Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry.

Supporting information

Practical synthesis and cytotoxic evaluation of the pyrazino[1,2-*b*]-isoquinoline ring system

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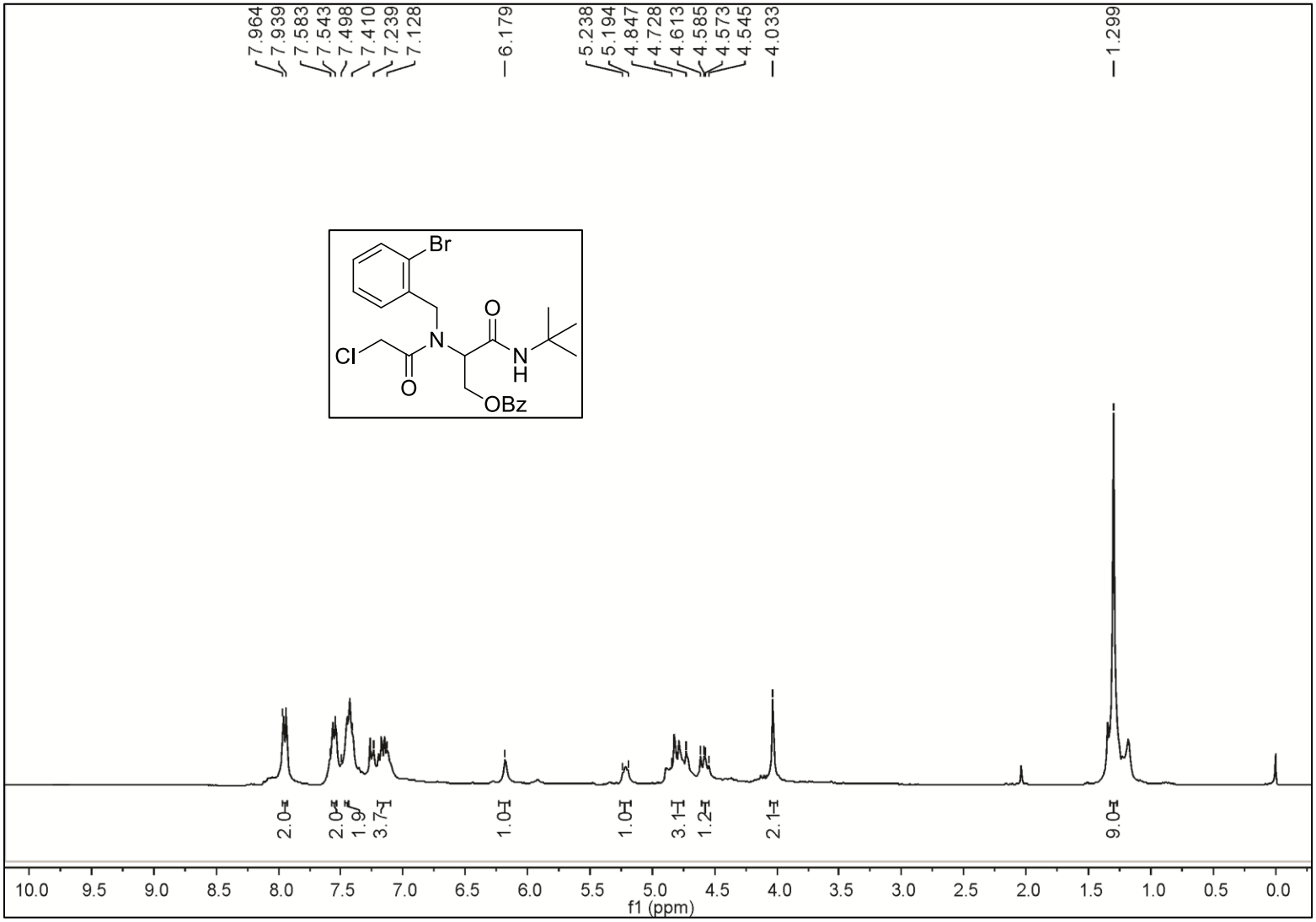
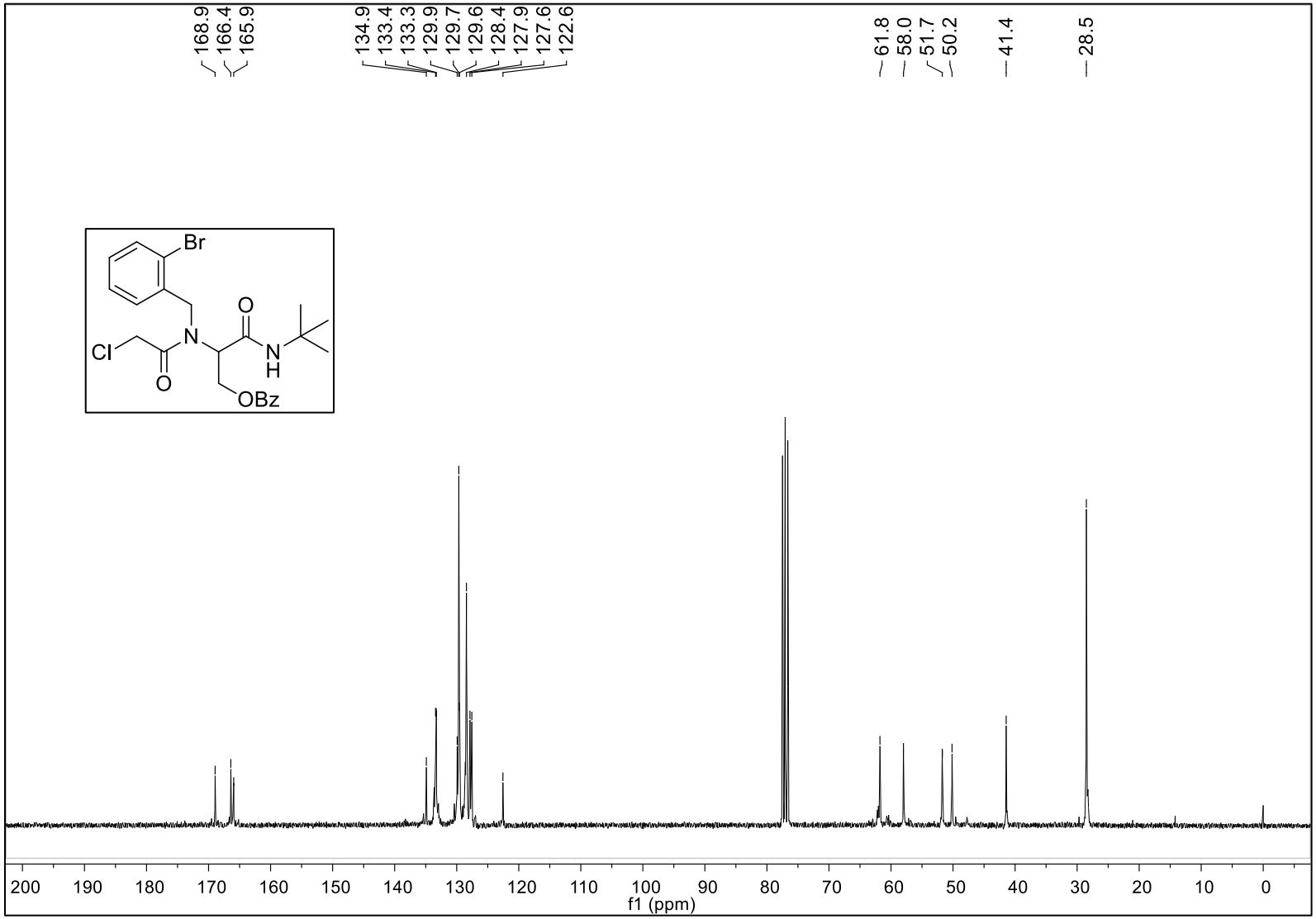
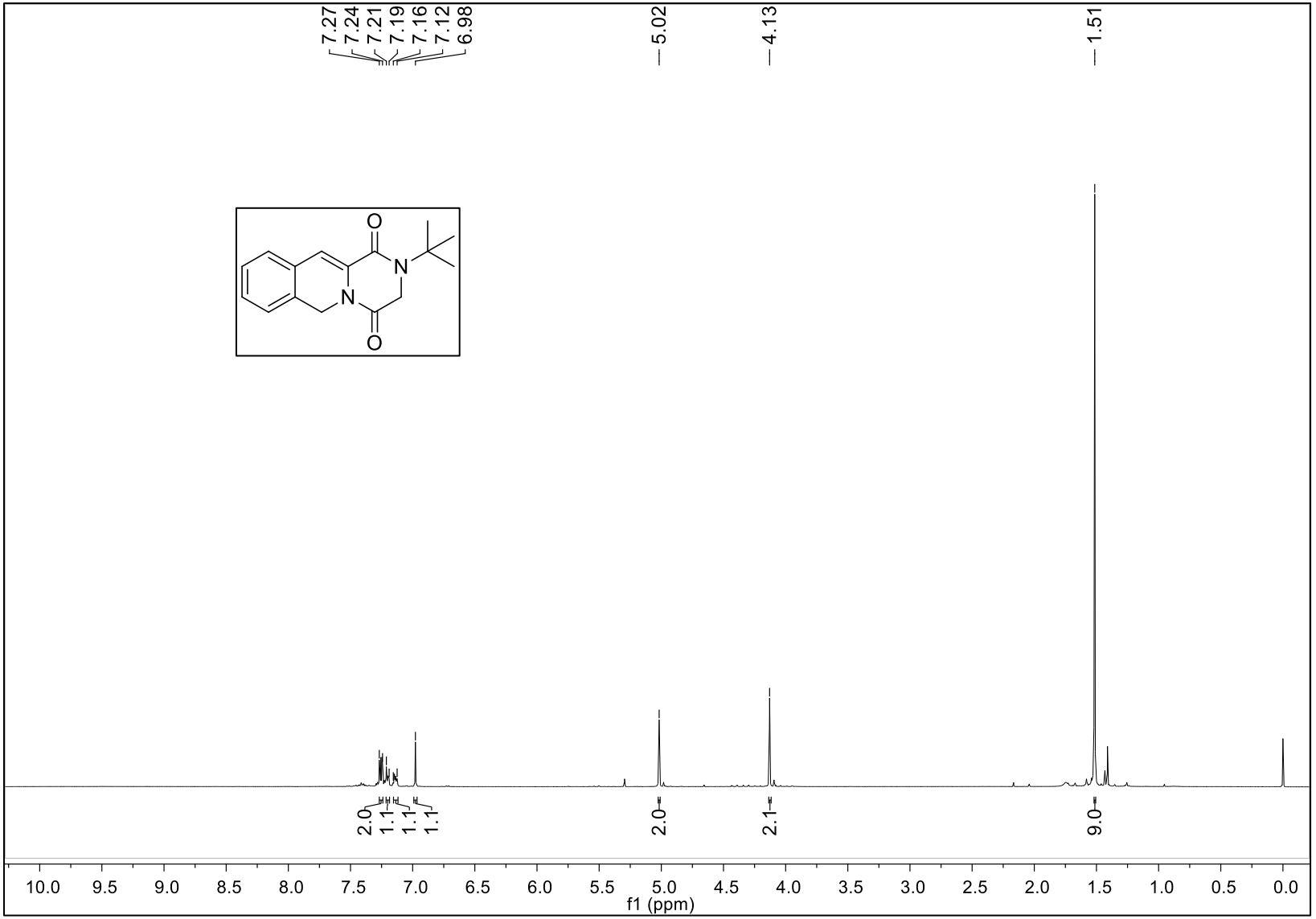
[1]H-NMR of 2-[(2-bromobenzyl)(chloroacetyl)amino]-3-(*tert*-butylamino)-3-oxopropyl benzoate (**4a**)



^{13}C-NMR of 2-[(2-bromobenzyl)(chloroacetyl)amino]-3-(*tert*-butylamino)-3-oxopropyl benzoate (**4a**)



^{1}H-NMR of 2-*tert*-butyl-2*H*-pyrazino[1,2-*b*]isoquinoline-1,4(3*H*,6*H*)-dione (**6a**)



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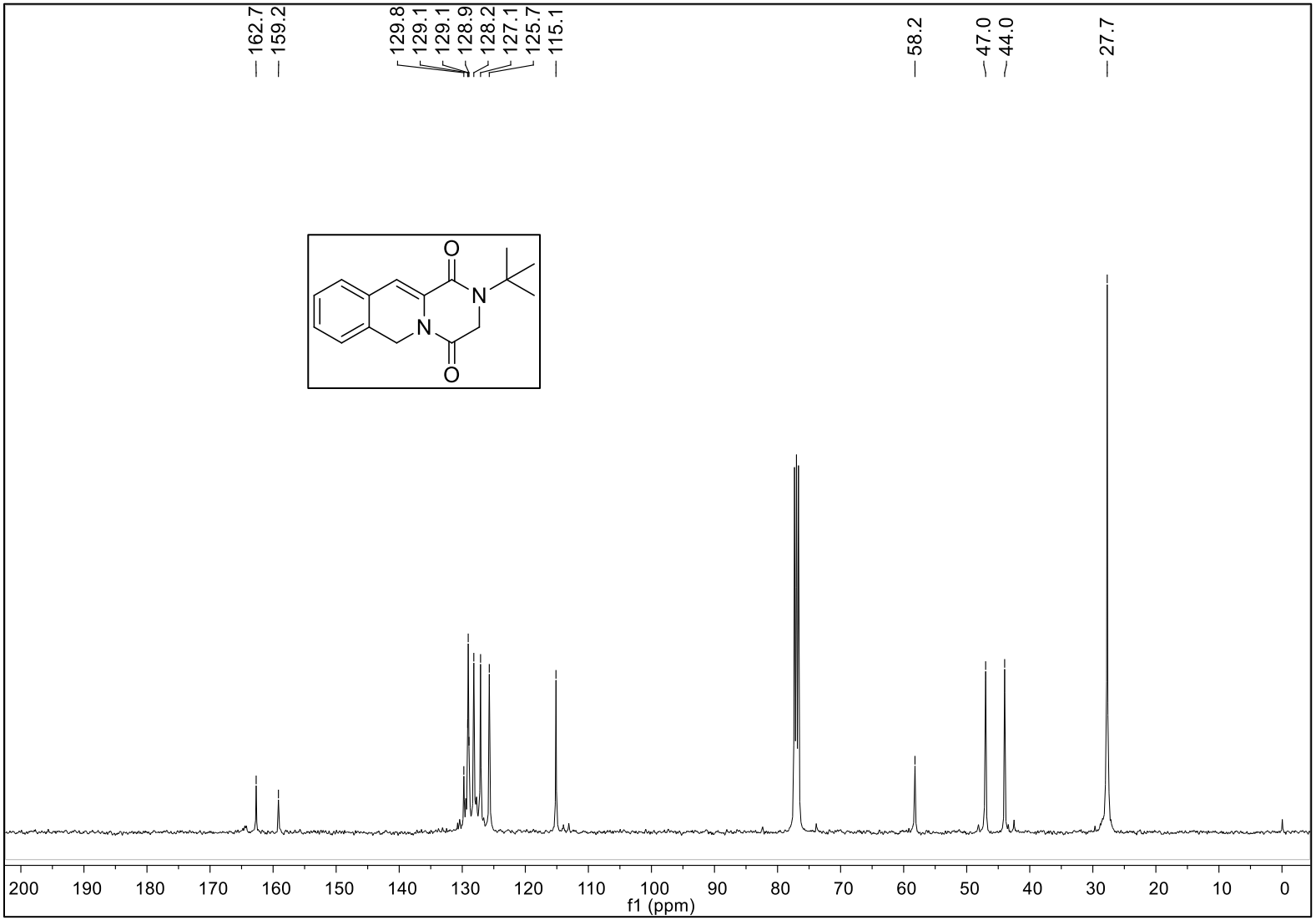
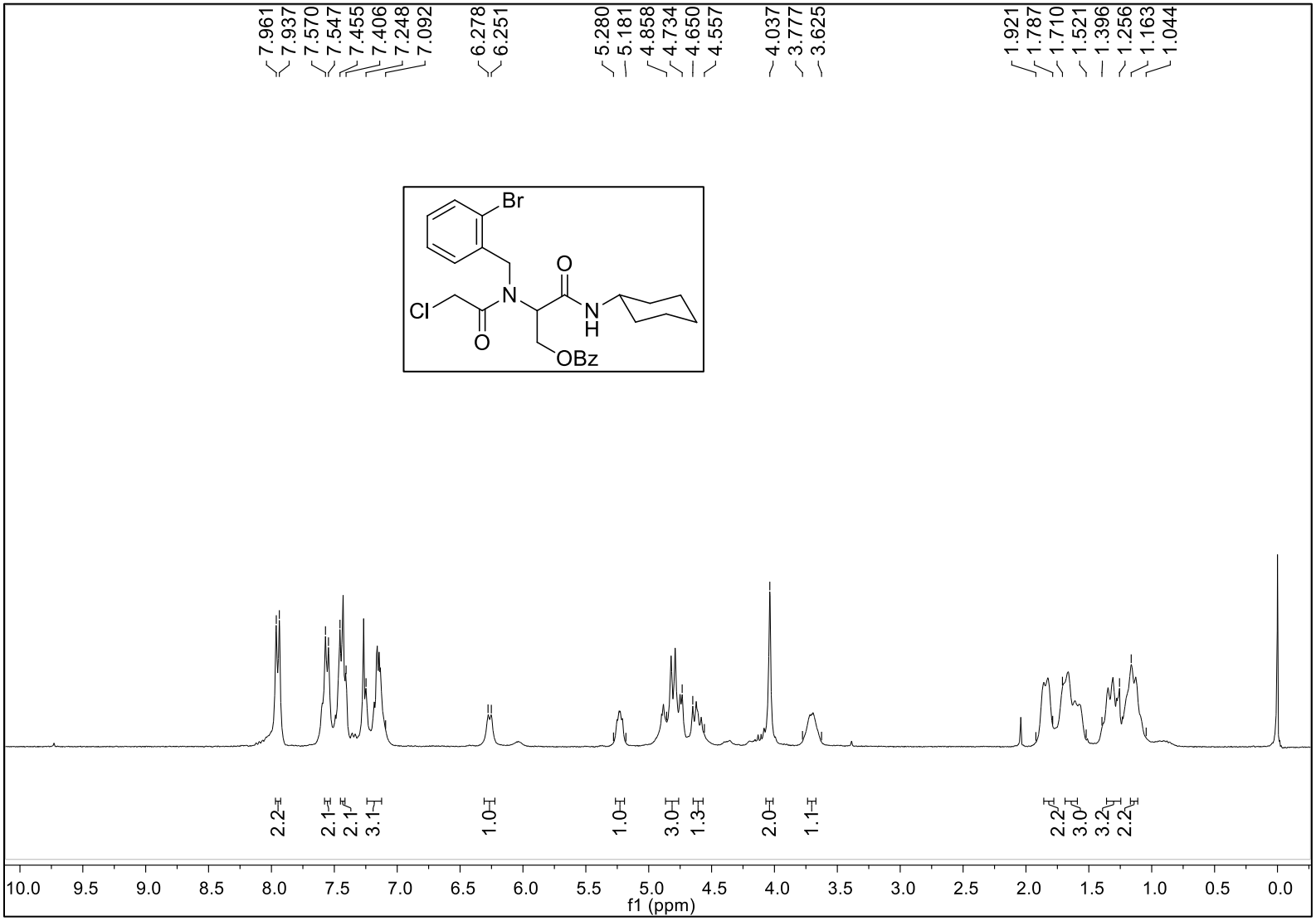
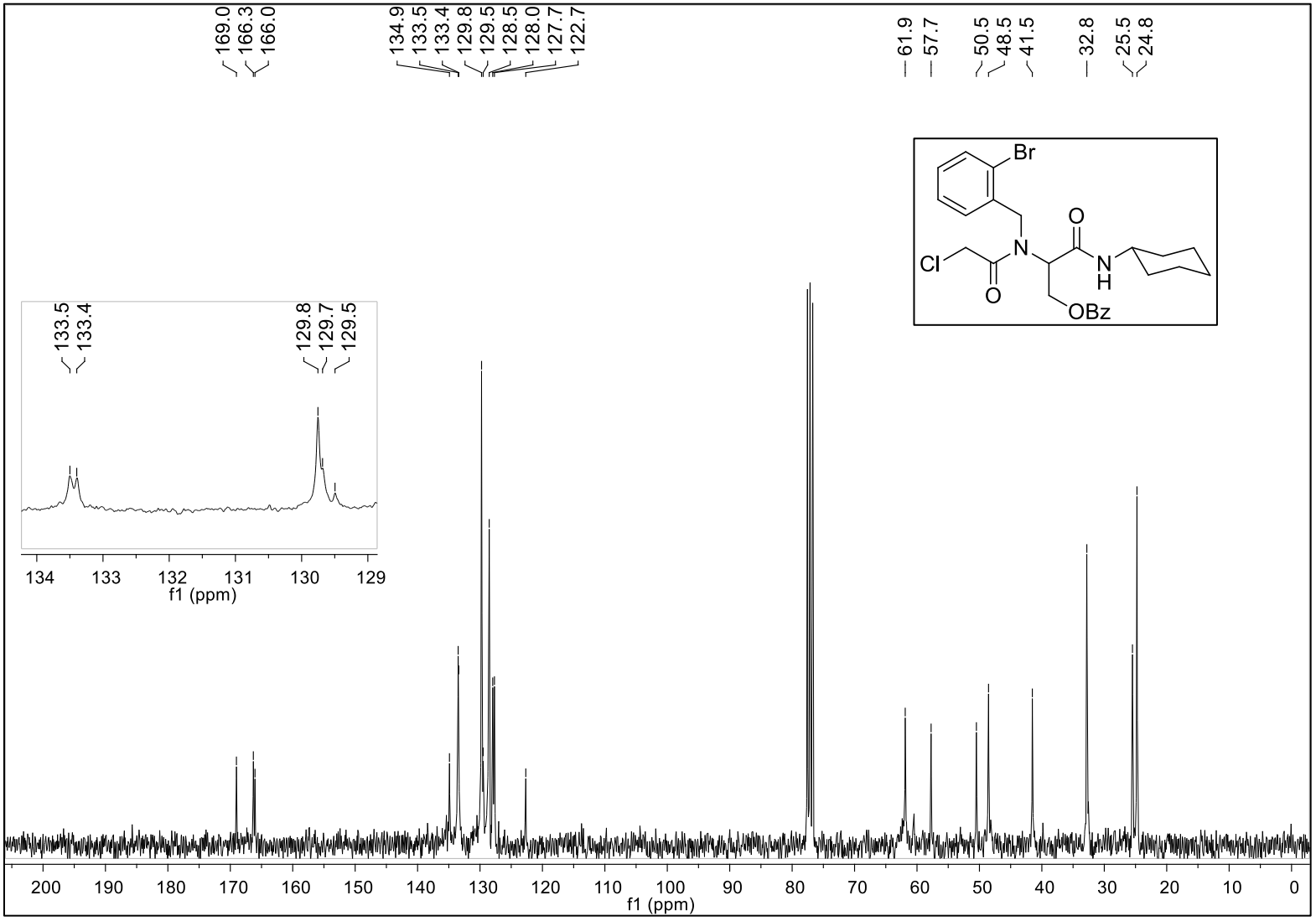


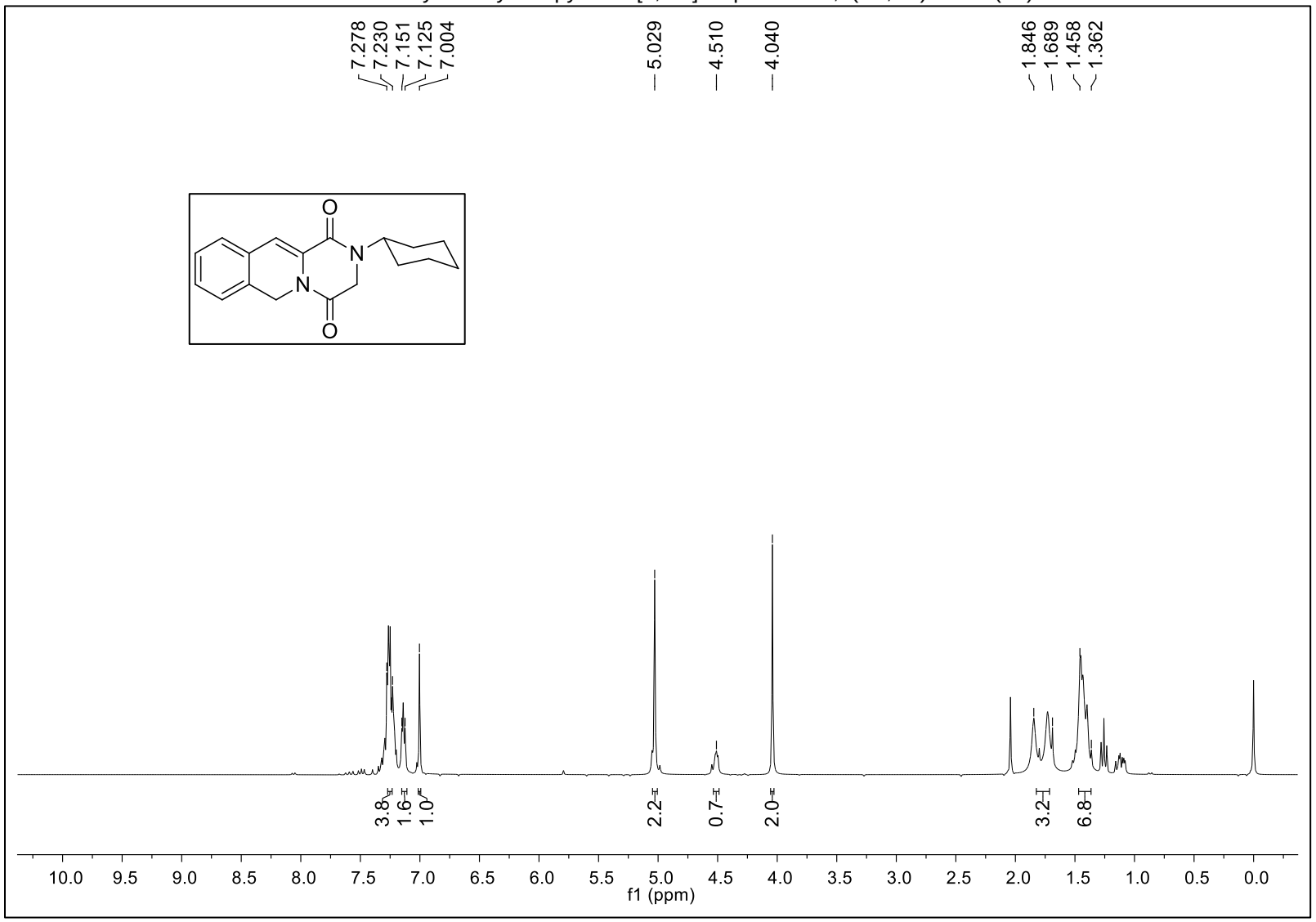
^{1}H-NMR of 2-[(2-bromobenzyl)(chloroacetyl)amino]-3-(cyclohexylamino)-3-oxopropyl benzoate (**4b**)



