SUPPORTING INFORMATION

Discovery and Characterization of XY101, a Potent, Selective, and Orally Bioavailable RORγ Inverse Agonist for Treatment of Castration-Resistant Prostate Cancer (CRPC)

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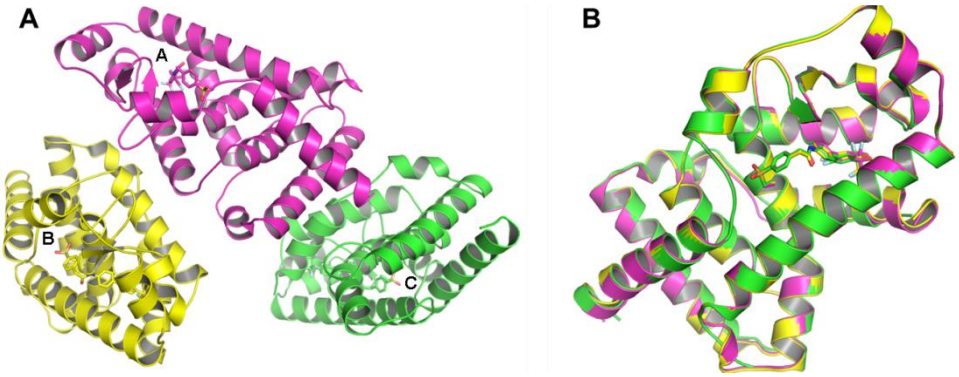
1. Table S1. Statistics of the data sets and structure refinement.

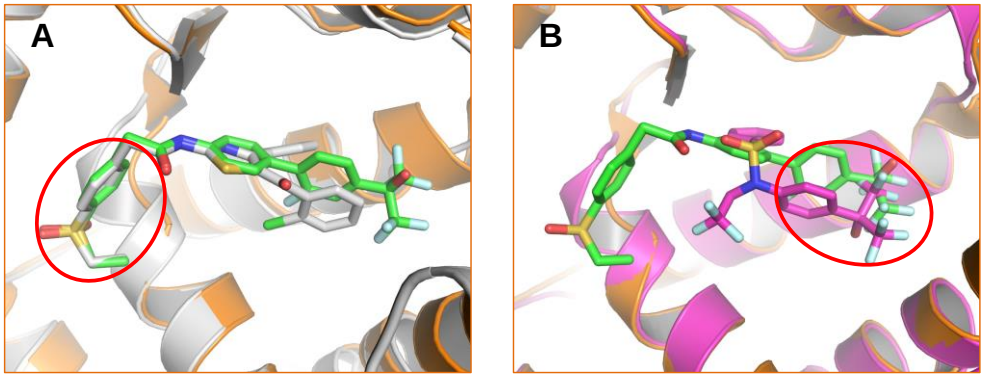
Protein/ligand	RORγ/**27**
PDB ID:	6J1L.pdb
Space group	$P6_1$
Cell dimensions *a*, *b*, *c* (Å)	110.14, 110.14, 114.23
Cell dimensions α, β, γ (°)	90.00, 90.00, 120.00
Resolution (Å)*	2.30 (2.38-2.30)
R_{merge}*	0.108 (2.015)
I/σI*	13.2 (2.2)
Completeness (%)*	100 (100)
Redundancy	18.9 (18.6)
R_{work}/R_{free}	0.202/0.226
No. of atoms (P/L/O)	5424/114/71
B_f (P/L/O) ($Å^2$)	66.97/59.59/48.58
rms deviation bond(Å)	0.015
rms deviation angle (°)	1.704

*Values in brackets show the statistics for the highest resolution shells.
[a] P/L/O indicate protein, ligand, and other (water and other molecules), respectively.

2. Figure S1. (A) The co-crystal structure of compound **27** in complex with the RORγ LDB. (B) Superimposition of 3 complex structures from the asymmetry unit.

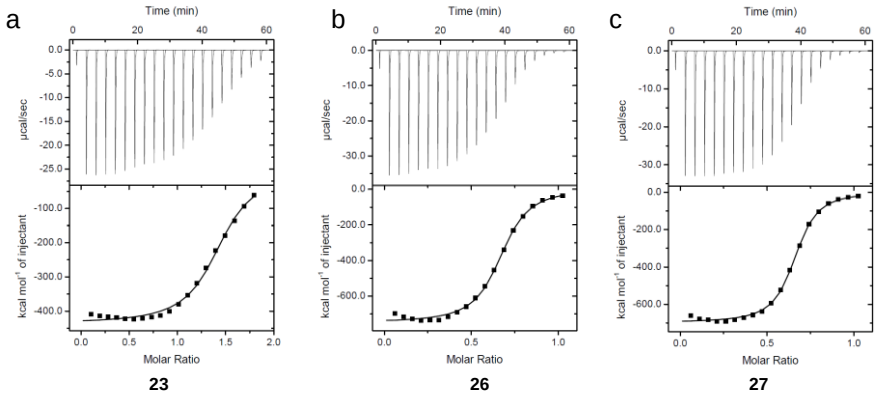


3. Figure S2. (A) Superposition of the crystal structures of **27** and GSK-8h bound to RORγ LBD (PDB IDs: 6JIL and 5NU1). (B) Superposition of the crystal structures of **27** and **1** bound to RORγ LBD (PDB IDs: 6JIL and 5NTQ).



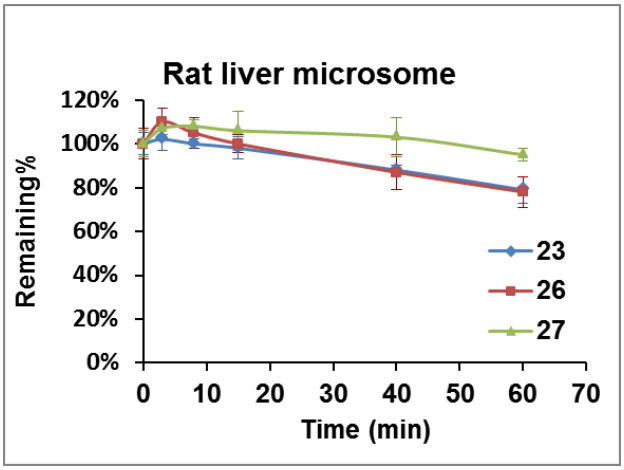
(A) (B)

4. Figure S3. ITC titration curves for the binding of **23** (A), **26** (B) and **27** (C) to the RORγ LBD. Corresponding parameters were listed.



Cmpd	Protein	N	K_D (nM)	ΔH (kcal/mol)	TΔS (kcal/mol)	ΔG (kcal/mol)
23	RORγ	0.994 ± 0.006	781	-418.1 ± 3.6	-408.3	-9.8
26	RORγ	1.020 ±0.006	564	-734.1 ± 5.7	-724.1	-10.0
27	RORγ	1.040 ± 0.004	380	-672.3 ± 3.6	-661.6	-10.7

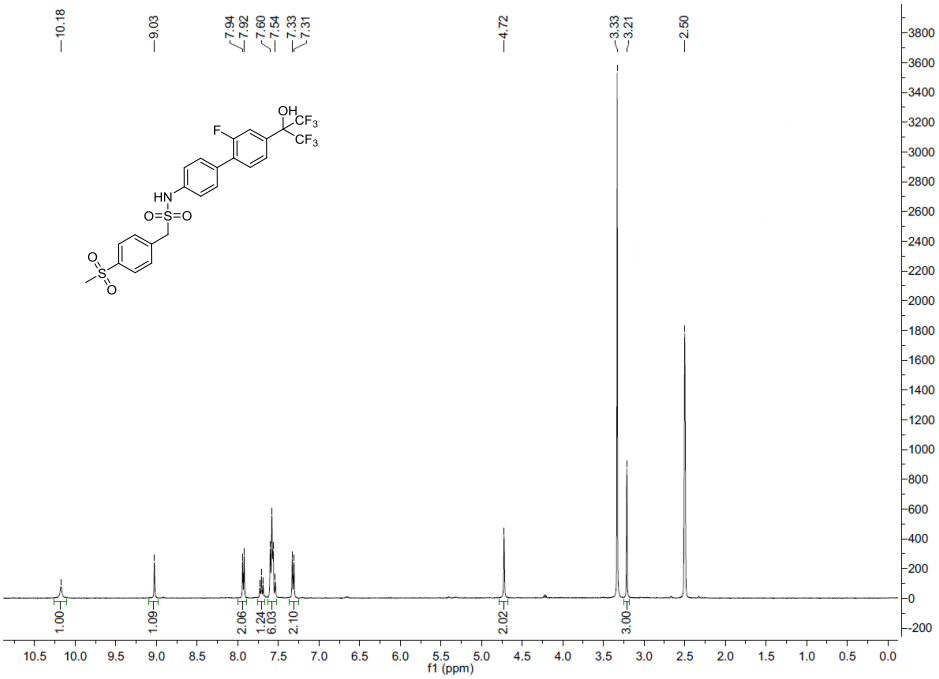
5. Figure S4. Metabolic stability of **23**, **26**, **27** in rat liver microsome at 10 μM.



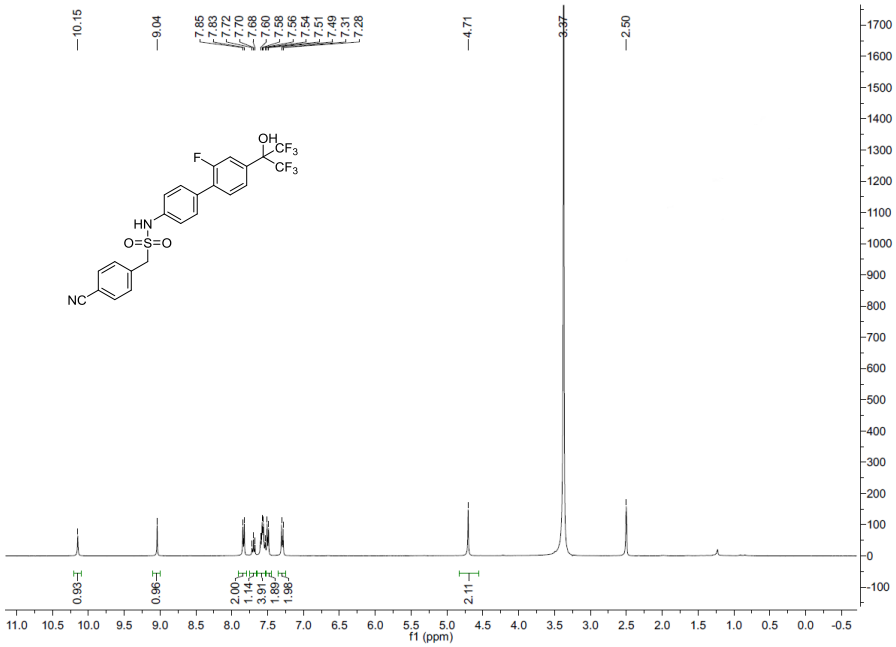
Cmpd	k	% of parent remaining after 1 h	T1/2 (min)
Testerone	-	26% (at 20 min)	-
23	0.00343	79%	202
26	0.00348	78%	199
27	0.00008	93%	>> 60

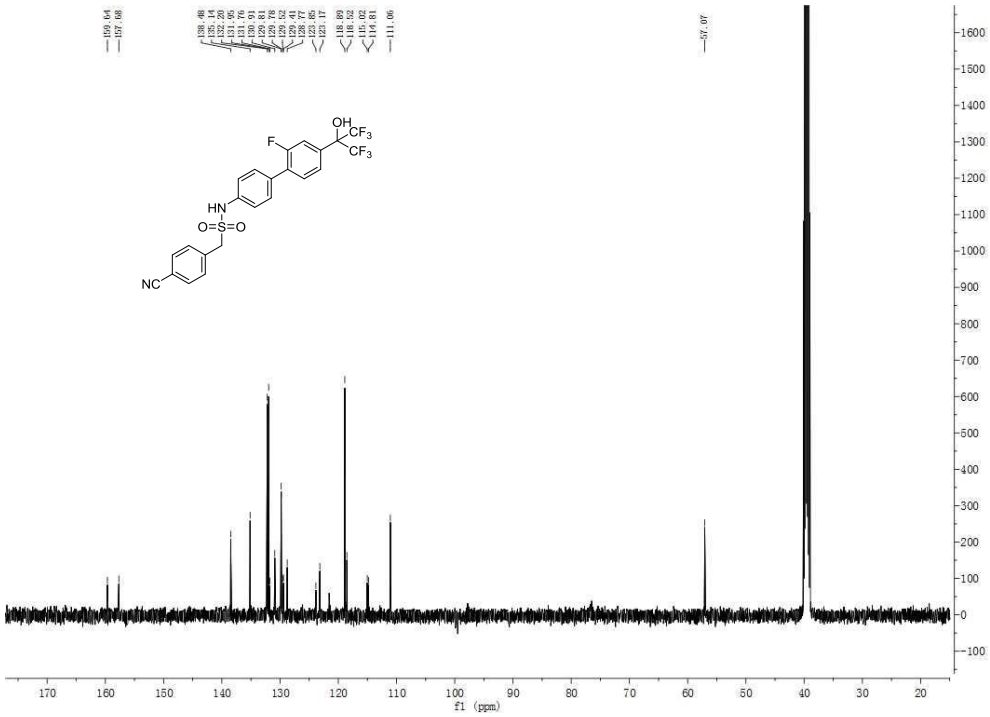
6. ^{1}H and ^{13}C NMR spectra of compounds **11**-**36**.

*N-(2'-fluoro-4'-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)-[1,1'-biphenyl]-4-yl)-1-(4-(methylsulfonyl)phenyl)methanesulfonamide (**11**).*

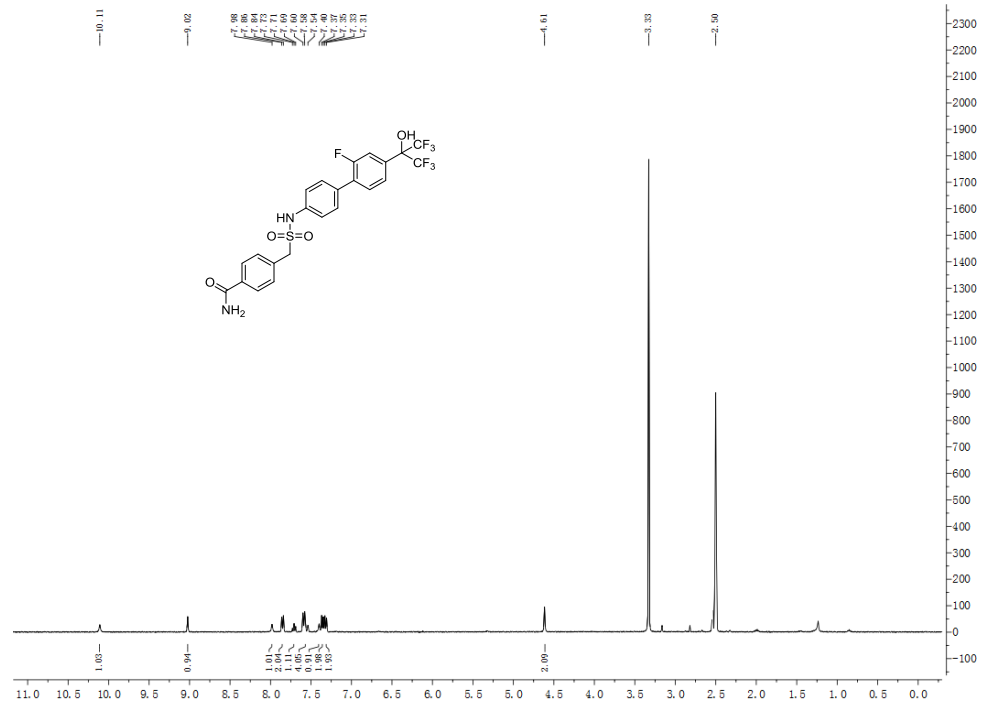


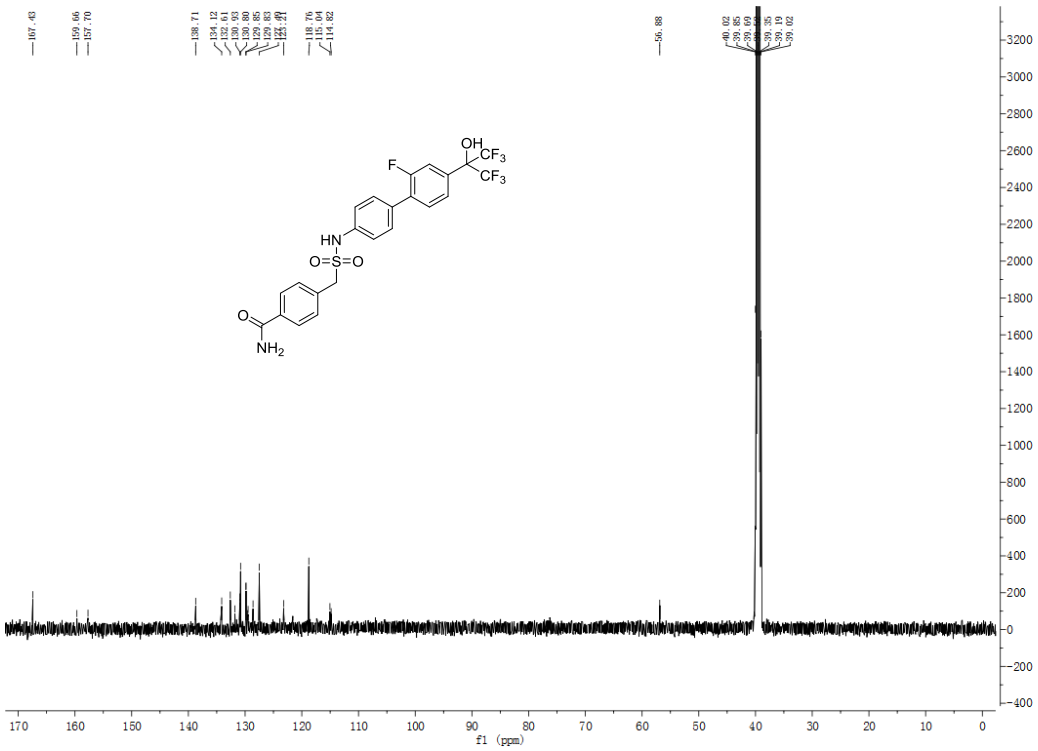
*1-(4-cyanophenyl)-N-(2'-fluoro-4'-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)-[1,1'-biphenyl]-4-yl)methanesulfonamide (**12**).*



