SUPPORTING INFORMATION

N,N,N-Tris(*tert*-butoxycarbonyl)-*L*-arginine: five isoforms whose obtainment depends on procedure and a scrupulous NMR confirmation of their structures

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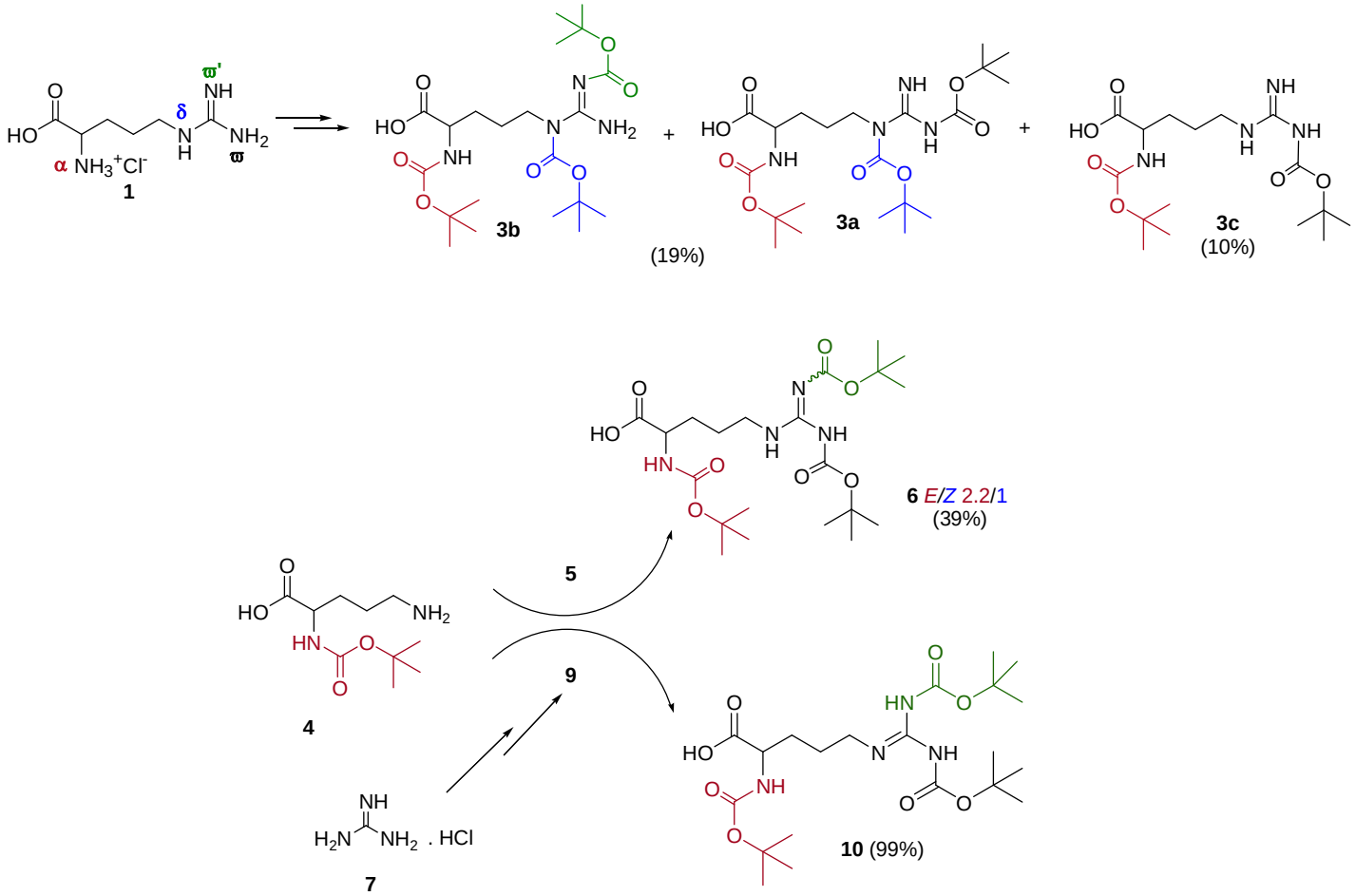


Figure S1. Graphical abstract

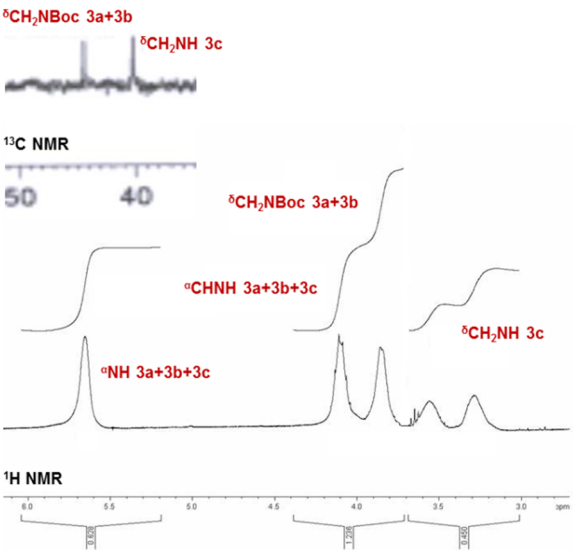


Figure S2. Significant portions of the ^{1}H NMR spectrum and of the ^{13}C NMR spectrum of the mixture **3a** + **3b** + **3c**

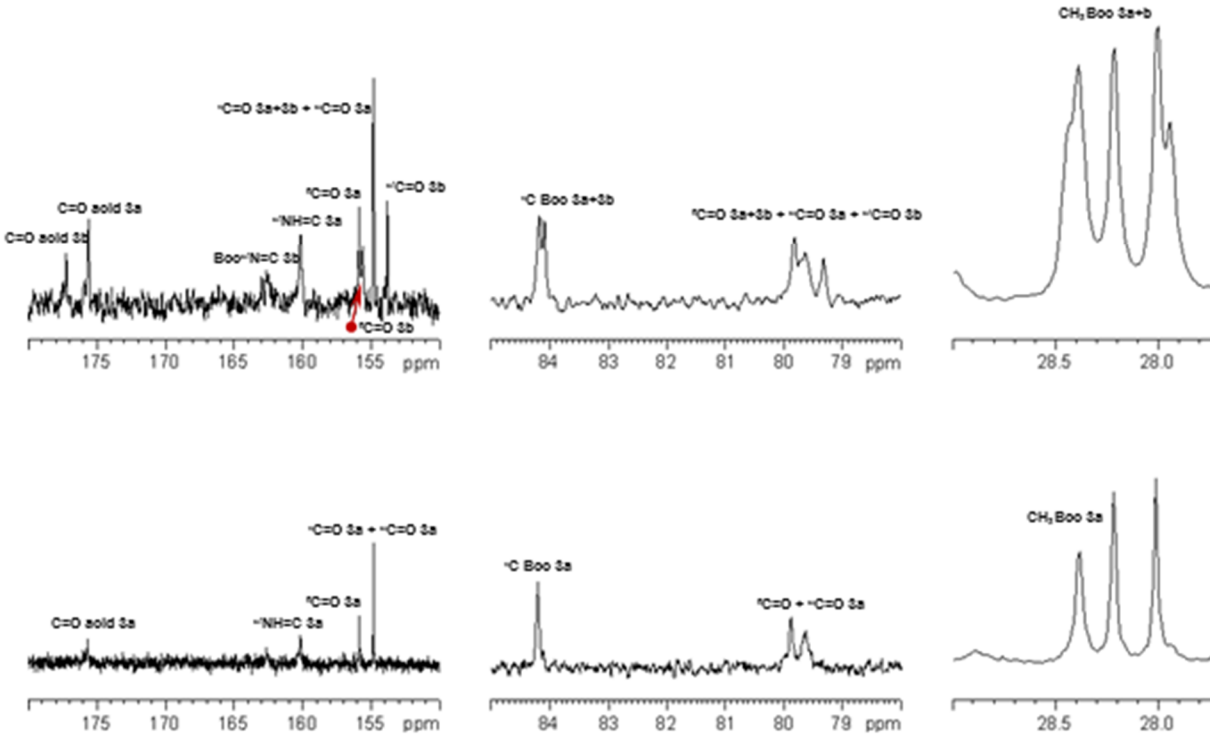


Figure S3. Significant portions of the ^{13}C NMR spectra of the mixture **3a** + **3b** and of isolated **3a**

