

SUPPLEMENTAL MATERIAL FOR

Isoxazol-5(2H)-one: a new scaffold for potent human neutrophil elastase (HNE) inhibitors

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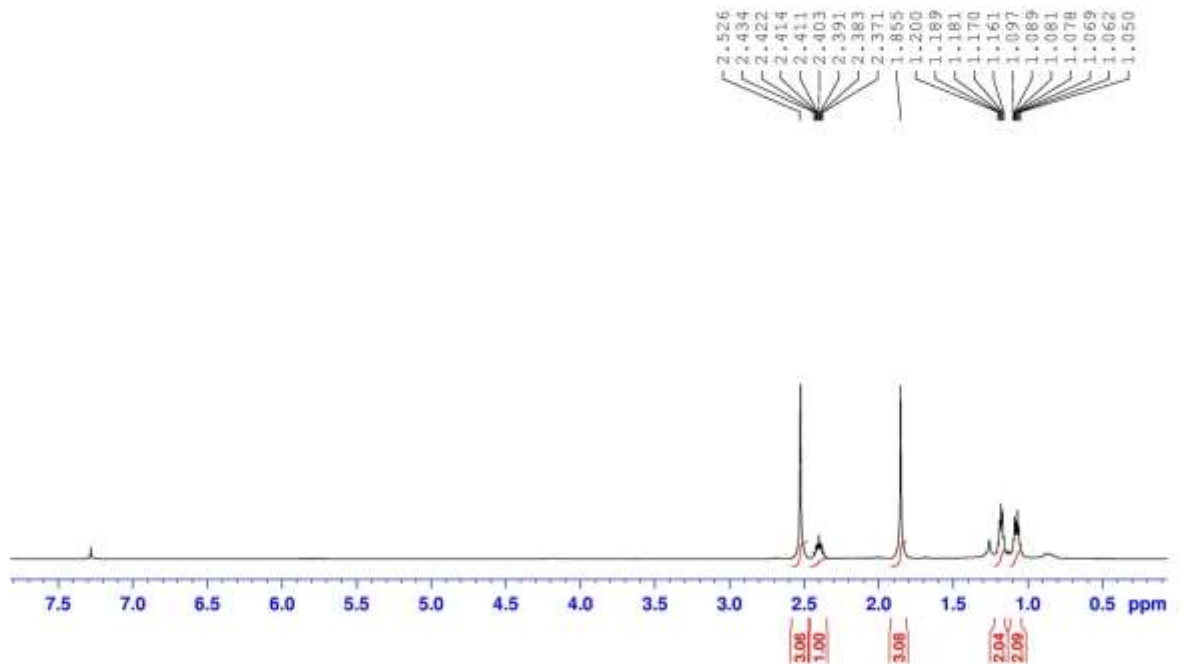
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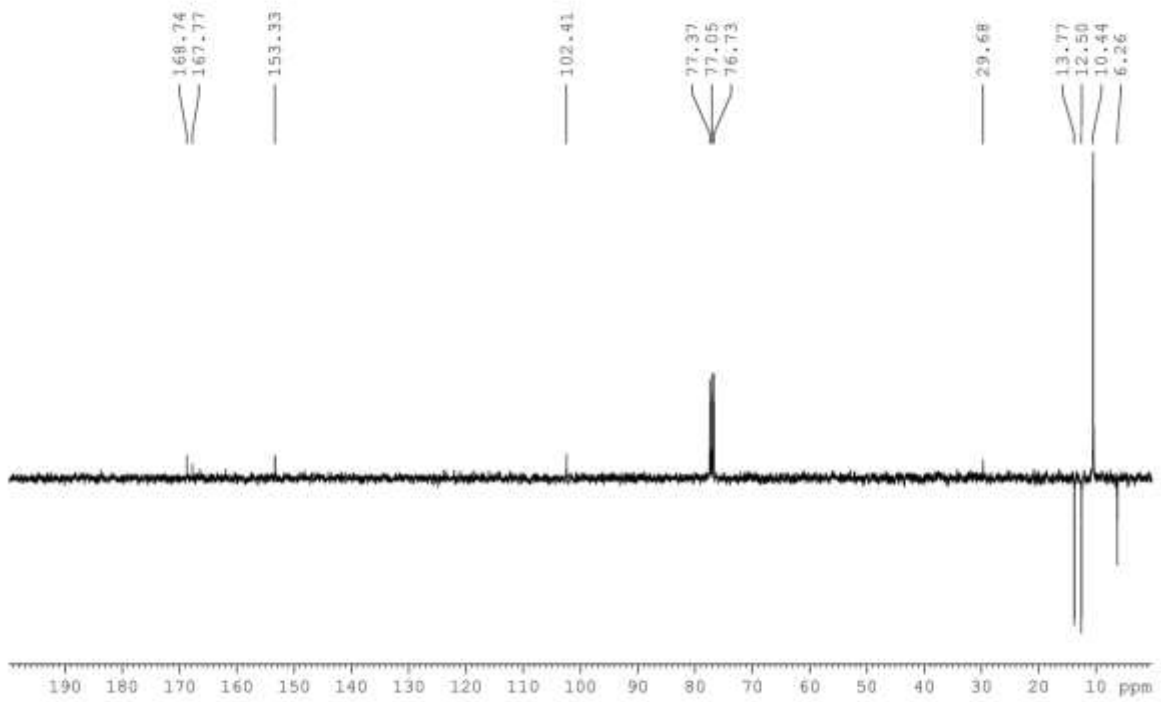
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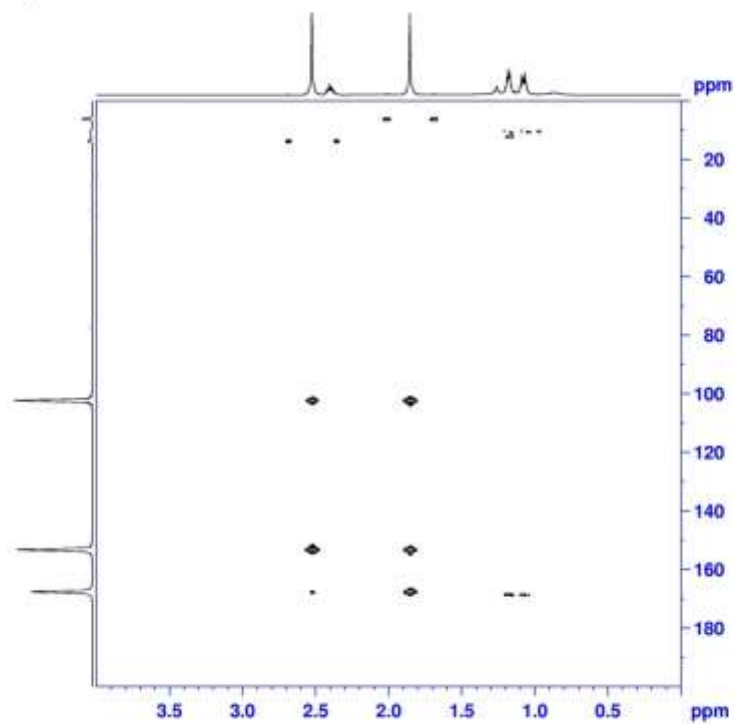
Compound 2a



