

# Synthesis and structure–activity relationship studies of pyrido[1,2-*e*]purine-2,4(1*H*,3*H*)-dione derivatives targeting *flavin-dependent thymidylate synthase* in *Mycobacterium tuberculosis*

Nicolas G. Biteau,<sup>1</sup> Vincent Roy,<sup>1,\*</sup> Cyril Nicolas,<sup>1</sup> Hubert F. Becker,<sup>2,3</sup> Jean-Christophe Lambry,<sup>2</sup> Hannu Myllykallio,<sup>2</sup> and Luigi A. Agrofoglio<sup>1,\*</sup>

<sup>1</sup> Institute of Organic and Analytical Chemistry, CNRS UMR 7311, Université d'Orléans, Rue de Chartres, 45067 Orleans CEDEX 2, France

<sup>2</sup> Laboratory of Optics and Biosciences, INSERM U 696-CNRS UMR 7645, Ecole Polytechnique, Route de Saclay, 91128 Palaiseau Cedex (France)

<sup>3</sup> Sorbonne Université, Faculté des Sciences et Ingénierie, 75005 Paris, France

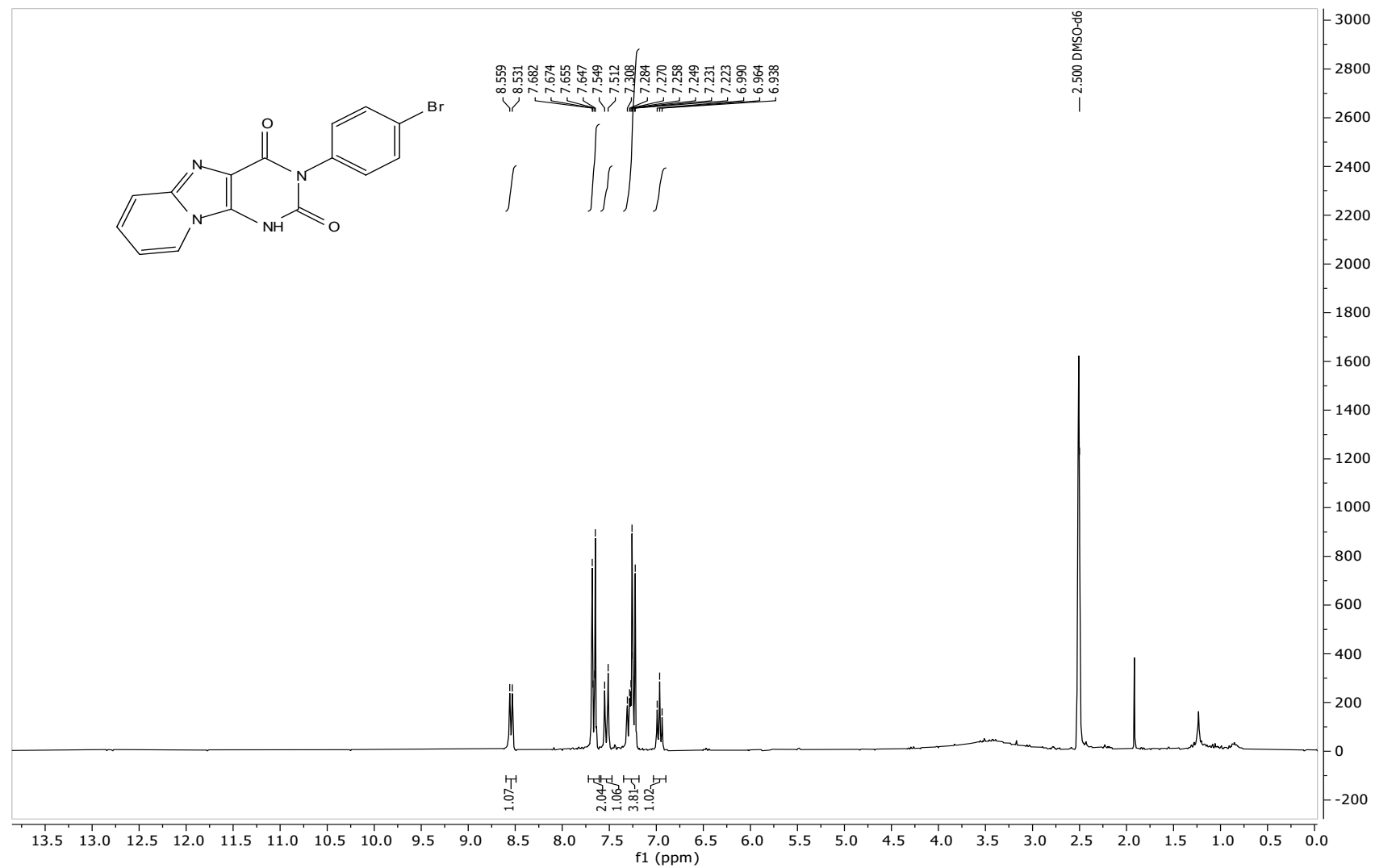
Corresponding authors : vincent.roy@univ-orleans.fr; luigi.agrofoglio@univ-orleans.fr

## Supplementary Informations

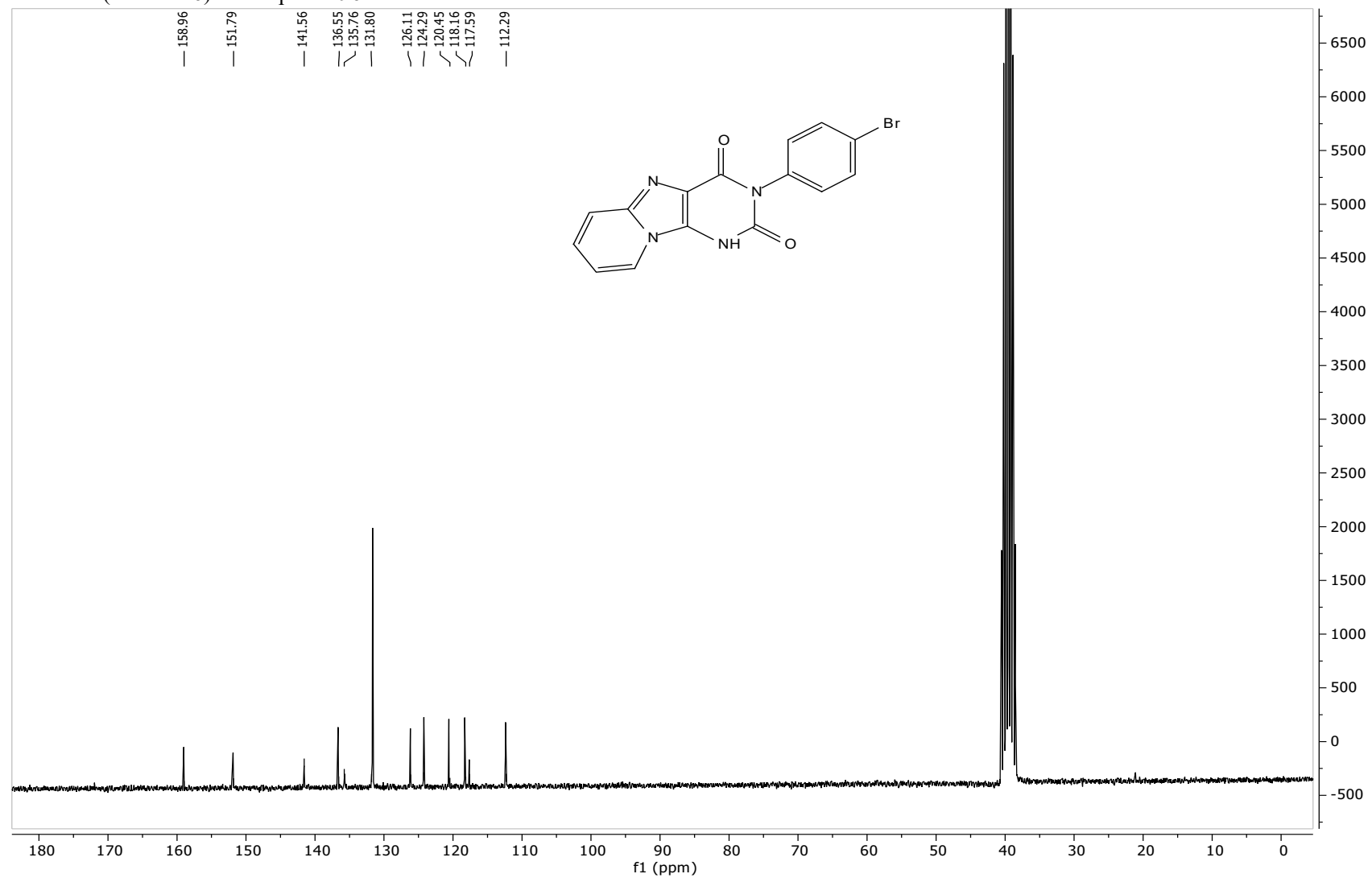
Copies of <sup>1</sup>H-, <sup>13</sup>C- and <sup>1</sup>H-<sup>13</sup>C HMBC NMR spectra of representative molecules

- ✓ NMR analysis of representative compounds from isocyanate cyclisation compounds (**9c**, **9e**, **9g-j**, **10b-d**)
- ✓ For the series **13**, **18**, **19**, **20** and **21**, we present copies of <sup>1</sup>H-, <sup>13</sup>C-NMR spectra of representative molecules which exhibit Mtb Thy X inhibition > 35%

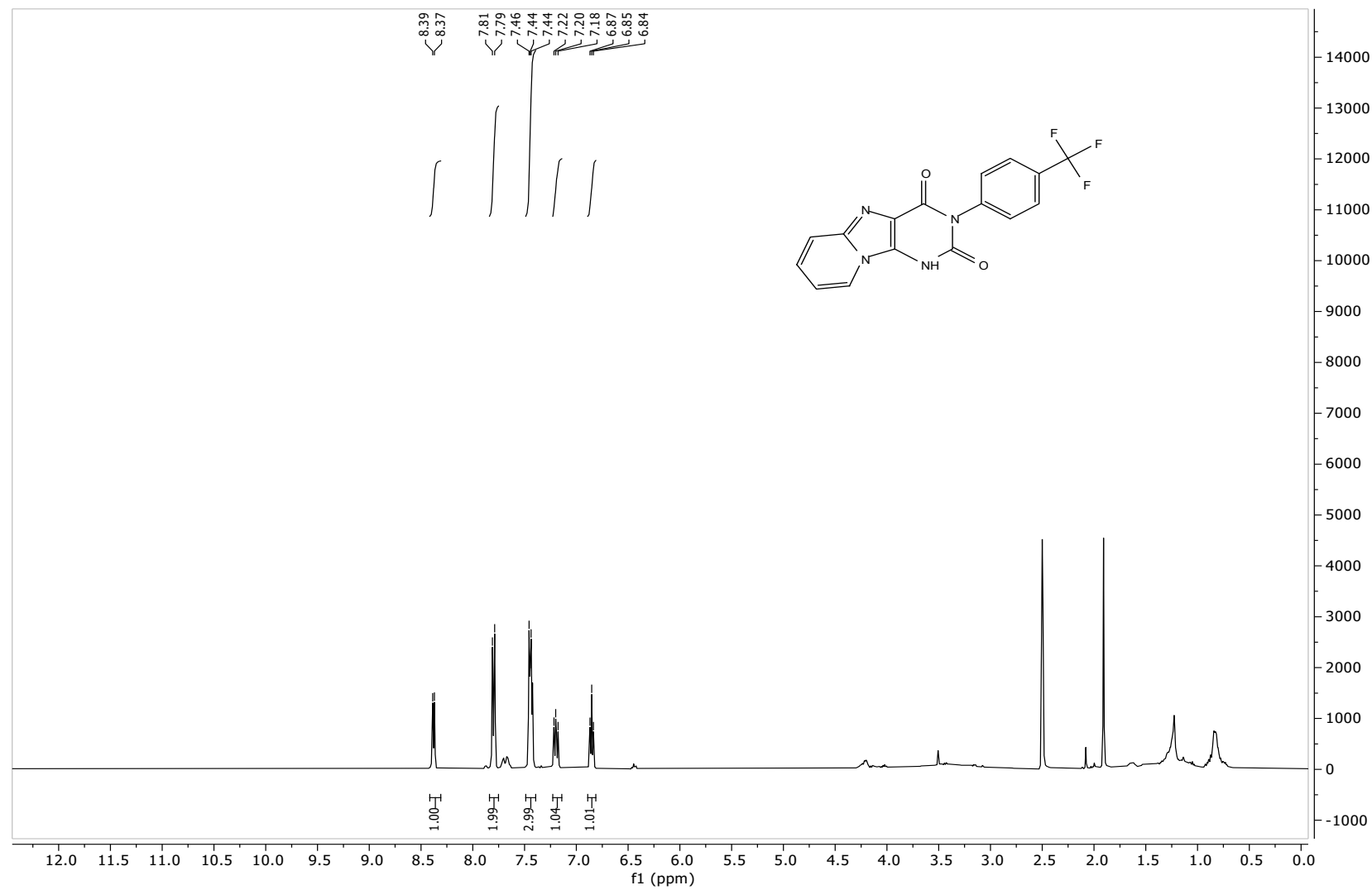
<sup>1</sup>H NMR (DMSO-d<sub>6</sub>) of compound **9c**



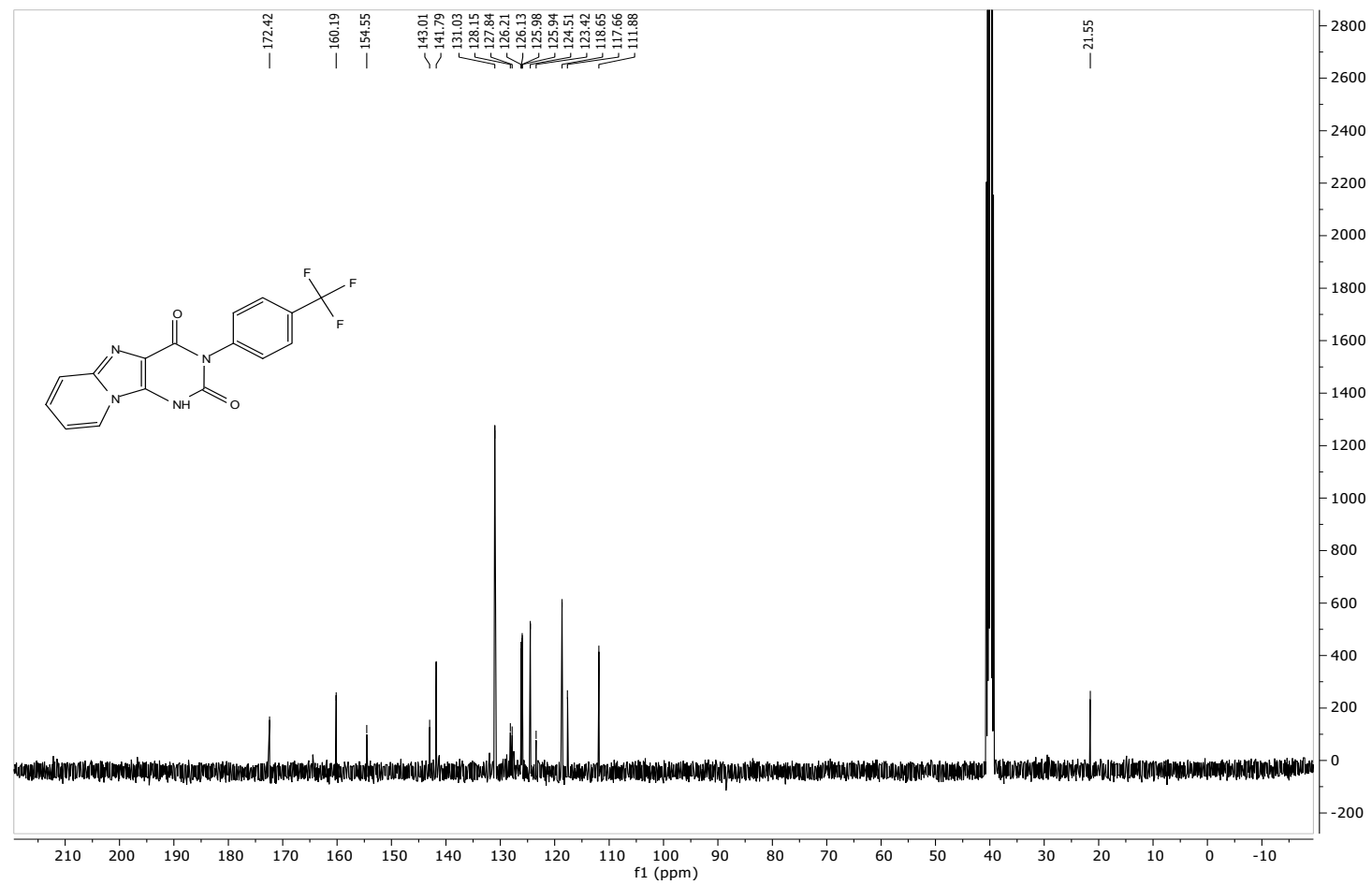
$^{13}\text{C}$  NMR (DMSO- $d_6$ ) of compound **9c**