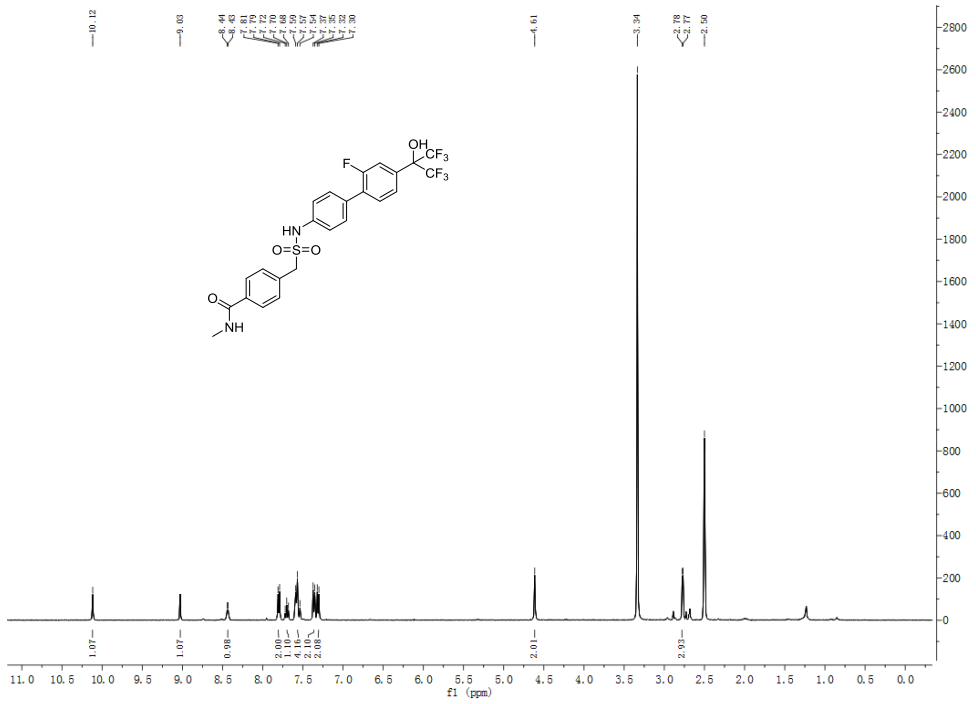


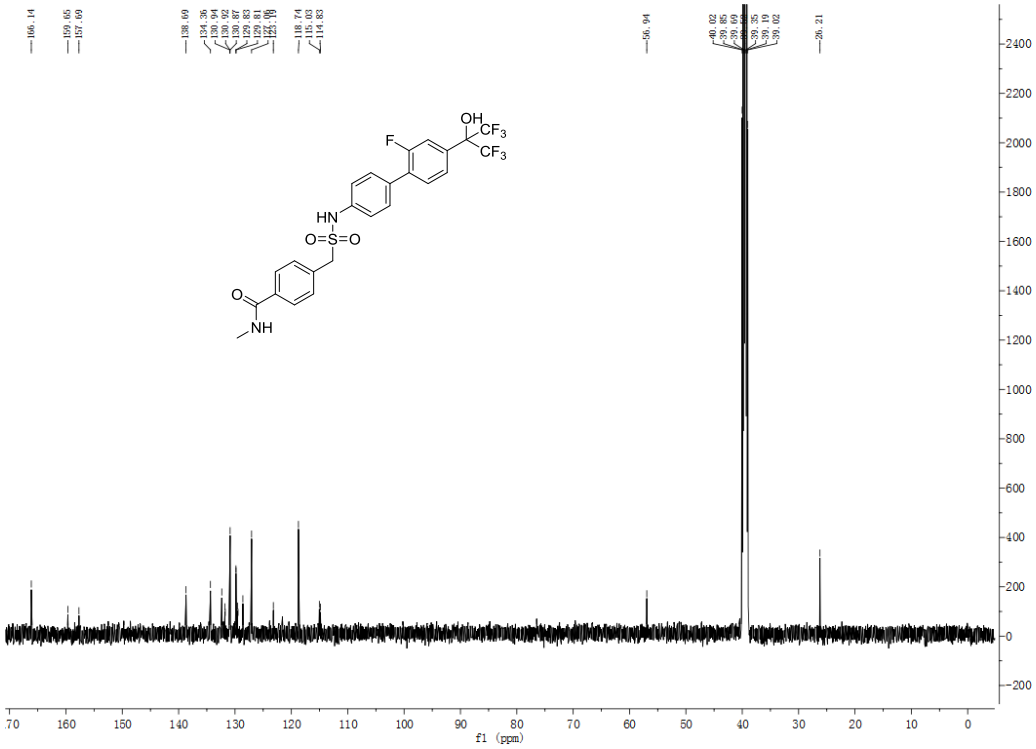
*4-((N-(2'-fluoro-4'-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)-[1,1'-biphenyl]-4-yl)sulfamoyl)methyl)benzamide (**13**).*



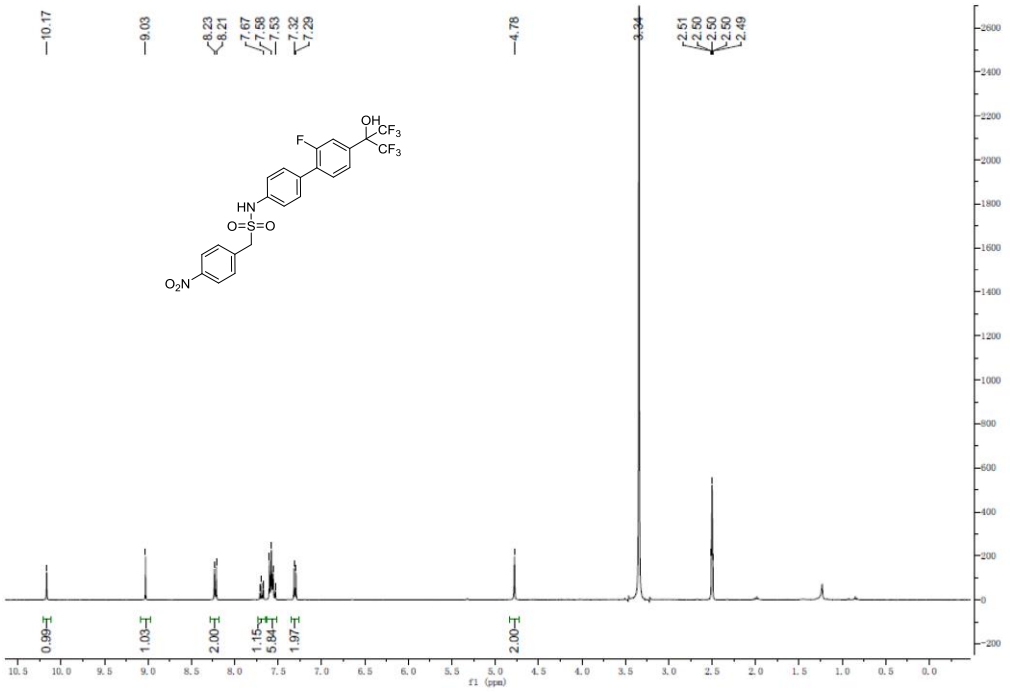


*4-((N-(2'-fluoro-4'-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)-[1,1'-biphenyl]-4-yl)sulfamoyl)methyl)-N-methylbenzamide (**14**).*

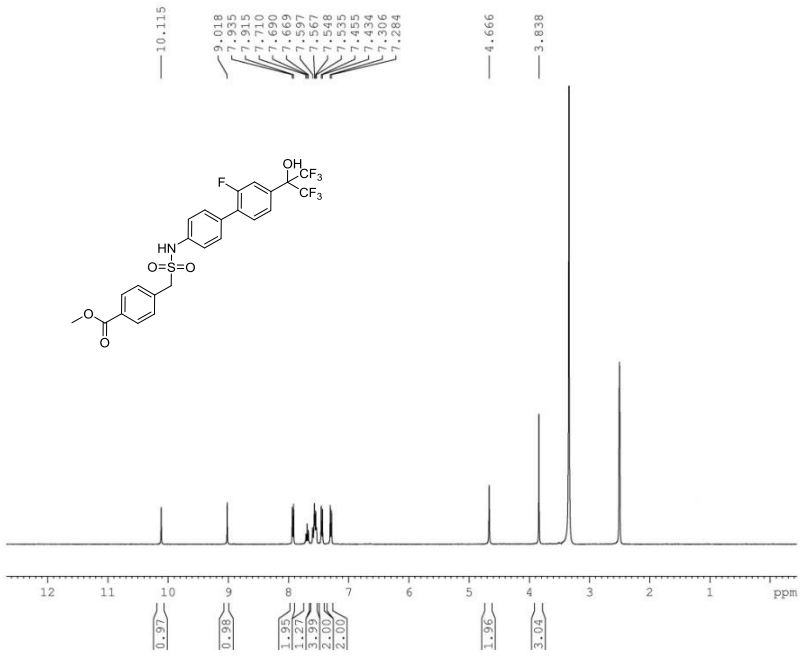


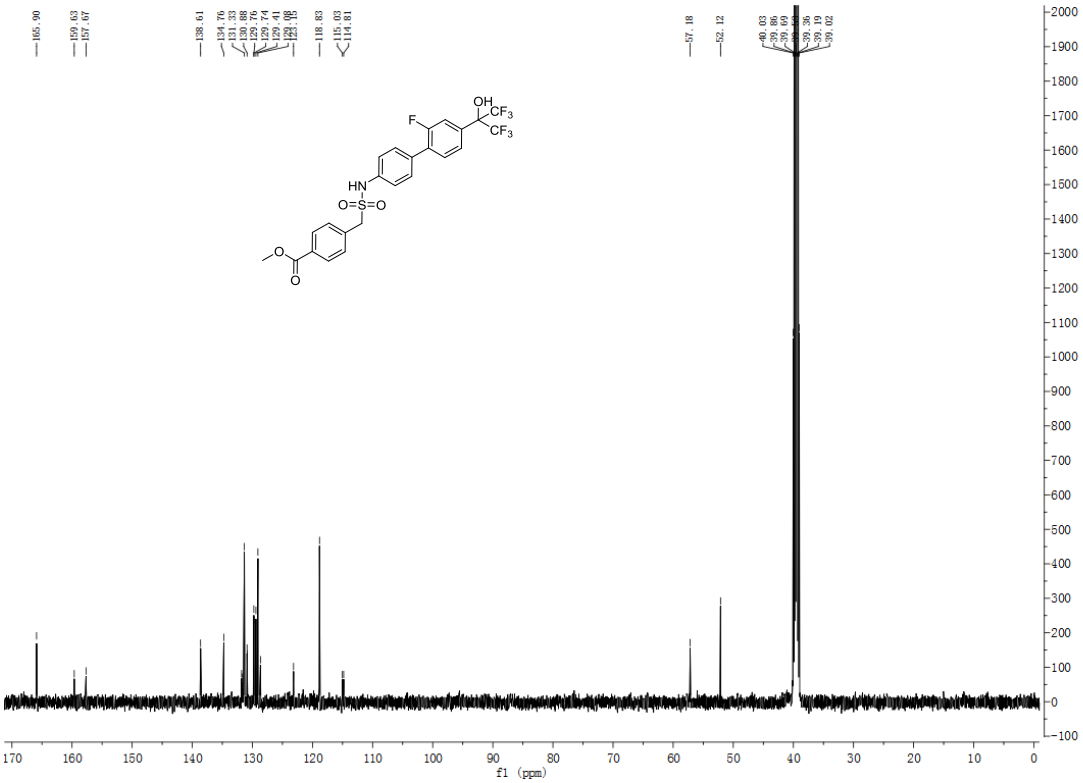


*N-(2'-fluoro-4'-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)-[1,1'-biphenyl]-4-yl)-1-(4-nitrophenyl)methanesulfonamide (**15**).*

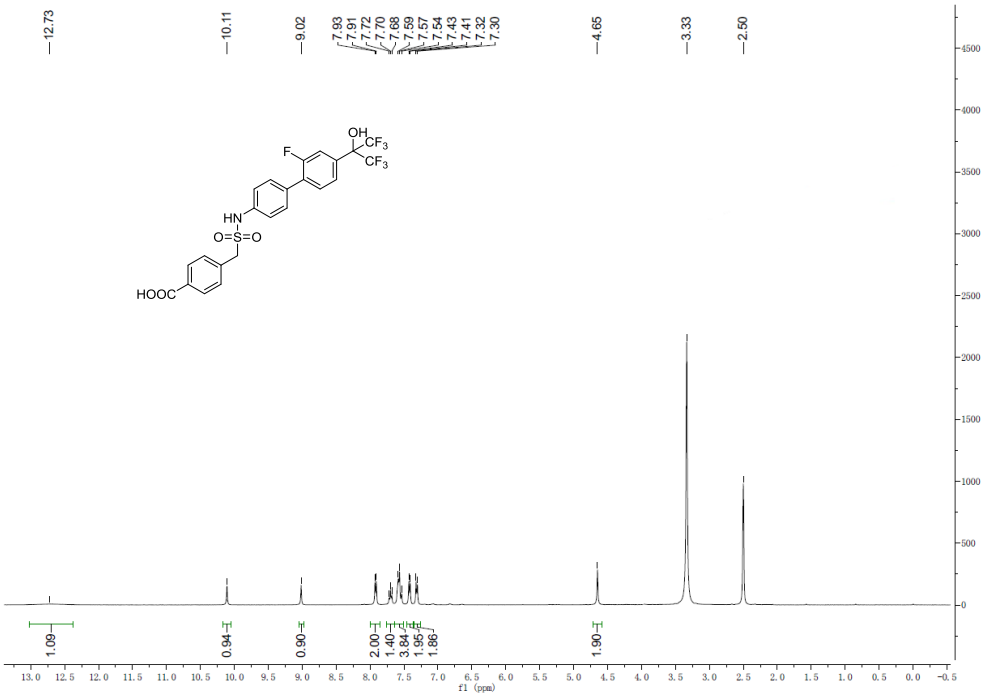


*Methyl-4-((N-(2'-fluoro-4'-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)-[1,1'-biphenyl]-4-yl)sulf amoyl)methyl)benzoate (**16**).*

