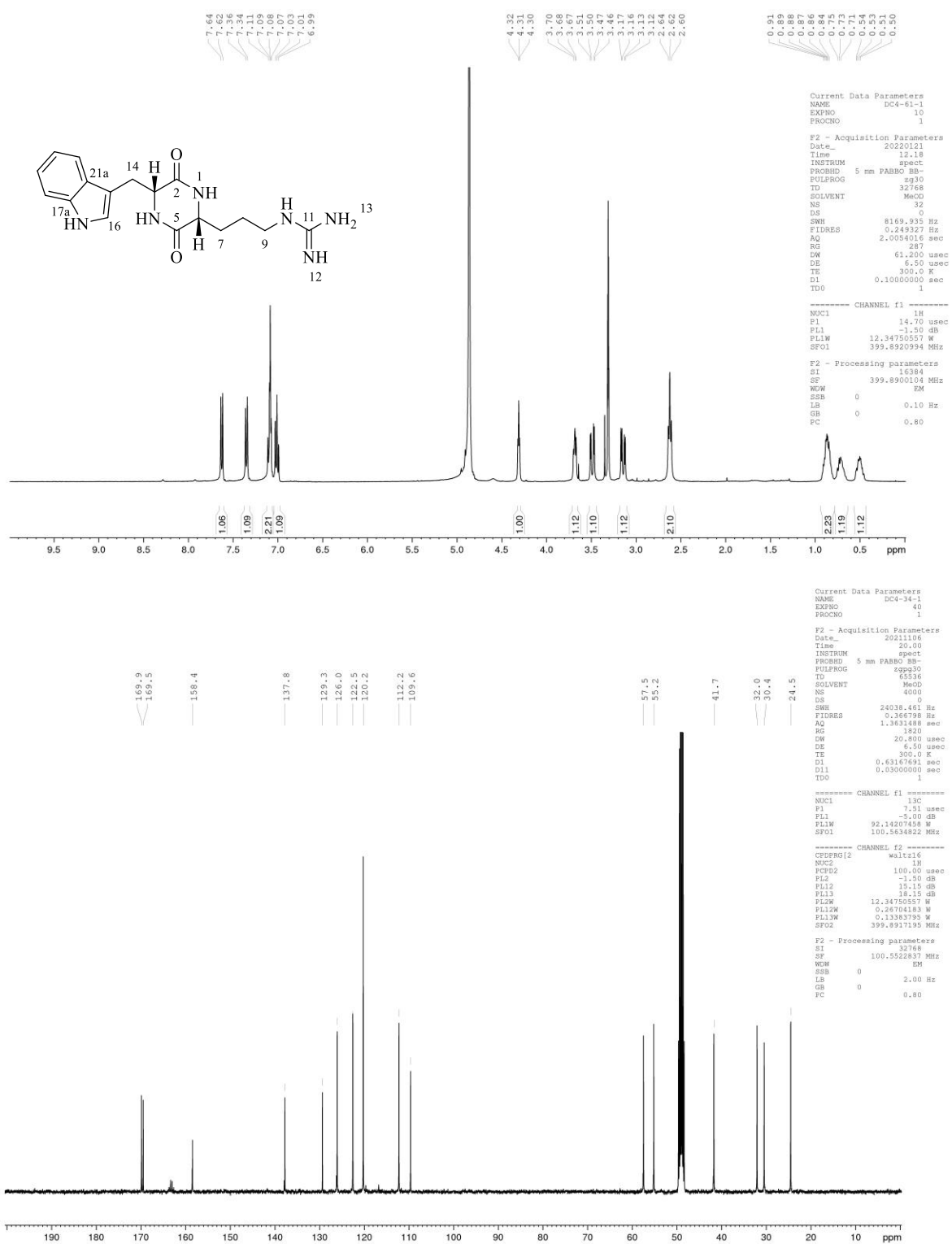


Figure S4. ¹H and ¹³C NMR data (CD₃OD) for cyclo(D-Trp-D-Arg) (5b).

