Supplementary Information for:

Gold(I) complexes based on six-membered phosphorus heterocycles as bio-active molecules against brain cancer

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1. General section:

Reactions were carried out in dry glassware and under inert atmosphere of purified argon or nitrogen using Schlenk techniques. Solvents such as CH_2Cl_2 and THF were used directly from a solvent purification system MB SPS-800. AcOEt, ethanol and acetone were purchased from commercial suppliers and used as received. Compound **1** was prepared as previously reported.[S1] Potassium ethyl xanthogenate, $AgNO_3$, KSCN, 1-thio-β-D-glucose tetraacetate, magnesium sulfate, were purchased from commercial suppliers and used as received.

NMR: ^{1}H, ^{13}C, ^{1}and ^{31}P NMR spectra were recorded on a Bruker Avance DRX-300, Bruker Avance 500 or Bruker Avance 600. Chemical shifts are expressed as parts per million (ppm, δ) and referenced to external 85% H_3PO_4 (^{31}P), or solvent signals (^{1}H / ^{13}C): CD_2Cl_2 (5.33 / 53.80 ppm) as internal standards. Signal descriptions include: s = singlet, d = doublet, t = triplet, m = multiplet and br = broad. All coupling constants are absolute values and *J* values are expressed in Hertz (Hz).

Mass spectrometry: MS and HRMS were measured at the Organisch-Chemisches Institut of the Heidelberg University. A Bruker ApexQe hybrid 9.4 T FT-ICR was used for DART spectra and a JEOL AccuTOFGCx time-of-flight for EI spectra.

Steric Hindrance of phosphorus ligands: %V were calculated by using the http://www.molnac.unisa.it/OMtools/sambvca.php software and considering 3.50 Å as sphere radius. Hydrogens atoms were omitted and scaled Bondi radii were 1.7.[S2]

X-Ray crystallography: X-ray crystal structure analyses were measured on Bruker Smart CCD or Bruker Smart APEX instrument using Mo-Kα radiation. Diffraction intensities were corrected for Lorentz and polarization effects. An empirical absorption correction was applied using SADABS[S3] based on the Laue symmetry of reciprocal space. Heavy atom diffractions were solved by direct methods and refined against F2 with the full matrix least square algorithm. Hydrogen atoms were either isotropically refined or calculated. The structures were solved and refined using the SHELXTL[S4] software package. Crystal structure of **2** was obtained from DCM/pentane at r.t. and crystal structure of **3** from DCM solutions by slow evaporation at r.t. CCDC 2001099 (**2**) and 2001100 (**3**), 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/data_request/cif.

Cell culture conditions: Adherent growing cell lines (NCH82, NCH89, NCH210, and NCH125) as well as glioma stem-like cell lines (NCH421k, NCH644, NCH660h) were established from intraoperatively obtained glioblastoma samples characterized and cultured as already described.[S5-S7] Cell lines were authenticated and written informed consent was obtained from patients according to the research proposals approved by the Institutional Review Board at the Medical Faculty of the University of Heidelberg.

Proliferation assay – adherent cell lines: The effect of different compounds on cell growth was evaluated by the crystal violet method as described earlier.[8] Briefly, cells were seeded in 96-well plates (10,000 cells/well). After 24 h cell culture medium was replaced by fresh compound-containing medium (ten different concentrations from 0.01 to 200 µM). After 48 h of exposure extent of cell proliferation inhibition was determined by crystal violet staining of surviving cells. Then, cells were washed and stained with 0.5 % crystal violet solution (2.5 g in 100 ml methanol, diluted with 400 ml aqua bidest) for 15 min, rinsed and dried overnight. Next, crystal violet was solubilized in methanol and absorbance was measured at 555 nm. The proliferative index was calculated as crystal violet absorption intensity as percentage relative to baseline (no cells) as described before.[9] Cell survival plotted against the decimal logarithm of drug concentration in µM and fitted to a sigmoidal dose-response curve using Graph Pad Prism 7.02 (GraphPad Software, San Diego, USA).

Proliferation assay – glioma stem-like cell (GSC) lines: To assess the effect of compound **4** on cell growth of glioma stem-like cells (GSC), cellular ATP levels were measured using the luminescent CellTiter-Glo Assay (Promega Corp, Madison, WI). GCS spheroid cultures were gently dissociated and cell suspensions were seeded in 96-well tissue culture plates (8,000 cells/well, 100 µl/well). After a 24 hours incubation period without any compound, freshly reconstituted compound in ten final concentrations ranging from 0.01 µM to 200 µM were added and cells were incubated for 48 hours. Before measurement, the plate was equilibrated at room temperature for 30 minutes. Then, 100 µl of CellTiter-Glo Reagent were added to each well and the plate was placed on an orbital shaker for 2 minutes to mix the content. Next, the plate was incubated for 10 minutes at room temperature and finally, the luminescence was measured. Cell viability was plotted against the decimal logarithm of drug concentration in µM and fitted to a sigmoidal dose-response curve using Graph Pad Prism 7.02 (GraphPad Software, San Diego, USA).

Effect of drugs on apoptosis (Annexin V apoptosis assay): To quantify the extent of apoptosis annexin V staining combined with DAPI was used. The double labeling allows the distinction between apoptotic (annexin V^{pos}/$DAPI^{neg}$) and necrotic (annexin V^{pos}/$DAPI^{pos}$) cells. Cells were seeded in a 6-well plate ($2.5x10^5$/well) and left to attach overnight. Medium was replaced by fresh medium containing defined drug concentrations or compound solvent DMSO (untreated control) and incubated for 24 h. As positive control cells were treated with 1 µM of the apoptosis-inducing reagent staurosporin (#9953, Cell Signaling Technology, Danvas, USA). After treatment, supernatant containing apoptotic and necrotic cells was collected, cells were harvested, washed, and up to $1x10^6$ cells were incubated with FITC-conjugated annexin V antibody diluted in 1:1000 DAPI solution following manufactures instructions (#51-65874X, BD Bioscienes, Franklin Lakes, USA). Cells were acquired by flow cytometry using a BD LSRII flow cytometer (BD Bioscienes, Franklin Lakes, USA) and analyzed by FlowJo Software v7.6.5 (TreeStar, Ahland, USA).

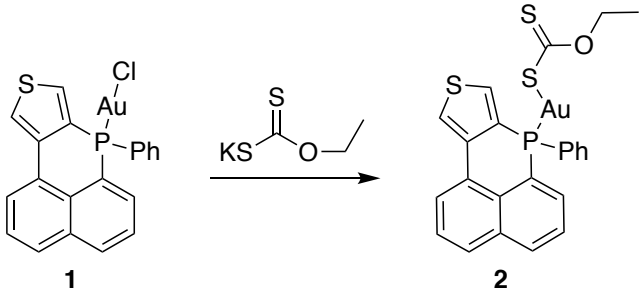
Effect of drugs on glioma cell migration (Scratch Assay): To assess the effect of the drugs on cell migration, *in vitro* cells were seeded in 6-well plates ($5x10^5$/Well) and left to attach. On the next day,

the cell monolayer was scraped in a straight line to create a “scratch” with a p200 pipet tip. Debris were removed by washing the cells and medium, and it was replaced with 5 ml of compound-containing medium in three different cell line specific concentrations (IC_{50}, $IC_{50}/2$, $IC_{50}/10$) for 24 h. Phase contrast images were acquired at 0 h and after 12 h of exposure to the respective drug concentration using a BX50 microscope with a SC30 camera (both Olympus, Tokyo, Japan). The cell-free areas at both time points were quantified and compared using the imaging software cellSens (Olympus, Tokyo, Japan).

2. Experimental details

2.1. Synthetic procedures

Compound 2

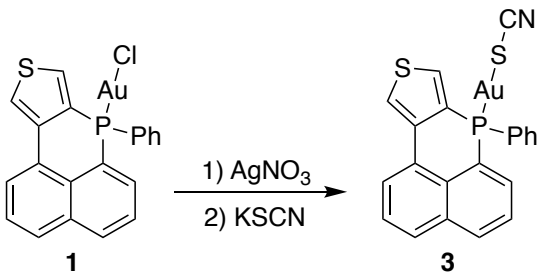


1 2

Compound **1** (1 eq, 0.076 mmol, 42 mg) was dissolved in 4 mL of DCM and potassium ethyl xanthogenate (1 eq, 0.076 mmol, 12 mg) was added at r.t. The crude was stirred 1.5 hours. Then, the mixture was washed with water, dried over $MgSO_4$ and the volatiles were removed under reduced pressure. The crude was washed with AcOEt x3, further purified by chromatography and crystalized by slow evaporation from DCM solutions. Yield: 88% (42 mg, 0.066 mmol).

