Synthesis, biological evaluation and X-ray analysis of bicalutamide sulfoxide analogues for the potential treatment of prostate cancer

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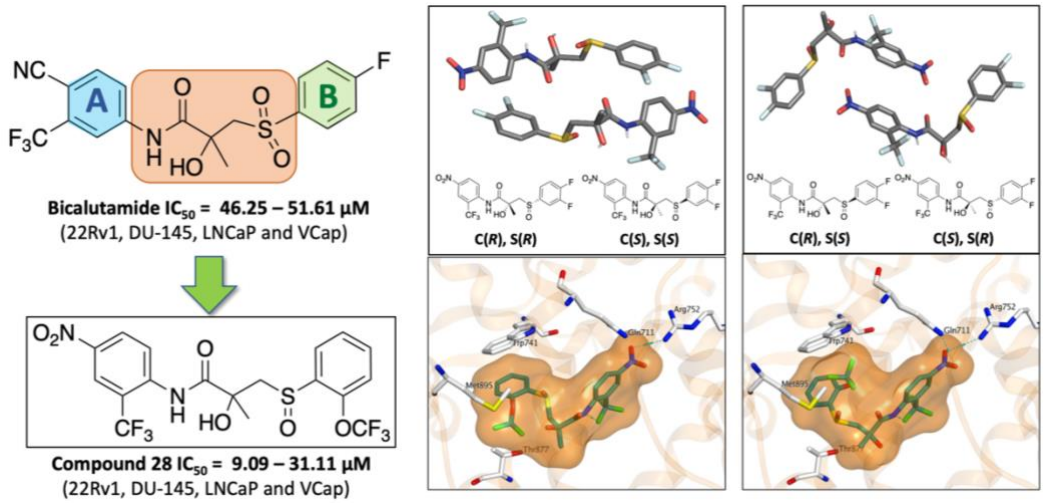
Keywords: Androgen receptor (AR), prostate cancer (PC), sulfoxide, oxidation, diastereotopic, diastereoisomers, diarylpropionamide**,** bicalutamide.

Graphical abstract



Highlights

- Efficient and facile synthesis of novel sulfoxide bicalutamide derivatives.
- Identification of compound **27** and **28** with enhanced anticancer activity across four PC cell lines (22Rv1, DU-145, LNCaP and VCap) compared to bicalutamide and enzalutamide.
- Separation of three pairs of sulfoxide diastereoisomers and NMR data comparison.
- X-ray diffraction crystal structure analysis confirms configuration assignment at the chiral sulfur and carbon centers.
- Molecular modelling study of the four diastereoisomers of compound **28**.

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Abstract

The androgen receptor (AR) is a pivotal target for the treatment of prostate cancer (PC) even when the disease progresses toward androgen-independent or castration-resistant forms. In this study, a series of sulfoxide derivatives were prepared and their antiproliferative activity evaluated *in vitro* against four different human prostate cancer cell lines (22Rv1, DU-145, LNCaP and VCap). Bicalutamide and enzalutamide were used as positive controls. Compound **28** displayed significant enhancement in anticancer activity across the four PC cell lines with IC_{50} = 9.09 - 31.11 µM compared to the positive controls: bicalutamide (IC_{50} = 45.20 - 51.61 µM*)* and enzalutamide (IC_{50} = 11.47 - 53.04 µM). Sulfoxide derivatives of bicalutamide were prepared efficiently from the corresponding sulfides using only one equivalent of *m*CPBA, limiting the reaction time to 15-30 minutes and maintaining the temperature at 0°C. Interestingly, three pairs of sulfoxide diastereomers were separated and NMR comparison of their diastereotopic methylene (CH_2) group is presented. X-ray diffraction crystal structure analysis provided relative configuration assignment at the chiral sulfur and carbon centres. Molecular modelling study of the four diastereoisomers of compound **28** is described.

The androgen receptor (AR) plays substantial anabolic and reproductive roles in men and women. Additionally, AR signaling plays a crucial function in tumourigenesis and metastasis of different cancer types, including prostate, bladder, kidney, lung, breast and liver [1-3]. AR is a member of the nuclear receptor family and consists of three main functional domains: a variable N-terminal domain, a highly conserved DNA-binding domain (DBD) and a conserved ligand binding domain (LBD). [4] Binding of testosterone and dihydrotestosterone (DHT) to the LBD induces AR conformational changes followed by translocation into the nucleus to interact with DNA and modulate prostate specific antigen (PSA) levels.[5] AR antagonists (anti-androgens) inhibit these processes and are used for the treatment of advanced prostate cancer (PC).[6,7] A variety of non-steroidal anti-androgens (NSAA) are approved for the treatment of PC. The first generation NSAAs include flutamide, hydroxyflutamide and bicalutamide, **Figure 1**. However, these antiandrogens eventually fail to inhibit the AR upon long term treatment switching from being AR antagonists to AR agonists with the development of castration resistant prostate cancer (CRPC), an aggressive form of the disease with poor prognosis. Similarly, resistance to the more recent second-generation anti-androgens (enzalutamide, apalutamide) is developing in PC patients via the upregulation of AR expression.[8] More recently, darolutamide (ODM-201) has been recently approved and clinically used in patients with non-metastatic CRPC.[9] New AR antagonists are continuously needed to improve the efficacy of the clinically used compounds.

In this paper, we present the design and synthesis of a series of new sulfoxide bicalutamide analogues, building on our previous work [10-14] to offer new therapeutic possibilities for combating resistance commonly observed in the clinical use of AR antagonists.

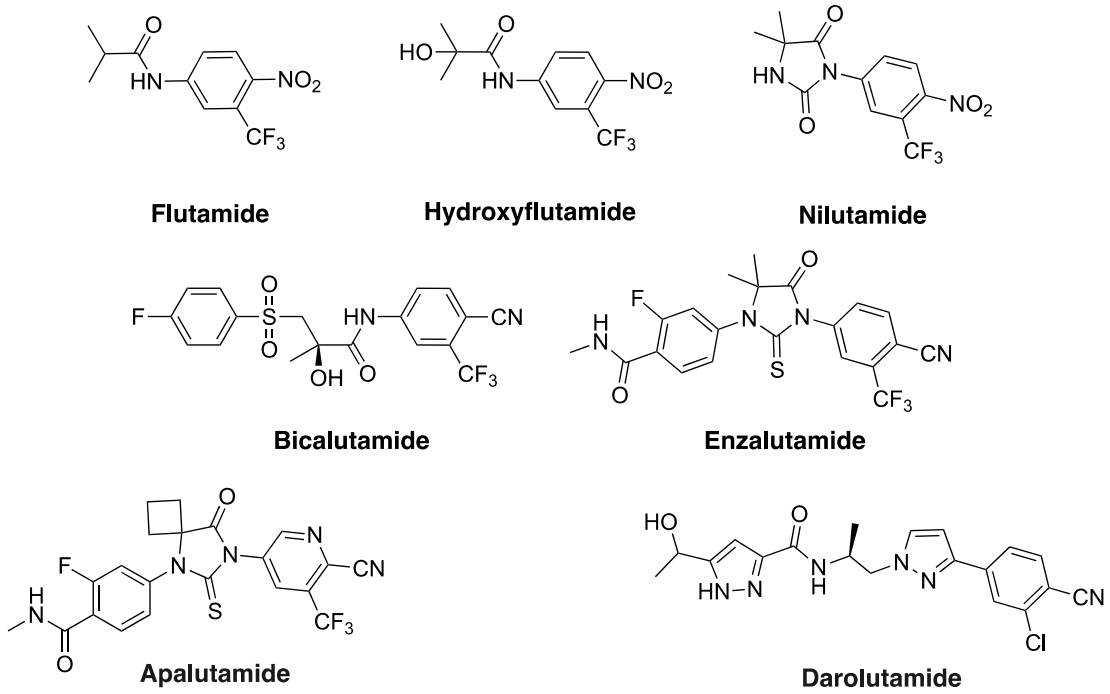


Figure 1. Chemical structures of the non-steroidal anti-androgens (NSAA); flutamide, hydroxyflutamide, nilutamide, bicalutamide, enzalutamide, apalutamide and darolutamide.

Small chemical changes in the structure of nonsteroidal AR ligands can play a major role in determining the pharmacological outcome.[15-16] We previously published extensive SAR studies on bicalutamide chemical structure modification. [10-14] Here we are covering additional modifications for further evaluation of the impact on the anti-proliferative activity in prostate cancer models. **Figure 2** shows the general three main areas of modification; ring **A**, ring **B** and linker area **C**. Herein, a series of sulfoxide bicalutamide derivatives (region C) were prepared and their anti-proliferative activity was evaluated *in vitro* against four different human prostate cancer cell lines (22Rv1, DU-145, LNCaP and VCap).

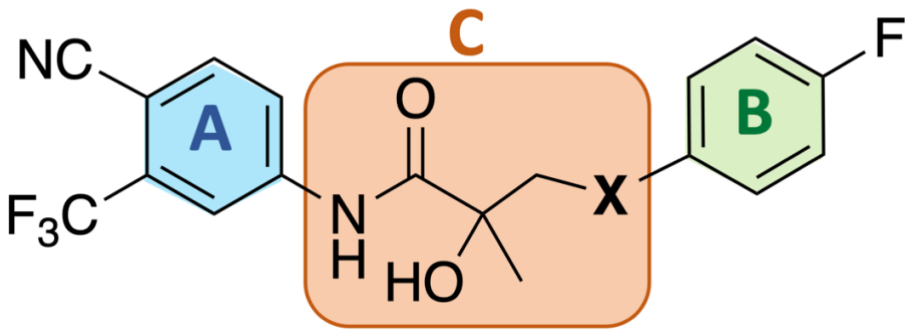


Figure 2. Chemical structure of bicalutamide (X=SO_2) and the areas of structural modifications, ring **A**, ring **B** and the linker area **C**.

Phenylacrylamides (**4** and **5**) were prepared by reacting the corresponding aniline (**1** or **2**) with methacryloyl chloride (**3**) in dimethylacetamide (DMA).[17]

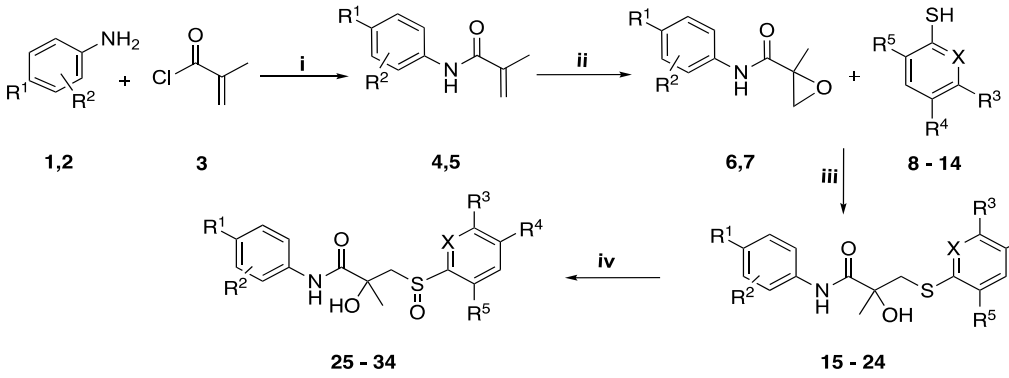
Phenylacrylamides (**4** and **5**) were epoxidised using hydrogen peroxide and trifluoroacetic anhydride (TFAA) in dichloromethane to give **6** and **7.** [18,19] Subsequently the epoxides were reacted with thiols (**8**-**14**) to afford the corresponding sulfide derivatives (**15**-**24**).

Previous studies of the non-steroidal propionamides showed that the heteroatom (X) linked to the B-ring (**Figure 2**) is the main point of metabolic lability and that there was no significant *in vivo* activity of some sulfide analogues because of rapid hepatic metabolism into the sulfoxide and sulfone analogues.[20- 22]

Bicalutamide and its analogues are clinically used in a single enantiomeric form at the asymmetric carbon atom (S-configuration if X = O, NH and R-configuration if X = S, SO_2) and this chirality has an important effect on anti-androgenic activity.[23-25] Upon oxidation of the sulfide bicalutamide analogues to the corresponding sulfoxide (SO), another chiral centre at the sulfur atom is created.[21] Miller and co-workers demonstrated that the nature of the linker plays a pivotal role in controlling the ultimate antagonistic/agonistic effect of these kinds of molecules. [26-28]

Previous literature states that the sulfoxide derivatives are usually obtained by the oxidation of sulfide precursors using sodium metaperiodate ($NaIO_4$) in aqueous methanol for 48 h. [17, 21, 29] It is also reported that the oxidation reaction of the sulfide bicalutamide derivatives with *m*-chloroperbenzoic acid (*m*CPBA) would give sulfones as the sole product. [17, 21, 29] However, we efficiently managed to prepare the bicalutamide sulfoxide analogues (**25**-**34**) from the corresponding sulfide precursors (**15**-**24**) using only one equivalent of *m*CPBA (rather than 2 equivalents in case of the sulfone), limiting the reaction time to 15-30 minutes and maintaining the temperature at 0°C while monitoring the progress of reaction using TLC, as outlined in **Scheme 1**.

Introduction of fluorinated groups into the chemical structure provides a combination of electronegativity, size and lipophilicity impacts and can affect physicochemical properties which in turn influences the biological activity. [30-33]



	R^1	R^2
1, 4, 6	CN	3-CF_3
2, 5, 7	NO_2	2-CF_3

	R^3	R^4	R^5	X
8	H	H	H	N
9	H	CF_3	H	C
10	H	H	OCF_3	C
11	H	F	F	C
12	H	OCF_3	H	C
13	H	CF_3	H	N
14	F	F	H	C

	R^1	R^2	R^3	R^4	R^5	X
15, 25	CN	3-CF_3	H	H	H	N
16, 26	NO_2	2-CF_3	H	H	H	N
17, 27	NO_2	2-CF_3	H	CF_3	H	C
18, 28	NO_2	2-CF_3	H	H	OCF_3	C
19, 29	NO_2	2-CF_3	H	F	F	C
20, 30	CN	3-CF_3	H	OCF_3	H	C
21, 31	NO_2	2-CF_3	H	OCF_3	H	C
22, 32	CN	3-CF_3	H	CF_3	H	N
23, 33	NO_2	2-CF_3	H	CF_3	H	N
24, 34	NO_2	2-CF_3	F	F	H	C

Scheme 1. Reagents and conditions, i) DMA, rt, 3h, ii) H_2O_2, TFAA, DCM, rt, 24h; iii) NaH, THF, RT, 24h, iv) *m*CPBA (1 equiv), DCM, 0° C, 15-30 min.

Interestingly, during the synthesis and purification of sulfoxide analogues (**32**-**34**)[34] using column chromatography, we obtained two sets of diastereomers, a fast-moving (**32a**, **33a**, **34a**) and a slow-moving (**32b**, **33b**, **34b**) product. The comparison of the NMR data of the separated sets of diastereoisomers of compounds (**32**-**34**) revealed consistent trends in the ^1H and ^{13}C NMR chemical. The clearest trend is the chemical shift separation of the two protons of the diastereotopic methylene (CH_2) group next to the chiral sulfoxide (**Figure 3** and **Table 1**). The coupling constant (*J*-value) between the two protons and the carbon chemical shift also show a consistent trend (**Table 1**).

ID	Difference in H - chemical shift	coupling constant (*J*-value) between the two protons	^{13}C - chemical shift
32 a	0.11	14	57.35
32 b	0.73	13	60.14
33 a	0.12	14	57.50
33 b	0.73	13	59.39
34 a	0.20	14	59.62
34 b	0.51	13	62.30

Table 1. NMR data of the diastereotopic methylene (CH_2) group of the separated diastereoisomers of the sulfoxide bicalutamide derivatives (**32**-**34**).

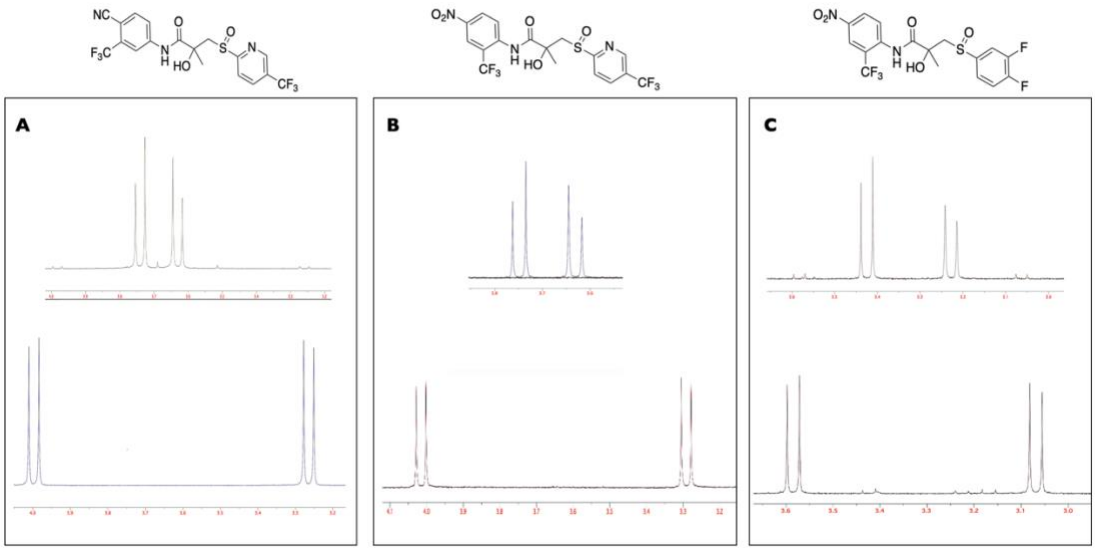


Figure 3. ^{1}H-NMR spectra of the three pairs of sulfoxide compounds showing the chemical shift difference between the diastereotopic methylene (CH_2) protons. The top panel represents the fast-moving products (**32a**-**33a**-**34a**) while the bottom panel shows the slow-moving products (**32b**-**33b**-**34b**).

Closer examination of compound **34** using X-ray diffraction crystal structure analysis [35,36] of the two separated sets of diastereoisomers, namely **34a** and **34b** in approximately (1 fast moving: 2 slow moving ratio), established the configuration of **34a** (fast moving, minor product) to be a mixture of C(*R*), S(*R*) and its C(*S*), S(*S*) antipode. Meanwhile **34b** (slow moving, major product) was shown to be a mixture of C(*R*), S(*S*) and its C(*S*), S(*R*) antipode, **Figure 4**, (CCDC 2040881-2040882).

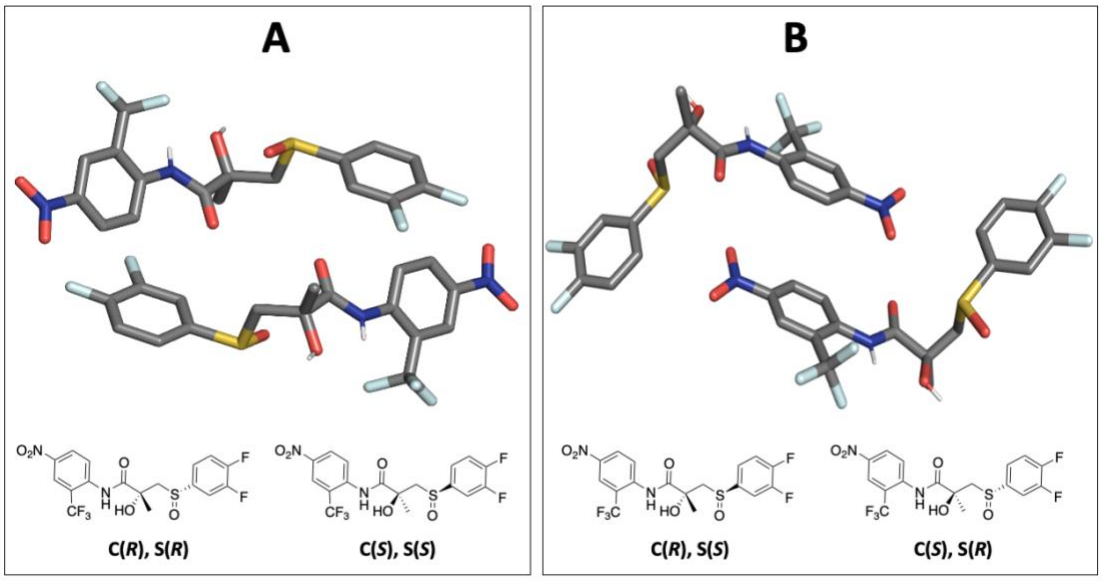


Figure 4. X-ray crystal structure and absolute configuration of the two sets of diastereoisomers of compound **34**, (A) C(*R*), S(R) and C(*S*), S(*S*) antipode, (B) C(*R*), S(*S*) and C(*S*), S(*R*) antipode, of **34a** and **34b** respectively. (CCDC 2040881-2040882).

Miller and co-workers established the absolute configuration of the chiral sulfoxide group of two bicalutamide sulfoxide analogues (carbon atom with R configuration) using X-ray analysis, NMR measurements and quantum chemical calculations. [21, 28, 37] Evaluation of the antiproliferative activity [38] of the sulfoxide compounds (**25** - **34**) in 22Rv1, DU-145, LNCaP and VCap human prostate cancer cell lines, showed that compound **28** has the most potent activity (IC_{50} **=** 9.09 – 31.11 µM) followed by compounds **27**, **29** and **30.** Loss of activity was observed with compounds **25**, **26**, **31**-**34**, **Table 4**.

ID	22Rv1 IC_{50} (µM)	DU-145 IC_{50} (µM)	LNCaP IC_{50} (µM)	VCap IC_{50} (µM)
25	>100	>100	>100	>100
26	>100	>100	>100	100
27	21.13	36.51	25.55	24.24
28	15.19	31.11	9.09	20.68
29	51.143	>100	24.402	>100
30	41.16	52.08	36.24	53.49
31	>100	>100	>100	>100
32a	65.45	100	95.43	>100
32b	77.04	>100	>100	>100
33a	>100	>100	>100	>100
33b	>100	>100	>100	>100
34a	>100	>100	>100	>100
34b	>100	>100	>100	>100
Bicalutamide	46.25	45.41	45.20	51.61
Enzalutamide	31.76	32.27	11.47	53.04

Table 2. *in vitro* antiproliferative activity of the sulfoxide analogues of bicalutamide (**25** - **34**) across four human prostate cancer cell lines (DU-145**,** 22Rv, LNCaP and VCap). All data are mean values from experiments carried out on three separate occasions.

A docking study using MOE [39] was performed to compare the predicted binding modes of the four diastereoisomers of sulfoxide compound **28** (IC_{50} **=** 9.09 - 31.11 µM). All the diastereoisomers share key interactions including a H-bond between the nitro group (NO_2) and the guanidine group of Arg 752 of helix 5 (**Figure 5**). Another H-bond was observed between the nitro group (NO_2) and the side chain amide (NH_2) group of Gln 711 in three out of four diastereoisomers (**Figure 5B-D**). Diastereoisomer C(*R*)S(*S*)

shows π-π stacking between the terminal phenyl ring and the indole side chain of Trp 741 (**Figure 5A**). In addition, hydrophobic interactions were observed with the surrounding hydrophobic pocket formed of residues; Trp 741, Met 745, Leu 712 and Met 787.

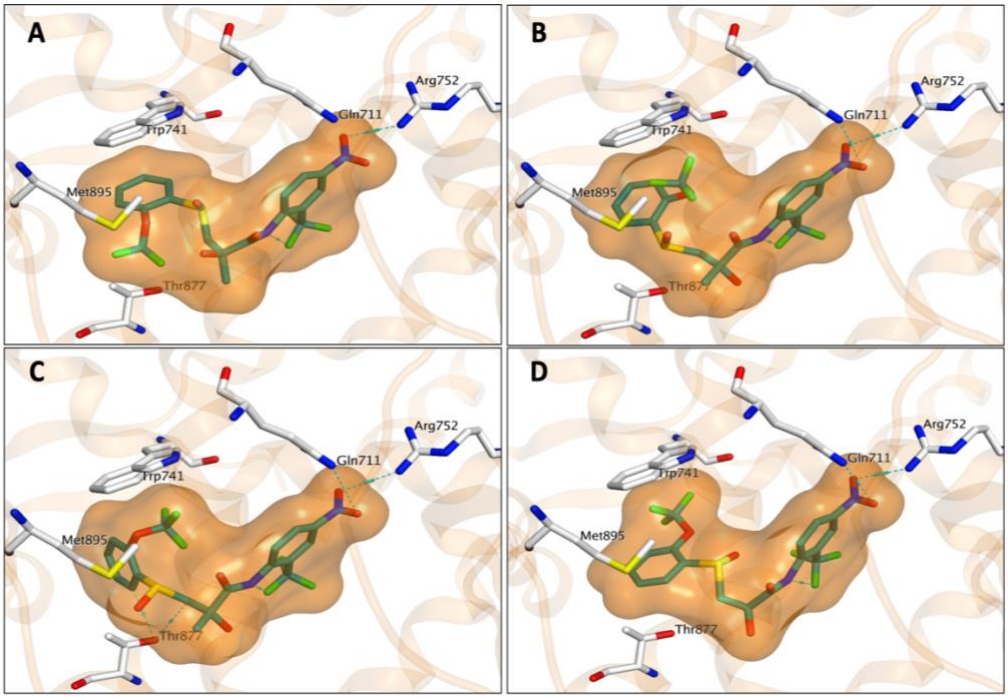


Figure 5. The predicted binding mode of compound **28A** [C(*R*), S(*S*)], **28B** [C(*S*), S(*R*)], **28C** [C(*S*), S(*S*)] and **28D** [C(*R*), S(*R*)] within the hAR-LBD showing H-bond interactions (blue dashed line) with Arg752, Gln711, Asn 705 and Thr 877.

In summary, sulfoxide bicalutamide derivatives were prepared efficiently and their antiproliferative activity was evaluated *in vitro* against four different human prostate cancer cell lines (22Rv1, DU-145, LNCaP and VCap). These modifications offer an insight on the SAR of various propionanilide analogues. Bicalutamide and enzalutamide were used as positive controls. The results summarised in **Tables 2** indicated that two compounds; **27** and **28** have displayed more potent antiproliferative activity than the positive controls; bicalutamide (IC_{50} = 45.20- 51.61 µM*)* and enzalutamide (IC_{50} = 11.47- 53.04 µM). Sulfoxide analogues were prepared via controlling the oxidation reaction time, temperature and the number of equivalents of the oxidising agent *m*-CPBA. Three pairs of diastereomers were separated and a comparison of their diastereotopic methylene (CH_2) group NMR data is presented in **Table 1** and **Figure 3**. Interestingly, X-ray diffraction crystal structure analysis provided relative configuration assignment at the chiral sulfur and carbon

centres, **Figure 4**. An *in silico* molecular modelling study performed on the four diastereoisomers of compound **28** is described **Figure 5,** indicating similar key interactions within the AR-LBD.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

This work is dedicated to the memory of Professor Christopher McGuigan (1958-2016). The authors would like to thank the Welsh Government Academic Expertise for Business (A4B) scheme for the financial support. The authors would like to thank Oncotest (Freiburg, Germany; now part of the Charles River Laboratories) for provision of human prostate cancer cell line testing as an out- sourced service.

Supplementary data

Supplementary data associated with this article can be found in the online version. These data include NMR, MS and HPLC data.

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34. **General method for the preparation of sulfoxide compounds 25-34.**
To a stirring solution of the different sulfide **15-24** (0.7 mmol) in 5 mL anhydrous dichloromethane (DCM) was added 3-chloroperbenzoic acid (*m*CPBA) (0.8 mmol) portion wise maintaining the temperature at 0° C for 20-30 min. After further dilution, a solution of 5% sodium carbonate is added and the mixture stirred for 1 hour, the phases are then separated. The combined organic layers were washed, dried over anhydrous sodium sulfate and concentrated in vacuo. The crude residue was purified by column chromatography, preparative TLC or crystallization from methanol.
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Supporting Information

Synthesis, biological evaluation and X-ray analysis of bicalutamide sulfoxide analogues for the potential treatment of prostate cancer

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1. Chemistry

All chemicals were purchased from Sigma-Aldrich or Alfa Aesar and were used without further purification. Thin Layer Chromatography (TLC): pre-coated aluminium backed plates (60 F254, 0.2 mm thickness, Merck) were visualized under both short and long wave UV light (254 and 366 nm). Flash column chromatography was carried out using silica gel supplied by Fisher (60A, 35-70 mm) ^{1}H NMR (500 MHz), ^{13}C NMR (125 MHz) and ^{19}F NMR (470 MHz) spectra were recorded on a Bruker Avance 500 MHz spectrometer at 25^{o}C. Chemical shifts (δ) are expressed in parts per million (ppm) and coupling constants (J) are given in hertz (Hz). The following abbreviations are used in the assignment of NMR signals: s (singlet), bs (broad singlet); d (doublet), t (triplet), q (quartet), qn (quintet), m (multiplet), dd (doublet of doublet), dt (doublet of triplet), td (triple doublet); dq (double quartet), m (multiplet), dm (double multiplet).

The purity of the final compounds was verified to be >95% by reverse-phase HPLC analysis using either I) Thermo SCIENTIFIC, SPECTRA SYSTEM P4000, detector SPECTRA SYSTEM UV2000, Varian Pursuit XRs 5 C18, 150 x 4.6 mm (as an analytic column) or II) Varian Prostar (LC Workstation-Varian Prostar 335 LC detector), Thermo SCIENTIFIC Hypersil Gold C18, 5µ, 150 x 4.6 mm (as an analytic column) with a gradient elution of H_2O/ CH_3CN from 90/10 to 0/100 in 30 min, Flow = 1 mL/min, λ = 275 nm. Mass spectra were measured by Bruker Daltonics microTof-LC, in positive mode electrospray ionization (ESI).

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1.1 General method for the preparation of intermediates 4-5

Methacryloyl chloride **3** (8.4 mL, 85.96 mmol) was added over the course of 10 minutes to a stirring solution of the appropriate trifluoromethylaniline **1-2** (10.75 mmol) in N,N-dimethylacetamide (10 mL) at room temperature for 24h. After the reaction was complete, the mixture was diluted with ethyl acetate (100 mL), extracted with saturated $NaHCO_3$ solution (2 x 50 mL) then cold brine (2 x 50 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. The crude oil residue was purified by flash column chromatography eluting with chloroform-ethyl acetate 95:5 v/v to obtain the titled compounds.