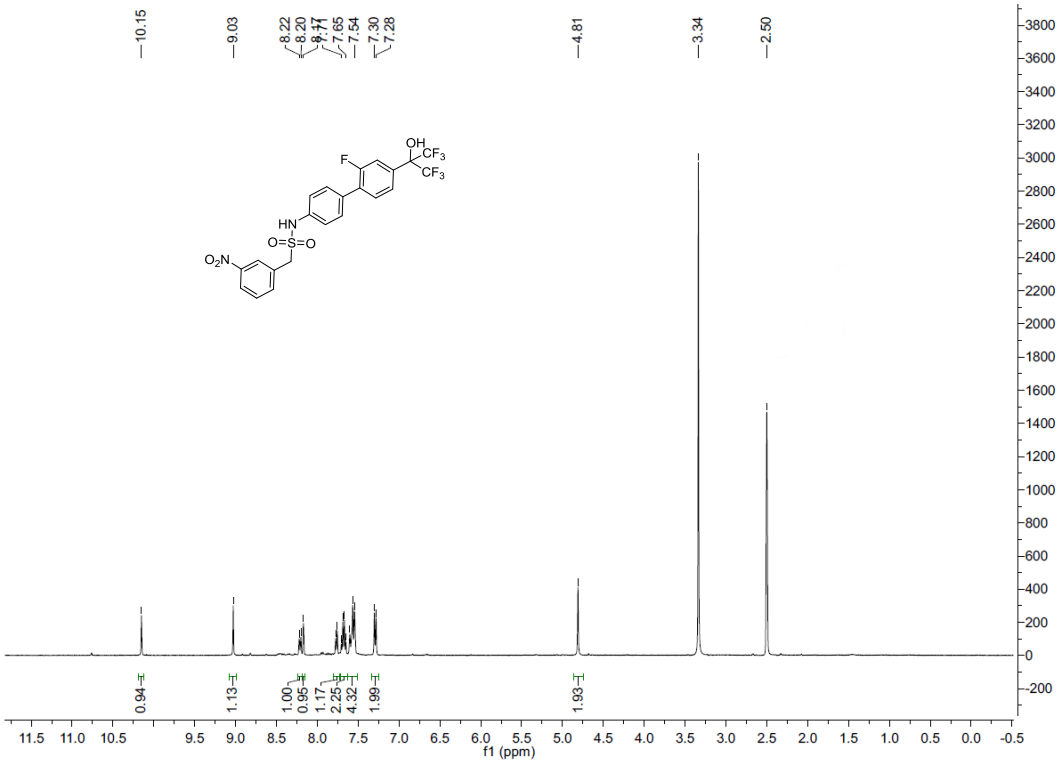


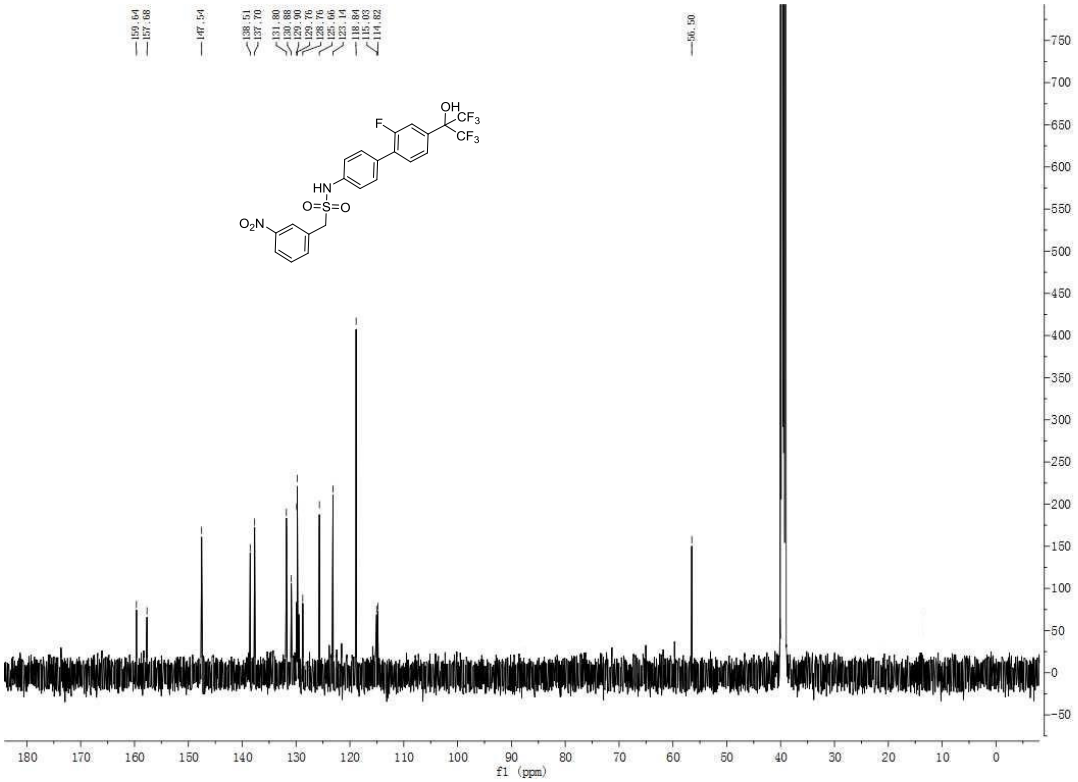


*4-((N-(2'-fluoro-4'-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)-[1,1'-biphenyl]-4-yl)sulfamoyl)methyl)benzoic acid (**17**).*



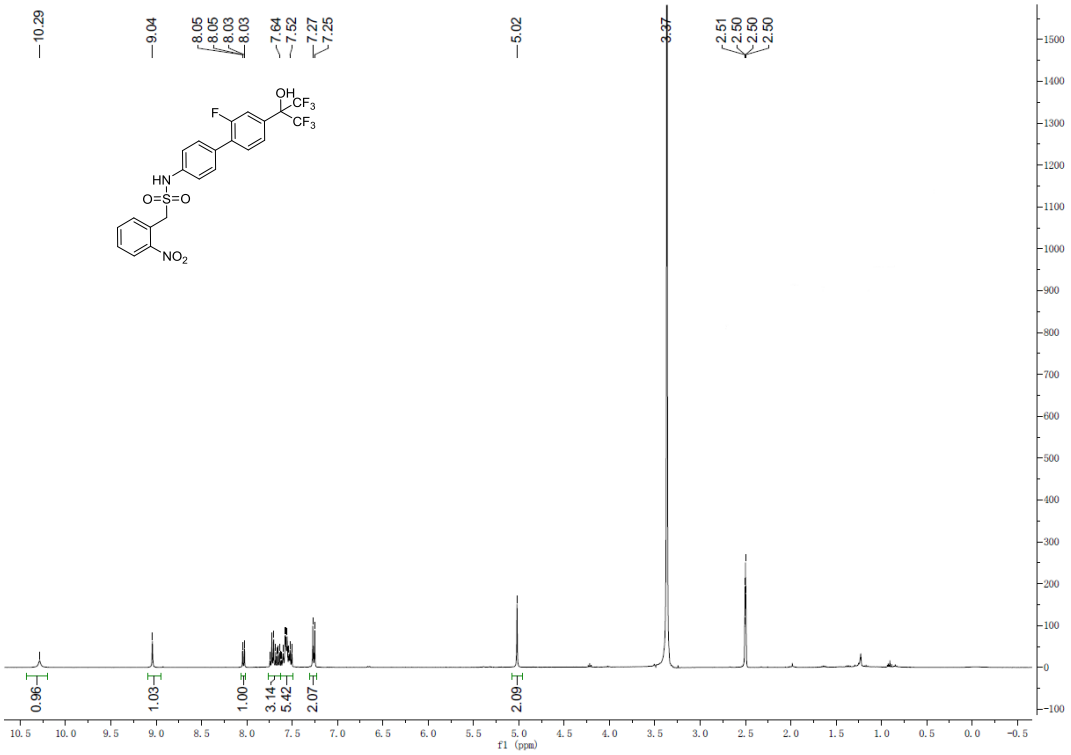
*N-(2'-fluoro-4'-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)-[1,1'-biphenyl]-4-yl)-1-(3-nitrophenyl)methanesulfonamide (**18**).*

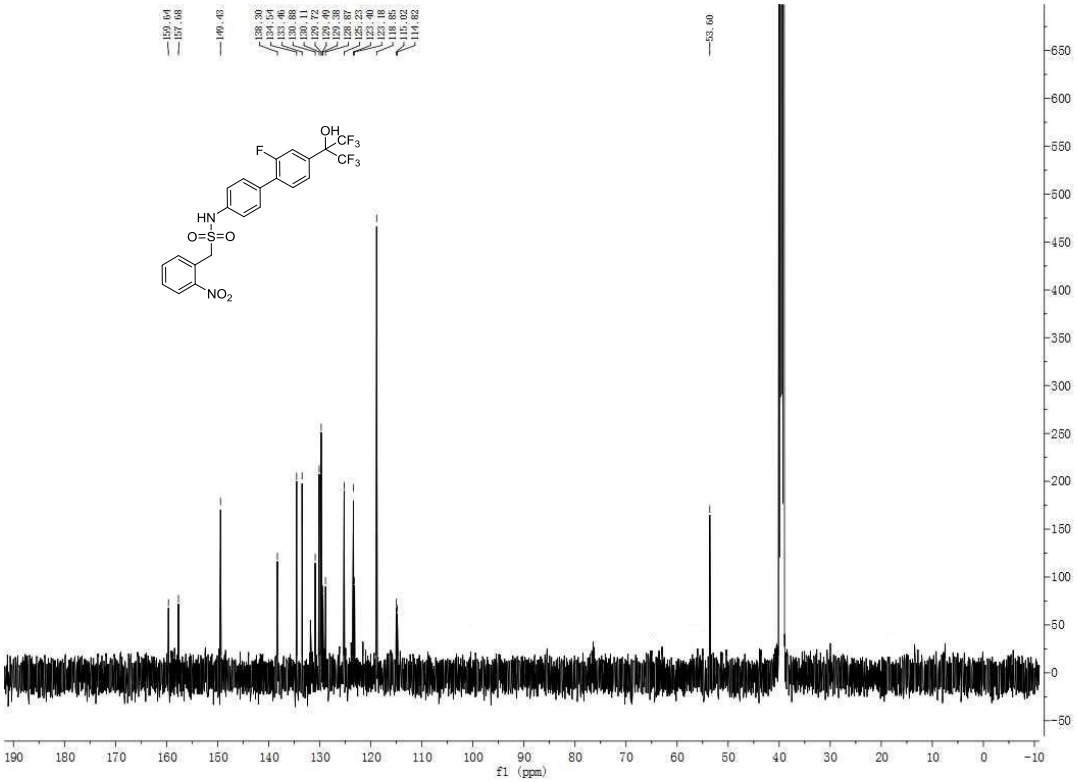




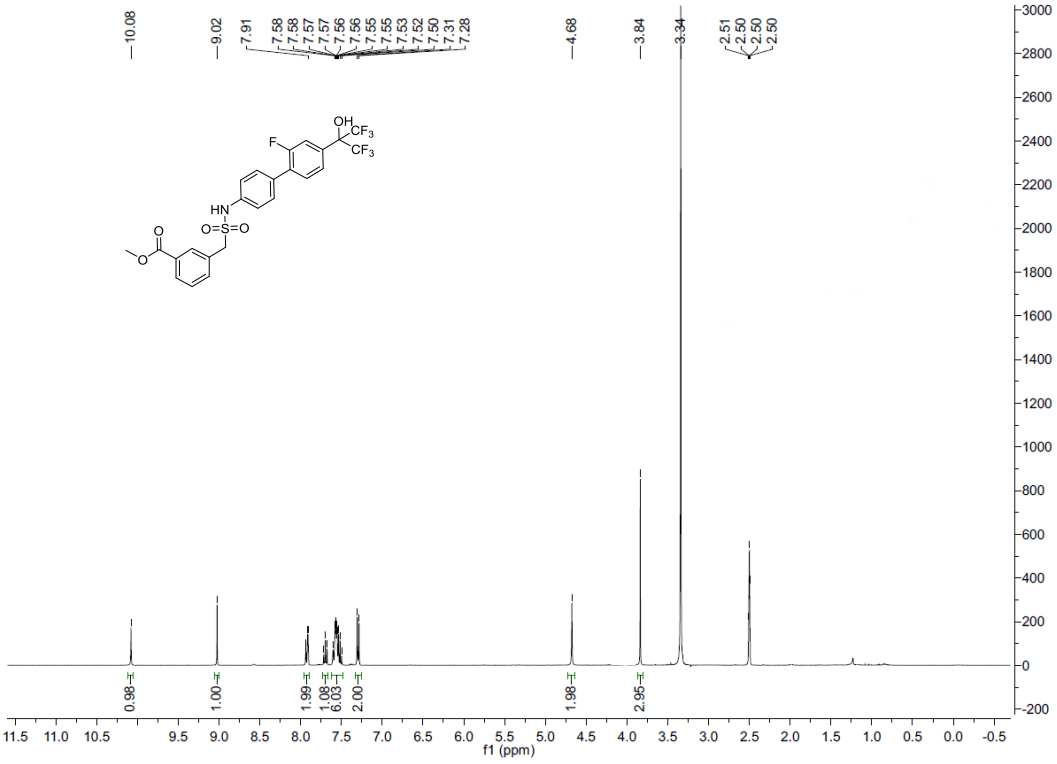
N-(2'-fluoro-4'-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)-[1,1'-biphenyl]-4-yl)-1-(2-nitrophen

