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Isolation of an Intermediate in the Platination of *p*-Nitroacetophenone 4-Methylthiosemicarbazone: Potential Application as an Antitumor Drug

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The investigation of the formation and reactivity of Pd and Pt thiosemicarbazone complexes has revealed an unstudied intermediate derived from *p*-nitroacetophenone 4-methylthiosemicabazone ($L1H_2$). The $L1H_2$ ligand leads to a new complex [Pt(L1)($L1H_2$)] that supports the postulated mechanism of how cyclometallation reactions take place. All the newly synthesized complexes, [$(Pd(L1)_4]$, [$(Pt(L1)_4]$, and [Pt(L1)($L1H_2$)] (**3**), have been characterized and tested against MCF7, SF268, and NCI H460 cell lines. The crystal structure of [Pt(L1)($L1H_2$)]·dmso is reported.

Introduction

Structure-based drug design has as its main objective the identification of appropriate compounds for biological evaluation.[1] In anticancer research, the study of new potential drugs and the relationship between their structure and activity has provided an important insight into how to improve the current clinical drug cisplatin. Nevertheless, there are still many problems to be addressed in this field, such as resistance to cisplatin and the important side effects that it produces.[2] The preparation of innovative chemical compounds seems to be the most successful approach to drug design for cancer treatment.[3]

With regard to innovative compounds, thiosemicarbazones (TSCNs) have turned out to be versatile molecules not only because of their broad profile in pharmacological activity,[4,5] but also because TSCN can act as a ligand in coordination chemistry in different ways. It has been demonstrated in previous publications that TSCNs afford a diverse variety of compounds with different activities.[6,7]

Organometallic complexes have been used as precatalyst precursors for C–C coupling reactions[8] and have recently attracted attention as potential anticancer agents.[9] In fact, some publications have indicated the potential of metallacycles as antineoplastic agents,[10] which leads to possible alternative modes of cytotoxic action.[11,12] Thiosemicarbazones are also suitable ligands for C–M bond formation with metals such as Pd and Pt. In 1998, our research group published the first orthometallated tetranuclear complexes of TSCNs with Pd and Pt as metals.[11] The design of these complexes was inspired by the idea of a synergism between the TSCNs and the metal ions. We expected that this synergism would result in new metal drugs with higher activity, and the results obtained were very promising.[11] The possibility of modulating the cytotoxic activity by changing the structure of the complex was also proved.[13,14] Moreover, the variation in the donor atom type and the substituents in the TSCN structure provided, to these small molecules, some structure–activity relationships.[6,15] Our studies on a broad series of benzaldehyde thiosemicarbazones with different substituents as ligands and Pd^{II} and Pt^{II} as metal ions resulted in three different kinds of complexes: (i) tetranuclear complexes, where metallation occurred on the *ortho* position of the ligand; (ii) dinuclear but not cyclometallated complexes, in which the thiosemicarbazone acts as a chelating NS-bidentate donor (this type of dinuclear complex has been reported as the first step of the cyclometallation process); and (iii) mononuclear complexes, with potential leaving groups that could afford active forms and where no orthometallation was observed.[6]

For the present study, we have selected *p*-nitroacetophenone 4-methylthiosemicabazone ($L1H_2$) as ligand because it is sterically and electronically different, with regard to the substituents, from the molecules already studied,[6] and because of its potential for the rapid generation of a library of compounds for evaluation and structural activity studies. The investigation of the stability and modular properties of the complexes will permit an easy comparison with the complexes already published.[6] Although TSCNs are usually expected to afford metallation complexes (C–M bond formation) via the dinuclear chlorido-bridged complexes, we have observed that formation of other intermedi-

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ates is also possible with this particular ligand. Here we present the synthesis and characterization of palladium(II) and platinum(II) complexes with $L1H_2$. The final complexes were screened for their cytotoxicity against various cancer cell lines used at the National Cancer Institute (NCI) for in vitro screens: MCF-7 (adenocarcinoma, from human mammary gland), NCI-H460 (large cell lung cancer from human), and SF268 (central nervous system epithelial cancer).

