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Synthesis, Characterization and Antiplasmodial Activities of Metal (II) Complexes of Artesuante

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Abstract:
Metal complexes of Cu (II), Co(II), Ni(II) and Mn(II) were synthesized with the antimalarial drug artesunate as ligand. The complexes were characterized by solubility, melting point, elemental analysis, conductivity measurement, IR and UV-Vis spectroscopy. The results indicated that the complexes possess either tetrahedral or octahedral geometries. The ligand coordinated with metals through the -OH group of the carboxylic functional group. The complexes have been screened for antiplasmodial activities against plasmodial falciparum parasites. The copper (II) complex was found to show higher activity against the parasites than the ligand and the complexes of Co(II), Nickel(II) and Mn(II).

Keywords: *Metal complex, In vitro, Antiplasmodial activity, Artesunate*

1. Introduction

The first successful biomedical application of organometallic compounds as drug is the discovery of the anti-syphilitic agent, the organo-arsenical salvarsan [xiv]. The discovery of cisplatin" as an anti-tumor agent in the mid-1960s was a major breakthrough, and a useful guide towards the utilization of metal ions as component of chemotherapeutic agents [xii].These compounds and several other related platinum(II) complexes are still among the most effective treatment for certain types of cancer [xvi]. This discovery has paved way for the development of drugs with metal centers, in an attempt to produce drugs having better efficacy and promising therapeutic properties. The emergence of drug resistant pathogenic micro-organisms brought about the introduction of metal ions into existing drugs or the synthesis of novel drugs with metal centers in an attempt to develop drugs with better efficacy to fight resistant strain of pathogenic micro-organisms [i].

An area where resistance, is of global concern is that of the *Plasmodium* parasite (i.e. malaria parasite), more especially *Plasmodium falciparum.* The resistance of plasmodium parasite to several anti-malarial drugs has necessitated the development of new antimalaria drugs. As a result, novel works have been conducted either in the synthesis of new antimalaria drugs or the modification of the existing ones. The synthesis of metal complexes of antimalarial drugs has been carried out and most of these complexes have shown better efficacy than the parent drugs [ii,xiv]. Ferrocene derivatives of the antimalaria drug chloroquine known as ferroquine has successfully passed clinical phase II trial as an antimalaria drug candidate [iii]. This compound is now undergoing field testing and may reach approval as a new antimalaria drug [v].

Following the successes recorded with ferroquine as an antimalaria agent, many organometallic compounds were synthesized, and tested for antiplasmodial activities. Some of these compounds have shown greater inhibitory activities against the different strains of plasmodium parasite. In this study metal complexes of Artesunate were synthesized and characterized with a view to improve the efficacy of the drug.The metal (II) complexes were screened for anti-plasmodial activities using the primary antimalaria screening protocol based on Giemsa stained slide.

2. Materials and Methods

2.1. Materials

All chemicals and solvents used were of analytical grade and were used as obtained without further purifications. The chemicals and solvents used were obtained either from British Drug House (BDH) ChemicalLimited, Pool, England, or Sigma-Aldrich, Company United Kingdom. The drugs Artesunate (product of Adams pharmaceutical Co. Ltd, China) used as ligands in this research were obtained from, Simple Pharmacy Maiduguri, Borno state.

2.2. Synthesis of the Metal (II) Complexes

The complex compounds were synthesized by dissolving3.844g (10 mmol) of Artesunate in 20ml methanol in a beaker and 10 mmol of the metal (II) salts were dissolved in 20 ml methanol [xi,xiii]. The ligand solution was mixed with the solution of each of the metal (II) salt. The mixture was refluxed for 4 hours on a hot plate magnetic stirrer. The refluxed solution was allowed to cool to room temperature and later on placed in ice and left over night for it to precipitate. The precipitate was filtered, washed with methanol and then with distilled water. The washed residue was placed in a desiccator for it to dry. The dried residue was weighed and placed into a sample bottle and stored in the desiccator. The same procedure was used for the preparation of all the metal (II) complexes.

