Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry.

5-Fluoro-1,2,3-triazole motif in peptides and its electronic properties

José Laxio-Arenas[a], Pascal Retailleau[b], Jean-Michel Gillet[c], Nour-Eddine Ghermani *[c,d], Sandrine Ongeri[a], Benoît Crousse *[a]

[a] UMR 8076, BioCIS, Univ. Paris-Sud, CNRS, Université Paris-Saclay, 92290 Châtenay-Malabry, France. E-mail: benoit.crousse@universite-paris-saclay.fr
[b] Université Paris-Saclay, CNRS, Institut de Chimie des Substances Naturelles, 91198 Gif-sur-Yvette, France.
[c] UMR CNRS 8580, Ecole Centrale Paris, Grande Voie des Vignes, 92290 Châtenay-Malabry, France
[d] UMR CNRS 8612, Université Paris-Saclay, Faculté de Pharmacie, 5 rue Jean- Baptiste Clément, 92296 Châtenay-Malabry, France

Table of contents

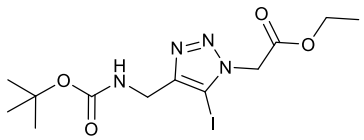
I. Material and method: General information.

All experiments dealing with air and moisture-sensitive compounds were conducted under an atmosphere of dry argon. The usual solvents were purchased from commercial sources without further purification. Reagents were used without further purification as received from commercial. TLC analyses were performed on silica gel, 60 F250 (0.26 mm thickness) plates. The plates were visualized with UV light (λ = 254 nm) or with a 3.5% solution of phosphomolybdic acid in ethanol or with a solution of $KMnO_4$ in water. Compounds were purified by silica gel chromatography using Merck 60 silica gel (230 – 400 mesh).

NMR spectra were recorded on a Bruker AMX 200 (^{1}H, 200MHz; ^{19}F, 188 MHz), an ultrafield Bruker AVANCE 300 (^{1}H, 300 MHz, ^{13}C, 75 MHz). Chemical shift values (δ) for are reported in ppm downfield from Me_4Si (δ = 0.0 ppm) with the solvent resonance as the internal standard (^{1}H NMR, $CDCl_3$: δ = 7.26 ppm, CD_3OD: δ = 3.31 ppm; ^{13}C NMR, $CDCl_3$: δ = 77.16 ppm, CD_3OD: δ = 49.00 ppm) and internal $CFCl_3$ (0.0 ppm for ^{19}F NMR). Data are reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, m = multiplet), coupling constant (Hz), integration, attribution. Melting points were determined on a Kofler melting point apparatus. High-resolution mass spectra (HRMS) were obtained using a TOF LCT Premier apparatus (Waters), with an electrospray ionization source. Melting point was measured on a W+M Heizbank System Kofler WME.

II. Characterization of compounds.

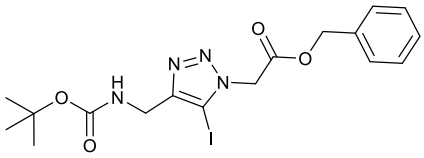
Ethyl 2-(4-(((tert-butoxycarbonyl)amino)methyl)-5-iodo-1H-1,2,3-triazol-1-yl)acetate 1a.



To a solution of ethyl 2-azidoacetate (486 mg, 3.8 mmol, 1.0 equiv.) in dry THF (0.3 M) was successively added *tert*-butyl (3-iodoprop-2-yn-1-yl) carbamate (1.1 g, 3.8 mmol, 1.0 equiv.), CuI (74 mg, 0.38 mmol, 0.1 equiv.), triethylamine (0.530 mL, 3.8 mmol, 1.0 equiv.). The mixture was stirred for 2 hours at room temperature. After completion, reaction was quenched using NH_4Cl sat., and extracted with EtOAc (3 x 15mL). The organic layers were washed with water and brine, dried over Na_2SO_4, filtered, and concentrated under vacuum. The crude product was purified by column chromatography using c-Hex/EtOAc: 6/4 to provide **1a** as a white solid (1.2 g, 2.9 mmol, 77%). Rf = 0.2 (c-Hex/EtOAc: 75/25); mp: 122-124 °C; ^{1}H NMR

(300 MHz, $CDCl_3$): δ 5.16 (m, 2H), 5.10 (br s, 1H), 4.40 (d, ^3J = 5.04 Hz, 2H), 4.27 (q, ^3J = 7.12 Hz, 2H) 1.45 (s, 9H), 1.29 (t, ^3J = 7.12 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): 165.5, 162.9, 149.3, 124.8, 79.5, 62.5, 51.2, 36.7, 28.2, 14.0; IR (neat): υ_{max} 3103, 2951, 1544, 1241, cm^{-1}; HRMS (ESI-TOF, ion polarity positive) m/z $C_{12}H_{19}IN_4O_4Na$ $[M+Na]^+$ cal. 433.0343, found 433.0345.

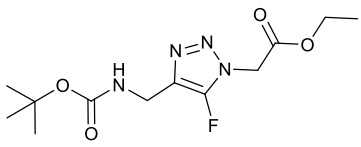
Benzyl 2-(4-(((tert-butoxycarbonyl)amino)methyl)-5-iodo-1H-1,2,3-triazol-1-yl)acetate 1b.



To a solution of benzyl 2-azidoacetate (669 mgs, 3.5 mmol, 1.0 equiv.) in dry THF (0.3 M) was successively added tert-butyl (3-iodoprop-2-yn-1-yl)carbamate (984 mgs, 3.5 mmol, 1.0 equiv.), CuI (68 mgs, 0.35 mmol, 0.1 equiv.), triethylamine (0.487 mL, 3.5 mmol, 1.0 equiv.). The mixture was stirred for 2 hours at room temperature. After completion, reaction was quenched using NH_4Cl sat., and extracted with EtOAc (3 x 15mL). The organic layers were washed with water and brine, dried over Na_2SO_4, filtered and concentrated under vacuum. The crude product was purified by column chromatography using c-Hex/EtOAc: 6/4 to provide **1b** as a pale-yellow solid (1.2 g, 2.6 mmol, 73%). mp: 100-102 °C; Rf = 0.2 (c-hex/EtOAc: 75/25) ; ^1H NMR (300 MHz, DMSO-d6): δ 7.39 (s, 5H), 7.24 (br s, 1H), 5.46 (s, 2H), 5.24 (s, 2H), 4.17 (d, ^3J = 5.84 Hz, 2H) 1.42 (s, 9H); ^{13}C NMR (75 MHz, DMSO-d6): 167.6, 166.4, 148.6, 135.3, 128.4, 128.2, 128.0, 82.2, 77.7, 67.0, 50.9, 35.8, 28.3; IR (neat): υ_{max} 3083, 2911, 1540, 1211 cm^{-1}; HRMS (ESI-TOF, ion polarity positive): *m/z* $C_{17}H_{21}IN_4O_4$ $[M+H]^+$ cal. 473.0645, found 473.0649.

Synthesis of 5-fluoro-1,2,3-triazoles 2a by silver-mediated fluorination

ethyl 2-(4-(((tert-butoxycarbonyl)amino)methyl)-5-fluoro-1H-1,2,3-triazol-1-yl)acetate ***2a***.



AgF (151 mgs, 1.2 mmol, 1.2 equiv.) and **1a** (410 mgs, 1.0 mmol, 1 equiv.) were added to an over-dried glassware charged with a stir bar. Then, freshly distillated TMEDA (30 μL, 0.2 mmol, 0.2 equiv.) and anhydrous toluene (0.3 M) were added. Finally, the glassware was capped and heated at 120°C for 18 hours. After completion, the mixture was cooled to room

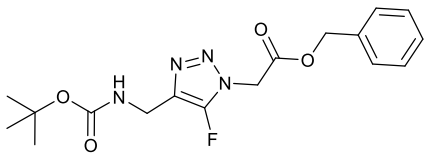
temperature and quenched CH_2Cl_2. The insoluble solid was removed by filtration on a short pad of celite. Then the solvent was removed, and the product was purified by flash silica column chromatography using as eluant c-Hex/EtOAc: 75/25 to obtain **2a** as a pale-yellow solid (169 mgs, 0.56 mmol, 56%). Rf = 0.2 (c-hex/EtOAc: 75/25); mp: 78-80 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.10 (br s, 1H), 4.99 (s, 2H), 4.33 (d, ^3J = 6.03 Hz, 2H), 4.26 (q, ^3J = 7.17 Hz, 2H), 1.42 (s, 9H), 1.28 (t, ^3J = 7.17 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): 165.1, 155.6, 150.6 (d, ^1J(C,F) = 279.4 Hz), 124.9 (d, ^2J(C,F) = 6.4 Hz), 79.8, 62.7, 47.9 (d, ^3J(C,F) = 1.7 Hz), 47.8, 28.3, 14.0; ^{19}F NMR (188, MHz, $CDCl_3$): δ -153.4 (s); IR (neat): υ_{max} 3112, 2977, 1580, 1199 cm^{-1}; HRMS (ESI-TOF) *m/z* $C_{12}H_{19}FN_4O_4Na$ $[M+Na]^+$ cal. 325.1284, found 325.1283.

Synthesis of 5-fluoro-1,2,3-triazoles 2a by halex reaction

To a 5 mL round-bottomed microwave vial equipped with a magnetic stir bar is added 5-iodo-1,2,3-triazole **1a** (300 mgs, 0.73 mmol, 1 equiv.) and KF (212 mgs, 3.7 mmol, 5 equiv.,). The solids are then first washed off the side with MeCN and then Water (0.23M overall). The mixture is stirred for several minutes and then capped with an appropriate Teflon microwave lid. The vial is place into the microwave reactor set at a "Very High" adsorption and heated at 180°C for 10 minutes. After the vial has cooled to room temperature, a distinct separation between the phases should be noted with a pale-yellow color persisting in the organic layer. The organic layer is diluted with EtOAc and extracted. The resulting aqueous phase was extracted three times more and dried over Na_2SO_4. The organics were concentrated, and the residue was purified by flash column chromatography (75% c-Hex/25% EtOAc) to yield 121 mgs of 5-fluoro-1,2,3-triazole **2a** (56% yield). Crystals of **2a** were obtain from a EtOAc/c-Hex/CH_2Cl_2 mixture.

Synthesis of 5-fluoro-1,2,3-triazoles 2b by silver-mediated fluorination

benzyl 2-(4-(((tert-butoxycarbonyl)amino)methyl)-5-fluoro-1H-1,2,3-triazol-1-yl)acetate ***2b***.



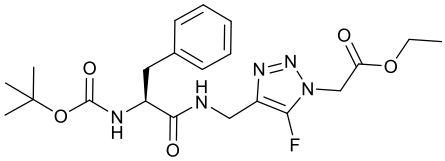
AgF (151 mgs, 1.2 mmol, 1.2 equiv.) and **1b** (472 mgs, 1.0 mmol, 1 equiv.) were added to an over-dried glassware charged with a stir bar. Then, freshly distillated TMEDA (30 uL, 0.2 mmol, 0.2 equiv.) and anhydrous toluene (0.3 M) were added. Finally, the glassware was capped and heated at 120°C for 18 hours. After completion, the mixture was cooled to room temperature and quenched CH_2Cl_2. The insoluble solid was removed by filtration on a short pad

of celite. Then the solvent was removed, and the product was purified by flash silica column chromatography using as eluant c-Hex/EtOAc: 75/25 to obtain **2b** as a pale-yellow solid (193 mgs, 0.53 mmol, 53%). Rf = 0.2 (c-hex/EtOAc: 75/25); mp: 88-90 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.36 (br s, 5H), 5.25 (s, 2H), 5.05 (s, 2H), 4.37 (d, ^{3}J = 5.90 Hz, 2H), 1.45 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.8, 165.0, 150.6 (d, ^{1}J(C,F) = 281.6 Hz), 134.3, 128.9, 128.8, 128.6, 124.8 (d, ^{2}J(C,F) = 11.2 Hz), 79.9, 68.3, 47.8, 34.2, 28.3. ^{19}F NMR (188, MHz, $CDCl_3$): δ -153.4 (s); IR (neat): υ_{max} 3003, 2891, 1576, 1221; HRMS (ESI-TOF, ion polarity positive) *m/z* $C_{17}H_{21}FN_4O_4Na$ $[M+Na]^+$ cal. 387.1439, found 387.1440.

Peptide coupling. General procedure A

To a solution of **2b** (1.0 equiv.) in CH_2Cl_2 (0.1 M) was added a solution of HCl in dioxane (4.0 M, 10 equiv.) at 0°C and stirred for 2 hours. After completion the crude product was concentrated under vacuum and used directly without further purification. To a solution of Boc-L-aminoacids (1.0 equiv.), deprotected 5-fluorotriazole, HOBt (1.2 equiv.) and EDC.HCl (1.2 equiv.) in dry DMF was added drop by drop DIPEA (3 equiv.) at 0°C and stirred for 5 hours. The mixture was diluted with water, extracted with EtOAc (3 x 10 mL), washed with citric acid (10%), K_2CO_3 (10%), NaCl sat. then dried over Na_2SO_4, filtered, concentrated under vacuum, and purified by flash column chromatography using the appropriate solvent.

*Ethyl (S)-2-(4-((2-((tert-butoxycarbonyl)amino)-3-phenylpropanamido)methyl)-5-fluoro-1H-1,2,3-triazol-1-yl)acetate **3a**.*



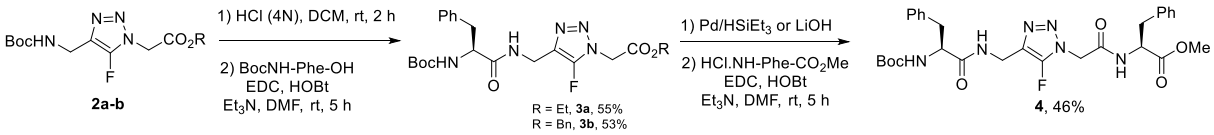
To a solution of **2a** (320 mg, 1.06 mmol, 1 equiv.) in CH_2Cl_2 (0.1 M) was added a solution of HCl in dioxane (4.0 M, 2.6 mL, 10.6 mmol, 10 equiv.) at 0°C and stirred for 2 hours. After completion the crude product was concentrated under vacuum and used directly without further purification. To a solution of Boc-L-Phenylalanine (281 mg, 1.06 mmol, 1 equiv.), deprotected 5-fluorotriazole, HOBt (198 mg, 1.27 mmol, 1.2 equiv.) and EDC.HCl (243 mg, 1.27 mmol, 1.2 equiv.) in dry DMF was added drop by drop DIPEA (500 µL. 2.65 mmol, 2.5 equiv.) at 0°C and stirred for 5 hours. The mixture was diluted with water, extracted with EtOAc (3x 10 mL), washed with citric acid (10%), K_2CO_3 (10%), NaCl sat. then dried over Na_2SO_4, filtered and concentrated under vacuum. The product was purified by silica column chromatography using as eluant c-Hex/EtOAc: 7/3 to obtain **3a**

(207 mg, 0.46 mmol, 43 %) as a white solid. mp = 104-106 °C; Rf = 0.2 (c-hex/EtOAc: 7/3); ^{1}H NMR (300 MHz, CD_3OD): δ 7.24-7.18 (m, 5H), 5.25 (s, 2H), 4.40 (d, ^{3}J = 6.9 Hz, 2H), 4.28 (q, ^{3}J = 7.3 Hz, 3H), 3.08 (dd, ^{2}J = 13.7 Hz, ^{3}J = 5.7 Hz, 1H), 2.83 (dd, ^{2}J = 13.7 Hz, ^{3}J = 5.7 Hz), 1.42 (s, 9H), 1.28 (t, ^{3}J = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, CD_3OD): 174.3, 167.3, 152.2 (d, ^{1}J(C,F) = 281.0 Hz), 138.5, 130.4, 129.4, 127.7, 125.4 (d, ^{2}J(C,F) = 21.2 Hz), 80.7, 63.5, 57.3, 48.8, 39.5, 33.6, 33.5, 28.6, 14.4; ^{19}F NMR (188, MHz, $CDCl_3$): δ -154.0 (s); IR (neat): υ_{max} 3001, 2853, 1577, 1239 cm^{-1}; HRMS (ESI-TOF, ion polarity positive) *m/z* $C_{21}H_{28}FN_4O_5Na$ $[M+Na]^+$ cal. 472.2177, found 472.2179.

