

Supporting Information

'Carba'-Analogues of Fentanyl are Opioid Receptor Agonists

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Stereochemical assignment of the two isomers of compound 1 by homonuclear decoupling NMR experiments

Figure 1. ^1H NMR spectra of compound **1** recorded in $\text{DMSO-}d_6$ (0.8-4.8 ppm region). Top panel: isomer 1, bottom panel: isomer 2.

Figure 2. NOESY/EXSY spectra of compound **1** in $\text{DMSO-}d_6$. Top panel: isomer 1, bottom panel: isomer 2. At 20°C , each isomer has two rotamers due to slow rotation of the N-CO bond.

Figure 3. Expansion of the ^1H NMR spectrum high-lighting the 1-H proton for isomer 1 (top panel) and isomer 2 (bottom panel). Clearly, the 1-H is an axial proton for both isomers.

Figures 4a and 4b. ^1H homonuclear decoupling experiments performed with isomer 1 in $\text{DMSO-}d_6$. Irradiation of the 2-,6-protons confirms that 1-H is an axial proton. 4-H could not be identified because it is overlapped with the 3- and 5-protons.

Figures 5a and 5b. ^1H homonuclear decoupling experiments performed with isomer 2 in $\text{DMDO-}d_6$. Irradiation of the 2-,6-protons confirms that 1-H is an axial proton. Irradiation of the 3-5-protons confirms that 4-H is an axial proton. Therefore isomer 2 is the *trans* isomer.

