Supporting information

Discovery of tert-butyl ester-based DON prodrugs for enhanced metabolic stability and tumor delivery

Authors: Kateřina Novotná[°1,8,9], Lukáš Tenora[°1,8], Eva Prchalová[1,8], James Paule[1], Jesse Alt[1], Vijay Veeravalli[1], Jenny Lam[1], Ying Wu[1], Ivan Šnajdr[8], Sadakatali Gori[1], Vijaya Saradhi Mettu[1], Takashi Tsukamoto[1], Pavel Majer[8*], Barbara S. Slusher[1,2,3,4,5,6.7*] and Rana Rais[1,2,4*]

[1]Johns Hopkins Drug Discovery, Departments of [2]Neurology, [3]Psychiatry and Behavioral Sciences, [4]Pharmacology and Molecular Sciences, [5]Neuroscience, [6]Medicine, [7]Oncology, Johns Hopkins School of Medicine, Baltimore, Maryland 21205, U.S.A.

[8]Institute of Organic Chemistry and Biochemistry, Academy of Sciences of the Czech Republic v.v.i., Prague, 16600, Czech Republic

[9]Department of Organic Chemistry, Charles University, Faculty of Science, Prague, 12800, Czech Republic

°*these authors have equally contributed to this manuscript*

Address Correspondence to:

*Rana Rais, PhD, Johns Hopkins Drug Discovery, 855 North Wolfe Street, Baltimore, Maryland, USA 21205, Phone: 410-502-0497, Fax: 410-614-0659, E-mail: rrais2@jhmi.edu

*Barbara S. Slusher, PhD, Johns Hopkins Drug Discovery, 855 North Wolfe Street, Baltimore, Maryland, USA 21205, Phone: 410-960-6162, Fax: 410-614-0659, E-mail: bslusher@jhmi.edu

*Pavel Majer, CSc, Institute of Organic Chemistry and Biochemistry, Academy of Sciences of the Czech Republic vvi, Flemingovo nam. 2, 166 10 Prague, Czech Republic, Phone: +420-220-183-125, E-mail: majer@uochb.cas.cz

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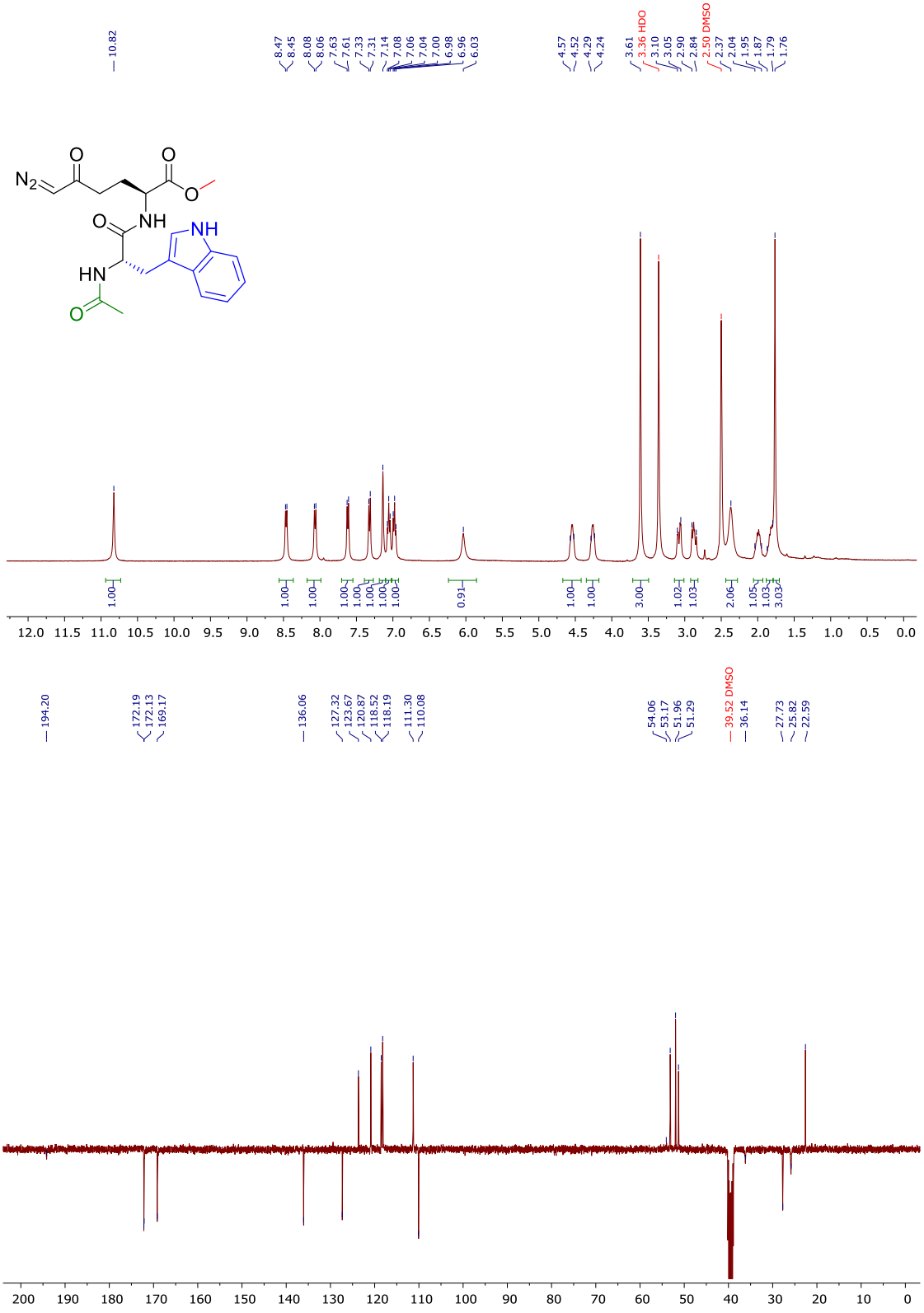
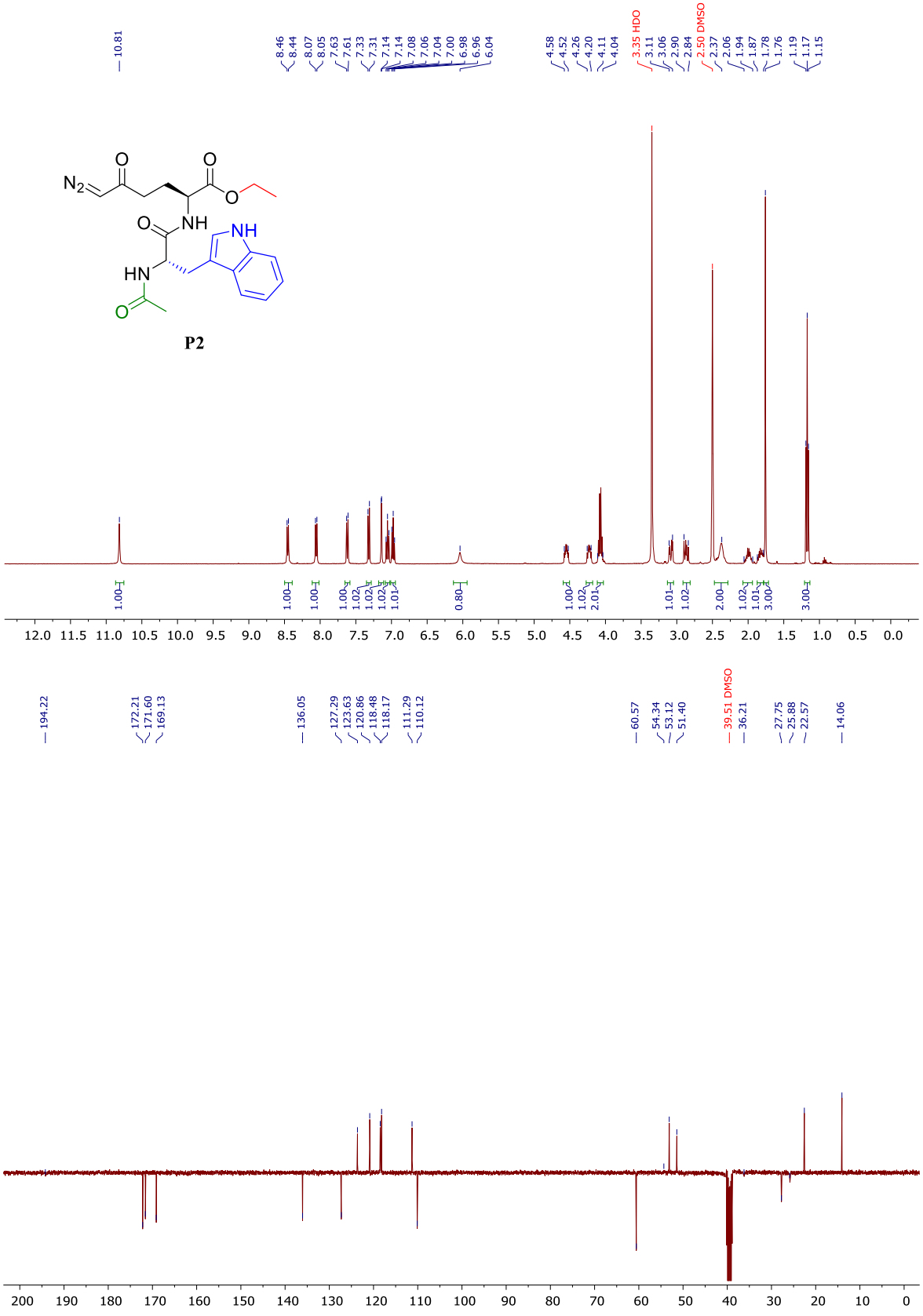
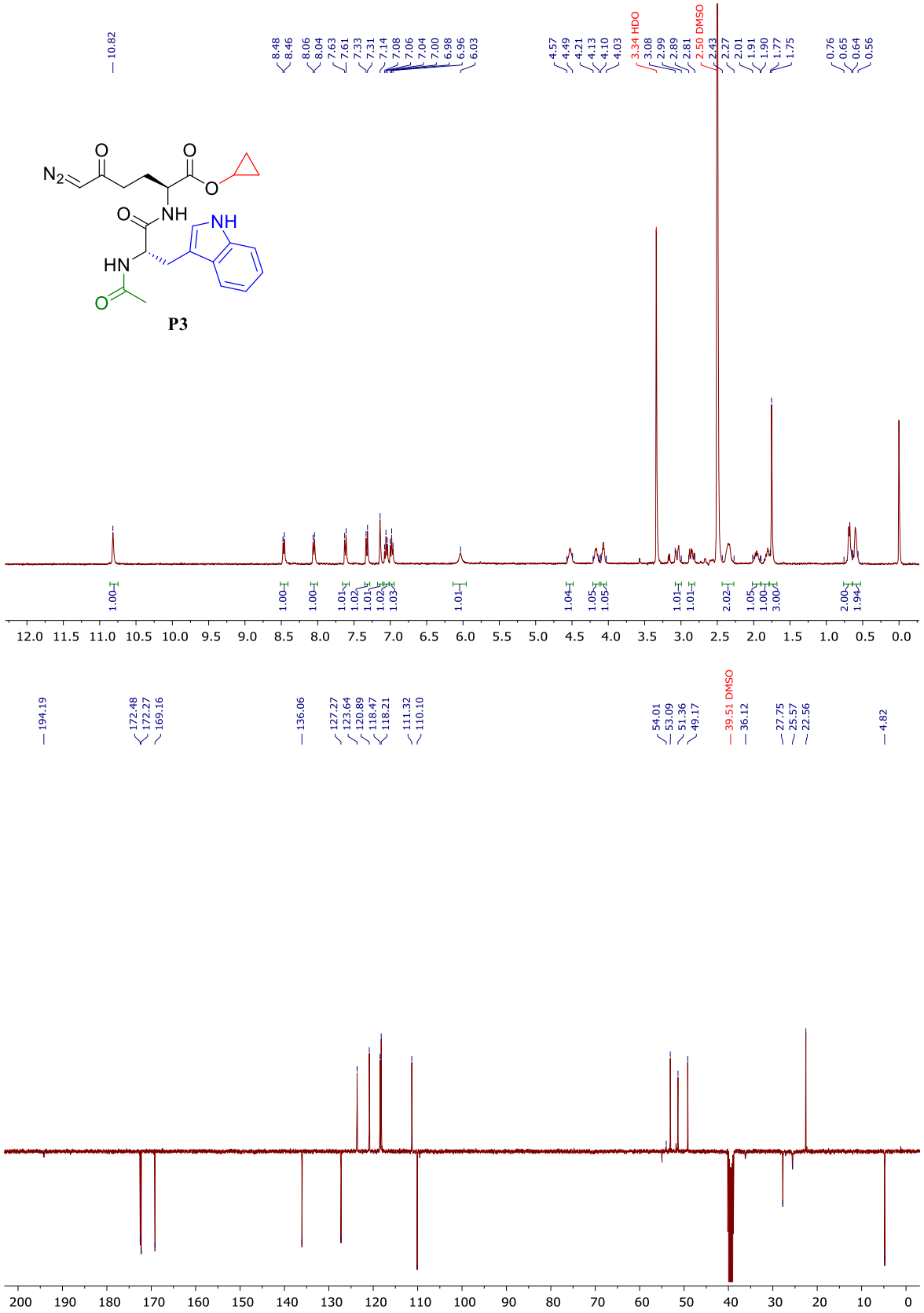


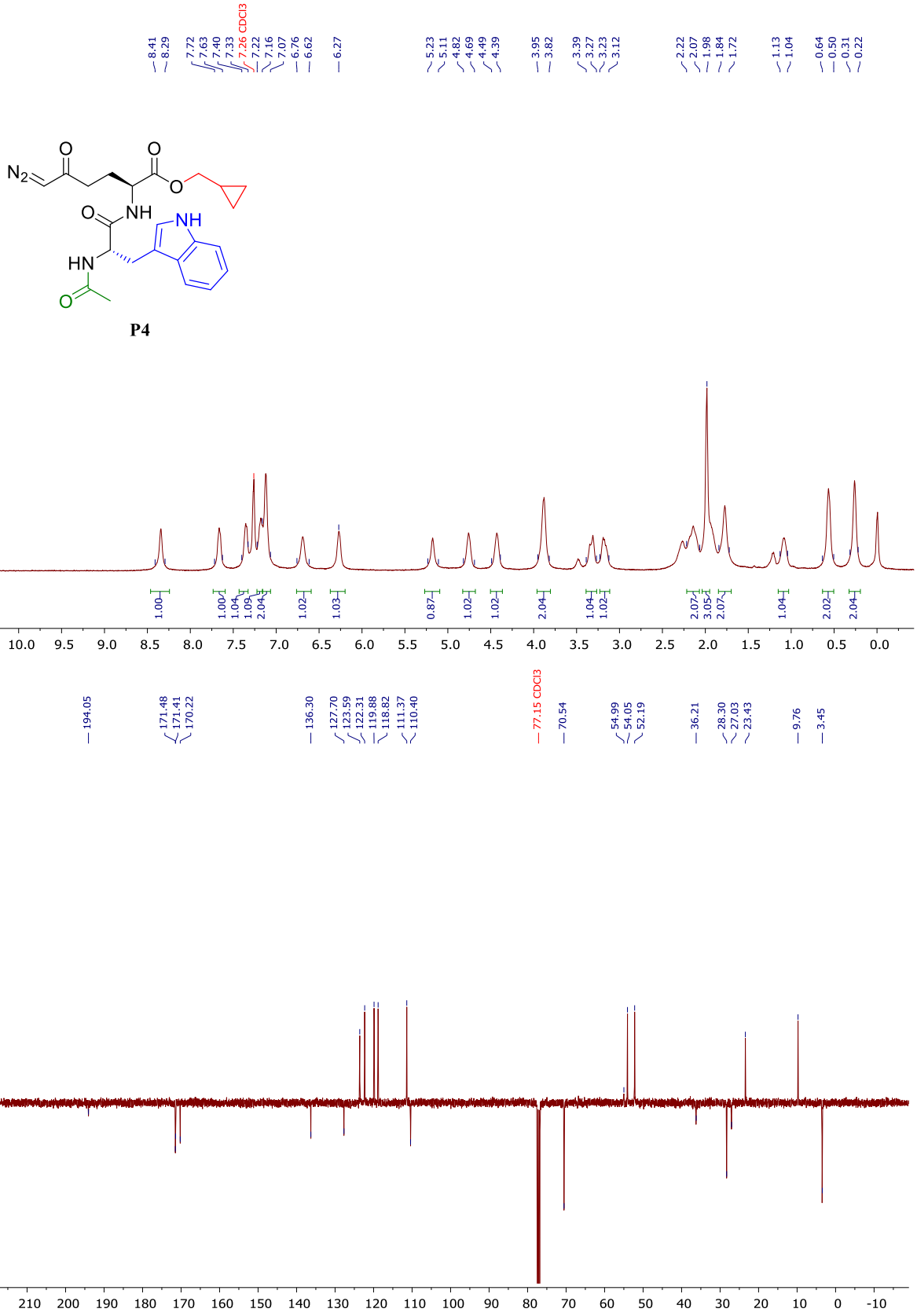
^{1}H and ^{13}C NMR Spectra of compound **P2**.



