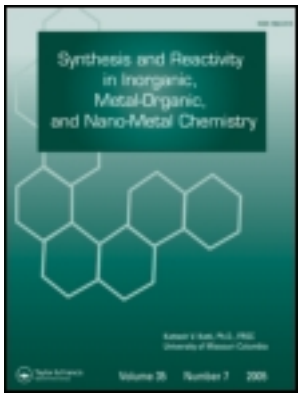

Synthesis and Reactivity in Inorganic, Metal-Organic, and Nano-Metal Chemistry

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Metallation of Some New Imines and Evaluation of Their Antimicrobial and Anticancer Activity

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Metallation of Some New Imines and Evaluation of Their Antimicrobial and Anticancer Activity

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Metallation of new imines 2-(4-(Dimethylamino)benzylideneamino)benzenethiol (1) and 2-(4-nitrobenzylideneamino)-benzenethiol(5) with Hg(II), Ni(II) acetate, and palladium chloride afforded metallated products (2), (3), and (4) in the form of monomercurated, dinickel nickel bis-, monopalladated products and monometallated products of Hg^{++} and Ni^{++} (6) and (7), and monopalladated cyclized product (8), respectively. Compounds (1) and (5) were prepared from the reaction of o-aminothiophenol with N,N-dimethylaminobenzaldehyde and p-nitrobenzaldehyde in ethyl alcohol. Elemental analyses, IR, ^{1}HNMR, and mass spectral elucidated the structures. All the newly synthesized compounds have been evaluated for their antimicrobial activity against gram positive and gram negative bacteria and fungi. Compounds (4) and (8) exhibited *in vitro* anticancer activity toward breast cancer.

Keywords anticancer activity, antimicrobial, imines, metallation

INTRODUCTION

Schiff bases derived from aromatic amines and aromatic aldehydes have a wide variety of applications in many fields (e.g., biological, inorganic, and analytical chemistry).[1,2] A series of Schiff bases have been synthesized from the condensation of (4.4′-diaminodiphenylsulphone) with various aromatic or heterocyclic aldehydes and the new compounds were evaluated for their in vitro activity against several microbes.[3,4] Schiff base derivatives of 4-methylpyridin-2-amine have been screened for their antimicrobial activities.[5] Some Schiff bases of [4-(amino)-5-phenyl-4H-1,2,4-triazole-3-thiol] were screened for their antianxietic activity.[6] Schiff bases derived from 2-amino 4,6- dimethyl benzothiazole and pyridine/pyrrole 2-carboxyaldehyde and their complexes were also screened for the antimicrobial activity, antibacterial activity against bacteria such as *S. aureus*, *E. coli*, and antifungal activity against *A. niger* and *A. flavus*.[7] Mild and significant Schiff bases have been synthesized from different aldehyde and diamine using P_2O_5/SiO2 as catalyst by crushing in a mortar at room temperature under free solvent conditions.[8] Some metallated Schiff bases with Ni(II), Co(II), and Cu(II) exhibited potential effect as killing agents for Biomphalaria alexandrina snails without affecting the surrounding environment.[9] Schiff base 2-(4-methoxybenzylidene amino) benzene-thiol, its metallation with mercury(II), nickel(II), palladium(II), and phosphorylation gave compounds exhibited antimicrobial and anticancer activity.[10] Organopalladium and organomercury compounds via metallation of some new Schiff bases were also synthesized.[11,12] Screening of organopalladium of the acetone Schiff bases of S-methyl-and S-benzyldithiocarbazate compounds for their cytotoxicities against T-lymphoblastic leukemia cancer cells shows that they exhibit strong cytotoxicities against this cancer; their activities being more than that of the standard anticancer drug tamoxifen.[13] Biological studies of some palladium(II) and platinum(II) compounds derived from biologically active sulfur donor ligands 1-H-indol-2,3-dione benzothiazoline and 5-nitro-1-H-indol-2,3-dione benzothiazoline have been noted that the growth-inhibiting potential of the compounds is greater than the parent benzothiazolines toward a variety of fungal and bacterial strains.[14] Environmentally benign studies of bivalent transition metal complexes with Co^{2+}, Ni^{2+}, and Zn^{2+} of tridentate Schiff base ligands were evaluated for their *in vitro* antimicrobial activity,[15] in continuation to our previous works on Schiff bases and their metallation. This work planned to synthesize new imines containing electron-attracting and electron-repelling groups followed by metallation with some metal salts such as Hg(II), Ni(II) acetates, and Pd(II) chloride to study their effect on orientation in each case and screening the antimicrobial and anticancer activity.

