

SYNTHESIS OF SUBSTITUTED PIPERDIN-4-ONES WITH DICHLORO (CYCLOOCTADIENE) PALLADIUM(II) AND ANTIMICROBIAL ACTIVITY

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ABSTRACT

Objective: The aim of this study is to report the synthesis and evaluate the biological screening for antimicrobial activity on substituted piperdin-4-ones and their complex by precursor Pd(COD)Cl₂. The complexes were synthesized using substituted piperdin-4-ones (ligands) and Pd(COD)Cl₂ (precursor) in dichloromethane(solvent)

Methods: The zone of inhibition by disc diffusion method and minimum inhibitory concentration by Muller Hinton Broth and Sabouraud's Dextrose Broth were assayed and screened by *in vitro* antimicrobial activities like *Escherichia coli*, *Staphylococcus aureus* and *Candida albicans* and *Aspergillus niger* using Ciprofloxacin and Clotrimazole as reference.

Results: In the zone of Inhibition, the ligands L₁ and L₂ against *Escherichia coli*, L₂ and L₅ in *Staphylococcus aureus* and L₂ against *Candida albicans* and *Aspergillus niger* are highly active. The activity of antibacterial is highly active in C₁ complex but in antifungal organisms the complexes C₁ and C₂ are less active and the complexes C₃ to C₉ resulted an improve activity. The ligands L₄, L₅, and L₈ exhibit similar minimum inhibitory concentration value (31.25 µgml⁻¹) in *Staphylococcus aureus*. In antifungal studies, the ligands L₂, L₆ and L₉ against *Candida albicans* and L₁, L₆ and L₉ against *Aspergillus niger* shows with a decrease in minimum inhibitory concentration Conclusion: Our results showed that C₂, C₅ and C₇ complexes against *Escherichia coli* and C₁, C₅ and C₇ complexes against *Staphylococcus aureus* has superior activity in the zone of inhibition. The minimum inhibitory concentration for C₁ and C₂, C₄ and C₅, C₆, C₇ and C₉ complexes against *Candida albicans* has identical values. The compound (C₇ and C₈) against *Staphylococcus aureus* and (L₂ and C₇) against *Aspergillus niger* shows the maximum inhibitory concentration at 500 µgml⁻¹.

Keywords: Piperdin-4-ones; *Escherichia coli*; *Staphylococcus aureus*; *Candida albicans*; *Aspergillus niger*.

INTRODUCTION

Heterocyclic compounds carrying piperidine skeleton are attractive of organic synthesis to their fertile field by exploring the area of research in chemical biology owing in pharmaceutical development, agrochemicals and wide occurrence in nature[1-4]. The studies of piperidin-4-one by substituting in 2, 3, 5 and 6 positions were carried out for biological activity [5-10]. 4-piperidones have been known to possess a large number of biological activities such as local anesthetic, analgesic, anti-inflammatory, central nervous system (CNS), anticancer and antimicrobial activity[2,11]. A series of 4-piperidones derivatives are synthesized by Mannich condensation[12] of substituted aromatic aldehydes, dialkylketone and ammonium acetate with palladium metal would result in compounds with potent biological activity [5-10, 12]. The aim of this study is to report the synthesis and biological screening for antimicrobial activity on pathogens of substituted piperdin-4-ones and their complex by anchoring with Pd(COD)Cl₂.

MATERIALS AND METHODS

General

The reagent grade chemicals and reagents were purchased from AR grade and purified by either distillation or recrystallisation before use. The purity of the synthesized compounds was checked by thin layer chromatography (TLC) with silica gel plates. Melting points of the synthesized compounds were taken in open glass capillaries using a Barnstead 9001 electro thermal melting point apparatus and are uncorrected. Infrared (IR) spectra (ν, cm⁻¹) were recorded on a Shimadzu FT/IR-330E, Fourier Transform Infrared Spectrometer using KBr discs. Nuclear Magnetic spectroscopic (NMR) measurements ¹H-NMR and [¹³C] NMR spectra were noted by Jeol GSX 400NB NMR spectrometer operating at 500.13 MHz and 125.76 MHz with DMSO-d₆ as solvent and tetramethylsilane (TMS) as an internal standard. Electron impact mass spectra (EI-MS) were measured on a Jeol GC mate instrument at 70 eV. Elemental analyses (C, H, N) in Elementar Vario EL 111-Germany in full agreement with the proposed structures.

