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# Isoeugenol and hybrid acetamides against *Candida albicans* isolated from the oral cavity

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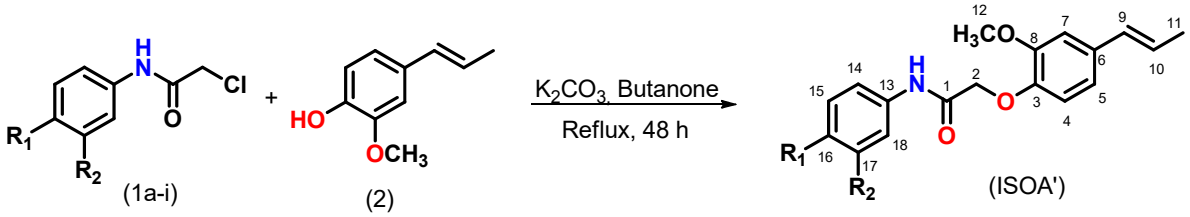
## Supplementary Material

### *2.1. Chemistry*

All reagents and solvents were purchased from commercial sources Sigma-Aldrich (São Paulo, Brazil). The recrystallization technique was used to purify the compound and its purity was confirmed from the melting point measurement using the MQAPF-302 (Microquímica) apparatus. The hydrogen and carbon nuclear magnetic resonance (NMR) spectra were obtained from a Bruker Avance 400 apparatus. The hydrogen spectra ($^{1}H$) were obtained at the frequency of 400 and 500 MHz using deuterated solvents chloroform ($CDCl_3$). The carbon spectra ($^{13}C$) were obtained at the frequency of 101 MHz using deuterated solvents chloroform ($CDCl_3$). The chemical distances ($\delta$) were generated in parts per million (ppm) and in hertz (Hz) the coupling constants ($J$) were determined. High Resolution Mass (HRMS) analysis was obtained with time-of-flight (TOF) mass spectrometer (microTOFII - Bruker) instrument using Electron Impact Ionization (EI) and reported as $m/z$ (relative intensity) for the molecular ion [M] and reporting the molecular ion [M+H].

### *2.2. General procedure for the preparation of isoeugenol derivatives*




(**ISOA1**): $R_1$ = H; $R_2$ = H
(**ISOA2**): $R_1$ = $NO_2$; $R_2$ = H
(**ISOA3**): $R_1$ = $CH_2CH_3$; $R_2$ = H
(**ISOA4**): $R_1$ = $CH_3$; $R_2$ = H
(**ISOA5**): $R_1$ = Br; $R_2$ = H
(**ISOA6**): $R_1$ = Cl; $R_2$ = H
(**ISOA7**): $R_1$ = $CH(CH_3)_2$; $R_2$ = H
(**ISOA10**): $R_1$ = Cl; $R_2$ = $NO_2$
(**ISOA11**): $R_1$ = $OCH_3$; $R_2$ = H

In a 50 mL flask, a mixture of isoeugenol (1.1 eq), $K_2CO_3$ (2.0 eq) solubilized in 10 mL of butanone was stirred at room temperature for 1 h. 2-chloro-*N*-arylacetamides[1] (1.0 eq) was added and the reaction mixture was refluxed for 48 h. At the end of the reaction, the mixture was cooled and water (30 mL) was added, extracted with ethyl acetate (2 x 30 mL), washed with water (2 x 30 mL), saturated sodium chloride solution (30 mL), dried over sodium sulfate and then evaporated under reduced pressure. The products were recrystallized using ethanol as the solvent.

(*E*)-2-(2-methoxy-4-(prop-1-en-1-yl)phenoxy)-*N*-phenylacetamide (**ISOA1**): Yield: 76%, m.p.: 80-82 °C. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.92 (s, 1H, N-H), 7.59 (d, $J$ = 8.0 Hz, 2H, H-14 and H-18), 7.34 (t, $J$ = 7.9 Hz, 2H, H-15 and H-17), 7.13 (t, $J$ = 7.4 Hz, 1H, H-16), 6.90 (t, $J$ = 7.7 Hz, 3H, H-4, H-5 and H-7), 6.34 (d, $J$ = 16.0 Hz, 1H, H-9), 6.15 (dq, $J$ = 13.1, 6.6 Hz, 1H, H-10), 4.63 (s, 2H, H-2), 3.94 (s, 3H, H-12), 1.87 (d, $J$ = 6.6 Hz, 3H, H-11). $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$ 166.96 (C-1), 149.82 (C-2), 146.27 (C-8), 137.28 (C-13), 133.97 (C-6), 130.25 (C-7), 129.05 (C-15 and C-17), 125.38 (C-4), 124.56 (C-16), 119.87 (C-14 and C-18), 119.00 (C-5), 116.63 (C-9), 109.32 (C-10), 70.63 (C-2), 55.89 (C-12), 18.39 (C-11). HRMS *m*/*z*, calculated for $C_{18}H_{19}NO_3$ [M + H] = 298.1443, found: 298.1438.

(*E*)-2-(2-methoxy-4-(prop-1-en-1-yl)phenoxy)-*N*-(4-nitrophenyl)acetamide (**ISOA2**): Yield: 80%, m.p.: 120-122 °C. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 9.36 (s, 1H, N-H), 8.23 (d, $J$ = 9.0 Hz, 2H, H-15 and H-17), 7.79 (d, $J$ = 8.9 Hz, 2H, H-14 and H-18), 6.93 (d, $J$ = 13.1 Hz, 3H, H-4, H-5 and H-7), 6.35 (d, $J$ = 15.7 Hz, 1H, H-9), 6.17 (dq, $J$ = 13.3, 6.5 Hz, 1H, H-10), 4.66 (s, 2H, H-2), 3.96 (s, 3H, H-12), 1.88 (d, $J$ = 6.6 Hz, 3H, H-11). $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$ 167.68 (C-1), 149.81 (C-3), 146.06 (C-8), 143.81 (C-16), 143.08 (C-13), 134.48 (C-6), 130.11 (C-7), 125.78 (C-4), 125.13 (C-15 and C-17), 119.23 (C-14 and C-18), 119.18 (C-5), 117.19 (C-9), 109.55 (C-10), 70.87 (C-2), 56.05 (C-12), 18.41 (C-11). HRMS *m*/*z*, calculated for $C_{18}H_{18}N_2O_5$ [M + H] = 343.1294, found: 343.1274

(*E*)-*N*-(4-ethylphenyl)-2-(2-methoxy-4-(prop-1-en-1-yl)phenoxy)acetamide (**ISOA3**): Yield: 92%, m.p.: 83-85 °C. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.85 (s, 1H, N-H), 7.49 (d, $J$ = 8.3 Hz, 2H, H-14 and H-18), 7.17 (d, $J$ = 8.3 Hz, 2H, H-15 and H-17), 6.94 – 6.88 (m, 3H, H-4, H-5 and H-7), 6.34 (d, $J$ = 15.7 Hz, 1H, H-9), 6.15 (dq, $J$ = 13.2, 6.6 Hz, 1H, H-10), 4.62 (s, 2H, H-2), 3.94 (s, 3H, H-12), 2.62 (q, $J$ = 7.6 Hz, 2H,

$CH_2$), 1.87 (d, *J* = 6.5 Hz, 3H, H-11), 1.22 (t, *J* = 7.6 Hz, 3H, $CH_3$). $^{13}C$ NMR (101 MHz, $CDCl_3$) $\delta$ 166.81 (C-1), 149.82 (C-3), 146.30 (C-8), 140.69 (C-16), 134.87 (C-13), 133.91 (C-6), 130.26 (C-7), 128.38 (C-14 and C-18), 125.34 (C-4), 120.04 (C-15 and C-17), 118.99 (C-5), 116.56 (C-9), 109.30 (C-10), 70.61 (C-2), 55.89 (C-12), 28.34 ($CH_2$), 18.40 (C-11), 15.66 ($CH_3$). HRMS *m*/*z*, calculated for $C_{20}H_{23}NO_3$ [M + H] = 326.1756, found: 326.1750.

(*E*)-2-(2-methoxy-4-(prop-1-en-1-yl)phenoxy)-*N*-(p-tolyl)acetamide (**ISOA4**): Yield: 84%, m.p.: 81-83 °C. $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 8.86 (s, 1H, N-H), 7.48 (d, *J* = 8.3 Hz, 2H, H-14 and H-18), 7.15 (d, *J* = 8.2 Hz, 2H, H-15 and H-17), 6.91 (d, *J* = 14.4 Hz, 3H, H-4, H-5 and H-7), 6.35 (dd, *J* = 15.7, 1.5 Hz, 1H, H-9), 6.16 (dq, *J* = 13.2, 6.6 Hz, 1H, H-10), 4.62 (s, 2H, H-2), 3.94 (s, 3H, H-12), 2.33 (s, 3H, $CH_3$), 1.88 (dd, *J* = 6.6, 1.5 Hz, 3H, H-11). $^{13}C$ NMR (101 MHz, $CDCl_3$) $\delta$ 166.83 (C-1), 149.84 (C-3), 146.31 (C-8), 134.75 (C-13), 134.22 (C-16), 133.91 (C-6), 130.29 (C-7), 129.56 (C-14 and C-18), 125.34 (C-4), 119.95 (C-15 and C-17), 119.00 (C-5), 116.57 (C-9), 109.32 (C-10), 70.61 (C-2), 55.90 (C-12), 20.92 ($CH_3$), 18.42 (C-11). HRMS *m*/*z*, calculated for $C_{19}H_{21}NO_3$ [M + H] = 312.1600, found: 312.1585.

(*E*)-*N*-(4-bromophenyl)-2-(2-methoxy-4-(prop-1-en-1-yl)phenoxy)acetamide (**ISOA5**): Yield: 72%, m.p.: 103-105 °C. $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 8.97 (s, 1H, N-H), 7.50 (d, *J* = 9.1 Hz, 2H, H-15 and H-17), 7.44 (d, *J* = 9.0 Hz, 2H, H-14 and H-18), 6.90 (t, *J* = 8.0 Hz, 3H, H4, H-5, H-7), 6.34 (dd, *J* = 15.7, 1.6 Hz, 1H, H-9), 6.15 (dq, *J* = 13.2, 6.6 Hz, 1H, H-10), 4.61 (s, 2H, H-2), 3.93 (s, 3H, H-12), 1.87 (dd, *J* = 6.6, 1.7 Hz, 3H, H-11). $^{13}C$ NMR (101 MHz, $CDCl_3$) $\delta$ 167.05 (C-1), 149.79 (C-3), 146.17 (C-8), 136.39 (C-13), 134.12 (C-6), 132.02 (C-14 and C-18), 130.19 (C-7), 125.51 (C-4), 121.36 (C-15 and C-17), 119.05 (C-5), 117.14 (C-16), 116.80 (C-9), 109.38 (C-10), 70.68 (C-2), 55.93 (C-12), 18.40 (C-11). HRMS *m*/*z*, calculated for $C_{18}H_{18}BrNO_3$ [M + H] = 376.0548, found: 376.0526.

(*E*)-*N*-(4-chlorophenyl)-2-(2-methoxy-4-(prop-1-en-1-yl)phenoxy)acetamide (**ISOA6**): Yield: 90%, m.p.: 92-94 °C. $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 8.96 (s, 1H, N-H), 7.55 (d, *J* = 8.9 Hz, 2H, H-15 and H-17), 7.30 (d, *J* = 8.8 Hz, 2H, H-14 and H-18), 6.91 (t, *J* = 7.8 Hz, 3H, H-4, H-5 and H-7), 6.34 (dd, *J* = 15.7, 1.6 Hz, 1H, H-9), 6.16 (dq, *J* = 15.7, 6.6 Hz, 1H, H-10), 4.62 (s, 2H, H-2), 3.94 (s, 3H, H-12), 1.88 (dd, *J* = 6.6, 1.6 Hz, 3H, H-11). $^{13}C$ NMR (101 MHz, $CDCl_3$) $\delta$ 167.03 (C-1), 149.81 (C-3), 146.19 (C-8), 135.89 (C-13), 134.13 (C-6), 130.20 (C-7), 129.54 (C-16), 129.08 (C-14 and C-18), 125.52 (C-4), 121.04 (C-15 and C-17), 119.06 (C-5), 116.80 (C-9), 109.39 (C-10), 70.67 (C-2), 55.94 (C-12), 18.40 (C-11). HRMS *m*/*z*, calculated for $C_{18}H_{18}ClNO_3$ [M + H] = 332.1053, found: 332.1036.

(*E*)-*N*-(4-isopropylphenyl)-2-(2-methoxy-4-(prop-1-en-1-yl)phenoxy)acetamide (**ISOA7**): Yield: 76%, m.p.: 98-100 °C. $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 8.85 (s, 1H, N-H), 7.49 (d, *J* = 8.6 Hz, 2H, H-14 and H-18), 7.20 (d, *J* = 8.4 Hz, 2H, H-15 and H-17), 6.93 – 6.88 (m, 3H, H-4, H-5 and H-7), 6.34 (dd, *J* = 15.7, 1.7 Hz, 1H, H-9), 6.15 (dq, *J* = 15.7, 6.6 Hz, 1H, H-10), 4.62 (s, 3H, H-2), 3.94 (s, 3H, H-12), 2.88 (hept, *J* = 6.9 Hz, 1H, CH), 1.87 (dd, *J* = 6.6, 1.6 Hz, 3H, H-11), 1.23 (d, *J* = 6.9 Hz, 6H, $CH_3$). $^{13}C$ NMR (101 MHz, $CDCl_3$) $\delta$ 166.83 (C-1), 149.81 (C-3), 146.30 (C-8), 145.32 (C-16), 134.92 (C-13), 133.90 (C-6), 130.27 (C-7), 126.94 (C-14 and C-18), 125.33 (C-4), 120.06 (C-15 and C-17), 118.99 (C-5), 116.55 (C-9), 109.30 (C-10), 70.61 (C-2), 55.88 (C-12), 33.63 (CH), 24.02 ($CH_3$), 18.39 (C-11). HRMS *m*/*z*, calculated for $C_{21}H_{25}NO_3$ [M + H] = 340.1913, found: 340.1899.

