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Supplementary Information

Stereoselective Total Synthesis of the Potent Anti-Asthmatic Compound CMI-977 (LDP-977)

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Experimental

Unless noted, all reactions were carried out under an atmosphere of argon in flame-dried glassware with magnetic stirring. Dichloromethane (CH_2Cl_2) and triethylamine (Et_3N) were distilled from CaH_2. Dimethyl sulfoxide (DMSO) was distilled under reduced pressure from CaH_2 and stored over molecular sieves. Tetrahydrofuran (THF) and diethylether (Et_2O) were distilled from Na/benzophenone. Purification of reaction products was carried out by flash column chromatography using silica gel (230-400 mesh). Analytical thin layer chromatography was performed on silica gel 60 and GF (5-40 μm thickness) plates. Visualization was accomplished with UV light and phosphomolybdic acid followed by heating. Optical rotations were measured on a Carl Zeiss LEP A2 with a sodium lamp and are reported as follows: $[\alpha]_{\lambda}^{T\ °C}$ (*c* = g *per* 100 mL, solvent). ^{1}H and proton-decoupled ^{13}C NMR (nuclear magnetic resonance) spectra were recorded in a Bruker spectrometer in DMSO or $CDCl_3$ at 250 MHz (^{1}H) and 62.9 MHz (^{13}C) or at 500 MHz (^{1}H) and 125 MHz (^{13}C). The chemical shifts (δ) are reported in ppm using solvent as an internal standard ($CDCl_3$ at 7.26 ppm). Data are reported as: s = singlet, d = doublet, t = triplet, q = quartet, quint = quintuplet, sext = sextet, br = broad singlet, dd = doublet of doublets, dt = doublet of triplets, ddd = doublet of doublet of doublets, tt = triplet of triplets, m = multiplet; coupling constant(s) in Hz; integration. High-resolution mass spectrometry (HRMS) was recorded on a Waters Xevo Q-Tof using electrospray ionization (ESI) or on a GCT Premier Waters using electron ionization (EI). The parent ions ($[M + H]^+$, $[M + Na]^+$ and $[M]^+$) are listed. Infrared spectra (IR) were recorded on a Bomem Hartman & Braun spectrometer. Wavelengths of maximum absorbance (max) are quoted in wavenumbers (cm^{-1}).

(±)-2,3-Epoxy-1-(4-fluorophenoxy)propane (**rac-5**)

Powdered KOH (26.8 g, 460 mmol) was added to a solution of *p*-fluorophenol **16** (10.0 g, 89.2 mmol) in rac-epichlorohydrin rac-**17** (72 mL), followed by the addition of tetrabutylammonium bromide (6.24 g, 19.6 mmol). The mixture was stirred overnight at room temperature and the reaction was quenched with distilled water (50 mL). The phases were separated and the aqueous phase was extracted with Et_2O (3 × 30 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography using a mixture of hexane/Et_2O (80:20) as eluent, providing 14.5 g (97%) of rac-**5** as a colorless oil; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 2.74 (dd, 1H, *J* 2.5 and 4.9 Hz), 2.85 (t, 1H, *J* 4.5 Hz), 3.30-3.36 (m, 1H), 3.90 (dd, 1H), *J* 5.7 and 11.1 Hz, 4.20 (dd, 1H, *J* 3.0 and 11.1 Hz), 6.8-7.2 (m, 4H); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 44.5 (CH_2), 50.1 (CH), 69.4 (CH_2), 115.6 (CH), 115.8 (CH), 116.0 (CH), 154.6 (C_0), 155.6 (C_0), 159.4 (C_0); IR (film) ν_{max}/cm^{-1} 3481, 3059, 3005, 2928, 2878, 2056, 1863, 1601, 1506, 1456, 1294, 1250, 1211, 1099, 1036, 916, 864, 829, 775, 750, 723.

(*S*)-2,3-Epoxy-1-(4-fluorophenoxy)propane ((***S***)-**5**)

To the epoxide rac-**5** (14.5 g; 86.3 mmol) in *t*-BuOMe (30 mL), it was added (*R*,*R*)-(salen)Co^{III}(OAc)[1] (**19**) (300 mg, 0.453 mmol), and the mixture was stirred at 0 ºC. Distilled water (0.91 mL, 49.6 mmol) was added dropwise over 1 h and the resulting mixture was stirred for 5 h at room temperature. The mixture was concentrated under reduced pressure and the residue was purified by flash column chromatography using a mixture of hexane/EtOAc (50:50) as eluent, providing 7.01 g (48%) of (*S*)-**5** as a colorless oil; $[\alpha]_D^{20}$ +13.0 (*c* 1.0, $CHCl_3$), $[\alpha]_D^{20}$ +5.0 (*c* 1.0, $CHCl_3$);[1] ^{1}H NMR ($CDCl_3$, 250 MHz) δ 2.74 (dd, 1H, *J* 2.5 and 4.9 Hz), 2.85 (t, 1H, *J* 4.5 Hz), 3.30-3.36 (m, 1H), 3.90 (dd, 1H, *J* 5.7 and 11.1 Hz), 4.20 (dd, 1H, *J* 3.0 and 11.1 Hz), 6.8-7.2 (m, 4H).

(*S*)-1-(4-Fluorophenoxy)hex-5-en-2-ol (**15**)

To a solution of allylmagnesium bromide (**18**) (17.8 mL, 17.8 mmol, 1 mol L^{-1} in Et_2O), CuCN (22 mg, 0.25 mmol) was added and the solution was cooled to 0 ºC. Then, a solution of (*S*)-**5** (1.50 g, 8.92 mmol) in Et_2O (18.3 mL)

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was added dropwise. The mixture was stirred for 30 min at 0 ºC, quenched with a saturated aqueous solution of NH_4Cl (5 mL) and stirred for 30 min at room temperature. The mixture was then filtered and the precipitate rinsed with Et_2O. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography using a mixture of hexane/Et_2O (60:40) as eluent, providing the homopropargylic alcohol **15** (1.88 g, 8.92 mmol) as a colorless oil in a quantitative yield; $[\alpha]_D^{20}$ +20 (*c* 1.5, $CHCl_3$), $[\alpha]_D$ −16.5 (*c* 1.5, $CHCl_3$);[1] ^{1}H NMR ($CDCl_3$, 250 MHz) δ 1.61-1.76 (m, 2H), 2.11-2.33 (m, 2H), 2.41 (d, 1H, *J* 2.5 Hz), 3.76-4.10 (m, 2H), 4.98-5.11 (m, 2H), 5.76-5.93 (m, 1H), 6.80-6.99 (m, 2H); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 29.6 (CH_2), 32.2 (CH_2), 69.5 (CH), 72.8 (CH_2), 115.1 (CH_2), 115.5 (CH), 115.7 (CH), 116.0 (CH), 138.0 (CH), 154.7 (C_0), 155.5 (C_0), 159.3 (C_0).

Reference

1. Gurjar, M. K.; Murugaiah, A. M. S.; Radhakrishna, P.; Ramana, C. V.; Chorghade, M. S.; *Tetrahedron: Asymmetry* **2003**, *14*, 1363.

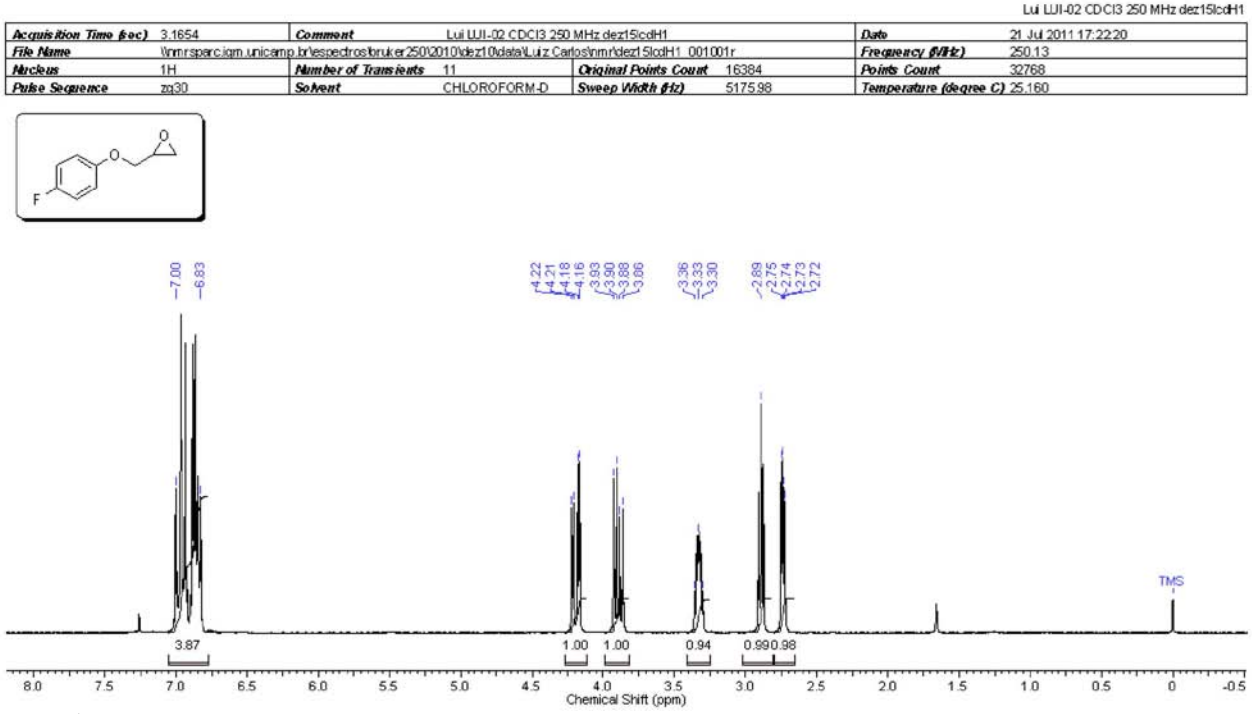

Figure S1. ^{1}H NMR spectrum (250 MHz, $CDCl_3$) of **rac-5**.

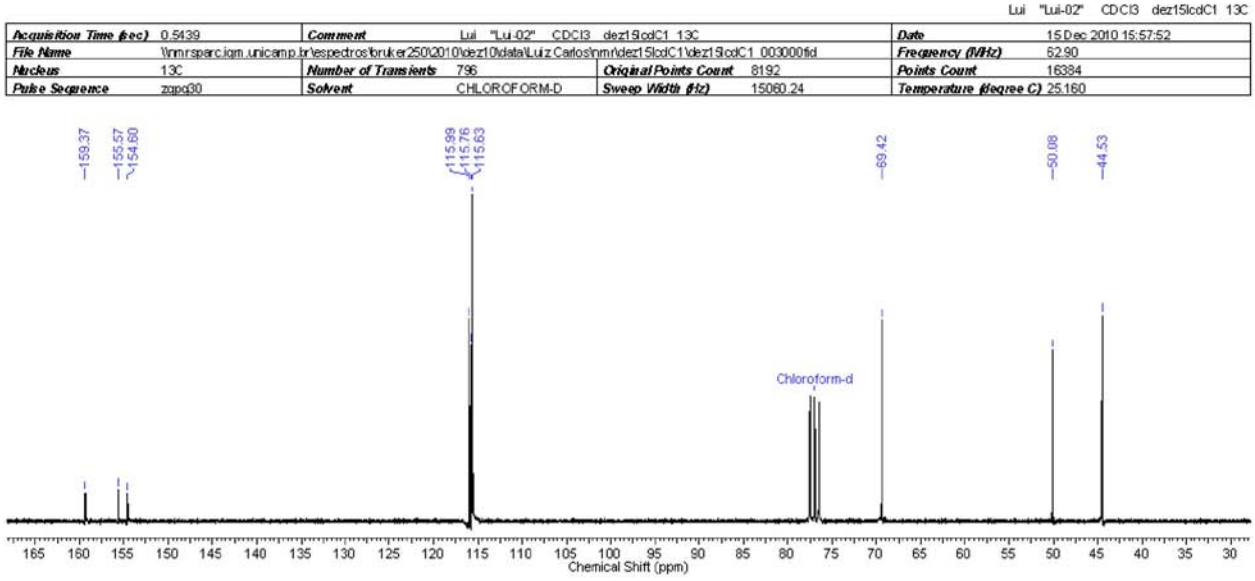

Figure S2. ^{13}C NMR spectrum (62.9 MHz, $CDCl_3$) of **rac-5**.

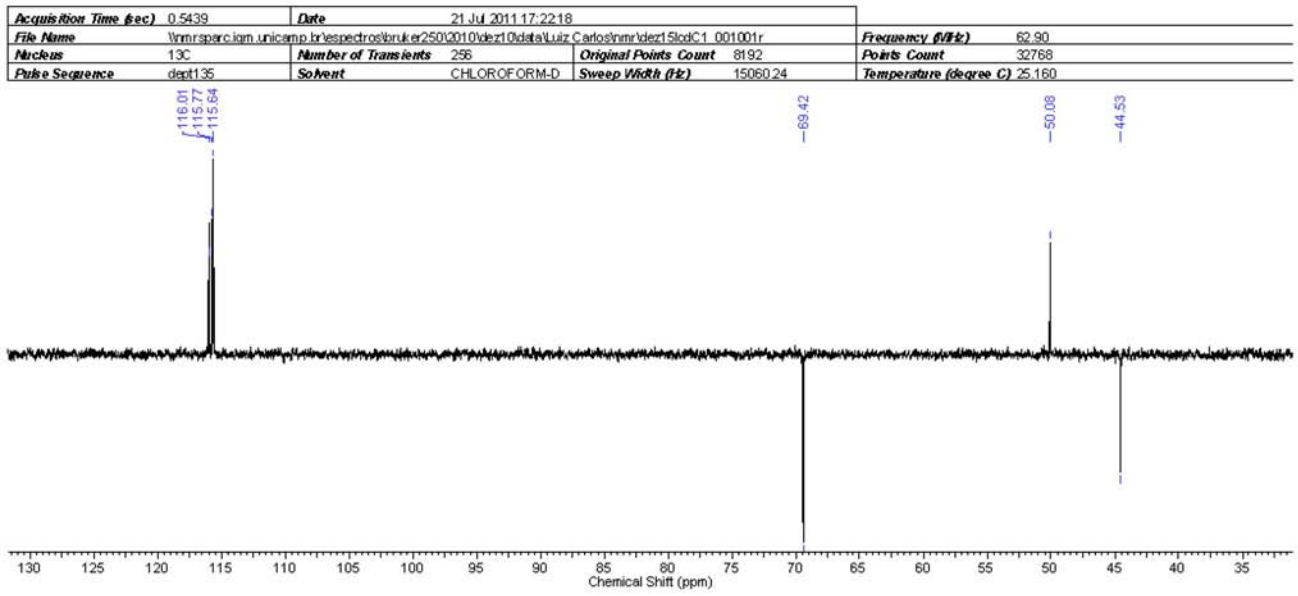

Figure S3. DEPT 135 NMR spectrum (62.9 MHz, $CDCl_3$) of **rac-5**.