*Benzyl (S)-2-(4-((2-acetamido-3-phenylpropanamido)methyl)-5-fluoro-1H-1,2,3-triazol-1-yl)acetate **3a***. **3a** was obtained following the general procedure **A** from **2a** (100 mgs, 0.33 mmol, 1.0 equiv.) and AcNH-Phe-OH (68 mgs, 0.33 mmol, 1.0 equiv.). The crude product was purified by flash chromatography (97% CH_2Cl_2/ 3% MeOH) to provide **3a** as a white solid (72 mgs, 0.16 mmol, 47%). Rf = 0.2 (CH_2Cl_2/MeOH:97/3); mp: 110-112 °C; ^{1}H NMR (200 MHz, DMSO-*d6*): δ 8.55 (brs, 1H), 8.04 (d, ^{3}J = 8.59 Hz, 3H), 7.38 (br s, 5H), 7.20 (br s, 5H), 5.48 (s, 2H, 12), 5.23 (s, 2H), 4.28 (d, ^{3}J = 5.53 Hz, 2H), 1.74 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): 165.1, 162.6, 150.6 (^{1}J(C,F) = 279.4 Hz), 62.7, 47.8, 34.2, 28.3, 14.0; ^{19}F NMR (188, MHz, $CDCl_3$): δ -152.8 (s); IR (neat): υ_{max} 3109, 2951, 1564, 1476, 1191; HRMS (ESI-TOF, ion polarity positive) *m/z* $C_{23}H_{24}FN_5O_4$ $[M+Na]^+$ cal. 454.1844, found 454.1849.

*Benzyl (S)-2-(4-((2-acetamidopropanamido)methyl)-5-fluoro-1H-1,2,3-triazol-1-yl)acetate **3b***. **3b** was obtained following the general procedure **A** from **2b** (100 mgs, 0.33 mmol, 1.0 equiv.) and BocNH-Ala-OH (62 mgs, 0.33 mmol, 1.0 equiv.). The crude product was purified by flash chromatography (96% CH_2Cl_2/ 4% MeOH) to provide **3b** as a white solid (64 mgs, 0.17 mmol, 51%). Rf = 0.2 (CH_2Cl_2/MeOH: 96/4); mp: 100-102 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.33 (br s, 5H), 6.78 (br s, 1H), 5.16 (s, 2H), 4.97 (s, 2H), 4.94 (br s, 1H), 4.41 (dt, ^{3}J = 5.6 Hz, ^{2}J = 1.1 Hz, 2H), 4.13-4.06 (m, 1H), 1.35 (s, 9H), 1.27 (d, ^{3}J = 7.08 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.7, 165.0, 150.6 (^{1}J(C,F) = 282.8 Hz), 134.4, 128.9, 128.8, 128.5, 124.1 (^{2}J(C,F) = 10.1 Hz), 68.3, 50.1, 47.8, 33.0, 32.9, 28.3, 18.4; ^{19}F NMR (188, MHz, $CDCl_3$): δ -152.8; IR (neat): υ_{max} 3201, 2944, 1576, 1502, 1220; HRMS (ESI-TOF) *m/z* $C_{20}H_{26}FN_5O_5Na$ $[M+Na]^+$ cal. 458.1810, found 458.1814.

*General procedure synthesis of **4***



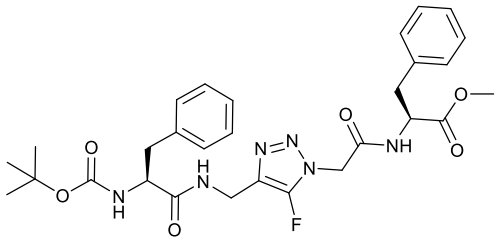
From 3b: To a solution of **3b** (1.0 equiv.) in MeOH (0.1M) was added Pd/C 10w% (0.15 equiv.) and triethylsilane (3 equiv.) drop by drop. The mixture was stirred for 1h at room temperature. After completion, the mixture was filtered on a short pad of celite. The filtrate was concentrated to provide the intermediate acid which was directly put under coupling conditions without further purification. To a solution of acid in DMF (0.1 M) were added corresponding L-aminoacid methyl ester hydrochloride (1.0 equiv.), HOBt (1.2 equiv.) and EDC.HCl (1.2 equiv.). DIPEA (3 equiv.) was added drop by drop at 0°C and the mixture was allowed to stir at room temperature. After 5 hours, the mixture was diluted with water and extracted with EtOAc (3x10ml) washed with citric acid (10%), K_2CO_3 (10%), water, brine and dried over Na_2SO_4. The organic layers were concentrated, and the residue was purified by flash column chromatography using the appropriate solvent.

From 3a:

To a solution of **3a** (99 mg, 0.22 mmol, 1 equiv.) in a mixture of THF/H_2O (0.1 M, 2.2 mL) was added LiOH.H_2O (28 mg, 0.66 mmol, 3 equiv.) at 0°C and stirred for 2 hours. After completion the crude product was concentrated under vacuum and acidified until pH = 2-3 with HCl solution (0.1 M). The mixture was extracted with EtOAc (3 x 10 mL). The organic layers were washed with H_2O and brine, dried over $Na_2S_2O_4$, concentrated under vacuum to provide the intermediate. To a solution of the intermediate acid, Phenylalanine hydrochloride (44 mg, 0.22 mmol, 1 equiv.), HOBt (41 mg, 0.26 mmol, 1.2 equiv.) and EDC.HCl (50 mg, 0.26 mmol, 1.2 equiv.) in dry DMF was added drop by drop DIPEA (100 µL. 0.55 mmol, 2.5 equiv.) at 0°C and stirred for 5 hours. The mixture was diluted with water, extracted with EtOAc (3x 10 mL), washed with citric acid (10%), K_2CO_3 (10%), NaCl sat. then dried over Na_2SO_4, filtered and concentrated under vacuum. The product was purified by silica column chromatography using as eluant CH_2Cl_2/MeOH: 94/6 to obtain **4** (57 mg, 0.12 mmol, 46%) as a white solid. Rf = 0.3 (c-CH_2Cl_2/MeOH: 93/7); mp = 130-132 °C; ^{1}H NMR (300 MHz, CD_3OD): δ 7.29-7.14 (m, 10H, H17, H18, H19), 5.20 (s, 2H, H11), 4.48 (s, 2H, H8), 4.28-4.24 (m, 2H, H5, H14), 3.09-2.84 (m, 4H, H17), 1.42 (s, 9H, H1); ^{13}C NMR (75 MHz, CD_3OD): 174.3, 172.2, 172.1, 167.3, 152.7 (d, ^1J(C,F) = 280.3 Hz), 138.5, 130.4, 129.4, 127.7, 80.7, 58.5, 58.4, 53.3, 35.4, 34.2, 28.4; ^{19}F NMR (188, MHz, CD_3OD): δ -153.8 (s); IR (neat): υmax 3200, 3192, 2856, 1510,

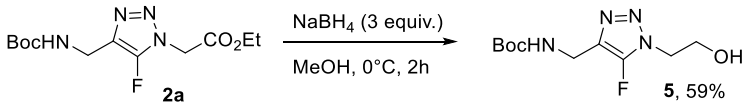
1423, 1289 cm-1; HRMS (ESI-TOF, ion polarity positive) m/z $C_{28}H_{35}FN_4O_5$ [M+H]+ cal. 568.2639, found 568.2642.

Methyl (2-(4-(((S)-2-((tert-butoxycarbonyl)amino)-3-phenylpropanamido)methyl)-5-fluoro-1H-1,2,3-triazol-1-yl)acetyl)-L-phenylalaninate ***3.12***.



To a solution of **3.11** (99 mg, 0.22 mmol, 1 equiv.) in a mixture of THF/H_2O (0.1 M, 2.2 mL) was added LiOH.H_2O (28 mg, 0.66 mmol, 3 equiv.) at 0°C and stirred for 2 hours. After completion the crude product was concentrated under vacuum and acidified until pH = 2-3 with HCl solution (0.1 M). The mixture was extracted with EtOAc (3 x 10 mL). The organic layers were washed with H_2O and brine, dried over $Na_2S_2O_4$, concentrated under vacuum to provide the intermediate. To a solution of the intermediate acid, Phenylalanine amide hydrochloride (44 mg, 0.22 mmol, 1 equiv.), HOBt (41 mg, 0.26 mmol, 1.2 equiv.) and EDC.HCl (50 mg, 0.26 mmol, 1.2 equiv.) in dry DMF was added drop by drop DIPEA (100 µL. 0.55 mmol, 2.5 equiv.) at 0°C and stirred for 5 hours. The mixture was diluted with water, extracted with EtOAc (3x 10 mL), washed with citric acid (10%), K_2CO_3 (10%), NaCl sat. then dried over Na_2SO_4, filtered and concentrated under vacuum. The product was purified by silica column chromatography using as eluant CH_2Cl_2/MeOH: 94/6 to obtain **4** (57 mg, 0.12 mmol, 46%) as a white solid. mp = 110-112 °C; Rf = 0.3 (c-CH_2Cl_2/MeOH: 95/5); ^{1}H NMR (300 MHz, CD_3OD): δ 7.33-7.20 (m, 10H), 5.21 (d, *J*= 16.8 Hz, 1H), 5.11 (d, J = 16.8 Hz, 1H), 4.75 (m, 2H), 4.43 (m, 2H), 4.36-4.30 (m, 2H), 3.73 (s, 3H), 3.21 (dd, *J* = 14.0 and 5.6 Hz 1H), 3.12 (dd, *J* = 19.0 and 5.4 Hz, 1H), 3.0 (dd, *J* = 14.0 and 8.4 Hz, 1H), 2.82 (dd, *J* = 13.7 and 8.6 Hz, 1H), 1.36 (s, 9H); ^{13}C NMR (75 MHz, CD_3OD): 174.1, 173.0, 172.9, 167.0, 138.6, 137.9, 130.4, 130.3, 130.2, 130.0, 129.7, 129.4, 128.0, 127.7, 68.9, 57.3, 55.5, 53.2, 52.8, 39.6, 38.4, 36.2, 35.7, 28.7; ^{19}F NMR (188, MHz, CD_3OD): δ -153.8 (s); IR (neat): υ_{max} 3200, 3192, 2856, 1510, 1423, 1289 cm^{-1}; HRMS (ESI-TOF, ion polarity positive) *m/z* $C_{29}H_{35}FN_6O_6$ $[M+H]^+$ cal. 583.2449, found 583.2445.

tert-butyl ((5-fluoro-1-(2-hydroxyethyl)-1H-1,2,3-triazol-4-yl)carbamate ***5.***



To a solution of **2a** (50 mg, 0.165 mmol, 1 equiv.) in methanol (0.4 M) was added $NaBH_4$ (19 mg, 0.5 mmol, 3 equiv.) at 0°C. The mixture was stirred for 2 hours at 0°C. After completion, the mixture was diluted with water (30 mL), extracted with EtOAc (3x 10 mL). The combined organic layers were washed with water, brine and dried over Na_2SO_4. filtered and concentrated under vacuum to provide the product **5** as a yellow liquid (59 %). The crude product was used without further purification. Rf = 0.2 (c-Hex/EtOAc 6/4); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.06 (br s, 1H), 4.27-4.02 (m, 4H), 4.00 (t, ^3J = 4.6 Hz, 2H), 1.37 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 166.0, 154.0 (^1J(C,F) = 256,9 Hz), 124.8 (^2J(C,F) = 10.4 Hz), 79.9, 60.3, 49.3, 34.2, 28.3; ^{19}F NMR ($CDCl_3$, 188 MHz): δ -154.0 (s, 1F); HRMS (ESI-TOF, ion polarity positive): m/z C10H18N4O3F [M+H]+ cal. 261.1318, found 261.1321

III. Crystallographic details:

X-ray diffraction experiments

Crystal samples of **2a** used in this study appeared after 72 h of slow evaporation at room temperature of supersaturated solution of cyclohexane/EtOAc/CH_2Cl_2. A colorless crystal of roughly cubic shape appears after **2a** h of evaporation at room temperature. The data of **2a** were collected at 100.0(1) K on a RIGAKU *XtaLabPro* diffractometer equipped with a Mo microfocus sealed tube *MM003* generator coupled to a double-bounce confocal Max-Flux® multilayer optic (wavelength λ = 0.71073 Å), a kappa goniometer, a HPAD *PILATUS3R 200K* detector, and an Oxford Cryosystems Series 800 nitrogen flow gas system. The data spots were recorded as 14 ω-scans for a total of 4068 frames of 0.25° oscillation each in order to reconstruct accurate three-dimensional diffracted intensity peak profiles to the θ_{max} = 45.2° high angles. The exposure time was of 15 seconds per frame. 75864 reflections were collected up to a resolution of $\sin\theta_{max}/\lambda$ = 1.00 $Å^{-1}$. The *CrysAlisPro 1.171.41.118a* [1] program was used for sorting and averaging data to 12529 unique reflections revealing the good quality of the measurements (internal R_{int} = 0.023) with data redundancy of 6.7. The crystal structure of the **2a** compound was solved using the SHEXL-T program[2] and refined using SHELX-L[3] implemented in the Olex2[4] package. Nonetheless, neither empirical absorption correction using spherical harmonics, implemented in SCALE3 ABSPACK scaling algorithm,[1] nor a spherical or even a numerical absorption correction based on gaussian integration over a multifaceted crystal model could reduce the positive electron density residual located nearby the fluoride atom under the influence of three vicinal oxygen atoms at distances comprised between 3.16 Å and 3.68Å. Refining the displacements of the F atom (and further more selected atoms) anharmonically in olex2.refine was useless. The residual peak could only be decreased from 1.7e/$Å^3$ to less than 0.8 e/$Å^3$ by truncating the resolution limit at $\sin\theta_{max}/\lambda$ = 1.16 $Å^{-1}$.

The Hansen-Coppens model[5] was used for the electron density refinement by means of the MOPRO program[6, 7] using all the structure factors F sorted and averaged by the SORTAV program with no statistical standard deviations cut-off ($I > 0$). The VMOPRO[6, 7] computer program was run to map out the static deformation density maps and to generate the electrostatic potential around **2a** in the crystal. This last property exhibits the nucleophilic (negative potential) and electrophilic (positive potential) regions of the molecule. Thus it is a good indicator of the chemical reactivity. Table 2 summarizes the crystal data and the structure refinement statistics.

Non-periodic theoretical calculations (isolated molecule) were performed using GAUSSIAN09.[8] All calculations were conducted at B3LYP/6-311++(2d,2p) level of theory. For better assessment of the robustness, the first calculations were also conducted with the standard cc-PVTZ basis set with no major difference in the outcomes. Self-consistent field computation was considered to have converged once the population matrix elements variation did not exceed 10^{-8} on average (RMS), and the change in energy was less than 10^{-6} Hartree. Geometry optimization was achieved when the resulting inter-nuclear forces in the system did not exceed 10^{-5} Hartrees/bohr (RMS) and 1.5 10^{-5} Hartrees/bohr (max) while the nuclei displacements were less than 6.0 10^{-5} Bohr (max) and 4.0 10^{-5} bohr (RMS). The total energies are estimated in *hartrees* (1 H = 1 atomic unit (a.u.) = 2625.5 kJ/mol). The experimental molecular geometries were systematically used as initial guess and optimized at B3LYP/6-311++(2d,2p) level of theory.

