JEOL ROYAL HFX NMR Probe

A New NMR Probe for
^{1}H, ^{19}F & X NMR Experiments

Why Fluorine NMR:

- Fluorine is increasingly being used in many new drugs
  - As of 2011 there were approximately 200 fluorine containing drugs.[1]
  - Fluoro-organic compounds account for 40% of the new chemical entities entering phase III trials in 2012 and 2013.[2]
  - Fluorine is used in a wide range of drug applications including: Anesthetics, Antacids, Anti-anxiety, Antibiotics, Antidepressants, Anti-fungal antibiotics, Antihistamines, Antilipemics, Anti-malarial, Antimetabolites, Appetite suppressants, Arthritis/anti-inflammatory agents, Psychotropic, Steroids/anti-inflammatory agents[3]
- Fluorine is now appearing in illicit and illegal synthetic drugs:
  - These include: Cannabinoids[4], and psychedelic phenethylamines[5]
- Fluoro Polymers are important to everyday life, for example PTFE (Teflon™)

1. Wang et al, *Chem. Rev.* 2014, 114, 2432−2506
2. Zhou et al, *Chem. Rev*. 2016, 116, 422−518
3. http://www.slweb.org/ftrcfluorinatedpharm.html
4. Banister et al*, ACS Chem. Neurosci.*, 2015, 6 (8), 1445–1458
5. Trachsel, D., Drug Test. Analysis, (2012) 4: 577–590

Fluorine NMR properties and difficulties

- *The potential Fluorine chemical shift range is 500 ppm, 188 kHz at 9.4T (^{1}H 400 MHz) to 282 kHz at 14.1T (^{1}H 600 MHz).*
- *^{19}F-^{1}H j coupling constants up to 60 Hz*
- *^{19}F-^{13}C j coupling constants up to 280 Hz*
- *^{19}F long range J coupling interactions complicate NMR spectra making interpretation difficult*

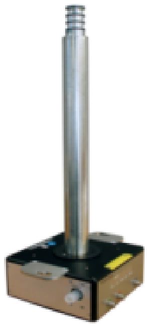
- *These spectral features combine to make ^{19}F difficult to excite and to decouple from other nuclei.*

NMR Probe for Fluorine NMR

What is needed is a Robust Routine HFX NMR Probe that can do every routine experiment well!

- *Including all HFX experiments, $^{1}H\{^{19}F\}$, $^{19}F\{^{1}H\}$, $^{13}C\{^{1}H,^{19}F\}$ & $X\{^{1}H,^{19}F\}$*

JEOL has merged two NMR probes into one –



^{1}H or ^{19}F
High Sensitivity

JEOL ROYAL probe

<u>JEOL ROYAL-HFX probe</u>

^{1}H ^{19} F
Dual Tune

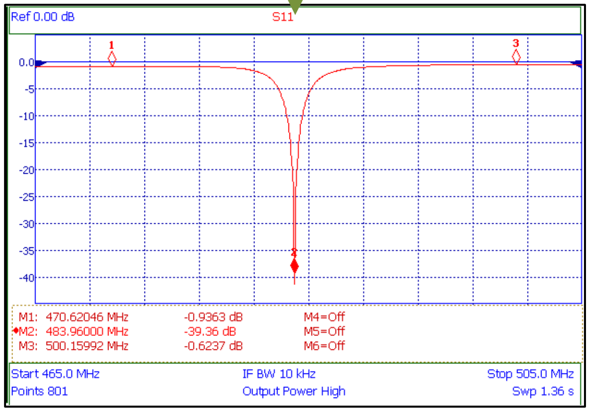
JEOL TFH probe

JEOL ECZ NMR & ROYAL HFX NMR Probe

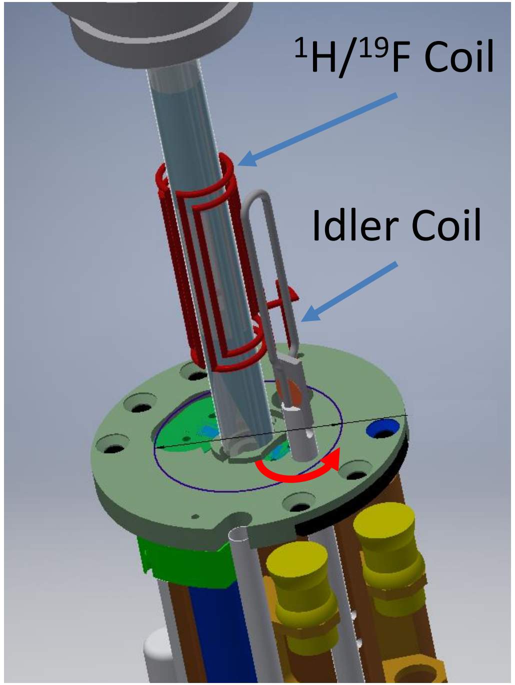
- JEOL ECZ NMR Spectrometer
  - ECZS routine NMR spectrometers can generate simultaneous ^{1}H and ^{19}F frequencies with no additional hardware
  - ECZR research NMR spectrometers with an optional 3rd channel can collect ^{1}H and ^{19}F data over wide ^{19}F frequency ranges.
- JEOL Royal HFX NMR Probe
  - Spec's Royal Probe = Spec's Royal HFX Probe
  - No Loss in RF or S/N performance relative to the standard ROYAL probe for ^{1}H, ^{19}F, ^{13}C, or X
  - Includes Auto-Tune compatibility to allow easy switching between modes.

ROYAL HFX Probe

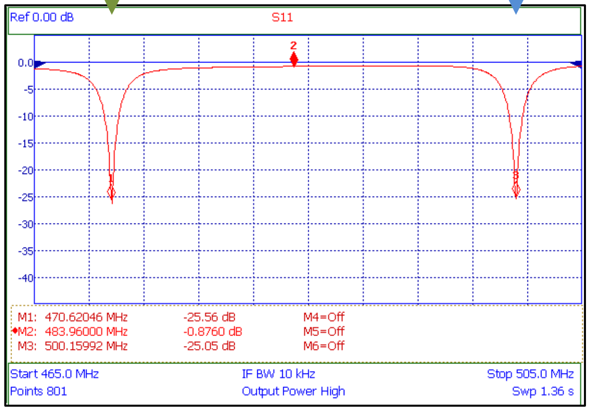
H-F Mid-Point



Single Tune
HFX Off



19F 1H



Dual Tune
HFX On

Figure 1. Illustration of magnetic coupling technology as a perfect switch between single tune and dual tune modes in the ROYAL-HFX Probe.