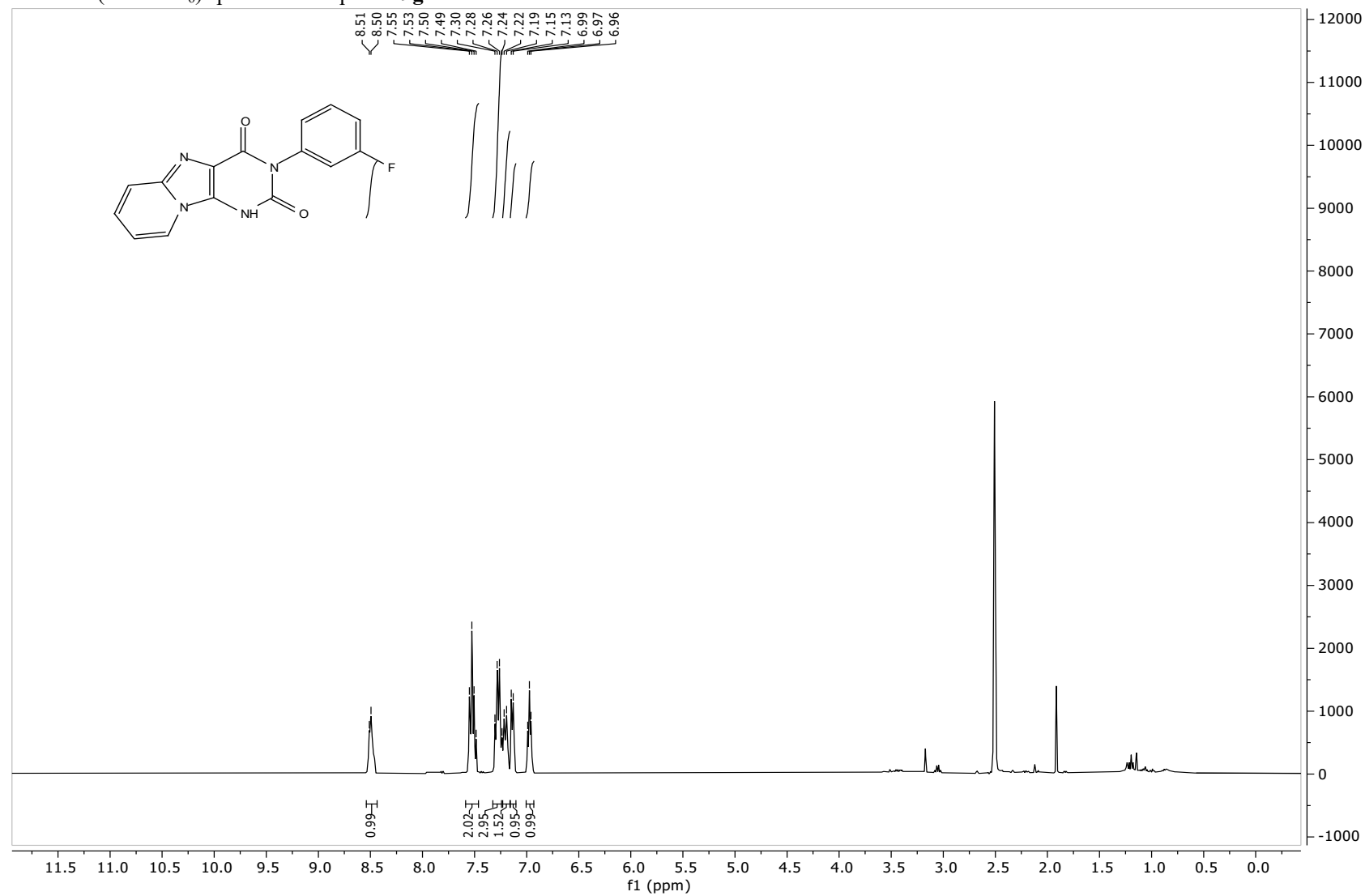
<sup>1</sup>H NMR (DMSO-d<sub>6</sub>) spectra of compound **9e**



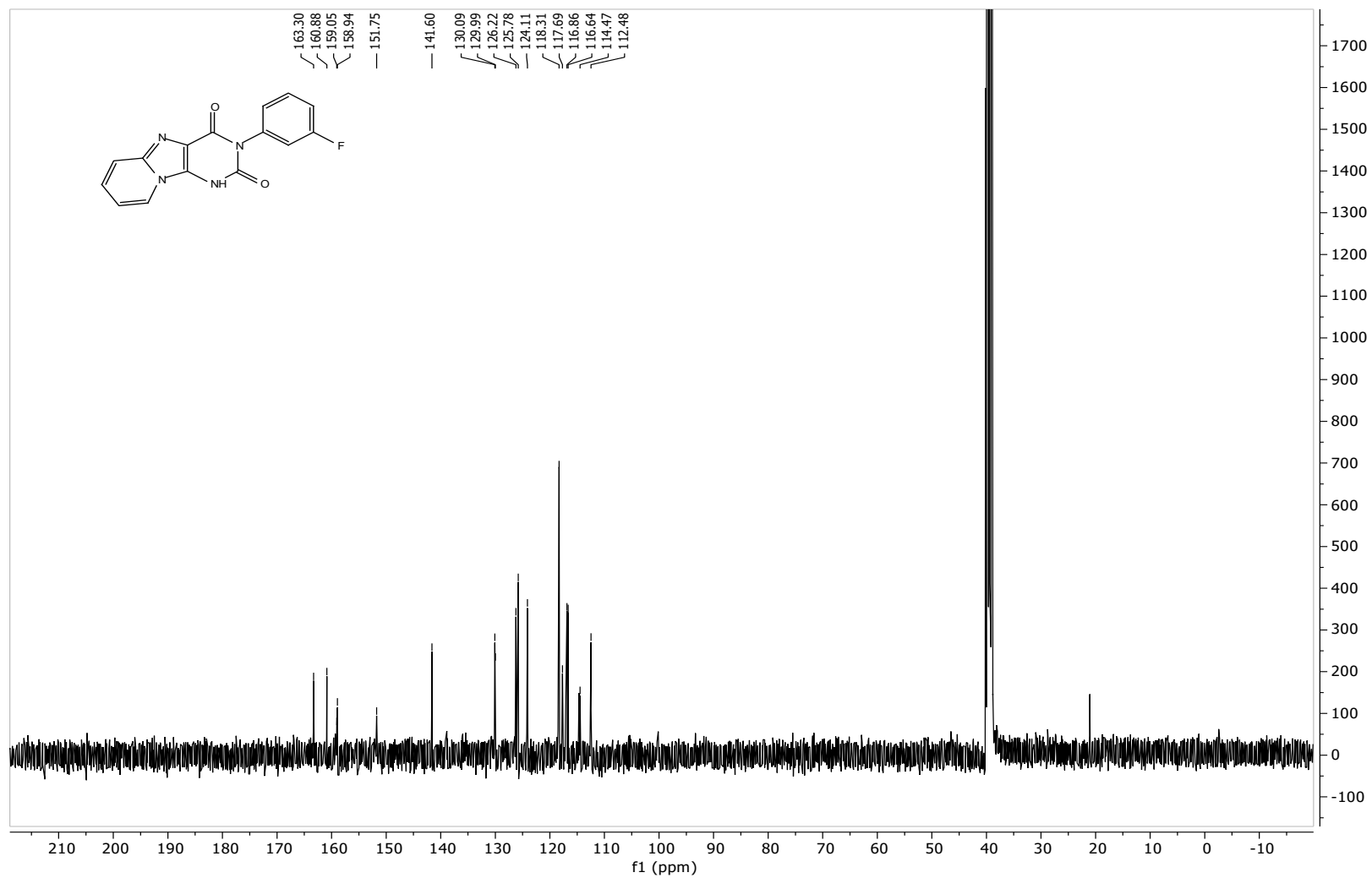
$^{13}\text{C}$  NMR (DMSO- $d_6$ ) spectra of compound **9e**



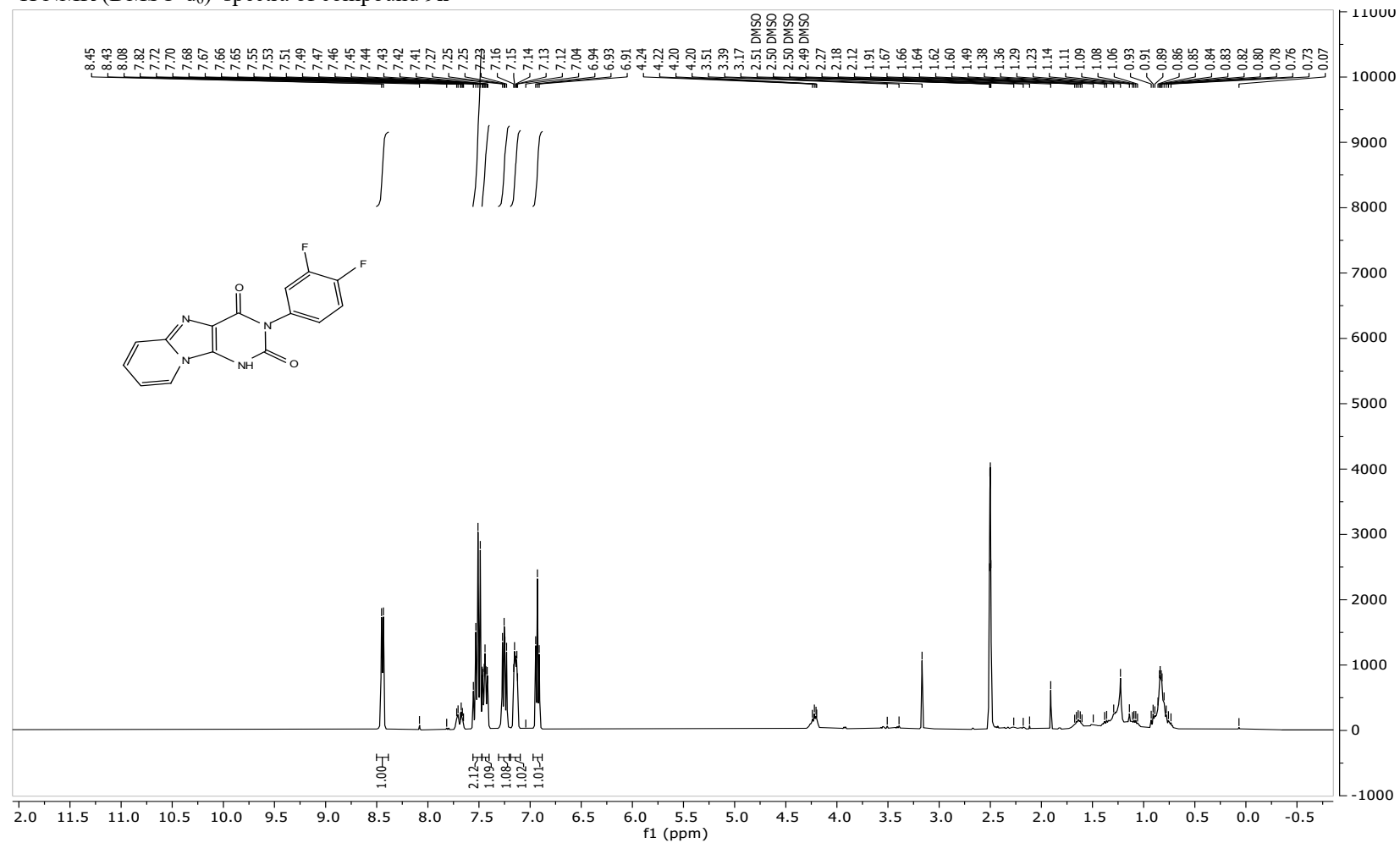
<sup>1</sup>H NMR (DMSO-d<sub>6</sub>) spectra of compound **9g**