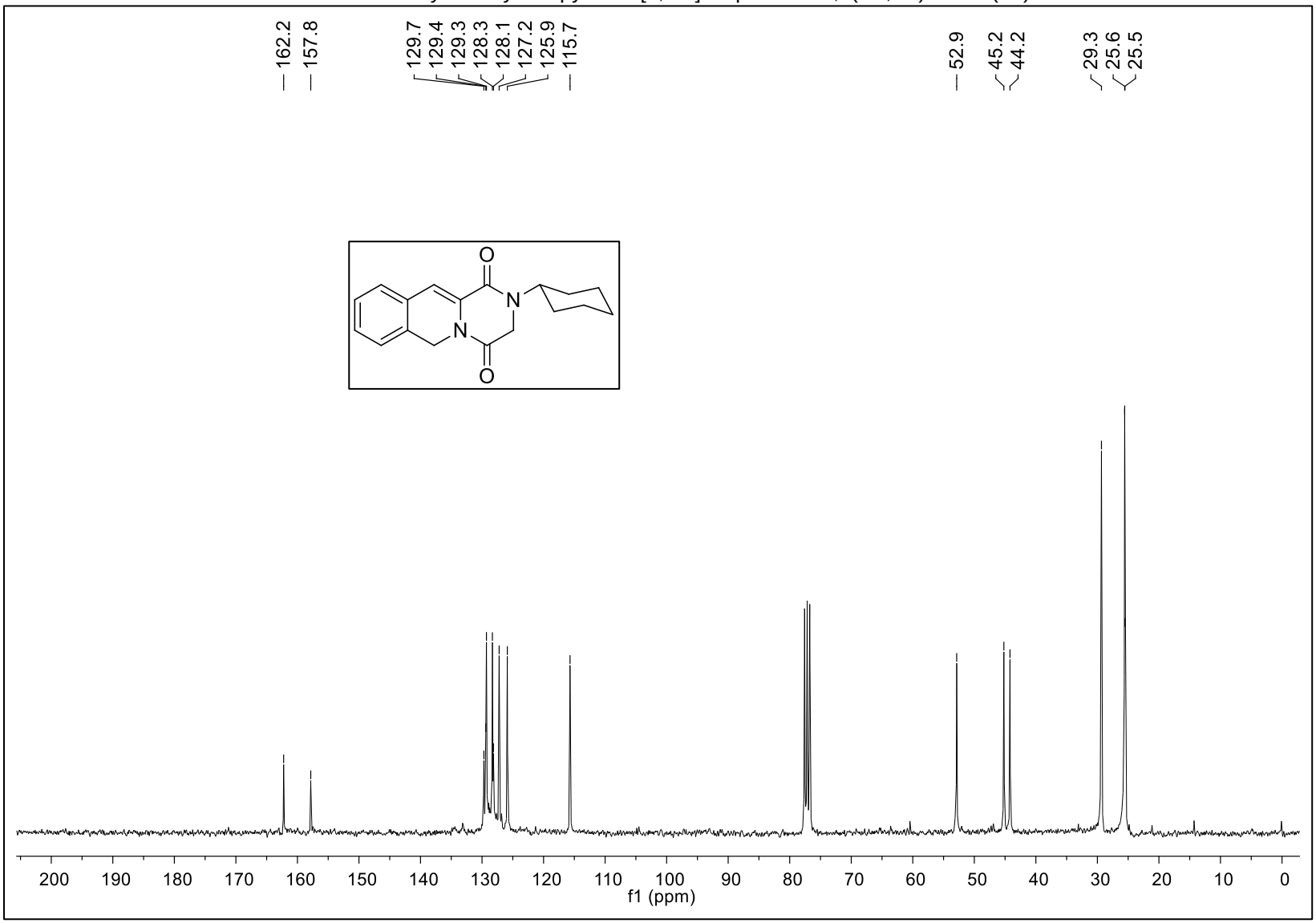
^{13}C-NMR of 2-[(2-bromobenzyl)(chloroacetyl)amino]-3-(cyclohexylamino)-3-oxopropyl benzoate (**4b**)



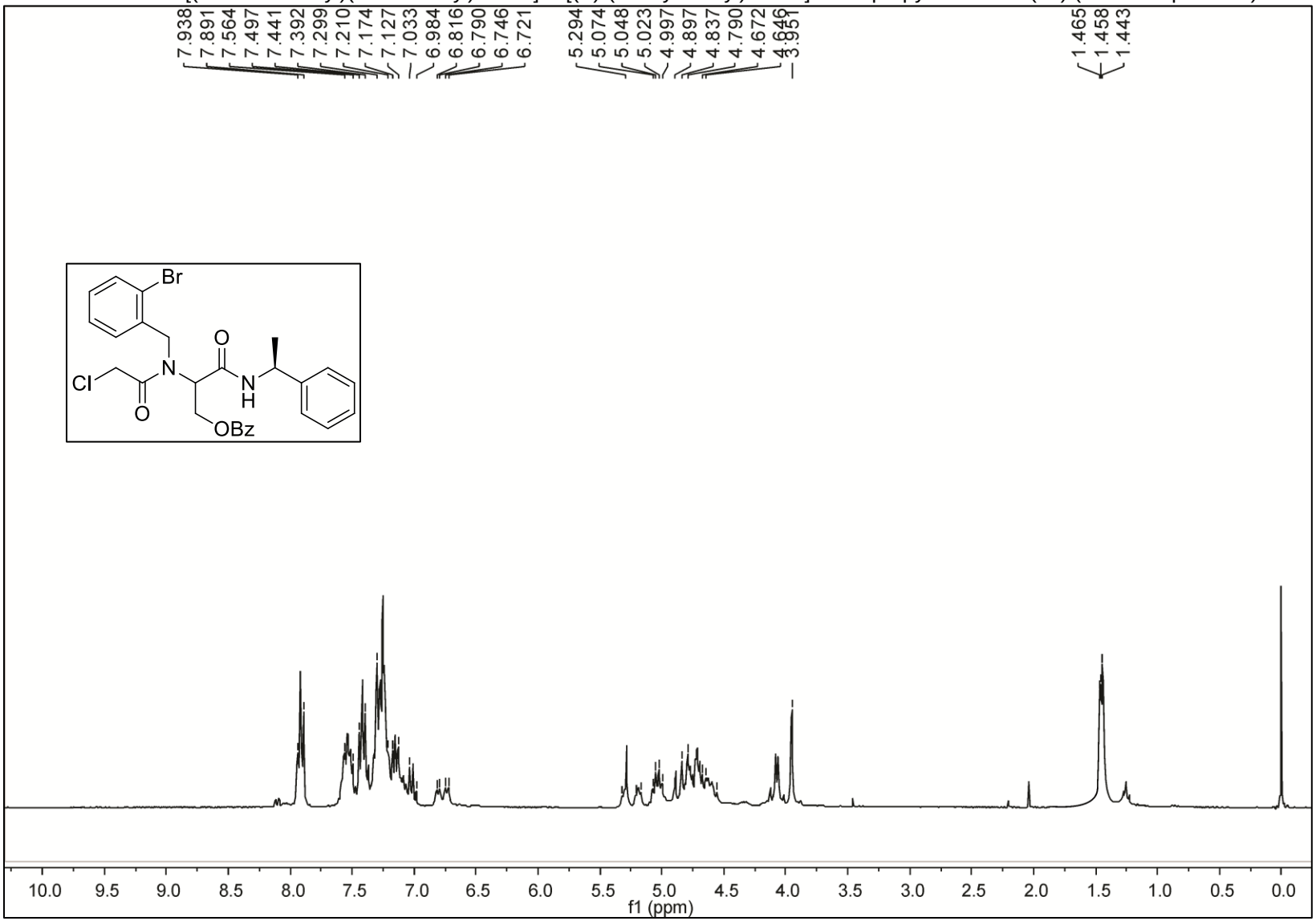
^{1}H-NMR of 2-cyclohexyl-2*H*-pyrazino[1,2-*b*]isoquinoline-1,4(3*H*,6*H*)-dione (**6b**)



^{13}C-NMR of 2-cyclohexyl-2*H*-pyrazino[1,2-*b*]isoquinoline-1,4(3*H*,6*H*)-dione (**6b**)



^{1}H-NMR of 2-[(2-bromobenzyl)(chloroacetyl)amino]-3-[(*S*)-(methylbenzyl)amino]-3-oxopropyl benzoate (**4c**) (room temperature)



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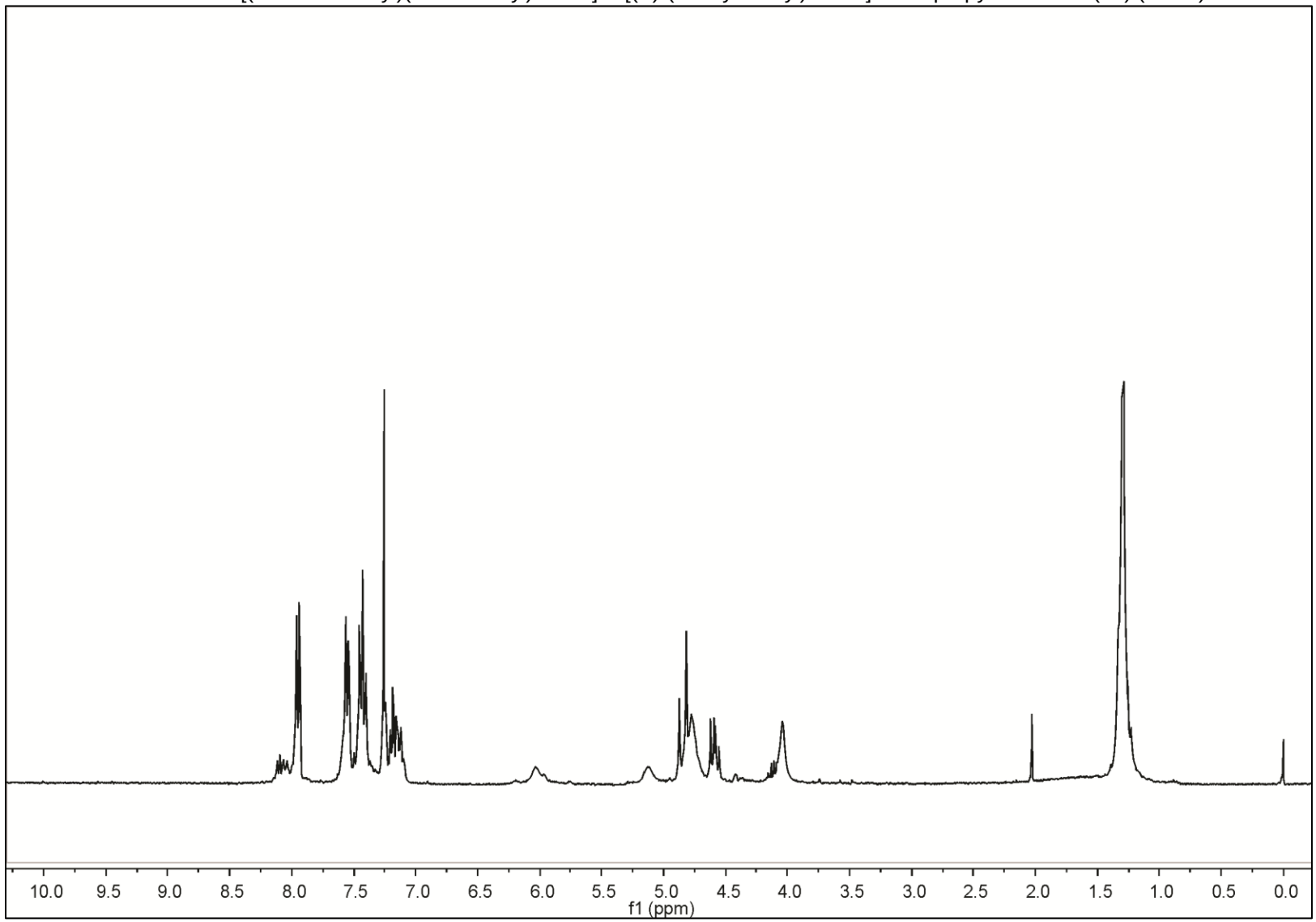

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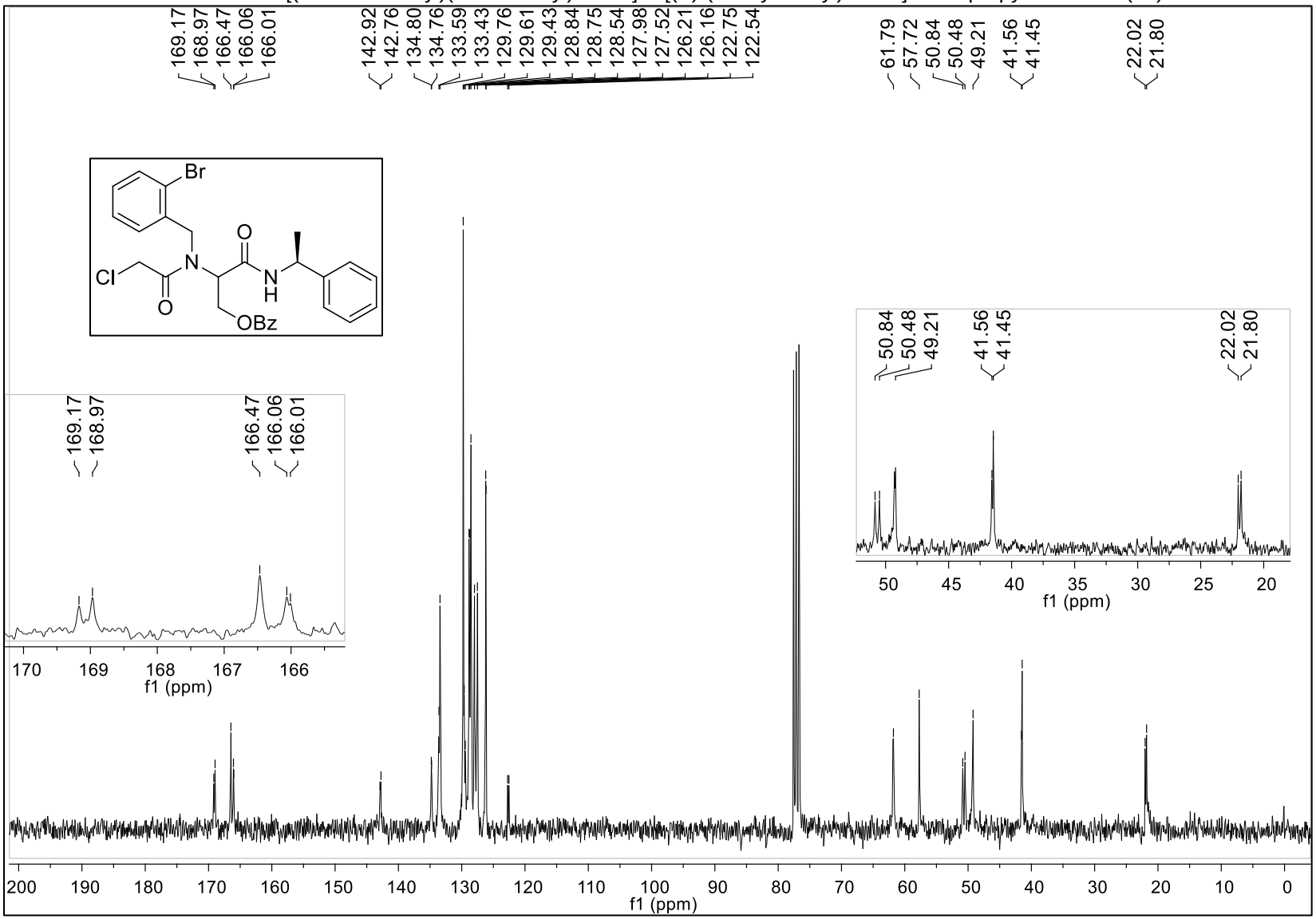

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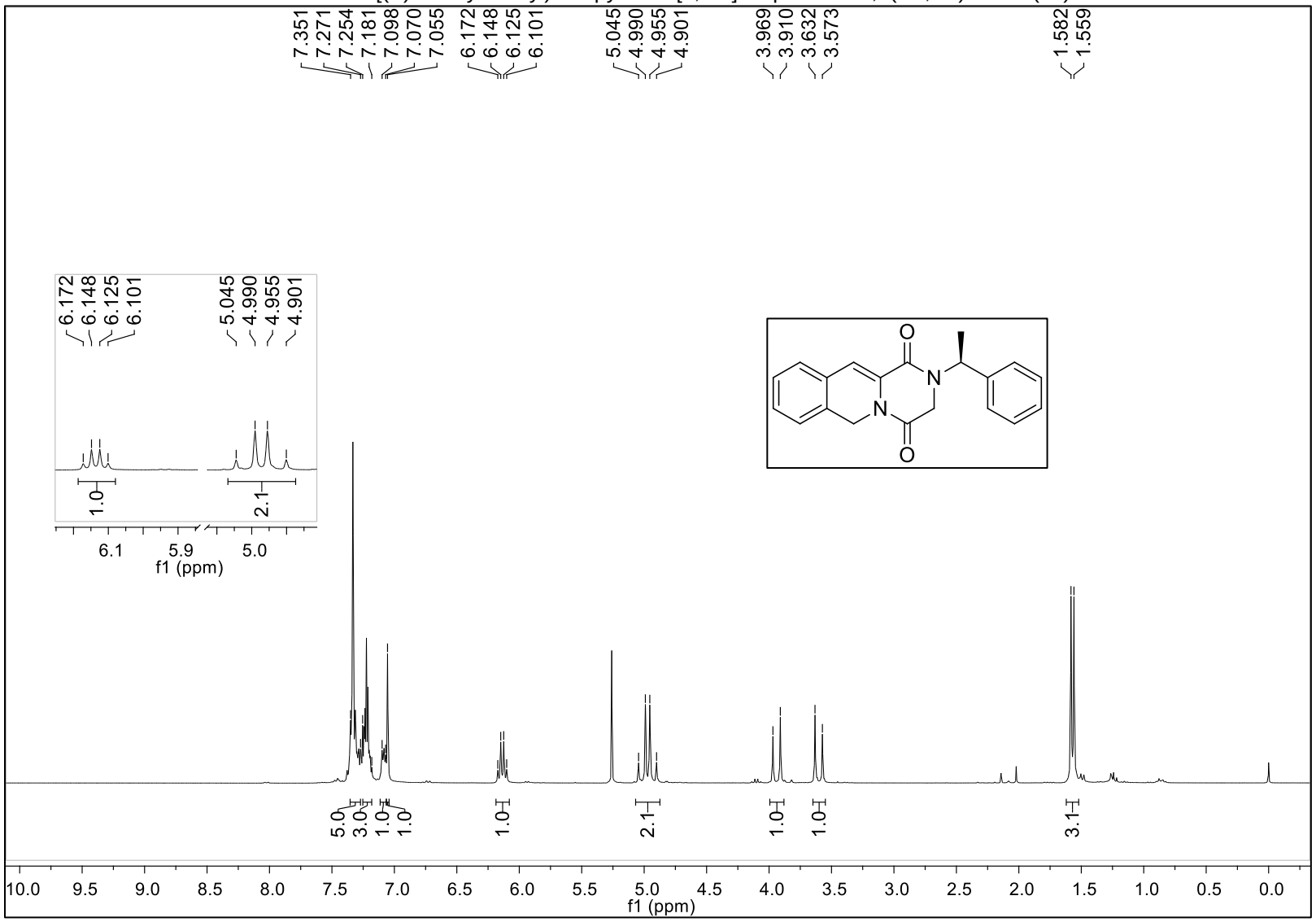

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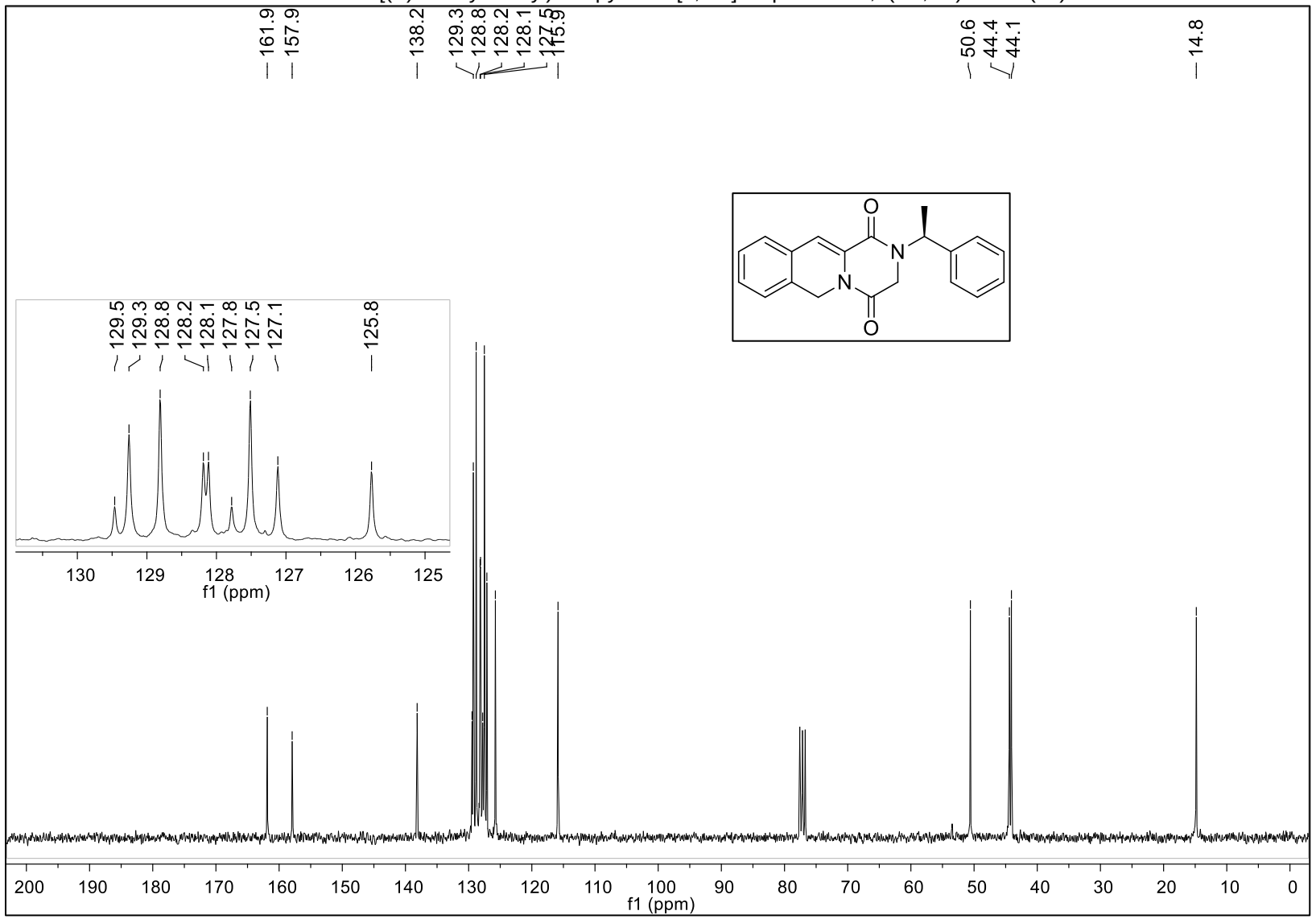
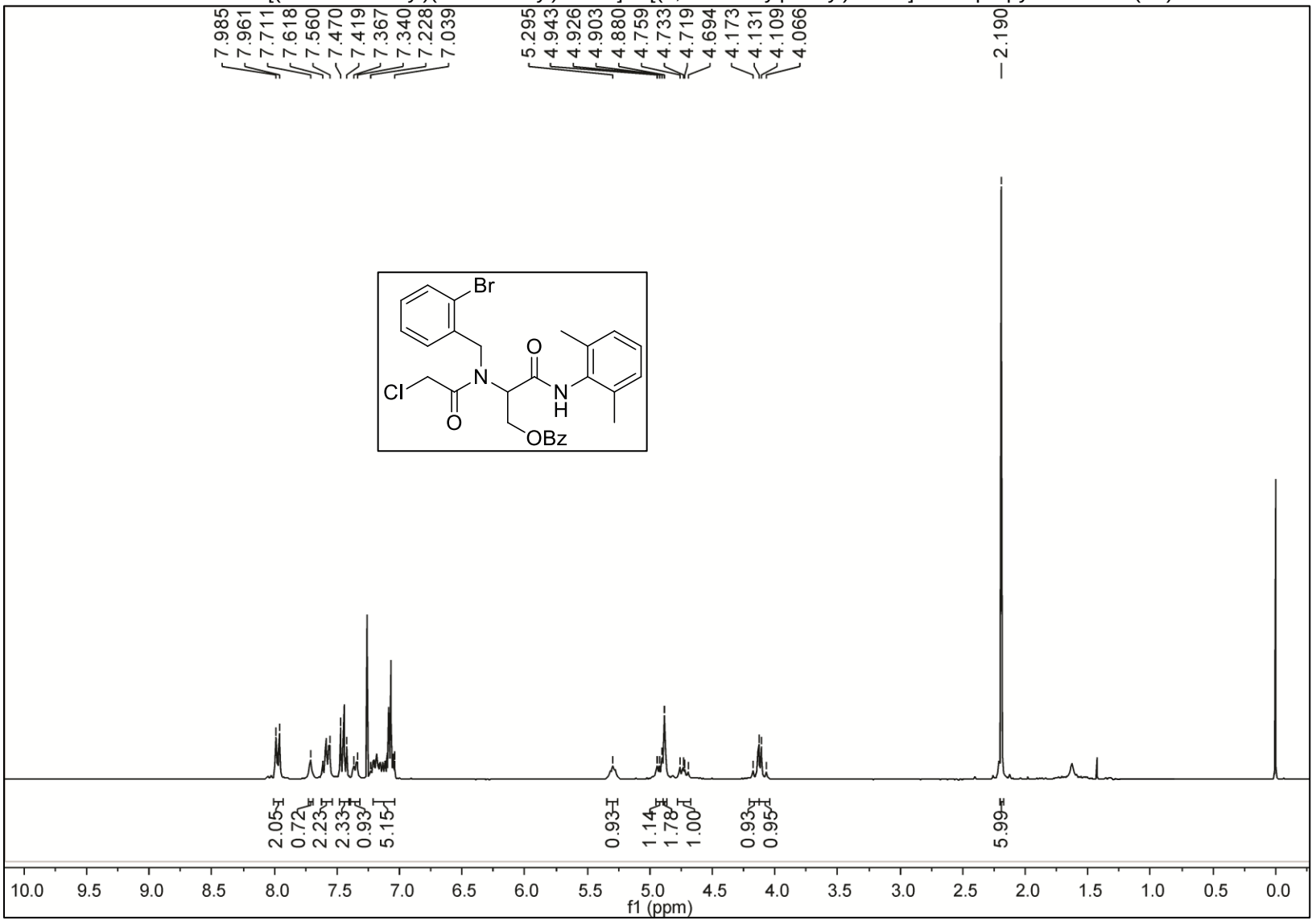


^{1}H-NMR of 2-[(2-bromobenzyl)(chloroacetyl)amino]-3-[(2,6-dimethylphenyl)amino]-3-oxopropyl benzoate (**4d**)



