Electronic Supplementary Material (ESI) for Faraday Discussions.

Computational driven design of an artificial metalloenzyme using supramolecular anchoring strategies of iridium complexes to alcohol dehydrogenases

Floriane L. Martins,[a] Anca Pordea [a] and Christof M. Jäger [a, *]

Supporting Information

Table of Contents

Table of tables

Table of figures

1 Docking

1.1 Cofactor NADP redocking

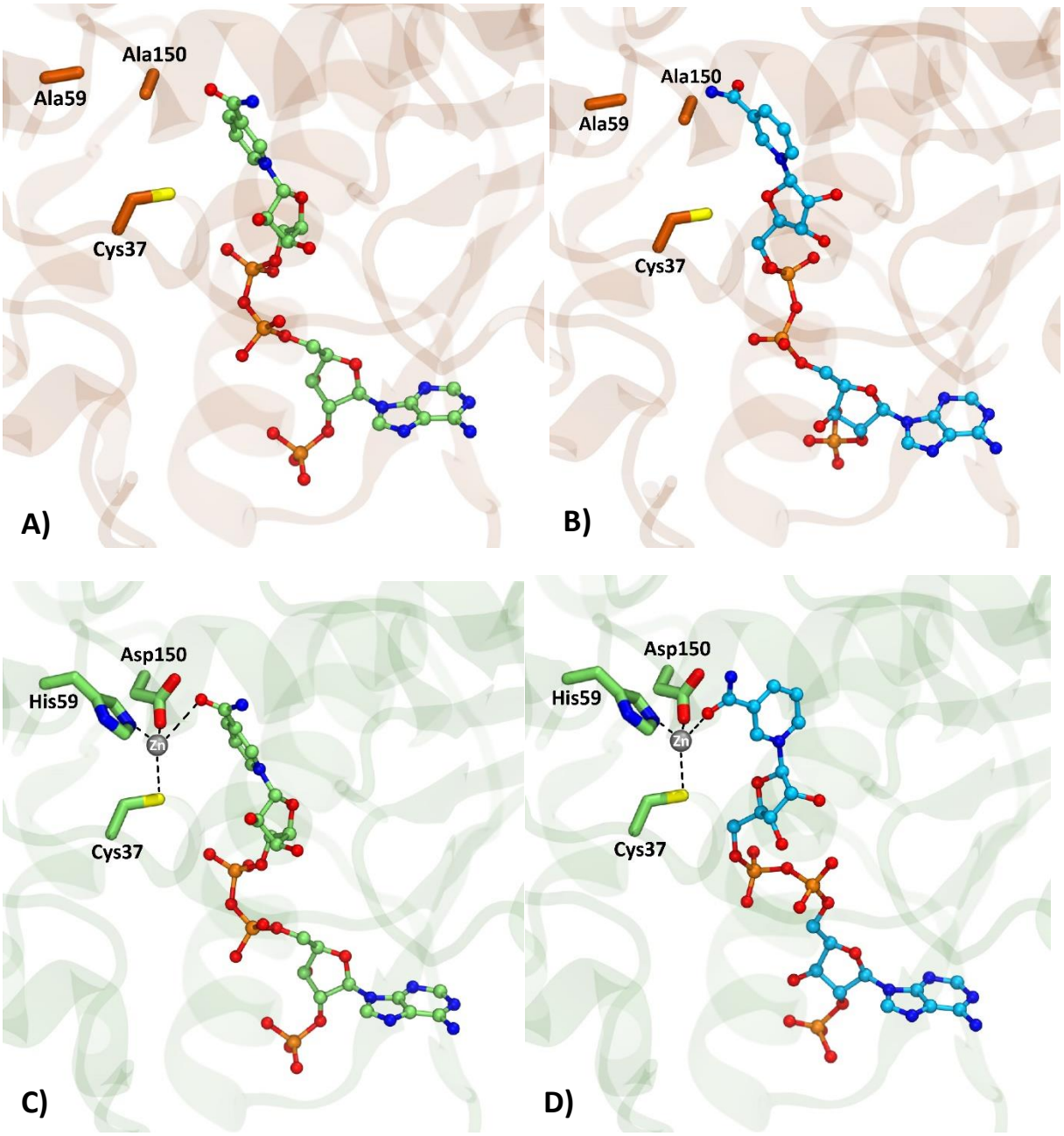


Figure S1: **A)** crystal structure of TbADH-5M with $NADP^+$. **B)** Re-docked $NADP^+$ inside TbADH-5M with RMSD<2Å. **C)** crystal structure of TbADH-WT with $NADP^+$. **D)** Re-docked $NADP^+$ inside TbADH-WT with RMSD<2Å.

1.2 High-throughput library screening

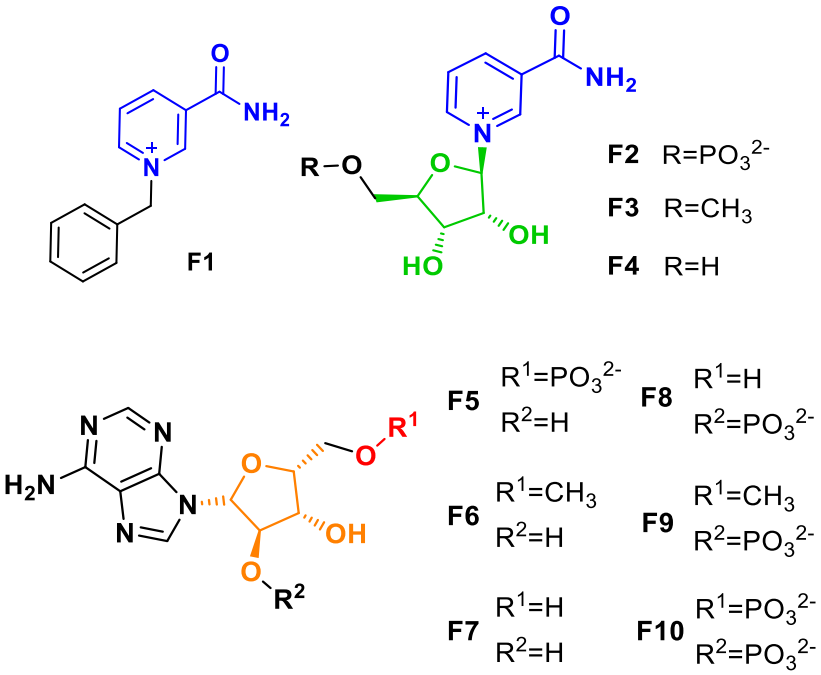
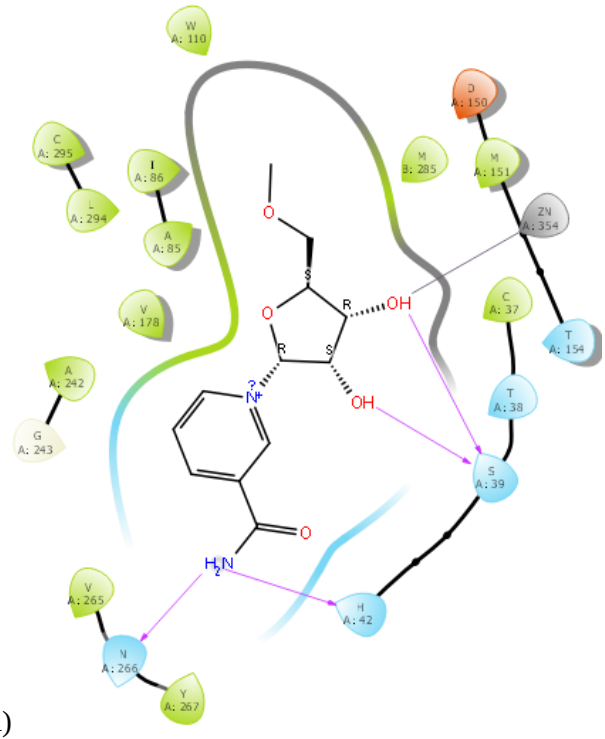


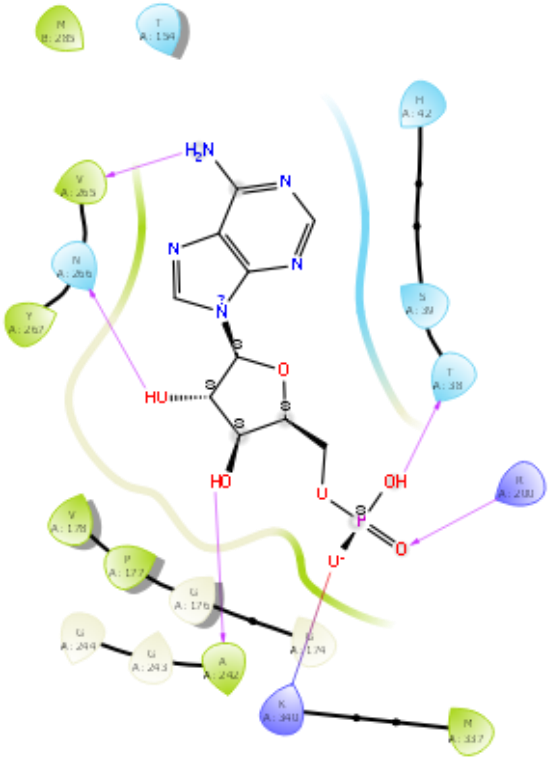
Figure S2: Fragments of NAD(P)H structure based on the nicotinamide and adenosine parts, designed for the docking inside HLADH and TbADH. Compound **F1** was used based on literature mimic.[104,109]

Table S1: XP score (kcal.mol^{-1}) of the NAD(P)H fragments after docking inside TbADH and TbADH-5M. The best ranked fragments are highlighted in red.

Fragments	TbADH XP Glide	TbADH 5M XP Glide
NADPH	-11.6	-12.3
NADP$^+$	-10.1	-10.7
F3	**-9.0**	-7.2
F2	-8.9	-7.3
F5	-8.8	**-9.1**
F10	-8.8	-7.7
F6	-7.3	-6.4
F7	-6.8	-6.6
F4	-6.7	-7.5
F9	-6.5	-7.7
F8	-6.2	-6.6
F1	-5.9	-6.1


W
A: 110
D
A: 150
C
A: 295
M
B: 285
M
A: 151
I
A: 86
L
A: 294
A
A: 85
ZN
A: 354
V
A: 178
C
A: 37
T
A: 154
A
A: 242
T
A: 38
G
A: 243
S
A: 39
H
A: 42
V
A: 265
N
A: 266
Y
A: 267
O
R
S
OH
NH
H2N

A)


H2N
N
HO
OH
O
U
P

B)

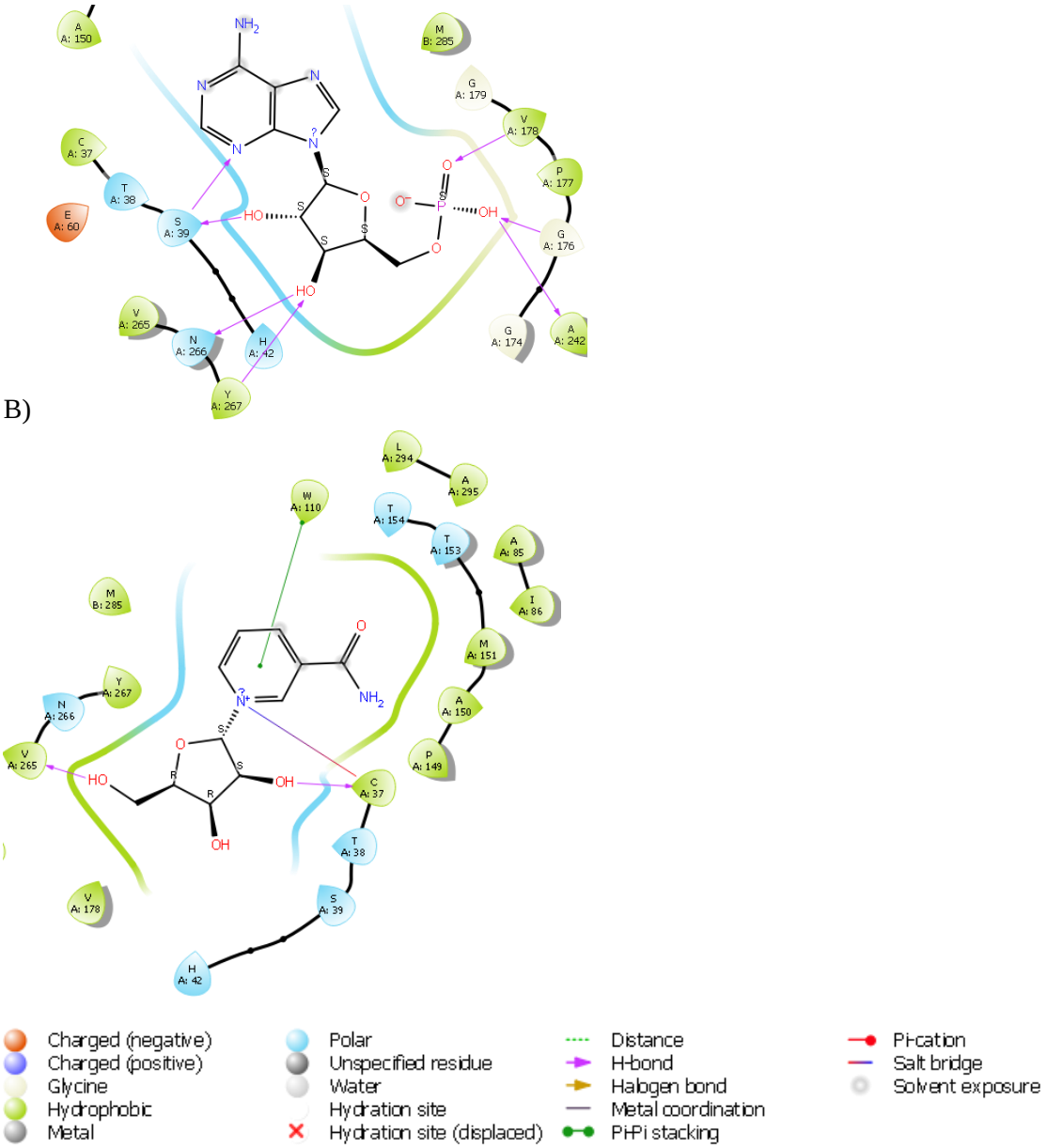


Figure S3: Interaction diagrams of docked $NADP^+$ fragments. A) TbADH-WT with fragment **3** and **5**. B) TbADH-5M with fragment **5** and **4**.

1.3 Ligand library docking

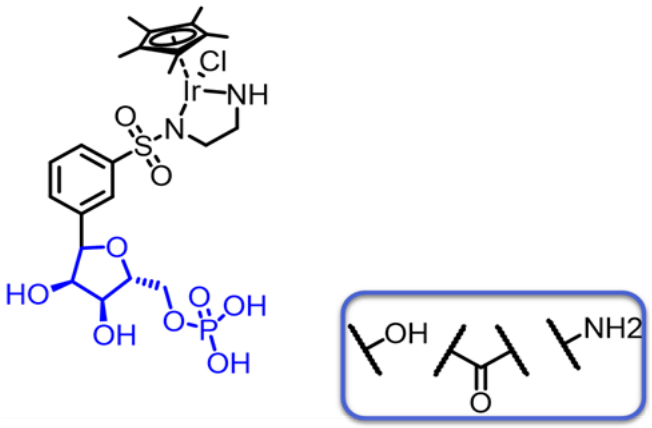


Figure S4: Template of a catalyst complex model composed of a metal supported by a bidentate ligand and a hydrophilic anchor (blue).

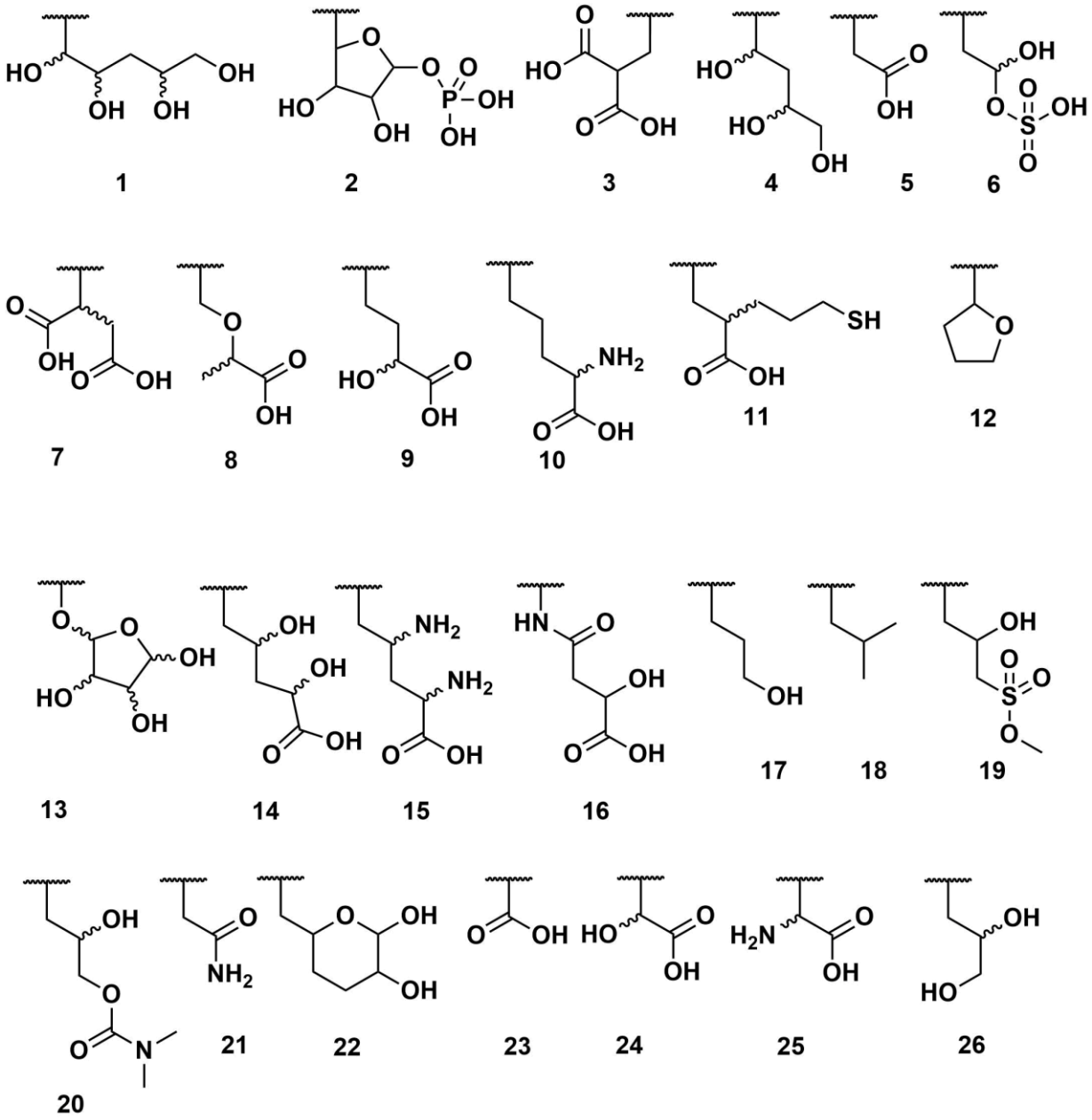


Figure S5: Ligand library created using variation of structure length and hydrophilic groups combinations. Only anchoring parts of the ligands shown, omitting the para substituted sulphonamide structure from the template shown in Figure S4.