(*E*)-*N*-(4-chloro-3-nitrophenyl)-2-(2-methoxy-4-(prop-1-en-1-yl)phenoxy)acetamide (**ISOA10**): Yield: 72%, m.p.: 118-120 °C. $^{1}$H NMR (400 MHz, $CDCl_3$) $\delta$ 9.31 (s, 1H, N-H), 8.20 (d, *J* = 2.5 Hz, 1H, H-18), 7.81 (dd, *J* = 8.8, 2.4 Hz, 1H, H-14), 7.48 (d, *J* = 8.8 Hz, 1H, H-15), 6.91 (d, *J* = 15.7 Hz, 3H, H-4, H-5 and H-7), 6.34 (dd, *J* = 15.7, 1.6 Hz, 1H, H-9), 6.16 (dq, *J* = 15.7, 6.5 Hz, 1H, H-10), 4.63 (s, 2H, H-2), 3.95 (s, 3H, H-12), 1.87 (dd, *J* = 6.6, 1.6 Hz, 3H, H-11). $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$ 167.73 (C-1), 149.84 (C-3), 147.96 (C-17), 146.13 (C-8), 137.04 (C-13), 134.57 (C-6), 132.34 (C-14), 130.18 (C-7), 125.89 (C-, 123.95 (C-15), 121.75 (C-16), 119.28 (C-5), 117.33 (C-4), 116.46 (C-9), 109.63 (C-10), 70.96 (C-2), 56.14 (C-12), 18.50 (C-11). HRMS *m*/*z*, calculated for $C_{18}H_{17}ClN_2O_5$ [M + H] = 377.0904, found: 377.0881.

(*E*)-2-(2-methoxy-4-(prop-1-en-1-yl)phenoxy)-*N*-(4-methoxyphenyl)acetamide (**ISOA11**): Yield: 80%, m.p.: 96-98 °C. $^{1}$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.80 (s, 1H, N-H), 7.49 (d, *J* = 9.0 Hz, 2H, H-14 and H-18), 6.94 – 6.86 (m, 5H, H-15, H-17, H-4, H-5 and H-7), 6.34 (dd, *J* = 15.7, 1.6 Hz, 1H, H-9), 6.15 (dq, *J* = 15.7, 6.6 Hz, 1H, H-10), 4.62 (s, 2H, H-2), 3.94 (s, 3H, H-12), 3.79 (s, 3H, $OCH_3$), 1.88 (dd, *J* = 6.6, 1.6 Hz, 3H, H-11). $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$ 166.68 (C-1), 156.61 (C-16), 149.80 (C-3), 146.29 (C-8), 133.88 (C-6), 130.40 (C-13), 130.26 (C-7), 125.34 (C-14 and C-18), 121.64 (C-4), 118.99 (C-5), 116.49 (C-9), 114.21 (C-15 and C-17), 109.30 (C-10), 70.53 (C-2), 55.89 ($OCH_3$), 55.48 (C-12), 18.40 (C-11). HRMS *m*/*z*, calculated for $C_{19}H_{21}NO_4$ [M + H] = 328.1549, found: 328.1543.