^{1}H-NMR (600 MHz, CD_2Cl_2): δ 8.26 (ddd, *J* = 18.8, 7.0, 1.2 Hz, 1H), 8.21 (dd, *J* = 7.4, 0.8 Hz, 1H), 8.17 (dd, *J* = 8.8, 2.9 Hz, 1H), 8.07 (dd, *J* = 2.9, 1.1 Hz, 1H), 8.04 (d, *J* = 8.2 Hz, 1H), 7.93 (d, *J* = 8.2 Hz, 1H), 7.66 (t, *J* = 7.8 Hz, 1H), 7.63-7.61 (m, 1H), 7.42 (ddd, *J* = 13.7, 8.3, 1.1 Hz, 2H), 7.33 (td, *J* = 7.4, 2.0 Hz, 1H), 7.26 (td, *J* = 7.5, 2.5 Hz, 2H), 4.55-4.50 (m, 2H), 1.40 (d, *J* = 14.2 Hz, 3H). **^{13}C{^{1}H}{^{31}P} NMR** (151 MHz, CD_2Cl_2): δ 138.3 (s, 1C), 136.8 (s, 1C), 136.1 (s, 1C), 135.2 (s, 1C), 134.5 (s, 1C), 133.6 (s, 1C), 132.4 (s, 1C), 131.6 (s, 1C), 129.9 (s, 1C), 129.4 (s, 1C), 128.4 (s, 1C), 127.6 (s, 1C), 127.2 (s, 1C), 126.2 (s, 1C), 124.8 (s, 1C), 124.6 (s, 1C), 123.0 (s, 1C), 123.0 (s, 1C), 70.6 (s, 1C), 14.3 (s, 1C). **^{31}P-NMR** (243 MHz, CD_2Cl_2): δ 6.55. **HRMS** (ESI+) calcd. for $C_{23}H_{18}AuOPS_3^+$ 634.9923, found 634.9996. Anal. $C_{23}H_{18}AuOPS_3$: calcd. C 43.54, H 2.86; found C 43.69, H 2.85.

Compound 3



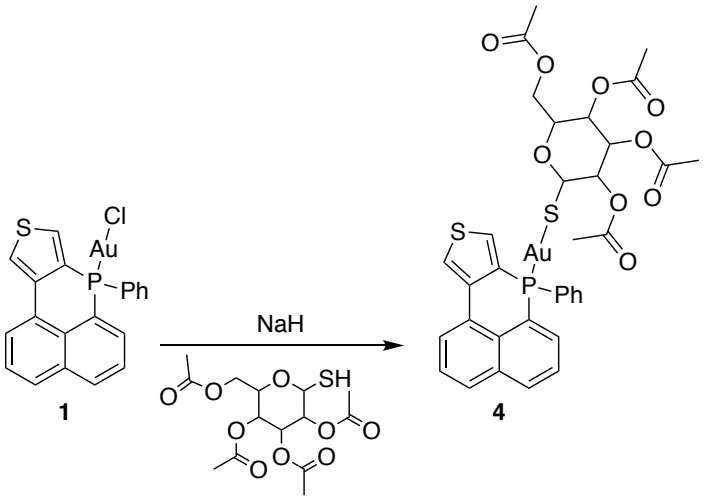
1 3

Compound **1** (1 eq, 0.273 mmol, 150 mg) was suspended in 4 mL of ethanol and mixed with $AgNO_3$ (1 eq, 0.273 mmol, 46 mg) dissolved in 4 ml of water. The mixture was stirred one hour and 5 mL of DCM were added. After stirring for 30 min, 80 μL of KSCN 8M in water. The mixture was stirred during one hour, the DCM phase was separated and the aqueous phase was extracted x3 with DCM. After drying

over $MgSO_4$, the crude was concentrated under reduced pressure and filtered through Celite. The product was purified by using eluent mixtures from DCM/pentane 6:4 to pure DCM and crystallized from a DCM/pentane mixture. Yield: 65% (102 mg, 0.179 mmol).

^{1}H-NMR (600 MHz, CD_2Cl_2): δ 8.26 (d, *J* = 7.4 Hz, 1H), 8.18 (dd, *J* = 19.1, 7.0 Hz, 1H), 8.13 (dd, *J* = 6.6, 3.3 Hz, 2H), 8.09 (d, *J* = 8.2 Hz, 1H), 7.97 (d, *J* = 8.1 Hz, 1H), 7.71-7.65 (m, 2H), 7.42-7.37 (m, 3H), 7.31 (td, *J* = 7.8, 2.2 Hz, 2H). **^{13}C{^{1}H}{^{31}P} NMR** (151 MHz, CD_2Cl_2): δ 138.2 (s, 1C), 136.9 (s, 1C), 136.3 (s, 1C), 134.6 (s, 1C), 134.1 (s, 1C), 134.0 (s, 1C), 132.6 (s, 1C), 132.1 (s, 1C), 130.1 (s, 1C), 129.6 (s, 1C), 128.3 (s, 1C), 127.4 (s, 1C), 126.2 (s, 1C), 125.0 (s, 1C), 123.3 (s, 1C), 123.3 (s, 1C), 121.9 (s, 1C). **^{31}P-NMR** (243 MHz, CD_2Cl_2): δ 7.10. **HRMS** (ESI+) calcd. for $C_{21}H_{13}AuNNaPS_2^+$ 593.9790, found 593.9785. Anal. $C_{21}H_{13}AuNPS_2$: calcd. C 44.14, H 2.29, N 2.45; found C 44.31, H 2.31, N 2.43.

Compound 4



NaH was added to 1-thio-β-D-glucose tetraacetate (1 eq, 0.182 mmol, 66 mg) in 5 mL of THF at r.t. The mixture was stirred one hour, filtered through Celite via cannula and added to compound **1** (0.9 eq, 0.164 mmol, 90 mg) dissolved in 5 mL of THF at r.t. The solution was stirred 1.5 hours and the solvent removed under vacuum. The crude was dissolved in DCM, filtered through Celite and subjected to chromatography using AcOEt/acetone 8:2 as eluent. Yield: 72% (104 mg, 0.118 mmol).

^{1}H-NMR (600 MHz, CD_2Cl_2): δ 8.31-8.24 (m, 3H), 8.12 (ddd, *J* = 6.2, 2.9, 1.1 Hz, 1H), 8.06 (dd, *J* = 8.2, 1.2 Hz, 1H), 7.94 (s, 1H), 7.69-7.64 (m, 2H), 7.45-7.39 (m, 2H), 7.35-7.32 (m, 1H), 7.30-7.26 (m, 2H), 5.20-5.14 (m, 2H), 5.08 (dt, *J* = 13.1, 9.5 Hz, 2H), 4.14 (qd, *J* = 12.0, 3.7 Hz, 2H), 3.77 (ddd, *J* = 10.0, 5.0, 2.5 Hz, 1H), 2.07 (s, 3H), 2.00 (s, 3H), 1.98 (s, 3H), 1.91 (s, 3H). **^{13}C{^{1}H}{^{31}P} NMR** (151 MHz, CD_2Cl_2): δ 170.3 (s, 1C), 169.9 (s, 1C), 169.5 (s, 1C), 169.4 (s, 1C), 137.9 (s, 1C), 137.9 (s, 1C), 136.4 (s, 1C), 136.32(s, 1C), 135.6 (s, 1C), 135.5 (s, 1C), 135.1 (s, 1C), 135.1 (s, 1C), 134.2 (s, 1C), 134.1 (s, 1C), 133.0 (s, 1C), 132.0 (s, 1C), 132.0 (s, 1C), 131.1 (s, 1C), 131.1 (s, 1C), 129.5 (s, 1C), 129.0 (s, 1C), 128.9 (s, 1C), 128.1 (s, 1C), 127.2 (s, 1C), 126.7 (s, 1C), 124.3 (s, 1C), 122.8 (s, 1C),

122.8 (s, 1C), 122.5 (s, 1C), 122.4 (s, 1C), 83.0 (s, 1C), 77.6 (s, 1C), 75.7 (s, 1C), 73.9 (s, 1C), 68.7 (s, 1C), 62.6 (s, 1C), 20.9 (s, 1C), 20.4 (s, 1C), 20.4 (s, 1C), 20.4 (s, 1C). **^{31}P-NMR** (122 MHz, $CDCl_3$) **HRMS** (ESI+) calcd. for $C_{34}H_{32}AuNaO_9PS_2$ 899.0789, found 899.0784. Anal. $C_{34}H_{32}AuO_9PS_2$: calcd. C 46.58, H 3.68; found C 46.77, H 3.71.

2.2 Structural characteristics of [1-phenyl-2,5-di(2-pyridyl)phosphole]AuCl, triphenylphosphine-AuCl, Triethylphosphine-AuCl and compounds 1-4.

Table S1. ^{31}P-NMR, P-Au distances and buried volume (V%) of compounds **1-4** and representative gold complexes.

