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Water-Soluble (Phosphane)gold(I) Complexes – Applications as Recyclable Catalysts in a Three-Component Coupling Reaction and as Antimicrobial and Anticancer Agents

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Dedicated to Professor Emeritus Martin A. Bennett[‡]

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Water-soluble compounds of the type [AuCl(PR_3)] with alkyl-bis(*m*-sulfonated-phenyl) ($mC_6H_4SO_3Na)_2$ and dialkyl-(*m*-sulfonated-phenyl) ($mC_6H_4SO_3Na$) (R = *n*Bu, Cp) phosphanes have been prepared. Dialkylphosphane compounds generate water-soluble nanoparticles of 10–15 nm radius when dissolved in water. These air-stable complexes have been evaluated as catalysts in the synthesis of propargylamines by a three-component coupling reaction of aldehydes, amines, and alkynes in water. The antimicrobial activity of the new complexes against gram-positive and gram-negative bacteria and yeast has been evaluated. The new compounds display moderate to high antibacterial activity. The more lipophilic compounds are also potent against fungi. Their cytotoxic properties have been analyzed in vitro by utilizing human Jurkat T-cell acute lymphoblastic leukemia cells. Compounds with dialkyl-(*m*-sulfonated-phenyl) ($mC_6H_4SO_3Na$) phosphanes displayed moderate to high cytotoxicity on this cell line. The cell death mechanism involves mainly early apoptosis. The catalytic/biological activity of the previously described compound with commercial *m*-trisulfonated-triphenylphosphane [AuCl(TPPTS)] (**6**) has also been evaluated to compare the effects of the higher basicity and lipophilicity of the alkyl- and dialkyl-(*m*-sulfonated-phenyl)phosphanes on these new compounds.

Introduction

Gold(I) compounds with phosphanes have been known for many years.[1] Most of gold compounds in the oxidation state +1 are two-coordinate, linear, and 14-electron species. Other complexes with different coordination numbers have also been characterized, although they are not that common. They are usually three-coordinate trigonal-planar complexes and four-coordinate gold(I) complexes (including those with diphosphane chelating ligands).[2] Several gold(I) compounds with phosphanes display interesting structural properties, dynamic behavior in solution, or luminescent properties.[2] Many of these compounds have allowed for the observation of *aurophilicity* or Au···Au interactions (due to relativistic effects).[3] An isolobal relationship of $[Au(PPh_3)]^+$ cations and H^+ and Li^+ has been proposed on the basis of the behavior of $[Au(PPh_3)]^+$ fragments in many homo- and heterometallic clusters;[4] some of them having a very unusual coordination number for the central atom (e.g. C and O).[5] The isolobality can be exploited in the application of organometallic compounds of gold(I) [AuR(PPh_3)] as a less toxic, air-stable, and room-temperature alternative to organolithium, organomagnesium, and organomercury compounds. Thus, these complexes can be used as transmetallating agents to other metallic centers.[6] Gold(I) complexes with phosphanes have displayed toxicity against different tumor cell lines while targeting mitochondria.[7] They have also displayed antimalarial properties,[8] moderate antimicrobial activities,[9] and have found applications as antirheumatic pharmaceuticals (auranofin).[10] More recently, an increasing number of papers based on the high catalytic activity of mainly $[Au(PR_3)]^+$ cations and other (phosphane)gold(I) derivatives in different chemical processes have been reported.[11]

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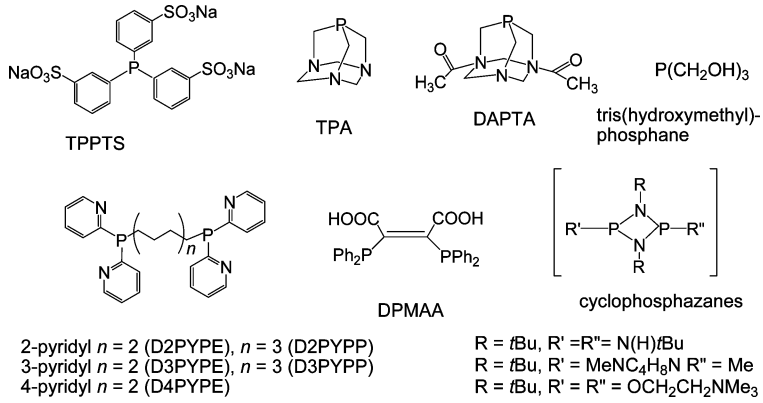


Figure 1. Water-soluble phosphanes used in the preparation of gold(I) compounds.

As green-chemistry principles are incorporated in academic and industrial settings, the development of water-based reactions and water-soluble catalysts has become extremely important. Because water is the biologically most relevant solvent, the synthesis of metal-based drugs with enough solubility and stability in water or physiological media is still a matter of increasing interest.

Gold(I) compounds with water-soluble phosphanes (di-, tri-, or even four-coordinate) have been described.[12] Some of the phosphanes used are depicted in Figure 1. Sulfonated arylphosphanes (abbreviated TPPMS, TPPDS, TPPTS),[13] mono-, or diphosphanes containing pyridyl groups such as D*n*PYPE, D*n*PYPP,[14] or maleic acid (DPMAA),[15] phosphanes like 1,3,5-triaza-7-phosphaadamantane (TPA) or 3,7-diacetyl-1,3,7-triaza-5-phosphabicyclo[3.3.1]nonane (DAPTA)[16] have been employed in the preparation of gold compounds with simple halide ligands (Cl, Br) or other coordination/organometallic complexes with thiolato, thionato, or alkynyl ligands. More recently, phosphanes containing hydroxy groups[17] and water-soluble cyclodiphosphazanes[18] have been employed in the preparation of gold(I) compounds. Some of the compounds have been structurally characterized (affording linear coordinated or polymeric structures depending on the phosphane) in the solid state. Some of the complexes with these phosphanes display interesting photoluminescence[13,15] and cytotoxic properties against different tumor cell lines.[14,15,16j,17,18]

[AuCl(TPPTS)] is a good co-catalyst in the biphasic palladium-catalyzed alkynylation reaction,[19a] whereas [AuR(TPPTS)] compounds (R = alkynyl) are efficient and recyclable catalysts in the hydration of alkynes.[20] Surprisingly, studies on the microbial activity of gold compounds with water-soluble phosphanes have been neglected.

