

## Supporting Information for

### **Application of the Ugi reaction with multiple amino acids-derived components: synthesis and conformational evaluation of piperazine-based minimalist peptidomimetics**

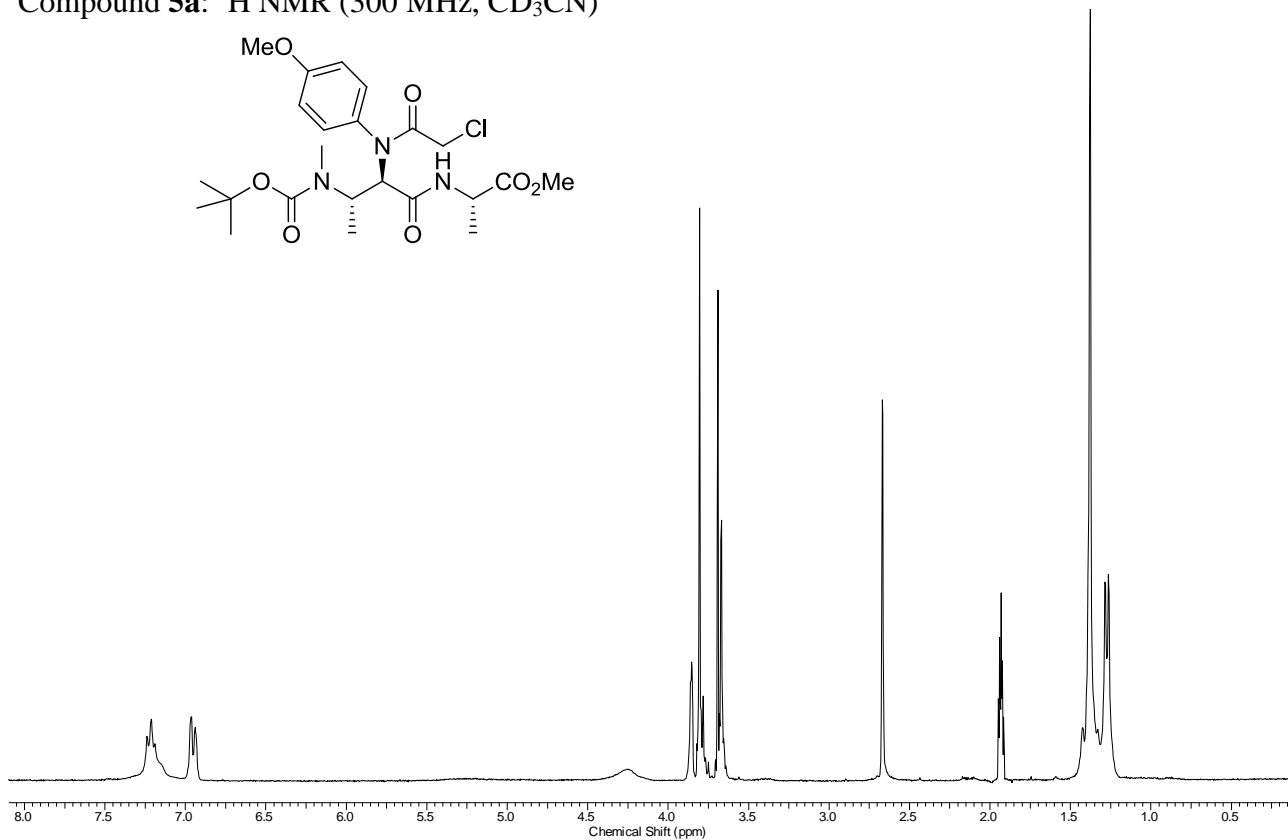
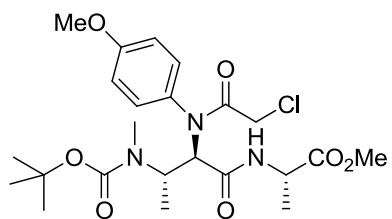
Mattia Stucchi,<sup>a</sup> Silvia Cairati,<sup>a</sup> Rengul Cetin-Atalay,<sup>b</sup> Michael S. Christodoulou,<sup>a</sup> Giovanni Grazioso,<sup>c</sup> Gennaro Pescitelli,<sup>d</sup> Alessandra Silvani,<sup>a,\*</sup> Deniz Cansen Yildirim<sup>e</sup> and Giordano Lesma.<sup>a</sup>

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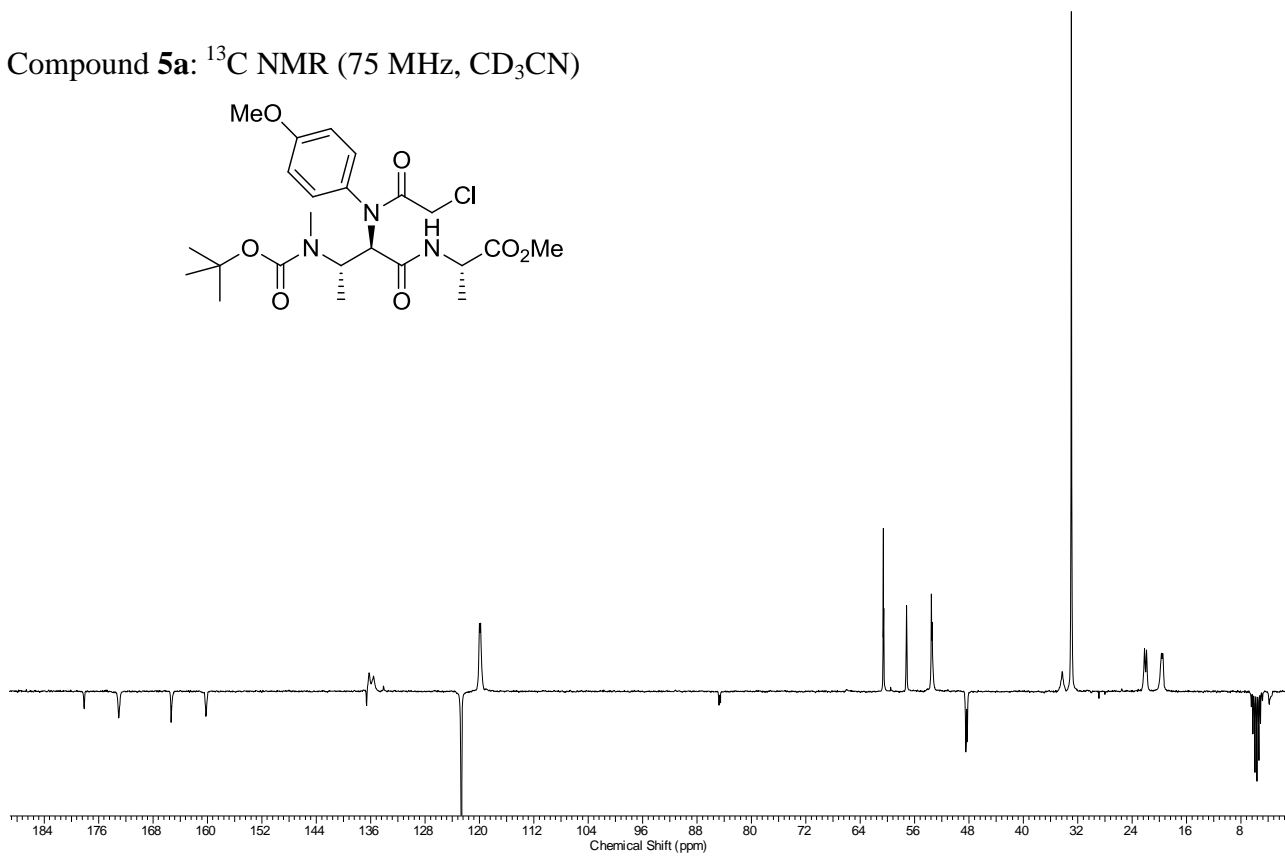
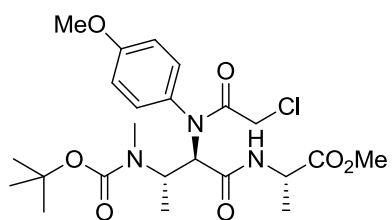
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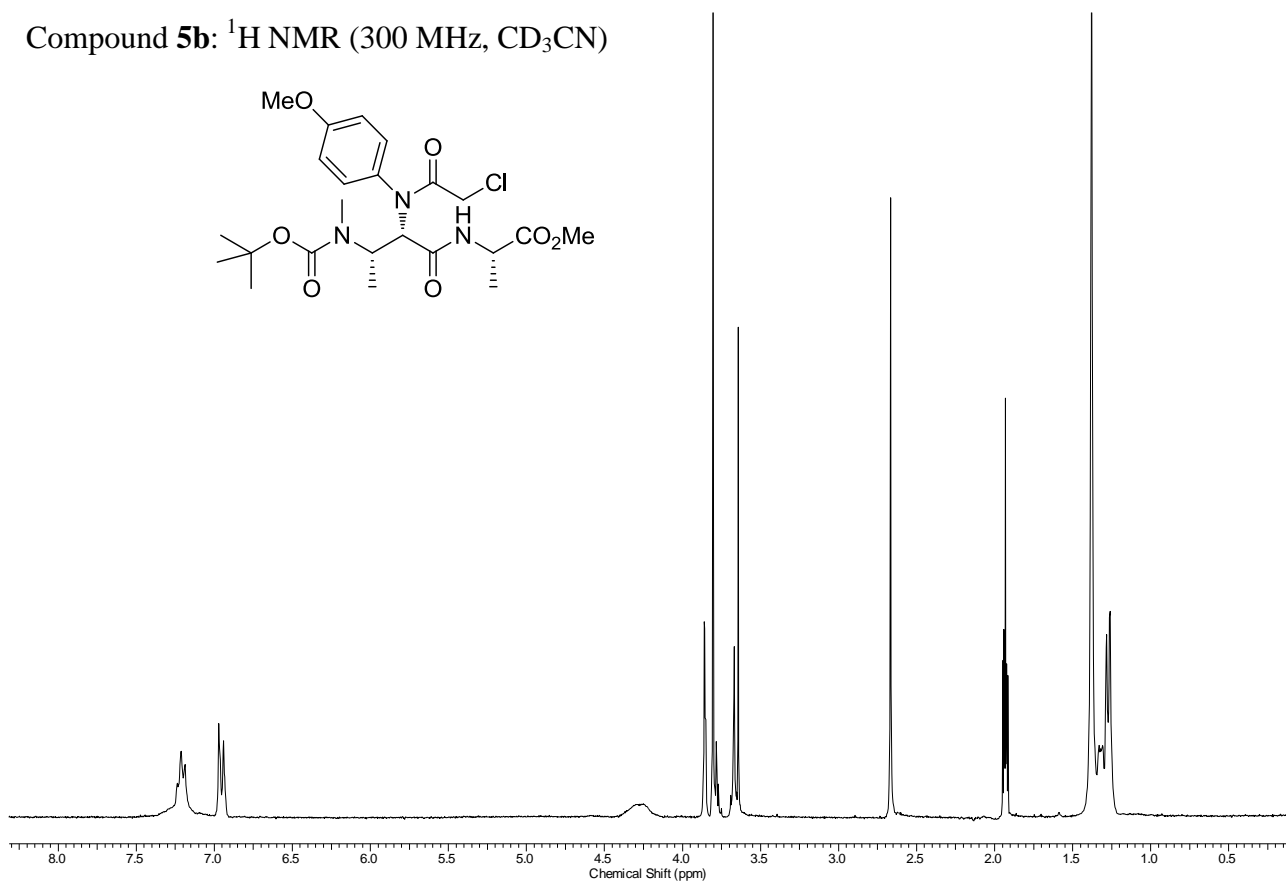
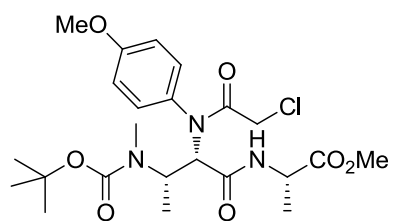
Compound **5a**:  $^1\text{H}$  NMR (300 MHz,  $\text{CD}_3\text{CN}$ )



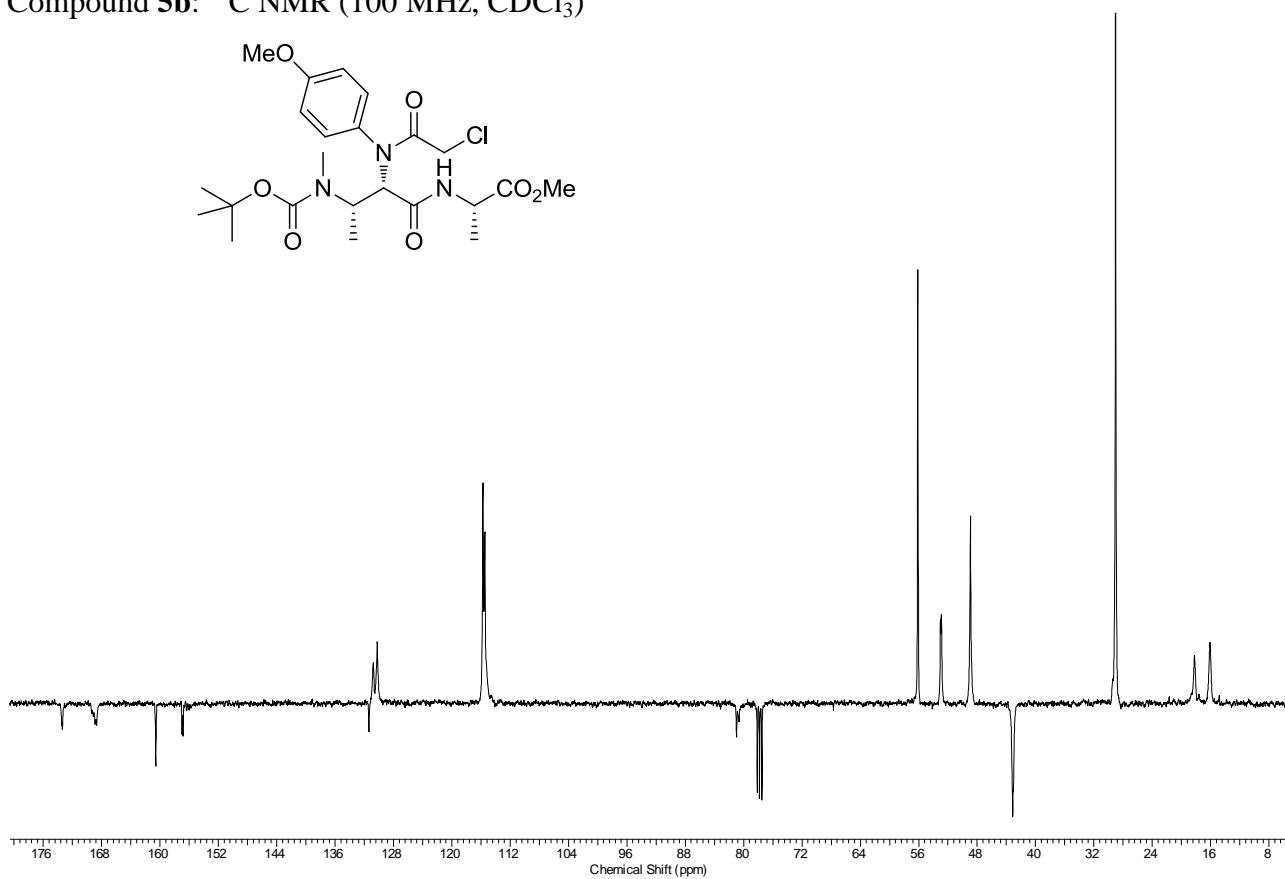
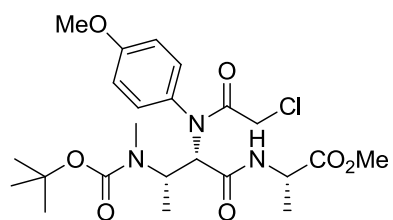
Compound **5a**:  $^{13}\text{C}$  NMR (75 MHz,  $\text{CD}_3\text{CN}$ )



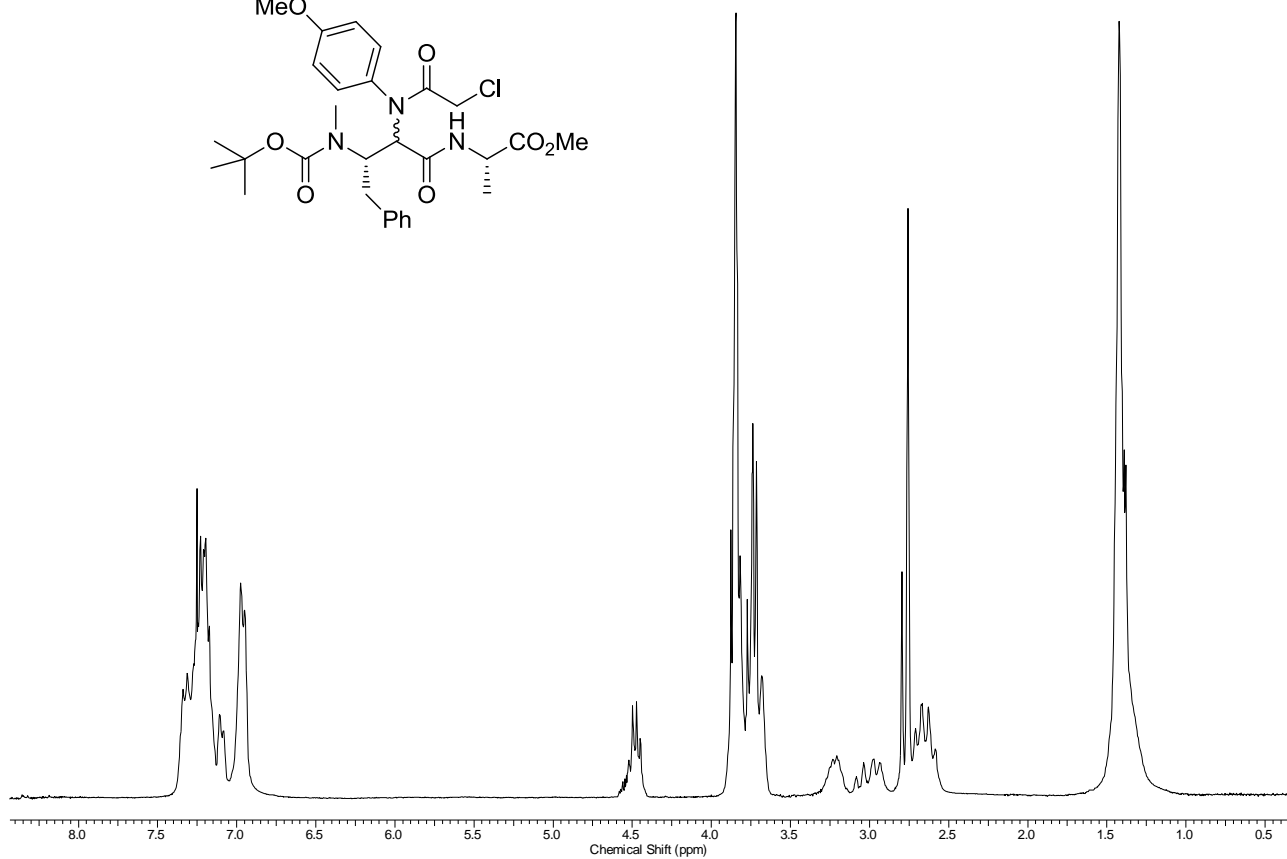
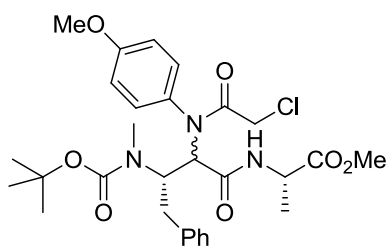
Compound **5b**:  $^1\text{H}$  NMR (300 MHz,  $\text{CD}_3\text{CN}$ )