^{1}H and ^{13}C NMR Spectra of compound **P3**.

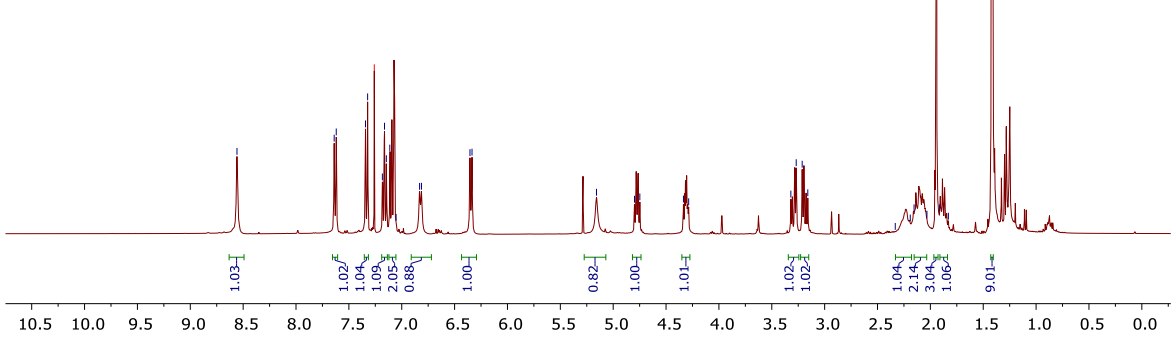


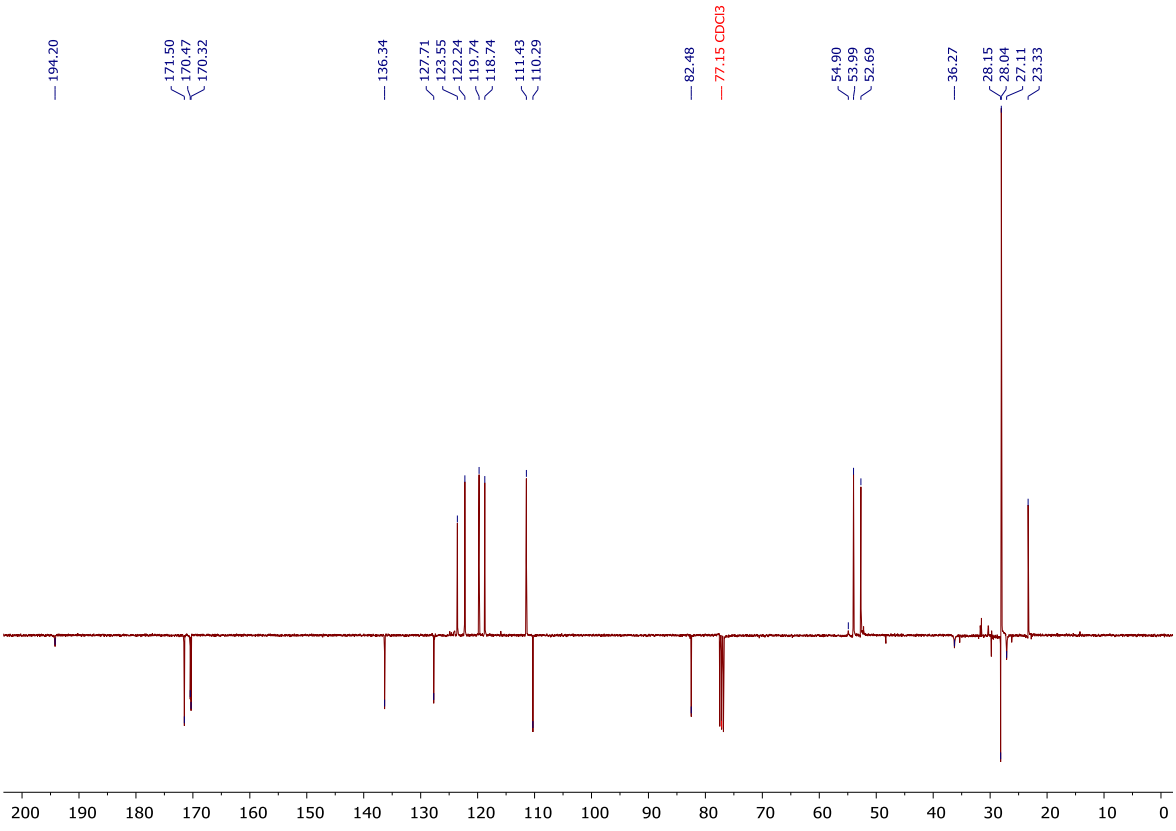
^{1}H and ^{13}C NMR Spectra of compound **P4**.



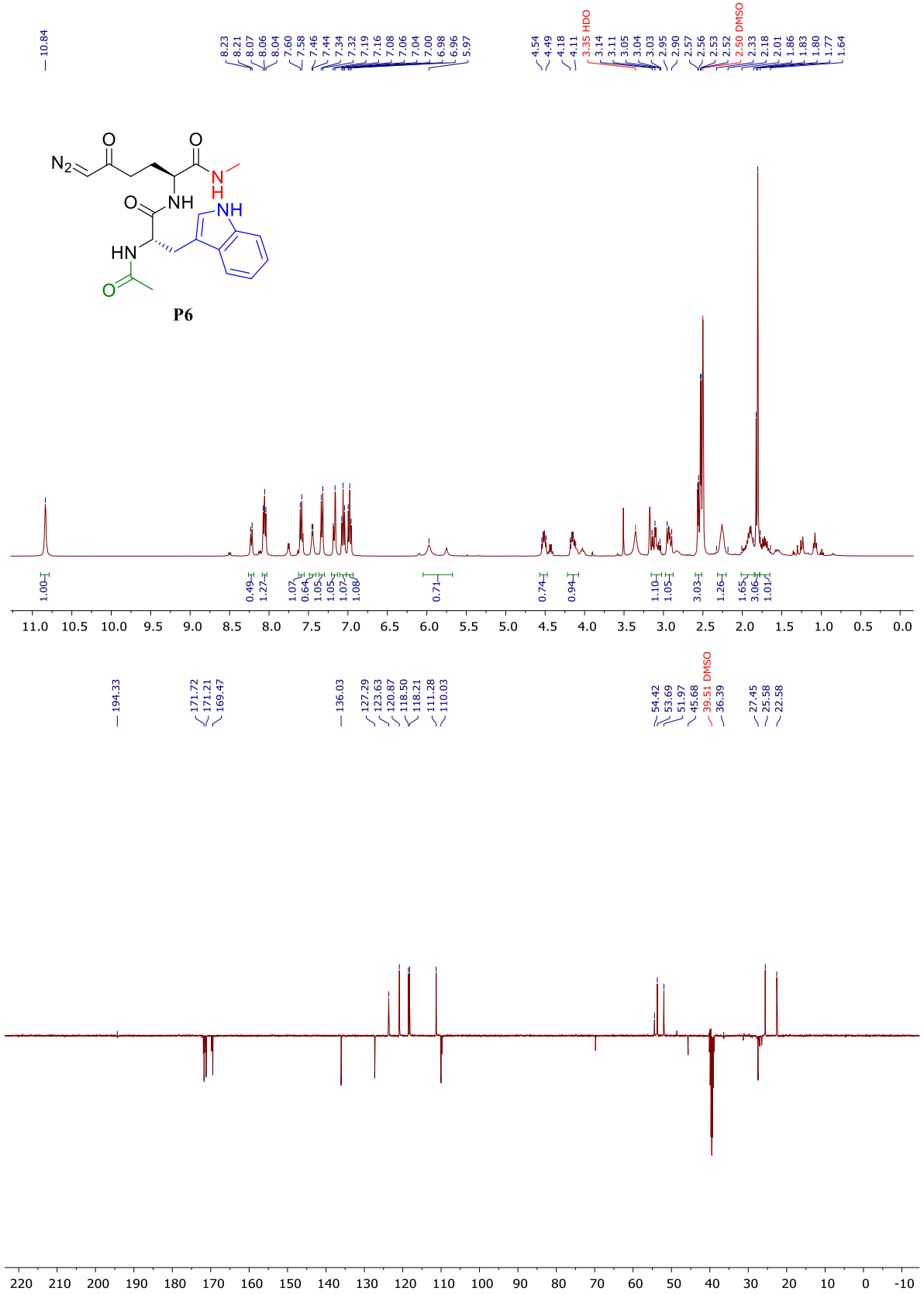
^{1}H and ^{13}C NMR Spectra of compound **P5**.