2.3. Physical Measurements

The metal (II) complexes were digested and the metal content analysis for copper, cobalt, nickel, and manganese was done using EDTA titration. The melting points of the metal (II) complexes were determined using Gallenkamp melting point apparatus (England). The solubility of the metal (II) complexes was determined using both polar and non-polar solvents such as: - distilled water, methanol, ethanol, benzene, chloroform, dimethylsulfoxide (DMSO), petroleum ether and ethylacetate. Molar conductivity of the metal (II) complexes at a concentration of 10^{-3} M in distilled water was determined at room temperature using a conductivity meter EC500meter/PH/Conductivity/TDS/Salinity, Extech instruments, China.Microanalysis for carbon, hydrogen, and nitrogen were performed on Perkin Elmer Model (2400 series 11CHN S/O Elemental analyser) at the Department of Chemistry, University of Zululand, South Africa.The infrared (IR) spectra of the metal (II) complexes and the ligand were obtained using NaBr disc with Nujol as solvent on a Perkin Elmer 300 Spectrophotometer, in the range of 4000 – 200cm^{-1} at the Multi- User Laboratory, Faculty of Science, Abubakar Tafawa Balewa University, Bauchi State, Nigeria.UV – Visible spectra of the complexes and the ligand were obtained at concentrations of 10^{-3} M on a Perkin Elmer Lambda 35 UV – Visible spectrophotometer using distilled water as solvent in the range of 190 – 800 nm at the Zonal Laboratory, National Agency for Food and Drug Administration and Control (NAFDAC), Maiduguri.

2.4. Invitro Antimalarial Screening of the Metal (II) complexes

The complexes were screened for antimalarial activities using the primary antimalarial screening protocol [iv], at the Department of Parasitology, Faculty of Veterinary medicine, University of Maiduguri.

2.5. Pre – evaluation of Test Subjects

Malaria infected blood samples were collected from malaria infected patients at the Department of Microbiology, Maiduguri Specialist Hospital. The researcher sought the consent of all subjects whose blood was taken for the test. All subjects were asked about recent Antimalarial drug use. Those subjects who admit to the use of Antimalarial drug within the last 56 days were excluded from the test.

2.6. Preparation of Malaria Culture Medium

About 16.49g of Rose Park Memorial Institute Medium (R.P.M.I 1640) powder incorporated with 4-(2-Hydroxyethyl) – Piperazine – Ethanesulfonic acid (HEPES) and L-glutamine were dissolved in 100ml distilled water. 0.5ml of gentamicin solution was added and the solution was made up to 1000 ml and stored in a refrigerator.

2.7. Culturing Plasmodium falciparum Malaria parasites

The malaria parasites were cultured using the method described by Ljugstrom *et al.,* [8].Infected human red blood cells with *Plasmodium falciparum* malaria parasites were collected in EDTA tube from the Department of Microbiology and Parasitology, Maiduguri Specialist Hospital, Maiduguri, Borno State. The blood samples collected were investigated for *Plasmodium falciparum* using lancet, 0.1ml blood sample was withdrawn from EDTA tube containing plasmodium falciparum infected human red blood cells and was added to 0.9ml of Malaria culture medium (MCM) to form 1ml Blood Medium Mixture (BMM). The blood medium mixture was put in a petri dish. The petri dish was put in glass desiccators and a candle was lit and placed in the desiccators. The edge of the cover of the desiccators was sealed with silicon grease to make it air tight. The burning candle consumed some of the oxygen in the desiccators and producedcarbon dioxide which extinguished the burning candle. At this point a special gas mixture of about 93% nitrogen, 4% carbon dioxide and 3% oxygen was established in the desiccators and the desiccator was placed in an incubator at a steady temperature of about 37.5^{o}C for 24 hours. The parasitemia was then determined using the method described by Ljungstrom, 2014 and Trig, 1985.

2.8. Giemsa Staining of a Thick Blood Film from Malaria Culture

A thick blood film from malaria culture was dropped on a glass slide and placed in an incubator to dry at 37^{O}C for 30 minutes. The slide was then placed on a staining rack and stained with Giemsa solution for 30 minutes. The slide was rinsed very carefully and gently with tap water and was allowed to dry in an upright position. The parasitemia was counted with light microscopy under an oil immersion.

