J. Braz. Chem. Soc., Vol. 27, No. 9, S1-S33, 2016.
Printed in Brazil - ©2016 Sociedade Brasileira de Química
0103 - 5053 $6.00+0.00

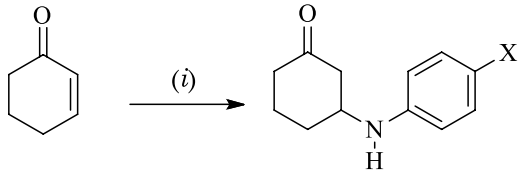
Supplementary Information

Cholinesterases Inhibition by Novel *cis*- and *trans*-3-Arylaminocyclohexyl *N,N*-Dimethylcarbamates: Biological Evaluation and Molecular Modeling

Diego A. S. Yamazaki,[a] Augusto A. Cândido,[a] Mariane C. Bagatin,[a] Miguel Machinski Jr.,[b] Simone A. G. Mossini,[b] Rodrigo M. Pontes,[a] Fernanda A. Rosa,[a] Ernani A. Basso[a] and Gisele F. Gauze*[a]

[a]Departamento de Química and [b]Departamento de Ciências Básicas da Saúde, Universidade Estadual de Maringá, Av. Colombo, 5790, 87020-900 Maringá-PR, Brazil

Table S1. Yields, physical aspect and melting points of 3-arylaminocyclohexanones (**2a**-**2c**)

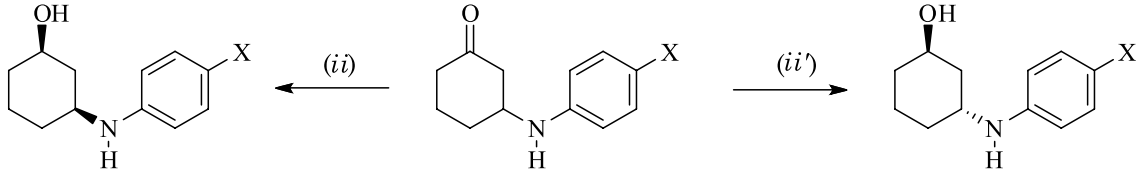


1 **2a-2c**

(*i*) arylamine, [DBU][Ac], r.t., 5 h.

Compound	X	Yield / %	Physical aspect	Melting point / °C
2a	H	72	white solid	58.4-58.6
2b	F	80	brown solid	71.2-73.5
2c	OCH_3	85	white solid	75.5-75.9

Table S2. Yields, physical aspect and melting points of *cis* and *trans* 3-arylaminocyclohexanols (**3a**-**3c**; **4a**-**4c**)



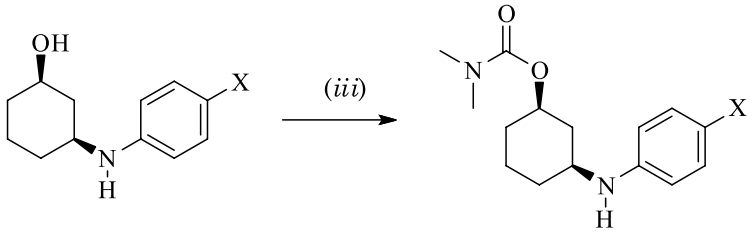
3a-3c **2a-2c** **4a-4c**

(*ii*) $NaBH_4$, THF, r.t., 48 h; (*ii'*) N-selectride, THF, –80 °C, 4 h.

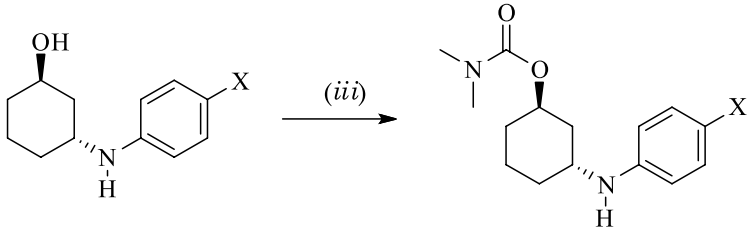
Compound	X	Yield / %	Physical aspect	Melting point / °C
3a	H	84	brown oil	–
3b	F	75	brown oil	–
3c	OCH_3	80	brown oil	–
4a	H	72	white solid	58.4-58.6
4b	F	80	brown solid	71.2-73.5
4c	OCH_3	85	white solid	75.5-75.9

*e-mail: gfgbandoch@uem.br

Table S3. Yields, physical aspect and melting points of *cis* and *trans* 3-arylaminocyclohexyl *N*.*N*-dimethylcarbamates (**5a**-**5c**; **6a**-**6c**)



3a-3c **5a-5c**



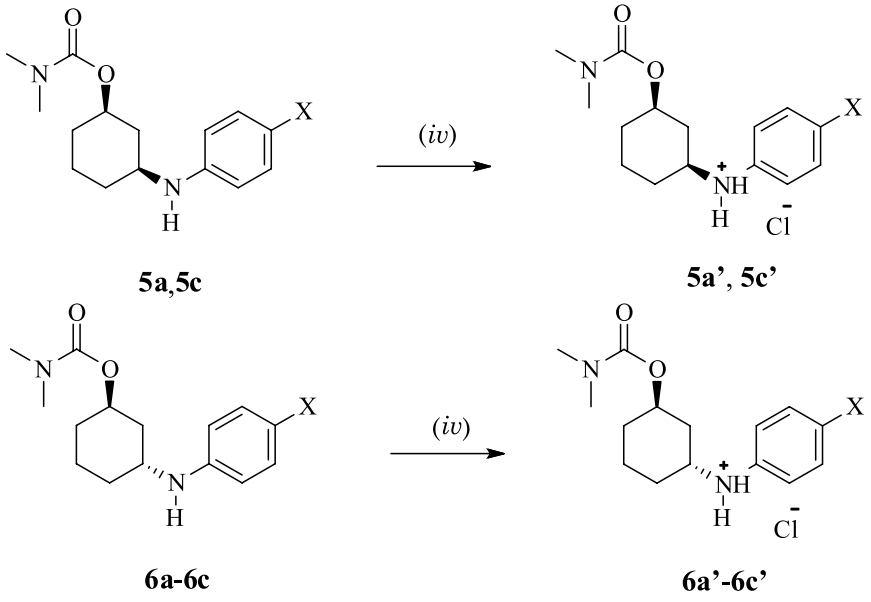
4a-4c **6a-6c**

(*iii*) NaH/THF, 80 °C, 8 h; *N*,*N*-dimethylcarbamoyl chloride, 16 h.

Compound	X	Yield / %	Physical aspect	Melting point / °C
5a	H	46	crystal solid	101.2-101.5
5b	F	30[a]	brown oil	–
5c	OCH_3	42	brown oil	–
6a	H	36	yellow oil	–
6b	F	42	brown oil	–
6c	OCH_3	40	brown oil	–

[a]Mixture of *cis* and *trans* isomers.

Table S4. Yields, physical aspect and melting points of *cis* and *trans* 3-arylaminocyclohexyl *N*,*N*-dimethylcarbamate hydrochlorides (**5a'**, **5c'**; **6a'-6c'**)



5a,5c **5a', 5c'**

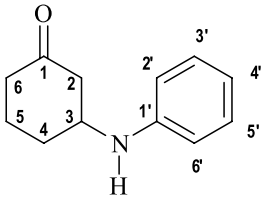
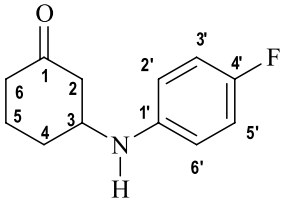
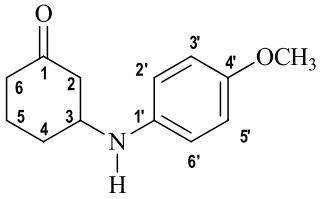
6a-6c **6a'-6c'**

(*iv*) CH_2Cl_2, 37% HCl, 0-5 °C, 5 min.

Compound	X	Yield / %	Physical aspect[a]
5a'	H	96	white solid
5c'	OCH_3	93	brown solid
5a'	H	91	yellow solid
5b'	F	95	gray solid
5c'	OCH_3	92	brown solid

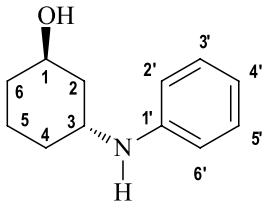
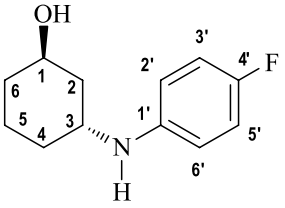
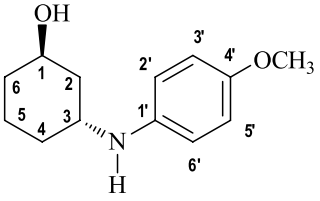
[a]Melting point was not possible to measure because the compounds are hygroscopic.

Table S5. ^{1}H and ^{13}C NMR chemical shift (ppm), coupling constants (Hz) and the signal multiplicity of 3-arylaminocyclohexanones (**2a**-**2c**) in $CDCl_3$

	 **2a**			 **2b**				 **2c**		
C/H	δ ^{1}H / ppm	Multiplicity (*J* / Hz)	δ ^{13}C / ppm	δ ^{1}H / ppm	Multiplicity (*J* / Hz)	δ ^{13}C / ppm	Multiplicity (*J* / H)	δ ^{1}H / ppm	Multiplicity (*J* / Hz)	δ ^{13}C / ppm
1	–	–	209.8	–	–	209.7	–	–	–	209.9
2 ax	2.29	m	48.8	2.25	m	48.5	–	2.25	m	48.7
2 eq	2.84	m	–	2.79	m	–	–	2.78	m	–
3	3.79	dddd (8.2, 8.2, 3.9, 3.9)	52.5	3.69	dddd (8.6, 8.6, 4.4, 4.4)	53.0	–	3.68	m	53.4
4 ax	1.70	m	31.3	1.67	m	31.1	–	1.66	m	31.2
4 eq	2.18	m	–	2.16	m	–	–	2.14	m	–
5 ax	1.75	m	22.3	1.70	m	22.2	–	1.68	m	22.2
5 eq	2.05	m	–	2.02	m	–	–	2.02	m	–
6 ax	2.36	m	41.3	2.36	m	41.2	–	2.34	m	41.2
6 eq	2.36	m	–	2.36	m	–	–	2.34	m	–
1’	–	m	146.4	–	–	142.7	d (1.9)	–	m	140.2
2’	6.59	m	113.5	6.51	m	114.5	d (7.3)	6.57	d (9.9)	115.0
3’	7.18	m	129.6	6.87	m	115.9	d (22.3)	6.76	d (9.9)	115.2
4’	6.72	m	118.1	–	–	156.0	d (235.6)	–	–	152.0
5’	7.18	m	129.6	6.87	m	115.9	d (22.3)	6.76	d (9.9)	115.2
6’	6.59	m	113.5	6.51	m	114.5	d (7.3)	6.57	d (9.9)	115.0
NH	3.59	sl	–	3.53	sl	–	–	3.35	sl	–
OCH_3	–	–	–	–	–	–	–	3.73	sl	56.0

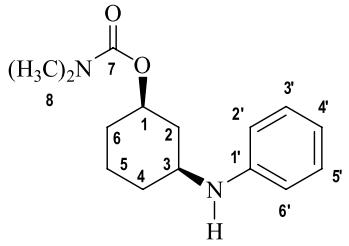
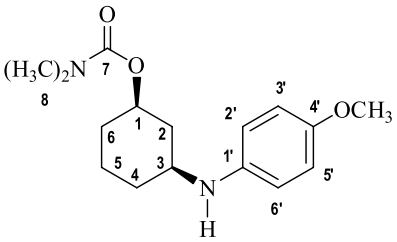
δ: Chemical shift; *J*: coupling constant.

Table S6. ^{1}H and ^{13}C NMR chemical shift (ppm), coupling constants (Hz) and the signal multiplicity of *trans*-3-arylaminocyclohexanols (**4a**-**4c**) in $CDCl_3$

	 **4a**			 **4b**				 **4c**		
C/H	δ ^{1}H / ppm	Multiplicity (*J* / Hz)	δ ^{13}C / ppm	δ ^{1}H / ppm	Multiplicity (*J* / Hz)	δ ^{13}C / ppm	Multiplicity (*J* / Hz)	δ ^{1}H / ppm	Multiplicity (*J* / Hz)	δ ^{13}C / ppm
1	4.15	m	67.3	4.17	m	67.0	–	4.13	m	67.2
2 ax	1.56	m	40.0	1.54	m	39.8	–	1.53	m	40.1
2 eq	1.99	m	–	2.00	m	–	–	1.97	m	–
3	3.76	dddd (9.1, 9.1, 3.8, 3.8)	47.5	3.70	dddd (9.1, 9.1, 3.8, 3.8)	48.0	–	3.66	dddd (8.9, 8.9, 3.9, 3.9)	48.5
4 ax	1.27	m	32.4	1.29	m	32.3	–	1.25	m	32.5
4 eq	1.97	m	–	1.99	m	–	–	1.94	m	–
5 ax	1.61	m	19.6	1.61	m	19.4	–	1.60	m	19.6
5 eq	1.80	m	–	1.79	m	–	–	1.76	m	–
6 ax	1.62	m	33.5	1.64	m	33.2	–	1.62	m	33.5
6 eq	1.62	m	–	1.64	m	–	–	1.62	m	–
1’	–	m	147.4	–	–	141.5	d (1.9)	–	m	141.5
2’	6.01	m	113.4	6.57	m	115.0	d (7.3)	6.59	d (9.9)	115.0
3’	7.16	m	129.5	6.87	m	115.1	d (22.3)	6.77	d (9.9)	115.1
4’	6.67	m	117.3	–	–	152.2	d (235.6)	–	–	152.2
5’	7.16	m	129.5	6.87	m	115.1	d (22.3)	6.77	d (9.9)	115.1
6’	6.01	m	113.4	6.57	m	115.0	d (7.3)	6.59	d (9.9)	115.0
NH	–	–	–	–	sl	–	–	–	–	–
OCH_3	–	–	–	–	–	–	–	3.74	sl	56.0

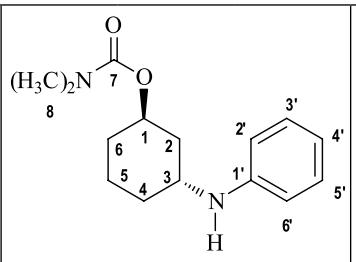
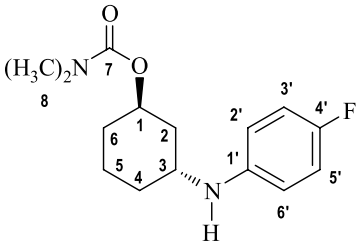
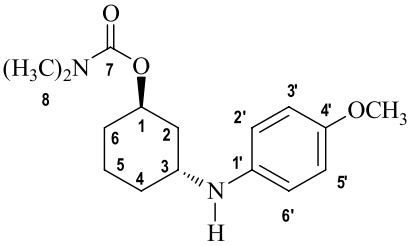
δ: Chemical shift; *J*: coupling constant.

Table S7. ^{1}H and ^{13}C NMR chemical shift (ppm), coupling constants (Hz) and the signal multiplicity of *cis*-3-arylaminocyclohexyl *N*,*N*-dimethylcarbamates (**5a**, **5c**) in $CDCl_3$

	 **5a**			 **5c**		
C/H	δ ^{1}H / ppm	Multiplicity (*J* / Hz)	δ ^{13}C / ppm	δ ^{1}H / ppm	Multiplicity (*J* / Hz)	δ ^{13}C / ppm
1	4.74	dddd (10.1, 10.1, 4.1, 4.1)	72.3	4.73	dddd (10.1, 10.1, 4.1, 4.1)	72.6
2 ax	1.25	m	38.8	1.23	m	39.6
2 eq	2.41	m	–	2.41	m	–
3	3.41	dddd (10.5, 10.5, 3.8, 3.8)	50.4	3.32	dddd (10.5, 10.5, 3.8, 3.8)	51.8
4 ax	1.33	m	31.9	1.11	m	32.2
4 eq	2.02	m	–	2.03	m	–
5 ax	1.36	m	21.4	1.38	m	21.8
5 eq	1.82	m	–	1.86	m	–
6 ax	1.15	m	32.5	1.33	m	32.8
6 eq	2.02	m	–	2.03	m	–
1’	–	m	147.1	–	m	141.5
2’	6.59	m	113.4	6.59	d (5.0)	115.3
3’	7.17	m	129.5	6.78	d (5.0)	115.2
4’	6.68	m	117.4	–	–	152.6
5’	7.17	m	129.5	6.78	d (5.0)	115.2
6’	6.59	m	113.4	6.59	d (5.0)	115.3
7	–	–	156.2	–	–	156.5
8	2.90	s	37.6	2.91	sl	35.9
NH	3.60	sl	–	–	–	–
OCH_3	–	–	–	3.76	s	56.2

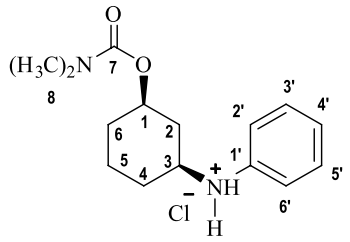
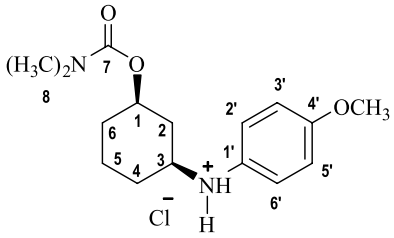
δ: Chemical shift; *J*: coupling constant.

Table S8. ^{1}H and ^{13}C NMR chemical shift (ppm), coupling constants (Hz) and the signal multiplicity of *trans*-3-arylaminocyclohexyl *N*,*N*-dimethylcarbamates (**6a**-**6c**) in $CDCl_3$

	 **6a**			 **6b**				 **6c**		
C/H	δ ^{1}H / ppm	Multiplicity (J / Hz)	δ ^{13}C / ppm	δ ^{1}H / ppm	Multiplicity (J / Hz)	δ ^{13}C / ppm	Multiplicity (J / Hz)	δ ^{1}H / ppm	Multiplicity (J / Hz)	δ ^{13}C / ppm
1	5.09	m	70.8	5.07	m	70.9	–	5.08	m	71.0
2 ax	1.41	m	37.5	1.43	m	39.5	–	1.43	m	37.8
2 eq	2.18	m	–	2.18	m	–	–	2.17	m	–
3	3.63	dddd (10.1, 10.1, 3.8, 3.8)	47.9	3.54	dddd (9.9, 9.9, 3.8, 3.8)	48.7	–	3.54	dddd (10.0, 10.0, 3.8, 3.8)	49.0
4 ax	1.55	m	30.2	1.53	m	30.3	–	1.53	m	30.4
4 eq	1.80	m	–	1.81	m	–	–	1.79	m	–
5 ax	1.68	m	20.0	1.66	m	20.2	–	1.67	m	20.2
5 eq	1.68	m	–	1.66	m	–	–	1.67	m	–
6 ax	1.24	m	32.5	1.22	m	32.5	–	1.21	m	32.7
6 eq	2.04	m	–	2.03	m	–	–	2.06	m	–
1’	–	m	147.4	–	–	143.6	d (1.9)	–	m	141.5
2’	6.58	m	113.0	6.50	m	114.1	d (7.3)	6.55		114.8
3’	7.16	m	129.5	6.86	m	116.0	d (22.3)	6.77	d (9.9)	115.2
4’	6.67	m	117.3	–	–	155.2	d (235.6)	–	–	152.2
5’	7.16	m	129.5	6.86	m	116.0	d (22.3)	6.77	d (9.9)	115.2
6’	6.58	m	113.0	6.50	m	114.1	d (7.3)	6.55	d (9.9)	114.8
7	–	–	156.0	–	–	157.3	–	–	–	157.3
8	2.95	s	36.3	2.94	s	36.3	–	2.94	s	36.3
NH	3.51	sl	–	–	sl	–	–	–	–	–
OCH_3	–	–	–	–	–	–	–	3.74	s	56.0

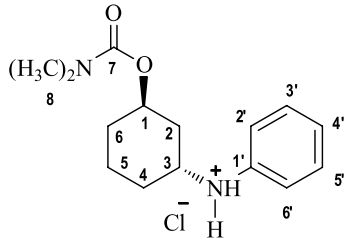
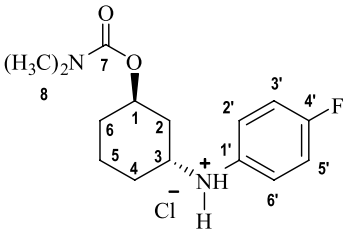
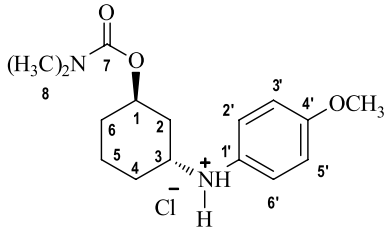
δ: Chemical shift; J: coupling constant.

Table S9. ^{1}H and ^{13}C NMR chemical shift (ppm), coupling constants (Hz) and the signal multiplicity of *cis*-3-arylaminocyclohexyl *N*,*N*-dimethylcarbamate hydrochlorides (**5a'**, **5c'**) in $CDCl_3$

	 **5a'**			 **5c'**		
C/H	δ ^{1}H / ppm	Multiplicity	δ ^{13}C / ppm	δ ^{1}H / ppm	Multiplicity (*J* / Hz)	δ ^{13}C / ppm
1	4.47	m	71.3	4.49	m	70.2
2 ax	1.75	m	40.6	1.71	m	33.6
2 eq	2.27	m	–	2.30	m	–
3	3.29	m	60.5	3.22	m	54.5
4 ax	1.25	m	28.6	1.55	m	27.6
4 eq	2.23	m	–	2.26	m	–
5 ax	1.23	m	21.7	1.26	m	20.1
5 eq	1.75	m	–	1.78	m	–
6 ax	1.91	m	31.2	1.27	m	30.1
6 eq	1.91	m	–	1.96	m	–
1'	–	m	134.0	–	m	125.9
2'	7.39	m	130.0	6.84	d (9.9)	123.6
3'	7.55	m	124.1	7.42	d (9.9)	113.9
4'	7.39	m	129.2	–	–	154.6
5'	7.55	m	124.1	7.42	d (9.9)	113.9
6'	7.39	m	130.0	6.84	d (9.9)	123.6
7	–	–	155.7	–	–	158.3
8	2.84	s	36.4	2.84	sl	35.3
NH	11.3	sl	–	–	–	–
OCH_3	–	–	–	3.79	s	58.8

δ: Chemical shift; *J*: coupling constant.

