

A Brand-New Metal Complex Catalyst-Free Approach to the Synthesis of 2,8-Dimethylimidazo[1,2-*b*]pyridazine-6-Carboxylic Acid—A Key Intermediate in Risdiplam Manufacturing Process

Georgiy Korenev *, Alexey A. Gutenev, Fyodor V. Antipin, Vladimir V. Chernyshov, Maria P. Korobkina, Maxim B. Nawrozkij and Roman A. Ivanov

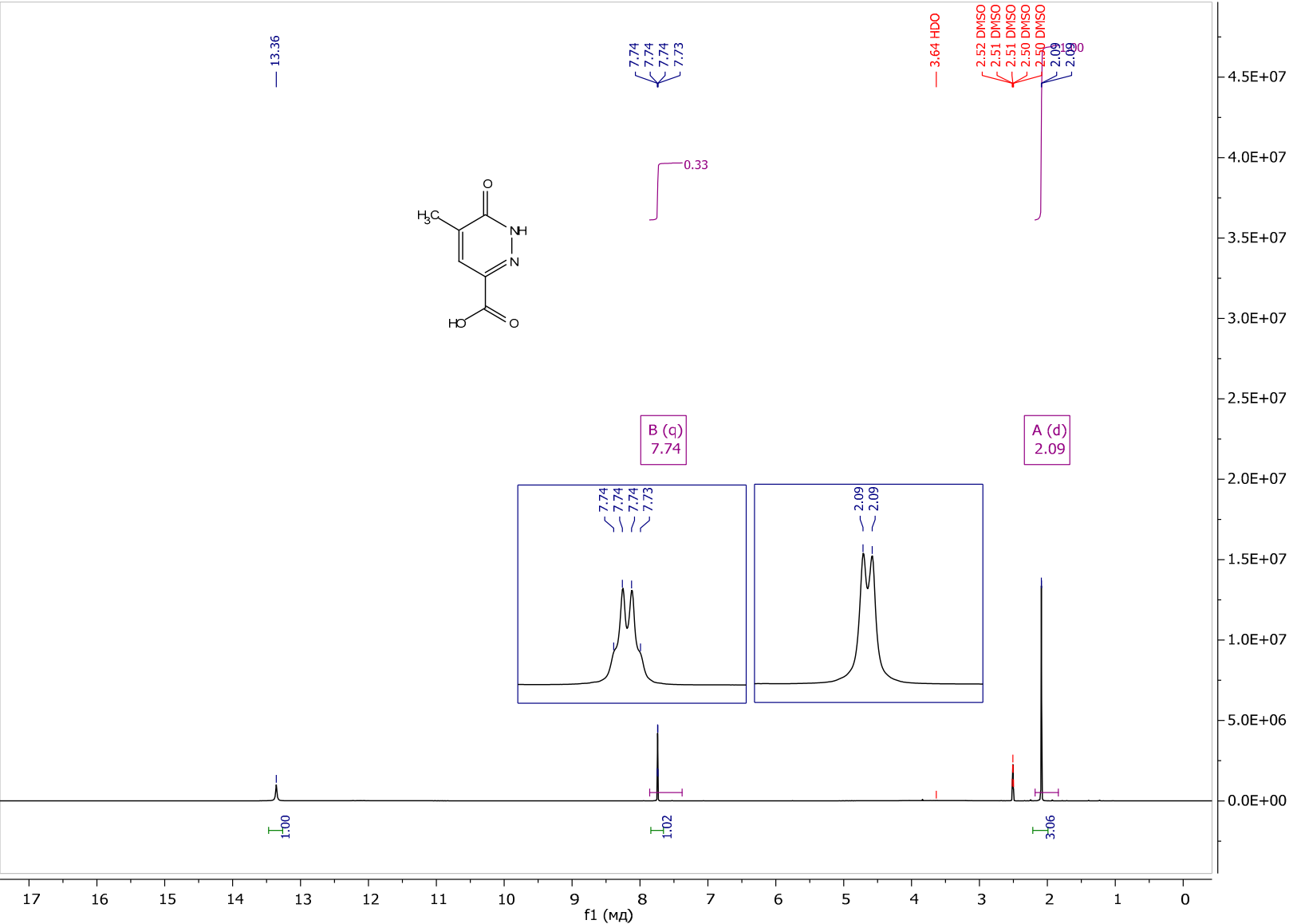
Medicinal Biotechnology Department, Sirius University of Science and Technology, Olimpiyskiy Ave. 1, 354340 Sirius, Krasnodar Region, Russia; vladimir.chernyshov2012@yandex.ru (V.V.C.)
ivanov.ra@talantiuspeh.ru (R.A.I.)

* Correspondence: korenev.g@talantiuspeh.ru

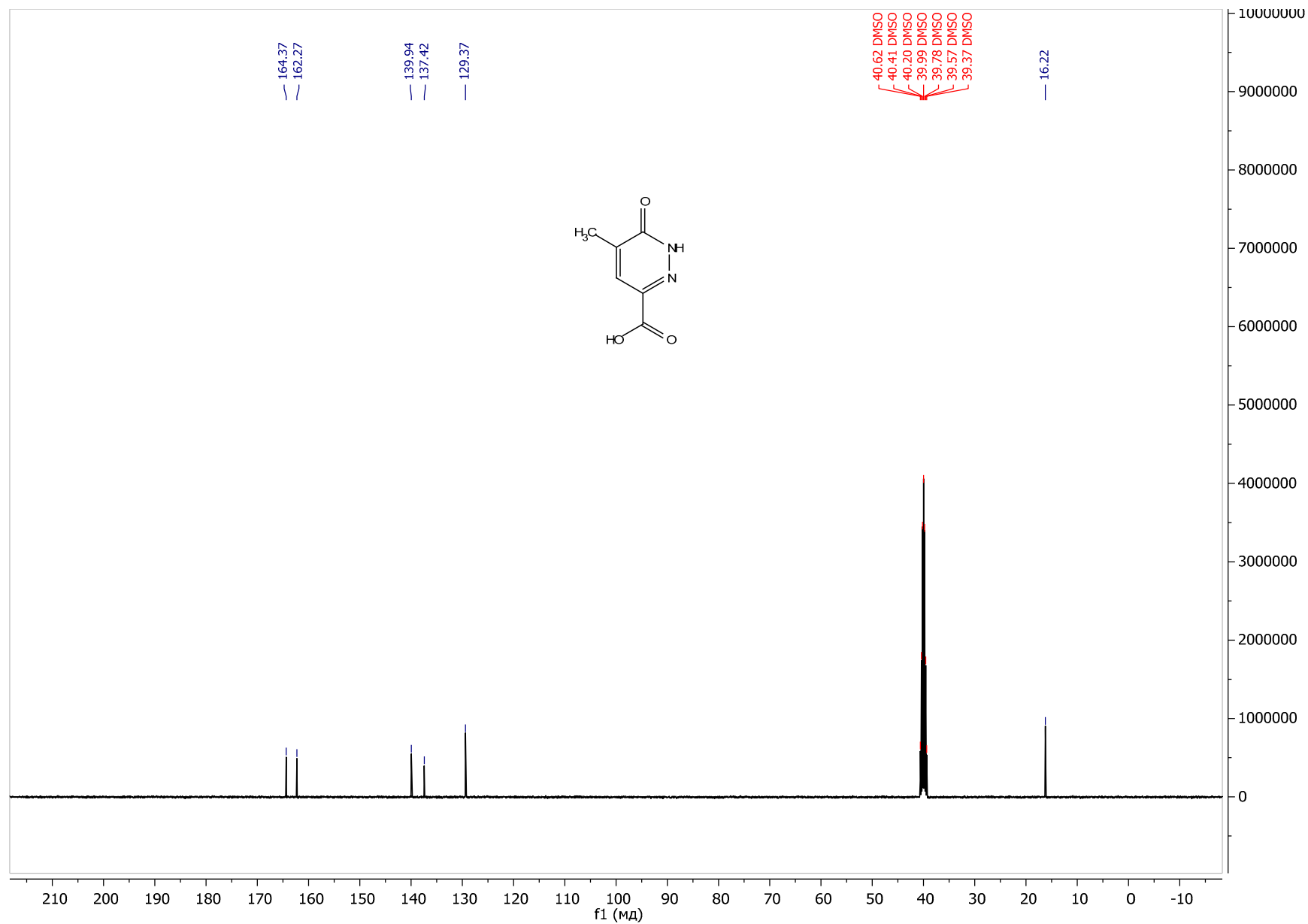
Table of Contents

Copies of NMR spectra.....	3
Copies of HRMS spectra	31

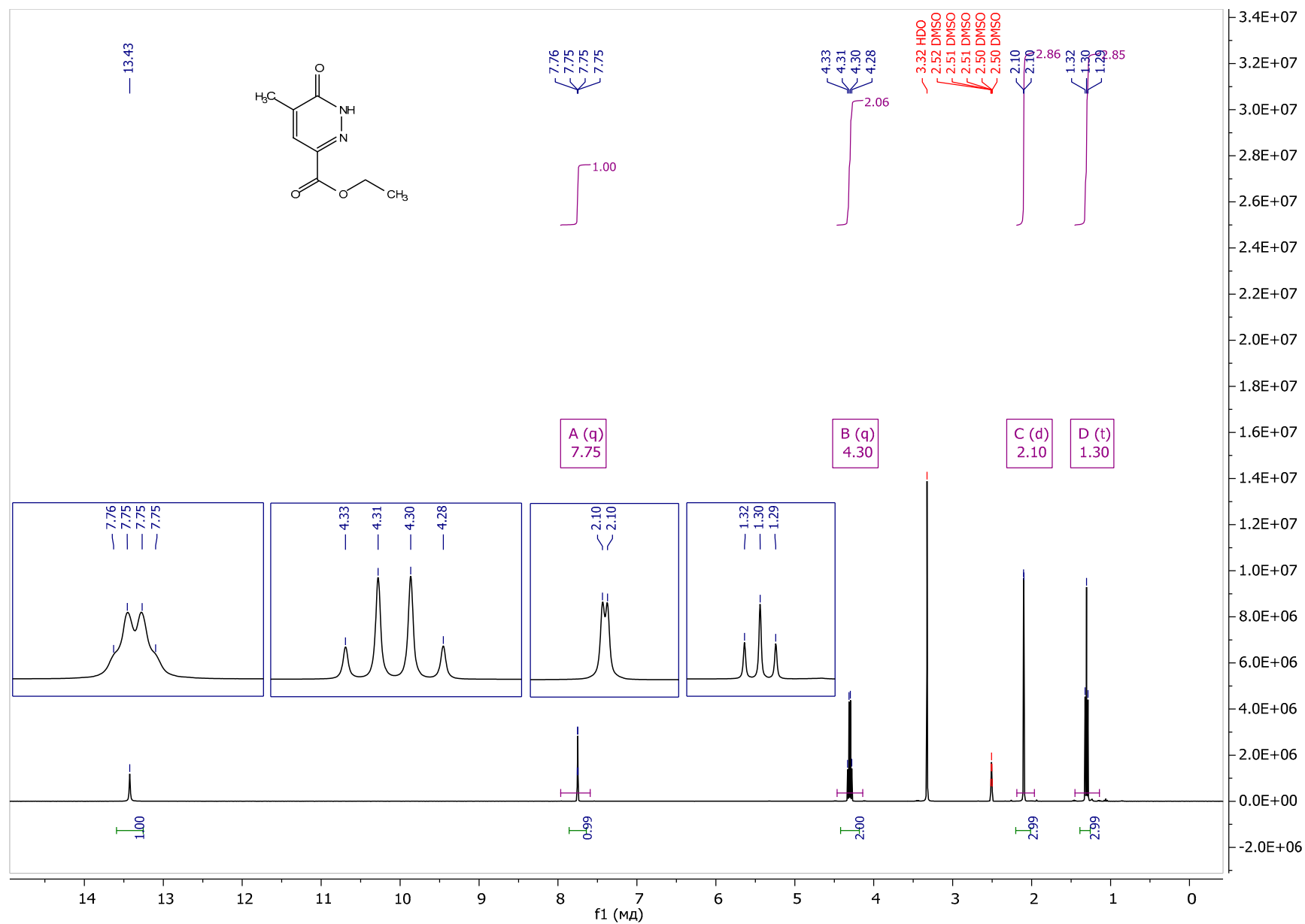
¹H NMR spectrum of 5-methyl-6-oxo-1,6-dihydropyridazine-3-carboxylic acid 17



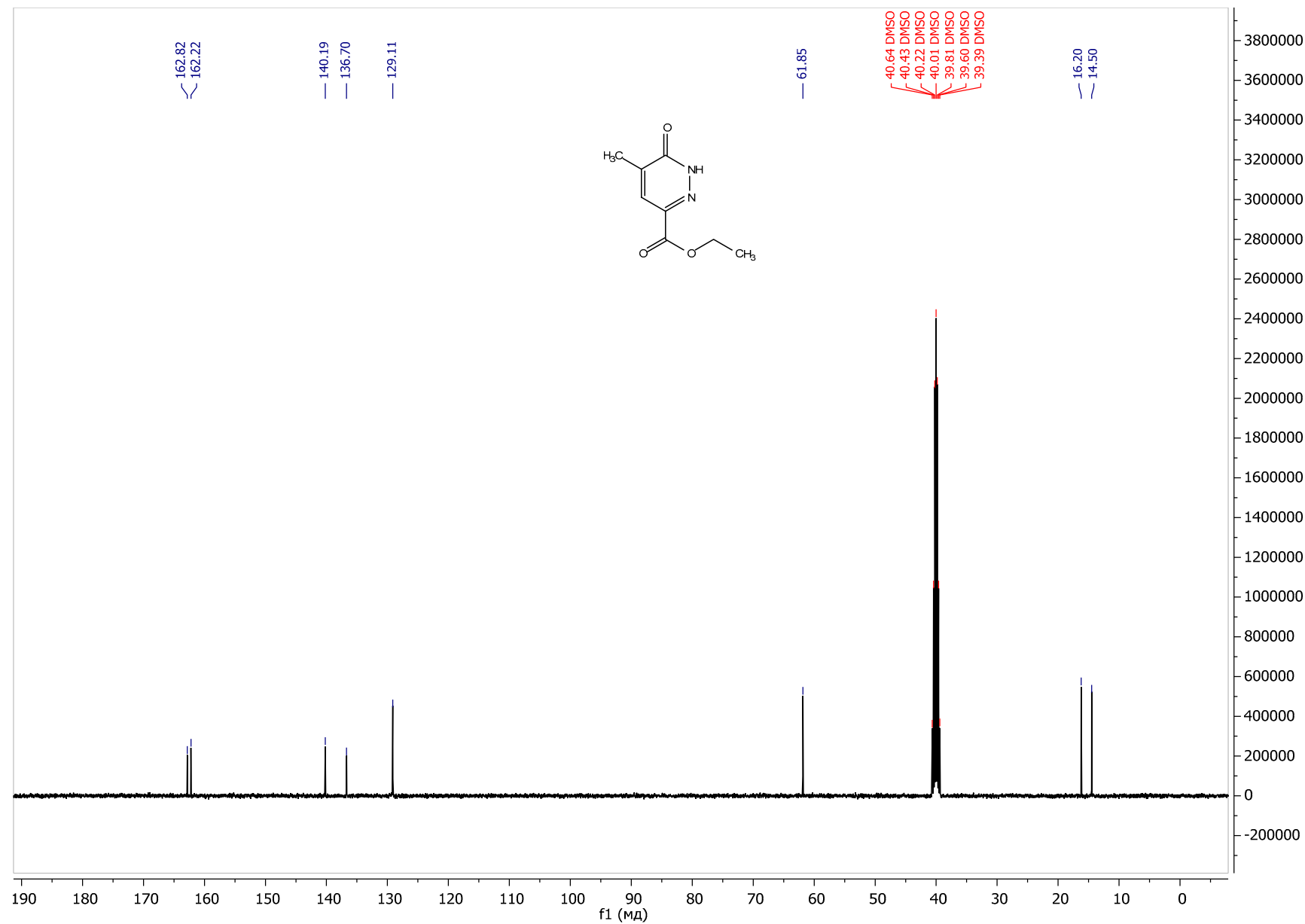
^{13}C NMR spectrum of 5-methyl-6-oxo-1,6-dihydropyridazine-3-carboxylic acid **17**