EXPERIMENTAL

Melting points were measured by a Gallen Kamp melting point apparatus. Thin-layer chromatography was performed with fluorescent silica gel plates HF_{254} (Merck), and plates were viewed under UV light at 254 and 265 nm. The elemental analyses for C, H, and N were determined by a Perkin-Elmer analyzer 2440 (Micro Analytical Center, Cairo University Giza,

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Egypt). Infrared spectra (λ-cm^{-1}) were recorded on Bruker Vector (Germany) and on Mattson FT-IR 1000 (Cairo University Giza, Egypt), using KBr disks. Mass spectra were measured on GCQ Finnigan MAT (Cairo University Giza, Egypt). ^{1}H-NMR spectra were recorded on Gemini 200 MHZ NMR spectrometer, in DMSO-d_6 solution with TMS as internal standard in the Micro Analytical Center, Cairo University, Giza, Egypt. Analyses of mercury were carried out by thiocyanate method[16] using ferric alum as indicator as well as by mercurometry using diphenyl carbazone-bromothymol blue as indicator.[17] The antibacterial activity was determined in a laboratory belongs to the Micro Analytical Center, Cairo University, and anticancer activity was checked in the National Cancer Institute, Cancer Biology Department, Pharmacology, Cairo University, Egypt.

Preparation of imine(1) 2-(4-(dimethylamino) benzylideneamino)benzenethiol

2-aminothiophenol (0.125 g, 1 mmol) in 20 mL ethyl alcohol was added to (0.149 g, 1mmol) of N,N-dimethylaminobenzaldhyde in 20 mL ethyl alcohol and the mixture was refluxed for 4 h then left to cool. The precipitated product was filtered, dried, and crystallized from ethyl alcohol to give compound (**1**)**:** white crystals from ethyl alcohol, m.p. 125-126°C, 39% yield, IR cm^{-1} ($\surd$): 2986–2888 (C-H, aliph. Str.), 2548 (SH), 1470 (C-H, aliph. bend.), 1608 (C=N). ^{1}HNMR showed δ 8.01 ppm (1H, HC=N), δ7.53–7 ppm (8H, arom.), δ3.2 ppm (1H, SH), and δ2.9 ppm(6H, $2CH_3$). Anal. Calcd. for $C_{15}H_{16}N_2S$: C 70.31, H 6.25, N 10.93. Found: C 70.52, H 6.28, N 10.95.

Metallation of (1) to Give (2), (3), and (4) (General Procedure)

A mixture of (0.256 g, 1 mmol) of Schiff base (**1**) and (1 mmol) of mercuric acetate or nickel acetate in 30 mL toluene and 2 mL acetic acid or palladium chloride in methanol with few drops of HCl was refluxed for 3 h, left to cool where crystalline products (**2**), (**3**), or (**4**) were precipitated after cooling, filtered, and dried and crystallized from acetic acid to give (**2**) or (**3**) and from methanol to give compound (**4**): violet crystals from acetic acid, m.p. 320–321°C, 42% yield, IR cm^{-1} ($\surd$): 3210 (NH) and at 510 (C-Hg).[18] MS spectrum m/z (%): the molecular ion peak at 554(2.5), the base peak at 93(100), 259(1) $HgOCOCH^3_+$, 256 (12) M-$HgOCOCH^3_+$, 200(22) Hg^+. Anal. Calcd. for $C_{17}H_{18}N_2SO_2Hg.2/3CH_3$ COOH: C 39.66, H 3.72, N 5.04, Hg 36.17. Found: C 39.50, H 3.50, N 4.98.