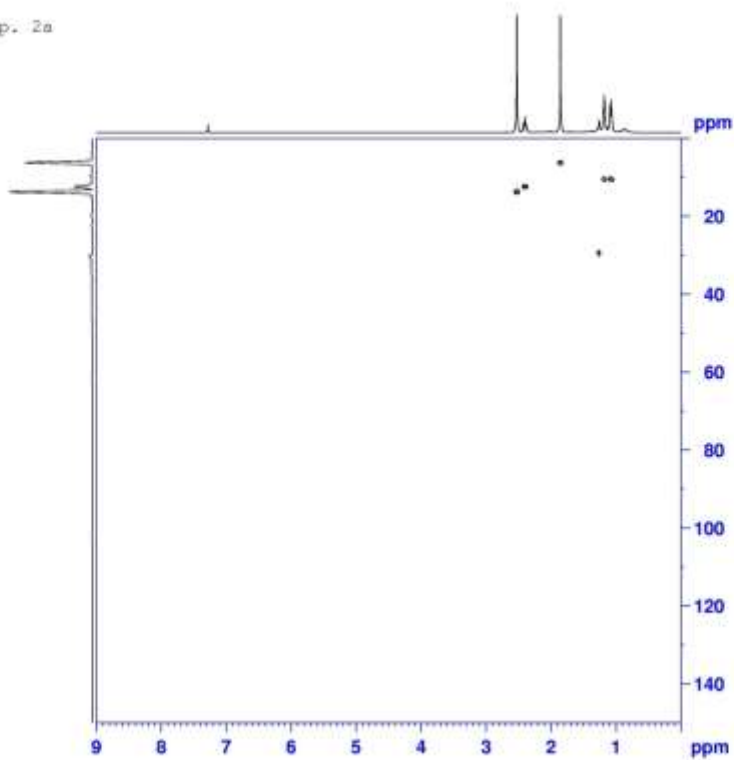
¹³C Comp. 2a



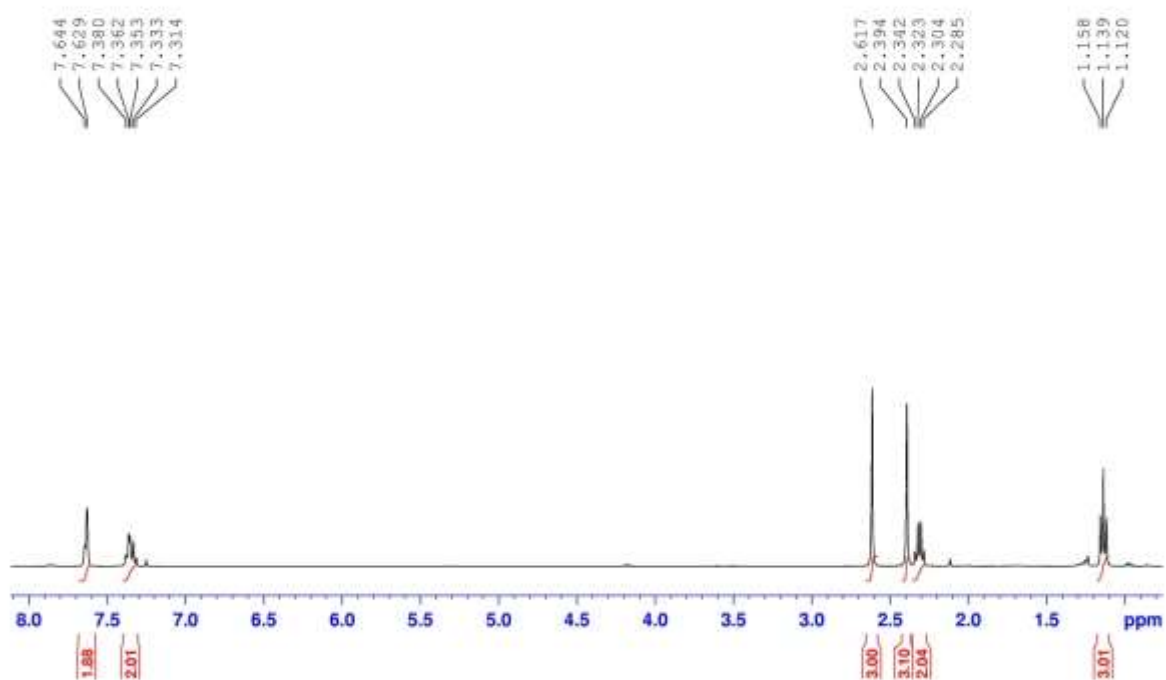
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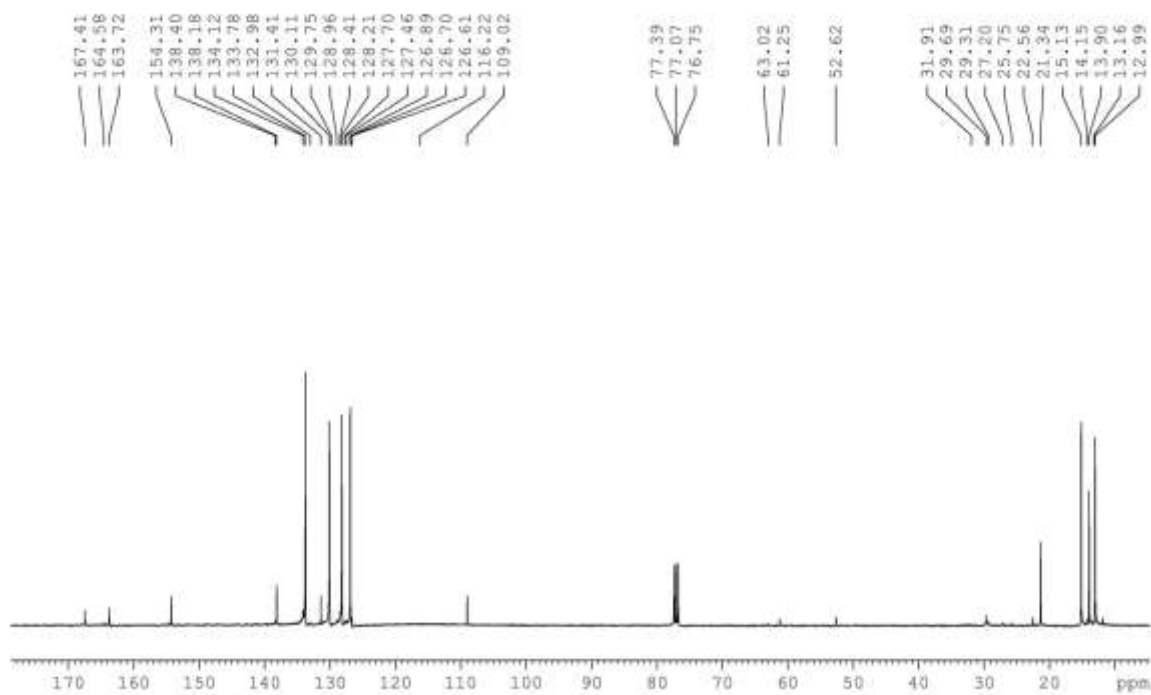
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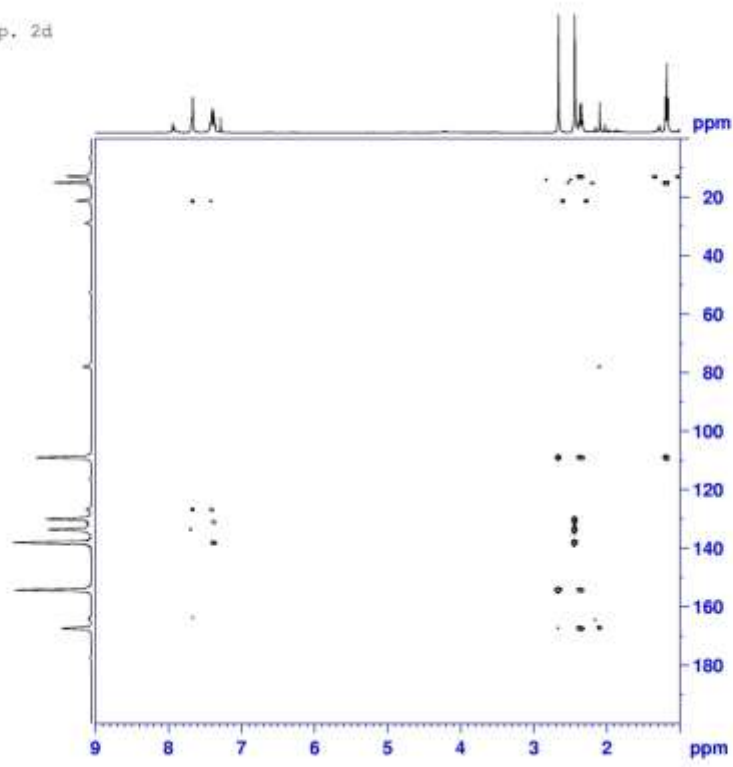
Compound 2d