	^{31}P-NMR (ppm)	P-Au distance (Å)	V%
Compound 1[S1]	2.56	2.225	30
[1-phenyl-2,5-di(2-pyridyl)phosphole]AuCl[S10]	39.9	2.23	32.8
Triphenylphosphine-AuCl[S11]	33.8	2.231	30.7
Triethylphosphine-AuCl[S12]	32.32	2.231	27.9
Compound 2	6.65	2.225	--
Compound 3	7.10	2.248	--
Compound 4	8.17	--	--

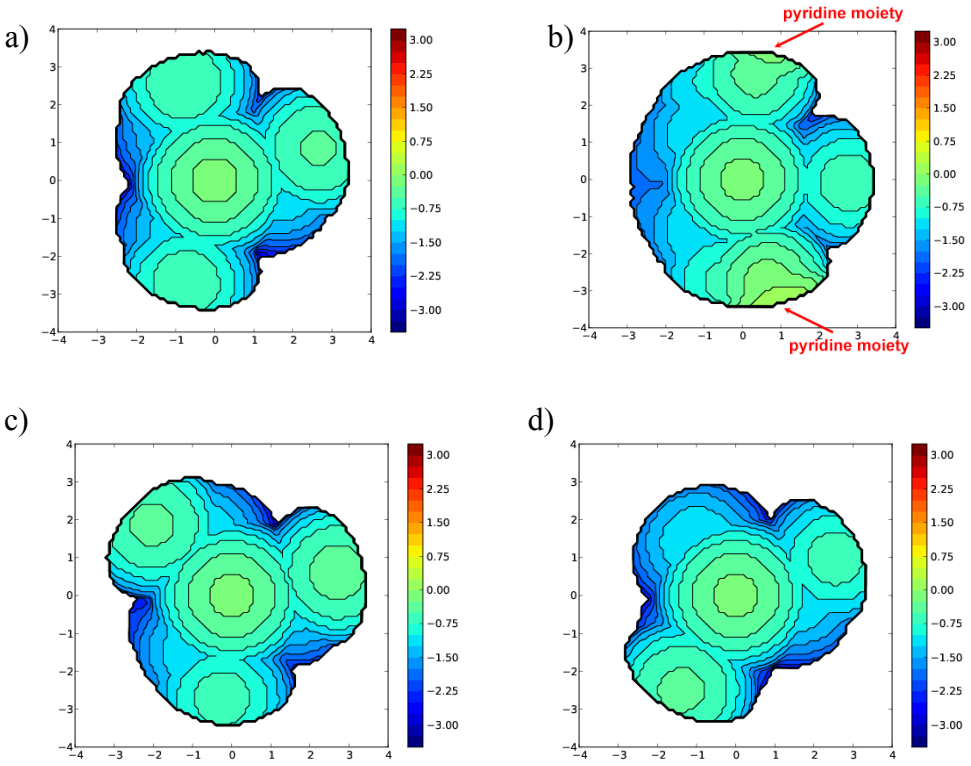
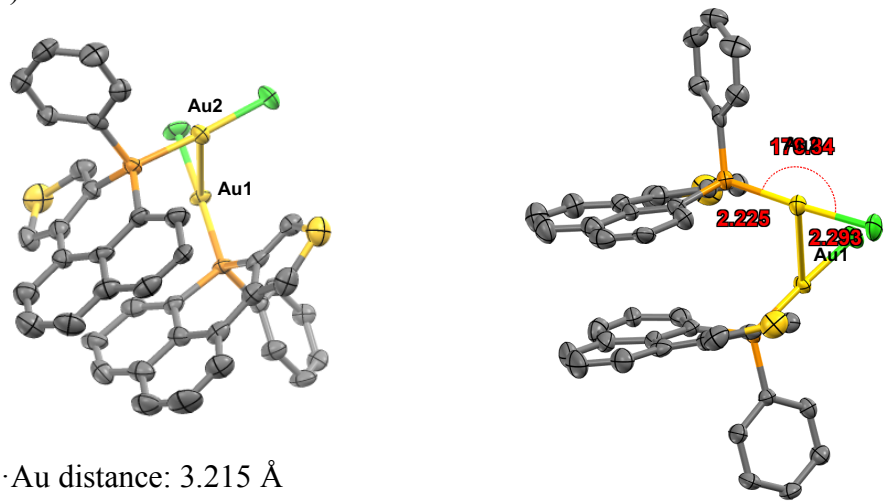


Figure S1. Steric mapping of the ligands corresponding to a) compound **1**, b) [1-phenyl-2,5-di(2-pyridyl)phosphole]AuCl, c) triphenylphosphine-AuCl and d) triethylphosphine-AuCl.

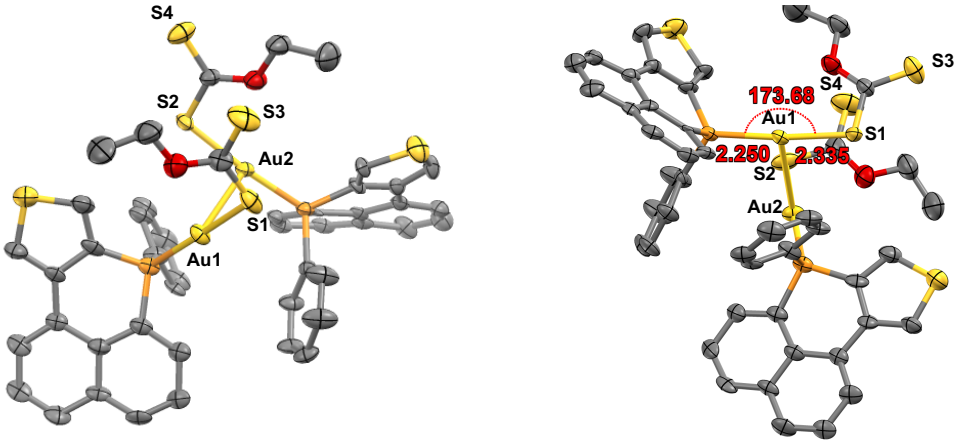
3. X-Ray structures of compounds 1[S1] 2, and 3.

a)



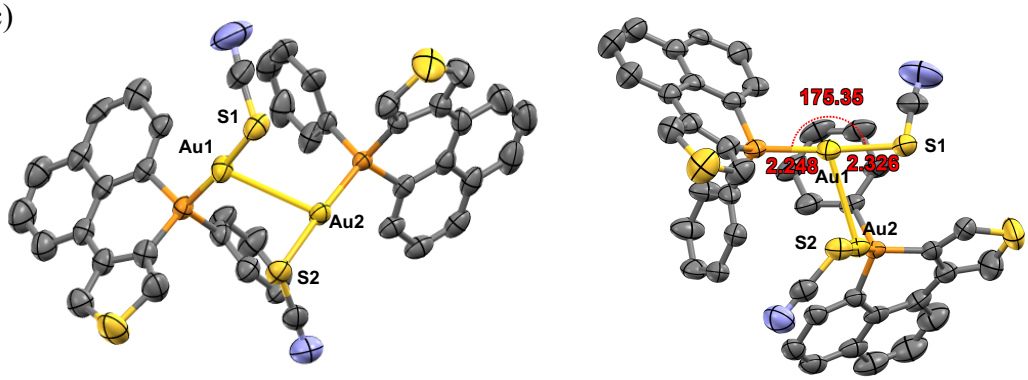
Au···Au distance: 3.215 Å

b)



Au···Au distance: 3.043 Å

c)



Au···Au distance: 3.106 Å

Figure S2. Single-crystal X-ray structures of: a) **1**,[S1] b) **2**, and c) **3**. Ellipsoids at the 50% level of probability. Hydrogen atoms and solvent molecules have been omitted for clarity. Note that all complexes show aurophilic interactions in the solid state. Au···Au distances are indicated in Angstrom.

4. Selected crystallographic data

Table S2: Selected crystallographic data of compounds **1**, **2**, and **3**.

Compound	**1** [S1]	**2**	**3**
Empirical formula	$C_{20}H_{13}AuClPS$	$C_{23}H_{18}AuOPS_3$	$C_{21}H_{13}AuNPS_2$
Formula weight	548.75	634.49	571.38
Temperature	200(2) K	200(2) K	200(2) K
Wavelength	0.71073 Å	0.71073 Å	0.71073 Å
Crystal system	monoclinic	triclinic	monoclinic
Space group	$P2_1/c$	$P\bar{1}$	$P2_1/c$
Z	8	8	8
a/Å	10.1435(5) Å	12.027(3) Å; α = 83.652(4)°	12.7527(3) Å; α = 90°
b/Å	17.4400(8) Å	12.230(3) Å; β = 86.895(4)°	18.7996(4) Å; β = 108.2708(7)°
c/Å	20.4343(10) Å	33.790(9) Å; γ = 62.035(3)°	16.5300(4) Å; γ = 90°
Volume	3511.3(3) $Å^3$	4363(2) $Å^3$	3763.20(15) $Å^3$
Density (calculated)	2.08 g/cm^3	1.93 g/cm^3	2.02 g/cm^3
Absorption coefficient	8.74 mm^{-1}	7.12 mm^{-1}	8.13 mm^{-1}
Crystal shape	plate	brick	brick
Crystal size	0.080 x 0.070 x 0.020 mm^3	0.164 x 0.119 x 0.075 mm^3	0.096 x 0.079 x 0.032 mm^3
Crystal colour	colourless	colourless	yellow
Theta range for data collection	1.6 to 25.1 deg.	0.6 to 29.4 deg.	2.0 to 27.2 deg.
Index Ranges	$-12\le h\le 12$, $-20\le k\le 20$, $-19\le l\le 24$	$-16\le h\le 16$, $-24\le k\le 24$, $-21\le l\le 21$	$-16\le h\le 16$, $-24\le k\le 24$, $-21\le l\le 21$
Reflections collected	21942	22859	49491
Independent reflections	6203 (R(int) = 0.0408)	11261 (R(int) = 0.0444)	8362 (R(int) = 0.0550)
Observed reflections	5147 (I > 2s(I))	6452 (I > 2σ(I))	5986 (I > 2σ(I))
Absorption correction	Semi-empirical from equivalents	Semi-empirical from equivalents	Semi-empirical from equivalents
Max. and min. transmission	0.82 and 0.61	0.65 and 0.48	0.81 and 0.68
Refinement method	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2
Data/restraints/parameters	6203 / 0 / 433	11261 / 2091 / 1049	8362 / 1386 / 599
Goodness-of-fit on F^2	1.05	1.05	1.02
Final R indices (I>2sigma(I))	R1 = 0.032, wR2 = 0.065	R1 = 0.079, wR2 = 0.162	R1 = 0.039, wR2 = 0.087
Largest diff. peak and hole	1.25 and -1.05 $eÅ^{-3}$	1.67 and -1.68 $eÅ^{-3}$	2.67 and -1.74 $eÅ^{-3}$