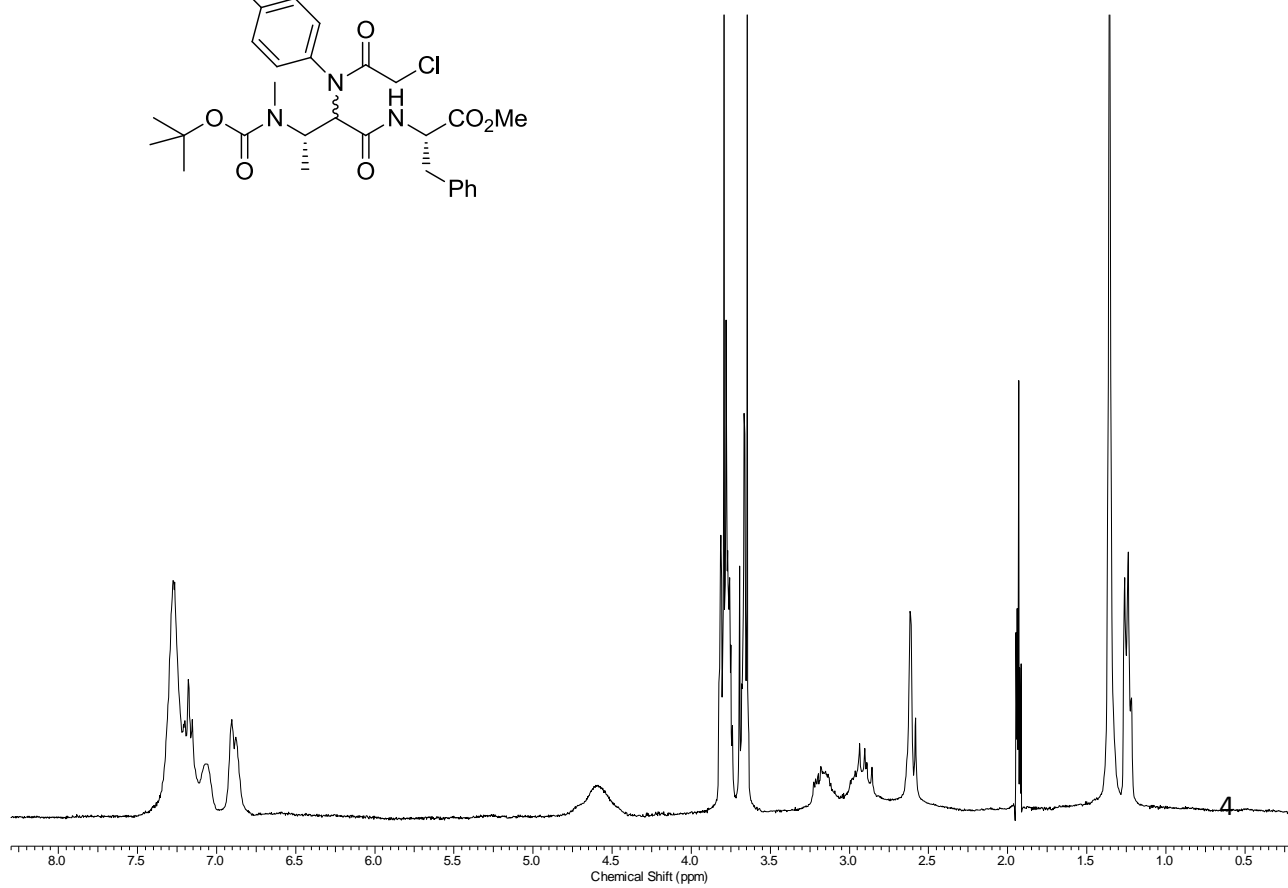
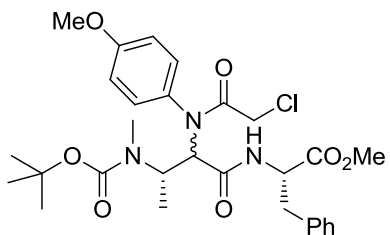
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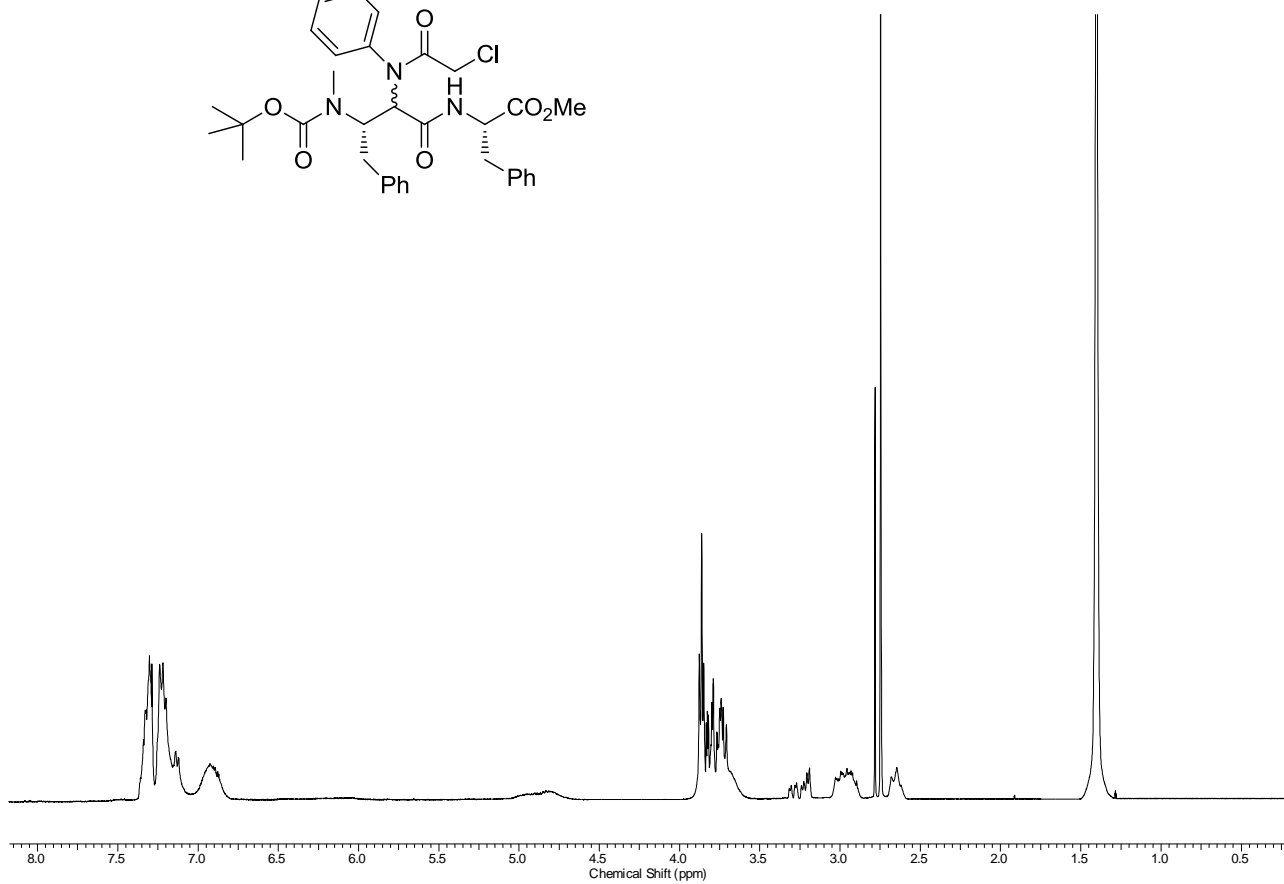
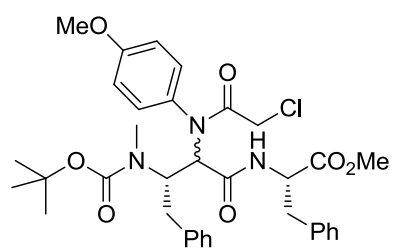
Compound 6:  $^1\text{H}$  NMR (300 MHz,  $\text{CD}_3\text{CN}$ )



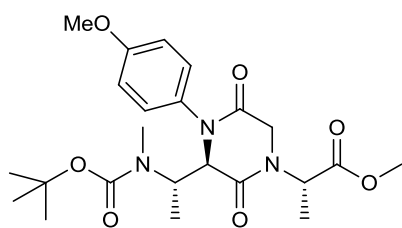
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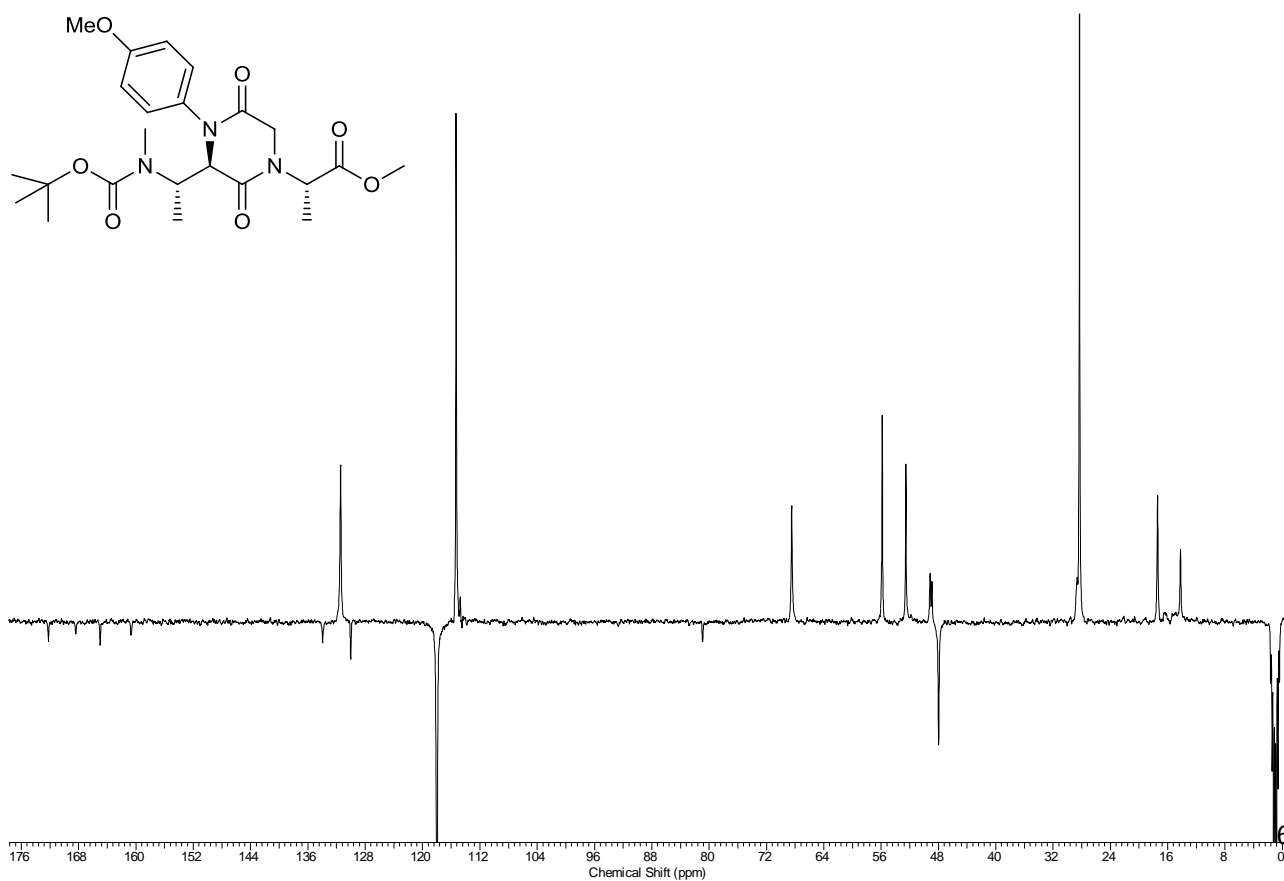
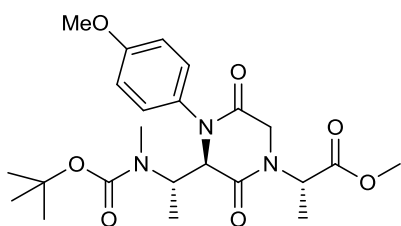
Compound **8**:  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )



Compound **9a**:  $^1\text{H}$  NMR (300 MHz,  $\text{CD}_3\text{CN}$ )



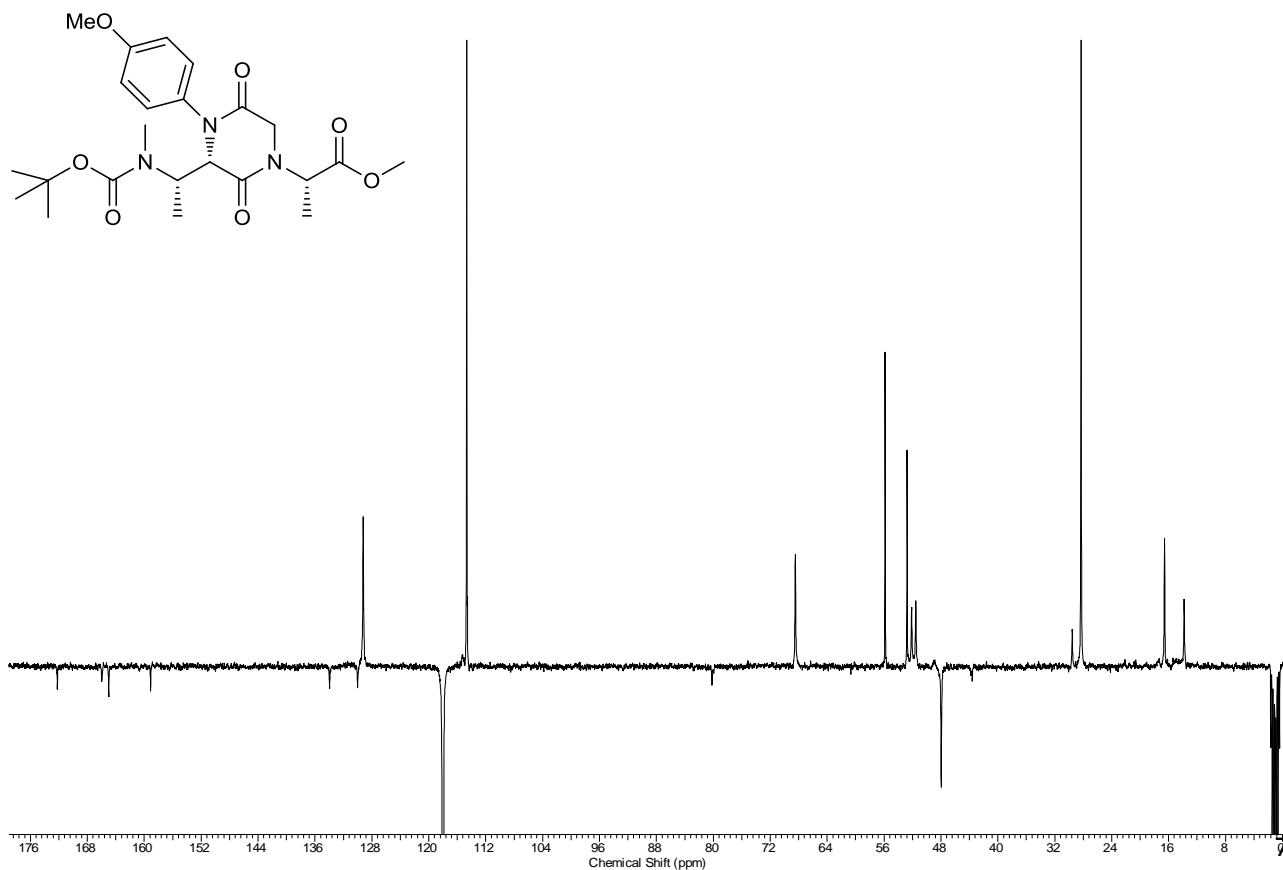
Compound **9a**:  $^{13}\text{C}$  NMR (100 MHz,  $\text{CD}_3\text{CN}$ )



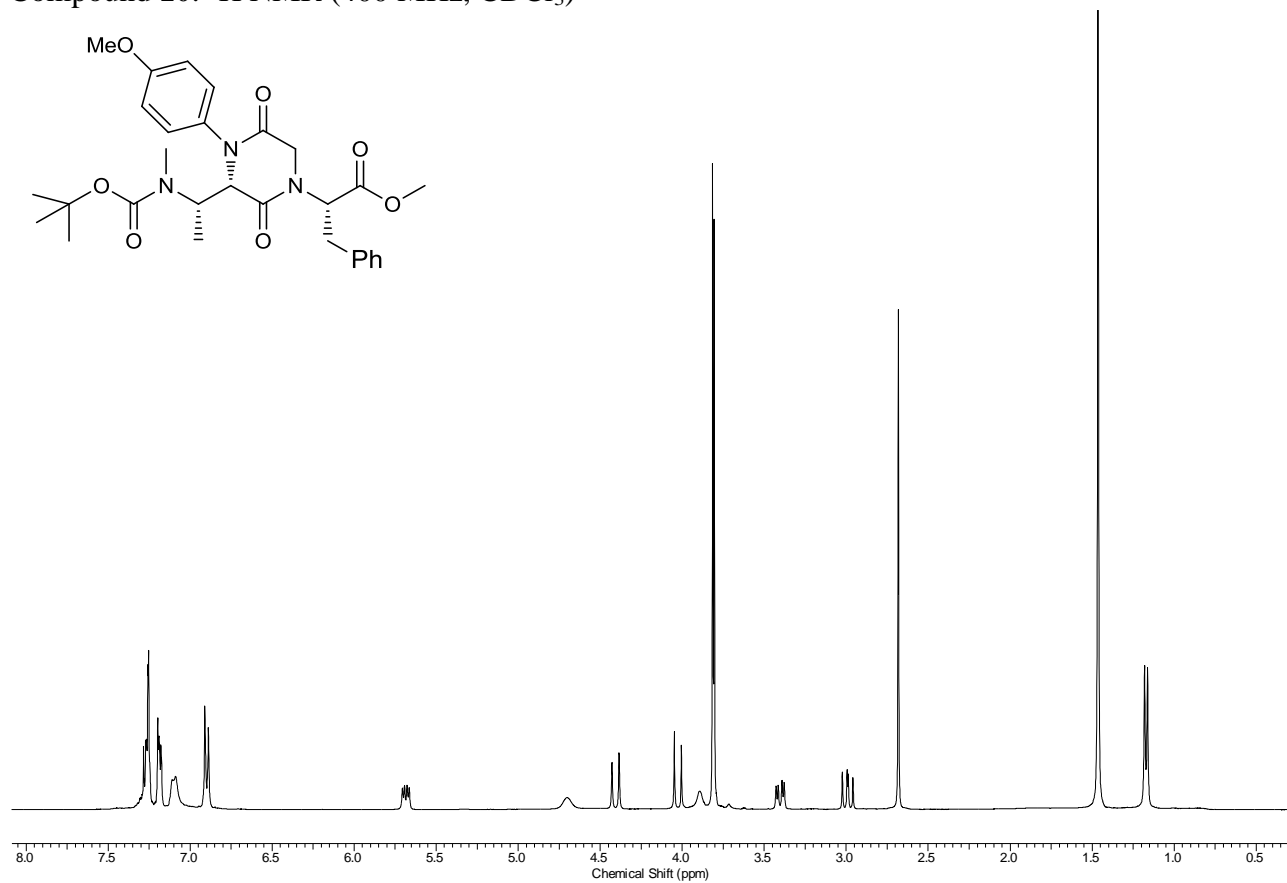
Compound **9b**:  $^1\text{H}$  NMR (400 MHz,  $\text{CD}_3\text{CN}$ )



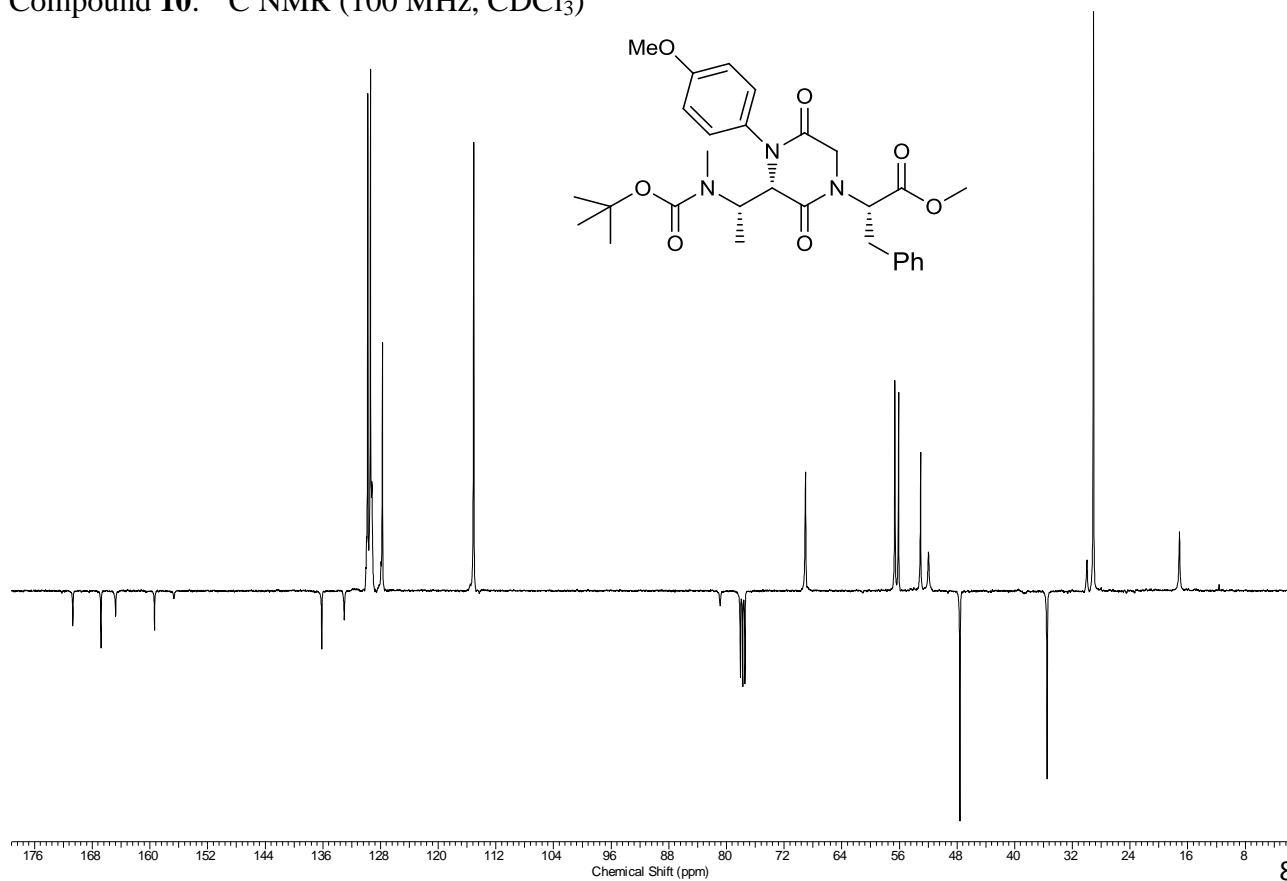
Compound **9b**:  $^{13}\text{C}$  NMR (100 MHz,  $\text{CD}_3\text{CN}$ )



