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Synthesis, Characterization and Biological Activities of Azo Ligand: 7-[(E)-(2,3-Dihydroxy-1,5-Dimethyl-3-oxo-2-Phenyl-IH-Pyrazol-4-yl)Diazenyl-1H-Indole-2,3-dione (L) and its Co(II) and Fe(III) Complexes

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Abstract

This study was carried out to synthesize, characterize and determine the antimicrobial Activities of Azo Ligand: 7-[(E)-(2,3-dihydroxy-1,5-dimethyl-3-oxo-2-phenyl-IH-pyrazol-4-yl) diazenyl-1H-indole-2,3-dione (L) and it's Co(II) and Fe(III) complexes. The ligand L was prepared by diazotizing 4-amino-antipyrine and coupling with isatin. L complexed with Co(II) and Fe(III) were also synthesized. L was characterized via UV, IR, NMR (^{l}H and ^{13}C NMR) spectroscopy. The complexes were characterized based on their conductance, stoichiometry, infrared and UV-visible spectra. L coordinated to Co(II) as a terdentate ligand through the azo nitrogen, isatin ring nitrogen and carbonyl group of pyrazolone. The complex presented a 1:1 stoichiometry with octahedral geometry. The Fe(III) complex, $[Fe_2O(L)_2Cl_2]$ is a µ-Oxo-bridged compound where each Fe has a coordination of five with a 1:1 metal to ligand ratio. The ligand was bidentate. L showed higher potency against *Pseudomonas. aeruginosa* and *Candida. albicans*, *Staphylococcus aureus* and *Escherichia coli* in comparison to ampicilin. The Co (II) and Fe (III) complexes had as high activity as the ligand at 20 µg/mL against all the microorganisms. The synthesized compounds have potency as antibacterial agents.

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Introduction

The biological and pharmacological applications of isatin and its derivatives have led to extensive use of these compounds as key intermediates in drug synthesis (Varun et.al, 2019). Isatin is a core constituent of many alkaloids (Jahng et.al, 2008) and drugs (Aboul-Fadl et.al, 2010) as well as dyes (Negar et.al., 2012) pesticides and analytical reagents. Literature reports reveal that various derivatives of isatin possess diverse activities such as antibacterial (Kassab et.al., 2010), antifungal (Dandia *et.al.*, 2006), antiviral (Jarrahpour *et.al*., 2007) anti-HIV (Bal *et.al*., 2005) anti-mycobacterial (Feng *et.al*., 2010) anticancer (Qachchachi et.al.,2016) anti-inflammatory (Sridhar & Ramesh., 2001) and anticonvulsant activities (Verma et.al., 2004). Azo compounds derived from isatin and 4-amino antipyrine has also been reported to have some biological activities (Al-Gaber *et.al*., 2023, Abdulghani and Ahmed., 2011) Their complexes with metal ions such as Ce(II), Pt(II), UO_2 +2, Cu(II), Mn(II), Ni(II) have been extensively investigated because of their biological, clinical, pharmacological and analytical importance (Abd El-Wahab et.al 2005; Barra *et.al*., 2005; Agarwal *et.al*., 2006). The Electrical Conductivity, Electronic Absorption, IR and NMR Studies On Cr(III), Sn(IV) and Pb(IV) Complexes of this Azo Ligand derived from Isatin and 4-Aminoantipyrine have also been reported (Chinyere *et.al*., 2018)

This research aims at synthesising, characterizing and determining the antimicrobial activities of an azo ligand: 7-[(E)-(2,3-dihydroxy-1,5-dimethyl 3-oxo-2-phenyl-IH-pyrazol-4-yl)diazenyl-IH-indole-2,3-dione(L) and its Co(II), Fe(III) complexes.

Materials and Methods

Materials

All chemicals used were analytical grade and were products of Sigma Aldrich. They were used as purchased without further purification unless otherwise stated.

Heating was done on a Gallonkaup Magnetic Stirrer/Thermostat hot plate. John-Fisher melting point apparatus was used in determining the melting points of compounds. UV Visible spectra were obtained on Cecil UV-Visible spectrophotometer whereas Perkin-Elmer FTIR spectrometer and Bruker DPX 400 NMR spectrophotometer was used to run ^{I}H and ^{13}CNMR spectra of compounds.