Synthesis of ligands

The general procedure for the preparation of substituted piperdin-4-ones is reported by Noller and Baliah [11]. The ligands (L₁-L₉) were

prepared by refluxing a mixture of substituted aldehydes, dry ammonium acetate and dialkylketones (2:1:1) in the presence of ethanol (30ml). This reaction mixture was allowed to stand overnight at room temperature followed by adding concentrated hydrochloric acid (30ml). Then the precipitated hydrochloride was collected and washed with ethanol and ether mixture (1:5) and it was transferred to one litre beaker. The hydrochloride was suspended in acetone and basified with a strong ammonia solution. On dilution with excess of water the free base was separated out. The product was filtered, washed with water and dried. Crystallization of the product from ethanol results in substituting piperidin-4-ones. (See Figure 1)

Preparation of metal ion complexes

The dichloro(cyclooctadiene)palladium (II) is used as a precursor. The dichloro(cyclo octadiene)palladium (II) with 2, 6-diaryl piperidin-4-ones ligands (L₁-L₉) were prepared by the following procedure: A mixture of dichloro(cyclooctadiene)palladium(II) (0.5m mol) and substituted piperidin-4-ones (L₁-L₉) (0.5m mol in dichloromethane (50 ml) was refluxed for 5 hours. The solvent was then distilled off under reduced pressure. The residue was repeatedly washed with hot ethanol, acetone and ether remove the unreacted piperidin-4-one and then dried through in *vacuo* phosphorus (V) oxide.

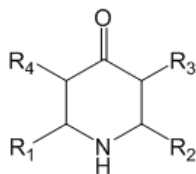
Microbial strains

The antibacterial and antifungal tests were assayed according to the disc diffusion method. The strains *Escherichia coli*, *Staphylococcus aureus*, *Candida albicans* and *Aspergillus niger* were used for the experiments and the inoculums were prepared in Nutrient agar media. The inoculums were standardized by adjusting the turbidity of the culture according to McFarland standards. The turbidity of the culture can be adjusted by the addition of sterile saline or broth (if excessive) or further incubation to reach the required level [13-15].

The standardized inoculum was prepared in the petriplates. Then the sterilized agar medium and the suspension of microbial cultures were poured into the petriplates under aseptic condition. The synthesized ligands and complexes were placed in the refrigerator at 4°C for one hour for diffusion on the surface of the culture and

followed by incubation at 37°C for 24 hours. Observe the zone of inhibition produced by different antibiotics using Ciprofloxacin

(10µg) and Clotrimazole (10µg) as standard molecules. The identity of all strains was confirmed.



Ligand	Ligand Name	R ₁	R ₂	R ₃	R ₄
L ₁	3-methyl-2,6-diphenylpiperidin-4-one	C ₆ H ₅	C ₆ H ₅	CH ₃	H
L ₂	3,5-dimethyl-2,6-diphenylpiperidin-4-one	C ₆ H ₅	C ₆ H ₅	CH ₃	CH ₃
L ₃	3-ethyl-2,6-diphenylpiperidin-4-one	C ₆ H ₅	C ₆ H ₅	C ₂ H ₅	H
L ₄	3-methyl-2,6-ditolylpiperidin-4-one	C ₆ H ₄ CH ₃	C ₆ H ₄ CH ₃	CH ₃	H
L ₅	3,5-dimethyl-2,6-ditolylpiperidin-4-one	C ₆ H ₄ CH ₃	C ₆ H ₄ CH ₃	CH ₃	CH ₃
L ₆	3-ethyl-2,6-ditolylpiperidin-4-one	C ₆ H ₄ CH ₃	C ₆ H ₄ CH ₃	C ₂ H ₅	H
L ₇	3-methyl-2,6-dianisylpiperidin-4-one	C ₆ H ₄ OCH ₃	C ₆ H ₄ OCH ₃	CH ₃	H
L ₈	3,5-dimethyl-2,6-dianisylpiperidin-4-one	C ₆ H ₄ OCH ₃	C ₆ H ₄ OCH ₃	CH ₃	CH ₃
L ₉	3-ethyl-2,6-dianisylpiperidin-4-one	C ₆ H ₄ OCH ₃	C ₆ H ₄ OCH ₃	C ₂ H ₅	H

Fig. 1: Synthesized Ligands

Determination of minimum inhibitory concentration (MIC'S)

The MIC was recorded by the experiments with antimicrobial agent prepared in 1ml of Muller Hinton Broth and Sabouraud's Dextrose Broth. A series of 10-15 dilutions of different concentrations are prepared. Overnight culture is grown at 37°C Kirby- Bauer procedure and diluted to the corresponding Broth. The sterile tubes were labeled to control. All the tubes were incubated at 37°C for 18-24hrs. After incubation the turbidity was observed or optical density (OD) value by spectrophotometric method at 600nm.