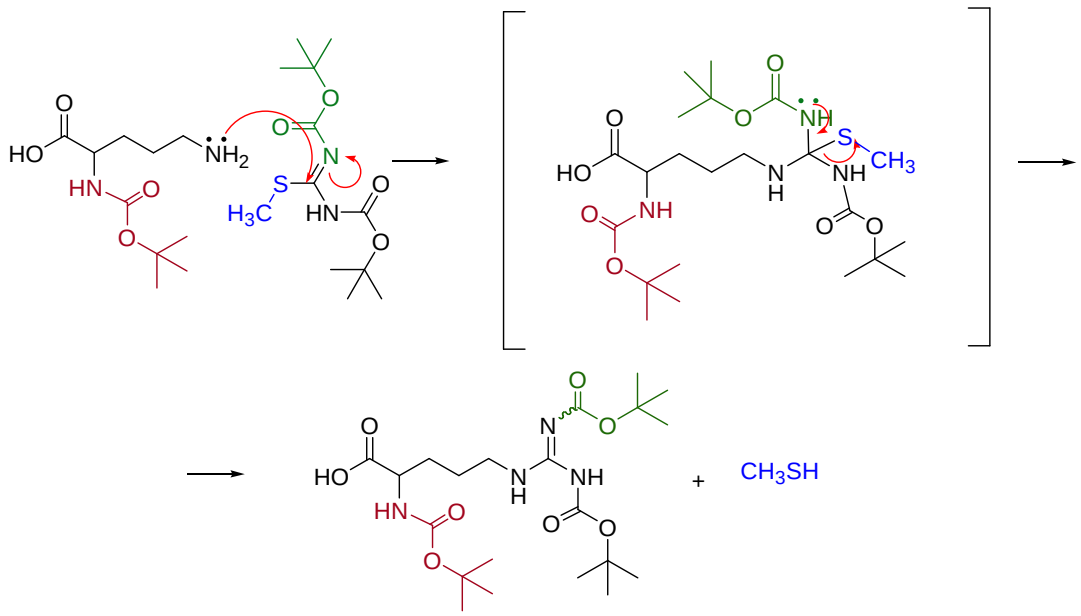


Figure S4. Plausible mechanism for the formation of **6** as mixture ***E, Z***

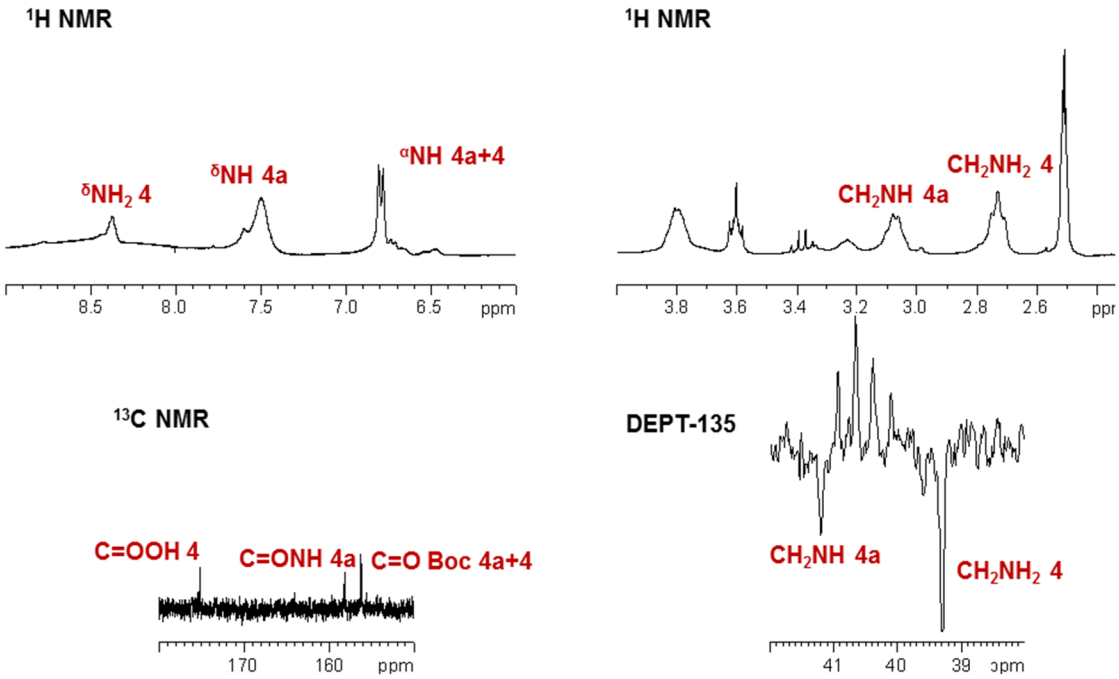


Figure S5. Significant portions of the ^{1}H NMR spectrum and of the ^{13}C NMR spectra of the mixture 1/1 **4** + **4a**

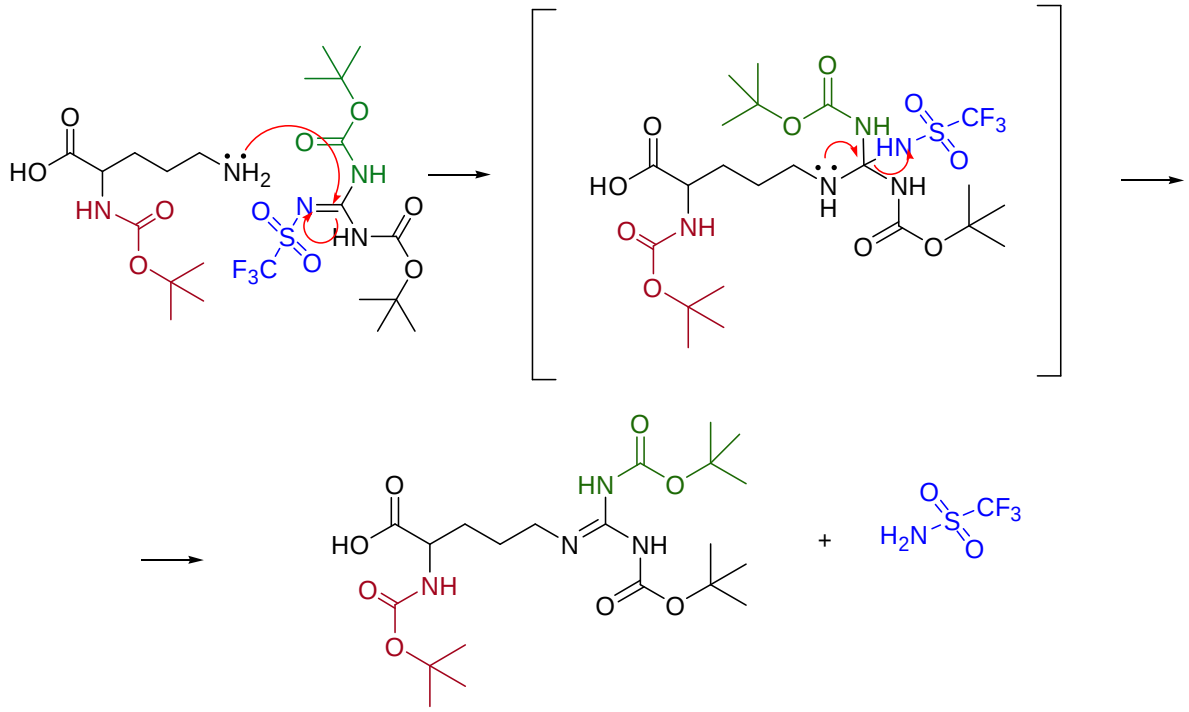


Figure S6. Plausible mechanism for the formation of **10**

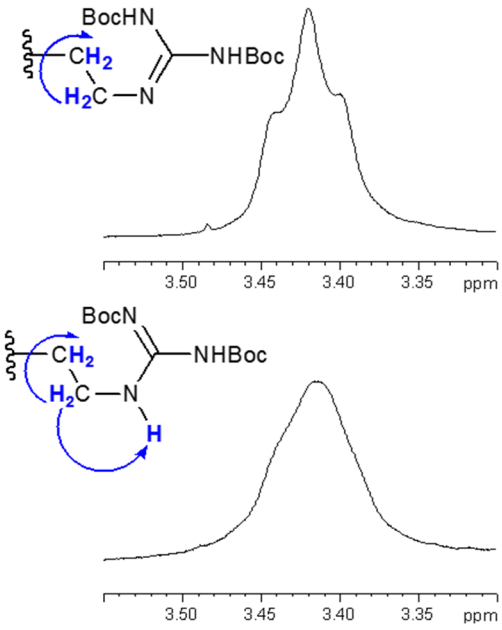


Figure S7. Shape of CH_2-N=C signal of **10** (above) and of CH_2-NH- signal of **6** ***E, Z*** (under) in the ^{1}H NMR spectra

Experimental procedure S8.

Synthesis of $^{\alpha}$N-tert-butoxycarbonyl-L-arginine (2) [16a, c]

In a one-neck flask, equipped with magnetic stirrer, we introduced *L*-arginine HCl (1.00; 4.8 mmol), dioxane (3.3 mL) and 1 N NaOH (5.0 mmol). After cooling at 0°C, Di-*tert*-butyl-carbonate (Boc_2O) was added (1.1 equiv.) and the reaction mixture was left under stirring for one night at r.t. The progress of the reaction was followed by TLC eluted in ethyl acetate (AcOEt)/MeOH 9/1. Then the reaction mixture was poured into a separating funnel and extracted with *n*-hexane. The organic phase was treated with saturated $NaHCO_3$ and the aqueous phases combined, acidified with 10% $KHSO_4$ to pH = 2, while cooled at 0°C, extracted with *tert*-butanol and dried on Na_2SO_4 overnight. After evaporation of the solvent at reduced pressure was obtained **2** that was investigated by IR and NMR analysis for checking the degree of purity and was used in the next step without further purifications.

$^{\alpha}$N-tert-butoxycarbonyl-L-arginine (**2**) [16a, b, c] 1.21 g, white solid, 92% yield; m.p. 150°C dec., lit. 159-160 °C dec. [16a], 145-150°C dec. [16c]; FTIR (KBr) 3500-2400 (OH), 3374 (NH), 3203 (NH), 1729 (C=O acid), 1671 (C=O ~~urethane~~carbamate) cm^{-1}; ^{1}H NMR (300 MHz; DMSO-d_6) δ 1.38 (s, 9H, CH_3 Boc), 1.49-1.69 (m, 4H, $^{\beta}CH_2{}^{\gamma}CH_2$), 3.09 (m, 2H, $^{\delta}CH_2$), 3.84 (m, 1H, $^{\alpha}$CH), 7.04 (d, J = 7.9 Hz, 1H $^{\alpha}$NH), 7.30 (brs, 3H, $^{\omega}NH_2$ + $^{\omega}$'NH), 7.92 (t, 1H, $^{\delta}$NH); ^{13}C NMR (75.5 MHz; DMSO-d_6) δ 25.45, 28.39, 31.30, 41.30, 53.42, 78.18, 155.71, 157.04, 174.29; Anal Calc. for $C_{11}H_{22}N_4O_4$ (274.32): C, 48.16% ; H, 8.08%;N, 20.42%; found: C, 47.75 %; H, 7.78%; N, 20.21%.

Experimental procedure S9.

Synthesis of $^{\alpha}$N-tert-butoxycarbonyl-L-ornithine (4) [22]

In a 50 mL two-neck flask $^{\alpha}$*N-tert*-butoxycarbonyl-$^{\delta}$*N*-Cbz-*L*-ornithine (2.05 g, 5.6 mmol), Pd/C 10% (1.19 g) and MeOH (38 mL) were introduced and the reaction mixture was maintained under stirring and at r.t. and under H_2 pressure (1.5 bar) for 5 h. After checking the completeness of the reaction by TLC (MeOH 100%), the catalyst is eliminated by filtration on a celite plug which was washed with H_2O two times. The filtrate was evaporated at reduced pressure and at temperature not exceeding 50-60°C to obtain an off-white solid which was treated with tetrahydrofuran (THF) and filtered. After washing with THF the solid was brought to constant weight under reduced pressure and then left overnight in a desiccator over P_2O_5 obtaining the desired product.