Rotate Idler Coil

ROYAL HFX NMR Probe & AutoTune HFX Extension

Knob for switching between ROYAL and HFX mode

AutoTune Extension Automatically switches between HX & HFX modes

600 MHz HFX

- ^{1}H SNR & 90° - 600 MHz (0.1% EB)
- ^{19}F SNR & 90° - 600 MHz (0.05% TFT)

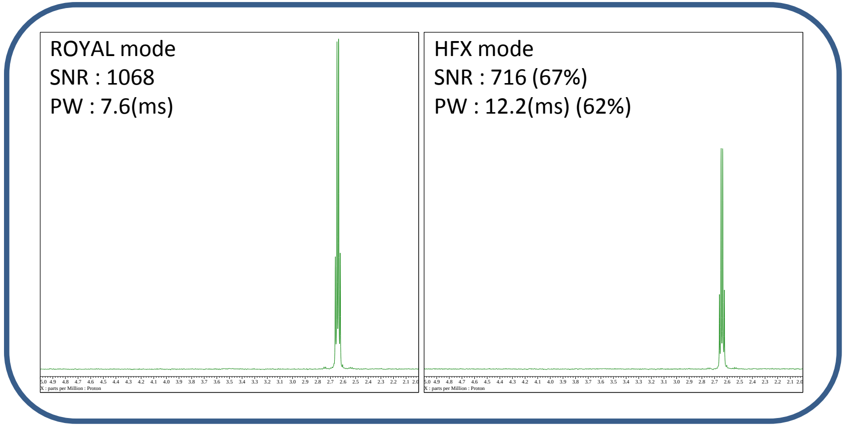


Figure 2: ^{1}H signal to noise and pw90 for a 500 MHz ROYAL-HFX Probe in single and dual-tune, illustrating the expected changes in performance when switching modes.

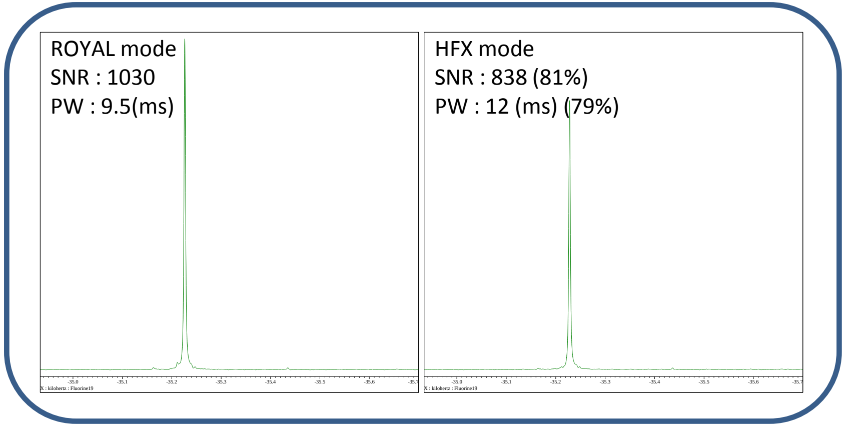


Figure 3: ^{19}F signal to noise and pw90 for a 500 MHz ROYAl-HFX Probe in single and dual-tune models.

Available HFX Experiments

Matrix of common out of the box 1D and 2D NMR techniques provided in the software.

- 1D
  - $^{1}H\{^{19}F\}$
  - $^{19}F\{^{1}H\}$
  - $^{13}C\{^{1}H,^{19}F\}$
  - $X\{^{1}H,^{19}F\}$, X= ^{15}N to ^{31}P
- 2D with ^{1}H, ^{19}F, or ^{1}H & ^{19}F Direct or Indirect Decoupling
  - HSQCAD - ^{13}C & ^{15}N
  - gHMBCAD - ^{13}C & ^{15}N
  - HOESY – ^{1}H-^{19}F

ROYAL HFX Probe

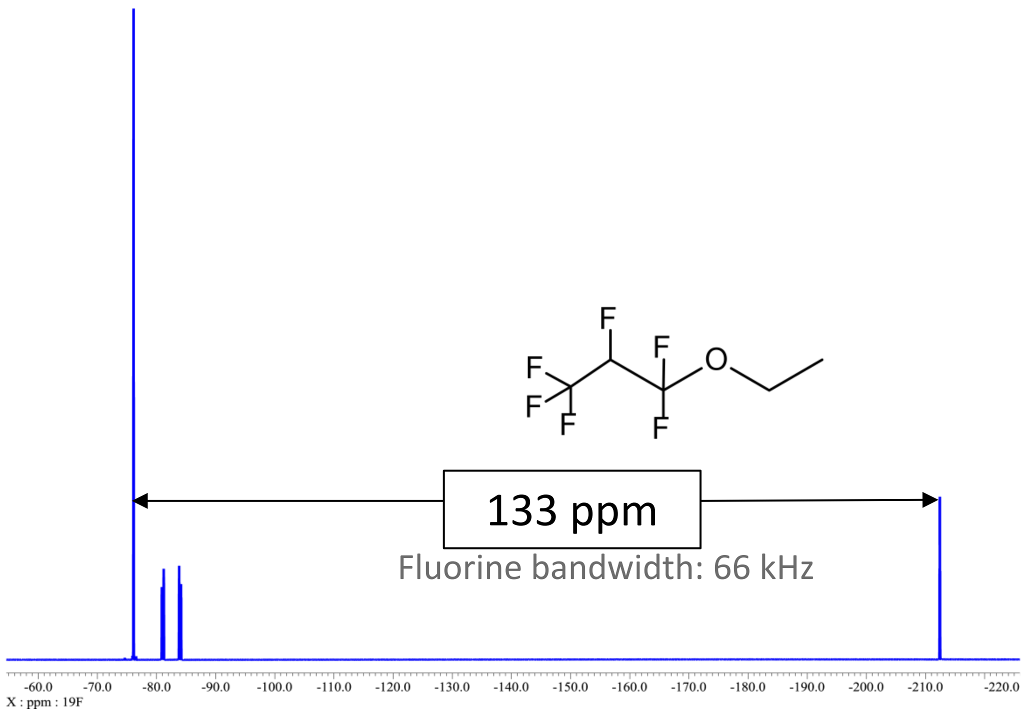


Figure 4: $^{19}F\{^{1}H\}$ 1D spectrum for a fluoro-ether illustrating the potential for large ^{19}F frequency bandwidth.