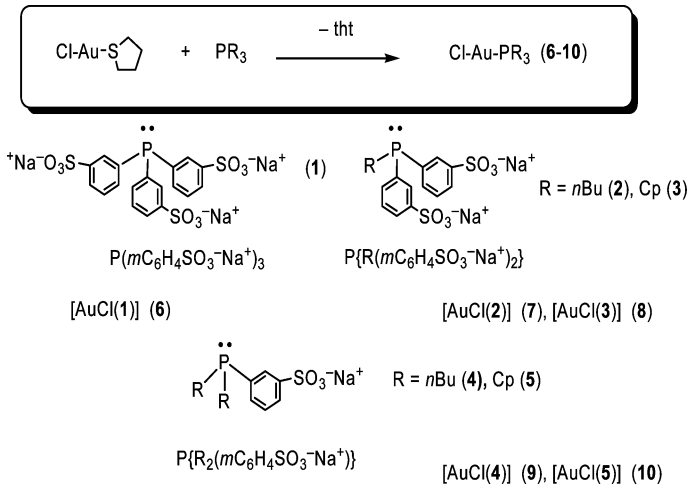
The increasing interest on homogeneous catalysis in water as alternative reaction medium with the recovery of the catalyst as well as the development of gold catalysis (a current scientific hotspot)[21] warrants the study of new water-soluble gold compounds. The study of the biological properties of these compounds becomes relevant in the search of new metallopharmaceuticals.

We describe here the synthesis of new water-soluble gold(I) compounds that contain the recently described alkyl-bis(*m*-sulfonated-phenyl)- and dialkyl-(*m*-sulfonated-phenyl)phosphanes.[22] The incorporation of other organic groups such alkyl groups (cyclopentyl and butyl) in these sulfonated phosphanes can modulate not only the electronic and steric parameters of these phosphanes (increasing their basicity) but their hydrophilicity/lipophilicity properties. This makes the new compounds good candidates to study their application as homogeneous catalysts in water and to explore some biological properties oriented to their use as pharmaceuticals. We have chosen a three-component coupling reaction of aldehydes, amines, and alkynes in water to synthesize propargylamines, which are extremely versatile building blocks for organic synthesis.[23,24] We have also evaluated the antimicrobial properties of these compounds against bacteria (gram-negative and gram-positive) and yeast. The cytotoxic and apoptotic properties of these complexes have been evaluated in vitro by utilizing human Jurkat T-cell acute lymphoblastic leukemia cells. We have used the previously described [AuCl(TPPTS)][19a] compound **6** with commercially available phosphane [P(*m*$C_6H_4SO_3Na)_3$] (TPPTS) (**1**) in order to compare the behavior of alkyl-substituted and unsubstituted sulfonated phosphanes in the catalytic/biological properties of the water-soluble gold compounds.

Results and Discussion

Synthesis of Gold(I) Compounds with Alkyl-bis(*m*-sulfonated-phenyl)- and Dialkyl-(*m*-sulfonated-phenyl)-phosphanes

The preparation of the new complexes and compound [AuCl(TPPTS)] (**6**)[19a] is achieved by displacing the labile ligand tht (tetrahydrothiophene) from the starting gold(I) material [AuCl(tht)] by the water-soluble phosphanes (Scheme 1).[19] The complexes are obtained as white solids that are stable in air. They are all soluble in water (with solubilities in the range of 125 to 75 g/L, see Experimental Section), but they have different stabilities in solution. The most stable compounds (in water solution and at room temp.) are derivatives with three sulfonated-aryl groups in the phosphane **6**, or one alkyl group and two sulfonated-



Scheme 1. Preparation of the new water-soluble compounds and complex **6**.[19]

aryl groups (**7**, **8**). Complexes with two alkyl groups and one sulfonated-aryl group (**9**, **10**) display a different behavior. The new compounds have been characterized by different spectroscopic ($^{31}P\{^1H\}$, $^{13}C\{^1H\}$, ^1H, NMR), spectrometric (ESI-MS), and analytical techniques (C, H, S microanalysis). $^{31}P\{^1H\}$ NMR spectroscopy is quite useful in the characterization and study of the stability of these complexes over time. In all cases the chemical shifts correspond to usual (phosphane)gold(I) chemical shifts for linear compounds. The $^{31}P\{^1H\}$ NMR spectroscopic data for the free phosphane ligands, for **6** and new gold(I) compounds **7**–**10** are collected in Table 1 (see also Supporting Information).

Table 1. $^{31}P\{^1H\}$ NMR chemical shifts (ppm) in D_2O (25 °C) for the water-soluble phosphane ligands **1**, **2**–**5**[22] and for the new gold(I)-phosphane complexes **6**–**10**.

Free ligands	**1**	**2**	**3**	**4**	**5**
δ^{31}P NMR	–5.88 (s)	–15.22 (s)	–3.11 (s)	–23.56 (s)	3.00 (s)
[AuClL]	**6**	**7**	**8**	**9**	**10**
δ^{31}P NMR	33.40 (s)	30.40 (s)	46.06 (s)	29.68 (s)	56.77 (s)

Compounds **1**–**3** are stable in aqueous solution at room temp. for 48 h as shown by $^{31}P\{^1H\}$ NMR spectroscopy. After this time, a little decomposition to metallic gold can be observed, but the signals in the $^{31}P\{^1H\}$ NMR spectra remain the same for weeks. Compounds with the more basic dialkyl-(*m*-sulfonated-phenyl) ($mC_6H_4SO_3Na$) phosphanes **9** and **10** have a different behavior. They can be obtained as analytically pure white compounds (see Experimental Section), but when dissolved in water, after a few minutes they give a solution of intense purple color indicative of water-soluble colloids. The $^{31}P\{^1H\}$ NMR spectra do not change much over time, and only small signals (singlets) accompanying the main singlet at δ = 51.94 (**9**) and 65.61 (**10**) ppm can be seen at room temp. after 24 h. In the case of **10** the extra signal at δ = 65.61 ppm becomes a major signal after 48 h (see Supporting Information). While we do not have information about the nature of these decomposition products, complexes **9** and **10** are stable enough at room temp. for 24 h to allow us to perform the biological tests described here.

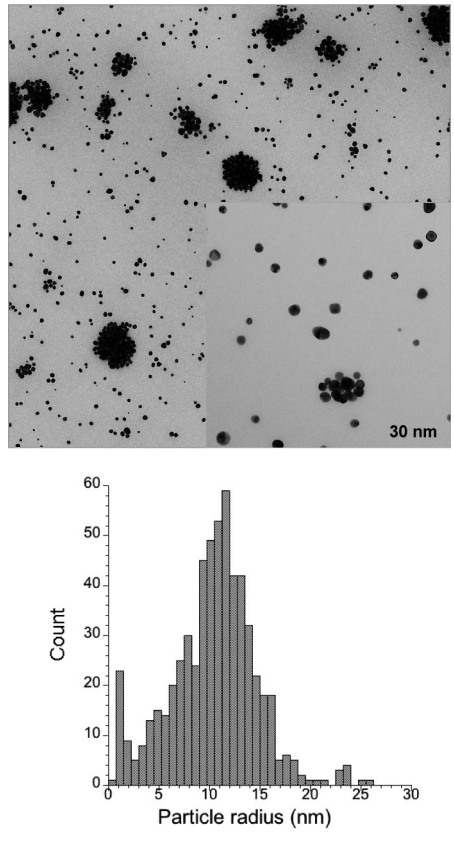


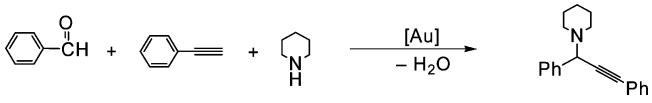
Figure 2. Top: TEM field-view image at 10000× of nano-**9**. The inset shows a detail at 50000×. Bottom: Histogram of particle count as a function of particle radius (nm) in the image.

