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Synthesis, Characterization and Anti-Cancer Activity of gold (III) and Nickel (II) Metal Ion Complexes Derived from Tetrazole-Triazole Compound

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Abstract

This research is for academic understanding to work out new ligand behavior 4-({(5-(4-hydroxyphenyl)-3-sulfanyl-1H-1,2,4-triazol-1-yl) amino} (1H-tetrazol-5-yl) methyl)-2-methoxyphenol (L) with gold (III) and nickel (II) metal ions. Ligand (L) has been synthesized from cyclization of the interaction of (4-hydroxy-3-methoxyphenyl) {[5-(4-hydroxyphenyl)-3-sulfanyl-1H-1,2,4-triazol-1-yl] amino} acetonitrile (F) with sodium azide. α-Amino nitrile compound (F) intern synthesized from interaction of aldehyde amine and KCN acidic medium as three components one put reaction. The presence of well oriented donor atoms (N_2-type) of ligand (L) interacted with gold (III) and nickel (II) ions under reflux to prepare [1:2] [M:L]Cl electrolytic complexes, the complexes $[Au(L)_3]Cl_3$ and $[Ni(L)_2]Cl_2$ were suggested to have square planar geometry. The resulting products were characterized via technical ^{1}H-NMR, UV-Vis, IR spectroscopy, conductivity and EDX.

The cytotoxic effect was studied on a breast cancer cell line (MCF-7 cell line). At different concentrations for both complexes. The results showed that gold (III) complex has higher cytotoxicity than nickel (II) complex against cancer cell line.

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1. Introduction

Tetrazole is a five membered ring (four nitrogen atoms with one carbon atom) in same structure, the compound is found in standard conditions as a soluble solid in water and ethanol [1], and its derivatives exhibited various biological activities such as antibacterial [2], antimalarial [3], antifungal [4], antitubercular [5] and anticancer [6] properties. Moreover, many tetrazole-based drugs such as Cilostazol, Cefamandole and Irbesartan have already been used in various diseases, demonstrating the therapeutic potential of tetrazole derivatives [7].

Imine bases are manufactured when any primary amine combines with just an aldehyde or a ketone, first discovered via Hugo Schiff in 1864 [8]. A Schiff base, commonly called as imine as well as azomethine. Generally, imine compounds considered as source of α-amino nitrile compound [9] in the reaction of cyanide source and imine bases. Triazole has two types of triazole rings both types are stable towards oxidizing agents, and the side chain are burned off, being converted into carboxyl groups [10]. Heterocyclic compounds depending on nitrogen have generated considerable concern in medicinal chemistry as anticancer treatments [11].

In medicine, the metal compounds widely used since ancient times, but their methods of action have only recently received extensive attention in the scientific community, establishing a strong link between inorganic and organic chemistry [12]. Research on the anticancer effects of metal complexes dominates the field of inorganic biomedical sciences (arsenic, antimony, bismuth, gold, vanadium, iron, rhodium, titanium, gallium, and platinum-based ones) [13,14], antimicrobial and anti-inflammatory metal-based medicines, such as the gold-based Auranofin used to treat rheumatoid arthritis, are being given a lot of attention [15].

Cancer is a broad category of illnesses defined by the development and spread of leukemic cells. It is a big worldwide concern [16]. As a result, current cancer research places a premium on the discovery of novel potent and specific anticancer agents.

The purpose of this study is to describe the synthesis and characterization of square planar gold (III) and nickel (II) complexes containing tetrazole and triazole groups, in the same ligand (L), in order to provide two hetercyclic molecules along with anticancer metal ions (gold and nickel) to achieve promising result.