ROYAL HFX Probe – $^{13}C\{^{1}H,^{19}F\}$

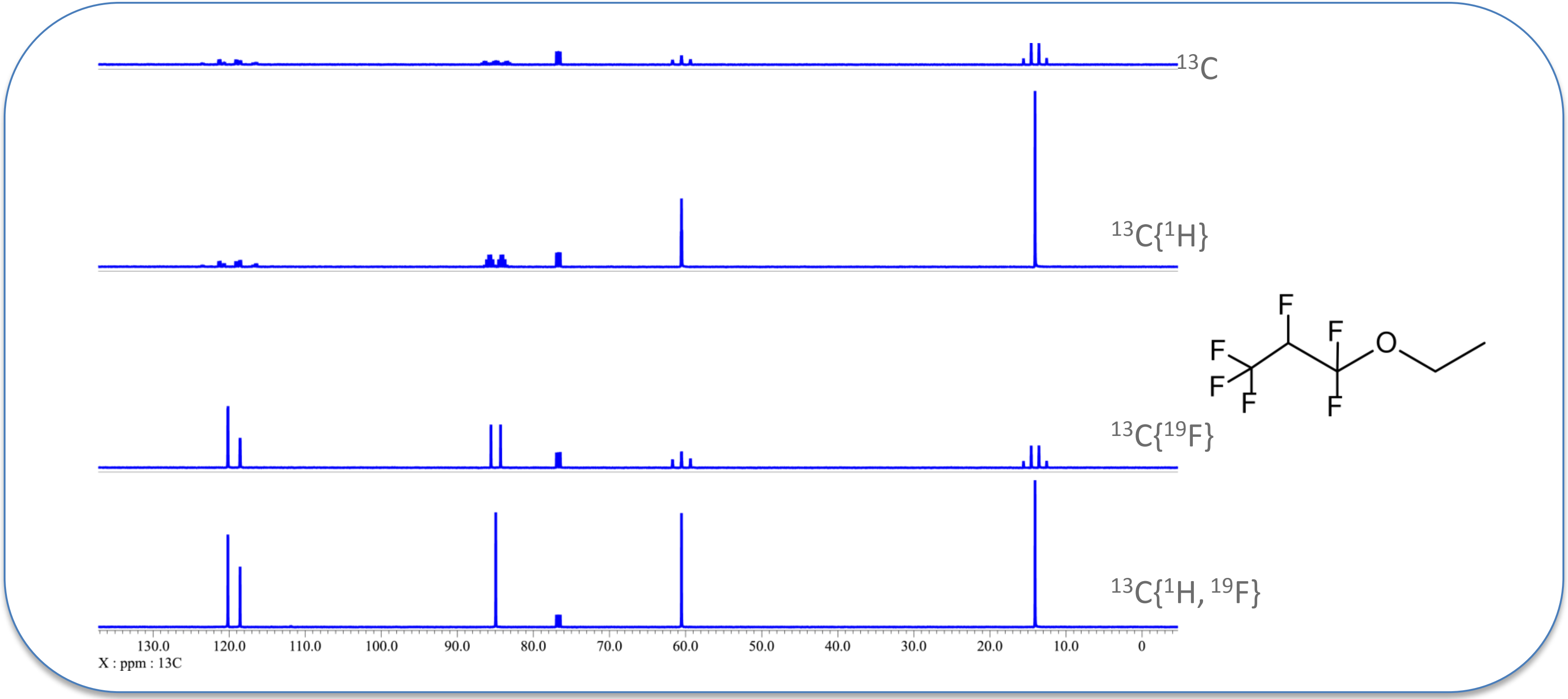
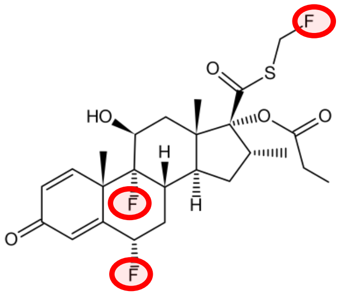
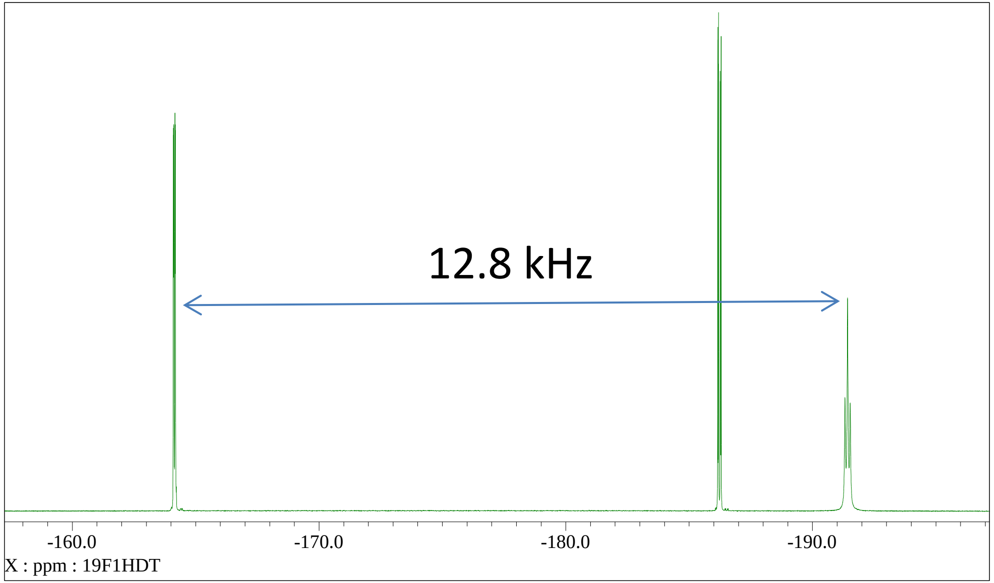


Figure 5: Full ^{13}C spectrum for the fluor-ether example showing all possible combinations of ^{1}H and ^{19}F decoupling. Results are shown with identical scaling to accentuate the dramatic improvement to ^{13}C spectra of flurorine containing molecules by dual $\{^{1}H,^{19}F\}$.