P5

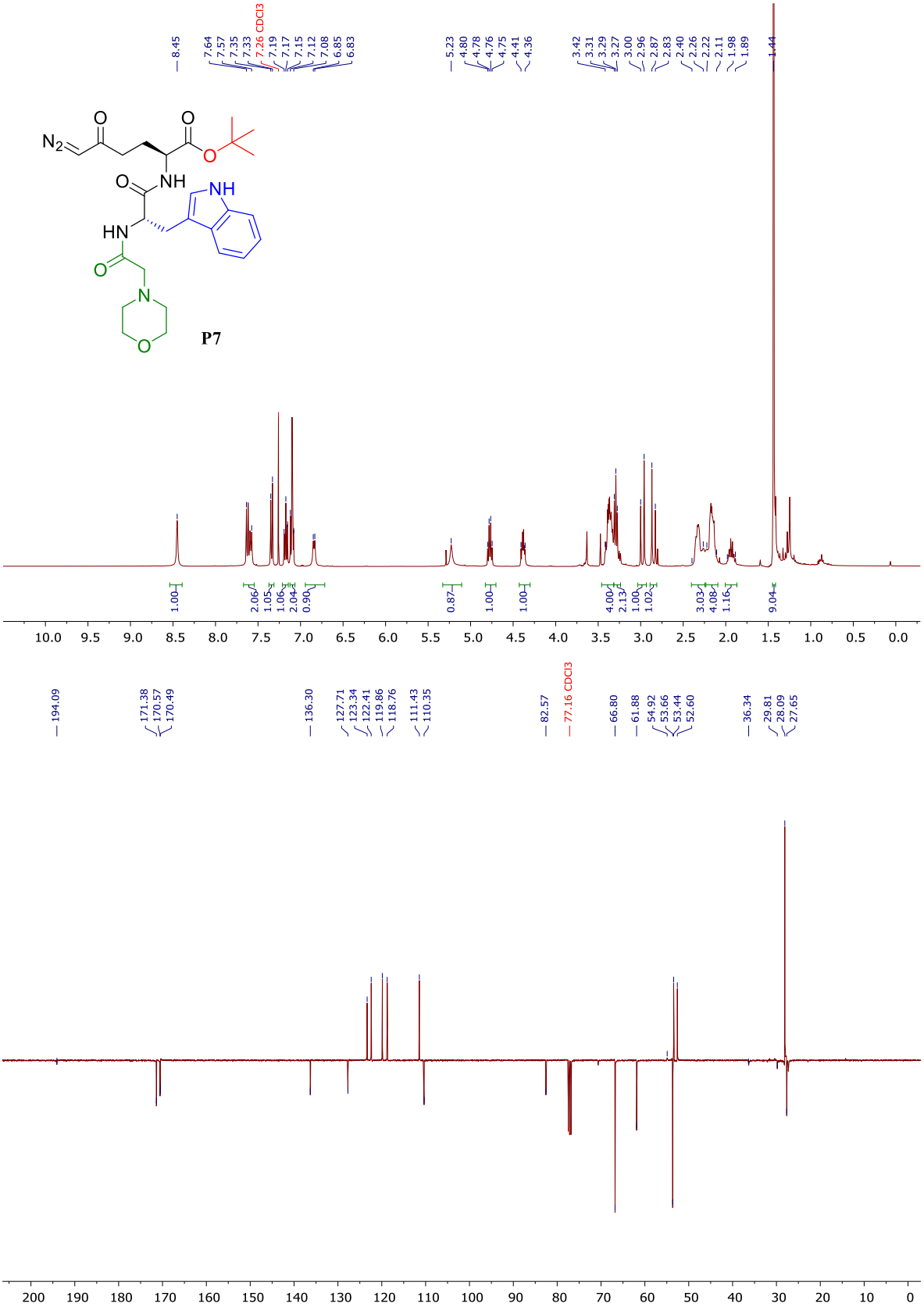




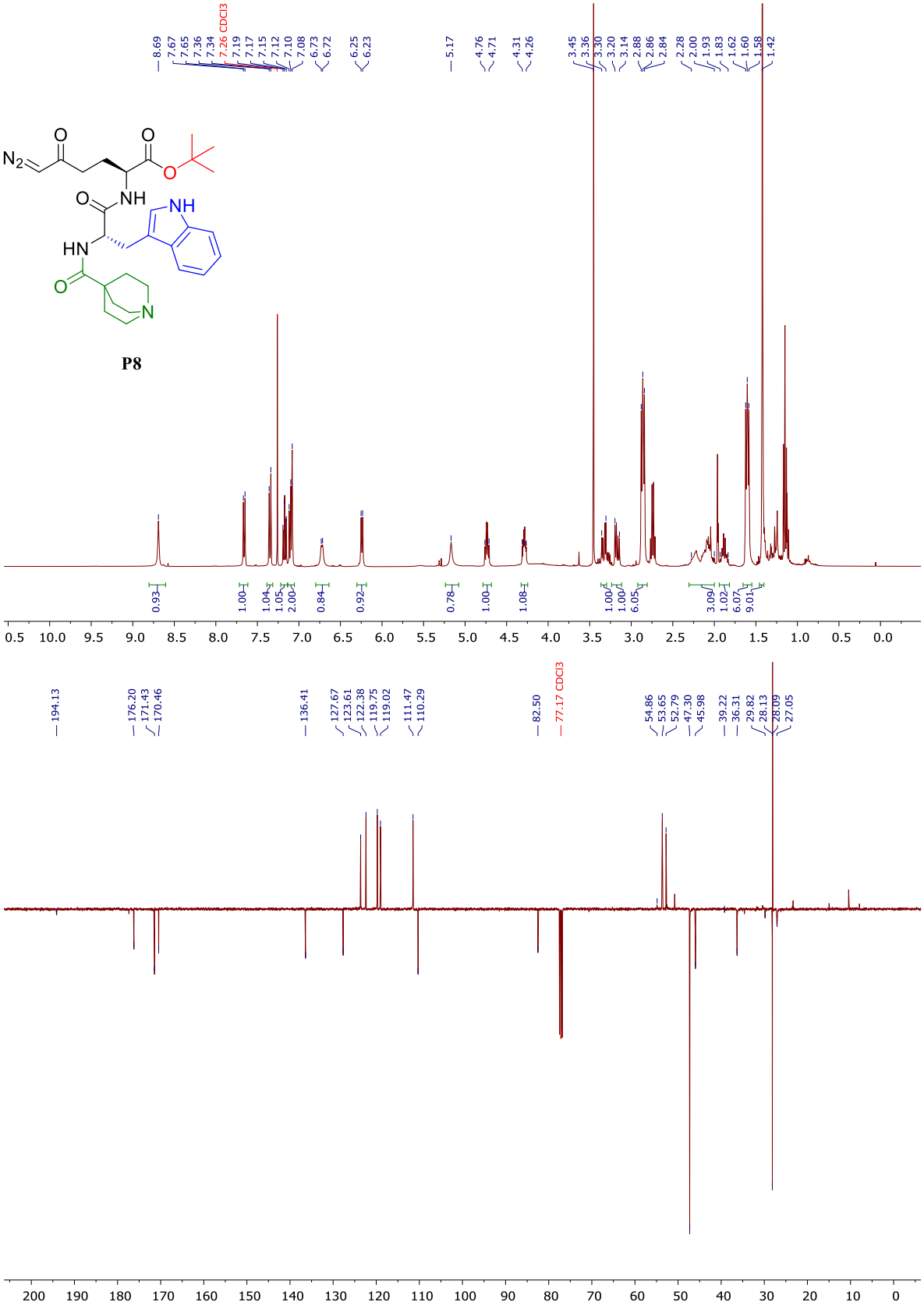
^{1}H and ^{13}C NMR Spectra of compound **P6**.



^{1}H and ^{13}C NMR Spectra of compound **P7**.

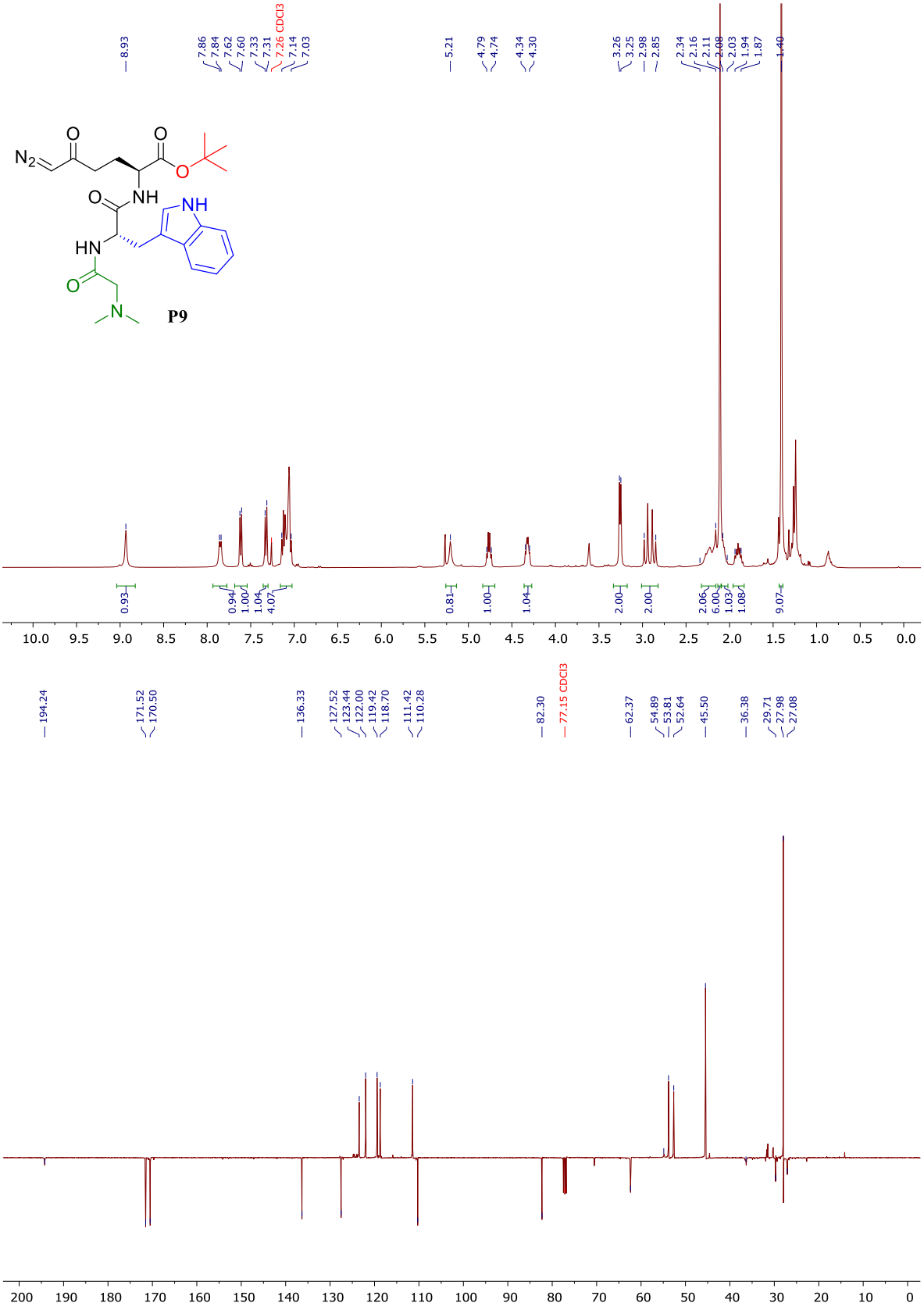


^{1}H and ^{13}C NMR Spectra of compound **P8**.

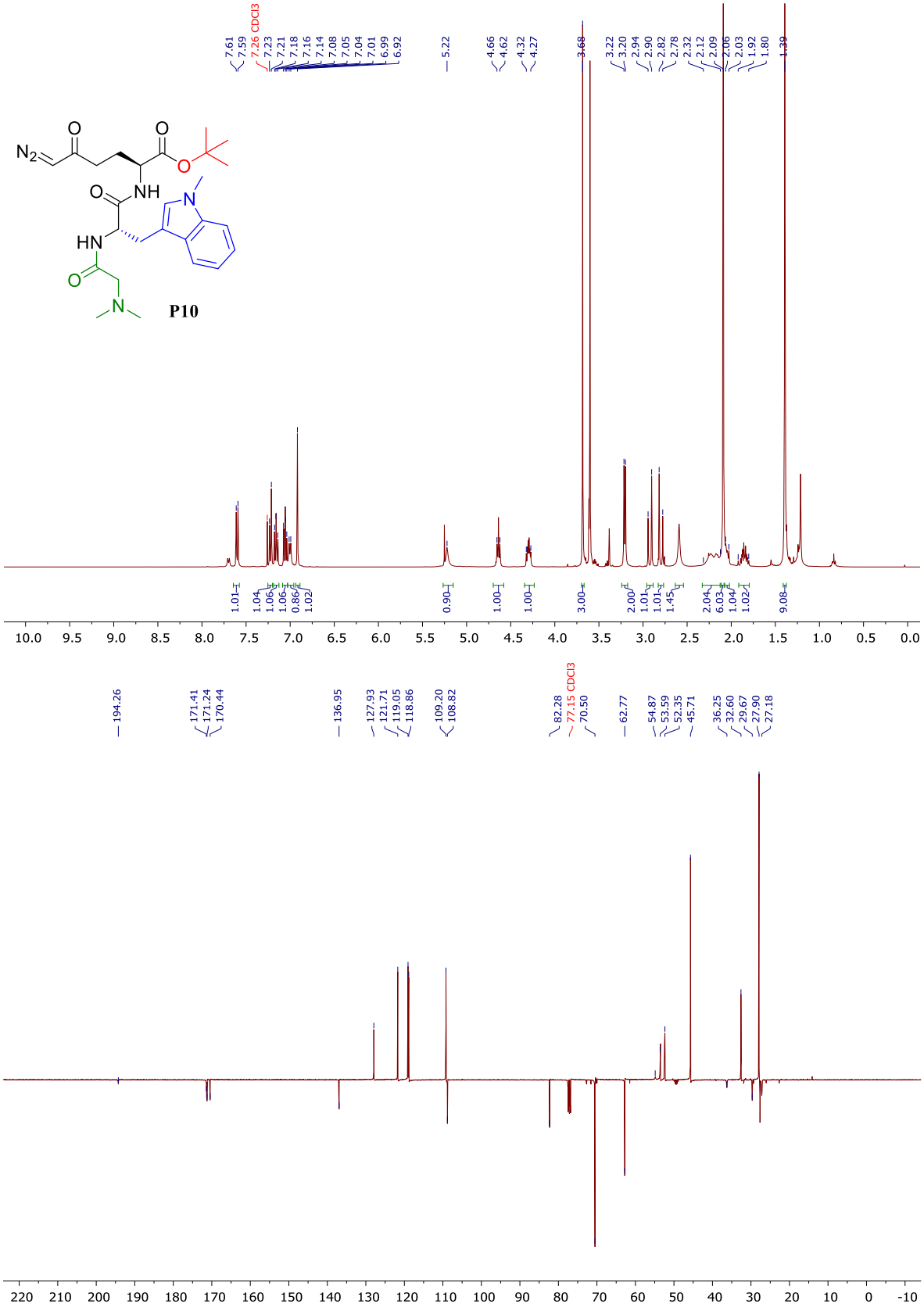


P8

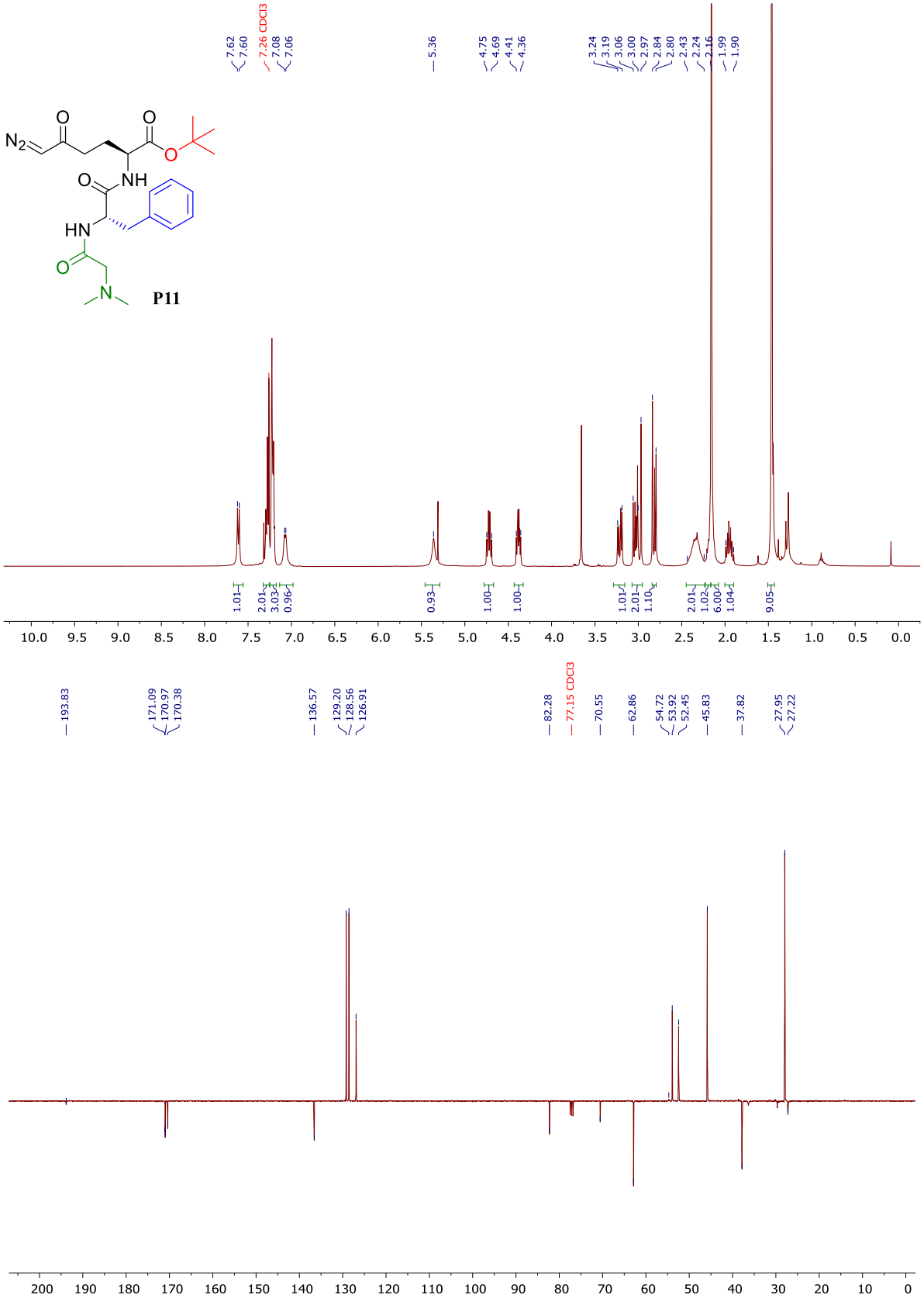
^{1}H and ^{13}C NMR Spectra of compound **P9**.