Table S2: Comparison of ligands XP score (kcal mol^{-1}) in TbADH and TbADH 5M.

Ligand	TbADH WT XP score	Ligand	TbADH 5M XP score
(3R)-1	-11.2	**(3R)-1**	-12.0
(R,R)-4	-9.5	**(S,S,R)-22**	-11.2
(R)-22	-9.1	**(R,R,R,S)-13**	-11.2
(R,R,S,S)-13	-8.8	**(R,R)-14**	-10.5

(R,R,S,S)-2	-7.3	**(S)-6**	-10.0
(S,R)-14	-7.6	**(R,R)-4**	-10.1
(R)-10	-7.1	**3**	-10.1
(R)-9	-6.9	**(R,R)-15**	-9.4
(S)-24	-6.6	**(R)-19**	-10.0
3	-6.5	**(S)-20**	-8.9
(S,S)-15	-6.4	**(R,R,R,S)-2**	-8.8
(R)-11	-6.3	**(S)-10**	-8.8
(S)-20	-6.3	**21**	-7.9
(S)-7	-6.1	**(S)-8**	-7.7
21	-7.4	**(R)-9**	-7.1
(R)-6	-5.2	**(S)-11**	-6.8
5	-4.9	**(R)-7**	-6.5
(S)-8	-4.8		
(S)-25	-4.7		

Table S3: XP scores (kcal mol^{-1}) for different isomers of ligand 4 in TbADH WT and TbADH 5M

Ligand configuration	TbADH Wt	Ligand configuration	TbADH 5M
(R,R)-4	-9.5	**(R,S)-4**	-11.4
(S,R)-4	-9.0	**(S,R)-4**	-10.4
(S,S)-4	-8.2	**(S,S)-4**	-10.1
(R,S)-4	-8.0	**(R,R)-4**	-10.1

1.4 Metal complexes catalyst docking

1.4.1 Score correction definition

In addition to the Glide XP score representing the affinity of ligands for TbADHs, a new scoring was defined, characterising the orientation and location of ligands. The location and the orientation of the ligand inside both TbADHs binding site were evaluated as follows:

Define total score is:

$$S = -2\ S_{XP} + 3\ S_L + 3\ S_O$$

With:

XP Score **(x -2)**

Location **(x3)** [0 .. 5]:

- 0: not in the pocket
- 1: minimal distance to pocket entrance (adenine part)
- 2: minimal distance to adenine-phosphate area

- 3: minimal distance to pyrophosphate area
- 4: minimal distance to the nicotinamide ribose area
- 5: perfectly aligned to the $NADP^+$ binding area

Orientation compared to $NADP^+$ crystal structure **(x4)** [0, 2, 5]:

- 0: reversed pose: rotation by 180 degrees from crystallised $NADP^+$
- 2: mix of poses reversed and poses in catalytic orientation
- 5: same catalytic orientation as $NADP^+$

1.4.2 Metal complexes docking

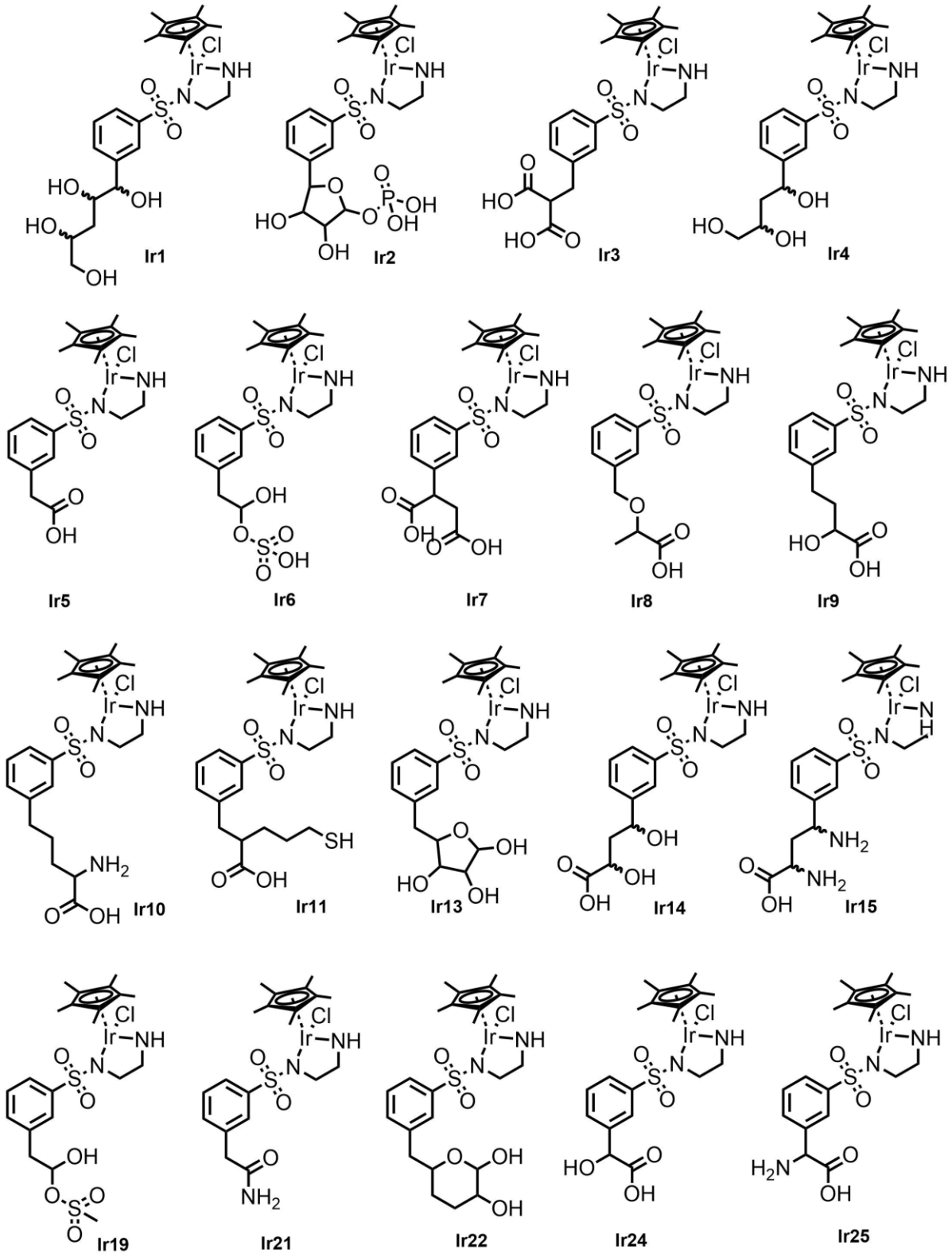


Figure S6: Metal complex library for IFD screening

Table S4: Metal Iridium complexes docked with IFD calculations inside TbADH WT and TbADH 5M, ranked based on their previous preceding ligands ranking. The ranking of metal catalysts is presented by applying new scoring IFD (S) and compared to ranking based on IFD (XP) (kcal .mol-1).

Ligand	TbADH WT			Ligand	TbADH-5M		
	ligand XP score	Ir IFD (S)	Ir IFD(XP)		ligand XP score	Ir IFD (S)	Ir IFD(XP)
(3R)-1	-11.2	36.6	-7.8	**(3R)-1**	-12.0	53.4	-12.2
(R,R)-4	-9.5	30	-6.9	**(S,S,R)-22**	-11.2	39.4	-11.2
(R)-22	-9.1	24	-7.5	**(R,R,R,S)-13**	-11.2	43.6	-11.6
(R,R,S,S)-13	-8.8			**(R,R)-14**	-10.5	50.4	-9.2
(R,R,S,S)-2	-7.3	32.4	-10.5	**(S)-6**	-10.0	41.0	-9.5
(S,R)-14	-7.6			**(R,R)-4**	-10.1	52.6	-8.8
(R)-10	-7.1			**3**	-10.1	53.6	-9.3
(R)-9	-6.9			**(R,R)-15**	-9.4	54.0	
(S)-24	-6.6	36.2	-10.2	**(R)-19**	-10.0		
3	-6.5	19	-6.5	**(S)-20**	-8.9		
(S,S)-15	-6.4			**(R,R,R,S)-2**	-8.8	42.6	-12.8
(R)-11	-6.3	22.8	-10.8	**(S)-10**	-8.8	43.8	-7.4
(S)-20	-6.3			**21**	-7.9		
(S)-7	-6.1	28.8	-6.9	**(S)-8**	-7.7	42.8	-8.4
21	-7.4			**(R)-9**	-7.1	46.6	-8.8
(R)-6	-5.2	23.8	-8.9	**(S)-11**	-6.8		
5	-4.9	38.6	-12.9	**(R)-7**	-6.5		
(S)-8	-4.8	13.8	-5.4				
(S)-25	-4.7	21	-6.0				

Table S5: XP and IFD screening of ligands **12** and **23** and their corresponding metal complexes in TbADH WT and TbADH 5M.

Ligand	TbADH WT			TbADH-5M		
	ligand XP score	Ir IFD (S)	Ir IFD(XP)	ligand XP score	Ir IFD (S)	Ir IFD(XP)
12	-3.3	20.2	-5.6	-6.2	24.4	-6.2
23	-4.2	19	-5.0	-5.5	20	-5.5

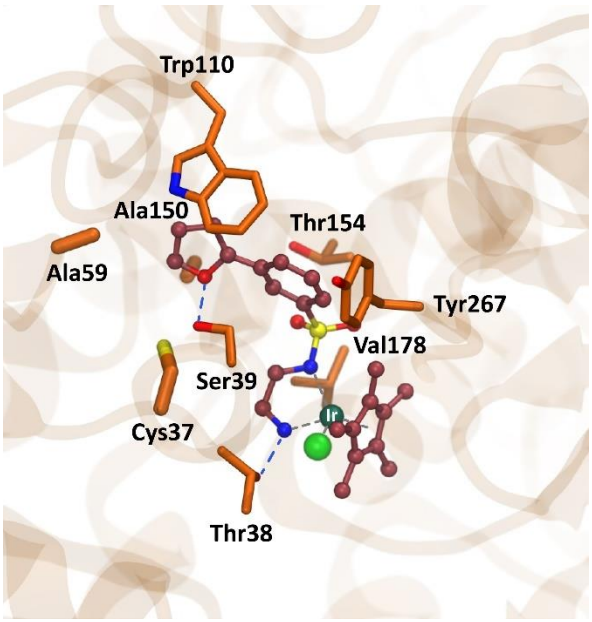


Figure S7: **Ir12** position reverted in TbADH 5M after IFD docking.