The conductivity of 1.0 x 10^{-3}mol/dm^{-3}methanol solution of compounds was determined using WTW-LF90 conductivity.

The microorganisms used for the study, *Pseudomonas aeruginosa, Staphylococcus aureus, Escherichia coli, Bacillus sabtilis. Streptococcus pneumeniae, Proteus mirabilis, Staphylococcus intermedius and Klebsiella*

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pneumoniae were clinical isolates obtained from the Department of Veterinary Medicine University of Nigeria, Nsukka.

Synthesis of Azo Ligand: 7-[(E)-(2,3-dihydro-1,5-dimethyl 3-oxo-2-phenyl-IH-pyrazol-4-yl)diazenyl-IH-indole-2,3-dione(L)

The azo ligand 7-[(E)-(2,3-dihydro-1,5-dimethyl 3-oxo-2-phenyl-IH-pyrazol-4-yl) diazenyl-IH-indole-2,3-dione(L) was prepared following Hiosonike method (Heinosuke Yasuda., **1967)**; Garnovskii *et.al*.,2004**).** It was done by dissolving 4-Aminoantipyrine in dilute hydrochloric acid and diazotizing with sodium nitrite solution below 5^{o}C under constant stirring. The resulting diazotized 4-amino antipyrine was poured into a solution of 2,3-Indolinedione and sodium acetate using mechanical stirring at room temperature. The product was collected and washed with methanol. The compound was recrystallized and dried in a desiccator over $CaCl_2$

Synthesis of metal complexes

The metal complexes were prepared following the method of (*El-Saied et.*al., 2001). A solution of 2mmoles of a metal salt with 1mmole of 1,2-dihydroxy-4-(E)-[3-hydroxy-4[(E)-Pheny(diaze-ny]-1-naphthalenyl]-1,5-dimethylphenyl-3H-pyrazol-3-one in about 50mL EtOH was stirred for a period of 6hrs at 60^{0}C. The resulting solids were filtered off, washed with EtOH and stored in desiccators over $CaCl_2$.

Spectroscopic Characterization

The stoichiometric studies were determined by employing Job,'s continuous variation method of analysis (Renny *et.al*., 2013, Kairdolf *et.al*., 2013). IR spectra were recorded on a Matson Genesis II Fourier Transformed infrared spectrophotometer using Nujol Mull. The ^{1}H and ^{13}C NMR spectra were recorded in DMSO using a 200MHz Varain nmr spectrophotometer. The electronic spectra were carried out in EtOH solution using a Cecil Ultraviolet-visible spectrophotometer. The molar conductivity measurements were made in methanol solution (10^{-3}M) using a Milwaukee Conductometer type CD600 series.

Antimicrobial activity

The preliminary screening of the antimicrobial activity of the synthesized ligand and its complexes in DMSO was examined by using agar-well diffusion method (Mohamed *et al*., 2018)

20mg/ml each of ligand and complexes were constituted by dissolving 0.02g of each in 1 mL of DMSO. A single colony of each test bacteria was suspended in 2mL of sterile nutrient broth. The suspension of each test bacteria was used to inoculate the surface of the already prepared nutrient agar and the excess fluid was drained into a discard pot containing disinfectant. Using a cork borer of 6mm in diameter wells were bored in the inoculated agar plates. With a micropipette, 50µL of each test compound was delivered into the well. The plates were left on the bench for 30 minutes to allow the extract to diffuse into the agar. Thereafter, the plates were incubated at 37^{0}C for 24 hours. After incubation, the plates were observed for inhibition zones around the wells, and the diameters of the zones were measured with the meter rule. Based on the preliminary test, the compound affecting significant zones of inhibition were then selected and used for the minimum inhibitory concentration (MIC) determination by double serial dilution of the test compound.