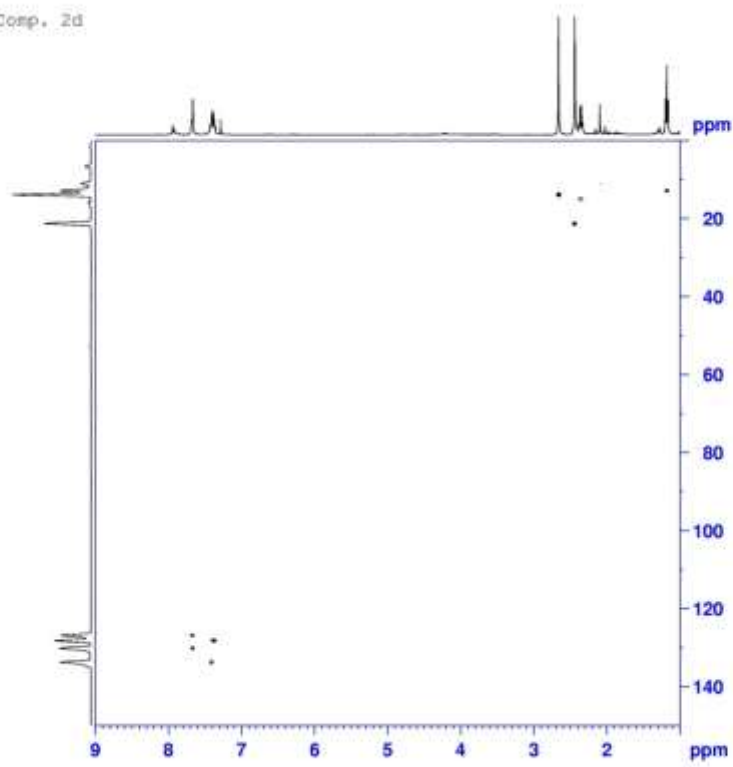
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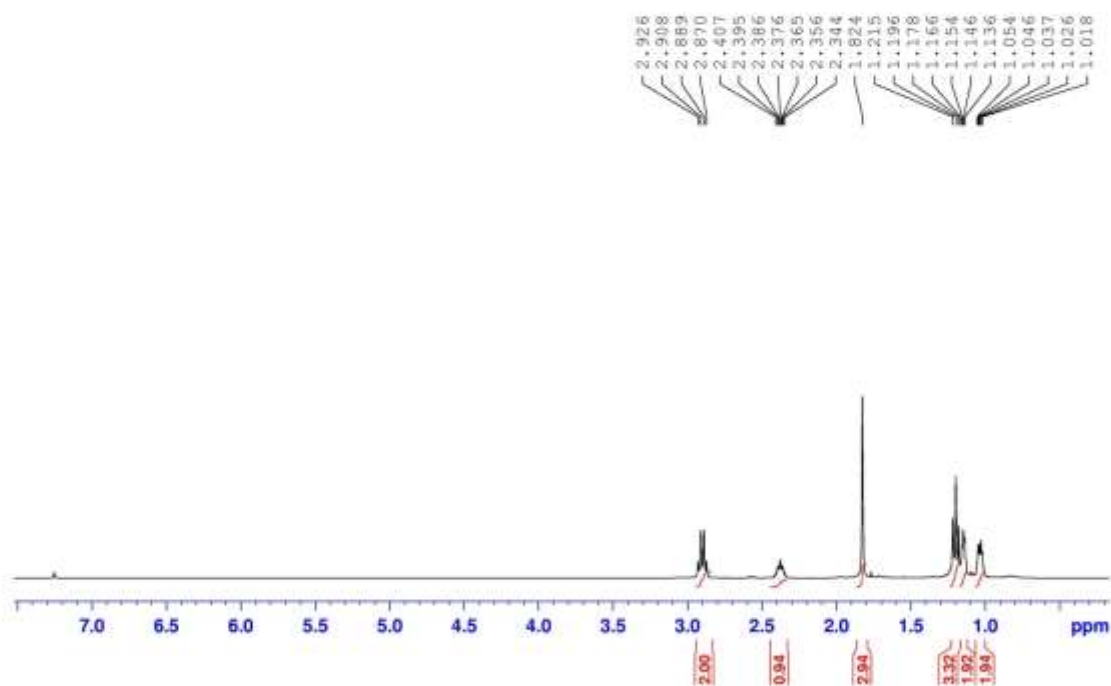
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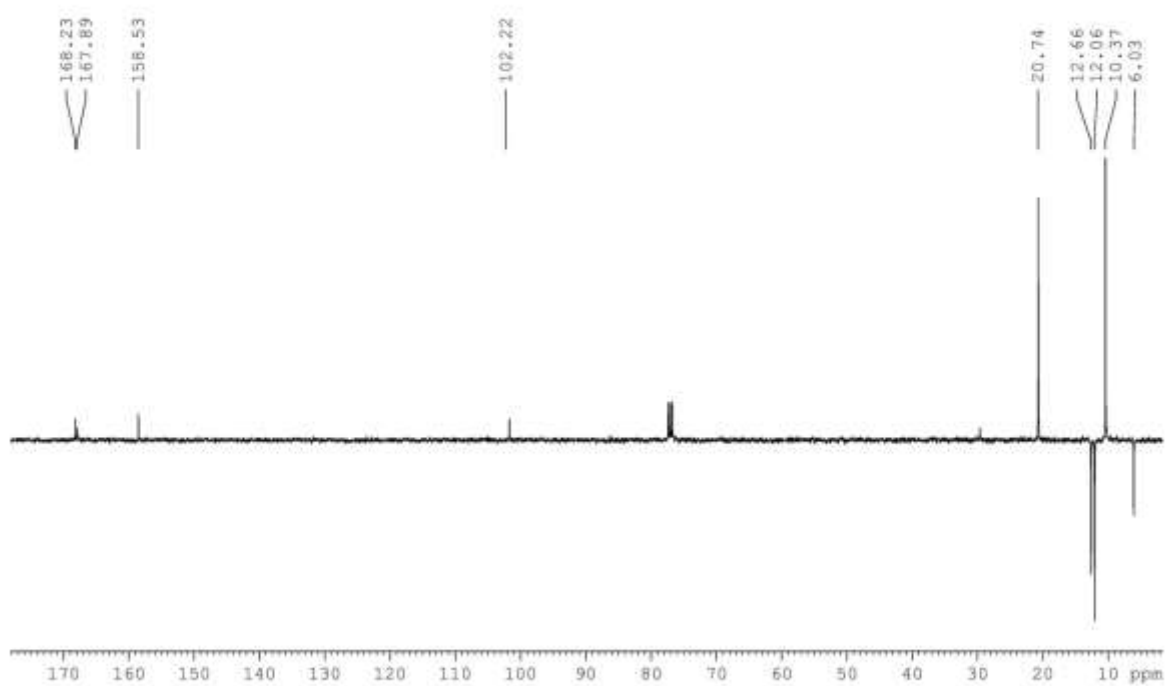
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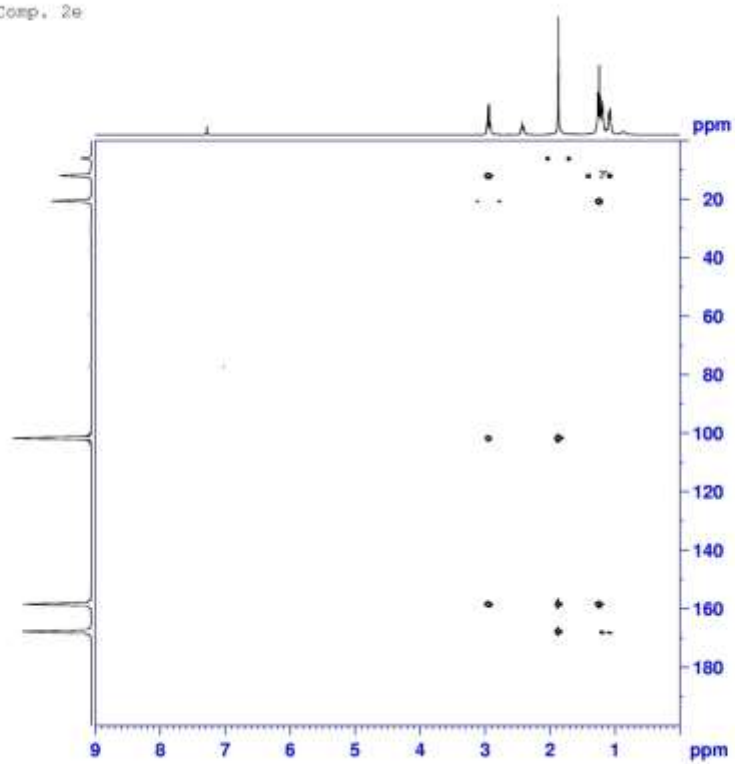
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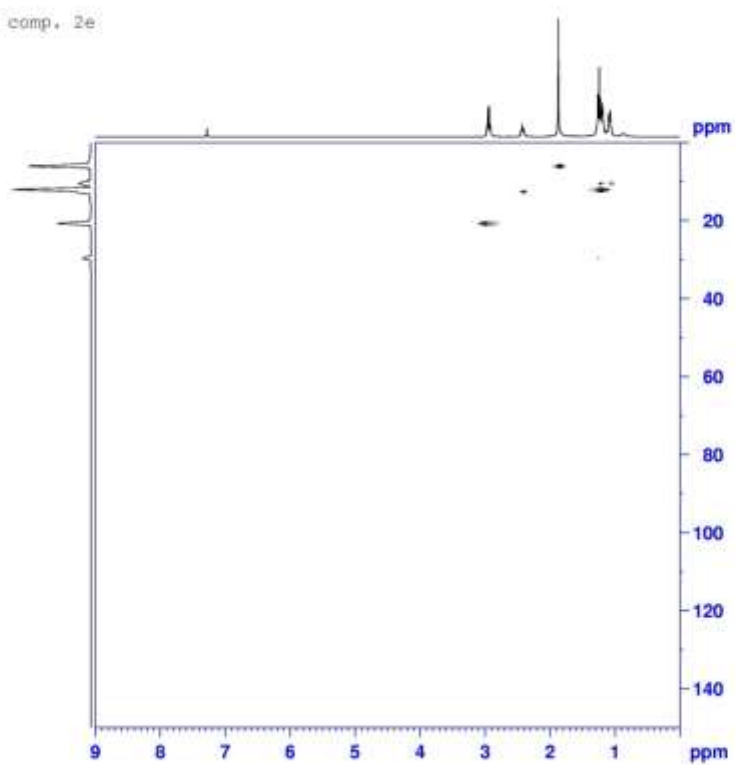
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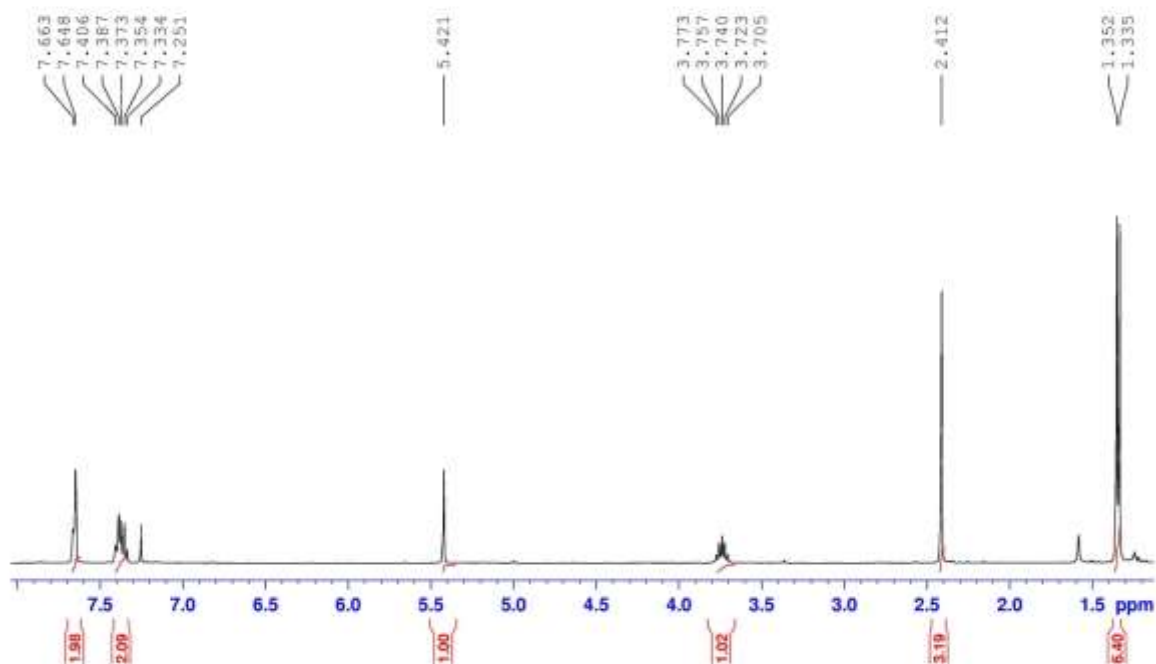
HMBC Comp. 2e



