J. Braz. Chem. Soc., Vol. 24, No. 11, S1-S8, 2013.
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0103 - 5053 $6.00+0.00

Supplementary Information

Molecular Modeling and Anticholinesterasic Activity of Novel 2-Arylaminocyclohexyl *N*,*N*-Dimethylcarbamates

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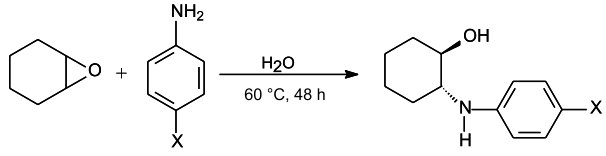
(A) Preparation of *trans*-2-arylaminocyclohexanols **1a-1c**[1]



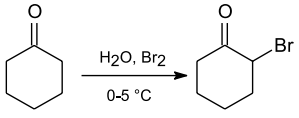
In a two-necked flask equipped with a magnetic stirrer, 51 mmol of appropriate arylamine (4.65 mL of aniline, 6.3 g of *p*-anisidine or 4.8 mL of *p*-fluoraniline) and cyclohexene oxide (49 mmol) were consecutively added in water (100 mL) and the resulting mixture was left under vigorous stirring at 60 °C for 48 h. The mixture was basified with 5 mol L^{-1} NaOH until pH 10 and extracted with ethyl acetate (3 × 30 mL). The combined organic layers were dried over anhydrous Na_2SO_4. The solvent was evaporated and the product pure was isolated.

trans-2-Phenylaminocyclohexanol **1a**: white solid; mp 58-59 °C; 50% yield.

trans-2-(4-Methoxyphenylamino)cyclohexanol **1b**: brown solid; mp 67-68 °C; 80% yield.

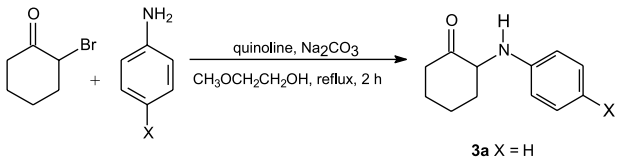
trans-2-(4-Fluoropheyilamino)cyclohexanol **1c**: white solid; mp 94-95 °C; 50% yield.

(B) Preparation of 2-bromocyclohexanone[2]



Cyclohexanone (19 mL, 180 mmol) and water (70 mL) were placed in a three-necked flask equipped with a stirrer and a dropping funnel. Bromine (9.5 mL, 180 mmol) was added dropwise to the stirred heterogeneous mixture during 1 h, and a water-ice bath (0-5 °C) was employed to cool the reaction. When addition was completed, stirring was continued until the reaction mixture was colorless (30-60 min). The mixture was extracted with ethyl ether (3 × 30 mL), the combined organic layers were dried over anhydrous Na_2SO_4. The filtrate was concentrated under reduced pressure (73 °C, 2 mmHg) to give the product (70% yield).

(C) Preparation of 2-arylaminocyclohexanones **3a-3c**[3]



0.2 mol of the appropriate arylamine (18.2 mL of aniline, 24.6 g of *p*-anisidine or 19.0 mL of *p*-fluoroaniline), 2-bromocyclohexanone (23 mL, 0.2 mmol), quinoline (2.4 mL, 0.02 mmol), 0.3 mol sodium carbonate (31.8 g, 0.3 mmol) and 150 mL of 2-methoxyethanol were

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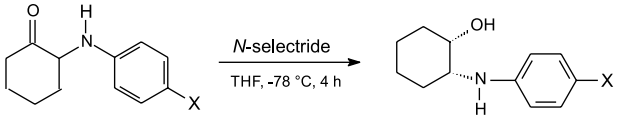
added to a dry flask and the resulting reaction mixture was heated to reflux for 2 h. The reaction mixture was cooled to room temperature. The solid was removed by filtration and washed with chloroform. The filtrate was concentrated under reduced pressure to give crude product. Pure racemic α-arylaminocycloalkanone was obtained by recrystallization from anhydrous methanol.

2-(Phenylamino)cyclohexanone **3a**: white solid; mp 81-82 °C; 30% yield.

2-(4-Methoxyphenylamino)cyclohexanone **3b**: brown solid; mp 91-93 °C; 30% yield.

2-(4-Fluorophenylamino)cyclohexanone **3c**: white solid; mp 75-76 °C; 30% yield.

(D) Preparation of *cis*-2-arylaminocyclohexanols **4a-4c**[4]



3a X = H
3b X = OCH_3
3c X = F

4a X = H
4b X = OCH_3
4c X = F

4.55 mmol of the appropriate 2-arylaminocyclohexanone (0.9 g of **3a,** 1.0 g of **3b** and 1.0 g of **3c**) were dissolved in dried THF (tetrahydrofuran, 25 mL) in a round-bottom flask under nitrogen atmosphere and magnetic stirring. After lowering the temperature to −78 °C, *N*-selectride (9.1 mL, 9.1 mmol) was added, and the reactor was kept under stirring for 4 h. The reaction mixture was allowed to attain room temperature, after which it was hydrolyzed with water (2.0 mL) and ethanol (5.0 mL). The organoborane was oxidized with 6.0 mol L^{-1} NaOH (4.0 mL) and 30% H_2O_2 (5.0 mL). The aqueous phase was than saturated with $CaCO_3$ and extracted with ethyl ether. The two organic portions were joined, dried with $MgSO_4$ and carried to a rotary evaporator where the solvent was removed.