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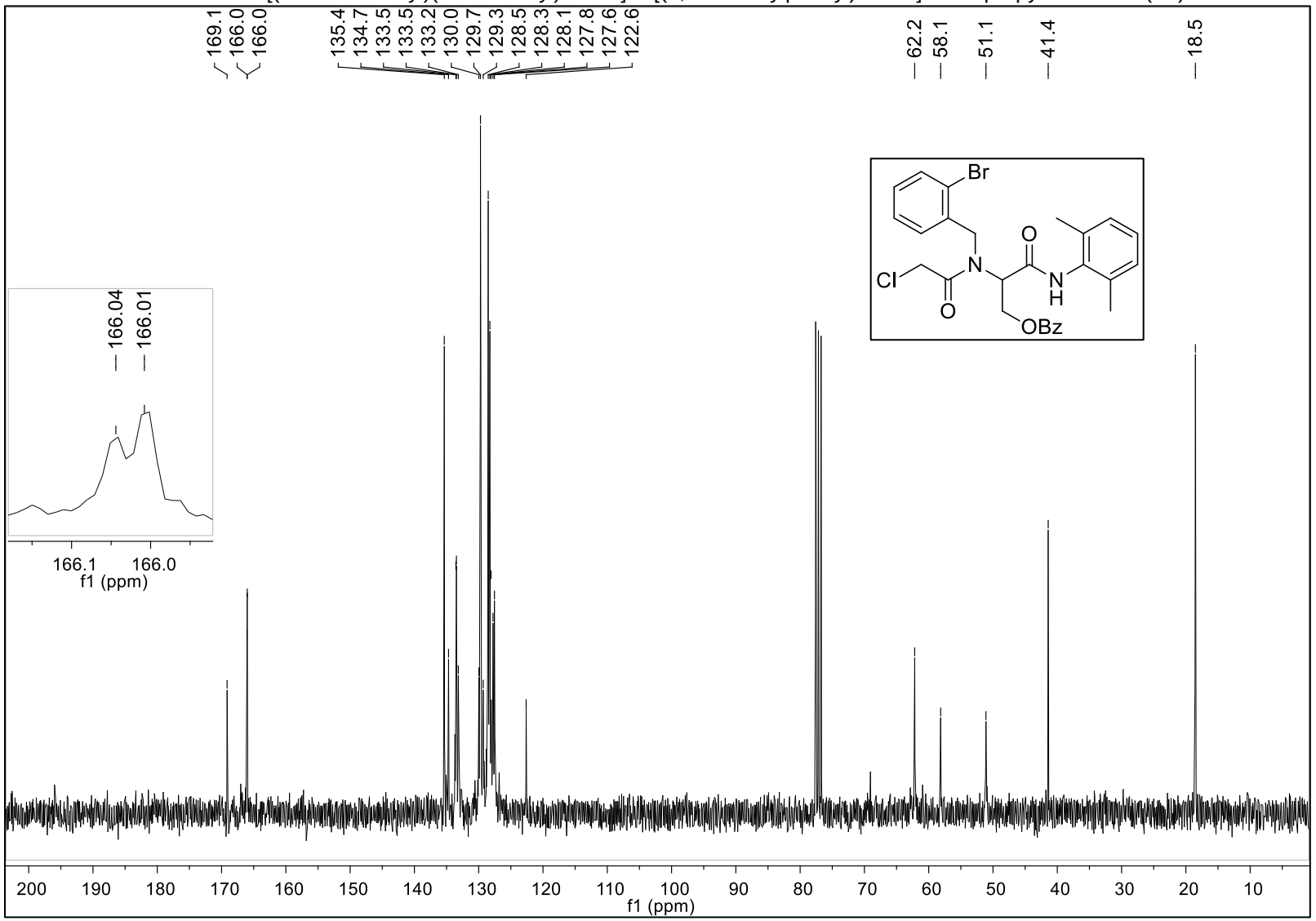
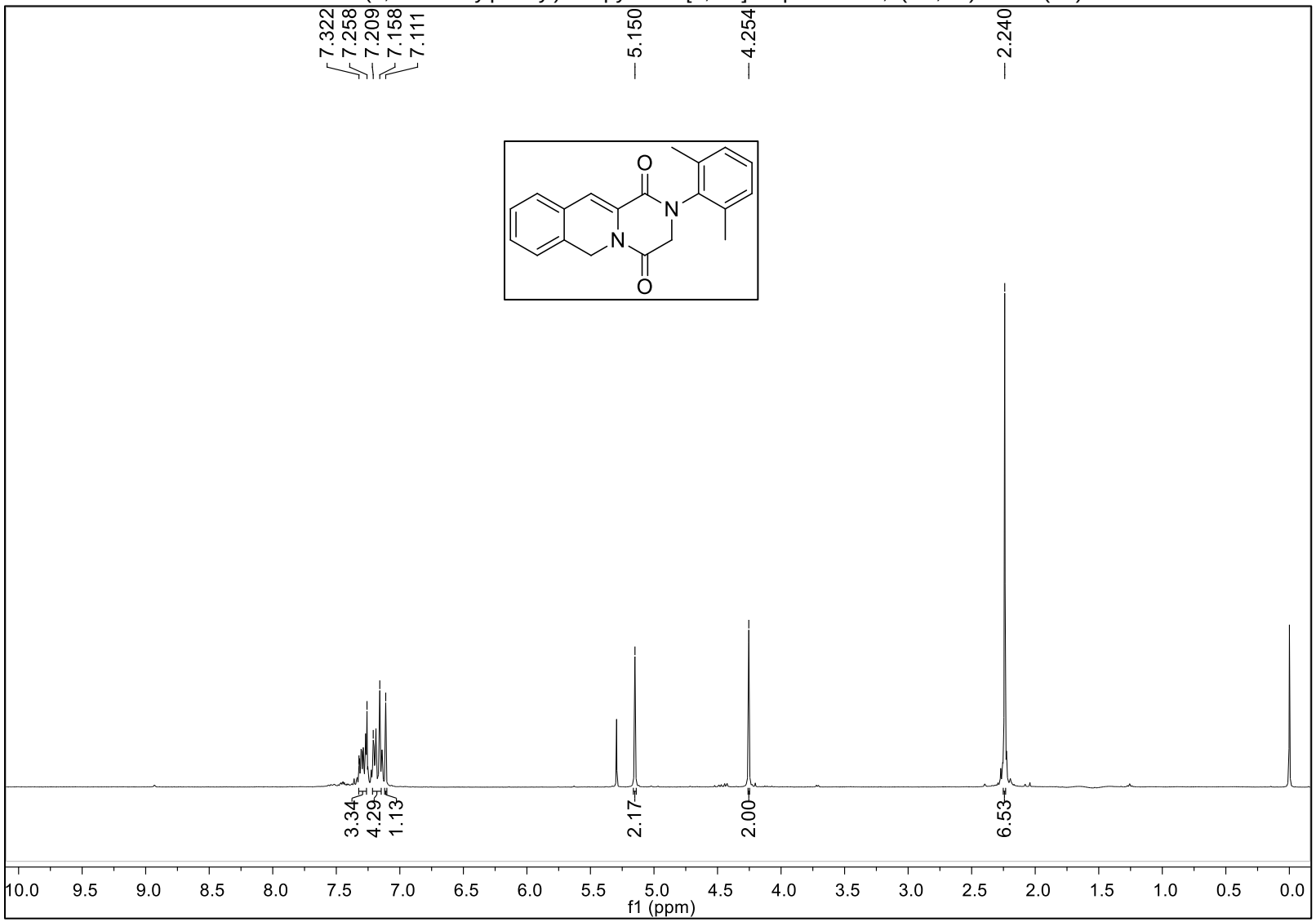


^{1}H-NMR of 2-(2,6-dimethylphenyl)-2*H*-pyrazino[1,2-*b*]isoquinoline-1,4(3*H*,6*H*)-dione (**6d**)



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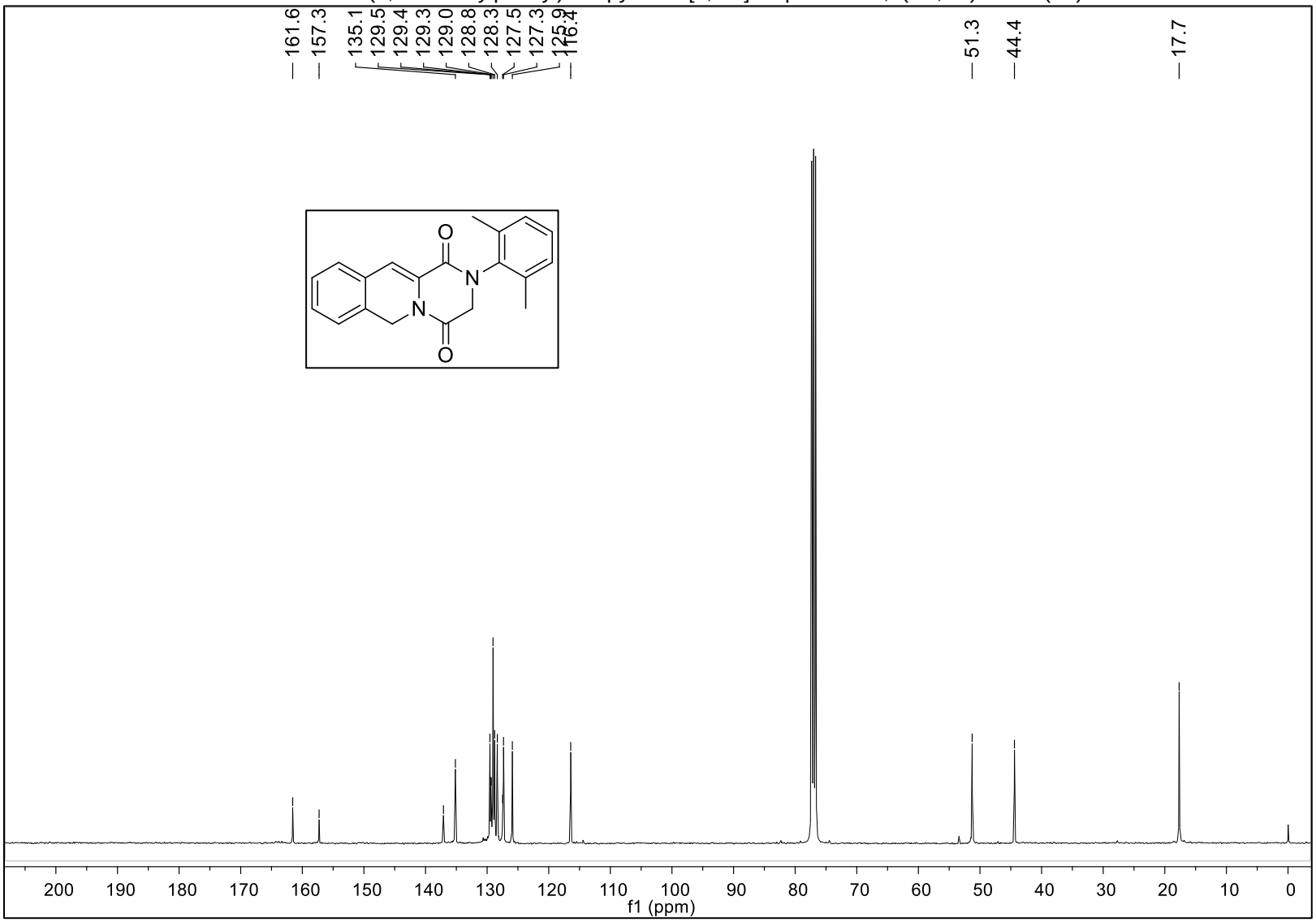
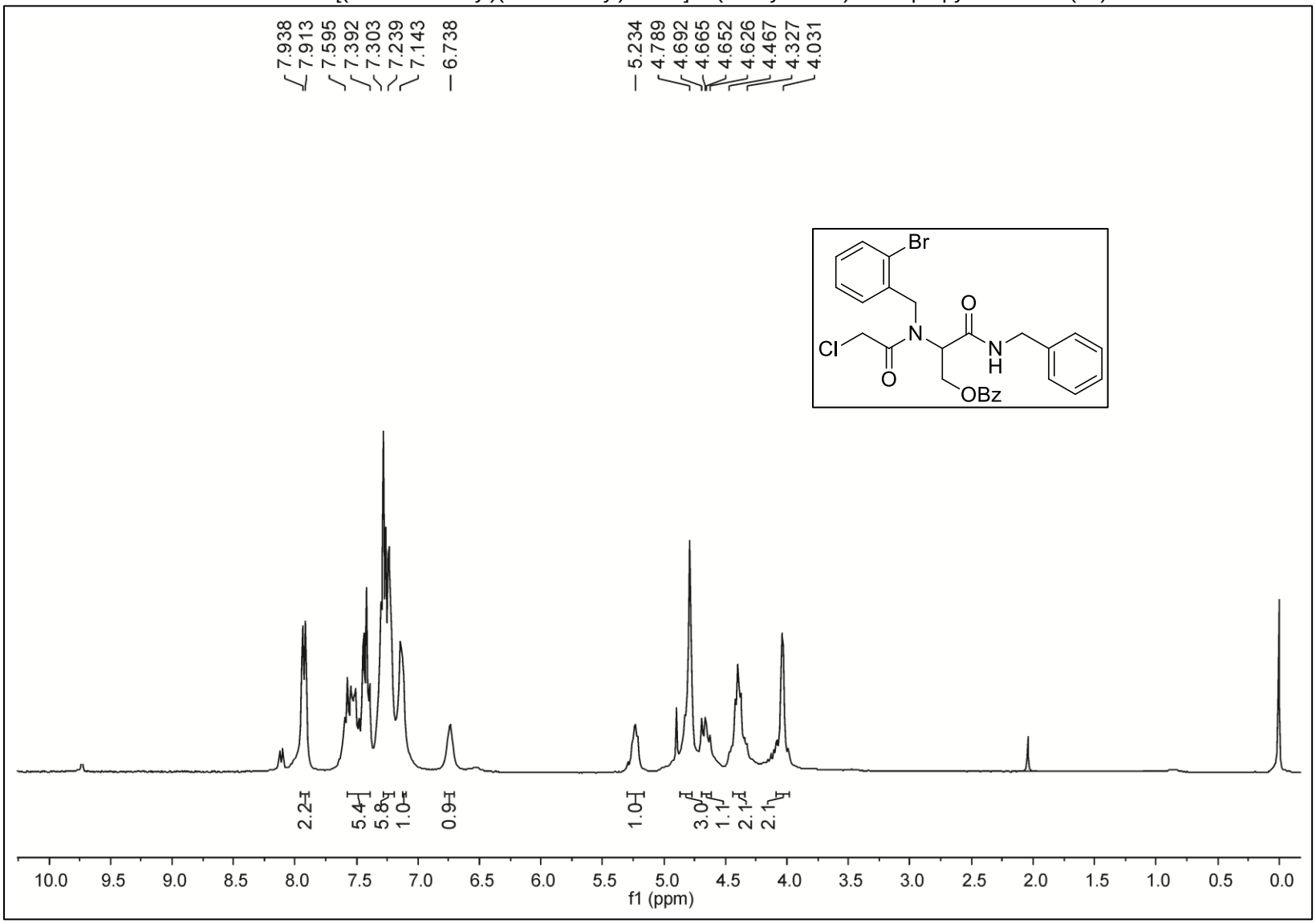
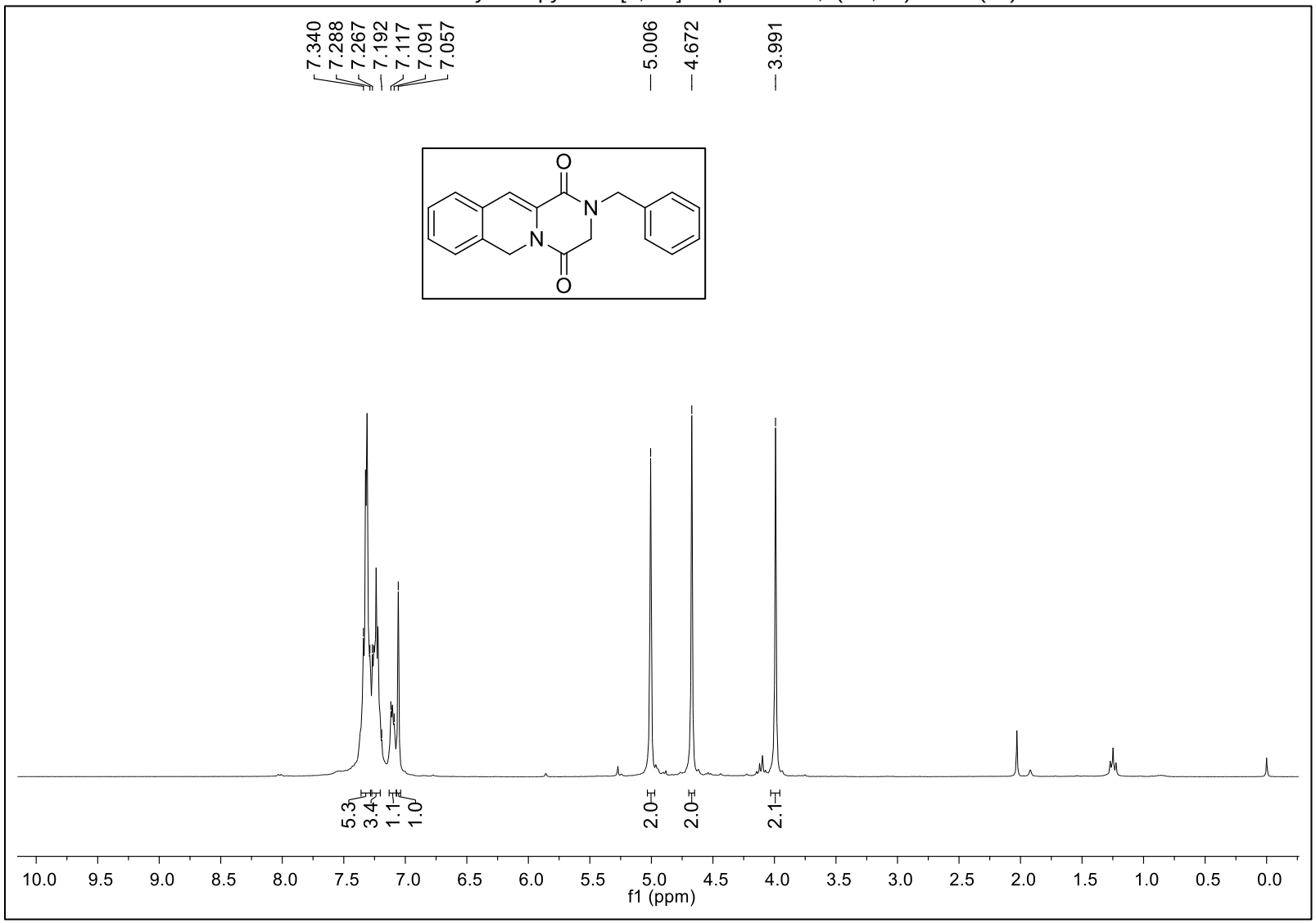


^{1}H-NMR of 2-[(2-bromobenzyl)(chloroacetyl)amino]-3-(benzylamino)-3-oxopropyl benzoate (**4e**)



^{1}H-NMR of 2-benzyl–2*H*-pyrazino[1,2-*b*]isoquinoline-1,4(3*H*,6*H*)-dione (**6e**)



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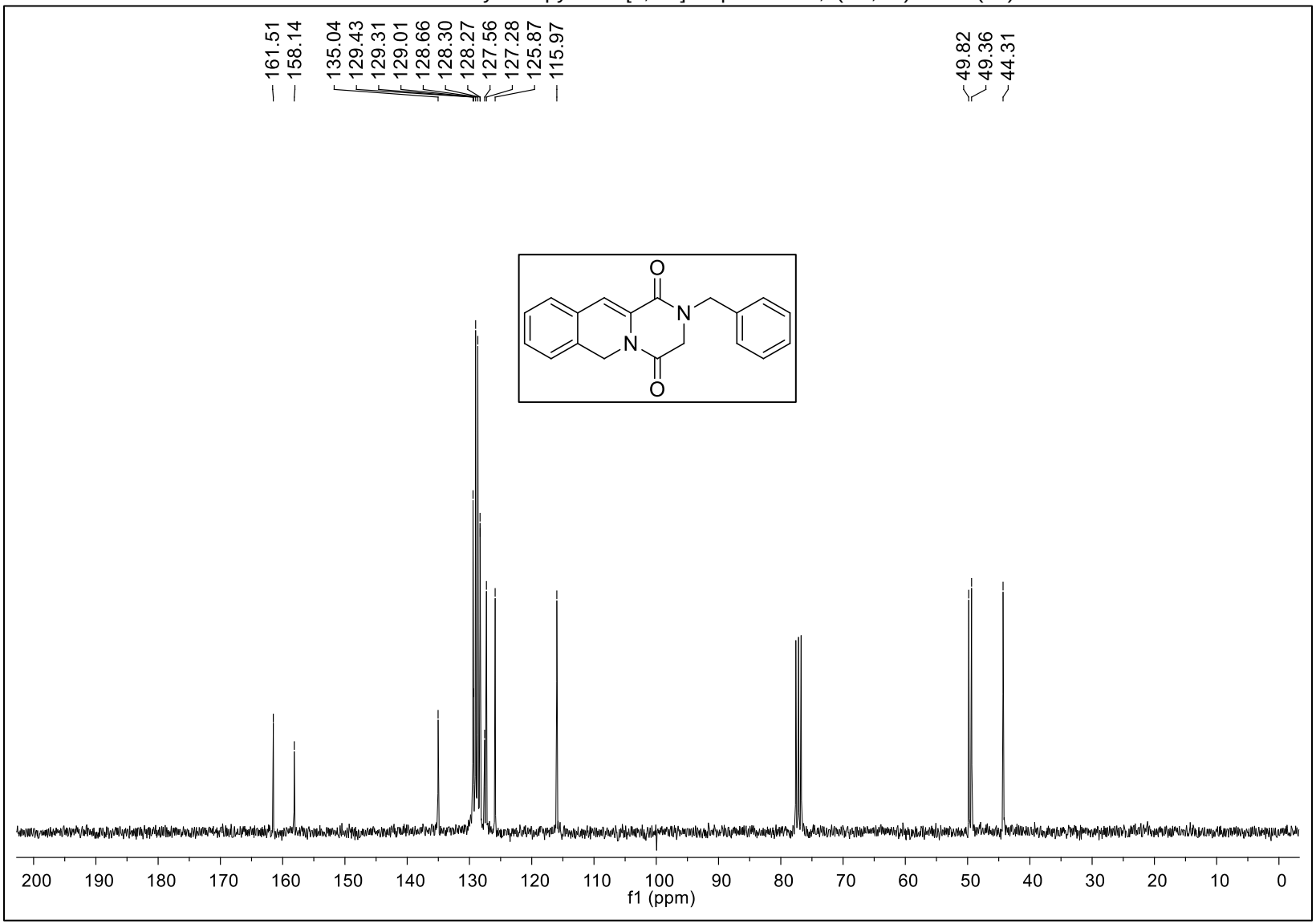
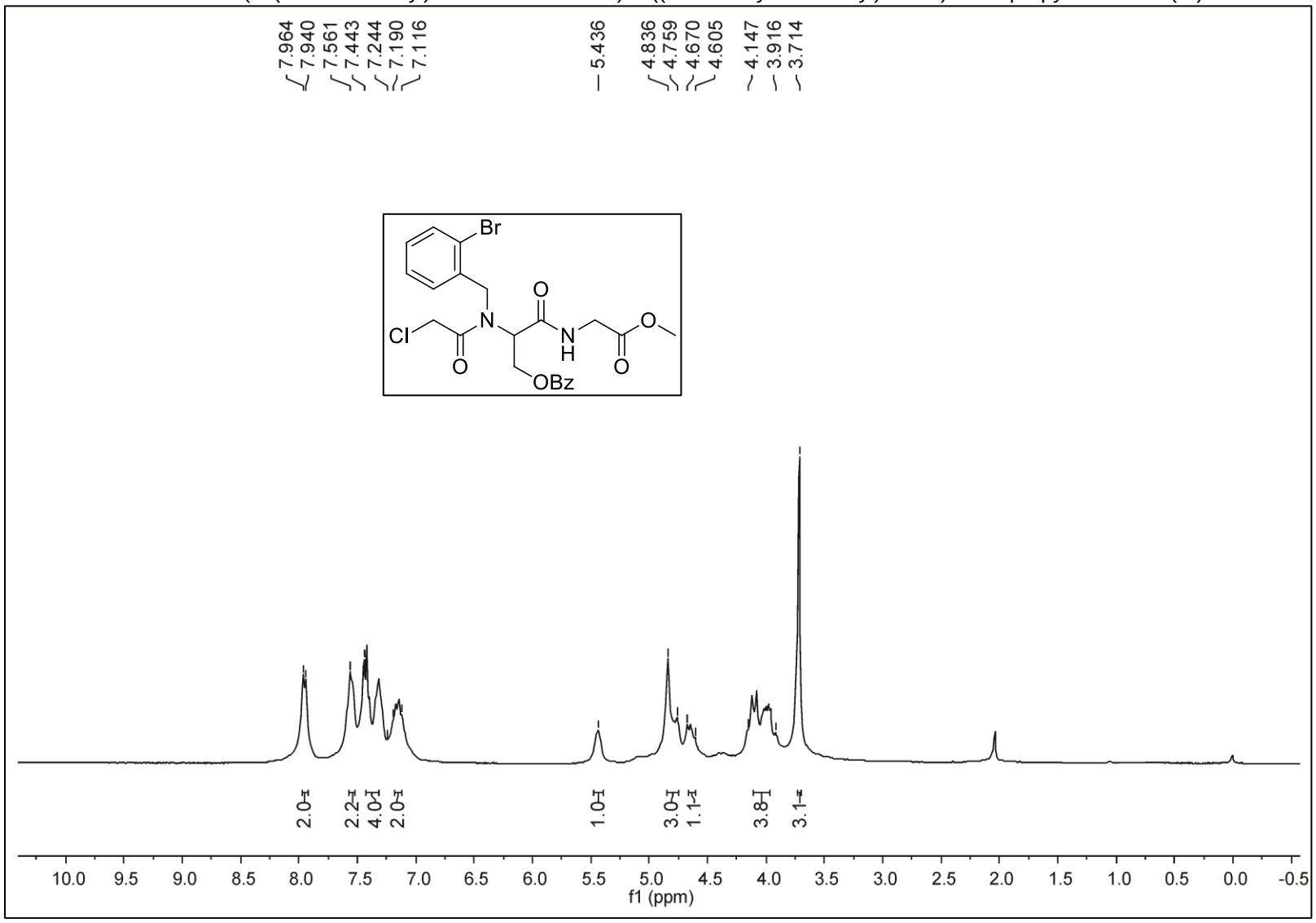
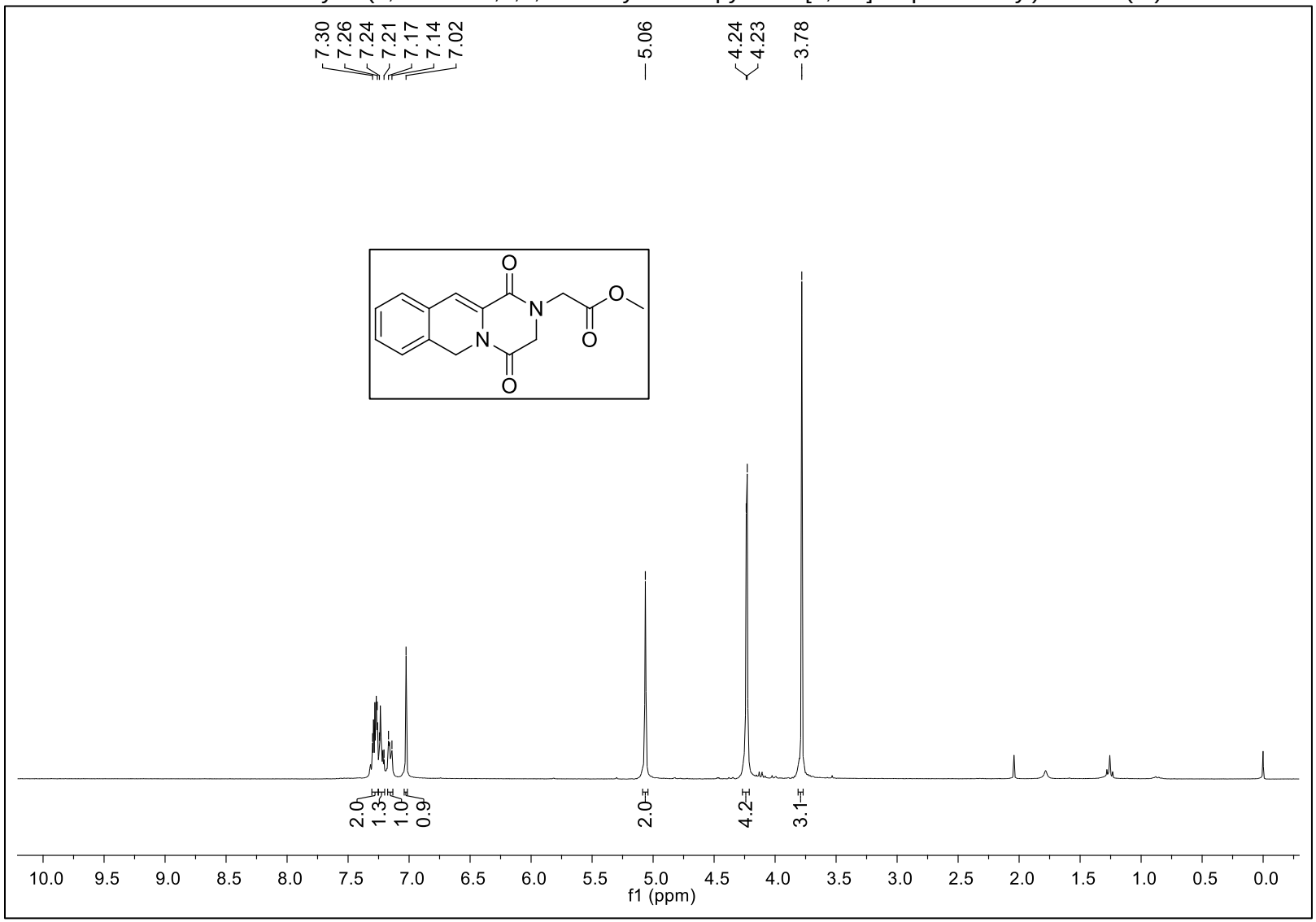


^{1}H-NMR of 2-(*N*-(4-bromobenzyl)-2-chloroacetamido)-3-((2-methoxy-2-oxoethyl)amino)-3-oxopropyl benzoate (**4f**)



^{1}H-NMR of methyl 2-(1,4-dioxo-1,3,4,6-tetrahydro-2*H*-pyrazino[1,2-*b*]isoquinolin-2-yl)acetate (**6f**).



