Supporting Information

Modulation of the fibrillogenesis inhibition properties of two transthyretin ligands by halogenation

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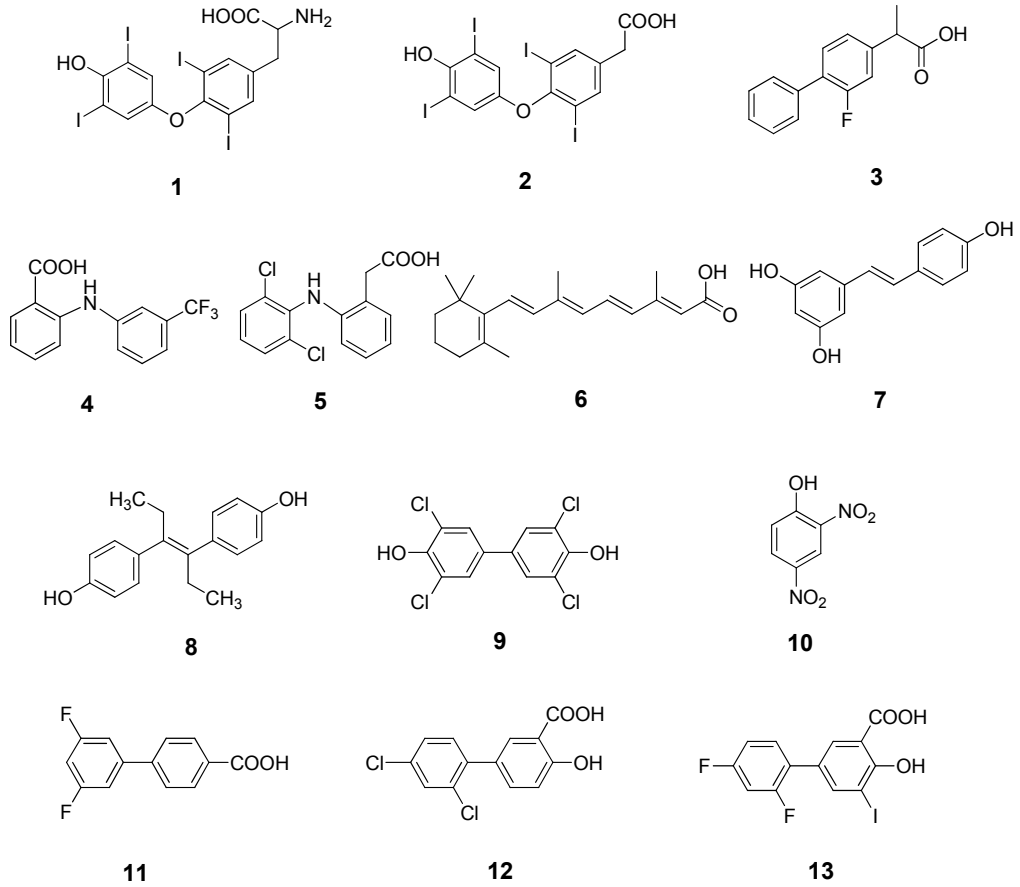

Figure S0. Selected TTR ligands from the Protein Data Bank:

1 thyroxine or T4, **ligand T44** in pdb 2ROX;
2 3,3',5,5'-tetraiodothyroacetic acid or T4Ac, **ligand T4A** in pdb1Z7J;
3 flurbiprofen, **ligand FLP** in pdb 1DVT;
4 flufenamic acid, **ligand FLF** in pdb 1BM7;
5 diclofenac, **ligand DIF**inpdb 1DVX;
6 retinoic acid, **ligand REA** in pdb 1TYR;
7 resveratrol, **ligand STL** in pdb1DVS;
8 diethylstilbestrol**, ligand DES** in pdb 1TT6;
9 3,5,3',5'-tetrachlorobiphenyl-4,4'-diol, **ligand PCQ** in pdb 2G5U;
10 2,4-dinitrophenol, **ligand DNF** in pdb 2B15;
11 3',5'-difluorobiphenyl-4-carboxylic acid, ligand FBC in pdb 2B9A;
12 2',4'-dichloro-4-hydroxy-1,1'-biphenyl-3-carboxylic acid, **ligand 3CA** in pdb 2B77;
13 iododiflunisal, **ligand FHI** in pdb 1Y1D.

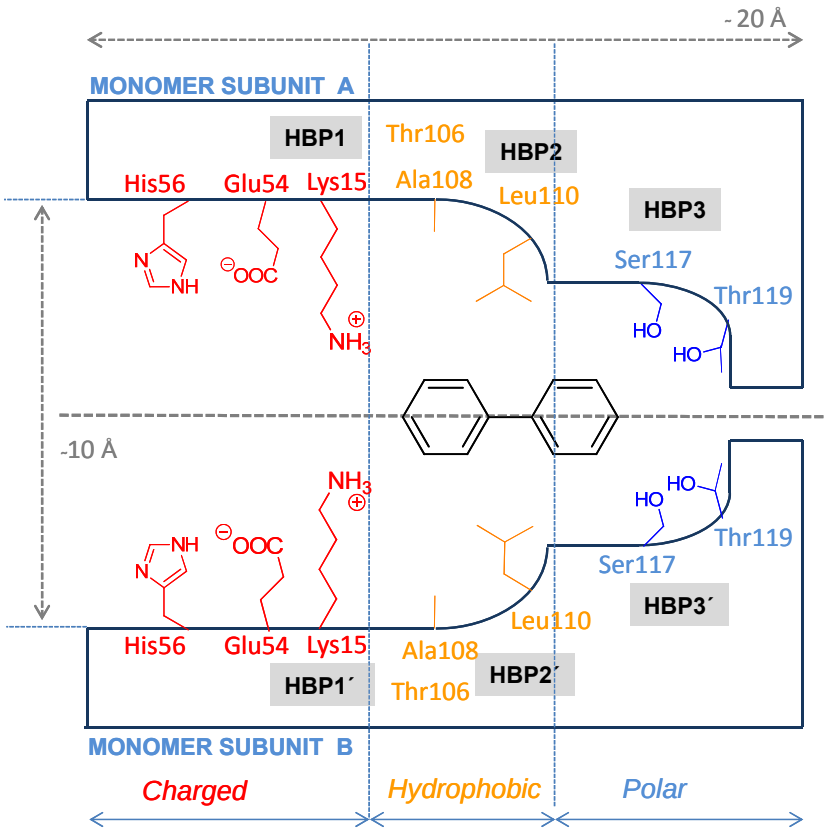

Figure S1. Chemical nature of the ligand binding site of TTR.

COMMENT 1:

Crystallographic properties of the TTR-ligand complexes. To properly compute the PDB crystal information it was important to take into account that, as the majority of human TTR-ligand crystal complexes, the ones considered in the present work belong to the orthorhombic space group $P2_12_12$. In all of them, the two binding sites located at the dimer-dimer interface are bisected by the crystallographic twofold axis (C_2). Consequently, the electron density observed for non-symmetric ligands in each binding site is an average of the two symmetry-related positions. Therefore, ligands not possessing twofold symmetry that adopt one single conformation or binding mode bound to TTR, must have a 50% statistical disorder or 0.50 of maximal occupation in each binding site. Taking into account the symmetry-related conformer or binding mode the maximal occupation for the majority of these ligands results to be of 100%. (Table S1). Flufenamic acid (**4**), for which it has been possible to distinguish two conformations (*cis* and *trans*) in the binding site of TTR is an exception. In this case, the occupation factor of each conformer is 0.25 and by considering the two symmetry-related conformers associated to each one of them, the resulting maximal occupation for (**4**) in the binding site is 1. In addition, this maximal value of occupancy is not observed in the TTR complexes with iododiflunisal (**13**), retinoic acid (**6**), tetraiodothyroacetic (**2**),and diclofenac (**5**) (Table 1). For these ligands, deviation from the maximum occupancy value could be due to the fact that their structures were not refined to obtain a final occupancy of 0.50 for the ligand atoms.

LIGAND	PDB	LIGAND PDB code	Binding mode	LIGAND OCCUPANCY	Reference In PDB
1	2ROX	T44	F	0.50	a
2	1Z7J	T4A	F	0.18	b
			R	0.22	
3	1DVT	FLP	F	0.50	c
4	1BM7	FLF	F	0.25	d
5	1DVX	DIF	R	0.33	c
6	1TYR	REA	F	0.25	e
7	1DVS	STL	F	0.50	c
8	1TT6	DES	F	0.50	f
9	2G5U	PCQ	R	0.50	g
10	2B15	DNF	R	0.50	h
11	2B9A	FBC	R	0.50	i
12	2B77	3CA	R	0.50	i
13	1Y1D	FHI	F	0.29	j

Table S1 Crystallographic properties of the ligands and ligand-TTR complexes. Forward and reverse binding modes are indicated by F and R, respectively.

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d) Peterson, S.A.; Klabunde, T.; Lashuel, H.A.; Purkey, H.; Sacchettini, J.C.; Kelly, J.W. Inhibiting transthyretin conformational changes that lead to amyloid fibril formation. *Proc. Natl. Acad. Sci. U S A*. **1998**, *95*, 12956-12960.

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COMMENT 2:

Hydrogen bonds involving Lys 15 can be either direct, such as in the case of (**3**), (**4**), (**6**) or (**8**) or mediated by a water molecule as in the case of (**7**), (**10**) or (**13**) (Figure S2)

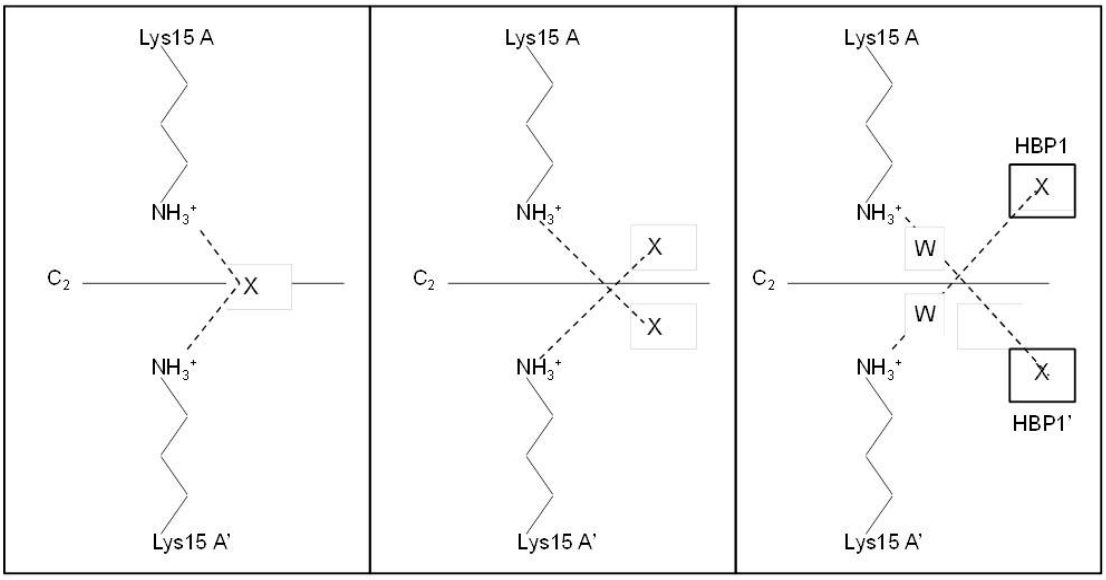


Figure S2. Types of hydrogen bond involving Lys15

COMMENT 3:

Besides the conformational changes observed for the Lys15 residues, other important structural rearrangements produced by ligand binding occur at the inner part of the binding site. In the apo-TTR form, the HBP3 and HBP3' are occupied by water molecules, each one acting as a bridge between the hydroxyl groups of the Ser117 and Thr119 of each pocket.The placement of a ligand substituent in any of these pockets displaces the initial water molecule, leading to a rotation of the side chains of these residues. The conformation adopted by residues Ser117 and Thr119 upon ligand binding depends on the nature of the substituting group that, in turn, triggers two major effects. On the one hand, it allows the formation of additional intermonomer

interactions which may contribute to stabilize the TTR tetramer. On the other hand, it modifies the surface polarity of the HBP3/3' pockets.

Figures S3 and S4 schematically describe the conformational changes of residues Ser117 and Thr119 upon ligand binding. In the apo-TTR form, only Thr119 takes part in intermonomer interactions, forming a hydrogen bond to the hydroxyl group of Ser115 from the adjacent monomer. This interaction is conserved in the TTR-(**3**) complex which has no substituents in the HBP3/3' pockets. Upon ligand binding, this hydrogen bond is replaced by two new additional interactions: Thr119 A (OH) – (O) Tyr114 B and Thr119 A (OH) – water – (O) Asp18 A' (or Thr119 A' (OH) – (O) Tyr114 B' and Thr119 A' (OH) – water – (O) Asp18 A). In contrast to Thr119, Ser117 only takes part in the intermonomer interaction network upon ligand binding.

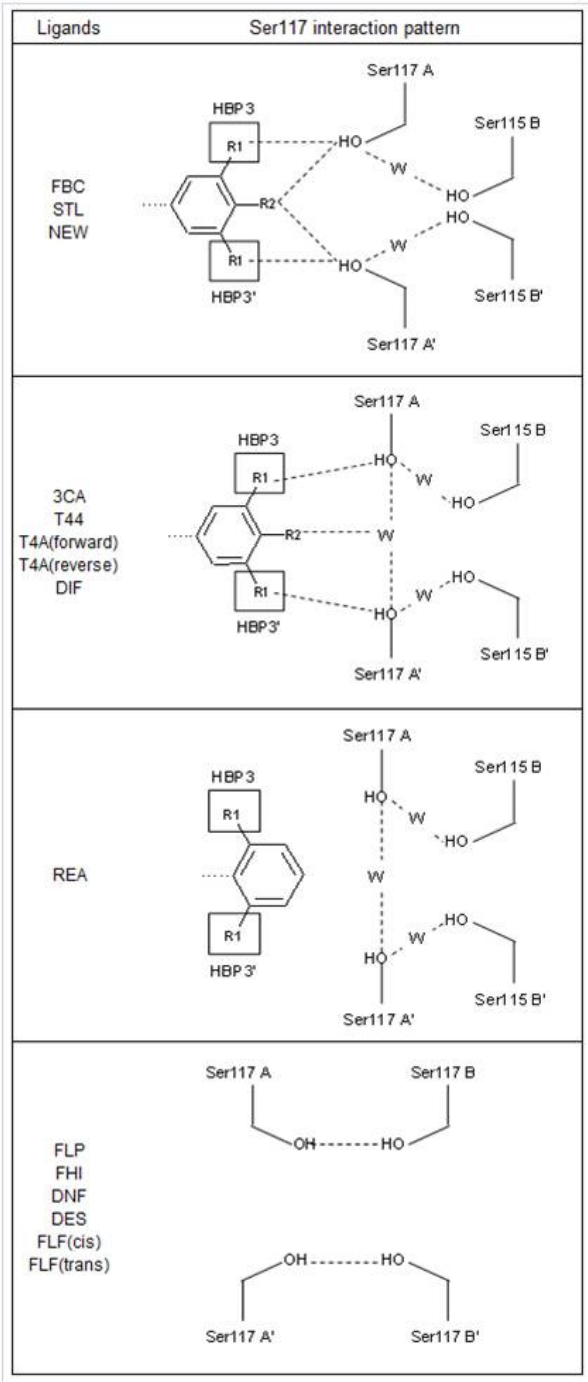


Figure S3

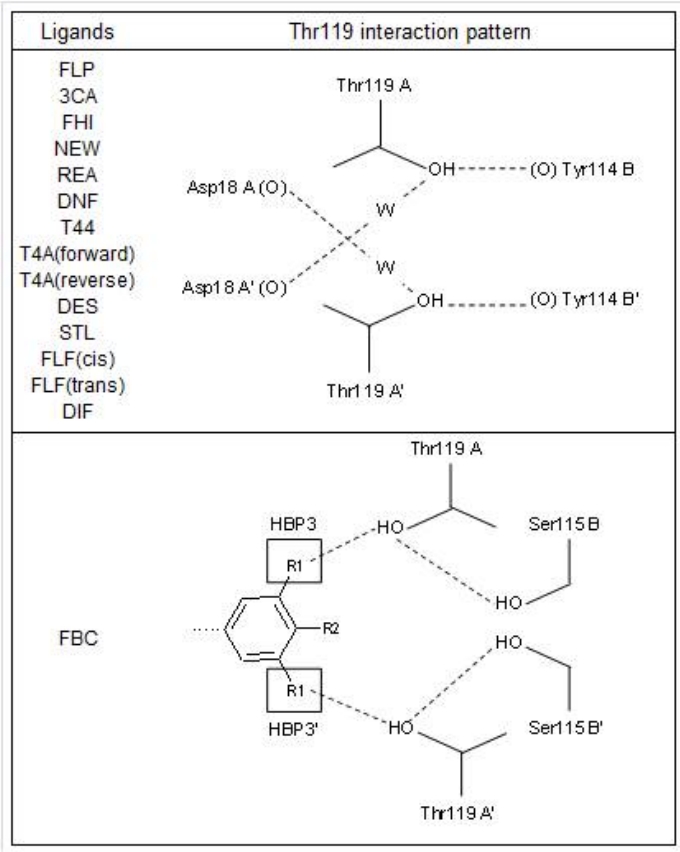


Figure S4

COMMENT 4

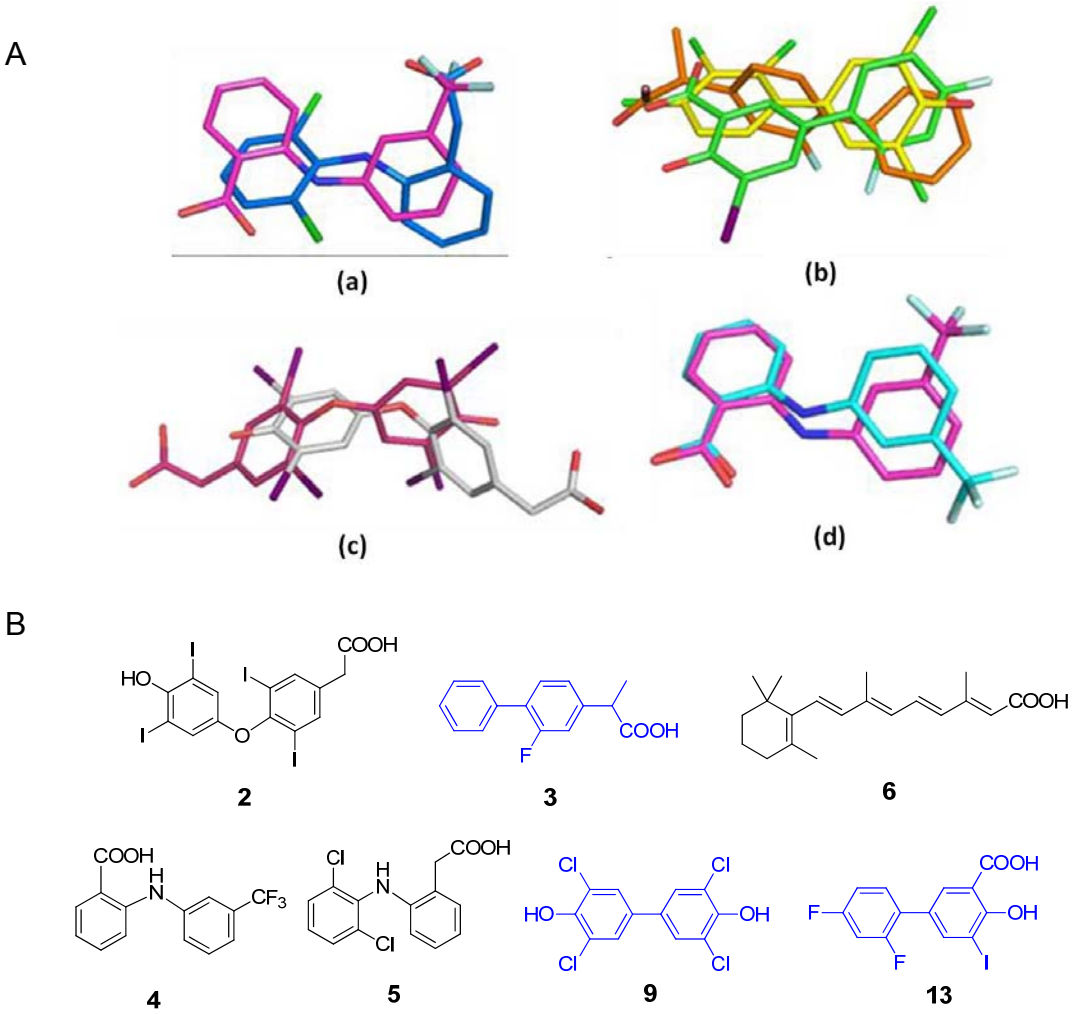


Figure S5: A) Some examples of the promiscuous ligand-binding properties of TTR. B) Selected ligands from TTR-ligand complexes available at the PDB (See Figure S0 for details on the related PDB structures)

A clear example of the lack of correlation between binding mode and biological activity is provided, in our case, by compounds (**3**) and (**6**).Both compounds bind to TTR in the forward mode, but their RA (%) are of 35% and 100% respectively. More generally, in spite of the large amount of information accumulated on the forward and reverse modes of many different families of ligands, a successful prediction of the ligand binding mode in the binding site of TTR is a very difficult task for several reasons: (a) very similar and structurally related compounds can bind to the protein in both modes. For example, (**4**) and (**5**) two bisarylamine compounds, bind to TTR in forward and reverse mode, respectively (Figure S5a); (b) ligands containing the same scaffold, *i.e.* biphenyls (**3**), (**9**) and (**13**), can be placed differently in the TTR binding site (Figure S5b); (c) some ligands adopt more than one orientation bound to TTR. This is the case of the thyroxine derivative 3,3',5,5'-tetraiodothyroacetic acid (**2**), which is able to bind transthyretin in both forward and reverse modes (Figure S5c); and (d) there are ligands that are able to adopt more than one conformation bound to TTR. This is the case of the crystallographic complex TTR-(**4**) which shows the ligand bound to the protein in both *cis* and *trans* conformations (Figure S5d).

LIGAND	PDB	LIGAND PDB code	Binding mode
2	1Z7J	T4A	F
			R
3	1DVT	FLP	F
4	1BM7	FLF	F
5	1DVX	DIF	*R*
6	1TYR	REA	F
9	2G5U	PCQ	*R*
13	1Y1D	FHI	F

COMMENT 5

Indeed, one of the clearest evidences pointing out that TTR constitutes an unusual system comes from the superposition of the ligand conformations deduced from the crystal structures that clearly demonstrate the impossibility to define a classical pharmacophore due to the promiscuous ligand-binding of TTR (Figure S5a, Comment 4).

Some examples of the promiscuous ligand-binding properties of TTR. (a) Very similar compounds (**4**) in fuchsia and (**5**)in blue bind to TTR in forward and reverse modes respectively; (b) The same compound (**2**) is able to bind to TTR in both forward (maroon) and reverse (grey) modes; (c) The same compound (**4**) is able to adopt both *cis* and *trans* conformations within the binding site of TTR.

The computational analysis performed on the series of 13 crystallographic TTR-ligand complexes considered in the present work provides good evidences about the promiscuous ligand–binding properties of TTR. This promiscuity is supported by: (1) the ability of TTR to accommodate a wide diversity of structures; (2) structurally related compounds can bind in forward or reverse mode; (3) structurally similar ligands can be placed rather differently within the binding site; (4) one single molecule can bind in both forward and reverse modes and, (5) a ligand can adopt more than one conformation into the binding site of TTR.

In addition and regardless of the structure, the chemical properties or the binding mode of the ligand to TTR, it is possible to deduce the following SAR correlations and binding features: (1) no single interaction can be qualitatively correlated with the fibrillogenesis inhibitory activity of the ligands; (2) A common feature in all these structures is that regardless of the ligand, there is always a contribution of the residues Lys15, Leu17, Ala108, Leu110, Ser117 and Thr119 of monomers A and A' to the van der Waals interaction energy between TTR and the ligand; (3) ligand binding allows residues Ser117 and Thr119 to make additional intermonomer interactions, reinforcing their contribution to the stability of the tetramer; (4) no relationship can be found between the binding mode or number of occupied HBPs and the inhibitory potency of a compound and finally, (5) the most active compounds have in common an halogen atom positioned in the HBP1/1' or HBP3/3' pockets.

The estimated interaction values for Ala108, Ser117 and Thr119 are generally lower and remain constant across the series. However, the involvement of Ser117 and Thr119 in the hydrogen bond network of the TTR-ligand complexes enhances their contribution to the stability of the complex. In contrast to these two residues, the contribution of residues Lys15 to ligand binding is highly variable but the most active compounds have a large contribution of the Lys15 residues to their binding (Figure S6).

Figure S6. Van der Waals contribution to ligand binding made by individual residues of monomers A and A'. Colour intensity is directly related with the strength of the interaction.

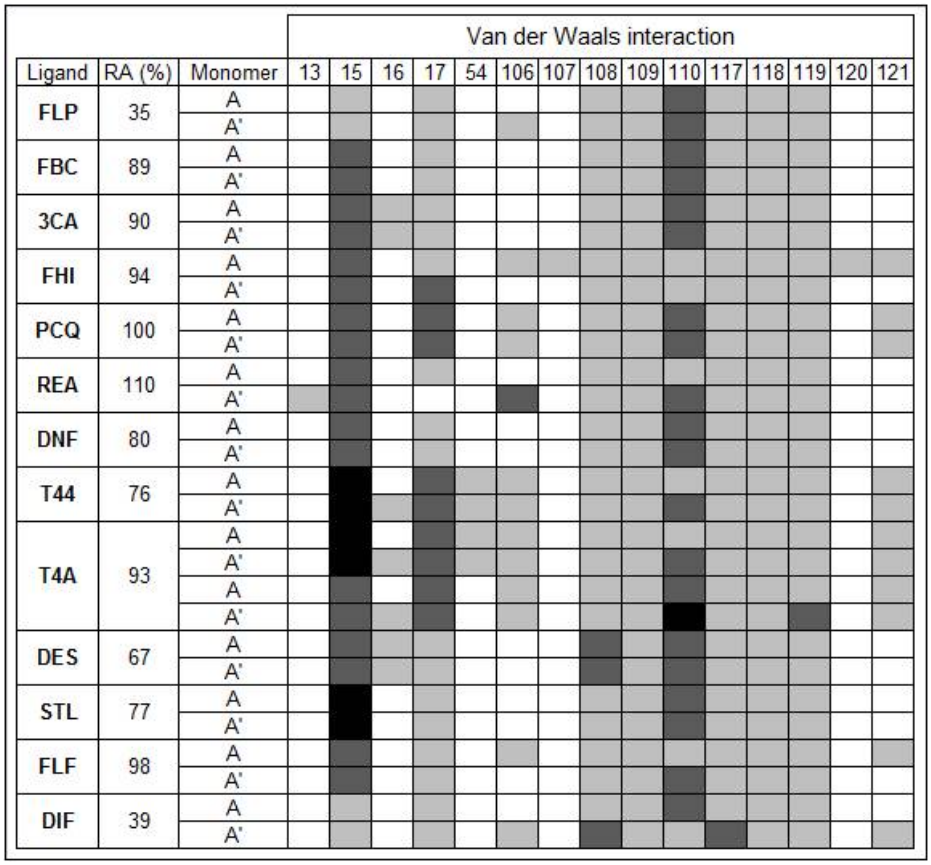
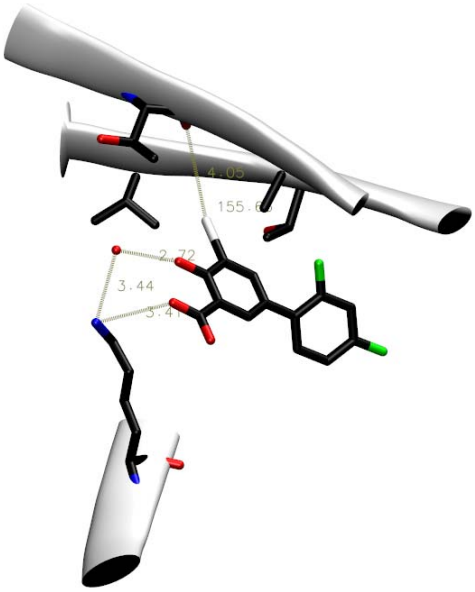


Figure S7. TTR-iododiflunisal (**13**) complex. Residues Thr106, Ala108, Thr119, and Val121 shape the halogen binding pocket establishing van der Waals contacts with the iodine atom. The –COOH and –OH groups of IDIF are only available for a badly oriented salt bridge and a water mediated hydrogen bond with Lys15, respectively.



CHEMISTRY

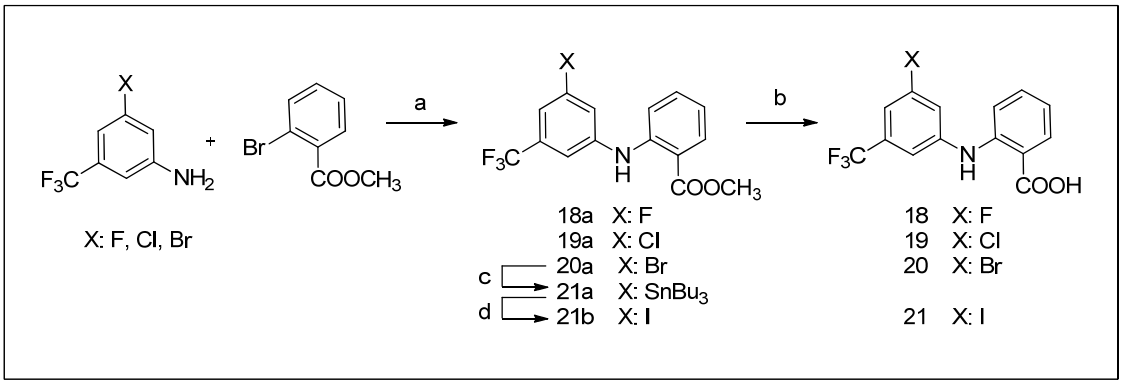
Synthesis of analogues.Flufenamic acid analogues are *N*-aryl anthranilic acids. Conventionally, substituted anthranilic acids can be prepared from anilines via isatins through the Sandmeyer methodology or via Ullmann reactions, this is, either the condensation between a 2-halobenzoic acid and an aryl amine or an anthranilic acid and an aryl halide. Palladium-catalyzed C-N bond-forming methods are widely recognized as convenient and efficient means for obtaining *N*-arylation products.[1] Here we used Buchwald–Hartwig cross coupling reactions of o-halobenzoic acids with arylamines.[2] Synthesis of these halogenated flufenamic acid analogues was achieved via two step reaction. The key feature is first a palladium-catalyzed Buchwald–Hartwig cross coupling reaction followed by saponification of the formed methyl ester (Scheme 1). [3]

Briefly, the methyl anthranilate derivatives **18a**-**20a** were synthesised by palladium catalyzed cross-coupling reaction between commercially available methyl 2-bromobenzoate and the corresponding 5-halogenated 3-trifluoromethyl substituted anilines (fluoro-, chloro- and bromo-). Briefly, the corresponding aniline (1.2 equiv), Cs_2CO_3 (120 mol%), BINAP (5 mol%) and $Pd_2(dba)_3$ (3 mol%) were added to a solution of methyl 2-bromobenzoate (1.2 equiv) in toluene (0.1 M) at room temperature. The reaction mixture was stirred at 120 ºC for 4-48 h.

