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Research Article

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)Cl_2. The complexes were synthesized using substituted piperdin-4-ones (ligands) and Pd(COD)Cl_2 (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 *invitro* 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 L_1 and L_2 against Esche *richia coli*, L2 and L_5 in *Staphylococcus aureus* and L_2 against *Candida albicans and Aspergillus niger* are highly active. The activity of antibacterial is highly active in C_1 complex but in antifungal organisms the complexes C_1 and C_2 are less active and the complexes C_3 to C_9 resulted an improve activity. The ligands L_4, L_5, and L_8 exhibit similar minimum inhibitory concentration value (31.25µgml^{-1}) in *Staphylococcus aureus*. In antifungal studies, the ligands L_2, L_6 and L_9 against *Candida albicans* and L_1,L_6 and L_9 against *Aspergillus niger* shows with a decrease in minimum inhibitory concentration Conclusion: Our results showed that C_2, C_5 and C_7 complexes against *Escherichia coli* and C_1, C_5 and C_7 complexes against *Staphylococcus aureus* has superior activity in the zone of inhibition. The minimum inhibitory concentration for C_1 and C_2, C_4 and C_5, C_6, C_7 and C_9 complexes against *Candida albicans* has identical values. The compound (C_7 and C_8) against *Staphylococcus aureus* and (L_2 and C_7) against *Aspergillus niger* shows the maximum inhibitory concentration at 500µgml^{-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)Cl_2.

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 ^{1}H-NMR and [13]C NMR spectra were noted by Jeol GSX 4OONB NMR spectrometer operating at 500.13 MHz and 125.76 MHz with$DMSOd_6$ 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(L_1-L_9) 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

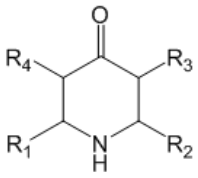
The dichloro(cyclooctadiene)palladium (II) is used as a precursor. The dichloro(cyclo octadiene)palladium (II) with 2, 6-diaryl piperidin-4-ones ligands (L_1-L_9) were prepared by the following procedure: A mixture of dichloro(cyclooctadiene)palladium(II) (0.5m mol) and substituted piperidin-4-ones (L_1-L_9) (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 4ºC for one hour for diffusion on the surface of the culture and

followed by incubation at 37ºC 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_6H_5	C_6H_5	CH_3	H
L_2	3,5-dimethyl-2,6-diphenylpiperidin-4-one	C_6H_5	C_6H_5	CH_3	CH_3
L_3	3-ethyl-2,6-diphenylpiperidin-4-one	C_6H_5	C_6H_5	C_2H_5	H
L_4	3-methyl-2,6-ditolylpiperidin-4-one	$C_6H_4\ CH_3$	$C_6H_4\ CH_3$	CH_3	H
L_5	3,5-dimethyl-2,6-ditolylpiperidin-4-one	$C_6H_4\ CH_3$	$C_6H_4\ CH_3$	CH_3	CH_3
L_6	3-ethyl-2,6-ditolylpiperidin-4-one	$C_6H_4\ CH_3$	$C_6H_4\ CH_3$	C_2H_5	H
L_7	3-methyl-2,6-dianisylpiperidin-4-one	$C_6H_4\ OCH_3$	$C_6H_4\ OCH_3$	CH_3	H
L_8	3,5-dimethyl-2,6-dianisylpiperidin-4-one	$C_6H_4\ OCH_3$	$C_6H_4\ OCH_3$	CH_3	CH_3
L_9	3-ethyl-2,6-dianisylpiperidin-4-one	$C_6H_4\ OCH_3$	$C_6H_4\ OCH_3$	C_2H_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^{0}C Kirby- Bauer procedure and diluted to the corresponding Broth. The sterile tubes were labeled to control. All the tubes were incubated at 37^{0}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-diarylpiperdin-4-ones. All the synthesized substituted 2, 6-diarylpiperdin-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-diarylpiperdin-4-ones is established on the basis of IR and NMR (^{1}H and [13]C) data obtained as given in Table 1 and 2.

Spectra for ligands and complexes

The infrared spectra for ligands (L_1-L_9),shows an absorption band lies around 1700 cm^{-1}and 3300cm^{-1}C=O groups and NH groups. In Palladium complexes (C_1-C_9), it is shifted corresponding of the ligands (Table 1). The ^{1}H-NMR shows a singlet at δ2.5 ppm to NH protons and [13]C NMR shows a peak δ204 ppm for C=O group in C_4 carbon by shifting the position on complexion with precursor (Table 2).