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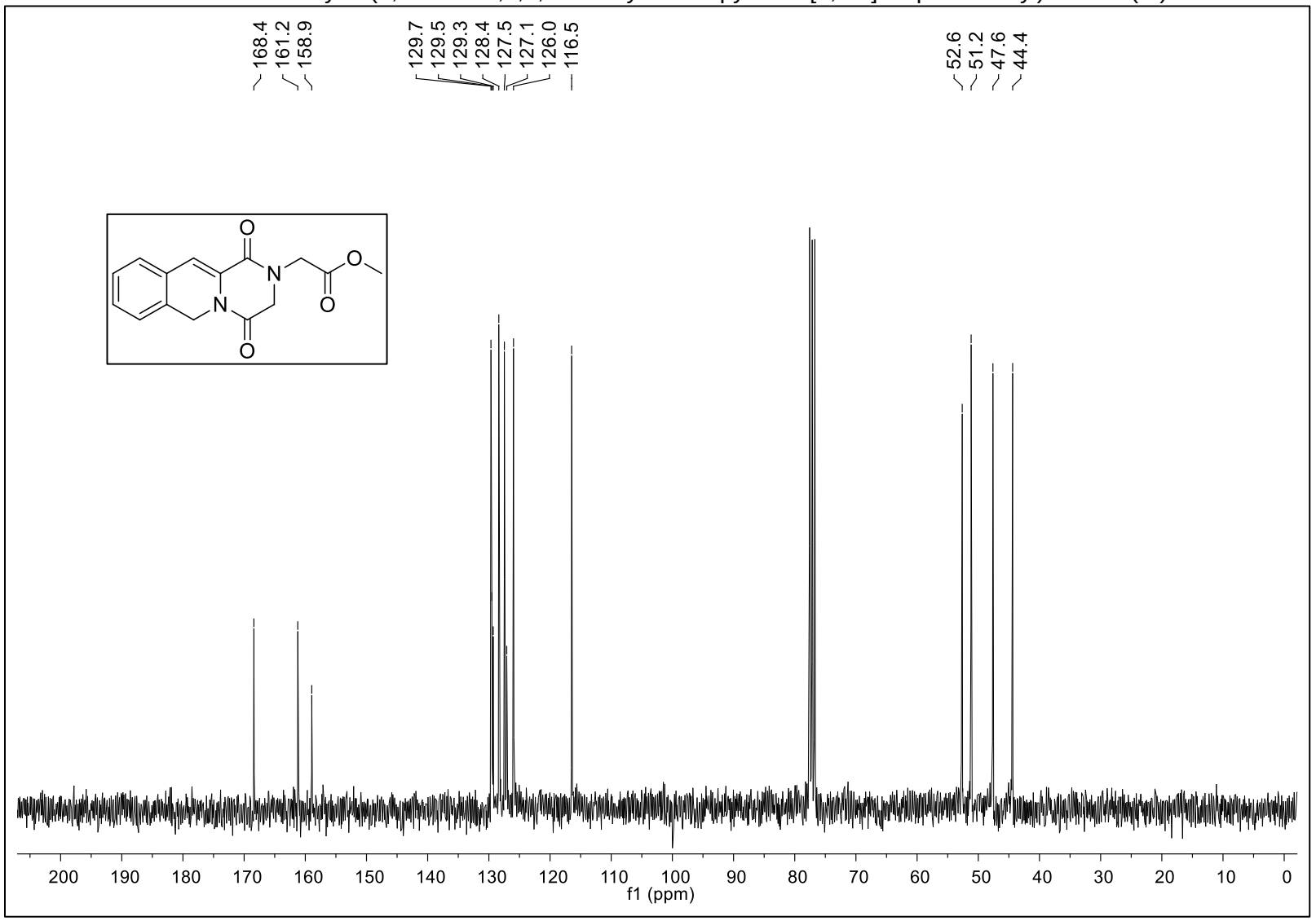
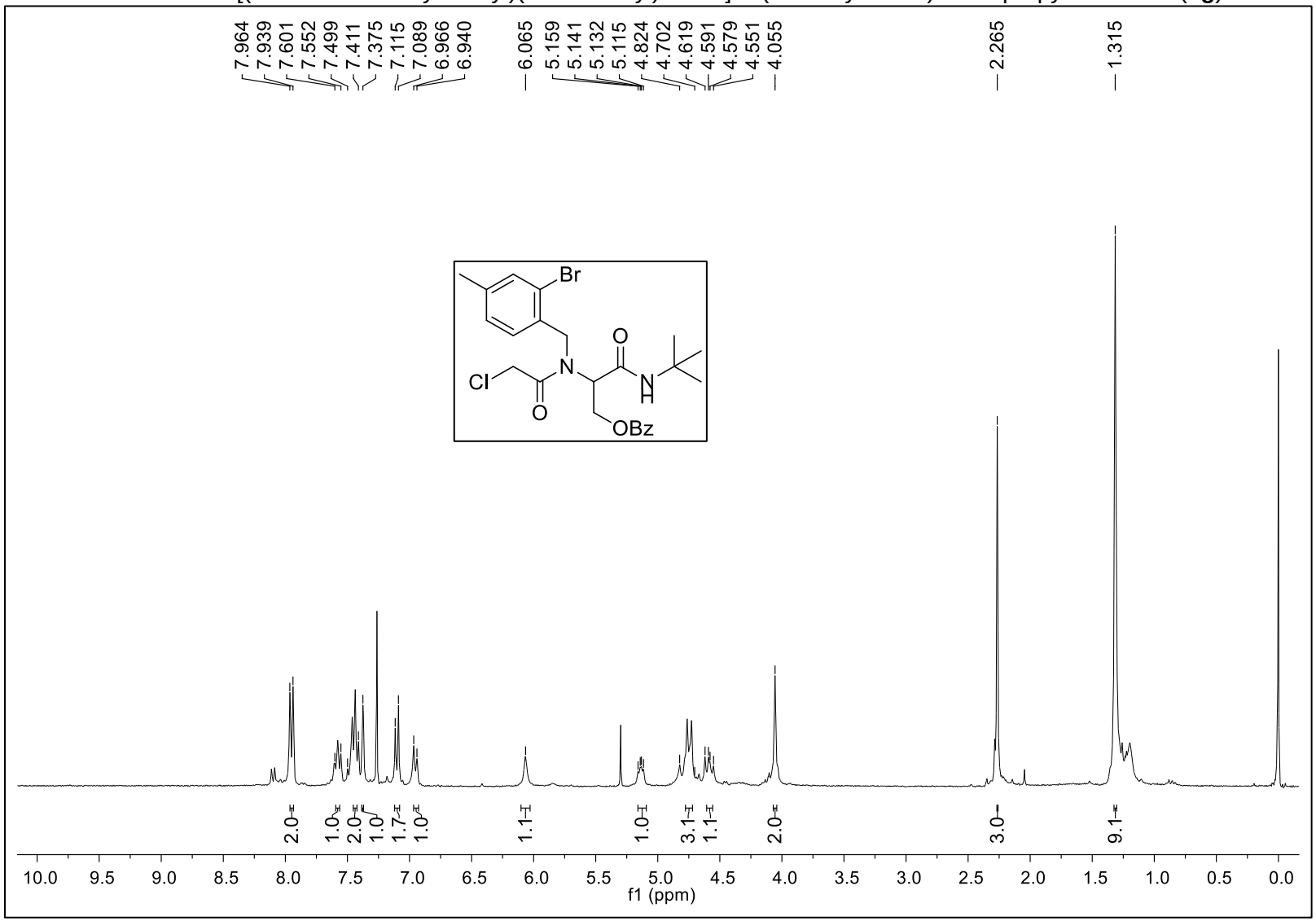
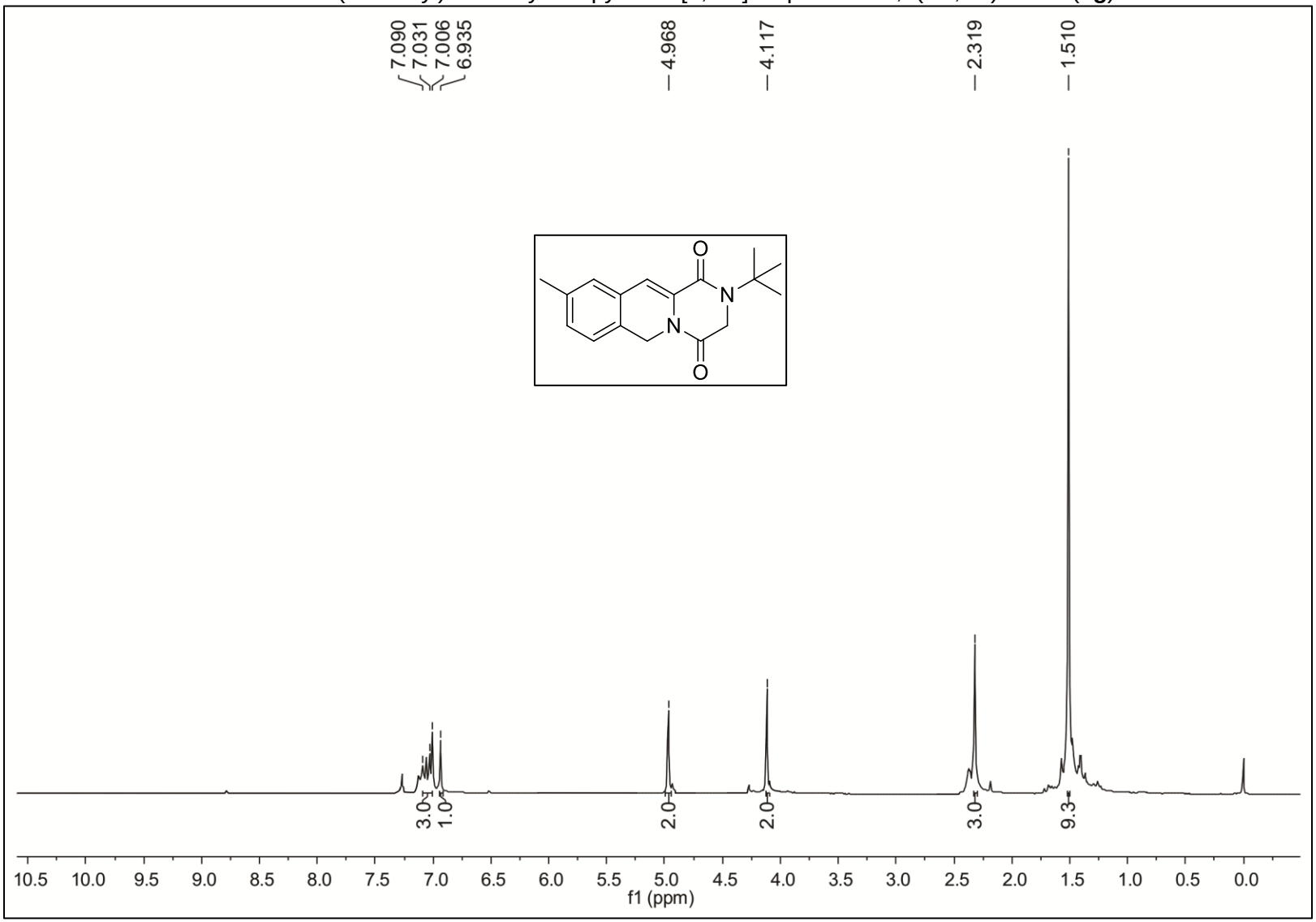


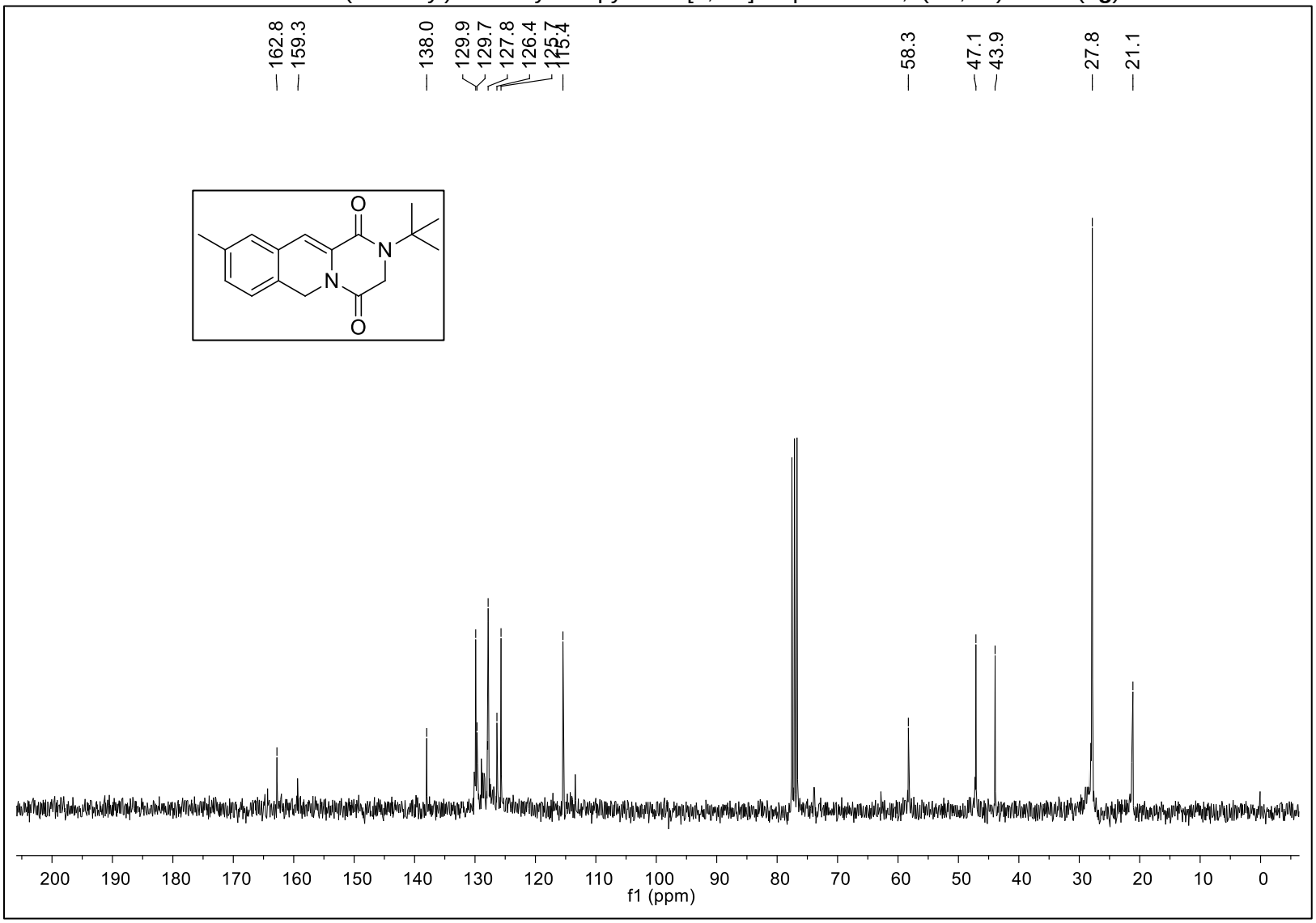
^{1}H-NMR of 2-[(2-bromo-4-methylbenzyl)(chloroacetyl)amino]-3-(*tert*-butylamino)-3-oxopropyl benzoate (**4g**)



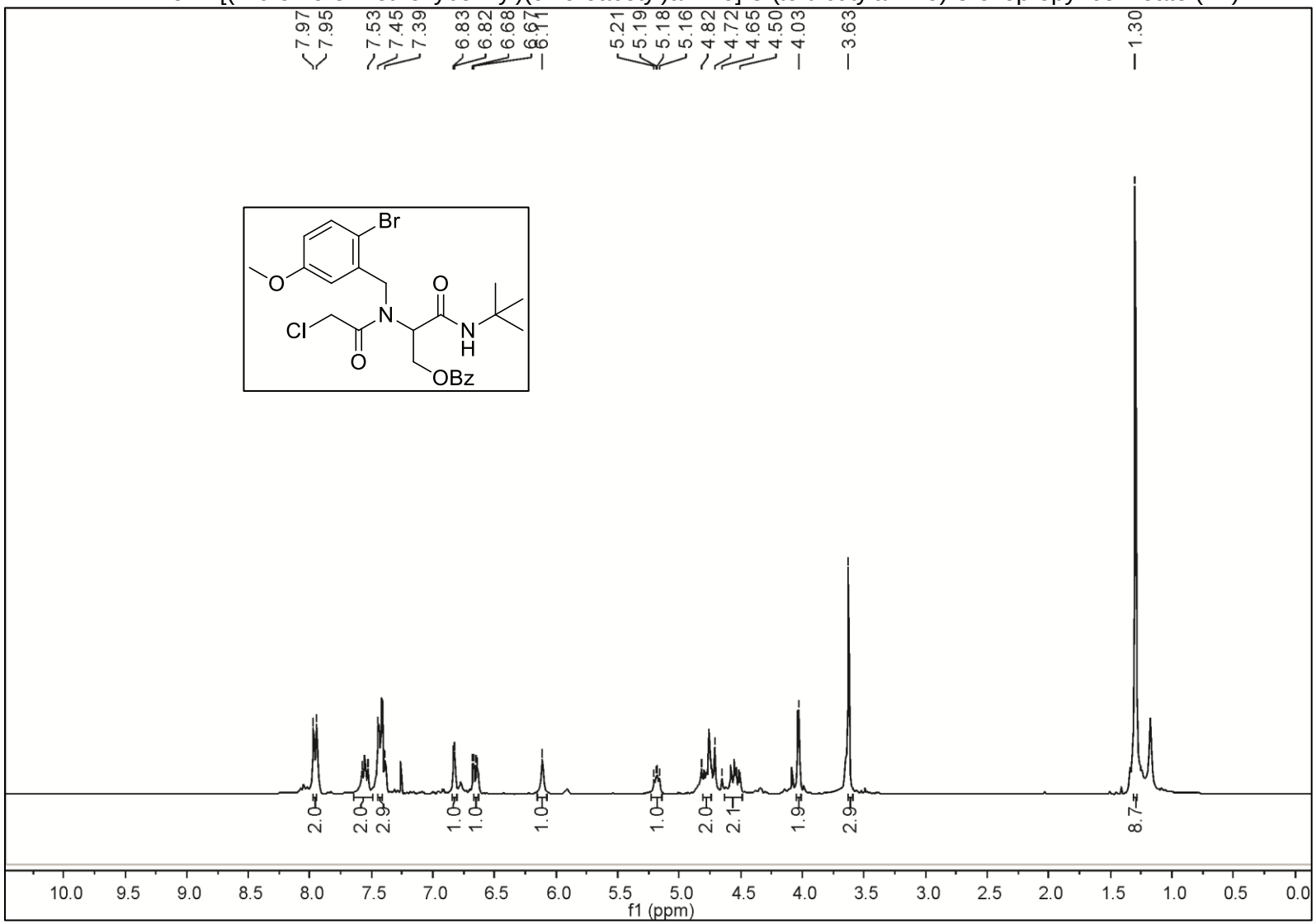
^{1}H-NMR of 2-(*tert*-butyl)-9-methyl-2*H*-pyrazino[1,2-*b*]isoquinoline-1,4(3*H*,6*H*)-dione (**6g**).



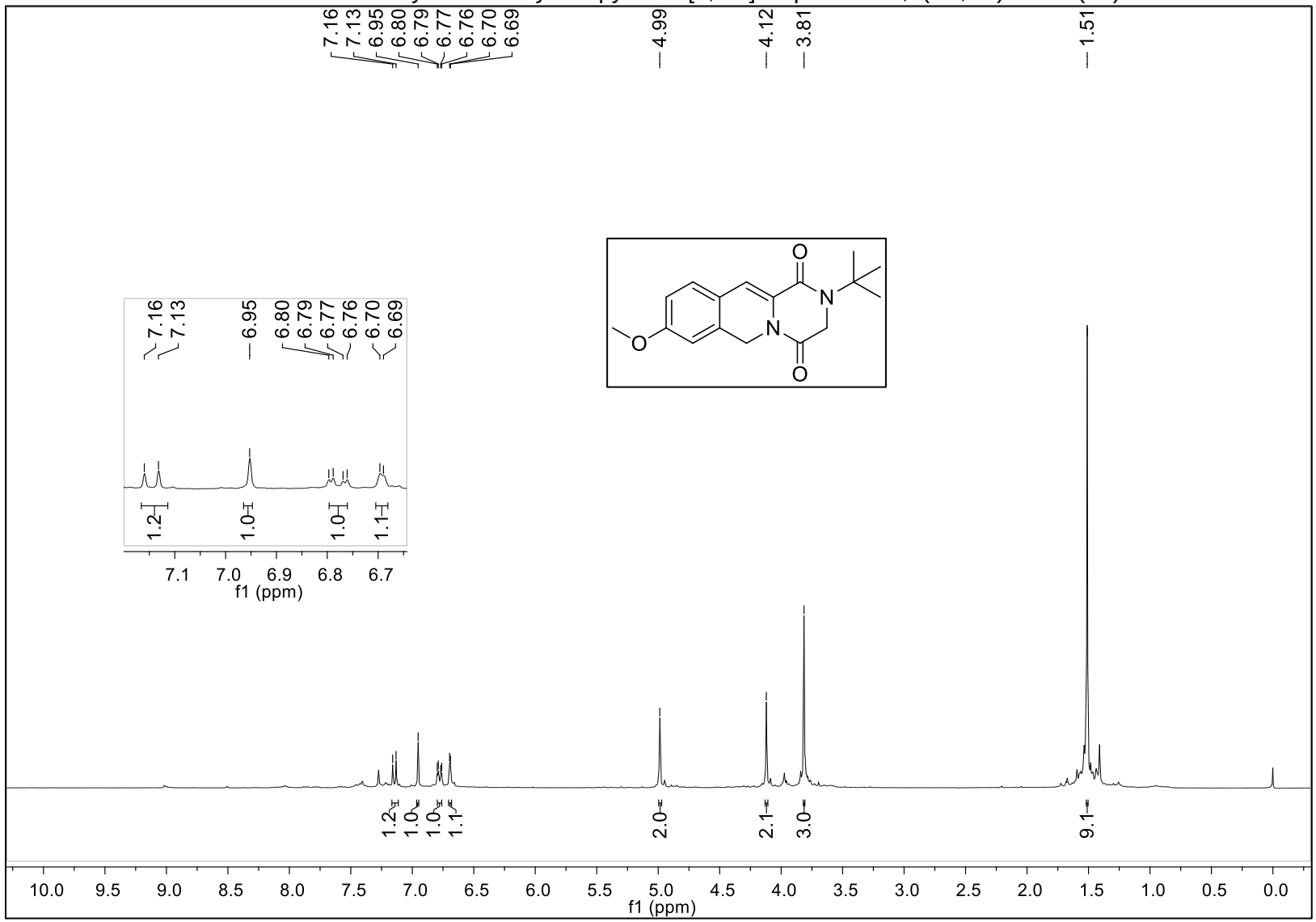
^{13}C-NMR of 2-(*tert*-butyl)-9-methyl-2*H*-pyrazino[1,2-*b*]isoquinoline-1,4(3*H*,6*H*)-dione (**6g**)



^{1}H-NMR of 2-[(2-bromo-5-methoxybenzyl)(chloroacetyl)amino]-3-(*tert*-butylamino)-3-oxopropyl benzoate (**4h**)



^{1}H-NMR of 2-*tert*-butyl-8-methoxy–2*H*-pyrazino[1,2-*b*]isoquinoline-1,4(3*H*,6*H*)-dione (**6h**)



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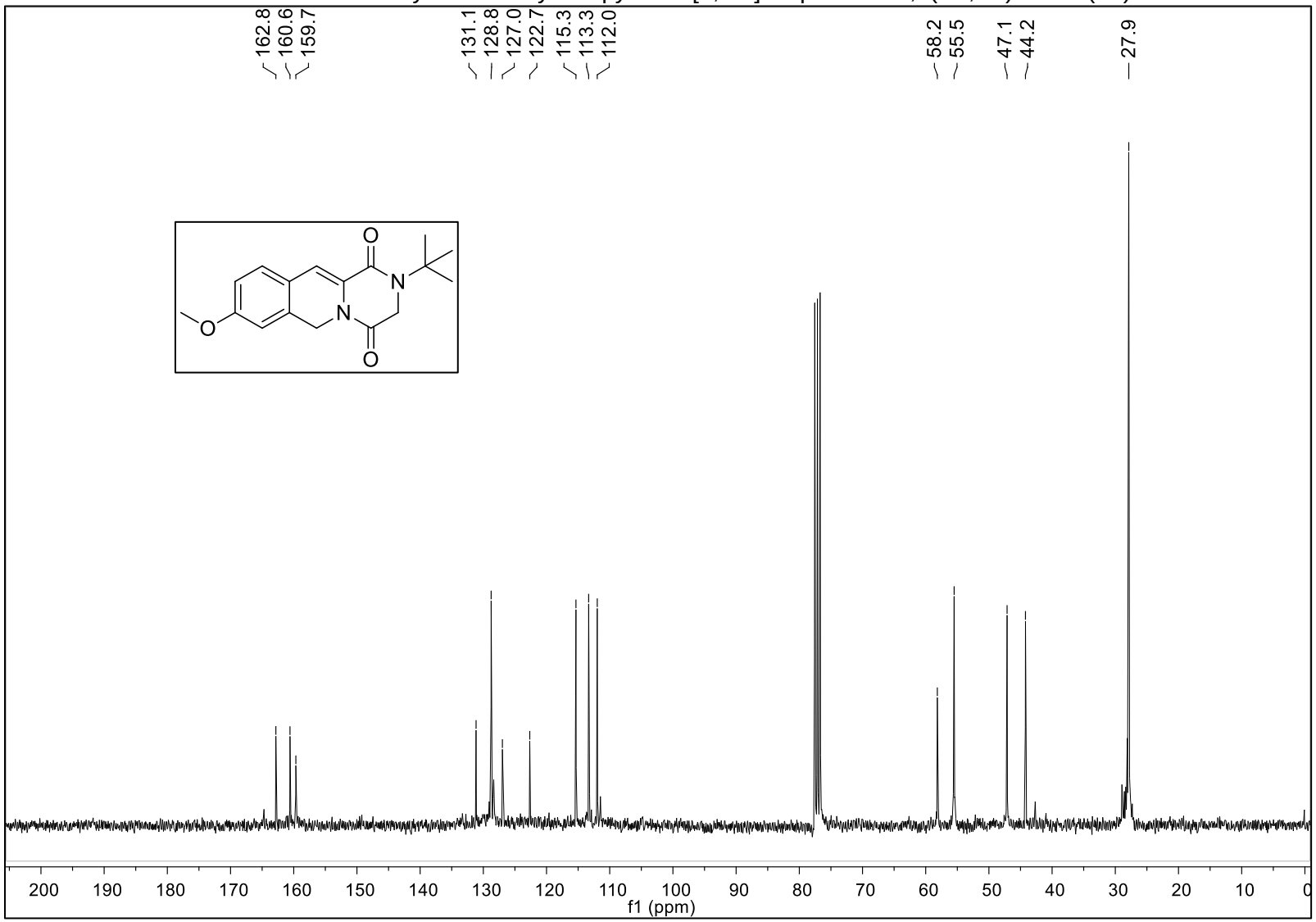
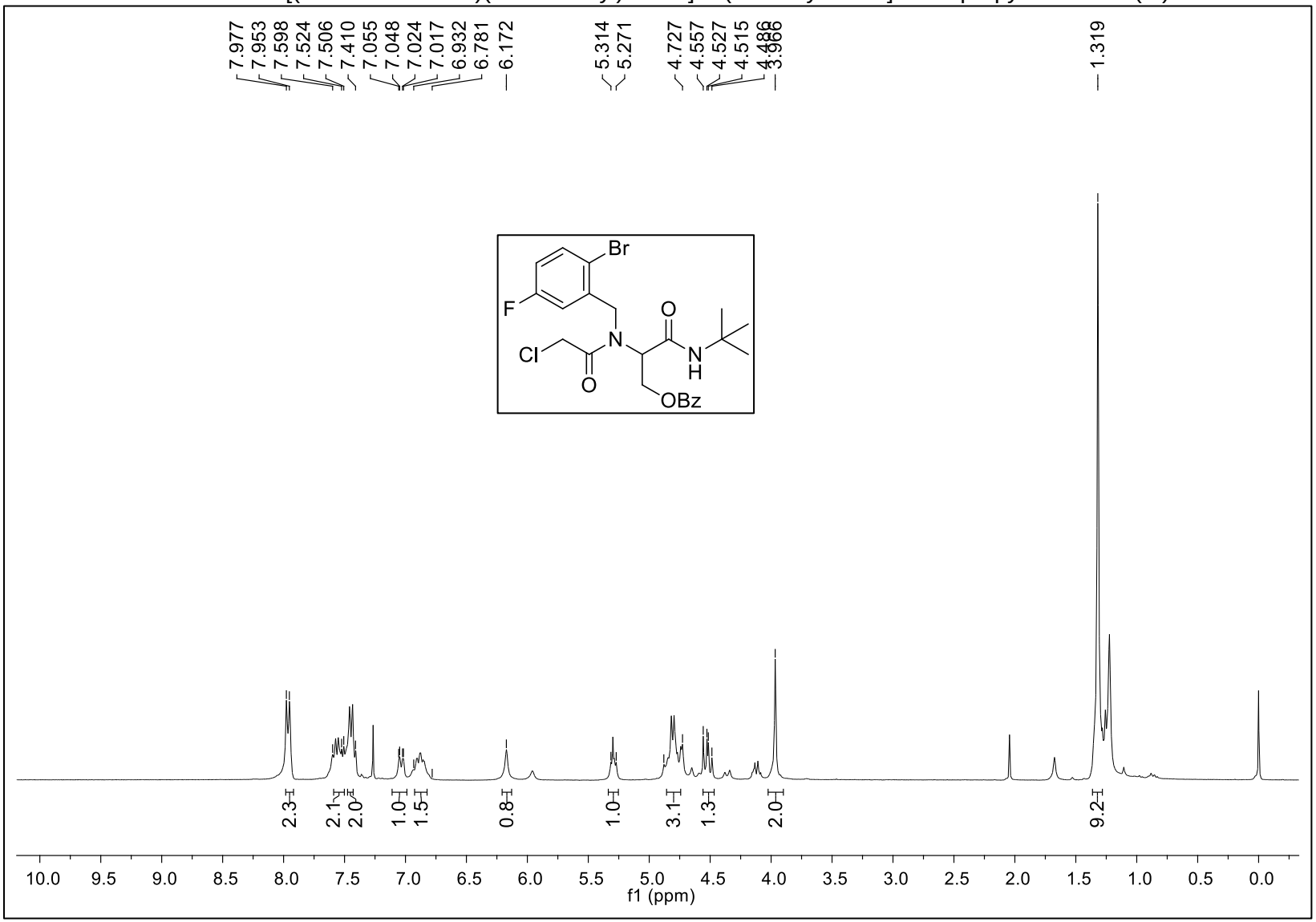
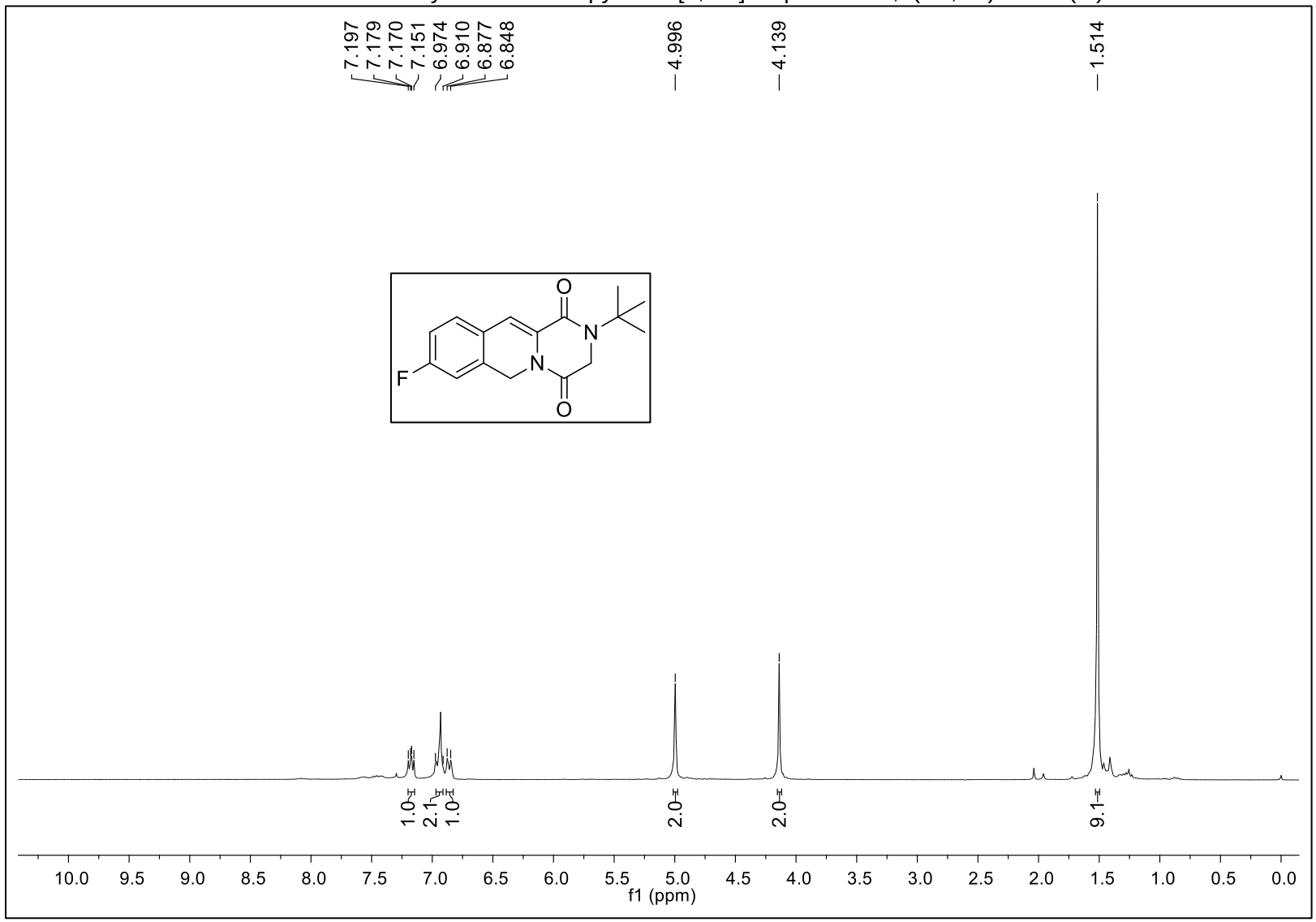