***N*-(4-cyano-3-(trifluoromethyl)phenyl)methacrylamide (4)** [19]

Data in accordance with literature data. Yield; 92%. ^{1}H NMR ($CDCl_3$) δ 8.10 (d, *J* = 2Hz, 1H, Ar*H*), 8.06 (bs, 1H, N*H*), 8.01 (dd, J = 2, 8.5 Hz, 1H, Ar*H*), 7.81 (d, *J* = 8.5Hz, 1H, Ar*H*), 5.89 (d, *J* = 1Hz, 1H, CH_2), 5.62 (q, *J* = 1.5Hz, 1H, CH_2), 2.10 (dd, *J* = 0.5, 1.5 Hz, 3H, CH_3). ^{19}F-NMR: ($CDCl_3$) δ -62.23**.**

***N*-(4-Nitro-2-(trifluoromethyl)phenyl)methacrylamide (5)** [19]

Data in accordance with literature data. Yield; 94 %.^{1}H NMR ($CDCl_3$) δ 8.73 (d, J= 9 Hz, 1H, Ar*H*), 8.46 (d, J= 3 Hz, 1H, Ar*H*), 8.37 (dd, J= 9 Hz, 2.5 Hz, 1H, Ar*H*), 8.17 (bs, 1H, N*H*), 5.85 (q, J= 0.5 Hz, 1H, CH_2), 5.58 (q, J= 1.5 Hz, 1H, CH_2), 2.15-2.13 (dd, J= 1, 1.5 Hz, 1H, CH_3). ^{19}F-NMR: ($CDCl_3$) d -61.31.

1.2 General method for the preparation of intermediates 6-7

To a stirred solution of the intermediate **4**-**5** (3 mmol) in DCM (7 mL) was added 30% hydrogen peroxide (3.6 mL, 32.03 mmol). The reaction mixture was placed in a water bath at rt and trifluoroacetic anhydride (3.7 mL, 26.7 mmol) was added slowly to the mixture, which was then stirred for 24 h. The reaction mixture was transferred to a separating funnel using DCM (30 mL). The organic layer was washed with distilled water (20 mL), sat. aq. $Na_2S_2O_3$ (4x20 mL), sat. aq. $NaHCO_3$ (3x20 mL) and brine (20 mL), dried over Na_2SO_4 and concentrated at reduced pressure.

***N*-(4-Cyano-3-(trifluoromethyl)phenyl)-2-methyloxirane-2-carboxamide** (**6**) [19]

The data are in accordance with literature data. Obtained in 86% yield as a yellow solid. ^{1}H-NMR ($CDCl_3$): δ 8.38 (bs, 1H), 8.00 (d, J= 2.1 Hz, 1H), 7.88 (dd, J= 8.5 Hz, 2.1 Hz, 1H), 7.78 (d, J= 8.5 Hz, 1H), 3.00 (s, 2H), 1.68 (s, 3H).

2-Methyl-*N*-(4-nitro-2-(trifluoromethyl)phenyl)oxirane-2-carboxamide (7) [12]

Obtained in 71% yield as a yellow wax. ^{1}H-NMR ($CDCl_3$): δ 8.92 (bs, 1H), 8.74 (d, J= 9.6 Hz, 1H), 8.53 (d, J= 2.5 Hz, 1H), 8.44 (dd, J= 9.6 Hz, 2.5 Hz, 1H), 3.04 (d, J= 4.6 Hz, 1H), 3.02 (d, J= 4.6 Hz, 1H), 1.72 (s, 3H). ^{19}F-NMR ($CDCl_3$): δ -61.69 (s, 3F). ^{13}C-NMR ($CDCl_3$): δ 169.2, 142.9, 140.4, 128.35 (m), 123.7, 122.3 (m), 121.6, 119.2 (m), 56.5, 53.9, 16.4.

1.3 General method for the preparation of compounds 15-24.

To a mixture of sodium hydride (NaH) (60% in mineral oil, 0.050 g, 1.23 mmol) in anhydrous THF (2 mL) at 0 °C under Ar atmosphere was added a solution of the differently substituted thiophenol **8 - 14** (1.11 mmol) in 1 mL of anhydrous THF. This mixture was stirred at rt for 20 min. A solution of the intermediate **6** or **7** (0.74 mmol) in anhydrous THF (3 mL) was added slowly. The reaction mixture was stirred at room temperature for 24h. The mixture was then diluted with ethyl acetate (30 mL), washed with brine (15 mL) and water (30 mL), dried over Na_2SO_4 and concentrated under *vacuum*. The crude residue was purified by flash column chromatography eluting with *n*-hexane/EtOAc 100:0 v/v increasing to *n*-hexane/EtOAc 90:10 v/v.

***N*-(4-cyano-3-(trifluoromethyl)phenyl)-2-hydroxy-2-methyl-3-(pyridin-2-ylthio) propanamide** (**15**) yield 79%.

^{1}H NMR ($CDCl_3$) *δ* 9.64 (s, 1H, N*H*), 8.89 (s, 1H, Ar*H*), 8.39 (ddd, *J*= 1, 1.5, 5 Hz, 1H, Ar*H*), 8.13 (d, *J* = 2 Hz, 1H, Ar*H*), 8.00 (dd, *J* = 2, 8.5 Hz, 1H, Ar*H*), 7.91 (d, *J*= 8.5 Hz, 1H, Ar*H*), 7.61 (ddd, *J*= 2, 8, 8.5 Hz, 1H, Ar*H*), 7.37 (dt, *J*= 1, 8 Hz, 1H, Ar*H*), 7.17 (ddd, *J*= 1, 5, 7.5 Hz, 1H, Ar*H*), 3.61 (d, *J*= 15.5 Hz, 1H, CH_2), 3.50 (d, *J* = 15 Hz, 1H, CH_2), 1.63 (s, 3H, CH_3); ^{19}F NMR ($CDCl_3$) *δ* -62.16 (s, 3F); ^{13}C NMR ($CDCl_3$) *δ* 175.18 (C=O), 158.85 (Ar*C*), 148.32 (Ar*C*H), 141.69 (Ar*C*), 137.45 (Ar*C*H), 135.80 (Ar*C*H), 133.92 (q, $^{2}J_{C-F}$ = 32.5 Hz, Ar*C*), 123.55 (Ar*C*H), 122.19 (q, $^{1}J_{C-F}$ = 271.3 Hz, *C*F_3), 121.66 (Ar*C*H), 120.92 (Ar*C*H), 117.16 (q, $^{3}J_{C-F}$ = 5 Hz, Ar*C*H), 115.67 (Ar*C*), 104.15 (CN), 77.01 (*C*OH), 41.48 (*C*H_2), 26.81 (*C*H_3). MS [ESI, m/z]: 382.1 [M+H^+], 404.1 [M+Na^+]. Reverse-phase HPLC, eluting with H_2O/CH_3CN from 90/10 to 0/100 in 30 min; flow = 1 mL/min, t_R = 21.17 mins 99.5%

2-Hydroxy-2-methyl-*N*-(4-nitro-2-(trifluoromethyl)phenyl)-3-(pyridin-2-ylthio)propenamide (**16**) yield 75 %.

^{1}H NMR ($CDCl_3$) *δ* 10.26 (s, 1H, N*H*), 9.08 (s, 1H, Ar*H*), 8.84 (d, *J* = 9 Hz, 1H, Ar*H*), 8.52 (d, *J* = 3 Hz, 1H, Ar*H*), 8.42 (m, 2H, Ar*H*), 7.61 (m, 1H, Ar*H*), 7.37 (d, *J* = 8.5 Hz, 1H, Ar*H*), 7.18 (m, 1H, Ar*H*), 3.60 (d, *J* = 15 Hz, 1H, CH_2), 3.52 (d, *J* = 15 Hz, 1H, CH_2), 1.65 (s, 3H,

C*H*$_3$); ^{19}F NMR ($CDCl_3$) *δ* -62.01 (s, 3F); ^{13}C NMR ($CDCl_3$) *δ* 175.24 (C=O), 158.68 (Ar*C*), 148.31 (Ar*C*H), 142.62 (Ar*C*), 141.00 (Ar*C*), 137.40 (Ar*C*H), 128.27 (Ar*C*H), 123.36 (Ar*C*H), 122.78 (q, $^1J_{C-F}$ = 272 Hz, *C*F*3*), 122.36 (q, $^3J_{C-F}$ = 5.5 Hz, Ar*C*H), 122.04 (Ar*C*H), 120.86 (Ar*C*H), 119.28 (q, $^2J_{C-F}$ = 32.5 Hz, Ar*C*), 77.13 (*C*OH), 41.46 (*C*H_2), 26.54 (*C*H_3). MS (ES+) m/z: 402.1 [M+H$^+$], 424.1 [M+Na$^+$]. Reverse-phase HPLC, eluting with H_2O/CH_3CN from 90/10 to 0/100 in 30 min; flow = 1 mL/min, t_R = 23.98 mins 99.75%

2-Hydroxy-2-methyl-*N*-(4-nitro-2-trifluoromethyl)phenyl)-3-(4-(trifluoromethyl) phenylthio)propanamide (17) yield 65 %.[12]

^{1}H-NMR ($CDCl_3$), δ: 9.59 (bs, 1H), 8.54 (d, *J* = 2.5 Hz, 1H), 8.49 (d, *J* = 9 Hz, 1H), 8.37 (dd, *J*$_1$ = 9, *J*$_2$ = 2.5 Hz, 1H), 7.52 (d, *J* = 9 Hz, 2H), 7.47 (d, *J* = 8 Hz, 2H), 3.87 (d, *J*= 14.5 Hz, 1H), 3.36 (s, 1H), 3.26 (d, *J*= 14.5 Hz, 1H), 1.62 (s, 3H). ^{19}F-NMR ($CDCl_3$), δ: -62.80 (s, 3F), -61.56 (s, 3F); ^{13}C-NMR ($CDCl_3$), δ: 172.80 (C=O), 142.95, 140.30, 138.97, 130.04, 129.13 (q, $^2J_{C-F}$ = 32.5 Hz), 128.21, 125.79 (q, $^3J_{C-F}$ = 3.6 Hz), 121.98, 123.73 (q, $^1J_{C-F}$ = 270 Hz), 122.79 (q, $^1J_{C-F}$ = 272.3 Hz, CF_3), 119.21 (q, $^2J_{C-F}$ = 31.5 Hz), 75.63 (*C*OH), 43.69 (*C*H_2), 26.16 (*C*H_3). MS [ESI, m/z]: 469.1 [M+H], 491.1 [M+Na]. Reverse-phase HPLC, eluting with H_2O/CH_3CN from 90/10 to 0/100 in 30 min; flow = 1 mL/min, t_R = 24.13 min.

2-Hydroxy-2-methyl-*N*-(4-nitro-2-(trifluoromethyl)phenyl)-3-((2-(trifluoromethoxy) phenyl)thio)propenamide (18) yield 58 %. [12]

^{1}H-NMR ($CDCl_3$): δ 9.64 (bs, 1H), 8.54 (d, *J* = 2.5 Hz, 1H), 8.47 (d, *J* = 9.0 Hz, 1H), 8.36 (dd, *J*= 9.0 Hz, 2.5 Hz, 1H), 7.58-7.55 (m, 1H), 7.29-7.24 (m, 1H), 7.23-7.17 (m, 2H), 3.84 (d, *J*= 14.5 Hz, 1H), 3.62 (bs, 1H), 3.15 (d, *J*= 14.5 Hz, 1H), 1.58 (s, 3H). ^{19}F-NMR ($CDCl_3$): δ -61.70 (s, 3F), -57.34 (s, 3F), ^{13}C-NMR ($CDCl_3$): δ 172.8 (C=O), 148.7, 142.8, 140.4, 133.8, 129.4, 128.0, 127.3, 127.1, 123.8, 122.3 (q, *J*= 5.5 Hz), 122.0, 121.1, 120.5 (q, *J*= 287.4 Hz, CF_3), 120.2 (q, *J*= 289.8 Hz), 75.4 (*C*OH), 43.9 (*C*H_2), 26.1 (*C*H_3). MS [ESI, m/z]: 485.1 [M+H]$^+$, 507.1 [M+Na]$^+$. Reverse-phase HPLC, eluting with H_2O/CH_3CN from 90/10 to 0/100 in 30 min; flow = 1 mL/min, t_R = 23.85 min.

3-((2,4-Difluorophenyl)thio)-2-hydroxy-2-methyl-N-(4-nitro-2-(trifluoromethyl) phenyl) propenamide (19) yield 74 %. [12]

^{1}H-NMR ($CDCl_3$): δ 9.64 (bs, 1H), 8.55 (d, *J* = 3.0 Hz, 1H), 8.49 (d, *J* = 9.5 Hz, 1H), 8.38 (dd, *J*= 9.5 Hz, 3.0 Hz, 1H), 7.49-7.43 (m, 1H), 6.80-6.70 (m, 2H), 3.83 (d, *J*= 14.5 Hz,

1H), 3.67 (bs, 1H), 3.03 (d, *J*= 14.5 Hz, 1H), 1.56 (s, 3H). ^{19}F-NMR ($CDCl_3$): δ -61.60 (s, 3F), -101.75 (s, F), -107.28 (s, F). ^{13}C-NMR ($CDCl_3$): δ 172.8 (C=O), 164.4, 161.8, 142.8, 140.4, 136.4 (dd, *J*= 9.5 Hz, 2.0 Hz), 128.1, 122.3 (q, *J*= 6.3 Hz), 122.8 (q, *J*= 275.3 Hz, CF_3), 115.3 (d, *J*= 17.6 Hz), 119.0 (q, *J*= 31.1 Hz), 121.7, 112.0 (dd, *J*= 21.6 Hz, 4.1 Hz), 104.7 (m), 75.3 (*C*OH), 44.6 (CH_2), 26.2 (CH_3). MS [ESI, m/z]: 437.1 $[M+H]^+$, 459.0 $[M+Na]^+$. Reverse-phase HPLC, eluting with H_2O/CH_3CN from 90/10 to 0/100 in 30 min; flow = 1 mL/min, t_R = 24.11 min.

***N*-(4-cyano-3-(trifluoromethyl)phenyl)-2-hydroxy-2-methyl-3-((4-(trifluoro methoxy) phenyl)thio)propenamide (20)** yield 81 %. [12]

^{1}H NMR ($CDCl_3$) *δ* 1.56 (s, 3H), 3.20 (d, *J* = 14 Hz, 1H), 3.75 (d, *J*= 14 Hz, 1H), 3.80 (s, 1H), 7.05 (d, *J* = 9 Hz, 2H), 7.46 (m, 2H), 7.76 (d, *J* = 8.5 Hz, 1H), 7.82 (dd, *J*= 2.5, 8.5 Hz, 1H), 8.00 (d, *J* = 2 Hz, 1H), 9.15 (s, 1H); ^{19}F NMR ($CDCl_3$) *δ* -58.09, -62.28; ^{13}C NMR ($CDCl_3$) *δ* 173.25 (C=O), 148.34 , 141.43 , 135.75 , 133.90 (q, $^2J_{C-F}$ = 32.6 Hz), 132.80 , 132.26 , 123.18 (m), 121.76 , 121.41 , 119.24 (m), 117.20 (q, $^3J_{C-F}$ = 4.9 Hz), 115.57 , 104.27 , 75.57 (*C*OH), 44.97 (CH_2), 26.13 (CH_3). MS (ES+) m/z: 465.1 ($M+H^+$), 487.1 ($M+Na^+$). Reverse-phase HPLC, eluting with H_2O/CH_3CN from 90/10 to 0/100 in 30 min; flow = 1 mL/min, t_R = 23.50 mins.

2-Hydroxy-2-methyl-*N*-(4-nitro-2-(trifluoromethyl)phenyl)-3-((4-(trifluoromethoxy) phenyl)thio)propenamide (21) yield 77 %. [12]

^{1}H NMR ($CDCl_3$) *δ* 1.59 (s, 3H), 3.18 (d, *J* = 14 Hz, 1H), 3.63 (s, 1H), 3.83 (d, *J*= 14.5 Hz, 1H), 7.06 (d, *J* = 8 Hz, 2H), 7.46 (d, *J* = 8.5 Hz, 1H), 8.37 (dd, *J* = 2.5, 9 Hz, 1H), 8.49 (d, *J* = 9 Hz, 1H), 8.53 (d, *J* = 2.5 Hz, 1H), 9.64 (s, 1H); ^{19}F NMR ($CDCl_3$) *δ* -61.64, -58.07; ^{13}C NMR ($CDCl_3$) *δ*: 172.95 (C=O), 148.54, 142.89, 140.38, 132.63, 132.32, 128.21, 123.91 (*C*F_3), 122.28 (q, $^3J_{C-F}$ = 5.9 Hz), 121.93, 121.74 (*C*F_3), 121.47, 119.24 (m), 73.54 (*C*OH), 44.90 (CH_2), 26.18 (CH_3). MS (ES+) m/z: 485.1 ($M+H^+$), 507.1 ($M+Na^+$). Reverse-phase HPLC, eluting with H_2O/CH_3CN from 90/10 to 0/100 in 30 min; flow = 1 mL/min, t_R = 25.64 mins.

***N*-(4-cyano-3-(trifluoromethyl)phenyl)-2-hydroxy-2-methyl-3-((5-(trifluoromethyl) pyridin-2-yl)thio)propenamide (22)** yield 79 %.[12]

^{1}H-NMR ($CDCl_3$): δ 9.51 (bs, 1H), 8.70-8.70 (m, 1H), 8.11 (d, *J*= 2.5 Hz, 1H), 8.00 (dd, *J*= 8.5 Hz, 2.5 Hz, 1H), 7.84-7.7.80 (m, 3H), 7.49 (d, *J* = 8.5 Hz, 1H), 3.60 (d, *J* = 15.0 Hz,

1H), 3.67 (d, *J* = 15.0 Hz, 1H), 1.65 (s, 3H). ^{19}F-NMR ($CDCl_3$): δ -62.20 (s, 3F), -62.42 (s, 3F). ^{13}C-NMR ($CDCl_3$): δ 174.4 (C=O), 164.0, 145.5 (q, J= 4.4 Hz), 141.4, 135.8, 134.0 (q, J= 3.0 Hz), 134.0 (q, J= 32.5 Hz), 125.3, 124.2 (m), 123.1, 122.1 (m), 121.6, 117.1 (q, J= 5.1 Hz), 115.5, 104.4, 77.2 (*C*OH), 41.0 (*C*H_2), 26.8 (*C*H_3). MS [ESI, m/z]: 450.1 $[M+H]^+$, 472.1 $[M+Na]^+$. Reverse-phase HPLC, eluting with H_2O/CH_3CN from 90/10 to 0/100 in 30 min; flow = 1 mL/min, t_R = 23.48 min.

2-Hydroxy-2-methyl-*N*-(4-nitro-2-(trifluoromethyl)phenyl)-3-((5-(trifluoromethyl) pyridin-2-yl)thio)propenamide (23) yield 76 %.[12]

^{1}H-NMR ($CDCl_3$), δ: 10.14 (bs, 1H), 8.81 (d, *J* = 9 Hz, 1H), 8.68 (m, 1H), 8.53 (d, *J* = 2.5 Hz, 1H),8.45 (dd, J_1 = 9.5, J_2 = *3* Hz, 1H), 7.94 (s, 1H), 7.82 (dd, J_1 = 8.5, J_2 = *2.5* Hz, 1H), 7.48 (d, *J= 8.5* Hz, 1H), 3.66 (d, *J*= 15 Hz, 1H), 3.61 (d, *J*= 15 Hz, 1H), 1.66 (s, 3H). ^{19}F-NMR ($CDCl_3$), δ: -61.95 (s, 3F), -62.42 (s, 3F); ^{13}C-NMR ($CDCl_3$), δ: 174.85 (C=O), 163.87, 145.57 (q, $^3J_{C-F}$ = 4.4 Hz), 142.78,140.79, 134.04 (q, $^3J_{C-F}$ = 6.5 Hz), 128.28, 124.09 (q, $^2J_{C-F}$ = 42.3 Hz), 123.00, 122.36 (q, $^3J_{C-F}$ = 5.5 Hz), 122.20, 123.13 (q, $^1J_{C-F}$ = 262.6 Hz, CF_3), 122.65 (q, 1JC-F = 272.4 Hz, CF_3), 119.42 (q, $^2J_{C-F}$ = 31.6 Hz*)*, 77.29 (*C*OH), 41.11 (*C*H_2), 26.58 (*C*H_3). MS [ESI, m/z]: 470.1 [M+H], 492.1 [M+Na]. Reverse-phase HPLC, eluting with H_2O/CH_3CN from 90/10 to 0/100 in 30 min; flow = 1 mL/min, t_R = 25.58 min.

3-((3,4-Difluorophenyl)thio)-2-hydroxy-2-methyl-*N*-(4-nitro-2-(trifluoromethyl) phenyl)propenamide (24) yield 78 %. [12]

^{1}H-NMR ($CDCl_3$), δ: 9.62 (bs, 1H), 8.58 -8.55 (m, 2H), 8.42 (dd, J_1 = 9.5, J_2 = 2.5 Hz, 1H), 7.28-7.25 (m, 1H), 7.05-7.00 (m, 1H), 3.78 (d, *J*= 14 Hz, 1H), 3.38 (bs, 1H), 3.17 (d, *J*= 14.5 Hz, 1H),1.59 (s, 3H). ^{19}F-NMR ($CDCl_3$), δ: -61.60 (s, 3F), -135.41 (s, F), -137.51 (s, F); ^{13}C-NMR ($CDCl_3$),δ: 172.79 (C=O), 150.14 (d, $^1J_{C-F}$ = 251.0 Hz), 150.02 (d, $^1J_{C-F}$ = 249.1 Hz), 142.94, 140.38, 130.07, 128.28,127.96 (q, $^3J_{C-F}$ = 2.8 Hz), 122.82 (q, $^1J_{C-F}$ = 272.4 Hz, CF_3),122.38 (q, $^3J_{C-F}$ = 5.5 Hz), 121.78, 120.72 (d, $^2J_{C-F}$ = 18.4 Hz), 119.18 (q, $^2J_{C-F}$ = 31.4 Hz*)*, 117.90 (d, $^2J_{C-F}$ = 17.9 Hz), 75.70 (*C*OH), 45.41 (*C*H_2), 26.21 (*C*H_3). MS [ESI, m/z]: 437.1 [M+H], 459.0 [M+Na]. Reverse-phase HPLC, eluting with H_2O/CH_3CN from 90/10 to 0/100 in 30 min; flow = 1 mL/min, t_R = 23.79 min.

1.4 General method for the preparation of sulfoxide compounds 25-34.

To a stirring solution of the different sulfide **15-24** (0.7 mmol) in 5 mL anhydrous dichloromethane (DCM) was added 3-chloroperbenzoic acid (*m*CPBA) (0.8 mmol) portion wise maintaining the temperature at 0° C for 20-30 min. After further dilution, a solution of 5% sodium carbonate is added and the mixture stirred for 1 hour, the phases are then separated. The combined organic layers were washed, dried over anhydrous sodium sulfate and concentrated in vacuo. The crude residue was purified by column chromatography, preparative TLC or crystallization from methanol.

***N*-(4-cyano-3-(trifluoromethyl)phenyl)-2-hydroxy-2-methyl-3-(pyridin-2-ylsulfinyl) propanamide** (1 isomer A:1 isomer B) **(25)** yield 75 %.

^{1}H NMR ($CDCl_3$) δ [9.50 (s), 9.30 (s), 1H, N*H*], [8.72 (d, *J*= 4.5 Hz), 8.68 (d, *J*= 5 Hz), 1H, Ar*H*], [8.21 (d, *J*= 1.5 Hz), 8.01 (m), 3H], 7.84 (m, 2H, Ar*H*), [7.50 (m), 7.44 (m), 1H, Ar*H*], [6.79 (s), 6.17 (s), 1H, O*H*], [3.69 (d, *J* = 13.5 Hz), 3.63 (d, *J* = 14 Hz), 1H, CH_2], [3.88 (d, *J* = 13.5 Hz), 3.31 (d, *J* = 13.5 Hz), 1H, CH_2], [1.73 (s), 1.66 (s), 3H, CH_3]; ^{19}F NMR ($CDCl_3$) δ -62.17; ^{13}C NMR ($CDCl_3$) δ (173.25, 172.78, *C*=O), 155.53 (Ar*C*), (150.09, 149.77, Ar*C*H), (141.50, 141.33, Ar*C*) (138.66, 138.47, Ar*C*H), (135.85, 135.78, Ar*C*H), 134.18 (m, Ar*C*), (125.50, 125.29, Ar*C*H), (122.01, 121.74, Ar*C*H) , (120.41, 120.13, Ar*C*H), 120.50 (q, $^{1}J_{C\text{-}F}$ = 263.8 Hz, *C*F_3), [117.49 (q, $^{3}J_{C\text{-}F}$ = 5 Hz), 117.24 (q, $^{3}J_{C\text{-}F}$ = 5 Hz), Ar*C*H], (115.45, 115.51, *C*N), (104.80, 104.68, Ar*C)*, (76.12, 75.88, *C*OH), (60.31, 59.02, *C*H_2), (27.73, 27.49, *C*H_3). MS (ES+) m/z: 398.1 [M+H^+], 420.1 [M+Na^+]. Reverse-phase HPLC, eluting with H_2O/CH_3CN from 90/10 to 0/100 in 30 min; flow = 1 mL/min, t_R = 14.62 mins 97.81%.

2-Hydroxy-2-methyl-*N*-(4-nitro-2-(trifluoromethyl)phenyl)-3-(pyridin-2-ylsulfinyl) propanamide [2 isomer A:1 isomer B] **(26)** yield 71%

^{1}H NMR ($CDCl_3$) δ 9.89 (s, 1H, N*H*), [8.65 (d, *J* = 9.5 Hz), isomer B, 8.82 (d, *J* = 9 Hz, 1H), isomer A, 1H, Ar*H*], [8.68 (d, *J* = 5 Hz) isomer B, 8.70 (d, *J* = 4.5 Hz) isomer A, 1H, Ar*H*], [8.55 (d, *J* = 2.5 Hz, isomer B), 8.59 (d, *J* = 2.5 Hz, isomer A), 1H, Ar*H*], [8.42 (dd, *J* = 2.5, 9 Hz, isomer B), 8.48 (dd, *J* = 3, 9.5 Hz, isomer A), 1H, Ar*H*), [7.92 (m), 8.04 (m), 2H, Ar*H*], [7.46 (ddd, *J* = 1, 4.5, 7.5 Hz) isomer B, 7.50 (ddd, *J* = 2, 4.5, 4.5 Hz) isomer A, 1H, Ar*H*], [6.39 (s), isomer A, 6.98 (s), isomer B, 1H, O*H*], [3.34 (d, *J* = 13.5 Hz), 3.92 (d, *J* = 13.5 Hz), 1H, isomer A, CH_2], [3.64 (d, *J* = 14 Hz), 3.70 (d, *J* = 13.5 Hz), 1H, isomer B, CH_2], [1.67 (s) isomer A, 1.75 (s) isomer B, 3H, CH_3]; ^{19}F NMR ($CDCl_3$) δ -61.64; ^{13}C NMR

($CDCl_3$) δ (173.31, 172.84, *C*=O), (163.81, 163.19, Ar*C*), (149.84, 149.57, Ar*C*H), 143.08 (Ar*C*), 140.63 (Ar*C*), (138.75, 138.62, Ar*C*H), (128.30, 128.25, Ar*C*H), 126.58 (m, *C*F_3), (125.38, 125.28, Ar*C*H), 123.61 (m, Ar*C*), (122.63, 122.01, Ar*C*H), 122.43 (m, Ar*C*H), (120.55, 120.16, Ar*C*H), (76.12, 75.59 *CO*H), (59.66, 59.48, *C*H_2), (27.63, 27.58, *C*H_3). MS (ES+) m/z: 418.1 [M+H^+], 440.1 [M+Na^+]. Reverse-phase HPLC, eluting with H_2O/CH_3CN from 90/10 to 0/100 in 30 min; flow = 1 mL/min, t_R = 16.02 mins.

2-Hydroxy-2-methyl-*N*-(4-nitro-2-(trifluoromethyl)phenyl)-3-(4-(trifluoromethyl) phenylsulfinyl)propanamide (27) yield 66 %

^{1}H NMR ($CDCl_3$) δ 9.90 (s, 1H, N*H*), 8.79 (d, *J* = 9 Hz, 1H, Ar*H*), 8.60 (d, *J* = 2.5 Hz, 1H, Ar*H*), 8.50 (dd, *J* = 2.5, 9 Hz, 1H, Ar*H*), 7.88 (d, *J* = 8.5 Hz, 2H, Ar*H*), 7.82 (d, *J* = 8.5 Hz, 2H, Ar*H*), 6.06 (bs, 1H, *OH*), 3.65 (d, *J*= 13 Hz, 1H, CH_2), 3.13 (d, *J* = 13.5 Hz, 1H, CH_2), 1.63 (s, 3H, CH_3); ^{19}F NMR ($CDCl_3$) δ -61.58 (s, 3F), -63.01 (s, 3F); ^{13}C NMR ($CDCl_3$) δ 173.37 (C=O), 147.11 (Ar*C*), 143.34 (Ar*C*), 140.37 (Ar*C*), 133.90 (q, $^2J_{C-F}$ = 32.6 Hz, Ar*C*), 128.25 (Ar*C*H), 126.74 (q, $^3J_{C-F}$ = 3.8 Hz, Ar*C*H), 124.23 (Ar*C*H), 123.28 (q, $^1J_{C-F}$ = 271 Hz, *C*F_3), 122.79 (Ar*C*H), 122.74 (q, $^1J_{C-F}$ = 271.9 Hz, *C*F_3), 122.47 (q, $^3J_{C-F}$ = 5.5 Hz, Ar*C*H), 120.35 (q, $^2J_{C-F}$ = 31.5 Hz, Ar*C*), 76.74 (*C*OH), 62.91 (*C*H_2), 28.09 (*C*H_3). MS [ESI, m/z]: 485.1 [M+H^+], 507.1 [M+Na^+], Reverse-phase HPLC, eluting with H_2O/CH_3CN from 90/10 to 0/100 in 30 min; flow = 1 mL/min, t_R = 19.66 min.

2-Hydroxy-2-methyl-*N*-(4-nitro-2-(trifluoromethyl)phenyl)-3-(2-(trifluoromethoxy) phenylsulfinyl)propanamide (28) yield 81%.