Ampicillin was used as the reference standard. The bacteria which include *E. coli*, *P. aeruginosa*, *Staphylococcus aureus* and *Fungus Candida albicans* were obtained from stock culture (clinical isolate) and were maintained separately on a solid medium containing agar. All the materials used were sterilize

Results and Discussion

^{1}H PROTON AND ^{13}C NMR SPECTRA OF THE ligand (L)

The ^{1}H and ^{13}C NMR spectral data of the ligand are given in Tables 1 and 2 respectively

Table 1. The ^{1}H NMR spectral data of L in $CDCl_3$ relative to TMS (ppm)

Peaks (δ)	Assignment
2.45 (3H, s)	C- CH_3 methyl protons from pyrazolone ring
3.4 (3H, s)	N-CH_3 methyl protons from pyrazo lone ring
7.0 (1H, d)	Phenyl protons
7.0 (1H, d)	Phenyl protons
11.04 (1H, s)	N-H proton of isatin ring

s- singlet, d- doublet, m-multiple

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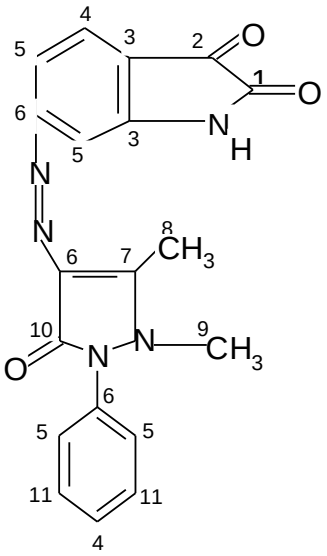
The ^{1}H NMR spectrum of 7-[(E)-(2,3-dihydro-1,5-dimethyl 3-oxo-2-phenyl-IH-pyrazol-4-yl) diazenyl-IH-indole-2,3-dione(L) was recorded in DMSO at room temperature. The spectrum of the ligand shows the signal at 2.45ppm (3H, s) and 3.40ppm (3H, s), due to C-CH_3 methyl protons and the N-CH_3 methyl protons respectively. The spectrum also shows a signal between 7-76ppm (5H,m), assigned to phenyl protons (Mahmoud *et.al*., 2014) in the compound. The N-H of the isatin ring has a signal at 11.04ppm (1H, s). The observed splitting patterns and integration values are consistent with the expected structure, providing evidence for the compound's identity and molecular structure (Chinyere *et.al*.,2018; Eledalachi *et.al*., 2019)

Table 2: The 13C NMR Spectral Data of L

Position	**^{13}C**	**Structure showing carbon numbering**
C_1	160.011ppm	
C_2	139.051 ppm	
C_3	40.975 ppm	
C_4	112.884 ppm	
C_5	40.971 ppm	
C_6	125.364ppm	
C_7	123.445 ppm	
C_8	39.336 ppm	
C_9	40.581 ppm	
C_{10}	151.379 ppm	
C_{11}	**118.475 ppm**	

The ^{13}C NMR spectral data of the ligand is given in Table 1. A previous report on ^{13}C NMR spectral studies on some pyrazolones (Mahmoud *et.al*., 2014) was taken into consideration in the assignments made. The ^{13}C NMR gave signals at 160.011, 151.379, 139.051, 125.364, 123.445, 118.475, and 112.884ppm, 40.975, and 39.336ppm corresponding to the carbon assignments given as shown in Table 1 respectively. These assignments were in agreement with related works done by Chinyere *et.al*.,2018 and Eledalachi *et.al*., 2019.

Electronic spectral of compounds: The Electronic spectral of the compounds are shown in Table 3

Table 3: electronic spectra of l, [colcl$_2$(oh$_2$)] and [feo(l)$_2$cl$_2$]

	ν_1	**ε_1**	**ν_2**	**ε_2**	**ν_3**	**ε_3**	**ν_4**	**ε_4**
	(cm^{-1})	**($Mol^{-1}cm^{-1}$)**	**(cm^{-1})**	**($Mol^{1}cm^{-1}$)**	**(cm^{-1})**	**($Mol^{-1}cm^{-1}$)**	**(cm^{-1})**	**($mol^{-1}cm^{-1}$)**

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L	47169	65908	41152	99094	33783	18395	23751	**40672**
$[CoLCl_2(OH_2)]$	46511	84142	41152	12034	33333	29025	23980	**87816**
$[FeO(L)_2Cl_2]$	**46082**	**83766**	**41666**	**12344**	**33557**	**32586**	**24449**	**90486**