$^{\alpha}$*N-tert-butoxycarbonyl-L-ornithine* (**4**) [22b] 1.06 g, white solid, 81.6% yield; m.p. dec.; FTIR (KBr) 3500-2400 (OH), 3380 (NH_2), 1690 (C=O acid + C=O ~~urethane~~carbamate), 1585 (NH) cm^{-1}; ^{1}H NMR (300 MHz; DMSO-d_6/D_2O) δ 1.41 (s, 9H, CH_3 Boc), 1.50-1.80 (m, 4H, $^{\beta}CH_2{}^{\gamma}CH_2$), 2.89 (t, J = 6.5 Hz, 2H $^{\delta}CH_2$) 3.80 (m, 1H, $^{\alpha}$CH); ^{13}C NMR (75.5 MHz; DMSO-d_6/D_2O) δ 25.42, 30.25, 31.58, 40.90, 57.01, 81.83, 158.35, 178.92; Anal Calc. for $C_{10}H_{20}N_2O_4$ (232.28): C, 51.71%; H, 8.68%; N, 12.06%; found: C, 51.47%; H, 8.94%; N, 12.28%.

Experimental procedure S10.

Synthesis of 1,3-Bis(tert-butoxycarbonyl)guanidine (8) [26]

In a 20 mL one-neck flask guanidine hydrochloride **7** (1.19 g, 12.5 mmol), H_2O (12.5 mL) and dioxane (2.5 mL) were inserted. The reaction mixture was added under stirring at 0 °C with di-*tert*-butyl carbonate (5.98 g, 27.4 mmol) and maintained at r.t. for 24 h, then was evaporated up to a third of the volume obtaining a white suspension which after dilution with H_2O (25 mL) was extracted with AcOEt (3 x 25 mL). The extracts were washed with 10% citric acid (15 mL), H_2O (15 mL), saturated NaCl (15 mL) and dried over anhydrous Na_2SO_4 overnight. The elimination of the solvent at reduced pressure gave a solid which was treated with petroleum ether and filtered, obtaining **8**.

1,3-Bis(tert-butoxycarbonyl)guanidine (**8**) [26] 1.94 g, white solid, 60% yield; m.p. 145-147°C (petroleum ether), lit. 144°C [26]; FTIR (KBr) 3370 (NH), 3310 (NH), 1588 (C=NH), 1730 (C=O), 1638 (NH) cm^{-1}; ^{1}H NMR (300 MHz; DMSO-d_6) δ 1.41 (s, 18H, CH_3 Boc), 8.00-11.00 (two brs, 3H, NH); ^{13}C NMR (75.5 MHz; DMSO-d_6) δ 28.80, 80.51, 159.21, 159.48; Anal Calc. for $C_{11}H_{21}N_3O_4$ (259.30): C, 50.95%; H, 8.16%; N, 16.21%; found: C, 50.74 %; H, 8.48%; N, 16.42%.

Experimental procedure S11.

Synthesis of 1,3-Bis(tert-butoxycarbonyl)-2-(trifluoromethylsulfonyl)guanidine (9) [26]

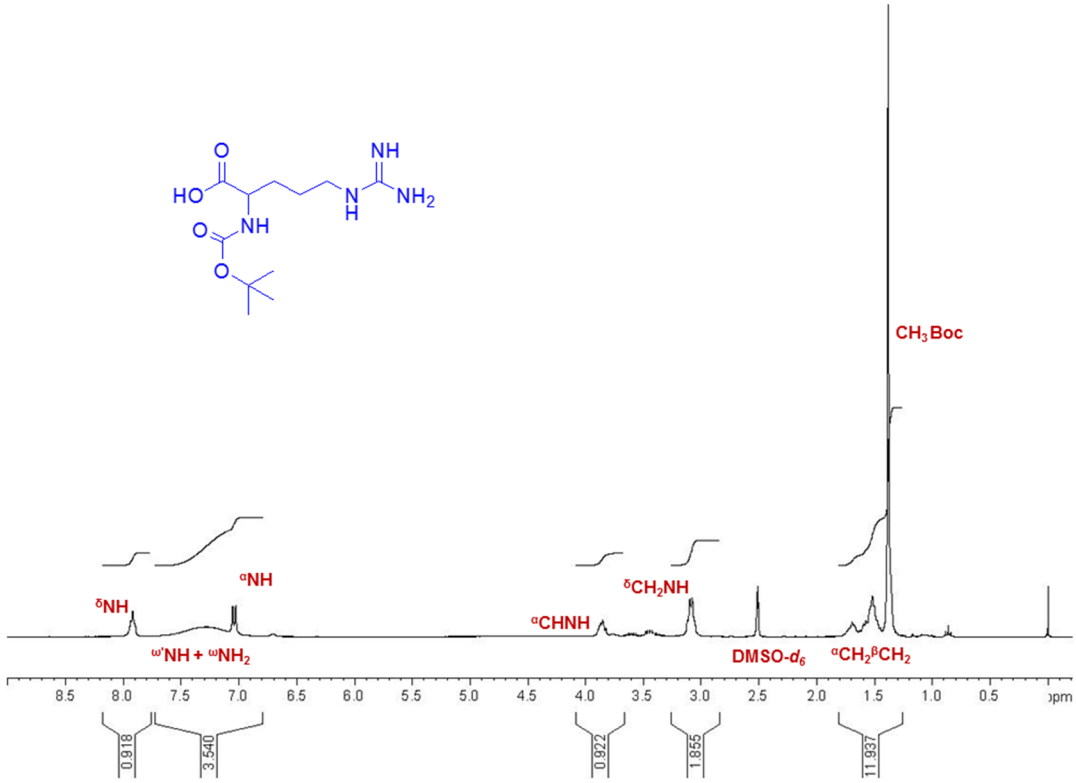
In a 50 ml two-neck flask equipped with a dropping funnel, magnetic stirrer and a nitrogen valve **8** (1.86 g, 7.2 mmol), CH_2Cl_2 (36 mL) and Et_3N (1.0 mL) were inserted. After cooling at -78°C, the mixture was added dropwise with triflic anhydride (1.3 mL), the solution was allowed to reach r.t. and was stirred under nitrogen stream for 24 h. The dark solution was then washed with 2 N $KHSO_4$ and H_2O and the organic phase was dried over anhydrous Na_2SO_4. The elimination of the solvent under reduced pressure provided the crude **9** which was dissolved in CH_2Cl_2 (10 mL) and was percolated on a small silica column (h = 10 cm, ø = 2 cm) eluting with CH_2Cl_2 (20 mL). The elimination of the solvent under reduced pressure provided **9**.

1,3- Bis(tert-butoxycarbonyl)-2-(trifluoromethylsulfonyl)guanidine (**9**) [26] 1.98 g, white solid, 70% yield; m.p. 105-108°C, lit. 115°C [26]; FTIR (KBr) 3377 (NH), 3306 (NH), 1787 ($C=NSO_2CF_3$), 1736 (C=O), 1631 (NH) cm^{-1}; ^1H NMR (300 MHz; $CDCl_3$) δ 1.54 (s, 18H CH_3 Boc), 10.1 (br s, 2H, NH); ^{13}C NMR (75.5 MHz; $CDCl_3$) δ 27.84, 86.02, 117.16, 121.40, 151.43; Anal Calcd for $C_{12}H_{20}F_3N_3O_6$ (391.36): C, 36.83%; H, 5.15%; N, 14.56%; Found: C, 36.77 %; H, 5.04%; N, 14.24%.

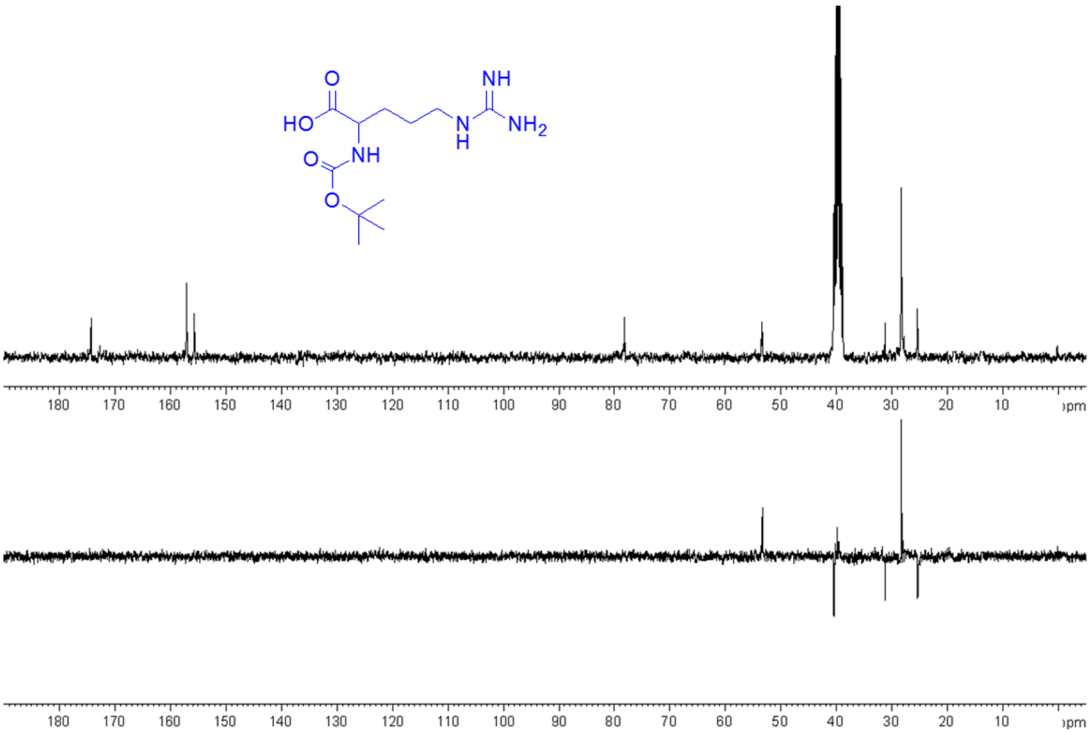
Table S12. Formulas, MW, physical state, melting point and elemental analysis results of the most important reported compounds