^{1}H NMR ($CDCl_3$) δ 9.82 (s, 1H, N*H*), 8.83 (d, *J* = 9 Hz, 1H, Ar*H*), 8.59 (d, *J* = 2.5 Hz, 1H, Ar*H*), 8.50 (dd, *J* = 2.5, 9 Hz, 1H, Ar*H*), 7.99 (m, 1H, Ar*H*), 7.63 (m, 2H, Ar*H*), 7.45 (m, 1H, Ar*H*), 5.85 (s, 1H, O*H*), 3.89 (d, *J*= 13 Hz, 1H, CH_2), 3.03 (d, *J*= 13 Hz, 1H, CH_2), 1.61 (s, 3H, CH_3); ^{19}F NMR ($CDCl_3$) δ -61.58 (s, 3*F*), -57.18 (s, 3*F*); ^{13}C NMR ($CDCl_3$) δ 173.14 (C=O), 154.94 (Ar*C*), 143.20 (Ar*C*), 141.94 (Ar*C*), 133.71, 133.20 (Ar*C*H), 131.83 (Ar*C*), 130.75 (Ar*C*), 130.24, 129.84 (Ar*C*H), 128.28, 128.03 (Ar*C*H), 125.53 (Ar*C*H), 124.64 (Ar*C*), 122.78 (Ar*C*H), 122.42 (q, $^3J_{C-F}$ = 5.6 Hz, Ar*C*H), 121.11 (Ar*C*), 119.81 (Ar*C*H), 77.20 (*C*OH), 59.41 (*C*H_2), 28.11 (*C*H_3). MS [ESI, m/z]: 501.1 [M+H^+], 523.0 [M+Na^+]. Reverse-phase HPLC, eluting with H_2O/CH_3CN from 90/10 to 0/100 in 30 min; flow = 1 mL/min, t_R = 20.01 mins**.**

3-(2,4-Difluorophenylsulfinyl)-2-hydroxy-2-methyl-*N*-(4-nitro-2-(trifluoromethyl) phenyl) propanamide (29) yield 80%.

^{1}H NMR ($CDCl_3$) δ 9.82 (s, 1H, N*H*), 8.81 (d, *J* = 9 Hz, 1H, Ar*H*), 8.60 (d, *J* = 3 Hz, 1H, Ar*H*), 8.50 (dd, *J* = 2.5, 9 Hz, 1H, Ar*H*), 7.21 (m, 1H, Ar*H*), 7.85 (m, 1H, Ar*H*), 6.99 (m, 1H, Ar*H*), 5.81 (s, 1H, O*H*), 3.85 (dd, *J*= 2, 13 Hz, 1H, CH_2), 3.12 (d, *J*= 13 Hz, 1H, CH_2), 1.62 (s, 3H, CH_3); ^{19}F NMR ($CDCl_3$) δ -61.58, -103.02, -109.35; ^{13}C NMR ($CDCl_3$) δ 173.18 (C=O), 157.92 (d, $^{1}J_{C-F}$ = 237.5 Hz, Ar*C*), 157.82 (d, $^{1}J_{C-F}$ = 237.5 Hz, Ar*C*), 143.29 (Ar*C*), 140.43 (Ar*C*), 128.26 (Ar*C*H), 127.38 (Ar*C*), 127.01 (m, Ar*C*H), 123.91 (m, *C*F_3), 122.84 (Ar*C*H), 122.44 (q, $^{3}J_{C-F}$ = 5 Hz, Ar*C*H), 119.97 (m, Ar*C*), 113.39 (m, Ar*C*H), 105.10 (m, Ar*C*H), 76.95 (*C*OH), 59.67 (*C*H_2), 28.16 (*C*H_3). MS (ES+) m/z: 453.1 [M+H^+], 475.0 [M+Na^+]. Reverse-phase HPLC, eluting with H_2O/CH_3CN from 90/10 to 0/100 in 30 min; flow = 1 mL/min, t_R = 18.00 mins.

***N*-(4-cyano-3-(trifluoromethyl)phenyl)-2-hydroxy-2-methyl-3-(4-(trifluoro methoxy)phenylsulfinyl)propanamide (30)** yield 76 %.

^{1}H NMR ($CDCl_3$) δ 9.46 (s, 1H, N*H*), 8.26 (d, *J* = 2 Hz, 1H, Ar*H*), 8.00 (dd, *J* = 2.5, 8.5 Hz, 1H, Ar*H*), 7.87 (d, *J* = 8.5 Hz, 1H, Ar*H*), 7.75 (d, *J*= 9 Hz, 2H, Ar*H*), 7.47 (d, *J*= 8 Hz, 2H, Ar*H*), 6.00 (s, 1H, O*H*), 3.57 (d, *J*= 13 Hz, 1H, CH_2), 3.07 (d, *J* = 13 Hz, 1H, CH_2), 1.61 (s, 3H, CH_3); ^{19}F NMR ($CDCl_3$) δ -62.18, -57.79; ^{13}C NMR ($CDCl_3$) δ 173.37 (C=O), 151.81 (Ar*C*), 141.23 (Ar*C*), 140.63 (Ar*C*), 135.89 (Ar*C*H), 134.06 (m, Ar*C*), 128.56 (m, *C*F_3), 125.79 (Ar*C*H), 122.12 (Ar*C*H), 122.00 (Ar*C*H), 121.05 (m, *C*F_3), 117.50 (q, $^{3}J_{C-F}$ = 4.6 Hz, Ar*C*H), 115.42 (*C*N), 105.13 (Ar*C*), 76.73 (*C*OH), 62.37 (*C*H_2), 28.25 (*C*H_3). MS (ES+) m/z: 481.1 [M+H^+], 503.1 [M+Na^+]. Reverse-phase HPLC, eluting with H_2O/CH_3CN from 90/10 to 0/100 in 30 min; flow = 1 mL/min, t_R = 19.58 mins.

2-Hydroxy-2-methyl-*N*-(4-nitro-2-(trifluoromethyl)phenyl)-3-(4-(trifluoromethoxy) phenylsulfinyl)propenamide (31) yield 73%.

^{1}H NMR ($CDCl_3$) δ 9.91 (s, 1H, N*H*), 8.79 (d, *J* = 9 Hz, 1H, Ar*H*), 8.60 (d, *J* = 2.5 Hz, 1H, Ar*H*), 8.50 (dd, *J* = 3, 9.5 Hz, 1H, Ar*H*), 7.75 (d, *J*= 9 Hz, 2H, Ar*H*), 7.46 (d, *J*= 8 Hz, 2H, Ar*H*), 6.22 (s, 1H, O*H*), 3.62 (d, *J*= 13.5 Hz, 1H, CH_2), 3.15 (d, *J*= 13 Hz, 1H, CH_2), 1.63 (s, 3H, CH_3); ^{19}F NMR ($CDCl_3$) δ -61.60 (s, 3F), -57.81 (s, 3F); ^{13}C NMR ($CDCl_3$) δ 173.45 (C=O), 151.71 (Ar*C*), 143.27 (Ar*C*), 140.84 (Ar*C*), 140.41 (Ar*C*), 128.26 (Ar*C*H), 125.77 (Ar*C*H), 122.74 (q, $^{1}J_{C-F}$ = 272.5 Hz, *C*F_3), 122.78 (Ar*C*H), 122.50 (q, $^{3}J_{C-F}$ = 6.3 Hz, Ar*C*H),

122.07 (Ar*C*H), 120.28 (q, $^{1}J_{C-F}$ = 257.9 Hz, *C*F_3), 120.13 (q, $^{2}J_{C-F}$ = 31.3 Hz, Ar*C*), 76.61 (*C*OH), 63.16 (*C*H_2), 28.10 (*C*H_3). MS (ES+) m/z: 501.1 [M+H^+], 523.1 [M+Na^+]. Reverse-phase HPLC, eluting with H_2O/CH_3CN from 90/10 to 0/100 in 30 min; flow = 1 mL/min, t_R = 21.23 mins.

***N*-(4-cyano-3-(trifluoromethyl)phenyl)-2-hydroxy-2-methyl-3-(5-(trifluoromethyl) pyridin-2-ylsulfinyl)propanamide (32a,** fast moving**)** yield 26%

^{1}H NMR ($CDCl_3$) δ 9.22 (s, 1H, N*H*), 8.94 (m, 1H, Ar*H*), 8.08 (m, 2H, Ar*H*), 7.97 (s, 1H, Ar*H*), 7.79 (m, 2H, Ar*H*), 6.18 (s, 1H, O*H*), 3.74 (d, *J*= 14 Hz, 1H, C*H*$_2$), 3.63 (d, *J* = 14 Hz, 1H, C*H*$_2$), 1.73 (s, 3H, C*H*$_3$); ^{19}F NMR ($CDCl_3$) δ -62.31 (s, 3F), -62.51 (s, 3F); ^{13}C NMR ($CDCl_3$) δ 172.33 (C=O), 166.85 (Ar*C*), 146.98 (q, $^{3}J_{C-F}$ = 3.8 Hz, Ar*C*H), 141.10 (Ar*C*), 135.86 (Ar*C*H), 135.28 (q, $^{3}J_{C-F}$ = 3.8 Hz, Ar*C*H), 134.31 (q, $^{2}J_{C-F}$ = 32.5 Hz, Ar*C*), 128.34 (q, $^{2}J_{C-F}$ = 33.6 Hz, Ar*C*), 122.01 (q, $^{1}J_{C-F}$ = 272.6 Hz, *C*F_3), 119.84 (q, $^{1}J_{C-F}$ = 269.1 Hz, *C*F_3), 117.01 (q, $^{3}J_{C-F}$ = 5 Hz, Ar*C*H), 115.34 (CN), 104.93 (Ar*C*), 76.56 (*C*OH), 57.35 (*C*H_2), 27.64 (*C*H_3). MS (ES+) m/z: 466.1 [M+H^+], 488.1 [M+Na^+]. Reverse-phase HPLC, eluting with H_2O/CH_3CN from 90/10 to 0/100 in 30 min; flow = 1 mL/min, t_R = 18.87 mins.

***N*-(4-cyano-3-(trifluoromethyl)phenyl)-2-hydroxy-2-methyl-3-(5-(trifluoro methyl) pyridin-2-ylsulfinyl)propanamide (32b,** slow moving**),** yield 43.7%.

^{1}H NMR ($CDCl_3$) δ 9.42 (s, 1H, N*H*), 8.97 (m, 1H, Ar*H*), 8.27 (dd, *J* = 2, 8 Hz, 1H, Ar*H*), 8.21 (d, *J* = 2 Hz, 1H, Ar*H*), 8.16 (d, *J* = 8 Hz, 1H, Ar*H*), 8.04 (dd, *J*= 2, 8.5 Hz, 1H, Ar*H*), 7.86 (d, *J*= 8.5 Hz, 1H, Ar*H*), 5.75 (s, 1H, O*H*), 4.00 (d, *J*= 13 Hz, 1H, C*H*$_2$), 3.27 (d, *J* = 13Hz, 1H, C*H*$_2$), 1.66 (s, 3H, C*H*$_3$); ^{19}F NMR ($CDCl_3$) δ -62.18 (s, 3F), -62.42 (s, 3F); ^{13}C NMR ($CDCl_3$) δ 172.94 (C=O), 167.70 (Ar*C*), 147.10 (q, $^{3}J_{C-F}$ = 3.8 Hz, Ar*C*H), 141.35 (Ar*C*), 135.90 (Ar*C*H), 135.80 (q, $^{3}J_{C-F}$ = 3.8 Hz, Ar*C*H), 134.00 (q, $^{2}J_{C-F}$ = 32.5 Hz, Ar*C*), 128.32 (q, $^{2}J_{C-F}$ = 33.8 Hz, Ar*C*), 122.71 (q, $^{1}J_{C-F}$ = 274.3 Hz, *C*F_3), 122.11 (q, $^{1}J_{C-F}$ = 272.3 Hz, *C*F_3), 122.02 (Ar*C*H), 119.88 (Ar*C*H), 117.49 (q, $^{3}J_{C-F}$ = 5 Hz, Ar*C*H), 115.45 (CN), 104.95 (Ar*C*), 76.40 (*C*OH), 60.14 (*C*H_2), 27.87 (*C*H_3). MS (ES+) m/z: 466.1 [M+H^+], 488.1 [M+Na^+]. t_R = 18.79 mins.

2-Hydroxy-2-methyl-*N*-(4-nitro-2-(trifluoromethyl)phenyl)-3-(5-(trifluoromethyl) pyridin-2-ylsulfinyl)propanamide (33a, fast moving**)** yield 31.2%.

^{1}H NMR ($CDCl_3$) δ 9.79 (s, 1H, N*H*), 8.95 (m, 1H, Ar*H*), 8.56 (d, *J* = 2.5 Hz, 1H, Ar*H*), 8.52 (d, *J* = 9.5 Hz, 1H, Ar*H*), 8.40 (dd, *J* = 2.5, 9.5 Hz, 1H, Ar*H*), 8.14 (d, 8.5 Hz, 1H, Ar*H*), 8.07

(ddd, *J*= 0.5, 2, 8.5 Hz, 1H, Ar*H*), 6.28 (s, 1H, O*H*), 3.75 (d, *J*= 14 Hz, 1H, CH_2), 3.63 (d, *J*= 14 Hz, 1H, CH_2), 1.76 (s, 3H, CH_3); ^{19}F NMR ($CDCl_3$) δ -61.60 (s, 3F), -62.47 (s, 3F); ^{13}C NMR ($CDCl_3$) δ 172.33 (*C*=O), 166.45 (Ar*C*), 146.87 (q, $^3J_{C-F}$ = 4.1 Hz, Ar*C*H), 142.96 (Ar*C*), 140.29 (Ar*C*), 135.39 (q, $^3J_{C-F}$ = 3.8 Hz, Ar*C*H), 128.30 (Ar*C*H), 128.05 (Ar*C*), 123.82 (Ar*C*), 122.44 (q, $^3J_{C-F}$ = 5 Hz, Ar*C*H), 121.76 (Ar*C*H), 121.64 (m, *C*F_3), 120.81 (m, *C*F_3), 120.36 (Ar*C*H), 76.53 (*C*OH), 57.50 (*C*H_2), 27.69 (*C*H_3). MS (ES+) m/z: 486.1 [M+H^+], 508.0 [M+Na^+]. Reverse-phase HPLC, eluting with H_2O/CH_3CN from 90/10 to 0/100 in 30 min; flow = 1 mL/min, t_R = 20.02 mins.

2-Hydroxy-2-methyl-*N*-(4-nitro-2-(trifluoromethyl)phenyl)-3-(5-(trifluoro methyl)pyridin-2-ylsulfinyl)propanamide (33b, slow moving**)** yield 49.7%.

^{1}H NMR ($CDCl_3$) δ 9.82 (s, 1H, N*H*), 8.97 (m, 1H, Ar*H*), 8.81 (d, *J* = 9 Hz, 1H, Ar*H*), 8.59 (d, *J* = 2.5 Hz, 1H, Ar*H*), 8.49 (dd, *J* = 2.5, 9 Hz, 1H, Ar*H*), 8.28 (dd, *J*=2, 8 Hz, 1H, Ar*H*), 8.19 (d, *J*= 8.5 Hz, 1H, Ar*H*), 5.77 (bs, 1H, O*H*), 4.02 (d, *J*= 13 Hz, 1H, CH_2), 3.29 (d, *J*= 13 Hz, 1H, CH_2), 1.65 (s, 3H, CH_3); ^{19}F NMR ($CDCl_3$) δ -61.58 (s, 3F), -62.40 (s, 3F); ^{13}C NMR ($CDCl_3$) δ 172.97 (*C*=O), 168.10 (Ar*C*), 147.01 (q, $^3J_{C-F}$ = 4.1 Hz, Ar*C*H), 143.22 (Ar*C*), 140.46 (Ar*C*), 135.85 (q, $^3J_{C-F}$ = 3.6 Hz, Ar*C*H), 128.34 (Ar*C*), 128.32 (Ar*C*H), 123.86 (Ar*C*), 122.74 (Ar*C*H), 122.47 (q, $^3J_{C-F}$ = 5.6 Hz, Ar*C*H), 119.12 (q, $^1J_{C-F}$ = 242.5, Hz, 2*C*F_3), 119.91 (Ar*C*H), 76.57(*C*OH), 59.39 (*C*H_2), 27.83 (*C*H_3). MS [ESI, m/z]: 486.1 [M+H^+], 508.0 [M+Na^+]. Reverse-phase HPLC, eluting with H_2O/CH_3CN from 90/10 to 0/100 in 30 min; flow = 1 mL/min, t_R = 19.99 mins.

3-(3,4-Difluorophenylsulfinyl)-2-hydroxy-2-methyl-*N*-(4-nitro-2-(trifluoromethyl) phenyl) propanamide (34a, fast moving**)** yield 26%.

^{1}H NMR ($CDCl_3$) δ 9.78 (s, 1H, N*H*), 8.59 (d, *J*= 9.5 Hz, 1H, Ar*H*), 8.57 (d, *J*= 2.5 Hz, 1H, Ar*H*), 8.42 (dd, *J* = 2.5, 9 Hz, 1H, Ar*H*), 7.56 (m, 1H, Ar*H*), 7.40 (m, 1H, Ar*H*), 7.35 (m, 1H, Ar*H*), 6.00 (s, 1H, O*H*), 3.43 (d, *J*= 14 Hz, 1H, CH_2), 3.23 (d, *J*= 14 Hz, 1H, CH_2), 1.84 (s, 3H, CH_3); ^{19}F NMR ($CDCl_3$) δ -61.64 (s, 3F), -130.81 (s, F), -132.56 (s, F); ^{13}C NMR ($CDCl_3$) δ 172.12 (C=O), 153.52 (Ar*C*), 153.44 (Ar*C*), 143.06 (Ar*C*), 140.33 (Ar*C*), 137.72 (Ar*C*), 128.22 (Ar*C*H), 123.81 (Ar*C*), 122.45 (q, $^3J_{C-F}$ = 5 Hz, Ar*C*H), 121.81 (Ar*C*H), 120.75 (m, Ar*C*H), 120.55 (Ar*C*), 118.83 (d, $^2J_{C-F}$ = 18.8 Hz, Ar*C*H), 113.93 (d, $^2J_{C-F}$ = 20 Hz, Ar*C*H), 76.66 (*C*OH), 59.62 (*C*H_2), 26.67 (*C*H_3). MS (ES+) m/z: 453.1 ([M+H]$^+$, 475.0 [M+Na]$^+$. HPLC, t_R = 20.39 min.

3-(3,4-Difluorophenylsulfinyl)-2-hydroxy-2-methyl-*N*-(4-nitro-2-(trifluoromethyl) phenyl)propanamide (34b, slow moving**)** yield 48%

^{1}H NMR ($CDCl_3$) δ 9.86 (s, 1H, N*H*), 8.79 (d, *J*= 9.5 Hz, 1H, Ar*H*), 8.60 (d, *J*= 2.5 Hz, 1H, Ar*H*), 8.51 (dd, *J* = 3, 9.5 Hz, 1H, Ar*H*), 7.60 (m, 1H, Ar*H*), 7.43 (m, 2H, Ar*H*), 5.94 (s, 1H, O*H*), 3.58 (d, *J*= 13 Hz, 1H, CH_2), 3.07 (d, *J*= 13 Hz, 1H, CH_2), 1.61 (s, 3H, CH_3). ^{19}F NMR ($CDCl_3$) δ -61.58 (s, 3F), -130.65 (s, F), -132.17 (s, F); ^{13}C NMR ($CDCl_3$) δ 173.37 (C=O), 152.28 (Ar*C*), 151.54 (Ar*C*), 143.32 (Ar*C*), 140.34 (Ar*C*), 139.22 (Ar*C*), 128.27 (Ar*C*H), 122.81 (Ar*C*H), 122.50 (q, $^{3}J_{C\text{-}F}$ = 6.3 Hz, Ar*C*H), 123.81 (Ar*C*), 120.08 (Ar*C*), 120.50 (m, Ar*C*H), 119.05 (d, $^{2}J_{C\text{-}F}$ = 18.8 Hz, Ar*C*H), 113.56 (d, $^{2}J_{C\text{-}F}$ = 18.8 Hz, Ar*C*H), 76.83 (*C*OH), 62.30 (CH_2), 28.22 (CH_3). MS (ES+) m/z: 453.1 [M+H$^+$], 475.0 [M+Na$^+$]. Reverse-phase HPLC, eluting with H_2O/CH_3CN from 90/10 to 0/100 in 30 min; flow = 1 mL/min, t_R = 20.16 mins**.**

2. Cell growth inhibition viability Assay

All bicalutamide derivatives were screened for their antiproliferative activity using the Oncotest monolayer assay against four human prostate cancer cell lines (22Rv1, DU-145, LNCaP and VCap). Bicalutamide and Enzalutamide were used as positive controls. A modified propidium iodide (PI) based monolayer assay was used to assess the anti-cancer activity of the compounds. Briefly, cells were harvested from exponential phase cultures, counted and plated in 96- well flat-bottom microtiter plates at a cell density of 8000–12,000 cells/well. After a 24 h recovery period to allow the cells to resume exponential growth, 10 μL of culture medium (six control wells/plate) or culture medium with test compound were added. The compounds were applied in half-log increments at 10 concentrations in triplicate. After a total treatment period of 96 h, cells were washed with 200 μL PBS to remove dead cells and debris. Then, 200 mL of a solution containing 7 mg/mL propidium iodide (PI) and 0.1% (v/v) Triton X-100 was added. After an incubation period of 1–2h at room temperature, fluorescence (FU) was measured using the EnSpire Multimode Plate Reader (excitation l= 530 nm, emission l = 620 nm) to quantify the amount of attached viable cells. IC_{50} values were calculated by 4 parameter non-linear curve fit using Oncotest Warehouse Software. For calculation of mean IC_{50} values the geometric mean was used.[38]

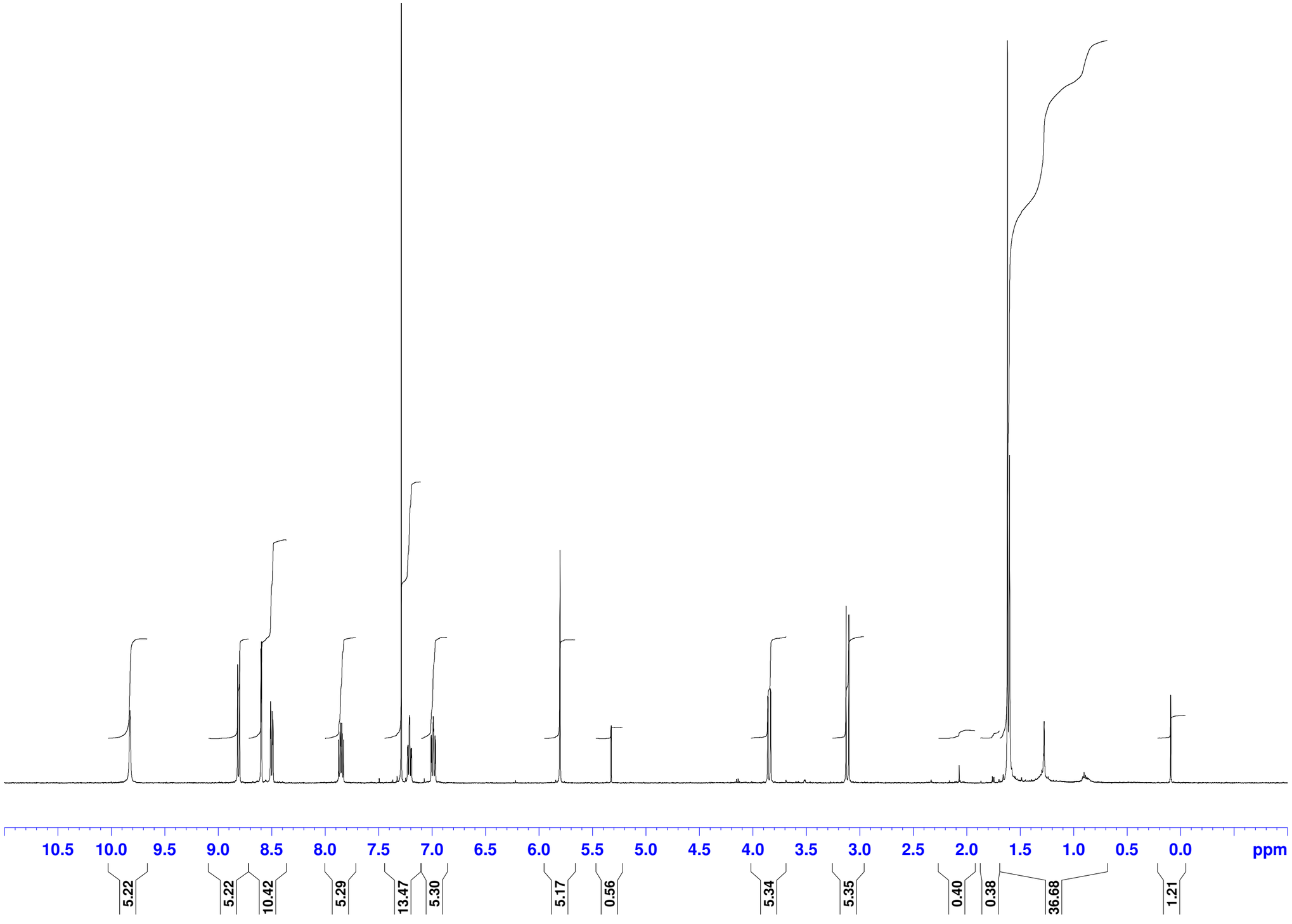
3. X-ray crystal structure determination of compound 34

Single-crystal XRD data were collected at room temperature on an Agilent SuperNova Dual Atlas diffractometer with a mirror monochromator using Cu (λ =1.5418 Å) radiation. Crystal structures were solved using SHELXS [35] and refined using SHELXL. [36] Non-hydrogen atoms were refined with anisotropic displacement parameters. Hydrogen atoms were inserted in idealized positions, and a riding model was used with Uiso set at 1.2 or 1.5 times the value of Ueq for the atom to which they are bonded. **34a**: $C_{17}H_{13}F_5N_2O_5S$, FW = 452.35, T = 296(2) K, Monoclinic, P21/c, a = 14.3383(3) Å, b = 12.1211(2) Å, c = 10.8432(2) Å, β = 93.254(2), V = 1881.47(6) $Å^3$, Z = 4, D_{cal} = 1.597 Mg/m^3, m = 2.309 mm^{-1}, Crystal size = 0.436 x 0.187 x 0.113 mm^3, Reflections collected = 17738, Independent reflections = 3946, R_{int} = 0.0268, Parameters = 274, G-o-f = 1.065, Final R1 = 0.0403, wR2 = 0.1116 on (I > 2s(I)), R1 = 0.0473, wR2 = 0.1199 on all data. **34b**: $C_{17}H_{13}F_5N_2O_5S$, FW = 452.35, T = 296(2) K, Monoclinic, I2/a, a = 13.1919(3) Å, b = 11.2526(2) Å, c = 25.9866(5) Å, β = 99.610(2), V = 3803.40(13) $Å^3$, Z = 8, D_{cal} = 1.580 Mg/m^3, m = 2.285 mm^{-1}, Crystal size = 0.395 x 0.225 x 0.173 mm^3, Reflections collected = 17851, Independent reflections = 3997, R_{int} = 0.0185, Parameters = 273, G-o-f = 1.051, Final R1 = 0.0381, wR2 = 0.1041 on (I > 2s(I)), R1 = 0.0401, wR2 = 0.1069 on all data. CCDC 2040881-2040882 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/structures.

4. Docking studies

The X-ray crystal structure of the human androgen receptor – ligand binding domain hAR-LBD was downloaded from the Protein Data Bank (PDB code; 3RLJ)[26] and prepared for docking using the MOE (Molecular Operating Environment)[39] protein preparation tools. The chemical structures of our compounds were constructed, rendered and minimized with the MMFF94x force field in MOE. The docking simulations were performed using MOE default settings. The docking output database was saved as a mol2 file, and the visual inspection of the docking modes was performed in MOE.