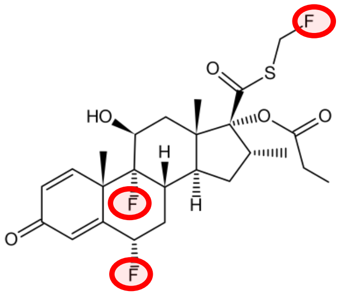
ROYAL HFX Probe – ^{19}F

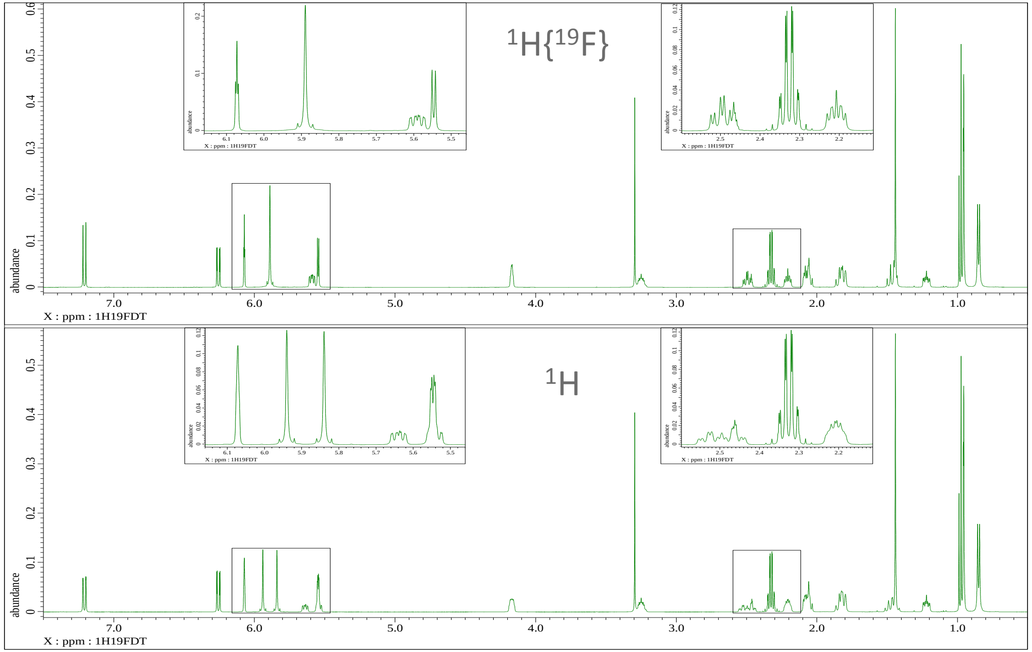




Fluticasone propionate

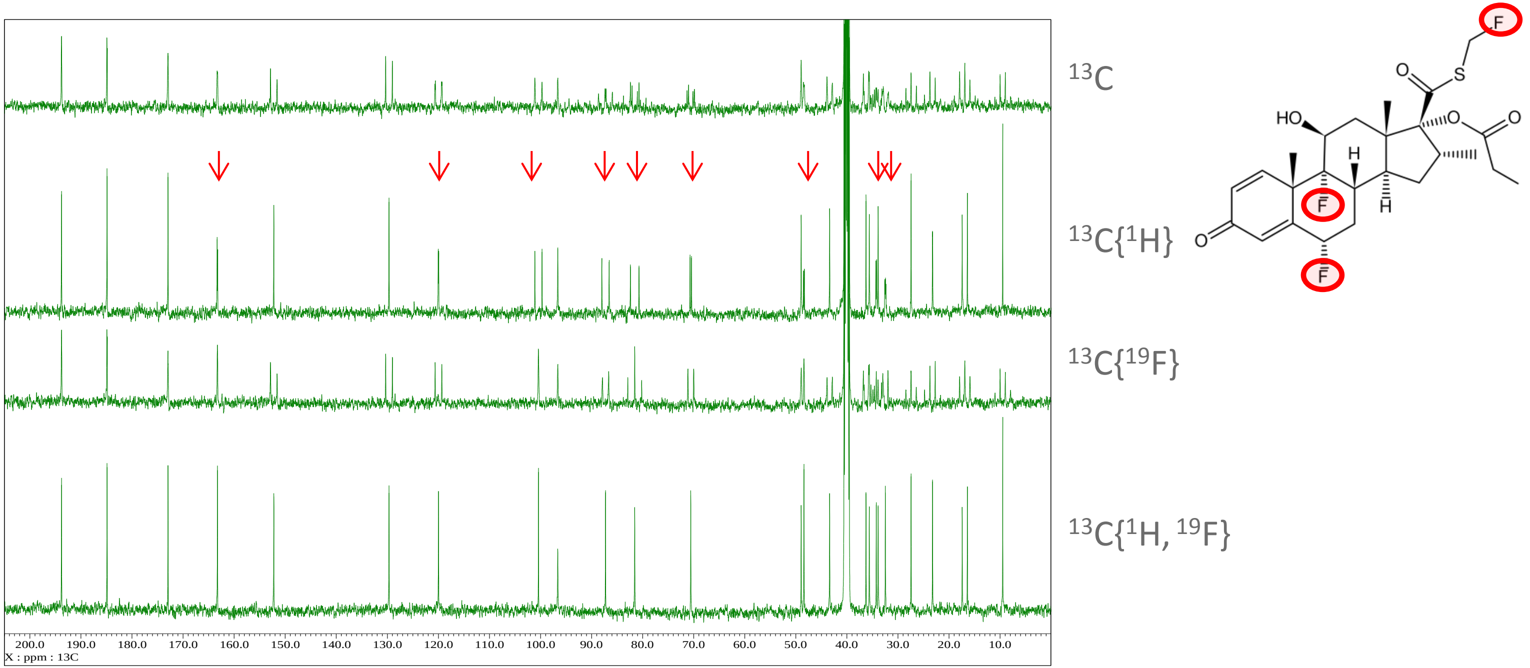
ROYAL HFX Probe – $^{1}H\{^{19}F\}$





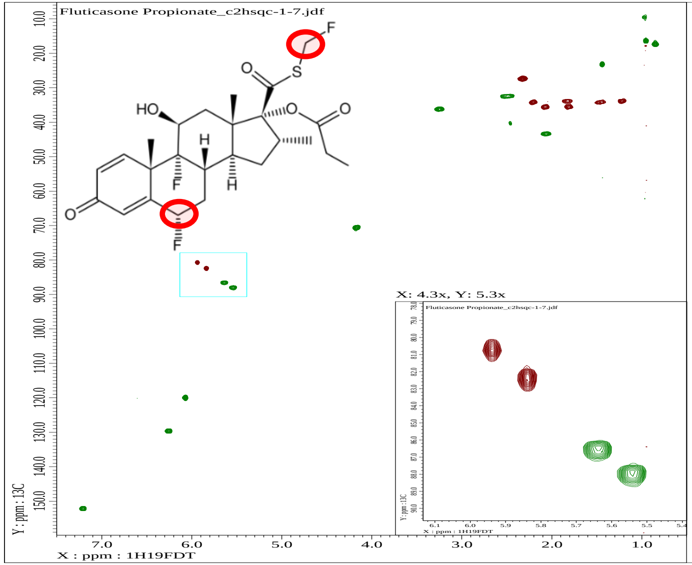
Fluticasone propionate

ROYAL HFX Probe – $^{13}C\{^{1}H,^{19}F\}$