2.9. Estimation of the Percentage of Erythrocytes Infected with Plasmodium falciparum in a thin Blood Film

A light microscopy was used to view cells under an oil immersion at objective of x 100 magnification. An area of Giemsa-stained thin blood film where erythrocytes were evenly distributed was chosen for counting. All erythrocytes were counted and without moving

the slide the number of infected erythrocytes in the whole area was also counted. The slide was moved to randomly adjacent fields and the counting continued as above until the sum of 1000 erythrocytes have been examined regarding parasites, total examination of three different parts of the slide was carried out. The mean number of infected erythrocyte per 1000 erythrocytes was taken and divided by 10 to get the percentage erythrocytes [viii].

2.10. Screening of Metal Complexes for Antimalaria Activity

A 96 well-cultured plate was allowed to acquire ambient temperature. All the wells of the appropriate column were dose with 50 µl of the blood – medium mixture using an eppenderf pipette starting with the control well in an increasing order of concentrations (i.e., 0.1µmol, 0.2µmol, 0.4µmol, 0.8µmol, 1.6µmol, 3.2µmol and 6.4µmol). The tip of the eppendorf pipette was changed after each dosing until all the scheduled wells have been dosed.

The plate was shaken gently on the laboratory bench without lifting it so that the metal (II) complexes in the well dissolved completely. The plates were then incubated at $37.5^{O}C$ using the candle jar techniques, for 24 hours. After incubation, the contents of the test wells were harvested with an eppendorf pipette, and transferred to a clean microscopy slide. The harvest proceeds well by well from the last well to be dosed to the control. The resultant thin films were dried in an incubator at $37.5^{O}C$ for 30 minutes.

The thin film was stained for 30 minutes with Giemsa solution and dried in an incubator at $37.5^{O}C$ for 30 minutes. The Giemsa-stained thin blood films were viewed in an oil immersion at an objective of x 100 magnification. The parasitemia was estimated by counting the number of schizonts out a total of 200 asexual parasites after incubation and number of schizonts per 200 parasites after incubation as a percentage of schizonts relative to control samples [xviii], i.e.:

$$\% \text{ of schizonts relative to control sample} = \frac{\text{No: of schizonts per 200 parasite after incubation}}{\text{No: of schinzonts with three or more nucleic per 200 asexual parasites}} X\ 100$$

Ligands/complexes	Colour	Melting point (^{o}C)	Yield (%)	Molar conductivity ($\Omega^{-1}cm^2mol^{-1}$)
AR	White	132-135		
$Cu(AR)_2 4H_2O$	Light green	235-239	37	1.36×10^{-2}
$Co(AR)_2 2H_2O$	Light green	209-213	35	3.63×10^{-2}
$Ni(AR)_2 2H_2O$	Yellowish green	274-275	35	1.05×10^{-2}
$[Mn(AR)_2(H_2O)_2X_2]\ X_2\ 2H_2O$	Light yellow	233-236	35	4.63×10^{-2}

Table 1: Physical properties of the ligand and the metal (II) complexes
AR = ArtesunateX = Cl

Ligands/complexes	Water		Methanol		Ethanol		Benzene		Chloroform		Petroleum ether		Ethyl acetate		Dimethyl sulfoxide	
	C	H	C	H	C	H	C	H	C	H	C	H	C	H	C	H
AR	ss	ss	s	s	s	s	i	i	s	s	i	i	i	i	s	s
$Cu(AR)_2 4H_2O$	ss	ss	i	i	ss	ss	i	i	i	i	i	i	i	i	s	s
$Co(AR)_2 2H_2O$	ss	ss	i	i	ss	ss	i	i	i	i	i	i	i	i	s	s
$Ni(AR)_2 2H_2O$	ss	ss	i	i	i	i	i	i	i	i	i	i	i	i	s	s
$[Mn(AR)_2(H_2O)_2X_2]\ X_2\ 2H_2O$	ss	i	i	i	i	i	i	i	i	i	i	i	i	i	s	s

Table 2: Solubility behaviours of the ligand and the metal complexes in some selected solvents
C = cold solvent H = hot solvent ss = slightly soluble i = insoluble