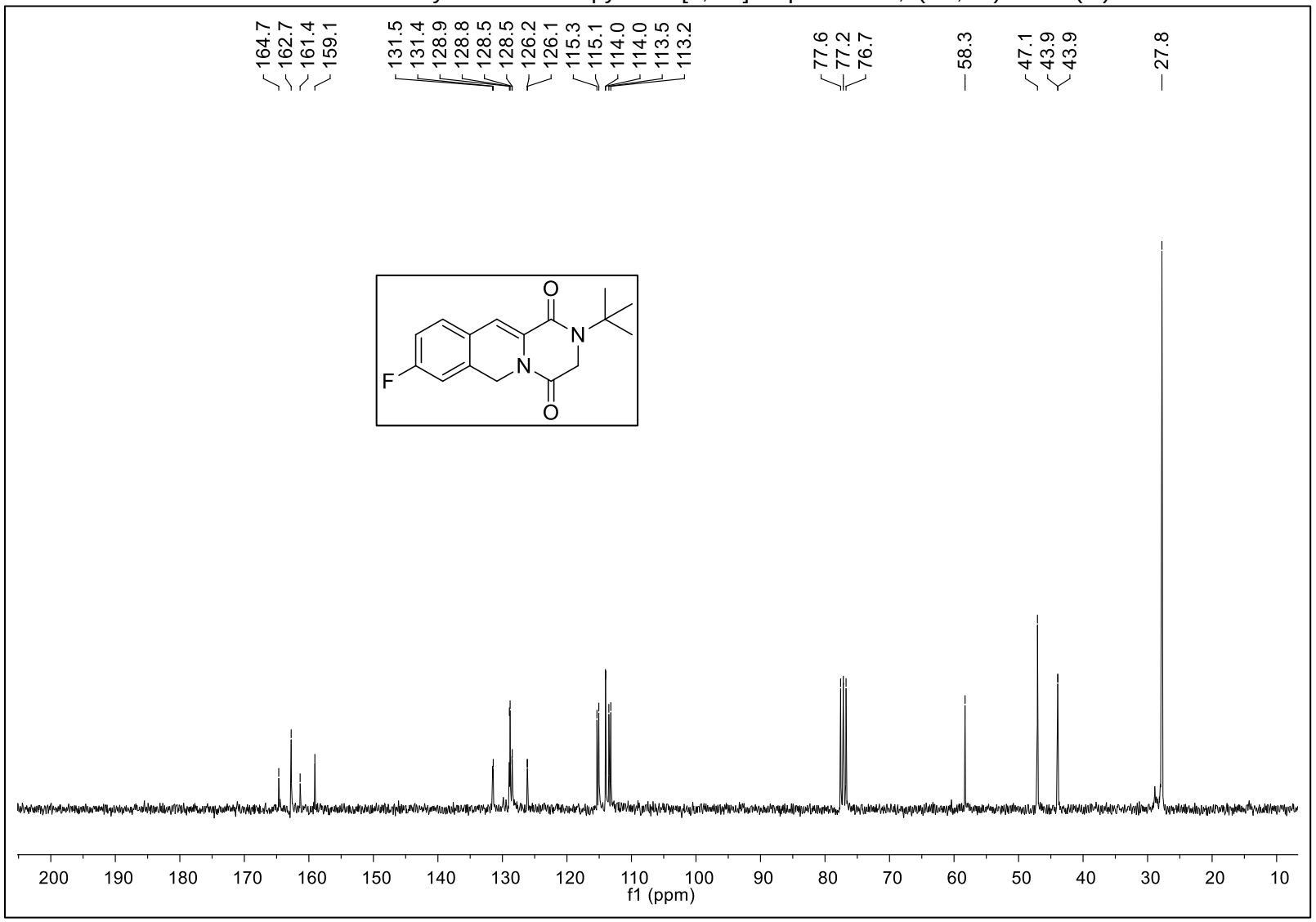
^{1}H-NMR of 2-[(2-bromo-5-fluoro)(chloroacetyl)amino]-3-(*tert*-butylamino]-3-oxopropyl benzoate (**4i**)



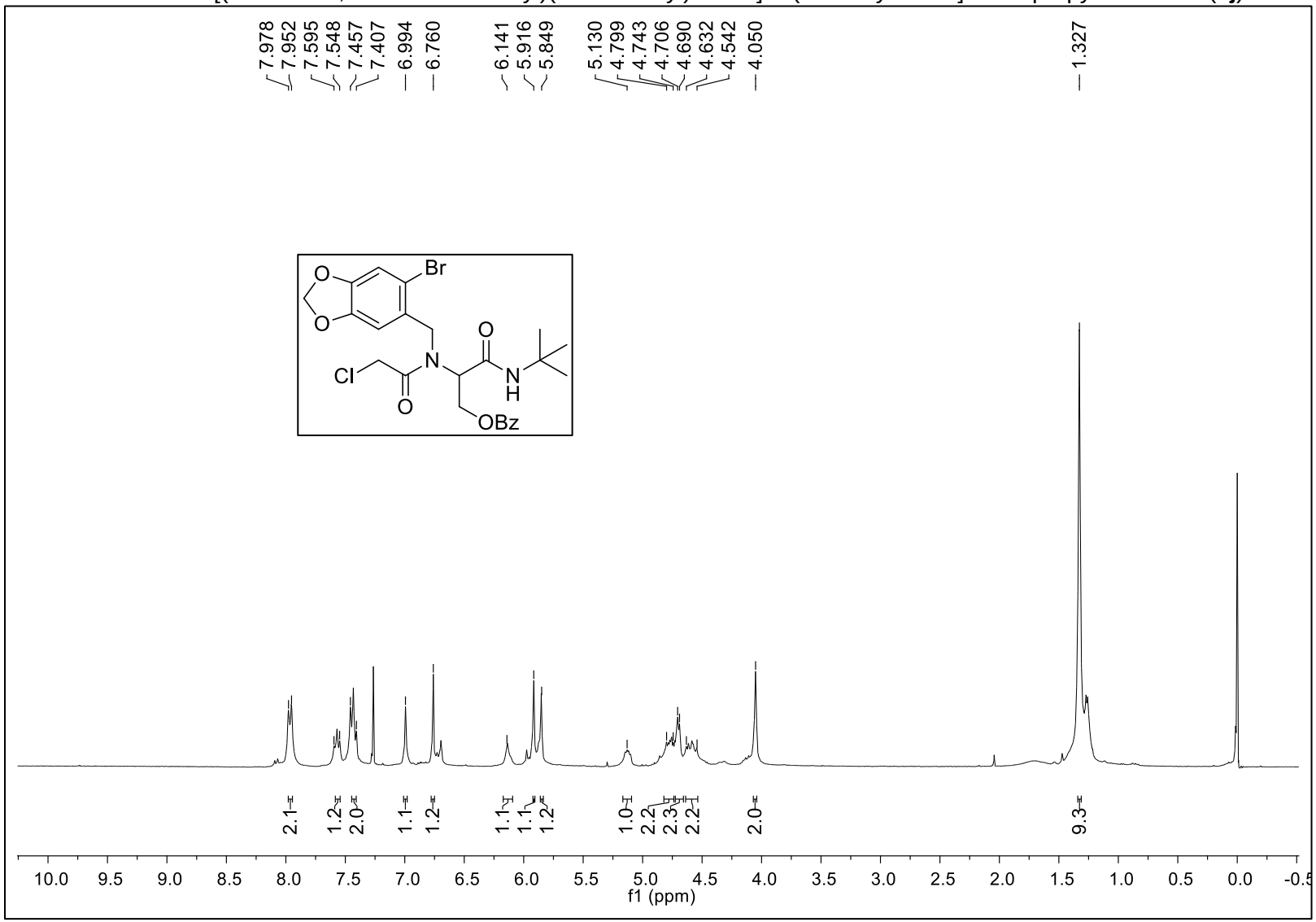
^{1}H-NMR of 2-*tert*-butyl-8-fluoro–2*H*-pyrazino[1,2-*b*]isoquinoline-1,4(3*H*,6*H*)-dione (**6i**)



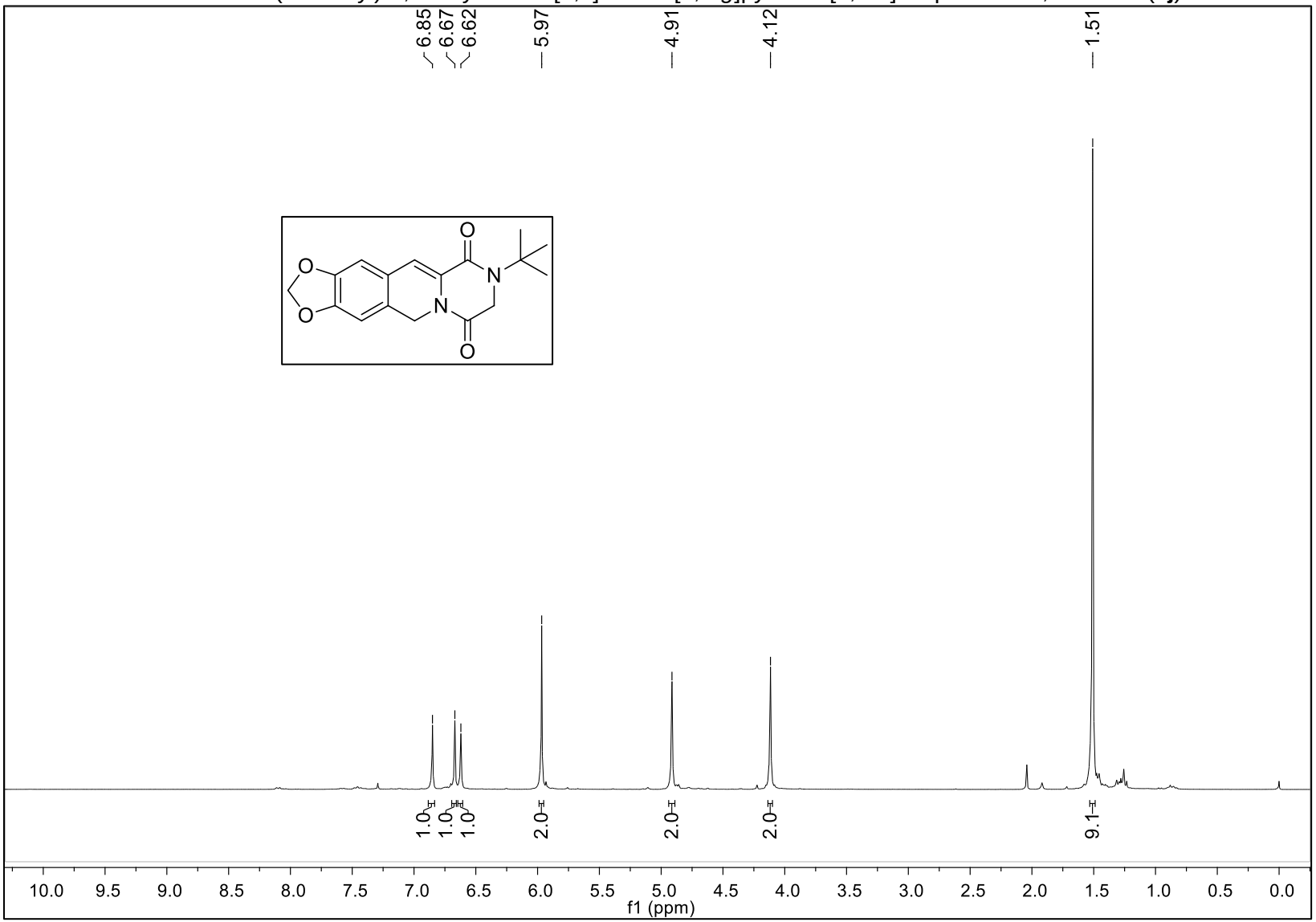
^{13}C-NMR of 2-*tert*-butyl-8-fluoro–2*H*-pyrazino[1,2-*b*]isoquinoline-1,4(3*H*,6*H*)-dione (**6i**)



^{1}H-NMR of 2-[(6-bromo-1,3-benzodioxol-5-yl)(chloroacetyl)amino]-3-(*tert*-butylamino]-3-oxopropyl benzoate (**4j**)



^{1}H-NMR of 9-(*tert*-butyl)-8,9-dihydro-5*H*-[1,3]dioxolo[4,5-*g*]pyrazino[1,2-*b*]isoquinoline-7,10-dione (**6j**)



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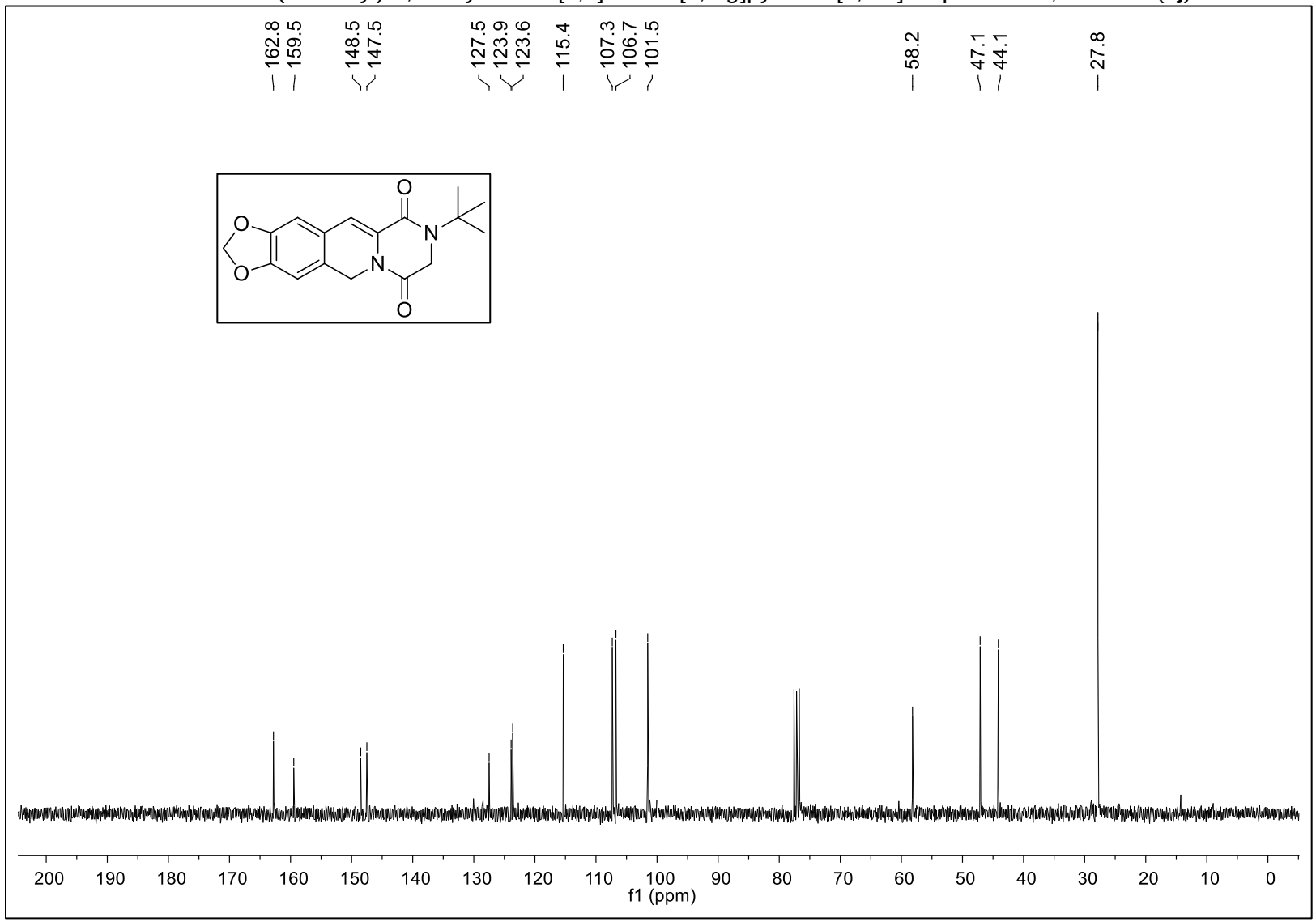
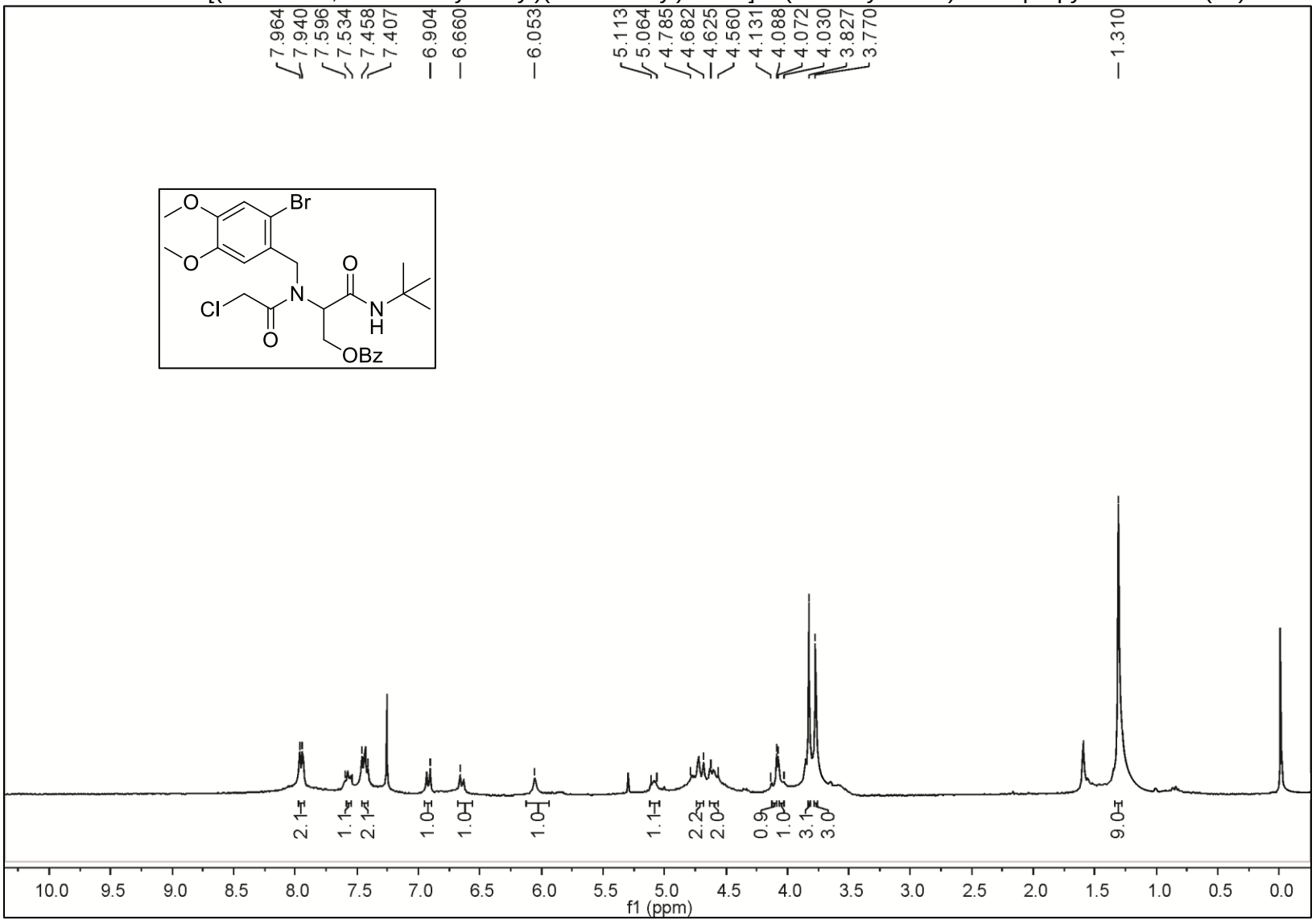


^{1}H-NMR of 2-[(2-bromo-4,5-dimethoxybenzyl)(chloroacetyl)amino]-3-(*tert*-butylamino)-3-oxopropyl benzoate. (**4k**)



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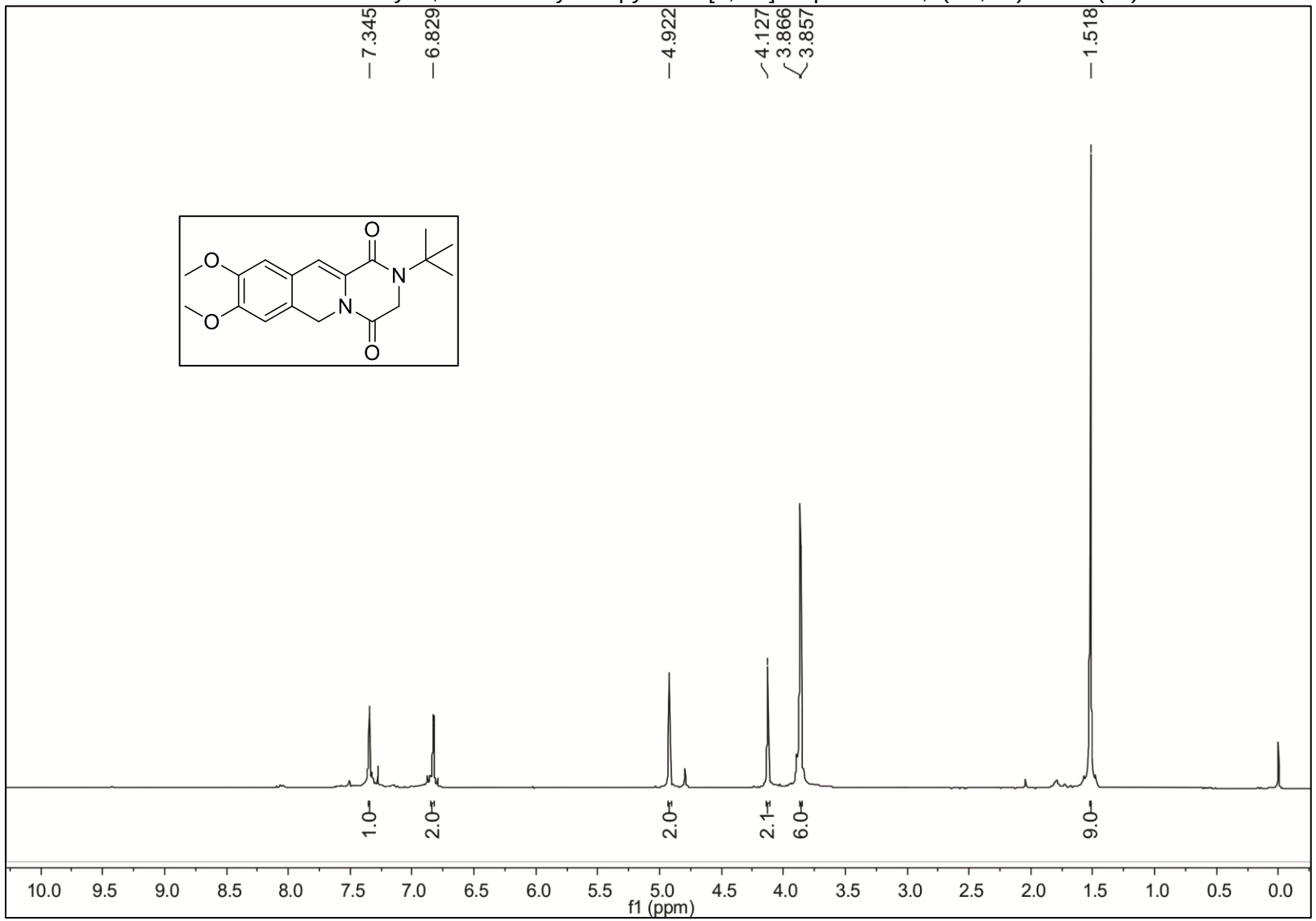

