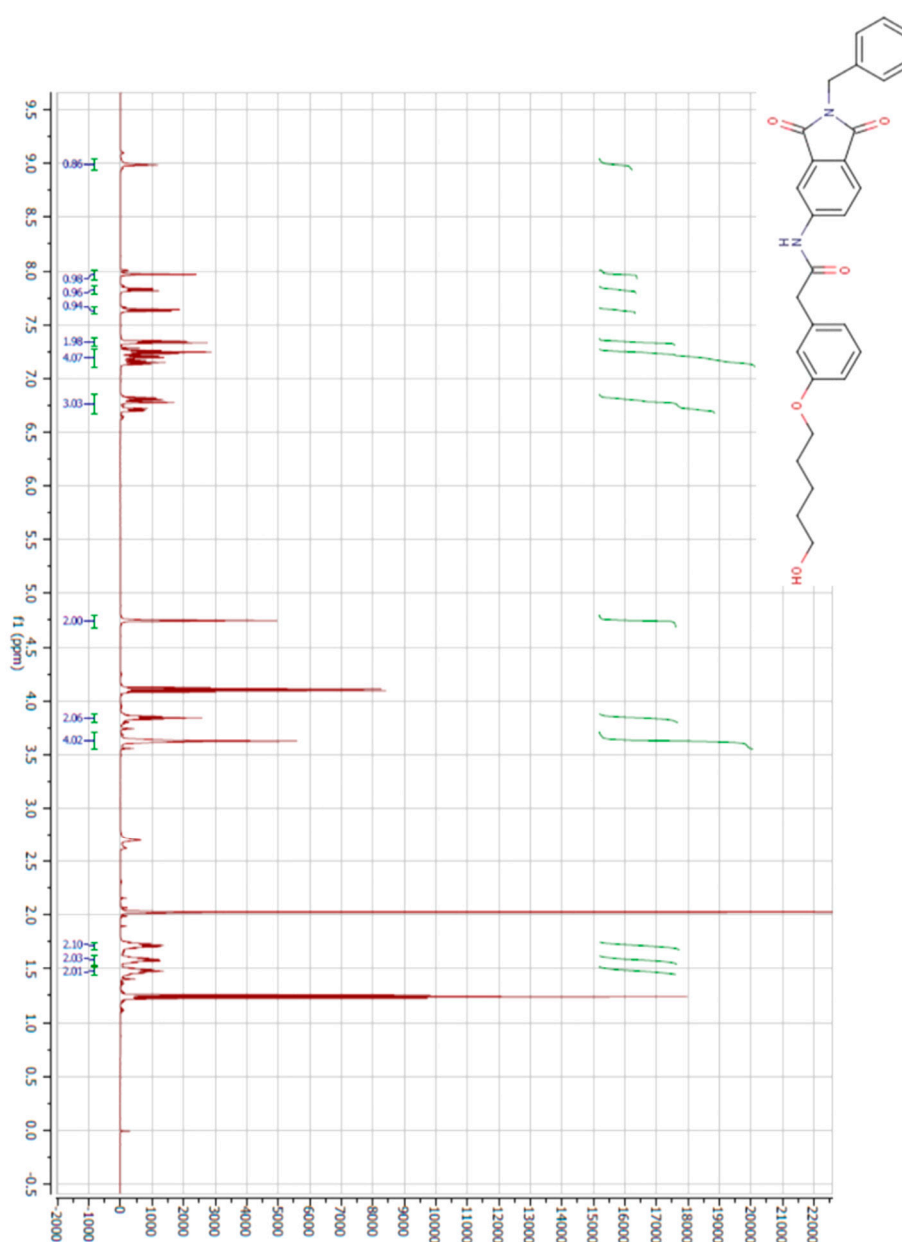


# Supplementary Materials: Molecular Recognition of the Catalytic Zinc(II) Ion in MMP-13: Structure-Based Evolution of an Allosteric Inhibitor to Dual Binding Mode Inhibitors with Improved Lipophilic Ligand Efficiencies

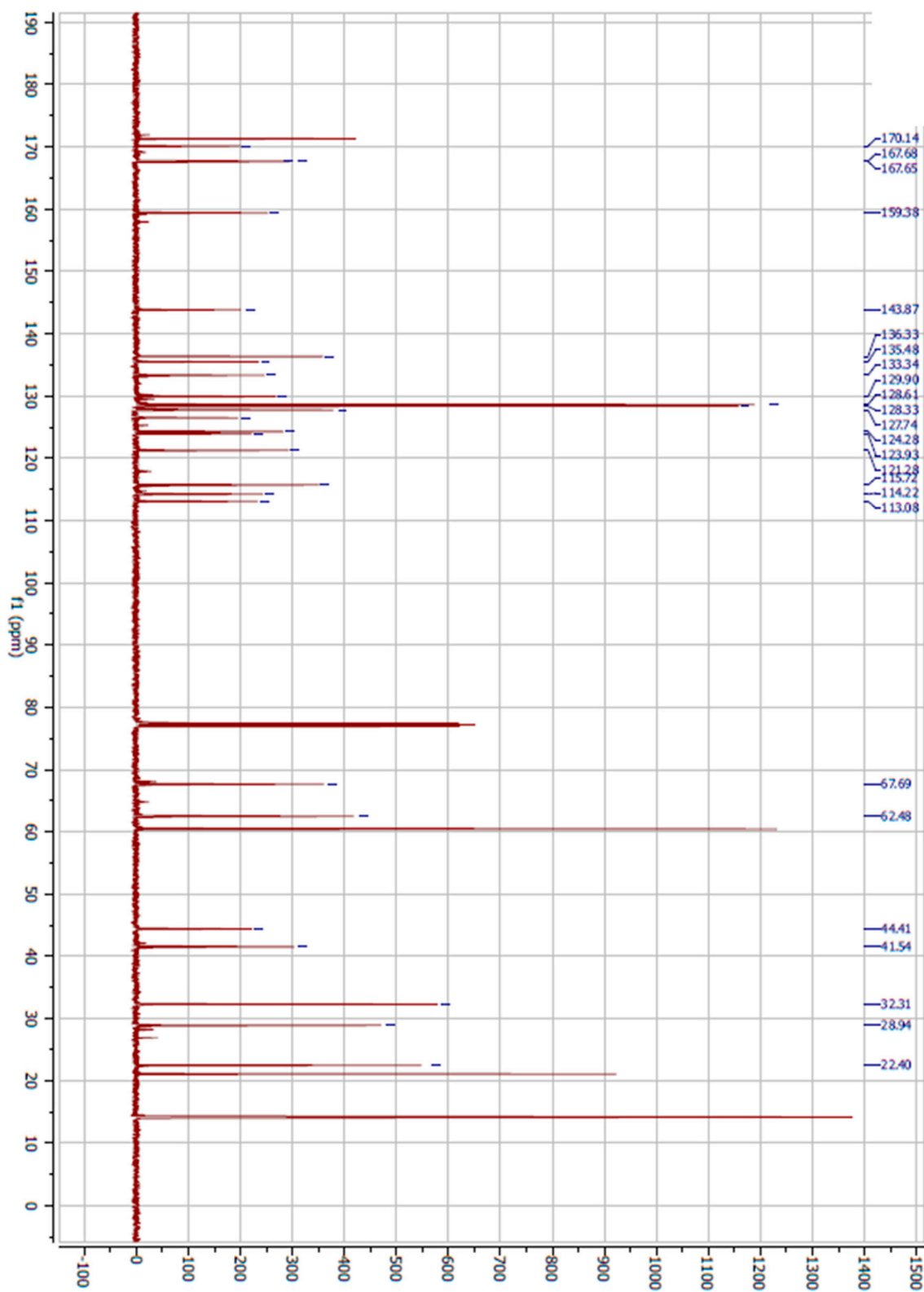
Thomas Fischer and Rainer Riedl

*N*-(2-benzyl-1,3-dioxo-2,3-dihydro-1*H*-isoindol-5-yl)-2-{3-[(5-hydroxypentyl)oxy]phenyl}acetamide (2; ZHAW5041)

## NMR

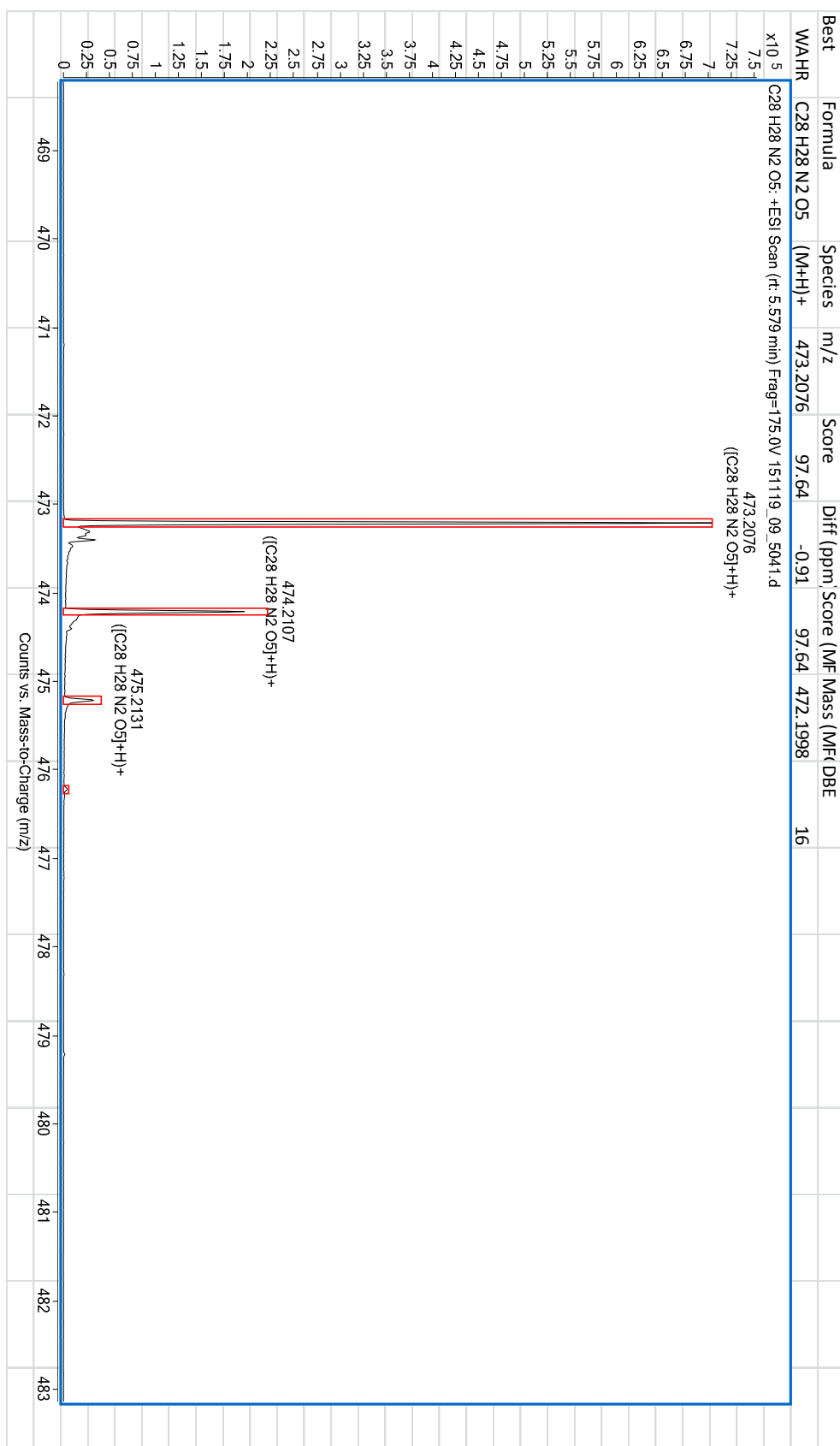


*N*-(2-benzyl-1,3-dioxo-2,3-dihydro-1*H*-isoindol-5-yl)-2-{3-[(5-hydroxypentyl)oxy]phenyl}acetamide (**2**; ZHAW5041)



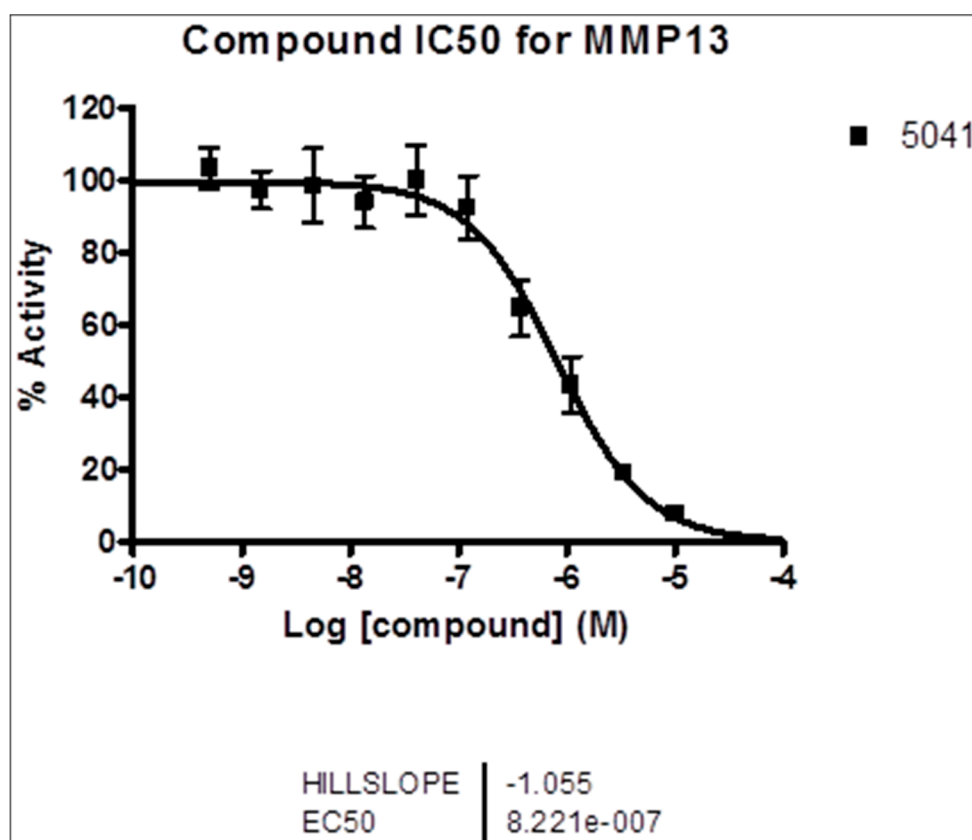
**HRMS**

***N*-(2-benzyl-1,3-dioxo-2,3-dihydro-1*H*-isoindol-5-yl)-2-{3-[(5-hydroxypentyl)oxy]phenyl}acetamide (2; ZHAW5041)**



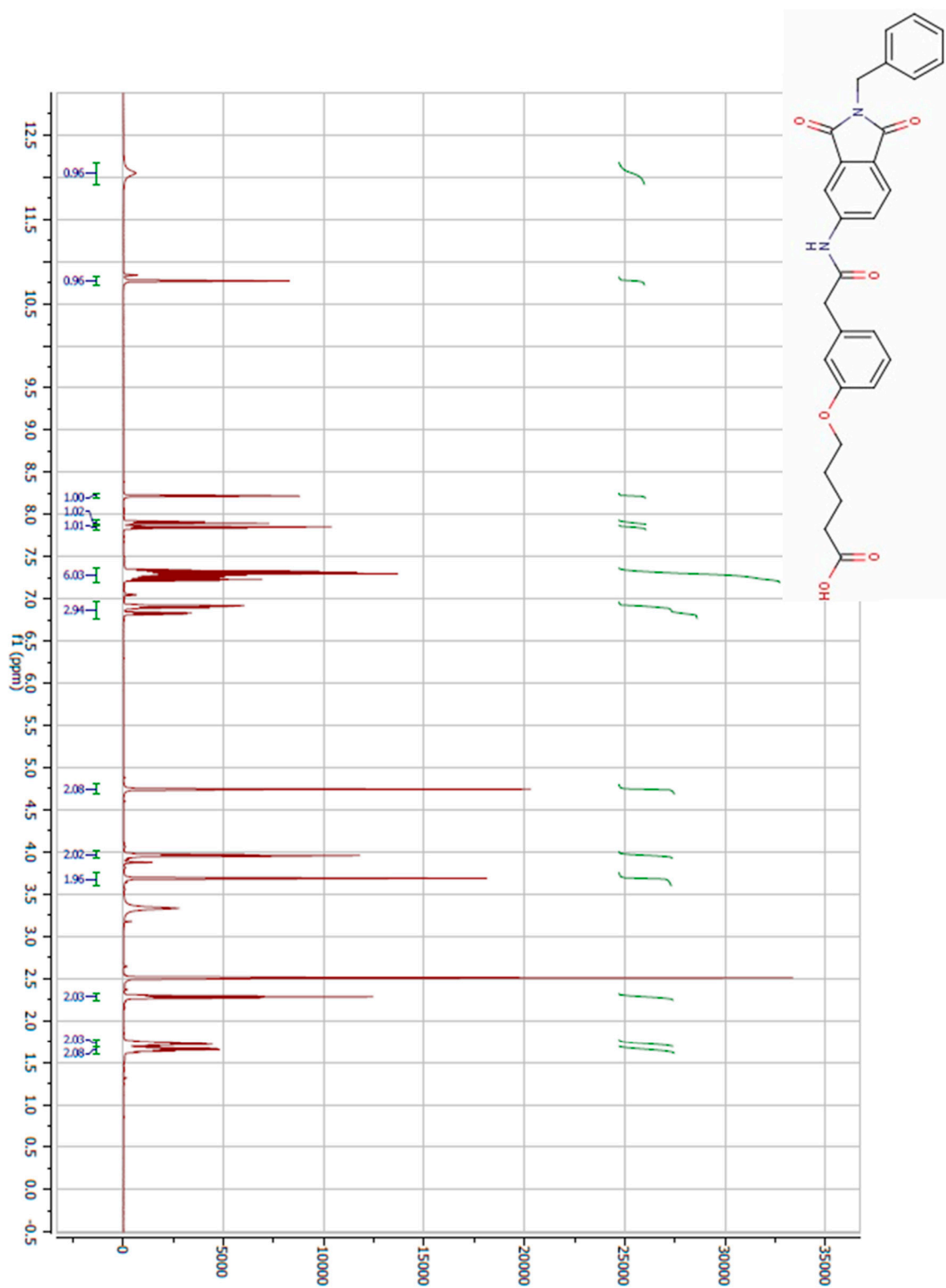
**IC<sub>50</sub>**

*N*-(2-benzyl-1,3-dioxo-2,3-dihydro-1*H*-isoindol-5-yl)-2-{3-[(5-hydroxypentyl)oxy]phenyl}acetamide (2; ZHAW5041)

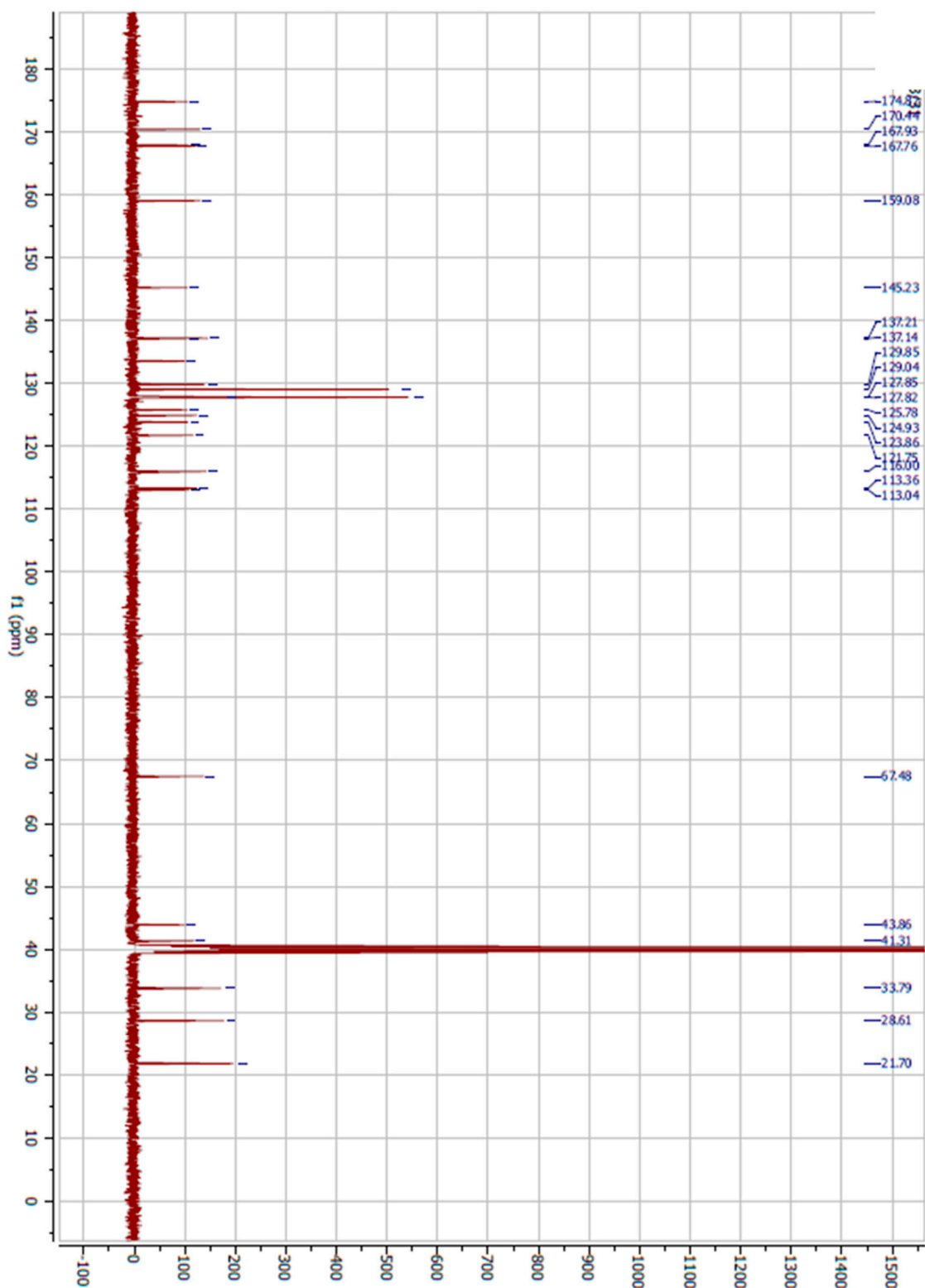


5-(3-((2-benzyl-1,3-dioxo-2,3-dihydro-1H-isoindol-5-yl)carbonyl)methyl)phenoxy)pentanoic acid  
(3; ZHAW5077)

**NMR**

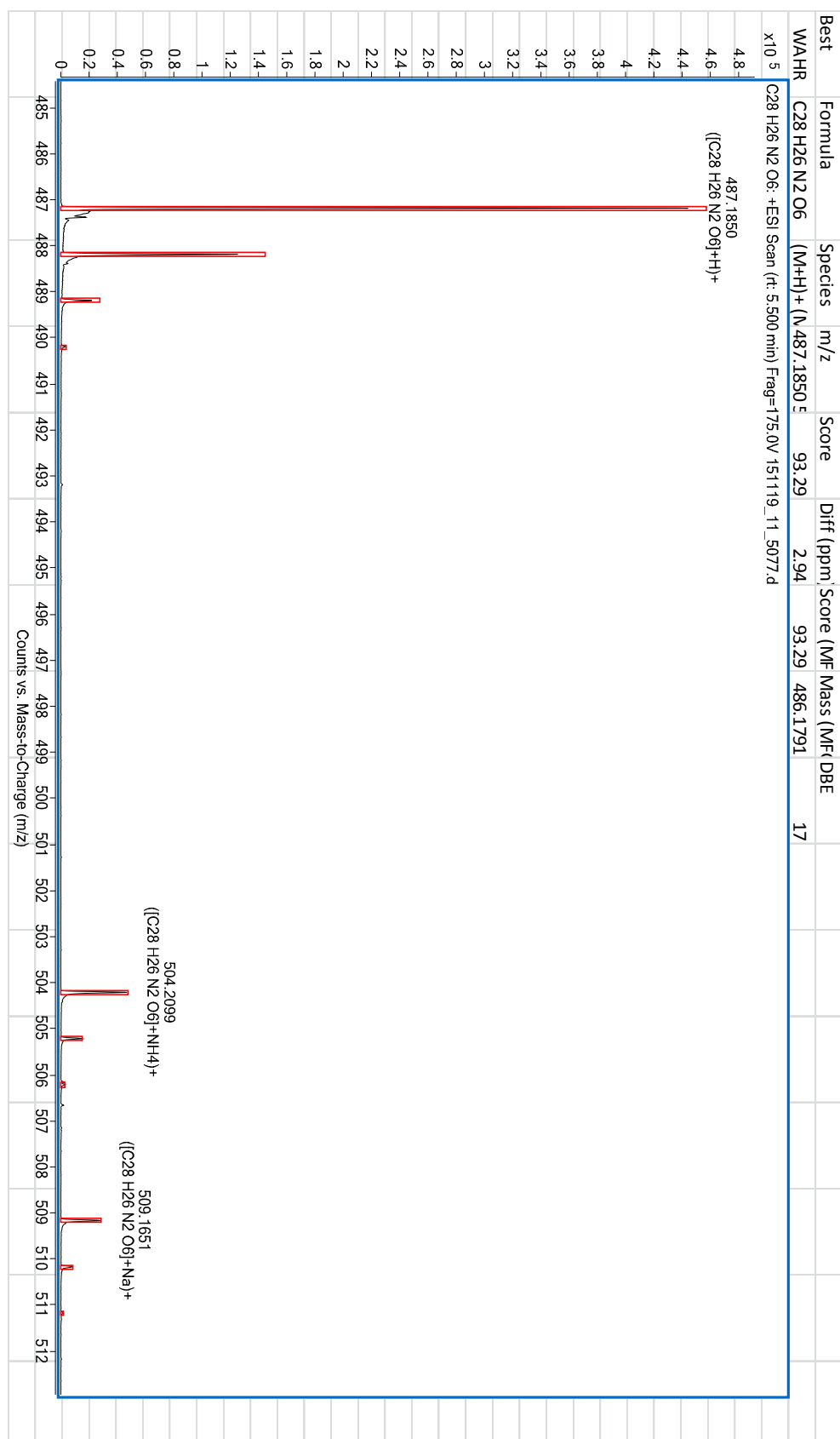


5-(3-((2-benzyl-1,3-dioxo-2,3-dihydro-1H-isoindol-5-yl)carbamoyl)methyl)phenoxy)pentanoic acid (3; ZHAW5077)



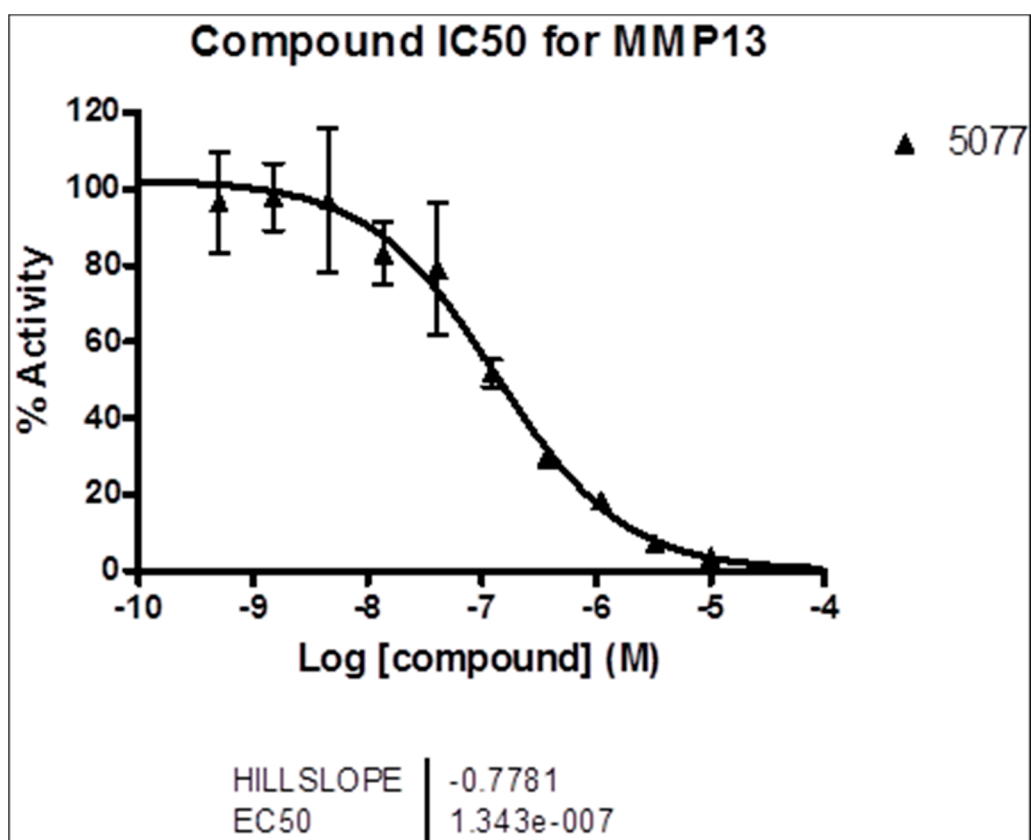
**HRMS**

5-(3-(((2-benzyl-1,3-dioxo-2,3-dihydro-1H-isoindol-5-yl)carbamoyl)methyl)phenoxy)pentanoic acid  
(**3**; ZHAW5077)



**IC<sub>50</sub>**

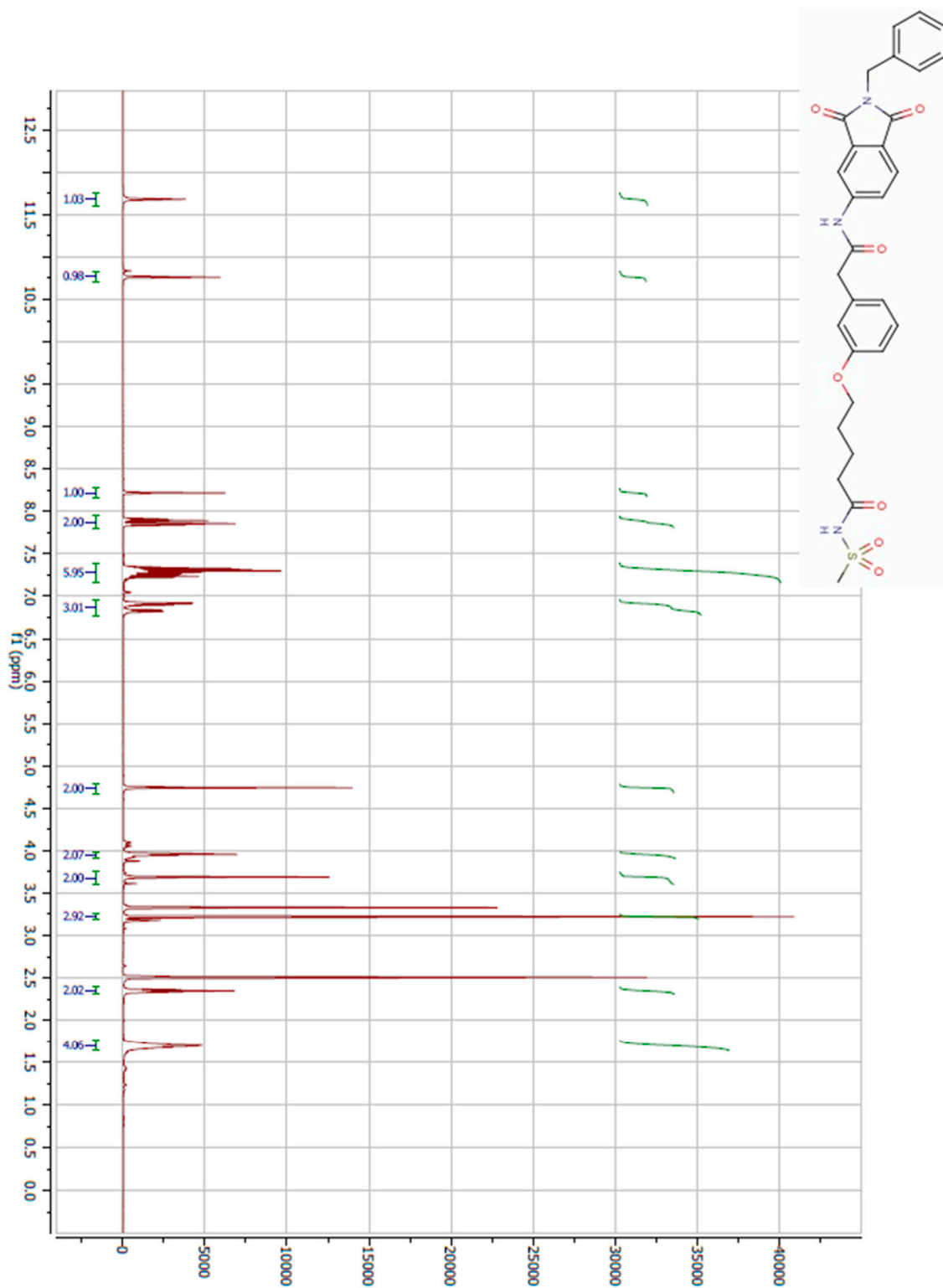
5-(3-(((2-benzyl-1,3-dioxo-2,3-dihydro-1H-isoindol-5-yl)carbamoyl)methyl}phenoxy)pentanoic acid (3; ZHAW5077)