Complexes	Molecular formula	Molar Mass	Microanalysis, % found (calculated)		
			C	H	M
$Cu(AR)_2 4H_2O$	$Cu(C_{38}H_{64}O_{20})$	904.38	51.10 (50.42)	9.76 (7.09)	7.12 (7.03)
$Co(AR)_2 2H_2O$	$Co(C_{38}H_{60}O_{18})$	863.77	53.14 (52.79)	4.89 (6.95)	6.12 (6.82)
$Ni(AR)_2 2H_2O$	$Ni(C_{38}H_{64}O_{20}Cl_2)$	970.55	46.04 (46.98)	8.82 (6.59)	6.10 (6.05)
$[Mn(AR)_2(H_2O)_2X_2]\ X_2\ 2H_2O$	$Mn(C_{38}H_{64}O_{20}Cl_4)$	930.75	48.70 (48.99)	4.58 (6.88)	6.12 (5.90)

Table 3: Microanalysis data for the metal complexes

Ligands /complexes	V_{OH}	$V_{C=O}$	M –OH	M – O
AR	3600 – 3320	1830		
$Cu(AR)_2 4H_2O$	3640	1650	890	720
$Co(AR)_2 2H_2O$	3340	1710	750	710
$Ni(AR)_2 2H_2O$	3540	1710	720	660
$[Mn(AR)_2(H_2O)_2X_2]\ X_2\ 2H_2O$	3640	1750	880	820

Table 4: Relevant infrared frequencies of the ligand and their metal (II) complexes
M = Cu^{2+}, Co^{2+}, Ni^{2+}, and Mn^{2+}

Ligands/Complexes	Wavelength (cm^{-1})	Energies (cm^{-1})	Assignment	Geometry
AR	226	44248	$\pi \rightarrow \pi *$	
$Cu(AR)_2 4H_2O$	240 342	41667 29240	$\pi \rightarrow \pi *$ MLCT	Octahedral
$Co(AR)_2 2H_2O$	550 650 800	18018 15385 12500	$^4A_{2g} \rightarrow {}^4T_{2g}(p)$ $^4A_{2g} \rightarrow {}^4T_{1g}$ $^4A_{2g} \rightarrow {}^4T_{1g}$	Tetrahedral
$Ni(AR)_2 2H_2O$	222 240 250 750	45045 41667 40000 13333	$\pi \rightarrow \pi *$ $\pi \rightarrow \pi *$ $\pi \rightarrow \pi *$ d – d transition	Tetrahedral
$[Mn(AR)_2(H_2O)_2X_2]\ X_2\ 2H_2O$	224 255550 590	44643 39216 18018 16949	$\pi \rightarrow \pi *$ $\pi \rightarrow \pi *$ $^6A \rightarrow {}^4T_{1g}(4D)$ $^6A_{1g} \rightarrow {}^4T_{1g}(4G)$	Octahedral

Table 5: Electronic absorption spectral data for the ligand and the metal (II) complexes

Ligands/complexes	Concentrations in µmol/1BMM of ligands/metal complexes/ percentage inhibition (%)							
	0.0	0.1µmol	0.2 µmol	0.4 µmol	0.8 µmol	1.6 µmol	3.2 µmol	6.4 µmol
AR	0	11.17	43.73	67.61	82.19	91.66	99.49	100
$Cu(AR)_2 4H_2O$	0	53.59	70.61	83.11	89.90	96.37	99.72	100
$Co(AR)_2 2H_2O$	0	33.86	54.49	72.81	84.54	96.25	99.38	100
$Ni(AR)_2 2H_2O$	0	37.83	58.64	73.12	85.99	93.75	99.16	100
$[Mn(AR)_2(H_2O)_2X_2]\ X_2\ 2H_2O$	0	39.44	62.71	79.20	88.54	95.88	99.41	100

Table 6: Percentage inhibition of the ligand and their metal (II) complexes (%)
BMM = Blood Medium Mixture

3. Results and Discussion

The metal chloride salts reacted with the ligand according to the following general chemical equation:
$MX_2.nH_2O + 2\ AR \rightarrow\ M(AR)_2X_2 + nH_2O$
AR = Artesunate, X = Cl^-n = 6, 4, or 2

