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Cyclopalladate Complexes of 4-Methoxy-N- {(E)-(piperidin-1-yl) phenyl) Methylene} Aniline: Synthesis, Spectral Characterization and Biological Evaluation

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THE REACTION of palladium acetate with 4-Methoxy-N-{(E)-(piperidin-1-yl)phenyl) methylidene}aniline (L) gave the cyclometallated acetate bridged complex (1) with open book-shape structure. Metathetical reaction of (1) with NaCl, NaBr and NaI gave the corresponding halidobridged complexes (2), (3) and (4), respectively. Monomerization of complex (3) with pyridine gave compound (5). The ligand and complexes have been characterized by IR, ^{1}H NMR, U.V-Vis and Mass Spectroscopy as well as by magnetic susceptibility measurements. Antimicrobial screening of the ligand and complexes showed that the acetate bridged complex (1) has higher activity than other compounds.

Keywords: Cyclopalladation, Complexes, Synthesis and Biolgical activity.

Since the first cyclometallated complex was synthesized, the cyclometallation process has become an important part of organometallic chemistry[(1-3)], especially for the preparation of complexes derived from Schiff bases which are known to undergo facile cyclometallation as nitrogen donors. These cyclometallated complexes are formed when an organic ligand is linked to the metal ion center through M-C bond and an additional bonding of the metal ion via an appropriate donor atom to complete the stability more often than five membered metallated rings. Also, the cyclometallation reactions were one of the first known examples of C-H bond activation and cyclometallated complexes of a wide variety of ligands containing N, O,P or S as a hetero-atom have been described [(1-3)] .

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The chemistry of cyclometallated compounds is thoroughly reviewed and have been published related to their synthesis, reactivity and fruited applications [4-6]. The cyclometalled complexes have numerous applications in organic and inorganic synthesis, insertions[7], in optical resolution[8] in determination of the enantiomeric excess[9], in the synthesis of new metal misogynic compounds[10], biologically active compounds[11-12], in catalytic materials[13] and in the building of new self assembly super molecular species [14] . The present study deals with the synthesis, spectral characterization and viewing the biological importance of a new series of cyclometallated complexes derived from Schiff base ligand (L) and evaluation of the antimicrobial potential of the ligand and its complexes.

Experimental

Materials and reagents

The analytical reagent grade NaCl, NaI , NaBr, pyridine , p-anizidine (Merk) and palladium acetate (Aldrich) were used. Organic solvents used (methanol, methylene chloride, ethanol, n-hexane, diethyl ether, chloroform, petroleum ether and acetone) were HPLC or extra pure grades and were used without further purification.

Instruments

Percentages of C, H and N were determined in the Mircoanalytical Laboratory, Cairo University, Giza. IR spectra were recorded using KBr pellets on a Perkin-Elmer 1430 Spectrometer in for the region (4000 – 200 cm^{-1}) at the Faculty of Science, Tanta University. Electronic spectra were measured in UV-Vis range (195- 1100 nm) using a Perkin -Elmer lambda 35 UV/Vis Spectrometer at the Faculty of Science, Al-Azhar University. The NMR spectra were record on DEITAZ NMR 500 MHZ Spectrometer at the National Research Centre, Dokki, Giza. The mass spectra were recorded on GC- MSA- QP 5050A Shimadzu at Cairo University, Giza. Magnetic susceptibility measurements were carried out at room temperature on a Sherwood Scientific Magnetic Balance at El-Mansoura University, Egypt. Antimicrobial activity experiments were carried out at Fermentation Biotechnology and Applied Microbiology Centre, Al-Azhar University, Cairo, Egypt.

Synthesis of the Schiff base ligand (L)

4-Methoxy -N- {(E) - (piperidin-1-yl) phenyl) methylidene} aniline (L**)** was prepared according to an established procedure [15] .

Synthesis of complex (1)

Mixed solutions of palladium acetate (0.45 g, 2mmol) and ligand (L) (0.588 g, 2mmol) in methylene chloride (20 ml) were stirred for 2hr at 30^{o}C, then filtered and the filtrate was concentrated to 10 ml. Addition of n-hexane (2 ml) to the filtrate induced precipitation of the brownish yellow complex (1) which was filtered, washed with diethyl ether, air-dried and recrystallized from chloroform-n-hexane.