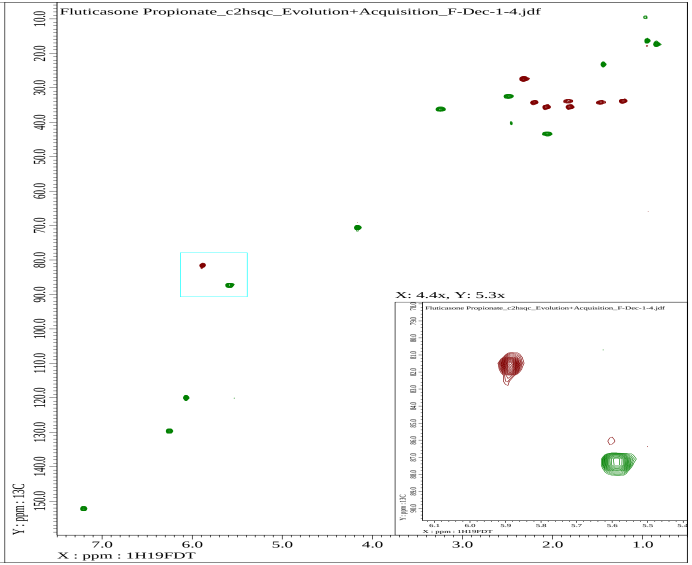


Fluticasone propionate

ROYAL HFX – $^{13}C\{^{1}H\}$ & $^{13}C\{^{1}H,^{19}F\}$ - HSQC



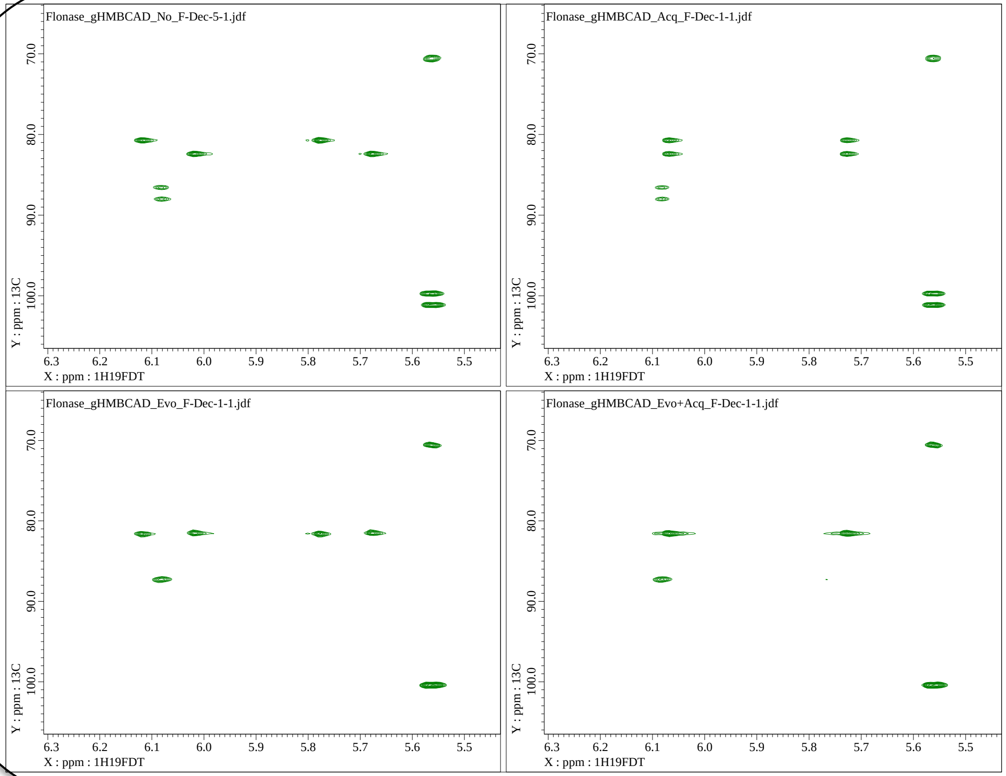
Edited HSQCAD
without ^{19}F decoupling
(NUS-25%)

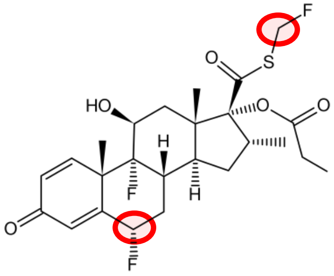


Edited HSQCAD
with ^{19}F decoupling
(NUS-25%)

