Electronic Supplementary Material (ESI) for Dalton Transactions.


# *Gold(I) metallocyclophosphazenes with antibacterial potency and antitumor efficacy. Synergistic antibacterial action of a heterometallic gold and silver-cyclophosphazene.*

*Elena Gascón, Isabel Otal, Sara Maisanaba, María Llana-Ruiz-Cabello, Eva Valero, Guillermo Repetto, Peter G. Jones, Luis Oriol, Josefina Jiménez **

## SUPPORTING INFORMATION

Table of Contents:

## 1. $^{31}P\{^{1}H\}$, $^{1}H$, $^{1}H\{^{31}P\}$, $^{13}C\{^{1}H\}$ APT, HSQC ($^{13}C$-$^{1}H$) NMR spectra of compound 7 in $CDCl_3$.

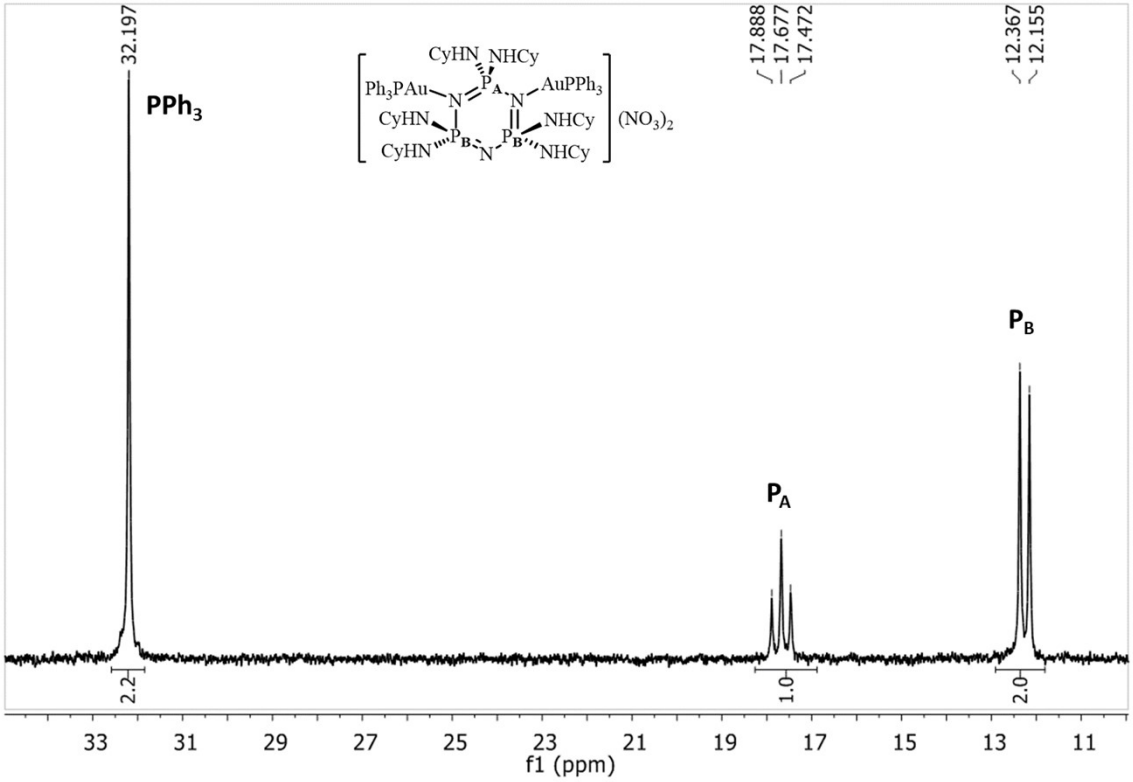