2 Creation and characterisation of ArMs

2.1 Inhibition assays

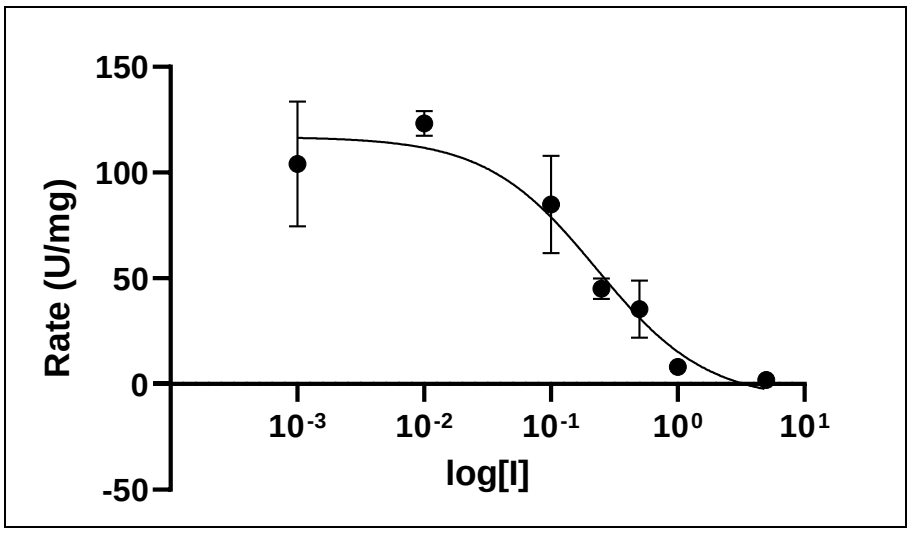


Figure S8: Inhibition curve of TbADH 5M with **Ir4**

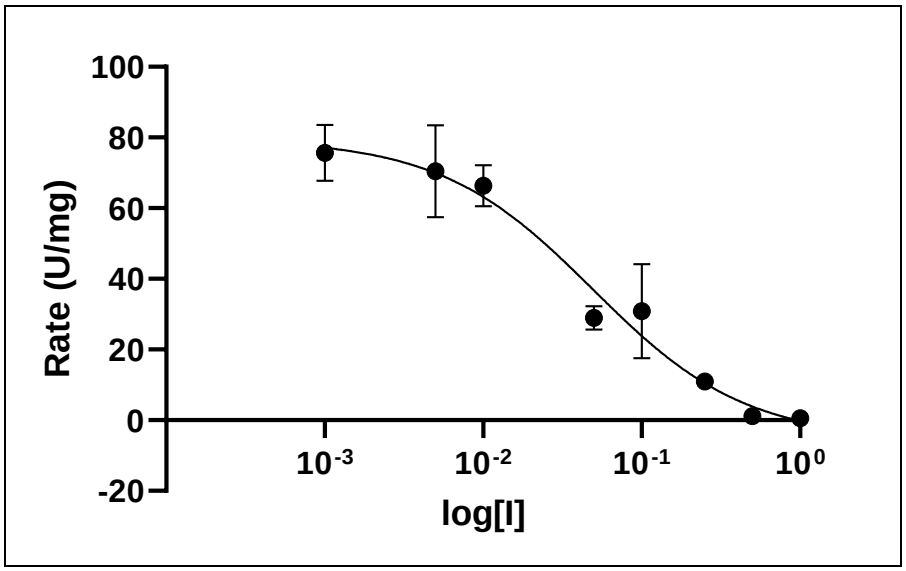


Figure S9: Inhibition curve of TbADH 5M with **Ir12**

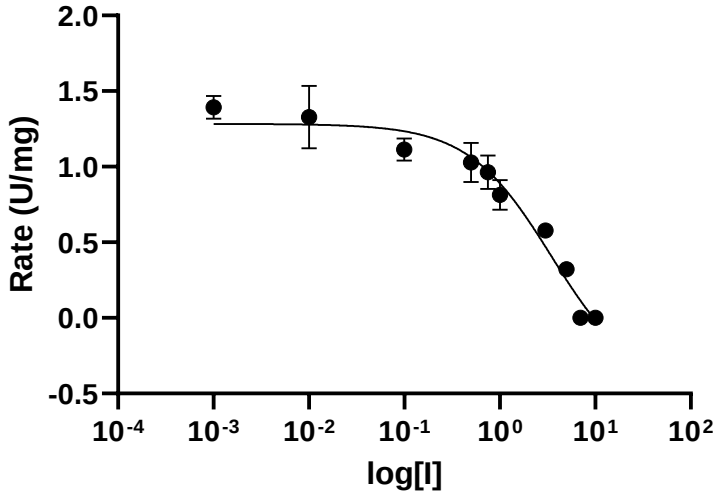


Figure S10: Inhibition curve of TbADH 5M with **Ir23**

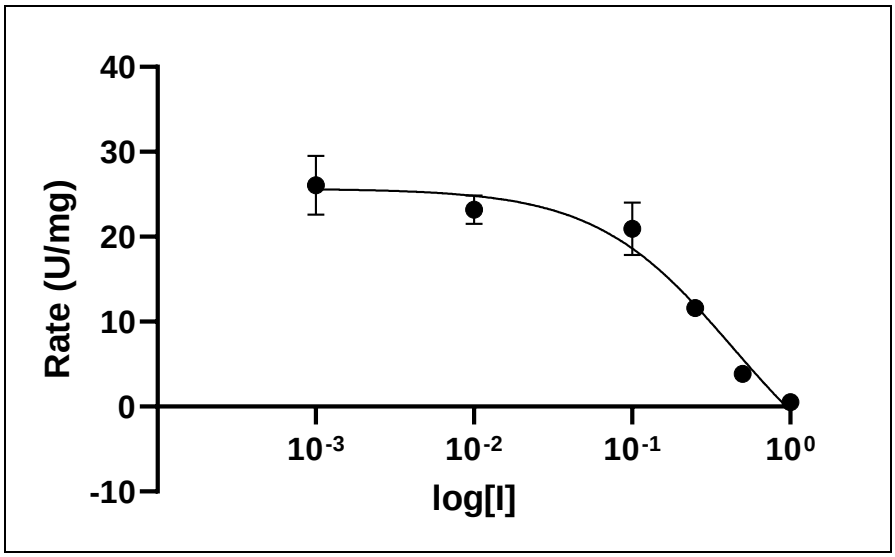


Figure S11: Inhibition curve of TbADH 5M with **4**

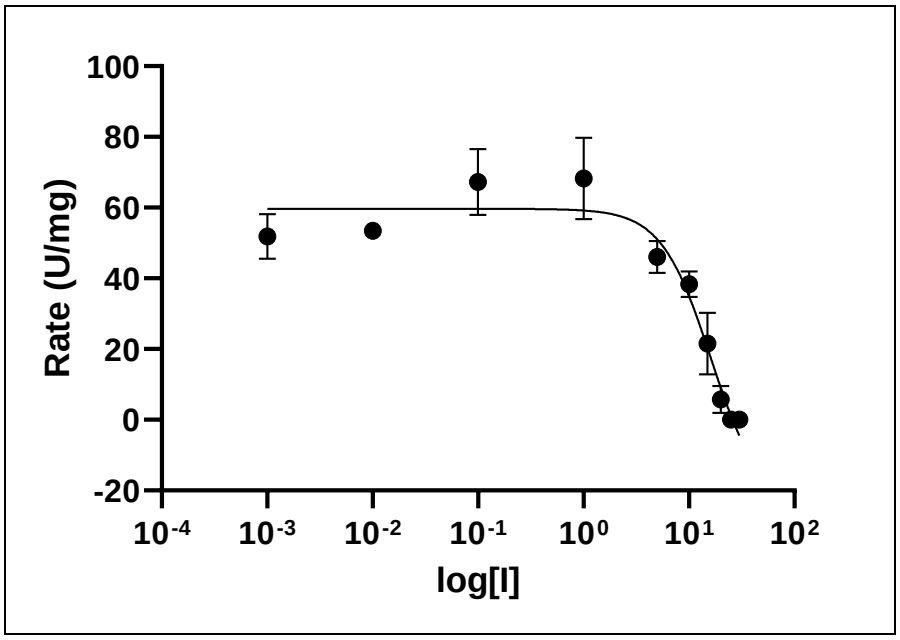


Figure S12: Inhibition curve of TbADH 5M with **12**

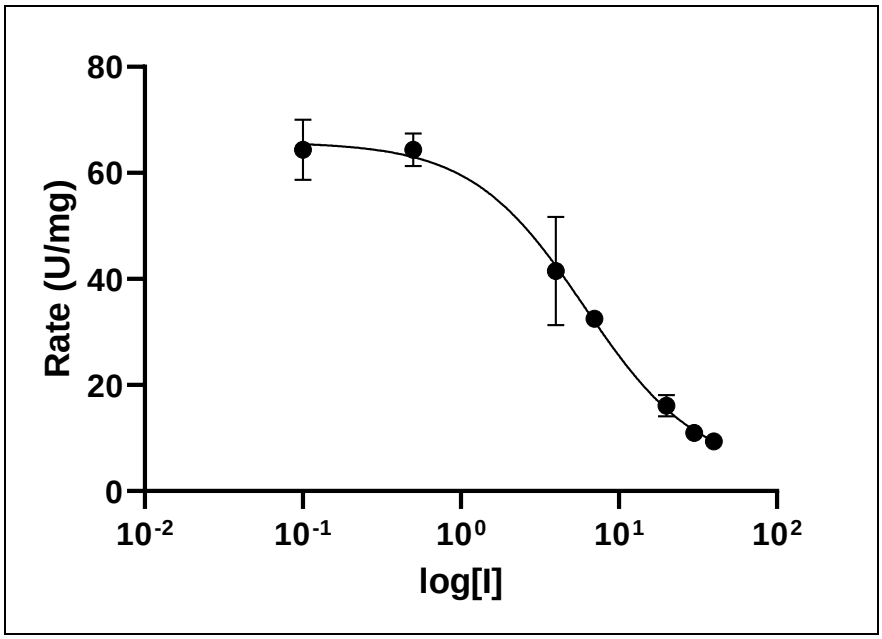


Figure S13: Inhibition curve of TbADH 5M with **23**

3 Synthesis of iridium complexes

3.1 Methods

Synthesis of ligands and metal complexes

All chemicals were purchased as analytical grade from Sigma Aldrich and Fisher Scientific and were used without further purification. All aqueous solutions were prepared using ultrapure (Milli-Q®) water. Analytical thin layer chromatography (TLC) was carried out on aluminium backed plates coated with Merck Kieselgel 60 GF254 and visualised under UV light at 254 and/or 360 nm. Chemical staining was also routinely used, with aqueous basic potassium permanganate solution. Flash column chromatography was carried out using Davisil silica 60 Å, with eluent specified. ^{1}H and ^{13}C NMR spectra were recorded using a Bruker AV(III)400, AV400. DPX400 (400 MHz 1H frequency, 100 MHz 13C frequency). Coupling constants *J* are in Hz. Multiplicity of the signals is abbreviated as follow: s, singlet; d, doublet; t, triplet; q, quartet; dd, doublet of doublet; dt, doublet of triplet; m, multiplet; br, broad. In the ^{13}C spectra, signals corresponding to C, CH, CH_2 and CH_3 were assigned from DEPT experiments. Mass spectra were recorded using a Bruker MicroTOF 61 mass spectrometer using electrospray ionisation (ESI).

Benzyl (2-((3-acetylphenyl)sulfonamido)ethyl)carbamate (27). To a cooled solution of ketone **31** (1 eq, 2.87 mmol, 987 mg) in dichloromethane (47 mL) was added dropwise under stirring trifluoroacetic acid (12.7 eq, 36.45 mmol, 2.8 mL). The solution was then stirred overnight at room temperature and monitored by TLC (CH_2Cl_2 95/5 CH_3OH + traces of acetic acid). The solution was evaporated under vacuum, after which TFA traces were removed by repeated addition and evaporation of dichloromethane under vacuum.[48] The obtained deprotected ketone (1 eq, 0.744 mmol, 253 mg) was dissolved in a bi-phasic diethyl ether (3 mL) and water (3.72 mL) mixture to which was added Na_2CO_3 (3 eq, 2.23 mmol, 237 mg). The solution was cooled on ice before the dropwise addition of benzylchloroformate (1 eq, 0.744

mmol, 0.106 mL). The solution was stirred at room temperature for 2.5 h and monitored by TLC (ethyl acetate 80/20 hexane). The two phases were then separated, and the organic layer was wash with brine and water, dried over $MgSO_4$, and filtered. The solvent was removed in vacuum and the resulting residue was purified by flash chromatography column on silica gel (ethyl acetate 80/20 hexane). The title compound **27** was collected as a yellow oil.[49]

Yield estimated at 60 %; ^{1}H NMR (400 MHz, $CDCl_3$): δ =8.40 (s, 1H, H aryl), 8.10 (d, *J*=8.0 Hz, 1H, H aryl), 8.03 (d, *J*=8.0 Hz, 1H, H aryl), 7.48 (t, *J*=8.0 Hz, 1H, H aryl), 7.30 (m, 5H, H aryl), 6.04 (m, 1H, NH), 5.54 (m, 1H, NH), 5.03 (s, 2H, CH_2), 3.28 (m, 2H, CH_2), 3.08 (m, 2H, CH_2), 2.60 (s, 3H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.70, 40.74, 43.31, 66.61, 125.83, 126.70, 127.97 (2C), 128.16, 128.53, 129.71, 131.10, 132.12, 136.24, 137.79, 140.8, 156.99, 196.80 ppm. ESI HRMS calcd. for $[M + (H)]^+$ 377.1093, found 399.0981 ([M + Na]) and 775.2032 ([2M + Na]).

***tert*-butyl (2-((3-acetylphenyl)sulfonamido)ethyl)carbamate (31).** This compound was synthesised by adapting a previously described protocol.[50,51] To a cooled solution of the compound **30** (1 eq, 0.145 mmol, 50 mg) in anhydrous dichloromethane (3 mL) was added dropwise under stirring thionyl chloride (7 eq, 1.016 mmol, 73 µL). The solution was then stirred at room temperature for 3h. The reaction was cooled at 0°C before adding dropwise *N*,*N*-diisopropylethylamine (4 eq, 0.58 mmol, 0.101 mL) followed by *N*,*O*-dimethylhydroxylamine (2 eq, 0.290 mmol, 28 mg). The reaction mixture was then stirred at room temperature overnight. The reaction was treated with saturated aqueous $NaHCO_3$ (pH=7) then washed twice with water and dried over Na_2SO_4, filtered, and evaporated under vacuum.

The crude extract was purified by flash chromatography column on silica gel (ethyl acetate 60/40 hexane) and directly used in the next step. To a cooled solution of the previously purified compound (1 eq, 0.098 mmol, 38 mg) in anhydrous THF (2 mL), was added dropwise under nitrogen a solution of methylmagnesium bromide (3 eq, 0.294 mmol, 0.15 mL). The solution was then stirred at room temperature for 3 h. The reaction was monitored by TLC (ethyl acetate 60/40 hexane). The solution was treated with saturated aqueous $NaHCO_3$ (pH=7) and extracted twice with ethyl acetate. The organic layers were washed with brine and water then dried over Na_2SO_4, filtered, and evaporated under vacuum. The crude extract was purified by flash chromatography column on silica gel (ethyl acetate 60/40 hexane) to afford product **31** as a yellow oil.

Yield estimated 54 %; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.41 (s, 1H, H aryl), 8.15-8.13 (d, 1H, *J*=8.0 Hz, H aryl), 8.06-8.04 (d, 1H, *J*=8.0 Hz, H aryl), 7.63 (t, 1H, *J*=8.0 Hz, H aryl), 6.04 (m, 1H, NH), 5.13 (m, 1H, NH), 3.22 (dd, 2H, J_1=4.0 Hz, J_2=12 Hz, CH_2), 3.07 (dd, 2H, J_1=4.0 Hz, J_2=12 Hz, CH_2), 2.65 (s, 3H, CH_3), 1.39 (s, 9H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.33 (3C), 26.70, 40.28, 43.83, 61.34, 126.92, 128.89, 129.05, 132.35, 135.07, 140.06, 168.00 (2C) ppm. ESI HRMS calcd. for $[M + (H)]^+$ 343.1249, found 365.1144 ([M + Na]), 685.2577 ($[2M + (H)]^+$) and 707.2407 ([2M + Na]).

General procedure for the synthesis of compounds 28 and 32.

This compound was synthesised by adapting a previously described protocol.[52] To a cooled solution of *t*-BuOLi 1 M (2.5 eq, 1.65 mmol, 1.65 mL) in anhydrous THF (5 mL) was added dropwise under nitrogen diethyl oxalate (2 eq, 1.36 mmol, 0.2 mL). The solution was stirred at 0 °C for 10 minutes before ketone **27** (1 eq, 0.66 mmol, 226 mg) in anhydrous THF (4 mL) was added dropwise. The mixture was stirred for 1.5 h at room temperature. The reaction was monitored by TLC (ethyl acetate 50/50 hexane) and treated with saturated aqueous $NaHCO_3$ (pH=6). The aqueous phase was extracted twice with dichloromethane. The organic layers were washed with brine and water, dried over Na_2SO_4 and filtered. The solvent was removed in

vacuum and the resulting residue was purified by flash chromatography column on silica gel (DCM 60/40 MeOH).

Methyl4-(3-(N-(2-(((benzyloxy)carbonyl)amino)ethyl)sulfamoyl)phenyl)-2,4-dioxobutanoate (**28**); yellow oil; yield estimated at 69 % as a E/Z mixture; ^{1}H NMR (400 MHz, CD_3Cl_3): δ = 8.41 (s, 1H, H aryl), 8.15 (d, 1H, H aryl), 7.93 (d, 1H, H aryl), 7.58 (t, 1H, H aryl), 7.33 (m, 5H, H aryl), 6.80 (s, 1H, CH), 5.01 (s, 2H, CH_2), 4.32 (dd, 2H, J_1=8.0 Hz, J_2=16 Hz, CH_2), 3.15 (m, 2H, CH_2), 2.96 (m, 2H, CH_2), 1.23 (s, 3H, CH_3) ppm. ^{13}C NMR (100 MHz, CD_3Cl_3): δ = 16.98, 40.37, 42.32, 45.90, 56.94, 60.17, 66.11, 125.50, 127.42 (2C), 128.06 (3C), 129.04 (3C), 130.72 (2C), 140.75, 157.44, 171.64, 218.50 ppm.

Ethyl4-(3-(N-(2-((tert-butoxycarbonyl)amino)ethyl)sulfamoyl)phenyl)-2,4-dioxobutanoate (**32**); yellow oil; yield estimated at 26 % as a 86%-14% Z-E mixture. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.62 (s, 1H, H aryl), 8.04 (d, 1H, *J*=8.0 Hz, H aryl), 7.93 (d, 1H, *J*=8.0 Hz, H aryl), 7.52 (t, 1H, *J*=8.0 Hz, H aryl), 6.73 (s, 1H, CH), 5.68 (m, 1H, NH), 5.24 (m, 1H, NH), 4.34 (dd, 2H, J_1=8.0 Hz, J_2=16 Hz, CH_2), 2.22 (m, 2H, CH_2), 2.07 (m, 2H, CH_2), 1.43 (s, 9H, CH_3), 1.35 (s, 3H, CH_3) ppm. ^{13}C (100 MHz, $CDCl_3$): δ= 14.11, 28.30 (3C), 40.30, 44.14, 59.02, 62.91, 97.92, 126.24, 129.96, 131.53, 131.57, 135.97, 141.32, 161.79, 171.01, 188.42 ppm. ESI HRMS calcd. for [M + (H)]+ 443.1410, found 465.1298 ([M + Na]), 885.2881 ([2M + (H)]+) and 907.2683 ([2M + Na]).

General procedure for the synthesis of compounds 29 and 33. This compound was synthesised by adapting a previously described protocol.[53] To a cooled stirred mixture of the *N*-Boc-2,4-diketoester **32** (1 eq, 1.36 mmol, 601 mg) in anhydrous THF (44 mL) under nitrogen, was slowly added lithium aluminium hydride (4 eq, 5.44 mmol, 206 mg). The reaction mixture was stirred for 3 h on ice and monitored by TLC (ethyl acetate 80/20 hexane). The reaction was treated with ethyl acetate and water at 0°C. The aqueous phase was extracted twice with ethyl acetate. The organic layers were washed with brine and water, dried over MgSO4 and filtered. The solvent was removed in vacuum and the resulting residue was purified by flash chromatography column on silica gel (ethyl acetate 50/50 hexane).

tert-butyl(2-((3-(3,4-dihydroxybutanoyl)phenyl)sulfonamido)ethyl)carbamate (**33**); yellow oil; yield estimated at 36 %; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.47 (s, 1H, H aryl), 8.19 (d, 1H, *J*=8.0 Hz, H aryl), 8.09 (d, 1H, *J*=8.0 Hz, H aryl), 7.66 (t, 1H, *J*=8.0 Hz, H aryl), 5.75 (m, 1H, NH), 4.98 (m, 1H, NH), 4.39 (m, 1H, CH), 3.67 (m, 1H, CH_2), 3.51 (m, 1H, CH_2), 3.34 (m, 2H, CH_2), 3.30 (m, 2H, CH_2), 3.11 (m, 2H, CH_2), 1.45 (s, 9H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.33 (3C), 40.24, 41.89, 43.41, 65.86, 68.45, 79.88, 124.76, 126.77, 129.68, 131.41, 137.64, 140.84, 156.58, 207.21 ppm. ESI HRMS calcd. for [M + (H)]+ 403.1461, found 425.1353 ([M + Na]) and 827.2820 ([2M + Na]).

Benzyl(2-((3-(3,4-dihydroxybutanoyl)phenyl)sulfonamido)ethyl)carbamate (**29**); yellow oil; yield estimated at 15 %; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.41 (s, 1H, H aryl), 8.06 (d, 1H, *J*=8.0 Hz, H aryl), 7.99 (d, 1H, *J*=8.0 Hz, H aryl), 7.51 (t, 1H, *J*=8.0 Hz, H aryl), 7.28 (m, 5H, H aryl), 6.31 (m, 1H, NH), 5.66 (m, 1H, NH), 4.98 (s, 2H, CH_2), 4.30 (m, 1H, CH), 3.66 (m, 1H, CH_2), 3.57 (m, 1H, CH_2), 3.22 (m, 2H, CH_2), 3.10 (m, 2H, CH_2), 3.04 (m, 2H, CH_2) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ =40.70, 41.83, 43.10, 65.84, 66.87, 68.43, 124.77, 126.69, 127.96 (2C), 128.18, 128.53, 248.53, 129.69, 131.37, 136.20, 137.58, 140.72, 157.01, 198.56 ppm. ESI HRMS calcd. for $[M + (H)]^+$ 437.1304, found 459.1196 ([M + Na]) and 895.2459 ([2M + Na]).

N-(2-aminoethyl)-3-(3,4-dihydroxybutanoyl)benzenesulfonamide (4). This compound was synthesised by adapting a previously described protocol.[54] To a Pd/C (1.3 eq, 46 mg, 0.43 mmol) powder purged under N_2, was added the Cbz-protected ketodiol **29** (1 eq, 0.39 mmol, 172 mg) in methanol (6 mL). The solution was then flushed with H_2 gas and stirred under H_2 atmosphere (balloon) at room temperature for 24 h. The suspension was filtered through a celite pad and

washed with MeOH (2 x 5 mL). The filtrate was removed in vacuum to afford the title compound **4** as a yellow oil. Yield estimated at 74 %. ^{1}H NMR (400 MHz, CD_3OD): δ = 7.96 (s, 1H, H aryl), 7.81 (t, 1H, *J*=8.0 Hz, H aryl), 7.71 (t, 1H, *J*=8.0 Hz, H aryl), 7.51 (m, 1H, H aryl), 3.96 (m, 1H, CH), 3.62 (m, 1H, CH), 3.53 (d, 2H, *J*=4.0 Hz, CH_2), 3.13 (m, 2H, CH_2), 3.05 (m, 2H, CH_2), 1.83 (m, 1H, CH_2), 1.74 (m, 1H, CH_2) ppm. ^{13}C NMR (100 MHz, CD_3OD): δ = 39.50, 40.52, 41.97, 65.79, 68.69, 69.97, 124.36, 125.64, 129.12, 130.50, 139.46, 139.51 ppm. ESI HRMS calcd. for $[M + (H)]^+$ 305.1093, found 305.1180 ($[M + (H)]^+$).

General procedure for synthesis of compounds 12 and 23

To a cooled solution of the ketodiol **33** (1 eq, 0.54 mmol, 220 mg) in dichloromethane (0.72 mL), was added dropwise under stirring trifluoroacetic acid (11 eq, 5.99 mmol, 0.46 mL). The solution was then stirred overnight at room temperature and monitored by TLC (ethyl acetate 60/40 hexane). The solution was evaporated under vacuum, after which TFA traces were removed by repeated addition and evaporation of dichloromethane under vacuum.[48]

N-(2-aminoethyl)-3-(furan-2-yl)benzenesulfonamide (**12**); yellow oil; yield estimated at 70 %; ^{1}H NMR (400 MHz, CD_3OD): δ = 8.19 (s, 1H, H aryl), 7.98 (d, 1H, *J*=8.0 Hz, H aryl), 7.77 (d, 1H, *J*=8.0 Hz, H aryl), 7.65 (t, 1H, *J*=8.0 Hz, H aryl), 7.64 (m, 1H, CH), 6.96 (m, 1H, CH), 6.59 (m, 1H, CH), 3.13 (m, 2H, CH_2), 3.09 (m, 2H, CH_2) ppm. ^{13}C NMR (100 MHz, CD_3OD): δ =39.28, 40.00, 106.74, 111.76, 121.40, 125.07, 127.39, 129.64, 132.10, 140.29, 143.21, 151.94 ppm. ESI HRMS calcd. for $[M + (H)]^+$ 267.0798, found 267.0813 ($[M + (H)]^+$).