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Figure 1

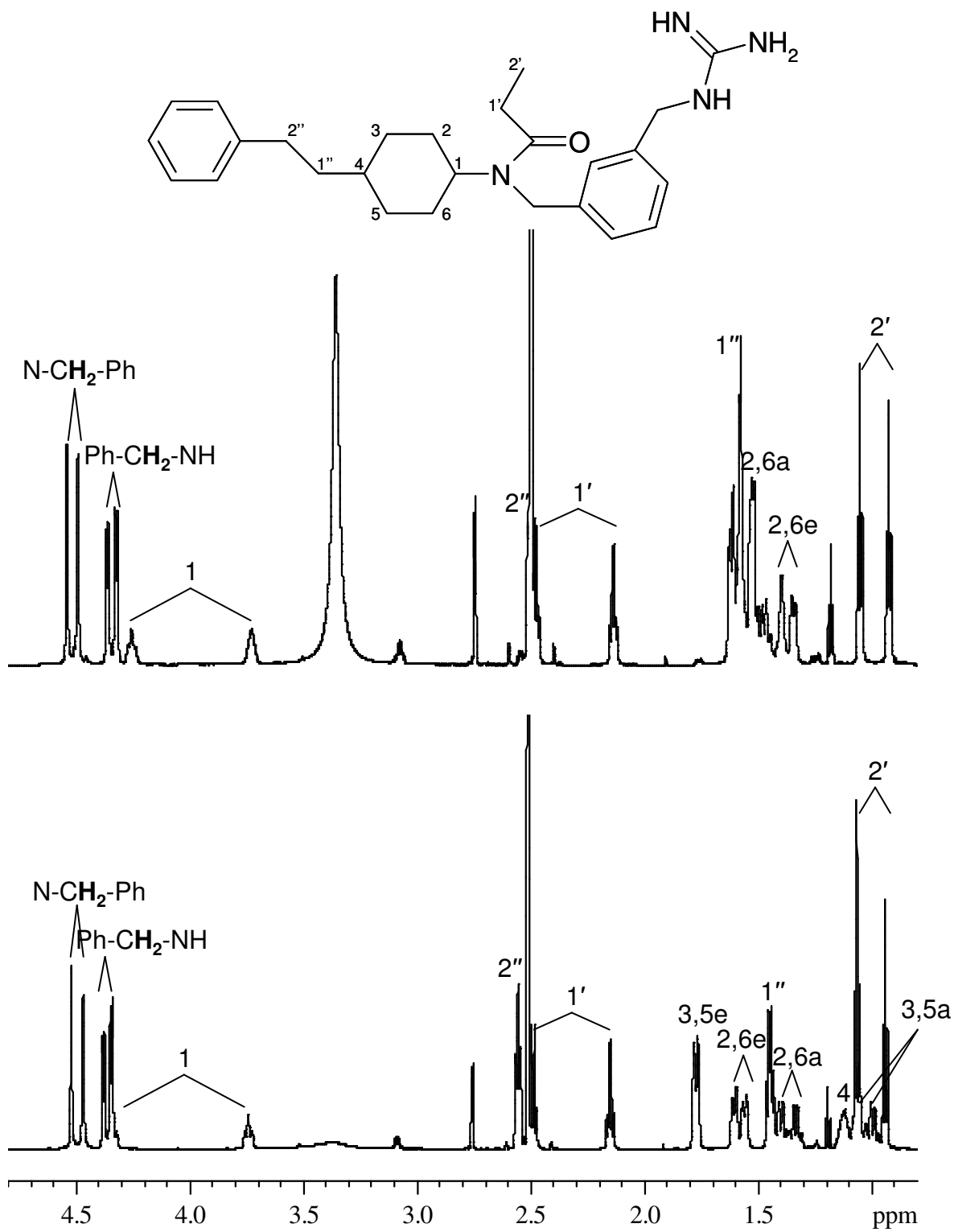