*2.3. NMR and Mass Spectrum*

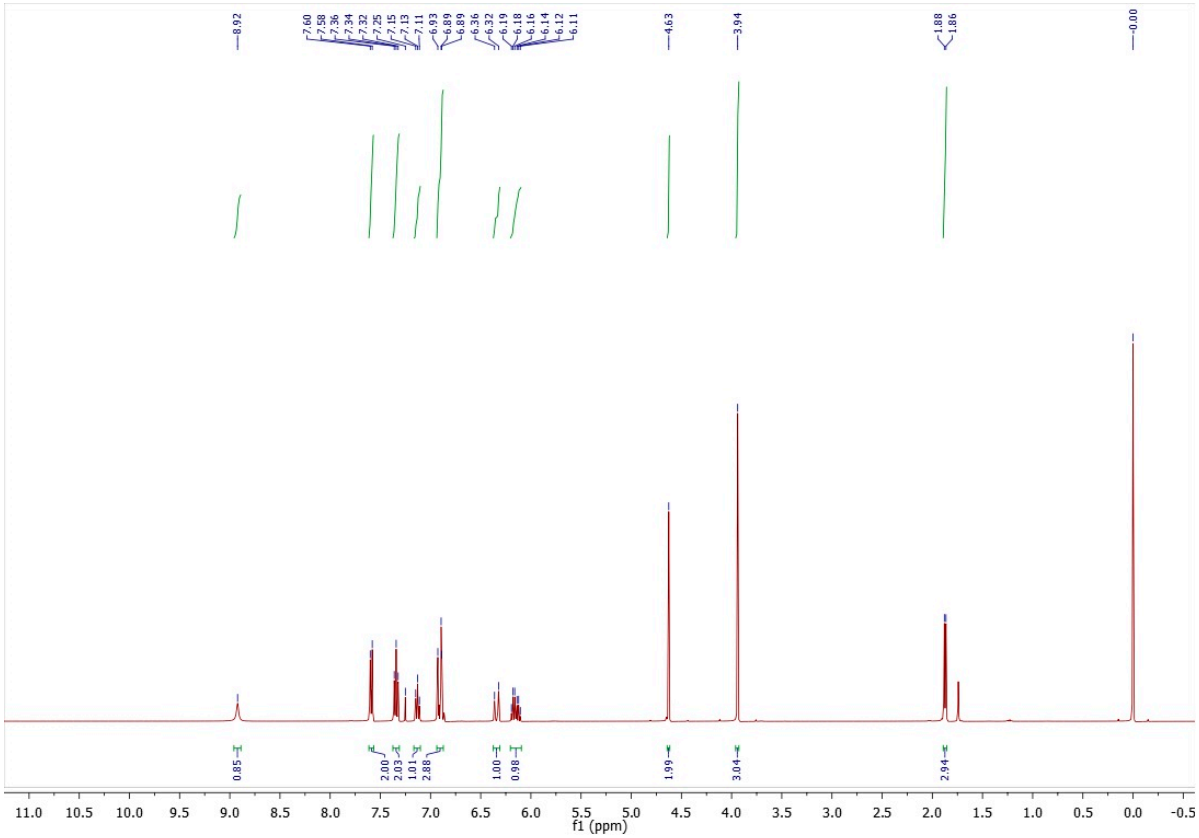



**Figure S1:** $^{1}$H NMR spectrum (400 MHz, $CDCl_3$) of compound ISOA1.

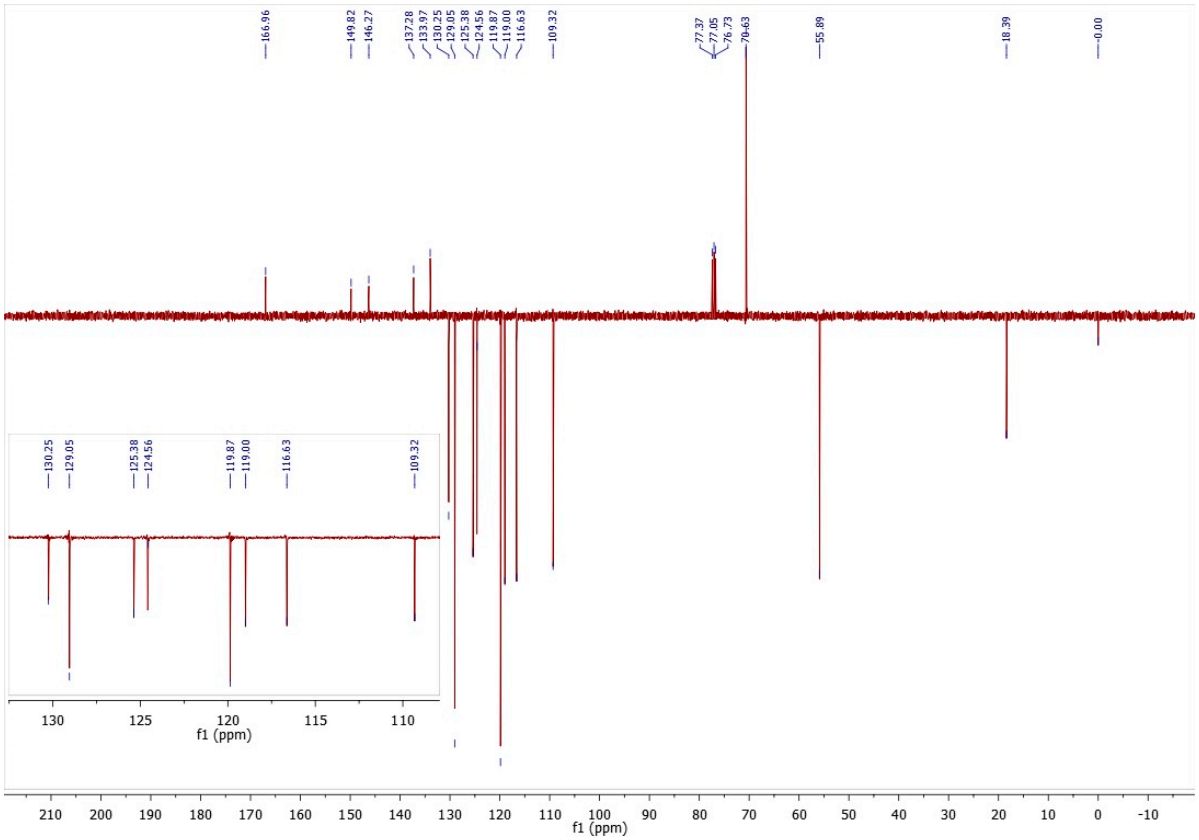



**Figure S2:** $^{13}C$ NMR spectrum (101 MHz, $CDCl_3$) of compound ISOA1.

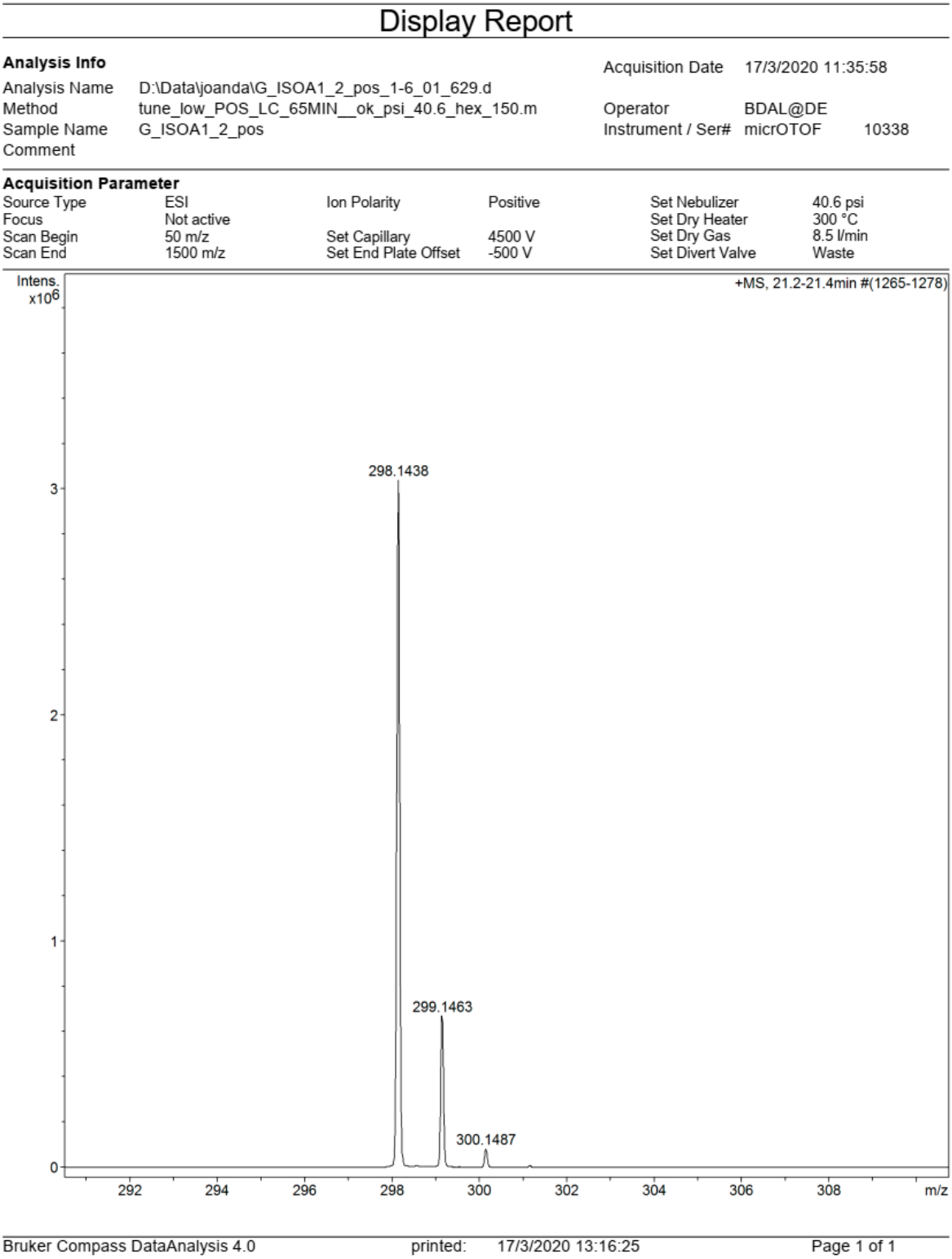



**Figure S3**: Mass spectrum of compound ISOA1.

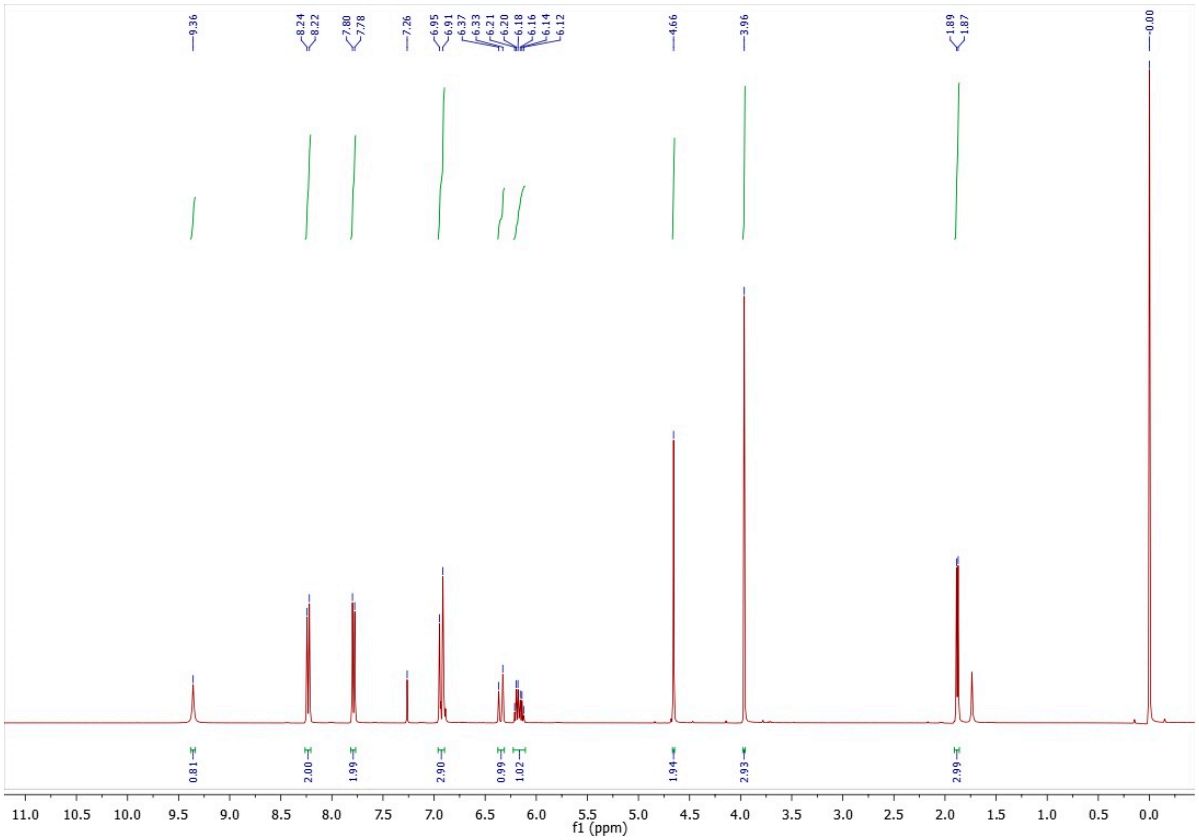



**Figure S4:** $^{1}$H NMR spectrum (400 MHz, $CDCl_3$) of compound ISOA2.

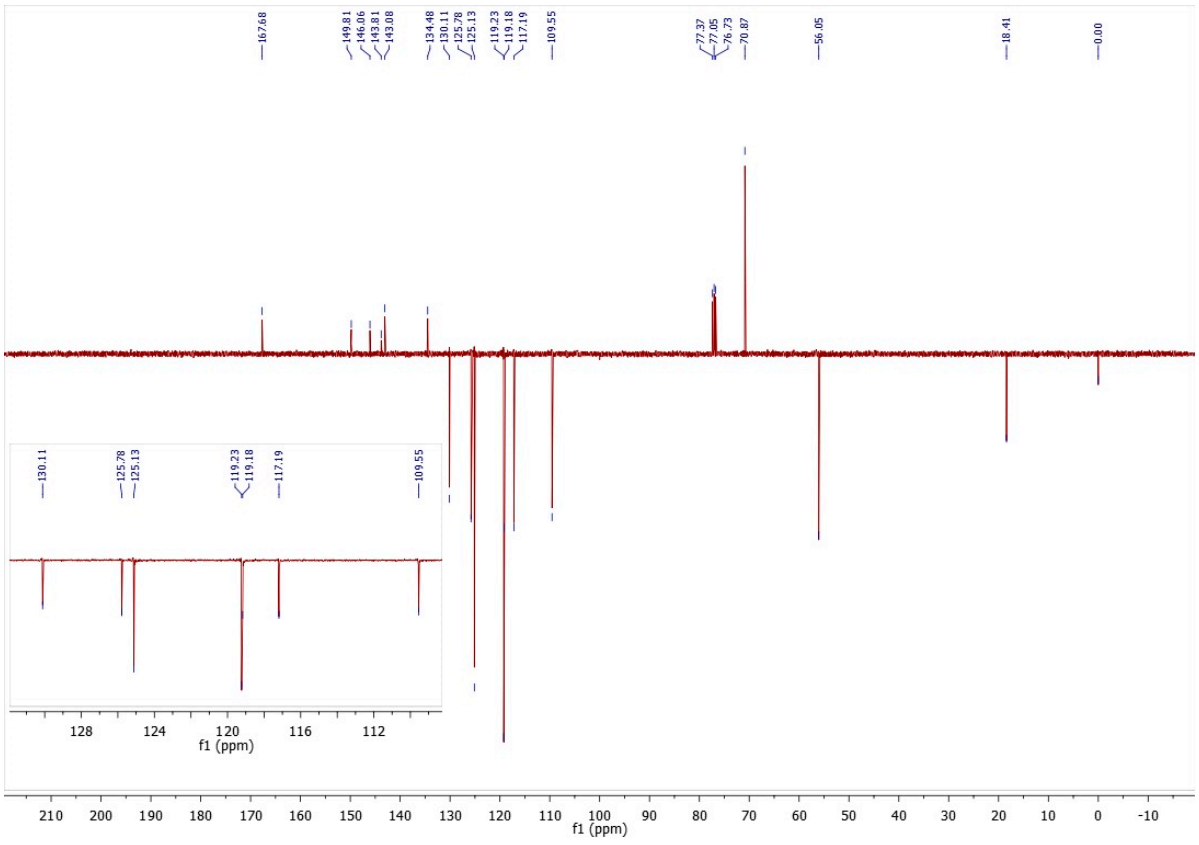
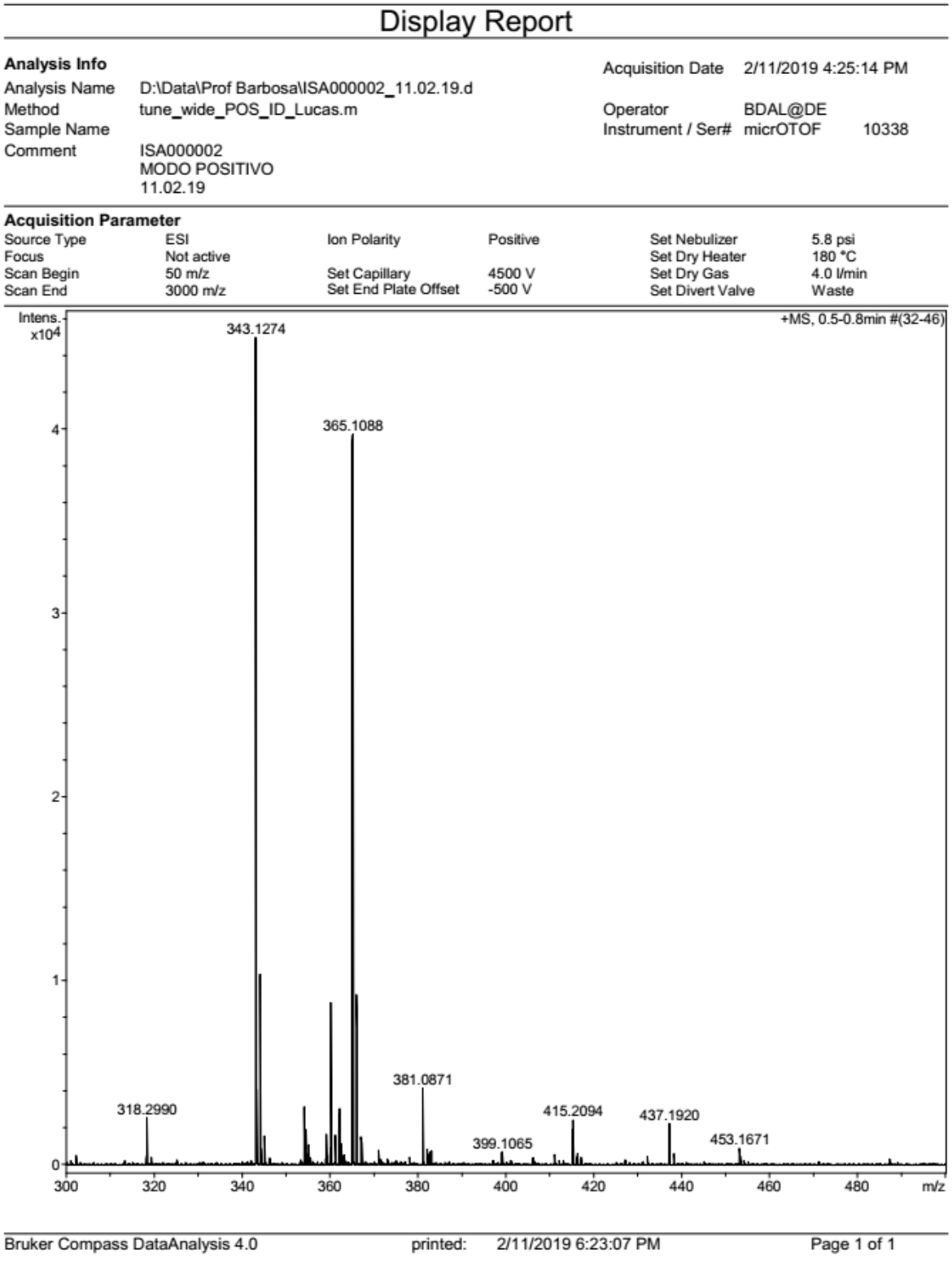



**Figure S5:** $^{13}$C NMR spectrum (101 MHz, $CDCl_3$) of compound ISOA2.

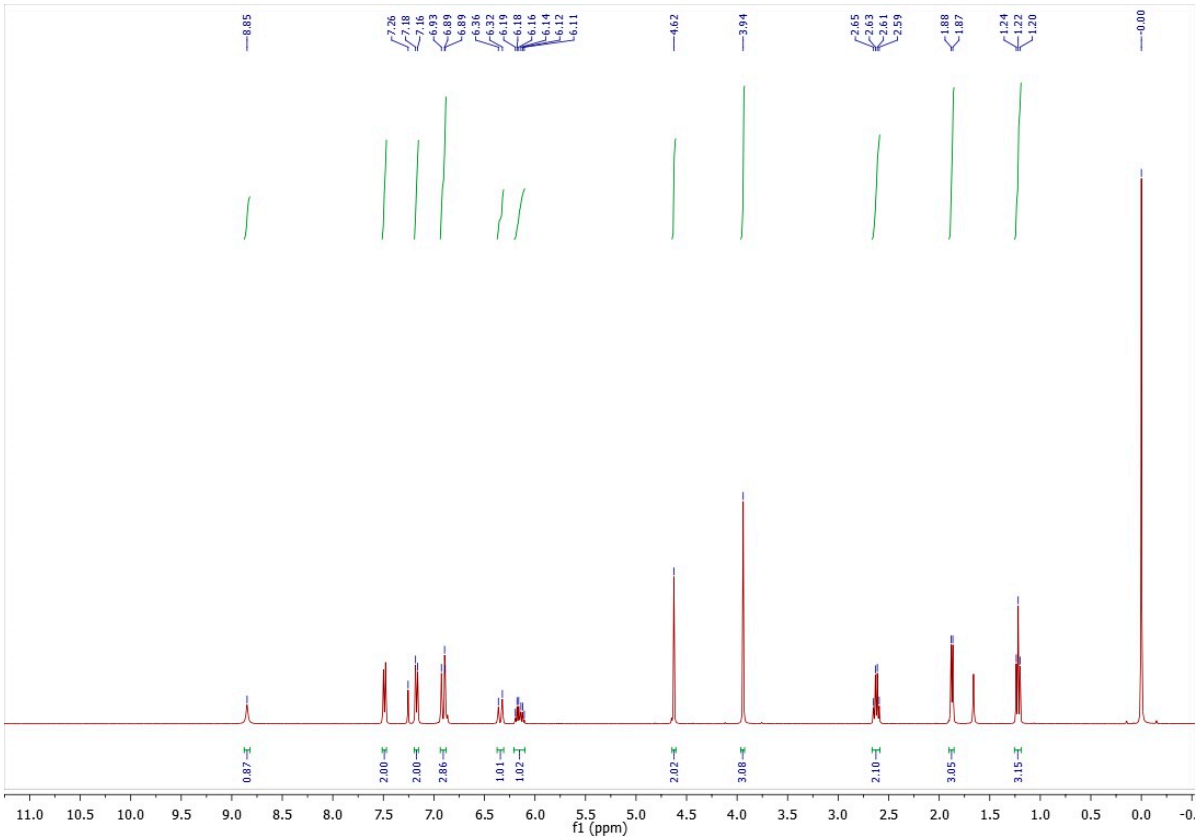
141




142

143 **Figure S6:** Mass spectrum of compound ISOA2.

144




145

146 **Figure S7:** $^{1}$H NMR spectrum (400 MHz, $CDCl_3$) of compound ISOA3.