The iodinated anthranilic ester compound **21b** could not be prepared following the same pathway. A new pathway was explored using the bromo methyl ester **20a**. Heating **20a** in the presence of sodium iodide and copper iodide (I) in *N*-methyl pyrrolidone at 160 ºC for 24h yielded a mixture (1:1) of the bromo and iodo analogues with a low conversion (58%) as analysed by HPLC. Thus, compound **21b** was synthesised in two steps from the brominated compound **20a** involving an organostanne as intermediate. The arylstannane intermediate was obtained by a Stille-type cross coupling reaction. Alternatively, treatment of the bromocompound **20a** with hexabutylditin in the presence of a catalytic amount of $Pd(PPh_3)_4$ afforded the desired aryl stannane**21a** containing a tributylstannyl group. The iodinated methyl anthranilate**21** was obtained by electrophilic iodination of the stannyl derivative with

a mixture of sodium iodide and *N*-chlorosuccinimide in equimolar amounts yielded. The final saponification step with lithium hydroxide in a mixture of dioxane/H_2O (5:1) at 80 ºC was performed to obtain the final *N*-aryl anthranilic acid derivatives **18-21**.

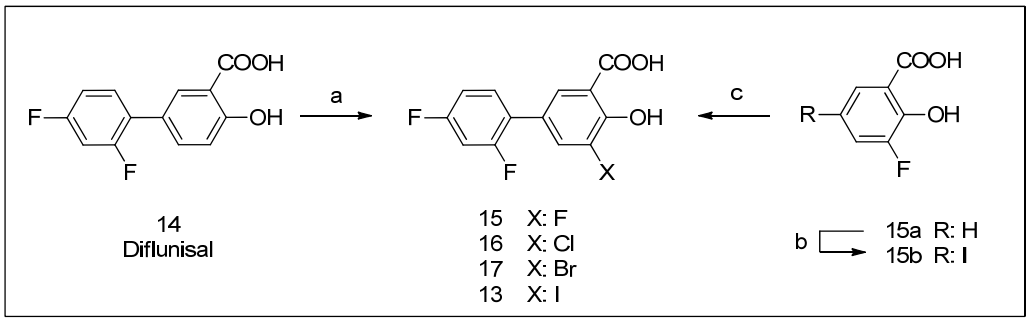
Scheme 1. Synthesis of halogenated flufenamic acid analogues[a]



[a] Reagents and conditions: (a) 2,5 mol% Tris(dibenzylideneacetone)dipalladium(0) ($Pd_2(dba)_3$), 5 mol% *rac*-2,2'-bis(diphenylphosphino)-1,1´-binaphthyl (BINAP), Cs_2CO_3, toluene, reflux, 15h; (b) LiOH (5 equiv), dioxane/H_2O (5:1) 80 ºC, 4h; (c) LiCl (5 equiv), $Pd(PPh_3)_4$ (0,3 equiv), hexabutylditin $(SnBu_3)_2$, dioxane, reflux, 4h; (d) NaI (1.1 equiv), NCS (1.1 equiv), acetonitrile, rt, 30 min.

Synthesis of halogenated diflunisal compounds **13**, **16** and **17** was achieved from the commmercially available NSAID drug diflunisal using different procedure involving halogenating reagents. First, the synthesis of the iododerivative **13** (*iododiflunisal*) was performed as already reported[4] using bis(pyridine)iodonium(I) tetrafluoroborate or Barluenga's reagent.[5] Solution-phase bromination of diflunisal using commercially available polymer bround brominating agent[6] (poly(4-vinylpyridine hydrobromide perbromide) suspended in acetonitrile yielded the corresponding analogue **17**. After unsuccessful attempts to directly fluorinate diflunisal using Selectfluor reagent[7] (F-TEDA: 1-Chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) in acetonitrile at rt, an alternative pathway was chosen starting with commercially available 3-fluorosalicylic acid (**15a**). A first step in this pathway implied the direct iodination of the salicylic compound **15a** which afforded the iodo compound **15b** in high yield. A second step was the palladium-catalysed cross-coupling reaction (Suzuki reaction) in neat water between the iodosalicylic derivative and the 2,4-difluorophenyl boronic acid using palladium acetate as catalyst (1 mol%) and sodium carbonate as a base. The coupling reaction yielded the fluorinated analogue **15** in a 95% yield.

Scheme 2. Synthesis of halogenated diflunisal analogues[a]



[a]Reagents and conditions: (a) for **13**: IPy_2BF_4 (Barluenga's reagent) (1.5 equiv), dichloromethane, rt, 1h; for 16: NCS (2.1 equiv), a drop of concentrated HCl, acetonitrile, rt, 1h; for 17: pyridine hydrobromide perbromide polymer-bound (PVPHP) (~1 mmol Br_3 per g of resin, 5 equiv), dichloromethane, rt, 18h; (b) from 3-fluorosalicylic acid (15a), then IPy_2BF_4 (Barluenga's reagent) (1.5 equiv), dichloromethane, rt, 1h; (c) 2,4-difluorophenyl boronic acid (1 equiv); 1 mol% $Pd(OAc)_2$, Na_2CO_3 (3 equiv), H_20, rt, 3h.

ABBREVIATIONS

AcOH, acetic acid; IPy_2BF_4, bis(pyridine)iodonium(I) tetrafluoroborate; NCS, *N*-chlorosuccimide; F-TEDA; 1-Chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate); DMSO, dimethylsulfoxide; EtOAc, ethyl acetate; HRMS; high resolution mass spectrometry; HPLC, high performance liquid chromatography; 1H NMR, proton nuclear magnetic resonance; PVPHP, pyridine hydrobromideperbromide polymer-bound; $Pd(PPh_3)_4$; RT, retention time; Tetrakis(triphenylphosphine)palladium(0); ($Pd_2(dba)_3$), Tris(dibenzylideneacetone)dipalladium(0).

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CHEMICAL SYNTHESIS OF COMPOUNDS

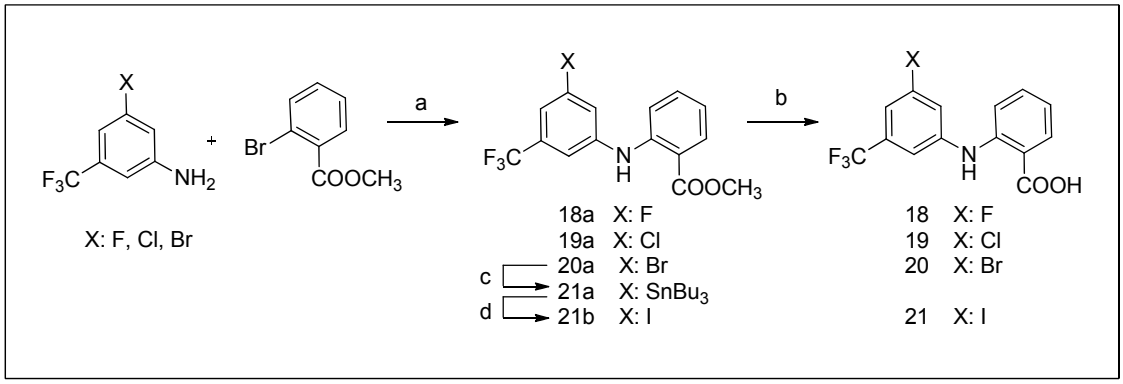
TLC analyses were carried out on Merck Kieselgel 60 F_{254} silica gel plates. Visualization was by UV light (254 nm). Chromatographic purification was carried out on Silica Gel columns 60 (70-200 μm, 70-230 mesh) from SDS. Solvents for synthesis purposes were used at GPR grade. Reverse-phase HPLC analyses were performed on a MERCK-HITACHI (D-6000) HPLC System with an UV L-4000 detector (λ =214 nm), a L-6200 pump, and an AS-2000 automatic injector, using a Merck LiChroCART 250-4 LiChrospher 100-5 RP-C18 column (250 mm × 4.6 mm) with injection volume at 10 μL and sample concentrations at 1−2 mg/0.5 mL in 100% water; the sample was detected at single wavelength of 214 nm with a mobile phase system composed with a mixture of acetonitrile:water each containing an 0.1 % of TFA at 1 mL/min flow. The column was maintained at room temperature. The gradient program used (GEN1) was as follows: from a initial (50:50) mixture of A:B to a (10:90) mixture of (A:B) in 25 min, then back to (50:50) in 15 min. All compounds reported here exhibited spectral data consistent with their proposed structures and had HPLC purities in excess of 97%. Chemical names were generated using ChemBioDraw version by CambridgeSoft. 1H and 13C NMR spectra were recorded at 400 MHz and 100,62 MHz, respectively, in $CDCl_3$ or $(CD_3)_2SO$ on a Varian Mercury-400 spectrometer. Chemical shifts are reported relative in parts per million (ppm) relative to the residual signal of the deuterated solvent (δ 7.27 for ^1H; δ 77.23 for ^{13}C) or deuterated or ^{13}C labeled dimethyl sulfoxide (δ 2.50 for ^1H, δ 39.53 for ^{13}C) as internal standards. 1H-NMR data are tabulated in the following order: multiplicity as follows (s, singlet; d, doublet; t, triplet; m, multiplet; br, broad), coupling constants (J) are reported in Hertz (Hz), and number of protons. HRMS spectra (UPLC-TOF/MS) were recorded on a Waters ACQUITY UPLC System with Waters LCT Premier XE Mass Spectrometer operating either in the positive ion electrospray mode or in negative electrospray mode. Water and acetonitrile were used as carrier solvents.

Compound characterization

All compounds were obtained in milligram quantities. Details of the synthesis and characterization of each compounds is described below. Selected spectra are included inn the Supporting Information. Structures of all reported compounds were confirmed by ^1H and ^{13}C NMR and their mass confirmed by HRMS. Purity was determined by HPLC analysis. All reported compounds had >95% purity.

Synthesis of compounds

ANTHRANILIC SERIES

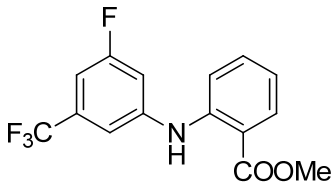


***General procedure A*: Pd^0-catalyzed reaction between 3-halo-5-(trifluoromethyl)anilines and methyl 2-bromobenzoate.**

A round bottom flask was charged with Cs_2CO_3 (1.20 mmol), *rac*-BINAP (0.05 mmol) and $Pd_2(dba)_3$ (0.025 mmol). The mixture was gently purged with argon, suspended in anhydrous toluene (8 mL) and refluxed for 5 min. Then, a solution of 3-halo-5-(trifluoromethyl)aniline (1.00 mmol) and methyl 2-bromobenzoate (1.10 mmol) in anhydrous toluene (2 mL) was added dropwise. The reaction mixture was refluxed overnight and then diluted with 50 mL of ethyl acetate, filtered over Celite and evaporated to dryness. The residue was then purified by silica gel column chromatography (hexane/ethyl acetate 85:15).

***General procedure B*: Saponification of methyl esters**

To a stirred solution of the corresponding anthranilic methyl ester (1.00 mmol) in 1,4-dioxane (5 mL) was added a solution of LiOH (5.00 mmol) in water (1 mL). The mixture was then heated at 80 ºC for 4 h, acidified with 0.25 M HCl (20 mL) and diluted with ethyl acetate (50 mL). The phases were separated and the aqueous phase was back extracted with more ethyl acetate (25 mL). The organic layer was separated and washed with brine, dried over anhydrous Na_2SO_4, and concentrated. The residue was purified by silica gel column chromatography (hexane/ethyl acetate (1:1)) to afford the pure acid.



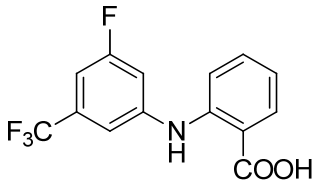
MethylN-(3-fluoro-5-(trifluoromethyl)phenyl)anthranilate (18a):

General procedure A: From 3-fluoro-5-(trifluoromethyl)aniline (361 mg, 2.01 mmol) and methyl 2-bromobenzoate (337 μL, 2.4 mmol). Silica gel column chromatography afforded **18a** (534 mg, 85%) as a white solid.

White solid.**RP-HPLC** (GEN1): RT = 23,85 min. **^{1}H-NMR (500 MHz, CD_3COCD_3):** 3.91 (s, 3H), 6.98 (ddd, *J* = 16.5, 11.0, 3.5,1H), 7.04-7.12 (m, 1H), 7.34 (dt, *J* = 18.0, 3.5, 1H), 7.41 (m, 1H), 7.45-7.47 (m, 2H), 8.00 (ddd, *J* = 13.5, 2.5, 1.1, 1H), 9.63 (br s, 1H). **^{13}C-NMR (75 MHz, CD_3COCD_3):** 53.3, 107.1 (dq, *J*= 25.1, 3.5), 111.1 (d, *J* = 24.8), 114.0 (dq, *J* = 3.3, 3.3), 116.5, 117.7, 121.6, 125.1 (qd, *J* = 267.4, 5.2), 133.4, 133.8 (qd, *J* = 34.2, 12.3), 136.0, 146.5 (d, *J* = 10.7), 146.5, 165.1 (d, *J* = 244.5), 169.8. **HRMS (ESI$^+$):** Calc. for $[C_{15}H_{11}F_4NO_2+H]^+$ = 314.0799; found 314.0806.

N-(3-Fluoro-5-(trifluoromethyl)phenyl)anthranilic acid (18)

General procedure B from **18a** (200 mg, 0.64 mmol). Silica gel column chromatography afforded **18** (190 mg, 89%) as a white solid.

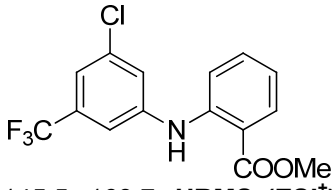


White solid.**RP-HPLC** (GEN1): RT = 14,93 min.**^{1}H-NMR (500 MHz, DMSO-d_6)**: 6.99 (ddd, *J* = 9.0, 7.0, 1.0, 1H), 7.13 (dt, *J* = 8.5, 1.5, 1H),

7.30-7.38 (m, 2H), 7.40 (dd, *J* = 8.0, 1.0, 1H), 7.50 (ddd, *J* = 10.0, 6.5, 1.5,1H), 7.94 (dd, *J* = 8.0, 2.0, 1H), 9.65 (s, 1H). **^{13}C-NMR (100 MHz, CDCl$_3$):** 104.8 (dq, *J* = 25.5, 3.8), 108.8 (d, *J* = 24.7), 111.4, 116.3, 116.7, 120.2, 123.3 (qd, *J* = 267.1, 3.4), 131.7 (qd, *J* = 34.2, 12.9), 131.8, 134.0, 143.9, 144.8, (d, *J* = 11.1), 162.8 (d, *J* = 243.4), 169.1. **HRMS (ESI$^-$):** Calc. for $[C_{14}H_9F_4NO_2\text{-}H]^-$ = 298.0497; found 298.0482.

Methyl N-(3-chloro-5-(trifluoromethyl)phenyl)anthranilate (19a)

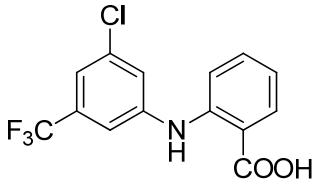
General procedure A: From 3-chloro-5-(trifluoromethyl)aniline (215 mg, 1.10 mmol) and methyl 2-bromobenzoate (143 μL, 1.00 mmol). Silica gel column chromatography afforded **19a** (106 mg, 32%)as an oil.



Colorless oil. R_f (hexane/EtOAc 70:30) = 0.65.**^{1}H-NMR (400 MHz, CDCl$_3$):** 3.92 (s, 3H), 6.89 (ddd, *J* = 8.1, 7.2, 1.2, 1H), 7.24 (s, 1H), 7.31-7.36 (m, 2H), 7.38-7.45 (m, 2H), 8.01 (dd, *J* = 8.0, 1.6, 1H), 9.65 (br s, 1H). **^{13}C-NMR (100 MHz, CDCl$_3$):** 52.1, 113.9, 115.7, 115.7 (quad, *J* = 3.8), 119.2 (quad, *J* = 3.9), 119.3, 123.1 (quad, *J* = 1.0), 123.2 (quad, *J* = 272.9), 131.9, 133.0 (quad, *J* = 32.9), 134.3, 135.7, 143.2, 145.5, 168.7. **HRMS (ESI$^+$):** Calc. for $[C_{15}H_{11}ClF_3NO_2+H]^+$ = 330.0504, 332.0527; found 330.0528, 332.0507.

N-(3-Chloro-5-(trifluoromethyl)phenyl)anthranilic acid (19)

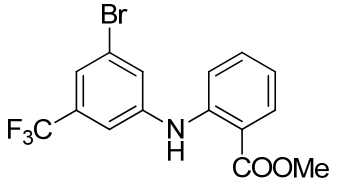
General procedure B: From **19a** (65 mg, 0.197 mmol). Silica gel column chromatography afforded **19** (41 mg, 66%) as a white solid.



White solid. **RP-HPLC** (GEN1): RT = 17,49 min.R_f (hexane/EtOAc 50:50) = 0.16. **^{1}H-NMR (400 MHz, DMSO-d$_6$):** 6.97 (ddd, *J* = 8.1, 7.2, 1.1, 1H), 7.31 (m, 1H), 7.36 (dd, *J* = 8.4, 1.1, 1H), 7.45-7.48 (m, 1H), 7.50 (ddd, *J* = 7.2, 7.0, 1.6, 1H), 7.51-7.53 (m, 1H), 7.92 (dd, *J* = 7.9, 1.6, 1H), 9.58 (s, 1H), 13.21 (br s, 1H). **^{13}C-NMR (100 MHz, CDCl$_3$):** 113.9 (quad, *J* = 3.7), 116.6, 116.9, 117.4 (quad, *J* = 4.0), 120.5, 121.6, 123.3 (quad, *J* = 273.0), 131.5 (quad, *J* = 32.5), 132.0, 134.2, 134.9, 143.9, 144.4, 169.2. **HRMS (ESI$^-$):** Calc. for $[C_{14}H_9ClF_3NO_2\text{-}H]^-$ = 314.0201, 316.0171; found 314.0220, 316.0161.

Methyl N-(3-bromo-5-(trifluoromethyl)phenyl)anthranilate (20a)

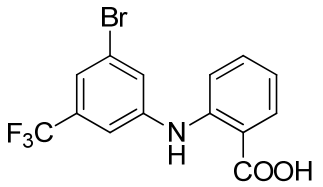
General procedure A: From 3-bromo-5-(trifluoromethyl)aniline (240 mg, 1.000 mmol) and methyl 2-bromobenzoate (351 μL, 2.50 mmol). Silica gel column chromatography afforded **20a** (106 mg, 32%)as a yellowish wax.



Yellowish wax. **RP-HPLC** (GEN1): RT = 25,17 min. R_f (hexane/EtOAc 85:15) = 0.40. **^{1}H-NMR (400 MHz, CDCl$_3$):** 3.92 (s, 3H), 6.89 (ddd, *J* = 8.1, 7.1, 1.2, 1H), 7.32 (dd, *J* = 8.5, 1.1, 1H), 7.39 (dd, *J* = 1.8, 0.7, 1H), 7.43 (dddd, *J* = 8.4, 7.2, 1.7, 0.5, 1H), 7.55 (tt, *J* = 1.9, 0.5, 1H), 8.01 (ddd, *J* = 8.0, 1.7, 0.4, 1H), 9.64 (s, 1H). **^{13}C-NMR (100 MHz, CDCl$_3$):** 52.1, 113.8, 114.8, 115.8 (quad, *J* = 3.8), 119.3 (quad, *J* = 1.0), 121.9 (quad, *J* = 3.8), 123.2 (quad, *J* = 272.9), 123.3, 126.0, 133.1 (quad, *J* = 32.9), 131.9, 134.3, 143.2, 145.5, 168.7. **HRMS (ESI$^+$):** Calc. for $[C_{15}H_{11}BrF_3NO_2+H]^+$ = 373.9999, 375.9978; found 374.0025, 375.9985.

N-(3-Bromo-5-(trifluoromethyl)phenyl)anthranilic acid (20)

General procedure B: **From 20a** (100 mg, 0.27 mmol) silica gel column chromatography afforded **20** (83 mg, 86%) as a white solid.

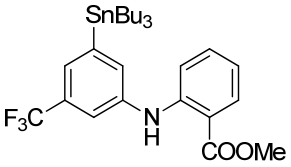


RP-HPLC (GEN1): RT = 18,23 min.R_f (hexane/EtOAc 70:30) = 0.15. **^{1}H-NMR (400 MHz, DMSO-d$_6$):** 6.97 (ddd, *J* = 7.4, 7.3, 1.1, 1H), 7.30 (dd, *J* = 13.0, 1.1, 1H), 7.39-7.42 (m, 1H), 7.44 (dd, *J* = 3.6, 1.7, 1H), 7.45-7.48 (m, 1H), 7.60-7.63 (m, 1H), 7.92 (t, *J* = 2.0, 1H), 9.70 (br s, 1H). **^{13}C-NMR (100 MHz, DMSO-d$_6$):** 114.1 (quad, *J* = 4.3), 116.7, 119.9 (quad, *J* = 3.8), 120.2, 120.3, 122.9, 123.0 (quad, *J* = 267.7), 124.4, 131.8 (quad, *J* =

32.0), 131.9, 133.8, 143.9, 144.4, 169.2. **HRMS (ESI$^-$):** Calc. for $[C_{14}H_9BRf\ _3NO_2\text{-}H]^-$ = 357.9696, 359.9675; found 357.9671, 359.9658.

Methyl N-(3-(tributylstannyl)-5-(trifluoromethyl)phenyl)anthranilate (21a)

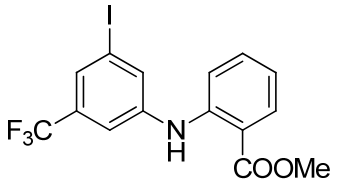
A round bottom flask was charged with LiCl (31 mg, 0.720 mmol), $Pd(PPh_3)_4$ (50 mg, 0.043 mmol) and **20a** (54 mg, 0.144 mmol). The flask was purged with argon and anhydrous 1,4-dioxane (1.5 mL) was added. Then, $(SnBu_3)_2$ (144 μL, 0.288 mmol) was added and the solution was refluxed for 4 h. Crude reaction mixture was adsorbed on silica gel and purified by silica gel column chromatography (hexane/Ethyl acetate 7:3) to afford **21a** (40 mg, 50%)as an oil.



Colorless oil.***R*$_f$** (hexane/EtOAc 70:30) = 0.51. **^{1}H-NMR (400 MHz, CDCl$_3$):** 0.92 (t, *J* = 7.3, 9H), 1.22-1.42 (m, 12H), 1.59-1.70 (m, 6H), 3.93 (s, 3H), 6.86 (ddd, *J* = 8.0, 7.0, 1.3, 1H), 7.32-7.44 (m, 2H), 7.46 (s, 1H), 7.53 (s, 1H), 7.57 (s, 1H), 8.01 (dd, *J* = 8.1, 1.6, 1H), 9.71 (br s, 1H).

Methyl N-(3-iodo-5-(trifluoromethyl)phenyl)anthranilate (21b)

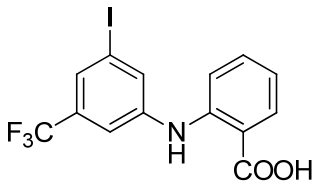
Compound **21a** (73 mg, 0.126 mmol) was dissolved in Acetonitrile and NaI (21 mg, 0.140 mmol) and *N*-chlorosuccinimide (17 mg, 0.140 mmol) were added. The mixture was stirred for 30 min at rt and diluted with Ethyl acetate (20 mL), water (10 mL) and 5% sodium thiosulphate solution (3 mL). Phases were separated and the aqueous phase extracted again with Ethyl acetate (10 mL). Organic layer was dried over Na_2SO_4 anhydrous, filtered and evaporated to dryness. Purification by silica gel column chromatography (hexane/ethyl acetate (85:15)) afforded **21b** (42 mg, 79%)as an oil.



Yellowish wax.***R*$_f$** (hexane/EtOAc 85:15) = 0.40. **^{1}H-NMR (400 MHz, CDCl$_3$):** 3.92 (s, 3H), 6.88 (ddd, *J* = 8.2, 7.1, 1.1, 1H), 7.30 (dd, *J* = 8.5, 1.1, 1H), 7.39-7.45 (m, 2H), 7.58 (s, 1H), 7.75 (s, 1H), 8.02 (dd, *J* = 8.0, 1.7, 1H), 9.61 (br s, 1H). **HRMS (ESI$^+$):** Calc. for $[C_{15}H_{11}F_3INO_2+H]^+$ = 421.9859; found 421.9873.

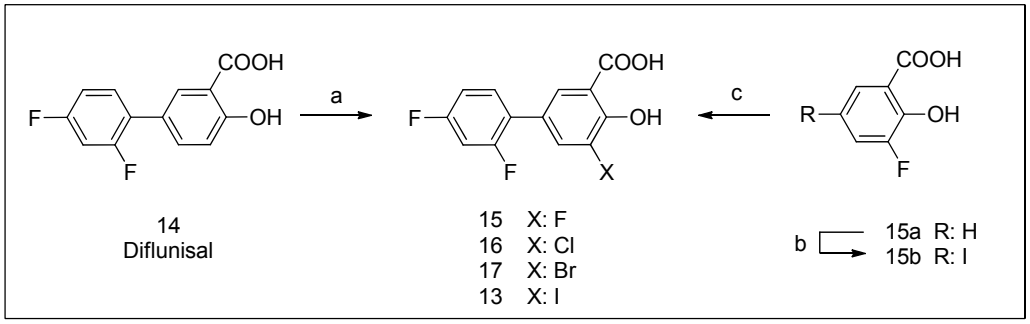
N-(3-Iodo-5-(trifluoromethyl)phenyl)anthranilic acid (21)

General procedure B: From **21b** (42 mg, 0.100 mmol). Silica gel column chromatography afforded **21** (17 mg, 41%) as a white solid.



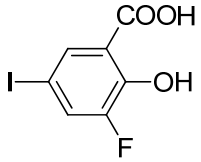
White solid. ***R*$_f$** (hexane/EtOAc 70:30) = 0.15. **RP-HPLC** (GEN1): RT = 19,27 min.**^{1}H-NMR (400 MHz, CDCl$_3$):** 6.89 (ddd, *J* = 8.1, 7.1, 1.2, 1H), 7.24-7.27 (m, 1H), 7.35-7.41 (m, 2H), 7.51 (s, 1H), 7.70 (s, 1H), 8.01 (dd, *J* = 8.0, 1.6, 1H), 9.68 (br s, 1H). **: ^{1}H-NMR (400 MHz, DMSO-d$_6$):** 6.98 (dt, *J* = 7.4, 1.1, 1H), 7.32 (dd, *J* = 12.9, 1.0, 1H), 7.45-7.48 (m, 1H), 7.48 (dd, *J* = 3.6, 1.7, 1H), 7.52-7.55 (m, 1H), 7.77-7.80 (m, 1H), 7.94 (t, *J* = 2.0, 1H), 9.67 (br s, 1H). **^{13}C-NMR (100 MHz, DMSO-d$_6$):** 95.9, 114.7 (quad, *J* = 4.1), 116.4, 120.4, 123.0 (quad, *J* = 272.9), 125.8 (quad, *J* = 3.7), 130.6, 131.8 (quad, *J* = 32.1), 131.9, 134.0, 143.9, 144.0, 169.2. **HRMS (ESI$^-$):** Calc. for $[C_{14}H_9F_3INO_2\text{-}H]^-$ = 405.9557; found 405.9558.

DIFLUNISAL SERIES



3-fluoro-5-iodosalicylic acid (15b)

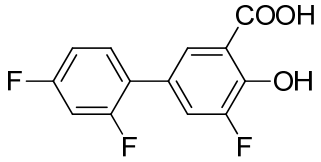
To a stirred solution of 3-fluorosalicylic acid (**15a**) (158 mg, 1.000 mmol) in CH_2Cl_2 (15 mL) was added, in small portions, IPy_2BF_4 (409 mg, 1.100 mmol). The mixture was stirred at rt for 2 h and then diluted with ethyl acetate (50 mL), washed with 0.5 M HCl (2 x 10 mL), with brine (15 mL) and dried over anhydrous Na_2SO_4, filtered and evaporated to dryness. The residue was further purified by silica gel column chromatography (CH_2Cl_2/MeOH/AcOH (90:10:0.5)) to afford pure **15b** (264 mg, 94%) as a white solid.



White solid.***Rf*** (CH_2Cl_2/MeOH/AcOH 90:10:0.5) = 0.13.**^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm):** 7.78-7.82 (m, 3H). **^{13}C-NMR (100 MHz, DMSO-d_6) δ (ppm):** 78.8 (d, *J* = 7.0), 118.0 (d, *J* = 3.4), 129.2 (d, *J* = 19.7), 133.8 (d, *J* = 3.7), 149.2 (d, *J* = 13.0), 151.0 (d, *J* = 249.3), 169.8 (d, *J* = 3.4). **HRMS (ESI$^-$):**Calc. for $[C_7H_4FIO_3\text{-}H]^-$ = 280.9116; found 280.9119.

2',4',5-trifluoro-4-hydroxy-[1,1'-biphenyl]-3-carboxylic acid (15)

Under Ar atmosphere degassed water (2.5 mL) was added over a mixture of 2,4-difluorophenyl boronic acid (45 mg, 0.285 mmol), sodium carbonate (82 mg, 0.774 mmol), $Pd(OAc)_2$ (0.6 mg, 1 mol%) and compound **15b** (73 mg, 0.258 mmol). The suspension was stirred at rt for 3 h and then diluted with ethyl acetate (50 mL) and water (10 mL). The pH was adjusted to 2-3 with 0.5 M HCl and the phases separated. The aqueous layer was back-extracted with more ethyl acetate (2x10 mL) and the combined organic phases dried over Na_2SO_4 anhydrous, filtered and evaporated to dryness. The residue was purified by silica gel column chromatography (CH_2Cl_2/ethyl acetate/AcOH (50:50:0.5)) to afford pure **15** (71 mg, 100%).

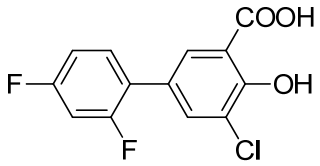


White solid. ***R_f*** (CH_2Cl_2/MeOH 85:15) = 0.13. **RP-HPLC** (GEN1): RT = 10,27 min; **^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm):** 7.19 (tdd, *J* = 8.6, 2.6, 1.0, 1H), 7.37 (ddd, *J* = 11.6, 9.3, 2.6, 1H), 7.62 (td, *J* = 9.0, 6.5, 1H), 7.70 (ddd, *J* = 11.9, 2.3, 1.3, 1H), 7.74 (dt, *J* = 2.5, 1.4, 1H). **^{13}C- NMR (100 MHz, DMSO-d_6) δ (ppm):** 104.6 (t, *J* = 26.0), 112.2 (dd, *J* = 21.2, 3.8), 115.8 (d, *J* = 3.9), 121.3 (dd, *J* = 19.3, 2.4), 122.5-123.1 (m), 124.4 (d, *J* = 6.7), 125.5 (d, *J* = 3.0), 131.7 (dd, *J* = 9.7, 4.4), 149.0 (d, *J* = 13.1), 150.7 (d, *J* = 243.6), 159.1 (dd, *J* = 248.7, 15.5), 161.7 (dd, 260.0, 12.3), 170.9 (d, *J* = 3.6). **HRMS (ESI$^-$):** Calc. for $[C_{13}H_7F_3O_3\text{-}H]^-$ = 268.0347; found 267.0295.