Table S10. ^{1}H and ^{13}C NMR chemical shift (ppm), coupling constants (Hz) and the signal multiplicity of *trans*-3-arylaminocyclohexyl *N*,*N*-dimethylcarbamate hydrochlorides (**6a'-6c'**) in $CDCl_3$

	 **6a'**			 **6b'**				 **6c'**		
C/H	δ ^{1}H / ppm	Multiplicity	δ ^{13}C / ppm	δ ^{1}H / ppm	Multiplicity	δ ^{13}C / ppm	Multiplicity (*J* / Hz)	δ ^{1}H / ppm	Multiplicity (*J* / Hz)	δ ^{13}C / ppm
1	5.02	m	69.5	5.07	m	69.3	–	5.05	m	71.2
2 ax	1.83	m	33.2	1.83	m	33.1	–	1.81	m	36.4
2 eq	2.20	m	–	2.22	m	–	–	2.20	m	–
3	3.52	m	58.9	3.48	m	59.3	–	3.46	m	55.5
4 ax	1.55	m	28.7	1.72	m	28.6	–	1.72	m	28.6
4 eq	1.79	m	–	2.23	m	–	–	2.26	m	–
5 ax	1.59	m	19.3	1.54	m	19.3	–	1.61	m	21.1
5 eq	1.59	m	–	1.63	m	–	–	1.61	m	–
6 ax	1.79	m	29.0	1.39	m	29.0	–	1.25	m	28.0
6 eq	2.21	m	–	2.21	m	–	–	1.83	m	–
1'	–	m	133.8	–	m	129.5	d (1.9)	–	m	127.6
2'	7.39	m	130.0	7.09	m	117.1	d (7.3)	6.86	d (9.9)	114.9
3'	7.55	m	124.3	7.56	m	126.4	d (22.3)	7.47	d (9.9)	124.6
4'	7.39	m	129.4	–	m	162.8	d (235.6)	–	–	155.6
5'	7.55	m	124.3	7.56	m	126.4	d (22.3)	7.47	d (9.9)	124.6
6'	7.39	m	130.0	7.09	m	117.1	d (7.3)	6.86	d (9.9)	114.6
7	–	–	155.5	–	–	155.4	–	–	–	159.3
8	2.83	s	36.3	2.85	s	36.3	–	2.85	s	36.3
NH	11.3	sl	–	11.3	sl	–	–	11.2	sl	–
OCH_3	–	–	–	–	–	–	–	3.80	s	59.9

δ: Chemical shift; *J*: coupling constant.

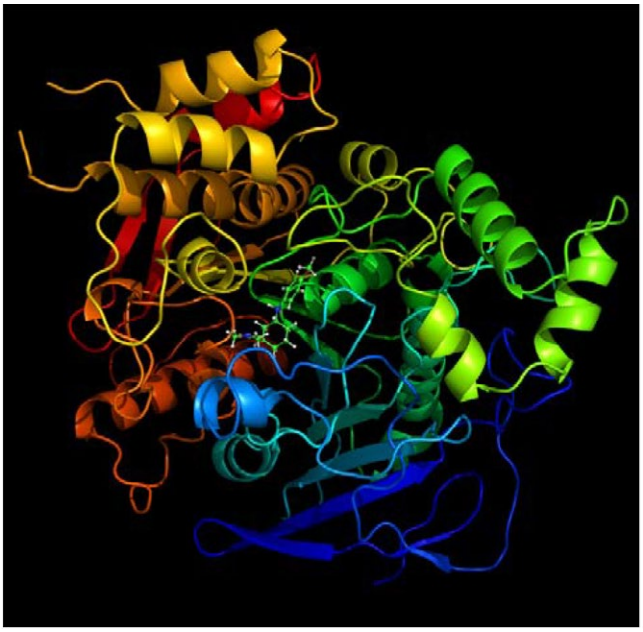


Figure S1. Representation of the full protein BuChE complexed with compound **6c'**.

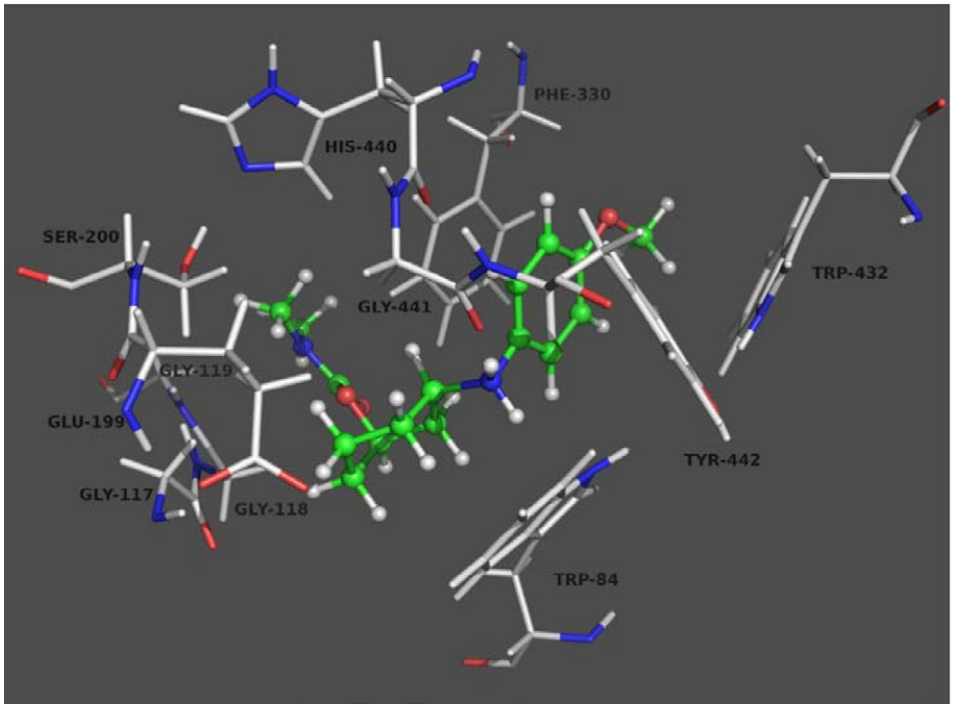


Figure S2. Binding mode of **6c'** and AChE. The compounds are rendered in green ball-and-stick models, and the residues are rendered in grey colored sticks.

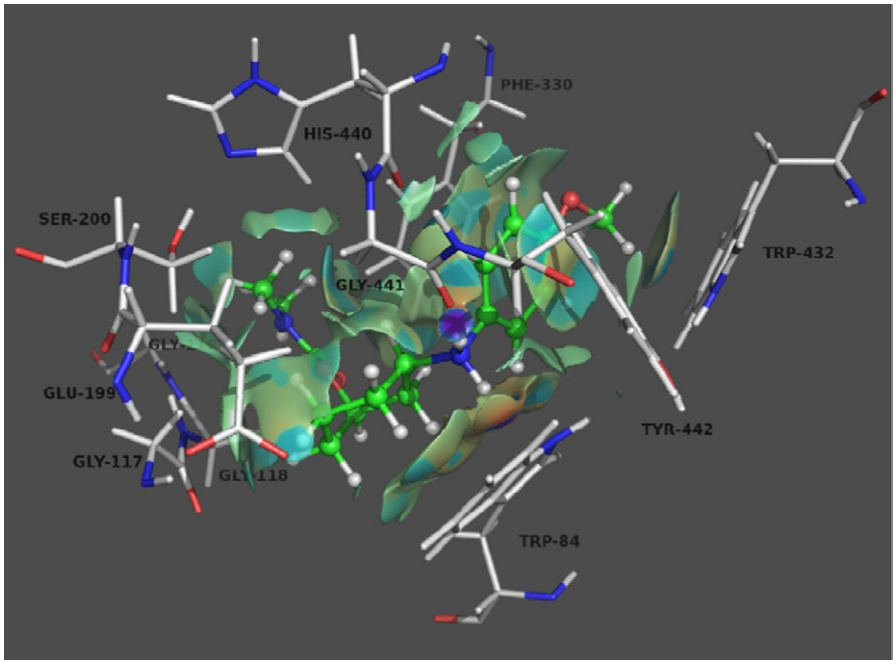


Figure S3. AChE non-covalent interaction (NCI) isosurfaces (blue to violet: strongly attractive; green: weakly attractive; red to orange: repulsive).

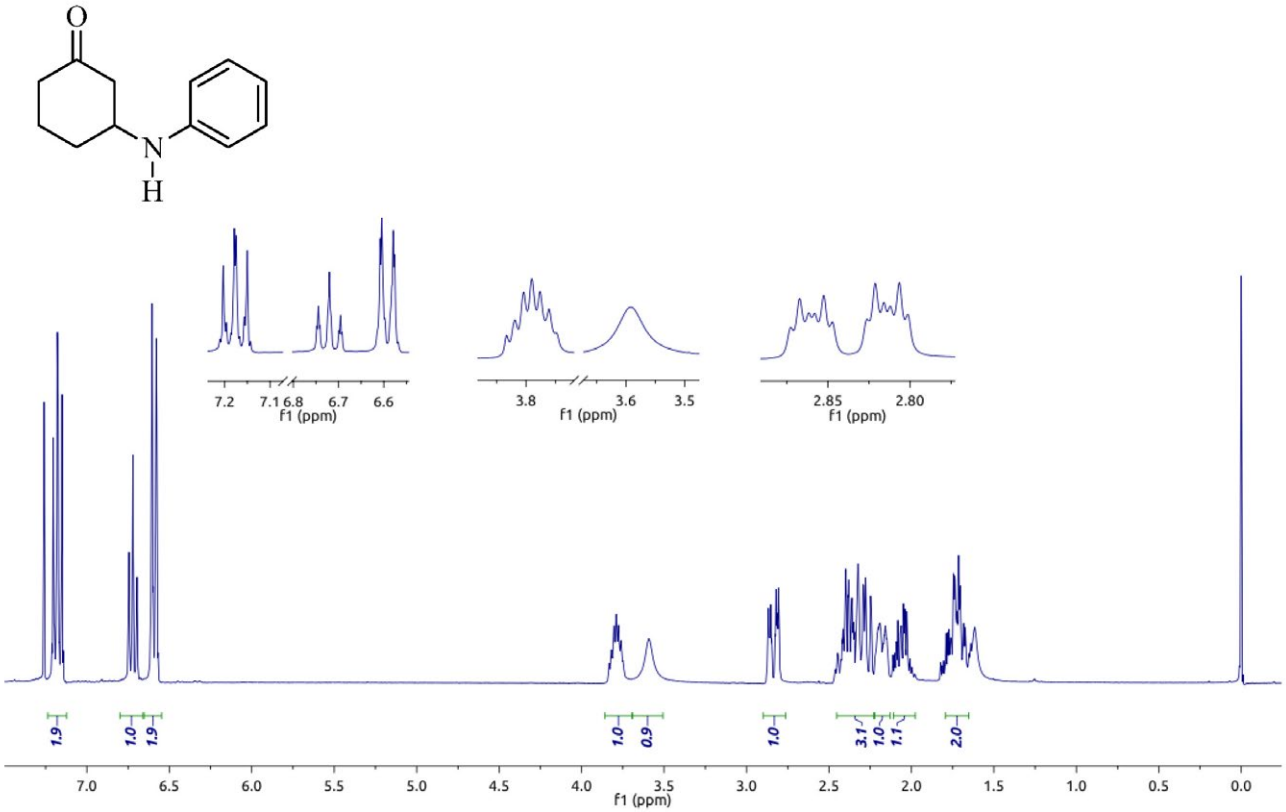


Figure S4. ^{1}H NMR spectrum (300 MHz, $CDCl_3$) of 3-(phenylamino)cyclohexanone (**2a**).

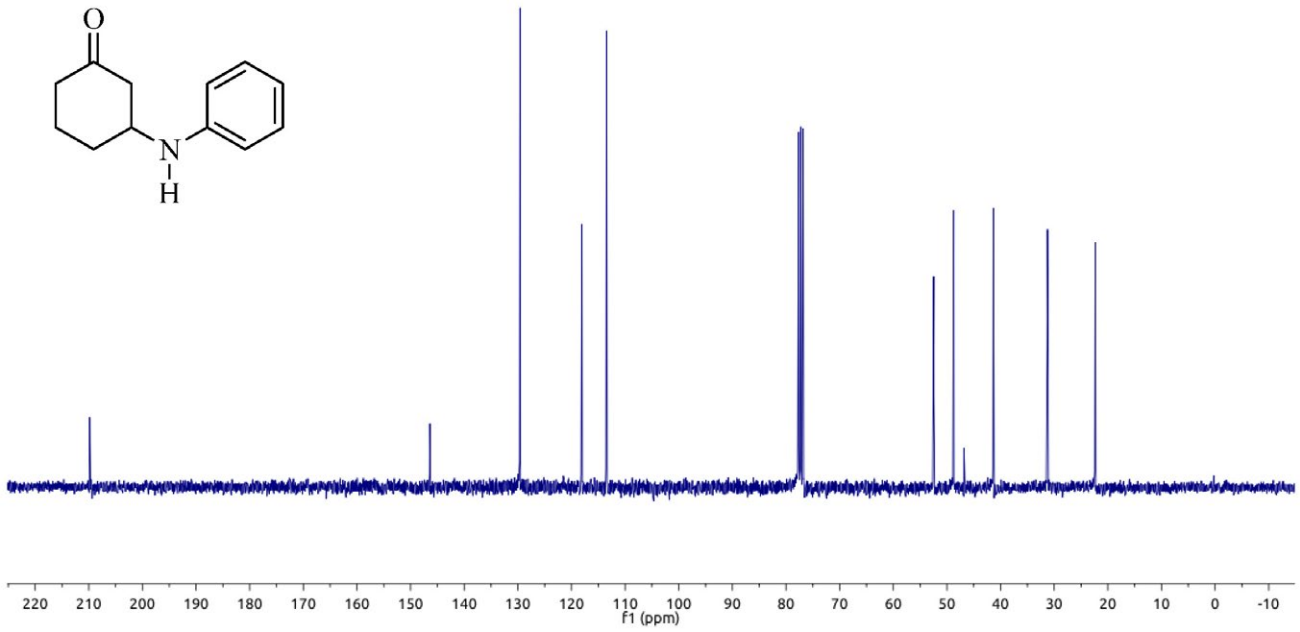


Figure S5. ^{13}C NMR spectrum (75 MHz, $CDCl_3$) of 3-(phenylamino)cyclohexanone (**2a**).

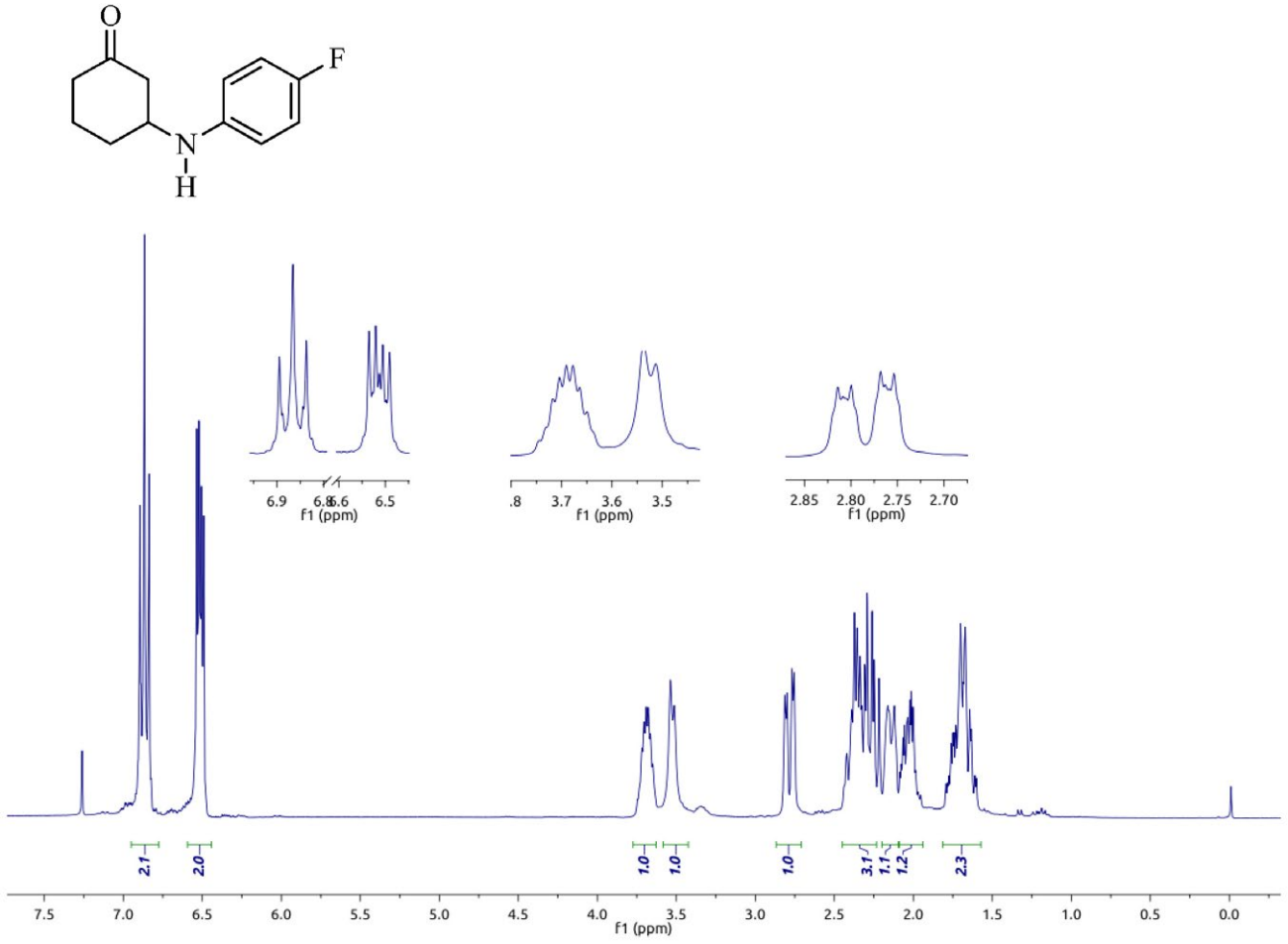


Figure S6. ^{1}H NMR spectrum (300 MHz, $CDCl_3$) of 3-(4-fluorophenylamino)cyclohexanone (**2b**).

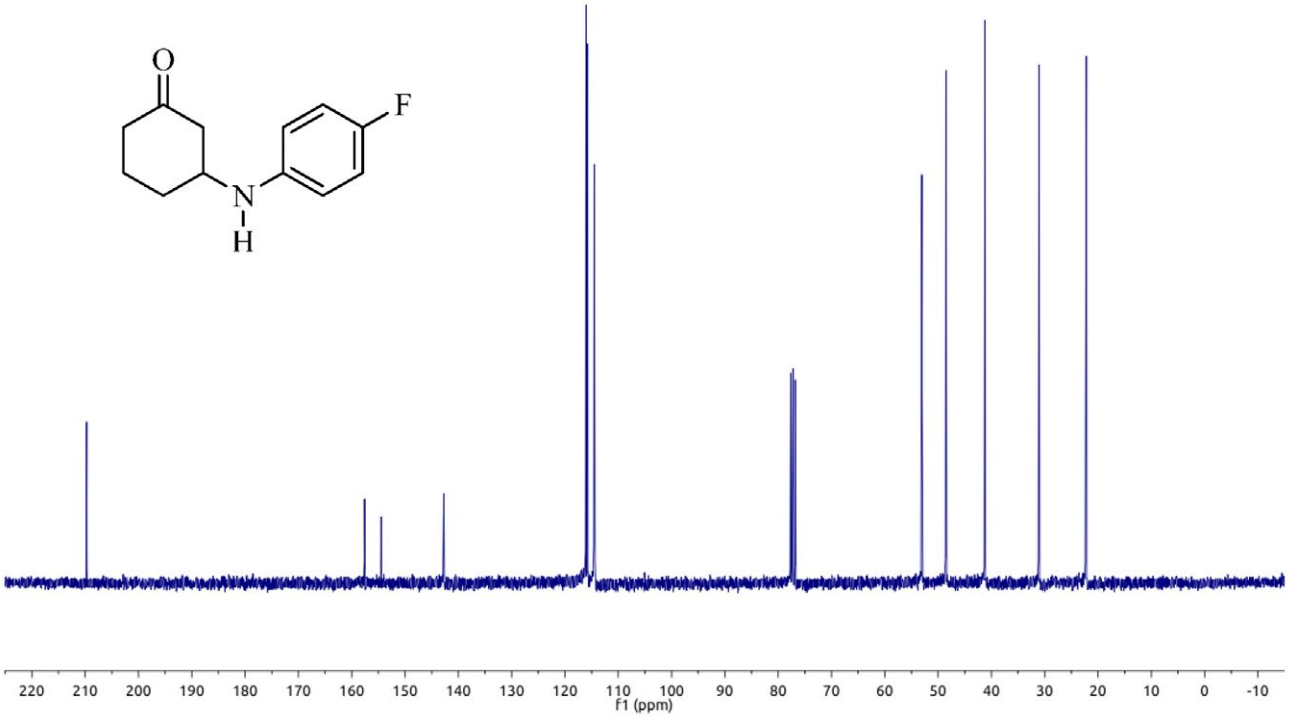


Figure S7. ^{13}C NMR spectrum (75 MHz, $CDCl_3$) of 3-(4-fluorophenylamino)cyclohexanone (**2b**).