CCDC 2141412 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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8 Gaussian 09, Revision A.1, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Montgomery, Jr., J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J. M. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, Ö. Farkas,

J. B. Foresman, J. V. Ortiz, J. Cioslowski, and D. J. Fox, Gaussian, Inc., Wallingford CT, 2009.

X-ray crystal

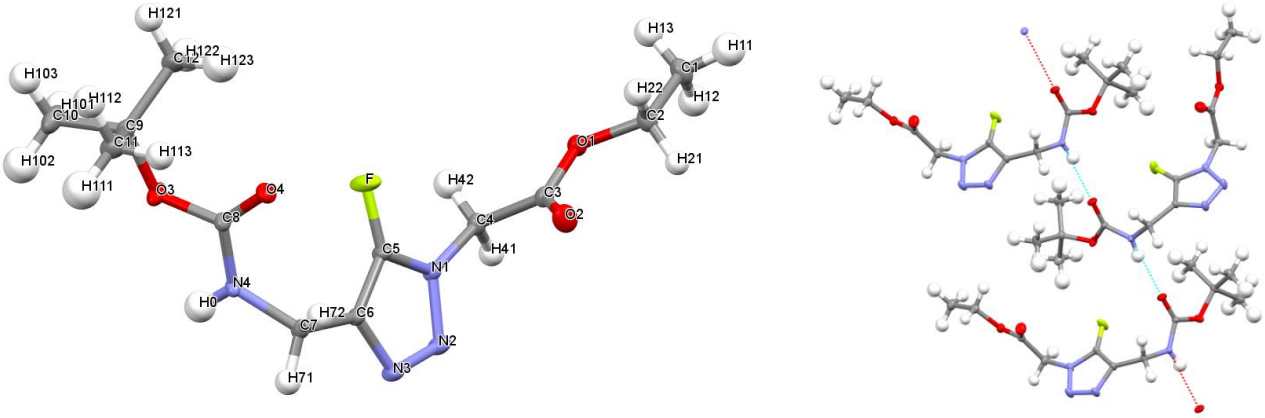
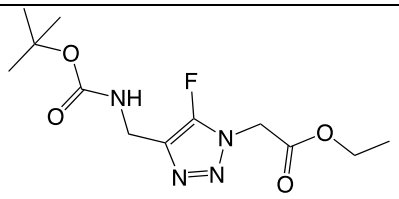


Table 1. Crystal data and structure refinement for **2a**

Identification code		**2a**  ethyl 2-(4-(((*tert*-butoxycarbonyl)amino)methyl)-5-fluoro-1*H*-1,2,3-triazol-1-yl)acetate	
Empirical formula		C_{12} H_{19} F N_4 O_4	
Formula weight		302.31	
Temperature (K)		100.0(3)	
Diffractometer		RIGAKU *XtaLabPro* Mo *MM003* generator with a HPAD *PILATUS3R 200K* detector	
Wavelength (Å)		0.71073	
Crystal system, space group		Monoclinic, $P2_1/n$	
Unit cell dimensions	a (Å) b c β (°)	5.8041(1) 27.2425(4) 9.8185(2) 106.473(2)	
Volume (Å^3)		1488.76(5)	
Z, Calculated density (Mg/m^3)		4, 1.349	
Absorption coefficient (mm^{-1})		0.110	
F(000)		640	
Crystal size (mm)		0.267 x 0.244 x 0.222	
θ range for data collection		2.630 - 45.460	
Limiting indices		-11 ≤ h ≤ 11, -54 ≤ k ≤ 54, -19 ≤ l ≤ 19	0 ≤ h ≤ 11, 0 ≤ k ≤ 54, -19 ≤ l ≤ 18
Reflections collected / unique		75864 / 12529	
Rint		0.0230	0.0 [#]
Completeness to θ_{full} (%)		99.8	99.5
Absorption correction		Multi-scan	
Tmax, Tmin		1.000, 0.656	
Refinement method		Full-matrix least-squares on F^2 IAM	MM
Data / restraints / parameters		12529 /0/ 266	12528 /0/ 266
Goodness-of-fit on F^2		1.029	3.237*
Final R indices [I>2σ(I)]	R1 wR2	0.0356, 0.1036	0.0347, 0.0562
R indices (all data)	R1 wR2	0.0420, 0.1070	0.0347, 0.0565
Largest diff. peak and hole (e.Å^{-3})		1.694/ -0.390	1.350/ -0.353

[#]*Equivalent reflexions were averaged by SORTAV before input into MOPRO.*
[*]*GOF(I) computed assuming all parameters refined in MM (915)*

Table 2. Integrated atomic charges (in e unit) from experiment and theory.

atom	**experiment**	**Theory (isolated)**	**Theory (periodic)**		atom	**experiment**	**Theory (isolated)**	**Theory (periodic)**
F	**9.65**	**9.58**	9.63		C12	6.03	5,86	6.10
O1	**8.99**	**9.12**	8.84		H11	1.03	0,95	0.93
O2	**9.02**	**9.00**	8.89		H12	0.99	1,01	0.58
O3	**8.93**	**9.02**	8.81		H13	0.93	0,97	0.89
O4	**9.01**	**9.06**	8.96		H21	0.95	1,00	0.93
N1	**7.69**	**7.72**	7.55		H22	0.96	1,02	0.92
N2	**7.06**	**7.08**	7.11		H41	0.89	1.01	0.86
N3	**7.36**	**7.51**	7.42		H42	0.73	1.06	0.89
N4	**8.17**	**8.11**	7.96		H71	0.97	1.01	0.94
C1	5.96	5.80	6.09		H72	0.81	1.03	0.88
C2	5.77	5.53	5.71		H101	0.89	1.00	1.00
C3	4.57	5.05	4.72		H102	0.94	1.05	1.00
C4	5.86	5.54	5.87		H103	1.00	1.04	0.93
C5	3.27	4.13	5.32		H111	0.84	1.01	0.95
C6	5.71	5.83	5.69		H112	1.04	1.04	0.91
C7	5.88	5.47	3.58		H113	1.06	1.06	0.96
C8	4.23	4.51	4.39		H121	1.05	1.04	0.97
C9	5.70	5.59	5.66		H122	0.90	1.04	0.91
C10	3.69	5.83	5.63		H123	0.77	1.01	0.95
C11	5.94	5.59	6.08		**H0**	**0.48**	**0.56**	**0.53**

Table 3. Theoretical electrostatic potential (isovalue surface cut-off as in Figure 3), dipole magnitudes (in Debye, last column, first line) and total energies (in a.u., last column, second line) for the chosen molecules given in first column.

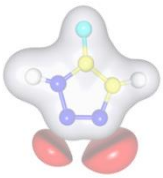
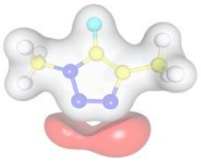
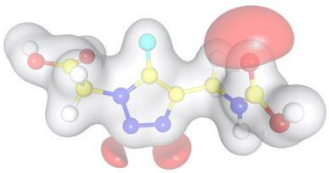
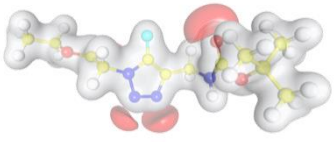
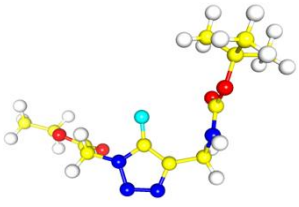
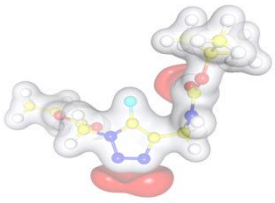
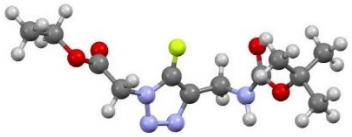
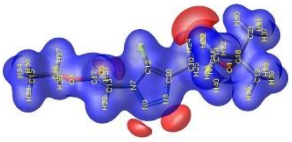
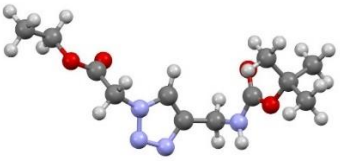
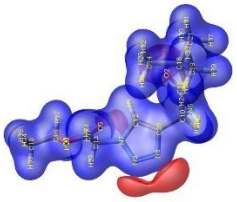
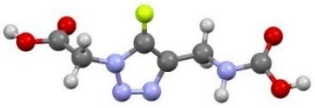
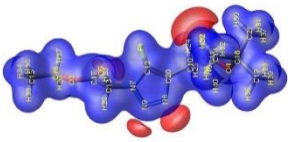
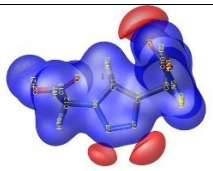
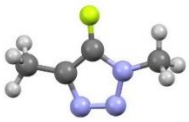
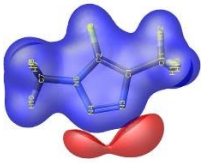
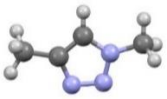
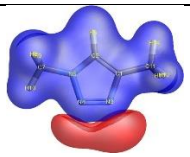
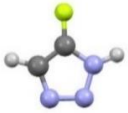
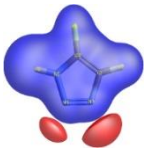
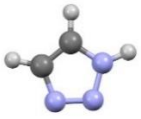
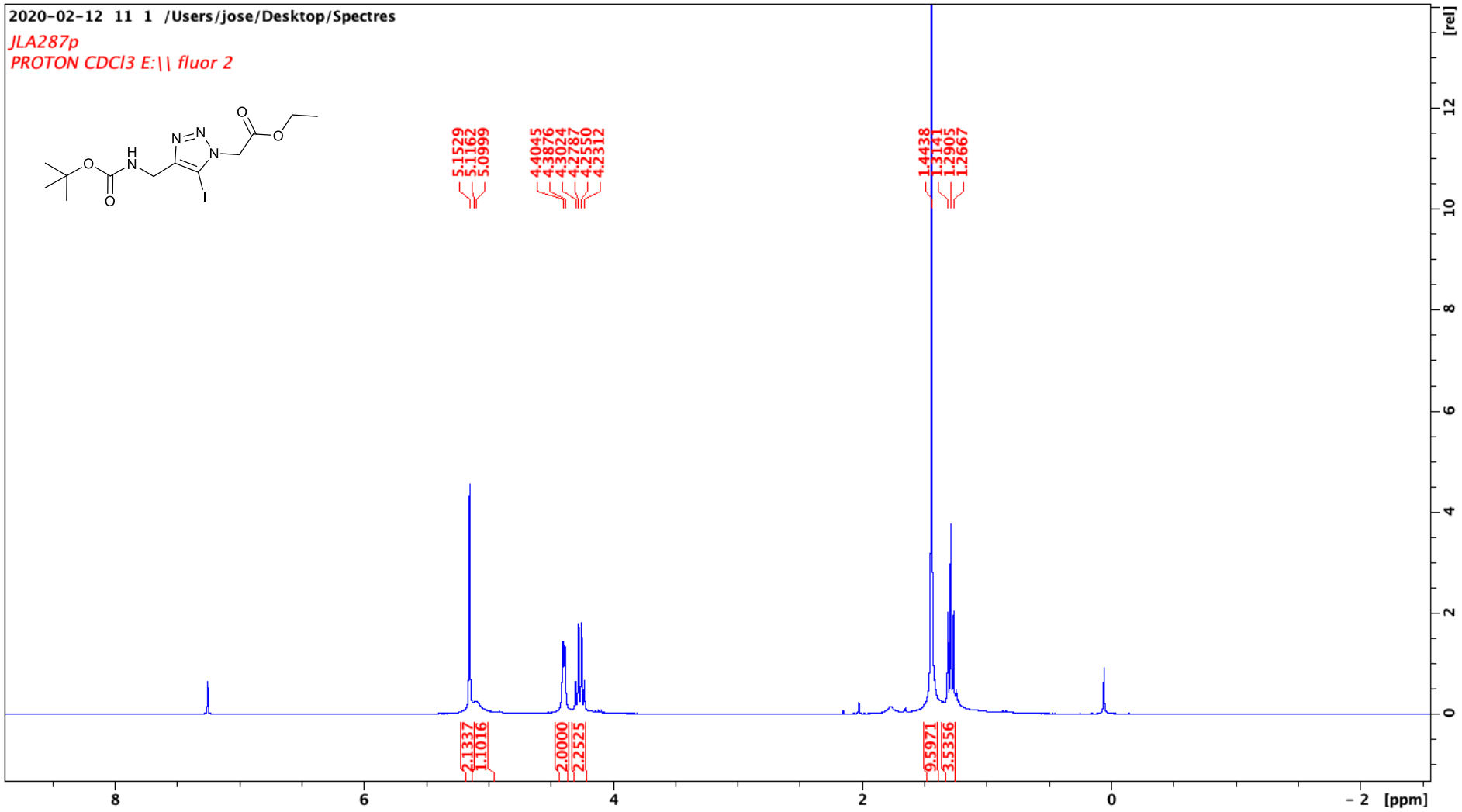
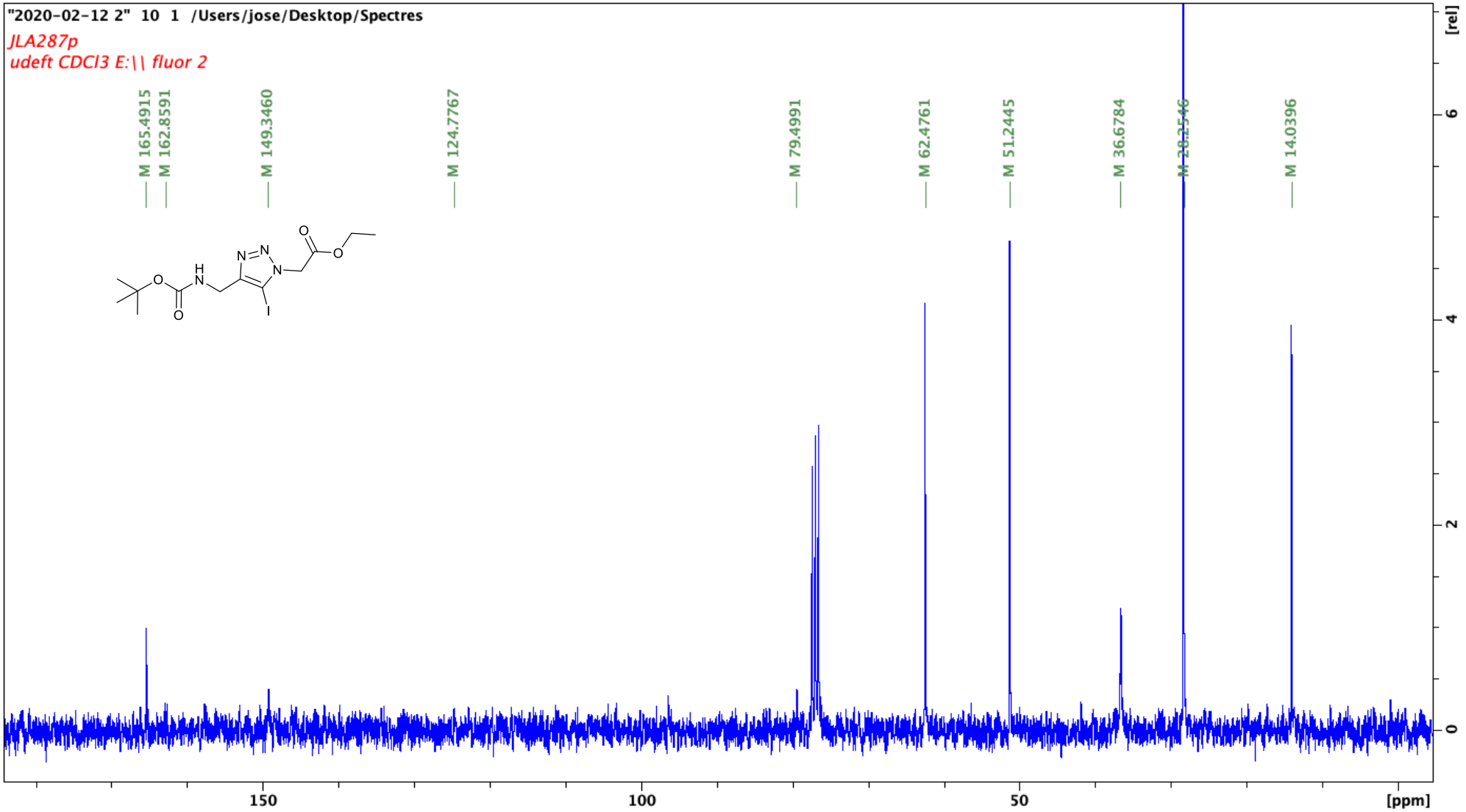
A **$C_2N_3H_2F$**			**3.2 D** **-341.6 a.u.**
B **$C_4N_3H_6F$**			**3.3 D** **-420.2 a.u.**
C **$C_6N_4H_7O_4F$**			**2.9 D** **-852.9 a.u.**
2a **Optimized geometry**			**3.8 D** **-1088.8 a.u.**
2a **Experimental geometry**			**4.8 D** **-1088.5 a.u.**

