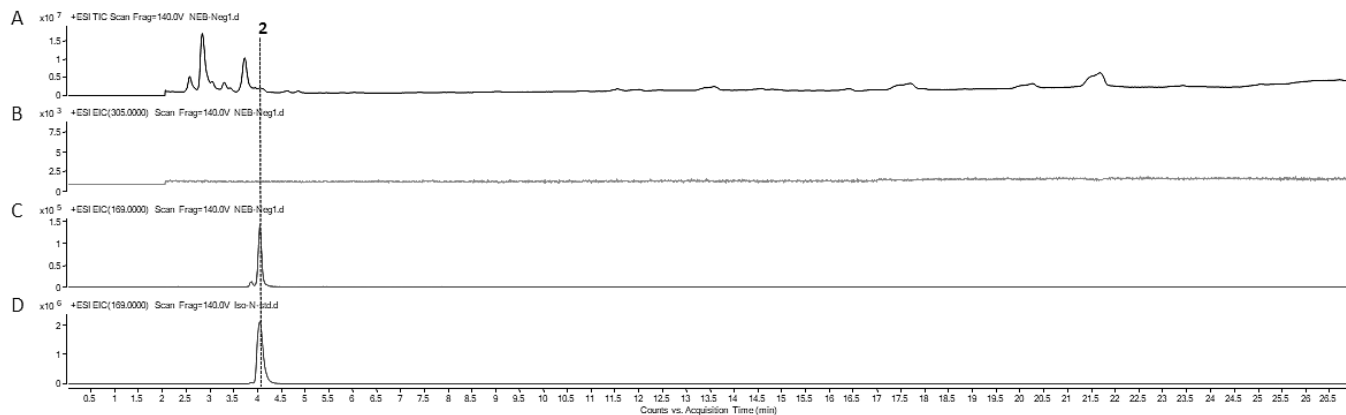


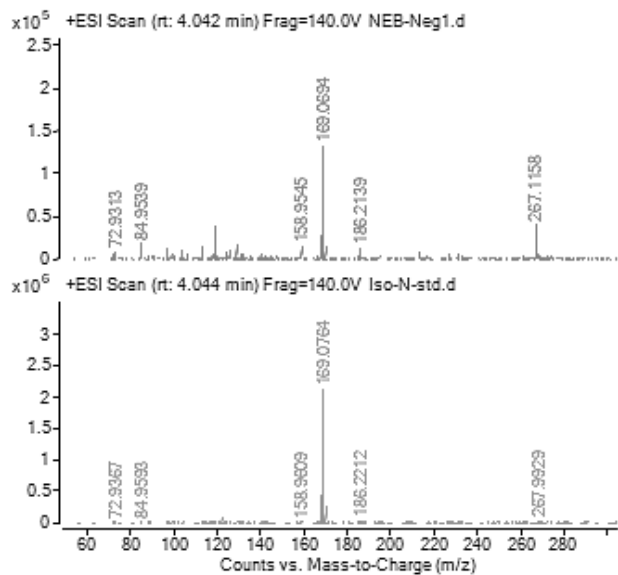
Supplemental Figure S1: Total ion chromatogram (TIC), extracted ion chromatogram (EIC) and comparative MS data of Figure 3 and Figure 4.

Panel 1: TIC (A) and EIC of hapalindole product (m/z 305) (B) and *cis*-indole isonitrile **2** (m/z 169) (C) compared with the standard **2** (D) for the *in vitro* TT-assay performed in the absence of cyclase and FamD2 plasmids (for Figure 3 A). **Panel 2:** MS data of the product (top) and the standard **2** (bottom) are shown.

Panel 1

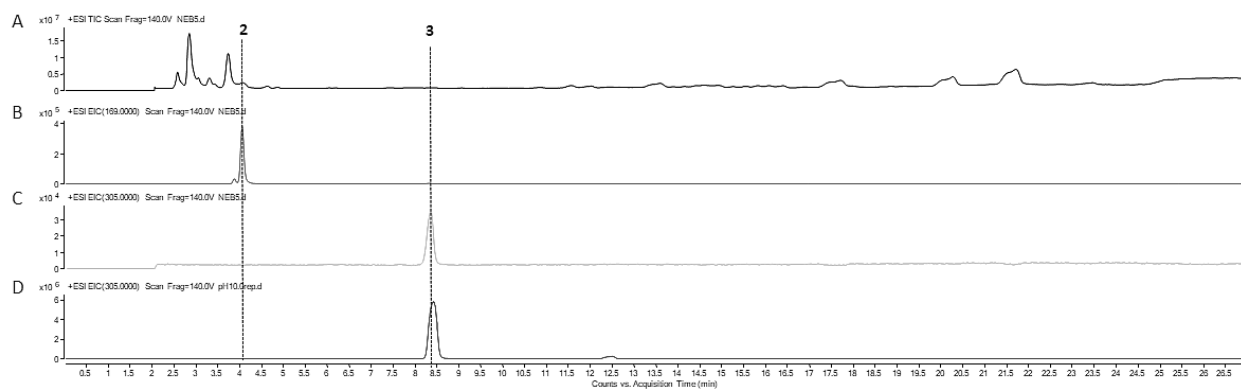


Panel 2

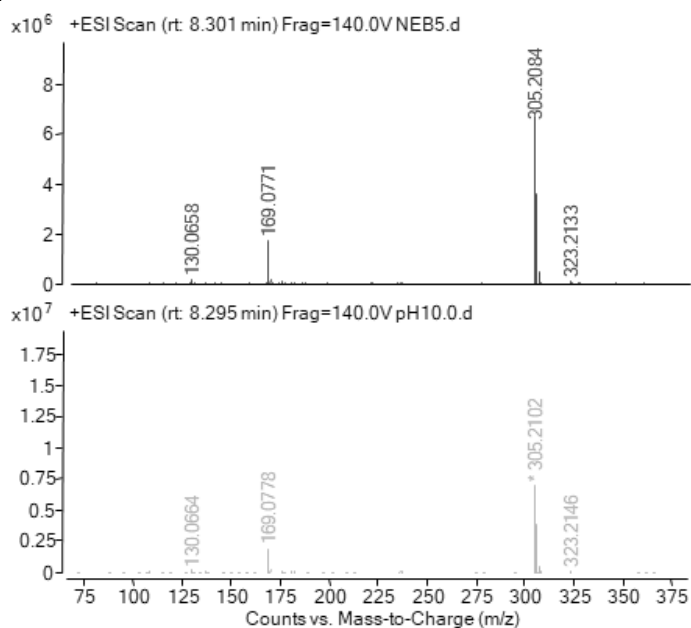


B. **Panel 1:** TIC (A) and EIC of *cis*-indole isonitrile **2** (m/z 169) (B) and *cis*-indole isonitrile-GPP intermediate **3** (m/z 305) (C) compared with the standard **3** (D) for the *in vitro* TT-assay performed in the presence of FamD2 plasmid alone (for Figure 3 B). **Panel 2:** MS data of the product (top) and the standard **3** (bottom) are shown.

Panel 1

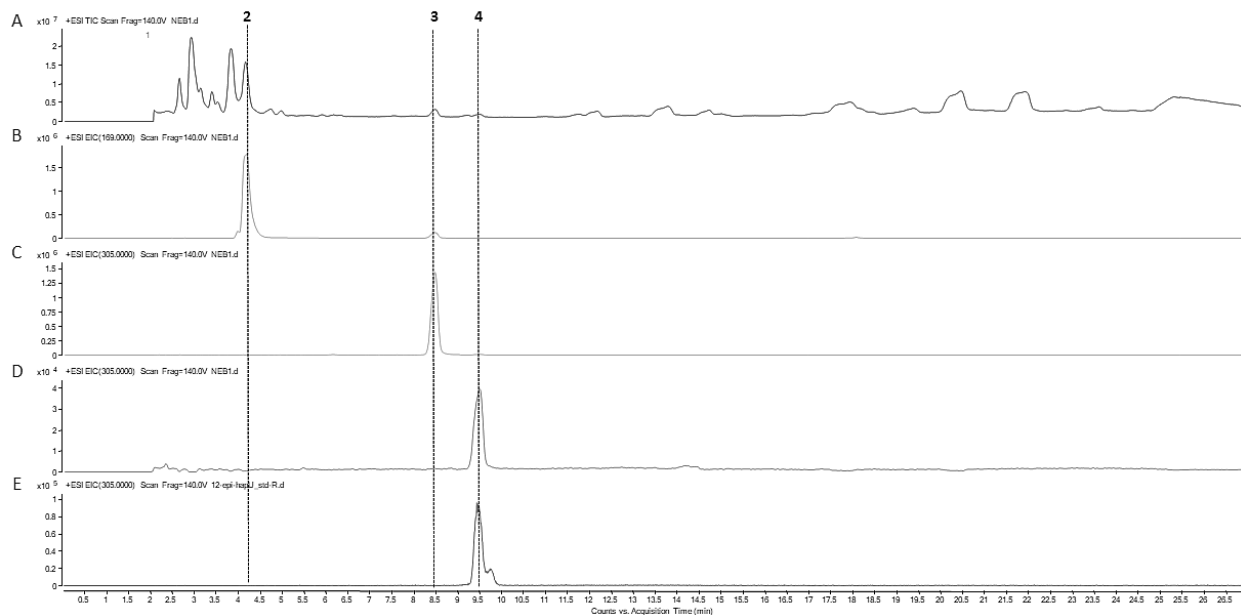


Panel 2

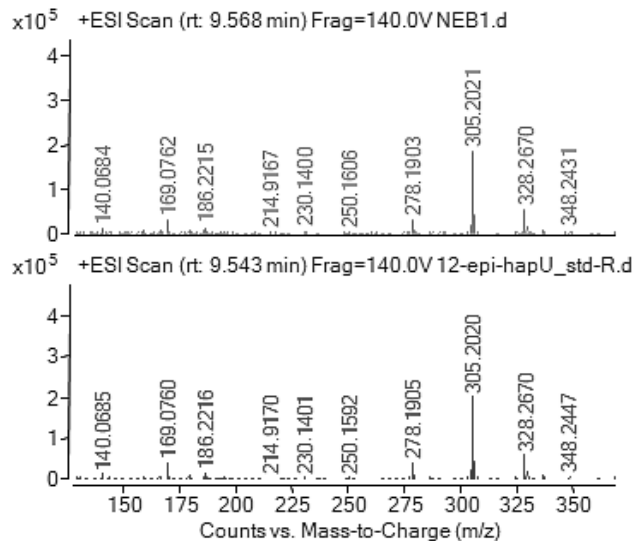


C. **Panel 1:** TIC (A) and EIC of *cis*-indole isonitrile **2** (m/z 169) (B), *cis*-indole isonitrile-GPP intermediate **3** (m/z 305) (C) and 12-*epi*-hupalindole U **4** (m/z 305) (D) compared with the standard **4** (E) for the *in vitro* TT-assay performed in the presence of FamD2 and FamC1 plasmids (for Figure 3 C). **Panel 2:** MS data of the product (top) and the standard **4** (bottom) are shown.