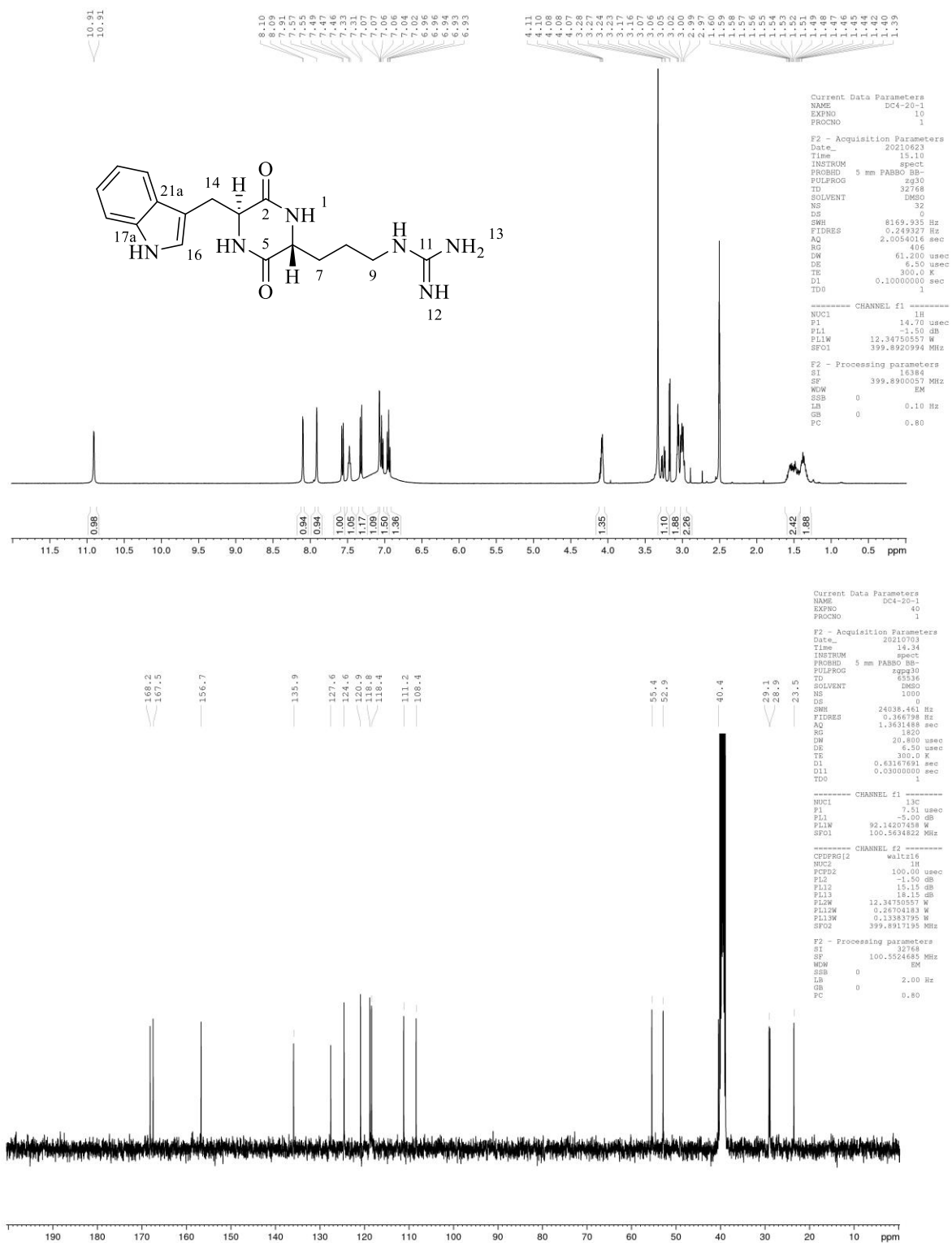


Figure S5. ¹H and ¹³C NMR data (DMSO-d₆) for cyclo(L-Trp-D-Arg) (5c).