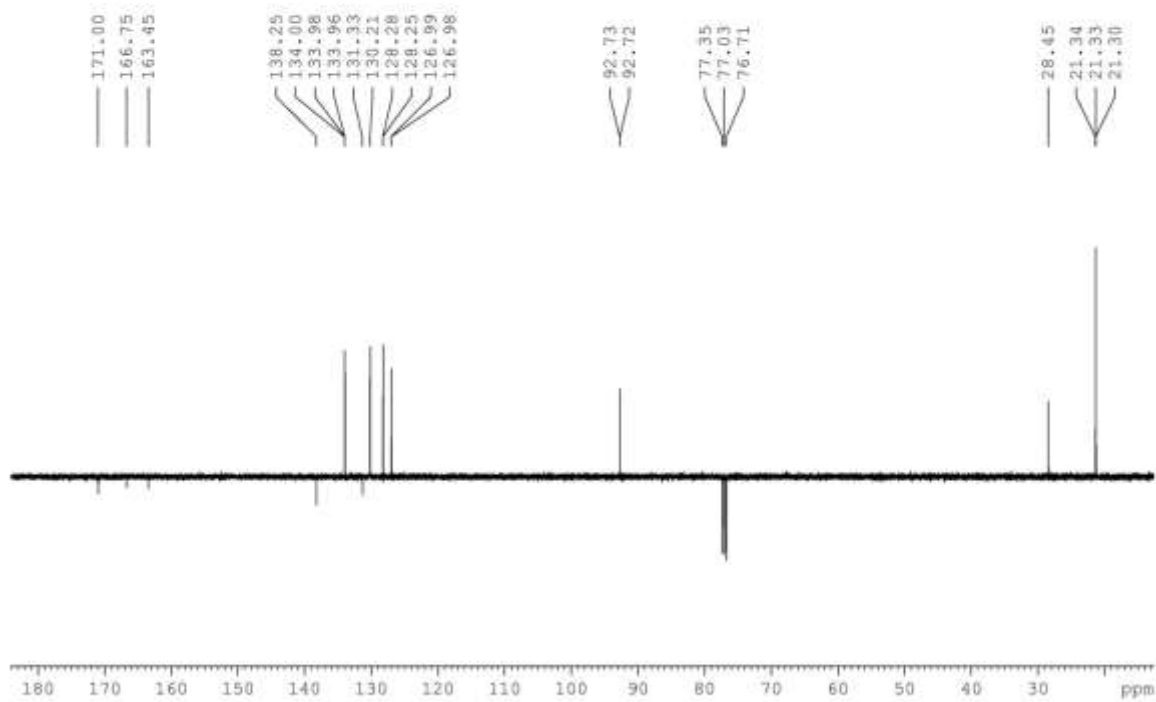
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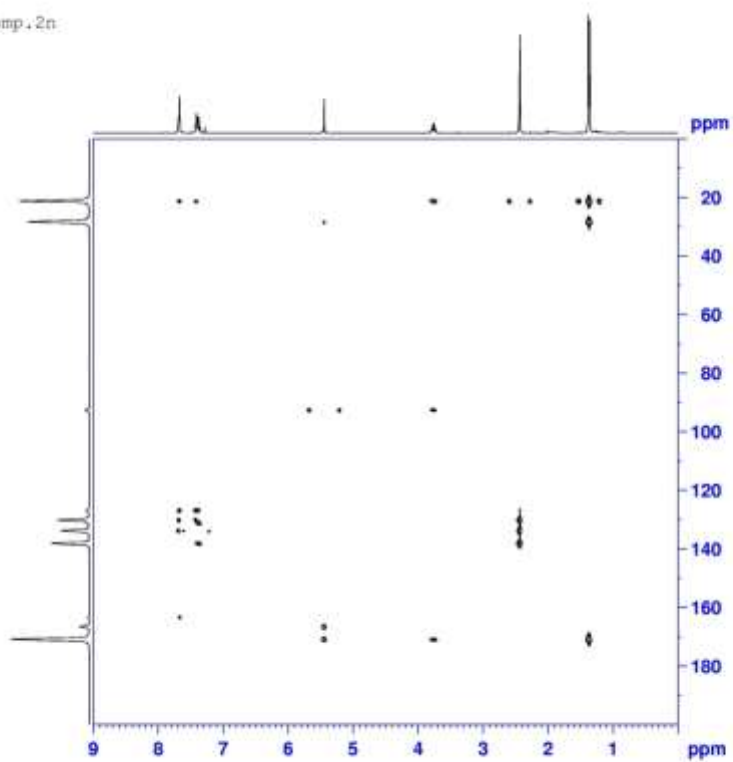
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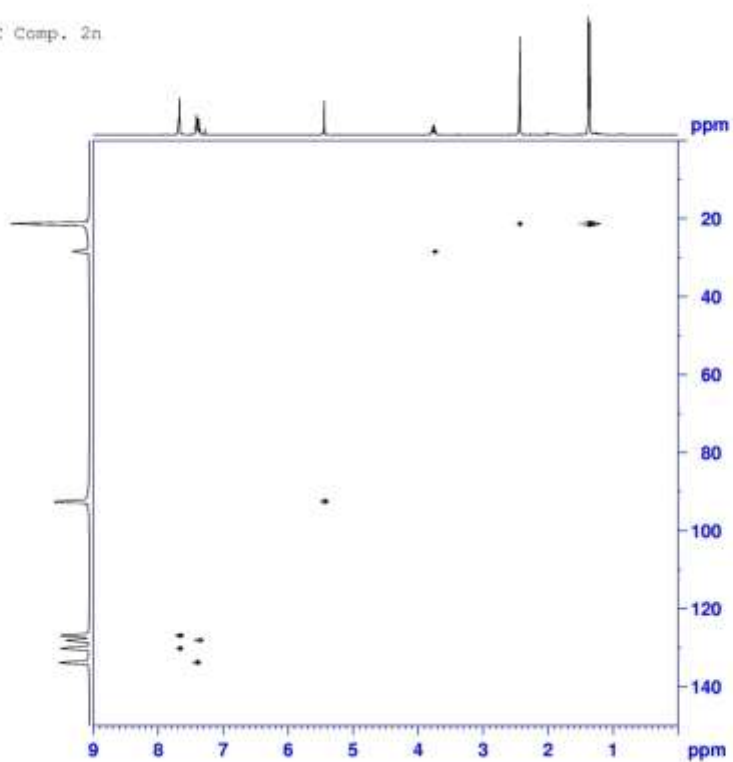
¹³C Comp. 2n