Compound (**3**): Green crystals from acetic acid, m.p. 335–336°C, IR cm^{-1} ($\surd$): 3243 (NH), at 552 (Ni-C) and absence of $\surd_{SH}$ and $\surd_{C=N}$. The MS spectrum m/z (%): the molecular ion peak at 905(0.7), the base peak at 51(100). Anal. Calcd. for $C_{34}H_{32}N_4SO_4Ni_3.10\ H_2$ O: C 43.03, H 5.48, N 5.90, Ni 18.57. Found: C 42.92, H 5.46, N 5.88, Ni 18.52.

Compound (**4**): Orange crystals from methyl alcohol, m.p. 260–261°C, IR cm^{-1} ($\surd$):537 (C-Pd). The ^{1}HNMR spectrum showed signals at δ7.8–6.9 ppm (aromatic protons), δ 4.6 ppm (NH) and δ 2.8 ppm ($2CH_3$) protons and absence of δ 8.1 ppm. MS spectrum m/z (%): the base beak at 253(100). Anal. Calcd. for $C_{15}H_{15}N_2SPdCl$: C 45.39,H 3.78, N 7.06, Pd 26.73. Found: C 45.22, H 3.76, N 7.00, Pd 26.62.

Preparation of Imine (5) 2-(4-nitrobenzylideneamino) benzenethiol

A mixture of 2-aminothiophenol (0.125 g, 1 mmol) and p-nitrobenzaldhyde (0.151 g, 1 mmol) in 20 mL ethanol was refluxed for 1 h; the formed precipitate was collected by filtration, dried, and crystallized from ethanol. Compound (**5**): yellow crystals, Yield: 92%; m.p: 189–190°C. IR cm^{-1} (ν): 3040 (ArC-H), 2978–2845 (Aliph. C-H str.), 2552 (SH), 1631(C=N), 1600 (Ar. C=C), 1426 (Aliph. CH bend.), 1512, 1360 (conjugated NO_2). MS spectrum m/z (%): 257 (0.3) for M–1^+, the base peak at 240 (100). Anal. Calcd. for $C_{13}H_{10}N_2\ O_2S$: C 60.46, H 3.87, N 10.85. Found: C 60.49, H 3.88, N 11.00.

Metallation of (5) to give (6),(7) (general procedure)

A mixture of (1 mmol) of (**1**) and (1 mmol) of metal acetate in 30 mL toluene and few drops of acetic acid was refluxed for 3 h, the precipitated product was filtered, dried, and crystallized from acetic acid. Metallated compound (**6**): gray crystals, 89% yield; m.p. d. 280–281°C. IR cm^{-1} (ν): 3072 (ArC-H), 2944–2856 (Aliph. C-H str.), 2550 (SH), 1649 (C=N), 1600 (Ar. C=C), 1471 (Aliph. CH bend.), 1515, 1362 (conjugated NO_2), 797–630 (Arom. out of plane bend.), 510 (Hg-C). MS spectrum m/z (%): 519 (0.2) M+2 $^+$, base peak at 93(100). Anal. Calcd. for $C_{15}H_{12}HgN_2O_4S$: C 34.88, H 2.32, N 5.42, Hg 38.87. Found (%): C 43.65, H 2.32, N 7.99, Hg 38.80.

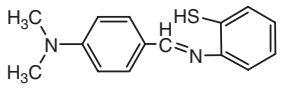
Metallated compound (**7**): green crystals, 85% yield, m.p above 350°C. IR cm^{-1} (ν): 3048 (ArC-H), 2954–2850 (Aliph. C-H str.), 2550 (SH), 1682 (C=O), 1649 (C=N), 1600 (Ar. C=C), 1418 (Aliph. CH bend.), 1560, 1315 (conjugated NO_2), 831–628 (Arom. out of plane bend.), 552 Ni-C. MS spectrum m/z (%): 448 (1) M+1 $^+$, base peak at 51(100). Anal. Calcd. for $C_{15}H_{12}N_2NiO_4S.4H_2O$: C 40.29, H 4.47, N 6.26, Ni 13.19. Found (%): C 40.16, H 4.58, N 6.88, Ni 13.00.