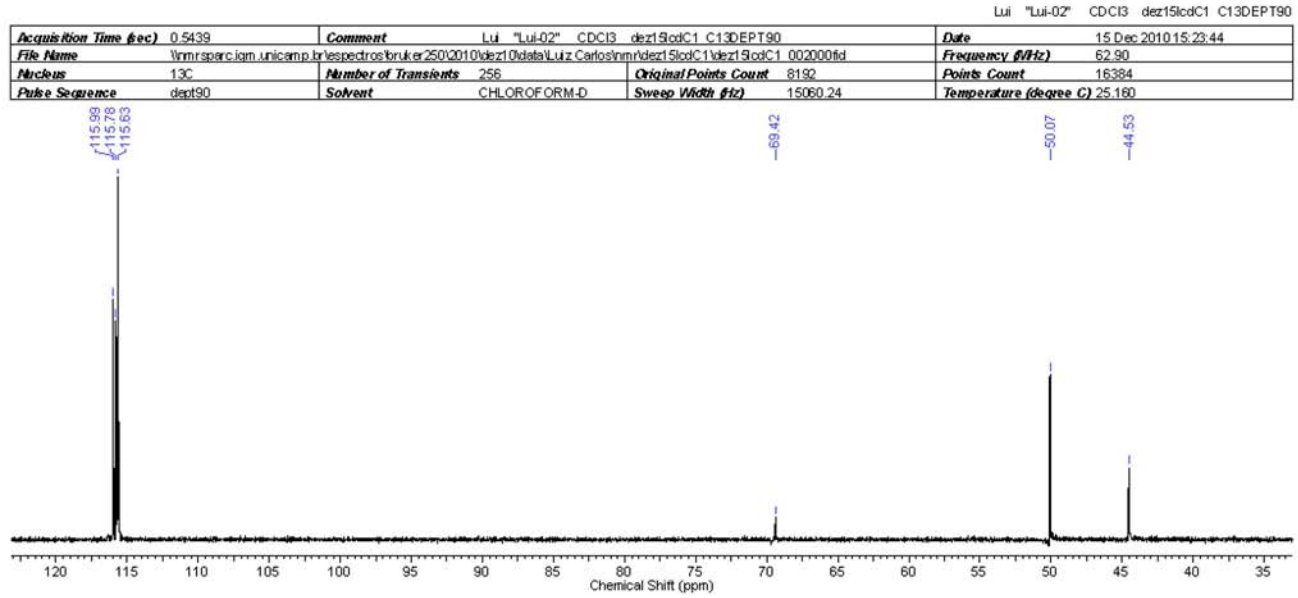

Figure S4. DEPT 90 NMR spectrum (62.9 MHz, $CDCl_3$) of **rac-5**.

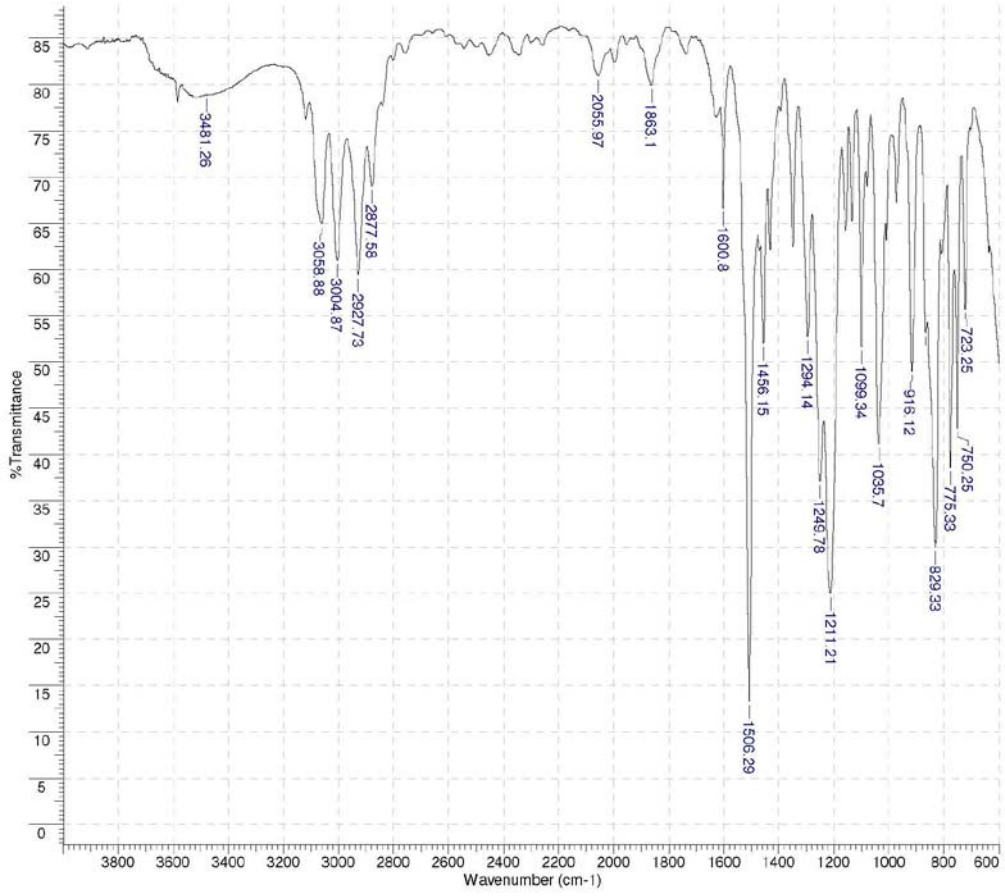

Figure S5. IR (film) spectrum of **rac-5**.

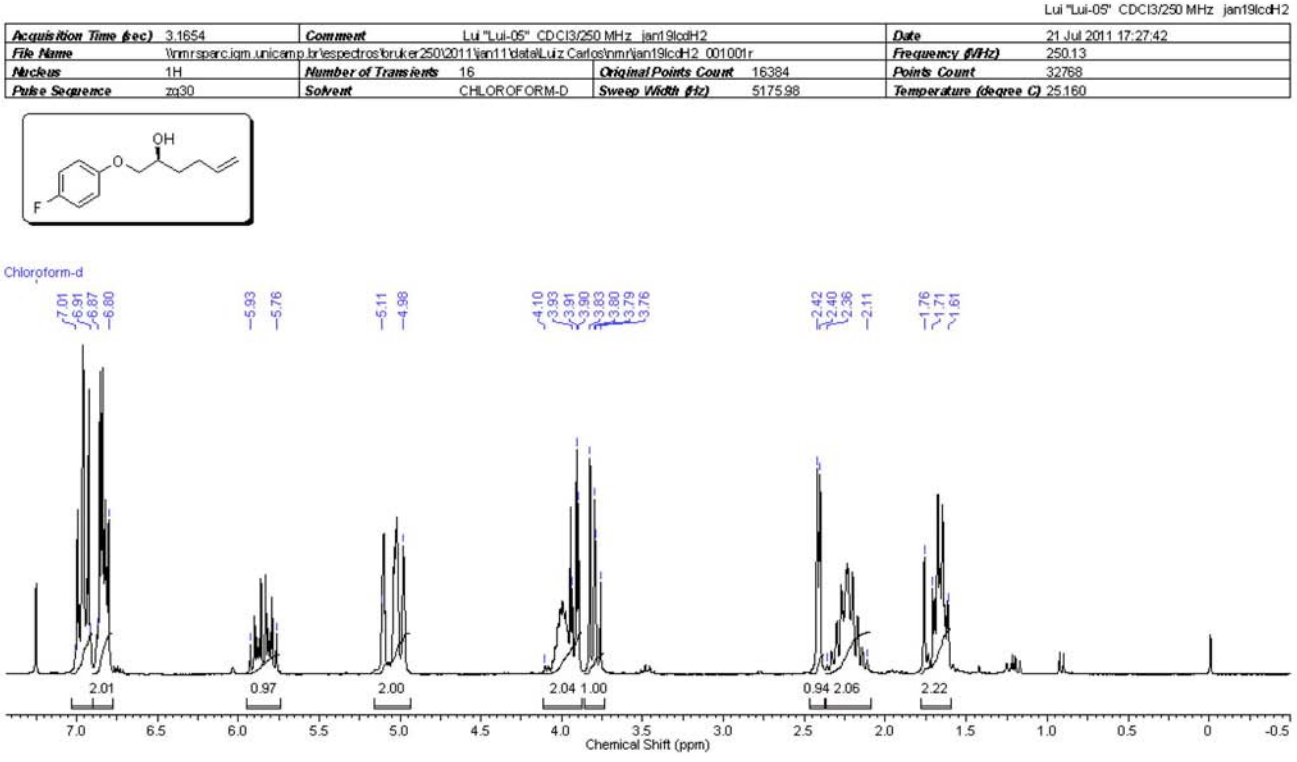

Figure S6. ^{1}H NMR spectrum (250 MHz, $CDCl_3$) of **15**.

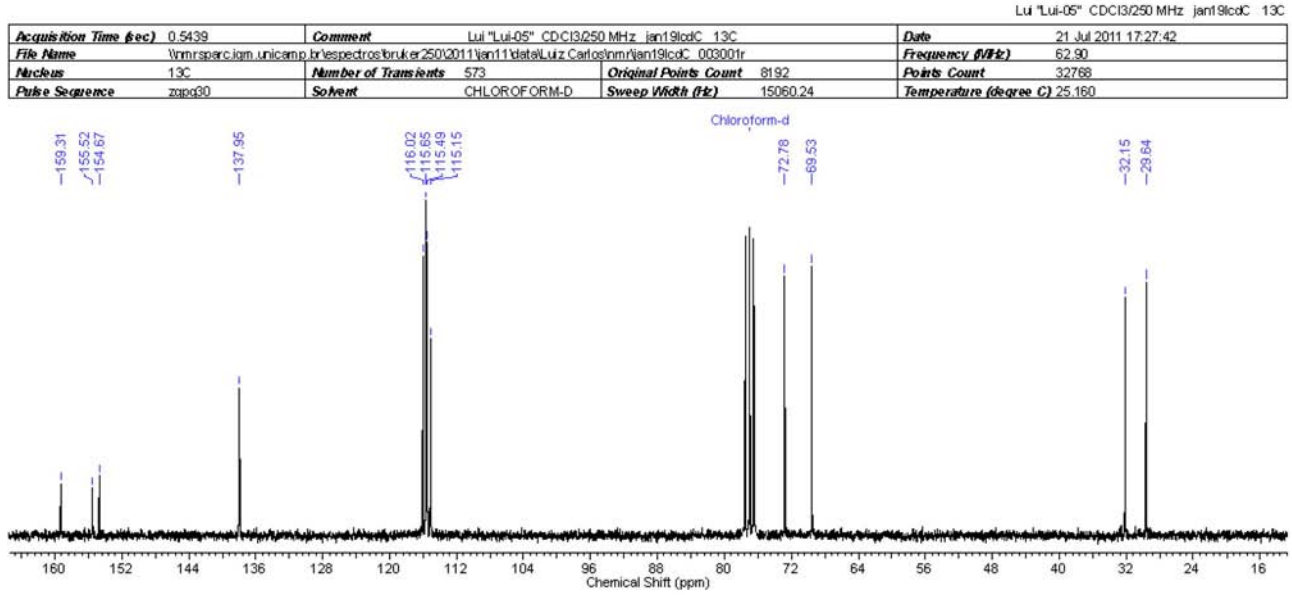

Figure S7. ^{13}C NMR spectrum (62.9 MHz, $CDCl_3$) of **15**.

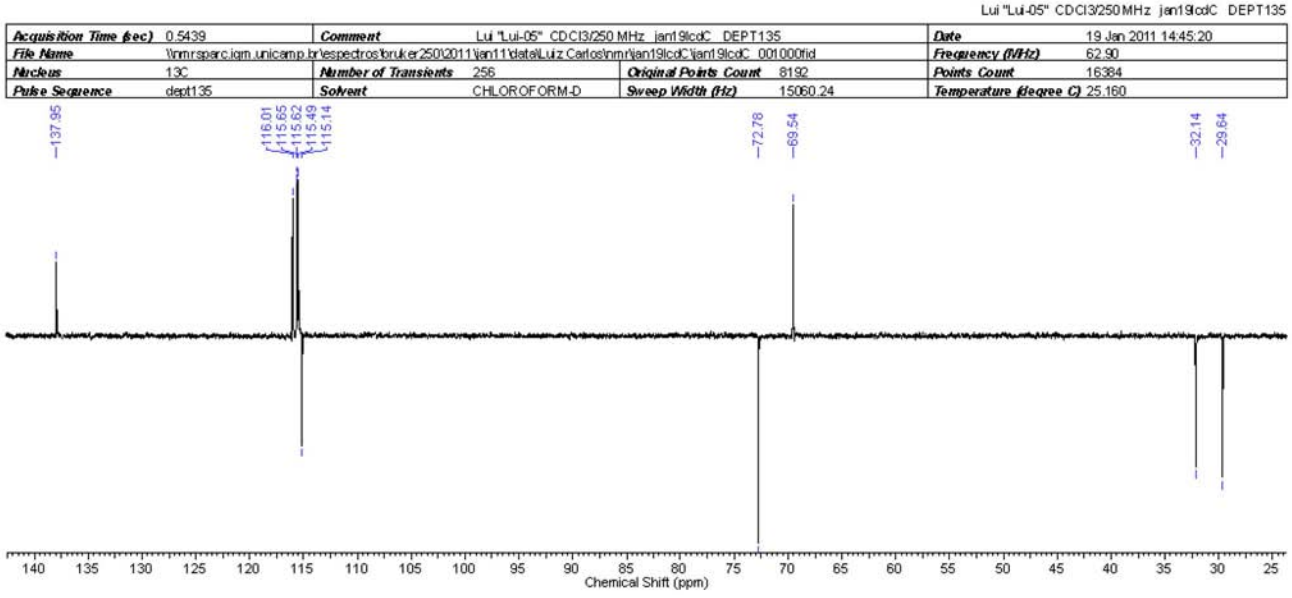

Figure S8. DEPT 135 NMR spectrum (62.9 MHz, $CDCl_3$) of **15**.