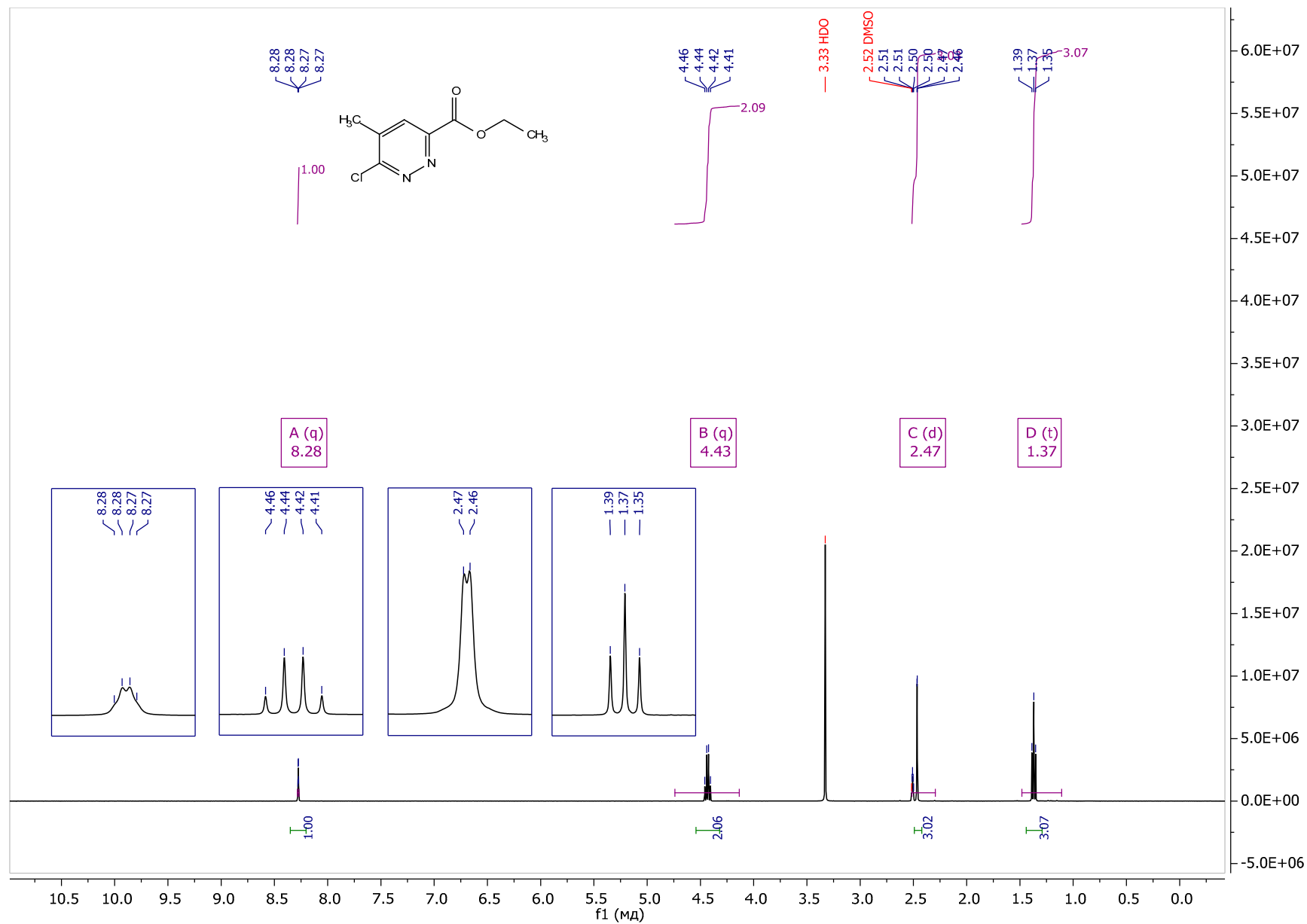
¹H NMR spectrum of ethyl 5-methyl-6-oxo-1,6-dihydropyridazine-3-carboxylate **18**



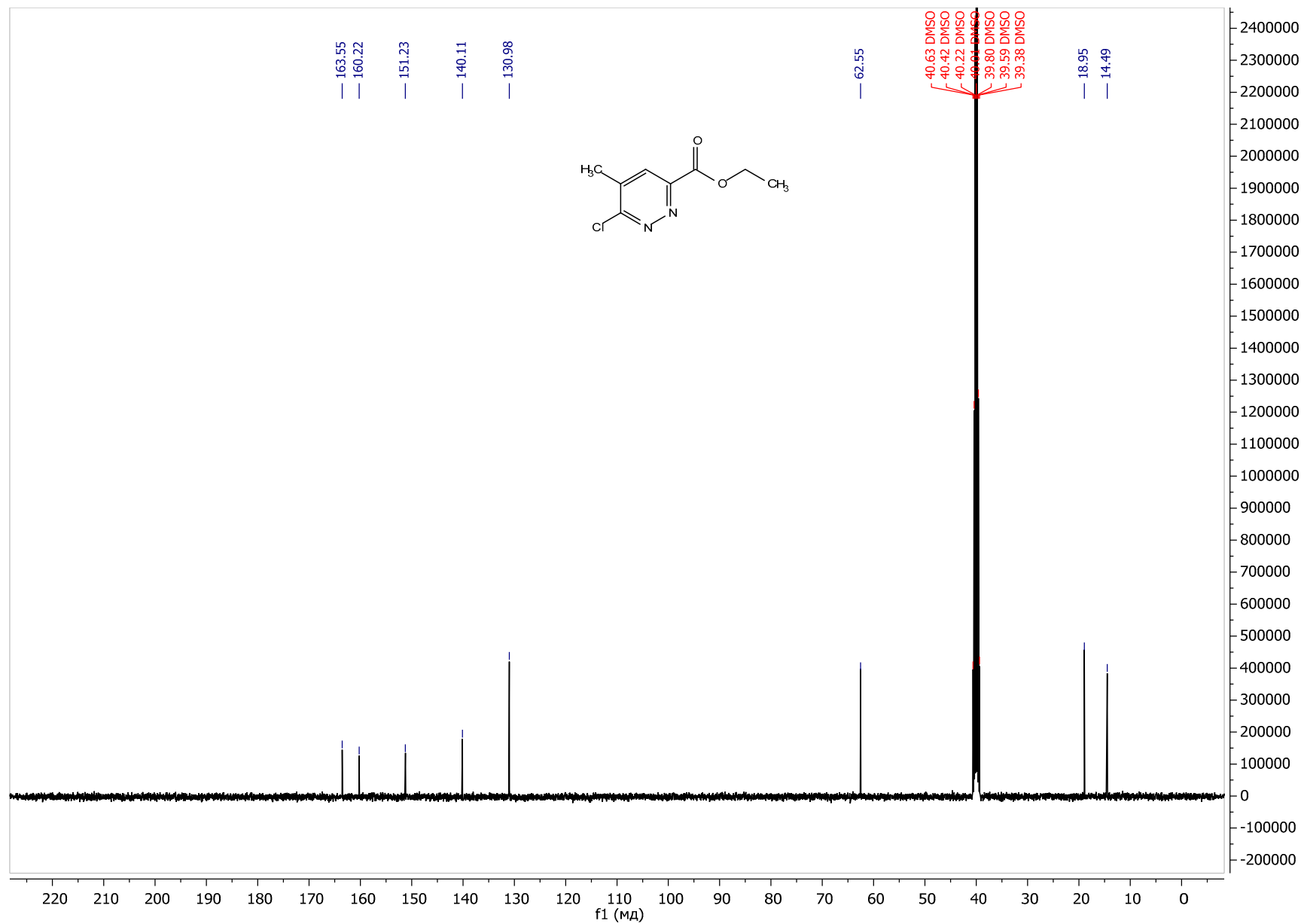
^{13}C NMR spectrum of ethyl 5-methyl-6-oxo-1,6-dihydropyridazine-3-carboxylate **18**



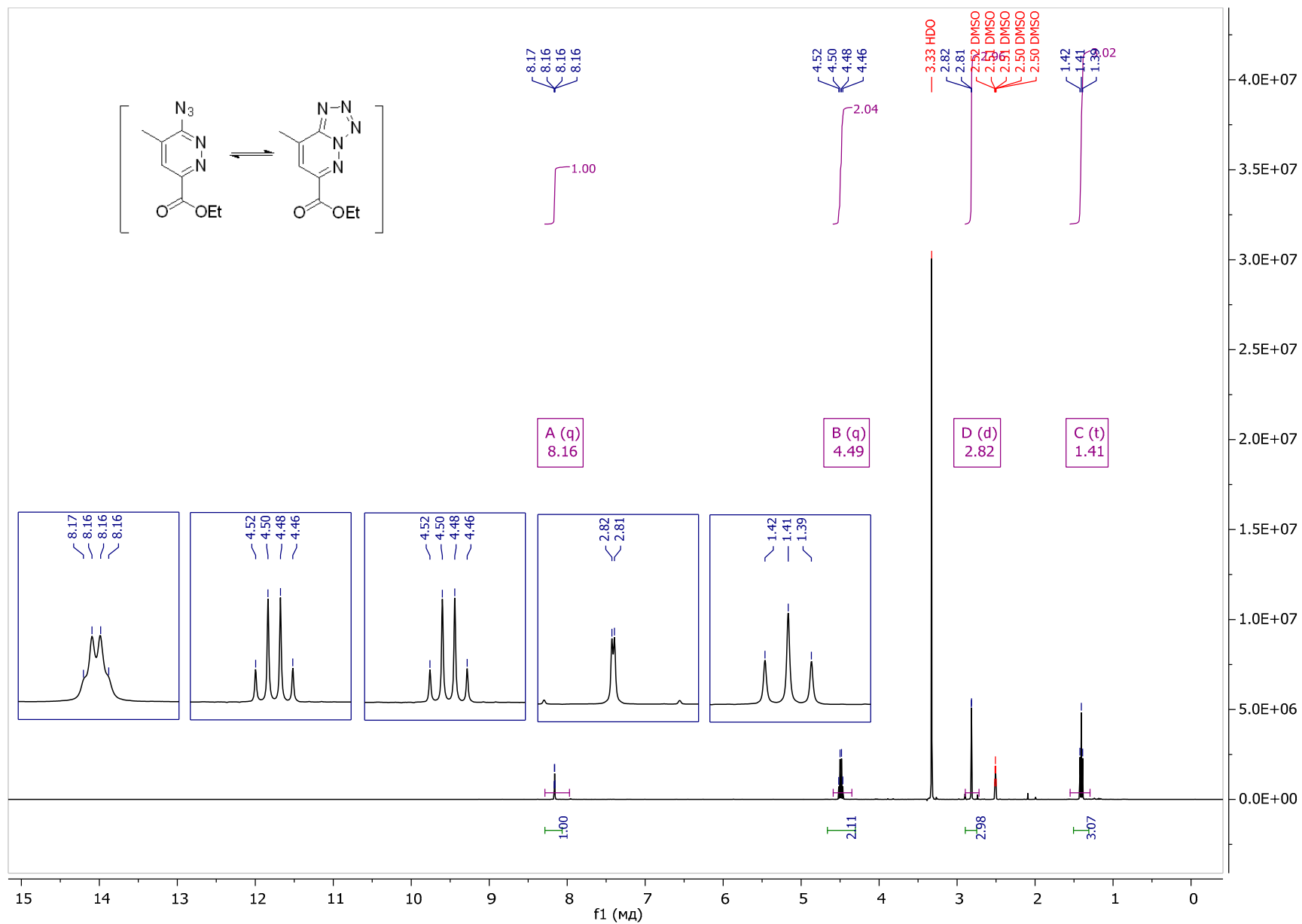
¹H NMR spectrum of ethyl 6-chloro-5-methylpyridazine-3-carboxylate **19**



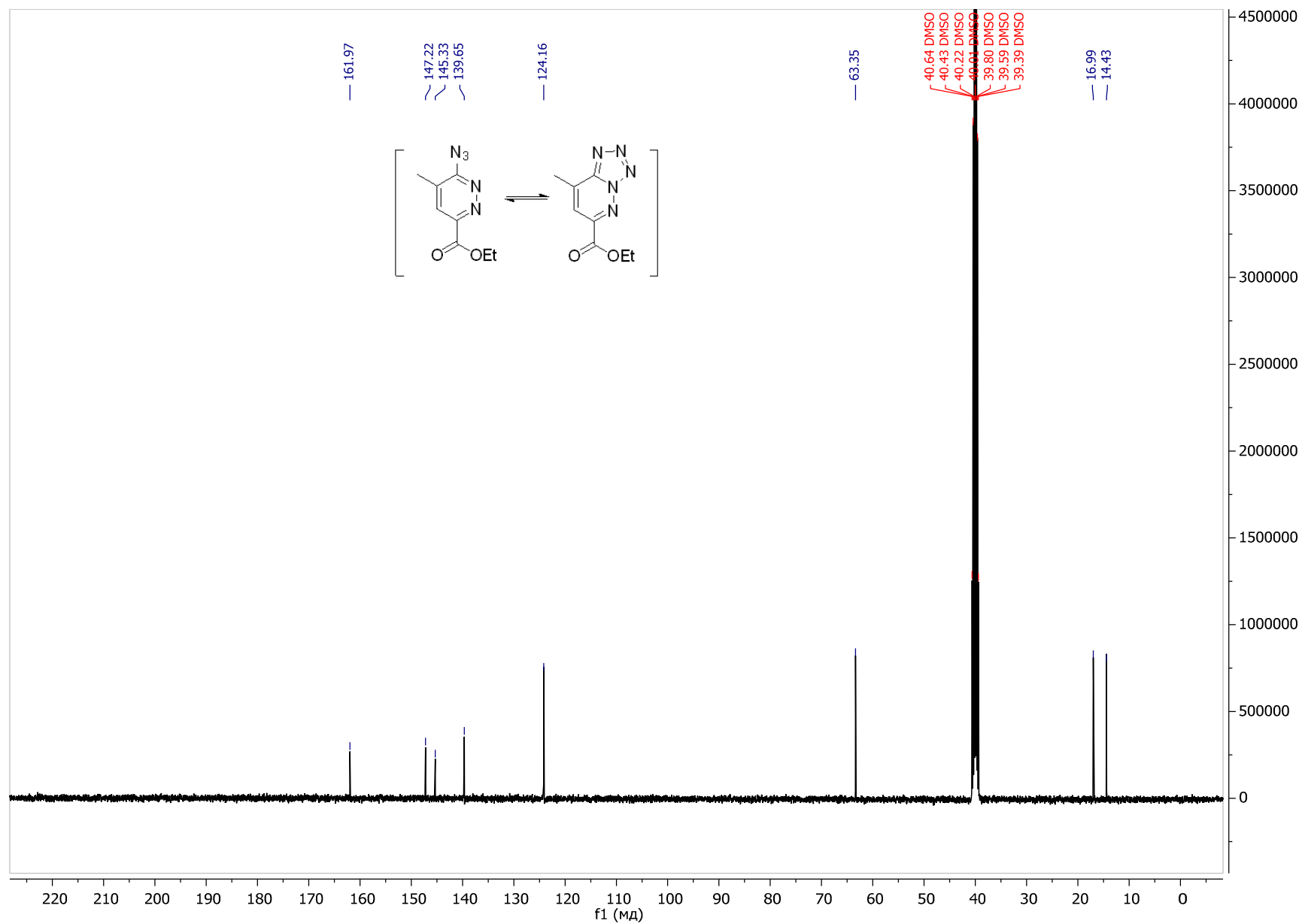
^{13}C NMR spectrum of ethyl 6-chloro-5-methylpyridazine-3-carboxylate **19**