Compound **10**:  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )

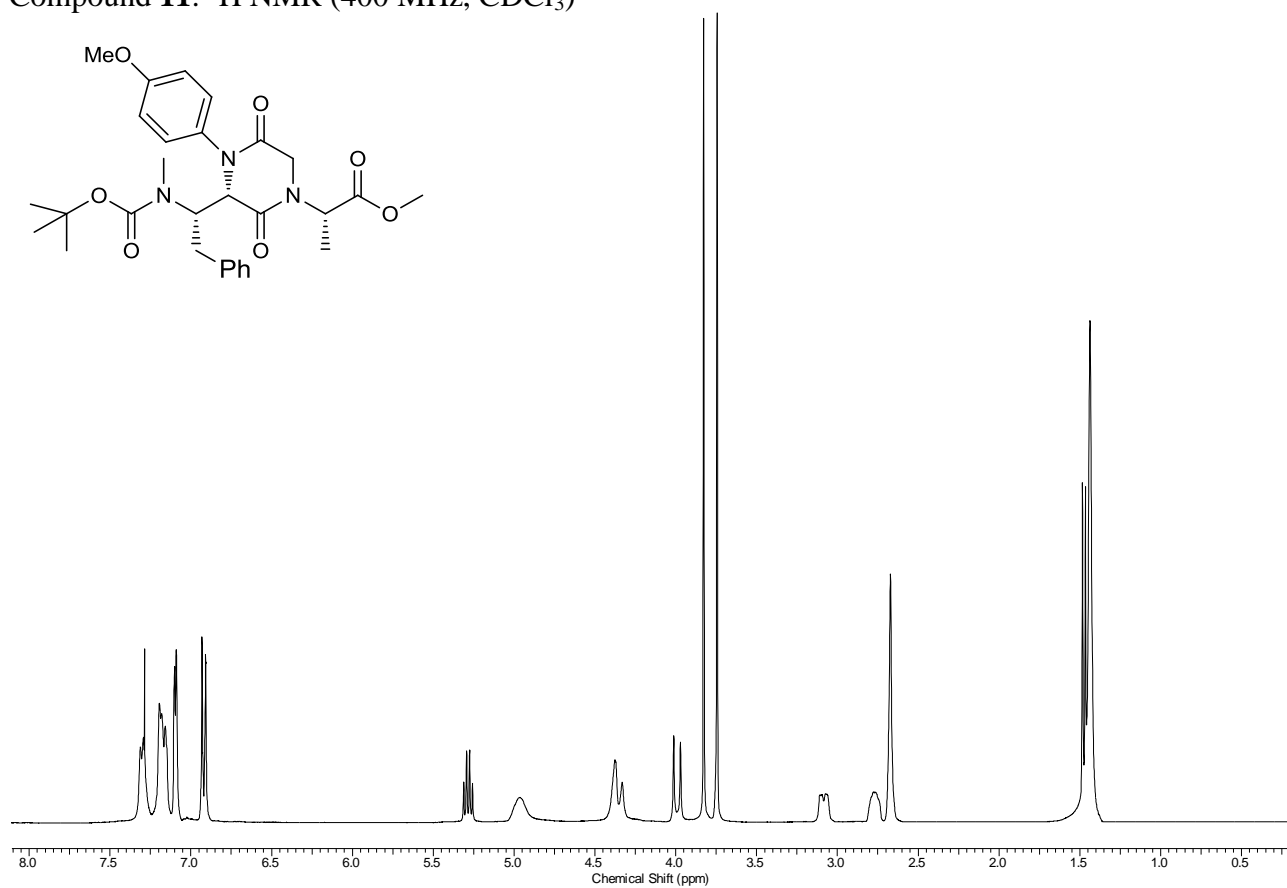


Compound **10**:  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )

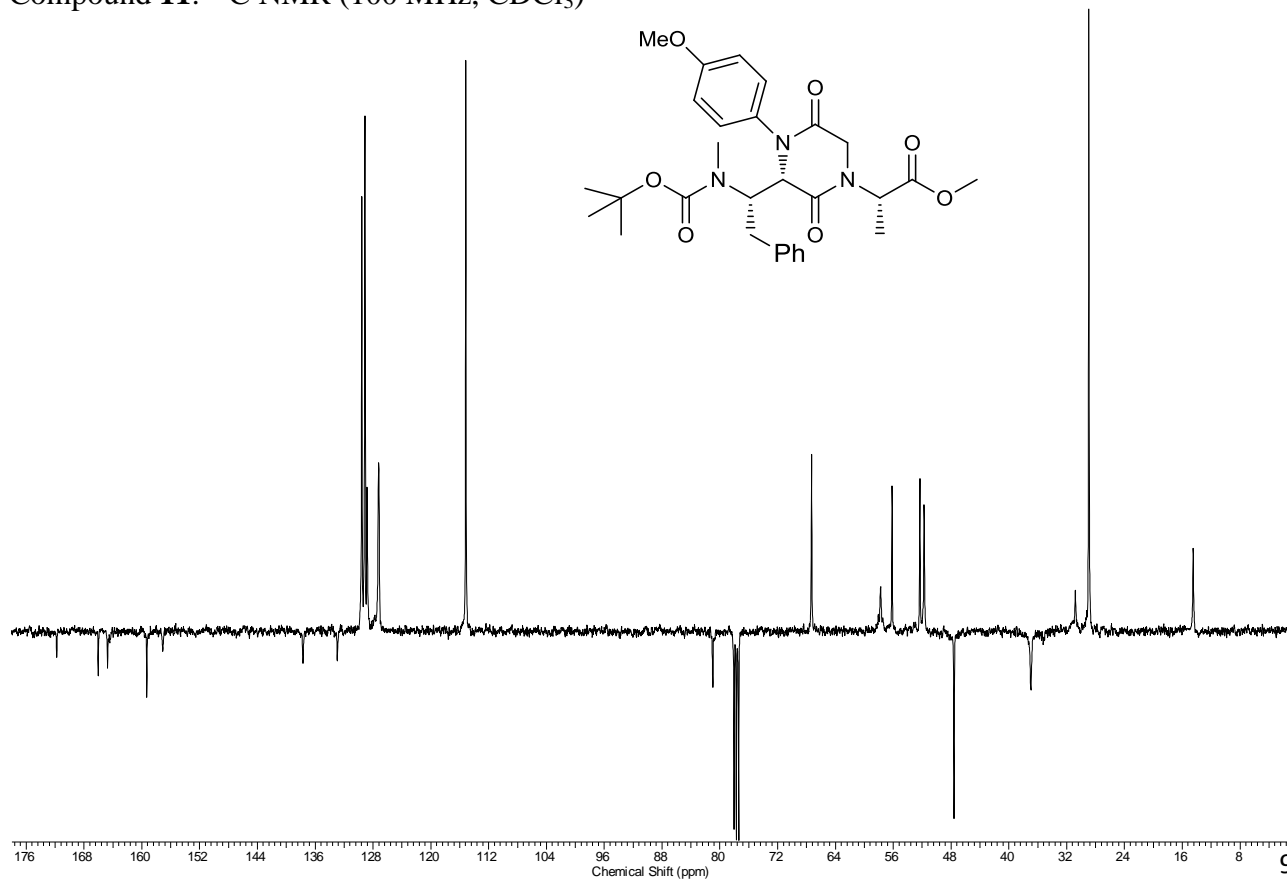




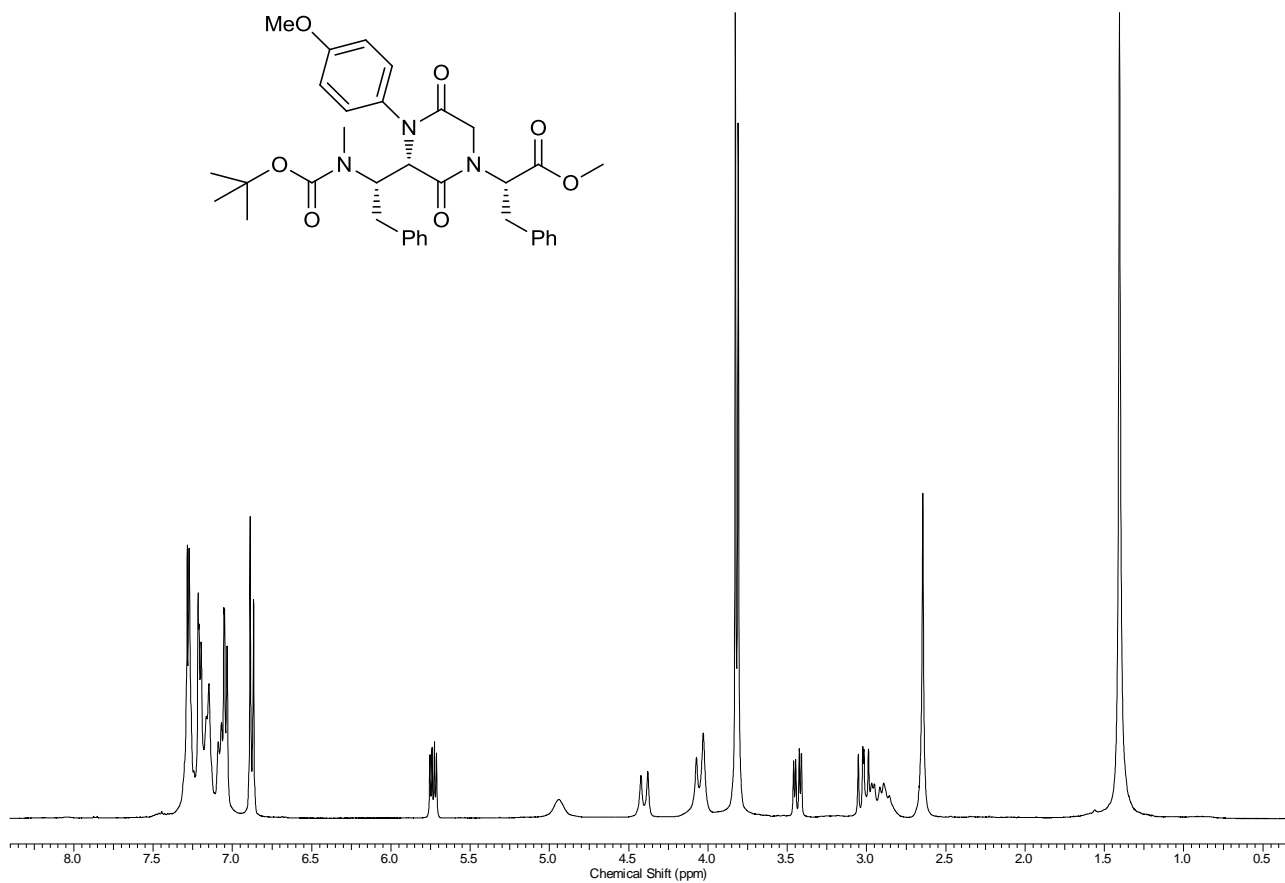
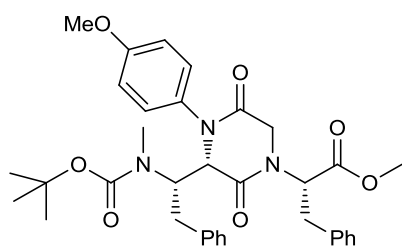
Compound **11**:  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )



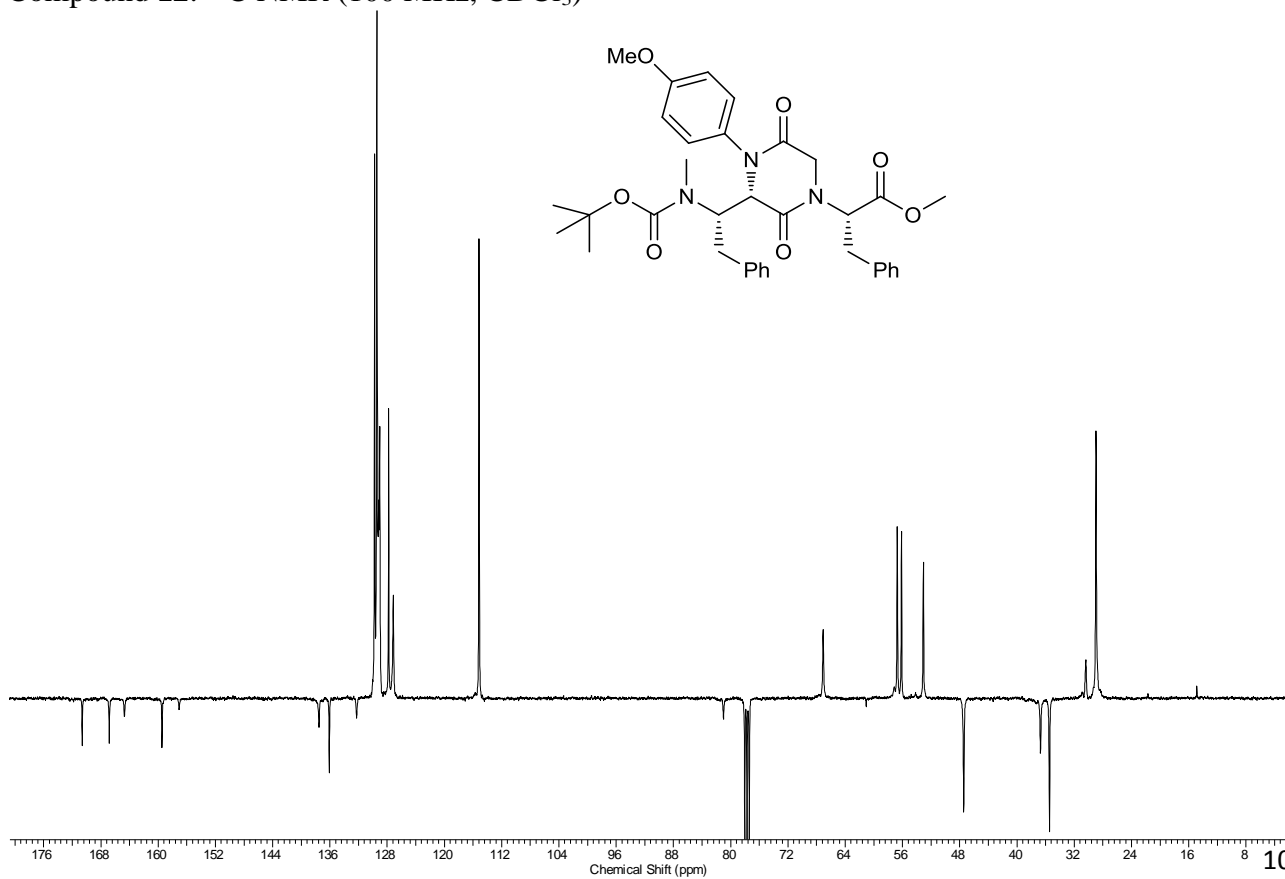
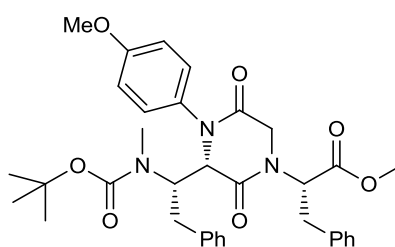
Compound **11**:  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )



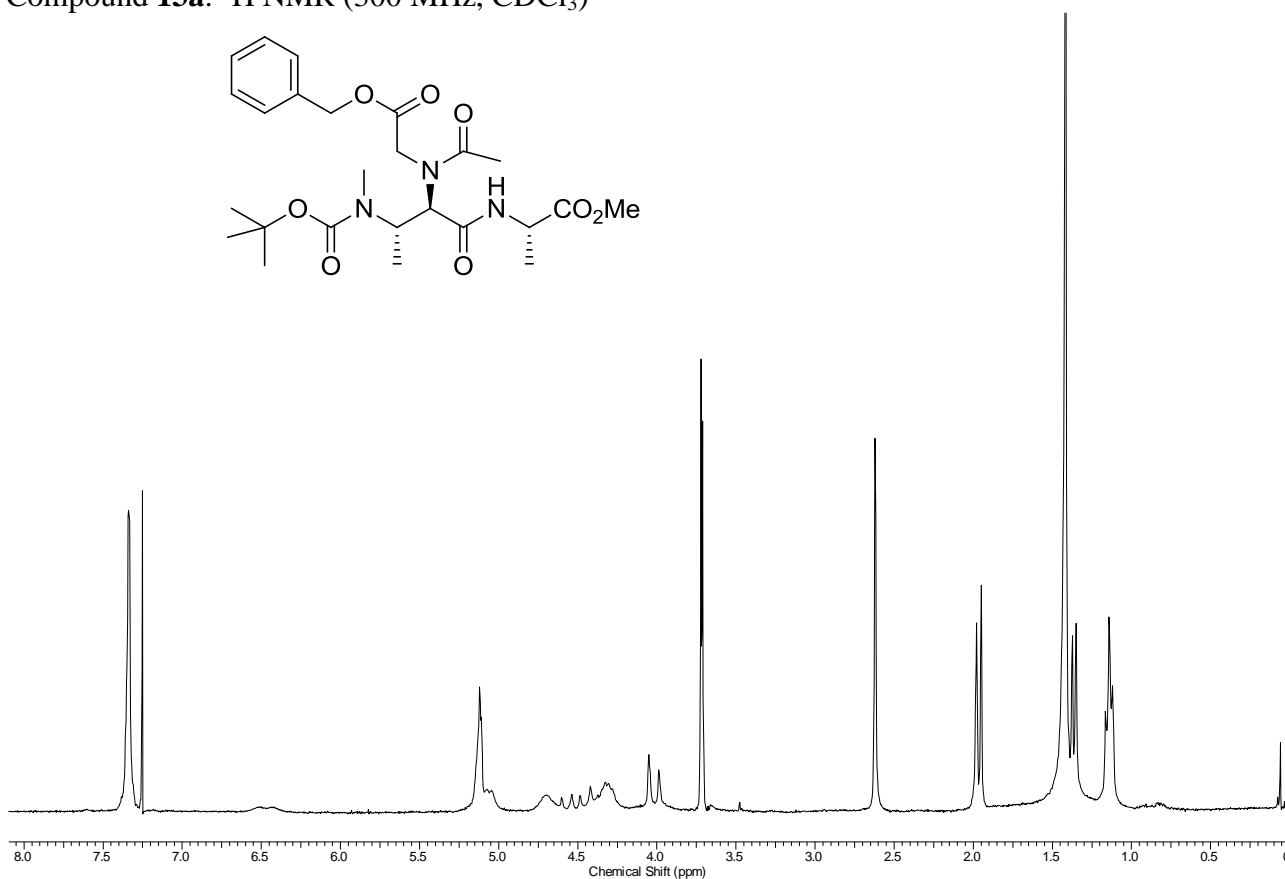
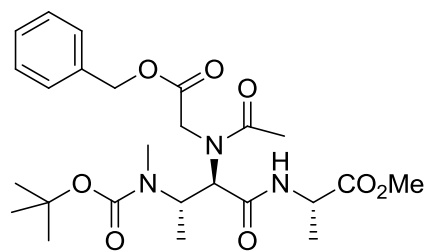
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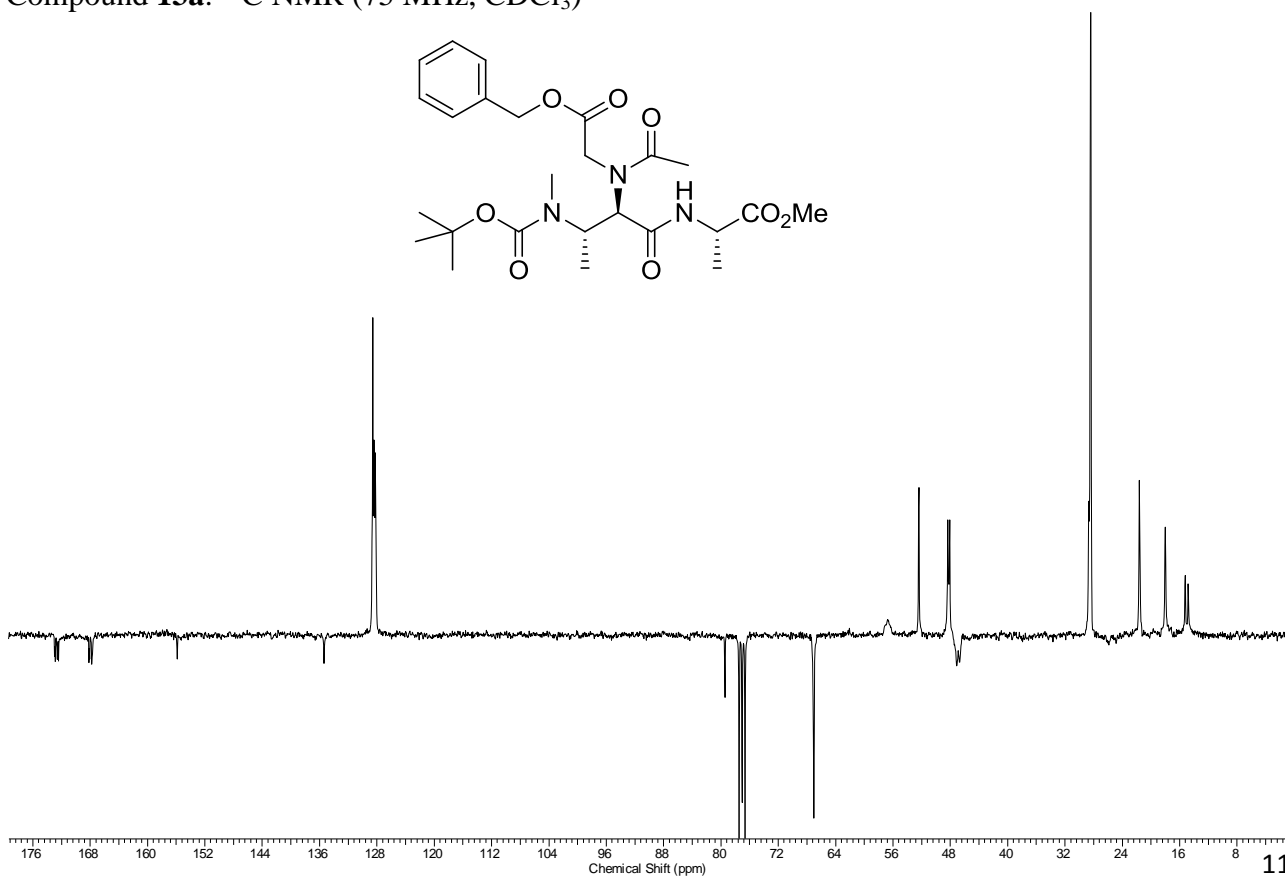
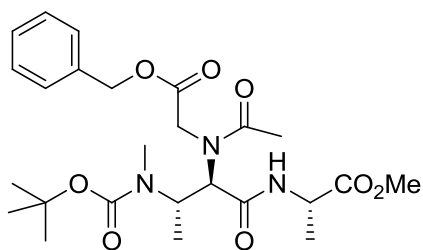
Compound 12:  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )



Compound **13a**:  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )

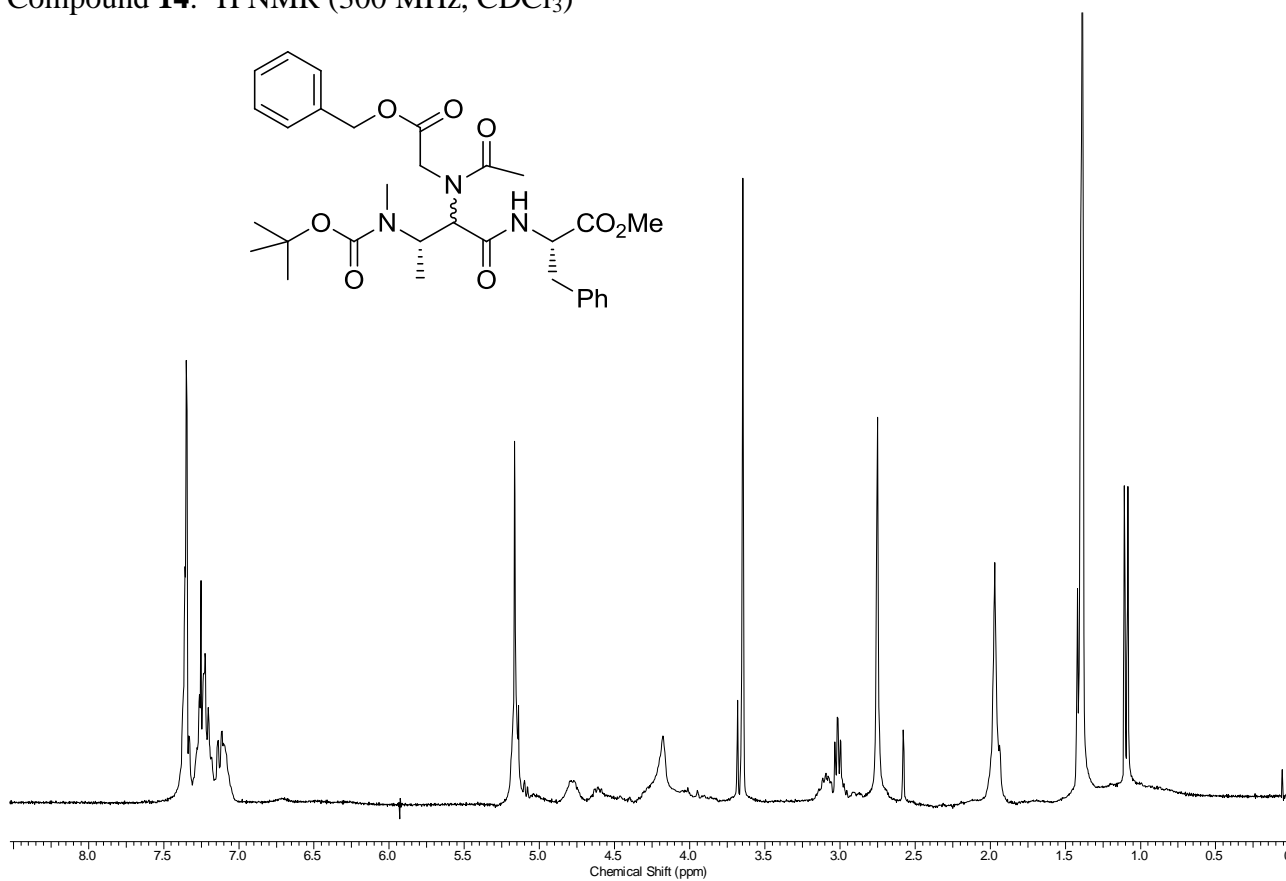
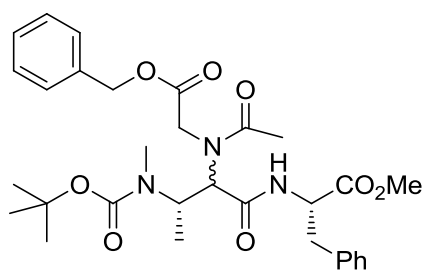


Compound **13a**:  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )

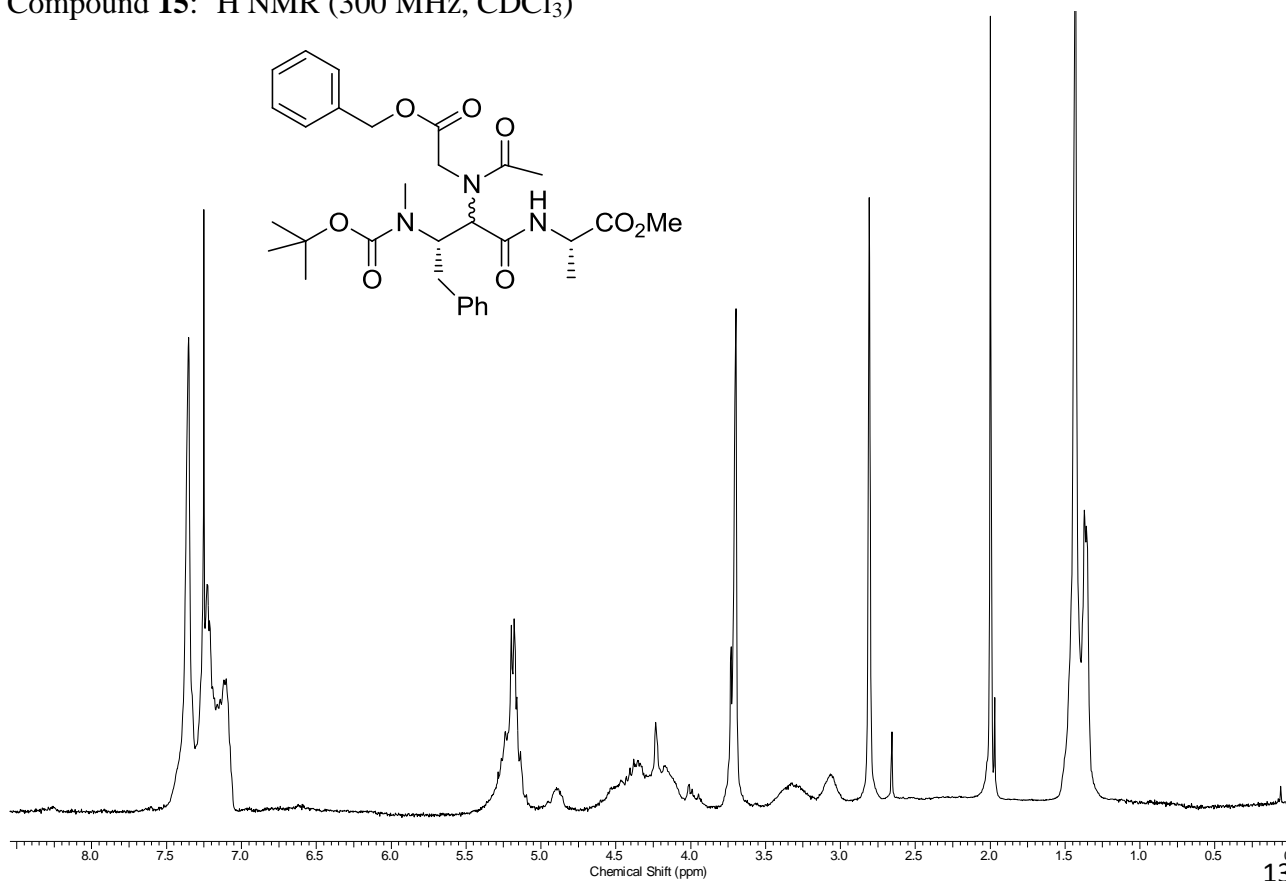
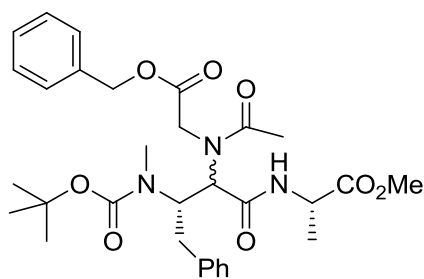




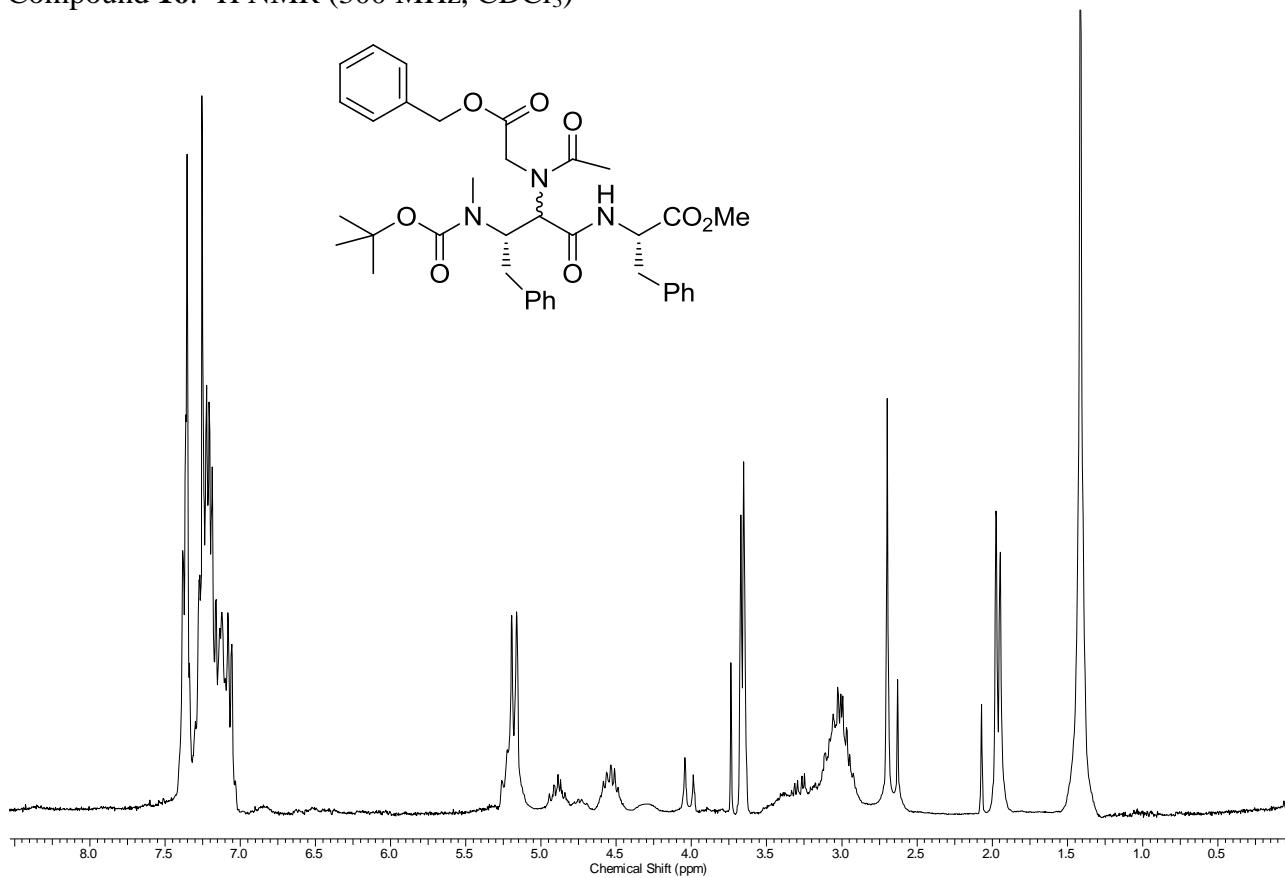
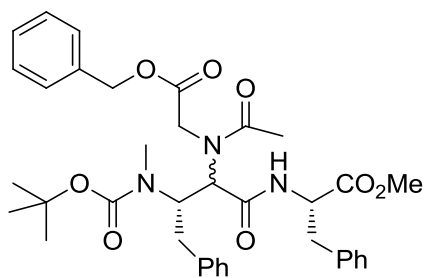
Compound 14:  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )



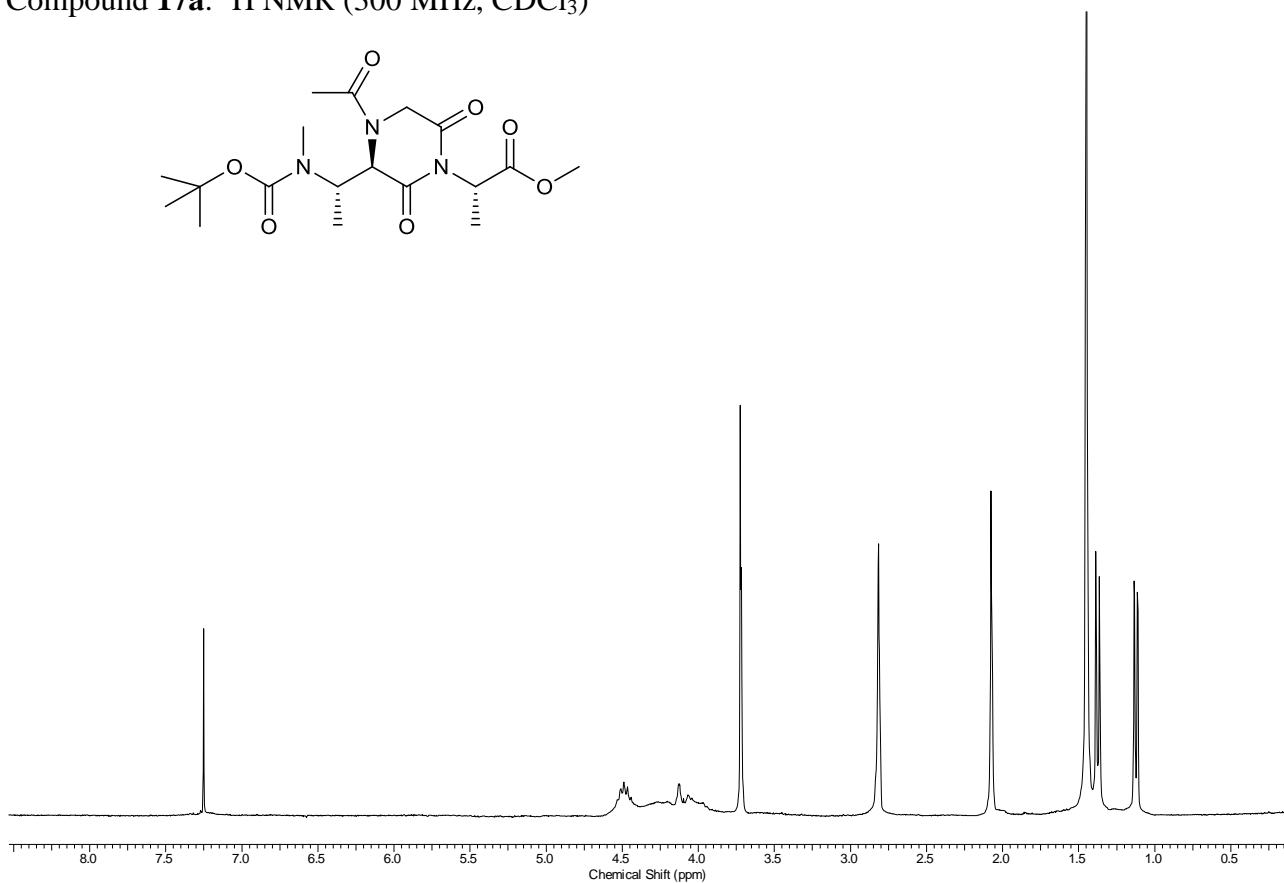
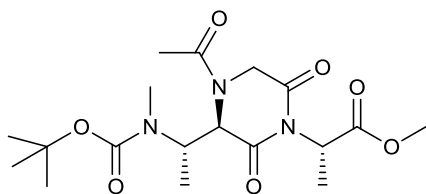
Compound 15:  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )



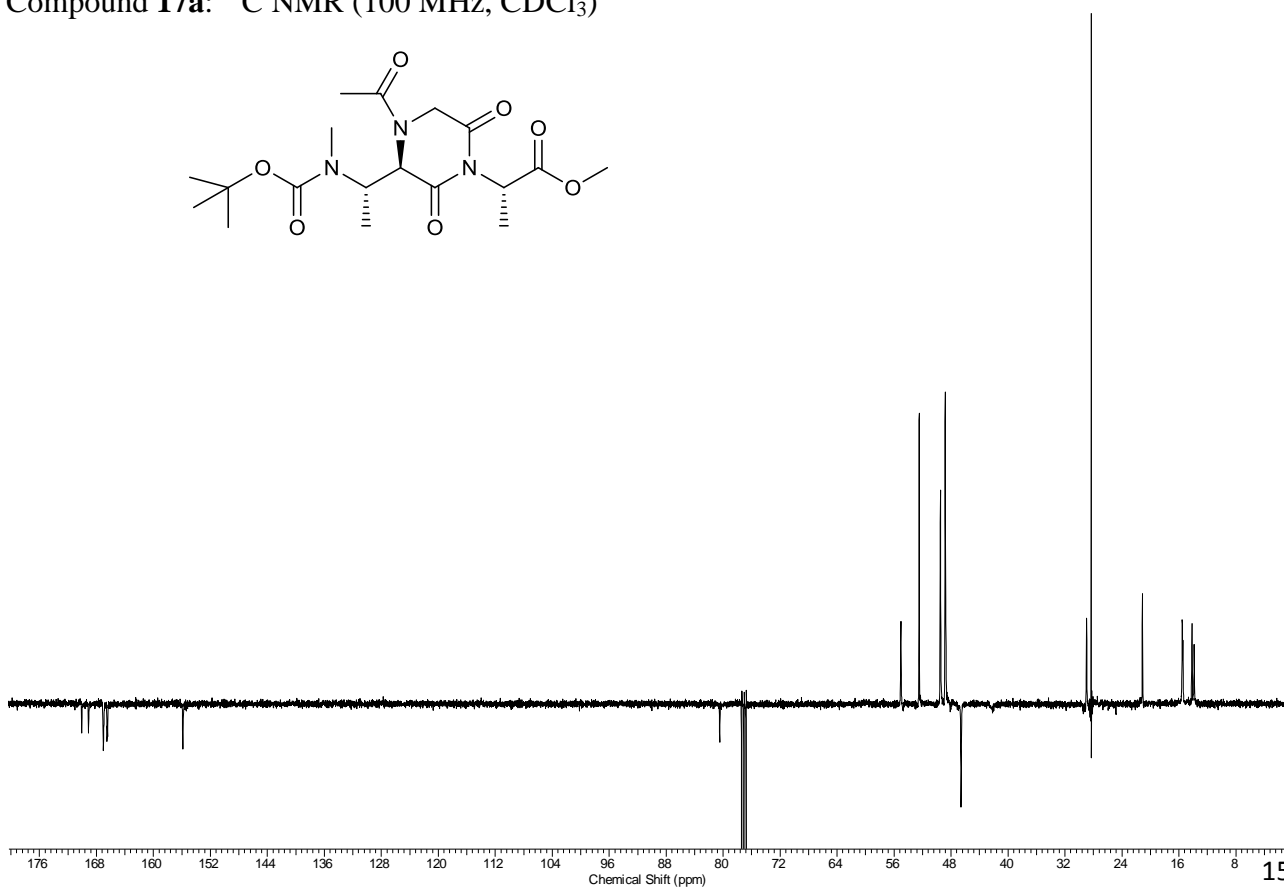
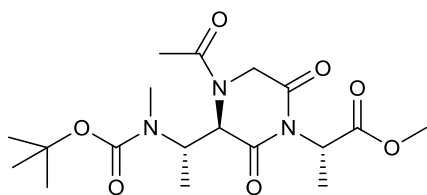
Compound **16**:  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )



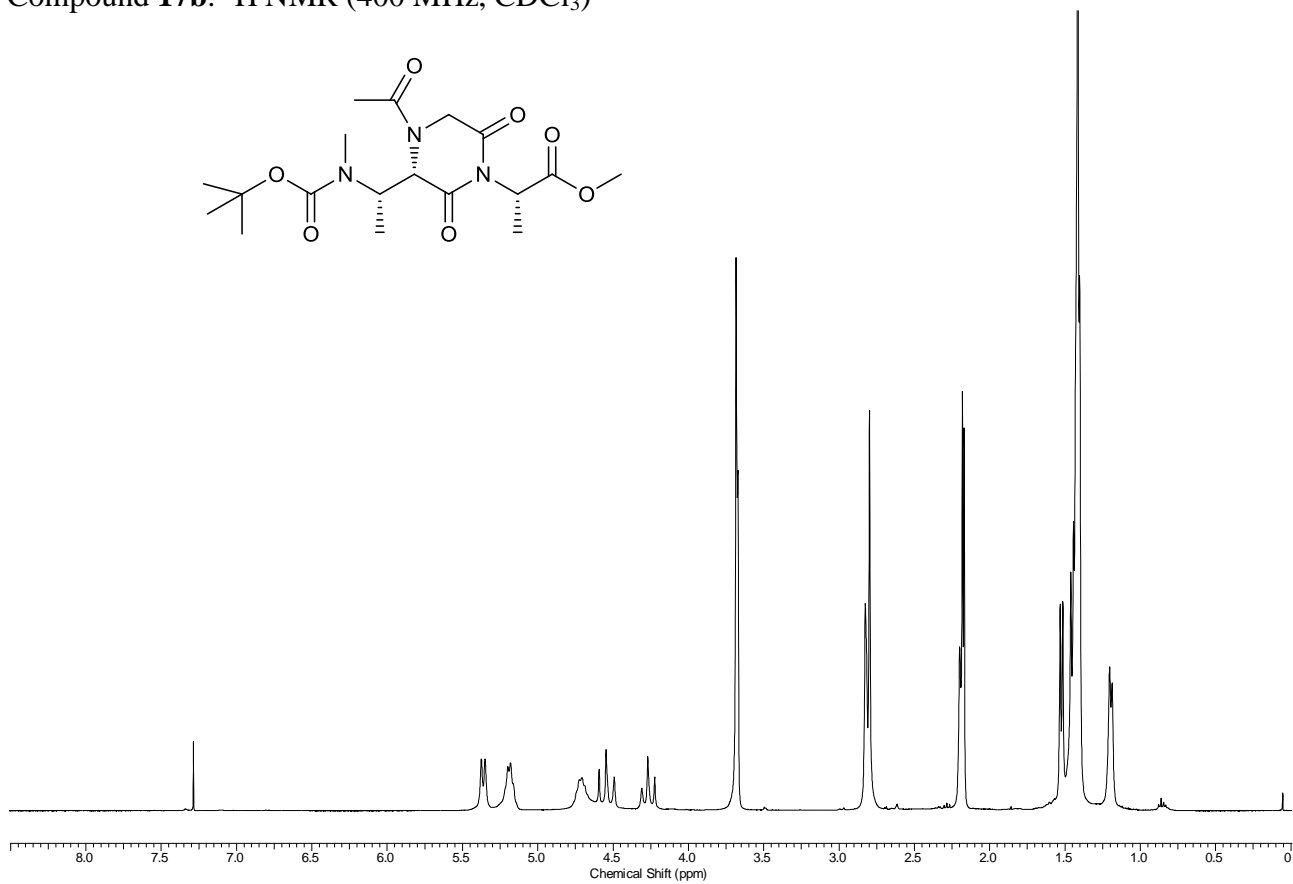
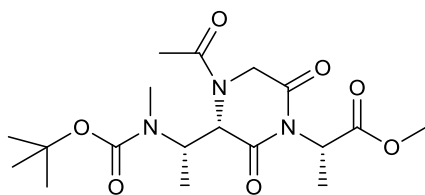
Compound **17a**:  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )



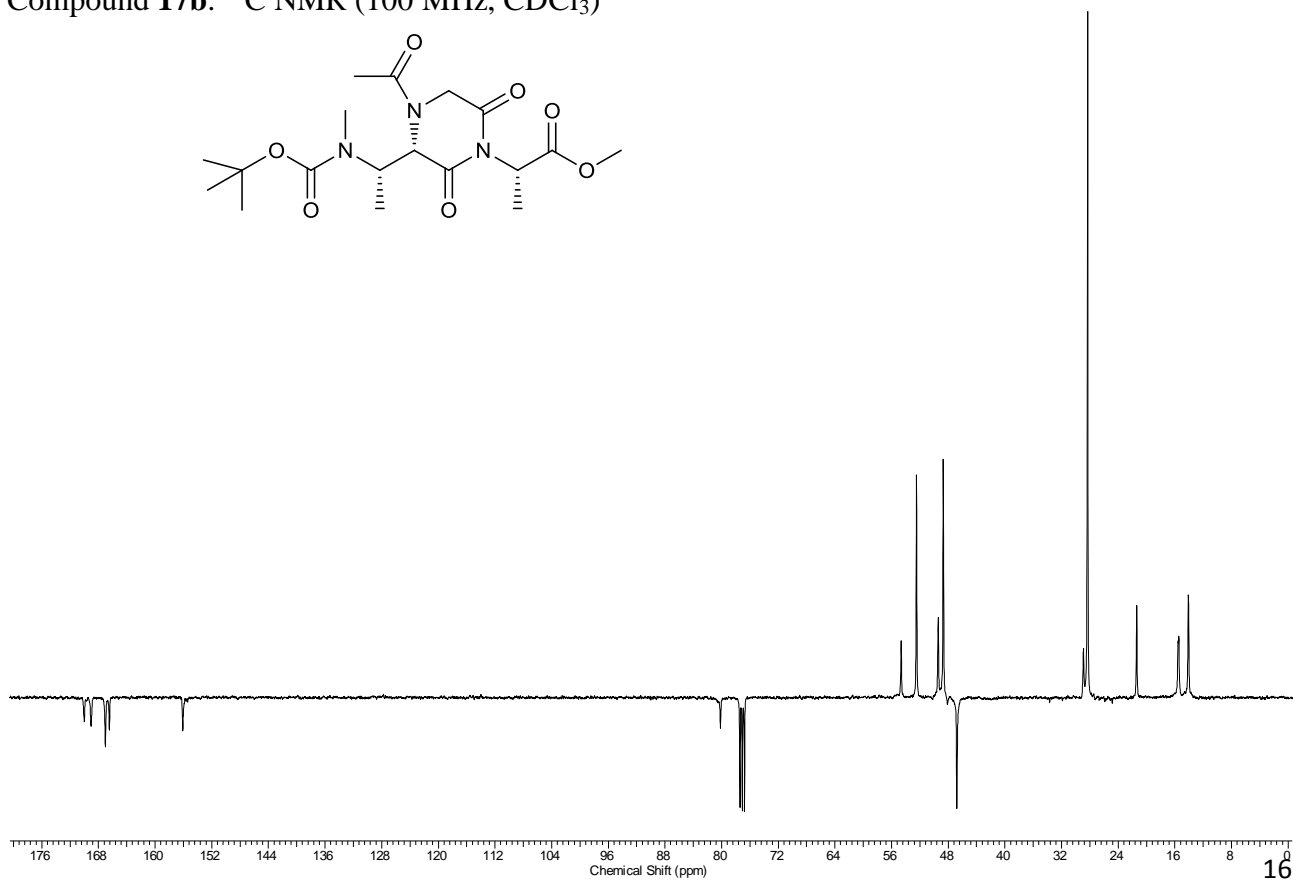
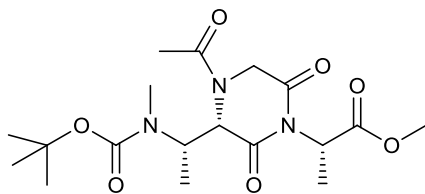
Compound **17a**:  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )



Compound **17b**:  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )

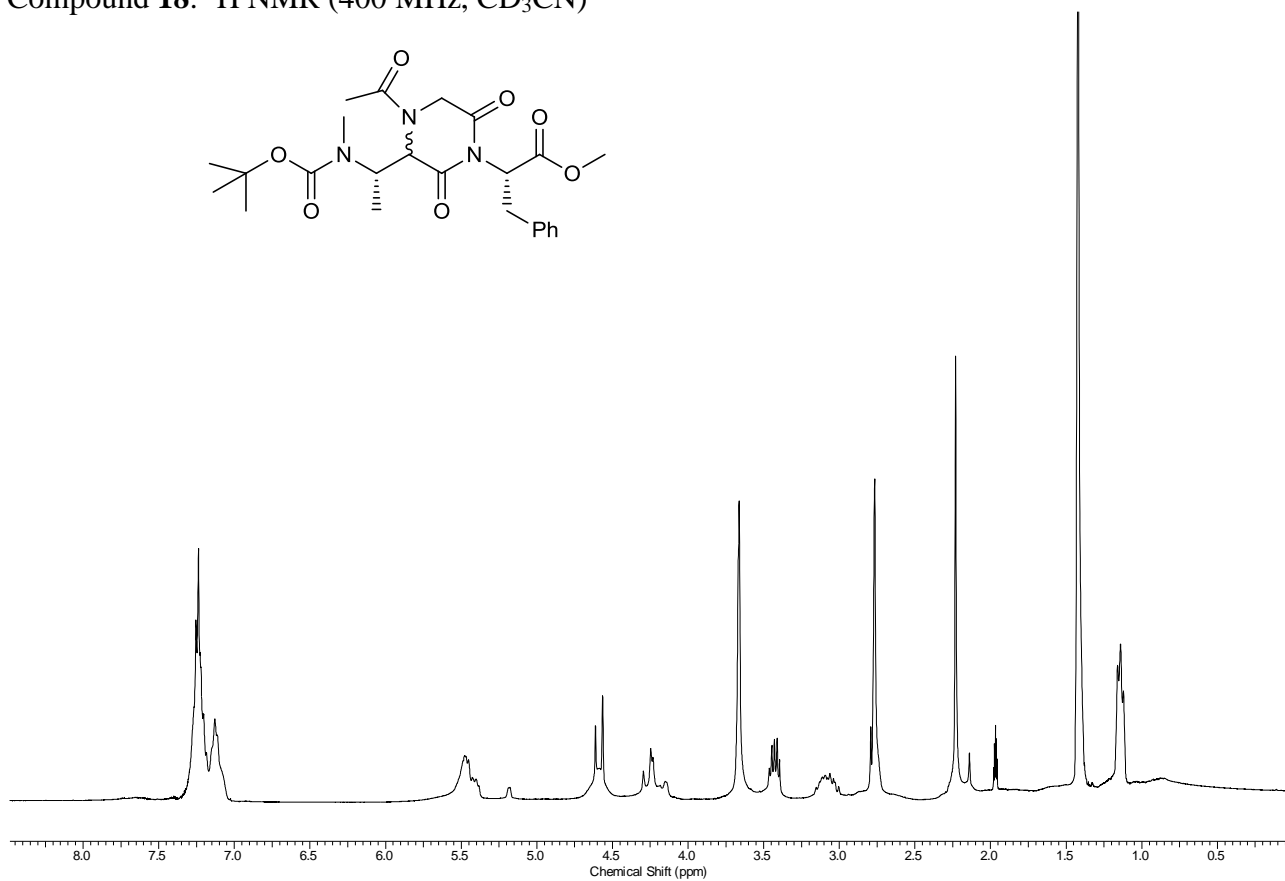
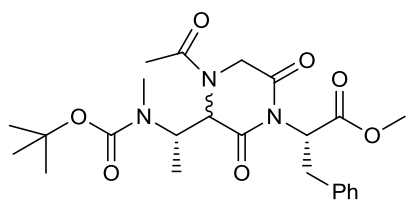


Compound **17b**:  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )

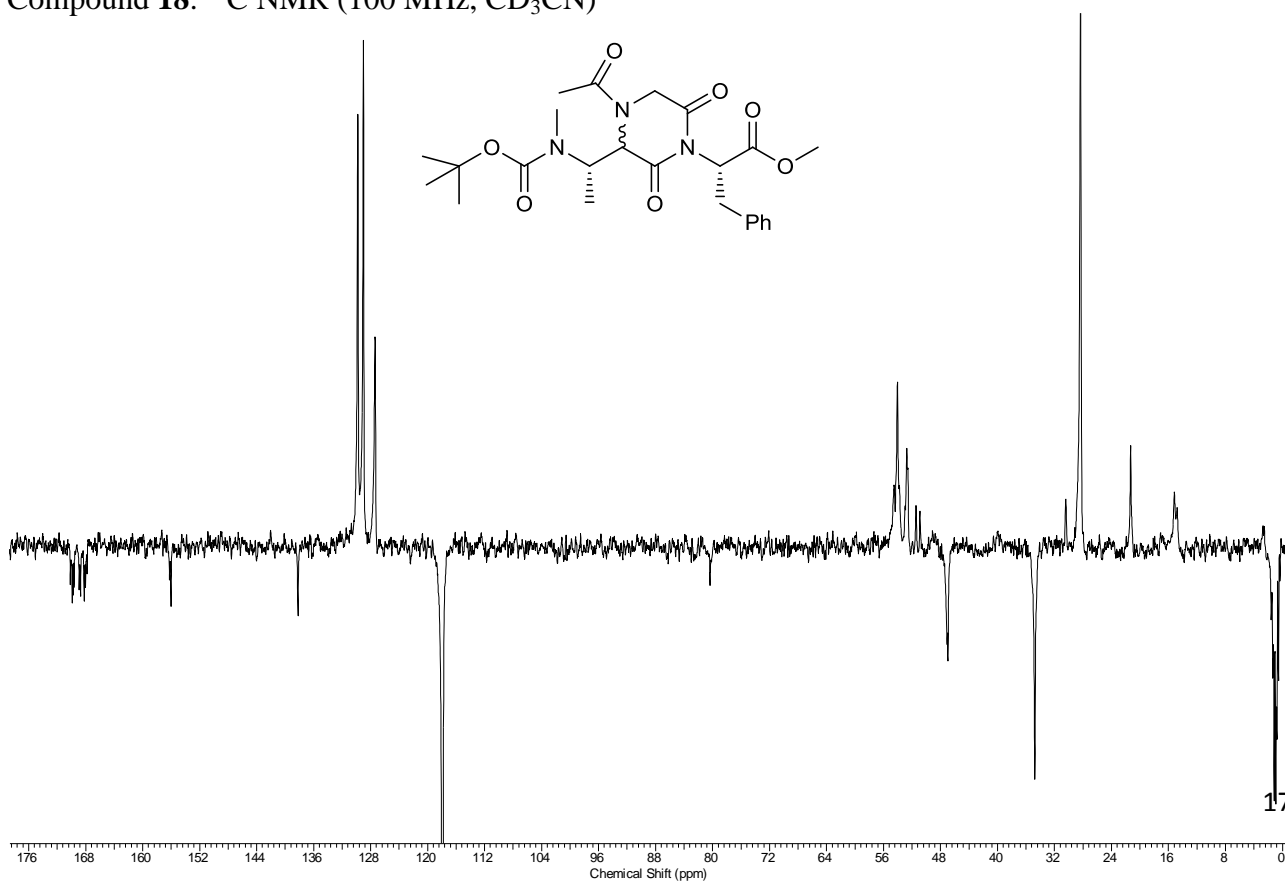
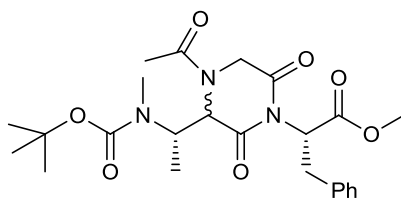