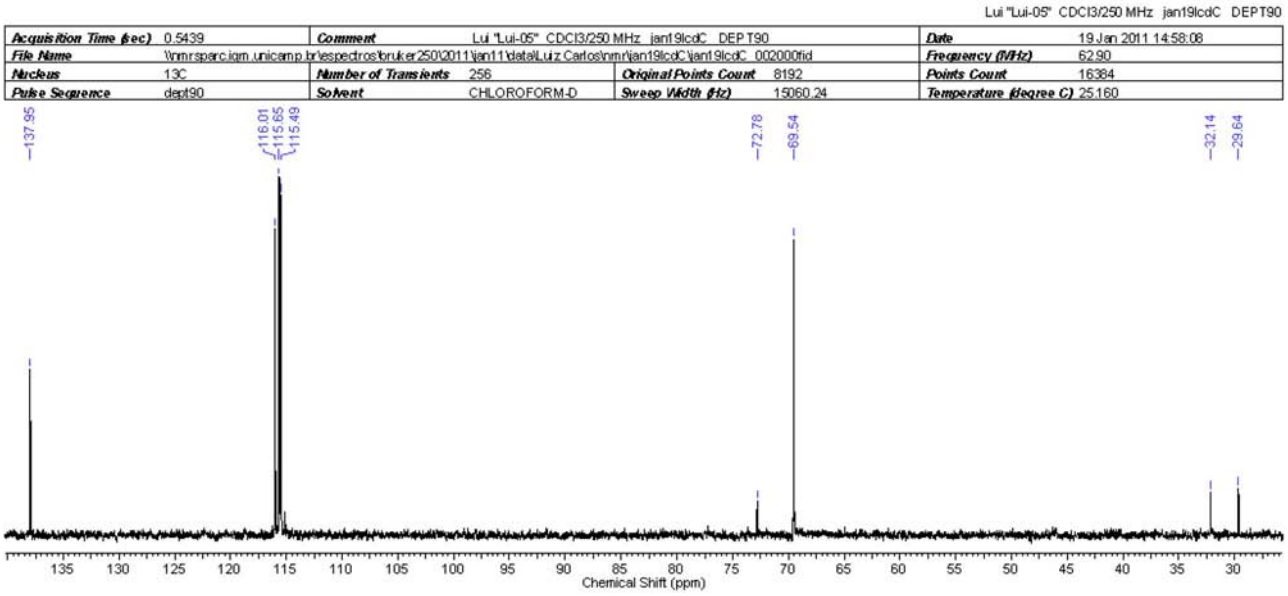

Figure S9. DEPT 90 NMR spectrum (62.9 MHz, $CDCl_3$) of **15**.

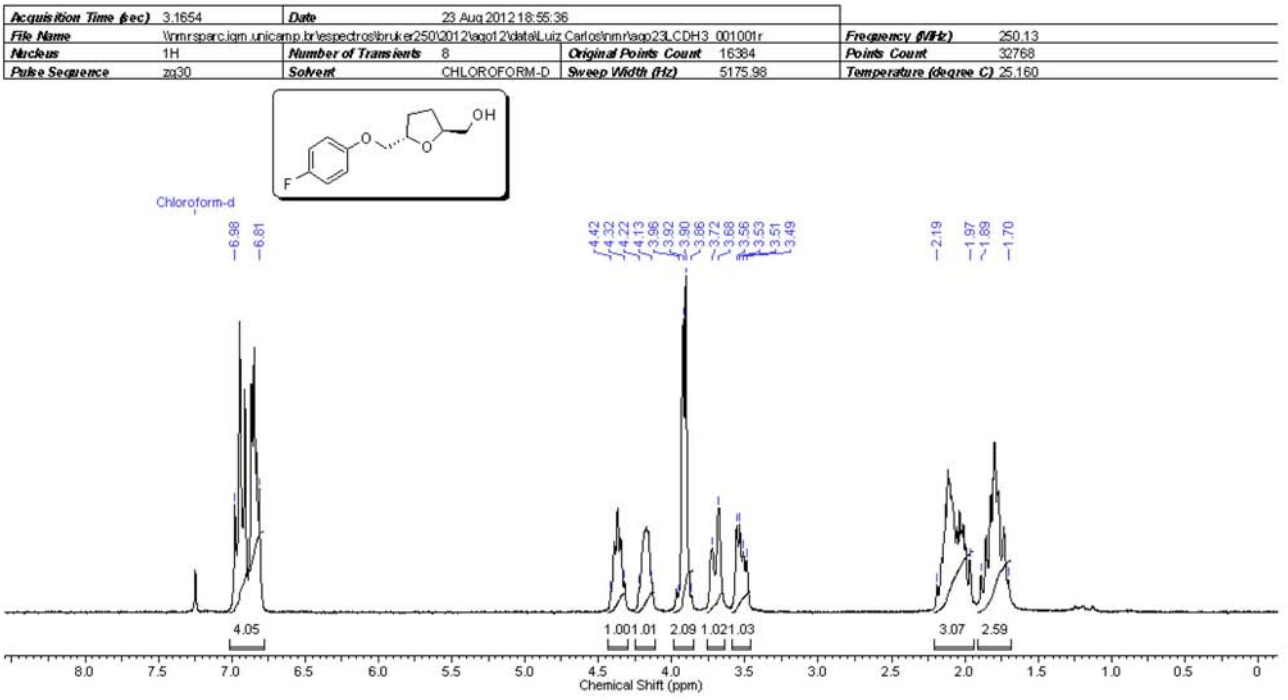

Figure S10. ^1H NMR spectrum (250 MHz, $CDCl_3$) of **14**.

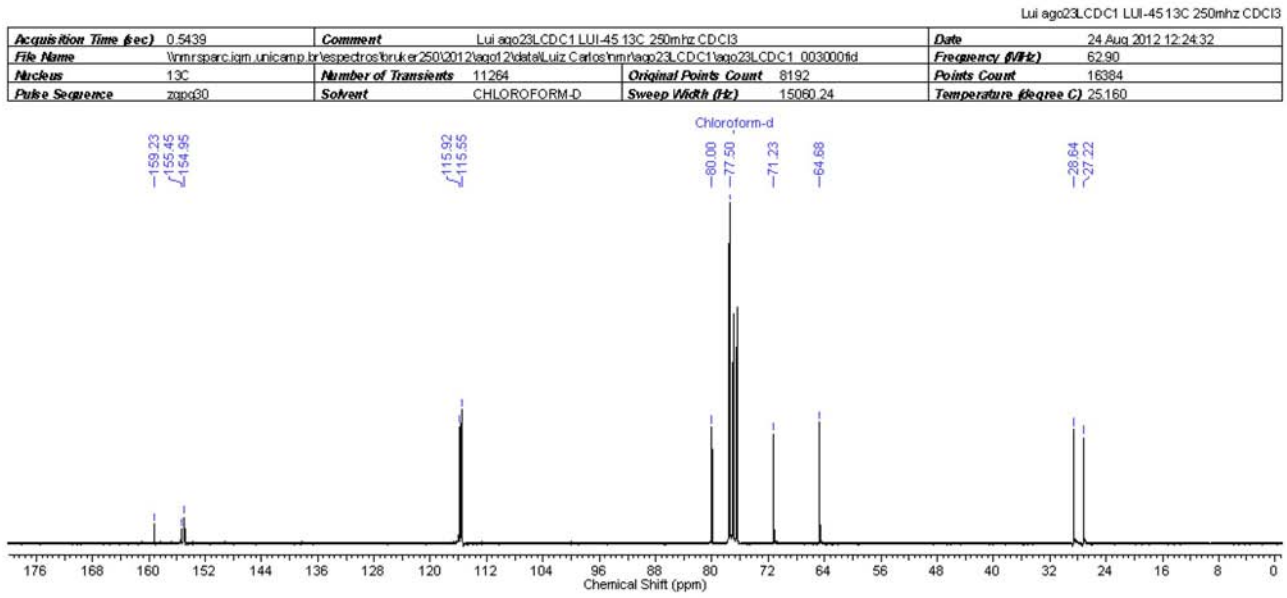

Figure S11. ^{13}C RMN spectrum (62.9 MHz, $CDCl_3$) of **14**.

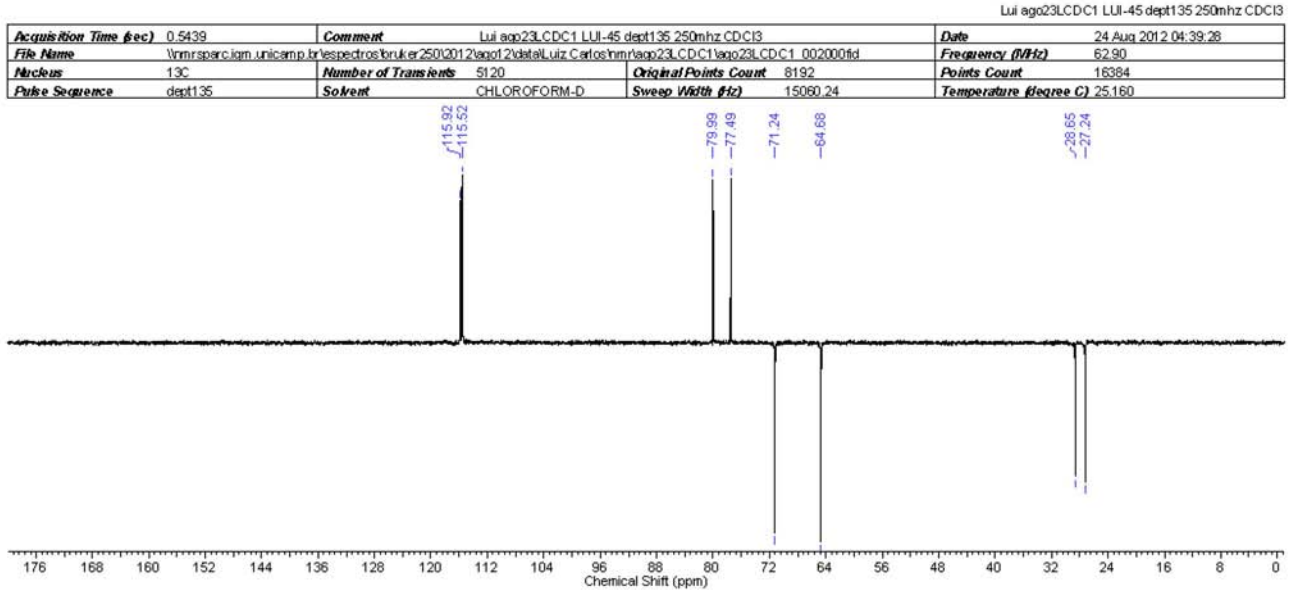

Figure S12. DEPT 135 NMR spectrum (62.9 MHz, $CDCl_3$) of **14**.

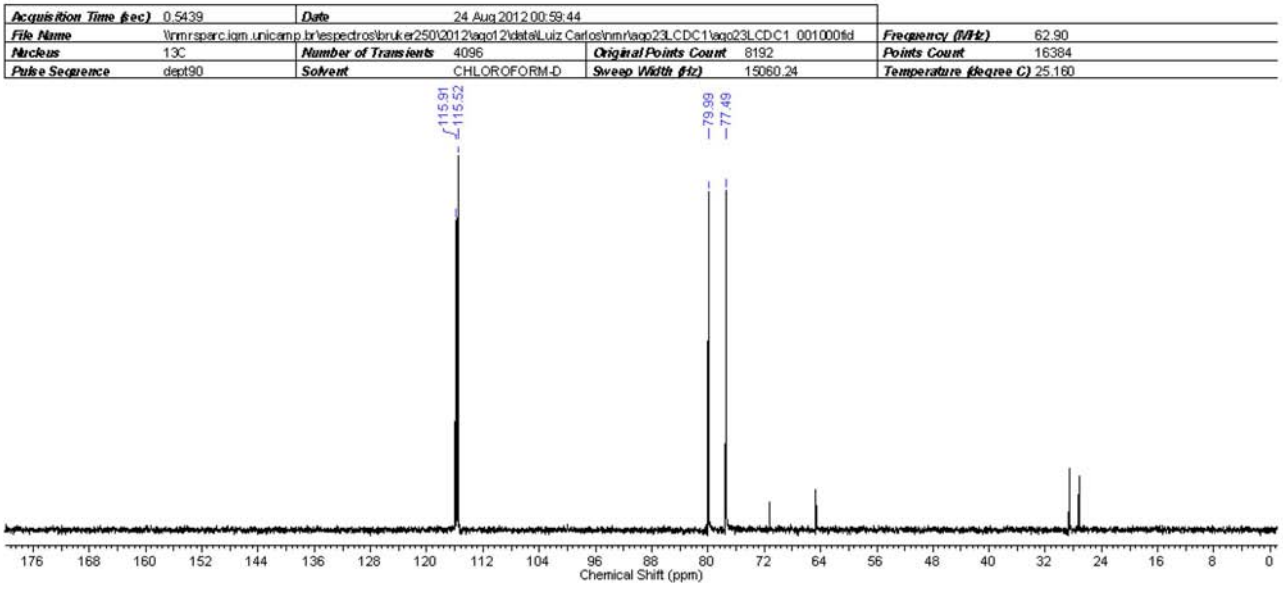

Figure S13. DEPT 90 NMR spectrum (62.9 MHz, $CDCl_3$) of **14**.

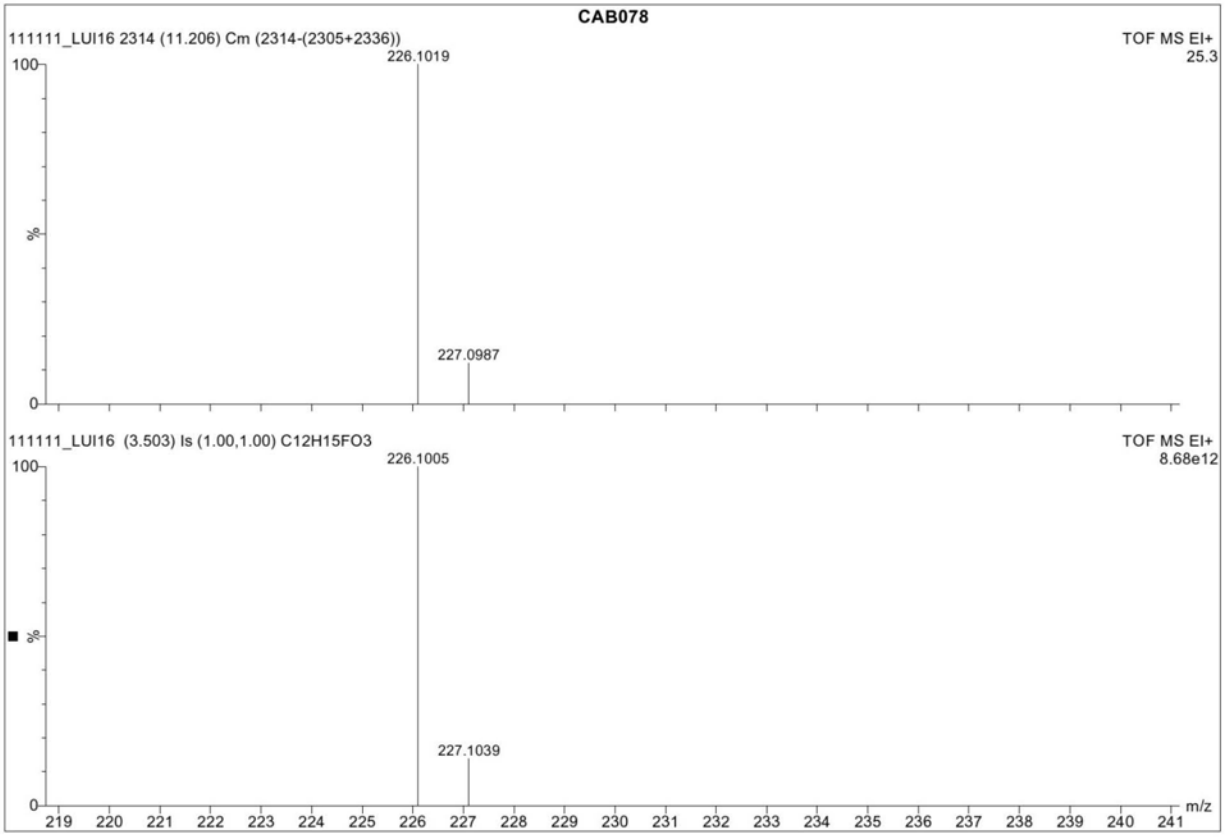

Figure S14. HRMS (EI-TOF) *m/z* $[M]^+$ for $C_{12}H_{15}FO_3$ of **14**.