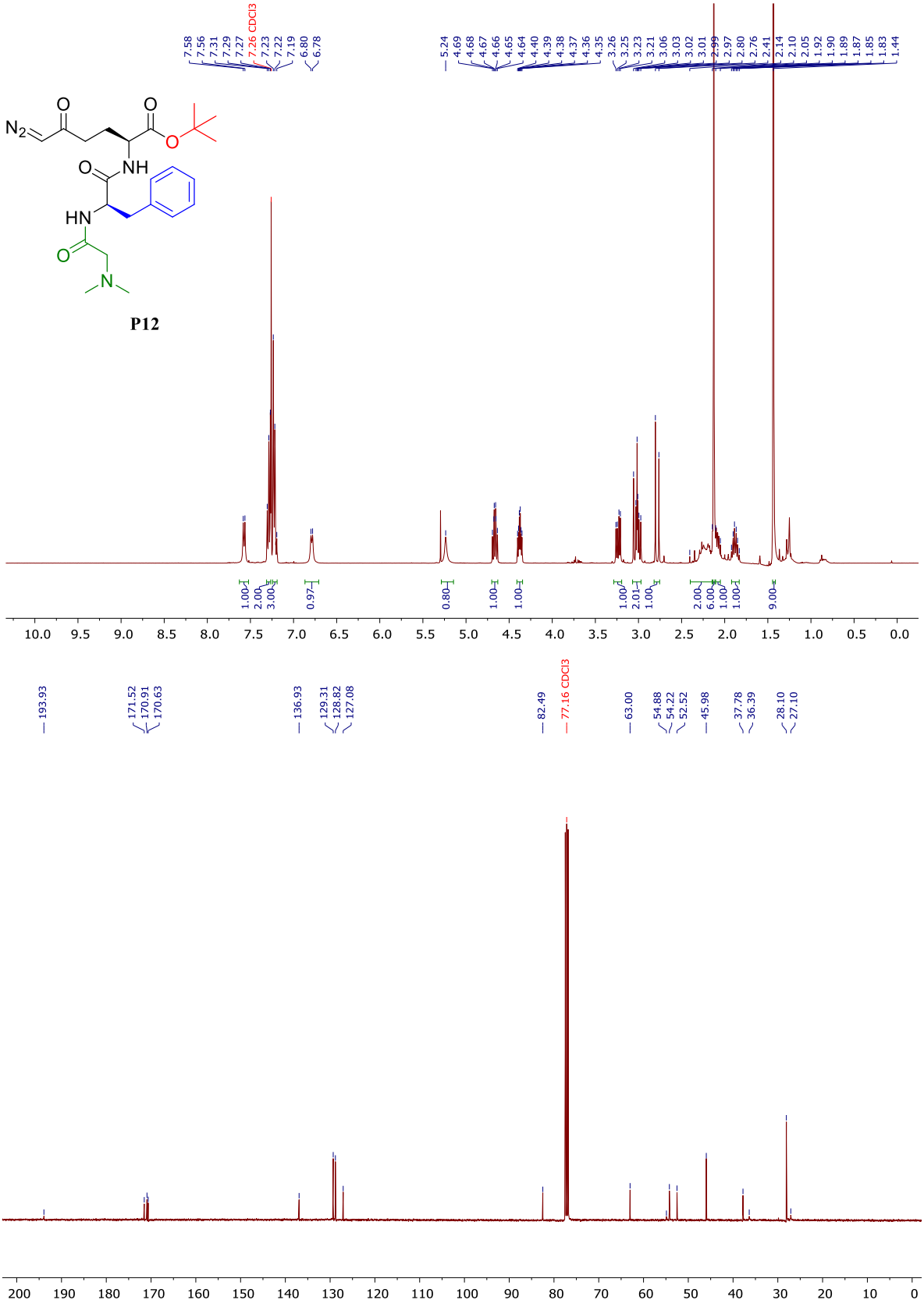
^{1}H and ^{13}C NMR Spectra of compound **P10**.



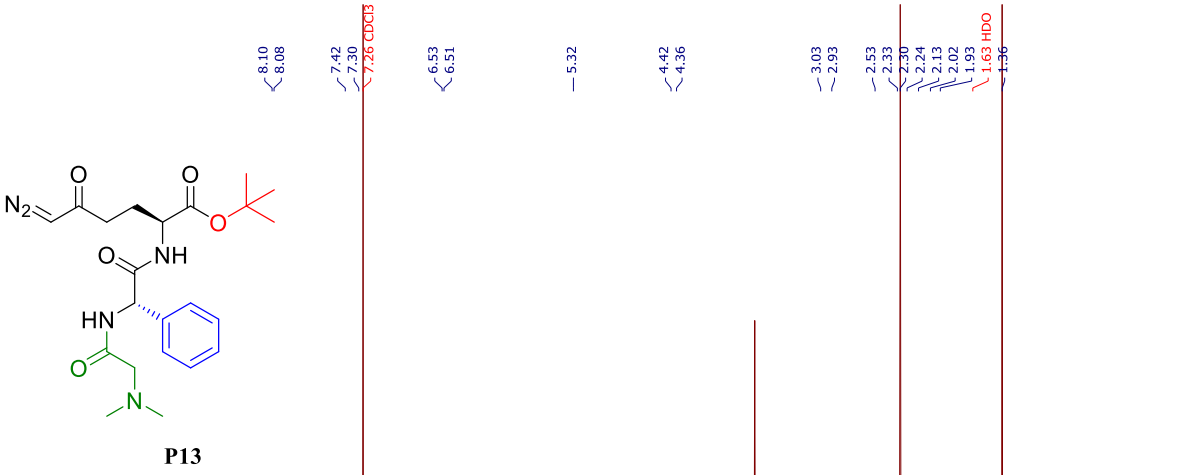
^{1}H and ^{13}C NMR Spectra of compound **P11**.



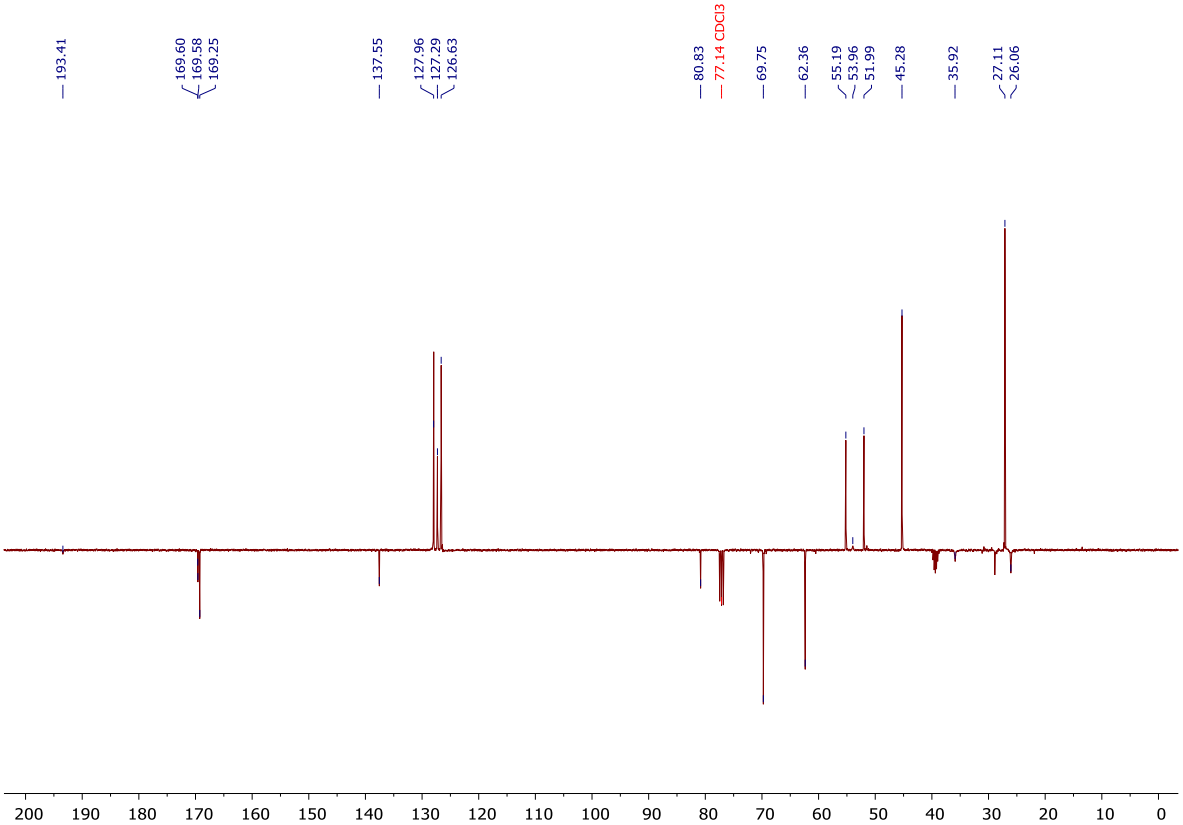
^{1}H and ^{13}C NMR Spectra of compound **P12**.



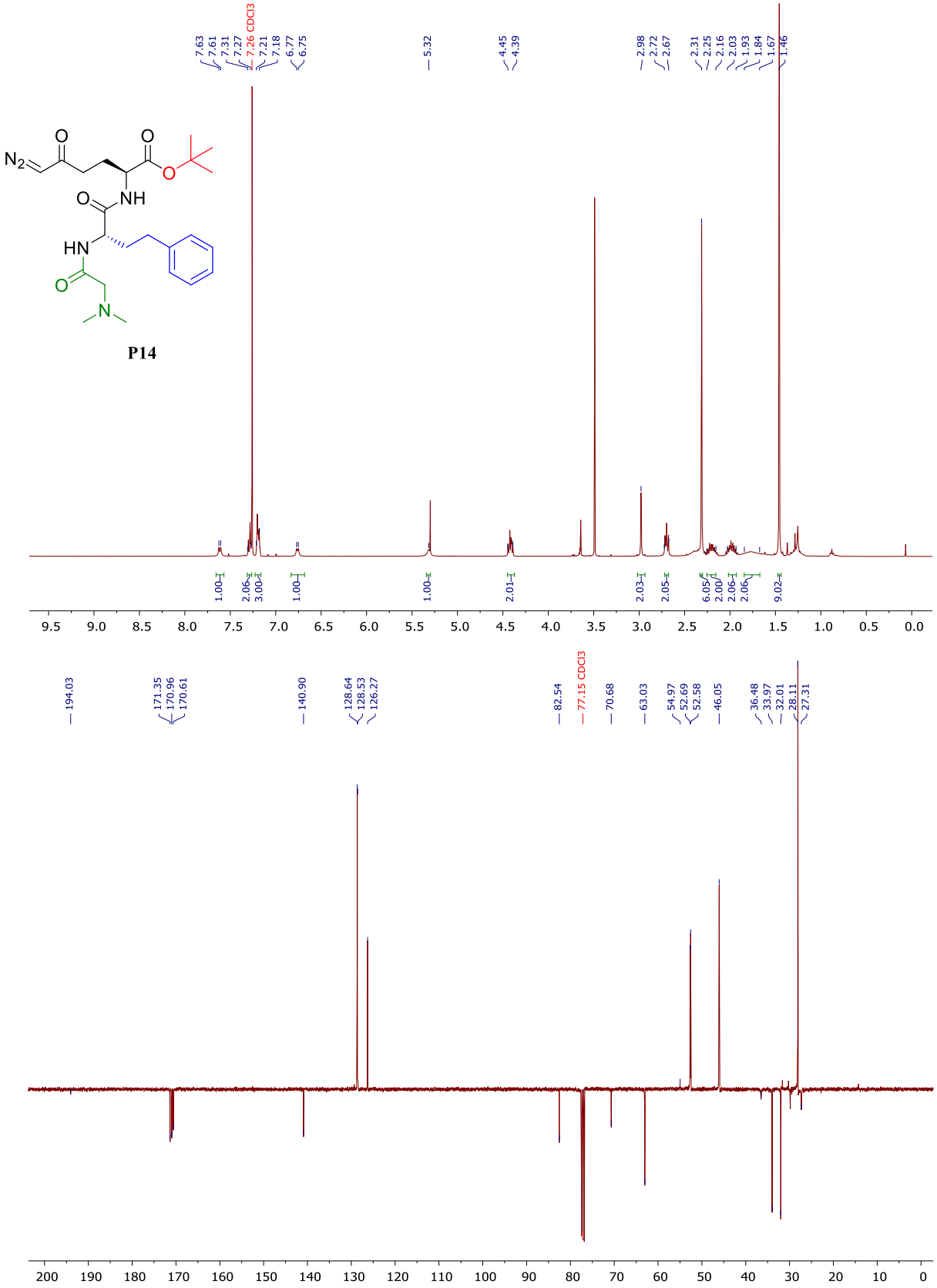
^{1}H and ^{13}C NMR Spectra of compound **P13**.



