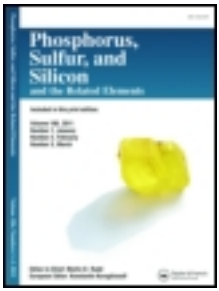

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Synthesis and In Vitro Anti-HIV Activity of Some New Schiff Base Ligands Derived from 5-Amino-4-phenyl-4H-1,2,4-triazole-3-thiol and Their Metal Complexes

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Synthesis and *In Vitro* Anti-HIV Activity of Some New Schiff Base Ligands Derived from 5-Amino-4-phenyl-4*H*-1,2,4-triazole-3-thiol and Their Metal Complexes

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*New Schiff base ligands (**6–9**) derived from 5-amino-4-phenyl-4H-1,2,4-triazole-3-thiol **1** and substituted benzaldehydes (**2–5**) as well as their metal complexes with Cu(II), Fe(II), Au(III), and Mn(II) (**12–17**) have been synthesized. A new benzothiazole derivative (**11**) was prepared from coupling of **7** with N-(benzothiazol-2-yl)-2-chloroacetamide **10**. Their spectral properties were investigated. The newly designed and synthesized Schiff base ligands and the metal complexes were assayed for anti-HIV-1 and HIV-2 activity by examination of their inhibition of HIV-induced cytopathogenicity in MT-4 cells. Compounds **11** and **16** were found to be the most active inhibitors in cell culture (EC_{50} = 12.2 $\mu g/mL$ (SI = 4) and > 2.11 $\mu g/mL$ (SI = > 1), respectively) against HIV-1, whereas **11** showed inhibition against HIV-2 of EC_{50} > 10.2 $\mu g/mL$ with SI = 9, which provided a good lead for further optimization.*

Keywords Anti-HIV activity; benzothiazole; metal complexes; Schiff bases; substituted 1,2,4-triazole

INTRODUCTION

Schiff bases form stable complexes with metals that perform an important role in biological systems where the C=N linkage is an

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essential structural requirement for biological activity.[1] Furthermore, many Schiff bases exhibit remarkable antibacterial,[2–6] antifungal,[7–9] anticancer,[10–13] and diuretic activities,[14] and can also be regarded as mimetic systems for enzyme models.[15,16] Some substituted Schiff bases, such as N^4-arylideneaminotriazole derivatives, have exhibited anti-HIV activity.[17] Many attempts have been made towards the synthesis, characterization, and structure–activity relationship (SAR) of Schiff bases.[18–21]

Considerable attention has been paid to the chemistry of the metal complexes of Schiff bases containing nitrogen and other donors.[22–25] This may be attributed to their stability, biological activity,[26] and potential applications in many fields such as oxidation catalysis,[27] electrochemistry,[28] etc. Louie and Meade[29] have extensively reported the biological importance of metal complexes for treatment of various diseases. Some Schiff base complexes were found to be very effective catalysts for hydrolytic cleavage or transesterfication of RNA phosphate diester backbone.[30]

The free thiol moiety (SH)/free mercaptoaryl group showed facile coordination with transition metal ions, such as Zn (ll), Cu (ll), and Fe (ll), giving products a high physiological importance. A large number of metallo-enzymes incorporate Zn (II) or Cu (II) ions coordinated by one or several –SH groups belonging to Cystein residues.[31] Therefore, metal complexes of Schiff bases have attained a prominent place in coordination chemistry, which was shown over many years by the large number of publications[32] and by the comprehensive reviews.[33,34]

In the present work, complexes of Cu(II), Fe(II), Au(III), and Mn (II) with four Schiff bases have been synthesized. Their structures were confirmed by IR and NMR spectral analysis, and their anti-HIV activity was evaluated.