The complexes are stable and non hygroscopic solids. The complexes possess colours, different from that of their parent drug. The melting point of the metal (II) complexes ranges from 209-275^{O}C which are higher than those of the ligand. The high melting point is usually an evidence for the formation of a complex compound, attributed to strong metal – ligand bond in the complexes [x,xiii].The percentage yield of the metal (II) complexes ranges from 35% -37%. The microanalytical results as well as the results for metal content analysis are in good agreement with theoretical values. The solubility behaviours of the ligand and their metal (II) complexes show that all the complexes are soluble indimethylsulfoxide (DMSO) and slightly solublein water. The complex compounds $Cu(AR)_2.4H_2O$, and $Co(AR)_2.2H_2O$ are slightly soluble in ethanol. All the complexes are insoluble in methanol, benzene, petroleum ether and ethylacetate. The molar conductivity values of the metal (II) complexes ranges from 1.36 x 10^{-2} to 4.63 x $10^{-2}\Omega^{-1}cm^2mol^{-1}$. The low molar conductivity values indicated that the complexes are non electrolytes [i].

3.1. IR-Spectra of Metal (II) complexes and Artesunate

The IR-Spectra of the drug ligand Artesunate with the metal (II) complexes were obtained within the range of 4000-200cm^{-1} and those for the metal (II) complexes were compared with those of the ligand. The drug ligand showed vibration bands between 3600-3320cm^{-1}regions for V_{OH} stretching in the IR – Spectra of Artesunate. The bands appeared in the spectra of the metal (II) complexes of copper, cobalt, nickel, and manganese at wavelengths of 3640cm^{-1}, 3340cm^{-1}, 3540cm^{-1}, and 3640cm^{-1}, respectively. The shifts of the bands in the spectra of the metal (II) complexes are due to coordination [xvii]. This was supported by the appearance of bands for M – OH bonding at 890cm^{-1} for copper (II) complex, 960-750cm^{-1} for cobalt (II) complex, 720cm^{-1} for nickel (II) complex, and 880cm^{-1} for manganese (II) complex.

The band due to Vc=o group which appeared at 1830 cm^{-1} in the spectra of Artesunate have been found to shift to lower wavelengths in the spectra of the metal (II) complexes of copper, cobalt, nickel, and manganese at lower wavelength of 1650 cm^{-1} for copper, 1710 cm^{-1} for cobalt (II), 1710 cm^{-1} for nickel, and 1750 cm^{-1} for manganese (II) complexes. This was further supported by the appearance of new bands in the spectra of metal (II) complexes of copper, cobalt, nickel, and manganese due to M – O bond at 720 cm^{-1}, 710 cm^{-1}, 660 cm^{-1},820 cm^{-1} and 660 cm^{-1} respectively.

3.2. Electronic Spectra of Metal (II) complexes and Artesunate

The electronic spectra of the drug ligand Artesunate as well as the metal (II) complexes were obtained within the region of 190-800 nm. From the results, the drug ligand Artesunate showed a single absorption band at 44248 cm^{-1} (226 nm) due to $\pi \rightarrow \pi^*$transition of C = O groups. However, the band was observed to have undergone either a bathochromic or hypsochrnmic shift due to coordination with

the metal (II) ions. The single absorption band expected in the visible region of the spectra for copper (II) complex compounds with d^9 configuration has not been observed but rather two bands appeared in the spectrum of copper (II) complexes at 41667 cm^{-1} (240 nm) and 29240 cm^{-1} (342 nm) which were assigned to $\pi\rightarrow\pi^*$ and MLCT transitions which occurred at the ultraviolet region. The electronic spectra of cobalt (II) complex $[Co(AR)_2(H_2O)_2]$ of the drug ligand gave three broad absorption bands in the visible region as expected for metal (II) ions with d^7 configuration (Housecraft and Sharpe, 2008), the bands occurred at 18018 cm^{-1} (550 nm), 15385 cm^{-1} (650 nm), and 12500 cm^{-1} (800 nm) and are assigned to the following transition $^4A_2g\rightarrow{}^4T_2g(p)$, $^4A_2g\rightarrow{}^4T_1g$ and $^4A_2g\rightarrow{}^4T_1g$ respectively. These transitions suggest octahedral geometry for the cobalt (II) complex [xv]. The nickel (II) complex of the drug ligand show absorption bands at 45045cm^{-1} (222 nm), 41667 cm^{-1} (240 nm), 4000 cm^{-1} (250 nm) and a broad band at 13333 cm^{-1} (750 nm). The shift of the bands either to higher or lower wavelength was due to coordination and the broadness of the band at 13333cm^{-1} (750 nm) are due to d-d transitions and hence suggest octahedral geometry for the nickel (II) complex [vi,vii]. The electronic spectra of manganese (II) complex show four absorption bands. Manganese (II) complexes with d^5 configuration are expected to show some series of weak absorption bands [vii] but four bands were observed in the spectra of manganese (II) complex with the ligand Artesunate. These bands are assigned the following transition; $\pi\rightarrow\pi^*$ 44643 cm^{-1} (224 nm), $\pi\rightarrow\pi^*$ 39216 cm^{-1} (255 nm), $^6A_2\rightarrow{}^4T_1$ (4D) 22222 – 18018 cm^{-1} (450 – 550 nm) and $^6A_2\rightarrow{}^4T_1$ (4G) 16949 cm^{-1} (590 nm). The assignments were consistent with reported values and hence suggest tetrahedral geometry for the manganese (II) complex [vii].