Metallation of Compound (5) to Give Compound (8)

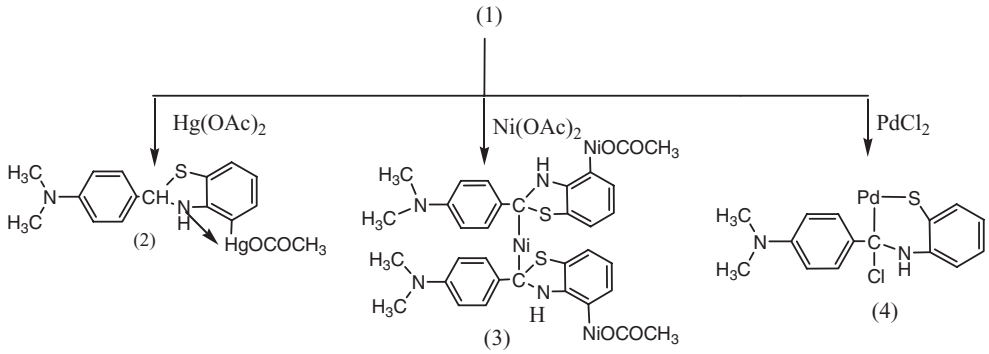
A mixture of (0.258 g, 1 mmol) of compound **1** and (0.177 g, 1 mmol) of palladium chloride in 30 mL methanol and 2 mL conc. HCl was refluxed for 3 h, and the crystalline product was formed, filtered, dried, and crystallized from methyl alcohol. Metallated compound (8): brown crystals, Yield: %, m.p above 300°C. IR cm^{-1} (ν): 3040 (ArC-H), 2853 (Aliph. C-H str.), 1650 (C=N), 1600 (Ar. C=C), 1418 (Aliph. CH bend.), 1512, 1360 (conjugated NO_2), 798–684 (Arom. out of plane bend.), 537 (Pd-C). MS spectrum m/z (%): 401 (4.38) M+2^+, base peak at 183(100). Anal. Calcd. for $C_{13}H_8N_2O_2PdS.HCl$: C 39.09, H 2.25, N 7.01, Pd 26.59. Found: C 40.12, H 2.20, N 7.04, Pd 26.50.

RESULTS AND DISCUSSION

N,N-dimethylaminobenzaldehyde reacted with o-aminothiophenol in ethyl alcohol to give new product (**1**).



2-(4-(dimethylamino)benzylideneamino)benzenethiol



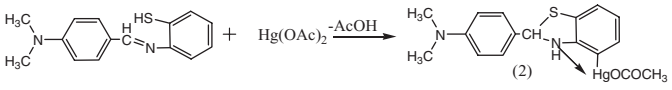
SCH. 1.

The reaction was done also under microwave irradiation, and by fusion with two times yield. Metallation of the product with mercuric acetate, nickel acetate and palladium chloride afforded compounds (**2**), (**3**), and (**4**) (Scheme 1).

The structure of product (**1**) was confirmed by IR, ^{1}H-NMR, elemental analysis, and chemical tests. The IR spectrum showed $\surd_{CH}$ aliphatic stretching at 2986–2888 cm^{-1}, $\surd_{SH}$ at 2548 cm^{-1}, $\surd_{CH}$ bending at 1470 cm^{-1}, and $\surd_{C=N}$ at 1608 cm^{-1}. ^{1}HNMR showed δ8.01 ppm (1H, HC=N), δ7.53–7 ppm (8H, arom.), δ3.2 ppm (1H, SH), and δ2.9 ppm (6H, 2CH_3). It gave negative azo dye and this proved that condensation occurred via NH_2 and the aldehydic carbonyl, also it gave positive spot test[19] for –SH as well as its solubility in sodium hydroxide