Results and Discussion

Chemistry

The reaction between $[Pd(AcO)_2]$ and $L1H_2$ resulted in a tetranuclear complex $[Pd(L1)]_4$, where *p*-nitroacetophenone 4-methylthiosemicabazone acts as a tridentate CNS ligand (L1). Orthoplatination was also achieved by reacting $L1H_2$ with the Pt dinuclear allyl complex $[Pt(\mu\text{-}Cl)(\eta^3\text{-}C_4H_7)]_2$ in refluxing acetone. However, instead of the expected tetranuclear complex, or the dinuclear intermediate previously reported for this type of complexes,[6] the new mononuclear complex $[Pt(L1)(L1H_2)]$ was isolated. This complex contains the TSCN ligand coordinated in two different forms: L1 acts as a tridentate ligand (C-, N-, S-coordinated) and orthometallation takes place through this ligand; $L1H_2$ acts as a monodentate ligand that coordinates through the sulfur atom of the thionic form of the ligand to the forth coordination site of the platinum atom ($L1H_2$: S-coordinated).

In order to isolate the platinum tetranuclear complex with the general formula $[Pt(L1)]_4$, the reaction mentioned above was also carried out in refluxing acetone, but with a longer reaction time. Whereas the mononuclear intermediate is uniformly obtained as the only product in a few hours, the formation of the $[Pt(L1)]_4$ complex needs a longer reaction time and careful purification by chromatography is required to obtain the final compound. Moreover, the yield of $[Pt(L1)]_4$ is poor.

The three complexes were characterized by the usual techniques: NMR and IR spectroscopy, elemental analysis, and mass spectrometry. The structure of the complex $[Pt(L1)(L1H_2)]$·dmso was also determined by X-ray crystallography. Figure 1 shows a view of the complex, where the one TSCN ligand is coordinated to the platinum atom through its sulfur atom, while the other TSCN ligand acts as a tridentate ligand. It is clear that activation of the C–H bond takes place, which leads to orthometallation and Pt–C bond formation.

Bond lengths between platinum and the atoms of the tridentate ligand are: Pt(1)–S(1) 2.3296(11) Å, Pt(1)–N(2) 2.006(4) Å, Pt(1)–C(3) 2.021(4) Å. The bond length Pt(1)–S(1L) [2.2832(12) Å] for the monodentate ligand was found to be slightly shorter than Pt(1)–S(1) (tridentate ligand). The angles around the platinum atom deviate from 90° presumably because of the strain induced by the tridentate ligand. The angles that involve the tridentate L1 ligand are 81.65(18)° [N(2)–Pt(1)–C(3)] and 83.70(12)° [N2–Pt1–S1]. The angles C(3)–Pt(1)–S(1L) and S(1L)–Pt(1)–S(1) are

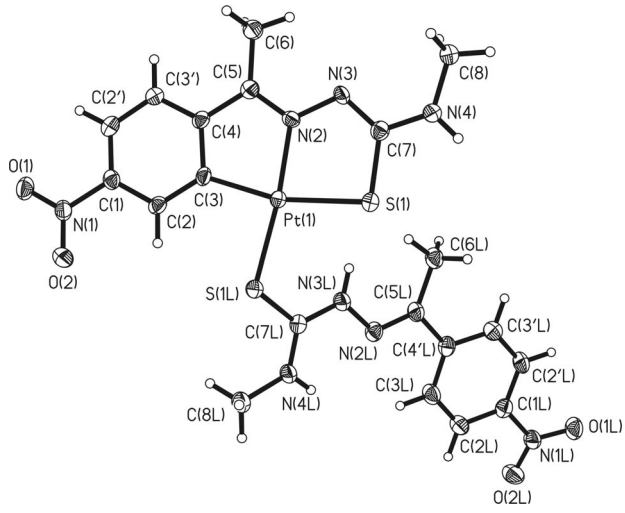

Figure 1. ORTEP view of complex $[Pt(L1)(LIH_2)]$.

92.76(14)° and 101.86(4)°. Both thiosemicarbazone ligands are nearly planar, with a dihedral angle of 43.78°. The structure also contains a solvent molecule dmso, which is hydrogen bonded to the monodentate ligand: O(1D)···H–N(4L) 2.832(6) Å. Another intermolecular hydrogen bond that involves two tridentate ligands contributes to the stabilization of the structure [N(4)–H···N(3) 3.166(6) Å]. One of the most relevant aspects of this mononuclear structure is the strength of the Pt–S bonds, which, as in the case of the tetranuclear compound,[11] is probably the reason for preventing its cleavage.

