Supporting information

Meta non-flat substituents: A novel molecular design to improving aqueous solubility in small molecule drug discovery

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Supplementary Table 1. List of melting points of disubstituted benzenes with medicinal chemistry-friendly substituents.

a) The order of melting points among the regioisomers.

			Substituent 1																			
			Non Flat													Flat						
			Me	Et	*t*-Bu	F	Cl	Br	CF_3	CN	NH_2	OH	OMe	SO_2NH_2	SO_2Me	Ph	CO_2H	Ac	NO_2	$CONH_2$	NHAc	NMe_2
	H	mono	-95.6	-95.0	-57.9	-42.2	-45.2	-30.7	-31.2	-12.8	-6.0	44.9	-37.1	156.0	90.0	70.3	122.0	20.5	5.8	128.0	114.0	2.5
Substituent 2 / Non Flat	Me	*ortho*	-25.2	-80.7	-50.3	-62.5	-35.9	-27.5	-	-10.5	-14.4	31.0	-34.1	156.3	57.4	-0.2	103.4	-	-3.6	145.0	111.0	-61.3
		meta	-47.9	-95.7	-41.4	-89.2	-47.8	-38.1	-	-23.0	-30.8	12.2	-55.5	108.0	35.0	4.5	109.3	-	15.9	94.5	65.9	-
		para	13.3	-62.7	-52.5	-56.6	7.4	26.2	-	28.0	43.3	34.8	-31.6	138.0	88.0	48.1	180.0	-19.0	51.7	162.5	151.0	-
	Et	*ortho*		-31.4	-	-	-83.3	-67.5	-	-23.6	-47.0	18.0	73.0	127.0	-	-6.1	75.6	-19.0	-12.2	153.5	114.0	-
		meta		-83.9	-75.4	-	-55.0	-	-	-	-64.0	0.0	-5.0	89.0	-	-27.6	47.6	-	-37.9	92.0	34.0	-
		para		-43.3	-38.4	-	-62.5	-43.4	-	-24.2	-5.1	45.0	-	109.0	44.0	34.5	112.0	-24.3	-12.3	164.7	94.5	-
	t-Bu	*ortho*			27.5	-	-	-	-	-	-60.0	-5.6	-	-	69.5	38.0	80.5	-	-2.6	-	165.0	2.8
		meta			10.6	-	-27.3	-	-	-	-	47.0	-	-	-	-	127.3	-	0.4	130.0	102.5	-
		para			77.6	-	23.9	19.0	-	-	15.0	100.0	19.1	139.6	95.0	53.0	164.0	17.7	28.4	174.0	173.3	-
	F	*ortho*				-47.1	-43.0	14.5	-51.2	-	-29.0	16.1	-39.0	158.5	50.0	73.5	124.2	-	-6.0	117.5	79.5	-
		meta				-69.1	-	-	-81.5	-16.1	-	14.0	-35.0	129.5	42.0	27.0	123.6	-	41.0	128.0	84.6	-
		para				-23.5	-26.8	-17.4	-41.7	34.8	-1.9	48.0	-45.0	126.0	80.0	74.2	183.9	-45.0	26.5	154.6	151.1	30.0
	Cl	*ortho*					-17.0	-12.6	-6.0	43.5	-2.3	8.0	-26.6	188.3	94.2	31.8	140.4	66.0	32.1	141.8	86.7	-
		meta					-24.8	-21.4	-56.0	41.0	-10.3	32.5	-	148.0	108.0	16.0	154.2	-	43.6	133.8	76.6	-
		para					53.1	64.8	-33.0	91.6	70.4	43.1	-18.0	146.0	98.0	75.4	239.5	18.4	82.2	180.0	178.4	35.5
	Br	*ortho*						6.0	-	55.5	30.9	5.6	2.5	186.0	108.5	0.8	149.0	50.6	38.5	161.5	99.2	-
		meta						-6.9	1.0	39.5	18.5	33.0	-	154.0	103.0	9.0	156.7	8.0	54.0	156.5	87.5	11.0
		para						87.3	-	114.0	78.2	63.0	13.4	166.5	105.0	87.0	254.0	51.0	133.0	192.5	168.0	55.0
	CF_3	*ortho*							-	18.0	35.5	45.5	-14.1	185.0	75.0	15.0	109.0	-	32.5	163.0	96.5	-
		meta							-	14.5	5.5	-0.9	-65.0	122.0	60.0	26.5	104.0	89.0	-2.4	121.0	103.5	-
		para							2.8	37.5	38.0	47.0	-9.1	184.0	101.0	71.5	220.0	29.0	43.0	187.5	152.4	70.8
	CN	*ortho*								140.9	51.0	98.0	59.0	160.0	104.0	39.0	190.0	49.0	115.0	173.0	199.5	-
		meta								162.0	53.0	82.8	23.0	153.0	105.0	49.0	223.0	98.5	116.6	224.0	131.0	27.0
		para								224.0	86.2	113.0	62.0	173.2	142.8	88.0	220.0	59.0	147.5	227.0	206.5	75.0
	NH_2	*ortho*									103.0	173.5	6.2	157.0	87.0	49.1	144.6	20.0	71.0	110.5	133.5	-
		meta									65.5	122.5	-1.0	140.2	73.0	31.5	179.7	98.5	112.0	117.5	88.0	-
		para									140.3	186.0	57.8	166.1	138.0	51.0	188.2	105.0	147.7	183.0	166.5	53.0
	OH	*ortho*										104.6	28.3	141.0	87.5	57.5	158.6	2.5	44.9	140.0	209.0	44.5
		meta										109.8	-	166.0	84.0	75.3	201.3	94.0	95.0	170.5	148.5	86.0
		para										173.0	54.0	178.0	96.5	168.0	213.0	108.2	113.8	162.0	168.0	77.0
	OMe	*ortho*											22.5	171.0	93.5	29.0	100.9	34.0	9.4	129.5	87.5	-
		meta											-35.3	130.0	47.0	88.0	107.0	60.0	38.0	134.0	81.0	-
		para											56.2	116.0	122.0	90.0	184.0	39.0	54.0	166.4	127.2	48.5
	SO_2NH_2	*ortho*												254.0	-	120.5	159.0	-	193.7	-	163.0	106.5
		meta												229.0	210.0	131.0	249.0	138.0	168.0	176.0	217.0	175.0
		para												289.0	244.0	228.0	291.0	178.0	181.0	238.0	219.0	216.0
	SO_2Me	*ortho*													228.0	101.0	140.0	103.0	136.0	155.0	147.0	95.0
		meta													200.0	85.0	236.5	106.0	148.0	177.0	142.5	85.0
		para													261.0	145.0	274.5	129.0	142.5	226.5	188.0	168.0
Flat	Ph	*ortho*														56.2	112.0	56.0	37.0	175.0	121.5	-
		meta														86.9	162.5	36.0	61.0	173.0	149.0	-
		para														213.8	228.8	121.0	112.9	223.0	171.2	126.0
	CO_2H	*ortho*															207.0	114.5	147.0	28.5	187.5	72.0
		meta															348.0	172.0	141.3	81.0	249.0	152.5
		para															440.0	208.0	241.0	80.0	256.5	242.5
	Ac	*ortho*																42.0	28.5	116.5	77.0	-
		meta																32.0	81.0	126.5	129.0	43.0
		para																113.0	80.0	192.0	169.0	105.5
	NO_2	*ortho*																	115.8	176.6	93.0	-20.0
		meta																	90.8	143.3	154.5	60.0
		para																	171.1	190.0	216.0	164.0
	$CONH_2$	*ortho*																		222.0	190.0	140.0
		meta																		280.0	219.5	153.0
		para																		322.3	274.5	208.0
	NHAc	*ortho*																			188.7	73.0
		meta																			188.0	86.5
		para																			310.0	132.0
	NMe_2	*ortho*																				8.9
		meta																				-2.0
		para																				51.0

Red and blue figures indicate the lowest and the highest melting point among the three regioisomers, respectively. For definitions of “flat” and “non-flat”, see Supplementary Table 2.

b) List of reference sources of melting points

		Substituent 1																			
Substituent 2		Me	Et	*t*-Bu	F	Cl	Br	CF_3	CN	NH_2	OH	OMe	SO_2NH_2	SO_2Me	Ph	CO_2H	Ac	NO_2	$CONH_2$	NHAc	NMe_2
H	*mono*	-95.6	-95.0	-57.9	-42.2	-45.2	-30.7	-31.2	-12.8	-6.0	44.9	-37.1	156.0	90.0	70.3	122.0	20.5	5.8	128.0	114.0	2.5
Me	*ortho*	-25.2	-80.7	-50.3	-62.5	-35.9	-27.5	-	-10.5	-14.4	31.0	-34.1	156.3	57.4	-0.2	103.4	-	-3.6	145.0	111.0	-61.3
	meta	-47.9	-95.7	-41.4	-89.2	-47.8	-38.1	-	-23.0	-30.8	12.2	-55.5	108.0	35.0	4.5	109.3	-	15.9	94.5	65.9	-
	para	13.3	-62.7	-52.5	-56.6	7.4	26.2	-	28.0	43.3	34.8	-31.6	138.0	88.0	48.1	180.0	-19.0	51.7	162.5	151.0	-
Et	*ortho*		-31.4	-	-	-83.3	-67.5	-	-23.6	-47.0	18.0	73.0	127.0	-	-6.1	75.6	-19.0	-12.2	153.5	114.0	-
	meta		-83.9	-75.4	-	-55.0	-	-	-	-64.0	0.0	-5.0	89.0	-	-27.6	47.6	-	-37.9	92.0	34.0	-
	para		-43.3	-38.4	-	-62.5	-43.4	-	-24.2	-5.1	45.0	-	109.0	44.0	34.5	112.0	-24.3	-12.3	164.7	94.5	-
t-Bu	*ortho*			27.5	-	-	-	-	-	-60.0	-5.6	-	-	69.5	38.0	80.5	-	-2.6	-	165.0	2.8
	meta			10.6	-	-27.3	-	-	-	-	47.0	-	-	-	-	127.3	-	0.4	130.0	102.5	-
	para			77.6	-	23.9	19.0	-	-	15.0	100.0	19.1	139.6	95.0	53.0	164.0	17.7	28.4	174.0	173.3	-
F	*ortho*				-47.1	-43.0	14.5	-51.2	-	-29.0	16.1	-39.0	158.5	50.0	73.5	124.2	-	-6.0	117.5	79.5	-
	meta				-69.1	-	-	-81.5	-16.1	-	14.0	-35.0	129.5	42.0	27.0	123.6	-	41.0	128.0	84.6	-
	para				-23.5	-26.8	-17.4	-41.7	34.8	-1.9	48.0	-45.0	126.0	80.0	74.2	183.9	-45.0	26.5	154.6	151.1	30.0
Cl	*ortho*					-17.0	-12.6	-6.0	43.5	-2.3	8.0	-26.6	188.3	94.2	31.8	140.4	66.0	32.1	141.8	86.7	-
	meta					-24.8	-21.4	-56.0	41.0	-10.3	32.5	-	148.0	108.0	16.0	154.2	-	43.6	133.8	76.6	-
	para					53.1	64.8	-33.0	91.6	70.4	43.1	-18.0	146.0	98.0	75.4	239.5	18.4	82.2	180.0	178.4	35.5
Br	*ortho*						6.0	-	55.5	30.9	5.6	2.5	186.0	108.5	0.8	149.0	50.6	38.5	161.5	99.2	-
	meta						-6.9	1.0	39.5	18.5	33.0	-	154.0	103.0	9.0	156.7	8.0	54.0	156.5	87.5	11.0
	para						87.3	-	114.0	78.2	63.0	13.4	166.5	105.0	87.0	254.0	51.0	133.0	192.5	168.0	55.0
CF_3	*ortho*							-	18.0	35.5	45.5	-14.1	185.0	75.0	15.0	109.0	-	32.5	163.0	96.5	-
	meta							-	14.5	5.5	-0.9	-65.0	122.0	60.0	26.5	104.0	89.0	-2.4	121.0	103.5	-
	para							2.8	37.5	38.0	47.0	-9.1	184.0	101.0	71.5	220.0	29.0	43.0	187.5	152.4	70.8
CN	*ortho*								140.9	51.0	98.0	59.0	160.0	104.0	39.0	190.0	49.0	115.0	173.0	199.5	-
	meta								162.0	53.0	82.8	23.0	153.0	105.0	49.0	223.0	98.5	116.6	224.0	131.0	27.0
	para								224.0	86.2	113.0	62.0	173.2	142.8	88.0	220.0	59.0	147.5	227.0	206.5	75.0
NH_2	*ortho*									103.0	173.5	6.2	157.0	87.0	49.1	144.6	20.0	71.0	110.5	133.5	-
	meta									65.5	122.5	-1.0	140.2	73.0	31.5	179.7	98.5	112.0	117.5	88.0	-
	para									140.3	186.0	57.8	166.1	138.0	51.0	188.2	105.0	147.7	183.0	166.5	53.0
OH	*ortho*										104.6	28.3	141.0	87.5	57.5	158.6	2.5	44.9	140.0	209.0	44.5
	meta										109.8	-	166.0	84.0	75.3	201.3	94.0	95.0	170.5	148.5	86.0
	para										173.0	54.0	178.0	96.5	168.0	213.0	108.2	113.8	162.0	168.0	77.0
OMe	*ortho*											22.5	171.0	93.5	29.0	100.9	34.0	9.4	129.5	87.5	-
	meta											-35.3	130.0	47.0	88.0	107.0	60.0	38.0	134.0	81.0	-
	para											56.2	116.0	122.0	90.0	184.0	39.0	54.0	166.4	127.2	48.5
SO_2NH_2	*ortho*												254.0	-	120.5	159.0	-	193.7	-	163.0	106.5
	meta												229.0	210.0	131.0	249.0	138.0	168.0	176.0	217.0	175.0
	para												289.0	244.0	228.0	291.0	178.0	181.0	238.0	219.0	216.0
SO_2Me	*ortho*													228.0	101.0	140.0	103.0	136.0	155.0	147.0	95.0
	meta													200.0	85.0	236.5	106.0	148.0	177.0	142.5	85.0
	para													261.0	145.0	274.5	129.0	142.5	226.5	188.0	168.0
Ph	*ortho*														56.2	112.0	56.0	37.0	175.0	121.5	-
	meta														86.9	162.5	36.0	61.0	173.0	149.0	-
	para														213.8	228.8	121.0	112.9	223.0	171.2	126.0
CO_2H	*ortho*															207.0	114.5	147.0	28.5	187.5	72.0
	meta															348.0	172.0	141.3	81.0	249.0	152.5
	para															440.0	208.0	241.0	80.0	256.5	242.5
Ac	*ortho*																42.0	28.5	116.5	77.0	-
	meta																32.0	81.0	126.5	129.0	43.0
	para																113.0	80.0	192.0	169.0	105.5
NO_2	*ortho*																	115.8	176.6	93.0	-20.0
	meta																	90.8	143.3	154.5	60.0
	para																	171.1	190.0	216.0	164.0
$CONH_2$	*ortho*																		222.0	190.0	140.0
	meta																		280.0	219.5	153.0
	para																		322.3	274.5	208.0
NHAc	*ortho*																			188.7	73.0
	meta																			188.0	86.5
	para																			310.0	132.0
NMe_2	*ortho*																				8.9
	meta																				-2.0
	para																				51.0

Sources

- CRC Handbook of Chemistry and Physics onDVD 93rd Edition Version 2013, CRC Press , 2013
- Beilsteins Handbuch der organischen Chemie, Springer, 1985-1993
- reaxys, https://www.reaxys.com, Elsevier

A blank column means that the melting points were not available in these three databases.

Supplementary Table 2. Dihedral angles of disubstituted benzenes with substituents bearing an sp^2 atom

R^1	R^2		CSD refcode	Measured dihedral angles				Corrected dihedral angles				Absolute difference value				result
				reference	1	2	3	reference	1	2'	3'	1	2'	3'	Mean	
Ph	H	-	BIPHN	0.1	-0.1	180.0	180.0	0.1	-0.1	0.0	0.0	0.2	0.1	0.1	0.1	Flat
Ph	Br	*para*	BRBIPH	15.6	23.8	-161.5	-159.1	15.6	23.8	18.5	20.9	8.2	2.9	5.3	5.5	Flat
Ph	OH	*ortho*	FIFMAI	-58.9	-54.3	123.3	123.4	-58.9	-54.3	-56.7	-56.6	4.6	2.3	2.4	3.1	Flat
Ph	OH	*para*	BOPSAA02	-2.8	-2.7	176.9	177.6	-2.8	-2.7	-3.1	-2.4	0.1	0.3	0.4	0.2	Flat
Ph	Ph	*ortho*	TERPHO02	-63.3	-60.6	119.9	116.2	-63.3	-60.6	-60.1	-63.8	2.7	3.2	0.5	2.1	Flat
Ph	Ph	*meta*	ZZZMTW01	-30.5	-32.1	149.1	148.4	-30.5	-32.1	-31.0	-31.6	1.6	0.5	1.1	1.1	Flat
Ph	Ph	*para*	TERPHE01	-0.7	-1.3	178.8	179.2	-0.7	-1.3	-1.2	-0.8	0.5	0.4	0.1	0.3	Flat
Ph	COOH	*ortho*	NOZVIH	-46.4	-46.7	131.7	135.2	-46.4	-46.7	-48.3	-44.8	0.3	1.9	1.6	1.3	Flat
Ph	COOH	*meta*	TEJMAW01	-31.5	-31.5	148.0	149.1	-31.5	-31.5	-32.0	-31.0	0.1	0.5	0.6	0.4	Flat
Ph	COOH	*para*	BOPSEE10	35.1	35.4	-145.3	-144.1	35.1	35.4	34.7	35.9	0.3	0.4	0.9	0.5	Flat
Ph	NO_2	*ortho*	LESYEN	-63.0	-63.3	115.2	118.6	-63.0	-63.3	-64.9	-61.4	0.3	1.9	1.6	1.3	Flat
Ph	NO_2	*meta*	ZENKIM	-25.3	-27.7	154.2	152.8	-25.3	-27.7	-25.8	-27.2	2.4	0.5	1.9	1.6	Flat
Ph	NO_2	*para*	NBPHEN	-32.5	-32.3	149.2	146.1	-32.5	-32.3	-30.8	-34.0	0.2	1.7	1.5	1.1	Flat
COOH	Me	*ortho*	OTOLIC02	1.5	1.7	-178.1	-178.7	1.5	1.7	1.9	1.3	0.2	0.4	0.2	0.2	Flat
COOH	Me	*meta*	ZZZKWI01	-2.9	-3.5	176.2	177.5	-2.9	-3.5	-3.8	-2.5	0.6	0.9	0.3	0.6	Flat
COOH	Me	*para*	PTOLIC	2.8	3.0	-177.4	-178.9	2.8	3.0	2.7	1.2	0.3	0.1	1.6	0.7	Flat
COOH	*t*-Bu	*para*	BONLOF	8.5	10.3	-171.0	-173.2	8.5	10.3	9.0	6.8	1.7	0.5	1.7	1.3	Flat
COOH	F	*ortho*	FBENZA02	-9.8	-10.4	170.7	169.1	-9.8	-10.4	-9.3	-10.9	0.6	0.5	1.1	0.7	Flat
COOH	F	*meta*	COVJIG	-5.0	-6.7	174.7	173.6	-5.0	-6.7	-5.3	-6.4	1.7	0.3	1.4	1.2	Flat
COOH	F	*para*	PFBAZAD01	-6.1	-6.5	174.0	173.4	-6.1	-6.5	-6.0	-6.6	0.4	0.1	0.5	0.3	Flat
COOH	Cl	*ortho*	CLBZAC01	-14.6	-14.4	167.4	163.7	-14.6	-14.4	-12.6	-16.3	0.2	1.9	1.8	1.3	Flat
COOH	Cl	*meta*	MCBZAC	2.1	-1.2	-179.3	-179.9	2.1	-1.2	0.7	0.1	3.3	1.4	2.0	2.2	Flat
COOH	Cl	*para*	CLBZAP01	-5.0	-6.1	175.3	173.6	-5.0	-6.1	-4.7	-6.4	1.1	0.3	1.4	0.9	Flat
COOH	Br	*meta*	BRBZAC	-19.5	-16.4	162.9	161.2	-19.5	-16.4	-17.1	-18.8	3.1	2.4	0.7	2.0	Flat
COOH	Br	*para*	BRBZAP	6.5	3.8	-175.4	-174.3	6.5	3.8	4.6	5.7	2.8	2.0	0.8	1.9	Flat
COOH	CF_3	*ortho*	UNUZIN	16.7	16.4	-164.4	-162.5	16.7	16.4	15.6	17.5	0.3	1.1	0.8	0.7	Flat
COOH	CN	*para*	TAGNAR	7.7	7.2	-173.1	-171.9	7.7	7.2	6.9	8.1	0.5	0.8	0.4	0.6	Flat
COOH	NH_2	*ortho*	AMBACO08	3.2	3.1	-177.4	-176.4	3.2	3.1	2.6	3.6	0.1	0.6	0.4	0.4	Flat
COOH	NH_2	*meta*	AMBNZA	-7.9	-7.0	172.9	172.2	-7.9	-7.0	-7.1	-7.8	1.0	0.8	0.1	0.7	Flat
COOH	NH_2	*para*	AMBNAC04	10.4	9.3	-170.2	-170.1	10.4	9.3	9.8	9.9	1.1	0.6	0.5	0.7	Flat
COOH	OH	*ortho*	SALIAC	0.5	1.1	178.8	179.6	0.5	1.1	-1.2	-0.4	0.7	1.6	0.9	1.1	Flat
COOH	OH	*meta*	BIODLOP	-1.1	-0.1	179.2	179.6	-1.1	-0.1	-0.8	-0.4	1.0	0.3	0.7	0.7	Flat
COOH	OMe	*ortho*	FUFBOX	4.3	5.9	-174.8	-175.0	4.3	5.9	5.2	5.0	1.6	0.9	0.7	1.1	Flat
COOH	OMe	*para*	ANISIC02	2.3	1.2	-176.3	-179.8	2.3	1.2	3.7	0.2	1.0	1.5	2.1	1.5	Flat
COOH	SO_2Me	*para*	COBFUU	4.9	5.5	-174.6	-175.9	4.9	5.5	5.4	4.1	0.6	0.5	0.9	0.6	Flat
COOH	Ph	*ortho*	NOZVIH	-50.2	-49.6	130.8	129.4	-50.2	-49.6	-49.2	-50.6	0.6	1.0	0.3	0.7	Flat
COOH	Ph	*meta*	TEJMAW	-1.3	-2.6	176.9	179.3	-1.3	-2.6	-3.1	-0.7	1.2	1.8	0.6	1.2	Flat
COOH	Ph	*para*	BOPSEE11	4.1	5.4	-173.3	-177.3	4.1	5.4	6.8	2.7	1.3	2.7	1.4	1.8	Flat
COOH	COOH	*ortho*	PHTHAC01	-33.7	-30.2	154.2	141.8	-33.7	-30.2	-25.8	-38.2	3.5	7.9	4.5	5.3	Flat
COOH	COOH	*meta*	BENZDC01	-4.3	-4.2	175.3	176.2	-4.3	-4.2	-4.7	-3.8	0.1	0.4	0.5	0.3	Flat
COOH	COOH	*para*	TEPHTH	5.2	5.2	-175.4	-174.2	5.2	5.2	4.6	5.8	0.0	0.6	0.6	0.4	Flat
COOH	Ac	*meta*	QUYREI	-2.4	-3.2	176.2	178.2	-2.4	-3.2	-3.8	-1.8	0.8	1.4	0.6	0.9	Flat
COOH	Ac	*para*	TIHLIG	0.4	0.4	179.8	179.8	0.4	0.4	-0.2	-0.2	0.0	0.6	0.6	0.4	Flat
COOH	NO_2	*ortho*	NBZOAO02	53.9	53.1	-129.3	-123.7	53.9	53.1	50.7	56.3	0.8	3.2	2.4	2.2	Flat
COOH	NO_2	*meta*	MNBZAC01	-4.8	-3.0	176.7	175.5	-4.8	-3.0	-3.3	-4.5	1.7	1.5	0.2	1.1	Flat
COOH	NO_2	*para*	NBZOAC03	-1.2	-1.7	178.2	179.0	-1.2	-1.7	-1.8	-1.0	0.5	0.6	0.2	0.4	Flat
COOH	NMe_2	*meta*	TACGUZ	-0.4	-2.0	178.1	179.5	-0.4	-2.0	-1.9	-0.5	1.6	1.5	0.1	1.1	Flat
COOH	NMe_2	*para*	PDABZA01	4.0	3.6	-176.8	-175.7	4.0	3.6	3.2	4.3	0.4	0.8	0.3	0.5	Flat
COOH	NHAc	*ortho*	ACANAC12	-3.5	-4.5	175.3	176.7	-3.5	-4.5	-4.8	-3.3	1.0	1.2	0.2	0.8	Flat
COOH	NHAc	*meta*	VIDLUQ	6.4	7.2	-175.9	-170.3	6.4	7.2	4.1	9.7	0.8	2.3	3.3	2.1	Flat
COOH	NHAc	*para*	DIXFAR02	5.5	5.2	-174.7	-174.6	5.5	5.2	5.3	5.4	0.3	0.1	0.1	0.2	Flat
Ac	H	-	ACETPH	-3.0	-3.8	175.6	177.7	-3.0	-3.8	-4.4	-2.3	0.9	1.5	0.6	1.0	Flat
Ac	Cl	*para*	EYISIO	-3.8	-4.5	175.6	176.0	-3.8	-4.5	-4.4	-4.0	0.7	0.6	0.1	0.5	Flat
Ac	Br	*para*	BRACPH02	8.9	9.1	-172.1	-170.0	8.9	9.1	7.9	10.0	0.1	1.0	1.1	0.7	Flat
Ac	NH_2	*para*	AMACPH	-4.2	-3.0	175.3	177.6	-4.2	-3.0	-4.7	-2.4	1.3	0.5	1.8	1.2	Flat
Ac	OH	*para*	HACTPH12	-1.9	-1.1	177.9	179.1	-1.9	-1.1	-2.1	-0.9	0.8	0.2	1.0	0.7	Flat
Ac	OMe	*para*	YAJOIJ	1.4	2.3	-179.5	-176.8	1.4	2.3	0.6	3.2	0.9	0.8	1.8	1.2	Flat
Ac	COOH	*meta*	QUYREI	4.0	4.5	-175.4	-176.0	4.0	4.5	4.6	4.0	0.5	0.5	0.1	0.4	Flat
Ac	COOH	*para*	TIHLIG	-7.2	-5.9	174.7	172.3	-7.2	-5.9	-5.3	-7.7	1.4	2.0	0.5	1.3	Flat
Ac	Ac	*para*	MEGWUR	-1.3	-1.6	177.7	179.4	-1.3	-1.6	-2.3	-0.6	0.3	1.0	0.7	0.6	Flat
Ac	NO_2	*meta*	HIHHAH	8.0	10.8	-170.7	-170.6	8.0	10.8	9.3	9.4	2.8	1.4	1.4	1.9	Flat
Ac	NO_2	*para*	NACPON10	-1.4	-2.5	177.5	178.6	-1.4	-2.5	-2.6	-1.4	1.0	1.1	0.1	0.7	Flat
Ac	NHAc	*para*	ODATUJ	4.5	3.1	-175.7	-176.8	4.5	3.1	4.3	3.2	1.4	0.1	1.3	0.9	Flat

NO_2	H	-	NITRBE01	1.7	2.6	-177.5	-178.2	1.7	2.6	2.5	1.8	0.9	0.8	0.1	0.6	Flat
NO_2	Me	*meta*	MOVVAV01	-5.4	-4.0	176.7	173.9	-5.4	-4.0	-3.3	-6.1	1.5	2.2	0.7	1.4	Flat
NO_2	Me	*para*	NITOLU01	-0.9	-1.1	179.1	178.8	-0.9	-1.1	-0.9	-1.2	0.2	0.1	0.3	0.2	Flat
NO_2	Cl	*meta*	SETVIX	-39.3	-43.5	141.0	136.2	-39.3	-43.5	-39.0	-43.8	4.2	0.3	4.5	3.0	Flat
NO_2	Cl	*meta*	CLNIBZ01	2.9	3.1	-177.4	-176.7	2.9	3.1	2.6	3.3	0.2	0.3	0.5	0.3	Flat
NO_2	Cl	*para*	CNITBZ01	0.0	0.4	-178.7	179.1	0.0	0.4	1.3	-0.9	0.4	1.3	0.9	0.9	Flat
NO_2	Br	*ortho*	YAQZUM	-45.3	-44.4	134.1	136.3	-45.3	-44.4	-45.9	-43.8	0.9	0.6	1.5	1.0	Flat
NO_2	Br	*meta*	BRNIBZ	-0.8	2.4	177.3	175.7	-0.8	2.4	-2.7	-4.3	3.2	1.9	3.5	2.9	Flat
NO_2	Br	*para*	ULEBOD	4.1	6.3	-175.4	-174.3	4.1	6.3	4.6	5.7	2.2	0.5	1.6	1.5	Flat
NO_2	NH_2	*ortho*	ONITAN	-0.7	-4.0	176.5	178.9	-0.7	-4.0	-3.5	-1.1	3.3	2.9	0.5	2.2	Flat
NO_2	NH_2	*meta*	MINANL02	-2.7	-2.5	178.0	176.9	-2.7	-2.5	-2.1	-3.1	0.2	0.6	0.5	0.4	Flat
NO_2	NH_2	*para*	NANILI	-2.6	-1.3	178.0	178.2	-2.6	-1.3	-2.0	-1.8	1.3	0.6	0.7	0.9	Flat
NO_2	OH	*ortho*	ONITPH	1.6	0.7	-177.9	-179.8	1.6	0.7	2.1	0.2	0.9	0.5	1.4	0.9	Flat
NO_2	OH	*meta*	MNPHOL02	0.9	-0.3	179.9	179.3	0.9	-0.3	-0.1	-0.8	1.2	1.0	1.7	1.3	Flat
NO_2	OH	*para*	NITPOL03	-1.6	-1.0	178.3	179.1	-1.6	-1.0	-1.7	-0.9	0.5	0.1	0.7	0.4	Flat
NO_2	SO_2NH_2	*ortho*	TIBPAW	-47.6	-47.8	133.1	131.5	-47.6	-47.8	-46.9	-48.5	0.3	0.7	0.9	0.6	Flat
NO_2	SO_2NH_2	*meta*	XUDTEV	-34.9	20.0	158.2	-173.1	-34.9	20.0	-21.8	6.9	54.9	13.1	41.8	36.6	Not
NO_2	SO_2NH_2	*para*	XUDTIZ01	-0.9	-1.9	178.8	178.4	-0.9	-1.9	-1.2	-1.6	1.0	0.3	0.7	0.6	Flat
NO_2	SO_2Me	*para*	VOHZUO	9.7	10.4	-169.9	-170.0	9.7	10.4	10.1	10.0	0.7	0.4	0.3	0.4	Flat
NO_2	Ph	*ortho*	LESYEN	-44.9	-44.2	133.8	137.2	-44.9	-44.2	-46.2	-42.8	0.7	1.4	2.1	1.4	Flat
NO_2	Ph	*meta*	ZENKIM	-6.4	-8.0	172.2	173.3	-6.4	-8.0	-7.8	-6.7	1.6	1.3	0.2	1.0	Flat
NO_2	Ph	*para*	NBPHEN	-0.2	-2.4	179.4	178.1	-0.2	-2.4	-0.6	-1.9	2.2	0.4	1.7	1.4	Flat
NO_2	COOH	*ortho*	NBZOAO02	53.9	53.1	-123.7	-129.3	53.9	53.1	56.3	50.7	0.8	2.4	3.2	2.2	Flat
NO_2	COOH	*meta*	MNBZAC01	2.2	2.8	-177.3	-177.8	2.2	2.8	2.7	2.2	0.6	0.5	0.0	0.4	Flat
NO_2	COOH	*para*	NBZOAC03	-13.9	-13.2	166.4	166.5	-13.9	-13.2	-13.6	-13.5	0.7	0.3	0.4	0.5	Flat
NO_2	Ac	*para*	HIHHAH	10.8	8.0	-170.7	-170.6	10.8	8.0	9.3	9.4	2.8	1.4	1.4	1.9	Flat
NO_2	NO_2	*ortho*	ZZZFYW01	41.8	40.5	-135.4	-142.4	41.8	40.5	44.6	37.7	1.3	2.9	4.1	2.7	Flat
NO_2	NO_2	*meta*	DNBENZ11	12.7	11.8	-167.7	-167.8	12.7	11.8	12.3	12.2	0.8	0.4	0.5	0.6	Flat
NO_2	NO_2	*para*	DNITBZ	-10.8	-12.1	170.8	166.3	-10.8	-12.1	-9.2	-13.7	1.2	1.7	2.9	1.9	Flat
NO_2	NMe_2	*meta*	MNTDMA	-9.0	-11.4	170.0	169.5	-9.0	-11.4	-10.0	-10.5	2.4	1.0	1.4	1.6	Flat
NO_2	NMe_2	*para*	DIMNAN	0.3	5.6	-176.4	-177.7	0.3	5.6	3.6	2.3	5.3	3.3	2.0	3.5	Flat
NO_2	$CONH_2$	*ortho*	ONBZAM	44.2	46.7	-131.4	-137.8	44.2	46.7	48.6	42.2	2.6	4.5	1.9	3.0	Flat
NO_2	$CONH_2$	*meta*	JACYOB	9.0	9.8	-171.7	-169.5	9.0	9.8	8.3	10.5	0.8	0.8	1.5	1.0	Flat
NO_2	$CONH_2$	*para*	NITBZAM01	-7.7	-7.9	172.6	171.8	-7.7	-7.9	-7.4	-8.2	0.2	0.3	0.5	0.3	Flat
NO_2	NHAc	*ortho*	DIXDUJ	-19.7	-18.2	161.1	161.0	-19.7	-18.2	-18.9	-19.1	1.5	0.8	0.7	1.0	Flat
NO_2	NHAc	*para*	UGUHEJ	-2.0	-1.1	178.2	178.8	-2.0	-1.1	-1.8	-1.2	0.9	0.2	0.8	0.6	Flat
NH_2	H	-	BAZGOY	28.5	-19.0	166.2	-156.6	28.5	-19.0	-13.8	23.4	47.5	42.4	5.2	31.7	Not
NH_2	Me	*para*	FANDOO	-19.0	-30.1	157.9	153.1	-19.0	-30.1	-22.1	-26.9	11.1	3.2	7.9	7.4	Flat
NH_2	F	*para*	IDAHUR	-29.2	21.8	-161.6	154.2	-29.2	21.8	18.4	-25.8	50.9	47.6	3.3	33.9	Not
NH_2	Cl	*ortho*	IGEHEI	0.0	-1.5	180.0	178.6	0.0	-1.5	0.0	-1.4	1.5	0.1	1.4	1.0	Flat
NH_2	Cl	*para*	CLANIC	31.7	-31.6	-165.8	165.8	31.7	-31.6	14.2	-14.2	63.3	17.4	45.9	42.2	Not
NH_2	Br	*ortho*	IGEHIM	-20.0	24.2	163.2	-159.1	-20.0	24.2	-16.8	20.9	44.2	3.3	41.0	29.5	Not
NH_2	Br	*para*	PBRANL01	16.9	-16.9	166.5	-166.5	16.9	-16.9	-13.5	13.5	33.7	30.4	3.4	22.5	Not
NH_2	CN	*ortho*	NAHQOC	-16.0	14.9	165.4	-66.6	-16.0	14.9	-14.6	113.4	30.9	1.4	129.4	53.9	Not
NH_2	CN	*meta*	BERTIB	30.2	-33.0	150.9	-153.7	30.2	-33.0	-29.1	26.4	63.2	59.3	3.9	42.1	Not
NH_2	CN	*para*	BERTOH	-4.9	2.8	174.7	-176.6	-4.9	2.8	-5.3	3.4	7.8	0.4	8.4	5.5	Flat
NH_2	NH_2	*ortho*	BAGFIY	11.0	-44.7	137.9	-171.5	11.0	-44.7	-42.1	8.5	55.6	53.1	2.5	37.1	Not
NH_2	NH_2	*meta*	PENDAM02	24.8	-27.9	156.4	-159.5	24.8	-27.9	-23.6	20.5	52.7	48.4	4.3	35.1	Not
NH_2	NH_2	*para*	VOJGIL	23.3	-35.3	149.3	-161.3	23.3	-35.3	-30.7	18.8	58.6	54.0	4.6	39.1	Not
NH_2	OH	*ortho*	AMPHOM03	15.3	-44.7	139.9	-169.3	15.3	-44.7	-40.1	10.7	60.0	55.4	4.6	40.0	Not
NH_2	OH	*meta*	MAMPOL	32.6	-40.5	-151.6	143.7	32.6	-40.5	28.4	-36.4	73.2	4.2	69.0	48.8	Not
NH_2	OH	*para*	AMPHOL01	-13.9	47.9	-134.5	168.6	-13.9	47.9	45.5	-11.4	61.8	59.4	2.4	41.2	Not
NH_2	OMe	*para*	PANISD01	18.9	-28.4	154.1	-163.6	18.9	-28.4	-25.9	16.4	47.3	44.8	2.5	31.5	Not
NH_2	SO_2NH_2	*para*	SULAMD03	7.3	-32.7	-173.0	147.6	7.3	-32.7	7.0	-32.4	39.9	0.3	39.7	26.6	Not
NH_2	COOH	*meta*	AMBNZA	-18.0	17.6	-165.5	165.1	-18.0	17.6	14.5	-14.9	35.6	32.5	3.1	23.7	Not
NH_2	COOH	*ortho*	AMBACO08	9.2	-14.6	167.7	-73.2	9.2	-14.6	-12.3	106.8	23.8	21.5	97.6	47.6	Not
NH_2	COOH	*para*	AMBNAC04	-32.9	26.8	-157.5	151.4	-32.9	26.8	22.5	-28.6	59.8	55.4	4.4	39.9	Not
NH_2	Ac	*para*	AMACPH	25.9	-19.0	163.7	-156.9	25.9	-19.0	-16.3	23.1	44.9	42.2	2.8	39.3	Not
NH_2	NO_2	*ortho*	ONITAN	12.8	15.8	-165.7	-165.7	12.8	15.8	14.3	14.4	3.0	1.5	1.5	2.0	Flat
NH_2	NO_2	*meta*	MNIANL02	23.4	-20.8	162.1	-159.6	23.4	-20.8	-17.9	20.4	44.2	41.3	3.0	29.5	Not
NH_2	NO_2	*para*	NANILI	13.9	18.8	-160.9	-166.4	13.9	18.8	19.1	13.6	4.9	5.2	0.3	3.4	Flat
NH_2	NMe_2	*para*	GILYOP	27.1	-27.1	155.5	-155.6	27.1	-27.1	-24.5	24.4	54.3	51.6	2.8	36.2	Not
NH_2	$CONH_2$	*ortho*	JIXCIC	-18.8	39.8	-141.8	162.8	-18.8	39.8	38.3	-17.2	58.7	57.1	1.6	39.1	Not
NH_2	$CONH_2$	*para*	AMBZAM10	-47.7	-18.9	133.2	160.2	-47.7	-18.9	-46.8	-19.8	28.7	0.8	27.9	19.1	Not
NH_2	NHAc	*para*	PACTAN	-25.4	33.4	-149.1	157.0	-25.4	33.4	30.9	-23.0	58.8	56.4	2.4	39.1	Not