2. Experimental

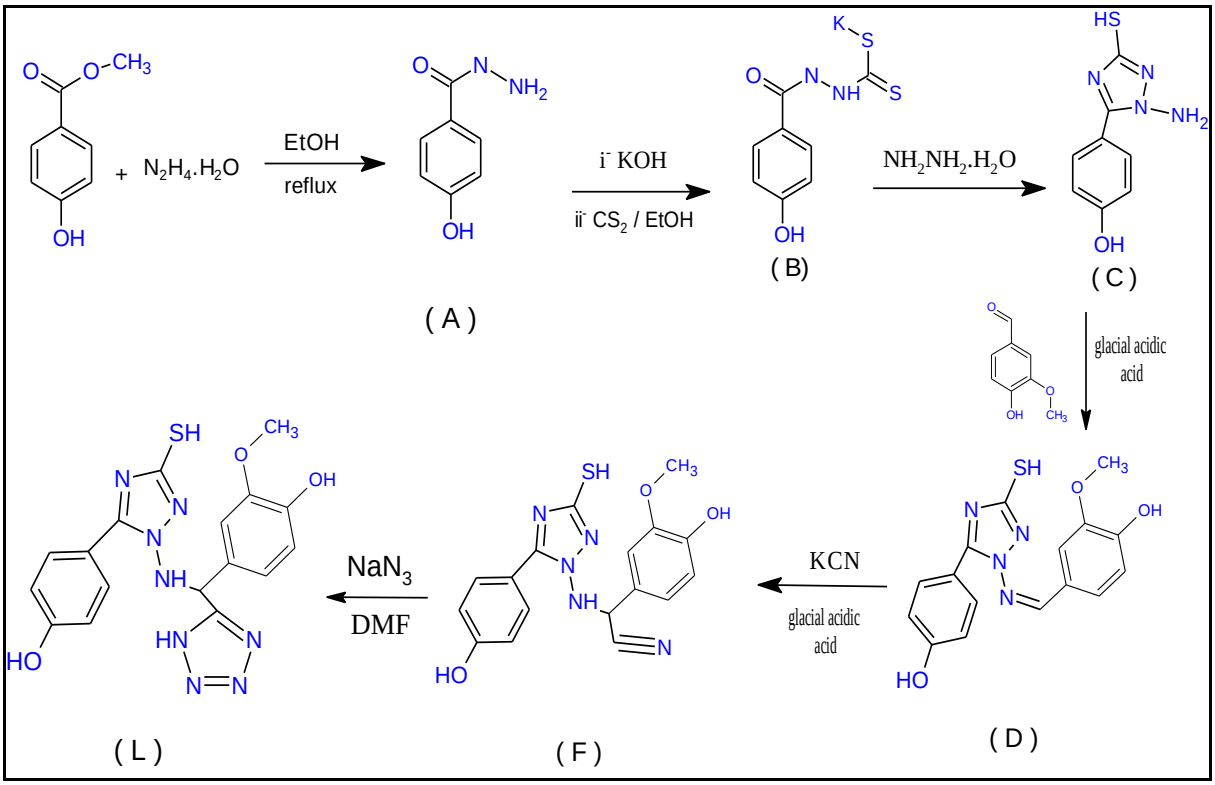
2.1 Materials and instruments:

Chemicals supplied from Aldrich, Fluka, Alfa, and B.D.H were used. The melting point was measured by a hot stage Gallenkamp melting point device. The 1H-NMR spectra obtained recorded on Bruker 400 MHz spectrometers. Infrared spectra throughout the region (4000-400) cm^{-1} were obtained using an FTIR spectrophotometer Bruker. The ultraviolet-visible spectra were measured in the range (200-1100) nm via using a Shimadzu 1600A. Conductivity

measurements were determined via Corning conductivity meter 220 and elemental composition of prepared complexes determined by FEI Company, Netherlands, Inspect S50 (Model).

2.2 Synthesis:

The desired ligand that poses two heterocyclic molecules was synthesized through long successive steps starting from ester to compounds (A-L). as shown in scheme.



Scheme 1. Synthesis steps for compound (L).