Figure 2

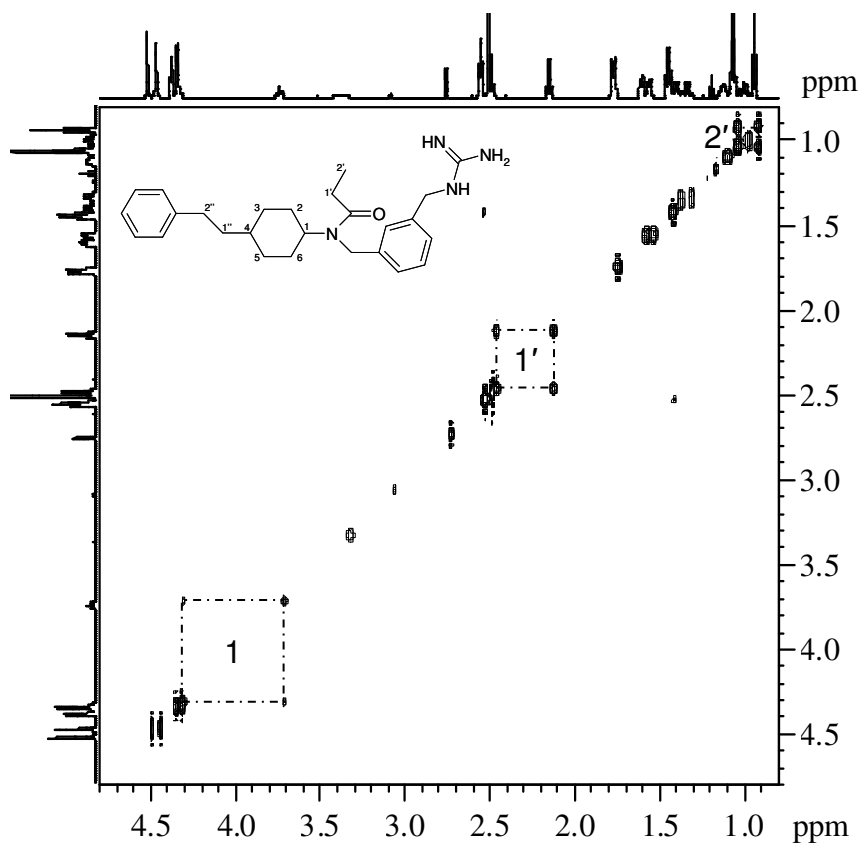
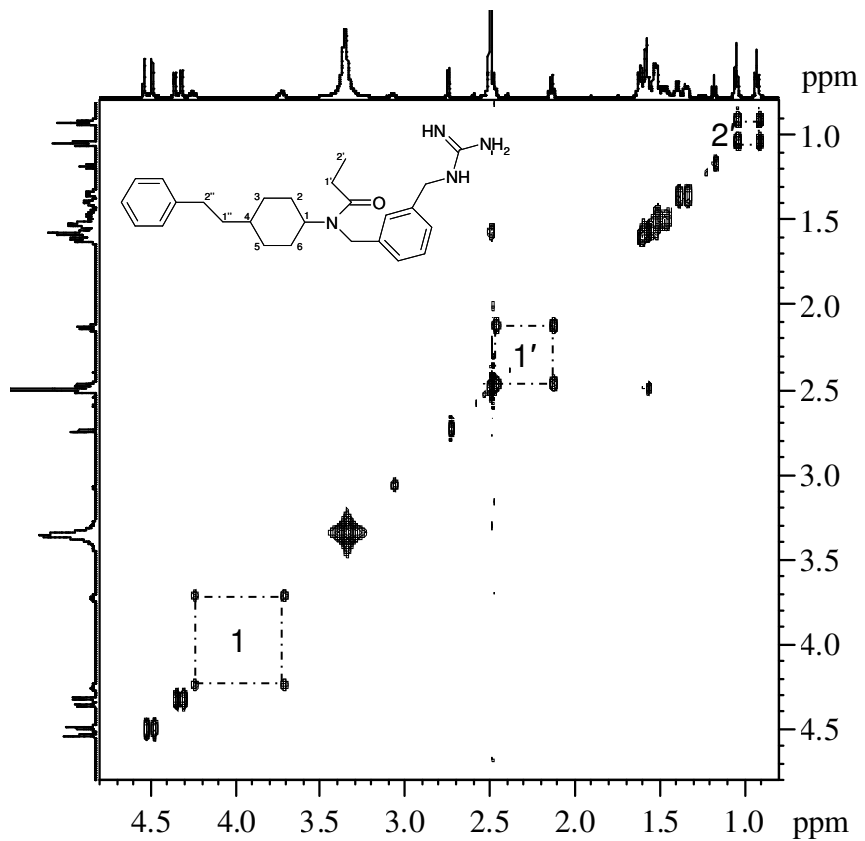