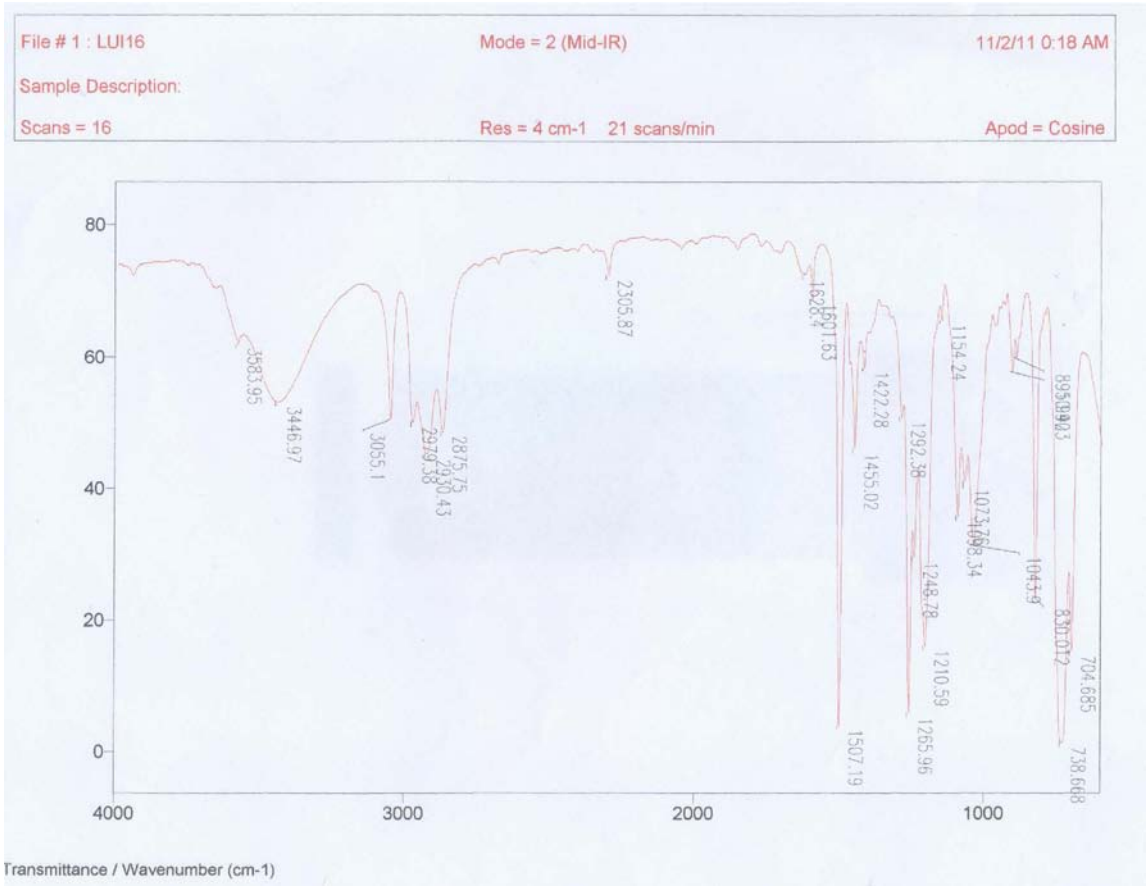

Figure S15. IR (film) spectrum of **14**.

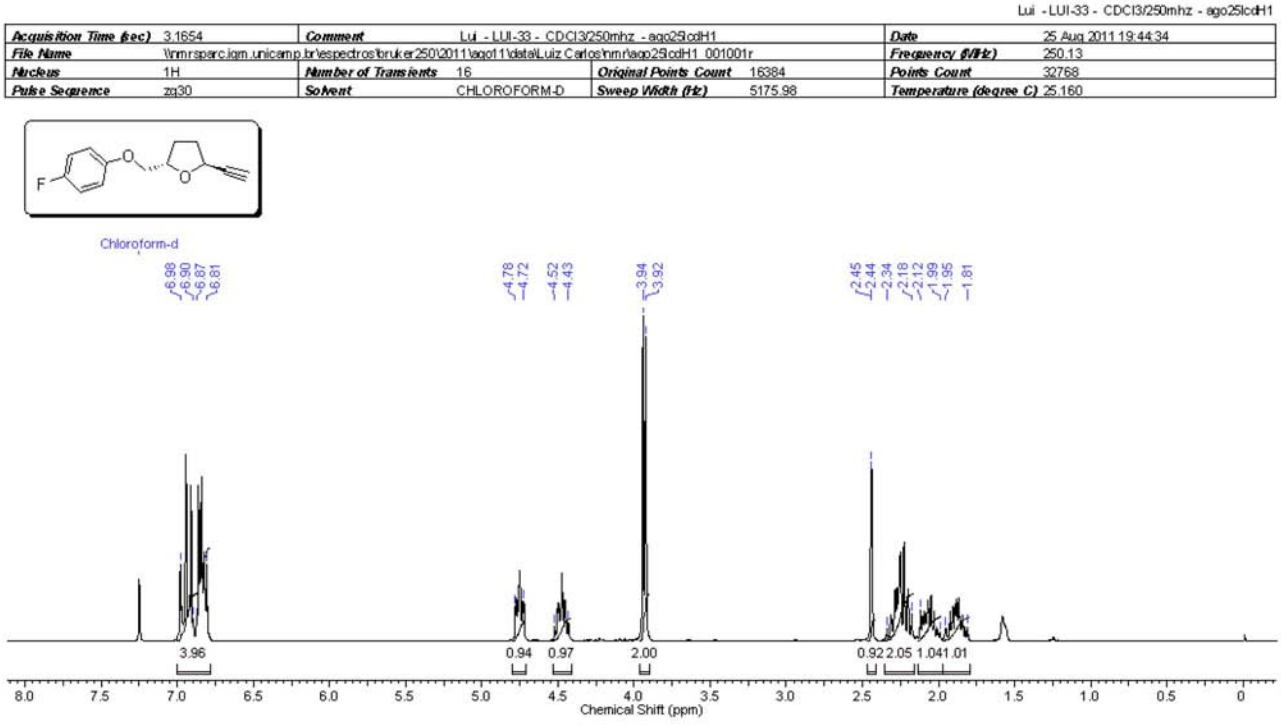

Figure S16. ^{1}H RMN spectrum (250 MHz, $CDCl_3$) of **7**.

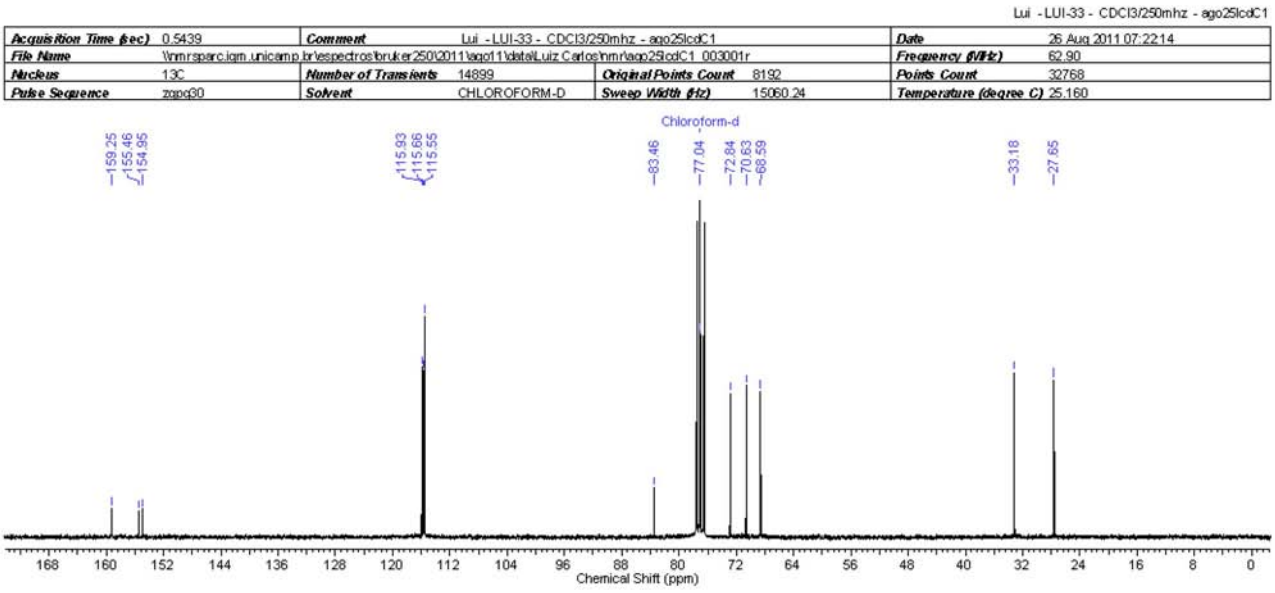

Figure S17. ^{13}C RMN spectrum (62.9 MHz, $CDCl_3$) of **7**.

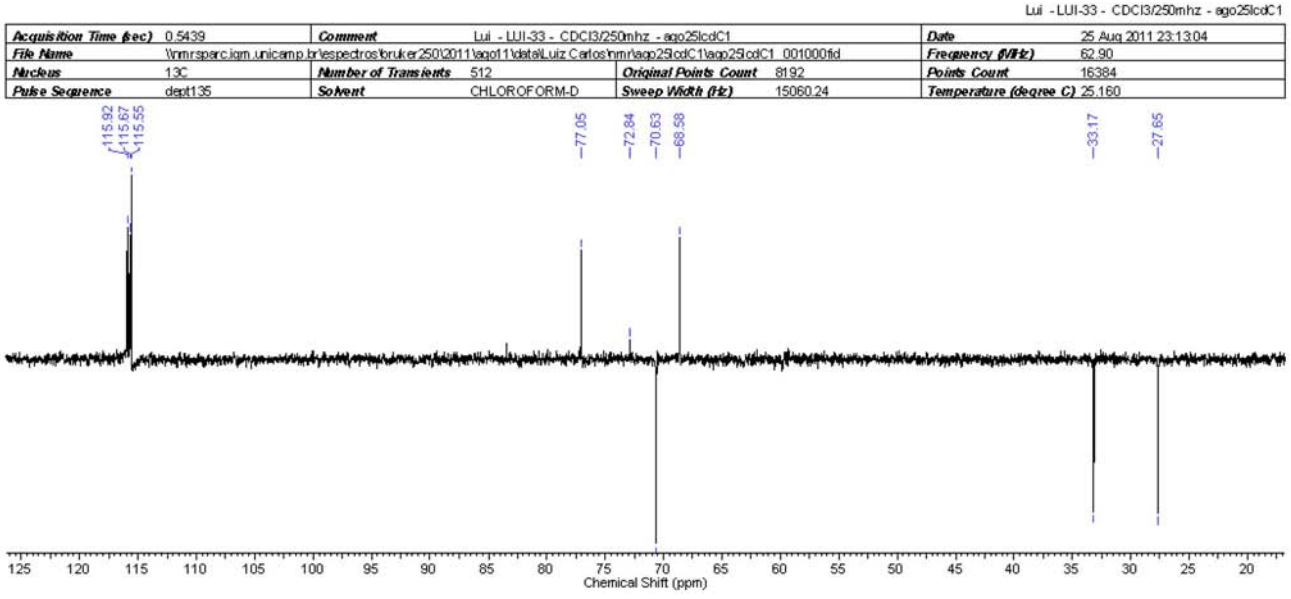

Figure S18. DEPT 135 NMR spectrum (62.9 MHz, $CDCl_3$) of **7**.

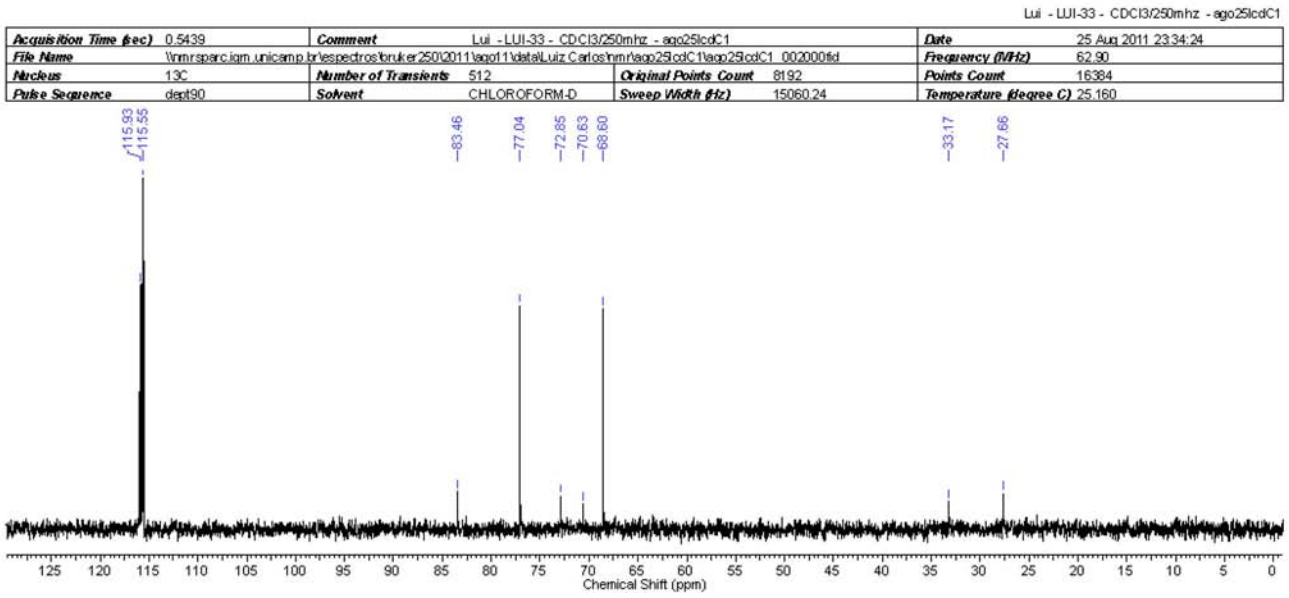

Figure S19. DEPT 90 NMR spectrum (62.9 MHz, $CDCl_3$) of **7**.