(4-carboxyphenylsulfonyl)-ethylenediamine acid (**23**); white powder; yield estimated at 30 %; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.35 (s, 1H, H aryl); 8.23-8.21 (d, 1H, J=8.0 Hz, H aryl), 8.10 (m, 1H, NH); 8.06-8.04 (d, 1H, J=8.0 Hz, H aryl); 7.87 (m, 3H, NH_3); 7.80-7.76 (t, 1H, J=8.0 Hz, H aryl); 2.98-2.94 (m, 2H, CH_2); 2.89-2.86 (m, 2H, CH_2). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 38.87; 40.33; 127.74; 130.58; 131.17; 132.45; 133.77; 140.55; 210.54 ppm. ESI HRMS calcd. for $[M + (H)]^+$ 245.0591, found 245.0589 ($[M^+]$) and 267.0395 ($[M+Na^+]$).

General procedure for synthesis of compounds Ir4, Ir12 and Ir23. The iridium complexes were synthesised by adapting a previously described protocol.[55] To a suspension of pentamethylcyclopentadienyl iridium(III) chloride dimer (1 eq, 0.063 mmol, 50 mg) in MeOH (2.3 mL) was added the deprotected triol **4** (3 eq, 0.19 mmol, 46 mg) in MeOH (1 mL) solution. Triethylamine (4 eq) was then added dropwise until the solution turned a clear yellow. The solution was then stirred for 1 h and the solvent was removed under vacuum. The resulting residue was purified by flash chromatography column on silica gel (DCM 98/2 MeOH to 100% MeOH).

[IrClCp*]-N-(2-aminoethyl)-3-(3,4dihydroxybutanoyl)benzenesulfonamide (**Ir4**); orange powder; yield= 43 %; as a stereoisomer mixture 81%-17%; ^{1}H NMR (400 MHz, CD_3OD): δ = 8.02 (s, 1H, H aryl), 7.85 (d, 1H, *J*=8.0 Hz, H aryl), 7.49 (d, 1H, *J*=8.0 Hz, H aryl), 7.40 (t, 1H, *J*=8.0 Hz, H aryl), 3.92 (m, 1H, CH), 3.60 (m, 1H, CH), 3.52 (m, 2H, CH_2), 2.60 (m, 2H, CH_2), 2.50 (m, 2H, CH_2), 1.92 (m, 2H, CH_2), 1.76 (s, 15H, Cp*) ppm. ^{13}C NMR (100 MHz, CD3OD): δ = 8.04 (5C), 41.80, 42.44, 48.03, 65.99, 66.34, 71.70, 85.41 (5C), 125.14, 125.60, 126.33, 126.59, 143.07, 145.06 ppm. ESI HRMS calcd. for $[M + (H)]^+$ 666.1428, found 629.1779 ($[M^+$-$^{37}Cl]$), 631.1793 ($[M^+$-$^{35}Cl]$) and 667.1558 ($[M + (2H)]^{2+}$).

[IrClCp*]-N-(2-aminoethyl)-3-(furan-2-yl)benzenesulfonamide (**Ir12**); red powder; yield= 43 %; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.29 (s, 1H, H_4 aryl), 7.82 (d, 1H, J=8.0 Hz, H aryl), 7.69 (d, 1H, J=8.0 Hz, H aryl), 7.51 (m, 1H, CH), 7.46 (t, 1H, J=8.0 Hz, H aryl), 6.80 (m, 1H, CH), 6.47 (m, 1H, CH), 2.74 (m, 2H, CH_2), 2.64 (m, 2H, CH_2), 1.78 (s, 15H, Cp*) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 9.42 (5C), 48.52, 50.61, 85.49 (5C), 105.95, 111.79, 123.45, 125.33, 126.74, 128.48, 130.73, 142.13, 143.75, 153.47 ppm. ESI HRMS calcd. for $[M + (H)]^+$ 628.1060,

found 591.1412 ([M^+-^{37}Cl]), 593.1451 ([M^+-^{35}Cl]), 629.1197 ([M + (2H)]$^{2+}$) and 651.1018 ([M + (H) + Na]$^+$).
[IrClCp*]-(4-carboxyphenylsulfonyl)-ethylenediamine acid (Ir23); yellow powder; yield= 55 %. ^{1}H NMR (400 MHz, DMSO-d^6): δ = 8.53 (s, 1H, H aryl), 8.19 (d, 1H, J=8.0 Hz, H aryl), 7.90 (d, 1H, J=8.0 Hz, H aryl), 7.40 (t, 1H, J=8.0 Hz, H aryl), 2.74 (m, 2H, CH_2), 2.63 (m, 2H, CH_2), 1.82 (s, 15H, Cp*) ppm. ^{13}C NMR (100 MHz, DMSO-d^6): δ = 7.99 (5C), 47.39, 48.03, 85.37 (5C), 127.74, 128.66, 130.02, 130.76, 131.05, 136.00, 178.45 ppm. ESI HRMS calcd. for [M + (H)]$^+$ 606.0853, found 605.1200 ([M]), 569.1490 ([M + (H)-^{37}Cl]) and 570.1483 ([M -^{35}Cl]).

3.2 NMR Spectra

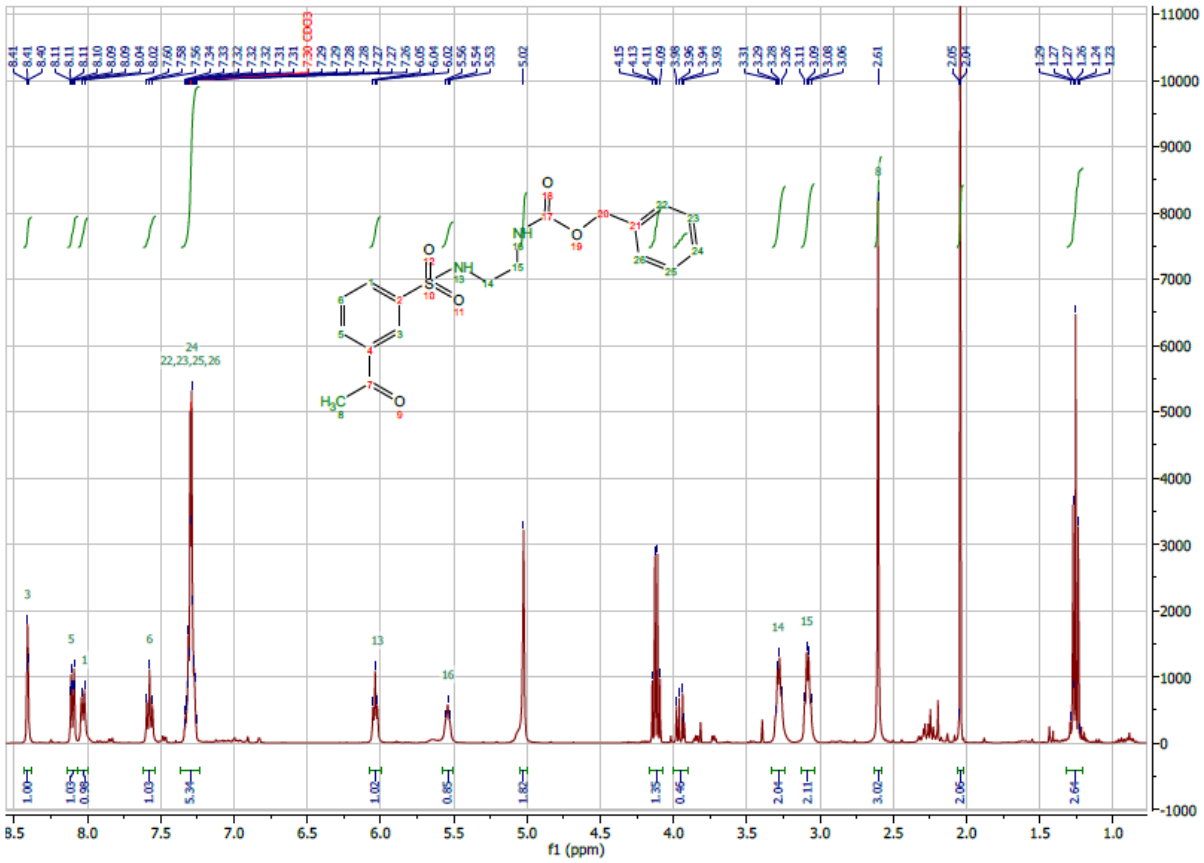


Figure S14: ^{1}H-NMR Benzyl (2-((3-acetylphenyl)sulfonamido)ethyl)carbamate (**27**)

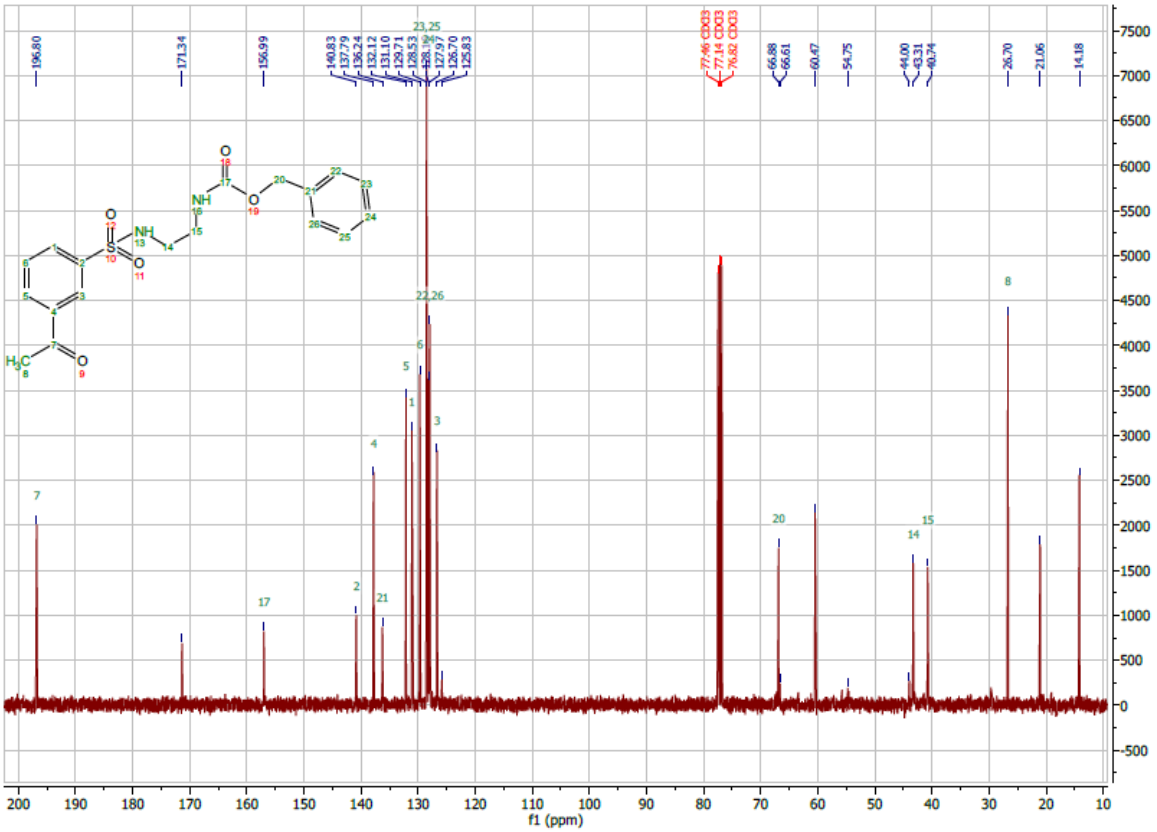


Figure S15: ^{13}C-NMR Benzyl (2-((3-acetylphenyl)sulfonamido)ethyl)carbamate (**27**)

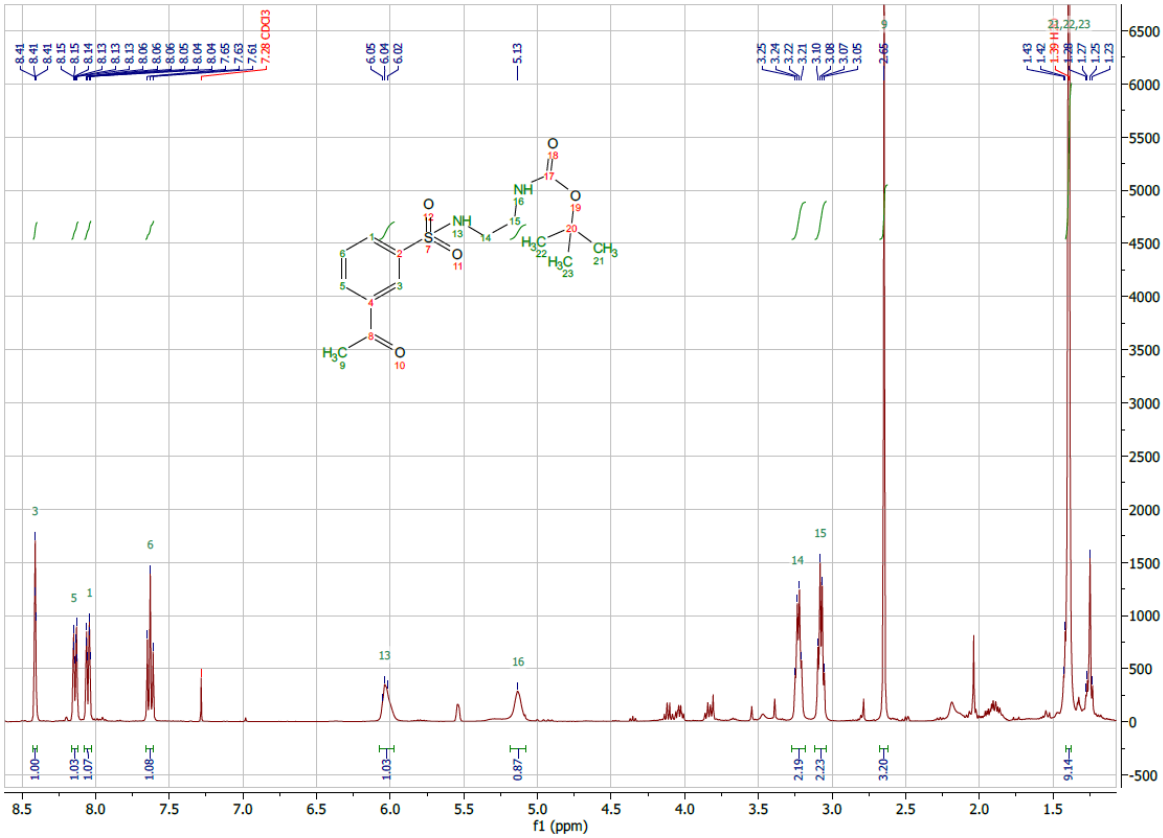


Figure S16: ^{1}H-NMR *tert*-butyl (2-((3-acetylphenyl)sulfonamido)ethyl)carbamate (**31**)

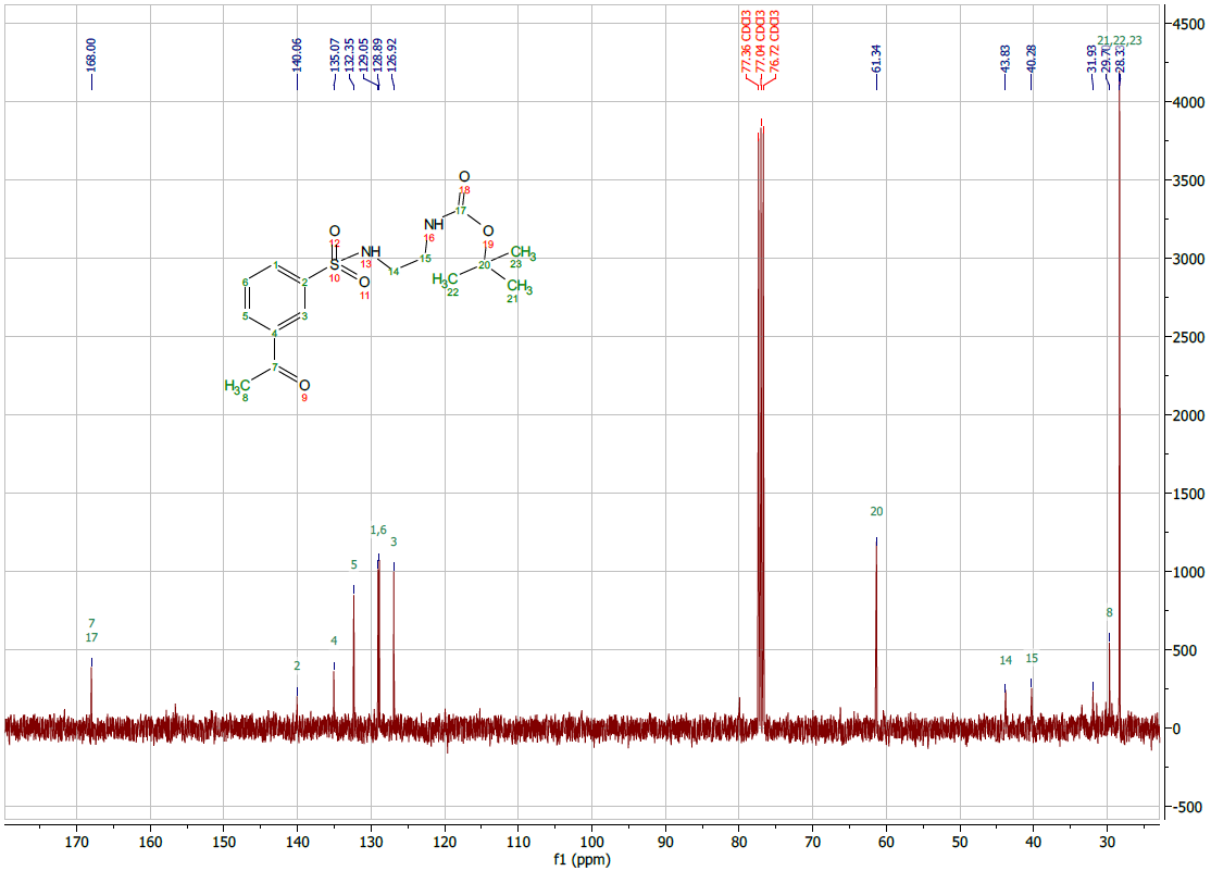


Figure S17: ^{13}C-NMR *tert*-butyl (2-((3-acetylphenyl)sulfonamido)ethyl)carbamate (**31**)