5. Antiproliferative assays of compounds 1-4

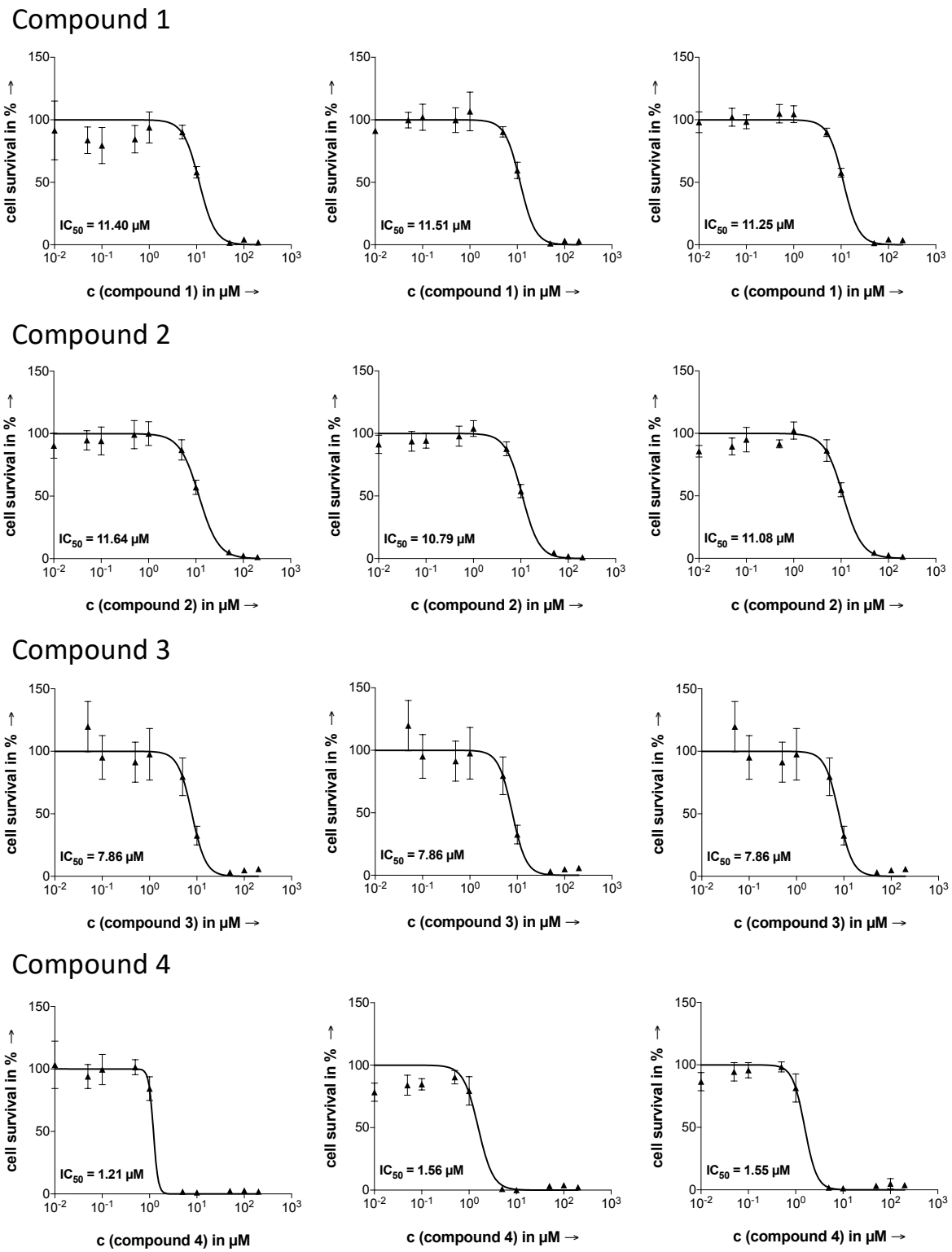


Figure S3: Antiproliferative effect of compounds 1,2, 3, and 4 on glioma cell line NCH82. Representative dose-response curves of compounds **1**, **2**, **3**, and **4** tested on glioma cell line NCH82 in three independent biological replicates using the crystal violet proliferation assay. Compounds were applied for 48 hours.

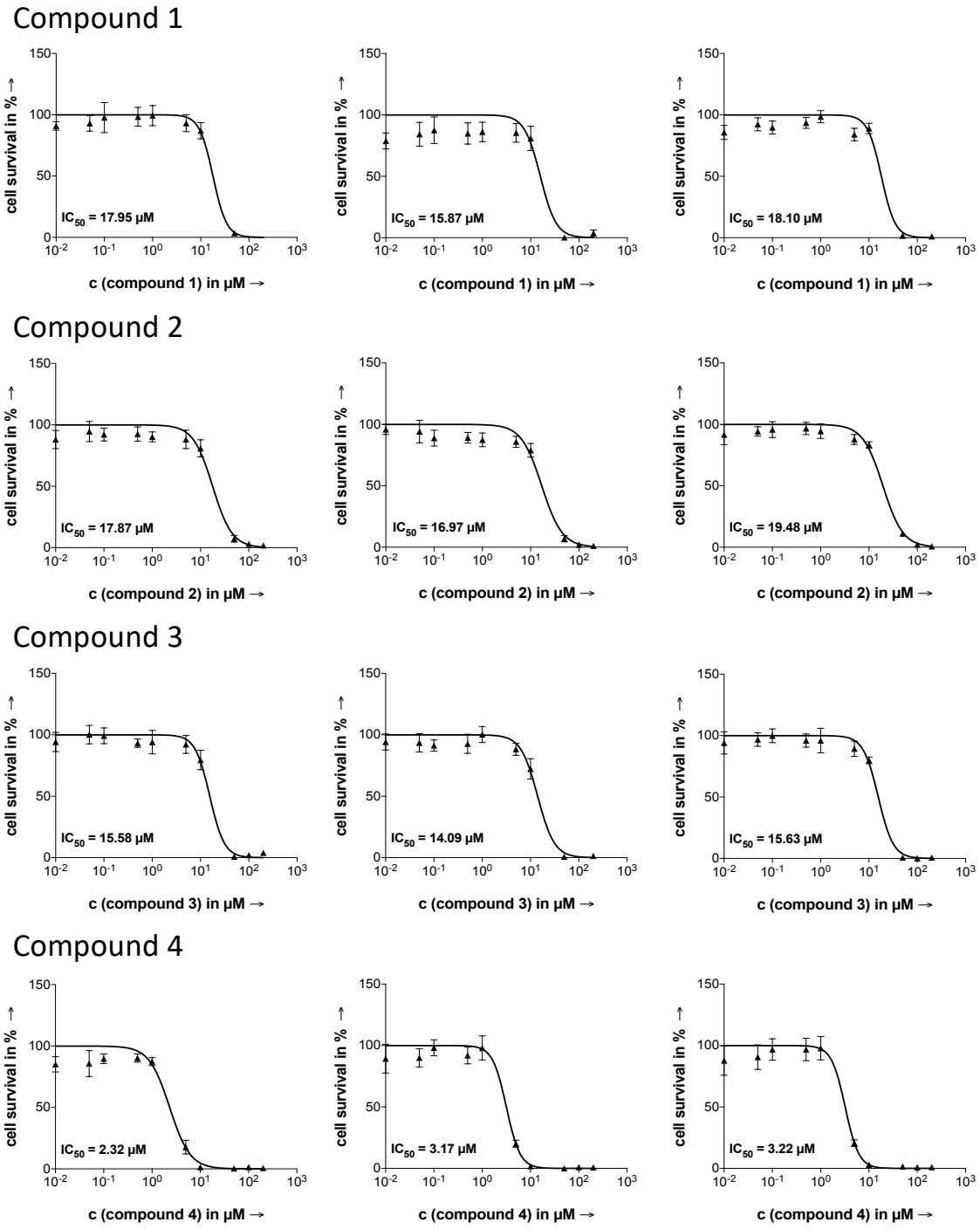


Figure S4: Antiproliferative effect of compounds 1,2, 3, and 4 on glioma cell line NCH89. Representative dose-response curves of compounds **1**, **2**, **3**, and **4** tested on glioma cell line NCH89 in three independent biological replicates using the crystal violet proliferation assay. Compounds were applied for 48 hours.