Unfortunately, attempts to obtain crystals of high enough quality for X-ray diffraction studies (**6**–**10**) were unsuccessful.

We characterized these purple solutions to test for the presence of gold colloids. Indeed, TEM analysis confirmed the formation of homogeneous nanoparticles with a 10–15 nm radius (Figure 2, see Experimental Section for details). Smaller dimensions (2–3 nm) have been previously observed for fluorous-soluble gold nanoparticles that were generated from gold(I)-fluorous phosphane derivatives.[25]

Catalytic Activity in the Synthesis of Propargylamines by a Three-Component Coupling Reaction of Aldehydes, Amines, and Alkynes

We used the water-soluble compounds in a coupling reaction with formation of C–C and C–N bonds. The reaction is a one-pot reaction with three components (aldehydes, alkynes, and amines) by C–H activation. Gold salts like AuCl or $AuBr_3$ had been shown to be very good catalysts for this reaction (in amounts of 5 or 1 mol-%).[24a] However, these salts are hygroscopic, highly acidic, and can not be handled in air. The reactions were generally run at 100 °C, and water was obtained as the only byproduct of the reaction (Scheme 2).



Scheme 2. Three-component coupling of benzaldehyde, piperidine, and phenylacetylene catalyzed by gold.[23,24]

More recently, other gold catalysts have been employed in this reaction;[23,24b–24g] (salen)gold(III) complexes afforded excellent yields at 40 °C, and when chiral prolinol derivatives were used as the amine component, excellent diastereoselectivities (up to 99:1) were obtained.[24c] A gold(III) C,O metallacycle (with a phosphinamide ligand) has also proved to be highly efficient for this three-component coupling.[24g] The synthesis of quinoline derivatives can be achieved by a sequential catalytic process by $AuCl_3$/CuBr (5 mol-%/30 mol-%).[24e] The recyclability of the system was achieved for 4 runs with gold nanoparticles (10 mol-%) at 75–80 °C.[24d] Supported gold catalysts (layered double-supported gold[24b] and gold nanoparticles supported on nanocrystalline ZrO_2 and CeO_2, 2.8 mol-%[24f]) are highly active, selective (high diastereoselectivities for chiral amines), and recyclable in this A^3 coupling in water at 100 °C.[24f] However, apart from the report on AuCl by Liu, there are no reports on the catalytic activity of gold(I) compounds in these reactions.

We tested the most stable of our compounds (**6**–**8**) under different reaction conditions in a biphasic system consisting of 1 mL of H_2O (where we dissolved the gold compounds) and the organic reagents. After the reaction had taken place, the separation of the gold catalyst was performed by simple decantation of the two layers. The results of these studies are collected in Table 2. We found good yields when reactions were run at 100 °C and with 5 mol-% of catalysts (Entries 2, 7, and 9). Yields improve by addition of $NaPF_6$ (which should facilitate the removal of chloride from the gold compounds). Moreover, with compound **6** we found good conversions at room temperature if reactions were run for 42 h (Entry 5). When reactions were run at room temp. or 40 °C, we did not observe decomposition to metallic gold (we observed this decomposition at 100 °C), and we decided to recycle the water layers from these runs in order to study the recyclability of the system.

Table 2. Three-component coupling of benzaldehyde, piperidine, and phenylacetylene catalyzed by water-soluble gold compounds **6**–**8**.

Run	Catalyst	Co-catalyst	Temp. [°C]	Time [h]	Yield (%)	Conv. (%)[b]
1	**6** (1 mol-%)	–	100	12	17	54
2	**6** (5 mol-%)	–	100	17	62	44
3	**6** (5 mol-%)	–	40	42	71	100
4	**6** (5 mol-%)	$NaPF_6$ (5 mol-%)	100	12	78	56
5	**6** (5 mol-%)	–	r.t.	42	81	98
6	**6** (2.5 mol-%)	$NaPF_6$ (5 mol-%) TPPTS (5 mol-%)	100	12	78	56
7	**7** (5 mol-%)	–	100	17	99	85
8	**7** (7 mol-%)	–	r.t.	42	12	70
9	**8** (5 mol-%)	$NaPF_6$ (5 mol-%)	100	12	94	93
10	**8** (5 mol-%)	$NaPF_6$ (5 mol-%)	50	24	48	91
11	**8** (5 mol-%)	$NaPF_6$ (5 mol-%)	40	21	25	88
12	**8** (7 mol-%)	–	r.t.	42	39	97
13	**6** (7 mol-%)	$NaPF_6$ (7 mol-%)	r.t.	42	75	96
14	RP[a] (run 13)	–	r.t.	42	65	83
15	RP[a] (run 14)	–	r.t.	42	53	77
16	RP[a] (run 15)	–	r.t.	42	38	85
17	**6** (7 mol-%)	–	r.t.	93	91	87
18	RP[a] (run 17)	–	r.t.	42	88	85
19	RP[a] (run 18)	–	r.t.	42	83	80
20	RP[a] (run 19)	–	r.t.	42	77	74

[a] RP: recycled water phase containing the gold catalyst. [b] Determined by ^1H NMR spectroscopic analysis of the crude reaction mixture on the basis of benzaldehyde conversion.

The study of recycling catalyst **6** is collected in Entries 13–16. With 7 mol-% of **1** and 7 mol-% of $NaPF_6$ the catalyst can be separated and re-used 4 times. However, the yields of product decrease steadily from run to run from 75 to 38 (4th run). Addition of $NaPF_6$ was, however, not necessary, and we could separate catalyst **6** and recycle it with higher conversion and less decrease in the yield/conversion from run to run (Entries 17–19) of product. It seems that at room temp. the addition of $NaPF_6$ is not as beneficial as at higher temperatures.

While we were preparing this manuscript, a study on the recyclability of an organogold(III) complex was reported.[23] The compound of type [Au(C–N)Cl_2] (N–CH = 2-phenylpyridine) was an efficient and selective catalyst (1 mol-%) for this three-component coupling reaction in

water at 40 °C. Notably this complex could be repeatedly used for 10 cycles, leading to an overall turnover number of 812.[23] While our system is not so efficient, it has allowed for the synthesis of propargylamines at room temp. These compounds are stable in water under mild conditions (up to 40 °C) for several hours, and this may allow their use as catalysts in some other processes in the future in which a higher basicity of the phosphanes coordinated to the gold centers are preferred.