**Figure S1.** $^{31}P\{^{1}H\}$ NMR spectrum of compound **7** measured in $CDCl_3$.

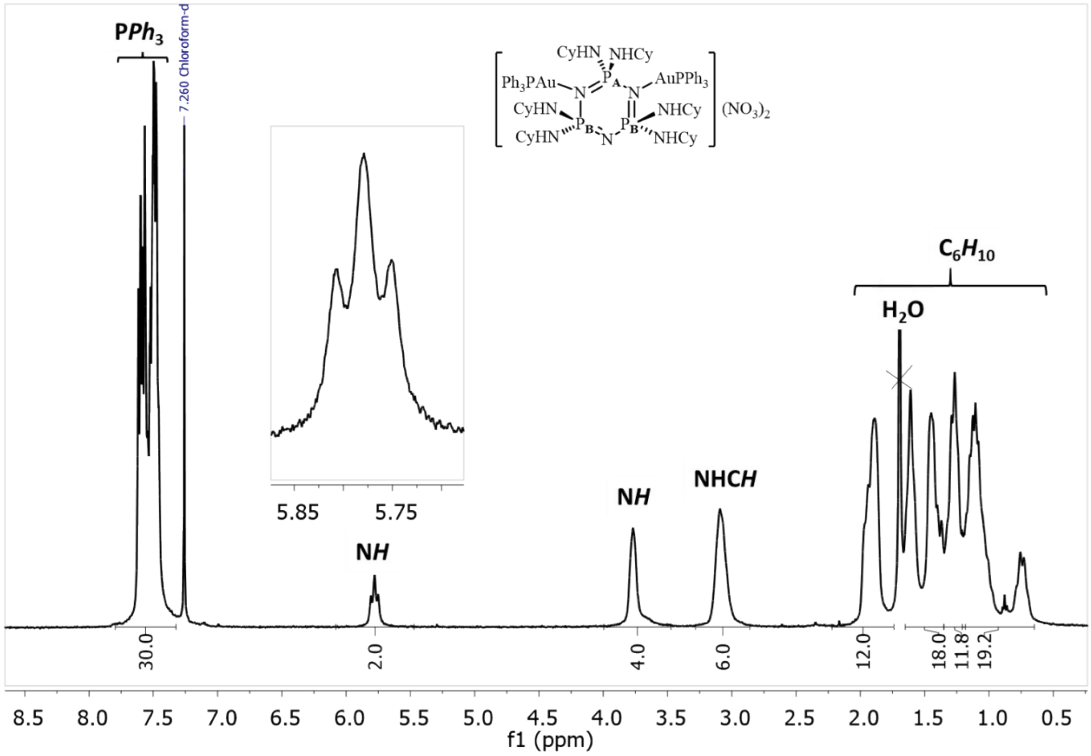



**Figure S2.** $^{1}H$ NMR spectrum of compound **7** measured in $CDCl_3$.

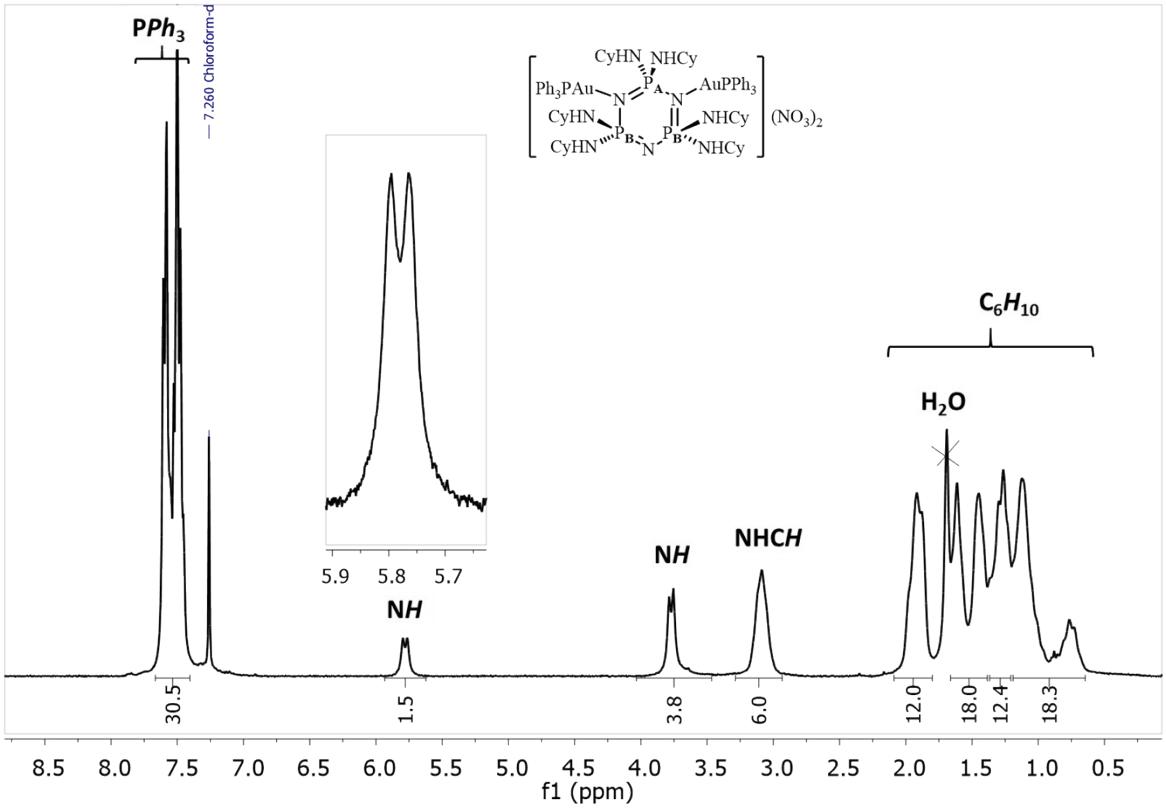



**Figure S3.** $^{1}H\{^{31}P\}$ NMR spectrum of compound **7** measured in $CDCl_3$.

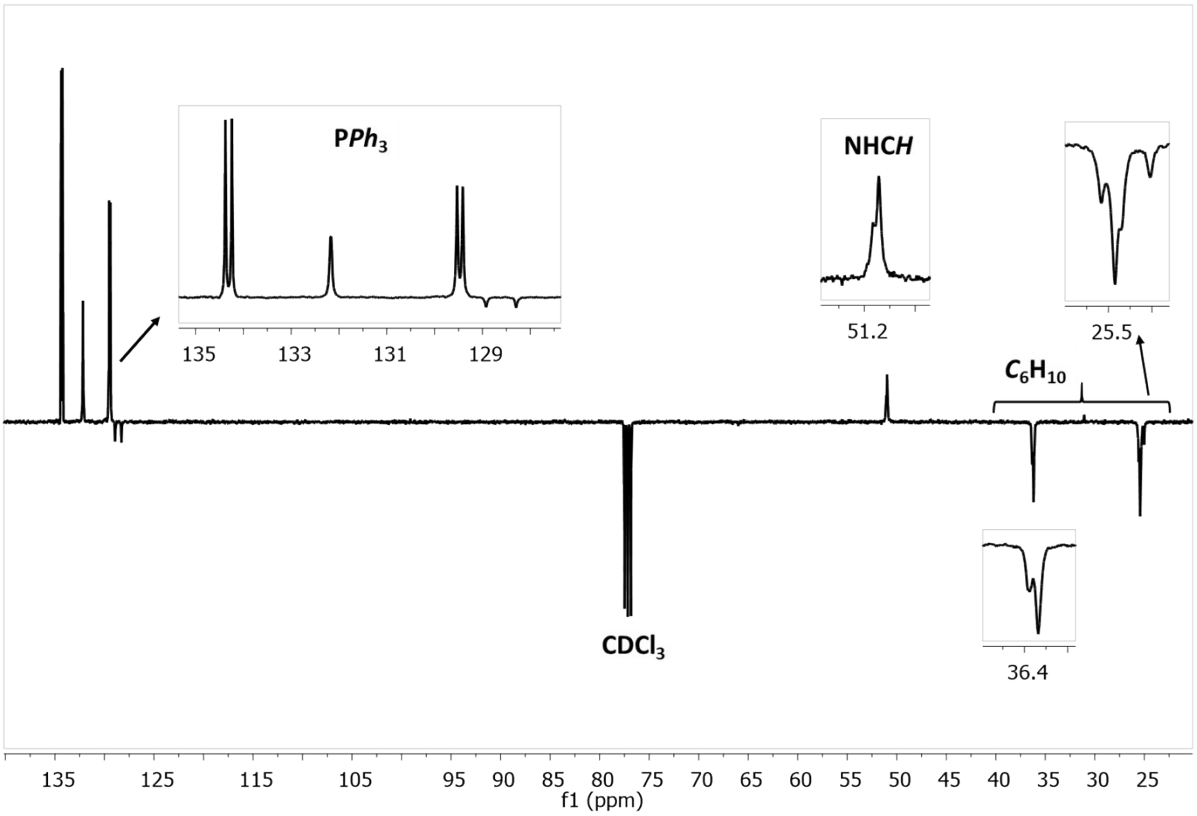



**Figure S4.** $^{13}C\{^{1}H\}$ APT NMR spectrum of compound **7** measured in $CDCl_3$.

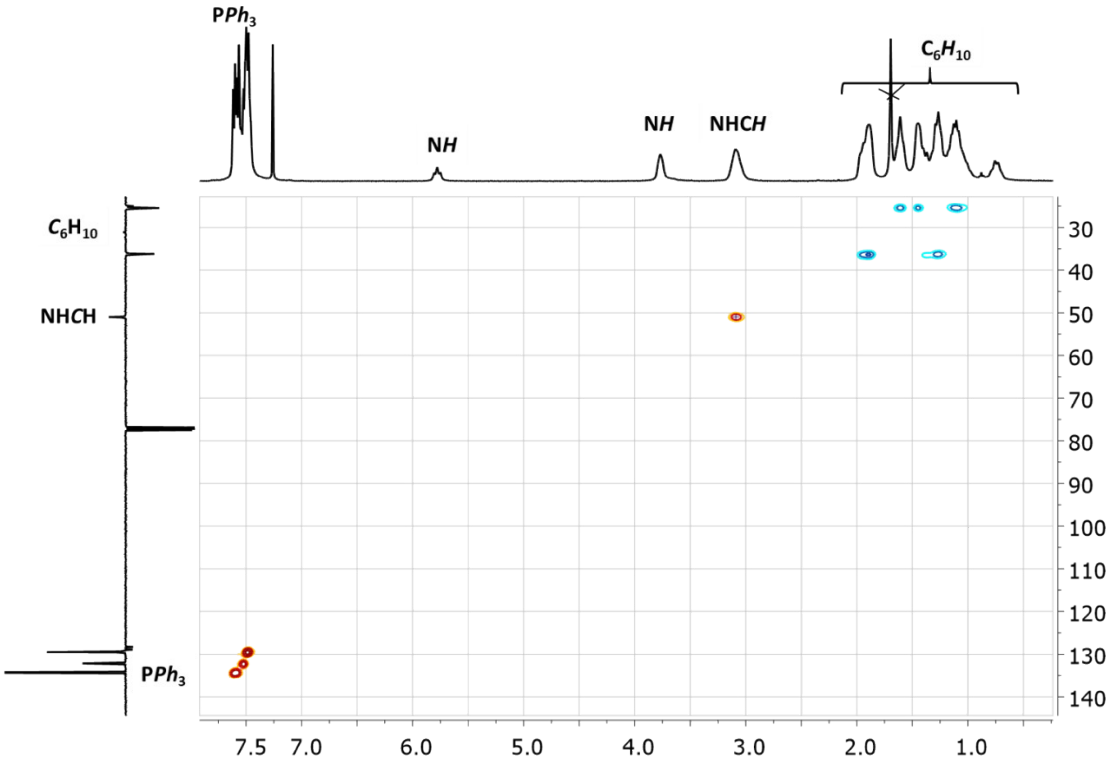



**Figure S5.** HSQC ($^{13}C$-$^{1}H$) NMR spectrum of compound **7** measured in $CDCl_3$.

**2. $^{31}P\{^{1}H\}$, $^{1}H$ NMR spectra of compound 7 measured in DMSO overtime (Figures S6, S7 and S8, S9 respectively).**