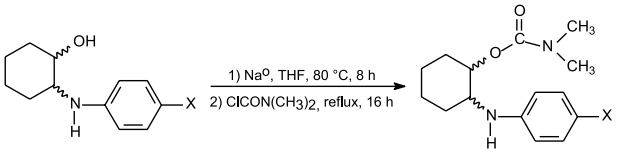
cis-2-Phenylaminocyclohexanol **4a**: white solid; mp 70-72 °C; 35% yield.

cis-2-(4-Methoxyphenylamino)cyclohexanol **4b**: brown solid; mp 51-52 °C; 45% yield.

cis-2-(4-Fluorophenylamino)cyclohexanol **4c**: white solid; mp 73-74 °C; 50% yield.

(E) Preparation of new *cis*- and *trans*-2-arylaminocyclohexyl *N,N*-dimethylcarbamates **2a, 2b, 5a** and **5b**[5]

23 mmol of the appropriate 2-arylaminocyclohexanol (4.4 g of **1a** or **1b,** 5.1 g of **4a** or **4b**) were dissolved in dried THF (30 mL) in a round-bottom flask under nitrogen atmosphere and magnetic stirring. Following metalic sodium (1.0 g, 45 mmol) addition, the resulting reaction



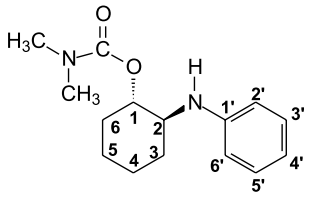
1a X = H
1b X = OCH_3
4a X = H
4b X = OCH_3

2a X = H
2b X = OCH_3
5a X = H
5b X = OCH_3

mixture was heated to 80 °C for 8 h. After this time, dimethylcarbamyl chloride (3.1 mL, 34 mmol) was added and the reaction was heated to reflux for 15 h.

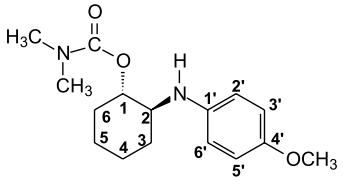
The reaction mixture was cooled to room temperature, added cold solution of sodium bicarbonate 1% (50 mL), and extracted with ethyl ether (3 × 30 mL) and cold water (2 × 20 mL). The organic layers were dried over anhydrous Na_2SO_4. The solvent was evaporated and the crude product was obtained. Compounds **2a** and **5a** were purified washing the obtained solid repeatedly with cold hexane. Pure compounds **2b** and **5b** were obtained by silica gel column chromatography (hexane/ether 8:2).

trans-2-(Phenylamino)cyclohexyl *N,N*-dimethylcarbamate **2a**



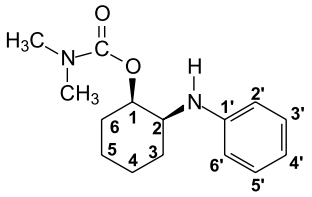
White solid; mp 72.9-73.5 °C; 50% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.16-1.30 (m, 1H, H_a6), 1.32-1.42 (m, 2H, H_a4 and H_a5), 1.40-1.52 (m, 1H, H_a3), 1.68-1.91 (m, 2H, H_e4 and H_e5), 1.94-2.06 (m, 1H, H_e3), 2.10-2.22 (m, 1H, H_e6), 2.67 (s, 1H, CH_3), 2.81 (s, 1H, CH_3), 3.32 (ddd, 1H, *J* 9.3, 9.3, 4.2 Hz, H2), 4.64 (ddd, 1H, *J* 9.3, 9.3, 4.2 Hz, H1), 6.54-6.64 (m, 2H, H2' and H6'), 6.58-6.66 (m, 1H, H4'), 7.12 (ddd, 2H, *J* 8.7, 7.2, 4.2 Hz, H3' and H5'); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.3 (C5), 24.4 (C4), 31.7 (C3), 32.2 (C6), 35.9 (CH_3), 36.5 (CH_3), 57.2 (C2), 76.8 (C1), 113.1 (C2' and C6'), 116.9 (C4'), 129.2 (C3' and C5'), 148.2 (C1'), 157.0 (C=O); ESI-HRMS calcd. for $C_{15}H_{23}N_2O_2$ ([M + H]$^+$): 263.1760; found: 263.1837.

trans-2-(4-Methoxyphenylamino)cyclohexyl *N,N*-dimethylcarbamate **2b**



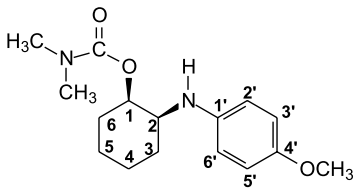
Brown oil; 50% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.17-1.28 (m, 1H, H_a6), 1.28-1.39 (m, 2H, H_a4 and H_a5), 1.38-1.50 (m, 1H, H_a3), 1.60-1.76 (m, 2H, H_e4 and H_e5), 1.94-2.04 (m, 1H, H_e3), 2.07-2.18 (m, 1H, H_e6), 2.67 (s, 1H, CH_3), 2.82 (s, 1H, CH_3), 3.28 (ddd, 1H, *J* 9.3, 9.3, 4.2 Hz, H2), 3.72 (s, 1H, OCH_3), 4.62 (ddd, 1H, *J* 9.3, 9.3, 4.2 Hz, H1), 6.57 (d, 2H, *J* 9.0 Hz, H2' and H6'), 6.73 (d, 2H, *J* 9.0 Hz, H3' and H5'); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.2 (C5), 24.4 (C4), 31.5 (C3), 32.3 (C6), 35.8 (CH_3), 36.4 (CH_3), 55.9 (OCH_3), 58.1 (C2), 76.9 (C1), 114.5 (C2' and C6'), 114.8 (C3' and C5'), 142.5 (C1'), 151.8 (C4'), 156.9 (C=O); ESI-HRMS calcd. for $C_{16}H_{25}N_2O_3$ ([M + H]$^+$): 293.1865; found: 293.1946.