Panel 1

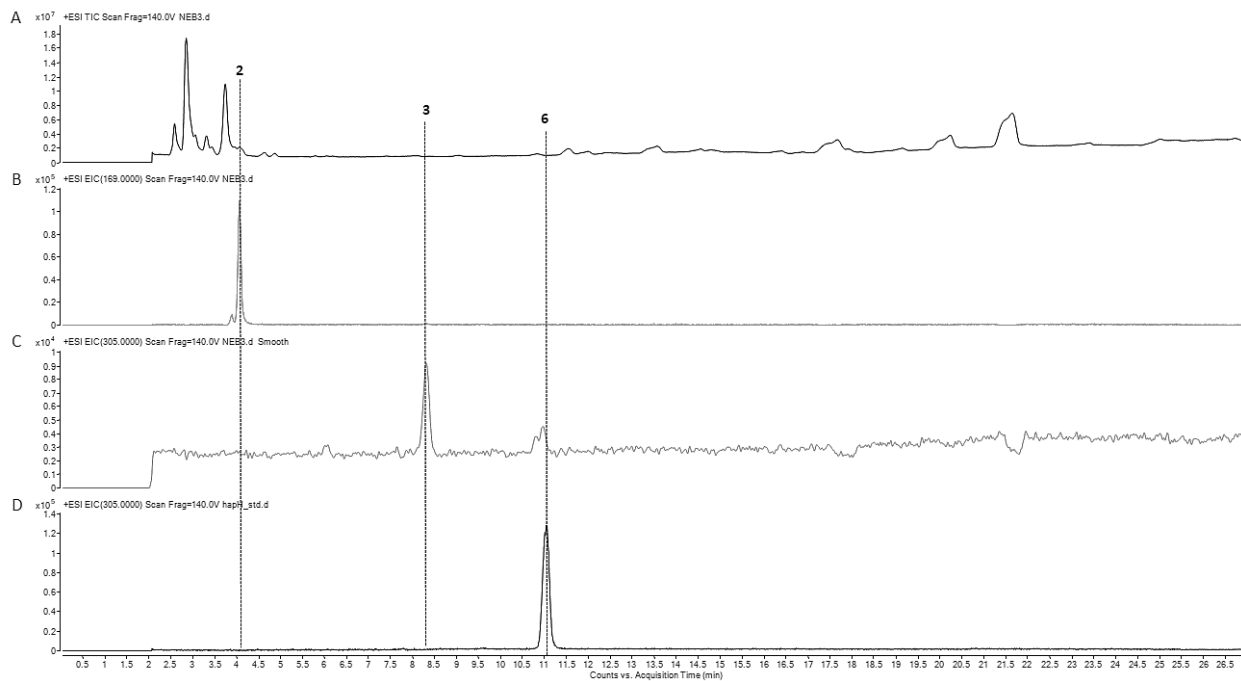


Panel 2

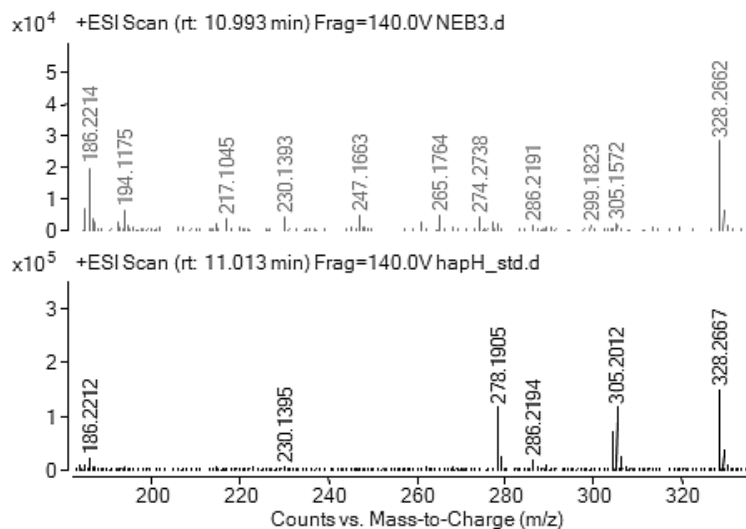


D. **Panel 1:** TIC (A) and EIC of *cis*-indole isonitrile **2** (m/z 169) (B), *cis*-indole isonitrile-GPP intermediate **3** (m/z 305) and hapalindole H **6** (m/z 305) product (C) were compared with the standard **6** (D) for the *in vitro* TT-assay performed in the presence of FamD2 and FamC2 plus FamC3 plasmids in the presence of lower 5 mM calcium (for Figure 3E). **Panel 2:** MS data of the product (top) and the standard **6** (bottom) are shown.

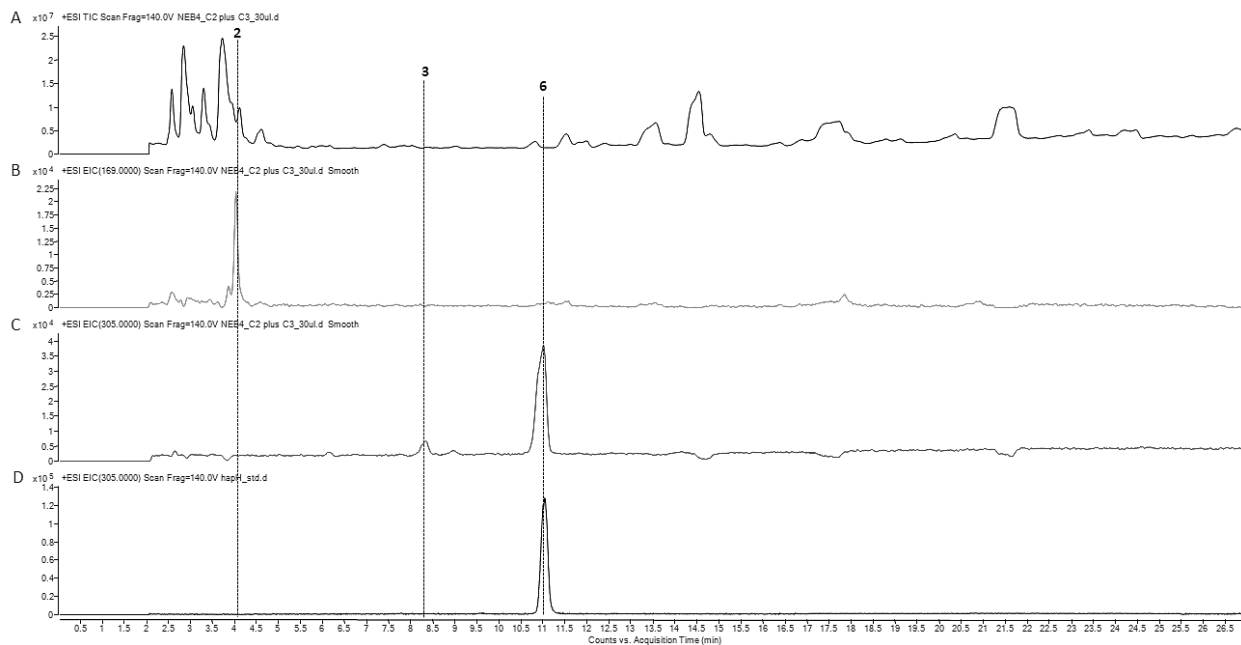
Panel 1



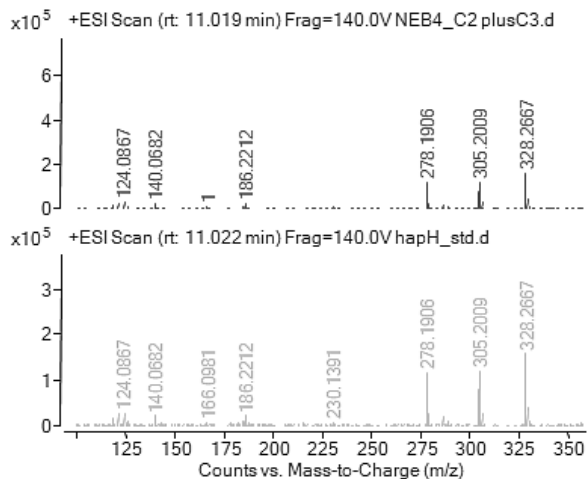
Panel 2



E. **Panel 1:** TIC (A) and EIC of *cis*-indole isonitrile **2** (m/z 169) (B), and *cis*-indole isonitrile-GPP intermediate **3** (m/z 305) and hapalindole H **6** (m/z 305) (C) compared with the standard **6** (D) for the *in vitro* TT-assay performed in the presence of FamD2 and FamC2 plus FamC3 plasmids in the presence of higher 20 mM calcium (for Figure 3 E). **Panel 2:** MS data of the product (top) and the standard **6** (bottom) are shown.

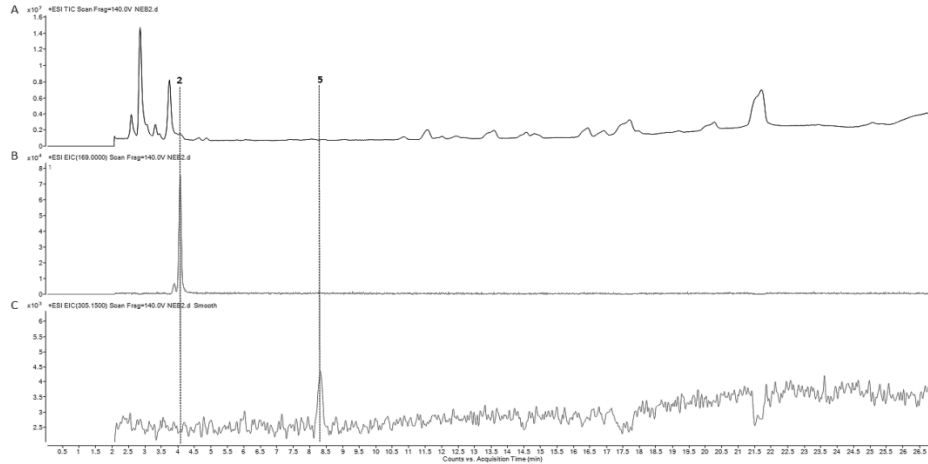


Panel 2

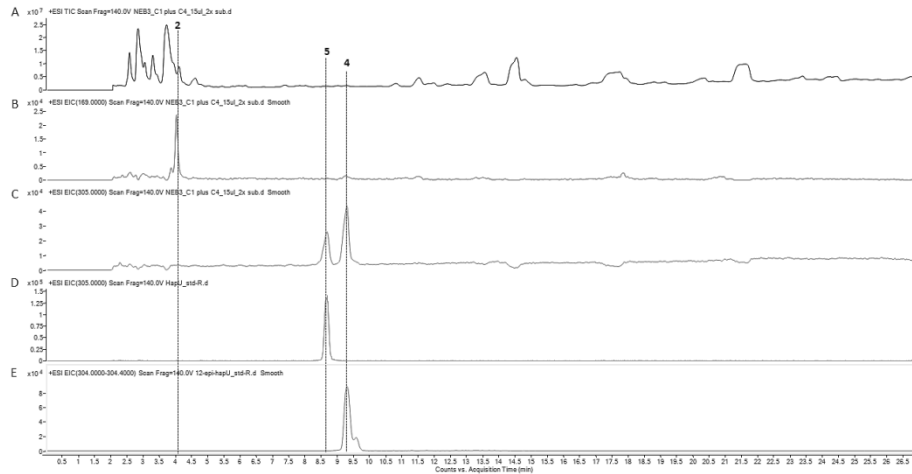


F. **Panel 1:** TIC (A) and EIC of *cis*-indole isonitrile **2** (*m/z* 169) (B) and hapalindole U **5** (*m/z* 305) (C) for the *in vitro* TT-assay performed in the presence of FamD2 and FamC1 plus FamC4 plasmids in the presence of lower 5 mM calcium concentration. Note that lower concentration of calcium did not show distinct product. **Panel 2:** TIC (A) and EIC of *cis*-indole isonitrile **2** (*m/z* 169) (B), and hapalindole U **5** and 12-*epi*-hapalindole U **4** (*m/z* 305) (C) compared with the standard **5** (D) and **4** (E) for the *in vitro* TT-assay performed in the presence of FamD2 and FamC2 plus FamC3 plasmids in the presence of higher 20 mM calcium concentration. **Panel 3:** MS data of the product (top) and the standard **5** (bottom) are shown.

