



# Manganese (II) and Cobalt (II) Acetylacetonates as Antimicrobial Agents

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# Abstract

Mn(II) and Co(II) complexes were prepared by reaction of the metal chlorides with acetylacetone in ammonical aqueous medium. The metal complexes were prepared in order to investigate their antimicrobial activity on some selected pathogens. The characterisation of the complexes was on the basis of various spectroscopic techniques like infrared and ultraviolet studies. The compounds were subjected to antimicrobial activity screening using serial broth dilution method. Minimum Inhibitory Concentration (MIC) and Minimum Bactericidal/Fungicidal Concentration (MBC/MFC) were determined. Mn(II) complex has shown significantly both antibacterial and antifungal activity with a MIC of 1.25  $\mu$ g/mL while Co(II) complex was noticeable for antifungal activity at the same concentration. Whereas Mn(II) acetylacetonate is a more potent bactericide while Co(II) acetylacetonate is a more potent fungicide, both with MBC/MFC value of 2.5  $\mu$ g/mL. Antimicrobial agent of the ligand has enhanced on complexation with Mn(II) and Co(II) ions. Though, the potency of the prepared antibiotics on the tested microbes is less compared to the standard drugs (Ciprofloxacin and Fulcin).

**Key words:** Transition Metal complex, Antimicrobial Activity, Pathogens, ligand, Minimum Inhibition Concentration



# Introduction

The chemistry of acetylacetone (acacH) also known as 2,4-pentadione and transition metals ions have been investigated for over two decades (Eshraq, 2007). The compound acetylacetone acts as bidente, that is, both oxygen atoms of acetylacetonate anion bind to the metals to form stable six-membered ring complexes (Eshraq, 2007; Judith and Frank, 1985). Metal acetylacetonates are coordination complexes with typical formula [M(acacH)z]<sup>n+</sup>. A large number of the metal complexes have been prepared using different synthetic routes. Literature has revealed earlier methods for the synthesis of metal acetylacetonates. However, some of these techniques have been found to have some limitations such as contamination of the target end-product by one of the reactant as well as involvement of extra preparation steps. Metal acetylacetonate complexes can easily be prepared by a method known as acid-base reaction. This method gives pure products and ensures shorter reaction time (Szafran et al., 1991; Chira. and Mihir, 1988).

Metal acetylacetonate complexes are usually covalent, non-hygroscopic and very stable against water and air. They are characterised by thermal stability, volatility and solubility in organic solvents. These properties have given rise to many applications, particularly in the area of basic research, industrial and agricultural processes. They are used as a catalyst in chemical transformations such as polymerisation and hydrogenation reactions. Acetylacetonate complexes of Zn(II), Cu(II), Co(II) and Mn(II) can be used as corrosion inhibitors due to their good adsorption properties on metal surfaces. In addition, metal acetylacetonate complexes are used as pesticides (Eshraq, 2007; Szafran et al., 1991; Lamprey, 2006; Wlodzimierz, et al., 2011).

Recently, much attention has been given to inorganic compounds due to an important role they play in biological processes. Many of the organic compounds used in medicine are activated by metal ions, particularly the metal chelates. Metal chelates have the ability to act as antibiotics and potential inhibitors for many enzymes. Besides, metal ions present in complexes accelerate the drug action and improve the efficacy of the organic therapeutic agents. Furthermore, different metal ion complexes synthesised from the same ligand possess different biological properties. So, there is an increasing need for the discovery of new metal complexes with more effective biological activities and possibly with more efficiency and distinct mechanism from those of well known antimicrobial agents to which

many pathogens are now resistant. Hence modern era medications can influence the quality and duration of human life in ways that was never possible before (Shamsuzzohal *et al.*, 2015; Kashar, 2013; Aderoju *et al.*, 2014; Ketan *et al.*, 2012; Elina, 2014).

Literatures on the use of metal acetylactonates as antibiotics (where acetylacetone singly coordinated to metal ions) are rare; perhaps those that are available were of mixed number of ligands. Therefore, the purpose of this work is to investigate the antimicrobial activity of manganese (II) and cobalt (II) acetylacetonates on some selected pathogens.

# Materials and method Materials

All chemicals used in this research work were analytical grade (AR). Manganese (II) chloride tetrahydrate (99% pure) and Cobalt (II) chloride hexahydrate (97% pure) were both from Kermel, China. Acetylacetone (99 % pure) and ammonia solution (99.99% pure) were from Qualiken Delhi and Lobal Chemie Mumbai, India, respectively. n-Hexane (97% pure), ethanol (99.9% pure), methanol (99.8% pure), and DMSO (99.5% pure), from JHD, BDH, Sigma Aldrich and Guangong Guanghua Science Technology Company respectively. All reagents were used as received.