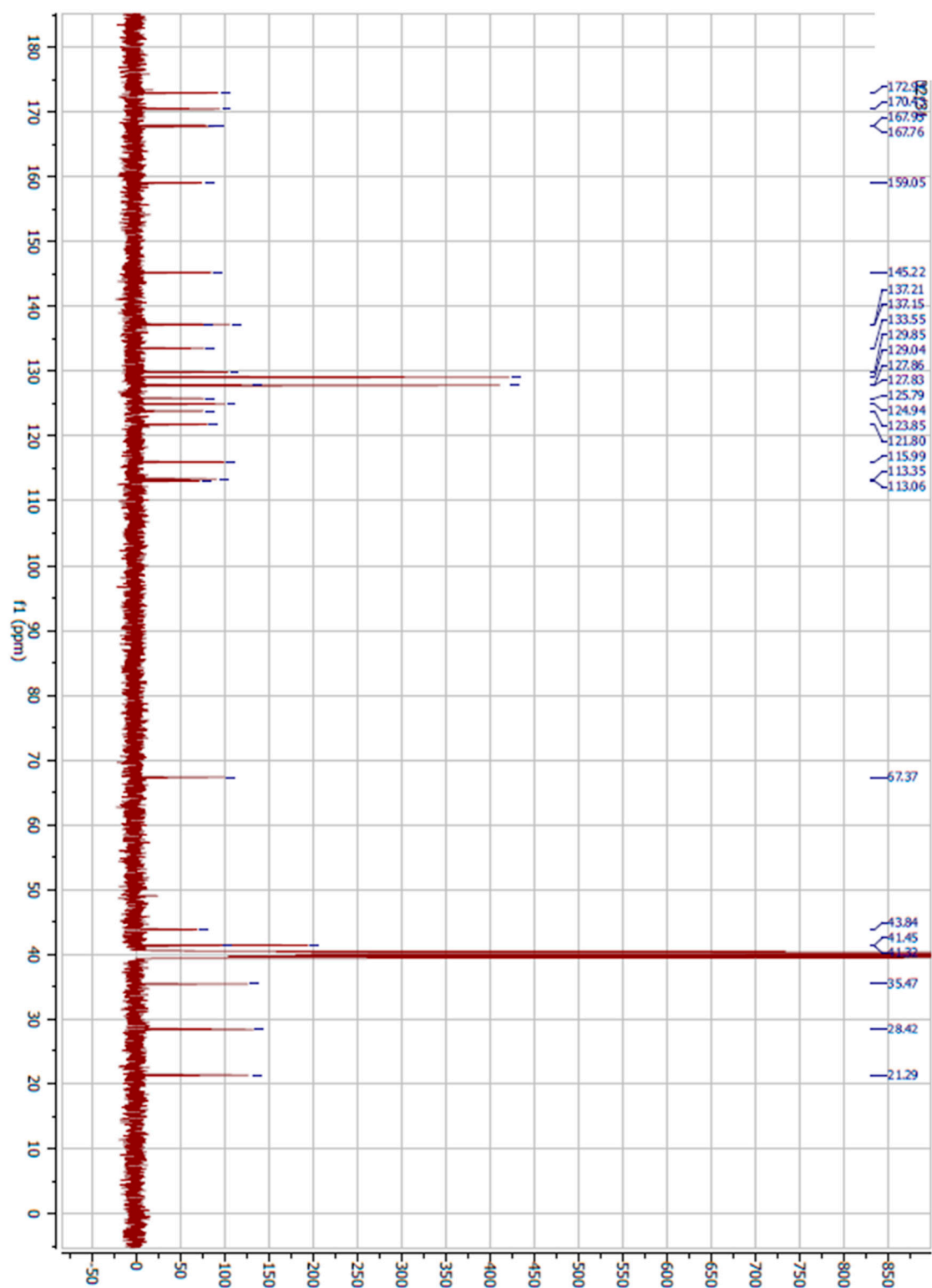


5-(3-[[2-benzyl-1,3-dioxo-2,3-dihydro-1H-isoindol-5-yl]carbonyl]methoxy)phenyl)-N-methanesulfonylpentanamide (**4**; ZHAW5079)

**NMR**

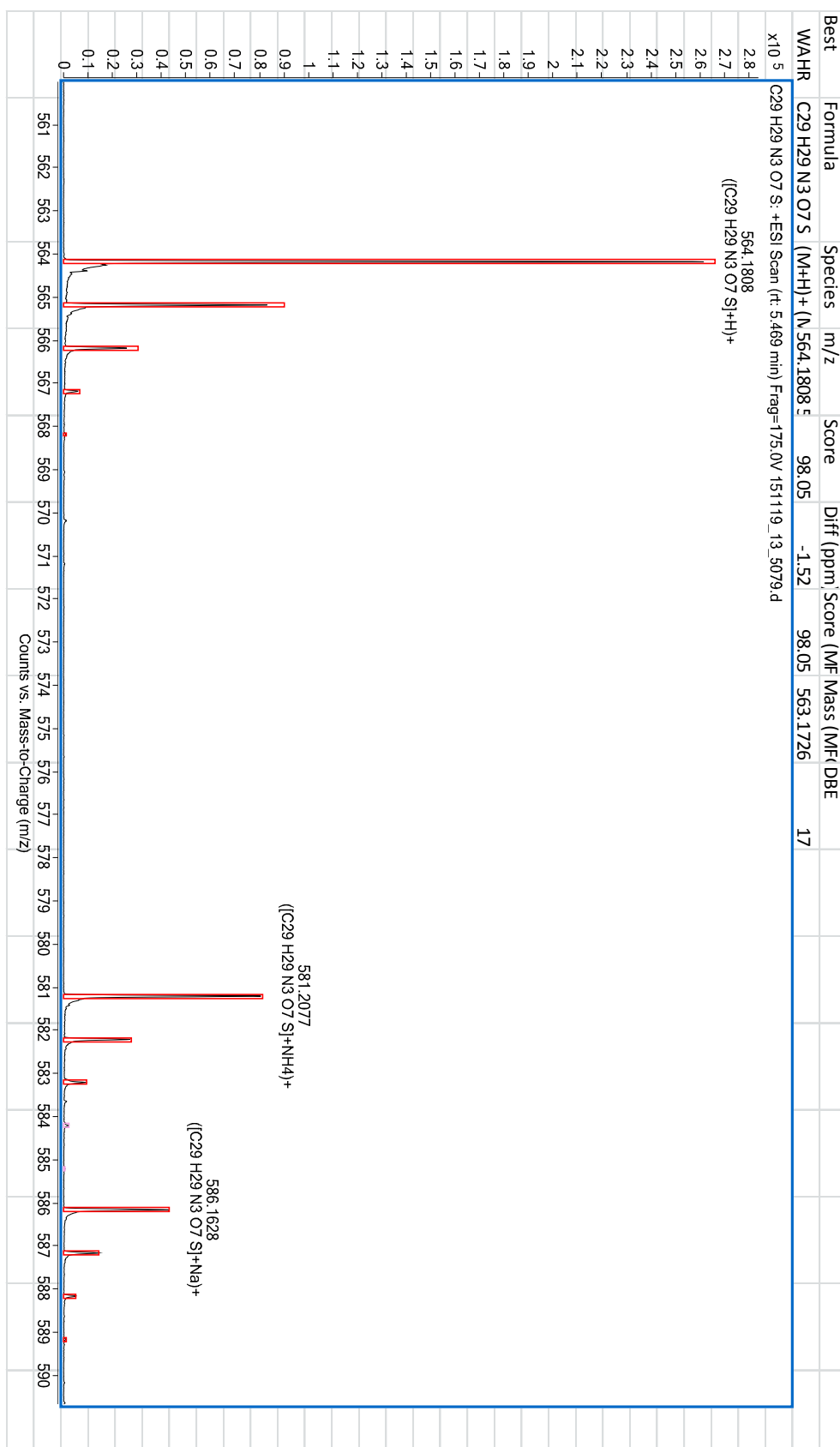


5-(3-((2-benzyl-1,3-dioxo-2,3-dihydro-1H-isoindol-5-yl)carbonyl)methyl)phenoxy)-N-methanesulfonylpentanamide (**4**; ZHAW5079)



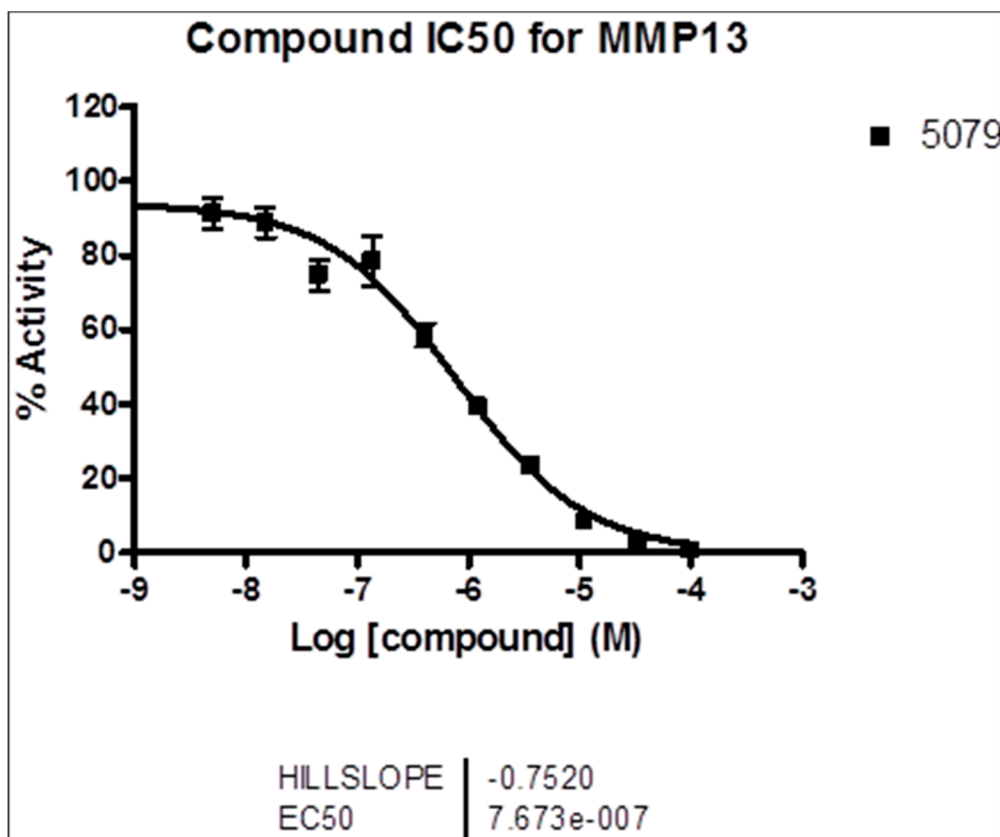
### HRMS

5-(3-[[[(2-benzyl-1,3-dioxo-2,3-dihydro-1H-isoindol-5-yl)carbamoyl]methyl]phenoxy]-N-methanesulfonylpentanamide (**4**; ZHAW5079)



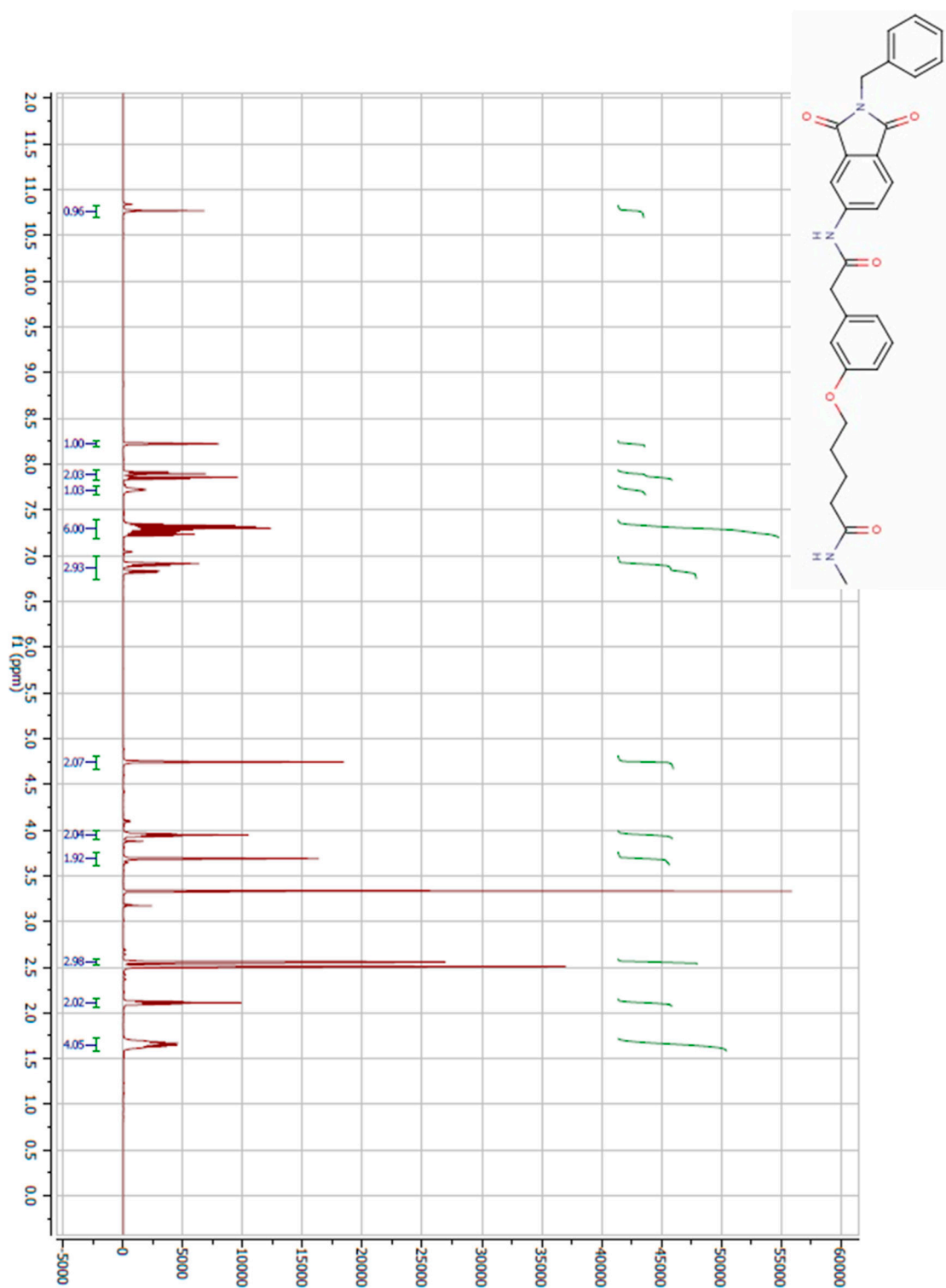
**IC<sub>50</sub>**

5-(3-(((2-benzyl-1,3-dioxo-2,3-dihydro-1H-isoindol-5-yl)carbamoyl)methyl}phenoxy)-N-methanesulfonylpentanamide (**4**; ZHAW5079)

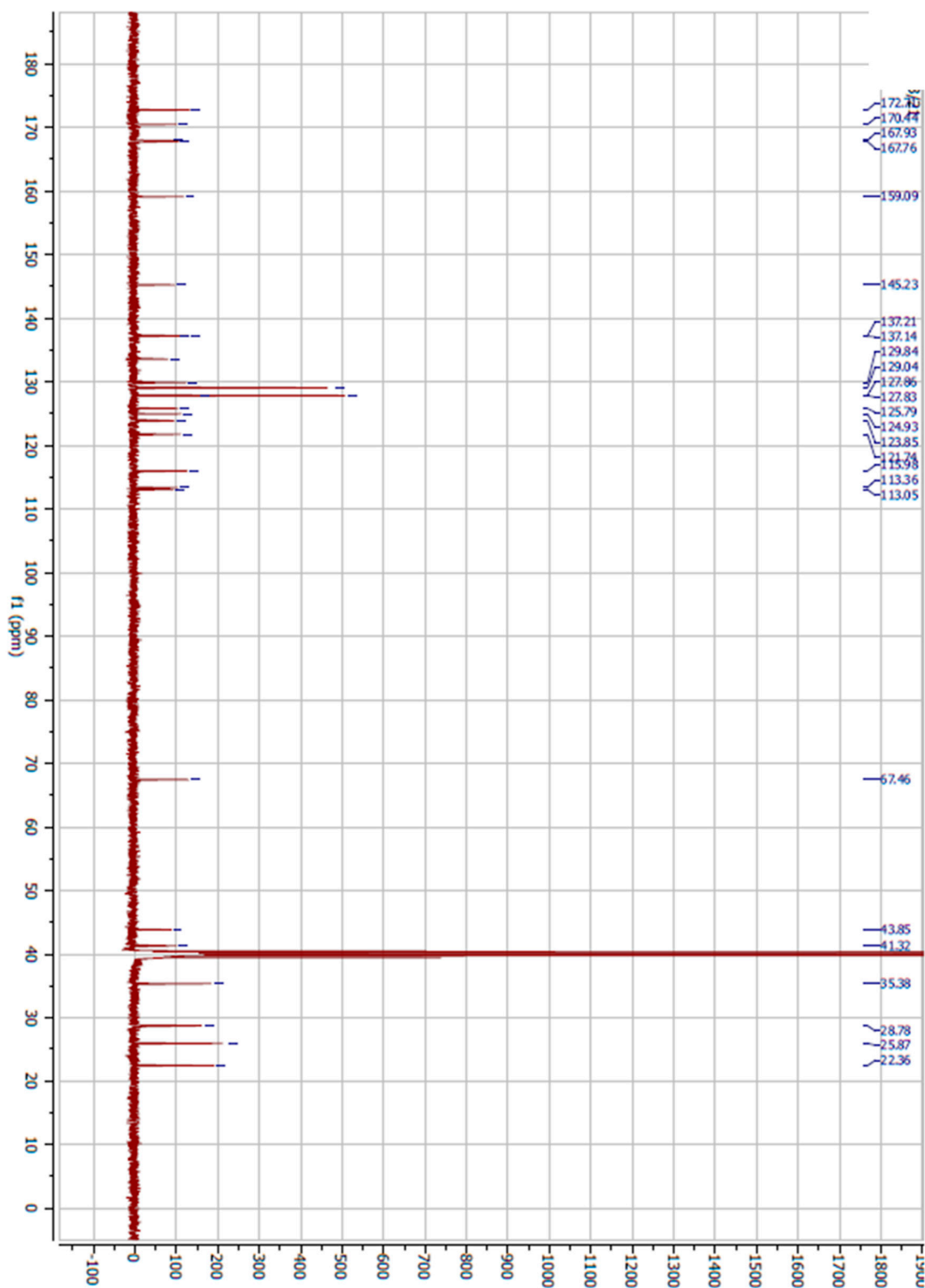


5-(3-((2-benzyl-1,3-dioxo-2,3-dihydro-1H-isoindol-5-yl)carbonyl)methyl)phenoxy)-N-methylpentanamide (5; ZHAW5080)

**NMR**

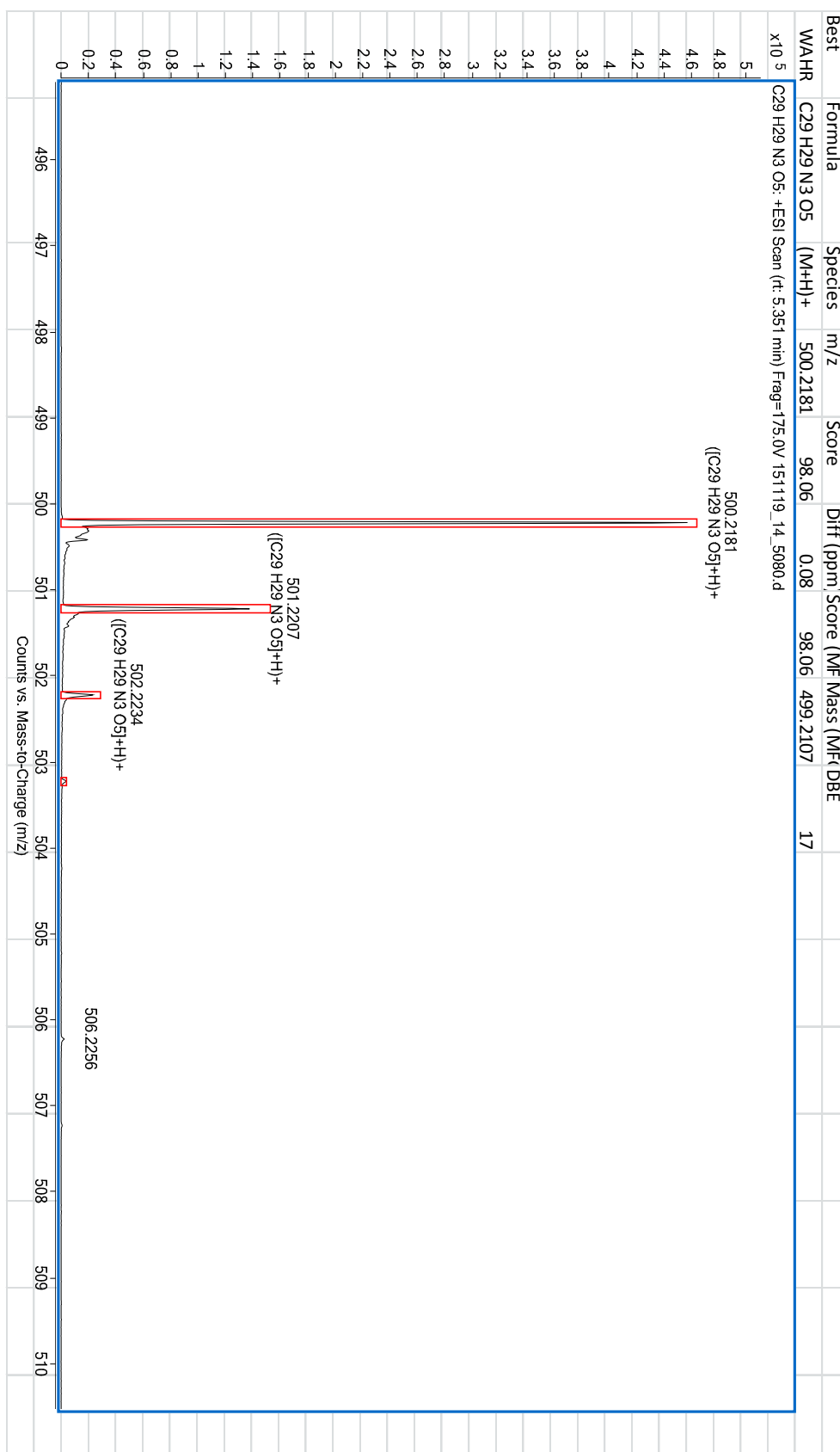


5-(3-{{(2-benzyl-1,3-dioxo-2,3-dihydro-1H-isoindol-5-yl)carbamoyl}methyl}phenoxy)-N-methylpentanamide (**5**; ZHAW5080)



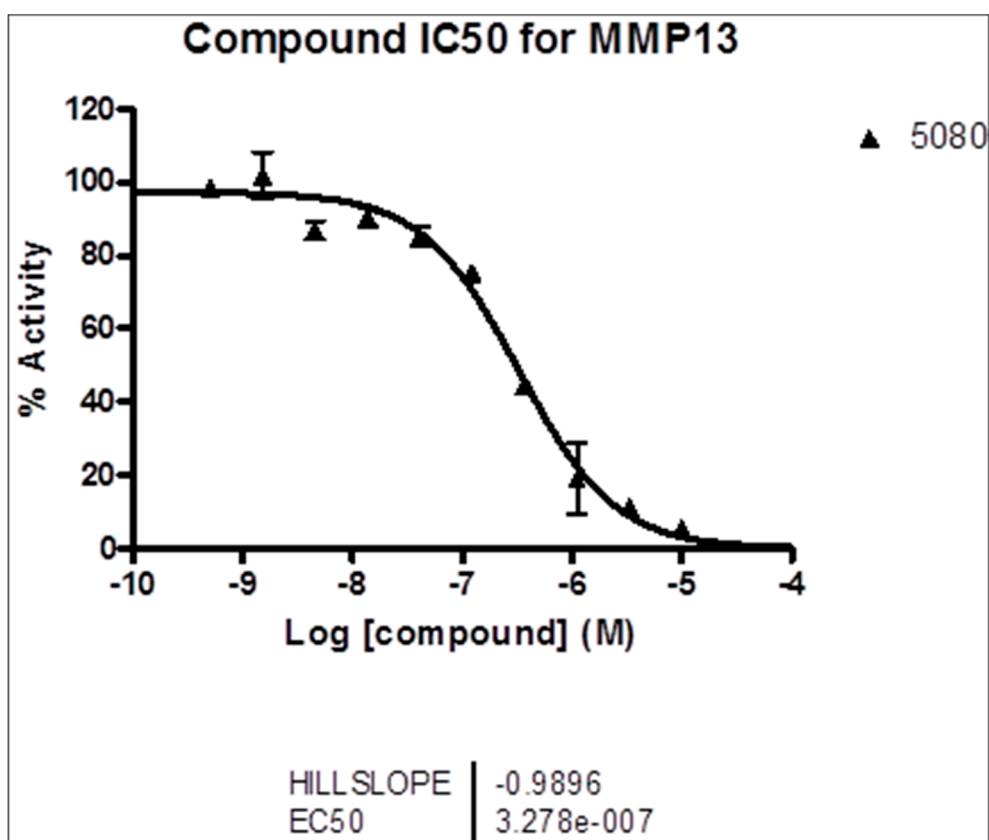
**HRMS**

5-(3-[[[(2-benzyl-1,3-dioxo-2,3-dihydro-1H-isoindol-5-yl)carbamoyl]methyl]phenoxy]-N-methylpentanamide (5; ZHAW5080)

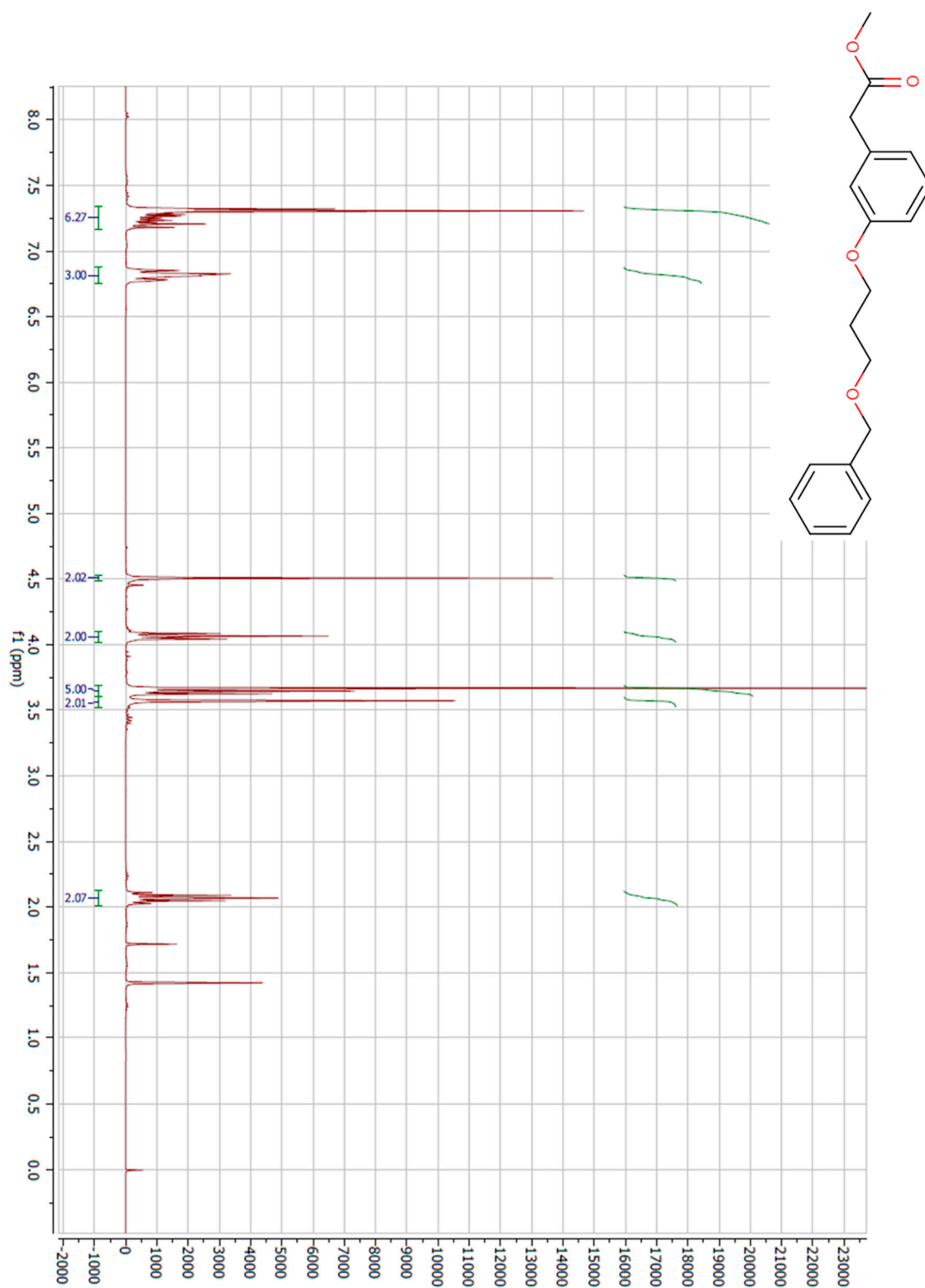


**IC<sub>50</sub>**

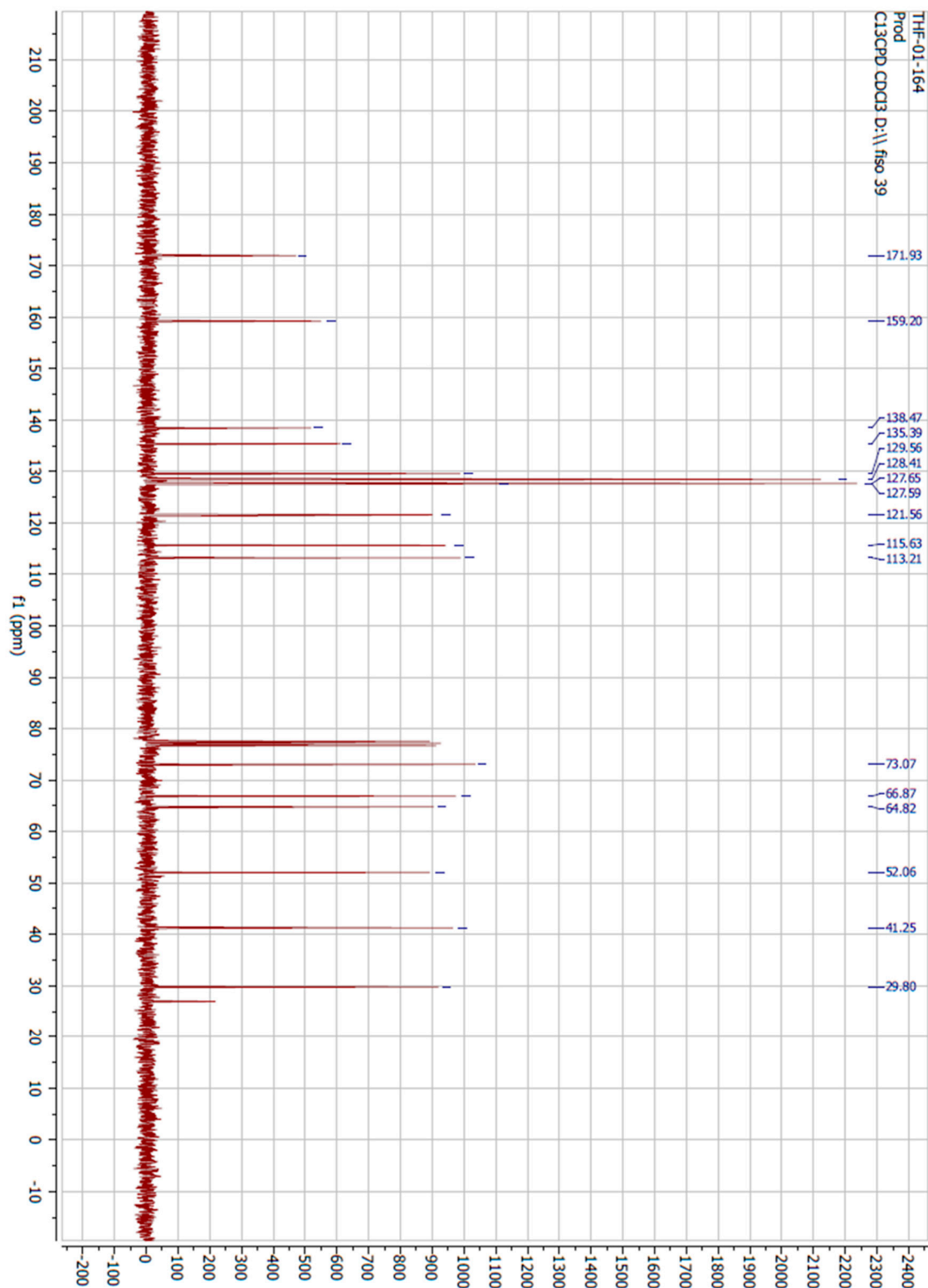
5-(3-[[[2-benzyl-1,3-dioxo-2,3-dihydro-1H-isoindol-5-yl]carbamoyl]methyl]phenoxy)-N-methylpentanamide (5; ZHAW5080)