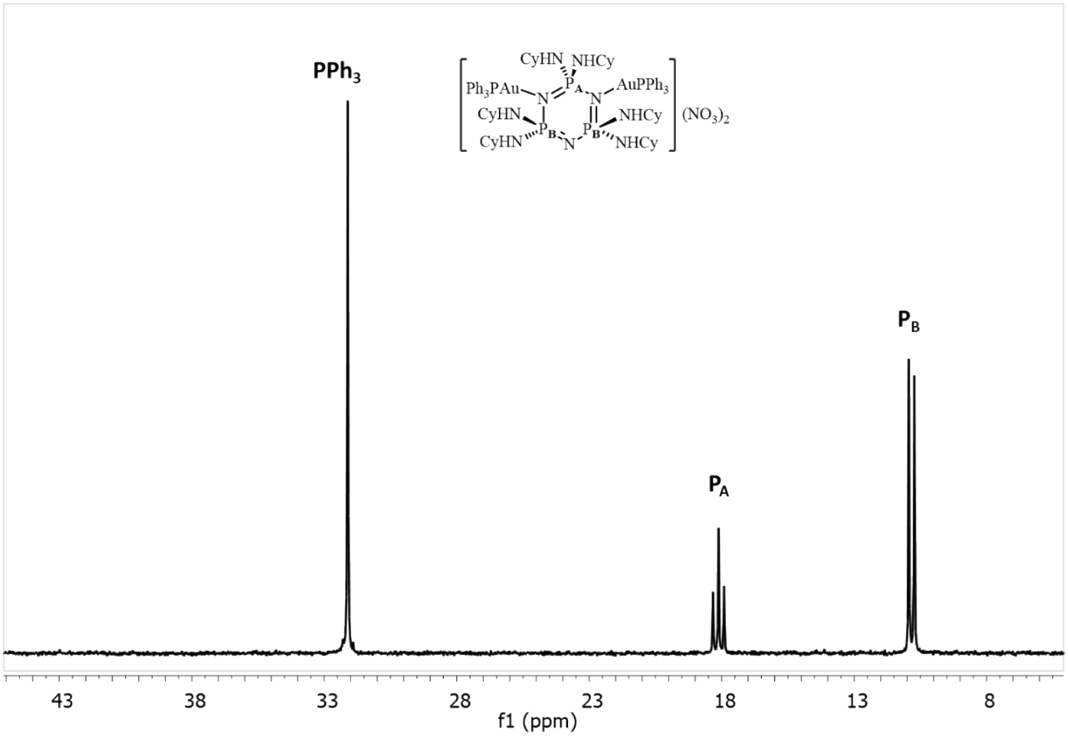



**Figure S6.** $^{31}P\{^{1}H\}$ NMR spectra of compound **7** measured in DMSO

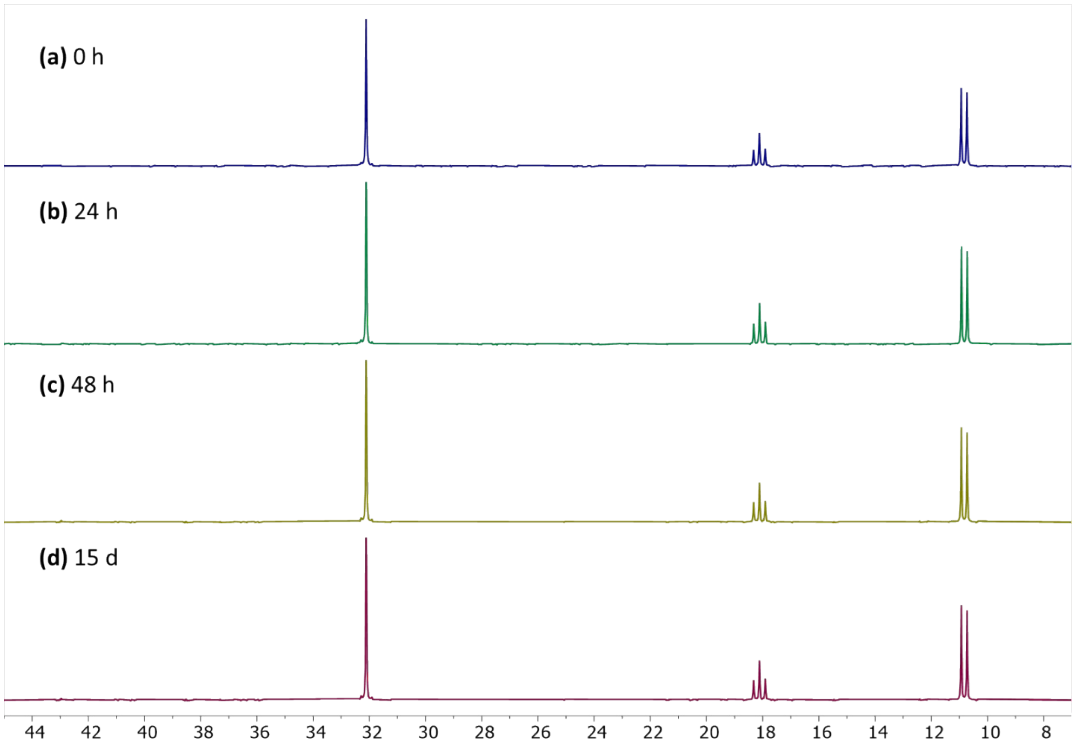



**Figure S7.** $^{31}P\{^{1}H\}$ NMR spectra of compound **7** measured in DMSO overtime

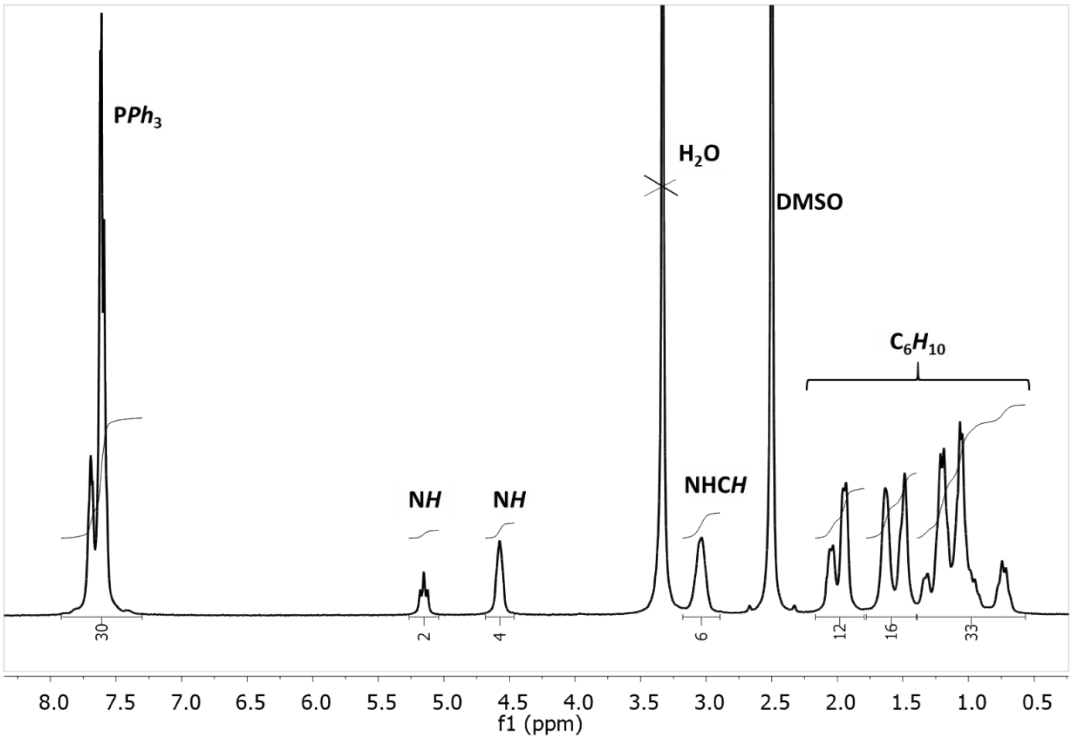



**Figure S8.** $^{1}H$ NMR spectra of compound **7** measured in DMSO

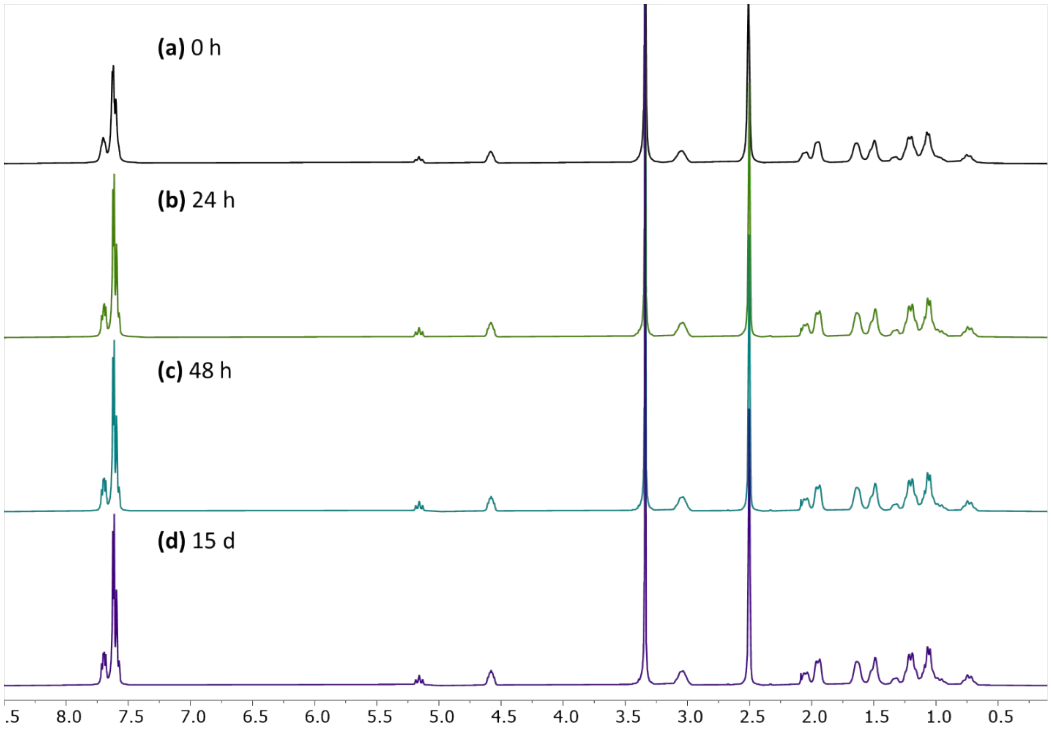



**Figure S9.** $^{1}$H NMR spectra of compound **7** measured in DMSO overtime

**3. $^{31}P\{^{1}H\}$, $^{1}H$, $^{13}C\{^{1}H\}$ APT, HSQC ($^{13}C$-$^{1}H$) NMR spectra of compound 8 in $CDCl_3$ (Figures S10-S13, respectively)**