Action of Mercuric Acetate on Compound (1)

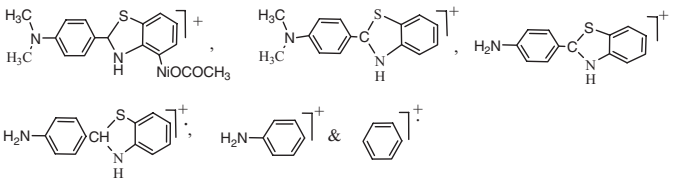
Mercuric acetate reacted with compound (**1**) in toluene under reflux to afford monomercurated product (**2**) via coordination to nitrogen followed by electrophilic substitution of the aromatic moiety.



Elucidation of the structure was based on elemental analysis, IR, and MS spectra. The IR spectrum showed the absence of SH group and the presence of the new absorption bands of $\surd_{NH}$ at 3210 cm^{-1} and $\surd_{C\text{-}Hg}$ at 510 cm^{-1}.[18] The MS spectrum showed the molecular ion peak at m/z 554 (2.5%), the base peak at m/z 93 (100%) $PhNH_2^+$ and fragments at m/z's 259 (1%) $HgOCOCH_3^+$, 256 (12%) M-$HgOCOCH_3^+$, and 200 (22%) Hg^+.

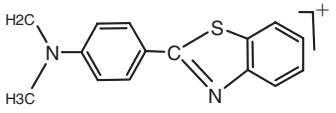
Action of Nickel Acetate on Compound (1)

The metallated product (**3**) was synthesized via the reaction of compound **1** with nickel acetate, where it gave dinickelated-nickel bis-compound (**3**). The data obtained from elemental analysis, IR, and MS spectra confirmed its structure. The IR spectrum showed new bands for $\surd_{NH}$ at 3243 cm^{-1}, $\surd_{Ni\text{-}C}$ at 552 cm^{-1}, and absence of $\surd_{SH}$ and $\surd_{C=N}$. The MS spectrum showed the molecular ion peak at m/z 905 (0.7%). The base peak at m/z 51 (100%) can be attributed to C_4 H_3^+. The fragment at m/z 371 (2.1%), 255 (8.1%), 227 (17.6), 228 (53.9%), 93 (12.8%), and 78 (66.8%) is due to

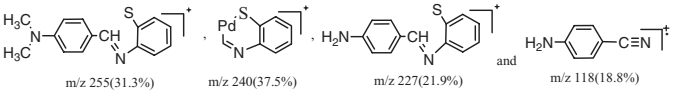


Action of Palladium Chloride on Compound (1)

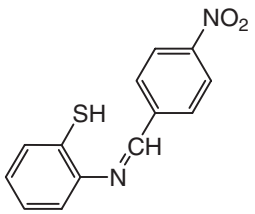
Reaction of palladium chloride with compound **1** in methanol with drops of conc. HCl gave mono palladated compound (**4**). The structure was consistent with the data obtained from elemental analysis, IR, and MS spectra. The IR spectrum showed new absorption band at 537 cm^{-1} due to $\surd_{C\text{-}Pd}$. The ^{1}HNMR spectrum showed signals at δ7. 8–6.9 ppm (aromatic protons), δ4.6 ppm (NH) and δ2.8 ppm (6H, 2CH_3) protons and absence of(1H, HC=N) at δ 8.1 ppm. The MS spectra did not show the molecular ion peak, the base beak at m/z 253 (100%) due to



the fragments at m/z's 255, 240, 227, and 118 can be attributed to p-Nitrobenzaldhyde reacted with o-aminothiophenol in ethyl



alcohol under reflux for 3 h to give 2-(4-nitrobenzylideneamino) benzenethiol (**5**). The reaction may proceeds via condensation reaction.