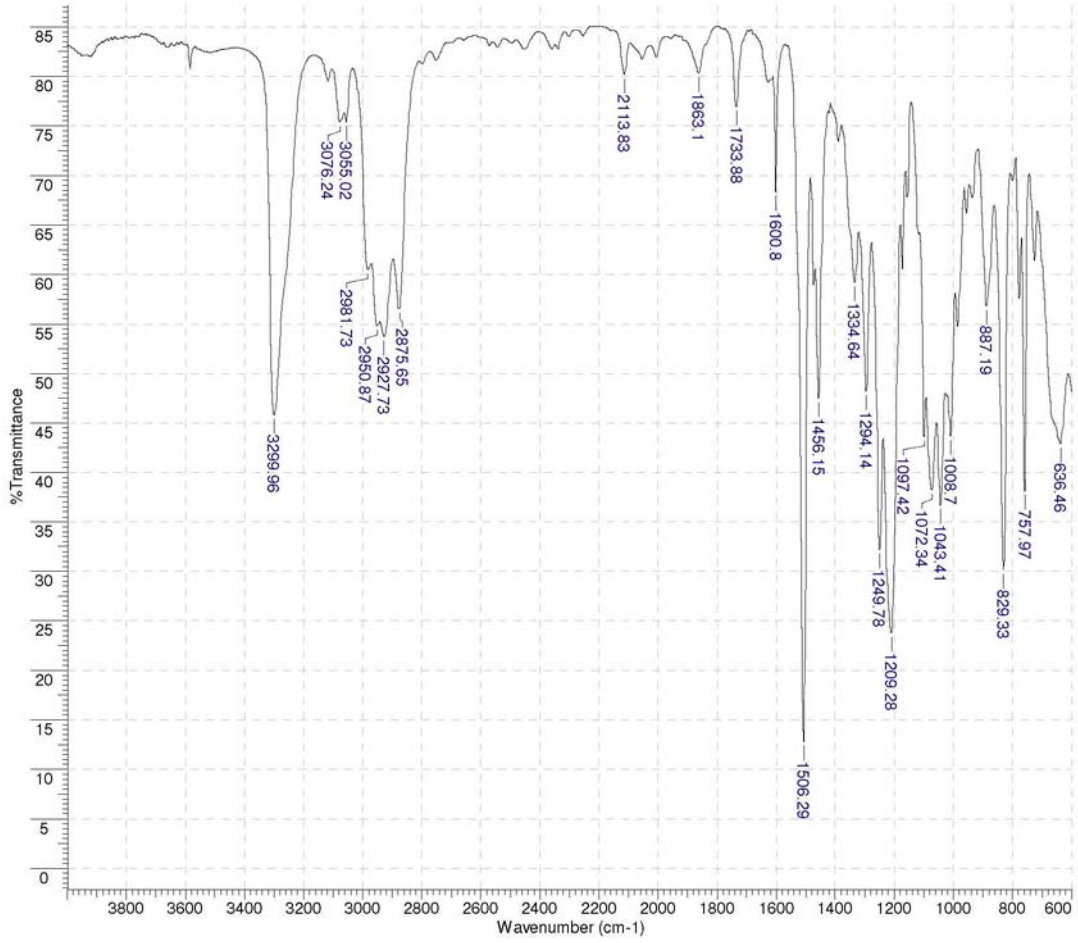

Figure S20. IR (film) spectrum of **7.**

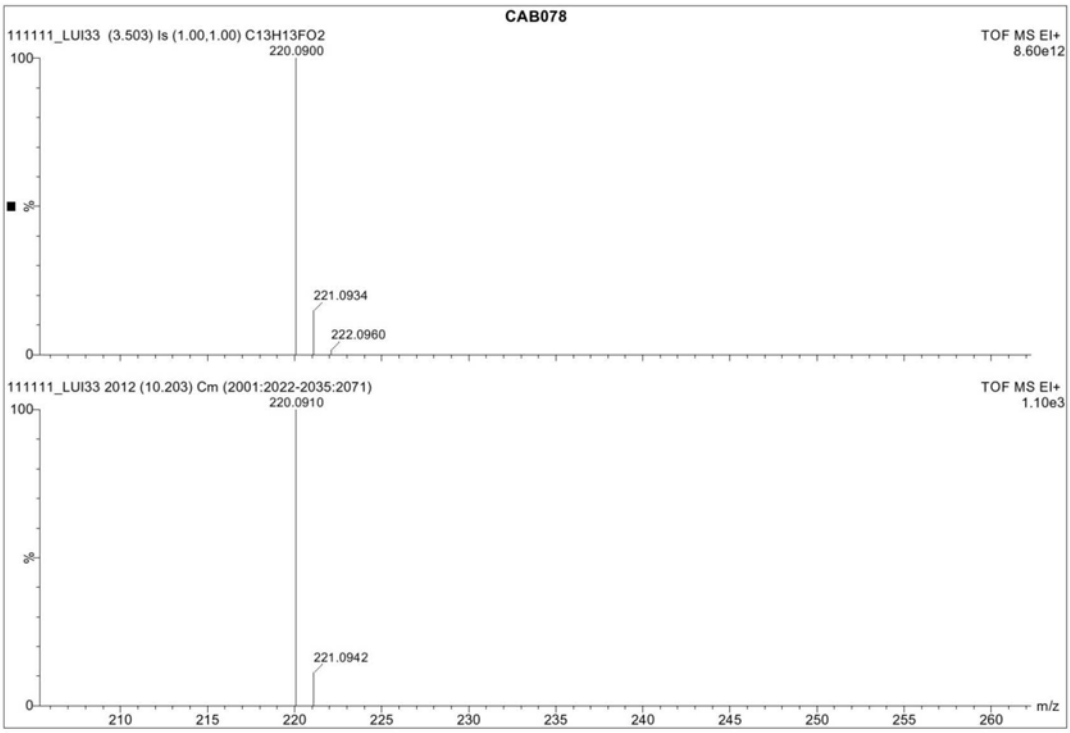

Figure S21. HRMS (EI-TOF) *m/z* $[M]^+$ for $C_{13}H_{13}FO_2$ of **7**.

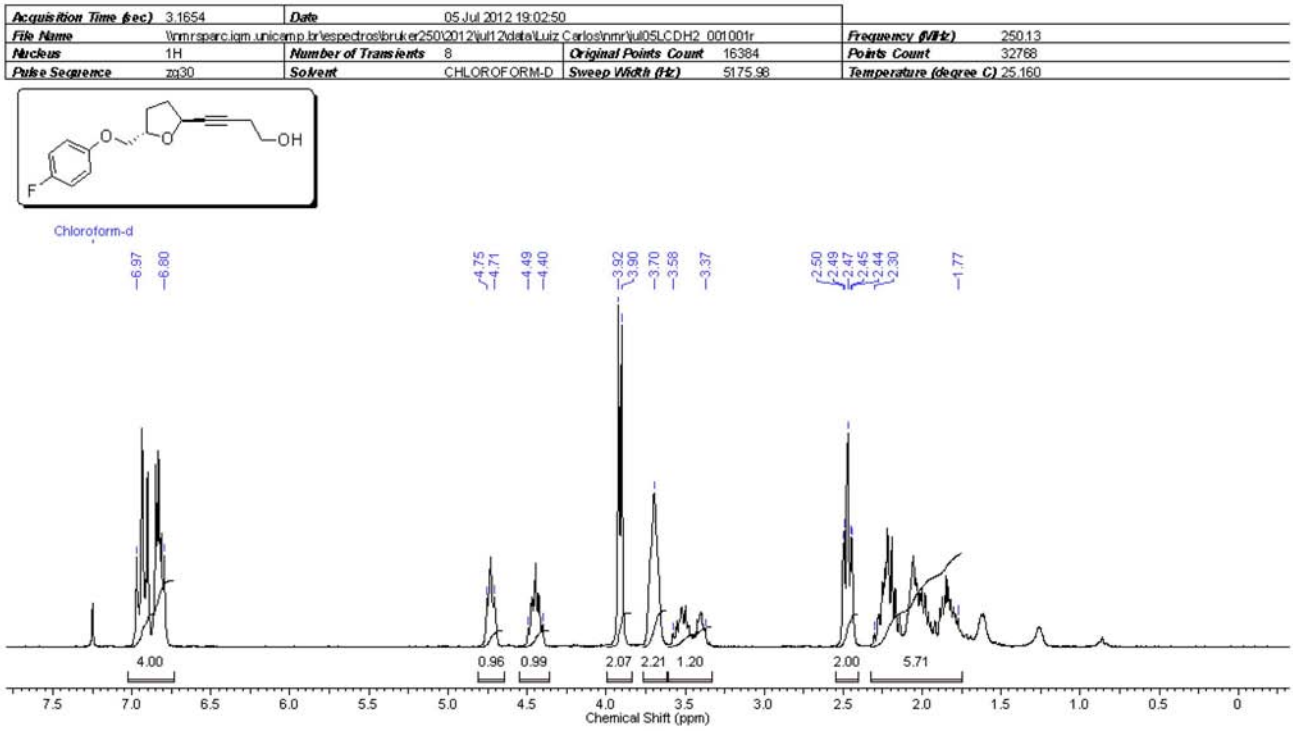

Figure S22. ^{1}H RMN spectrum (250 MHz, $CDCl_3$) of **4**.

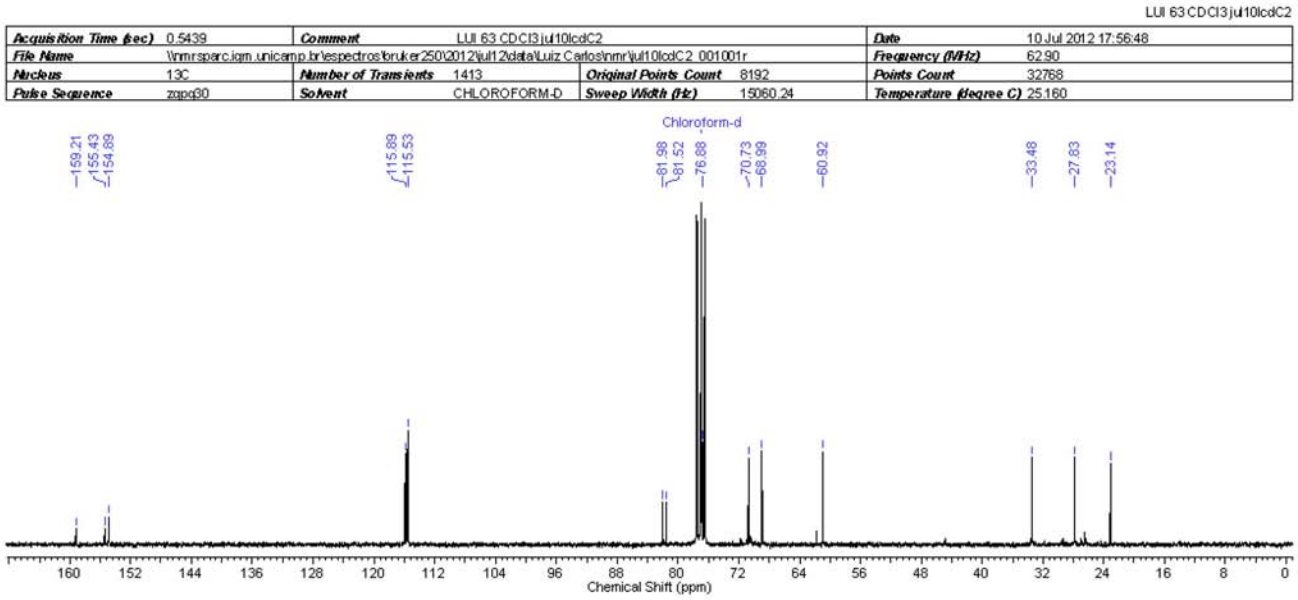

Figure S23. ^{13}C RMN spectrum (62.9 MHz, $CDCl_3$) of **4**.

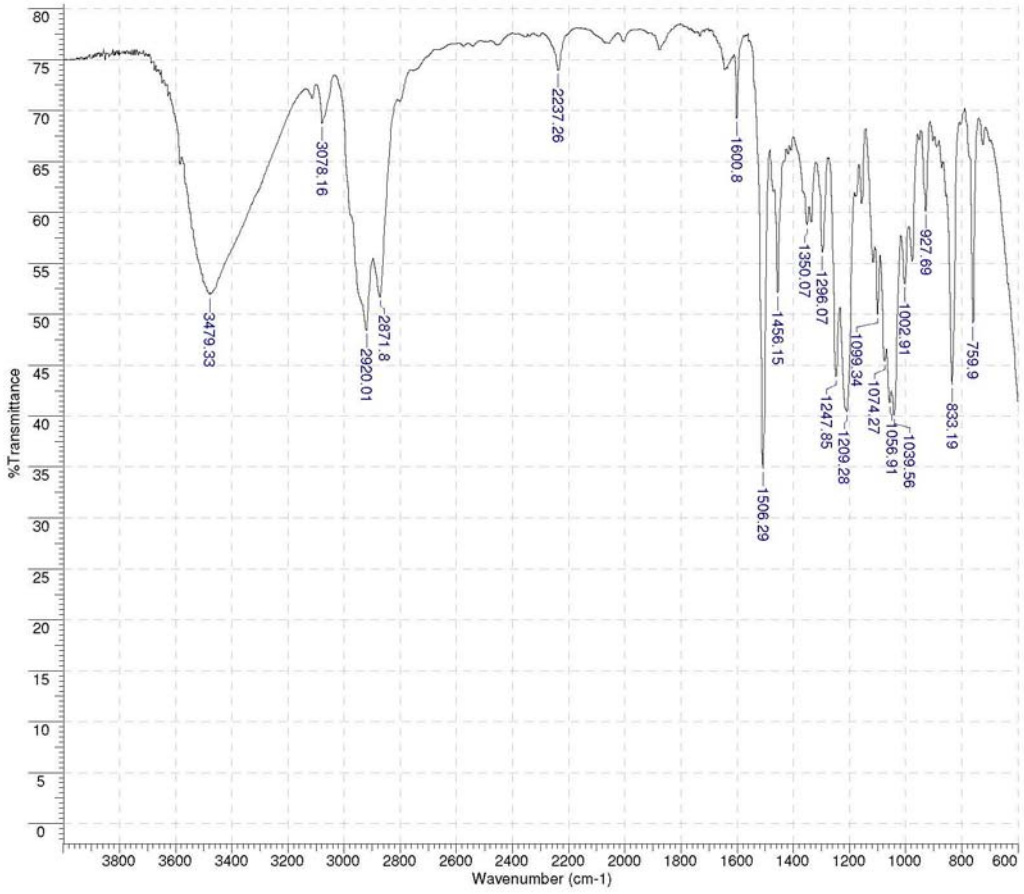

Figure S24. IR (film) spectrum of **4**.