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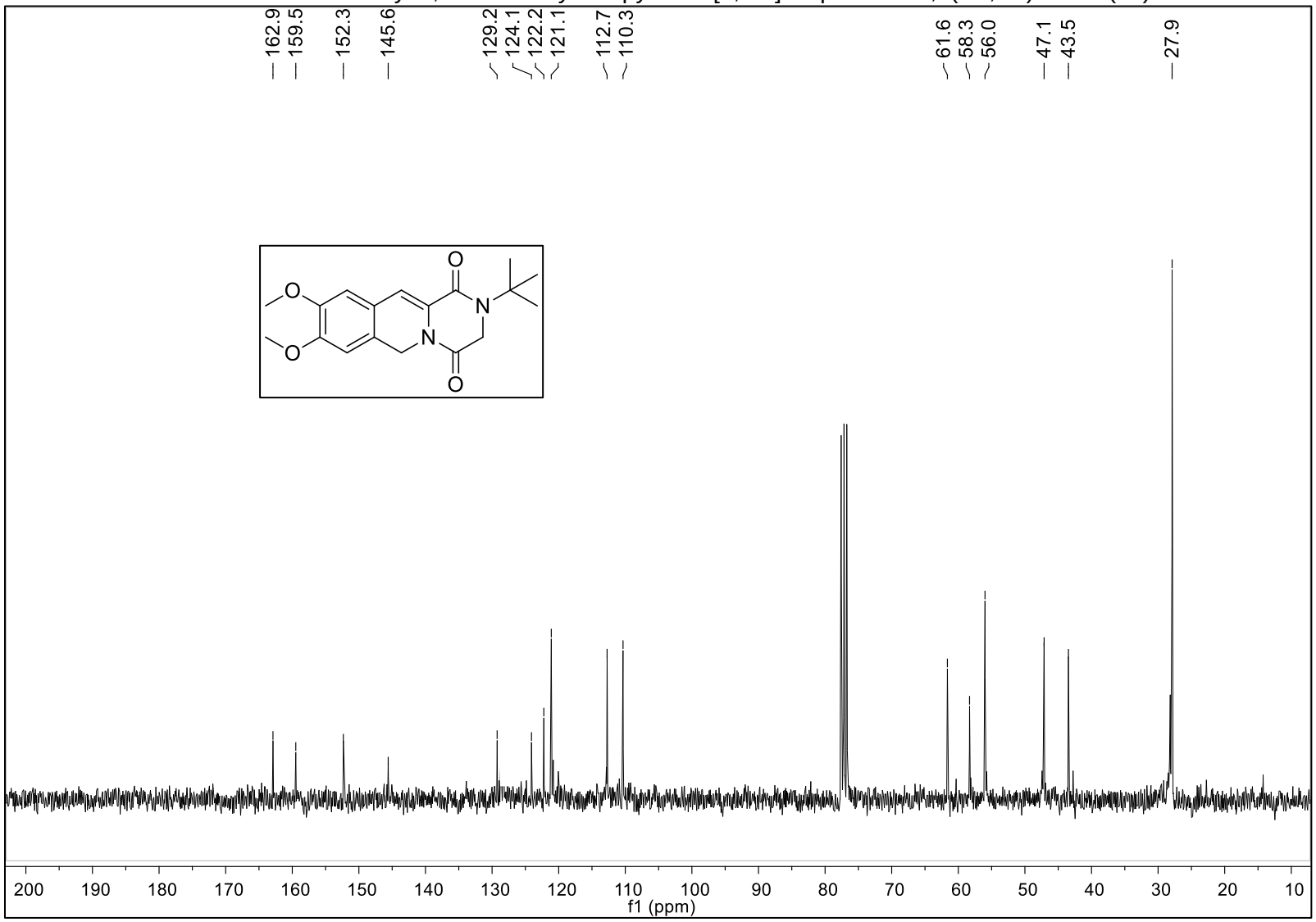
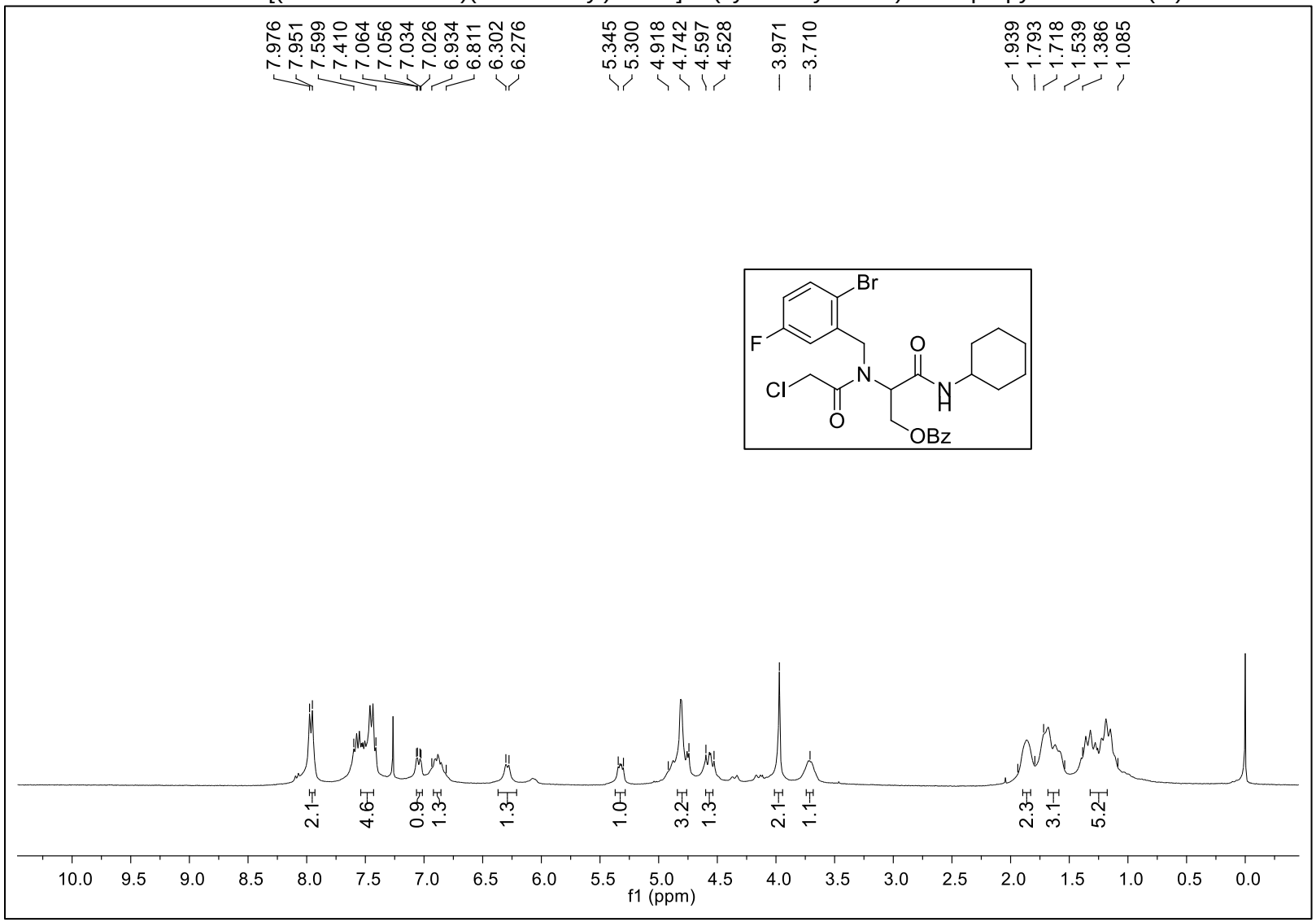
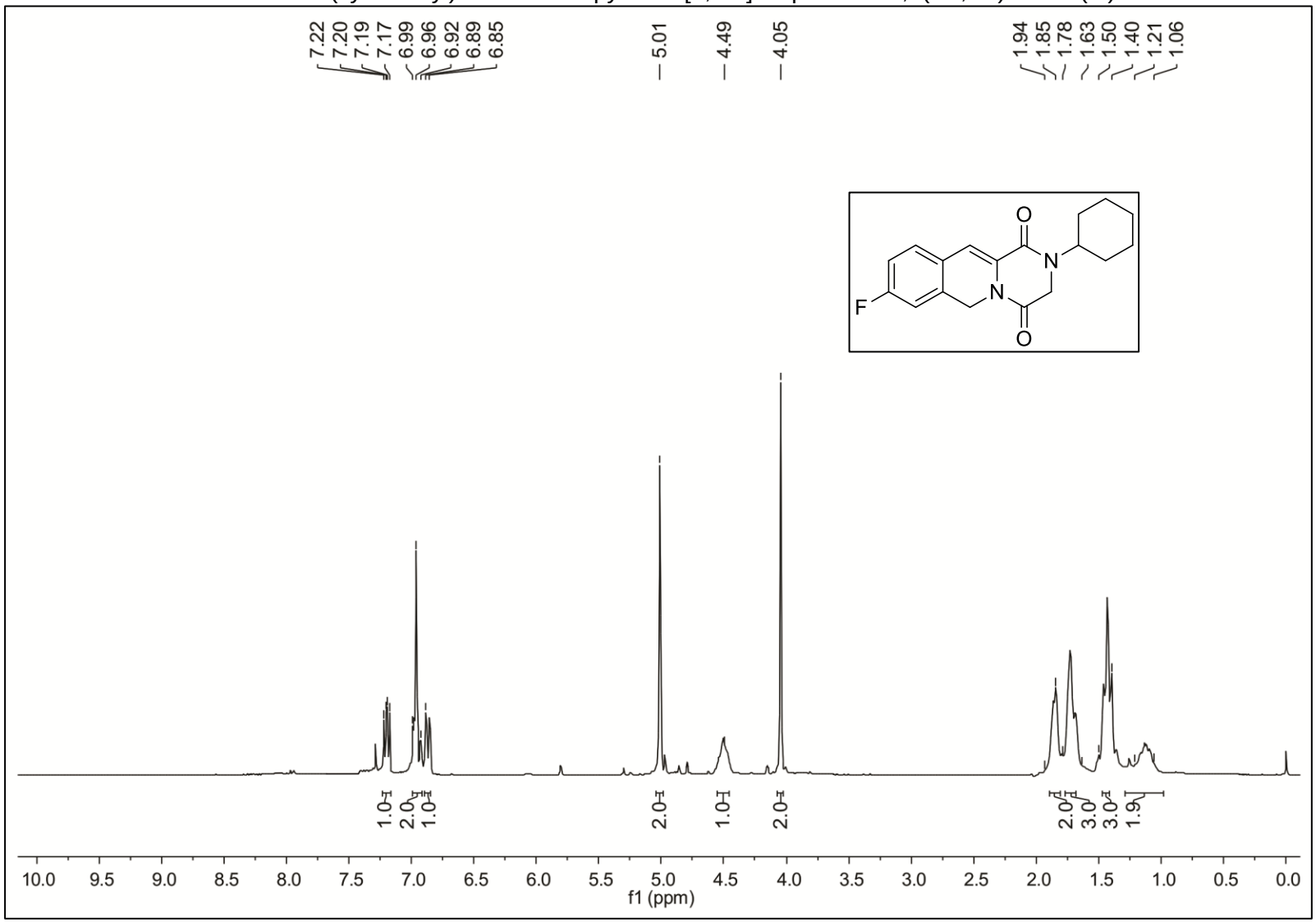


^{1}H-NMR of 2-[(2-bromo-5-fluoro)(chloroacetyl)amino]-3-(cyclohexylamino)-3-oxopropyl benzoate (**4l**).



^{1}H-NMR of 2-(cyclohexyl)-8-fluoro-2*H*-pyrazino[1,2-*b*]isoquinoline-1,4(3*H*,6*H*)-dione (**6l**).



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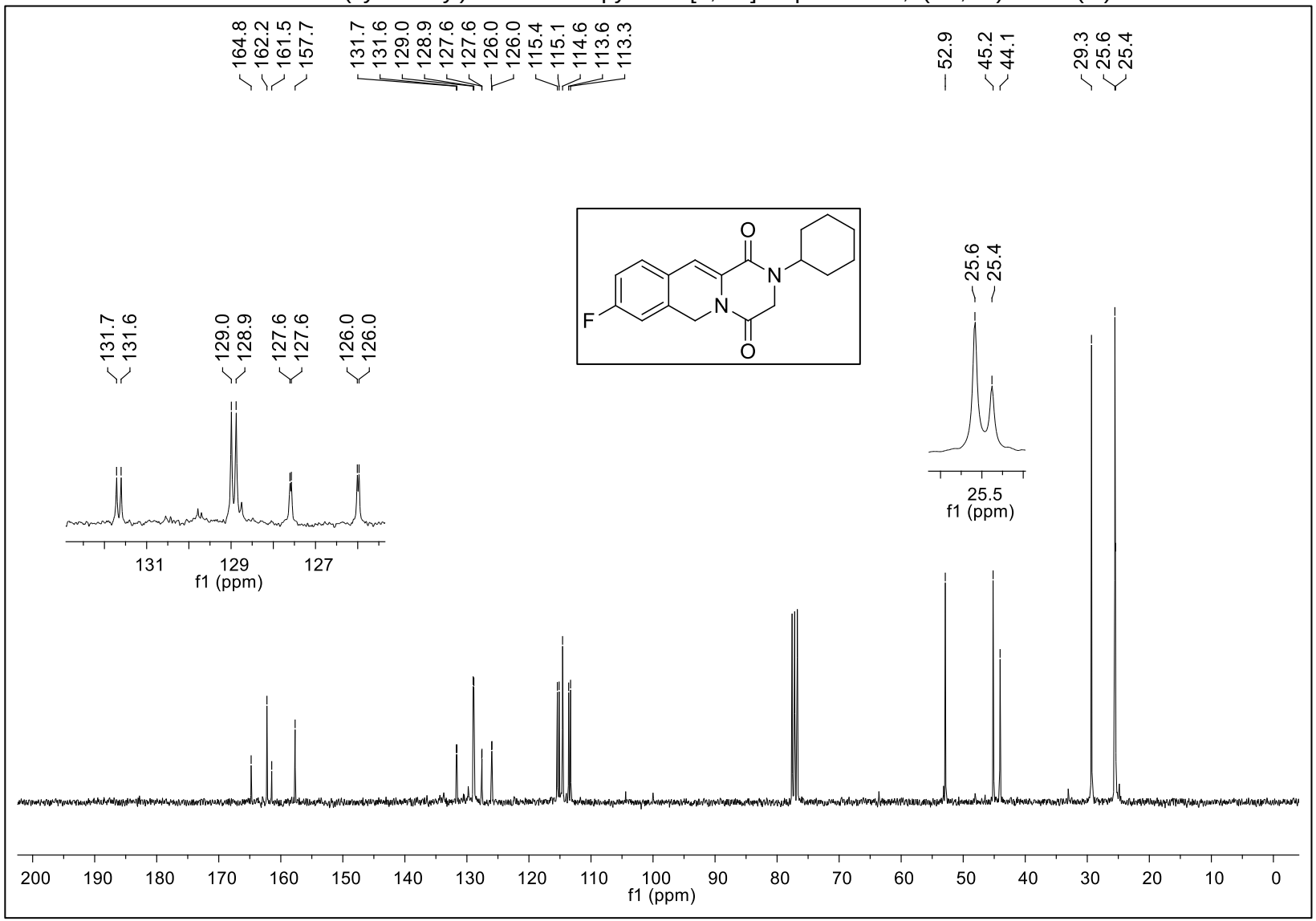
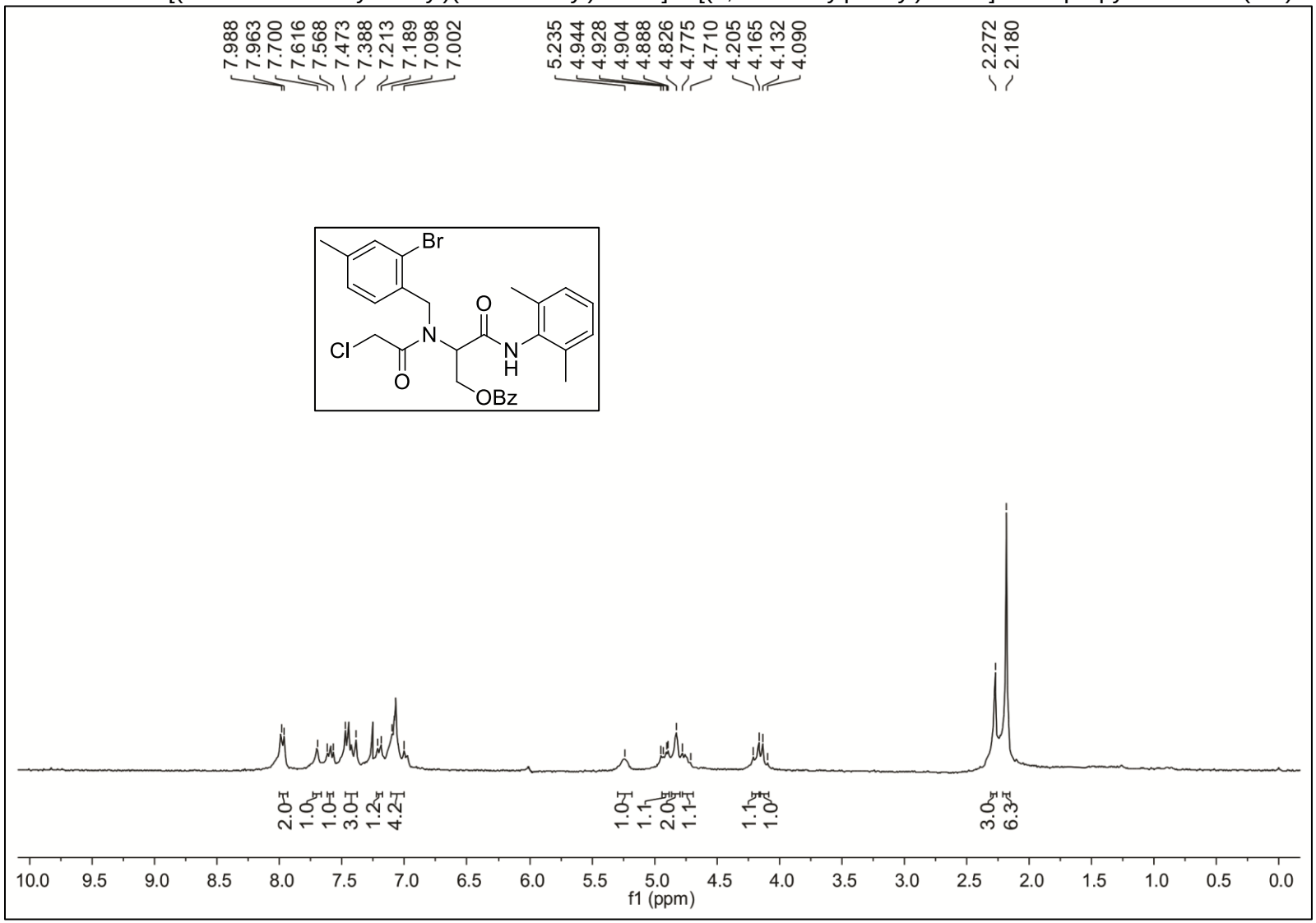


[1]H-NMR of 2-[(2-bromo-4-methylbenzyl)(chloroacetyl)amino]-3-[(2,6-dimethylphenyl)amino]-3-oxopropyl benzoate (**4m**)



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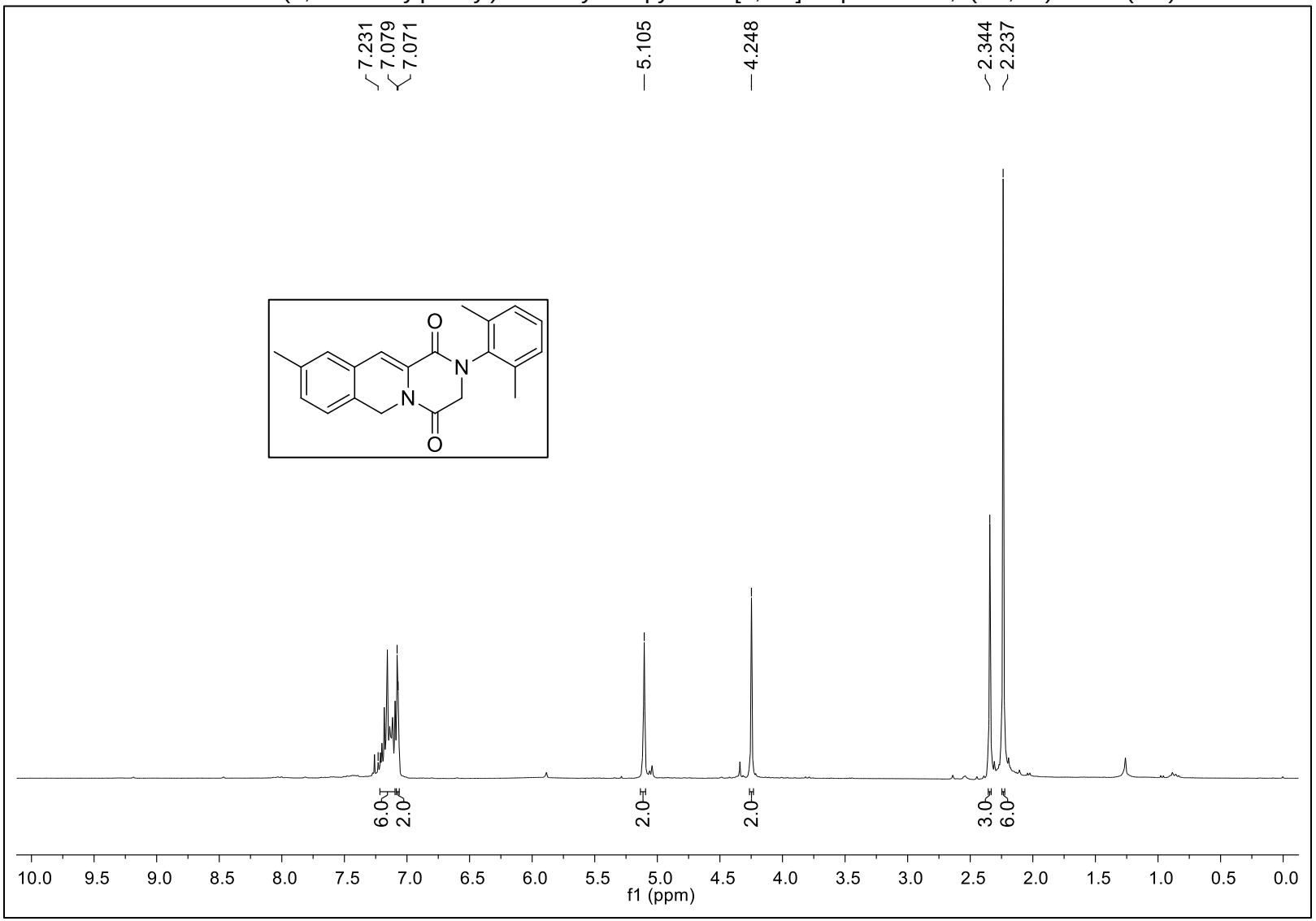
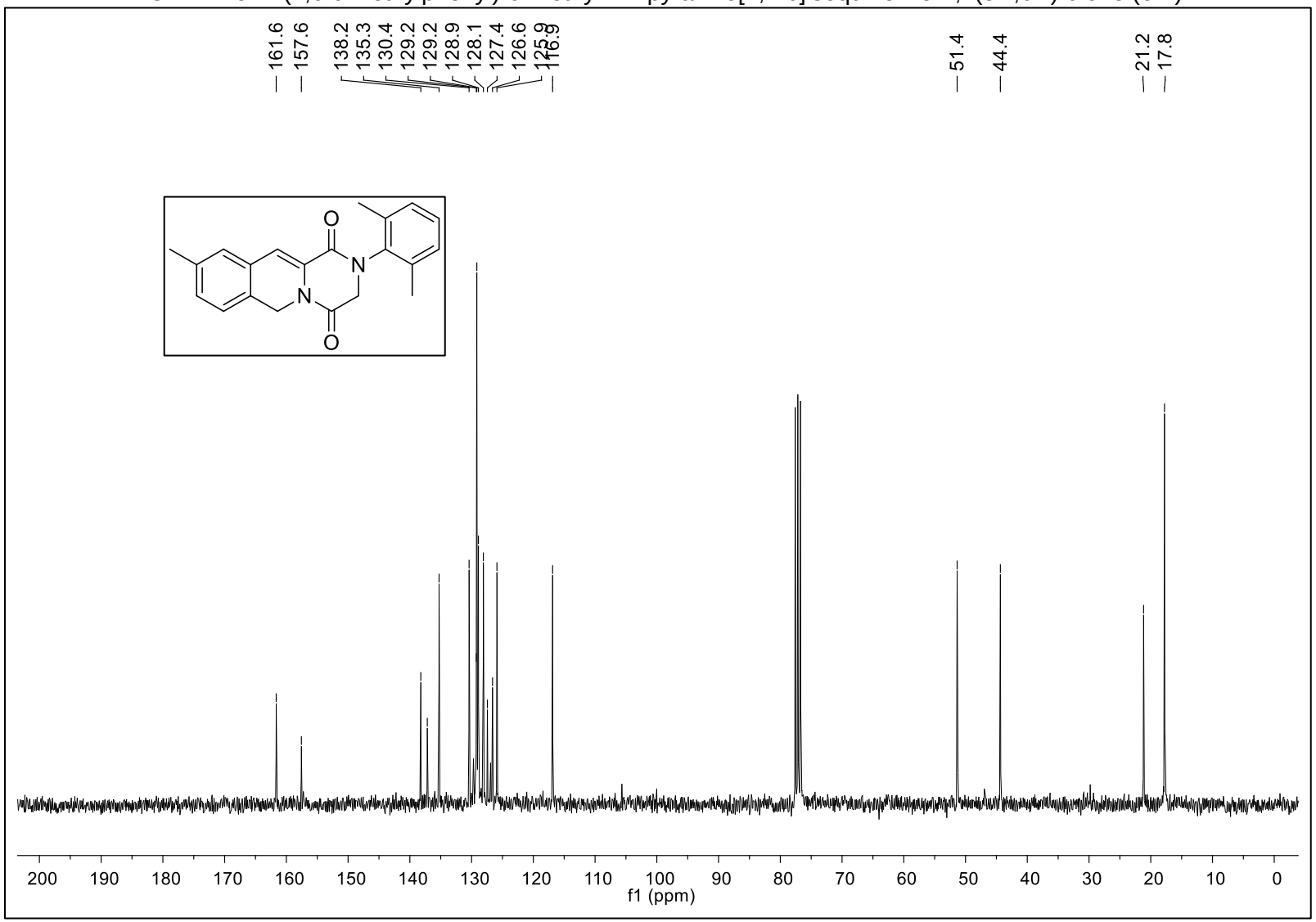
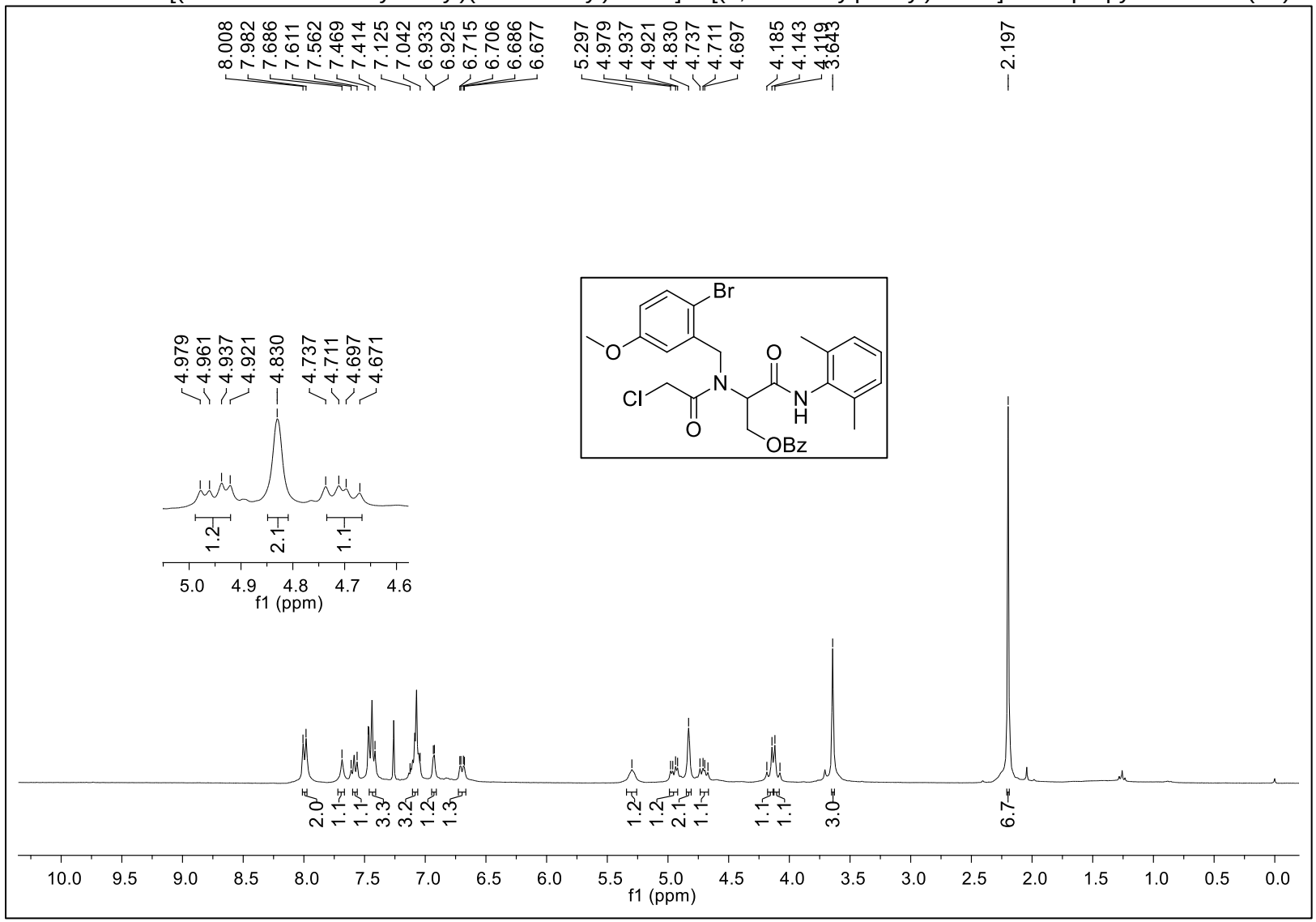