Figure 3

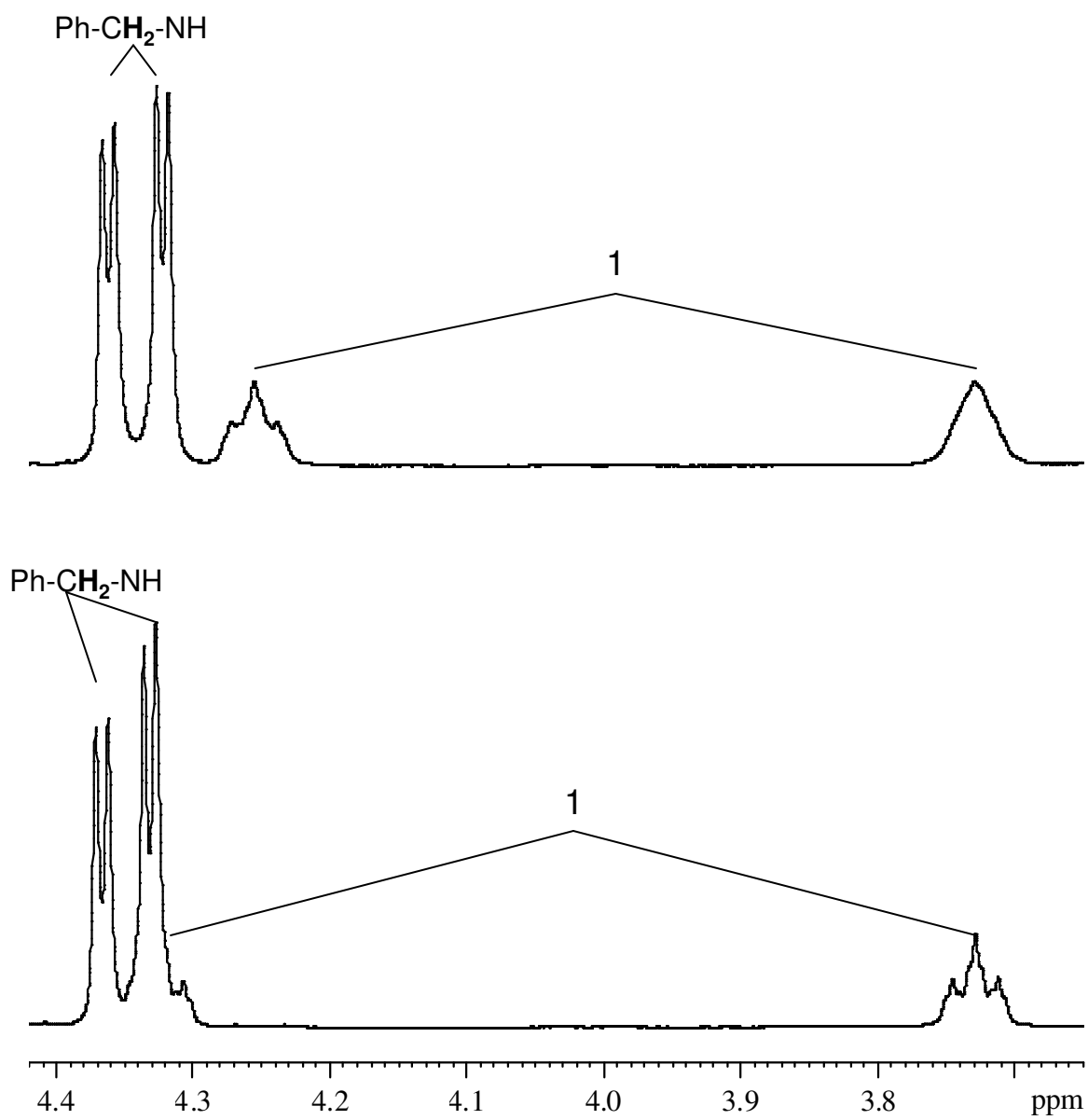


Figure 4a