Table 4. Theoretical electrostatic potential of 5-H and 5-F triazoles

1			**3.784 D** **-1088.817 a.u.** **_6-311Gpp-2d2p**
2			**4.242 D** **-989.553 a.u.** **_6-311Gpp-2d2p**
3			**2.909 D** **-852.869 a.u.** **_6-311Gpp-2d2p**
4			**3.048 D** **-753.612 a.u.** **_6-311Gpp-2d2p**
5			**3.291 D** **-420.218 a.u.** **_6-311Gpp-2d2p**
6			**3.291 D** **-420.218 a.u.** **_6-311Gpp-2d2p**
7			**3.175 D** **-341.575 a.u.** **ccPVTZ**
8			**4.353 D** **-242.312 a.u.** **ccPVTZ**

VI. NMR spectra

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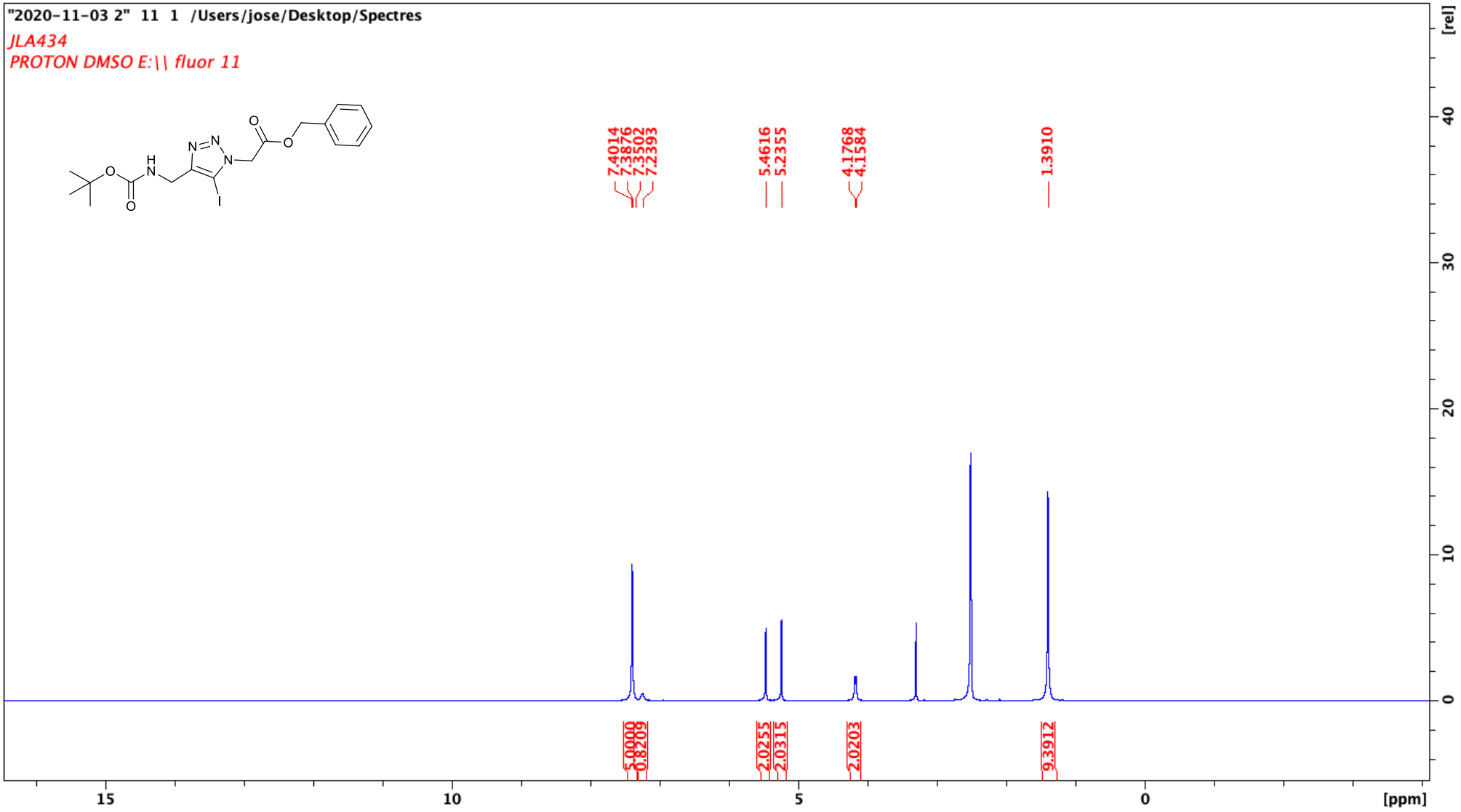
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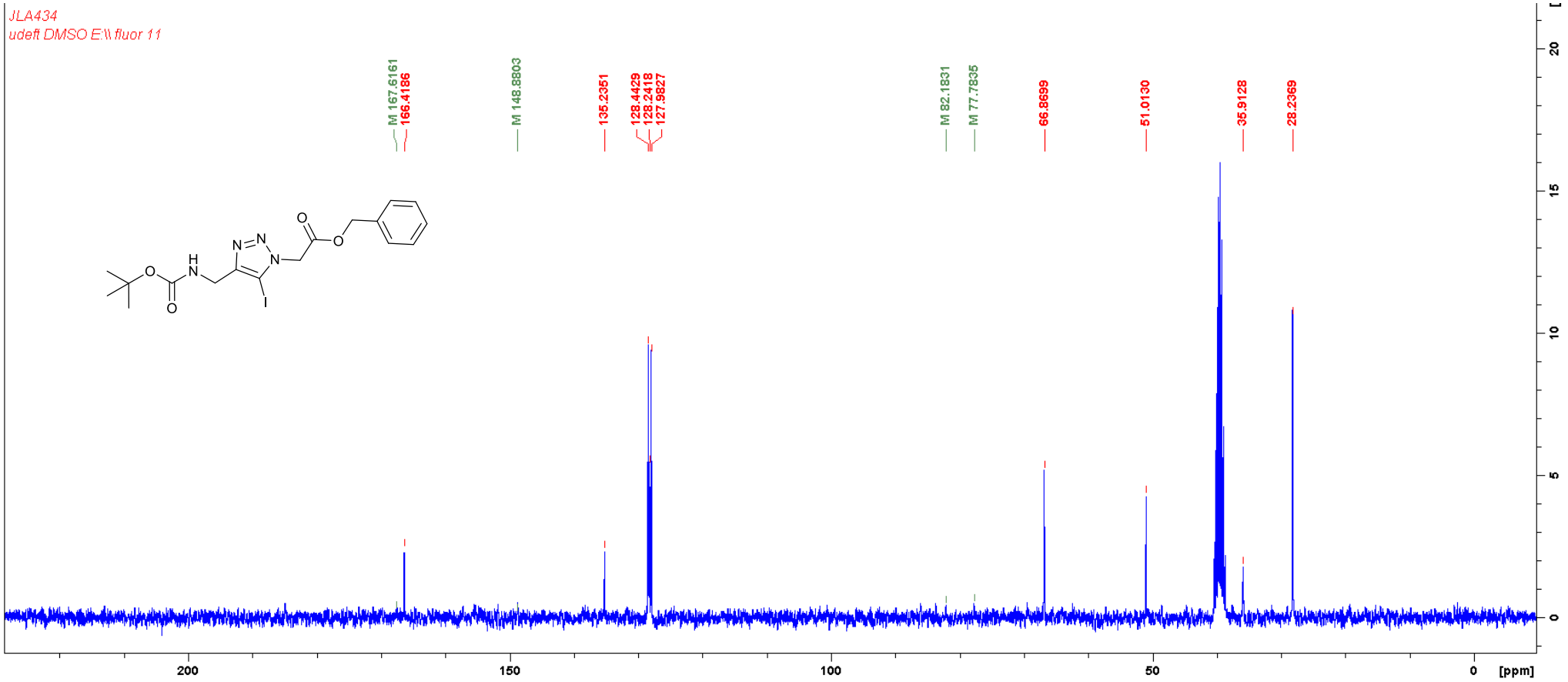
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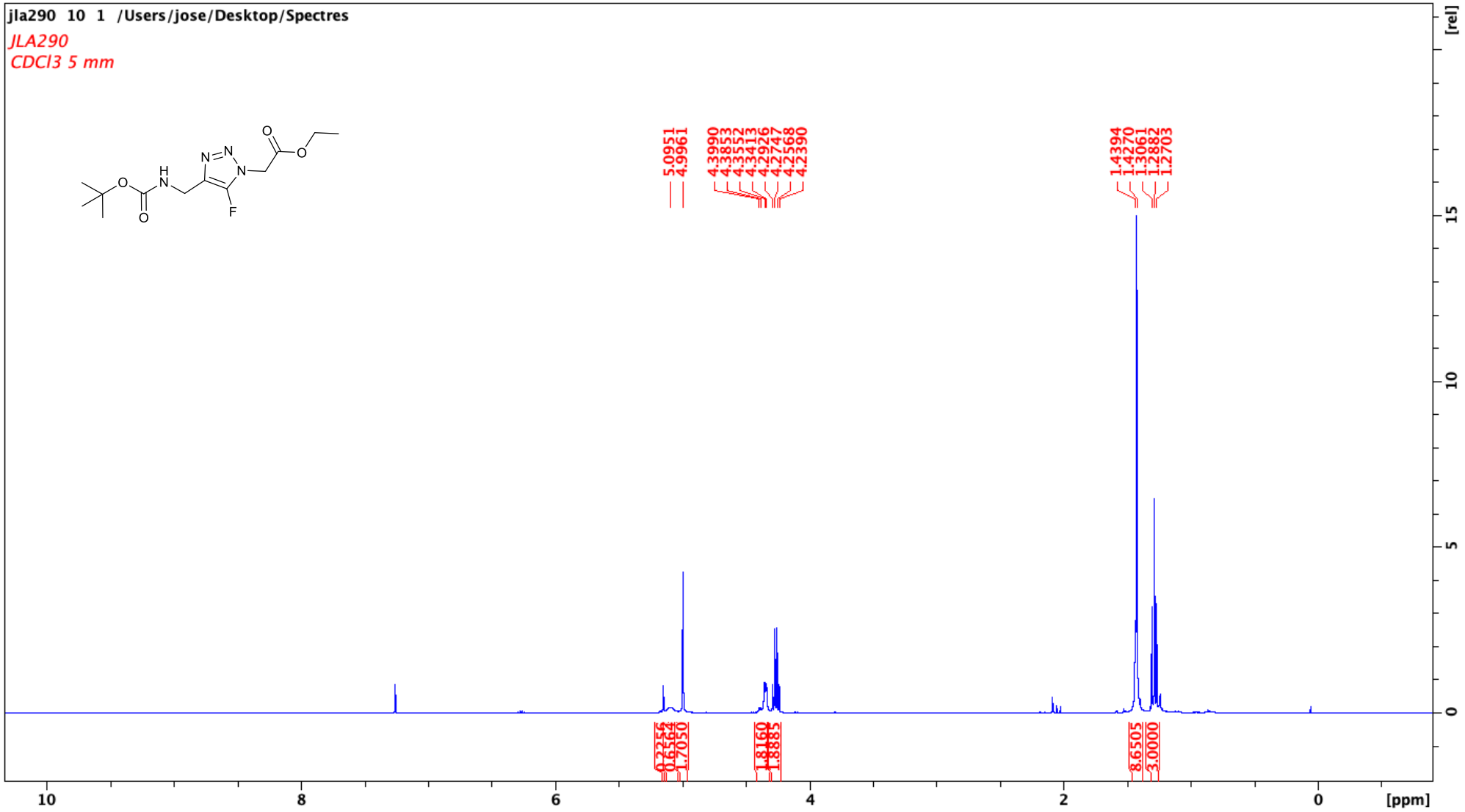
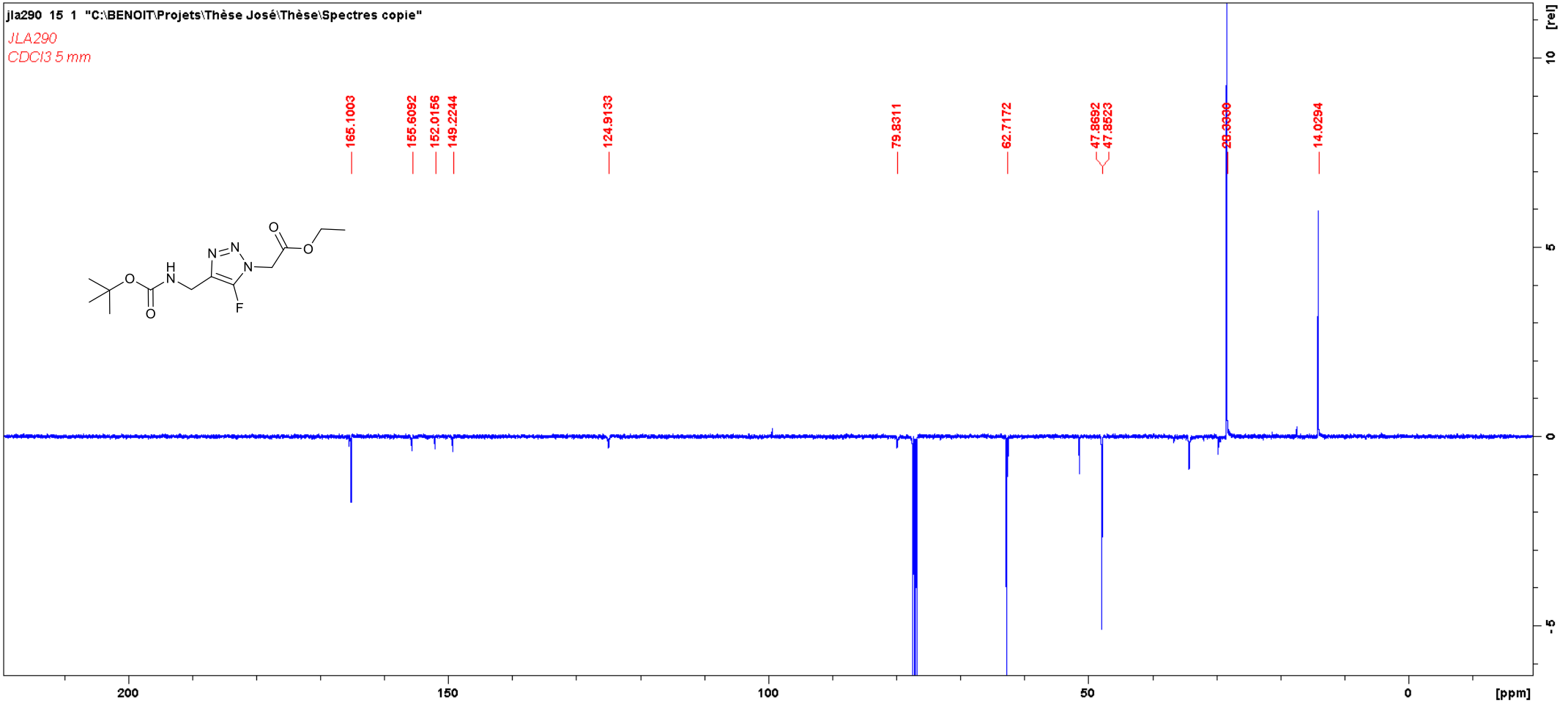
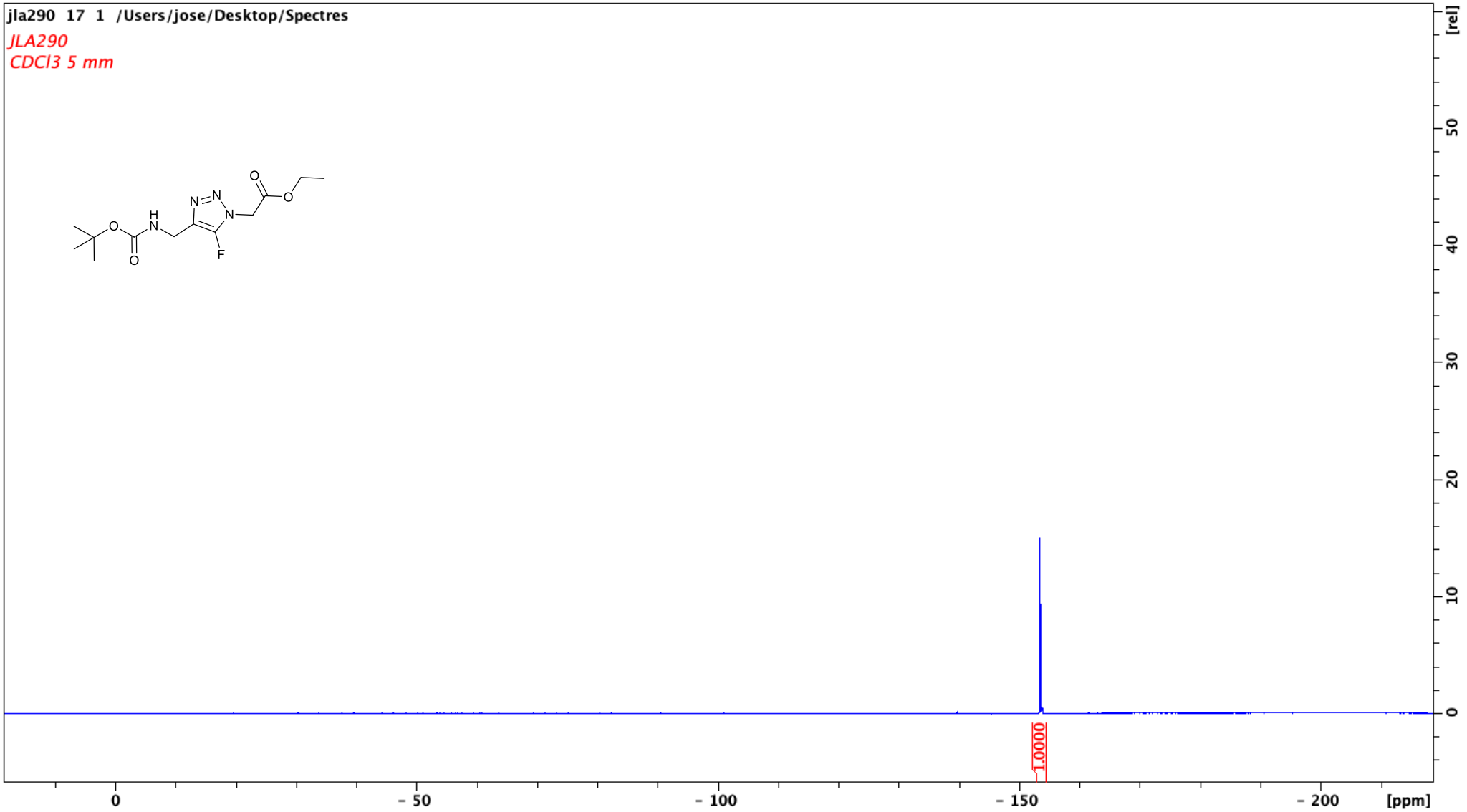
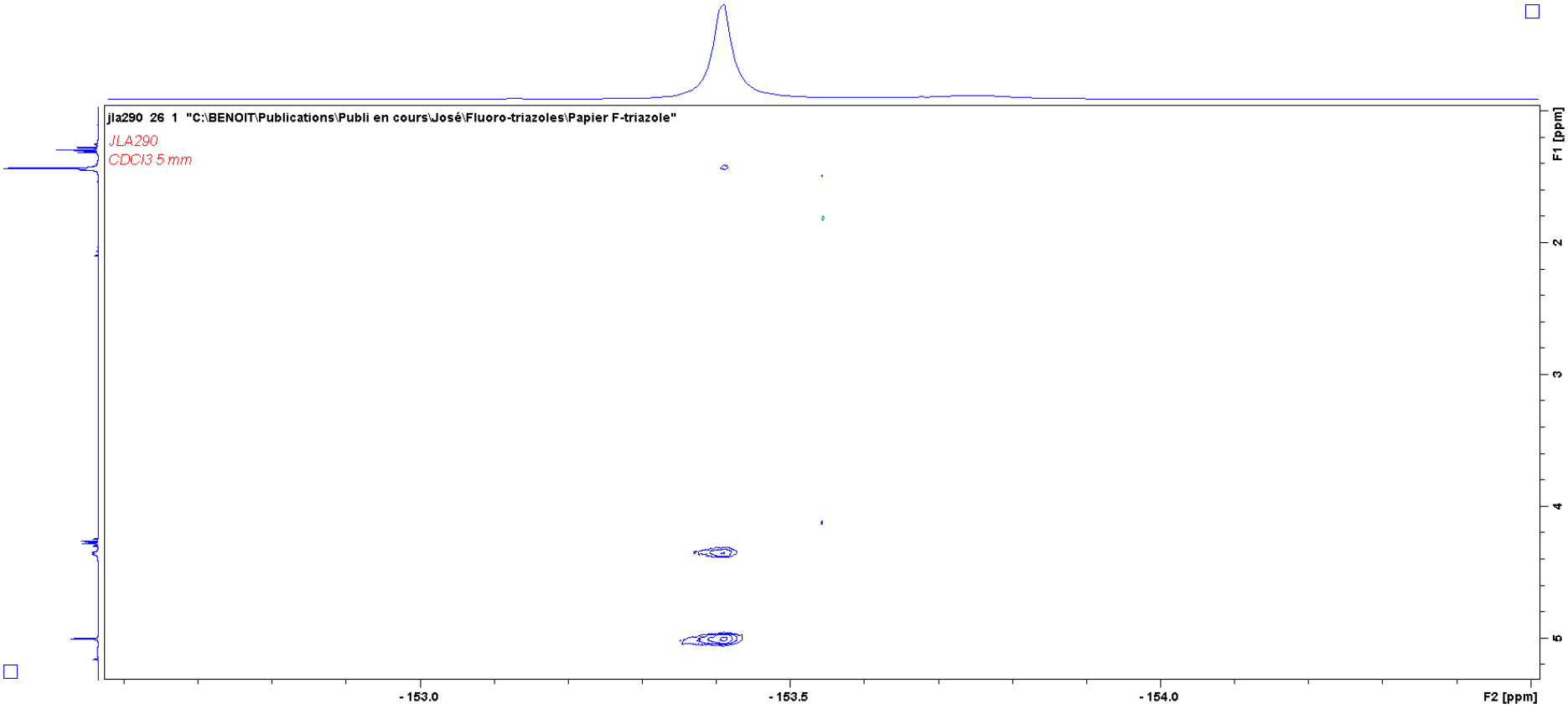
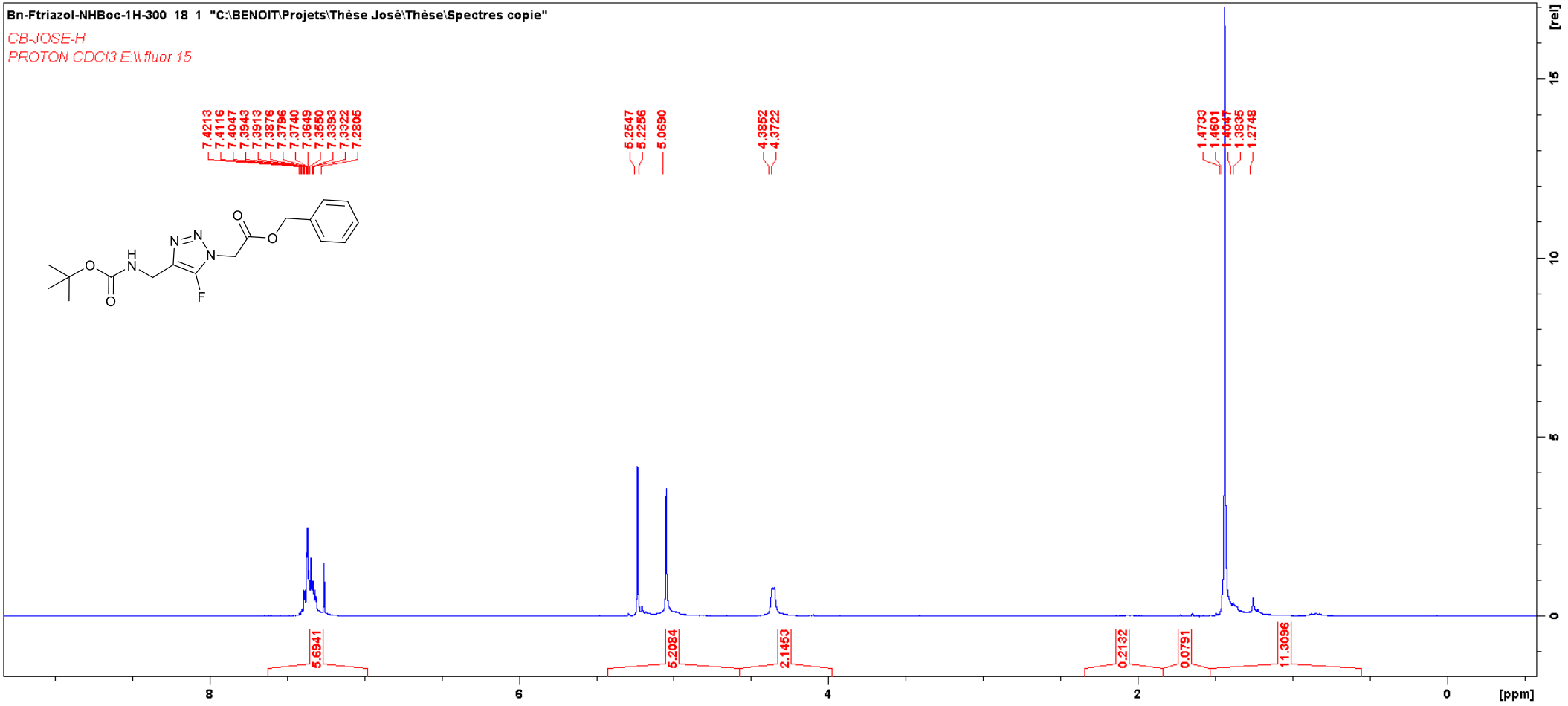