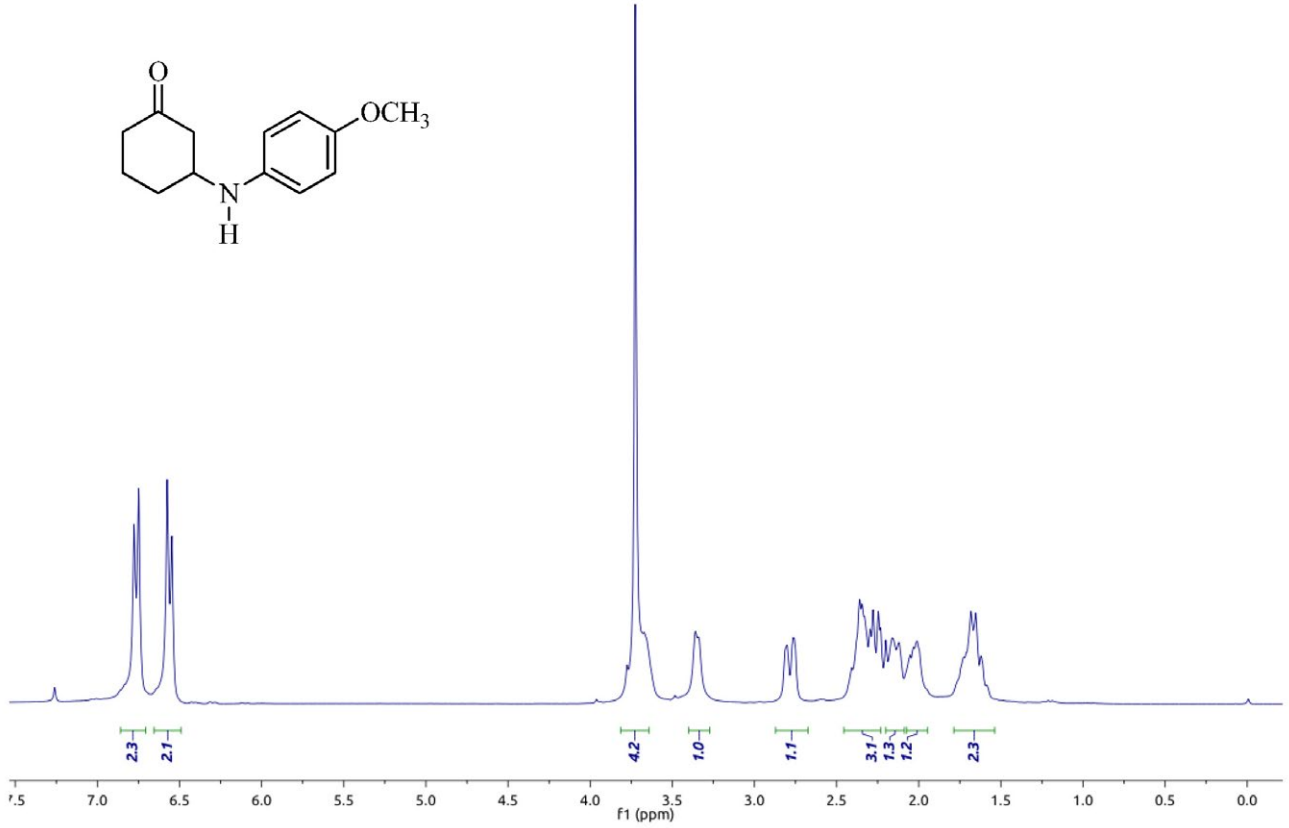


Figure S8. ^{1}H NMR spectrum (300 MHz, $CDCl_3$) of 3-(4-methoxyphenylamino)cyclohexanone (**2c**).

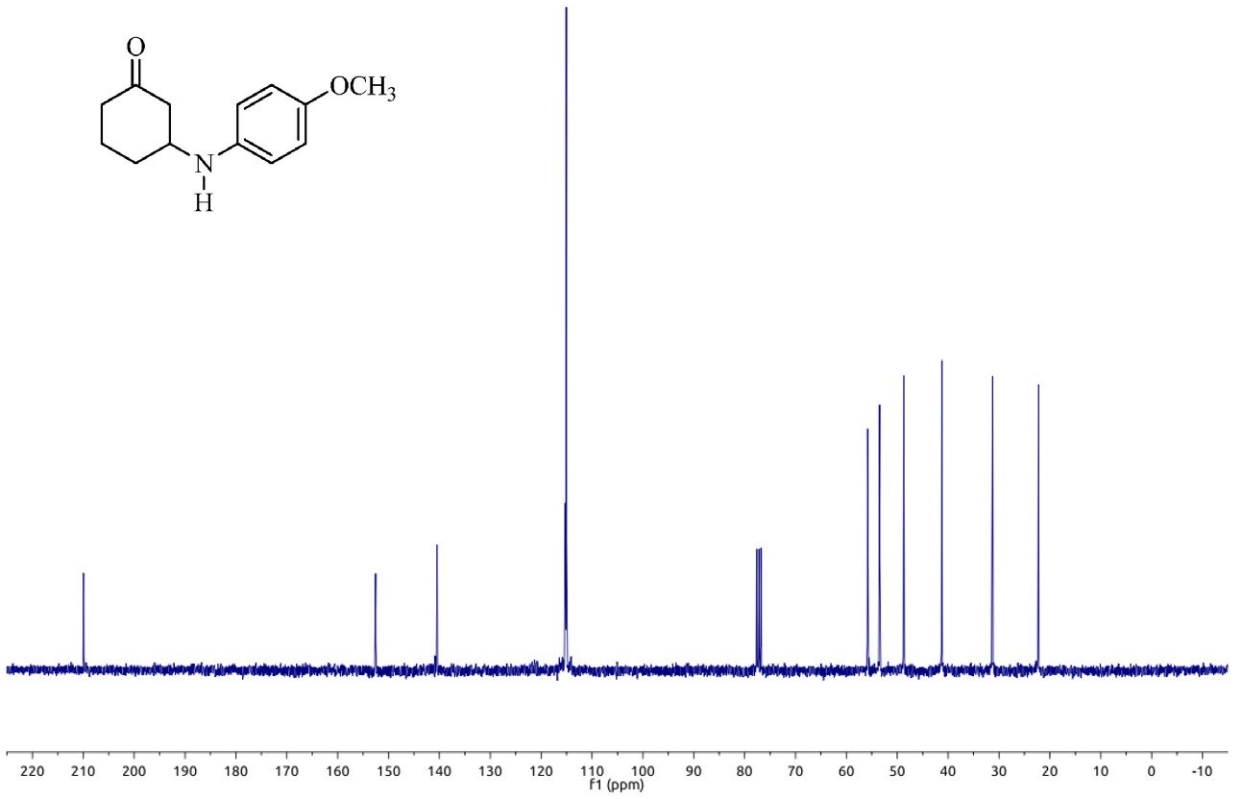


Figure S9. ^{13}C NMR spectrum (75 MHz, $CDCl_3$) of 3-(4-methoxyphenylamino)cyclohexanone (**2c**).

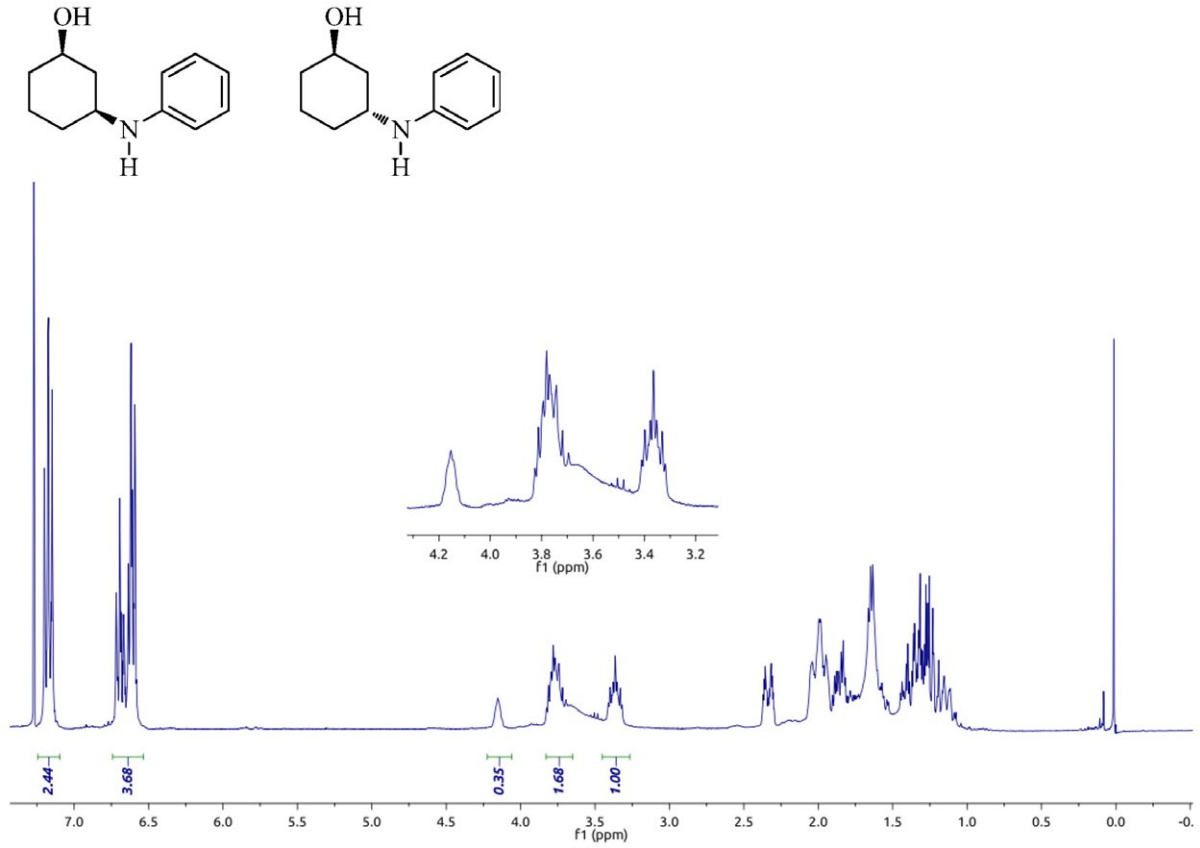


Figure S10. ^{1}H NMR spectrum (300 MHz, $CDCl_3$) of mixture (75:25) of *cis*-3-(phenylamino)cyclohexanol (**3a**) and *trans*-3-(phenylamino)cyclohexanol (**4a**).

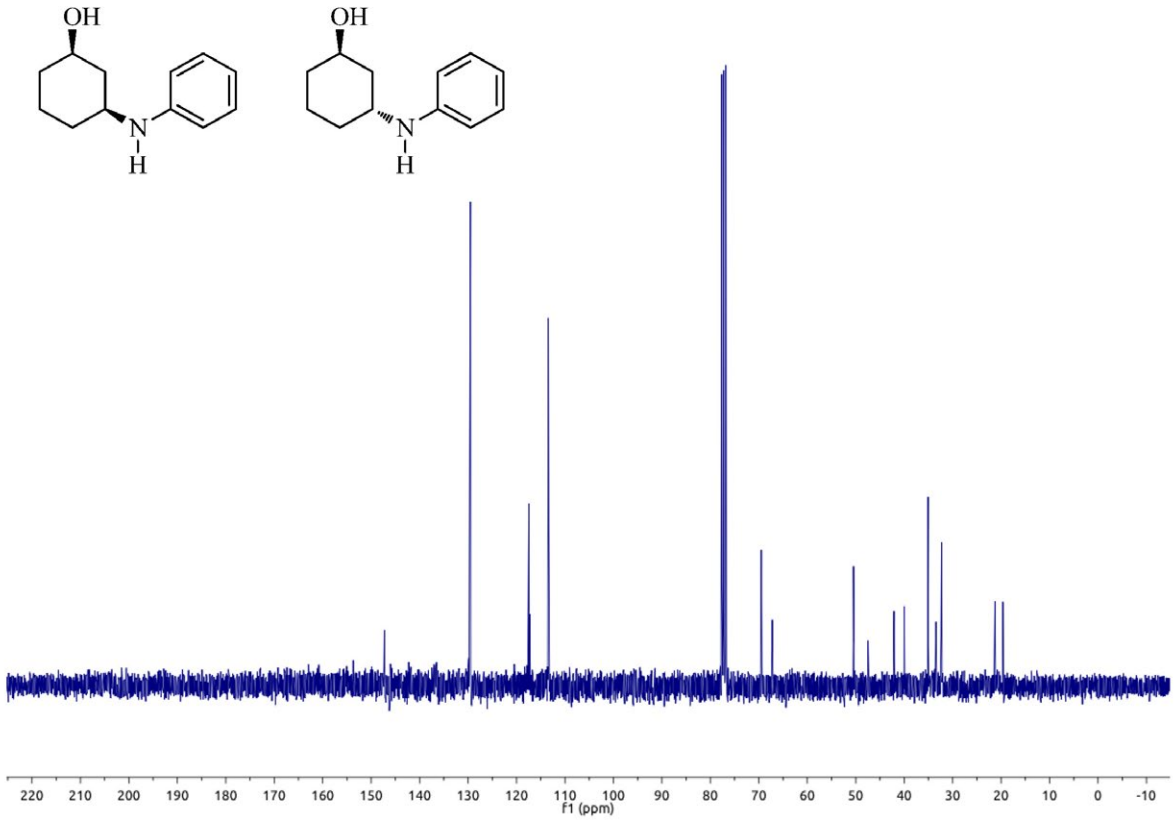


Figure S11. ^{13}C NMR spectrum (75 MHz, $CDCl_3$) of mixture (75:25) of *cis*-3-(phenylamino)cyclohexanol (**3a**) and *trans*-3-(phenylamino)cyclohexanol (**4a**).

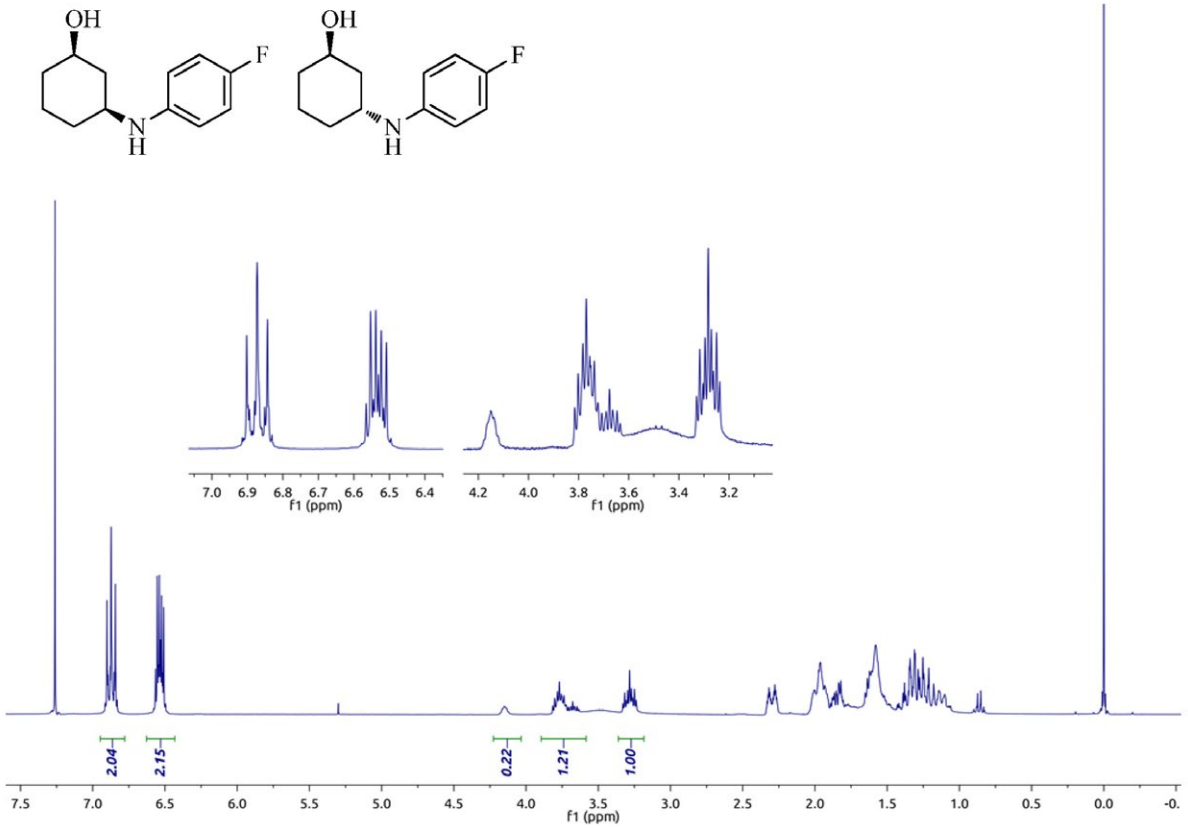


Figure S12. ^{1}H NMR spectrum (300 MHz, $CDCl_3$) of mixture (75:25) of *cis*-3-(4-fluorophenylamino)cyclohexanol (**3b**) and *trans*-3-(4-fluorophenylamino) cyclohexanol (**4b**).

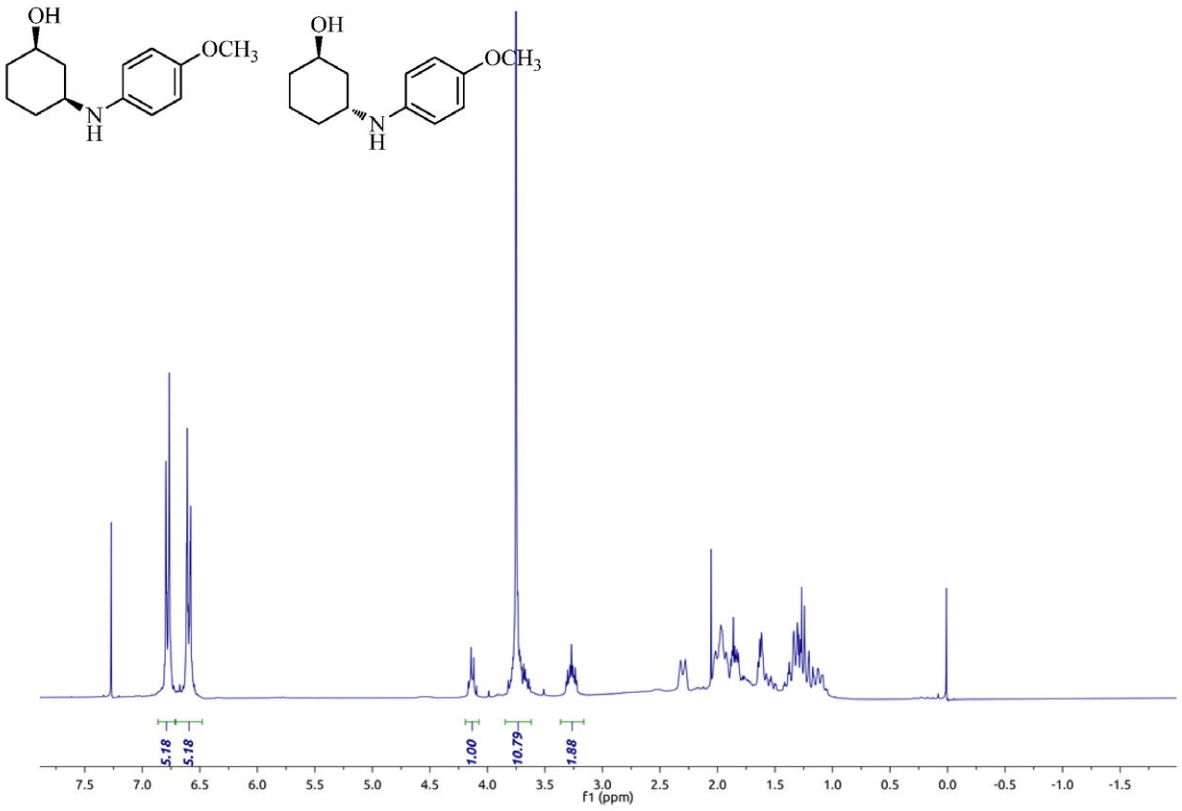


Figure S13. ^{1}H NMR spectrum (300 MHz, $CDCl_3$) of mixture (75:25) of *cis*-3-(4-methoxyphenylamino)cyclohexanol (**3c**) and *trans*-3-(4-methoxyphenylamino)cyclohexanol (**4c**).

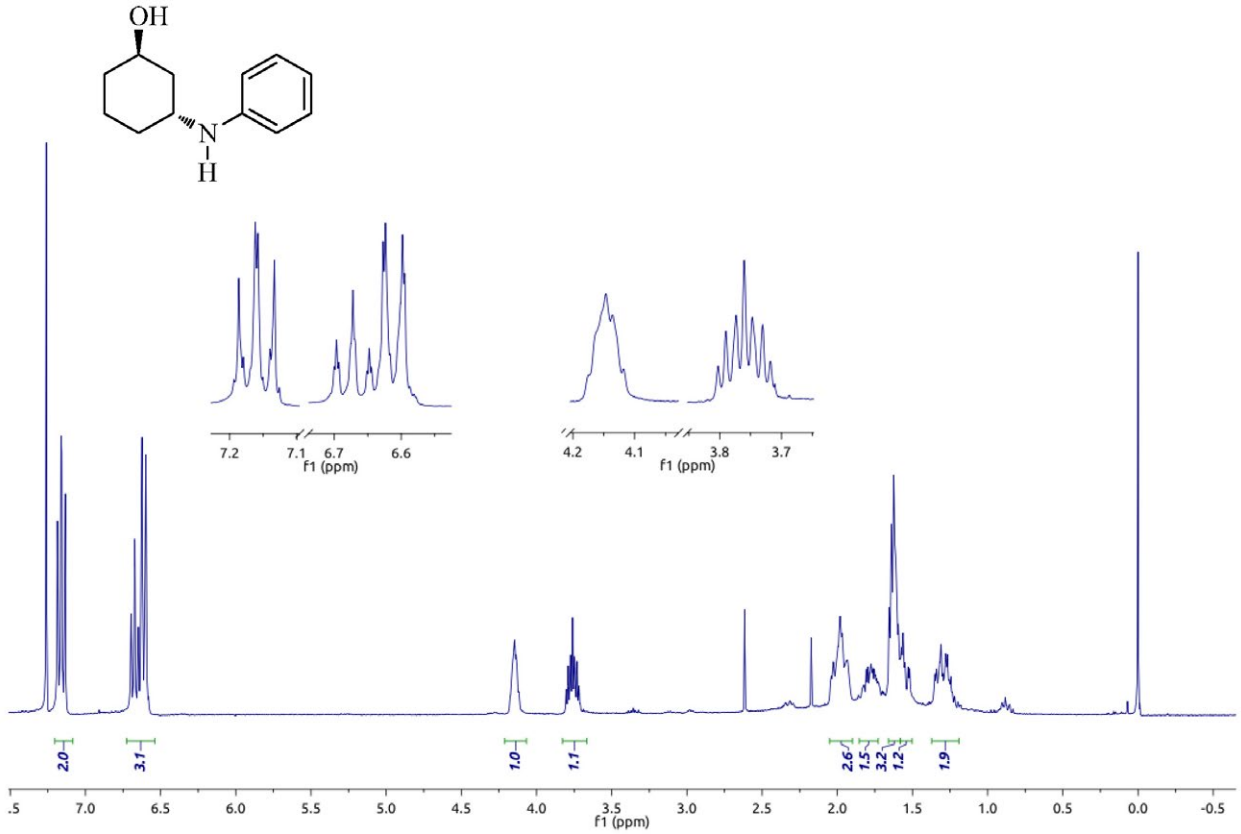


Figure S14. ^{1}H NMR spectrum (300 MHz, $CDCl_3$) of *trans*-3-(phenylamino)cyclohexanol (**4a**).