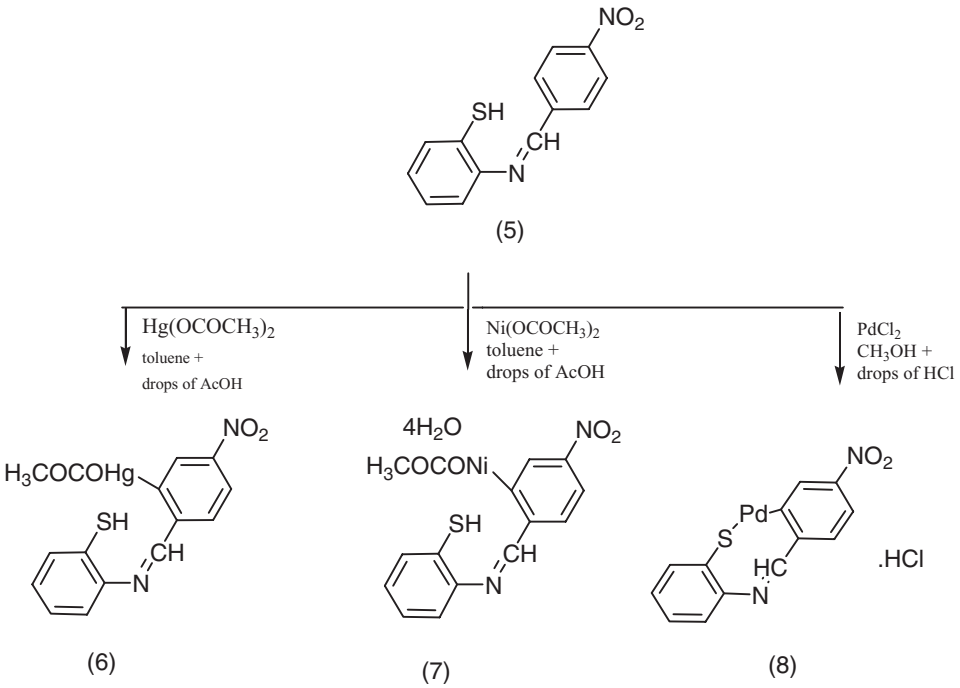


(5)

Considering the data of IR, MS spectroscopy, and elemental analysis, the structure of (**5**) was investigated and gave negative azo dye; it also gave a positive spot test[19] for SH as well as its solubility in sodium hydroxide. The IR spectrum showed $\surd_{SH}$ 2552, $\surd_{C=N}$ 1649, and $\surd NO_2$ 1515, 1362 (conjugated NO_2). The metallation of compound (**5**) with mercuric acetate, nickel acetate, and palladium chloride takes place in good yield and the reaction may take place via substitution reaction in the m position with respect to the nitro group. The structures were confirmed by elemental analyses, IR, ^{1}H NMR, and MS spectra. The IR showed $\surd_{S\text{-}H}$ for compounds (**6**) and (**7**) and showed new bands for Hg-C at 512 cm^{-1} and N i-C at 552 cm^{-1}. The MS showed m/z 519 (0.2%) M+2$^+$, m/z 448 (1%) M+1$^+$, and base peak at 93 (100%) and m/z 51 (100%), respectively. The reaction took place in the case of palladium chloride via electrophilic substitution in the m-position followed by elimination of HCl with the formation of ArC-Pd-S-. The IR for compound (**8**) showed the absence of $\surd_{S\text{-}H}$ (confirmed also by spot test[19]), and new band for Pd-C at 539. The ^{1}H NMR spectrum showed signal at δ 8.4 ppm (−N=CH Ar proton) and signals at δ8.2–6.9 ppm (aromatic protons) (Scheme 2).