jla290 10 1 /Users/jose/Desktop/Spectres
JLA290
CDCl3 5 mm
5.0951
4.9961
4.3990
4.3853
4.3552
4.3413
4.2926
4.2747
4.2568
4.2390
1.4394
1.4270
1.3061
1.2882
1.2703
0.2256
0.6564
1.7050
1.8160
1.8882
8.6505
3.0000
10
8
6
4
2
0
[ppm]
[rel]
15
10
5
0

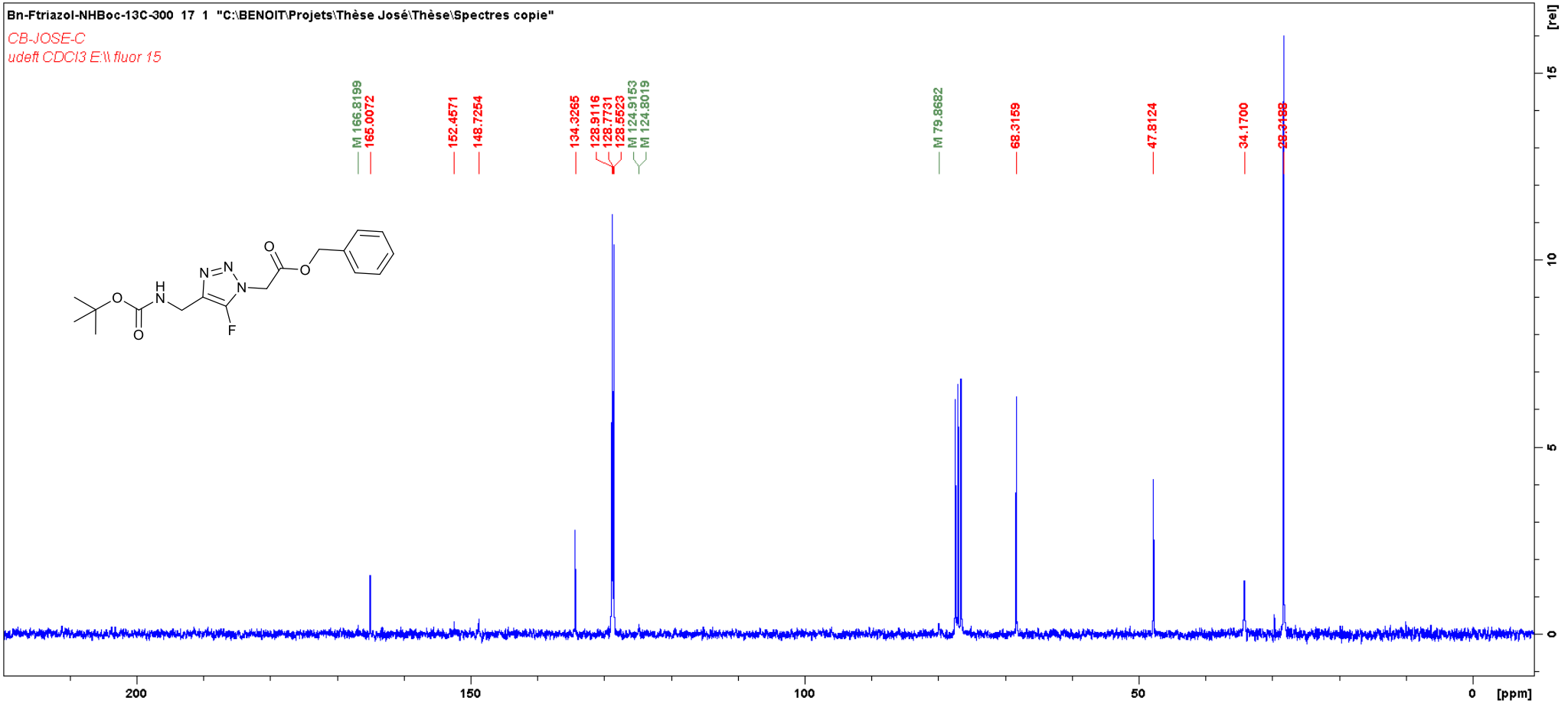

jla290 15 1 "C:\BENOIT\Projets\Thèse José\Thèse\Spectres copie"
JLA290
CDCl3 5 mm
165.1003
155.6092
152.0156
149.2244
124.9133
79.8311
62.7172
47.8692
47.8523
29.0330
14.0294
[rel]
10
5
0
-5
200
150
100
50
0
[ppm]