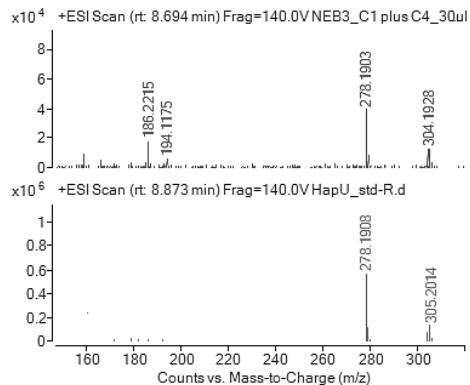
Panel 1



Panel 2

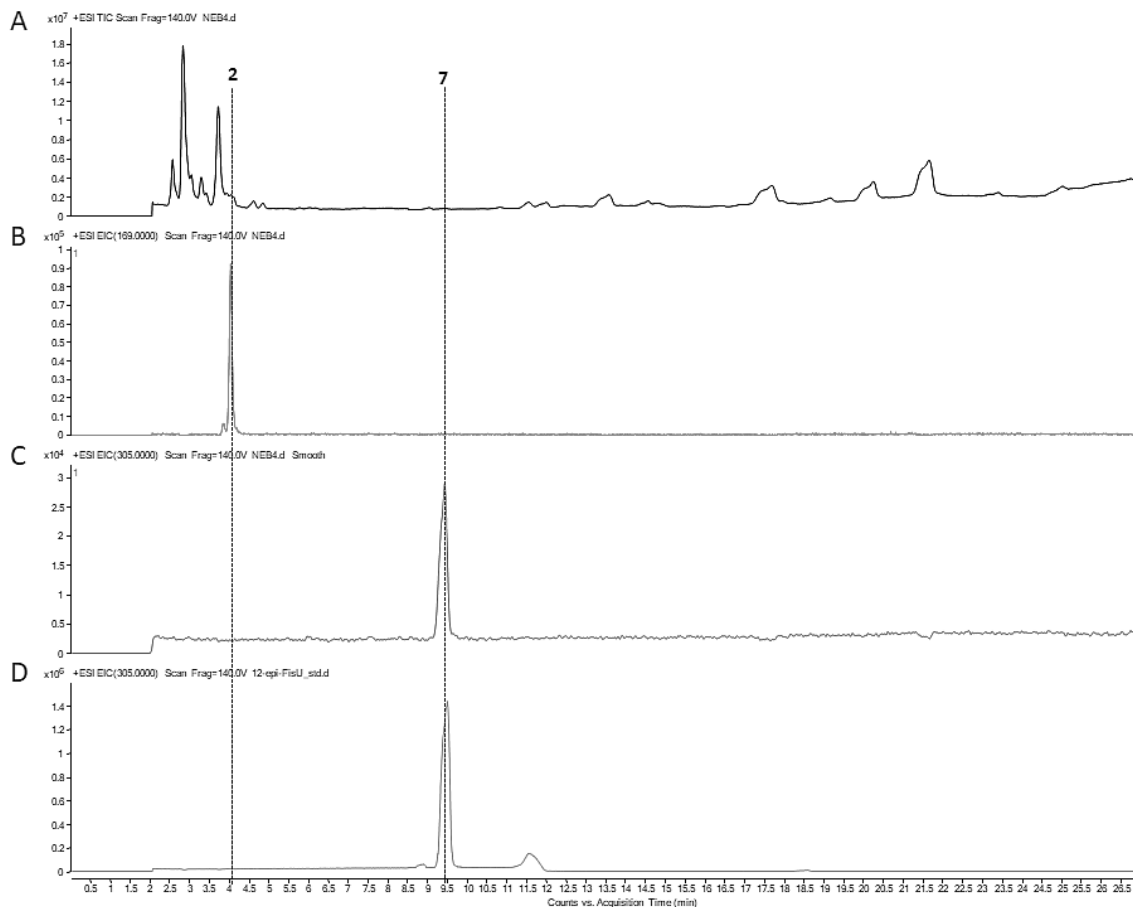


Panel 3

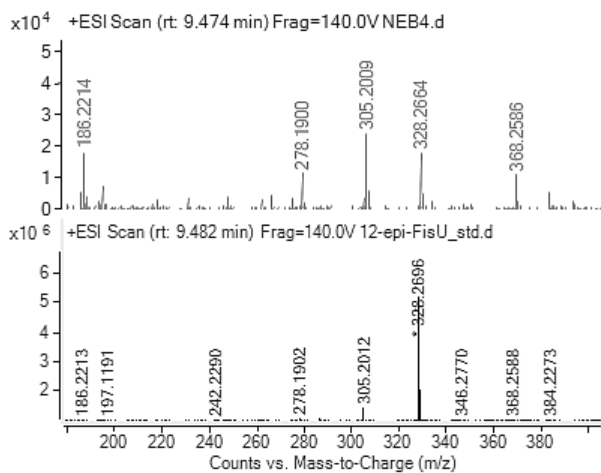


G. **Panel 1:** TIC (A) and EIC of *cis*-indole isonitrile **2** (m/z 169) (B) and 12-*epi*-fischerindole U **7** (m/z 305) (C) compared with the standard **7** (D) for the *in vitro* TT-assay performed in the presence of FamD2 and FisC plasmids (for Figure 4C). **Panel 2:** MS data of the product (top) and the standard **7** (bottom) are shown.

Panel 1



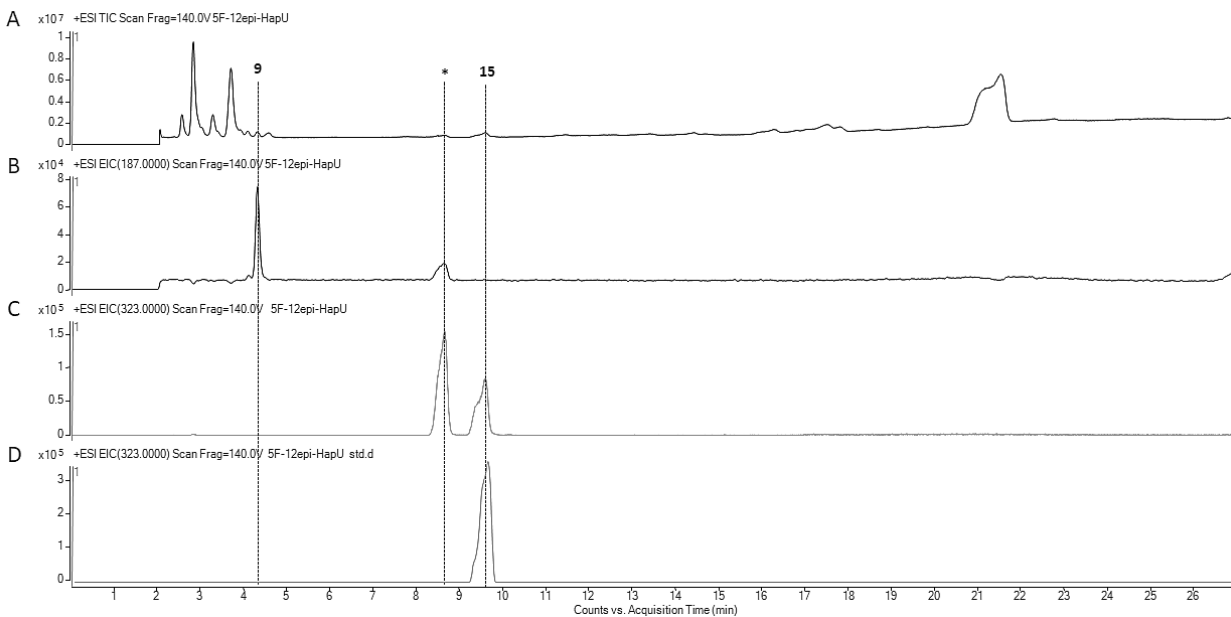
Panel 2



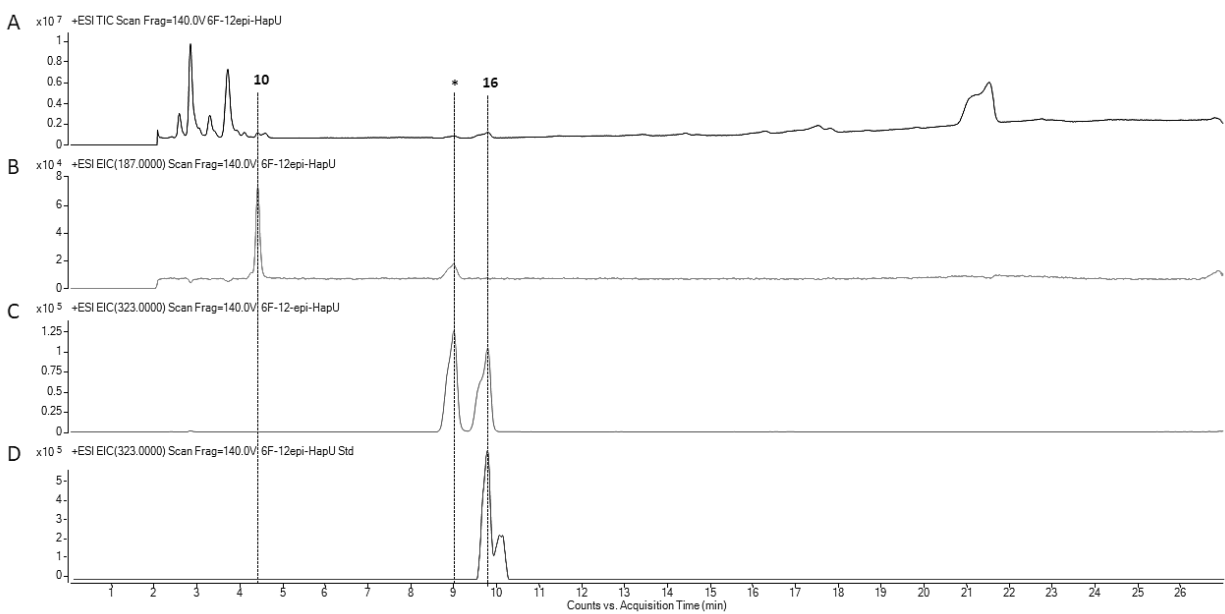
Supplemental Figure S2: Total ion chromatogram (TIC), extracted ion chromatogram (EIC) and comparative MS data of Figure 6 (A-C).

TIC (A) and EIC (m/z 187.02) of fluorinated *cis*-indole isonitrile substrate **9** (Panel 1 and 3) and **10** (Panel 2 and 4), and the fluorinated hapalindole products **15**, **16** (Panel 1-2) and fischerindole products **17**, **18** (Panel 3-4) were compared with the standard **15**, **16**, **17** and **18** for the *in vitro* TT-assay performed in the presence FamD2 with FamC1 (Panel 1-2) or FisC (Panel 3-4) plasmids (for Figure 6). The '*' represents 5F-/6F-12-*epi*-hapalindole-GPP (Panel 1-2) and 5F-/6F-12-*epi*-fischerindole-GPP (Panel 3-4). Panel 1, 2, 3 and 4 represents the Figure 6 A, 6B, 6C and 6D.