NMe_2	NH_2	*para*	GILYOP	2.1	53.4	-129.4	-175.2	2.1	53.4	50.6	4.8	51.3	48.5	2.8	34.2	Not
NMe_2	CN	*para*	YAMHID	-5.3	6.2	173.1	-173.9	-5.3	6.2	-6.9	6.1	11.5	1.6	11.4	8.1	Flat
NMe_2	COOH	*meta*	TACGUZ	-11.5	12.0	-170.5	171.0	-11.5	12.0	9.5	-9.0	23.4	21.0	2.5	15.6	Not
NMe_2	COOH	*para*	PDABZA01	-2.6	-2.9	176.7	177.8	-2.6	-2.9	-3.3	-2.2	0.3	0.7	0.4	0.4	Flat
NMe_2	COOH	*para*	PDABZA02	-5.0	9.7	-170.2	174.9	-5.0	9.7	9.8	-5.1	14.7	14.8	0.1	9.9	Flat
NMe_2	NO_2	*meta*	MNTDMA	7.5	-3.7	-174.0	177.7	7.5	-3.7	6.0	-2.3	11.2	1.4	9.8	7.5	Flat
NMe_2	NO_2	*para*	DIMNAN	-6.4	-7.3	175.1	171.3	-6.4	-7.3	-4.9	-8.7	0.9	1.4	2.4	1.6	Flat
NMe_2	NHAc	*para*	PAVJEC	-4.6	7.0	177.4	-175.0	-4.6	7.0	-2.6	5.0	11.6	2.0	9.6	7.8	Flat
NMe_2	COOEt	*para*	DUNHIE	-3.2	-1.0	177.2	178.5	-3.2	-1.0	-2.8	-1.5	2.2	0.4	1.7	1.5	Flat
NMe_2	COH	*para*	EVAXUV	-0.7	3.1	-179.8	-177.8	-0.7	3.1	0.2	2.3	3.8	0.9	2.9	2.5	Flat
NMe_2	COH	*para*	CIKCEF	-1.3	3.3	179.3	-177.3	-1.3	3.3	-0.7	2.7	4.7	0.6	4.1	3.1	Flat
NMe_2	COH	*para*	HUMYOE	0.2	-0.6	179.8	179.9	0.2	-0.6	-0.2	-0.2	0.7	0.4	0.3	0.5	Flat
NMe_2	COH	*para*	ISACOV	4.5	-3.6	-176.1	177.0	4.5	-3.6	3.9	-3.0	8.0	0.5	7.5	5.3	Flat
NMe_2	2-hydroxyphenoxymethyl	*para*	ISACOV	-5.0	2.9	-177.0	175.0	-5.0	2.9	3.0	-5.0	7.9	8.0	0.1	5.3	Flat
NMe_2	dimethylaminophenyl	*ortho*	KAHRAM	-11.7	-61.8	120.2	166.4	-11.7	-61.8	-59.9	-13.6	50.1	48.2	1.9	33.4	Not
NMe_2	benzoyl	*para*	KOFHET	7.8	-1.9	-172.1	178.0	7.8	-1.9	7.9	-2.0	9.7	0.1	9.8	6.6	Flat
NMe_2	thiazolidin-2-yl	*para*	KONXOA	5.7	-13.8	167.1	-175.3	5.7	-13.8	-12.9	4.7	19.5	18.6	0.9	13.0	Not
NMe_2	naphthalen-1-yl	*para*	OJUBAX	5.0	-10.0	171.2	-176.1	5.0	-10.0	-8.8	3.9	15.1	13.9	1.2	10.0	Not
NMe_2	phthalimido	*para*	ZZZAWP10	-7.0	-7.0	173.0	173.0	-7.0	-7.0	-7.0	-7.0	0.0	0.0	0.0	0.0	Flat
NMe_2	A	*para*	FAXSUT	-15.0	13.7	166.2	-167.5	-15.0	13.7	-13.8	12.5	28.8	1.2	27.6	19.2	Not
NMe_2	B	*para*	HIVNEG	4.3	1.4	-179.0	-175.3	4.3	1.4	1.0	4.8	2.9	3.3	0.4	2.2	Flat
N^+HMe_2	H	*para*	GEBYER	65.3	-60.2	-114.7	119.8	65.3	-60.2	65.3	-60.2	125.5	0.0	125.5	83.7	Not
N^+HMe_2	Br	*para*	AFUXUU	-60.1	-4.1	122.3	173.5	-60.1	-4.1	-57.7	-6.5	56.0	2.4	53.6	37.3	Not
N^+HMe_2	COH	*para*	VOJMEO	63.7	-62.6	-117.8	115.8	63.7	-62.6	62.2	-64.2	126.3	1.6	127.9	85.3	Not
NMe_2	N^+Me_3	*para*	YIMKAH	-3.9	-13.2	167.7	175.3	-3.9	-13.2	-12.4	-4.7	9.2	8.4	0.8	6.1	Flat
$CONH_2$	H	-	BZAMID	-26.6	-24.2	153.7	155.5	-26.6	-24.2	-26.3	-24.6	2.4	0.3	2.0	1.6	Flat
$CONH_2$	Me	*ortho*	NABQEM	40.0	42.0	-138.3	-139.7	40.0	42.0	41.7	40.3	2.0	1.7	0.3	1.3	Flat
$CONH_2$	Me	*meta*	MEBENA	29.9	26.6	-152.3	-151.2	29.9	26.6	27.7	28.8	3.3	2.2	1.1	2.2	Flat
$CONH_2$	Me	*para*	DABVAD01	24.6	27.0	-152.2	-156.3	24.6	27.0	27.8	23.8	2.4	3.2	0.9	2.1	Flat
$CONH_2$	F	*ortho*	BIGSUF	-30.2	-31.8	149.0	148.9	-30.2	-31.8	-31.0	-31.1	1.6	0.7	0.8	1.0	Flat
$CONH_2$	F	*meta*	BENAFM10	-29.5	-27.9	150.2	152.4	-29.5	-27.9	-29.8	-27.6	1.6	0.3	1.9	1.2	Flat
$CONH_2$	F	*para*	BENAFP01	-29.1	-26.7	150.4	153.8	-29.1	-26.7	-29.6	-26.2	2.4	0.5	2.9	1.9	Flat
$CONH_2$	Cl	*ortho*	CLBZAM11	-47.6	-49.7	133.2	129.6	-47.6	-49.7	-46.8	-50.4	2.1	0.8	2.9	1.9	Flat
$CONH_2$	Cl	*meta*	NABRAJ	-27.3	-28.4	150.4	154.0	-27.3	-28.4	-29.6	-26.0	1.1	2.3	1.3	1.6	Flat
$CONH_2$	Cl	*para*	PCBZAM10	29.0	27.8	-150.9	-152.7	29.0	27.8	29.1	27.4	1.2	0.1	1.6	1.0	Flat
$CONH_2$	CN	*meta*	WUKHUF	21.8	21.1	-158.9	-158.3	21.8	21.1	21.1	21.7	0.7	0.7	0.1	0.5	Flat
$CONH_2$	NH_2	*ortho*	JIXCIC	-32.1	-32.4	149.9	145.6	-32.1	-32.4	-30.1	-34.4	0.4	2.0	2.3	1.6	Flat
$CONH_2$	NH_2	*para*	AMBZAM10	-29.6	-25.5	154.4	150.6	-29.6	-25.5	-25.6	-29.4	4.1	4.0	0.1	2.7	Flat
$CONH_2$	OH	*ortho*	SALMID01	2.2	2.0	-177.7	-178.1	2.2	2.0	2.3	1.9	0.2	0.1	0.3	0.2	Flat
$CONH_2$	OH	*meta*	HXBNZM	22.3	22.7	-156.1	-156.9	22.3	22.7	23.9	23.1	0.4	1.6	0.8	0.9	Flat
$CONH_2$	OH	*para*	VIDMAX	-7.0	-6.2	172.9	173.9	-7.0	-6.2	-7.1	-6.1	0.8	0.1	0.9	0.6	Flat
$CONH_2$	OMe	*ortho*	RECQIA	29.9	34.9	-146.5	-148.7	29.9	34.9	33.5	31.3	5.0	3.6	1.4	3.4	Flat
$CONH_2$	NO_2	*ortho*	ONBZAM	45.0	41.5	-141.2	-132.3	45.0	41.5	38.8	47.7	3.5	6.2	2.7	4.1	Flat
$CONH_2$	NO_2	*meta*	JACYOB	14.5	14.8	-166.3	-164.4	14.5	14.8	13.7	15.6	0.3	0.8	1.1	0.7	Flat
$CONH_2$	NO_2	*para*	NTBZAM01	2.0	3.8	-177.8	-176.4	2.0	3.8	2.2	3.6	1.7	0.2	1.5	1.2	Flat
$CONH_2$	NHAc	*ortho*	ACBNZA	28.1	27.4	-151.8	-152.8	28.1	27.4	28.2	27.2	0.7	0.2	0.9	0.6	Flat
NHAc	H	-	ACANIL06	-18.1	-18.5	161.9	161.8	-18.1	-18.5	-18.2	-18.2	0.4	0.0	0.0	0.1	Flat
NHAc	Me	*ortho*	REZRIY	-64.4	-65.9	115.5	114.1	-64.4	-65.9	-64.5	-65.9	1.5	0.1	1.4	1.0	Flat
NHAc	Me	*para*	ACTOLD07	-14.0	-18.0	163.9	164.1	-14.0	-18.0	-16.1	-15.9	4.0	2.1	1.9	2.7	Flat
NHAc	Cl	*ortho*	MEJPIB01	-42.4	-42.7	138.6	136.4	-42.4	-42.7	-41.4	-43.7	0.3	1.0	1.2	0.8	Flat
NHAc	Cl	*meta*	GISPOO	21.2	14.5	-163.0	-161.3	21.2	14.5	17.0	18.7	6.7	4.2	2.5	4.4	Flat
NHAc	Br	*ortho*	MAVFAR	42.6	42.6	-138.6	-136.3	42.6	42.6	41.5	43.8	0.1	1.2	1.1	0.8	Flat
NHAc	Br	*meta*	HOTDOK	-19.2	-22.2	160.8	157.8	-19.2	-22.2	-19.2	-22.2	3.0	0.0	3.0	2.0	Flat
NHAc	Br	*para*	MEWFUR	-18.6	-7.3	170.1	164.1	-18.6	-7.3	-9.9	-15.9	11.4	8.7	2.7	7.6	Flat
NHAc	CF_3	*ortho*	PETLEH	-51.6	-51.9	128.1	128.3	-51.6	-51.9	-51.9	-51.7	0.3	0.3	0.1	0.2	Flat
NHAc	CF_3	*meta*	PETLAD	-0.3	-1.3	178.7	179.6	-0.3	-1.3	-1.3	-0.4	1.0	0.9	0.0	0.7	Flat
NHAc	CF_3	*para*	PETKUW	-8.0	-9.0	172.0	170.9	-8.0	-9.0	-8.0	-9.1	1.0	0.0	1.1	0.7	Flat
NHAc	OH	*meta*	MENSEE	-5.9	-6.2	174.1	173.8	-5.9	-6.2	-5.9	-6.2	0.3	0.0	0.3	0.2	Flat
NHAc	OH	*para*	HXACAN	17.9	14.8	-163.1	-164.2	17.9	14.8	16.9	15.8	3.0	1.0	2.1	2.0	Flat
NHAc	OMe	*para*	ACACTA	-23.1	-28.9	149.9	158.1	-23.1	-28.9	-30.1	-21.9	5.8	7.0	1.2	4.6	Flat
NHAc	CN	*ortho*	FOMRIJ	-37.8	-33.3	146.0	142.9	-37.8	-33.3	-34.0	-37.1	4.6	3.8	0.7	3.0	Flat
NHAc	NH_2	*para*	PACTAN	36.3	36.7	-140.0	-147.1	36.3	36.7	40.0	32.9	0.4	3.7	3.3	2.5	Flat
NHAc	COOH	*ortho*	ACANAC12	-0.7	-2.7	177.2	179.4	-0.7	-2.7	-2.8	-0.6	2.0	2.1	0.1	1.4	Flat
NHAc	COOH	*meta*	VIDLUQ	-6.3	-3.1	177.6	173.0	-6.3	-3.1	-2.4	-7.0	3.2	3.9	0.7	2.6	Flat
NHAc	COOH	*para*	DIXFAR02	-30.4	-30.6	142.9	147.1	-30.4	-30.6	-37.1	-32.9	0.3	6.8	2.5	3.2	Flat
NHAc	Ac	*ortho*	ODATUJ	-16.7	-14.9	173.7	164.8	-16.7	-14.9	-6.3	-15.3	1.8	10.4	1.4	4.5	Flat
NHAc	NO_2	*ortho*	DIXDUJ	25.9	11.3	-169.1	-153.8	25.9	11.3	10.9	26.2	14.6	15.0	0.3	10.0	Flat
NHAc	NO_2	*meta*	UGIUHEJ	-7.6	-7.5	172.3	172.5	-7.6	-7.5	-7.7	-7.5	0.2	0.1	0.1	0.1	Flat
NHAc	$CONH_2$	*ortho*	ACBNZA	-6.5	-9.2	169.6	174.8	-6.5	-9.2	-10.4	-5.2	2.7	3.9	1.2	2.6	Flat
NHAc	NHAc	*ortho*	WIVYIJ	-39.6	-50.3	138.1	132.0	-39.6	-50.3	-41.9	-48.0	10.6	2.3	8.3	7.1	Flat

A: 6-amino-3-methyl-1-phenyl-1*H*-pyrazolo[3,4-b]pyridine-5-carbonitrile, B: 2,6-bis(pyridin-2-yl)pyridine

The molecular shapes of substituents can be classified into not only flat/non-flat, but also linear (e.g. CN), spherical (e.g. halogen), and so on. Here, we defined a flat substituent as one possessing extension in two dimensions.

Among the compounds listed in Supplementary Table 1, all available single X-ray crystal structures of the compounds bearing substituent(s) containing an sp^2 atom (Ph, CO_2H, Ac, NO_2, NH_2, NMe_2, $CONH_2$ and NHAc) were picked up from the Cambridge Structural Database (CSD). In the case of the NMe_2 group, because only seven single X-ray crystal data were available, seventeen crystal data sets of compounds not listed in Supplementary Table 1 were also picked up. Next, four dihedral angles between the phenyl ring and the sp^2-substituent were measured. If the absolute value of the measured dihedral angle exceeded 90 º, it was corrected by adding 180 º with the opposite sign; we designated the resulting value as the corrected dihedral angle. The mean absolute difference values between a reference dihedral angle and the other three corrected dihedral angles was next calculated. When this mean absolute difference value is less than 10 º, the substituent is defined as flat. The angles of each substituent are shown in Supplementary Table 2. As a result, we defined Ph, CO_2H, Ac, NO_2, $CONH_2$ and NHAc groups as flat substituents, whereas Me, Et, *t*-Bu, F, Cl, Br, CF_3, CN, NH_2, OH, OMe, SO_2NH_2 and SO_2Me were defined as non-flat substituents. The NMe_2 group was excluded from the analyses shown in Figure 1b-c because we could not define NMe_2 as either flat or non-flat.

Supplementary Table 3. List of melting points and the melting point differences of the disubstituted benzenes used for statistical analysis in Fig. 1b-c.

a) Disubstituted benzenes containing flat substituent(s).

substituent		Melting point (°C)			difference of melting point (°C)	
R^1	R^2	*ortho*	*meta*	*para*	*(para)-(ortho)*	*(para)-(meta)*
Me	CO_2H	103.4	109.3	180	76.6	70.7
Me	$CONH_2$	145	94.5	162.5	17.5	68
Me	NO_2	-3.6	15.9	51.7	55.3	35.8
Me	NHAc	111	65.9	151	40	85.1
Et	CO_2H	75.6	47.6	112	36.4	64.4
Et	$CONH_2$	133.5	92	164.7	31.2	72.7
Et	NO_2	-12.2	-37.9	-12.3	-0.1	25.6
Et	NHAc	114	34	94.5	-19.5	60.5
t-Bu	CO_2H	80.5	127.3	164	83.5	36.7
t-Bu	NO_2	-2.6	0.4	28.4	31	28
t-Bu	NHAc	165	102.5	173.3	8.3	70.8
F	CO_2H	124.2	123.6	183.9	59.7	60.3
F	$CONH_2$	117.5	128	154.6	37.1	26.6
F	NO_2	-6	41	26.5	32.5	-14.5
F	NHAc	79.5	84.6	151.1	71.6	66.5
Cl	CO_2H	140.4	154.2	239.5	99.1	85.3
Cl	$CONH_2$	141.8	133.8	180	38.2	46.2
Cl	NO_2	32.1	43.6	82.2	50.1	38.6
Cl	NHAc	86.7	76.6	178.4	91.7	101.8
Br	CO_2H	149	156.7	254	105	97.3
Br	Ac	50.6	8	51	0.4	43
Br	$CONH_2$	161.5	156.5	192.5	31	36
Br	NO_2	38.5	54	133	94.5	79

Br	NHAc	99.2	87.5	168	68.8	80.5
CF_3	CO_2H	109	104	220	111	116
CF_3	$CONH_2$	163	121	187.5	24.5	66.5
CF_3	NO_2	32.5	-2.4	43	10.5	45.4
CF_3	NHAc	96.5	103.5	152.4	55.9	48.9
CO_2H	CO_2H	207	348	440	233	92
CO_2H	Ac	114.5	172	208	93.5	36
CO_2H	CN	190	223	220	30	-3
CO_2H	$CONH_2$	28.5	81	80	51.5	-1
CO_2H	NH_2	144.6	179.7	188.2	43.6	8.5
CO_2H	NO_2	147	141.3	241	94	99.7
CO_2H	NHAc	187.5	249	256.5	69	7.5
CO_2H	OH	158.6	201.3	213	54.4	11.7
CO_2H	OMe	100.9	107	184	83.1	77
CO_2H	SO_2NH_2	159	249	291	132	42
CO_2H	SO_2Me	140	236.5	274.5	134.5	38
Ac	Ac	42	32	113	71	81
Ac	CN	49	98.5	59	10	-39.5
Ac	$CONH_2$	116.5	126.5	192	75.5	65.5
Ac	NH_2	20	98.5	105	85	6.5
Ac	NO_2	28.5	81	80	51.5	-1
Ac	NHAc	77	129	169	92	40
Ac	OH	2.5	94	108.2	105.7	14.2
Ac	OMe	34	60	39	5	-21
Ac	SO_2Me	103	106	129	26	23
CN	$CONH_2$	173	224	227	54	3
CN	NO_2	115	116.6	147.5	32.5	30.9
CN	NHAc	199.5	131	206.5	7	75.5
$CONH_2$	$CONH_2$	222	280	322.3	100.3	42.3
$CONH_2$	NH_2	110.5	117.5	183	72.5	65.5

$CONH_2$	NO_2	176.6	143.3	190	13.4	46.7
$CONH_2$	NHAc	190	219.5	274.5	84.5	55
$CONH_2$	OH	140	170.5	162	22	-8.5
$CONH_2$	OMe	129.5	134	166.4	36.9	32.4
$CONH_2$	SO_2Me	155	177	226.5	71.5	49.5
NH_2	NO_2	71	112	147.7	76.7	35.7
NH_2	NHAc	133.5	88	166.5	33	78.5
NO_2	NO_2	115.8	90.8	171.1	55.3	80.3
NO_2	NHAc	93	154.5	216	123	61.5
NO_2	OH	44.9	95	113.8	68.9	18.8
NO_2	OMe	9.4	38	54	44.6	16
NO_2	SO_2NH_2	193.7	168	181	-12.7	13
NO_2	SO_2Me	136	148	142.5	6.5	-5.5
NHAc	NHAc	188.7	188	310	121.3	122
NHAc	OH	209	148.5	168	-41	19.5
NHAc	OMe	87.5	81	127.2	39.7	46.2
NHAc	SO_2NH_2	163	217	219	56	2
NHAc	SO_2Me	147	142.5	188	41	45.5
Ph	Me	-0.2	4.5	48.1	48.3	43.6
Ph	Et	-6.1	-27.6	34.5	40.6	62.1
Ph	F	73.5	27	74.2	0.7	47.2
Ph	Cl	31.8	16	75.4	43.6	59.4
Ph	CO_2H	112	162.5	228.8	116.8	66.3
Ph	Ac	56	36	121	65	85
Ph	$CONH_2$	175	173	223	48	50
Ph	NO_2	37	61	112.9	75.9	51.9
Ph	NHAc	121.5	149	171.2	49.7	22.2
Ph	Br	0.8	9	87	86.2	78
Ph	CF_3	15	26.5	71.5	56.5	45
Ph	CN	39	49	88	49	39

Ph	NH_2	49.1	31.5	51	1.9	19.5
Ph	OH	57.5	75.3	168	110.5	92.7
Ph	OMe	29	88	90	61	2
Ph	SO_2NH_2	120.5	131	228	107.5	97
Ph	SO_2Me	101	85	145	44	60
Ph	Ph	56.2	86.9	213.8	157.6	126.9

b) Disubstituted benzenes with solely non-flat substituents

Substituent		Melting point (°C)			Difference of melting point (°C)	
R^1	R^2	*ortho*	*meta*	*para*	*(para)-(ortho)*	*(para)-(meta)*
Me	Me	-25.2	-47.9	13.3	38.5	61.2
Me	Et	-80.7	-95.7	-62.7	18	33
Me	*t*-Bu	-50.3	-41.4	-52.5	-2.2	-11.1
Me	F	-62.5	-89.2	-56.6	5.9	32.6
Me	Cl	-35.9	-47.8	7.4	43.3	55.2
Me	Br	-27.5	-38.1	26.2	53.7	64.3
Me	CN	-10.5	-23	28	38.5	51
Me	NH_2	-14.4	-30.8	43.3	57.7	74.1
Me	OH	31	12.2	34.8	3.8	22.6
Me	OMe	-34.1	-55.5	-31.6	2.5	23.9
Me	SO_2NH_2	156.3	108	138	-18.3	30
Me	SO_2Me	57.4	35	88	30.6	53
Et	Et	-31.4	-83.9	-43.3	-11.9	40.6
Et	Cl	-83.3	-55	-62.5	20.8	-7.5
Et	NH_2	-47	-64	-5.1	41.9	58.9
Et	OH	18	0	45	27	45
Et	SO_2NH_2	127	89	109	-18	20
t-Bu	*t*-Bu	27.5	10.6	77.6	50.1	67
t-Bu	OH	-5.6	47	100	105.6	53
F	F	-47.1	-69.1	-23.5	23.6	45.6
F	CF_3	-51.2	-81.5	-41.7	9.5	39.8
F	OH	16.1	14	48	31.9	34
F	OMe	-39	-35	-45	-6	-10
F	SO_2NH_2	158.5	129.5	126	-32.5	-3.5
F	SO_2Me	50	42	80	30	38

Cl	Cl	-17	-24.8	53.1	70.1	77.9
Cl	Br	-12.6	-21.4	64.8	77.4	86.2
Cl	CF_3	-6	-56	-33	-27	23
Cl	CN	43.5	41	91.6	48.1	50.6
Cl	NH_2	-2.3	-10.3	70.4	72.7	80.7
Cl	OH	8	32.5	43.1	35.1	10.6
Cl	SO_2NH_2	188.3	148	146	-42.3	-2
Cl	SO_2Me	94.2	108	98	3.8	-10
Br	Br	6	-6.9	87.3	81.3	94.2
Br	CN	55.5	39.5	114	58.5	74.5
Br	NH_2	30.9	18.5	78.2	47.3	59.7
Br	OH	5.6	33	63	57.4	30
Br	SO_2NH_2	186	154	166.5	-19.5	12.5
Br	SO_2Me	108.5	103	105	-3.5	2
CF_3	CN	18	14.5	37.5	19.5	23
CF_3	NH_2	35.5	5.5	38	2.5	32.5
CF_3	OH	45.5	-0.9	47	1.5	47.9
CF_3	OMe	-14.1	-65	-9.1	5	55.9
CF_3	SO_2NH_2	185	122	184	-1	62
CF_3	SO_2Me	75	60	101	26	41
CN	CN	140.9	162	224	83.1	62
CN	NH_2	51	53	86.2	35.2	33.2
CN	OH	98	82.8	113	15	30.2
CN	OMe	59	23	62	3	39
CN	SO_2NH_2	160	153	173.2	13.2	20.2
CN	SO_2Me	104	105	142.8	38.8	37.8
NH_2	NH_2	103	65.5	140.3	37.3	74.8
NH_2	OH	173.5	122.5	186	12.5	63.5
NH_2	OMe	6.2	-1	57.8	51.6	58.8
NH_2	SO_2NH_2	157	140.2	166.1	9.1	25.9

NH_2	SO_2Me	87	73	138	51	65
OH	OH	104.6	109.8	173	68.4	63.2
OH	SO_2NH_2	141	166	178	37	12
OH	SO_2Me	87.5	84	96.5	9	12.5
OMe	OMe	22.5	-35.3	56.2	33.7	91.5
OMe	SO_2NH_2	171	130	116	-55	-14
OMe	SO_2Me	93.5	47	122	28.5	75
SO_2NH_2	SO_2NH_2	254	229	289	35	60
SO_2Me	SO_2Me	228	200	261	33	61

Supplementary Table 4. List of the differences of melting points between disubstituted benzenes and monosubstituted benzenes

Substituent 2		Me	Et	*t*-Bu	F	Cl	Br	CF_3	CN	NH_2	OH	OMe	SO_2NH_2	SO_2Me	Ph	CO_2H	Ac	NO_2	$CONH_2$	NHAc	NMe_2		average difference of melting point
		Substituent 1																					
H	mono	-95.6	-95.0	-57.9	-42.2	-45.2	-30.7	-31.2	-12.8	-6.0	44.9	-37.1	156.0	90.0	70.3	122.0	20.5	5.8	128.0	114.0	2.5		
Me	*ortho*	70.39	14.31	7.58	-20.31	9.32	3.23		2.25	-8.46	-13.90	3.00	0.30	-32.60	-70.50	-18.60		-9.35	17.00	-3.00	-63.75	*o*-Me	-6.28
	meta	47.70	-0.69	16.52	-47.01	-2.58	-7.37		-10.25	-24.85	-32.70	-18.40	-48.00	-55.00	-65.80	-12.70		10.15	-33.50	-48.10		*m*-Me	-19.56
	para	108.85	32.31	5.39	-14.41	52.62	56.93		40.75	49.25	-10.13	5.50	-18.00	-2.00	-22.20	58.00	-39.5	45.95	34.50	37.00		*p*-Me	23.38
Et	*ortho*	14.85	63.61			-38.08	-36.77		-10.85	-41.05	-26.90	110.10	-29.00		-76.43	-46.40	-39.5	-17.95	25.50	-		*o*-Et	-9.92
	meta	-0.15	11.11	-17.52		-9.78				-58.05	-44.90	32.10	-67.00		-97.87	-74.40		-43.65	-36.00	-80.00		*m*-Et	-37.39
	para	32.85	51.71	19.48		-17.28	-12.67		-11.45	0.85	0.10		-47.00	-46.00	-35.80	-10.00	-44.75	-18.05	36.70	-19.50		*p*-Et	-7.55
t-Bu	*ortho*	45.25		85.38						-54.05	-50.50			-20.50	-32.30	-41.50		-8.31		51.00	0.35	*o*-*t*-Bu	-2.52
	meta	54.19	19.61	68.48		17.92					2.10					5.30		-5.35	2.00	-11.50		*m*-*t*-Bu	16.97
	para	43.06	56.61	135.51		69.12	49.73			20.95	55.10	56.20	-16.40	5.00	-17.30	42.00	-2.8	22.66	46.00	59.30		*p*-*t*-Bu	39.05
F	*ortho*	33.05			-4.91	2.22	45.23	-20		-23.05	-28.80	-1.90	2.50	-40.00	3.20	2.20		-11.75	-10.50	-34.50		*o*-F	-5.80
	meta	6.35			-26.92			-50.35	-3.30		-30.90	2.10	-26.50	-48.00	-43.30	1.60		35.25	-	-29.40		*m*-F	-16.41
	para	38.95			18.69	18.42	13.33	-10.55	47.55	4.05	3.10	-7.90	-30.00	-10.00	3.90	61.90	-65.5	20.75	26.60	37.10	27.55	*p*-F	11.00
Cl	*ortho*	59.65	11.71		-0.81	28.22	18.13	25.15	56.25	3.65	-36.90	10.54	32.30	4.20	-38.52	18.40	45.5	26.35	13.80	-27.30		*o*-Cl	13.91
	meta	47.75	40.01	30.58		20.42	9.33	-24.85	53.75	-4.35	-12.40		-8.00	18.00	-54.30	32.20		37.85	5.80	-37.40		*m*-Cl	9.65
	para	102.95	32.51	81.78	15.39	98.32	95.51	-1.85	104.35	76.35	-1.80	19.10	-10.00	8.00	5.10	117.50	-2.1	76.45	52.00	64.40	33.05	*p*-Cl	48.35
Br	*ortho*	68.05	27.51		56.69	32.62	36.73		68.25	36.85	-39.30	39.61	30.00	18.50	-69.50	27.00	30.1	32.75	33.50	-14.80		*o*-Br	24.39
	meta	57.45				23.82	23.83	32.15	52.25	24.45	-11.90		-2.00	13.00	-61.30	34.70	-12.5	48.25	28.50	-26.50	8.55	*m*-Br	14.55
	para	121.75	51.61	76.88	24.79	110.00	118.03		126.75	84.15	18.10	50.51	10.50	15.00	16.70	132.00	30.5	127.25	64.50	54.00	52.55	*p*-Br	67.66
CF_3	*ortho*				-8.96	39.22			30.75	41.45	0.60	23.00	29.00	-15.00	-55.30	-13.00		26.75	35.00	-17.50		*o*-CF_3	8.92
	meta				-39.31	-10.78	31.73		27.25	11.45	-45.80	-27.90	-34.00	-30.00	-43.80	-18.00	68.5	-8.15	-7.00	-10.50		*m*-CF_3	-9.09
	para				0.49	12.22		33.93	50.25	43.95	2.10	28.00	28.00	11.00	1.20	98.00	8.5	37.25	59.50	38.40	68.35	*p*-CF3	32.57
CN	*ortho*	85.05	71.41			88.72	86.23	49.15	153.60	56.95	53.10	96.10	4.00	14.00	-31.30	68.00	28.5	109.25	45.00	85.50		*o*-CN	62.54
	meta	72.55			26.14	86.22	70.23	45.65	174.75	58.95	37.90	60.10	-3.00	15.00	-21.30	101.00	78	110.85	96.00	17.00	24.55	*m*-CN	58.37
	para	123.55	70.81		76.99	136.82	144.73	68.65	236.75	92.15	68.10	99.10	17.20	52.80	17.70	98.00	38.5	141.75	99.00	92.50	72.55	*p*-CN	91.98
NH_2	*ortho*	81.14	48.01	-2.12	13.19	42.92	61.63	66.65	63.75	108.95	128.60	43.30	1.00	-3.00	-21.17	22.60	-0.5	65.25	-17.50	19.50		*o*-NH_2	38.01
	meta	64.75	31.01			34.92	49.23	36.65	65.75	71.45	77.60	36.10	-15.80	-17.00	-38.80	57.70	78	106.25	-10.50	-26.00		*m*-NH_2	35.37
	para	138.85	89.91	72.88	40.29	115.62	108.93	69.15	98.95	146.25	141.10	94.90	10.10	48.00	-19.30	66.20	84.5	141.95	55.00	52.50	50.55	*p*-NH_2	80.32
OH	*ortho*	126.55	113.01	52.28	58.29	53.22	36.33	76.65	110.75	179.45	59.70	65.40	-15.00	-2.50	-12.85	36.60	-18	39.15	12.00	95.00	42.05	*o*-OH	55.40
	meta	107.75	95.01	104.88	56.19	77.72	63.73	30.25	95.55	128.45	64.90		10.00	-6.00	5.00	79.30	73.5	89.25	42.50	34.50	83.55	*m*-OH	65.05
	para	130.32	140.01	157.88	90.19	88.32	93.73	78.15	125.75	191.95	128.10	91.10	22.00	6.50	97.70	91.00	87.7	108.05	34.00	54.00	74.55	*p*-OH	94.55
OMe	*ortho*	61.45	168.01		3.19	18.66	33.24	17.05	71.75	12.15	-16.60	59.60	15.00	3.50	-41.30	-21.10	13.5	3.65	1.50	-26.50		*o*-MeO	20.93
	meta	40.05	90.01		7.19			-33.85	35.75	4.95		1.80	-26.00	-43.00	17.70	-15.00	39.5	32.25	6.00	-33.00		*m*-MeO	8.29
	para	63.95		76.98	-2.81	27.22	44.14	22.05	74.75	63.75	9.10	93.30	-40.00	32.00	19.70	62.00	18.5	48.25	38.40	13.20	46.05	*p*-MeO	37.40
SO_2NH_2	*ortho*	251.85	222.01		200.69	233.52	216.73	216.15	172.75	162.95	96.10	208.10	98.00		50.20	37.00		187.95		49.00	104.05	*o*-SO_2NH_2	156.69
	meta	203.55	184.01		171.69	193.22	184.73	153.15	165.75	146.15	121.10	167.10	73.00	120.00	60.70	127.00	117.5	162.25	48.00	103.00	172.55	*m*-SO_2NH_2	140.76
	para	233.55	204.01	197.48	168.19	191.22	197.23	215.15	185.95	172.05	133.10	153.10	133.00	154.00	157.70	169.00	157.5	175.25	110.00	105.00	213.55	*p*-SO_2NH_2	171.30
SO_2Me	*ortho*	152.95		127.38	92.19	139.42	139.23	106.15	116.75	92.95	42.60	130.60		138.00	30.70	18.00	82.5	130.25	27.00	33.00	92.55	*o*-SO_2Me	94.01
	meta	130.55			84.19	153.22	133.73	91.15	117.75	78.95	39.10	84.10	54.00	110.00	14.70	114.50	85.5	142.25	49.00	28.50	82.55	*m*-SO_2Me	88.54
	para	183.55	139.01	152.88	122.19	143.22	135.73	132.15	155.55	143.95	51.60	159.10	88.00	171.00	74.70	152.50	108.5	136.75	98.50	74.00	165.55	*p*-SO_2Me	129.42
Ph	*ortho*	95.35	88.88	95.88	115.69	77.00	31.53	46.15	51.75	55.08	12.55	66.10	-35.50	11.00	-14.11	-10.00	35.5	31.25	47.00	7.50		*o*-Ph	42.56
	meta	100.05	67.44		69.19	61.22	39.73	57.65	61.75	37.45	30.40	125.10	-25.00	-5.00	16.60	40.50	15.5	55.25	45.00	35.00		*m*-Ph	45.99
	para	143.65	129.51	110.88	116.39	120.62	117.73	102.65	100.75	56.95	123.10	127.10	72.00	55.00	143.50	106.80	100.5	107.15	95.00	57.20	123.55	*p*-Ph	105.50
CO_2H	*ortho*	198.95	170.61	138.38	166.39	185.62	179.73	140.15	202.75	150.55	113.70	138.00	3.00	50.00	41.70	85.00	94	141.25	-99.50	73.50	69.55	*o*-CO_2H	112.17
	meta	204.85	142.61	185.18	165.79	199.42	187.43	135.15	235.75	185.65	156.40	144.10	93.00	146.50	92.20	226.00	151.5	135.55	-47.00	135.00	150.05	*m*-CO_2H	151.26
	para	275.55	207.01	221.88	226.09	284.72	284.73	251.15	232.75	194.15	168.10	221.10	135.00	184.50	158.50	318.00	187.5	235.25	-48.00	142.50	240.05	*p*-CO_2H	206.03
Ac	*ortho*		76.01			111.22	81.33		61.75	25.95	-42.40	71.10		13.00	-14.30	-7.50	21.5	22.75	-11.50	-37.00		*o*-Ac	26.57
	meta						38.73	120.15	111.25	104.45	49.10	97.10	-18.00	16.00	-34.30	50.00	11.5	75.25	-1.50	15.00	40.55	*m*-Ac	45.02
	para	76.55	70.76	75.58	-2.81	63.62	81.73	60.15	71.75	110.95	63.30	76.10	22.00	39.00	50.70	86.00	92.5	74.25	64.00	55.00	103.05	*p*-Ac	66.71
NO_2	*ortho*	91.95	82.81	55.32	36.19	77.32	69.23	63.65	127.75	76.95	-	46.50	37.70	46.00	-33.30	25.00	8	110.05	48.60	-21.00	-22.45	*o*-NO_2	46.31
	meta	111.45	57.11	58.28	83.19	88.82	84.73	28.75	129.35	117.95	50.10	75.10	12.00	58.00	-9.30	19.30	60.5	85.09	15.30	40.50	57.55	*m*-NO_2	61.19
	para	147.25	82.71	86.29	68.69	127.42	163.73	74.15	160.25	153.65	68.90	91.10	25.00	52.50	42.60	119.00	59.5	165.35	62.00	102.00	161.55	*p*-NO_2	100.68
$CONH_2$	*ortho*	240.55	248.51		159.69	187.02	192.23	194.15	185.75	116.45	95.10	166.60		65.00	104.70	-93.50	96	170.85	94.00	76.00	137.55	*o*-$CONH_2$	135.37
	meta	190.05	187.01	187.88	170.19	179.02	187.23	152.15	236.75	123.45	125.60	171.10	20.00	87.00	102.70	-41.00	106	137.55	152.00	105.50	150.55	*m*-$CONH_2$	136.54
	para	258.05	259.71	231.88	196.79	225.22	223.23	218.65	239.75	188.95	117.10	203.50	82.00	136.50	152.70	-42.00	171.5	184.25	194.30	160.50	205.55	*p*-$CONH_2$	180.41
NHAc	*ortho*	206.55	209.01	222.88	121.69	131.92	129.93	127.65	212.25	139.45	164.10	124.60	7.00	57.00	51.20	65.50	56.5	87.25	62.00	74.70	70.55	*o*-NHAc	116.09
	meta	161.45	129.01	160.38	126.79	121.82	118.23	134.65	143.75	93.95	103.60	118.10	61.00	52.50	78.70	127.00	108.5	148.75	91.50	74.00	84.05	*m*-NHAc	111.89
	para	246.55	189.51	231.18	193.29	223.62	198.73	183.55	219.25	172.45	123.10	164.30	63.00	98.00	100.90	134.50	148.5	210.25	146.50	196.00	129.55	*p*-NHAc	168.64
NMe_2	*ortho*	34.25		60.68							-0.40		-49.50	5.00		-50.00	21.5	-25.75	12.00	-41.00	6.45	*o*-NMe_2	-4.83
	meta						41.73		39.75		41.10		19.00	-5.00		30.50	22.5	54.25	25.00	-27.50	-4.45	*m*-NMe_2	21.53
	para				72.19	80.72	85.73	101.95	87.75	58.95	32.10	85.60	60.00	78.00	55.70	120.50	85	158.25	80.00	18.00	48.55	*p*-NMe_2	77.00

Values in the main table are the difference of melting points: melting points of monosubstituted benzenes were subtracted from melting points of disubstituted benzenes. Average difference of melting points shown in the right column is the mean of the differences of melting points in each row. These average melting points are plotted in Figure 2.

Supplementary Table 5. List of Log*P* of disubstituted benzenes with medicinal chemistry-friendly substituents.

a) The order of Log*P* among the regioisomers.

Substituent 2		Substituent 1: Me	Et	*t*-Bu	F	Cl	Br	CF_3	CN	NH_2	OH	OMe	SO_2NH_2	SO_2Me	Ph	CO_2H	Ac	NO_2	$CONH_2$	NHAc	NMe_2
H	*mono*	2.73	3.15	4.11	2.27	2.84			1.56	0.90	1.48	2.11	0.31		3.76	1.88	1.63	1.85			2.31
Me	*ortho*	3.12	3.53			3.42				1.32	1.96	2.74	0.84			2.32		2.30			2.85
	meta	3.20				3.28				1.41	1.96	2.66	0.85			2.37		2.45	1.18	1.52	
	para	3.15	3.65			3.33				1.39	1.94	2.66	0.82		4.63	2.34	2.10	2.42	1.18		
Et	*ortho*										2.47										
	meta										2.40										
	para									1.96	2.42										
t-Bu	*ortho*																				
	meta																				
	para																				
F	*ortho*				3.38					1.26	1.68					1.77			0.64		
	meta				3.48					1.30	1.93					2.15					
	para				3.38					1.15	1.79	1.72				2.08				1.47	
Cl	*ortho*									1.90	2.19		0.74		4.59	1.98	2.09	2.24		1.28	
	meta									1.88	2.48		1.29		4.71	2.68	2.51	2.46			
	para									1.83	2.40		0.84		4.61	2.65		2.39		2.05	
Br	*ortho*									2.19	2.35					2.20			0.73		
	meta									2.10	2.63					2.87					
	para									2.05	2.65	2.43	1.36			2.86			2.29		
CF_3	*ortho*										2.80							2.64			
	meta									2.39	2.95					2.95	2.63	2.62		2.20	
	para									1.95									1.71		
CN	*ortho*										1.60										
	meta									1.07	1.70					1.48	1.16	1.17	0.52		
	para										1.60		0.23			1.56	1.22	1.19	0.48		
NH_2	*ortho*									0.15	0.62	0.95					1.62	1.83	0.35		
	meta										0.17	0.93						1.37			
	para										0.04	0.95	-0.60	-0.12				1.39	-0.20		
OH	*ortho*											1.32				2.24	1.90	1.79	1.28		
	meta											1.58				1.50	1.39	2.00	0.39		
	para											1.39	0.06			1.58	1.30	1.91	0.33		
OMe	*ortho*															1.59		1.73	0.84	0.98	
	meta													0.86		2.02	1.84	2.16	0.85		
	para												0.47			1.96	1.74	2.03	0.86	1.14	
SO_2NH_2	*ortho*																	0.34			
	meta												-0.55					0.55			
	para																0.20	0.64			0.76
SO_2Me	*ortho*																				
	meta																				
	para															0.67					
Ph	*ortho*																				
	meta																				
	para																				
CO_2H	*ortho*															0.79	0.81	1.46		1.88	
	meta															1.66		1.83			
	para															2.00		1.89		1.31	
Ac	*ortho*																	1.28			
	meta																	1.42			
	para																	1.48			2.10
NO_2	*ortho*																	1.58		1.00	
	meta																	1.49	0.77	1.47	
	para																	1.49	0.82	1.66	2.27
$CONH_2$	*ortho*																		-1.73		
	meta																		-0.21		0.95
	para																			0.01	1.14
NHAc	*ortho*																				
	meta																				
	para																				
NMe_2	*ortho*																				
	meta																				
	para																				

Red and blue highlights indicate cases where the Log*P* value difference exceeds 0.3 among other regioisomers.

b) List of reference sources of Log*P*

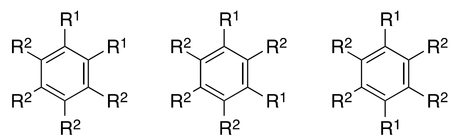
Substituent 2		Me	Et	*t*-Bu	F	Cl	Br	CF_3	CN	NH_2	OH	OMe	SO_2NH_2	SO_2Me	Ph	CO_2H	Ac	NO_2	$CONH_2$	NHAc	NMe_2
		Substituent 1																			
H	*mono*	2.73	3.15	4.11	2.27	2.84			1.56	0.90	1.48	2.11	0.31		3.76	1.88	1.63	1.85			2.31
Me	*ortho*	3.12	3.53			3.42				1.32	1.96	2.74	0.84			2.32		2.30			2.85
	meta	3.20				3.28				1.41	1.96	2.66	0.85			2.37		2.45	1.18	1.52	
	para	3.15	3.65			3.33				1.39	1.94	2.66	0.82		4.63	2.34	2.10	2.42	1.18		
Et	*ortho*										2.47										
	meta										2.40										
	para									1.96	2.42										
t-Bu	*ortho*																				
	meta																				
	para																				
F	*ortho*				3.38					1.26	1.68					1.77			0.64		
	meta				3.48					1.30	1.93					2.15					
	para				3.38					1.15	1.79	1.72				2.08				1.47	
Cl	*ortho*									1.90	2.19		0.74		4.59	1.98	2.09	2.24		1.28	
	meta									1.88	2.48		1.29		4.71	2.68	2.51	2.46			
	para									1.83	2.40		0.84		4.61	2.65		2.39		2.05	
Br	*ortho*									2.19	2.35					2.20			0.73		
	meta									2.10	2.63					2.87					
	para									2.05	2.65	2.43	1.36			2.86			2.29		
CF_3	*ortho*										2.80							2.64			
	meta									2.39	2.95					2.95	2.63	2.62		2.20	
	para									1.95									1.71		
CN	*ortho*										1.60										
	meta									1.07	1.70					1.48	1.16	1.17	0.52		
	para										1.60		0.23			1.56	1.22	1.19	0.48		
NH_2	*ortho*									0.15	0.62	0.95					1.62	1.83	0.35		
	meta										0.17	0.93						1.37			
	para										0.04	0.95	-0.60	-0.12				1.39	-0.20		
OH	*ortho*											1.32				2.24	1.90	1.79	1.28		
	meta											1.58				1.50	1.39	2.00	0.39		
	para											1.39	0.06			1.58	1.30	1.91	0.33		
OMe	*ortho*															1.59		1.73	0.84	0.98	
	meta													0.86		2.02	1.84	2.16	0.85		
	para												0.47			1.96	1.74	2.03	0.86	1.14	
SO_2NH_2	*ortho*																	0.34			
	meta												-0.55					0.55			
	para																0.20	0.64			0.76
SO_2Me	*ortho*																				
	meta																				
	para															0.67					
Ph	*ortho*																				
	meta																				
	para																				
CO_2H	*ortho*															0.79	0.81	1.46		1.88	
	meta															1.66		1.83			
	para															2.00		1.89		1.31	
Ac	*ortho*																	1.28			
	meta																	1.42			
	para																	1.48			2.10
NO_2	*ortho*																	1.58		1.00	
	meta																	1.49	0.77	1.47	
	para																	1.49	0.82	1.66	2.27
$CONH_2$	*ortho*																		-1.73		
	meta																		-0.21		0.95
	para																			0.01	1.14
NHAc	*ortho*																				
	meta																				
	para																				
NMe_2	*ortho*																				
	meta																				
	para																				

Sources

- CRC Hndbook of Chemistry and Physics onDVD 93rd Edition Version 2013, CRC Press , 2013
- A. Leo, *J. Chem. Soc., Perkin Trans. 2*, 1983, 825.
- K. B. Woodburn, W. J. Doucette, and A. W. Andren, *Environ. Sci. Technol.*, 1984, 18, 457
- A. Leo, C. Hansch, and D. Elkins, *Chem. Rev.*, 1971, 71, 526

A blank column in Supplementary Table 5 means the Log*P* was not available in these sources. When different Log*P* values were available, the highest Log*P* value was selected.