Biological Activity: Antimicrobial Activity and Cytotoxic Properties in vitro

Antimicrobial Activity

The antimicrobial activity of the new compounds as well as that of compound **6** were evaluated against yeast (*Saccharomyces cerevisiae*) gram-negative (*Escherichia coli and Salmonella tiphymurium*) and gram-positive (*Bacillus cereus* and *Staphyloccocus aureus*) bacteria. The results of the experiments are collected in Table 3. They all have moderate to high antibacterial activity. The compounds with the highest lipophilicity (**9** and **10**) are also potent against fungi.

Table 3. Toxicity assesment of compounds **6**–**10** against microbial organisms.[a]

Compd.	*S. cerevisiae*	*E. coli*	*S. tiphymurium*	*B. cereus*	*S. aureus*
6	–	10	100	10	100
7	–	100	100	100	100
8	–	100	10	100	100
9	100	100	100	1	1
10	100	100	10	10	10

[a] Minimum number of μg required to create a zone of clearing of 0.5 cm diameter on a lawn of fungal or bacterial cells: 100, 10, 1, or – no toxicity.

Saccharomyces cerevisiae appears resistant to this class of compounds. The plasma membrane appears to be an effective barrier to the more hydrophilic compounds **6**–**8**, whereas the more lipophilic compounds with dialkyl-(*m*-sulfonated-phenyl) ($mC_6H_4SO_3Na$) phosphanes **9**, **10** are able to penetrate the plasma membrane to suppress growth. Compounds **9** and **10** suppress yeast growth in a zone of about 2.5 cm diameter. Further testing with other fungal species is required to see if this pattern of resistance is uniform across the fungi.

Among the bacteria we found that gram-positive ones are 100 times more sensitive to [AuCl{PR_2-($mC_6H_4SO_3Na$)}] than gram-negative ones, whether R is cyclopentyl (**9**) or *n*-butyl (**10**). Gram-negative bacteria are moderately resistant, showing growth suppression at only at 100 μg/disk; however, individual species may show selective sensitivity to a particular molecule. Thus, *Escherichia coli* was more sensitive to [AuCl{$PmC_6H_4SO_3Na\}_3$] (**6**), whereas the cyclopentyl group in [AuCl{$PCp(mC_6H_4SO_3Na)$}] (**8**) and [AuCl{$PCp_2(mC_6H_4SO_3Na)$}] (**10**) increases toxicity to *Salmonella typhimurium*. For both gram-negative organisms, clearance zones were 1.0–1.4 cm in diameter regardless of the quantity of each compound.

The behavior for *Bacillus cereus* and *Staphyloccocus aureus* is nearly identical, and compounds **9** and **10** (the more lipophilic) turned out to be the more toxic to these organisms. For both compounds the zones of growth suppression exceeded 2.0 cm in diameter at 100 μg/disk. The relative difference in toxicity between **9** and **10** could be due to the fact that the phosphane in compound **9** contains a bulkier Cp group (because both phosphanes should have similar lipophilicity).

A similar general trend (more toxic for gram-positive bacteria than gram-negative ones or fungi) has been noted previously with auranofin[9a] and some other (phosphane)-gold(I) derivatives.[9b–9d,9f,9g] However, caution has to be applied when generalizing the results, because many factors are involved in the antimicrobial activities. Thus, the nature of other ligands coordinated to the gold centers (besides the phosphanes) plays a decisive role. For instance, a more complicated pattern is found for thiol-phosphanegold derivatives, and the antimicrobial potency can be higher for gram-negative ones or fungi depending on the combination thiol-phosphane.[9a]

An explanation for the behavior displayed by the new complexes **7**–**10** could be as follows: if these compounds interfere with respiration (a mitochondrial function), then the fungi should be most resistant, because electron transport is shielded inside internal organelles, whereas in bacteria electron transport occurs at the plasma membrane. Gram-negative bacteria have a protective outer second membrane; therefore, the compounds do not have ready access to the electron-transport chain. Finally, the most lipophilic (hydrophobic) molecules are the most effective for gram-positive ones. This is explained by the ability of **9** and **10** to partition into or through the membrane, whereas **6**, the most highly charged compound, is less likely to pass through the plasma membrane.

Cytotoxic Properties and Apoptosis Studies

The cytotoxic properties of gold(I) compounds **6**–**10** were analyzed in vitro according to the procedures described by Montoya et al.[26] and our laboratories[27] by utilizing Jurkat T-cell acute lymphoblastic leukemia cells (Table 4). Before use, all tested compounds were dissolved in physiological saline solution (NaCl 0.9%), and dilutions of each compound were then added to the cells in normal growth medium. All the tested complexes have proven, by ^{31}P NMR spectroscopic studies, to be stable in D_2O over 24 h or more. Compounds **9** and **10** produce stable water-soluble nanoparticles when dissolved in water.

Cisplatin was used as a positive control as previously reported by our laboratories with organogold(III) complexes containing iminophosphorane ligands.[27]

Compounds with dialkyl-(*m*-sulfonated-phenyl) ($mC_6H_4SO_3Na$) phosphanes that produced nanoparticles when dissolved in water displayed moderate to high cytoto-

Table 4. IC_{50} values [μM][a] of compounds **6**–**10** compared to cisplatin.

Cell line	cisplatin[b]	**6**	**7**	**8**	**9**	**10**
Jurkat-GFP	31	97	113	76	50	23

[a] IC_{50} is defined as the concentration of drug required to disrupt the plasma membrane of 50% of the cell population, as compared to untreated cells, after 22 h of incubation. Cells with compromised plasma membranes were monitored with Propidium iodide (PI) and flow cytometry. Cisplatin was used as reference compound. [b] Ref.[27]

xicity on this cell line. It appears that an increase in the lipophilic properties of the phosphanes increases the cytotoxicity of this type of compounds. The cytotoxicity of **9** was not much higher than that displayed by cisplatin. Compound **10** was the most cytotoxic compound of all tested, even more than cisplatin for this cell line. The IC_{50} values for **9** and **10** are similar to those found for some organogold(III) complexes with iminophosphorane C,N skeletons and chloride and/or water-soluble phosphanes recently described by us,[27] but not as high as those with the combination of iminophosphorane and dithiocarbamate ligands (1–2 μM).[27] Very recently, Bindoli and co-workers have reported that well-known (phosphane)gold(I) complexes such *S*-[(triethylphosphane)gold(I)]-2,3,4,6-tetra-*O*-acetyl-1-thio-B-D-glucopyranoside (auranofin) and (triethylphosphane)-gold(I) chloride induced apoptosis in Jurkat T cells.[28] Although IC_{50} values were not provided, different experiments were run with 1 μM of gold compounds for which cell mortality was between 20 and 27%. This apoptosis appeared to be triggered by inhibition exerted by the gold(I) compounds on the cytosolic and mitochondrial isoforms of thioredoxin reductase, which resulted in an increase in H_2O_2. However, no significant lipid peroxidation or nitric oxide formation were observed after incubation with gold(I) complexes, indicating that the cells had not been subjected to extensive oxidative stress. Polymeric gold(I) compound aurothiomalate was poorly effective, both in inhibiting thioredoxine reductase and in inducing apoptosis.[28]

In order to gain some insight of the type of cell death that complexes **6**–**10** induce in this cancer cell line, we performed some apoptosis assays with Jurkat cells (see Experimental Section for details). As cells may undergo programmed cell death (apoptosis) or necrosis, the mode of death mediated by our compounds was investigated. In early stages of apoptosis, one of the significant biochemical features is loss of plasma membrane phospholipid asymmetry, due to translocation of phosphatidylserine (PS) from the cytoplasmic to the extracellular side. This characteristic allows detection of externalized PS by the specific binding of Annexin V (FITC-conjugatated). Initiation of cell death will eventually result in the permeabilization of the cell membrane, allowing PI to stain DNA within the nucleus. The results of these studies are summarized in Figure 3.