The mechanism for the formation of the observed mononuclear species is not completely clear; however, oligomerization by the bridging M–S–M unit of TSCN observed by other authors[16,17] may be the clue to the activation of the second coordinated ligand molecule.

Since we first published the orthometallation of thiosemicarbazones, some interesting work has been done in this field, especially with respect to the reactivity of the tetranuclear complexes.[18] These polynuclear complexes are very stable in solution, and no substitution of the coordinated ligands by a classical Lewis base (nitrogen donor) has been observed, such as a nitrogen-DNA base model. By only using phosphane ligands as Lewis bases, mononuclear complexes have been isolated by cleavage of the M–S bond of the tetranuclear complexes.[16] Moreover, we have not been able to find a single example of complexes characterized by X-ray diffraction in which the TSCN ligand is coordinated in two different manners to the platinum atom, one molecule metallated (CNS-coordinated) and the other molecule available to be metallated (NS-coordinated).

Only a platinum mononuclear derivative has been found to be in some way similar; the acetylpyridine thiosemicarbazone ligands are not equivalent in structure, one being tridentate with NNS donation and the other being monodentate with only the sulfur atom as donor.[19] But no cyclometallation takes place because the ligand is a pyridine derivative, and the possible oligomerization of this monomer

has not been reported either, even though it is possible to find in the literature tetranuclear complexes in which the ligand is NNS-coordinated to the palladium ion.[20] With respect to the biological activity, antibacterial studies have been performed with this complex, and it has been proved that *B. Cereus* bacteria was the most sensitive microorganism to this drug.[21]

Biology

To check the anticancer properties of the new series of complexes, we screened them for their ability to inhibit the in vitro growth of a panel of cell lines that include examples of adenocarcinoma from the human mammary gland (MCF7), large cell lung cancer from a human (NCI-H460), central nervous system epithelial cancer (SF268). The tumor cell lines are also used in the NCI to identify novel potential anticancer drugs.

The new series of complexes were evaluated, and their results were compared with those of $L1H_2$ (free ligand) and the structurally related complex $[Pt(L2)]_4$, where L2 is *p*-isopropylbenzaldehyde thiosemicarbazone. This last complex was selected as it was the best candidate as a metallodrug found from our previous investigations.[6]

The cytotoxic activity was evaluated after 96 h and expressed as IC_{50} (drug concentration that reduces the number of viable cells by 50%). The formation of the metal complexes with the TSCN selected, $L1H_2$, produced metallodrugs with antitumor activity, as shown by the IC_{50} values presented in Table 1. As mentioned before, the synergism between the TSCNs and the metal ions results in a high antitumor activity. The complexes $[Pt(L1)]_4$ and $[Pt(L1)(L1H_2)]$ gave lower values of IC_{50} than the free ligand $L1H_2$, which, in fact, did not produce cell death at the concentrations tested (Table 1). The most noteworthy effect is the high activity of these drugs at sub-micromolar range, as has already been mentioned specially for the platinum derivatives. Within this group of platinum complexes screened, L1 platinum derivatives are more active than the L2 derivative used as the model. The replacement of the isopropyl substituent [$-CH(CH_3)_2$] in the phenyl group with a nitro substituent ($-NO_2$) provides an even better potential as anticancer drug candidates, as can be observed in the IC_{50} values from both tetranuclear platinum derivatives $[Pt(L2)]_4$ and $[Pt(L1)]_4$ (see Table 1).

Table 1. IC_{50} values for Pd and Pt TSCN complexes.

Drug [μM]	MCF7	NCI-H460	SF268
$L1H_2$	>100	>100	>100
$[Pt(L1)(L1H_2)]$	0.28	1.88	0.17
$[Pd(L1)]_4$	>100	>100	>100
$[Pt(L1)]_4$	0.23	2.99	0.44
$[Pt(L2)]_4$	1.15	12.58	0.97

Platinum complexes have been demonstrated to be better candidates as antitumor agents because of their lower reactivity,[21] although we have noticed that palladacycles formed with TSCN ligands,[6] and also with a broad variety of other organic molecules,[11] have shown a notable antitumor activity as well. Surprisingly, the tetranuclear palladium complex with the nitro substituent, $[Pd(L1)]_4$, shows no activity at all against the tumor cell lines checked. The platinum derivatives $[Pt(L1)]_4$ and $[Pt(L1)(L1H_2)]$ seem to be very active against those tumor cell lines screened.