Supplementary Table 6. List of melting points of tetrasubstituted and hexasubstituted benzenes with simple substituents.

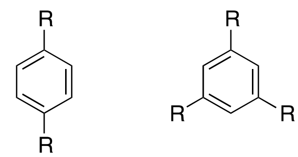


1,2,3,4-R^2 1,2,3,5-R^2 1,2,4,5-R^2

Substituent 2		Substituent 1	H			Me			Cl			Br		
		position of R^1	*ortho*	*meta*	*para*	*ortho*	*meta*	*para*	*ortho*	*meta*	*para*	*ortho*	*meta*	*para*
		symmetry No.	2	2	4	2	2	4	2	2	4	2	2	4
		position of R^2	1,2,3,4	1,2,3,5	1,2,4,5	1,2,3,4	1,2,3,5	1,2,4,5	1,2,3,4	1,2,3,5	1,2,4,5	1,2,3,4	1,2,3,5	1,2,4,5
Substituent 2	Non Flat	Me	-6.3	-23.7	79.3	168.0	168.0	168.0	228	220	223	261	252	253
		Et	11.6	-21.0	13.0	45	36	102	-	45	72	64.5	78.2	115.5
		t-Bu	-	-	156.0	-	-	-	-	-	-	-	-	-
		F	-42.2	-48.0	3.9	-	-	61	87	54	76.5	125	87	-
		Cl	46.9	54.0	139.7	195	190	191	228.4	228.4	228.4	285	282	283
		Br	62.0	98.5	180.0	208	198.5	202	251	-	248	325.7	325.7	325.7
		CF_3	21.0	50.0	74.0	-	-	-	-	-	-	-	-	-
		CN	-	155.0	272.0	229.2	180	209	257	252	307.8	324	-	-
		NH_2	-	-	281.0	144	-	150	235	220.5	225	-	213	255
		OH	161.0	170.0	233.0	111	162.5	233	193	142	236	193	167	250
		OMe	89.5	46.0	103.0	21	-	115	90	102	165	127.5	118	231
		SO_2NH_2	-	-	-	-	-	-	-	-	-	-	-	-
		SO_2Me	-	-	-	-	-	-	-	-	-	-	-	-
	Flat	Ph	191.4	224.0	267.5	-	-	-	-	-	-	-	-	-
		CO_2H	241.0	247.0	283.0	249	270	-	255.3	290	335	280	292	300
		Ac	-	-	-	-	-	-	-	-	-	-	-	-
		NO_2	121.0	127.0	191.0	178.4	183.5	207.5	151	165	234	223	242	320
		$CONH_2$	-	-	300.0	-	-	-	-	-	-	-	-	342
		NHAc	-	245.0	267.5	-	-	-	-	-	-	-	-	-
		NMe_2	-	-	95.0				-	-	-	-	-	-

Red and blue figures indicate the lowest and the highest melting point among the three regioisomers, respectively. For definitions of “flat” and “non-flat” substituents, see Supplementary Table 2. Melting points of tetrasubstituted and hexasubstituted benzenes were taken from reaxys, https://www.reaxys.com, Elsevier.

Supplementary Table 7. Comparison of melting points between 1,4-disubstituted benzenes and 1,3,5-trisubstituted benzenes



1,4-R^2 1,2,3-R^3

	position of R	1,4	1,3,5
	symmetry No.	4	6
Non Flat	Me	13.3	-45.9
Non Flat	Et	-43.3	-66.5
Non Flat	t-Bu	77.6	75.0
Non Flat	F	-23.5	-5.5
Non Flat	Cl	53.1	62.9
Non Flat	Br	87.3	122.1
Non Flat	CF_3	2.8	9.0
Non Flat	CN	224.0	258.0
Non Flat	NH_2	140.3	112.0
Non Flat	OH	173.0	218.3
Non Flat	OMe	56.2	56.0
Non Flat	SO_2NH_2	289.0	347.0
Non Flat	SO_2Me	261.0	353.0
Flat	Ph	213.8	175.0
Flat	CO_2H	440.0	380.0
Flat	Ac	113.0	168.0
Flat	NO_2	171.1	122.9
Flat	$CONH_2$	322.3	-
Flat	NHAc	310.0	242.0
	NMe_2	51.0	44.0

Red figures indicate the lower melting point. For definitions of “flat” and “non-flat” substituents, see Supplementary Table 2. Melting points of trisubstituted benzenes were taken from reaxys, https://www.reaxys.com, Elsevier.

Supplementary Table 8. List of melting points of pharmaceutical compounds bearing disubstituted benzene with non-flat groups used for matched molecular pair analysis

						compound No			melting point		
entry	year	vol	page	R^1	R^2	*o*	*m*	*p*	*o*	*m*	*p*
1	2017	60	9575	CH_2Ar	F	17	16	15	155	138	126
2				CH_2Ar	Cl	20	19	18	144	137	153
3				CH_2Ar	Me	28	27	26	144	127	145
4				CH_2Ar	CF_3	34	33	32	154	136	142
5				CH_2Ar	Br	23	22	21	128	146	157
6				CH_2Ar	MeO	31	30	29	104	106	153
7				CH_2Ar	CN	37	36	35	127	131	118
8	2017	60	8441	$(CH_2)_3NHCOAr$	HO	4b	4a	4c	222	245	222
9	2017	60	6942	CH_2CONHR	Cl	5a	5b	5c	210	183	223
10				CH_2CONHR	MeO	5d	5e	5f	211	139	144
11				CH_2Ar	Cl	28e	28f	24c	178	25	200
12				$CH_2NHCOAr$	MeO	115c	115b	115a	140	130	204
13	2017	60	4963	OSO_2Ar	Me	6	12	22	158	125	157
14				OSO_2Ar	MeO	8	13	23	136	113	185
15				OSO_2Ar	MeO	26	27	35	134	97	140
16				OSO_2Ar	MeO	38	43	51	138	66	107
17				OSO_2Ar	Me	36	42	50	141	78	88
18				OSO_2Ar	MeO	55	56	68	115	57	68
19	2017	60	4424	CH_2Het	F	25h	25g	25f	177	158	262
20				CH_2Het	Br	25k	25j	25i	167	182	194
21				CH_2Het	Cl	25n	25m	25l	168	164	184
22				CH_2Het	CN	25t	25s	25r	125	185	180
23	2016	59	10564	CH_2NHAr	MeO	13	14	12	256	201	192
24	2016	59	7991	CH_2Het	CN	18	21	17	87	200	100
25	2016	59	7223	CH_2Ar	MeO	15e	15d	15c	134	154	116
26	2016	59	867	CH_2Ar	Me	50	51	52	99	87	102
27				CH_2Ar	MeO	53	54	55	121	64	112
28				CH_2Ar	F	56	57	58	100	110	123
29	2015	58	7341	CbCONHAr	Br	1e	1f	1g	182	171	165
30				CbCONHAr	Cl	1b	1c	1d	181	189	167
31	2015	58	4610	CH_2Ar	MeO	10c	10e	10h	156	179	156
32				CH_2Ar	MeO	11c	11e	11h	175	181	152
33	2014	57	10314	CH_2Het	Br	8	9	10	189	174	181
34	2014	57	6030	OCH_2Ar	MeO	6	5	4	110.8	78.7	130.2
35				OCH_2Ar	HO	9	8	7	63.4	110.6	153.7
36				OCH_2Ar	NH_2	18	17	16	100.1	154.8	140
37	2014	57	4239	CH_2Ar	MeO	40d	40e	40f	161.3	139.3	143.6
38	2014	57	1473	$SO_2CH{=}CHAr$	MeO	12a	11a	10a	119	75	95
39				$SO_2CH{=}CHAr$	MeO	12b	11b	10b	139	75	106
40				$SO_2CH{=}CHAr$	MeO	12c	11c	10c	114	102	137
41				$SO_2CH{=}CHAr$	MeO	12d	11d	10d	113	25	113
42				$SO_2CH{=}CHAr$	MeO	12e	11e	10e	119	25	93
43				$SO_2CH{=}CHAr$	MeO	12f	11f	10f	124	25	114
44	2013	56	7243	OCH_2Ar	F	16j	16k	16l	280	152.8	280
45	2013	56	3783	OCH_2CONRR	Me	11p	11o	11m	98	25	136.5
46	2012	55	10909	CH_2NHCOR	F	7	6	1	187.7	168.8	194
47	2012	55	10074	$(CH_2)_7SO_2F$	BnO	20c	20b	20a	25	25	38
48				$(CH_2)_7SO_2F$	HO	21c	21b	21a	25	25	51
49	2012	55	7614	$(CH_2)_2Het$	MeO	5g	5h	5a	98	121	170
50	2012	55	6194	OSO_2Ar	Me	4	5	6	101	25	25
51	2012	55	5760	$(CH_2)_2OAr$	Me	33b	33c	33d	122	111	191
52				$(CH_2)_2OAr$	CF_3	33e	33f	33g	91	92	181
53				$(CH_2)_2OAr$	F	33h	33i	33j	115	116	165
54				$(CH_2)_2OAr$	Cl	33k	33l	33m	120	131	194
55				$(CH_2)_2OAr$	Br	33n	33o	33p	120	135	156
56	2011	54	6432	CH_2NHCOR	CF_3O	15	16	17	55	25	64
57				CH_2NHCOR	CF_3O	44	45	ref.8 49	134	104	102
58				$(CH_2)_2NHCOR$	F	56	57	58	52	25	25
59				$(CH_2)_2NHCOR$	F	60	61	62	133	132	133
60	2010	53	8619	$CH(NHCOAr)CH_2CO_2H$	F	4A1	4A2	4A3	190.4	194.8	193.1

61				$CH(NHCOAr)CH_2CO_2H$	Cl	4A4	4A5	4A6	213.9	156.1	222.3
62				$CH(NHCOAr)CH_2CO_2H$	MeO	4A7	4A8	4A9	182	145	198.9
63				$CH(NHCOAr)CH_2CO_2H$	Me	4A13	4A14	4A15	190.8	130.1	216.1
64				$CH(NHCOAr)CH_2CO_2H$	F	4A17	4A18	4A19	168.2	168.5	165.3
65	2010	53	6228	CH_2Het	EtO	25	26	27	25	25	64
66				CH_2Het	$F(CH_2)_2O$	28	29	30	25	25	78
67				CH_2Het	$F(CH_2)_3O$	34	35	36	25	25	60
68				CH_2Het	MeO	11	12	13	25	84	94
69				CH_2Het	HO	19	20	21	127	125	149
70	2010	53	3756	CH_2OAr	F	21	10	22	174	152	167
71	2010	53	1288	CH_2NHCOR	F	4	5	6	175	151	145
72				CH_2NHCOR	CF_3O	7	8	9	131	148	135
73	2008	51	7144	CH_2OAr	Me	6	5	4	213	203	207
74				CH_2OAr	CH_2NH_2	3	2	1	170	160	185
75	2008	51	3203	CH_2CO_2R	MeO	6i	6j	6k	149	150	150
76				$(CH_2)_2CO_2R$	MeO	6m	6n	6o	159	164	172
77	2008	51	1764	CH_2OAr	Cl	5k	5l	5m	99.8	99.5	126
78	2007	50	5579	$(CH_2)_2NHAr$	Cl	3	4	5	100	123	100
79				CH_2NHAr	F	13	14	15	134	114	137
80	2007	50	3290	$(CH_2)_2Ar$	MeO	4	3	2	140	127.5	156
81				$(CH_2)_2Ar$	MeO	9	8	7	223	169	204.6
82	2007	50	807	$CH_2OCOHet$	Me	20h	20i	20j	25	25	100
83				$CH_2OCOHet$	F	20e	20f	20g	47	71	127
84	2006	49	1433	CH_2OAr	F	11a	11e	11l	108	121	102
85				CH_2OAr	Cl	11b	11f	11m	86	111	108
86				CH_2OAr	F	14a	14e	14k	92	91	100
87				CH_2OAr	Cl	14b	14f	14l	107	108	110
88	2006	49	947	SO_2Ar	MeO	18	20	22	250	173	232
89	2005	48	7750	$O(CH_2)_2NH(CH_2)_2OAr$	Cl	5	6	7	165	136	162
90				$O(CH_2)_2NH(CH_2)_2OAr$	Me	8	9	10	156	127	146
91	2005	48	7172	$(CH_2)_2NHAr$	F	3c	3d	3e	114	97	92
92				$(CH_2)_2NHAr$	Cl	3f	3g	3h	120	91	112
93				$(CH_2)_2NHAr$	Cl	5i	5j	5k	115	100	106
94	2005	48	1367	OCH_2Ar	CN	53	54	55	226	217	226
95	2005	48	1237	CH_2OCMe_2Ar	MeO	5b	5c	5d	202.5	171.3	200.2
96	2004	47	4570	CH_2OCb	Cl	11aj	11ak	11al	195	220	220
97	2004	47	3546	CH_2OAr	Cl	15	16	17	109	123	149
98	2004	47	1807	CH_2OAr	MeO	21	22	23	210	191	167
99				CH_2OAr	Cl	18	19	20	247	229	205
100	2001	44	3195	CH_2OAr	Me	2	3	9	145	114	123
101	2000	43	4747	CH_2OAr	Me	49	51	62	145	114	123
102	2000	43	4667	OCH_2Ar	Cl	20	19	18	165	149	245
103	2000	43	2946	$(CH_2)_2C(CH_2OH)_2NH_2$	*n*-Octyl	25	26	6	159	98	108
104	1999	42	3412	$(CH_2)_2NHCOR$	HO	33	32	27	179	142	167
105	1999	42	1789	OCH_2CONHR	Me	12b	12c	12d	72	60	70
106				$CH_2NHCOHet$	Me	21c	21d	21e	115	117	116
107	1998	41	2972	OCH_2Ar	HO	9	10	11	173	220	200
108				OCH_2Ar	F	12	13	14	110	105	144
109	1998	41	503	CH_2OAr	F	3	4	5	224	204	199
110	1990	33	1818	$O(CH_2)_4NMe_2$	phenethyl	7c	8a	8b	118	129	171
111				$(CH_2)_2Ar$	Cl	9e	9h	9j	123	94	154
112	1987	30	1348	CH_2OAr	Cl	35	27	25	70.5	150	181
113	1985	28	1436	$(CH_2)_2NHR$	Me	23	24	25	92	165	70
114	1979	22	352	CH_2NRR	Me	5	7	9	148.5	159.5	175
115	1978	21	1073	$OCH_2CH(OH)CH_2Ar$	Cl	11	10	5	200	174	201
116	1977	20	1653	$O(CH_2)_2NHR$	Me	8	9	10	100	168	113
117				$O(CH_2)_2NHR$	Cl	18	19	20	152	172	125
118	1970	13	968	OCH_2Ar	Cl	2	3	4	201	154	190

Red and blue figures indicate the lowest and the highest melting point among the three regioisomers, respectively. Ar, aromatic; Het, nonaromatic heterocycle; Cb, aliphatic carbocycle.

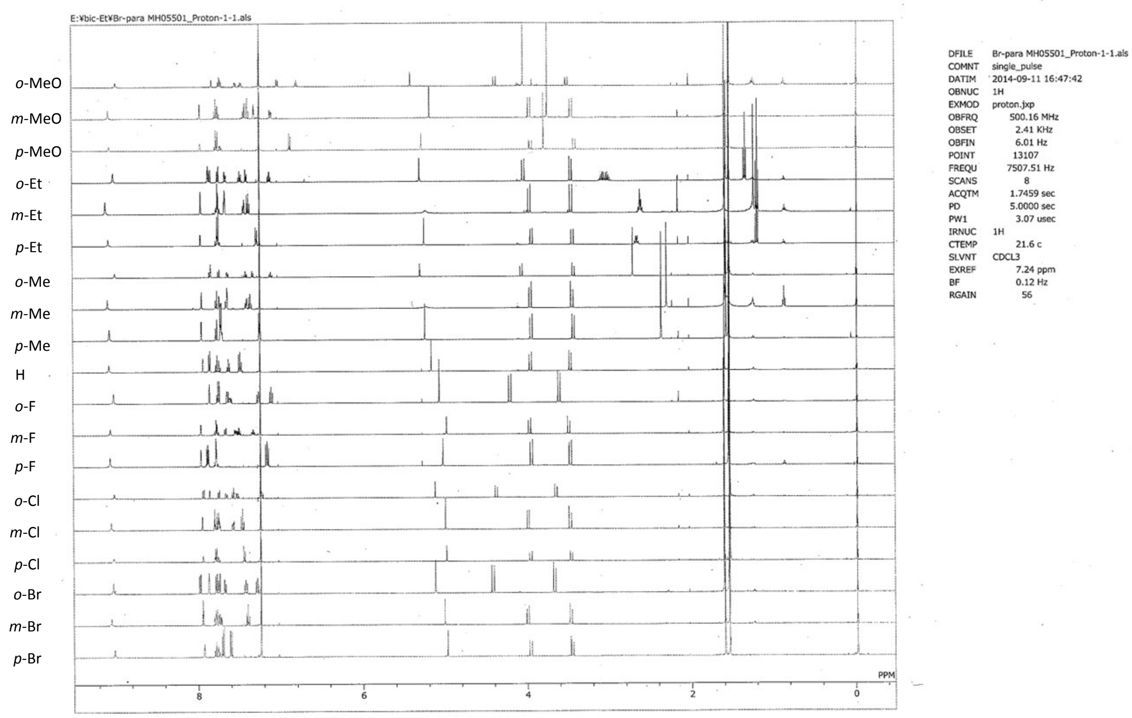
Supplementary Table 9. HLPC conditions for the purity check

comp.	mobile phase 1	%	2	%	UV detection (nm)
1a	MeOH	70	H_2O	30	242
1b	MeOH	70	H_2O	30	230
1c	MeOH	70	H_2O	30	242
2a	MeOH	35	H_2O	65	268
2b	MeOH	20	H_2O	80	268
2c	MeOH	20	H_2O	80	268
3a	CH_3CN	35	H_2O	65	262
3b	CH_3CN	35	H_2O	65	262
3c	CH_3CN	35	H_2O	65	262
4a	MeOH	20	0.02M NH_4HCO_2	80	254
4b	MeOH	20	0.02M NH_4HCO_2	80	254
4c	MeOH	20	0.02M NH_4HCO_2	80	254
5a	CH_3CN	40	H_2O	60	242
5b	CH_3CN	40	H_2O	60	242
5c	CH_3CN	40	H_2O	60	242
6a	CH_3CN	50	0.1% TFA	50	262
6b	CH_3CN	50	0.1% TFA	50	242
6c	CH_3CN	50	0.1% TFA	50	236
7a	CH_3CN	60	0.1% TFA	40	232
7b	CH_3CN	60	0.1% TFA	40	232
7c	CH_3CN	60	0.1% TFA	40	232

comp.	mobile phase				UV detection (nm)
	1	%	2	%	
8a	CH_3CN	70	H_2O	30	320
8b	CH_3CN	70	H_2O	30	320
8c	CH_3CN	70	H_2O	30	320
9a	CH_3CN	70	H_2O	30	270
9b	CH_3CN	70	H_2O	30	280
9c	CH_3CN	70	H_2O	30	240
10a	CH_3CN	50	H_2O	50	271
10b	CH_3CN	50	H_2O	50	271
10c	CH_3CN	50	H_2O	50	271
11a	CH_3CN	60	H_2O	40	272
11b	CH_3CN	60	H_2O	40	272
11c	CH_3CN	60	H_2O	40	272
12a	CH_3CN	50	H_2O	50	271
12b	CH_3CN	50	H_2O	50	275
12c	CH_3CN	50	H_2O	50	271
13a	CH_3CN	50	H_2O	50	271
13b	CH_3CN	50	H_2O	50	271
13c	CH_3CN	50	H_2O	50	271
14a	CH_3CN	50	H_2O	50	275
14b	CH_3CN	50	H_2O	50	275
14c	CH_3CN	50	H_2O	50	275
15a	CH_3CN	50	H_2O	50	275
15b	CH_3CN	50	H_2O	50	275
15c	CH_3CN	50	H_2O	50	268
16	CH_3CN	50	H_2O	50	271

HPLC analyses to check purity were performed on an analytical column (GL Science Inc. Inertsil ODS-4 reversed-phase column, 5 μm, 4.6 mm x 150 mm) at 37 °C. Flow rate was 1 mL/min.

Supplementary Figure 1. ^{1}H NMR charts of bicalutamide analogs **10**-**16**



Experimental Section

Chemistry

General

Melting points were determined on a Yanagimoto hot-stage melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a JEOL JNM-ECA500 (500 MHz) spectrometer. ^{13}C NMR spectra were recorded on JEOL JNM-ECA500 (125 MHz) spectrometer. Chemical shifts are expressed in parts per million relative to tetramethylsilane (TMS) with coupling constants in Hz. Fast atom bombardment mass spectra (FAB-MS) were recorded on a JEOL JMS-HX110 spectrometer with *m*-nitrobenzyl alcohol as a matrix. Electrospray ionization mass spectra (ESI-MS) were recorded on a Bruker micrOTOF II spectrometer. Infrared spectra (FT-IR) were recorded on a JASCO FT/IR-470 PLUS spectrometer. The FT-IR spectra were assigned with the aid of DFT predictions (Gaussian 09, M062X/6-31G*). Flash column chromatography was performed on silica gel 60N Kanto Kagaku (40–50 mm). HPLC analyses to check purity were performed on an analytical column (GL Science Inc. Inertsil ODS-4 reversed-phase column, 5 µm, 4.6 mm x 150 mm, MeOH or CH_3CN / H_2O, 0.02M NH_4HCO_2 or 0.01% TFA, flow rate 1.0 mL/min, 37 °C; Supplementary Table 8). The purity of all compounds evaluated here was confirmed to be >95%.

Preparation of disubstituted benzenes 1-7

2-Bromobenzonitrile (1a)

2-Bromobenzonitrile was recrystallized from EtOH/water to afford white needles.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.69 (dd, 1H, *J* = 8.0, 1.2 Hz), 7.66 (dd, 1H, *J* = 7.5, 2.2 Hz), 7.46 (ddd, 1H, *J* = 7.9, 7.9, 2.0 Hz), 7.42 (ddd, 1H, *J* = 7.7, 7.7, 1.4 Hz). Elem. Anal. Calcd for C_7H_4BrN: C, 46.09; H, 2.22; N, 7.70. Found: C 46.19, H 2.31, N7.58. IR (KBr, cm^{-1}): 2224 (CN, m), 1584 (m), 1466 (m), 1435 (m), 1044 (m), 757 (CH, CH-wag, s). Purity: 100% (HPLC area %).

3-Bromobenzonitrile (1b)

3-Bromobenzonitrile was recrystallized from EtOH/water to afford white needles.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.79 (dd, 1H, *J* = 1.7, 1.7 Hz), 7.74 (br d, 1H, *J* = 8.0 Hz), 7.60 (ddd, 1H, *J* = 8.0, 1.29, 1.29 Hz), 7.36 (dd, 1H, *J* = 8.0 Hz). Elem. Anal. Calcd for C_7H_4BrN: C, 46.09; H, 2.22; N, 7.70. Found: C 45.90, H 2.31, N7.58. IR (KBr, cm^{-1}): 2230 (CN, m), 1559 (m), 1466 (m), 1409 (m), 1189 (m), 1076 (m), 894 (m), 784 (m), 675 (packer, m). Purity: 100% (HPLC area %).

4-Bromobenzonitrile (1c)

4-Bromobenzonitrile was recrystallized from EtOH/water to afford white needles.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.63 (ddd, 2H, J = 8.6, 2.3, 2.3 Hz), 7.52 (ddd, 2H, J = 8.6, 2.3, 2.3 Hz). Elem. Anal. Calcd for C_7H_4BrN: C, 46.09; H, 2.22; N, 7.70. Found: C 45.86, H 2.39, N7.55. IR (KBr, cm^{-1}): 2224 (CN, m), 1584 (m), 1479 (m), 1067 (m), 1013 (m), 824 (CH, CH-wag, s). Purity: 100% (HPLC area %).

1,2-Bis(methanesulfonyl)benzene (2a)

A mixture of 1,2-dithiophenol (345 mL, 3.00 mmol) and K_2CO_3 (445 mg, 3.00 mmol) in CH_2Cl_2 (15 mL) was stirred at 0 ºC. After 5 min, triethylamine (776 mg, 6.00 mmol) and iodomethane (557 µL, 9.00 mmol) were added. After 4.5 h, 2 M HCl (20 mL) was added, and the mixture was extracted with CH_2Cl_2 (20 mL). The organic layer was washed with brine (20 mL), dried over Na_2SO_4, and concentrated. The residue was purified by silica gel column chromatography (AcOEt/hexane) to afford 1,2-bis(methylsulfanyl)benzene (489 mg, 96%) as a yellow oil. To a suspension of 1,2-bis(methylsulfanyl)benzene (488 mg, 2.90 mmol) in water (20 mL) was added oxone (2760 mg, 4.30 mmol). The mixture was stirred at 60 ºC for 8.5 h, then extracted with CH_2Cl_2 (15 mL) 3 times. The organic layer was dried over Na_2SO_4, and concentrated. The crude residue was purified by recrystallization from EtOH/water to afford **2a** as white columnar crystals (408 mg, 61%).

^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.35 (dd, 2H, J = 5.7, 3.4 Hz), 7.87 (dd, 2H, J = 5.7, 3.4 Hz), 3.43 (6H, s). HRMS (ESI-TOF) m/z (M-H)$^-$ calcd. for 232.9937; Found 232.9950, Elem. Anal. Calcd for $C_8H_{10}S_2O_4$: C, 41.01; H, 4.30, Found: C 40.92, H 4.33. IR (KBr, cm^{-1}): 3432 (CH, aliphatic, br), 1294 (SO_2, s), 1152 (SO_2, s), 764 (CH, CH-wag, m). Purity: 99.1% (HPLC area %).

1,3-Bis(methanesulfonyl)benzene (2b)

1,3-Bis(methanesulfonyl)benzene was recrystallized from EtOH/water to afford white plates.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.53 (t, 1H, J =1.7 Hz), 8.24 (dd, 2H, J = 8.0, 1.7 Hz), 7.83 (t, 1H, J = 7.7 Hz), 3.12 (s, 6H). HRMS (ESI-TOF) m/z (M-H)$^-$ calcd. for 232.9937; Found 232.9923, Elem. Anal. Calcd for $C_8H_{10}S_2O_4$: C, 41.01; H, 4.30, Found: C 40.94, H 4.24. IR (KBr, cm^{-1}): 3464 (CH, aliphatic, br), 1302 (SO_2, s), 1135 (SO_2, s), 675 (packer, m). Purity: 99.7% (HPLC area %).

1,4-Bis(methaneslufonyl)benzene (2c)[1]

4-Bromothioanisole (1020 mg, 5.00 mmol), CuI (241 mg, 1.25 mmol), $Cu(OAc)_2$ (1830 mg, 10.0 mmol) were stirred in dry DMSO in a sealed tube at 160 ºC. After 24 h, AcOEt (30 mL) was added, and the precipitate was removed by filtration. Water (150 mL) was added to the filtrate, and the mixture was extracted with ethyl acetate (20 mL). The organic layer was washed with brine (20 mL) twice, dried over Na_2SO_4, and concentrated. The residue was recrystallized from EtOH/water twice to afford 1,4-bis(methylsulfanyl)benzene as white crystals (349 mg, 41%). A suspension of 1,4-bis(methylsulfanyl)benzene (256 mg, 1.51 mmol) in water (20 mL) was treated with oxone (1500 mg, 2.34 mmol) at 60 ºC for 5.5 h, then extracted with CH_2Cl_2 (12 mL) twice. The combined organic layer was dried over Na_2SO_4, and concentrated. The residue was purified by recrystallization from EtOH/water to afford **2c** (248 mg, 70%) as white plates.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.17 (s, 4H), 3.11 (s, 6H). HRMS (ESI-TOF) *m*/*z* $(M-H)^-$ calcd. for 232.9937; Found 232.9954. Elem. Anal. Calcd for $C_8H_{10}S_2O_4$: C, 41.01; H, 4.30, Found: C 40.93, H 4.39. IR (KBr, cm^{-1}): 3466 (CH, aliphatic, br), 1318 (SO_2, s), 1155 (s), 963 (s), 840 (CH, CH-wag, m), 755 (s). Purity: 100% (HPLC area %).

2-Toluenesulfonamide (3a)

2-Toluenesulfonamide was recrystallized from hexane/AcOEt to afford white crystals.

^{1}H NMR (500 MHz, $CDCl_3$) δ:8.02 (d, 1H, *J* = 8.6 Hz), 7.47 (dd, 1H, *J* = 8.6, 7.4 Hz), 7.33 (d, 1H, *J* = 7.4 Hz), 7.32 (dd, 1H, *J* = 7.4, 7.4 Hz), 4.88-4.76 (m, 2H) 2.69 (s, 3H). HRMS (ESI-TOF) *m*/*z* $(M-H)^-$ calcd. for 170.0270; Found 170.0258, Elem. Anal. Calcd for $C_7H_9NSO_2$: C, 49.11; H, 5.30, N, 8.18 Found: 49.12; H, 5.32, N, 8.16. IR (KBr, cm^{-1}): 3382 (NH_2, s), 3261 (NH_2, s) 1315 (SO_2, s), 1152 (SO_2, s), 767 (CH, CH-wag, m). Purity: 99.5% (HPLC area %).

3-Toluenesulfonamide (3b)

NH_3 aq (ca. 28%, 3.0 mL) was added to a stirred solution of 3-toluenesulfonyl chloride (787 mg, 4.13 mmol) in acetone (4.0 mL) at 0 ^{o}C, and then the reaction mixture was stirred for 3.5 h at rt in a sealed tube. To remove excess NH_3, the reaction mixture was stirred for 2 h at rt after the tube had been opened. The reaction mixture was quenched with H_2O and partitioned. The organic layer was washed with H_2O, dried over $MgSO_4$, and concentrated. The resulting residue was purified by silica gel chromatography (hexane/AcOEt = 3/2) to afford **3b** (580 mg, 3.39 mmol, 82%) as a white solid. This sample was recrystallized from AcOEt/hexane to afford as colorless plates.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.78-7.70 (m, 2H), 7.45-7.37 (m, 2H), 4.84-4.67 (m, 2H) 2.44 (s, 3H).. HRMS (ESI-TOF) *m/z* $(M-H)^-$ calcd. for 170.0270; Found 170.0269, Elem. Anal. Calcd for $C_7H_9NSO_2$: C, 49.11; H, 5.30, N, 8.18 Found: 48.91; H, 5.30, N, 8.05. IR (KBr, cm^{-1}): 3323 (NH_2, s), 3238 (NH_2, s) 1330 (SO_2, s), 1159 (SO_2, s), 687 (packer, m). Purity: 99.6% (HPLC area %).

4-Toluenesulfonamide (3c)

4-Toluenesulfonamide was recrystallized from hexane/AcOEt to afford white crystals.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.82 (d, 2H, J = 8.0 Hz), 7.32 (d, 2H, J = 8.0 Hz), 4.85-4.72 (m, 2H) 2.44 (s, 3H) HRMS (ESI-TOF) *m/z* $(M-H)^-$ calcd. for 170.0270; Found 170.0263, Elem. Anal. Calcd for $C_7H_9NSO_2$: C, 49.11; H, 5.30, N, 8.18 Found: 49.11; H, 5.29, N, 7.98. IR (KBr, cm^{-1}): 3327 (NH_2, s), 3241 (NH_2, s) 1327 (SO_2, s), 1151 (SO_2, s), 809 (CH, CH-wag, m). Purity: 99.0% (HPLC area %).

1,2-Phenylenediamine (4a)

1,2-Phenylenediamine was recrystallized from hexane/AcOEt to afford colorless plates. This sample was kept shielded from direct light.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 6.79-6.63 (m, 4H), 3.50-3.26 (m, 4H). HRMS (ESI-TOF) *m/z* $(M+H)^+$ calcd. for 109.0760; Found 109.0734, Elem. Anal. Calcd for $C_6H_6N_2$: C 66.64, H 7.46, N25.90, Found: C 66.88, H 7.57, N25.75. IR (KBr, cm^{-1}): 3385 (NH_2, s), 3364 (NH_2, s) 1631 (m), 1592 (m), 1500 (s), 1458 (m), 1274 (s), 748 (CH, CH-wag, m). Purity: 100% (HPLC area %).

1,3-Phenylenediamine (4b)

1,3-Phenylenediamine was recrystallized from hexane/AcOEt to afford white needles. This sample was kept shielded from direct light.

^{1}HNMR (500 MHz, $CDCl_3$) δ: 6.94 (t, 1H, J = 7.6 Hz), 6.12 (dd, 2H, J = 7.6, 2.2 Hz), 6.03 (t, 1H, J = 2.2 Hz), 3.70-3.43 (m, 4H). HRMS (ESI-TOF) *m/z* $(M+H)^+$ calcd. for 109.0760; Found 109.0737, Elem. Anal. Calcd for $C_6H_6N_2$: C 66.64, H 7.46, N25.90, Found: C 66.72, H 7.58, N25.79. IR (KBr, cm^{-1}): 3395 (NH_2, s), 3326 (NH_2, s), 1603 (br), 1493 (br), 1196 (m), 1159 (m), 841 (m), 781 (m), 687 (packer, m). Purity: 100% (HPLC area %).

1,4-Phenylenediamine (4c)

1,4-Phenylenediamine was recrystallized from AcOEt to afford pale pink plates. This sample was kept shielded from direct light.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 6.57 (s, 4H), 3.41-3.24 (m, 4H). HRMS (ESI-TOF) *m/z* $(M+H)^+$ calcd. for 109.0760; Found 109.0735, Elem. Anal. Calcd for $C_6H_6N_2$: C 66.64, H 7.46, N25.90, Found: C 66.94, H 7.60, N25.91. IR (KBr, cm^{-1}): 3410 (NH_2, s), 3374 (NH_2, s) 1630 (m), 1516 (br), 1263 (s), 833 (CH, CH-wag, m), 717 (br). Purity: 100% (HPLC area %).

2-Bromoacetanilide (5a)

2-Bromoacetanilide was recrystallized from H_2O/EtOH to afford white needles.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.33 (d, J = 8.0 Hz, 1H), 7.60 (br s, 1H), 7.52 (d, J = 8.0 Hz, 1H), 7.31 (br dd, J = 7.7, 7.7 Hz, 1H), 6.97 (dd, J = 7.4, 7.4 Hz, 1H), 2.23 (s, 3H). HRMS (ESI-TOF) *m/z* $(M+H)^+$ calcd. for 213.9862; Found 213.9857. Elem. Anal. Calcd for C_8H_8NBrO: C 44.89, H 3.77, N6.54, Found: C 44.86, H 3.79, N6.54. IR (KBr, cm^{-1}): 3475 (NH, br), 3278 (CH_3, s) 1660 (CO, s), 1532 (m), 1298 (m), 762 (CH, CH-wag, m). Purity: 100% (HPLC area %).

3-Bromoacetanilide (5b)

A mixture of 3-bromoaniline (869 mg, 5.05 mmol), Ac_2O (540 mg, 5.29 mmol), DMAP (61.0 mg, 0.500 mmol) in toluene (10 mL) was stirred at room temperature overnight. Saturated $NaHCO_3$.aq. was added, and the mixture was extracted with AcOEt. The organic layer was dried over Na_2SO_4 and concentrated. A mixture was recrystallized from hexane/AcOEt to afford **5b** (412 mg, 38 %) as colorless yellow needles.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.75 (br s, 1H), 7.40 (br d, J = 8.0 Hz, 1H), 7.21 (br d, J = 8.0 Hz, 1H), 7.16 (dd, J = 8.0, 8.0 Hz, 1H), 2.17 (s, 3H). HRMS (ESI-TOF) *m/z* $(M+H)^+$ calcd. for 213.9862; Found 213.9857, Elem. Anal. Calcd for C_8H_8NBrO: C 44.89, H 3.77, N6.54, Found: C 44.53, H 3.80, N6.53. IR (KBr, cm^{-1}): 3294 (s) 3249 (s), 3181 (m), 3112 (m), 3077 (m), 1686 (s), 1666 (s), 1592 (s), 1543 (s), 1473 (s), 1418 (s), 1311 (m), 1281 (m), 777 (m), 680 (packer, m). Purity: 100% (HPLC area %).

4-Bromoacetanilide (5c)

4-Bromoacetanilide was recrystallized from AcOEt to afford white needles.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.44-7.37 (m, 4H), 7.21 (br s, 1H), 2.02 (s, 3H). HRMS (ESI-TOF) *m/z* $(M+H)^+$ calcd. for 213.9862; Found 213.9859, Elem. Anal. Calcd for C_8H_8NBrO: C 44.89, H 3.77, N6.54, Found: C 44.92, H 3.85, N6.53. 3511 (NH, br), 3294 (s) 3260 (s), 3187 (m), 3115 (m), 1669 (CO, s), 1602 (s), 1586 (s), 1533 (s), 1487 (s), 1394 (s), 1308 (s), 1255 (s), 1096 (s), 1008 (s), 831 (CH, CH-wag, s), 820 (s), 741 (s). Purity: 100% (HPLC area %).

2-Toluic acid (6a)

2-Toluic acid was recrystallized from H_2O/EtOH to afford white needles.

^{1}H NMR (500 MHz, DMSO-d_6) δ: 7.77 (br d, 1H, J = 8.0 Hz), 7.40 (ddd, J = 7.4, 7.4, 1.2 Hz, 1H), 7.26 (d, H, J = 6.9 Hz), 7.24 (dd, H, J = 8.0, 7.5 Hz), 2.45 (s, 3H). HRMS (ESI-TOF) m/z $(M\text{-}H)^-$ calcd. for 135.0441; Found 135.0432. Elem. Anal. Calcd for $C_8H_8O_2$: C 70.57, H 5.92, Found: C 70.18, H 5.83. IR (KBr, cm^{-1}): 2972 (OH, br), 1920 (CO, s), 1408 (m), 1316 (s), 1272 (s), 1088 (m), 916 (m), 471 (CH, CH-wag, m). Purity: 99.9% (HPLC area %).

3-Toluic acid (6b)

3-Toluic acid was recrystallized from H_2O/EtOH to afford faintly yellow needles.

^{1}H NMR (500 MHz, DMSO-d_6) δ: 7.73 (br s, H), 7.70 (br d, 1H, J = 7.5 Hz), 7.39 (br d, 1H, J = 7.5 Hz), 7.34 (dd, 1H, J = 7.4, 7.4 Hz), 2.32 (s, 3H). HRMS (ESI-TOF) m/z $(M\text{-}H)^-$ calcd. for 135.0441; Found 135.0432 Elem. Anal. Calcd for $C_8H_8O_2$: C 70.57, H 5.92, Found: C 70.36, H 6.00. IR (KBr, cm^{-1}): 2925 (OH, br), 1687 (CO, s), 1433 (s), 1416 (s), 1311 (s), 1283 (s), 1215 (s), 931 (m), 747 (CH, CH-wag, m). Purity: 100% (HPLC area %).