RESULTS

The general schematic representation describing the routes of synthesis was furnished (see Figure 2). By the condensation of substituted aldehyde, ammonium acetate and dialkyl ketones in the

ratio of 2:1:1 for obtaining substituted 2, 6-diarylpiperidin-4-ones. All the synthesized substituted 2, 6-diarylpiperidin-4-ones are soluble in solvents such as ethanol, methanol, dimethylsulphoxide, dichloromethane and ether but insoluble in water. The structure of the synthesized substituted 2, 6-diarylpiperidin-4-ones is established on the basis of IR and NMR (¹H and [¹³C]) data obtained as given in Table 1 and 2.

Spectra for ligands and complexes

The infrared spectra for ligands (L₁-L₉), shows an absorption band lies around 1700 cm⁻¹ and 3300 cm⁻¹ for C=O groups and NH groups. In Palladium complexes (C₁-C₉), it is shifted corresponding of the ligands (Table 1). The ¹H-NMR shows a singlet at δ2.5 ppm to NH protons and [¹³C] NMR shows a peak δ204 ppm for C=O group in C₄ carbon by shifting the position on complexation with precursor (Table 2).

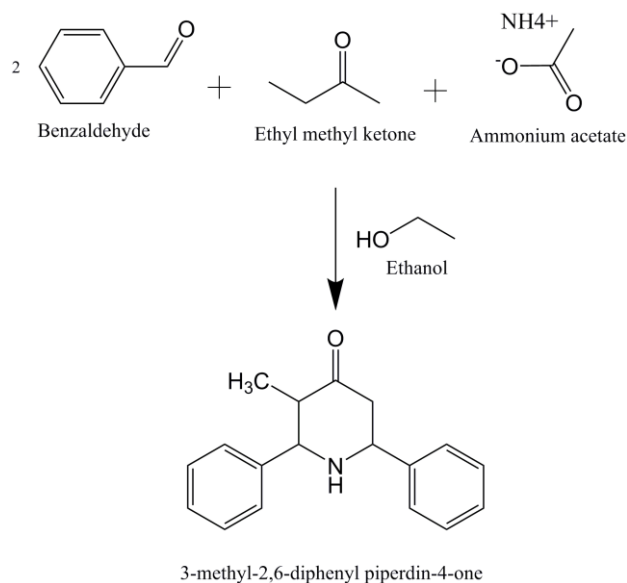


Fig. 2: Synthesis of 3-methyl-2,6-diphenylpiperidin-4-one

Table 1: IR spectral data for ligands and complexes

Complex	IR							
	$\nu(\text{C}=\text{O})^a$	$\nu(\text{C}=\text{O})^b$	$\nu(\text{N}-\text{H})$	$\nu(\text{O}-\text{H})$	$\nu(\text{HOH})$	$\nu(\text{Ar}-\text{H})$	$\nu(\text{M}-\text{N})$	$\nu(\text{M}-\text{O})$
C ₁	1710	1716	2928	3200-3700	1633	802	698	435
C ₂	1712	1716	2924	3200-3700	1624	868	551	513
C ₃	1713	1716	2924	3200-3700	1625	867	547	460
C ₄	1697	1716	2928	3200-3700	1631	810	516	451
C ₅	1712	1716	3207	3200-3700	1620	817	516	455
C ₆	1720	1722	2926	3200-3700	1618	812	514	422
C ₇	1705	1716	2928	3200-3700	1621	829	536	424
C ₈	1701	1718	3209	3200-3700	1612	804	540	401
C ₉	1707	1714	3089	3200-3700	1612	831	538	418

$\nu(\text{C}=\text{O})^a$ -for ligands; $\nu(\text{C}=\text{O})^b$ - for complexes

For each complex (C₁-C₉) IR spectral data are reported.