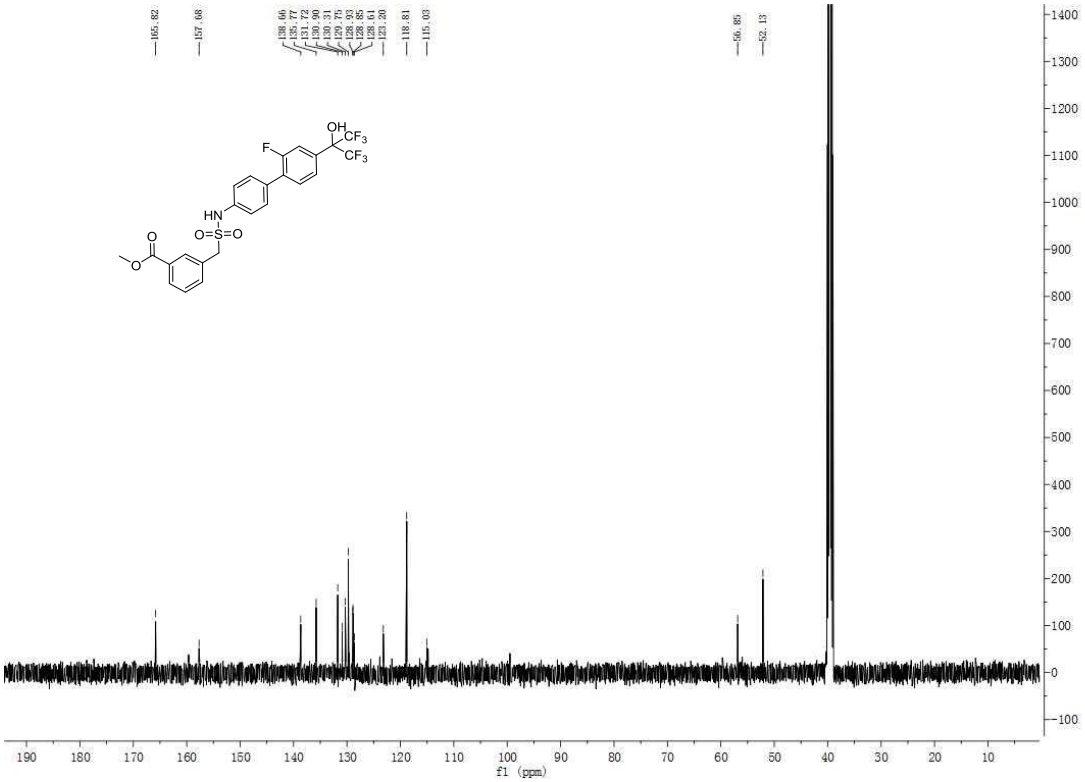
*yl)methanesulfonamide (**19**)*



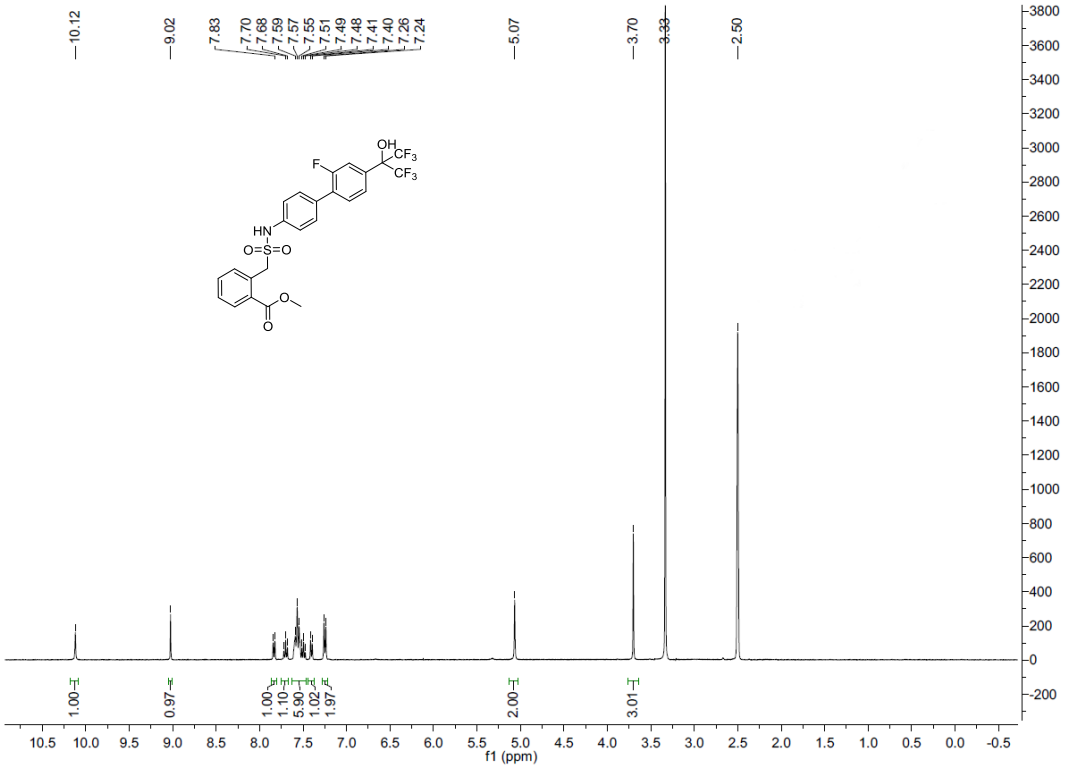


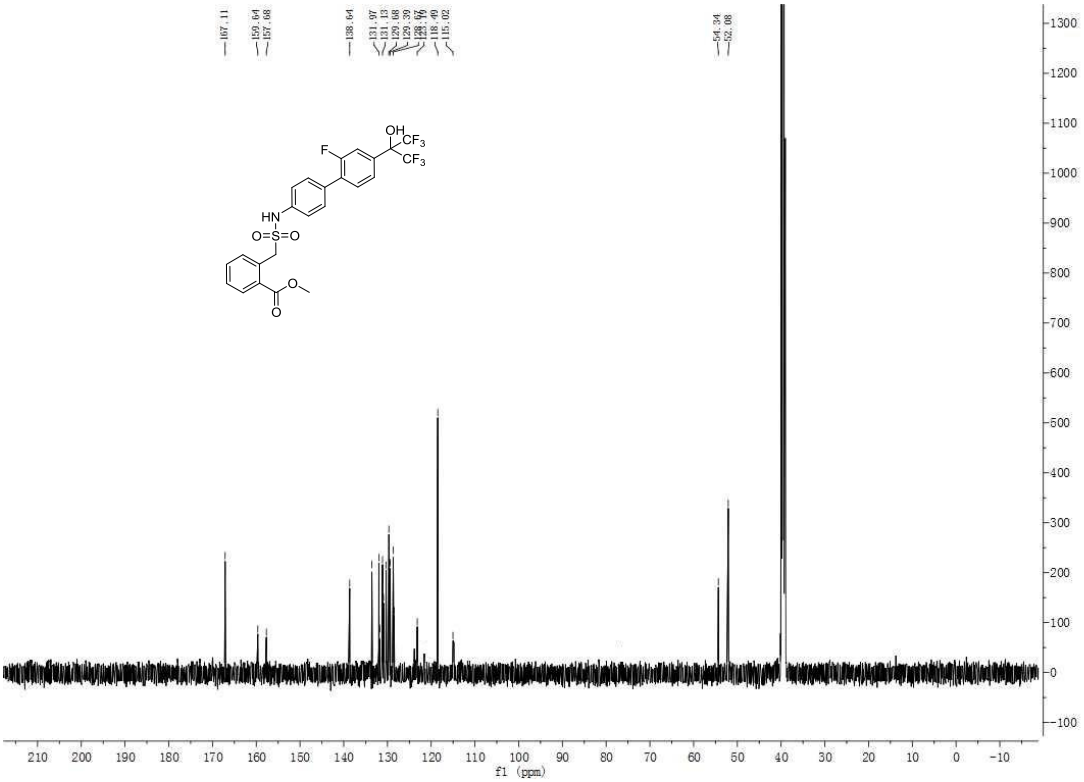
*Methyl-3-((N-(2'-fluoro-4'-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)-[1,1'-biphenyl]-4-yl)sulf amoyl)methyl)benzoate (**20**).*



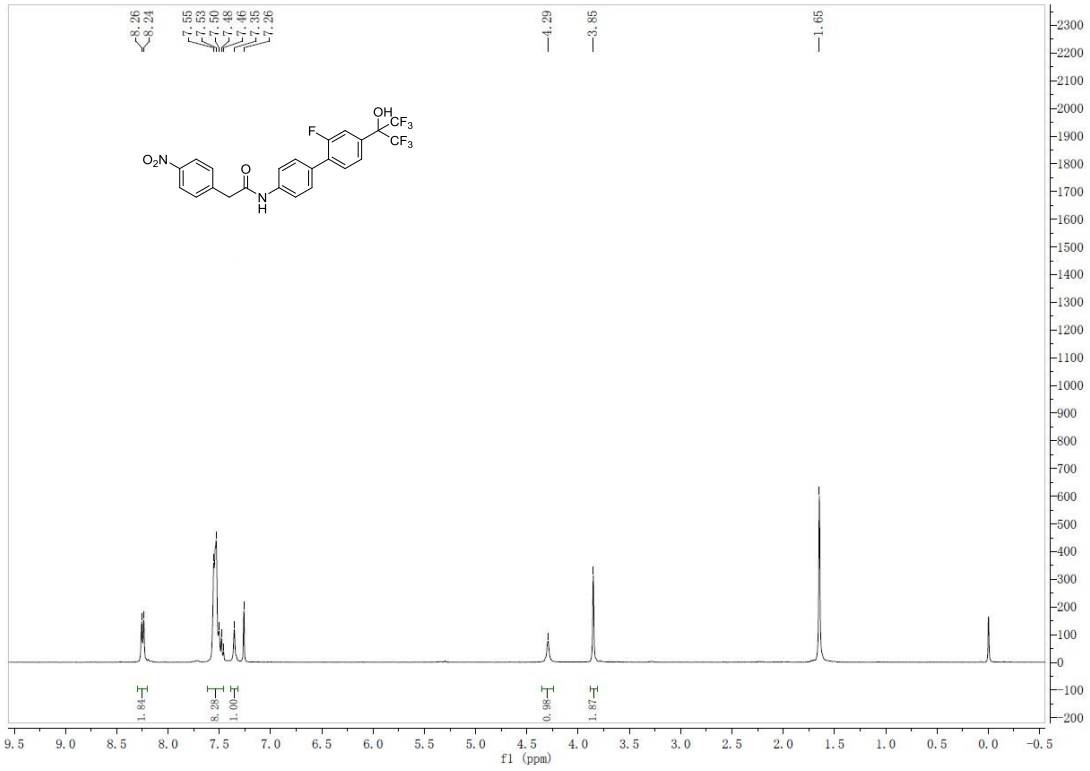


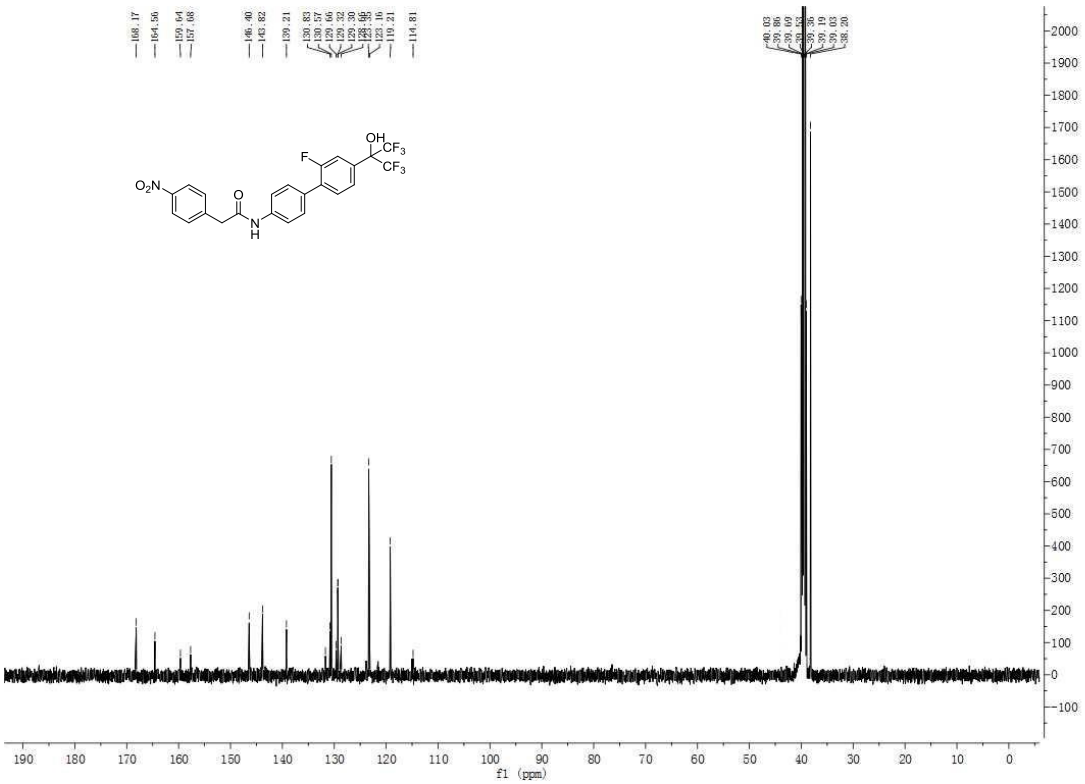
*Methyl-2-((N-(2'-fluoro-4'-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)-[1,1'-biphenyl]-4-yl)sulf amoyl)methyl)benzoate (**21**)*



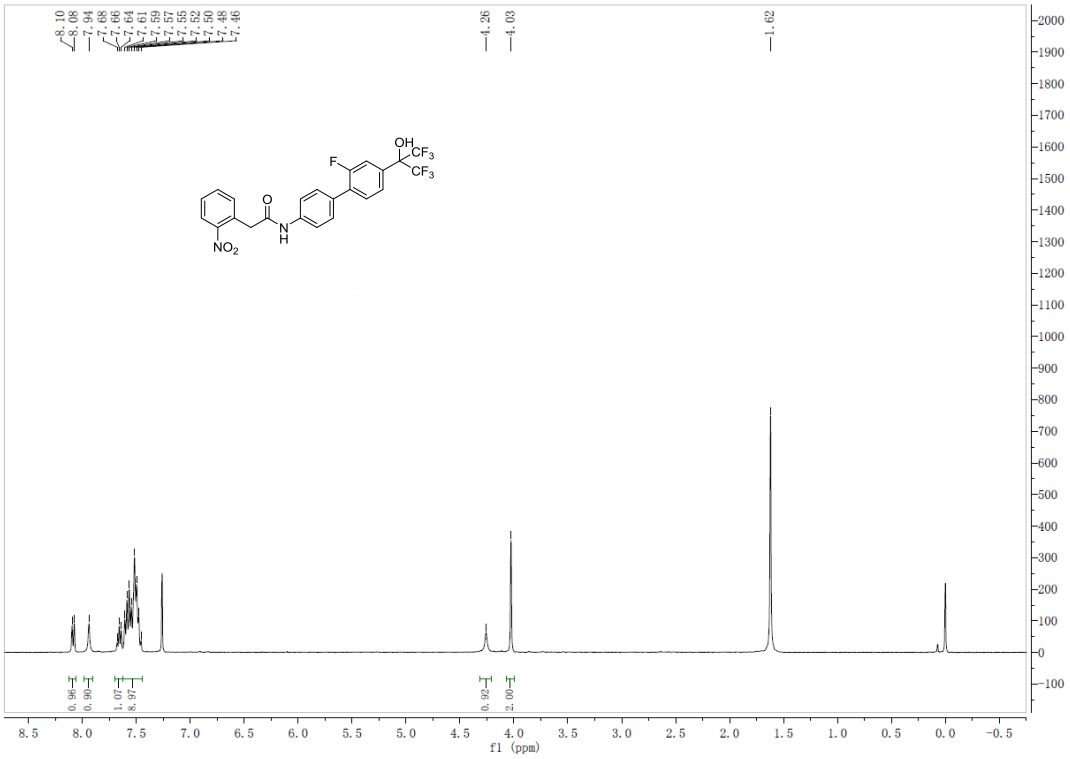


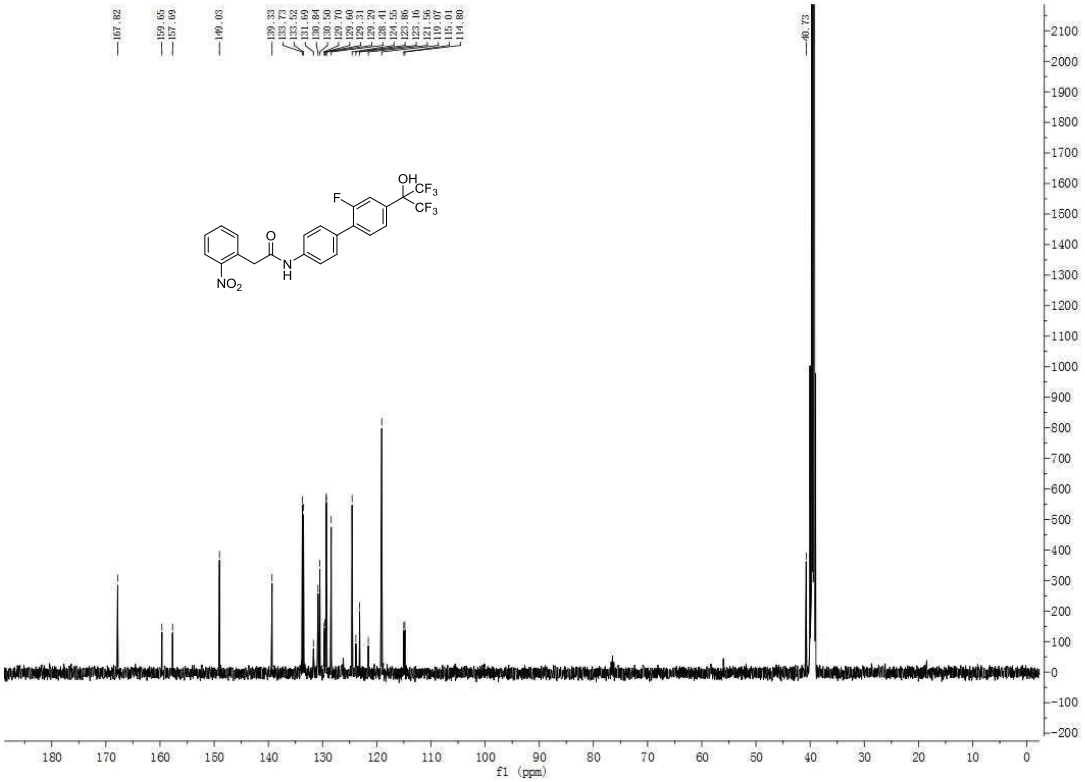
*N-(2'-fluoro-4'-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)-[1,1'-biphenyl]-4-yl)-2-(4-nitrophen yl)acetamide (**22**).*