RESULTS AND DISCUSSION

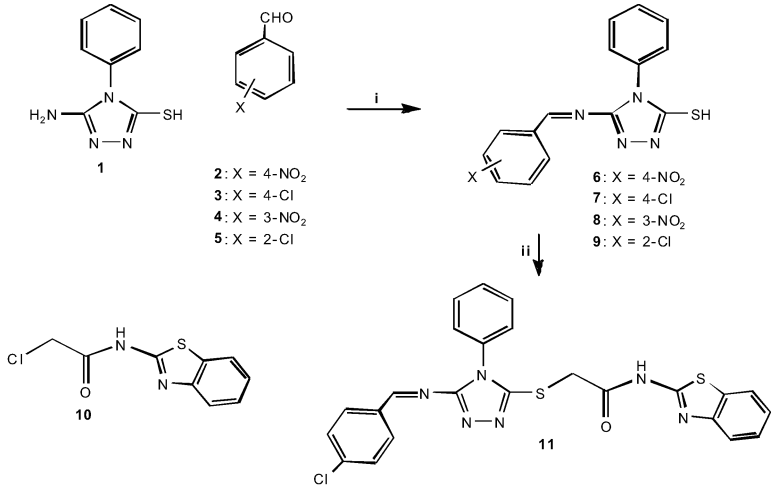
The Schiff base ligands 5-(4-arylideneamino)-4-phenyl-4*H*-1,2,4-triazole-3-thiols **6–9** were obtained in 82%, 80%, 70%, and 78% yields, respectively, by condensation reactions of 5-amino-4-phenyl-4*H*-1,2,4-triazole-3-thiol with 2-nitro-, 4-chloro-, 3-nitro-, and 2-chlorobenzaldehyde, respectively, in refluxing EtOH. The structures of **6–9** were confirmed by their ^{1}H, ^{13}C NMR, IR, and mass spectra.

Compound **6** was selected for the spectroscopic analysis, since the analogues **6–9** showed a similar spectral pattern. The IR spectrum of **6** revealed the presence of characteristic bands for -SH at 2550 cm^{-1} and 1625 cm^{-1} for C=N. The ^{1}H NMR spectra showed similar patterns, and

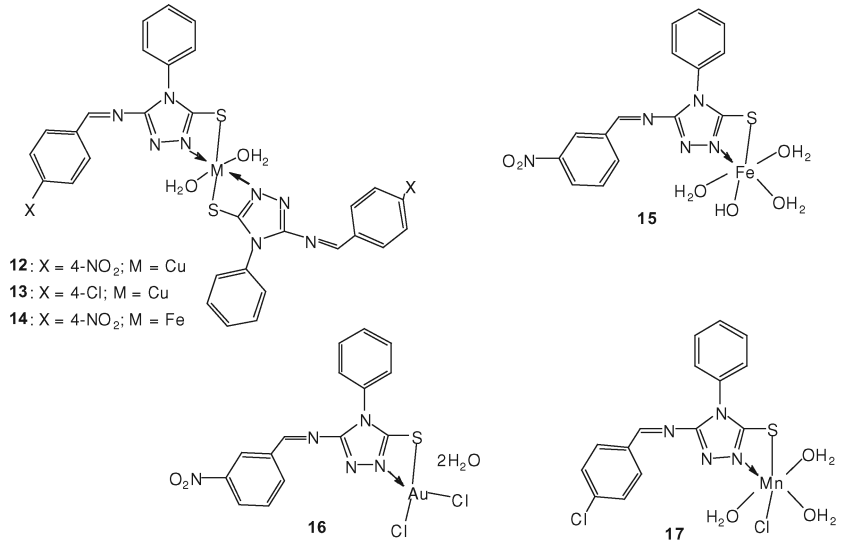
was characterized by the presence of two signals that appeared at low field. The lower one (δ_H 12.2–11.8 ppm), exchangeable with deuterium oxide, corresponds to the NH proton (tautomer of the SH), and the other one (δ 8.32–8.29 ppm) is attributed to the N=CH− group proton. ^{13}C NMR spectra exhibited signals at δ ~166.4 ppm, attributed to the C-S carbons, and then supporting the existence of these compounds in the tautomeric forms (C−SH ↔ C=S), while the resonances at δ_C 163.5–162.9 ppm were attributed to N=*C*H carbons of the Schiff bases. C=N groups of the 1,2,4-triazole ring appeared at ~ δ_C 151.5 ppm, whereas the signals at δ_C 147.3 ppm and δ_C 134.0 ppm were assigned to C−Cl and C−NO_2 carbons of the aromatic ring.