cis-2-(Phenylamino)cyclohexyl *N,N*-dimethylcarbamate **5a**



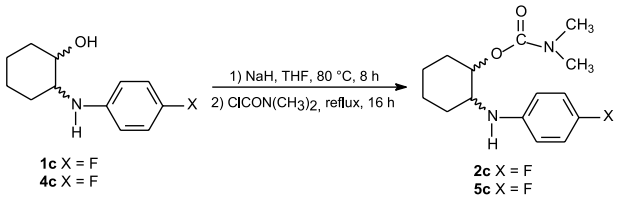
White solid; mp 68.1-70.0 °C; 39% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.34-1.44 (m, 1H, H_a4), 1.44-1.58 (m, 2H, H_a5 and H_e5), 1.50-1.62 (m, 1H, H_a6), 1.52-1.66 (m, 1H, H_a3), 1.69-1.77 (m, 1H, H_e4), 1.85-1.94 (m, 1H, H_e3), 1.94-2.06 (m, 1H, H_e6), 2.91 (s, 2H, CH_3), 3.50 (ddd, 1H, *J* 9.9, 3.3, 3.3 Hz, H2), 5.00-5.06 (m, 1H, H1), 6.55-6.64 (m, 2H, H2' and H6'), 6.62-6.70 (m, 1H, H4'), 7,14 (ddd, 2H *J* 6.9, 6.9, 1.8 Hz, H3' and H5'); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.0 (C5), 23.9 (C4), 28.3 (C3), 29.6 (C6), 36.1 (CH_3), 36.6 (CH_3), 53.6 (C2), 73.3 (C1), 113.4 (C2' and C6'), 117.4 (C4'), 129.4 (C3' and C5'), 147.3 (C1'), 156.4 (C=O); ESI-HRMS calcd. for $C_{15}H_{23}N_2O_2$ ([M + H]$^+$): 263.1760; found: 263.1842.

cis-2-(4-Methoxyphenylamino)cyclohexyl *N,N*-dimethylcarbamate **5b**



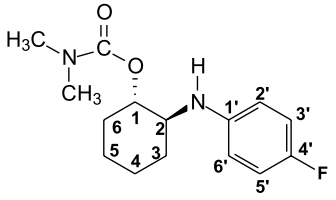
Brown oil; 23% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.28-1.42 (m, 1H, H_a4), 1.34-1.42 (m, 1H, H_a5), 1.44-1.56 (m, 2H, H_e5 and H_a6), 1.47-1.62 (m, 1H, H_a3), 1.64-1.76 (m, 1H, H_e4), 1.80-1.92 (m, 1H, H_e3), 1.92-2.06 (m, 1H, H_e6), 2.90 (s, 2H, CH_3), 3.38 (ddd, 1H, *J* 9.6, 3.3, 3.3 Hz, H2), 3.72 (s, 1H, OCH_3), 4.96-5.04 (m, 1H, H1), 6.57 (d, 2H, *J* 9.3 Hz, H3' and H5'), 6.75 (d, 2H, *J* 9.0 Hz, H2' and H6'); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.8 (C5), 23.9 (C4), 28.4 (C3), 29.5 (C6), 36.0 (CH_3), 36.4 (CH_3), 54.7 (C2), 55.8 (OCH_3), 73.0 (C1), 115.0 (C2' and C6'), 115.1 (C3' and C5'), 141.3 (C1'), 152.1 (C4'), 156.1 (C=O); ESI-HRMS calcd. for $C_{16}H_{25}N_2O_3$ ([M + H]$^+$): 293.1865; found: 293.1944.

(F) Preparation of *cis*- and *trans*-2-(4-fluorophenylamino) cyclohexyl *N,N*-dimethylcarbamate **2c** and **5c**



12 mmol of the appropriate 2-arylaminocyclohexanol were dissolved in dried THF (30 mL) in a round-bottom flask under nitrogen atmosphere and magnetic stirring. Following, sodium hydride (0.6 g, 24 mmol) was added and the resulting reaction mixture was heated to 80 °C for 8 h. After this time, dimethylcarbamyl chloride (3.1 mL, 34 mmol) was added and the reaction was heated to reflux for 15 h. The reaction mixture was cooled to room temperature, added cold solution of sodium bicarbonate 1% (50 mL) and extracted with ethyl ether (3 × 30 mL) and cold water (2 × 20 mL). The organic layers were dried over anhydrous Na_2SO_4. The solvent was evaporated and the crude product was obtained. Pure compounds **2b** and **5b** were obtained by silica gel column chromatography (hexane/ether 8:2).

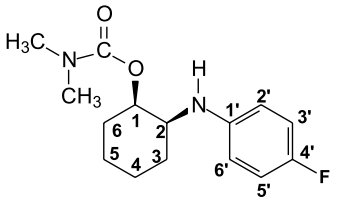
trans-2-(4-Fluorophenylamino)cyclohexyl *N,N*-dimethylcarbamate **2c**



White solid; mp 54.5-56.4 °C; 35% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.19-1.29 (m, 1H, H_a6), 1.29-1.40 (m, 2H, H_a4 and H_a5), 1.41-1.52 (m, 1H, H_a3), 1.67-1.81 (m, 2H, H_e4 and H_e5), 1.96-2.05 (m, 1H, H_e3), 2.09-2.19 (m, 1H, H_e6), 2.67 (s, 1H, CH_3), 2.82 (s, 1H, CH_3), 3.25 (ddd, 1H, *J* 9.6, 9.6, 3.9 Hz, H2), 4.63 (ddd, 1H, *J* 9.3; 9.3; 4.0 Hz, H1), 6.49-6.56 (m, 2H, H2' and H6'), 6.79-6.87 (m, 2H, H3' and H5'); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.3 (C5), 24.5 (C4), 31.7 (C3), 32.3 (C6), 35.9 (CH_3), 36.5 (CH_3), 58.0 (C2), 76.9 (C1), 114.0 (C2' and C6'), 115.5 (C3' and C5'),