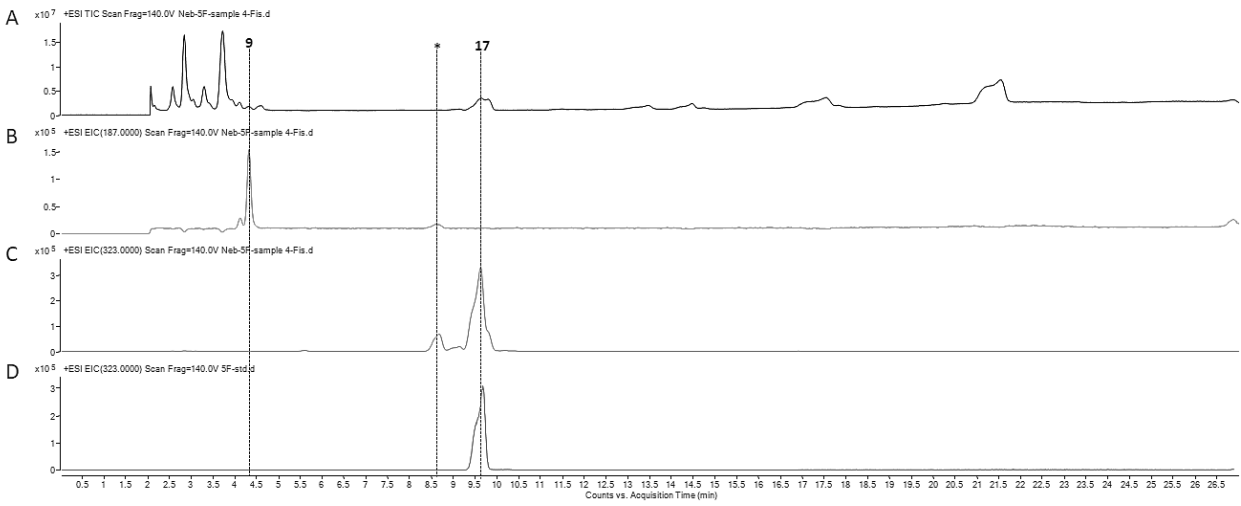
Panel 1



Panel 2



Panel 3



Panel 4

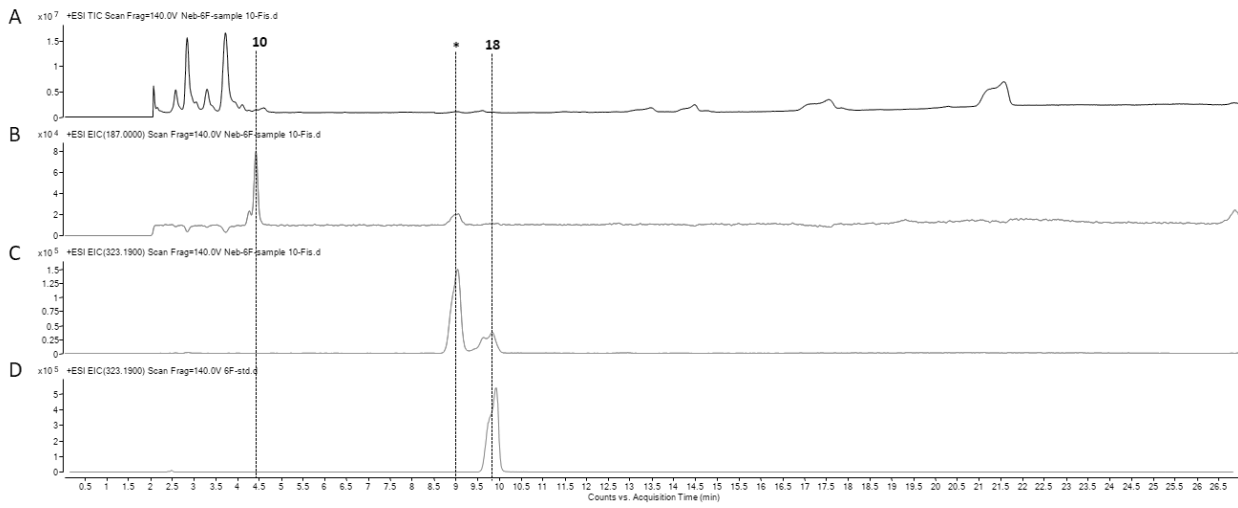
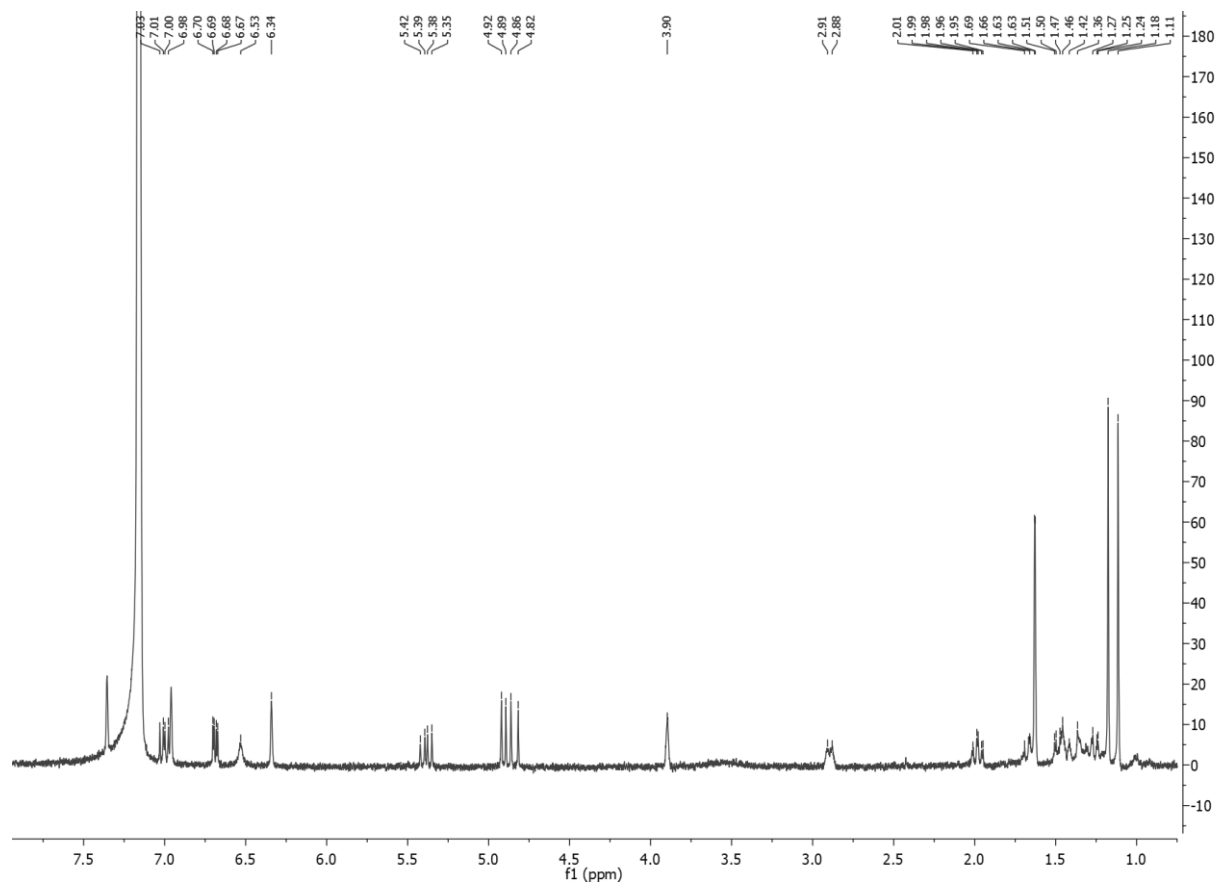
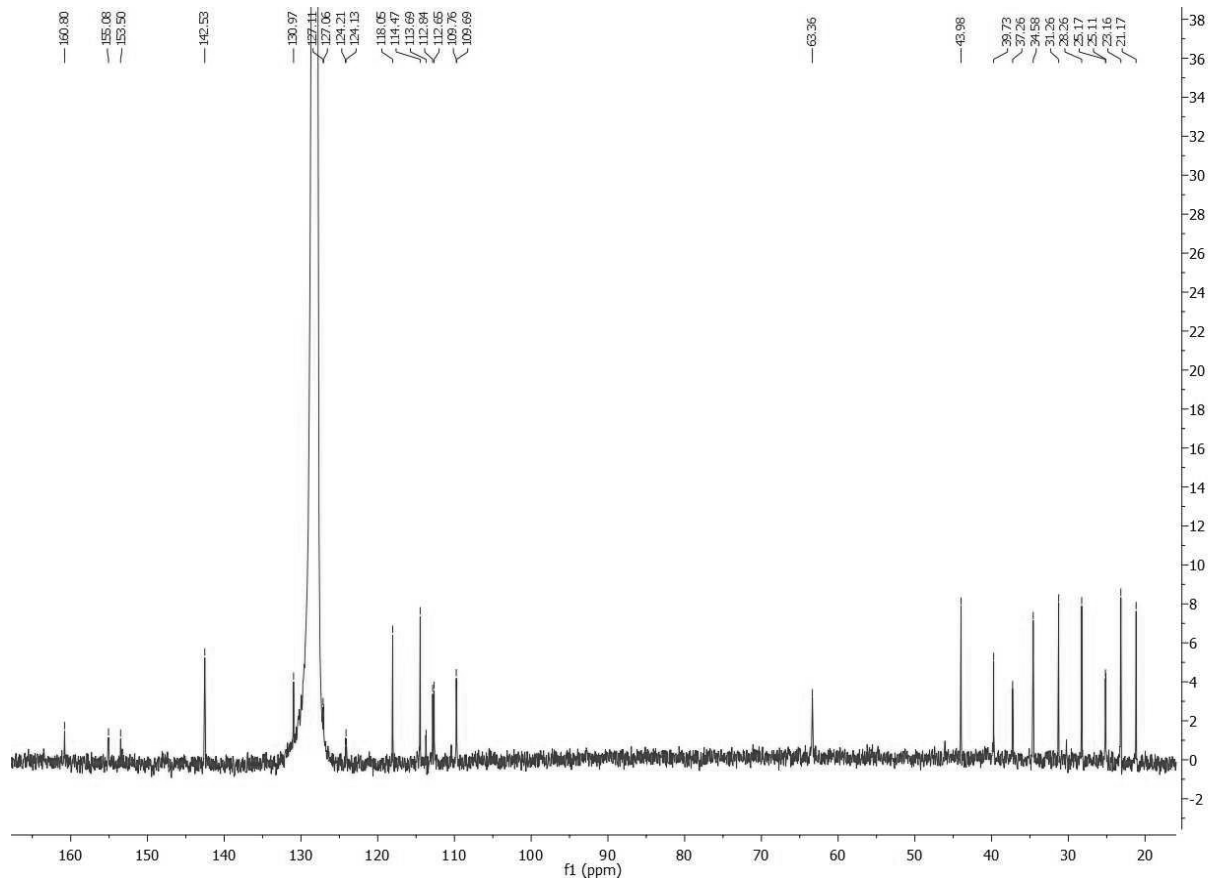
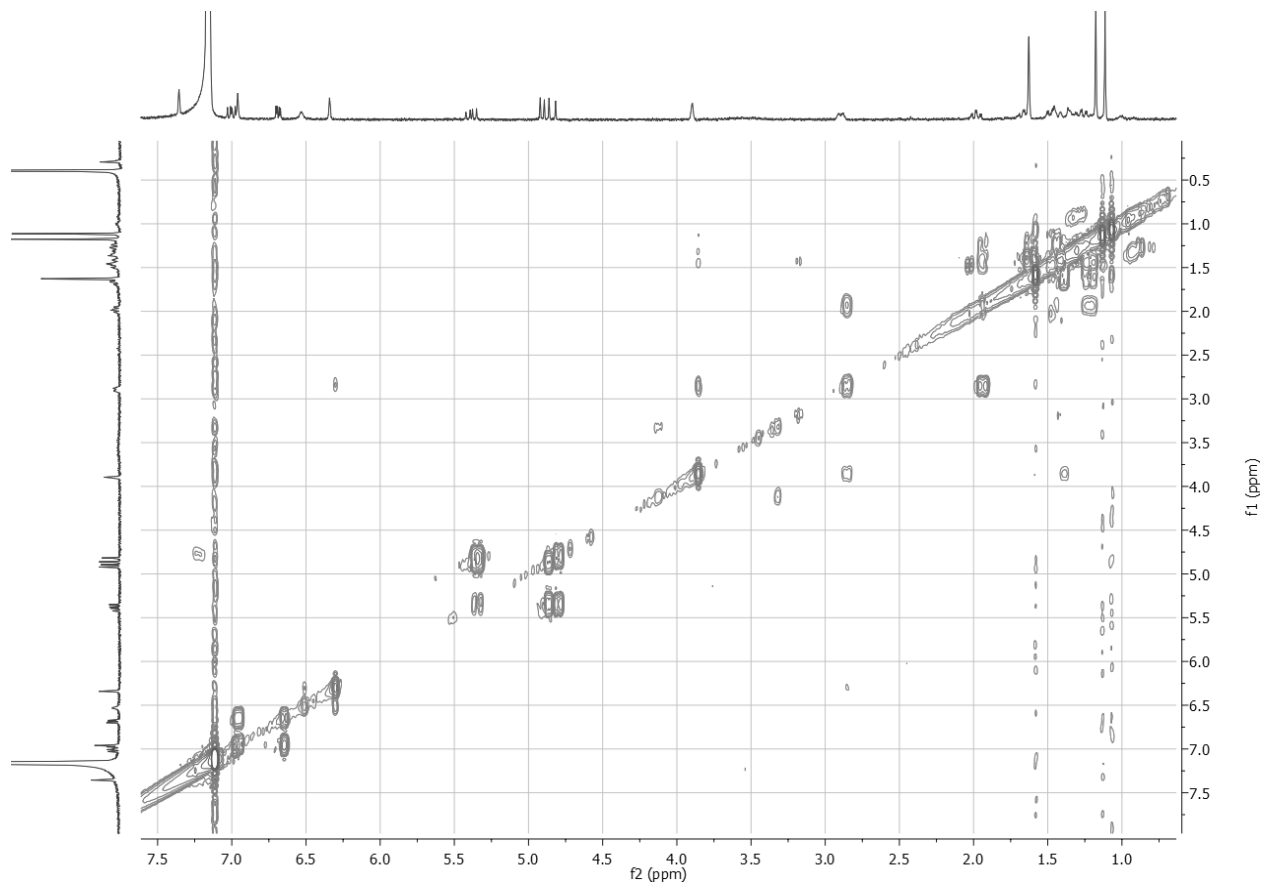


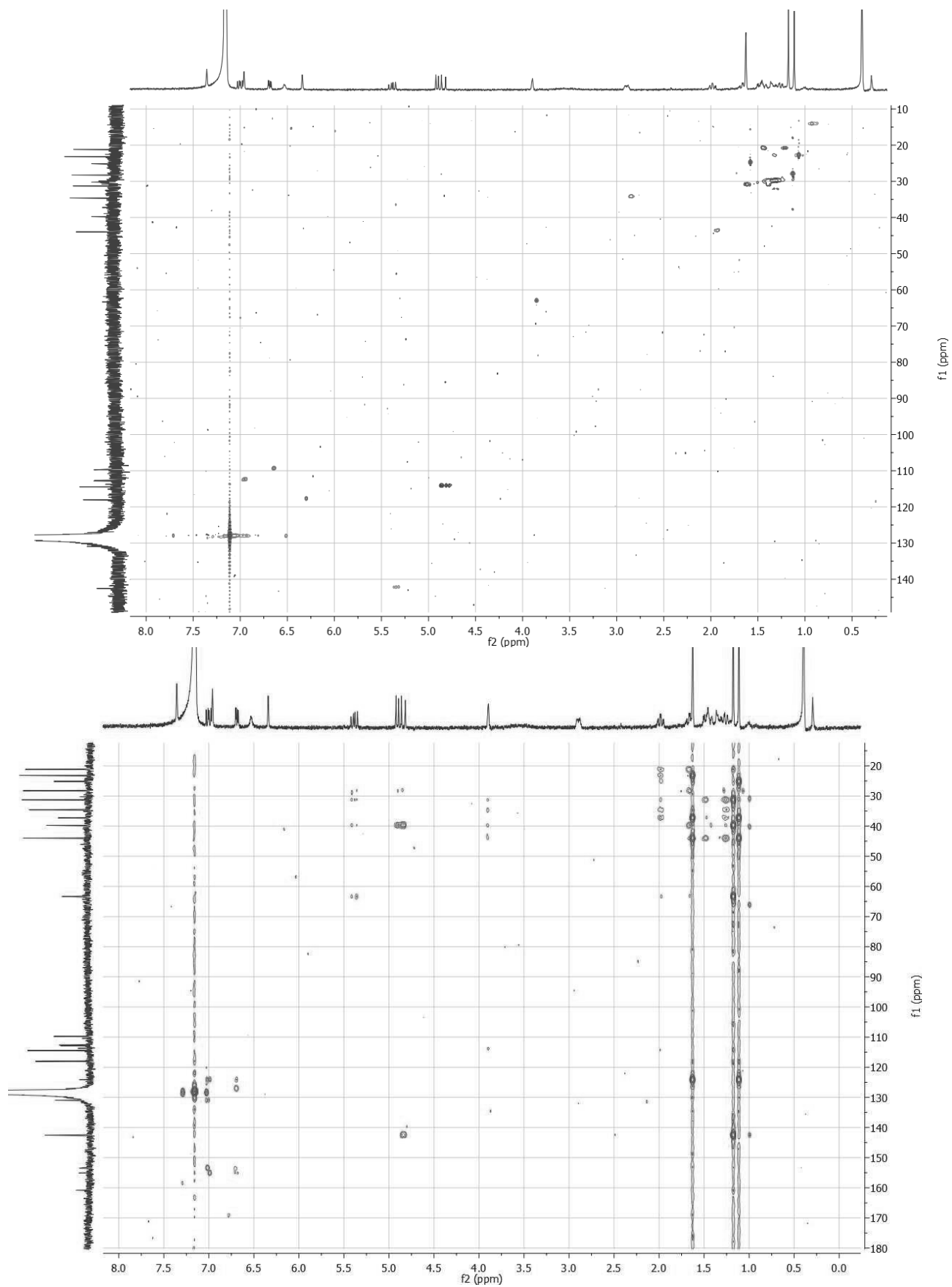
Figure S3: Spectra of 5-fluoro-12-*epi*-hapalindole U (15)