All five compounds tested demonstrated that the inflicted cell damage was preferentially due to apoptosis instead of necrosis. The preferential apoptosis induced is markedly much higher than that for the gold(I) phosphane compounds described by Bandoli and co-workers.[28] Apparently, compound **10** may be slightly more toxic than the other four compounds tested, since it induces higher levels of late apoptosis in 16 h of incubation time. As described in the Experimental Section, three controls were included: untreated cells, cells treated with H_2O_2, and samples treated with physiological saline solution. There was no significant difference between untreated cells and cells treated with sodium chloride. Auranofin is known to also induce apoptosis in HL-60 cells,[29] ovarian cancer cells,[30] and cardiac tissue.[31] Other (phosphane or phosphite)gold(I) complexes such as water-soluble compounds with the D2PYPP diphosphane ligand,[32] cyclodiphosphazanes,[17] or compounds with bis(phosphite) ligands containing mesocyclic thioether moieties[33] have induced apoptosis in HeLa, breast cancer, and/or HCT-116 cell lines by activation of p53 protein.

We also performed a study of the cytotoxicity of compound **10** after it was dissolved in the medium and kept in the absence of light and at –20 °C for 30 d. In Figure 4, the cytotoxicity of a freshly prepared solution of **10** is shown as 1. The cytotoxicity of this complex after 30 d at –20 °C is shown as 2. We also measured the cytotoxicity of solutions that were kept in the dark and at –20 °C for 28 d and then kept at room temp. for 2 d extra either in the dark (4) or in the presence of artificial light (3). Basically, the

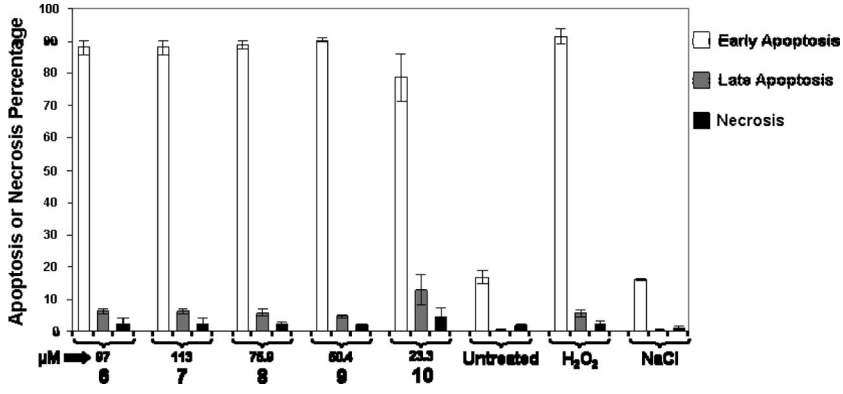


Figure 3. Preferential induction of early apoptosis in Jurkat cells after treatment with the gold(I) complexes. The IC_{50} concentration shown in Table 4 was used for each gold compound.

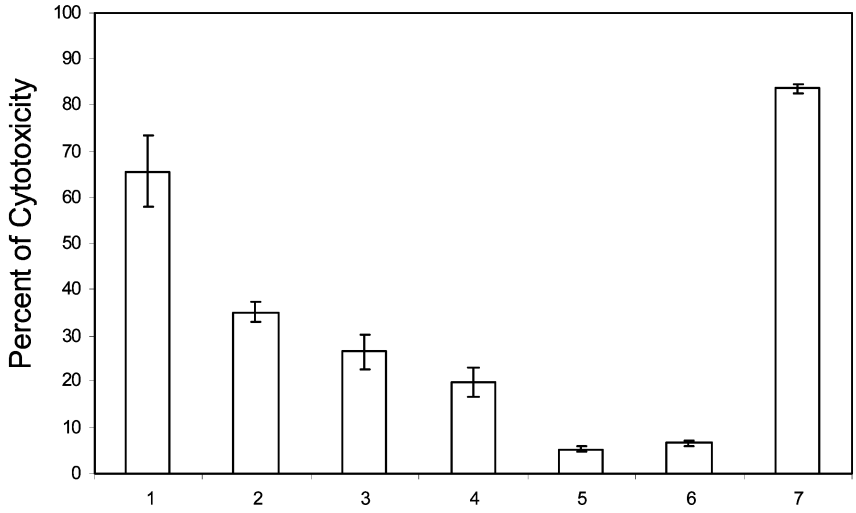


Figure 4. Testing of cytotoxic activity against Jurkat cells of compound **10** after exposure to artificial light at room temperature and time after dissolution. (1) Freshly prepared sample of **10** (25 μM in saline solution); (2) solution of **10** kept at –20 °C for 30 d in the dark; (3) solution of **10** kept at –20 °C for 28 d in the dark and additionally at room temp. in the presence of light for 2 d; (4) solution of **10** kept at –20 °C in the dark for 28 d and additionally at room temp. in the dark for 2 d; (5) untreated cells; (6) cells treated with 1 μL of NaCl (0.9%); (7) cells treated with 500 μM of H_2O_2 (positive control). Incubation time: 22 h.

cytotoxicity of these solutions decreases to approximately half of the value of that for a freshly prepared solution of compound **10**.

Compounds **6**–**10** yield $[AuPR_3]^+$ species in solution, which may enable them to pass more easily through the lipid bilayer of membranes and, possibly, mitochondria, as it happens for some delocalized lipophilic cations (DLCs) of gold(I).[33] The degree of lipophilicity of the ligands has been recently connected to the in vitro cytotoxicity. A higher lipophilicity of the gold(I) drugs with phosphanes results in a higher in vitro antitumor and hepatotoxic potency.[34] We believe that further modification of the gold(I) compounds described here by exchange of chloride by other organic or inorganic ligands may render promising stable, water-soluble cytotoxic compounds with an optimized lipophilicity value. Interestingly, gold nanoparticles have been found to enhance the anti-leukemia action of a 6-mercaptopurine chemotherapeutic agent.[35] The most cytotoxic compounds described here (**9** and **10**) generate water-soluble nanoparticles when dissolved in water. Further biochemical assays will be performed in order to determine the mechanism that triggers apoptosis for these complexes as well as their toxicity against normal human cells.