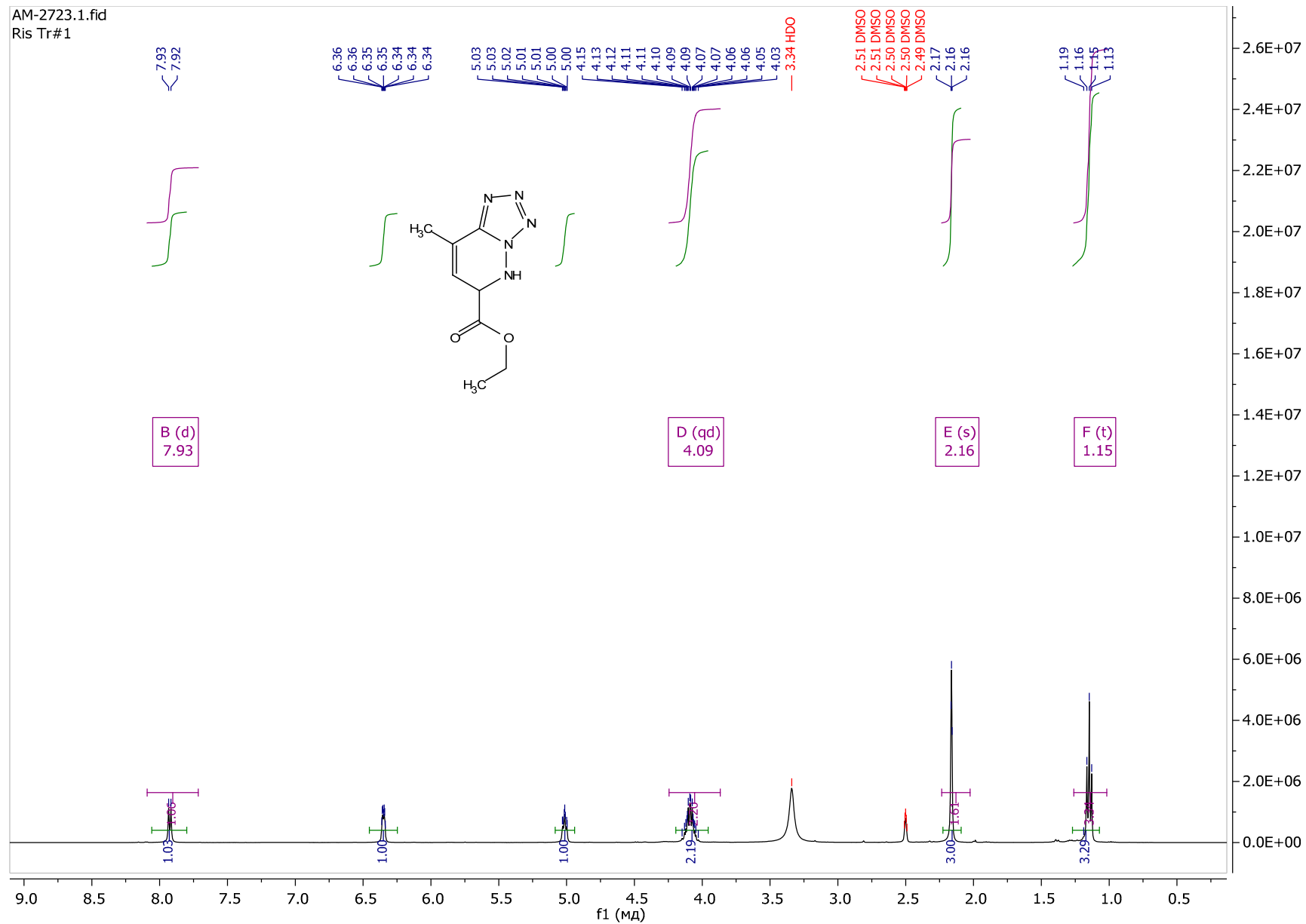
¹H NMR spectrum of ethyl 6-azido-5-methylpyridazine-3-carboxylate **20**



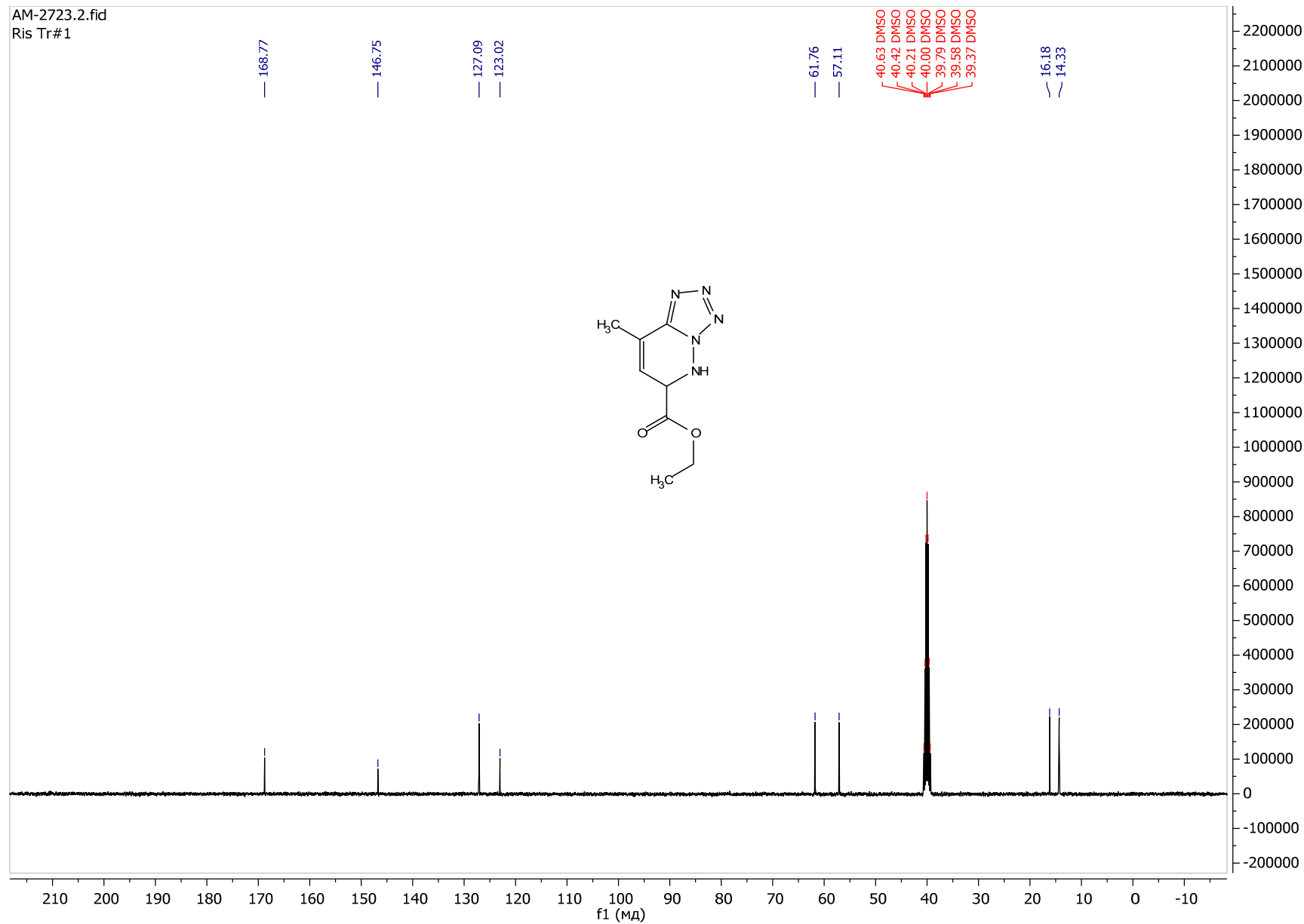
¹³C NMR spectrum of ethyl 6-azido-5-methylpyridazine-3-carboxylate **20**



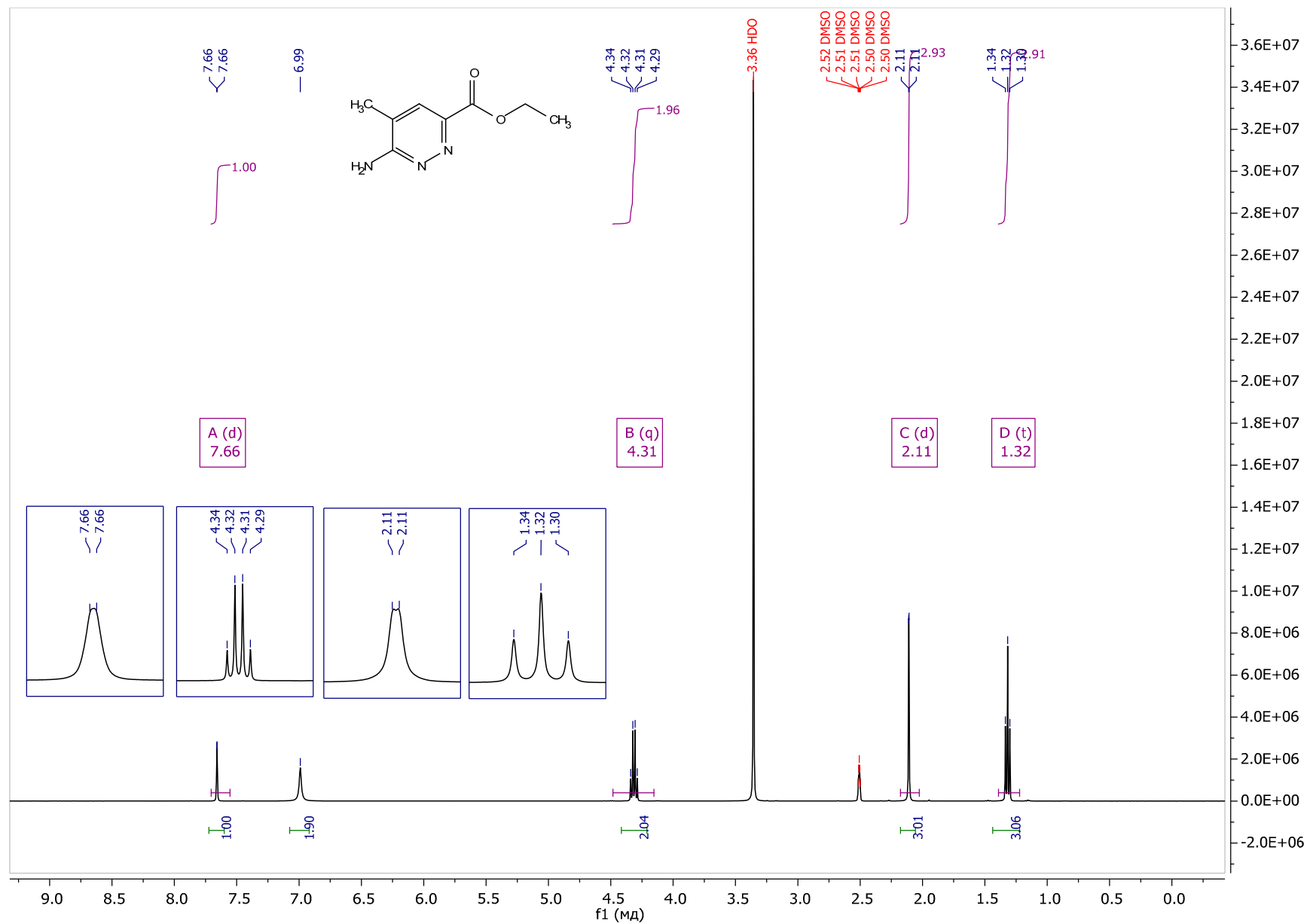
¹H NMR spectrum of ethyl 8-methyl-5,6-dihydrotetrazolo[1,5-b]pyridazine-6-carboxylate **20a**



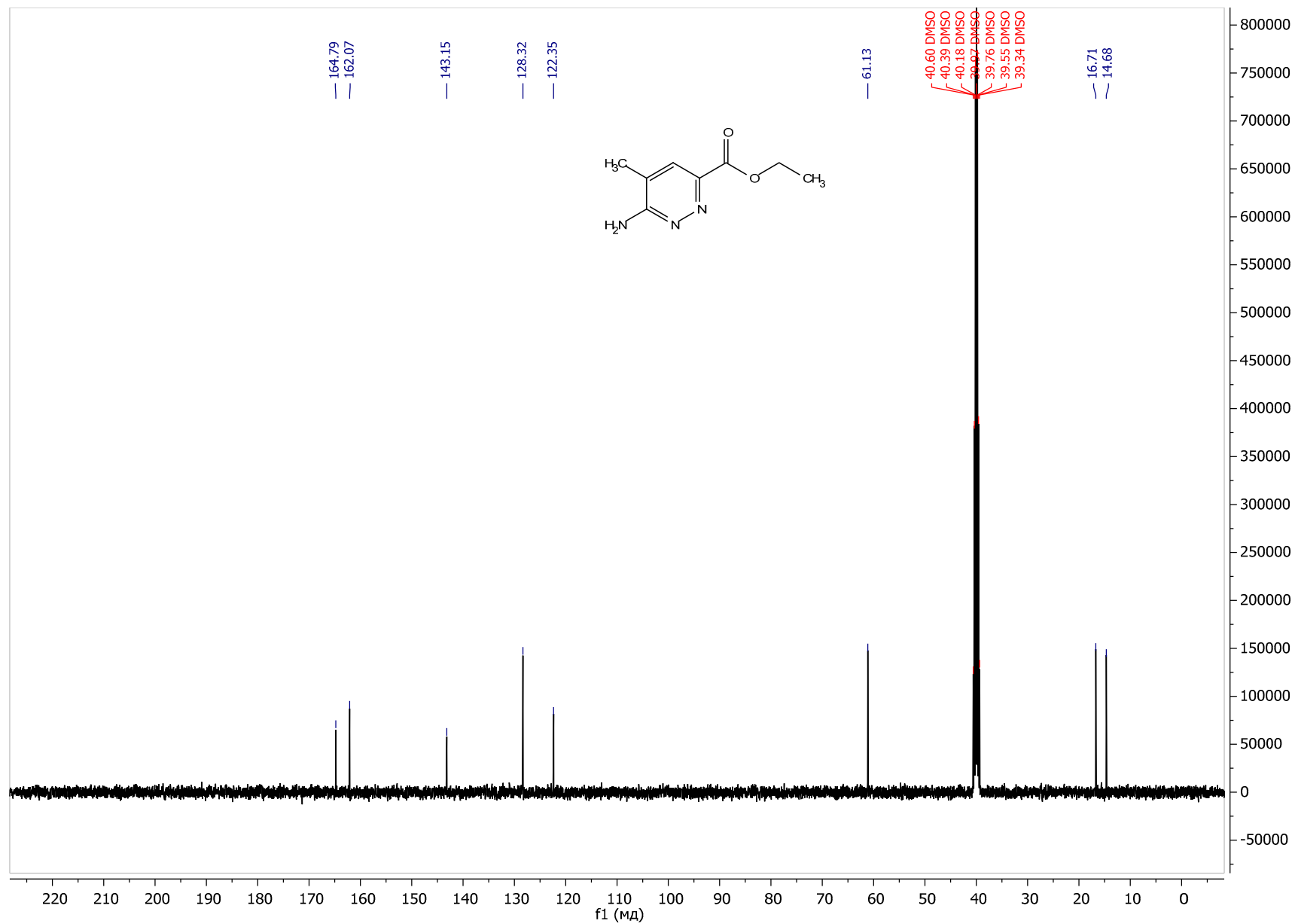
^{13}C NMR spectrum of ethyl 8-methyl-5,6-dihydro-1H-tetrazolo[1,5-b]pyridazine-6-carboxylate **20a**



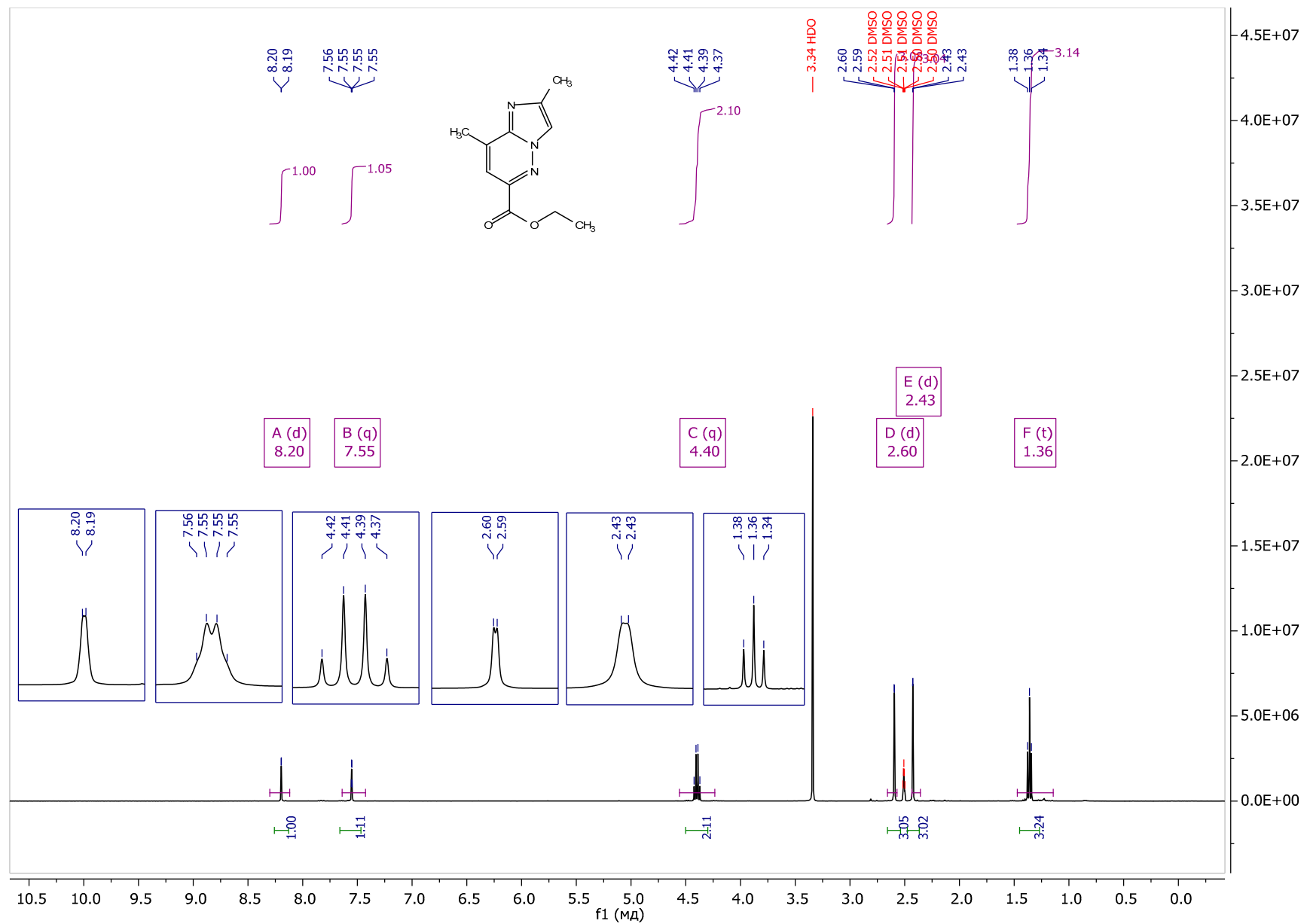
¹H NMR spectrum of ethyl 6-amino-5-methylpyridazine-3-carboxylate **21**