$^{13}\text{C}$  NMR (DMSO- $d_6$ ) spectra of compound **9g**

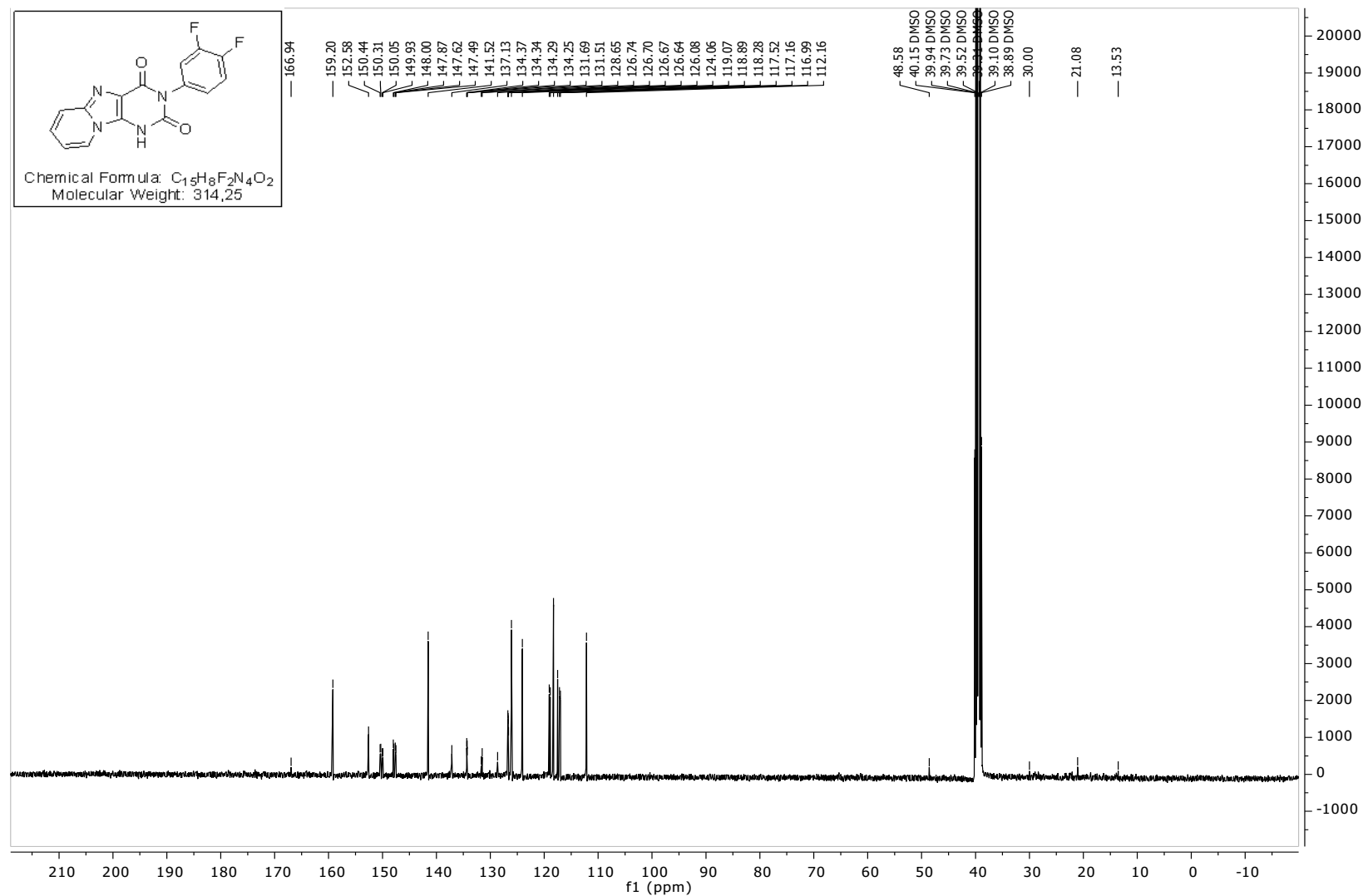


<sup>1</sup>H NMR (DMSO-d<sub>6</sub>) spectra of compound **9h**

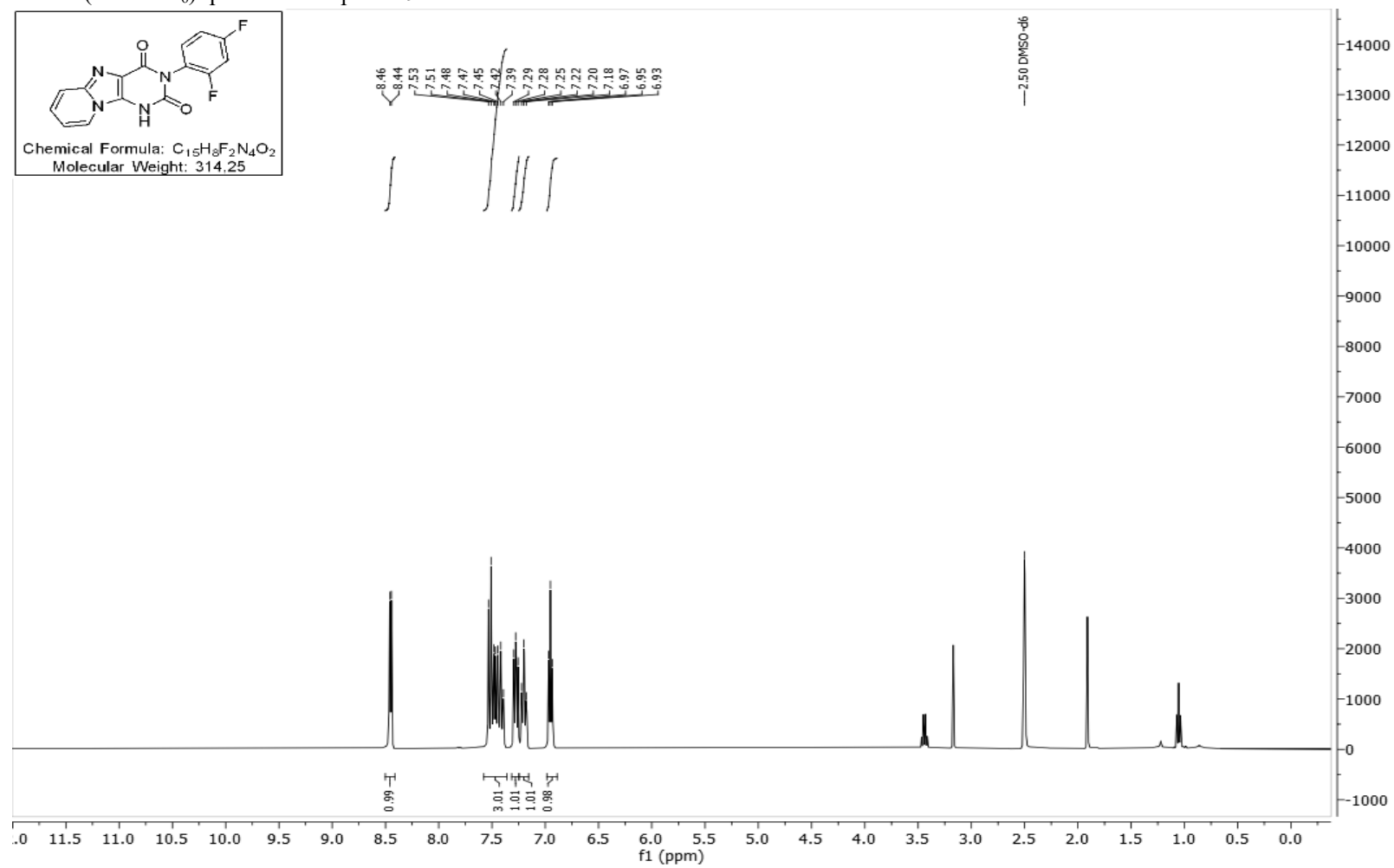




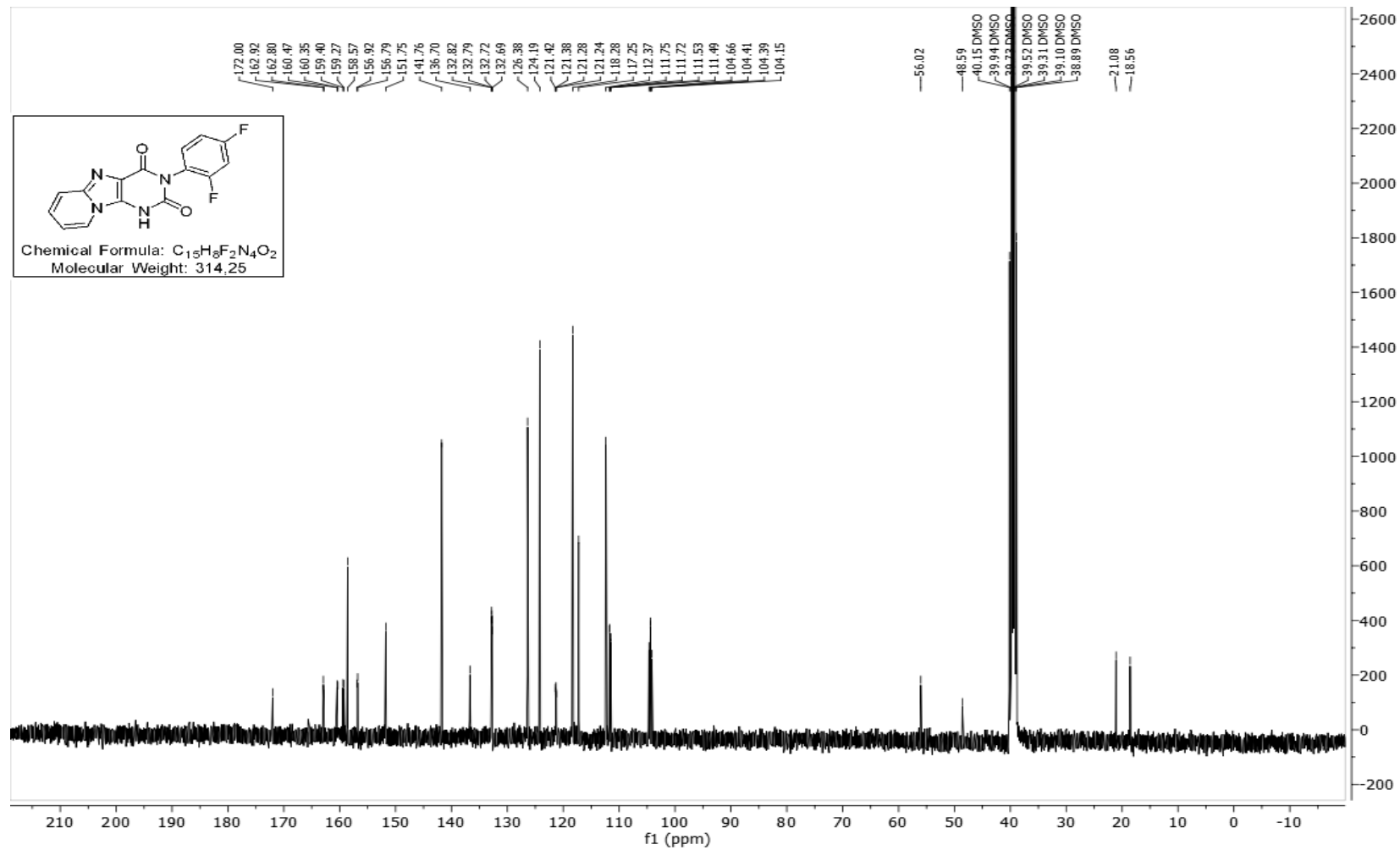
$^{13}\text{C}$  NMR (DMSO- $d_6$ ) spectra of compound **9h**



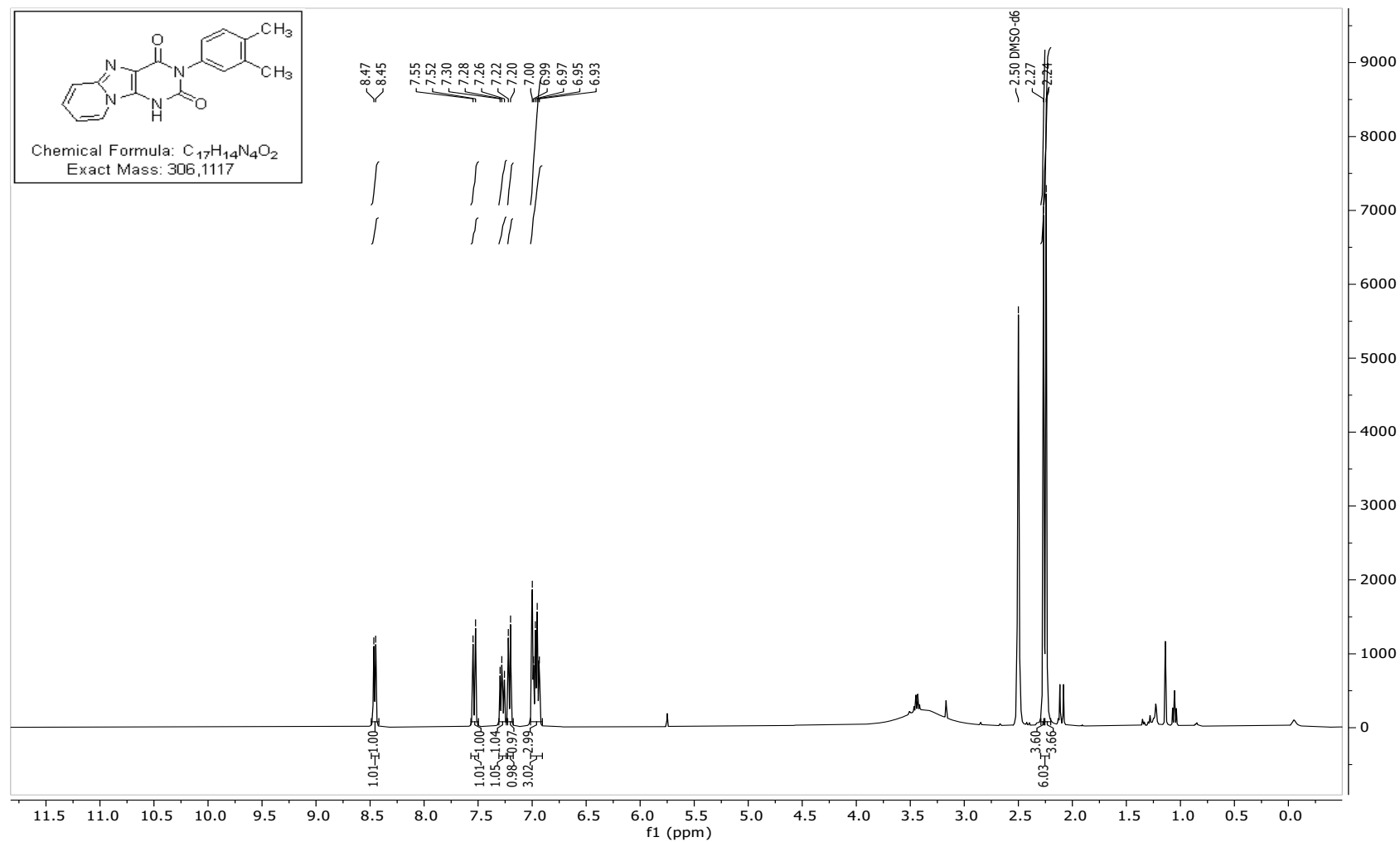
$^1\text{H}$  and (DMSO- $d_6$ ) spectra of compound **9i**



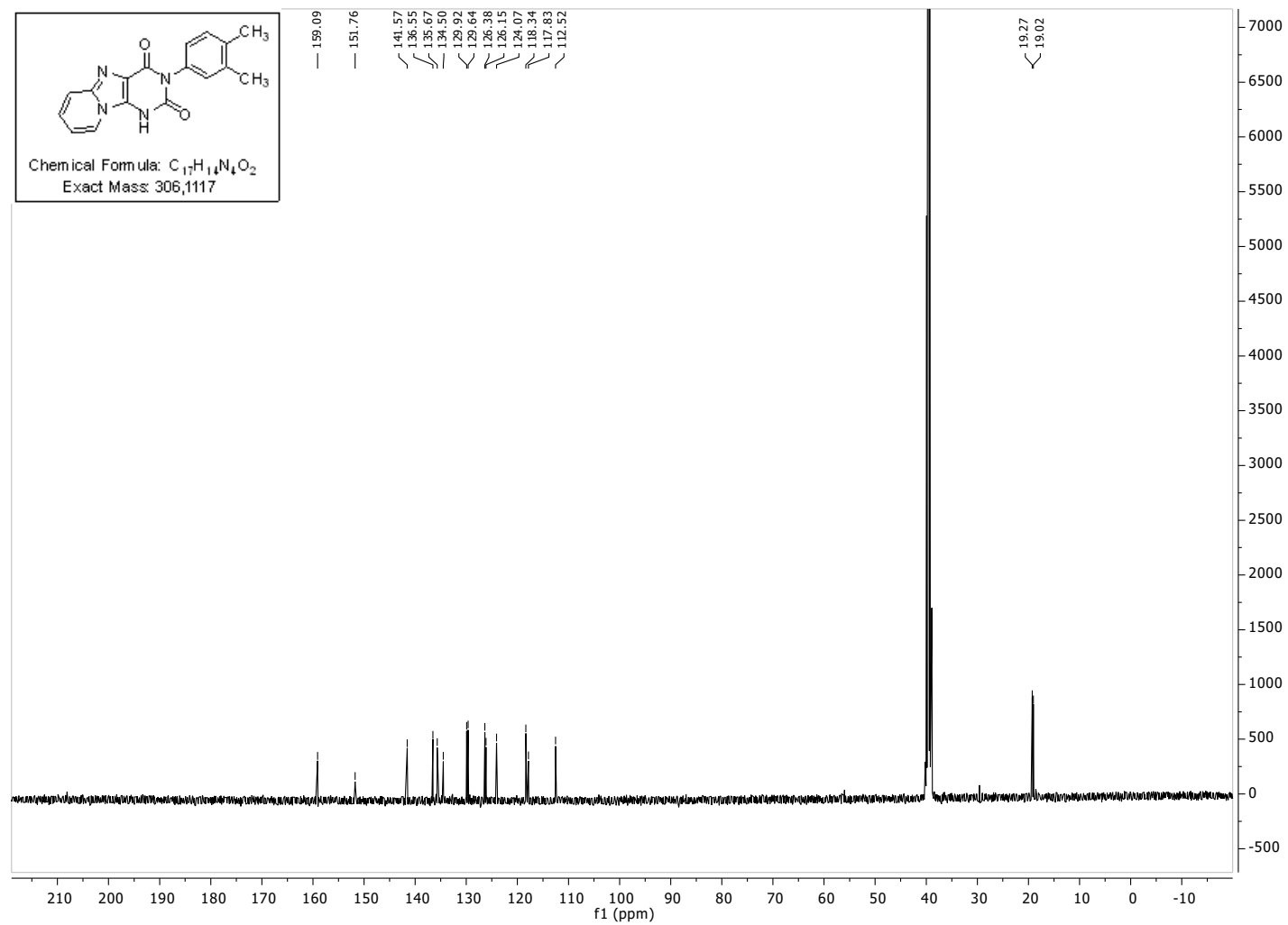
$^{13}\text{C}$  NMR (DMSO- $d_6$ ) of compound **9i**



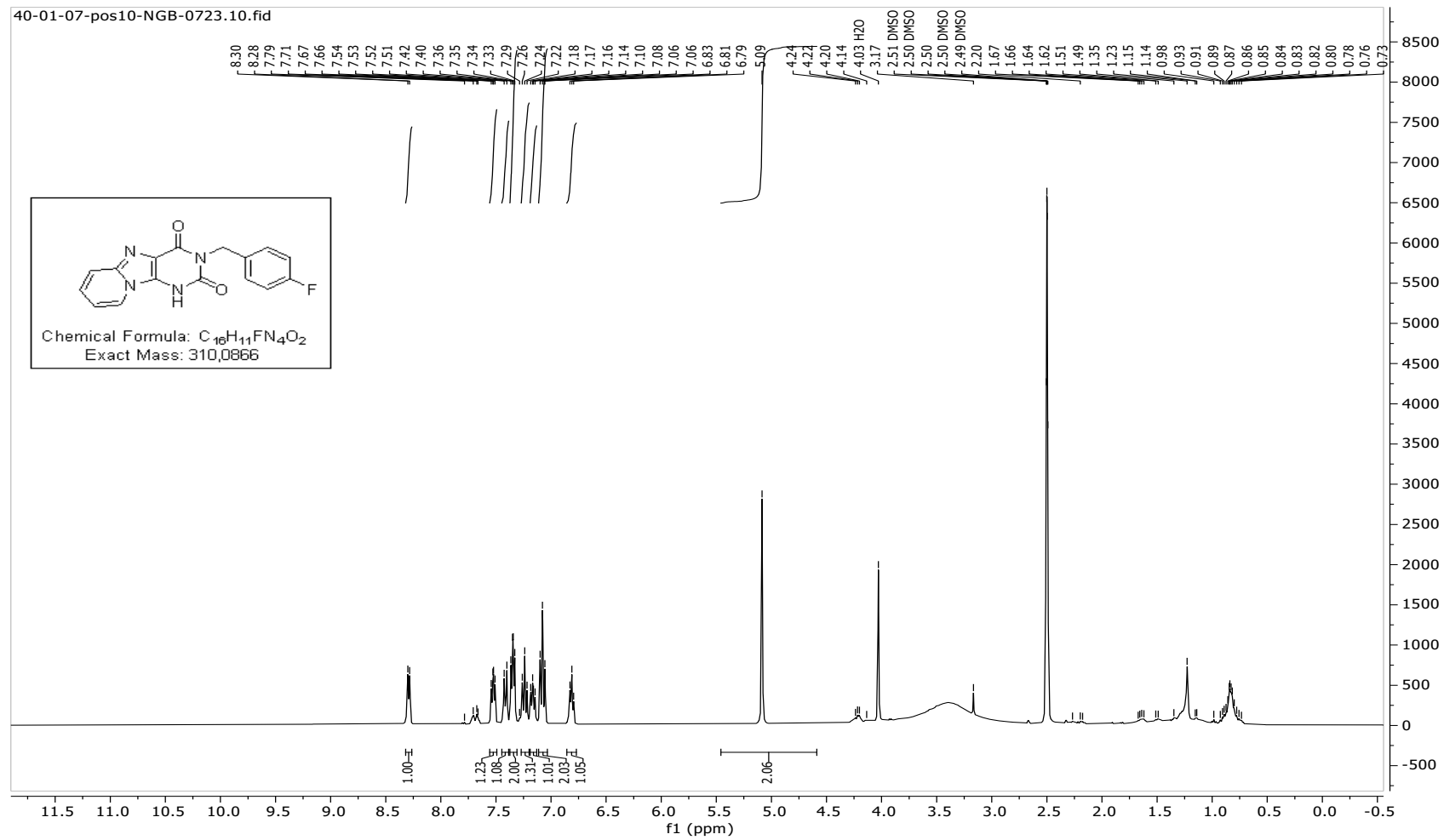
<sup>1</sup>H NMR (DMSO-d<sub>6</sub>) of compound **9j**