147

148

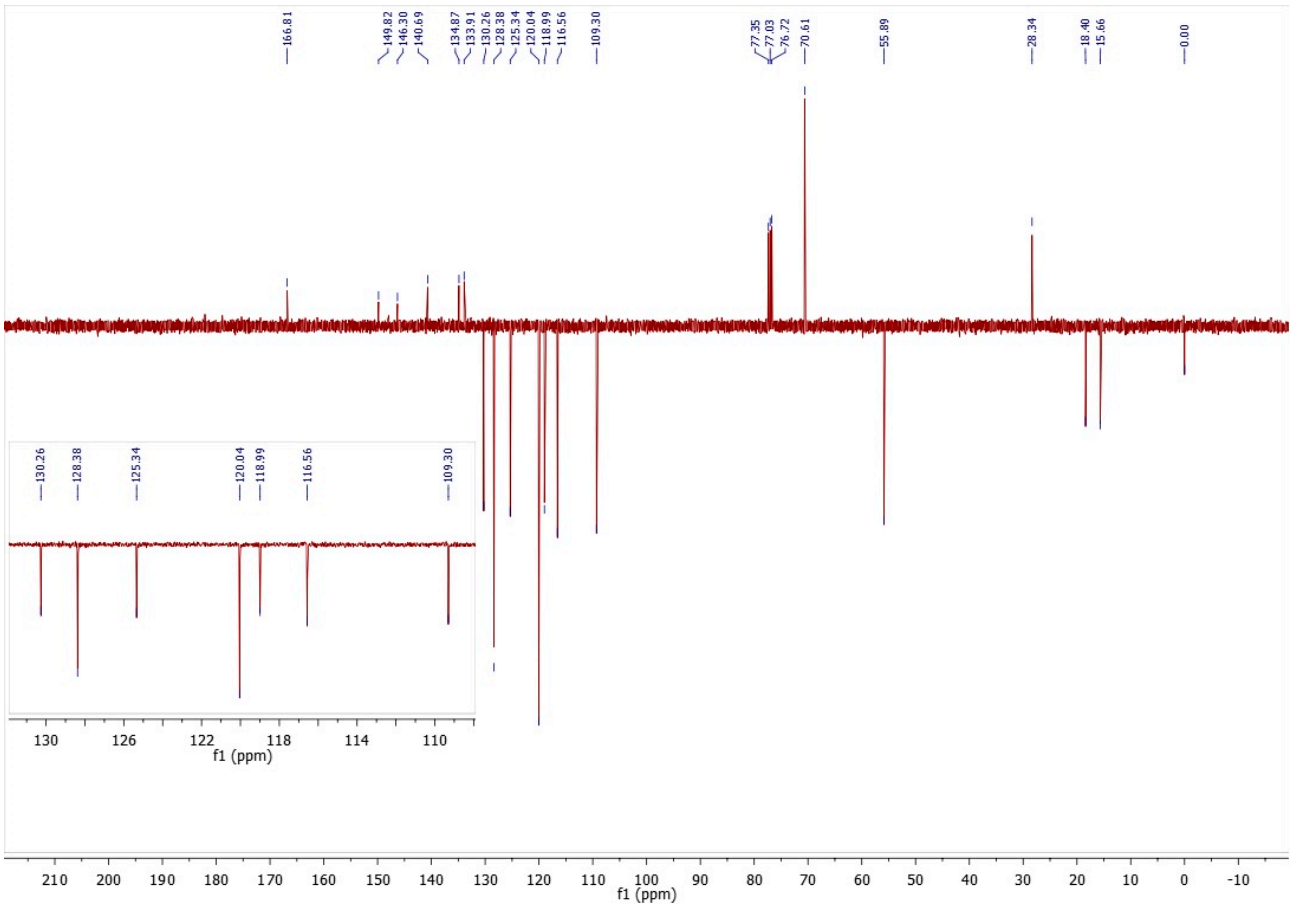
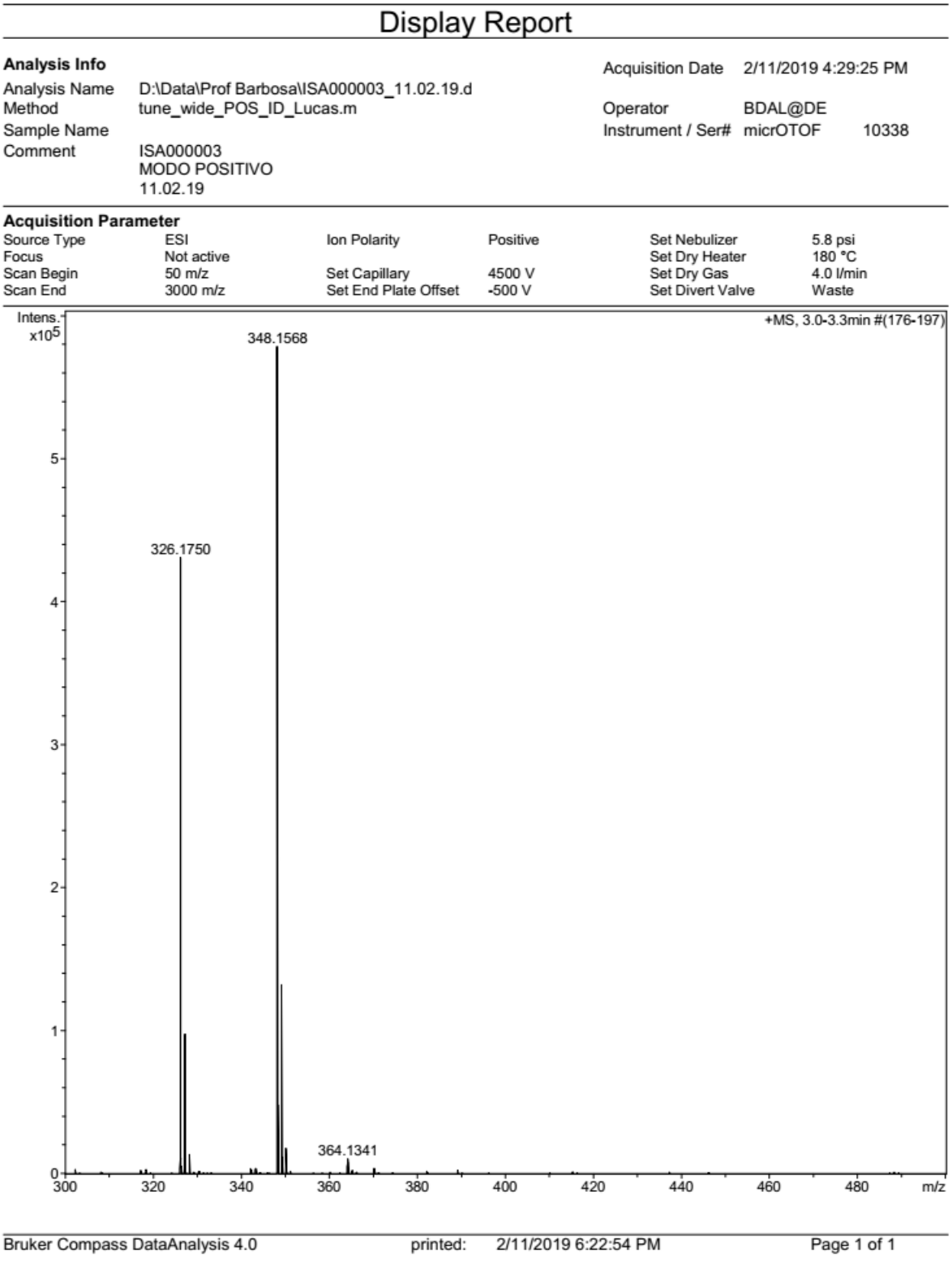


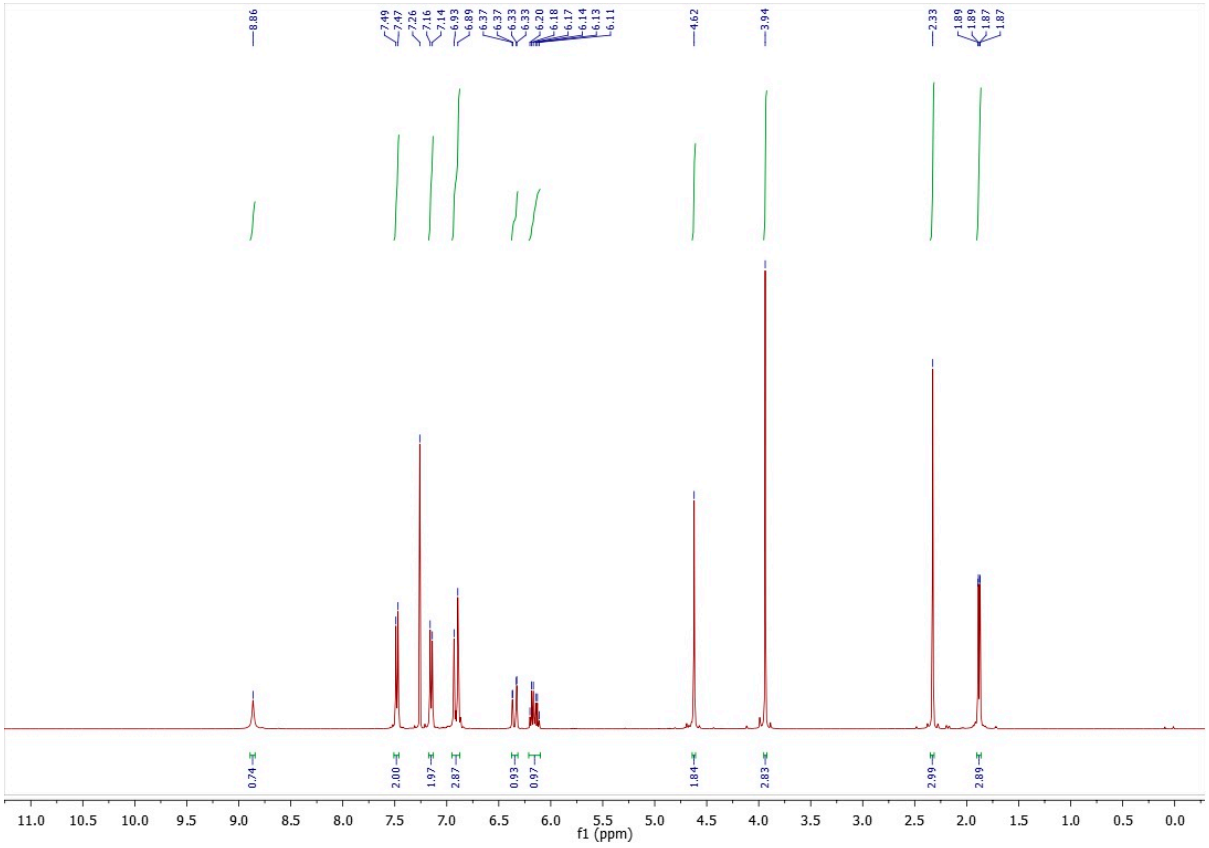

**Figure S8:** $^{13}C$ NMR spectrum (101 MHz, $CDCl_3$) of compound ISOA3.




153

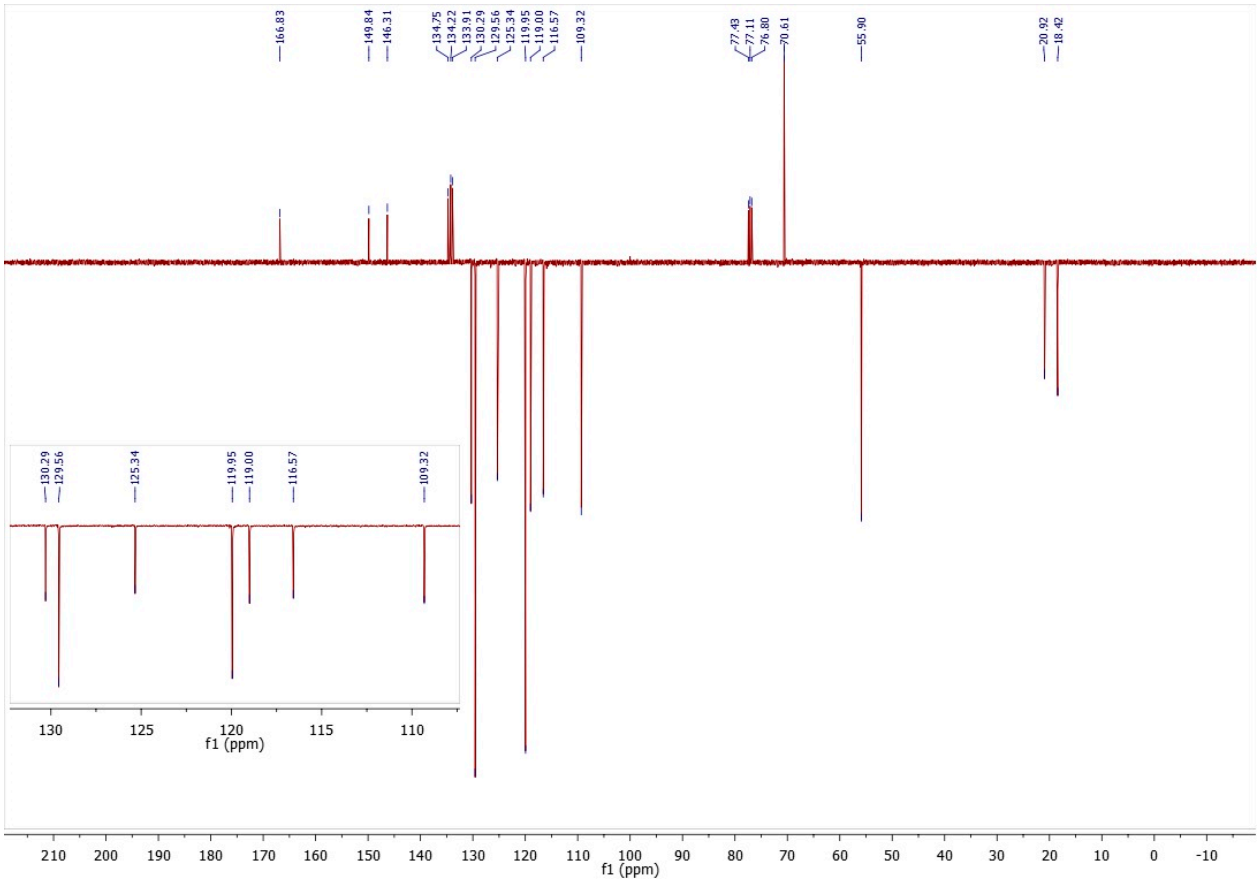
154 **Figure S9:** Mass spectrum of compound ISOA3.

155




156

157 **Figure S10**: $^{1}$H NMR spectrum (400 MHz, $CDCl_3$) of compound ISOA4.




158

159 **Figure S11:** $^{13}$C NMR spectrum (101 MHz, $CDCl_3$) of compound ISOA4.