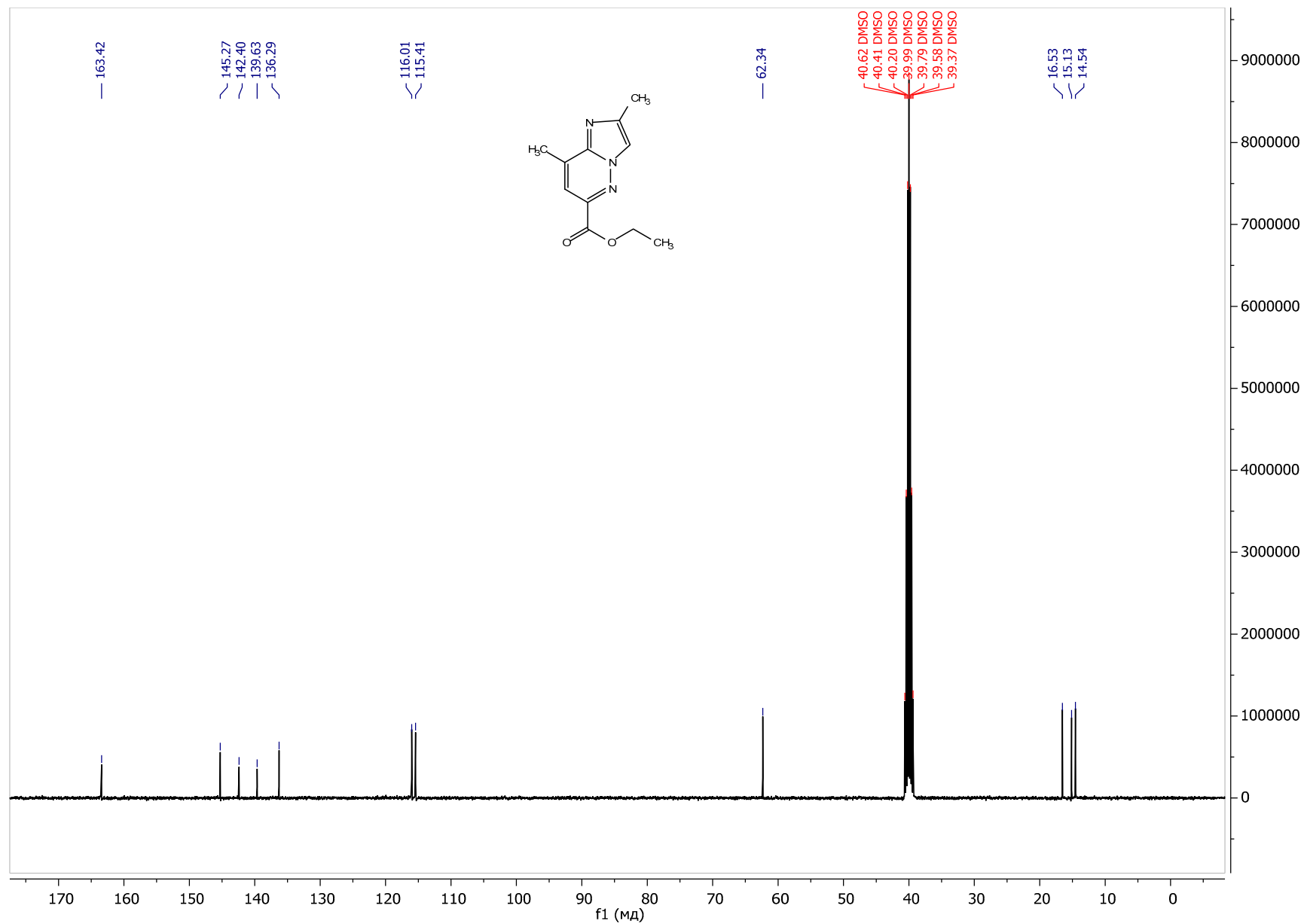
^{13}C NMR spectrum of ethyl 6-amino-5-methylpyridazine-3-carboxylate **21**



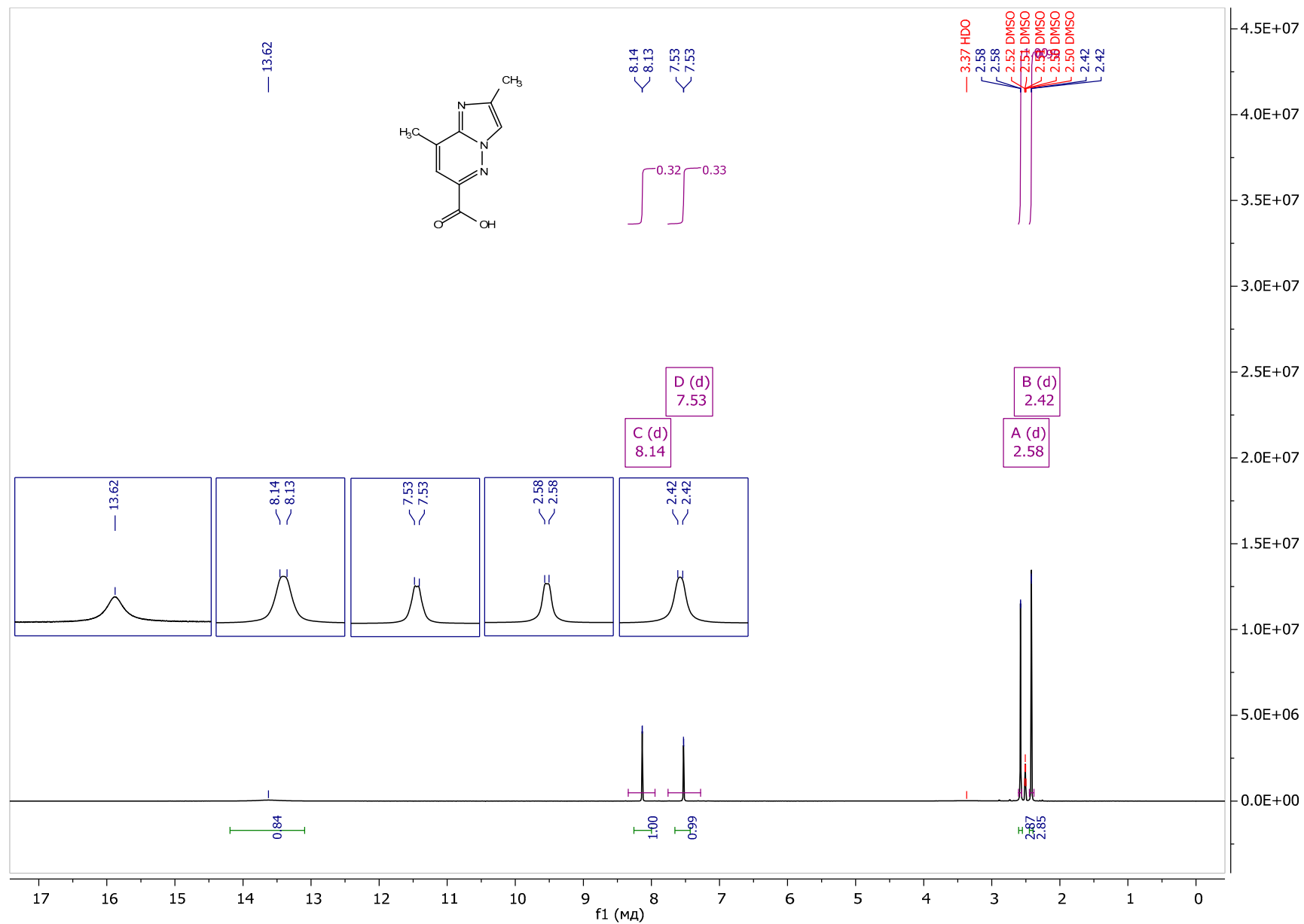
^1H NMR spectrum of ethyl 2,8-dimethylimidazo[1,2-*b*]pyridazine-6-carboxylate **22**



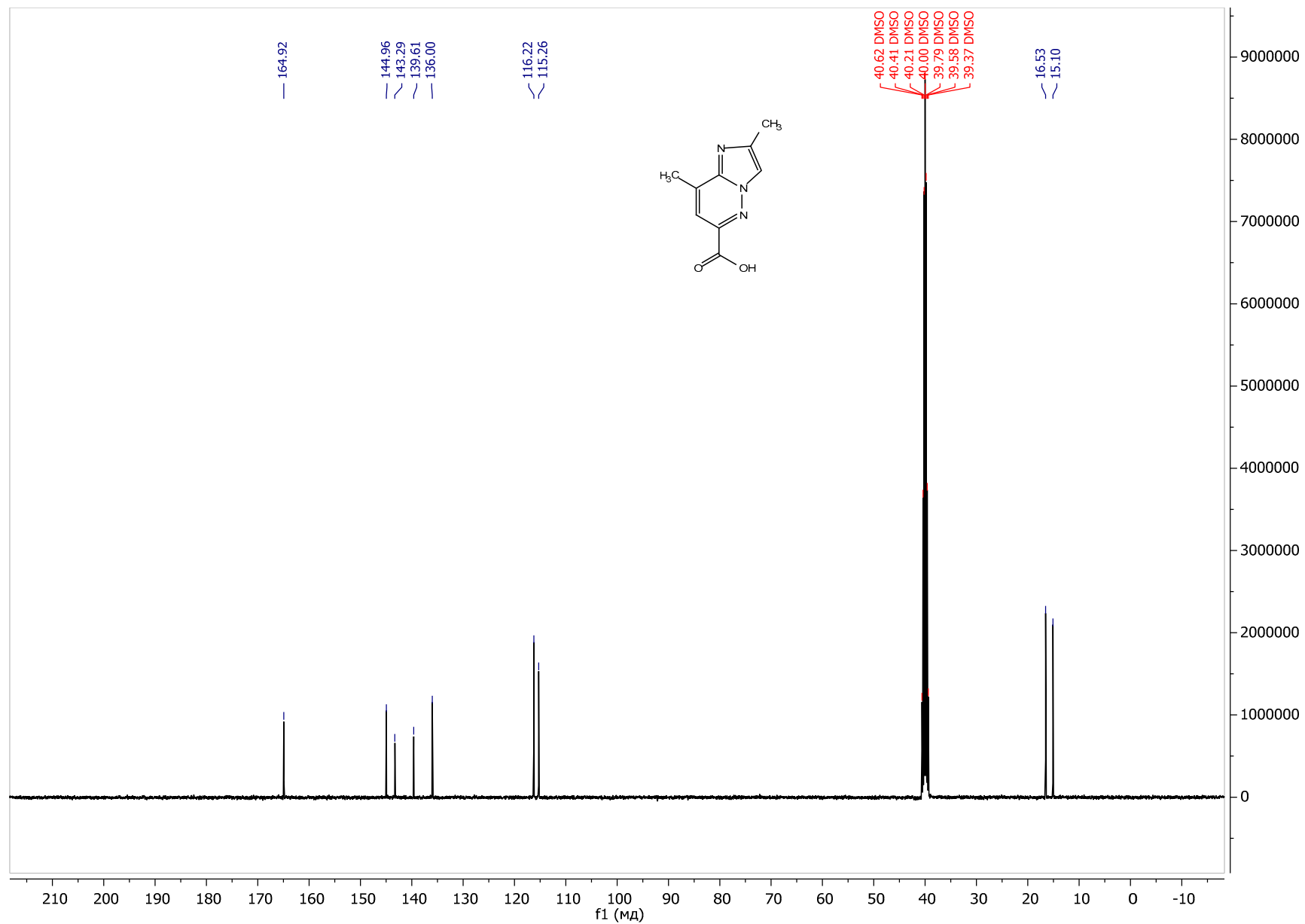
^{13}C NMR spectrum of ethyl 2,8-dimethylimidazo[1,2-b]pyridazine-6-carboxylate **22**



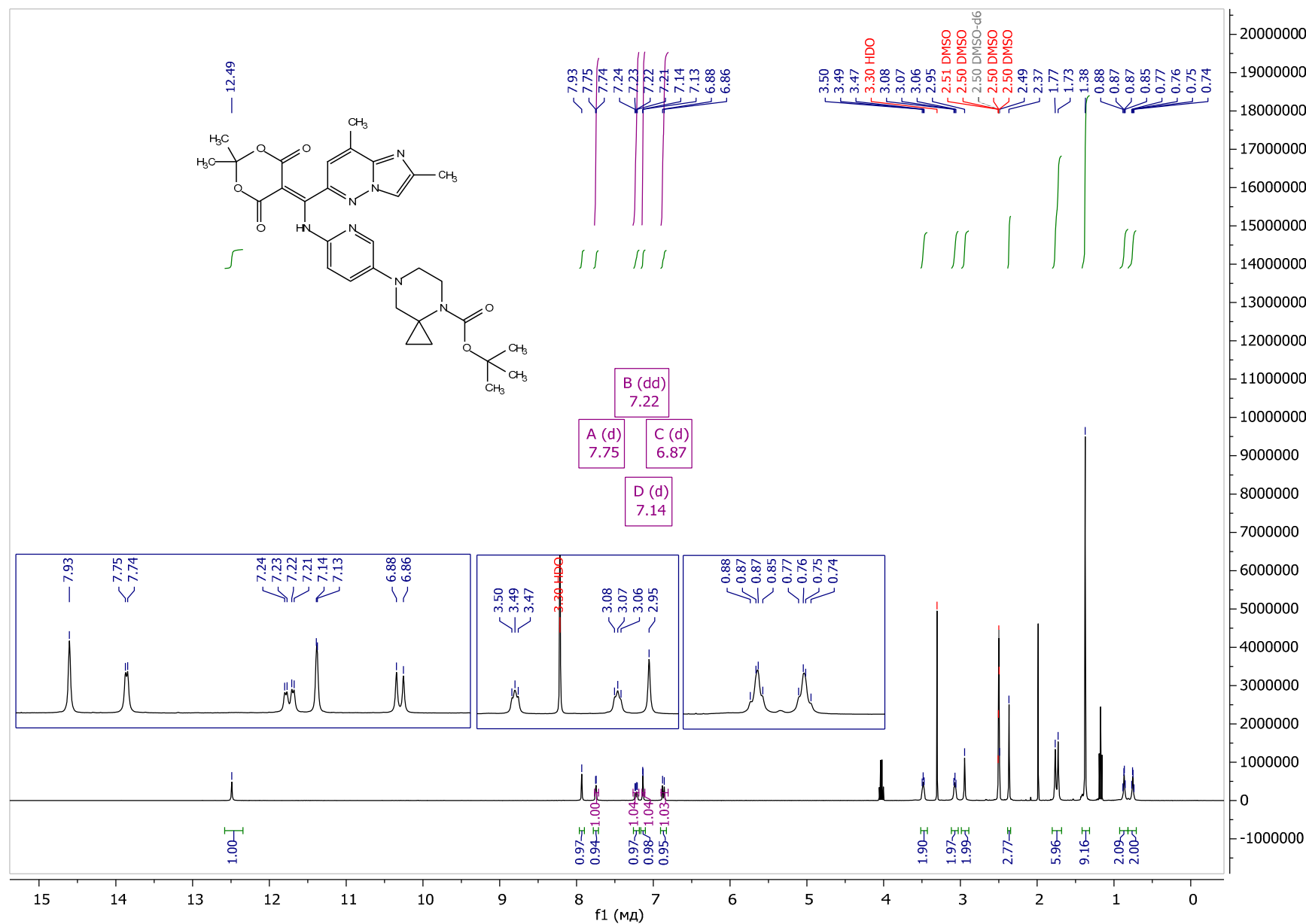
¹H NMR spectrum of 2,8-dimethylimidazo[1,2-b]pyridazine-6-carboxylic acid **13**