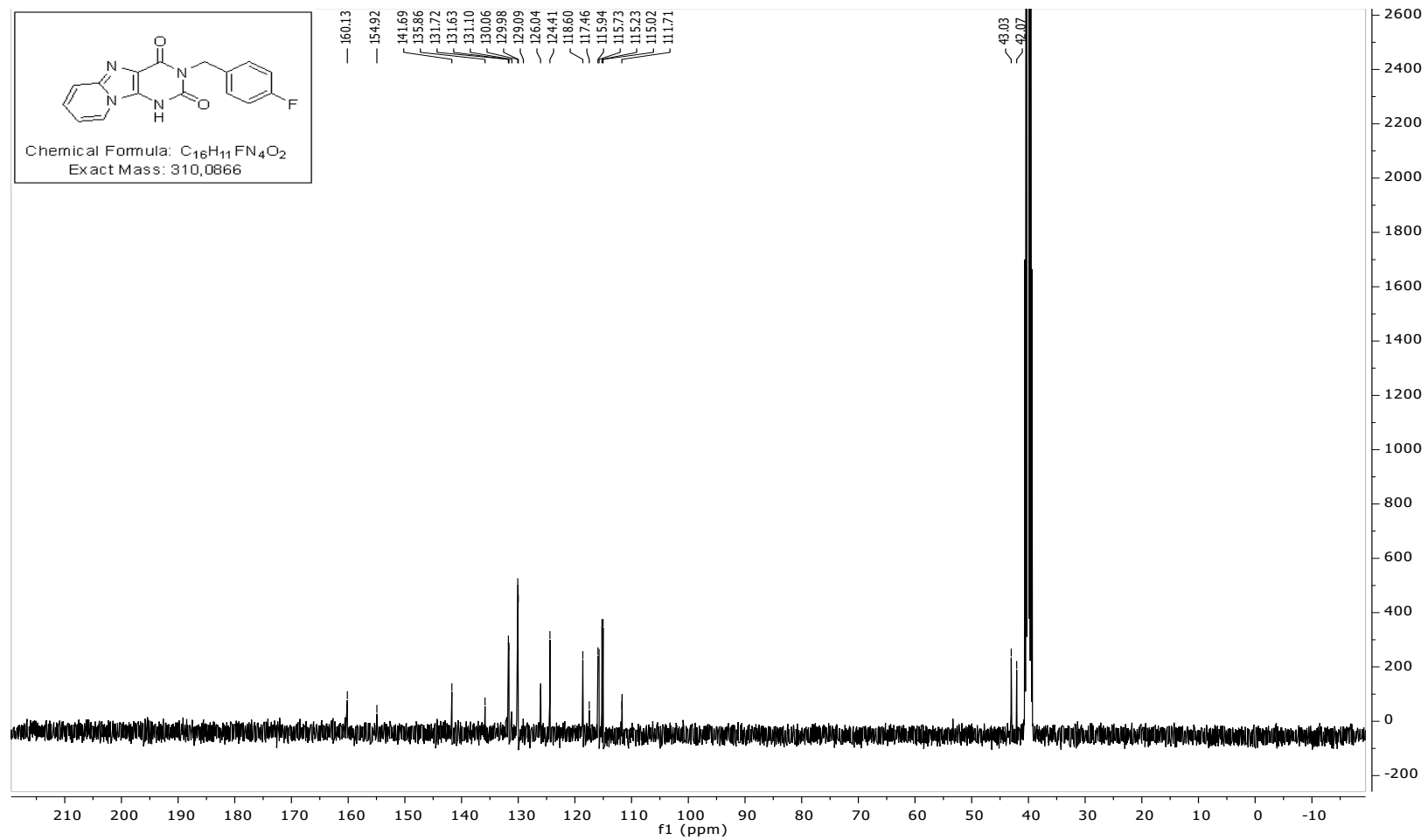
$^{13}\text{C}$  NMR (DMSO- $d_6$ ) of compound **3a**



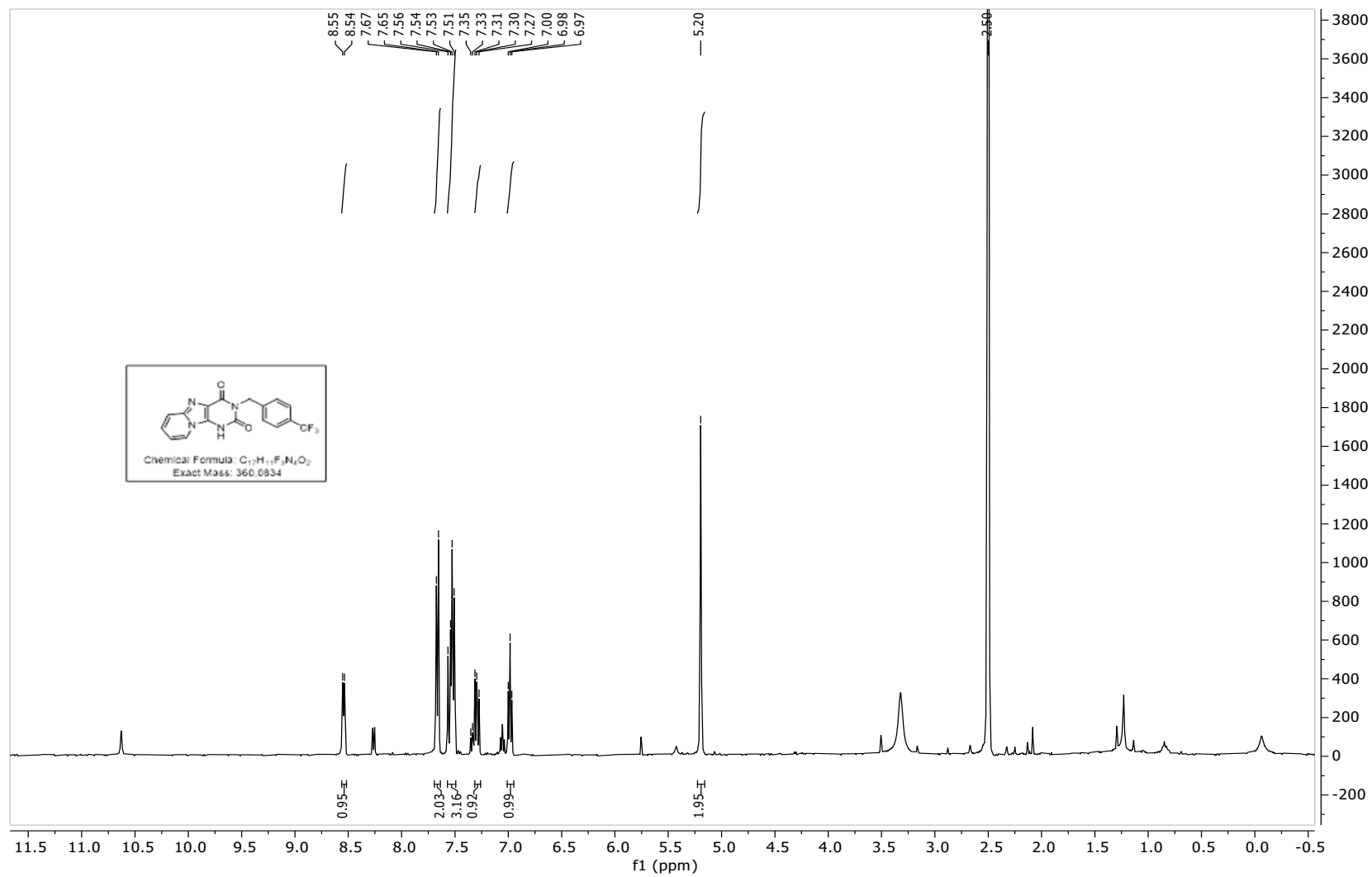
<sup>1</sup>H NMR (DMSO-d<sub>6</sub>) of compound **10b**