2.2.1 Synthesis of 4-hydroxy benzoic acid hydrazide (A) [19]:

0.03 Mole (6 gm) of 4-hydroxy methyl benzoate refluxed for 4 hours with 4 ml hydrazine hydrate 80% (1.5 gm), then 25 ml of EtOH that added and reflux for four hours. Overnight, the solution product was cooled and the white crystals were collected, the melting point of compound A was 109-112 °C.

2.2.2 Synthesis of 4-(1-amino-3-sulfanyl-1H-1,2,4-triazol-5-yl) phenol (C) [20]:

0.01 Mole (1.5 gm) Compound A was added to 0.03 mole (1.1 gm) potassium hydroxide dissolved in 25 ml absolute ethanol. The mixture was cooled in ice bath with stirring. 0.19 mole of carbon disulphide (99 %) was added in a small portion, the stirring was about 24 hours at room temperature to form salt of compound B. The compound B was refluxed with 10 ml hydrazine hydrate for about eight hours, the solution color was dark green after changed, the H_2S was liberated (tested by lead acetate paper, which changed to black color). By adding 20 mL cold water and acidifying with strong hydrochloric acid, a white substance was precipitated. Filtration and drying of the final triazole compound (C). The product was triazol derivative (C), melting point 189-19 °C.

2.2.3 Synthesis of (4-hydroxy-3-methoxyphenyl) {(5-(4-hydroxy-phenyl)-3-sulfanyl-1H-1,2,4-triazol-1-yl) amino} acetonitrile (F) [21]:

5 Mmole of compound C, an amine was refluxed with 5 mmole (0.76 gm) of 4-Hydoxy-3-methoxybenzaldehyde an aldehyde about 1 hour with glacial acidic acid as solvent to form imine compound (D). 10 mmole of Potassium cyanide (1.3 gm) was added carefully under reflux for 24 hours (three components as one pot reaction). An ammonia solution is added to the colored liquid, which is then poured over the crushed ice (tested by red litmus paper). When the precipitate of -amino nitrile was filtered, it became light yellow and washed with water before drying off. NaOH solution (10%) was used to identify the presence of the nitrile group in α-amino nitrile, and wet red litmus paper confirmed the presence of ammonia, the melting point of product (F) was 145-148 °C.

2.2.4 Synthesis of 4-({(5-(4-hydroxyphenyl)-3-sulfanyl-1H-1,2,4-triazol-1-yl) amino} (1H-tetrazol-5-yl) methyl)-2-methoxyphenol (L):

5 Mmole (1.2 gm) of compound (L) was refluxed with 5 mmole (0.76 gm) of sodium azide in 10 ml of dimethylformamide (DMF) about 24 hours with a minor quantity of ammonium chloride. After solvent evolution,

the dark brown solution is dried to get the desired product compound L, which has a melting point of 142-145 °C. Compounds (A-L) are listed in Table 1. Scheme 1 describe of Synthesis steps to produce compound (L).

Table 1. The physiochemical properties of compounds (A-L).

Compound	Chemical formula	Molecular weight (g. mole^{-1})	Melting Point °C	Color
A	$C_7H_8N_2O_2$	152.15	195-190	White
C	$C_8H_8N_4OS$	208.24	–	yellow
F	$C_{17}H_{15}N_5O_3S$	369.39	145-147	Pale yellow
L	$C_{17}H_{16}N_8O_3S$	412.42	142-145	Brown black

2.2.5 Synthesis of Au (III) complex (A1) [22]:
1 Mmole (0.25 gm) of chloroauric acid was dissolved in 5 ml of absolute ethanol which was added into 2 mmole (0.32 gm) to product A1 complex after refluxed for 1 hours. The product golden brown filtered after evaporation of solvent and collected with melting point 124-127 °C.

2.2.6 Synthesis of Ni (II) complex (B1) [22]:
1 Mmole (0.12 gm) of nickel chloride hexahydrate was dissolved in 5 ml of absolute ethanol which was added into 2 mmole (0.32 gm) ligand (L) to produce (B1) complex after refluxed for 1 hour. The produced brown color filtered after evaporation of solvent and collected, with melting Point 198-202 °C.