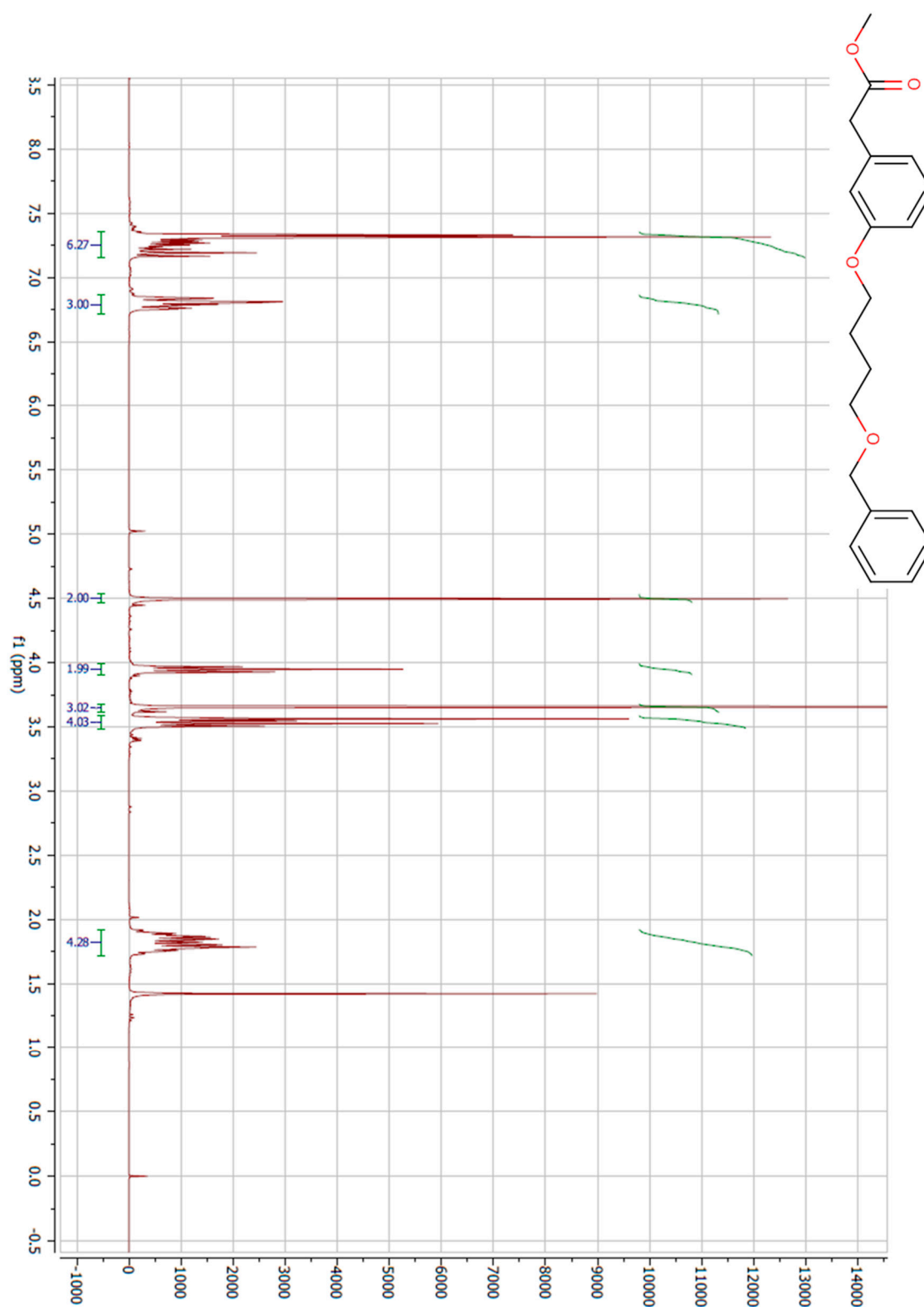




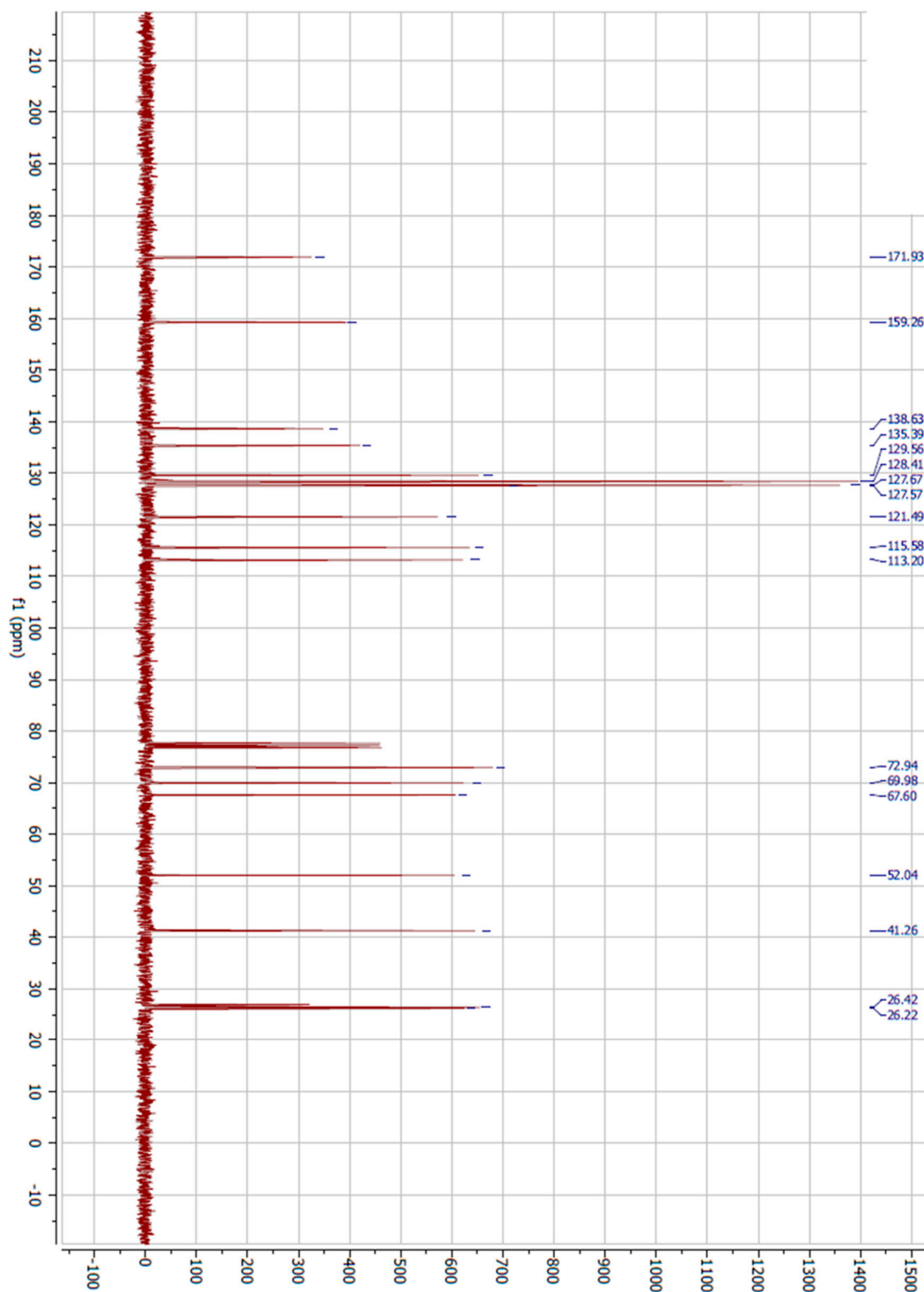
Methyl 2-(3-{{3-(benzyloxy)propyl}oxy}phenyl)acetate (**8a**; ZHAW4557)**NMR**

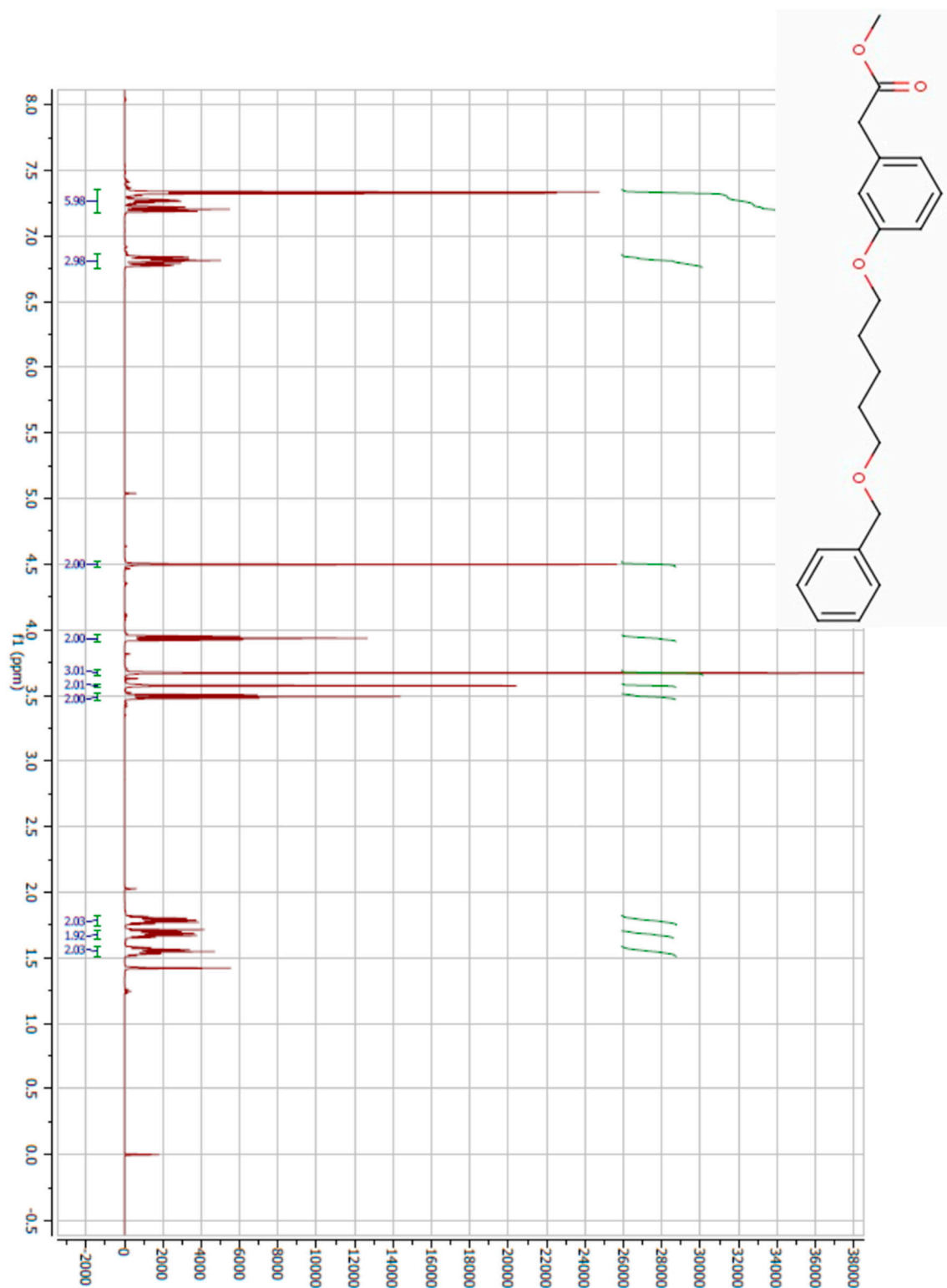
Methyl 2-(3-{{3-(benzyloxy)propyl}oxy}phenyl)acetate (8a; ZHAW4557)



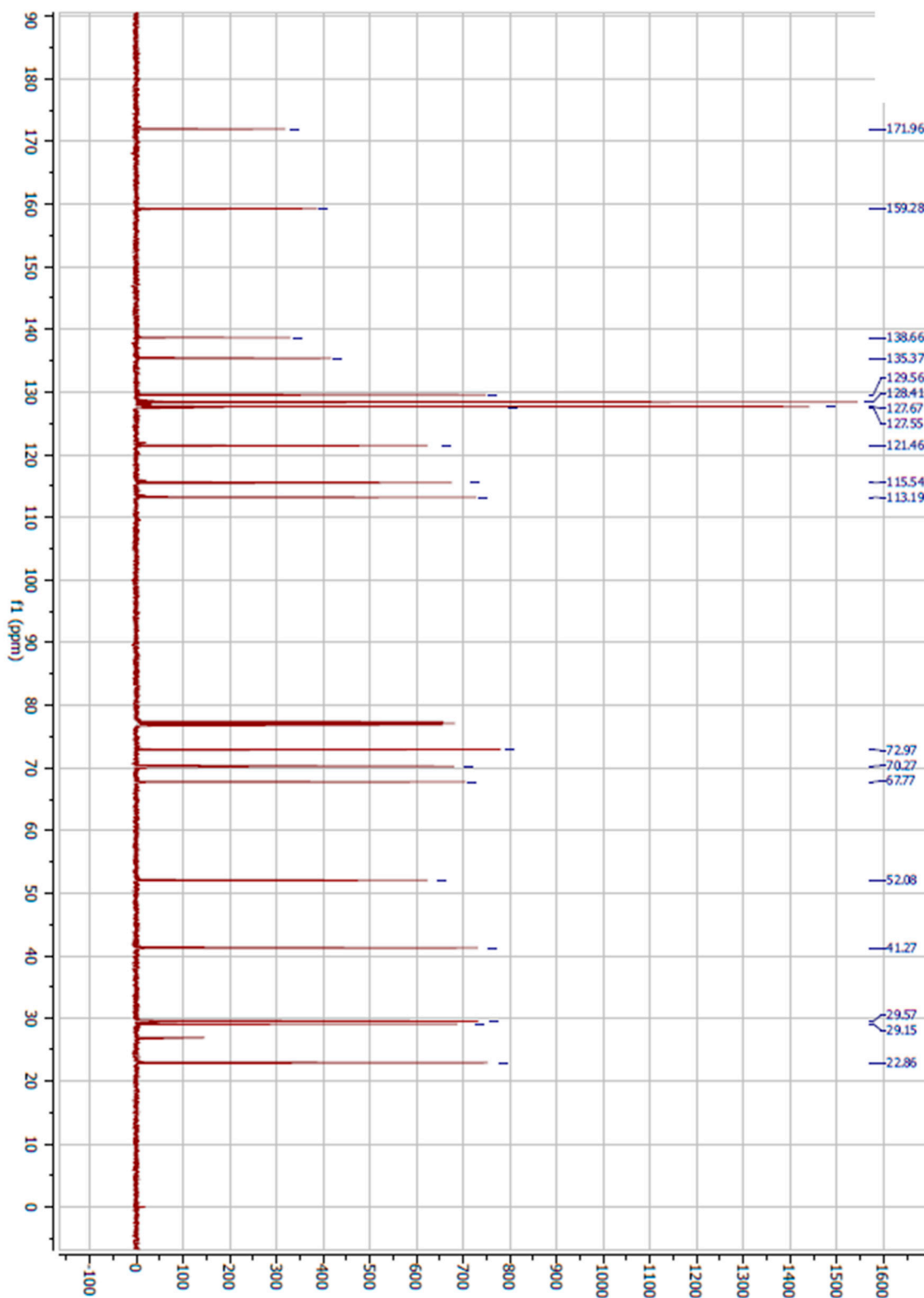
Methyl 2-(3-{{4-(benzyloxy)butyl}oxy}phenyl)acetate (**8b**; ZHAW4558)**NMR**

Methyl 2-(3-{{4-(benzyloxy)butyl}oxy}phenyl)acetate (**8b**; ZHAW4558)



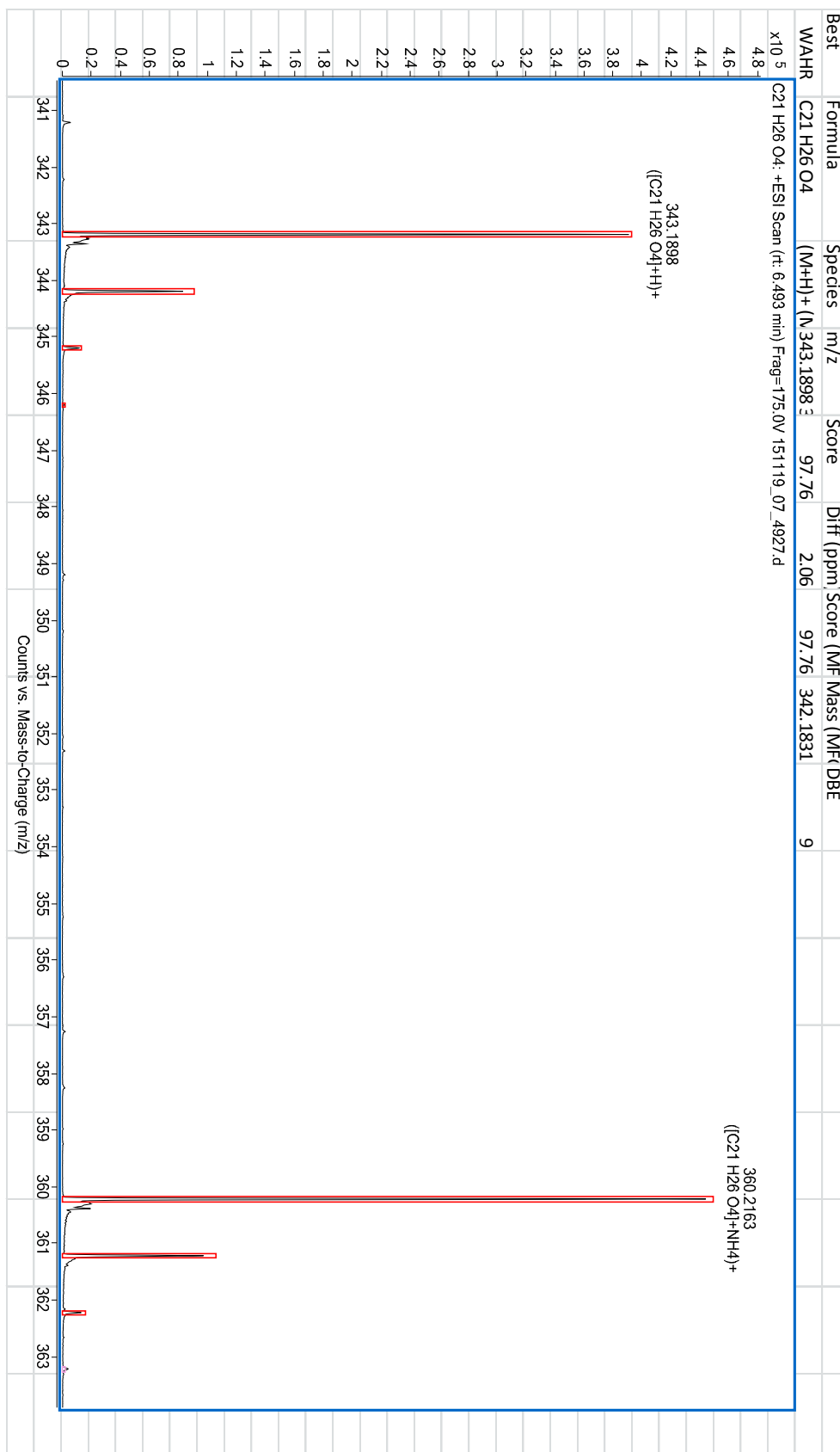
Methyl 2-(3-[[5-(benzyloxy)pentyl]oxy]phenyl)acetate (**8c**; ZHAW4927)**NMR**

Methyl 2-(3-[[5-(benzyloxy)pentyl]oxy]phenyl)acetate (**8c**; ZHAW4927)



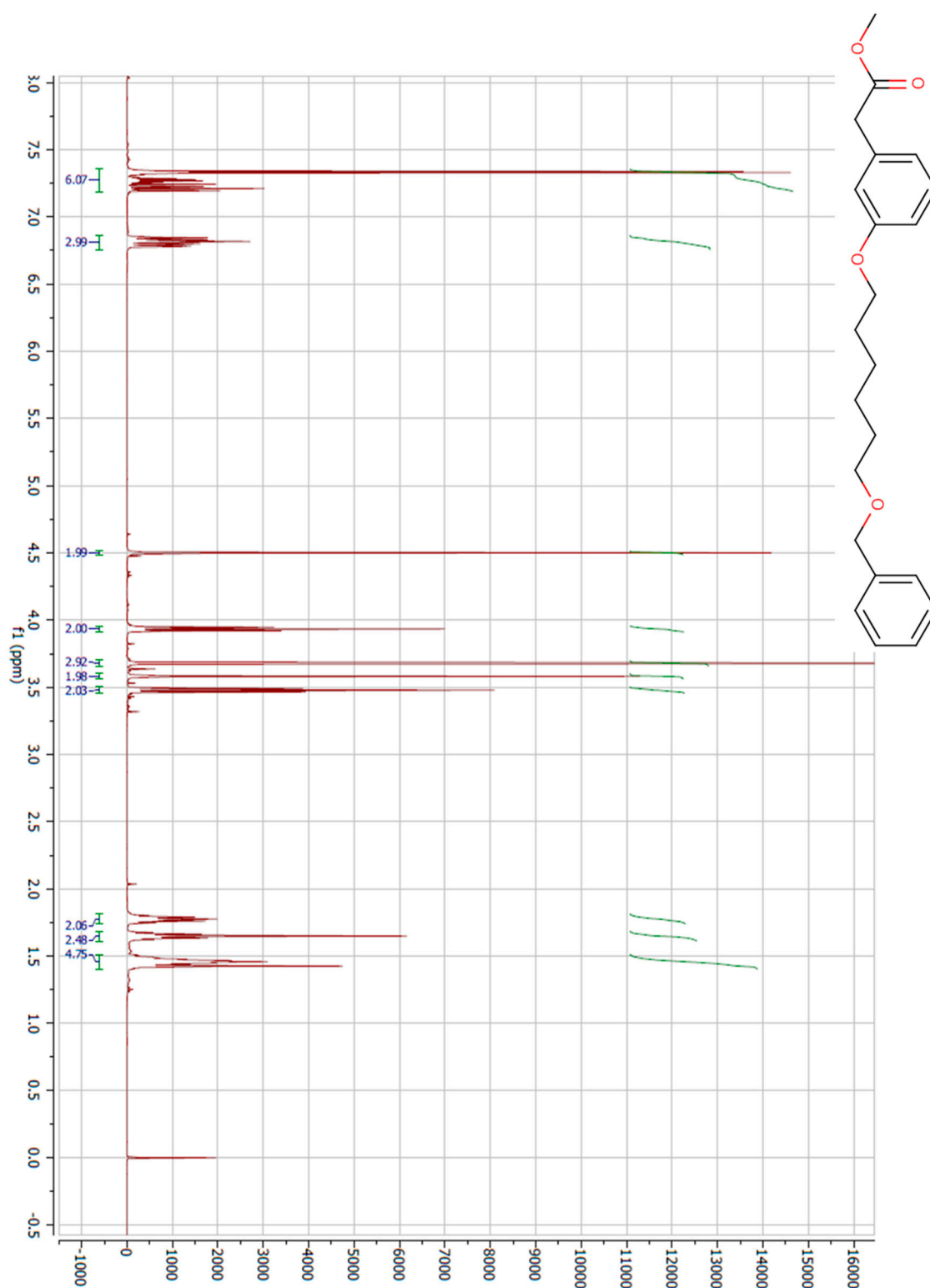
**HRMS**

**Methyl 2-(3-[[5-(benzyloxy)pentyl]oxy]phenyl)acetate (8c; ZHAW4927)**



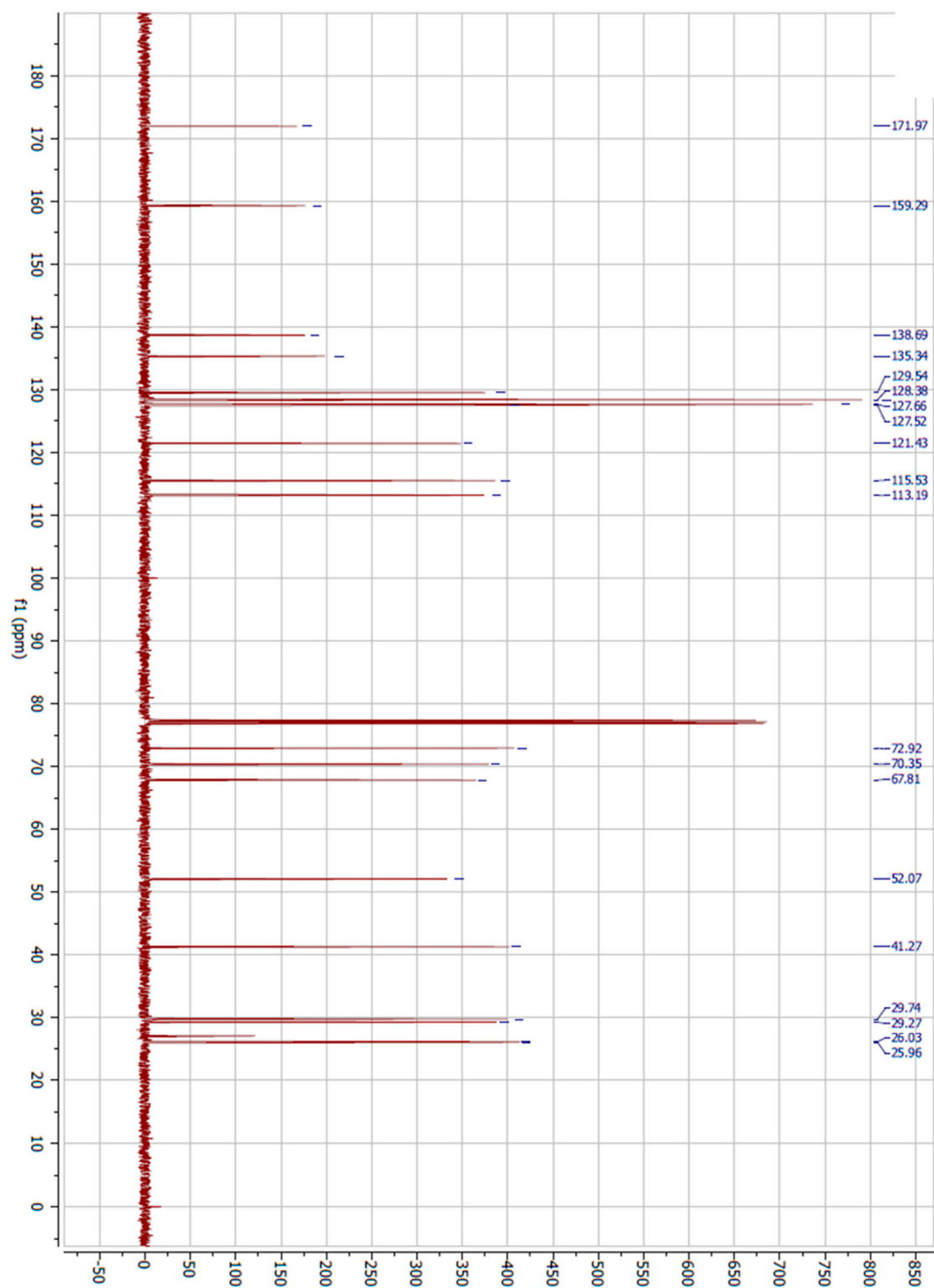
Methyl 2-(3-{{6-(benzyloxy)hexyl}oxy}phenyl)acetate (**8d**; ZHAW4928)