Compound 29




```
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PROCNO                   1
Date_             20140206
Time                 16.09
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PULPROG               zg30
TD                   65536
SOLVENT              CDCl3
NS                      16
DS                       2
SWH              10330.578 Hz
FIDRES            0.157632 Hz
AQ               3.1719923 sec
RG                     812
DW                  48.400 use
DE                   6.50 use
TE                  291.2 K
D1               1.00000000 sec
TD0                      1

======== CHANNEL f1 =======
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P1                   11.50 use
PL1                  -1.00 dB
PL1W           11.38419914 W
SFO1           500.1330885 MHz
SI                   65536
SF             500.1300000 MHz
WDW                     EM
SSB                      0
LB                    0.30 Hz
GB                       0
PC                    1.00
```
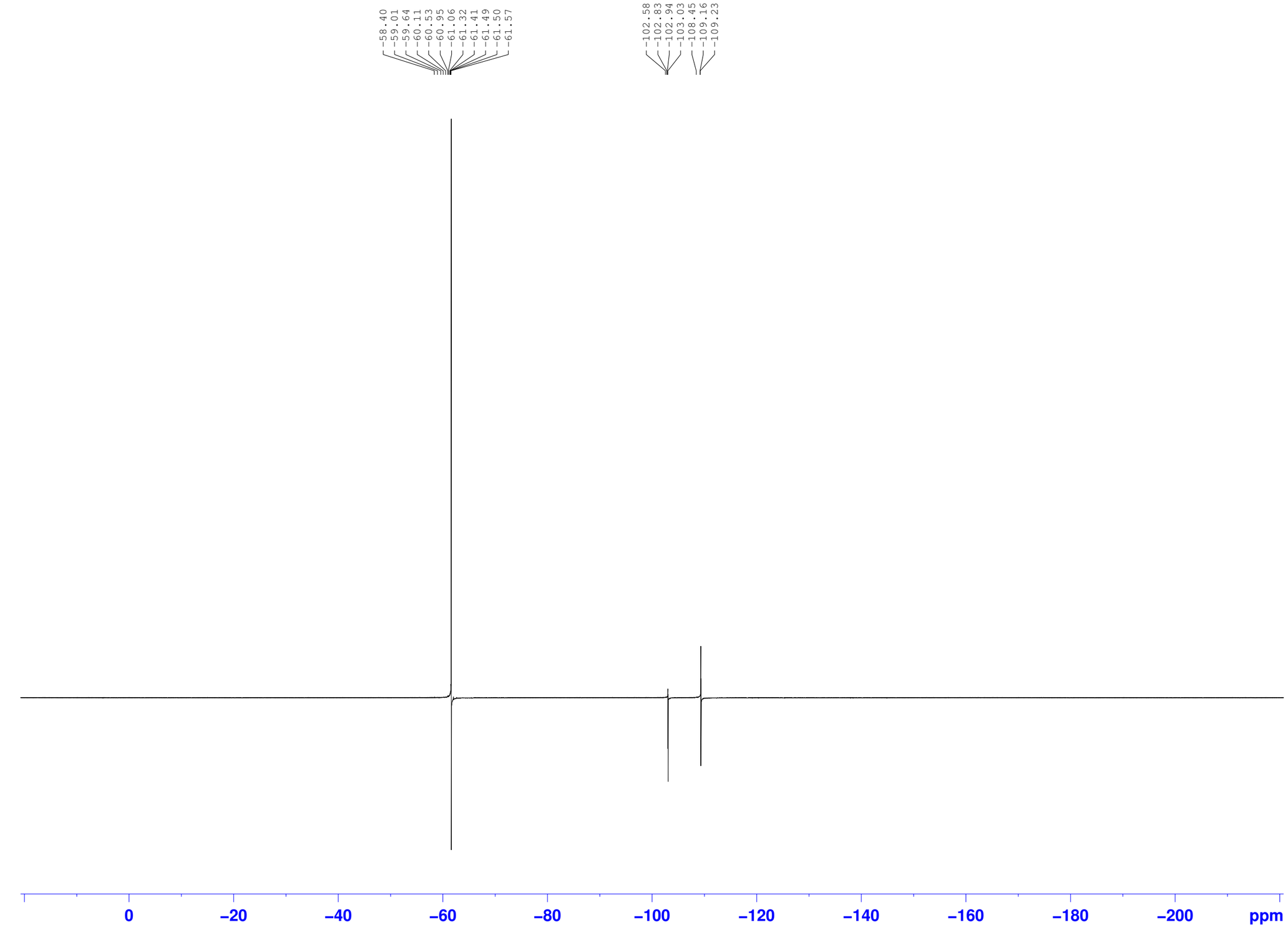
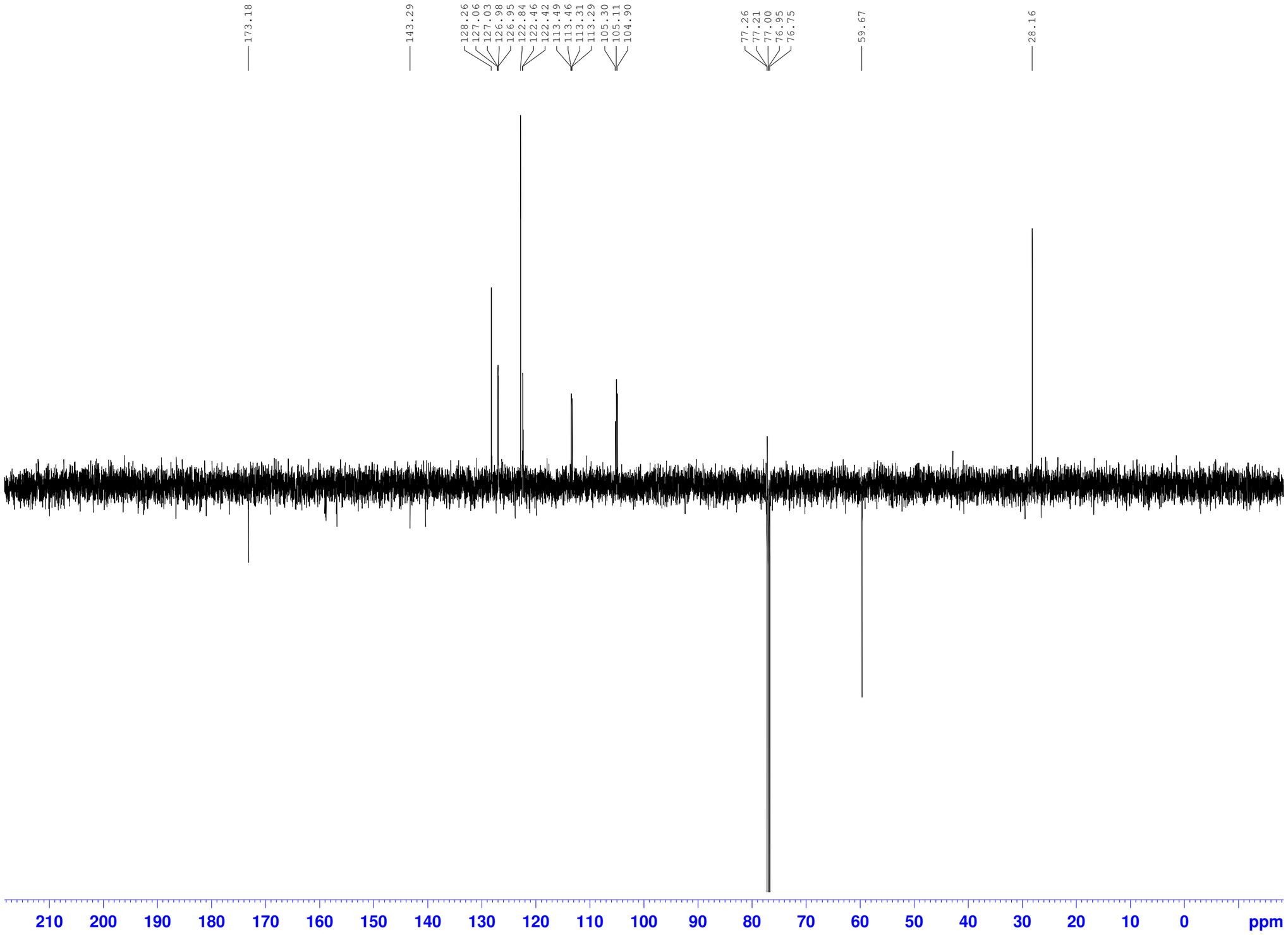

Compound 29




```
NAME          CM-SK65ox(4)
EXPNO                    2
PROCNO                   1
Date_             20140206
Time                 16.11
INSTRUM          Avance500
PROBHD    5 mm QNP 1H/13
PULPROG           zgfhigqn
TD                 131072
SOLVENT              CDCl3
NS                      16
DS                       4
SWH             113636.367 Hz
FIDRES            0.866977 Hz
AQ                0.5767668 sec
RG                     2300
DW                    4.400 use
DE                     6.00 use
TE                   291.2 K
D1              1.00000000 sec
D11             0.03000000 sec
D12             0.00002000 sec
TD0                      1

======== CHANNEL f1 =======
NUC1                   19F
P1                   18.60 use
PL1                  -1.50 dB
PL1W          11.14113998 W
SFO1          470.5453180 MHz

======== CHANNEL f2 =======
CPDPRG2            waltz16
NUC2                    1H
PCPD2                80.00 use
PL2                  -2.00 dB
PL12                 14.85 dB
PL2W          14.33185768 W
PL12W          0.29600734 W
SFO2          500.1320005 MHz
SI                   65536
SF            470.5923770 MHz
WDW                     EM
SSB                      0
LB                    0.30 Hz
GB                       0
PC                    1.40
```

Compound 29

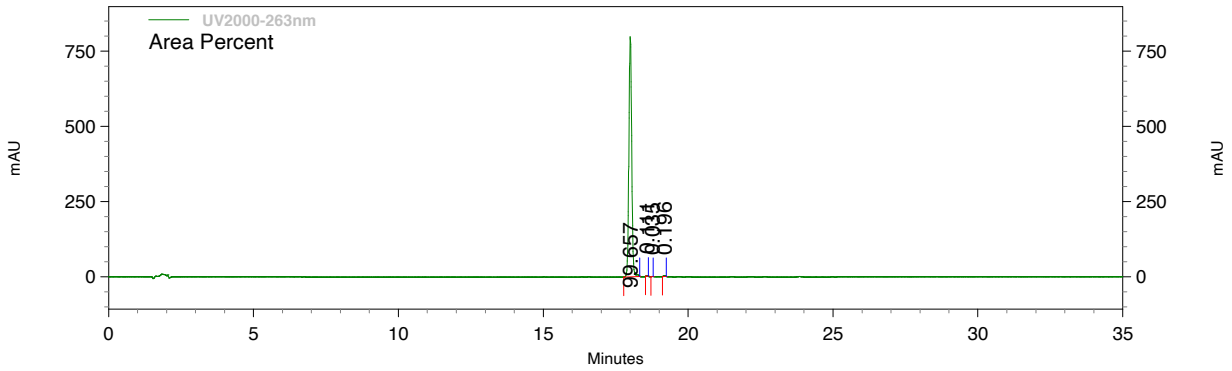


NAME	CM-SK64(65ox_4)
EXPNO	1
PROCNO	1
Date_	20140211
Time	19.16
INSTRUM	Avance500
PROBHD	5 mm QNP 1H/13
PULPROG	pendant
TD	65536
SOLVENT	CDCl3
NS	512
DS	4
SWH	29761.904 Hz
FIDRES	0.454131 Hz
AQ	1.1010548 sec
RG	3250
DW	16.800 usec
DE	12.00 usec
TE	298.1 K
CNST2	145.0000000
D1	2.00000000 sec
D4	0.00172414 sec
D12	0.00002000 sec
D15	0.00431034 sec
D20	0.00345000 sec
TD0	4
======== CHANNEL f1 ========	
NUC1	13C
P1	7.20 usec
P2	14.40 usec
PL1	-2.00 dB
PL1W	101.27846527 W
SFO1	125.7703643 MHz
======== CHANNEL f2 ========	
CPDPRG2	waltz16
NUC2	1H
P3	11.50 usec
P4	23.00 usec
PCPD2	80.00 usec
PL2	-2.00 dB
PL12	14.85 dB
PL2W	14.33185768 W
PL12W	0.29600734 W
SFO2	500.1320005 MHz
SI	32768
SF	125.7577890 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.40

Compound 29

Area % Report

Sample ID: SK64_2nd -- C:\Documents and Settings\user\Desktop\Sahar\Data\SK64_2nd-ACN_W_10-90-263nm.met-14-02-2014 11-40-54.dat
Method: C:\Documents and Settings\user\Desktop\Sahar\ACN_W_10-90-263nm.met
Acquired: 14/02/2014 11:41:38; Printed: 14/02/2014 12:20:19
Analysis Comment: {Data Description}

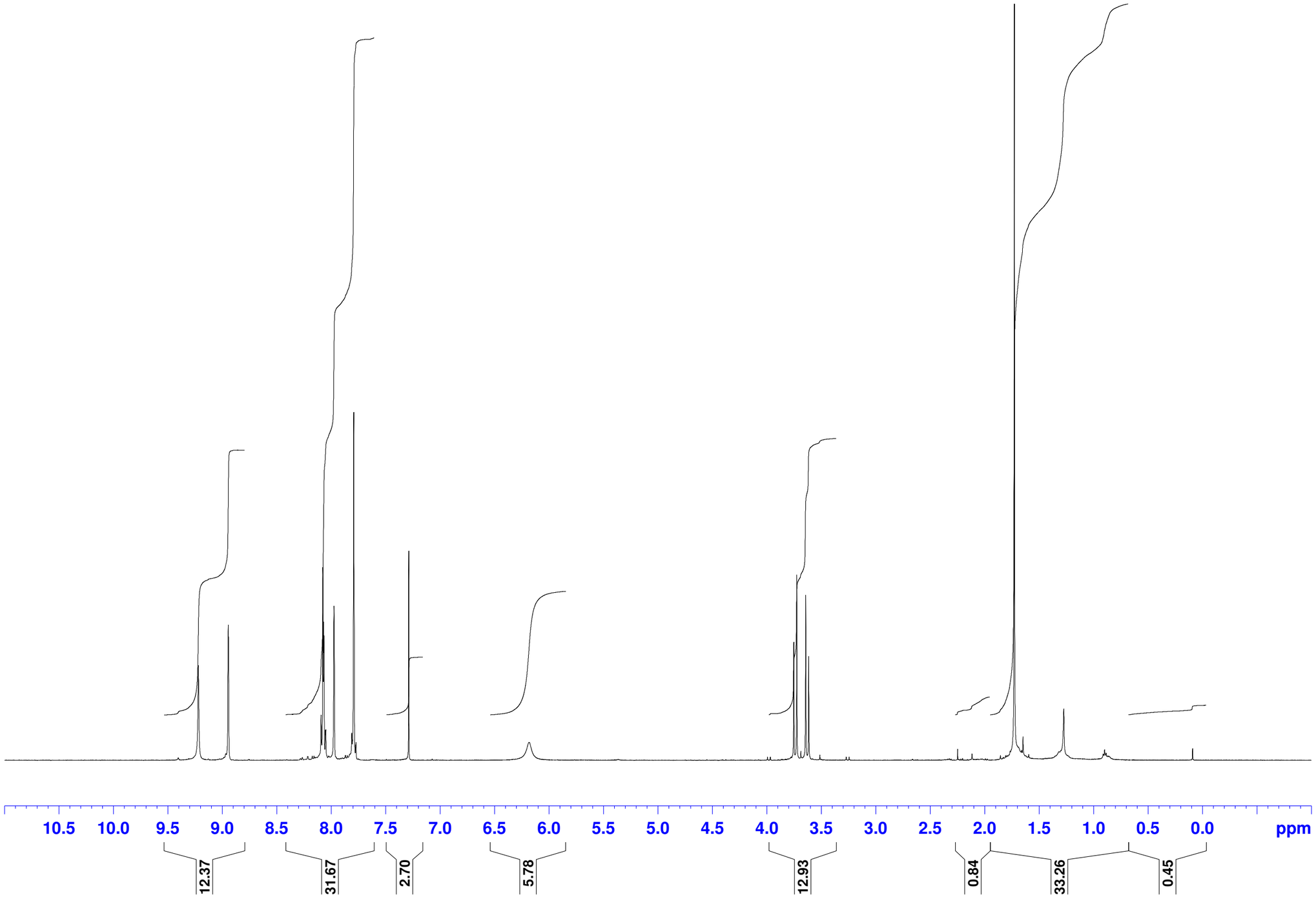


UV2000-263nm Results (System (14/02/2014 12:19:57) (Reprocessed))

Retention Time	Area	Area %	Height	Height %
18.003	5343414	99.66	797818	99.43
18.573	5977	0.11	1757	0.22
18.763	1897	0.04	608	0.08
19.175	10515	0.20	2192	0.27

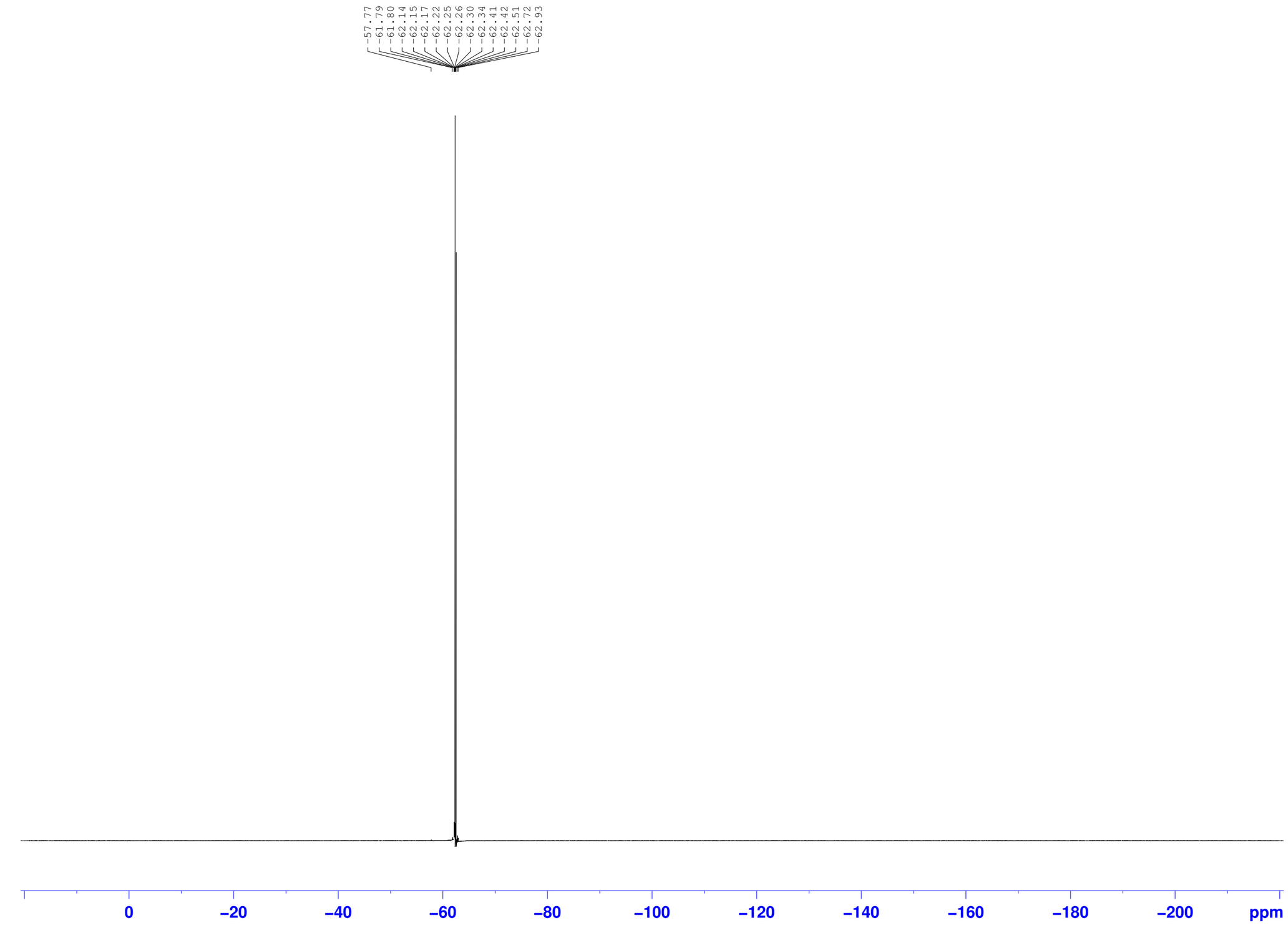
Totals	5361803	100.00	802375	100.00

Compound 32a



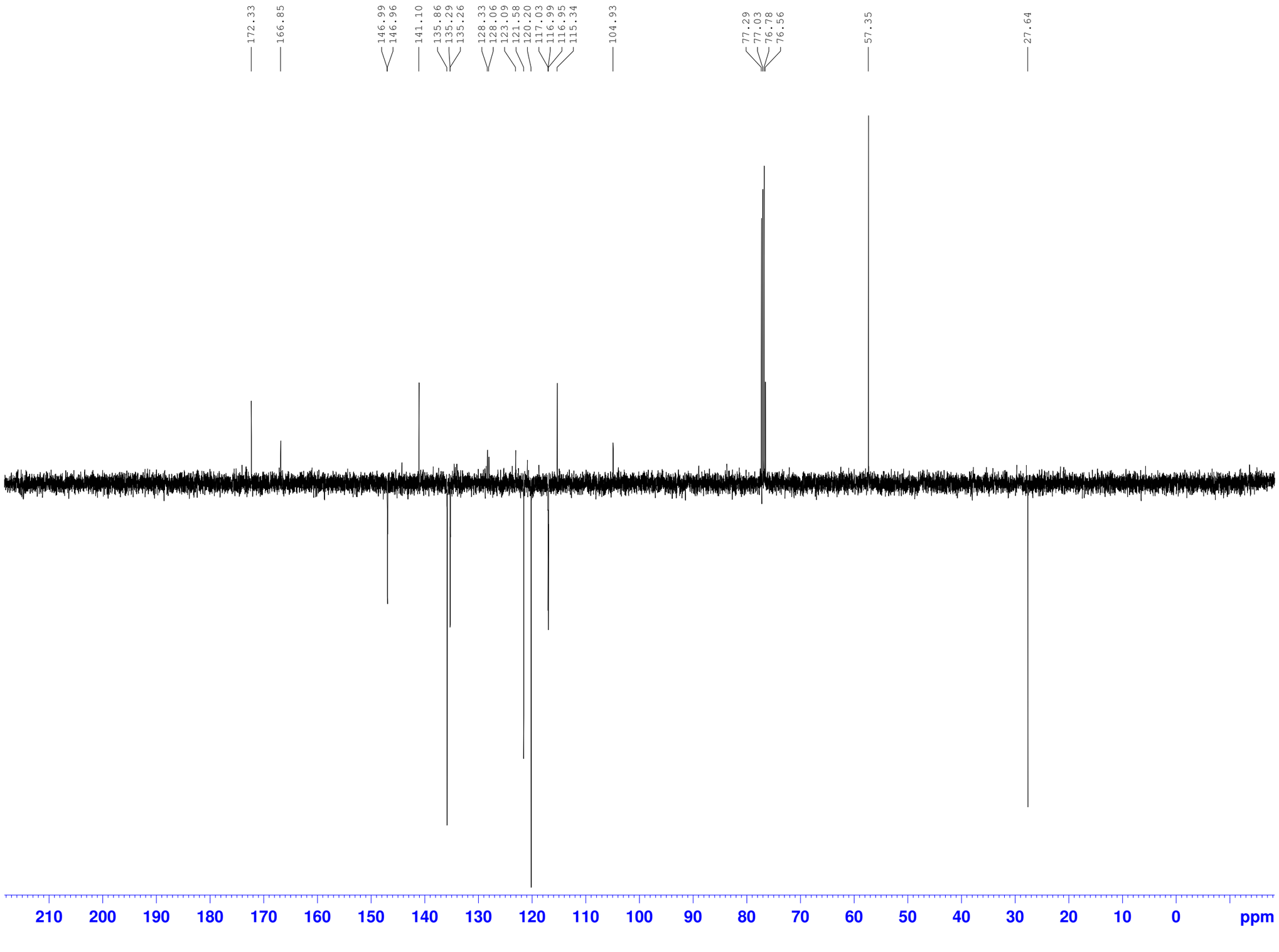

```
NAME      CM-SK41_31ox(2)
EXPNO                  1
PROCNO                 1
Date_           20131204
Time               13.46
INSTRUM        Avance500
PROBHD   5 mm QNP 1H/13
PULPROG             zg30
TD                 65536
SOLVENT            CDCl3
NS                    16
DS                     2
SWH           10330.578 Hz
FIDRES         0.157632 Hz
AQ             3.1719923 sec
RG                   512
DW                48.400 use
DE                 6.50 use
TE                292.3 K
D1            1.00000000 sec
TD0                    1

======== CHANNEL f1 =======
NUC1                  1H
P1                 11.50 use
PL1                -1.00 dB
PL1W        11.38419914 W
SFO1        500.1330885 MHz
SI                 65536
SF          500.1300000 MHz
WDW                   EM
SSB                    0
LB                0.30 Hz
GB                     0
PC                 1.00
```

Compound 32a




```
NAME          CM-SK41_31ox(2)
EXPNO                       2
PROCNO                      1
Date_            20131204
Time                  13.48
INSTRUM           Avance500
PROBHD     5 mm QNP 1H/13
PULPROG            zgfhigqn
TD                    131072
SOLVENT               CDCl3
NS                       16
DS                        4
SWH              113636.367 Hz
FIDRES             0.866977 Hz
AQ                 0.5767668 sec
RG                      1440
DW                     4.400 use
DE                     6.00 use
TE                    292.6 K
D1               1.00000000 sec
D11              0.03000000 sec
D12              0.00002000 sec
TD0                         1

======== CHANNEL f1 =======
NUC1                      19F
P1                     18.60 use
PL1                    -1.50 dB
PL1W            11.14113998 W
SFO1           470.5453180 MHz

======== CHANNEL f2 =======
CPDPRG2             waltz16
NUC2                      1H
PCPD2                  80.00 use
PL2                    -2.00 dB
PL12                   14.85 dB
PL2W            14.33185768 W
PL12W            0.29600734 W
SFO2           500.1320005 MHz
SI                      65536
SF             470.5923770 MHz
WDW                        EM
SSB                         0
LB                      0.30 Hz
GB                          0
PC                      1.40
```

Compound 32a

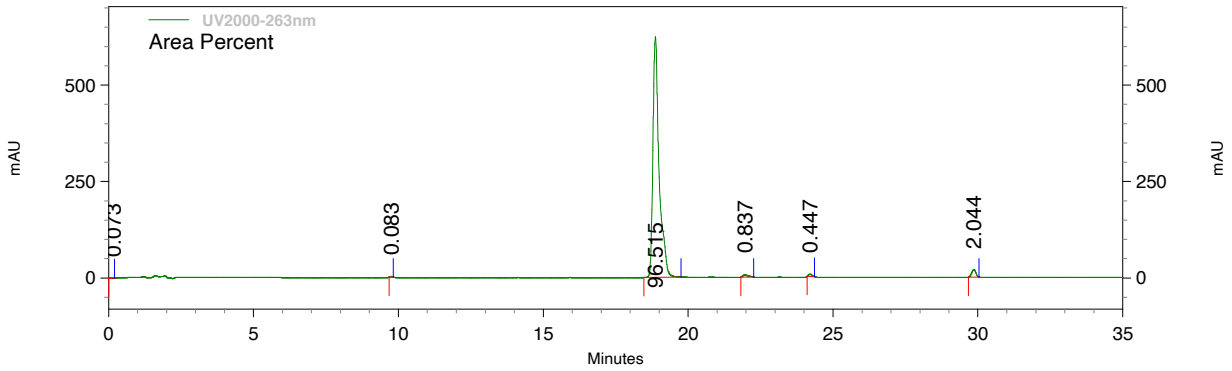


NAME	CM-SK41_31ox(2)	
EXPNO	3	
PROCNO	1	
Date_	20131204	
Time	13.55	
INSTRUM	Avance500	
PROBHD	5 mm QNP 1H/13	
PULPROG	pendant	
TD	65536	
SOLVENT	CDCl3	
NS	256	
DS	4	
SWH	29761.904	Hz
FIDRES	0.454131	Hz
AQ	1.1010548	sec
RG	3250	
DW	16.800	usec
DE	12.00	usec
TE	292.8	K
CNST2	145.0000000	
D1	2.00000000	sec
D4	0.00172414	sec
D12	0.00002000	sec
D15	0.00431034	sec
D20	0.00345000	sec
TD0	2	
======== CHANNEL f1 ========		
NUC1	13C	
P1	7.20	usec
P2	14.40	usec
PL1	-2.00	dB
PL1W	101.27846527	W
SFO1	125.7703643	MHz
======== CHANNEL f2 ========		
CPDPRG2	waltz16	
NUC2	1H	
P3	11.50	usec
P4	23.00	usec
PCPD2	80.00	usec
PL2	-2.00	dB
PL12	14.85	dB
PL2W	14.33185768	W
PL12W	0.29600734	W
SFO2	500.1320005	MHz
SI	32768	
SF	125.7577890	MHz
WDW	EM	
SSB	0	
LB	1.00	Hz
GB	0	
PC	1.40	

Compound 32a

Area % Report

Sample ID: SK41 -- C:\Documents and Settings\user\Desktop\Sahar\Data\SK41-ACN_W_10-90-263nm.met-02-12-2013 15-34-41.dat
Method: C:\Documents and Settings\user\Desktop\Sahar\ACN_W_10-90-263nm.met
Acquired: 02/12/2013 15:35:15; Printed: 02/12/2013 16:18:18
Analysis Comment: {Data Description}

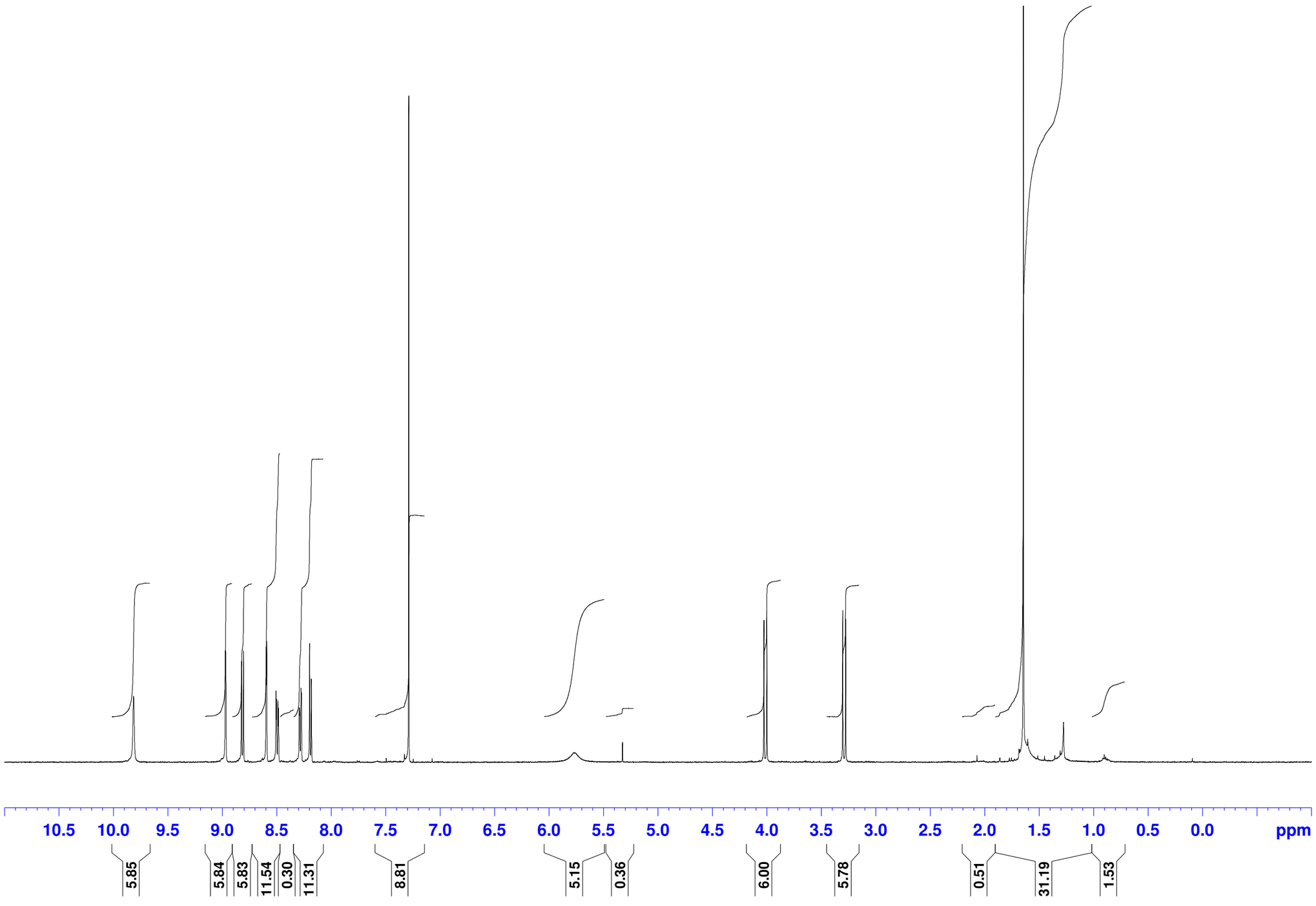


UV2000-263nm Results (System (02/12/2013 16:17:44) (Reprocessed))