144.6 (C1'), 155.6 (C4'), 156.9 (C=O); ESI-HRMS calcd. for $C_{15}H_{22}FN_2O_2$ ([M + H]$^+$): 281.1665; found: 281.1741.

cis-2-(4-Fluorophenylamino)cyclohexyl *N,N*-dimethylcarbamate **5c**



White solid; mp 66.4-67.5 °C; 45% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.30-1.40 (m, 1H, H_a4), 1.42-1.52 (m, 2H, H_e4 and H_a5), 1.46-1.55 (m, 1H, H_a6), 1.46-1.58 (m, 1H, H_a3), 1.64-1.74 (m, 1H, H_e5), 1.78-1.88 (m, 1H, H_e3), 1.90-2.02 (m, 1H, H_e6), 2.88 (s, 2H, CH_3), 3.38 (ddd, 1H, *J* 9.6;3.3;3.3 Hz, H2), 4.94-5.02 (m, 1H, H1), 6.44-6.52 (m, 2H, H2' and H6'), 6.76-6.87 (m, 2H, H3' and H5'); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.7 (C5), 23.8 (C4), 28.1 (C3), 29.4 (C6), 35.8 (CH_3), 36.3 (CH_3), 54.2 (C2), 72.7 (C1), 114.2 (C2' and C6'), 115.5 (C3' and C5'), 143.5 (C1'), 155.6 (C4'), 156.0 (C=O); ESI-HRMS calcd. for $C_{15}H_{22}FN_2O_2$ ([M + H]$^+$): 281.1665; found: 281.1847.

References

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(G) NMR spectra for new *cis*- and *trans*-2-arylaminocyclohexyl *N,N*-dimethylcarbamates

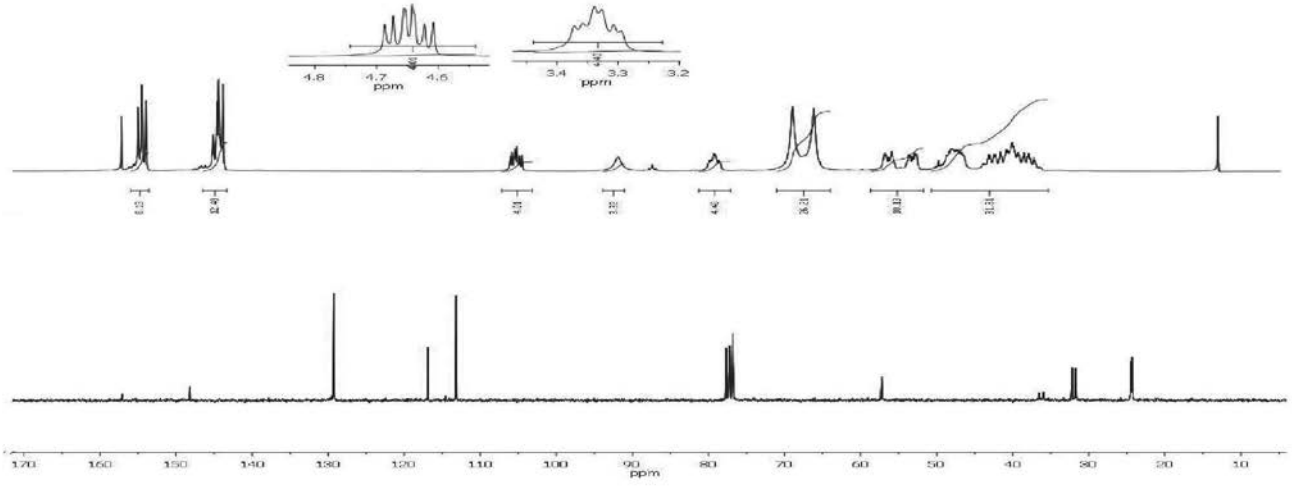

Figure S1. ^{1}H NMR ($CDCl_3$, 300 MHz) and ^{13}C NMR ($CDCl_3$, 75 MHz) spectra of *trans*-2-(phenylamino)cyclohexyl *N,N*-dimethylcarbamate **2a**.