Synthesis of complexes (2), (3) and (4)

Methanolic solution of NaX (X= Cl, Br or I) was added dropwise to a solution of the acetate bridged complex in methylene chloride. The products were immediately precipitated out. After stirring for 1hr, the formed chloro-bridged complex (2), bromo-bridged complex (3) and iodo-bridged complex (4) as yellow, brown or dark brown solids, respectively were filtered off, then washed several times with methanol and water to remove the unreacted NaX.

Synthesis of complex (5)

To a suspension of the cyclopalladate bromo-bridged complex (3) in 15ml chloroform, five drops of pyridine were added. The mixture was stirred for 8hr, and then petroleum ether was added to precipitate complex (5) as dark yellow solid. This was filtered off , washed with n-hexane and recrystallized from chloroform.

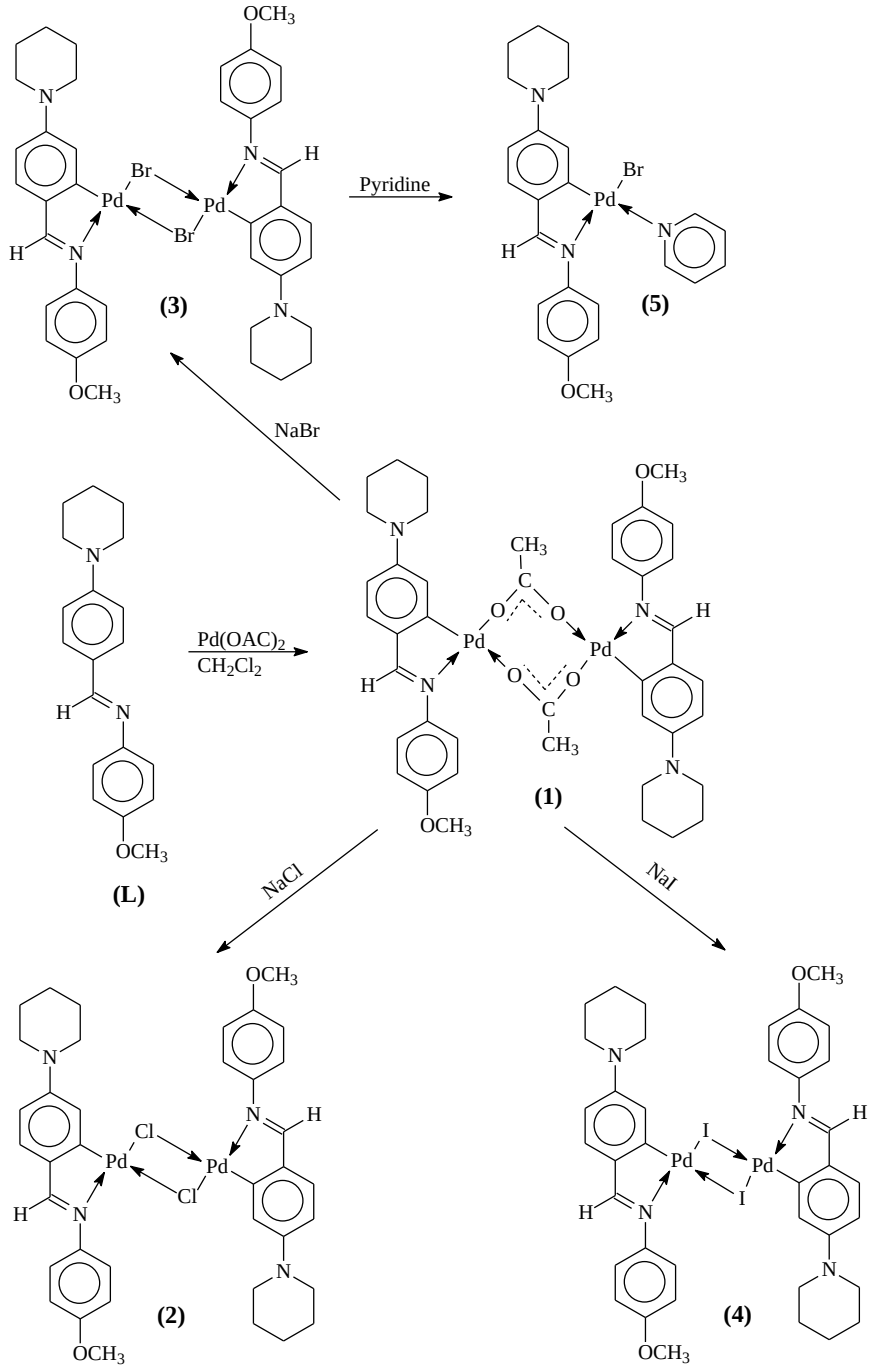
Growth of test organisms for antimicrobial studies