The electronic spectra bands of L and its metal complexes were determined. The free ligand displayed absorption bands at 421, 296, 243 and 212 nm. The band at 421nm was assigned to n - π^* transition while the bands at 296nm, 243nm and 212nm were assigned to $\pi \rightarrow \pi^*$ transition centered primarily on the azo group (Kalia and Chakravorty.,1970).
The band at 24449cm^{-1} refers to the $^6A_{1g} \rightarrow {}^5T_{2g}(G)$ transition in the octahedral geometry of the complex (Bryan et.al., 1971 and Mondal et.al., 2000). The bands at 33557cm^{-1}, 41666cm^{-1}, and 46082cm^{-1} indicated charge transferred band (L→MCT) [24]. Also, the positions of these bands are consistent with the expected energy range for LMCT transitions involving the specific ligand and metal center (Chinyere *et.al*.,2018).

In the spectrum of $[CoLCl_2(OH_2)]$, four absorption bands were observed. The bands are 23980cm^{-1}, 33333cm^{-1}, 41152cm^{-1} and 46511cm^{-1}. These bands could be attributed to be due to charge transfer.
In the spectrum of $[Fe_2O(L)_2Cl_2]$ four absorption bands were observed. The absorption bands are at 24449cm^{-1}, 33557cm^{-1}, 41666cm^{-1}, and 46082cm^{-1}.
The number, position, and splitting pattern of absorption bands observed in the spectrum are consistent with the expected number of transitions for an octahedral complex indicating that the metal centre is in an octahedral environment (Mahmoud *et.al*., 2014; Chinyere *et.al*.,2018 and Eledalachi *et.al*., 2019)

Infrared Spectral of the compounds
The Infrared spectral of the compounds is presented in table 5 below

Table 4: Infrared spectra of L and its complexes

L	$[CoLCl_2(OH_2)]$	$[Fe_2O(L)_2Cl_2]$	Assignment
3445.85 (sh)	3412.18(br)	3450.33 (sh)	ν(OH)
3191.39 (m)		3191.94 (m)	ν (N-H) of isatin
2916(sh)	2925.05(sh)	2916 (sh)	
2832.8(sh)	2834 (sh)	2814.17 (sh)	ν (C-CH_3)
1747.35(S)	1736.45(sh)	1737.25 (s)	ν (N-CH_3)
1727.53(s)	1711.08(sh)	1615.63 (s)	
1615.58(s)	1654.10(m)		ν (C=O)
1550(w)	1517.87(w)	-	
1483.09(sh)	1457.4(sh)	1483.01(sh)	
1460.51(s)		1460.66(s)	
1401.881(sh)		1402.01(sh)	ν (N=N)
			ν (C-C)
1331.56	1337.06(sh)	1331.68(s)	(ν)Pyrazolone ring
	1318.13(sh)		
1289.49 (sh)	1243.00(sh)	1289.70(sh)	ν (C-O)
1201.18 (m)	1159.03(sh)	1269.48(sh)	
1189.16(sh)	1059.84(m)	1244.53(sh)	
	560..24(sh)	548.04(w)	M–O bond stretching
		538.13(w)	
	468.06(sh)	479.82(sh)	M-N bond stretching

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The IR spectrum of the ligand (Table 2) shows peaks at 3445.85cm^{-1}, 3191.39cm^{-1} and between 1747.35cm^{-1} -161538cm^{-1} , assigned to be from the (OH) Stretch of H_2O, Isatin (N-H) and carbonyl group of both isatin and Pyrazolone rings respectively.

Table -2 lists the most important IR spectral peaks of the metal complexes. In the spectra of all the complexes the v(N=N) shifts to lower frequency due to its involvement in coordination (Mohamed *et.al.*, 2018)

In the spectrum of $[CoLCl_2(OH_2)]$ peaks at 1736.45cm^{-1} 1711.08cm^{-1} and 1654.10cm^{-1}were assigned to (C=O) group. The values shifted from that obtained for the ligand suggesting the participation of the carbonyl in coordination with the metal ion (Okafor., 1991)

The (C=O) vibrational peaks of $[Fe_2O(L)_2Cl_2]$, was not observed in this complex. These peaks were found to be absent in this complex while they were present in the ligand. Therefore, we can conclude that this carbonyl group (C=O) was used for complexation.