Table 2: ¹H and [¹³C] NMR spectral data for complexes

NMR	Complex								
	C1	C2	C3	C4	C5	C6	C7	C8	C9
H(2)(s,1H)	3.327	3.332	3.344	3.344	3.322	3.502	3.359	3.363	3.336
H(3) and H(5)(m,3H)	2.148	2.508	2.509	3.790	3.402	2.740	3.781	3.608	3.796
H(6) (s,1H)	3.584	3.514	4.728	4.145	4.412	3.344	5.511	5.489	5.502
C(3)-R(d,3H)	0.668	0.664	0.717	0.770	0.629	0.731	0.642	0.624	0.720
NH(s,1H)	2.501	2.306	2.509	2.506	2.502	2.505	2.505	2.504	2.504
Aromatic protons	7.735	7.394	7.426	6.437	7.268	7.426	7.125	6.910	7.452
-	7.865	7.540	7.516	7.611	9.994	10.544	7.750	7.375	10.790
C(2)	70.417	70.281	68.172	60.321	70.185	63.416	67.553	67.849	61.953
C(3)	64.126	64.561	64.068	53.901	64.649	59.560	60.508	55.460	55.563
C(4)	204.320	209.018	206.940	208.270	209.159	203.821	209.673	211.590	210.123
C(5)	56.140	48.328	59.432	49.449	48.932	45.266	55.769	51.421	51.466
C(6)	46.266	40.264	40.187	40.190	40.280	40.265	40.184	40.196	40.276
C(3)-R	11.180	11.167	11.134	10.806	11.180	11.114	11.837	11.119	12.076
Aromatic carbons	127.430 - 128.880	128.878 - 138.322	128.722 - 139.218	106.065 - 155.696	127.248 - 139.151	128.828 - 135.722	110.052 - 128.877	129.151 - 135.080	128.256 - 130.032

For each complex (C₁-C₉) ¹H and [¹³C] NMR spectral data are reported.

Antimicrobial evaluation

Table 3 and 4 shows the *in vitro* antimicrobial activities of zone of inhibition and MIC for substituted 2,6-diarylpiperidin-4-ones, ligands L₁-L₉ and their complexes C₁-C₉ using ciprofloxacin (10 μg) and clotrimazole (10 μg) as reference drugs on a panel of strains *Escherichia coli*, *Staphylococcus aureus*, *Candida albicans* and *Aspergillus*

niger. The precursor dichloro(cyclooctadiene)palladium(II) shows high efficiency against all organisms.

For each ligand and complex the R-group substitution, zone of inhibition and minimum inhibitory concentration obtained for *Escherichia coli* (*E.coli*) and *Staphylococcus aureus* (*S.aureus*) are reported with the standard molecules ciprofloxacin.