Compounds	Formula	MW	Physical state	M.p. Lit.[]	Required (%)	Found (%)	Error
2	$C_{11}H_{22}N_4O_4$	274.32	White solid	150°C, dec. 159-160°C[16a] 145-150°C[16c]	C 48.16 H 8.08 N 20.42	C 47.75 H 7.78 N 20.21	C-0.43 H-0.30 N-0.21
3a	$C_{21}H_{38}N_4O_8$	474.55	Yellowish glassy solid	Low melting	C 53.15 H 8.07 N 11.81	C 53.12 H 8.21 N 11.67	C-0.03 H+0.14 N-0.14
3a+3b	$C_{21}H_{38}N_4O_8$	474.55	White solid	124-125°C 123-124°C[17]	C 53.15 H 8.07 N 11.81	C 53.21 H 8.45 N 11.67	C+0.06 H+0.38 N-0.14
3c	$C_{16}H_{30}N_4O_6$	374.22	White solid	139°C	C 51.32 H 8.08 N 14.96	C 51.23 H 8.28 N 15.27	C -0.09 H +0.20 N +0.31
4	$C_{10}H_{20}N_2O_4$	232.28	white solid	dec.	C 51.71 H 8.68 N 12.06	C 51.47 H 8.94 N 12.28	C-0.24 H+0.26 N+0.22
6 ***E, Z***	$C_{21}H_{38}N_4O_8$	474.55	white solid	102-104°C	C 53.15 H 8.07 N 11.81	C 53.27 H 8.47 N 11.77	C+0.12 H+0.40 N-0.04
6 ***E***	$C_{21}H_{38}N_4O_8$	474.55	white solid	102°C	C 53.15 H 8.07 N 11.81	C 53.28 H 8.45 N 11.74	C+0.13 H+0.38 N-0.07
6 ***Z***	$C_{21}H_{38}N_4O_8$	474.55	white solid	102-104°C	C 53.15 H 8.07 N 11.81	C 53.25 H 8.41 N 11.79	C+0.10 H+0.34 N-0.02
8	$C_{11}H_{21}N_3O_4$	259.30	white solid	145-147°C 144°C[26]	C 50.95 H 8.16 N 16.21	C 50.74 H 8.48 N 16.42	C-0.21 H+0.32 N+0.21
9	$C_{12}H_{20}F_3N_3O_6S$	391.36	white solid	105-108°C 115°C[26]	C 36.83 H 5.15 N 14.56	C 36.67 H 5.04 N 14.24	C-0.16 H-0.11 N-0.32
10	$C_{21}H_{38}N_4O_8$	474.55	white solid	102-104°C	C 53.15 H 8.07 N 11.81	C 53.30 H 8.27 N 12.00	C+0.15 H+0.20 O+0.19