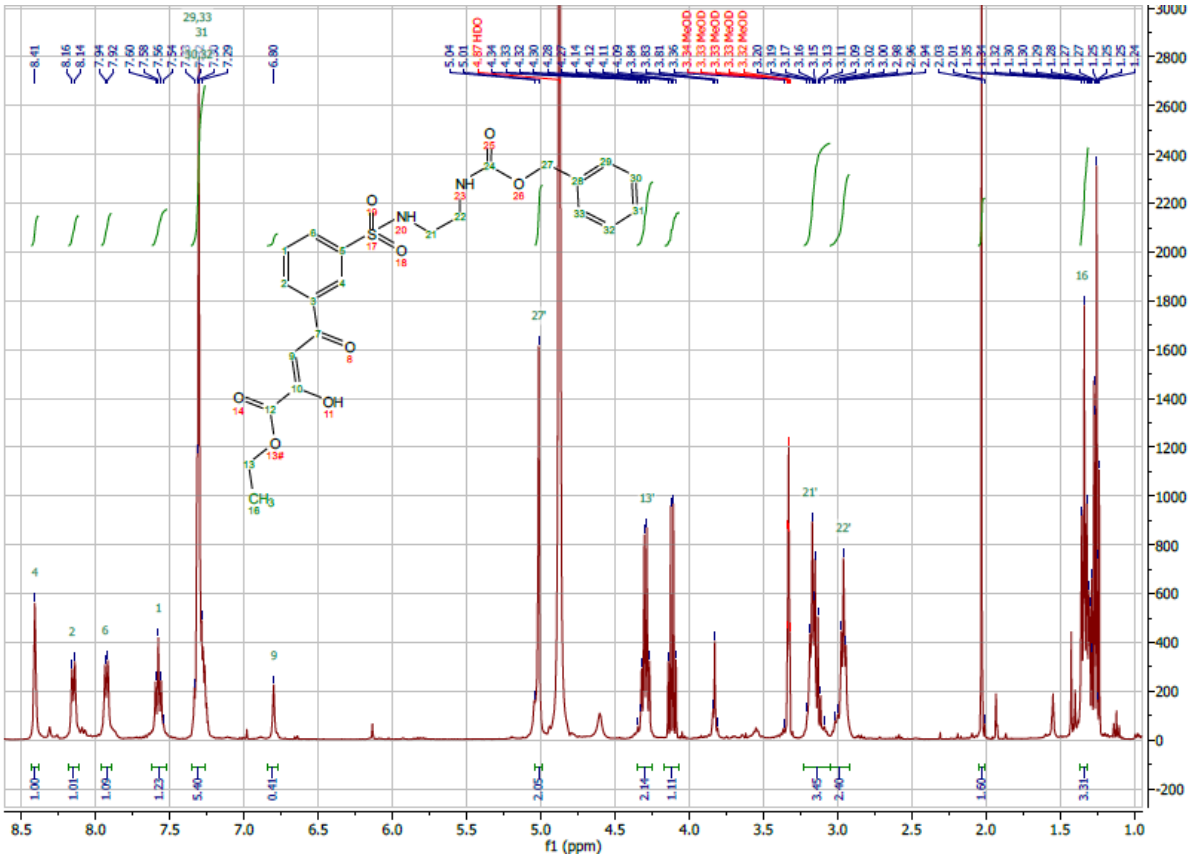


Figure S18: 1H-NMR Methyl4-(3-(N-(2-(((benzyloxy)carbonyl)amino)ethyl)sulfamoyl)phenyl)-2,4-dioxobutanoate (**28**)

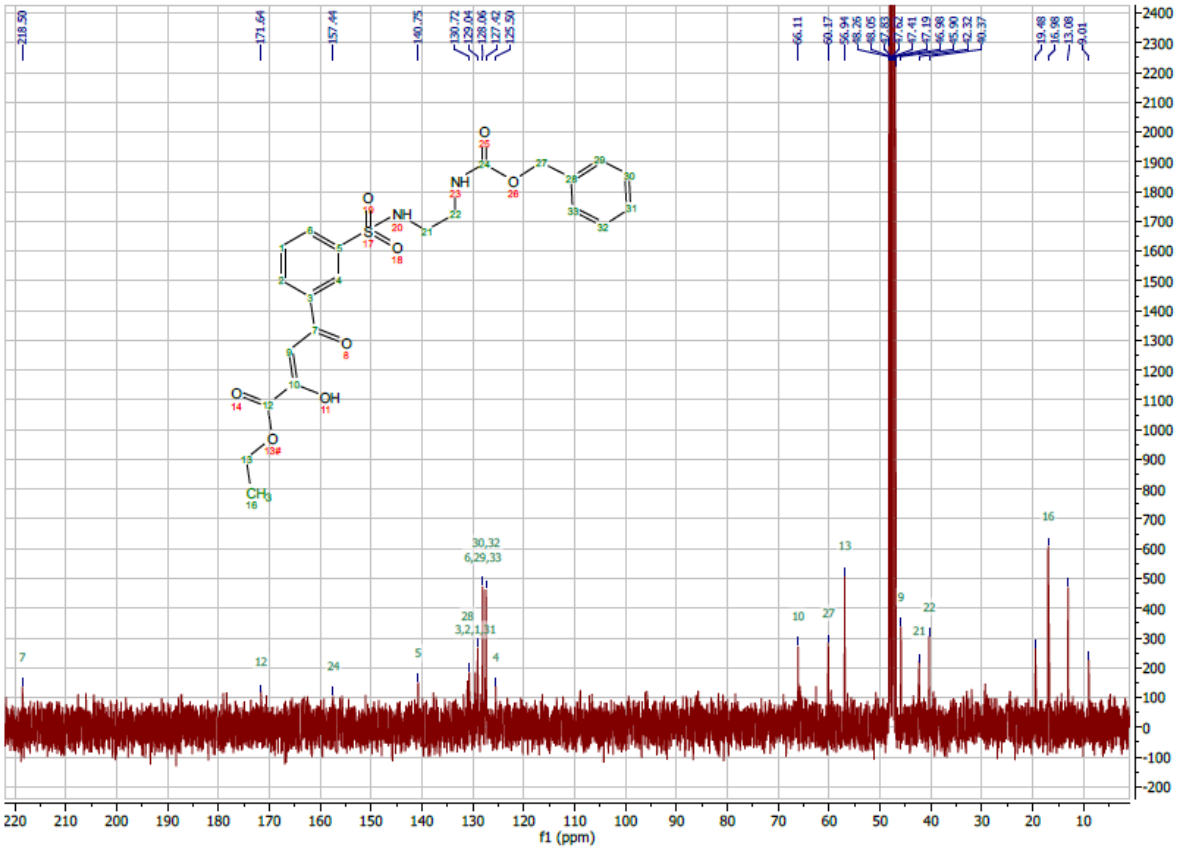


Figure S19: ^{13}C-NMR Methyl4-(3-(N-(2-(((benzyloxy)carbonyl)amino)ethyl)sulfamoyl)phenyl)-2,4-dioxobutanoate (**28**)

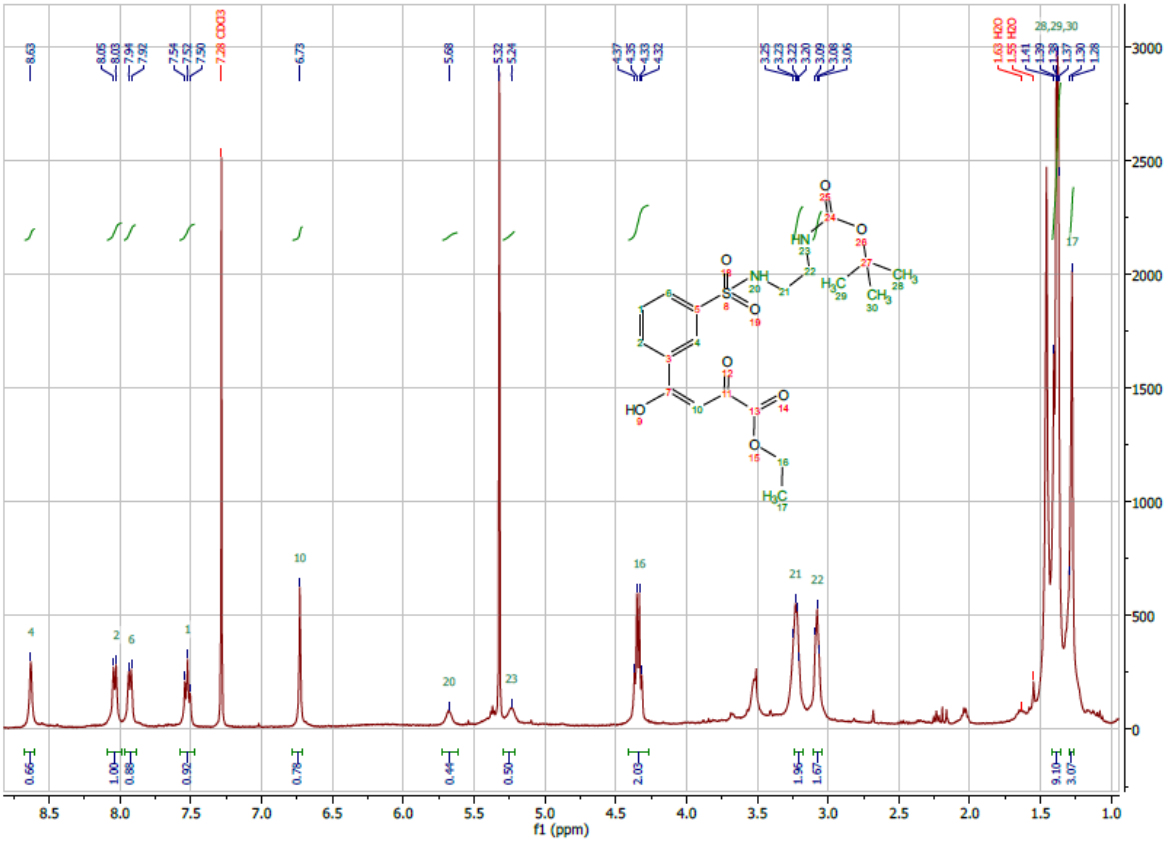


Figure S20: ^{1}H-NMR Ethyl4-(3-(N-(2-((tert-butoxycarbonyl)amino)ethyl)sulfamoyl)phenyl)-2,4-dioxobutanoate (**32**)

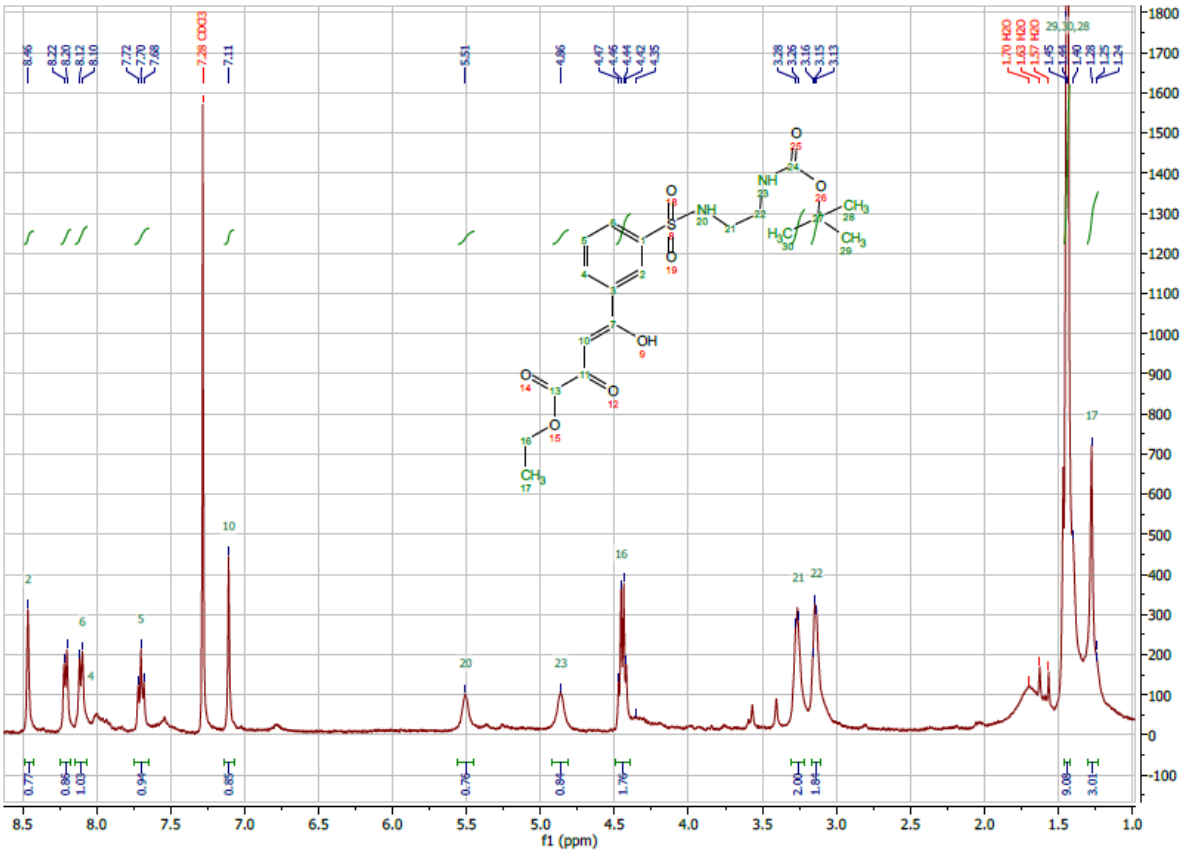


Figure S21: ^{1}H-NMR Ethyl4-(3-(N-(2-((tert-butoxycarbonyl)amino)ethyl)sulfamoyl)phenyl)-2,4-dioxobutanoate (**32**)

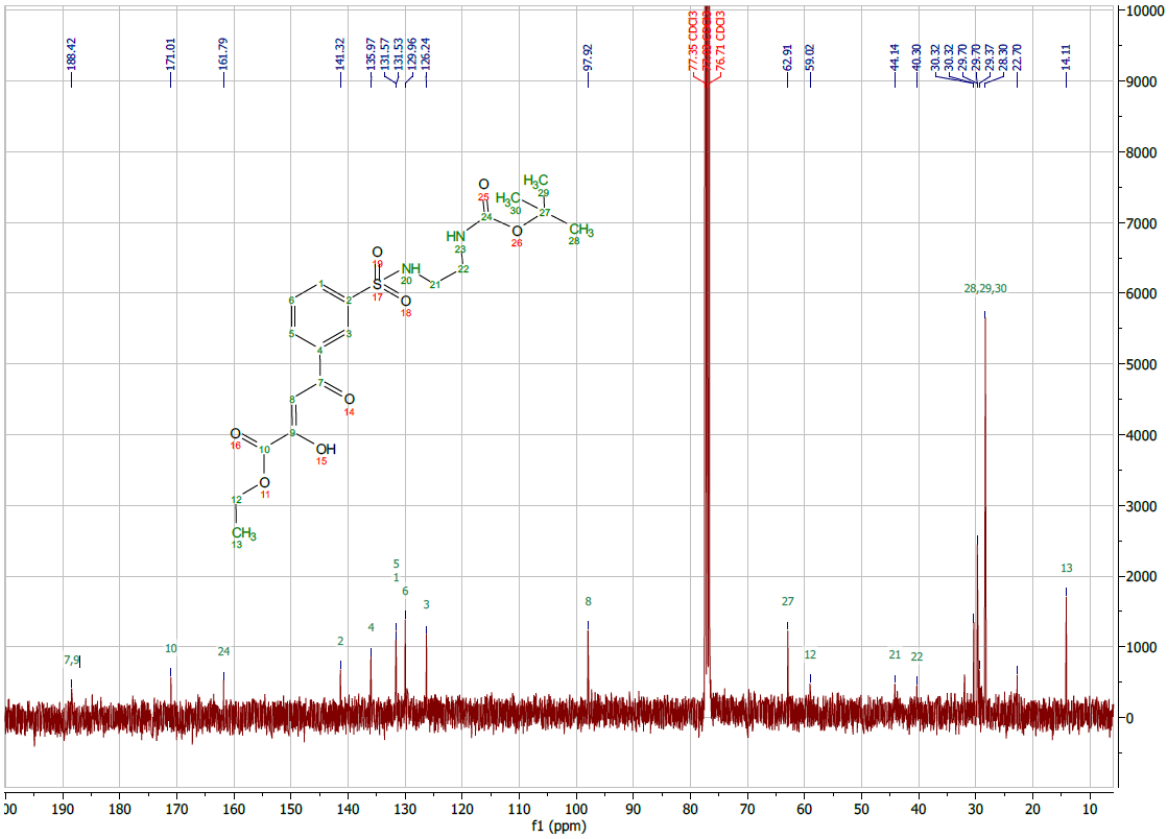


Figure S22: ^{13}C-NMR Ethyl4-(3-(N-(2-((tert-butoxycarbonyl)amino)ethyl)sulfamoyl)phenyl)-2,4-dioxobutanoate (**32**)