5-chloro-2',4'-difluoro-4-hydroxy-[1,1'-biphenyl]-3-carboxylic acid (16)

To a stirred solution of Diflunisal (50 mg, 0.200 mmol) in acetonitrile (2 ml) was added a solution of *N*-chlorosuccinimide (56 mg, 0.420 mmol) in acetonitrile (1.5 mL). Next, 1 drop of HCl (c) was added and the mixture was stirred for 1 h at rt The mixture was then diluted with CH_2Cl_2 (20 mL), washed with 5% solution of Na_2SO_3 (5 mL) and brine (5 mL) and dried over anhydrous Na_2SO_4,

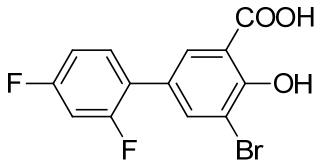
filtered and evaporated to dryness. Further purification by silica gel column chromatography (CH_2Cl_2/MeOH/AcOH (95:5:0.5)) afforded pure **16** (27 mg, 47%) as a white solid.



White solid.R_f (CH_2Cl_2/MeOH/AcOH 95:5:0.5) = 0.11. **RP-HPLC** (GEN1): RT = 12,46 min.**^{1}H-NMR (400 MHz, $CDCl_3$/CD_3OD 95:5) δ (ppm):** 6.86-7.00 (m, 2H), 7.31-7.42 (m, 1H), 7.71 (s, 1H), 7.96 (s, 1H), 9.14 (br s, 1H). **^{13}C-NMR (100 MHz, $CDCl_3$/CD_3OD 95:5) δ (ppm):** 104.5 (dd, *J* = 25.4, 26.5), 111.7 (dd, *J* = 21.2, 3.8), 113.9, 122.1, 123.1 (dd, *J* = 13.6, 4.0), 126.2, 129.3 (d, *J* = 2.6), 131.0 (dd, *J* = 9.5, 4.6), 135.9 (d, *J* = 3.2), 157.0, 159.6 (dd, *J* = 250.4, 11.9), 162.4 (dd, *J* = 249.7, 11.8), 178.0. **HRMS (ESI$^-$):** Calc. for $[C_{13}H_7ClF_2O_3\text{-}H]^-$ = 282.9979; found 282.998.

5-bromo-2',4'-difluoro-4-hydroxy-[1,1'-biphenyl]-3-carboxylic acid (17)

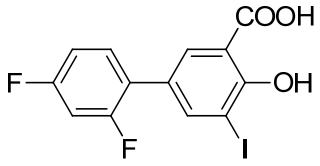
To 600 mg of the polymer bound brominating agent (pyridine hydrobromideperbromide polymer-bound, PVPHP, ~1 mmol Br_3 per g of resin, 3 equiv) in CH_2Cl_2 (5 ml) a solution of Diflunisal (50 mg, 0.200 mmol) in CH_2Cl_2 (1 ml) was added and the mixture was shaken o/n. After removing the resin, the filtrate was diluted with more CH_2Cl_2 (20 mL), and washed with 5% aq. solution of Na_2SO_3 (5 mL) and brine (5 mL) and dried over anhydrous Na_2SO_4, filtered and evaporated to dryness. Further purification by silica gel column chromatography (CH_2Cl_2/MeOH/AcOH (95:5:0.5)) afforded pure **17** (34 mg, 52%) as a white solid.



RP-HPLC (GEN1): RT = 13,32 min. **^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm):** 7.17 (ddd, *J* = 8.5, 8.4, 2.7, 1H), 7.35 (ddd, *J* = 11.6, 9.3, 2.7, 1H), 7.61 (ddd, *J* = 9.0, 9.0, 6.6, 1H), 7.92 (t, *J* = 1.9, 1H), 7.97 (t, *J* = 1.9, 1H).**^{13}C-NMR (100 MHz, DMSO-d_6) δ (ppm):** 104.6 (dd, *J* = 26.9, 25.9), 110.6, 112.2 (dd, *J* = 21.1, 3.7), 114.5, 122.6 (dd, *J* = 13.3, 3.7), 126.1, 129.8 (d, *J* = 3.5), 131.8 (dd, *J* = 9.7, 4.4), 138.2 (d, *J* = 2.3), 157.4, 159.0 (dd, *J* = 248.4, 11.6), 161.8 (dd, *J* = 259.7, 11.6), 171.3. **HRMS (ESI$^-$):** Calc. for $[C_{13}H_7BrF_2O_3\text{-}H]$ = 326.9473, 328.9453; found 326.9463, 328.9445.

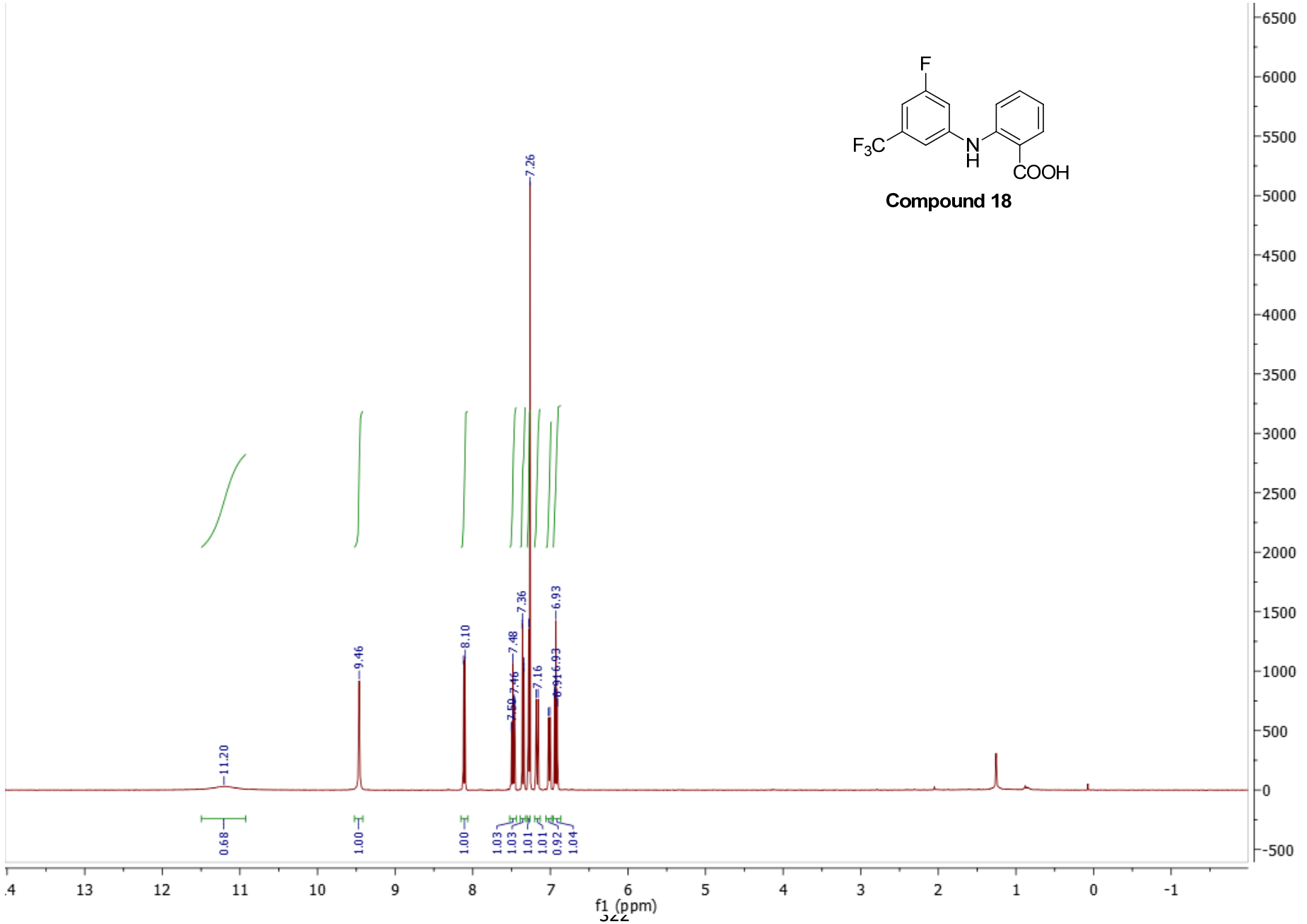
2',4'-difluoro-4-hydroxy-5-iodo-[1,1'-biphenyl]-3-carboxylic acid or Iododiflunisal(13)

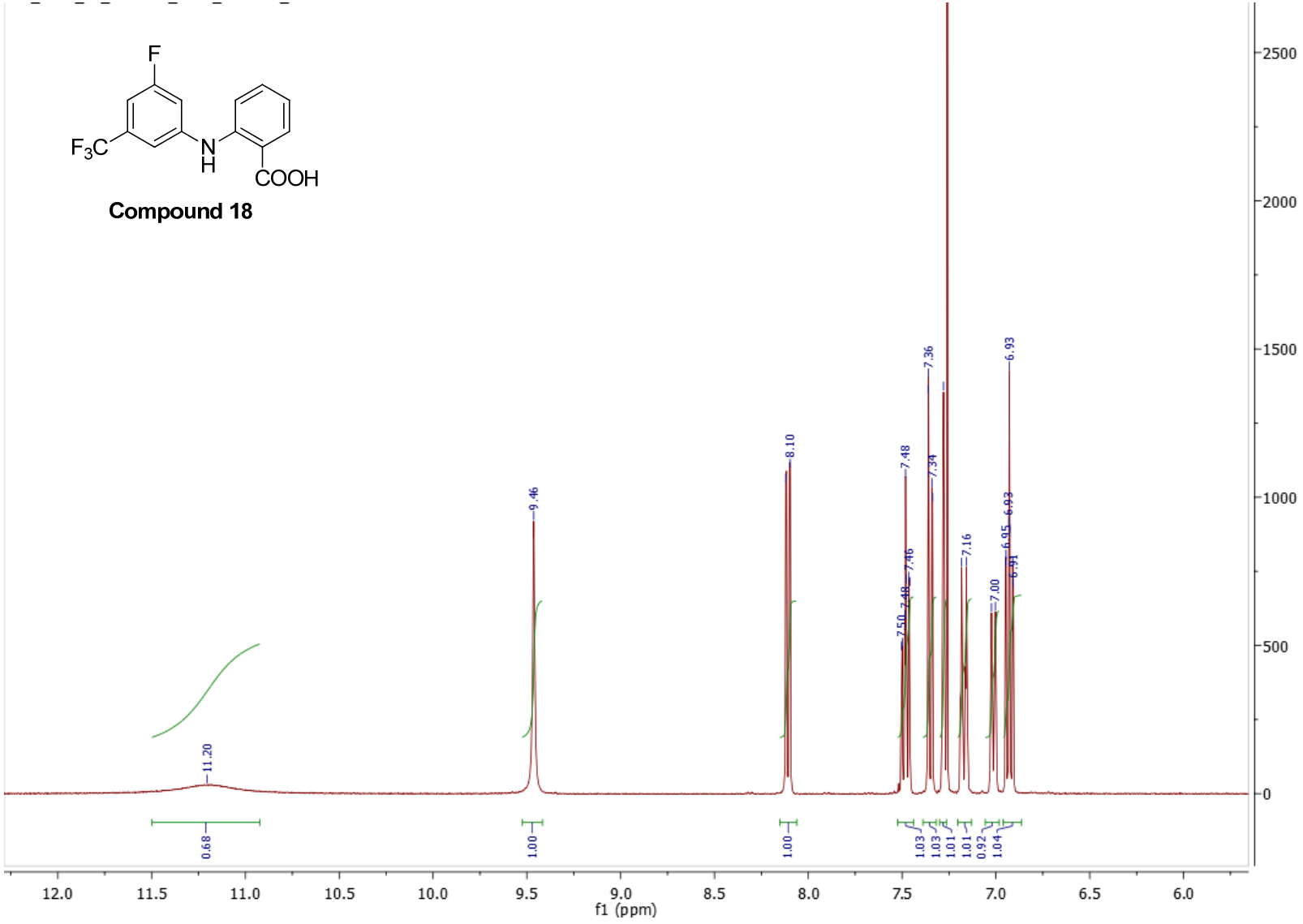
To a solution of 200 mg (0.80 mmol) of diflunisal in 5 ml of dichloromethane, 357 mg (1.2 mmol) of IPy_2BF_4 were added to obtain a substrate/iodinating reagent ratio of (1:1.5) equivalents. The reaction was left under stirring at rt and monitored by HPLC until full conversion to the iodo derivative. After 1,5 h the solution was diluted with dicloromethane and the organic phase was successively washed with HCl 1N and a 0.1N sodium thiosulfate solution. The organic phase was dried over $MgSO_4$ and after evaporation yielded a residue (> 98% purity) which was further purified by column chromatography on silica gel using Cl_3CH/MeOH gradient mixture or HPLC



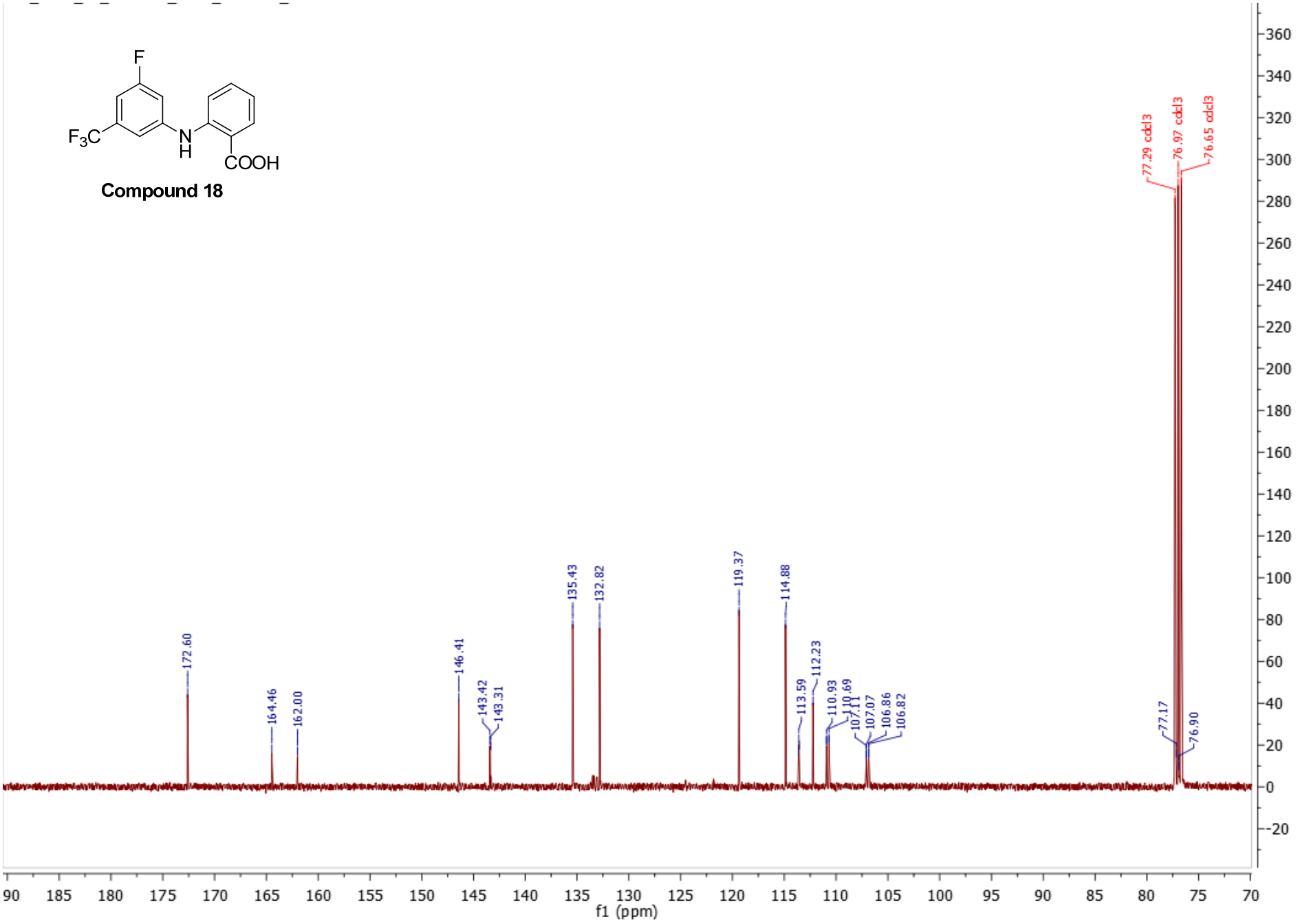
White solid.**HPLC (GEN1) RT:** 14.32 min; **^{1}H-NMR (500 MHz; DMSO-d_6) δ (ppm):** 7.12-7.16 (m, 1H). 7.27-7.31 (m, 1H), 7.57 (ddd, *J* = 9.0, 9.0, 6.5, 1H), 7.92-7.93 (m, 1H), 8.09-8.10 (m, 1H). **^{13}C-NMR (125.7 MHz; DMSO-d_6) δ (ppm):** 171.2, 161.6 (dd, *J*= 12.6, 247.6), 159.7, 158.9 (dd, *J*= 12.3, 248.5), 144.1, 131.5 (dd, *J*= 4.5, 9.5), 130.4, 126.8, 122.4 (dd, *J*= 3.6, 13.3), 113.2, 111.9 (d, *J*= 20.9), 104.3 (t, *J* = 26.4), 85.9. **HRMS (ESI^{-1}):** Calc. for [C13H7F2IO3-1] = 374,9408; found 374,9306.

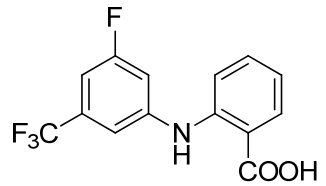
Selected HPLC, NMR and HRMS data of target compounds:


F
F3C
N
H
COOH
Compound 18
11.20
9.46
8.10
7.48
7.36
7.26
7.16
6.93
0.68
1.00
1.00
1.03
1.03
1.01
1.01
0.92
1.04
f1 (ppm)


F
F3C
N
H
COOH
11.20
9.46
8.10
7.48
7.46
7.36
7.34
7.16
7.00
6.95
6.93
6.91
0.68
1.00
1.00
1.03
1.03
1.01
1.01
0.92
1.04
2500
2000
1500
1000
500
0
12.0
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
f1 (ppm)

Compound 18


F
F3C
N
H
COOH
Compound 18
172.60
164.46
162.00
146.41
143.42
143.31
135.43
132.82
119.37
114.88
113.59
112.23
110.93
110.69
107.11
107.07
106.86
106.82
77.29 cdcl3
76.97 cdcl3
76.65 cdcl3
77.17
76.90
f1 (ppm)

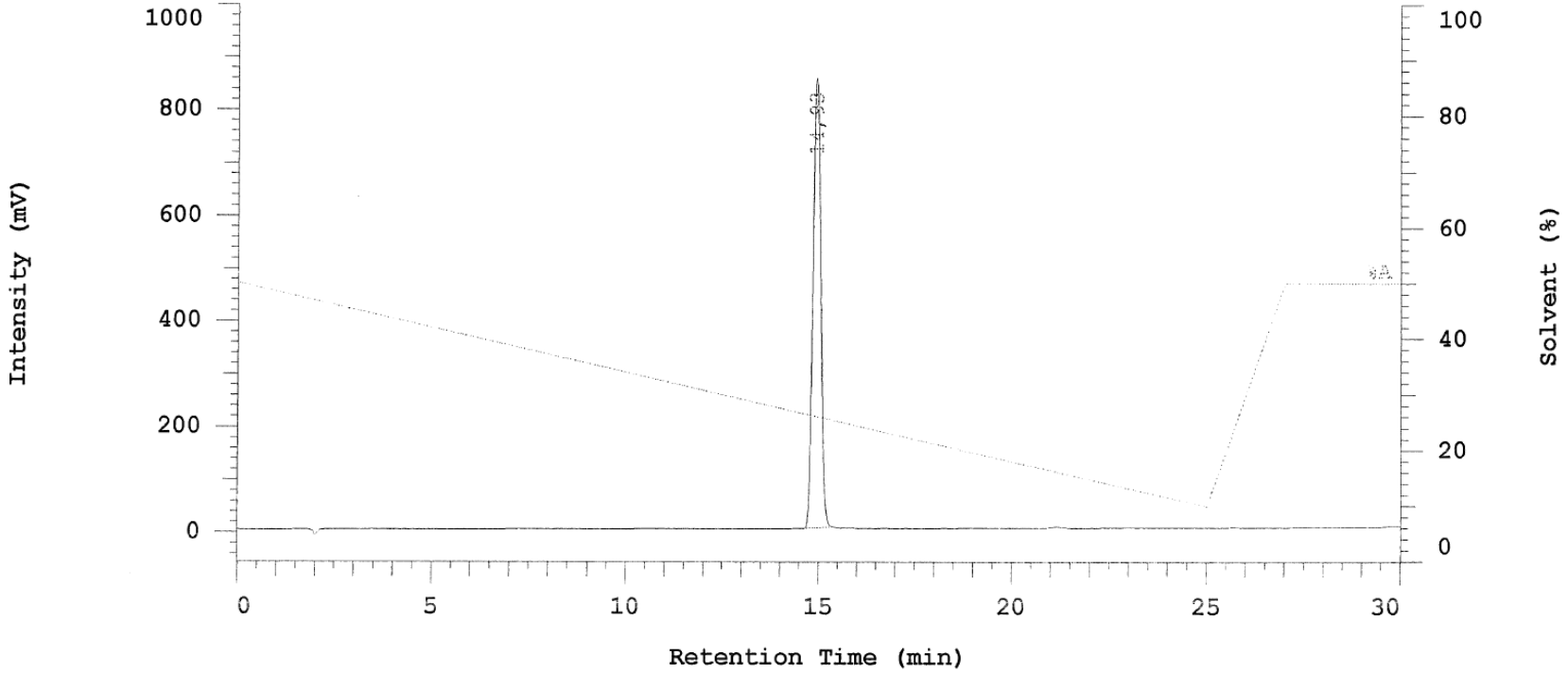


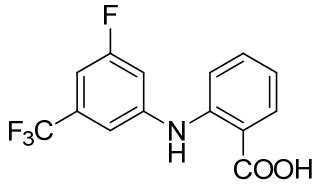
Compound 18

Processing Method: GEN1

Sample Name: Muestra
Injection from this vial: 1 of 1

Series:7157
Vial Number: 1
Volume: 30,0 ul





Compound 18

Chemical Formula: $C_{14}H_9F_4NO_2$
Exact Mass: 299,0569

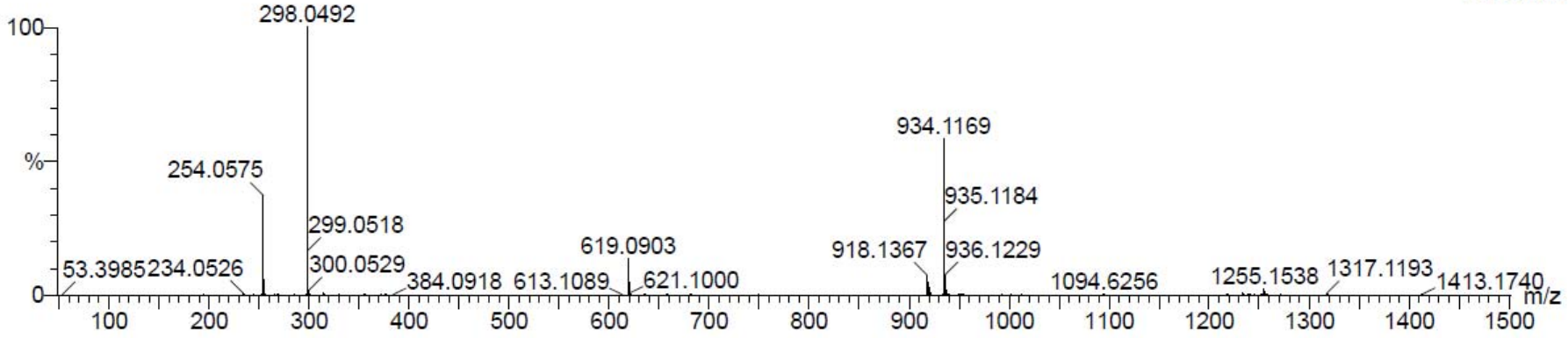
Single Mass Analysis

Tolerance = 20.0 mDa / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
27 formula(e) evaluated with 1 results within limits (up to 50 best isotopic matches for each mass)
Elements Used:
C: 0-14 H: 0-10 N: 0-1 O: 0-2 F: 0-4

F-antranilic acid
241012-24 61 (0.753)

1: TOF MS ES-
1.09e+005



Minimum:				-1.5		
Maximum:		20.0	10.0	50.0		
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula
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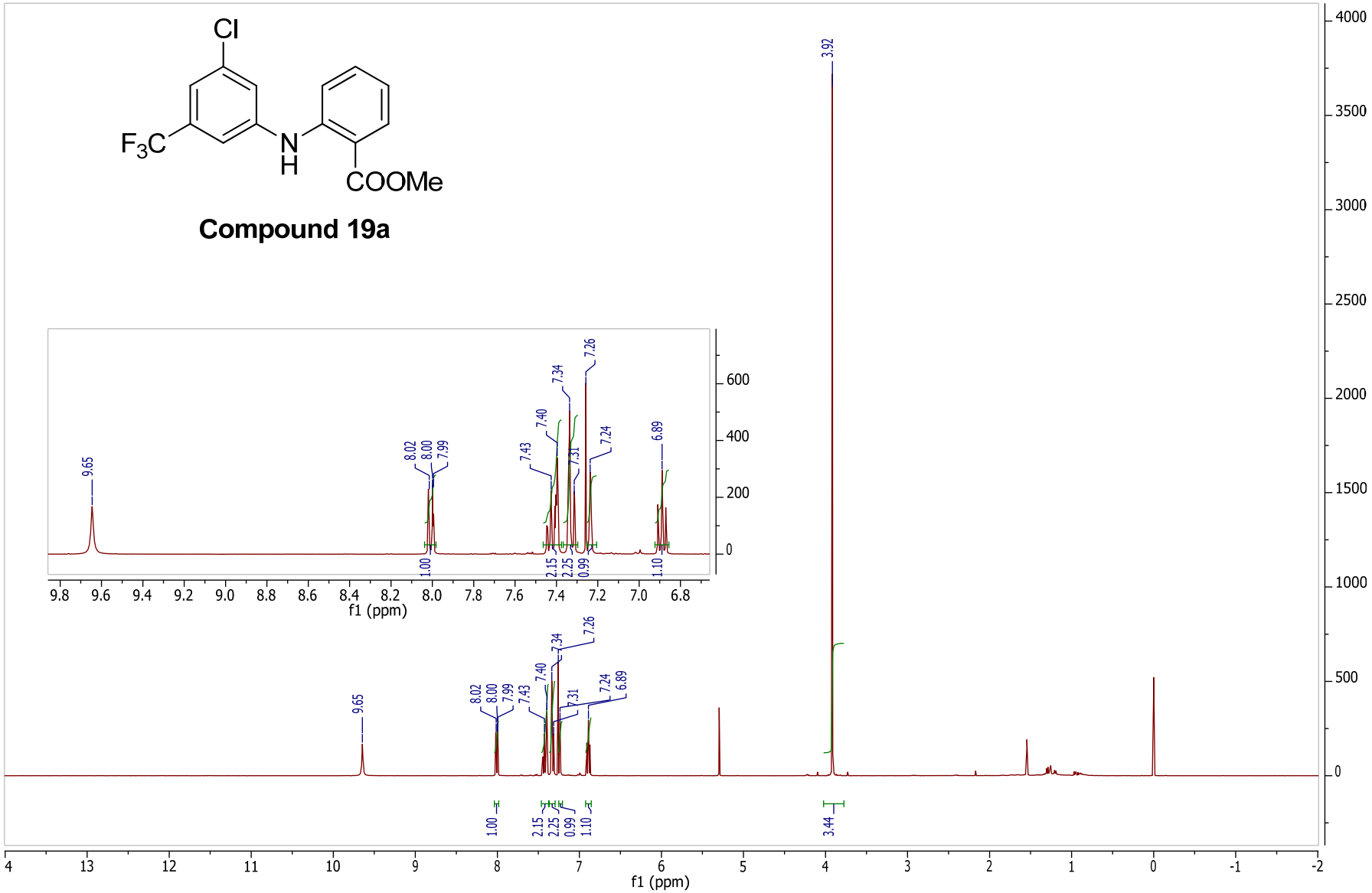
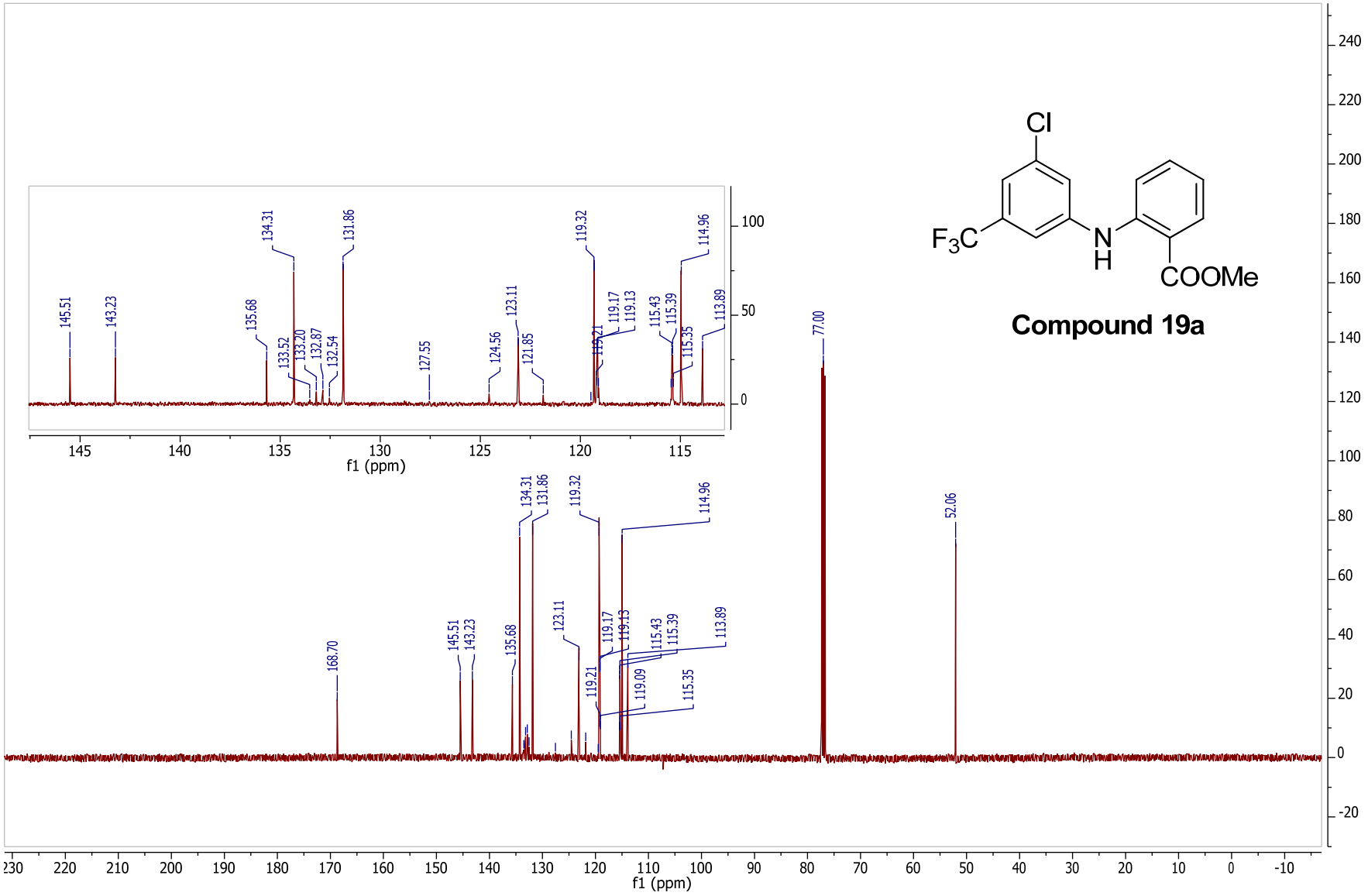
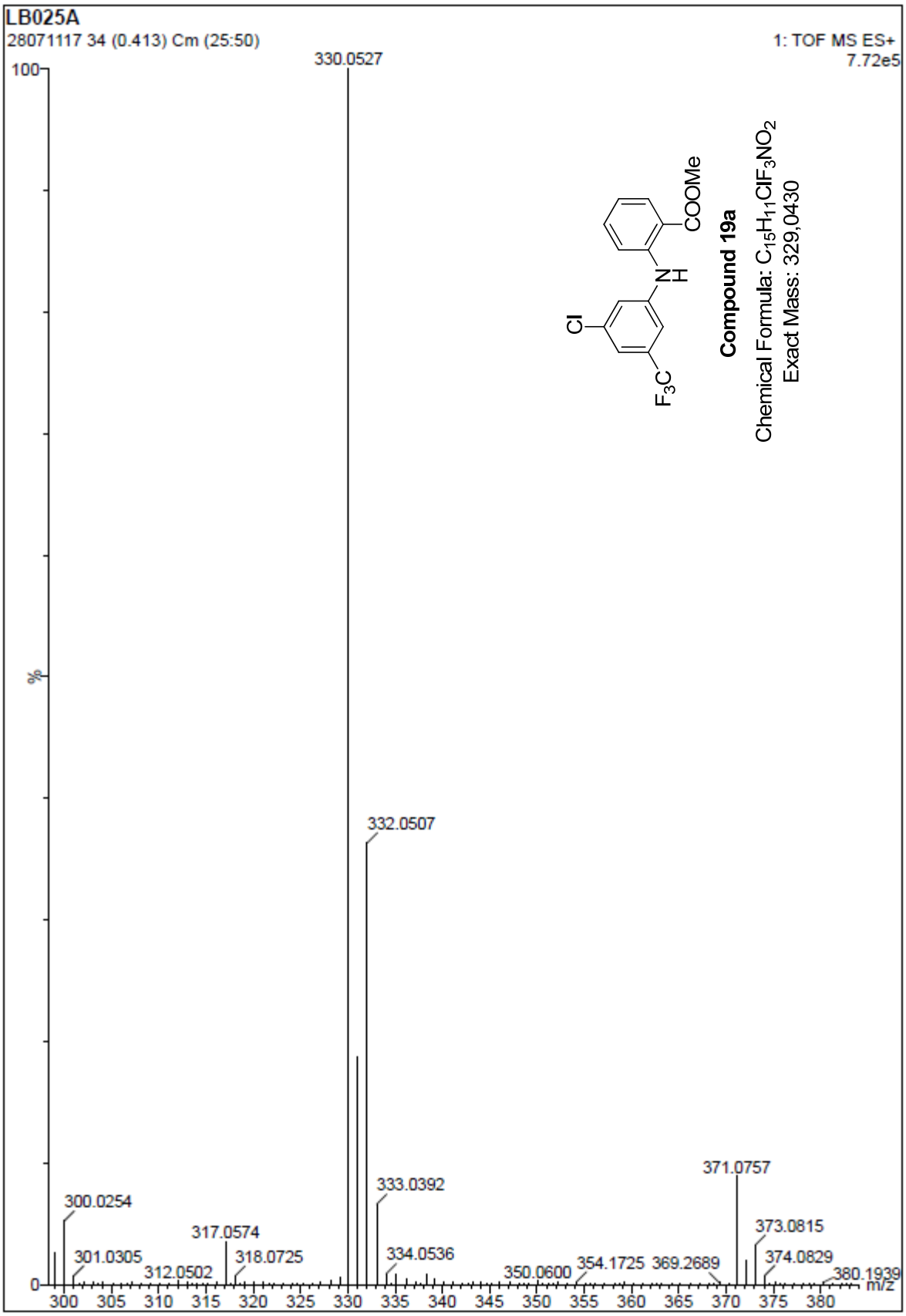
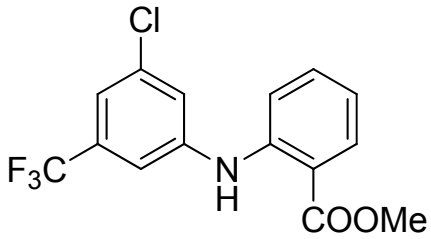