Compound 2

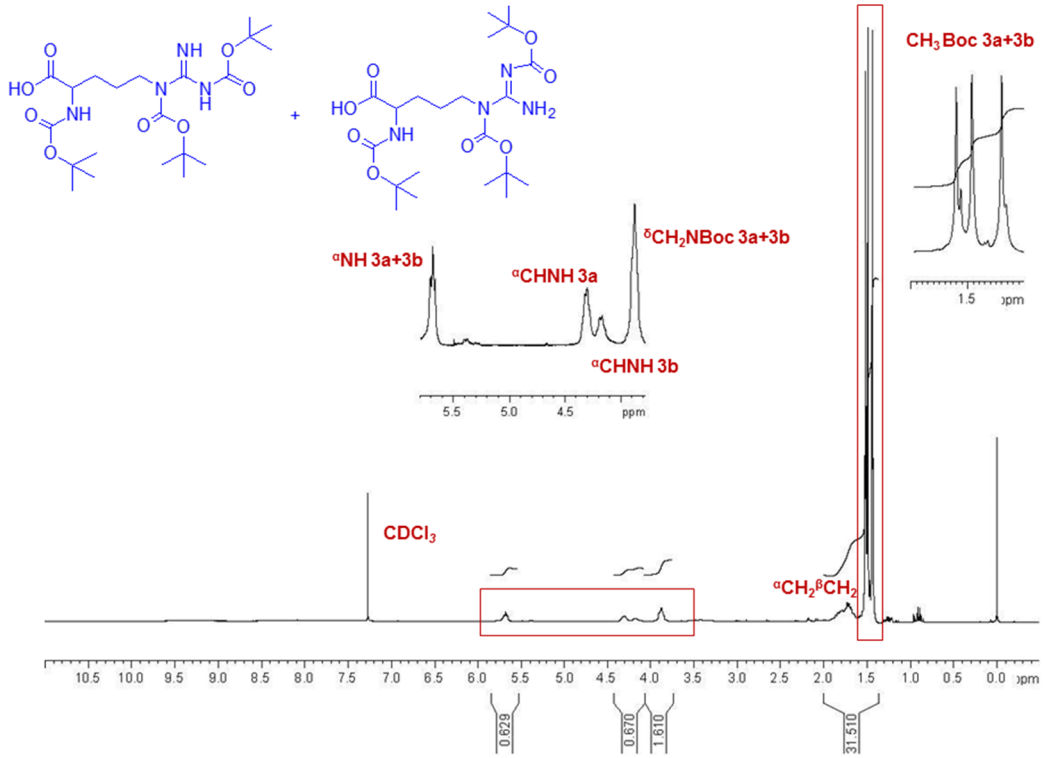


Spectrum S13. ^{1}H NMR (300 MHz, DMSO) of compound **2**

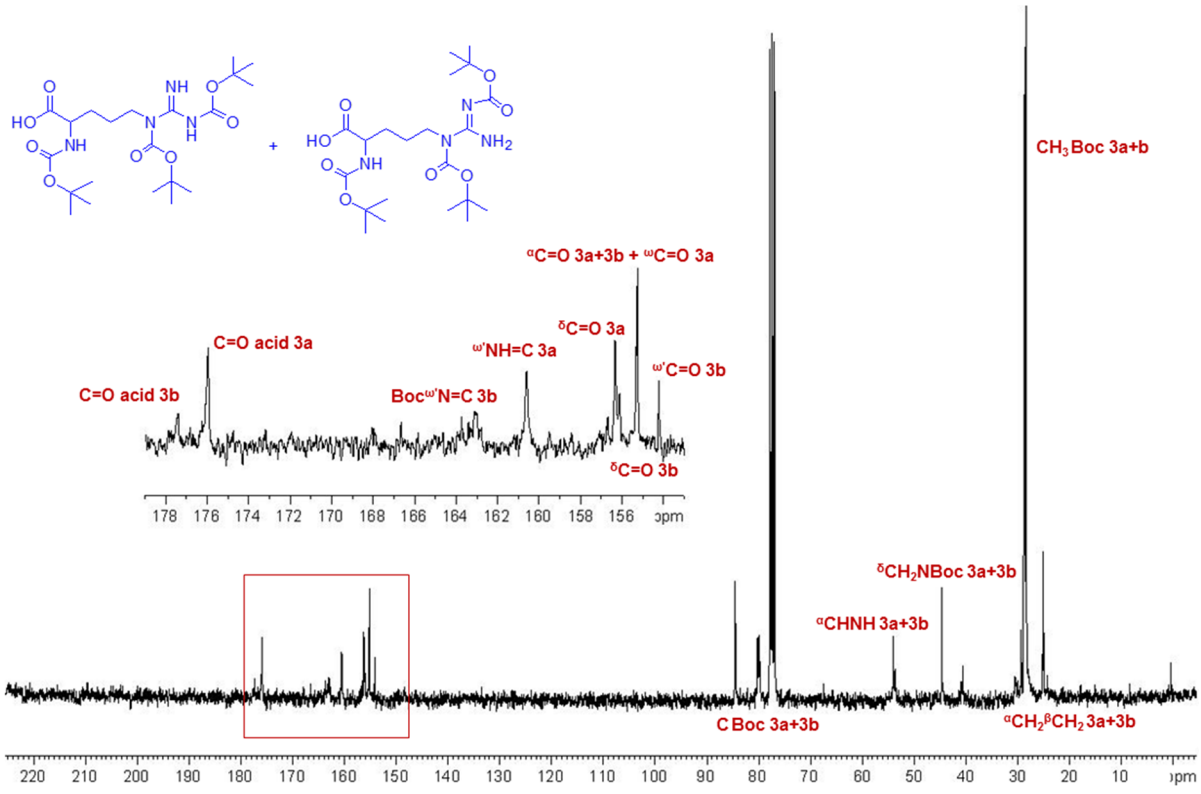


Spectrum S14. ^{13}C NMR and DEPT-135 (75.5 MHz, DMSO) of compound **2**

Compounds 3a+3b

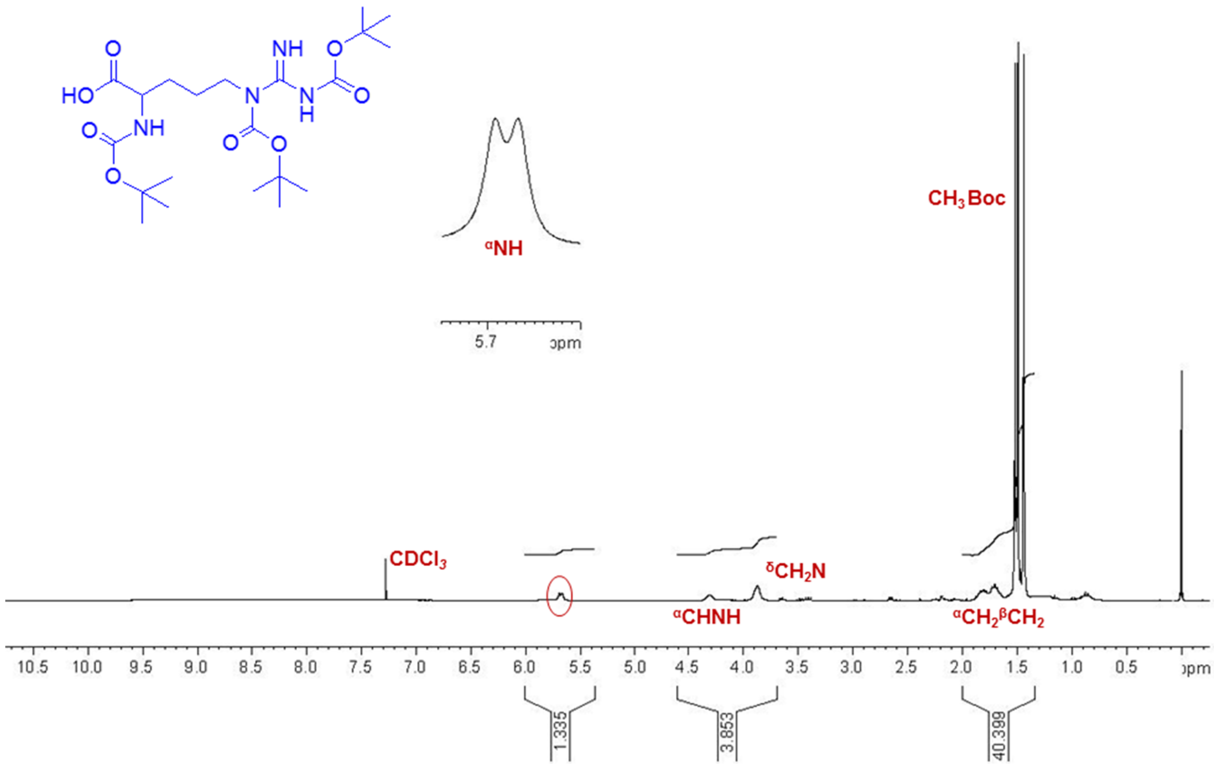


Spectrum S15. ^{1}H NMR (300 MHz, $CDCl_3$) of compounds **3a+3b**

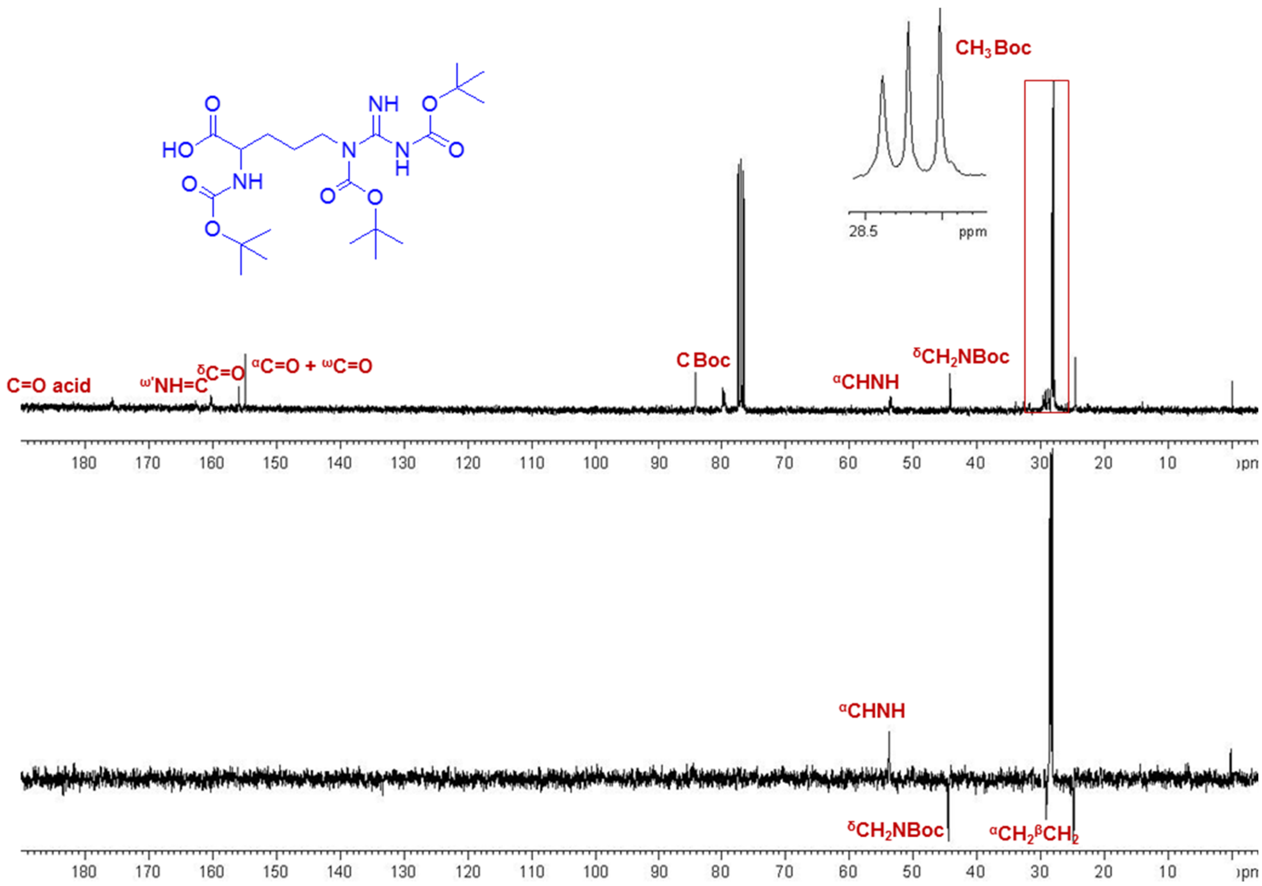


Spectrum S16. ^{13}C NMR (75.5 MHz, $CDCl_3$) of compounds **3a+3b**

Compound 3a