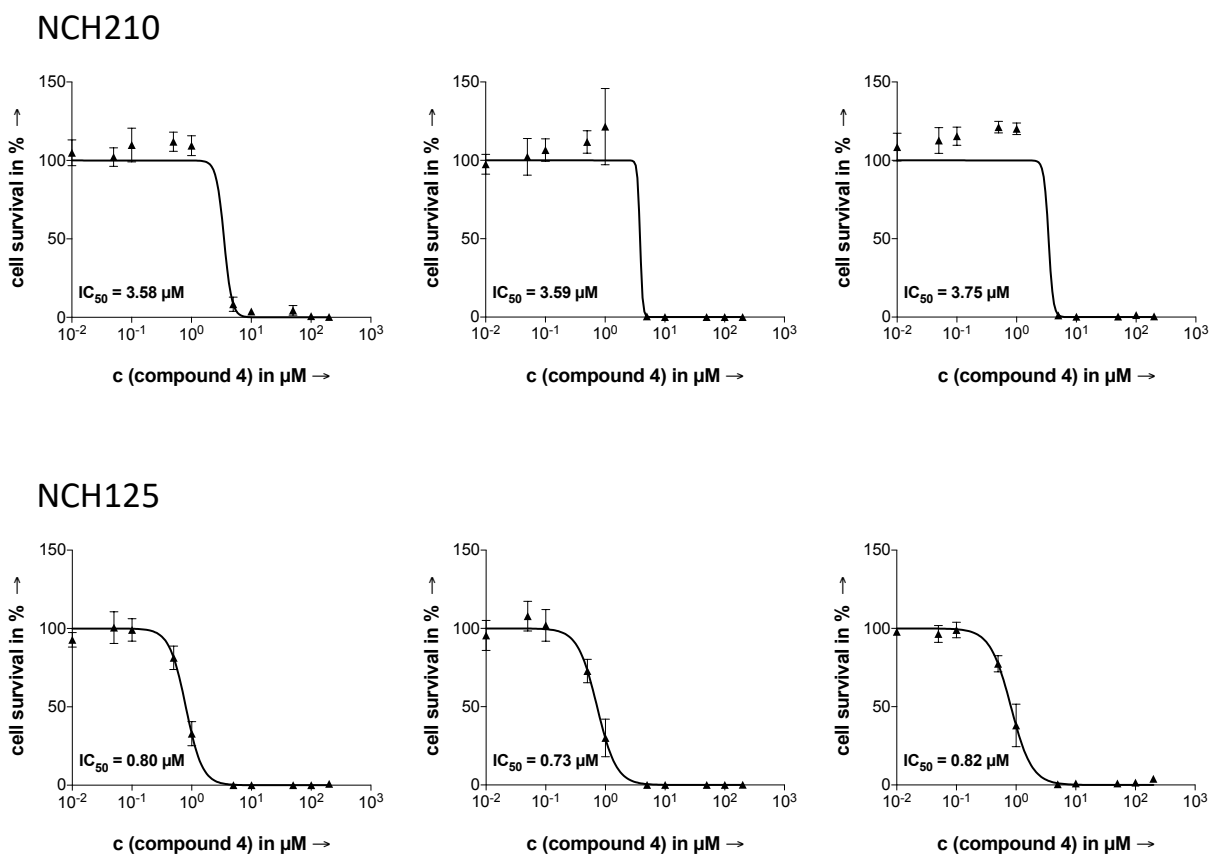


Figure S5: Antiproliferative effect of compound 4 on glioma cell lines NCH210 and NCH125. Representative dose-response curves of compound **4** tested on glioma cell lines NCH210 and NCH125 in three independent biological replicates performing a crystal violet proliferation assay. Compound was applied for 48 hours.

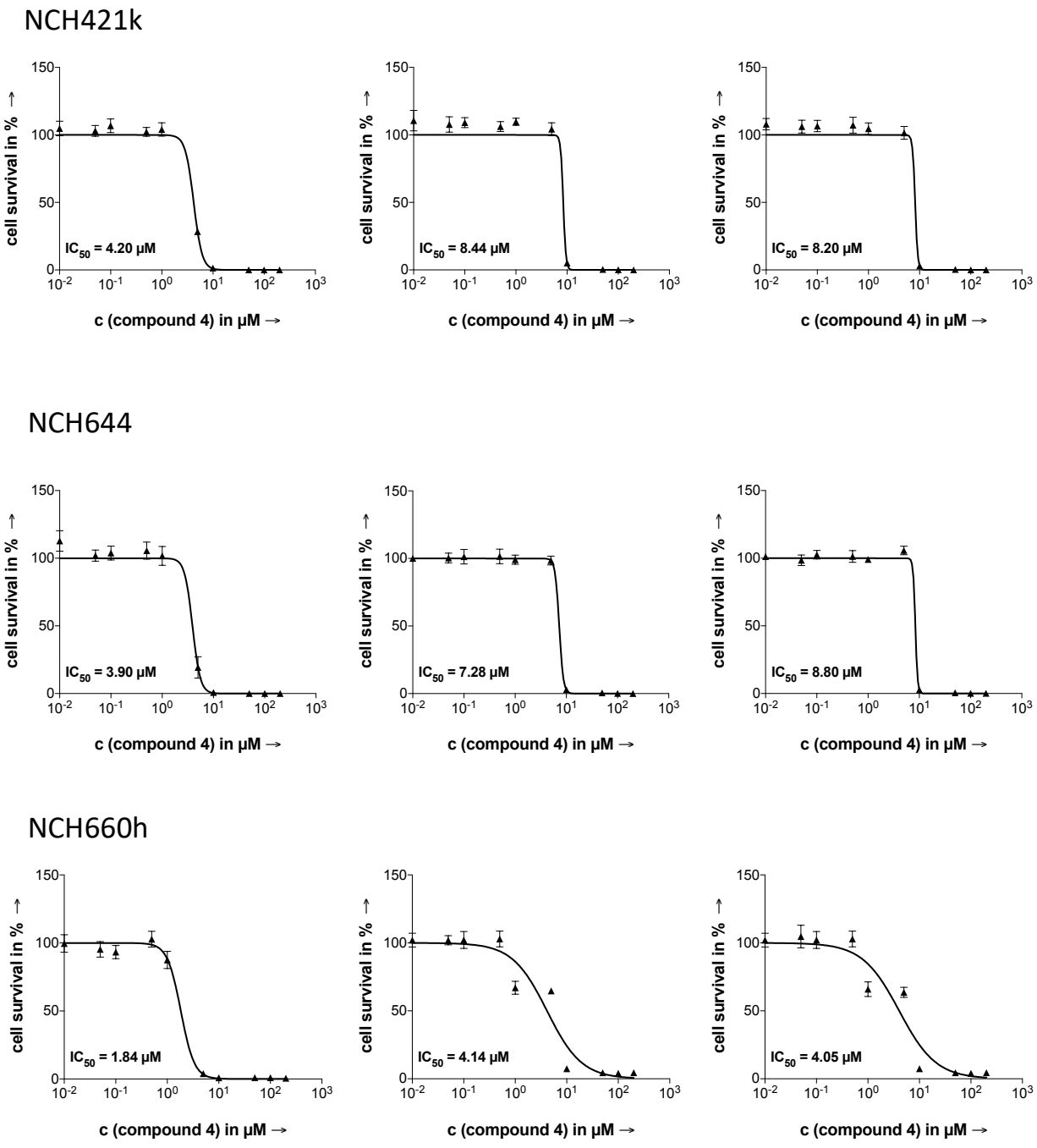
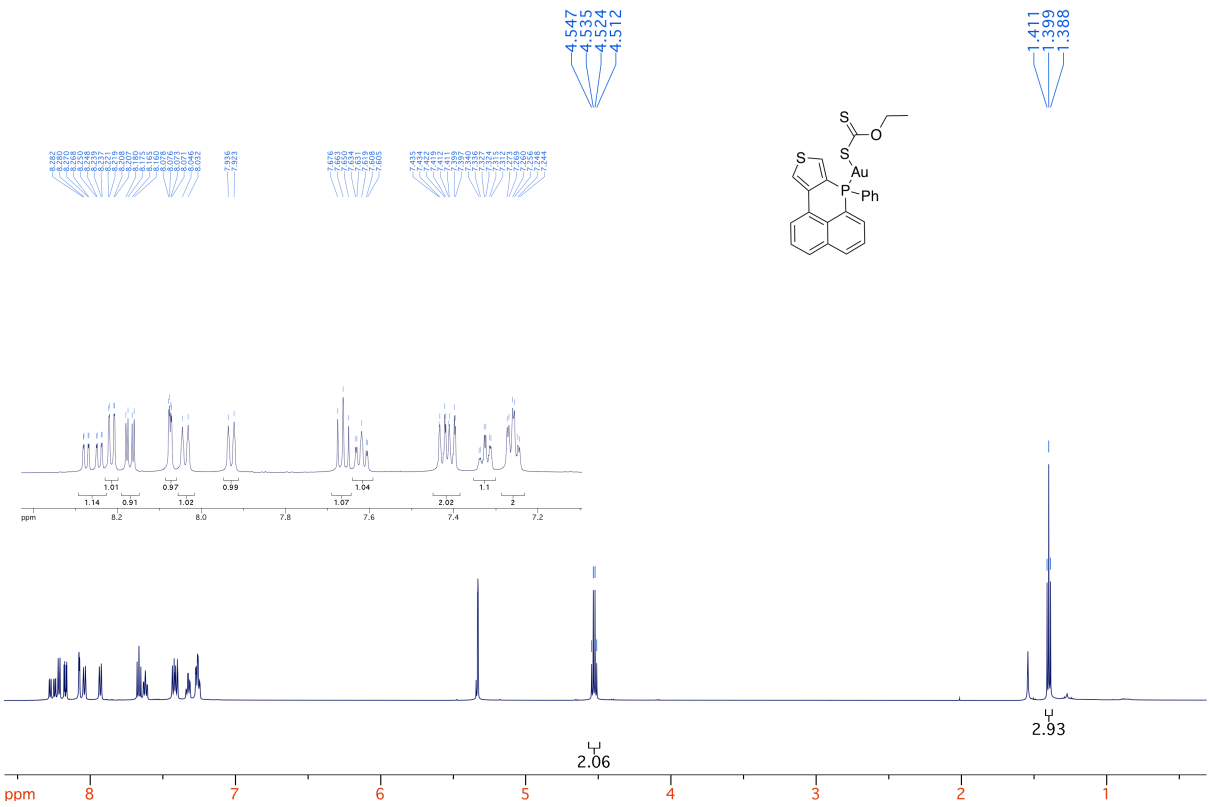