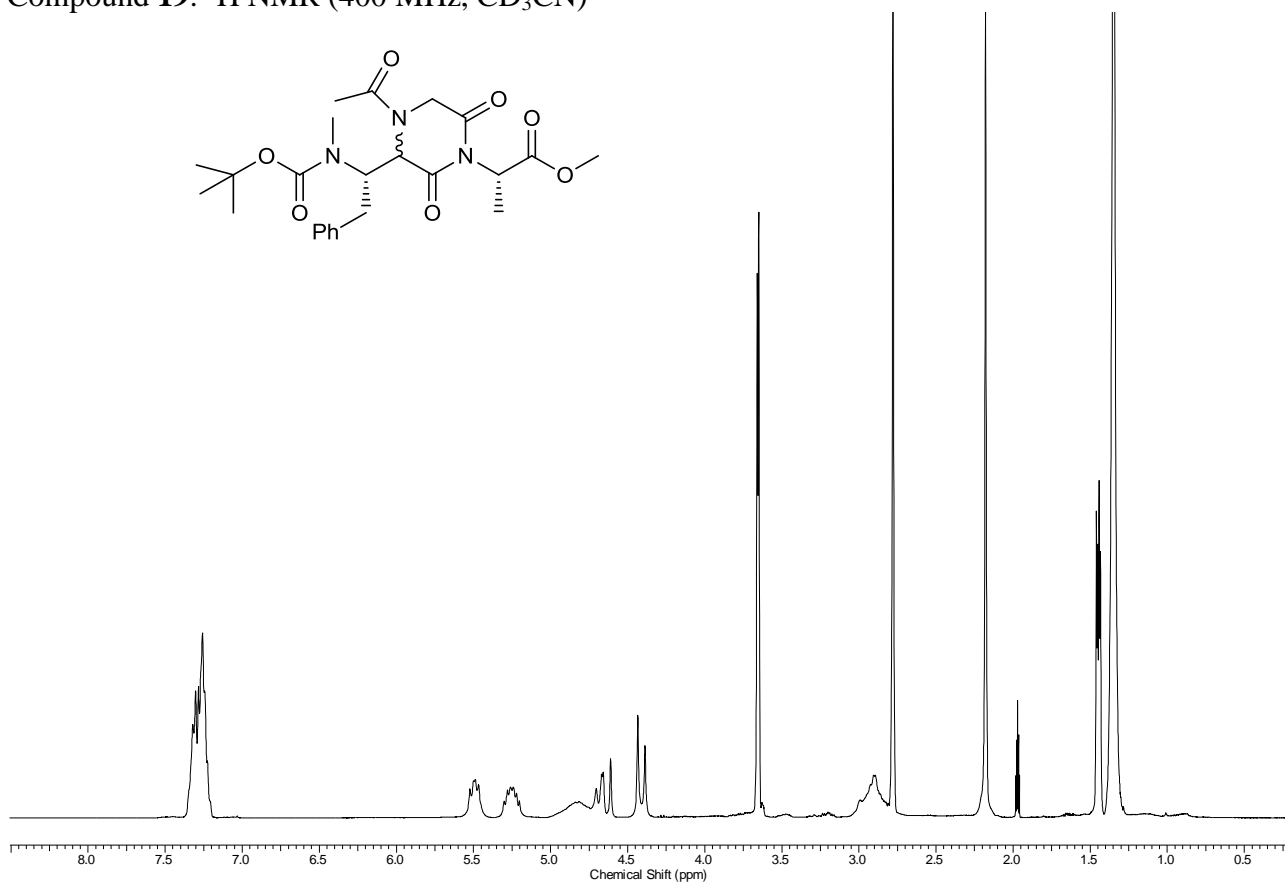
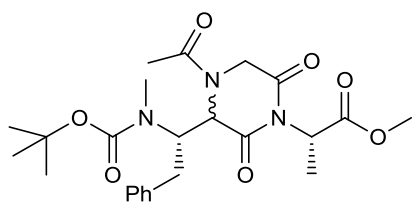
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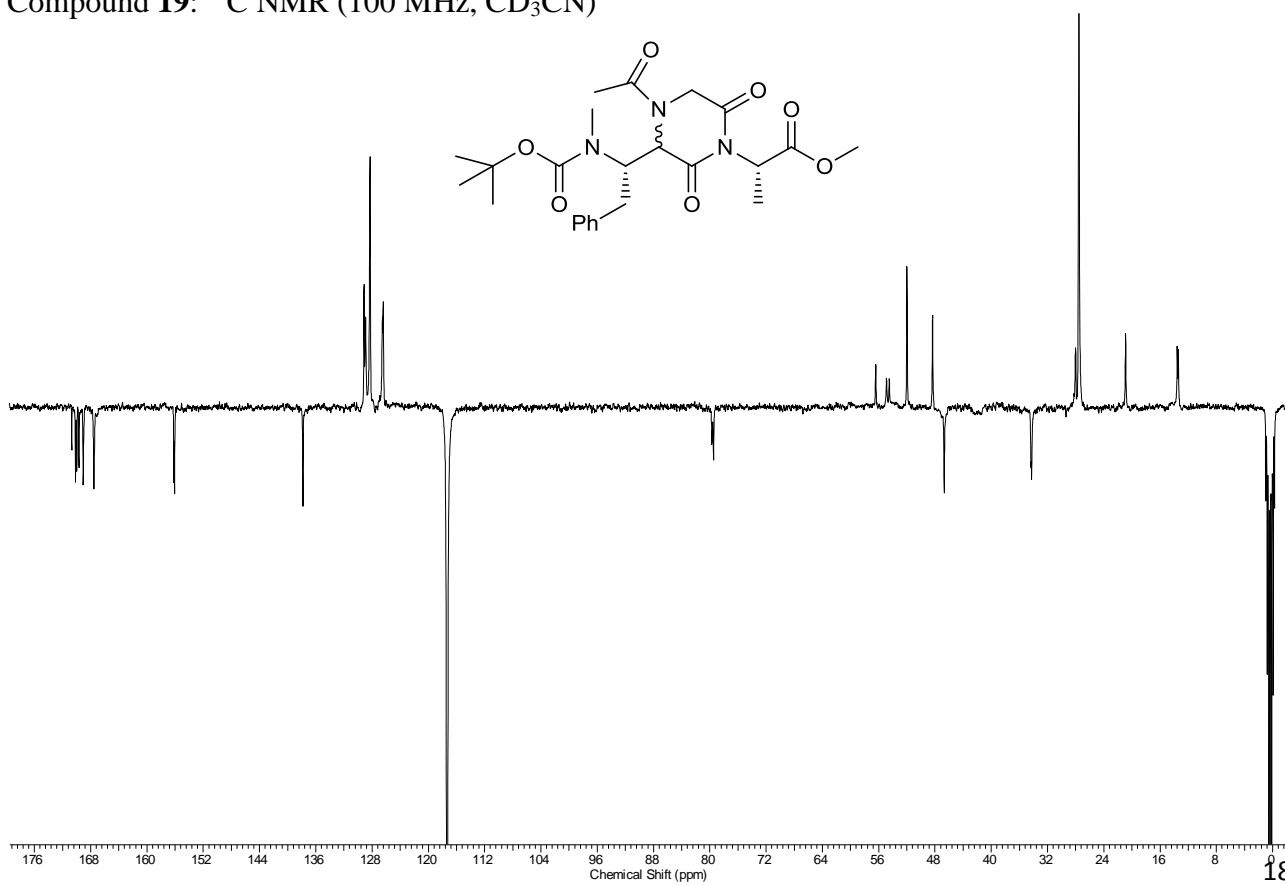
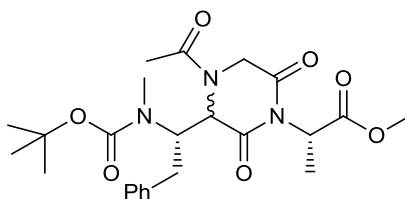
Compound **18**:  $^{13}\text{C}$  NMR (100 MHz,  $\text{CD}_3\text{CN}$ )



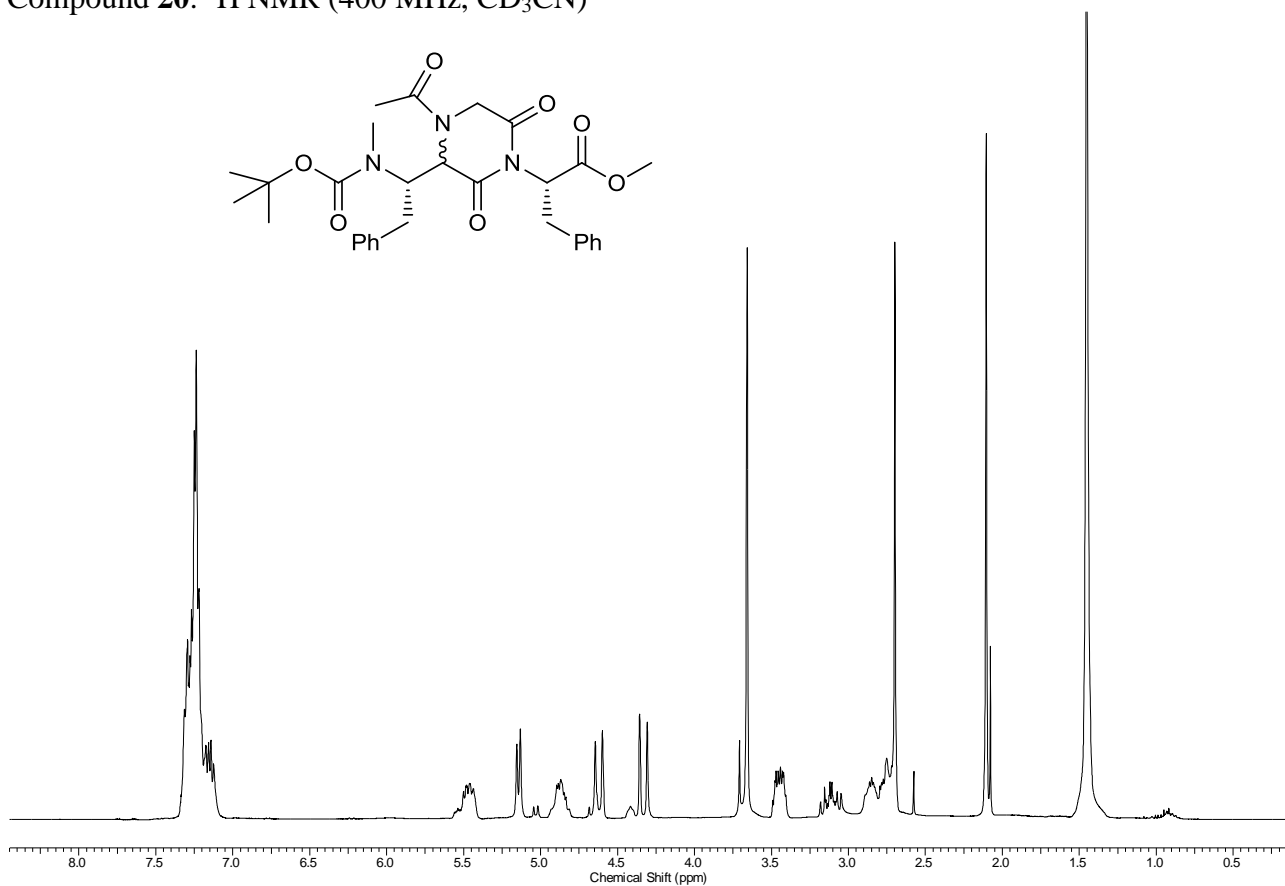
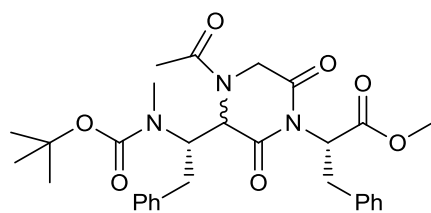
Compound **19**:  $^1\text{H}$  NMR (400 MHz,  $\text{CD}_3\text{CN}$ )



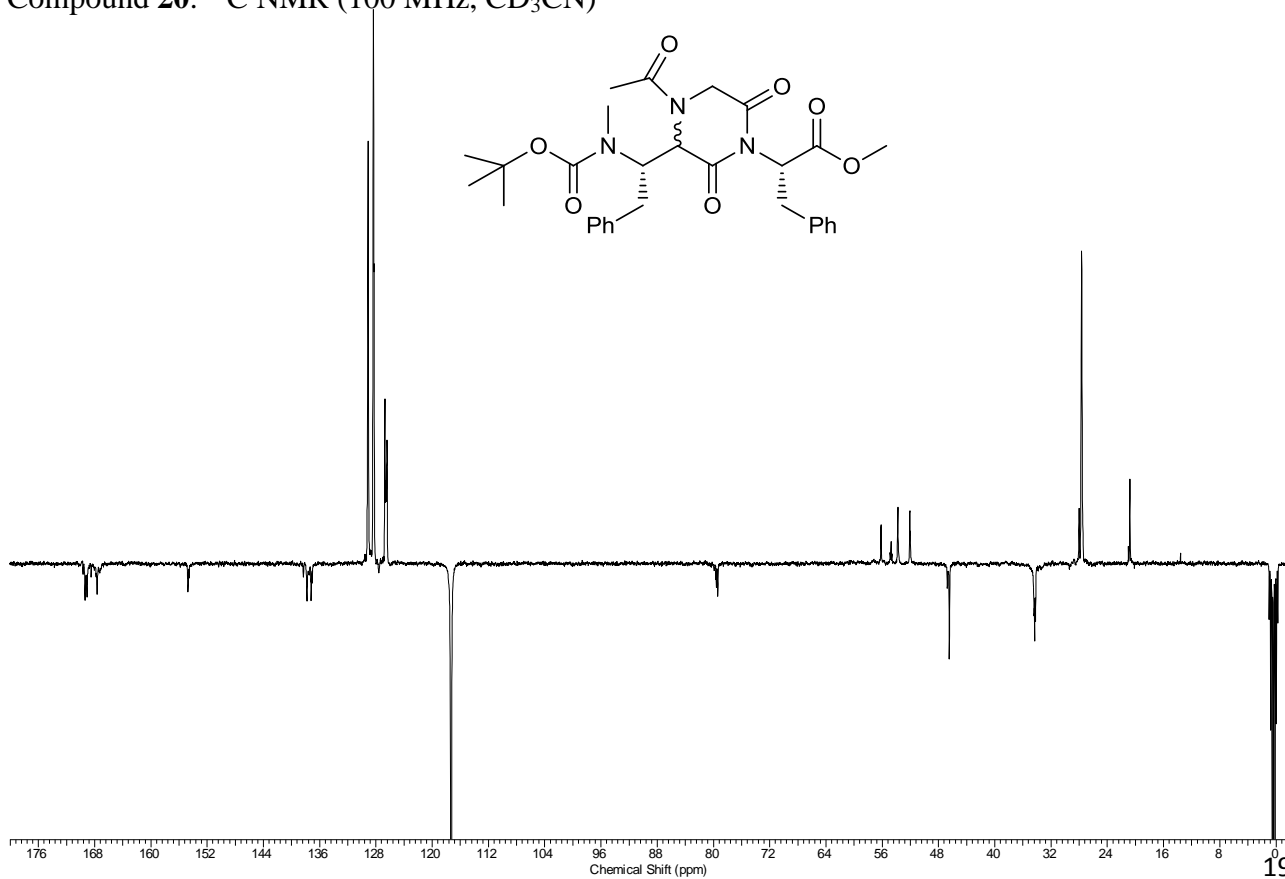
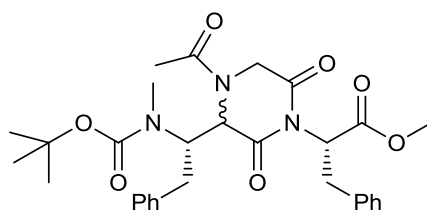
Compound **19**:  $^{13}\text{C}$  NMR (100 MHz,  $\text{CD}_3\text{CN}$ )



Compound **20**:  $^1\text{H}$  NMR (400 MHz,  $\text{CD}_3\text{CN}$ )

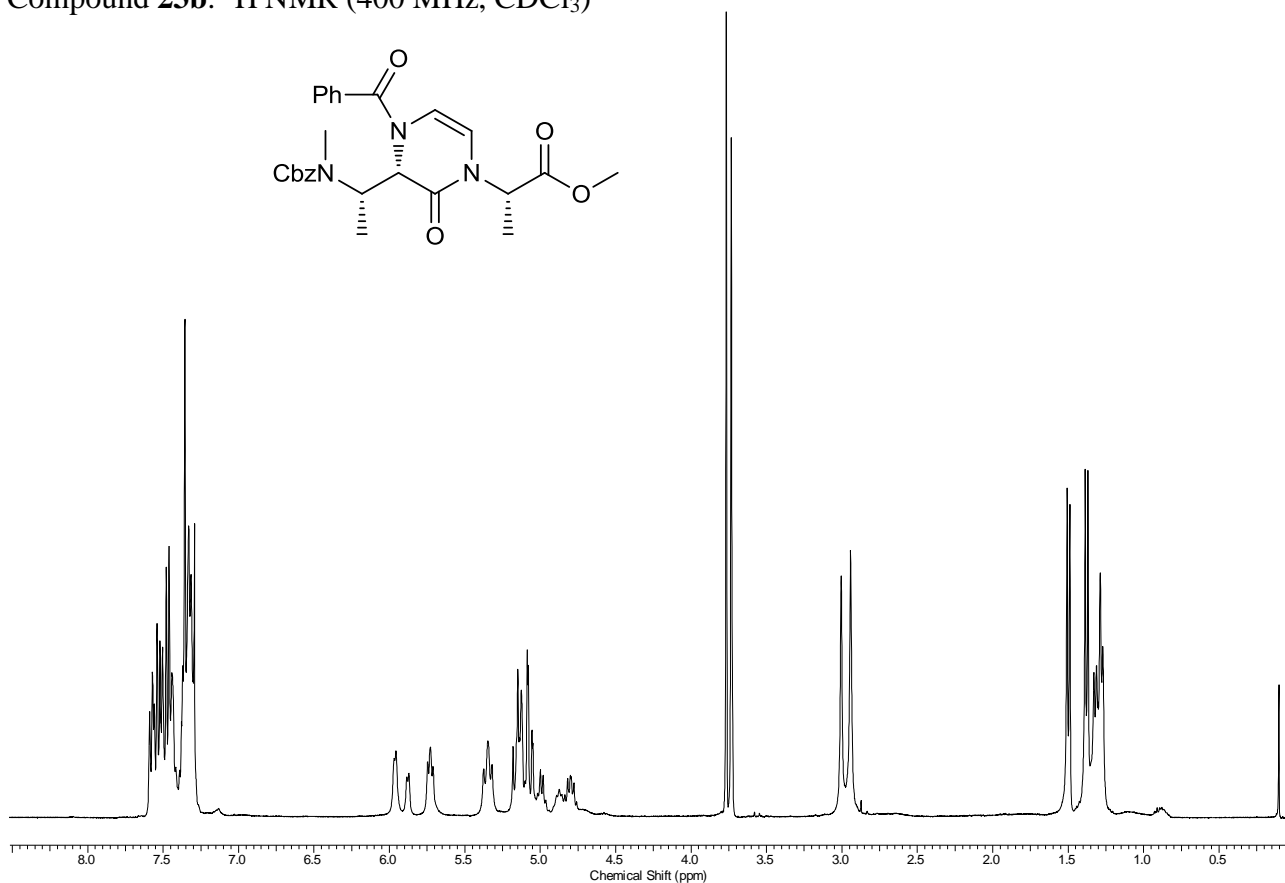
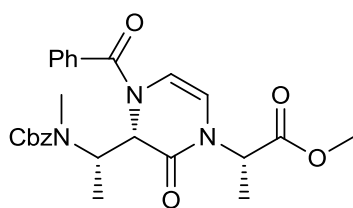


Compound **20**:  $^{13}\text{C}$  NMR (100 MHz,  $\text{CD}_3\text{CN}$ )

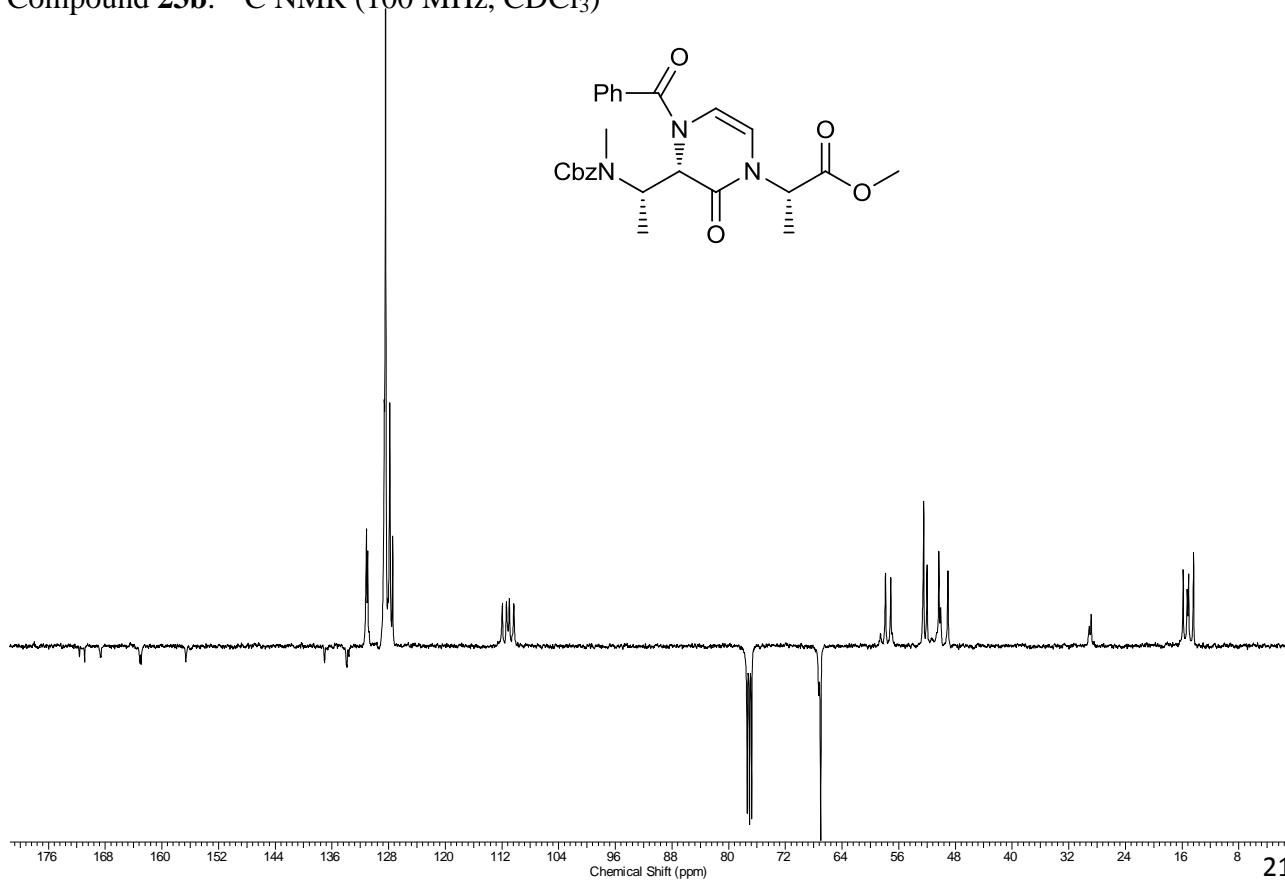
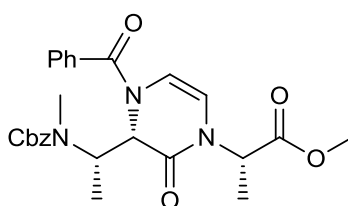