Table 3: Antibacterial activity

Ligands	R1	R2	R3	R4	Zone of inhibition (mm)		Minimum inhibitory concentration (μg/ml-1)	
					<i>E.coli</i>	<i>S.aureus</i>	<i>E.coli</i>	<i>S.aureus</i>
L ₁	C ₆ H ₅	C ₆ H ₅	CH ₃	H	13	10	62.5	125
L ₂	C ₆ H ₅	C ₆ H ₅	CH ₃	CH ₃	13	11	31.25	7.125
L ₃	C ₆ H ₅	C ₆ H ₅	C ₂ H ₅	H	0	8	125	125
L ₄	C ₆ H ₄ CH ₃	C ₆ H ₄ CH ₃	CH ₃	H	7	9	125	31.25
L ₅	C ₆ H ₄ CH ₃	C ₆ H ₄ CH ₃	CH ₃	CH ₃	7	11	15.625	31.25
L ₆	C ₆ H ₄ CH ₃	C ₆ H ₄ CH ₃	C ₂ H ₅	H	9	10	7.812	62.5
L ₇	C ₆ H ₄ OCH ₃	C ₆ H ₄ OCH ₃	CH ₃	H	7	9	125	15.625
L ₈	C ₆ H ₄ OCH ₃	C ₆ H ₄ OCH ₃	CH ₃	CH ₃	7	10	31.25	31.25
L ₉	C ₆ H ₄ OCH ₃	C ₆ H ₄ OCH ₃	C ₂ H ₅	H	0	7	125	15.625
C ₁	C ₆ H ₅	C ₆ H ₅	CH ₃	H	24	25	62.5	62.5
C ₂	C ₆ H ₅	C ₆ H ₅	CH ₃	CH ₃	11	9	15.625	125
C ₃	C ₆ H ₅	C ₆ H ₅	C ₂ H ₅	H	11	8	125	125
C ₄	C ₆ H ₄ CH ₃	C ₆ H ₄ CH ₃	CH ₃	H	14	9	62.5	62.5
C ₅	C ₆ H ₄ CH ₃	C ₆ H ₄ CH ₃	CH ₃	CH ₃	14	11	31.25	7.812
C ₆	C ₆ H ₄ CH ₃	C ₆ H ₄ CH ₃	C ₂ H ₅	H	12	13	125	125
C ₇	C ₆ H ₄ OCH ₃	C ₆ H ₄ OCH ₃	CH ₃	H	12	10	31.25	500
C ₈	C ₆ H ₄ OCH ₃	C ₆ H ₄ OCH ₃	CH ₃	CH ₃	13	9	250	500
C ₉	C ₆ H ₄ OCH ₃	C ₆ H ₄ OCH ₃	C ₂ H ₅	H	12	11	15.625	15.625
P	Pd(COD)Cl ₂				20	18	250	250
Standard	Ciprofloxacin				29	31		

Table 4: Antifungal activity

Ligands	R1	R2	R3	R4	Zone of inhibition (mm)		Minimum inhibitory concentration (μgml^{-1})	
					<i>C.albicans</i>	<i>A.niger</i>	<i>C.albicans</i>	<i>A.niger</i>
L ₁	C ₆ H ₅	C ₆ H ₅	CH ₃	H	7	12	125	62.5
L ₂	C ₆ H ₅	C ₆ H ₅	CH ₃	CH ₃	21	16	15.625	500
L ₃	C ₆ H ₅	C ₆ H ₅	C ₂ H ₅	H	0	0	125	125
L ₄	C ₆ H ₄ CH ₃	C ₆ H ₄ CH ₃	CH ₃	H	8	0	15.625	15.625
L ₅	C ₆ H ₄ CH ₃	C ₆ H ₄ CH ₃	CH ₃	CH ₃	0	0	31.25	15.625
L ₆	C ₆ H ₄ CH ₃	C ₆ H ₄ CH ₃	C ₂ H ₅	H	13	0	7.812	7.812
L ₇	C ₆ H ₄ OCH ₃	C ₆ H ₄ OCH ₃	CH ₃	H	0	0	31.25	62.5
L ₈	C ₆ H ₄ OCH ₃	C ₆ H ₄ OCH ₃	CH ₃	CH ₃	0	0	31.25	31.25
L ₉	C ₆ H ₄ OCH ₃	C ₆ H ₄ OCH ₃	C ₂ H ₅	H	8	0	7.812	7.812
C ₁	C ₆ H ₅	C ₆ H ₅	CH ₃	H	9	18	31.25	31.25
C ₂	C ₆ H ₅	C ₆ H ₅	CH ₃	CH ₃	11	9	31.25	62.5
C ₃	C ₆ H ₅	C ₆ H ₅	C ₂ H ₅	H	21	16	62.5	125
C ₄	C ₆ H ₄ CH ₃	C ₆ H ₄ CH ₃	CH ₃	H	25	18	7.812	62.5
C ₅	C ₆ H ₄ CH ₃	C ₆ H ₄ CH ₃	CH ₃	CH ₃	26	18	7.812	7.812
C ₆	C ₆ H ₄ CH ₃	C ₆ H ₄ CH ₃	C ₂ H ₅	H	23	19	31.25	31.25
C ₇	C ₆ H ₄ OCH ₃	C ₆ H ₄ OCH ₃	CH ₃	H	23	18	31.25	500
C ₈	C ₆ H ₄ OCH ₃	C ₆ H ₄ OCH ₃	CH ₃	CH ₃	25	16	62.5	250
C ₉	C ₆ H ₄ OCH ₃	C ₆ H ₄ OCH ₃	C ₂ H ₅	H	28	20	31.25	15.625
P	Pd(COD)Cl ₂				33	24	250	250
Standard	Clotrimazole				16	13		

For each ligand and complex the R-group substitution, zone of inhibition and minimum inhibitory concentration obtained for *Candida albicans* (*C.albicans*) and *Aspergillus niger* (*A.Niger*) are reported with the standard molecules ciprofloxacin.