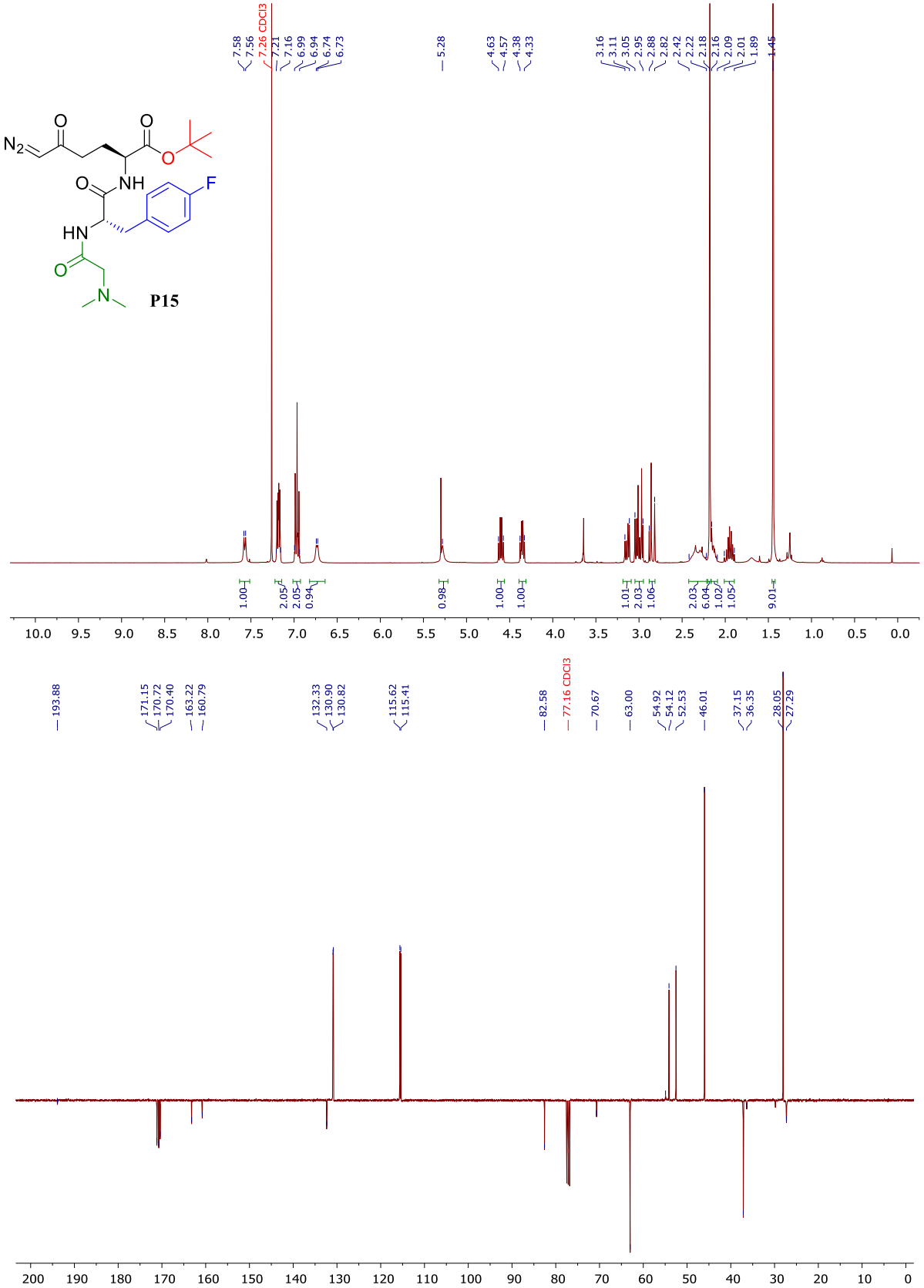
P13



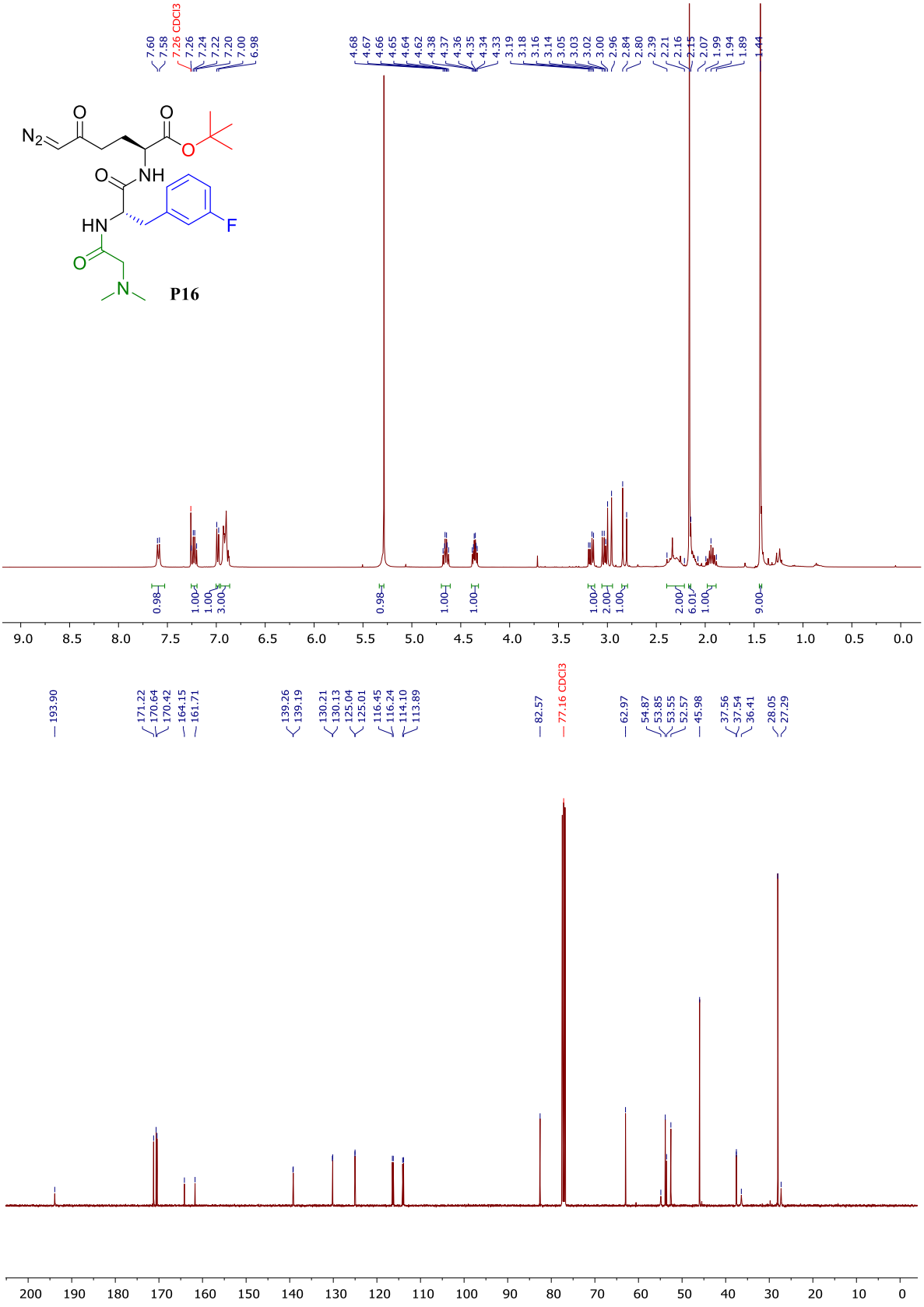
^{1}H and ^{13}C NMR Spectra of compound **P14**.



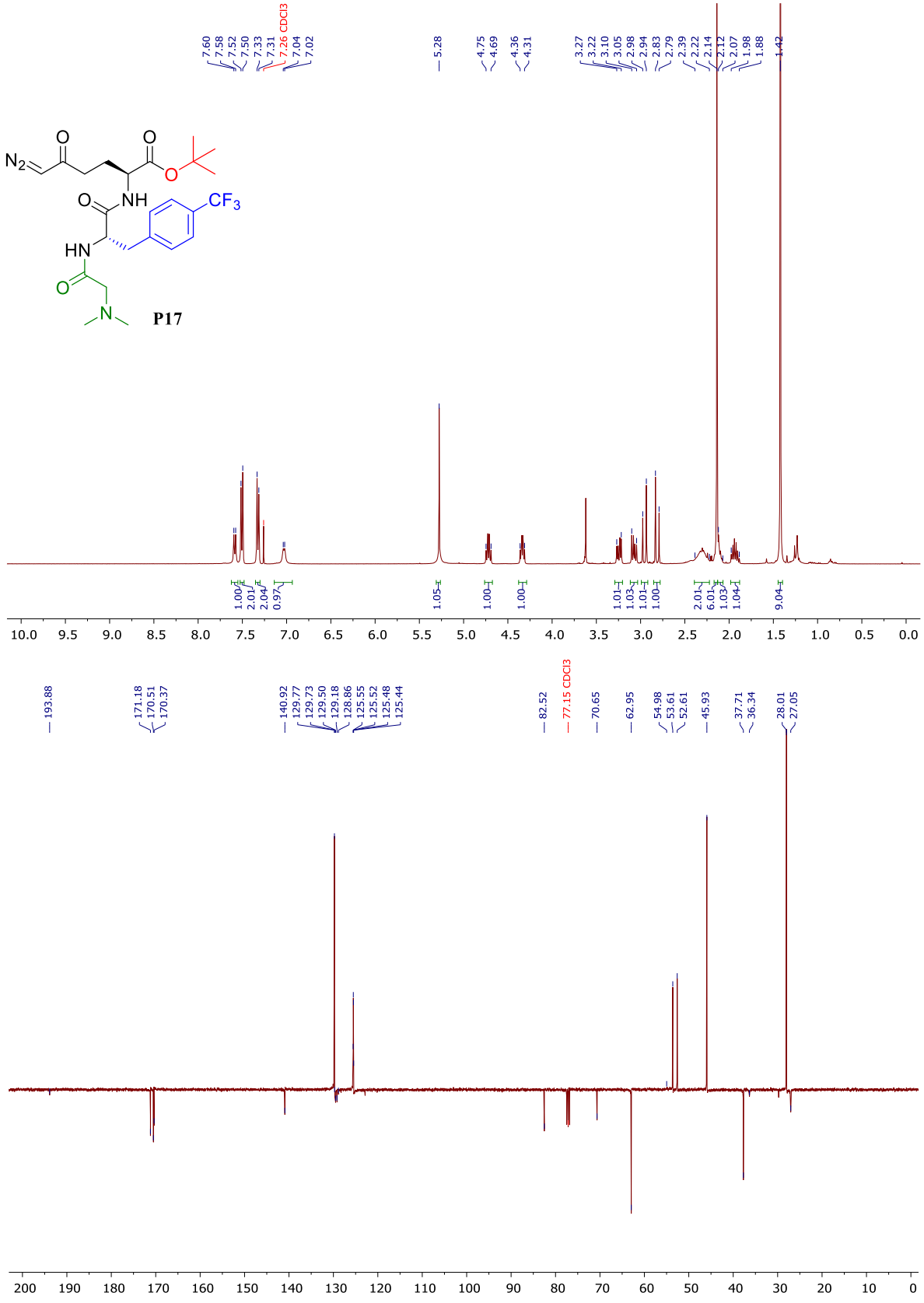
^{1}H and ^{13}C NMR Spectra of compound **P15**.



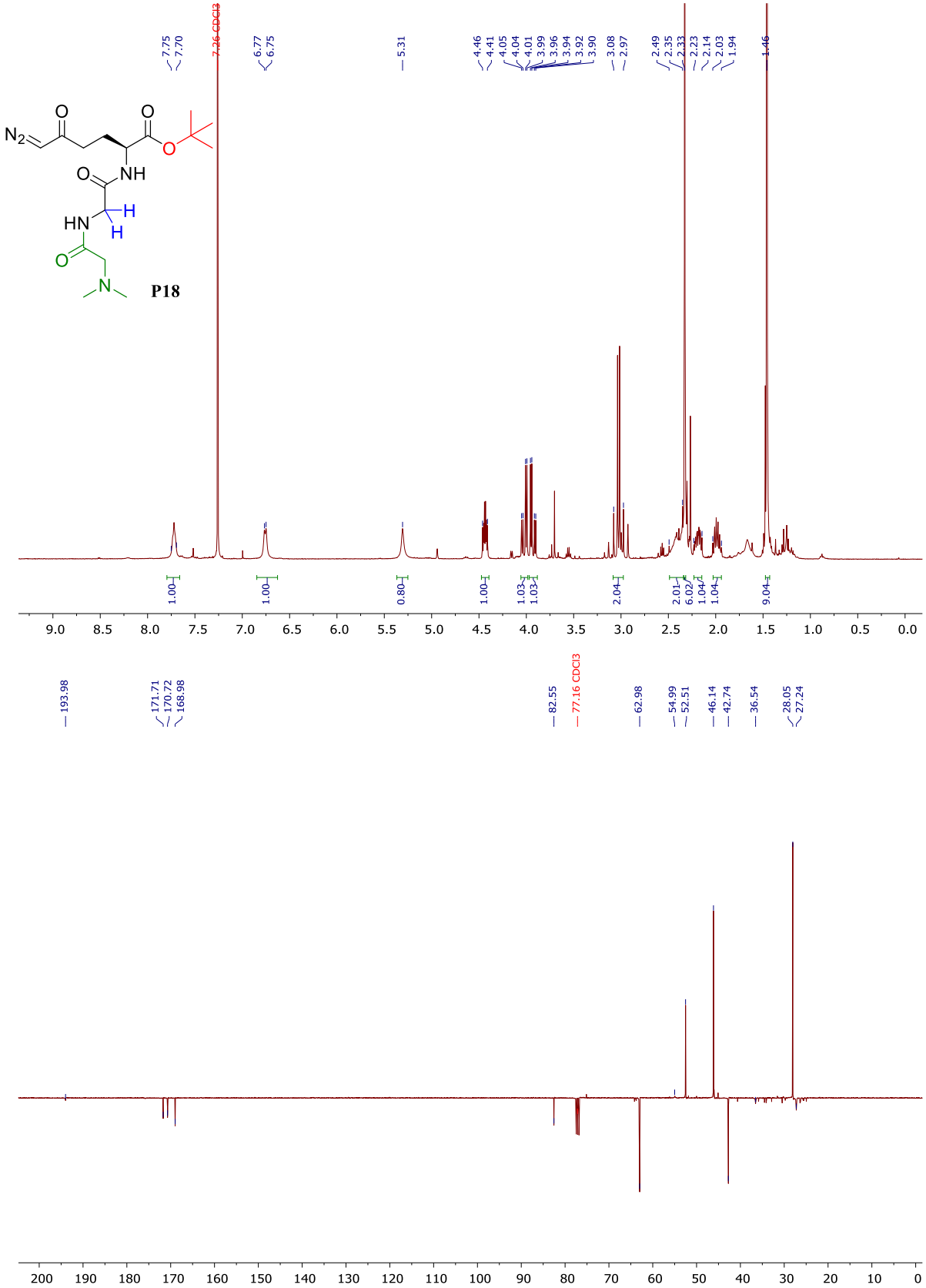
^{1}H and ^{13}C NMR Spectra of compound **P16**.



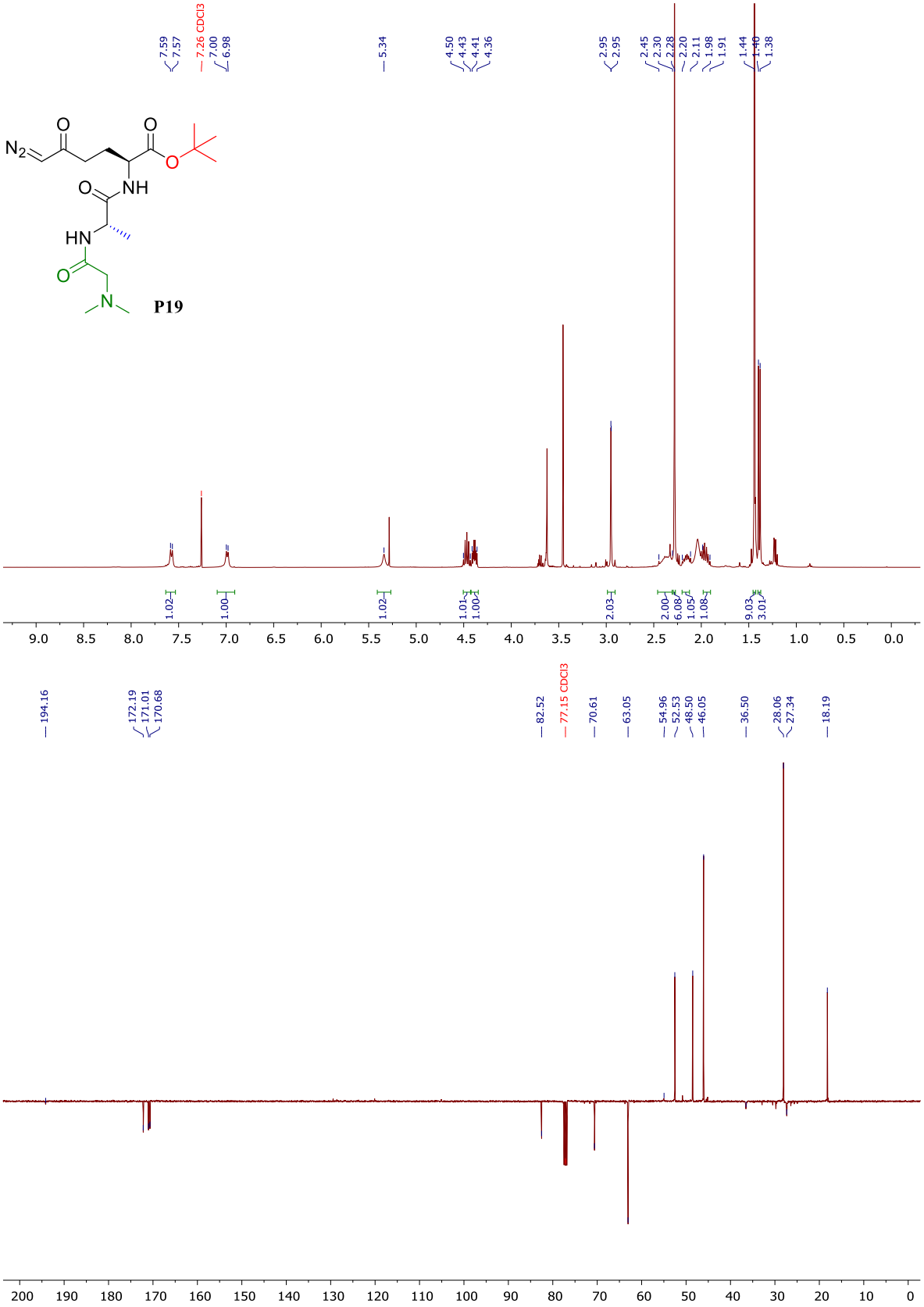
^{1}H and ^{13}C NMR Spectra of compound **P17**.