Bacterial cultures of Gram positive *Bacillus subtilis*, *Staphylococcus aureus* and Gram negative *Escherichia coli*, *Pseudomonas aeurginosa*, and fungal cultures of *Aspergillus niger*, and *C. albicans*, were obtained from the culture collection of Fermentation Biotechnology and Applied Microbiology Centre, Al-Azhar University ,Cairo,Egypt, and used for antimicrobial evaluation. The bacteria were maintained on nutrient broth (NB) at 37°C and fungi were maintained on potato dextrose agar (PDA) at 28°C.

Results and Discussion

Reaction of equimolar amounts of $Pd(OAc)_2$ and the Schiff base (L) in CH_2Cl_2 resulted in the formation of the acetate bridged cyclopalladate complex (1) (Scheme 1).

The complex molecule may be described as a dimer with the *anti*-conformation which the cyclometallated fragment is present in the characteristic open-book disposition, linked by two acetate bridging molecules. Each palladium atom is bonded to the Schiff base ligand through a phenyl carbon atom and the imine nitrogen atom and two oxygen atoms from the acetate bridging molecules. The metathetical reaction of (1) with NaCl, NaBr and NaI in methanol led to the formation of the halide bridged complexes (2), (3) and (4), respectively. On the other hand, the reaction of the bromide bridged complex (3) with pyridine in chloroform led to cleavage of the Pd_2Br_2 ring to give the mononuclear cyclopalladate complex (5) with a terminal Pd-Br bond.



Scheme 1. Cyclopalladation reactions of ligand L .

Characterization of the Schiff base ligand

The Schiff base is prepared [15] and subjected to elemental analyses and IR, ^{1}H NMR and mass spectral analyses. The results of elemental analyses are presented in Table 1.

Characterization of the complexes

The prepared solid complexes were subjected to elemental analyses (C, H, N and metal content), and spectral (IR,1HNMR electronic spectra and magnetic susceptibility) studies.

Elemental analyses of the complexes

The results of elemental analyses are in good agreement with those required for the proposed structure given in Table 1.

TABLE 1. Elemental analyses, colors and melting points of ligand (L) and its complexes .

Compound No	M.P(°C)	Color	Molecular formula	Elemental analysis (calcd. / found).			
				% C	%H	%N	%Pd
L	160-162	Pale yellow	$C_{19}H_{22}N_2O$ (294.39)	77.52	7.53	9.52	-
				77.53	7.45	9.50	-
1	195-197	Brownish yellow	$C_{42}H_{48}N_4O_6Pd_2$ (917.69)	54.97	5.27	6.11	23.19
				54.95	5.40	6.30	22.99
2	282-284	Yellow	$C_{38}H_{42}N_4O_2Pd_2Cl_2$ (870.47)	52.43	4.86	6.44	24.45
				52.40	4.80	6.40	24.45
3	215-217	Brown	$C_{38}H_{42}N_4O_2Pd_2Br_2$ (959.41)	47.57	4.41	5.84	22.18
				47.51	4.35	5.80	22.20
4	203-205	Dark Brown	$C_{38}H_{42}N_4O_2Pd_2I_2$ (1053.41)	43.33	4.02	5.32	20.20
				43.40	3.95	5.10	19.35
5	220-222	Dark yellow	$C_{24}H_{26}N_3OPd\ Br$ (558.81)	51.58	4.69	7.52	19.04
				51.55	4.65	7.50	19.00

Infrared spectra

All of the complexes display weak multiple bands in the ranges 3000-2980

and 2870-2840cm^{-1} due to aromatic and aliphatic stretches, respectively. All the orthopalladate species display strong band in the range 1585-1565cm^{-1}. This band is due to the azomethine bond (-C=N) of the Schiff base. The shift of the C = N stretch to lower wave number as compared to that (1600 cm^{-1}) of the free Schiff base is expected due to the N-coordination of the azomethine nitrogen in all complexes[16].