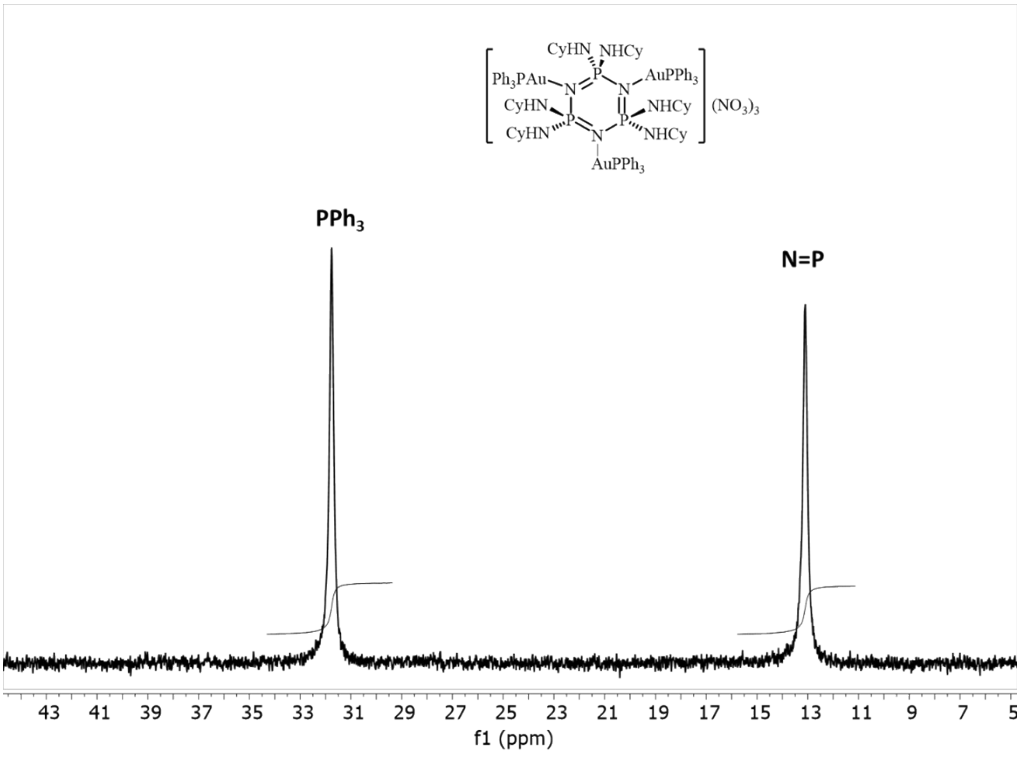



**Figure S10.** $^{31}P\{^{1}H\}$ NMR spectrum of compound **8** measured in $CDCl_3$.

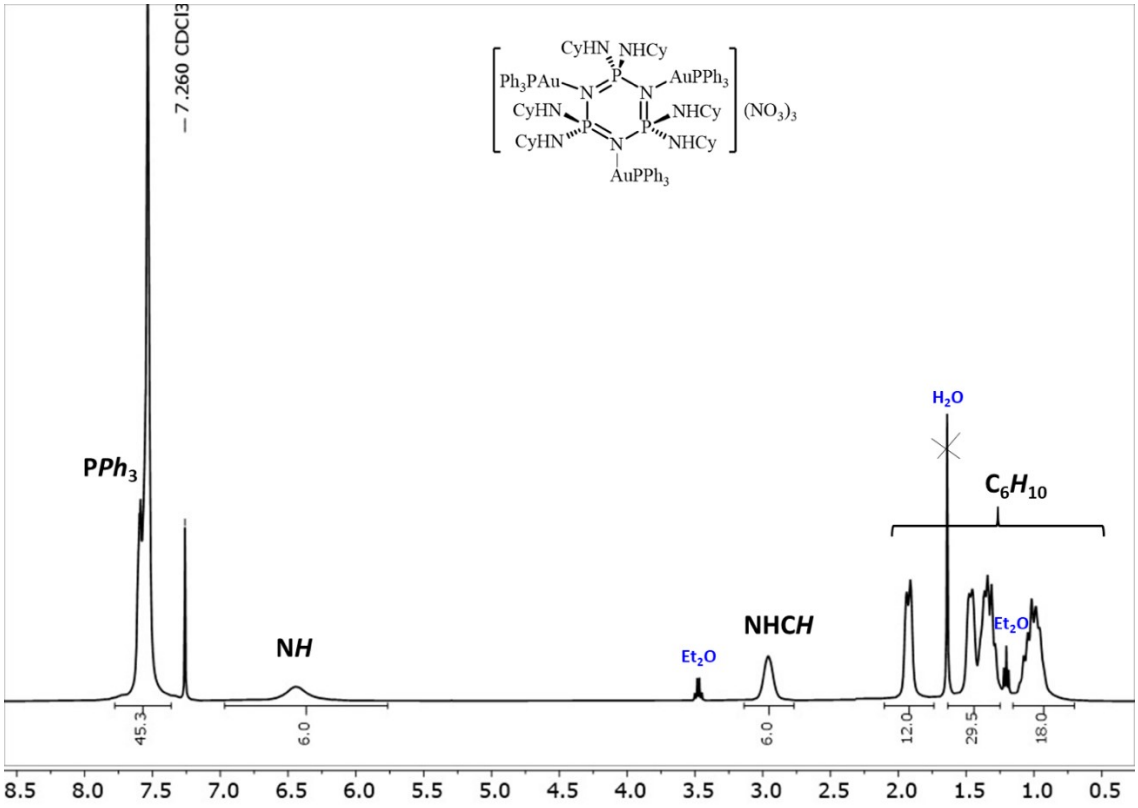



**Figure S11.** $^{1}$H NMR spectrum of compound **8** measured in $CDCl_3$.

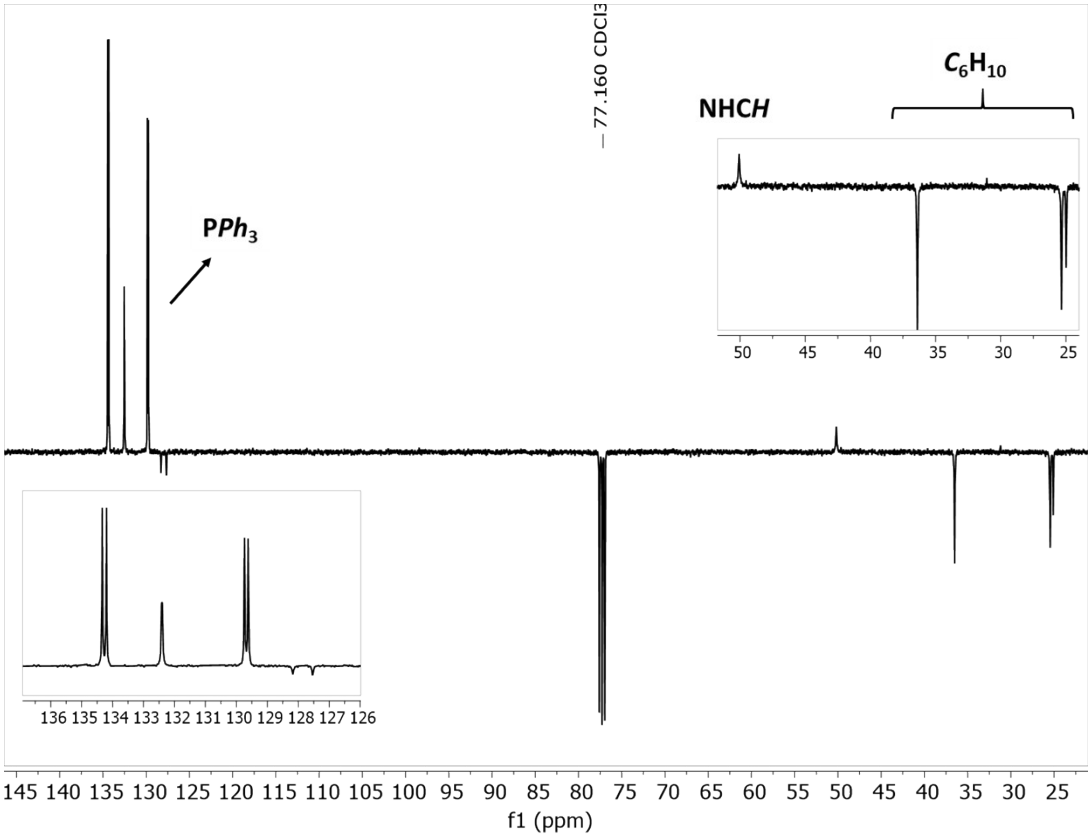



**Figure S12.** $^{13}$C{$^{1}$H} APT NMR spectrum of compound **8** measured in $CDCl_3$.

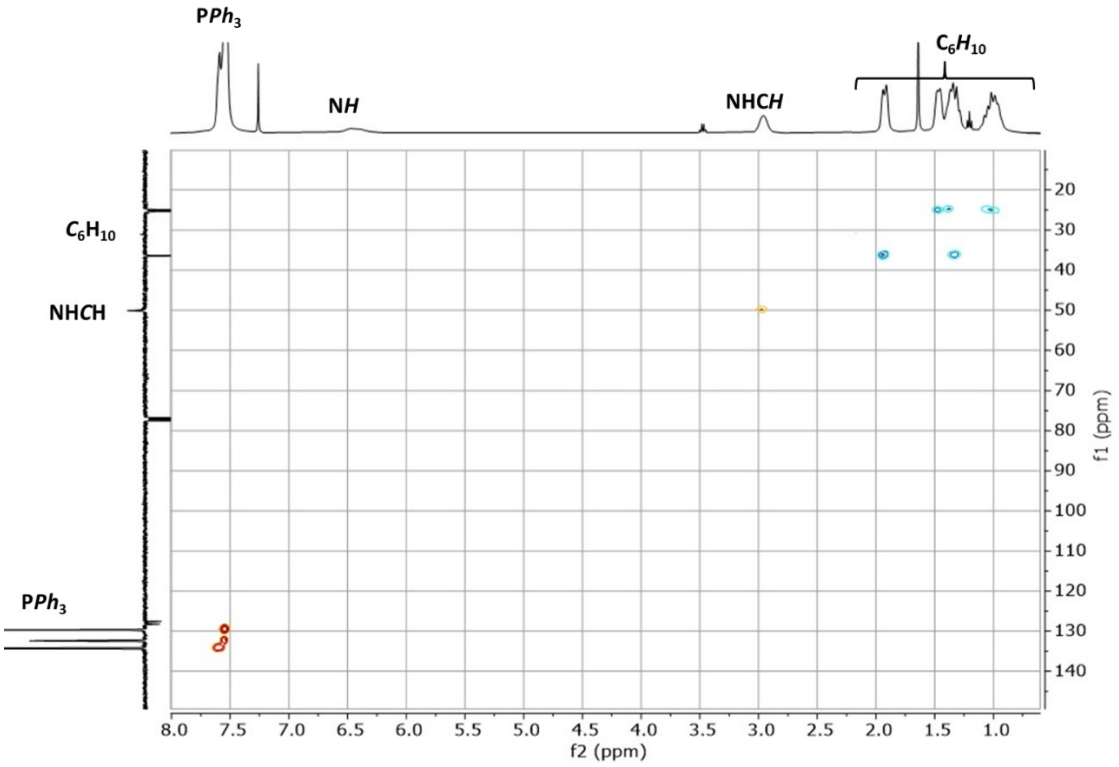



**Figure S13.** HSQC ($^{13}C$-$^{1}H$) NMR spectrum of compound **8** measured in $CDCl_3$.

## 4. $^{31}P\{^{1}H\}$ and $^{1}H$ NMR spectra of compound 8 in DMSO (Figures S14 and S15, respectively)

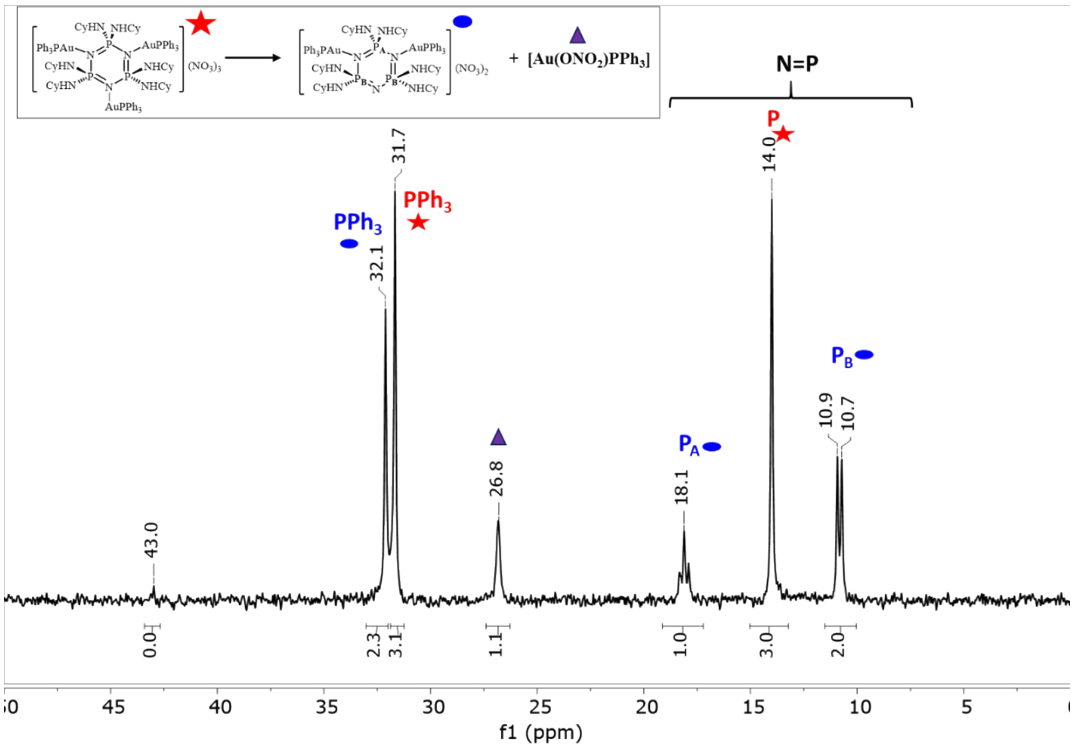