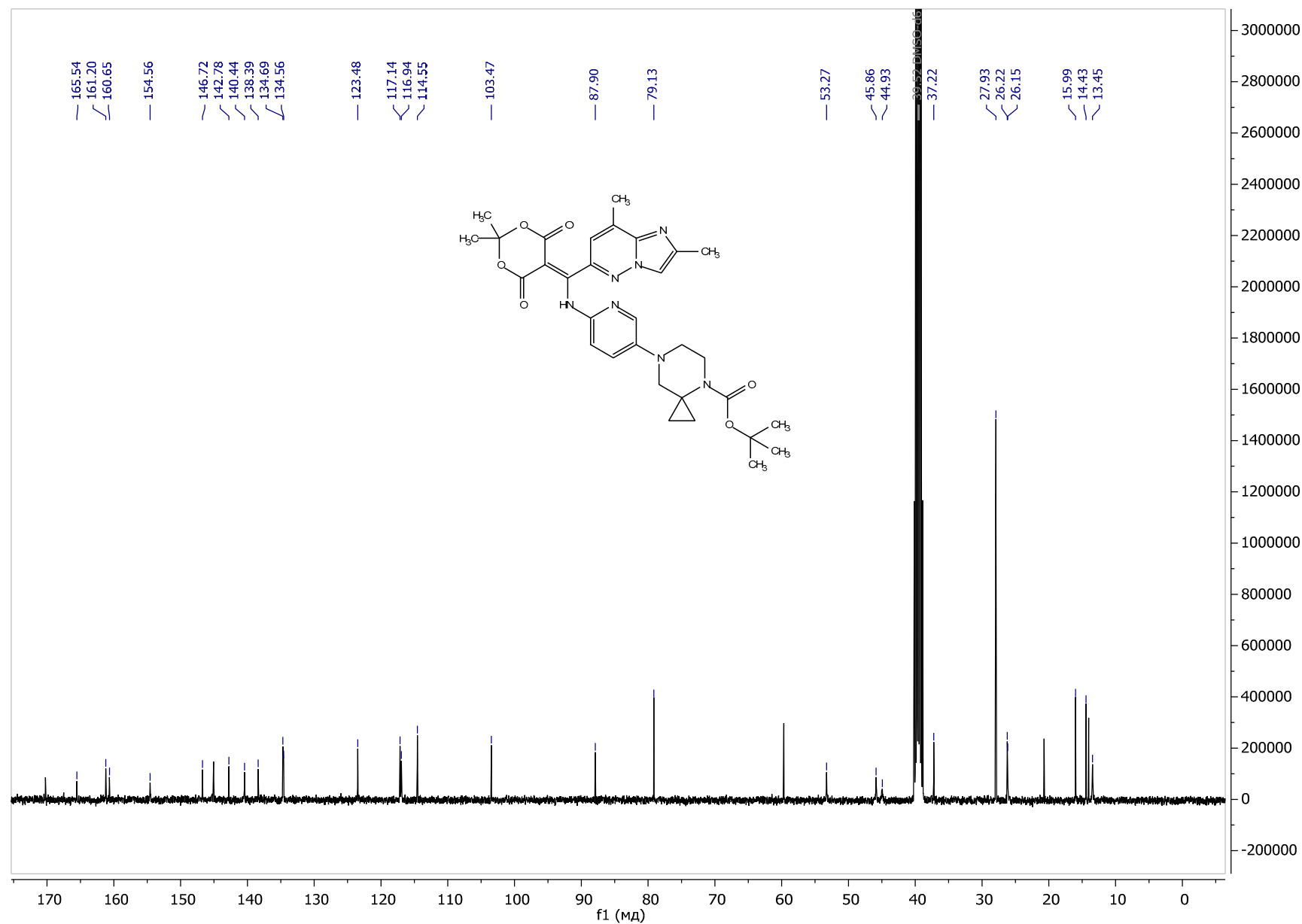
^{13}C NMR spectrum of 2,8-dimethylimidazo[1,2-b]pyridazine-6-carboxylic acid **13**



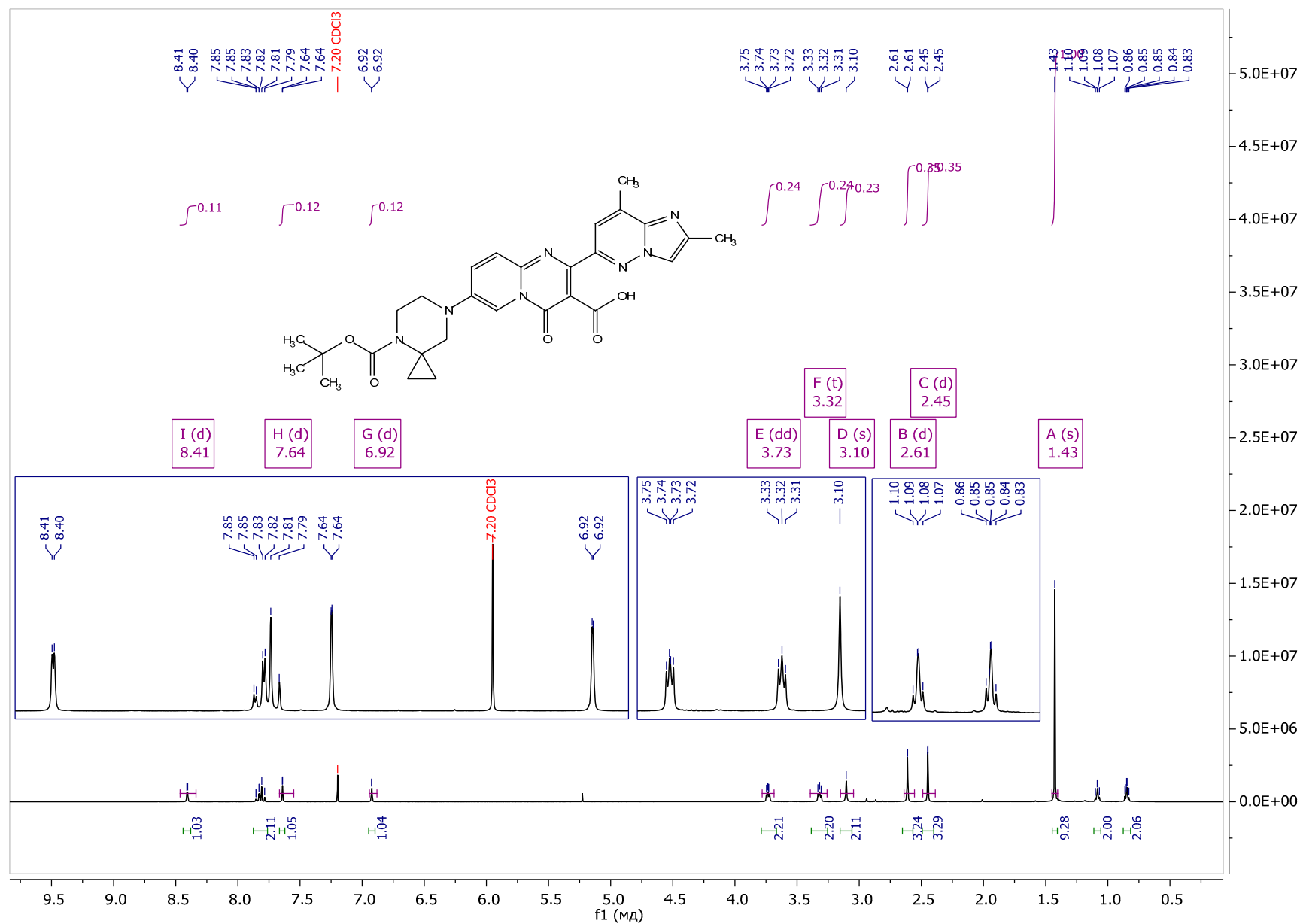
^1H NMR spectrum of *tert*-butyl 7-(((((2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-ylidene)(2,8-dimethylimidazo[1,2-*b*]pyridazin-6-yl)methyl)amino)pyridin-3-yl)-4,7-diazaspiro[2.5]octane-4-carboxylate **26**



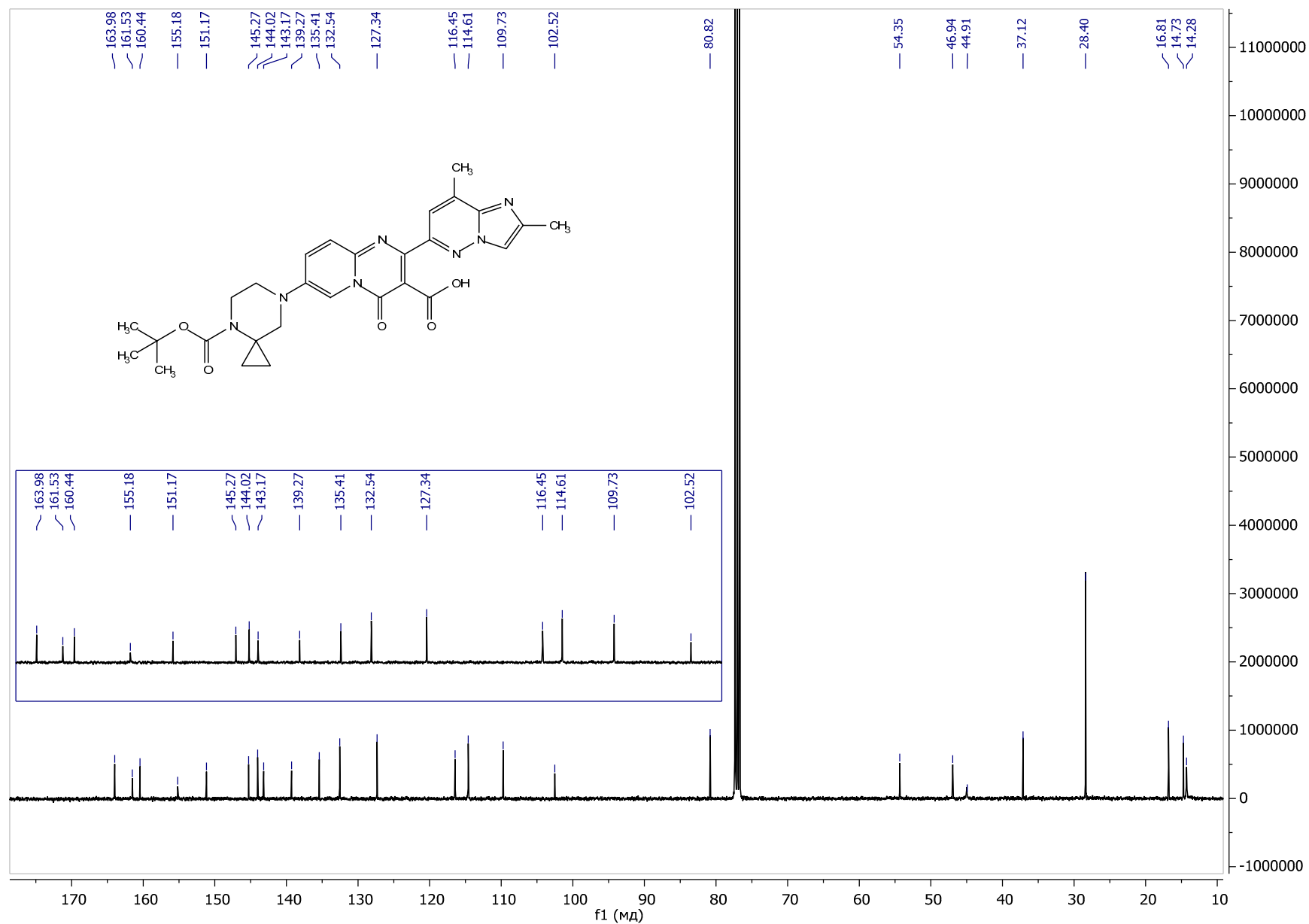
^{13}C NMR spectrum of *tert*-butyl 7-(6-(((2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-ylidene)(2,8-dimethylimidazo[1,2-*b*]pyridazin-6-yl)methyl)amino)pyridin-3-yl)-4,7-diazaspiro[2.5]octane-4-carboxylate **26**



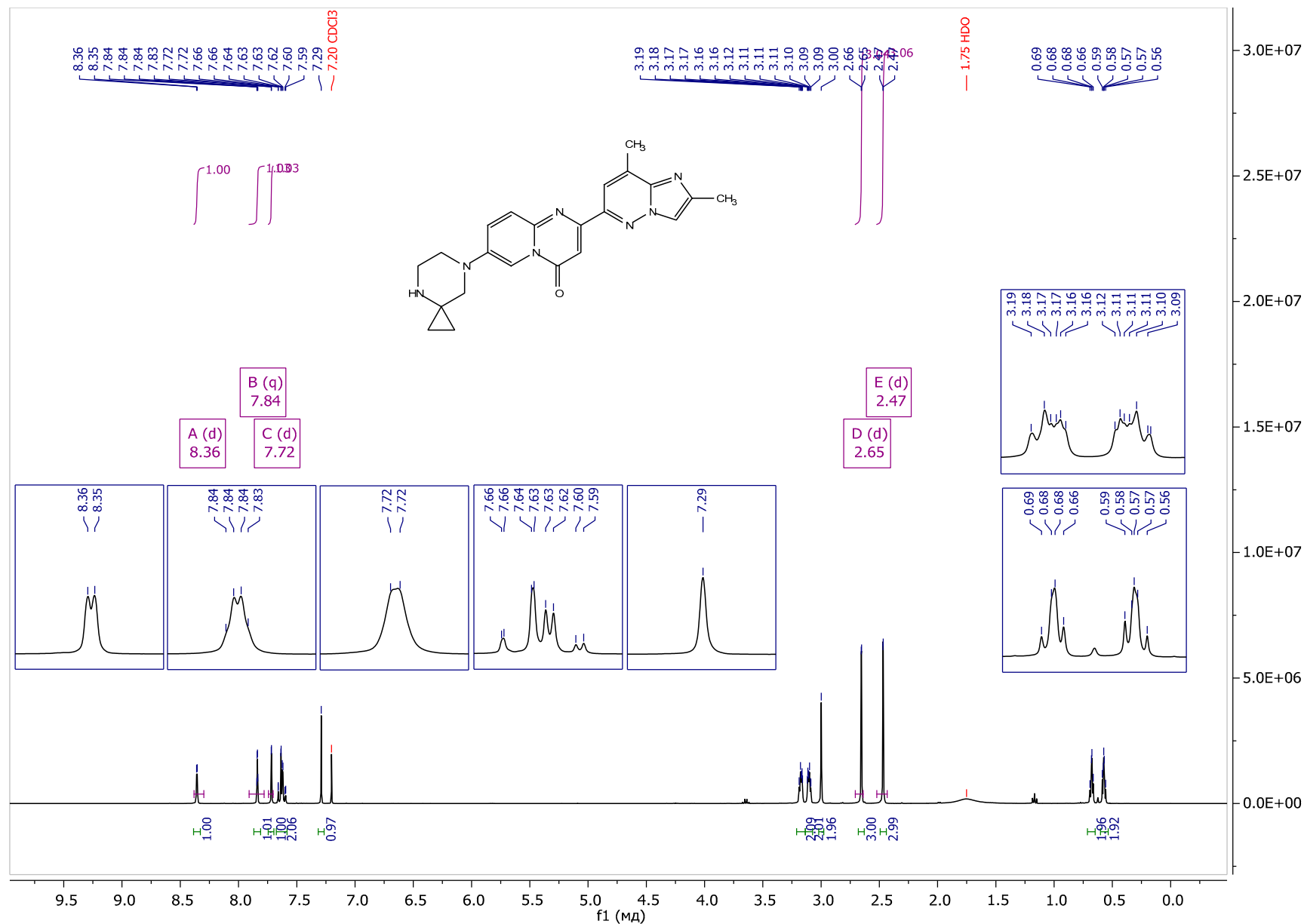
^1H NMR spectrum of 7-(4-(tert-butoxycarbonyl)-4,7-diazaspiro[2.5]octan-7-yl)-2-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-4-oxo-4H-pyrido[1,2-a]pyrimidine-3-carboxylic acid **27**