$^{13}\text{C}$  NMR (DMSO- $d_6$ ) of compound **10b**

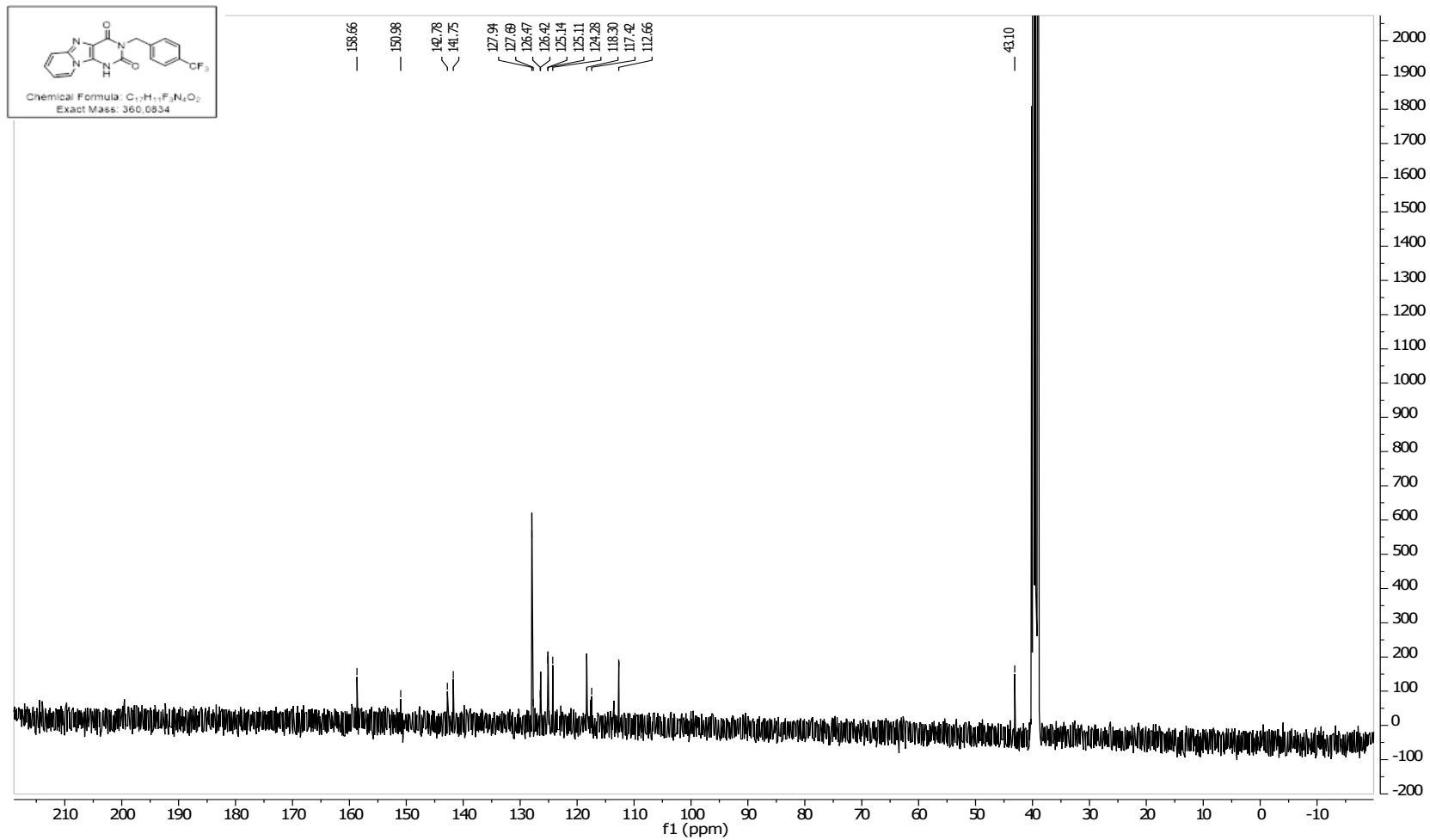


$^1\text{H}$  NMR (DMSO- $d_6$ ) of compound **10c**

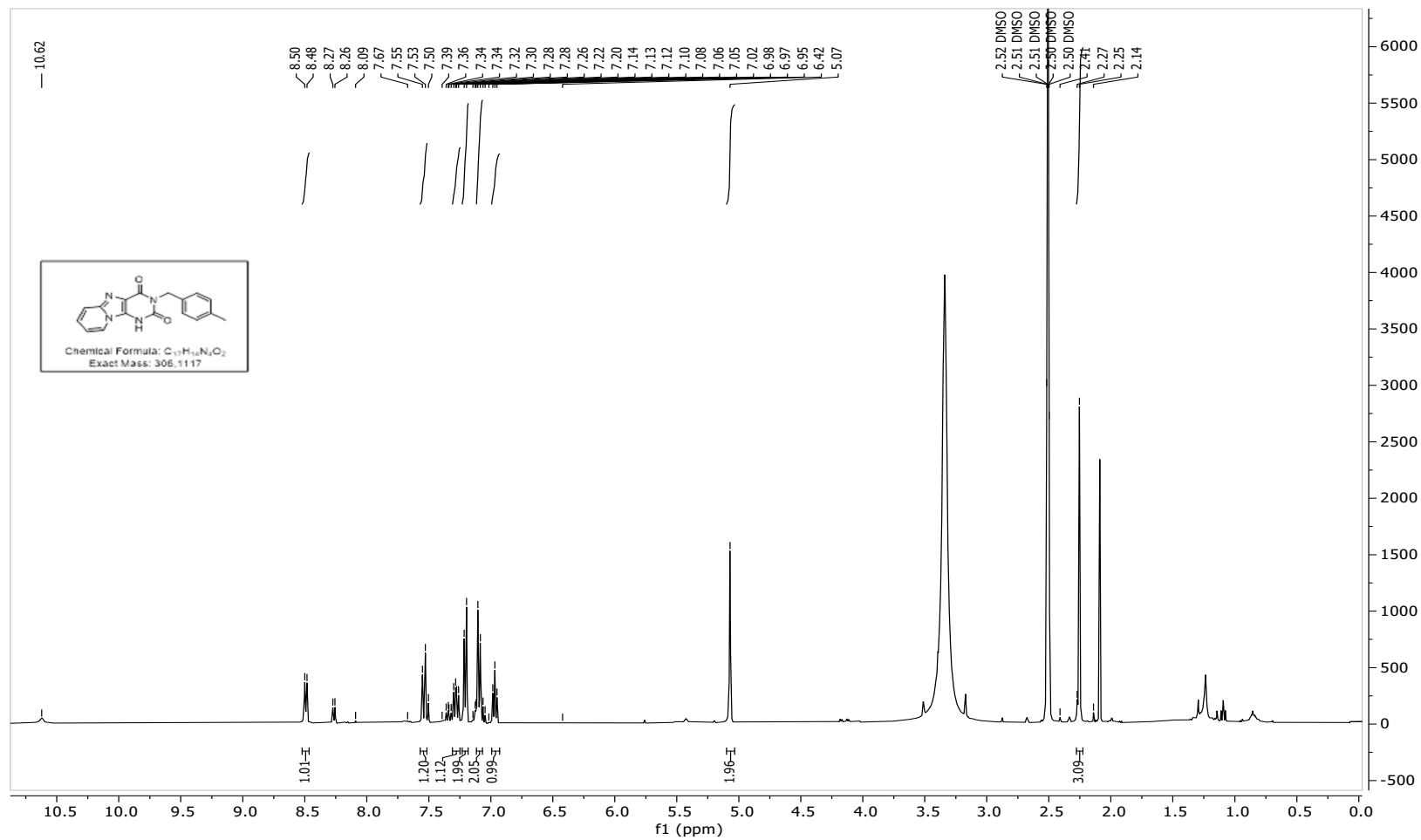




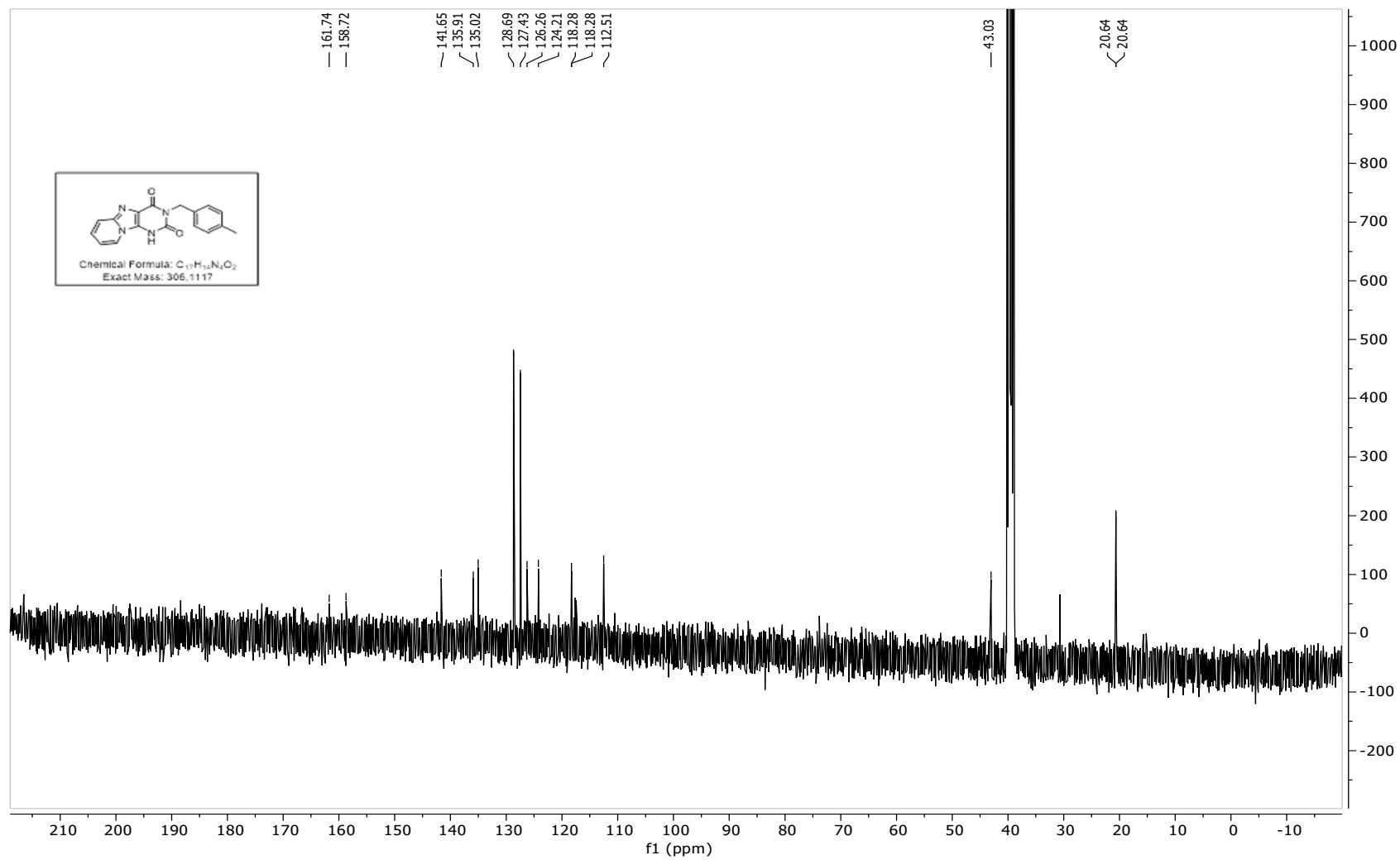
$^{13}\text{C}$  NMR (DMSO- $d_6$ ) of compound **10c**



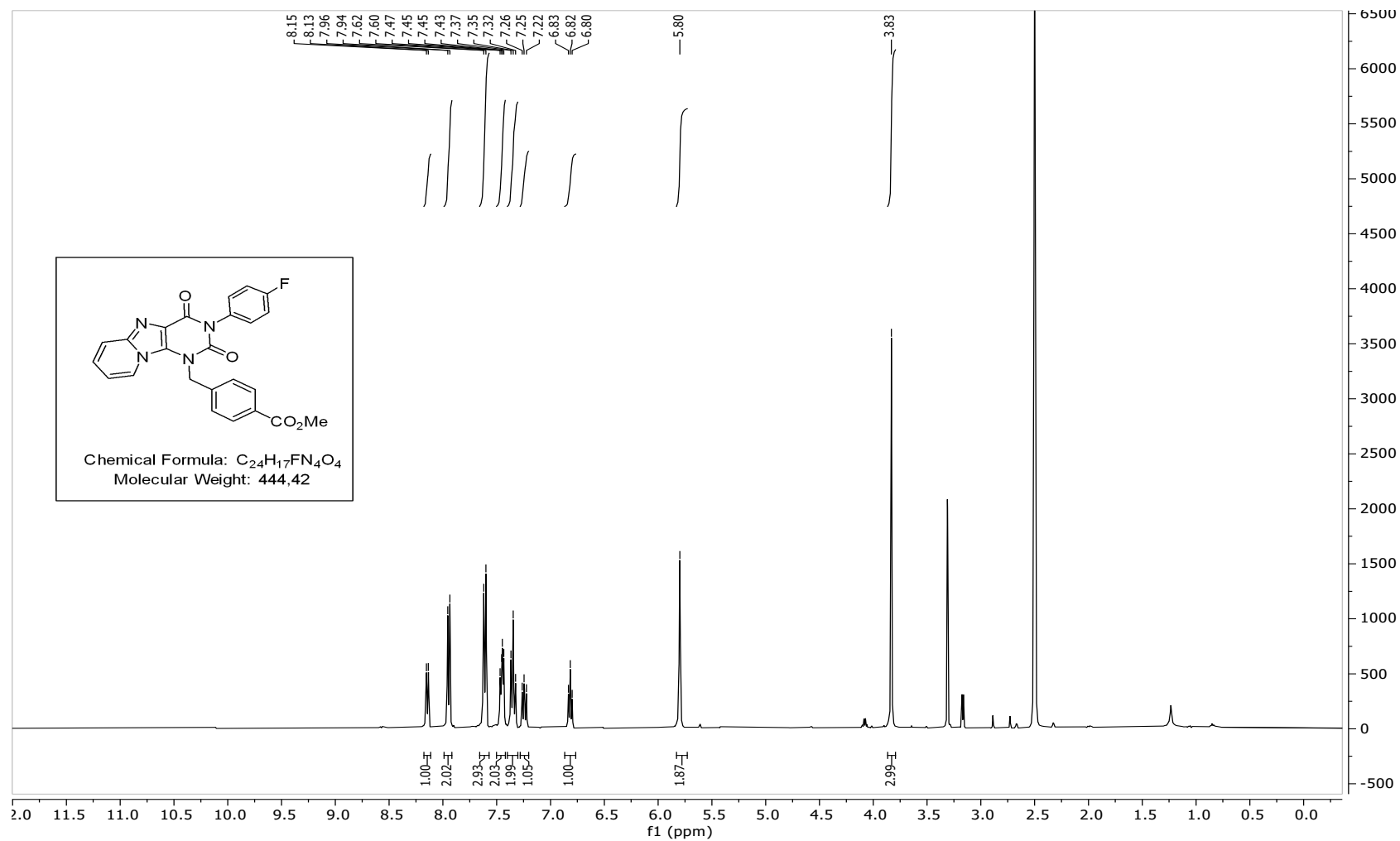
<sup>1</sup>H NMR (DMSO-d<sub>6</sub>) of compound **10d**



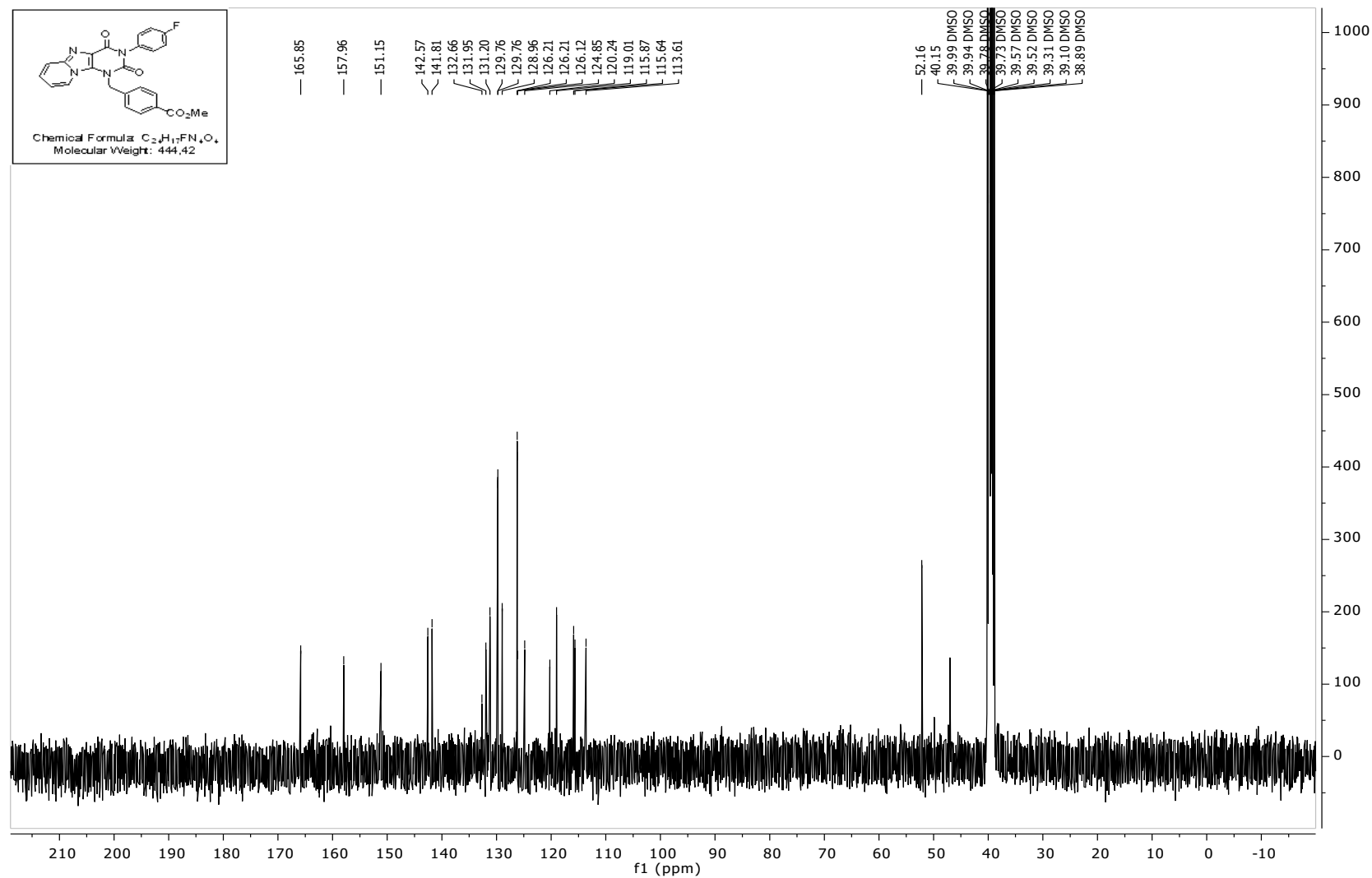
$^{13}\text{C}$  NMR (DMSO- $d_6$ ) of compound **10d**



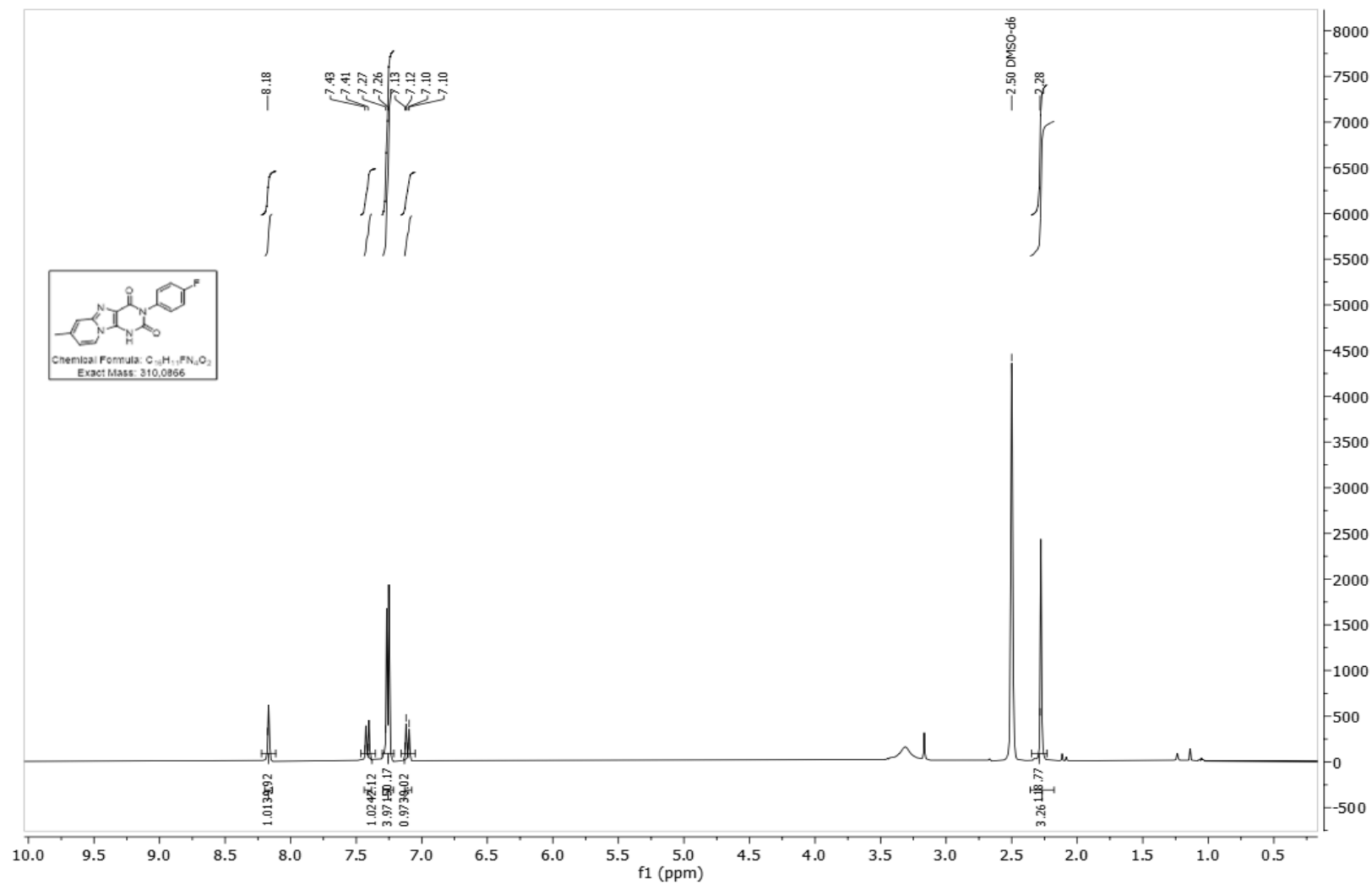
<sup>1</sup>H NMR (DMSO-d<sub>6</sub>) of compound **13e**



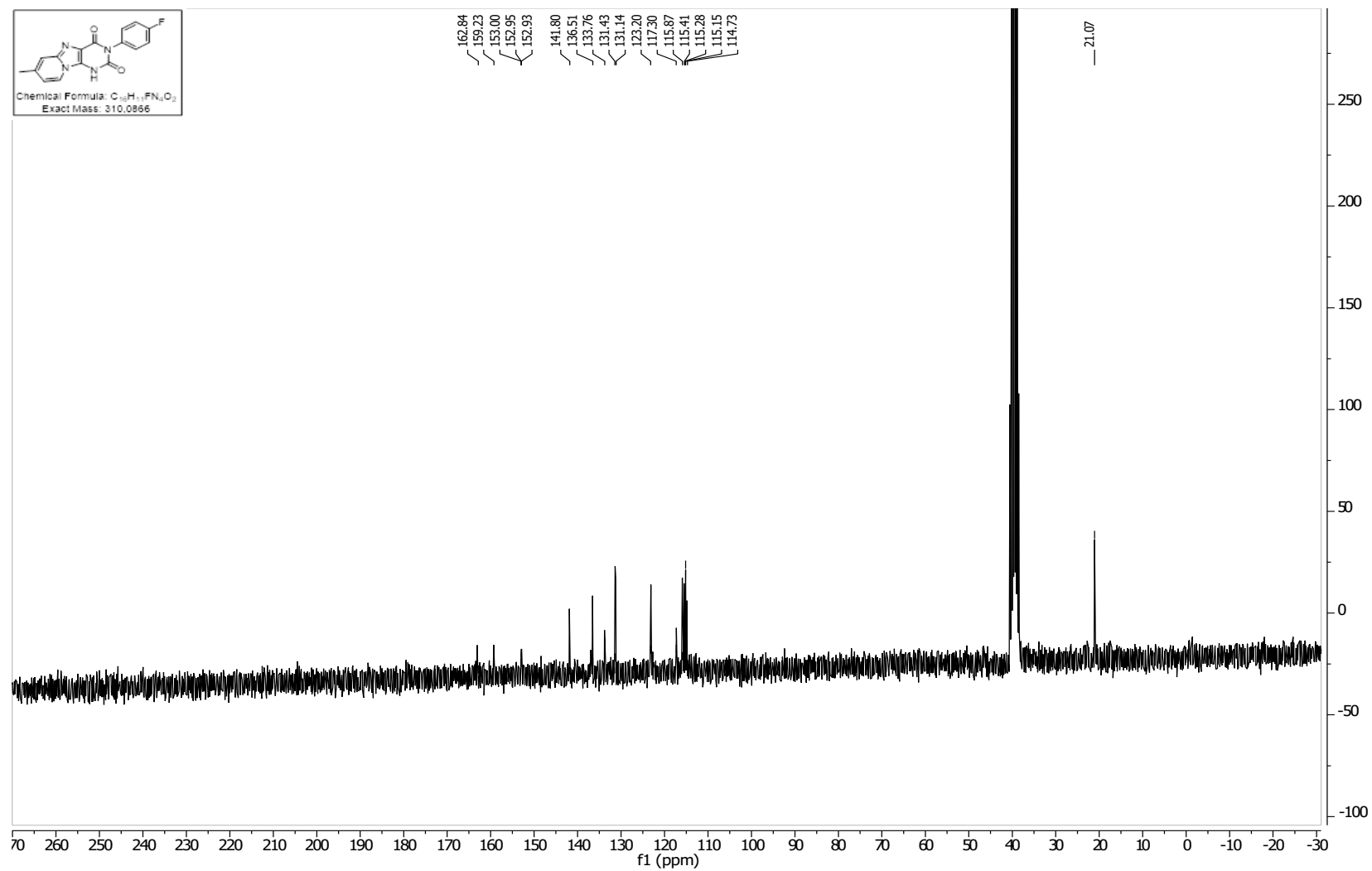
$^{13}\text{C}$  NMR (DMSO-d<sub>6</sub>) of compound **13e**