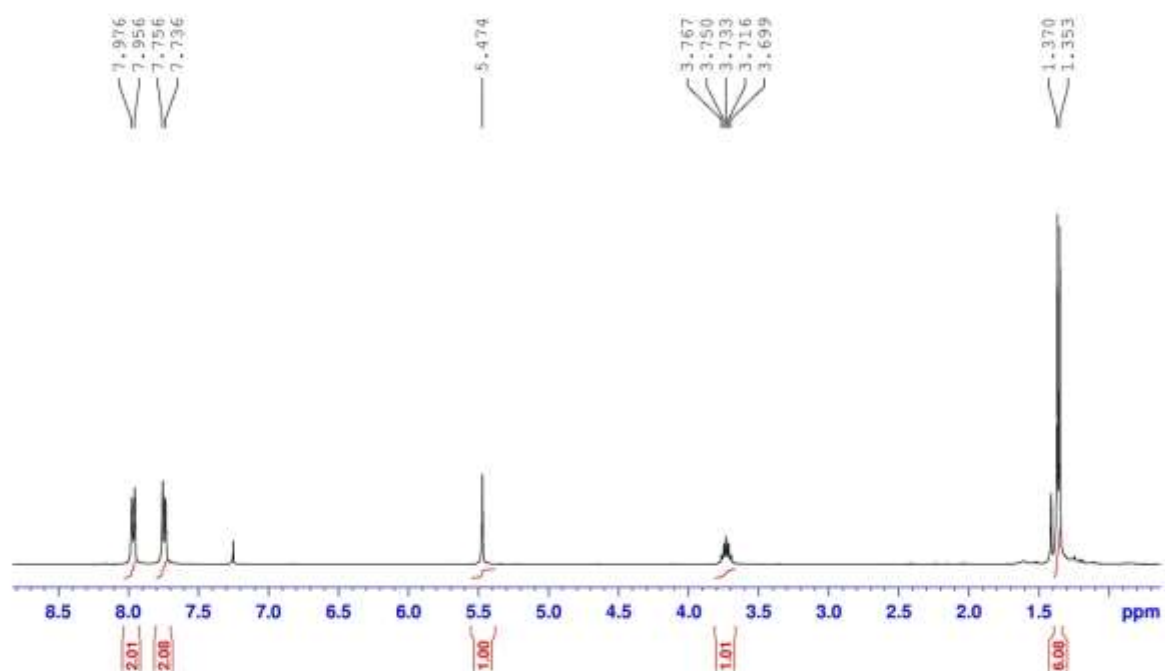
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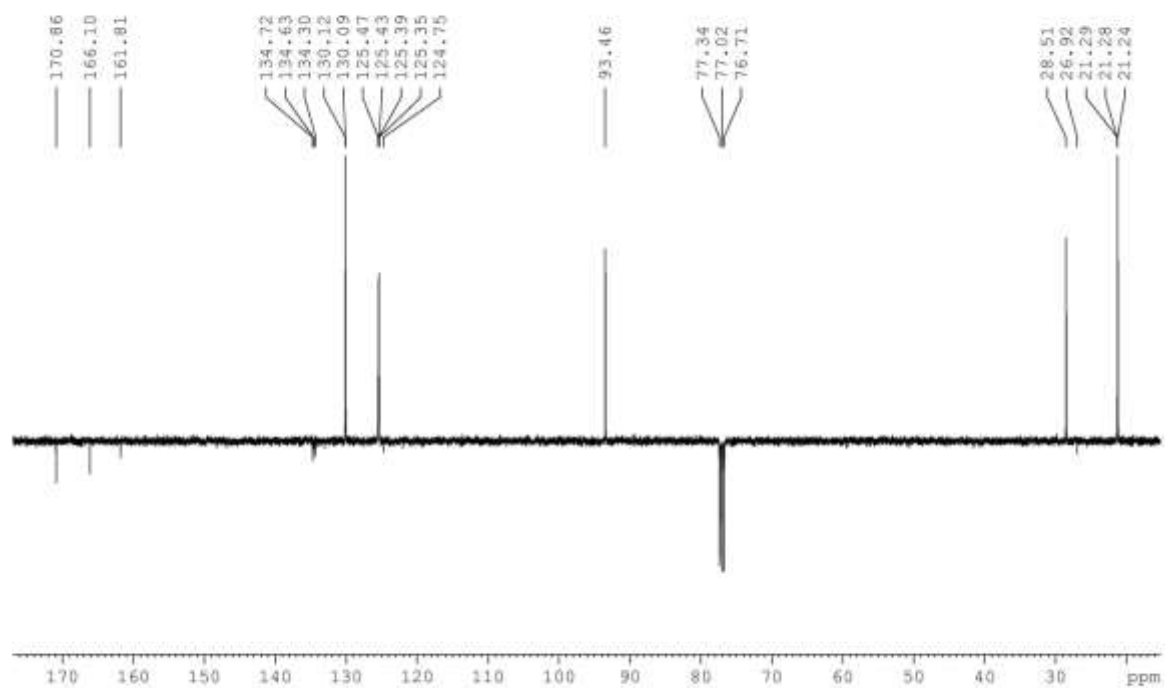
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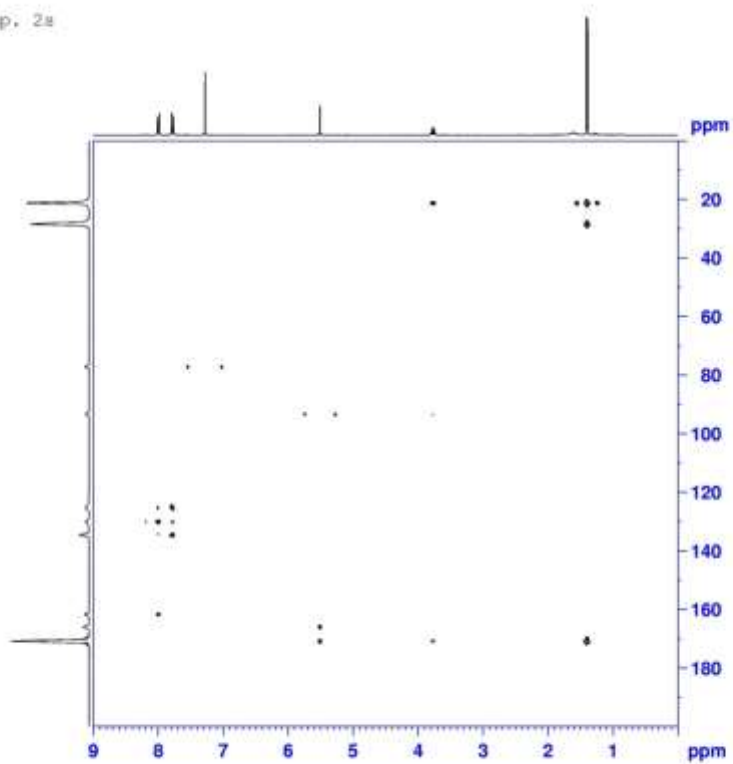
Compound 2a