The key intermediate **10**, which was used for coupling with compound **7**, was prepared by the reaction of chloroacetyl chloride with 2-aminobenzothiazole.[35] The benzothiazole derivative **11** was obtained in 61% yield by condensation of **10** with compound **7**, using anhydrous K_2CO_3 in acetone. The structure of **11** was confirmed from the IR, ^{1}H, ^{13}C NMR, and mass spectra. The ^{1}H NMR spectra exhibited additional signals in the aromatic region, in addition to a singlet for SCH_2 protons of acetamido part at δ 4.44. The signal for SCH_2 carbon was oriented in the ^{13}C NMR spectra in the region δ 36.1 ppm. The FABMAS spectrum showed the protonated molecular ion of this compound (Scheme 1).

Metal complexes of the Schiff base were prepared from salts of Cu(II), Fe(II), Au (III), and Mn(II). Characterization of the metal complexes



SCHEME 1 *Reagents and conditions:* (i) EtOH, reflux, 2 h; (ii) **10**, K_2CO_3, acetone, 23°C, then reflux.



SCHEME 2

was carried out by elemental analysis, IR, ^{1}H, ^{13}C NMR, and mass spectra. The Schiff base behaves as a flexidentate ligand and commonly coordinates through the sulfur atom of the 1,2,4-triazole ring and the nitrogen atom of the azomethine group.

The IR spectra of the Schiff bases exhibited a band at ~ 1625 cm^{-1} assigned to ν(C=N) of azomethine. This band shifts to a lower wave number by about 25–30 cm^{-1} on the chelation of the ligand with a metal ion. The major shift of $\nu C{=}N$ is observable in the IR spectra of **12** and **13** as compared to the Cu(II) complex with a band around 1596 cm^{-1}, indicating the participation of N atoms in the coordination to the Cu atom.[36]

Elemental analyses (Table I) confirmed the ML_2 composition of the complexes, in which M is Cu (II) nitrate, Fe (II) sulfate, and L the Schiff base ligand, using M:L (1:2) molar ratio. On the other hand, Fe (II), gold (III), and manganese (II) complexes, with monodentate Schiff bases (ML), were isolated by using M:L (1:1) molar ratio (Scheme 2). Karl–Fischer titration indicated the presence of water molecules. Further, these complexes exhibited a broad band around 3390–3520 cm^{-1}, which is assigned to water molecules, ν(OH), associated with the complexes.[37] Additional support of the proposed structures comes from mass spectral data; mass spectra of the prepared compounds showed the correct molecular ions, as suggested by their molecular formulas.