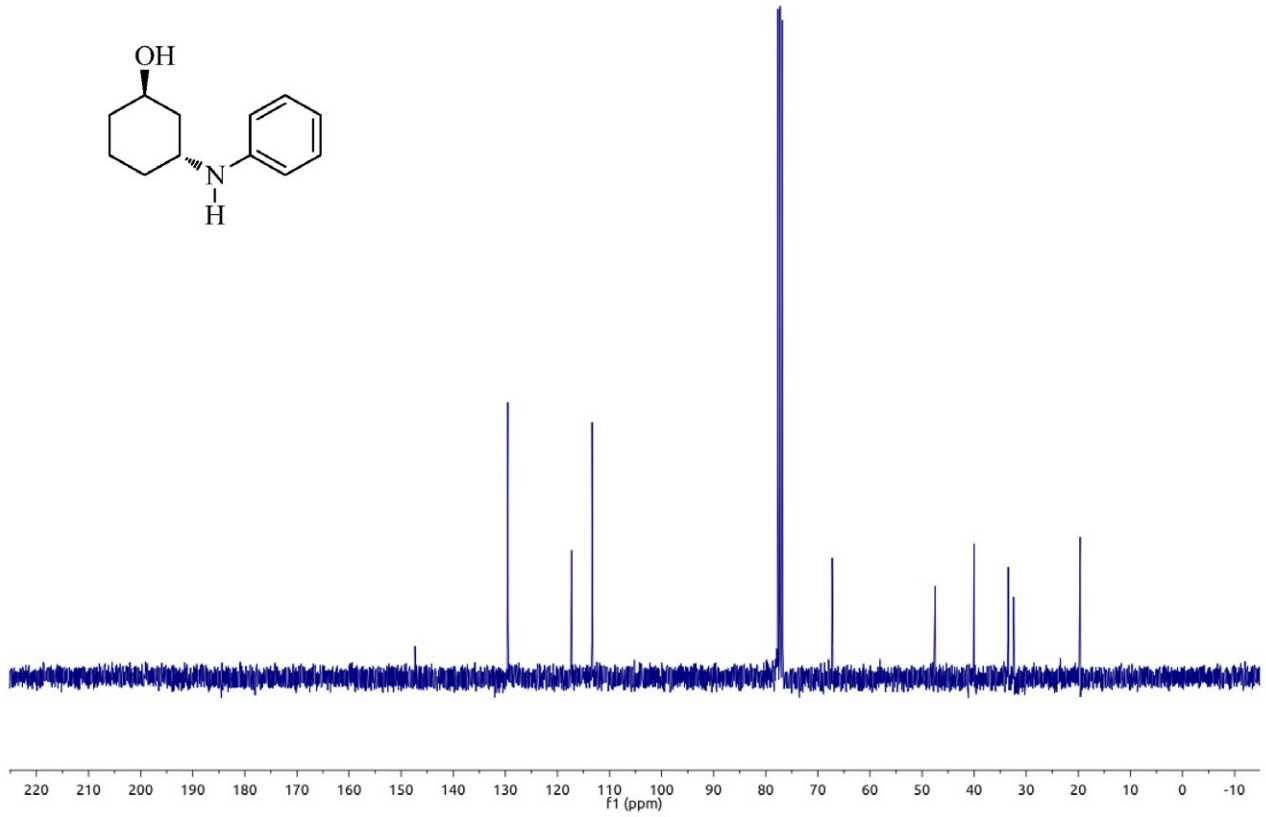


Figure S15. ^{13}C NMR spectrum (75 MHz, $CDCl_3$) of *trans*-3-(phenylamino)cyclohexanol (**4a**).

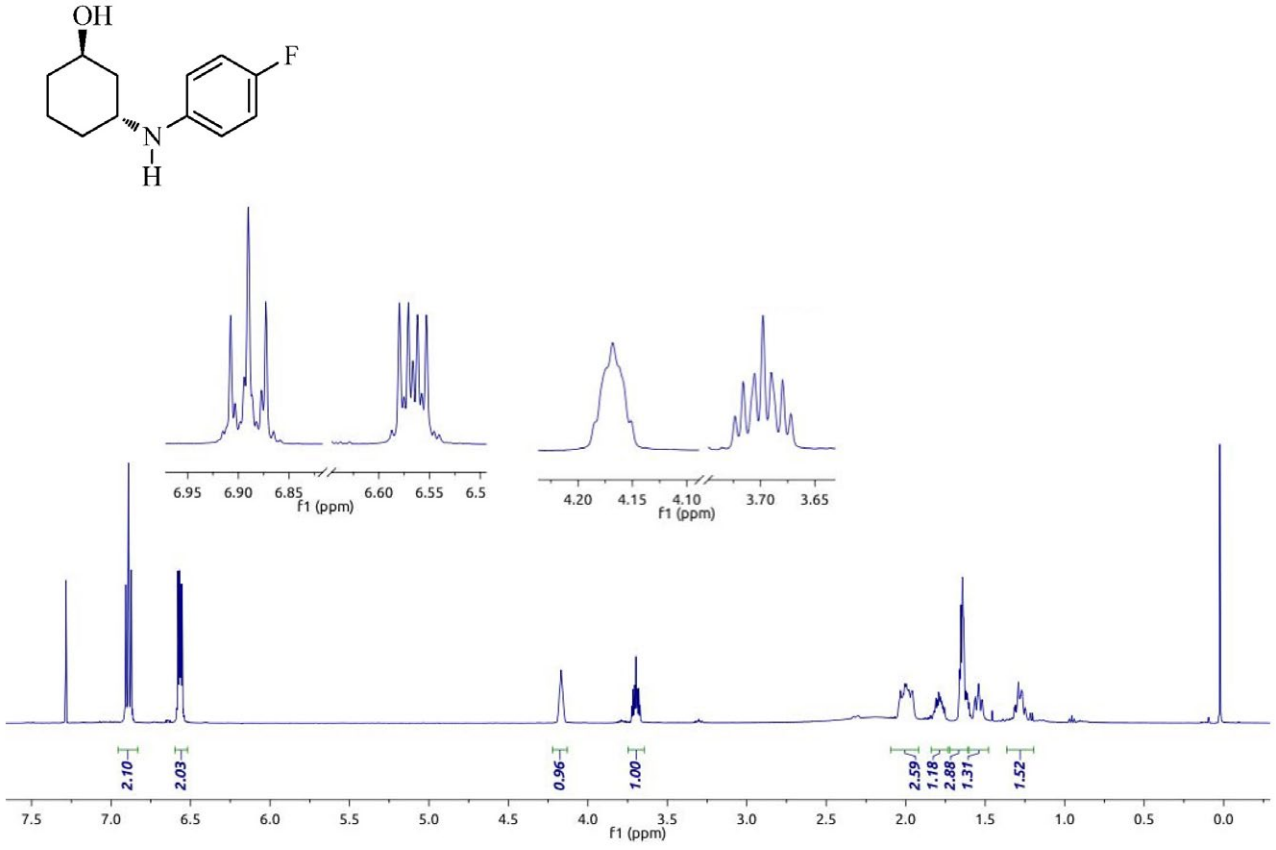


Figure S16. ^{1}H NMR spectrum (300 MHz, $CDCl_3$) of *trans*-3-(4-fluorophenylamino)cyclohexanol (**4b**).

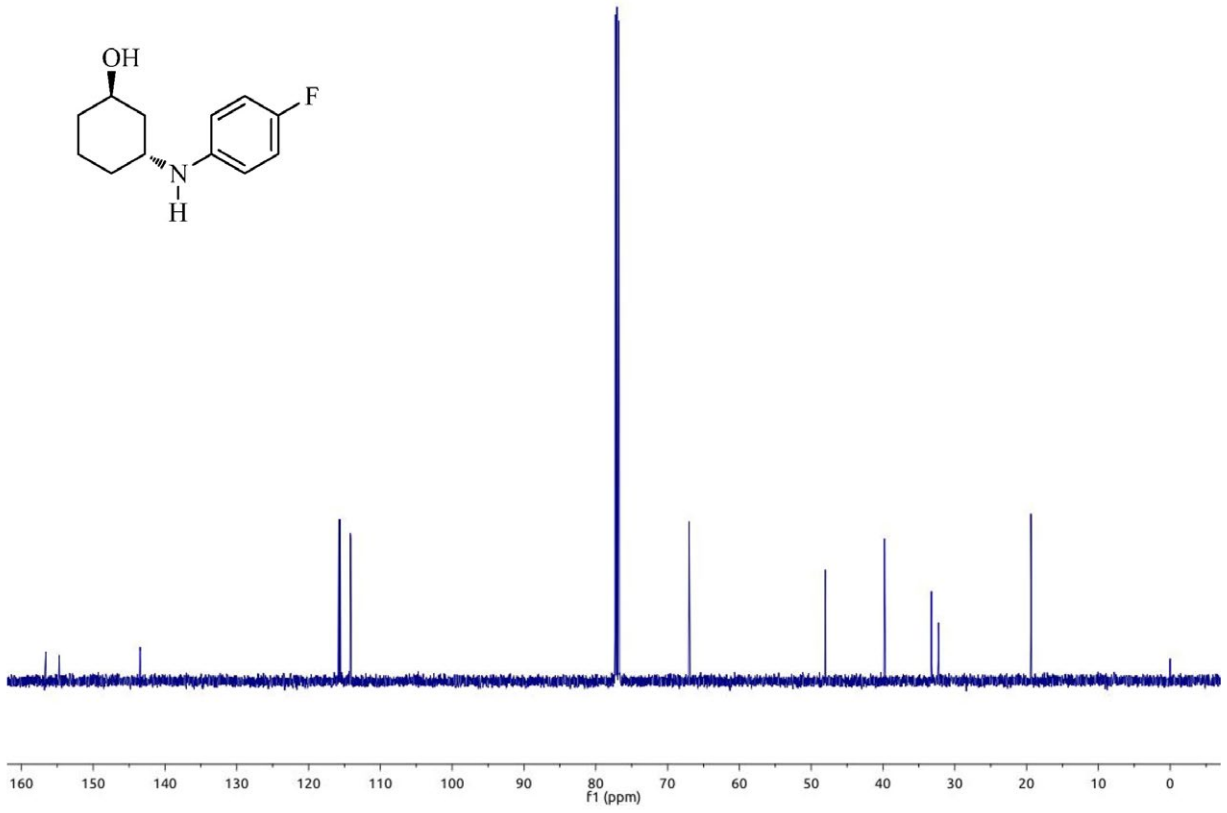


Figure S17. ^{13}C NMR spectrum (75 MHz, $CDCl_3$) of *trans*-3-(4-fluorophenylamino)cyclohexanol (**4b**).

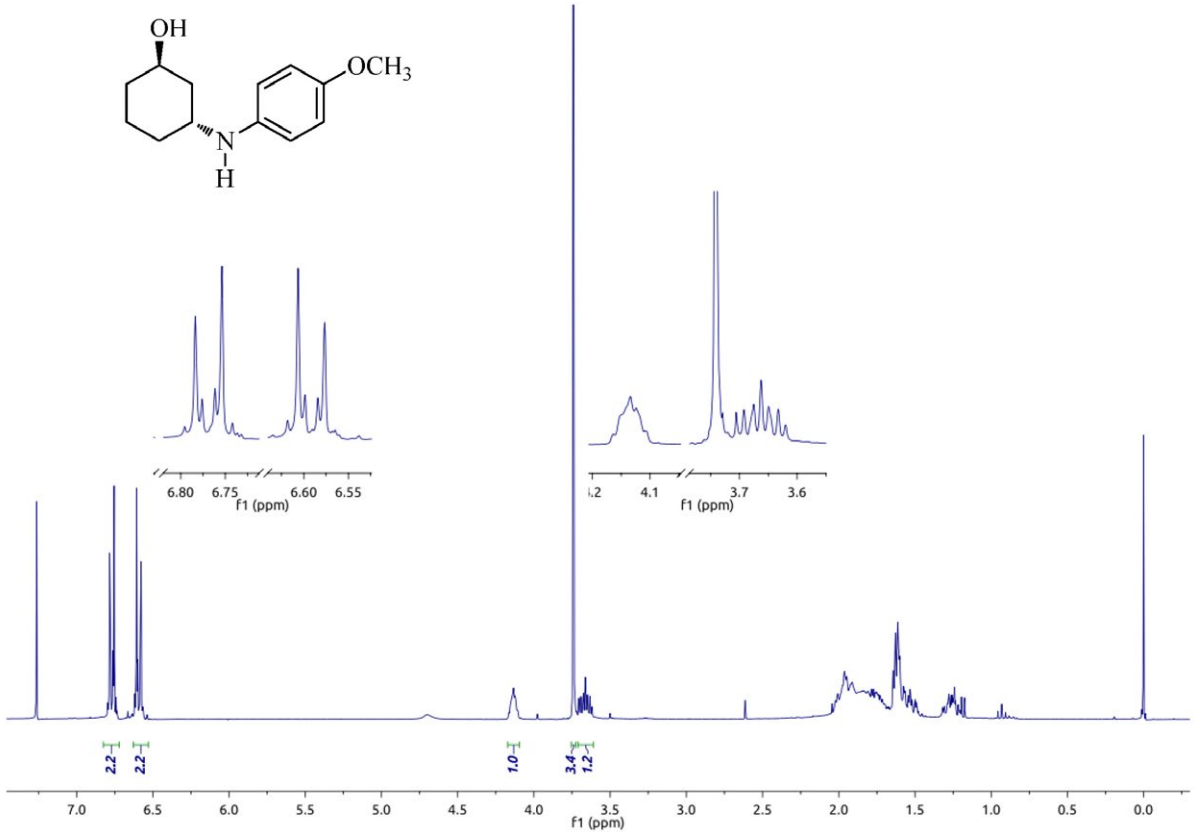


Figure S18. ^{1}H NMR spectrum (300 MHz, $CDCl_3$) of *trans*-3-(4-methoxyphenylamino)cyclohexanol (**4c**).

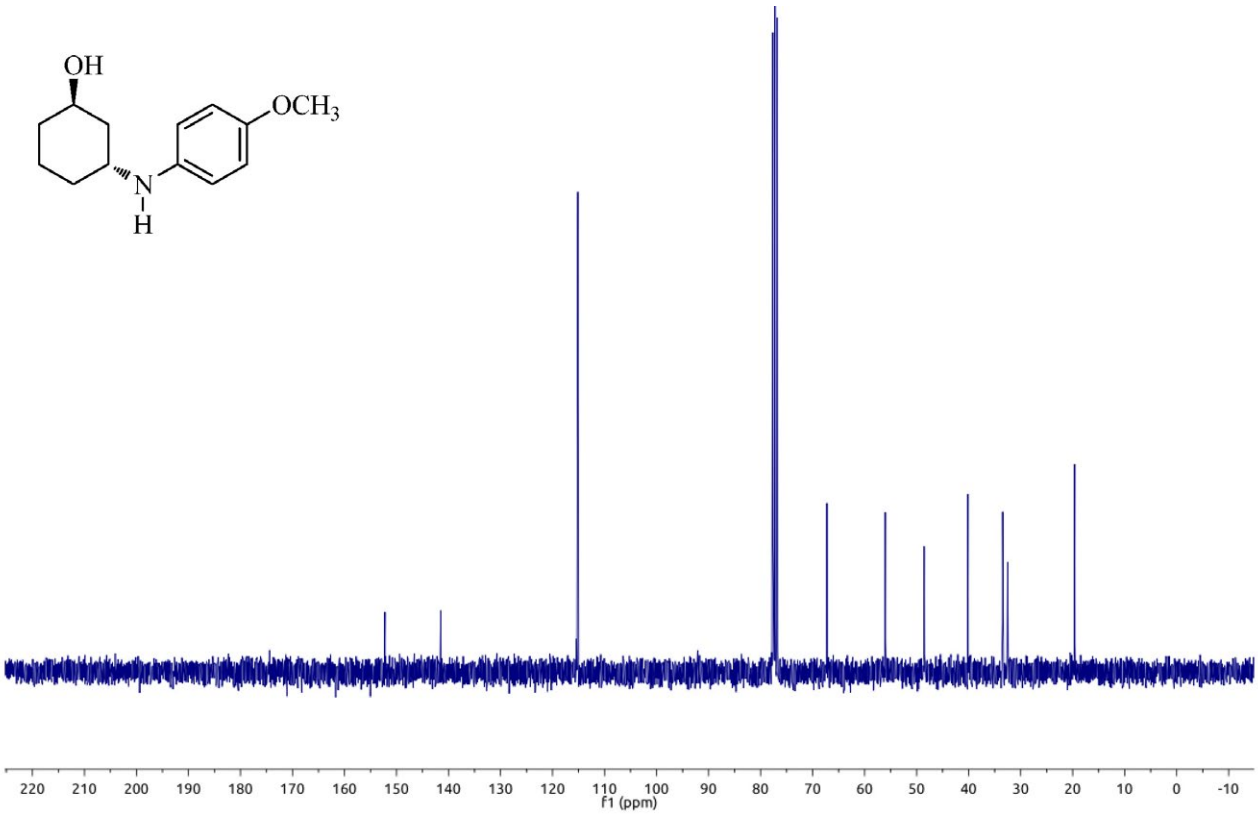


Figure S19. ^{13}C NMR spectrum (75 MHz, $CDCl_3$) of *trans*-3-(4-methoxyphenylamino)cyclohexanol (**4c**).

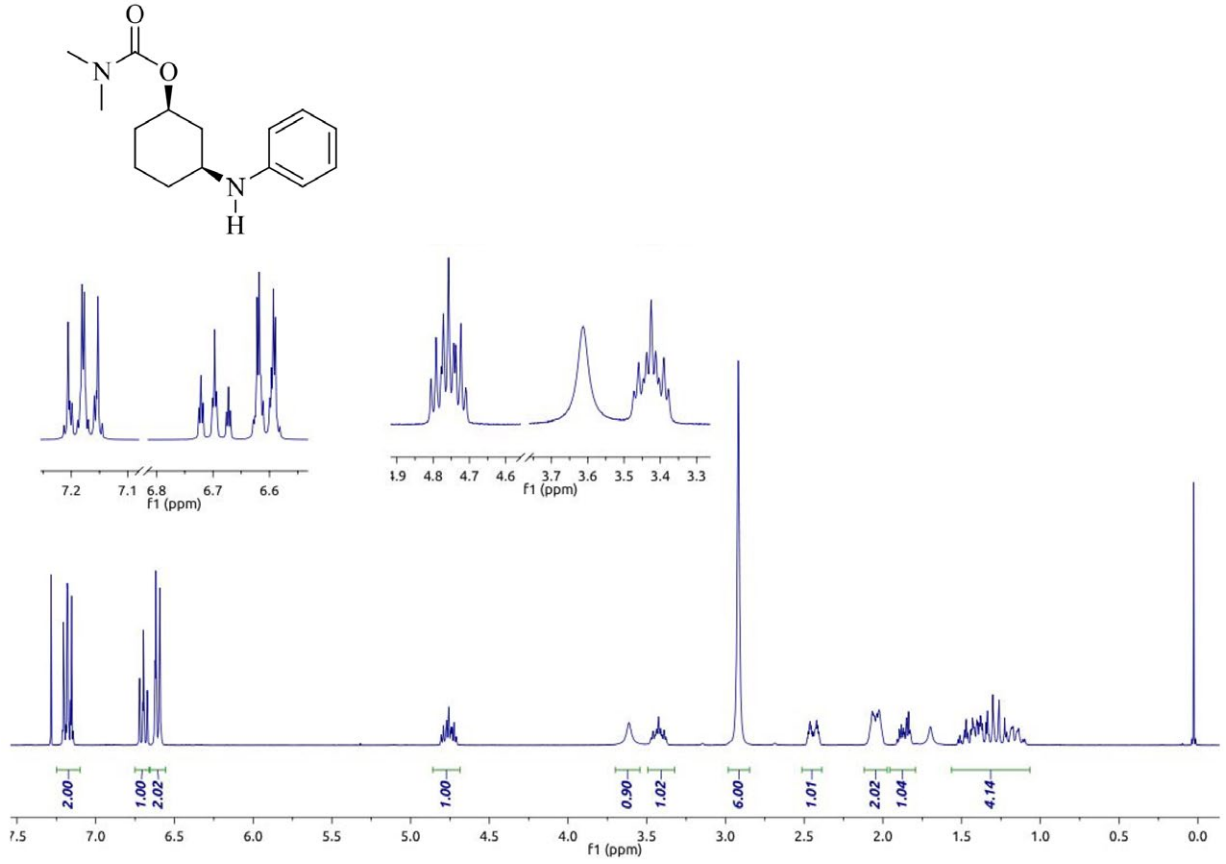


Figure S20. ^{1}H NMR spectrum (300 MHz, $CDCl_3$) of *cis*-3-(phenylamino)cyclohexyl *N*,*N*-dimethylcarbamate (**5a**).