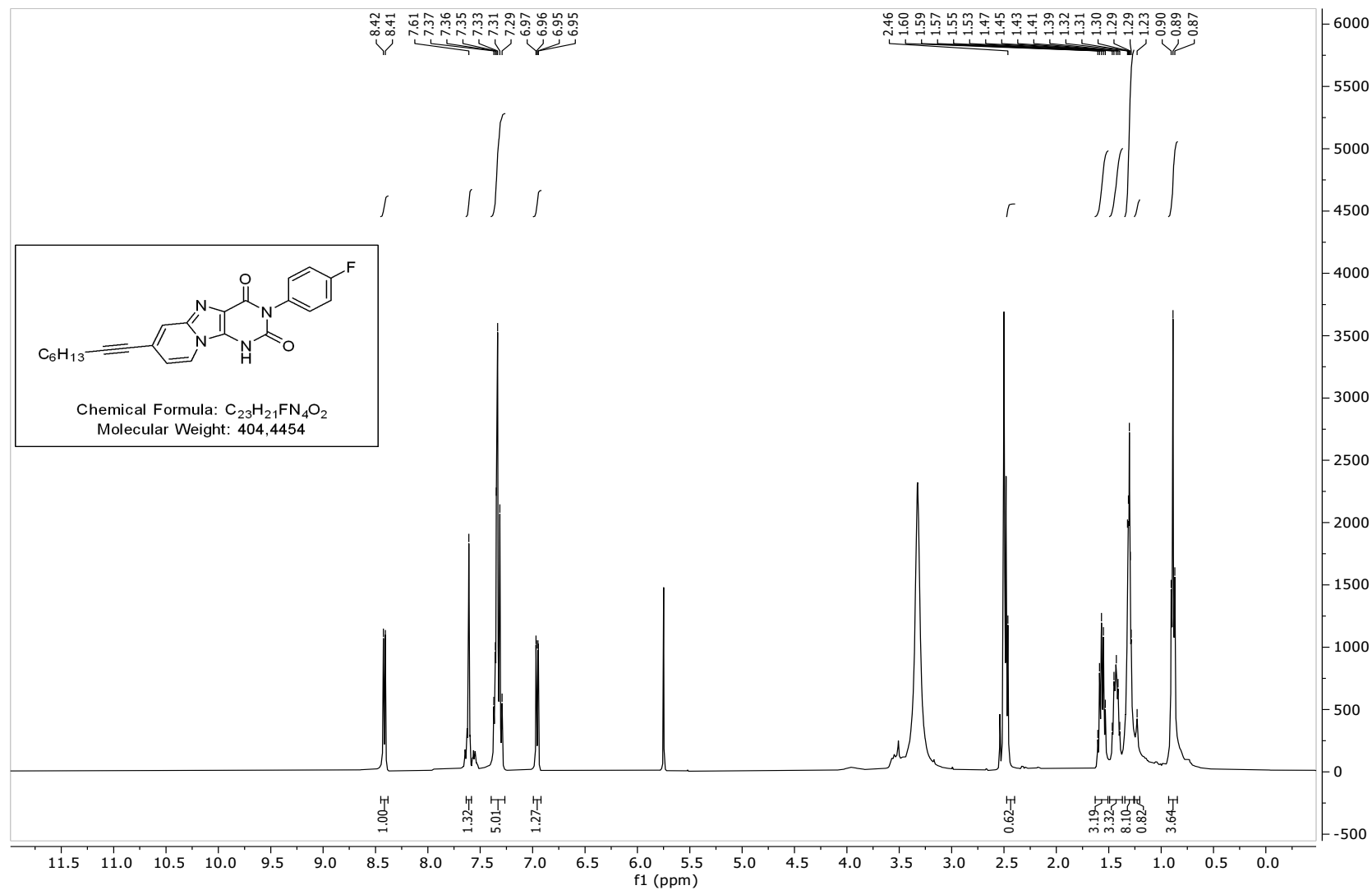
$^1\text{H}$  NMR (DMSO- $d_6$ ) of compound **18a**



$^{13}\text{C}$  NMR (DMSO-d<sub>6</sub>) of compound **18a**

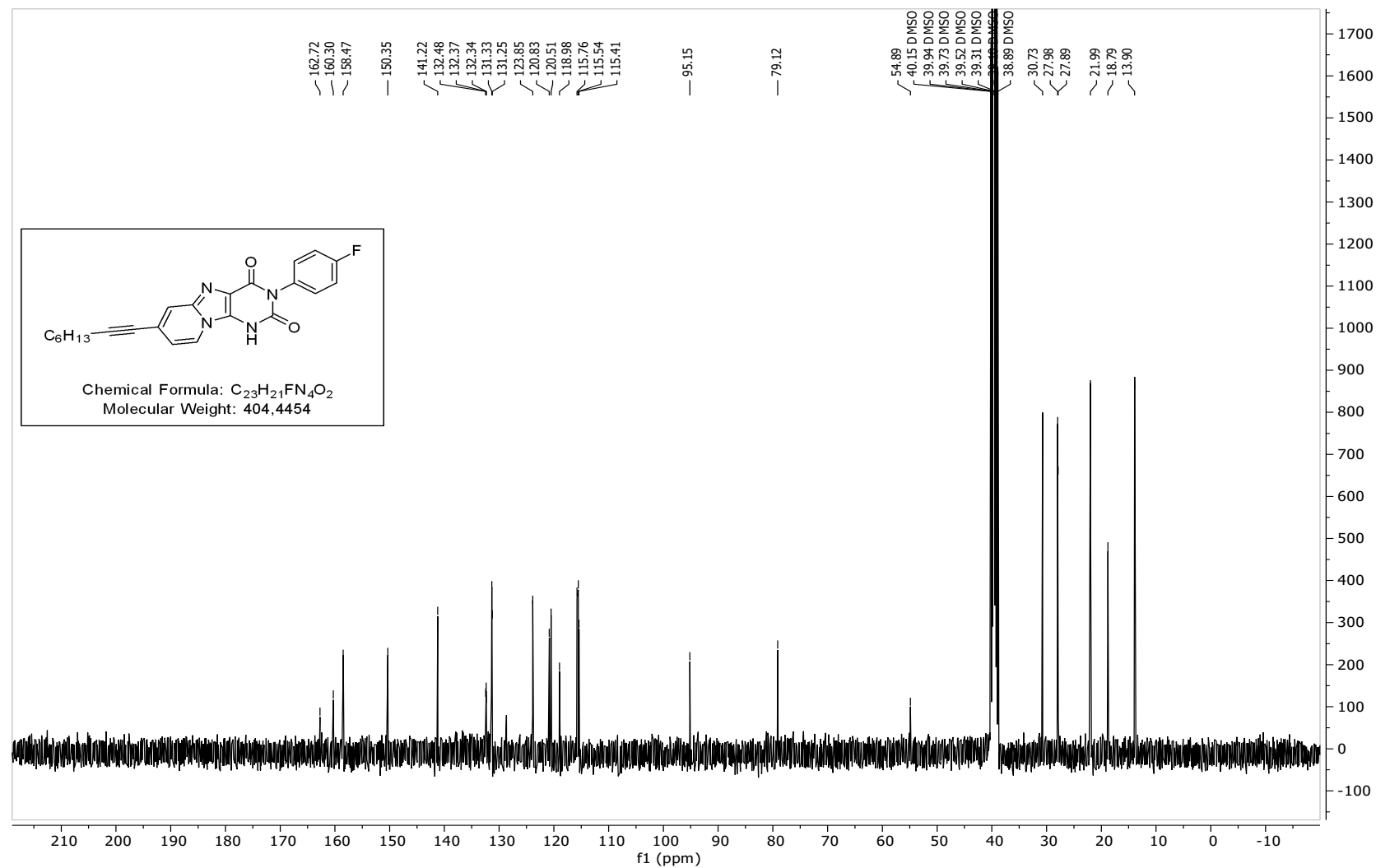


$^1\text{H}$  NMR (DMSO- $d_6$ ) of compound **20e**

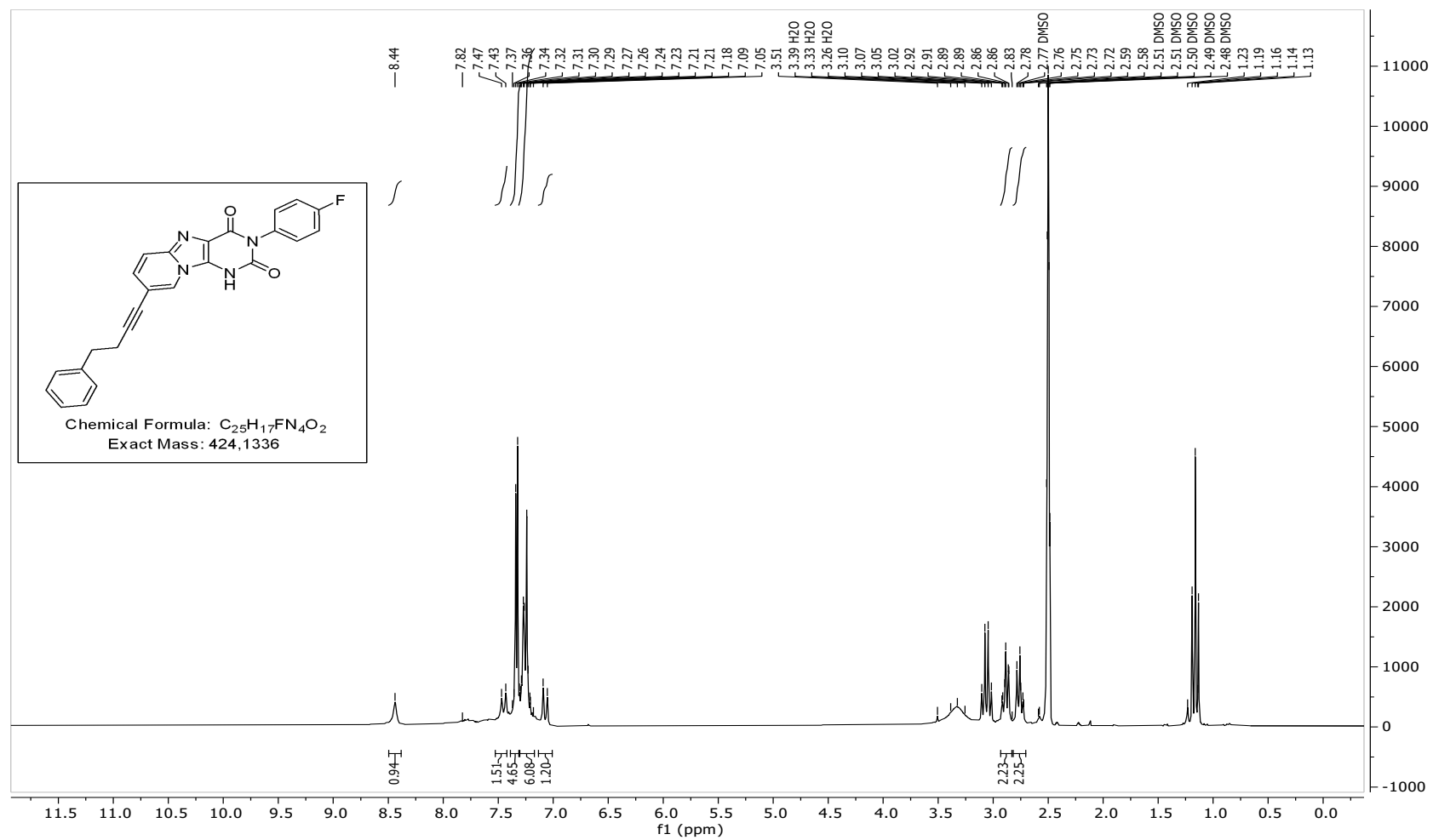




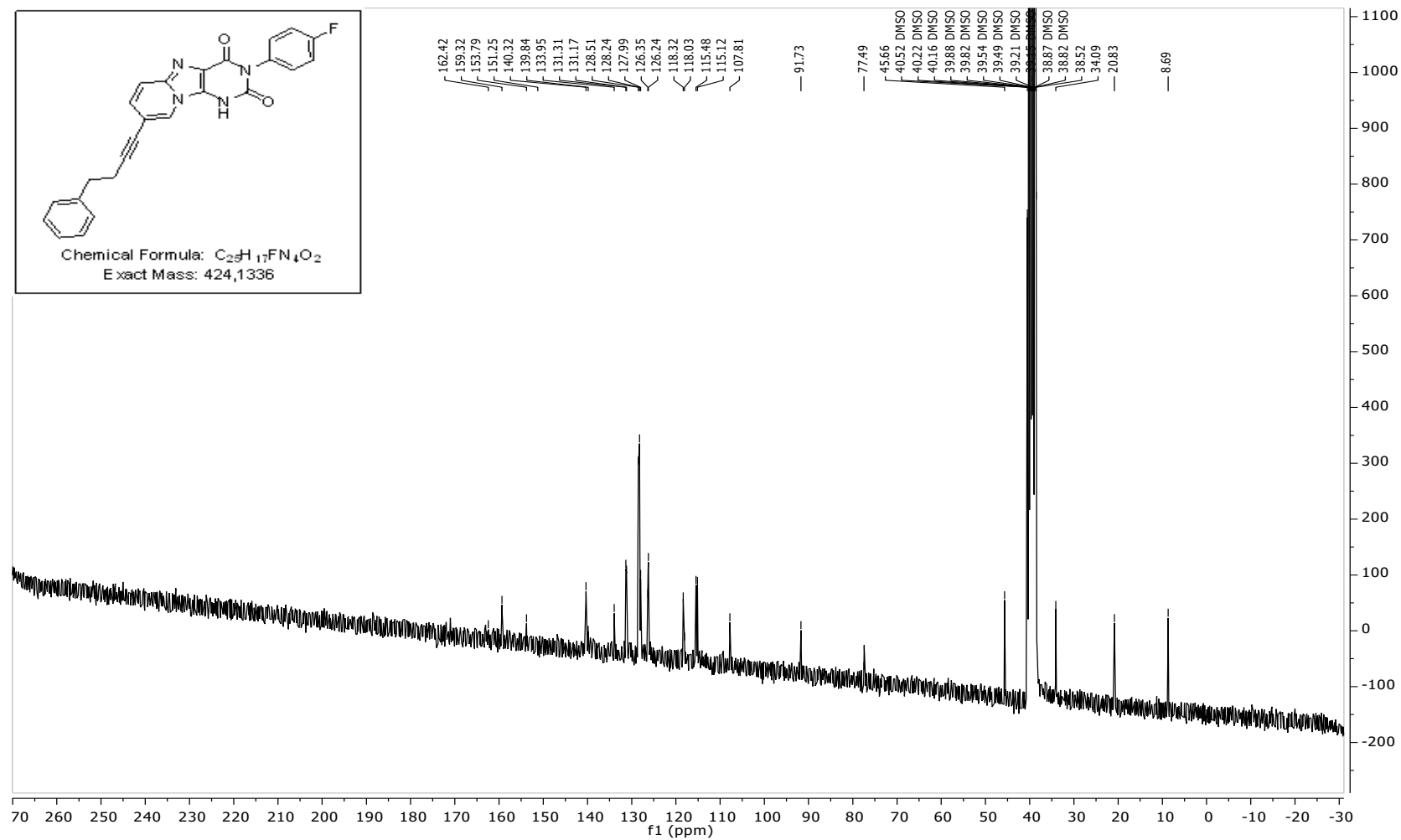
$^{13}\text{C}$  NMR (DMSO-d<sub>6</sub>) of compound **20e**