**Figure S14.** $^{31}P\{^{1}H\}$ NMR spectrum of compound **8** measured in DMSO.

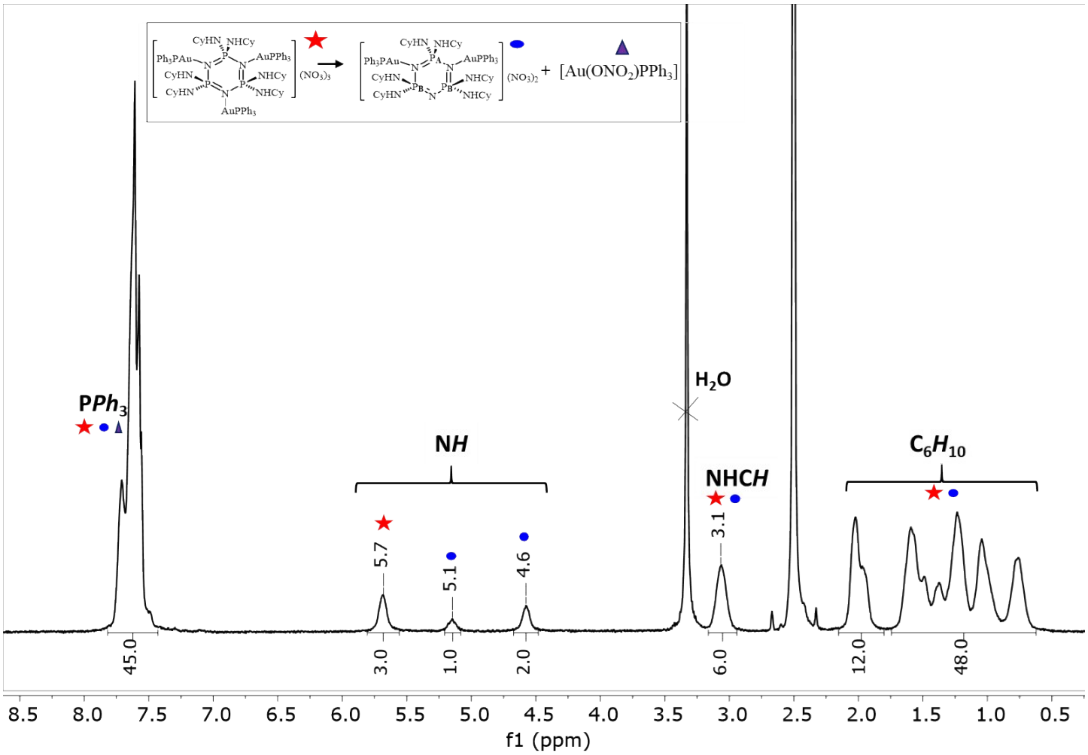



**Figure S15.** $^{1}$H NMR spectrum of compound **8** measured in DMSO.

## 5. $^{31}$P{$^{1}$H} NMR spectrum of compound 8 in DMSO after 7 days in solution (Figure S16)

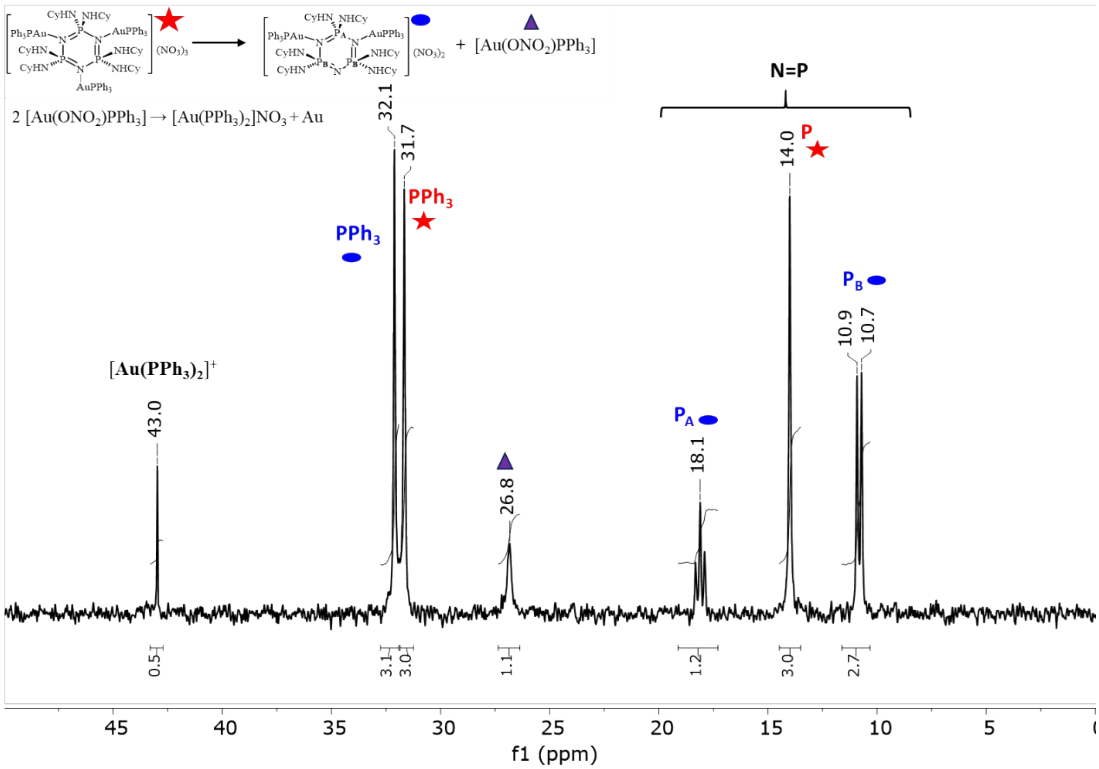



**Figure S16.** $^{31}$P{$^{1}$H} NMR spectrum of compound **8** measured in DMSO after 7 days.

6. **$^{31}P\{^{1}H\}$ NMR spectrum of starting product $[Au(ONO_2)PPh_3]$ in DMSO and those after 48 h and 7 days in solution (Figure S17-S19).**