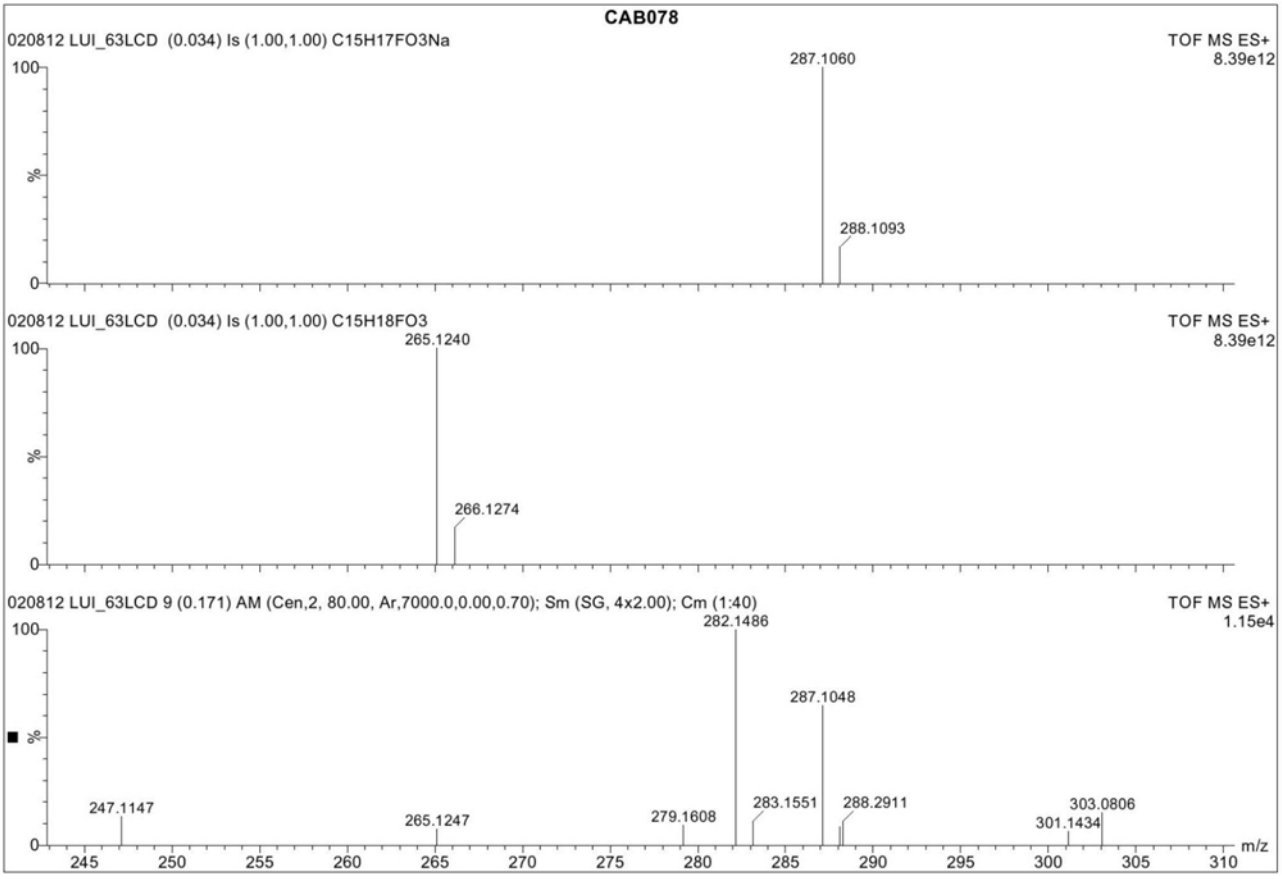

Figure S25. HRMS (ESI-TOF) *m/z* $[M + Na]^+$ for $C_{15}H_{17}FO_3$ of **4**.

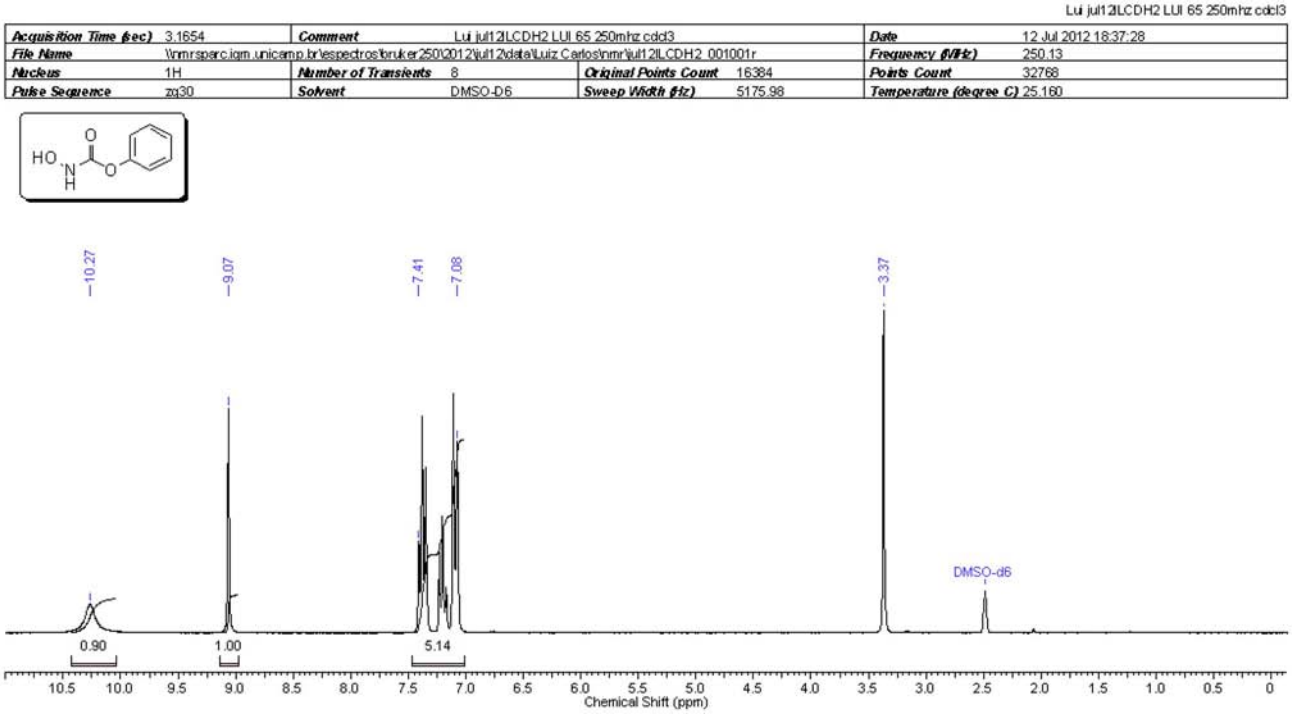

Figure S26. ^{1}H RMN spectrum (250 MHz, DMSO-d_6) of **26**.

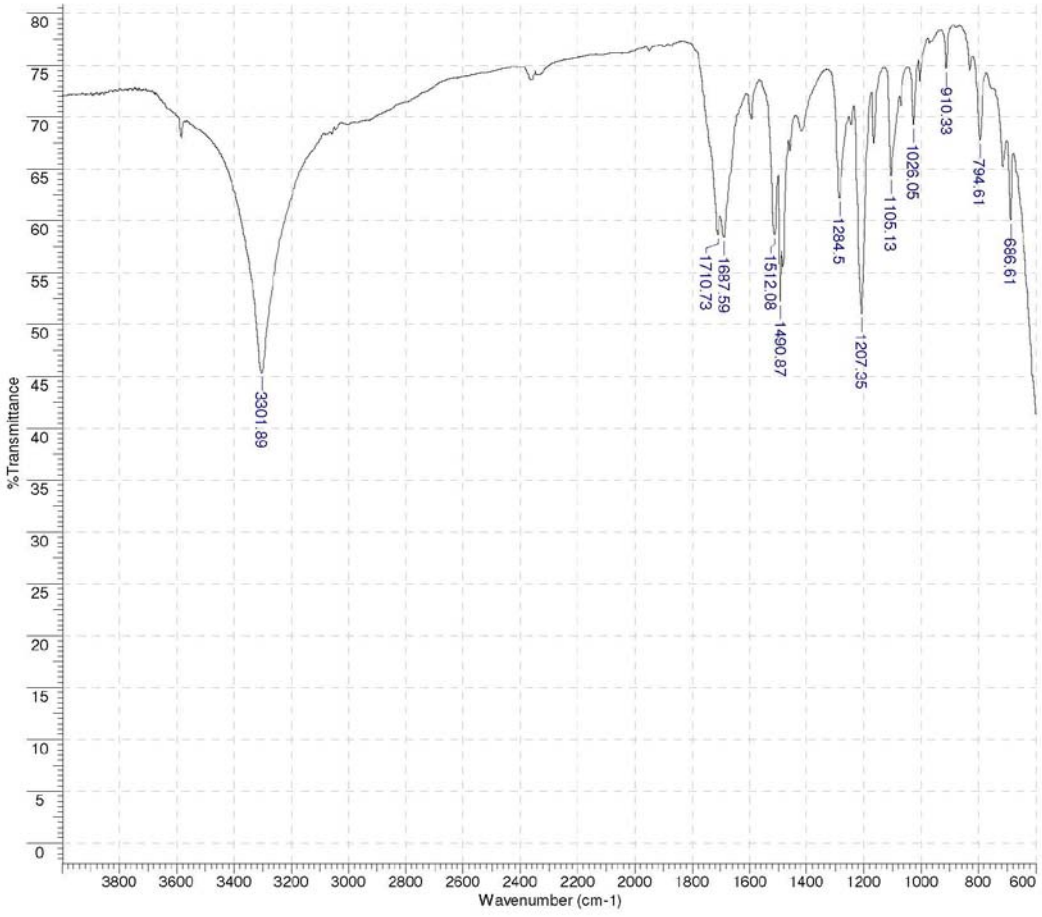

Figure S27. IR (film) spectrum of **26**.

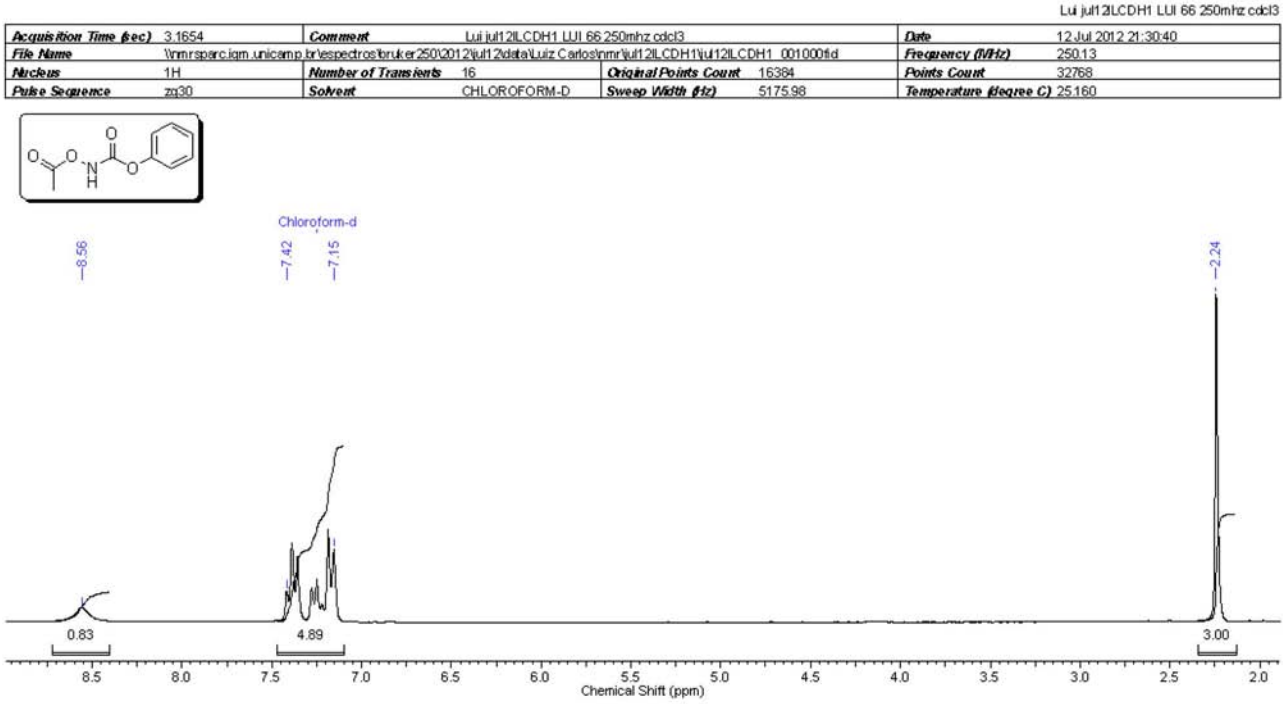

Figure S28. ^{1}H RMN spectrum (250 MHz, $CDCl_3$) of **12**.