Retention Time	Area	Area %	Height	Height %
0.165	7002	0.07	326	0.05
9.747	7991	0.08	1487	0.23
18.870	9276786	96.52	624297	95.06
21.953	80487	0.84	6096	0.93
24.198	43005	0.45	5271	0.80
29.853	196472	2.04	19287	2.94

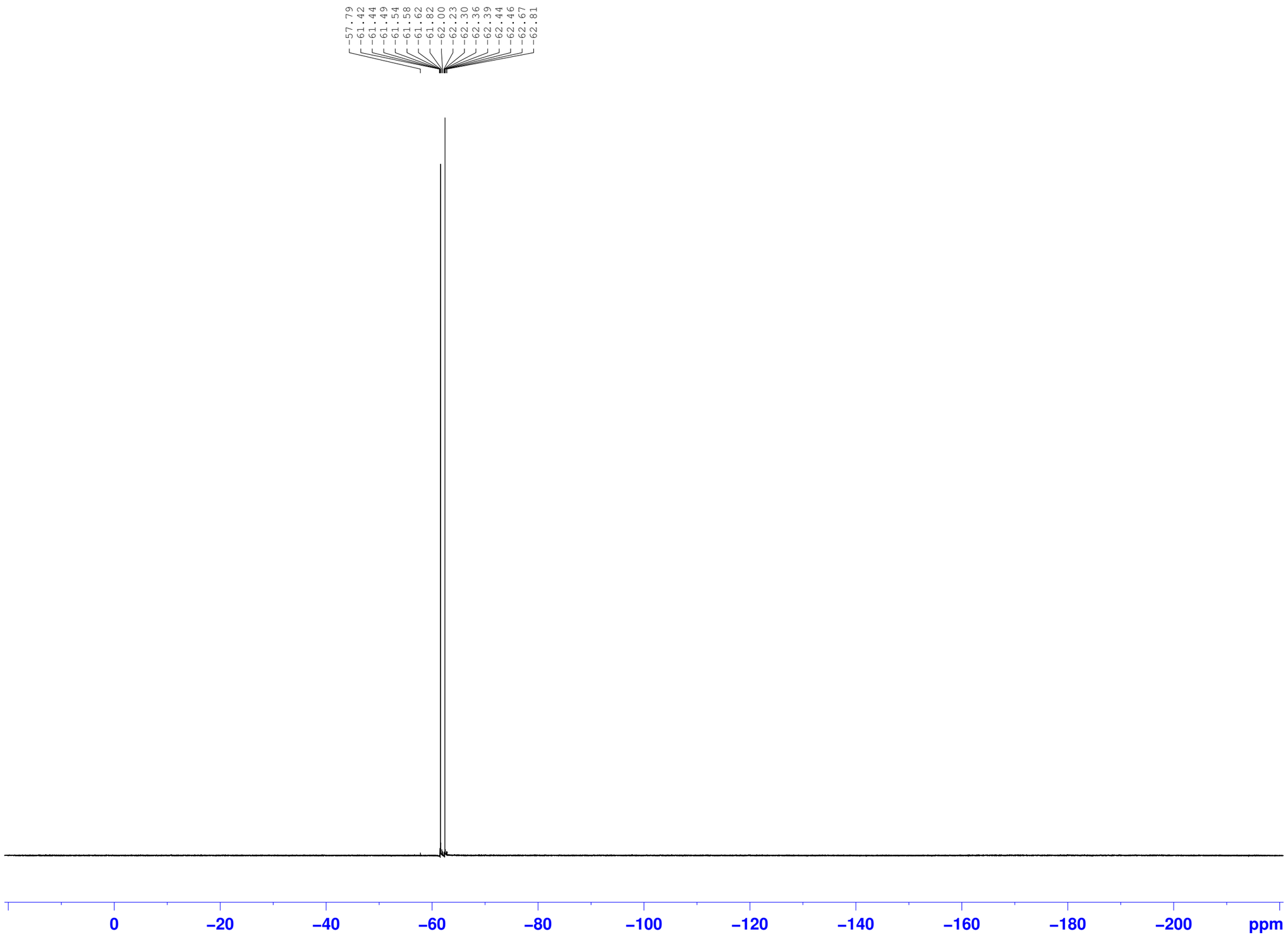
Totals	9611743	100.00	656764	100.00

Compound 33b



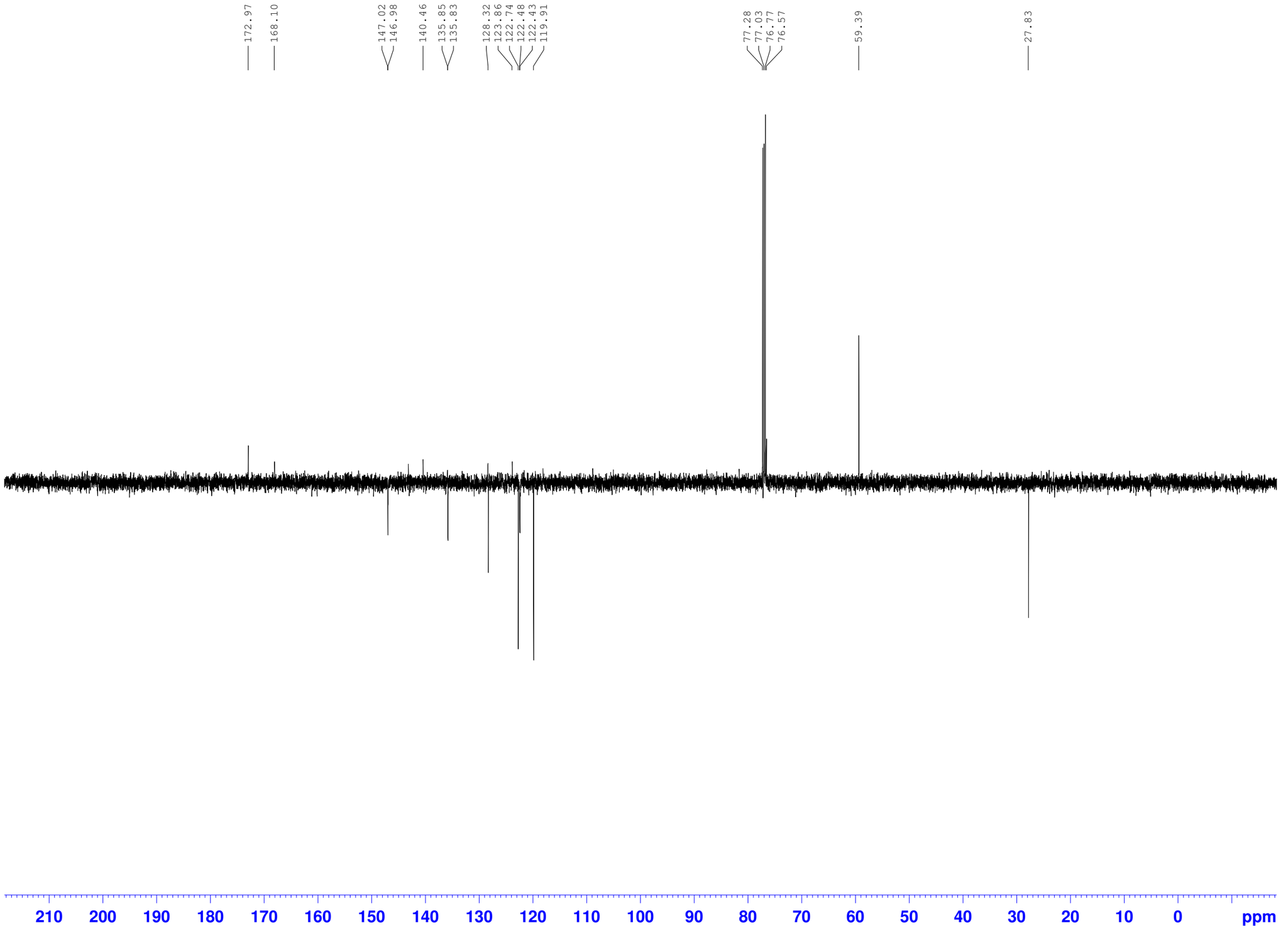

```
NAME          CM-SK62(62B)
EXPNO                    1
PROCNO                   1
Date_             20140117
Time                 9.11
INSTRUM          Avance500
PROBHD   5 mm QNP 1H/13
PULPROG               zg30
TD                   65536
SOLVENT              CDCl3
NS                      16
DS                       2
SWH             10330.578 Hz
FIDRES           0.157632 Hz
AQ               3.1719923 sec
RG                     724
DW                  48.400 use
DE                   6.50 use
TE                  291.2 K
D1              1.00000000 sec
TD0                      1

======== CHANNEL f1 =======
NUC1                    1H
P1                   11.50 use
PL1                  -1.00 dB
PL1W           11.38419914 W
SFO1           500.1330885 MHz
SI                   65536
SF             500.1300000 MHz
WDW                     EM
SSB                      0
LB                  0.30 Hz
GB                       0
PC                    1.00
```

Compound 33b




```
NAME          CM-SK62(62B)
EXPNO                    2
PROCNO                   1
Date_             20140117
Time                 9.12
INSTRUM         Avance500
PROBHD    5 mm QNP 1H/13
PULPROG          zgfhigqn
TD                 131072
SOLVENT              CDCl3
NS                      16
DS                       4
SWH            113636.367 Hz
FIDRES           0.866977 Hz
AQ               0.5767668 sec
RG                    2300
DW                   4.400 use
DE                   6.00 use
TE                  291.4 K
D1             1.00000000 sec
D11            0.03000000 sec
D12            0.00002000 sec
TD0                      1

======== CHANNEL f1 =======
NUC1                   19F
P1                   18.60 use
PL1                  -1.50 dB
PL1W          11.14113998 W
SFO1          470.5453180 MHz

======== CHANNEL f2 =======
CPDPRG2           waltz16
NUC2                   1H
PCPD2                80.00 use
PL2                  -2.00 dB
PL12                 14.85 dB
PL2W          14.33185768 W
PL12W          0.29600734 W
SFO2          500.1320005 MHz
SI                   65536
SF            470.5923770 MHz
WDW                     EM
SSB                      0
LB                    0.30 Hz
GB                       0
PC                    1.40
```

Compound 33b

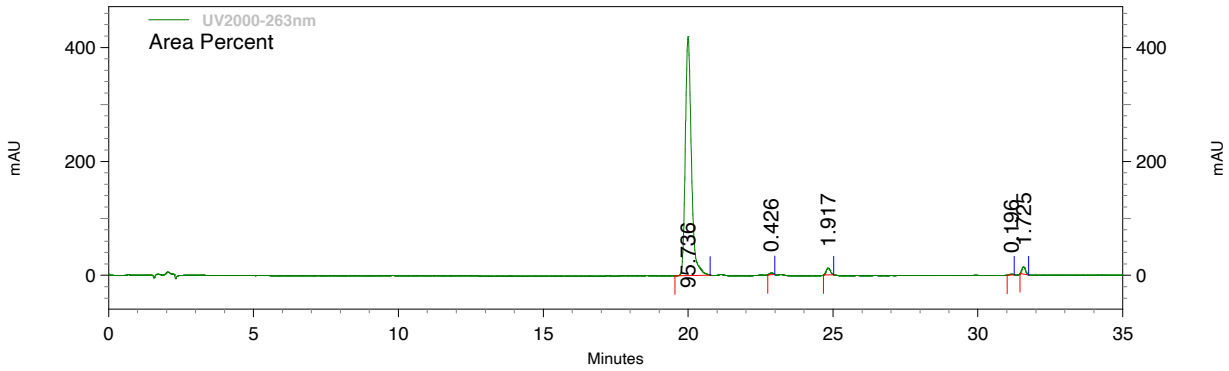


NAME	CM-SK62(B)	
EXPNO	1	
PROCNO	1	
Date_	20140121	
Time	19.11	
INSTRUM	Avance500	
PROBHD	5 mm QNP 1H/13	
PULPROG	pendant	
TD	65536	
SOLVENT	CDCl3	
NS	512	
DS	4	
SWH	29761.904	Hz
FIDRES	0.454131	Hz
AQ	1.1010548	sec
RG	3250	
DW	16.800	usec
DE	12.00	usec
TE	291.7	K
CNST2	145.0000000	
D1	2.00000000	sec
D4	0.00172414	sec
D12	0.00002000	sec
D15	0.00431034	sec
D20	0.00345000	sec
TD0	4	
======== CHANNEL f1 ========		
NUC1	13C	
P1	7.20	usec
P2	14.40	usec
PL1	-2.00	dB
PL1W	101.27846527	W
SFO1	125.7703643	MHz
======== CHANNEL f2 ========		
CPDPRG2	waltz16	
NUC2	1H	
P3	11.50	usec
P4	23.00	usec
PCPD2	80.00	usec
PL2	-2.00	dB
PL12	14.85	dB
PL2W	14.33185768	W
PL12W	0.29600734	W
SFO2	500.1320005	MHz
SI	32768	
SF	125.7577890	MHz
WDW	EM	
SSB	0	
LB	1.00	Hz
GB	0	
PC	1.40	

Compound 33b

Area % Report

Sample ID: SK62B -- C:\Documents and Settings\user\Desktop\Sahar\Data\SK62B-ACN_W_10-90-263nm.met-16-01-2014 16-17-57.dat
Method: C:\Documents and Settings\user\Desktop\Sahar\ACN_W_10-90-263nm.met
Acquired: 16/01/2014 16:20:43; Printed: 16/01/2014 17:01:28
Analysis Comment: {Data Description}



UV2000-263nm Results (System (16/01/2014 17:01:10) (Reprocessed))

Retention Time	Area	Area %	Height	Height %
19.997	6105512	95.74	419343	93.48
22.868	27186	0.43	3126	0.70
24.828	122253	1.92	11997	2.67
31.150	12477	0.20	1410	0.31
31.573	110032	1.73	12711	2.83

Totals	6377460	100.00	448587	100.00

Supporting Information

Synthesis, biological evaluation and X-ray analysis of bicalutamide sulfoxide analogues for the potential treatment of prostate cancer

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[b]School of Chemistry, Cardiff University, Park Place, Cardiff, CF10 3AT, Wales, United Kingdom.

1. Chemistry

All chemicals were purchased from Sigma-Aldrich or Alfa Aesar and were used without further purification. Thin Layer Chromatography (TLC): pre-coated aluminium backed plates (60 F254, 0.2 mm thickness, Merck) were visualized under both short and long wave UV light (254 and 366 nm). Flash column chromatography was carried out using silica gel supplied by Fisher (60A, 35-70 mm) ^{1}H NMR (500 MHz), ^{13}C NMR (125 MHz) and ^{19}F NMR (470 MHz) spectra were recorded on a Bruker Avance 500 MHz spectrometer at 25^{o}C. Chemical shifts (δ) are expressed in parts per million (ppm) and coupling constants (J) are given in hertz (Hz). The following abbreviations are used in the assignment of NMR signals: s (singlet), bs (broad singlet); d (doublet), t (triplet), q (quartet), qn (quintet), m (multiplet), dd (doublet of doublet), dt (doublet of triplet), td (triple doublet); dq (double quartet), m (multiplet), dm (double multiplet).

The purity of the final compounds was verified to be >95% by reverse-phase HPLC analysis using either I) Thermo SCIENTIFIC, SPECTRA SYSTEM P4000, detector SPECTRA SYSTEM UV2000, Varian Pursuit XRs 5 C18, 150 x 4.6 mm (as an analytic column) or II) Varian Prostar (LC Workstation-Varian Prostar 335 LC detector), Thermo SCIENTIFIC Hypersil Gold C18, 5µ, 150 x 4.6 mm (as an analytic column) with a gradient elution of H_2O/ CH_3CN from 90/10 to 0/100 in 30 min, Flow = 1 mL/min, λ = 275 nm. Mass spectra were measured by Bruker Daltonics microTof-LC, in positive mode electrospray ionization (ESI).

* Email: kandils1@cf.ac.uk

1.1 General method for the preparation of intermediates 4-5

Methacryloyl chloride **3** (8.4 mL, 85.96 mmol) was added over the course of 10 minutes to a stirring solution of the appropriate trifluoromethylaniline **1-2** (10.75 mmol) in N,N-dimethylacetamide (10 mL) at room temperature for 24h. After the reaction was complete, the mixture was diluted with ethyl acetate (100 mL), extracted with saturated $NaHCO_3$ solution (2 x 50 mL) then cold brine (2 x 50 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. The crude oil residue was purified by flash column chromatography eluting with chloroform-ethyl acetate 95:5 v/v to obtain the titled compounds.

***N*-(4-cyano-3-(trifluoromethyl)phenyl)methacrylamide (4)** [19]

Data in accordance with literature data. Yield; 92%. ^{1}H NMR ($CDCl_3$) δ 8.10 (d, *J* = 2Hz, 1H, Ar*H*), 8.06 (bs, 1H, N*H*), 8.01 (dd, J = 2, 8.5 Hz, 1H, Ar*H*), 7.81 (d, *J* = 8.5Hz, 1H, Ar*H*), 5.89 (d, *J* = 1Hz, 1H, CH_2), 5.62 (q, *J* = 1.5Hz, 1H, CH_2), 2.10 (dd, *J* = 0.5, 1.5 Hz, 3H, CH_3). ^{19}F-NMR: ($CDCl_3$) δ -62.23**.**

***N*-(4-Nitro-2-(trifluoromethyl)phenyl)methacrylamide (5)** [19]

Data in accordance with literature data. Yield; 94 %.^{1}H NMR ($CDCl_3$) δ 8.73 (d, J= 9 Hz, 1H, Ar*H*), 8.46 (d, J= 3 Hz, 1H, Ar*H*), 8.37 (dd, J= 9 Hz, 2.5 Hz, 1H, Ar*H*), 8.17 (bs, 1H, N*H*), 5.85 (q, J= 0.5 Hz, 1H, CH_2), 5.58 (q, J= 1.5 Hz, 1H, CH_2), 2.15-2.13 (dd, J= 1, 1.5 Hz, 1H, CH_3). ^{19}F-NMR: ($CDCl_3$) d -61.31.

1.2 General method for the preparation of intermediates 6-7

To a stirred solution of the intermediate **4**-**5** (3 mmol) in DCM (7 mL) was added 30% hydrogen peroxide (3.6 mL, 32.03 mmol). The reaction mixture was placed in a water bath at rt and trifluoroacetic anhydride (3.7 mL, 26.7 mmol) was added slowly to the mixture, which was then stirred for 24 h. The reaction mixture was transferred to a separating funnel using DCM (30 mL). The organic layer was washed with distilled water (20 mL), sat. aq. $Na_2S_2O_3$ (4x20 mL), sat. aq. $NaHCO_3$ (3x20 mL) and brine (20 mL), dried over Na_2SO_4 and concentrated at reduced pressure.

***N*-(4-Cyano-3-(trifluoromethyl)phenyl)-2-methyloxirane-2-carboxamide** (**6**) [19]

The data are in accordance with literature data. Obtained in 86% yield as a yellow solid. ^{1}H-NMR ($CDCl_3$): δ 8.38 (bs, 1H), 8.00 (d, J= 2.1 Hz, 1H), 7.88 (dd, J= 8.5 Hz, 2.1 Hz, 1H), 7.78 (d, J= 8.5 Hz, 1H), 3.00 (s, 2H), 1.68 (s, 3H).

2-Methyl-*N*-(4-nitro-2-(trifluoromethyl)phenyl)oxirane-2-carboxamide (7) [12]

Obtained in 71% yield as a yellow wax. ^{1}H-NMR ($CDCl_3$): δ 8.92 (bs, 1H), 8.74 (d, J= 9.6 Hz, 1H), 8.53 (d, J= 2.5 Hz, 1H), 8.44 (dd, J= 9.6 Hz, 2.5 Hz, 1H), 3.04 (d, J= 4.6 Hz, 1H), 3.02 (d, J= 4.6 Hz, 1H), 1.72 (s, 3H). ^{19}F-NMR ($CDCl_3$): δ -61.69 (s, 3F). ^{13}C-NMR ($CDCl_3$): δ 169.2, 142.9, 140.4, 128.35 (m), 123.7, 122.3 (m), 121.6, 119.2 (m), 56.5, 53.9, 16.4.

1.3 General method for the preparation of compounds 15-24.

To a mixture of sodium hydride (NaH) (60% in mineral oil, 0.050 g, 1.23 mmol) in anhydrous THF (2 mL) at 0 °C under Ar atmosphere was added a solution of the differently substituted thiophenol **8 - 14** (1.11 mmol) in 1 mL of anhydrous THF. This mixture was stirred at rt for 20 min. A solution of the intermediate **6** or **7** (0.74 mmol) in anhydrous THF (3 mL) was added slowly. The reaction mixture was stirred at room temperature for 24h. The mixture was then diluted with ethyl acetate (30 mL), washed with brine (15 mL) and water (30 mL), dried over Na_2SO_4 and concentrated under *vacuum*. The crude residue was purified by flash column chromatography eluting with *n*-hexane/EtOAc 100:0 v/v increasing to *n*-hexane/EtOAc 90:10 v/v.

***N*-(4-cyano-3-(trifluoromethyl)phenyl)-2-hydroxy-2-methyl-3-(pyridin-2-ylthio) propanamide** (**15**) yield 79%.

^{1}H NMR ($CDCl_3$) *δ* 9.64 (s, 1H, N*H*), 8.89 (s, 1H, Ar*H*), 8.39 (ddd, *J*= 1, 1.5, 5 Hz, 1H, Ar*H*), 8.13 (d, *J* = 2 Hz, 1H, Ar*H*), 8.00 (dd, *J* = 2, 8.5 Hz, 1H, Ar*H*), 7.91 (d, *J*= 8.5 Hz, 1H, Ar*H*), 7.61 (ddd, *J*= 2, 8, 8.5 Hz, 1H, Ar*H*), 7.37 (dt, *J*= 1, 8 Hz, 1H, Ar*H*), 7.17 (ddd, *J*= 1, 5, 7.5 Hz, 1H, Ar*H*), 3.61 (d, *J*= 15.5 Hz, 1H, CH_2), 3.50 (d, *J* = 15 Hz, 1H, CH_2), 1.63 (s, 3H, CH_3); ^{19}F NMR ($CDCl_3$) *δ* -62.16 (s, 3F); ^{13}C NMR ($CDCl_3$) *δ* 175.18 (C=O), 158.85 (Ar*C*), 148.32 (Ar*C*H), 141.69 (Ar*C*), 137.45 (Ar*C*H), 135.80 (Ar*C*H), 133.92 (q, $^{2}J_{C-F}$ = 32.5 Hz, Ar*C*), 123.55 (Ar*C*H), 122.19 (q, $^{1}J_{C-F}$ = 271.3 Hz, *C*F_3), 121.66 (Ar*C*H), 120.92 (Ar*C*H), 117.16 (q, $^{3}J_{C-F}$ = 5 Hz, Ar*C*H), 115.67 (Ar*C*), 104.15 (CN), 77.01 (*C*OH), 41.48 (*C*H_2), 26.81 (*C*H_3). MS [ESI, m/z]: 382.1 [M+H$^+$], 404.1 [M+Na$^+$]. Reverse-phase HPLC, eluting with H_2O/CH_3CN from 90/10 to 0/100 in 30 min; flow = 1 mL/min, t_R = 21.17 mins 99.5%

2-Hydroxy-2-methyl-*N*-(4-nitro-2-(trifluoromethyl)phenyl)-3-(pyridin-2-ylthio)propenamide (**16**) yield 75 %.

^{1}H NMR ($CDCl_3$) *δ* 10.26 (s, 1H, N*H*), 9.08 (s, 1H, Ar*H*), 8.84 (d, *J* = 9 Hz, 1H, Ar*H*), 8.52 (d, *J* = 3 Hz, 1H, Ar*H*), 8.42 (m, 2H, Ar*H*), 7.61 (m, 1H, Ar*H*), 7.37 (d, *J* = 8.5 Hz, 1H, Ar*H*), 7.18 (m, 1H, Ar*H*), 3.60 (d, *J* = 15 Hz, 1H, CH_2), 3.52 (d, *J* = 15 Hz, 1H, CH_2), 1.65 (s, 3H,

C*H*$_3$); ^{19}F NMR ($CDCl_3$) *δ* -62.01 (s, 3F); ^{13}C NMR ($CDCl_3$) *δ* 175.24 (C=O), 158.68 (Ar*C*), 148.31 (Ar*C*H), 142.62 (Ar*C*), 141.00 (Ar*C*), 137.40 (Ar*C*H), 128.27 (Ar*C*H), 123.36 (Ar*C*H), 122.78 (q, $^1J_{C-F}$ = 272 Hz, *C*F*3*), 122.36 (q, $^3J_{C-F}$ = 5.5 Hz, Ar*C*H), 122.04 (Ar*C*H), 120.86 (Ar*C*H), 119.28 (q, $^2J_{C-F}$ = 32.5 Hz, Ar*C*), 77.13 (*C*OH), 41.46 (*C*H_2), 26.54 (*C*H_3). MS (ES+) m/z: 402.1 [M+H$^+$], 424.1 [M+Na$^+$]. Reverse-phase HPLC, eluting with H_2O/CH_3CN from 90/10 to 0/100 in 30 min; flow = 1 mL/min, t_R = 23.98 mins 99.75%

2-Hydroxy-2-methyl-*N*-(4-nitro-2-trifluoromethyl)phenyl)-3-(4-(trifluoromethyl) phenylthio)propanamide (17) yield 65 %.[12]

^{1}H-NMR ($CDCl_3$), δ: 9.59 (bs, 1H), 8.54 (d, *J* = 2.5 Hz, 1H), 8.49 (d, *J* = 9 Hz, 1H), 8.37 (dd, *J*$_1$ = 9, *J*$_2$ = 2.5 Hz, 1H), 7.52 (d, *J* = 9 Hz, 2H), 7.47 (d, *J* = 8 Hz, 2H), 3.87 (d, *J*= 14.5 Hz, 1H), 3.36 (s, 1H), 3.26 (d, *J*= 14.5 Hz, 1H), 1.62 (s, 3H). ^{19}F-NMR ($CDCl_3$), δ: -62.80 (s, 3F), -61.56 (s, 3F); ^{13}C-NMR ($CDCl_3$), δ: 172.80 (C=O), 142.95, 140.30, 138.97, 130.04, 129.13 (q, $^2J_{C-F}$ = 32.5 Hz), 128.21, 125.79 (q, $^3J_{C-F}$ = 3.6 Hz), 121.98, 123.73 (q, $^1J_{C-F}$ = 270 Hz), 122.79 (q, $^1J_{C-F}$ = 272.3 Hz, CF_3), 119.21 (q, $^2J_{C-F}$ = 31.5 Hz), 75.63 (*C*OH), 43.69 (*C*H_2), 26.16 (*C*H_3). MS [ESI, m/z]: 469.1 [M+H], 491.1 [M+Na]. Reverse-phase HPLC, eluting with H_2O/CH_3CN from 90/10 to 0/100 in 30 min; flow = 1 mL/min, t_R = 24.13 min.

2-Hydroxy-2-methyl-*N*-(4-nitro-2-(trifluoromethyl)phenyl)-3-((2-(trifluoromethoxy) phenyl)thio)propenamide (18) yield 58 %. [12]

^{1}H-NMR ($CDCl_3$): δ 9.64 (bs, 1H), 8.54 (d, *J* = 2.5 Hz, 1H), 8.47 (d, *J* = 9.0 Hz, 1H), 8.36 (dd, *J*= 9.0 Hz, 2.5 Hz, 1H), 7.58-7.55 (m, 1H), 7.29-7.24 (m, 1H), 7.23-7.17 (m, 2H), 3.84 (d, *J*= 14.5 Hz, 1H), 3.62 (bs, 1H), 3.15 (d, *J*= 14.5 Hz, 1H), 1.58 (s, 3H). ^{19}F-NMR ($CDCl_3$): δ -61.70 (s, 3F), -57.34 (s, 3F), ^{13}C-NMR ($CDCl_3$): δ 172.8 (C=O), 148.7, 142.8, 140.4, 133.8, 129.4, 128.0, 127.3, 127.1, 123.8, 122.3 (q, *J*= 5.5 Hz), 122.0, 121.1, 120.5 (q, *J*= 287.4 Hz, CF_3), 120.2 (q, *J*= 289.8 Hz), 75.4 (*C*OH), 43.9 (*C*H_2), 26.1 (*C*H_3). MS [ESI, m/z]: 485.1 [M+H]$^+$, 507.1 [M+Na]$^+$. Reverse-phase HPLC, eluting with H_2O/CH_3CN from 90/10 to 0/100 in 30 min; flow = 1 mL/min, t_R = 23.85 min.

3-((2,4-Difluorophenyl)thio)-2-hydroxy-2-methyl-N-(4-nitro-2-(trifluoromethyl) phenyl) propenamide (19) yield 74 %. [12]

^{1}H-NMR ($CDCl_3$): δ 9.64 (bs, 1H), 8.55 (d, *J* = 3.0 Hz, 1H), 8.49 (d, *J* = 9.5 Hz, 1H), 8.38 (dd, *J*= 9.5 Hz, 3.0 Hz, 1H), 7.49-7.43 (m, 1H), 6.80-6.70 (m, 2H), 3.83 (d, *J*= 14.5 Hz,

1H), 3.67 (bs, 1H), 3.03 (d, *J*= 14.5 Hz, 1H), 1.56 (s, 3H). ^{19}F-NMR ($CDCl_3$): δ -61.60 (s, 3F), -101.75 (s, F), -107.28 (s, F). ^{13}C-NMR ($CDCl_3$): δ 172.8 (C=O), 164.4, 161.8, 142.8, 140.4, 136.4 (dd, *J*= 9.5 Hz, 2.0 Hz), 128.1, 122.3 (q, *J*= 6.3 Hz), 122.8 (q, *J*= 275.3 Hz, CF_3), 115.3 (d, *J*= 17.6 Hz), 119.0 (q, *J*= 31.1 Hz), 121.7, 112.0 (dd, *J*= 21.6 Hz, 4.1 Hz), 104.7 (m), 75.3 (*C*OH), 44.6 (CH_2), 26.2 (CH_3). MS [ESI, m/z]: 437.1 $[M+H]^+$, 459.0 $[M+Na]^+$. Reverse-phase HPLC, eluting with H_2O/CH_3CN from 90/10 to 0/100 in 30 min; flow = 1 mL/min, t_R = 24.11 min.