# Method

Mn(II) and Co(II) acetylacetonates were prepared by dissolving 5.0 g of MnCl<sub>2</sub>.4H<sub>2</sub>O (25 mmol), and CoCl<sub>2</sub>.6H<sub>2</sub>O (21 mmol) in 25 mL of distilled water in a 500 mL separate flask, followed by the addition of 10 mL portions of ammonia solution. To the resulting solution, 11 mL of acetylacetone was added drop wise for about 20 minutes. The reaction mixture was heated with constant stirring at the temperature of 65 °C for one hour. The reaction flask was allowed to cool at ambient conditions and then in ice-bath. The precipitates were collected by filtration using a funnel with Whatman filter paper No.42. They were washed with 15 mL of ice-cold distilled water and dried in vacuum desiccators.

# **Physical Property Measurements**

IR spectra were recorded as Nujol mulls using KBr pellets on FT-IR spectrophotometer (FT-IR 8400S). Three milligrams of each sample was weighed into a small agate mortar and a drop of nujol was added and ground. The mull obtained was suspended on the cell of the spectrophotometer and scanned between 4000-400 cm<sup>-1</sup> at 32 runs per minute. Electron transition studies were conducted using UV-Visible spectrophotometer (2500PC Series). A dilute solution of 2 mg in 10 mL of each sample was prepared in DMSO solution. Two millilitres was withdrawn into the cell of the spectrophotometer and a matched cell containing pure solvent was used as a reference. Both cells were placed in their appropriate holders in the spectrophotometer and scanned between 200-800 nm to obtain  $\lambda_{max}$ . Molar conductivities of each complex were measured using conductivity meter (EC 215). One millimolar of the complex was prepared and 20 mL of the solution was transferred into an electrolytic cell, measurements were taken when the meter readings were steady. The solubility of the metal complex was tested using distilled water, ethanol, methanol, DMSO and n-hexane. The test was conducted by dissolving 10 mg of each complex in each of the test-tube containing 2 mL of the corresponding solvent to check for the solubility. Thin layer chromatography (TLC) of the complexes was performed on 2 cm x 4 cm aluminium plate coated with silica gel. A solvent combination of benzene, acetone and methanol in the ratio 4:3:1 was used. The plates containing the mixture were placed in a chromatographic chamber saturated with mobile-phase vapour. The substances were separated as a mixture and were detected as coloured spots by using iodine crystals.

# Antimicrobial Activity Studies

The ligand and corresponding metal (II) complexes were screened against four bacteria and four fungi. The bacteria were *Staphylococcus aureus*, *Streptococcus pyogenes*, *Pseudomonas aeruginosa* and *Proteus mirabilis* while the fungi were *Candida krusei*, *Microsporum distortum*, *Mucor muceller* and *Penillium chrysogenum*. The antimicrobial property of the ligand and its metal complexes were obtained using the disc diffusion method (Ahmet *et al.*, 2009, Neerji and Kshama, 2014). The sterilised Mueller Hinton and Saubouraud dextrose agars were used as the growth media for bacteria and fungi, respectively.

The media were fed with 0.1 mL standard inoculum of the test microbes. A cork borer of 6 mm in diameter was used to cut a well at the centre of each inoculated medium. The concentration of 10  $\mu$ g/mL of each complex in DMSO was prepared and 0.1 mL of the concentration was introduced into each well on the inoculated medium. The plates were incubated at 37 °C for 24 h for bacteria and at 30 °C for 72 h for fungi, after which each plate was observed for zone of inhibition of growth. DMSO solvent was used as a negative control, and experimental data were compared with 10  $\mu$ g/mL concentration of the standard drugs (Ciprofloxacin for bacteria and Fulcin for fungi).

# Determination of Minimum Inhibition Concentration

The minimum inhibition concentration (MIC) of the complexes was determined by broth dilution technique (Omoruyi *et al.*, 2012). The concentration of each complex was between (0.625 and 10  $\mu$ g/mL). Each microbe (0.1 mL) was introduced into the different concentrations of the metal complexes and incubated as before. The lowest concentration of the complexes which shows no turbidity was recorded as the minimum inhibition concentration.

# Minimum Bactericidal/Fungicidal Concentration MBC/MFC

The contents of the MIC were then sub cultured onto the transparent media and incubated at 37 °C for 24 h for bacteria and at 30 °C for 72 h for fungi (Omoruyi *et al.*, 2012). The lowest concentration of the antimicrobial agents at which all microbes were killed was taken as the minimum bactericidal/fungicidal concentration.