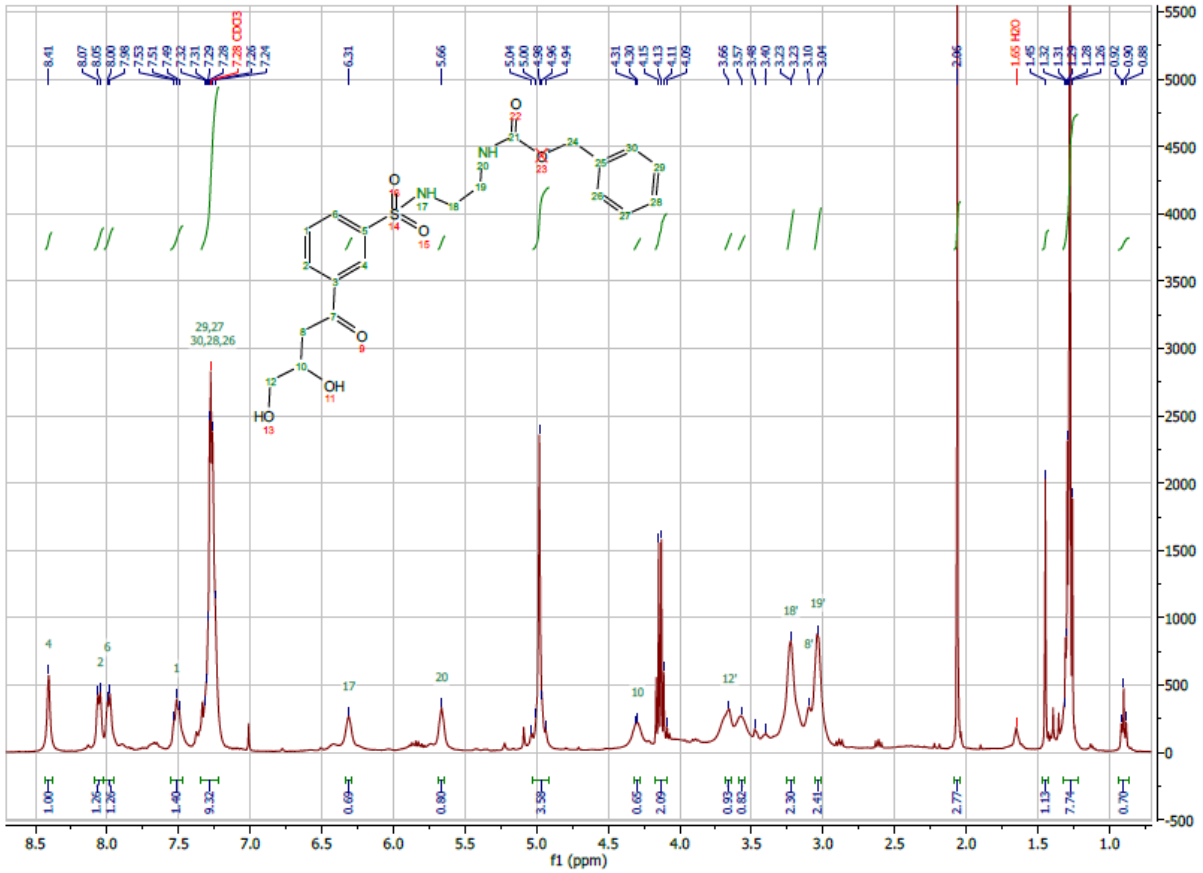


Figure S23: ^{1}H-NMR Benzyl(2-((3-(3,4-dihydroxybutanoyl)phenyl)sulfonamido)ethyl)carbamate (**29**)

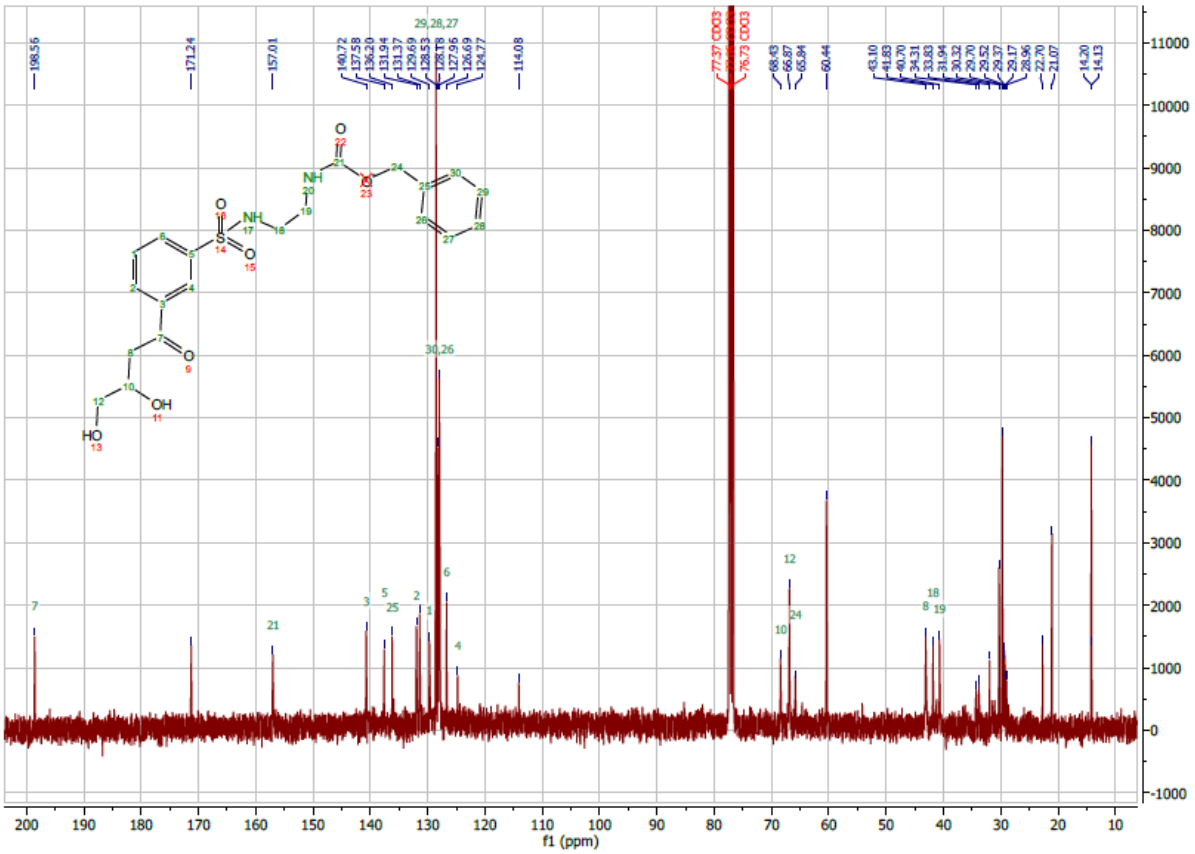


Figure S24: ^{13}C-NMR Benzyl(2-((3-(3,4-dihydroxybutanoyl)phenyl)sulfonamido)ethyl)carbamate (**29**)

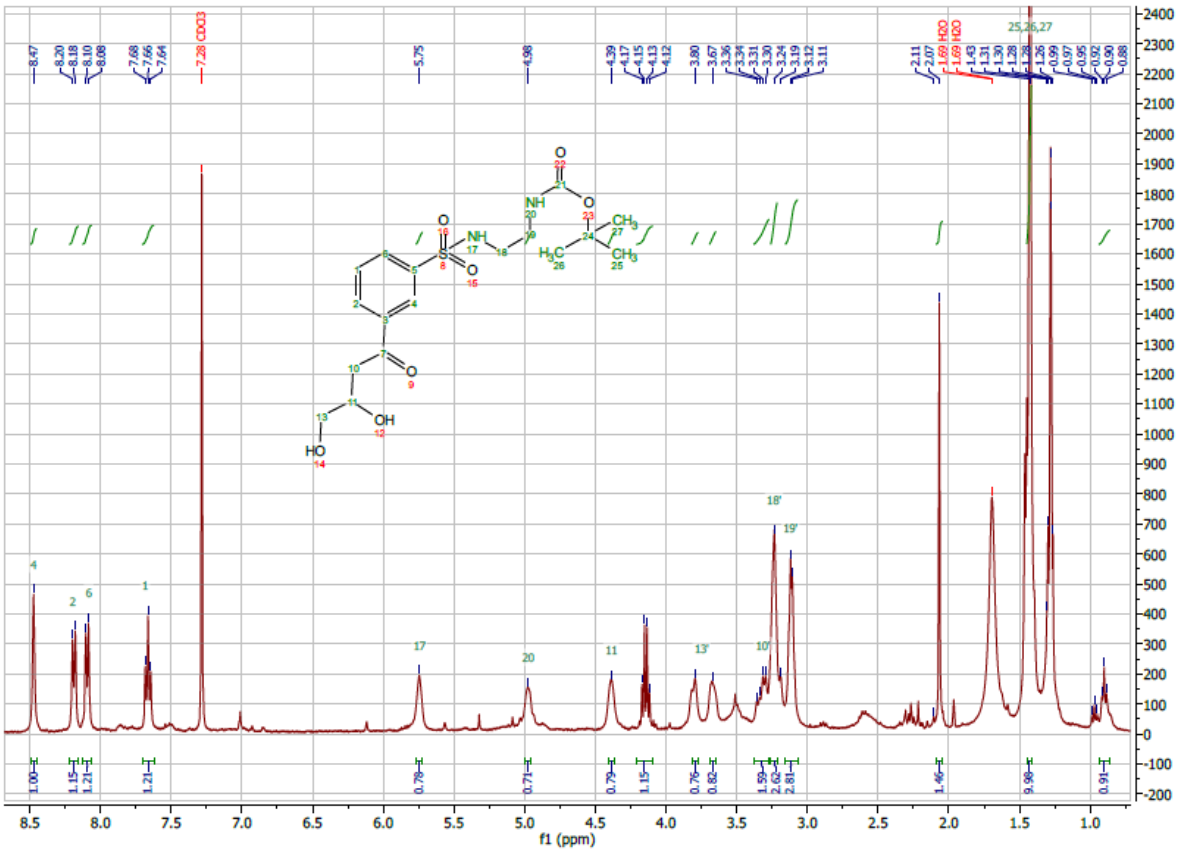


Figure S25: ^{1}H-NMR tert-butyl(2-((3-(3,4-dihydroxybutanoyl)phenyl)sulfonamido)ethyl)carbamate (**33**)

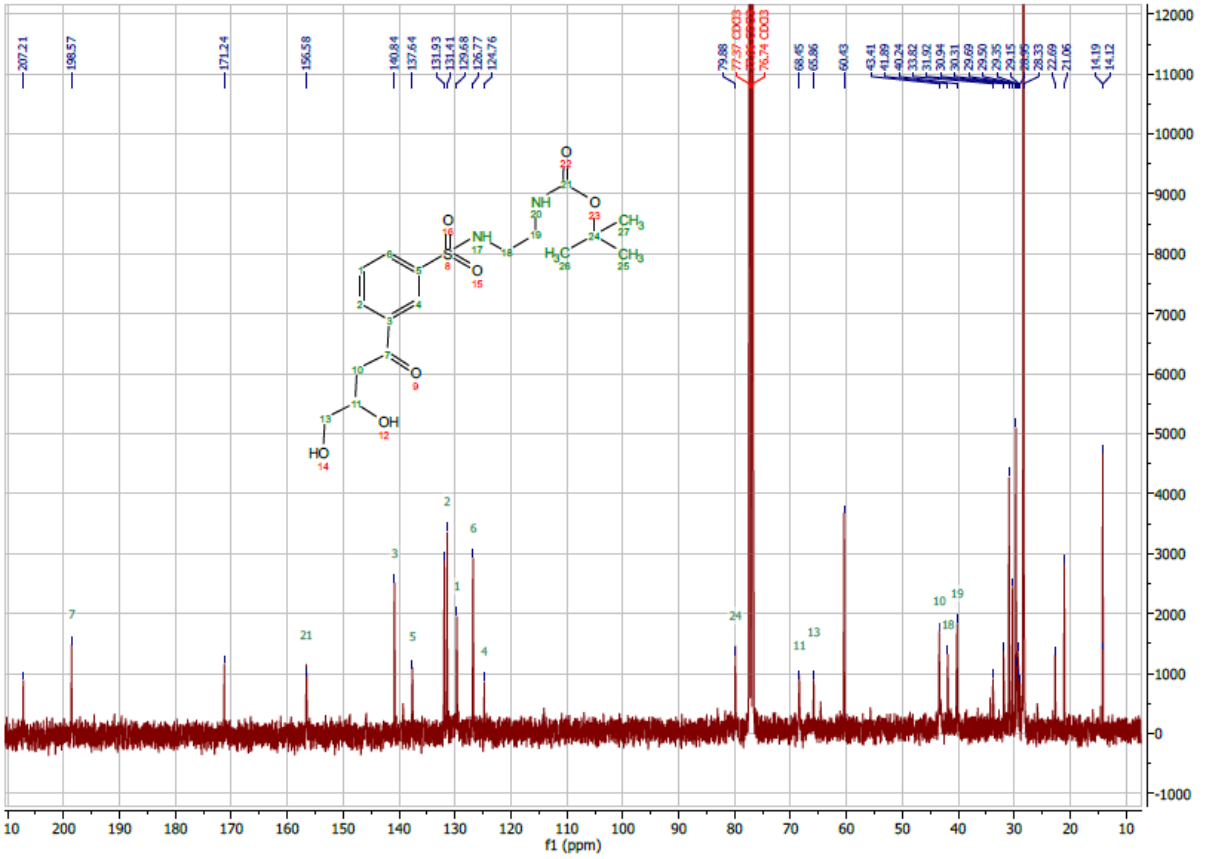


Figure S26: ^{13}C-NMR tert-butyl(2-((3-(3,4-dihydroxybutanoyl)phenyl)sulfonamido)ethyl)carbamate (**33**)

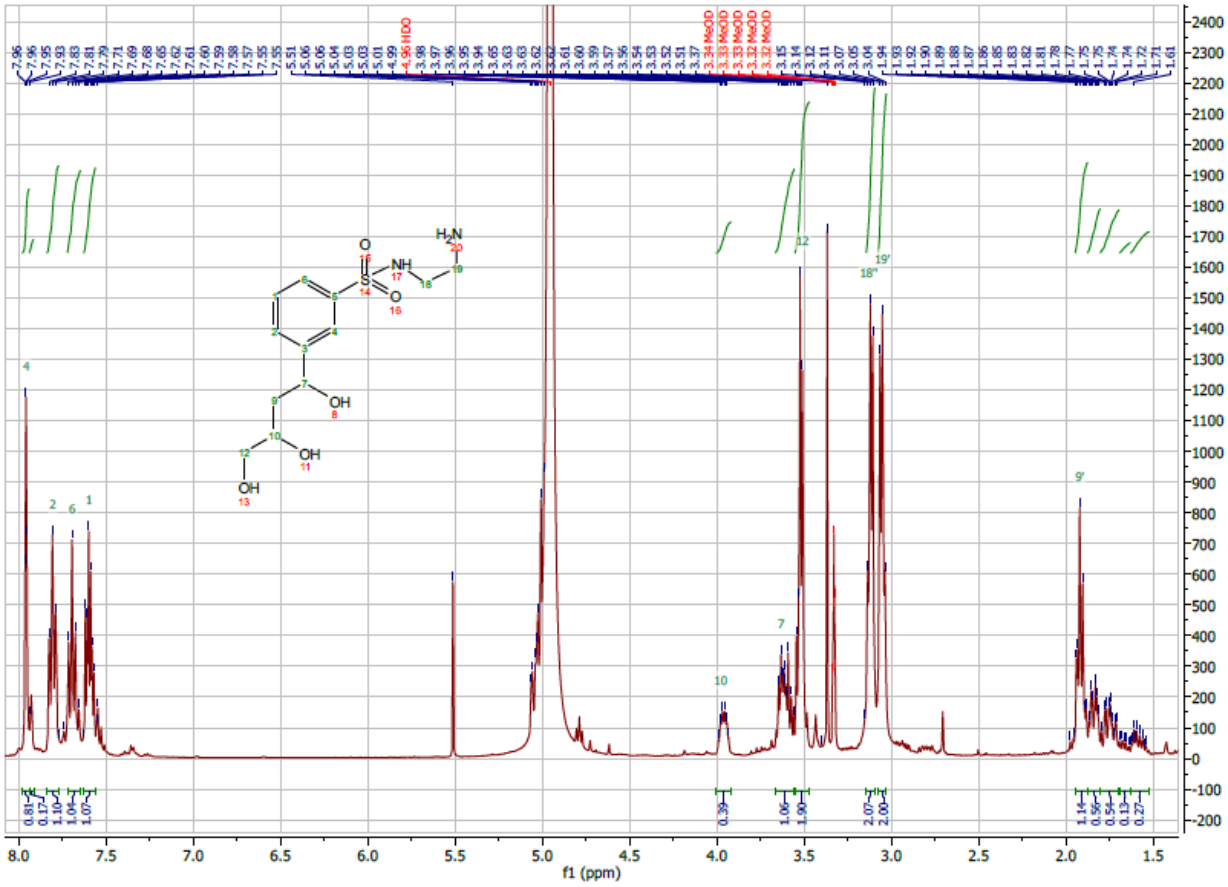


Figure S27: ^{1}H-NMR N-(2-aminoethyl)-3-(3,4-dihydroxybutanoyl)benzenesulfonamide (**4**).

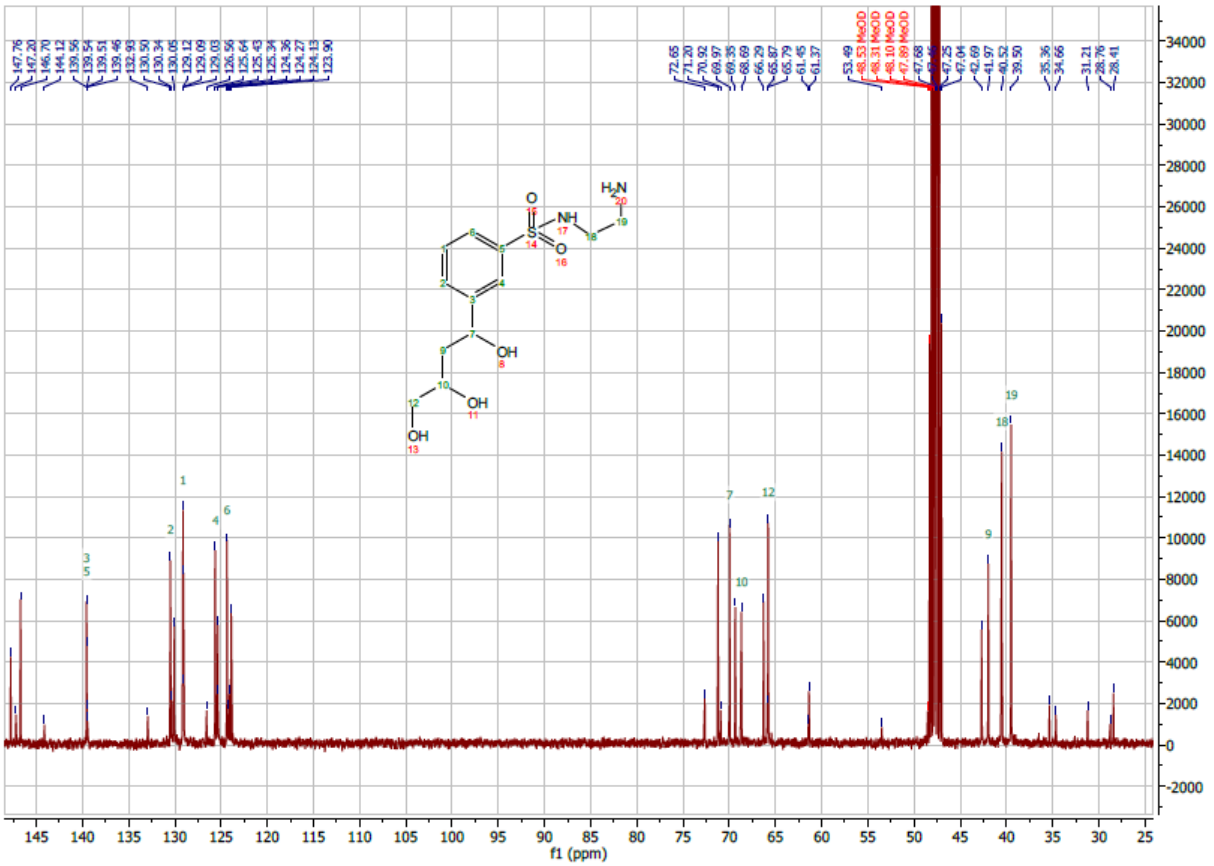


Figure S28: ^{13}C-NMR N-(2-aminoethyl)-3-(3,4-dihydroxybutanoyl)benzenesulfonamide (**4**).