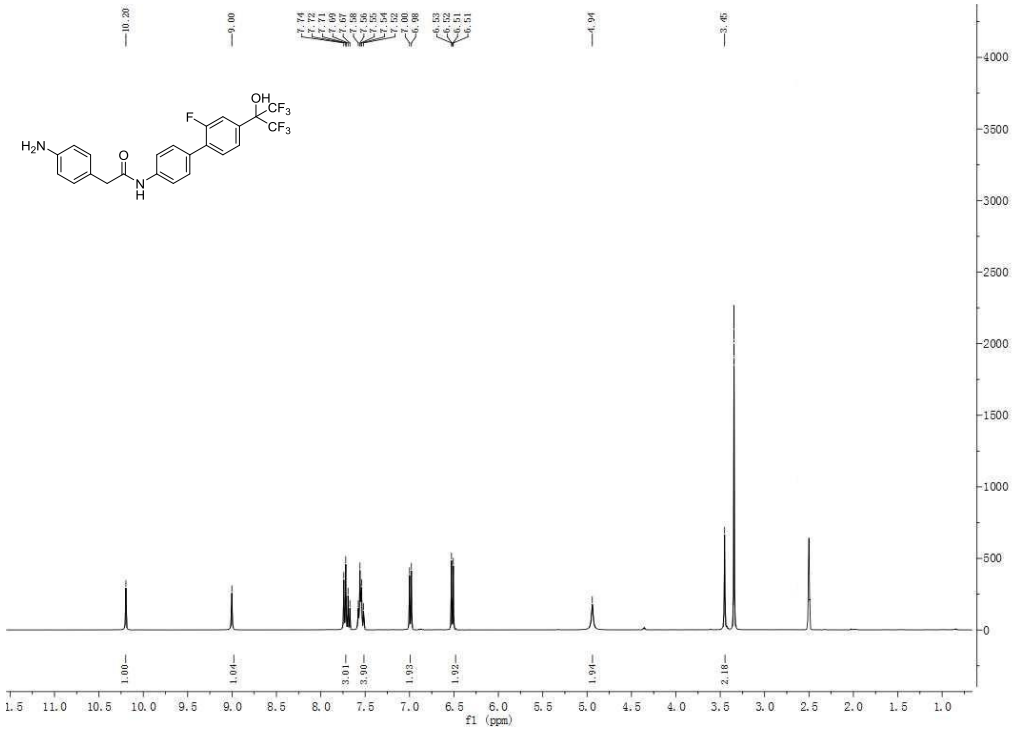


*N-(2'-fluoro-4'-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)-[1,1'-biphenyl]-4-yl)-2-(2-nitrophen yl)acetamide (**23**).*

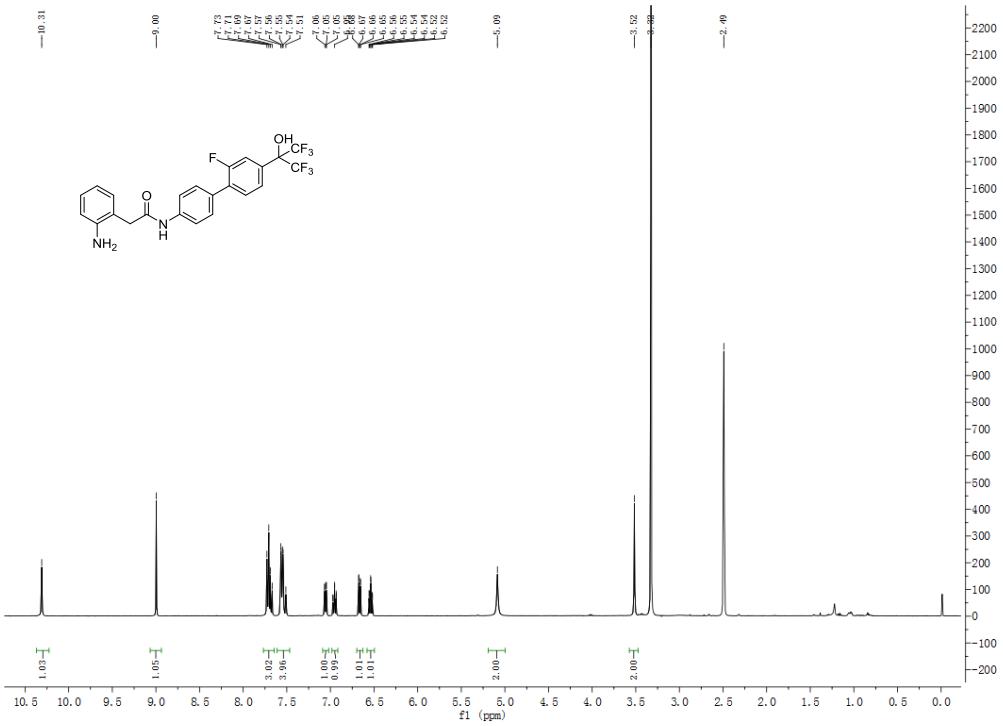




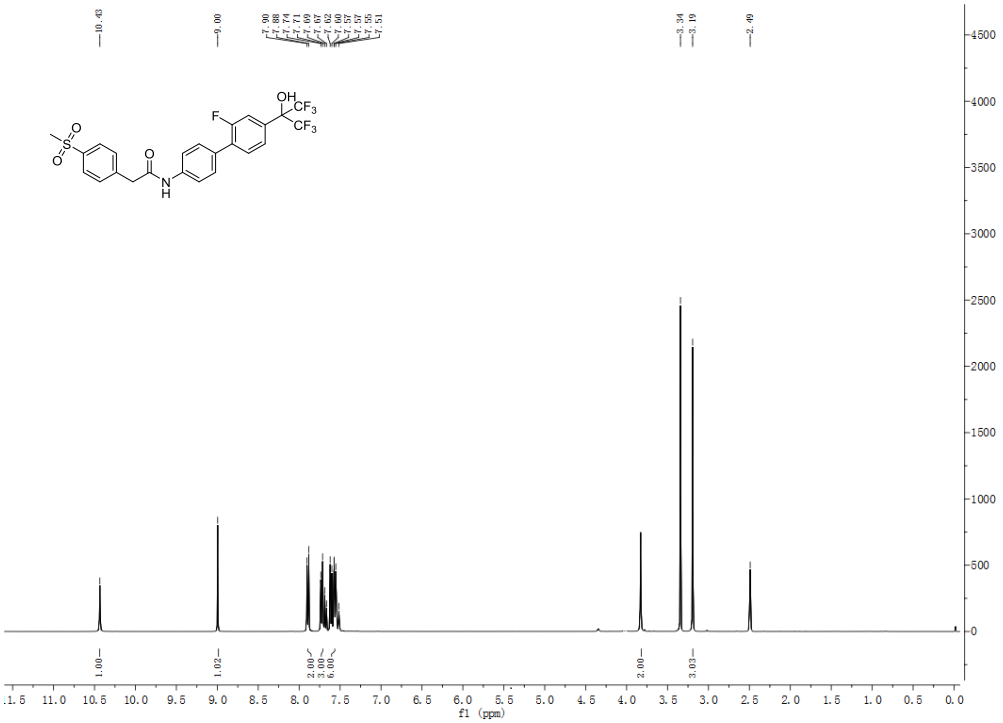
*2-(4-aminophenyl)-N-(2'-fluoro-4'-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)-[1,1'-biphenyl]-4-yl)acetamide (**24**).*

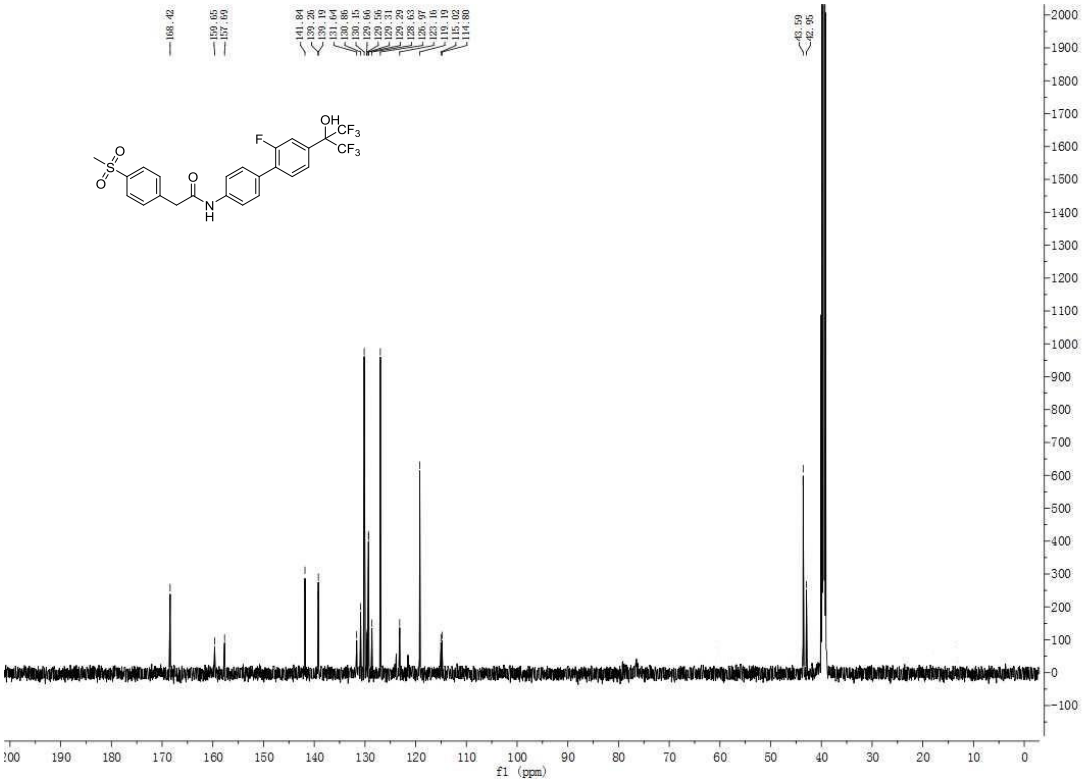


*2-(2-aminophenyl)-N-(2'-fluoro-4'-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)-[1,1'-biphenyl]-4-yl)acetamide (**25**).*



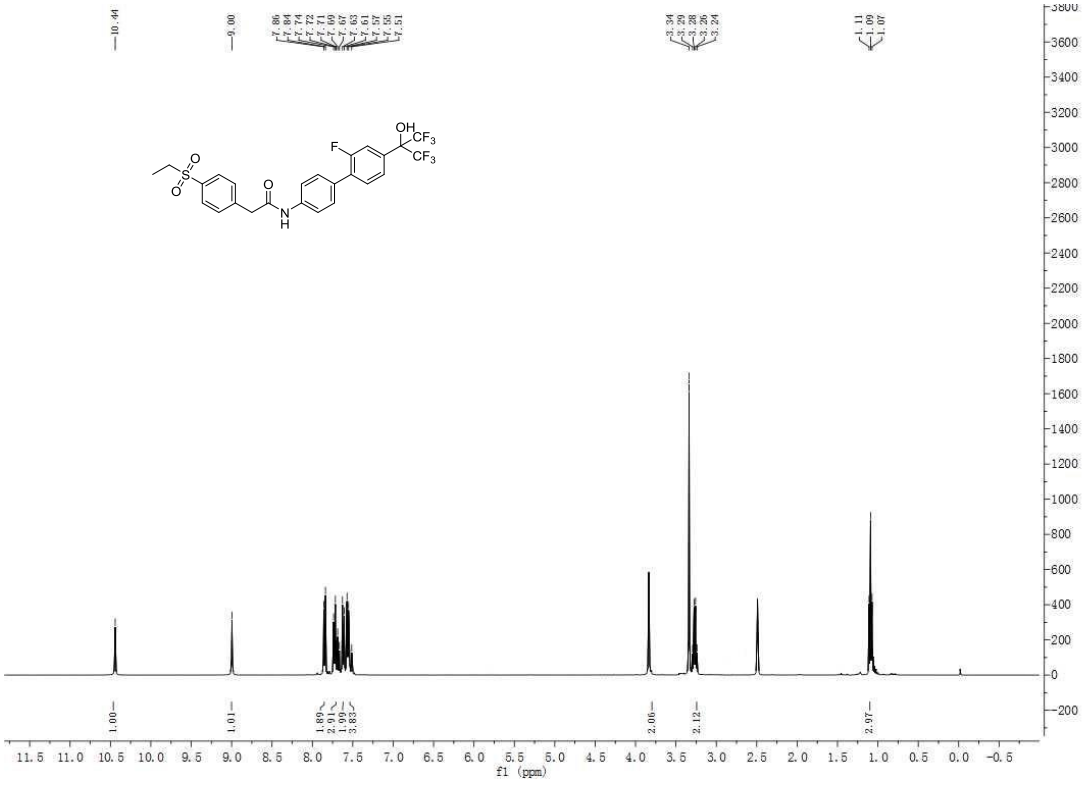
*N-(2'-fluoro-4'-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)-[1,1'-biphenyl]-4-yl)-2-(4-(methylsulfonyl)phenyl)acetamide (**26**).*

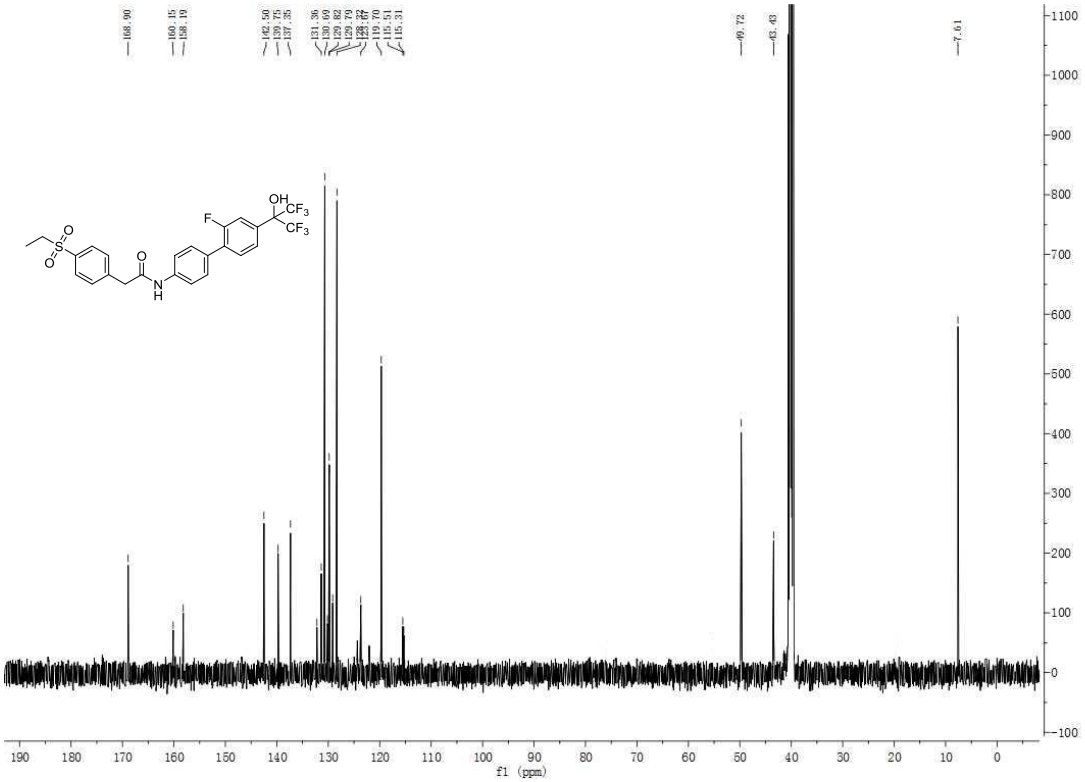




2-(4-(ethylsulfonyl)phenyl)-N-(2'-fluoro-4'-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)-[1,1'-bi