The infrared spectrum of complex (1) exhibits the typical asymmetric and symmetric stretching modes of the acetate groups with strong absorptions at 1545 cm^{-1} and 1420cm^{-1}. The $\Delta\nu$ of acetate group indicates the presence of a bridging mode.

The infrared spectrum of complex (2) shows two asymmetric Pd-Cl stretching absorptions at 330 and 315cm^{-1} which give good evidence for the presence of bridging chloride. The ν Pd-Br (bridging) shows stretching absorptions at 315 and 295 cm^{-1} and the ν Pd-I (bridging) shows absorptions at 309 and 270 cm^{-1}, in complexes (3) and (4), respectively.

The far infrared region in all complexes shows a medium intensity band in the range 440-400 cm^{-1} which is not observed in the spectrum of the free Schiff base. This band is attributed to $\nu_{Pd\text{-}N}$ [17].

All of the orthopalladate species show strong bands in the range (770-750 cm^{-1}) which are characteristic of the out-of-plane (C-H) bond of the ortho substituted aromatic ring[18],which give good evidence for the electrophonic substitution of the ortho hydrogen by Pd, which is also confirmed by the appearance of a weak band in the range 590-580cm^{-1} due to $\nu_{Pd\text{-}C}$ [19].

^{1}H NMR spectra

The ^{1}H NMR spectra of the ligand (L) and complexes (1) and (3) were recorded in DMSO-d_6. The spectra were assigned on the basis of chemical shifts and spin-spin coupling information and were confirmed by selective hydrogen decoupling.

The ^{1}H NMR spectrum of the ligand (L) shows a singlet at δ=8.4 ppm attributed to resonance of the azomethine proton. A singlet is also observed at δ =3.7 ppm for the methoxy group protons. The spectrum shows two AA^{-}BB^{-} system at 6.9-7.2 ppm for the p-anisidine ring and another at δ=7.0-7.6 ppm for the other 1,4-disubstituted benzene ring. Also, the piperidine ring protons appeared as a multiplet (10H) centered at δ=2.9 ppm.

The ^{1}H NMR spectrum of complex (1) showed the presence of a broadened unresolved pattern in the aromatic region which can explain the folded open-book shape structure of the complex. The folded structure of the acetate bridged complexes caused signals of the aromatic protons to be broadened, probably due to the anisotropic effect of the ring currents.

There are two possible structures for the arrangement of the ligands in the acetates, ab,-hg type in which the methyl hydrogens are magnetically equivalent (A) and non equivalent methyl hydrogens in an ab-gh type (B), (Fig. 1).

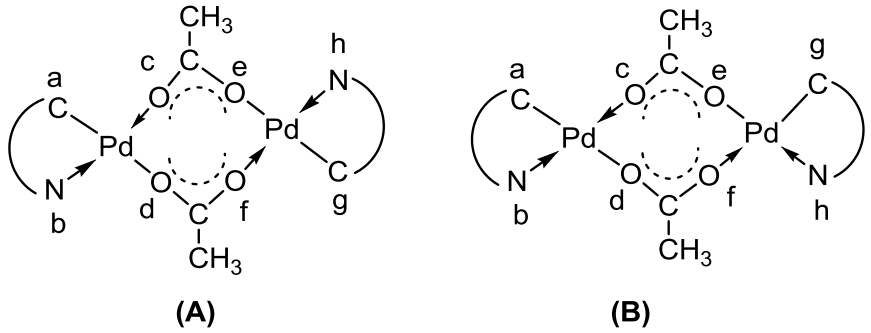


Fig. 1. Geometrical structures for isomers of complex (1) .

In case of ab-hg type, the magnetically equivalent methyl hydrogens appear as sharp singlet in the range 1.8-2.2 ppm, but in case of ab-gh type, the non-equivalent methyl hydrogens appear as two resonances at δ=2.12-2.29 ppm[20].

Thus, the ^{1}H NMR spectrum of (1) shows trans arrangement of the ligand in the acetates, inferred from the acetate bridging methyl hydrogens appearing as a singlet at δ=1.8 ppm which is ascribable to the ab-hg structural isomer.