As the values for the platinum derivatives are in the submicromolar range for some tumor cell lines analyzed, nanomolar concentrations need to be checked in order to find the most appropriate drug concentration for therapeutic purposes. We therefore suggest that the toxic concentration needed with these compounds is probably lower than that of complexes published before, and these complexes are therefore more valuable for therapeutic purposes. They deserve to be checked in vivo.

The substitution of the nitro group by the isopropyl group in the TSCN moiety seems to be an important factor that influences the structures and cytotoxicity. Further investigations in this field should be conducted to fully comprehend the substituents effects; we are in fact proceeding in this direction.

Conclusions

In summary, polynuclear TSCNs platinum complexes have been demonstrated, once more, to be good candidates as antitumor drugs. Although the tetranuclear molecule does not undergo ligand substitution by a Lewis base, TSCN oligomerization may be of crucial importance in its antitumor activity. Some authors have postulated that weak M···M interactions are possible between d^8 metal ions in polynuclear complexes, with similar distances between the metal ions as those found for the TSCN tetranuclear complexes, which suggests that binding or interaction of Lewis acids and/or donor bases to these metal atoms at the axial position can be modulated by these M···M interactions.[22] The mononuclear complexes also showed high antitumor activity, probably because of certain interactions of the DNA bases with the metal ion, since the breaking of the Pt–S bond is not expected. Because M···M interactions cannot be detected in the mononuclear structure, the availability of the metal in the mononuclear complex is probably higher.

Experimental Section

Materials and Methods: 4-Methyl-3-thiosemicarbazide, 4-nitroacetophenone, and other reagents and solvents were obtained from commercial sources and used without prior purification. $[Pt(\mu\text{-}Cl)(\eta^3\text{-}C_4H_7)]_2$ was synthesized as described in the literature.[23] All compounds synthesized were appropriately characterized by the usual techniques. ^1H NMR, ^{13}C NMR, and 2D NMR (HMBC and HMQC)[24] spectra were recorded on a Bruker AMX-300 (300 MHz) spectrometer in $[D_6]$dmso solution. The spectra were double-checked over 72 h, and neither coordination of dmso to the metal nor decomposition of the sample was detected. Elemental analyses were performed on a Perkin–Elmer 2400 series II micro-

analyzer. FAB mass spectra (*m*/*z*) were obtained with a V.G. AUTOSPECT high resolution spectrometer. The experimental part was achieved with the L-SIMS techniques by using *m*-NBA. The relative abundance of the peaks is given without taking into account the matrix peak (*m*-NBA).

Synthesis

***p*-Nitroacetophenone 4-Methylthiosemicarbazone ($L1H_2$):** $L1H_2$ was synthesized following a method previously reported[25] with some modifications. 4-Methyl-3-thiosemicarbazide (1 g) was previously dissolved in an aqueous solution of 5% glacial AcOH and added to an EtOH solution of 4-nitroacetophenone (1.5 g) at 40 °C. The mixture was stirred at this temperature for 24 h. $L1H_2$ was isolated by filtration as a yellow solid and recrystallized from methanol. Yield: 1.4 g (60%). $C_{10}H_{12}N_4O_2S$ (252.06): calcd. C 47.61, H 4.50, N 22.22, S 12.68; found C 47.21, H 4.59, N 22.33, S 12.60. IR: $\tilde{\nu}_{max}$ = 3361, 3203, 1546, 855 cm^{-1}. ^1H NMR ([D$_6$]dmso): δ = 8.37 (br. s, 4 H, 2-H and 3-H), 2.34 (s, 3 H, 6-H), 3.11 (s, 3 H, 8-H), 10.53 (br. s, 1 H, 1-NH), 8.62 (s, 1 H, 2-NH) ppm. ^{13}C NMR ([D$_6$]-dmso): δ = 147.49 (C-1), 123.40 (C-2), 127.77 (C-3), 144.09 (C-4), 145.09 (C-5), 14.08 (C-6), 178.97 (C-7), 31.34 (C-8) ppm.