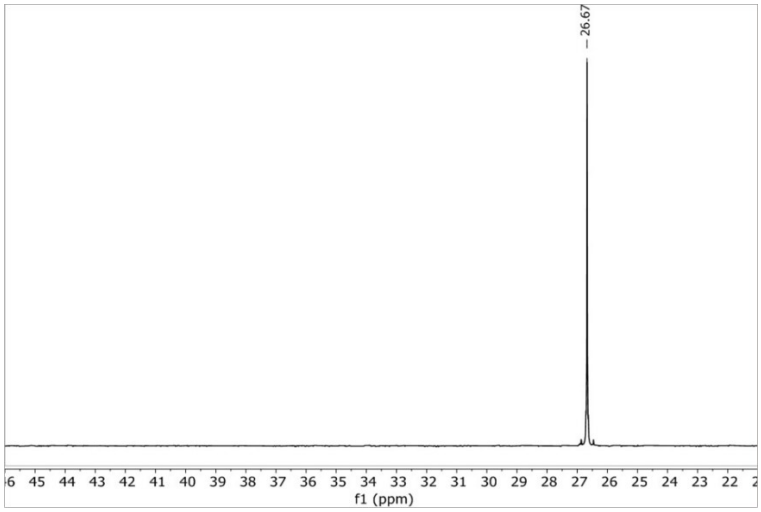



**Figure S17.** $^{31}P\{^{1}H\}$ NMR spectrum of **$[Au(ONO_2)PPh_3]$** in DMSO.

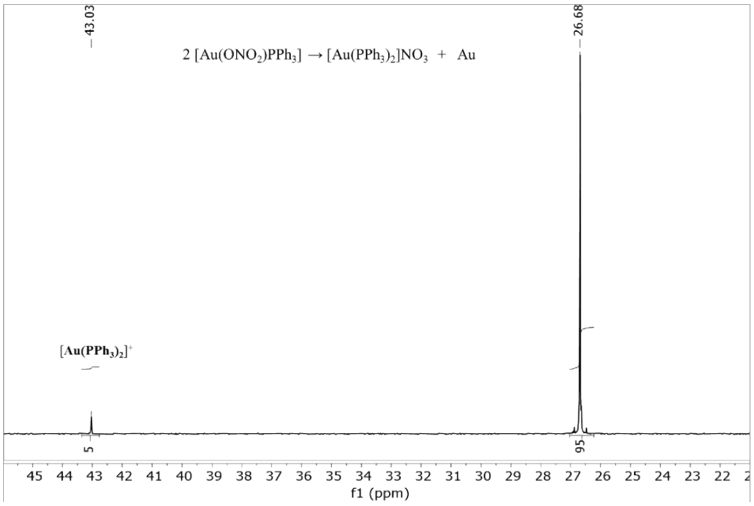



**Figure S18.** $^{31}P\{^{1}H\}$ NMR spectrum of **$[Au(ONO_2)PPh_3]$** in DMSO after 48 h.

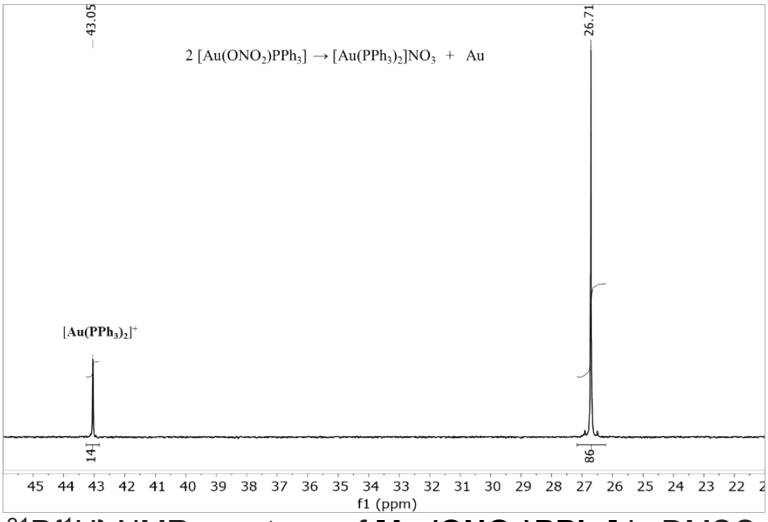



**Figure S19.** $^{31}P\{^{1}H\}$ NMR spectrum of **$[Au(ONO_2)PPh_3]$** in DMSO after 7 days.

## 7. $^{31}P\{^{1}H\}$ and $^{1}H$ NMR spectra of compound 13 in $CDCl_3$ (Figures S20 and S21, respectively)

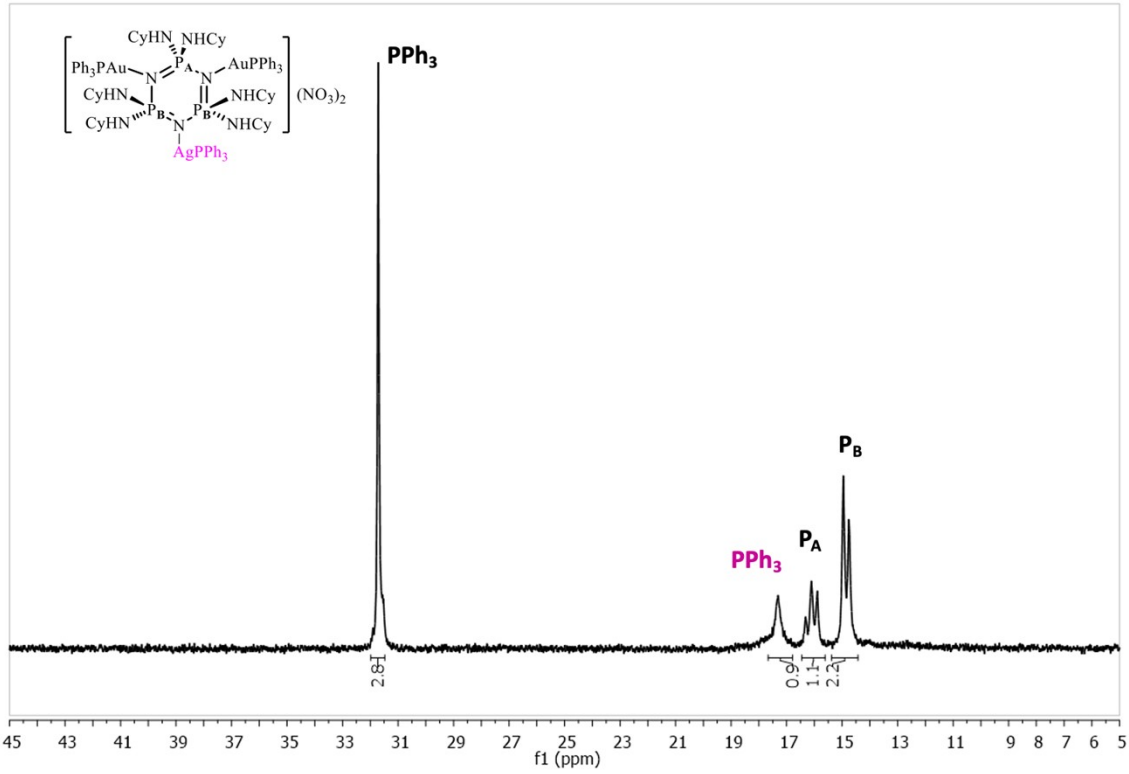



**Figure S20.** $^{31}P\{^{1}H\}$ NMR spectrum of compound **13** measured in $CDCl_3$.

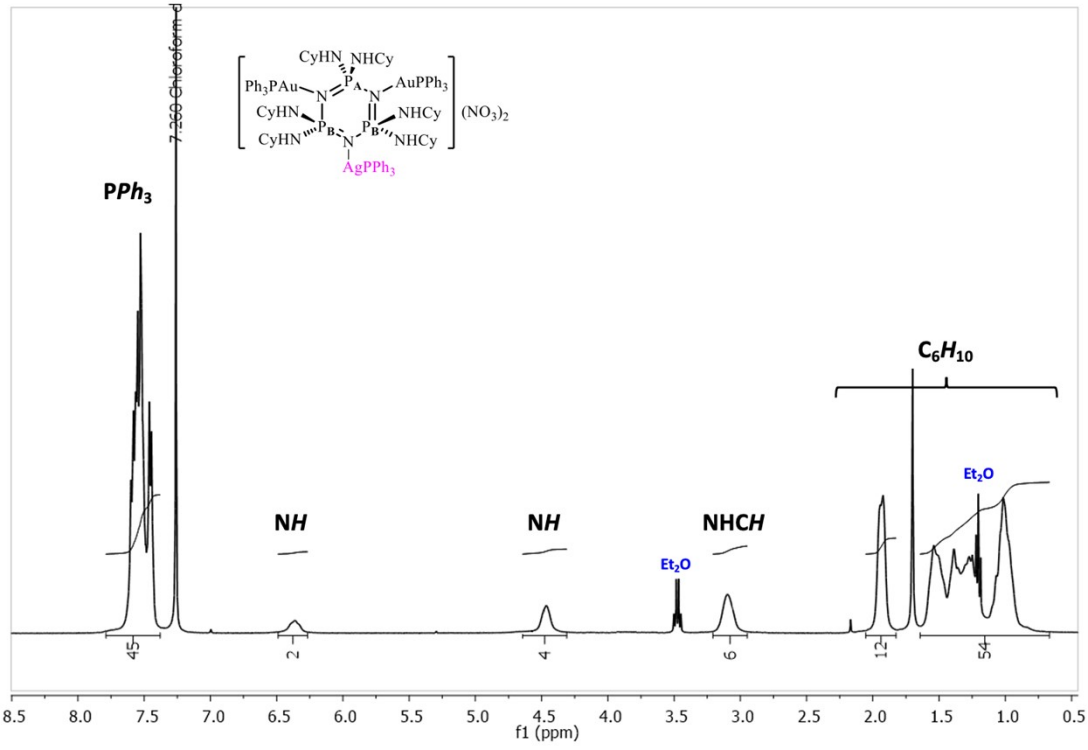



**Figure S21.** $^{1}H$ NMR spectrum of compound **13** measured in $CDCl_3$.

## 8. $^{31}P\{^{1}H\}$ and $^{1}H$ NMR spectra of compound 13 measured in DMSO over time (Figures S22-S25)

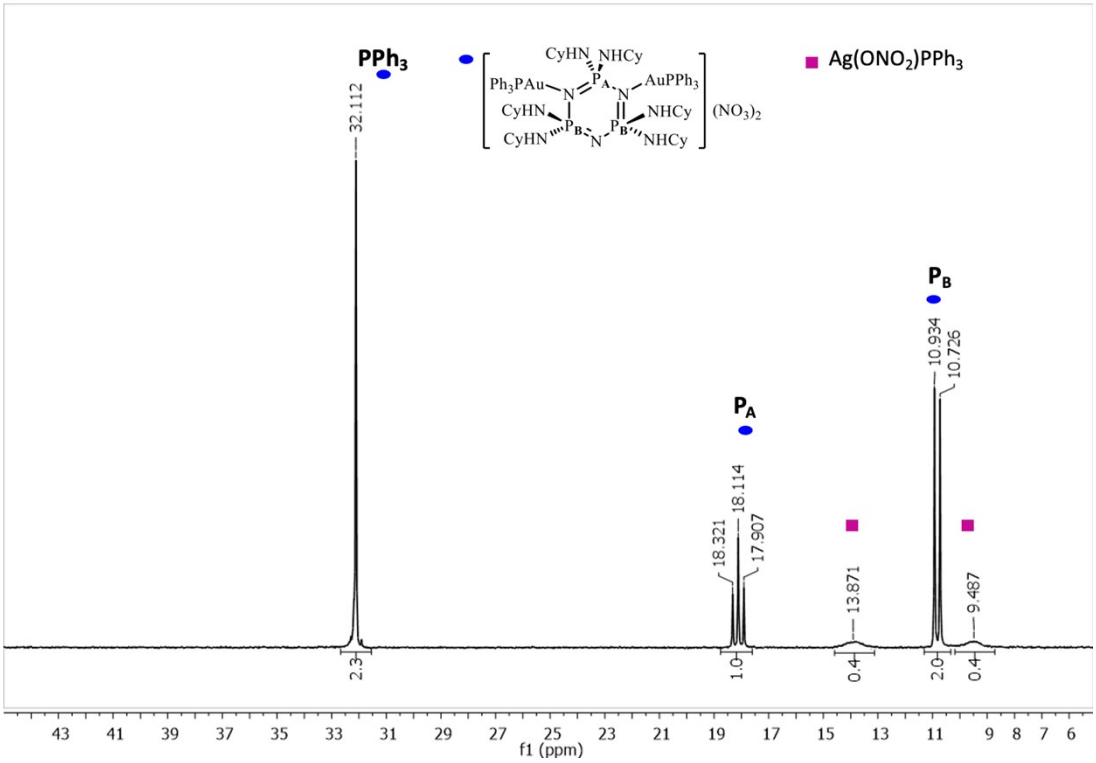



**Figure S22.** $^{31}P\{^{1}H\}$ NMR spectrum of compound **13** measured in DMSO.

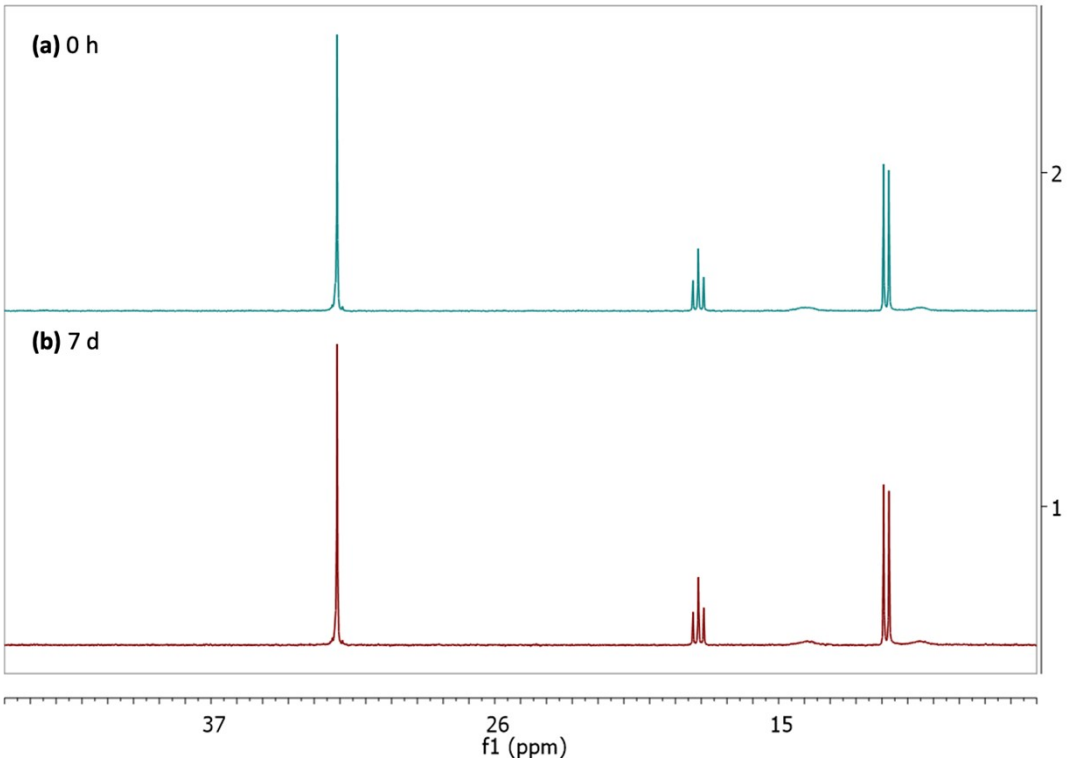



**Figure S23.** $^{31}P\{^{1}H\}$ NMR spectra of compound **13** measured in DMSO over time

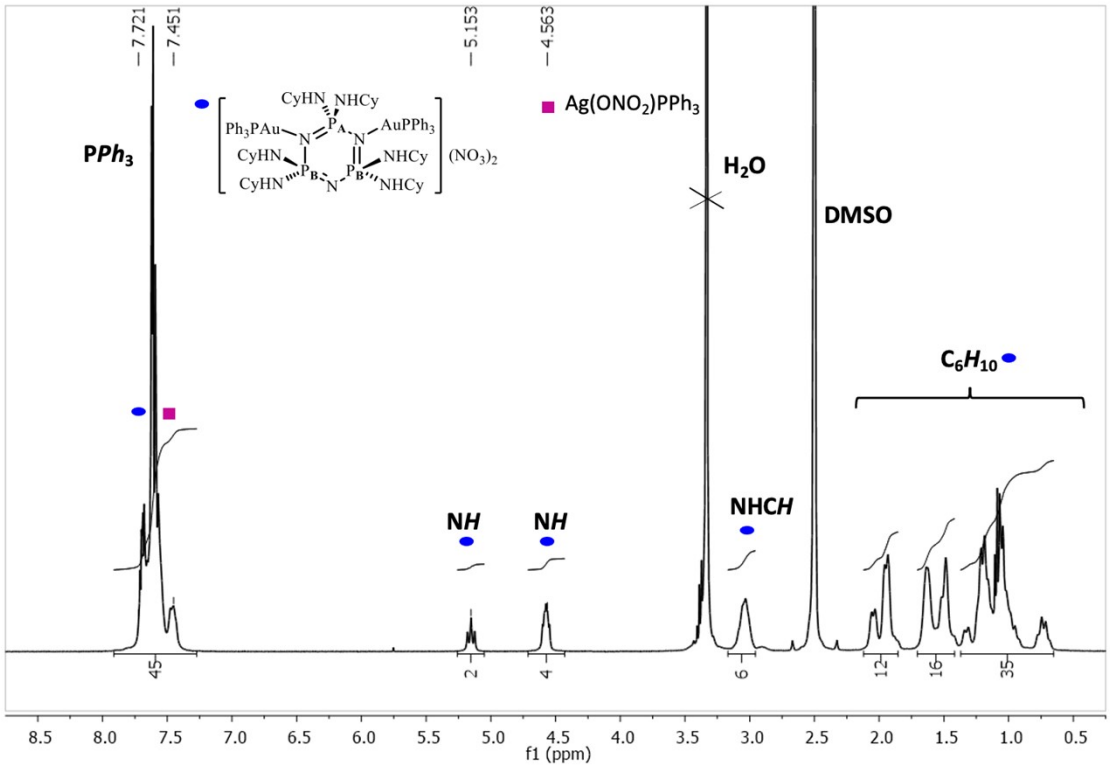



**Figure S24.** $^{1}$H NMR spectrum of compound **13** measured in DMSO.

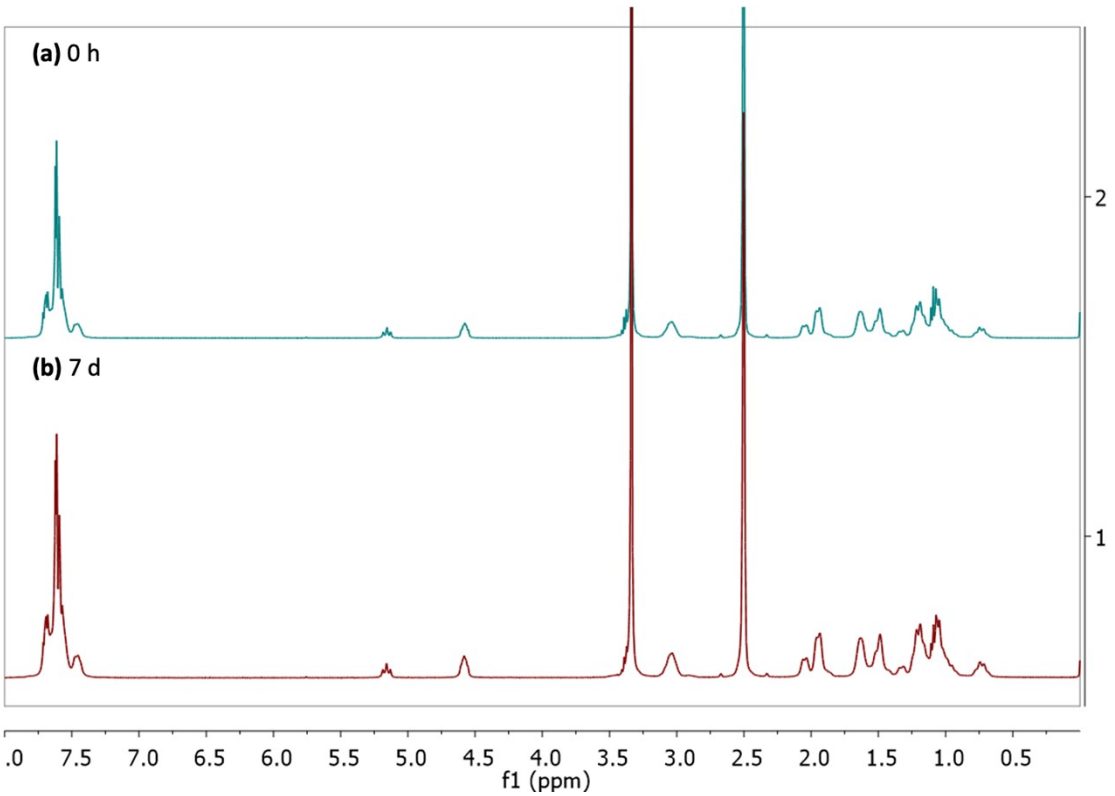



**Figure S25.** $^{1}$H NMR spectrum of compound **13** measured in DMSO over time.

## 9. X-Ray Studies. Tables containing details of data collection and structure refinement (Table S1) and selected bond lengths and angles (Table S2) for compound 7

**Table S1.** Selected bond lengths [Å] and angles [°], and ring torsion angles [°] for compound **7**.$C_2H_4Cl_2$

| | | | |