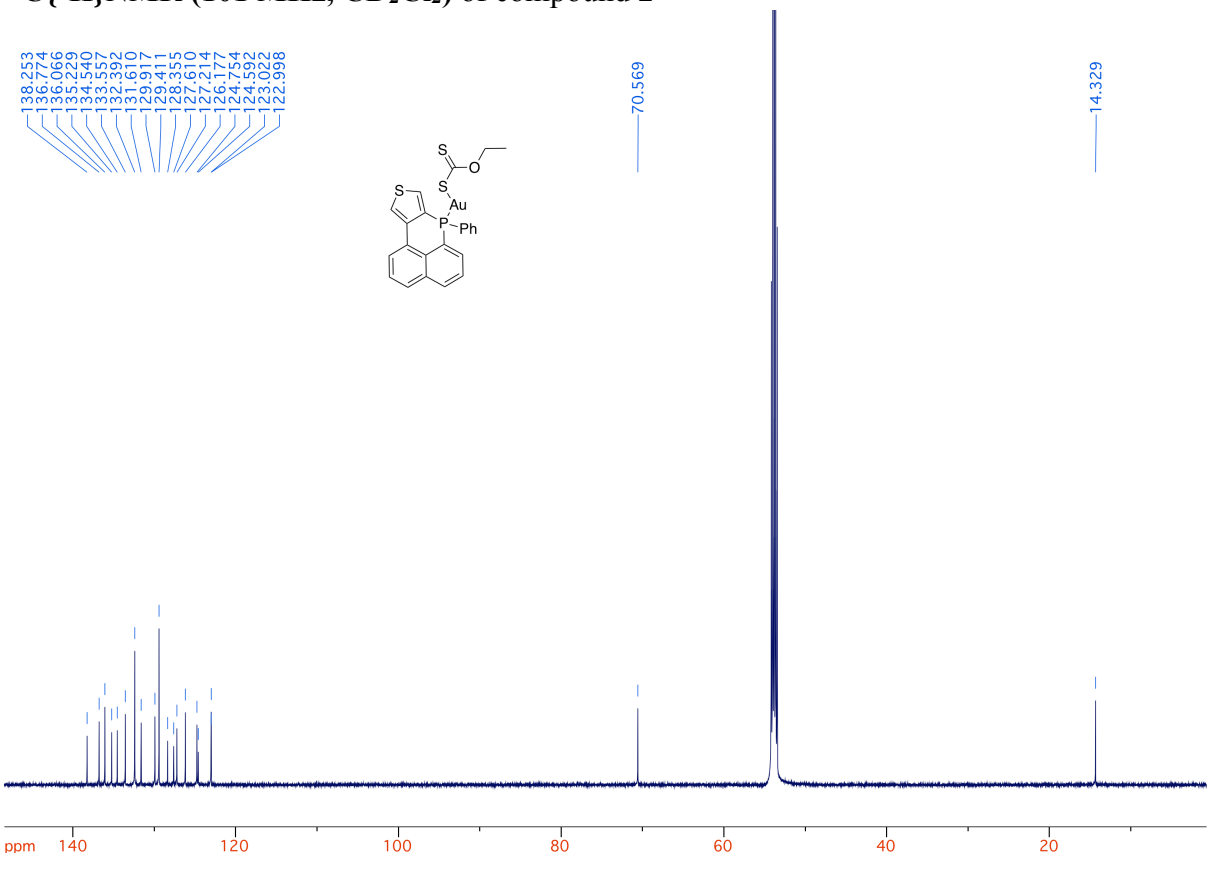
Figure S6: Antiproliferative effect of compound 4 on different glioma stem-like cell lines NCH421k, NCH644, and NCH660h.
Representative dose-response curves of compound **4** tested on glioma stem-like cell lines NCH421k, NCH644, and NCH660h in three independent biological replicates using the CellTiter-Glow assay. Compound was applied for 48 hours.

9. NMR data

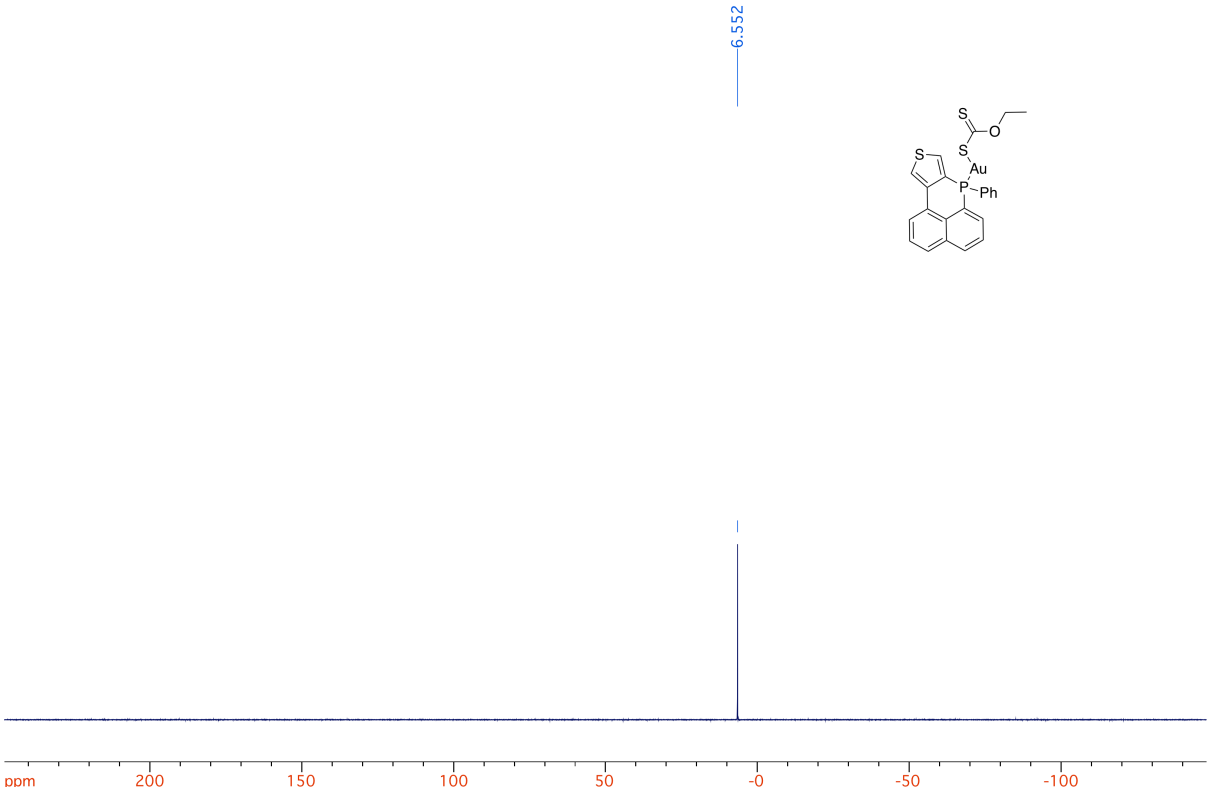
^{1}H NMR (400 MHz, CD_2Cl_2) of compound **2**



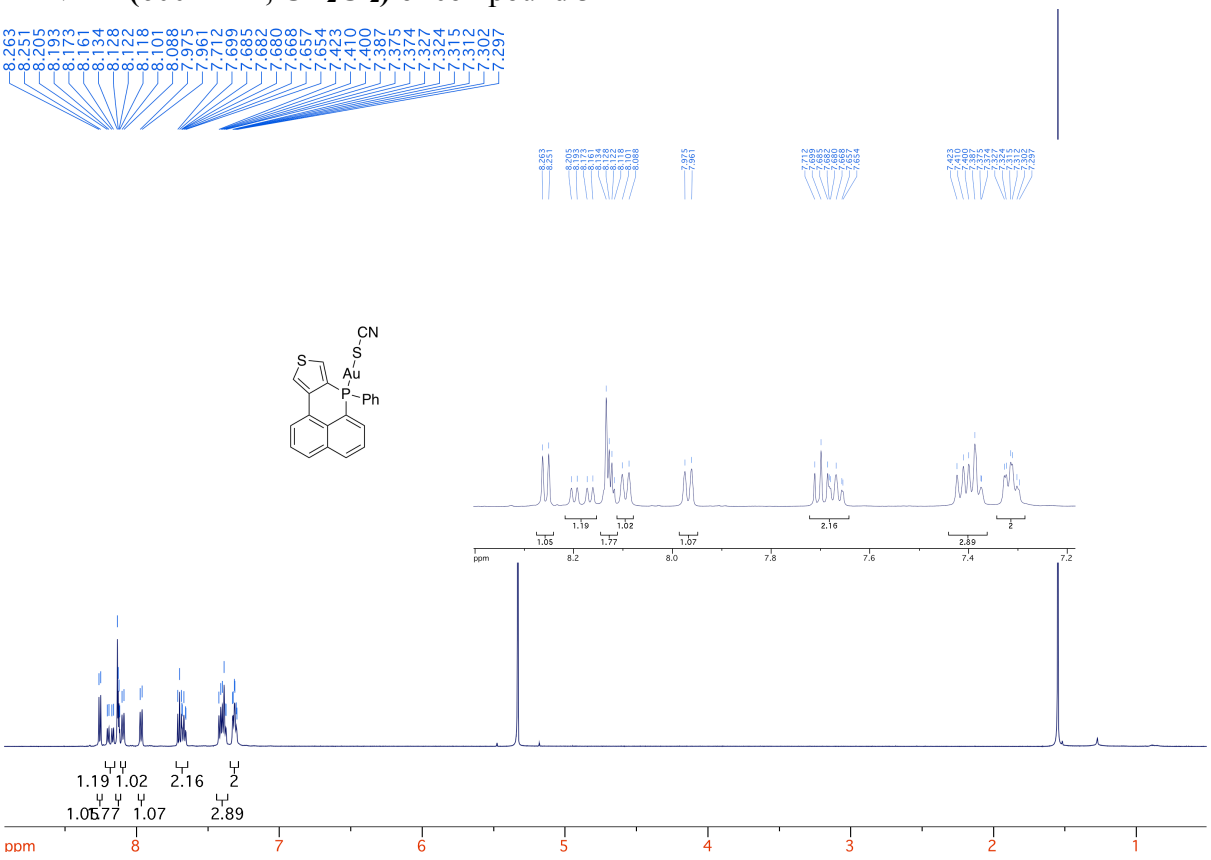
^{13}C{^{1}H}NMR (101 MHz, CD_2Cl_2) of compound **2**