Conclusions

We have prepared gold(I) compounds with water-soluble phosphanes with higher basicity and lipophilicity than previously reported {[AuCl{P(mC$_6$H$_4$SO$_3$Na)$_3$}] (**6**)}[19a] by introduction of one or two alkyl groups {R = *n*Bu or Cp) in the (sulfonated-aryl)phosphane ([PR(mC$_6$H$_4$SO$_3$Na)$_2$] or [PR$_2$(mC$_6$H$_4$SO$_3$Na)]}. The complexes with two alkyl groups on the phosphanes (**9** and **10**) produce nanoparticles when dissolved in water as opposed to **6** or compounds with just one alkyl group (**7** and **8**). Whereas these compounds have shown to be not as efficient catalysts as **6** (the most hydrophilic complex) in a biphasic three-component coupling reaction in the synthesis of propargylamines, they have displayed interesting biological activities (antimicrobial and anticancer). They all have moderate to high antimicrobial activity. The compounds with the highest lipophilicity (**9** and **10**) are the most potent for gram-positive bacteria and fungi. Also the higher lipophilicity of, especially, compounds with dialkyl-(*m*-sulfonated-phenyl) (mC$_6$H$_4$SO$_3$Na) phosphanes (**9** and **10**) makes them the most cytotoxic of the group (**6**–**10**) in vitro against human Jurkat T-cell acute lymphoblastic leukemia cells. Compound **10** is even more cytotoxic than cisplatin for this cell line. The cell-death mechanism involves mainly early apoptosis for all the compounds studied (**6**–**10**) as for some other (phosphane)gold(I) complexes (although compounds **6**–**10** are more apoptotic than those described previously).

The higher basicity of the new gold complexes can be further exploited for some other homogeneous biphasic catalytic processes. Subsequent modification of these complexes by exchange of chloride for other ligands may afford complexes with an optimized lipophilicity value with potential applications as more efficient antimicrobial and anticancer agents.

Experimental Section

1. Sythesis and Characterization of the Water-Soluble Gold(I) Complexes: Solvents were purified by use of a PureSolv purification unit from Innovative Technology, Inc.; all other chemicals were used as received. Elemental analyses were carried out by Atlantic Microlab, Inc. (US). The ^{1}H, ^{13}C{^{1}H} and ^{31}P{^{1}H} NMR spectra were recorded in D_2O solutions at 25 °C with a Bruker 400 spectrometer (δ, ppm; *J*, Hz); ^{1}H and ^{13}C{^{1}H} NMR data were referenced by using the solvent signal as internal standard, whereas ^{31}P{^{1}H} NMR data were externally referenced to H_3PO_4 (85%). Mass spec-

tra (ESI) were recorded from acetone or water solutions by the mass spectrometry facility of the University of California Riverside (US). The preparation[19] of compound **6** is slightly different from that previously reported.[19a] Phosphanes **2**–**5** [PR(mC$_6$H$_4$SO$_3$Na)$_2$] and [PR$_2$(mC$_6$H$_4$SO$_3$Na)] (R = nBu, Cp) were prepared as recently described.[22] [AuCl(tht)] was prepared according to the procedure of Uson et al.[36] The rest of chemicals and solvents were purchased from Sigma–Aldrich.

[AuCl{P(mC$_6$H$_4$SO$_3$Na)$_3$}] (6):[19a] A solution of [P(mC$_6$H$_4$SO$_3$Na)$_3$] (0.341 g, 0.6 mmol) in 5 mL of acetone and 9 drops of water was added dropwise to a solution of [AuCl(tht)] (0.192 g, 0.6 mmol) in 15 mL of dichloromethane. The reaction mixture was stirred at room temp. for 30 min, and all the solvents were removed under vacuum. By addition of 5 mL of acetone/10 mL of diethyl ether, compound **6** was obtained as a white solid that was filtered off and dried under vacuum. Yield: 0.480 g, 99%. Solubility in H_2O: 125 g/L. $^{31}P\{^1H\}$ NMR (D_2O): δ = 33.4 (s) ppm.

[AuCl{PnBu(mC$_6$H$_4$SO$_3$Na)$_2$}] (7): A solution of [PnBu(mC$_6$H$_4$SO$_3$Na)$_2$] (0.134 g/0.3 mmol) in 5 mL of acetone and 9 drops of water was added dropwise to a solution of [AuCl(tht)] (0.0962 g/0.3 mmol) in 15 mL of dichloromethane. The reaction mixture was stirred at room temp. for 30 min, and all the solvents were removed under vacuum. By addition of 5 mL of acetone/10 mL of diethyl ether, compound **7** was obtained as a white solid. Yield: 0.195 g, 96%. Solubility in H_2O: 125 g/L. $C_{12}H_{15}AuClNa_2O_6PS_2$ (628.74): calcd. C 28.31, H 2.52, S 9.44; found C 27.75, H 3.15, S 9.33. MS (ESI–): m/z = 654.94 [M – Na]$^-$. $^{31}P\{^1H\}$ NMR (D_2O): δ = 30.40 (s) ppm. ^1H NMR (D_2O): δ = 0.71 (br., 3 H, CH_3 Bu), 1.33 (br. m, 4 H, CH_2CH_2CH$_2$P), 2.53 (br., 2 H, CH_2P), 7.53 (br., 2 H, H^5, mC$_6$H$_4$SO$_3$Na), 7.67 (br., 2 H, H^6, mC$_6$H$_4$SO$_3$Na), 7.87 (br., 2 H, H^4, mC$_6$H$_4$SO$_3$Na), 7.97 (d, $^3J_{P\text{-}H}$ = 12 Hz, 2 H, H^2, mC$_6$H$_4$SO$_3$Na) ppm. $^{13}C\{^1H\}$ NMR (D_2O): δ = 12.99 (s, CH$_3$, Bu), 23.21 (d, $^3J_{P,C}$ = 16.4 Hz, CH$_2$CH$_2$P, Bu), 27.05 (s, CH$_3$$CH_2$), 40.10 (s, CH$_2$P), 129.26 (br., C^2, mC$_6H_4SO_3$Na), 129.72 (d, $^1J_{P,C}$ = 12.68 Hz, C^1, mC$_6$H$_4$SO$_3$Na), 130.16 (br., C^4, mC$_6$H$_4$SO$_3$Na), 130.29 (br., C^5, mC$_6$H$_4$SO$_3$Na), 136.14 (d, $^2J_{P,C}$ = 12.98 Hz, C^6, mC$_6$H$_4$SO$_3$Na), 143.83 (br., C^3, m-C$_6$H$_4$-SO$_3$Na) ppm.