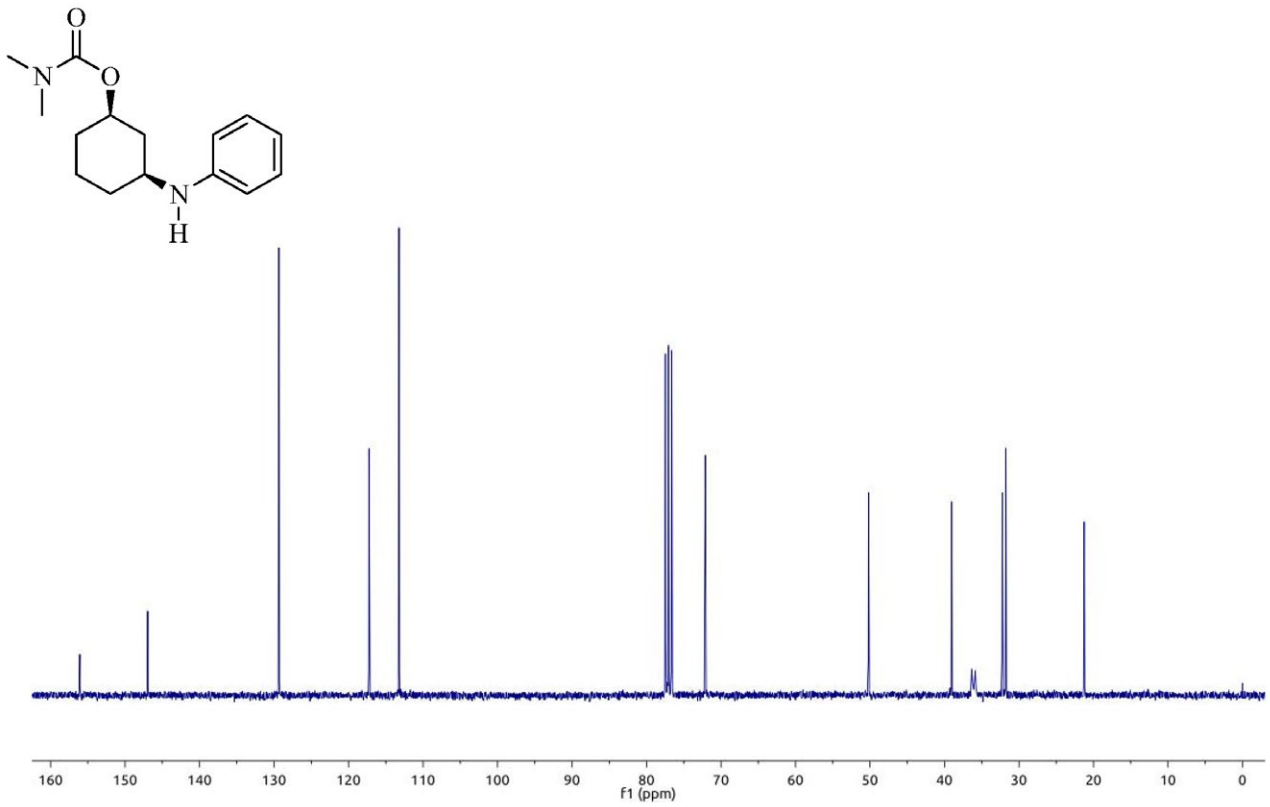


Figure S21. ^{13}C NMR spectrum (75 MHz, $CDCl_3$) of *cis*-3-(phenylamino)cyclohexyl *N*,*N*-dimethylcarbamate (**5a**).

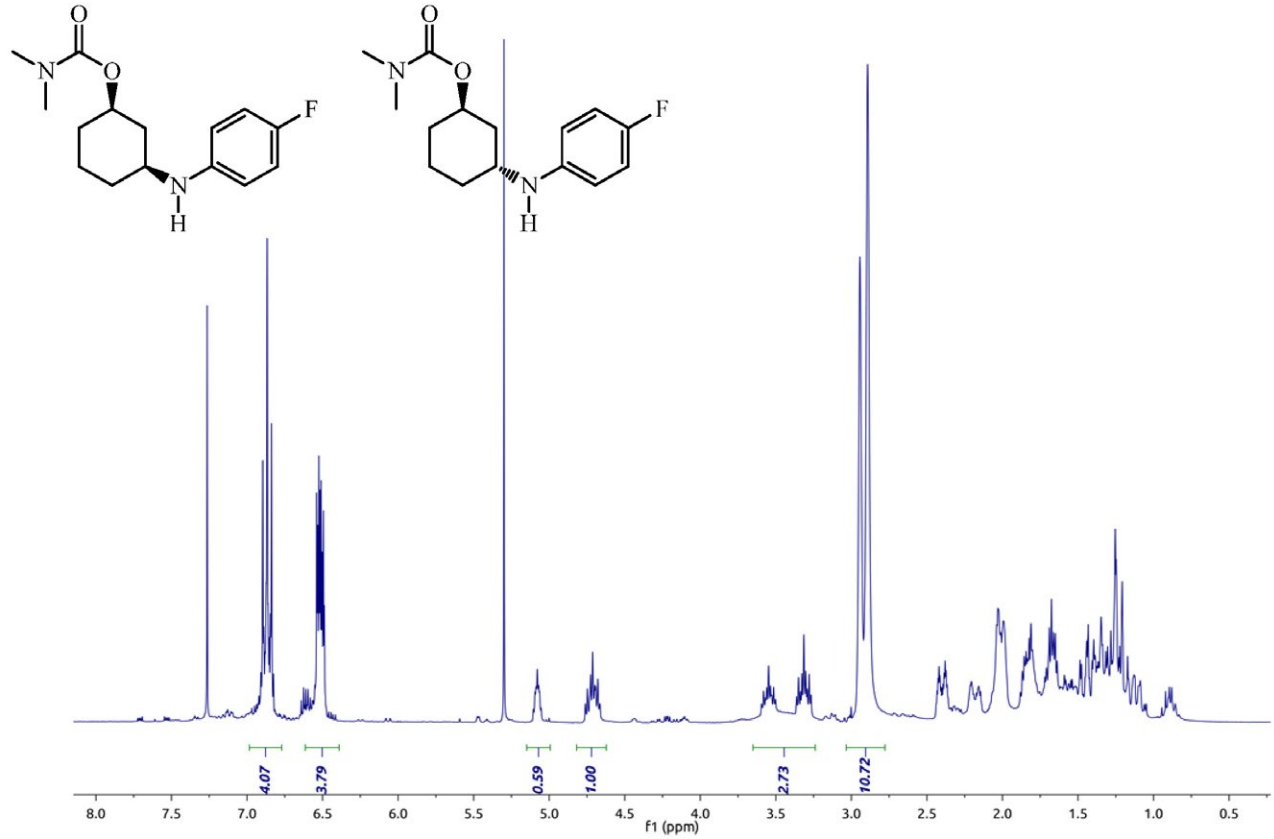


Figure S22. ^{1}H NMR spectrum (300 MHz, $CDCl_3$) of *cis*-3-(4-fluorophenylamino)cyclohexyl *N*,*N*-dimethylcarbamate (**5b**) and *trans*- 3- (4-fluorophenylamino) cyclohexyl *N*,*N*-dimethylcarbamate (**6b**).

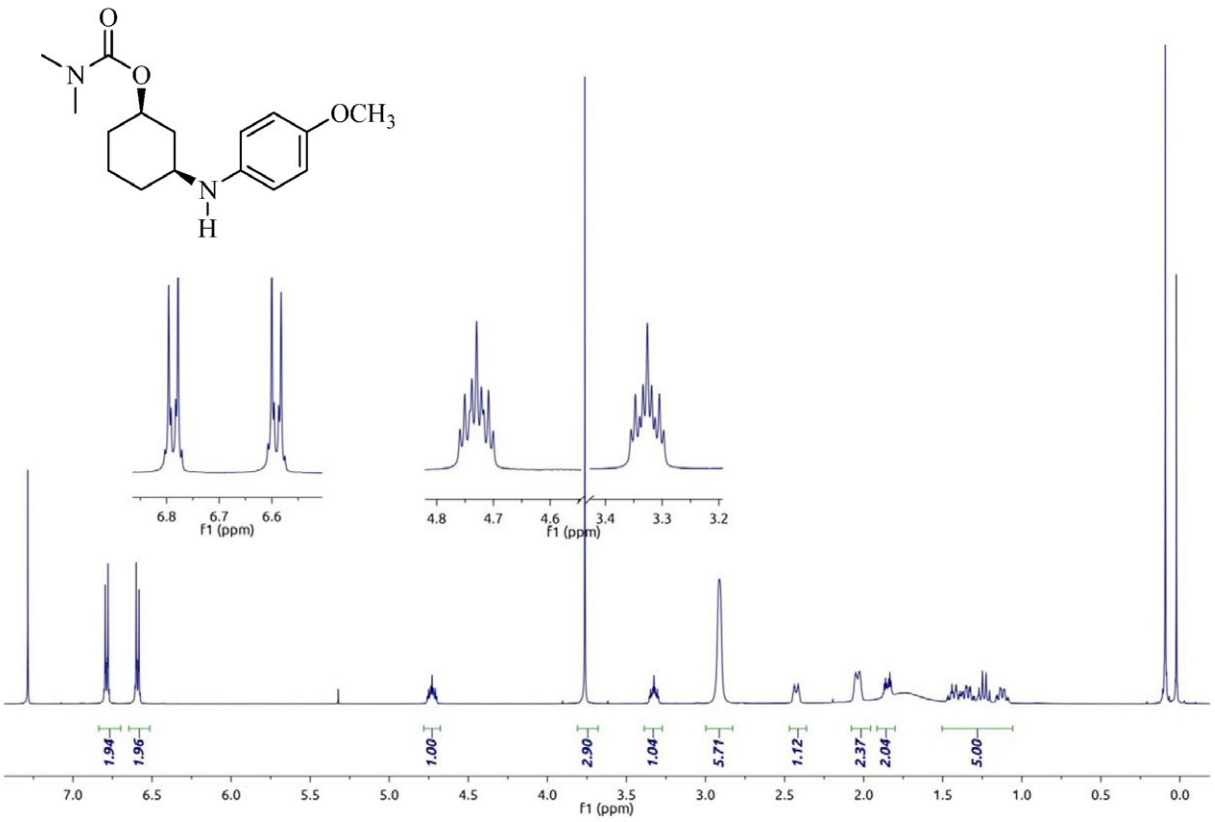


Figure S23. ^{1}H NMR spectrum (300 MHz, $CDCl_3$) of *cis*-3-(4-methoxyphenylamino)cyclohexyl *N*,*N*-dimethylcarbamate (**5c**).

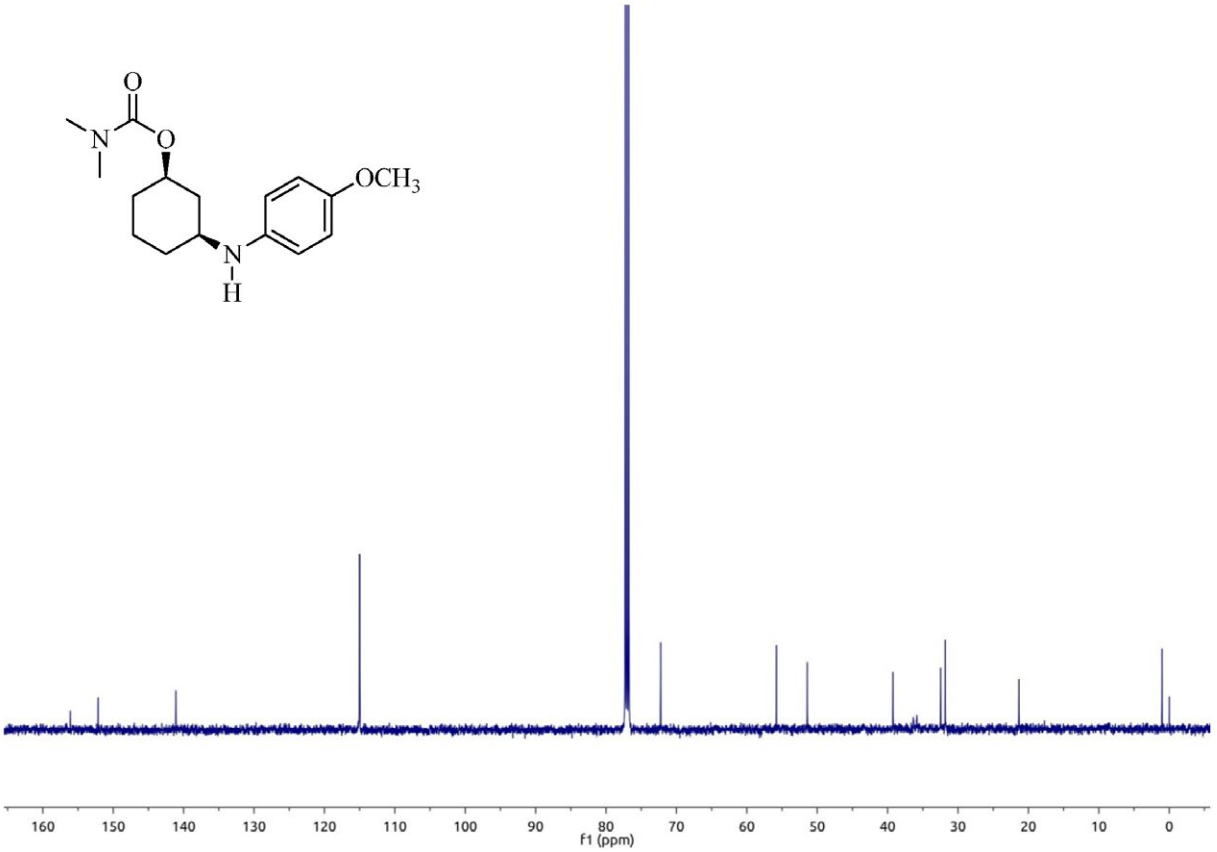


Figure S24. ^{13}C NMR spectrum (75 MHz, $CDCl_3$) of *cis*-3-(4-methoxyphenylamino)cyclohexyl *N*,*N*-dimethylcarbamate (**5c**).

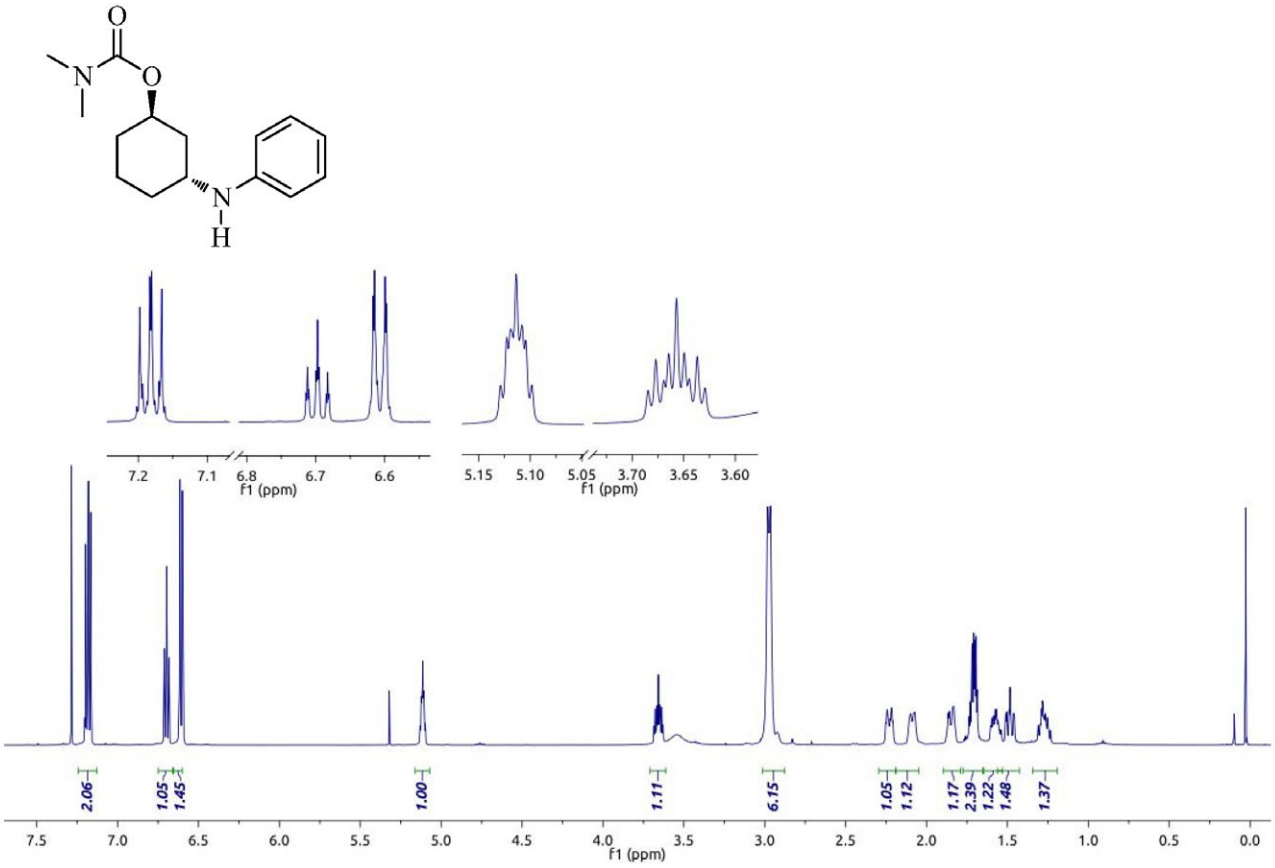


Figure S25. ^{1}H NMR spectrum (300 MHz, $CDCl_3$) of *trans*-3-(phenylamino)cyclohexyl *N*,*N*-dimethylcarbamate (**6a**).

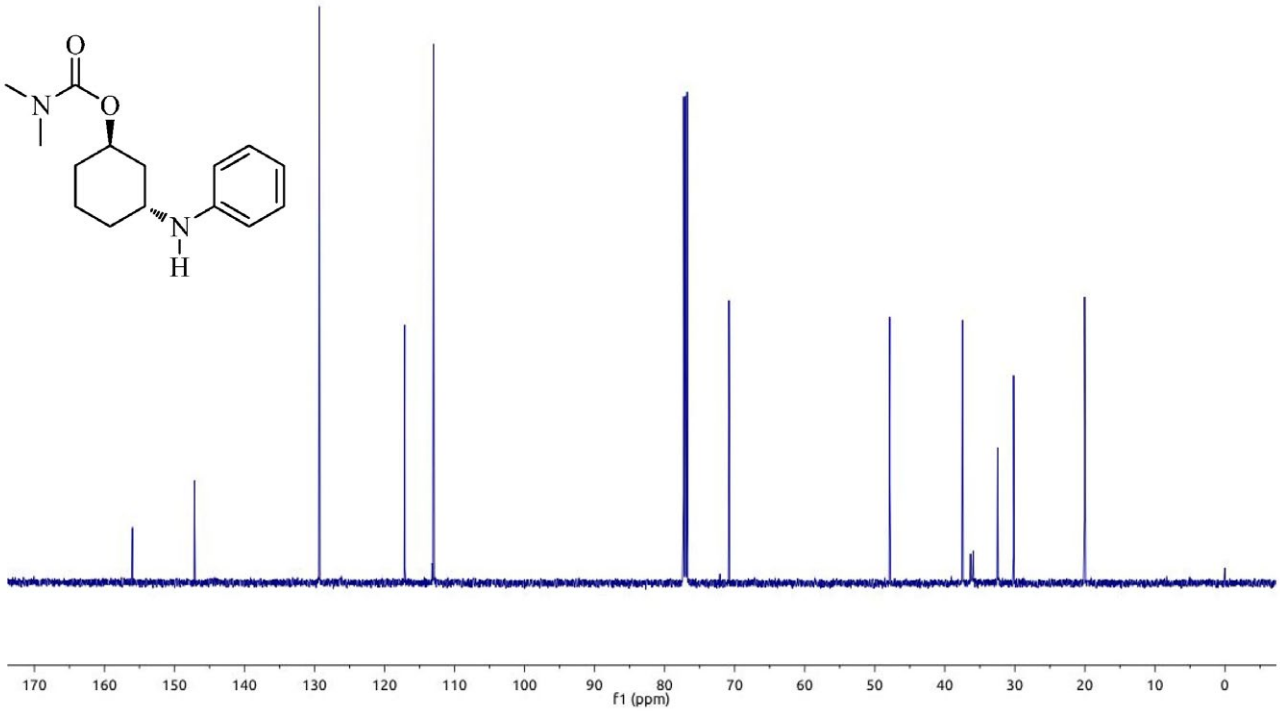


Figure S26. ^{13}C NMR spectrum (75 MHz, $CDCl_3$) of *trans*-3-(phenylamino)cyclohexyl *N*,*N*-dimethylcarbamate (**6a**).