4-Toluic acid (6c)

4-Toluic acid was recrystallized from H_2O/EtOH to afford faintly yellow needles.

^{1}H NMR (500 MHz, DMSO-d_6) δ: 7.80 (br d, 2H, J = 8.0 Hz), 7.25 (d, 2H, J = 8.0 Hz), 2.32 (s, 3H). HRMS (ESI-TOF) m/z $(M\text{-}H)^-$ calcd. for 135.0441; Found 135.0427, Elem. Anal. Calcd for $C_8H_8O_2$: C 70.57, H 5.92, Found: C 70.25, H 5.93. IR (KBr, cm^{-1}): 2979 (OH, br), 1680 (CO, s), 1611 (s), 1577 (s), 1418 (s), 1322 (s), 1183 (s), 1118 (s), 961 (m), 949 (m), 840 (m), 755 (CH, CH-wag, m). Purity: 100% (HPLC area %).

2-*tert*-Butylbenzoic acid (7a)[3]

To a stirred solution of 2-fluorobenzoic acid (426 mg, 2.50 mmol) in anhydrous THF (10 mL) at -78 ºC was added dropwise *t*-BuLi (3.20 mL, 5.00 mmol). After 2 h, 1 M HCl (20 mL) was added, and the mixture was warmed to room temperature, and extracted with AcOEt (20 mL) 2 times. The organic layer was washed with brine (20 mL), dried over Na_2SO_4 and concentrated. The crude product was purified by column chromatography (hexane/AcOEt) followed by recrystallization (EtOH/water) to afford **7a** (170 mg, 39%) as white needles.

^{1}H NMR (500 MHz, CD_3OD) δ: 7.49 (br d, 1H, *J* = 8.0 Hz), 7.34 (ddd, 1H, *J* = 7.7, 7.7, 1.7 Hz), 7.28 (dd, 1H, *J* = 7.5, 1.7 Hz), 7.19 (ddd, 1H, *J* = 7.5, 7.5, 1.2 Hz) 1.41 (s, 9H). HRMS (ESI-TOF) *m/z* $(M-H)^-$ calcd. for 177.0910; Found 177.0910, Elem. Anal. Calcd for $C_{11}H_{14}O_2$: C 74.13, H 7.92, Found: C 73.88, H 8.13. IR (KBr, cm^{-1}): 2971 (OH, br), 1690 (CO, s), 1405 (s), 1302 (s), 1264 (s), 1074 (s), 924 (m), 760 (CH, CH-wag, m). Purity: 100% (HPLC area %).

3-*tert*-Butylbenzoic acid (7b)

To a stirred solution of 3-bromo-*tert*-butylbenzene (426 mL, 2.50 mmol) in anhydrous THF (10 mL) at -78 ºC was added dropwise *n*-BuLi (1.6 M, 3.20 mL, 5.00 mmol). After 15 min, an excess of dry ice was added. After 10 min, the mixture was allowed to warm to room temperature, and 1 M HCl (20 mL) was added. The whole was extracted with AcOEt (20 mL). The organic layer was washed with brine (20 mL), dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography (hexane/AcOEt) and recrystallization (EtOH/water) to afford **7b** as white crystals (253 mg, 57%).

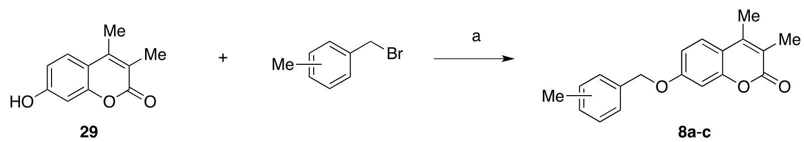
^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.16 (dd, 1H, *J* = 1.7, 1.7 Hz), 7.95 (dd, 1H, *J* = 1.7, 1.2 Hz), 7.93 (br s, 1H), 7.66 (br d, 1H, *J* = 8.0 Hz), 7.41 (dd, 1H, *J* = 8.0, 7.5 Hz), 1.36 (9H, s). HRMS (ESI-TOF) *m/z* $(M-H)^-$ calcd. for 177.0910; Found 177.0921 Elem. Anal. Calcd for $C_{11}H_{14}O_2$: C 74.13, H 7.92, Found: C 74.05, H 7.87. IR (KBr, cm^{-1}): 2967 (OH, br), 1684 (CO, s), 1300 (s), 1259 (s), 953 (m), 764 (CH, CH-wag, m). Purity: 100% 100% (HPLC area %).

4-*tert*-Butylbenzoic acid (7c)

To a stirred solution of 4-bromo-*tert*-butylbenzene (426 mL, 2.50 mmol) in anhydrous THF (10 mL) at -78 ºC was added dropwise *n*-BuLi (1.6 M, 3.20 mL, 5 mmol). After 15 min, an excess of dry ice was added. After 10 min, the mixture was allowed to warm to room temperature, and 1 M HCl (20 mL) was added. The whole was extracted with AcOEt (20 mL) twice. The combined organic layer was washed with brine (20 mL), dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography (hexane/AcOEt) and recrystallization (EtOH/water) to give **7c** (239 mg, 54%) as white plates.

^1H NMR (500 MHz, $CDCl_3$) δ: 8.04 (br d, 2H, *J* = 8.6 Hz), 7.49 (br d, 2H, *J* = 8.6 Hz), 1.35 (s, 9H). HRMS (ESI-TOF) *m*/*z* $(M-H)^-$ calcd. for 177.0910; Found 177.0912 Elem. Anal. Calcd for $C_{11}H_{14}O_2$: C 74.13, H 7.92, Found: C 74.04, H 7.88. IR (KBr, cm^{-1}): 2964 (OH, br), 1686 (CO, s), 1610 (s), 1424 (s), 1318 (s), 1289 (s), 941 (m), 856 (CH, CH-wag, m). Purity: 100% (HPLC area %).

Preparation of MAO inhibitors 8a-c[3]



Scheme S1. Reagents and conditions: a) K_2CO_3, DMF, 100 °C.

General procedure B (GP-B)

7-Hydroxy-3,4-dimethyl-2*H*-chromen-2-one **(29)**[4] (1.0 eq) was dissolved in dry DMF, and α-bromoxylene (1.2 eq), and K_2CO_3 (1.0 eq) were added. The suspension was refluxed at 100 ºC for 12 h. After cooling to room temperature, the precipitate was removed by filtration. Water was added to the filtrate, and the mixture was extracted with AcOEt. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The resulting mixture was purified by recrystallization (MeOH/water) to give the product.

3,4-Dimethyl-7-(2-methylbenzyloxy)-2*H*-chromen-2-one (8a)

This compound was prepared according to GP-B and purified by recrystallization (MeOH/water) to give **8a** as colorless needles (75%).

^{1}H-NMR (DMSO-d_6) δ: 7.67 (d, 1H, J = 7.5 Hz), 7.39 (d, 1H, J = 7.5 Hz), 7.25-7.15 (m, 3H), 7.06 (d, 1H, J = 2.9 Hz), 6.99 (dd, 1H, J = 9.2, 2.9 Hz), 5.16 (s, 2H), 2,33 (s, 3H), 2.30 (s, 3H), 2.04 (s, 3H). HR-MS (ESI-TOF) m/z $(M+H)^+$ calcd. for 295.1329; Found 295.1353, Elem. Anal. Calcd for $C_{19}H_{18}O_3$: C 77.53, H 6.16, Found: C 77.32, H 6.24. Purity: 99.3% (HPLC area %).

3,4-Dimethyl-7-(3-methylbenzyloxy)-2*H*-chromen-2-one (8b)

This compound was prepared according to GP-B and purified by recrystallization (MeOH/water) to give **8b** as colorless needles (67%).

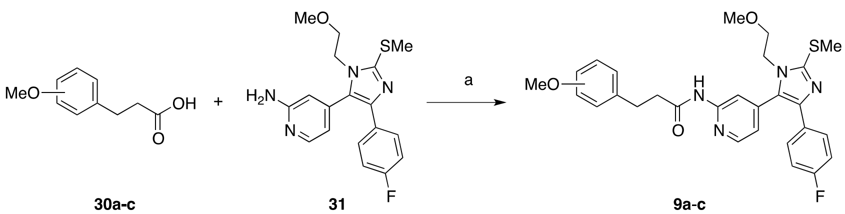
^{1}H-NMR (DMSO-d_6) δ: 7.63 (d, 1H, J = 8.6 Hz), 7.26-7.20 (m, 3H), 7.11 (d, 1H, J = 7.5 Hz), 6.98-6.93 (m, 2H), 5.11 (s, 2H), 2,30 (s, 3H), 2.28 (s, 3H), 2.02 (s, 3H), HRMS (ESI-TOF) m/z $(M+H)^+$ calcd. for 295.1329; Found 295.1327, Elem. Anal. Calcd for $C_{19}H_{18}O_3$: C 77.53, H 6.16, Found: C 77.31, H 6.30. Purity: 99.2% (HPLC area %)

3,4-Dimethyl-7-(4-methylbenzyloxy)-2*H*-chromen-2-one (8c)

This compound was prepared according to GP-B and purified by recrystallization (MeOH/water) to give **8c** as colorless needles (83%).

^{1}H-NMR (DMSO-d_6): δ: 7.64 (d, 1H, J = 9.2 Hz), 7.32 (d, 2H, J = 8.0 Hz), 7.17 (d, 2H, J = 7.5 Hz), 6.98 (d, 1H, J = 2.9 Hz), 6.95 (dd, 1H, J = 9.2, 2.9 Hz), 5.11 (d, 2H), 2.31 (d, 3H), 2.67 (s, 3H), 2.03 (s, 3H), HRMS (ESI-TOF) m/z (M+H)$^+$ calcd. for 295.1329; Found 295.1323, Elem. Anal. Calcd for $C_{19}H_{18}O_3$: C 77.53, H 6.16, Found: C 77.43, H 6.33. Purity: 99.8% (HPLC area %).

Preparation of p38 MAP kinase inhibitors 9a-c



Scheme S2. Reagents and conditions: a) EDCI, DMAP, THF, reflux.

General procedure C (GP-C)

Under an argon atmosphere, a mixture of 4-[5-(4-fluorophenyl)-3-(2-methoxyethyl)-2-methylsulfanyl-3*H*-imidazol-4-yl]pyridin-2-ylamine **(31**) (1.0 eq), (methoxyphenyl)propionic acid (3.0 eq), DMAP (3.0 eq) and EDCI (3.0 eq) in dry THF was stirred under reflux until the reaction was completed. The solvent was removed in vacuo, and AcOEt was added to the residue. The organic layer was washed with H_2O, dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by flash chromatography ($CHCl_3$: MeOH) and recrystallization (EtOH: H_2O).

***N*-{4-[5-(4-Fluorophenyl)-3-(2-methoxyethyl)-2-methylsulfanyl-3*H*-imidazol-4-yl] pyridin-2-yl}-3-(2-methoxyphenyl)propionamide (9a)**

This compound was prepared according to GP-C and purified by recrystallization (EtOH: H_2O) to give a white solid (52%).

^{1}H-NMR ($CDCl_3$) δ: 8.50 (br s, 1H), 8.30 (s, 1H), 8.22 (d, 1H, J = 5.2 Hz), 7.39 (br dd, 2H, J = 8.6, 5.4 Hz), 7.20 (ddd, 1H, J = 8.0, 8.0, 1.7 Hz), 7.16 (d, 1H, J = 7.5 Hz), 6.93-6.84 (m, 5H), 4.09 (t, 2H, J = 6.0 Hz), 3.82 (s, 3H), 3.48 (t, 2H, J = 6.0 Hz), 3.22 (s, 3H), 3.03 (t, 2H, J = 7.5 Hz), 2.71 (s, 3H), 2.69 (t, 2H, J = 7.5 Hz). HRMS (ESI-TOF) m/z (M+H)$^+$ calcd. for 521.2017; Found 521.2037. Purity: 99.7% (HPLC area %).

***N*-{4-[5-(4-Fluorophenyl)-3-(2-methoxyethyl)-2-methylsulfanyl-3*H*-imidazol-4-yl] pyridin-2-yl}-3-(3-**

methoxyphenyl)propionamide (9b)

This compound was prepared according to GP-C and purified by recrystallization (EtOH: H_2O) to give a white solid (62%).

^{1}H-NMR ($CDCl_3$) δ: 8.78 (s, 1H) 8.30 (s, 1H), 8.20 (d, 1H, *J* = 5.2 Hz), 7.39 (br dd, 2H, *J* = 9.2, 5.7 Hz), 7.18 (dd, 1H, *J* = 7.7, 7.7 Hz), 6.93 (dd, 1H, *J* = 5.2, 1.7 Hz), 6.89 (dd, 2H, J = 8,9, 8.9 Hz), 6.78 (d, 1H, *J* = 7.5 Hz), 6.76-6.72 (m, 2H). 4.08 (t, 2H, *J* = 6.0 Hz), 3.75 (s, 3H), 3.49 (t, 2H, *J* = 5.7 Hz), 3.21 (s, 3H), 3.00 (t, 2H, *J* = 7.7 Hz), 2.73-2.68 (m, 5H). HRMS (ESI-TOF) *m*/*z* $(M+H)^+$ calcd. for 521.2017; Found 521.2012, 99.6% (HPLC area %).

***N*-{4-[5-(4-Fluorophenyl)-3-(2-methoxyethyl)-2-methylsulfanyl-3*H*-imidazol-4-yl]- pyridin-2-yl}-3-(4-methoxyphenyl)-propionamide (9c)**

This compound was prepared according to GP-C and purified by recrystallization (EtOH: H_2O) to give a white solid (65%).

^{1}H NMR ($CDCl_3$) δ: 8.63 (br s, 1H), 8.29 (s, 1H), 8.21 (d, 1H, *J* = 5.2 Hz), 7.40 (br dd, 2H, *J* = 9.2, 5.8 Hz), 7.11 (d, 2H, *J* = 8.6 Hz), 6.93 (dd, 1H, *J* = 5.2, 1.7 Hz), 6.90 (dd, 1H, *J* = 8.9, 8.9 Hz), 6.81 (br d, 1H, *J* = 8.6 Hz), 4.08 (t, 2H, *J* = 6.0 Hz), 3.76 (s, 3H), 3.49 (t, 2H, *J* = 6.0 Hz), 3.22 (s, 3H), 2.97 (t, 2H, *J* = 7.4 Hz), 2.71 (s, 3H), 2.67 (t, 2H, *J* = 7.7 Hz), HRMS (ESI-TOF) *m*/*z* $(M+H)^+$ calcd. for 521.2017; Found 521.2036, 99.9% (HPLC area %).

(*R*)-1-(2-Methylacryloyl)pyrrolidine-2-carboxylic acid (18)

A solution of methacryloyl chloride (2.32 g, 22.1 mmol) in acetone (12 mL) was added dropwise to a solution of D-proline (**17**) (2.50 g, 21.7 mmol) in 2 M NaOHaq (12 mL) at 0 °C. During the addition, the pH was monitored and kept within the range of 10.3±0.3 via simultaneous addition of 2 M NaOHaq. After the addition, the reaction mixture was allowed to warm to room temperature and then stirred for 3 h. After evaporation of the acetone, the aqueous phase was acidified to pH 2 with 1 M HCl, and NaCl was added till saturation. The resulting solution was extracted with AcOEt, and the combined organic extract was dried over Na_2SO_4 and concentrated. Purification of the residue by silica gel column chromatography ($CHCl_3$/MeOH=10/3) afforded **18** as a white solid (2.91 g, 73.1%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.39 (s, 1H), 5.27 (s, 1H), 4.65-4.56 (m, 1H), 3.65-3.58 (m, 2H), 2.48-2.44 (m, 1H), 2.20-2.08 (m, 1H), 2.06-2.01 (m, 2H), 1.96-1.86 (m, 1H), 1.99 (s, 3H). FAB-MS *m/z* 184 $(M+H)^+$.

(3*R*,8a*R*)-3-(Bromomethyl)-3-methyltetrahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazine-1,4(3*H*)-dione (19)

To a solution of **18** (3.19 g, 17.4 mmol) in CCl_4 (9 mL) and dry DMF (11.3 mL), a solution of NBS (4.02 g, 22.6 mmol) in dry DMF (14.2 mL) was added dropwise in a light-shielded environment at 0 °C. After the addition, the reaction mixture was stirred at 0 °C for 2 h, allowed to warm to room temperature, and then stirred for an additional 23 h. After the evaporation of CCl_4, brine was added, and the mixture was extracted with AcOEt. The combined organic extract was dried over Na_2SO_4 and concentrated. Purification of the residue by silica gel column chromatography (hexane/AcOEt=1/2) afforded **19** as a white solid (3.91 g, 86%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.56-4.51 (m, 1H), 3.88 (d, 1H, J = 11.4 Hz), 3.75-3.70 (m, 1H), 3.65-3.57 (m, 2H), 2.54-2.47 (m, 1H), 2.15-2.02 (m, 2H), 2.00-1.92 (m, 1H), 1.74 (s, 3H). FAB-MS *m/z* 262 $(M+H)^+$.

(*R*)-3-Bromo-2-hydroxy-2-methylpropanoic acid (20)

A solution of **19** (1.00 g, 3.82 mmol) in 24% aqueous HBr (17 mL) was heated to 100 °C for 90 min, then cooled to room temperature, and NaCl was added till saturation. The mixture was extracted with AcOEt. The organic phase was extracted with saturated $NaHCO_3$ aqueous solution, and the resulting aqueous phase was acidified to pH 1, and extracted with AcOEt. The combined organic extract was dried over Na_2SO_4 and concentrated. Purification of the residue by silica gel column chromatography (hexane/AcOEt=1/1) afforded **20** as a white solid (515 mg, 74%).

^{1}H NMR (500 MHz, DMSO-d_6) δ 3.68 (d, 1H, J = 10.3 Hz), 3.58 (d, 1H, J = 10.3 Hz), 1.41 (s, 3H). FAB-MS

m/z 154 $(M+H)^+$.

(*R*)-3-Bromo-*N*-[4-cyano-3-(trifluoromethyl)phenyl]-2-hydroxy-2-methylpropanamide (21)

Thionyl chloride (0.471 mL, 6.49 mmol) was added to a stirred solution of **20** (500 mg, 2.73 mmol) in CH_3CN (10 mL) at 5 °C. Stirring was continued for 2 h at the same temperature, and then triethylamine (0.691 mL, 4.96 mmol) was added slowly. A solution of 4-amino-(2-trifluoromethyl)benzonitrile (615 mg, 3.30 mmol) in CH_3CN was added to the reaction mixture at 5 °C. Stirring was continued at the same temperature for 3 h and then at room temperature for an additional 20 h. The reaction mixture was diluted with AcOEt and washed with $NaHCO_3$ aqueous solution and brine. The combined organic phase was dried over Na_2SO_4 and concentrated. Purification of the residue by silica gel column chromatography (CH_2Cl_2) afforded **21** as a white solid (702 mg, 73%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.09 (d, 1H, J = 2.3 Hz), 7.96 (dd, 1H, J = 8.6, 2.3 Hz), 7.82 (d, 1H, J = 8.6 Hz), 4.03 (d, 1H, J = 10.6 Hz), 3.60 (d, 1H, J = 10.6 Hz), 1.64 (s, 3H). FAB-MS m/z 352 $(M+H)^+$.

General procedure A (GP-A)

A solution of **21** (1.0 eq) in dry THF was added to a suspension of the sodium salt of thiophenol (prepared from a 60% sodium hydride dispersion in oil and thiophenol in dry THF, 1.3 eq). The mixture was stirred for 20 h, then water was added carefully, and the whole was extracted with AcOEt. The combined AcOEt extract was dried over Na_2SO_4 and concentrated to yield a sulfide **22**-**28** as a brown oil.

To a solution of sulfide **22**-**28** in dry CH_2Cl_2 was added 70% *m*CPBA (2.6 eq). The reaction mixture was stirred overnight at room temperature, then diluted with $Na_2S_2O_3$ aqueous solution, and extracted with AcOEt. The combined organic layer was washed with $NaHCO_3$ aqueous solution, dried over Na_2SO_4, and concentrated in reduced pressure. Purification of the residue by silica gel column chromatography (AcOEt/hexane=1/1) afforded the target compound as a white solid.

(*R*)-*N*-(4-Cyano-3-(trifluoromethyl)phenyl)-2-hydroxy-2-methyl-3-(*o*-tolylsulfonyl)propanamide (10a)

This compound was prepared from compound **21** (100 mg, 0.285 mmol), 2-methylthiophenol (44.6 µL, 0.379 mmol), 60% NaH (15.0 mg, 0.625 mmol), THF (3.5 mL), 70% *m*CPBA (181 mg, 0.735 mmol) and CH_2Cl_2 (3.5 mL) according to GP-A, and purified by recrystallization using a vapor diffusion method (AcOEt/hexane) to give a white solid (16.2 mg, 13%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.01 (s, 1H), 7.87-7.84 (m, 2H), 7.75 (d, 1H, *J* = 8.6 Hz), 7.64 (dd, 1H, *J* = 8.6, 2.3 Hz), 7.42 (ddd, 1H, *J* = 7.4, 7.4, 1.2 Hz), 7.34 (d, 1H, *J* = 7.5 Hz), 7.12 (dd, 1H, *J* = 7.4, 7.4 Hz), 5.31 (s, 1H), 4.07 (d, 1H, *J* = 14.3 Hz), 3.44 (d, 1H, *J* = 14.3 Hz), 2.72 (s, 3H), 1.59 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.4, 141.0, 138.9, 136.8, 135.7, 134.6, 134.0 (q, *J* = 32.2 Hz), 133.2, 129.5, 126.5, 122.1 (q, *J* = 271.8 Hz), 121.9, 117.4 (q, *J* = 4.8 Hz), 115.5, 105.0, 74.3, 60.0, 28.0, 20.3. FAB-MS *m*/*z* 427 $(M+H)^+$. Anal. Calcd for $C_{19}H_{17}F_3N_2O_4S$: C, 53.52; H, 4.02; N, 6.57. Found: C, 53.24; H, 4.12; N, 6.69. Purity: 99.3% (HPLC area %).

(*R*)-*N*-(4-Cyano-3-(trifluoromethyl)phenyl)-2-hydroxy-2-methyl-3-(*m*-tolylsulfonyl)propanamide (10b)

This compound was prepared from compound **21** (100 mg, 0.285 mmol), 3-methylthiophenol (45.1 μL, 0.379 mmol), 60% NaH (15.0 mg, 0.625 mmol), THF (3.5 mL), 70% *m*CPBA (181 mg, 0.735 mmol) and CH_2Cl_2 (3.5 mL) according to GP-A, and purified by recrystallization using a vapor diffusion method (AcOEt/hexane) to give a white solid (30.9 mg, 25%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.10 (s, 1H), 7.97 (d, 1H, *J* = 2.3 Hz), 7.79 (d, 1H, *J* = 8.0 Hz), 7.74 (dd, 1H, *J* = 8.6, 2.3 Hz), 7.68-7.64 (m, 2H), 7.43 (br d, 1H, 7.5 Hz), 7.38 (dd, 2H, 7.7 Hz), 5.25 (br s, 1H), 3.98 (d, 1H, *J* = 14.3 Hz), 3.47 (d, 1H, *J* = 14.3 Hz), 2.32 (s, 3H), 1.59 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.5, 141.1, 134.0, 138.7, 135.7, 135.4, 134.0 (q, *J* = 32.8 Hz), 129.4, 128.1, 125.0, 122.1 (q, *J* = 273.9 Hz), 121.8, 117.3 (q, *J* = 4.8 Hz), 115.4, 104.9, 74.3, 61.2, 27.8, 21.2. FAB-MS *m*/*z* 427 $(M+H)^+$. Anal. Calcd for $C_{19}H_{17}F_3N_2O_4S$: C, 53.52; H, 4.02; N, 6.57. Found: C, 53.41; H, 4.07; N, 6.54. Purity: 99.5% (HPLC area %).

(*R*)-*N*-(4-Cyano-3-(trifluoromethyl)phenyl)-2-hydroxy-2-methyl-3-tosylpropanamide (10c)

This compound was prepared from compound **21** (100 mg, 0.285 mmol), 4-methylthiophenol (44.8 μL, 0.379 mmol), 60% NaH (15.0 mg, 0.625 mmol), THF (3.5 mL), 70% *m*CPBA (181 mg, 0.735 mmol) and CH_2Cl_2 (3.5 mL) according to GP-A, and purified by recrystallization using a vapor diffusion method (AcOEt/hexane) to give a white solid (29.8 mg, 25%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.07 (s, 1H), 7.96 (d, 1H, *J* = 2.3 Hz), 7.78 (d, 1H, *J* = 8.6 Hz), 7.74-7.70 (m, 3H), 7.27-7.24 (m, 2H), 5.25 (s, 1H), 3.96 (d, 1H, *J* = 14.3 Hz), 3.45 (d, 1H, *J* = 14.3 Hz), 2.37 (s, 3H), 1.58 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.6, 146.0, 141.2, 135.9, 135.8, 135.7, 134.1 (q, *J* = 32.2 Hz), 130.1, 128.0, 122.1 (q, *J* = 271.8 Hz), 121.9, 117.4 (q, *J* = 4.8 Hz), 115.4, 105.0, 74.4, 61.3, 27.9, 21.7. FAB-MS *m*/*z* 427 $(M+H)^+$. HRMS (ESI-TOF) *m*/*z* $(M-H)^-$ calcd. for 425.0794; Found 425.0777. Purity: 99.2% (HPLC area

%).

(R)-*N*-(4-Cyano-3-(trifluoromethyl)phenyl)-3-((2-ethylphenyl)sulfonyl)-2-hydroxy-2-methylpropanamide (11a)

This compound was prepared according to GP-A, and purified by recrystallization (2-butanone/hexane) to give colorless needles (68%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.02 (s, 1H), 7.88 (d, 1H, *J* = 1.7 Hz), 7.85 (dd, 1H, *J* = 8.0, 1.2 Hz), 7.76 (d, 1H, *J* = 8.6 Hz), 7.66 (dd, 1H, *J* = 8.6, 2.3 Hz), 7.49 (ddd, 1H, *J* = 7.4, 7.4, 1.2 Hz), 7.41 (d, 1H, *J* = 8.0 Hz), 7.14 (br dd, 1H, *J* = 7.4 Hz), 5.31 (s, 1H), 4.05 (d, 1H, *J* = 14.3 Hz), 3.48 (d, 1H, *J* = 14.3 Hz), 3.13-2.98 (m, 2H), 1.59 (s, 3H), 1.35 (t, 3H, *J* = 7.4 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.5, 145.0, 141.1, 136.5, 135.8, 134.7, 134.0 (q, *J* = 32.2 Hz), 131.4, 129.6, 126.4, 122.1 (q, *J* = 273.0 Hz), 121.9, 117.5 (q, *J* = 4.8 Hz), 115.5, 105.0, 74.4, 61.0, 27.9, 26.1, 15.7. HRMS (ESI-TOF) *m*/*z* $(M-H)^-$ calcd. for 439.0934; Found 439.0960. Purity: 99.3% (HPLC area %).

(*R*)-*N*-(4-Cyano-3-(trifluoromethyl)phenyl)-3-((3-ethylphenyl)sulfonyl)-2-hydroxy-2-methylpropanamide (11b)

This compound was prepared according to GP-A, and purified by recrystallization (*i*-Pr_2O/hexane) to give colorless needles (76%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.12 (s, 1H), 8.01 (d, 1H, *J* = 1.7 Hz), 7.80-7.74 (m, 2H), 7.70-7.66 (m, 2H), 7.46 (br d, 1H, *J* = 8.0 Hz), 7.40 (dd, 1H, *J* = 8.0 Hz), 5.25 (br s, 1H), 3.99 (d, 1H, *J* = 14.3 Hz), 3.48 (d, 1H, *J* = 14.3 Hz), 2.67-2.59 (m, 2H), 1.26 (s, 3H), 1.21 (t, 3H, *J* = 7.4 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.7, 146.3, 138.9, 135.8, 134.3, 134.0 (q, *J* = 33.4 Hz), 129.5, 127.1, 125.3, 122.2 (q, *J* = 273.0 Hz), 122.0, 117.5 (q, *J* = 4.8 Hz), 115.5, 104.9, 76.9, 61.5, 28.6, 27.9, 15.2. HRMS (ESI-TOF) *m*/*z* $(M-H)^-$ calcd. for 439.0934; Found 439.0936. Purity: 99.8% (HPLC area %).

(*R*)-*N*-(4-Cyano-3-(trifluoromethyl)phenyl)-3-((4-ethylphenyl)sulfonyl)-2-hydroxy-2-methylpropanamide (11c)

This compound was prepared according to GP-A, and purified by recrystallization (AcOEt/hexane) to give faint pink needles (72%)

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.07 (s, 1H), 7.96 (d, 1H, *J* = 1.7 Hz), 7.77-7.72 (m, 4H), 7.31 (d, 2H, *J* = 8.6

Hz), 5.25 (s, 1H), 3.94 (d, 1H, *J* = 14.6 Hz), 3.44 (d, 1H, *J* = 14.6 Hz), 2.67 (dq, 2H, *J* = 7.7, 2.3 Hz), 1.58 (s, 3H), 1.19 (t, 3H, *J* = 7.7 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.6, 152.1, 141.2, 136.1, 135.8, 134.1 (q, *J* = 32.2 Hz), 129.0, 128.1, 122.1 (q, *J* = 271.9 Hz), 117.4 (q, *J* = 4.8 Hz), 105.0, 74.4, 61.3, 28.9, 27.9, 15.0. HRMS (ESI-TOF) *m*/*z* $(M-H)^-$ calcd. for 439.0934; Found 439.0957. Purity: 99.5% (HPLC area %).

(*R*)-*N*-(4-Cyano-3-(trifluoromethyl)phenyl)-3-((2-fluorophenyl)sulfonyl)-2-hydroxy-2-methylpropanamide (12a)

This compound was prepared from compound **21** (100 mg, 0.285 mmol), 2-fluorothiophenol (40.4 μL, 0.379 mmol), 60% NaH (15.0 mg, 0.625 mmol), THF (3.5 mL), 70% *m*CPBA (180 mg, 0.728 mmol) and CH_2Cl_2 (3.5 mL) according to GP-A, and purified by recrystallization using a vapor diffusion method (AcOEt/hexane) to give a white solid (21.7 mg, 18%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.03 (s, 1H), 7.88 (d, 1H, *J* = 2.3 Hz), 7.79-7.76 (m, 2H), 7.66 (dd, 1H *J* = 8.6, 1.7 Hz), 7.64-7.60 (m, 1H), 7.30-7.28 (m, 1H), 7.13 (ddd, 1H, *J* = 7.7, 7.7, 1.2 Hz), 5.09 (s, 1H), 4.23 (d, 1H, *J* = 14.9 Hz), 3.63 (d, 1H, *J* = 14.9 Hz), 1.62 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.2, 159.9 (d, *J* = 256.7 Hz), 140.9, 137.1 (d, *J* = 8.4 Hz), 135.7, 134.0 (q, *J* = 32.8 Hz), 129.6, 126.9 (d, *J* = 14.4 Hz), 124.6 (d, *J* = 3.6 Hz), 122.0 (q, *J* = 274.3 Hz), 121.8, 117.6 (d, *J* = 21.6 Hz), 117.3 (q, *J* = 5.2 Hz), 115.3, 105.0, 74.3, 60.8, 27.6. FAB-MS *m*/*z* 431 $(M+H)^+$. Anal. Calcd for $C_{18}H_{14}F_4N_2O_4S$: C, 50.23; H, 3.28; N, 6.51. Found: C, 50.14; H, 3.34; N, 6.53. Purity: 98.8% (HPLC area %).

(*R*)-*N*-(4-Cyano-3-(trifluoromethyl)phenyl)-3-((3-fluorophenyl)sulfonyl)-2-hydroxy-2-methylpropanamide (12b)

This compound was prepared from compound **21** (92.0 mg, 0.262 mmol), 3-fluorothiophenol (37.1 μL, 0.349 mmol), 60% NaH (13.8 mg, 0.575 mmol), THF (3.5 mL), 70% *m*CPBA (126 mg, 0.511 mmol) and CH_2Cl_2 (3.5 mL) according to GP-A, and purified by recrystallization using a vapor diffusion method (AcOEt/hexane) to give a white solid (13.2 mg, 16%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.08 (s, 1H), 7.98 (d, 1H, *J* = 1.7 Hz), 7.82-7.78 (m, 2H), 7.68 (br d, 1H, *J* = 8.6 Hz), 7.56 (ddd, 1H, *J* = 9.7, 2.3, 2.3 Hz), 7.52 (ddd, 1H, *J* = 8.0, 8.0, 5.2 Hz), 7.35 (br ddd, 1H, *J* = 8.0, 8.0, 3.4 Hz), 5.01 (s, 1H), 3.99 (d, 1H, *J* = 14.3 Hz), 3.52 (d, 1H, *J* = 14.3 Hz), 1.63 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.3, 162.5 (d, *J* = 253.0 Hz), 141.0, 141.0, 135.9, 134.2 (q, *J* = 33.6 Hz), 131.6 (d, *J* = 7.2 Hz), 123.8 (d, *J* = 3.6 Hz), 122.1 (q, *J* = 273.8 Hz), 122.1, 121.9, 117.4 (q, *J* = 4.8 Hz), 115.4 (d, *J* = 12.6 Hz), 115.4, 105.3, 74.5, 61.5, 27.8. FAB-MS *m/z* 431 $(M+H)^+$. Anal. Calcd for $C_{18}H_{14}F_4N_2O_4S$: C, 50.23; H, 3.28; N, 6.51. Found: C, 50.09; H, 3.28; N, 6.51. Purity: 98.9% (HPLC area %).

(*R*)-*N*-(4-Cyano-3-(trifluoromethyl)phenyl)-3-((4-fluorophenyl)sulfonyl)-2-hydroxy-2-methylpropanamide (12c)

This compound was prepared from compound **21** (92.0 mg, 0.262 mmol), 4-fluorothiophenol (37.1 μL, 0.349 mmol), 60% NaH (13.8 mg, 0.575 mmol), THF (3.5 mL), 70% *m*CPBA (208 mg, 0.847 mmol) and CH_2Cl_2 (3.5 mL) according to GP-A, and purified by recrystallization using a vapor diffusion method (AcOEt/hexane) to give a white solid (18.0 mg, 16%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.08 (s, 1H), 7.98 (d, 1H, *J* = 1.7 Hz), 7.90 (ddd, 2H, *J* = 9.2, 5.2, 2.3 Hz) 7.81-7.77 (m, 2H), 7.18 (br dd, 2H, *J* = 9.2, 8.0 Hz), 5.05 (s, 1H), 3.97 (d, 1H, *J* = 14.3 Hz), 3.50 (d, 1H, *J* = 14.3 Hz), 1.62 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.4, 166.3 (d, *J* = 259.1 Hz), 141.0, 135.8, 135.0, 134.1 (q, *J* = 33.2 Hz), 130.9 (d, *J* = 9.6 Hz), 122.0 (q, *J* = 274.3 Hz), 121.8, 117.3 (q, *J* = 6.0 Hz), 116.9 (d, *J* = 22.8 Hz), 115.3, 105.1, 74.5, 61.5, 27.7. FAB-MS *m/z* 431 $(M+H)^+$. Anal. Calcd for $C_{18}H_{14}F_4N_2O_4S$: C, 50.23; H, 3.28; N, 6.51. Found: C, 50.23; H, 3.36; N, 6.44. Purity: 99.6% (HPLC area %).

(*R*)-3-((2-Chlorophenyl)sulfonyl)-*N*-(4-cyano-3-(trifluoromethyl)phenyl)-2-hydroxy-2-methylpropanamide (13a)

This compound was prepared from compound **21** (100 mg, 0.285 mmol), 2-chlorothiophenol (43.2 μL, 0.380 mmol), 60% NaH (15.0 mg, 0.624 mmol), THF (3.5 mL), 70% *m*CPBA (211 mg, 0.856 mmol) and CH_2Cl_2 (3.5 mL) according to GP-A, and purified by recrystallization using a vapor diffusion method (AcOEt/hexane) to give a white solid (56.9 mg, 45%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.03 (s, 1H), 7.95 (dd, 1H, *J* = 8.0, 1.8 Hz), 7.88 (d, 1H, *J* = 1.8 Hz), 7.77 (d, 1H, *J* = 8.0 Hz), 7.67 (dd, 1H, *J* = 8.0, 1.5 Hz), 7.60 (dd, 1H, *J* = 8.0, 1.5 Hz), 7.54 (ddd, 1H, *J* = 8.0, 7.5, 1.7 Hz), 7.29-7.25 (m, 1H), 5.15 (s, 1H), 4.40 (d, 1H, *J* = 14.6 Hz), 3.67 (d, 1H, *J* = 14.6 Hz), 1.62 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.4, 141.1, 136.6, 135.8, 135.6, 134.0 (q, *J* = 32.2 Hz), 133.4, 132.3, 130.9, 127.3, 122.1 (q, *J* = 271.8 Hz), 121.9, 117.4 (q, *J* = 4.8 Hz), 115.5, 105.0, 74.50, 59.7, 27.7. FAB-MS *m/z* 447 $(M+H)^+$. Anal. Calcd for $C_{18}H_{14}ClF_3N_2O_4S$: C, 48.39; H, 3.16; N, 6.27. Found: C, 48.38; H, 3.26; N, 6.32. Purity: 98.2% (HPLC area %).

(*R*)-3-((3-Chlorophenyl)sulfonyl)-*N*-(4-cyano-3-(trifluoromethyl)phenyl)-2-hydroxy-2-methylpropanamide (13b)

This compound was prepared from compound **21** (100 mg, 0.285 mmol), 3-chlorothiophenol (43.2 μL, 0.380 mmol), 60% NaH (15.0 mg, 0.624 mmol), THF (3.5 mL), 70% *m*CPBA (211 mg, 0.856 mmol) and CH_2Cl_2 (3.5 mL) according to GP-A, and purified by recrystallization using a vapor diffusion method (AcOEt/hexane) to give a white solid (92.8 mg, 73%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.07 (s, 1H), 7.97 (d, 1H, *J* = 1.7 Hz), 7.82 (dd, 1H, *J* = 1.7, 1.7 Hz), 7.79-7.75 (m, 3H), 7.60-7.58 (m, 1H), 7.48 (dd, 1H, *J* = 8.0, 8.0 Hz), 5.02 (s, 1H), 4.01 (d, 1H, *J* = 14.6 Hz), 3.49 (d, 1H, *J* = 14.6 Hz), 1.62 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.3, 140.9, 140.6, 135.9, 135.9, 134.8, 134.2 (q, *J* = 33.4 Hz), 131.0, 128.1, 126.2, 122.1 (q, *J* = 271.8 Hz), 121.9, 117.4 (q, *J* = 4.8 Hz), 115.4, 105.0, 74.5, 61.5, 27.9. FAB-MS *m/z* 447 $(M+H)^+$. Anal. Calcd for $C_{18}H_{14}ClF_3N_2O_4S$: C, 48.39; H, 3.16; N, 6.27. Found: C, 48.28; H, 3.32; N, 6.26. Purity: 99.4% (HPLC area %).

(*R*)-3-((4-Chlorophenyl)sulfonyl)-*N*-(4-cyano-3-(trifluoromethyl)phenyl)-2-hydroxy-2-methylpropanamide (13c)

This compound was prepared from compound **21** (100 mg, 0.285 mmol), 4-chlorothiophenol (43.2 μL, 0.380 mmol), 60% NaH (15.0 mg, 0.624 mmol), THF (3.5 mL), 70% *m*CPBA (211 mg, 0.856 mmol) and CH_2Cl_2 (3.5 mL) according to GP-A, and purified by recrystallization using a vapor diffusion method (AcOEt/hexane) to give a white solid (95.5 mg, 75%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.04 (s, 1H), 7.96 (d, 1H, *J* = 2.3 Hz), 7.82-7.79 (m, 3H), 7.77 (dd, 1H, *J* = 8.6, 2.0 Hz), 7.46 (br d, 2H, *J* = 8.6 Hz), 5.01 (s, 1H), 7.47-7.45 (m, 2H), 3.98 (d, 1H, *J* = 14.3 Hz), 3.49 (d, 1H, *J* = 14.3 Hz), 1.61 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.3, 141.6, 140.9, 137.2, 135.8, 134.2 (q, *J* = 32.8 Hz), 129.8, 129.4, 122.0 (q, *J* = 274.3 Hz), 121.8, 117.2 (q, *J* = 4.8 Hz), 115.3, 105.1, 74.4, 61.4, 27.8. FAB-MS *m/z* 447 $(M+H)^+$. Anal. Calcd for $C_{18}H_{14}ClF_3N_2O_4S$: C, 48.39; H, 3.16; N, 6.27. Found: C, 48.39; H, 3.34; N, 6.31. Purity: 98.9% (HPLC area %).

(*R*)-3-((2-Bromophenyl)sulfonyl)-*N*-(4-cyano-3-(trifluoromethyl)phenyl)-2-hydroxy-2-methylpropanamide (14a)

This compound was prepared from compound **21** (143 mg, 0.407 mmol), 2-bromothiophenol (65.3 μL, 0.543 mmol), 60% NaH (21.4 mg, 0.892 mmol), THF (3.5 mL), 70% *m*CPBA (301 mg, 1.22 mmol) and CH_2Cl_2

(3.5 mL) according to GP-A, and purified by recrystallization using a vapor diffusion method (AcOEt/hexane) to give a white solid (108 mg, 54%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.04 (s, 1H), 7.99 (dd, 1H, *J* = 8.0, 1.7 Hz), 7.88 (d, 1H, *J* = 1.7 Hz), 7.79 (dd, 1H, *J* = 8.0, 1.2 Hz), 7.76 (d, 1H, *J* = 8.6 Hz), 7.69 (dd, 1H, *J* = 8.6, 2.3 Hz), 7.43 (ddd, 1H, *J* = 8.0, 7.5, 1.7 Hz), 7.30 (ddd, 1H, *J* = 8.0, 7.5, 1.2 Hz), 5.14 (s, 1H), 4.44 (d, 1H, *J* = 14.9 Hz), 3.68 (d, 1H, *J* = 14.9 Hz), 1.62 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.4, 141.1, 138.3, 135.9, 135.8, 135.5, 134.1 (q, *J* = 33.4 Hz), 131.3, 127.9, 122.1 (q, *J* = 271.8 Hz), 122.0, 121.5, 117.4 (q, *J* = 4.8 Hz), 115.5, 105.0, 74.5, 59.3, 27.7. FAB-MS *m/z* 491 $(M+H)^+$. Anal. Calcd for $C_{18}H_{14}BrF_3N_2O_4S$: C, 44.01; H, 2.87; N, 5.70. Found: C, 44.07; H, 2.97; N, 5.73. Purity: 99.8% (HPLC area %).