[AuCl{PCp(mC$_6$H$_4$SO$_3$Na)$_2$}] (8): A solution of [PCp(mC$_6$H$_4$SO$_3$Na)$_2$] (0.136 g/0.3 mmol) in 5 mL of acetone and 9 drops of water was added dropwise to a solution of [AuCl(tht)] (0.0962 g/0.3 mmol) in 15 mL of dichloromethane. The reaction mixture was stirred at room temp. for 30 min, and all the solvents were removed under vacuum. By addition of 5 mL of acetone/10 mL of diethyl ether, compound **8** was obtained as a white solid. Yield: 0.188 g, 92%. Solubility in H_2O: 125 g/L. $C_{17}H_{16}AuClNa_2O_6PS_2$ (700.33): calcd. C 29.15, H 2.30, S 9.15; found C 29.11, H 3.22, S 10.1. MS (ESI-): m/z = 666.94 [M – Na]$^-$. $^{31}P\{^1H\}$ NMR (D_2O): δ = 45.06 (s) ppm. ^1H NMR (D_2O): δ = 1.4–1.6 (br. m, 9 H, Cp), 7.51 (t, $^3J_{H,H}$ = 8 Hz, 2 H, H^5, m-C$_6$H$_4$-SO$_3$Na), 7.76 (q, 2 H, H^6, m-C$_6$H$_4$-SO$_3$Na), 7.82 (d, $^3J_{H,H}$ = 16 Hz, 2 H, H^4, m-C$_6$H$_4$-SO$_3$Na), 8.11 (d, $^3J_{P\text{-}H}$ = 12 Hz, 2 H, H^2, m-C$_6$H$_4$-SO$_3$Na) ppm. $^{13}C\{^1H\}$ NMR (D_2O): δ = 26.5 (d, $^2J_{P,C}$ = 9.33 Hz, C$_b$, Cp), 30.31 (d, $^3J_{P,C}$ = 5.82 Hz, C_c, Cp), 34.51 (d, $^1J_{P,C}$ = 38.47 Hz, C$_a$, Cp), 129.24 (br., C^2, mC$_6$H$_4$SO$_3$Na), 129.87 (d, $^1J_{P,C}$ = 75.68 Hz, C^1, mC$_6$H$_4$SO$_3$Na), 129.93 (br., C^4, mC$_6$H$_4$SO$_3$Na), 130.10 (br., C^5, mC$_6$H$_4$SO$_3$Na), 136.44 (d, $^2J_{P,C}$ = 12.98 Hz, C^6, mC$_6$H$_4$SO$_3$Na), 143.83 (d, $^3J_{P,C}$ = 10.72 Hz, C^3, mC$_6$H$_4$SO$_3$Na) ppm.

[AuCl{PnBu$_2$(m-C$_6$H$_4$SO$_3$Na)}] (9): A solution of [PnBu$_2$(mC$_6$H$_4$SO$_3$Na)] (0.181 g, 0.556 mmol) in 1.5 mL of deoxygenated of water was added dropwise to a solution of [AuCl(tht)] (0.178 g, 0.556 mmol) in 6 mL of dry acetonitrile. The reaction mixture was stirred under argon at room temp. for 30 min, and all the solvents were removed under vacuum. By addition of 5 mL of acetone/10 mL of diethyl ether, compound **9** was obtained as a white solid. Yield: 0.22 g, 71%. Solubility in H_2O: 75 g/L. $C_{14}H_{22}AuClNaO_3PS$ (556.77): calcd. C 30.20, H 3.98, S 5.76; found C 30.11, H 4.20, S 6.01. MS (ESI-): m/z = 533.03.94 [M – Na]$^-$. $^{31}P\{^1H\}$ NMR (D_2O): δ = 29.68 (s) ppm. ^1H NMR (D_2O): δ = 0.61 (br., 6 H, CH_3, Bu), 1.27 (br. m, 8 H, CH_2CH_2CH$_2$P), 2.07 (br., 4 H, CH_2P), 7.43 (br., 1 H, H^5, mC$_6$H$_4$SO$_3$Na), 7.5–8.05 (v. br., 3 H, H^6, H^4, H^2, mC$_6$H$_4$SO$_3$Na) ppm. $^{13}C\{^1H\}$ NMR (D_2O): δ = 12.99 (s, CH$_3$, Bu), 23.21 (d, $^3J_{P,C}$ = 16.4 Hz, CH$_2$CH$_2$P, Bu), 27.05 (s, CH$_3$$CH_2$), 40.10 (s, CH$_2$P), 129.26 (br., C^2, mC$_6H_4SO_3$Na), 129.72 (d, $^1J_{P,C}$ = 12.68 Hz, C^1, mC$_6$H$_4$SO$_3$Na), 130.16 (br., C^4, mC$_6$H$_4$SO$_3$Na), 130.29 (br., C^5, mC$_6$H$_4$SO$_3$Na), 136.14 (d, $^2J_{P,C}$ = 12.98 Hz, C^6, mC$_6$H$_4$SO$_3$Na), 143.83 (br., C^3, mC$_6$H$_4$SO$_3$Na) ppm.

[AuCl{PCp$_2$(mC$_6$H$_4$SO$_3$Na)}] (10): A solution of [PCp$_2$(mC$_6$H$_4$SO$_3$Na)] (0.1021 g/0.3 mmol) in 1.5 mL of deoxygenated of water was added dropwise to a solution of [AuCl(tht)] (0.0961 g/0.3 mmol) in 6 mL of dry acetonitrile. The reaction mixture was stirred under argon at room temp. for 30 min, and all the solvents were removed under vacuum. By addition of 5 mL of acetone/10 mL of diethyl ether, compound **10** was obtained as a white solid. Yield: 0.0468 g, 92%. Solubility in H_2O: 75 g/L. $C_{16}H_{20}AuClNaO_3PS$ (578.78): calcd. C 33.20, H 3.48, S 5.54; found C 33.19, H 4.43, S 5.60. MS (ESI–): m/z = 557.03 [M – Na]$^-$. $^{31}P\{^1H\}$ NMR (D_2O): δ = 56.77 (s) ppm. ^1H NMR (D_2O): δ = 0.85–1.99 (v br. m, 10 H, Cp), 7.46 (m, 1 H, H^5, mC$_6$H$_4$SO$_3$Na), 7.84 (m, 2 H, H^6, H^4, mC$_6$H$_4$SO$_3$Na), 7.82 (d, $^3J_{H,H}$ = 16 Hz, 2 H, H^4, mC$_6$H$_4$SO$_3$Na), 8.04 (d, $^3J_{P\text{-}H}$ = 10.8 Hz, 1 H, H^2, mC$_6$H$_4$SO$_3$Na) ppm. $^{13}C\{^1H\}$ NMR (D_2O): δ = 25.63 (d, $^2J_{P,C}$ = 7.02 Hz, C$_b$, Cp), 26.54 (d, $^2J_{P,C}$ = 6.172 Hz, C$_b$, Cp′), 30.51 (br., C$_c$, Cp), 30.90 (br., C$_c$, Cp′), 36.05 (br., C$_a$, Cp), 36.42 (br., C$_a$, Cp′), 129.29 (br., C^2, mC$_6$H$_4$SO$_3$Na), 129.60 (br., C^1, C^4, mC$_6$H$_4$SO$_3$Na), 130.14 (br., C^5, mC$_6$H$_4$SO$_3$Na), 130.10 (br., C^5, mC$_6$H$_4$SO$_3$Na), 136.78 (br., C^6, mC$_6$H$_4$SO$_3$Na), 144.58 (d, $^3J_{P,C}$ = 8.78 Hz, C^3, mC$_6$H$_4$SO$_3$Na) ppm.