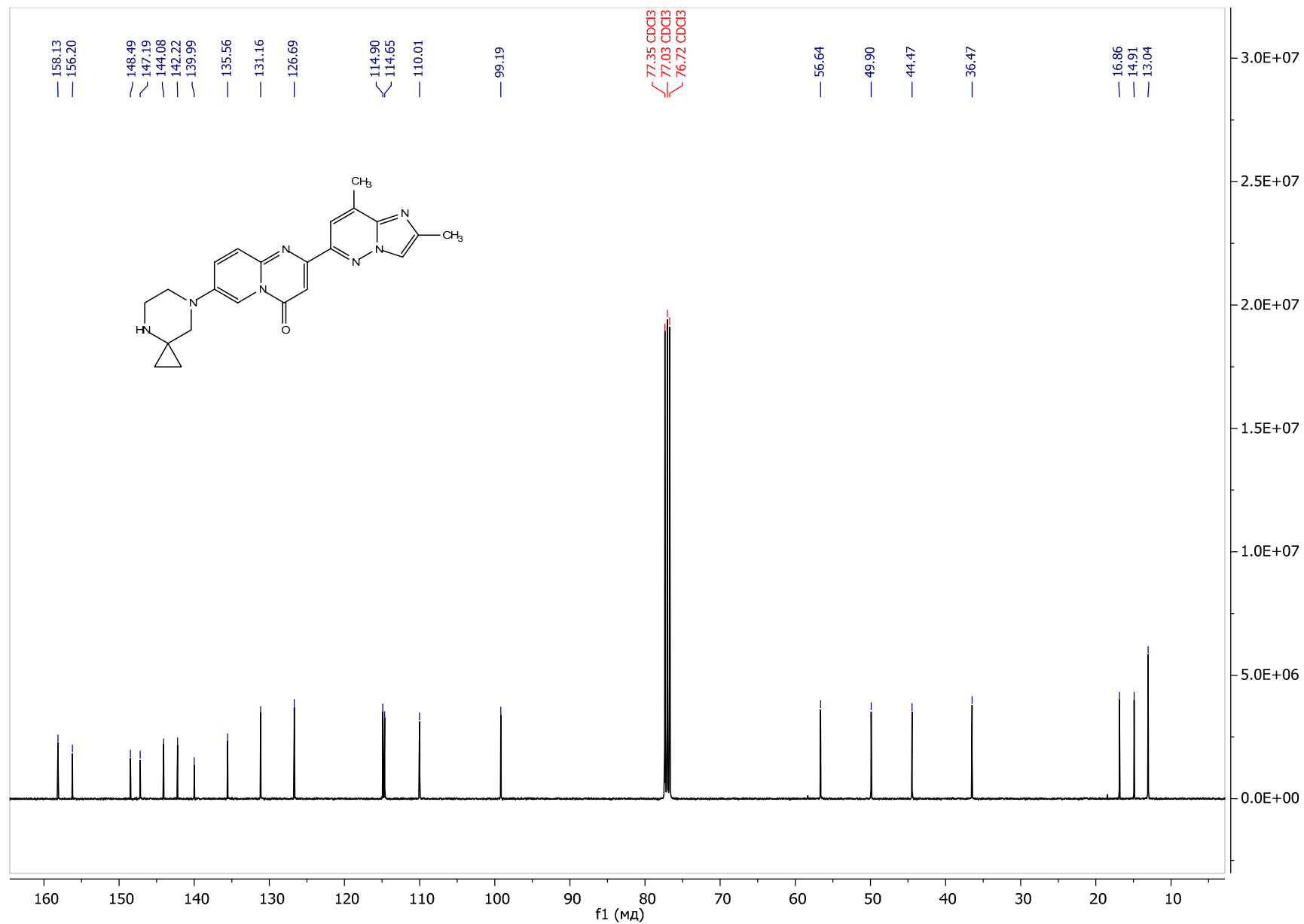
^{13}C NMR spectrum of 7-(4-(tert-butoxycarbonyl)-4,7-diazaspiro[2.5]octan-7-yl)-2-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-4-oxo-4H-pyrido[1,2-a]pyrimidine-3-carboxylic acid **27**



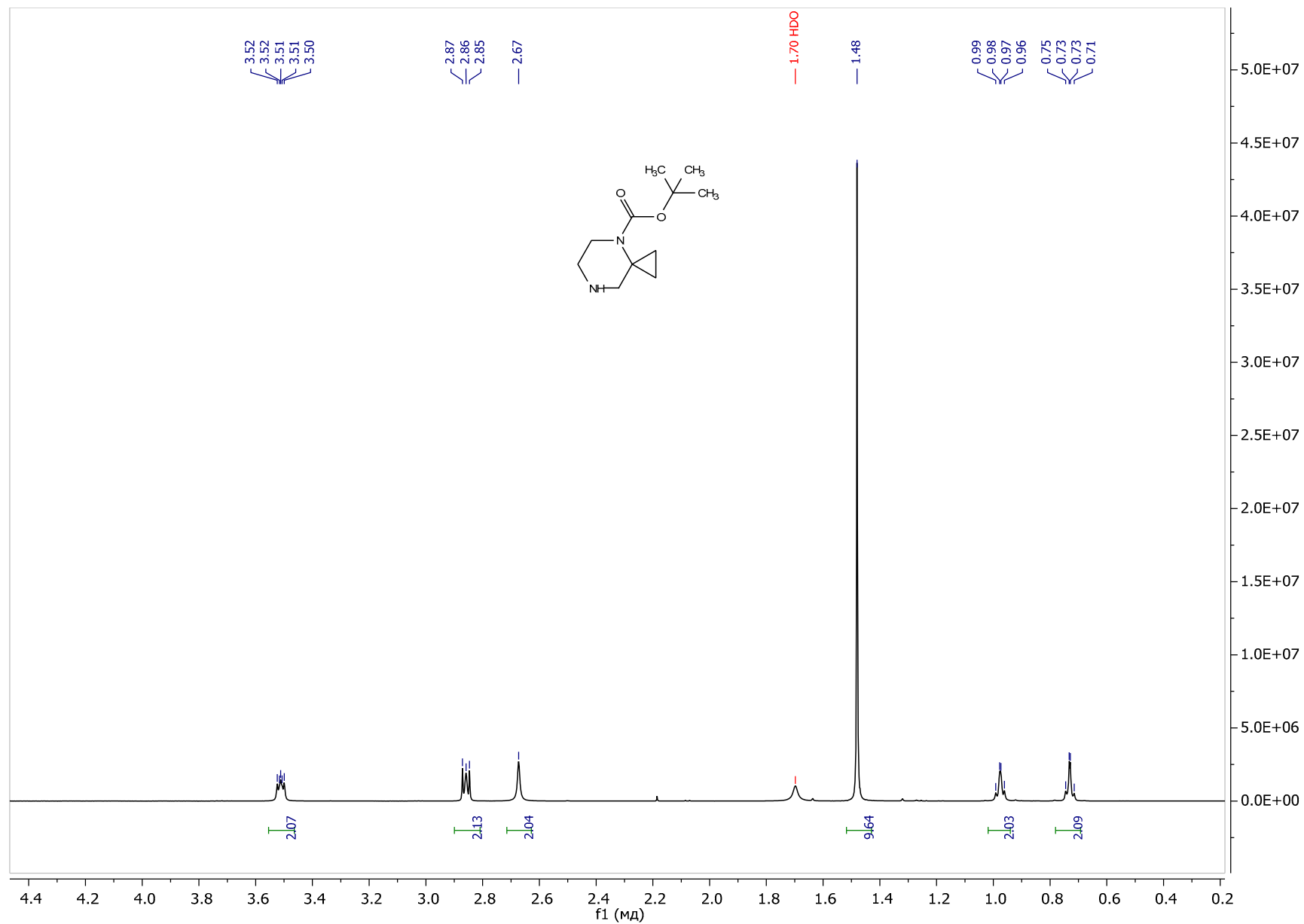
^1H NMR spectrum of 2-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-7-(4,7-diazaspiro[2.5]octan-7-yl)-4H-pyrido[1,2-a]pyrimidin-4-one (Risdiplam)



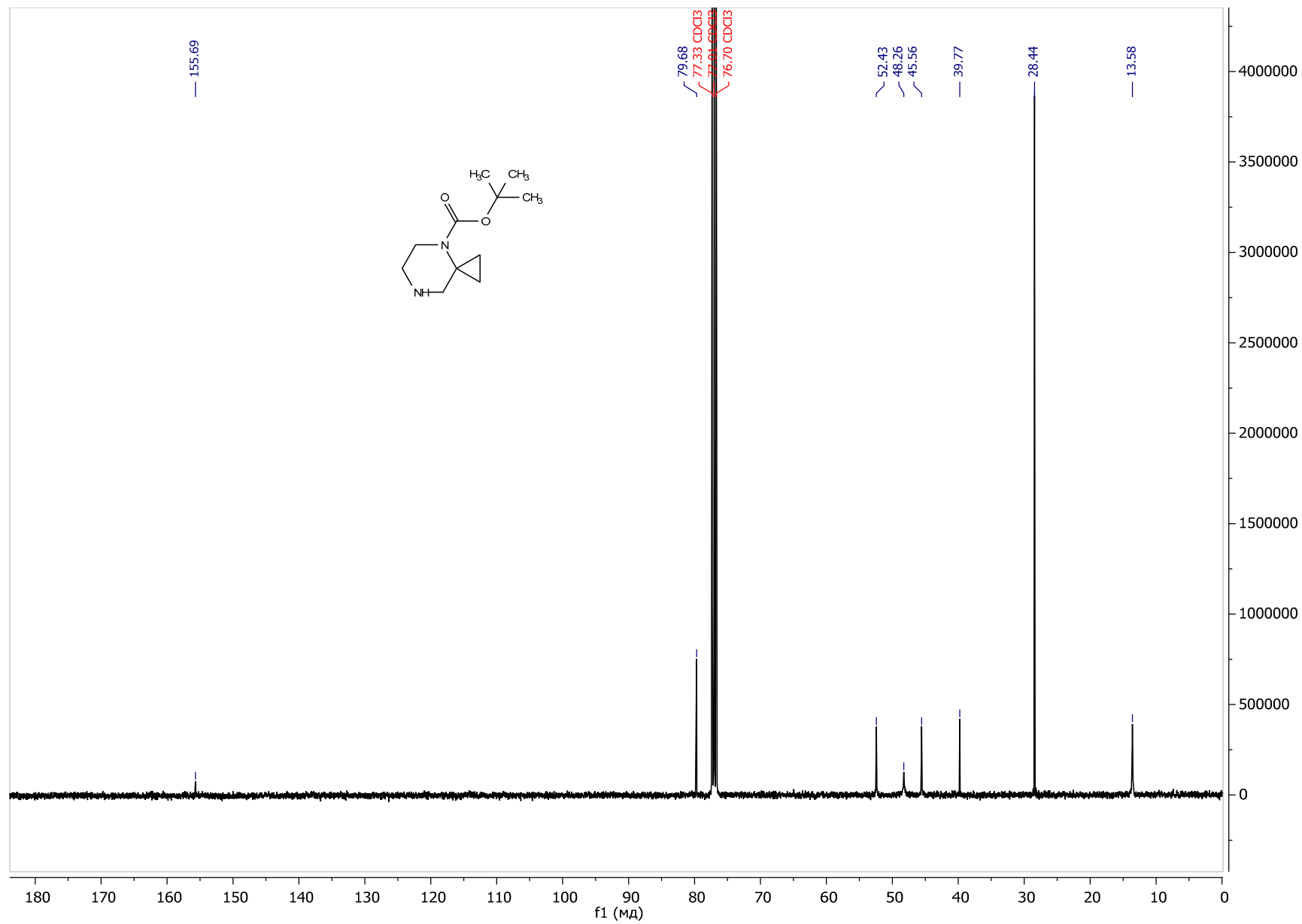
^{13}C NMR spectrum of 2-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-7-(4,7-diazaspiro[2.5]octan-7-yl)-4H-pyrido[1,2-a]pyrimidin-4-one (Risdiplam)



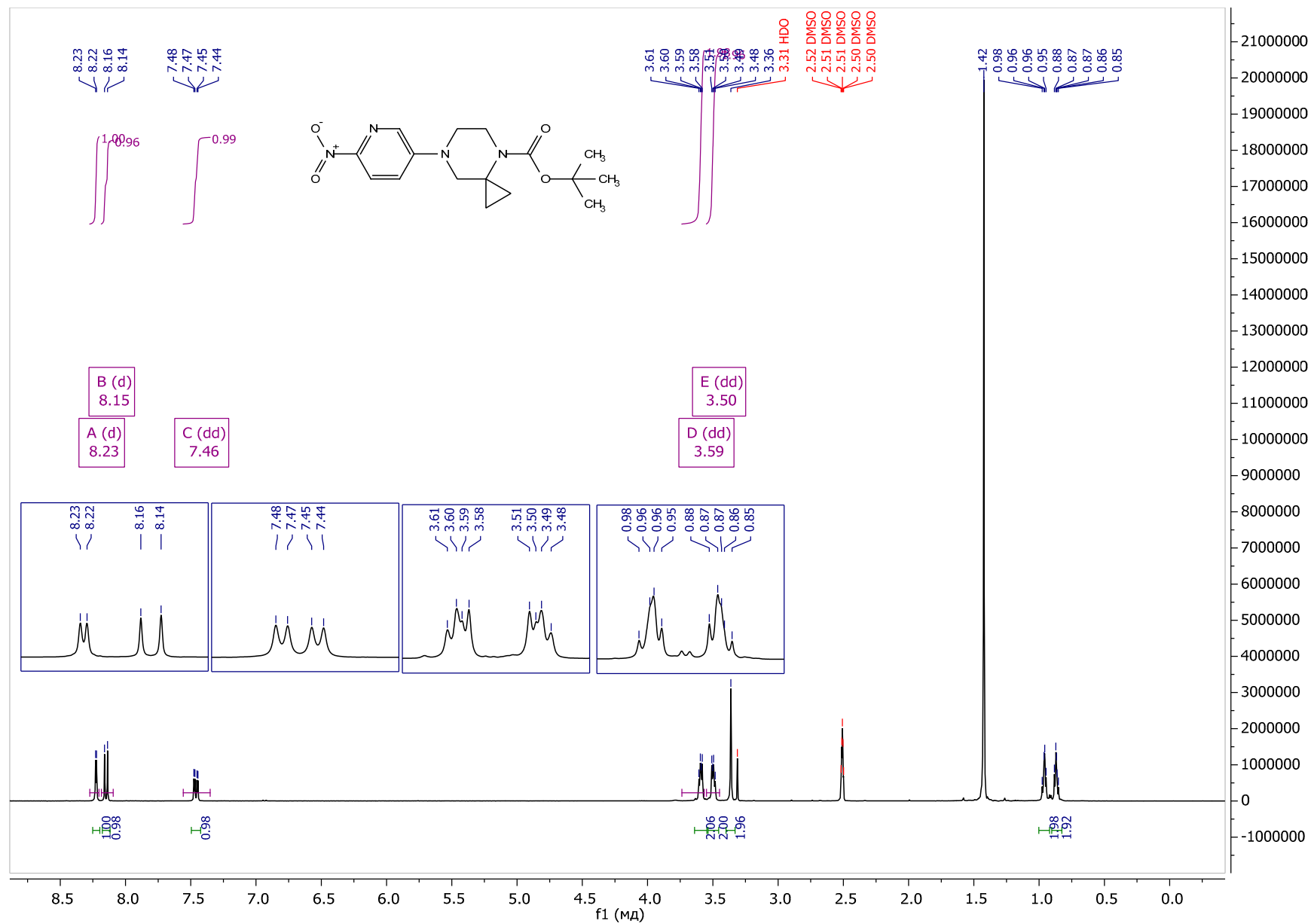
*¹H NMR spectrum of tert-butyl 4,7-diazaspiro[2.5]octane-4-carboxylate **30***