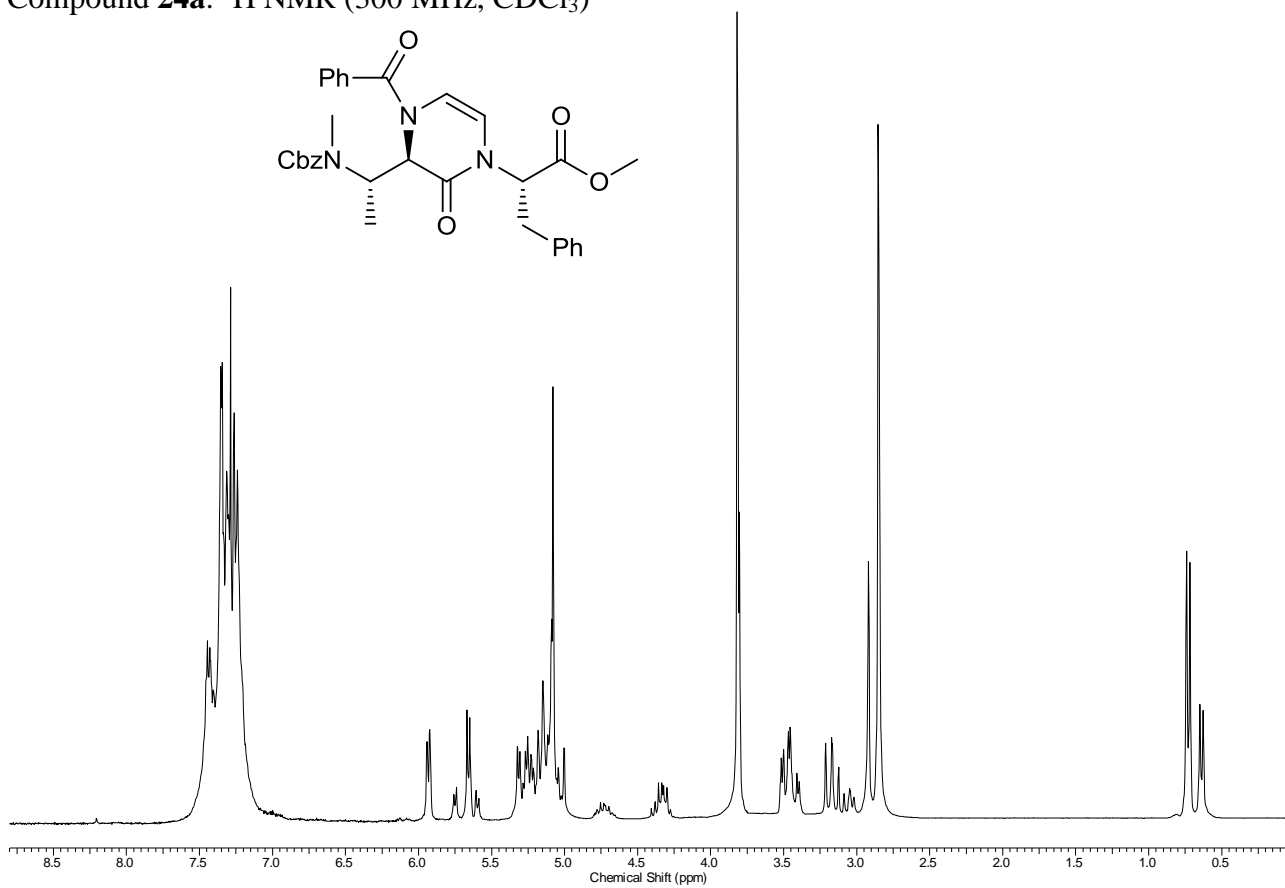
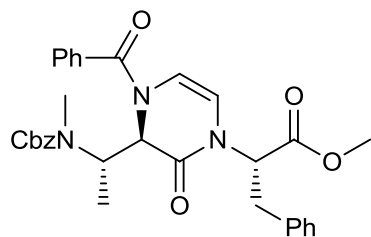
Compound **23b**:  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )



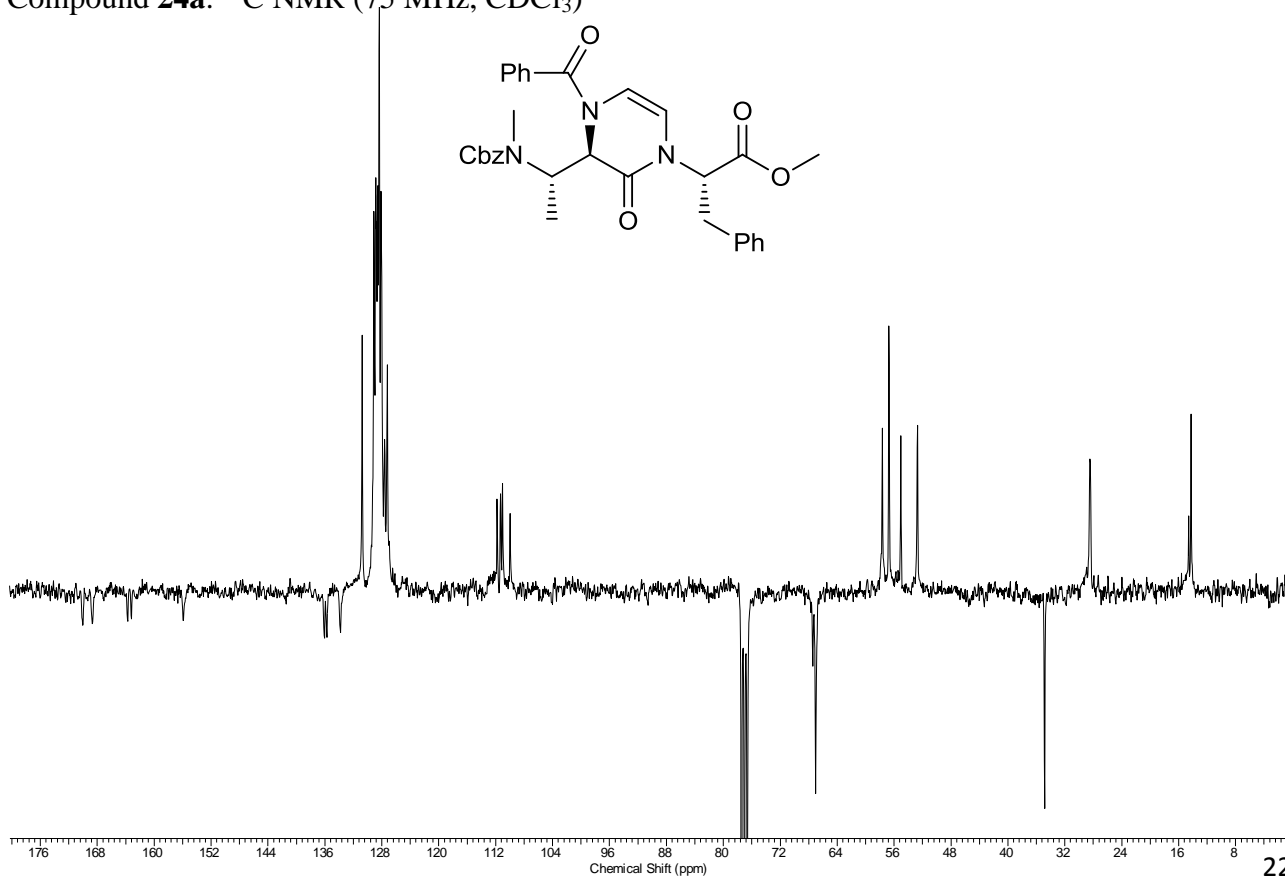
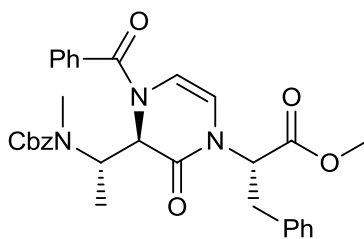
Compound **23b**:  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )



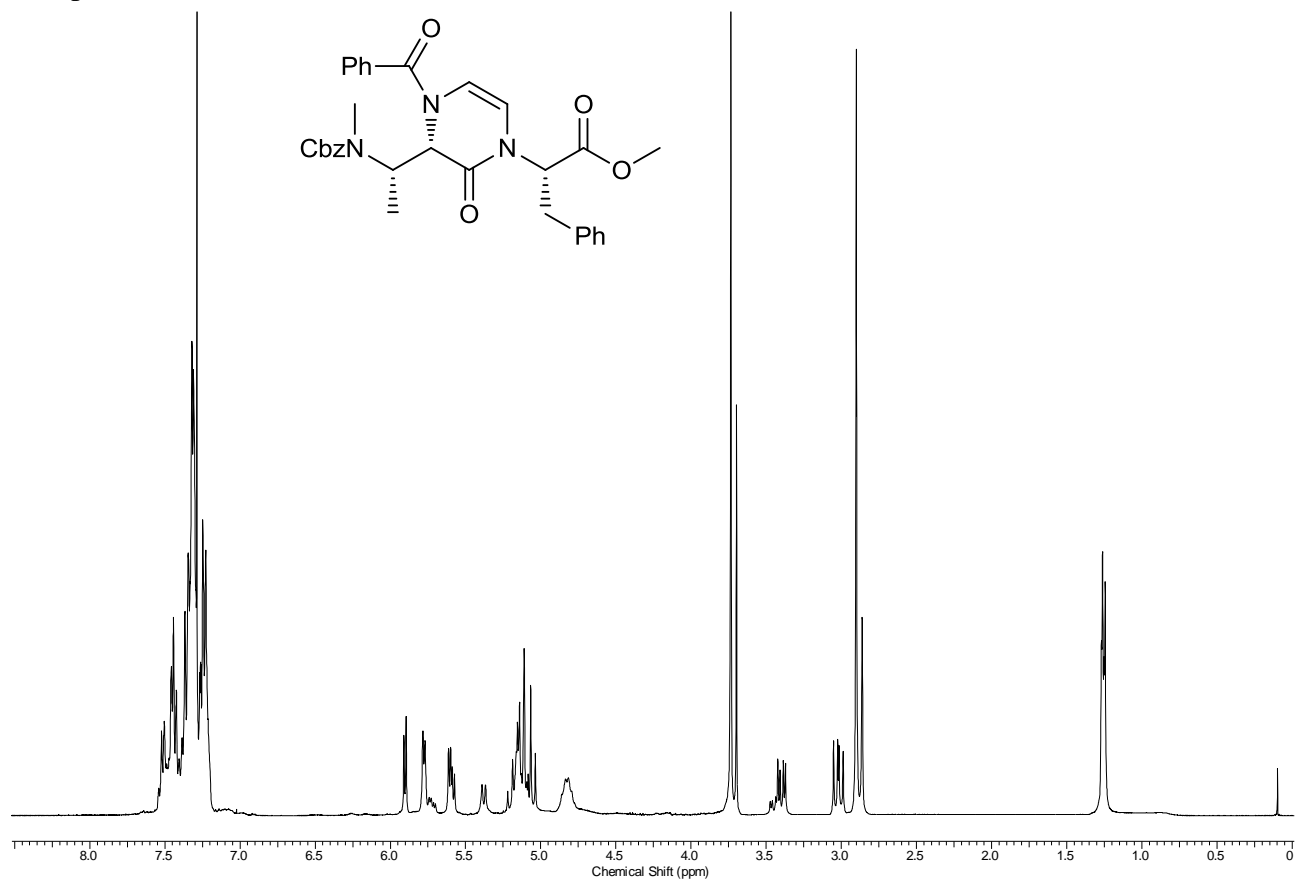
Compound **24a**:  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )



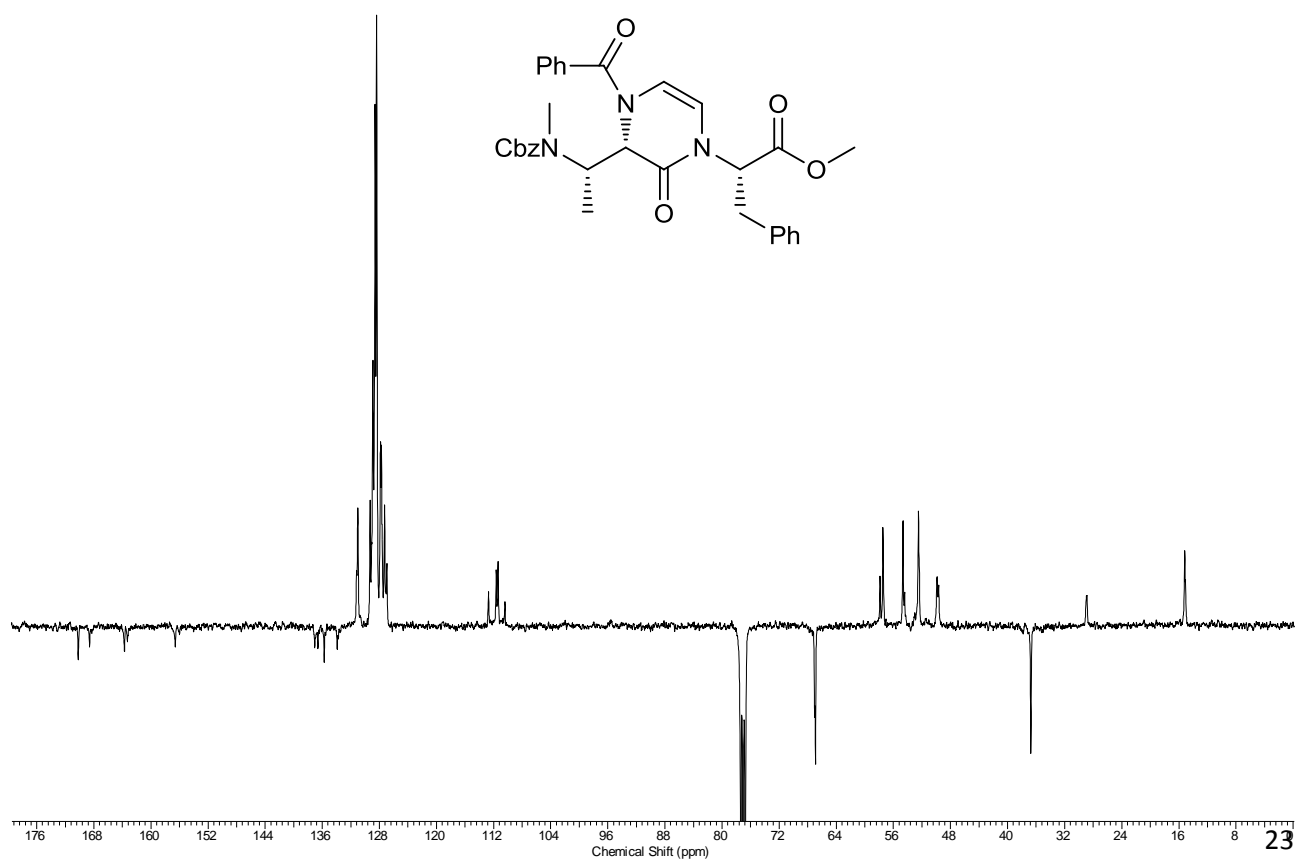
Compound **24a**:  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )



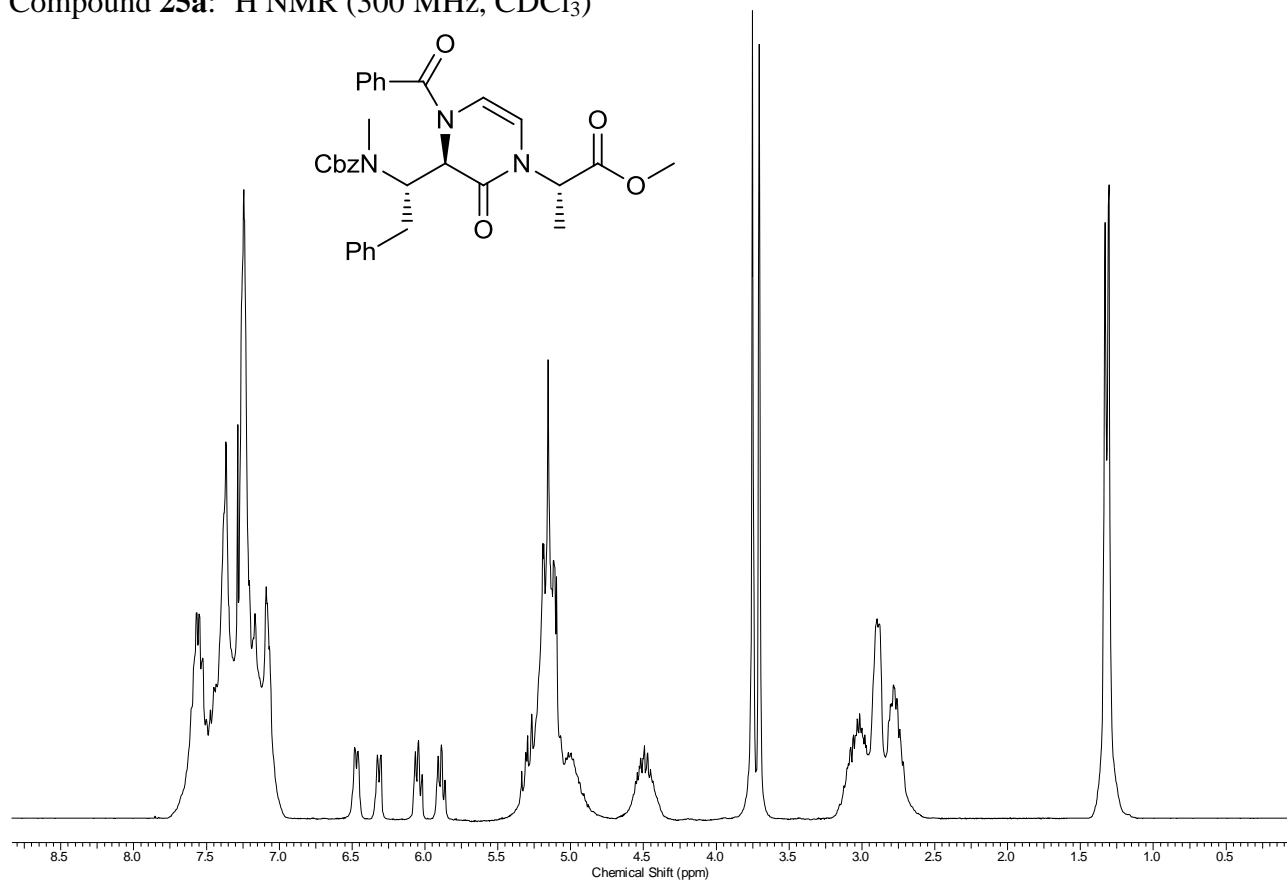
Compound **24b**:  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )