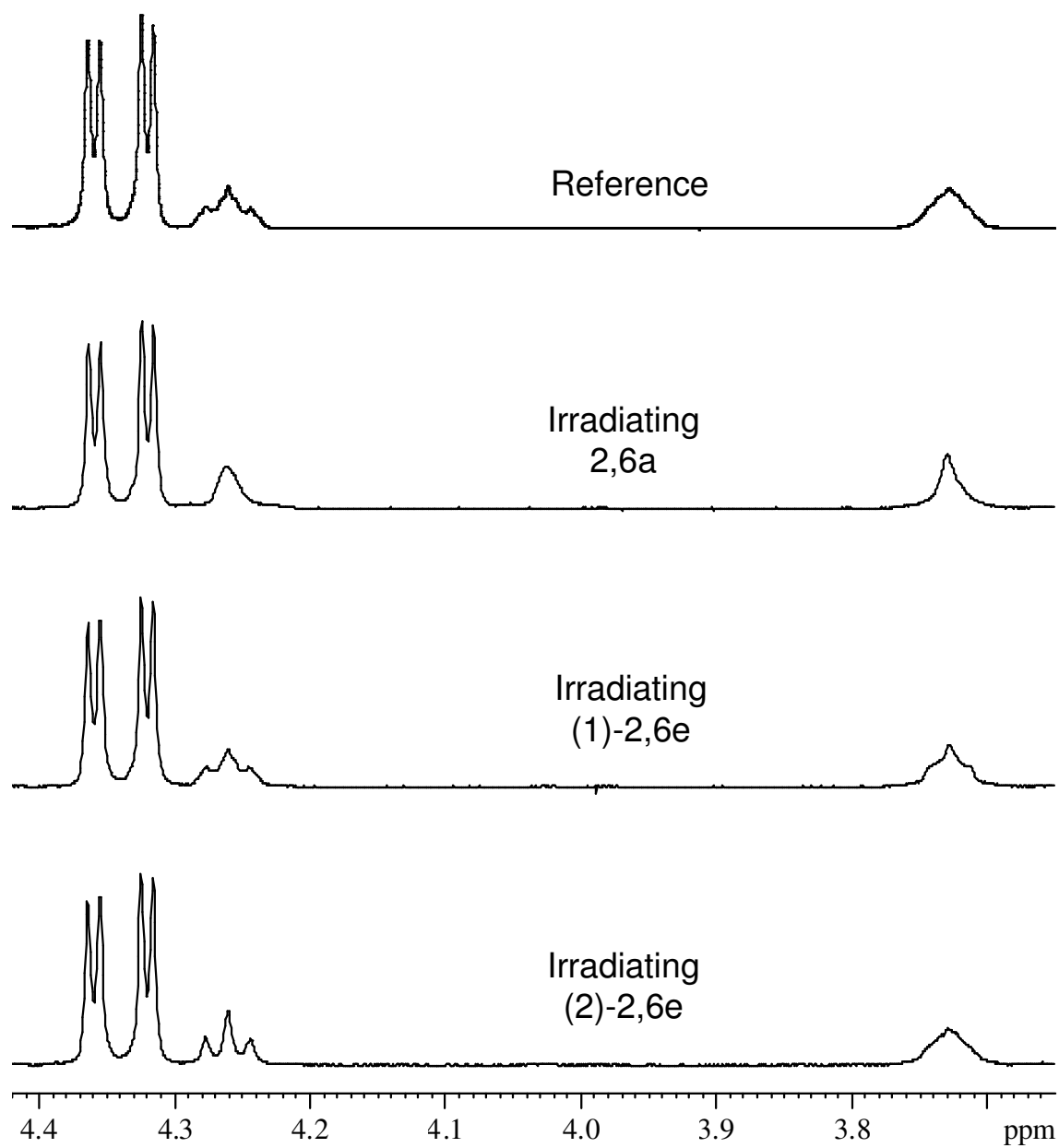


Figure 4b

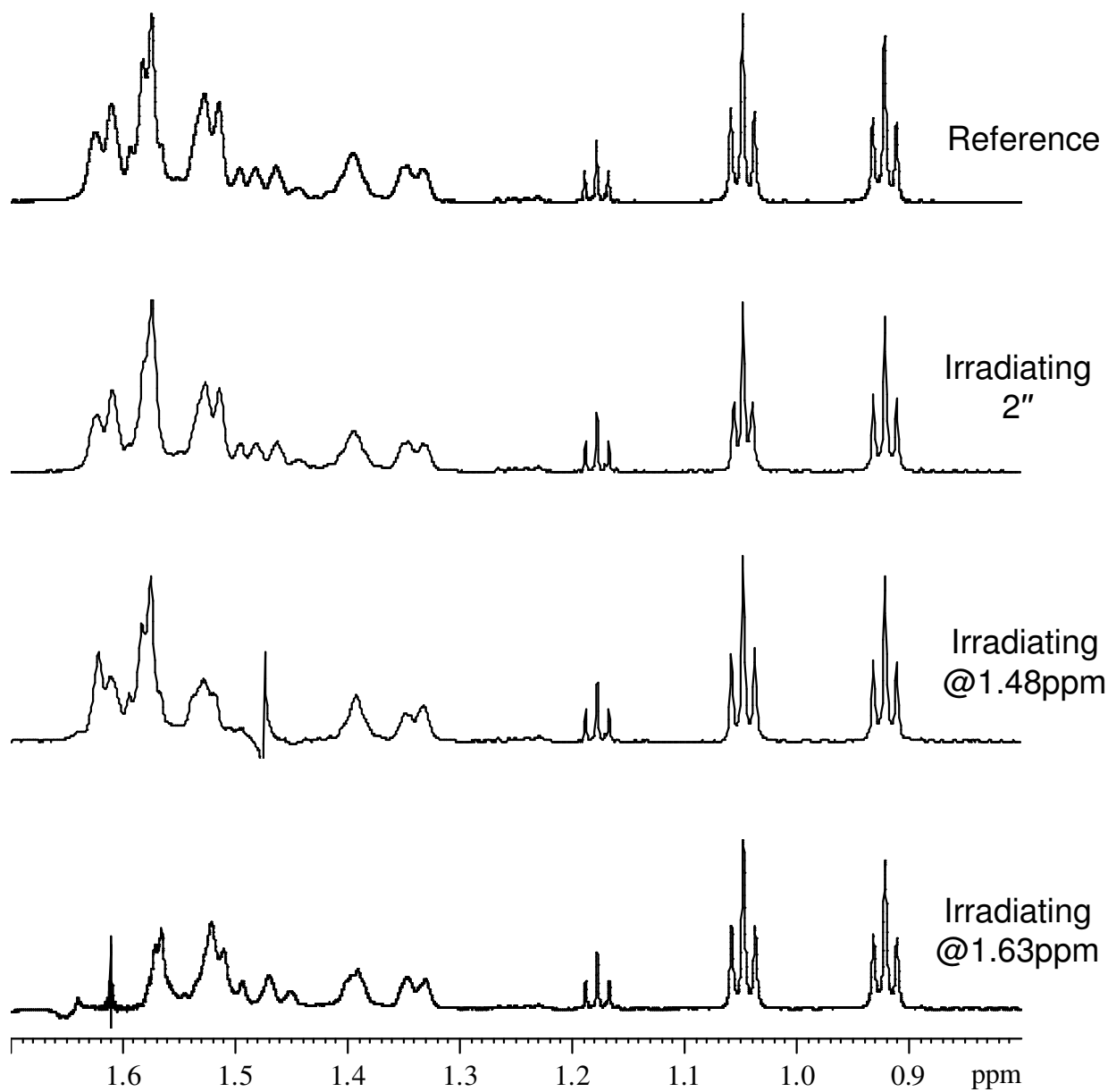