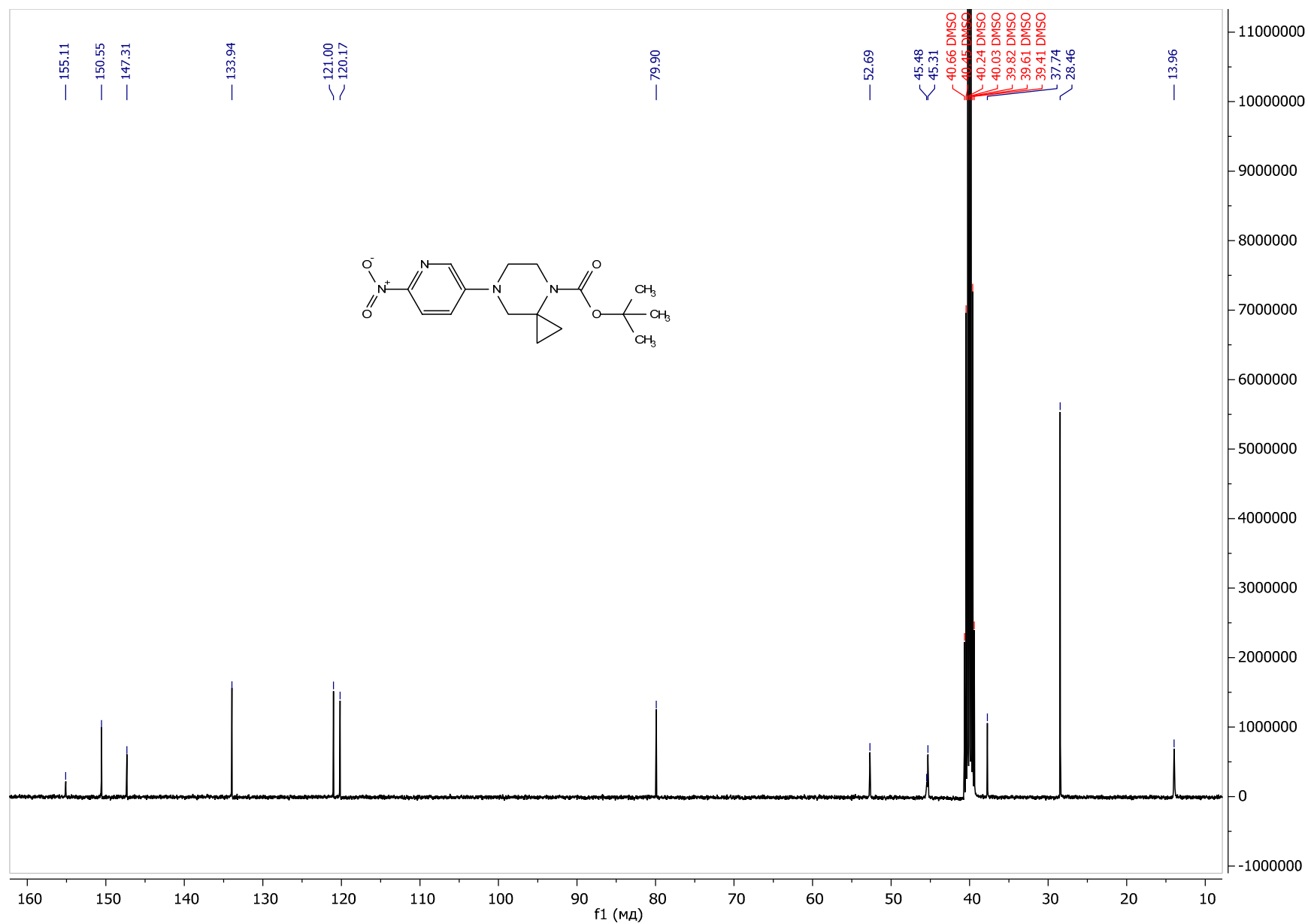
^{13}C NMR spectrum of *tert*-butyl 4,7-diazaspiro[2.5]octane-4-carboxylate **30**



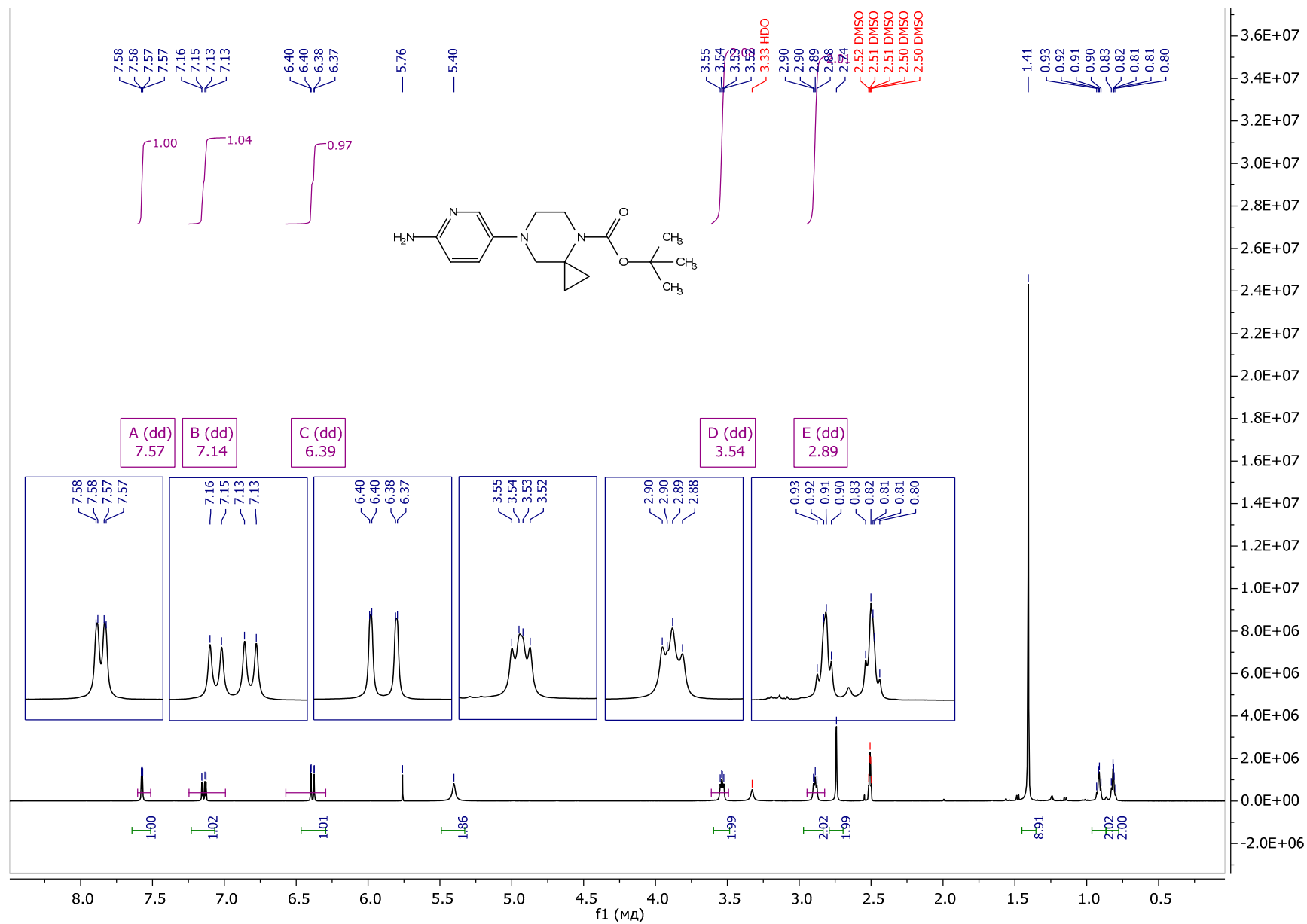
¹H NMR spectrum of tert-butyl 7-(6-nitropyridin-3-yl)-4,7-diazaspiro[2.5]octane-4-carboxylate **31**



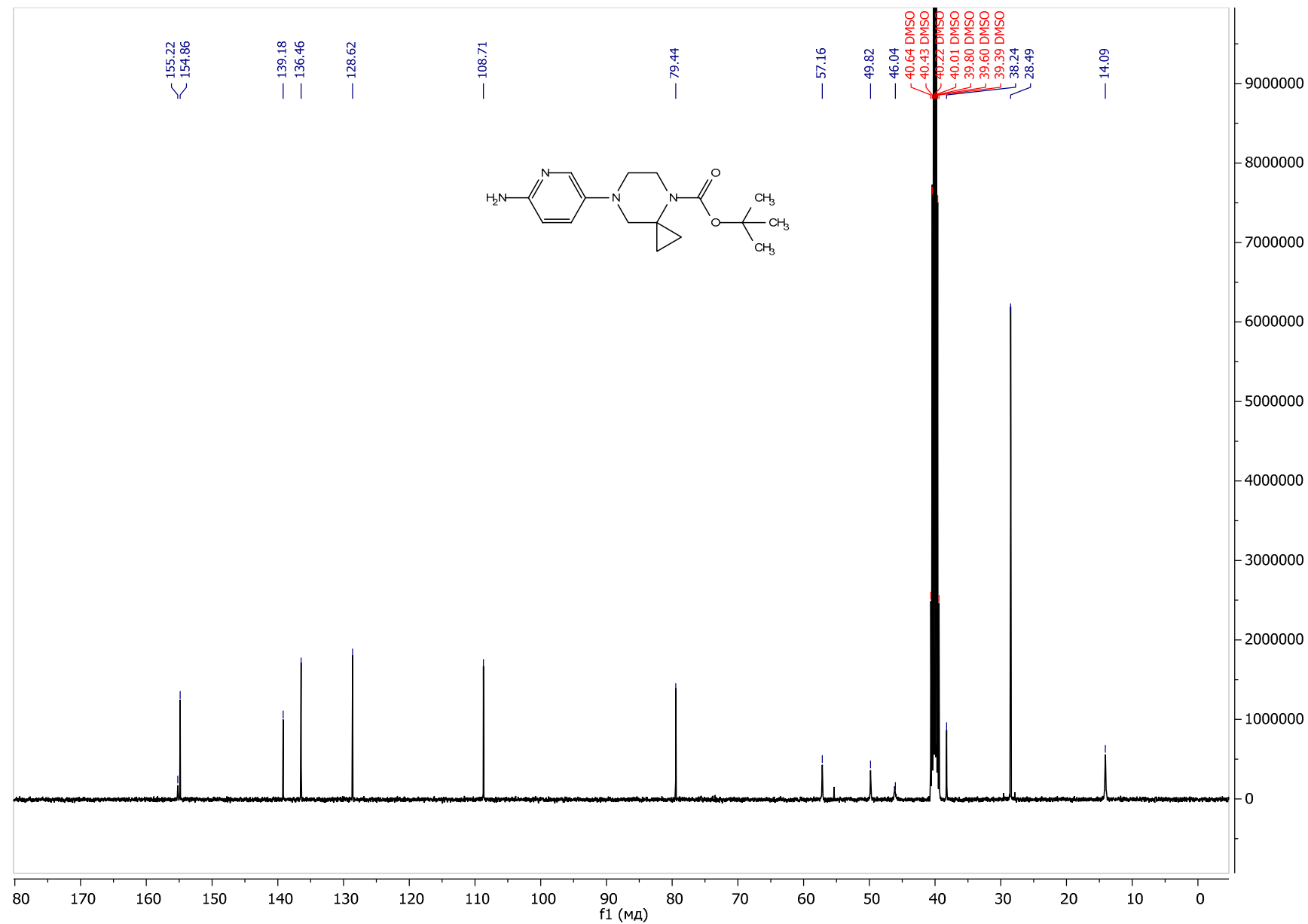
^{13}C NMR spectrum of *tert*-butyl 7-(6-nitropyridin-3-yl)-4,7-diazaspiro[2.5]octane-4-carboxylate **31**



¹H NMR spectrum of *tert*-butyl 7-(6-aminopyridin-3-yl)-4,7-diazaspiro[2.5]octane-4-carboxylate **28**



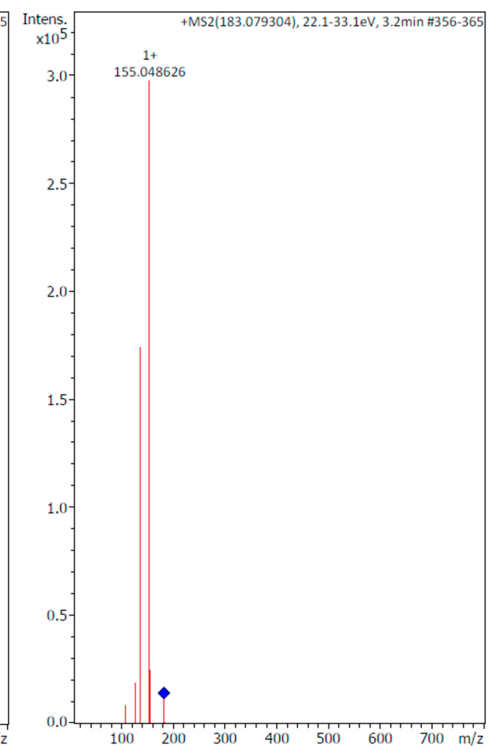
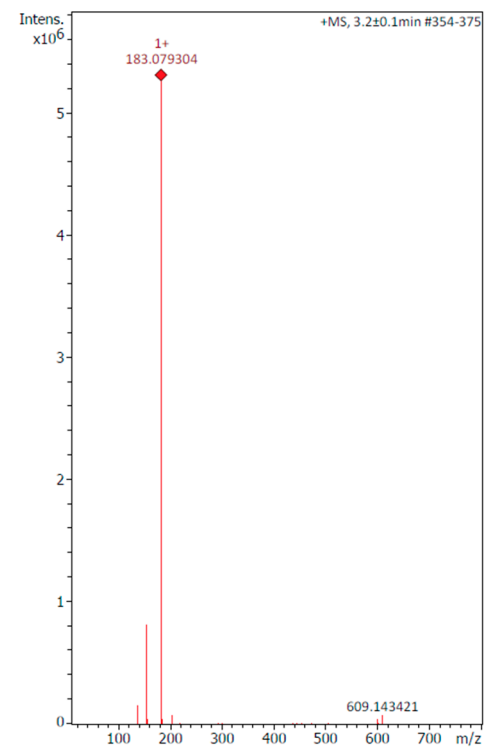
¹³C NMR spectrum of tert-butyl 7-(6-aminopyridin-3-yl)-4,7-diazaspiro[2.5]octane-4-carboxylate **28**



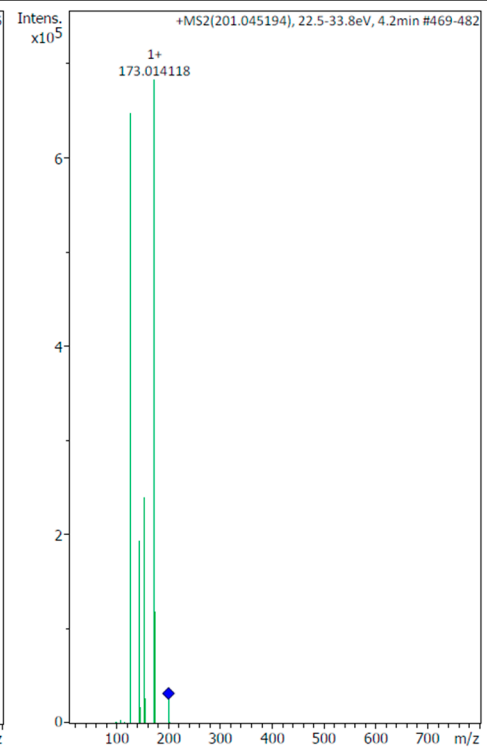
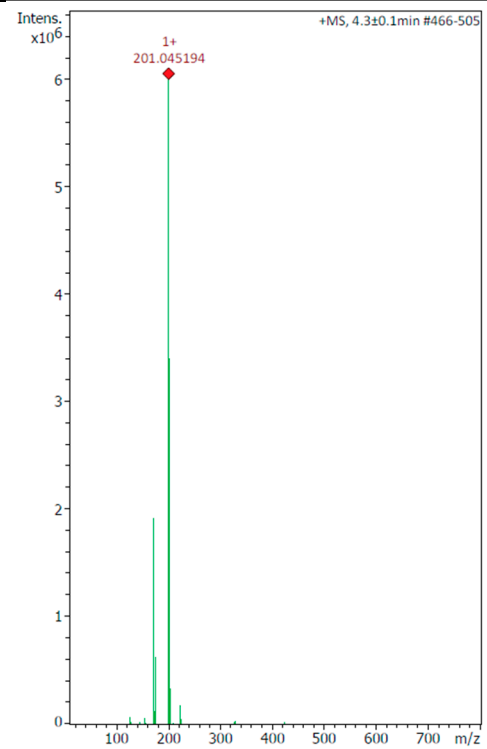
Copies of HRMS spectra

Compound	Structure	HRMS spectra (MS and MS2, correspondingly)
13		Intens. x10⁶ -MS, 1.1min #123-133 1- 146.071531 1- 190.060875 1- 489.063486 1- 626.119244 m/z Intens. x10⁴ -MS2(190.060875), 17.3-25.9eV, 1.1min #128 1- 146.071420 m/z
17		Intens. x10⁵ AM_2150_SM_AT_NEG_2-17-2024_GD6_1_5045.d: -MS, 1.6min #175 109.0415 153.0304 368.9949 495.1456 514.0167 Intens. x10⁴ AM_2150_SM_AT_NEG_2-17-2024_GD6_1_5045.d: -MS2(153.0304), 16.3-24.5eV, 1.6min #176 109.0413