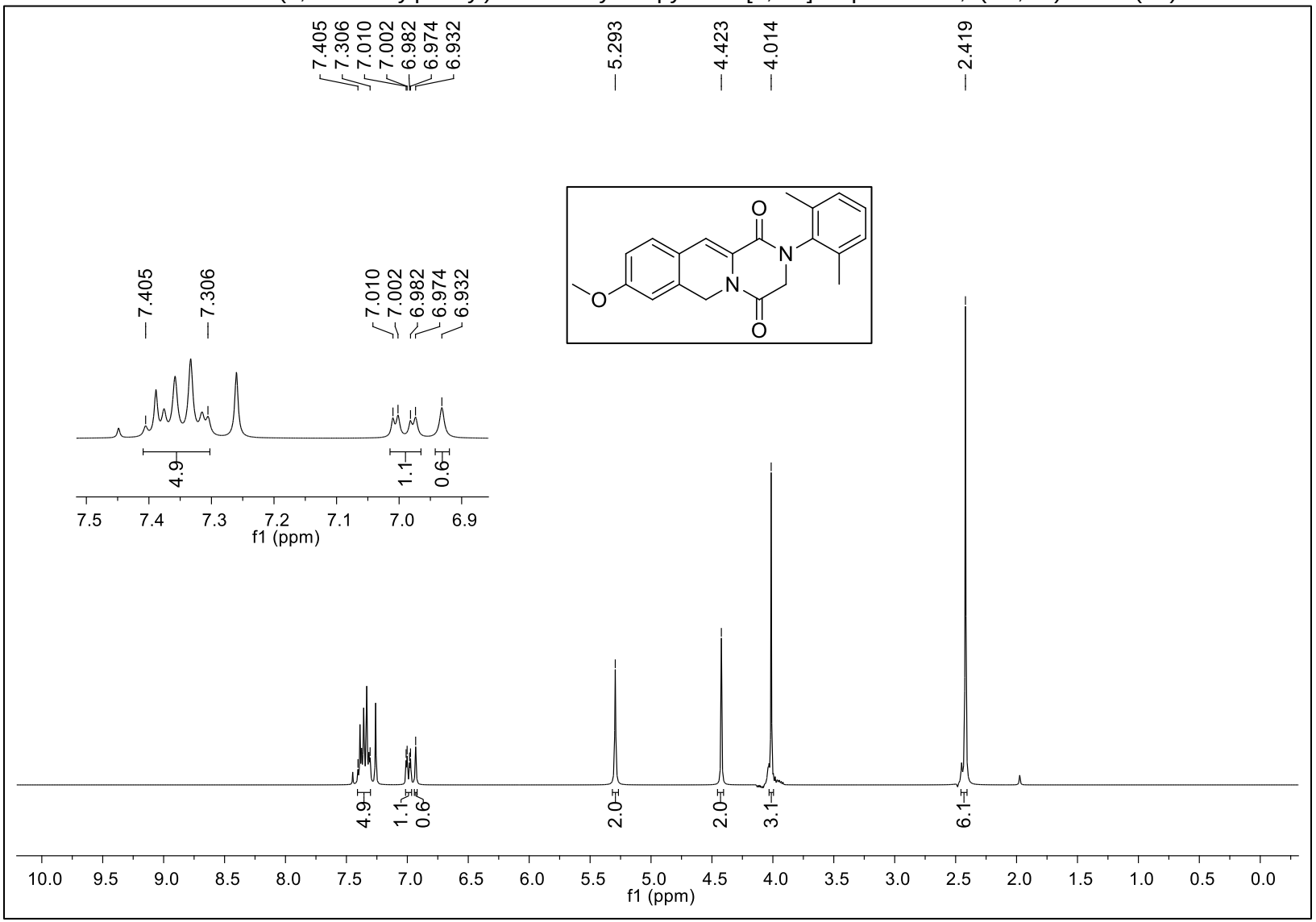
^{13}C-NMR of 2-(2,6-dimethylphenyl)-9-methyl-2*H*-pyrazino[1,2-*b*]isoquinoline-1,4(3*H*,6*H*)-dione (**6m**)



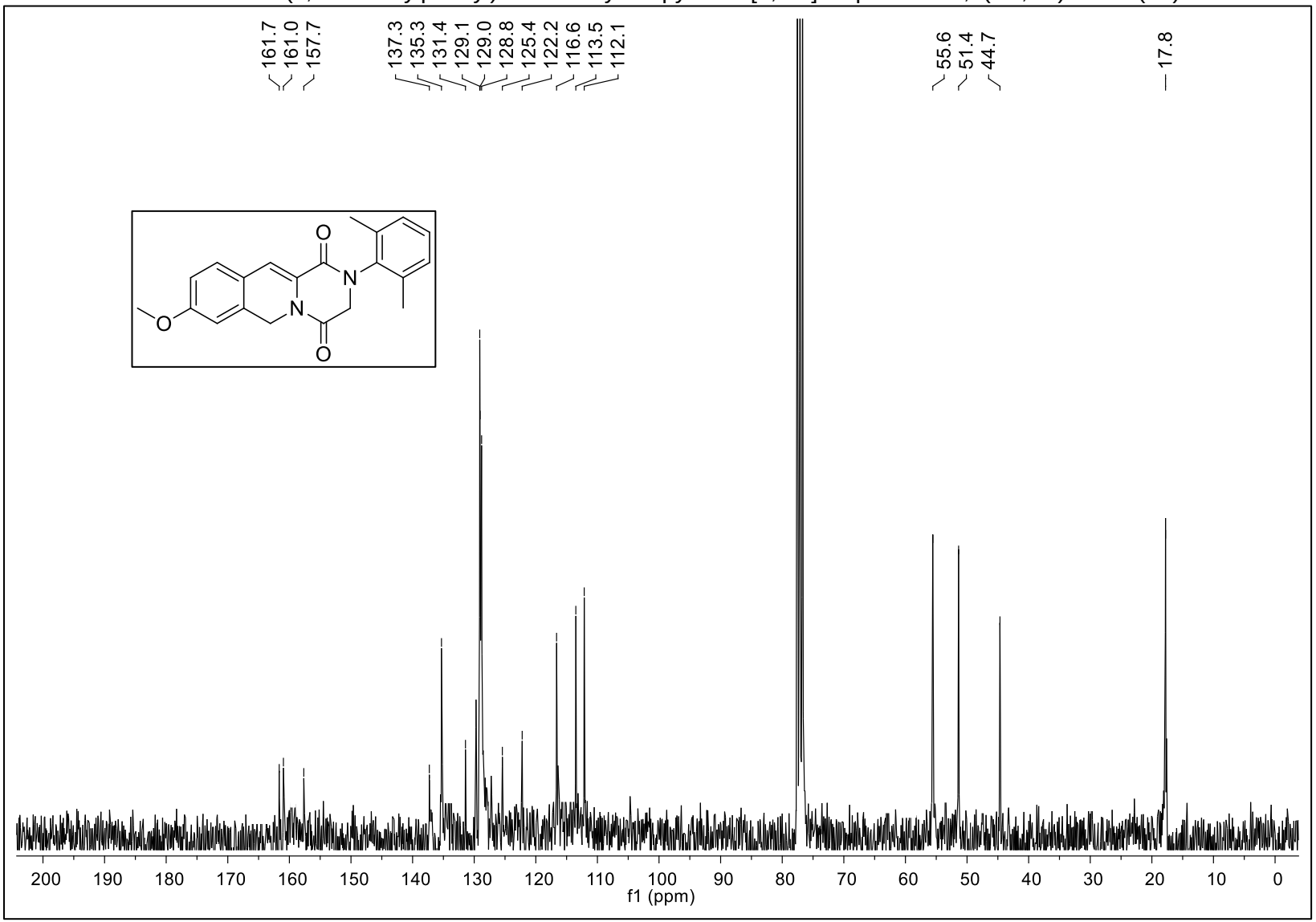
^{1}H-NMR of 2-[(2-bromo-5-methoxybenzyl)(chloroacetyl)amino]-3-[(2,6-dimethylphenyl)amino]-3-oxopropyl benzoate (**4n**)



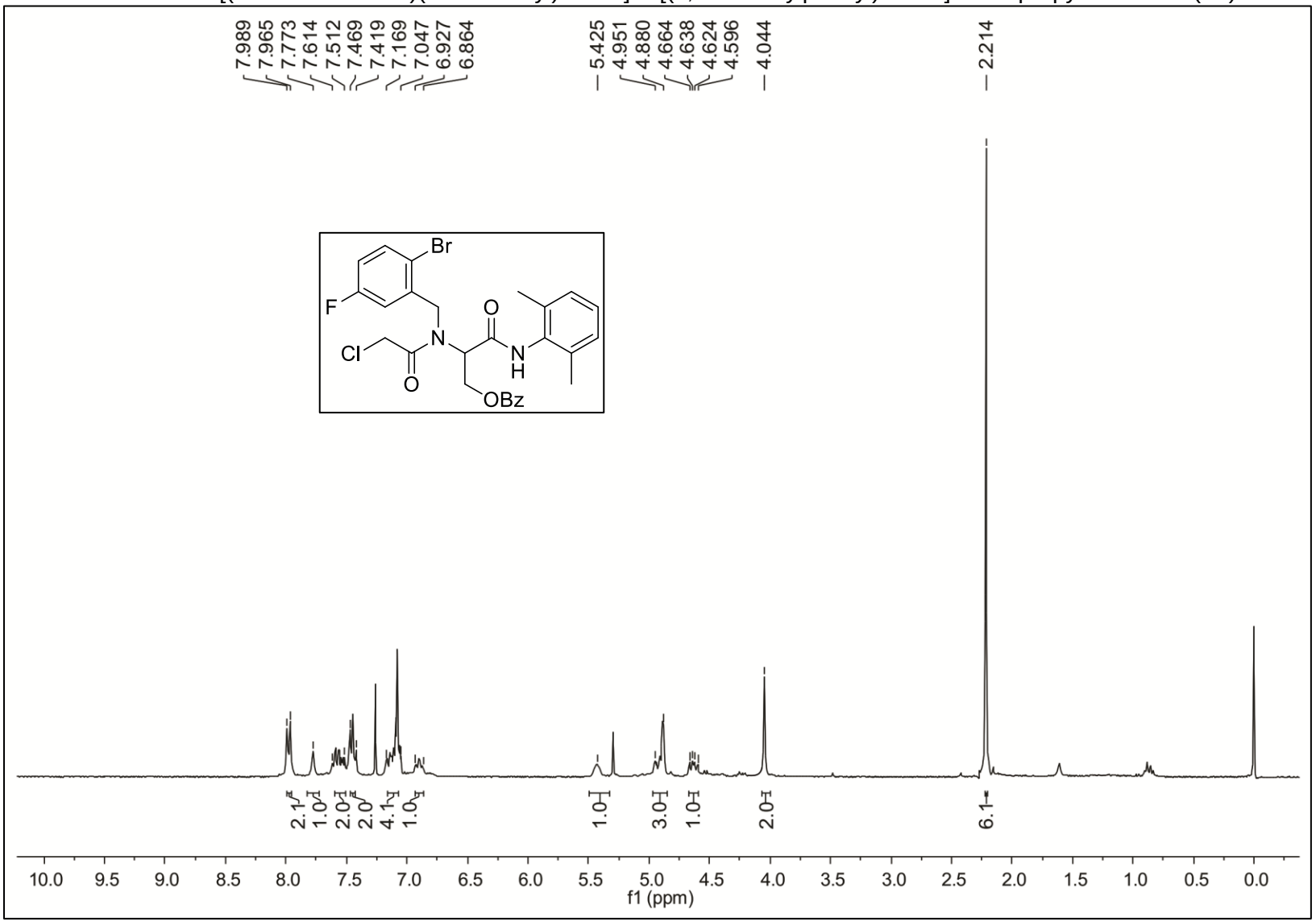
^{1}H-NMR of 2-(2,6-dimethylphenyl)-8-methoxy-2*H*-pyrazino[1,2-*b*]isoquinoline-1,4(3*H*,6*H*)-dione (**6n**)



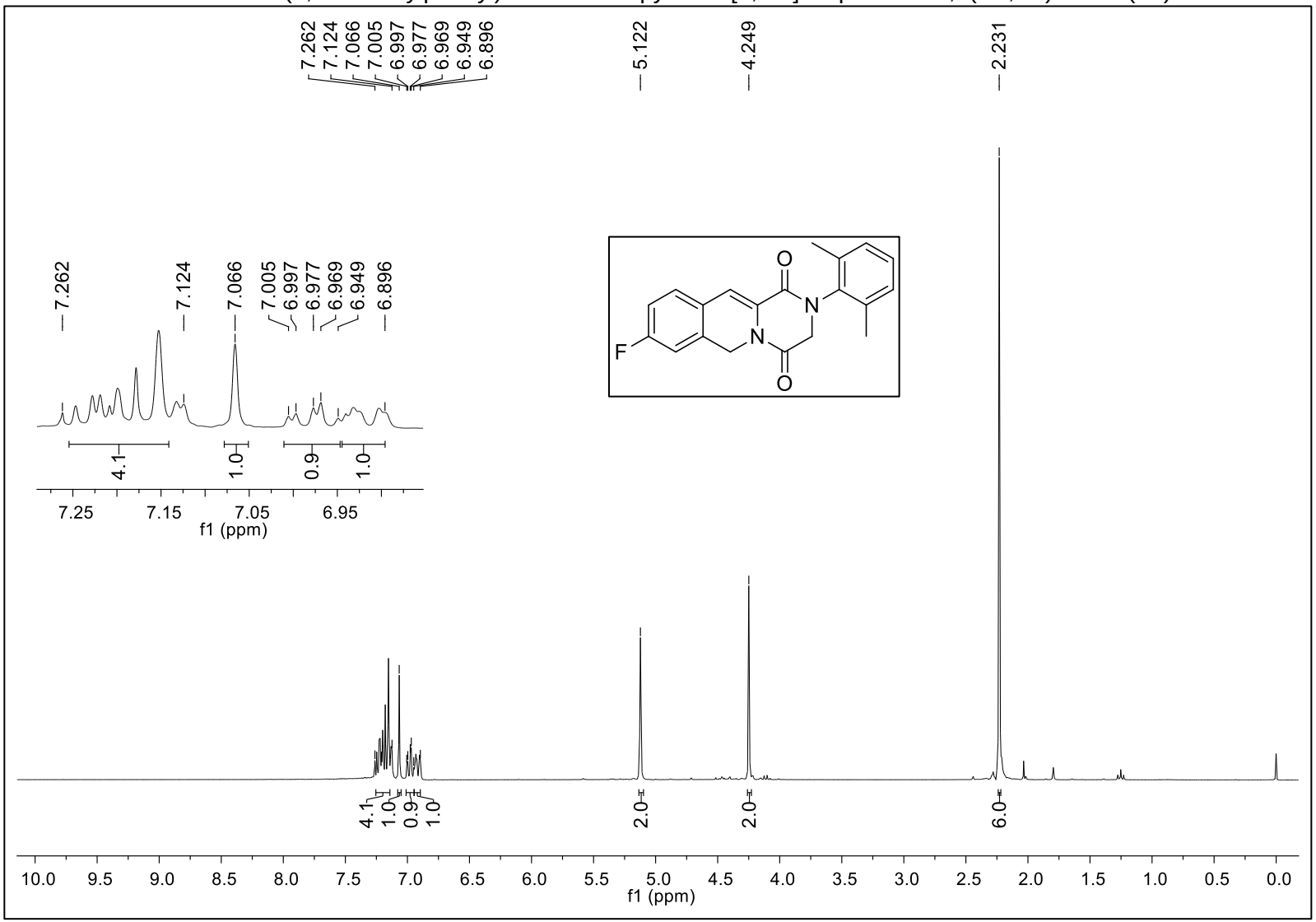
^{13}C-NMR of 2-(2,6-dimethylphenyl)-8-methoxy-2*H*-pyrazino[1,2-*b*]isoquinoline-1,4(3*H*,6*H*)-dione (**6n**)



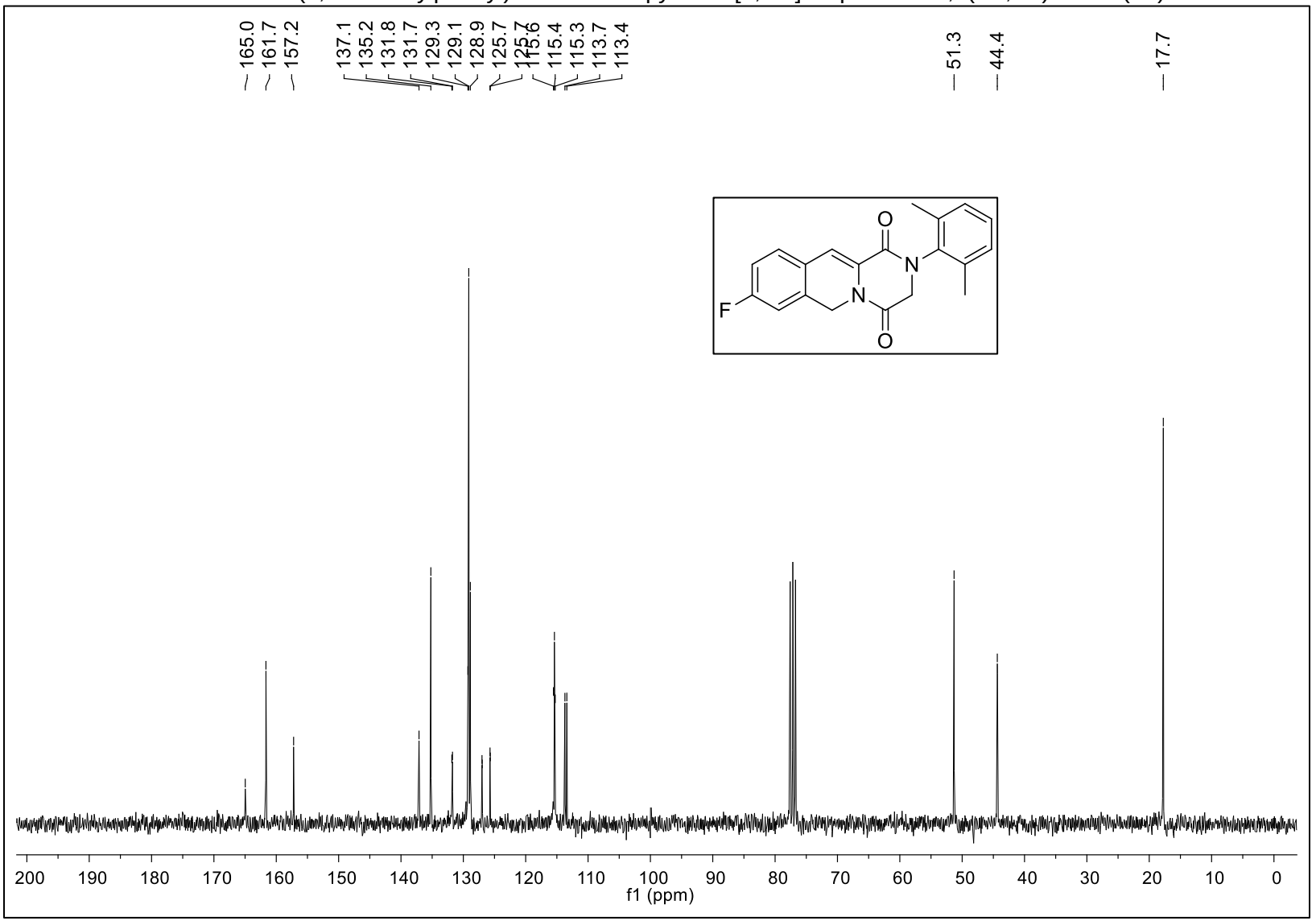
^{1}H-NMR of 2-[(2-bromo-5-fluoro)(chloroacetyl)amino]-3-[(2,6-dimethylphenyl)amino]-3-oxopropyl benzoate (**4o**)



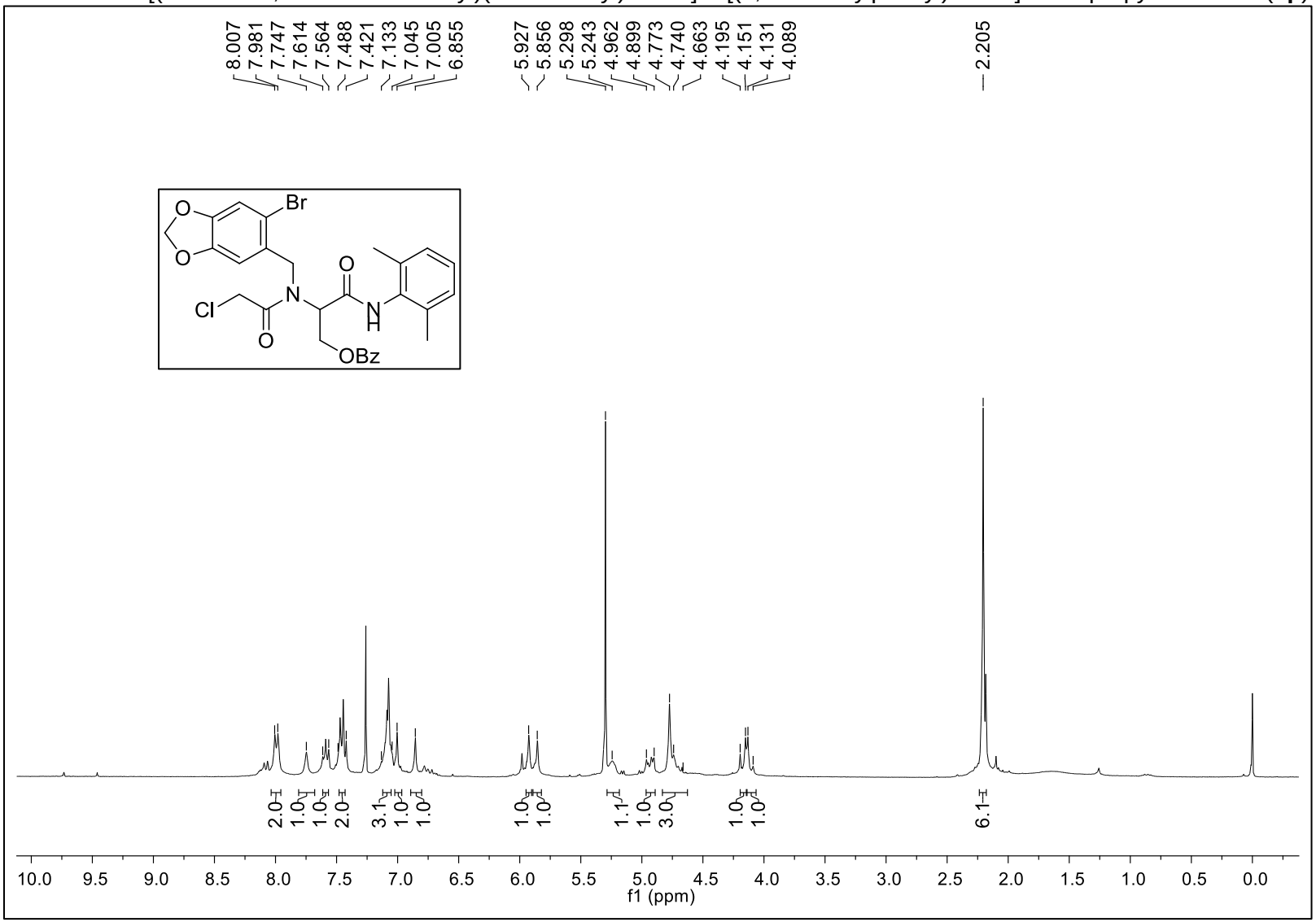
^{1}H-NMR of 2-(2,6-dimethylphenyl)-8-fluoro-2*H*-pyrazino[1,2-b]isoquinoline-1,4(3*H*,6*H*)-dione (**6o**)



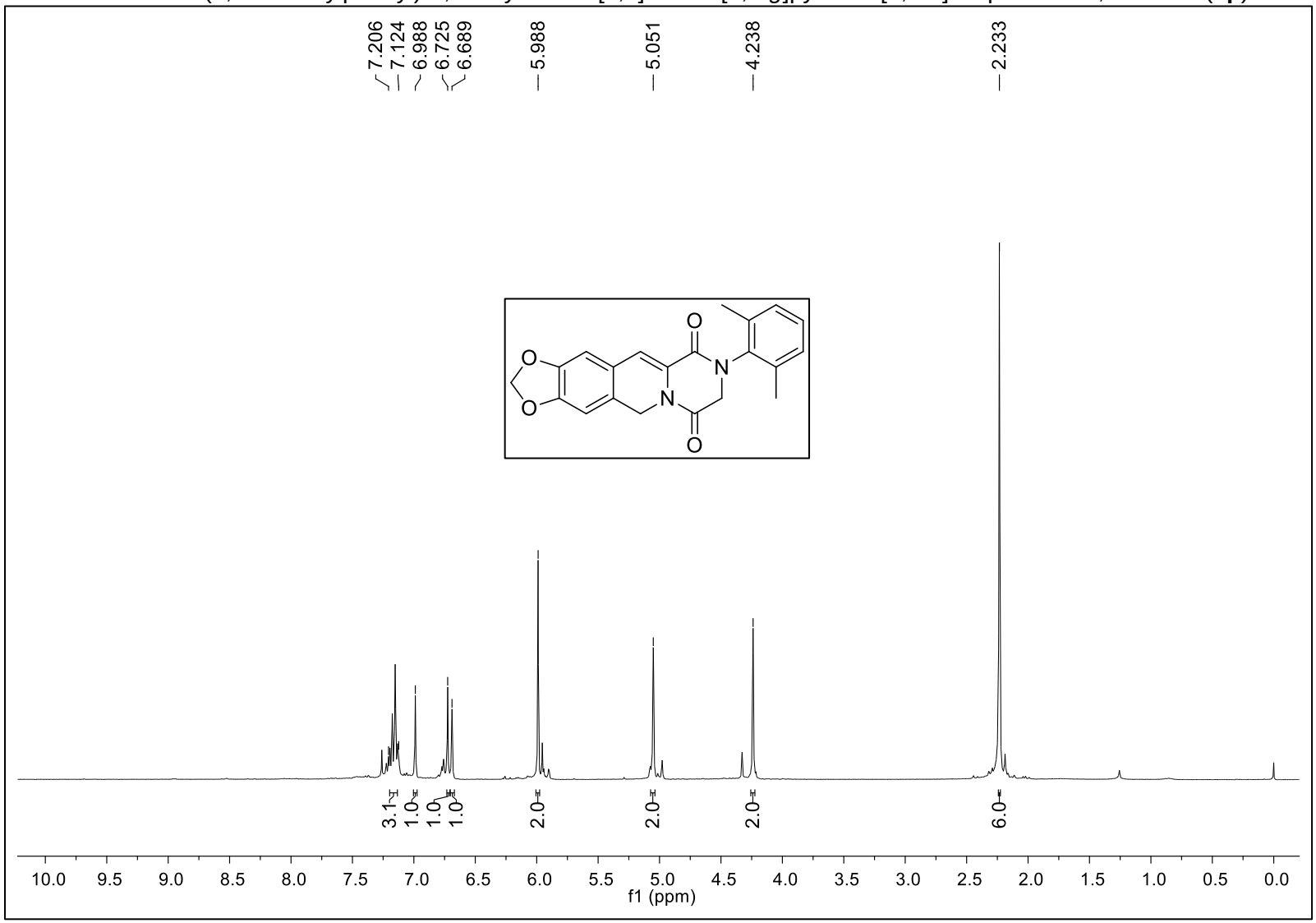
^{13}C-NMR of 2-(2,6-dimethylphenyl)-8-fluoro-2*H*-pyrazino[1,2-b]isoquinoline-1,4(3*H*,6*H*)-dione (**6o**)