|---|---|---|---|
| Au(1)-N(3) | 2.0746(18) | N(2)-P(2)-N(7) | 114.43(11) |
| Au(1)-P(5) | 2.2310(6) | N(6)-P(2)-N(7) | 104.47(11) |
| Au(2)-N(1) | 2.0785(18) | N(2)-P(2)-N(1) | 110.96(10) |
| Au(2)-P(4) | 2.2302(6) | N(6)-P(2)-N(1) | 111.81(11) |
| P(1)-N(4) | 1.620(2) | N(7)-P(2)-N(1) | 107.49(10) |
| P(1)-N(5) | 1.621(2) | N(2)-P(3)-N(9) | 112.20(11) |
| P(1)-N(3) | 1.6293(19) | N(2)-P(3)-N(8) | 111.03(10) |
| P(1)-N(1) | 1.6350(19) | N(9)-P(3)-N(8) | 107.30(11) |
| P(2)-N(2) | 1.5843(19) | N(2)-P(3)-N(3) | 110.57(10) |
| P(2)-N(6) | 1.625(2) | N(9)-P(3)-N(3) | 105.77(10) |
| P(2)-N(7) | 1.636(2) | N(8)-P(3)-N(3) | 109.78(10) |
| P(2)-N(1) | 1.6465(19) | P(1)-N(1)-P(2) | 129.33(11) |
| P(3)-N(2) | 1.5800(19) | P(1)-N(1)-Au(2) | 110.99(10) |
| P(3)-N(9) | 1.623(2) | P(2)-N(1)-Au(2) | 118.84(10) |
| P(3)-N(8) | 1.635(2) | P(3)-N(2)-P(2) | 126.17(12) |
| P(3)-N(3) | 1.6524(19) | P(1)-N(3)-P(3) | 126.06(11) |
| N(3)-Au(1)-P(5) | 176.28(5) | P(1)-N(3)-Au(1) | 114.18(10) |
| N(1)-Au(2)-P(4) | 178.65(5) | P(3)-N(3)-Au(1) | 117.94(10) |
| N(4)-P(1)-N(5) | 101.03(10) | N(3)-P(1)-N(1)-P(2) | -0.79(18) |
| N(4)-P(1)-N(3) | 108.90(10) | N(2)-P(2)-N(1)-P(1) | 2.61(19) |
| N(5)-P(1)-N(3) | 115.44(11) | N(3)-P(3)-N(2)-P(2) | 33.55(18) |
| N(4)-P(1)-N(1) | 113.37(10) | N(1)-P(2)-N(2)-P(3) | -20.99(18) |
| N(5)-P(1)-N(1) | 109.40(10) | N(1)-P(1)-N(3)-P(3) | 16.08(17) |
| N(3)-P(1)-N(1) | 108.67(9) | N(2)-P(3)-N(3)-P(1) | -30.98(18) |
| N(2)-P(2)-N(6) | 107.57(11) | | |