(*R*)-3-((3-Bromophenyl)sulfonyl)-*N*-(4-cyano-3-(trifluoromethyl)phenyl)-2-hydroxy-2-methylpropanamide (14b)

This compound was prepared from compound **21** (143 mg, 0.407 mmol), 3-bromothiophenol (56.0 μL, 0.543 mmol), 60% NaH (21.4 mg, 0.892 mmol), THF (3.5 mL), 70% *m*CPBA (301 mg, 1.22 mmol) and CH_2Cl_2 (3.5 mL) according to GP-A, and purified by recrystallization using a vapor diffusion method (AcOEt/hexane) to give a white solid (141 mg, 71%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.06 (s, 1H), 7.97-7.96 (m, 2H), 7.82-7.73 (m, 4H), 7.41 (dd, 1H, *J* = 8.0, 8.0 Hz), 5.03 (s, 1H), 4.02 (d, 1H, *J* = 14.3 Hz), 3.50 (d, 1H, *J* = 14.3 Hz), 1.61 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.4, 141.0, 140.8, 137.7, 136.0, 134.3 (q, *J* = 32.8 Hz), 131.2, 131.0, 126.7, 123.5, 122.2 (q, *J* = 273.5 Hz), 122.0, 117.5 (q, *J* = 4.8 Hz), 115.5, 105.3, 74.5, 61.5, 28.0. FAB-MS *m/z* 491 $(M+H)^+$. HRMS (ESI-TOF) *m/z* $(M-H)^-$ calcd. for 490.9707; Found 490.9716. Purity: 97.1% (HPLC area %).

(*R*)-3-((4-Bromophenyl)sulfonyl)-*N*-(4-cyano-3-(trifluoromethyl)phenyl)-2-hydroxy-2-methylpropanamide (14c)

This compound was prepared from compound **21** (143 mg, 0.407 mmol), 4-bromothiophenol (103 mg, 0.543 mmol), 60% NaH (21.4 mg, 0.892 mmol), THF (3.5 mL), 70% *m*CPBA (301 mg, 1.22 mmol) and CH_2Cl_2 (3.5 mL) according to GP-A, and purified by recrystallization using a vapor diffusion method (AcOEt/hexane) to give a white solid (145 mg, 73%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.03 (s, 1H), 7.94 (d, 1H, *J* = 1.7 Hz), 7.81 (d, 1H, *J* = 8.6 Hz), 7.76 (dd, 1H, *J* = 8.6, 2.3 Hz), 7.72 (br d, 2H, *J* = 8.6 Hz), 7.62 (br d, 2H, *J* = 8.6 Hz), 5.00 (s, 1H), 4.00 (d, 1H, *J* = 14.6 Hz), 3.47 (d, 1H, *J* = 14.3 Hz), 1.60 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.7, 141.2, 138.1, 135.9, 134.2 (q, *J* = 33.4 Hz), 132.8, 130.1, 129.6, 122.1 (q, *J* = 273.0 Hz), 121.9, 117.33 (q, *J* = 4.8 Hz), 115.5, 105.0, 74.2, 62.0, 27.9. FAB-MS *m/z* 491 $(M+H)^+$. Anal. Calcd for $C_{18}H_{14}BrF_3N_2O_4S$: C, 44.01; H, 2.87; N, 5.70. Found: C, 43.92; H, 2.90; N, 5.67. Purity: 99.7% (HPLC area %).

(*R*)-*N*-(4-Cyano-3-(trifluoromethyl)phenyl)-2-hydroxy-3-((2-methoxyphenyl)sulfonyl)-2-methylpropanamide (15a)

This compound was prepared from compound **21** (97 mg, 0.276 mmol), 2-methoxythiophenol (45.2 μL, 0,368 mmol), 60% NaH (15 mg, 0.604 mmol), THF (3.5 mL), 70% *m*CPBA (204 mg, 0.828 mmol) and CH_2Cl_2 (3.5 mL) according to GP-A, and purified by recrystallization using a vapor diffusion method (AcOEt/hexane) to give a white solid (39.9 mg, 33%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.05 (s, 1H), 7.85 (d, 1H, *J* = 1.7 Hz), 7.74 (dd, 1H, *J* = 8.0, 1.7 Hz), 7.72 (d, 1H, *J* = 8.6 Hz), 7.57 (dd, 1H, *J* = 8.6, 2.3 Hz), 7.49 (ddd, 1H, J = 8.0, 8.0, 1.7 Hz), 7.04 (d, 1H, *J* = 8.0 Hz), 6.81 (dd, 1H, *J* = 8.0, 7.5 Hz), 5.40 (s, 1H), 4.41 (d, 1H, *J* = 14.6 Hz), 4.06 (s, 3H), 3.54 (d, 1H, *J* = 14.6 Hz), 1.56 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) □ 171.7, 158.1, 141.1, 136.6, 135.7, 133.9 (q, *J* = 32.8 Hz), 129.7, 126.2, 122.2 (q, *J* = 274.3 Hz), 121.9, 120.5, 117.4 (q, *J* = 4.8 Hz), 115.6, 112.8, 104.8, 74.2, 59.3, 56.7, 27.9. FAB-MS *m/z* 443 $(M+H)^+$. Anal. Calcd for $C_{19}H_{17}F_3N_2O_5S$: C, 51.58; H, 3.87; N, 6.33. Found: C, 51.84; H, 3.99; N, 6.43. Purity: 99.5% (HPLC area %).

(*R*)-*N*-(4-Cyano-3-(trifluoromethyl)phenyl)-2-hydroxy-3-((3-methoxyphenyl)sulfonyl)-2-methylpropanamide (15b)

This compound was prepared from compound **21** (97.0 mg, 0.276 mmol), 3-methoxythiophenol (45.2 μL, 0.368 mmol), 60% NaH (15.0 mg, 0.604 mmol), THF (3.5 mL), 70% *m*CPBA (204 mg, 0.828 mmol) and CH_2Cl_2 (3.5 mL) according to GP-A, and purified by recrystallization using a vapor diffusion method (AcOEt/hexane) to give a white solid (54.9 mg, 45%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.22 (s, 1H), 8.02 (d, 1H, *J* = 1.7 Hz), 7.80 (dd, 1H, *J* = 8.0, 1.7 Hz), 7.76 (d, 1H, *J* = 8.0 Hz), 7.45 (d, 1H, *J* = 8.0 Hz), 7.40 (dd, 1H, *J* = 8.0, 7.5 Hz), 7.34 (dd, 1H, J = 2.0 Hz), 7.14-7.11 (m, 1H), 5.15 (s, 1H), 4.03 (d, 1H, *J* = 14.3Hz), 3.77 (s, 3H), 3.52 (d, 1H, *J* = 14.3 Hz), 1.61 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.8, 160.2, 141.4, 140.1, 135.8, 134.0 (q, *J* = 32.8 Hz), 130.7, 122.2 (q, *J* = 274.3 Hz), 122.1, 120.6, 120.0, 117.5 (q, *J* = 4.8 Hz), 115.6, 112.8, 104.8, 74.5, 61.7, 55.8, 27.9. FAB-MS *m/z* 443 $(M+H)^+$. Anal. Calcd for $C_{19}H_{17}F_3N_2O_5S$: C, 51.58; H, 3.87; N, 6.33. Found: C, 51.61; H, 3.95; N, 6.43. Purity: 99.3% (HPLC area %).

(*R*)-*N*-(4-Cyano-3-(trifluoromethyl)phenyl)-2-hydroxy-3-((4-methoxyphenyl)sulfonyl)-2-methylpropanamide (15c)

This compound was prepared from compound **21** (97.0 mg, 0.276 mmol), 4-methoxythiophenol (45.2 µL, 0.368 mmol), 60% NaH (15.0 mg, 0.604 mmol), THF (3.5 mL), 70% *m*CPBA (204 mg, 0.828 mmol) and CH_2Cl_2 (3.5 mL) according to GP-A, and purified by recrystallization using a vapor diffusion method (AcOEt/hexane) to give a white solid (75.5 mg, 62%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.07 (s, 1H), 7.98 (d, 1H, *J* = 2.3 Hz), 7.80-7.76 (m, 3H), 7.72 (dd, 1H, *J* = 8.6, 2.3 Hz), 6.89 (br d, 2H, 8.6 Hz), 5.30 (s, 1H), 3.97 (d, 1H, *J* = 14.3 Hz), 3.81 (s, 3H), 3.44 (d, 1H, *J* = 14.3 Hz), 1.59 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.7, 164.5, 141.3, 135.8, 134.1 (q, *J* = 33.4 Hz), 133.9, 130.4, 130.1, 122.1 (q, *J* = 273.0 Hz), 121.9, 117.4 (q, *J* = 4.8 Hz), 115.5, 115.2, 114.7, 104.9, 74.3, 61.5, 55.8, 28.0. FAB-MS *m/z* 443 $(M+H)^+$. Anal. Calcd for $C_{19}H_{17}F_3N_2O_5S$: C, 51.58; H, 3.87; N, 6.33. Found: C, 51.56; H, 3.91; N, 6.36. Purity: 99.5% (HPLC area %).

(*R*)-*N*-(4-Cyano-3-(trifluoromethyl)phenyl)-2-hydroxy-2-methyl-3-(phenylsulfonyl)propanamide (16)

This compound was prepared from compound **21** (100 mg, 0.285 mmol), thiophenol (38.7 µL, 0.38 mmol), 60% NaH (15.0 mg, 0.624 mmol), THF (3.5 mL), 70% *m*CPBA (186 mg, 0.754 mmol) and CH_2Cl_2 (3.5 mL) according to GP-A, and purified by recrystallization using a vapor diffusion method (AcOEt/hexane) to give a white solid (31.2 mg, 27%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.09 (s, 1H), 7.95 (d, 1H, *J* = 2.3 Hz), 7.88-7.86 (m, 2H), 7.79 (d, 1H, *J* = 8.6 Hz), 7.75 (dd, 1H, *J* = 8.6, 1.7 Hz), 7.64 (ddd, 1H, *J* = 7.5, 7.5, 1.2 Hz), 7.52-7.47 (m, 2H), 5.19 (s, 1H), 3.98 (d, 1H, *J* = 14.9 Hz), 3.50 (d, 1H, *J* = 14.9 Hz), 1.61 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.5, 141.1, 139.0, 135.8, 134.7, 134.2 (q, *J* = 33.4 Hz), 129.6, 128.0, 122.1 (q, *J* = 273.1 Hz), 122.0, 117.5 (q, *J* = 4.8 Hz), 115.4, 105.1, 74.5, 61.3, 27.8. FAB-MS *m/z* 413 $(M+H)^+$. Anal. Calcd for $C_{18}H_{15}F_3N_2O_4S$: C, 52.43; H, 3.67; N, 6.79. Found: C, 52.22; H, 3.69; N, 6.97. Purity: 98.9% (HPLC area %).

Physicochemical properties

X-ray crystallography

Crystal data for **1a**: C_7H_4BrN, white needle crystal, monoclinic, a= 3.8910(2) Å, b= 10.2919(4) Å, c= 16.3686(7) Å, α= 90º, β= 94.963(2)º, γ= 90º, V= 653.036 Å^3. CCDC 1828335

Crystal data for **1b**: C_7H_4BrN, white needle crystal, monoclinic, a= 7.5162(4) Å, b= 3.9503(2) Å, c= 22.2292(13) Å, α= 90º, β= 93.257(3)º, γ= 90º, V= 658.947 Å^3. CCDC 1828336

Crystal data for **1c**: C_7H_4BrN, white needle crystal, monoclinic, a= 9.4437(1) Å, b= 8.5227(1) Å, c= 4.0482(1) Å, α= 90º, β= 91.2214(1)º, γ= 90º, V= 325.749 Å^3. CCDC 1828334

Crystal data for **2a**: $C_8H_{10}S_2O_4$, FW 232.9937, white columnar crystal, orthorhombic, a= 10.1116(2) Å, b= 12.9234(3) Å, c= 7.4954(1) Å, α= 90º, β= 90º, γ= 90º, V= 979.471 Å^3. CCDC 1828329

Crystal data for **2b**: $C_8H_{10}S_2O_4$, FW 232.9937, white plate crystal, monoclinic, a= 17.8295(5) Å, b= 6.9792(2) Å, c= 7.9202(2) Å, α= 90º, β= 92.3238(12)º, γ= 90º, V= 984.745 Å^3. CCDC 1828328

Crystal data for **2c**: $C_8H_{10}S_2O_4$, FW 232.9937, white plate crystal, triclinic, a= 5.3453(1) Å, b= 6.6576(1) Å, c= 6.9904(1) Å, α= 86.1628(1)º, β= 88.9324(1)º, γ= 82.6823(1)º, V= 246.174 Å^3. CCDC 1828330

Crystal data for **3a**: $C_7H_9NSO_2$, FW 170.027, white crystal, tetragonal, a= 18.5210(4) Å, b= 18.5210(4) Å, c= 9.0228(2) Å, α= 90º, β= 90º, γ= 90º, V= 3095.07 Å^3. CCDC 1828325

Crystal data for **3b**: $C_7H_9NSO_2$, FW 170.027, white crystal, monoclinic, a= 6.9213(2) Å, b= 14.3941(4) Å, c= 15.9579(5) Å, α= 90º, β= 90.6969(14)º, γ= 90º, V= 1589.7 Å^3. CCDC 1828327

Crystal data for **3c**: $C_7H_9NSO_2$, FW 170.027, white crystal, monoclinic, a= 6.6299(2) Å, b= 16.2473(4) Å, c= 7.5792(2) Å, α= 90º, β= 91.6792(11)º, γ= 90º, V= 816.065 Å^3. CCDC 1828326

Crystal data for **4a**: $C_6H_6N_2$, FW 109.76, colorless plate crystal, monoclinic, a= 10.1687(11) Å, b= 7.4132(13) Å, c= 7.6623(15) Å, α= 90º, β= 100.344(5)º, γ= 90º, V= 568.217 Å^3. CCDC 1828331

Crystal data for **4b**: $C_6H_6N_2$, FW 109.76, white needle crystal, monoclinic, a= 8.0887(1) Å, b= 11.9923(2) Å, c= 23.8075(4) Å, α= 90º, β= 90.9951(6)º, γ= 90º, V= 23.8075(4) Å^3. CCDC 1828332

Crystal data for **4c**: $C_6H_6N_2$, FW 109.76, pale pink plate crystal, monoclinic a= 8.3017(2) Å, b= 5.8957(1) Å, c= 22.7478(5) Å, α= 90º, β= 93.5648(10)º, γ= 90º, V= 1111.22 Å^3. CCDC 1828333

CCDC 1828325-1828336 contain the supplementary crystallographic data for this paper. These data are provided free of charge by The Cambridge Crystallographic Data Centre.

Crystal density and packing coefficient were derived from X-ray crystallographic analysis.

Physicochemical properties

Differential scanning calorimetry (DSC)

Entropy and enthalpy of melting were recorded on Shimadzu DSC-60. DSC runs were performed within the temperature range of (melting point - 50 °C) to (melting point + 50 °C) at a heating rate of 5 °C/ min.

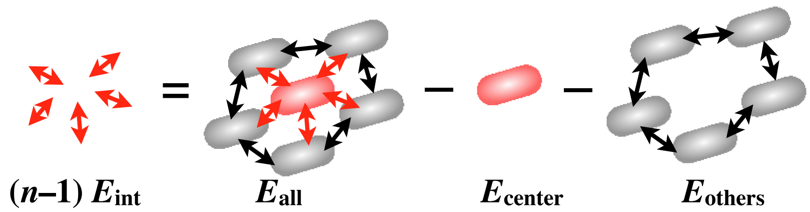
Computational details

Density functional calculations were performed using the Gaussian09 program package.[5] M06-2X density functional[6] and 6-31G* basis sets[7-9] were used for all calculations. IR spectra and dipole moments of disubstituted benzenes were calculated for their optimized structures.

Intermolecular interaction energy (E_{int}): Intermolecular interaction energy (E_{int}) of a molecule in a crystal was estimated according to equation 1:

$$E_{int} = \frac{1}{n-1}(E_{all} - E_{center} - E_{others}) \tag{1}$$

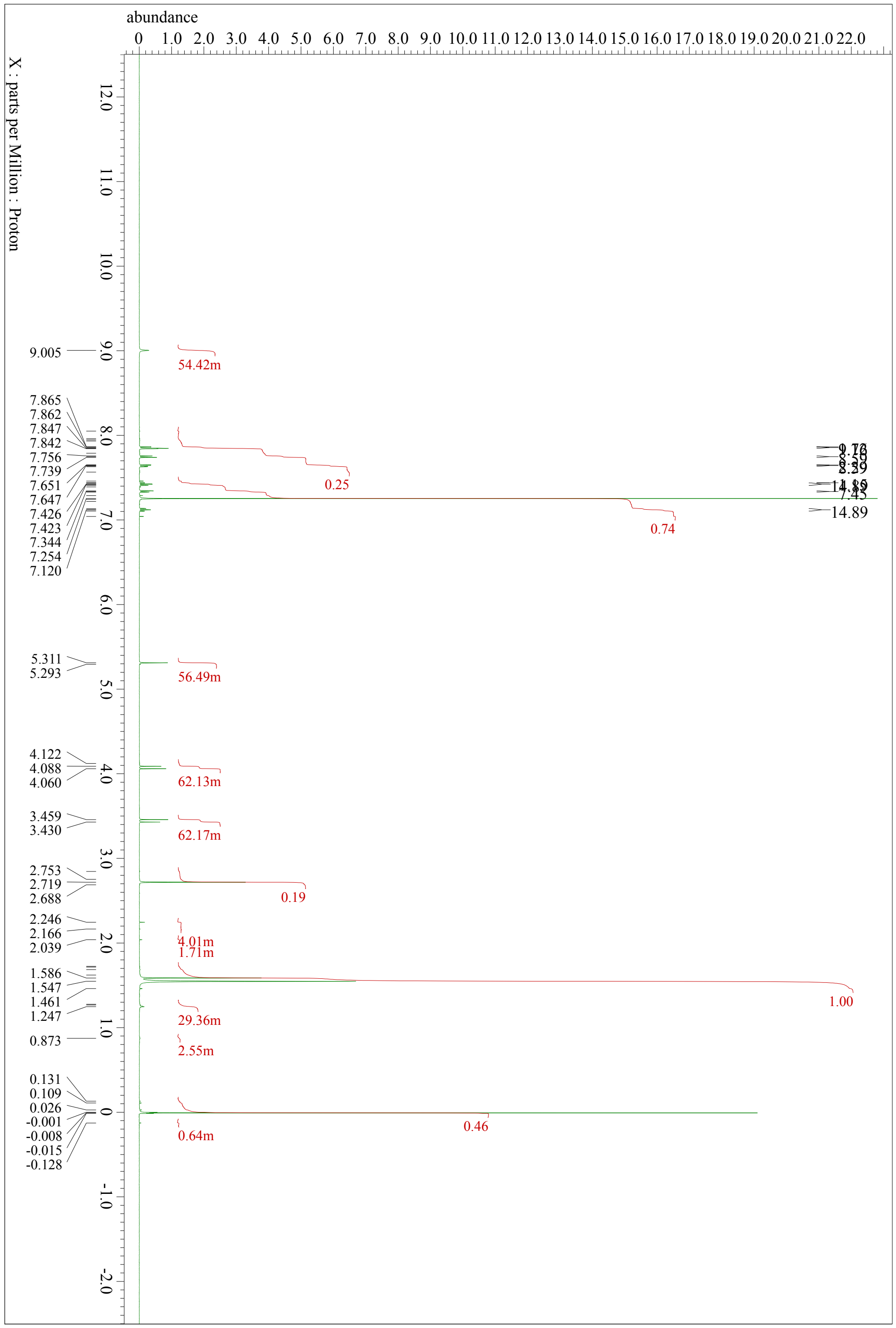
where n is the number of molecules considered, E_{all} is the energy of a central molecule and non-central molecules whose distance from the central molecule is less than 5 Å in the crystal, E_{center} is the energy of the central molecule, and E_{others} is the energy of the non-central molecules (Supplementary Fig. 2). Counterpoise corrections[10,11] were used for calculating E_{all}, E_{center}, and E_{others}. Molecular geometries were taken from the X-ray crystal structures.



Supplementary Figure 2. Schematic illustration of intermolecular interaction energy (E_{int}) of a molecule in a crystal. The arrows indicate interactions between two neighboring molecules.

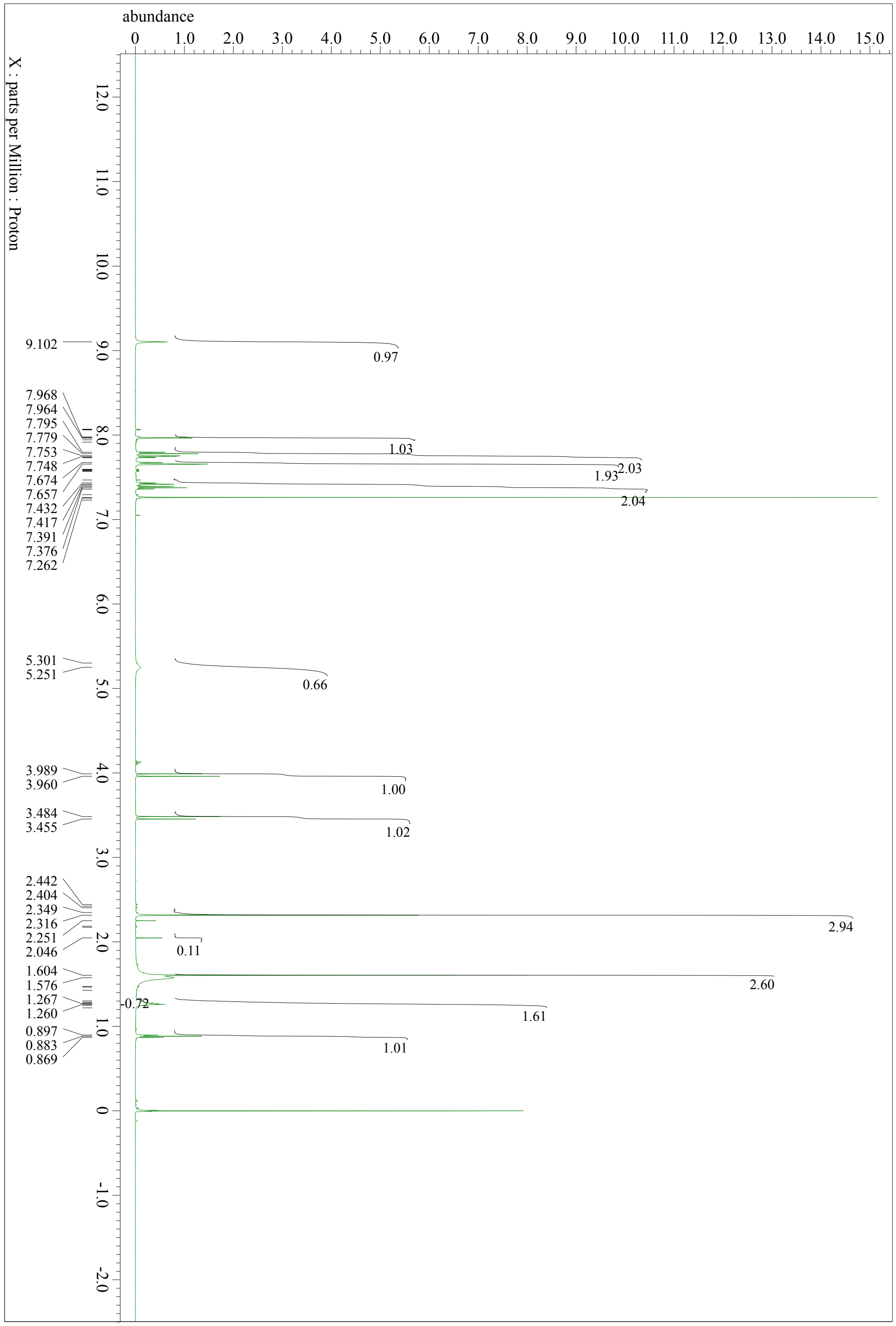
^{1}H NMR spectra

10a



10b

10c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7.964
7.795
7.779
7.753
7.748
7.674
7.657
7.432
7.417
7.391
7.376
7.262
5.301
5.251
3.989
3.960
3.484
3.455
2.442
2.404
2.349
2.316
2.251
2.046
1.604
1.576
1.267
1.260
0.897
0.883
0.869
0.97
1.03
1.93
2.03
2.04
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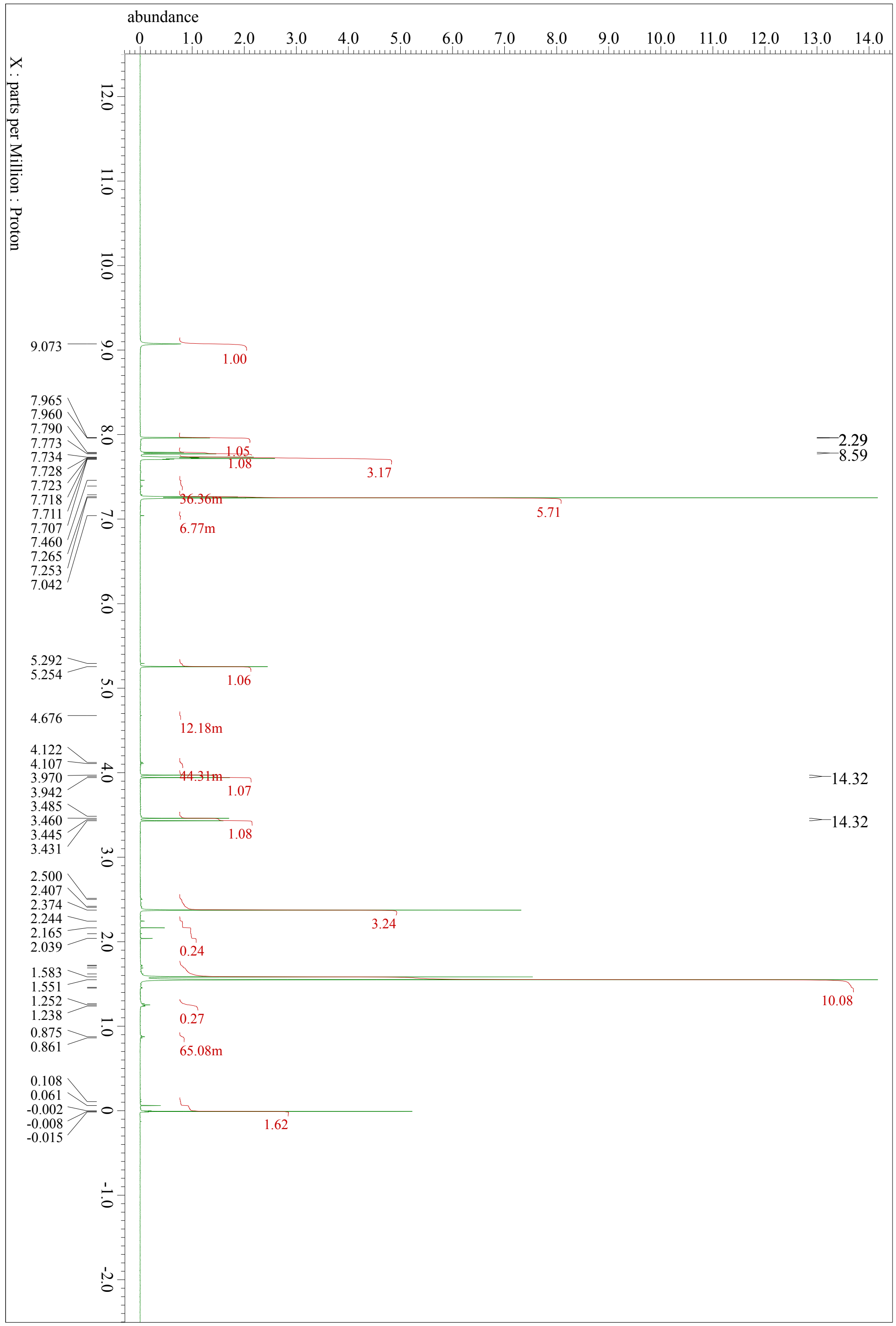
1.02
2.94
0.11
2.60
-0.72
1.61
1.01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7.718
7.711
7.707
7.460
7.265
7.253
7.042
5.292
5.254
4.676
4.122
4.107
3.970
3.942
3.485
3.460
3.445
3.431
2.500
2.407
2.374
2.244
2.165
2.039
1.583
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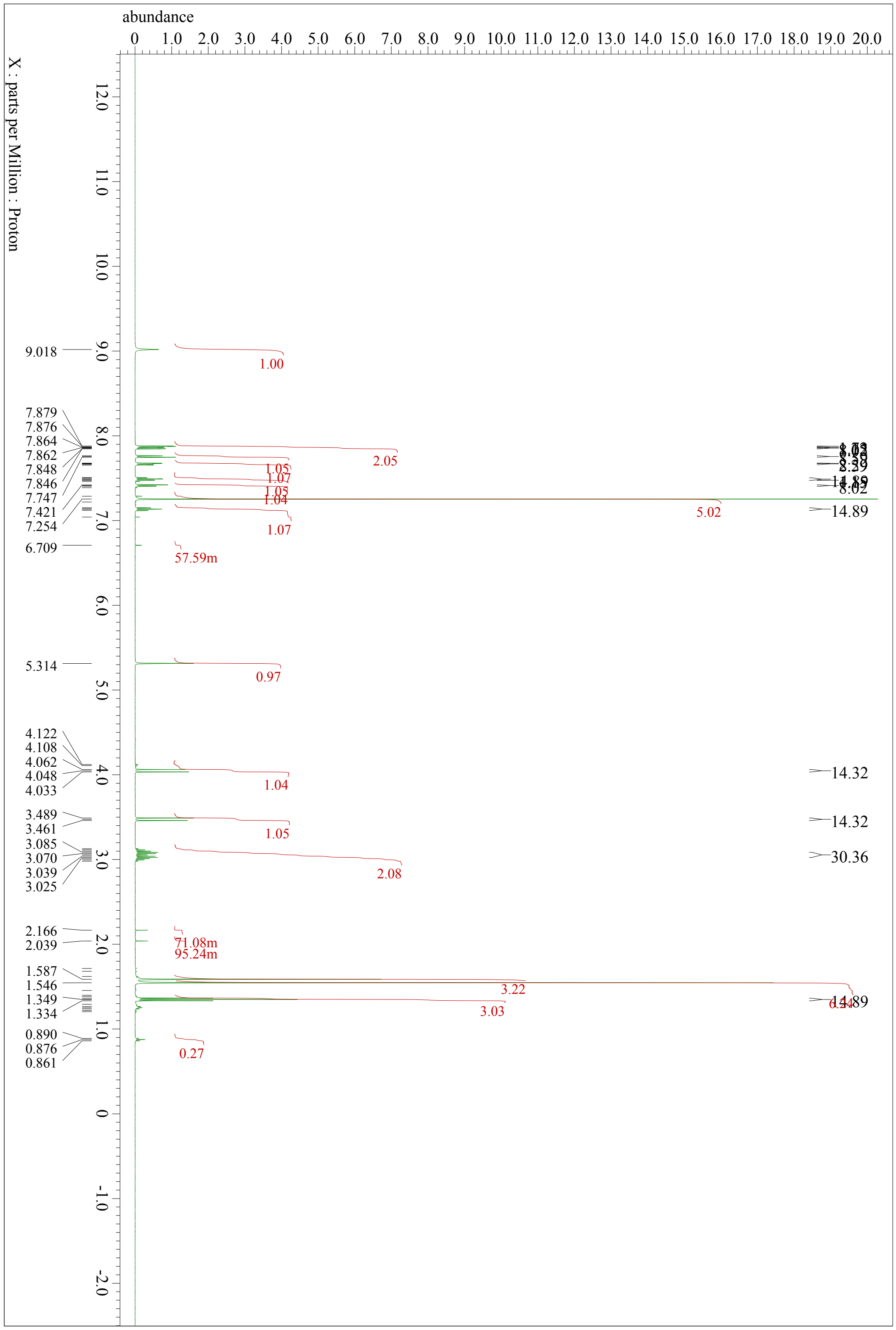
-0.015

11a



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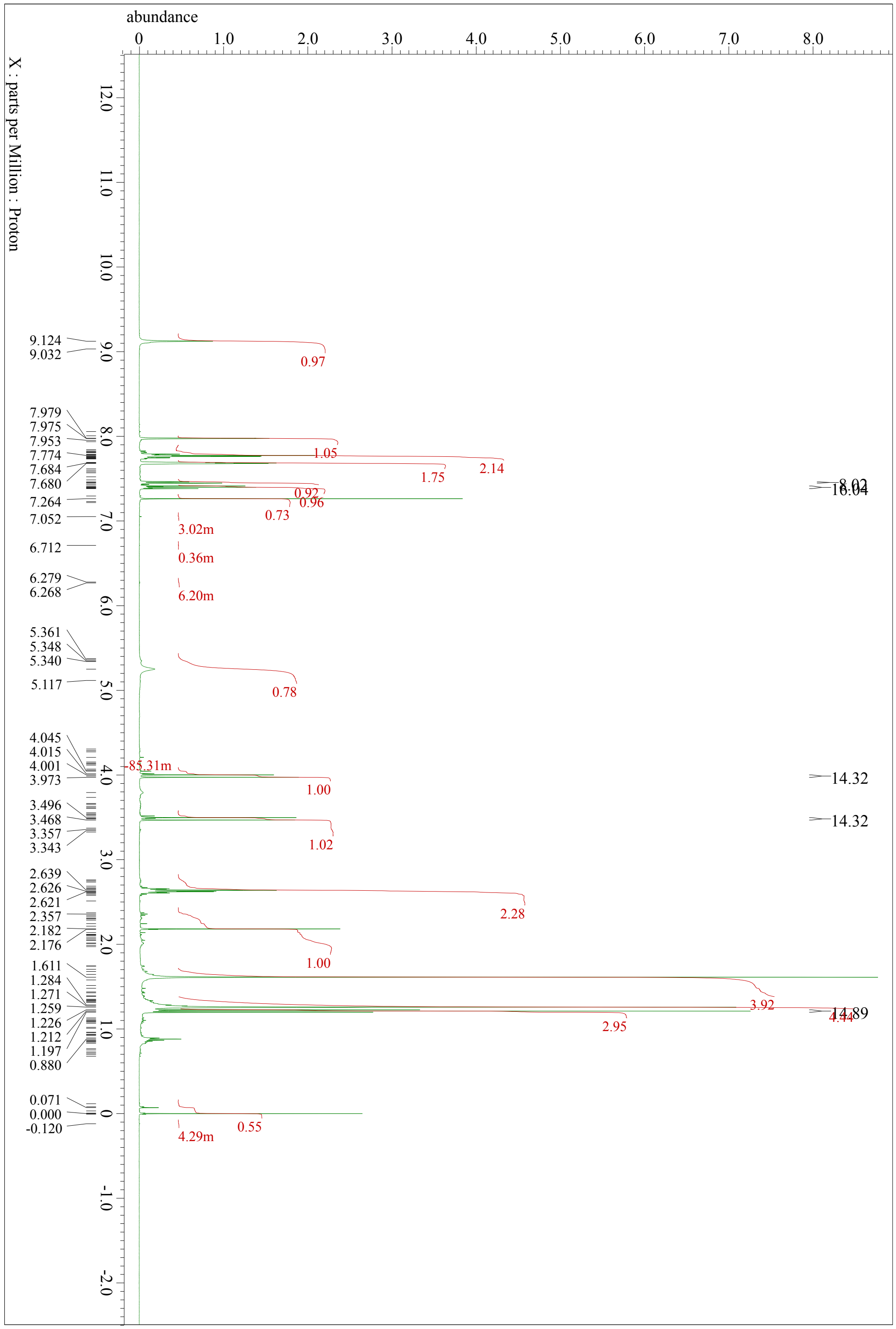
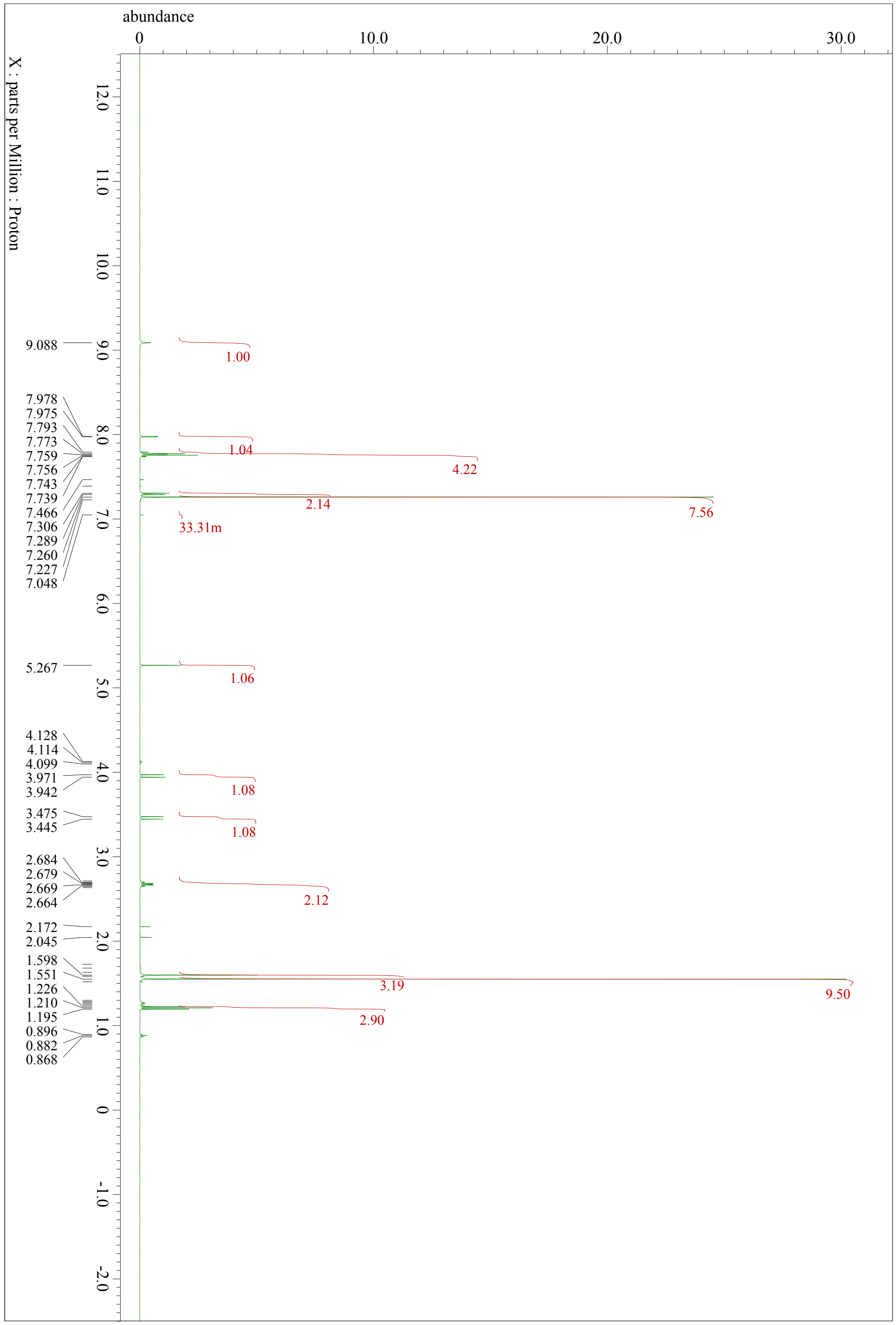