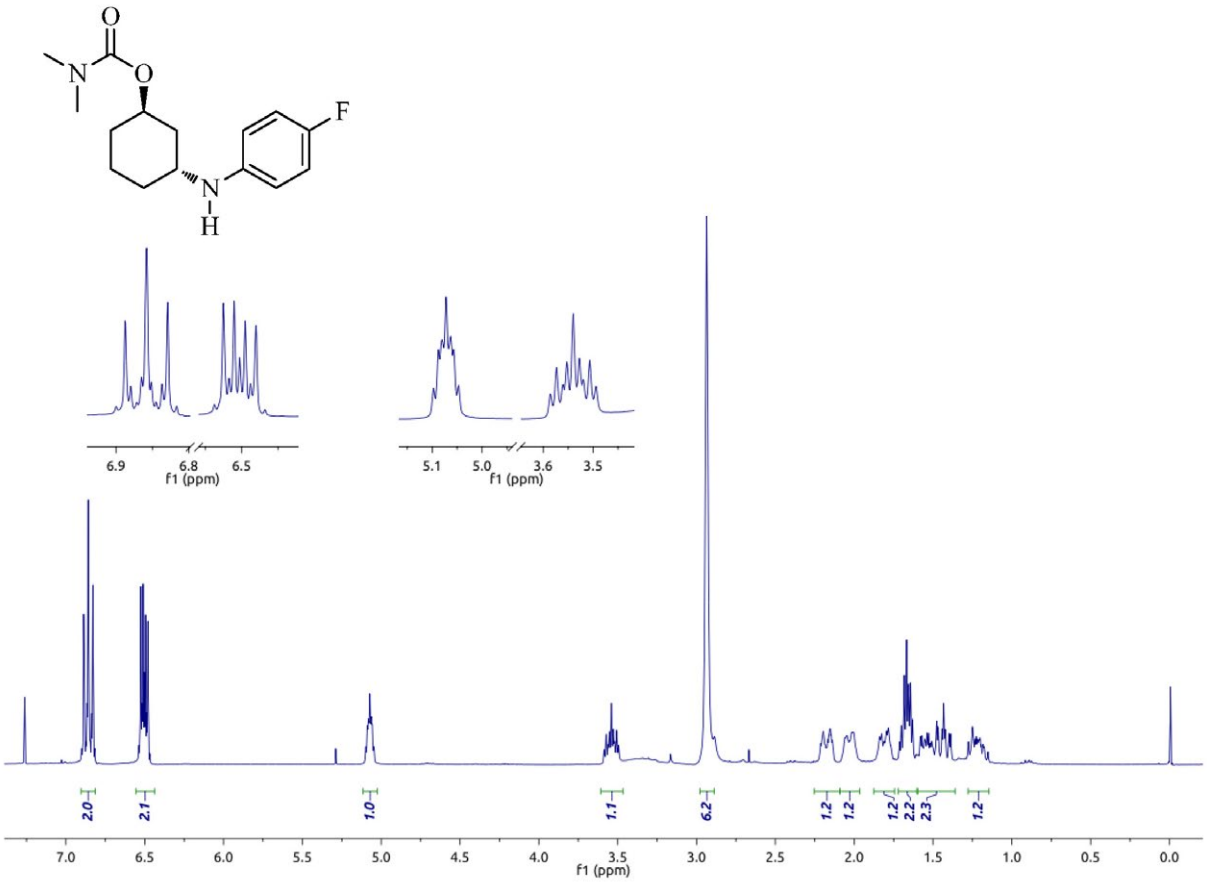


Figure S27. ^{1}H NMR spectrum (300 MHz, $CDCl_3$) of *trans*-3-(4-fluorophenylamino)cyclohexyl *N*,*N*-dimethylcarbamate (**6b**).

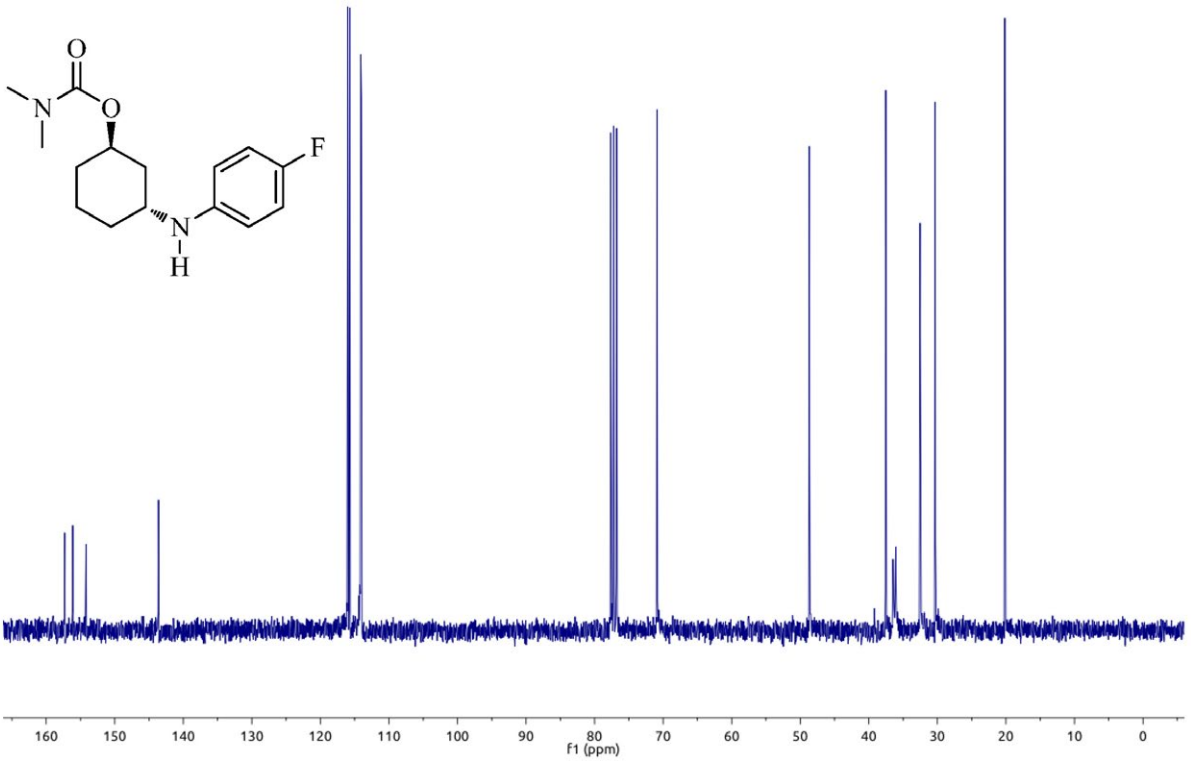


Figure S28. ^{13}C NMR spectrum (75 MHz, $CDCl_3$) of *trans*-3-(4-fluorophenylamino)cyclohexyl *N*,*N*-dimethylcarbamate (**6b**).

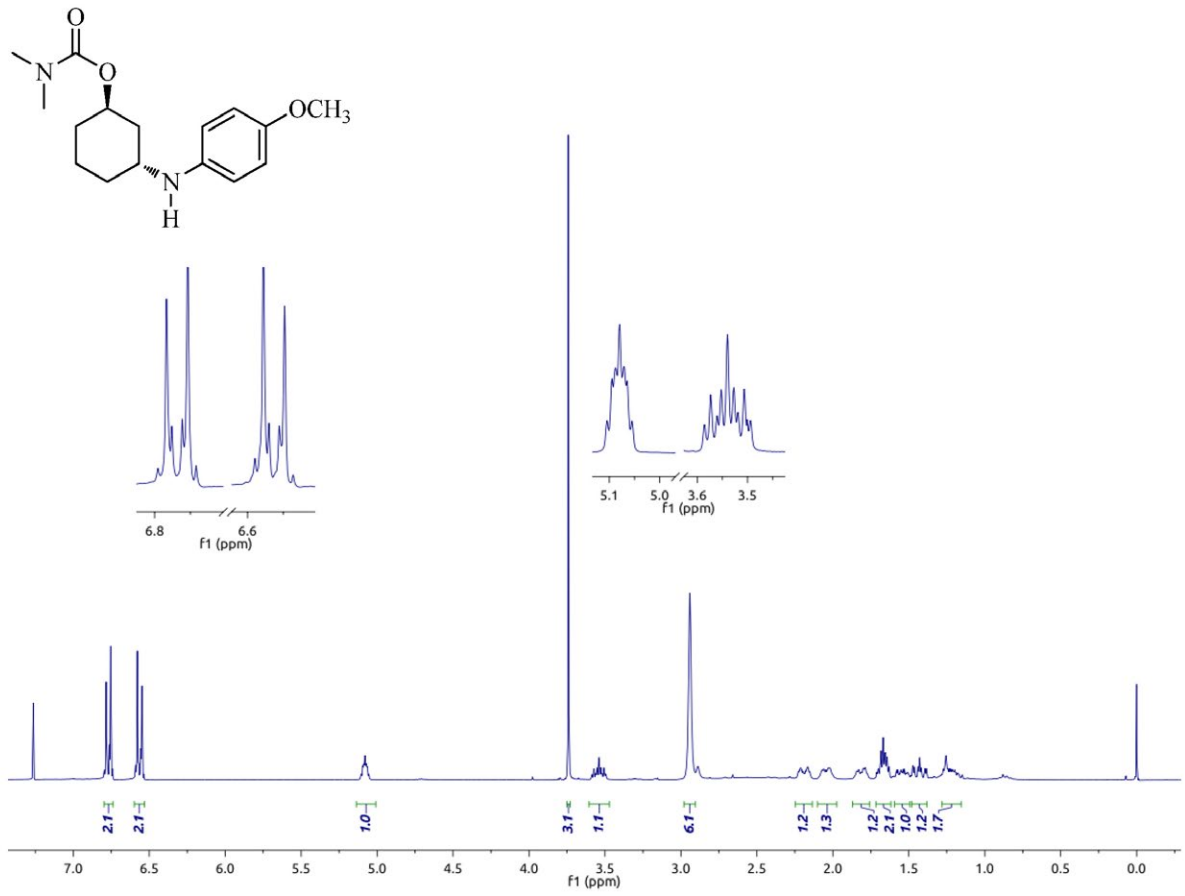


Figure S29. ^{1}H NMR spectrum (300 MHz, $CDCl_3$) of *trans*-3-(4-methoxyphenylamino)cyclohexyl *N*,*N*-dimethylcarbamate (**6c**).

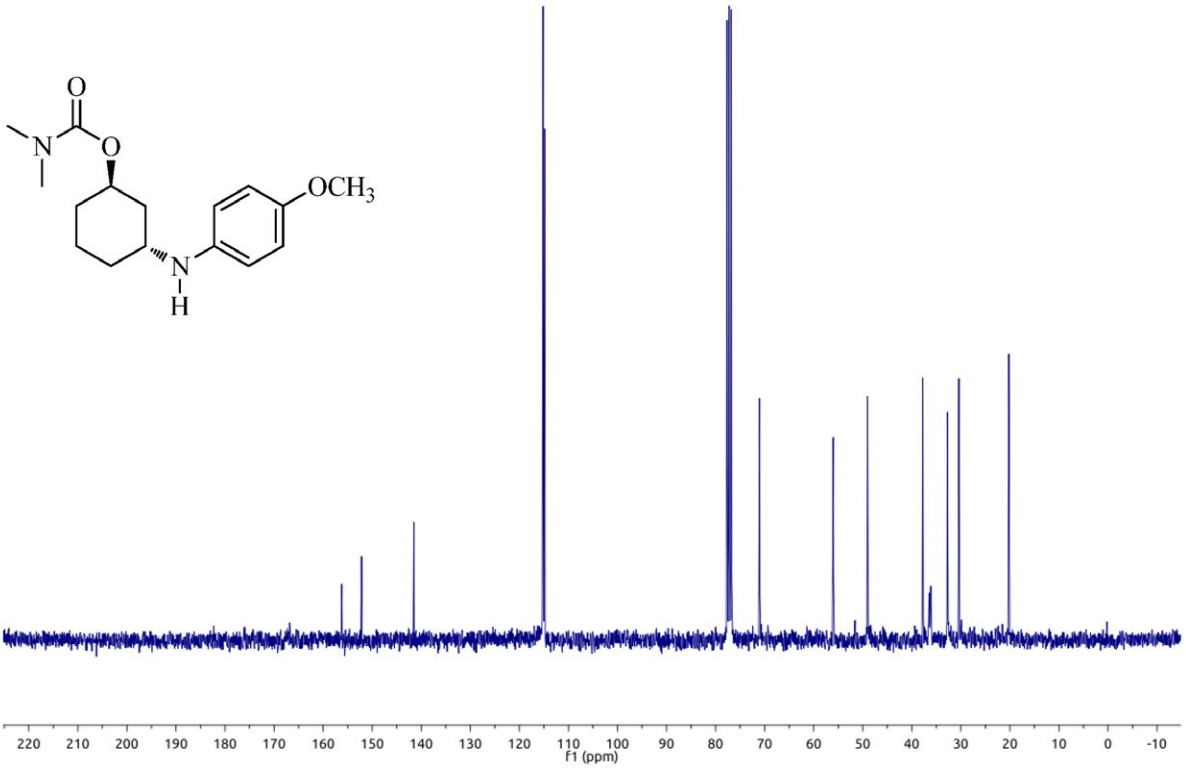


Figure S30. ^{13}C NMR spectrum (75 MHz, $CDCl_3$) of *trans*-3-(4-methoxyphenylamino)cyclohexyl *N*,*N*-dimethylcarbamate (**6c**).

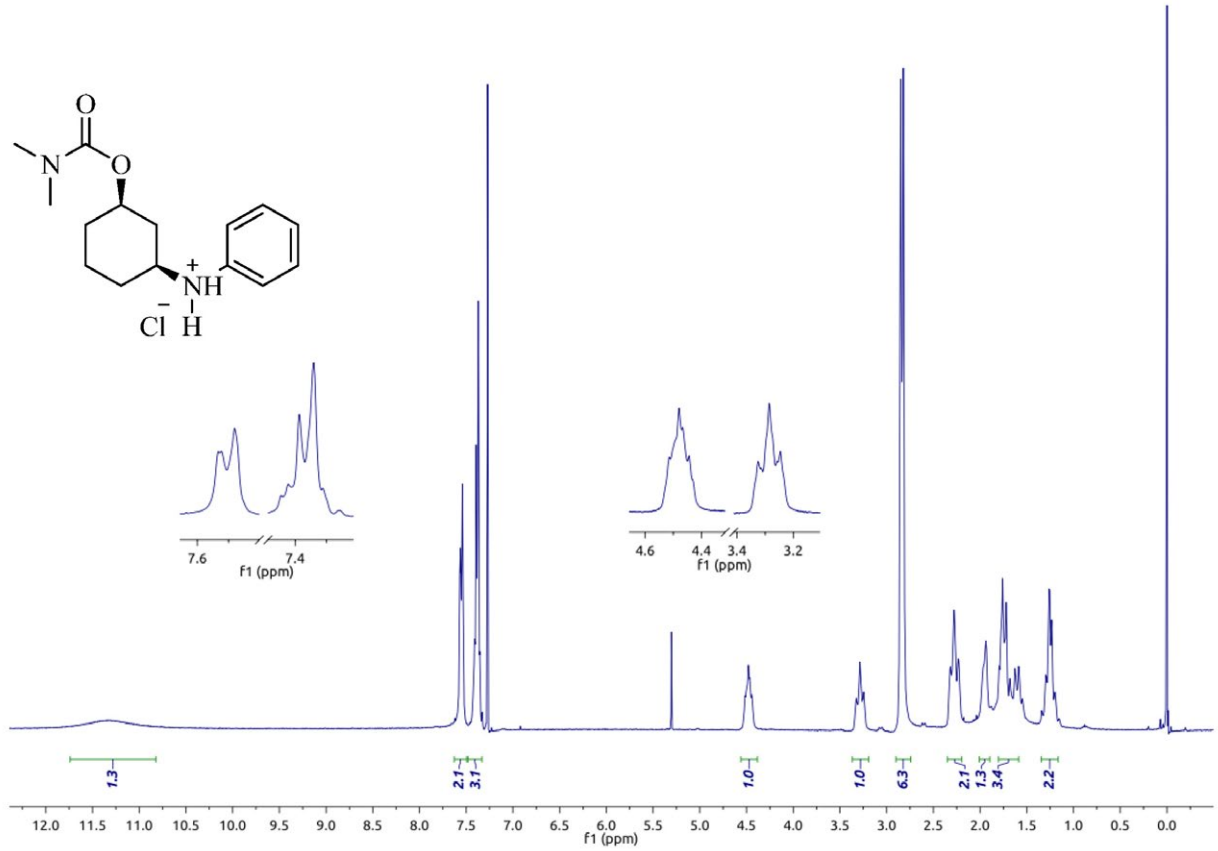


Figure S31. ^{1}H NMR spectrum (300 MHz, $CDCl_3$) of *cis*-3-(phenylamino)cyclohexyl *N*,*N*-dimethylcarbamate hydrochloride (**5a'**).

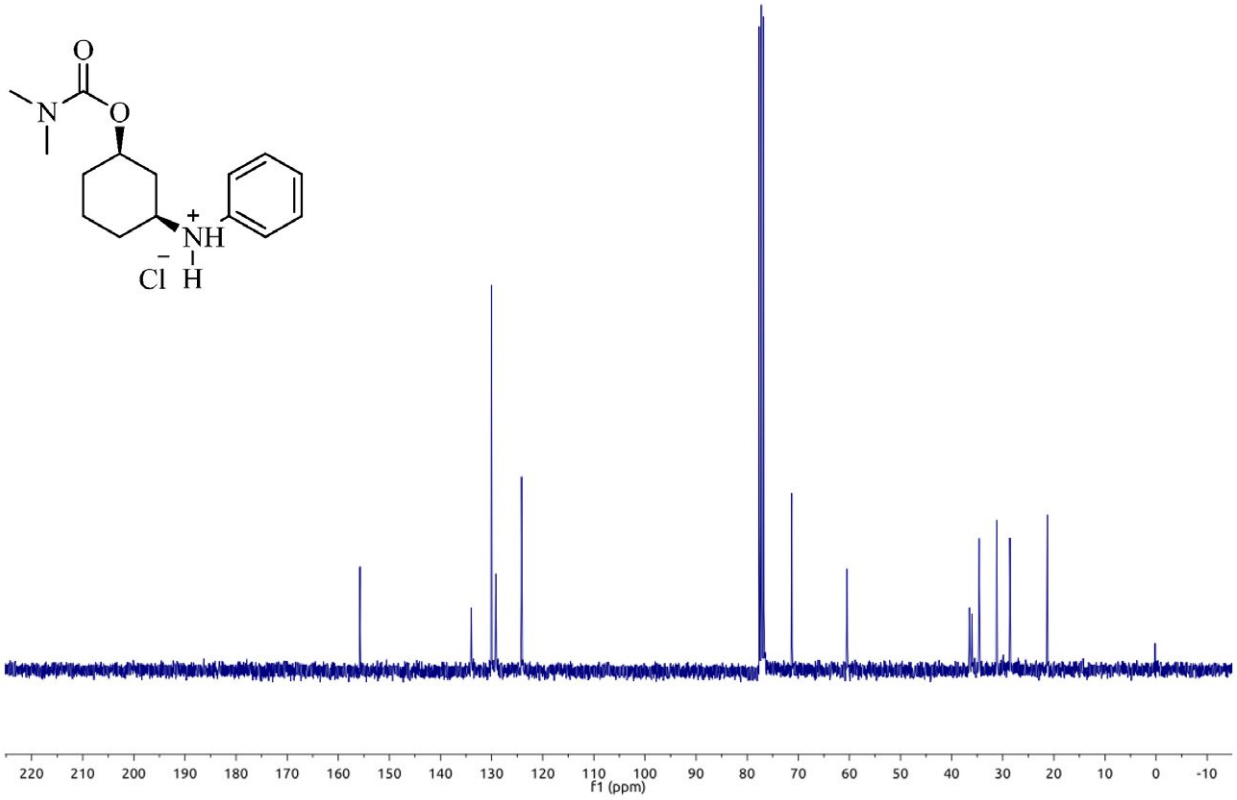


Figure S32. ^{13}C NMR spectrum (75 MHz, $CDCl_3$) of *cis*-3-(phenylamino)cyclohexyl *N*,*N*-dimethylcarbamate hydrochloride (**5a'**).

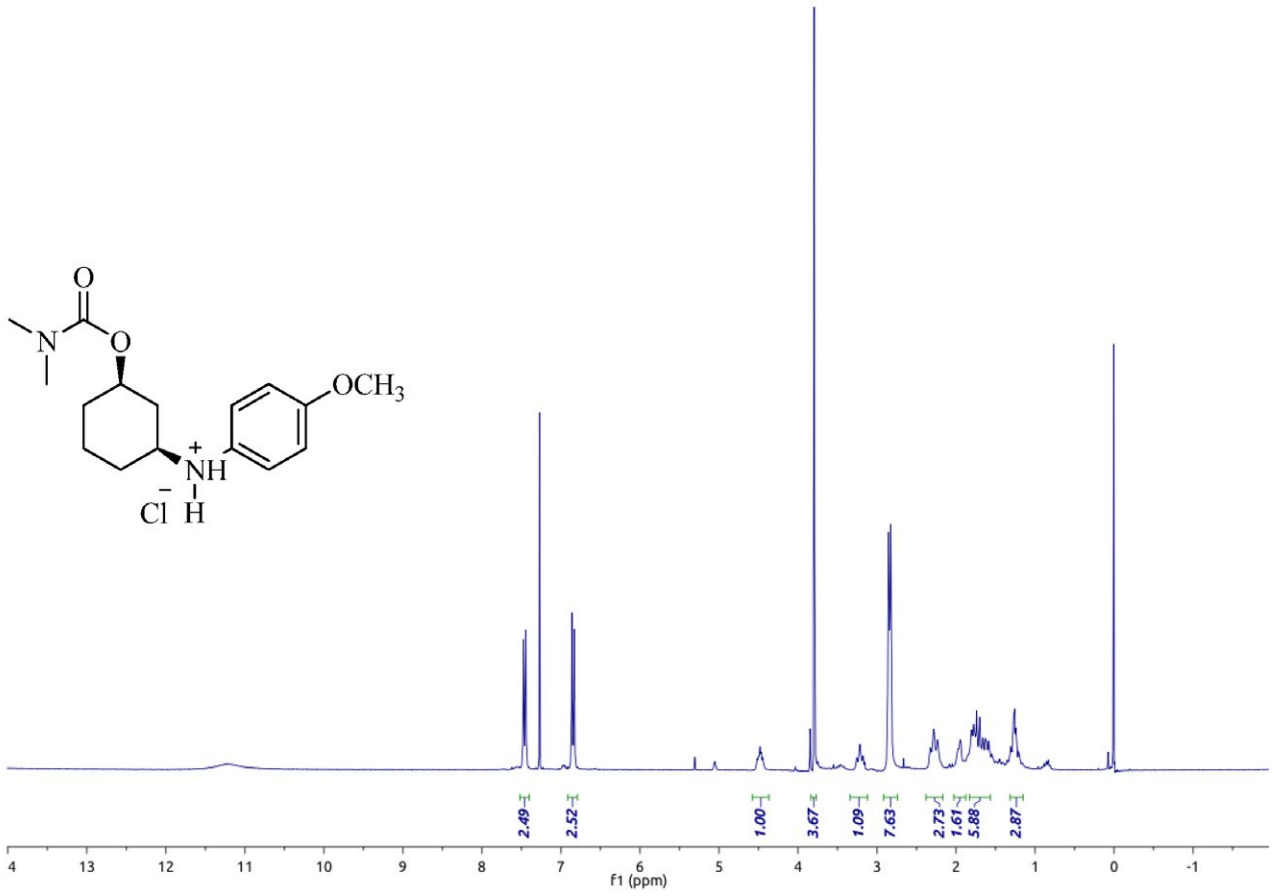


Figure S33. ^{1}H NMR spectrum (300 MHz, $CDCl_3$) of *cis*-3-(4-methoxyphenylamino)cyclohexyl *N*,*N*-dimethylcarbamate hydrochloride (**5c'**).