The physical properties of the ligand and complexes: The physical properties of the ligand and complexes are shown in table 6

Table-6: physical properties of L and its Co(II) and Fe(III) complexes

Compound	Colour	Texture	Melting point ^{o}c	Molar conductivity (μohm^{-1} m^{-1})	Yield	% yield
L	Red	Granular	200	00.00	0.12	33.22
$[CoLCl_2(OH_2)]$	Red	Crystalline	185	00.00	0.02	2..38
$[Fe_2O(L)_2Cl_2]$	Red	Crystalline	192-194	00.00	0.06	7.19

The molar conductance values of the complexes are presented in Table 3. The molar conductance values of $[CoLCl_2(OH_2)]$and $[Fe_2O(L)_2Cl_2]$ revealed that they were essentially non-electrolytes. This is because there was no dissociation of ions on the complexes compared with $CuSO_4$ salt which was used as the control. The stoichiometry of $[CoLCl_2(OH_2)]$ and $[FeO(L)_2Cl_2]$ complexes were observed to have the same ligand to metal mole ratio of 1:1.

3Proposed structure of the compounds

Based on the data gathered, the following structures were given to the compounds

Fig 1-3 shows the structures of the compounds

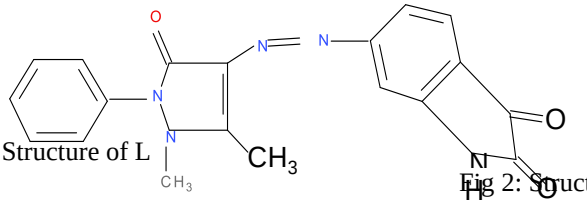

Fig 1: Structure of L

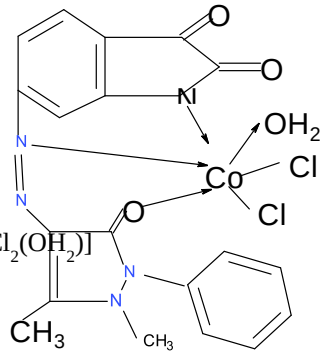

Fig 2: Structure of $[CoLCl_2(OH_2)]$

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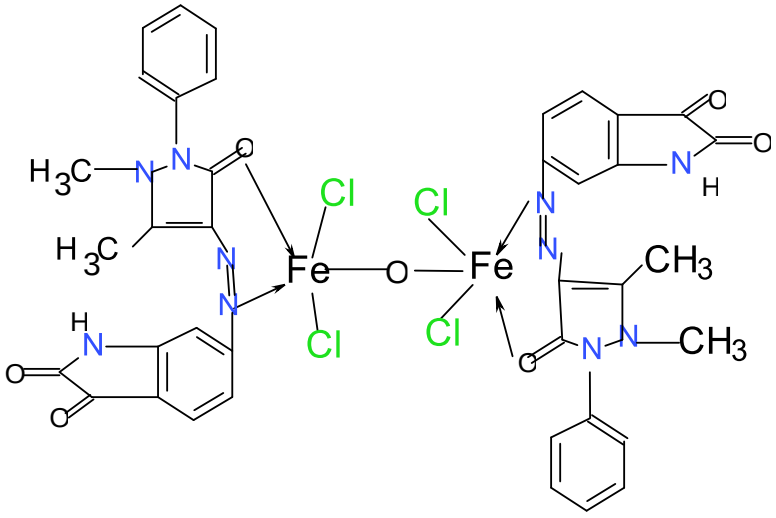

Fig-3: Chemical structure of $[Fe_2O(L)_2Cl_2]$

Antimicrobial activity

The experimental inhibition zones (mm) and the MIC are shown in Table-7 and 8 respectively