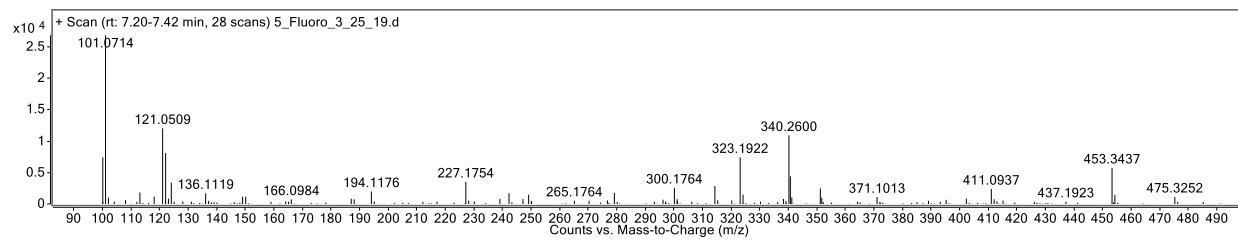
^1H , ^{13}C , COSY, HSQC, HMBC NMR spectra and HRMS of 5-F-12-*epi*-Hapalindole U **15** in C_6D_6 at 600 MHz and 125 MHz respectively.







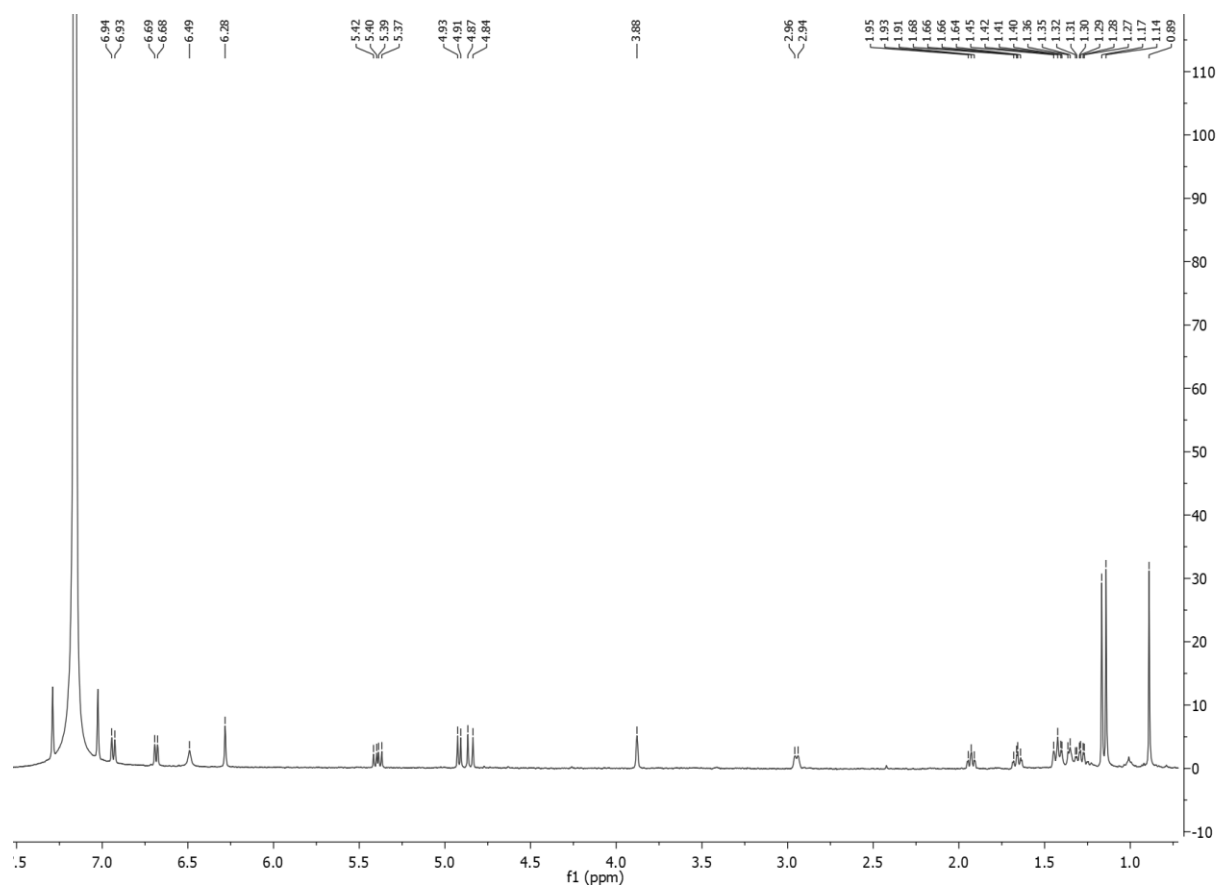


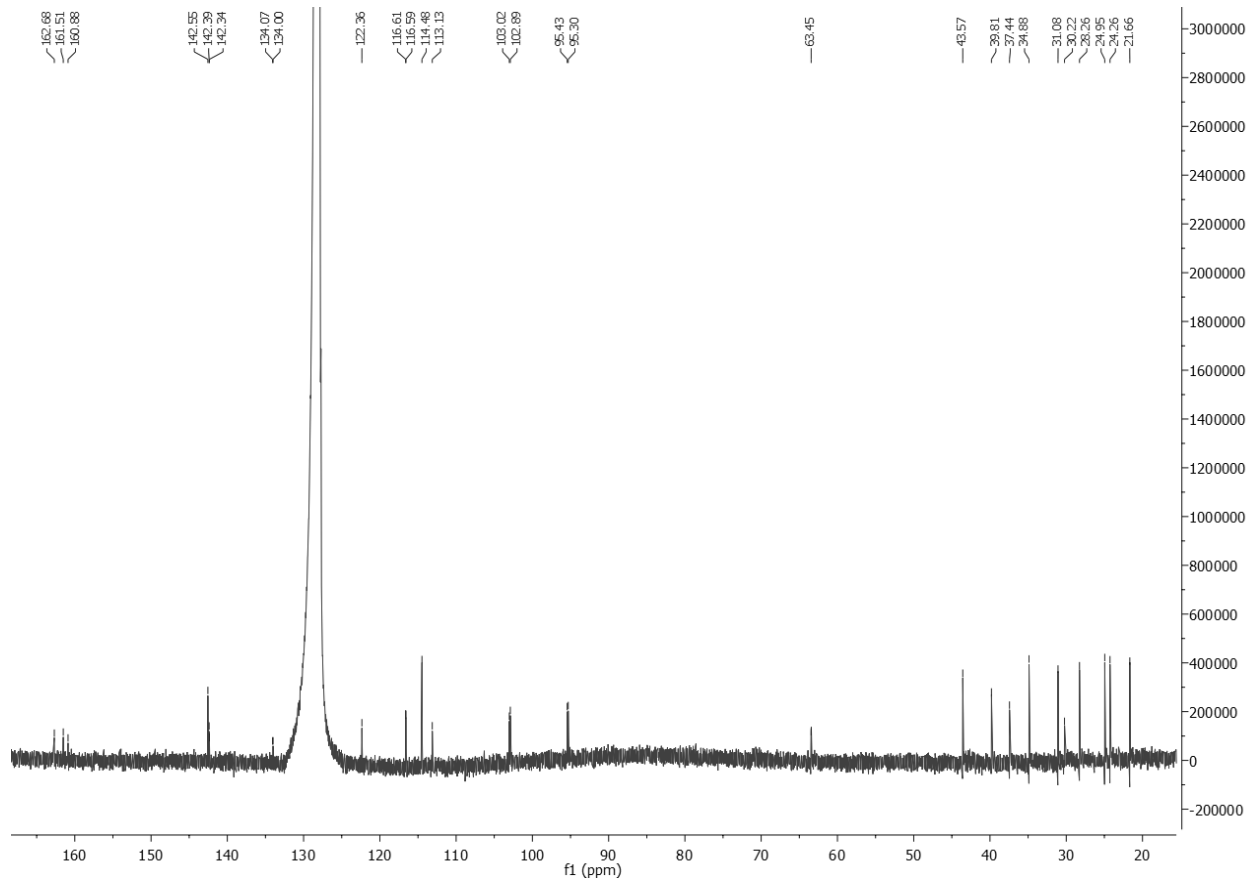


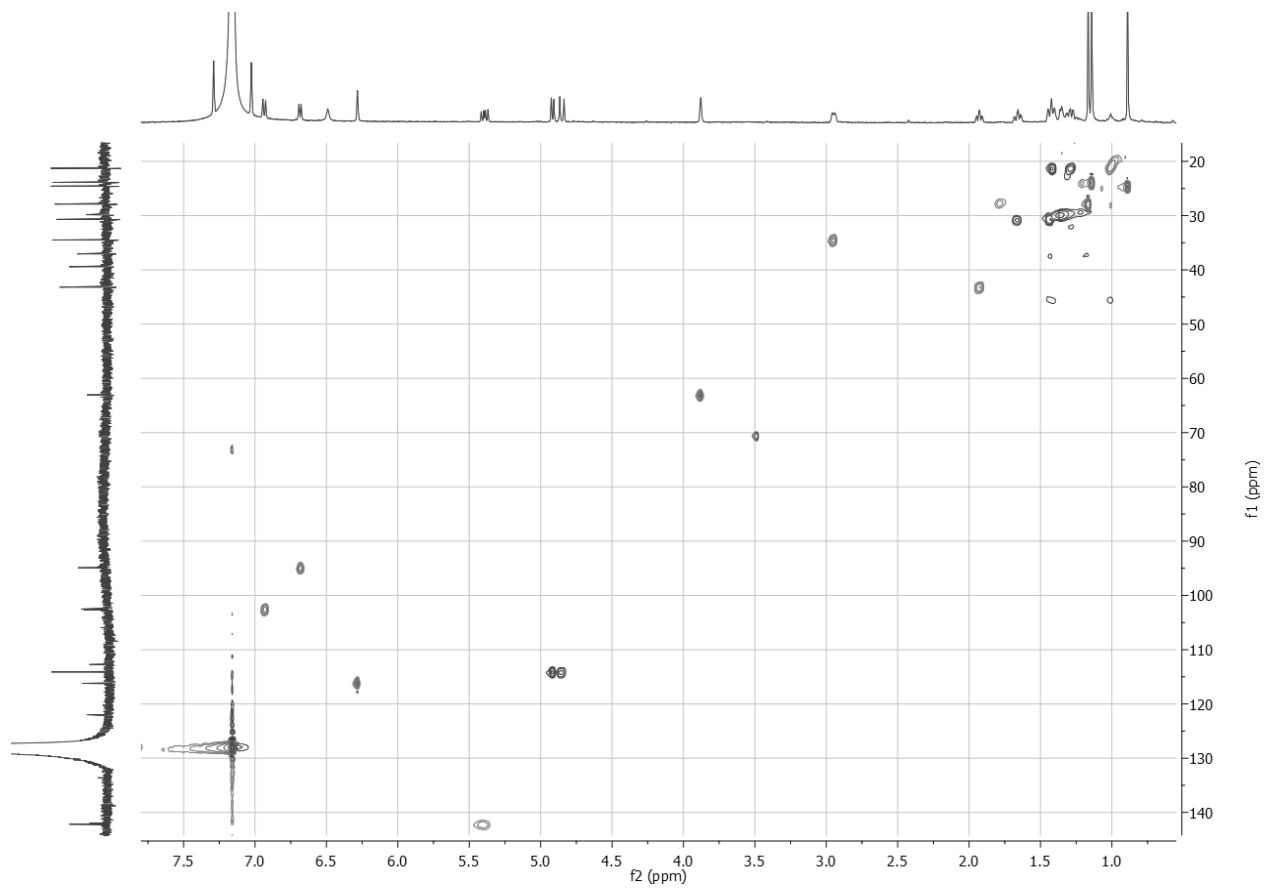
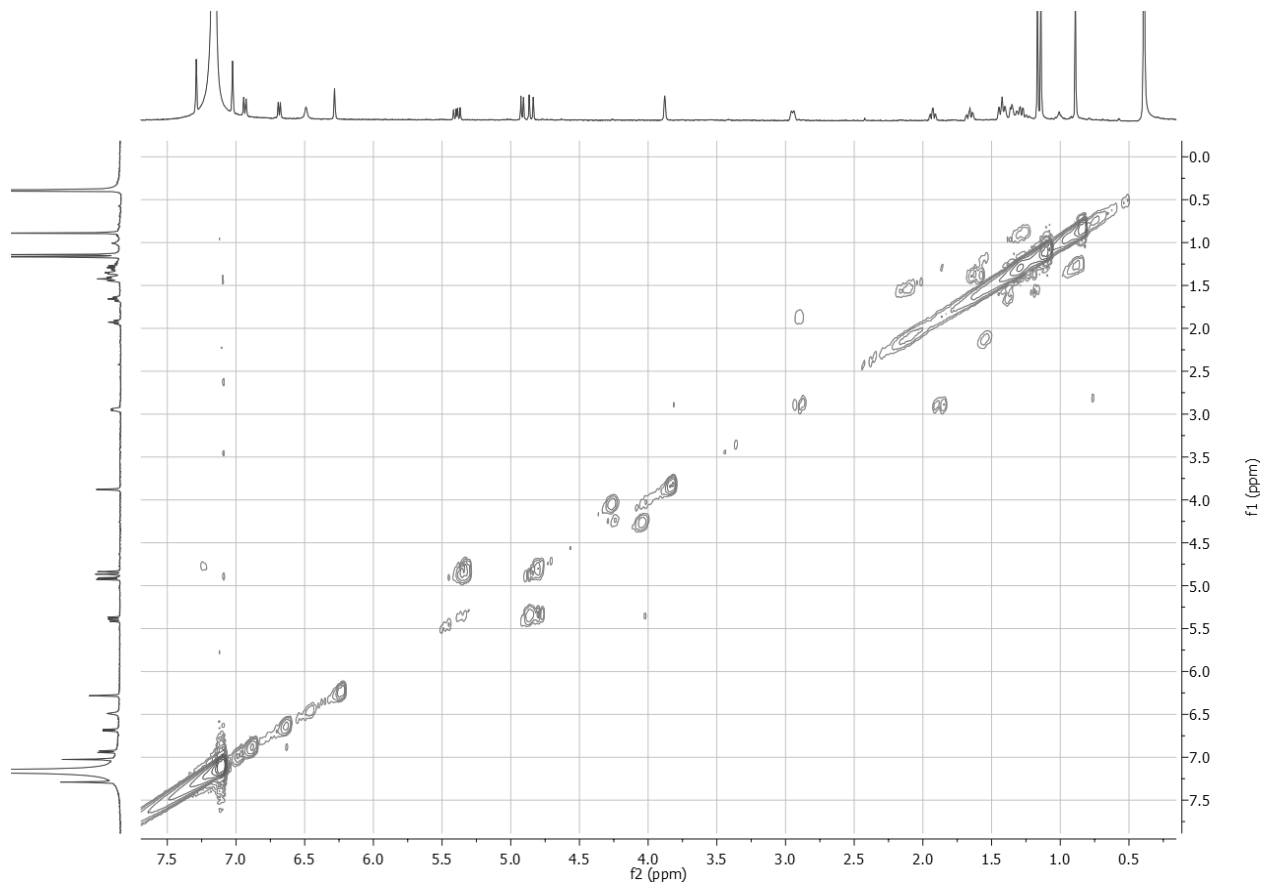
Calc. [M+H]⁺ 323.1918 Obsv. 323.1922