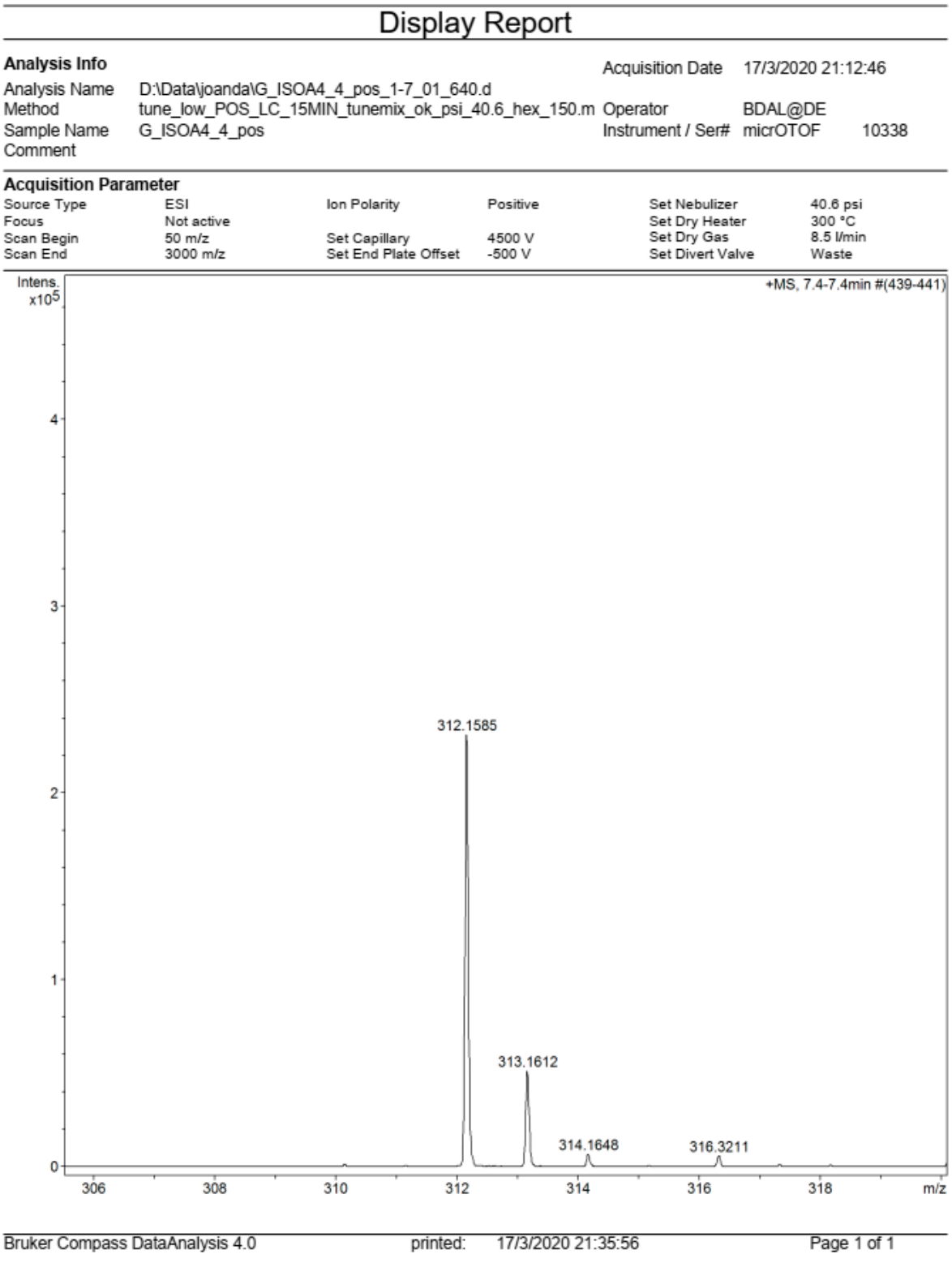



**Figure S12:** Mass spectrum of compound ISOA4.

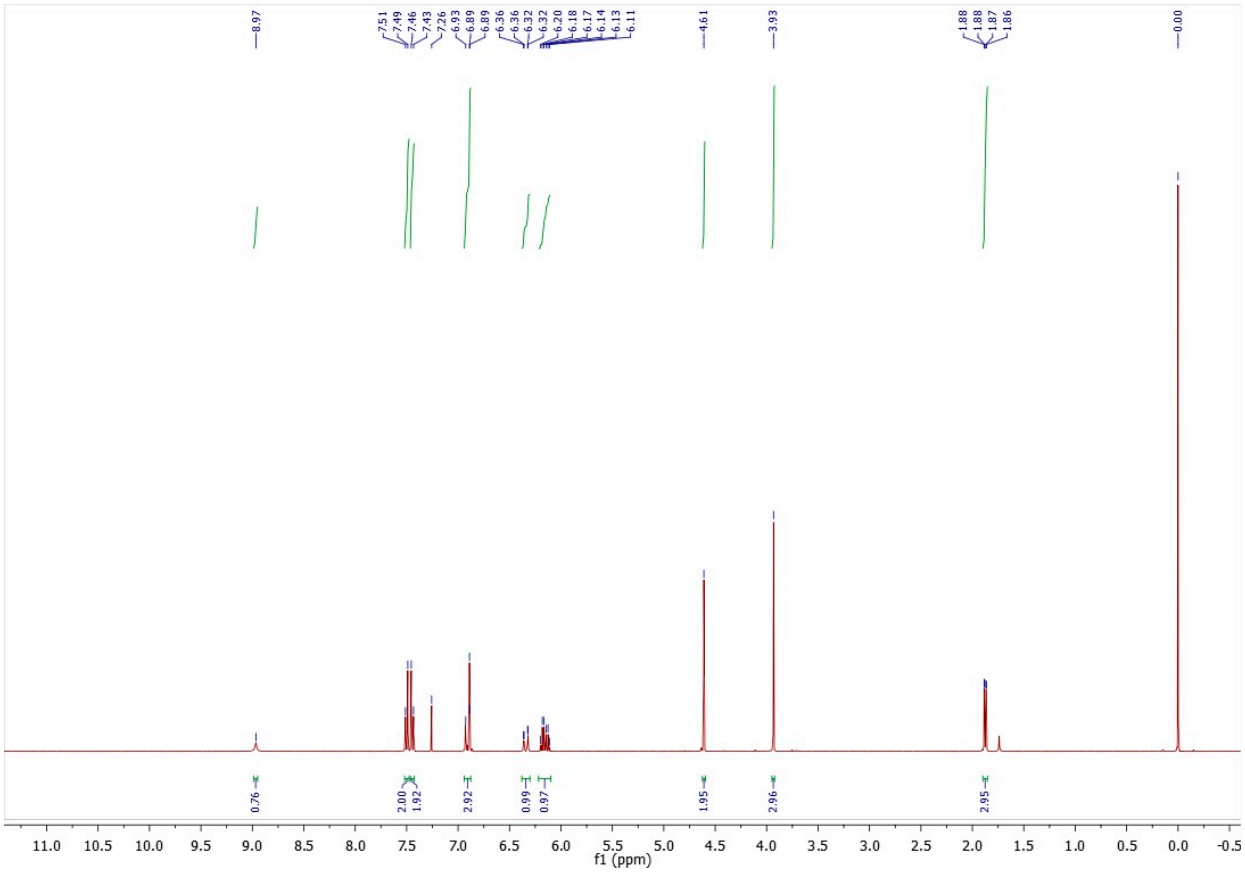



**Figure S13:** $^{1}$H NMR spectrum (400 MHz, $CDCl_3$) of compound ISOA5.

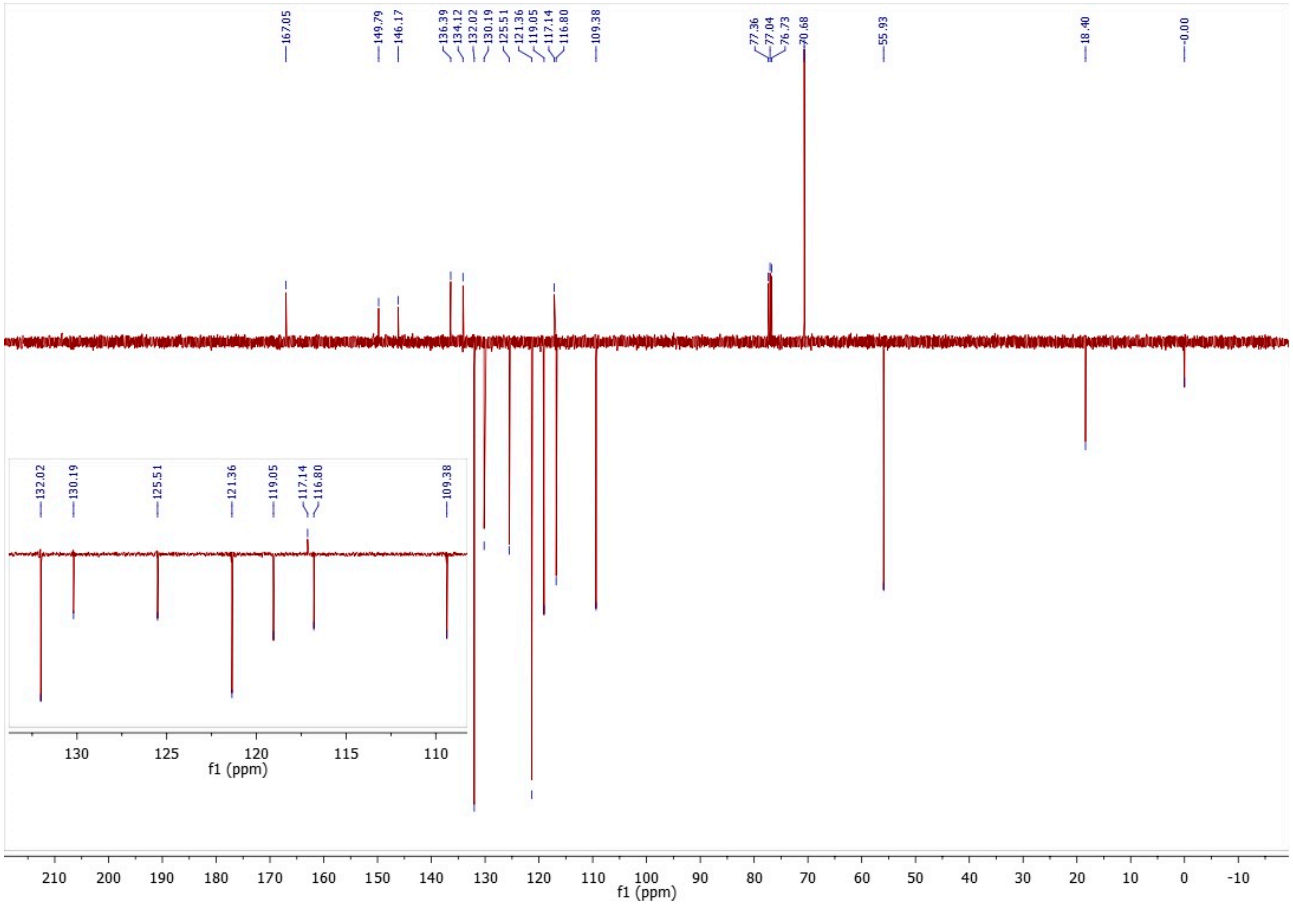



**Figure S14:** $^{13}$C NMR spectrum (101 MHz, $CDCl_3$) of compound ISOA5.

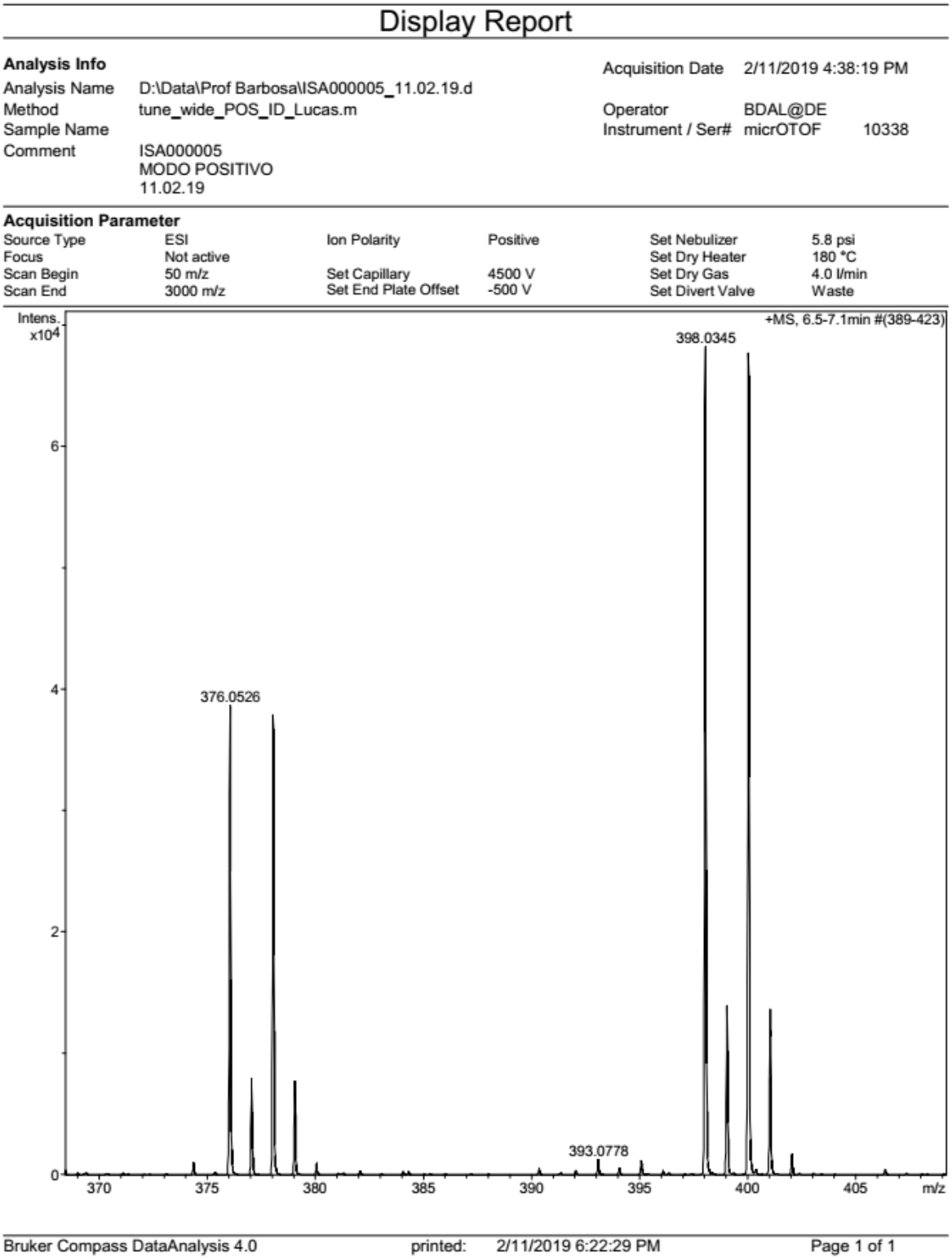



**Figure S15:** Mass spectrum of compound ISOA5.

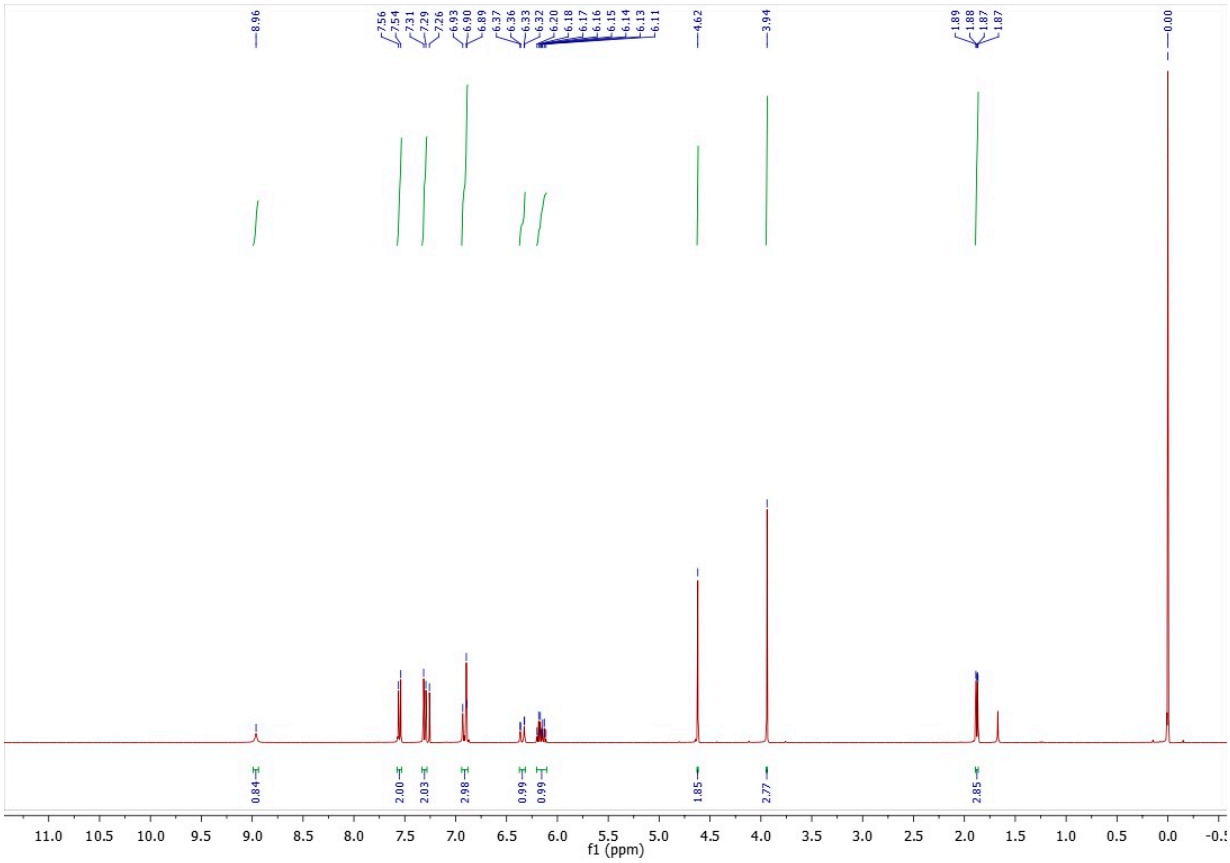