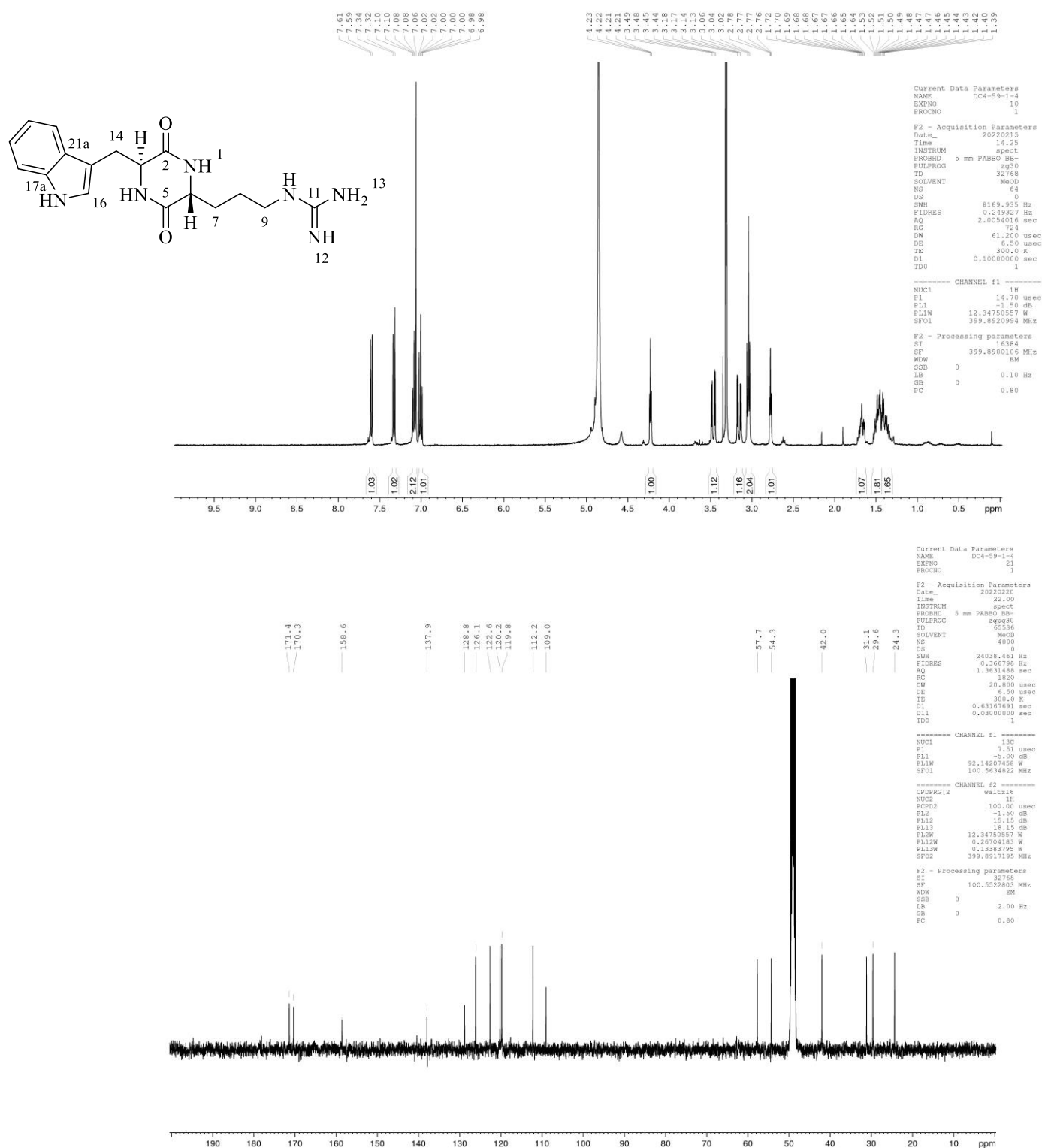


Figure S6. ¹H and ¹³C NMR data (CD₃OD) for cyclo(L-Trp-D-Arg) (5c).