Fluticasone propionate

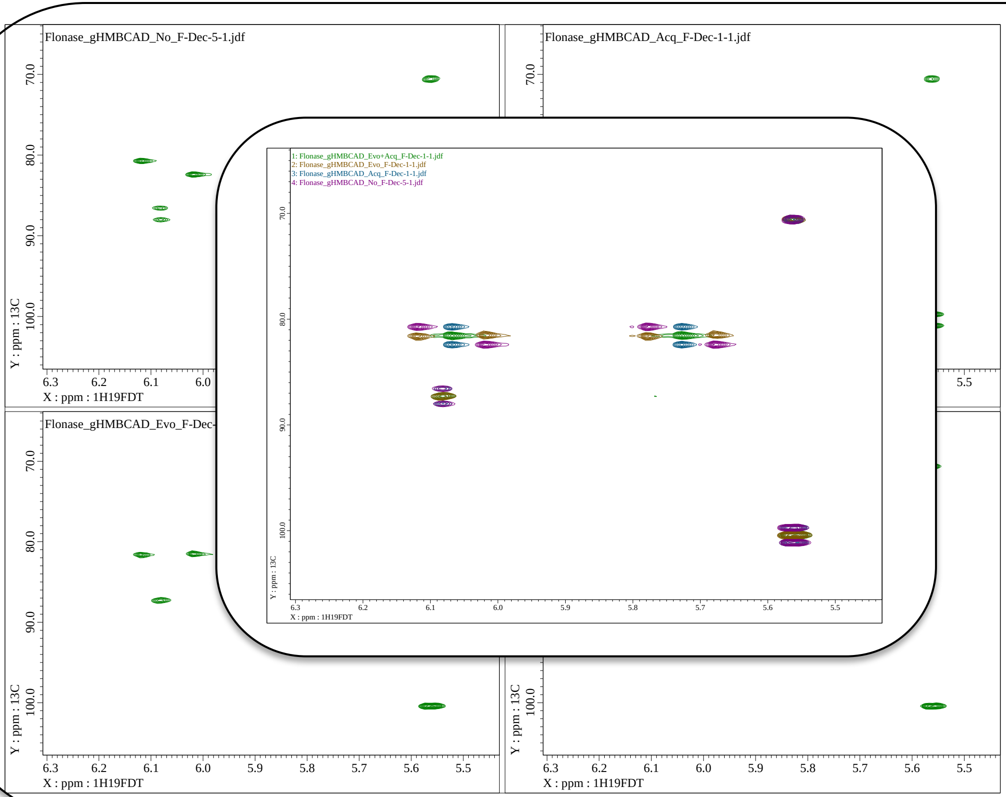
ROYAL HFX – $^{13}C\{^{1}H\}$ & $^{13}C\{^{1}H,^{19}F\}$ - gHMBCAD



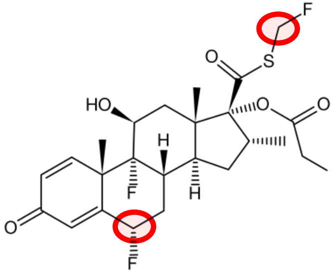


Fluticasone propionate

ROYAL HFX – $^{13}C\{^{1}H\}$ & $^{13}C\{^{1}H,^{19}F\}$ - gHMBCAD



$\{^{19}F\}$ =
- No Dec
- Y Dec
- X Dec
- X & Y Dec



Fluticasone propionate

ROYAL HFX – $^{13}C\{^1H\}$ & $^{13}C\{^1H,^{19}F\}$ - gHMBCAD

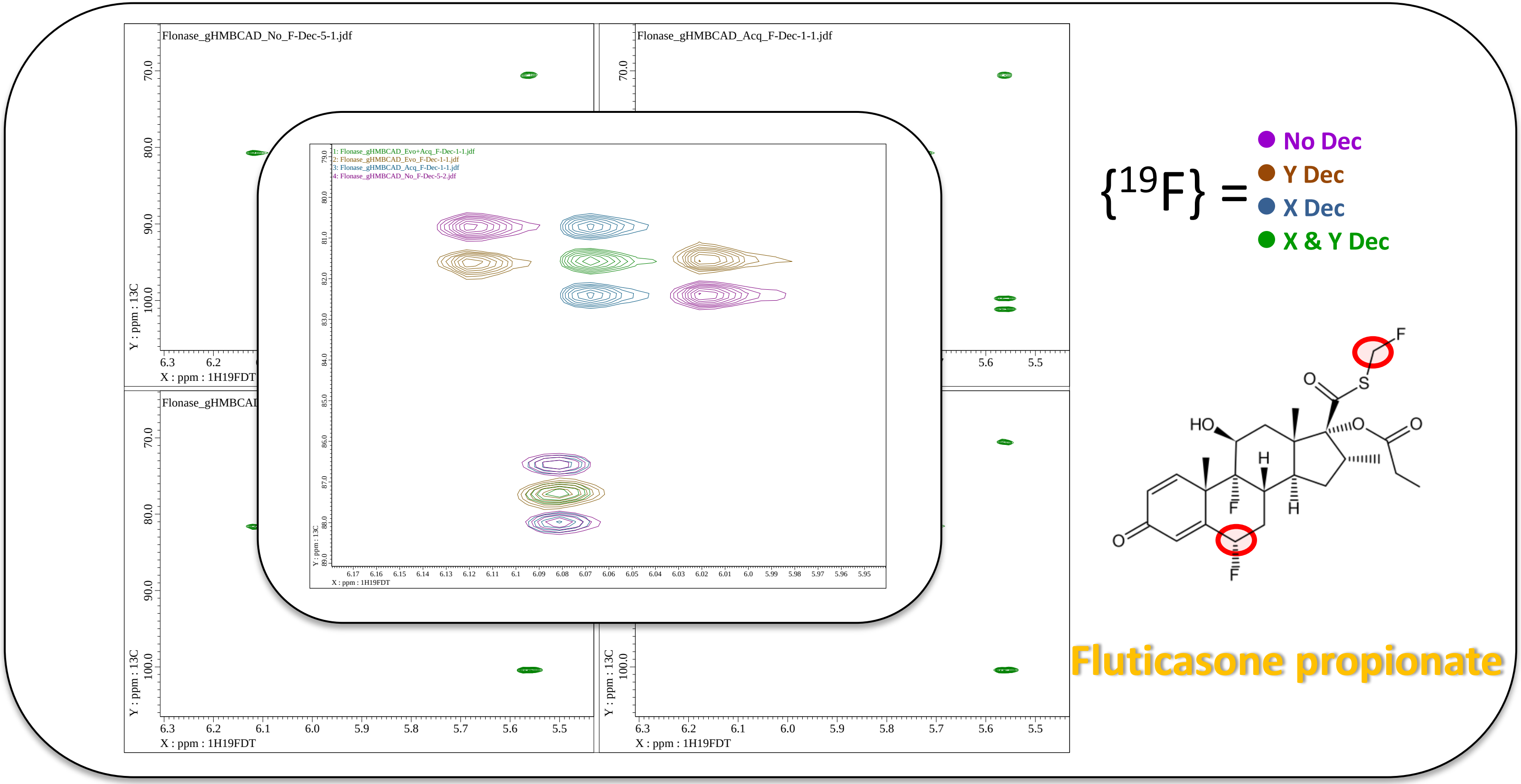
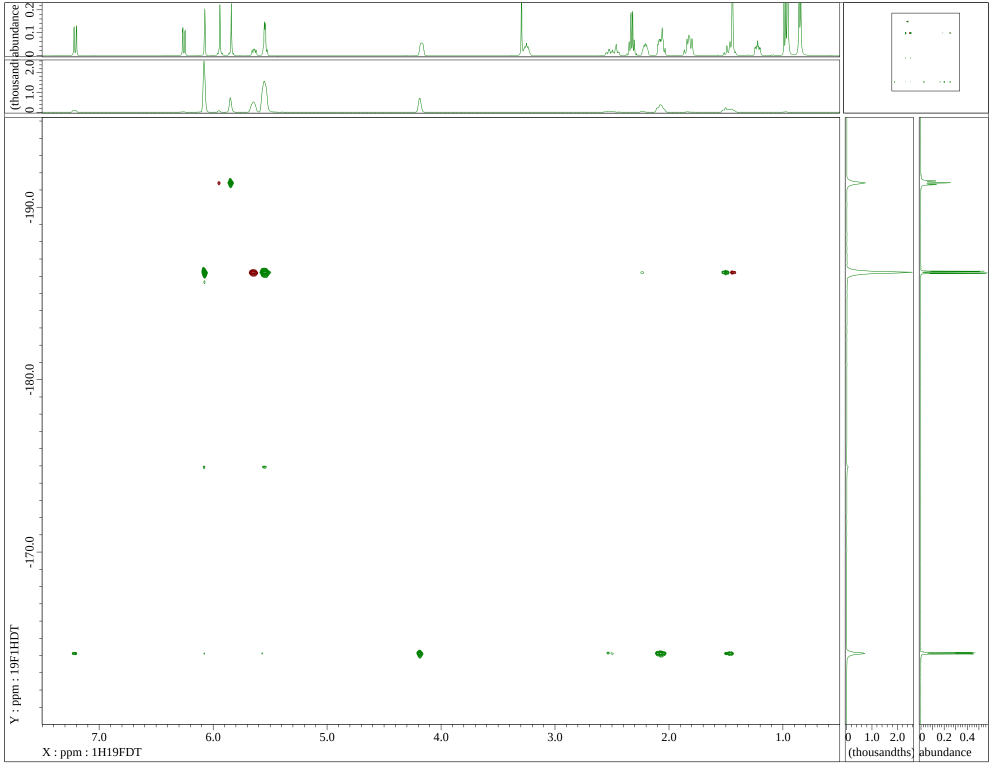
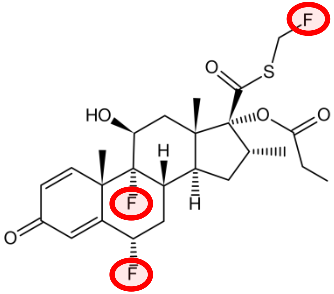