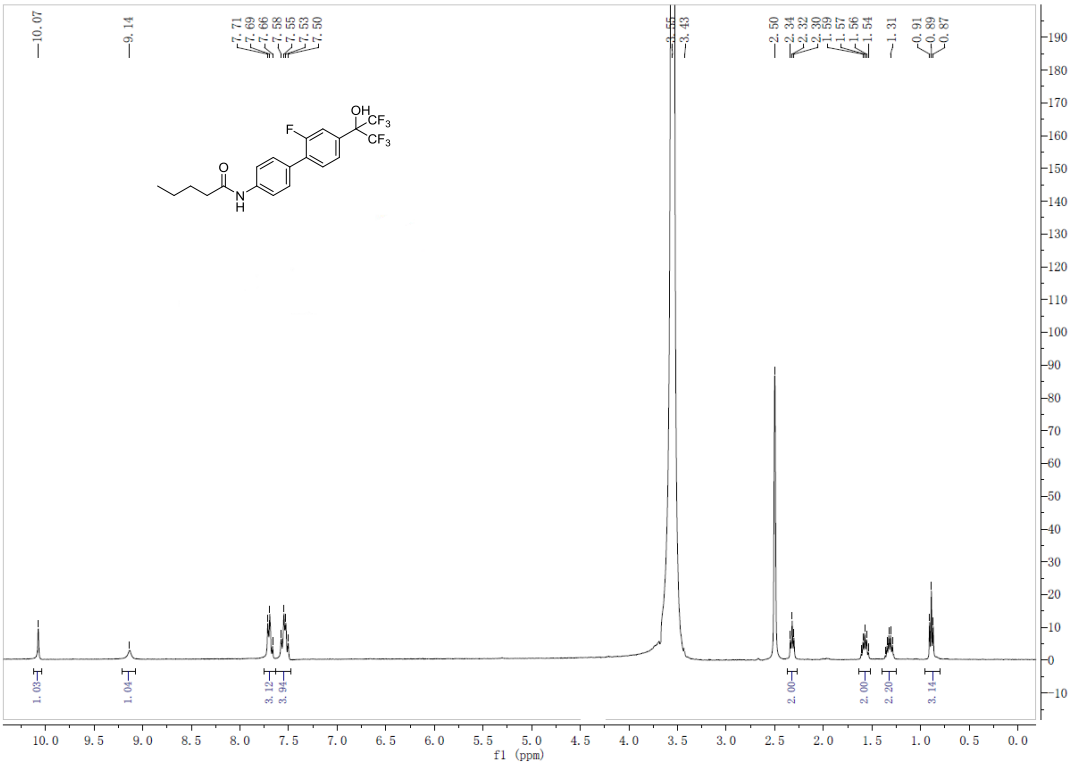
*phenyl]-4-yl)acetamide (**27**).*

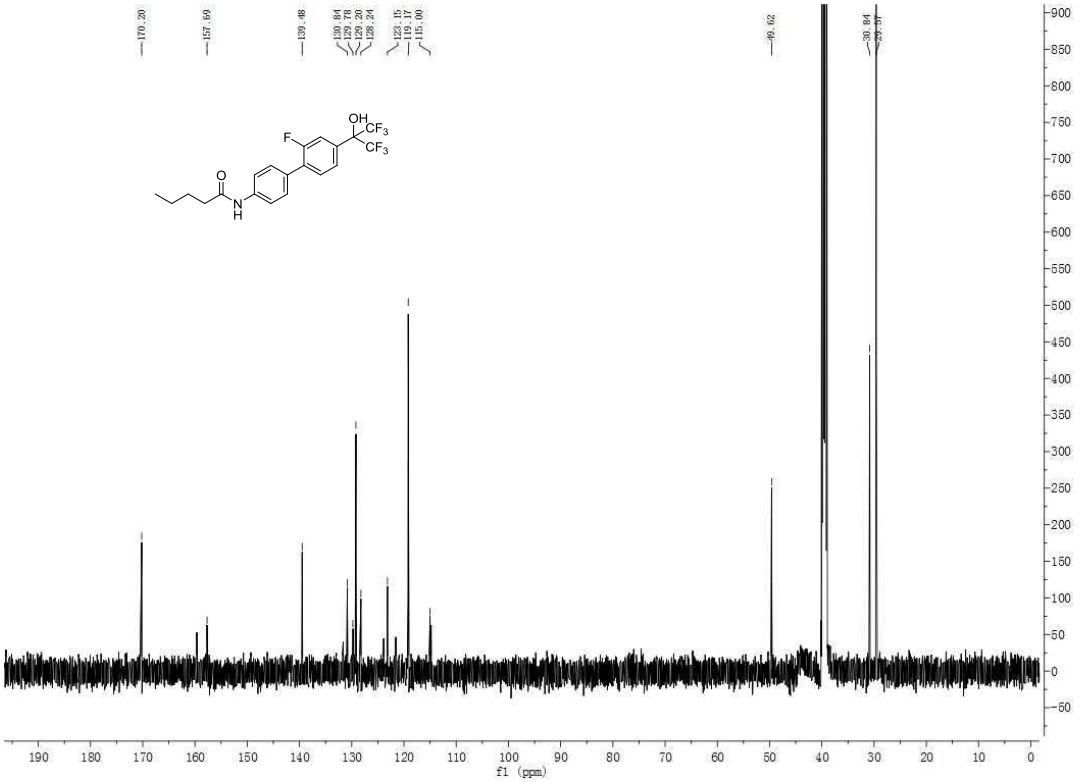




N-(2'-fluoro-4'-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)-[1,1'-biphenyl]-4-yl)pentanamide

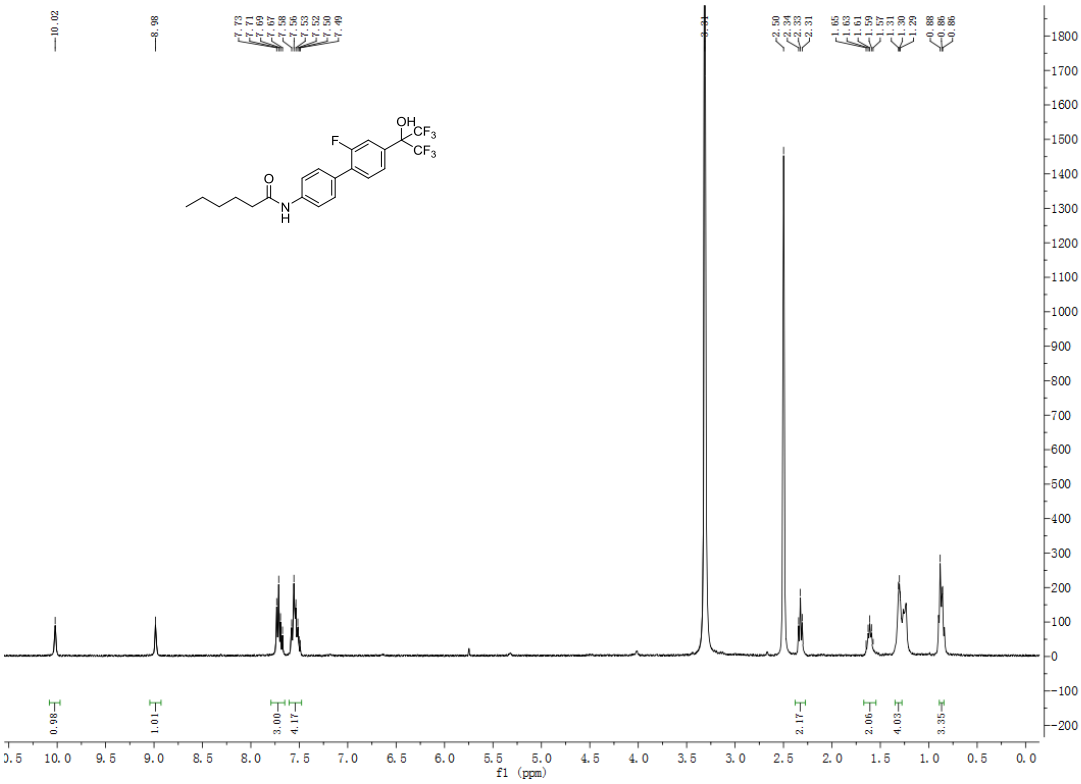
(28).

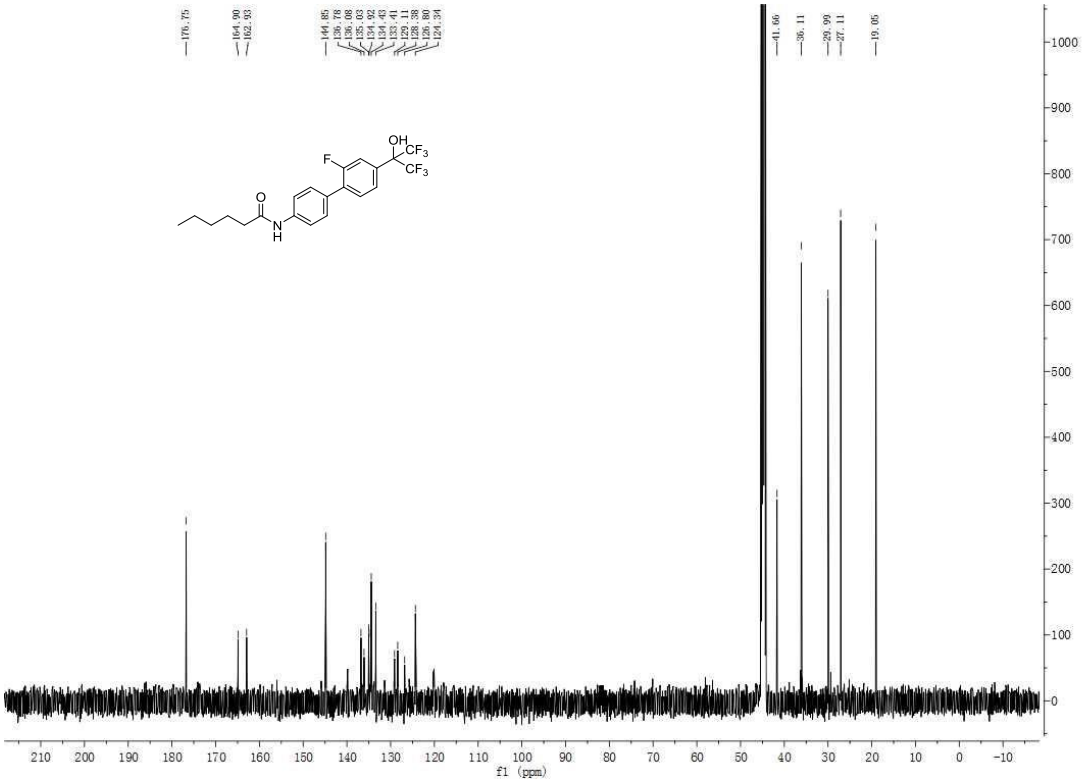




N-(2'-fluoro-4'-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)-[1,1'-biphenyl]-4-yl)hexanamide

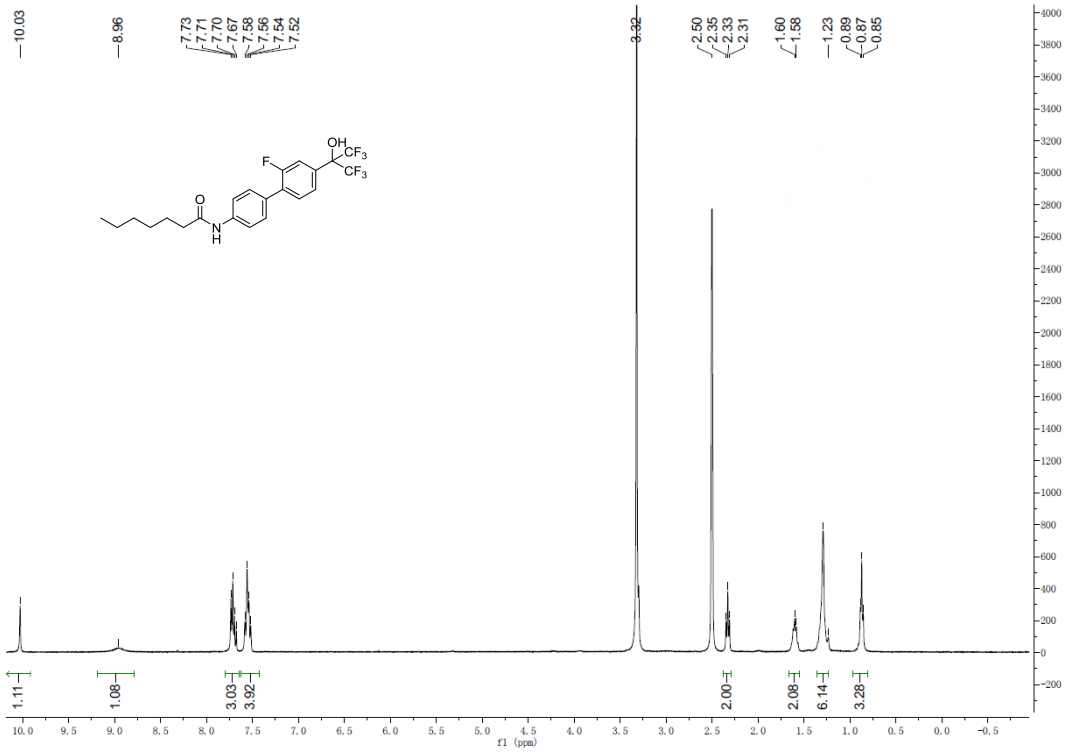
(29).