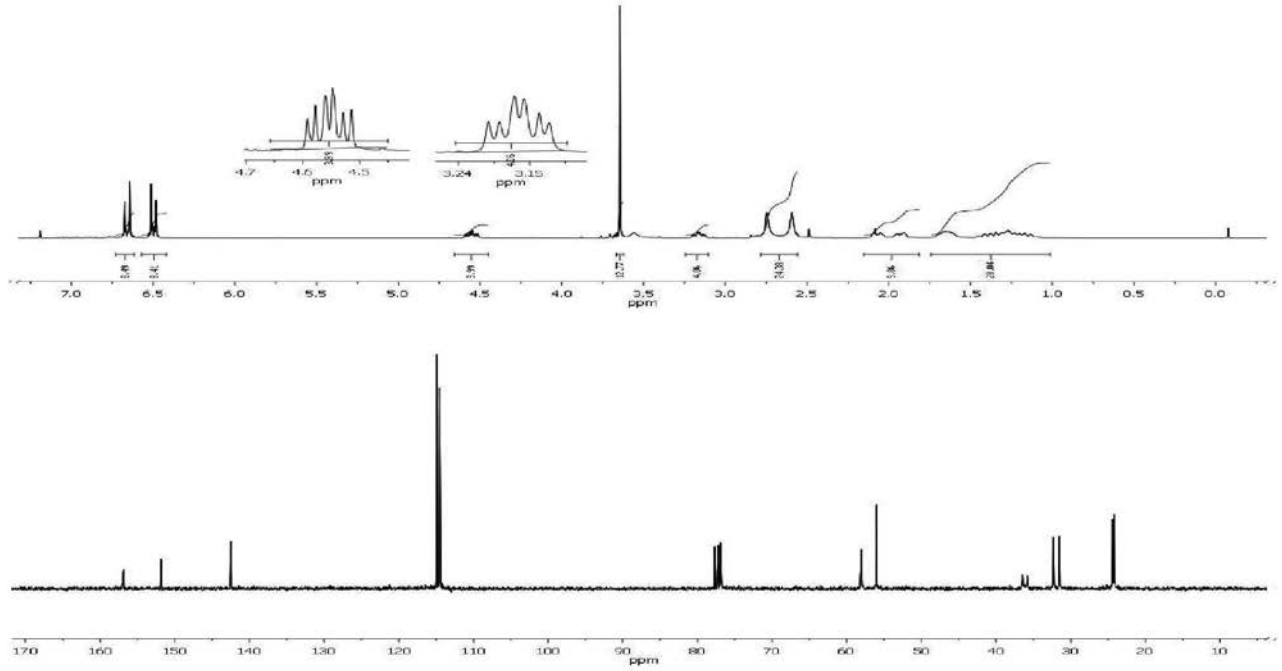

Figure S2. ^{1}H NMR ($CDCl_3$, 300 MHz) and ^{13}C NMR ($CDCl_3$, 75 MHz) spectra of *trans*-2-(4-methoxyphenylamino)cyclohexyl *N,N*-dimethylcarbamate **2b**.

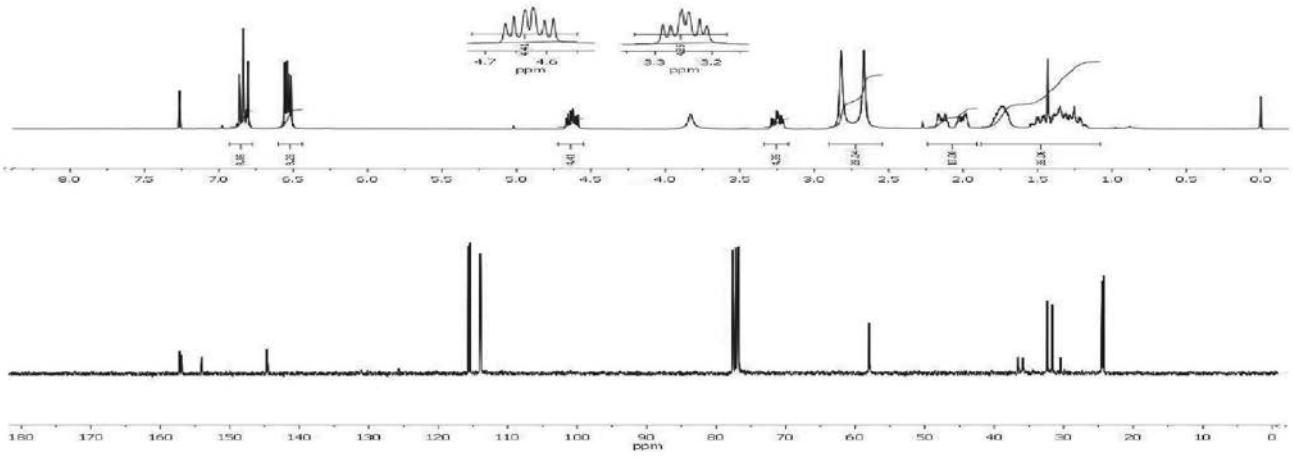

Figure S3. ^{1}H NMR ($CDCl_3$, 300 MHz) and ^{13}C NMR ($CDCl_3$, 75 MHz) spectra of *trans*-2-(4-fluorophenylamino)cyclohexyl *N,N*-dimethylcarbamate **2c**.