11c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20.0
30.0
X : parts per Million : Proton
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11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
-1.0
-2.0
9.088
7.978
7.975
7.793
7.773
7.759
7.756
7.743
7.739
7.466
7.306
7.289
7.260
7.227
7.048
5.267
4.128
4.114
4.099
3.971
3.942
3.475
3.445
2.684
2.679
2.669
2.664
2.172
2.045
1.598
1.551
1.226
1.210
1.195
0.896
0.882
0.868
1.00
1.04
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7.56
33.31m
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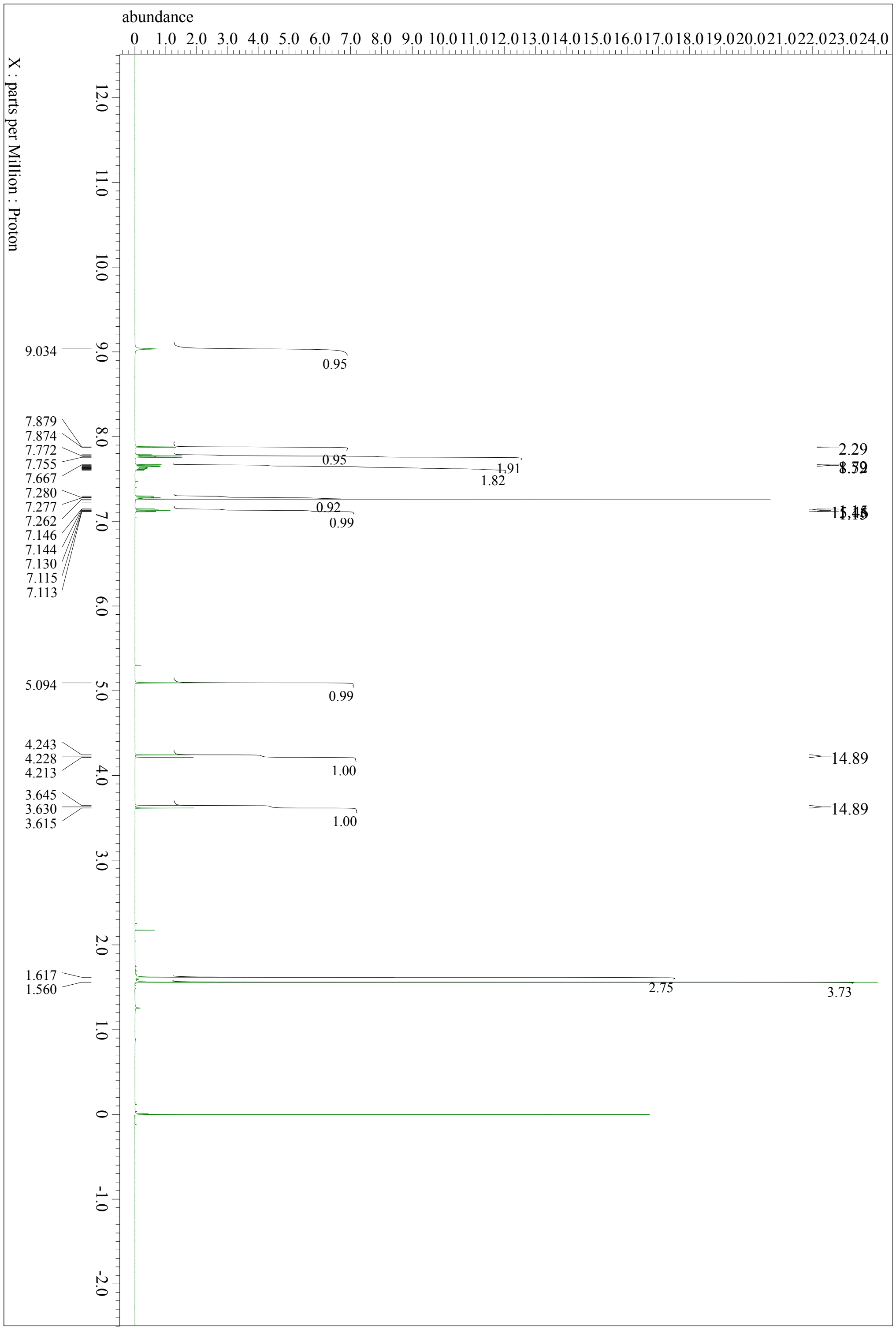
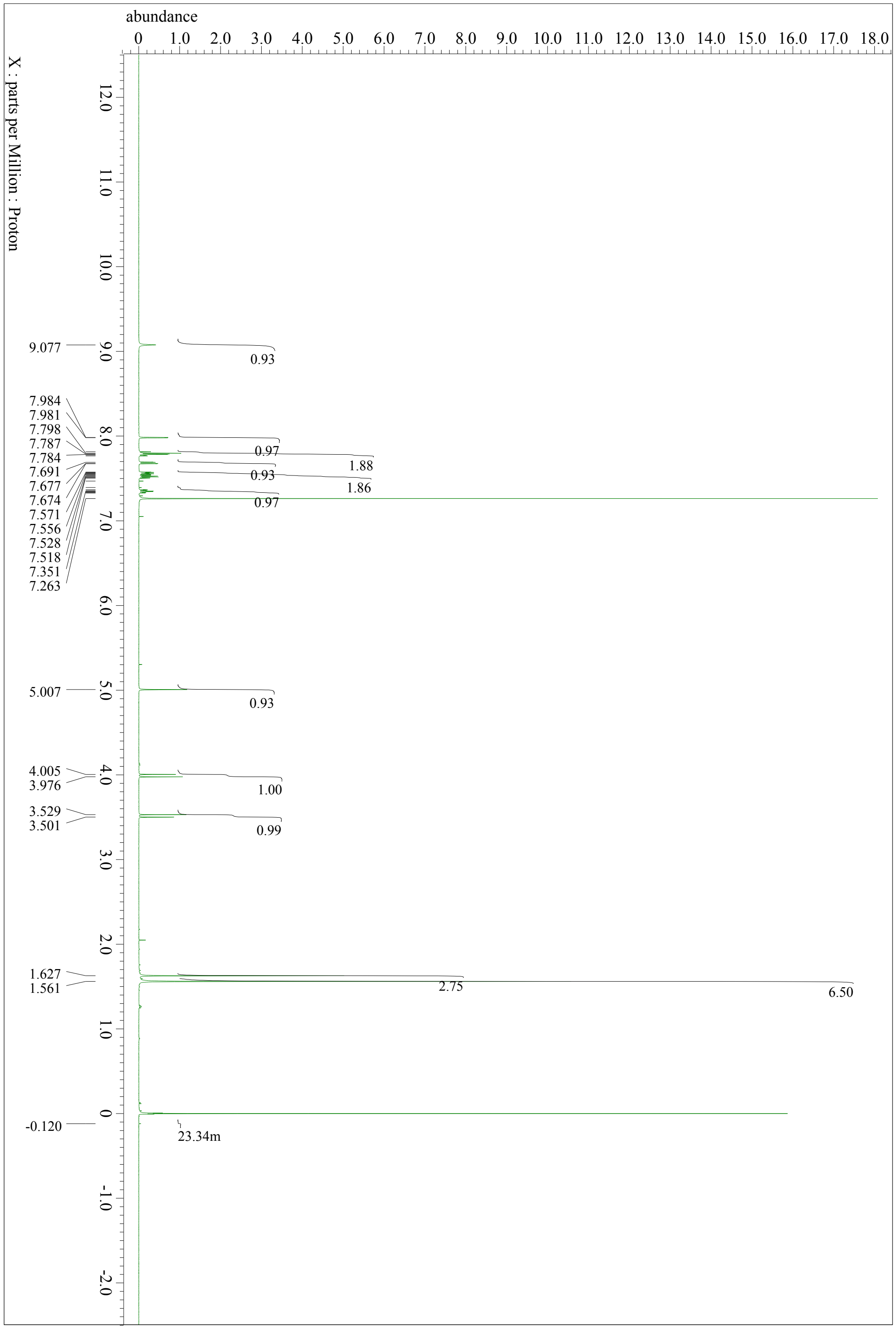
2.12
3.19
9.50
2.90

12a



12b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7.674
7.571
7.556
7.528
7.518
7.351
7.263
5.007
4.005
3.976
3.529
3.501
1.627
1.561
-0.120
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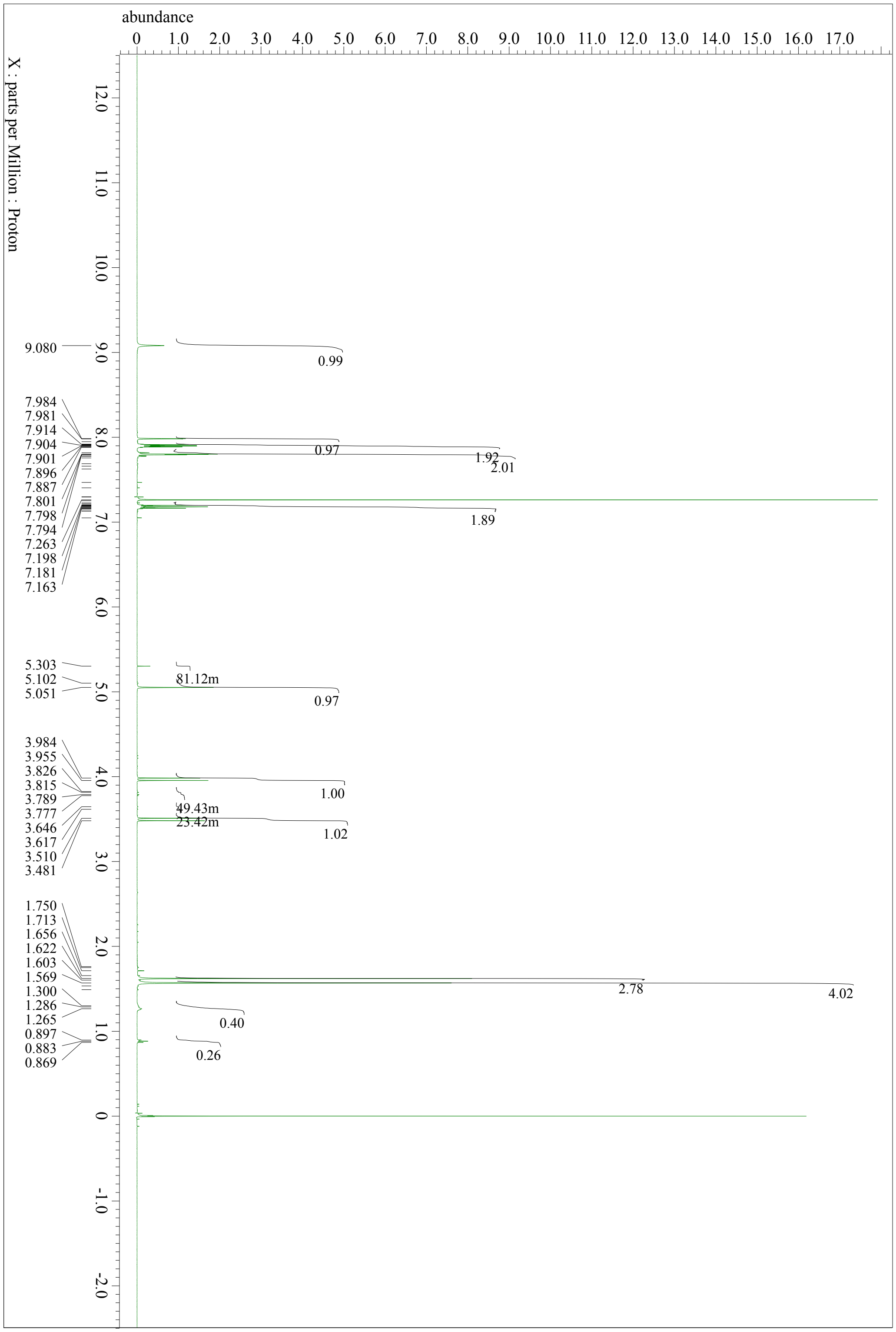
6.50
23.34m

12c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X : parts per Million : Proton
12.0 11.0 10.0 9.0 8.0 7.0 6.0 5.0 4.0 3.0 2.0 1.0 0 -1.0 -2.0
9.080
7.984
7.981
7.914
7.904
7.901
7.896
7.887
7.801
7.798
7.794
7.263
7.198
7.181
7.163
5.303
5.102
5.051
3.984
3.955
3.826
3.815
3.789
3.777
3.646
3.617
3.510
3.481
1.750
1.713
1.656
1.622
1.603
1.569
1.300
1.286
1.265
0.897
0.883
0.869
0.99
0.97
1.92
2.01
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4.02
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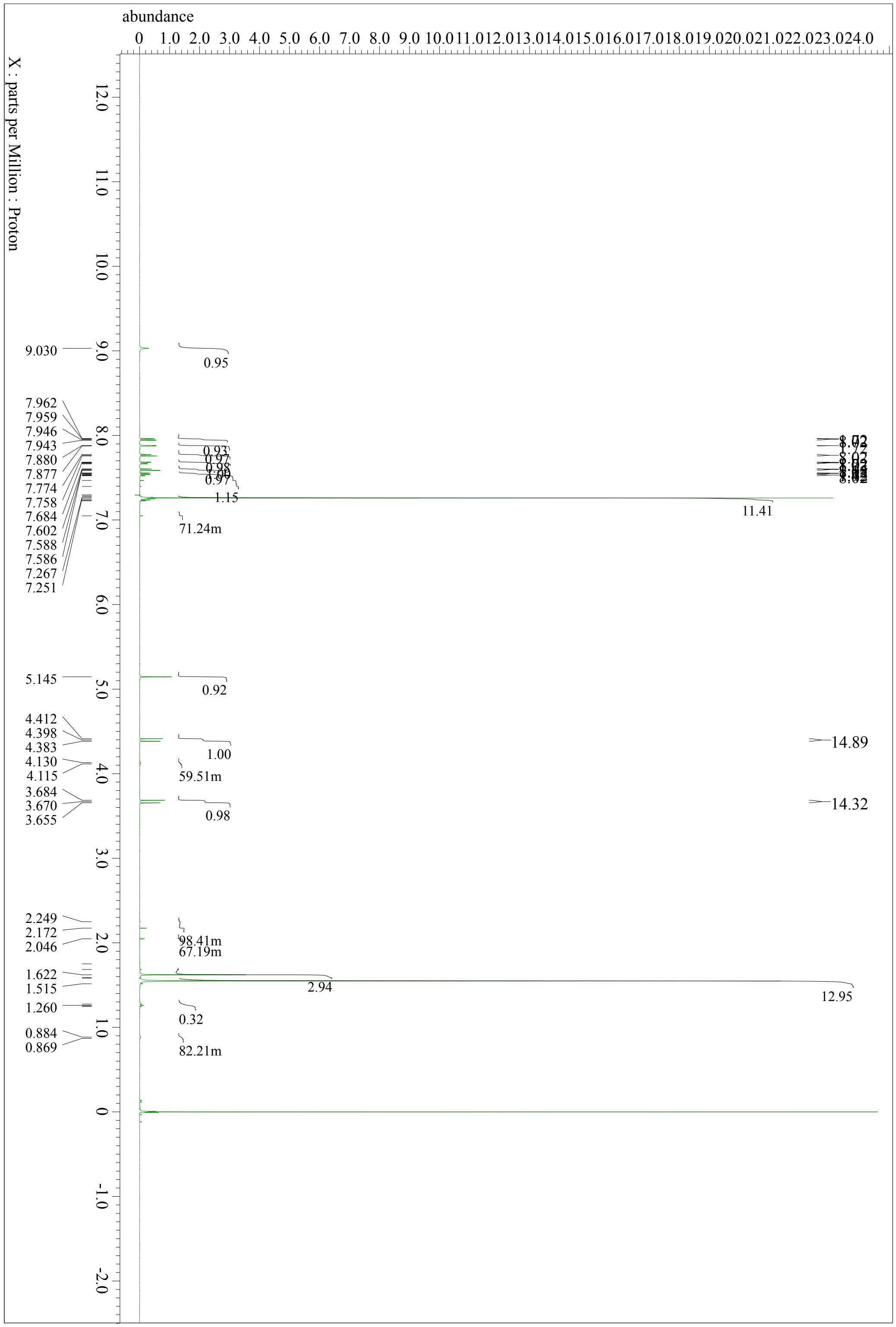
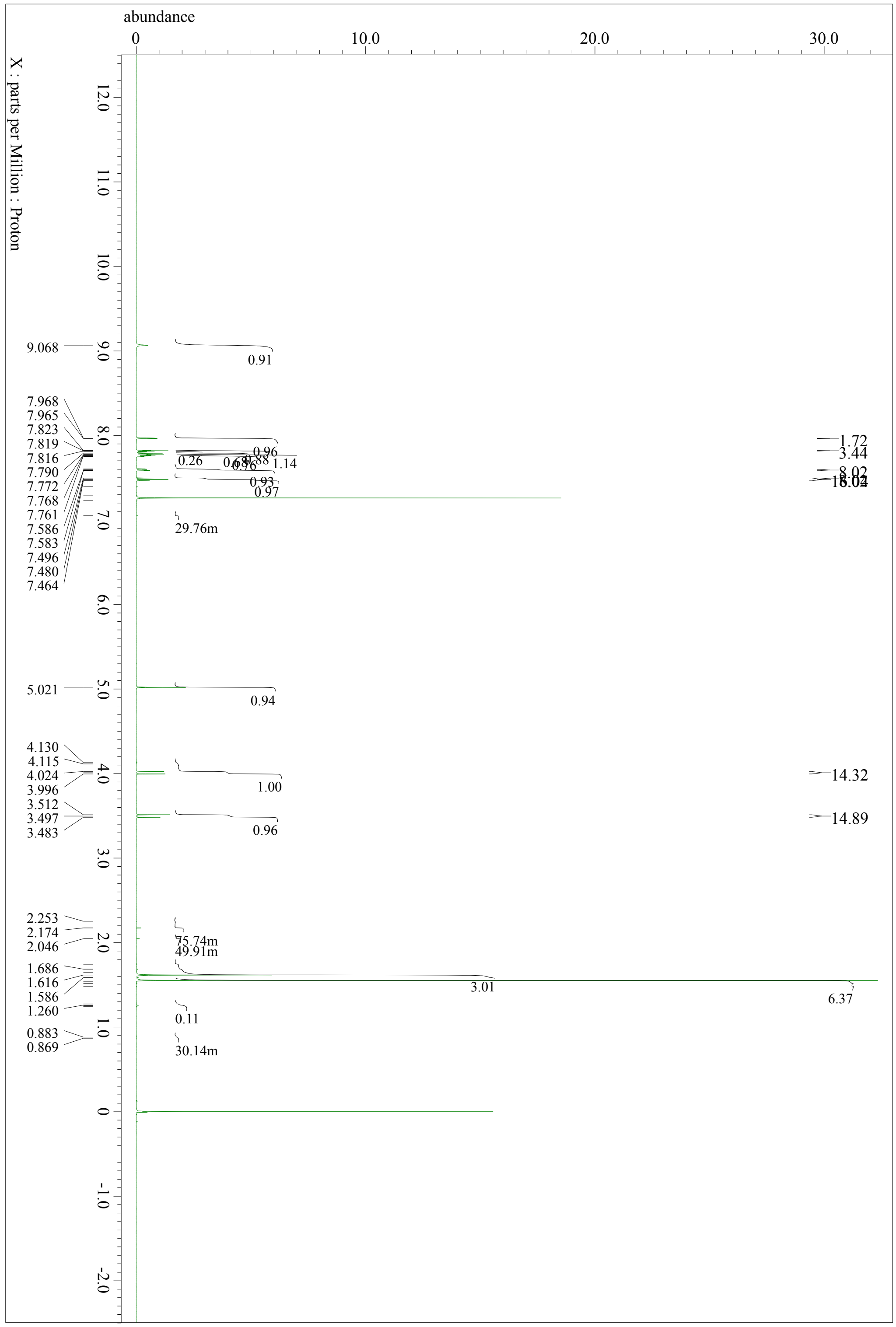
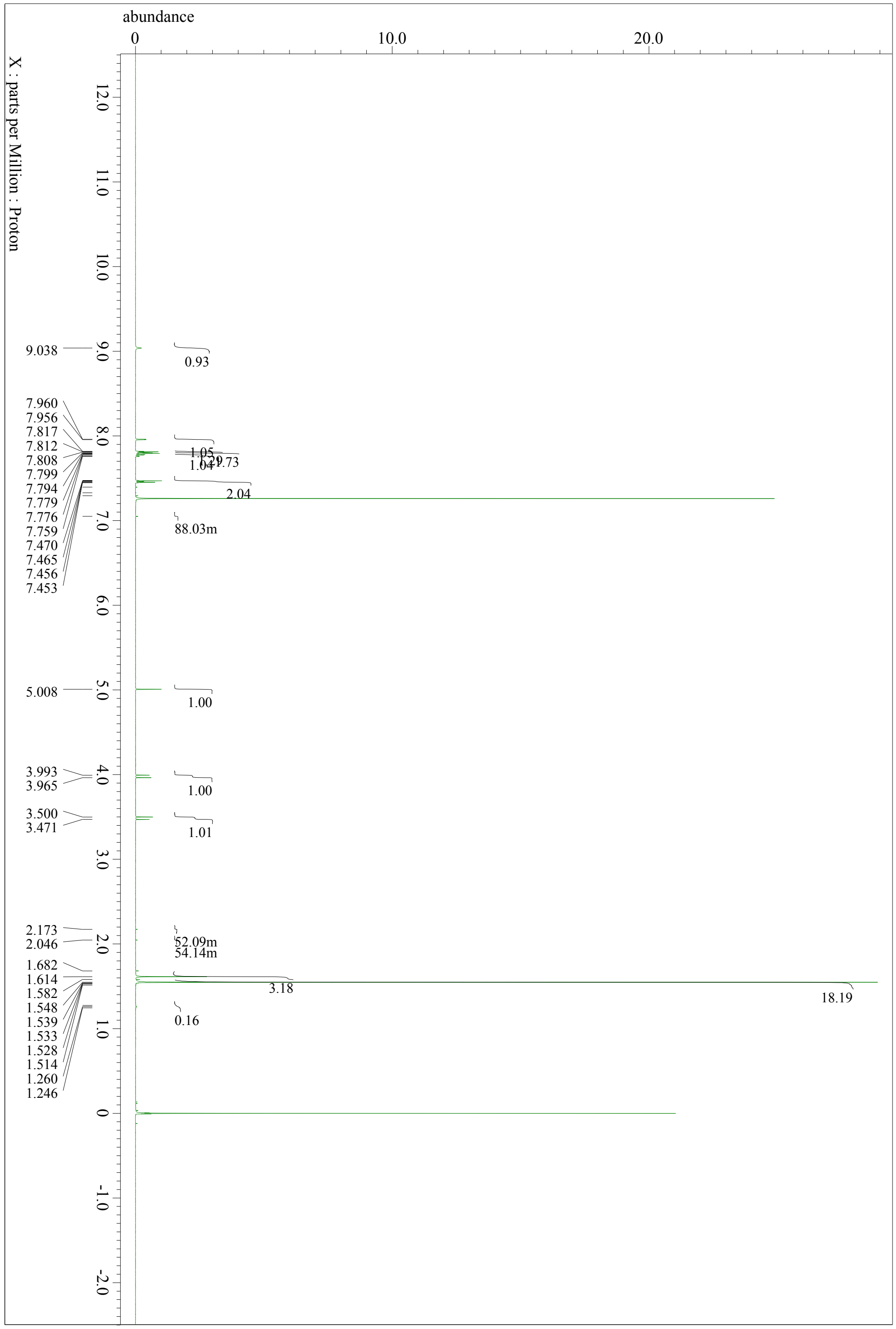
13a



13b

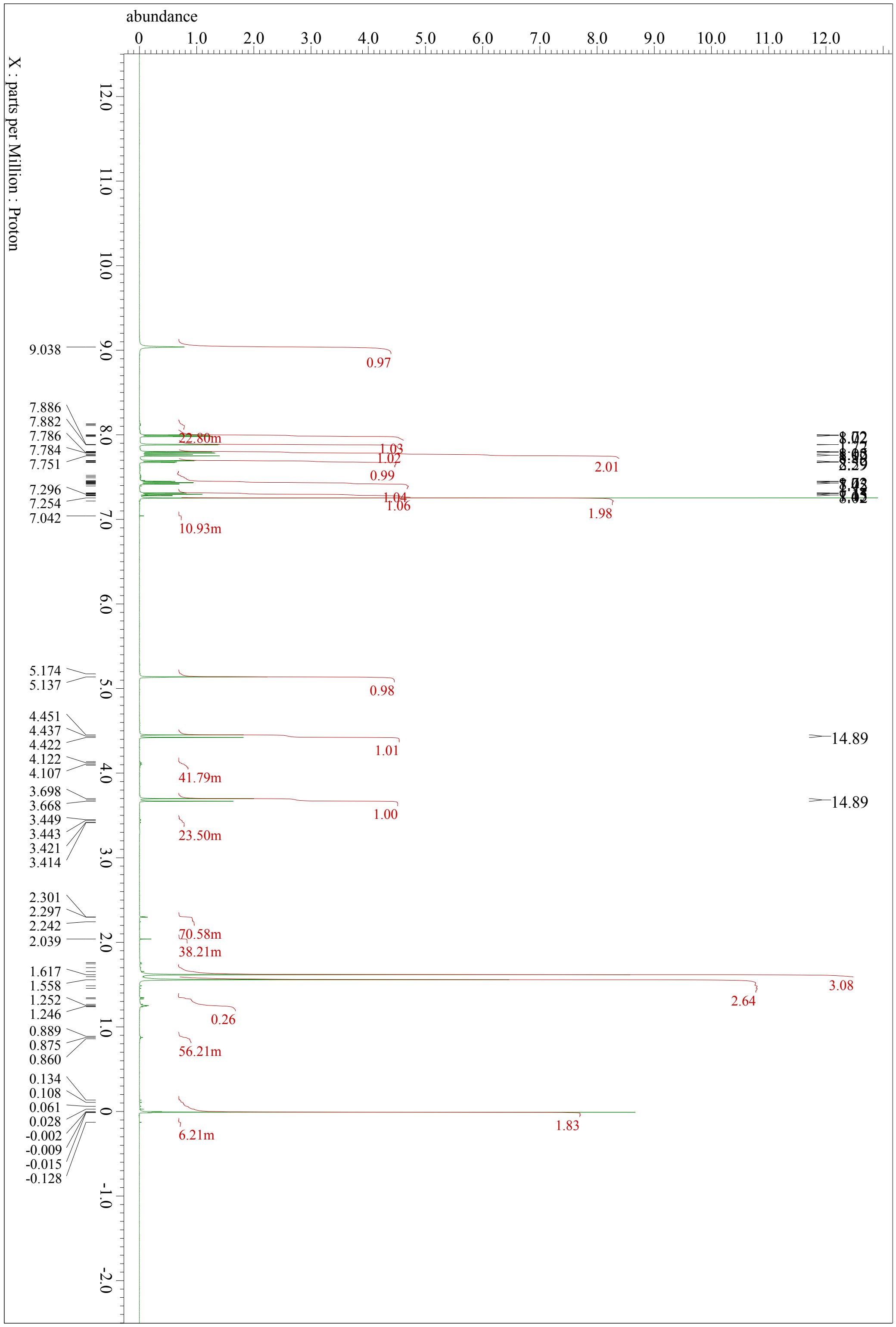


13c



14a

14b


abundance
X : parts per Million : Proton
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7.042
5.174
5.137
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4.422
4.122
4.107
3.698
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3.449
3.443
3.421
3.414
2.301
2.297
2.242
2.039
1.617
1.558
1.252
1.246
0.889
0.875
0.860
0.134
0.108
0.061
0.028
-0.002
-0.009
-0.015
-0.128
0.97
1.03
1.02
2.01
0.99
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1.01
1.00
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2.64
0.26
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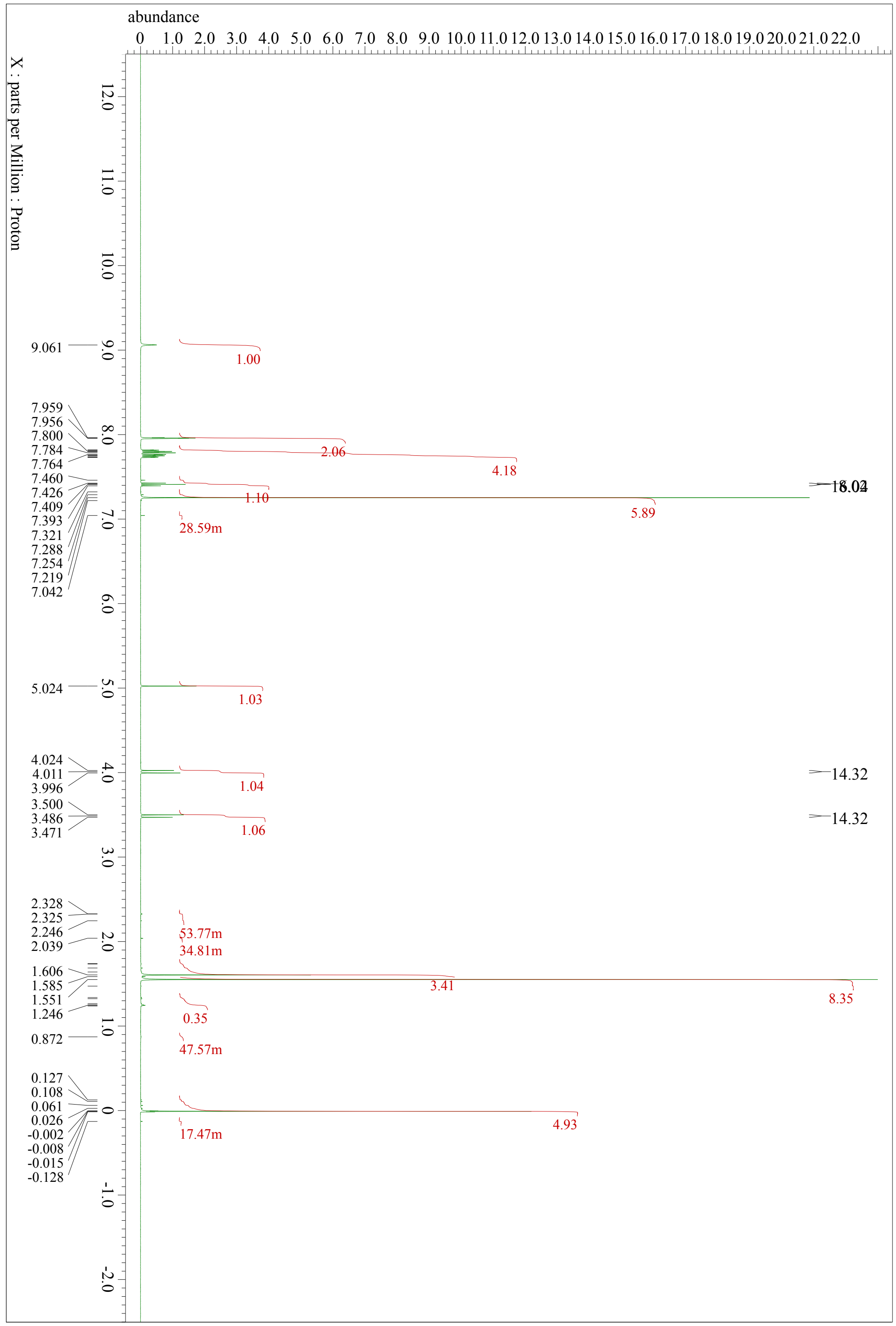
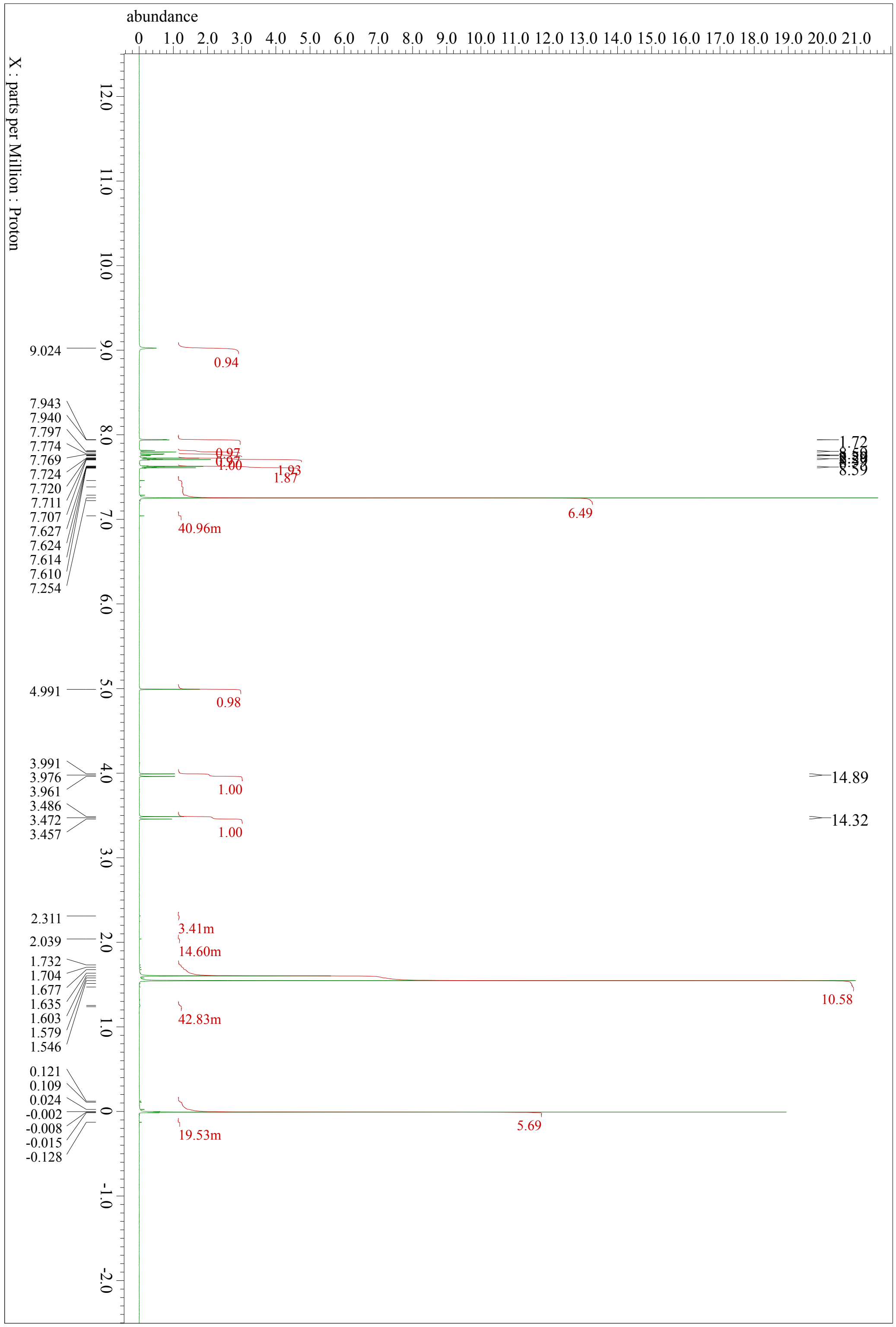
14.89



14c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7.711
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7.627
7.624
7.614
7.610
7.254
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3.991
3.976
3.961
3.486
3.472
3.457
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2.039
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1.635
1.603
1.579
1.546
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0.109
0.024
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-0.008
-0.015
-0.128
0.94
0.97
1.00
1.93
1.87
6.49
40.96m
0.98
1.00
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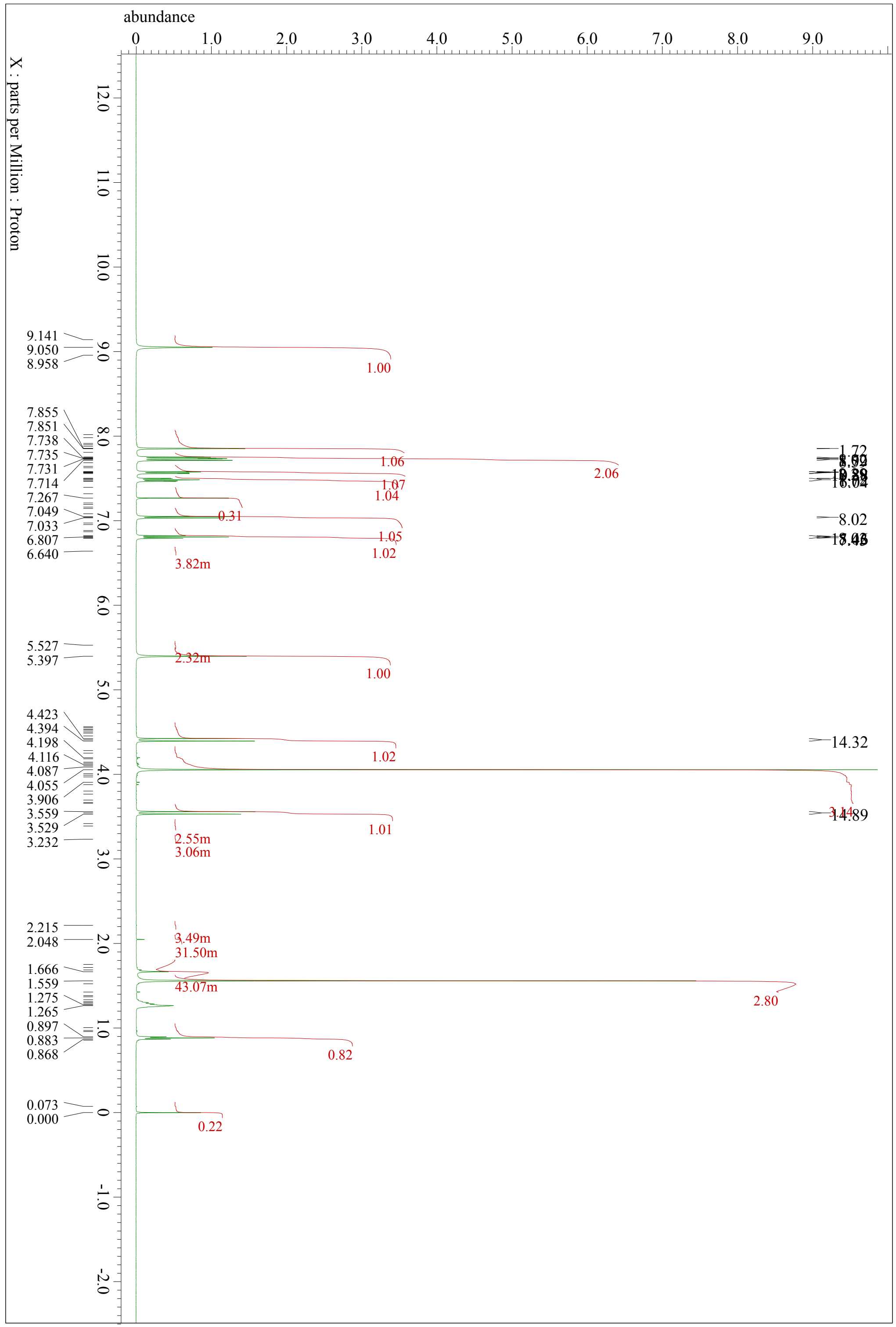
14.89
14.32

15a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X : parts per Million : Proton
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7.049
7.033
6.807
6.640
5.527
5.397
4.423
4.394
4.198
4.116
4.087
4.055
3.906
3.559
3.529
3.232
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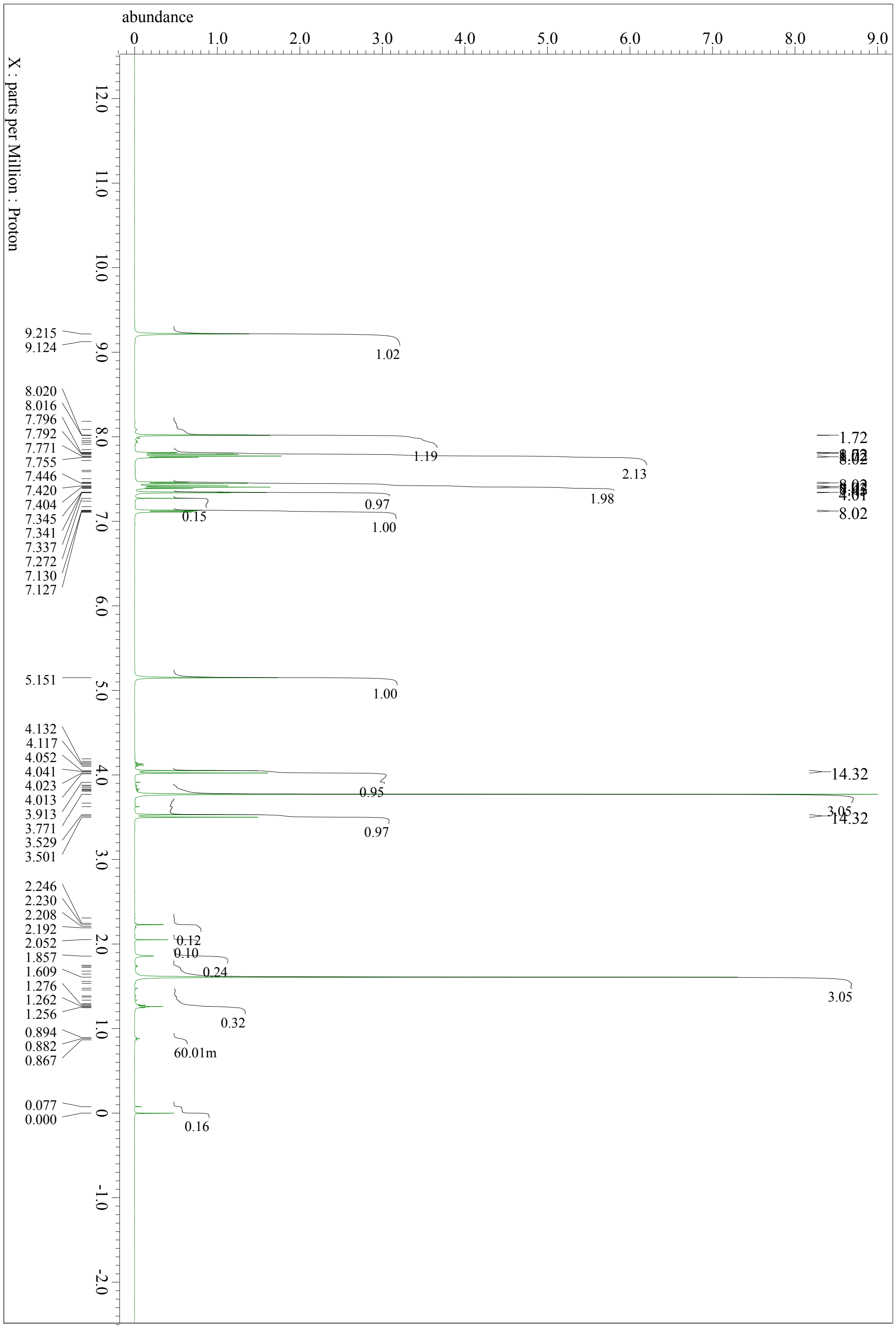
0.073
0.000