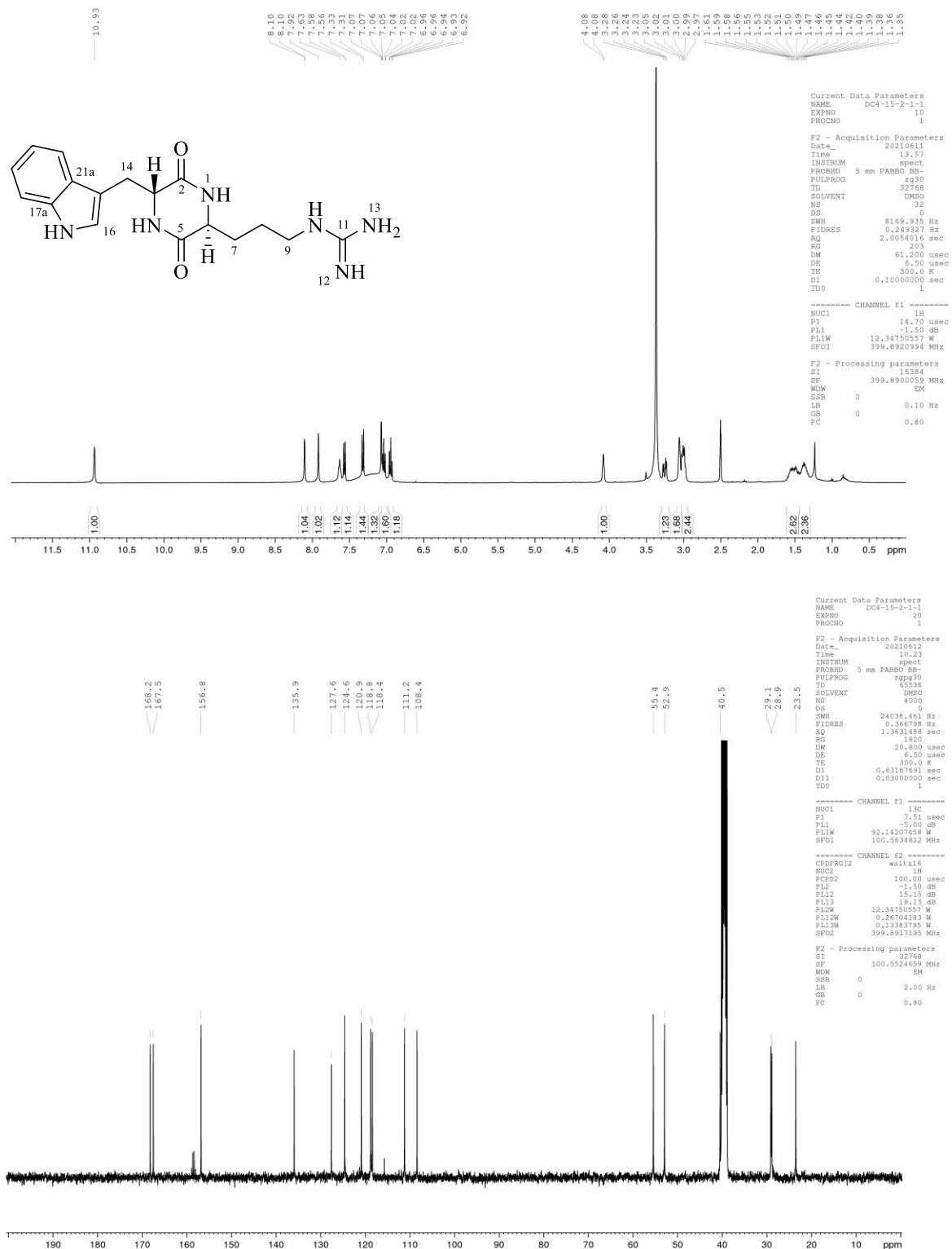


Figure S7. ¹H and ¹³C NMR data (DMSO-d₆) for cyclo(D-Trp-L-Arg) (5d).