***N*-(4-cyano-3-(trifluoromethyl)phenyl)-2-hydroxy-2-methyl-3-((4-(trifluoro methoxy) phenyl)thio)propenamide (20)** yield 81 %. [12]

^{1}H NMR ($CDCl_3$) *δ* 1.56 (s, 3H), 3.20 (d, *J* = 14 Hz, 1H), 3.75 (d, *J*= 14 Hz, 1H), 3.80 (s, 1H), 7.05 (d, *J* = 9 Hz, 2H), 7.46 (m, 2H), 7.76 (d, *J* = 8.5 Hz, 1H), 7.82 (dd, *J*= 2.5, 8.5 Hz, 1H), 8.00 (d, *J* = 2 Hz, 1H), 9.15 (s, 1H); ^{19}F NMR ($CDCl_3$) *δ* -58.09, -62.28; ^{13}C NMR ($CDCl_3$) *δ* 173.25 (C=O), 148.34 , 141.43 , 135.75 , 133.90 (q, $^2J_{C-F}$ = 32.6 Hz), 132.80 , 132.26 , 123.18 (m), 121.76 , 121.41 , 119.24 (m), 117.20 (q, $^3J_{C-F}$ = 4.9 Hz), 115.57 , 104.27 , 75.57 (*C*OH), 44.97 (CH_2), 26.13 (CH_3). MS (ES+) m/z: 465.1 ($M+H^+$), 487.1 ($M+Na^+$). Reverse-phase HPLC, eluting with H_2O/CH_3CN from 90/10 to 0/100 in 30 min; flow = 1 mL/min, t_R = 23.50 mins.

2-Hydroxy-2-methyl-*N*-(4-nitro-2-(trifluoromethyl)phenyl)-3-((4-(trifluoromethoxy) phenyl)thio)propenamide (21) yield 77 %. [12]

^{1}H NMR ($CDCl_3$) *δ* 1.59 (s, 3H), 3.18 (d, *J* = 14 Hz, 1H), 3.63 (s, 1H), 3.83 (d, *J*= 14.5 Hz, 1H), 7.06 (d, *J* = 8 Hz, 2H), 7.46 (d, *J* = 8.5 Hz, 1H), 8.37 (dd, *J* = 2.5, 9 Hz, 1H), 8.49 (d, *J* = 9 Hz, 1H), 8.53 (d, *J* = 2.5 Hz, 1H), 9.64 (s, 1H); ^{19}F NMR ($CDCl_3$) *δ* -61.64, -58.07; ^{13}C NMR ($CDCl_3$) *δ*: 172.95 (C=O), 148.54, 142.89, 140.38, 132.63, 132.32, 128.21, 123.91 (CF_3), 122.28 (q, $^3J_{C-F}$ = 5.9 Hz), 121.93, 121.74 (CF_3), 121.47, 119.24 (m), 73.54 (*C*OH), 44.90 (CH_2), 26.18 (CH_3). MS (ES+) m/z: 485.1 ($M+H^+$), 507.1 ($M+Na^+$). Reverse-phase HPLC, eluting with H_2O/CH_3CN from 90/10 to 0/100 in 30 min; flow = 1 mL/min, t_R = 25.64 mins.

***N*-(4-cyano-3-(trifluoromethyl)phenyl)-2-hydroxy-2-methyl-3-((5-(trifluoromethyl) pyridin-2-yl)thio)propenamide (22)** yield 79 %.[12]

^{1}H-NMR ($CDCl_3$): δ 9.51 (bs, 1H), 8.70-8.70 (m, 1H), 8.11 (d, *J*= 2.5 Hz, 1H), 8.00 (dd, *J*= 8.5 Hz, 2.5 Hz, 1H), 7.84-7.7.80 (m, 3H), 7.49 (d, *J* = 8.5 Hz, 1H), 3.60 (d, *J* = 15.0 Hz,

1H), 3.67 (d, *J* = 15.0 Hz, 1H), 1.65 (s, 3H). ^{19}F-NMR ($CDCl_3$): δ -62.20 (s, 3F), -62.42 (s, 3F). ^{13}C-NMR ($CDCl_3$): δ 174.4 (C=O), 164.0, 145.5 (q, J= 4.4 Hz), 141.4, 135.8, 134.0 (q, J= 3.0 Hz), 134.0 (q, J= 32.5 Hz), 125.3, 124.2 (m), 123.1, 122.1 (m), 121.6, 117.1 (q, J= 5.1 Hz), 115.5, 104.4, 77.2 (*C*OH), 41.0 (*C*H_2), 26.8 (*C*H_3). MS [ESI, m/z]: 450.1 $[M+H]^+$, 472.1 $[M+Na]^+$. Reverse-phase HPLC, eluting with H_2O/CH_3CN from 90/10 to 0/100 in 30 min; flow = 1 mL/min, t_R = 23.48 min.

2-Hydroxy-2-methyl-*N*-(4-nitro-2-(trifluoromethyl)phenyl)-3-((5-(trifluoromethyl) pyridin-2-yl)thio)propenamide (23) yield 76 %.[12]

^{1}H-NMR ($CDCl_3$), δ: 10.14 (bs, 1H), 8.81 (d, *J* = 9 Hz, 1H), 8.68 (m, 1H), 8.53 (d, *J* = 2.5 Hz, 1H),8.45 (dd, J_1 = 9.5, J_2 = *3* Hz, 1H), 7.94 (s, 1H), 7.82 (dd, J_1 = 8.5, J_2 = *2.5* Hz, 1H), 7.48 (d, *J= 8.5* Hz, 1H), 3.66 (d, *J*= 15 Hz, 1H), 3.61 (d, *J*= 15 Hz, 1H), 1.66 (s, 3H). ^{19}F-NMR ($CDCl_3$), δ: -61.95 (s, 3F), -62.42 (s, 3F); ^{13}C-NMR ($CDCl_3$), δ: 174.85 (C=O), 163.87, 145.57 (q, $^3J_{C-F}$ = 4.4 Hz), 142.78,140.79, 134.04 (q, $^3J_{C-F}$ = 6.5 Hz), 128.28, 124.09 (q, $^2J_{C-F}$ = 42.3 Hz), 123.00, 122.36 (q, $^3J_{C-F}$ = 5.5 Hz), 122.20, 123.13 (q, $^1J_{C-F}$ = 262.6 Hz, CF_3), 122.65 (q, 1JC-F = 272.4 Hz, CF_3), 119.42 (q, $^2J_{C-F}$ = 31.6 Hz*)*, 77.29 (*C*OH), 41.11 (*C*H_2), 26.58 (*C*H_3). MS [ESI, m/z]: 470.1 [M+H], 492.1 [M+Na]. Reverse-phase HPLC, eluting with H_2O/CH_3CN from 90/10 to 0/100 in 30 min; flow = 1 mL/min, t_R = 25.58 min.

3-((3,4-Difluorophenyl)thio)-2-hydroxy-2-methyl-*N*-(4-nitro-2-(trifluoromethyl) phenyl)propenamide (24) yield 78 %. [12]

^{1}H-NMR ($CDCl_3$), δ: 9.62 (bs, 1H), 8.58 -8.55 (m, 2H), 8.42 (dd, J_1 = 9.5, J_2 = 2.5 Hz, 1H), 7.28-7.25 (m, 1H), 7.05-7.00 (m, 1H), 3.78 (d, *J*= 14 Hz, 1H), 3.38 (bs, 1H), 3.17 (d, *J*= 14.5 Hz, 1H),1.59 (s, 3H). ^{19}F-NMR ($CDCl_3$), δ: -61.60 (s, 3F), -135.41 (s, F), -137.51 (s, F); ^{13}C-NMR ($CDCl_3$),δ: 172.79 (C=O), 150.14 (d, $^1J_{C-F}$ = 251.0 Hz), 150.02 (d, $^1J_{C-F}$ = 249.1 Hz), 142.94, 140.38, 130.07, 128.28,127.96 (q, $^3J_{C-F}$ = 2.8 Hz), 122.82 (q, $^1J_{C-F}$ = 272.4 Hz, CF_3),122.38 (q, $^3J_{C-F}$ = 5.5 Hz), 121.78, 120.72 (d, $^2J_{C-F}$ = 18.4 Hz), 119.18 (q, $^2J_{C-F}$ = 31.4 Hz*)*, 117.90 (d, $^2J_{C-F}$ = 17.9 Hz), 75.70 (*C*OH), 45.41 (*C*H_2), 26.21 (*C*H_3). MS [ESI, m/z]: 437.1 [M+H], 459.0 [M+Na]. Reverse-phase HPLC, eluting with H_2O/CH_3CN from 90/10 to 0/100 in 30 min; flow = 1 mL/min, t_R = 23.79 min.

1.4 General method for the preparation of sulfoxide compounds 25-34.

To a stirring solution of the different sulfide **15-24** (0.7 mmol) in 5 mL anhydrous dichloromethane (DCM) was added 3-chloroperbenzoic acid (*m*CPBA) (0.8 mmol) portion wise maintaining the temperature at 0° C for 20-30 min. After further dilution, a solution of 5% sodium carbonate is added and the mixture stirred for 1 hour, the phases are then separated. The combined organic layers were washed, dried over anhydrous sodium sulfate and concentrated in vacuo. The crude residue was purified by column chromatography, preparative TLC or crystallization from methanol.

***N*-(4-cyano-3-(trifluoromethyl)phenyl)-2-hydroxy-2-methyl-3-(pyridin-2-ylsulfinyl) propanamide** (1 isomer A:1 isomer B) **(25)** yield 75 %.

^{1}H NMR ($CDCl_3$) δ [9.50 (s), 9.30 (s), 1H, N*H*], [8.72 (d, *J*= 4.5 Hz), 8.68 (d, *J*= 5 Hz), 1H, Ar*H*], [8.21 (d, *J*= 1.5 Hz), 8.01 (m), 3H], 7.84 (m, 2H, Ar*H*), [7.50 (m), 7.44 (m), 1H, Ar*H*], [6.79 (s), 6.17 (s), 1H, O*H*], [3.69 (d, *J* = 13.5 Hz), 3.63 (d, *J* = 14 Hz), 1H, CH_2], [3.88 (d, *J* = 13.5 Hz), 3.31 (d, *J* = 13.5 Hz), 1H, CH_2], [1.73 (s), 1.66 (s), 3H, CH_3]; ^{19}F NMR ($CDCl_3$) δ -62.17; ^{13}C NMR ($CDCl_3$) δ (173.25, 172.78, *C*=O), 155.53 (Ar*C*), (150.09, 149.77, Ar*C*H), (141.50, 141.33, Ar*C*) (138.66, 138.47, Ar*C*H), (135.85, 135.78, Ar*C*H), 134.18 (m, Ar*C*), (125.50, 125.29, Ar*C*H), (122.01, 121.74, Ar*C*H) , (120.41, 120.13, Ar*C*H), 120.50 (q, $^{1}J_{C\text{-}F}$ = 263.8 Hz, *C*F_3), [117.49 (q, $^{3}J_{C\text{-}F}$ = 5 Hz), 117.24 (q, $^{3}J_{C\text{-}F}$ = 5 Hz), Ar*C*H], (115.45, 115.51, *C*N), (104.80, 104.68, Ar*C)*, (76.12, 75.88, *C*OH), (60.31, 59.02, *C*H_2), (27.73, 27.49, *C*H_3). MS (ES+) m/z: 398.1 [M+H^+], 420.1 [M+Na^+]. Reverse-phase HPLC, eluting with H_2O/CH_3CN from 90/10 to 0/100 in 30 min; flow = 1 mL/min, t_R = 14.62 mins 97.81%.

2-Hydroxy-2-methyl-*N*-(4-nitro-2-(trifluoromethyl)phenyl)-3-(pyridin-2-ylsulfinyl) propanamide [2 isomer A:1 isomer B] **(26)** yield 71%

^{1}H NMR ($CDCl_3$) δ 9.89 (s, 1H, N*H*), [8.65 (d, *J* = 9.5 Hz), isomer B, 8.82 (d, *J* = 9 Hz, 1H), isomer A, 1H, Ar*H*], [8.68 (d, *J* = 5 Hz) isomer B, 8.70 (d, *J* = 4.5 Hz) isomer A, 1H, Ar*H*], [8.55 (d, *J* = 2.5 Hz, isomer B), 8.59 (d, *J* = 2.5 Hz, isomer A), 1H, Ar*H*], [8.42 (dd, *J* = 2.5, 9 Hz, isomer B), 8.48 (dd, *J* = 3, 9.5 Hz, isomer A), 1H, Ar*H*), [7.92 (m), 8.04 (m), 2H, Ar*H*], [7.46 (ddd, *J* = 1, 4.5, 7.5 Hz) isomer B, 7.50 (ddd, *J* = 2, 4.5, 4.5 Hz) isomer A, 1H, Ar*H*], [6.39 (s), isomer A, 6.98 (s), isomer B, 1H, O*H*], [3.34 (d, *J* = 13.5 Hz), 3.92 (d, *J* = 13.5 Hz), 1H, isomer A, CH_2], [3.64 (d, *J* = 14 Hz), 3.70 (d, *J* = 13.5 Hz), 1H, isomer B, CH_2], [1.67 (s) isomer A, 1.75 (s) isomer B, 3H, CH_3]; ^{19}F NMR ($CDCl_3$) δ -61.64; ^{13}C NMR

($CDCl_3$) δ (173.31, 172.84, *C*=O), (163.81, 163.19, Ar*C*), (149.84, 149.57, Ar*C*H), 143.08 (Ar*C*), 140.63 (Ar*C*), (138.75, 138.62, Ar*C*H), (128.30, 128.25, Ar*C*H), 126.58 (m, *C*F_3), (125.38, 125.28, Ar*C*H), 123.61 (m, Ar*C*), (122.63, 122.01, Ar*C*H), 122.43 (m, Ar*C*H), (120.55, 120.16, Ar*C*H), (76.12, 75.59 *CO*H), (59.66, 59.48, *C*H_2), (27.63, 27.58, *C*H_3). MS (ES+) m/z: 418.1 [M+H^+], 440.1 [M+Na^+]. Reverse-phase HPLC, eluting with H_2O/CH_3CN from 90/10 to 0/100 in 30 min; flow = 1 mL/min, t_R = 16.02 mins.

2-Hydroxy-2-methyl-*N*-(4-nitro-2-(trifluoromethyl)phenyl)-3-(4-(trifluoromethyl) phenylsulfinyl)propanamide (27) yield 66 %

^{1}H NMR ($CDCl_3$) δ 9.90 (s, 1H, N*H*), 8.79 (d, *J* = 9 Hz, 1H, Ar*H*), 8.60 (d, *J* = 2.5 Hz, 1H, Ar*H*), 8.50 (dd, *J* = 2.5, 9 Hz, 1H, Ar*H*), 7.88 (d, *J* = 8.5 Hz, 2H, Ar*H*), 7.82 (d, *J* = 8.5 Hz, 2H, Ar*H*), 6.06 (bs, 1H, *OH*), 3.65 (d, *J*= 13 Hz, 1H, CH_2), 3.13 (d, *J* = 13.5 Hz, 1H, CH_2), 1.63 (s, 3H, CH_3); ^{19}F NMR ($CDCl_3$) δ -61.58 (s, 3F), -63.01 (s, 3F); ^{13}C NMR ($CDCl_3$) δ 173.37 (C=O), 147.11 (Ar*C*), 143.34 (Ar*C*), 140.37 (Ar*C*), 133.90 (q, $^2J_{C-F}$ = 32.6 Hz, Ar*C*), 128.25 (Ar*C*H), 126.74 (q, $^3J_{C-F}$ = 3.8 Hz, Ar*C*H), 124.23 (Ar*C*H), 123.28 (q, $^1J_{C-F}$ = 271 Hz, *C*F_3), 122.79 (Ar*C*H), 122.74 (q, $^1J_{C-F}$ = 271.9 Hz, *C*F_3), 122.47 (q, $^3J_{C-F}$ = 5.5 Hz, Ar*C*H), 120.35 (q, $^2J_{C-F}$ = 31.5 Hz, Ar*C*), 76.74 (*C*OH), 62.91 (*C*H_2), 28.09 (*C*H_3). MS [ESI, m/z]: 485.1 [M+H^+], 507.1 [M+Na^+], Reverse-phase HPLC, eluting with H_2O/CH_3CN from 90/10 to 0/100 in 30 min; flow = 1 mL/min, t_R = 19.66 min.

2-Hydroxy-2-methyl-*N*-(4-nitro-2-(trifluoromethyl)phenyl)-3-(2-(trifluoromethoxy) phenylsulfinyl)propanamide (28) yield 81%.

^{1}H NMR ($CDCl_3$) δ 9.82 (s, 1H, N*H*), 8.83 (d, *J* = 9 Hz, 1H, Ar*H*), 8.59 (d, *J* = 2.5 Hz, 1H, Ar*H*), 8.50 (dd, *J* = 2.5, 9 Hz, 1H, Ar*H*), 7.99 (m, 1H, Ar*H*), 7.63 (m, 2H, Ar*H*), 7.45 (m, 1H, Ar*H*), 5.85 (s, 1H, O*H*), 3.89 (d, *J*= 13 Hz, 1H, CH_2), 3.03 (d, *J*= 13 Hz, 1H, CH_2), 1.61 (s, 3H, CH_3); ^{19}F NMR ($CDCl_3$) δ -61.58 (s, 3*F*), -57.18 (s, 3*F*); ^{13}C NMR ($CDCl_3$) δ 173.14 (C=O), 154.94 (Ar*C*), 143.20 (Ar*C*), 141.94 (Ar*C*), 133.71, 133.20 (Ar*C*H), 131.83 (Ar*C*), 130.75 (Ar*C*), 130.24, 129.84 (Ar*C*H), 128.28, 128.03 (Ar*C*H), 125.53 (Ar*C*H), 124.64 (Ar*C*), 122.78 (Ar*C*H), 122.42 (q, $^3J_{C-F}$ = 5.6 Hz, Ar*C*H), 121.11 (Ar*C*), 119.81 (Ar*C*H), 77.20 (*C*OH), 59.41 (*C*H_2), 28.11 (*C*H_3). MS [ESI, m/z]: 501.1 [M+H^+], 523.0 [M+Na^+]. Reverse-phase HPLC, eluting with H_2O/CH_3CN from 90/10 to 0/100 in 30 min; flow = 1 mL/min, t_R = 20.01 mins**.**

3-(2,4-Difluorophenylsulfinyl)-2-hydroxy-2-methyl-*N*-(4-nitro-2-(trifluoromethyl) phenyl) propanamide (29) yield 80%.

^{1}H NMR ($CDCl_3$) δ 9.82 (s, 1H, N*H*), 8.81 (d, *J* = 9 Hz, 1H, Ar*H*), 8.60 (d, *J* = 3 Hz, 1H, Ar*H*), 8.50 (dd, *J* = 2.5, 9 Hz, 1H, Ar*H*), 7.21 (m, 1H, Ar*H*), 7.85 (m, 1H, Ar*H*), 6.99 (m, 1H, Ar*H*), 5.81 (s, 1H, O*H*), 3.85 (dd, *J*= 2, 13 Hz, 1H, CH_2), 3.12 (d, *J*= 13 Hz, 1H, CH_2), 1.62 (s, 3H, CH_3); ^{19}F NMR ($CDCl_3$) δ -61.58, -103.02, -109.35; ^{13}C NMR ($CDCl_3$) δ 173.18 (C=O), 157.92 (d, $^{1}J_{C-F}$ = 237.5 Hz, Ar*C*), 157.82 (d, $^{1}J_{C-F}$ = 237.5 Hz, Ar*C*), 143.29 (Ar*C*), 140.43 (Ar*C*), 128.26 (Ar*C*H), 127.38 (Ar*C*), 127.01 (m, Ar*C*H), 123.91 (m, *C*F_3), 122.84 (Ar*C*H), 122.44 (q, $^{3}J_{C-F}$ = 5 Hz, Ar*C*H), 119.97 (m, Ar*C*), 113.39 (m, Ar*C*H), 105.10 (m, Ar*C*H), 76.95 (*C*OH), 59.67 (*C*H_2), 28.16 (*C*H_3). MS (ES+) m/z: 453.1 [M+H^+], 475.0 [M+Na^+]. Reverse-phase HPLC, eluting with H_2O/CH_3CN from 90/10 to 0/100 in 30 min; flow = 1 mL/min, t_R = 18.00 mins.

***N*-(4-cyano-3-(trifluoromethyl)phenyl)-2-hydroxy-2-methyl-3-(4-(trifluoro methoxy)phenylsulfinyl)propanamide (30)** yield 76 %.

^{1}H NMR ($CDCl_3$) δ 9.46 (s, 1H, N*H*), 8.26 (d, *J* = 2 Hz, 1H, Ar*H*), 8.00 (dd, *J* = 2.5, 8.5 Hz, 1H, Ar*H*), 7.87 (d, *J* = 8.5 Hz, 1H, Ar*H*), 7.75 (d, *J*= 9 Hz, 2H, Ar*H*), 7.47 (d, *J*= 8 Hz, 2H, Ar*H*), 6.00 (s, 1H, O*H*), 3.57 (d, *J*= 13 Hz, 1H, CH_2), 3.07 (d, *J* = 13 Hz, 1H, CH_2), 1.61 (s, 3H, CH_3); ^{19}F NMR ($CDCl_3$) δ -62.18, -57.79; ^{13}C NMR ($CDCl_3$) δ 173.37 (C=O), 151.81 (Ar*C*), 141.23 (Ar*C*), 140.63 (Ar*C*), 135.89 (Ar*C*H), 134.06 (m, Ar*C*), 128.56 (m, *C*F_3), 125.79 (Ar*C*H), 122.12 (Ar*C*H), 122.00 (Ar*C*H), 121.05 (m, *C*F_3), 117.50 (q, $^{3}J_{C-F}$ = 4.6 Hz, Ar*C*H), 115.42 (*C*N), 105.13 (Ar*C*), 76.73 (*C*OH), 62.37 (*C*H_2), 28.25 (*C*H_3). MS (ES+) m/z: 481.1 [M+H^+], 503.1 [M+Na^+]. Reverse-phase HPLC, eluting with H_2O/CH_3CN from 90/10 to 0/100 in 30 min; flow = 1 mL/min, t_R = 19.58 mins.

2-Hydroxy-2-methyl-*N*-(4-nitro-2-(trifluoromethyl)phenyl)-3-(4-(trifluoromethoxy) phenylsulfinyl)propenamide (31) yield 73%.

^{1}H NMR ($CDCl_3$) δ 9.91 (s, 1H, N*H*), 8.79 (d, *J* = 9 Hz, 1H, Ar*H*), 8.60 (d, *J* = 2.5 Hz, 1H, Ar*H*), 8.50 (dd, *J* = 3, 9.5 Hz, 1H, Ar*H*), 7.75 (d, *J*= 9 Hz, 2H, Ar*H*), 7.46 (d, *J*= 8 Hz, 2H, Ar*H*), 6.22 (s, 1H, O*H*), 3.62 (d, *J*= 13.5 Hz, 1H, CH_2), 3.15 (d, *J*= 13 Hz, 1H, CH_2), 1.63 (s, 3H, CH_3); ^{19}F NMR ($CDCl_3$) δ -61.60 (s, 3F), -57.81 (s, 3F); ^{13}C NMR ($CDCl_3$) δ 173.45 (C=O), 151.71 (Ar*C*), 143.27 (Ar*C*), 140.84 (Ar*C*), 140.41 (Ar*C*), 128.26 (Ar*C*H), 125.77 (Ar*C*H), 122.74 (q, $^{1}J_{C-F}$ = 272.5 Hz, *C*F_3), 122.78 (Ar*C*H), 122.50 (q, $^{3}J_{C-F}$ = 6.3 Hz, Ar*C*H),

122.07 (Ar*C*H), 120.28 (q, $^{1}J_{C-F}$ = 257.9 Hz, *C*F_3), 120.13 (q, $^{2}J_{C-F}$ = 31.3 Hz, Ar*C*), 76.61 (*C*OH), 63.16 (*C*H_2), 28.10 (*C*H_3). MS (ES+) m/z: 501.1 [M+H^+], 523.1 [M+Na^+]. Reverse-phase HPLC, eluting with H_2O/CH_3CN from 90/10 to 0/100 in 30 min; flow = 1 mL/min, t_R = 21.23 mins.

***N*-(4-cyano-3-(trifluoromethyl)phenyl)-2-hydroxy-2-methyl-3-(5-(trifluoromethyl) pyridin-2-ylsulfinyl)propanamide (32a,** fast moving**)** yield 26%

^{1}H NMR ($CDCl_3$) δ 9.22 (s, 1H, N*H*), 8.94 (m, 1H, Ar*H*), 8.08 (m, 2H, Ar*H*), 7.97 (s, 1H, Ar*H*), 7.79 (m, 2H, Ar*H*), 6.18 (s, 1H, O*H*), 3.74 (d, *J*= 14 Hz, 1H, C*H*$_2$), 3.63 (d, *J* = 14 Hz, 1H, C*H*$_2$), 1.73 (s, 3H, C*H*$_3$); ^{19}F NMR ($CDCl_3$) δ -62.31 (s, 3F), -62.51 (s, 3F); ^{13}C NMR ($CDCl_3$) δ 172.33 (C=O), 166.85 (Ar*C*), 146.98 (q, $^{3}J_{C-F}$ = 3.8 Hz, Ar*C*H), 141.10 (Ar*C*), 135.86 (Ar*C*H), 135.28 (q, $^{3}J_{C-F}$ = 3.8 Hz, Ar*C*H), 134.31 (q, $^{2}J_{C-F}$ = 32.5 Hz, Ar*C*), 128.34 (q, $^{2}J_{C-F}$ = 33.6 Hz, Ar*C*), 122.01 (q, $^{1}J_{C-F}$ = 272.6 Hz, *C*F_3), 119.84 (q, $^{1}J_{C-F}$ = 269.1 Hz, *C*F_3), 117.01 (q, $^{3}J_{C-F}$ = 5 Hz, Ar*C*H), 115.34 (CN), 104.93 (Ar*C*), 76.56 (*C*OH), 57.35 (*C*H_2), 27.64 (*C*H_3). MS (ES+) m/z: 466.1 [M+H^+], 488.1 [M+Na^+]. Reverse-phase HPLC, eluting with H_2O/CH_3CN from 90/10 to 0/100 in 30 min; flow = 1 mL/min, t_R = 18.87 mins.

***N*-(4-cyano-3-(trifluoromethyl)phenyl)-2-hydroxy-2-methyl-3-(5-(trifluoro methyl) pyridin-2-ylsulfinyl)propanamide (32b,** slow moving**),** yield 43.7%.

^{1}H NMR ($CDCl_3$) δ 9.42 (s, 1H, N*H*), 8.97 (m, 1H, Ar*H*), 8.27 (dd, *J* = 2, 8 Hz, 1H, Ar*H*), 8.21 (d, *J* = 2 Hz, 1H, Ar*H*), 8.16 (d, *J* = 8 Hz, 1H, Ar*H*), 8.04 (dd, *J*= 2, 8.5 Hz, 1H, Ar*H*), 7.86 (d, *J*= 8.5 Hz, 1H, Ar*H*), 5.75 (s, 1H, O*H*), 4.00 (d, *J*= 13 Hz, 1H, C*H*$_2$), 3.27 (d, *J* = 13Hz, 1H, C*H*$_2$), 1.66 (s, 3H, C*H*$_3$); ^{19}F NMR ($CDCl_3$) δ -62.18 (s, 3F), -62.42 (s, 3F); ^{13}C NMR ($CDCl_3$) δ 172.94 (C=O), 167.70 (Ar*C*), 147.10 (q, $^{3}J_{C-F}$ = 3.8 Hz, Ar*C*H), 141.35 (Ar*C*), 135.90 (Ar*C*H), 135.80 (q, $^{3}J_{C-F}$ = 3.8 Hz, Ar*C*H), 134.00 (q, $^{2}J_{C-F}$ = 32.5 Hz, Ar*C*), 128.32 (q, $^{2}J_{C-F}$ = 33.8 Hz, Ar*C*), 122.71 (q, $^{1}J_{C-F}$ = 274.3 Hz, *C*F_3), 122.11 (q, $^{1}J_{C-F}$ = 272.3 Hz, *C*F_3), 122.02 (Ar*C*H), 119.88 (Ar*C*H), 117.49 (q, $^{3}J_{C-F}$ = 5 Hz, Ar*C*H), 115.45 (CN), 104.95 (Ar*C*), 76.40 (*C*OH), 60.14 (*C*H_2), 27.87 (*C*H_3). MS (ES+) m/z: 466.1 [M+H^+], 488.1 [M+Na^+]. t_R = 18.79 mins.

2-Hydroxy-2-methyl-*N*-(4-nitro-2-(trifluoromethyl)phenyl)-3-(5-(trifluoromethyl) pyridin-2-ylsulfinyl)propanamide (33a, fast moving**)** yield 31.2%.