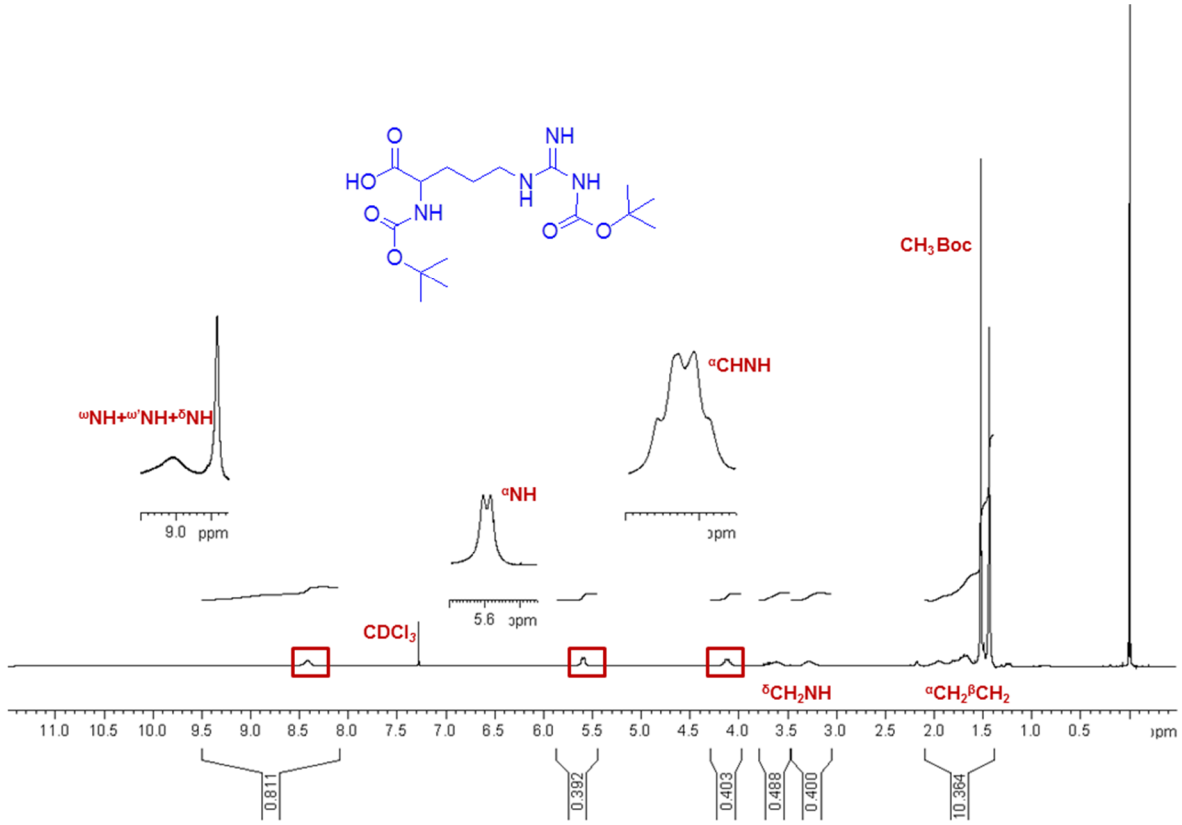


Spectrum S17. ^{1}H NMR (300 MHz, $CDCl_3$) of compound **3a**

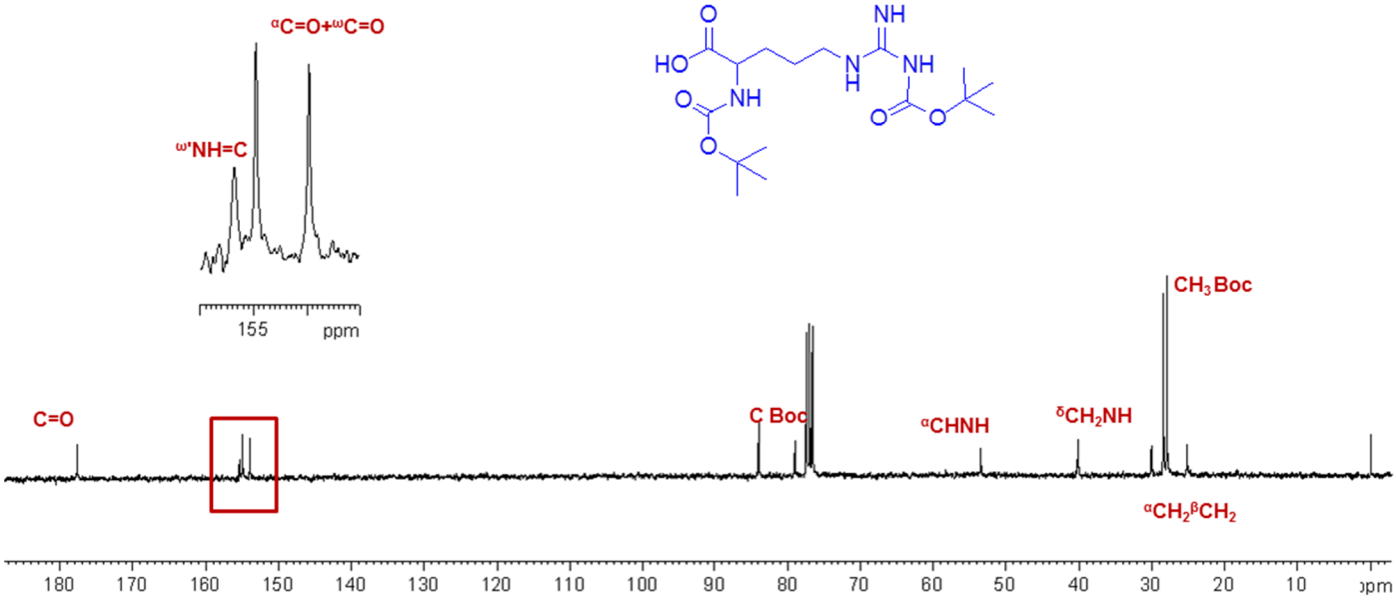


Spectrum S18. ^{13}C NMR and DEPT-135 (75.5 MHz, $CDCl_3$) of compound **3a**

Compound 3c

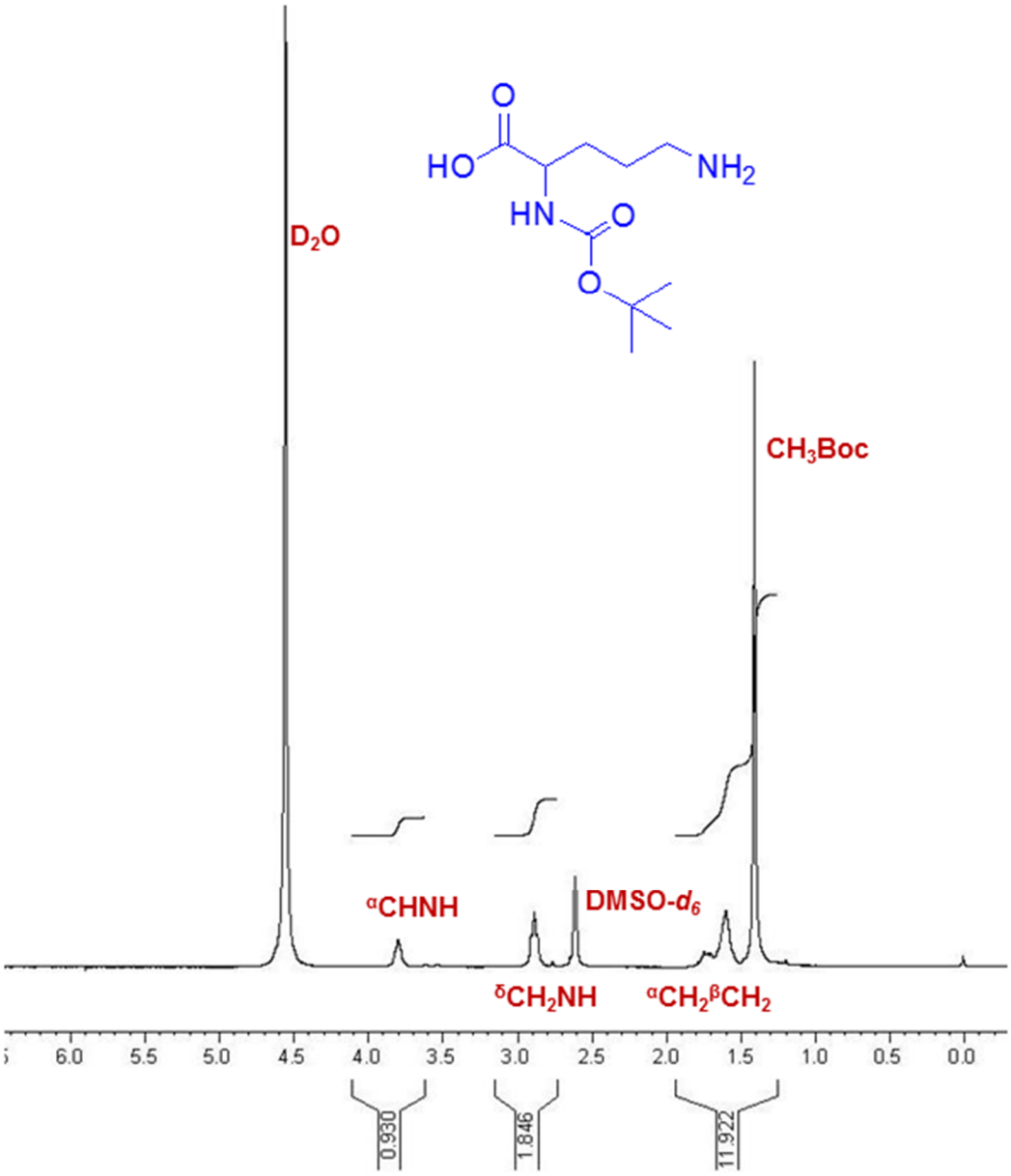


Spectrum S19. ^{1}H NMR (300 MHz, $CDCl_3$) of compound **3c**

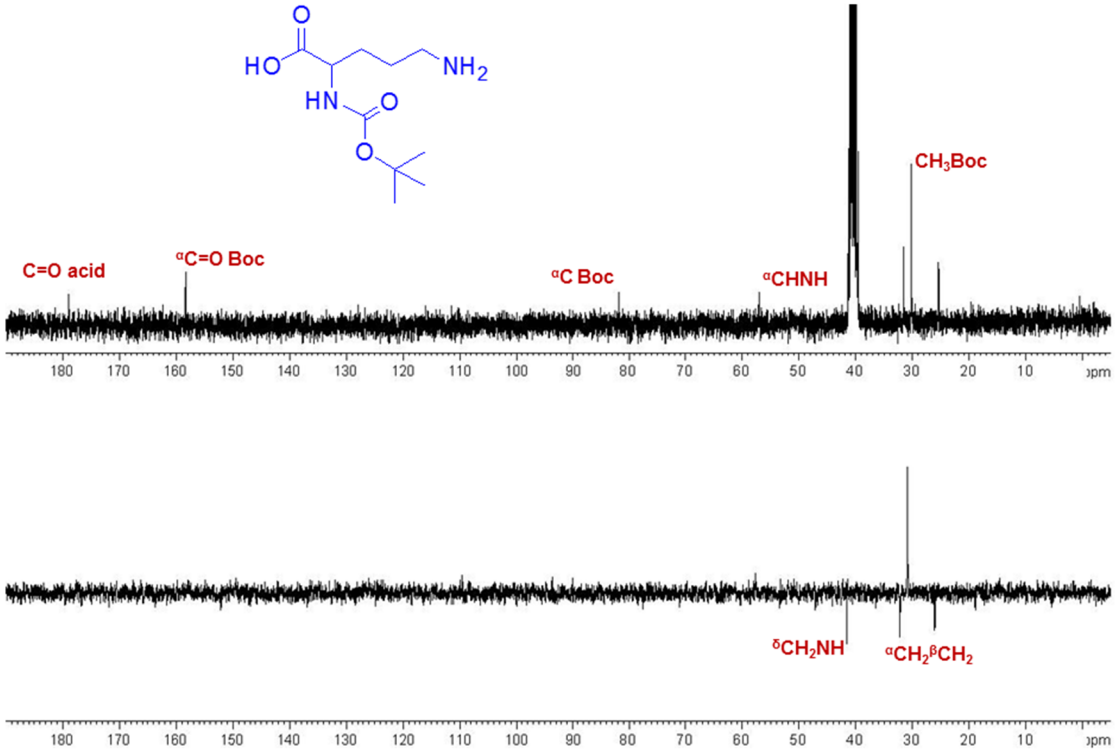


Spectrum S20. ^{13}C NMR (75.5 MHz, $CDCl_3$) of compound **3c**

Compound 4

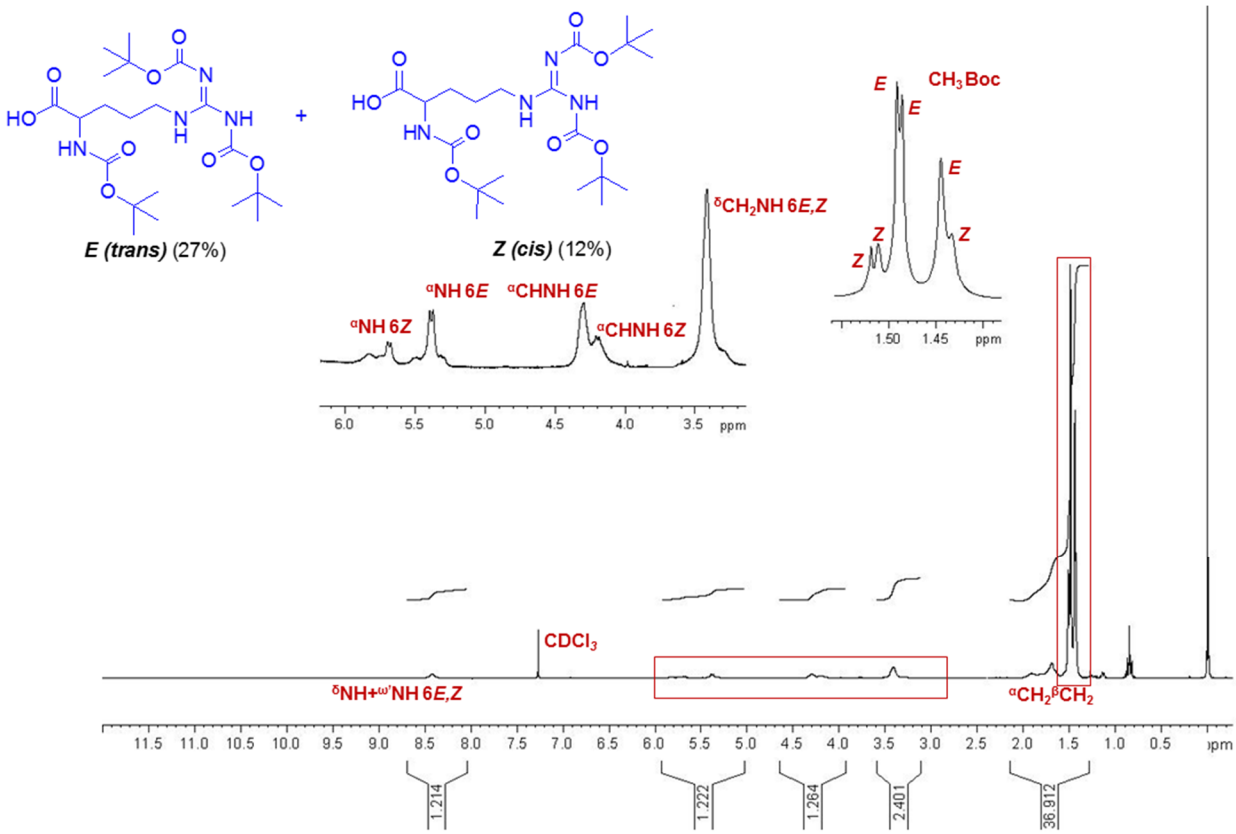