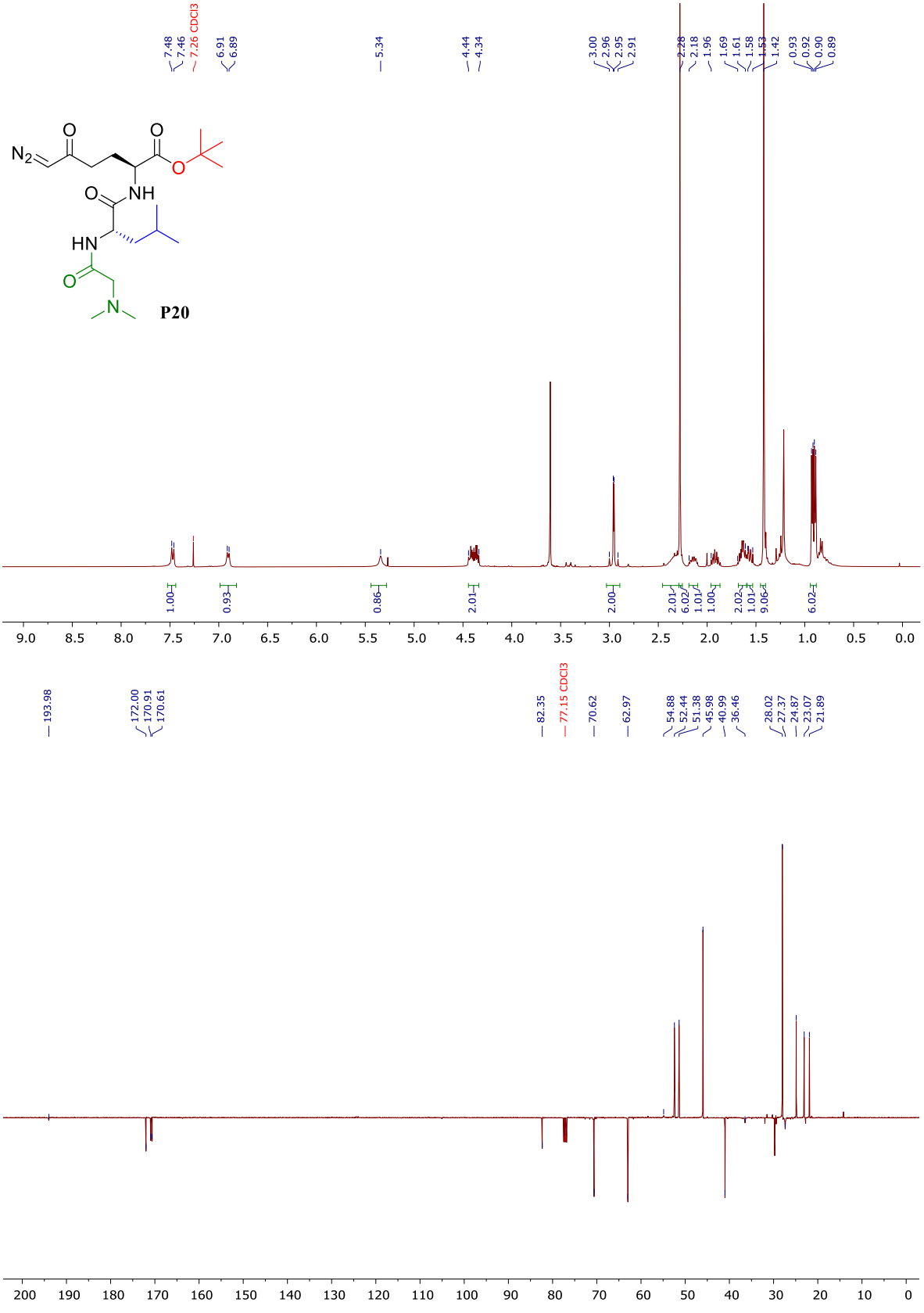
^{1}H and ^{13}C NMR Spectra of compound **P18**.



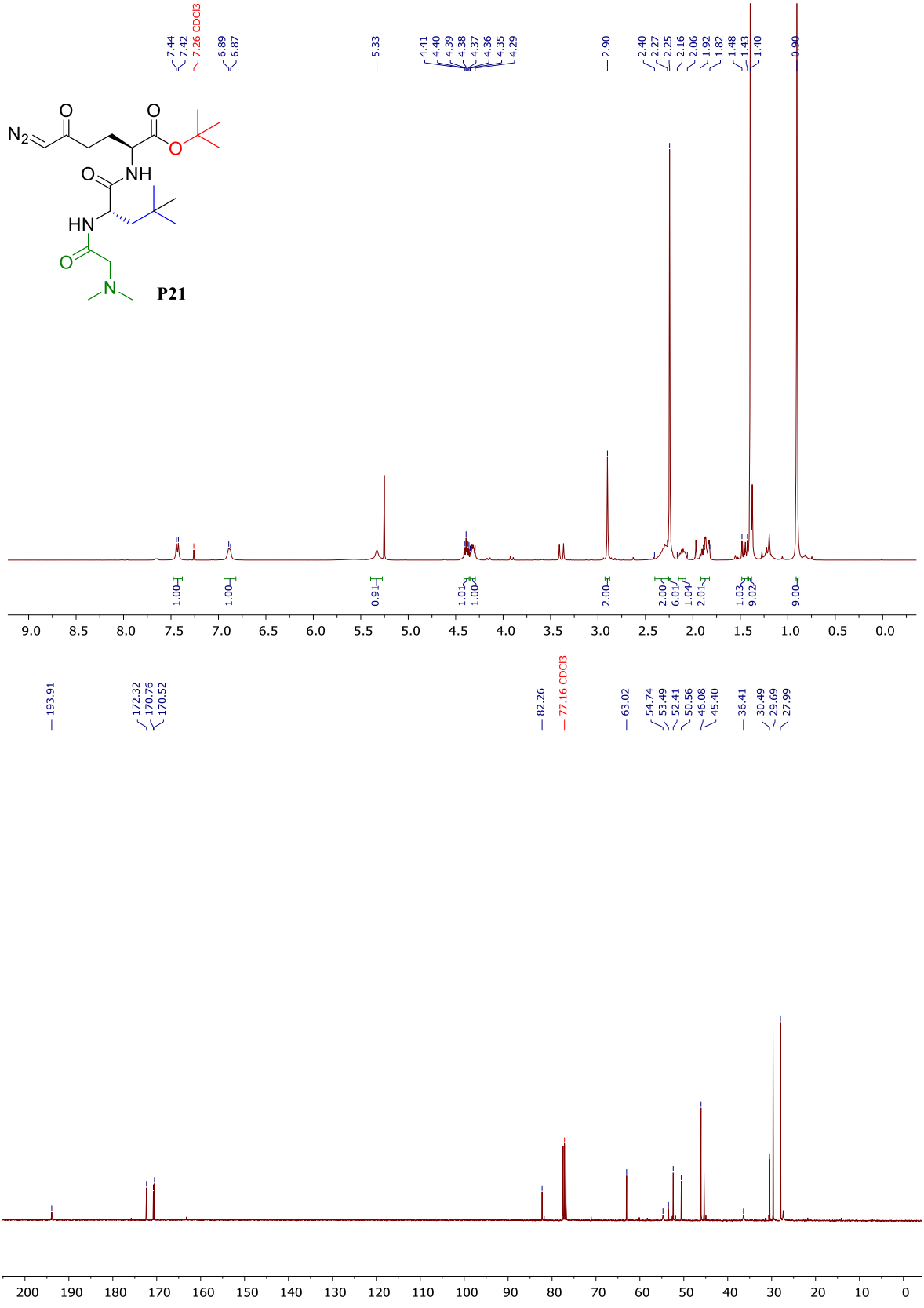
^{1}H and ^{13}C NMR Spectra of compound **P19**.



^{1}H and ^{13}C NMR Spectra of compound **P20**.

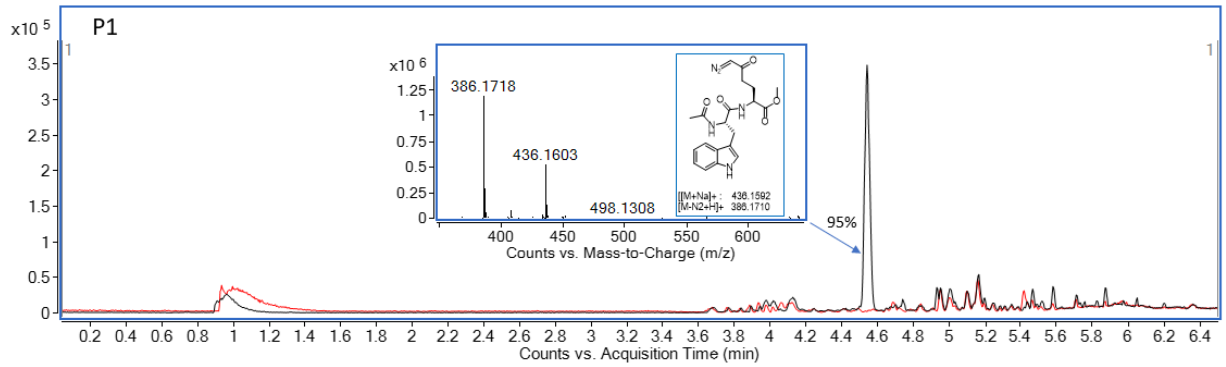


^{1}H and ^{13}C NMR Spectra of compound **P21**.