DISCUSSION

In vitro antimicrobial activity

By diffusion method, the ligands (L₁-L₉) and their complexes (C₁-C₉) *invitro* antimicrobial activity was examined using Muller Hinton Broth and Sabouraud's Dextrose Broth (Hi-media)[13-16]. Each compound was tested at the concentration of 100 μgml^{-1} in dimethylsulphoxide solution. The zone of inhibition was measured after 24 hours of incubation at 37°C. The results of the *invitro* antibacterial activity measurements are presented in Table 3. Inhibition zone size of 13mm clearly indicates that the ligands L₁ and L₂ against *Escherichia coli* and 11mm for the ligands L₂ and L₅ in *Staphylococcus aureus* are highly active in comparable to the remaining ligands. Inhibition of the complexes has shown maximum antibacterial potency compare to ligands (L₁-L₉) except L₁ and L₂. In C₁ complex, methyl group at 3-position of 2,6-di phenylpiperidin-4-one shows high activity against *Escherichia coli* and *Staphylococcus aureus*.

Table 4 shows the zone of inhibition for *invitro* antifungal activity. The ligand (L₂) is highly active against *Candida albicans* and *Aspergillus niger* due to the presence of methyl group in 3, 5-positions. The ligands (L₁, L₄, L₆ and L₉) against *Candida albicans* and L₁ against *Aspergillus niger* are moderately active. In comparison to standard Clotrimazole, complexes C₁ and C₂ are less active against antifungal organisms, whereas complexes C₃ to C₉ resulted an enhance activity [17-23].

Minimum inhibitory concentration (MIC)

Introduction of alkyl groups in ortho position of aryl groups at position-2,6 of the six membered heterocyclic moiety in the place of 3 and 3,5-positions exhibit the activity against *Escherichia coli*, *Staphylococcus aureus*, *Candida albicans* and *Aspergillus niger*.

In antibacterial studies, substituted 2,6-diarylpiperidin-4-ones (aryl=phenyl, tolyl, anisyl), methyl group of 3 and 3,5-positions of L₂, L₈ for *Escherichia coli* and L₄, L₅, and L₈ for *staphylococcus aureus* exhibit same minimum inhibitory concentration value (31.25 μgml^{-1}). In C₂, C₅ and C₇ complexes against *Escherichia coli* and C₁, C₅ and C₇ complexes against *Staphylococcus aureus* has enhanced activity of their corresponding aryl groups at position-2,6 of the six membered heterocyclic moieties [16].

For antifungal studies, ligands of L₂, L₆ and L₉ against *Candida albicans* and L₁, L₆ and L₉ against *Aspergillus niger* shows less activity when compared to other ligands of substituted 2,6-diarylpiperidin-4-ones (aryl= phenyl, tolyl, anisyl). The ligands (L₄ and L₅) and in

complexes (C₁, C₅ and C₆) show the same concentration of 15.625 μgml^{-1} against *Aspergillus niger*. Complexes have no appreciable change in the C₁, C₂, C₄, C₅, C₆, C₇ and C₉ in the minimum inhibitory concentration against *Candida albicans* has similar values of their corresponding substituted 2,6-diarylpiperidin-4-ones (aryl=phenyl, tolyl, anisyl) [16].

CONCLUSIONS

To conclude, the study showed a series of substituted piperidin-4-one ligands (L₁-L₉) and their complexes (C₁-C₉) were synthesized and screened for the antimicrobial activity by using ciprofloxacin and clotrimazole as reference drugs on a panel of strains *Escherichia coli*, *Staphylococcus aureus*, *Candida albicans* and *Aspergillus niger*. The compound C₁ has highly active against *Escherichia coli* and *Staphylococcus aureus* compared with *Ciprofloxacin* and C₉ has highly active against *Candida albicans* and *Aspergillus niger* compared with Clotrimazole. The compound (C₇ and C₈) against *Staphylococcus aureus* and (L₂ and C₇) against *Aspergillus niger* shows the maximum inhibitory concentration at 500 μgml^{-1} .

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