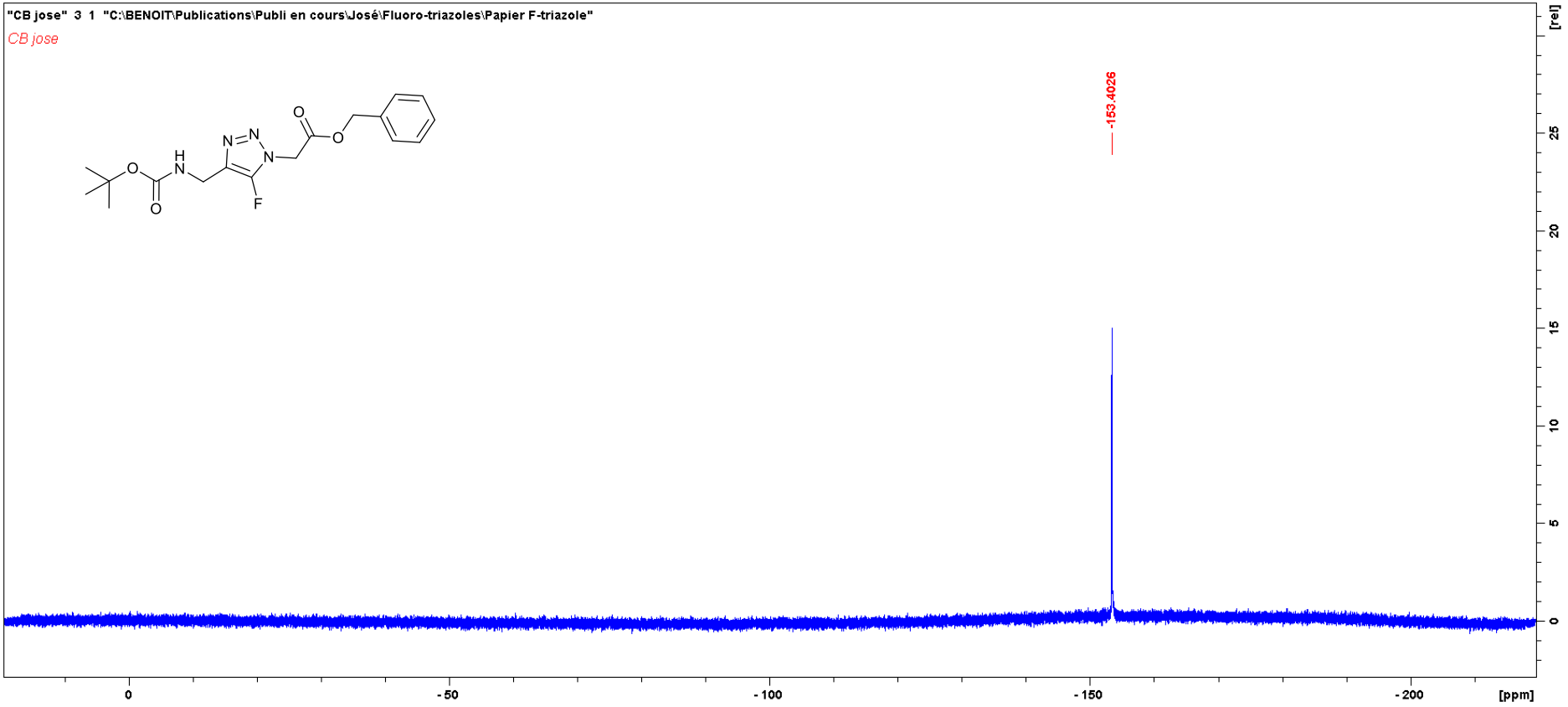

jla290 17 1 /Users/jose/Desktop/Spectres
JLA290
CDCl3 5 mm
O
O
N
N
N
H
N
O
O
F
[rel]
50
40
30
20
10
0
1.0000
0
- 50
- 100
- 150
- 200
[ppm]

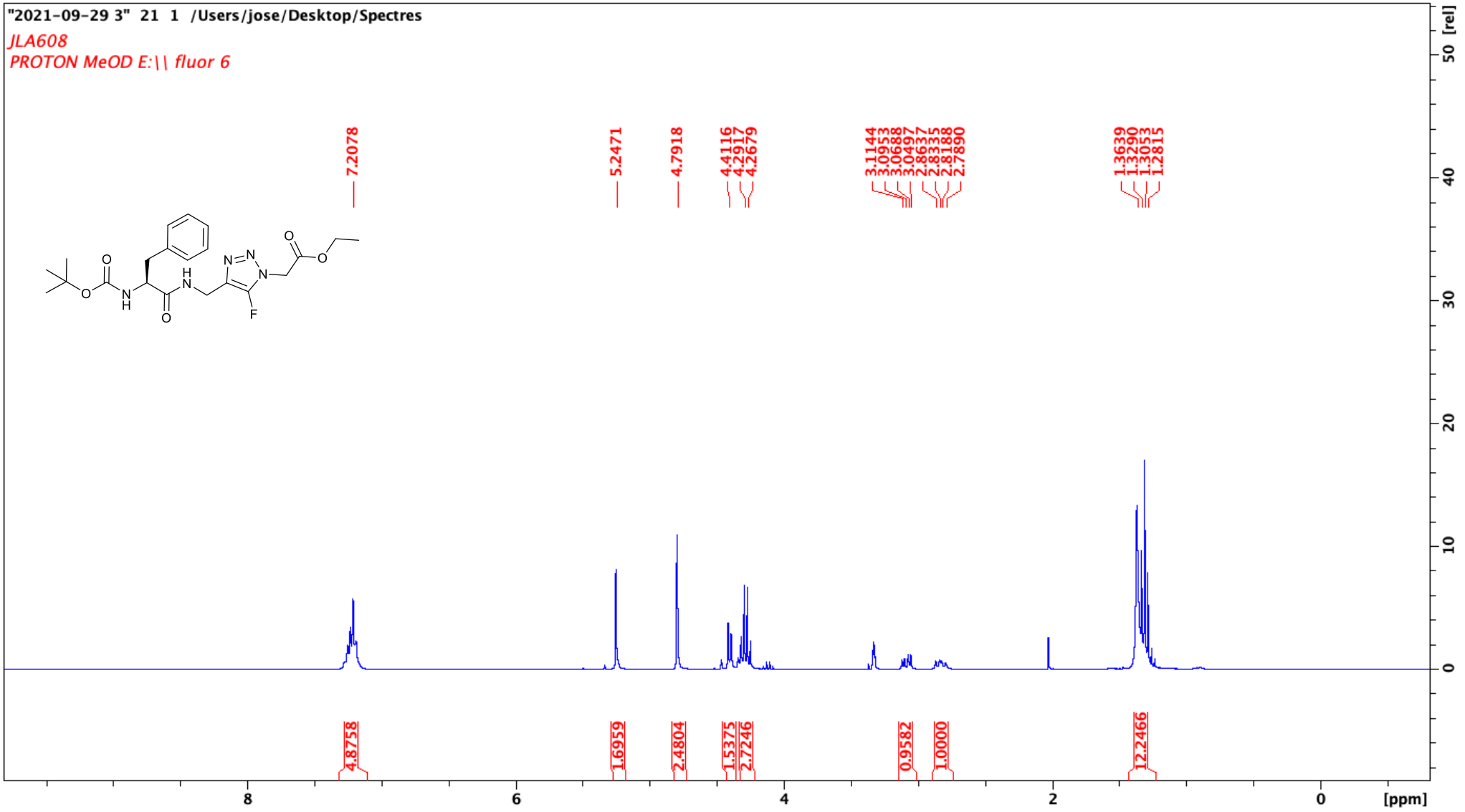
^{19}F-^{1}H HOESY of **2a**

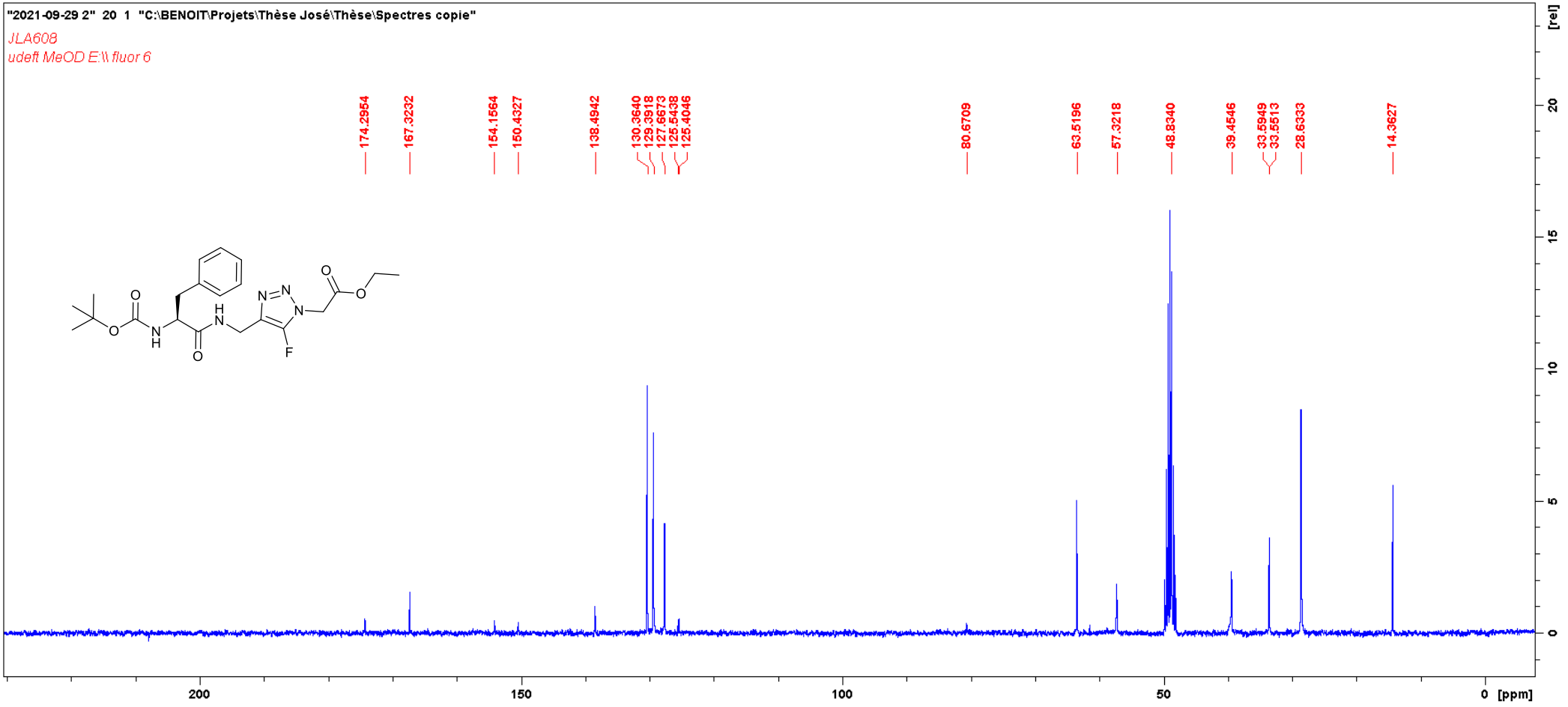


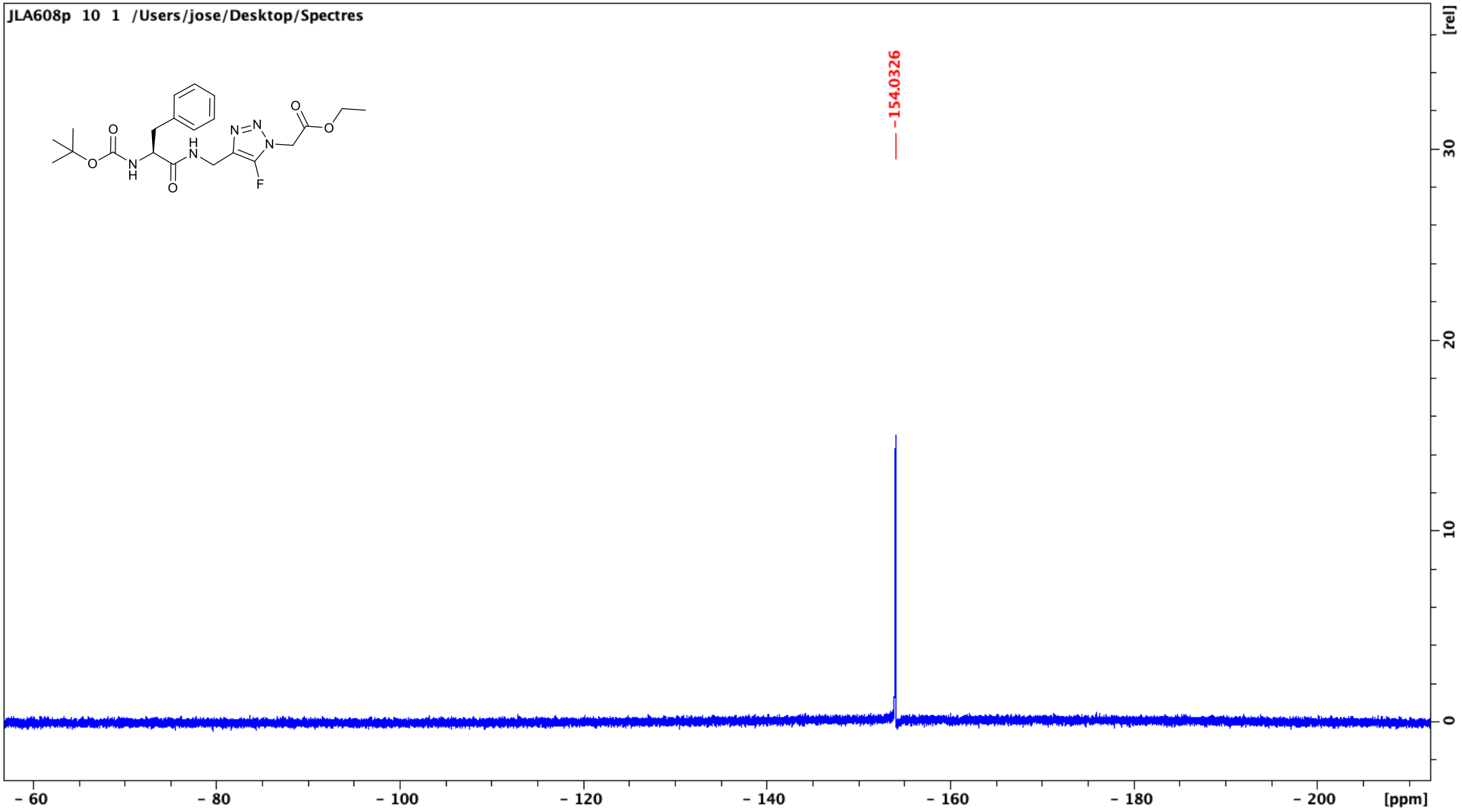

Bn-Ftriazol-NHBoc-1H-300 18 1 "C:\BENOIT\Projets\Thèse José\Thèse\Spectres copie"
CB-JOSE-H
PROTON CDCl3 E:\\ fluor 15
7.4213
7.4116
7.4047
7.3943
7.3913
7.3876
7.3796
7.3740
7.3649
7.3650
7.3393
7.3322
7.2805
5.2547
5.2256
5.0690
4.3852
4.3722
1.4733
1.4601
1.4047
1.3835
1.2748
5.6941
5.2084
2.1453
0.2132
0.0791
11.3096
8
6
4
2
0
[ppm]
[rel]
15
10
5
0