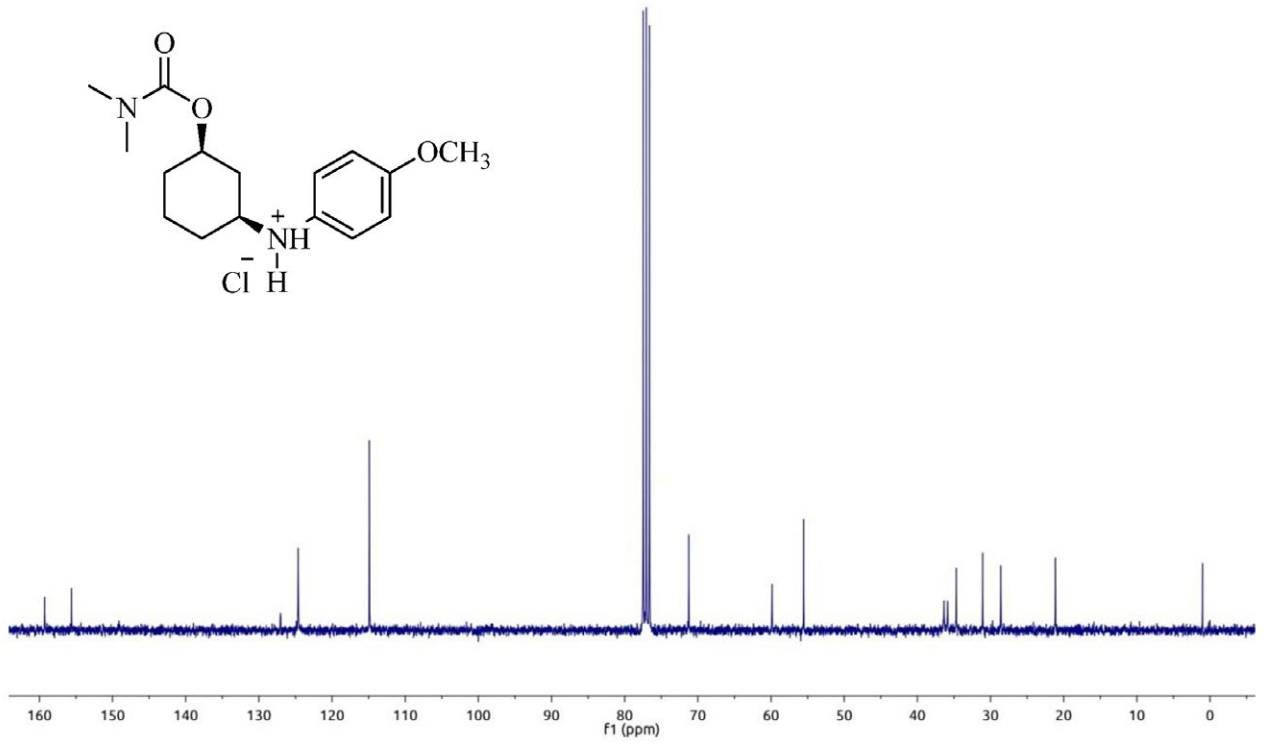


Figure S34. ^{13}C NMR spectrum (75 MHz, $CDCl_3$) of *cis*-3-(4-methoxyphenylamino)cyclohexyl *N*,*N*-dimethylcarbamate hydrochloride (**5c'**).

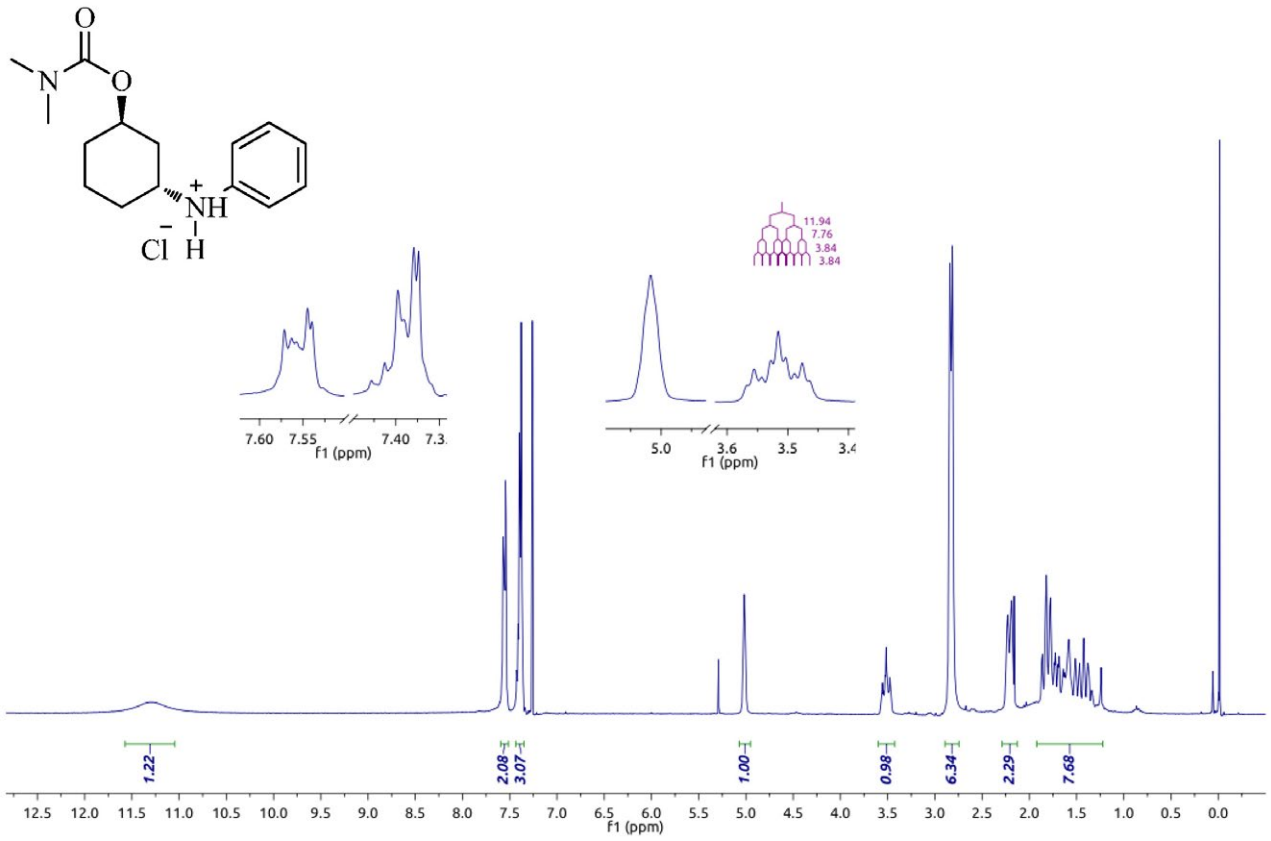


Figure S35. ^{1}H NMR spectrum (300 MHz, $CDCl_3$) of *trans*-3-(phenylamino)cyclohexyl *N*,*N*-dimethylcarbamate hydrochloride (**6a'**).

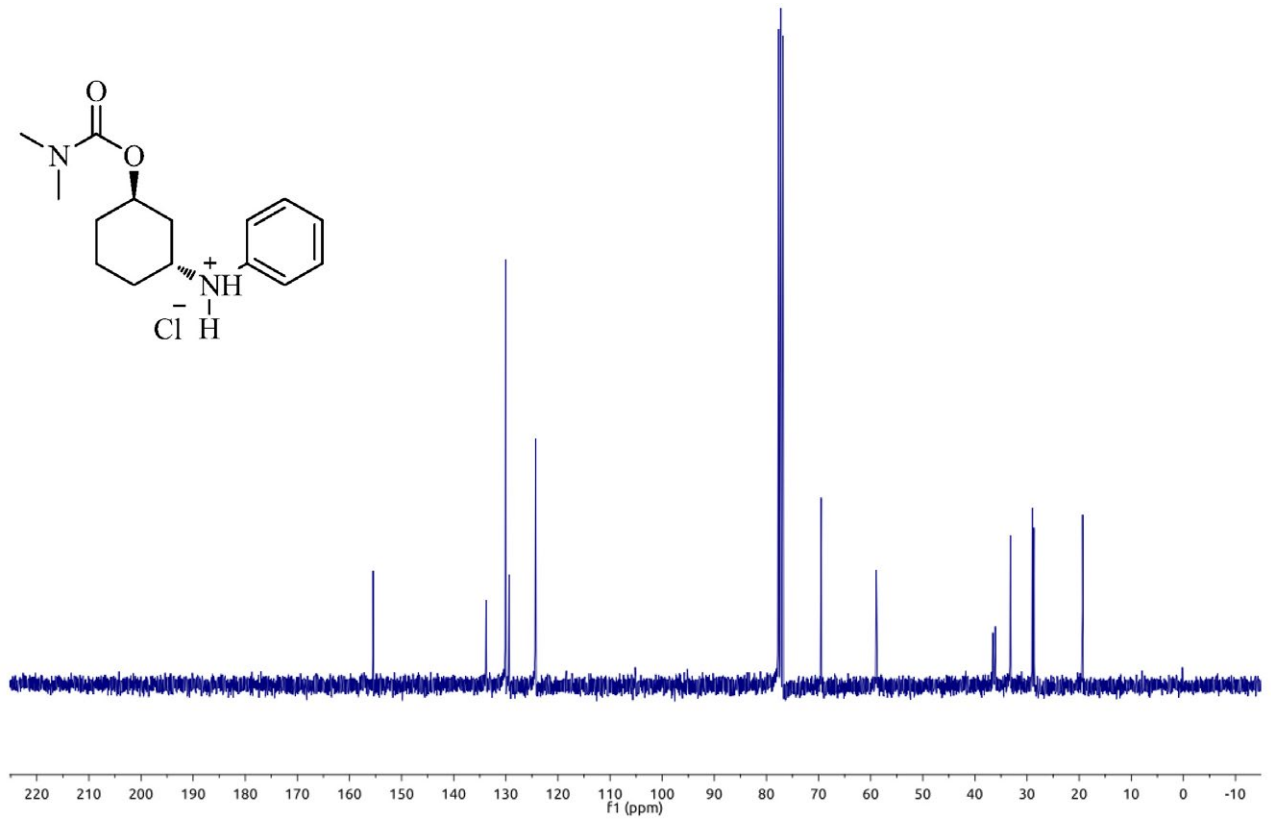


Figure S36. ^{13}C NMR spectrum (75 MHz, $CDCl_3$) of *trans*-3-(phenylamino)cyclohexyl *N*,*N*-dimethylcarbamate hydrochloride (**6a'**).

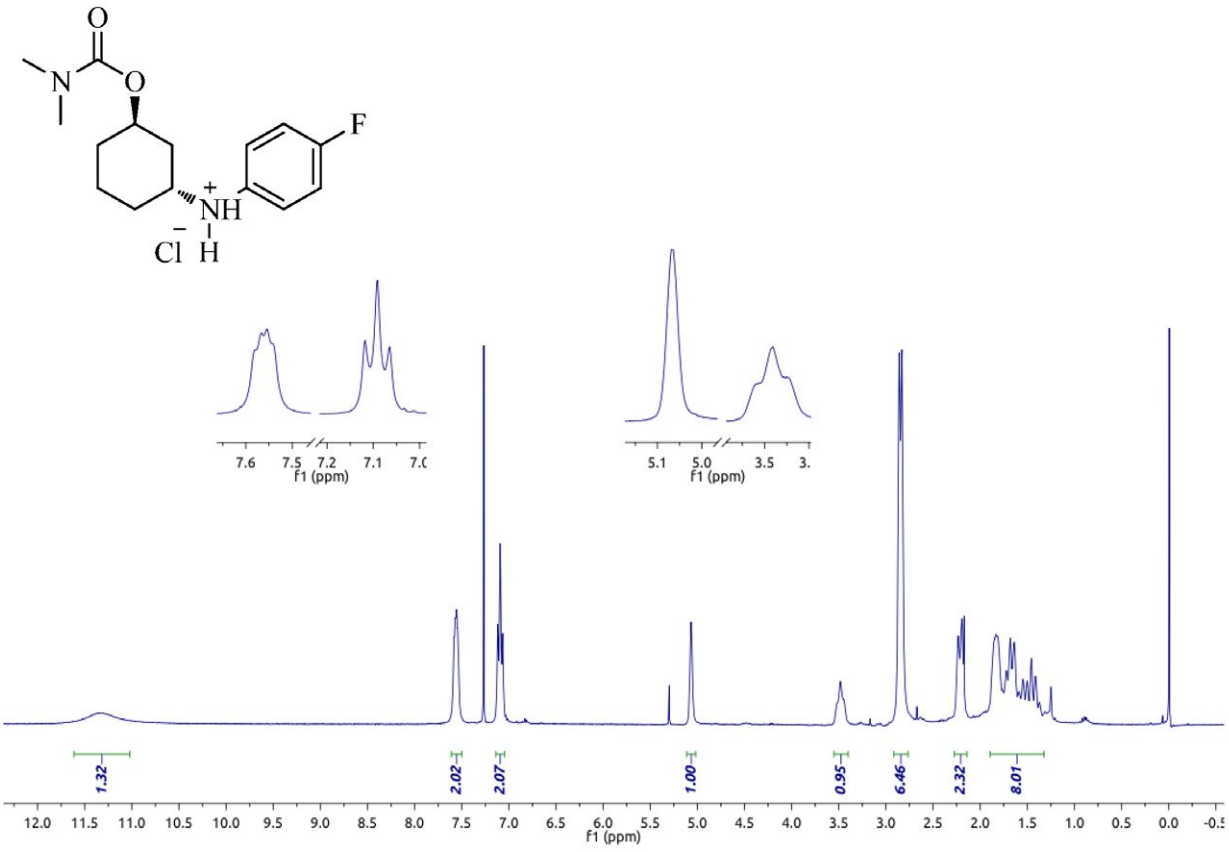


Figure S37. ^{1}H NMR spectrum (300 MHz, $CDCl_3$) of *trans*-3-(4-fluorophenylamino)cyclohexyl *N*,*N*-dimethylcarbamate hydrochloride (**6b'**).

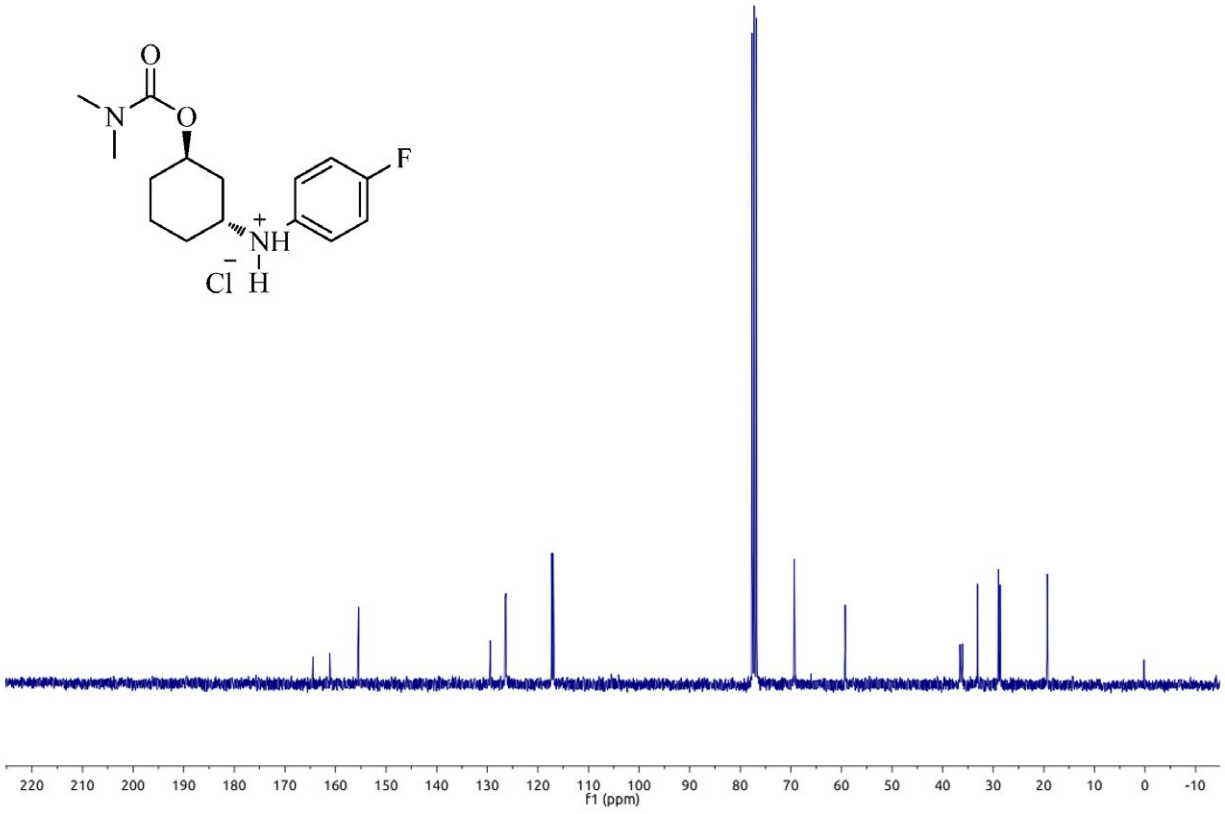


Figure S38. ^{13}C NMR spectrum (75 MHz, $CDCl_3$) of *trans*-3-(4-fluorophenylamino)cyclohexyl *N*,*N*-dimethylcarbamate hydrochloride (**6b'**).

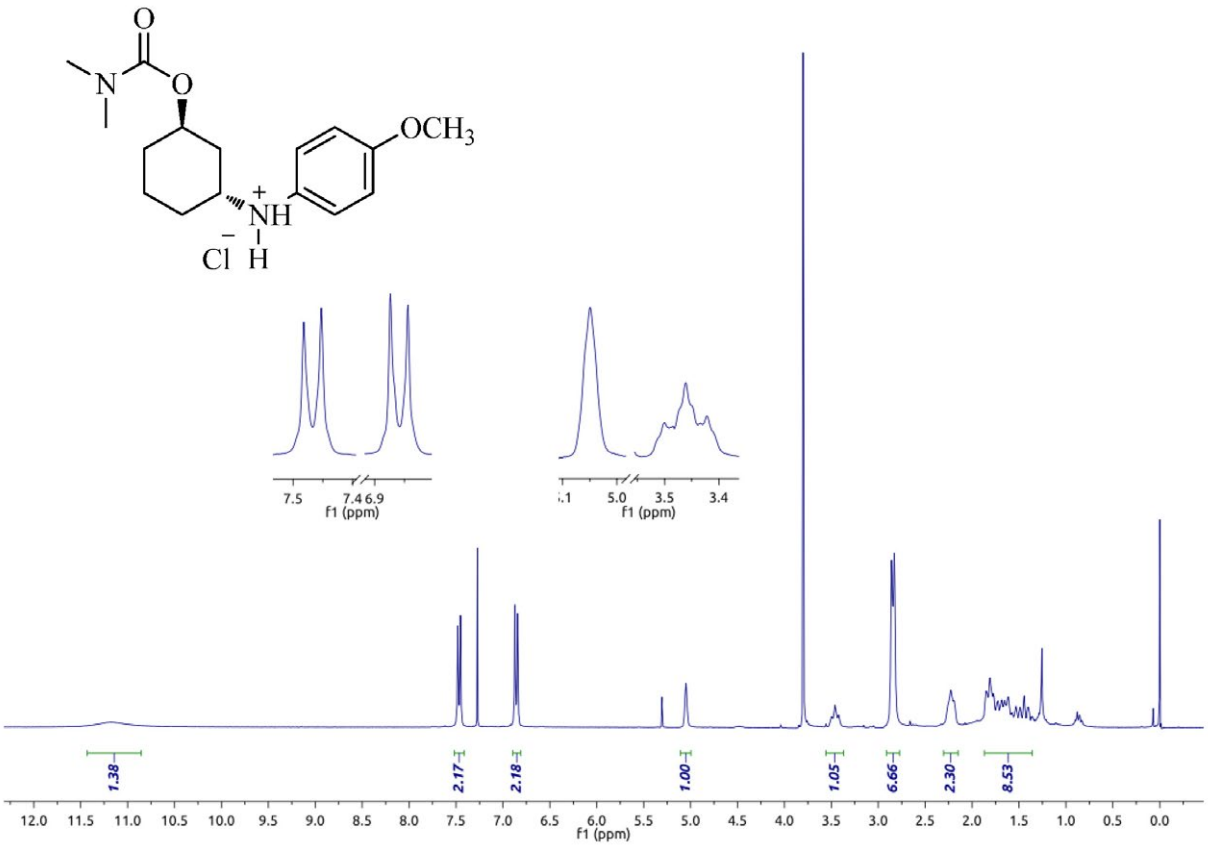


Figure S39. ^{1}H NMR spectrum (300 MHz, $CDCl_3$) of *trans*-3-(4-methoxyphenylamino)cyclohexyl *N*,*N*-dimethylcarbamate hydrochloride (**6c'**).