Cl
F3C
N
H
COOMe
Compound 19a
9.65
8.02
8.00
7.99
7.43
7.40
7.34
7.31
7.26
7.24
6.89
3.92
1.00
2.15
2.25
0.99
1.10
3.44
f1 (ppm)


Cl
F3C
N
H
COOMe
Compound 19a
f1 (ppm)


LB025A
28071117 34 (0.413) Cm (25:50)
1: TOF MS ES+
7.72e5
100
%
0
330.0527
332.0507
333.0392
300.0254
317.0574
301.0305
318.0725
312.0502
334.0536
350.0600
354.1725
369.2689
371.0757
373.0815
374.0829
380.1939
300 305 310 315 320 325 330 335 340 345 350 355 360 365 370 375 380
m/z
COOMe
N
H
Cl
F3C
Compound 19a
Chemical Formula: C15H11ClF3NO2
Exact Mass: 329,0430



Compound 19a

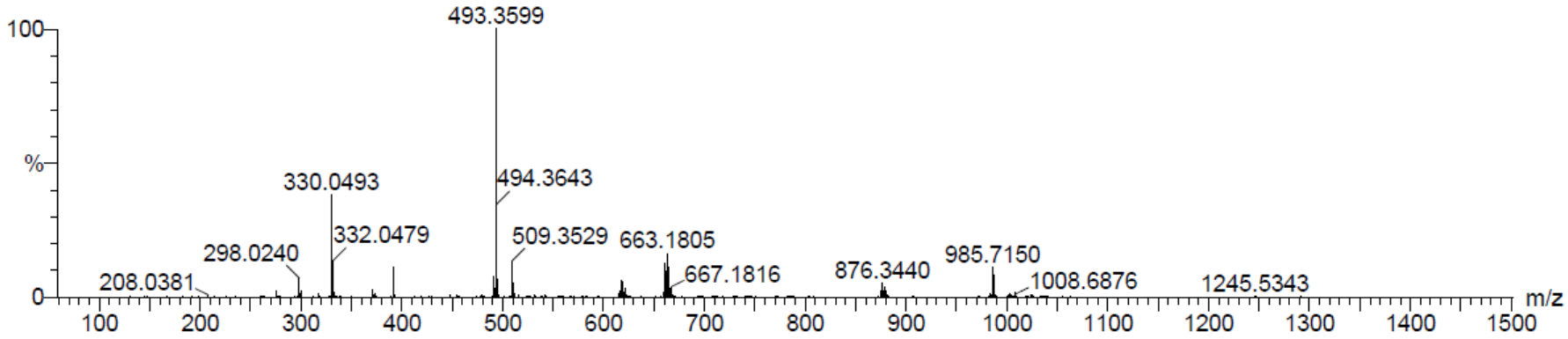
Single Mass Analysis

Tolerance = 10.0 mDa / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
45 formula(e) evaluated with 1 results within limits (up to 50 best isotopic matches for each mass)
Elements Used:
C: 0-15 H: 0-12 N: 0-1 O: 0-2 F: 0-3 Cl: 0-1

LB025A
28071117 34 (0.413)

1: TOF MS ES+
1.13e+005



Minimum:				-1.5		
Maximum:		10.0	10.0	50.0		
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula
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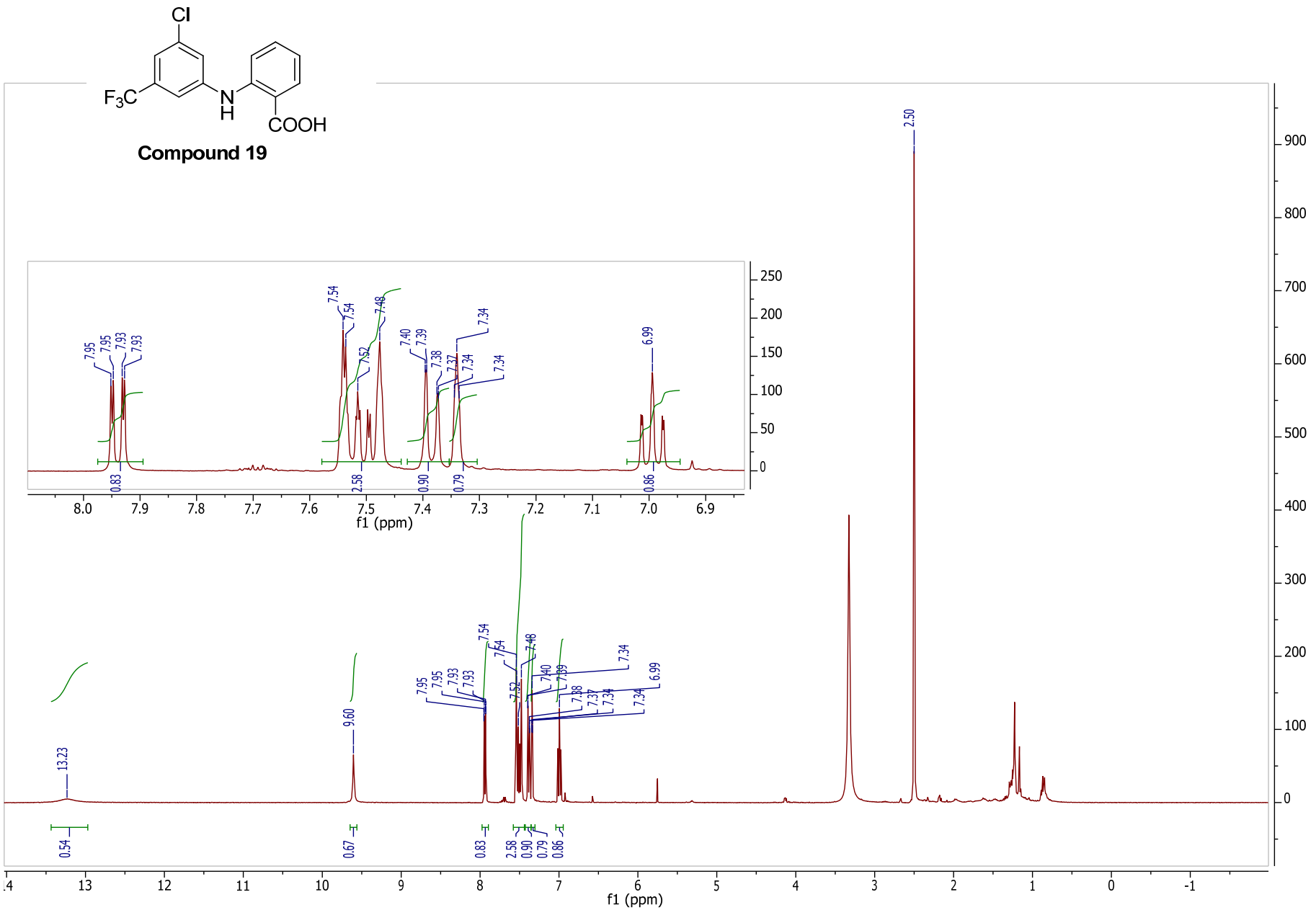
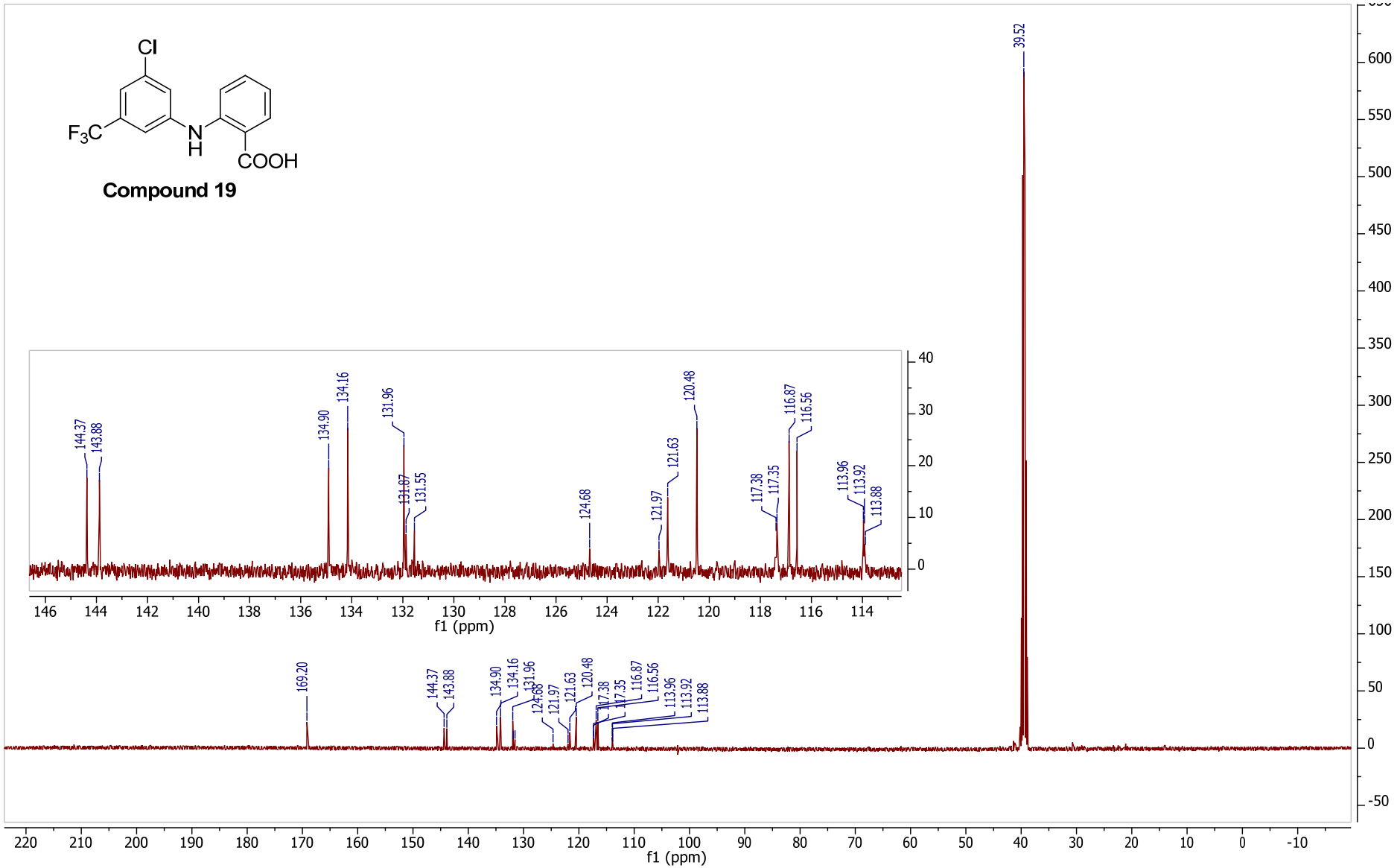
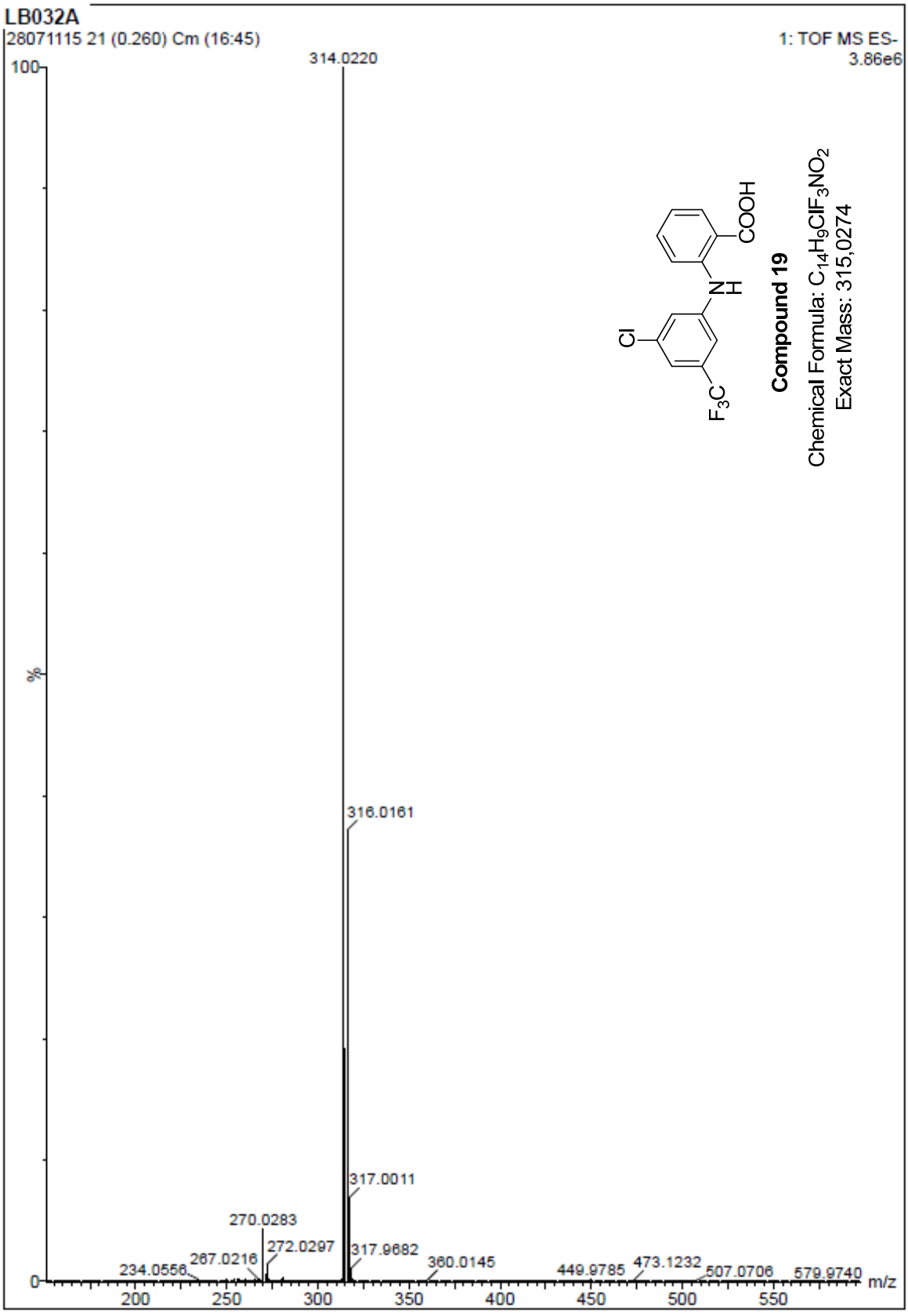

Cl
F3C
N
H
COOH
Compound 19
f1 (ppm)


Cl
F3C
N
H
COOH
Compound 19
144.37
143.88
134.90
134.16
131.96
131.87
131.55
124.68
121.97
121.63
120.48
117.38
117.35
116.87
116.56
113.96
113.92
113.88
39.52
169.20
f1 (ppm)


LB032A
28071115 21 (0.260) Cm (16:45)
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%
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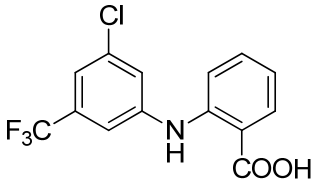
316.0161
317.0011
270.0283
272.0297
267.0216
234.0556
317.9682
360.0145
449.9785
473.1232
507.0706
579.9740
200
250
300
350
400
450
500
550
m/z
COOH
N
H
Cl
F3C
Compound 19
Chemical Formula: C14H9ClF3NO2
Exact Mass: 315,0274

Elemental Composition Report



Compound 19

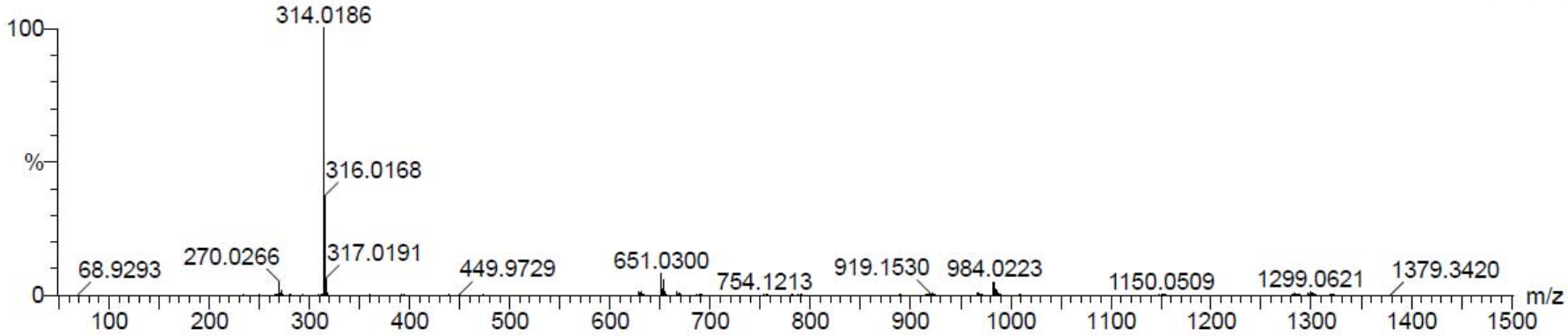
Chemical Formula: $C_{14}H_9ClF_3NO_2$
Exact Mass: 315,0274

Tolerance = 10.0 mDa / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

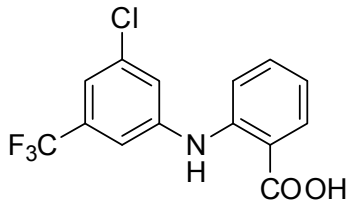
Monoisotopic Mass, Even Electron Ions
55 formula(e) evaluated with 1 results within limits (up to 50 best isotopic matches for each mass)
Elements Used:
C: 10-14 H: 5-10 N: 0-1 O: 0-2 F: 0-3 Cl: 0-2

LB032A
28071115 35 (0.424)

1: TOF MS ES-
1.60e+005



Minimum:	80.00				-1.5		
Maximum:	100.00		10.0	10.0	50.0		
Mass	RA	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula
314.0186	100.00	314.0196	-1.0	-3.2	9.5	294.4	C14 H8 N O2 F3 Cl

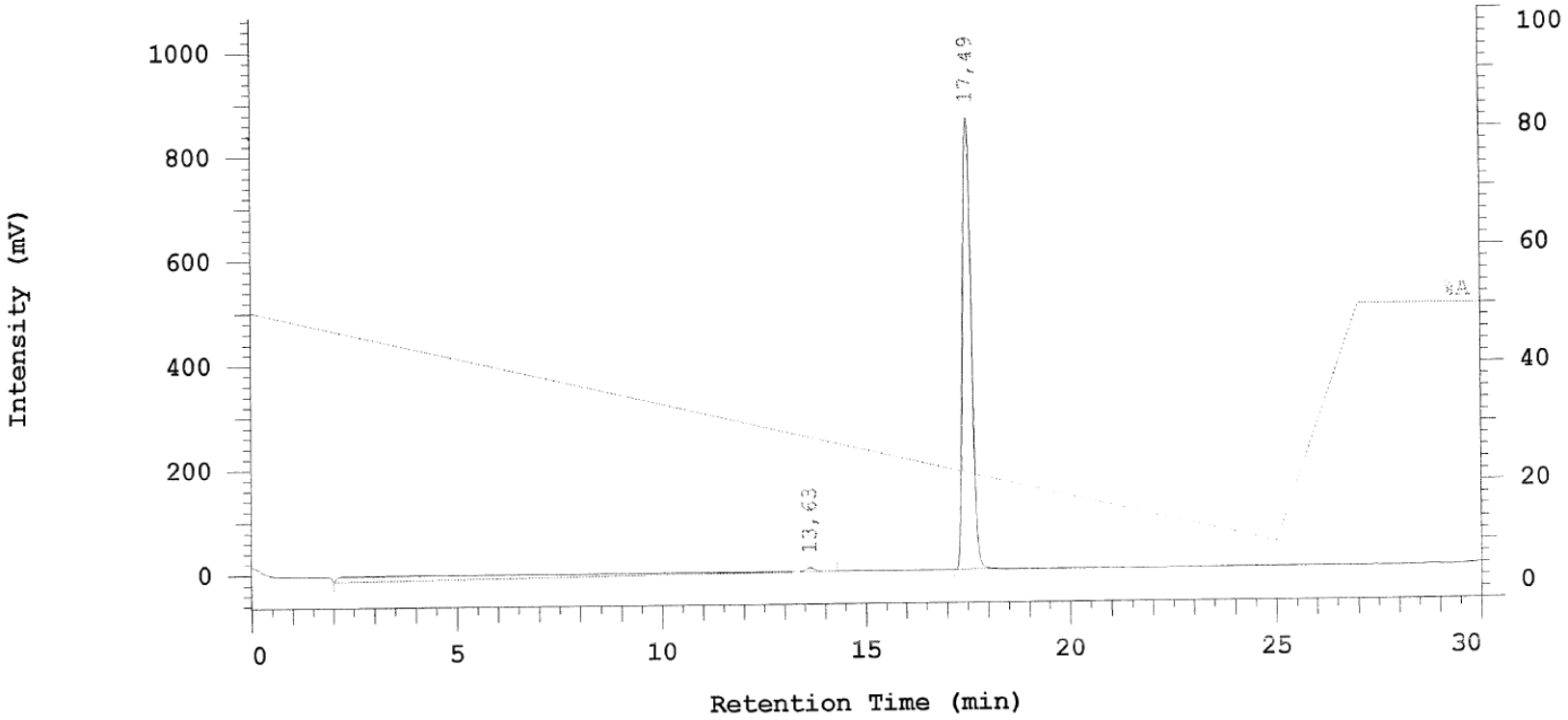


Compound 19

Chemical Formula: $C_{14}H_9ClF_3NO_2$
Exact Mass: 315,0274

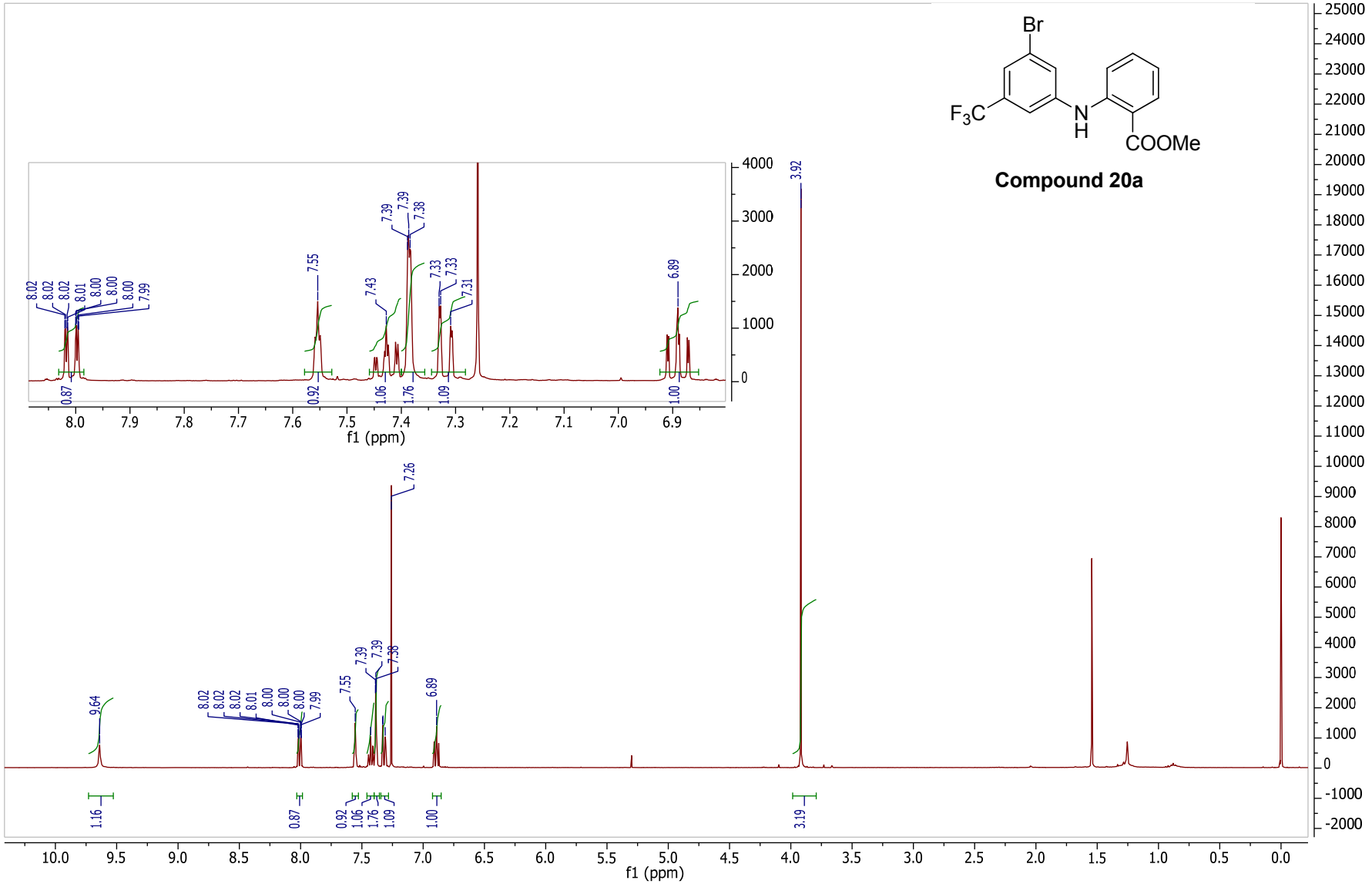
Processing Method: GEN1
Sample Name: Muestra
Injection from this vial: 1 of 1