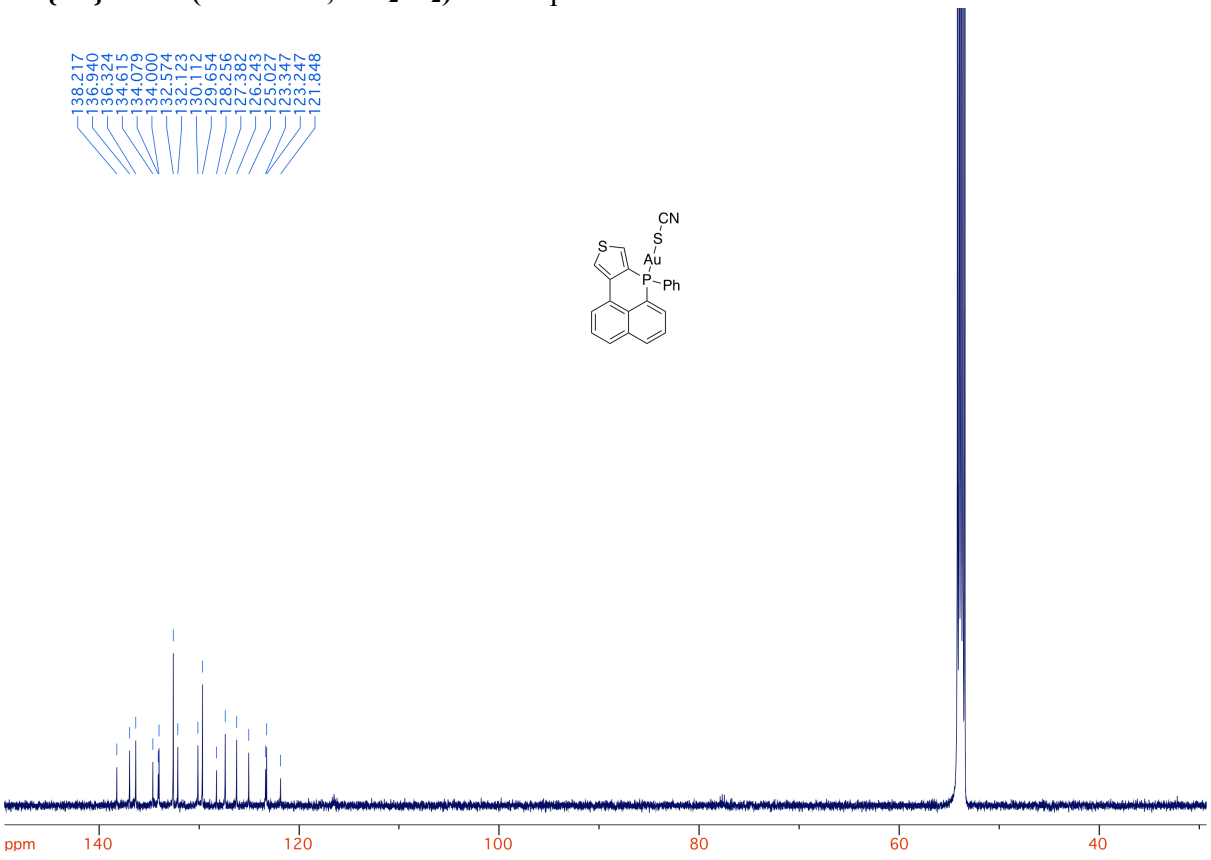
$^{31}P\{^{1}H\}$NMR (101 MHz, CD_2Cl_2) of compound **2**



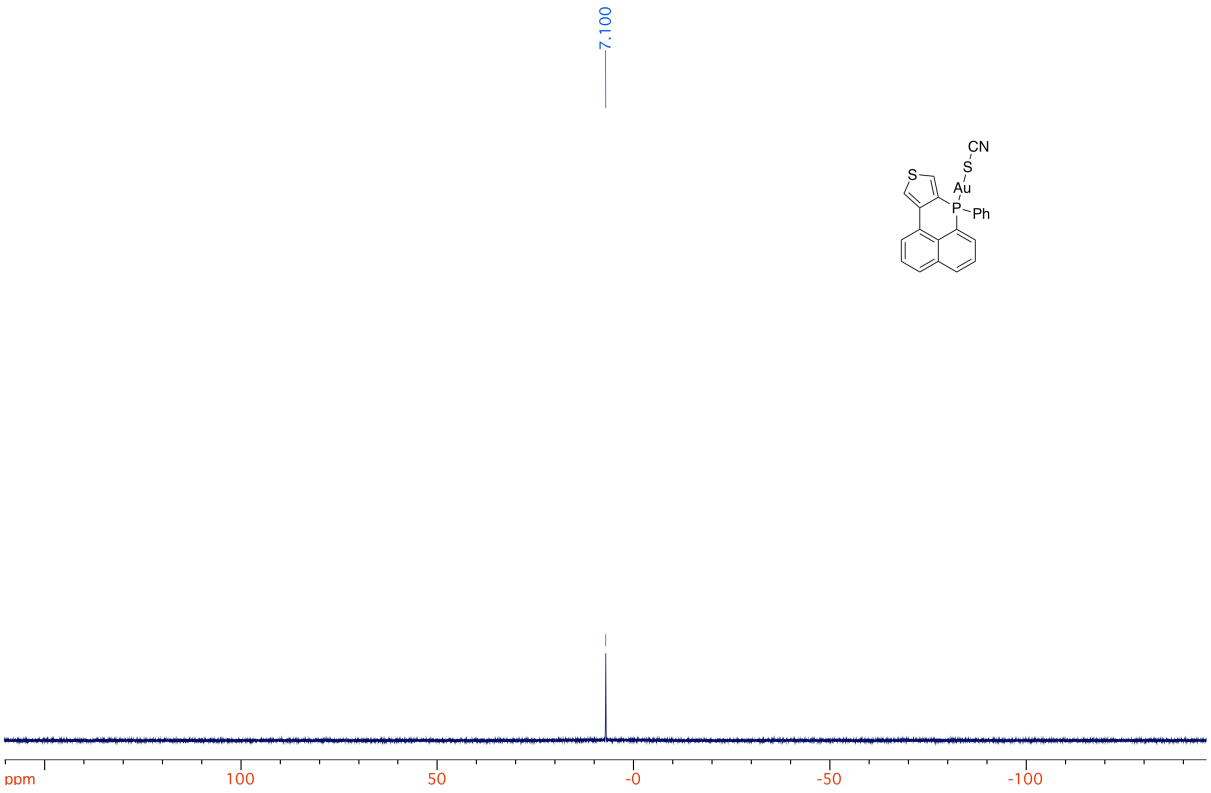
^{1}H NMR (600 MHz, CD_2Cl_2) of compound **3**