2.3 MTT Assay method:
MTT Microculture tetrazolium viability assay was used to evaluate gold and nickel complexes for their cytotoxicity. A final volume of 200 µL of total culture media was added to each well of tumor cells in 96-well Microtiter plates (with a cell density of $1\times10^4\times10^6$ cells/mL). Parafilm was applied to the microplate and gently shaken to distribute the solution evenly. For 24 hours, the plates were kept at 37 °C and 5% CO_2. Before adding the desired drug (12.5, 25, 50, 100, 200 and 400 µg/mL) in doubling dilution, the medium was removed from each well. For each concentration, triplicates and controls were employed (cells treated with serum free medium). A sample's cytotoxicity for cancer cells was measured in terms of IC_{50} values, which are the percentage decrease in absorbance of treated cells compared to untreated cells as a result of drug levels.

3. Results and Discussion
3.1 Infra-red spectroscopy:
3.1.1 4-Hydroxy benzoic acid hydrazide compound (A) [23]:
The compound (A), the bands appearance at υ (3300 and 3200) cm^{-1} that retuned to amine group (–NH). The carbonyl group band showed at 1680 cm^{-1} is stretching. The stretching 1462 cm^{-1} and bending 1584 cm^{-1} peaks for the active groups, υ C=C aromatic group and –NH group respectively.

3.1.2 4-(1-Amino-3-sulfanyl-1H-1,2,4-triazol-5-yl) phenol (C) [24,25]:
The two band 3331 cm^{-1} and 3247 cm^{-1} for amine group (–NH). The υ S–H group at 2588 cm^{-1} and thiol at 1109 cm^{-1}. υ C=N stretching appeared at 1640 cm^{-1}.

3.1.3 (4-Hydroxy-3-methoxyphenyl) {(5-(4-hydroxy-phenyl)-3-sulfanyl-1H-1,2,4-triazol-1-yl)amino} acetonitrile (F) [2]:
Appearance 2219 cm^{-1} for nitrile group [26], which appear between 2280 and 2200 cm^{-1} [27]. The amino group was disappearance and appear a one band at 3201 cm^{-1} duo N–H, in addition to υ (–OCH_3) that founded in vanilline compound appeared at 1170 cm^{-1} for υ (C–O).

3.1.4 4-({(5-(4-Hydroxyphenyl)-3-sulfanyl-1H-1,2,4-triazol-1-yl) amino} (1H-tetrazol-5-yl) methyl)-2-methoxyphenol (L) [28]
Described the disappearance of nitrile group and appearance of υ (N=N) band at 1418 cm^{-1} of tetrazole duo to electrophilic-nucleophilic reaction between azide and nitrile groups.

3.1.5 Gold (III) complex compound (A1)
The infrared spectrum of complex A1 included the band for the N–H group that showed at 3200 cm^{-1} with shifting about 44 cm^{-1} duo to coordination [29].

3.1.6 Nickel (III) complex compound (B1):
The infrared spectrum of complex B1 included the disappearance of amino group as υ N–H group appearance at 3200 cm^{-1} with shifting about 4 cm-1 due to coordination. The suggested coordination bonding was through (C=N) group of teterazole and (NH) group which both suffered shifting to lower frequency at (1583) cm^{-1} and (3200) cm^{-1}, respectively.

3.2 Proton nuclear magnetic resonance spectroscopy (^{1}HNMR):
3.2.1 (4-Hydroxy-3-methoxyphenyl) {(5-(4-hydroxy-phenyl)-3-sulfanyl-1H-1,2,4-triazol-1-yl) amino} acetonitrile (F):
Set 11.4 ppm as singlet signal for thiol group. 3.8 ppm set for amino group as doublet signal. The C–H signal of

methoxy group (–OCH_3) appeared as singlet at 3.5 ppm, while of aromatic protons occur as multiplet at the range (7.3-8.8) ppm [29].