**Figure S16:** $^{1}$H NMR spectrum (400 MHz, $CDCl_3$) of compound ISOA6.

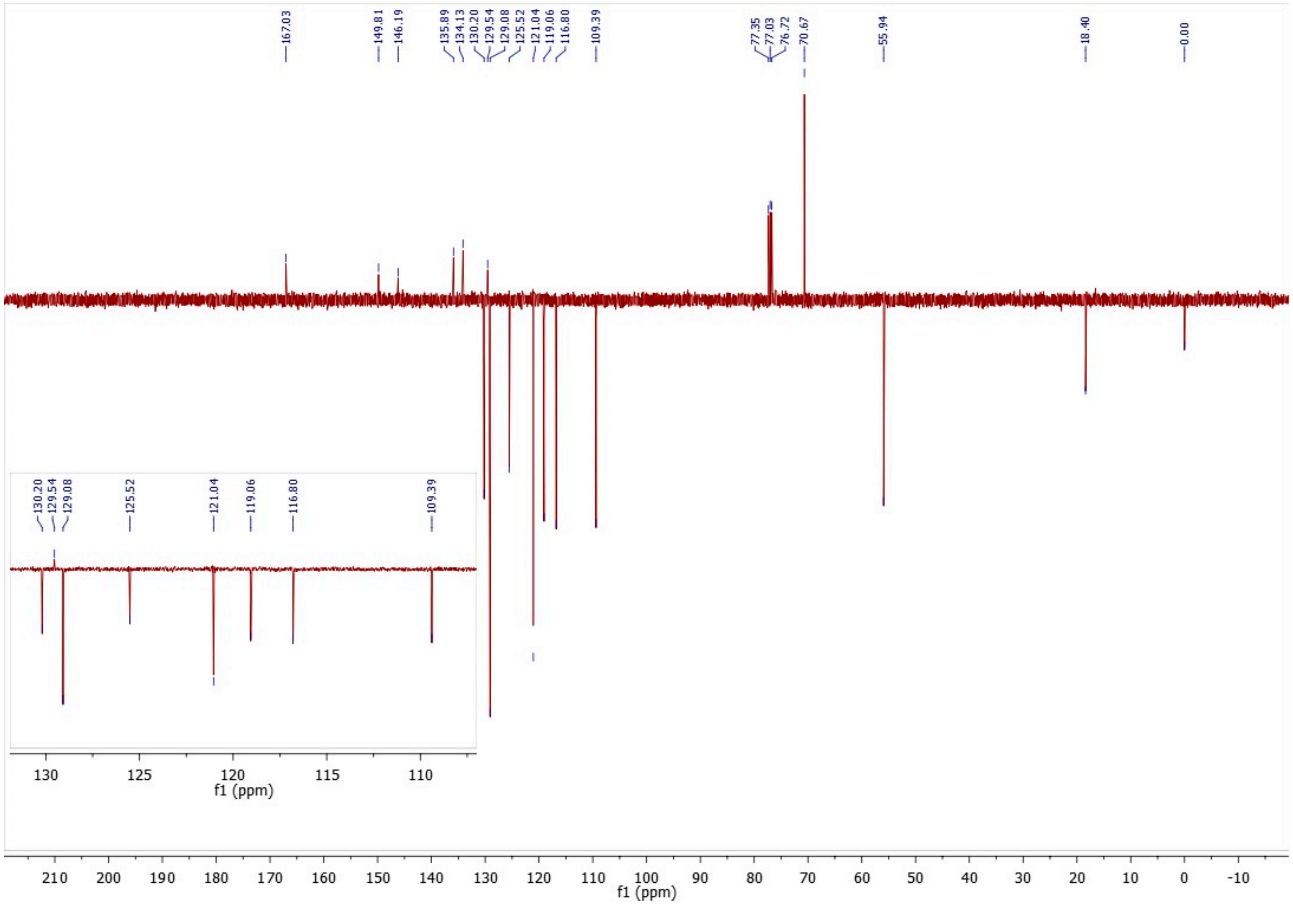



**Figure S17:** $^{13}$C NMR spectrum (101 MHz, $CDCl_3$) of compound ISOA6.

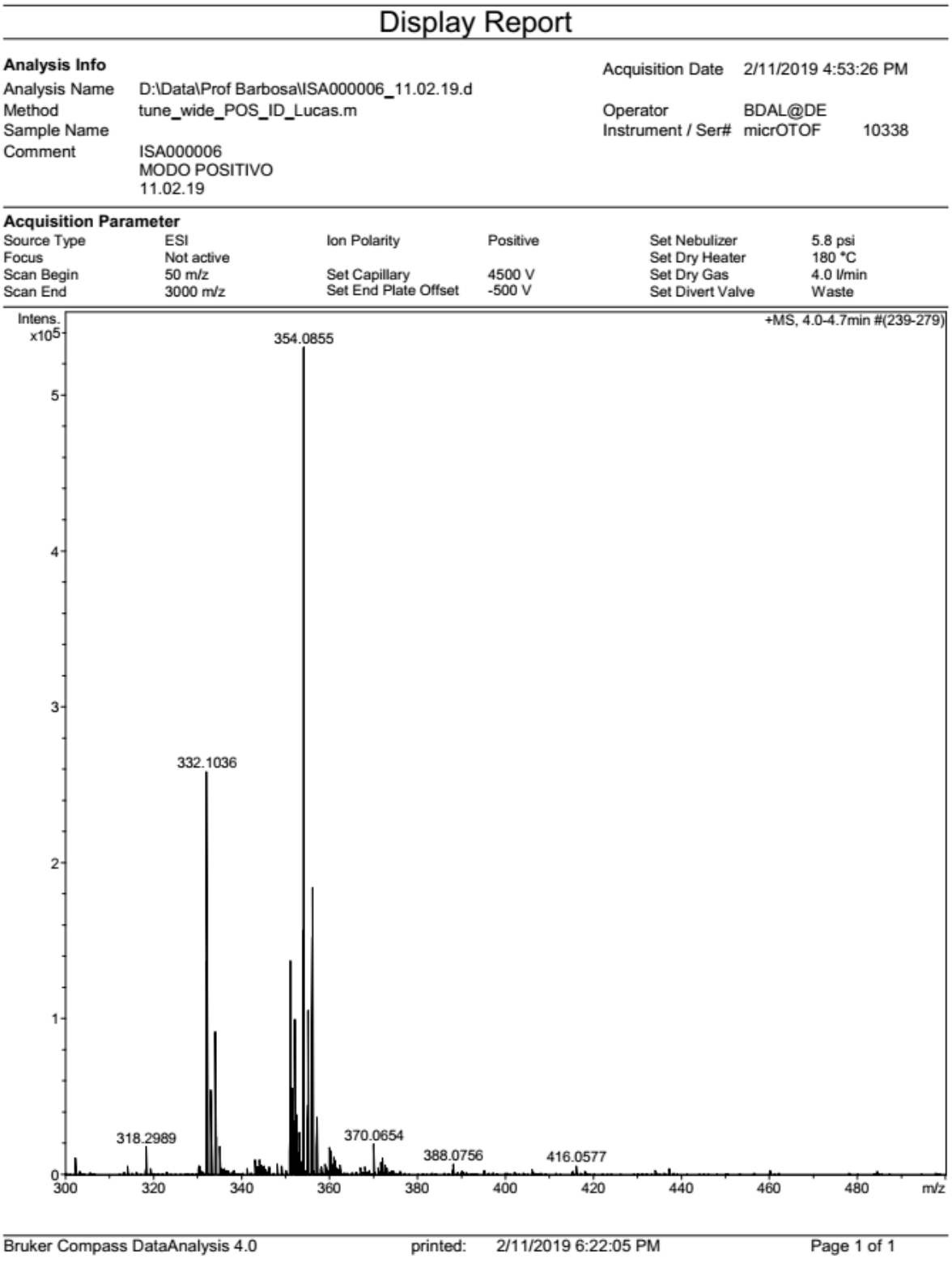



**Figure S18:** Mass spectrum of compound ISOA6.

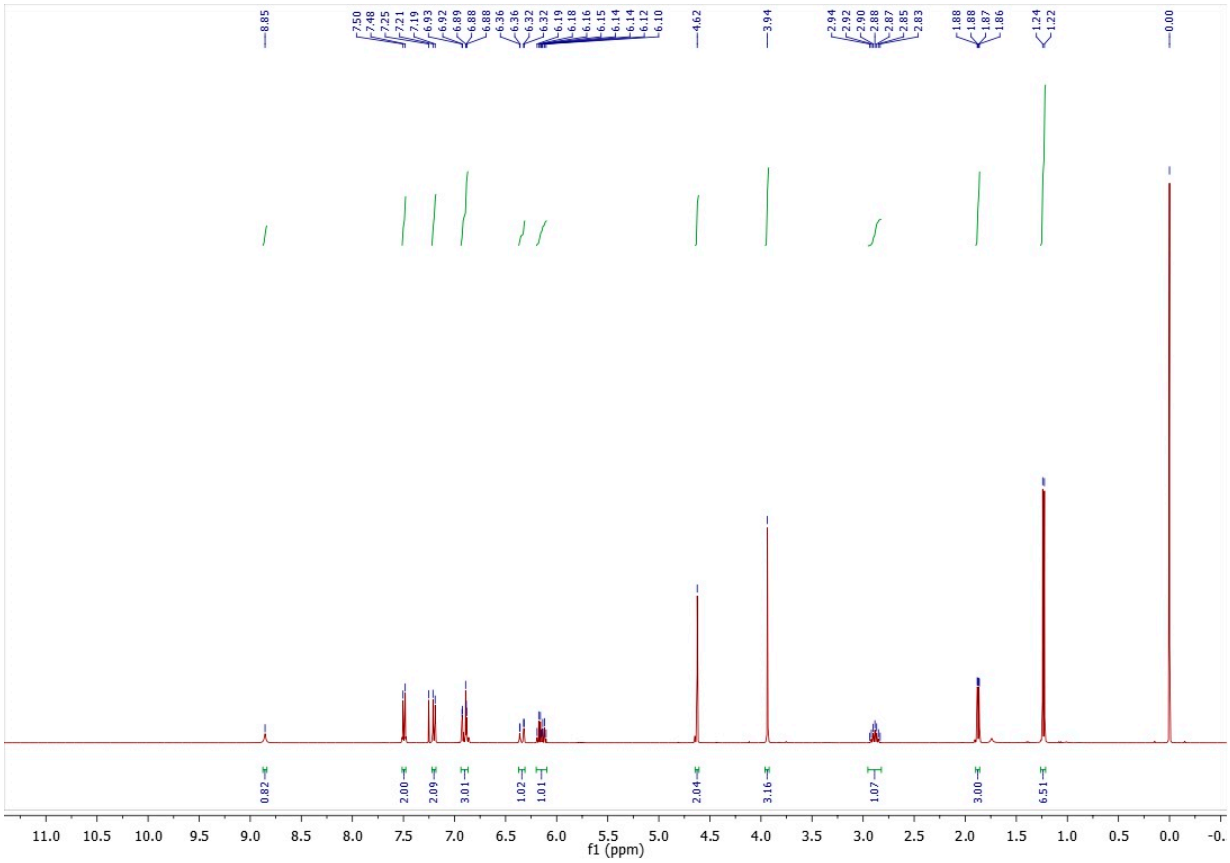



**Figure S19:** $^{1}$H NMR spectrum (400 MHz, $CDCl_3$) of compound ISOA7.

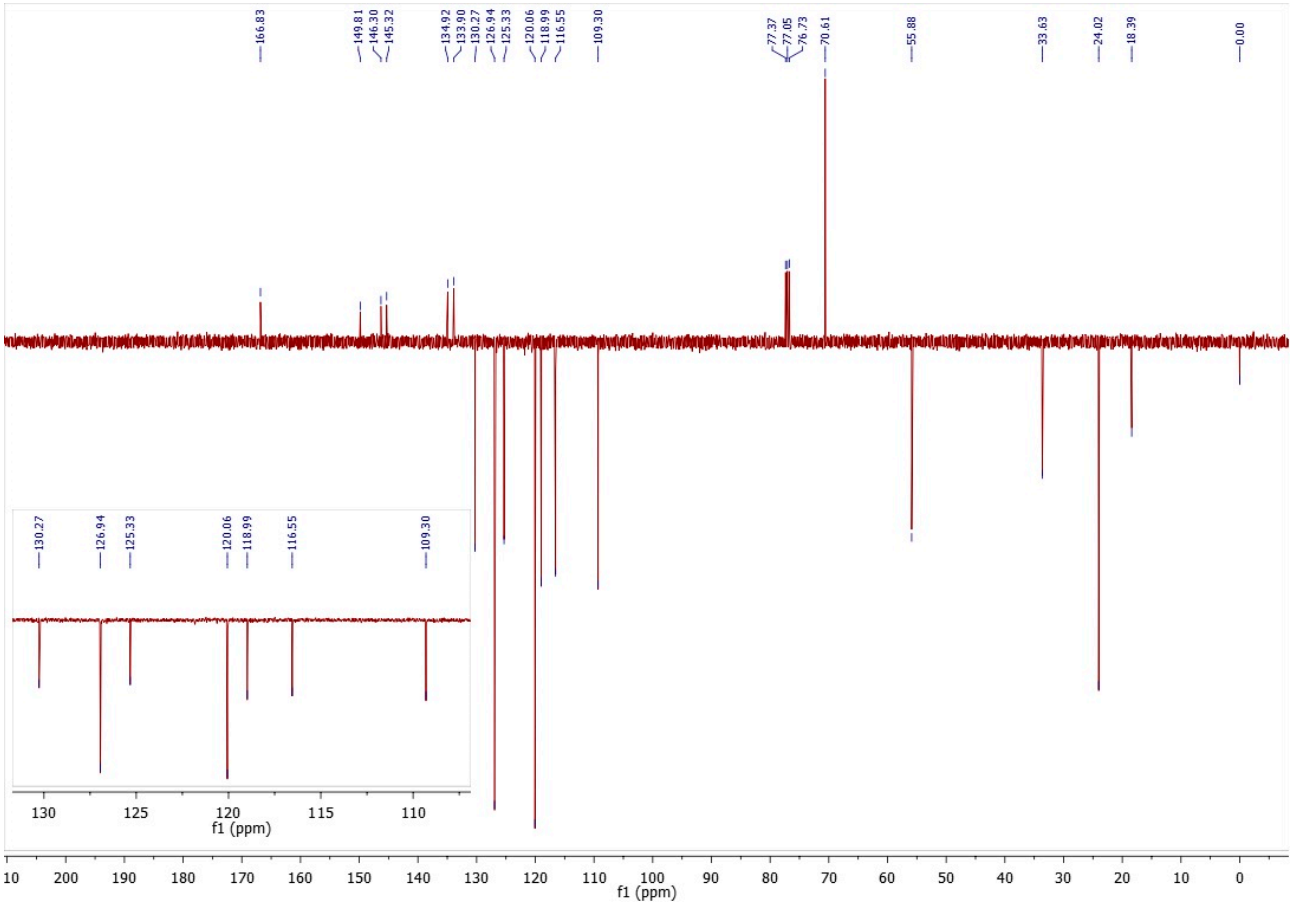