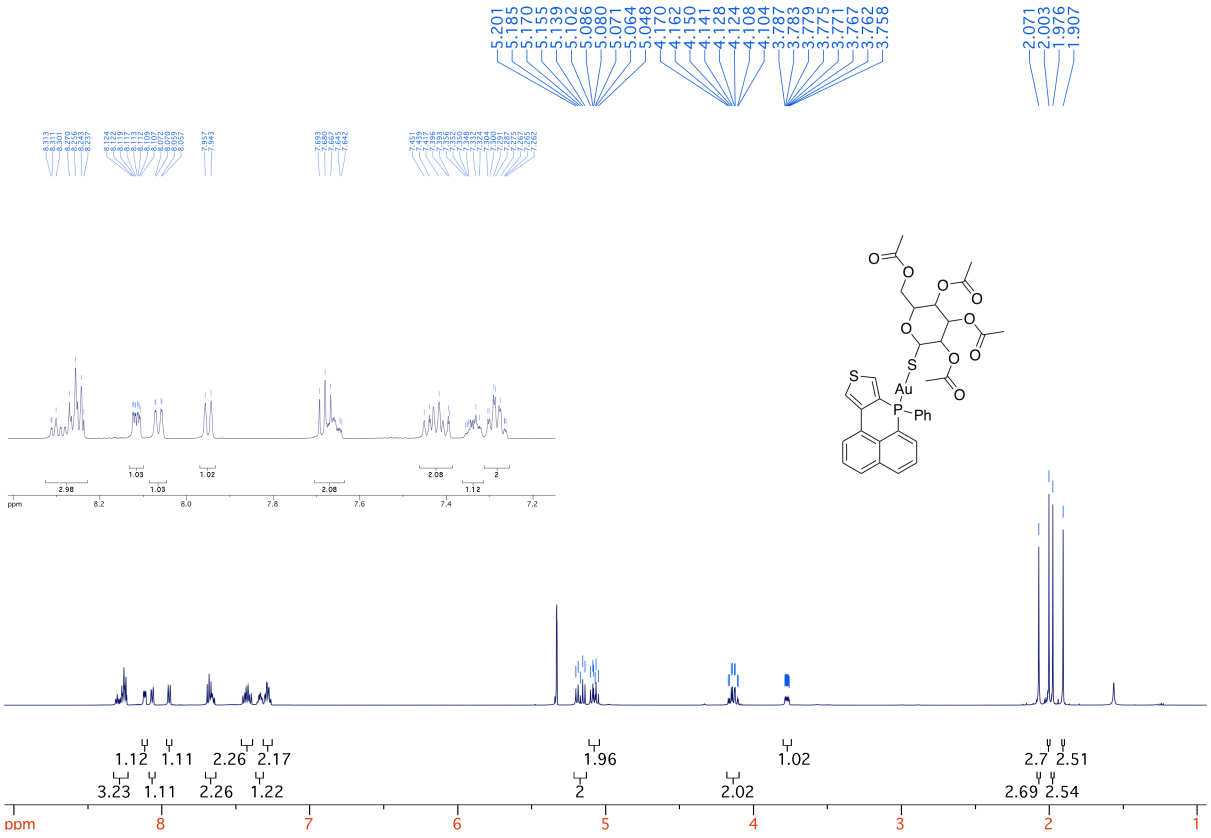
^{13}C{^{1}H}NMR (151 MHz, CD_2Cl_2) of compound **3**



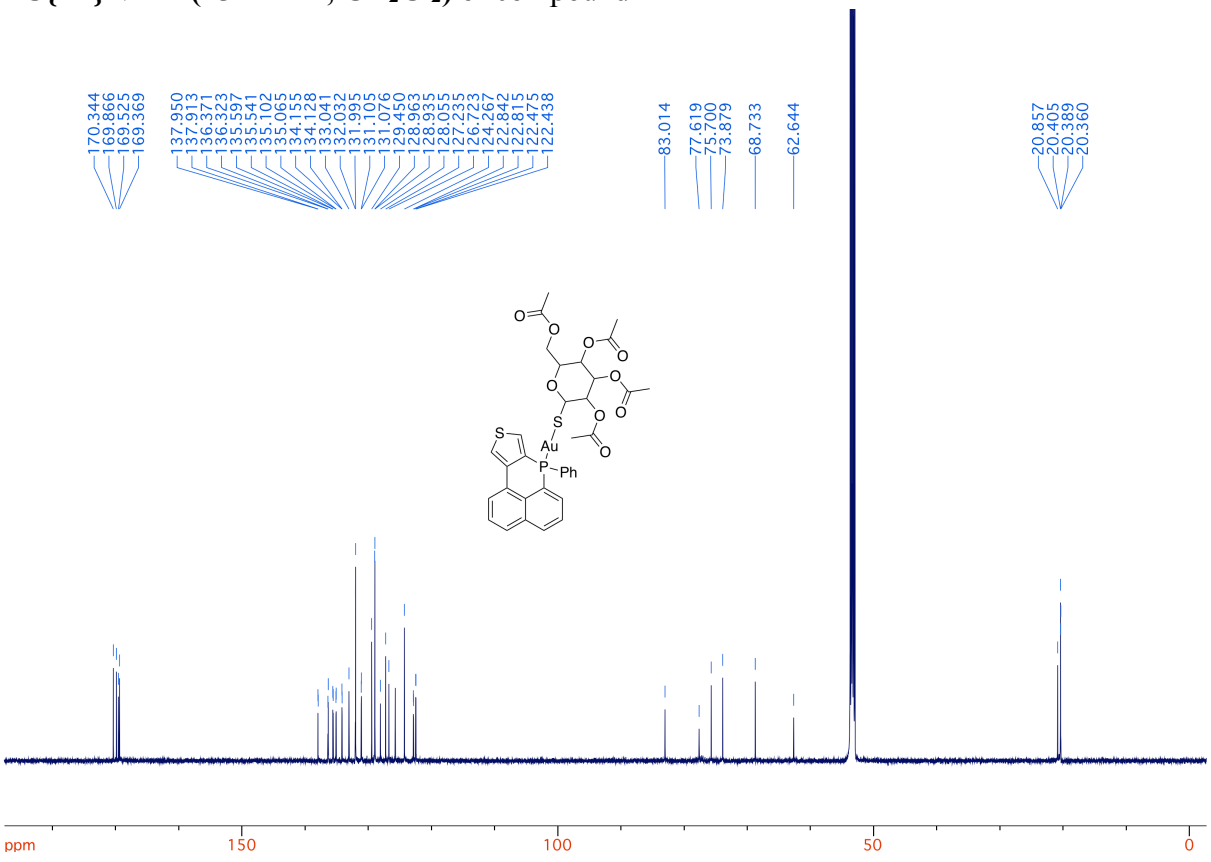
$^{31}P\{^{1}H\}$NMR (101 MHz, CD_2Cl_2) of compound **3**



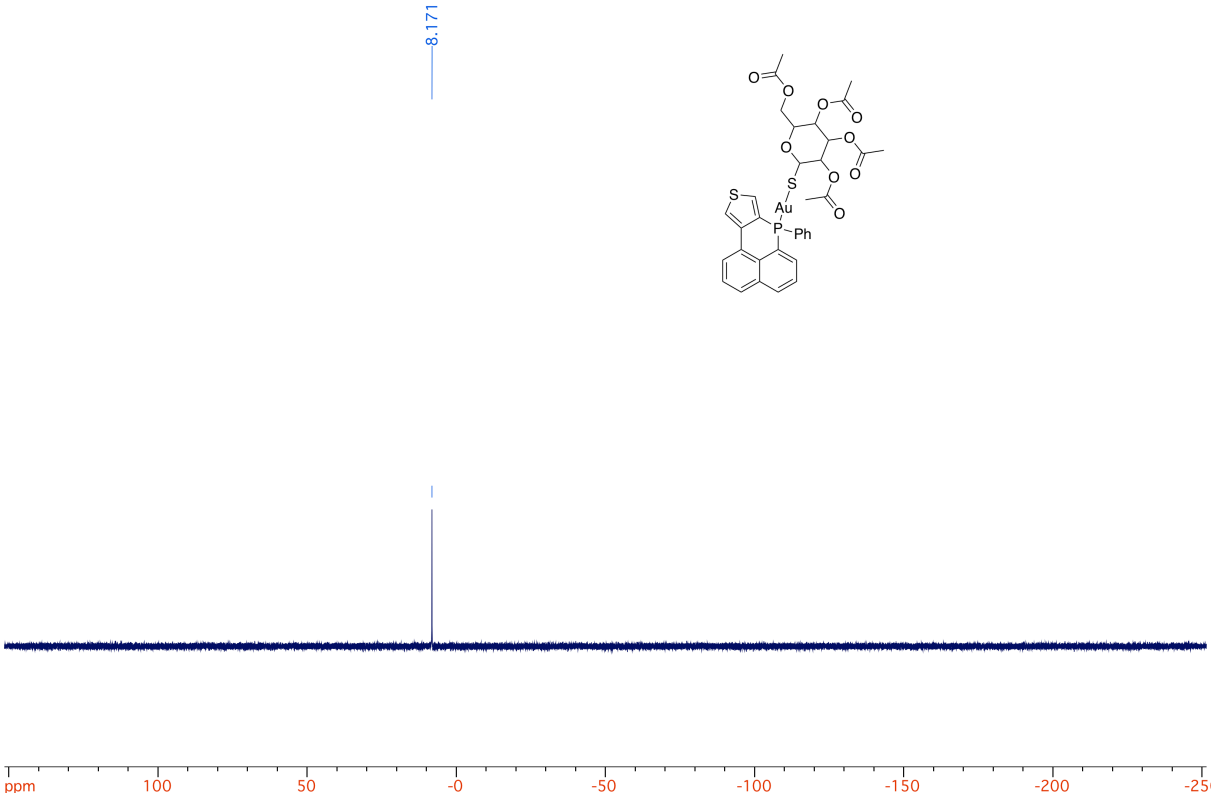
^{1}H NMR (600 MHz, CD_2Cl_2) of compound **4**



^{13}C{^{1}H}NMR (151 MHz, CD_2Cl_2) of compound **4**



$^{31}P\{^{1}H\}$NMR (101 MHz, CD_2Cl_2) of compound **4**



10. Literature

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