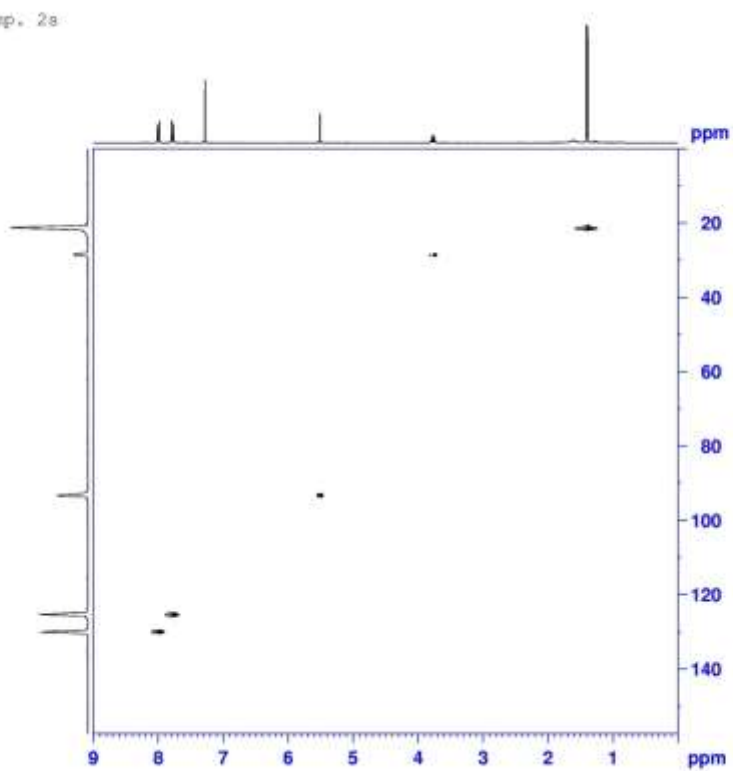
¹³C Comp. 2a



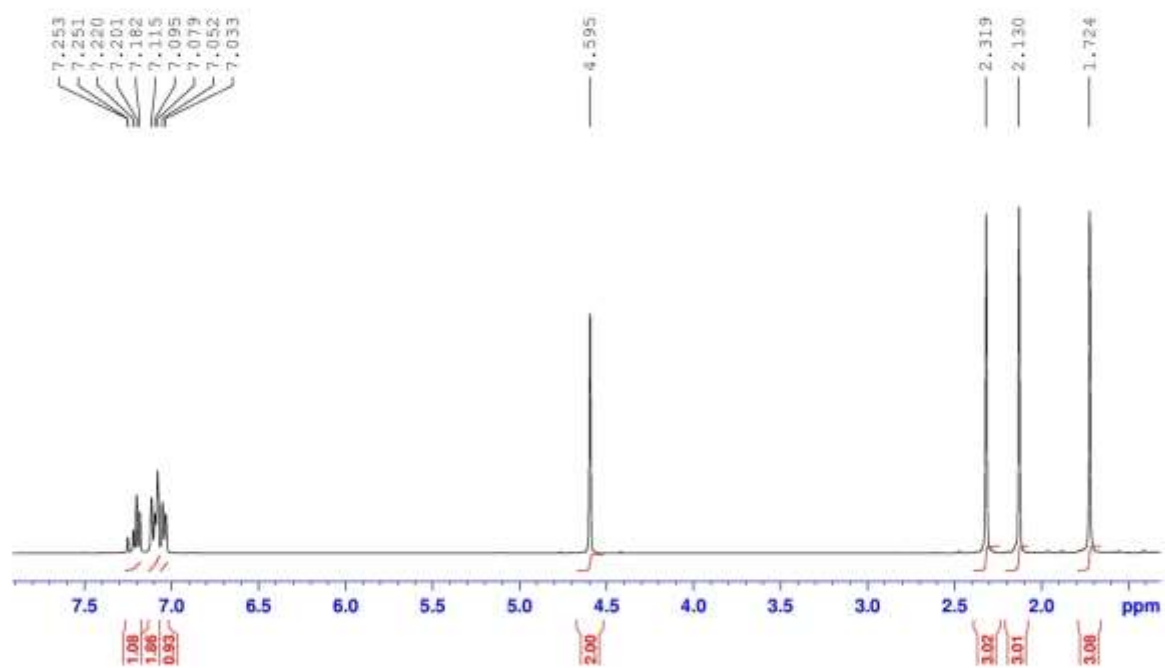
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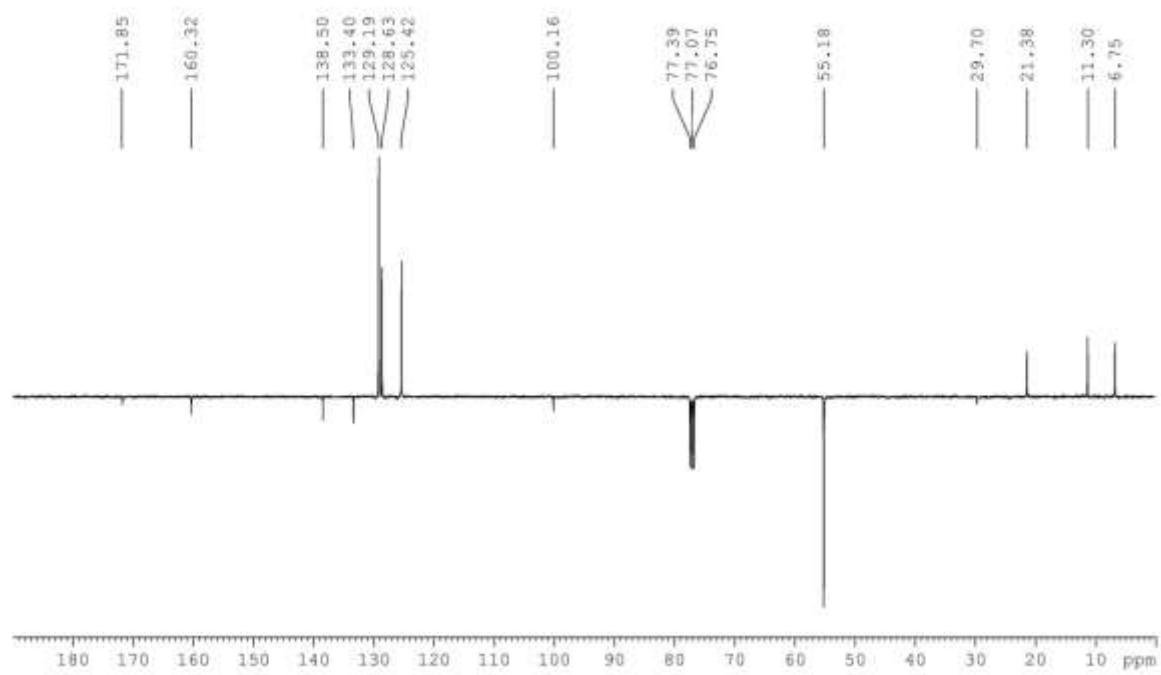
HSQC Comp. 2a



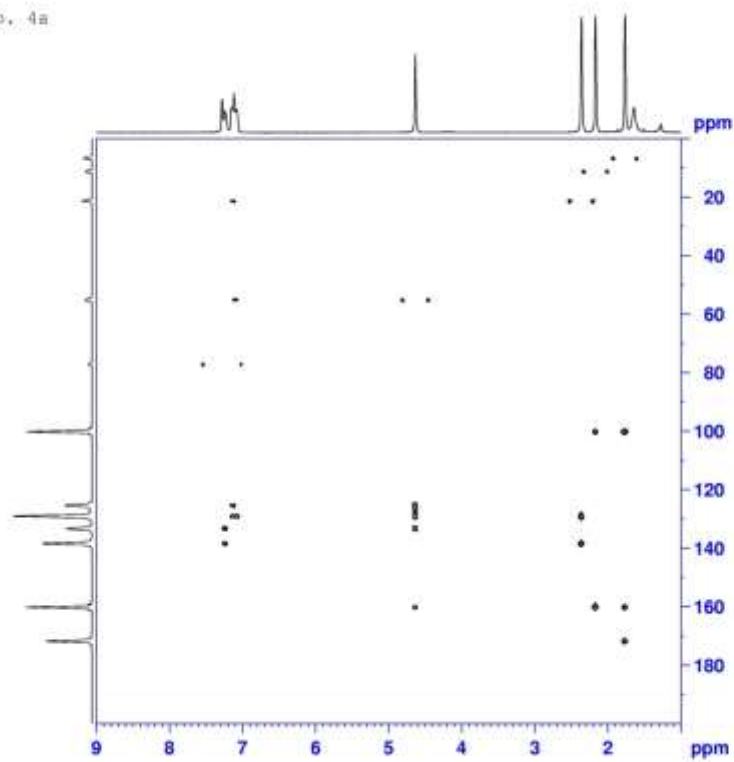
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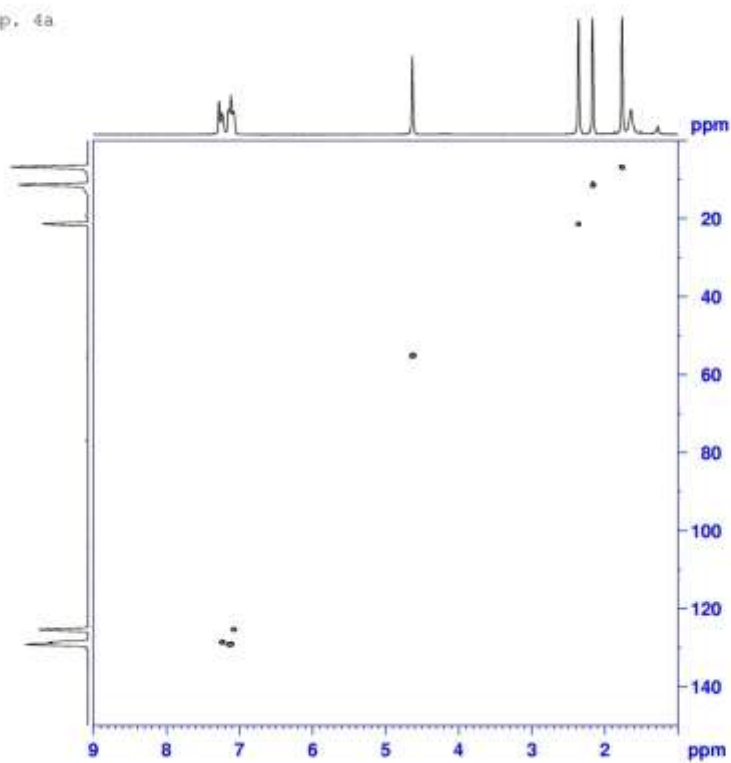
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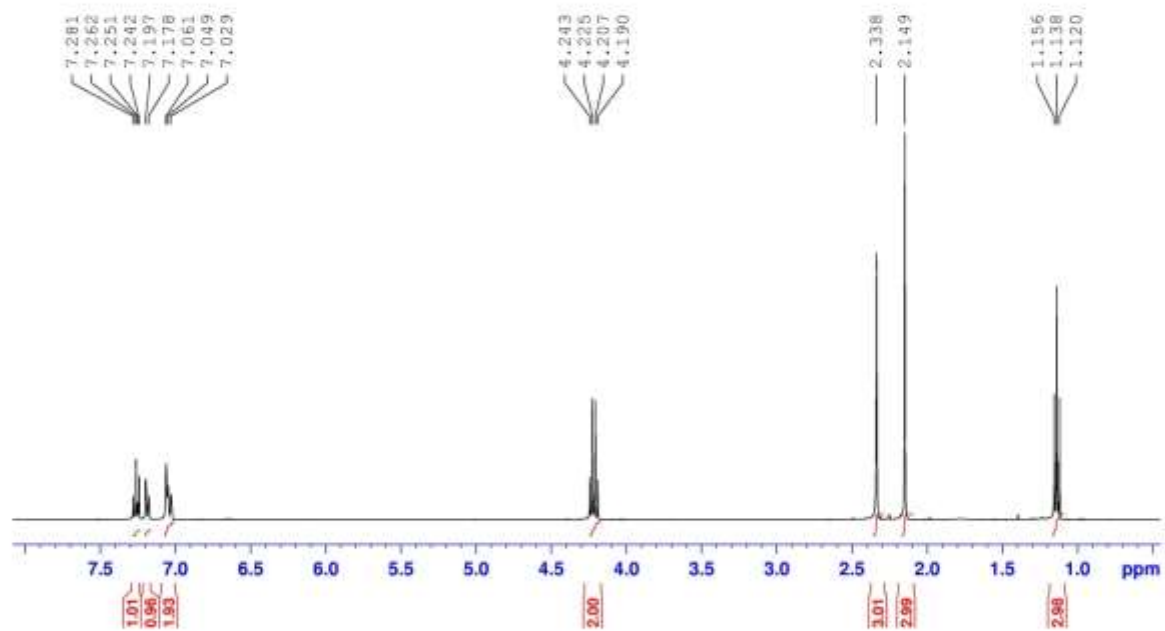
HMBC Comp. 4a