**NMR**

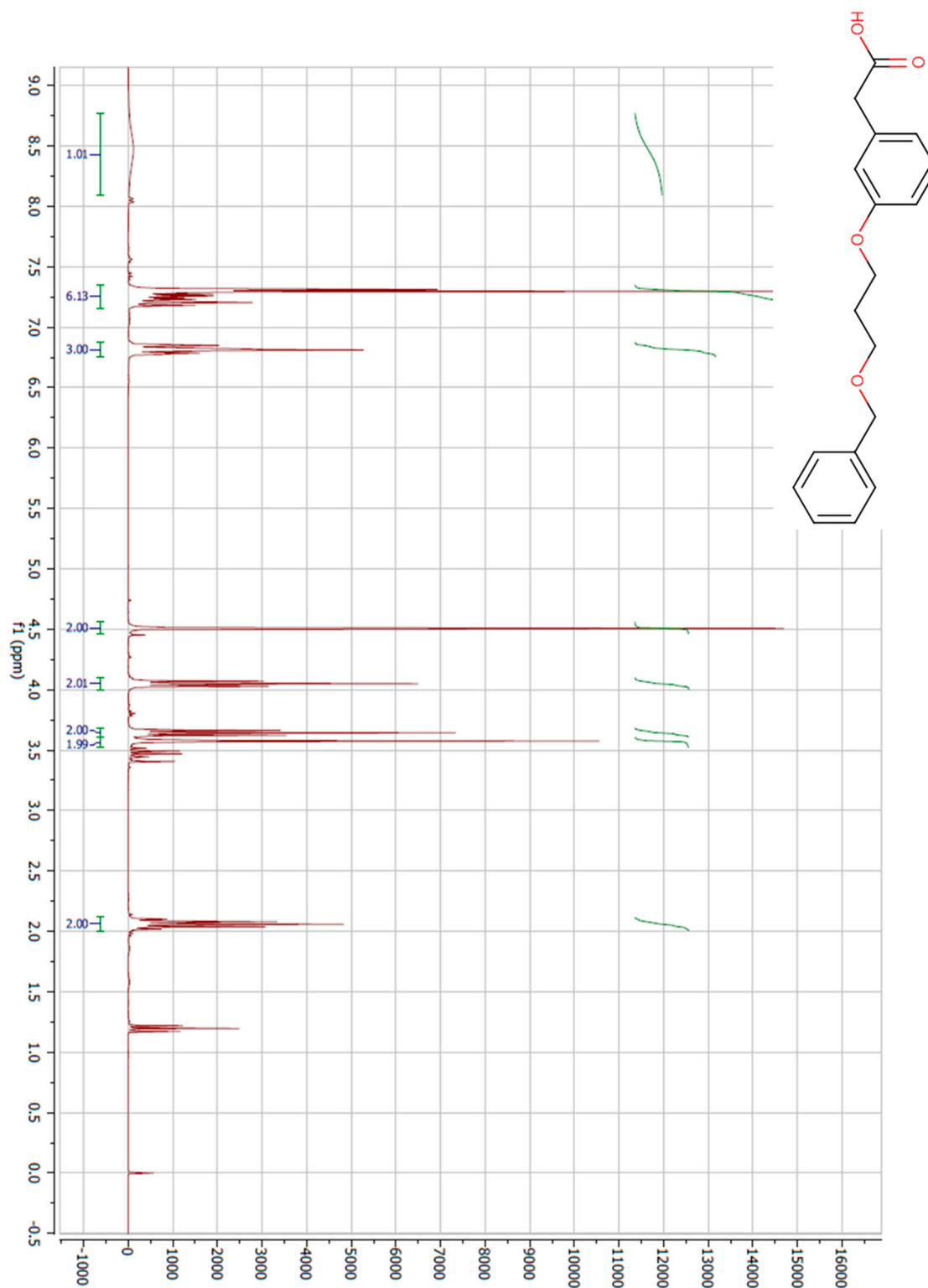




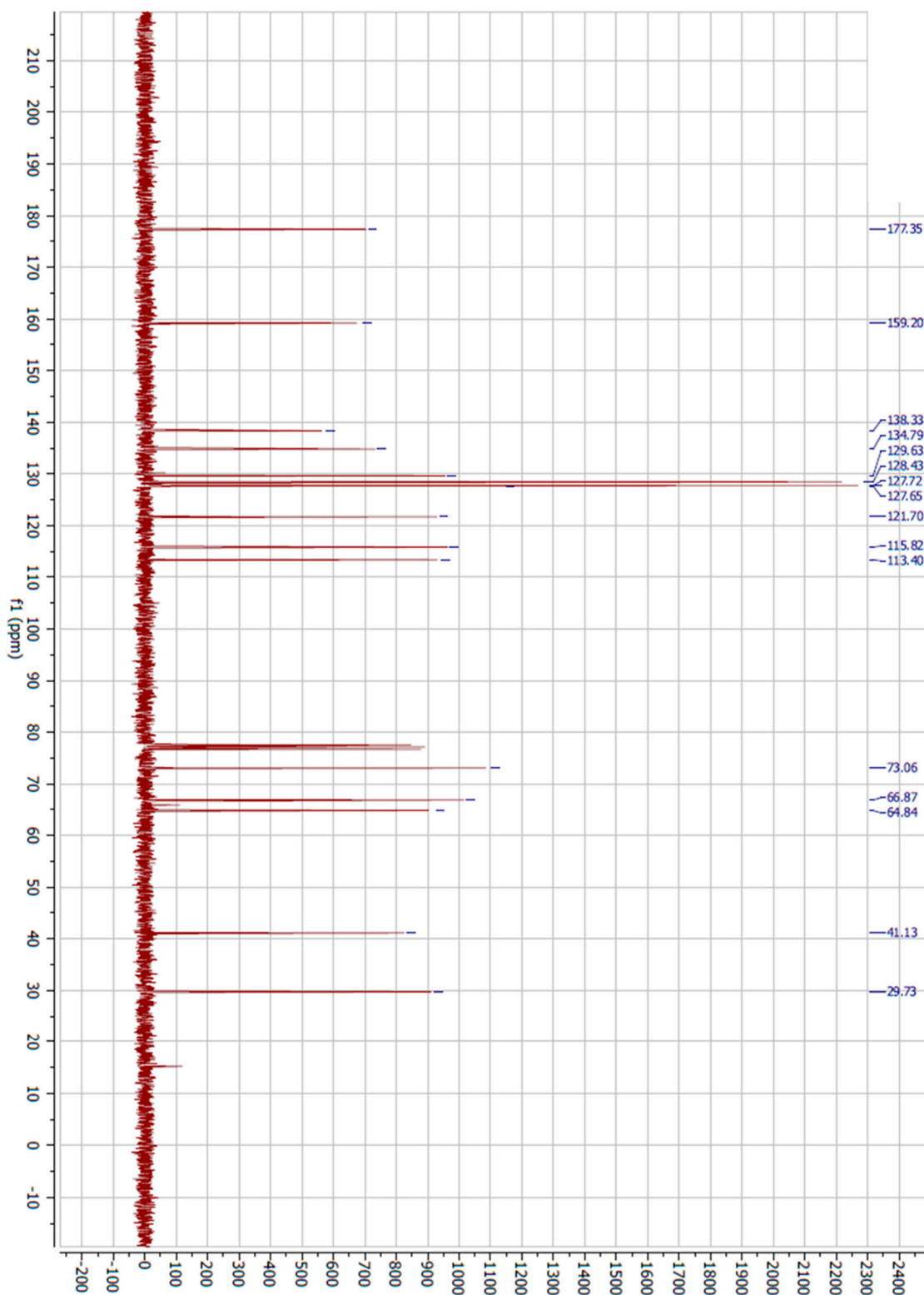
Methyl 2-(3-[[6-(benzyloxy)hexyl]oxy]phenyl)acetate (**8d**; ZHAW4928)



## 2-(3-{{3-(benzyloxy)propyl}oxy}phenyl)acetic acid (9a; ZHAW4559)

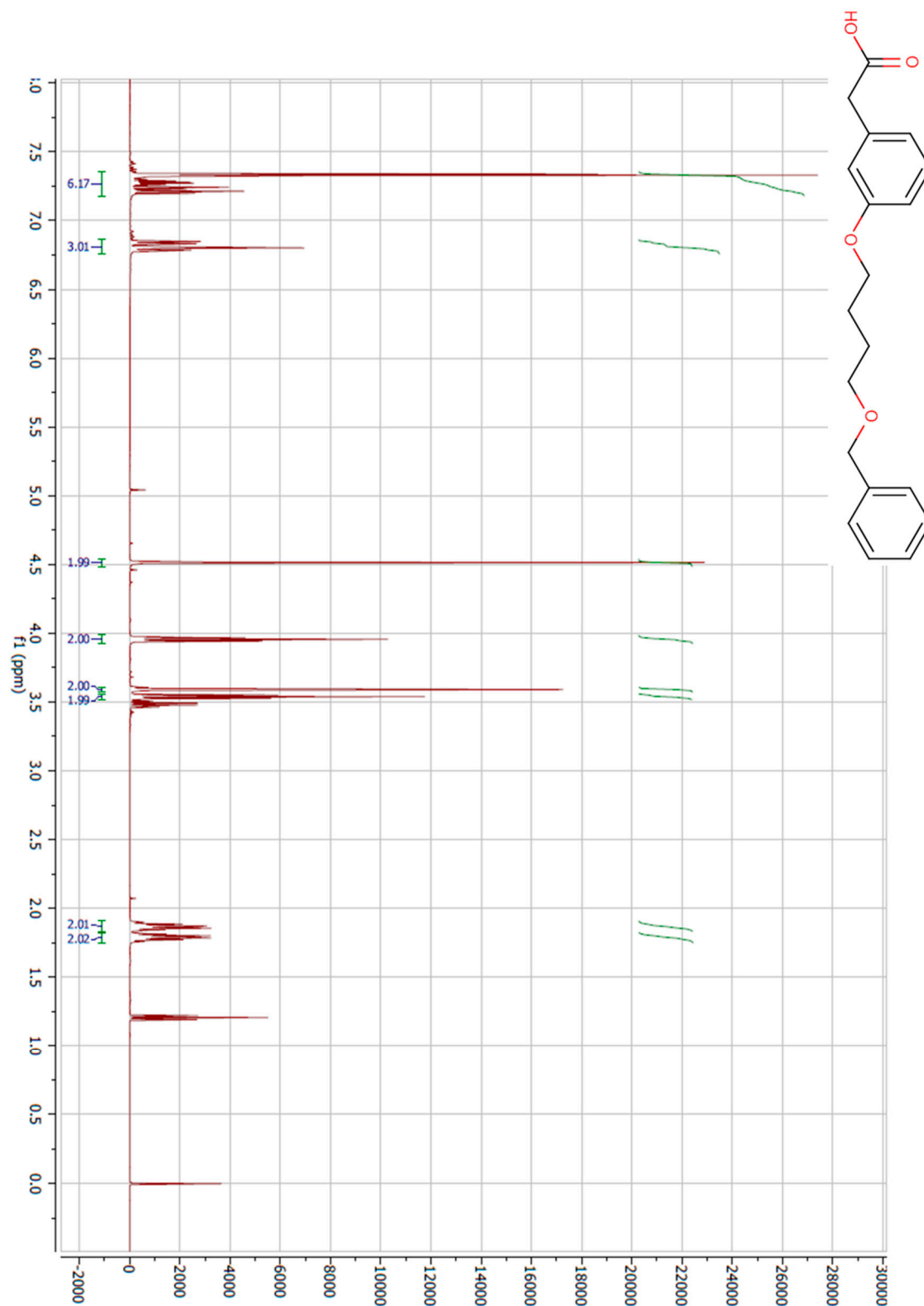
**NMR**

2-(3-{{3-(benzyloxy)propyl}oxy}phenyl)acetic acid (9a; ZHAW4559)

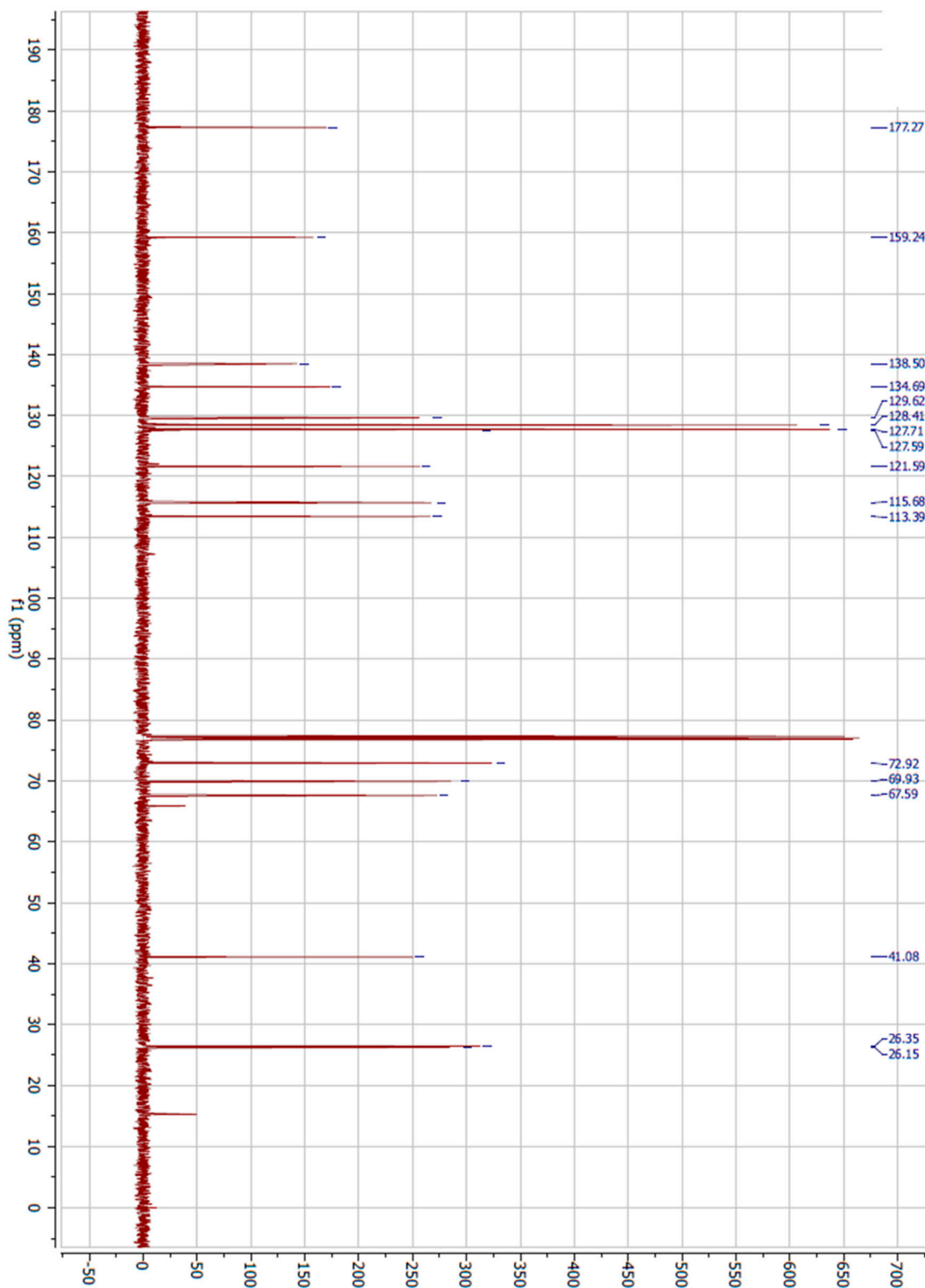


2-(3-{{4-(benzyloxy)butyl}oxy}phenyl)acetic acid (**9b**; ZHAW4560)

**NMR**

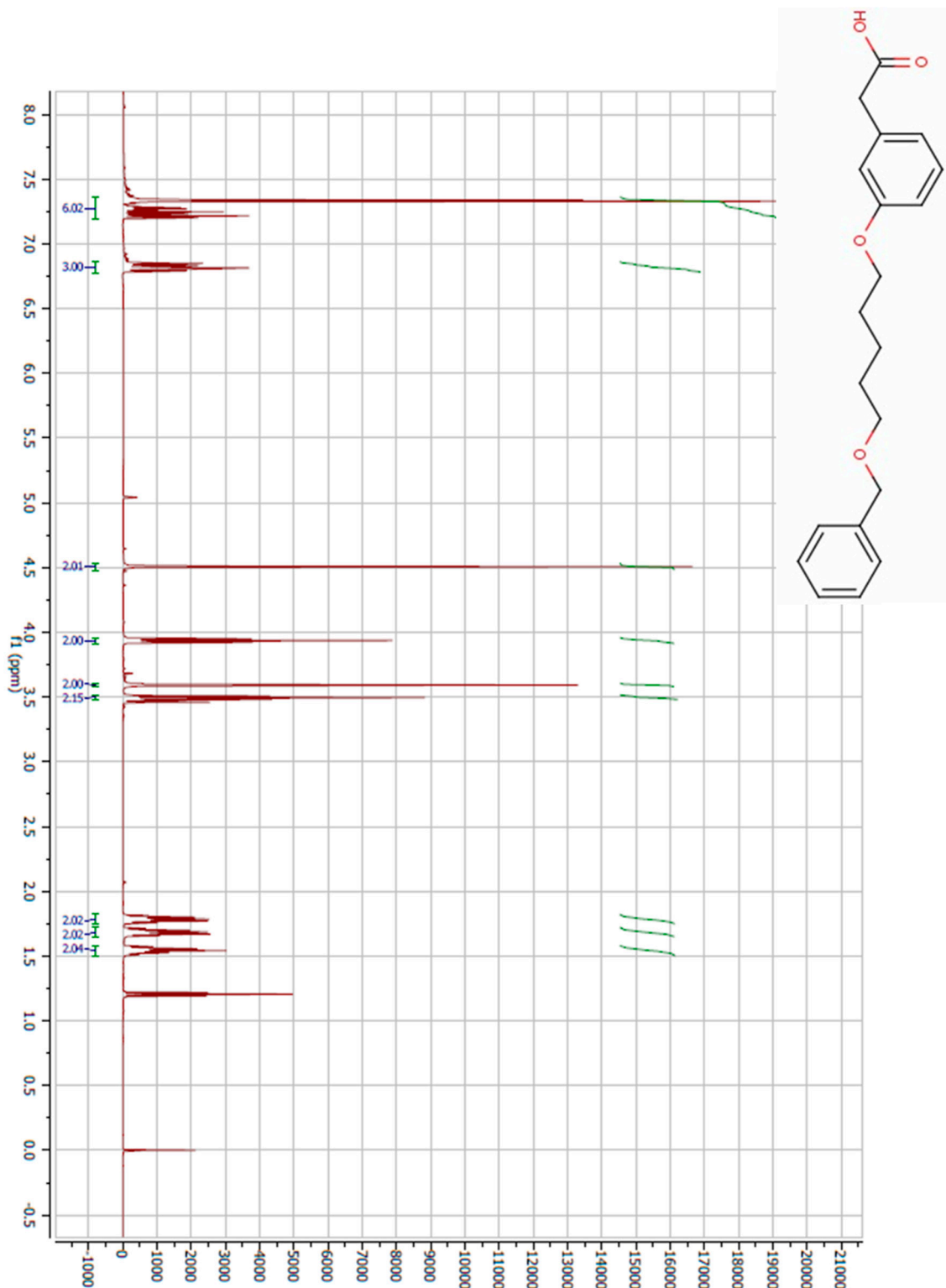


2-(3-{4-(benzyloxy)butyl}oxy)phenyl)acetic acid (**9b**; ZHAW4560)

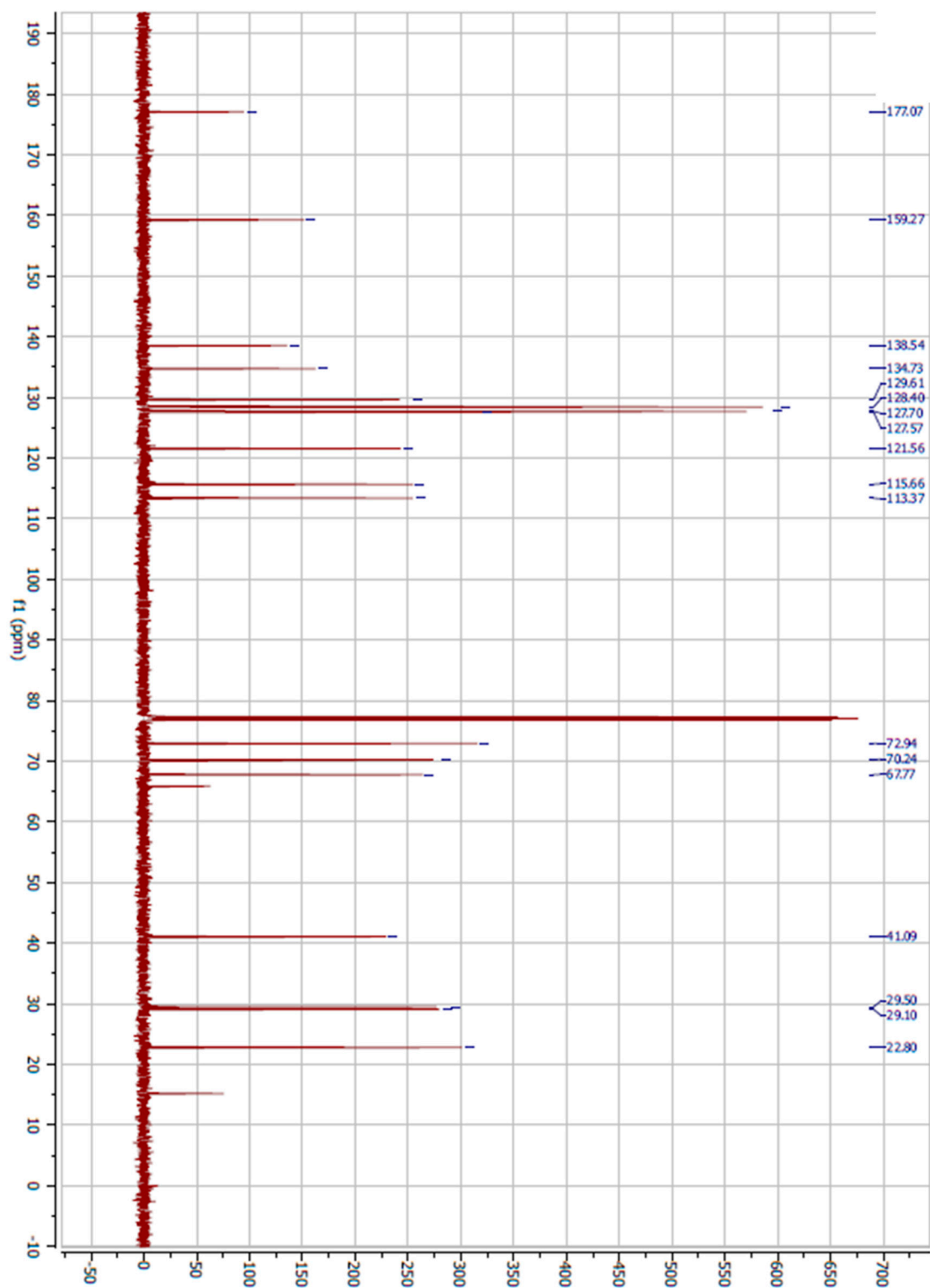


2-(3-{{5-(benzyloxy)pentyl}oxy}phenyl)acetic acid (**9c**; ZHAW4929)

**NMR**

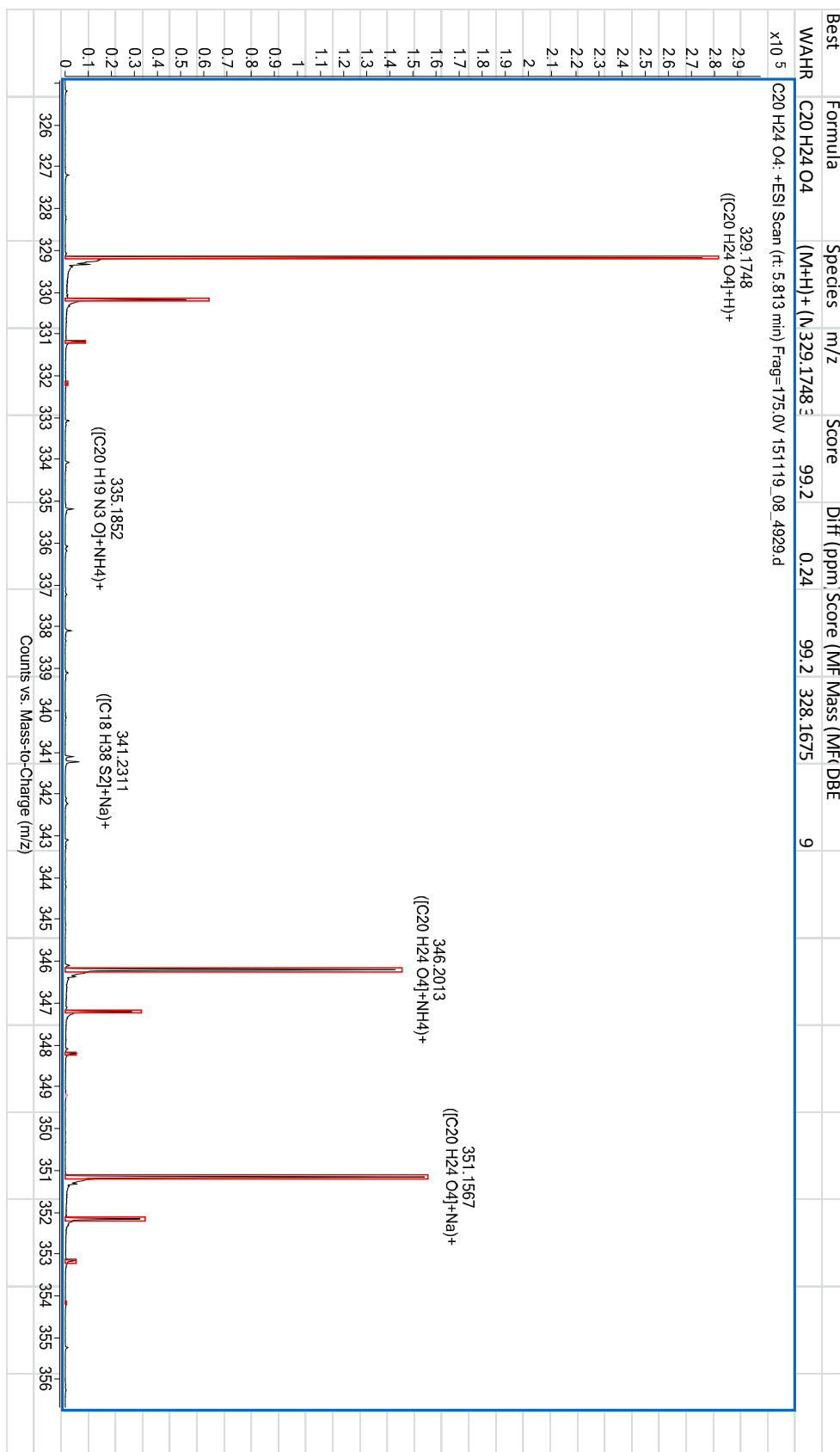


2-(3-{{5-(benzyloxy)pentyl}oxy}phenyl)acetic acid (**9c**; ZHAW4929)



**HRMS**

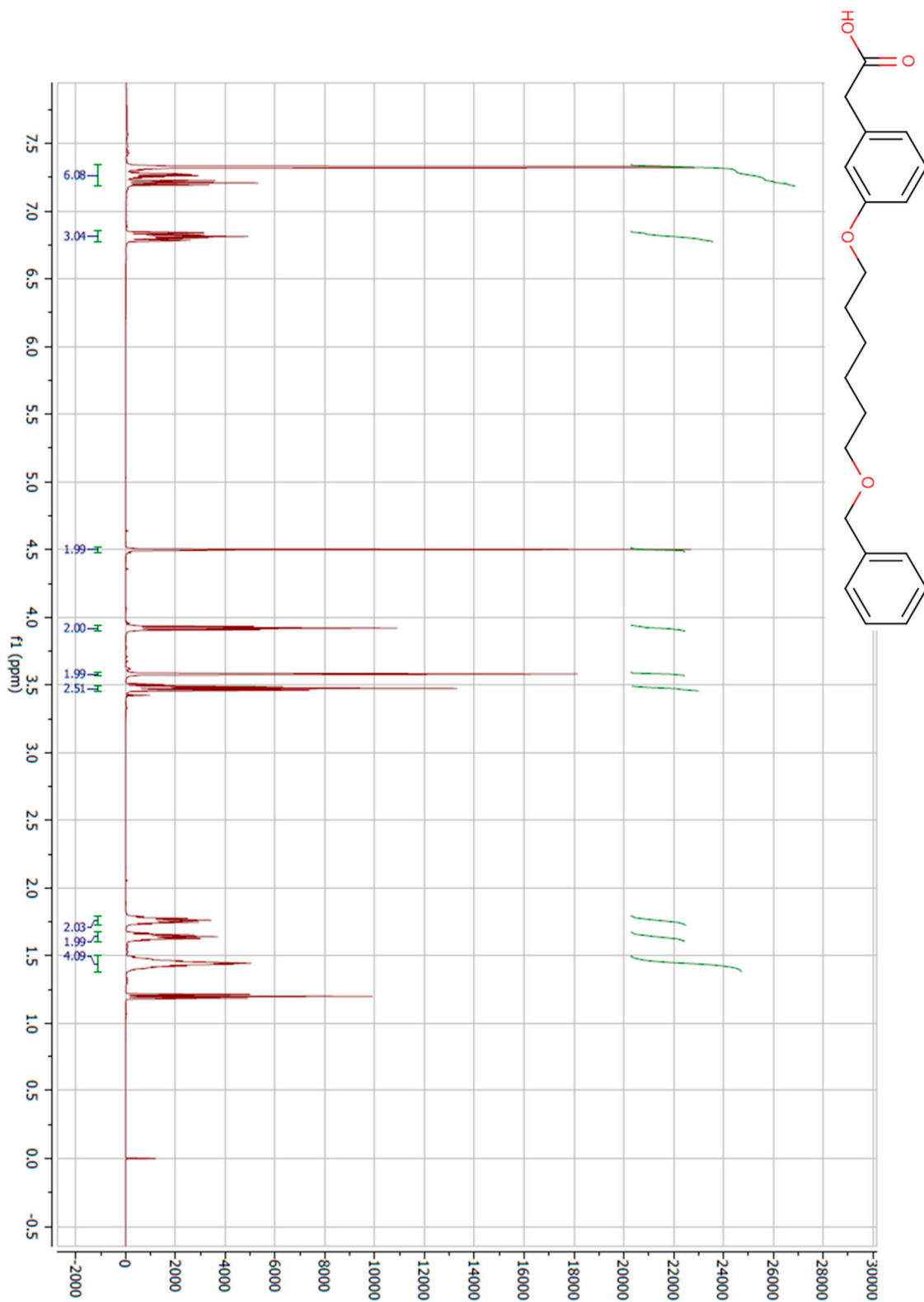
**2-(3-([5-(benzyloxy)pentyl]oxy}phenyl)acetic acid (9c; ZHAW4929)**



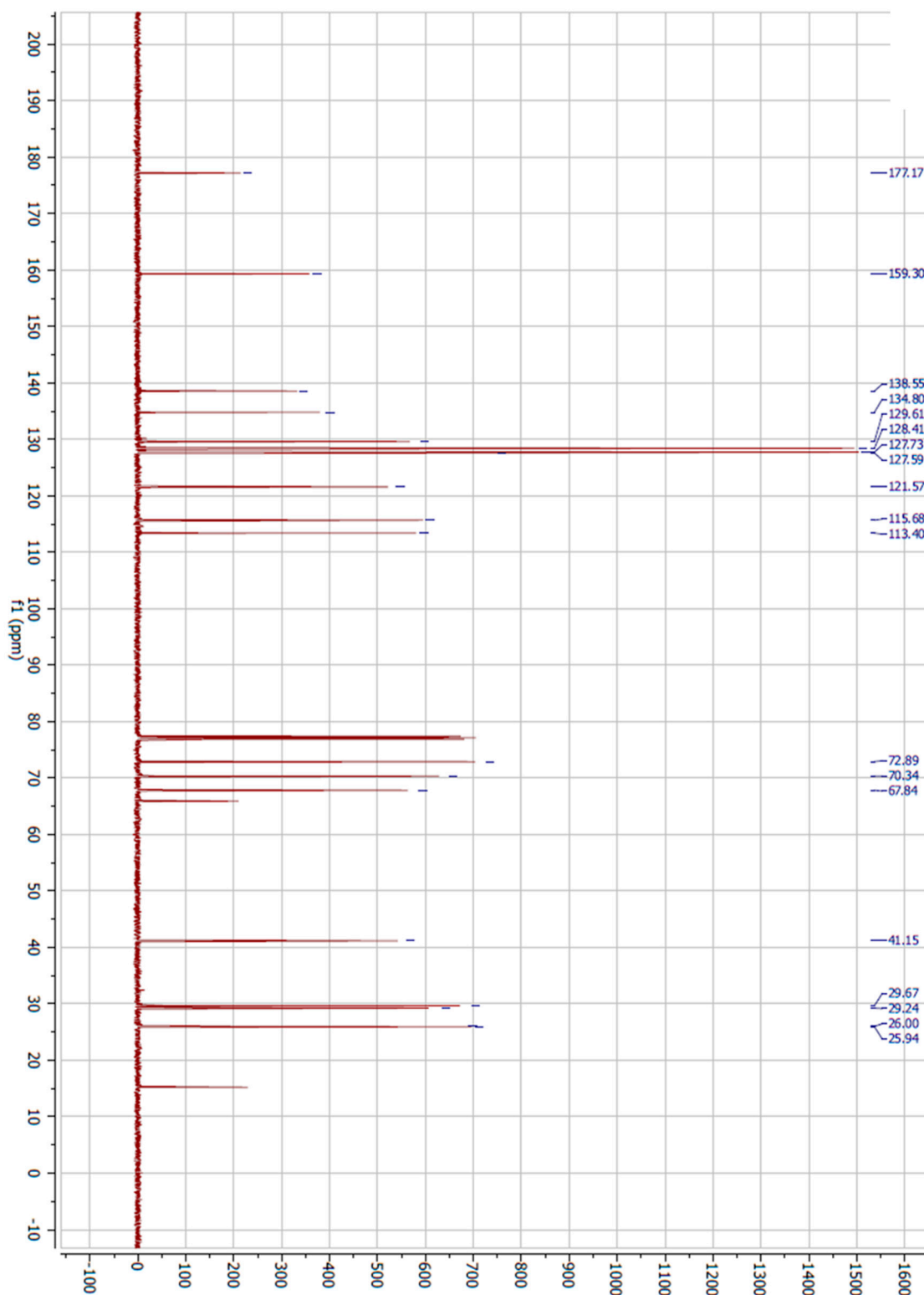


2-(3-{{6-(benzyloxy)hexyl}oxy}phenyl)acetic acid (**9d**; ZHAW4930)