# **Results and discussion Physico-Chemical Properties**

The percentage yields, colours, and molar conductivities of the coordination compounds are presented in Table 1.

**Table 1:** Some physical properties of the compounds

Complex	% Yield	Colour	Molar conductance ( $\mu$ S m <sup>2</sup> mol <sup>-1</sup> )
Mn(II) acetylacetonate	79	Yellow	28
Co(II) acetylacetonate	86	Orange	55

The yields were found to vary according to moles of the reactants. However, the percentage yield of Mn(II) complex is lower (79 %) than that of Co(II) complex (86 %). the difference is due to fact that the theoretical yield of Mn(II) complex is higher than that of Co(II) complex. The

percentage yield data agree with that reported by Rohini and Urul (2014) and Mihir *et al.*, (2004). The Mn(II) and Co(II) complexes were yellow and orange respectively. The difference in colours could be due to their different in absorption wavelength in UV-Visible spectrum. Theodore *et*  *al* (1977) have reported that a yellow and orange colour has approximately absorption maxima ranges from 380-430 nm and 430-490 nm respectively. The complexes have colours similar to the same coordination compounds obtained by other researchers (Robert and Mohammad, 1968; Papadopoulos *et al.*, 2008). Molar conductivity values of the complexes are below 10 mS m<sup>2</sup>mol<sup>-1</sup>, the expected value for an electrolyte (Peter and Julio, 2010). The low value of molar conductivity shows that the complexes are non-electrolytes (Aliyu and Ado, 2011).

The metal acetylacetonates are soluble only in DMSO. The solubility of metal complexes in DMSO is due to hydrophobic nature of metal acetylacetonate, because  $\beta$ -diketonate forms a lipophilic shell around the metal ion (Koen, 2005). Besides, DMSO is a polar aprotic solvent; polar aprotic solvents have lipophilic portions through which organic compounds dissolve (Ajit, 2010). Apart from its lipophilicity, the sulphur-oxygen bond in DMSO molecule is quite polar with high dielectric constant (46.7) to permits easy charge separation, hence good solubility for variety of ionic, polar and polarisable molecules (Warren, 1967). The solubility of metal complexes in distilled water, methanol, ethanol and n-hexane is slight. This means there is an interaction between the metal complexes and these solvents. Therefore, we presumed that the chemical structure of acetylacetone metal complex compose partly of hydrophobic and hydrophilic portions. TLC of Mn(II) complex yielded a major spot and a faint spot while that of Co(II) complex has a major spot and two faint spots. The presence of faint spot is an indication of a small amount of binary solvent present in the two complexes (Ram et al., 1990).

#### **Electronic Spectra**

The maximum absorption bands of the free ligand acetylacetone and the metal complexes in DMSO are shown in Table 2.

Table 2: Data for UV-Visible spectra of acetylacetone and its metal complex

Compound	Absorbance	$\lambda_{max}$	Transition
Acetylacetone	0.047	672	-
Mn(II) acetylacetonate	1.846	391	${}^{6}A1_{g}?$ ${}^{4}E_{g}$
Co(II) acetylacetonate	0.334	497	${}^{4}T_{1g}$ ? ${}^{4}A_{2g}$

The ligand shows absorption maximum  $(\lambda_{max})$  at 672 nm which shifted to 391 nm and 497 nm in Mn(II) and Co(II) complexes respectively. The shifts of  $\lambda_{max}$  absorption towards the higher energy (hypersochromic shift) are evidence for the binding of acetylacetone with metal ions (Rajendran *et al.*, 2014). The visible spectrum of Mn(II) complex with d<sup>5</sup> displayed  $\lambda_{max}$  absorption band at 391 nm is assigned to  ${}^{6}A_{1g} \rightarrow {}^{4}E_{g}$  transition. Co(II) complex with 3d<sup>7</sup> exhibited  $\lambda_{max}$  at 497 nm is ascribed to  ${}^{4}T_{1g} \rightarrow {}^{4}A_{2g}$  transition (Ketan *et al.*,

2012; Manku, 1980; Gonzalo, 1981; Cox, 2004; Lakshmi, 2012). The spectra bands of the divalent metal complexes have shown similar characteristics by exhibiting weak bands, which signify that they are Laporte forbidden d-d transitions in octahedral complexes (Lee, 2009).

#### Infrared Spectrum of Acetylacetone

Figure 1 shows the infrared spectrum of acetylacetone.