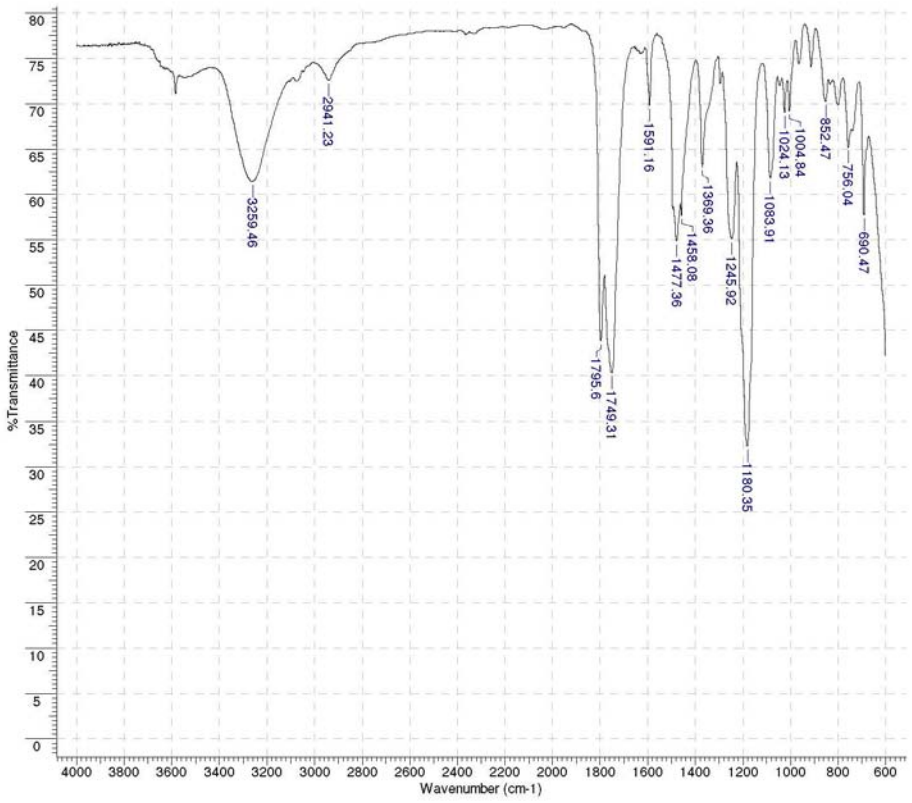

Figure S29. IR (film) spectrum of **12.**

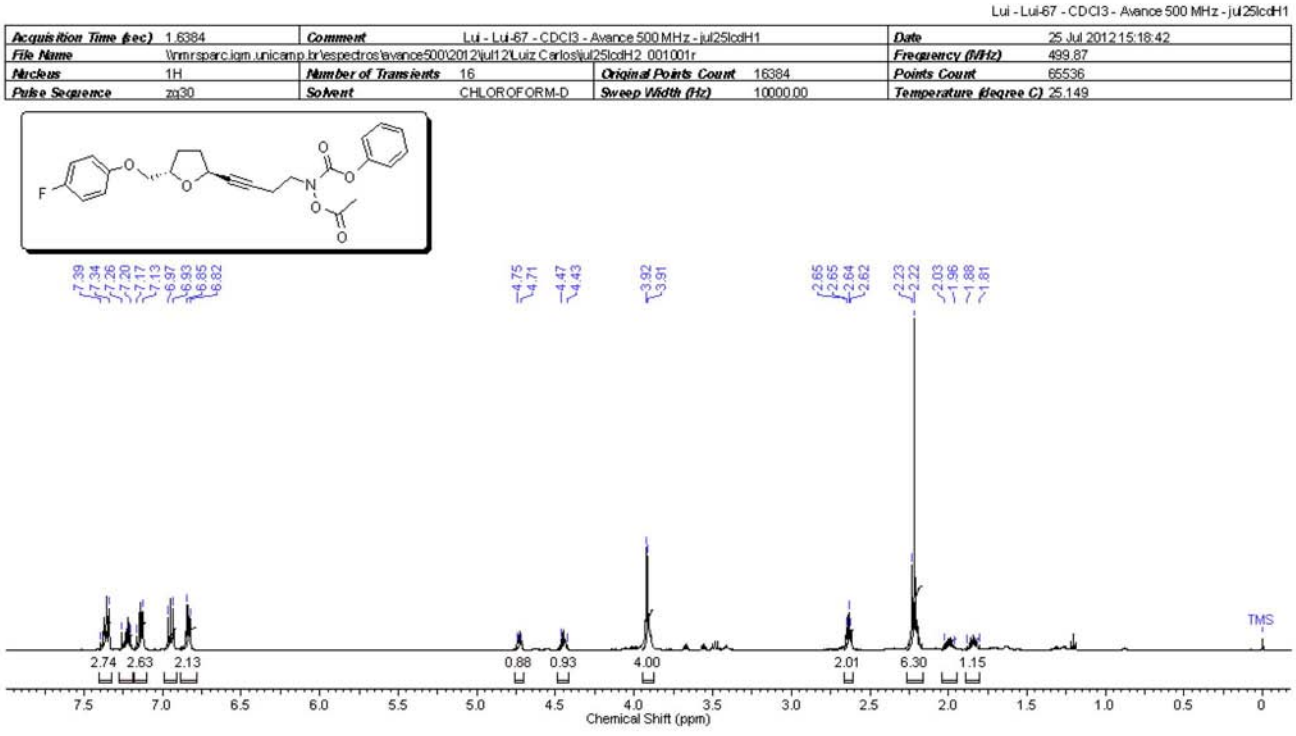

Figure S30. ^{1}H RMN spectrum (500 MHz, $CDCl_3$) of **15**.

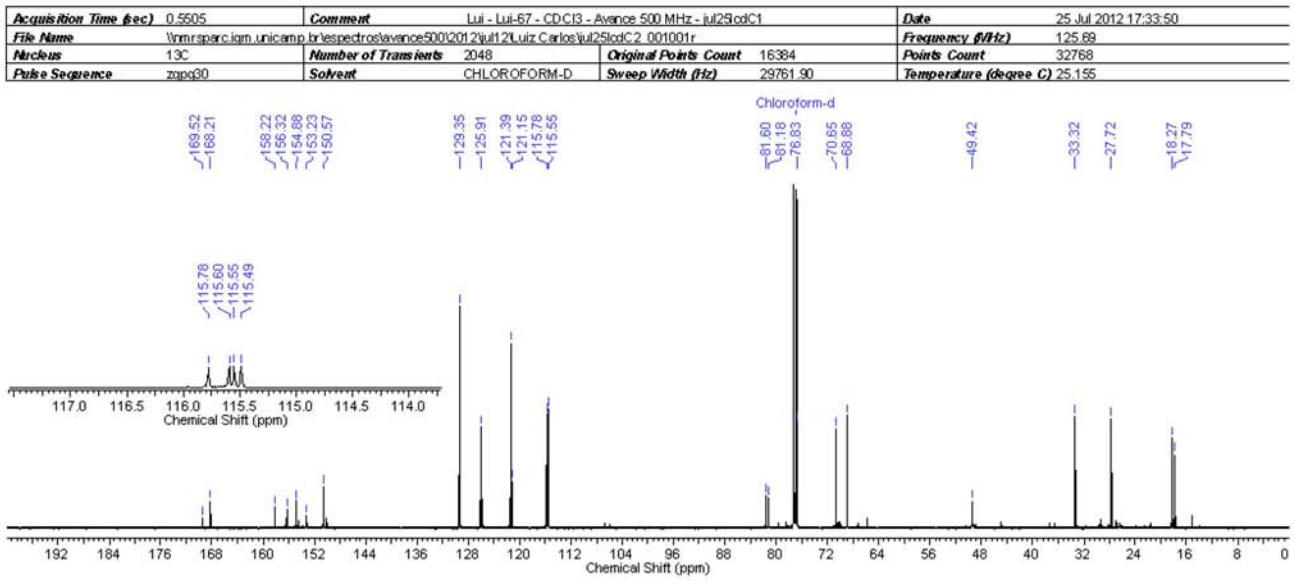

Figure S31. ^{13}C RMN spectrum (125.7 MHz, $CDCl_3$) of **15**.

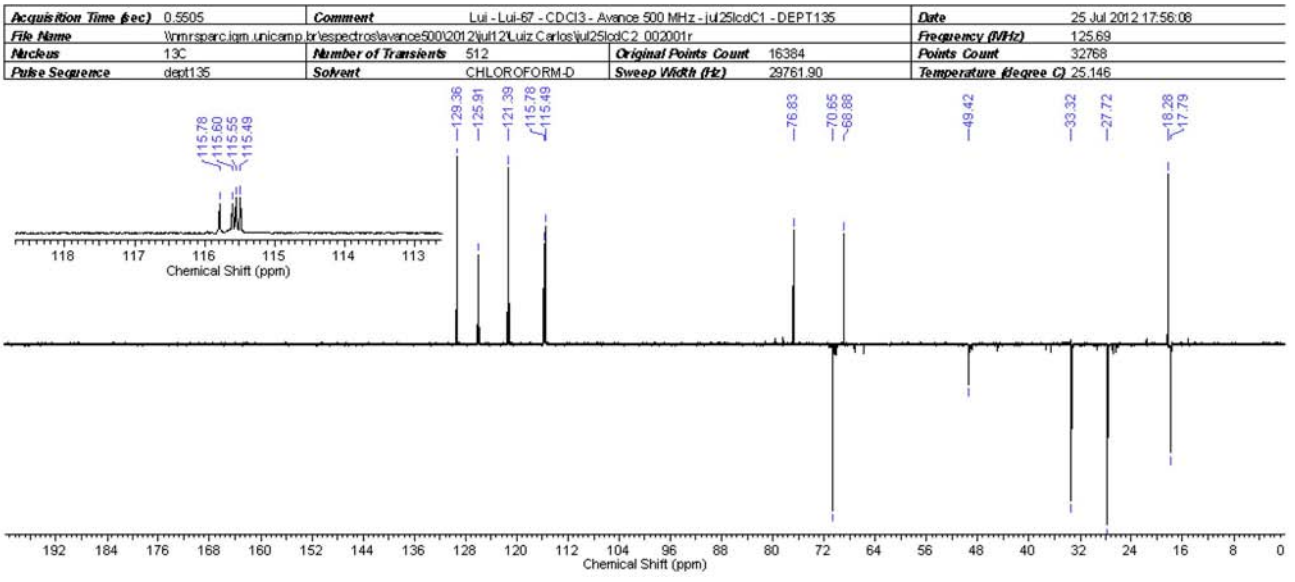

Figure S32. DEPT 135 NMR spectrum (125.7 MHz, $CDCl_3$) of **15**.

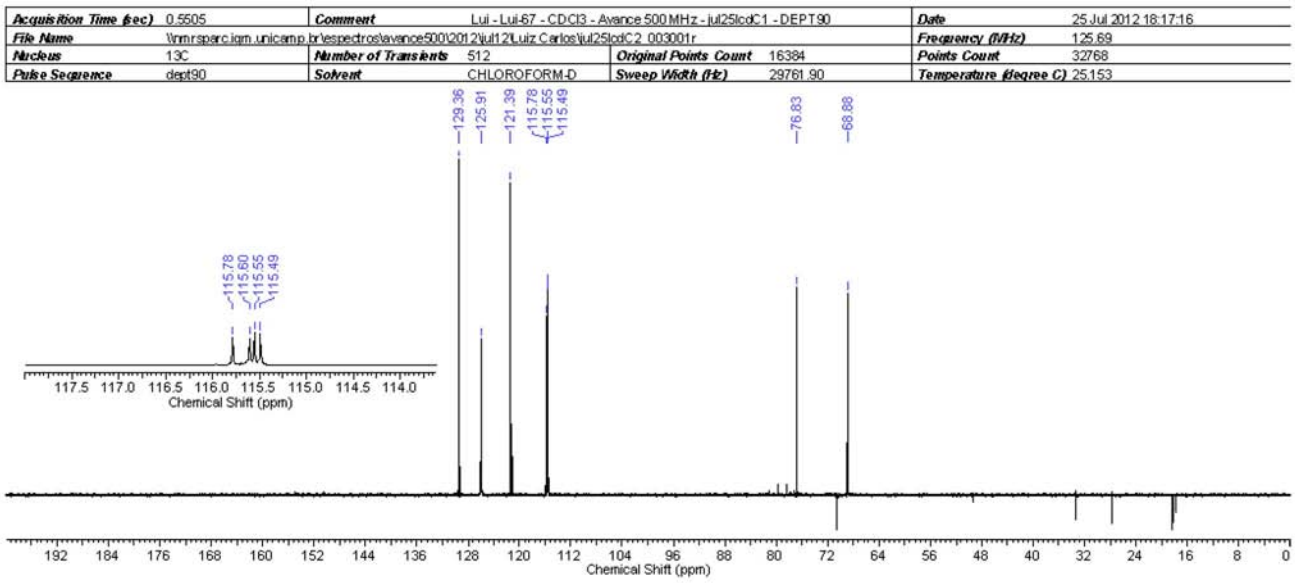

Figure S33. DEPT 90 NMR spectrum (62.9 MHz, $CDCl_3$) of **15**.

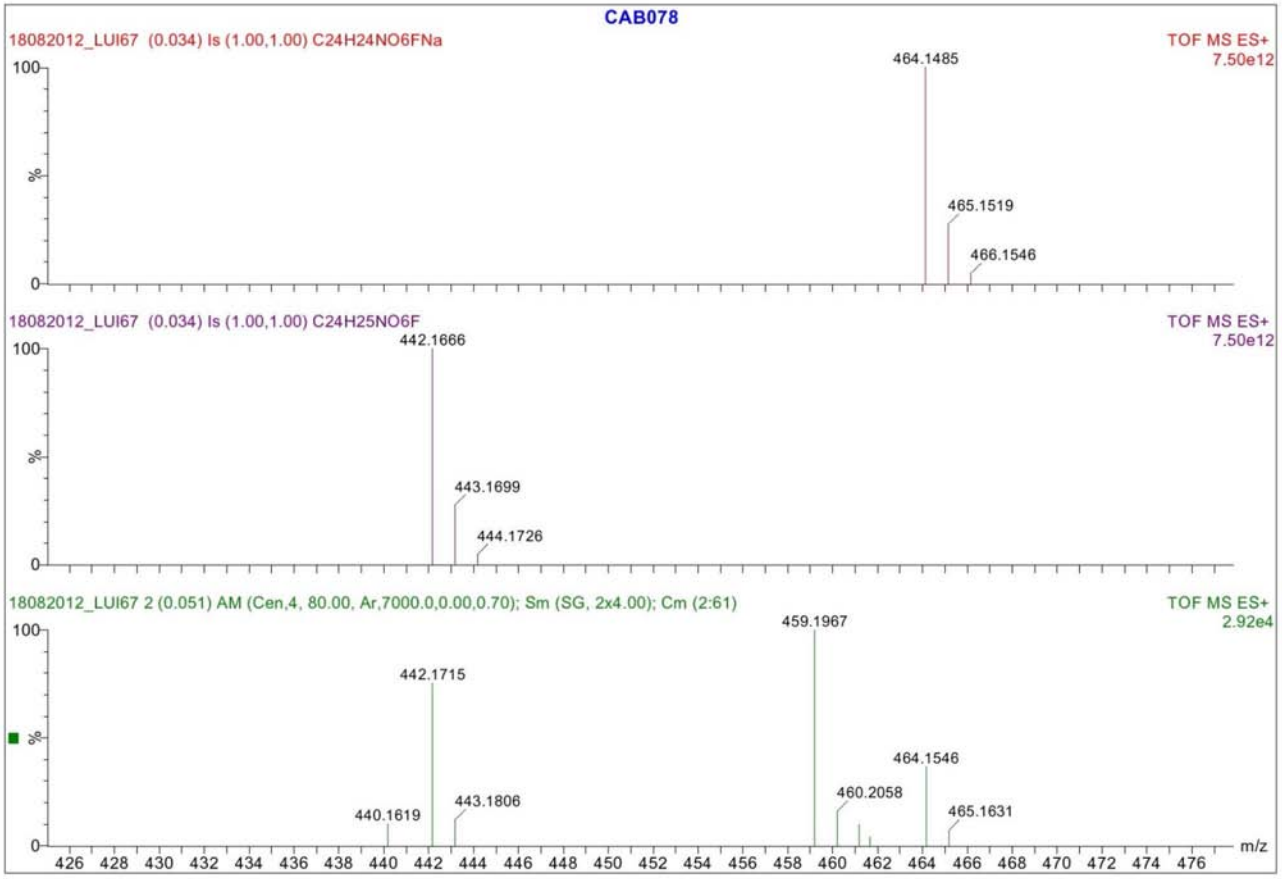

Figure S34. HRMS (ESI-TOF) *m/z* $[M + H]^+$ for $C_{24}H_{25}FNO_6$ of **15**.