**NMR**

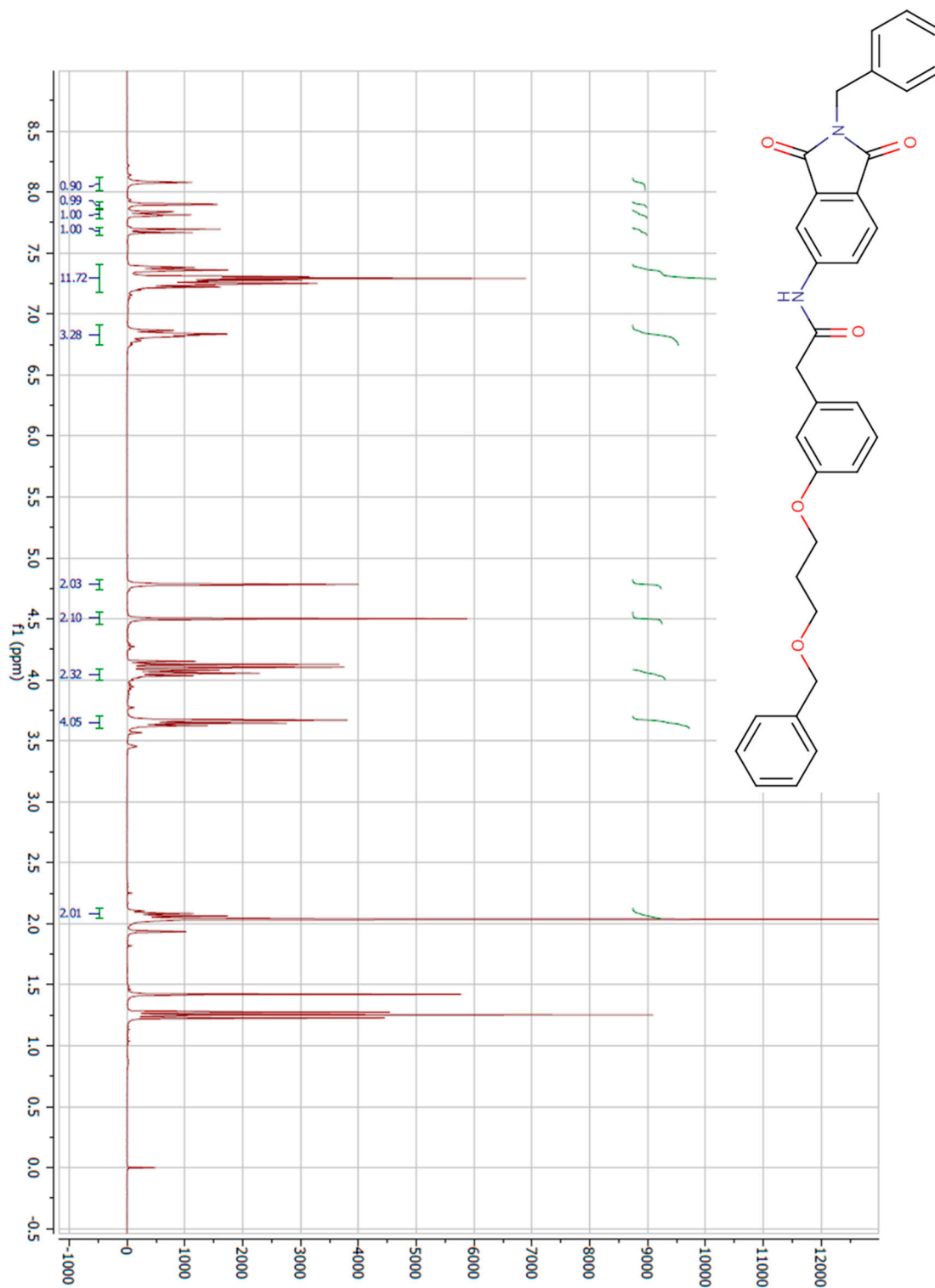


2-(3-{{6-(benzyloxy)hexyl}oxy}phenyl)acetic acid (**9d**; ZHAW4930)

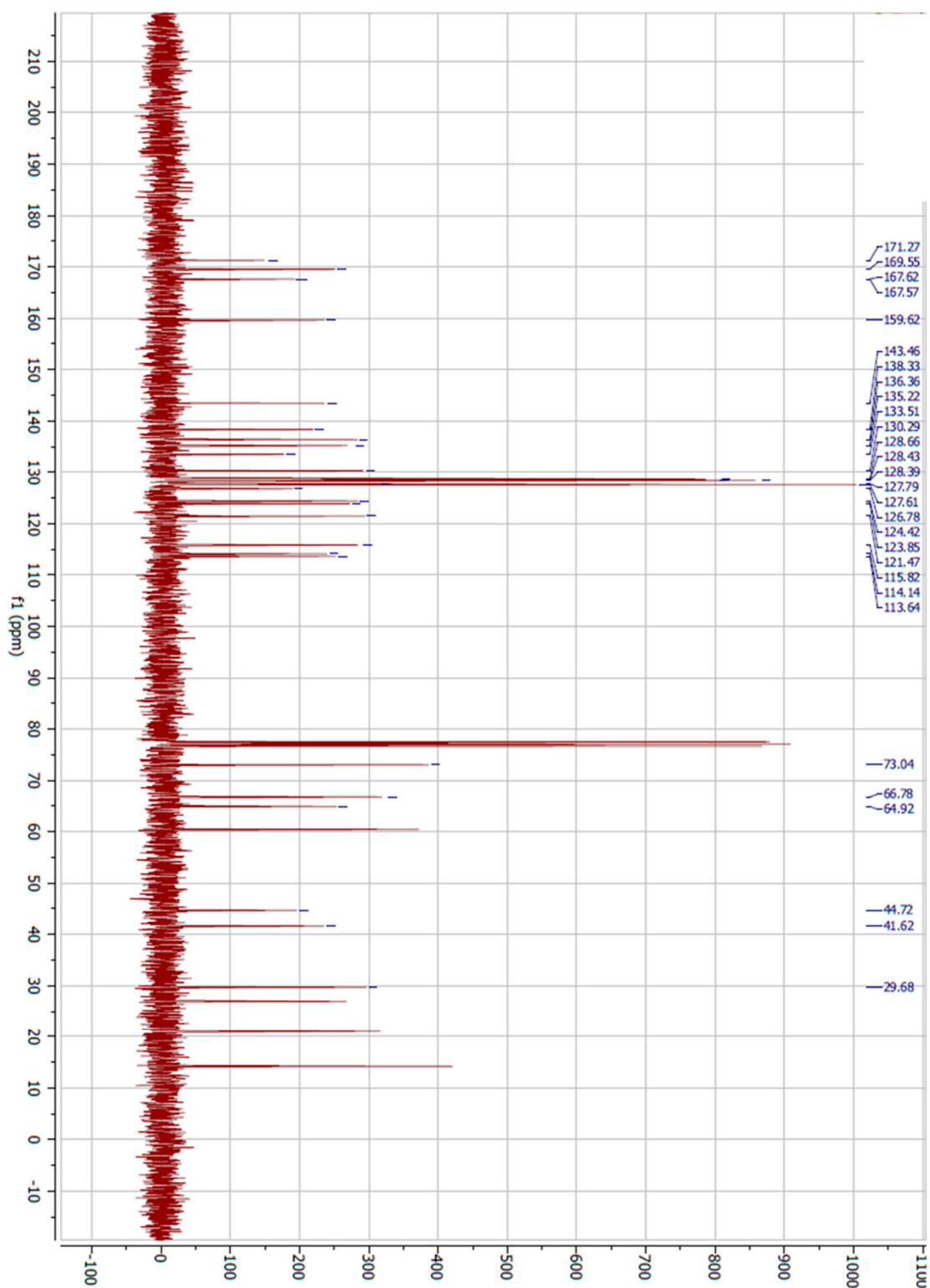


*N*-(2-benzyl-1,3-dioxo-2,3-dihydro-1*H*-isoindol-5-yl)-2-(3-{{3-(benzyloxy)propyl}oxy}phenyl)acetamide (**10a**; ZHAW4754)

### NMR

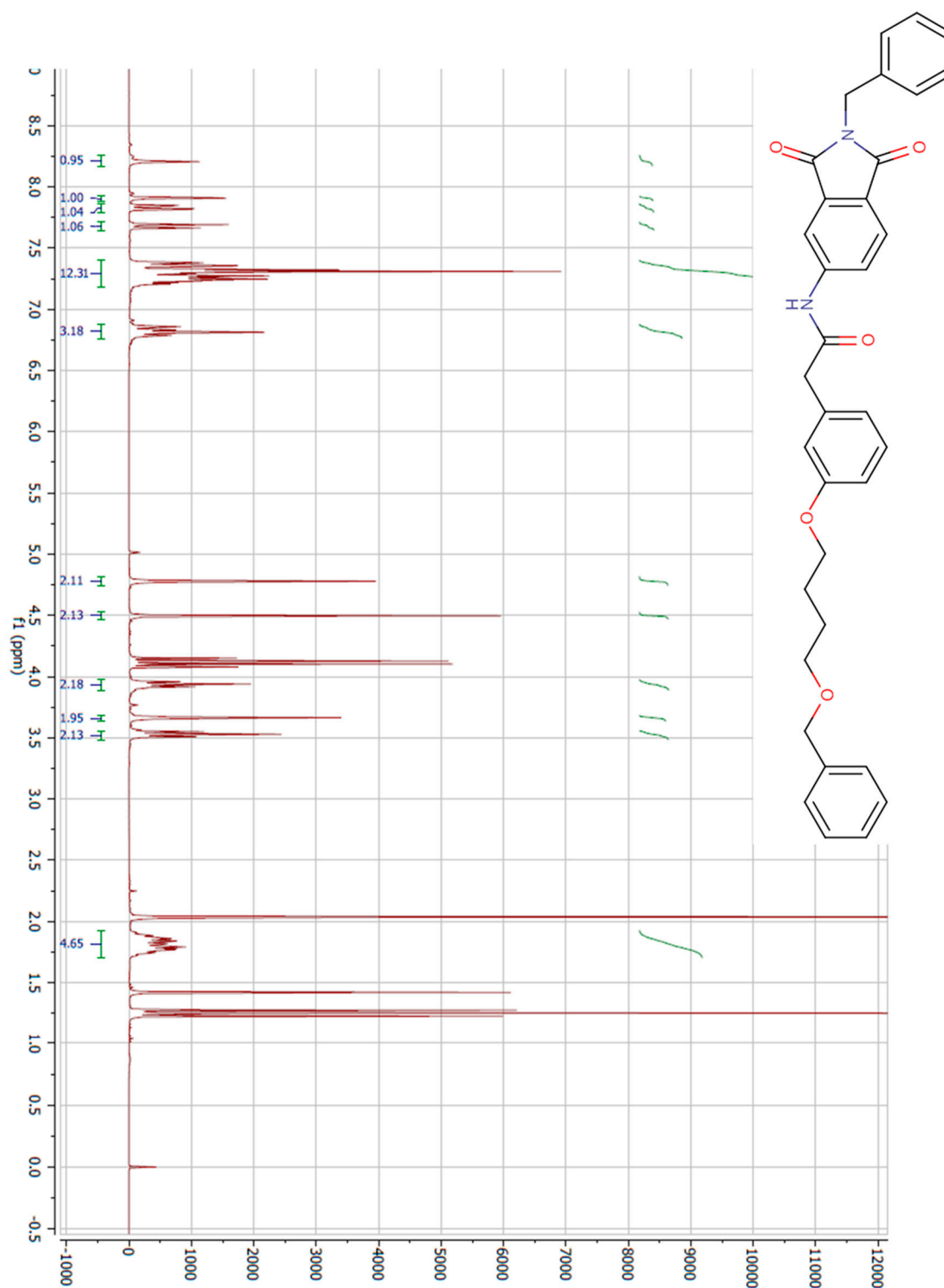


*N*-(2-benzyl-1,3-dioxo-2,3-dihydro-1*H*-isoindol-5-yl)-2-(3-{{3-(benzyloxy)propyl}oxy}phenyl)acetamide (**10a**; ZHAW4754)

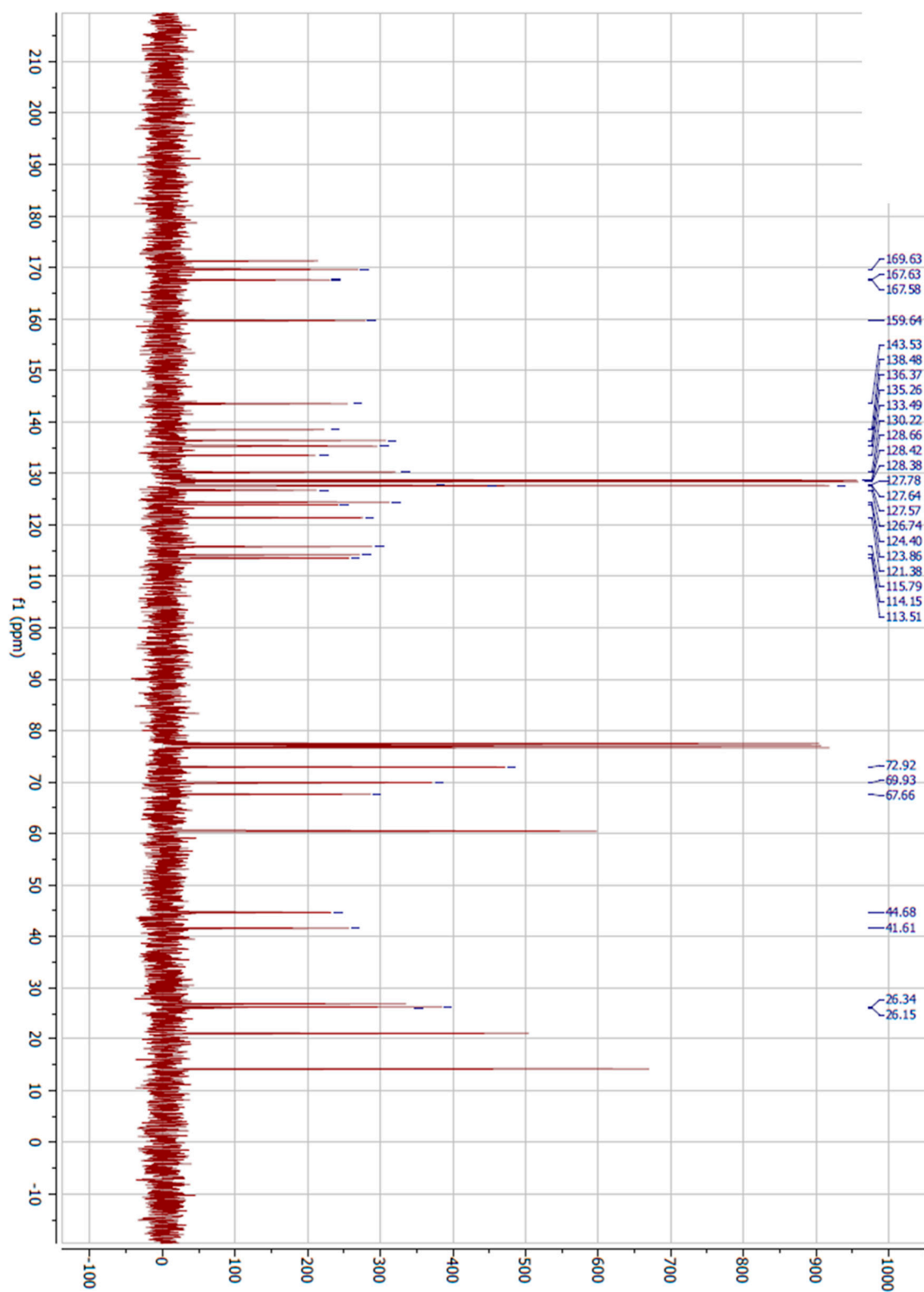


*N*-(2-benzyl-1,3-dioxo-2,3-dihydro-1*H*-isoindol-5-yl)-2-(3-{{4-(benzyloxy)butyl}oxy}phenyl)acetamide (**10b**; ZHAW4755)

### NMR

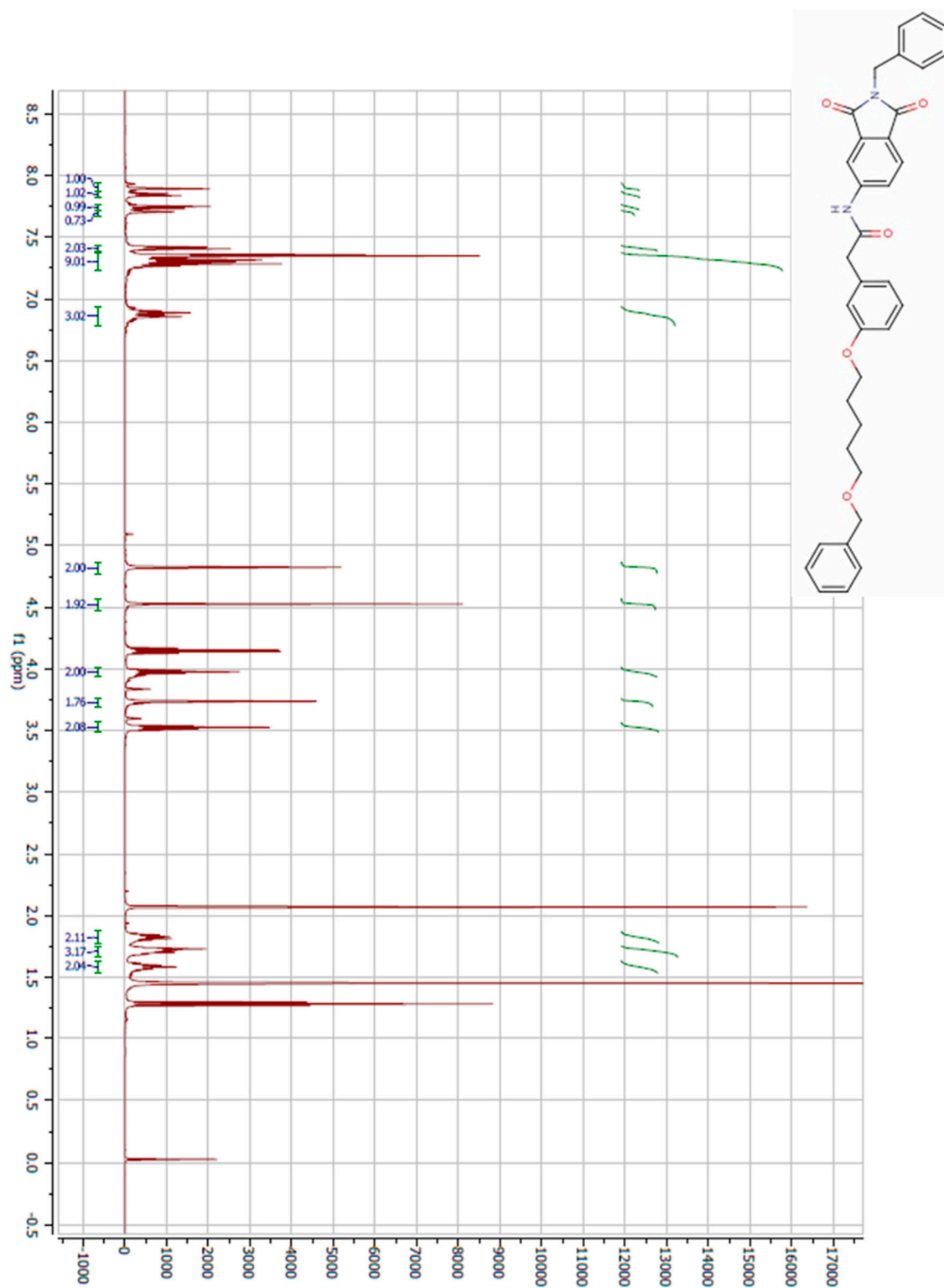


*N*-(2-benzyl-1,3-dioxo-2,3-dihydro-1*H*-isoindol-5-yl)-2-(3-{{4-(benzyloxy)butyl}oxy}phenyl)acetamide (**10b**; ZHAW4755)

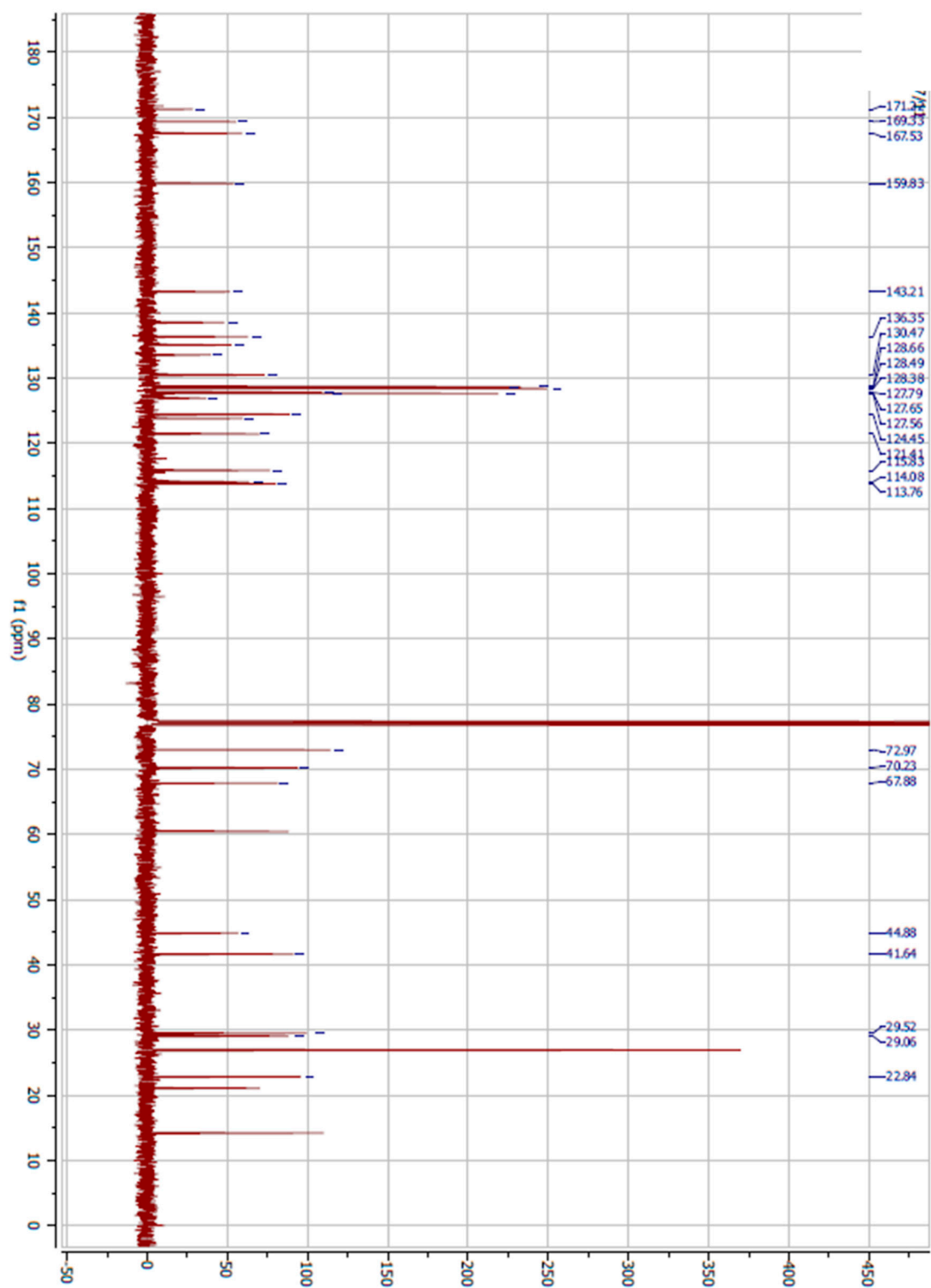


*N*-(2-benzyl-1,3-dioxo-2,3-dihydro-1*H*-isoindol-5-yl)-2-(3-[[5-(benzyloxy)pentyl]oxy]phenyl)acetamide (**10c**; ZHAW5606)

### NMR



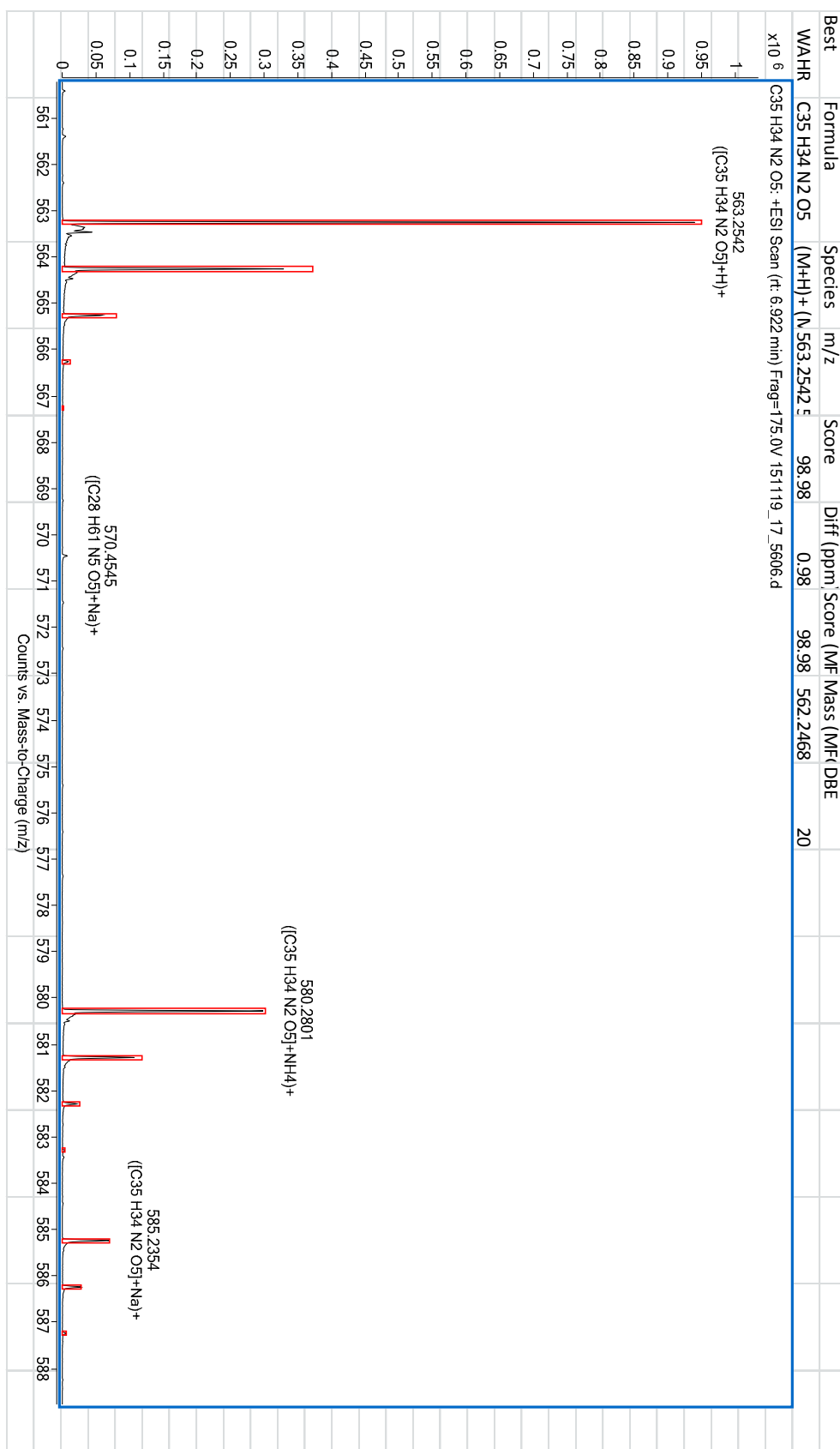
*N*-(2-benzyl-1,3-dioxo-2,3-dihydro-1*H*-isoindol-5-yl)-2-(3-{{5-(benzyloxy)pentyl}oxy}phenyl)acetamide (**10c**; ZHAW5606)





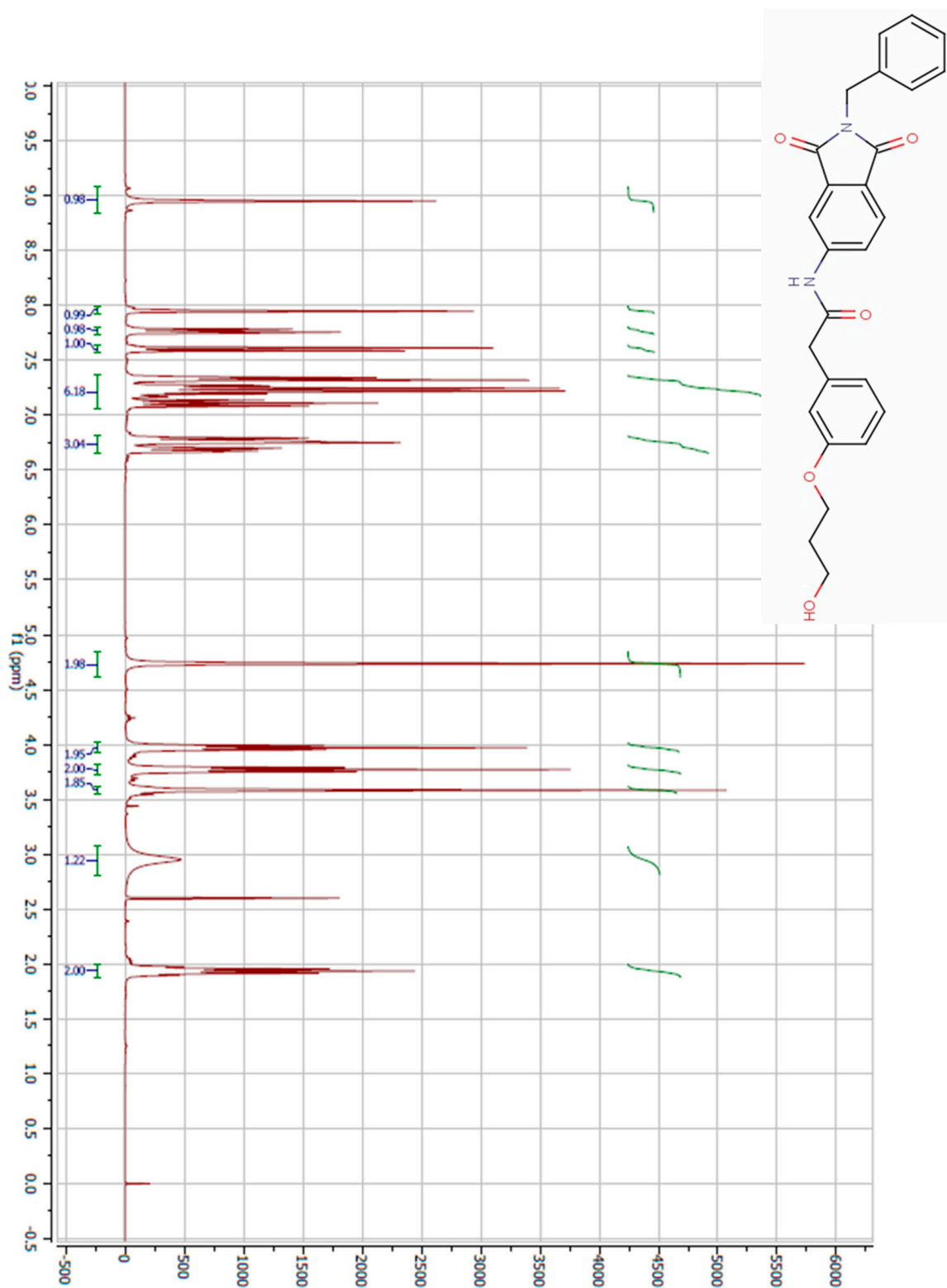
### HRMS

*N*-(2-benzyl-1,3-dioxo-2,3-dihydro-1*H*-isoindol-5-yl)-2-(3-{{5-(benzyloxy)pentyl}oxy}phenyl)acetamide (**10c**; ZHAW5606)