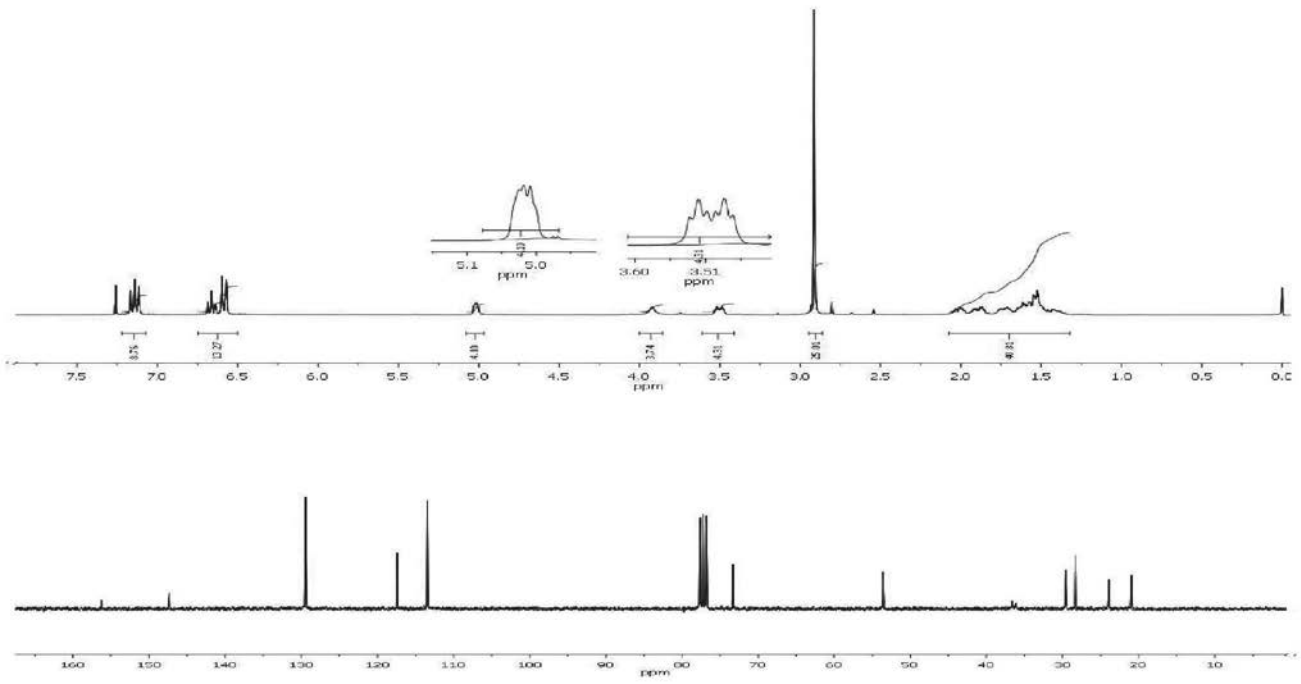

Figure S4. ^{1}H NMR ($CDCl_3$, 300 MHz) and ^{13}C NMR ($CDCl_3$, 75 MHz) spectra of *cis*-2-(phenylamino)cyclohexyl *N,N*-dimethylcarbamate **5a**.

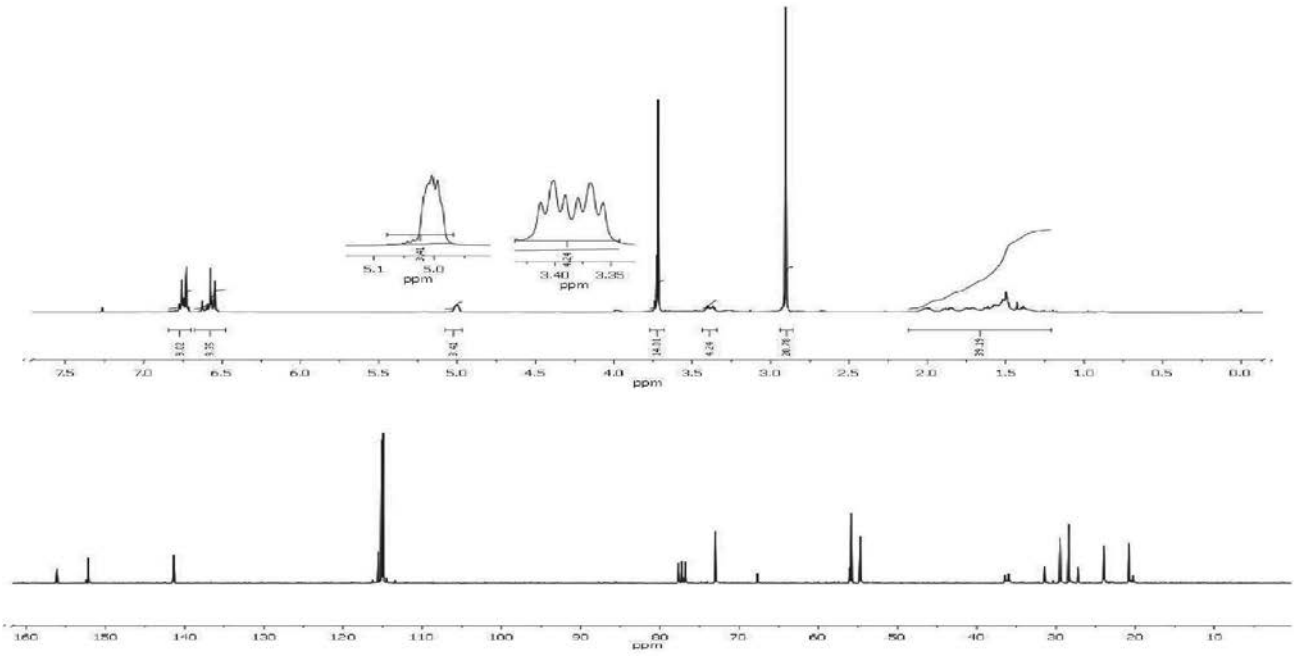

Figure S5. ^{1}H NMR ($CDCl_3$, 300 MHz) and ^{13}C NMR ($CDCl_3$, 75 MHz) spectra of *cis*-2-(4-methoxyphenylamino)cyclohexyl *N,N*-dimethylcarbamate **5b**.