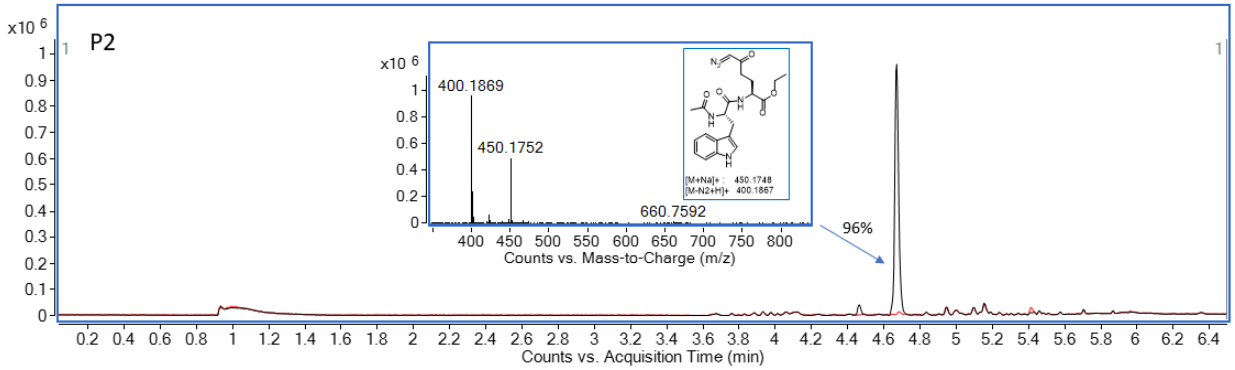


HPLC spectra of final prodrugs P1-P21

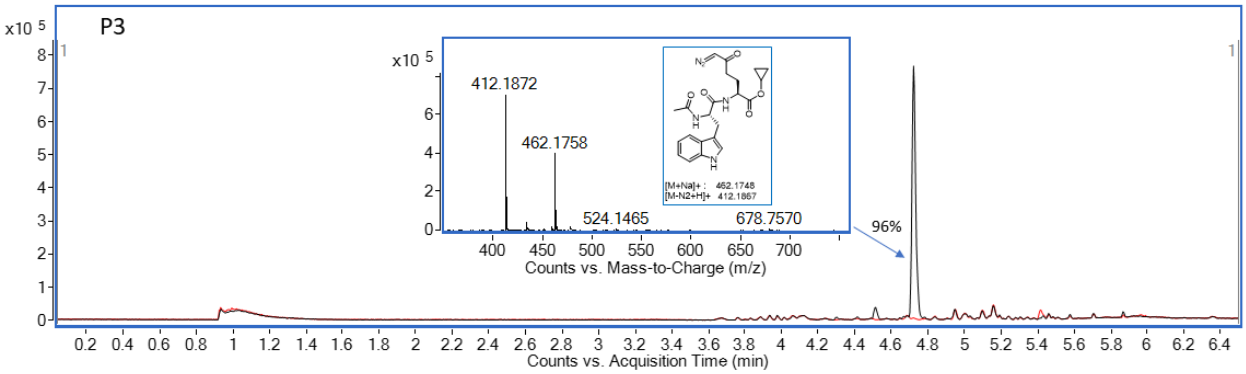
HPLC spectrum of prodrug **P1**



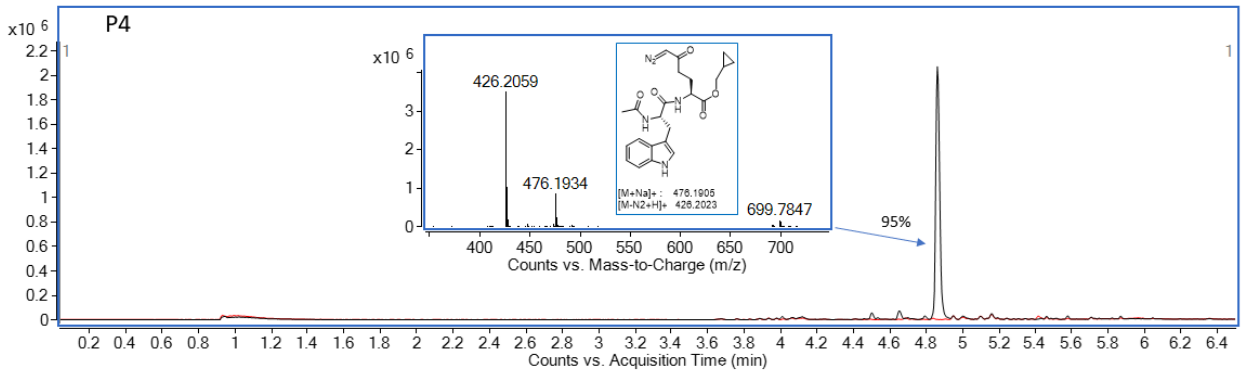
HPLC spectrum of prodrug **P2**



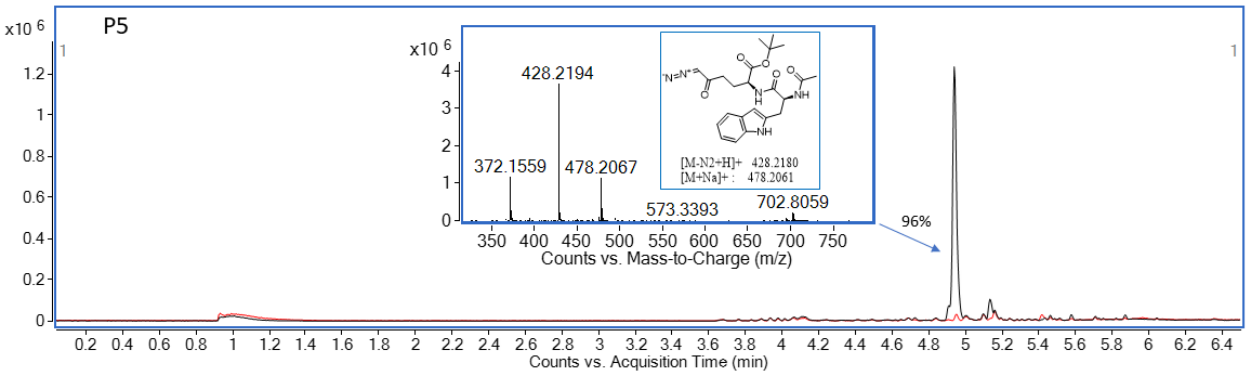
HPLC spectrum of prodrug **P3**



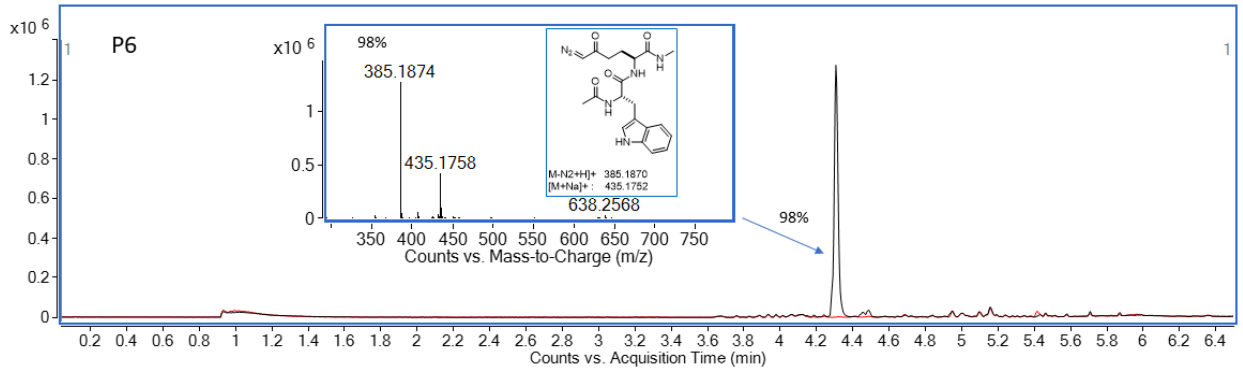
HPLC spectrum of prodrug **P4**



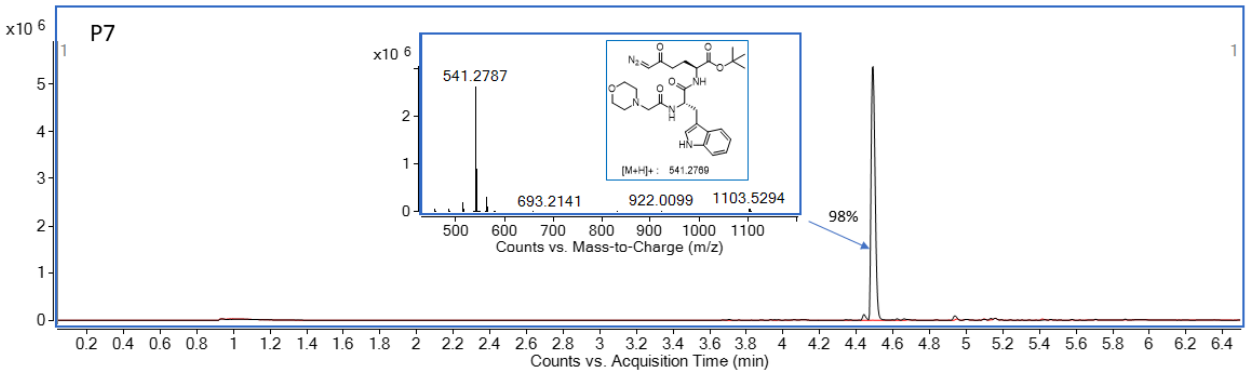
HPLC spectrum of prodrug **P5**



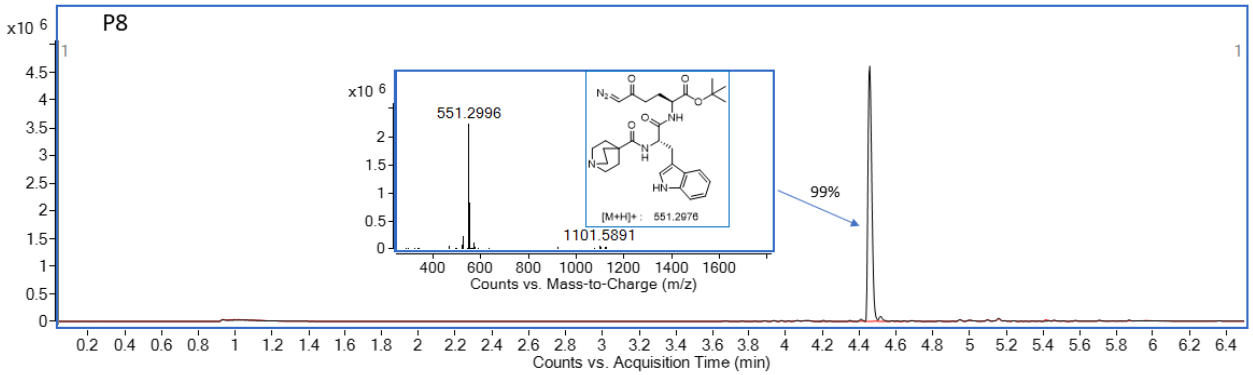
HPLC spectrum of prodrug **P6**



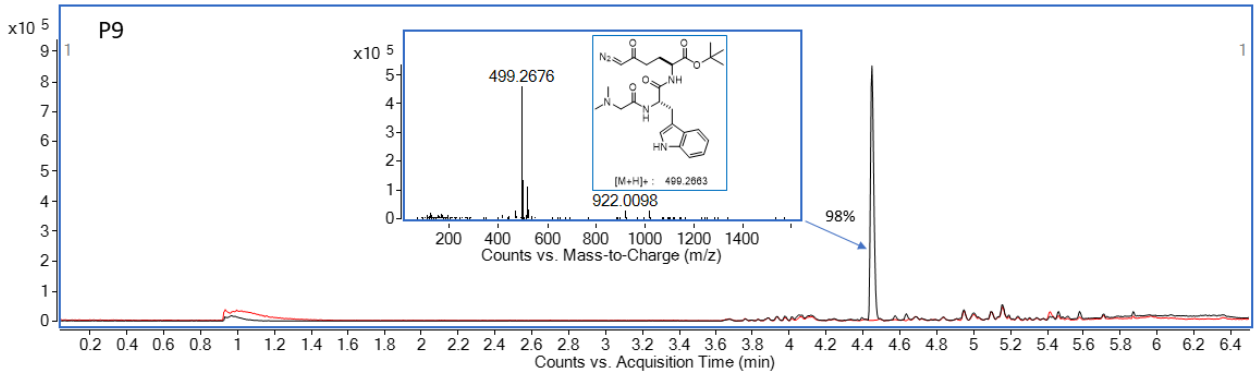
HPLC spectrum of prodrug **P7**



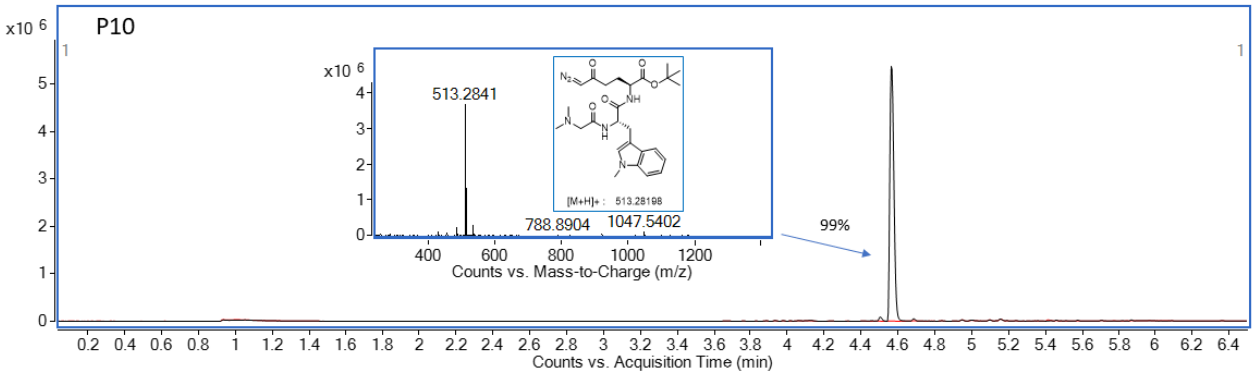
HPLC spectrum of prodrug **P8**



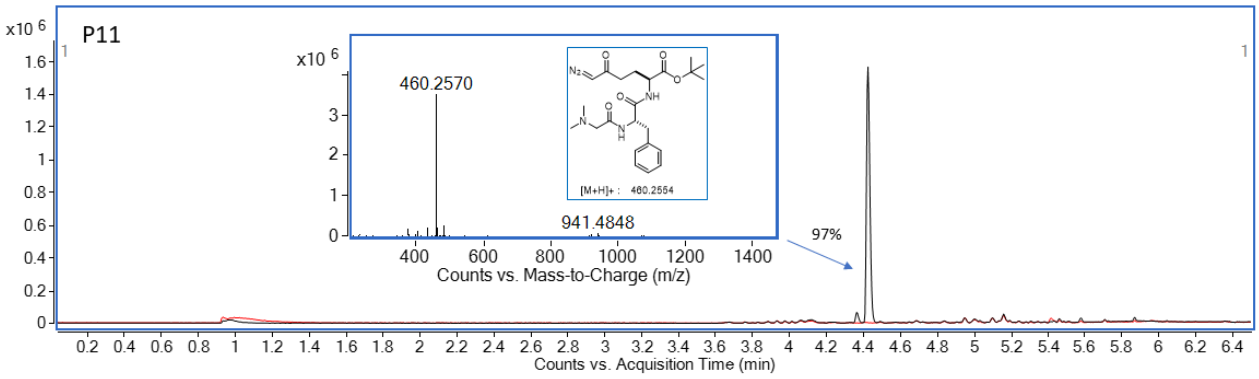
HPLC spectrum of prodrug **P9**



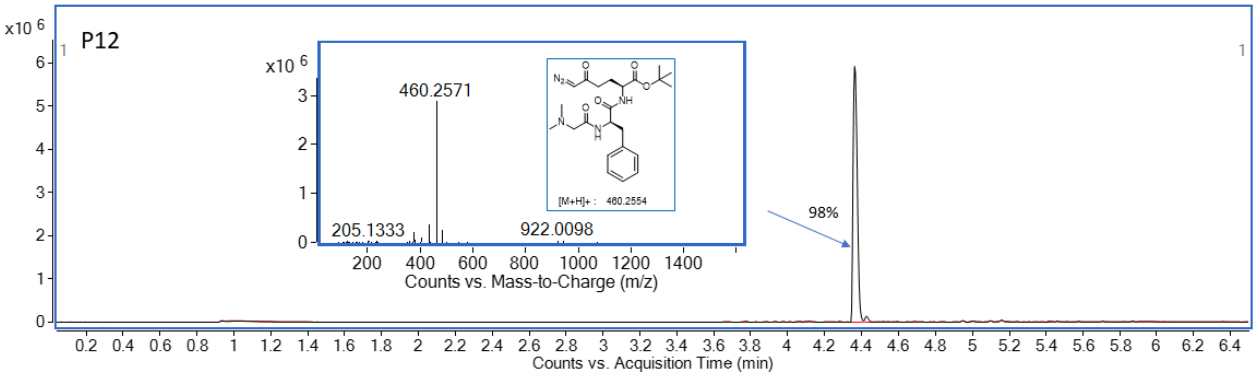
HPLC spectrum of prodrug **P10**



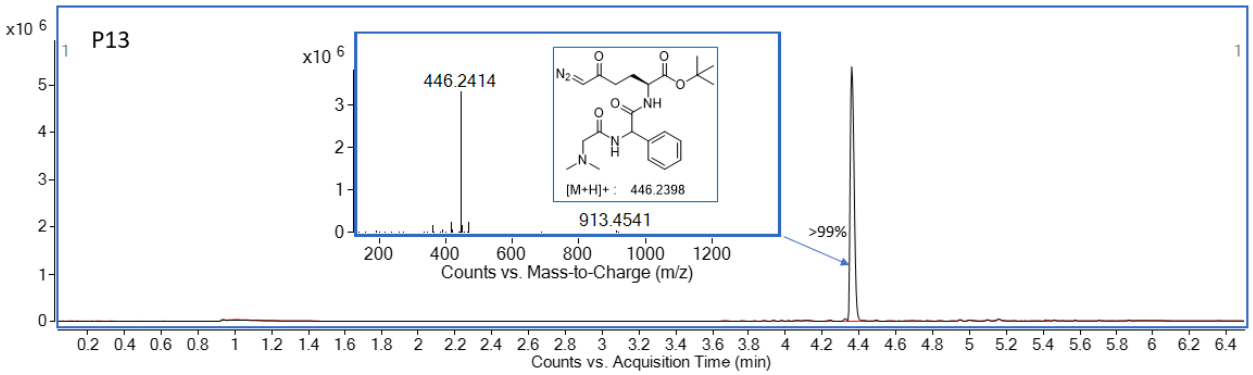
HPLC spectrum of prodrug **P11**



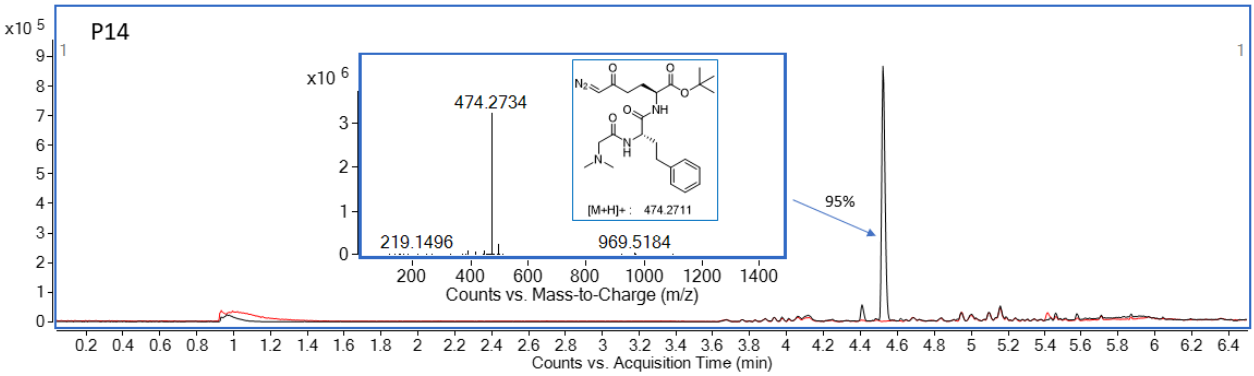
HPLC spectrum of prodrug **P12**



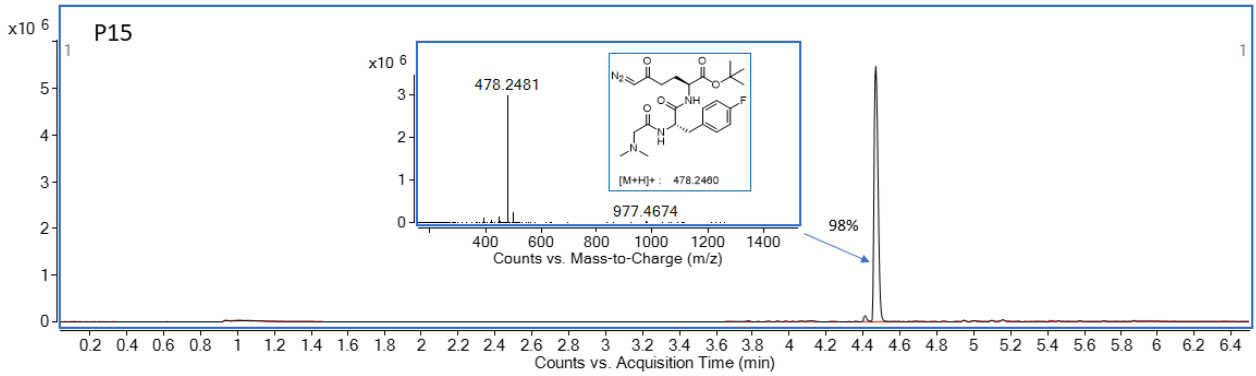
HPLC spectrum of prodrug **P13**



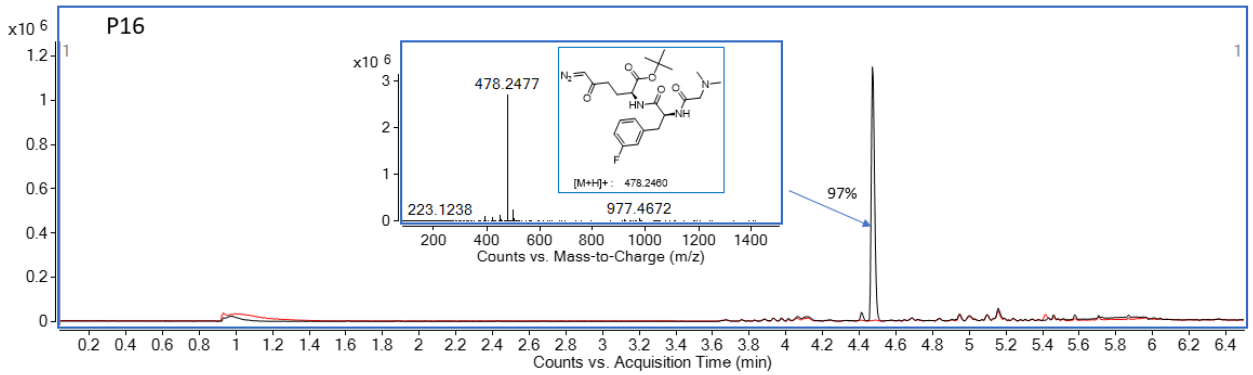
HPLC spectrum of prodrug **P14**