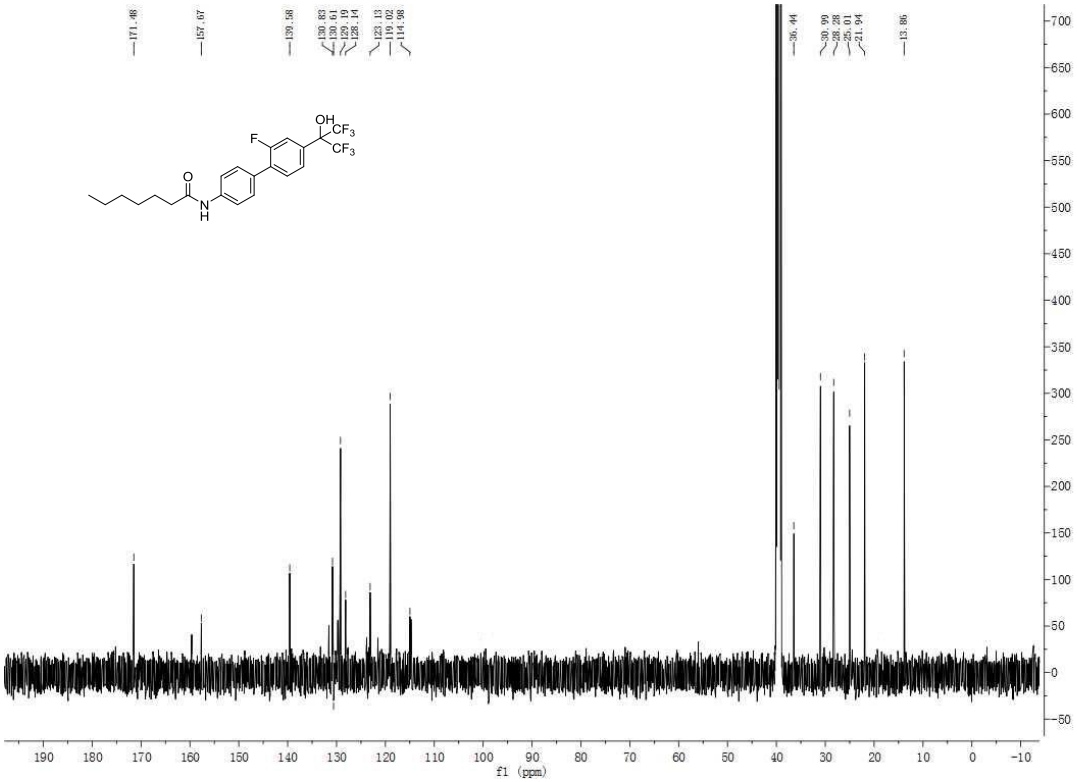




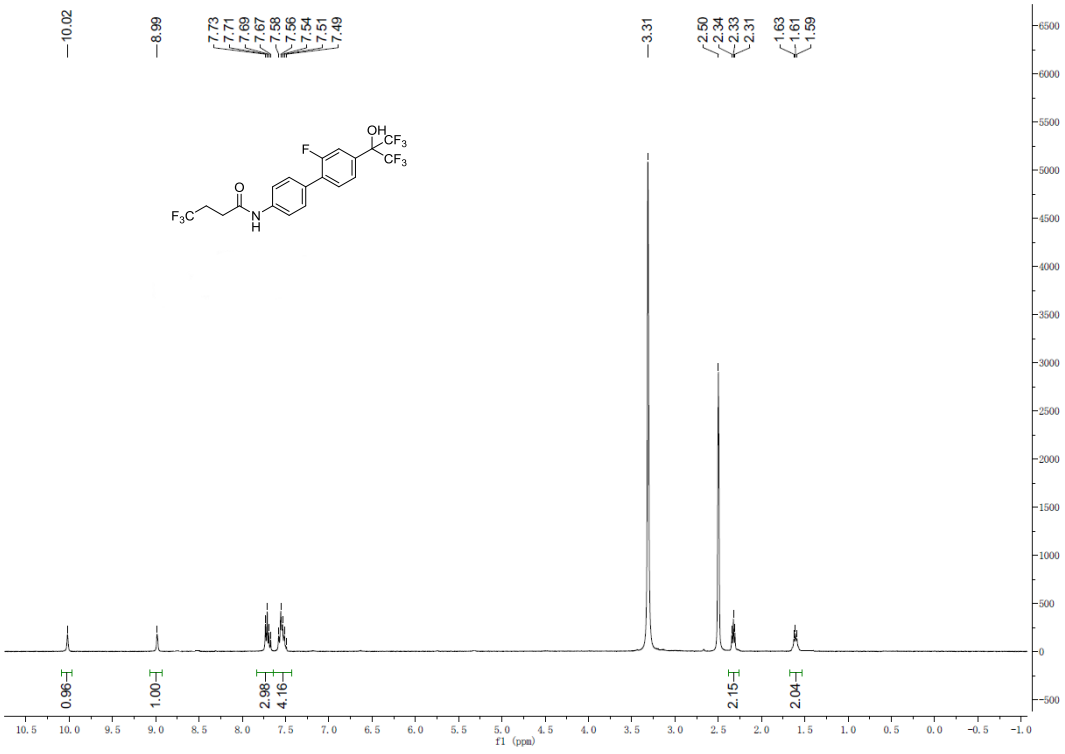
N-(2'-fluoro-4'-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)-[1,1'-biphenyl]-4-yl)heptanamide

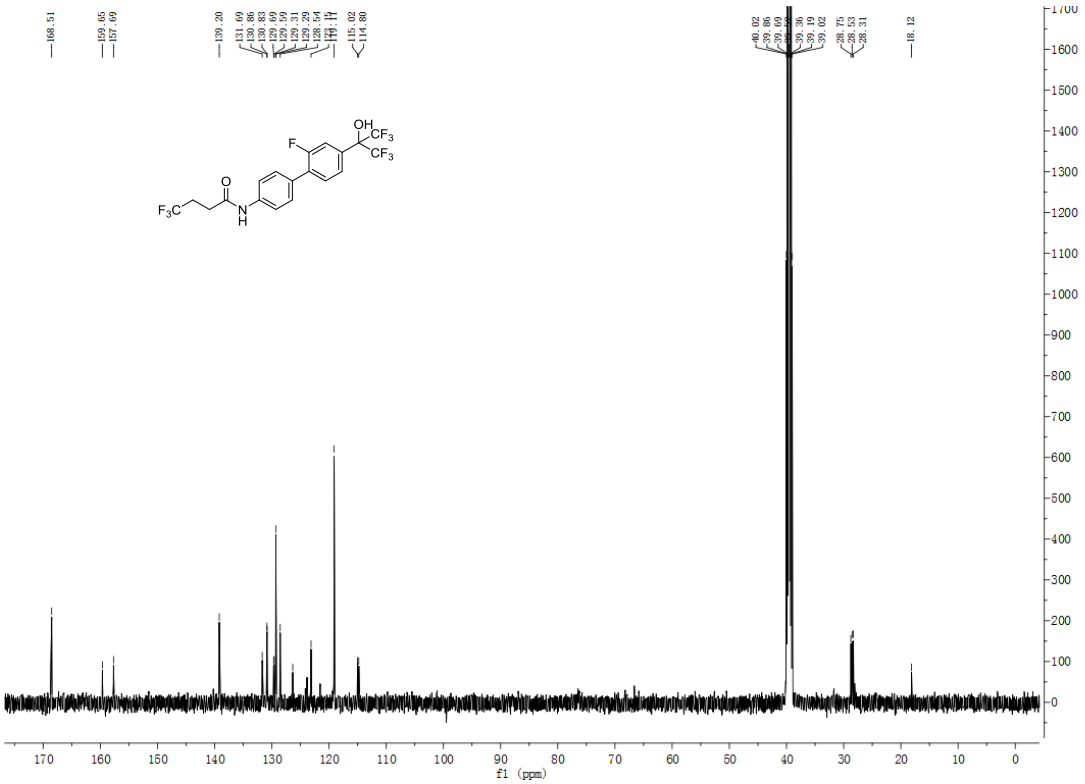
***(30)*.**



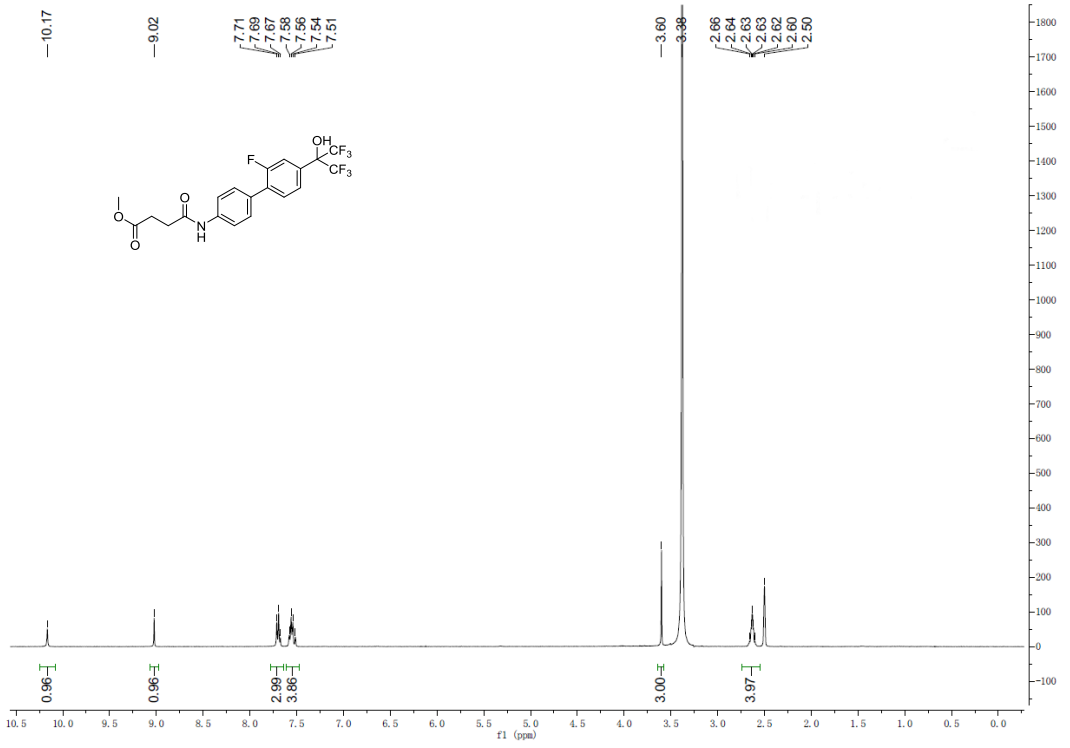


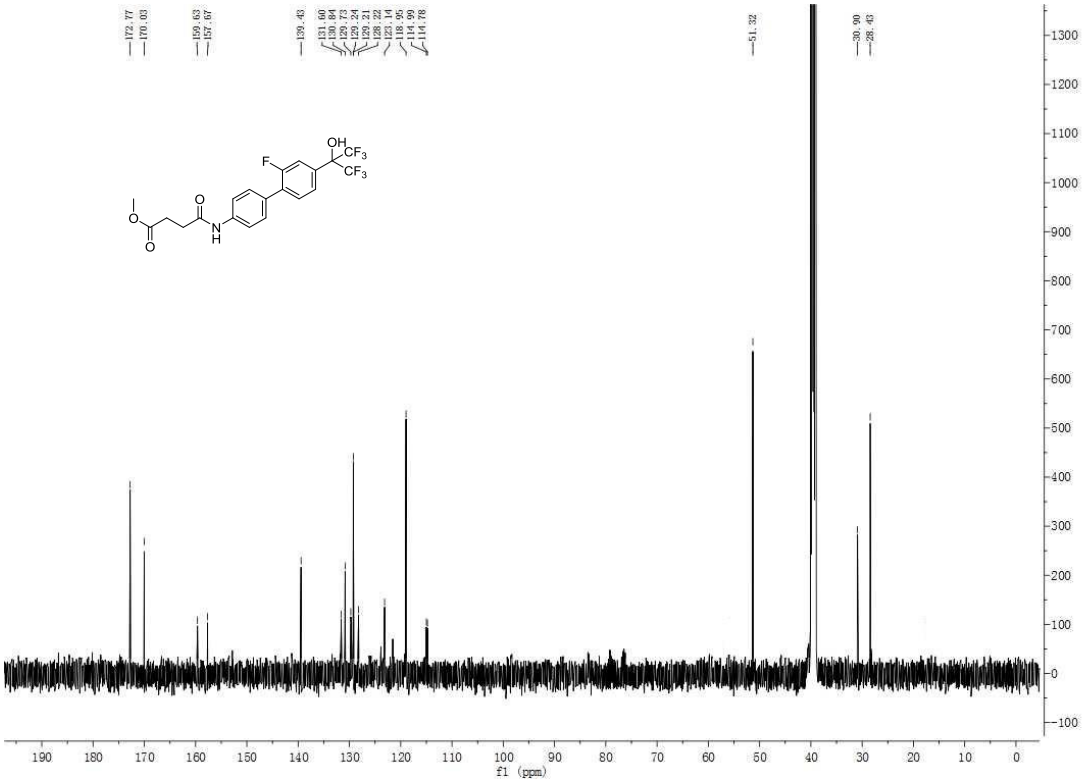
*4,4,4-trifluoro-N-(2'-fluoro-4'-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)-[1,1'-biphenyl]-4-yl) butanamide (**31**).*



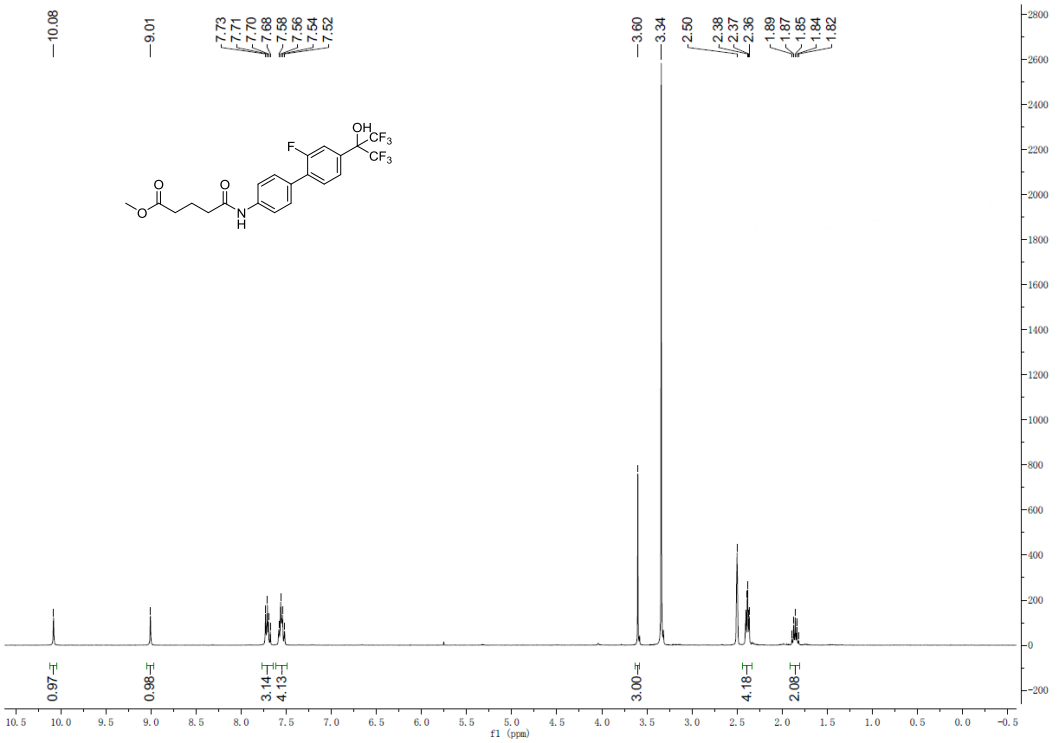


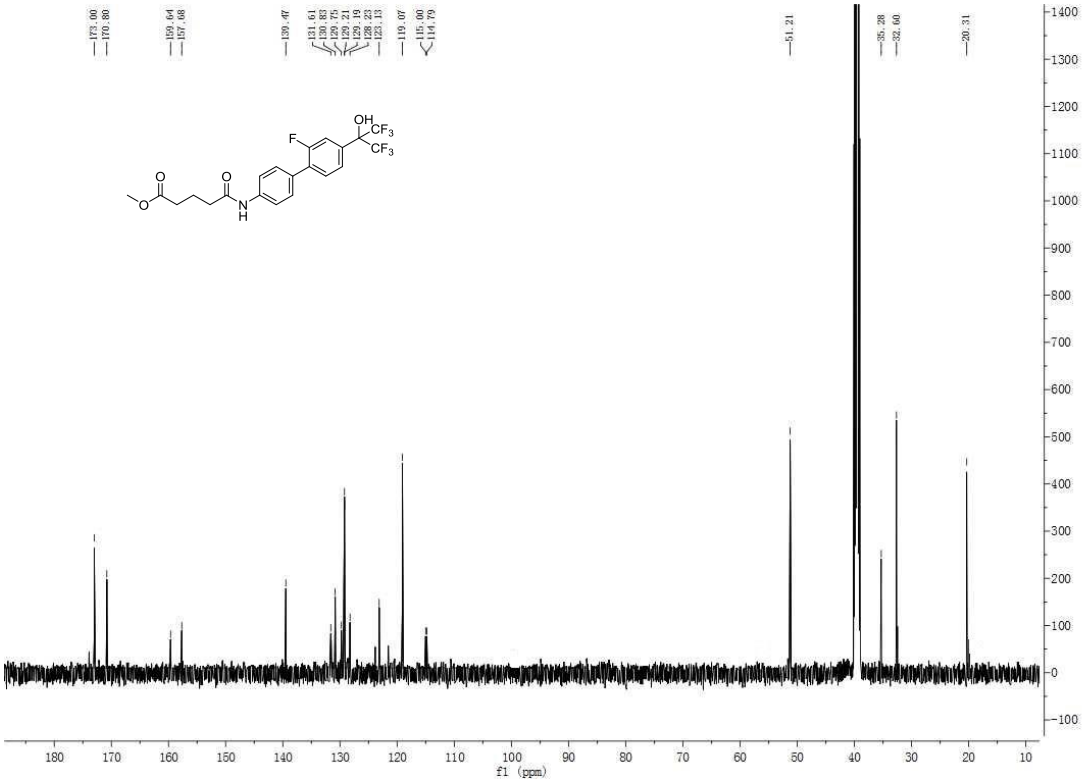
*Methyl-4-((2'-fluoro-4'-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)-[1,1'-biphenyl]-4-yl)amino) -4-oxobutanoate (**32**).*