On the other hand, the ^{1}H NMR spectrum of complex (3) shows the absence of signals in the region δ=1.8-2.23 ppm, indicating the absence of the acetate group (which was removed completely by metathetical reaction of the acetate groups with the bromide anions). The aromatic region of the complex (3) shows sharp resolved pattern which indicates the unfolded planar structure of this complex.

Ortho metallation is supported by comparing the ^{1}H NMR spectra of the free ligand and its palladium complexes. The ^{1}H NMR spectrum of the ligand shows the AA^-BB^- system. On the other hand, the ^{1}H NMR spectra of complexes (1) and (3) show a change in AA^-BB^- system which was represented by a set of three different signals (XYZ), indicating the electrophonic substitution of the ortho proton by Pd^{+2} .

The ^{1}H NMR spectra of the cyclopalladate species show that the CH=N hydrogen appear as a singlet, but shifted upfield as compared to that of (L). The upfield shift of the azomethine hydrogen is consistent with the weak link of the C=N bond due to the N-coordination and the trans disposition of the Pd and hydrogens around C=N[21].

Electronic spectra and magnetic measurements

The electronic spectra of all orthopalladate complexes show three d-d spin allowed transitions corresponding to the transitions from the three lower lying "d" level to the empty $d_{x^2-y^2}$ orbital. The ground state is $^1A_{1g}$ and exited states corresponding to the above transitions are $^1A_{2g}$, $^1B_{1g}$ and ^1E_g in order of increasing energy. Three d-d bands are observed in the regions 365nm, 379nm and 425nm. These bands are due to $^1A_{1g} \rightarrow {}^1A_{2g}$, $^1A_{1g} \rightarrow {}^1B_{1g}$ and $^1A_{1g} \rightarrow {}^1E_g$, respectively. All of the cyclopalladate complexes show diamagnetic behavior. The magnetic measurements and the electronic spectral data indicate the square planar geometrical structure of all of the cyclopalladate complexes[22].

Evaluation of antimicrobial potential of the Schiff base ligand (L) and its complexes

It has been shown[23] that some substances that exhibit broad biological activities, contain thiazole /azomethine, thiazole /carbazone, azomethine / hydroxylamine, and azomethine/ indolinylidene hydrazine groups. Since the new compounds of the present study have similar functional groups comparable to those mentioned above, they are expected to exhibit biological activities.

Anti-bacterial activity

Antimicrobial activity of the Schiff base (L) and its cyclopalladate complexes were tested by the disc diffusion method[24]. About (100 µml) of the sample was loaded onto the filter paper disc. The tested bacteria were seeded into the respective medium by spread plate method with the 24hr cultures of bacterial growth in nutrient broth. After solidification, the filter paper discs (5 mm in diameter) impregnated with the extracts were placed on test organism-seeded plates. *B. subtilis, E. coli, P. aeurginosa,* and *S. aureus* were used for the antibacterial evaluation . The antibacterial assay plates were incubated at 37°C for 24hr. The diameters of the inhibition zones were measured in mm.

Antifungal activity

The antifungal activity was evaluated by the disc diffusion method[25]. The potato dextrose agar plates were inoculated with each fungal culture (10 days old) by point inoculation. The filter paper discs (5 mm in diameter) impregnated with 100 µml of the sample were placed on test organism-seeded plates. The activity was determined after 72 hr of incubation at 28°C. The diameters of the inhibition zones were measured in mm.

Results of the antimicrobial activity

The antibacterial and antifungal activities of the Schiff base ligand (L) and its cyclopalladate complexes were determined against six different bacteria and fungi, which are mentioned in Table 2 and Fig. 2. In the present study, it has been suggested that the Schiff base ligand is unable to inhibit the enzyme production needed for the organism, since enzymes which require a specific group for their activity appear to be especially unsusceptible for deactivation. On the other hand, the cyclopalladate complexes might have inhibited the

enzyme production, that, their activity appears to be especially susceptible to deactivation by ions of the complexes. So, complexes (1), (3) and (4) showed antibacterial activities against *B. subtilis*, *P. aeurginosa*, and *S. aureus.* Also, complexes (1) and (4) showed activity against *E. coli* and *C. albicans* as antibacterial and antifungal, respectively. On the other hand, only complex (2) showed antifungal activity against *A. niger*. Thus, these complexes have been effectively proven for their utilization as a source for antimicrobial agents.

TABLE 2. Antimicrobial activity of the Schiff base ligand(L) and its cyclopalladate complexes .