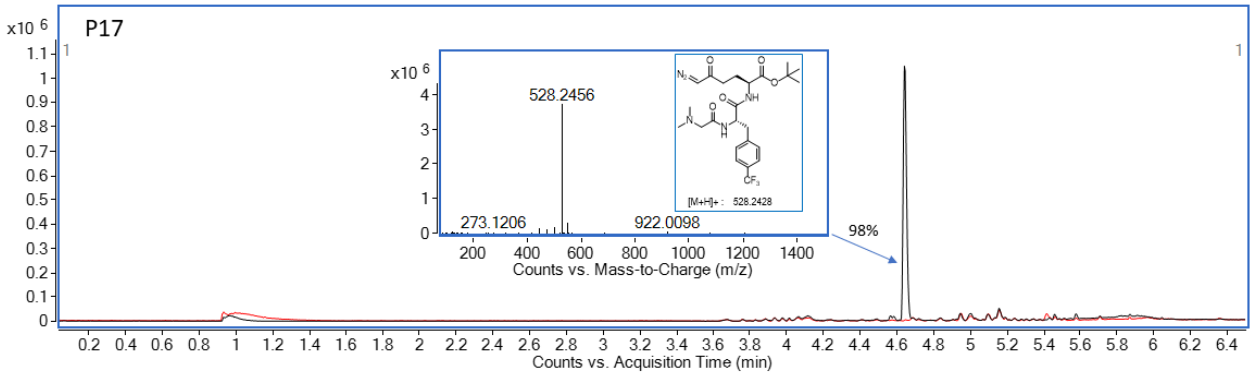
HPLC spectrum of prodrug **P15**



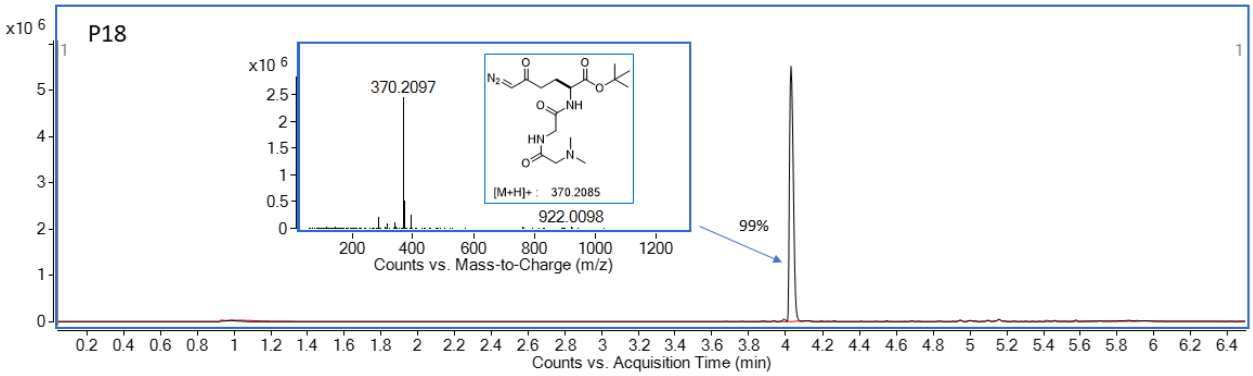
HPLC spectrum of prodrug **P16**



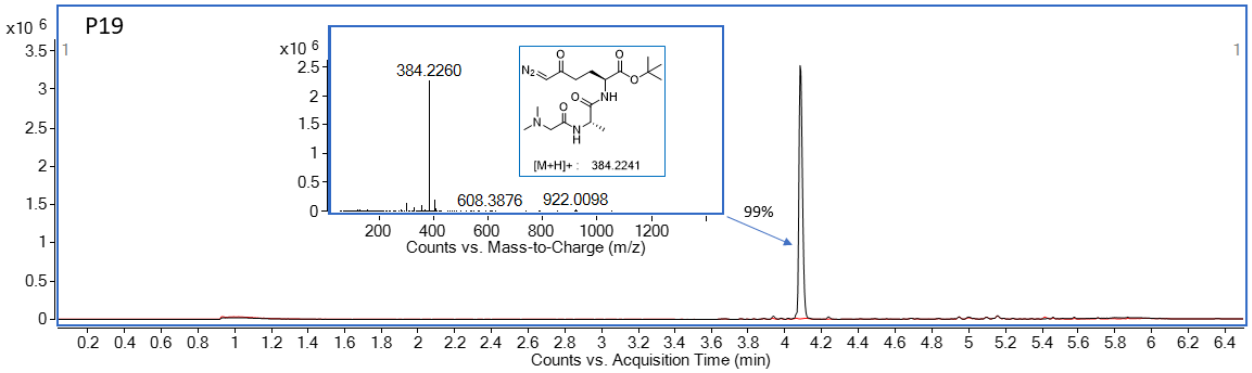
HPLC spectrum of prodrug **P17**



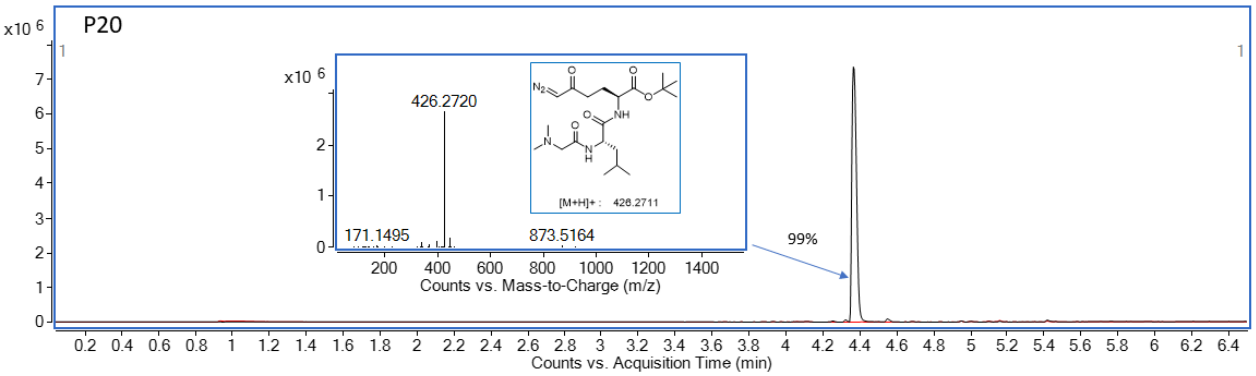
HPLC spectrum of prodrug **P18**



HPLC spectrum of prodrug **P19**



HPLC spectrum of prodrug **P20**



HPLC spectrum of prodrug **P21**

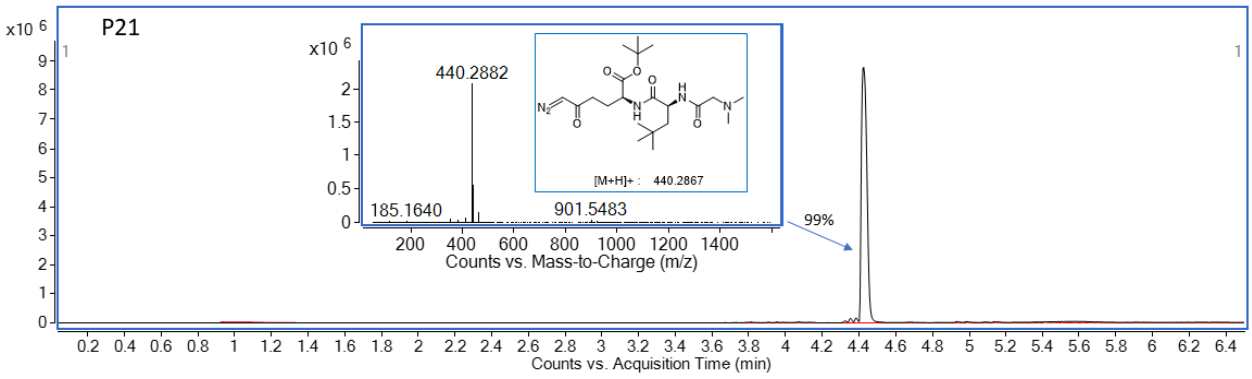


Table S1: clogD$_{7.4}$*values of prodrugs P1-P21 and DRP-104

Cmpd #	clogD
DRP-104	-0.07
P1	-0.84
P2	-0.48
P3	-0.37
P4	-0.06
P5	0.21
P6	-1.57
P7	-0.11
P8	0.41
P9	-0.01
P10	0.21
P11	-0.11
P12	-0.11
P13	-0.40
P14	0.34
P15	0.03
P16	0.03
P17	0.77
P18	-2.33
P19	-1.77
P20	-0.51
P21	-0.21

**Calculated using Chemaxon online calculator*

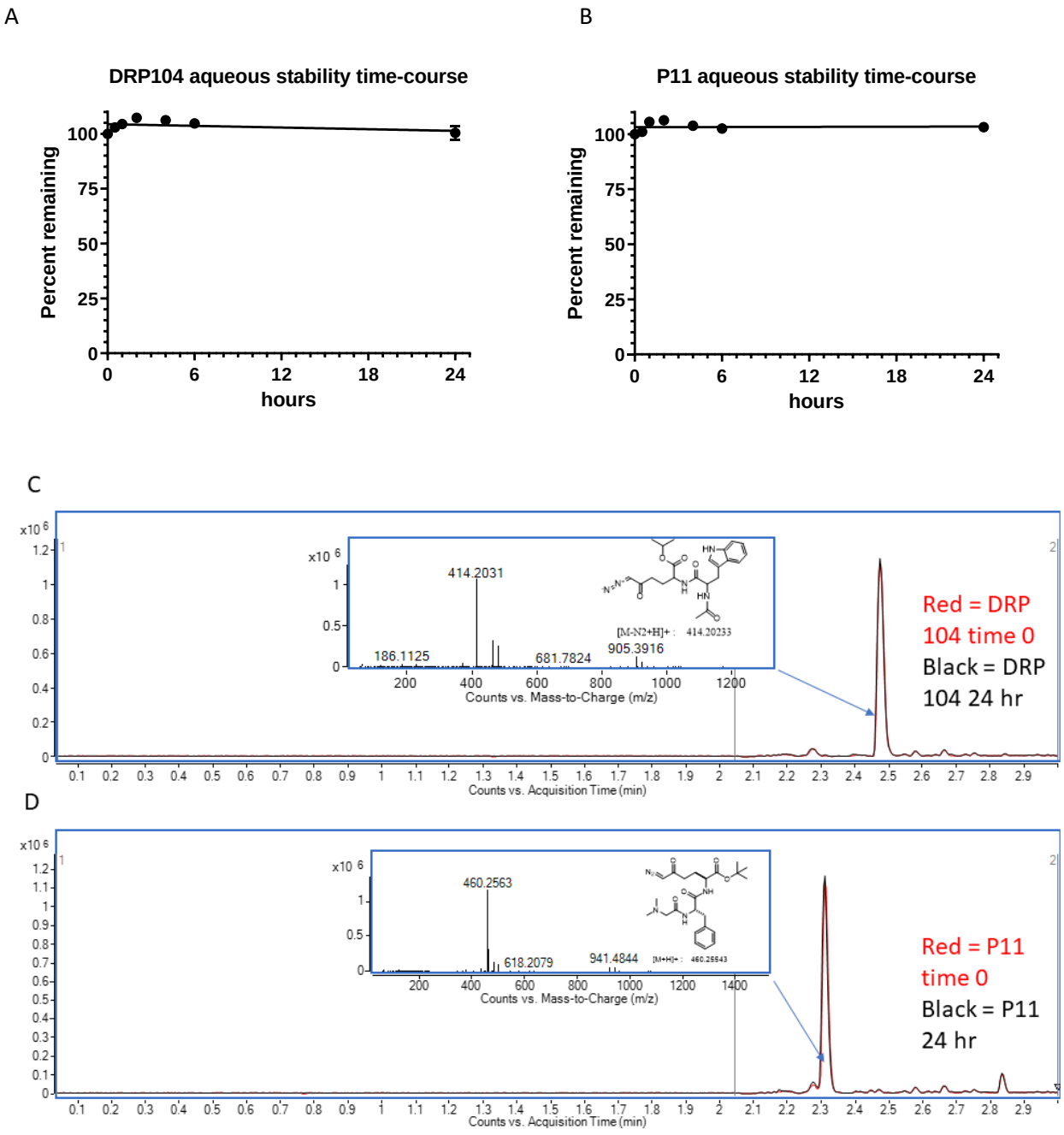


Figure S1. Aqueous stability of DRP 104 and P11. DRP 104 (**A**) and **P11** (**B**) were spiked into PBS (n = 3) and incubated at 37°C. Aliquots were removed at each time-point and percent remaining was measured over 24hr by LCMS; Chromatographic traces of DRP 104 (**C**) and **P11** (**D**) at time 0 vs 24 h showed complete stability with no degradation.