Spectrum S21. ^{1}H NMR (300 MHz, DMSO/D_2O) of compound **4**

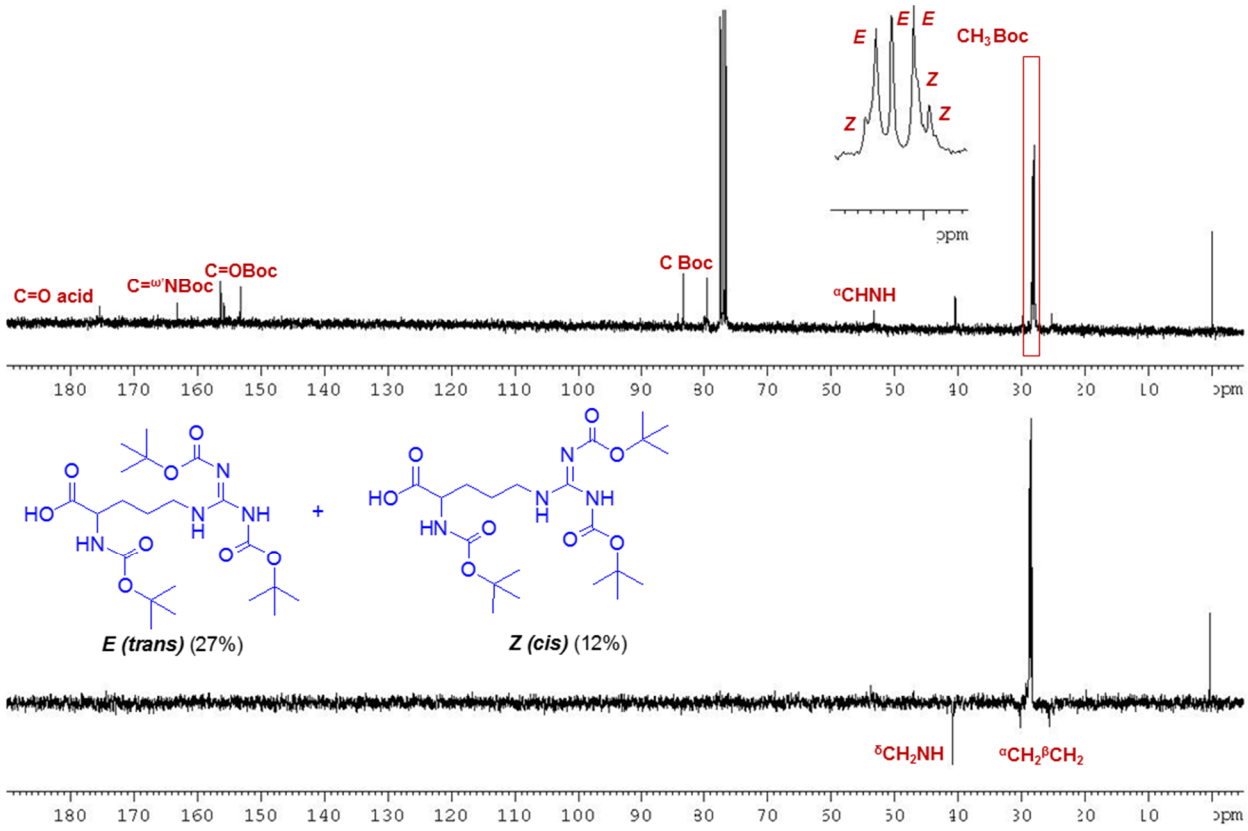


Spectrum S22. ^{13}C NMR and DEPT-135 (75.5 MHz, DMSO/D_2O) of compound **4**

Compound 6 *E/Z*

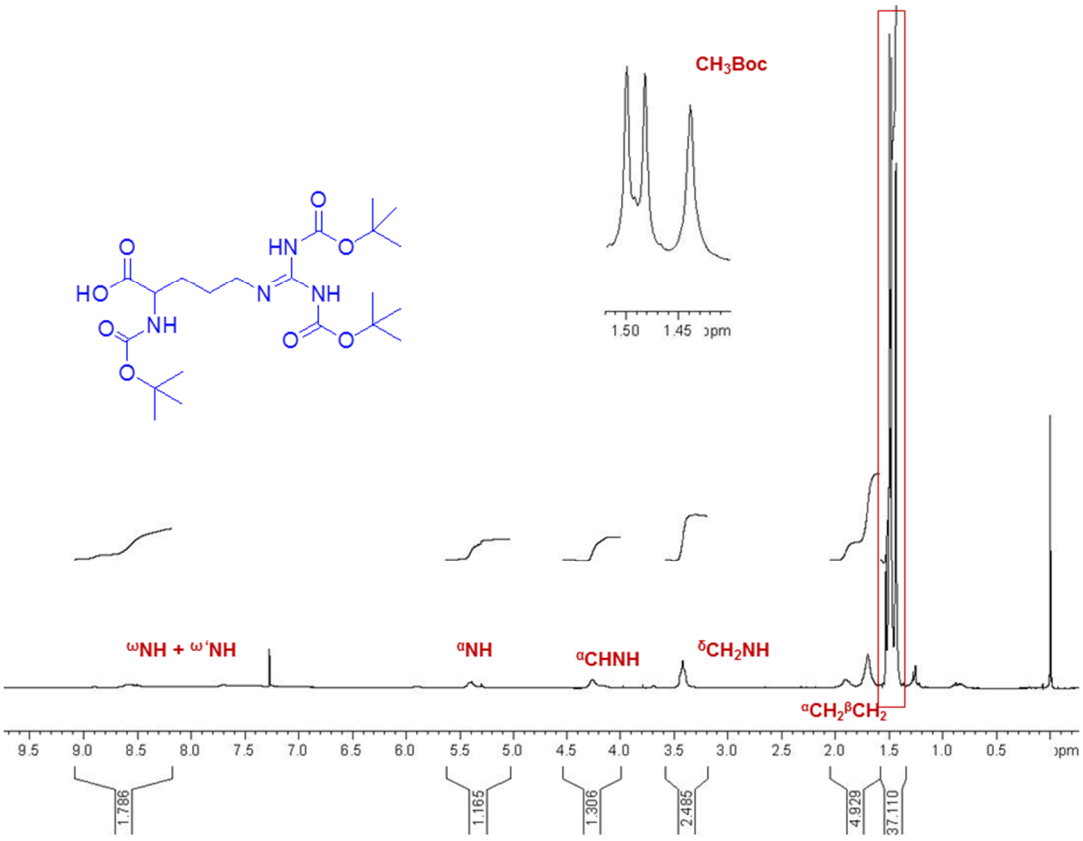


Spectrum S23. ^{1}H NMR (300 MHz, $CDCl_3$) of compound **6 *E, Z***

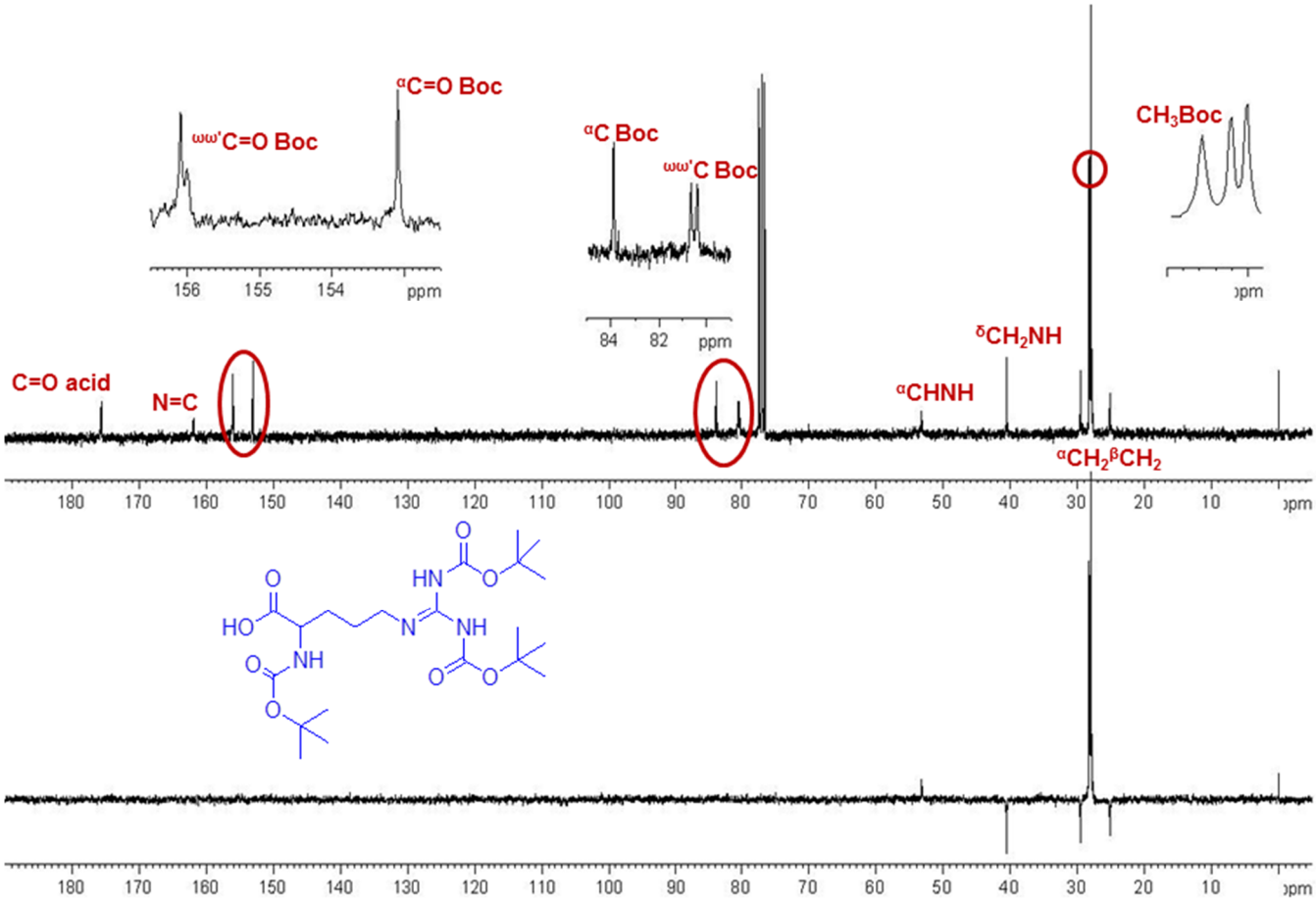


Spectrum S24. ^{13}C NMR and DEPT-135 (75.5 MHz, $CDCl_3$) of compound **6** ***E, Z***

Compound 10