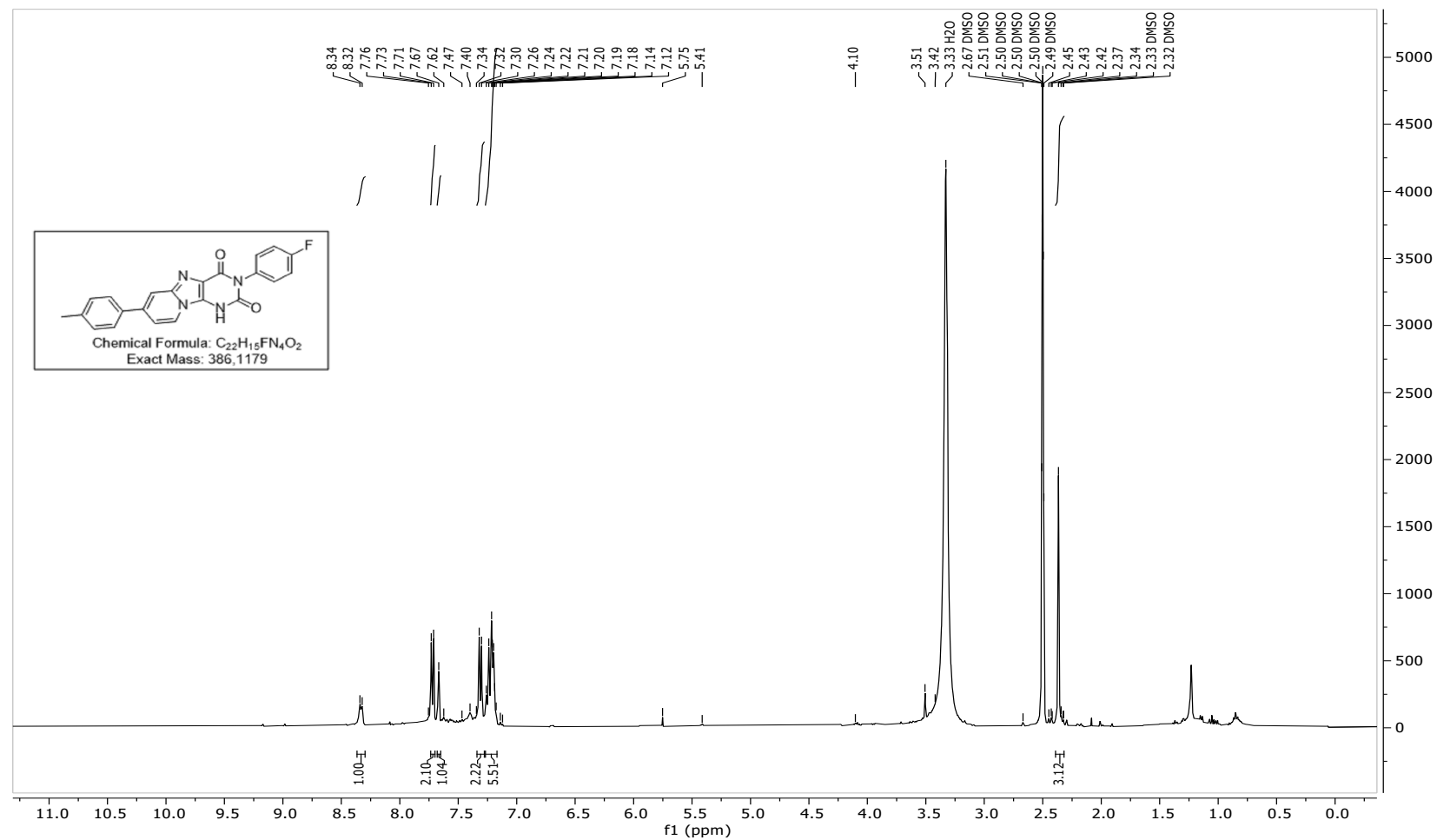
<sup>1</sup>H NMR (DMSO-d<sub>6</sub>) of compound **21a**



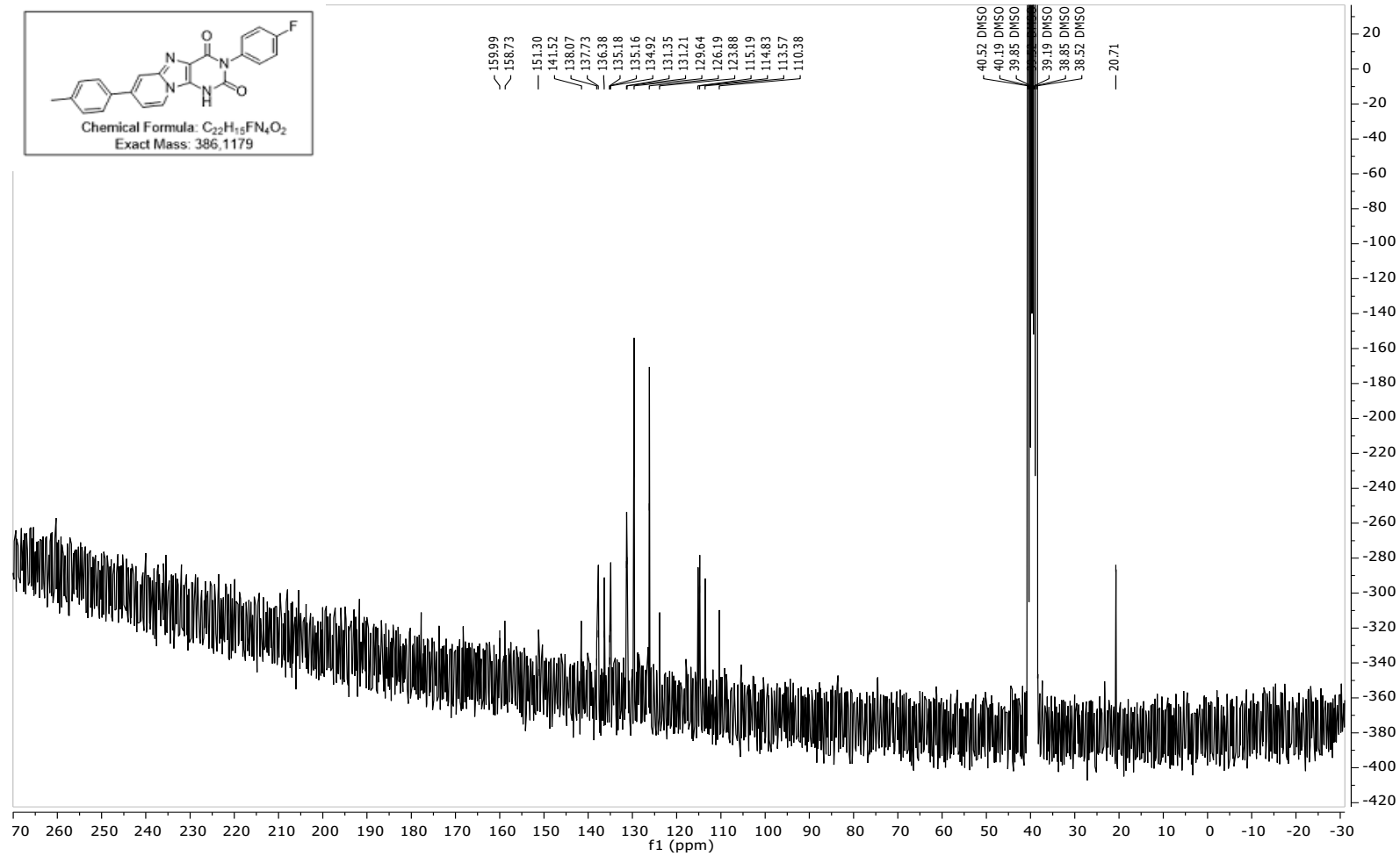
$^{13}\text{C}$  NMR (DMSO-d<sub>6</sub>) of compound **21a**



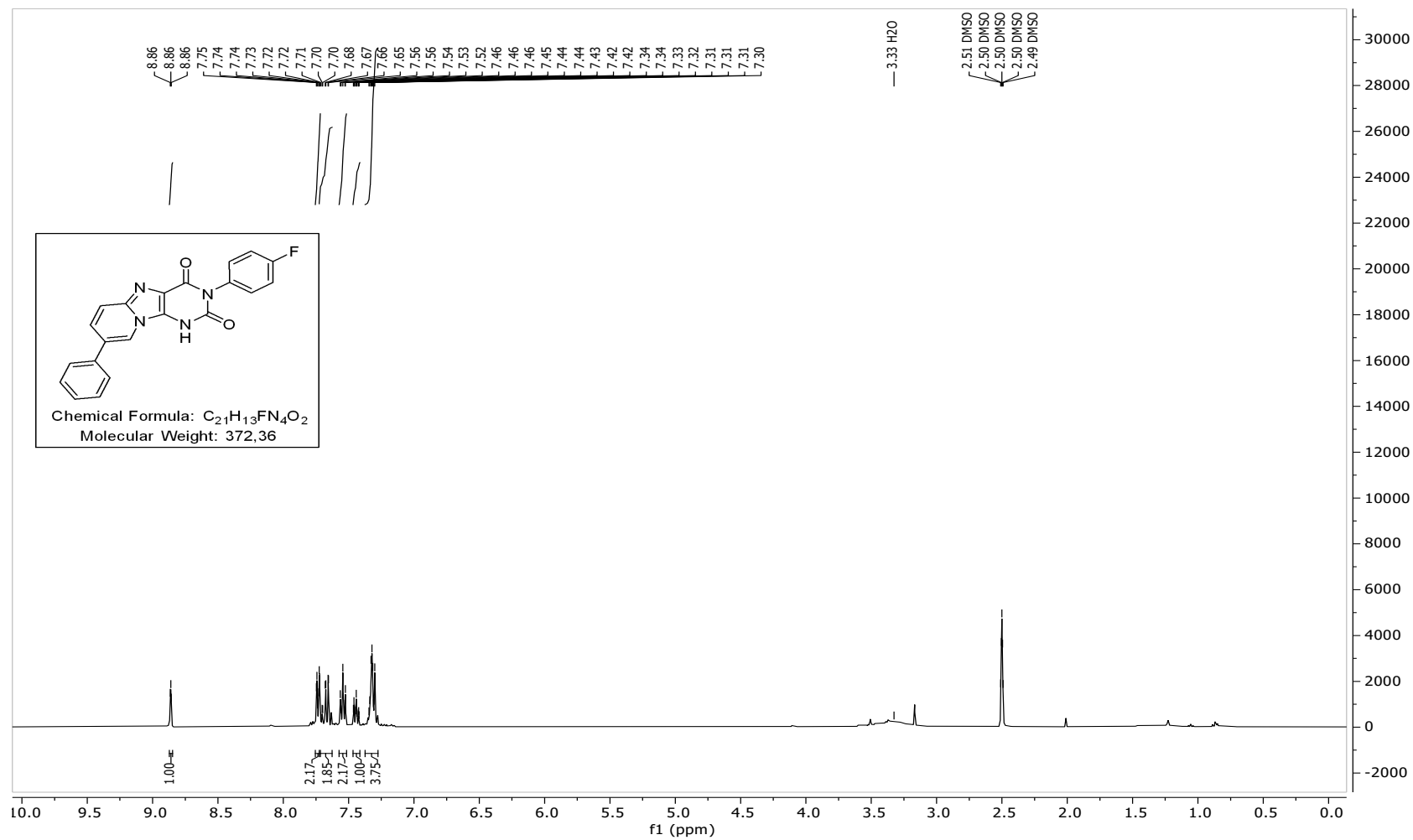
<sup>1</sup>H NMR (DMSO-d<sub>6</sub>) of compound **22b**



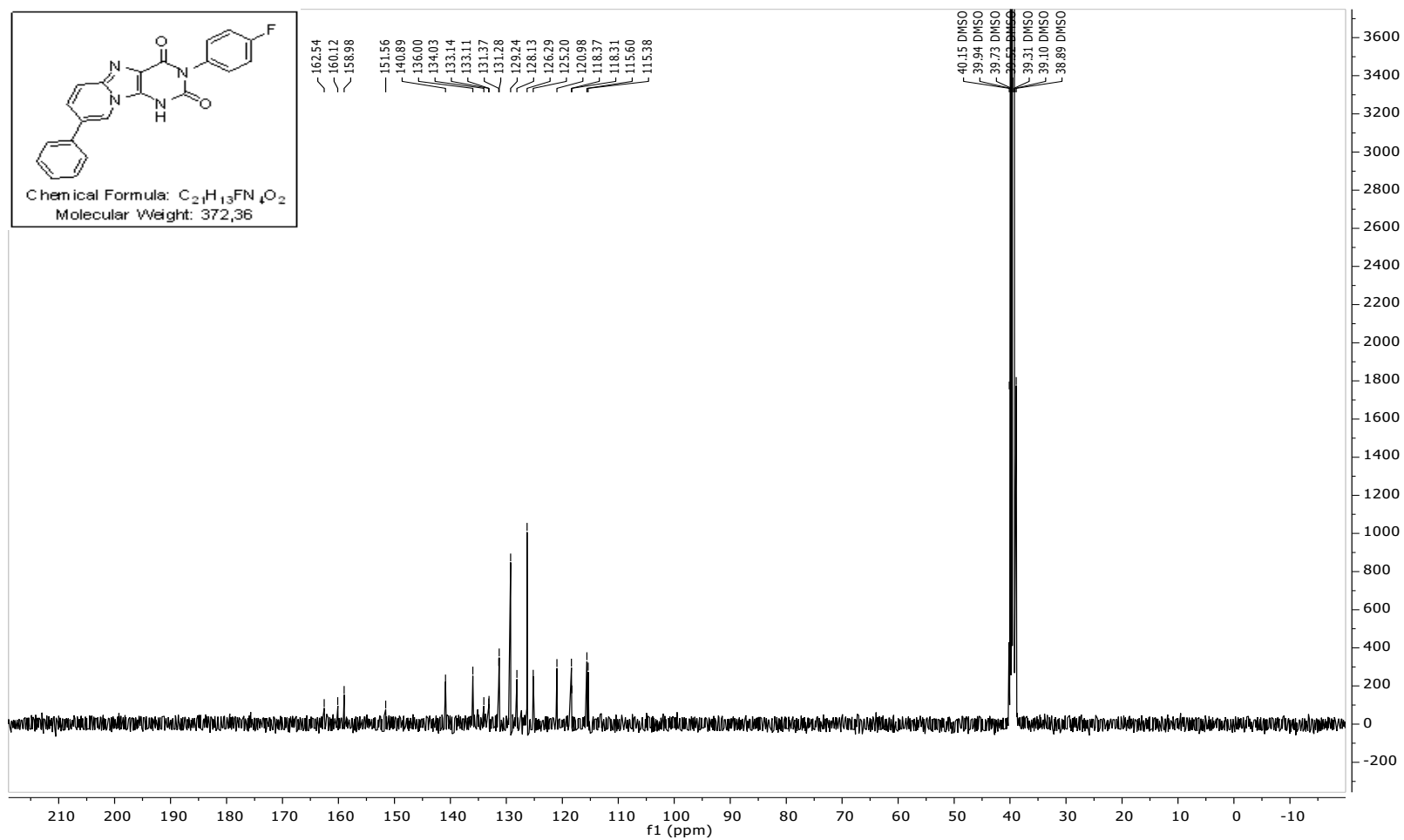
$^{13}\text{C}$  NMR (DMSO- $d_6$ ) of compound **22b**



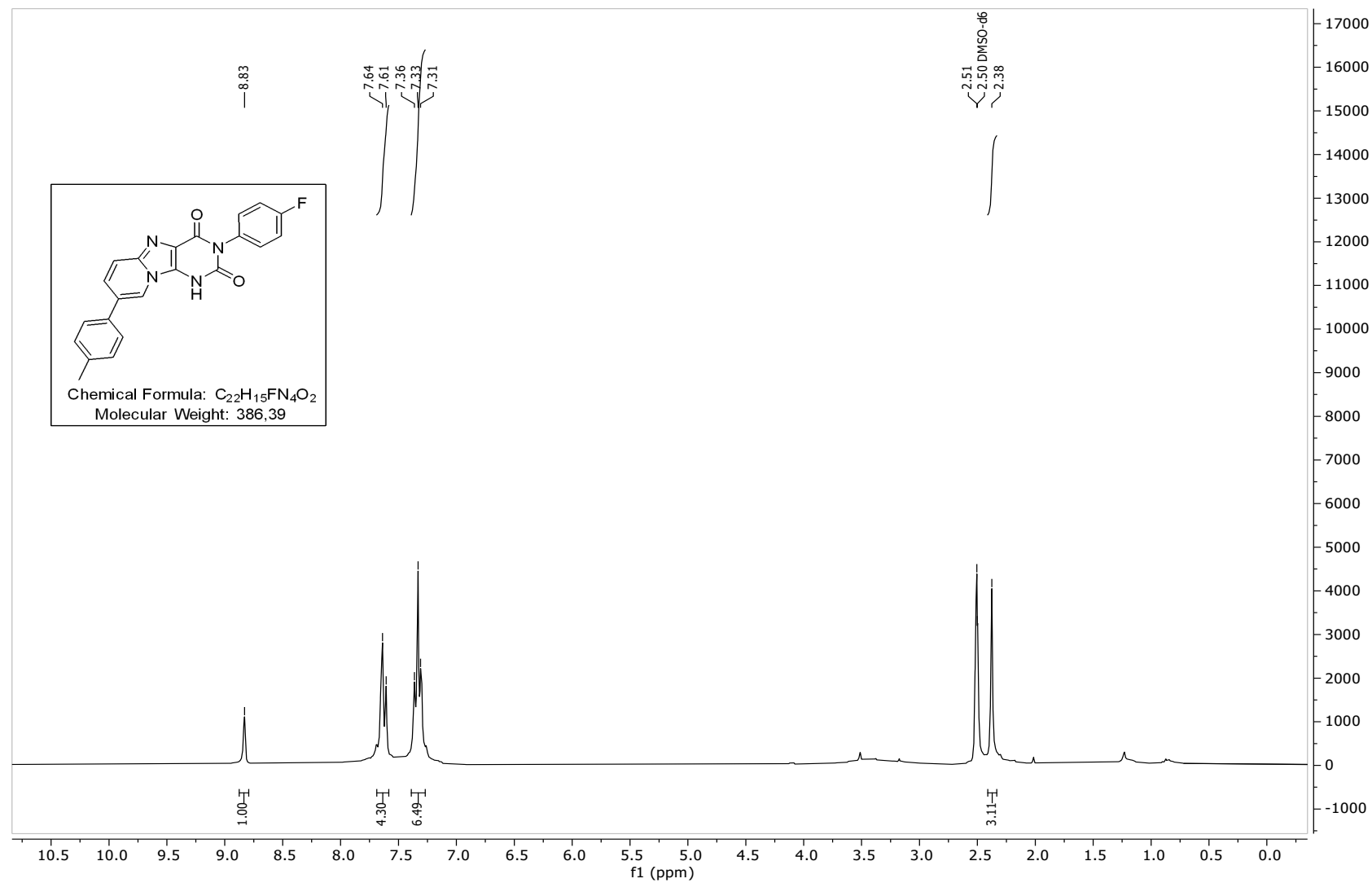
<sup>1</sup>H NMR (DMSO-d<sub>6</sub>) of compound **23a**