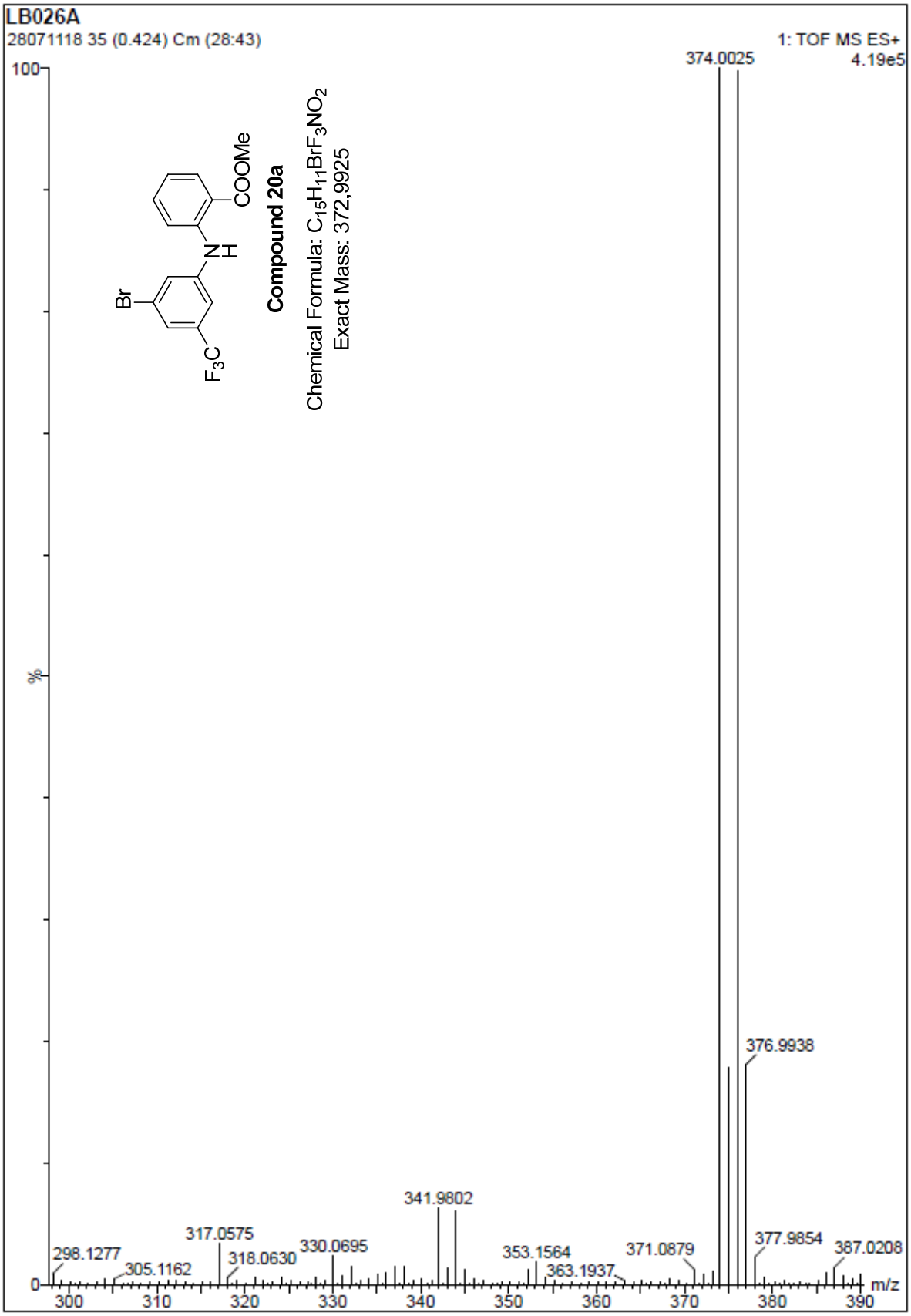
Series:7159
Vial Number: 1
Volume: 30,0 ul



Pump A Type: L-6200
Solvent A: Agua

Solvent B: ACN


Br
F3C
N
H
COOMe
Compound 20a
f1 (ppm)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100
%
0
COOMe
N
H
Br
F3C
Compound 20a
Chemical Formula: C15H11BrF3NO2
Exact Mass: 372,9925
376.9938
341.9802
317.0575
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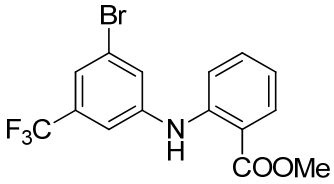
363.1937
371.0879
377.9854
387.0208
300
310
320
330
340
350
360
370
380
390
m/z



Compound 20a

Chemical Formula: $C_{15}H_{11}BrF_3NO_2$
Exact Mass: 372,9925

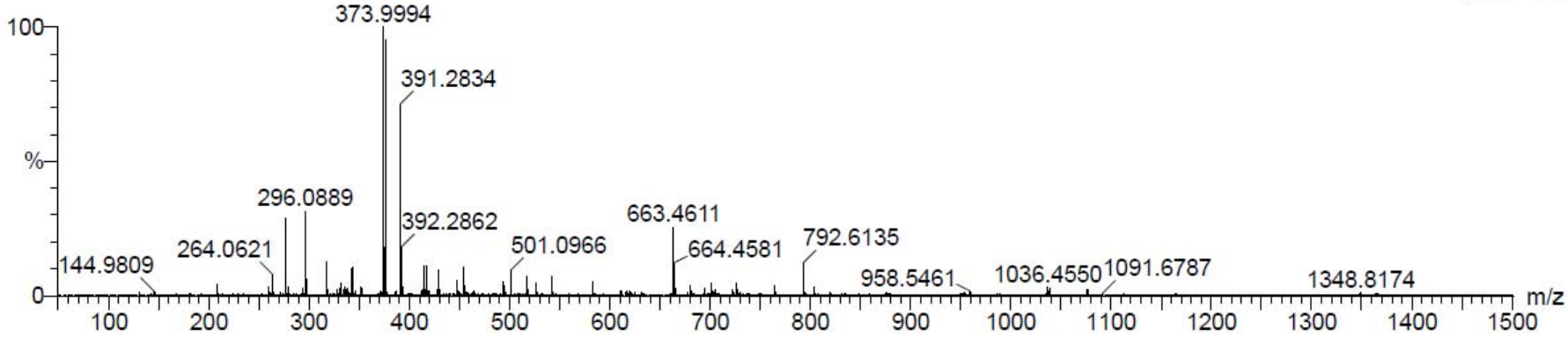
Multiple Mass Analysis: 2 mass(es) processed

Tolerance = 20.0 mDa / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

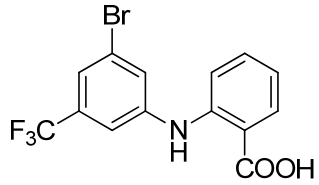
Monoisotopic Mass, Even Electron Ions
185 formula(e) evaluated with 2 results within limits (up to 50 best isotopic matches for each mass)
Elements Used:
C: 0-15 H: 11-12 N: 0-1 O: 0-2 F: 0-3 79Br: 0-8 81Br: 0-8

LB026A
28071118 20 (0.249)

1: TOF MS ES+
2.80e+004



Minimum:	80.00				-1.5		
Maximum:	100.00		20.0	10.0	50.0		
Mass	**RA**	**Calc. Mass**	**mDa**	**PPM**	**DBE**	**i-FIT**	**Formula**
373.9994	100.00	374.0003	-0.9	-2.4	8.5	12858.3	C15 H12 N O2 F3 79Br
375.9977	95.04	375.9983	-0.6	-1.6	8.5	84.3	C15 H12 N O2 F3 81Br

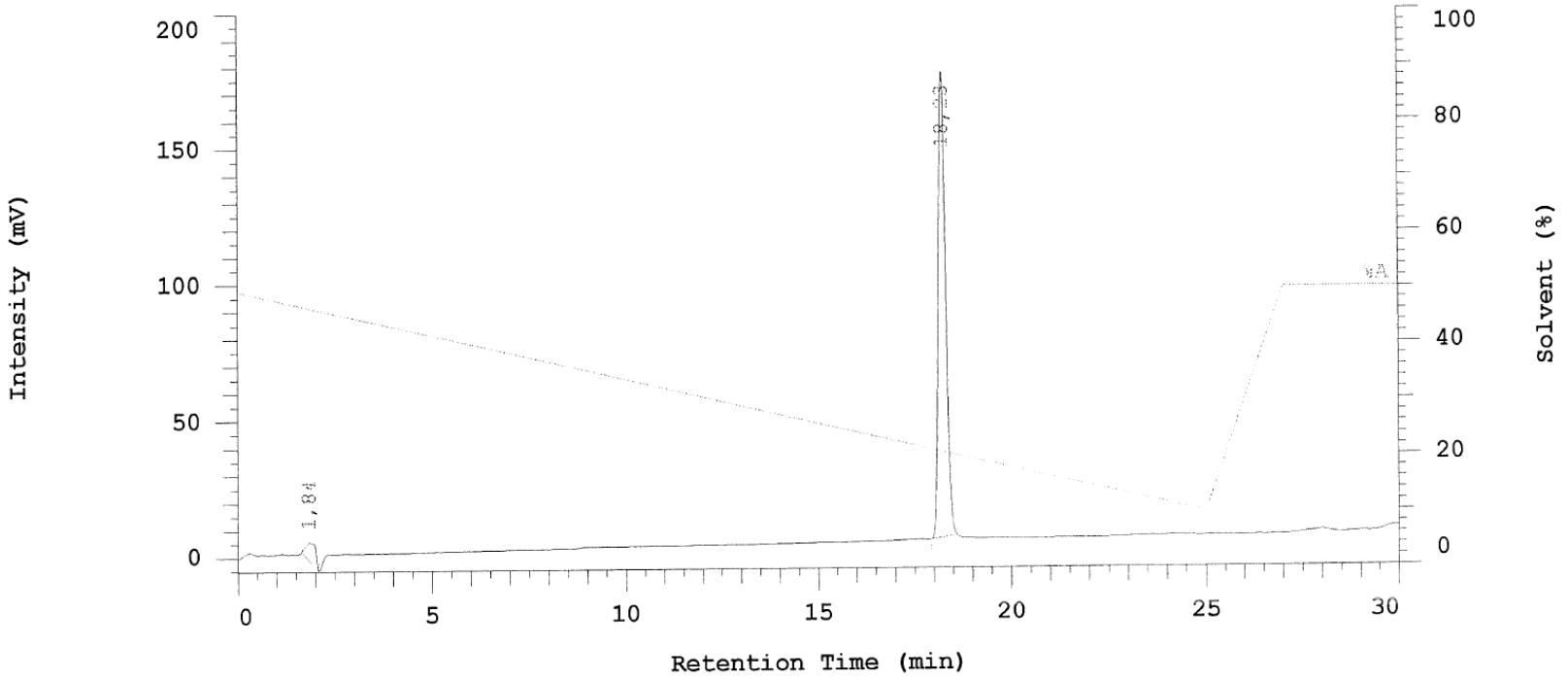


Compound 20

Processing Method: GEN1

Sample Name: Muestra
Injection from this vial: 1 of 1

Series:7176
Vial Number: 1
Volume: 70,0 ul



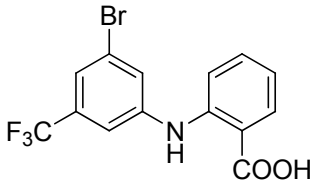
Pump A Type: L-6200
Solvent A: Agua

Solvent B: ACN

Multiple Mass Analysis: 2 mass(es) processed

Tolerance = 10.0 mDa / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
137 formula(e) evaluated with 2 results within limits (up to 50 best isotopic matches for each mass)
Elements Used:
C: 0-15 H: 8-8 N: 0-1 O: 0-2 F: 0-3 79Br: 0-8 81Br: 0-8

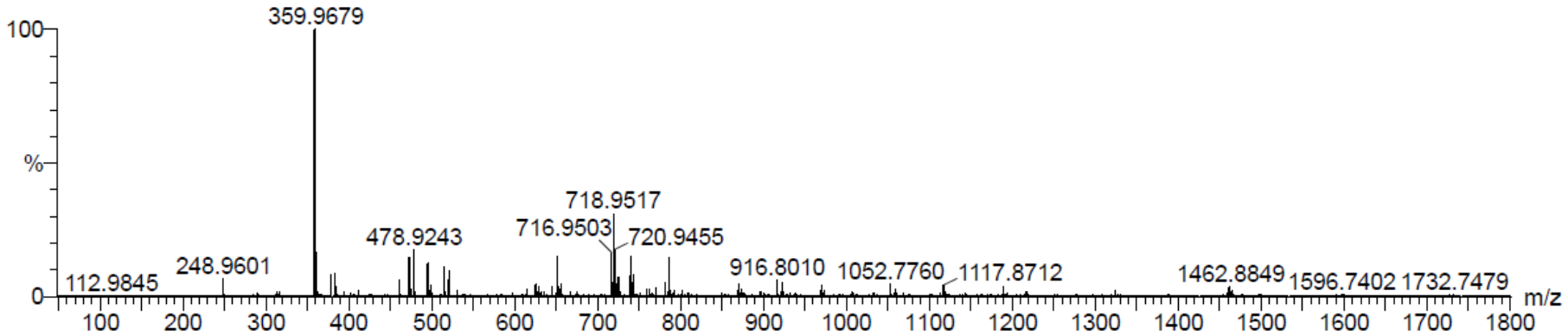


Compound 20

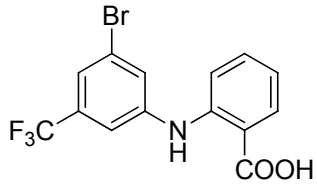
Chemical Formula: $C_{14}H_9BrF_3NO_2$
Exact Mass: 358,9769

Fia Gemma
Br_CF3_ANTH_Acid 4 (0.208)

2: TOF MS ES-
3.09e+004



Minimum:	80.00				-1.5		
Maximum:	100.00		10.0	10.0	50.0		
Mass	RA	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula
357.9702	99.58	357.9690	1.2	3.4	9.5	15017.8	C14 H8 N O2 F3 79Br
359.9679	100.00	359.9670	0.9	2.5	9.5	8.3	C14 H8 N O2 F3 81Br



Compound 20

Chemical Formula: $C_{14}H_9BrF_3NO_2$
Exact Mass: 358,9769

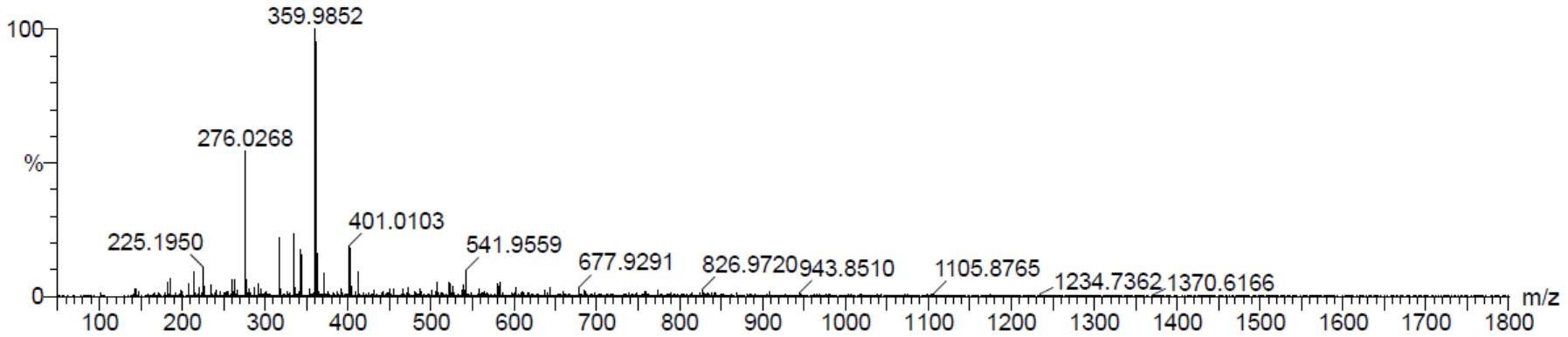
Multiple Mass Analysis: 2 mass(es) processed

Tolerance = 10.0 mDa / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

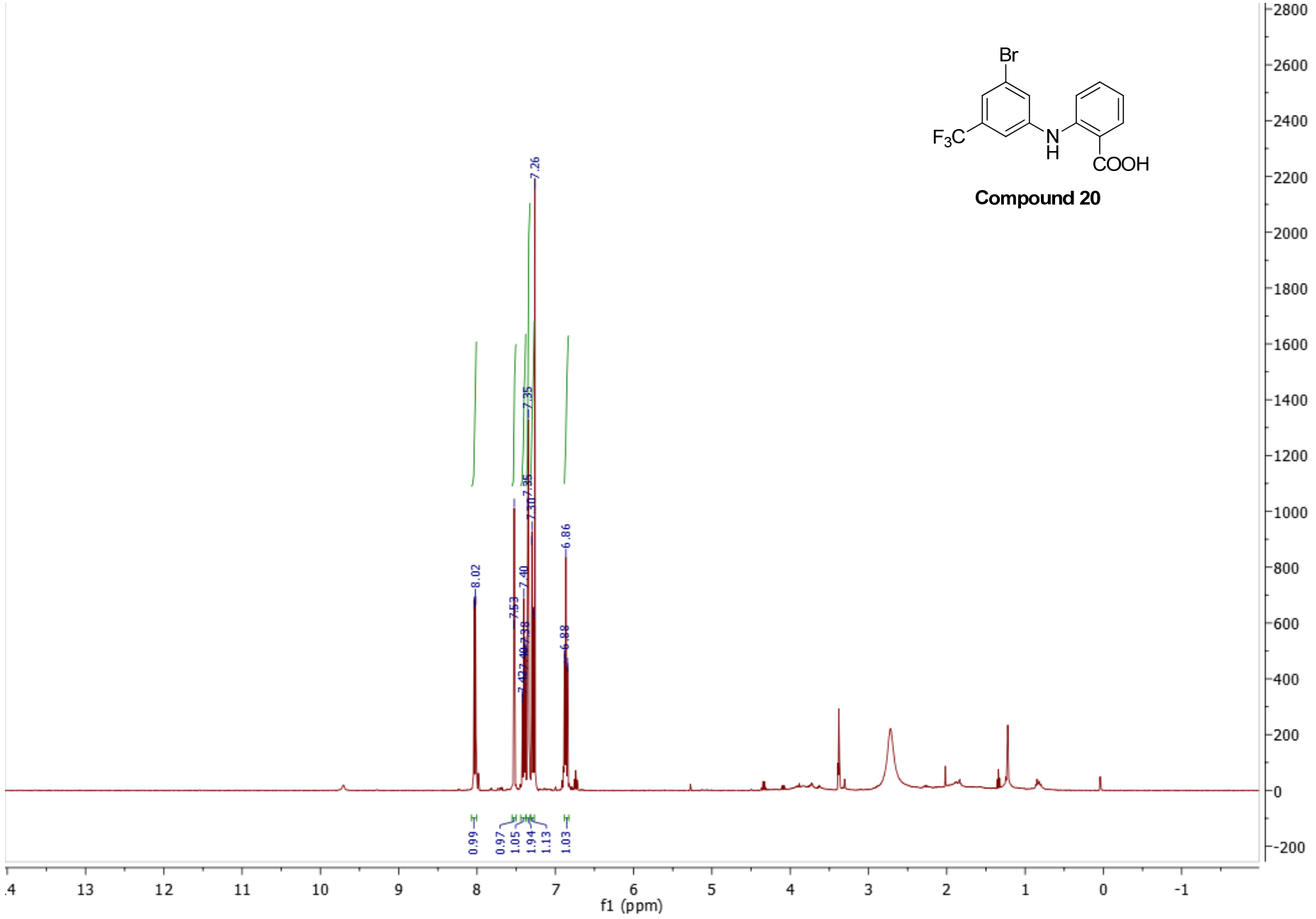
Monoisotopic Mass, Even Electron Ions
137 formula(e) evaluated with 2 results within limits (up to 50 best isotopic matches for each mass)
Elements Used:
C: 0-15 H: 10-10 N: 0-1 O: 0-2 F: 0-3 79Br: 0-8 81Br: 0-8

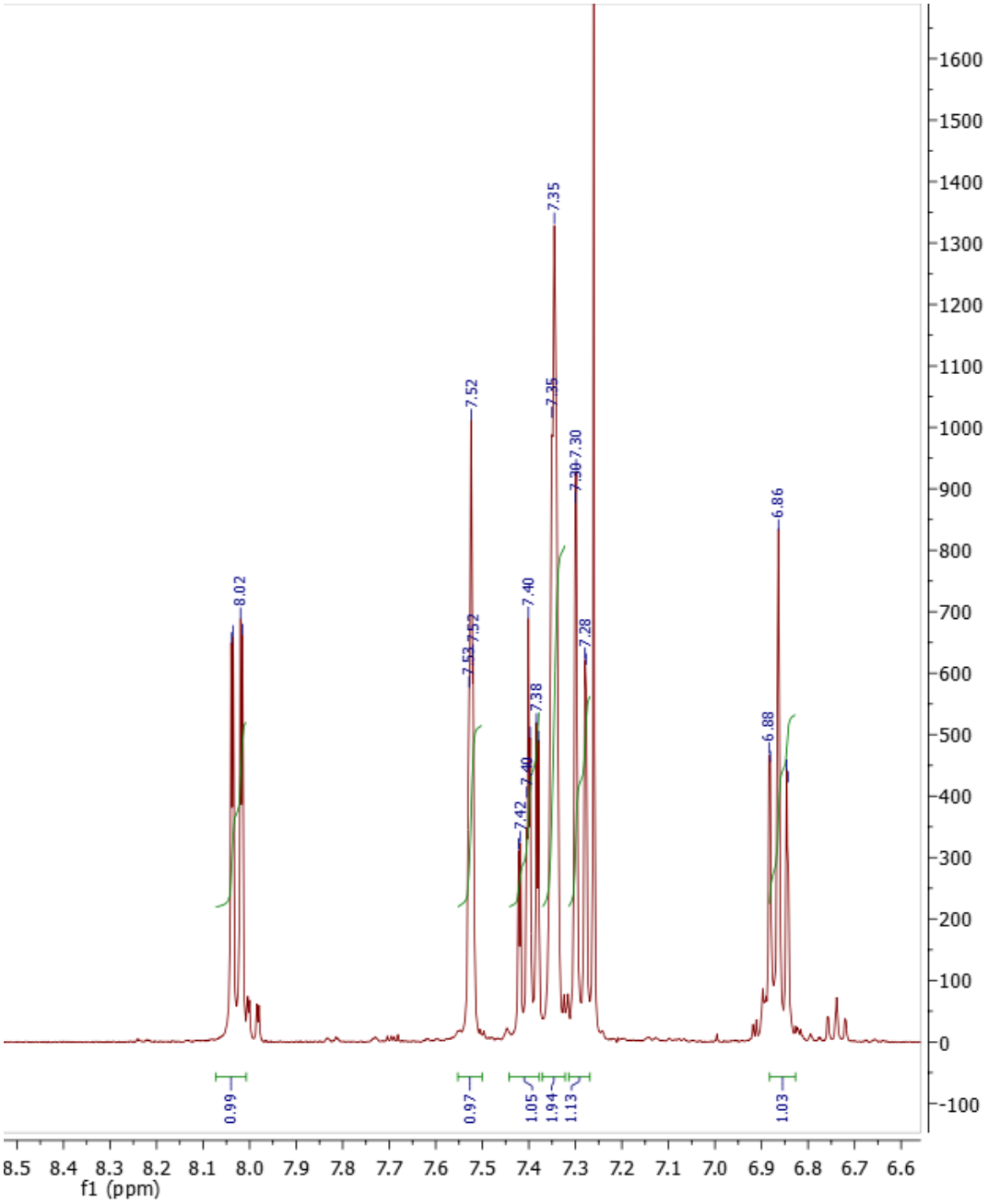
Fia Gemma
Br_CF3_ANTH_Acid 9 (0.408)

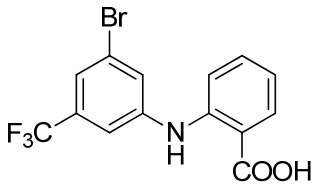
1: TOF MS ES+
3.48e+003



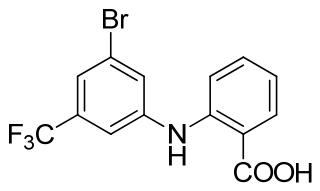
Minimum:	80.00				-1.5		
Maximum:	100.00		10.0	10.0	50.0		
Mass	**RA**	**Calc. Mass**	**mDa**	**PPM**	**DBE**	**i-FIT**	**Formula**
359.9852	100.00	359.9847	0.5	1.4	8.5	1600.2	C14 H10 N O2 F3 79Br
361.9827	94.99	361.9827	0.0	0.0	8.5	0.7	C14 H10 N O2 F3 81Br


Br
F3C
N
H
COOH
Compound 20
7.26
7.35
8.02
7.53
7.40
6.86
6.88
0.99
0.97
1.05
1.94
1.13
1.03
f1 (ppm)

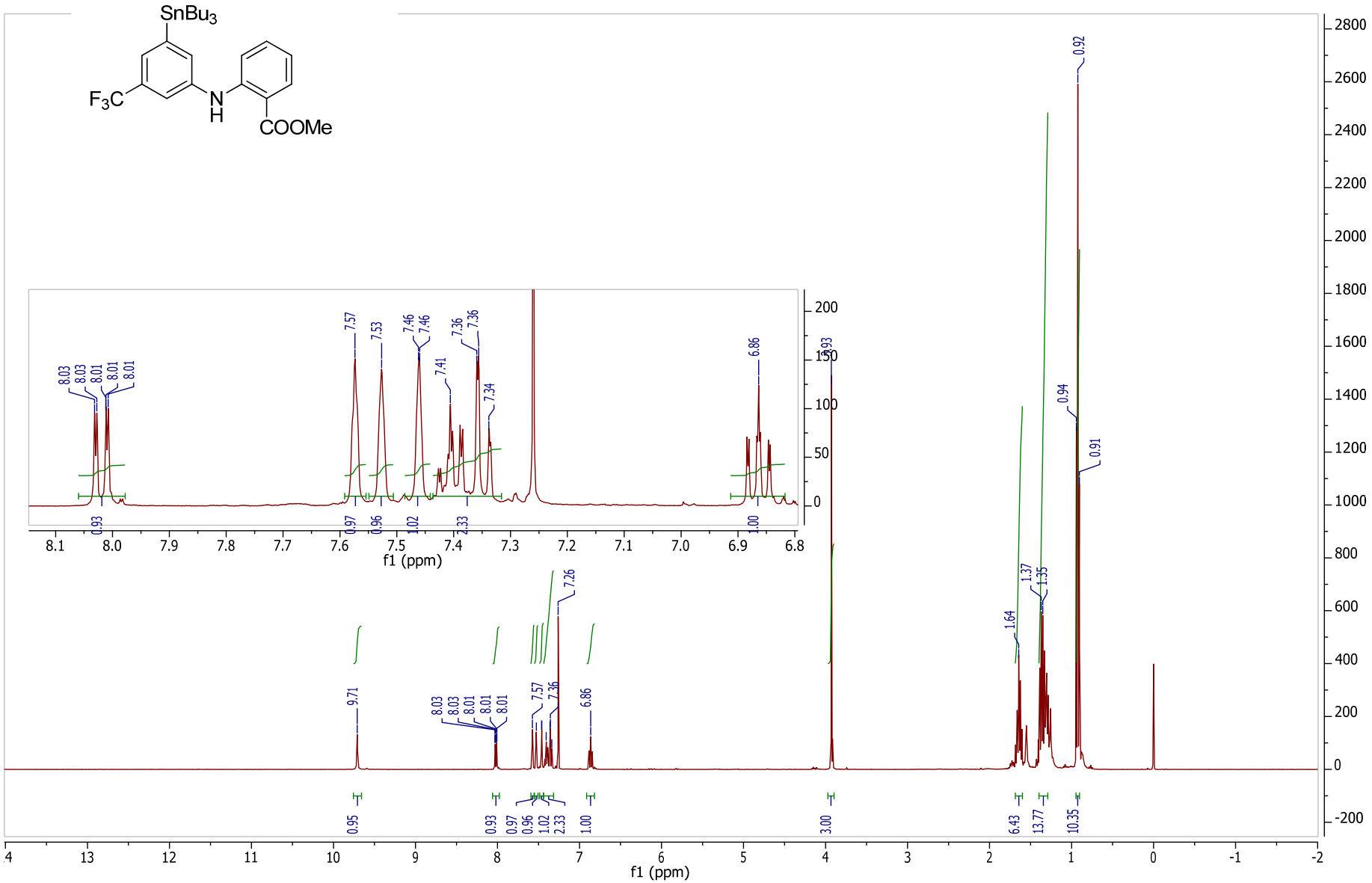

8.02
7.52
7.53
7.52
7.40
7.38
7.42
7.40
7.35
7.35
7.30
7.30
7.28
6.88
6.86
0.99
0.97
1.05
1.94
1.13
1.03
8.5 8.4 8.3 8.2 8.1 8.0 7.9 7.8 7.7 7.6 7.5 7.4 7.3 7.2 7.1 7.0 6.9 6.8 6.7 6.6
f1 (ppm)
1600
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
-100