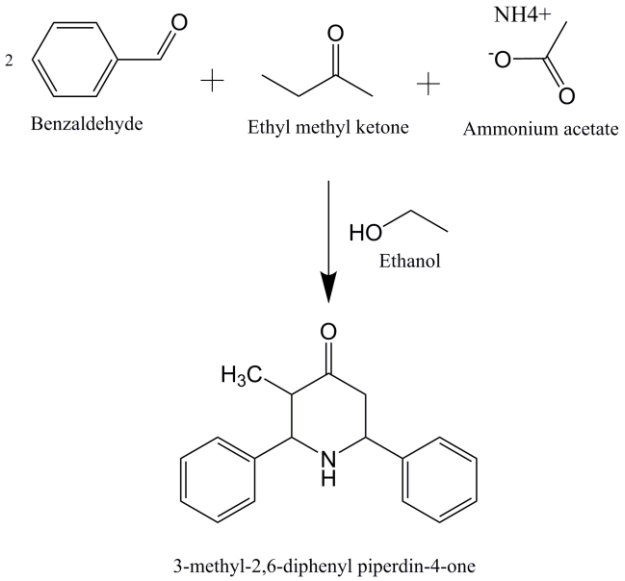


Fig. 2: Synthesis of 3-methyl-2,6-diphenylpiperidin-4-one

Table 1: IR spectral data for ligands and complexes

Complex	IR							
	ν(C=O)[a]	ν(C=O)[b]	ν(N-H)	ν(O-H)	ν(HOH)	ν(Ar-H)	ν(M-N)	ν(M-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

ν(C=O)[a]-for ligands; ν(C=O)[b]- for complexes

For each complex (C_1-C_9) IR spectral data are reported.

Table 2:^{1}H and [13]C 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 - 7.865	7.394 - 7.540	7.426 - 7.516	6.437 - 7.611	7.268 - 9.994	7.426 - 10.544	7.125 - 7.750	6.910 - 7.375	7.452 - 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 (C_1-C_9) ^{1}H and [13]C NMR spectral data are reported.

Antimicrobial evaluation

Table 3 and 4 shows the *invitro* antimicrobial activities of zone of inhibition and MIC for substituted 2,6-diarylpiperdin-4-ones,ligands L_1-L_9 and their complexesC_1-C_9 using cipr ofloxacin(10µg) and clotrimazole(10µg) as reference drugs on a panel of strains *Esche richia 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 repored with the standard molecules ciprofloxacin.