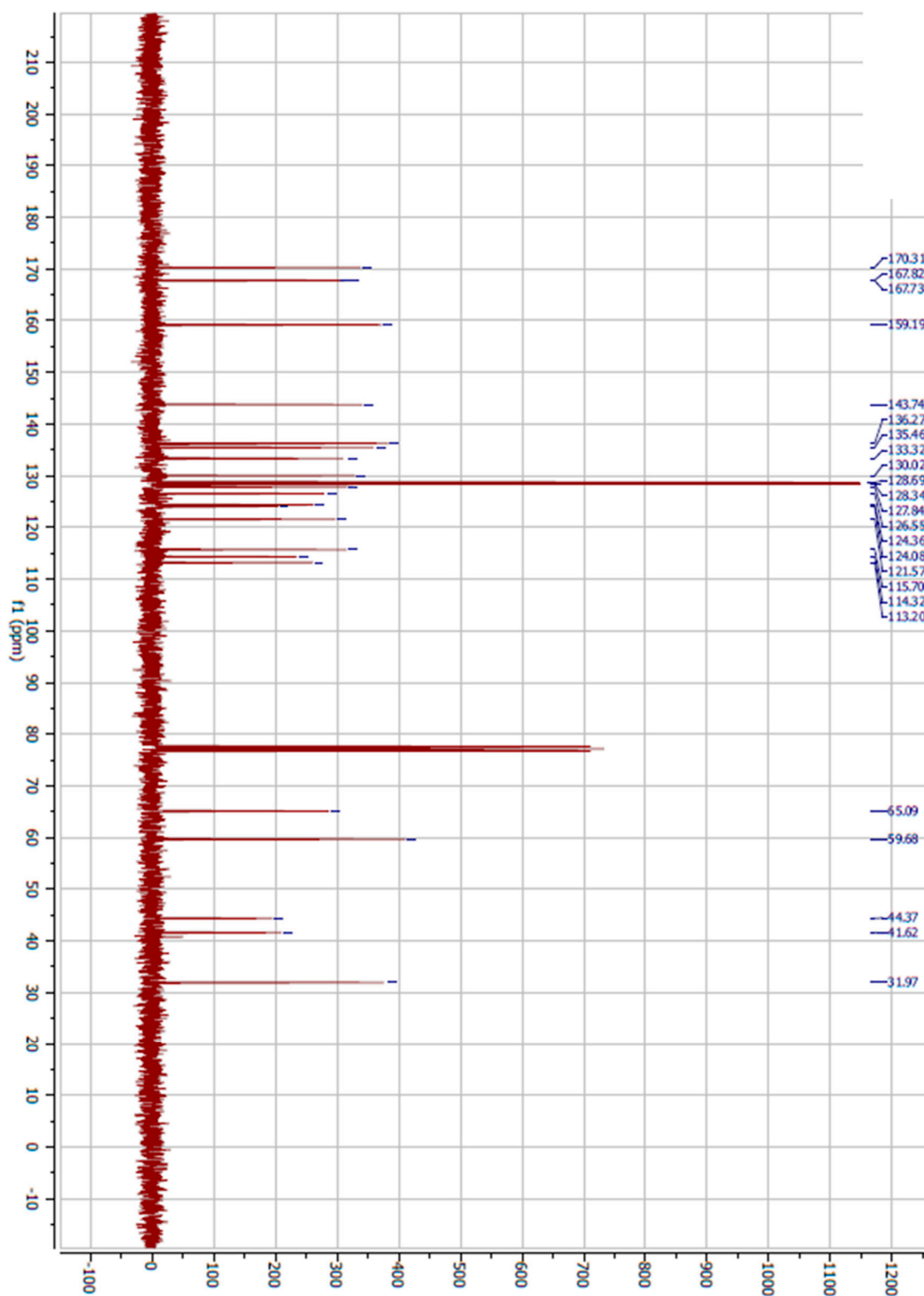


*N*-(2-benzyl-1,3-dioxo-2,3-dihydro-1*H*-isoindol-5-yl)-2-[3-(3-hydroxypropoxy)phenyl]acetamide  
(11; ZHAW4756)

**NMR**

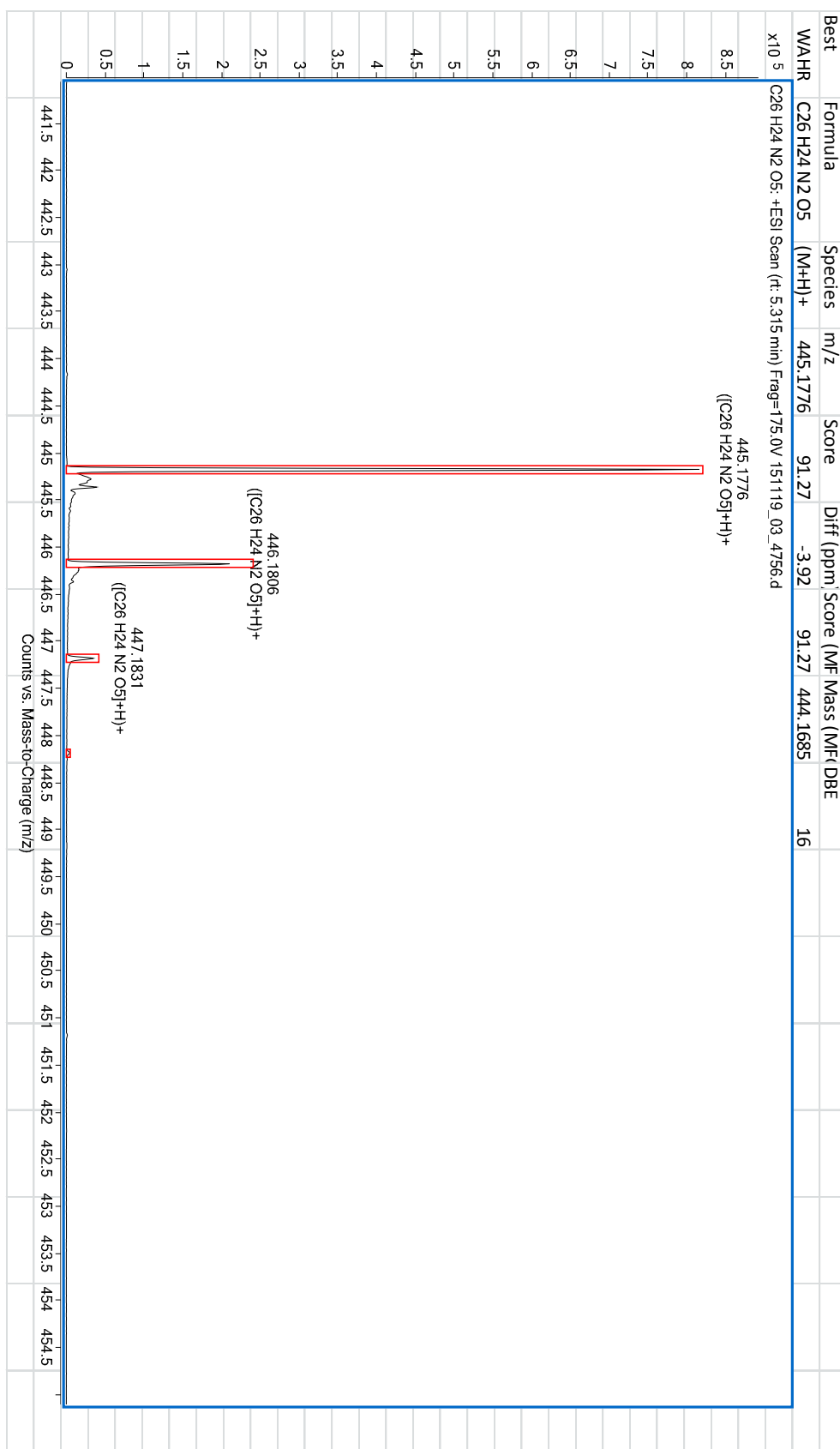


*N*-(2-benzyl-1,3-dioxo-2,3-dihydro-1*H*-isoindol-5-yl)-2-[3-(3-hydroxypropoxy)phenyl]acetamide  
(**11**; ZHAW4756)



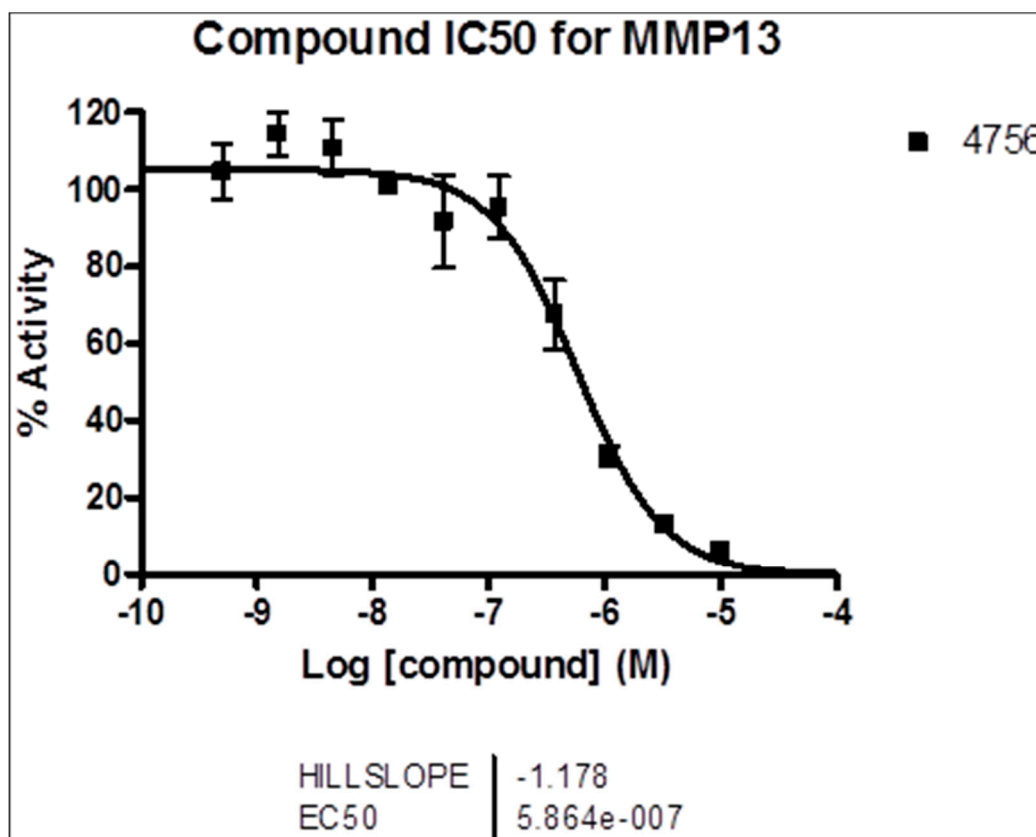
**HRMS**

***N*-(2-benzyl-1,3-dioxo-2,3-dihydro-1*H*-isoindol-5-yl)-2-[3-(3-hydroxypropoxy)phenyl]acetamide (11; ZHAW4756)**



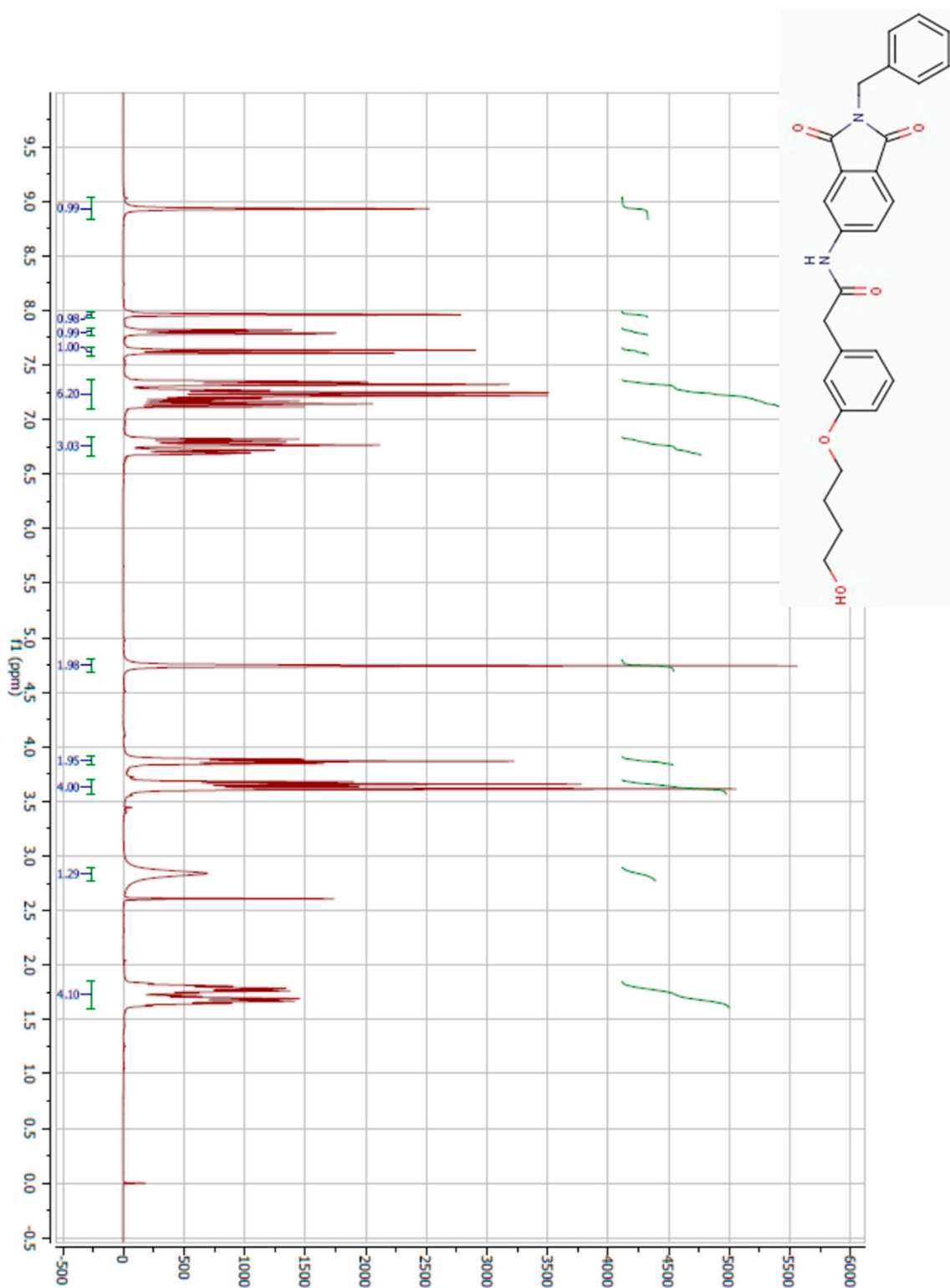
**IC<sub>50</sub>**

*N*-(2-benzyl-1,3-dioxo-2,3-dihydro-1*H*-isoindol-5-yl)-2-[3-(3-hydroxypropoxy)phenyl]acetamide (11; ZHAW4756)

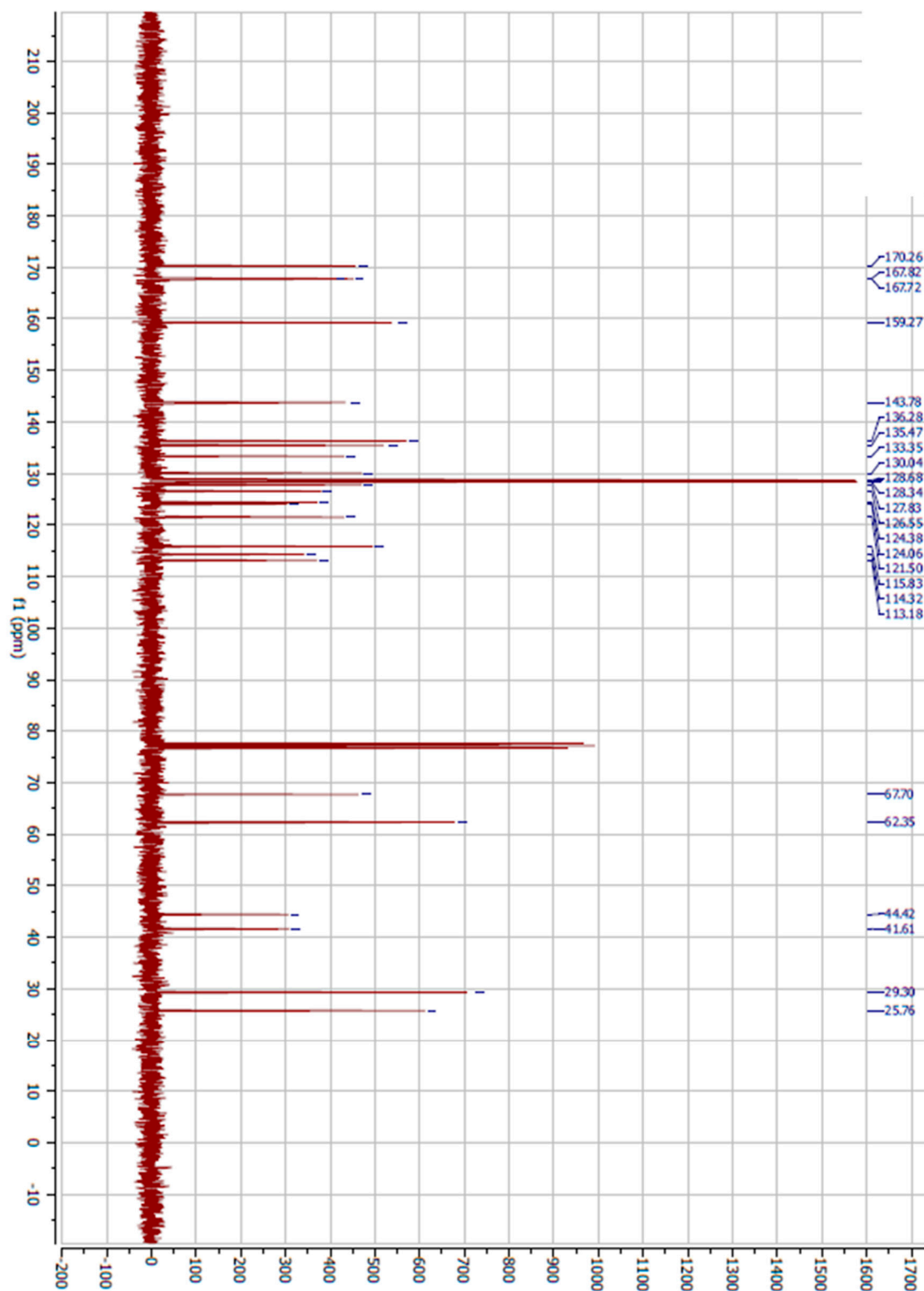


*N*-(2-benzyl-1,3-dioxo-2,3-dihydro-1*H*-isoindol-5-yl)-2-[3-(4-hydroxybutoxy)phenyl]acetamide (12; ZHAW4757)

**NMR**

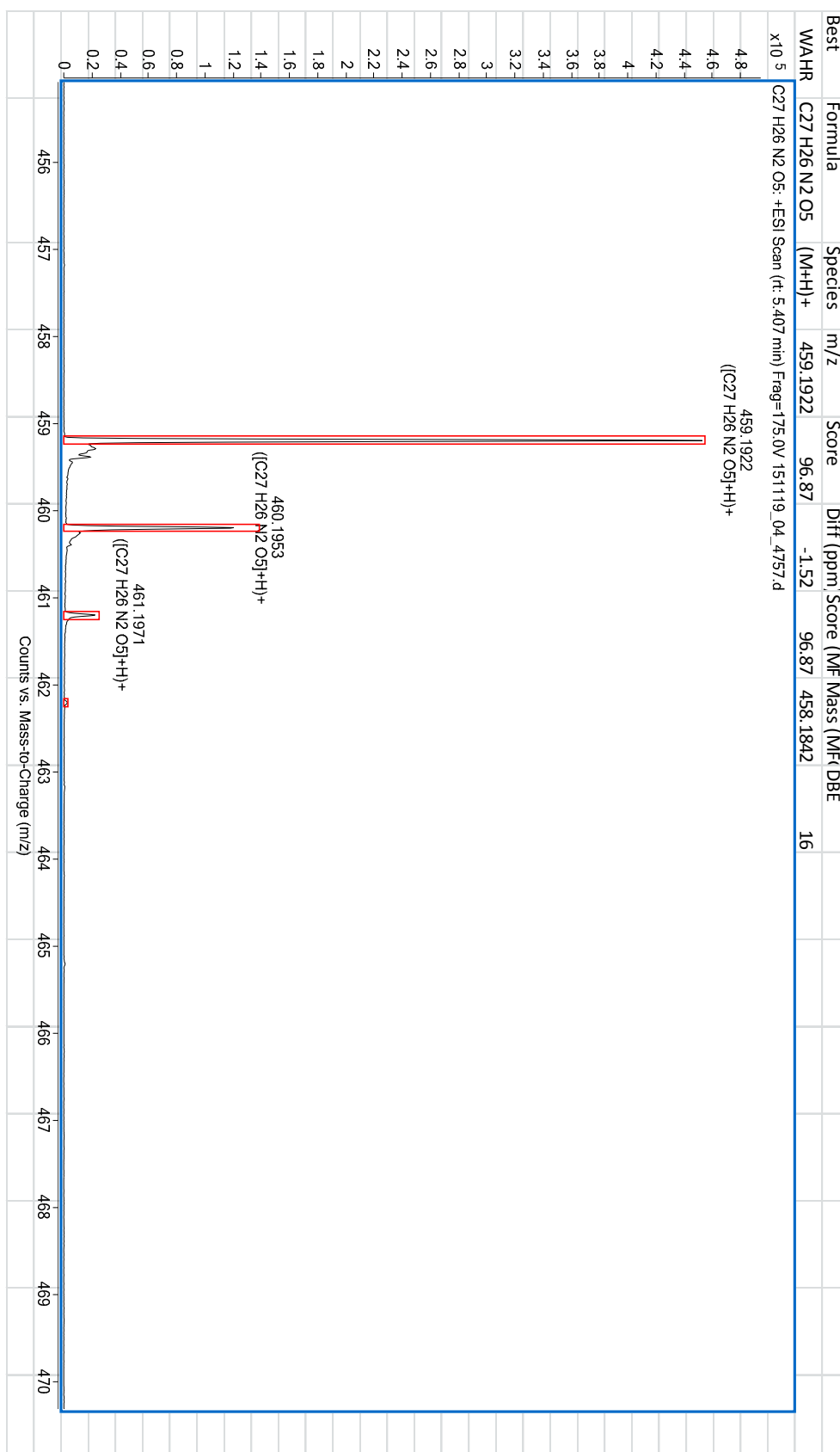


*N*-(2-benzyl-1,3-dioxo-2,3-dihydro-1*H*-isoindol-5-yl)-2-[3-(4-hydroxybutoxy)phenyl]acetamide (12; ZHAW4757)



**HRMS**

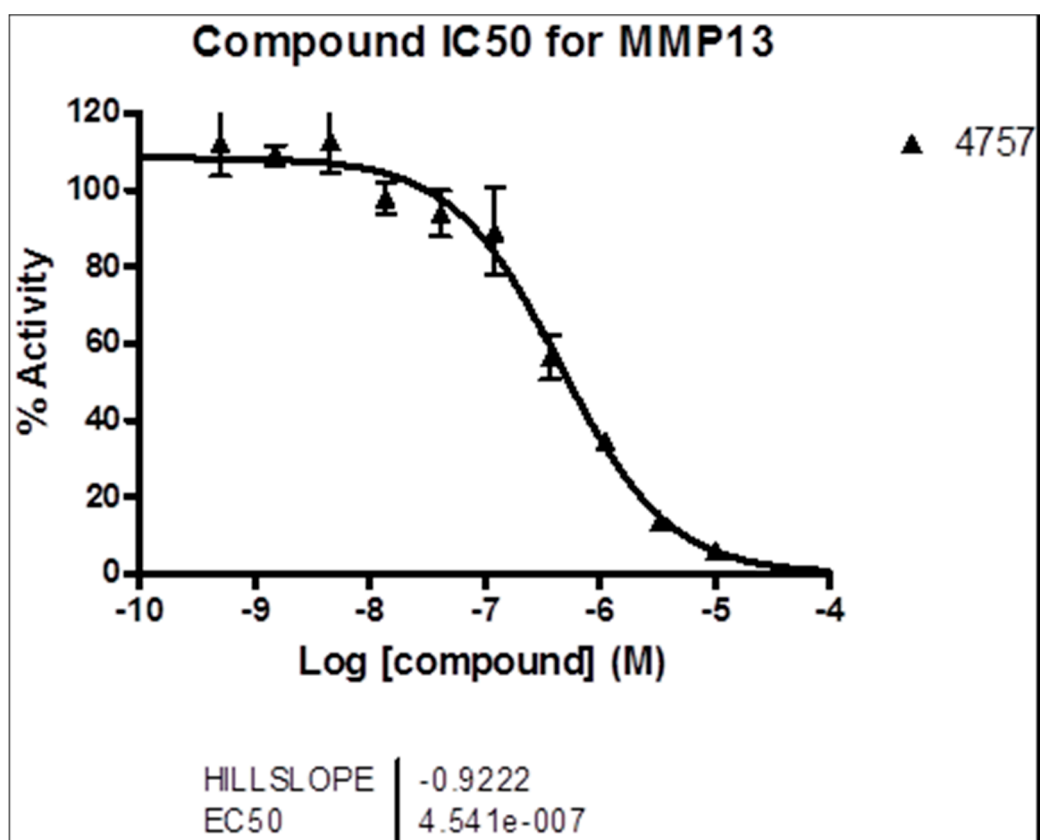
***N*-(2-benzyl-1,3-dioxo-2,3-dihydro-1*H*-isoindol-5-yl)-2-[3-(4-hydroxybutoxy)phenyl]acetamide (12; ZHAW4757)**





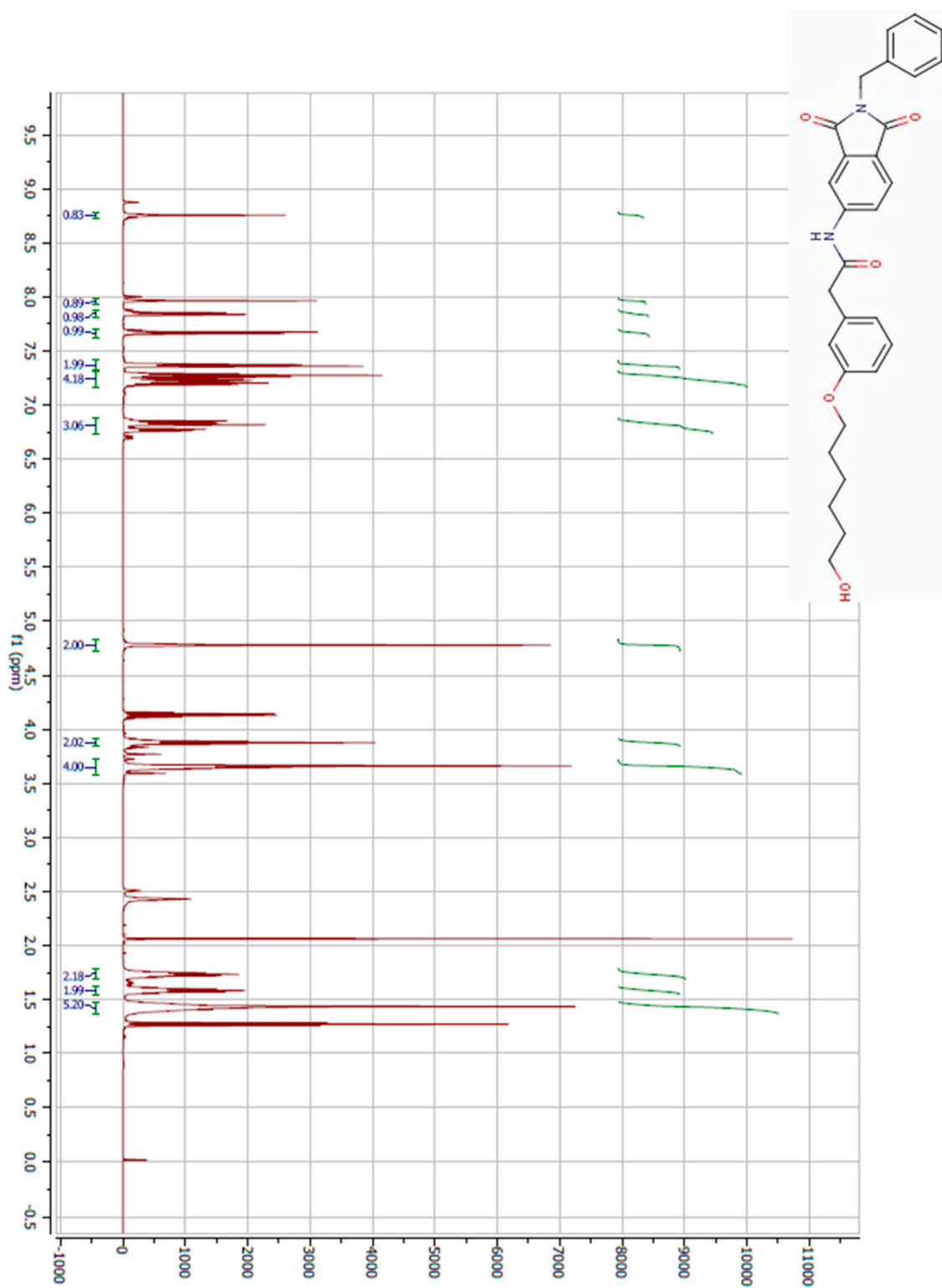
**IC<sub>50</sub>**

*N*-(2-benzyl-1,3-dioxo-2,3-dihydro-1*H*-isoindol-5-yl)-2-[3-(4-hydroxybutoxy)phenyl]acetamide (12; ZHAW4757)