Figure 12: gHMBCAD example illustrating the simplifying effects of F decoupling for 2D $^1H/^{13}C$ responses being applied in either F1 (blue), F2 (brown), or both in dimensions (green). The diagonal purple responses clearly show how the ^{19}F coupling exists in both dimensions.

ROYAL HFX – $^{1}H\{^{19}F\}$ HOESY





Fluticasone propionate

Figure 13: HFHOESY obtained for Fluticasone propionate aka Flonase™.

ROYAL HFX Probe – $^{31}P\{^{1}H,^{19}F\}$

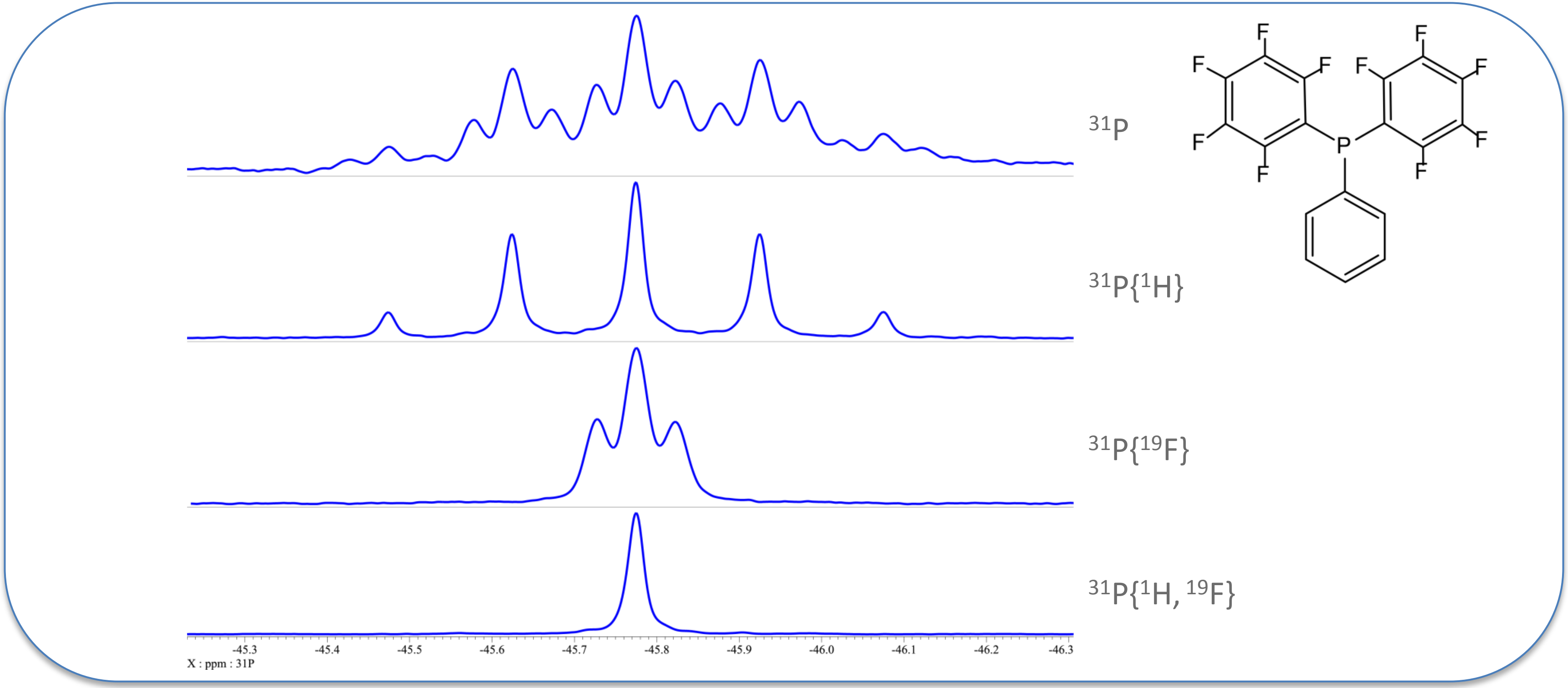


Figure 14: Effects of all combinations of ^{1}H and ^{19}F decoupling for a ^{31}P resonance. In this figure the results for either no decoupling of single nucleus decoupling have the vertical scaling greatly increased relative to the $\{^{1}H, ^{19}F\}$ example.