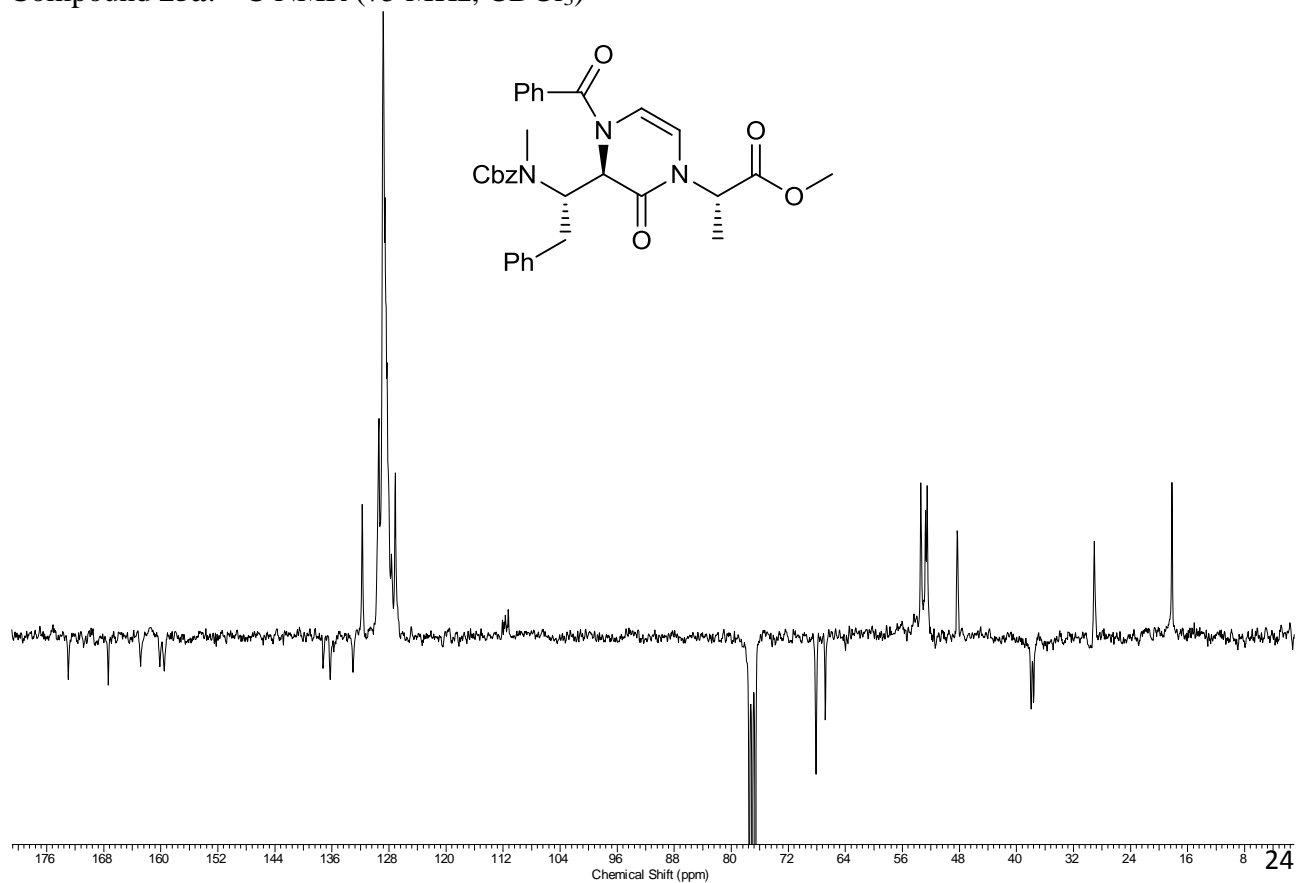
Compound **24b**:  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )



Compound **25a**:  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )



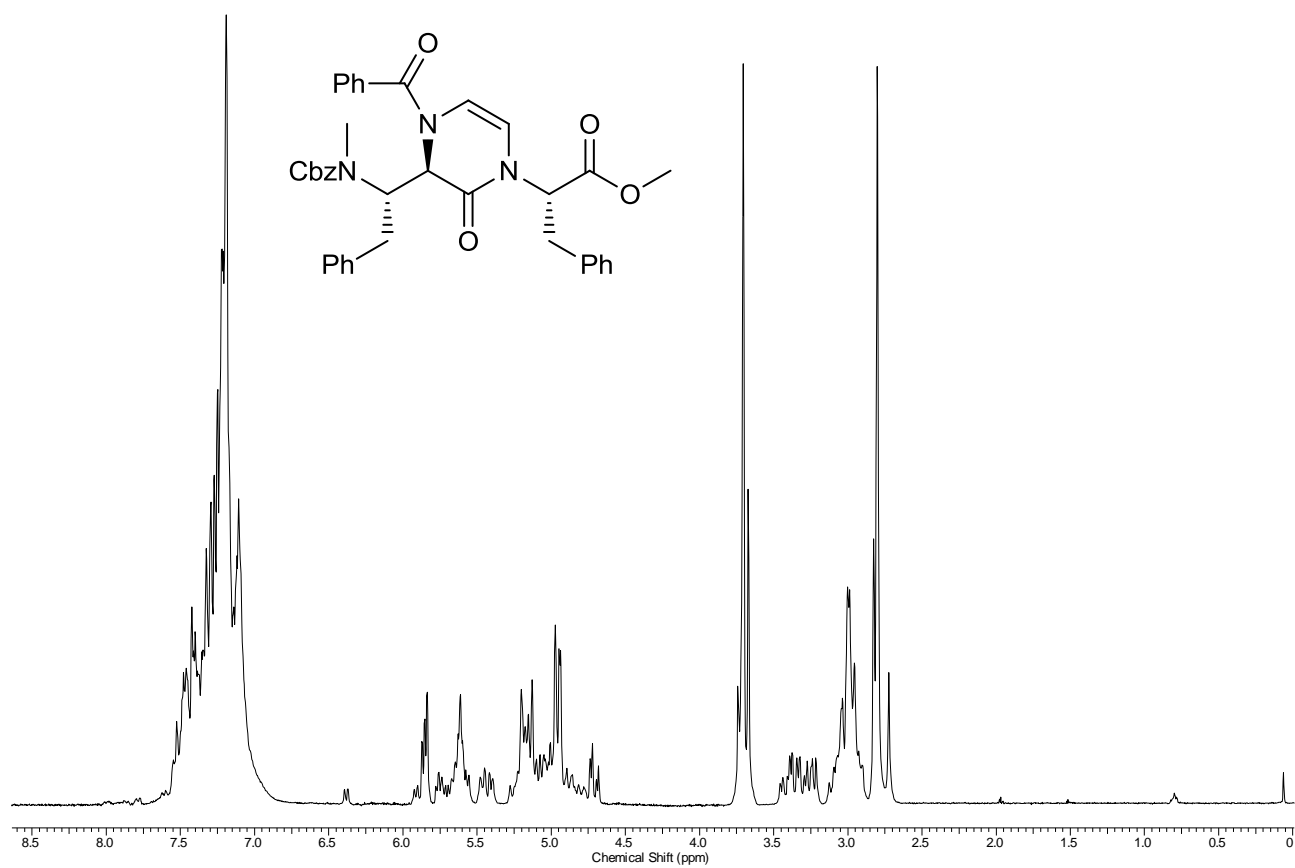
Compound **25a**:  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )



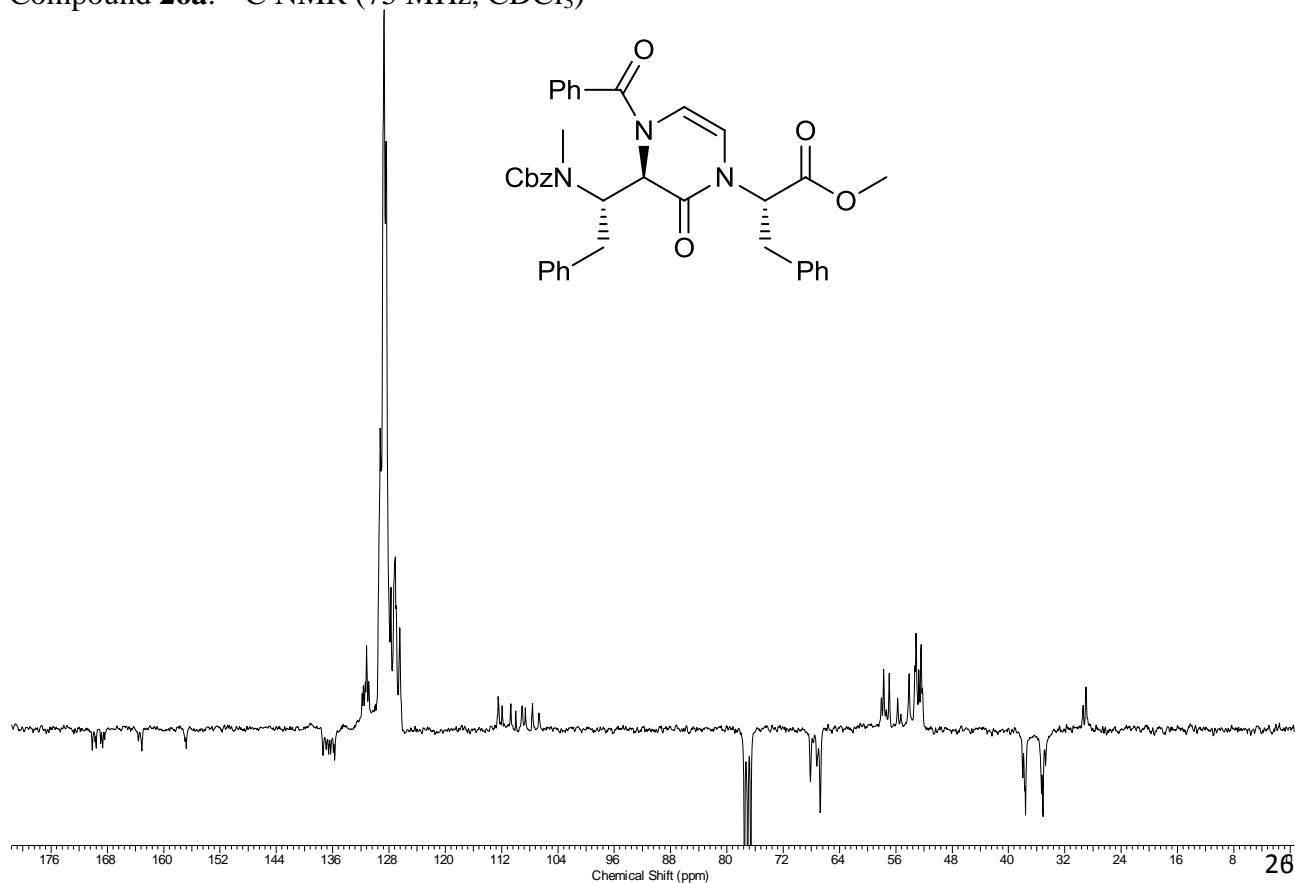




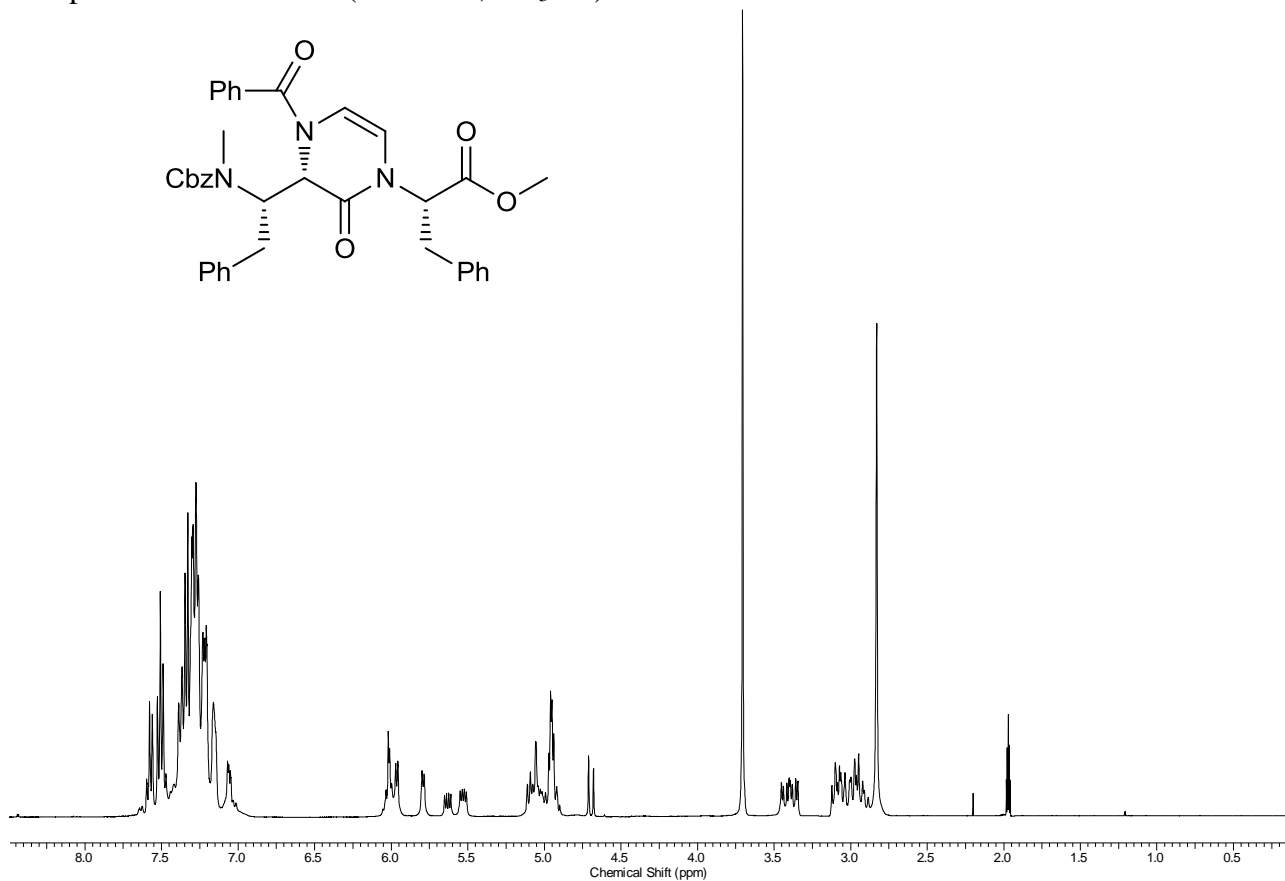
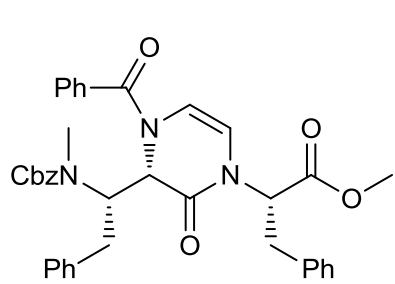
Compound **26a**:  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )



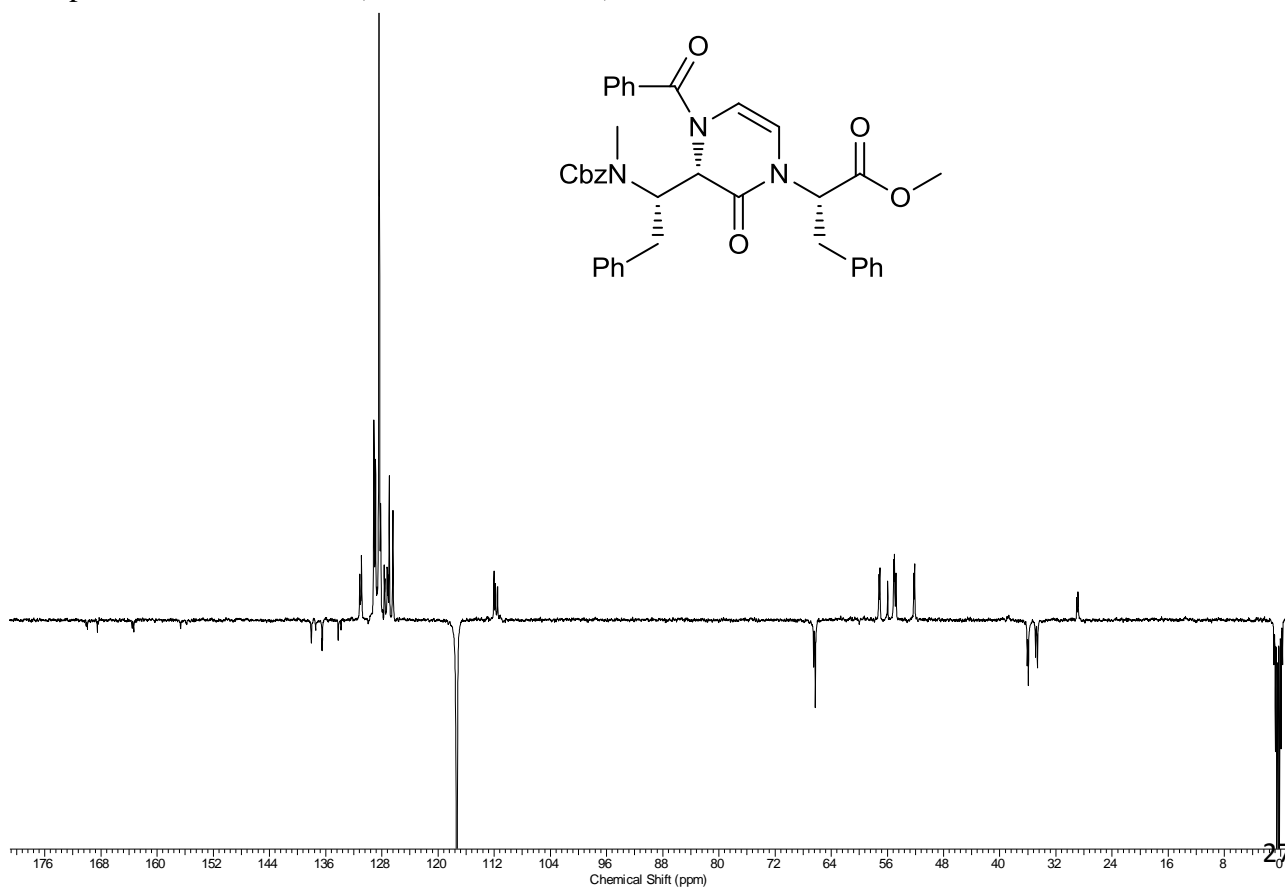
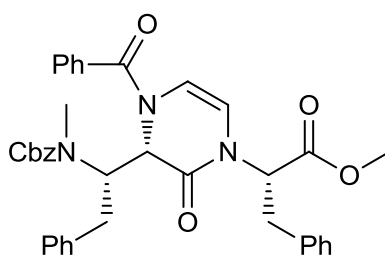
Compound **26a**:  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )



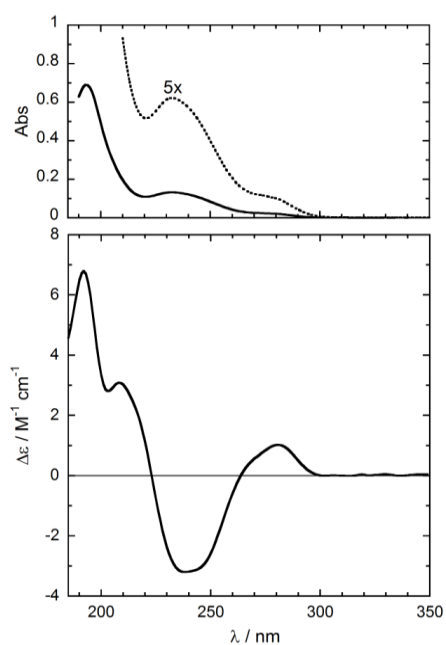
Compound **26b**:  $^1\text{H}$  NMR (400 MHz,  $\text{CD}_3\text{CN}$ )



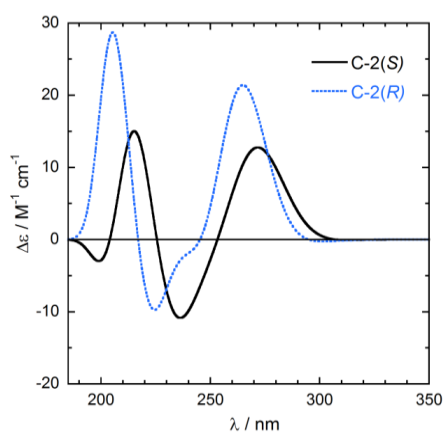
Compound **26b**:  $^{13}\text{C}$  NMR (100 MHz,  $\text{CD}_3\text{CN}$ )



### CD studies:



**Fig. 1** Experimental UV (top) and CD (bottom) spectra of the major diastereoisomer **9b**, measured in acetonitrile solution (2.0 mM). Cell length 0.01 cm and 0.05 cm (expansion).



**Fig. 2** Calculated CD spectra for C-2(S) and C-2(R) isomers of **9** with CAM-B3LYP/SVP//B3LYP/6-31G(d) method. Boltzmann averages at 300K; Gaussian bandshape with 0.3 eV width; red-shift 30 nm.

**Biological evaluation (cytotoxicities of compounds 9-12, 17-20 and 23-26).**

IC<sub>50</sub> values in Huh7 and Mahlavu cell lines.

Compound	Huh7			MV		
	IC50(μM)	R2	s.d	IC50(μM)	R2	s.d
<b>12</b>	15,2	1,0	1,8	11,3	0,9	0,4
<b>25b</b>	16,2	0,9	1,1	30,5	0,8	3,7

Non growth inhibition for compounds **9-11, 17-20, 23, 24, 25a** and **26**.