[Pd(L1)]$_4$: $L1H_2$ (169 mg, 0.67 mmol) in glacial AcOH (10 mL) was added to palladium(II) acetate (150 mg, 0.67 mmol) under argon whilst stirring; the mixture was then heated (ca. 40 °C) for 48 h. The resulting bright red solid was filtered off and washed several times with water, a 5-% aqueous solution of sodium hydrogen carbonate, water, and acetone. Yield: 763 mg (85%). $C_{40}H_{40}N_{16}O_8Pd_4S_4$ (1425.82): calcd. C 33.52, H 3.08, N 14.89, S 8.52; found C 33.54, H 2.73, N 14.93, S 8.45. IR: $\tilde{\nu}_{max}$ = 3388, 1517, 1564, 749 cm^{-1}. FAB-MS: *m*/*z* = 1427.3 (100) $[M + 1]^+$. ^1H NMR ([D$_6$]dmso): δ = 7.83 (dd, ^1J = 2.0 Hz, ^2J = 8.3 Hz, 1 H, 2-H), 8.09 (d, ^1J = 2.0 Hz, 1 H, 2′-H); 6.90 (d, ^2J = 8.3 Hz, 1 H, 3-H), 1.60 (s, 3 H, 6-H), 2.83 (s, 3 H, 1-NH), 7.68 (s, 1 H, 2-NH) ppm. ^{13}C NMR ([D$_6$]dmso): δ = 143.65 (C-1), 116.12 (C-2), 123.15 (C-2′), 124.97 (C-3), 152.73 (C-3′), 152.69 (C-4), 163.58 (C-5), 12.73 (C-6), 161.90 (C-7), 32.97 (C-8) ppm.

[Pt(L1)(L1H$_2$)]: $L1H_2$ (136 mg, 0.52 mmol) in acetone (4 mL) was added to [Pt(μ-Cl)(η^3-C_4H_7)]$_2$ (150 mg, 0.26 mmol) and stirred at high temperature (70 °C) for 6 h. The resulting solution was concentrated by rotary evaporation, which led to the precipitation of a red solid. The red solid was filtered, recrystallized in acetone/ether (1:1), and finally characterized as the compound [Pt(L1)(L1H$_2$)]. Yield: 112 mg (62%). $C_{20}H_{22}N_8O_4PtS_2$ (697.08): calcd. C 34.43, H 3.17, N 16.06, S 6.19; found C 34.23, H 3.05, N 16.00, S 6.01. IR: $\tilde{\nu}_{max}$ = 3440, 3262, 3082, 1709, 1601, 1578, 1512, 818, 778 cm^{-1}. ^1H NMR ([D$_6$]dmso): δ (L1) = 2.39 (s, 3 H, 6-H), 3.15 (s, 3 H, 1-NH), 7.87 [dd, ^1J = 2.3 Hz, ^2J = 8.5 Hz, 1 H, 2-H], 8.34 (d, ^1J = 2.3 Hz, 1 H, 2′-H), 6.93 (d, ^2J = 8.5 Hz, 1 H, 3-H), 7.34 (s, 1 H, 2-NH) ppm; δ ($L1H_2$) = 2.50 (s, 3 H, 6-H), 2.90 (s, 3 H, 1-NH), 8.19 (br. s, 4 H, 2-H and 3-H), 10.49 (br. s, 1 H, 1-NH), 8.45 (s, 1 H, 2-NH) ppm. ^{13}C NMR ([D$_6$]dmso): δ (L1) = 143.88 (C-1), 119.72 (C-2), 124.57 (C-2′), 126.21 (C-3), 150.00 (C-3′), 152.69 (C-4), 156.33 (C-5), 13.33 (C-6), 161.90 (C-7), 32. 67 (C-8) ppm; δ ($L1H_2$) = 147.69 (C-1), 123.17 (C-2), 127.57 (C-3), 144.89 (C-4), 147.29 (C-5), 13.85 (C-6), 178.76 (C-7), 31.09 (C-8) ppm.