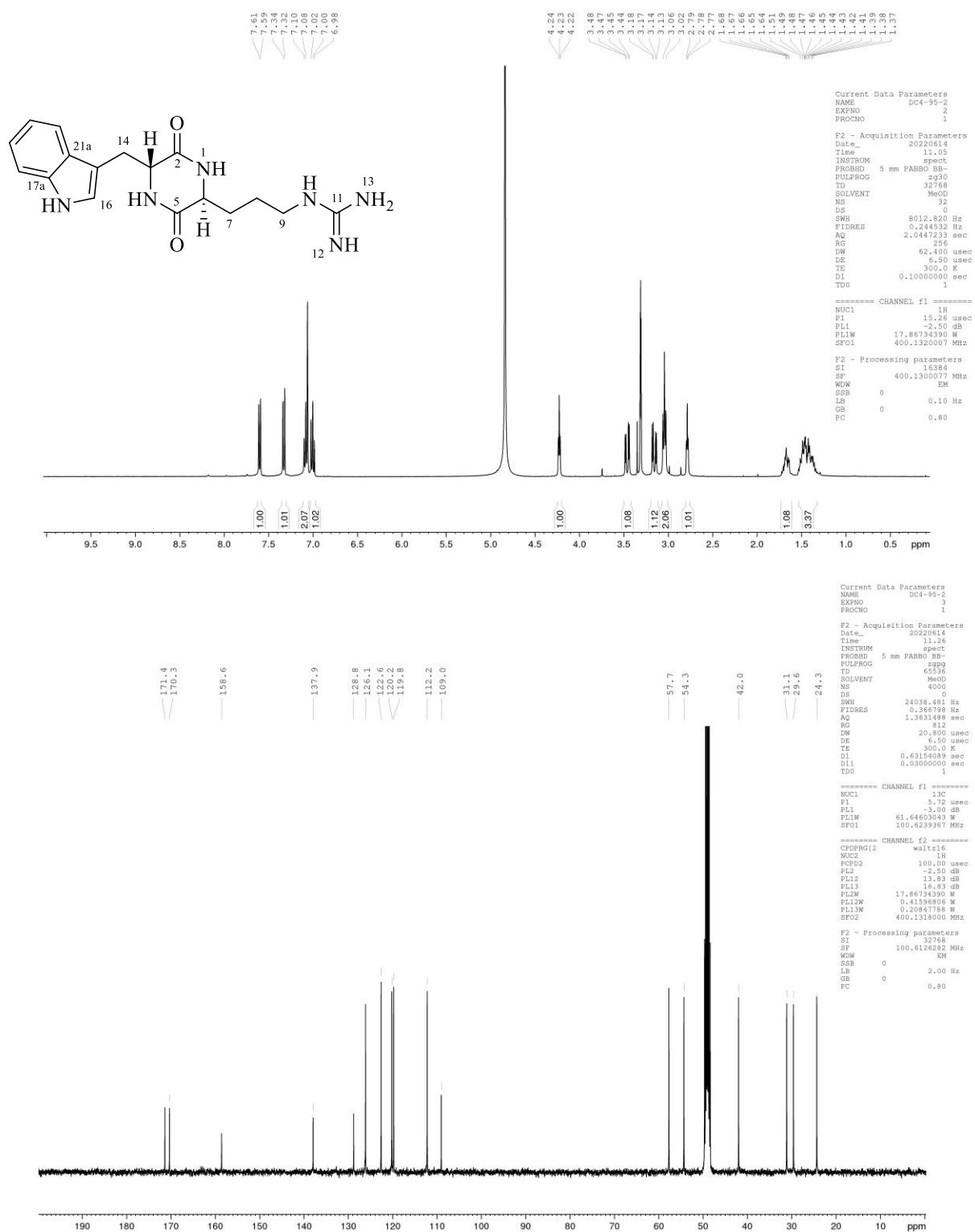


Figure S8. ¹H and ¹³C NMR data (CD₃OD) for cyclo(D-Trp-L-Arg) (5d).

Table S1. Comparison of ^1H NMR chemical shifts observed¹ for **5a** and **5c** with corresponding shifts reported by Li *et al.* and calculated values of mean absolute error (MAE).

	cyclo(L-Trp-L-Arg) (5a)		cyclo(L-Trp-L-Arg)			cyclo(L-Trp-D-Arg) (5c)		cyclo(L-Trp-D-Arg)
	(current work)		Li et al. ²			(current work)		Li et al. ²
Position	^1H (ppm)¹	ABS(δ-δ)	^1H (ppm)		Position	^1H (ppm)	ABS(δ-δ)	^1H (ppm)
NH-1	7.99	0.02	8.01		NH-1	7.91	0.01	7.92
3	4.31	0.00	4.31		3	4.22	0.01	4.23
NH-4	8.09	0.01	8.10		NH-4	8.10	0.01	8.11
6	3.69	0.01	3.68		6	2.77	0.00	2.77
7a	0.86	0.01	0.87		7a	1.67	0.00	1.67
7b	0.51	0.02	0.49		7b	1.43	0.01	1.44
8a	0.86	0.07	0.79		8	1.43	0.01	1.44
8b	0.71	0.08	0.79		9	3.04	0.00	3.04
9	2.62	0.00	2.62		NH-10	7.47	0.03	7.44
NH-10	7.23	0.02	7.21		14a	3.46	0.01	3.47
14a	3.49	0.00	3.49		14b	3.15	0.00	3.15
14b	3.14	0.00	3.14		16	7.06	0.00	7.06
16	7.08	0.00	7.08		NH-17	10.91	0.00	10.91
NH-17	10.86	0.00	10.86		18	7.33	0.00	7.33
18	7.35	0.01	7.34		19	7.08	0.00	7.08
19	7.09	0.00	7.09		20	7.00	0.00	7.00
20	7.01	0.00	7.01		21	7.60	0.00	7.60
21	7.63	0.00	7.63					
	MAE (ppm)³	0.014				MAE (ppm)³	0.005	