Table 4: Antimicrobial activities of the L and its Co(II) and Fe(III) complexes·

Compound	Pseudomonas aeruginosa	Candida albicans	Staphyllococcus aureus	Escherichia coli
		Zone of Inhibitions (mm)		
L	15	20	25	23
$[CoLCl_2(OH_2)]$	13	15	20	20
$[Fe_2O(L)_2Cl_2]$	16	16	25	22
$Fe\ Cl_3.6(H_2O)$	13	12	18	13
$Co\ Cl_2.6(H_2O)$	22	13	25	13
Ampicilin	Nil	Nil	29	25

Table-5: Minimium Inhibitory concentration MIC for L and its complexes

Ligand/complexes	Zone of inhibition (mm).				
	20µglmL	10µglmL	5 µglmL	2.5 µglmL	1.5µglmL
L	25	22	19	14	12
$[CoLCl_2(OH_2)]$	20	16	15	11	Nil
$[Fe_2O(L)_2Cl_2]$	25	20	17	11	Nil
		Organisms –Candida albicans.			
L	20	14	11	Nil	Nil
$[CoLCl_2(OH_2)]$	15	10	Nil	Nil	Nil
$[Fe_2O(L)_2Cl_2]$	15	10	Nil	Nil	Nil
		Organisims psuedomonas earuginosa			
L	15	Nil	Nil	Nil	Nil
$[CoLCl_2(OH_2)]$	13	Nil	Nil	Nil	Nil
$[Fe_2O(L)_2Cl_2]$	15	10	Nil	Nil	Nil

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	Organisms Escherishia coli (E_2)				
L	23	20	17	12	10
$[CoLCl_2(OH_2)]$	20	17	12	10	10
$[Fe_2O(L)_2Cl_2]$	22	17	14	12	10

The experimental inhibition zones (mm) and the MIC are shown in Table 4 and 5 respectively. All the compounds had different antibacterial activity in vitro against the tested micro-organisms. The activities of the ligands and complexes were checked against gram-positive bacteria. In Table 4, Ampicilin standard drug showed no zones of inhibition in (mm) against Pseudomonas aeruginosa and Candida albican, had activity against *S. aeureus* and *E. coli.* All the compounds had activity against all the microorganisms. In other words, the compounds show antimicrobial activity against a wide range of microorganisms, including bacteria and fungi, indicating their potential as broad-spectrum antimicrobial agents. This is a desirable property for antimicrobial compounds, as it suggests they could be effective against a variety of infections.

Ligand (L), $[CoLCl_2(OH_2)]$ and $[Fe_2O(L)_2Cl_2]$ had activity against *S. aeureus*, up to concentration 2.5µg/mL and also on *Escherichia coli*, the activities proceeded till the last concentration 1.5µg/mL and their zones of inhibitions of, 10 overall.

On Candida –albcan, L, and its complexes were active at concentration 10µg/mL.

Analyzing both MIC (Minimum Inhibitory Concentration) and zone of inhibition provides a comprehensive understanding of a compound's antimicrobial activity. These compounds had low MIC values which indicated their potency for antimicrobials.

Conclusion

The L and $[CoLCl_2(OH_2)]$, $[Fe_2O(L)_2Cl_2]$ complexes were successfully synthesized. The ligand L and complexes were characterized by spectral, stoichiometry, molar conductance and biological activities data. The spectral data showed the absences of π-bonding interaction in the complexes. Bonding of the ligand to the central metal atom in the complexes occurred by s-bonding through the participation of enol oxygen, carbonyl oxygen and azo nitrogen group of pyrazolone ring.

Based on these data, an octahedral geometry has been assigned to $[CoLCl_2(OH_2)]$ complex while square planar geometry was assigned to $[Fe_2O(L)_2Cl_2]$. Metal –ligand mole ratio indicated a 1:2 for Co (II) complex while Fe (III) complex had 2:2.

The molar conductivity value revealed that $[CoLCl_2(OH_2)]$ and $[Fe_2O(L)_2Cl_2]$ are non-electrolytes when compared with $CuSO_4$ salt.

The L have higher antimicrobial activity than its complexes suggesting that the good activities were as a result the ligand. The antimicrobial properties of the ligand and complexes suggested that they could be used in pharmaceutical industry as drugs.

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