TABLE I Physical Data of the Newly Prepared Compounds

Comp.	Mol. Formula (M*r*)	Mp (°C)	Yield (%)	Found/caldd (%) C	H	N	MS (*m*/*z*) (FAB)
6	$C_{15}H_{11}N_5O_2S$	220	82	55.02	3.32	21.32	326
	(325.35)			55.38	3.41	21.53	$(M+H)^+$
7	$C_{15}H_{11}ClN_4S$	72	80	57.03	3.47	17.62	314/316
	(314.79)			57.23	3.52	17.80	$(M+H)^+$
8	$C_{15}H_{11}N_5O_2S$	230	70	55.12	3.35	21.38	326
	(325.35)			55.38	3.41	21.53	$(M+H)^+$
9	$C_{15}H_{11}ClN_4S$	124	78	57.00	3.49	17.67	314/316
	(314.79)			57.23	3.52	17.80	$(M+H)^+$
11	$C_{24}H_{17}ClN_6OS_2$	189	61	56.82	3.28	16.46	505/507
	505.01			57.08	3.39	16.64	$(M+H)^+$
12	$C_{30}H_{22}CuN_{10}O_4S_2.2H_2O$	300	74	47.92	3.19	18.53	735
	(748.25)			48.16	3.23	18.72	$(M+Na)^+$
13	$C_{30}H_{22}$ $Cl_2CuN_8S_2.2H_2O$	240	80	49.31	3.19	15.13	714/716
	(727.15)			49.55	3.33	15.41	$(M+Na)^+$
14	$C_{30}H_{22}FeN_{10}O_4S_2.2H_2O$	156	84	48.41	3.18	18.72	727
	(740.55)			48.66	3.27	18.91	$(M+Na)^+$
15	$C_{15}H_{11}FeN_5O_3S.3H_2O$	278	70	40.93	3.80	15.52	452
	(451.24)			41.59	3.49	16.17	$(M+H)^+$
16	$C_{15}H_{10}AuCl_2N_5O_3S.2H_2O$	143	74	28.43	2.18	10.89	614/616
	(628.24)			28.68	2.25	11.15	$(M+Na)^+$
17	$C_{15}H_{12}Cl_2MnN_4OS.2H_2O$	153	60	39.07	3.45	12.02	444/446
	(458.22)			39.32	3.52	12.23	$(M+Na)^+$

The ^1H and ^{13}C spectra of the complexes **12–17** were fully analyzed (Table II).

In Vitro Anti-HIV Assay

Compounds **6–9**, **11**, and **12–17** were evaluated for their in vitro HIV-1 (strain IIIB) and HIV-2 (strain ROD) activity in human T-lymphocyte (MT-4) cells using the MT-4/MTT assay,[38] and the results are reported in Table III, in which the data for efavirenz[39] and capravirine[40] were included for comparison purposes.

The gp41 subunit of the human immunodeficiency virus type-1 (HIV-1) envelope glycoprotein plays an important role in HIV-1 entry and serves as an attractive target for the development of HIV-1 entry inhibitors, a new class of anti-HIV drugs.[41] Our target was the disruption of the gp41 six-helix bundle formation by the newly synthesized Schiff base ligands and their metal complexes, leading to inhibition of HIV. Compounds **11** and **16** were found to be the only compounds from the

TABLE II ^{1}H NMR, ^{13}C NMR, and IR Data of the Newly Synthesized Schiff Base Ligands