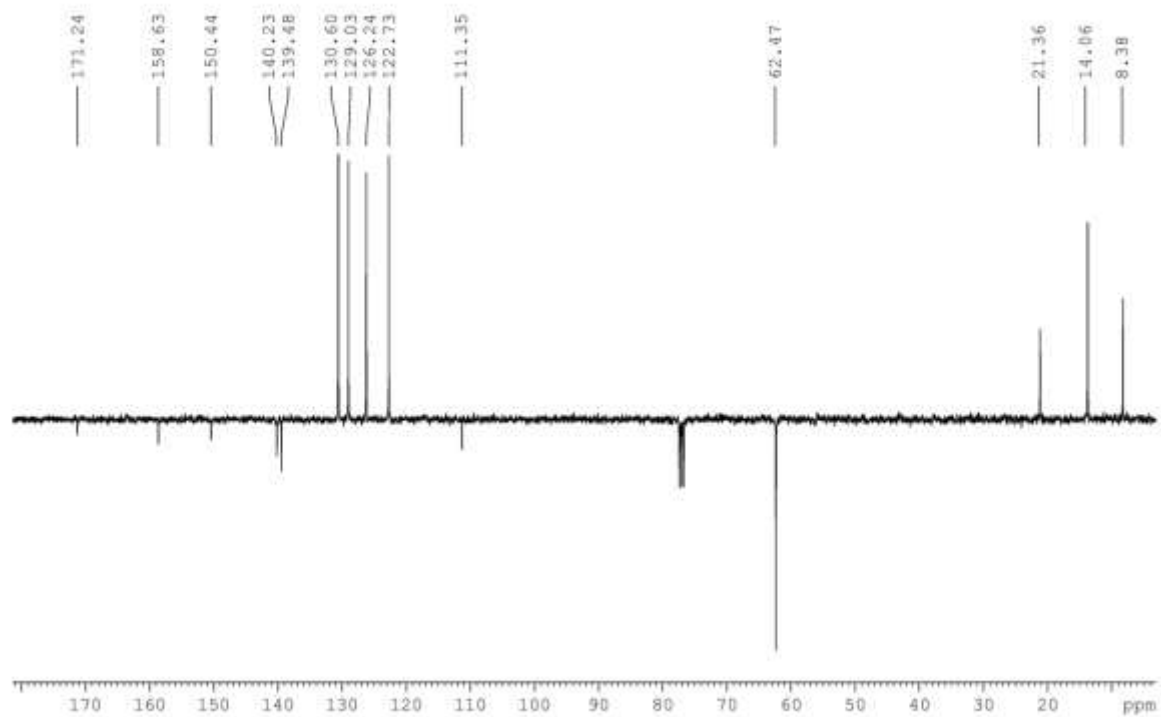
HSQC Comp. 4a



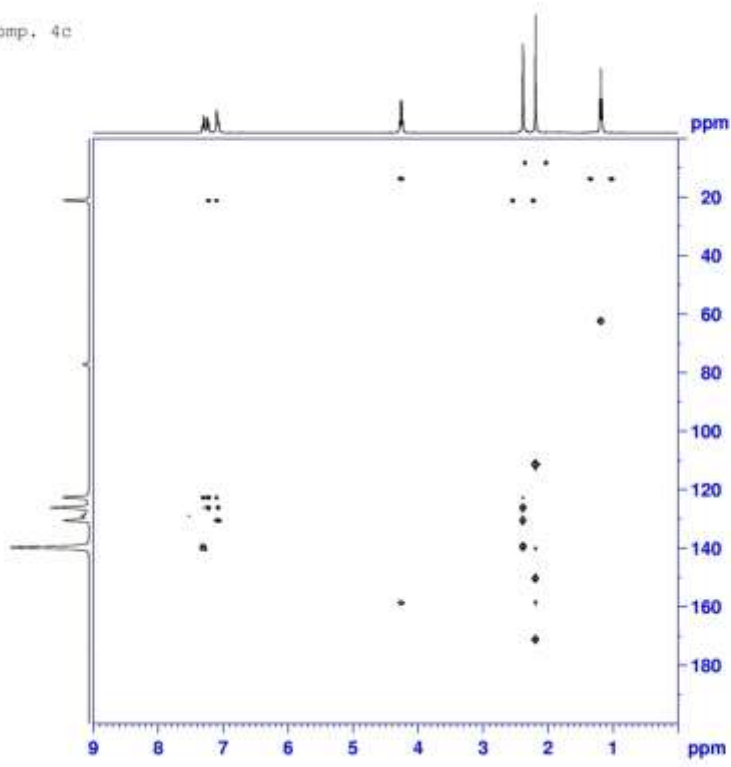
Compound 4c



¹³C Comp. 4c



HMBC Comp. 4c



HMQC Comp. 4c

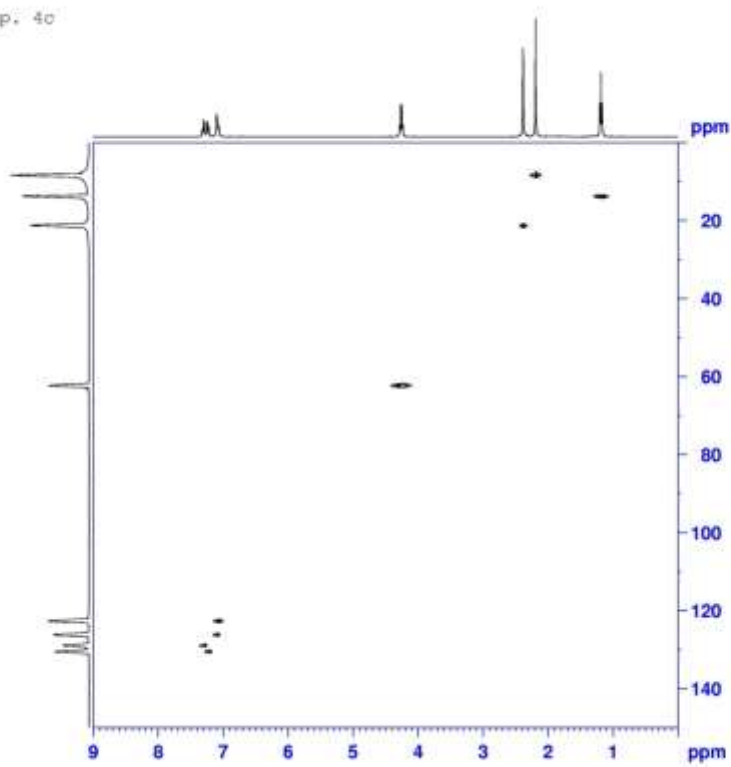


Table S1. Crystal data and structure refinement for **2j**

Empirical formula	C ₁₃ H ₁₃ N O ₃
Formula weight	231.24
Temperature	298(2) K
Wavelength	1.54184 Å
Crystal system	Monoclinic
space group	P 21/c
Unit cell dimensions	a = 9.7480(2) Å alpha = 90°. b = 14.0846(3) Å beta = 91.372(2)°. c = 8.10170(10) Å gamma = 90°.
Volume	1112.02(4) Å ³
Z	4
Calculated density	1.381 Mg/m ³
Absorption coefficient	0.814 mm ⁻¹
F(000)	488
Crystal size	0.35 x 0.25 x 0.22 mm
Theta range for data collection	5.520 to 72.227 deg.
Limiting indices	-11 ≤ h ≤ 11, -16 ≤ k ≤ 16, -9 ≤ l ≤ 7
Reflections collected / unique	6174 / 2114 [R(int) = 0.0276]
Completeness to theta =	70.000 98.9 %
Refinement method	Full-matrix least-squares on F ²
Data / restraints / parameters	2114 / 0 / 206
Goodness-of-fit on F ²	1.100
Final R indices [I > 2σ(I)]	R1 = 0.0386, wR2 = 0.0937
R indices (all data)	R1 = 0.0498, wR2 = 0.1017
Largest diff. peak and hole	0.203 and -0.349 e.Å ⁻³

Table S2. Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for **2j**.

U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
O(2)	6704(1)	281(1)	6209(1)	18(1)
O(1)	5491(1)	2160(1)	3730(1)	23(1)
O(3)	6653(1)	-709(1)	8385(1)	24(1)
N(1)	5853(1)	1020(1)	5617(2)	17(1)
C(11)	4713(2)	1092(1)	6603(2)	16(1)
C(7)	7569(2)	1417(1)	1733(2)	17(1)
C(6)	7577(2)	1316(1)	3453(2)	17(1)
C(8)	6254(2)	1539(1)	4246(2)	17(1)
C(10)	4841(2)	449(1)	7829(2)	18(1)
C(2)	8764(2)	1304(1)	852(2)	18(1)
C(1)	8748(2)	1380(1)	-1000(2)	21(1)
C(5)	8800(2)	1117(1)	4310(2)	19(1)
C(4)	10004(2)	1029(1)	3435(2)	20(1)
C(3)	9987(2)	1117(1)	1732(2)	20(1)
C(12)	3570(2)	1767(1)	6219(2)	19(1)
C(9)	6082(2)	-75(1)	7639(2)	18(1)
C(13)	2370(2)	1628(1)	7372(2)	25(1)

Table S3. Anisotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for **2j**.