Footnotes.

- ¹H NMR shifts acquired in CD₃OD solvent, with exchangeable NH shifts acquired in DMSO-*d*₆ (highlighted yellow).
- Li et al. dx.doi.org/10.1021/jp311151h. *J. Phys. Chem. A* **2013**, *117*, 1721–1736.
- MAE calculated using $\text{MAE} = \text{sum}(\text{ABS}(\delta - \delta))/n$, where $\text{ABS}(\delta - \delta)$ is the absolute value of the difference between the chemical shifts observed for our compound versus their compound and *n* is the number of values compared.

Table S2. Comparison of ^{13}C NMR chemical shifts (CD_3OD) observed for **5a** and **5c** with corresponding shifts reported by Li *et al.* and calculated values of mean absolute error (MAE).

	cyclo(L-Trp-L-Arg) (5a)		cyclo(L-Trp-L-Arg)		cyclo(L-Trp-D-Arg) (5c)		cyclo(L-Trp-D-Arg)	cyclo(L-Trp-D-Arg)
	(current work)		Li et al. ¹		(current work)		Li et al. ¹	Li et al. ¹
							reference corrected	as published
Position	^{13}C ppm	ABS($\delta-\delta$)	^{13}C ppm		^{13}C ppm	ABS($\delta-\delta$)	^{13}C ppm	^{13}C ppm
2	169.9	0.00	169.9		171.4	0.00	171.4	169.9
3	57.5	0.00	57.5		57.7	0.00	57.7	56.2
5	169.5	0.00	169.5		170.3	0.00	170.3	168.9
6	55.2	0.00	55.2		54.3	0.00	54.3	52.8
7	32.1	0.00	32.1		29.6	0.00	29.6	28.1
8	24.5	0.00	24.5		24.3	0.00	24.3	22.9
9	41.7	0.00	41.7		42.0	0.00	42.0	40.5
11	158.5	0.10	158.4		158.6	0.00	158.6	157.1
14	30.5	0.00	30.5		31.1	0.00	31.1	29.7
15	109.6	0.10	109.7		109.0	0.00	109.0	107.6
16	126.1	0.00	126.1		126.1	0.00	126.1	124.7
17a	137.8	0.00	137.8		137.9	0.00	137.9	136.5
18	112.2	0.00	112.2		112.2	0.00	112.2	110.7
19	122.5	0.00	122.5		122.6	0.00	122.6	121.1
20	120.3	0.10	120.2		120.2	0.00	120.2	118.8
21	120.2	0.10	120.3		119.8	0.00	119.8	118.3
21a	129.4	0.00	129.4		128.8	0.00	128.8	127.3
	MAE (ppm)²	0.02			MAE (ppm)²	0.00		

Footnotes.

1. Li *et al.* dx.doi.org/10.1021/jp311151h. *J. Phys. Chem. A* **2013**, *117*, 1721–1736. Examination of the original ^{13}C NMR data collected by Li *et al.* for cyclo(L-Trp-D-Arg) identified that the spectrum has been incorrectly referenced (offset required +1.44 ppm). Corrected data was used for the MAE calculation.
2. MAE calculated using $\text{MAE} = \text{sum}(\text{ABS}(\delta-\delta))/n$, where $\text{ABS}(\delta-\delta)$ is the absolute value of the difference between the chemical shifts observed for our compound versus their compound and n is the number of values compared.