2. General Procedure for the Gold(I)-Catalyzed A^3 Coupling of Benzaldehyde, Piperidine, and Phenylacetylene: In a Schlenk or Kontex (for reactions at temperature higher than room temperature) tube, under N_2 (g), the appropriate amount of the catalyst was dissolved in 1 mL of deoxygenated water. Then, phenylacetylene (150 μL, 1.5 mmol), benzaldehyde (100 μL, 1.0 mmol), and piperidine (105 μL, 1.1 mmol) were added. The reaction mixtures were stirred for the time and temperature specified in Table 1. Once the reaction had taken place, 2–3 mL of Et_2O was added, and the two layers (water/organic) were separated. Another 20 mL of Et_2O was added to the organic layer, and it was washed with 10 mL of a brine solution and 2 × 10 mL of H_2O. After drying with anhydrous $MgSO_4$, the organic solvents were completely removed, and the residue was weighed (yield) and analyzed by NMR spectroscopy (conversion). When recycling the catalyst, we used the aqueous layer and added an extra amount (0.5 mL) of deoxygenated water.

3. Antimicrobial Assays: The gold compounds were tested for microbial toxicity in a Kirby–Bauer disk diffusion assay. Compounds **6**–**10** were solvated in methanol to a concentration of 10 mg/mL and serially diluted in methanol by factors of 10 to create solutions ranging down to 0.1 mg/mL. 10 μL aliquots of the solution were transferred onto filter paper disks (5 mm diameter × 1 mm thickness), which were then vacuum-dried and stored at –20 °C prior to the experiment. For the assay, 100 μL of a cell suspension containing 3×10^7 cells/mL were spread uniformly on a Mueller–Hinton (MH for bacteria) or Yeast Extract (YPD for fungi) agar plate (100 mm × 15 mm). After spreading, four paper disks impregnated

with either 100, 10, 1, or 0.1 μg of a compound were placed on the agar surface with a solvent control in the center of the plate. The plates were incubated at either 30 °C (fungi) or 37 °C (bacteria) for 48 h, and the resulting zones of growth suppression were measured.

4. Cytotoxicity Assay: Jurkat cells, non-adherent human T leukemia lymphoblast-like cell line (American Type Culture Collection), were seeded at 100000 cells/well by using RPMI media (HyClone, Logan, UT) supplemented with antibiotics and 10% heat-inactivated newborn calf serum (also referred to as complete media). After overnight incubation, cells were exposed for 22 h to several concentrations of chemical compounds. Cells from each individual well were collected in an ice-cold tube, placed on ice, and washed with cold complete media, and then, with cold PBS. After centrifugation at 1400 rpm at 4 °C for 5 min, the supernatant was removed, and the cell pellets were resuspended in 500 μL of staining solution, containing 2 μg/mL propidium iodide dissolved in FACS buffer (PBS, 0.5 mM EDTA, 2% heat-inactivated fetal bovine serum, and 0.1% sodium azide). The cells were then incubated in the dark at room temperature for 15 min and analyzed by flow cytometry, using Cytomic FC 500 (Beckman-Coulter, Miami, FL). The data were acquired and analyzed by using CXP software (Beckman-Coulter). To calculate the IC_{50}, the average of PI-positive cells (dead cells) obtained from triplicates of untreated cells was subtracted from each experimental point to obtain normalized values, and also to eliminate culture-inherent effects. In these studies, only untreated cells that were at 90% viability or higher were utilized. The average cytotoxicity (annotated as a percentage) over three independent experiments was plotted against chemical compound concentration in an *xy* (scatter) chart function (Microsoft Excel). The IC_{50} values were then calculated from the triplicate values by using the linear regression plot with its respective R^2 value between data points, to calculate the concentration of compounds disrupting 50% of the plasma membranes of the test cells. For each experimental set, three controls were prepared in triplicate: (1) untreated cells, (2) cells treated with hydrogen peroxide, and (3) cells treated with physiological saline solution. Hydrogen peroxide, which is well known as inducer of apoptosis and necrosis,[37] was added to a final concentration of 500 μM as a positive control of cell death and utilized to ensure that the flow cytometer was calibrated properly. Physiological saline solution (NaCl 0.9%), the diluent of chemical compounds, was tested at the same concentration as contained in the experimental samples, as a control for nonspecific diluent effects. The average of triplicate values from untreated cells was used as 100% of viability. No significant differences were observed in cells treated with physiological saline solution when compared with untreated cells.

5. Apoptosis Assay: Jurkat cells were seeded and cultured as described above and exposed to IC_{50} concentrations of the chemical compounds as determined by the cytotoxicity assays for 16 h. Cells from each individual well were collected and washed as described above. After centrifugation at 1400 rpm at 4 °C for 5 min, the media and PBS were removed. The staining procedure was performed by resuspending the cell pellets in 100 μL of binding buffer (0.1 M HEPES, pH = 7.4; 140 mM NaCl; 2.55 mM $CaCl_2$) containing 1 μL of 25 μg/mL Annexin V-FITC (Beckman Coulter, Miami, FL) and 5 μL of 250 μg/mL PI. After incubation for 15 min on ice in the dark, ice-cold binding buffer (400 μL) was added to the cell suspensions, gently homogenized, and immediately analyzed by flow cytometry. For each sample, 10000 individual events were acquired and analyzed by using CXP software (Beckman Coulter, Miami, FL). After exposure of cells to the chemical compounds, all subsequent procedures were carried out on ice or at 4 °C to arrest or slow down progression of cell damage. Prior to data acquisition, the flow cytometer was set up and calibrated by utilizing unstained, single- (PI or Annexin V-FITC) and double- (Annexin V-FITC plus PI) stained cells. The same three control groups (as described in the previous section) were used: untreated cells, cells treated with 250 μM H_2O_2, and cells treated with 4 μL of physiological saline solution.

6. Electron Microscopy and Image Analysis: A 2 mL aliquot of compound **9** in aqueous solution was applied onto a glow discharged carbon coated copper grid and blotted. The specimen was imaged with a JEOL-2100 transmission electron microscope, and images were recorded with a Tietz 2kx2k CCD camera at a nominal magnification of 50000x. At this magnification, the effective pixel size at the specimen was 3.06 Å. Particle selection and measurement were performed with the program ImageJ.[38]

Supporting Information (see footnote on the first page of this article): Selected $^{31}P\{^1H\}$ NMR spectra of compounds **1**–**10**.

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