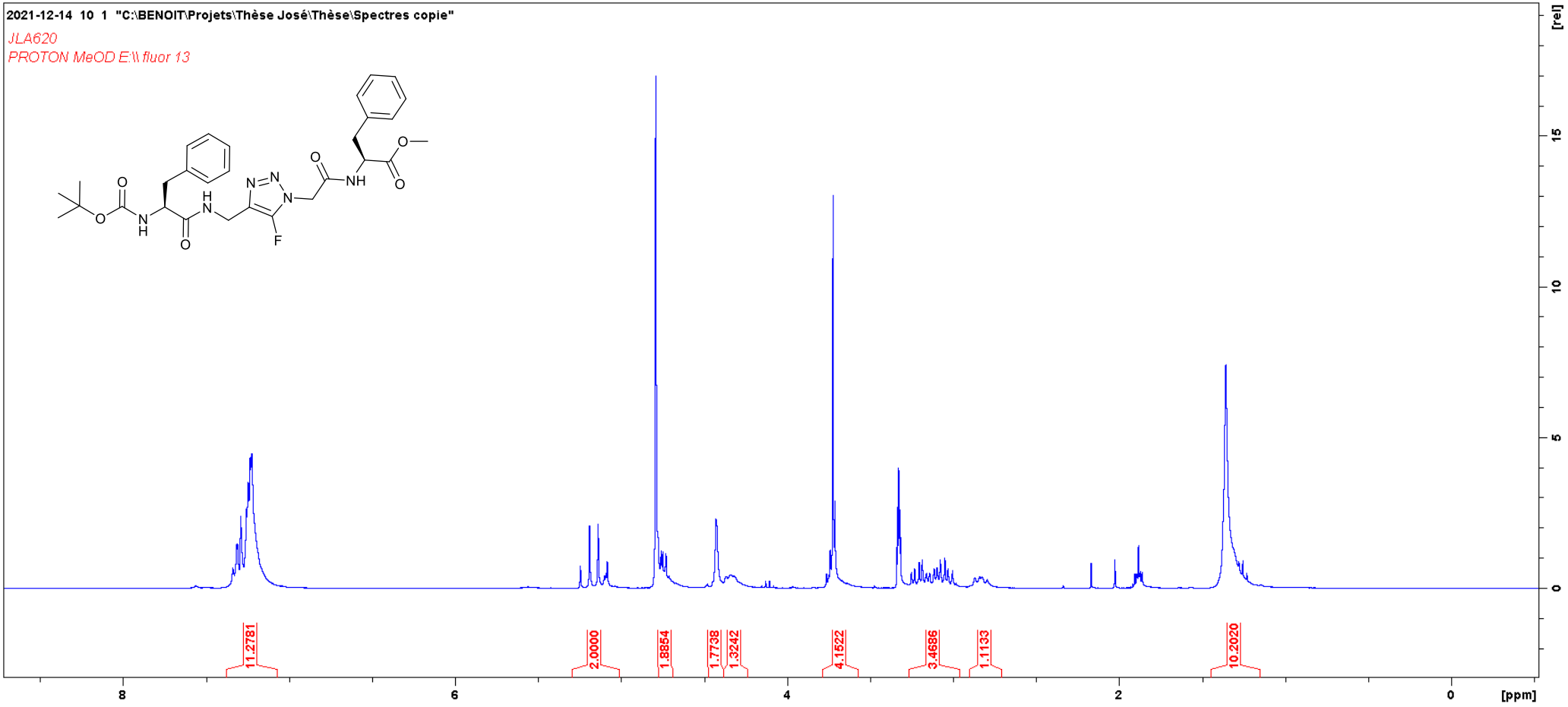

Bn-Ftriazol-NHBoc-13C-300 17 1 "C:\BENOIT\Projets\Thèse José\Thèse\Spectres copie"
CB-JOSE-C
udeft CDCl3 E:\\ fluor 15
M 166.8199
165.0072
152.4571
148.7254
134.3265
128.9116
128.7731
128.5523
M 124.9153
M 124.8019
M 79.8682
68.3159
47.8124
34.1700
28.3188
[rel]
15
10
5
0
200
150
100
50
0
[ppm]

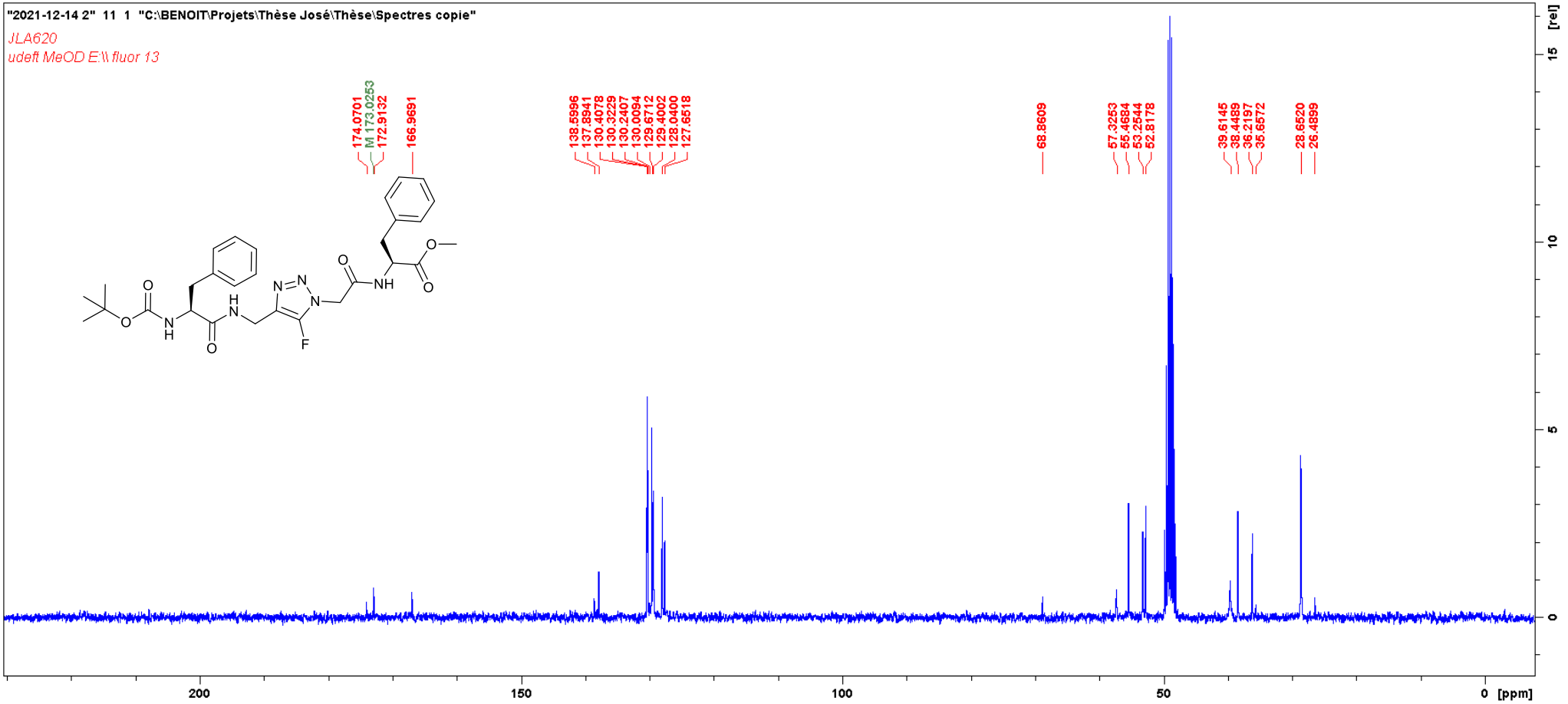

"CB jose" 3 1 "C:\BENOIT\Publications\Publi en cours\José\Fluoro-triazoles\Papier F-triazole"
CB jose
-153.4026
[rel]
25
20
15
10
5
0
0
-50
-100
-150
-200
[ppm]

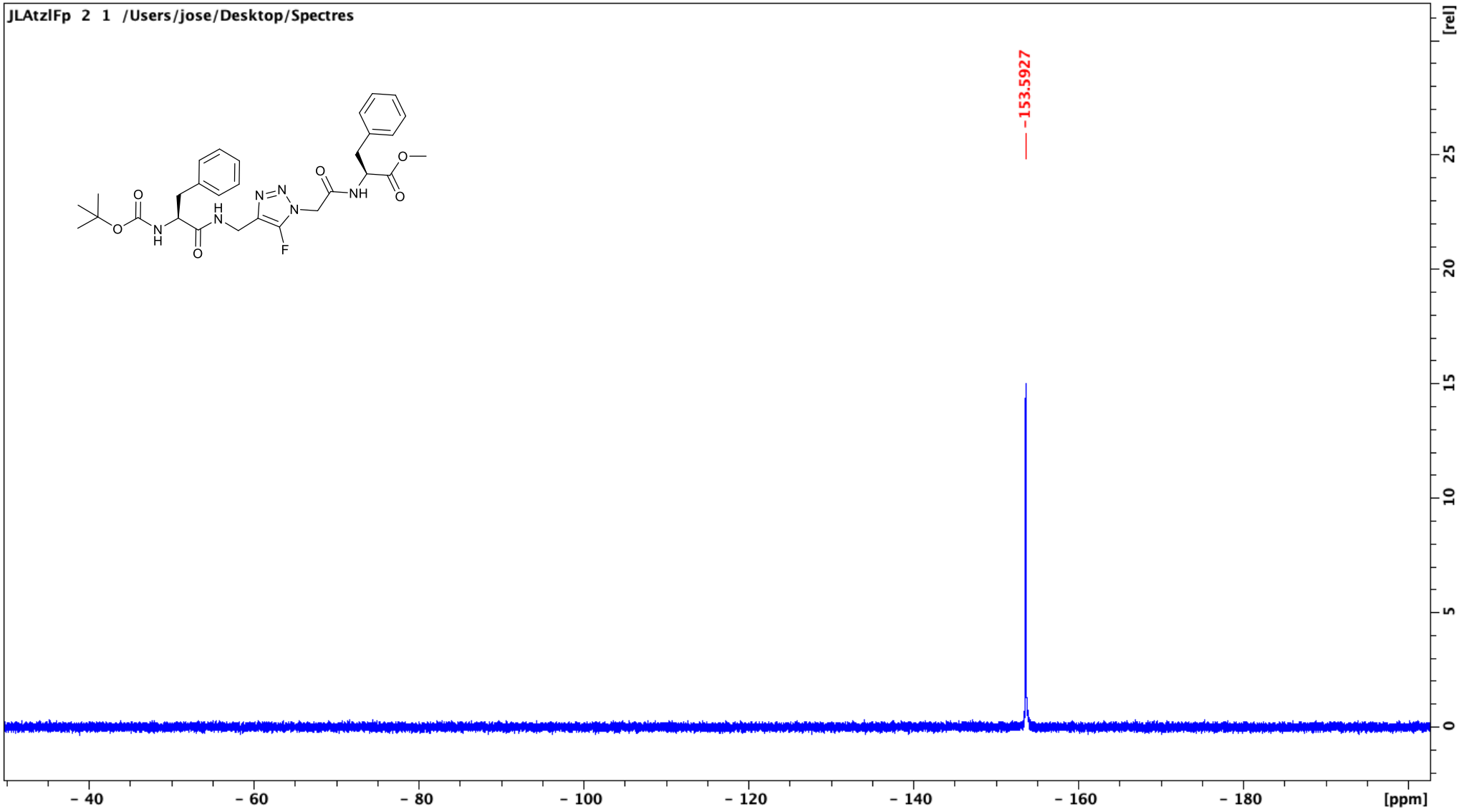

"2021-09-29 3" 21 1 /Users/jose/Desktop/Spectres
JLA608
PROTON MeOD E:\\ fluor 6
7.2078
5.2471
4.7918
4.4116
4.2917
4.2679
3.1144
3.0953
3.0688
3.0497
2.8637
2.8335
2.8188
2.7890
1.3639
1.3290
1.3053
1.2815
4.8758
1.6959
2.4804
1.5375
2.7246
0.9582
1.0000
12.2466
8
6
4
2
0
[ppm]
50 [rel]
40
30
20
10
0


"2021-09-29 2" 20 1 "C:\BENOIT\Projets\Thèse José\Thèse\Spectres copie"
JLA608
udeft MeOD E:\\ fluor 6
174.2954
167.3232
154.1564
150.4327
138.4942
130.3640
129.3918
127.6673
125.5438
125.4046
80.6709
63.5196
57.3218
48.8340
39.4546
33.5949
33.5513
28.6333
14.3627
[rel]
200
150
100
50
0 [ppm]