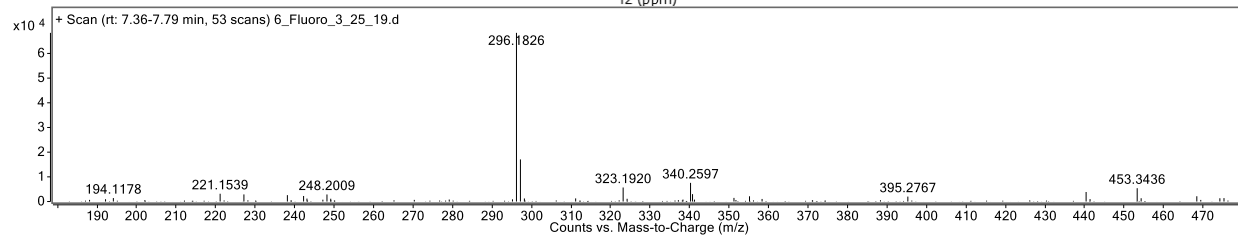
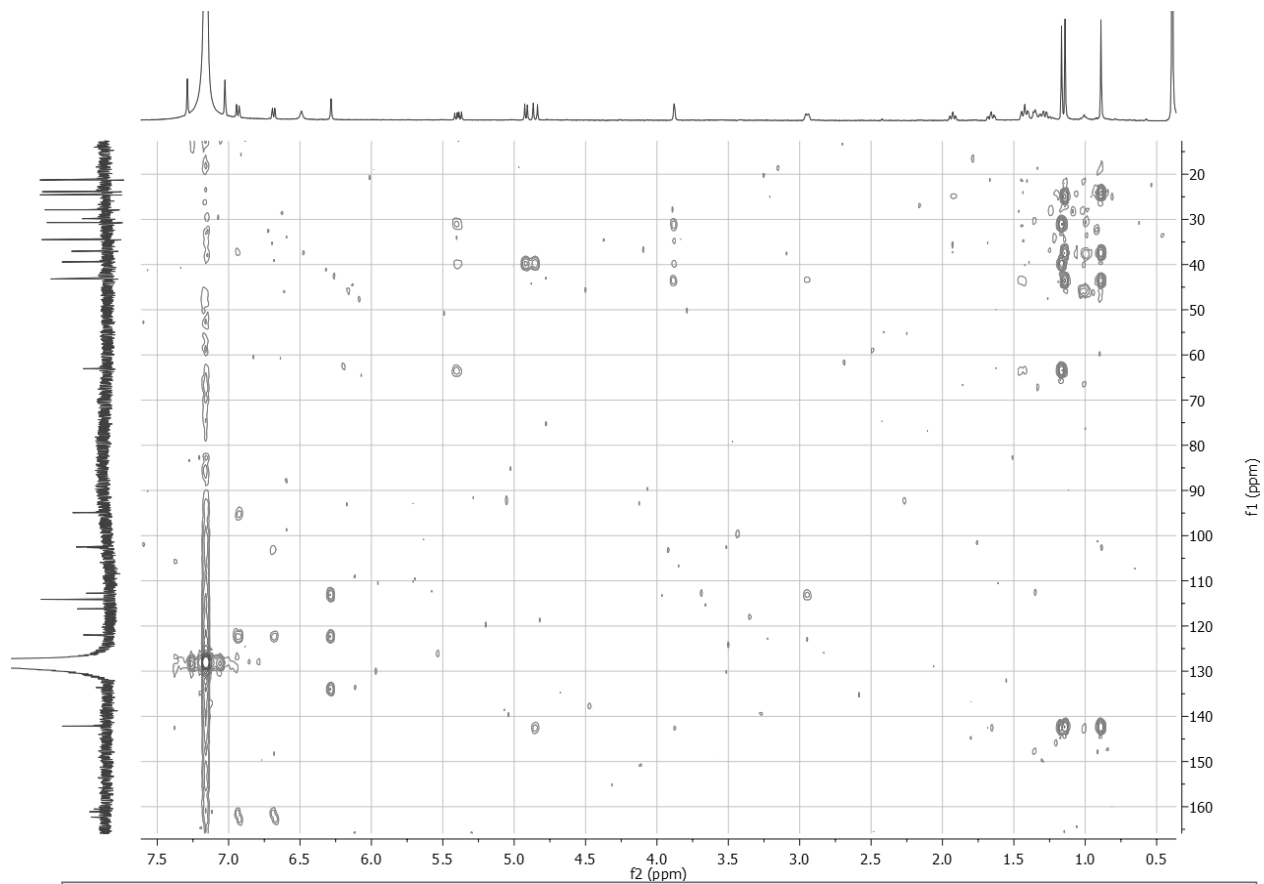
Figure S4: Spectra of 6-fluoro-12-*epi*-hapalindole U (16)

^1H , ^{13}C , COSY, HSQC, HMBC NMR spectra and HRMS of 6-F-12-*epi*-Hapalindole U **16** in C_6D_6 at 600 MHz for ^1H and COSY, 800 MHz for HSQC and HMBC, and 201 MHz respectively.