Comp./ν cm^{-1}	^{1}H NMR (δ, ppm) and ^{13}C NMR (δ, ppm)
6	12.2 (s, 1H, SH); 8.29 (s, 1H, N=*C*H); 7.95–43 (m, 9H, Ar-H).
1625 (C=N)	166.5 (C−SH); 163.5 (N=*C*H); 151.5 ($C_{triazol}$ = N); 147.3
2550 (SH)	(C_{arom}-NO_2); 135.0, 133.1, 131.5, 129.2, 128.4, 128.0 (C_{arom})
7	12.4 (s, 1H, SH); 8.34 (s, 1H, N=*C*H); 8.51–7.43 (m, 9H, Ar-H).
1625 (C=N)	166.4 (C−SH); 162.9 (N=*C*H); 151.4 ($C_{triazol}$ = N); 134.0 (C_{arom}-Cl);
2552 (SH)	133.7, 132.2, 129.4, 128.7, 128.2 (C_{arom})
8	12.1 (s, 1H, SH); 8.29 (s, 1H, N=*C*H); 7.95–43 (m, 9H, Ar-H).
1624 (C=N)	166.3 (C−SH); 163.1 (N=*C*H); 151.3 ($C_{triazol}$ = N); 147.3
2552 (SH)	(C_{arom}-NO_2); 134.9, 133.2, 129.2, 128.6, 128.3 (C_{arom})
9	12.0 (s, 1H, SH); 8.32 (s, 1H, N=*C*H); 7.55–41 (m, 9H, Ar-H).
1623 (C=N)	166.4 (C−SH); 162.9 (N=*C*H); 151.4 ($C_{triazol}$ = N); 134.0 (C_{arom}-Cl);
2553 (SH)	133.7, 132.2, 129.4, 128.7, 128.2 (C_{arom})
11	12.10 (s, 1H, NH); 8.12 (m, 2H, Ar-H); 8.30 (s, 1H, N=*C*H); 7.96 (d,
1625 (C=N)	1H, J = 7.7 Hz, ArH); 7.75 (d, 1H, J = 8.0 Hz, ArH); 7.58–7.50 (m, 7H, ArH); 7.44 (1H, dt, J = 0.5 Hz, 7.8 Hz, ArH); 4.32 (s, 2H, SCH_2).
	168.8 (S-$C_{thiazol}$-N), 166.9 (C=O); 161.5 (N=*C*H); 152.1 ($C_{thiazol}$-3a); 151.6 ($C_{triazol}$ = N); 146.3 (N-$C_{triazol}$-S); 135.1 (C_{arom}-Cl); 132.2, 129.4, 128.7, 128.2, 126.7, 126, 0, 124.3, 121.2, 122.3, 118.2 (C_{arom})
12	8.52, 8.34, (2s, 2H, N=*C*H); 8.30–7.43 (m, 18H, Ar-H).
1595 (C=N)	160.2 (C-SCu, N=*C*H); 152.5 ($C_{triazol}$ = N); 148.1 (C_{arom}-NO_2); 141.0, 129.6 128.8, 128.4, 127.6, 123.8 (C_{arom})
13	8.50, 8.32 (2s, 2H, N=*C*H); 7.53–7.42 (m, 18H, Ar-H).
1596 (C=N)	160.0 (C-SCu, N=*C*H); 152.0 ($C_{triazol}$ = N); 135.6 (C_{arom}-Cl); 133.9, 129.8, 129.2, 128.8, 128.5 (C_{arom})
14	8.55, 8.35, (2s, 2H, N=*C*H); 8.32–7.45 (m, 18H, Ar-H).
1585 (C=N)	160.1 (C-SFe, N=*C*H); 153.2 ($C_{triazol}$ = N); 149.0 (C_{arom}-NO_2); 141.7, 129.8 128.7, 127.7, 123.7 (C_{arom})
15	8.32 (s, 1H, N=*C*H); 8.39–7.42 (m, 9H, Ar-H).
1586 (C=N)	160.1 (C-SFe, N=*C*H); 153.8 ($C_{triazol}$ = N); 147.5 (C_{arom}-NO_2); 135.2, 129.1, 128.4, 125.2 (C_{arom})
16	8.34 (s, 1H, N=*C*H); 8.35–7.43 (m, 9H, Ar-H).
1597 (C=N)	159.8 (C-SAu, N=*C*H); 152.3 ($C_{triazol}$ = N); 147.2 (C_{arom}-NO_2); 136.2, 134.1, 129.4, 128.8, 125.4 (C_{arom})
17	8.33 (2s, 1H, N=*C*H); 7.67–7.41 (m, 9H, Ar-H).
1596(C=N)	160.1 (C-SMn, N=*C*H); 152.7 ($C_{triazol}$ = N); 135.7 (C_{arom}-Cl); 133.8, 130.0, 129.3, 128.8 (C_{arom})

series inhibiting HIV-1 and HIV-2 replication in cell culture, which showed EC_{50} of 12.4 μg/mL and 2.11 μg/mL, respectively, and CC_{50} of 50.20 ± 2.17 μg/mL and 2.11 ± 1.13 μg/mL against HIV-1, resulting in a selectivity index of 4 and <1, respectively. Compound **11** showed an

TABLE III *In Vitro* Anti-HIV-1[a] and HIV-2[b] of Some New Schiff Bases and Their Metal Complexes