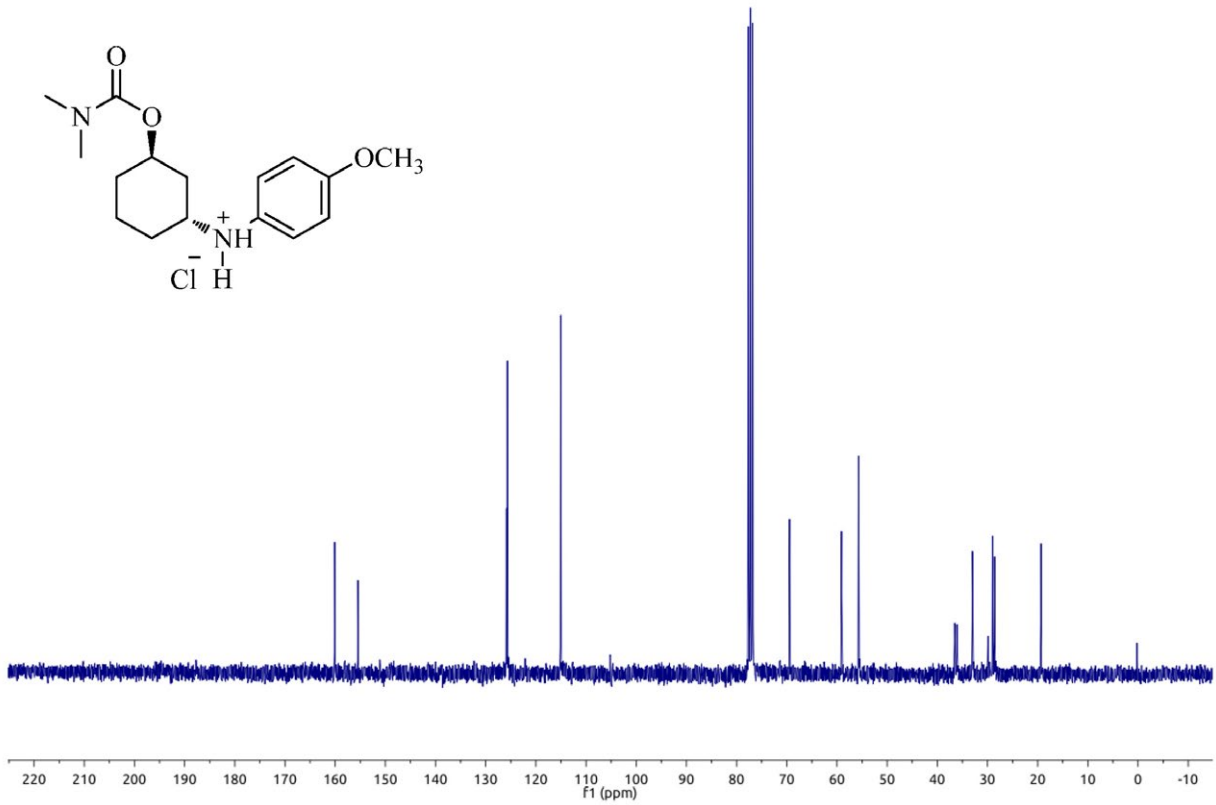


Figure S40. ^{13}C NMR spectrum (75 MHz, $CDCl_3$) of *trans*-3-(4-methoxyphenylamino)cyclohexyl *N*,*N*-dimethylcarbamate hydrochloride (**6c'**).

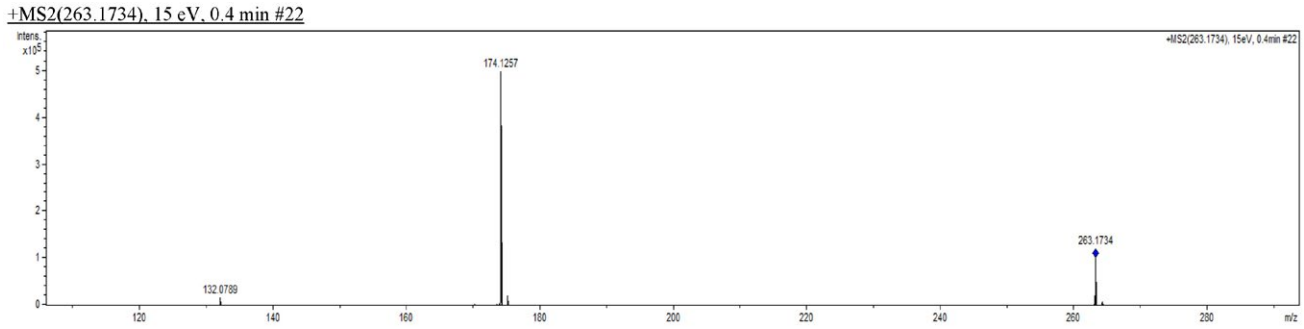


Figure S41. HRMS (ESI+) spectra of *cis*-3-(phenylaminocyclohexyl) *N*,*N*-dimethylcarbamate (**5a**).

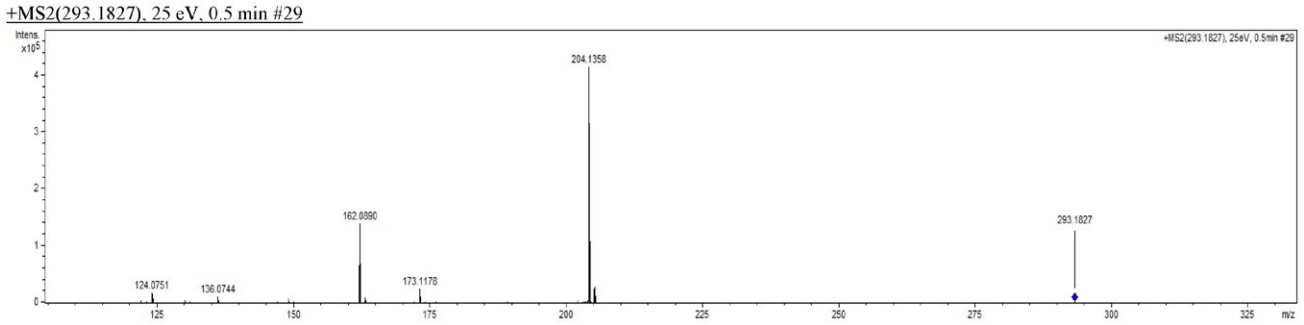


Figure S42. HRMS (ESI+) spectra of *cis*-3-(4-methoxyphenylamino)cyclohexyl *N*,*N*-dimethylcarbamate (**5c**).

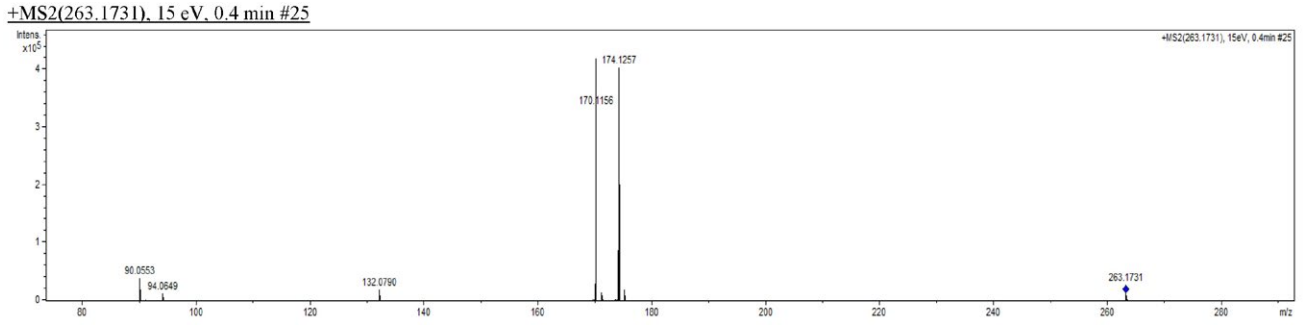


Figure S43. HRMS (ESI+) spectra of *cis*-3-(phenylaminocyclohexyl) *N*,*N*-dimethylcarbamate (**6a**).

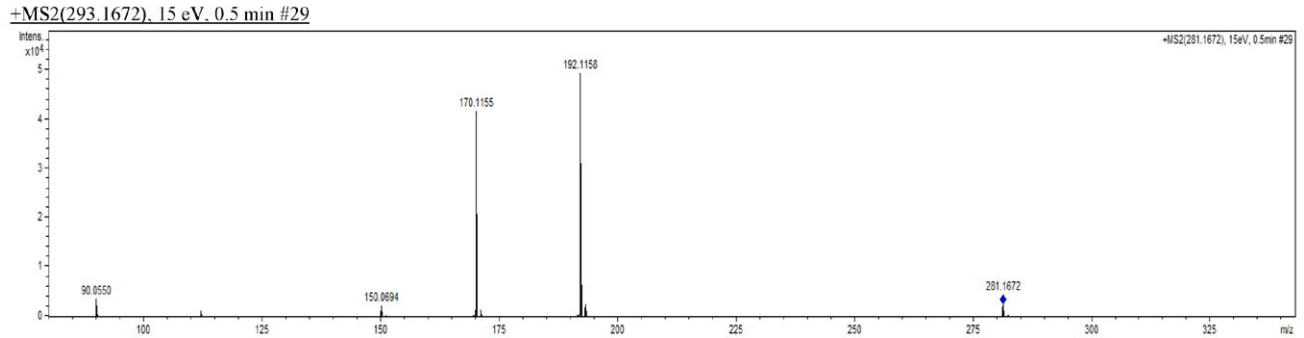


Figure S44. HRMS (ESI+) spectra of *trans*-3-(4-fluorophenylamino)cyclohexyl *N*,*N*-dimethylcarbamate (**6b**).

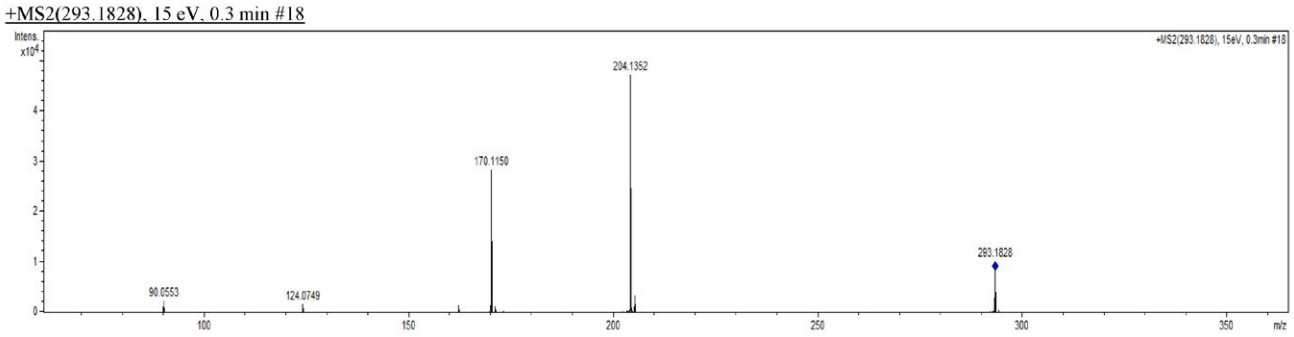


Figure S45. HRMS (ESI+) spectra of *trans*-3-(4-methoxyphenylamino)cyclohexyl *N*,*N*-dimethylcarbamate (**6c**).

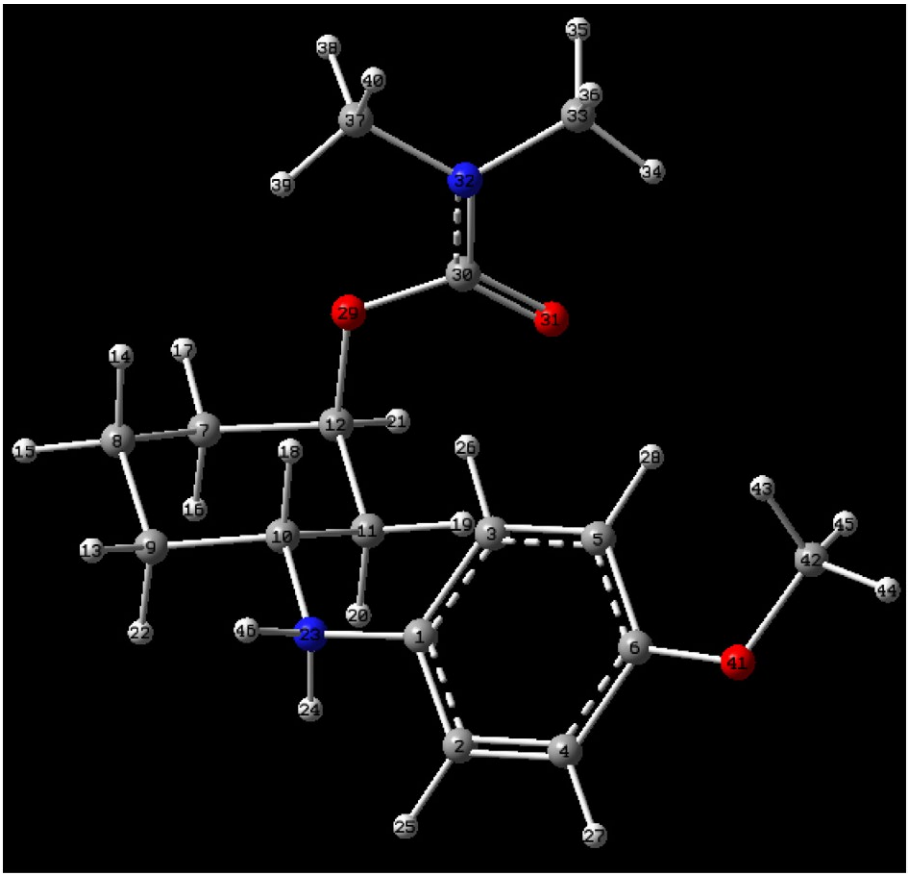


Figure S46. Representation of the chemical structure of ligand **6c'**.

Parameters of ligand 6c'

Bonds

HCMM CR 342.991 1.0930
CR NC=O 335.651 1.4360
HNRP NRP 443.528 1.0280
CR CR 306.432 1.5080
HCMM CB 381.853 1.0840
NRP CR 276.638 1.4800
NRP CB 312.837 1.4500
NC=O C=O 419.491 1.3690
CB CB 401.068 1.3740
CB OR 404.019 1.3760
CR OR 363.214 1.4180
OR C=O 417.476 1.3550
C=O O=C 931.963 1.2220

Angles

CB CB CB 48.145 119.9770
CB CB NRP 74.125 116.4230
CB CB HCMM 40.517 120.5710
CB CB OR 69.663 116.4950
CR CR CR 61.243 109.6080
CR CR HCMM 45.770 110.5490
HCMM CR HCMM 37.134 108.8360
CR CR NRP 84.848 106.4930
HCMM CR NRP 62.754 106.2240
CR CR OR 71.390 108.1330
HCMM CR OR 56.205 108.5770
CB NRP CR 82.113 109.0450
CB NRP HNRP 51.599 108.6680
CR NRP HNRP 41.452 111.2060
HNRP NRP HNRP 41.596 107.7870
CR OR C=O 66.424 108.0550
OR C=O O=C 83.120 124.4250
OR C=O NC=O 101.112 112.1870
O=C C=O NC=O 65.273 127.1520
C=O NC=O CR 59.084 119.6000
CR NC=O CR 80.386 117.9090
NC=O CR HCMM 53.255 107.6460
CB OR CR 77.363 102.8460

Dihedrals

CB CB CB CB 3.500 2 180.00
CB CB CB HCMM 3.500 2 180.00
CB NRP CR CR 0.125 3 0.00
CB NRP CR HCMM 0.125 3 0.00
CB CB NRP CR 0.000 1 0.00
CB CB NRP HNRP 0.000 1 0.00
CB CB CB OR 3.500 2 180.00
CB CB CB NRP 3.500 2 180.00
CB CB OR CR 2.191 2 180.00
CB OR CR HCMM 0.053 3 0.00
CR CR CR CR 0.051 1 0.00
CR CR CR CR 0.341 2 180.00
CR CR CR CR 0.166 3 0.00
CR CR CR HCMM 0.320 1 0.00
CR CR CR HCMM –0.315 2 180.00
CR CR CR HCMM 0.132 3 0.00
CR CR OR C=O –0.274 1 0.00
CR CR OR C=O 0.160 3 0.00
CR CR CR OR –0.344 1 0.00
CR CR CR OR 0.879 2 180.00
CR CR CR OR 0.238 3 0.00
CR CR CR NRP –0.324 1 0.00
CR CR CR NRP 0.275 2 180.00
CR CR CR NRP 0.295 3 0.00
CR CR NRP HNRP 0.093 3 0.00
CR OR C=O O=C 0.341 1 0.00
CR OR C=O O=C 3.592 2 180.00
CR OR C=O O=C –0.468 3 0.00
CR OR C=O NC=O 2.750 2 180.00
HCMM CR CR HCMM 0.142 1 0.00
HCMM CR CR HCMM –0.693 2 180.00
HCMM CR CR HCMM 0.157 3 0.00
HCMM CR CR NRP 0.346 1 0.00
HCMM CR CR NRP –0.265 2 180.00
HCMM CR CR NRP 0.139 3 0.00
HCMM CR CR OR –0.327 1 0.00
HCMM CR CR OR 0.536 2 180.00
HCMM CR CR OR 0.140 3 0.00
HCMM CR NRP HNRP 0.130 3 0.00
HCMM CR OR C=O 0.286 1 0.00
HCMM CR OR C=O –0.152 3 0.00
NRP CB CB HCMM 3.500 2 180.00
HCMM CB CB HCMM 3.500 2 180.00
HCMM CB CB OR 3.500 2 180.00
OR C=O NC=O CR 3.000 2 180.00
C=O NC=O CR HCMM –1.050 1 0.00
C=O NC=O CR HCMM 0.681 2 180.00
C=O NC=O CR HCMM 0.011 3 0.00
O=C C=O NC=O CR –0.160 1 0.00
O=C C=O NC=O CR 3.147 2 180.00
O=C C=O NC=O CR –0.073 3 0.00
CR NC=O CR HCMM 0.390 3 0.00

Improper

CB CB NRP CB 2.519 0 0.00
CB CB CB HCMM 1.079 0 0.00
NRP CR CB HNRP 0.000 0 0.00
NRP HNRP CB HNRP 0.000 0 0.00
CR CR NRP CR 0.000 0 0.00
CR CR NRP HCMM 0.000 0 0.00
CR CR CR HCMM 0.000 0 0.00
CR HCMM CR HCMM 0.000 0 0.00
CR CR CR OR 0.000 0 0.00
CR OR CR HCMM 0.000 0 0.00
C=O NC=O OR O=C 9.356 0 0.00

NC=O CR C=O CR –1.439 0 0.00
CR HCMM NC=O HCMM 0.000 0 0.00
CB CB CB OR 3.454 0 0.00
CR HCMM OR HCMM 0.000 0 0.00

Nonbonded nbxmod 5 atom cdiel shift vatom vdistance vswitch - cutnb 14.0 ctofnb 12.0 ctonnb 10.0 eps 1.0 e14fac 1.0 wmin 1.5
CB 0.000000 –0.070000 1.992400
CR 0.000000 –0.055000 2.175000 0.000000 –0.010000 1.900000
HCMM 0.000000 –0.022000 1.320000
NRP 0.000000 –0.200000 1.850000
HNRP 0.000000 –0.046000 0.224500
OR 0.000000 –0.152100 1.770000
C=O 0.000000 –0.110000 2.000000
O=C 0.000000 –0.120000 1.700000 0.000000 –0.120000 1.400000
NC=O 0.000000 –0.200000 1.850000

Topology of ligand 6c'

MASS 201 CB 12.011000
MASS 202 CR 12.011000
MASS 203 HCMM 1.007940
MASS 204 NRP 14.006700
MASS 205 HNRP 1.007940
MASS 206 OR 15.999400
MASS 207 C=O 12.011000
MASS 208 O=C 15.999400
MASS 209 NC=O 14.006700

AUTOGENERATE ANGLES DIHE
DEFA FIRS NONE LAST NONE
RESI LIG 1.000
GROUP
ATOM C6 CB 0.3640
ATOM C7 CB –0.1500
ATOM C8 CB –0.1500
ATOM C9 CB –0.1500
ATOM C10 CB –0.1500
ATOM C11 CB 0.0825
ATOM C CR 0.0000
ATOM C1 CR 0.0000
ATOM C2 CR 0.0000
ATOM C3 CR 0.5030
ATOM C4 CR 0.0000
ATOM C5 CR 0.2800
ATOM H HCMM 0.0000
ATOM H1 HCMM 0.0000
ATOM H2 HCMM 0.0000
ATOM H3 HCMM 0.0000
ATOM H4 HCMM 0.0000
ATOM H5 HCMM 0.0000
ATOM H6 HCMM 0.0000
ATOM H7 HCMM 0.0000
ATOM H8 HCMM 0.0000
ATOM H9 HCMM 0.0000
ATOM N NRP –0.7670
ATOM H10 HNRP 0.4500
ATOM H11 HCMM 0.1500
ATOM H12 HCMM 0.1500
ATOM H13 HCMM 0.1500
ATOM H14 HCMM 0.1500
ATOM O OR –0.4300
ATOM C12 C=O 0.7800
ATOM O1 O=C –0.5700
ATOM N1 NC=O –0.6602
ATOM C13 CR 0.3001
ATOM H15 HCMM 0.0000
ATOM H16 HCMM 0.0000
ATOM H17 HCMM 0.0000
ATOM C14 CR 0.3001
ATOM H18 HCMM 0.0000
ATOM H19 HCMM 0.0000
ATOM H20 HCMM 0.0000
ATOM O2 OR –0.3625
ATOM C15 CR 0.2800
ATOM H21 HCMM 0.0000
ATOM H22 HCMM 0.0000
ATOM H23 HCMM 0.0000
ATOM H24 HNRP 0.4500
BOND H20 C14
BOND H19 C14
BOND H C2
BOND C14 H18
BOND C14 N1
BOND H1 C1
BOND H24 N
BOND H5 C3
BOND H2 C1
BOND H21 C15
BOND H17 C13
BOND C2 C1
BOND C2 C3
BOND C2 H9
BOND C1 C
BOND H12 C8
BOND N C3
BOND N C6
BOND N H10
BOND N1 C13
BOND N1 C12
BOND C8 C6
BOND C8 C10
BOND H14 C10
BOND C3 C4