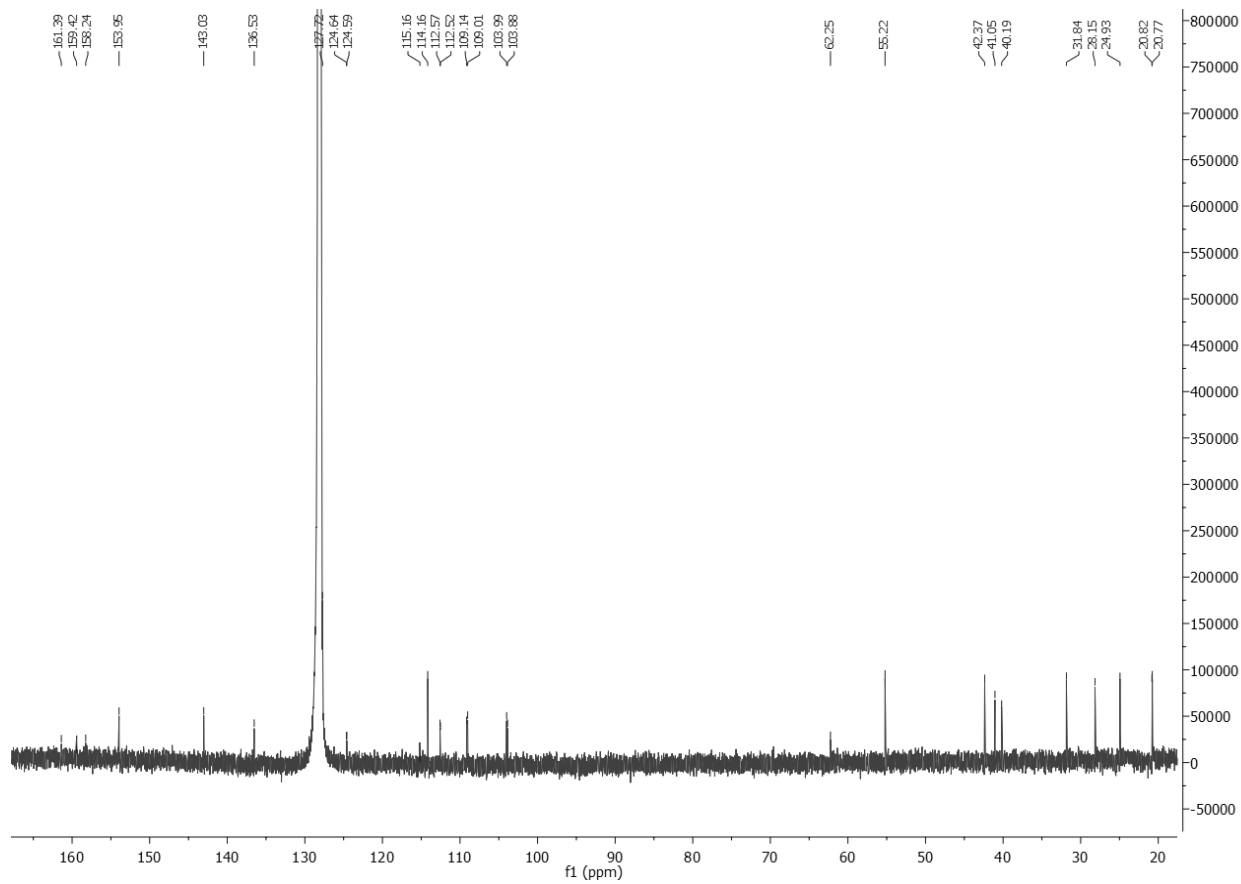


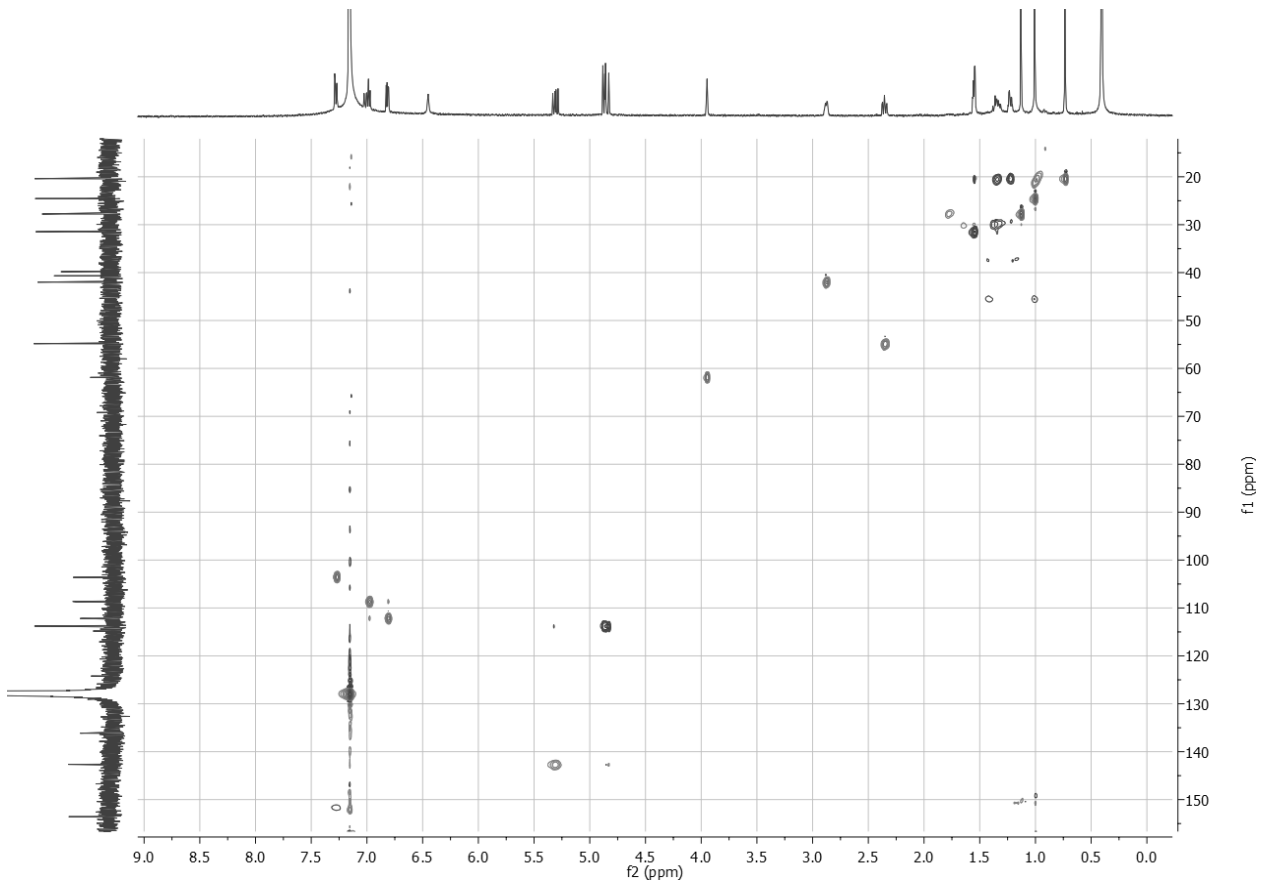
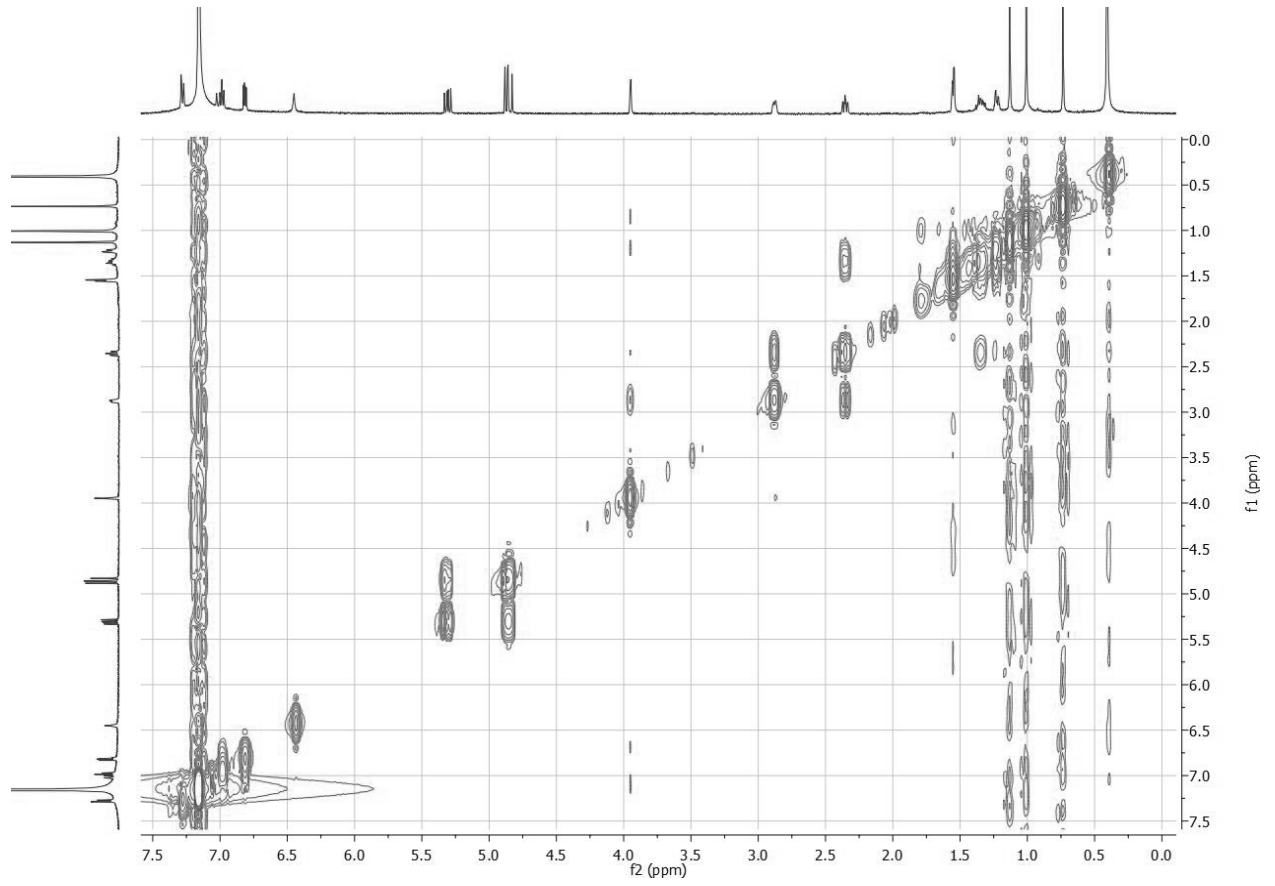


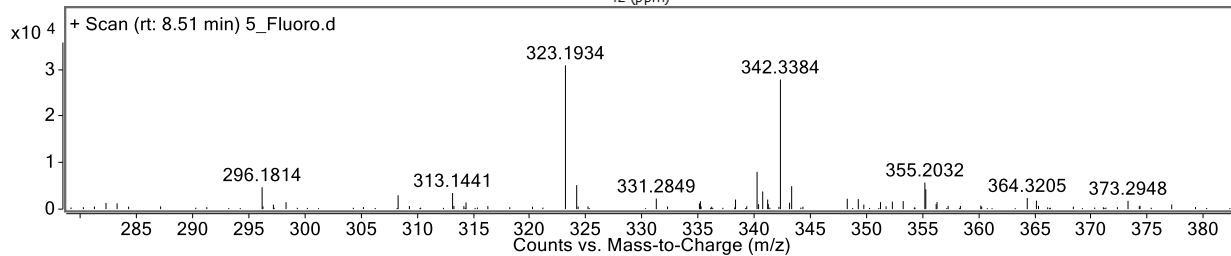
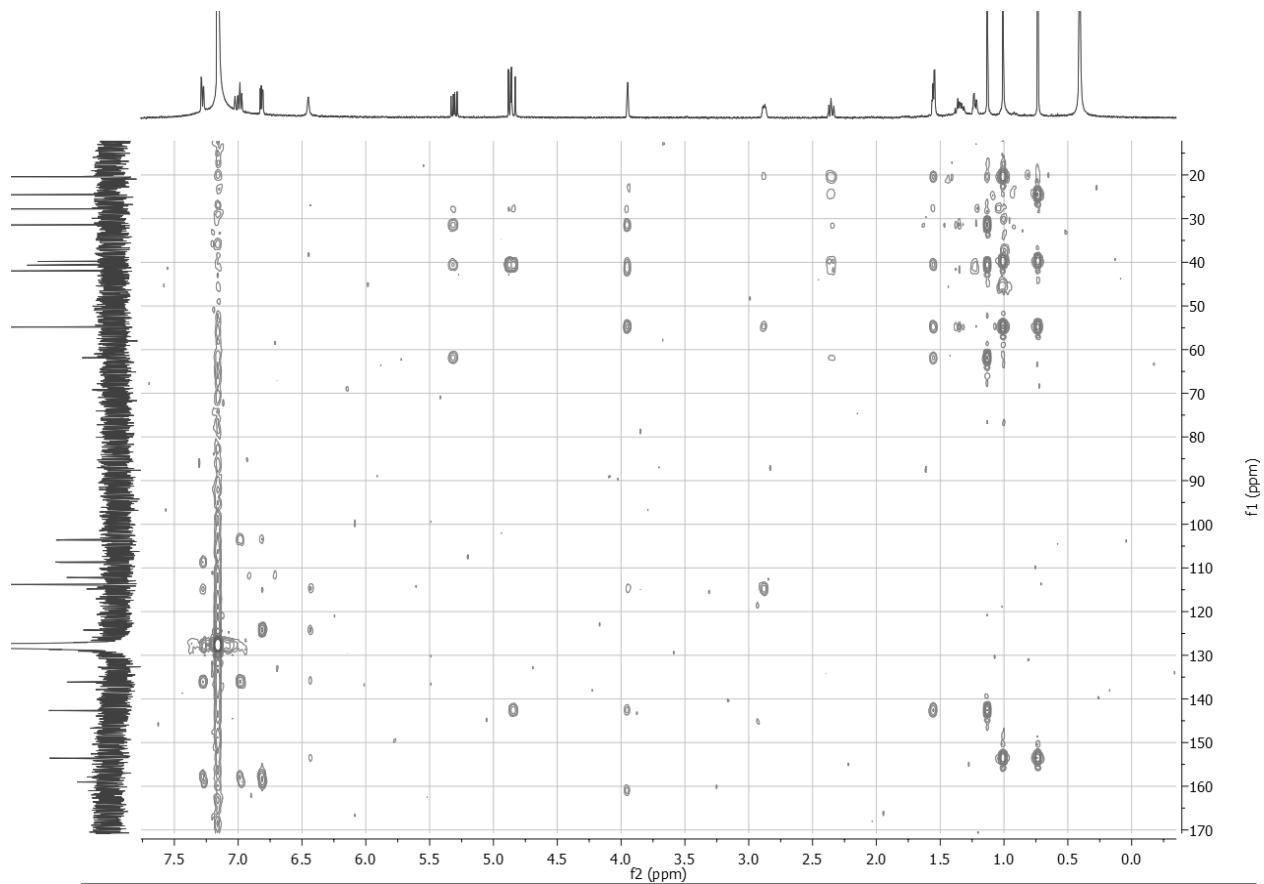