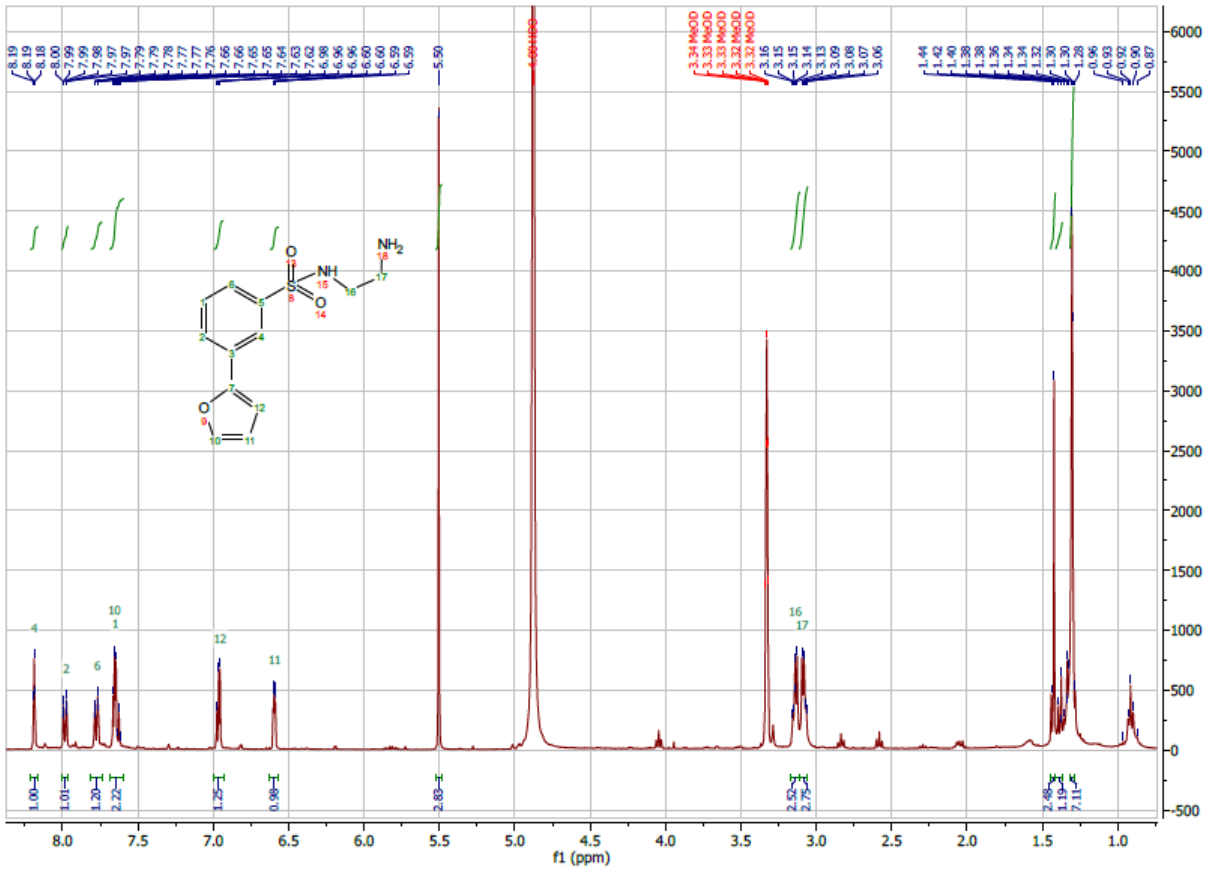


Figure S29: ^{1}H-NMR N-(2-aminoethyl)-3-(furan-2-yl)benzenesulfonamide (**12**)

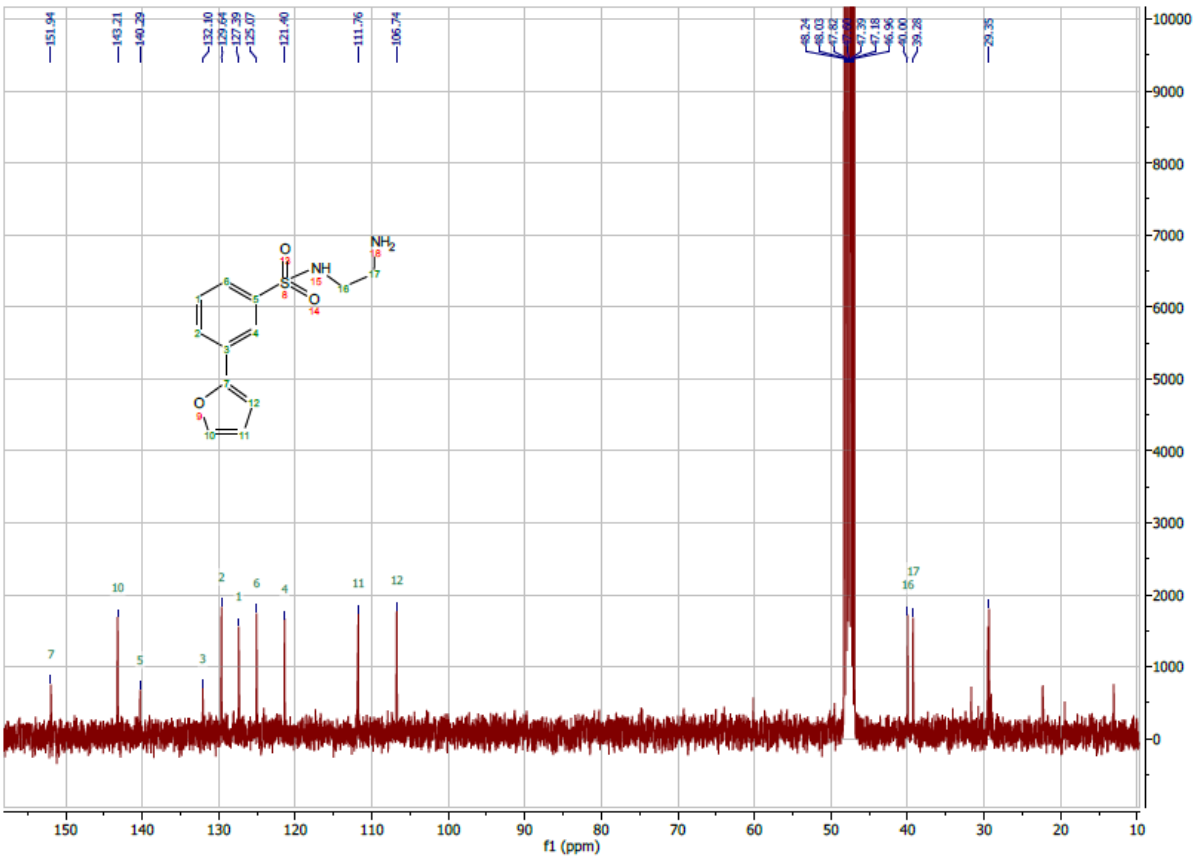


Figure S30: ^{13}C-NMR N-(2-aminoethyl)-3-(furan-2-yl)benzenesulfonamide (**12**)

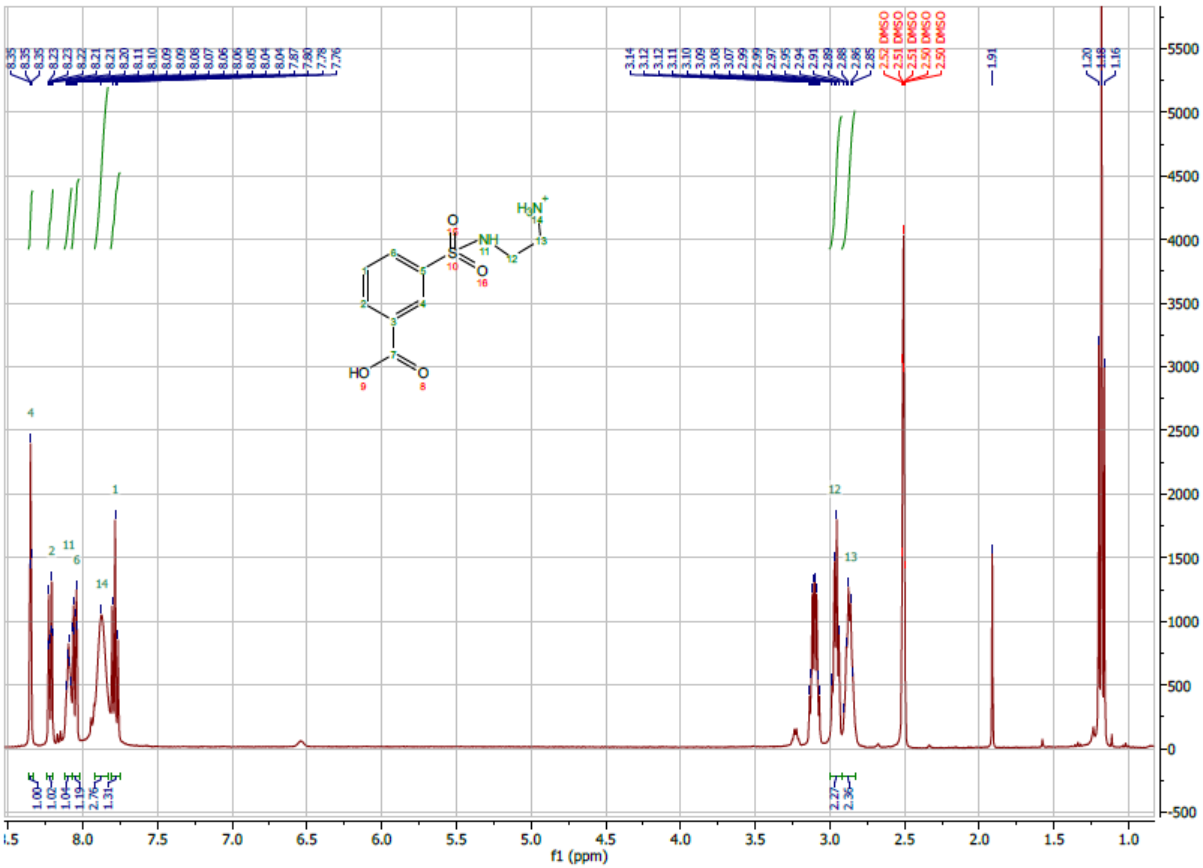


Figure S31:^{1}H-NMR (4-carboxyphenylsulfonyl)-ethylenediamine acid (**23**)

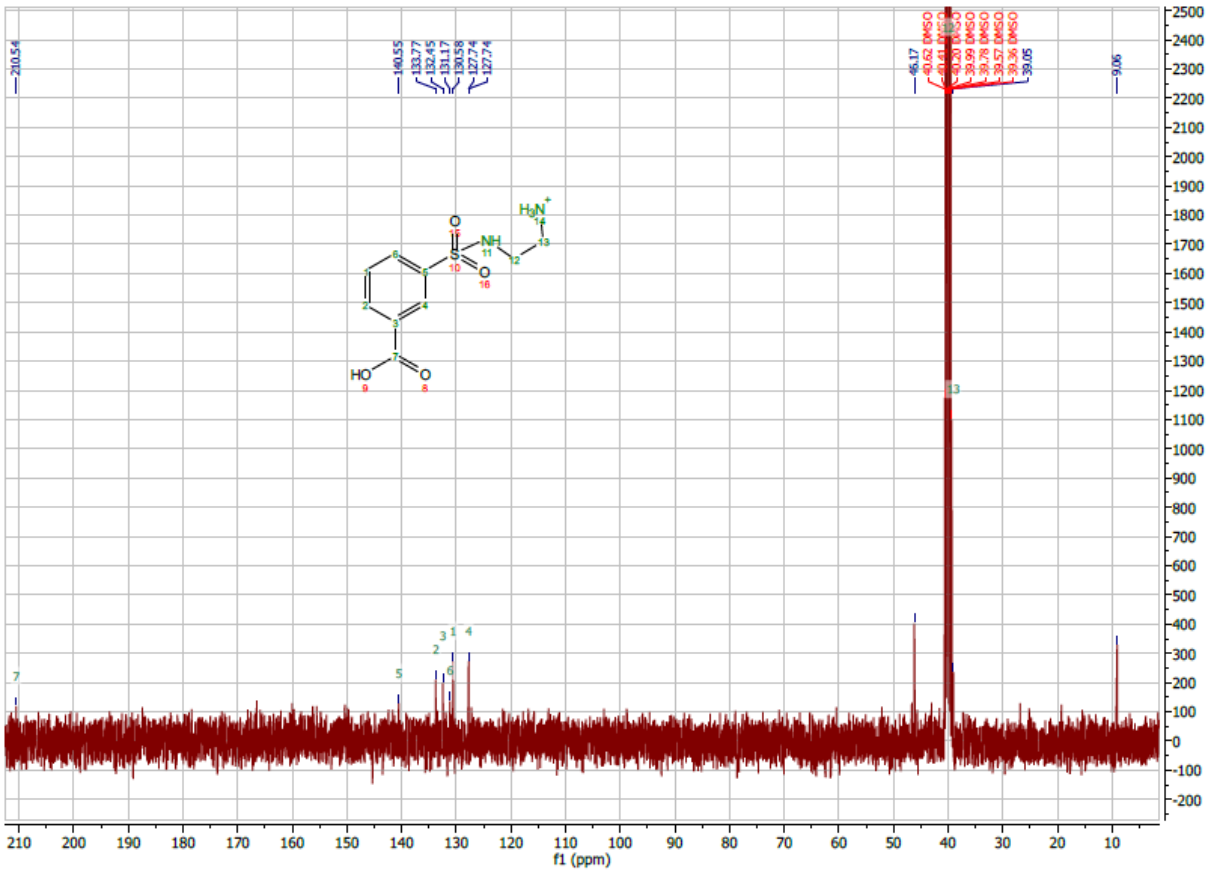


Figure S32: ^{13}C-NMR (4-carboxyphenylsulfonyl)-ethylenediamine acid (**23**)

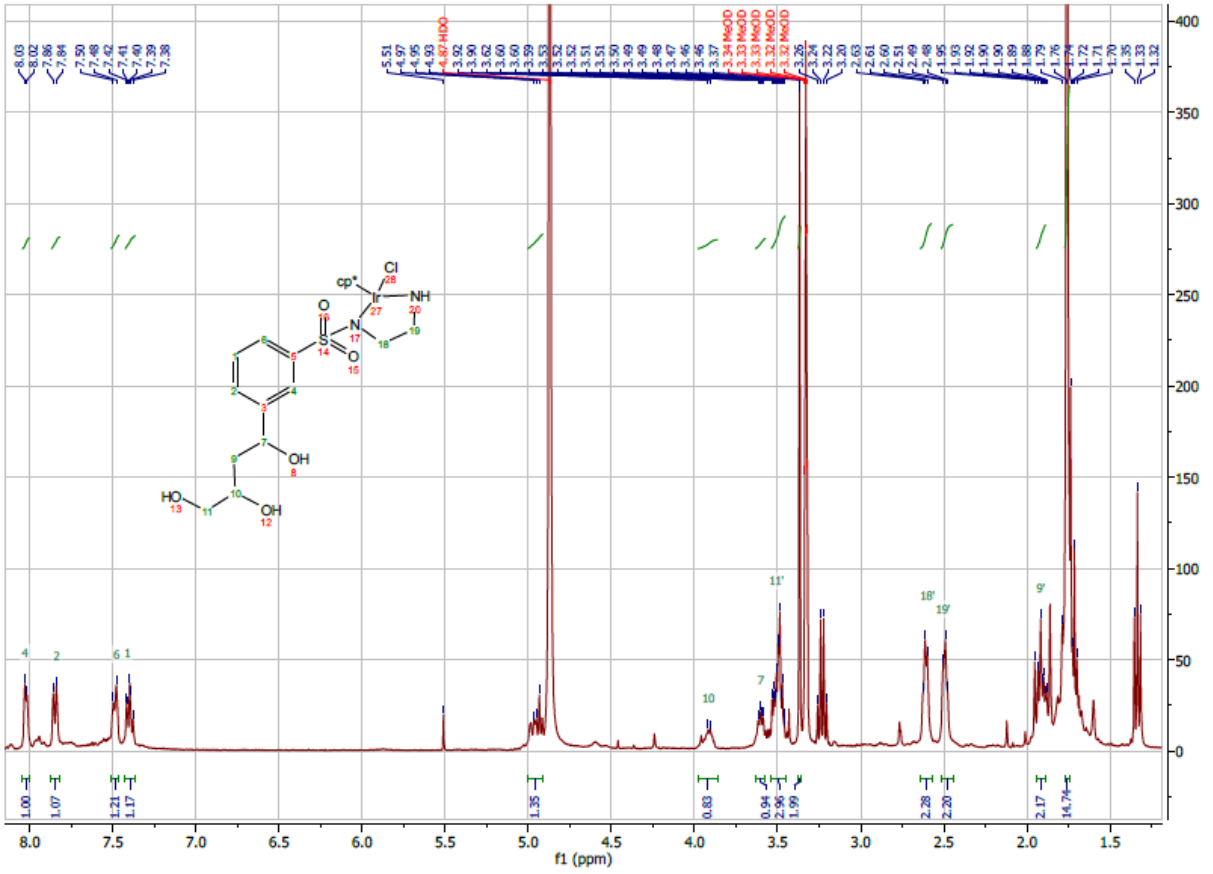


Figure S33:^{1}H-NMR [IrClCp*]-N-(2-aminoethyl)-3-(3,4dihydroxybutanoyl)benzenesulfonamide (**Ir4**)