The anisotropic displacement factor exponent takes the form:

$$-2 \pi^2 [h^2 a^{*2} U_{11} + \dots + 2 h k a^* b^* U_{12}]$$

	U11	U22	U33	U23	U13	U12
O(2)	19(1)	17(1)	18(1)	4(1)	2(1)	3(1)
O(1)	23(1)	24(1)	22(1)	6(1)	2(1)	6(1)
O(3)	23(1)	25(1)	24(1)	9(1)	2(1)	2(1)
N(1)	17(1)	16(1)	17(1)	3(1)	2(1)	4(1)
C(11)	17(1)	17(1)	16(1)	-6(1)	1(1)	-3(1)
C(7)	18(1)	13(1)	19(1)	1(1)	0(1)	-2(1)
C(6)	18(1)	13(1)	19(1)	0(1)	2(1)	-2(1)
C(8)	20(1)	16(1)	14(1)	-1(1)	-1(1)	-1(1)
C(10)	18(1)	20(1)	17(1)	0(1)	1(1)	-2(1)
C(2)	22(1)	13(1)	18(1)	-1(1)	3(1)	-2(1)
C(1)	27(1)	19(1)	18(1)	-1(1)	5(1)	-1(1)
C(5)	21(1)	17(1)	19(1)	2(1)	-1(1)	-1(1)
C(4)	16(1)	20(1)	25(1)	2(1)	-2(1)	-1(1)
C(3)	19(1)	17(1)	24(1)	0(1)	5(1)	0(1)
C(12)	19(1)	18(1)	20(1)	-2(1)	1(1)	2(1)
C(9)	20(1)	19(1)	15(1)	0(1)	0(1)	-3(1)
C(13)	21(1)	26(1)	29(1)	1(1)	6(1)	6(1)

Table S4. Hydrogen coordinates ($\times 10^4$) and isotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for **2j**

	x	y	z	U(eq)
H(13A)	2660(19)	1727(13)	8570(20)	31(5)
H(12A)	3923(17)	2399(12)	6310(20)	18(4)
H(5)	8815(17)	1068(12)	5520(20)	23(4)
H(13B)	1972(18)	972(13)	7280(20)	23(4)
H(12B)	3267(17)	1659(12)	5030(20)	23(4)
H(7)	6710(18)	1564(12)	1150(20)	21(4)
H(3)	10836(19)	1044(13)	1140(20)	30(5)
H(10)	4214(19)	365(13)	8720(20)	27(5)
H(4)	10859(19)	917(13)	4040(20)	27(5)
H(13C)	1655(19)	2086(13)	7100(20)	28(5)
H(1B)	9430(20)	1858(15)	-1360(30)	40(6)
H(1C)	7790(20)	1580(13)	-1440(20)	34(5)
H(1A)	8980(20)	770(15)	-1510(20)	36(5)

Table S5. Molecular formula strings

compd_ID	SMILES
2a	<chem>CC(N(C(C1CC1)=O)O2)=C(C)C2=O</chem>
2b	<chem>CC(N(C(C1=CC=CC(C)=C1)=O)O2)=C(C)C2=O</chem>
2c	<chem>CC1=C(CC)N(C(C2CC2)=O)OC1=O</chem>
2d	<chem>CC(N(C(C1=CC=CC(C)=C1)=O)O2)=C(CC)C2=O</chem>
2e	<chem>O=C1ON(C(C2CC2)=O)C(CC)=C1</chem>
2f	<chem>CC1=C(CC)N(C(C2=CC=CC(C)=C2)=O)OC1=O</chem>
2g	<chem>O=C1ON(C(C2CC2)=O)C(C(OCC)=O)=C1C</chem>
2h	<chem>O=C1ON(C(C2=CC=CC(C)=C2)=O)C(C(OCC)=O)=C1C</chem>
3a	<chem>S=C1ON(C(C2CC2)=O)C(C(C)C)=C1</chem>
3b	<chem>S=C1ON(C(C2=CC=CC(C)=C2)=O)C(C(C)C)=C1</chem>
2i	<chem>O=C1ON(C(C2CC2)=O)C(CC)=C1</chem>
2j	<chem>O=C1ON(C(C2=CC=CC(C)=C2)=O)C(CC)=C1</chem>
2k	<chem>O=C1ON(C(CC)=O)C(C(C)C)=C1</chem>
2l	<chem>O=C1ON(C(C2CC2)=O)C(C(C)C)=C1</chem>
2m	<chem>O=C1ON(C(C2CCCC2)=O)C(C(C)C)=C1</chem>
2n	<chem>O=C1ON(C(C2=CC=CC(C)=C2)=O)C(C(C)C)=C1</chem>
2o	<chem>O=C1ON(C(C2=CC=C(C)C=C2)=O)C(C(C)C)=C1</chem>
2p	<chem>O=C1ON(C(C2=CC=CC(C#N)=C2)=O)C(C(C)C)=C1</chem>
2q	<chem>O=C1ON(C(C2=CC=C(C#N)C=C2)=O)C(C(C)C)=C1</chem>
2r	<chem>O=C1ON(C(C2=CC=CC(C(F)(F)F)=C2)=O)C(C(C)C)=C1</chem>
2s	<chem>O=C1ON(C(C2=CC=C(C(F)(F)F)C=C2)=O)C(C(C)C)=C1</chem>
4a	<chem>CC(N(CC1=CC=CC=C1)O2)=C(C)C2=O</chem>
4b	<chem>O=C1ON(CC2=CC=CC(C)=C2)C(C(C)C)=C1</chem>
4c	<chem>CC1=C(C(OCC)=O)N(C2=CC=CC(C)=C2)OC1=O</chem>

Table S6. Elemental analysis

Comp.	Formula (MW)	Anal. Calcd.			Anal. Found		
		C	H	N	C	H	N
2a	C ₉ H ₁₁ NO ₃ (181.19)	59.66	6.12	7.33	59.89	6.14	7.76
2b	C ₁₃ H ₁₃ NO ₃ (231.25)	67.52	5.67	6.06	67.79	5.69	6.08
2c	C ₁₀ H ₁₃ NO ₃ (195.22)	61.53	6.71	7.18	61.77	6.73	7.20
2d	C ₁₄ H ₁₅ NO ₃ (245.27)	68.56	6.16	5.71	68.83	6.18	5.73
2e	C ₁₀ H ₁₃ NO ₃ (195.22)	61.53	6.71	7.18	61.77	6.73	7.20
2f	C ₁₄ H ₁₅ NO ₃ (245.27)	68.56	6.16	5.71	68.83	6.18	5.73
2g	C ₁₁ H ₁₃ NO ₅ (239.22)	55.23	5.48	5.86	55.45	5.50	5.88
2h	C ₁₅ H ₁₅ NO ₅ (289.28)	62.28	5.23	4.84	62.52	5.25	4.85
2i	C ₉ H ₁₁ NO ₃ (181.19)	59.66	6.12	7.33	59.89	6.14	7.76
2j	C ₁₃ H ₁₃ NO ₃ (231.25)	67.52	5.67	6.06	67.79	5.69	6.08
2k	C ₉ H ₁₃ NO ₃ (183.20)	59.00	7.15	7.65	59.23	7.17	7.68
2l	C ₁₀ H ₁₃ NO ₃ (195.22)	61.53	6.71	7.18	61.77	6.73	7.20
2m	C ₁₂ H ₁₇ NO ₃ (223.27)	64.55	7.67	6.27	64.80	7.70	6.29
2n	C ₁₄ H ₁₅ NO ₃ (245.27)	68.56	6.16	5.71	68.83	6.18	5.73
2o	C ₁₄ H ₁₅ NO ₃ (245.27)	68.56	6.16	5.71	68.83	6.18	5.73
2p	C ₁₄ H ₁₂ N ₂ O ₃ (256.26)	65.62	4.72	10.93	65.88	4.73	10.97
2q	C ₁₄ H ₁₂ N ₂ O ₃ (256.26)	65.62	4.72	10.93	65.88	4.73	10.97
2r	C ₁₄ H ₁₂ F ₃ NO ₃ (299.25)	56.19	4.04	4.68	56.41	4.05	4.69
2s	C ₁₄ H ₁₂ F ₃ NO ₃ (299.25)	56.19	4.04	4.68	56.41	4.05	4.69

3a	C ₁₀ H ₁₃ NO ₂ S (211.28)	56.85	6.20	6.63		57.07	6.22	6.65
3b	C ₁₄ H ₁₅ NO ₂ S (261.34)	64.34	5.79	5.36		64.59	5.81	5.38
4a	C ₁₃ H ₁₅ NO ₂ (217.26)	71.87	6.96	6.45		72.15	6.98	6.47
4b	C ₁₄ H ₁₇ NO ₂ (231.29)	72.70	7.41	6.06		72.99	7.43	6.08
4c	C ₁₄ H ₁₅ NO ₄ (261.27)	64.36	5.79	5.36		64.61	5.81	5.38