^{1}H NMR ($CDCl_3$) δ 9.79 (s, 1H, N*H*), 8.95 (m, 1H, Ar*H*), 8.56 (d, *J* = 2.5 Hz, 1H, Ar*H*), 8.52 (d, *J* = 9.5 Hz, 1H, Ar*H*), 8.40 (dd, *J* = 2.5, 9.5 Hz, 1H, Ar*H*), 8.14 (d, 8.5 Hz, 1H, Ar*H*), 8.07

(ddd, *J*= 0.5, 2, 8.5 Hz, 1H, Ar*H*), 6.28 (s, 1H, O*H*), 3.75 (d, *J*= 14 Hz, 1H, CH_2), 3.63 (d, *J*= 14 Hz, 1H, CH_2), 1.76 (s, 3H, CH_3); ^{19}F NMR ($CDCl_3$) δ -61.60 (s, 3F), -62.47 (s, 3F); ^{13}C NMR ($CDCl_3$) δ 172.33 (*C*=O), 166.45 (Ar*C*), 146.87 (q, $^3J_{C-F}$ = 4.1 Hz, Ar*C*H), 142.96 (Ar*C*), 140.29 (Ar*C*), 135.39 (q, $^3J_{C-F}$ = 3.8 Hz, Ar*C*H), 128.30 (Ar*C*H), 128.05 (Ar*C*), 123.82 (Ar*C*), 122.44 (q, $^3J_{C-F}$ = 5 Hz, Ar*C*H), 121.76 (Ar*C*H), 121.64 (m, *C*F_3), 120.81 (m, *C*F_3), 120.36 (Ar*C*H), 76.53 (*C*OH), 57.50 (*C*H_2), 27.69 (*C*H_3). MS (ES+) m/z: 486.1 [M+H$^+$], 508.0 [M+Na$^+$]. Reverse-phase HPLC, eluting with H_2O/CH_3CN from 90/10 to 0/100 in 30 min; flow = 1 mL/min, t_R = 20.02 mins.

2-Hydroxy-2-methyl-*N*-(4-nitro-2-(trifluoromethyl)phenyl)-3-(5-(trifluoro methyl)pyridin-2-ylsulfinyl)propanamide (33b, slow moving**)** yield 49.7%.

^{1}H NMR ($CDCl_3$) δ 9.82 (s, 1H, N*H*), 8.97 (m, 1H, Ar*H*), 8.81 (d, *J* = 9 Hz, 1H, Ar*H*), 8.59 (d, *J* = 2.5 Hz, 1H, Ar*H*), 8.49 (dd, *J* = 2.5, 9 Hz, 1H, Ar*H*), 8.28 (dd, *J*=2, 8 Hz, 1H, Ar*H*), 8.19 (d, *J*= 8.5 Hz, 1H, Ar*H*), 5.77 (bs, 1H, O*H*), 4.02 (d, *J*= 13 Hz, 1H, CH_2), 3.29 (d, *J*= 13 Hz, 1H, CH_2), 1.65 (s, 3H, CH_3); ^{19}F NMR ($CDCl_3$) δ -61.58 (s, 3F), -62.40 (s, 3F); ^{13}C NMR ($CDCl_3$) δ 172.97 (*C*=O), 168.10 (Ar*C*), 147.01 (q, $^3J_{C-F}$ = 4.1 Hz, Ar*C*H), 143.22 (Ar*C*), 140.46 (Ar*C*), 135.85 (q, $^3J_{C-F}$ = 3.6 Hz, Ar*C*H), 128.34 (Ar*C*), 128.32 (Ar*C*H), 123.86 (Ar*C*), 122.74 (Ar*C*H), 122.47 (q, $^3J_{C-F}$ = 5.6 Hz, Ar*C*H), 119.12 (q, $^1J_{C-F}$ = 242.5, Hz, 2*C*F_3), 119.91 (Ar*C*H), 76.57(*C*OH), 59.39 (*C*H_2), 27.83 (*C*H_3). MS [ESI, m/z]: 486.1 [M+H$^+$], 508.0 [M+Na$^+$]. Reverse-phase HPLC, eluting with H_2O/CH_3CN from 90/10 to 0/100 in 30 min; flow = 1 mL/min, t_R = 19.99 mins.

3-(3,4-Difluorophenylsulfinyl)-2-hydroxy-2-methyl-*N*-(4-nitro-2-(trifluoromethyl) phenyl) propanamide (34a, fast moving**)** yield 26%.

1H NMR ($CDCl_3$) δ 9.78 (s, 1H, N*H*), 8.59 (d, *J*= 9.5 Hz, 1H, Ar*H*), 8.57 (d, *J*= 2.5 Hz, 1H, Ar*H*), 8.42 (dd, *J* = 2.5, 9 Hz, 1H, Ar*H*), 7.56 (m, 1H, Ar*H*), 7.40 (m, 1H, Ar*H*), 7.35 (m, 1H, Ar*H*), 6.00 (s, 1H, O*H*), 3.43 (d, *J*= 14 Hz, 1H, CH_2), 3.23 (d, *J*= 14 Hz, 1H, CH_2), 1.84 (s, 3H, CH_3); ^{19}F NMR ($CDCl_3$) δ -61.64 (s, 3F), -130.81 (s, F), -132.56 (s, F); ^{13}C NMR ($CDCl_3$) δ 172.12 (C=O), 153.52 (Ar*C*), 153.44 (Ar*C*), 143.06 (Ar*C*), 140.33 (Ar*C*), 137.72 (Ar*C*), 128.22 (Ar*C*H), 123.81 (Ar*C*), 122.45 (q, $^3J_{C-F}$ = 5 Hz, Ar*C*H), 121.81 (Ar*C*H), 120.75 (m, Ar*C*H), 120.55 (Ar*C*), 118.83 (d, $^2J_{C-F}$ = 18.8 Hz, Ar*C*H), 113.93 (d, $^2J_{C-F}$ = 20 Hz, Ar*C*H), 76.66 (*C*OH), 59.62 (*C*H_2), 26.67 (*C*H_3). MS (ES+) m/z: 453.1 ([M+H]$^+$, 475.0 [M+Na]$^+$. HPLC, t_R = 20.39 min.

3-(3,4-Difluorophenylsulfinyl)-2-hydroxy-2-methyl-*N*-(4-nitro-2-(trifluoromethyl) phenyl)propanamide (34b, slow moving**)** yield 48%

^{1}H NMR ($CDCl_3$) δ 9.86 (s, 1H, N*H*), 8.79 (d, *J*= 9.5 Hz, 1H, Ar*H*), 8.60 (d, *J*= 2.5 Hz, 1H, Ar*H*), 8.51 (dd, *J* = 3, 9.5 Hz, 1H, Ar*H*), 7.60 (m, 1H, Ar*H*), 7.43 (m, 2H, Ar*H*), 5.94 (s, 1H, O*H*), 3.58 (d, *J*= 13 Hz, 1H, CH_2), 3.07 (d, *J*= 13 Hz, 1H, CH_2), 1.61 (s, 3H, CH_3). ^{19}F NMR ($CDCl_3$) δ -61.58 (s, 3F), -130.65 (s, F), -132.17 (s, F); ^{13}C NMR ($CDCl_3$) δ 173.37 (C=O), 152.28 (Ar*C*), 151.54 (Ar*C*), 143.32 (Ar*C*), 140.34 (Ar*C*), 139.22 (Ar*C*), 128.27 (Ar*C*H), 122.81 (Ar*C*H), 122.50 (q, $^{3}J_{C-F}$ = 6.3 Hz, Ar*C*H), 123.81 (Ar*C*), 120.08 (Ar*C*), 120.50 (m, Ar*C*H), 119.05 (d, $^{2}J_{C-F}$ = 18.8 Hz, Ar*C*H), 113.56 (d, $^{2}J_{C-F}$ = 18.8 Hz, Ar*C*H), 76.83 (*C*OH), 62.30 (CH_2), 28.22 (CH_3). MS (ES+) m/z: 453.1 [M+H$^+$], 475.0 [M+Na$^+$]. Reverse-phase HPLC, eluting with H_2O/CH_3CN from 90/10 to 0/100 in 30 min; flow = 1 mL/min, t_R = 20.16 mins**.**

2. Cell growth inhibition viability Assay

All bicalutamide derivatives were screened for their antiproliferative activity using the Oncotest monolayer assay against four human prostate cancer cell lines (22Rv1, DU-145, LNCaP and VCap). Bicalutamide and Enzalutamide were used as positive controls. A modified propidium iodide (PI) based monolayer assay was used to assess the anti-cancer activity of the compounds. Briefly, cells were harvested from exponential phase cultures, counted and plated in 96- well flat-bottom microtiter plates at a cell density of 8000–12,000 cells/well. After a 24 h recovery period to allow the cells to resume exponential growth, 10 μL of culture medium (six control wells/plate) or culture medium with test compound were added. The compounds were applied in half-log increments at 10 concentrations in triplicate. After a total treatment period of 96 h, cells were washed with 200 μL PBS to remove dead cells and debris. Then, 200 mL of a solution containing 7 mg/mL propidium iodide (PI) and 0.1% (v/v) Triton X-100 was added. After an incubation period of 1–2h at room temperature, fluorescence (FU) was measured using the EnSpire Multimode Plate Reader (excitation l= 530 nm, emission l = 620 nm) to quantify the amount of attached viable cells. IC_{50} values were calculated by 4 parameter non-linear curve fit using Oncotest Warehouse Software. For calculation of mean IC_{50} values the geometric mean was used.[38]

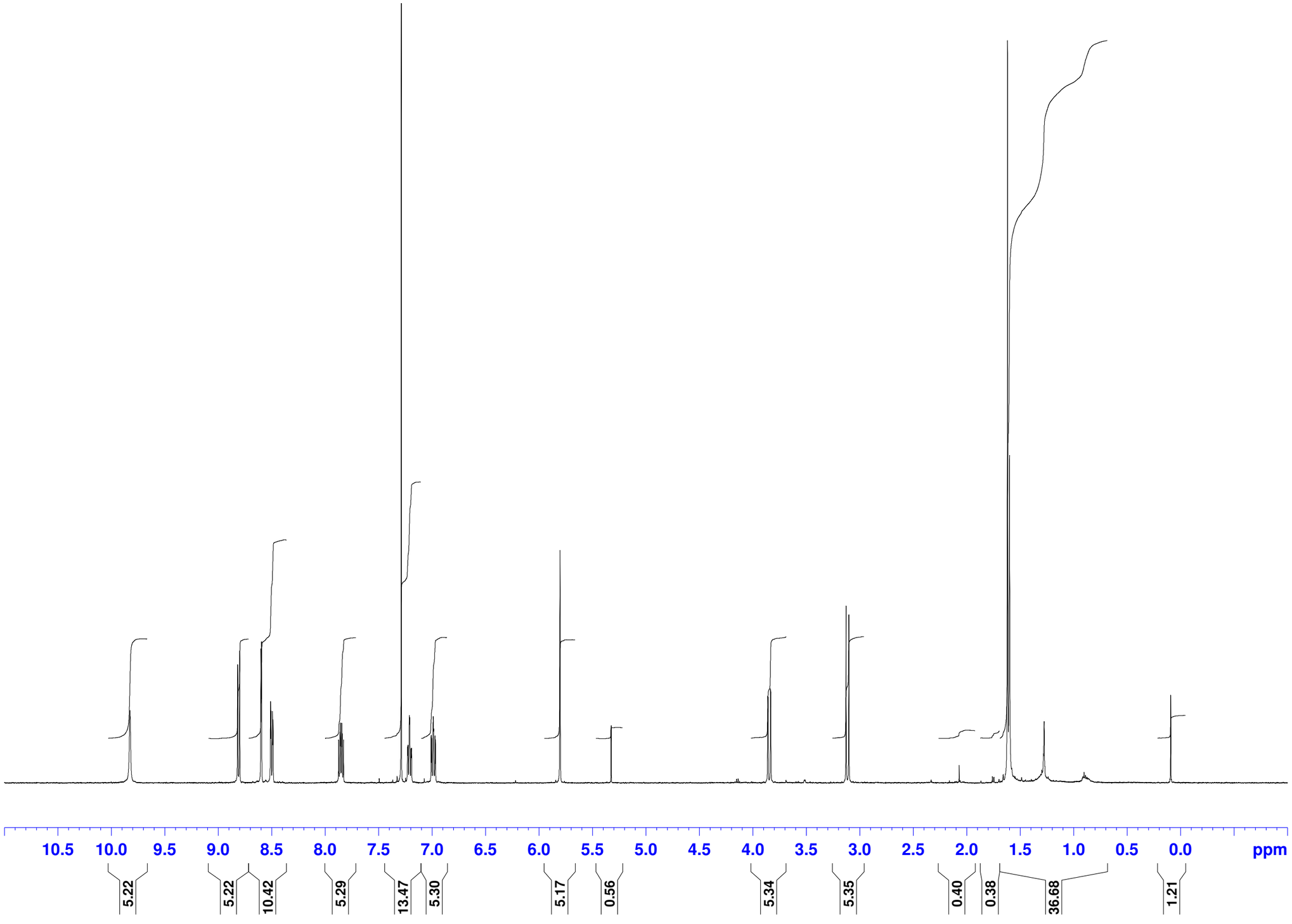
3. X-ray crystal structure determination of compound 34

Single-crystal XRD data were collected at room temperature on an Agilent SuperNova Dual Atlas diffractometer with a mirror monochromator using Cu (λ =1.5418 Å) radiation. Crystal structures were solved using SHELXS [35] and refined using SHELXL. [36] Non-hydrogen atoms were refined with anisotropic displacement parameters. Hydrogen atoms were inserted in idealized positions, and a riding model was used with Uiso set at 1.2 or 1.5 times the value of Ueq for the atom to which they are bonded. **34a**: $C_{17}H_{13}F_5N_2O_5S$, FW = 452.35, T = 296(2) K, Monoclinic, P21/c, a = 14.3383(3) Å, b = 12.1211(2) Å, c = 10.8432(2) Å, β = 93.254(2), V = 1881.47(6) Å^3, Z = 4, D_{cal} = 1.597 Mg/m^3, m = 2.309 mm^{-1}, Crystal size = 0.436 x 0.187 x 0.113 mm^3, Reflections collected = 17738, Independent reflections = 3946, R_{int} = 0.0268, Parameters = 274, G-o-f = 1.065, Final R1 = 0.0403, wR2 = 0.1116 on (I > 2s(I)), R1 = 0.0473, wR2 = 0.1199 on all data. **34b**: $C_{17}H_{13}F_5N_2O_5S$, FW = 452.35, T = 296(2) K, Monoclinic, I2/a, a = 13.1919(3) Å, b = 11.2526(2) Å, c = 25.9866(5) Å, β = 99.610(2), V = 3803.40(13) Å^3, Z = 8, D_{cal} = 1.580 Mg/m^3, m = 2.285 mm^{-1}, Crystal size = 0.395 x 0.225 x 0.173 mm^3, Reflections collected = 17851, Independent reflections = 3997, R_{int} = 0.0185, Parameters = 273, G-o-f = 1.051, Final R1 = 0.0381, wR2 = 0.1041 on (I > 2s(I)), R1 = 0.0401, wR2 = 0.1069 on all data. CCDC 2040881-2040882 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/structures.

4. Docking studies

The X-ray crystal structure of the human androgen receptor – ligand binding domain hAR-LBD was downloaded from the Protein Data Bank (PDB code; 3RLJ)[26] and prepared for docking using the MOE (Molecular Operating Environment)[39] protein preparation tools. The chemical structures of our compounds were constructed, rendered and minimized with the MMFF94x force field in MOE. The docking simulations were performed using MOE default settings. The docking output database was saved as a mol2 file, and the visual inspection of the docking modes was performed in MOE.

Compound 29

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PROCNO                   1
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PULPROG               zg30
TD                   65536
SOLVENT              CDCl3
NS                      16
DS                       2
SWH              10330.578 Hz
FIDRES            0.157632 Hz
AQ               3.1719923 sec
RG                     812
DW                  48.400 use
DE                   6.50 use
TE                  291.2 K
D1               1.00000000 sec
TD0                      1

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P1                   11.50 use
PL1                  -1.00 dB
PL1W           11.38419914 W
SFO1           500.1330885 MHz
SI                   65536
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PC                    1.00
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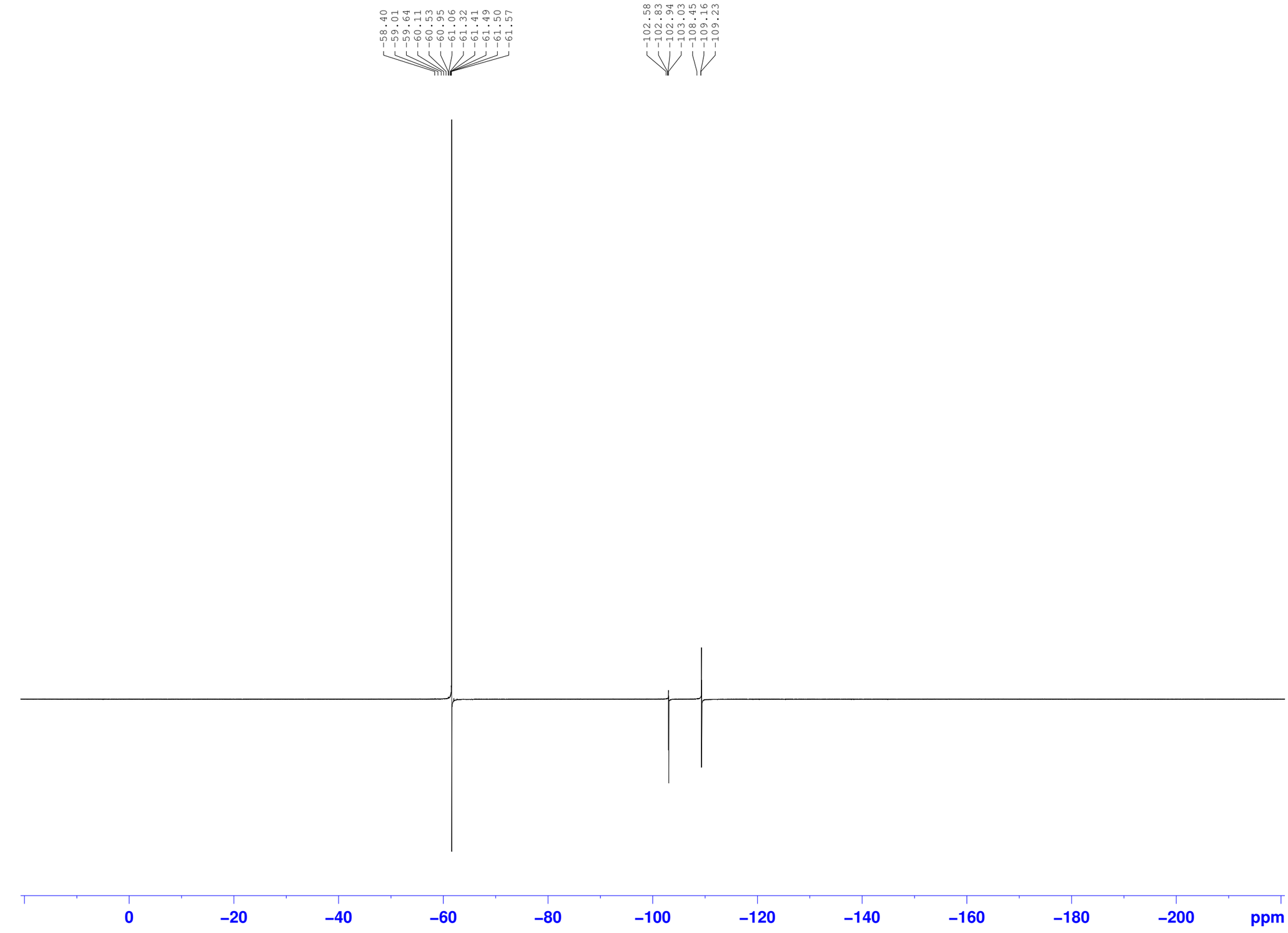
Compound 29



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SOLVENT	CDCl3
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DS	4
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FIDRES	0.866977 Hz
AQ	0.5767668 sec
RG	2300
DW	4.400 use
DE	6.00 use
TE	291.2 K
D1	1.00000000 sec
D11	0.03000000 sec
D12	0.00002000 sec
TD0	1
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PL1W	11.14113998 W
SFO1	470.5453180 MHz
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PL2	-2.00 dB
PL12	14.85 dB
PL2W	14.33185768 W
PL12W	0.29600734 W
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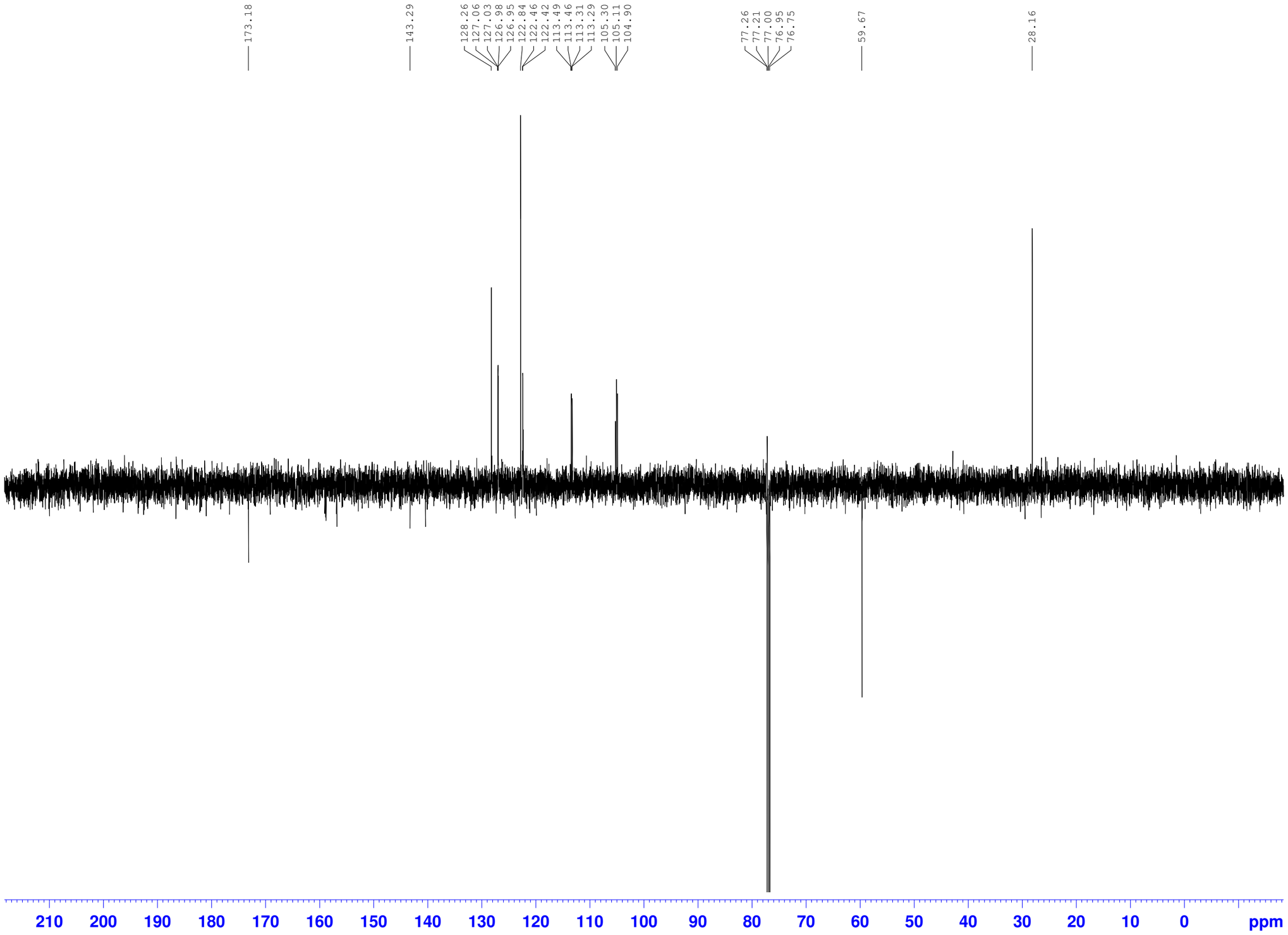
Compound 29



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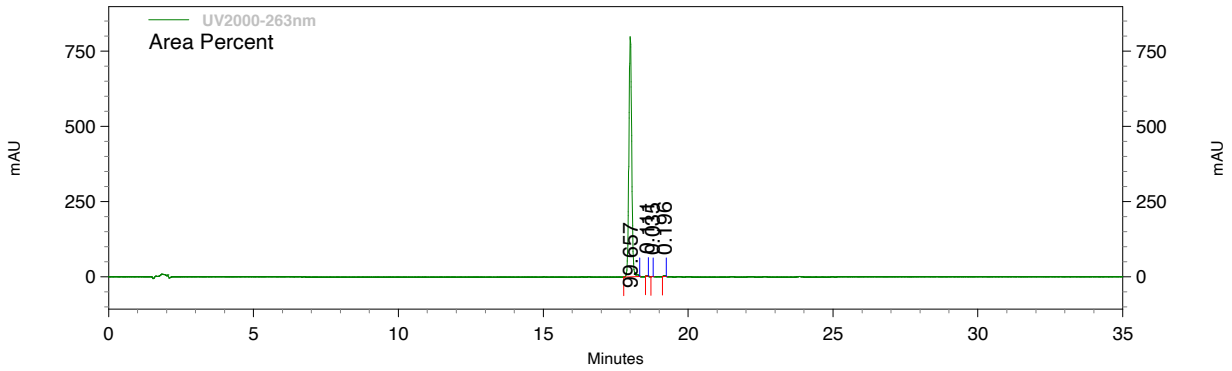
FIDRES	0.454131 Hz
AQ	1.1010548 sec
RG	3250
DW	16.800 usec
DE	12.00 usec
TE	298.1 K
CNST2	145.0000000
D1	2.00000000 sec
D4	0.00172414 sec
D12	0.00002000 sec
D15	0.00431034 sec
D20	0.00345000 sec
TD0	4
======== CHANNEL f1 ========	
NUC1	13C
P1	7.20 usec
P2	14.40 usec
PL1	-2.00 dB
PL1W	101.27846527 W
SFO1	125.7703643 MHz
======== CHANNEL f2 ========	
CPDPRG2	waltz16
NUC2	1H
P3	11.50 usec
P4	23.00 usec
PCPD2	80.00 usec
PL2	-2.00 dB
PL12	14.85 dB
PL2W	14.33185768 W
PL12W	0.29600734 W
SFO2	500.1320005 MHz
SI	32768
SF	125.7577890 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.40

Compound 29

Area % Report

Sample ID: SK64_2nd -- C:\Documents and Settings\user\Desktop\Sahar\Data\SK64_2nd-ACN_W_10-90-263nm.met-14-02-2014 11-40-54.dat
Method: C:\Documents and Settings\user\Desktop\Sahar\ACN_W_10-90-263nm.met
Acquired: 14/02/2014 11:41:38; Printed: 14/02/2014 12:20:19
Analysis Comment: {Data Description}

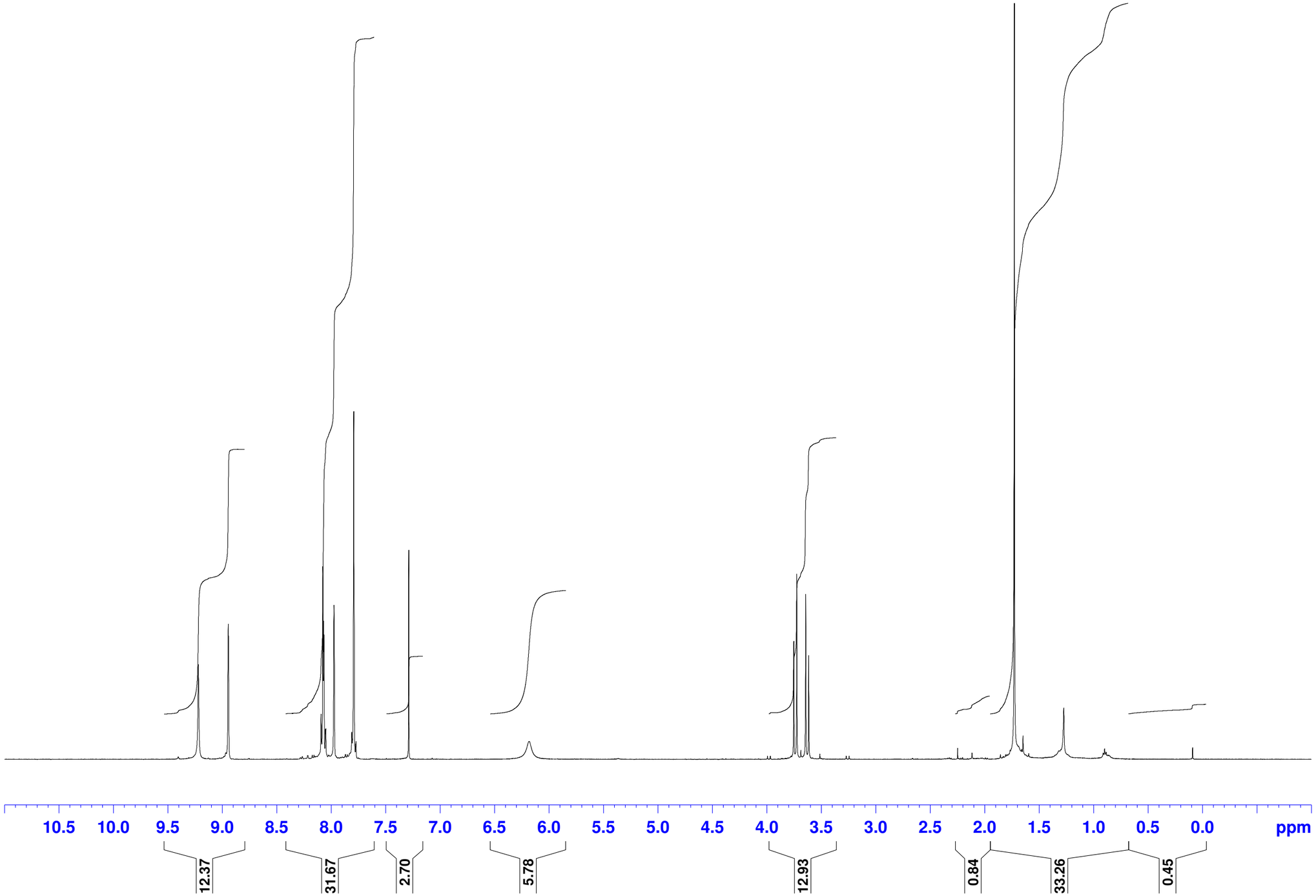


UV2000-263nm Results (System (14/02/2014 12:19:57) (Reprocessed))

Retention Time	Area	Area %	Height	Height %
18.003	5343414	99.66	797818	99.43
18.573	5977	0.11	1757	0.22
18.763	1897	0.04	608	0.08
19.175	10515	0.20	2192	0.27