Measurement of Potential Cytotoxicity of Compound 4 by SRB Assay

Potential cytotoxicity of the compound was tested using the method of Skehan.[20] Cells were plated in 96-multiwell plate (10^4 cells/well) for 24 h before treatment with the compound to allow attachment of cells to the wall of the plate. Different concentrations of the compound under test (0, 5, 12.5, 25, 50 μg/mL) were prepared for each individual dose. Monolayer cells were inocubated with the compound for 48 h at 37°C and in an atmosphere of 5% CO. After 48 h they were fixed, washed, and stained with sulfo-rhodamine-B stain. Excess stain was washed with acetic acid and attached stain was recovered with Tris base. Color intensity is measured in an ELIZA reader. The relation between surviving fraction and drug conc. is plotted (Figure 1) and (Figure 2) to get the survival curve of each tumor cell line after the specified compound. The antitumor activity result indicated that compounds (**4**) and (**8**) showed antitumor activity against the tested human breast carcinoma cell line MCF7 (*in vitro*) with varying intensities in comparison to the known anticancer drugs doxorubicin. Moreover compound (**4**) showed cytotoxic activity (IC50 = 4.04 μg/mL) while



SCH. 2.

TABLE 1
Antimicrobial activity of the products toward some types of bacteria and fungus

Sample	Inhibition zone diameter (mm/mg) sample					
	Escherichia coli (G^-)	*Pseudomonas aeruginosa* (G^-)	*Staphylococcus aureus* (G^+)	*Streptococcus faecalis* (G^+)	*Aspergillus flavus* (Fungus)	*Candida albicans* (Fungus)
Control: DMSO	**00**	**00**	**00**	**00**	**00**	**00**
Tetracycline	27	19	26	29	**0**	0
Amphotericin B	0	0	0	0	**18**	19
(1)	**17**	**13**	**22**	**15**	**17**	**13**
(2)	**26**	**30**	**25**	**29**	**00**	**00**
(3)	**19**	**22**	**28**	**16**	**0.0**	**22**
(4)	**22**	**15**	**18**	**19**	**35**	**25**
(5)	**7**	**12**	**7**	**19**	**0.0**	**0.0**
(6)	**21**	**14**	**29**	**22**	**9**	**11**
(7)	**11**	**9**	**11**	**27**	**0.0**	**0.0**
(8)	**22**	**32**	**22**	**11**	**12**	**23**

Drug Cytotoxicity

conc:ug/mL	MCF7-DOX	MCF7 -4
0.0	1.000000	1.00000
5.0	0.194273	0.37187
12.5	0.171715	0.21802
25.0	0.185526	0.210021
50.0	0.201330	0.280528

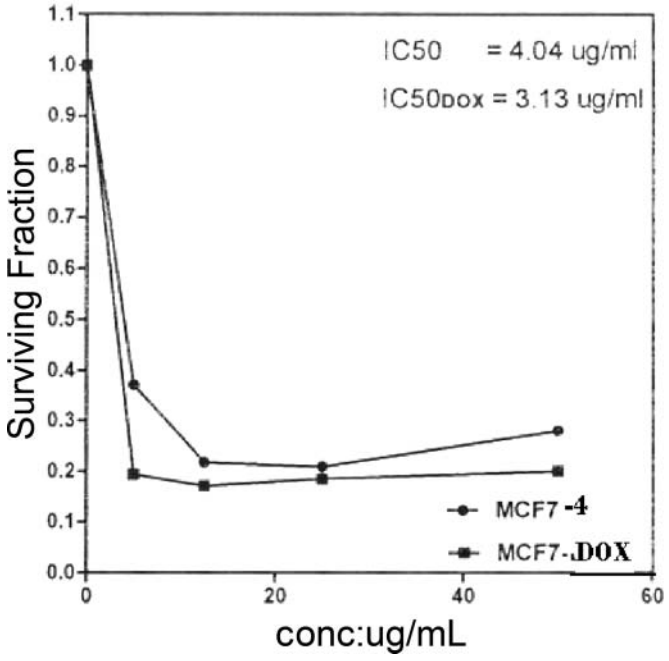


FIG. 1. Drug Cytotoxicity of Product (4) and doxorubicin.