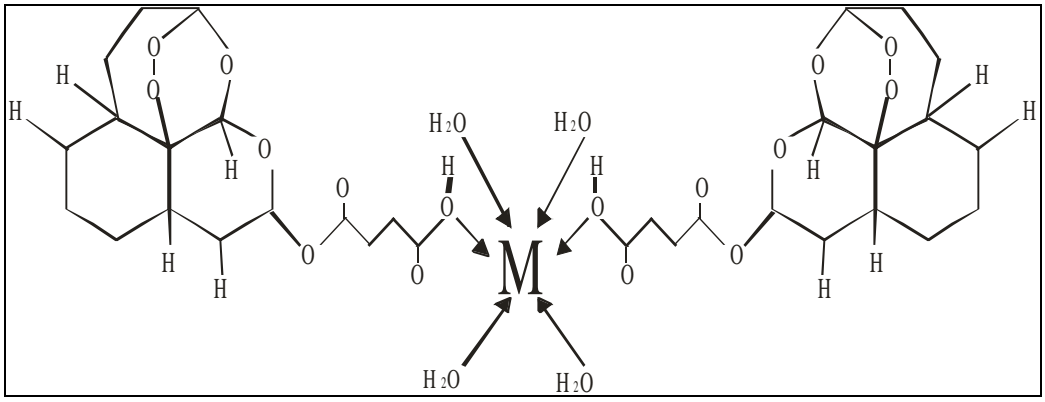

Figure 1: Proposed Structure of $M(AR)_2.4H_2O$ M = Cu(II), Co(II), Ni(II) and Mn(II)AR = Artesunate

3.3. The in vitro studies

The results for *in vitro* studies of the ligand and the metal (II) complexes are presented in Table 5. From the results, the percentage inhibition of the ligand at concentration of 0.1µmol, 0.2 µmol, 0.4 µmol, 0.8 µmol, 1.6 µmol, 3.2 µmol, and 6.4 µmol/IBMM are 11.17%, 43.73%, 67.61%, 82.19%, 91.66%, 99.49%, and 100% respectively. The complex $Cu(AR)_2.2H_2O$ show greater activity at concentrations of 0.2 µmol, 0.4 µmol, 0.8 µmol and 3.2 µmol with percentage inhibition 70.61%, 83.11%, 89.80% and 99.72%respectively as compared to the ligand and the other metal (II) complexes. All the metal (II) complexes show percentage inhibition above 99%at concentration of 3.2 µmol and 100% at concentration of 6.4 µmol. The greater activity shown by some of the complexes against the parasites (*Plasmodium falciparum)* might be due to the complexes binding first at the receptor site without being decomposed. The metal ions could be reduced to the free state and could be toxic; its deposition in the membrane of the parasites will lead consequently to death of the parasites [ix]. The result further indicated that coordination of the ligand to the metal ions enhances the activity of the drugs.

4. Conclusion

In this study, metal (II) complexes of copper, cobalt, nickel, and manganese with the anti-malarial drug artesunate, as ligand have been synthesized. The complexes were characterized by solubility, conductivity, elemental analysis, electronic and IR spectroscopy. The results obtained revealed that the metal complexes possess either octahedral or tetrahedral geometry. The antiplasmodial studies using *Plasmodium falciparum* as test organism showed that some of the metal (II) complexes exhibited higher activities than the parent drug ligand.

5. References

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