Table 3: Antibacterial activity

Ligands	R1	R2	R3	R4	Zone of inhibition (mm)		Minimum inhibitory concentration (µgml-1)	
					E.coli	S.aureus	E.coli	S.aureus
L_1	C_6H_5	C_6H_5	CH_3	H	13	10	62.5	125
L_2	C_6H_5	C_6H_5	CH_3	CH_3	13	11	31.25	7.125
L_3	C_6H_5	C_6H_5	C_2H_5	H	0	8	125	125
L_4	C_6H_4 CH_3	C_6H_4 CH_3	CH_3	H	7	9	125	31.25
L_5	C_6H_4 CH_3	C_6H_4 CH_3	CH_3	CH_3	7	11	15.625	31.25
L_6	C_6H_4 CH_3	C_6H_4 CH_3	C_2H_5	H	9	10	7.812	62.5
L_7	C_6H_4 OCH_3	C_6H_4 OCH_3	CH_3	H	7	9	125	15.625
L_8	C_6H_4 OCH_3	C_6H_4 OCH_3	CH_3	CH_3	7	10	31.25	31.25
L_9	C_6H_4 OCH_3	C_6H_4 OCH_3	C_2H_5	H	0	7	125	15.625
C_1	C_6H_5	C_6H_5	CH_3	H	24	25	62.5	62.5
C_2	C_6H_5	C_6H_5	CH_3	CH_3	11	9	15.625	125
C_3	C_6H_5	C_6H_5	C_2H_5	H	11	8	125	125
C_4	C_6H_4 CH_3	C_6H_4 CH_3	CH_3	H	14	9	62.5	62.5
C_5	C_6H_4 CH_3	C_6H_4 CH_3	CH_3	CH_3	14	11	31.25	7.812
C_6	C_6H_4 CH_3	C_6H_4 CH_3	C_2H_5	H	12	13	125	125
C_7	C_6H_4 OCH_3	C_6H_4 OCH_3	CH_3	H	12	10	31.25	500
C_8	C_6H_4 OCH_3	C_6H_4 OCH_3	CH_3	CH_3	13	9	250	500
C_9	C_6H_4 OCH_3	C_6H_4 OCH_3	C_2H_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)	
					C.albicans	*A.niger*	*C.albicans*	*A.niger*
L_1	C_6H_5	C_6H_5	CH_3	H	7	12	125	62.5
L_2	C_6H_5	C_6H_5	CH_3	CH_3	21	16	15.625	500
L_3	C_6H_5	C_6H_5	C_2H_5	H	0	0	125	125
L_4	C_6H_4 CH_3	C_6H_4 CH_3	CH_3	H	8	0	15.625	15.625
L_5	C_6H_4 CH_3	C_6H_4 CH_3	CH_3	CH_3	0	0	31.25	15.625
L_6	C_6H_4 CH_3	C_6H_4 CH_3	C_2H_5	H	13	0	7.812	7.812
L_7	C_6H_4 OCH_3	C_6H_4 OCH_3	CH_3	H	0	0	31.25	62.5
L_8	C_6H_4 OCH_3	C_6H_4 OCH_3	CH_3	CH_3	0	0	31.25	31.25
L_9	C_6H_4 OCH_3	C_6H_4 OCH_3	C_2H_5	H	8	0	7.812	7.812
C_1	C_6H_5	C_6H_5	CH_3	H	9	18	31.25	31.25
C_2	C_6H_5	C_6H_5	CH_3	CH_3	11	9	31.25	62.5
C_3	C_6H_5	C_6H_5	C_2H_5	H	21	16	62.5	125
C_4	C_6H_4 CH_3	C_6H_4 CH_3	CH_3	H	25	18	7.812	62.5
C_5	C_6H_4 CH_3	C_6H_4 CH_3	CH_3	CH_3	26	18	7.812	7.812
C_6	C_6H_4 CH_3	C_6H_4 CH_3	C_2H_5	H	23	19	31.25	31.25
C_7	C_6H_4 OCH_3	C_6H_4 OCH_3	CH_3	H	23	18	31.25	500
C_8	C_6H_4 OCH_3	C_6H_4 OCH_3	CH_3	CH_3	25	16	62.5	250
C_9	C_6H_4 OCH_3	C_6H_4 OCH_3	C_2H_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(L_1-L_9) and their complexes(C_1-C_9) *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 100ugml^{-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 L_1 and L_2 against *Escherichia coli* and 11mm for the ligands L_2 and L_5 in *Staphylococcus aureus* are highly active in comparable to the remaining ligands. Inhibition of the complexes has shown maximum antibacterial potency compare to ligands (L_1-L_9) except L_1 and L_2. In C_1 complex, methyl group at 3-positon of 2,6-di phenylpiperdin-4-one shows high activity against *Escherichia coli* and *Staphylococcus aureus.*

Table 4 shows the zone of inhibition for *invitro* antifungal activity. The ligand (L_2) is highly active against *Candida albicans* and *Aspergillus niger* due to the presence of methyl group in 3, 5-positions. The ligands (L_1, L_4, L_6,and L_9) against *Candida albicans* and L_1 against *Aspergillus niger* are moderately active. In comparison to standard Clotrimazole, complexes C_1 and C_2 are less active against antifungal organisms, whereas complexes C_3 to C_9 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-diarylpiperdin-4-ones(aryl=phenyl,tolyl,anisyl), methyl group of 3 and 3,5-positions of L_2,L_8 for *Escherichia coli* and L_4, L_5, and L_8 for staphylococcus aureus exhibit same minimum inhibitory concentration value(31.25µgml^{-1}).In C_2, C_5 and C_7 complexes against *Escherichia coli* and C_1,C_5 and C_7 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 L_2, L_6 and L_9 against *Candida albicans* and L_1,L_6 and L_9 against *Aspergillus niger* shows less activity when compared to other ligands of substituted 2,6-diarylpiperdin-4-ones (aryl= phenyl,tolyl,anisyl).The ligands(L_4 and L_5) and in complexes(C_1 ,C_5 and C_6) show the same concentration of 15.625 µgml^{-1}against *Aspergillus niger*. Complexes have no appreciable change in the C_1 C_2, C_4 C_5, C_6,C_7 and C_9 in the minimum inhibitory concentration against *Candida albicans* has similar values of their corresponding substituted 2,6-diarylpiperdin-4-ones(aryl=phenyl, tolyl,anisyl) [16].

CONCLUSIONS

To conclude, the study showed a series of substituted piperdin-4-one ligands (L_1-L_9) and their complexes (C_1-C_9) 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 C_1 has highly active against *Escherichia coli and Staphylococcus aureus* compared with *Ciprofloxacin* and C_9 has highly active against *Candida albicans* and *Aspergillus niger* compared with Clotrimazole. The compound (C_7 and C_8) against *Staphylococcus aureus* and (L_2 and C_7) against *Aspergillus niger* shows the maximum inhibitory concentration at 500µgml^{-1}.

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