Drug Cytotoxicity

conc:ug/mL	MCF7-8	MCF7-DOX
0.000	1.000000	1.000000
5.000	0.860377	0.421530
12.500	0.620755	0.413581
25.000	0.365566	0.410807
50.000	0.336604	0.444679

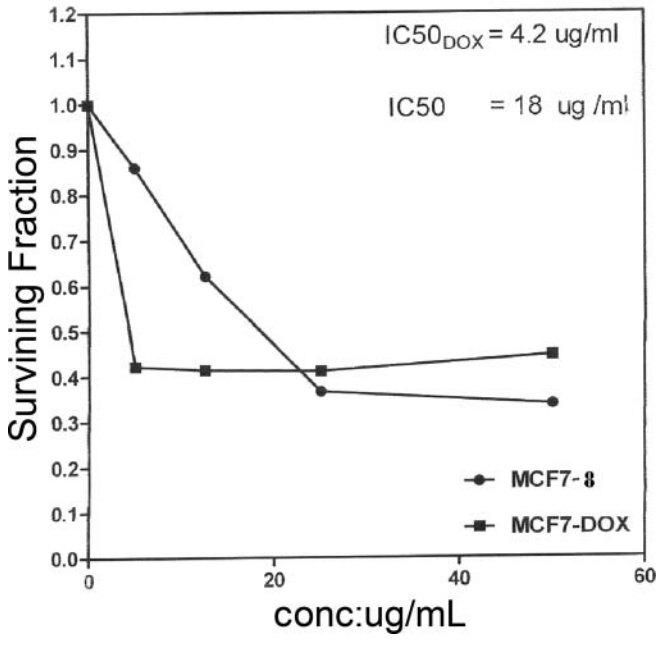


FIG. 2. Drug cytotoxicity of product (8) and and doxorubicin.

doxorubicin IC50 = 3.13 μg/mL and compound (**8**) showed IC50 = 18 μg/mL while doxorubicin IC50 = 4.20 μg/mL.

Antimicrobial Investigation

For these investigation the filter paper disc method was applied with nutrient broth (NB).The seeded NB (1 cm^3) was homogenized in the tubes with 9 cm3 of melted (45°C) nutrient agar (NA).The homogeneous suspensions were poured into Petri dishes. The discs of filter paper (diameter 5 mm) were ranged on the cool medium. After cooling on the formed solid medium, $2 \times 10^{-5} dm^3$ of the investigated compounds were applied using a micropipette. After incubation for 24 h in a thermostat at 25–27°C, the inhibition (sterile) zone diameters (including disc) were measured and expressed in mm. An inhibition zone diameter over 8 mm indicates that the tested compounds are active against some of bacteria and fungi under investigation.[21–24] The antibacterial activities of the investigated compounds were tested against *E. coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Streptococcus faecalis*, and some kinds of fungi; *Streptococcus faecalis* and *Candida albican*. In the same time with the antibacterial and antifungal investigations of the new compounds were also tested as well as the pure solvent. The concentration of each solution was 1.0×10^{-3} mol dm^3. Commercial DMSO was employed to dissolve the tested samples. The results of antibacterial and antifungal activities in vitro are shown in Table 1. It was found that compound (**2**) exhibited greater activity than the standard toward *Escherichia coli* and compound (**8**) exhibited greater activity than the standard toward *Pseudomonas aeruginosa*, compound (**6**) the more active toward *Staphylococcus aurous* (G+), compound (**2**) the more active toward *Streptococcus faecalis* (G+), while compound (**4**) exhibited greater activity than the standard toward *Aspergillus flavus* (fungus), and compound (**4**) exhibited greater activity than the standard toward *Candida albicans* (fungus) with respect to the standard.

CONCLUSION

2-(4-(Dimethylamino)benzylideneamino)benzenethiol (**1**) and 2-(4-nitrobenzylidene-amino)-benzenethiol(5) were synthesized and metallated with Hg(II), Ni(II) acetate, and palladium chloride to afford metallated products (**2**), (**3**), and (**4**) in the form of monomercurated, dinickel nickel bis-, and monopalladated products and monometallated products of Hg^{++} & Ni^{++} (**6**), (**7**), and monopalladated cyclized product (**8**). All the newly synthesized compounds exhibited antibacterial and antifungal activities. Compound (**4**) and (**8**) exhibited *in vitro* anticancer activity toward breast cancer.

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