Compd.	Virus strain	*av.EC*$_{50}$ (μg/mL)	*av.CC*$_{50}$ (μg/mL) ± SD	*SI*
6	III_B	> 75.4	75.4 ± 6.71	<1
	ROD	> 75.4	75.4 ± 6.71	<1
7	III_B	> 12.0	12.0 ± 1.13	<1
	ROD	> 12.0	12.0 ± 1.13	<1
8	III_B	> 72.83	72.83 ± 3.36	<1
	ROD	> 72.83	72.83 ± 3.36	<1
9	III_B	> 4.12	4.12 ± 2.08	<1
	ROD	> 4.12	4.12 ± 2.08	<1
11	III_B	12.4	50.20 ± 2.17	4
	ROD	> 10.2	91.80 ± 2.26	9
12	III_B	> 108.3	108.3 ± 8.86	<1
	ROD	> 108.3	108.3 ± 8.86	<1
13	III_B	> 67.8	67.8 ± 13.86	<1
	ROD	> 67.8	67.8 ± 13.86	<1
14	III_B	> 19.61	19.61 ± 20.84	<1
	ROD	> 19.61	19.61 ± 20.84	<1
15	III_B	> 80.05	80.05 ± 11.17	<1
	ROD	> 80.05	80.05 ± 11.17	<1
16	III_B	> 2.11	2.11 ± 1.13	<1
	ROD	> 2.11	2.11 ± 1.13	<1
17	III_B	> 68.48	68.48 ± 5.63	<1
	ROD	> 68.48	68.48 ± 5.63	<1
Efavirenz	III_B	> 0.003	40	13333
Capravirin	III_B	> 0.0014	11	7857

[a]Anti-HIV-1 activity measured with strain III_B.
[b]Anti-HIV-2 activity measured with strain ROD.

EC$_{50}$ of 10.2 μg/mL and a *CC*$_{50}$ of 91.80 ± 2.26 μg/mL against HIV-2, resulting in a selectivity index of 9. This result encouraged us to modify such molecules with another potential group that might fulfill the need of our target.

From the screening results (Table III), most of the compounds had lost their effectiveness, compared with the prototype gold-ligand complex **16**, which is probably due to the stereochemistry of the tetradentate complexes and the nitro substituent at positions 2 and 3 of the aromatic ring.

Compound **16** was subjected to the quantitative structure–activity relationship (QSAR) study using comparative molecular field analysis (CoMFA).[42] The study suggested the importance of a Au(III) atom with its dichloro group by manifesting a higher HIV inhibitory activity other

than that of the corresponding analogues having Cu(II), Fe(II), and Mn(II) metals. In addition, the chlorophenyl residues on the triazole ring would optimize the inhibitory activity, as well. Such a result would lead us to modify our new target molecules by introduction of more potential groups with various Schiff bases ligands.

CONCLUSION

In summary, the results showed that compounds **11** and **16** were active inhibitors against HIV replication in cell culture [$EC_{50} = > 12.4$ μg/mL (SI = 4) and > 2.11 μg/mL (SI = <1) against HIV-1, respectively], which provides a good lead for design and discovery of new high potent HIV non-nucleoside reverse transcriptase inhibitors (NNRTIs) by structure-based molecular modification.

EXPERIMENTAL

Melting points are uncorrected and were measured on Stuart Scientific Melting Point SMP1. NMR spectra were recorded on 250 MHz (^{1}H) and at 62.9 MHz (^{13}C) spectrometers (Bruker, Germany) with TMS as internal standard and on δ scale in ppm. Infrared spectra were recorded on a Perkin-Elmer FT-IR type 1650 spectrophotometer in wave number region 4000–200 cm^{-1}. The spectra were recorded as KBr pellets. Microanalytical data were obtained with a Vario, Elementar apparatus (Shimadzu, Japan). Mass spectra were recorded at 70 eV on EI, and FAB mass spectra were measured on a MAT 8200 spectrometer (Finnigana MAT, USA) using 3-nitrobenzyl alcohol (NBOH) or glycerol as matrices. Some molecular ions were detected by doping the sample with Na^+.