**Figure S20:** $^{13}$C NMR spectrum (101 MHz, $CDCl_3$) of compound ISOA7.

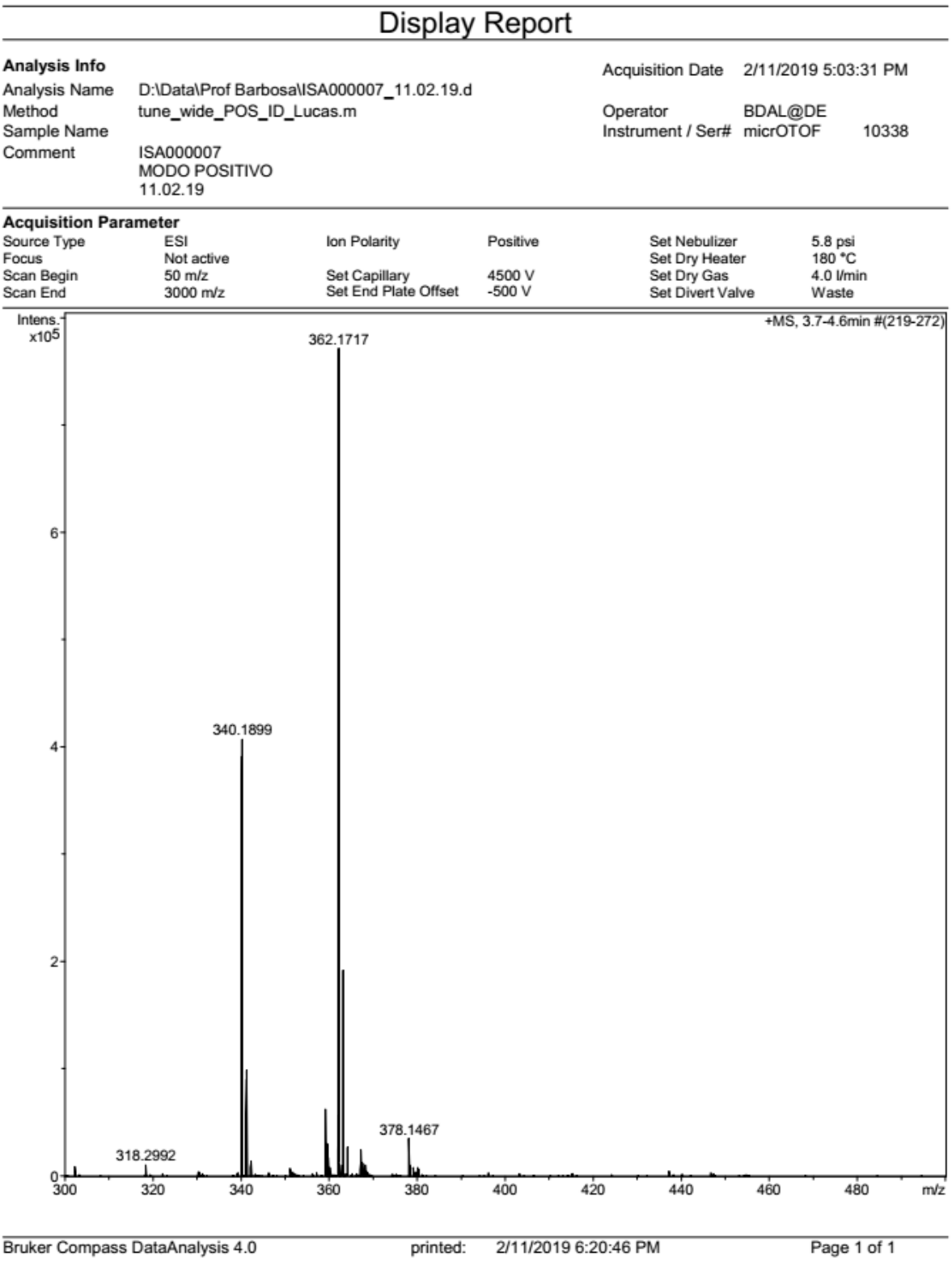



**Figure S21:** Mass spectrum of compound ISOA7.

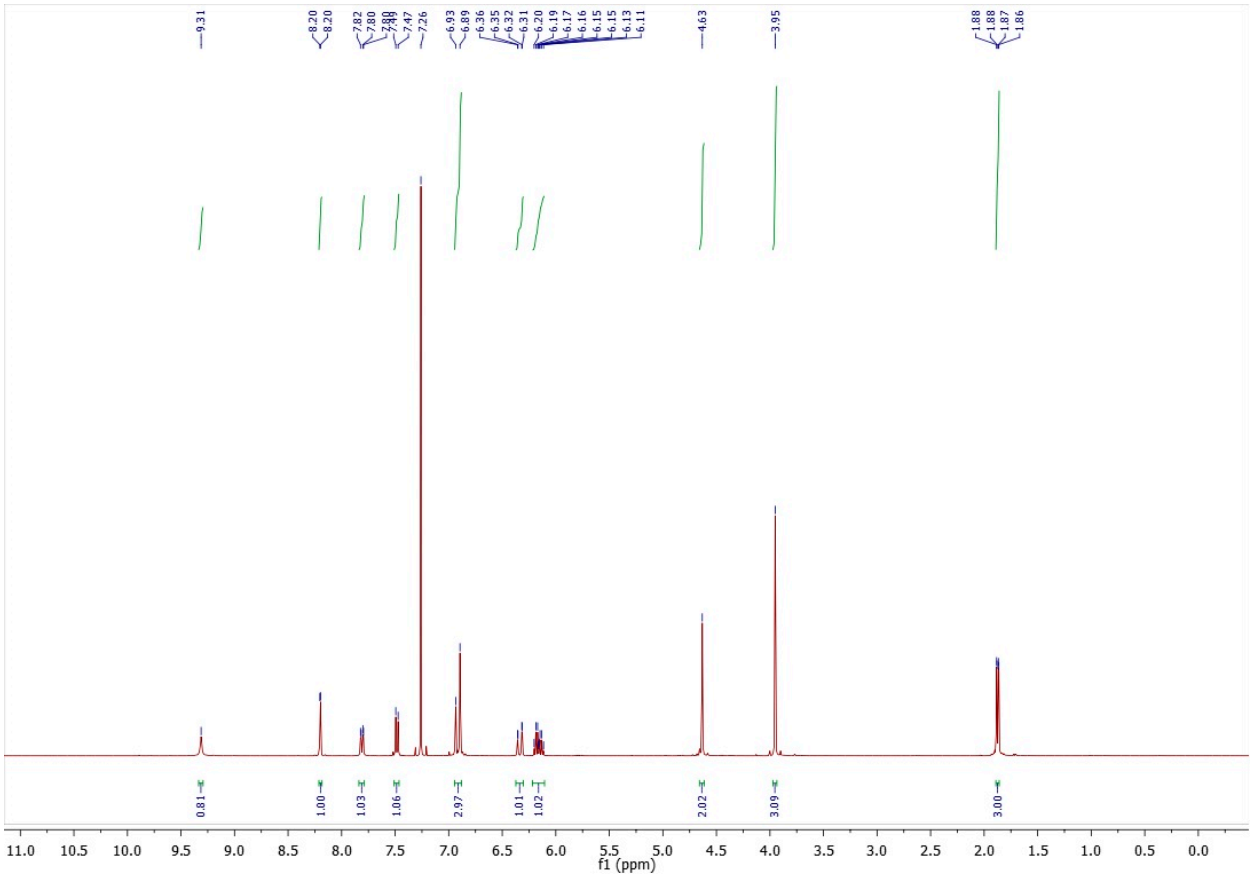



**Figure S22:** $^{1}$H NMR spectrum (400 MHz, $CDCl_3$) of compound ISOA10.

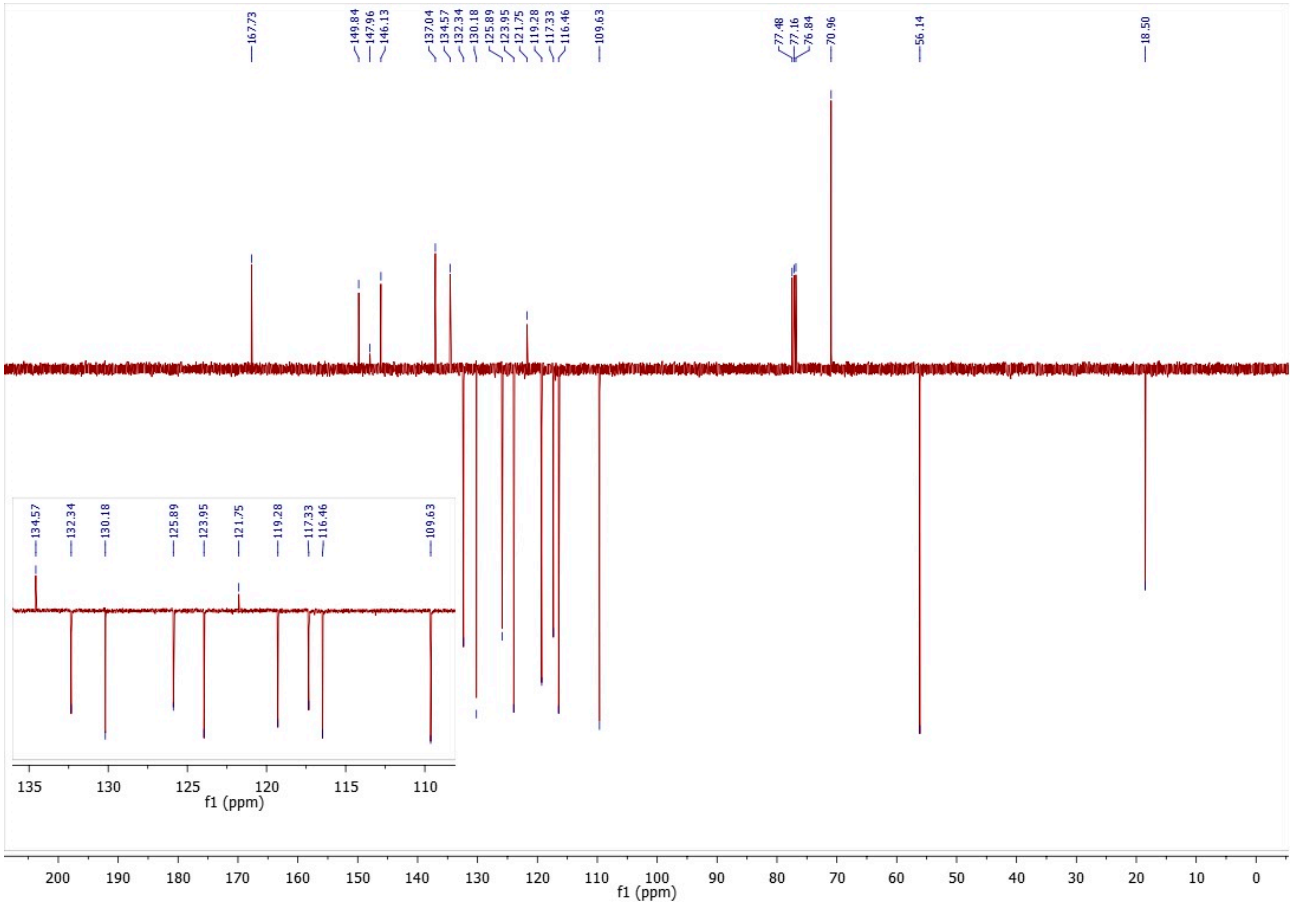
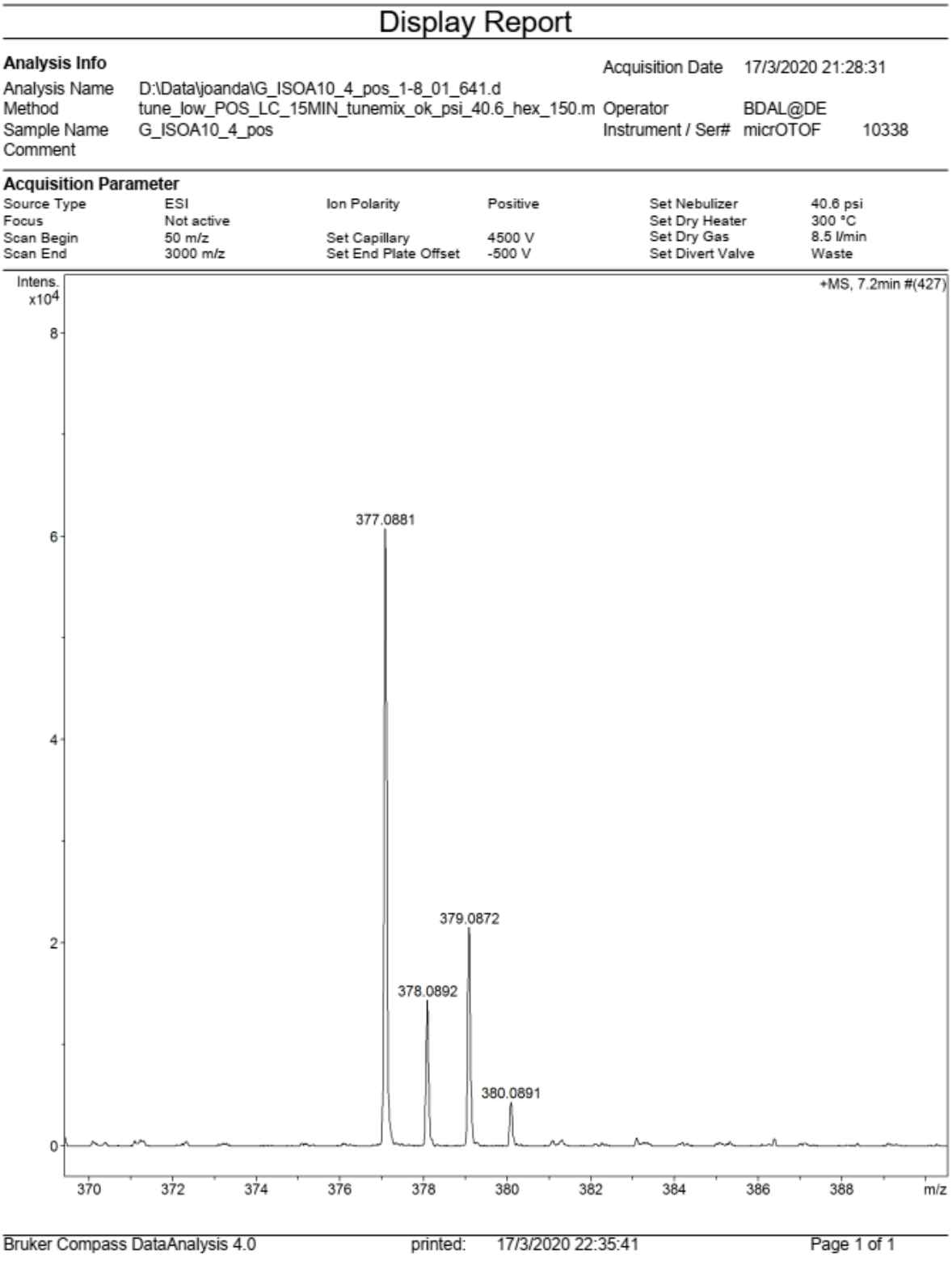
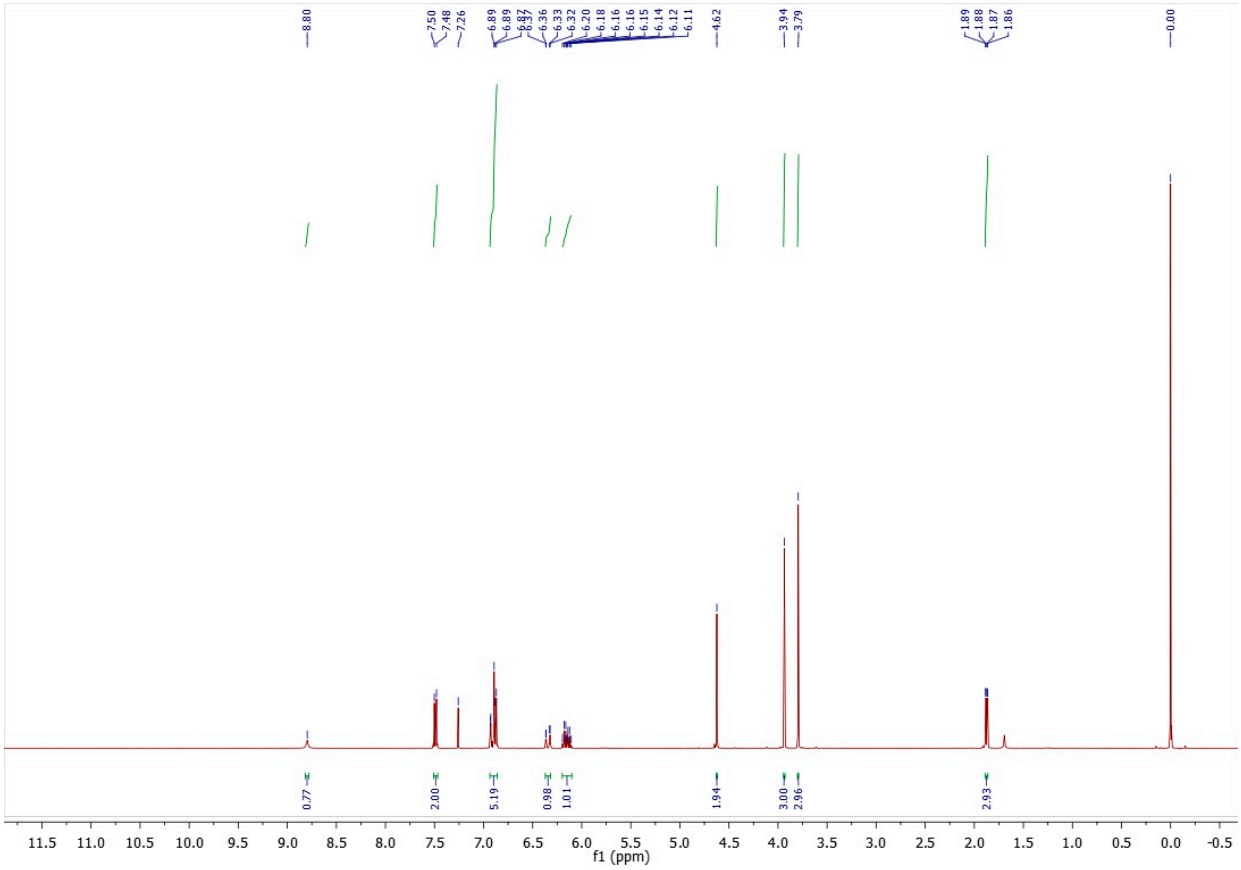