Totals	5361803	100.00	802375	100.00

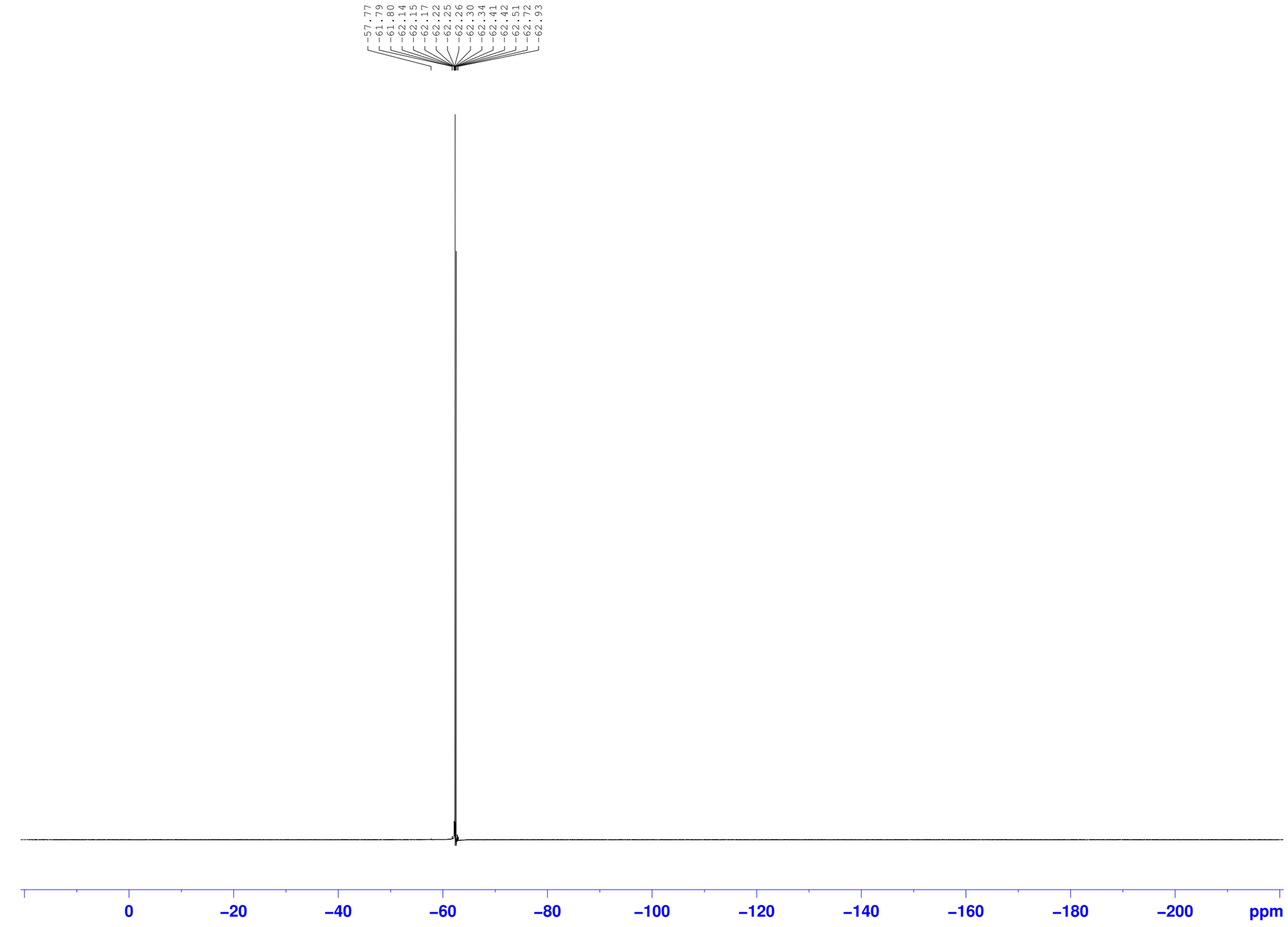
Compound 32a




```
NAME      CM-SK41_31ox(2)
EXPNO                  1
PROCNO                 1
Date_           20131204
Time               13.46
INSTRUM        Avance500
PROBHD   5 mm QNP 1H/13
PULPROG             zg30
TD                 65536
SOLVENT            CDCl3
NS                    16
DS                     2
SWH           10330.578 Hz
FIDRES         0.157632 Hz
AQ             3.1719923 sec
RG                   512
DW                48.400 use
DE                 6.50 use
TE                292.3 K
D1            1.00000000 sec
TD0                    1

======== CHANNEL f1 =======
NUC1                  1H
P1                 11.50 use
PL1                -1.00 dB
PL1W        11.38419914 W
SFO1        500.1330885 MHz
SI                 65536
SF          500.1300000 MHz
WDW                   EM
SSB                    0
LB                0.30 Hz
GB                     0
PC                 1.00
```

Compound 32a

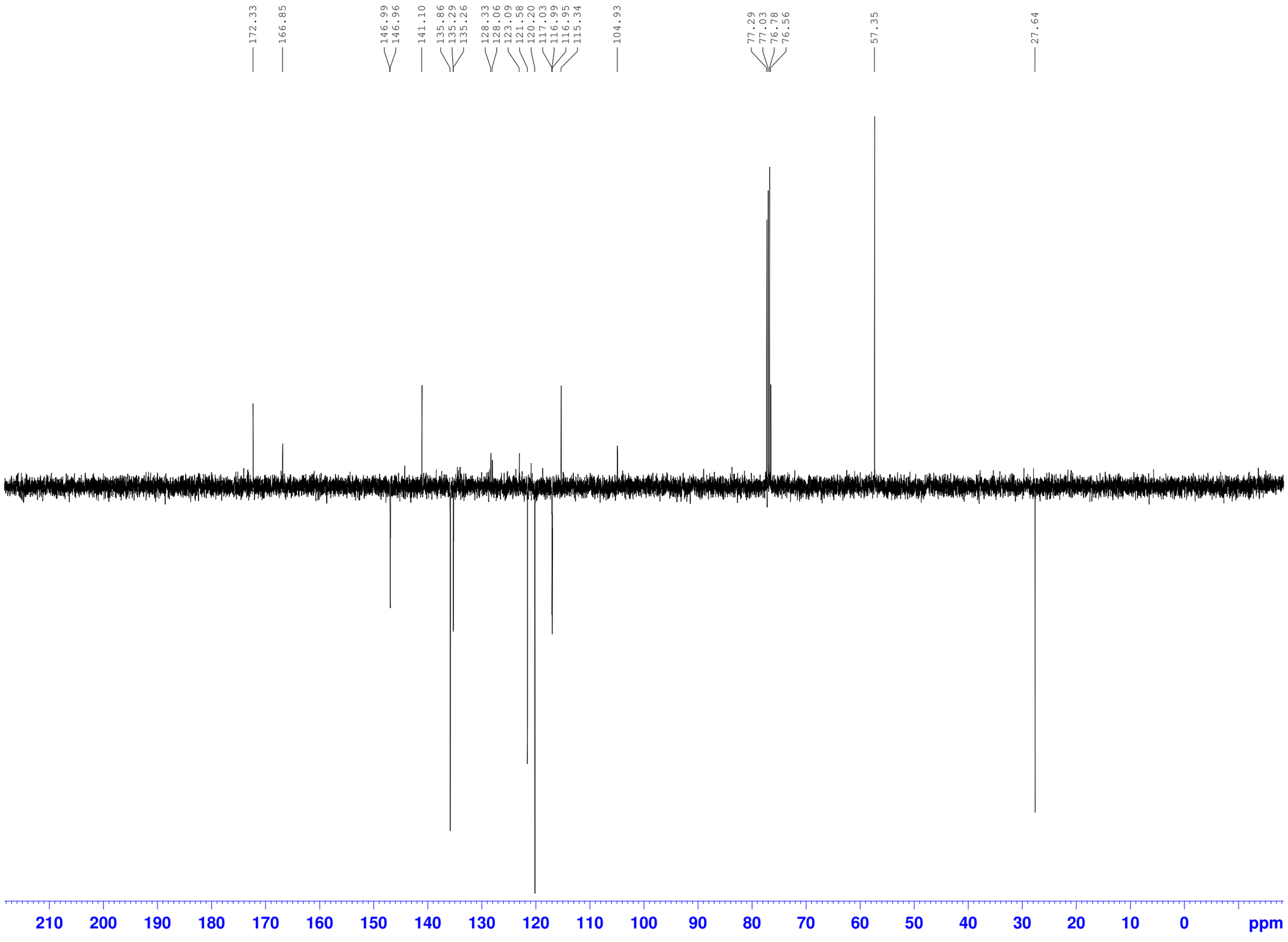



```
NAME      CM-SK41_31ox(2)
EXPNO                   2
PROCNO                  1
Date_            20131204
Time                13.48
INSTRUM         Avance500
PROBHD    5 mm QNP 1H/13
PULPROG          zgfhigqn
TD                 131072
SOLVENT              CDCl3
NS                      16
DS                       4
SWH            113636.367 Hz
FIDRES           0.866977 Hz
AQ               0.5767668 sec
RG                    1440
DW                   4.400 use
DE                    6.00 use
TE                   292.6 K
D1             1.00000000 sec
D11            0.03000000 sec
D12            0.00002000 sec
TD0                     1

======== CHANNEL f1 =======
NUC1                   19F
P1                   18.60 use
PL1                  -1.50 dB
PL1W          11.14113998 W
SFO1         470.5453180 MHz

======== CHANNEL f2 =======
CPDPRG2           waltz16
NUC2                   1H
PCPD2                80.00 use
PL2                  -2.00 dB
PL12                 14.85 dB
PL2W          14.33185768 W
PL12W          0.29600734 W
SFO2         500.1320005 MHz
SI                   65536
SF           470.5923770 MHz
WDW                     EM
SSB                      0
LB                    0.30 Hz
GB                       0
PC                    1.40
```

Compound 32a

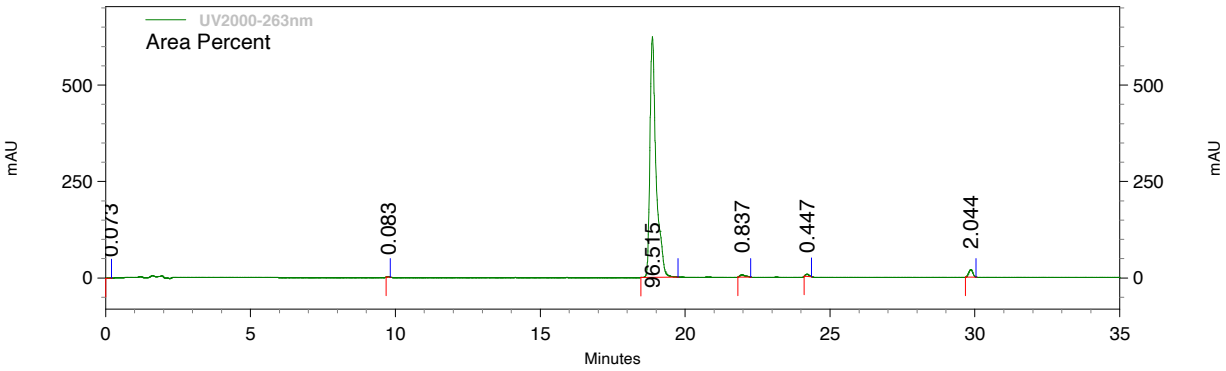


NAME	CM-SK41_31ox(2)	
EXPNO	3	
PROCNO	1	
Date_	20131204	
Time	13.55	
INSTRUM	Avance500	
PROBHD	5 mm QNP 1H/13	
PULPROG	pendant	
TD	65536	
SOLVENT	CDCl3	
NS	256	
DS	4	
SWH	29761.904	Hz
FIDRES	0.454131	Hz
AQ	1.1010548	sec
RG	3250	
DW	16.800	usec
DE	12.00	usec
TE	292.8	K
CNST2	145.0000000	
D1	2.00000000	sec
D4	0.00172414	sec
D12	0.00002000	sec
D15	0.00431034	sec
D20	0.00345000	sec
TD0	2	
======== CHANNEL f1 ========		
NUC1	13C	
P1	7.20	usec
P2	14.40	usec
PL1	-2.00	dB
PL1W	101.27846527	W
SFO1	125.7703643	MHz
======== CHANNEL f2 ========		
CPDPRG2	waltz16	
NUC2	1H	
P3	11.50	usec
P4	23.00	usec
PCPD2	80.00	usec
PL2	-2.00	dB
PL12	14.85	dB
PL2W	14.33185768	W
PL12W	0.29600734	W
SFO2	500.1320005	MHz
SI	32768	
SF	125.7577890	MHz
WDW	EM	
SSB	0	
LB	1.00	Hz
GB	0	
PC	1.40	

Compound 32a

Area % Report

Sample ID: SK41 -- C:\Documents and Settings\user\Desktop\Sahar\Data\SK41-ACN_W_10-90-263nm.met-02-12-2013 15-34-41.dat
Method: C:\Documents and Settings\user\Desktop\Sahar\ACN_W_10-90-263nm.met
Acquired: 02/12/2013 15:35:15; Printed: 02/12/2013 16:18:18
Analysis Comment: {Data Description}

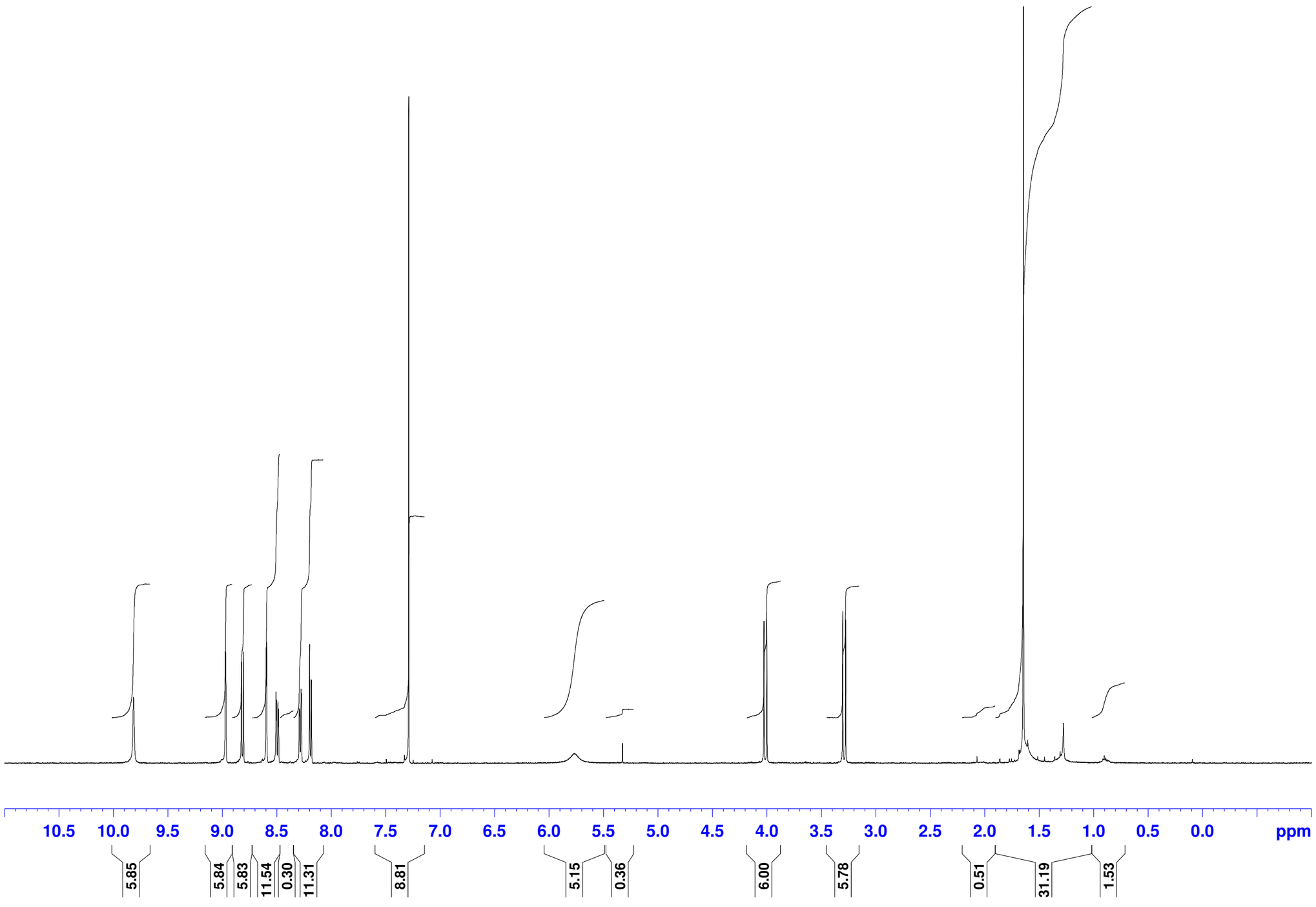


UV2000-263nm Results (System (02/12/2013 16:17:44) (Reprocessed))

Retention Time	Area	Area %	Height	Height %
0.165	7002	0.07	326	0.05
9.747	7991	0.08	1487	0.23
18.870	9276786	96.52	624297	95.06
21.953	80487	0.84	6096	0.93
24.198	43005	0.45	5271	0.80
29.853	196472	2.04	19287	2.94

Totals	9611743	100.00	656764	100.00

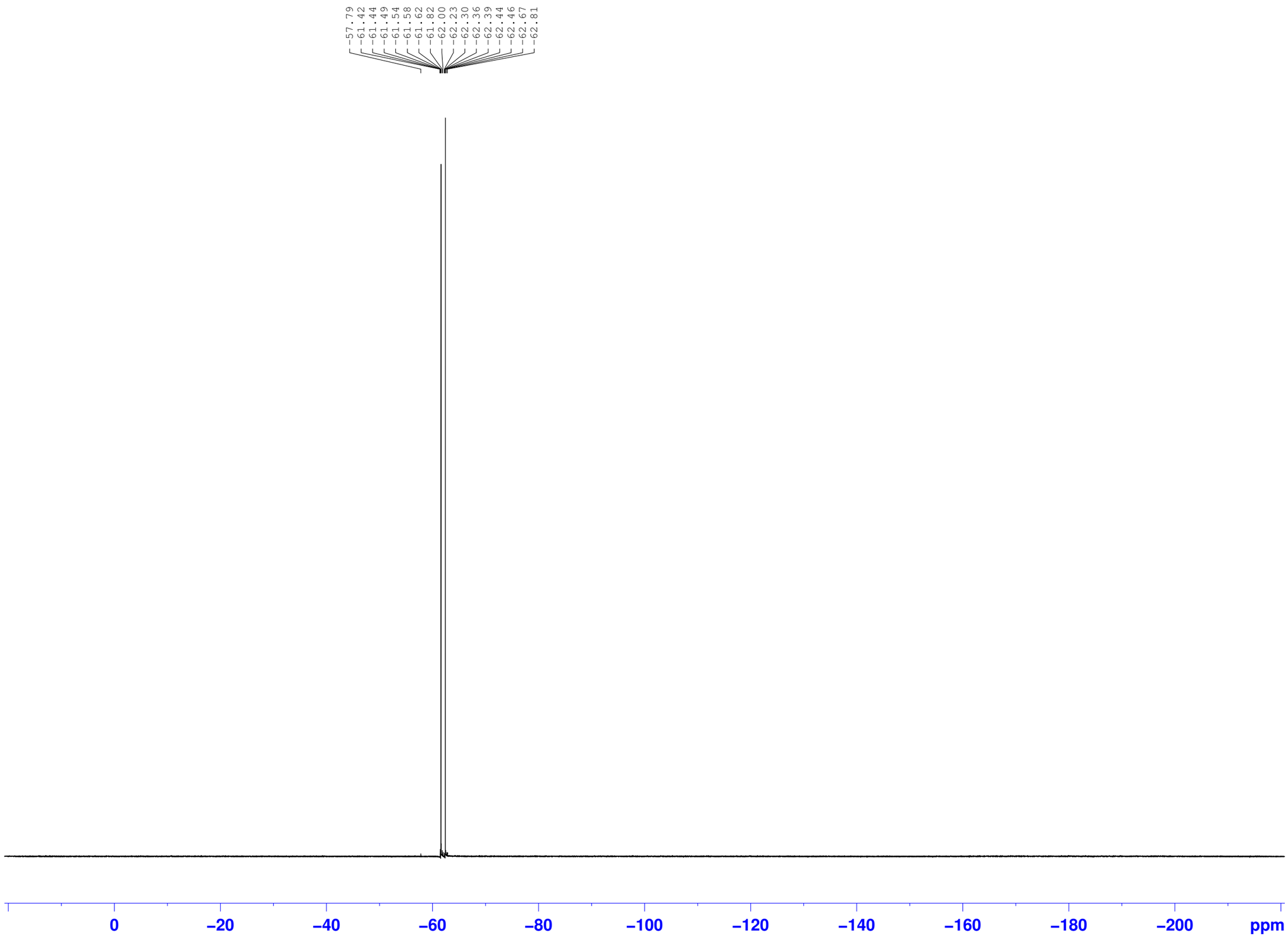
Compound 33b




```
NAME          CM-SK62(62B)
EXPNO                    1
PROCNO                   1
Date_             20140117
Time                 9.11
INSTRUM          Avance500
PROBHD    5 mm QNP 1H/13
PULPROG               zg30
TD                   65536
SOLVENT              CDCl3
NS                      16
DS                       2
SWH             10330.578 Hz
FIDRES           0.157632 Hz
AQ               3.1719923 sec
RG                     724
DW                  48.400 use
DE                   6.50 use
TE                  291.2 K
D1              1.00000000 sec
TD0                      1

======== CHANNEL f1 =======
NUC1                    1H
P1                   11.50 use
PL1                  -1.00 dB
PL1W           11.38419914 W
SFO1           500.1330885 MHz
SI                   65536
SF             500.1300000 MHz
WDW                     EM
SSB                      0
LB                  0.30 Hz
GB                       0
PC                    1.00
```

Compound 33b

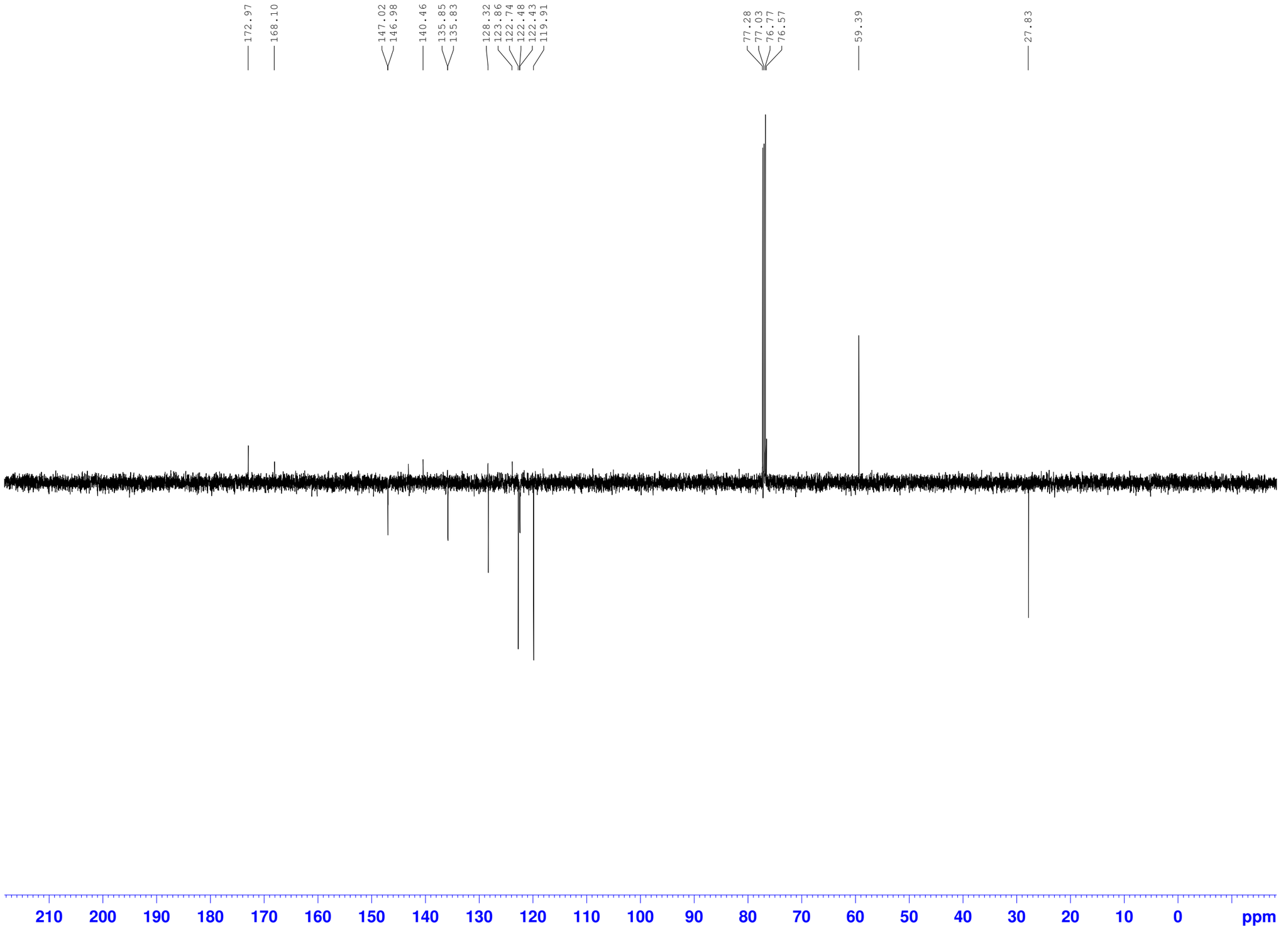



```
NAME          CM-SK62(62B)
EXPNO                    2
PROCNO                   1
Date_             20140117
Time                 9.12
INSTRUM         Avance500
PROBHD    5 mm QNP 1H/13
PULPROG          zgfhigqn
TD                 131072
SOLVENT              CDCl3
NS                      16
DS                       4
SWH            113636.367 Hz
FIDRES           0.866977 Hz
AQ               0.5767668 sec
RG                    2300
DW                   4.400 use
DE                    6.00 use
TE                  291.4 K
D1             1.00000000 sec
D11            0.03000000 sec
D12            0.00002000 sec
TD0                      1

======== CHANNEL f1 =======
NUC1                   19F
P1                   18.60 use
PL1                  -1.50 dB
PL1W          11.14113998 W
SFO1          470.5453180 MHz

======== CHANNEL f2 =======
CPDPRG2           waltz16
NUC2                   1H
PCPD2                80.00 use
PL2                  -2.00 dB
PL12                 14.85 dB
PL2W          14.33185768 W
PL12W          0.29600734 W
SFO2          500.1320005 MHz
SI                   65536
SF            470.5923770 MHz
WDW                     EM
SSB                      0
LB                    0.30 Hz
GB                       0
PC                    1.40
```

Compound 33b

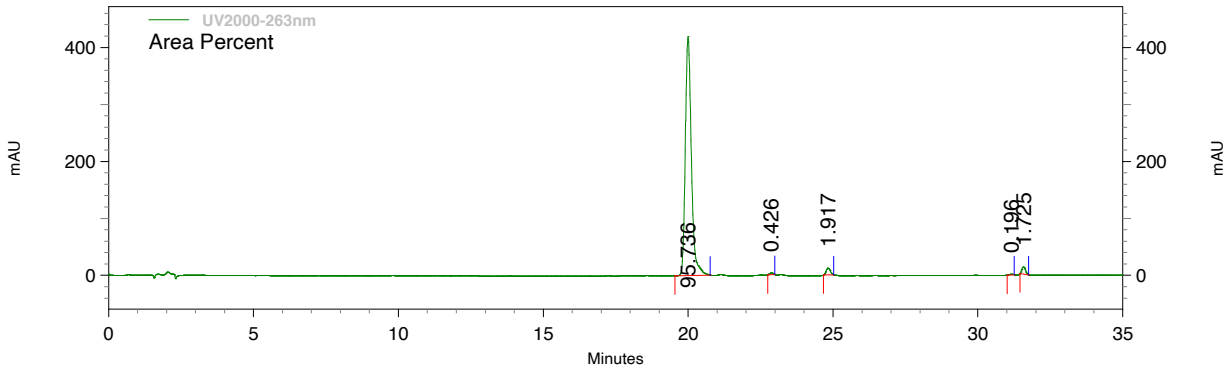


NAME	CM-SK62(B)	
EXPNO	1	
PROCNO	1	
Date_	20140121	
Time	19.11	
INSTRUM	Avance500	
PROBHD	5 mm QNP 1H/13	
PULPROG	pendant	
TD	65536	
SOLVENT	CDCl3	
NS	512	
DS	4	
SWH	29761.904	Hz
FIDRES	0.454131	Hz
AQ	1.1010548	sec
RG	3250	
DW	16.800	usec
DE	12.00	usec
TE	291.7	K
CNST2	145.0000000	
D1	2.00000000	sec
D4	0.00172414	sec
D12	0.00002000	sec
D15	0.00431034	sec
D20	0.00345000	sec
TD0	4	
======== CHANNEL f1 ========		
NUC1	13C	
P1	7.20	usec
P2	14.40	usec
PL1	-2.00	dB
PL1W	101.27846527	W
SFO1	125.7703643	MHz
======== CHANNEL f2 ========		
CPDPRG2	waltz16	
NUC2	1H	
P3	11.50	usec
P4	23.00	usec
PCPD2	80.00	usec
PL2	-2.00	dB
PL12	14.85	dB
PL2W	14.33185768	W
PL12W	0.29600734	W
SFO2	500.1320005	MHz
SI	32768	
SF	125.7577890	MHz
WDW	EM	
SSB	0	
LB	1.00	Hz
GB	0	
PC	1.40	

Compound 33b

Area % Report

Sample ID: SK62B -- C:\Documents and Settings\user\Desktop\Sahar\Data\SK62B-ACN_W_10-90-263nm.met-16-01-2014 16-17-57.dat
Method: C:\Documents and Settings\user\Desktop\Sahar\ACN_W_10-90-263nm.met
Acquired: 16/01/2014 16:20:43; Printed: 16/01/2014 17:01:28
Analysis Comment: {Data Description}



UV2000-263nm Results (System (16/01/2014 17:01:10) (Reprocessed))

Retention Time	Area	Area %	Height	Height %
19.997	6105512	95.74	419343	93.48
22.868	27186	0.43	3126	0.70
24.828	122253	1.92	11997	2.67
31.150	12477	0.20	1410	0.31
31.573	110032	1.73	12711	2.83

Totals	6377460	100.00	448587	100.00