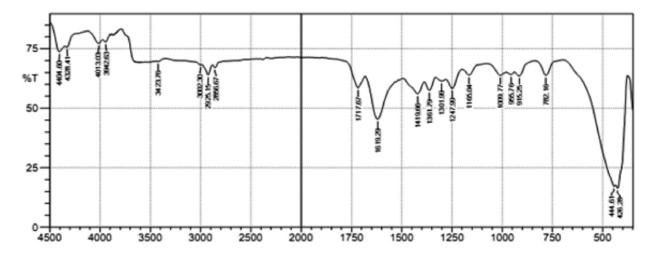


Figure 1: Infrared spectrum of acetylacetone

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The ligand shows a weak band at 2925 cm<sup>-1</sup> similar to the results reported by Eshrad (2007). The band is due to symmetric stretching mode of the methyl group,  $v_s$  (CH<sub>3</sub>), for keto form and enol form (Eshrad, 2007). The ligand shows two other bands; a weak band at 1717 cm<sup>-1</sup> and broad band at 1619 cm<sup>-1</sup>. The band at 1717 cm<sup>-1</sup> is attributed to carbonyl group (C=O) stretching frequency of the keto form whereas the band at 1619 cm<sup>-1</sup> is interpreted as superimposition of the C=O stretching and C=C stretching coupled with C-H

in plane of the enol form. The large lowering in the C=O frequency of the enol form is ascribed to an internal hydrogen bond and resonance effect, which indicates that enol is present as conjugated system (Figure 2) (Neeraji and Kshama, 2014; Abood and Ajam, 1985). The bands observed at 1717 cm<sup>-1</sup> and 1619 cm<sup>-1</sup> assigned to v (C=O) vibrations of acacH, are an indication of the two distinctive existing forms of acetylacetone (Neeraji and Kshama, 2014) as shown in Figure 2.

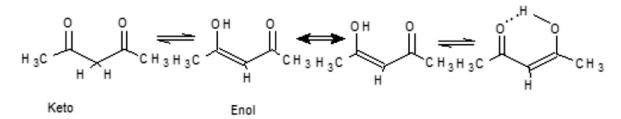


Figure 2: Keto-enol equilibrium

Co(II) acetylacetonate

The band at  $1361 \text{ cm}^{-1}$  is attributed to the out of plane bending (wagging) of the methyl groups,  $\omega$  (CH<sub>3</sub>) for both keto and enol forms. The band at 1301 cm<sup>-1</sup> is assigned to out of plane bending (twisting) of the methylene groups,  $\tau$  (CH<sub>2</sub>), for keto form, and in enol form, the band is referred to in plane bending of the hydroxyl group,  $\delta$  (OH). The vibrational band at 955 cm<sup>-1</sup> is attributed to the out of plane bending (wagging) of the  $\omega$  (C-H) bond of the methyl groups for both keto and enol forms (Eshraq, 2007). The bands at 2925 w, 1361w

and 955vw clearly shows the existence of keto and enol forms of acacH at equilibrium (Figure 2).

### Infrared Spectra of Acetylacetone Metal Complexes

Figure 3 and 4 are the IR spectra of Mn(II) and Co(II) complexes, respectively.

The IR spectral assignment of the metal complexes was achieved by comparing their vibrational frequencies with those of the free ligand.

1260w

1613m,1518m

575, 673

 Table 3: Infrared spectra of acetylacetone and its metal complexes

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Compound	v(OH)	v(CH <sub>3</sub> )	v(C=O)	δ(OH)	v(M-O)
acacH	-	2925w	1717w,1619m	1301vw	-
Mn(II)acetylacetonate	3434b	2932vw	1601m, 1514s	1251m	538, 647