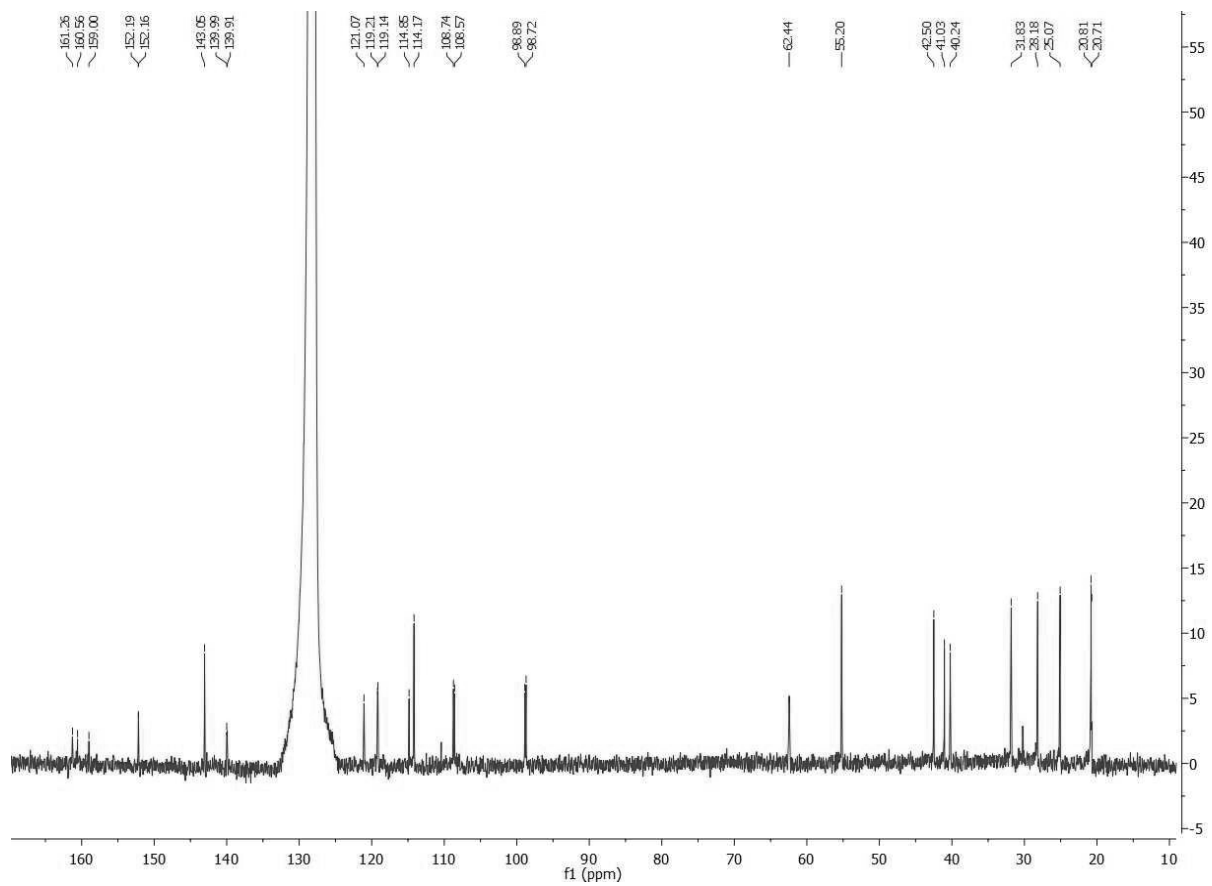
Calc. [M+H]⁺ 323.1918 Obsv. 323.1920

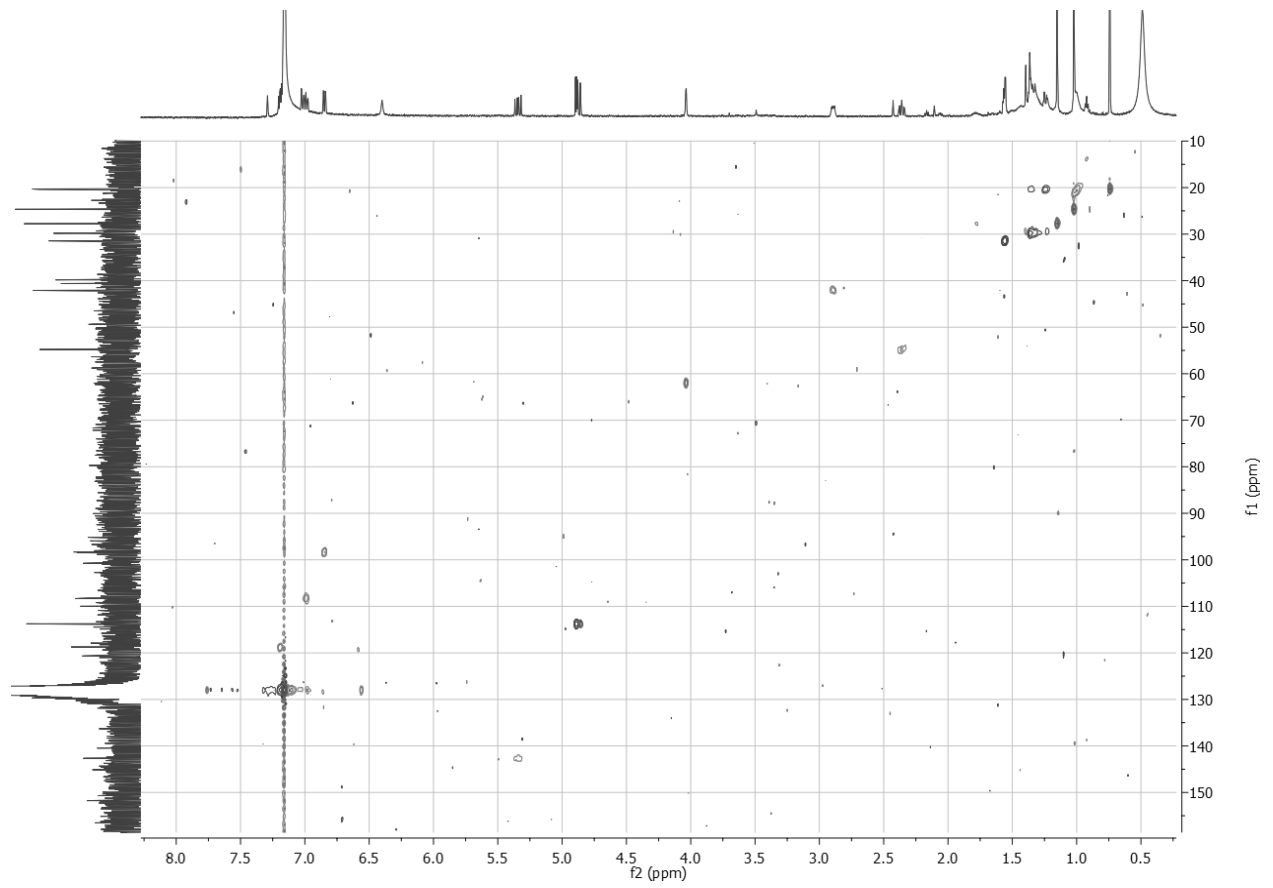
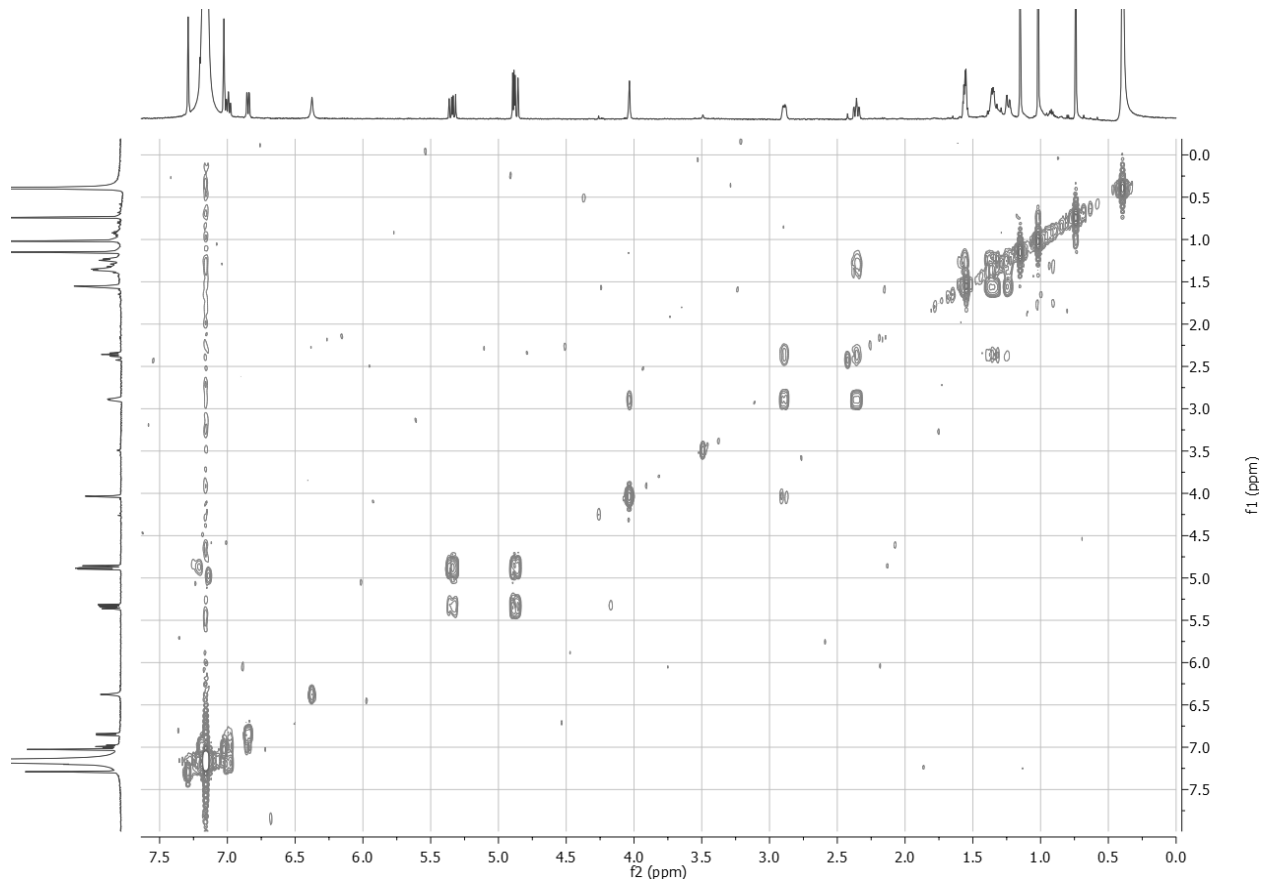


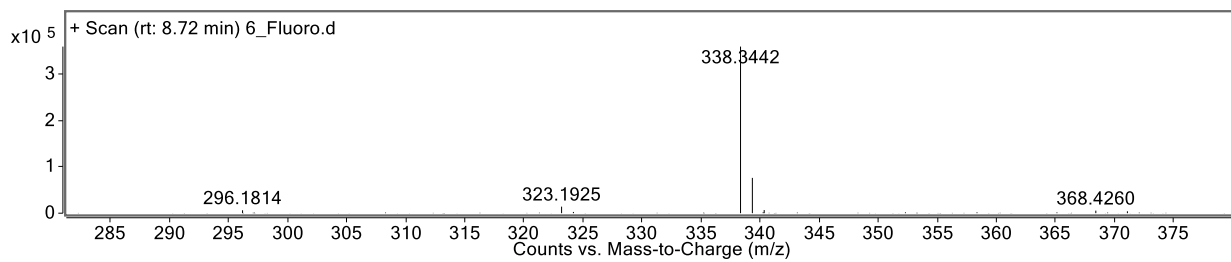
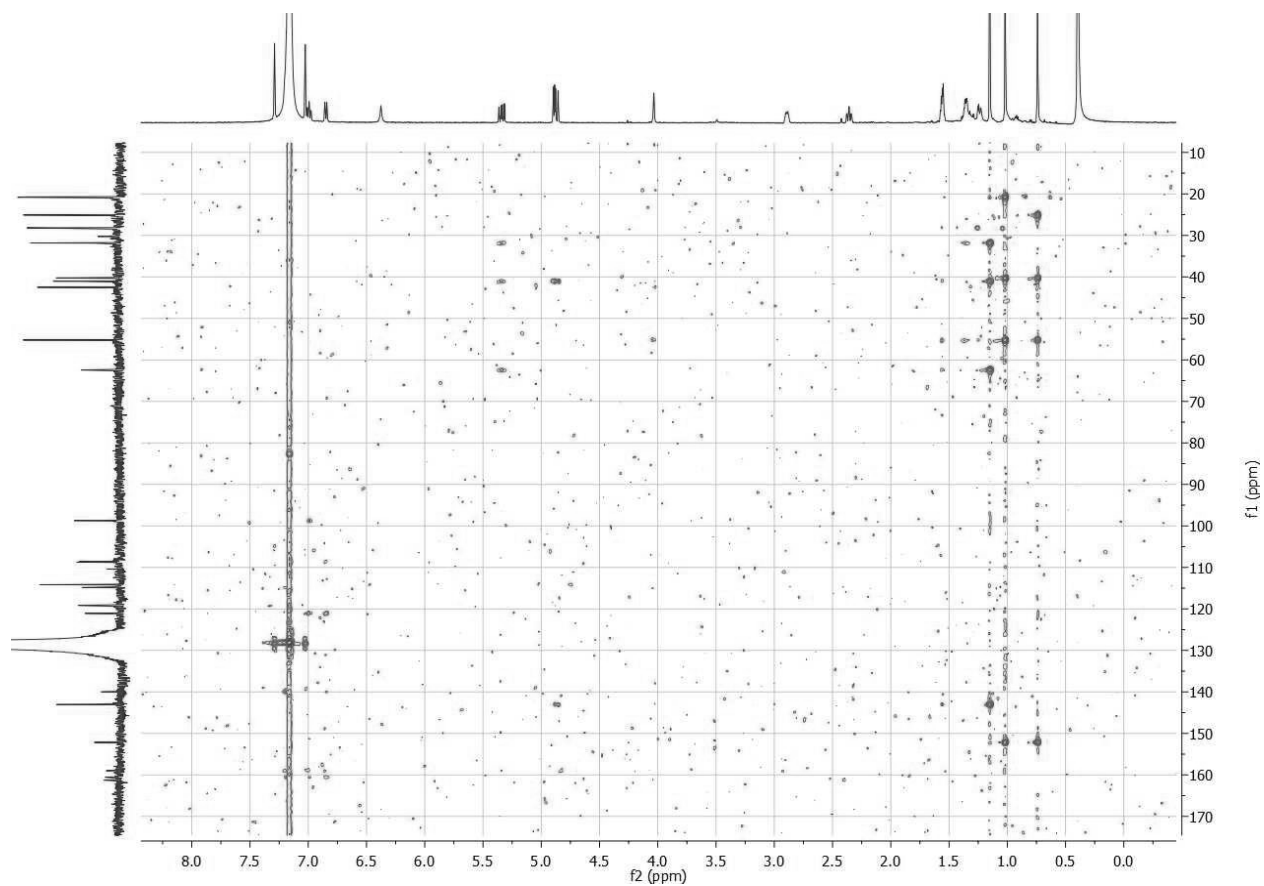




Calc. [M+H]⁺ 323.1918 Obsv. 323.1934







Calc. [M+H]⁺ 323.1918 Obsv. 323.1925