Figure 5a

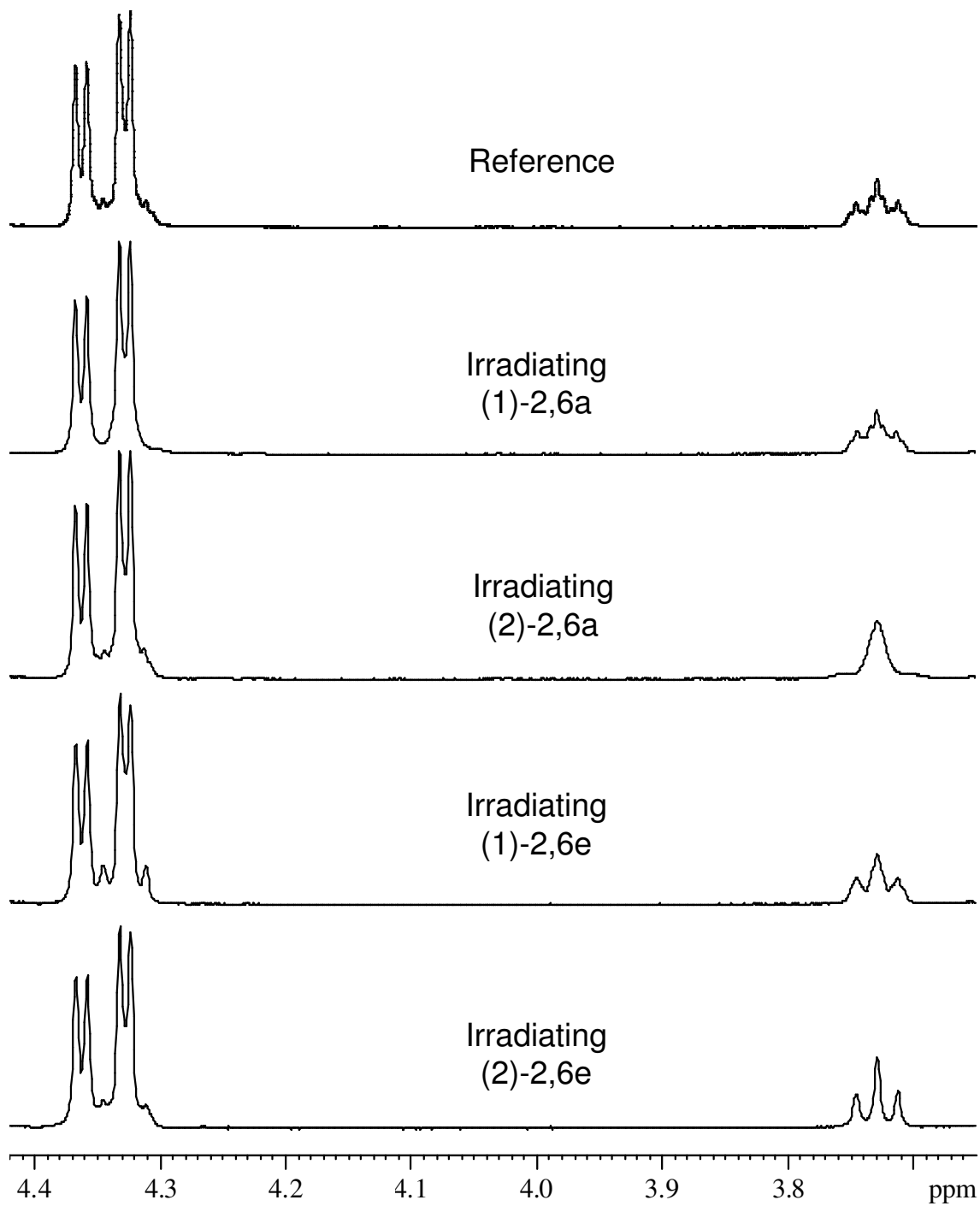


Figure 5b