[Pt(L1)]$_4$: An acetone solution (4 mL) of $L1H_2$ (136 mg, 0.52 mmol) was added to [Pt(μ-Cl)(η^3-C_4H_7)]$_2$ (150 mg, 0.26 mmol) and stirred at high temperature (70 °C) for 10 d. The solvent was removed from the filtrate solution by rotary evaporation. The residue was dispersed in Celite and purified by chromatography on a silica gel column. The products were eluted in the following order: the starting material first (CH_2Cl_2) followed by the tetranuclear complex (CH_2Cl_2/EtOH, 100:1). Yield: 285 mg (62%). $C_{40}H_{40}N_{16}O_8Pt_4S_4$ (1780): calcd. C 26.97, H 2.26, N 12.58, S 7.20; found C 26.62, H 2.51, N 12.89, S 6.94. IR: $\tilde{\nu}_{max}$ 3382, 1517, 1564, 749 cm^{-1}. FAB-MS: *m*/*z* = 1780.6 (100) $[M]^+$. ^1H NMR ([D$_6$]dmso): δ = 2.07 (s, 3 H, 6-H), 2.89 (br. s, 3 H, 1-NH), 7.84 (dd, ^1J = 1.9 Hz, ^2J = 8.2 Hz, 1 H, 2-H), 8.48 (d, ^1J = 1.9 Hz, 1 H, 2′-H), 7.31 (d, ^1J = 1.9 Hz, 1 H, 3-H), 7.70 (s, 1 H, 1-NH) ppm. ^{13}C NMR ([D$_6$]-dmso): δ = 143.65 (C-1), 116.12 (C-2), 123.15 (C-2′), 124.97 (C-3), 152.73 (C-3′), 152.69 (C-4), 163.58 (C-5), 12.73 (C-6), 161.90 (C-7), 32.97 (C-8) ppm.

X-ray Diffraction Studies and Crystal Data: The diffraction data were collected at 100 K on a Bruker SMART 6K CCD diffractometer (Cu-K_α radiation, λ = 1.54178 Å). The structure was solved by conventional Patterson methods[26] and subsequent Fourier syntheses and refined by full-matrix least-squares for F^2 with the SHELX programs.[27] The positions of all non-hydrogen atoms were deduced from difference Fourier maps and refined anisotropically. Hydrogen atoms were included in calculated positions and refined with isotropic displacement parameters. Crystal data: [$C_{20}H_{22}N_8O_4PtS_2 \cdot C_2H_6OS$], M = 775.79, monoclinic, $P2_1/c$, a = 15.3137(3), b = 22.0656(4), c = 7.9268(2) Å, β = 91.5350(10)°, V = 2677.55(10) $Å^3$, Z = 4, $D_{calcd.}$ = 1.924 $g\,cm^{-3}$, R = 0.0311 (wR = 0.077), GOOF = 0.999, number of reflections = 5037. CCDC-651025 contains 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 Lines and Culture Conditions

Materials: All cell lines were grown in Dulbecco's modified Eagles medium (DMEM) supplemented with 10% fetal calf serum (FCS), fungizone and penicillin/streptomycin.

Cytotoxicity Assessment: The compounds were tested in 96-well trays. Cells growing in a flask were harvested just before they became confluent, counted using a haemocytometer, and diluted with media thus adjusting the concentration to the required number of cells per 0.2 mL (volume for each well). Cells were then seeded in 96-well trays at a density between 1000 and 4000 cells/well, depending on the cell size. Cells were left to plate down and grow for 24 h before adding the drugs.

The drugs were weighed and diluted with dmso to a concentration of 10 mM. A "mother plate" with serial dilutions was prepared from this at 200 times the final concentration in the culture. The final concentration of dmso in the tissue culture media did not exceed 0.5%. The appropriate volume of the compound solution (usually 2 μL) was added automatically (Beckman FX 96 tip) to the media to make up the final concentration for each drug.

The medium was removed from the cells and replaced with 0.2 mL of medium dosed with the drug. Each concentration was assayed in triplicate. Two sets of control wells were left on each plate, which contained either medium without the drug or medium with the same concentration of dmso. A third control set was used in which the cells were untreated just before the addition of the drugs (seeding control, number of cells starting the culture).

The cells were exposed to the drugs for 96 h and then washed twice with phosphate-buffered saline solution before being fixed with 10% glutaraldehyde. The cells were washed twice and fixed with crystal violet (0.5%) for 30 min. They were then washed extensively and solubilized with 15% acetic acid, and the absorbance was measured at 595 nm.

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