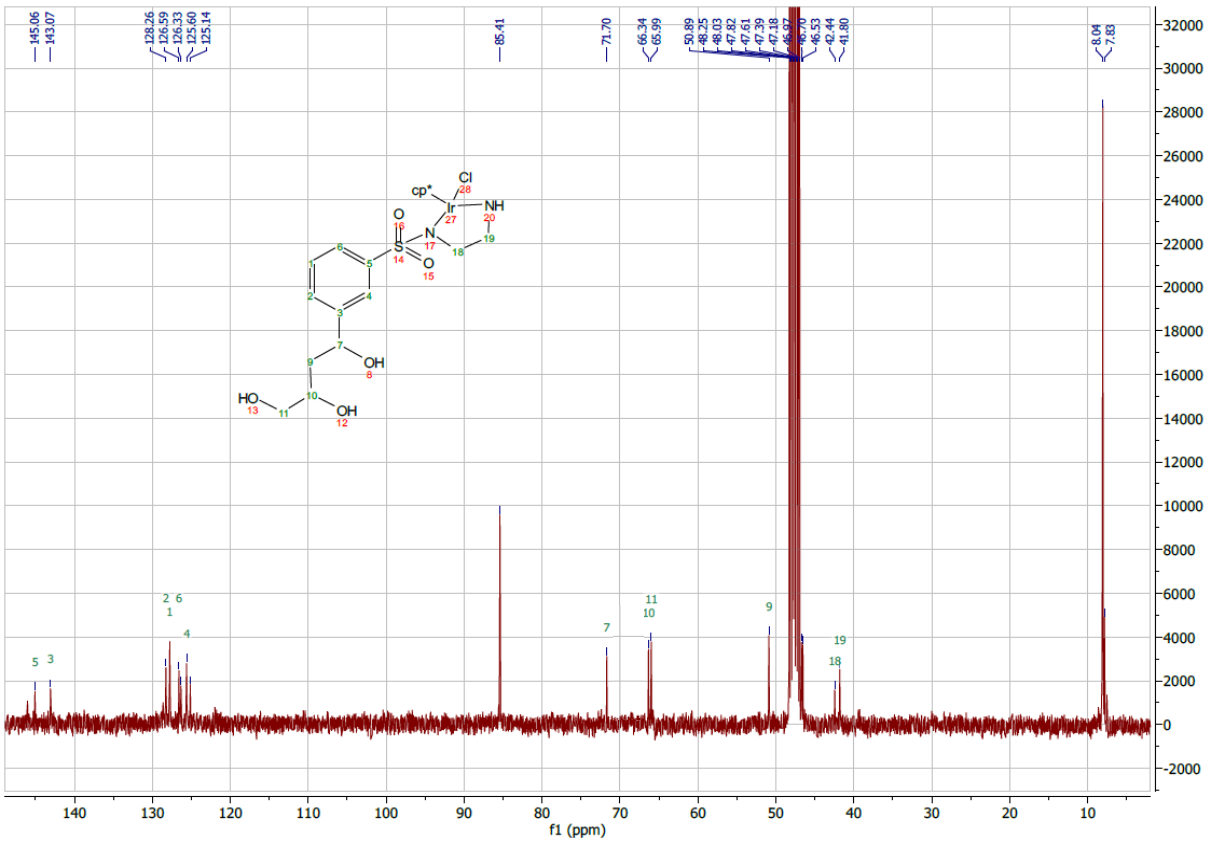


Figure S34: ^{13}C-NMR [IrClCp*]-N-(2-aminoethyl)-3-(3,4dihydroxybutanoyl)benzenesulfonamide (**Ir4**)

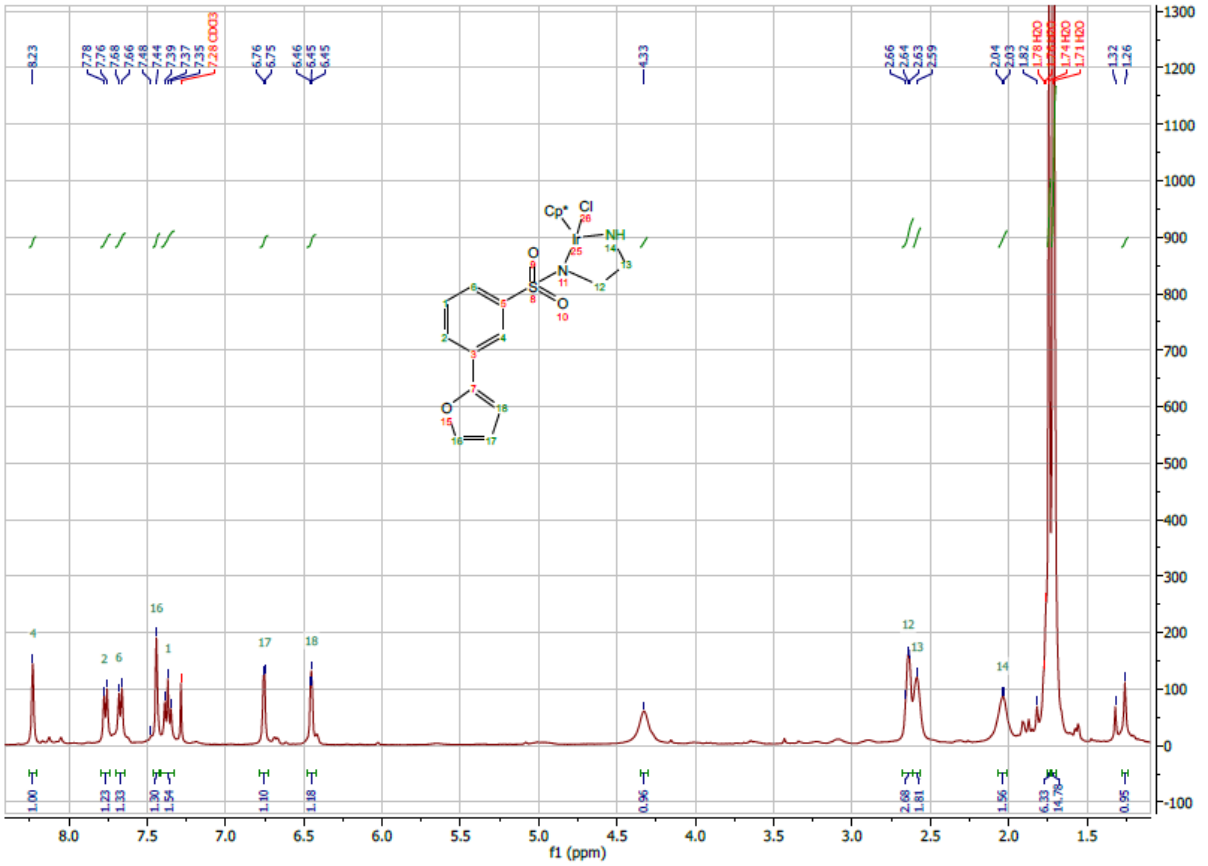


Figure S35: ^{1}H-NMR [IrClCp*]-N-(2-aminoethyl)-3-(furan-2-yl)benzenesulfonamide (**Ir12**)

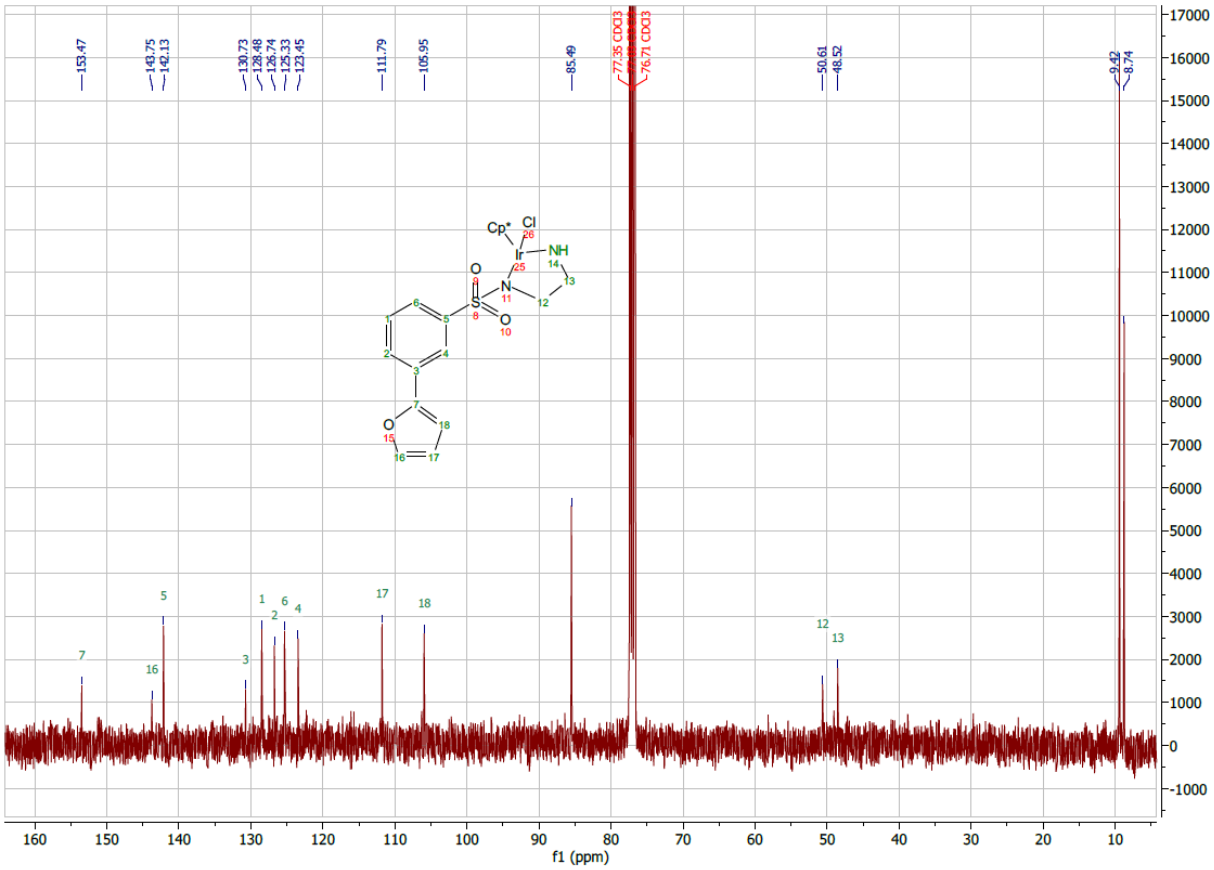


Figure S36: ^{13}C-NMR [IrClCp*]-N-(2-aminoethyl)-3-(furan-2-yl)benzenesulfonamide (**Ir12**)

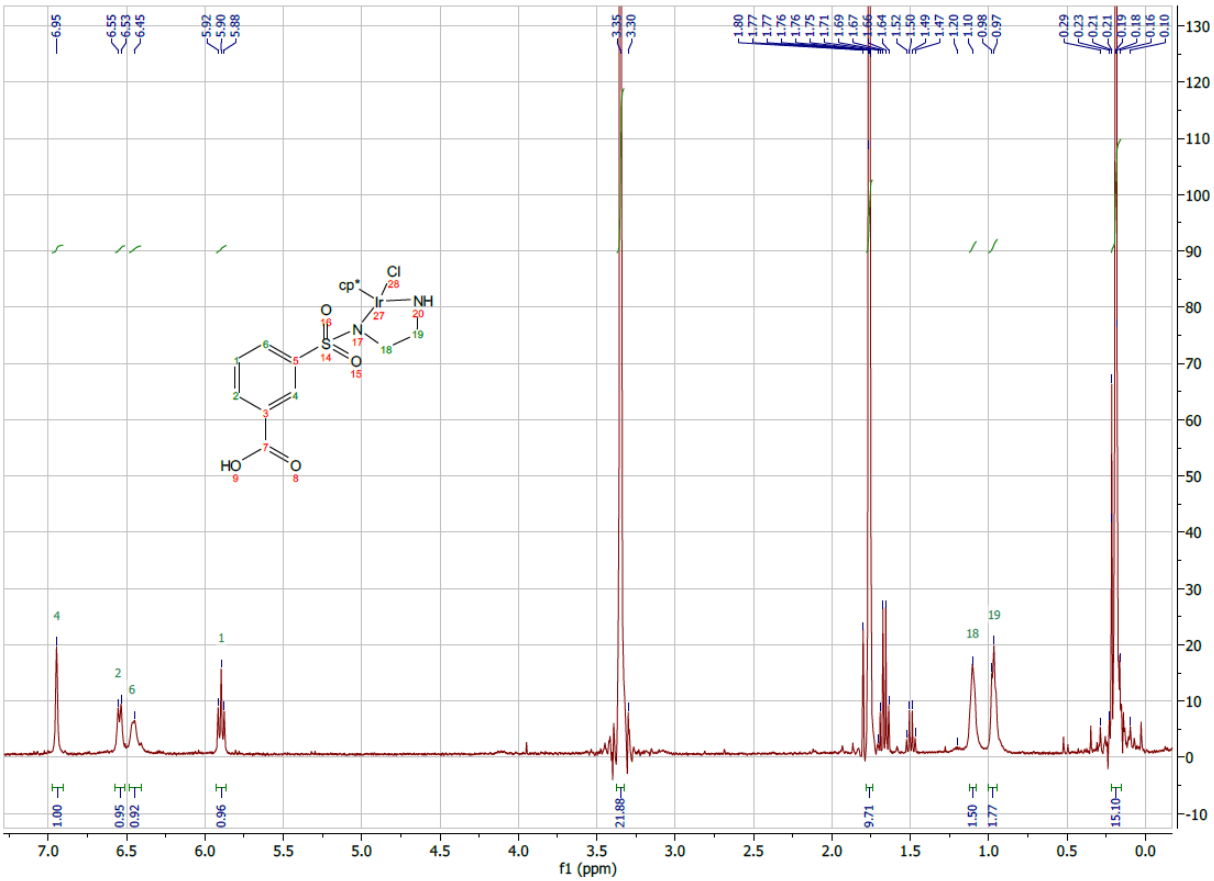


Figure S37: ^{1}H-NMR [IrClCp*]-(4-carboxyphenylsulfonyl)-ethylenediamine acid (**Ir23**)

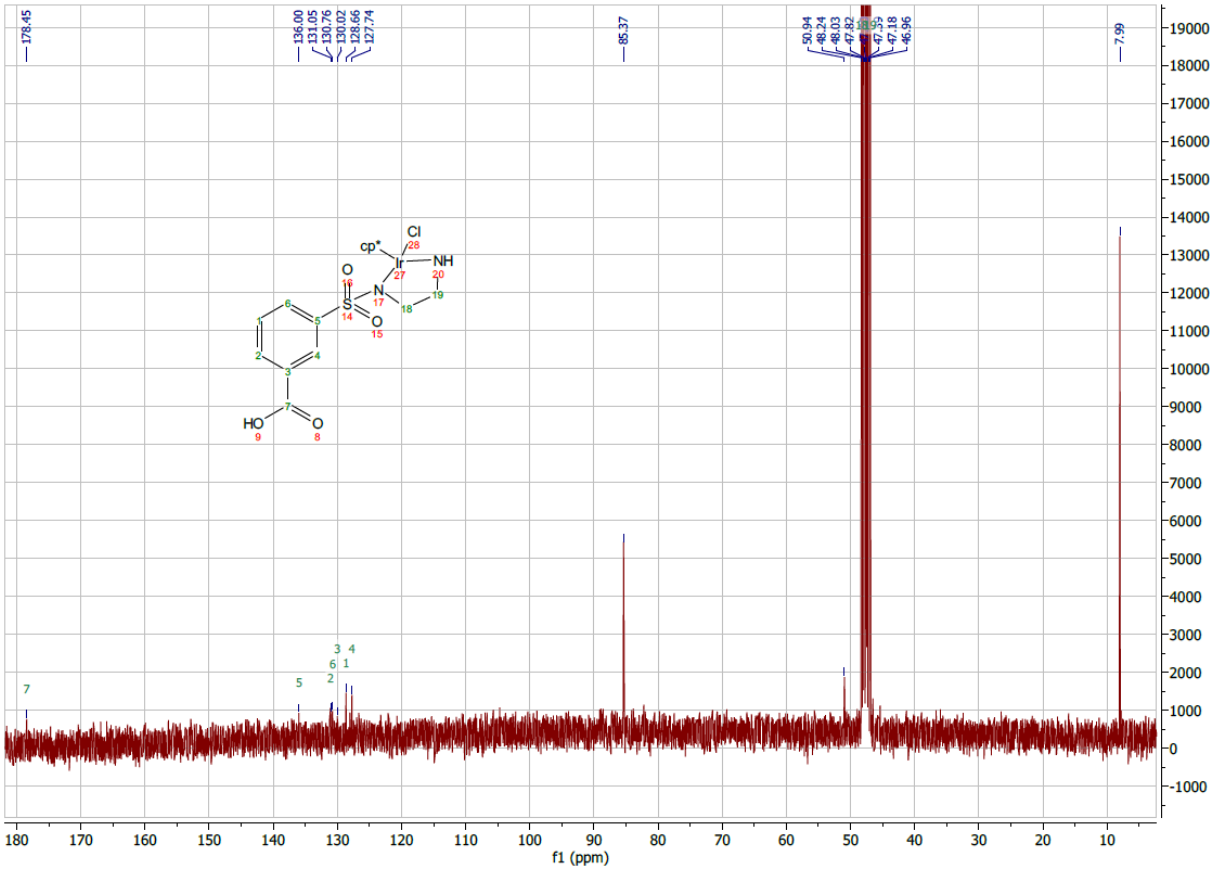


Figure S38: ^{13}C-NMR [IrClCp*]-(4-carboxyphenylsulfonyl)-ethylenediamine acid (**Ir23**)