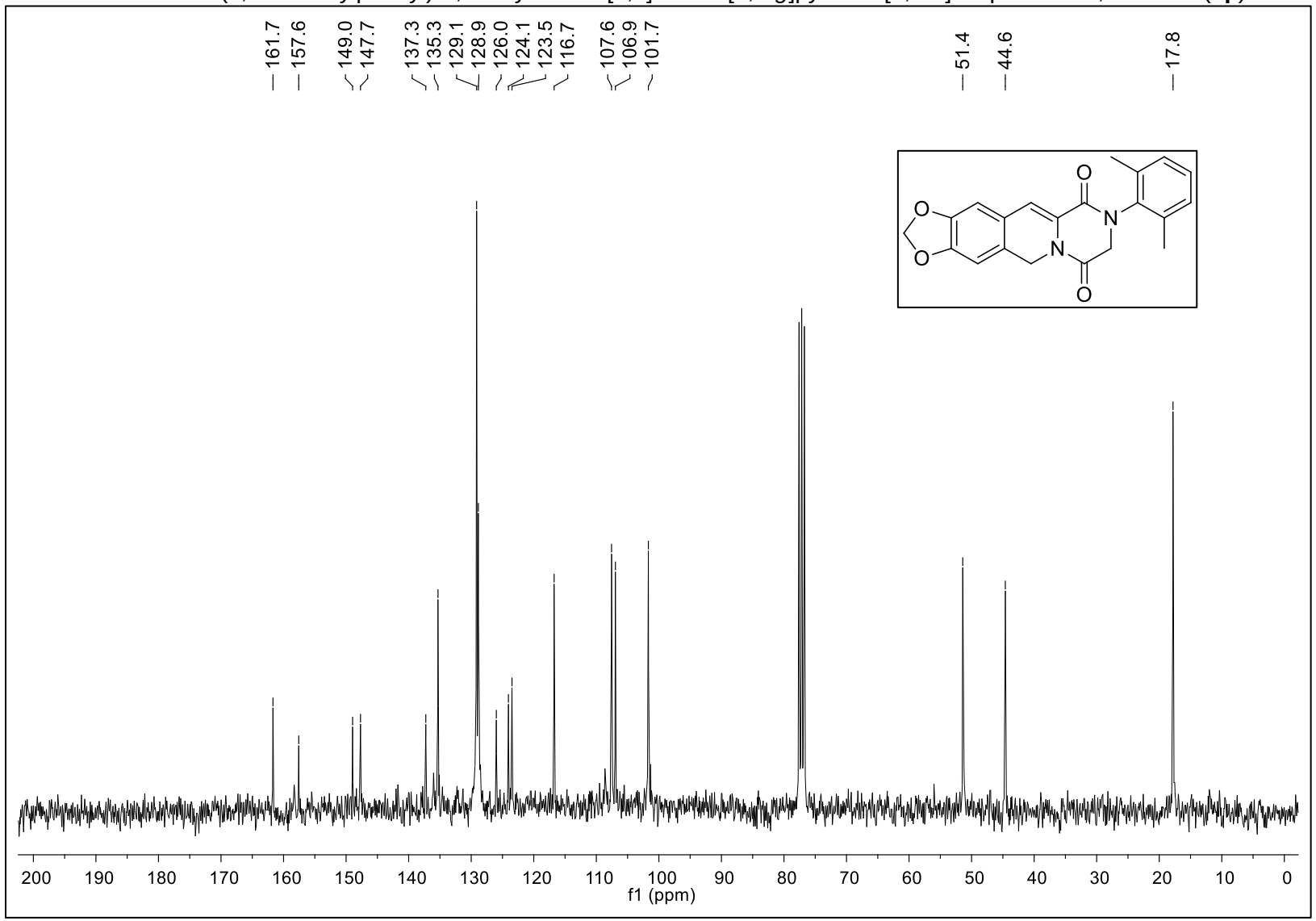
^{1}H-NMR of 2-[(6-bromo-1,3-benzodioxol-5-yl)(chloroacetyl)amino]-3-[(2,6-dimethylphenyl)amino]-3-oxopropyl benzoate (**4p**)



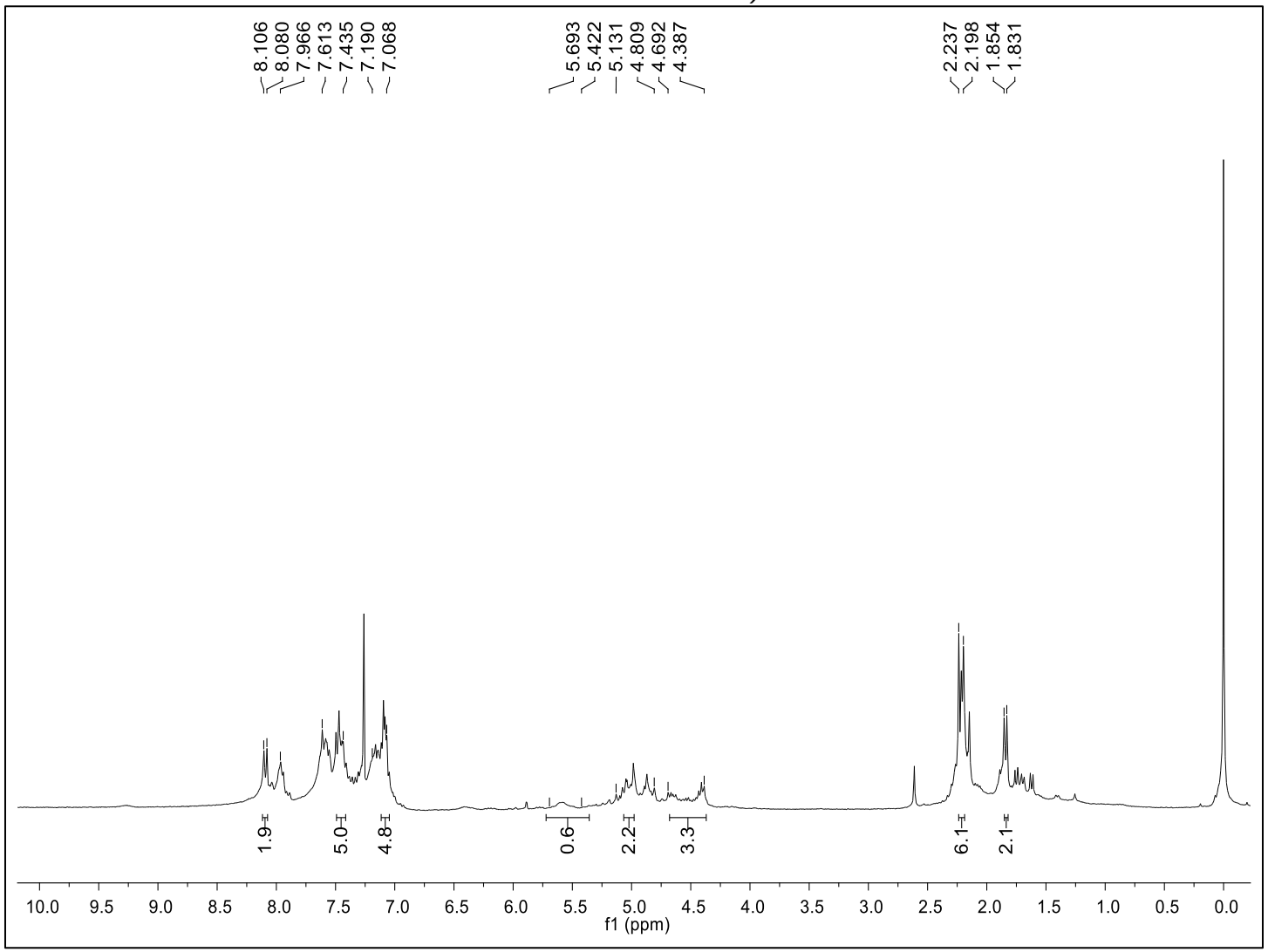
^{1}H-NMR of 9-(2,6-dimethylphenyl)-8,9-dihydro-5*H*-[1,3]dioxolo[4,5-*g*]pyrazino[1,2-*b*]isoquinoline-7,10-dione (**6p**).



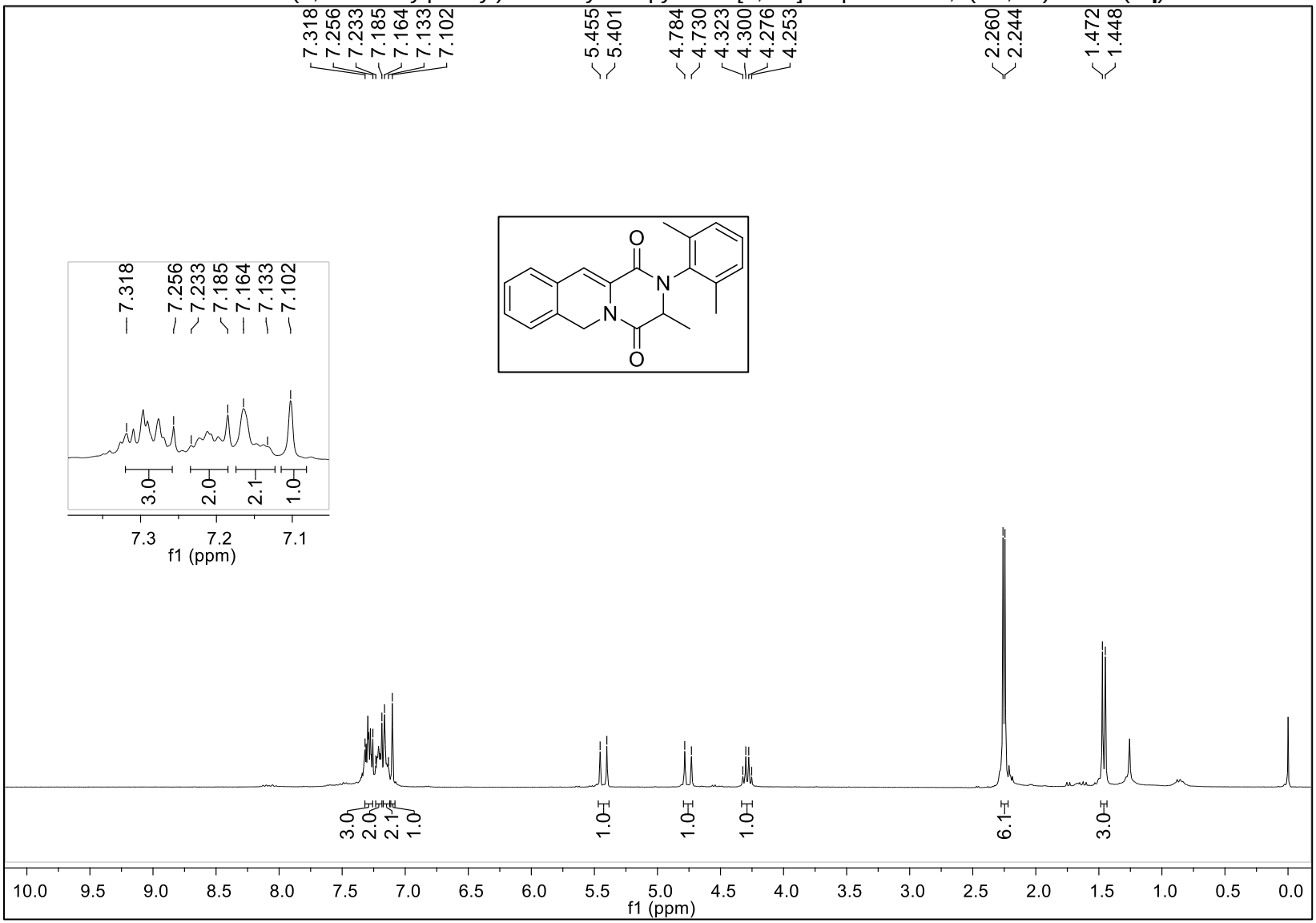
^{13}C-NMR of 9-(2,6-dimethylphenyl)-8,9-dihydro-5*H*-[1,3]dioxolo[4,5-*g*]pyrazino[1,2-*b*]isoquinoline-7,10-dione (**6p**)



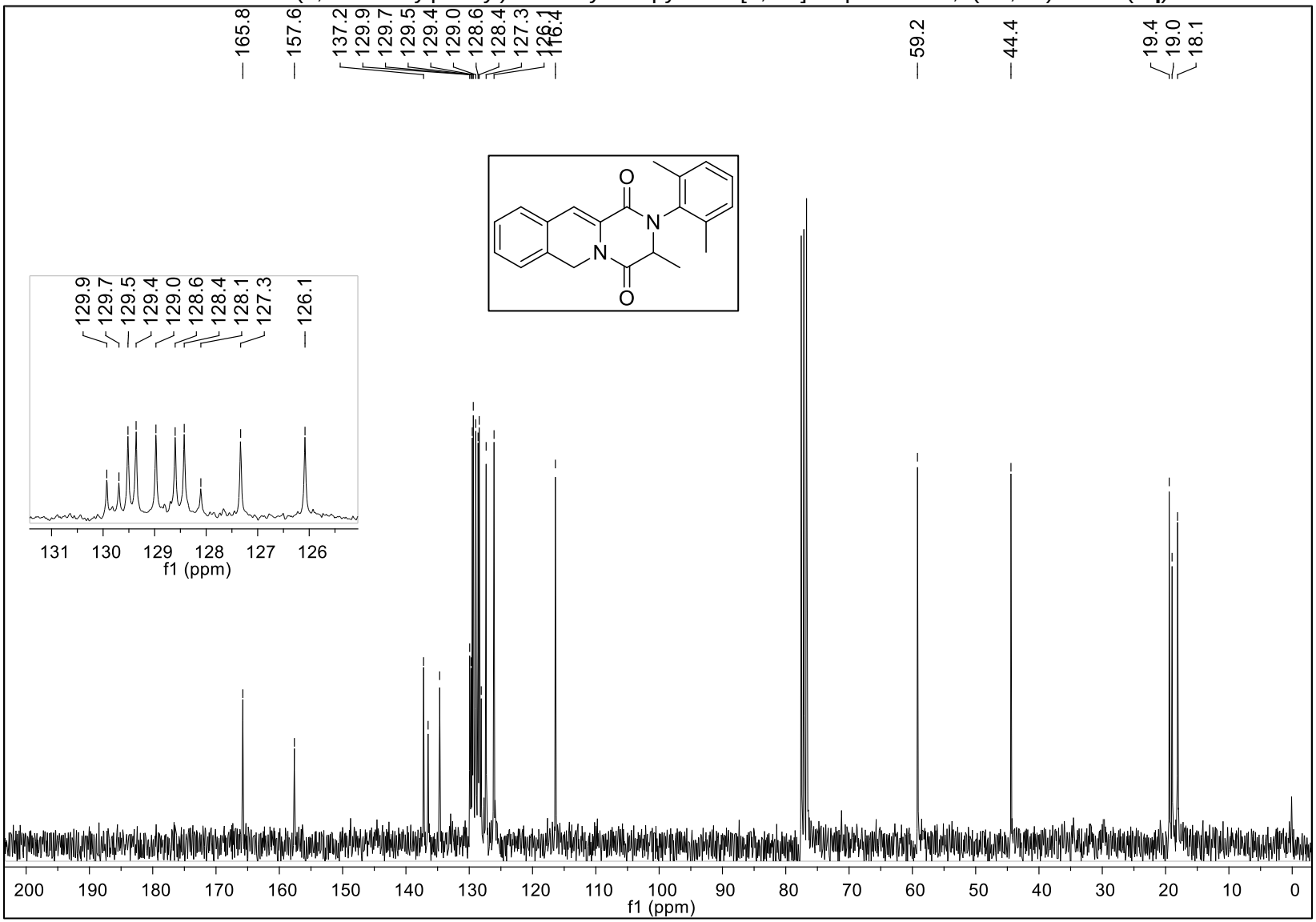
^{1}H-NMR of 2-[(2-bromobenzyl)(2-bromopropanoyl)amino]- 3-[(2,6-dimethylphenyl)amino]-3-oxopropyl benzoate (**4q**). *(Complex diasteromeric mixture)*



^{1}H-NMR of 2-(2,6-dimethylphenyl)-3-methyl-2*H*-pyrazino[1,2-*b*]isoquinoline-1,4(3*H*,6*H*)-dione (**6q**)



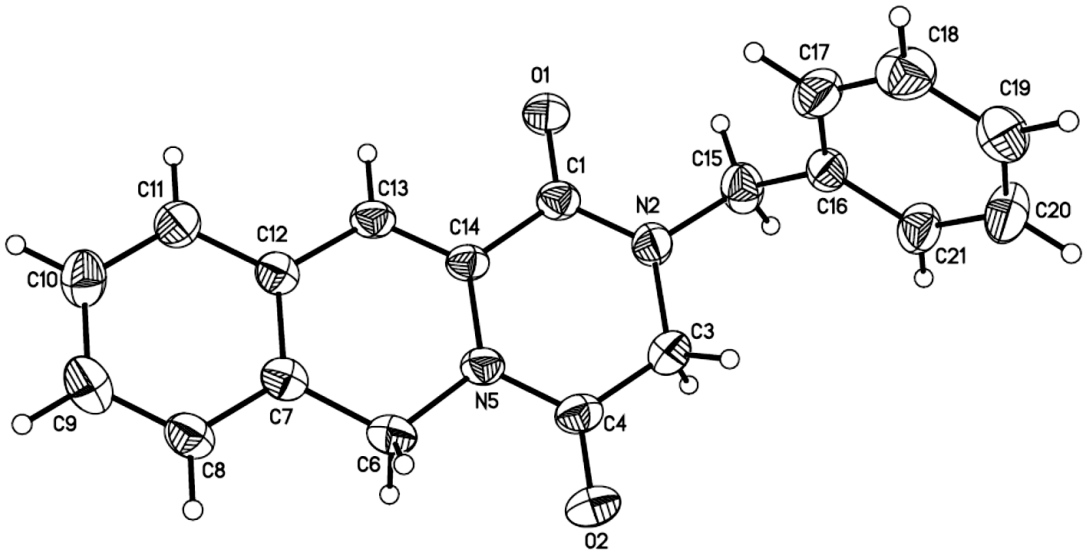
^{13}C-NMR of 2-(2,6-dimethylphenyl)-3-methyl-2*H*-pyrazino[1,2-*b*]isoquinoline-1,4(3*H*,6*H*)-dione (**6q**)

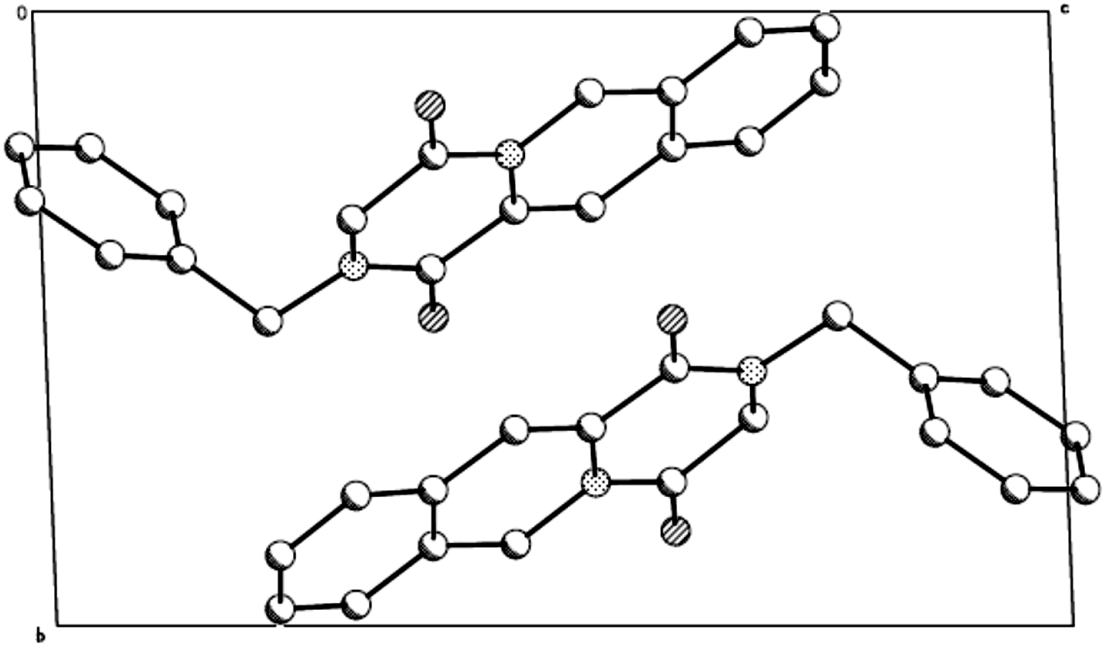


Crystal data and structure refinement for **6e** (CCDC number 1051289)

Empirical formula	$C_{19}H_{16}N_2O_2$	
Formula weight	304.34	
Temperature	298(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P -1	
Unit cell dimensions	a = 6.0126(2) Å	α= 87.1650(10)°.
	b = 8.6199(2) Å	β= 79.5970(10)°.
	c = 14.4875(4) Å	γ = 86.9100(10)°.
Volume	736.84(4) $Å^3$	
Z	2	
Density (calculated)	1.372 Mg/m^3	
Absorption coefficient	0.090 mm^{-1}	
F(000)	320	
Crystal size	0.359 x 0.240 x 0.090 mm^3	
Theta range for data collection	2.368 to 25.395°.	
Index ranges	-7<=h<=7, -10<=k<=10, -17<=l<=17	
Reflections collected	10958	
Independent reflections	2713 [R(int) = 0.0467]	
Completeness to theta = 25.242°	99.9 %	
Absorption correction	None	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2713 / 243 / 264	
Goodness-of-fit on F^2	1.038	
Final R indices [I>2sigma(I)]	R1 = 0.0395, wR2 = 0.1018	
R indices (all data)	R1 = 0.0585, wR2 = 0.1134	
Extinction coefficient	0.024(5)	
Largest diff. peak and hole	0.186 and -0.220 $e.Å^{-3}$	

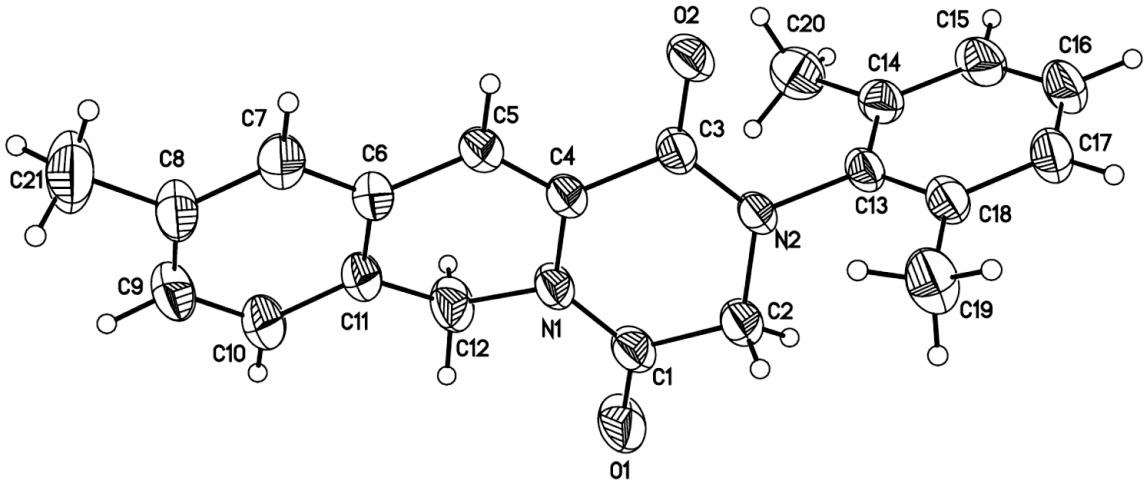
The phenyl group is disordered and was refined in two major contributors. Using a variable site of occupational factor (SOF). The ratio of SOF for was 0.65/0.35.

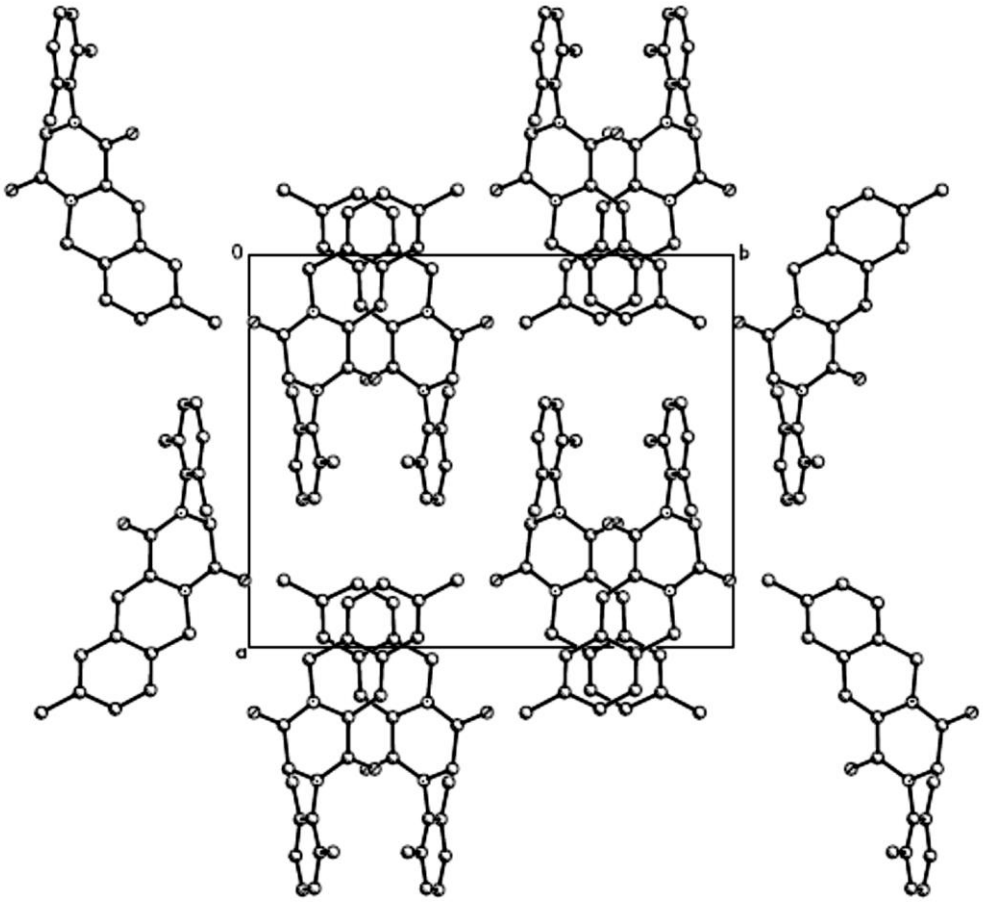

O1
C1
N2
C15
C16
C17
C18
C19
C20
C21
C11
C12
C13
C14
C10
C3
N5
C4
C9
C7
C8
C6
O2


0
c
b

Crystal data and structure refinement for **6m** (CCDC number 1042677)

Empirical formula	$C_{21}H_{20}N_2O_2$	
Formula weight	332.39	
Temperature	298(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	$P\ 2_1/c$	
Unit cell dimensions	a = 13.7074(4) Å	α= 90°.
	b = 16.5340(5) Å	β= 103.803(2)°.
	c = 7.8722(2) Å	γ = 90°.
Volume	1732.62(9) $Å^3$	
Z	4	
Density (calculated)	1.274 Mg/m^3	
Absorption coefficient	0.083 mm^{-1}	
F(000)	704	
Crystal size	0.439 x 0.077 x 0.068 mm^3	
Theta range for data collection	1.964 to 25.306°.	
Index ranges	-16<=h<=14, -19<=k<=19, -9<=l<=9	
Reflections collected	12483	
Independent reflections	3139 [R(int) = 0.1534]	
Completeness to theta = 25.242°	99.6 %	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3139 / 0 / 230	
Goodness-of-fit on F^2	0.912	
Final R indices [I>2sigma(I)]	R1 = 0.0500, wR2 = 0.1121	
R indices (all data)	R1 = 0.1155, wR2 = 0.1404	
Extinction coefficient	0.0103(17)	
Largest diff. peak and hole	0.208 and -0.213 $e.Å^{-3}$	


O2
C20
C15
C16
C14
C7
C5
C3
C17
C8
C6
C4
C21
C13
C18
N2
C9
C11
N1
C2
C19
C10
C12
C1
O1


0
b
a