$^{13}\text{C}$  NMR (DMSO- $d_6$ ) of compound **23a**

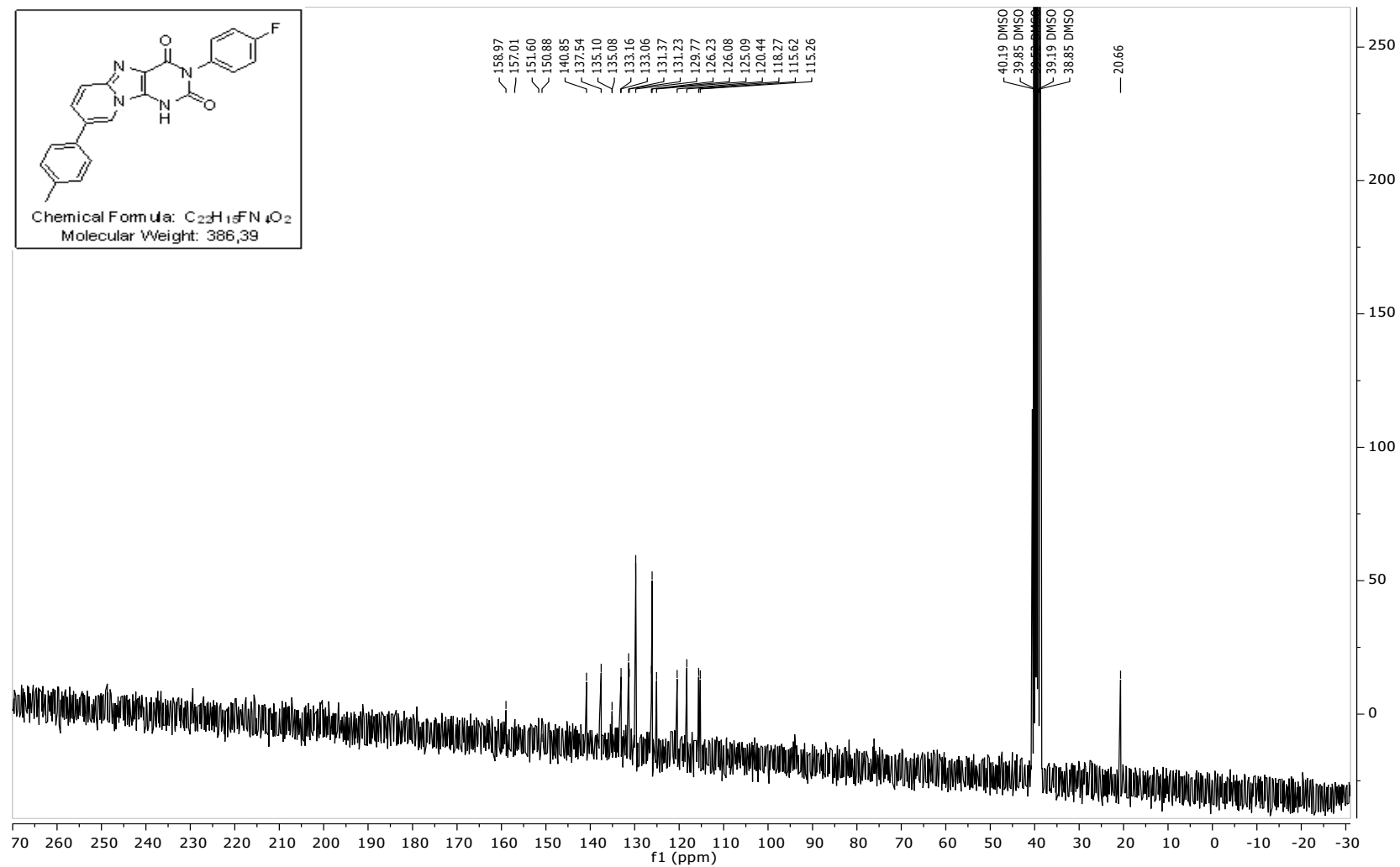


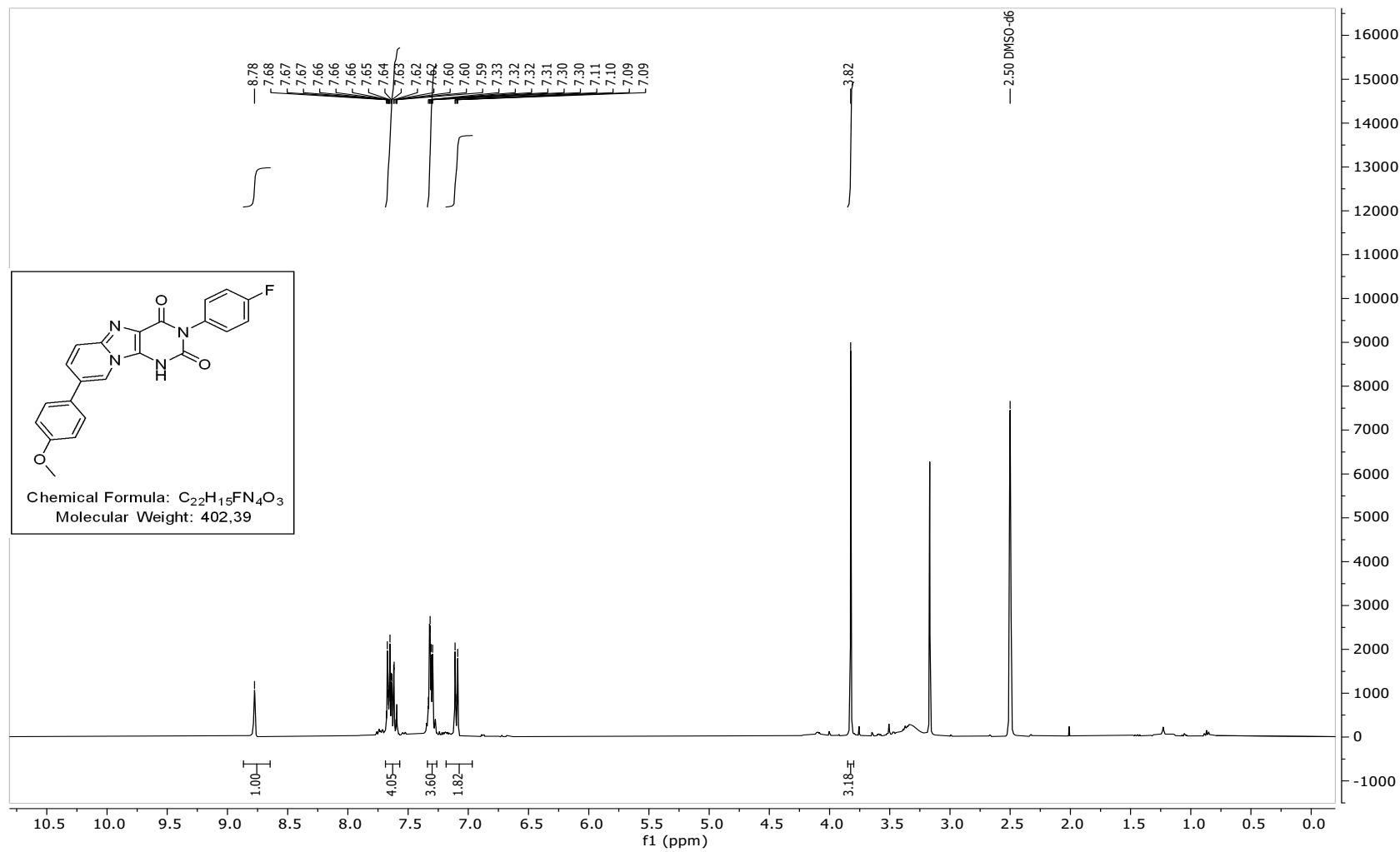
<sup>1</sup>H NMR (DMSO-d<sub>6</sub>) of compound **23b**



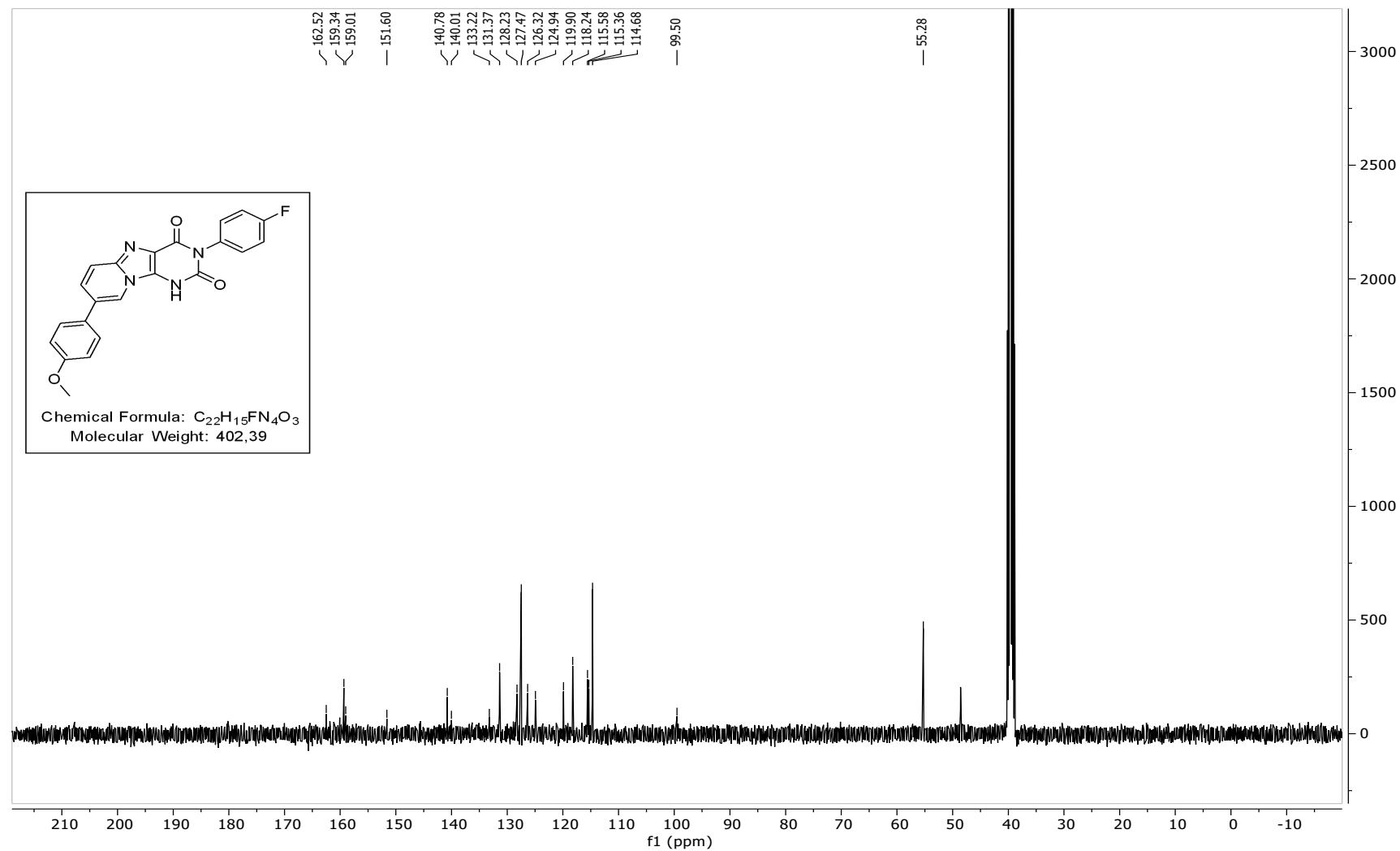


$^{13}\text{C}$  NMR (DMSO- $d_6$ ) of compound **23b**

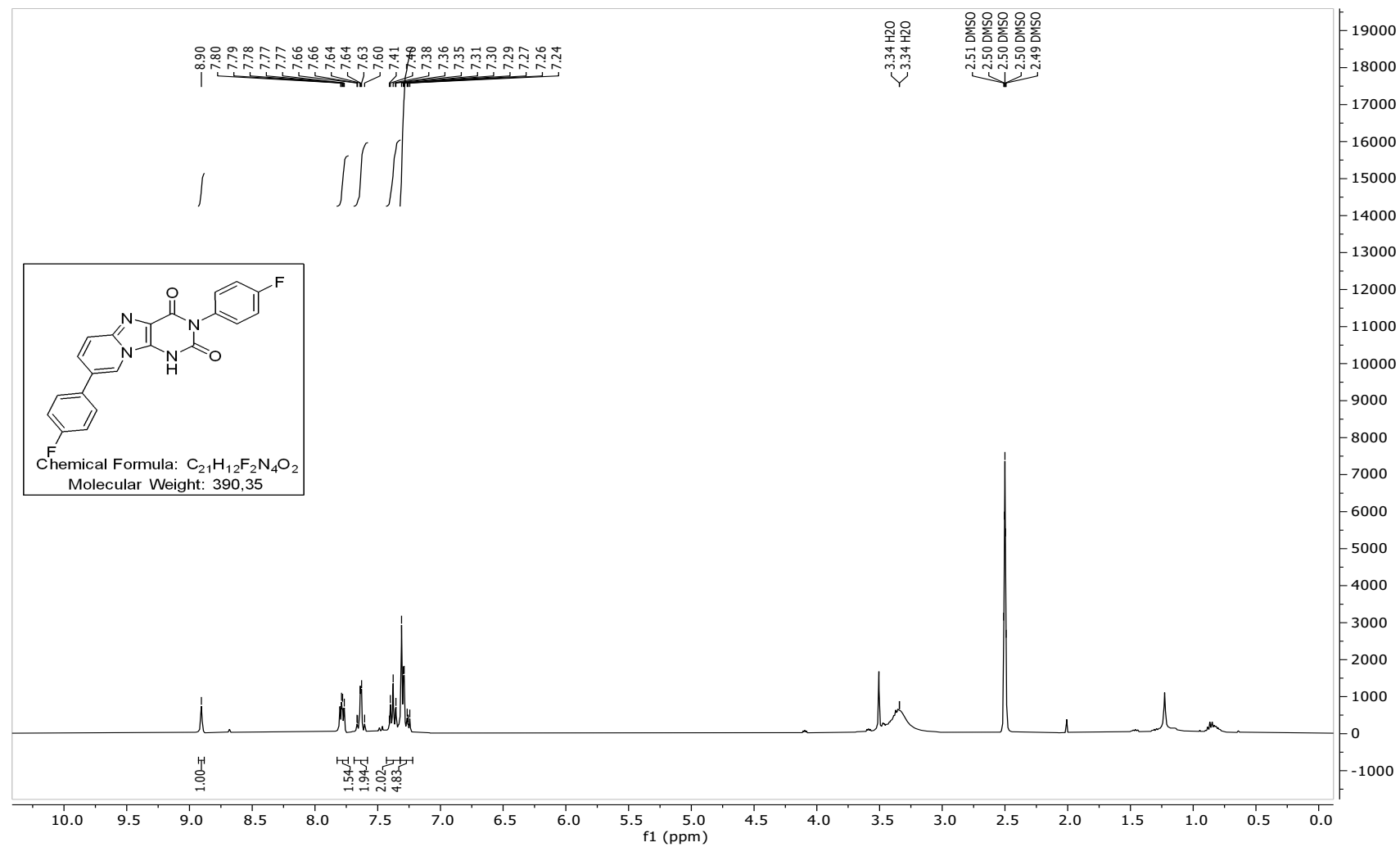


<sup>1</sup>H NMR (DMSO-d<sub>6</sub>) of compound **23c**

$^{13}\text{C}$  NMR (DMSO- $d_6$ ) of compound **23c**



<sup>1</sup>H NMR (DMSO-d<sub>6</sub>) of compound **23e**



$^{13}\text{C}$  NMR (DMSO- $d_6$ ) of compound **23e**