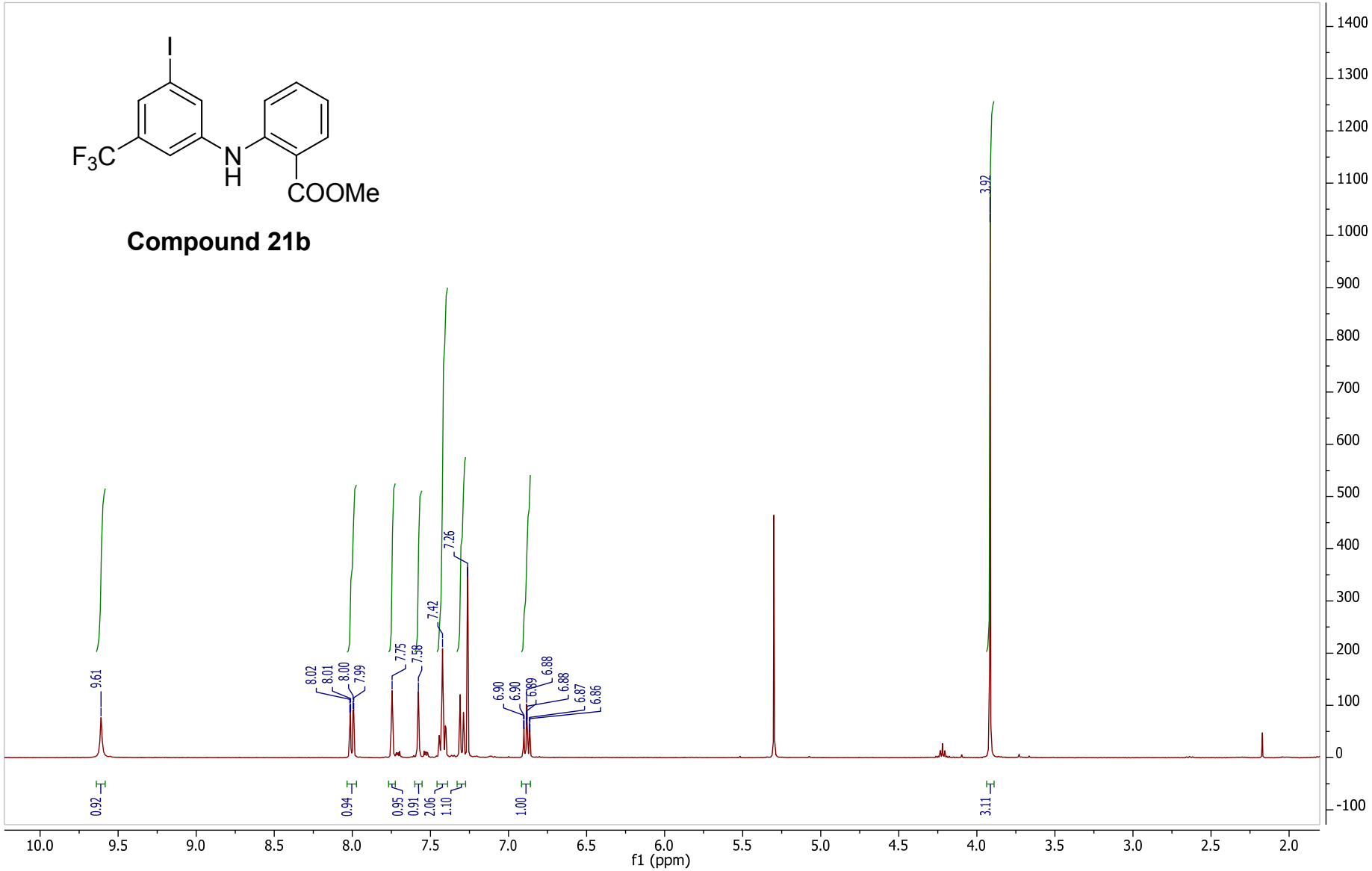

Br
F3C
N
H
COOH

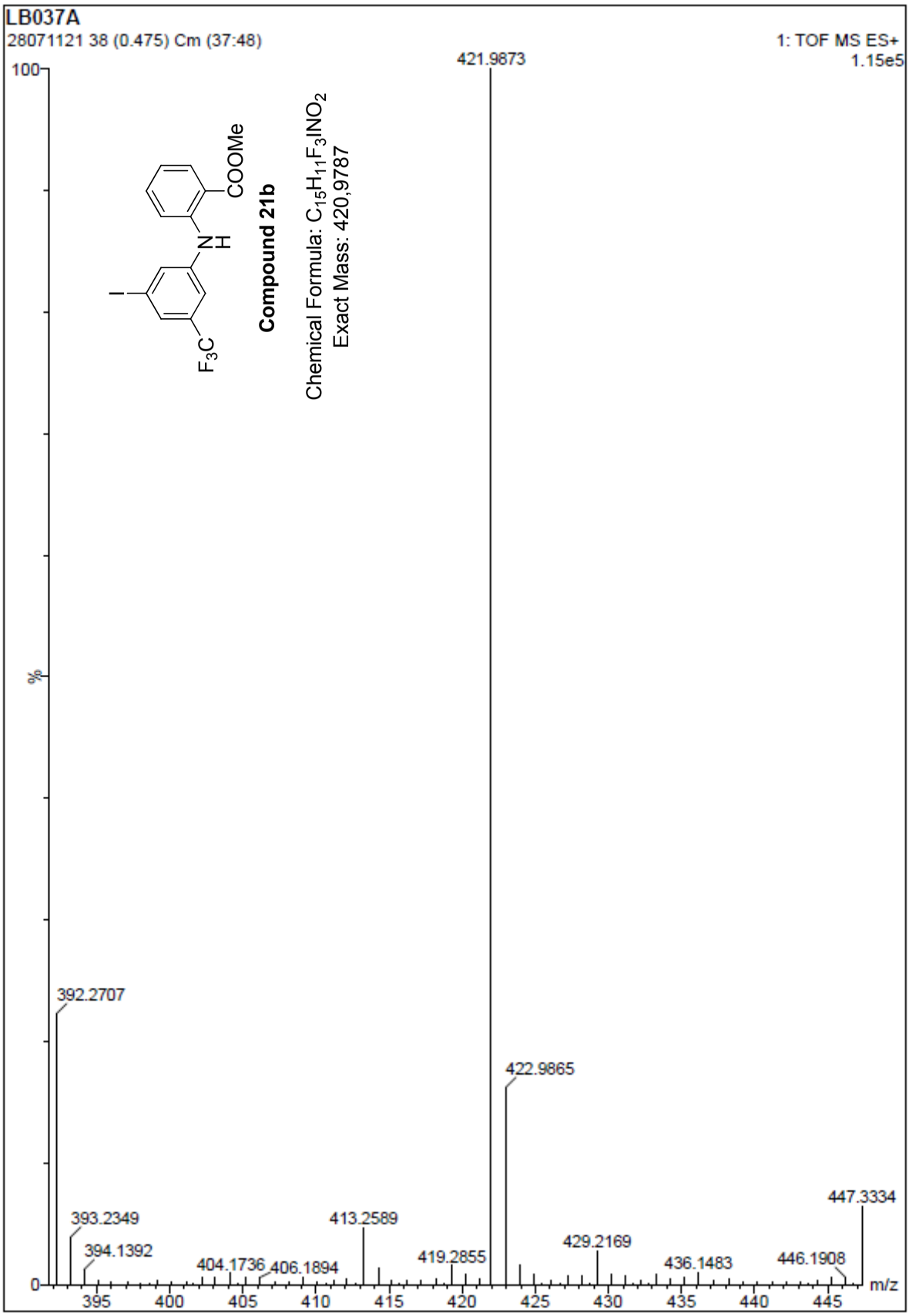
Compound 20

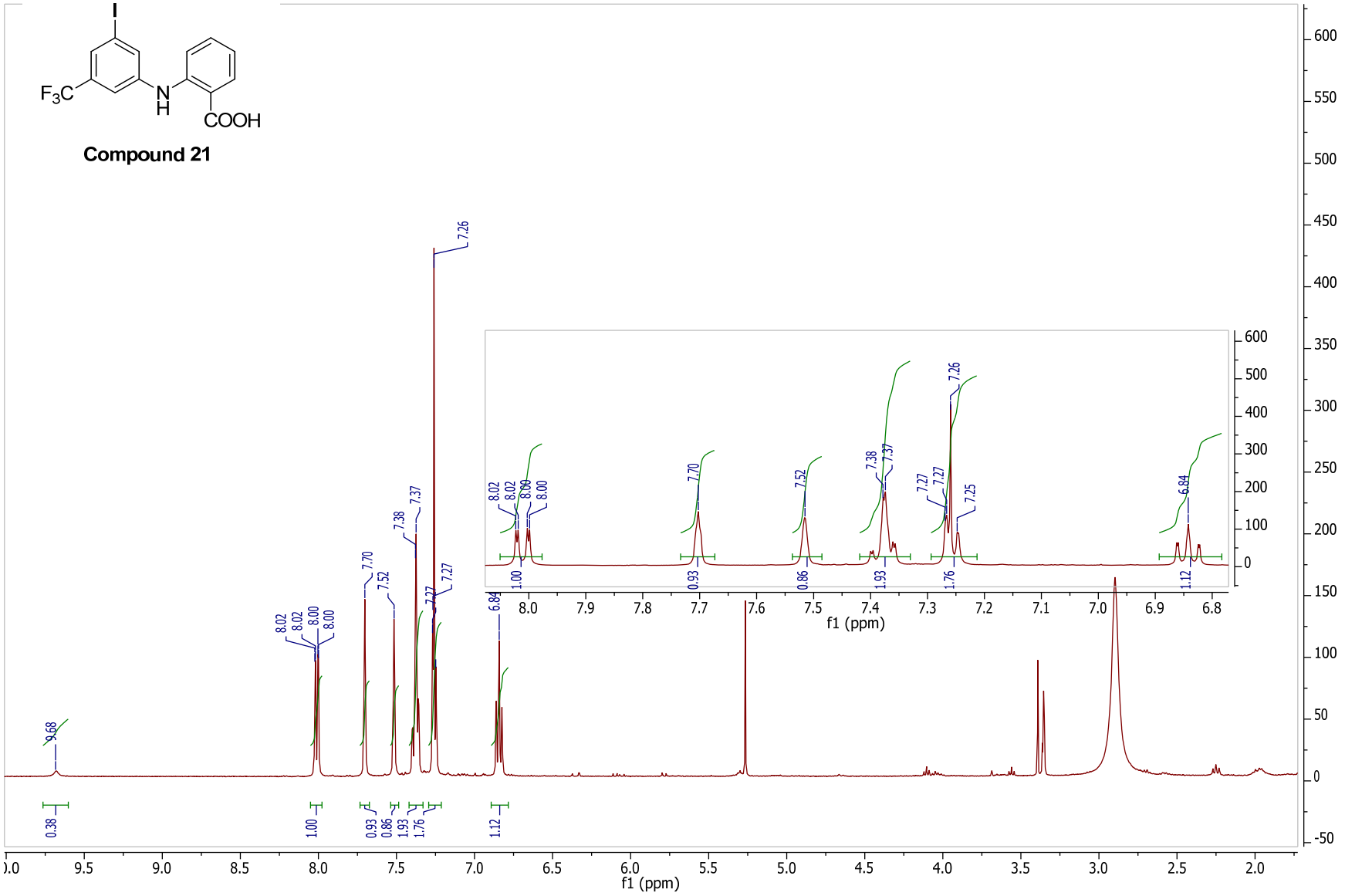


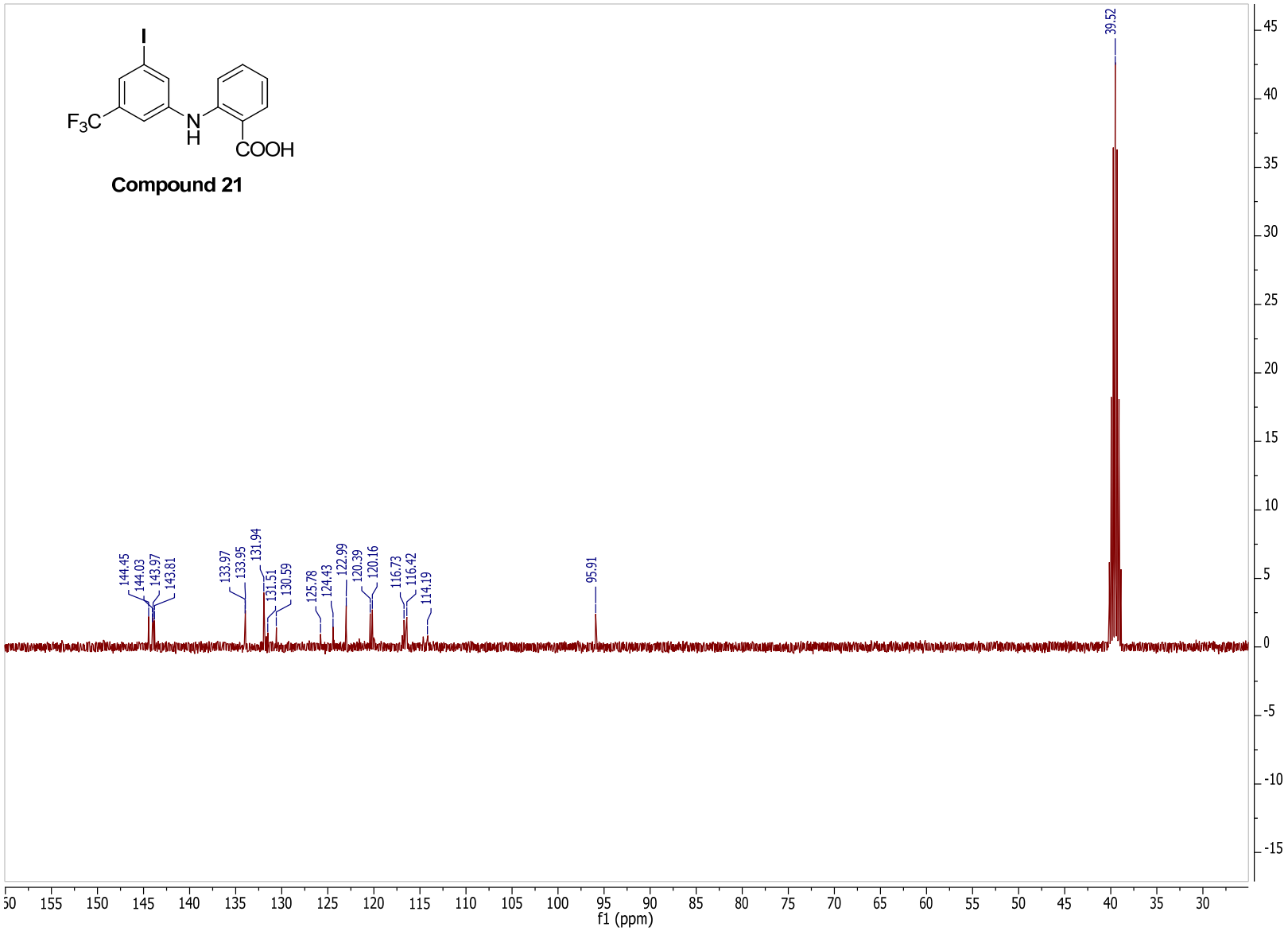
Compound 20

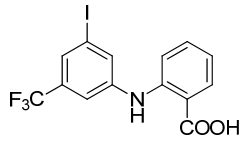

SnBu3
F3C
N
H
COOMe
f1 (ppm)


I
F3C
N
H
COOMe
Compound 21b
9.61
8.02
8.01
8.00
7.99
7.75
7.56
7.42
7.26
6.90
6.90
6.89
6.88
6.88
6.87
6.86
3.92
0.92
0.94
0.95
0.91
2.06
1.10
1.00
3.11
f1 (ppm)


LB037A
28071121 38 (0.475) Cm (37:48)
1: TOF MS ES+
1.15e5
100
%
0
421.9873
392.2707
422.9865
447.3334
393.2349
413.2589
394.1392
429.2169
404.1736
406.1894
419.2855
436.1483
446.1908
395
400
405
410
415
420
425
430
435
440
445
m/z
COOMe
N
H
I
F3C
Compound 21b
Chemical Formula: C15H11F3INO2
Exact Mass: 420,9787


I
F3C
N
H
COOH
Compound 21
f1 (ppm)

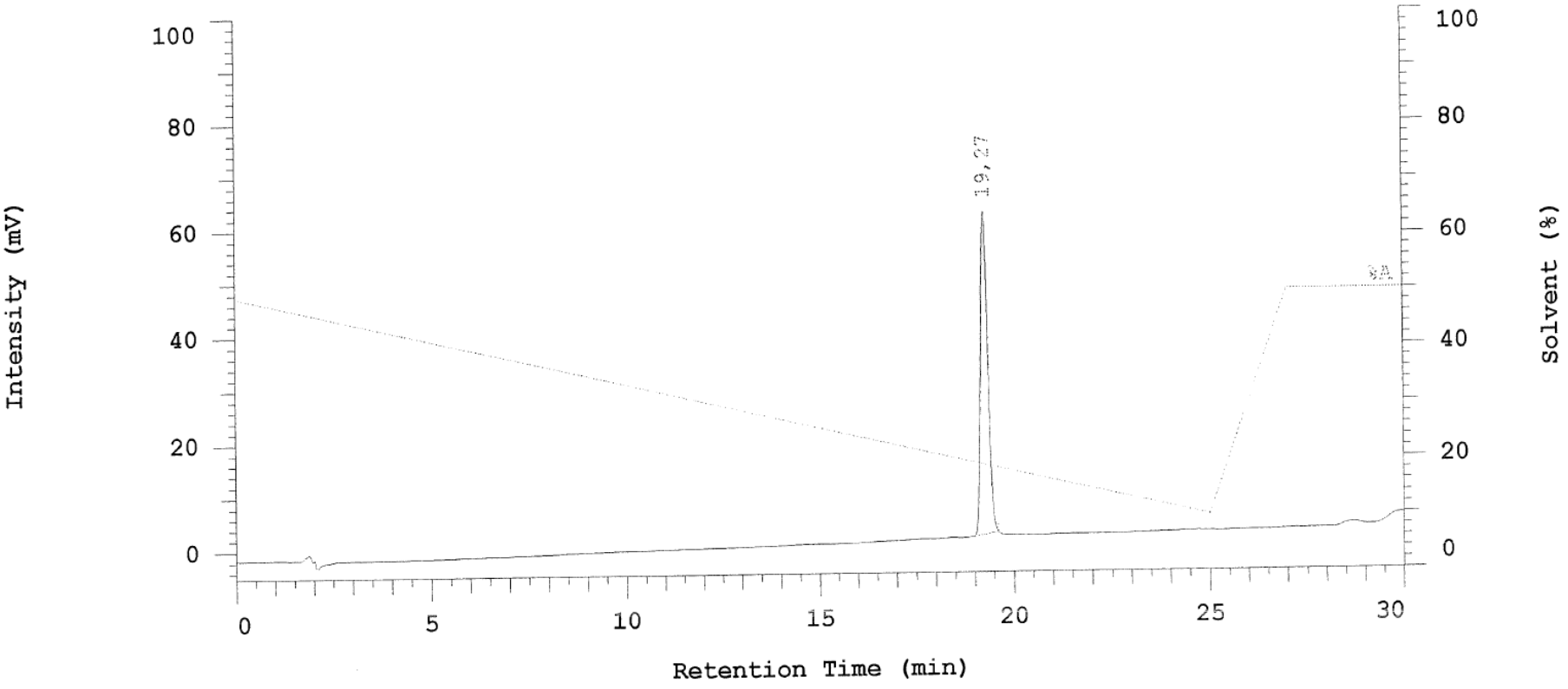

I
F3C
N
H
COOH
Compound 21
39.52
144.45
144.03
143.97
143.81
133.97
133.95
131.94
131.51
130.59
125.78
124.43
122.99
120.39
120.16
116.73
116.42
114.19
95.91
f1 (ppm)



Compound 21

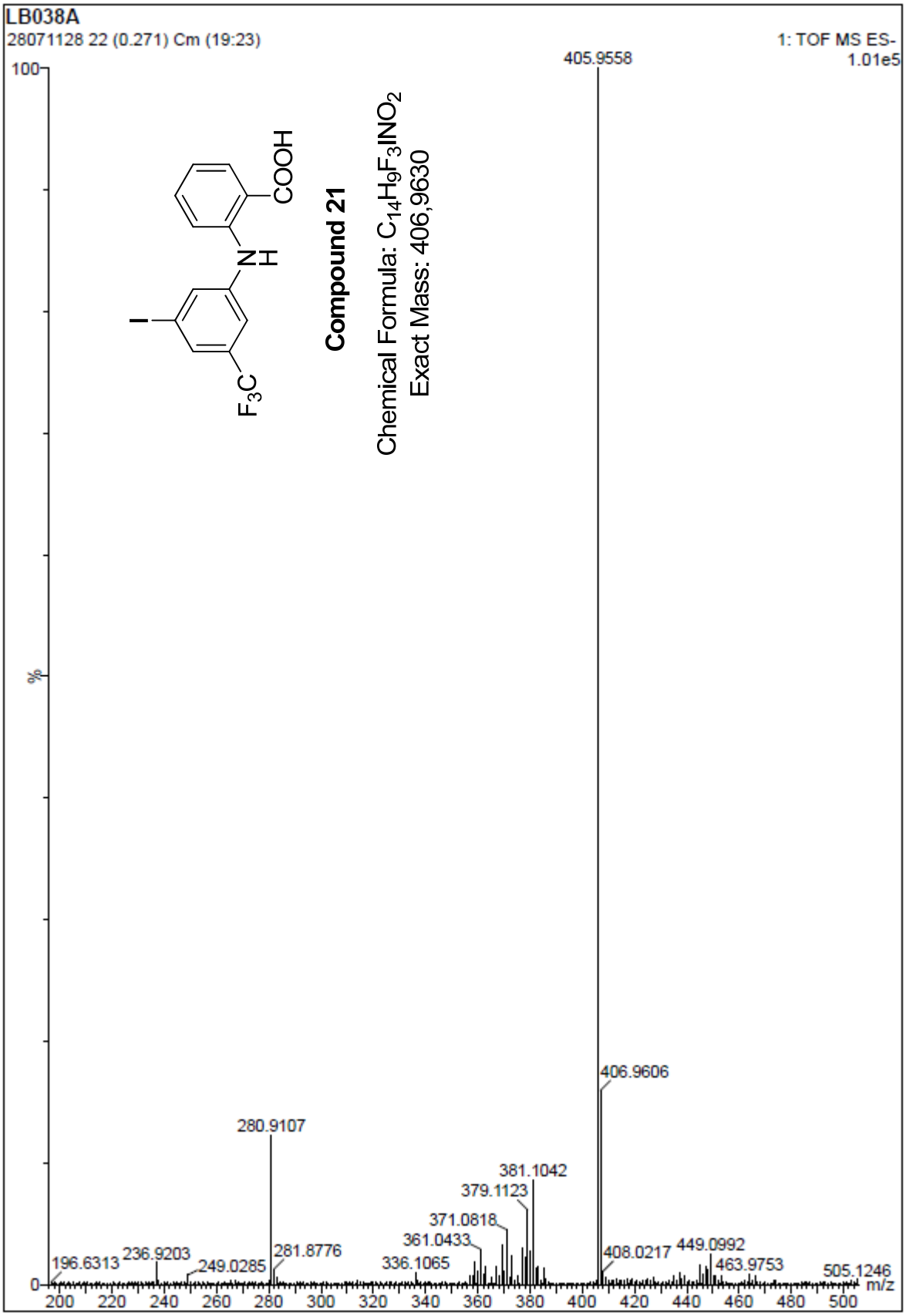
Sample Name: Muestra
Injection from this vial: 1 of 1

Series:7170
Vial Number: 1
Volume: 30,0 ul



Pump A Type: L-6200
Solvent A: Agua

Solvent B: ACN

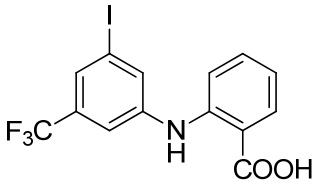

LB038A
28071128 22 (0.271) Cm (19:23)
1: TOF MS ES-
1.01e5
100
%
0
405.9558
406.9606
280.9107
381.1042
379.1123
371.0818
361.0433
336.1065
196.6313
236.9203
249.0285
281.8776
408.0217
449.0992
463.9753
505.1246
m/z
200 220 240 260 280 300 320 340 360 380 400 420 440 460 480 500
COOH
NH
I
F3C
Compound 21
Chemical Formula: C14H9F3INO2
Exact Mass: 406,9630

Elemental Composition Report

Single Mass Analysis

Tolerance = 10.0 mDa / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
43 formula(e) evaluated with 1 results within limits (up to 50 best isotopic matches for each mass)
Elements Used:
C: 10-14 H: 5-10 N: 0-1 O: 0-2 F: 0-3 127I: 0-1

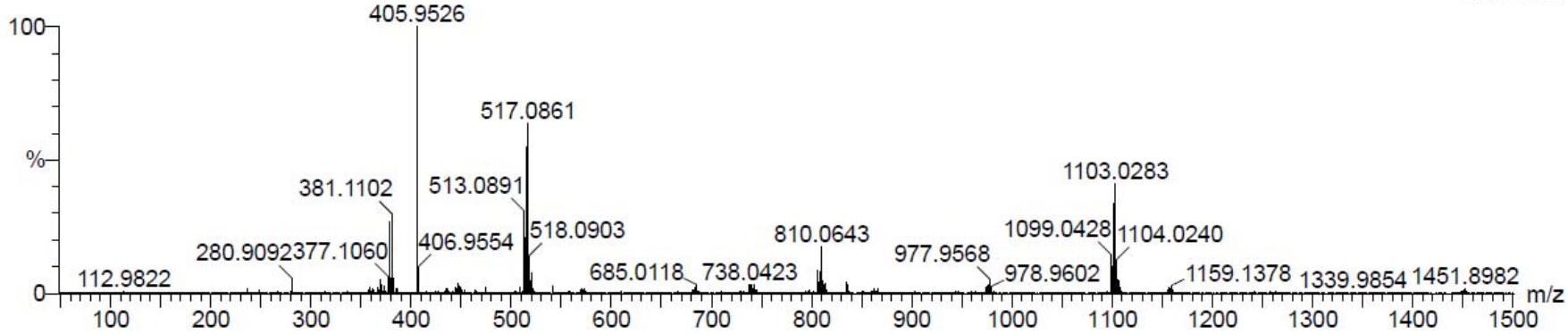


Compound 21

Chemical Formula: $C_{14}H_9F_3INO_2$
Exact Mass: 406,9630

LB038A
28071128 43 (0.524)

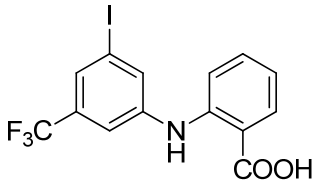
1: TOF MS ES-
5.09e+003



Minimum:				-1.5		
Maximum:		10.0	10.0	50.0		
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula
405.9526	405.9552	-2.6	-6.4	9.5	87.6	C14 H8 N O2 F3 127I

Single Mass Analysis

Tolerance = 20.0 mDa / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3



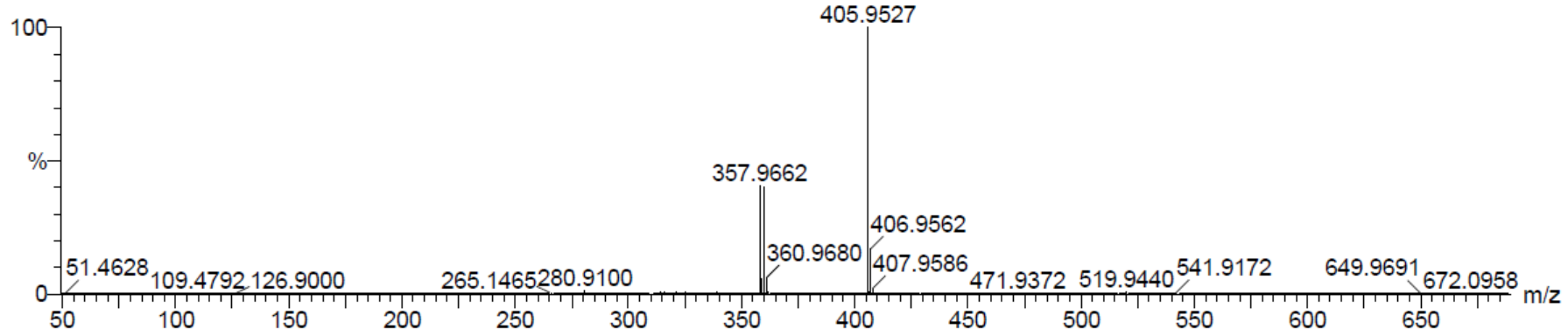
Compound 21

Chemical Formula: $C_{14}H_9F_3INO_2$
Exact Mass: 406,9630

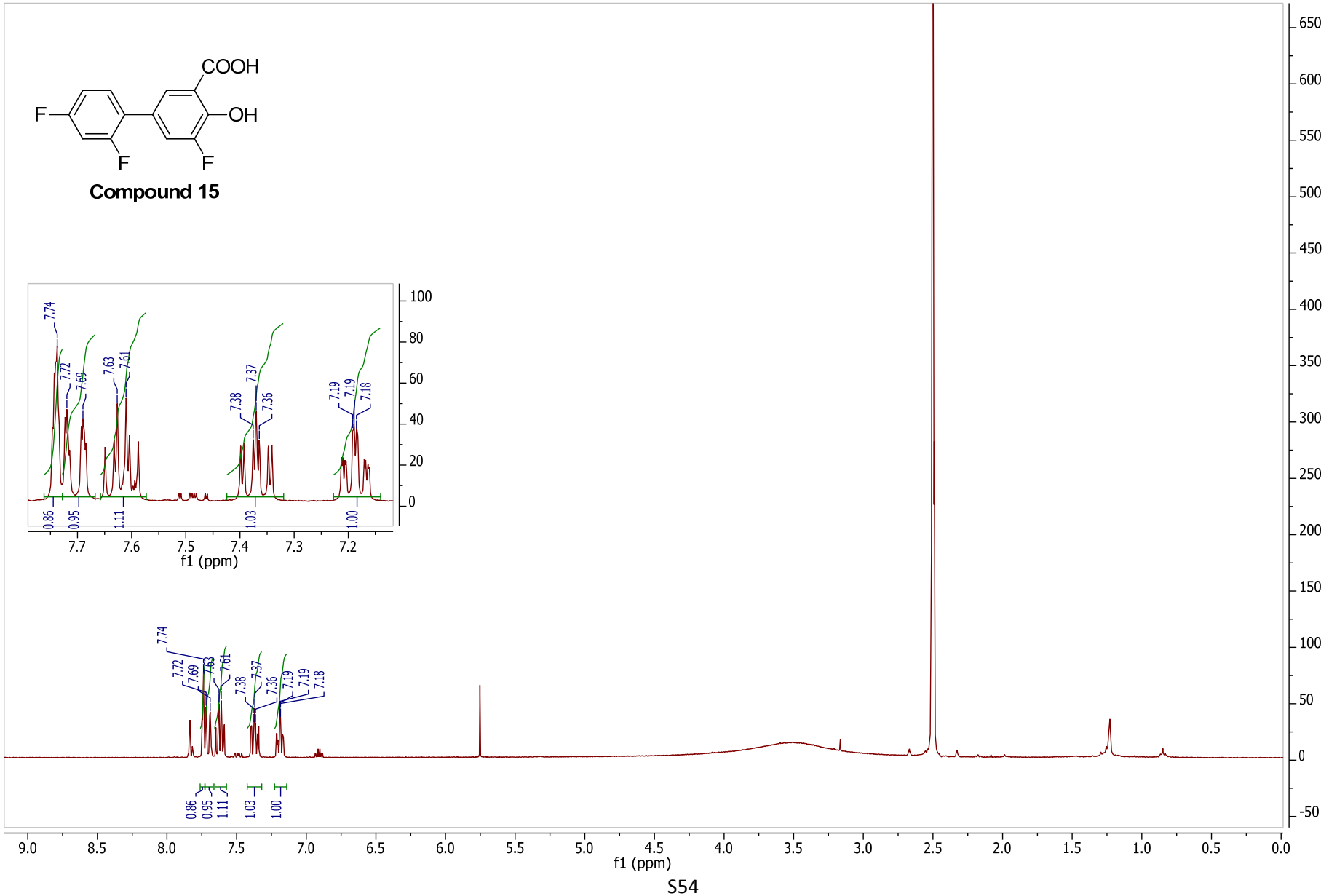
Monoisotopic Mass, Even Electron Ions
45 formula(e) evaluated with 1 results within limits (up to 50 best isotopic matches for each mass)
Elements Used:
C: 0-14 H: 0-8 N: 0-1 O: 0-2 F: 0-3 I: 0-1

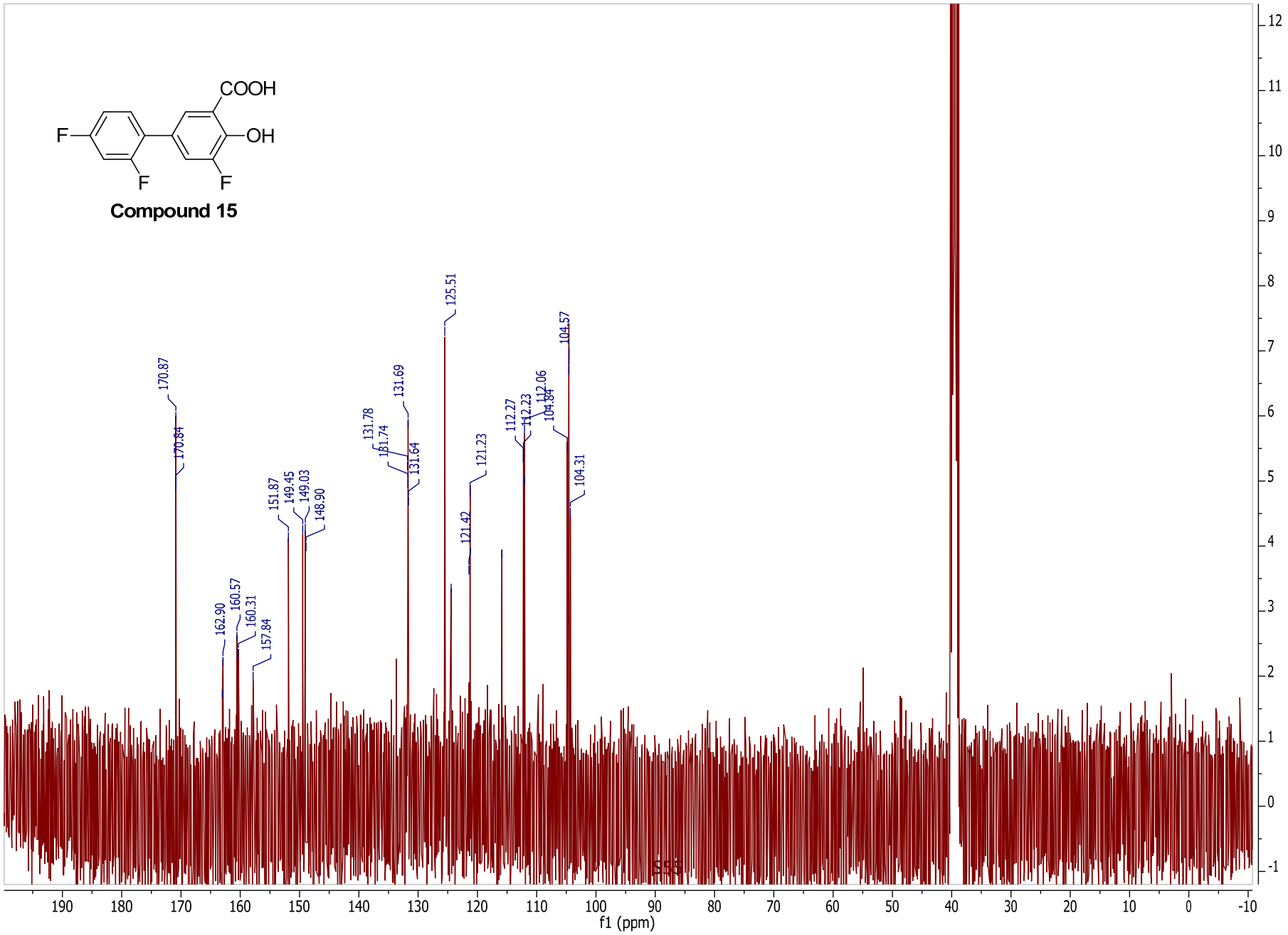
LB033AB
28071116 33 (0.407)