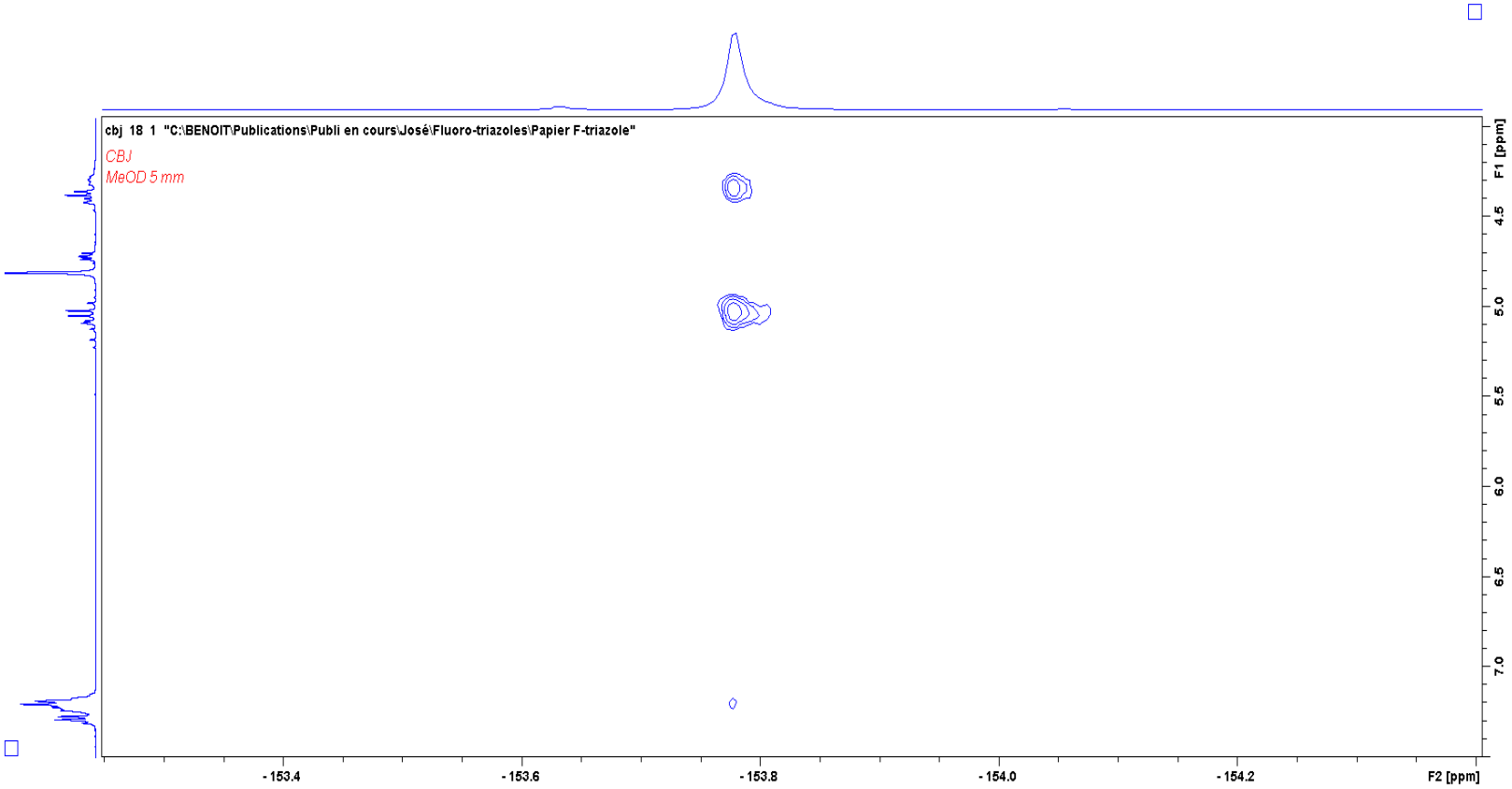

JLA608p 10 1 /Users/jose/Desktop/Spectres
-154.0326
[rel]
30
20
10
0
- 60
- 80
- 100
- 120
- 140
- 160
- 180
- 200
[ppm]

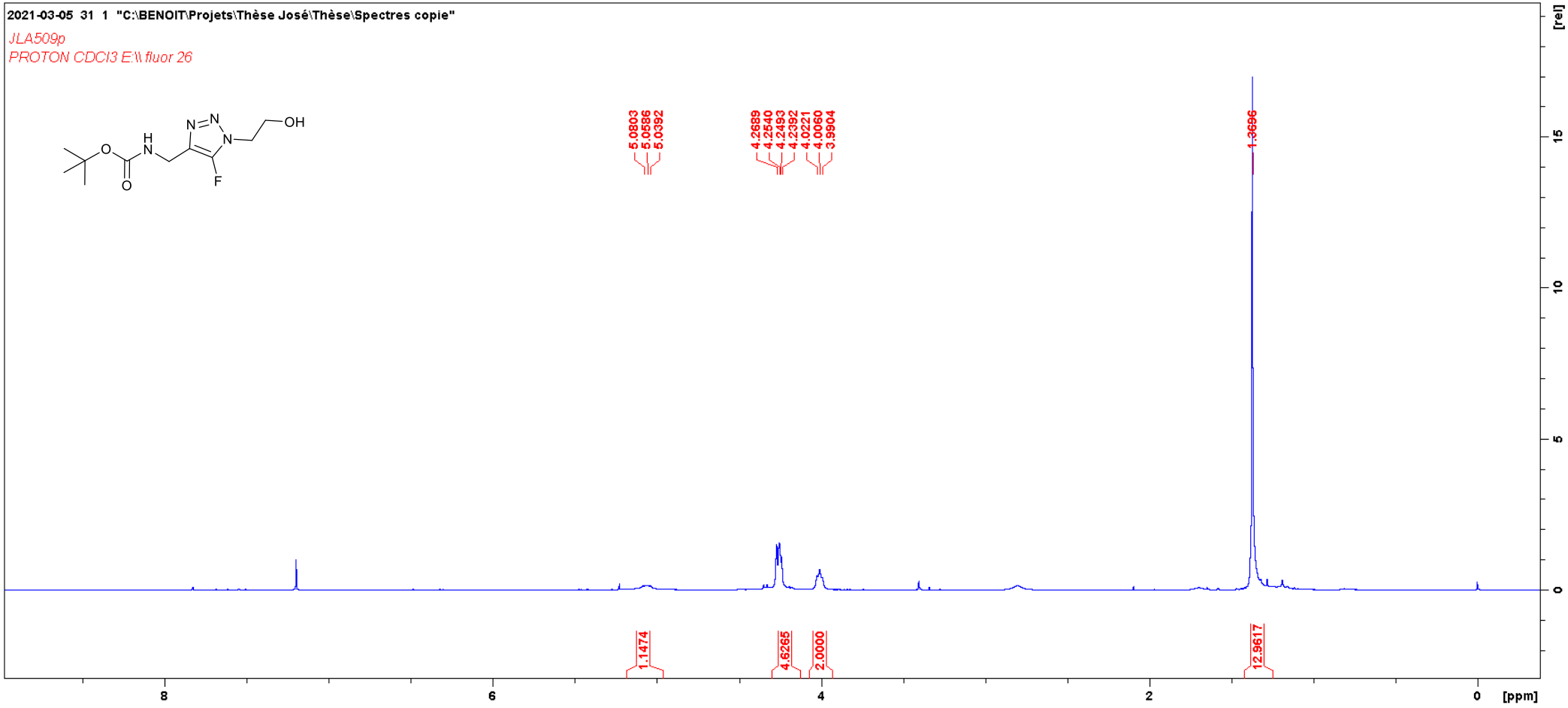

2021-12-14 10 1 "C:\BENOIT\Projets\Thèse José\Thèse\Spectres copie"
JLA620
PROTON MeOD E:\\ fluor 13
[rel]
15
10
5
0
11.2781
2.0000
1.8854
1.7738
1.3242
4.1522
3.4686
1.1133
10.2020
8
6
4
2
0
[ppm]

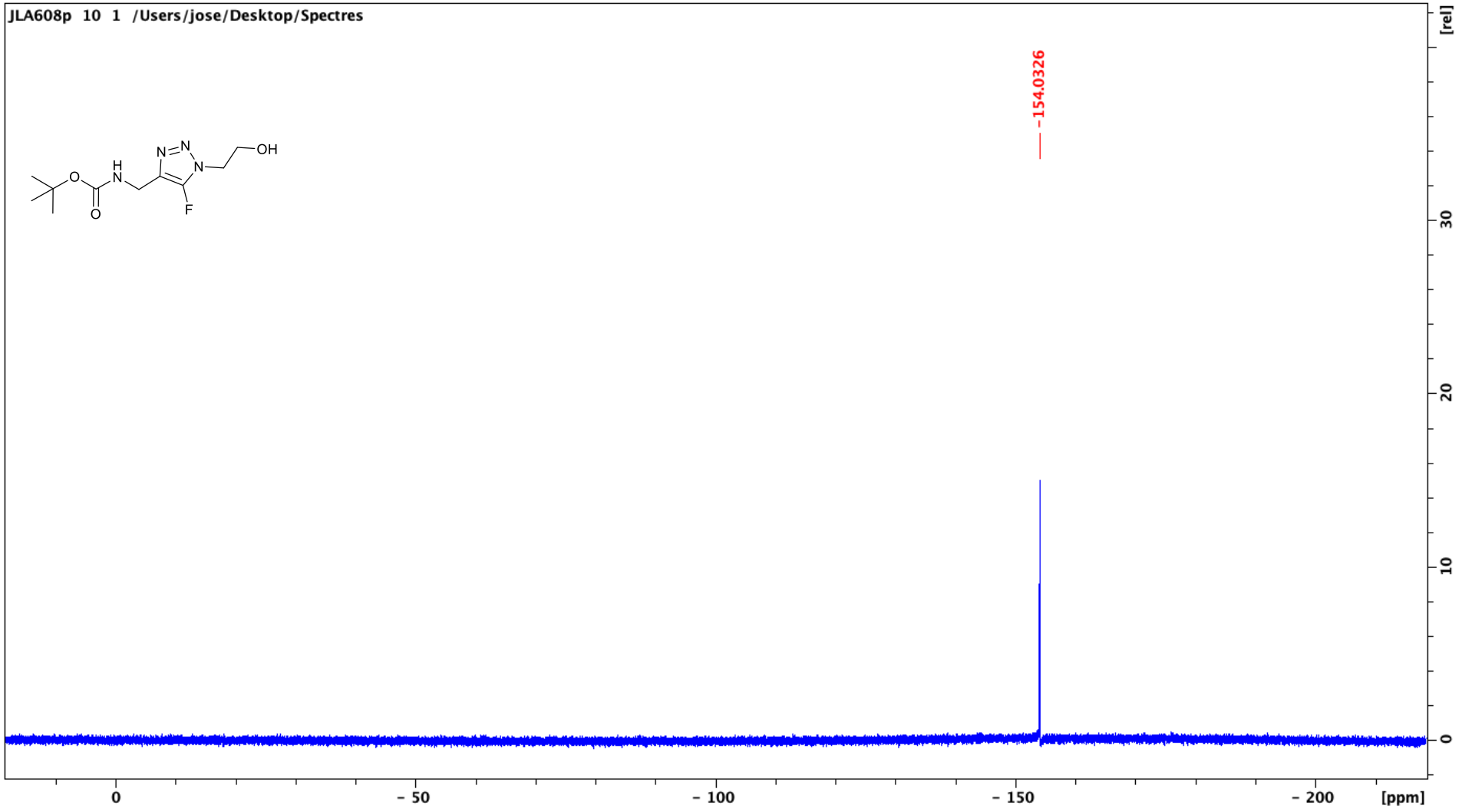

"2021-12-14 2" 11 1 "C:\BENOIT\Projets\Thèse José\Thèse\Spectres copie"
JLA620
udefi MeOD E:\\ fluor 13
174.0701
M 173.0253
172.9132
166.9691
138.5996
137.8941
130.4078
130.3229
130.2407
130.0094
129.6712
129.4002
128.0400
127.6518
68.8609
57.3253
55.4684
53.2544
52.8178
39.6145
38.4489
36.2197
35.6572
28.6520
26.4899
[rel]
15
10
5
0
200
150
100
50
0 [ppm]

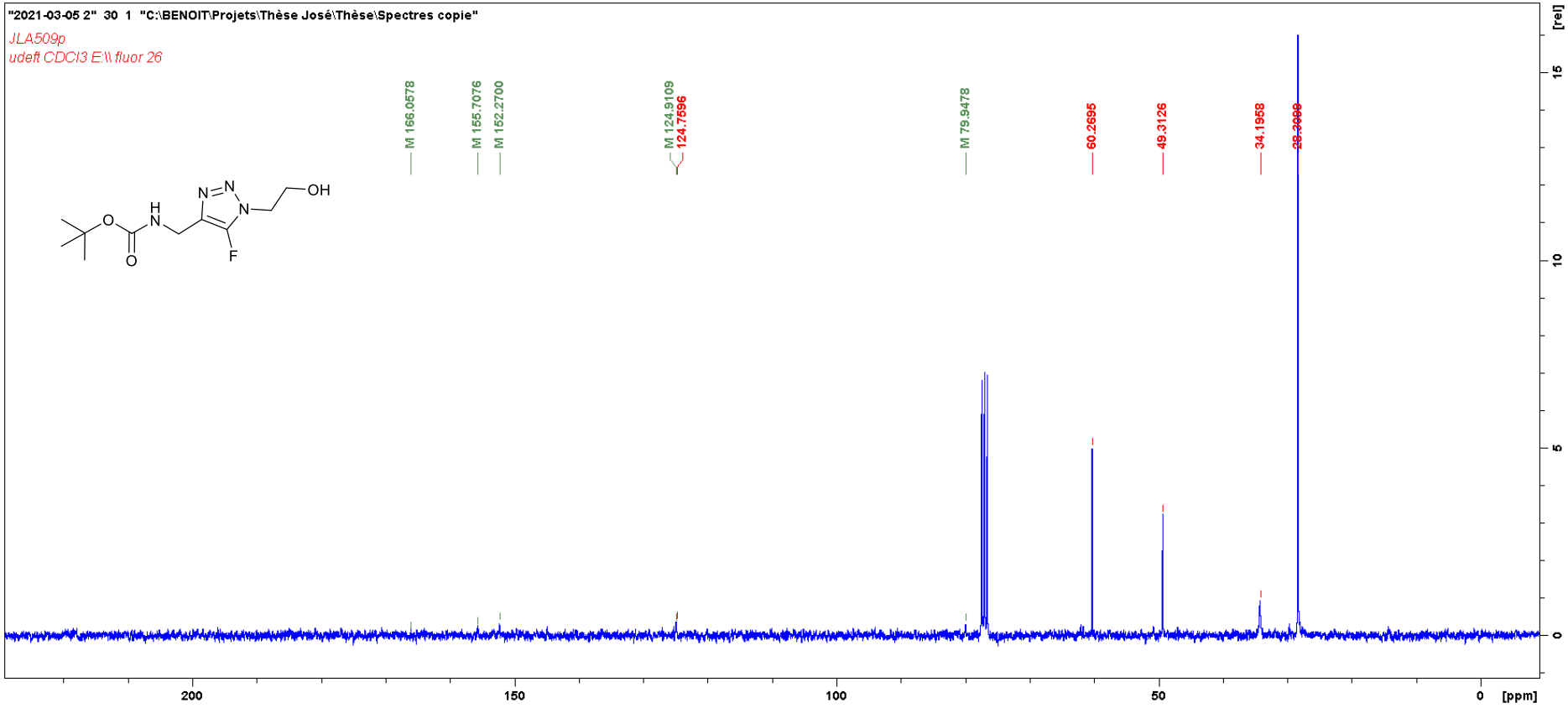

JLAtzlFp 2 1 /Users/jose/Desktop/Spectres
-153.5927
[rel]
25
20
15
10
5
0
- 40
- 60
- 80
- 100
- 120
- 140
- 160
- 180
[ppm]

^{19}F-^{1}H HOESY of **4**




2021-03-05 31 1 "C:\BENOIT\Projets\Thèse José\Thèse\Spectres copie"
JLA509p
PROTON CDCl3 E:\\ fluor 26
5.0803
5.0586
5.0392
4.2689
4.2540
4.2493
4.2392
4.0221
4.0060
3.9904
1.3696
1.1474
4.6265
2.0000
12.9617
[rel]
[ppm]


JLA608p 10 1 /Users/jose/Desktop/Spectres
-154.0326
[rel]
30
20
10
0
0
- 50
- 100
- 150
- 200
[ppm]
OH
N
N
N
H
O
O
F


"2021-03-05 2" 30 1 "C:\BENOIT\Projets\Thèse José\Thèse\Spectres copie"
JLA509p
udeft CDCl3 E:\\ fluor 26
M 166.0578
M 155.7076
M 152.2700
M 124.9109
124.7596
M 79.9478
60.2695
49.3126
34.1958
29.3080
OH
N
N
N
H
O
O
F
[rel]
15
10
5
0
200
150
100
50
0
[ppm]