15b



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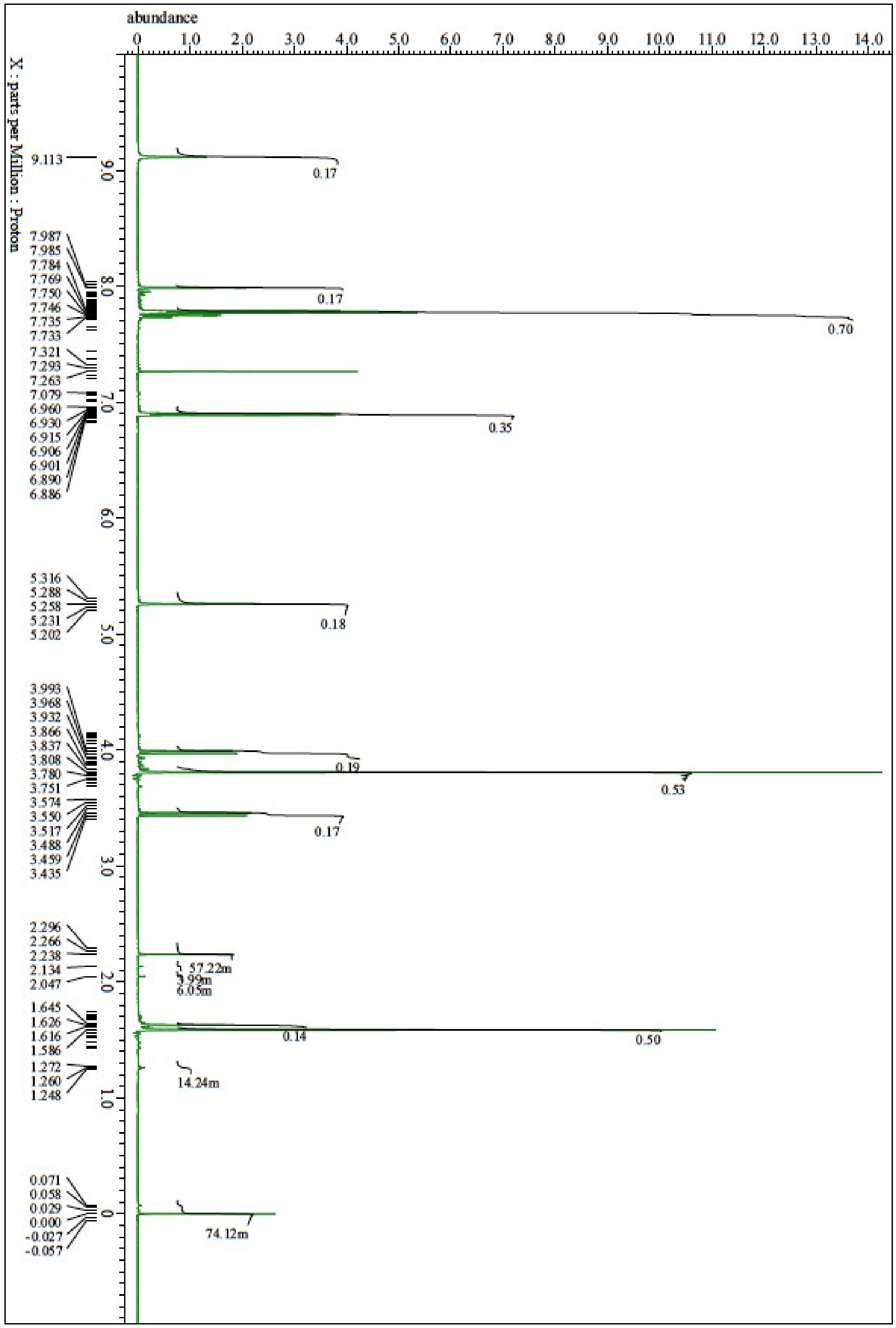
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X : parts per Million : Proton
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7.784
7.769
7.750
7.746
7.735
7.733
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6.915
6.906
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6.890
6.886
5.316
5.288
5.258
5.231
5.202
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3.968
3.932
3.866
3.837
3.808
3.780
3.751
3.574
3.550
3.517
3.488
3.459
3.435
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2.266
2.238
2.134
2.047
1.645
1.626
1.616
1.586
1.272
1.260
1.248
0.071
0.058
0.029
0.000
-0.027
-0.057
9.0 8.0 7.0 6.0 5.0 4.0 3.0 2.0 1.0 0
0.17
0.17
0.70
0.35
0.18
0.19
0.53
0.17
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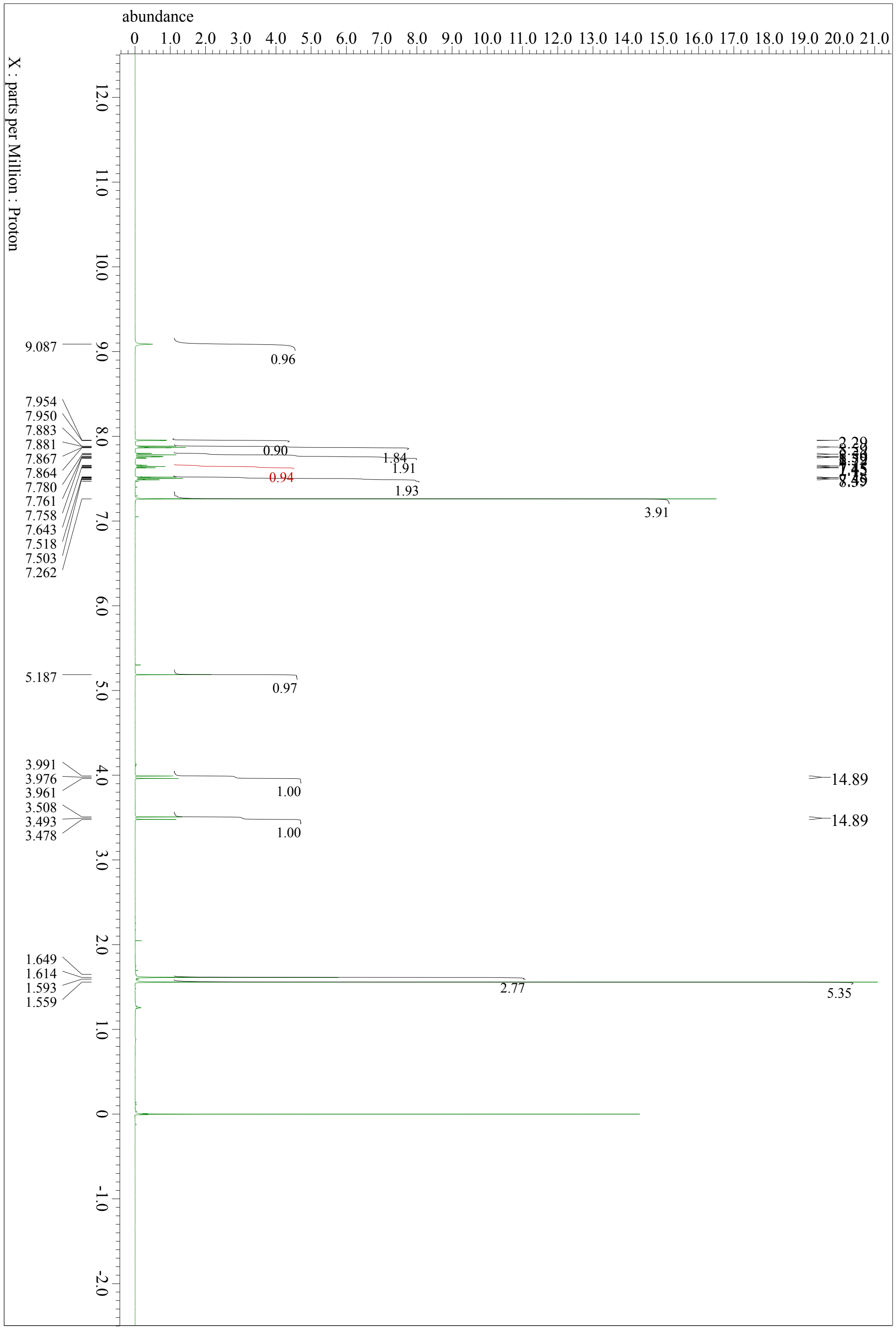
3.99m
6.05m
0.14
0.50
14.24m
74.12m

16



X : parts per Million : Proton
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7.758
7.643
7.518
7.503
7.262
5.187
3.991
3.976
3.961
3.508
3.493
3.478
1.649
1.614
1.593
1.559
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0.90
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1.91
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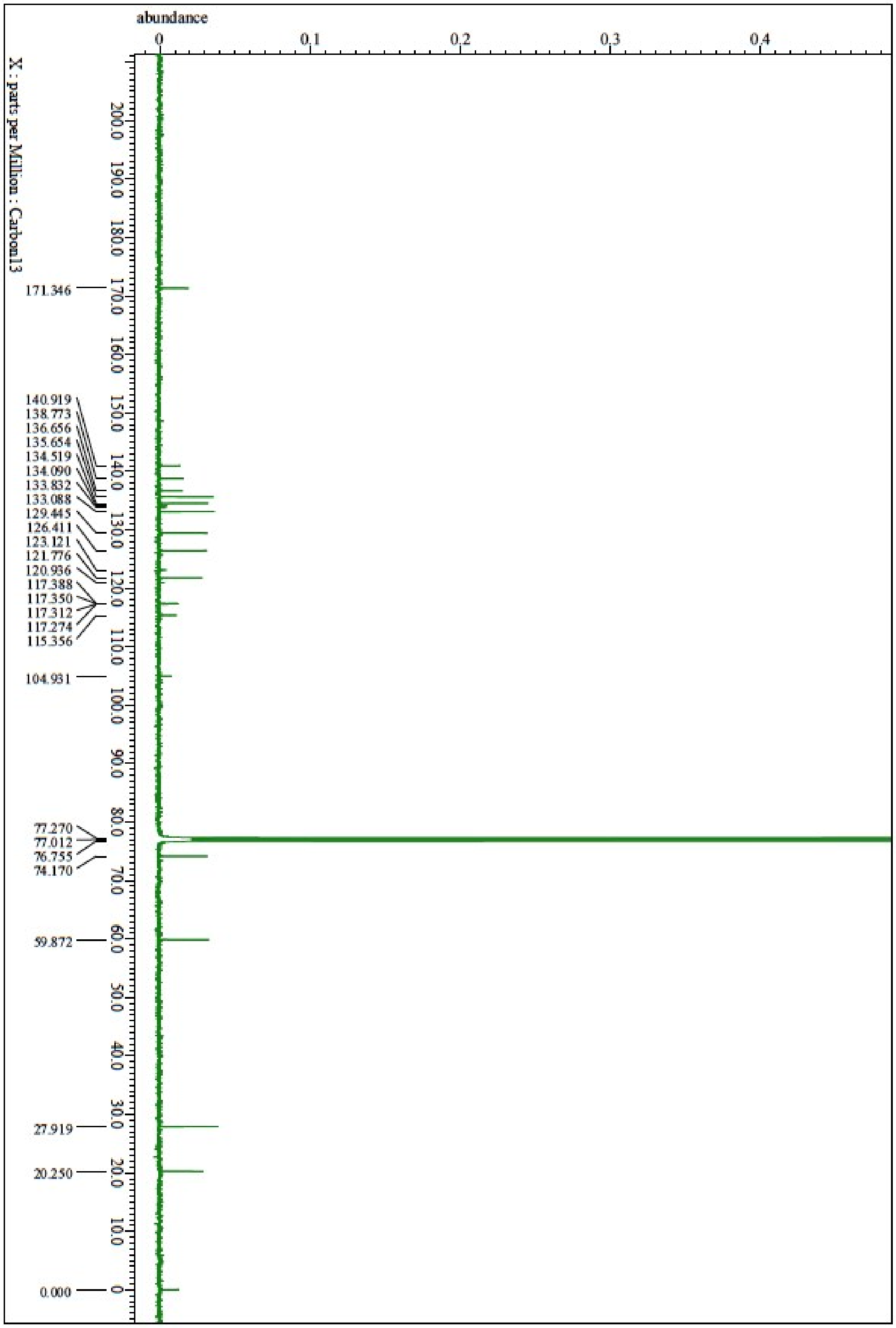
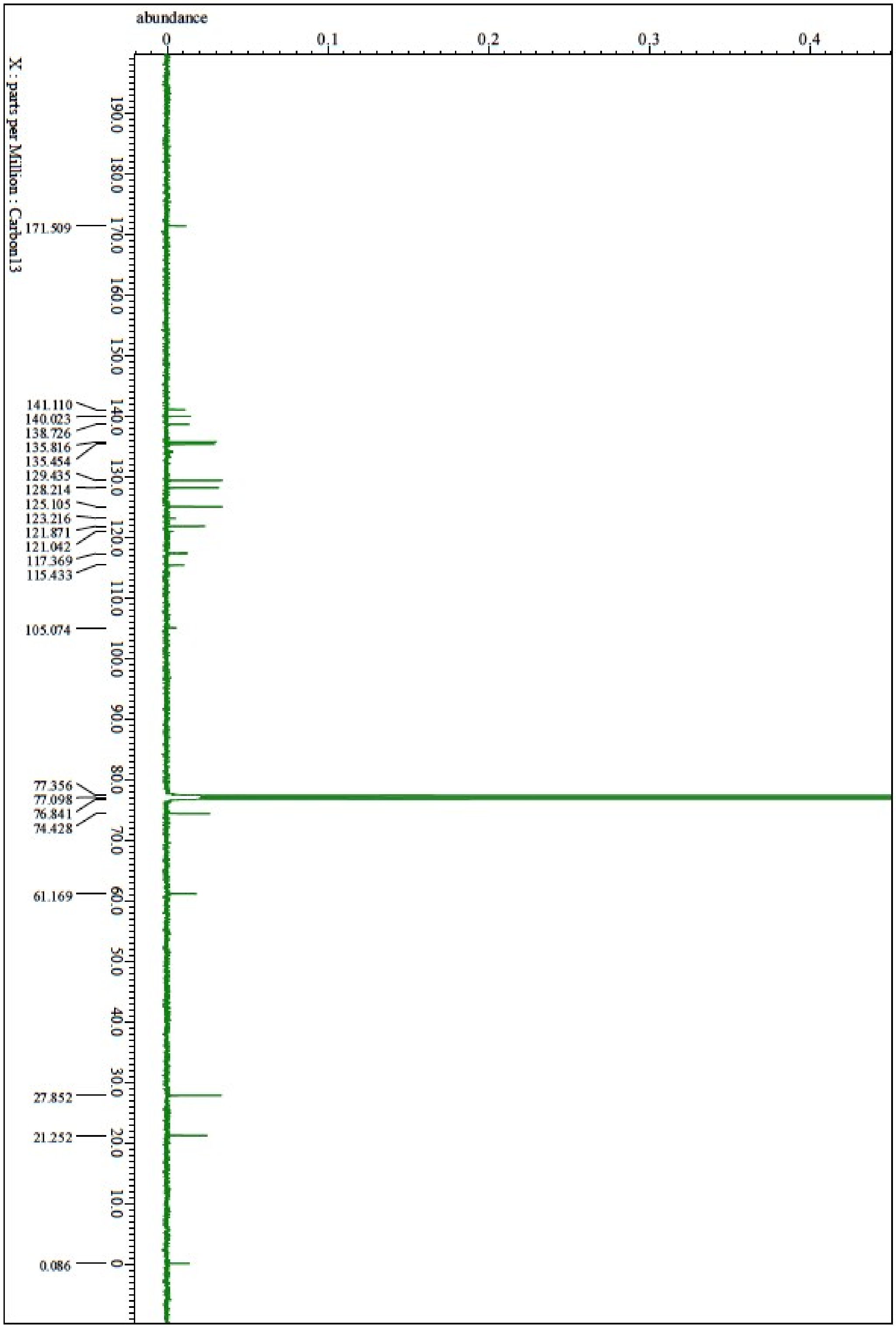
^{13}C NMR spectra

10a



10b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135.454
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128.214
125.105
123.216
121.871
121.042
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27.852
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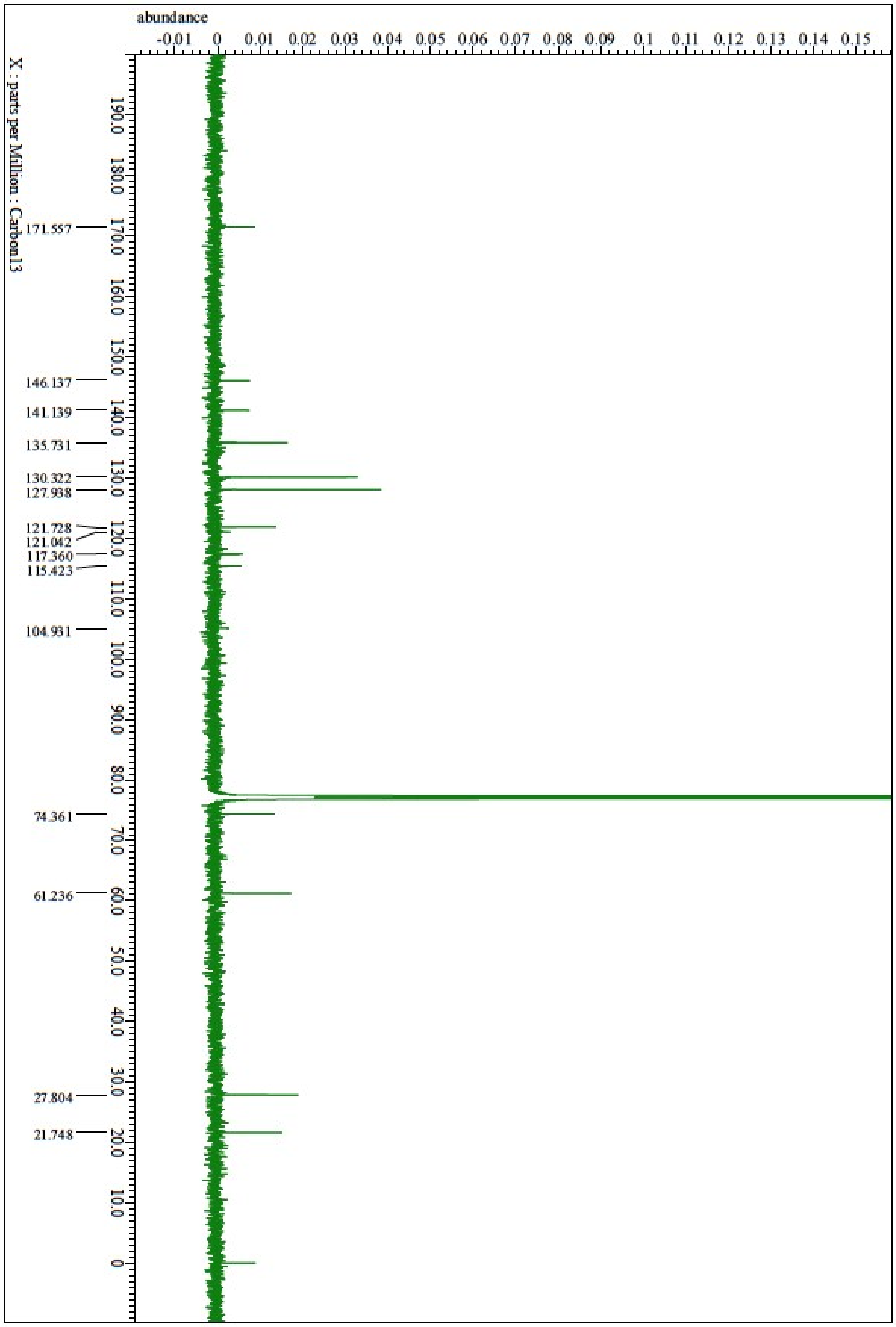
0.086

10c

11a


abundance
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X : parts per Million : Carbon13
190.0 180.0 170.0 160.0 150.0 140.0 130.0 120.0 110.0 100.0 90.0 80.0 70.0 60.0 50.0 40.0 30.0 20.0 10.0 0
171.557
146.137
141.139
135.731
130.322
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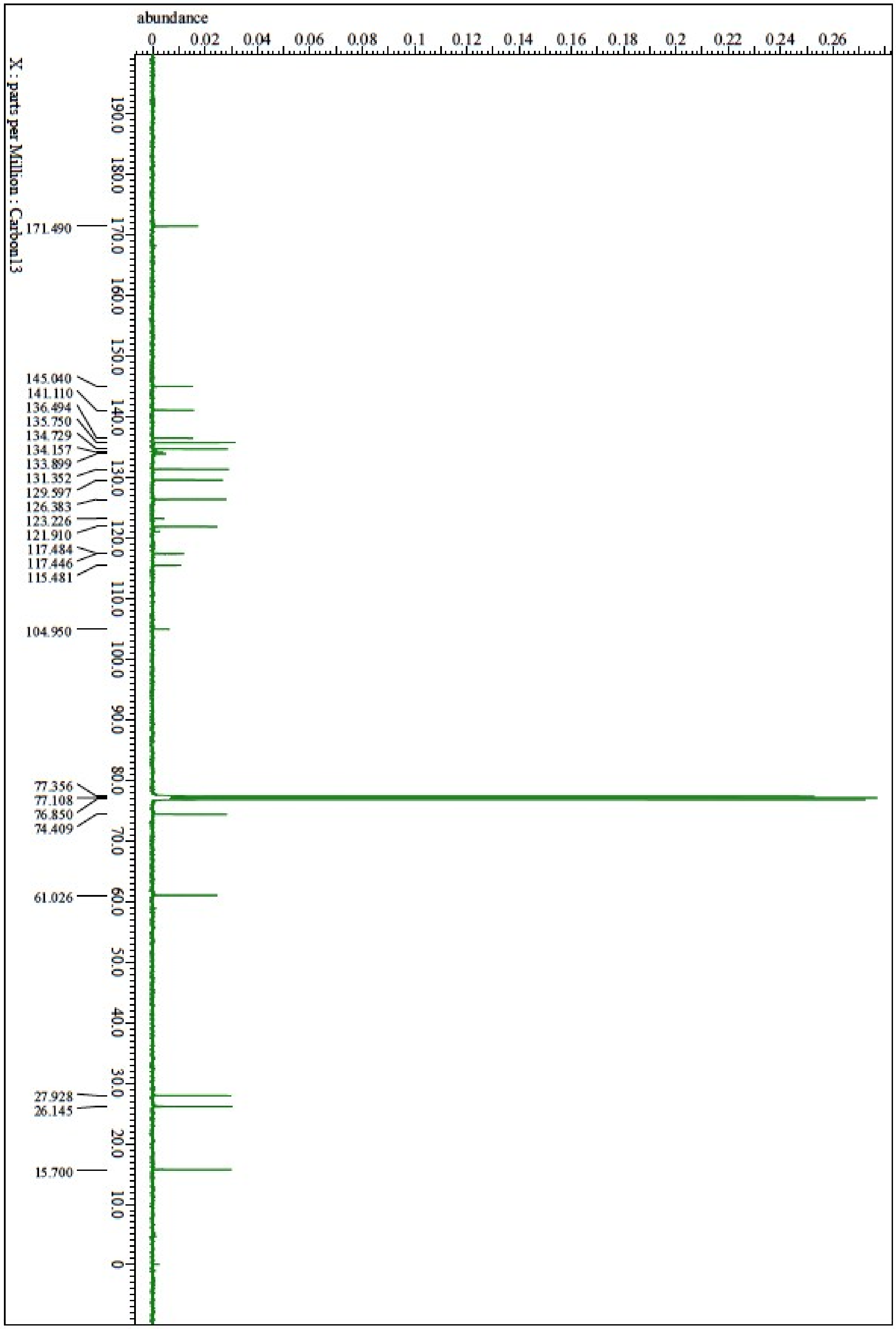
121.728
121.042
117.360
115.423
104.931
74.361
61.236
27.804
21.748

11b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123.226
121.910
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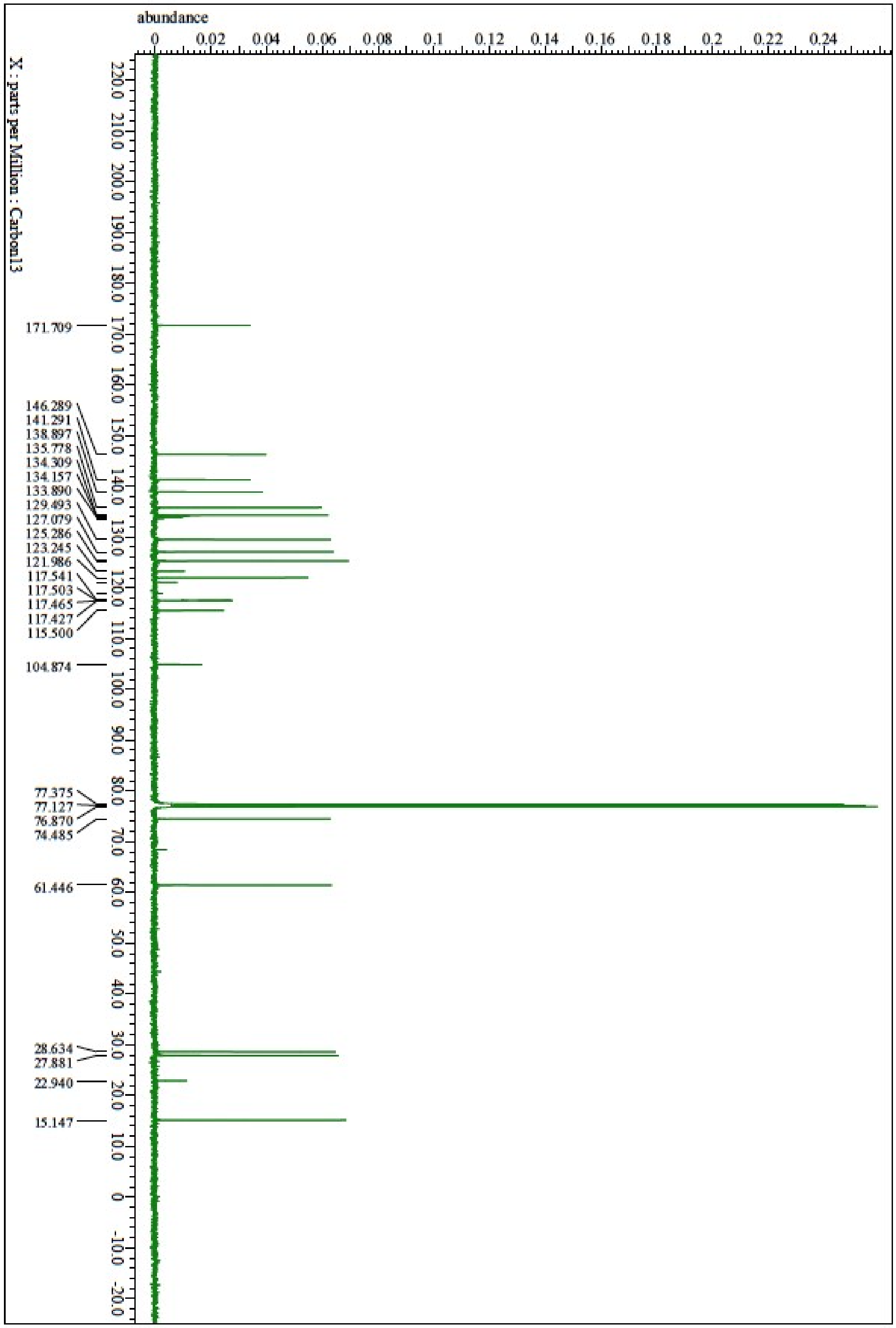
26.145
15.700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123.245
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117.541
117.503
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117.427
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77.127
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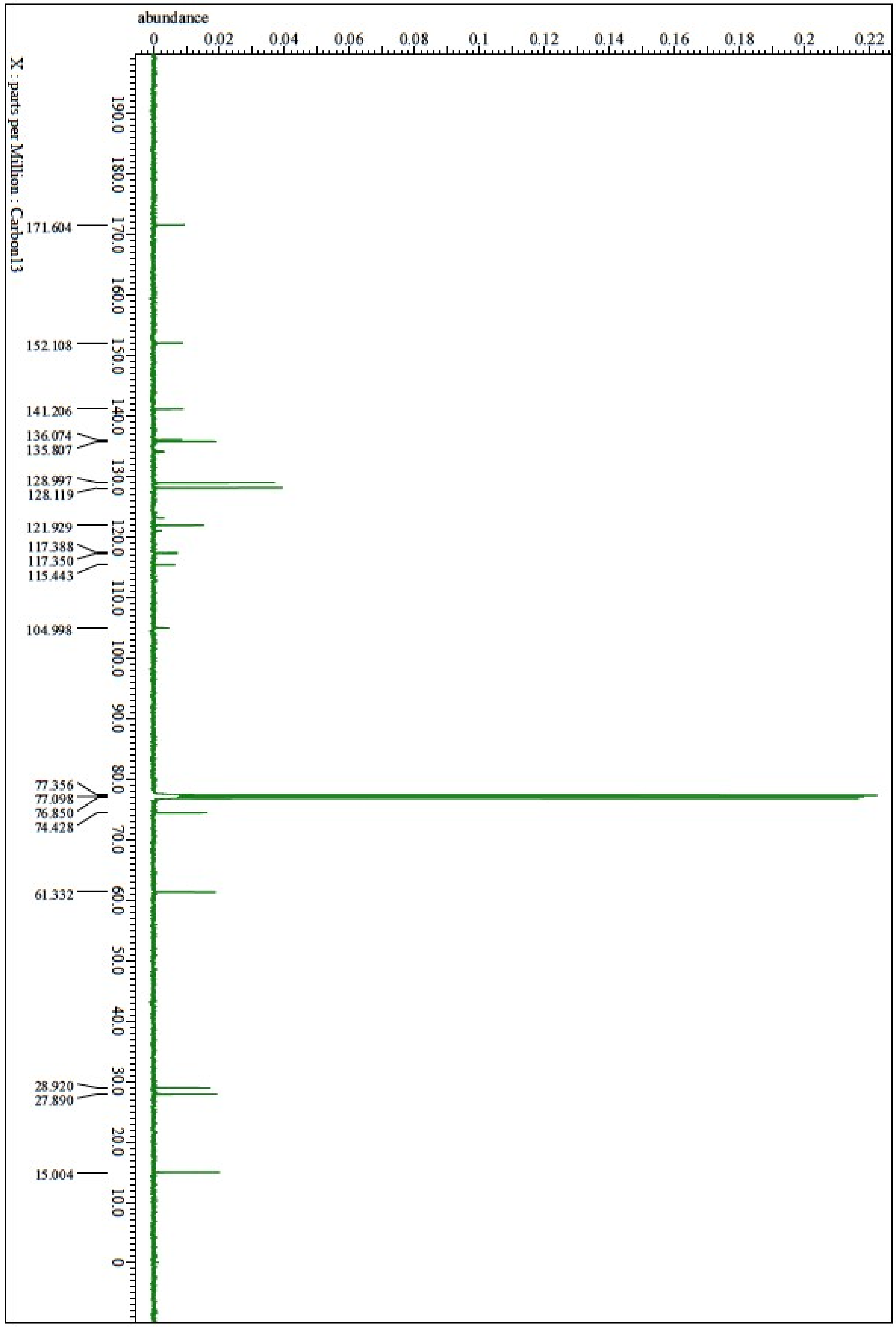
27.881
22.940
15.147

11c

12a



abundance
X : parts per Million : Carbon13
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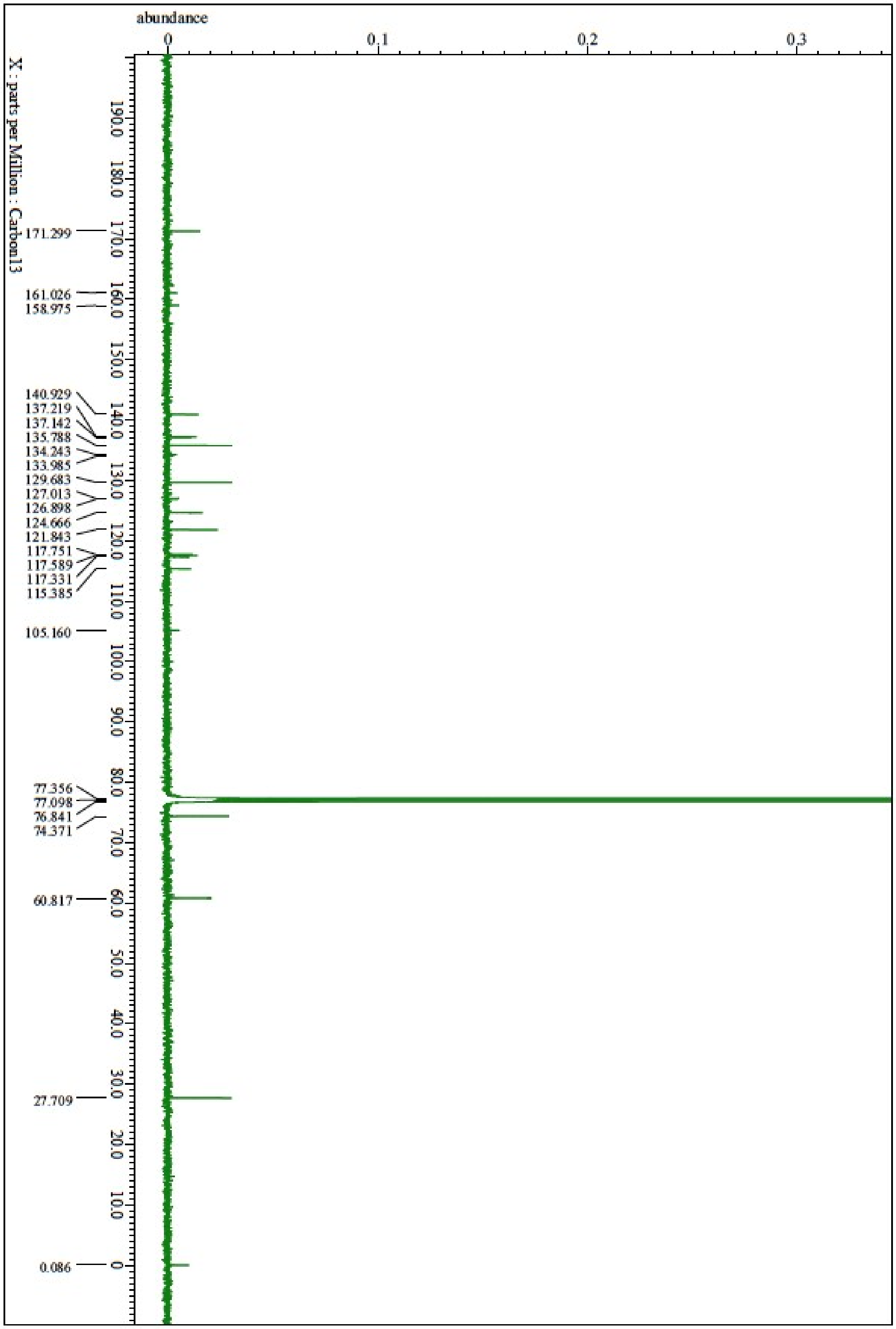
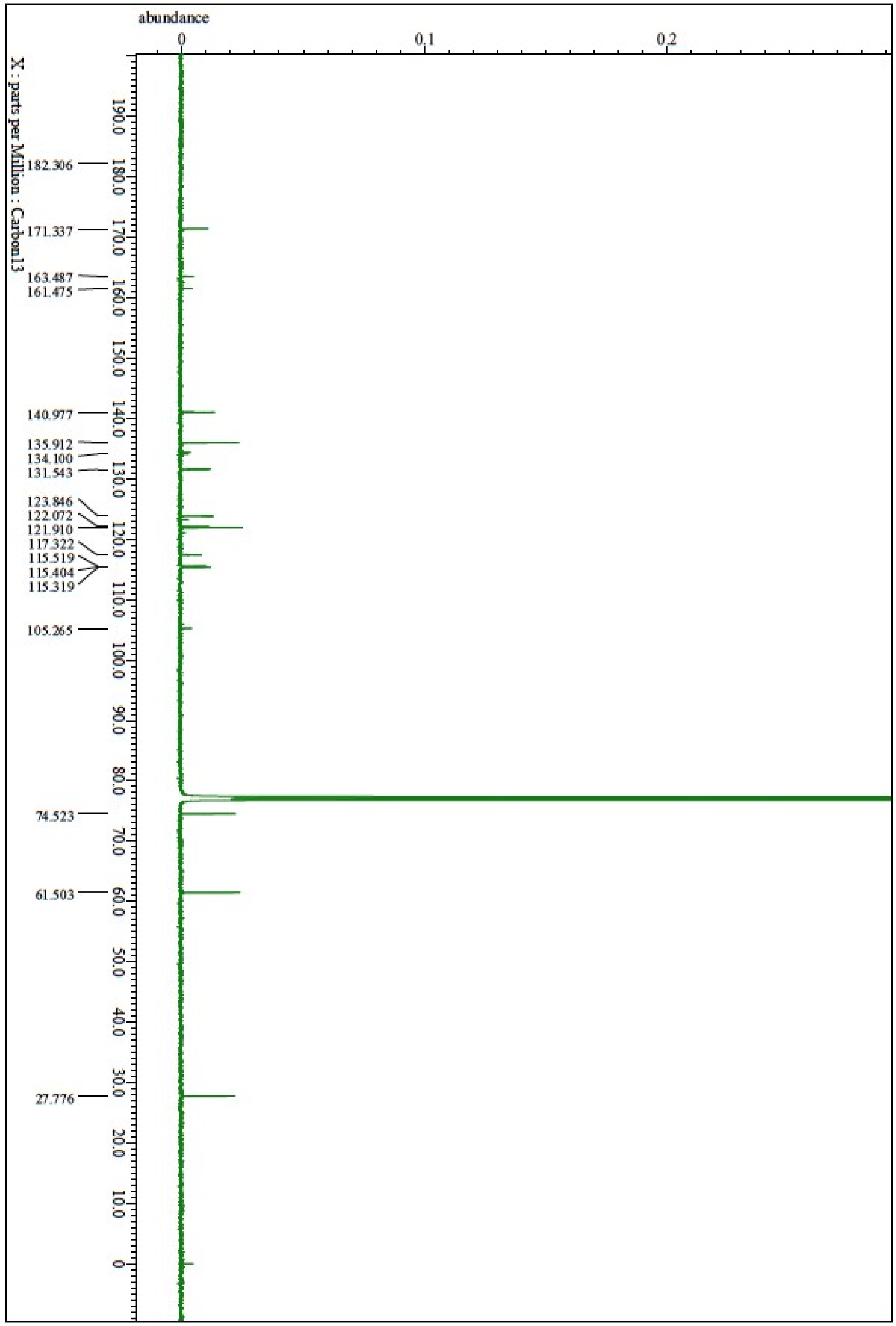
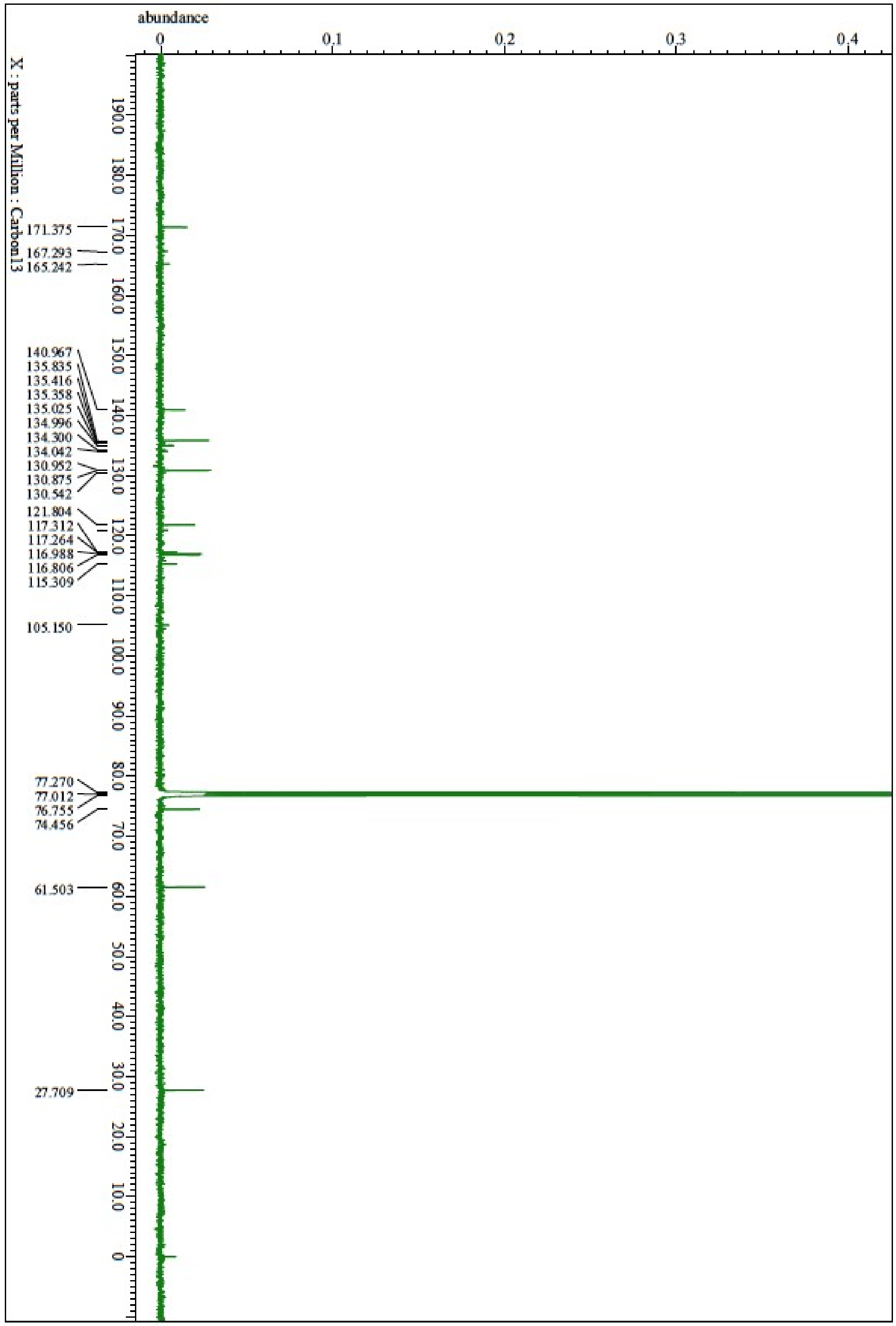
136.074
135.807
128.997
128.119
121.929
117.388
117.350
115.443
104.998
77.356
77.098
76.850
74.428
61.332
28.920
27.890
15.004


abundance
0
0.1
0.2
0.3
X : parts per Million : Carbon13
171.299
161.026
158.975
140.929
137.219
137.142
135.788
134.243
133.985
129.683
127.013
126.898
124.666
121.843
117.751
117.589
117.331
115.385
105.160
77.356
77.098
76.841
74.371
60.817
27.709
0.086