General Preparation of Ligands 5-(4-Arylideneamino)-4-phenyl-4*H*-1,2,4-triazole-3-thiols (6–9)

To a solution of 5-amino-4-phenyl-1,2,4-triazol-3-thiol (**1**) (1.92 g, 10.0 mmol) in abs. EtOH (15 mL), the appropriate aldehyde (**2–5**) (10.0 mmol) dissolved in abs. EtOH was added with stirring. After 2 h under reflux, the solution was cooled in an ice bath, and a yellow precipitate was formed. The precipitate was filtered and washed with cooled abs. EtOH, and recrystallized from CH_2Cl_2.

5-(2-Nitrobenzylideneamino)-4-phenyl-4*H*-1,2,4-triazole-3-thiol (**6**), 5-(4-chlorobenzylideneamino)-4-phenyl-4*H*-1,2,4-triazole-3-thiol (**7**), (3-nitrobenzylideneamino)-4-phenyl-4*H*-1,2,4-triazole-3-thiol (**8**), and

5-(2-chlorobenzylideneamino)-4-phenyl-4*H*-1,2,4-triazole-3-thiol (**9**) were prepared from 4-nitrobenzaldehyde **2** (1.51 g), 4-chlorobenzaldehyde **3** (1.40 g), 3-nitrobenzaldehyde **4** (1.51 g), and 2-chlorobenzaldehyde **5** (1.40 g), respectively. The physical data are shown in Tables I and II.

N-(Benzothiazol-2-yl)-2-(4-chlorobenylideneamino)-4-phenyl-4*H*-1,2,4-triazole-3-ylthiol) acetamide (11)

To a solution of **7** (0.30 g, 0.95 mmol) in acetone (30 mL), benzothiazolyl chloroacetamide **10** (0.29 g, 1.05 mmol) and anhyd. K_2CO_3 (0.53 g, 3.81 mmol) were added, and the mixture was stirred at 23 °C for 5 h. The resulting reddish solution was heated under reflux until completion of the reaction. After cooling, the reaction mixture was filtered, and the filtrate was concentrated to 10 mL, followed by addition of cold water (10 mL). The resulting solid was filtered, dissolved in acetone, and boiled with decolorizing charcoal. The charcoal was filtered, and the filtrate was evaporated to dryness to afford pure benzothiazole derivative **11**.

Preparation of Metal Complexes (12–17)

To a solution of a metal salt (0.25 mmol) dissolved in a minimum quantity of warm absolute EtOH, (**6–8**) (0.50 mmol) dissolved in CH_2Cl_2 (20 mL) was added with stirring. The mixture was heated under reflux for 2 h and then cooled to room temperature. A dark precipitate was formed after 24 h. The precipitate was filtered and washed with cooled CH_2Cl_2 to give the desired complex.

Bis - (5 - (4 - nitrobenzyledieneamino) - 4-phenyl- 4*H*-1,2,4-triazol-3-ylthio)copper dihydrate (**12**), bis-(5-(4-chlorobenzyledieneamino)-4-phenyl-4*H*-1,2,4-triazol-3-ylthio)copper dihydrate (**13**), bis-(5-(4-nitrobenzyledieneamino)-4-phenyl-4*H*-1,2,4-triazol-3-ylthio)iron dihydrate (**14**), aqua-hydroxy-(5-(3-nitrobenzyledieneamino)-4-phenyl-4*H*-1,2,4-triazol-3-ylthio)iron hydrate (**15**), (5-(4-nitrobenzyledieneamino)-4-phenyl-4*H*-1,2,4-triazol-3-ylthio)gold dichloride dihydrate (**16**), and aqua (5-(4-chlorobenzyledieneamino)-4-phenyl-4*H*-1,2,4-triazol-3-ylthio)manganese chloride hydrate (**17**) were prepared from **6** (163 mg), **7** (157 mg), **6** (163 mg), **8** (163 mg), **6** (163 mg), and **7** (157 mg), respectively, and $Cu(NO_3)_2.3H_2O$ (61 mg), $FeSO_4.7H_2O$ (91 mg), $HAuCl_4.H_2O$ (85.5 mg), and $MnCl_2.4H_2O$ (50 mg), respectively. The physical data are shown in Tables I and II.

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