**Figure S23:** $^{13}$C NMR spectrum (101 MHz, $CDCl_3$) of compound ISOA10.



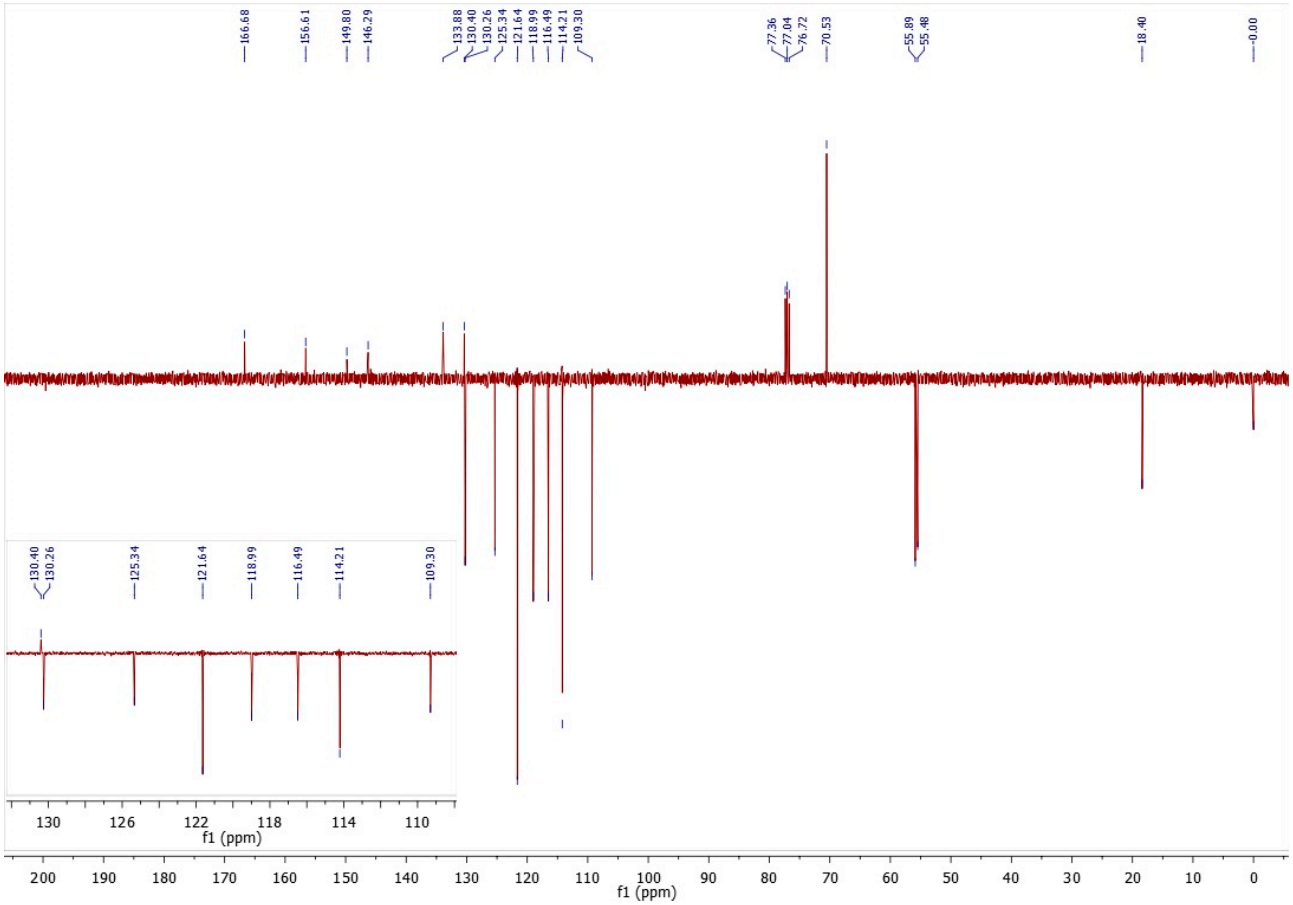

185

186 **Figure S24:** Mass spectrum of compound ISOA10.




187

188 **Figure S25:** [1]H NMR spectrum (400 MHz, $CDCl_3$) of compound ISOA11.




189

190 **Figure S26:** [13]C NMR spectrum (101 MHz, $CDCl_3$) of compound ISOA11.

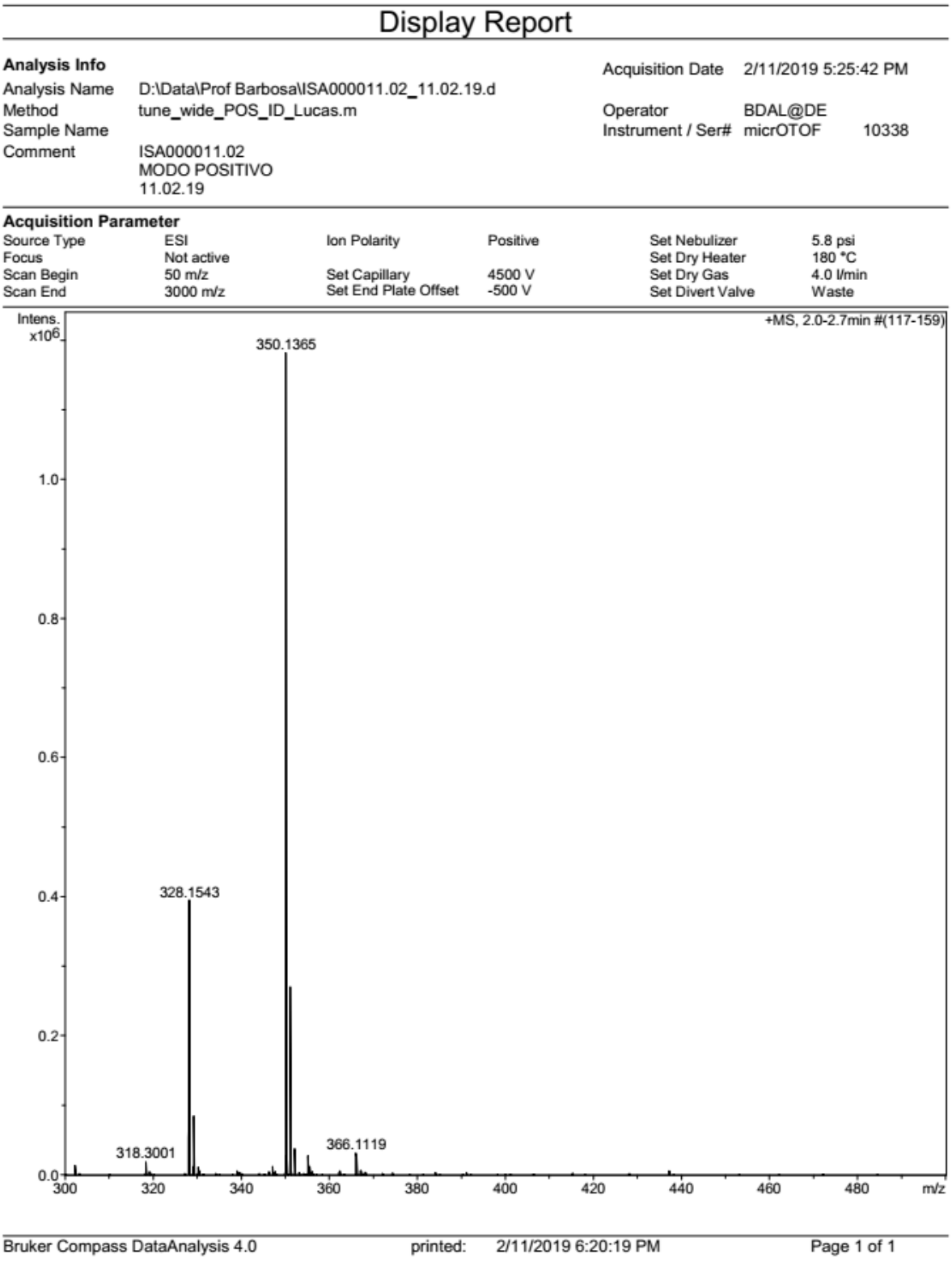



**Figure S27:** Mass spectrum of compound ISOA11.

199 **Rerefences**

200

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