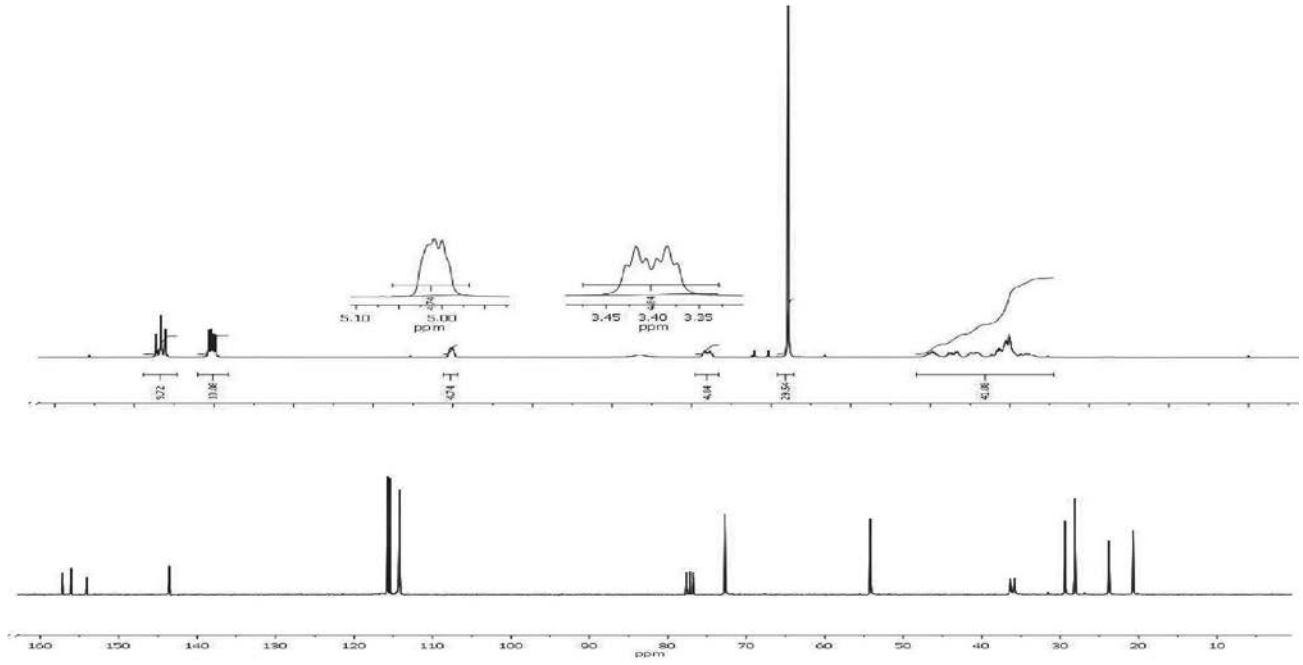

Figure S6. ^{1}H NMR ($CDCl_3$, 300 MHz) and ^{13}C NMR ($CDCl_3$, 75 MHz) spectra of *cis*-2-(4-fluorophenylamino)cyclohexyl *N,N*-dimethylcarbamate **5c**.

(H) ESI-HRMS spectra for new *cis*- and *trans*-2-arylaminocyclohexyl *N,N*-dimethylcarbamates

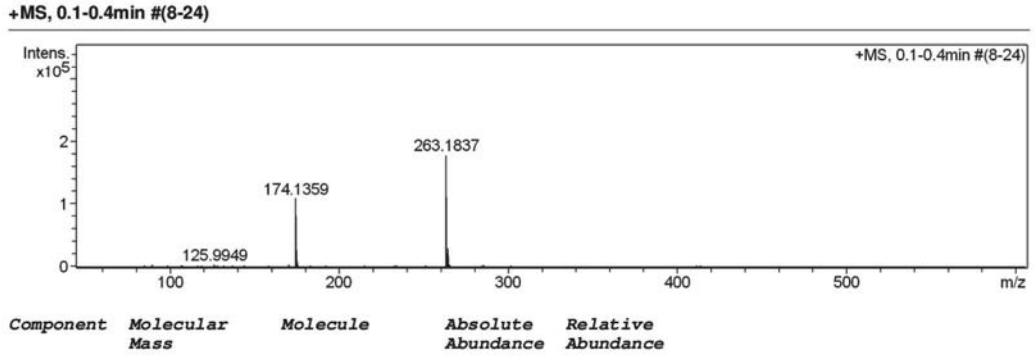

Figure S7. ESI-HRMS spectra of *trans*-2-(phenylamino)cyclohexyl *N,N*-dimethylcarbamate **2a**.

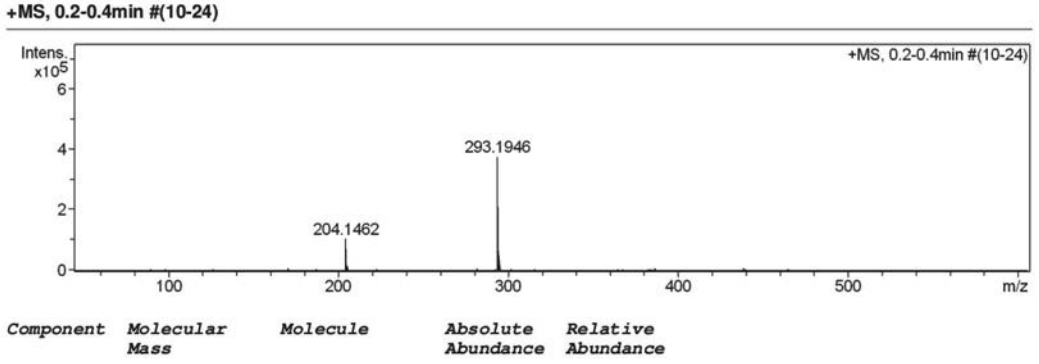

Figure S8. ESI-HRMS spectra of *trans*-2-(4-methoxyphenylamino)cyclohexyl *N,N*-dimethylcarbamate **2b**.