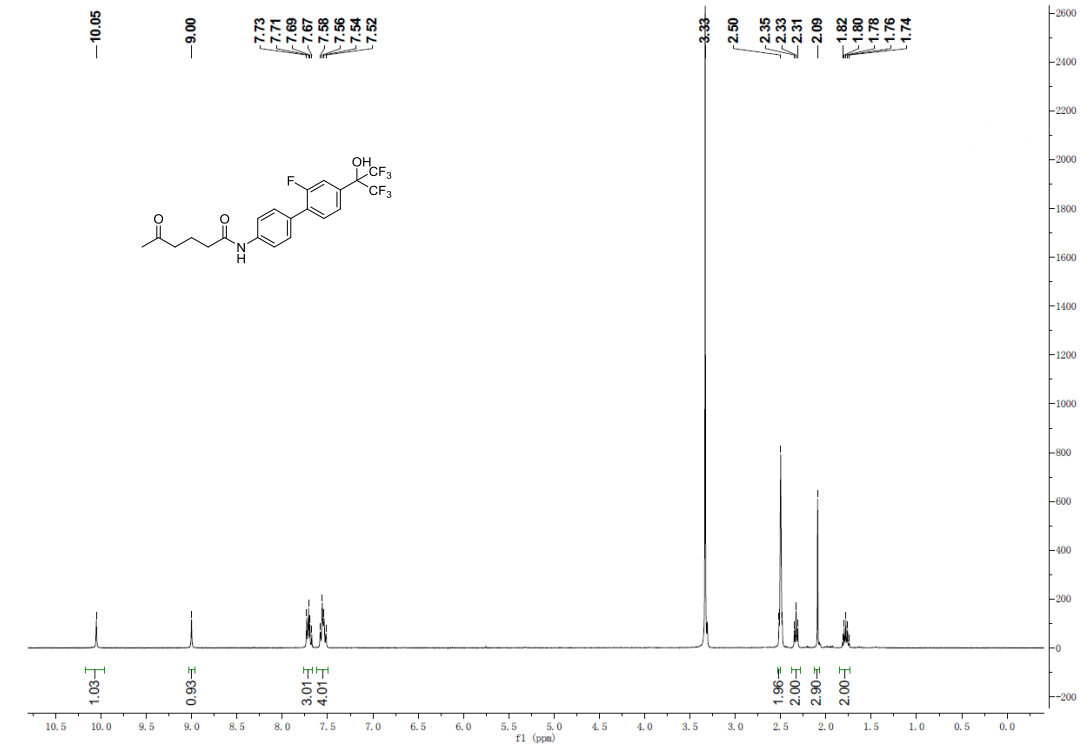


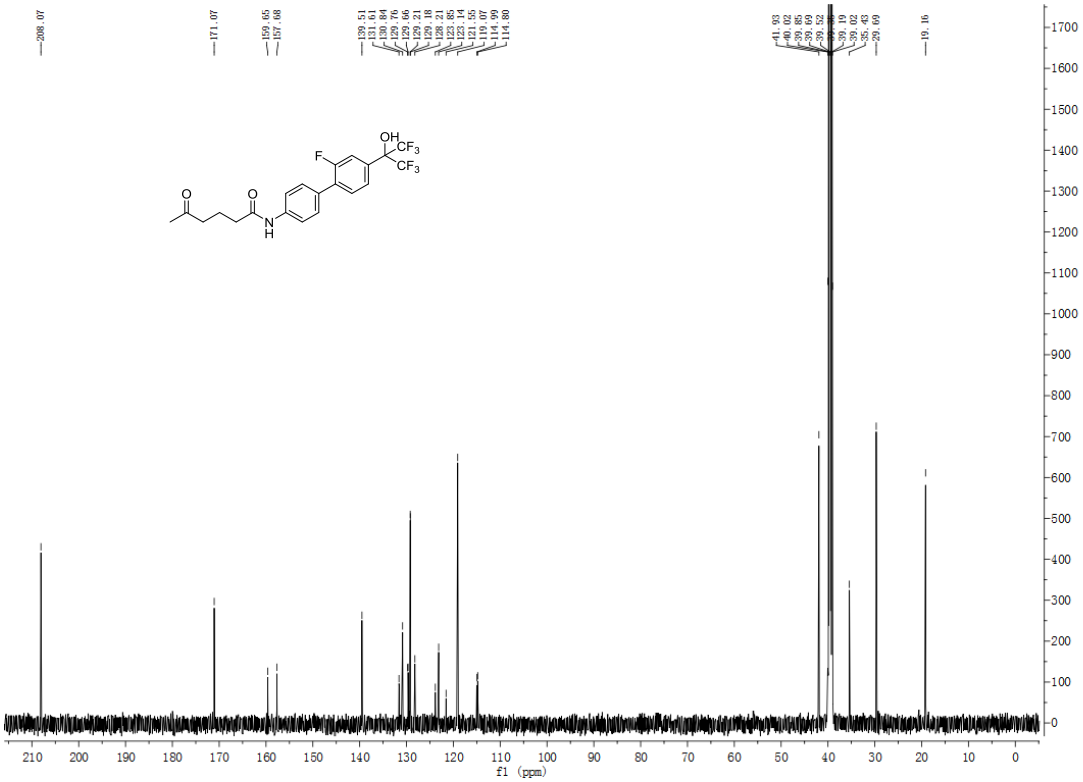
Methyl-5-((2'-fluoro-4'-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)-[1,1'-biphenyl]-4-yl)amino) -5-oxopentanoate ***(33)****.*





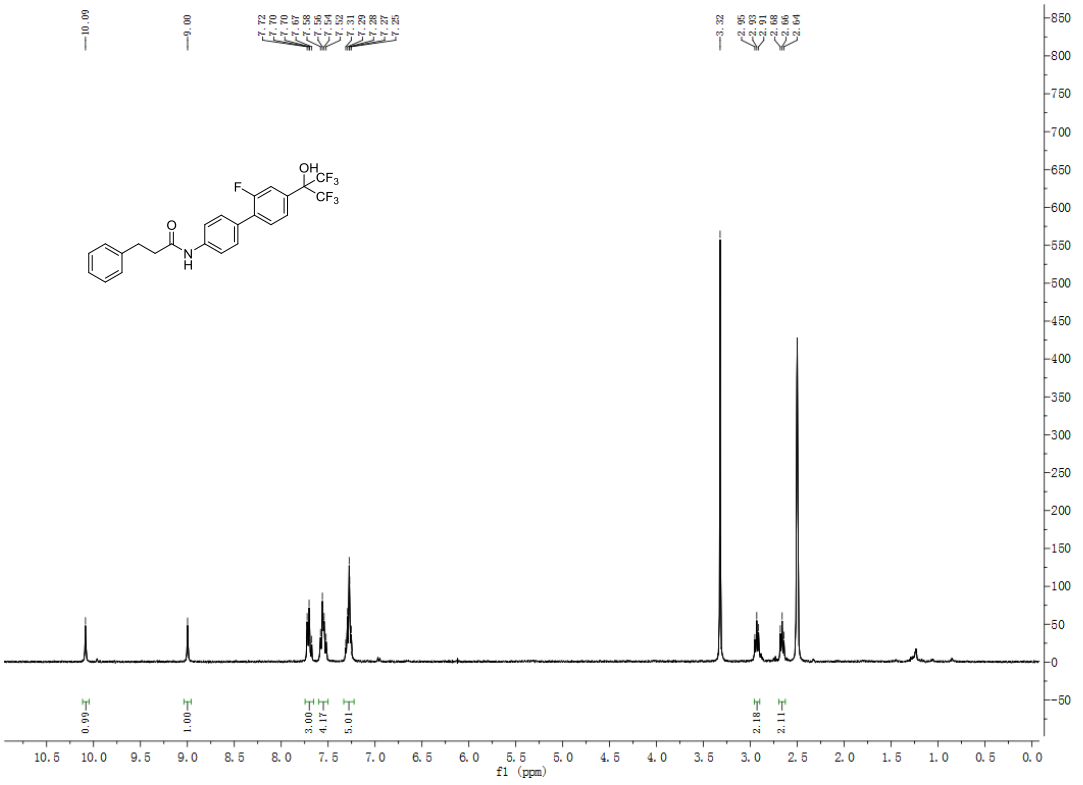
*N-(2'-fluoro-4'-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)-[1,1'-biphenyl]-4-yl)-5-oxohexana mide (**34**).*

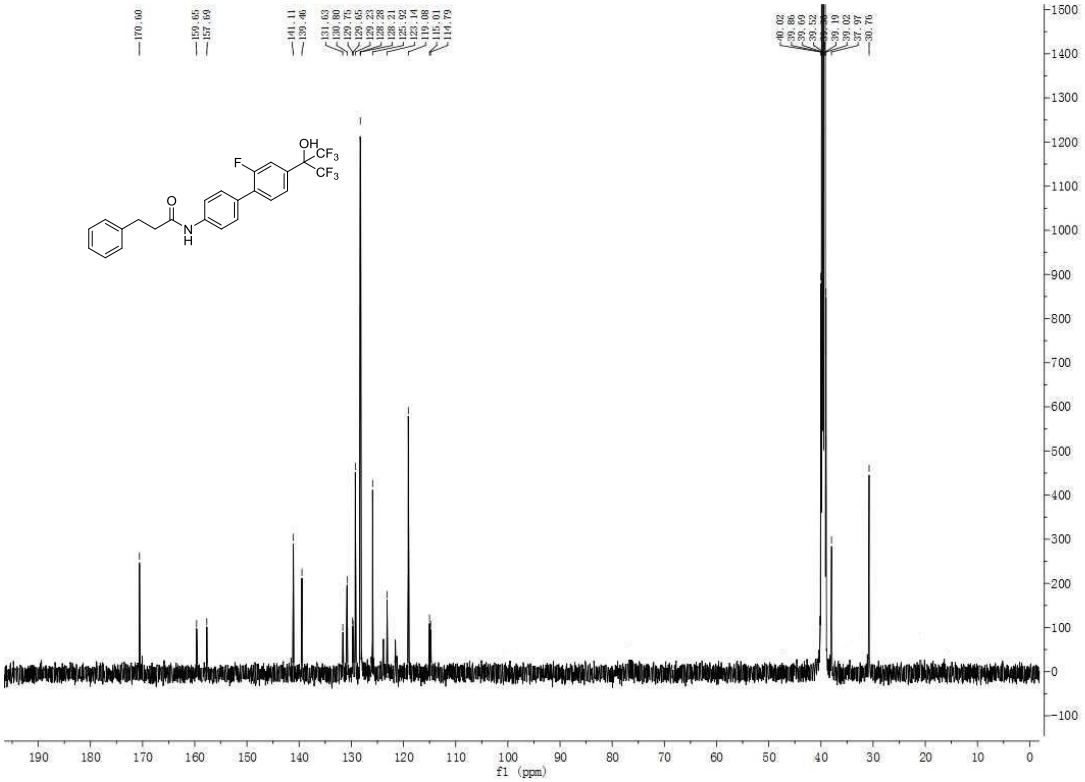




N-(2'-fluoro-4'-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)-[1,1'-biphenyl]-4-yl)-3-phenylpropa

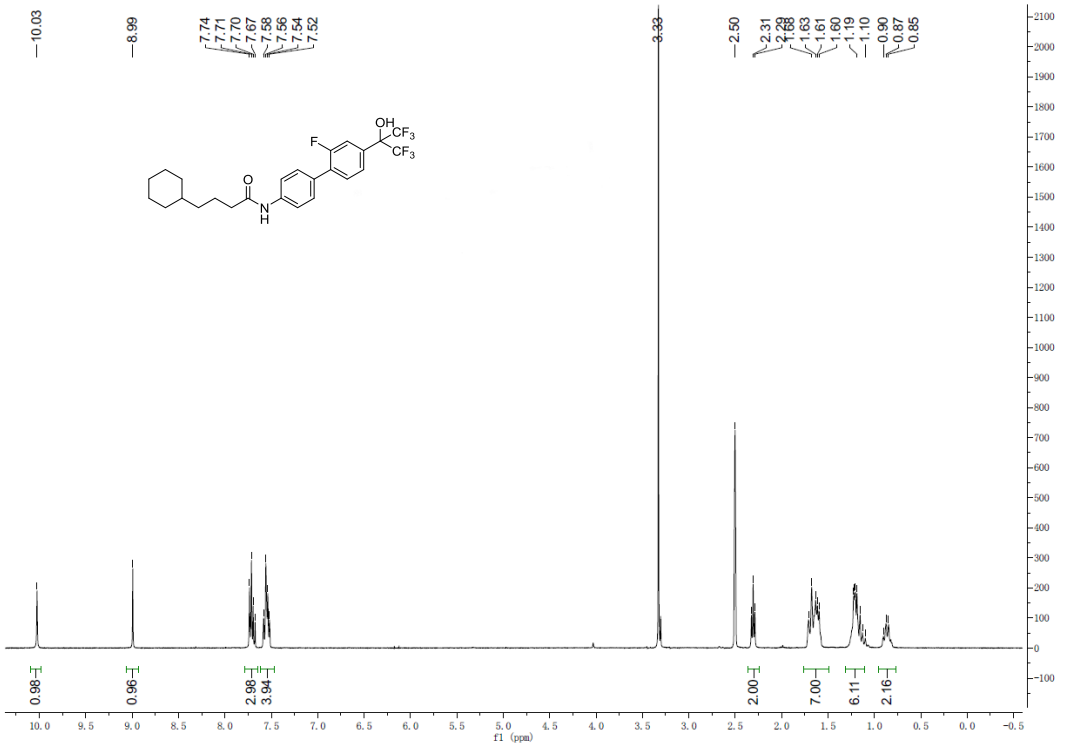
*namide (**35**).*

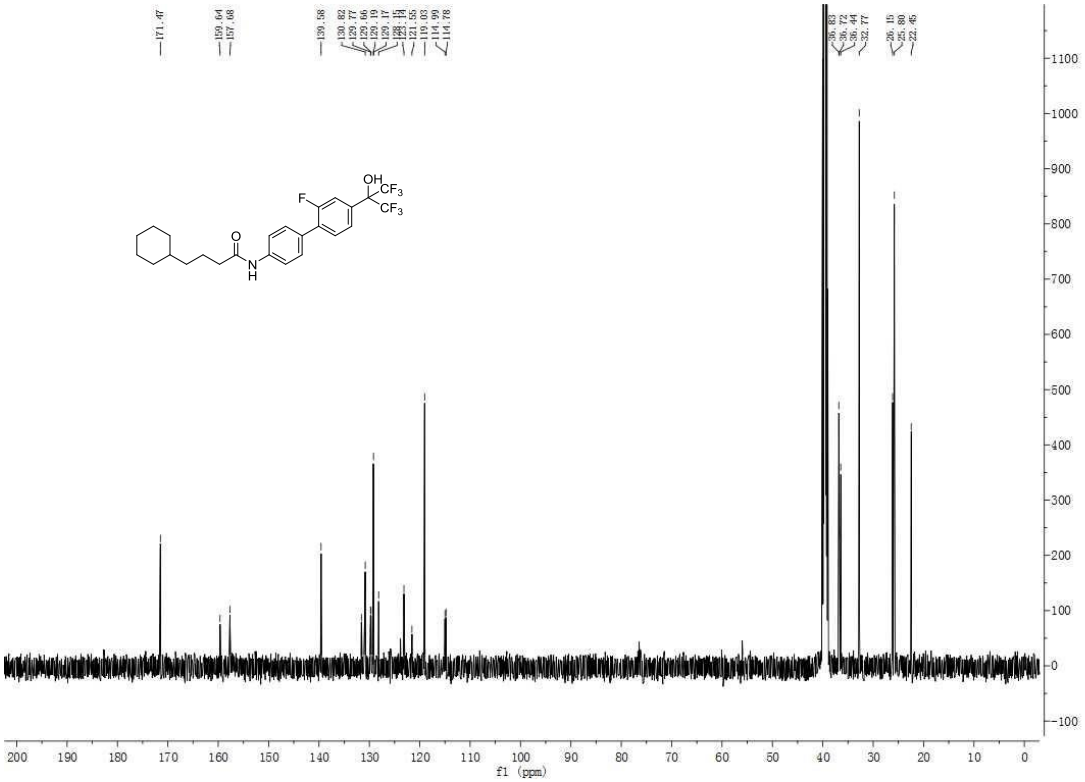




4-cyclohexyl-N-(2'-fluoro-4'-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)-[1,1'-biphenyl]-4-yl)b

*utanamide (**36**).*

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129.77
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121.55
119.03
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36.83
36.72
36.47
36.14
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26.15
25.80
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OH
CF3
CF3
F
O
N
H
f1 (ppm)