	Antimicrobial Activity (mm)					
	G+ve Bacteria		**G-ve Bacteria**		**Fungi**	
	B. subtilis	***S. aeures***	***E. coli***	***P. aeurginosa***	***C. albicans***	***A.niger***
L	—	—	—	—	—	—
1	21	22	13	20.5	15	18
2	—	—	—	—	—	20
3	15	12	—	12	—	26
4	13.5	17	16.5	12	13	—

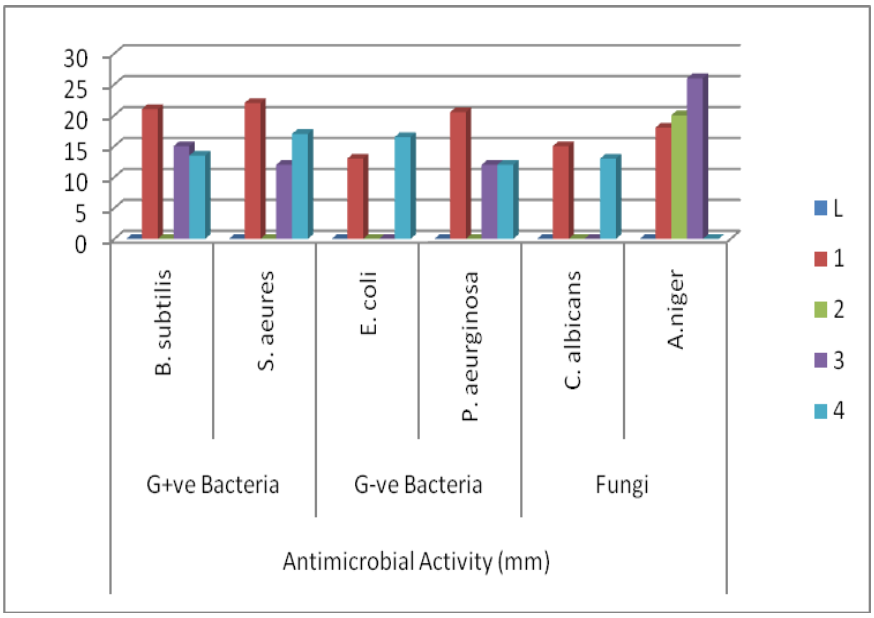


Fig.2. Anti microbial G+Ve bacteria(*B.subtillis* and *S.aeures*),G-Ve Bacteria (*E,Coli* and *P.aeurginosa*) and Antifungi (*C.Albicans* and *A.Niger*) of ligand (L) and its complexes.

Conclusion

A new series of organopalladium complexes have been synthesized by cyclopalladation of the novel Schiff base (L). All the complexes are dimers except complex (5) which is obtained by monomerization of dimeric complex (3).The Schiff base (L) was unable to inhibit the enzyme production needed for the organism. On the other hand, its cyclopalladate complexes have inhibited the enzyme production, especially complex (1) which shows the highest biological activity.

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التخليق والتوصيف الطيفى والتقييم البيولوجى لمتراكبات البالاديوم الحلقيه لمركب ٤ – ميثوكسى ن – ببريدينيل فنيل مثيلين أنيلين

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التفاعل بين خلات البلاديوم مع (٤-ميثوكسى –بيبريدين-١-يل-فينيل ميثيليدين انيلين) اعطى المتراكب ذو القنطرة الخلية (١) على شكل كتاب مفتوح . بتفاعل المتراكب (١) مع كلوريد الصوديوم وبروميد الصوديوم ويوديد الصوديوم نتجت المتراكبات (٢) و(٣) و(٤) على الترتيب ذوى القنطرة الهالوجينية .تم تحويا المتراكب (٣) وهو دايمر الى مونومر بالتفاعل مع البريدين لينتج المتراكب (٥). تم التوصل الى تراكيب المرتبط والمتراكبات باستخدام الاشعة تحت الحمراء واشعة الرنين النووى المغناطيسى والاشعة فوق البنفسجية واشعة مطياف الكتلة بالاضافة الى قياسات القابلية المغناطيسية . باختبار المرتبط والمتراكبات كمضادات للميكروبات وجد ان المتراكب (١) ذو القنطرة الخلية هو اعلى نشاطا بين المركبات كمضاد للميكروبات .