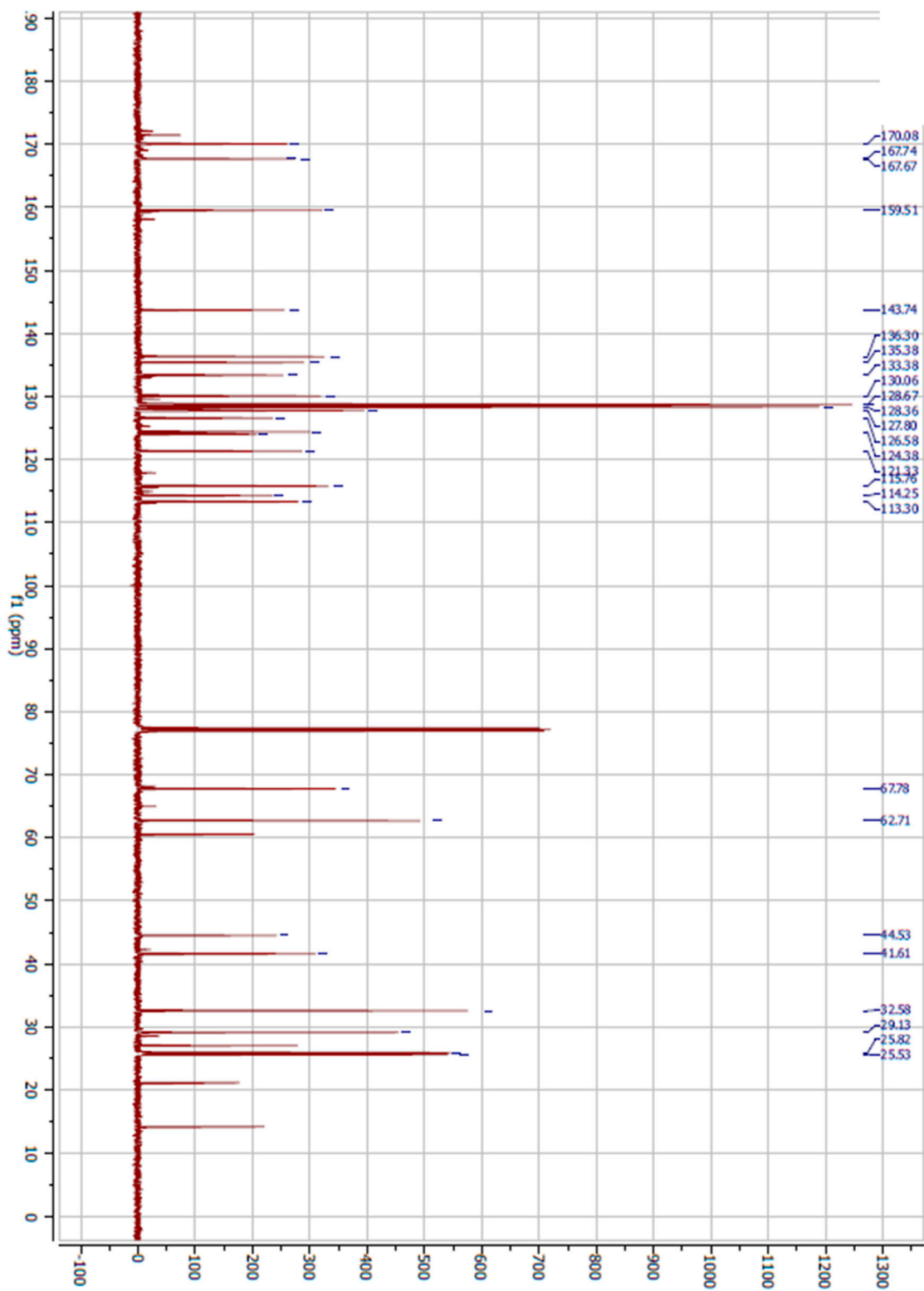


*N*-(2-benzyl-1,3-dioxo-2,3-dihydro-1*H*-isoindol-5-yl)-2-{3-[(6-hydroxyhexyl)oxy]phenyl}acetamide  
(13; ZHAW5042)

**NMR**

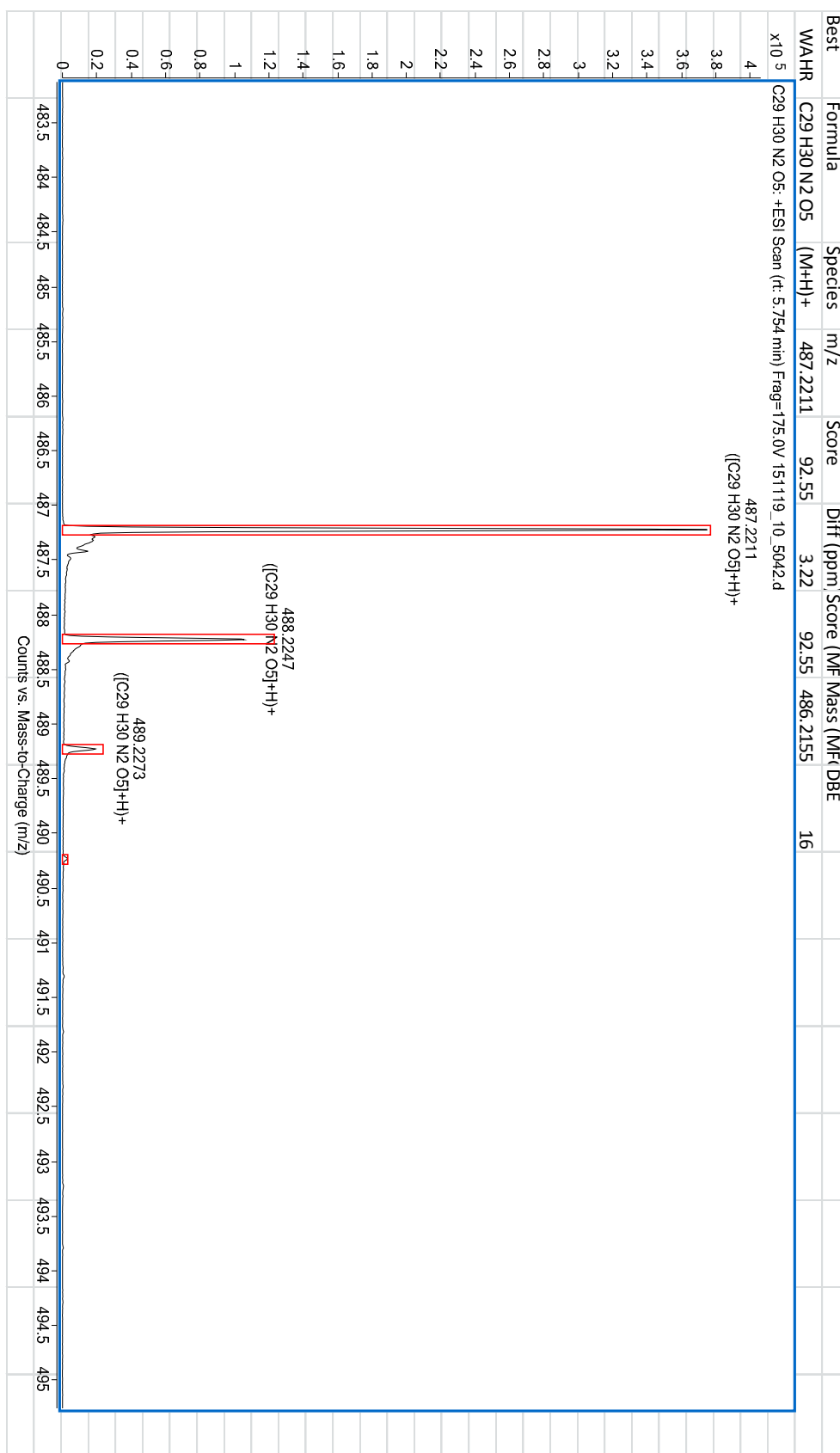


*N*-(2-benzyl-1,3-dioxo-2,3-dihydro-1*H*-isoindol-5-yl)-2-{3-[(6-hydroxyhexyl)oxy]phenyl}acetamide (**13**; ZHAW5042)



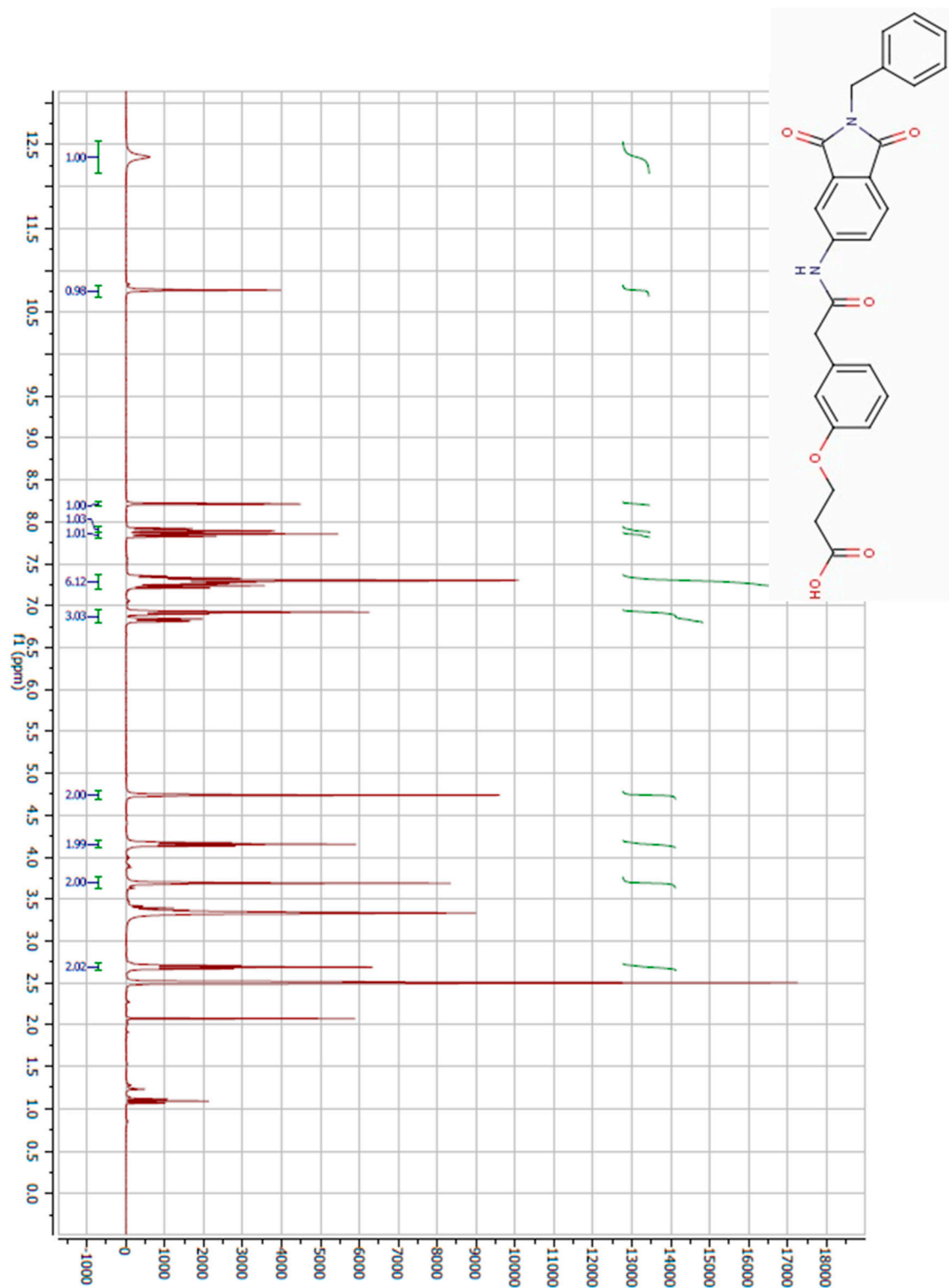
**HRMS**

*N*-(2-benzyl-1,3-dioxo-2,3-dihydro-1*H*-isoindol-5-yl)-2-{3-[(6-hydroxyhexyl)oxy]phenyl}acetamide (13; ZHAW5042)

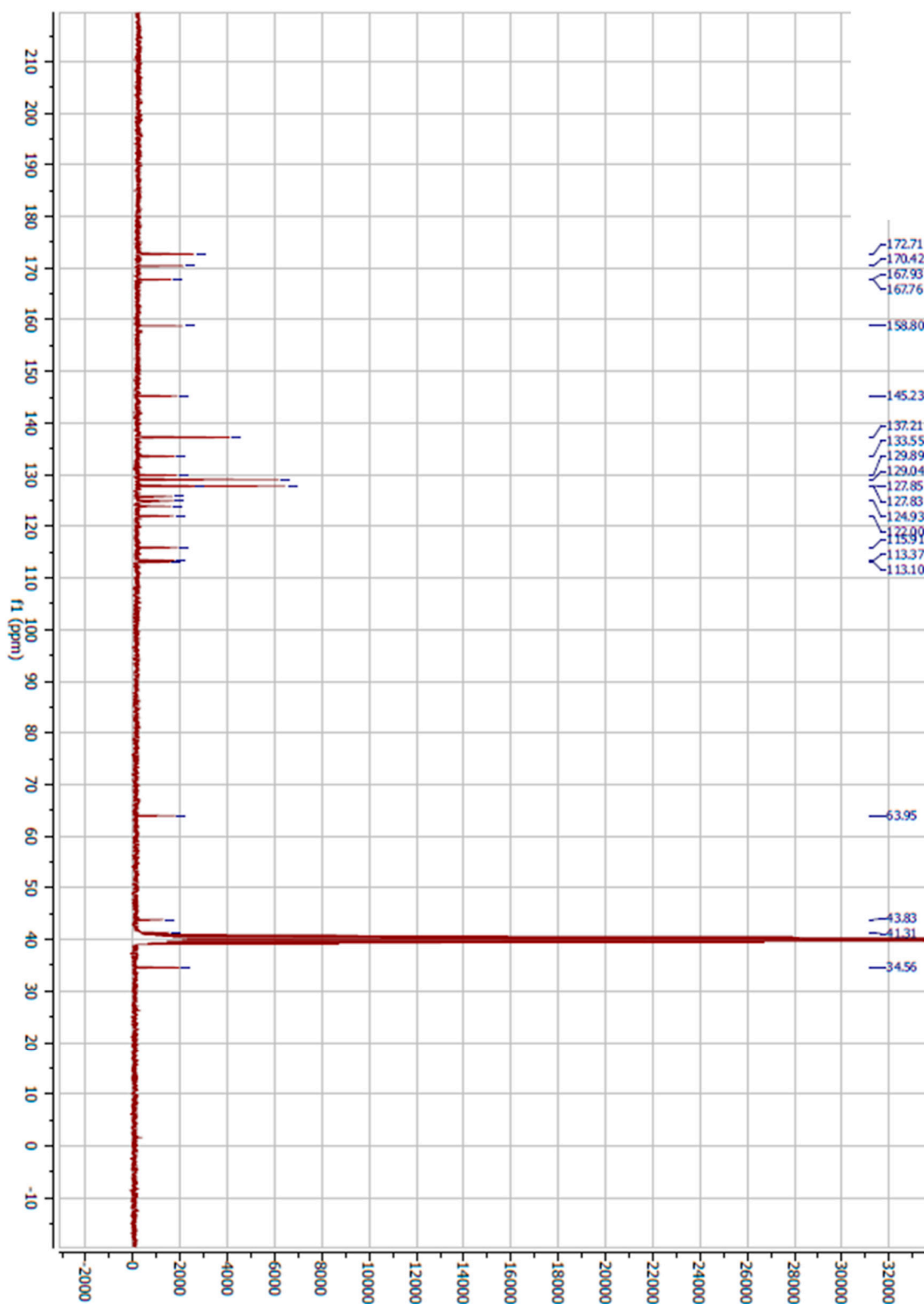


3-(3-((2-benzyl-1,3-dioxo-2,3-dihydro-1H-isoindol-5-yl)carbamoyl)methyl)phenoxy)propanoic acid (14; ZHAW4767)

**NMR**



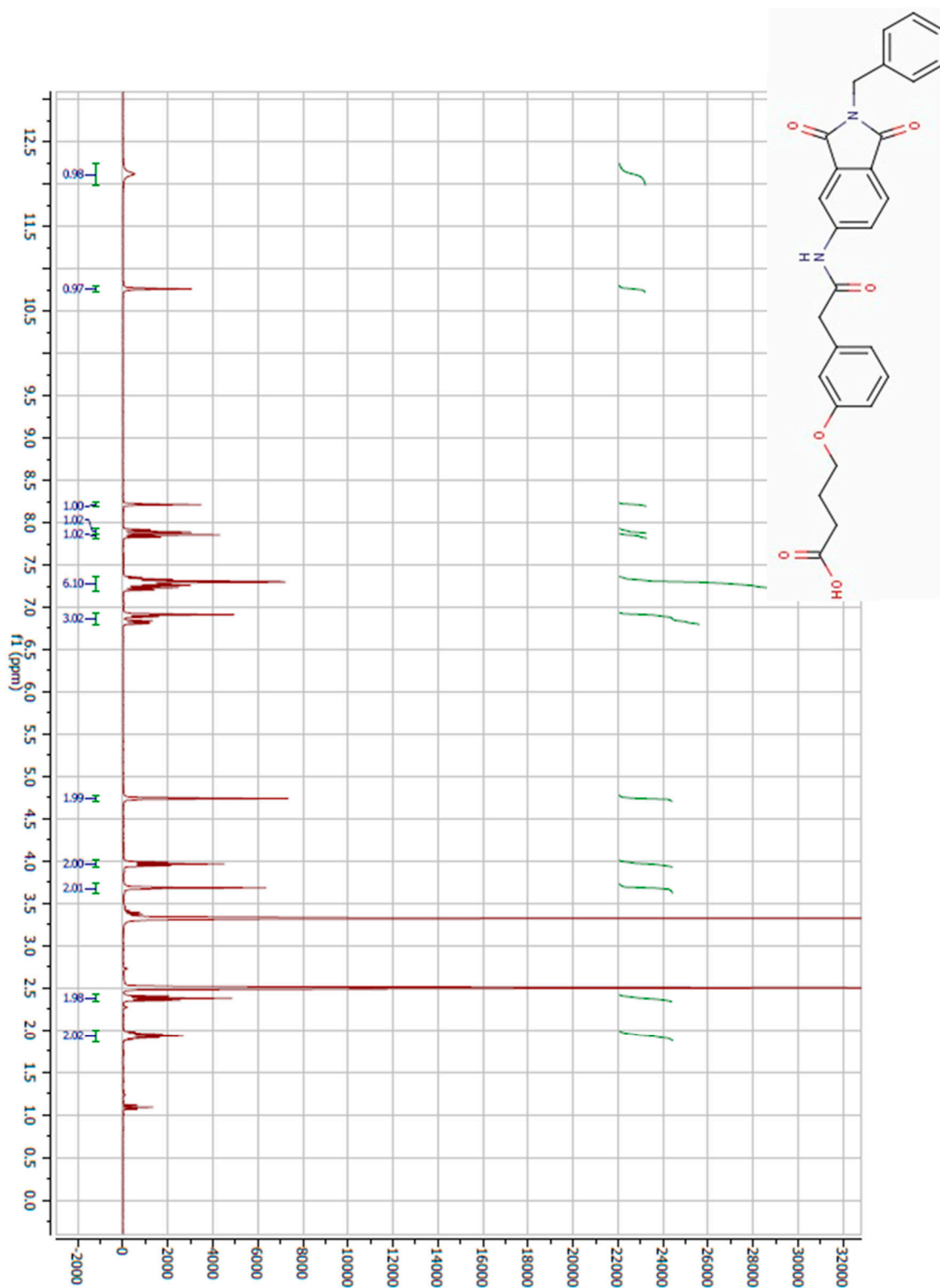
3-(3-{{(2-benzyl-1,3-dioxo-2,3-dihydro-1H-isoindol-5-yl)carbamoyl}methyl}phenoxy)propanoic acid (14; ZHAW4767)





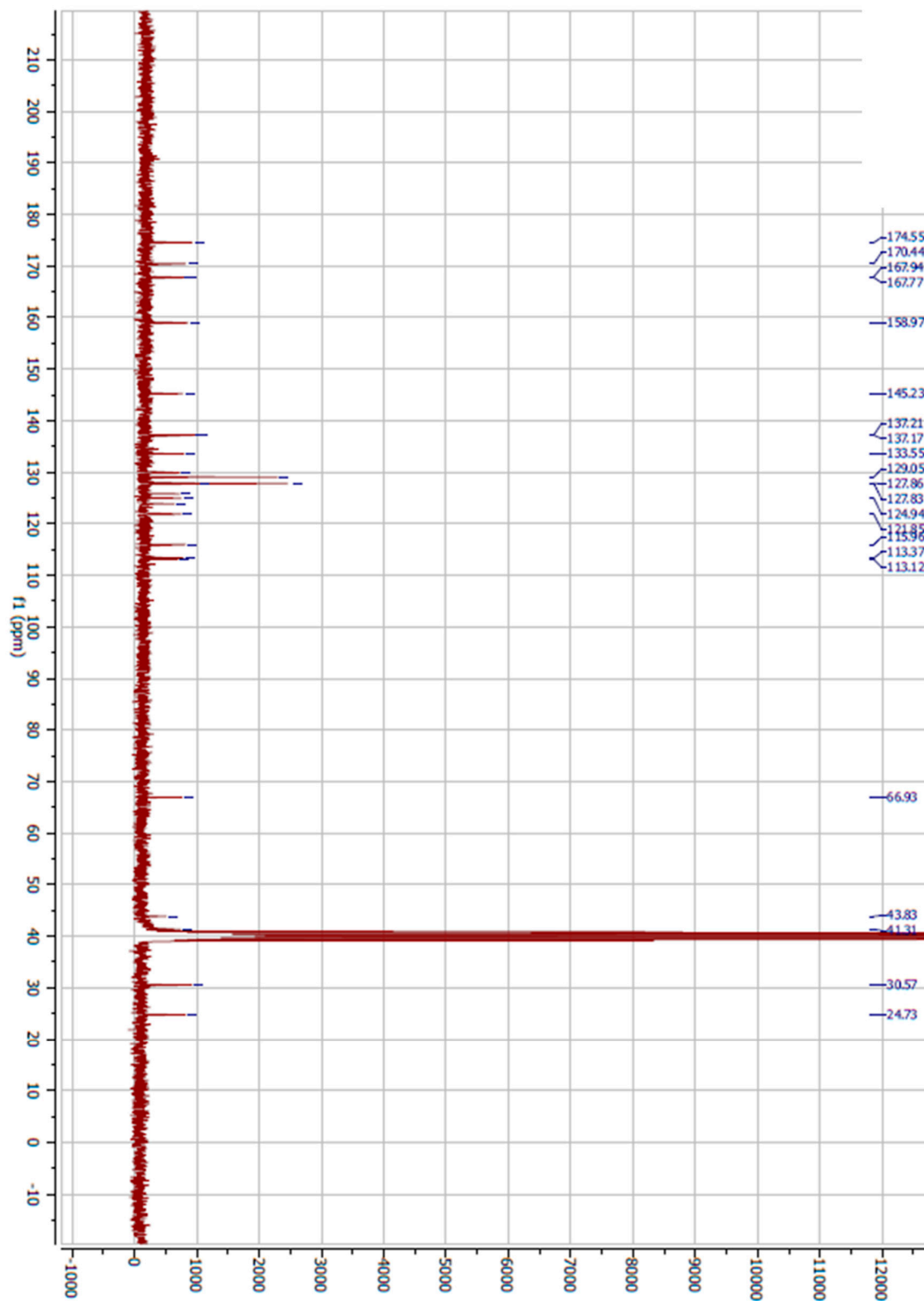
4-(3-((2-benzyl-1,3-dioxo-2,3-dihydro-1H-isoindol-5-yl)carbamoyl)methyl)phenoxy)butanoic acid (15; ZHAW4768)

**NMR**



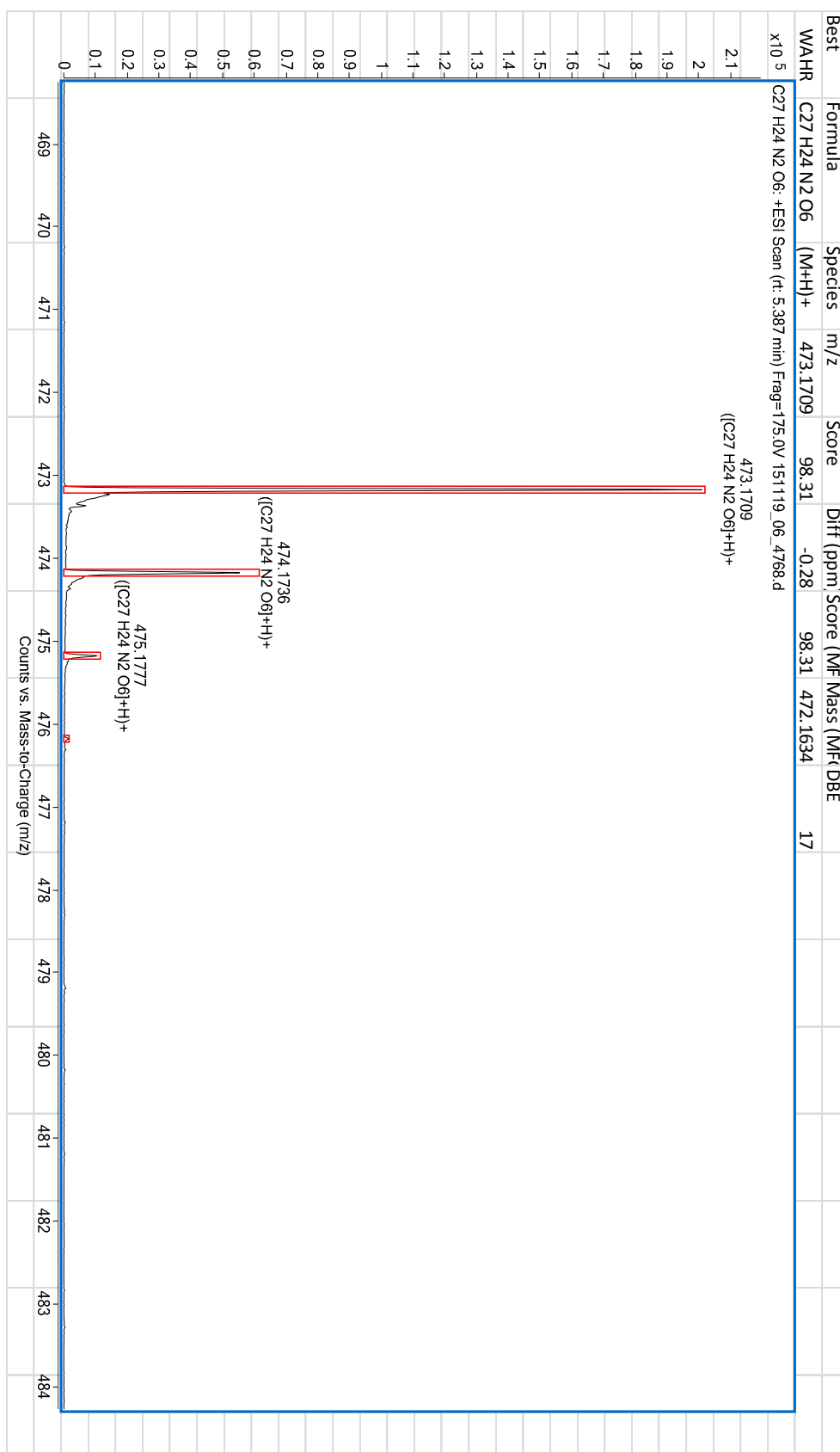


4-(3-((2-benzyl-1,3-dioxo-2,3-dihydro-1H-isoindol-5-yl)carbonyl)methyl)phenoxy)butanoic acid (15; ZHAW4768)



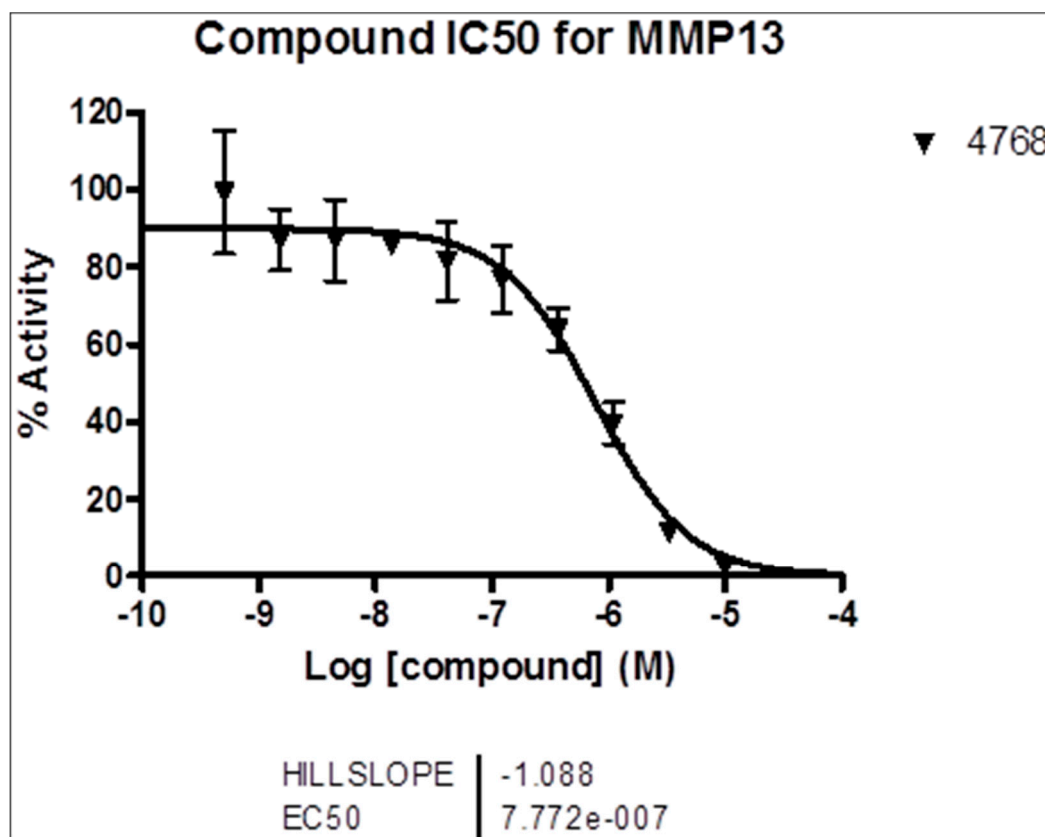
**HRMS**

4-(3-[[[(2-benzyl-1,3-dioxo-2,3-dihydro-1H-isoindol-5-yl)carbamoyl]methyl]phenoxy]butanoic acid (15; ZHAW4768)



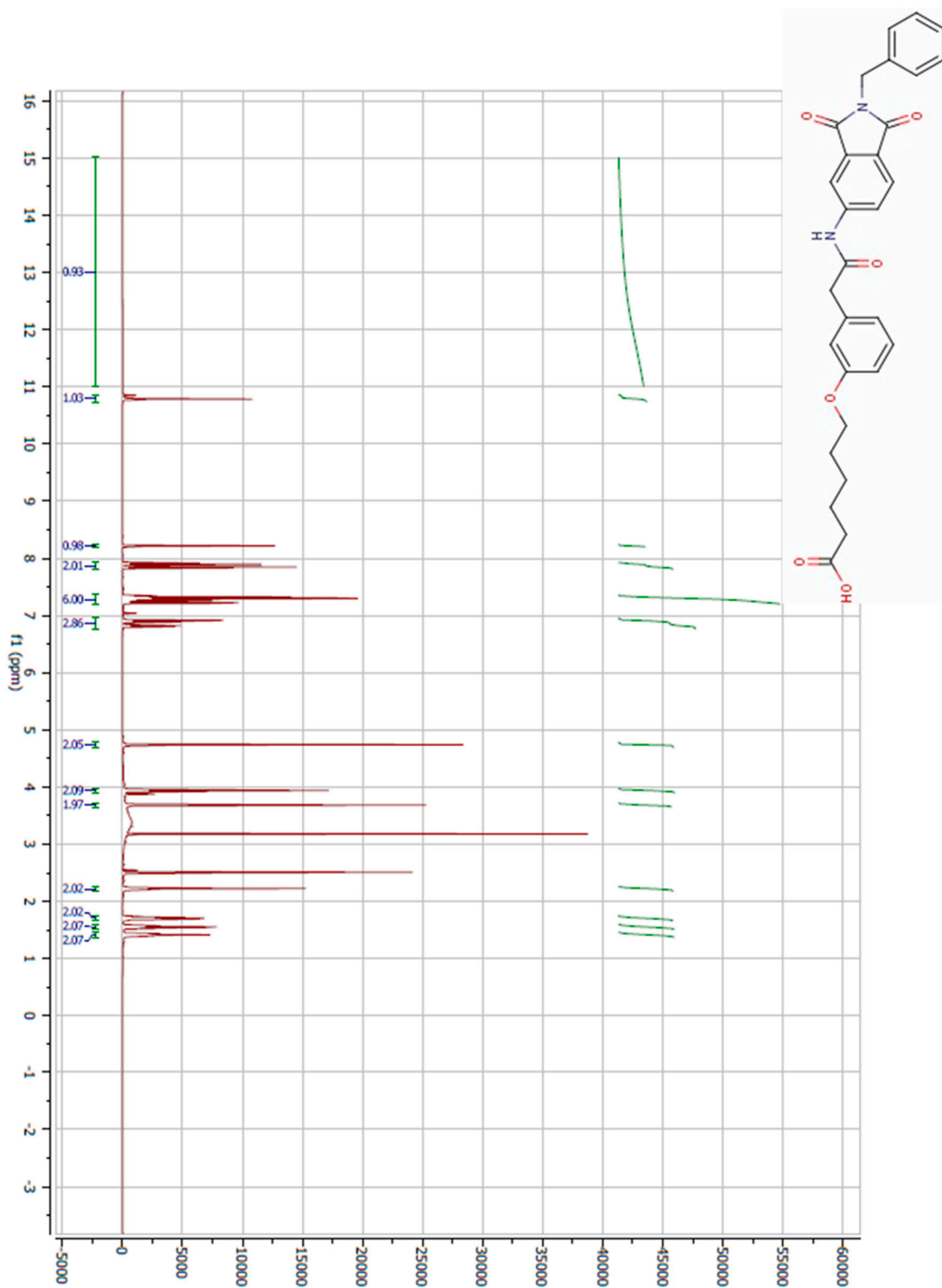
**IC<sub>50</sub>**

4-(3-[[[2-benzyl-1,3-dioxo-2,3-dihydro-1H-isoindol-5-yl]carbonyl]methyl]phenoxy)butanoic acid (15; ZHAW4768)