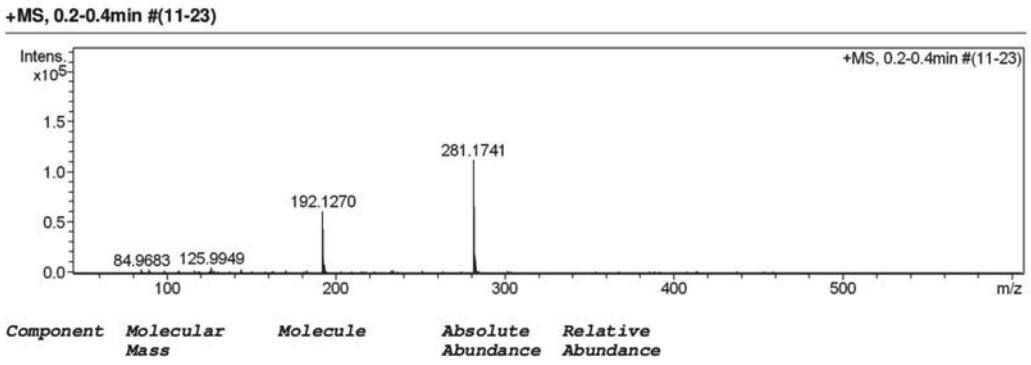

Figure S9. ESI-HRMS spectra of *trans*-2-(4-fluorophenylamino)cyclohexyl *N,N*-dimethylcarbamate **2c**.

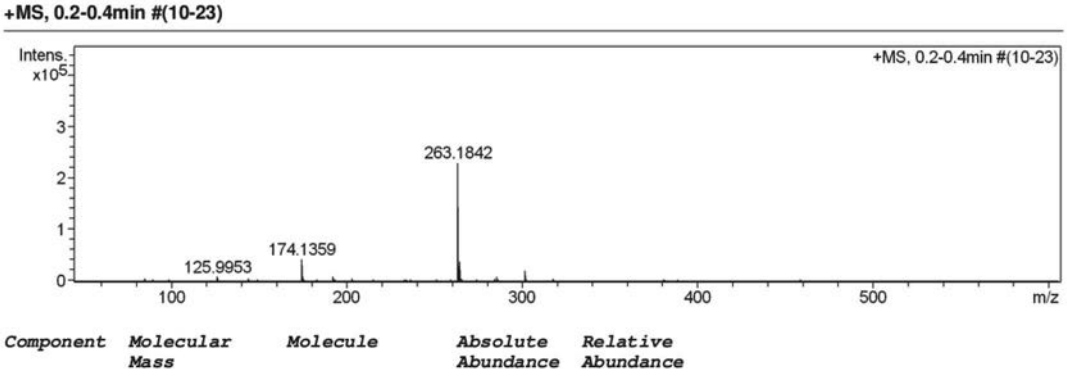

Figure S10. ESI-HRMS spectra of *cis*-2-(phenylamino)cyclohexyl *N,N*-dimethylcarbamate **5a**.

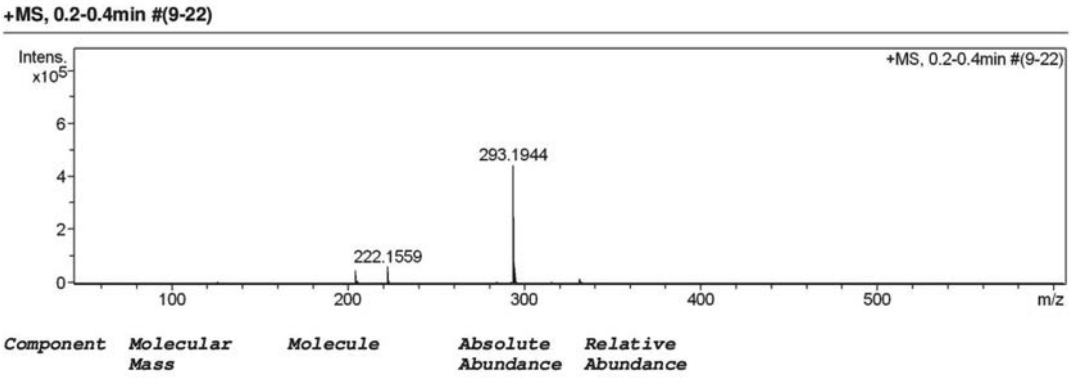

Figure S11. ESI-HRMS spectra of *cis*-2-(4-methoxyphenylamino)cyclohexyl *N,N*-dimethylcarbamate **5b**.

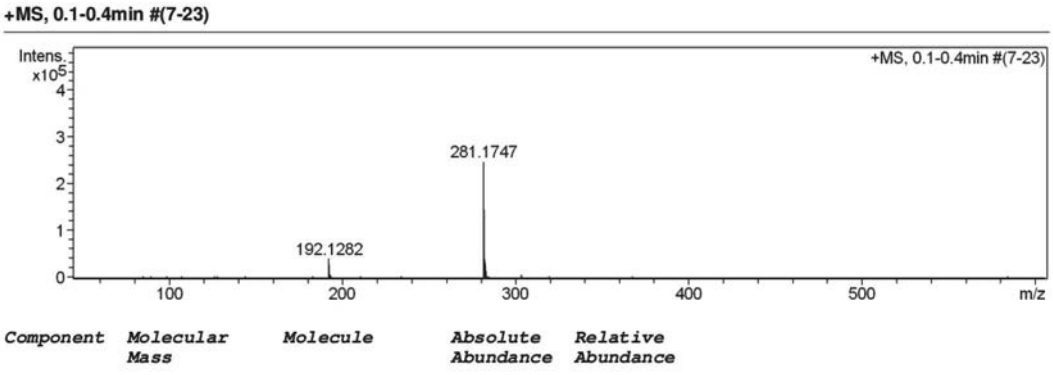

Figure S12. ESI-HRMS spectra of *cis*-2-(4-fluorophenylamino)cyclohexyl *N,N*-dimethylcarbamate **5c**.