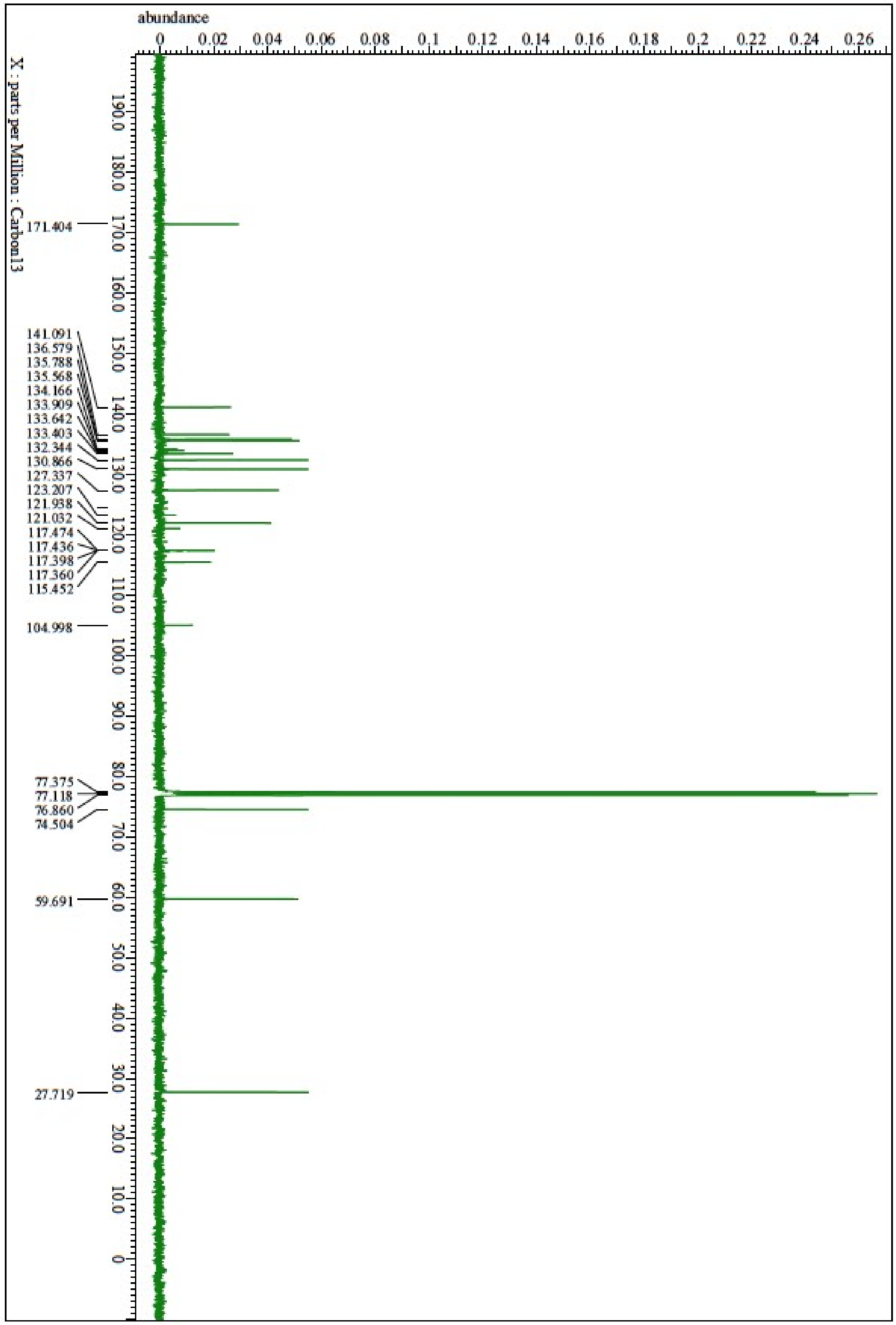
12b


abundance
0
0.1
0.2
X : parts per Million : Carbon13
182.306
171.337
163.487
161.475
140.977
135.912
134.100
131.543
123.846
122.072
121.910
117.322
115.519
115.404
115.319
105.265
74.523
61.503
27.776

12c

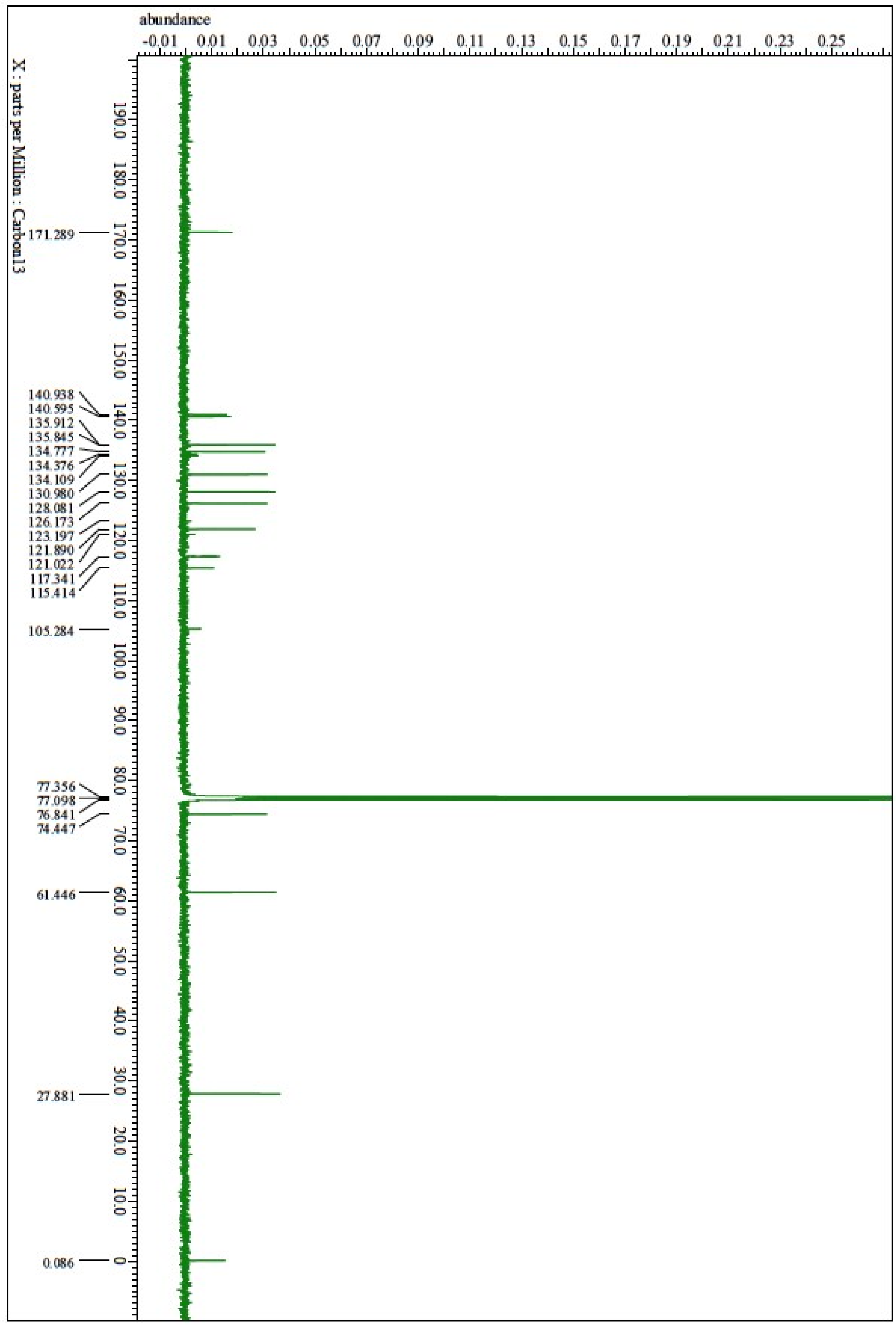

abundance
0
0.1
0.2
0.3
0.4
X : parts per Million : Carbon13
171.375
167.293
165.242
140.967
135.835
135.416
135.358
135.025
134.996
134.300
134.042
130.952
130.875
130.542
121.804
117.312
117.264
116.988
116.806
115.309
105.150
77.270
77.012
76.755
74.456
61.503
27.709

13a



abundance
X : parts per Million : Carbon13
171.404
141.091
136.579
135.788
135.568
134.166
133.909
133.642
133.403
132.344
130.866
127.337
123.207
121.938
121.032
117.474
117.436
117.398
117.360
115.452
104.998
77.375
77.118
76.860
74.504
59.691
27.719

13b


abundance
X : parts per Million : Carbon13
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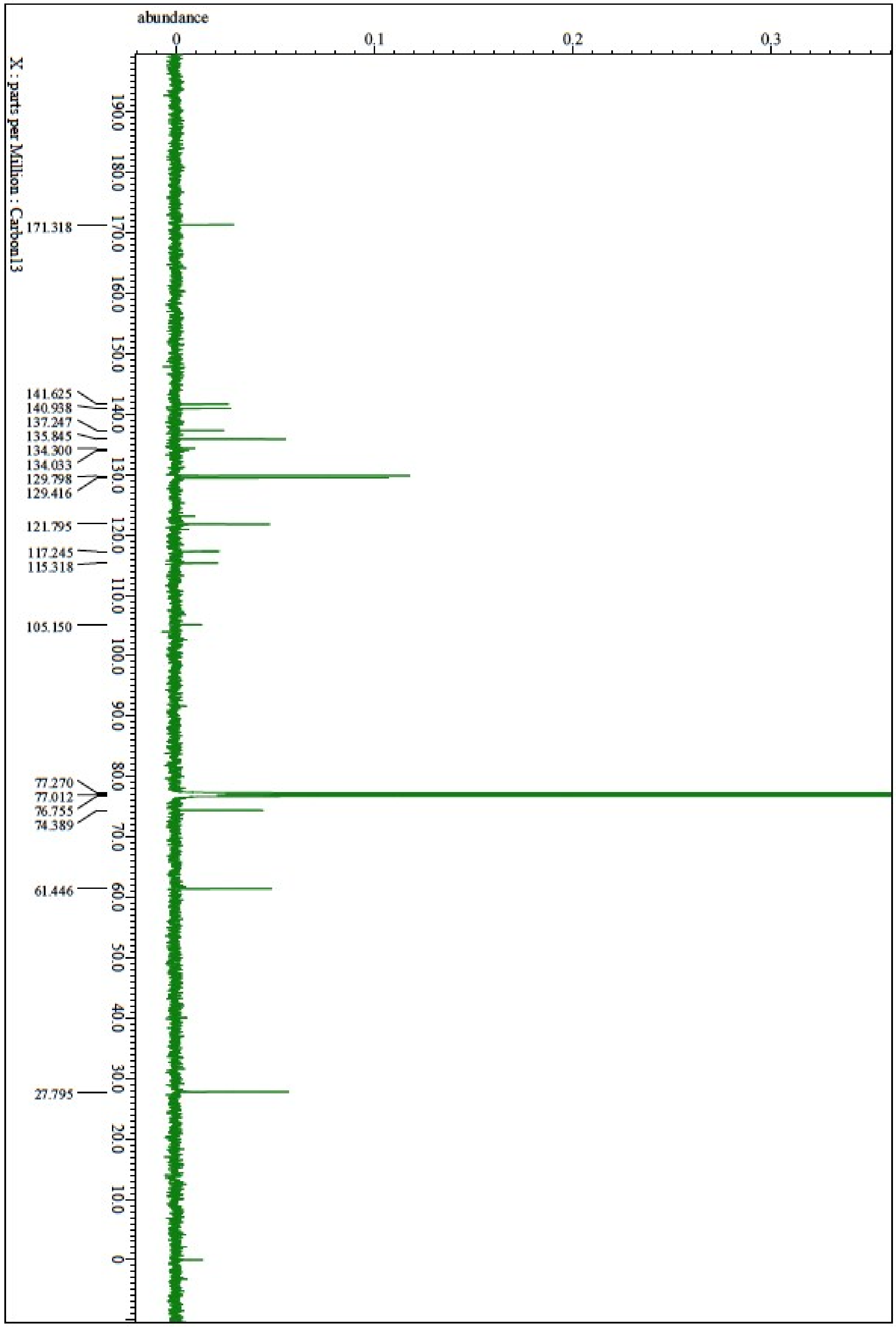
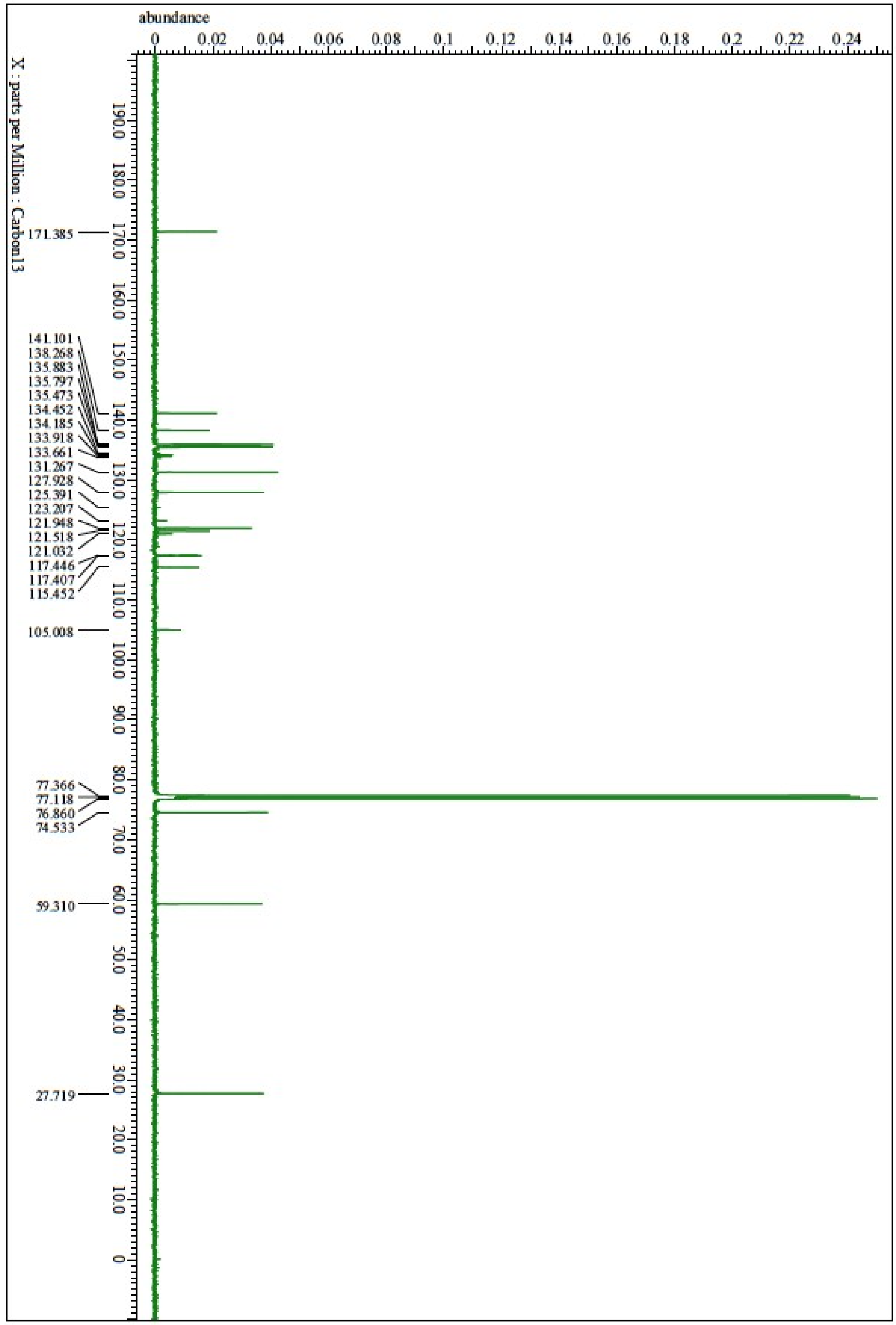
140.938
140.595
135.912
135.845
134.777
134.376
134.109
130.980
128.081
126.173
123.197
121.890
121.022
117.341
115.414
105.284
77.356
77.098
76.841
74.447
61.446
27.881
0.086

13c


abundance
0
0.1
0.2
0.3
X : parts per Million : Carbon13
171.318
141.625
140.938
137.247
135.845
134.300
134.033
129.798
129.416
121.795
117.245
115.318
105.150
77.270
77.012
76.755
74.389
61.446
27.795

14a

14b


abundance
0 0.02 0.04 0.06 0.08 0.1 0.12 0.14 0.16 0.18 0.2 0.22 0.24
X : parts per Million : Carbon13
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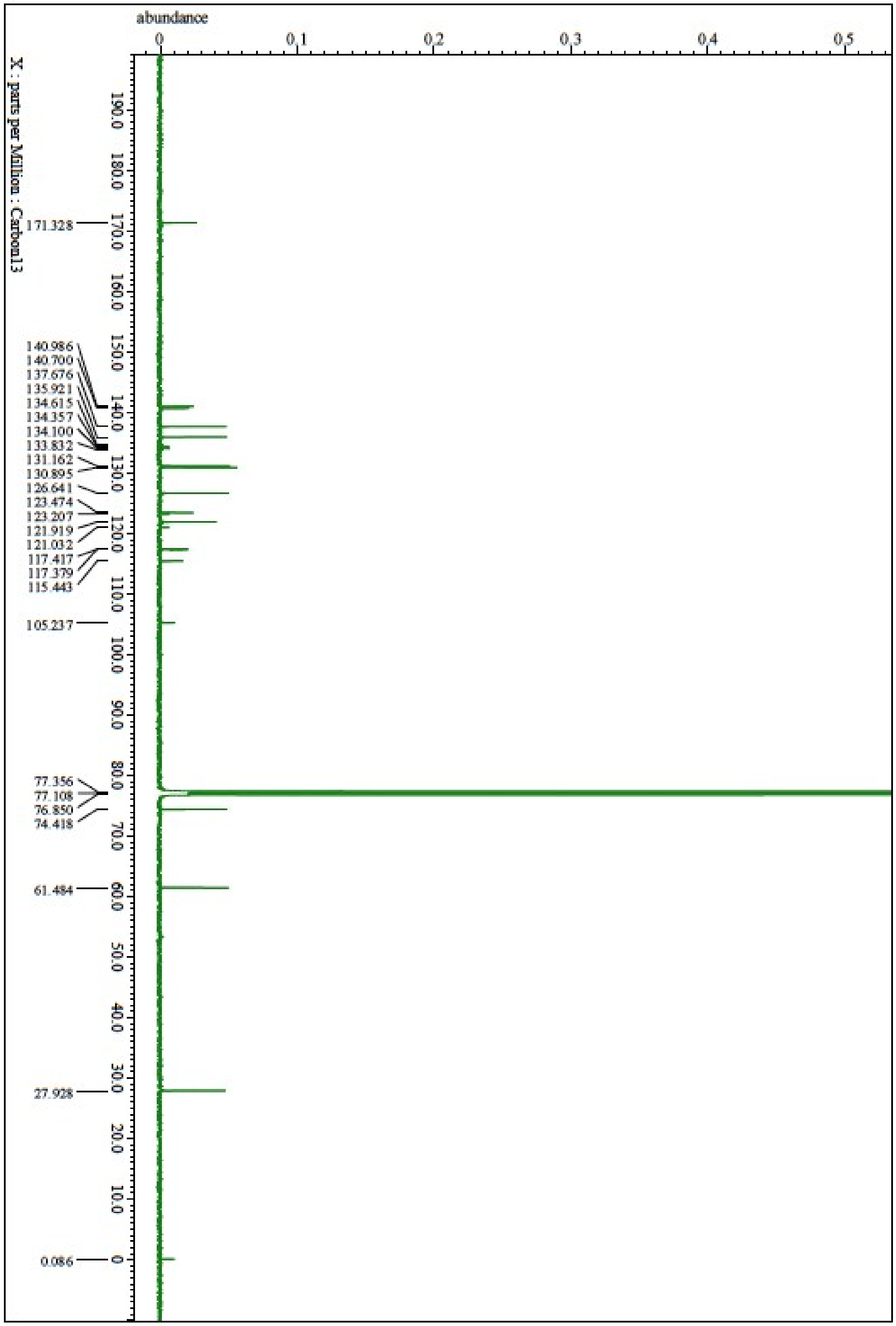
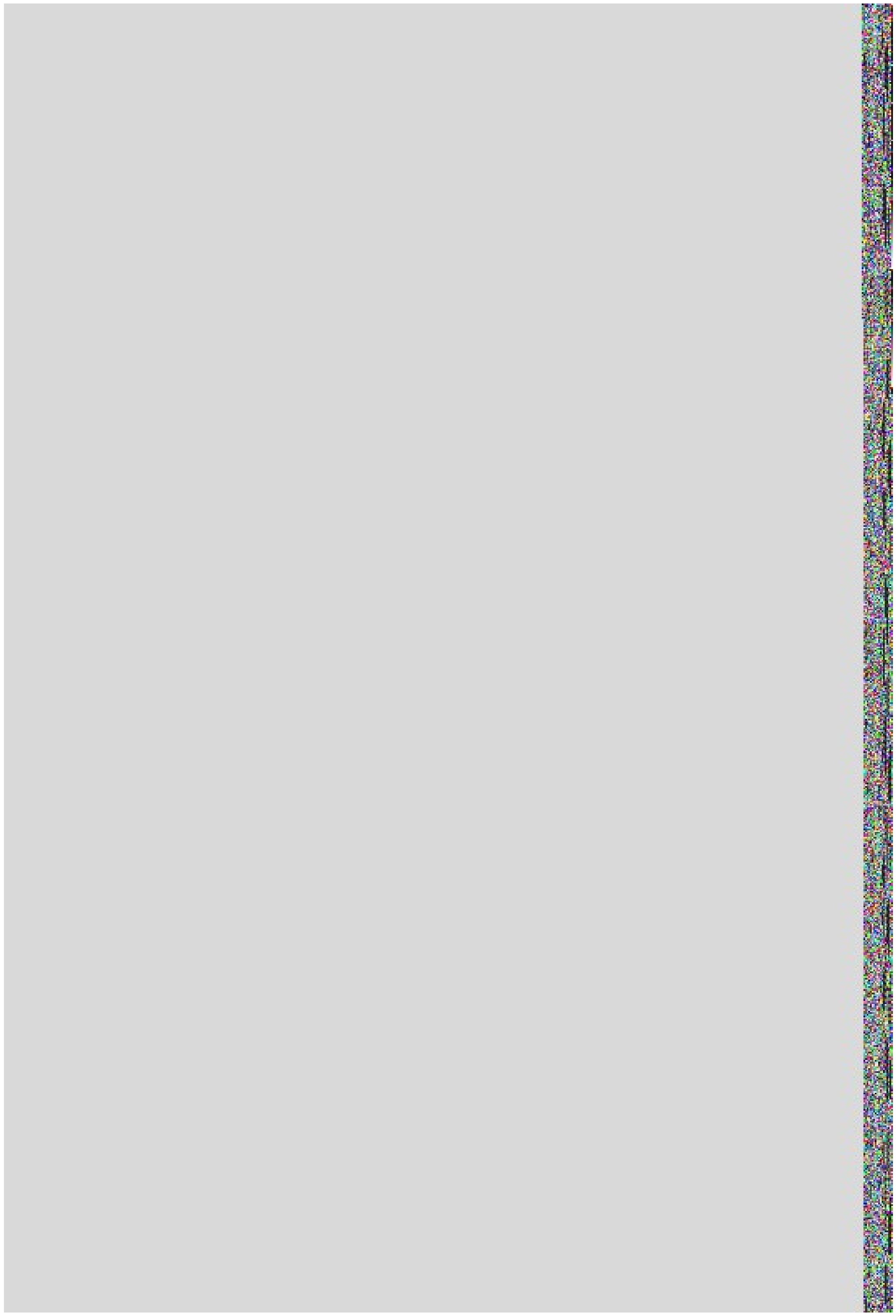
141.101
138.268
135.883
135.797
135.473
134.452
134.185
133.918
133.661
131.267
127.928
125.391
123.207
121.948
121.518
121.032
117.446
117.407
115.452
105.008
77.366
77.118
76.860
74.533
59.310
27.719
190.0 180.0 170.0 160.0 150.0 140.0 130.0 120.0 110.0 100.0 90.0 80.0 70.0 60.0 50.0 40.0 30.0 20.0 10.0 0

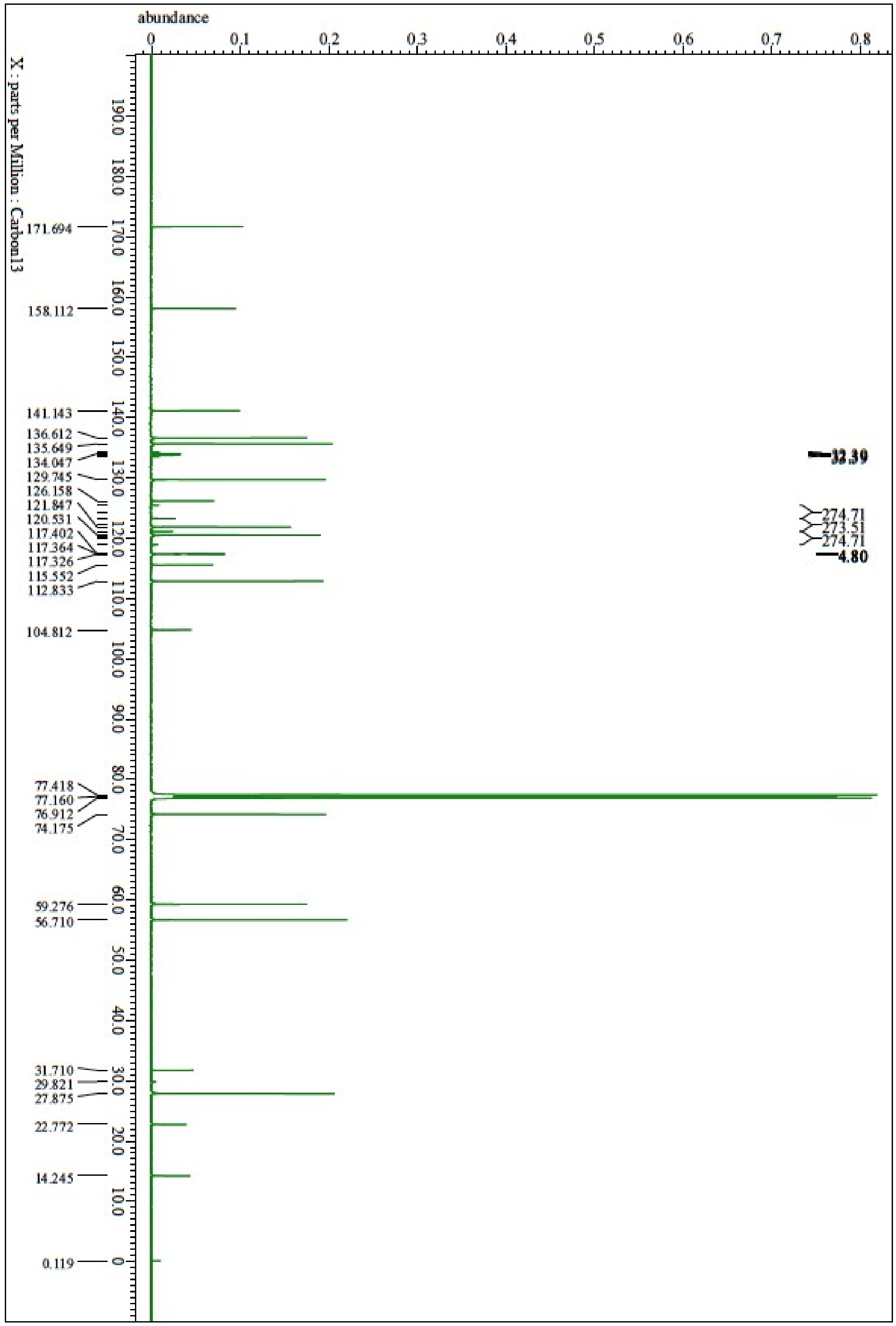
14c

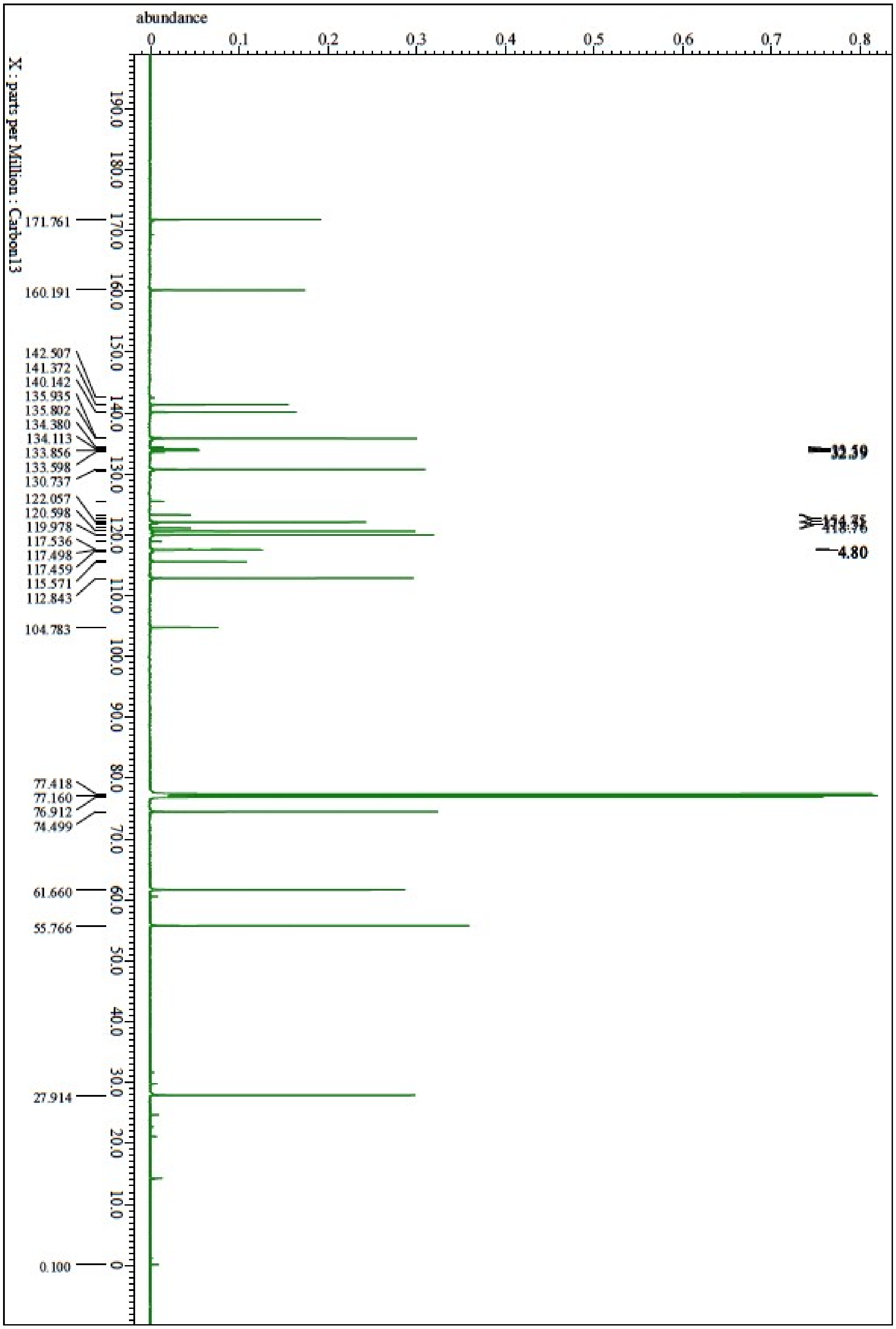

abundance
0
0.1
0.2
0.3
0.4
0.5
X : parts per Million : Carbon13
171.328
140.986
140.700
137.676
135.921
134.615
134.357
134.100
133.832
131.162
130.895
126.641
123.474
123.207
121.919
121.032
117.417
117.379
115.443
105.237
77.356
77.108
76.850
74.418
61.484
27.928
0.086

15a

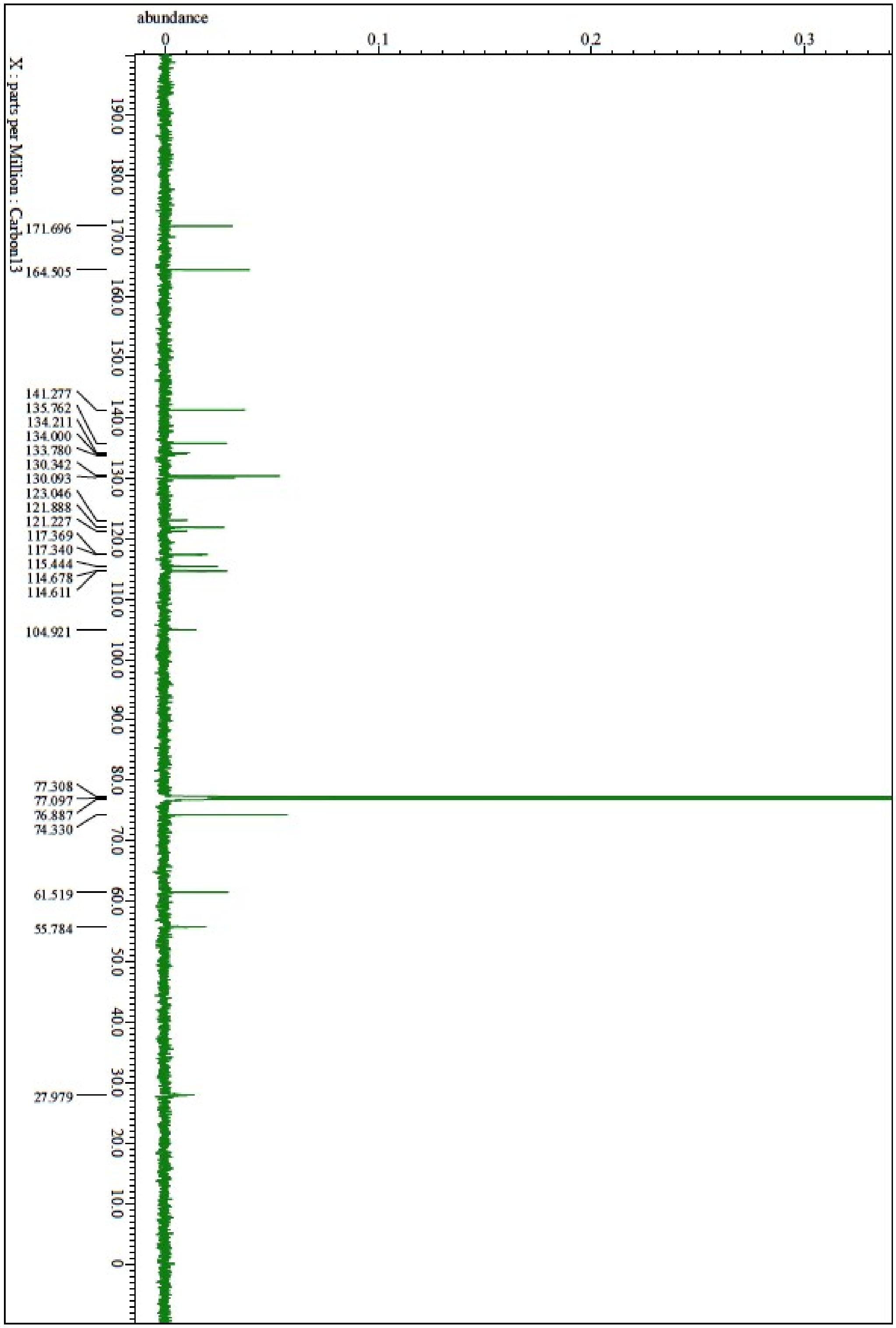


15b

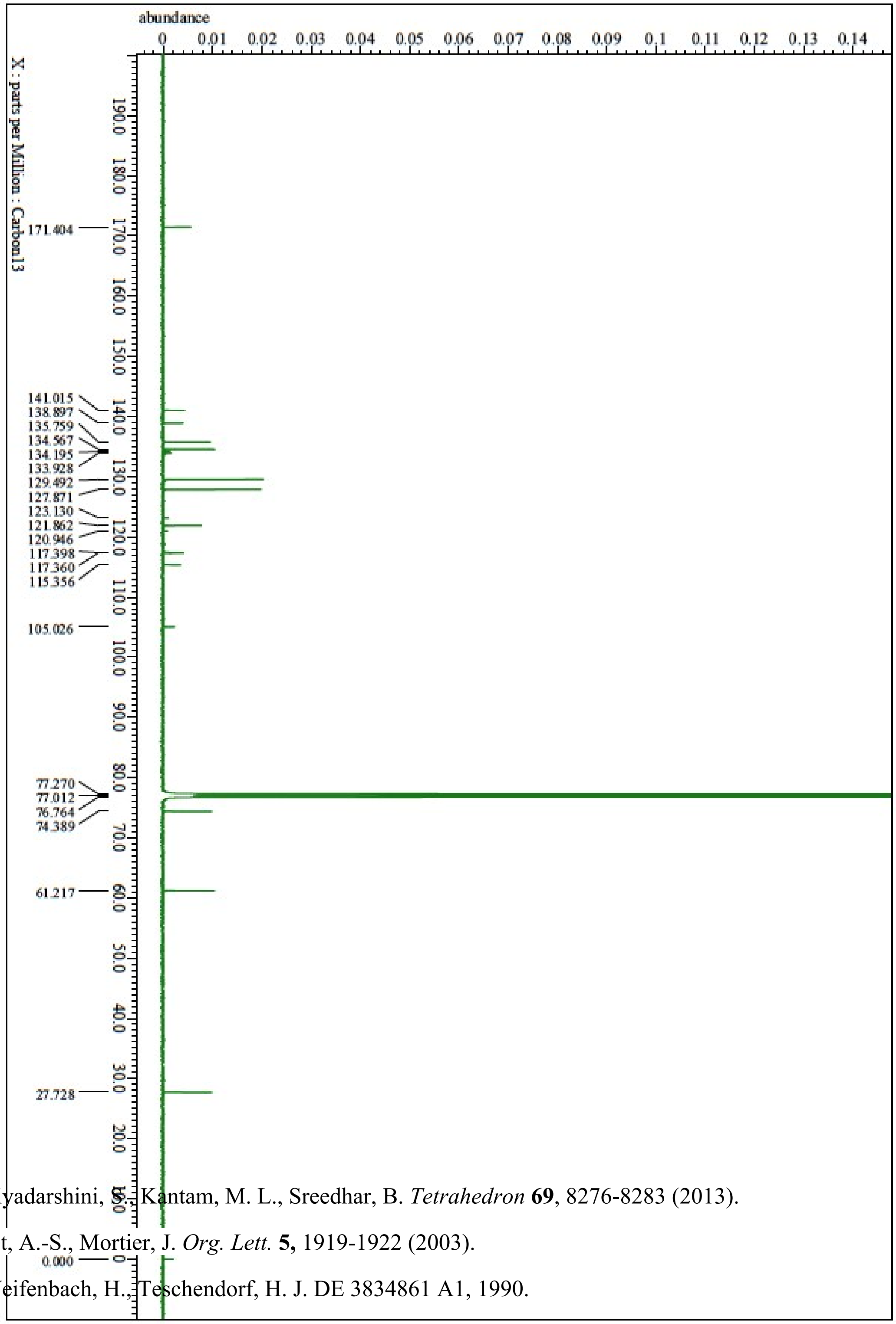

abundance
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
X : parts per Million : Carbon13
171.694
158.112
141.143
136.612
135.649
134.047
129.745
126.158
121.847
120.531
117.402
117.364
117.326
115.552
112.833
104.812
77.418
77.160
76.912
74.175
59.276
56.710
31.710
29.821
27.875
22.772
14.245
0.119
32.39
274.71
273.51
274.71
4.80



15c


abundance
0
0.1
0.2
0.3
X : parts per Million : Carbon13
171.696
164.505
141.277
135.762
134.211
134.000
133.780
130.342
130.093
123.046
121.888
121.227
117.369
117.340
115.444
114.678
114.611
104.921
77.308
77.097
76.887
74.330
61.519
55.784
27.979

16



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