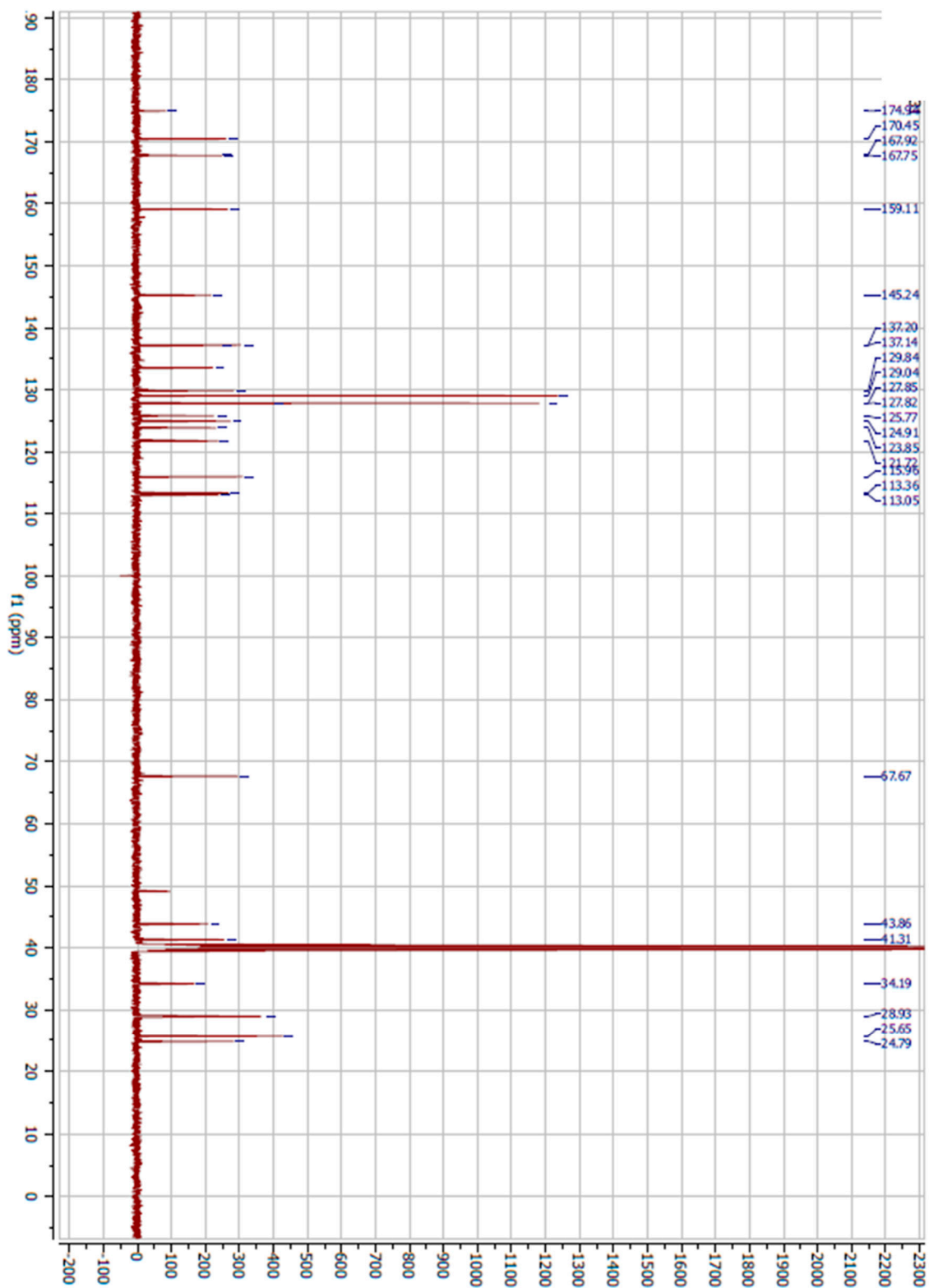


6-(3-((2-benzyl-1,3-dioxo-2,3-dihydro-1H-isoindol-5-yl)carbamoyl)methyl)phenoxy)hexanoic acid (16; ZHAW5078)

**NMR**

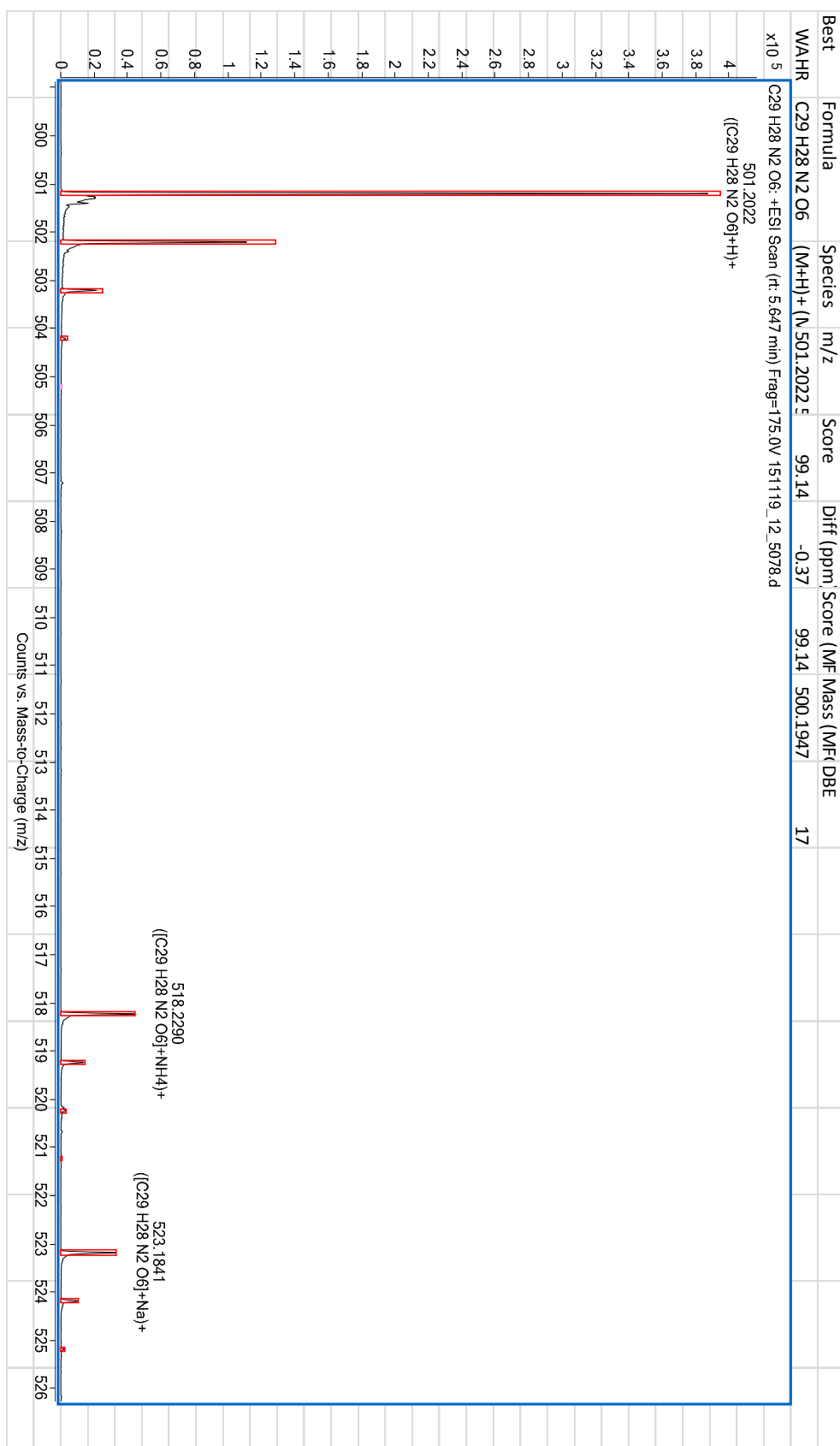


6-(3-{{(2-benzyl-1,3-dioxo-2,3-dihydro-1H-isoindol-5-yl)carbamoyl}methyl}phenoxy)hexanoic acid (16; ZHAW5078)



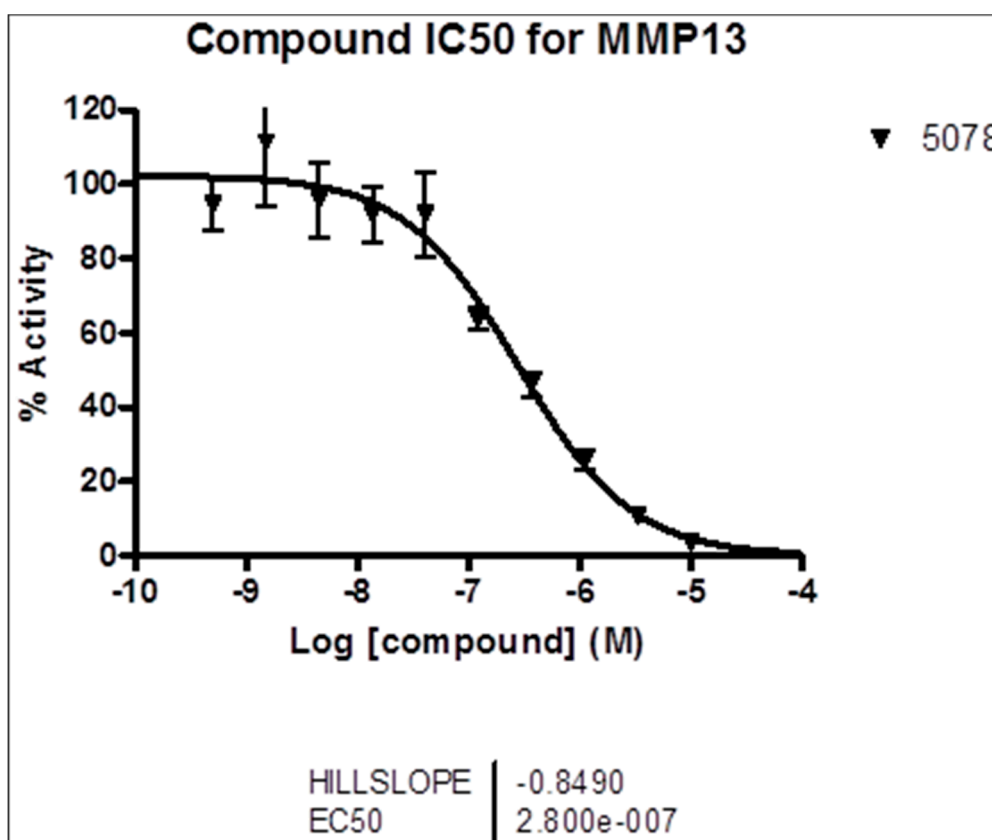
**HRMS**

6-(3-[[[(2-benzyl-1,3-dioxo-2,3-dihydro-1H-isoindol-5-yl)carbamoyl]methyl]phenoxy]hexanoic acid (16; ZHAW5078)



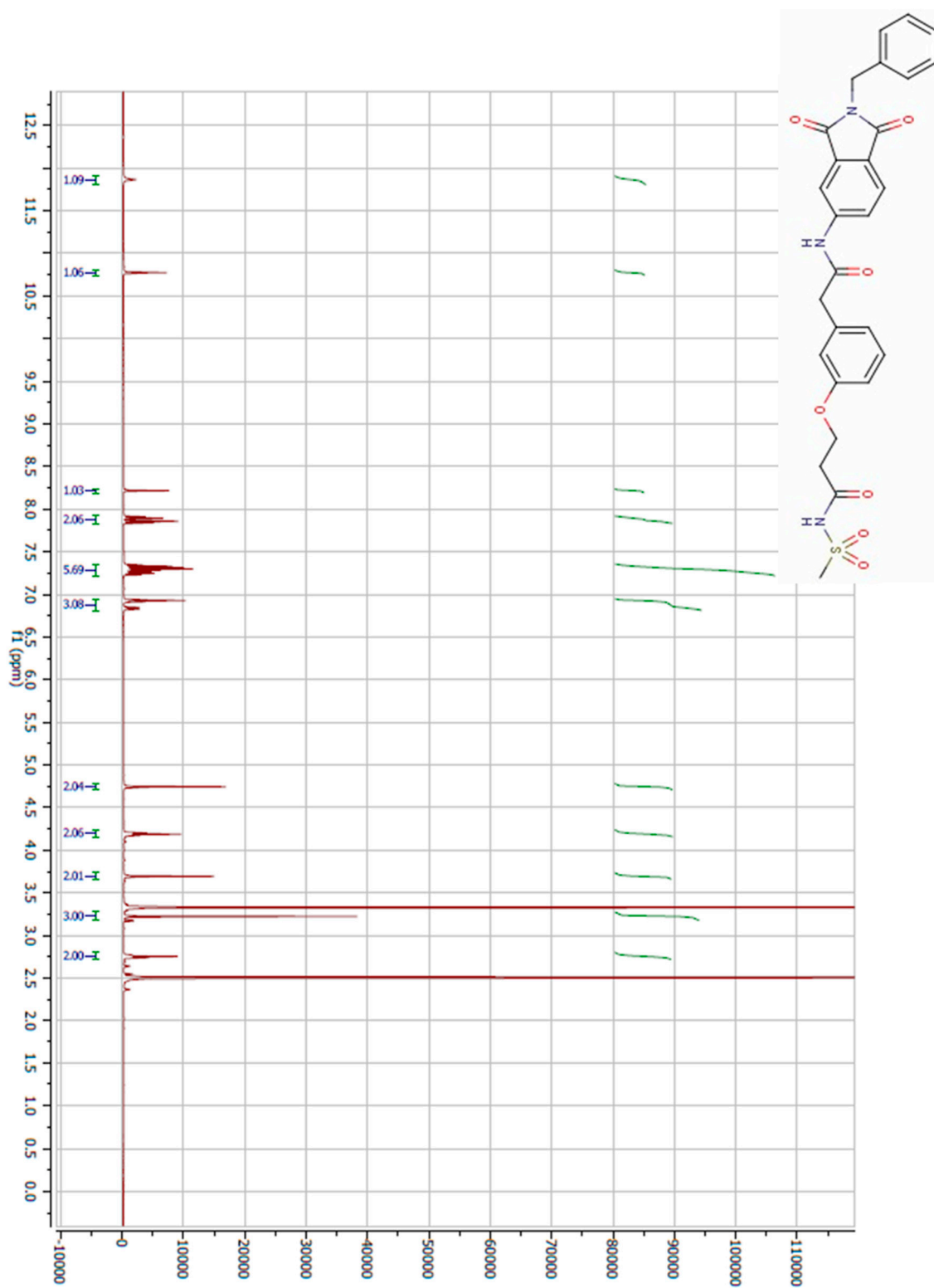
**IC<sub>50</sub>**

6-(3-[[[(2-benzyl-1,3-dioxo-2,3-dihydro-1H-isoindol-5-yl)carbamoyl]methyl]phenoxy)hexanoic acid (16; ZHAW5078)



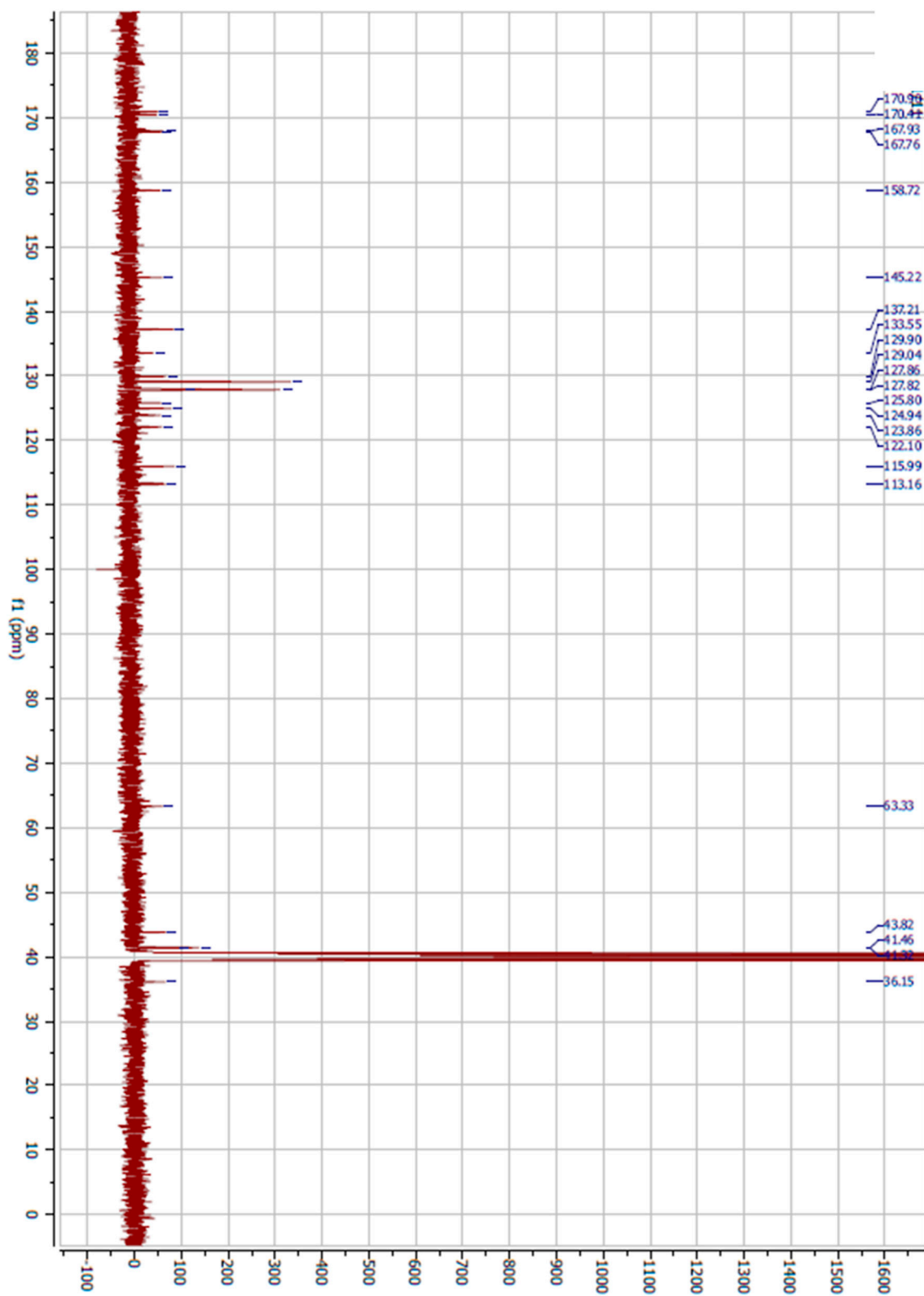
3-(3-((2-benzyl-1,3-dioxo-2,3-dihydro-1H-isoindol-5-yl)carbamoyl)methyl)phenoxy)-N-methanesulfonylpropanamide (**17**; ZHAW5136)

**NMR**



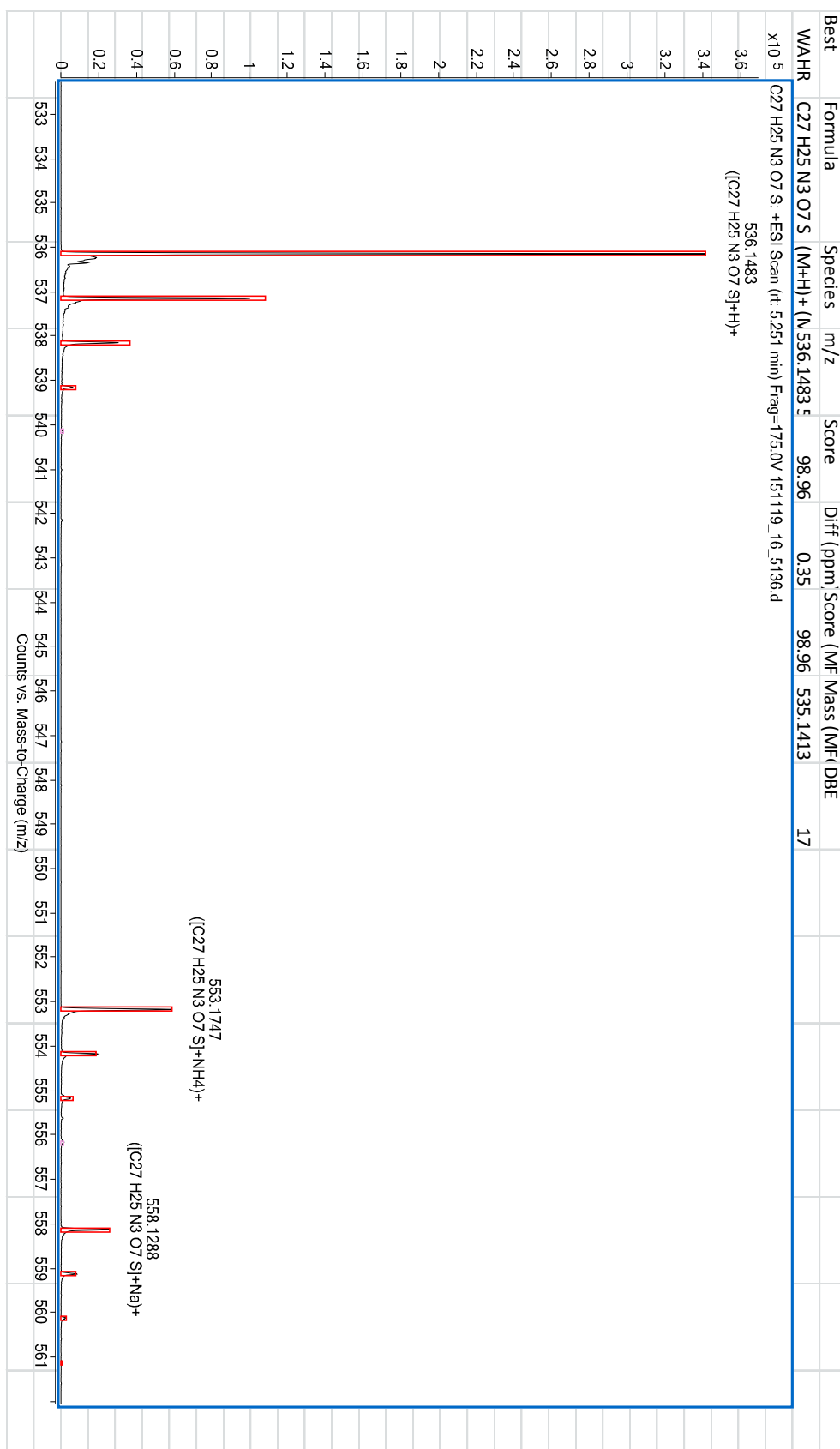


3-(3-{{(2-benzyl-1,3-dioxo-2,3-dihydro-1H-isoindol-5-yl)carbamoyl}methyl}phenoxy)-N-methanesulfonylpropanamide (**17**; ZHAW5136)



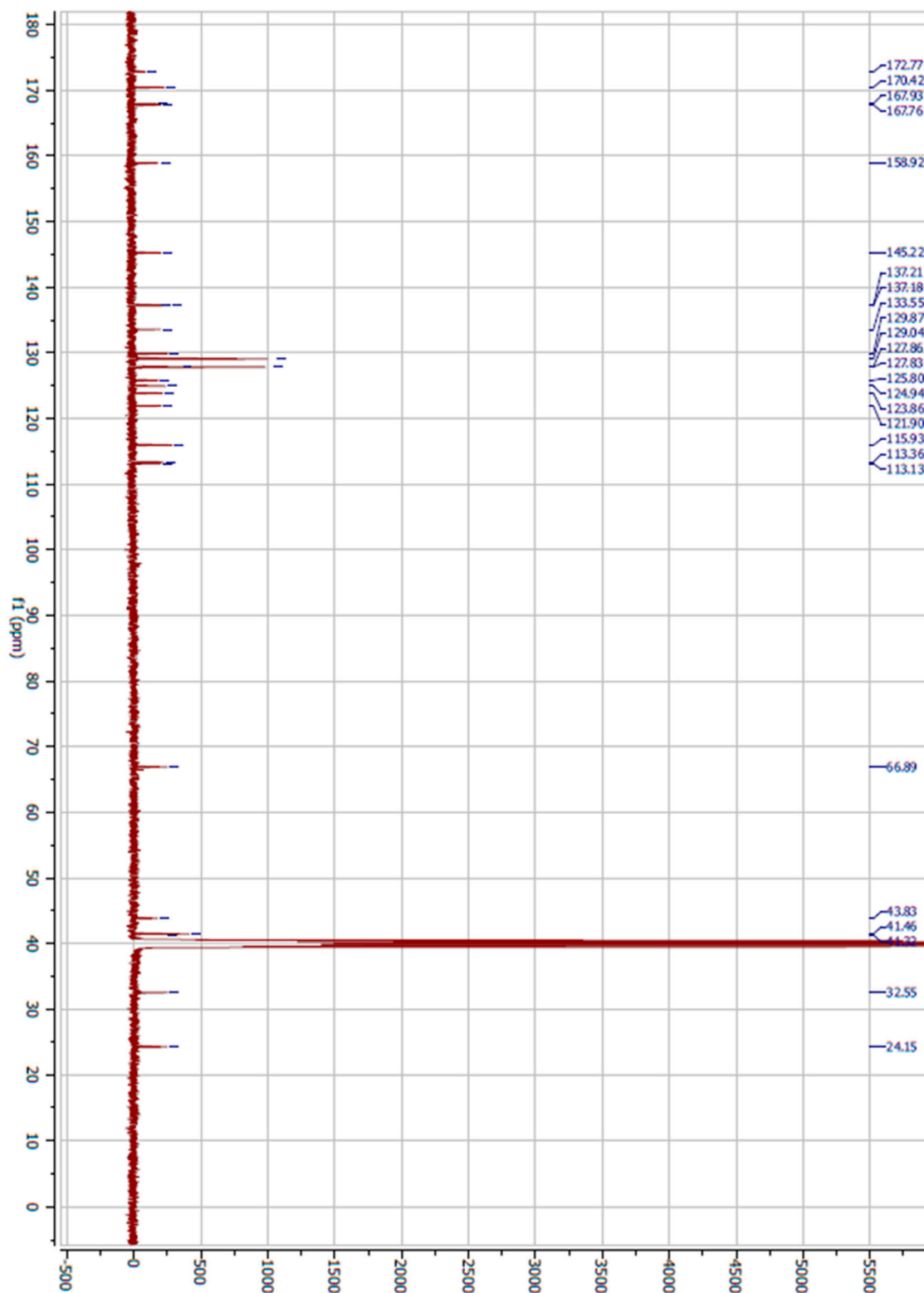
**HRMS**

3-(3-(((2-benzyl-1,3-dioxo-2,3-dihydro-1H-isoindol-5-yl)carbamoyl)methyl}phenoxy)-N-methanesulfonylpropanamide (**17**; ZHAW5136)



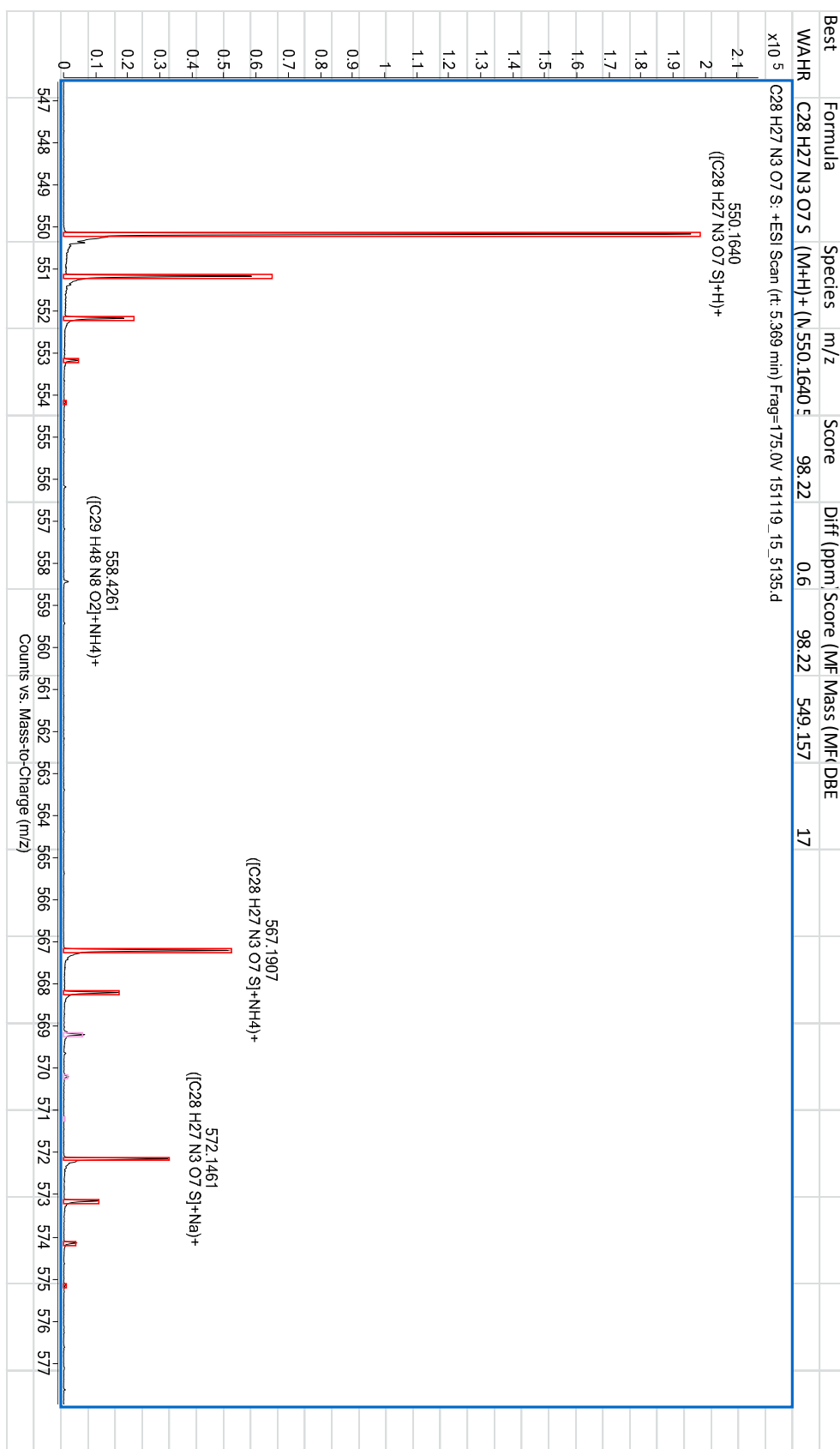


4-(3-{{(2-benzyl-1,3-dioxo-2,3-dihydro-1H-isoindol-5-yl)carbamoyl}methyl}phenoxy)-N-methanesulfonylbutanamide (**18**; ZHAW5135)



**HRMS**

4-(3-[[[(2-benzyl-1,3-dioxo-2,3-dihydro-1H-isoindol-5-yl)carbamoyl]methyl]phenoxy]-N-methanesulfonylbutanamide (**18**; ZHAW5135)



**IC<sub>50</sub>**

4-(3-[[[2-benzyl-1,3-dioxo-2,3-dihydro-1H-isoindol-5-yl]carbonyl]methyl]phenoxy)-N-methanesulfonylbutanamide (**18**; ZHAW5135)