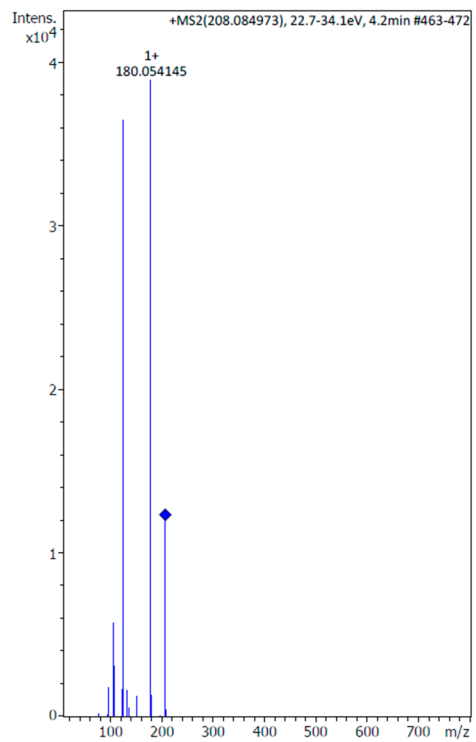
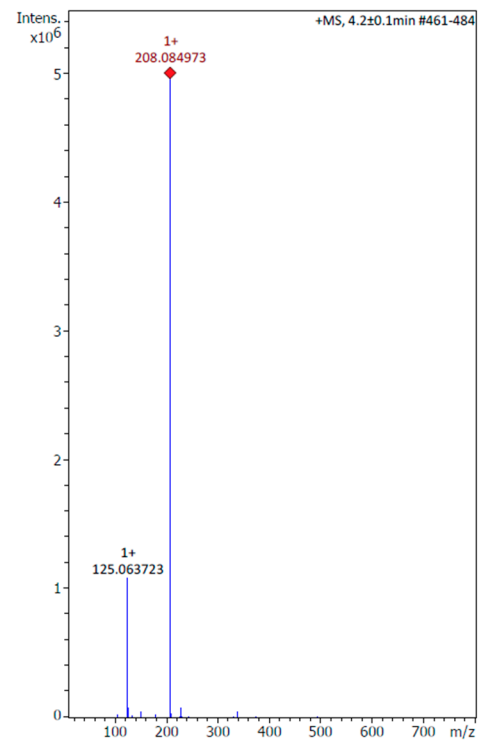
18



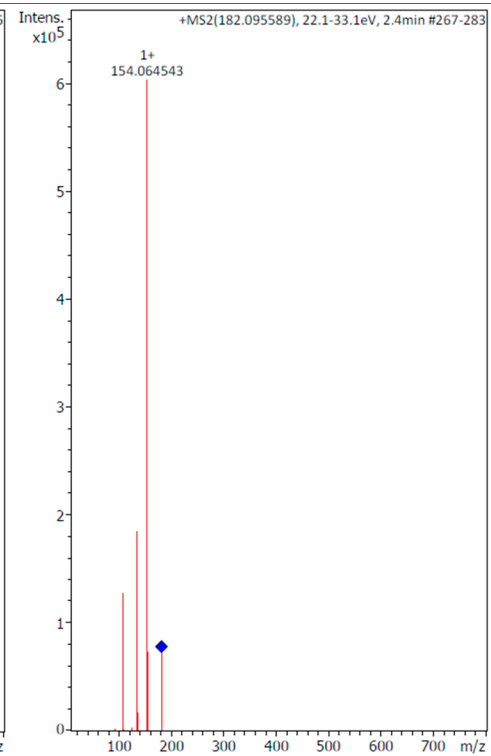
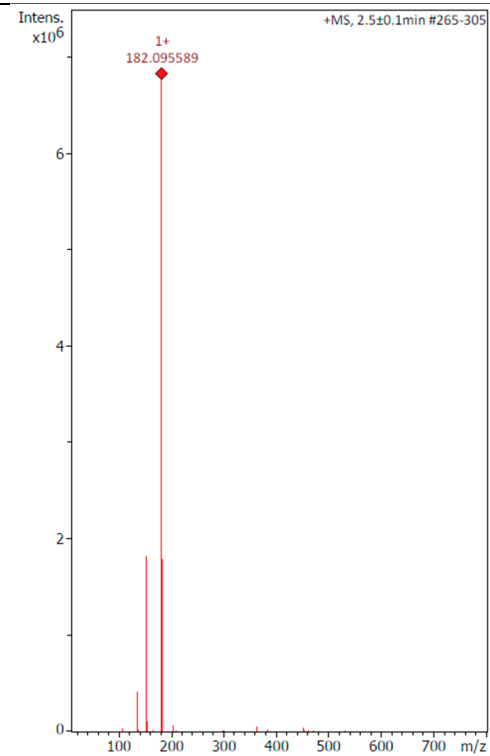
19



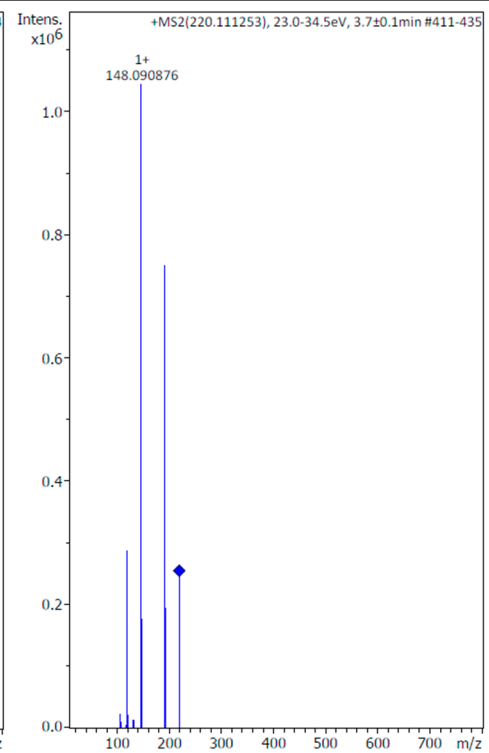
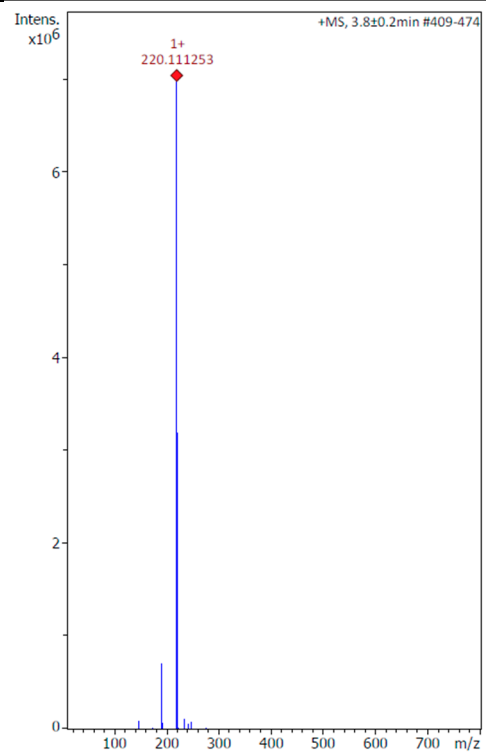
20



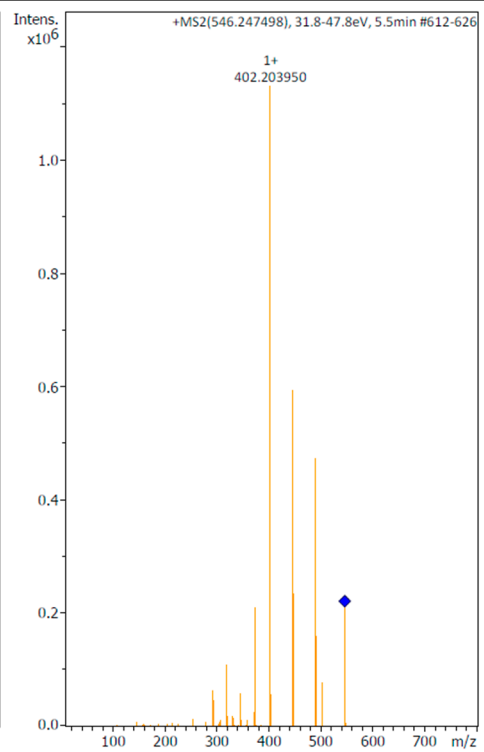
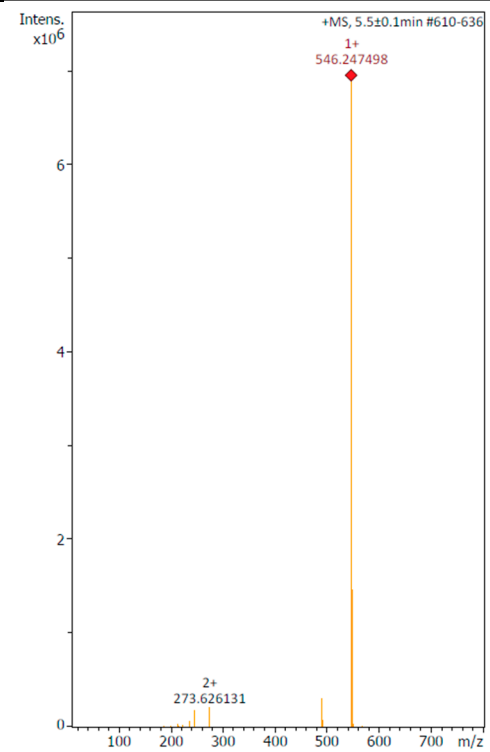
21



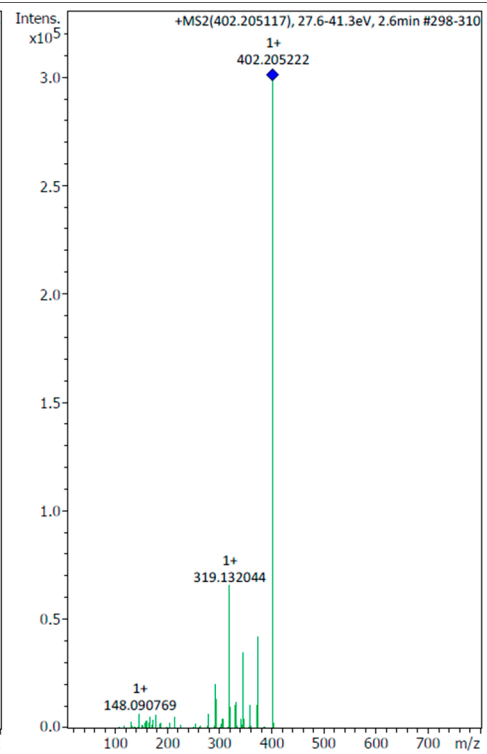
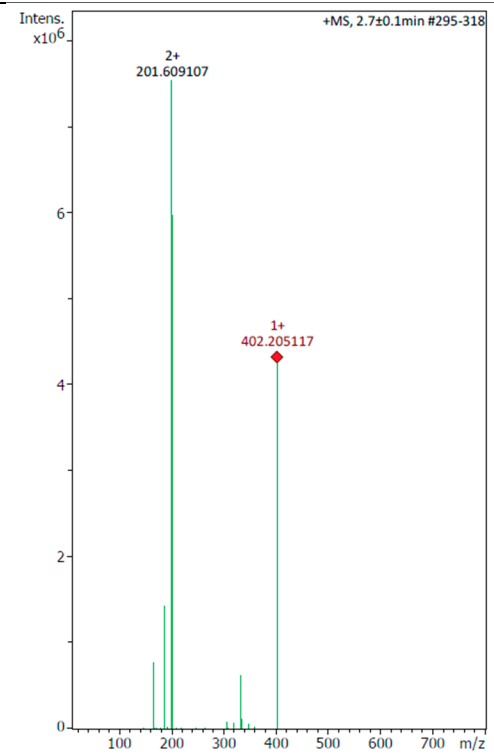
22



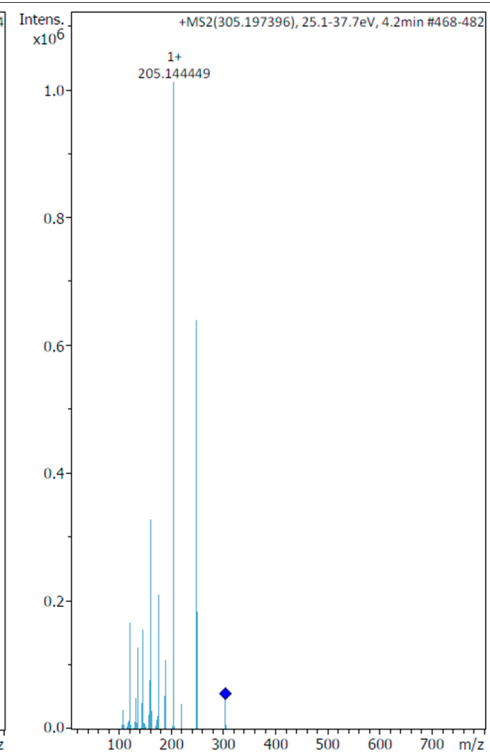
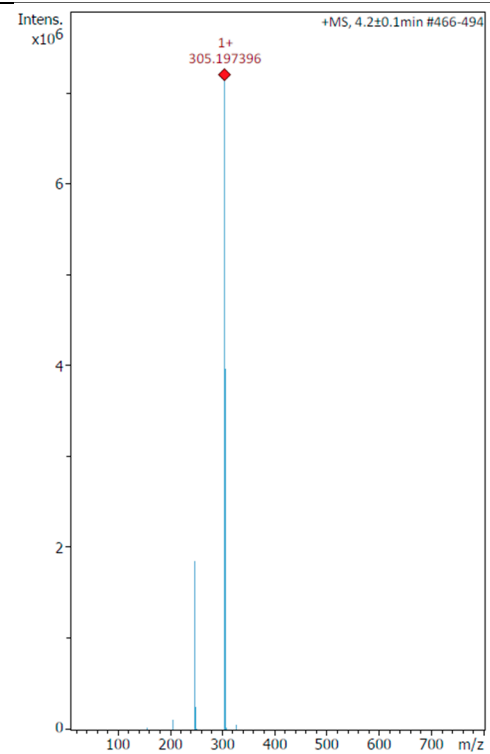
27



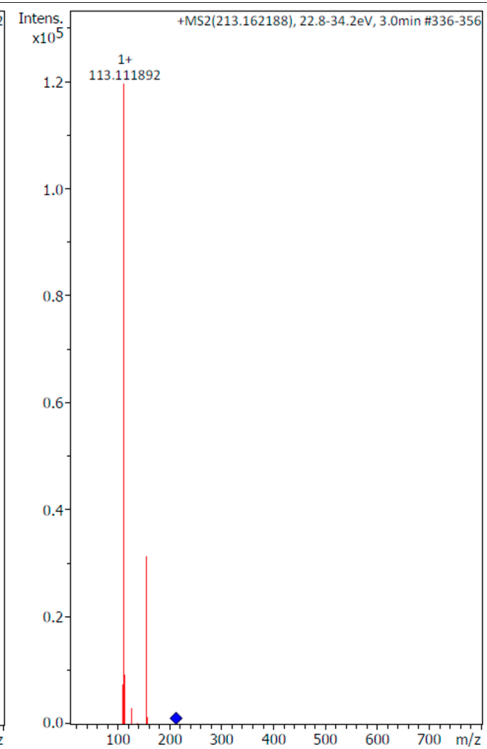
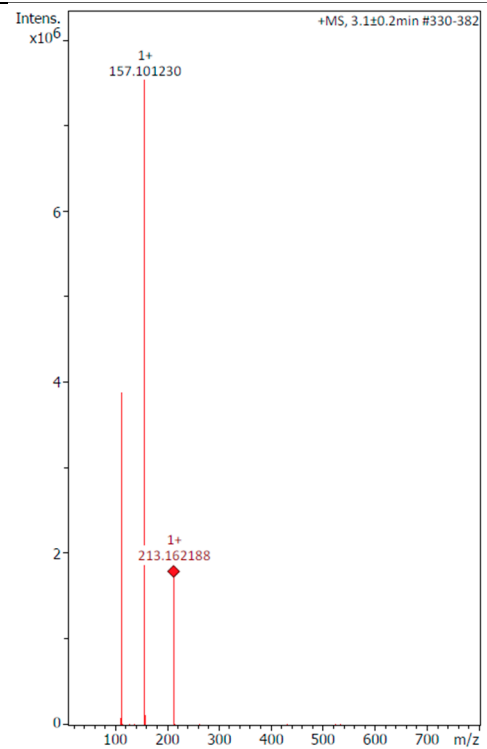
Risdiplam



28



30



31