ROYAL HFX Probe – $^{13}C\{^{1}H,^{19}F\}$

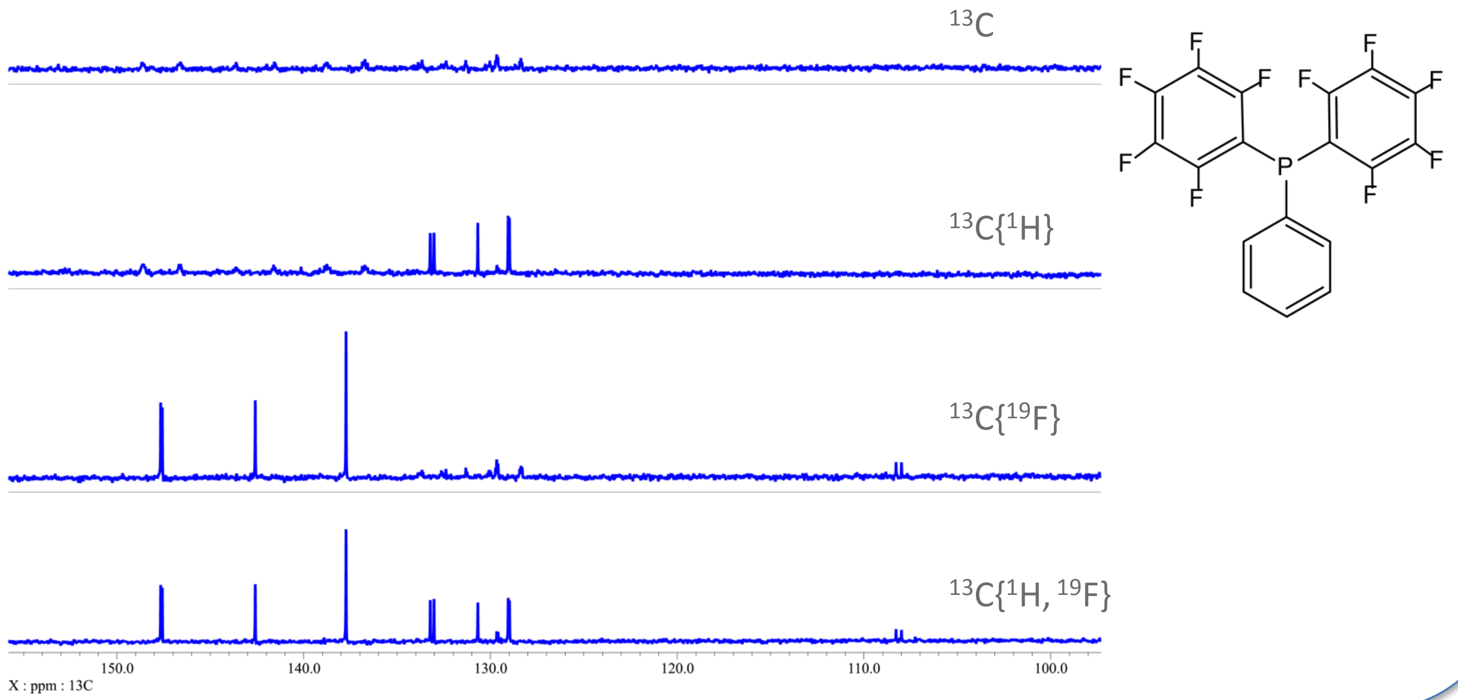
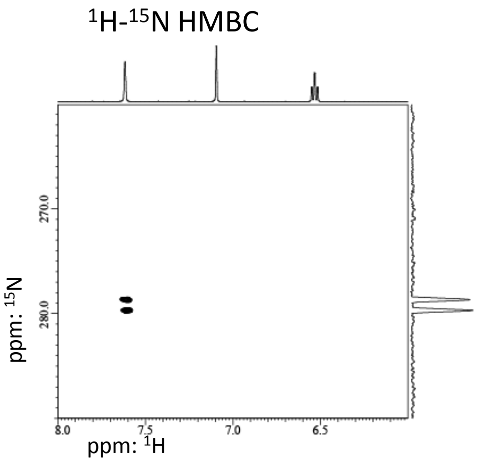
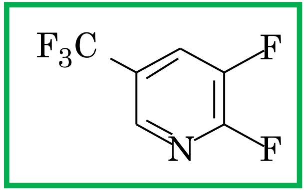


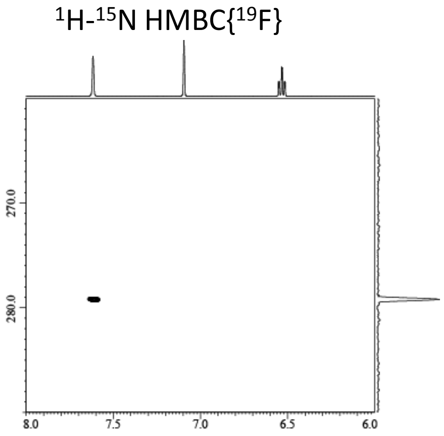
Figure 15: Another example of the impressive improvement obtained by $\{^{1}H,^{19}F\}$ for ^{13}C observe with a fluorine containing molecule.

JEOL

ROYAL HFX Probe – $^{15}N\{^{1}H,^{19}F\}$







JEOL ROYAL HFX NMR Probe

- Flexible automatic operation for demanding HFX NMR experiments with no loss of performance in non-HFX mode
- Fully integrated with the ECZ Auto-tune NMR capabilities for maximum sensitivity
- Available at 400, 500, and 600 MHz for JEOL ECZS and ECZR NMR spectrometers