1: TOF MS ES-
5.82e+004



Minimum:				-1.5		
Maximum:		20.0	10.0	50.0		
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula
405.9527	405.9552	-2.5	-6.2	9.5	18.4	C14 H8 N O2 F3 I


COOH
F
OH
F
F
Compound 15
7.74
7.72
7.69
7.63
7.61
7.38
7.37
7.36
7.19
7.19
7.18
0.86
0.95
1.11
1.03
1.00
f1 (ppm)


COOH
OH
F
F
F
Compound 15
170.87
170.84
162.90
160.57
160.31
157.84
151.87
149.45
149.03
148.90
131.78
131.74
131.69
131.64
125.51
121.42
121.23
112.27
112.23
112.06
104.84
104.57
104.31
f1 (ppm)

Processing Method: GEN1

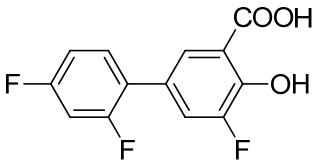
Sample Name: Muestra

Injection from this vial: 1 of 1

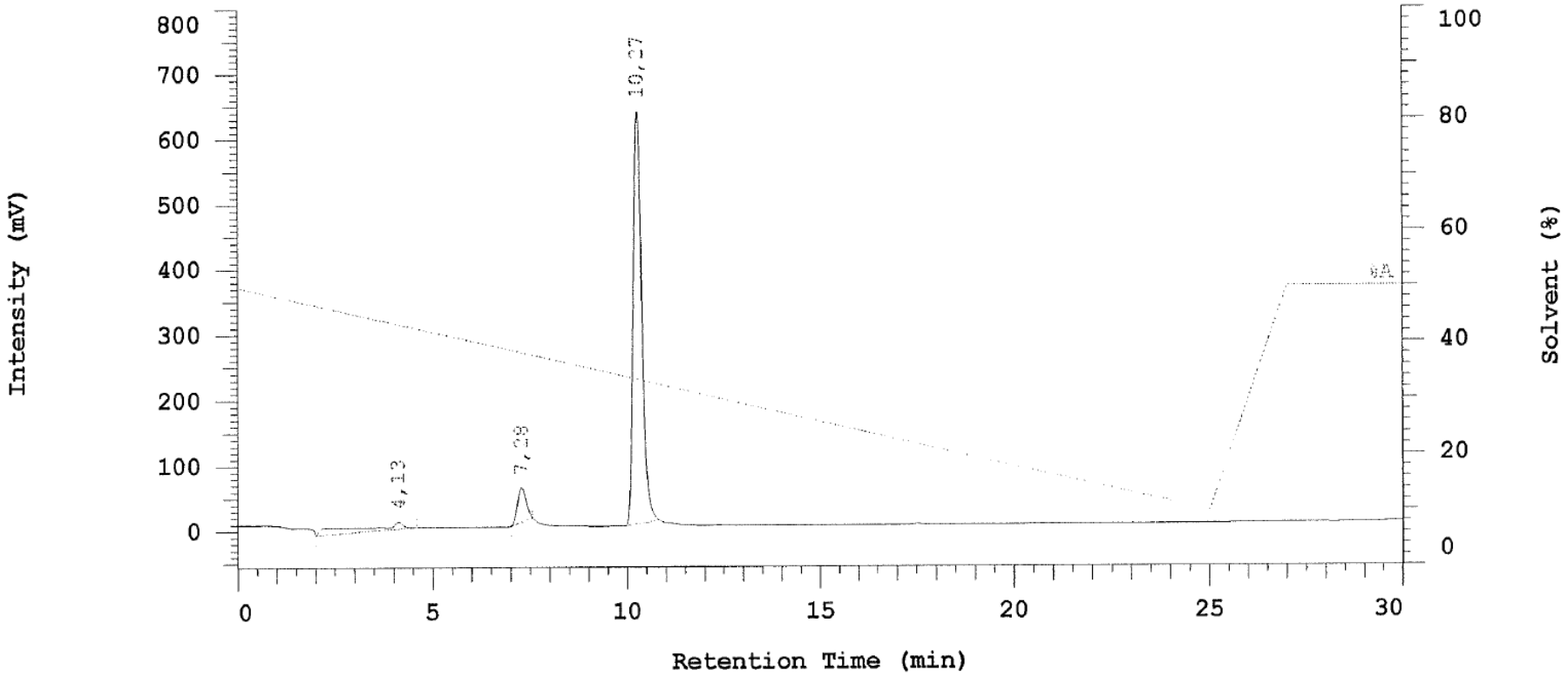
Series:7153

Vial Number: 1

Volume: 30,0 ul



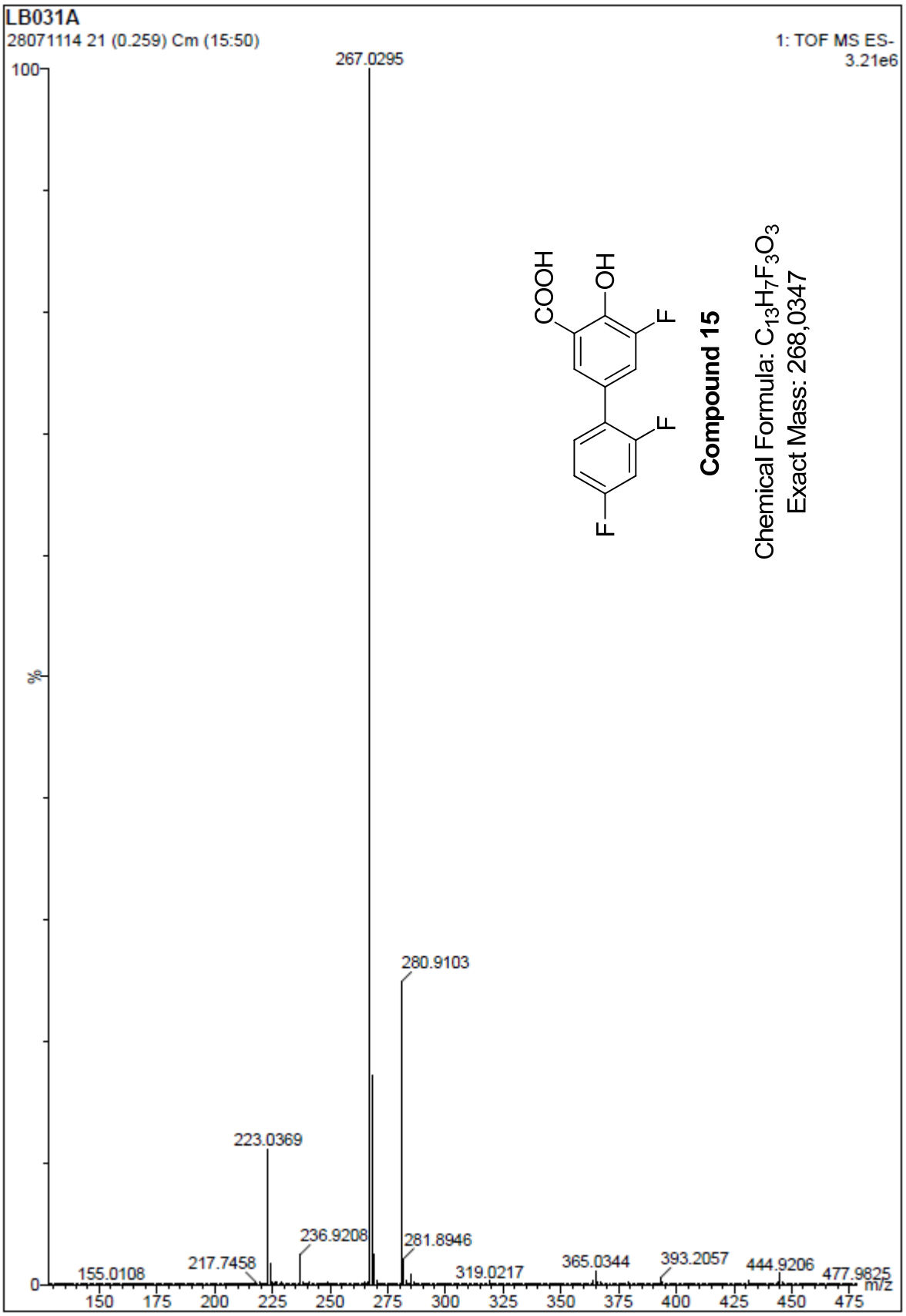
Compound 15



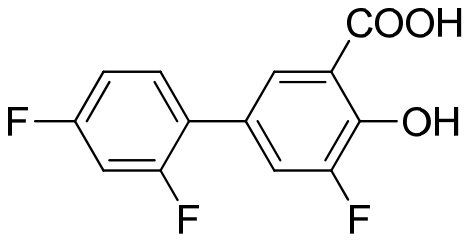
Pump A Type: L-6200

Solvent A: Agua

Solvent B: ACN


LB031A
28071114 21 (0.259) Cm (15:50)
1: TOF MS ES-
3.21e6
100
%
0
267.0295
280.9103
223.0369
236.9208
281.8946
155.0108
217.7458
319.0217
365.0344
393.2057
444.9206
477.9825
150
175
200
225
250
275
300
325
350
375
400
425
450
475
m/z
COOH
OH
F
F
F
Compound 15
Chemical Formula: $C_{13}H_7F_3O_3$
Exact Mass: 268,0347

Elemental Composition Report



Compound 15

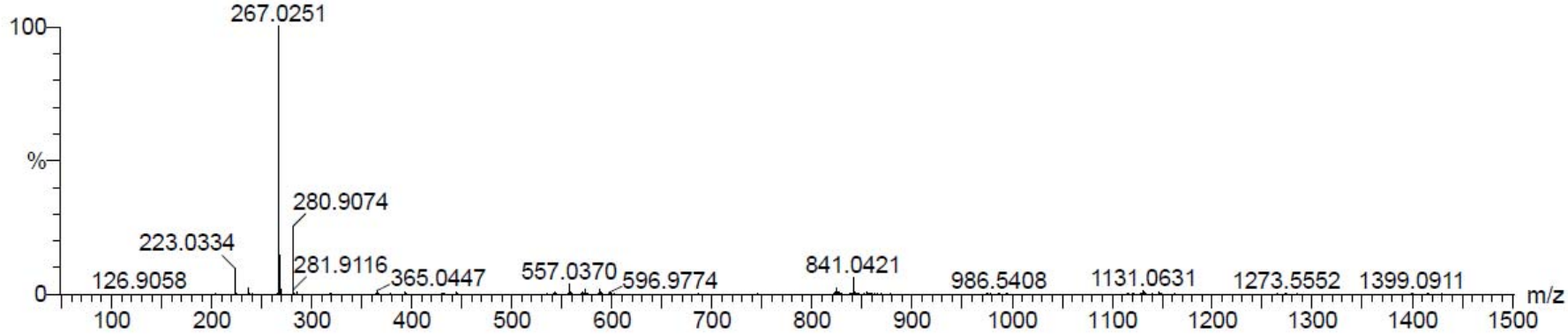
Chemical Formula: $C_{13}H_7F_3O_3$
Exact Mass: 268,0347

Tolerance = 10.0 mDa / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

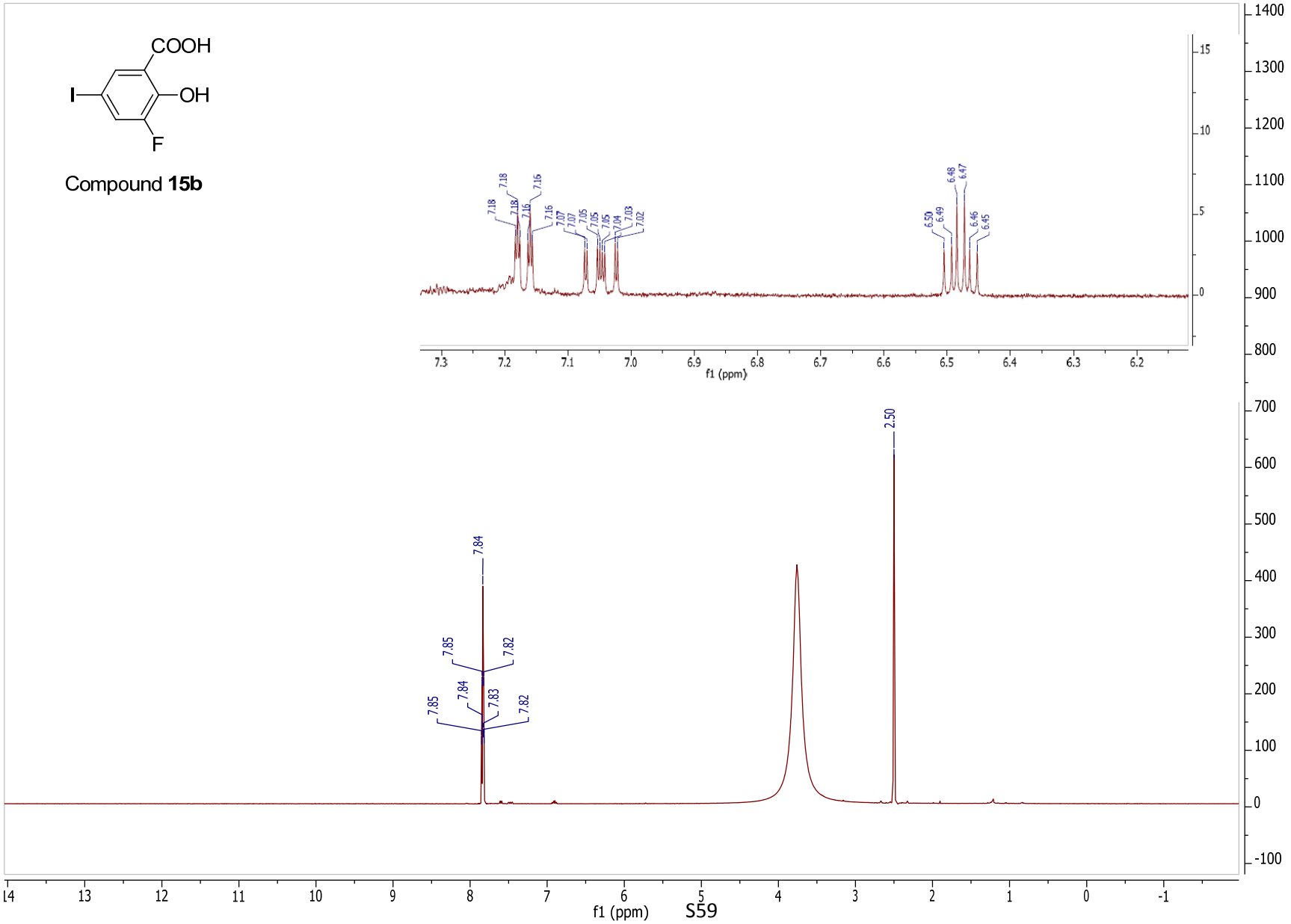
Monoisotopic Mass, Even Electron Ions
5 formula(e) evaluated with 1 results within limits (up to 50 best isotopic matches for each mass)
Elements Used:
C: 10-13 H: 5-8 O: 3-5 F: 0-3

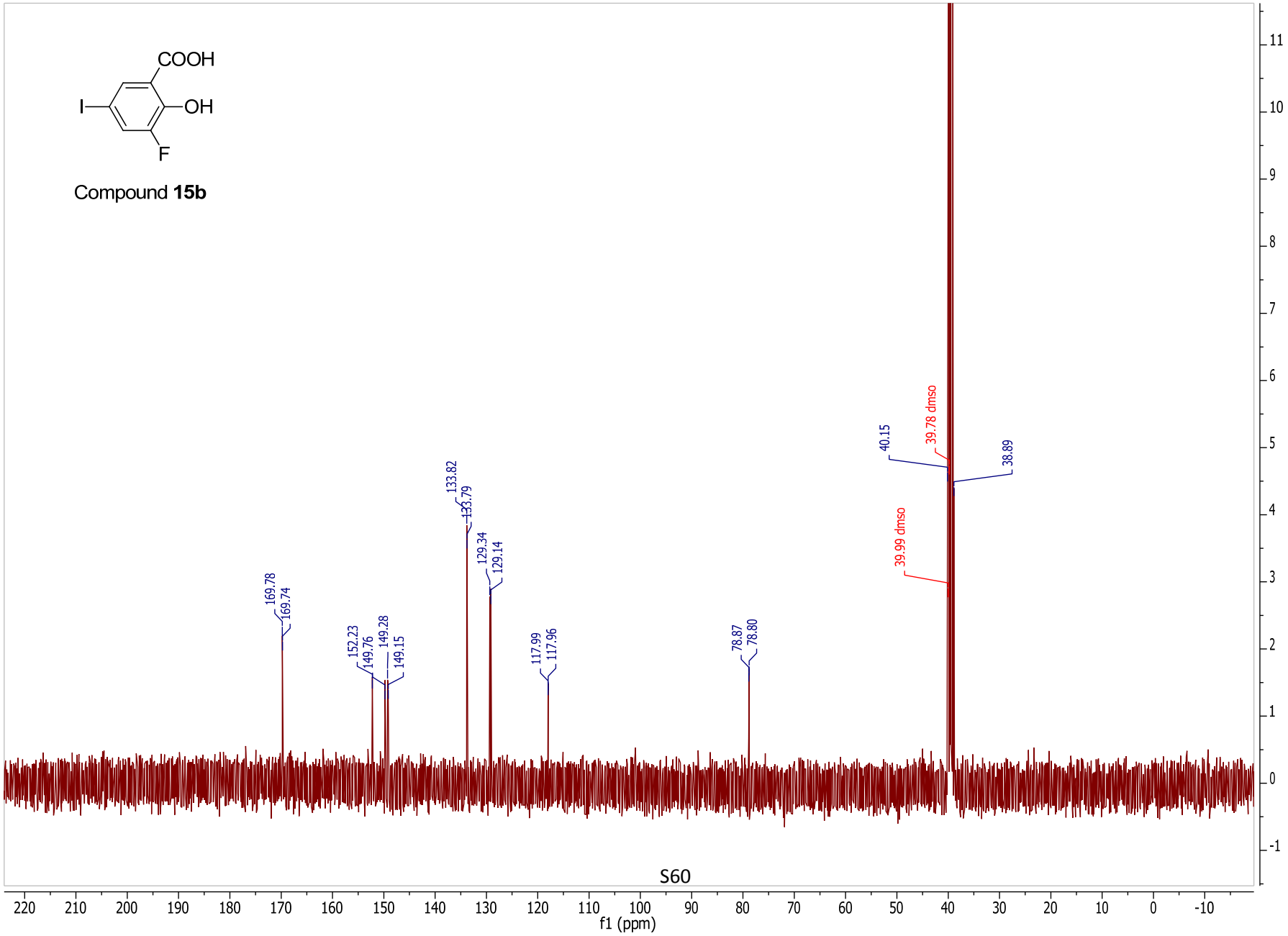
LB031A
28071114 36 (0.434)

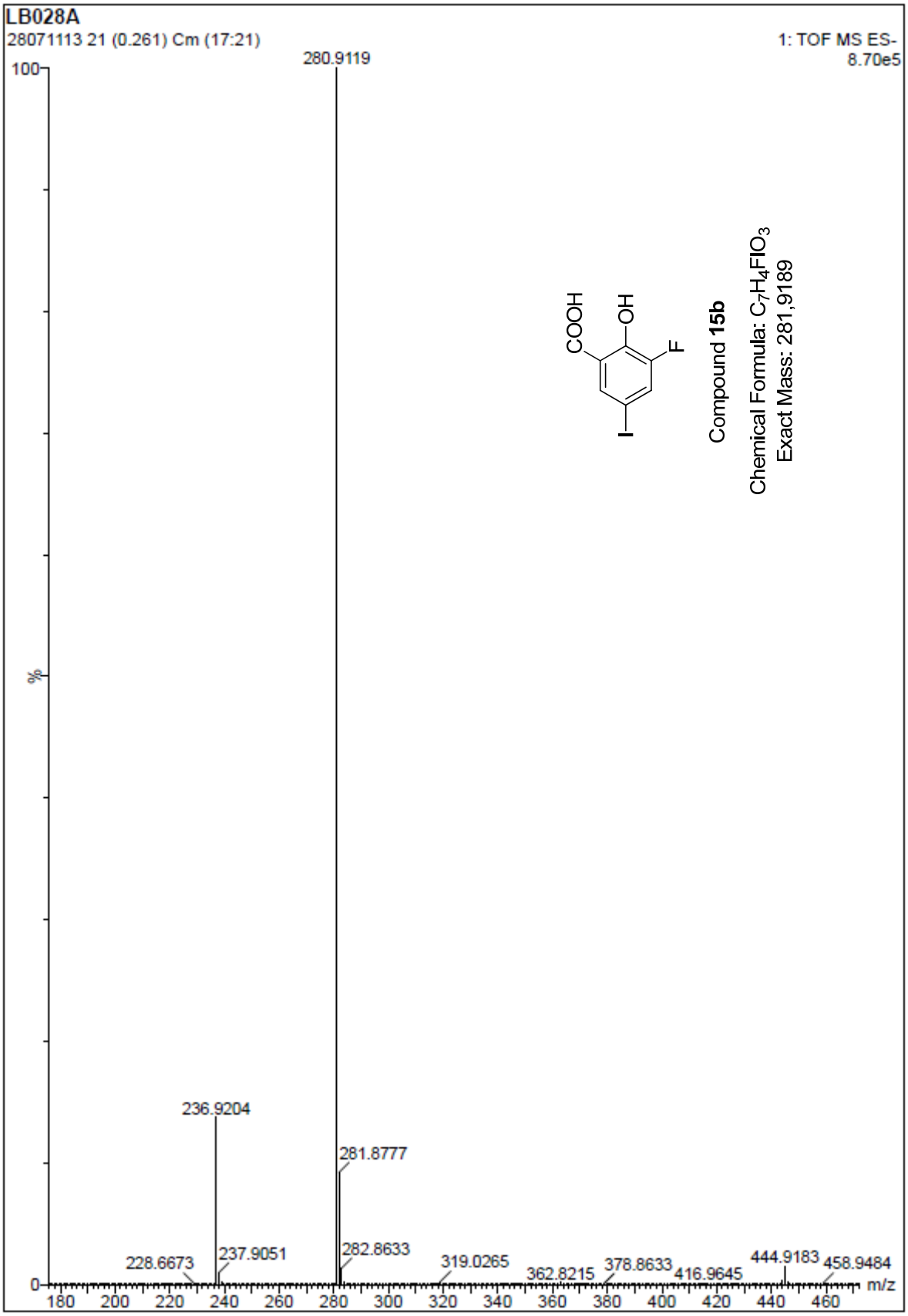
1: TOF MS ES-
1.36e+005

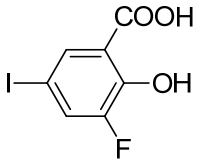


Minimum:	80.00				-1.5		
Maximum:	100.00		10.0	10.0	50.0		
Mass	RA	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula
267.0251	100.00	267.0269	-1.8	-6.7	9.5	32.5	C13 H6 O3 F3


COOH
I
OH
F
Compound 15b
7.18
7.18
7.18
7.16
7.16
7.16
7.07
7.07
7.05
7.05
7.05
7.04
7.03
7.02
6.59
6.49
6.48
6.47
6.46
6.45
f1 (ppm)
7.84
7.85
7.82
7.85
7.84
7.83
7.82
2.50
f1 (ppm)


COOH
I
OH
F
Compound 15b
169.78
169.74
152.23
149.76
149.28
149.15
133.82
133.79
129.34
129.14
117.99
117.96
78.87
78.80
40.15
39.78 dmso
39.99 dmso
38.89
S60
f1 (ppm)


LB028A
28071113 21 (0.261) Cm (17:21)
1: TOF MS ES-
8.70e5
100
%
0
280.9119
236.9204
281.8777
228.6673
237.9051
282.8633
319.0265
362.8215
378.8633
416.9645
444.9183
458.9484
180
200
220
240
260
280
300
320
340
360
380
400
420
440
460
m/z
COOH
OH
F
I
Compound 15b
Chemical Formula: C7H4FIO3
Exact Mass: 281,9189



Compound **15b**

Chemical Formula: $C_7H_4FIO_3$
Exact Mass: 281,9189

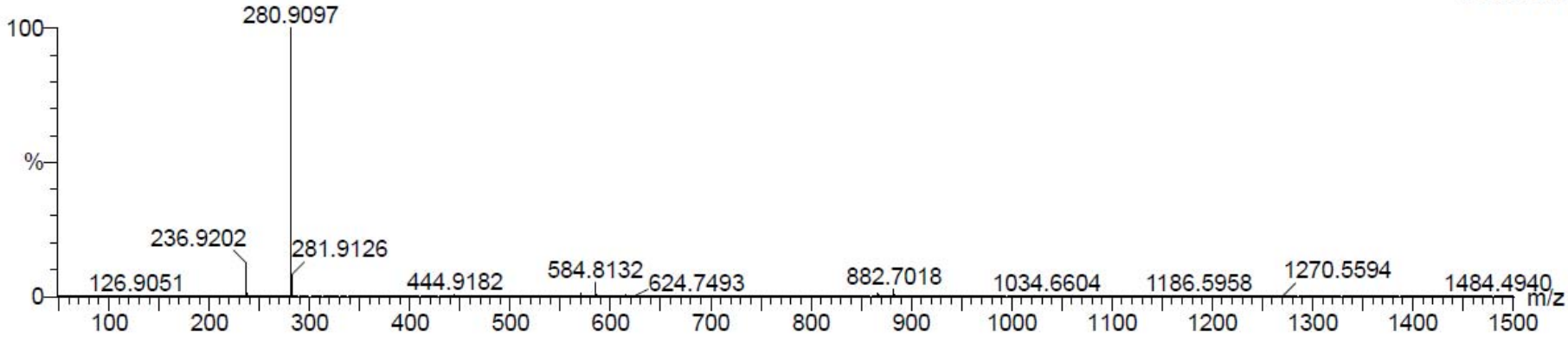
Single Mass Analysis

Tolerance = 20.0 mDa / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

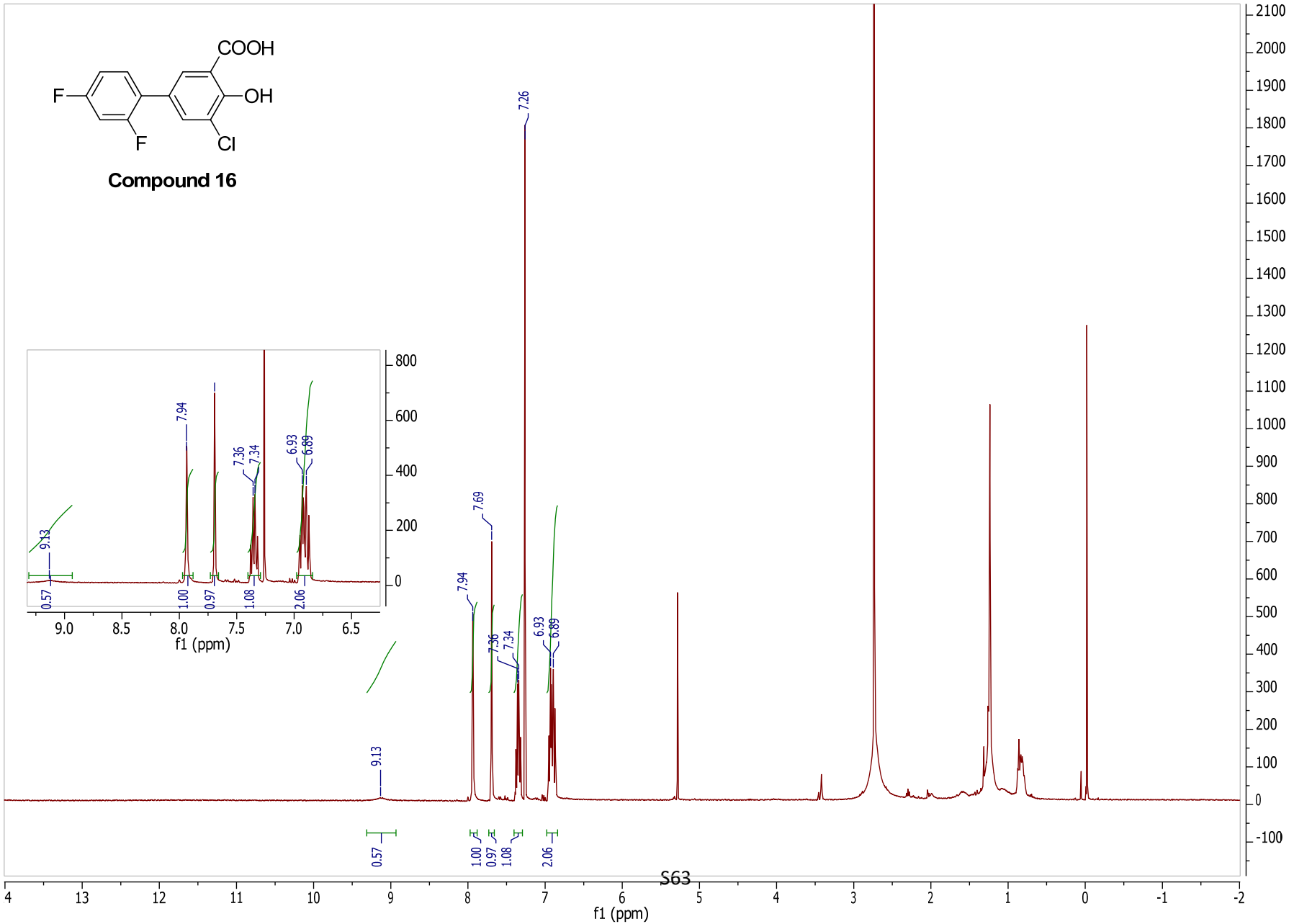
Monoisotopic Mass, Even Electron Ions
14 formula(e) evaluated with 1 results within limits (up to 50 best isotopic matches for each mass)
Elements Used:
C: 0-7 H: 0-4 O: 0-3 F: 0-1 I: 0-1