Table S3. Comparison of ^1H NMR chemical shifts reported for CDP 2 (**1**) with corresponding shifts observed for **5a** (cyclo(L-Trp-L-Arg) in either DMSO- d_6 or CD $_3$ OD (with exchangeables in DMSO- d_6) and calculated values of mean absolute error (MAE).

	CDP 2 ¹			L,L synthetic (5a)		L,L synthetic (5a)
	“DMSO- d_6 ”			DMSO- d_6		CD $_3$ OD + DMSO- d_6 ²
Position	^1H (ppm)	ABS(δ-δ) (DMSO-d_6)	ABS(δ-δ) (CD$_3$OD + DMSO-d_6)	^1H (ppm)		^1H (ppm)
NH-1	8.11	0.12	0.12	7.99		7.99
3	4.37	0.26	0.06	4.11		4.31
NH-4	8.17	0.08	0.08	8.09		8.09
6	3.74	0.18	0.05	3.56		3.69
7a	0.81	0.21	0.05	1.02		0.86
7b	0.54	0.07	0.03	0.61		0.51
8	0.79	0.08	0.01	0.87		0.78
9	2.72	0.04	0.10	2.68		2.62
NH-10	7.28	0.05	0.05	7.23		7.23
14a	3.51	0.28	0.02	3.23		3.49
14b	3.19	0.15	0.05	3.04		3.14
16	7.12	0.06	0.04	7.06		7.08
NH-17	10.77	0.09	0.09	10.86		10.86
18	7.41	0.08	0.06	7.33		7.35
19	7.15	0.13	0.06	7.02		7.09
20	7.01	0.06	0.00	6.95		7.01
21	7.69	0.12	0.06	7.57		7.63
	MAE (ppm)³	0.12	0.05			

Footnotes.

1. CDP 2 data from Deepa *et al.* [dx.doi.org/10.3389/fmicb.2015.00876](https://doi.org/10.3389/fmicb.2015.00876)
2. ‘CD $_3$ OD+DMSO- d_6 ’ is ^1H shifts observed in CD $_3$ OD with exchangeable NH signals observed in DMSO- d_6 .
3. MAE calculated using $\text{MAE} = \text{sum}(\text{ABS}(\delta-\delta))/n$, where ABS(δ - δ) is the absolute value of the difference between the chemical shifts observed for our compound versus their compound and n is the number of values compared.

Table S4. Comparison of ^1H NMR chemical shifts reported for CDP 3 (**2**) with corresponding shifts observed for **5a** (cyclo(L-Trp-L-Arg) in either DMSO- d_6 or CD $_3$ OD (with exchangeables in DMSO- d_6) and calculated values of mean absolute error (MAE).

	CDP 3 ¹			L,L synthetic (5a)		L,L synthetic (5a)
	"DMSO- d_6 "			DMSO- d_6		CD $_3$ OD + DMSO- d_6 ²
Position	^1H (ppm)	ABS(δ - δ) (DMSO- d_6)	ABS(δ - δ) (CD $_3$ OD + DMSO- d_6)	^1H (ppm)		^1H (ppm)
NH-1	8.24	0.25	0.25	7.99		7.99
3	4.43	0.32	0.12	4.11		4.31
NH-4	8.21	0.12	0.12	8.09		8.09
6	3.88	0.32	0.19	3.56		3.69
7a	0.88	0.14	0.02	1.02		0.86
7b	0.61	0.00	0.10	0.61		0.51
8	0.79	0.08	0.01	0.87		0.78
9	2.77	0.09	0.15	2.68		2.62
NH-10	7.34	0.11	0.11	7.23		7.23
14a	3.61	0.38	0.12	3.23		3.49
14b	3.33	0.29	0.19	3.04		3.14
16	7.22	0.16	0.14	7.06		7.08
NH-17	10.91	0.05	0.05	10.86		10.86
18	7.43	0.10	0.08	7.33		7.35
19	7.21	0.19	0.12	7.02		7.09
20	7.01	0.06	0.00	6.95		7.01
21	7.77	0.20	0.14	7.57		7.63
	MAE (ppm) ³	0.17	0.11			

Footnotes.