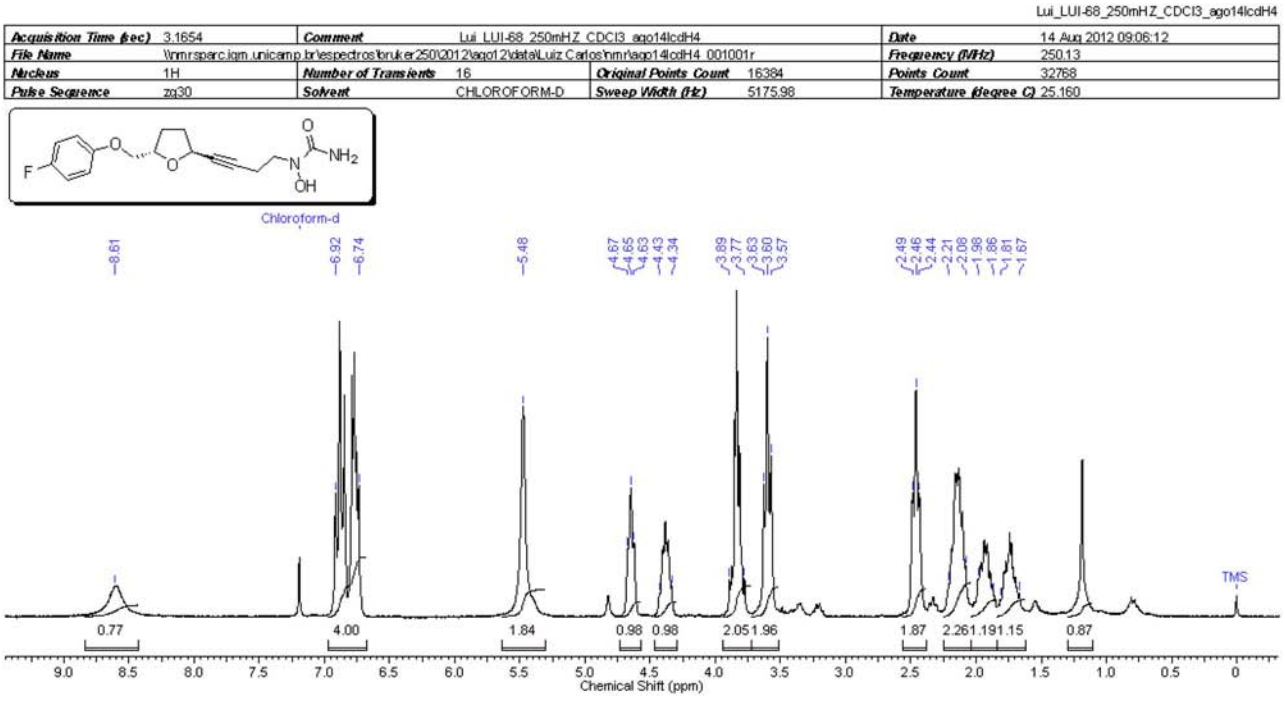

Figure S35. ^{1}H RMN spectrum (250 MHz, $CDCl_3$) of **1**.

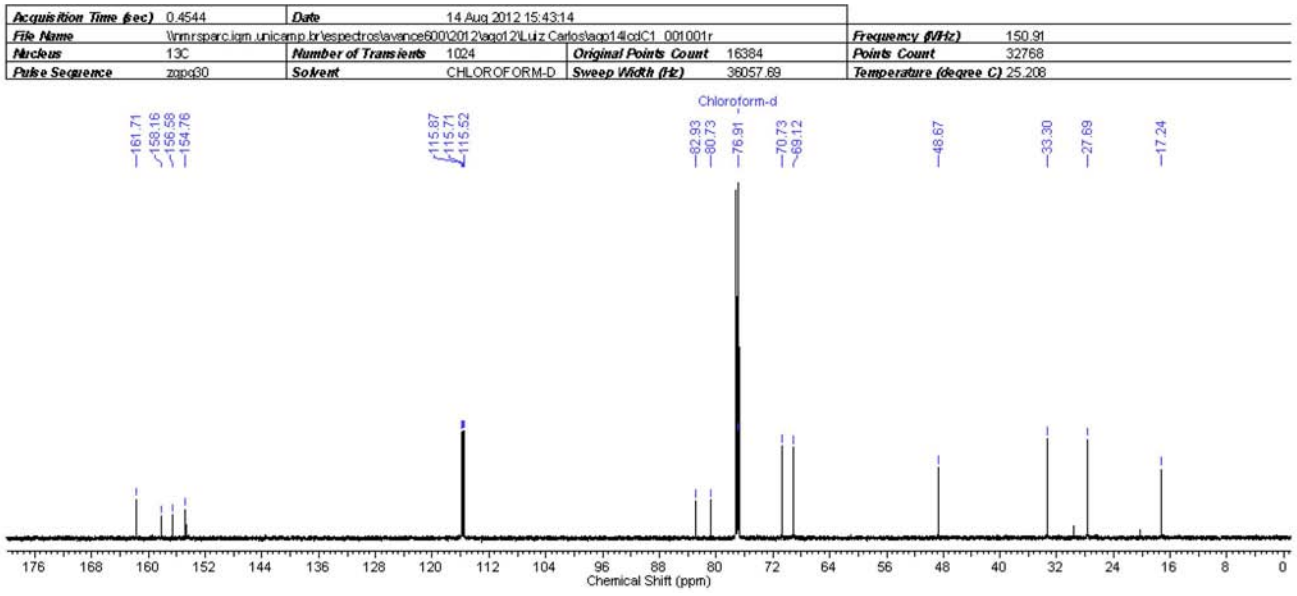

Figure S36. ^{13}C RMN spectrum (150.9 MHz, $CDCl_3$) of **1**.

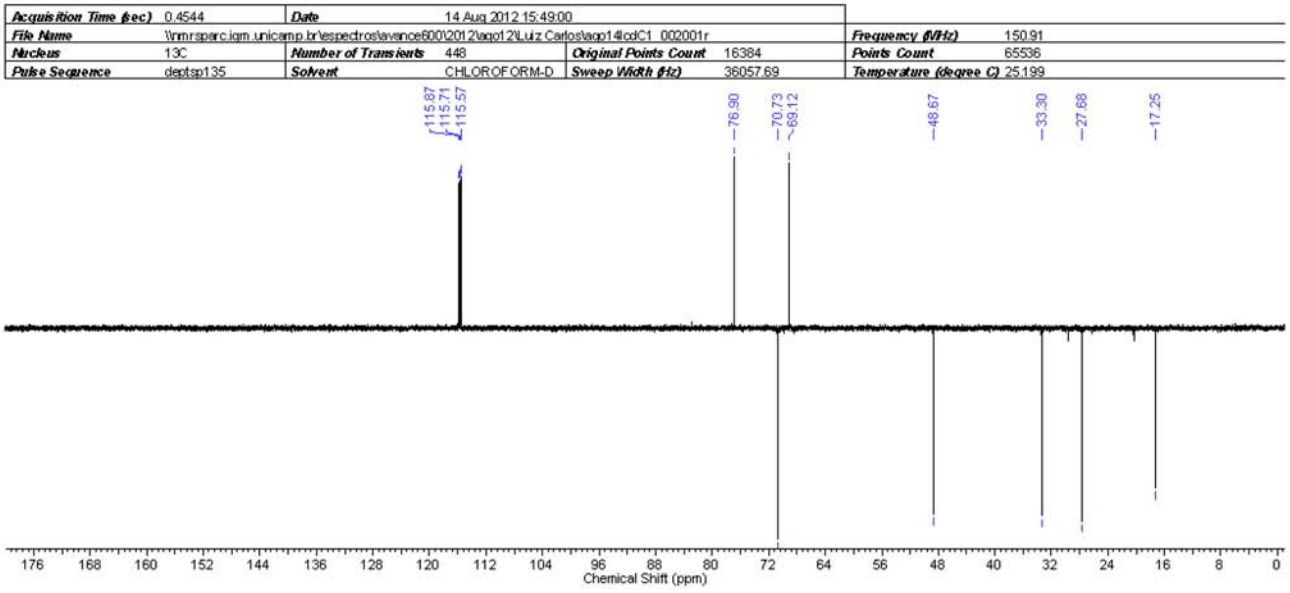

Figure S37. DEPT 135 NMR spectrum (150.9 MHz, $CDCl_3$) of **1**.

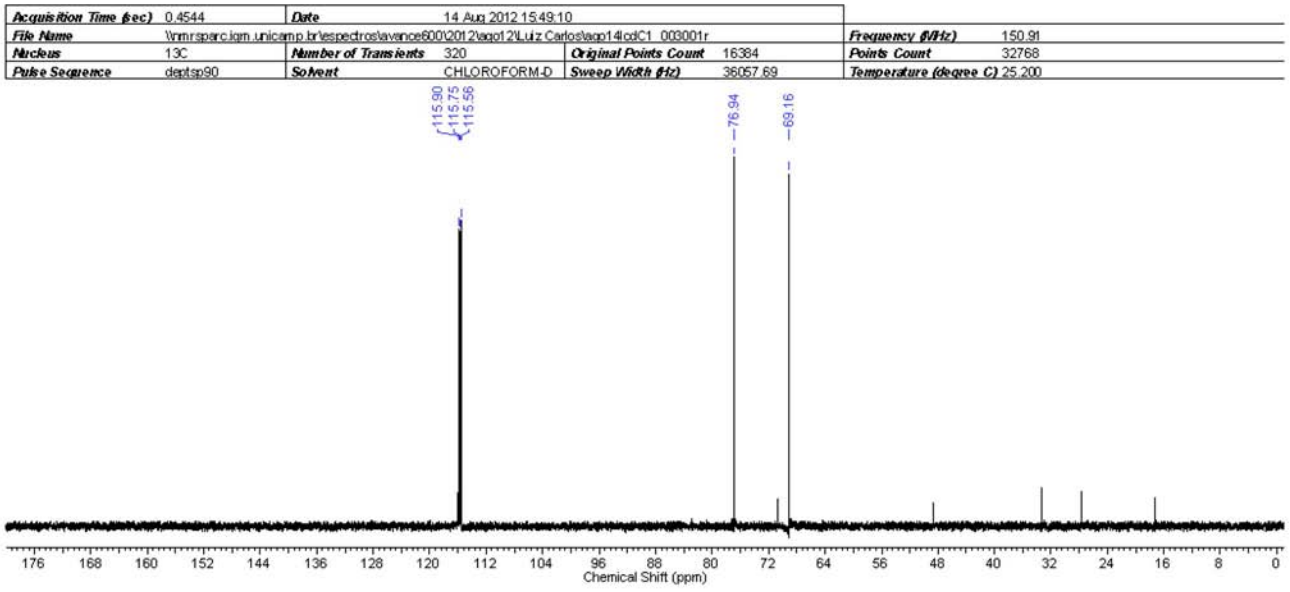

Figure S8. DEPT 90 NMR spectrum (62.9 MHz, $CDCl_3$) of **1**.

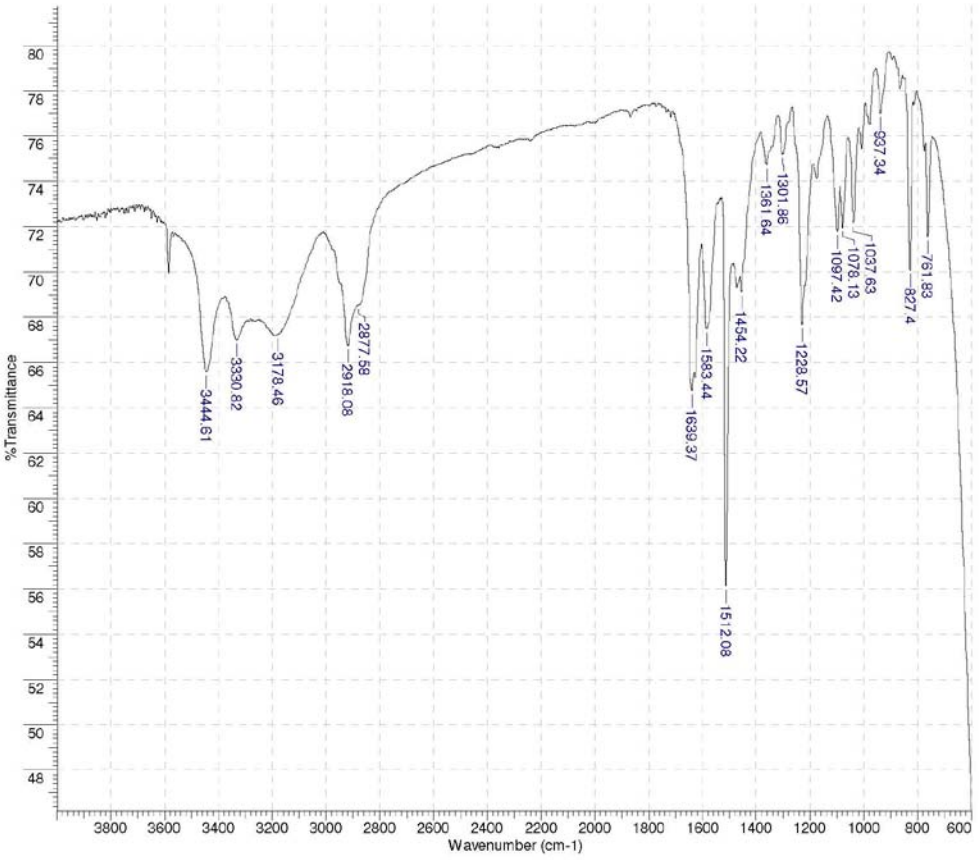

Figure S39. IR (film) spectrum of **1**.

Figure S40. HRMS (ESI-TOF) *m/z* $[M + H]^+$ for $C_{16}H_{19}FN_2O_4$ of **1**.