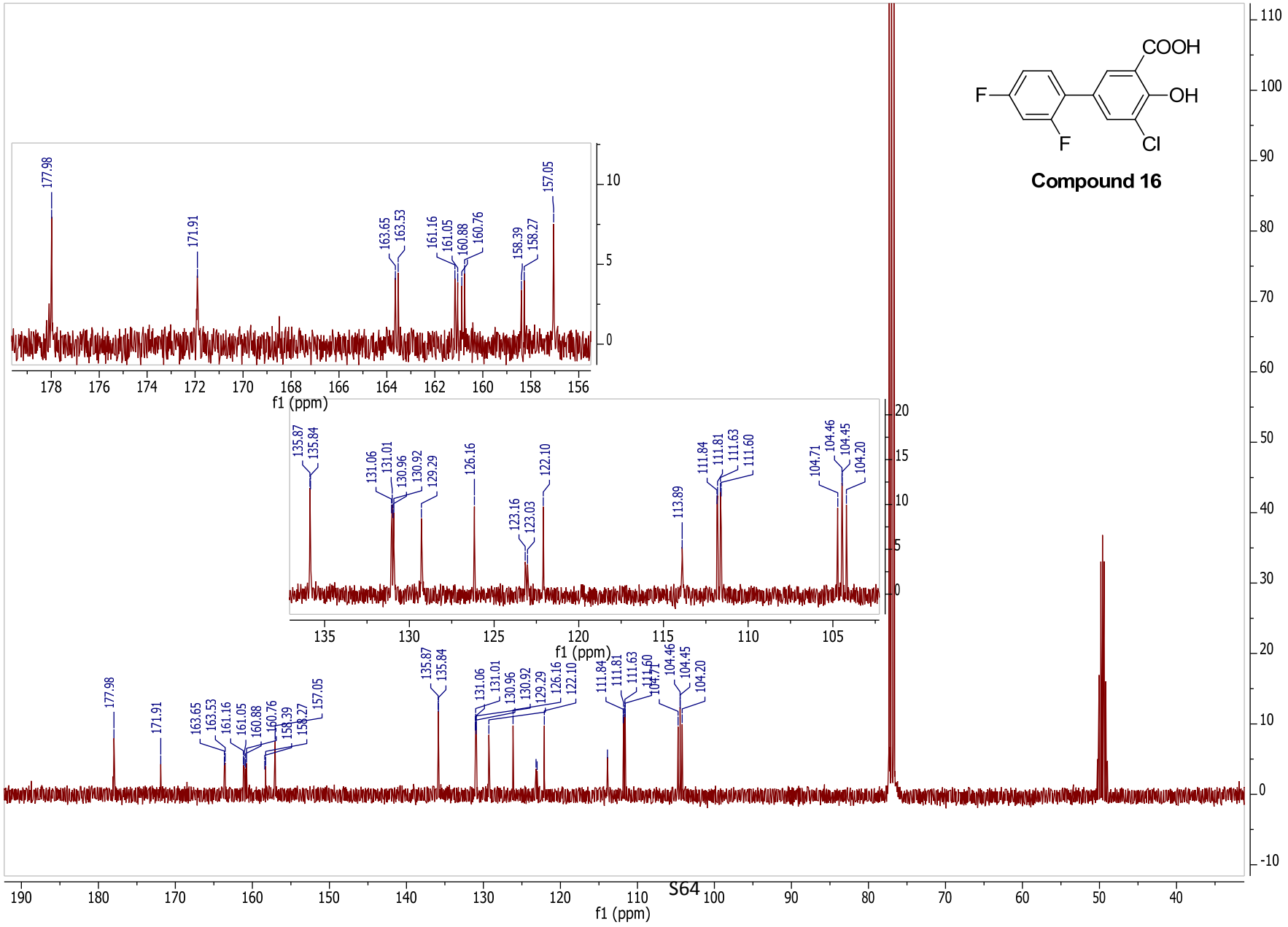
LB028A
28071113 37 (0.461)

1: TOF MS ES-
2.06e+005



Minimum:				-1.5		
Maximum:		20.0	10.0	50.0		
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula
280.9097	280.9111	-1.4	-5.0	5.5	36.7	C7 H3 O3 F I


COOH
F
OH
F
Cl
Compound 16
7.26
7.94
7.69
7.36
7.34
6.93
6.89
9.13
0.57
1.00
0.97
1.08
2.06
f1 (ppm)


COOH
OH
F
F
Cl
Compound 16
177.98
171.91
163.65
163.53
161.16
161.05
160.88
160.76
158.39
158.27
157.05
135.87
135.84
131.06
131.01
130.96
130.92
129.29
126.16
123.16
123.03
122.10
113.89
111.84
111.81
111.63
111.60
104.71
104.46
104.45
104.20
f1 (ppm)

Processing Method: GEN1

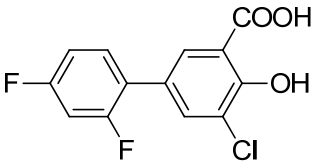
Sample Name: Muestra

Injection from this vial: 1 of 1

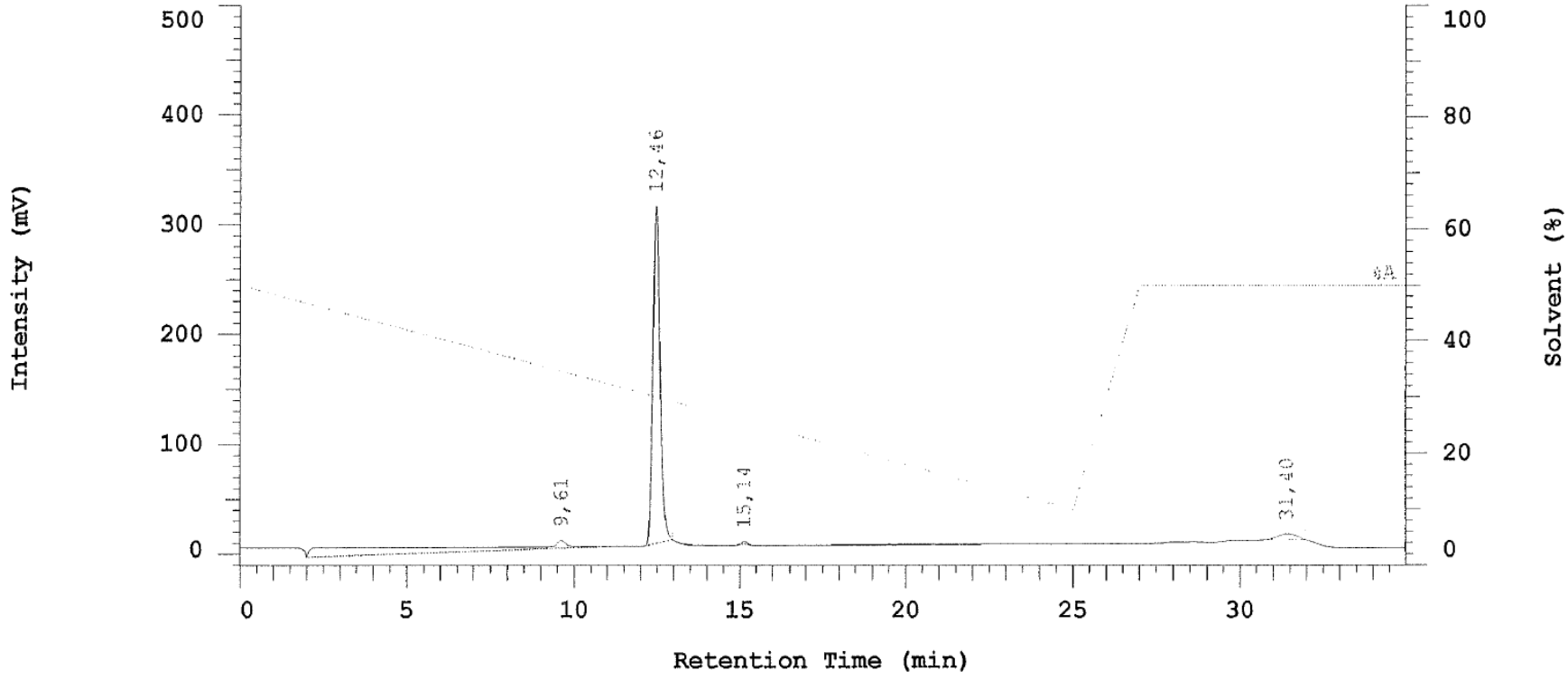
Series:7135

Vial Number: 1

Volume: 30,0 ul



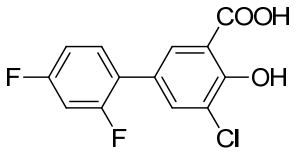
Compound 16



Pump A Type: L-6200

Solvent A: Agua

Solvent B: ACN



Compound 16

Chemical Formula: $C_{13}H_7ClF_2O_3$
Exact Mass: 284,0052

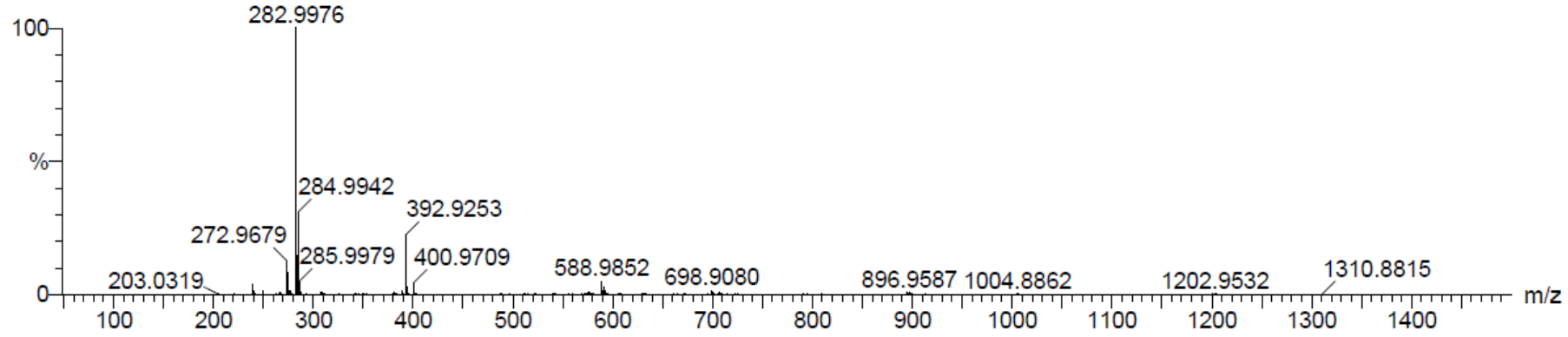
Single Mass Analysis

Tolerance = 10.0 mDa / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

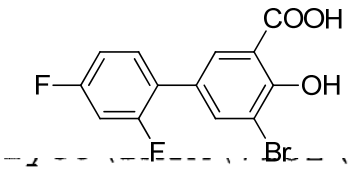
Monoisotopic Mass, Even Electron Ions
22 formula(e) evaluated with 1 results within limits (up to 50 best isotopic matches for each mass)
Elements Used:
C: 0-13 H: 0-8 O: 0-3 F: 0-2 Cl: 0-1

LB011
02061146 38 (0.471)

1: TOF MS ES-
5.98e+004



Minimum:				-1.5		
Maximum:		10.0	10.0	50.0		
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula
282.9976	282.9974	0.2	0.7	9.5	51.4	C13 H6 O3 F2 Cl



Compound 17

Processing Method: GEN1

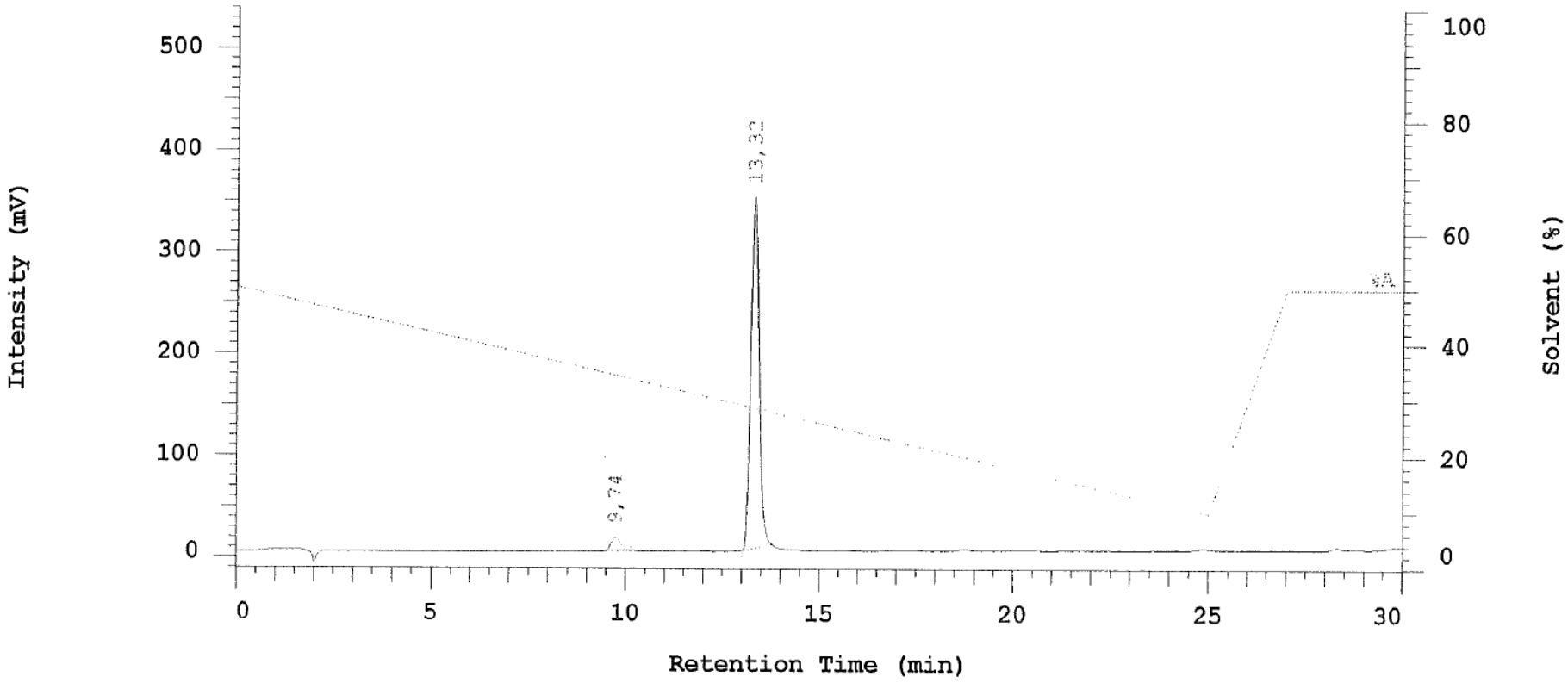
Sample Name: Muestra

Injection from this vial: 1 of 1

Series:7132

Vial Number: 1

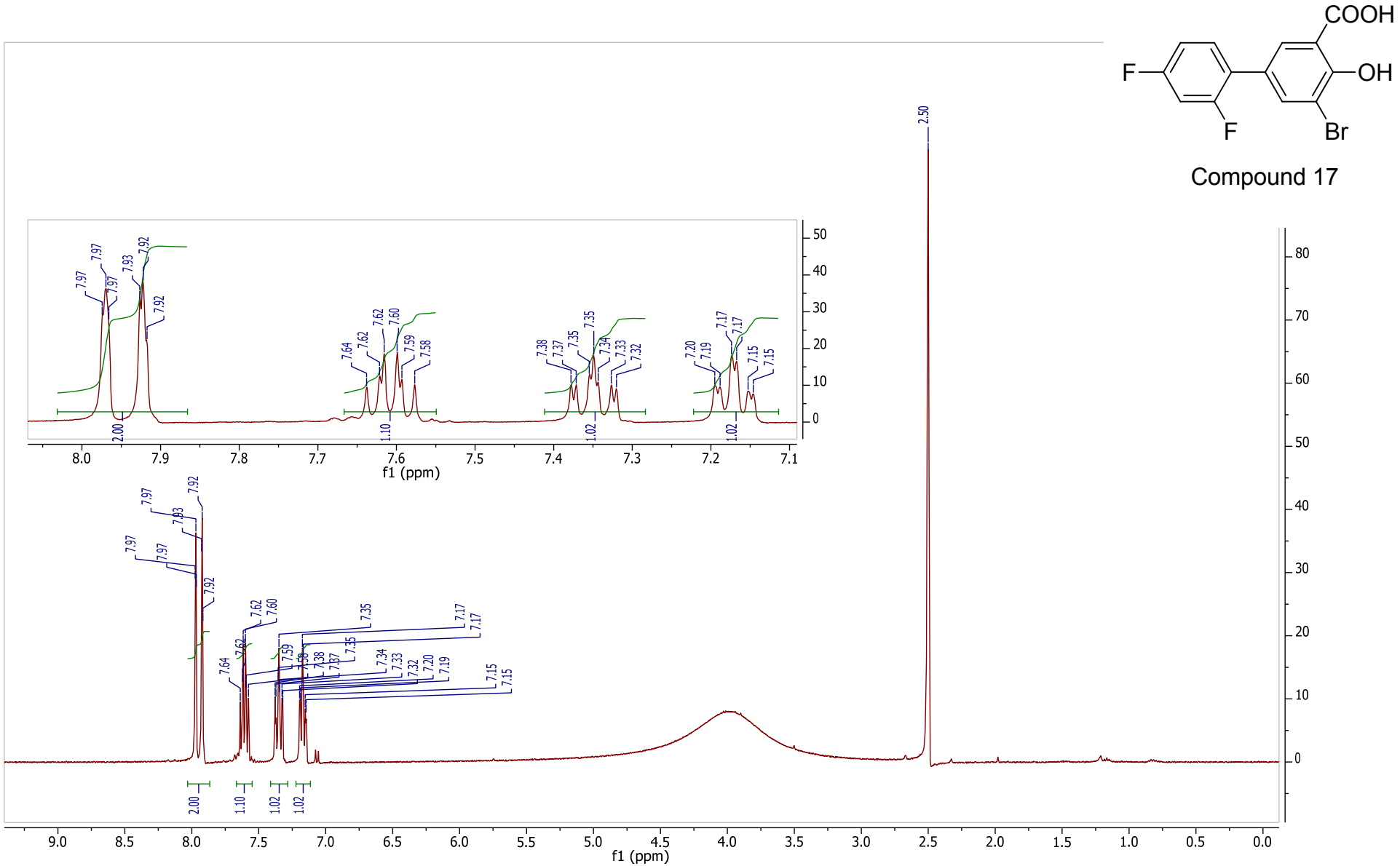
Volume: 30,0 ul

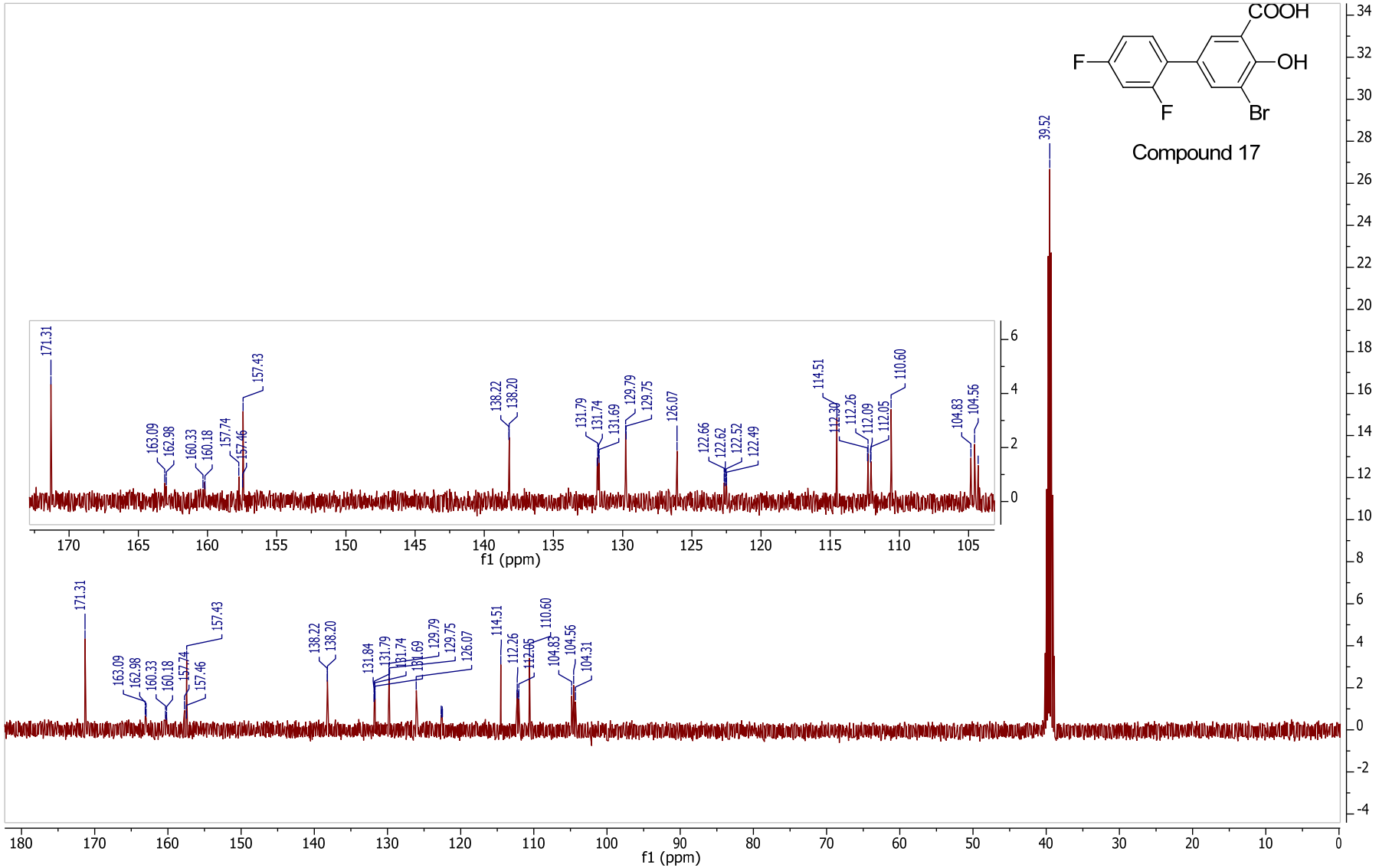


Pump A Type: L-6200

Solvent A: Agua

Solvent B: ACN

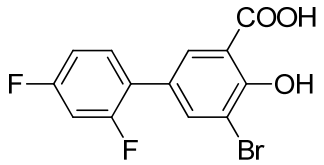

COOH
F
OH
F
Br
Compound 17
f1 (ppm)
f1 (ppm)


COOH
F
OH
F
Br
Compound 17
f1 (ppm)
f1 (ppm)

Multiple Mass Analysis: 2 mass(es) processed

Tolerance = 10.0 mDa / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
229 formula(e) evaluated with 2 results within limits (up to 50 best isotopic matches for each mass)
Elements Used:
C: 0-14 H: 0-10 O: 0-3 F: 0-2 79Br: 0-8 81Br: 0-8

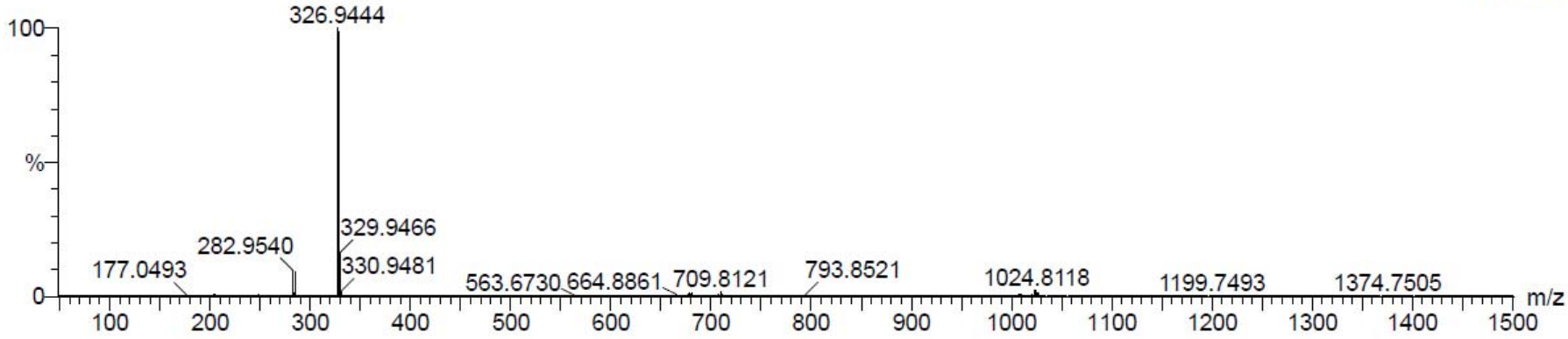


Compound 17

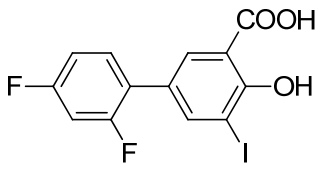
Chemical Formula: $C_{13}H_7BrF_2O_3$
Exact Mass: 327,9547

BrDiF
30111204 58 (0.723)

1: TOF MS ES-
1.28e+005



Minimum:	80.00				-1.5		
Maximum:	100.00		10.0	10.0	50.0		
Mass	RA	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula
326.9444	100.00	326.9468	-2.4	-7.3	9.5	61416.4	C13 H6 O3 F2 79Br
328.9424	98.59	328.9448	-2.4	-7.3	9.5	130.1	C13 H6 O3 F2 81Br

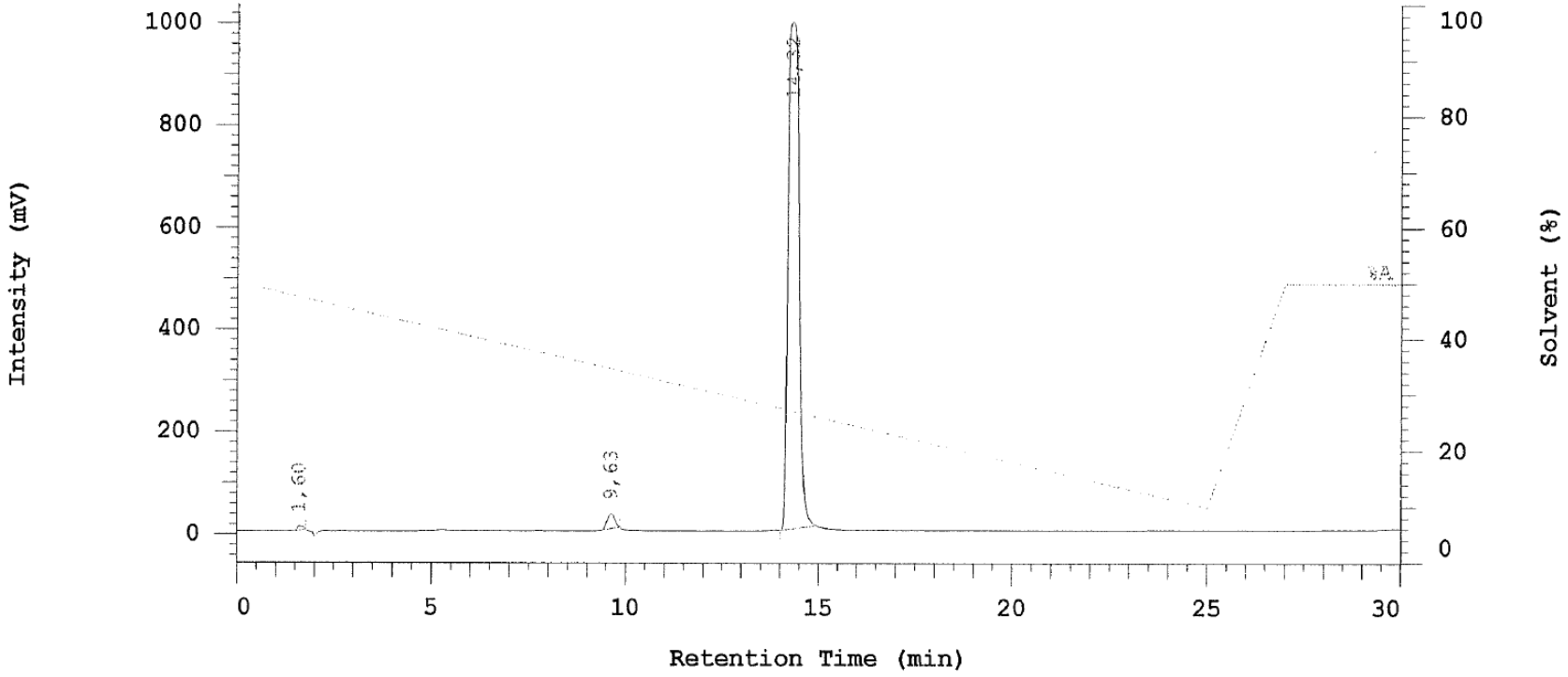


Compound 13

Processing Method: GEN1

Sample Name: Muestra
Injection from this vial: 1 of 1

Series:7137
Vial Number: 1
Volume: 30,0 ul

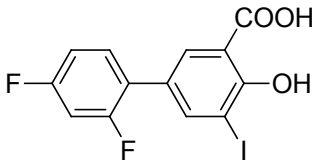


Pump A Type: L-6200
Solvent A: Agua

Solvent B: ACN

Single Mass Analysis

Tolerance = 20.0 mDa / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3



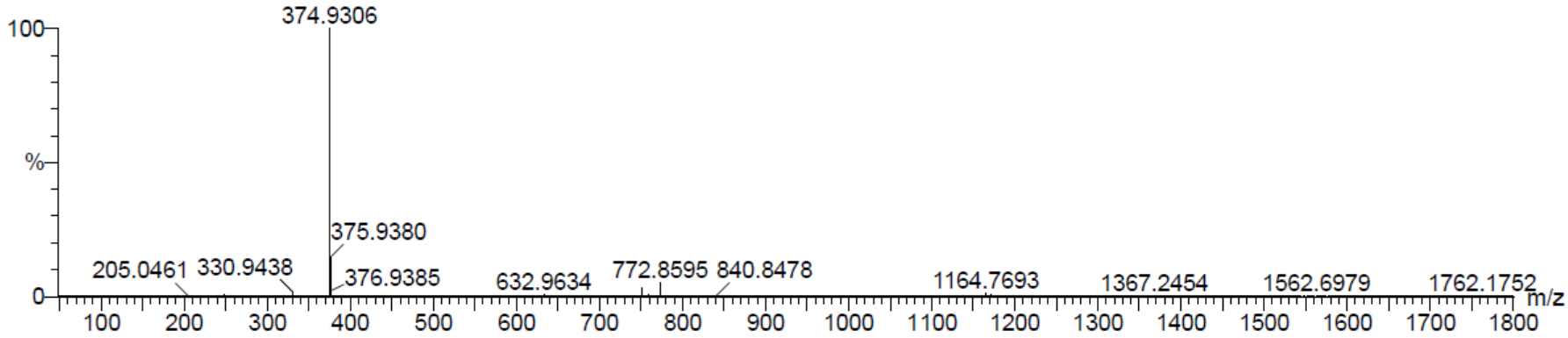
Compound 13

Chemical Formula: $C_{13}H_7F_2IO_3$
Exact Mass: 375,9408

Monoisotopic Mass, Even Electron Ions
18 formula(e) evaluated with 1 results within limits (up to 50 best isotopic matches for each mass)
Elements Used:
C: 0-15 H: 0-10 O: 0-3 F: 0-2 I: 0-1

Fia Gemma
IDIF 8 (0.386)

2: TOF MS ES-
3.08e+005



Minimum:				-1.5		
Maximum:		20.0	10.0	50.0		
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula
374.9306	374.9330	-2.4	-6.4	9.5	112.0	C13 H6 O3 F2 I