1. CDP 3 data from Deepa *et al.* [dx.doi.org/10.3389/fmicb.2015.00876](https://doi.org/10.3389/fmicb.2015.00876)
2. 'CD $_3$ OD+DMSO- d_6 ' is ^1H shifts observed in CD $_3$ OD with exchangeable NH signals observed in DMSO- d_6 .
3. MAE calculated using $\text{MAE} = \text{sum}(\text{ABS}(\delta-\delta))/n$, where ABS(δ - δ) is the absolute value of the difference between the chemical shifts observed for our compound versus their compound and n is the number of values compared.

Table S5. Comparison of ^{13}C NMR chemical shifts reported for CDP 2 (**1**) with corresponding shifts observed for **5a** (cyclo(L-Trp-L-Arg) in either DMSO- d_6 or CD $_3$ OD and calculated values of mean absolute error (MAE).

	CDP 2 ¹			L,L synthetic		L,L synthetic
	"DMSO- d_6 "			DMSO- d_6		CD $_3$ OD
Position	^{13}C	ABS(δ - δ) (DMSO- d_6)	ABS(δ - δ) (CD $_3$ OD)	^{13}C		^{13}C
2	169.8	2.6	0.1	167.2		169.9
3	57.2	1.7	0.3	55.5		57.5
5	169.3	2.4	0.2	166.9		169.5
6	55.2	1.8	0.0	53.4		55.2
7	32.2	1.6	0.1	30.6		32.1
8	24.6	1.2	0.1	23.4		24.5
9	41.7	1.6	0.0	40.1		41.7
11	158.5	1.8	0.0	156.7		158.5
14	30.5	1.5	0.0	29.0		30.5
15	109.6	1.0	0.0	108.6		109.6
16	126.2	1.6	0.1	124.6		126.1
17a	137.9	2.0	0.1	135.9		137.8
18	112.3	1.1	0.1	111.2		112.2
19	122.4	1.6	0.1	120.8		122.5
20	120.3	1.9	0.0	118.4		120.3
21	120.4	1.4	0.2	119.0		120.2
21a	129.4	1.6	0.0	127.8		129.4
	MAE (ppm) ²	1.7	0.1			

Footnotes.

1. CDP 2 data from Deepa *et al.* dx.doi.org/10.3389/fmicb.2015.00876
2. MAE calculated using $\text{MAE} = \text{sum}(\text{ABS}(\delta - \delta))/n$, where $\text{ABS}(\delta - \delta)$ is the absolute value of the difference between the chemical shifts observed for our compound versus their compound and n is the number of values compared.

Table S6. Comparison of ^{13}C NMR chemical shifts reported for CDP 3 (**2**) with corresponding shifts observed for **5a** (cyclo(L-Trp-L-Arg) in either DMSO- d_6 or CD $_3$ OD and calculated values of mean absolute error (MAE).

	CDP 3 ¹			L,L synthetic		L,L synthetic
	"DMSO- d_6 "			DMSO- d_6		CD $_3$ OD
Position	^{13}C	ABS(δ - δ) (DMSO- d_6)	ABS(δ - δ) (CD $_3$ OD)	^{13}C		^{13}C
2	170.1	2.9	0.2	167.2		169.9
3	59	3.5	1.5	55.5		57.5
5	170.0	3.1	0.5	166.9		169.5
6	54.7	1.3	0.5	53.4		55.2
7	32.7	2.1	0.6	30.6		32.1
8	25.5	2.1	1.0	23.4		24.5
9	42.0	1.9	0.3	40.1		41.7
11	158.8	2.1	0.3	156.7		158.5
14	31.5	2.5	1.0	29.0		30.5
15	109.7	1.1	0.1	108.6		109.6
16	127.2	2.6	1.1	124.6		126.1
17a	138.2	2.3	0.4	135.9		137.8
18	113.3	2.1	1.1	111.2		112.2
19	123.1	2.3	0.6	120.8		122.5
20	121.3	2.9	1.0	118.4		120.3
21	121.4	2.4	1.2	119.0		120.2
21a	130.3	2.5	0.9	127.8		129.4
	MAE (ppm) ²	2.3	0.7			

Footnotes.

1. CDP 3 data from Deepa *et al.* dx.doi.org/10.3389/fmicb.2015.00876
2. MAE calculated using $\text{MAE} = \text{sum}(\text{ABS}(\delta - \delta))/n$, where $\text{ABS}(\delta - \delta)$ is the absolute value of the difference between the chemical shifts observed for our compound versus their compound and n is the number of values compared.