3.2.2 4-({(5-(4-Hydroxyphenyl)-3-sulfanyl-1H-1,2,4-triazol-1-yl) amino} (1H -tetrazol-5-yl) methyl)-2-methoxyphenol (L)

Depicts the removal of the S–H signal as a result of the thion form becoming stabilised (C–S). That a broad signal might be assigned to the -SH group as comparable as compound on low field at 9.5 ppm (L). The single that appeared of the –SH group was duo to the increase of hydrogen bonding by the nitrie group and the lack of steric factor in compound (L3) due to the bulky tetrazole group and SP^2 hybridization (non-linear geometry). The presence of phenyl groups in C–H was suggested by the multiplet signals at (6.8-7.8) ppm. The doublet signal at 6.9 ppm corresponds to the –NH group, whereas the singlet signal at 6.8 ppm duo to the amino group. 2.5 and 3.5 ppm, as two singlet signals duo the –CH and –OCH_3 groups, respectively.

3.3 Ultraviolet-Visible spectroscopy:

The synthesized complexes compounds recorded via ultraviolet-visible electronic spectra at room temperature via DMSO that used as solvent [31].

The A3 complex, included one peak at ~325 nm. Ligand field while charge transfer appeared at range (425-350) nm, the suggested shape of A1 is square planer geometry [2].

Due to the huge size of the gold complex ion, it belongs to the third transition series [32]. This means that the ~325 nm charge transfer band appears at longer wavelength, at the same time ligand filed transition are expected to appears at shorter wavelength [34]. These results in an overlap at these absorption band, which make the interpretation of the spectra more difficult [33,34].

The B1 complex, included two peaks at ~330 nm refers to $^1A_{1g} \longrightarrow {}^1E_g$ transition, in addition to the peak at 895 nm attached to d-d electronic transition, finally masking peak, these refer to in square planer geometry [35].

4. Cytotoxic Effect Complexes on MCF-7 Cell Line (MTT Assay)

The results showed, the MCF7 cell line compared to WRL68, and they were also less toxic as anti-normal cell line [36].

On the normal cell line, the concentration of gold complex (A1) at 400 g/mL was compared to the viability rate percentage of the nickel complex (B1), revealing that the A1 complex was more toxic than the B1 complex (Table 2).

Table 3 shows the MCF-7 viability on breast cancer cell line at doses ranging from 400 to 12.5 g/mL for produced chemicals. With increase an in concentration, cell viability decreases, implying that cytotoxicity grows. The viability of the produced compounds at 400 g/mL found that A1 had significantly higher cytotoxicity than B1 anti-MCF-7.

The half-maximal inhibitory concentration (IC50) of the synthesized complexes in both WRL86 and MCF-7 cell.

Table 2. Cytotoxicity effect of complexes on the WRL68 cell.

Compound	Viability at different concentrations (µg/mL)						Growth inhibition	IC_{50} (µg/mL)
	400	200	100	50	25	12.5		
A1	71.95	76.70	84.34	86.07	95.22	95.95	28.05	115.2
B1	71.95	76.70	84.34	86.07	95.22	95.95	28.05	107.1

Table 3. Cytotoxicity effect of complexes on the MCF7 cell.

Compound	Viability at different concentrations (µg/mL)						Growth inhibition	IC_{50} (µg/mL)
	400	200	100	50	25	12.5		
A1	53.47	61.06	75.06	90.76	94.87	95.60	46.53	106.9
B1	61.96	68.33	78.69	85.81	94.71	94.83	38.04	107.1

5. Conclusion

The coordination was bye dentate via atoms as two nitrogen, despite complexes being multidentate with various donor atoms. Gold (III) and nickel (II) complexes with square planer shapes and chemical formulae; $[AuL_2]Cl_3$, $[NiL_2]Cl_2$ respectively. MTT assay method, cytotoxicity in which the A2 and B2 complexes have a more values anti-MCF-7 cell line. The high charging of gold (+3) could be significant and could have impacted anticancer activity.

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Conflicts of Interest

The authors declare that there is no conflict of interest.

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