Spectrum S25. ^{1}H NMR (300 MHz, $CDCl_3$) of compound **10**



Spectrum S26. ^{13}C NMR and DEPT-135 (75.5 MHz, $CDCl_3$) of compound **10**

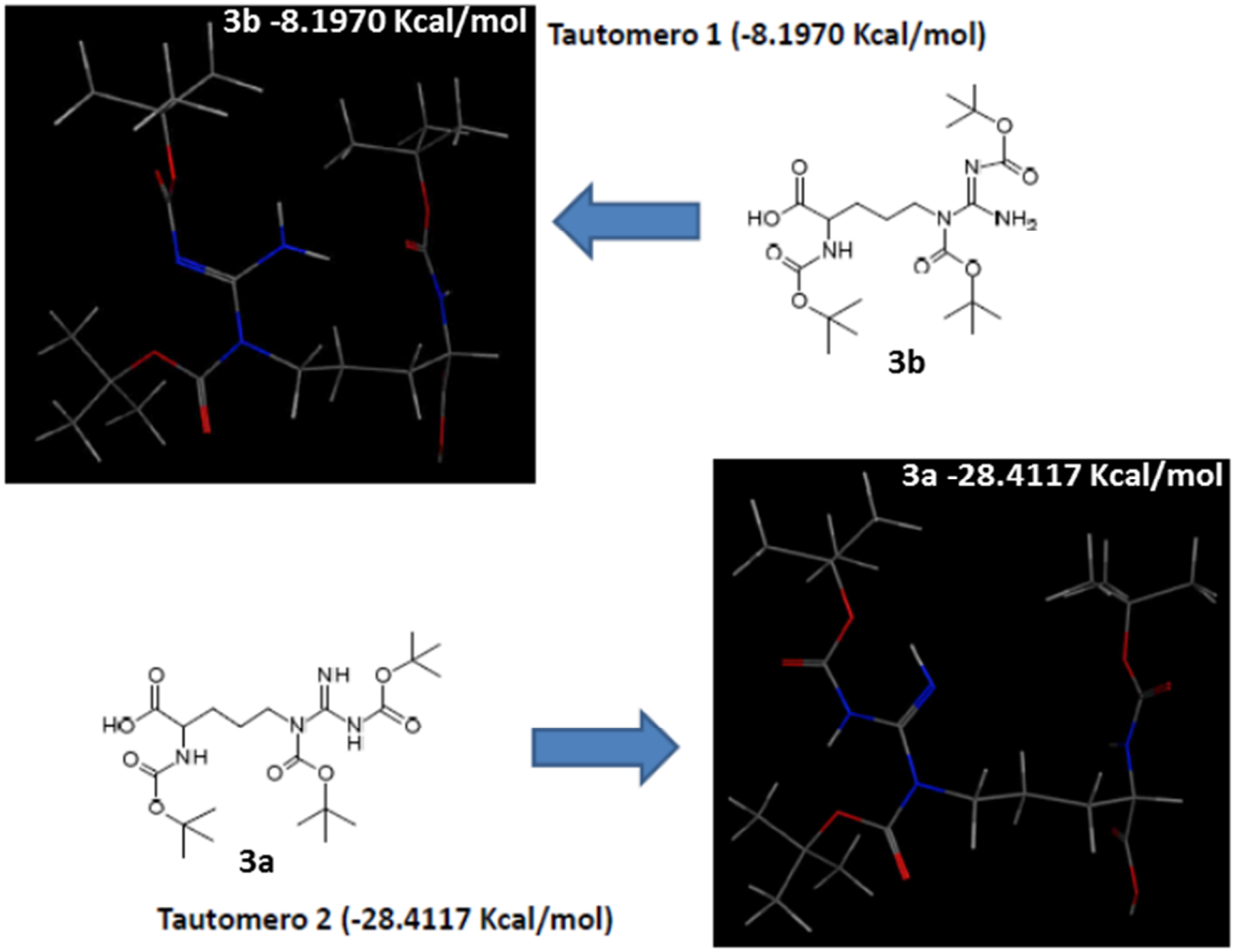


Figure S27. 3D images of the two tautomers **3a** and **3b** with the calculated energy associated to their structure

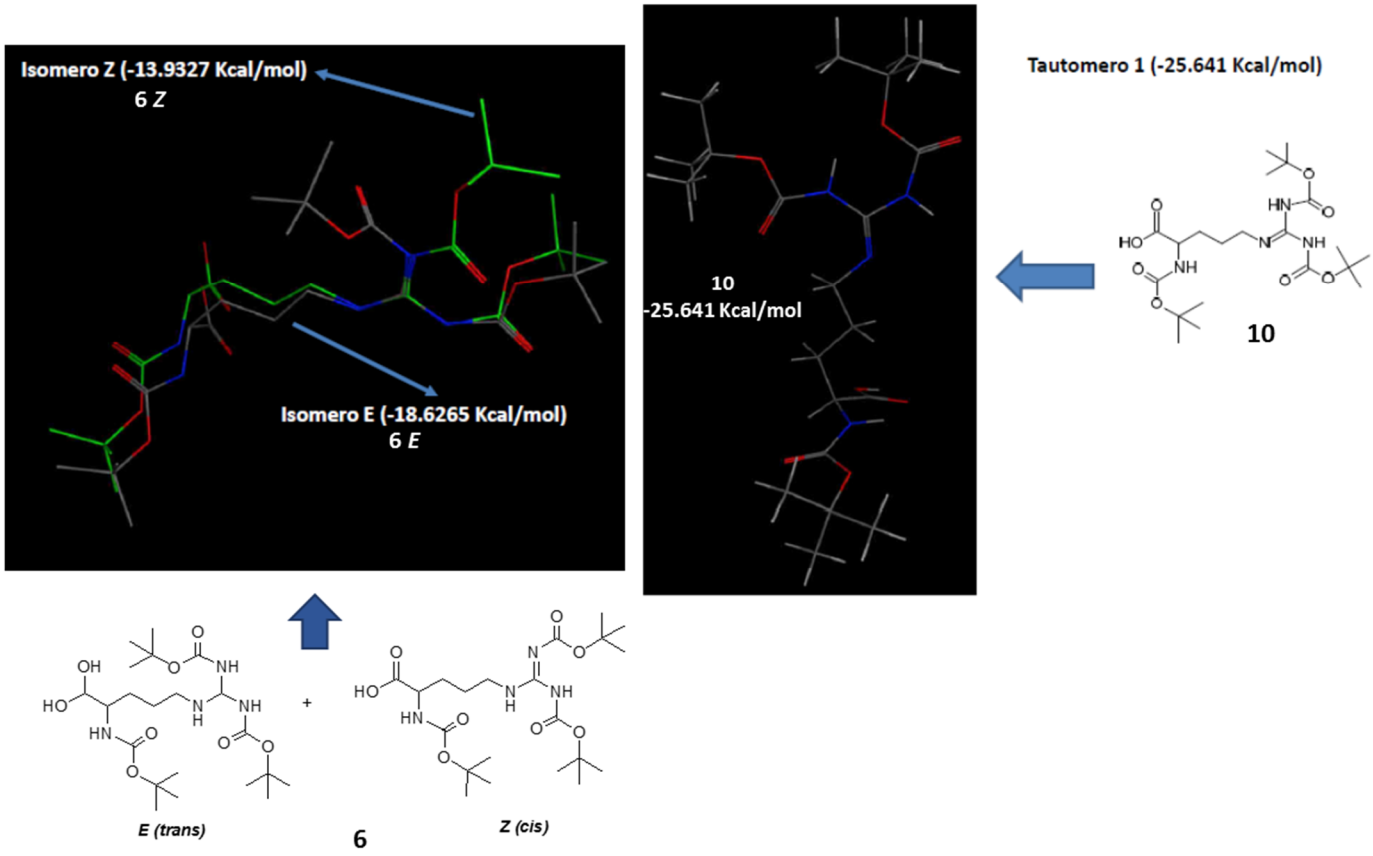


Figure S28. 3D overlapping images of the two rotamers **6** ***E, Z*** and of their tautomer **10** with the calculated energy associated to their structure