Symmetry transformations used to generate equivalent atoms: #1 -x+3/2,y-1/2,-z+1/2

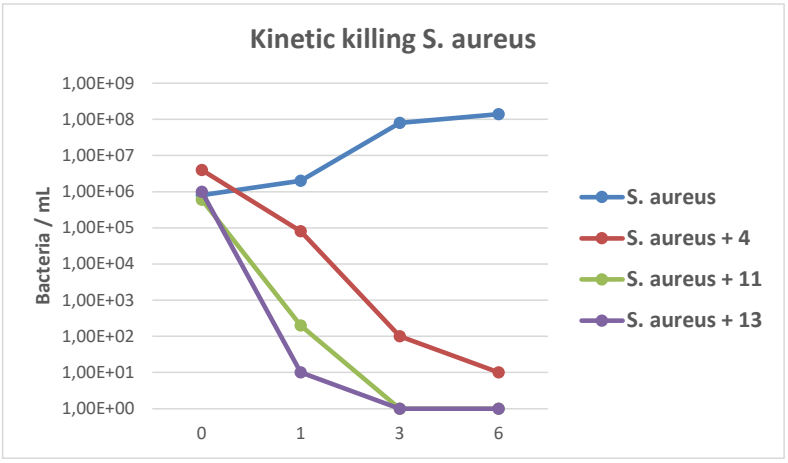
**Table S2.** Crystal data and structure refinement for compound **7**.$C_2H_4Cl_2$ [a]

| | | |
|---|---|---|
| Identification code | roset | |
| Empirical formula | $C_{74}H_{106}Au_2Cl_2N_{11}O_6P_5$ | |
| Formula weight | 1865.37 | |
| Temperature | 143(2) K | |
| Wavelength | 0.71073 Å | |
| Crystal system | Monoclinic | |
| Space group | $P2_1/n$ | |
| Unit cell dimensions | a = 20.0011(7) Å | α= 90° |
| | b = 18.7057(6) Å | β= 99.277(2)° |
| | c = 21.6215(8) Å | γ = 90° |
| Volume | 7983.5(5) Å$^3$ | |
| Z | 4 | |
| Density (calculated) | 1.552 Mg/m$^3$ | |
| Absorption coefficient | 3.895 mm$^{-1}$ | |
| F(000) | 3768 | |
| Crystal size | 0.25 x 0.25 x 0.16 mm$^3$ | |
| Theta range for data collection | 1.287 to 30.037° | |
| Index ranges | -28<=h<=28, -26<=k<=26, -30<=l<=30 | |
| Reflections collected | 171009 | |
| Independent reflections | 23338 [R(int) = 0.0539] | |
| Completeness to theta = 30.000° | 99.9 % | |
| Absorption correction | Semi-empirical from equivalents | |
| Max. and min. transmission | 0.928 and 0.789 | |
| Refinement method | Full-matrix least-squares on $F^2$ | |
| Data / restraints / parameters | 23338 / 123 / 936 | |
| Goodness-of-fit on $F^2$ | 0.965 | |
| Final R indices [I>2sigma(I)] | R1 = 0.0259, wR2 = 0.0518 | |
| R indices (all data) | R1 = 0.0436, wR2 = 0.0559 | |
| Largest diff. peak and hole | 1.314 and -0.696 e.Å$^{-3}$ | |

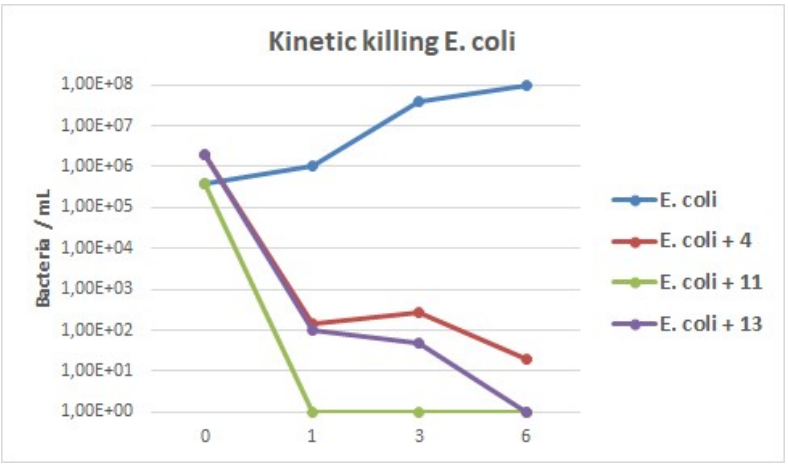
[a] The solvent molecule is disordered. Despite the use of appropriate restraints, the dimensions and the U values of this molecule are unsatisfactory and should be interpreted with caution.

**10. Bactericidal activity of 4, 11 and 13 at 2 x MIC by Kinetic killing assay against *S. aureus, E. coli* and *P. aeruginosa* strains.**

**(a)**




**(b)**




**(c)**

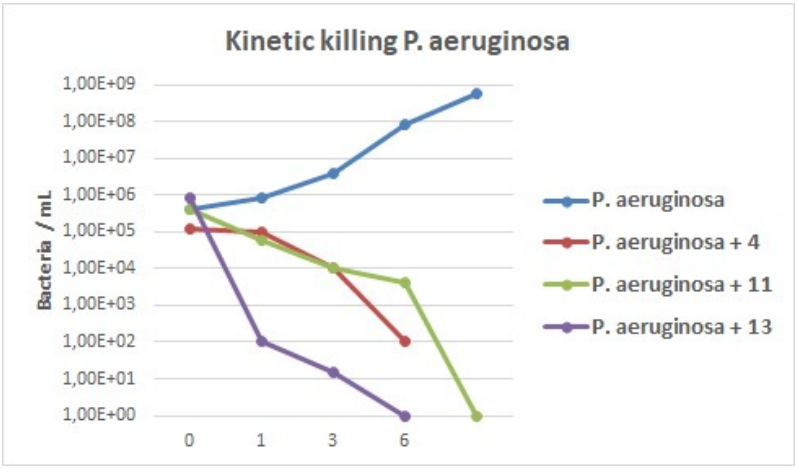



**Figure S20.** Bactericidal activity of **4**, **11** and **13** at 2xMIC by Kinetic killing assay against *S. aureus, E. coli* and *P. aeruginosa* strains. At each time point (hours), dilutions of the bacterial cultures were plated onto LB plates and the number of colony forming units were used to calculate the bacteria concentration. Bacteria control incubated in the absence of compounds continued to grow as expected.

## 11. Expected $IC_{50}$ after 24 h for metallophosphazenes and their precursors exposure on MCF7, HepG2 and HDF cells under microscope analysis (Table S3).

**Table S3.** Expected $IC_{50}$(μM) after 24 h for metallophosphazenes and their precursors exposure on MCF7, HepG2 and HDF cells under microscope analysis.

| Compound | MCF7 | HepG2 | HDF |
|---|---|---|---|
| $N_3P_3(NHCy)_6$ **(phos-1)** | >25 | >25 | - |
| $[N_3P_3(NHCy)_6\{AuCl\}]$ (**1**) | 4-6 | 2-4 | - |
| $[N_3P_3(NHCy)_6\{Au(C_6F_5)\}_2]$ (**4**) | 2-4 | 1-2 | 6-8 |
| $[N_3P_3(NHCy)_6\{Au(PPh_3)\}](NO_3)$ (**6**) | 2-4 | 2-4 | - |
| $[N_3P_3(NHCy)_6\{Au(PPh_3)\}_2](NO_3)_2$ (**7**) | 2-4 | 2-4 | 4-6 |
| $[N_3P_3(NHCy)_6\{Au(PPh_3)\}_3](NO_3)_3$ (**8**) | 2-4 | 1-2 | 2-4 |
| $[Au(ONO_2)PPh_3]$ | 4-6 | 4-6 | - |
| $[N_3P_3(NHCy)_6\{Au(PPh_2Me)\}](NO_3)$ (**9**) | 4-6 | 4-6 | - |
| $[N_3P_3(NHCy)_6\{Au(PPh_2Me)\}_2](NO_3)_2$ (**10**) | 2-4 | 2-4 | 4-6 |
| $[N_3P_3(NHCy)_6\{Au(PPh_2Me)\}_3](NO_3)_3$ (**11**) | 2-4 | 4-6 | - |
| $[N_3P_3(NHCy)_6\{AuTPA\}_2](TfO)_2$ (**12**) | 6-8 | 4-6 | - |
| [AuCl(TPA)] | 6-8 | 6-8 | - |
| $N_3P_3(NHCy)_6\{Au(PPh_3)\}_2\{Ag(PPh_3)\}](NO_3)_3$ (**13**) | 2-4 | 2-4 | 2-4 |