2990 w

Key: b = broad, m = medium, s = strong, w = weak, vw = very weak

3422b

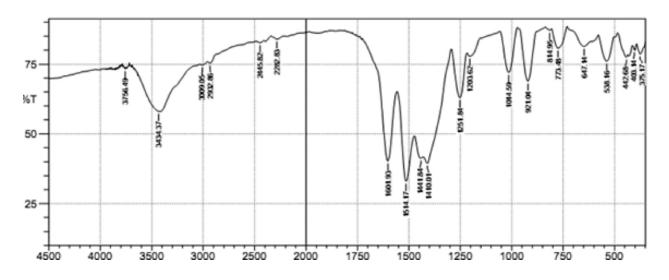


Figure 3: Infrared spectrum of Mn(II) acetylacetone

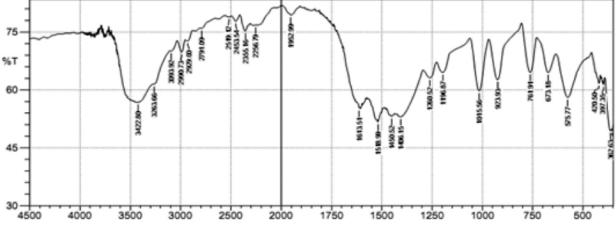


Figure 4: Infrared spectrum of Co(II) acetylacetone

Infrared spectra of divalent metal acetylacetonates in Table 3 show specific spectral regions with characteristic differences between the free ligand and the metal complexes. The broad band absorptions appeared at 3434cm<sup>-1</sup> and 3422  $cm^{-1}$  in the spectra of Mn(II) and Co(II) respectively, ascribed to v (OH) were absence in the spectrum of the parent reagent. This implies that a water molecule is present in the prepared complexes (Khalid, 2007; Palakuri and Laxma, 2014). The band at 2925cm<sup>-1</sup> assigned to vibration stretching mode of methyl group, v (CH<sub>3</sub>), in the ligand, upon chelation, the band shifted to higher frequencies in the complexes, suggesting change in environment of methyl proton from olefin to aromatic (Roy, 1965). The C=O stretching vibrations at 1717 cm<sup>-1</sup> and 1619 cm<sup>-1</sup> in acacH, upon complexation shifted to lower frequencies. The shift signifies the involvement of carbonyl group of 1,4-pentadione in coordination with metal ion through oxygen atom instead of other sites of the molecule (Khalid, 2007; Roy, 1965). The shift of v (C=O) to lower frequencies in metal complexes is due to delocalised  $\pi$ -electron between C=O and metal ion in the ring, which influence the bond order between carbon and oxygen linkage as reflected in the decreased vibrational frequency of C=O on coordination (Enusali, 2015). The weak band observed at 1301  $cm^{-1}$  in the spectrum of the free ligand assigned to  $\delta$ (OH), is shifted to lower frequencies in the complexes. The shift is an indication of coordinated oxygen atom with metal ion resulting in the formation of C-O-M bond (George et al., 2012). The involvement of C-O in the coordination is further supported by the appearance of new bands in the regions 538-647 cm<sup>-1</sup> and 575-673 cm<sup>-1</sup> assigned to v (Mn-O) and v (Co-O), respectively (Enusali, 2015). From these results, it was observed that there is a strong correlation between IR and TLC data, indicating that all the prepared complexes contain small amount of binary solvent molecules. Therefore, on the basis of TLC, UV-visible and IR techniques, the proposed structure of the ligand and the metal ions is represented in Figure 5.

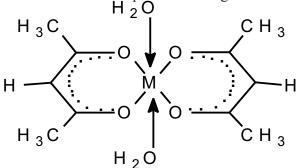


Figure 5: Proposed structure of M(II) acetylacetonate complex, where M = Mn(II), Co(II)

#### **Antimicrobial Activity**

The ligand and its metal complexes were screened for their antibacterial and antifungal activities. The results obtained for zone of growth of inhibition are presented in Table 5 and the results were compared with those of the standard drugs.

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Microbes	AcacH	Mn(II) L	Co(II) L	Ciprofloxicin	Fulcin
S. aureus	24	28	26	35	-
S. pyogenes	R	R	24	32	-
P. eruginosa	R	30	R	37	-
P. mirabilis	21	31	R	35	-
C. kusei	24	28	26	-	32
M. distortum	R	29	R	-	30
M. muceller	20	26	30	-	31
P. chrysogenum	R	29	32	-	34

**Table 5:** Zone of inhibition by compounds on some pathogens (mm)

R = Resistant, L = acetylacetonate

From Table 5, it can observed that Mn(II) acetylacetonate is a wide spectrum antibiotic compare to Co(II) acetylacetonate, hence it is sensitive to the microbes except *S. pyogenes*. Besides, Mn(II) complex is more of antibacterial with highest activity on *P. mirabilis*. Co(II)

complex on the other hand is more of antifungal with highest activity on *P. chrysogenum*.

The MIC of the active compounds was determined by broth diffusion technique and the results are presented in Tables 6 and 7.

**Table 6:** MIC values of Mn(II) acetylacetonate on some pathogens (µg/mL)

Microbes	10	5	2.5	1.25	0.625
S. aureus	-	-	-	o+	+
S. pyogenes	R				
P. eruginosa	-	-	-	o+	+
P. mirabilis	-	-	-	o+	+
C. kusei	-	-	-	o+	+
M. distortum	-	-	-	o+	+
M. muceller	-	-	o+	+	++
P. chrysogenum	-	-	-	o+	+

**Table 7:** MIC values of Co(II) acetylacetonate on some pathogens (µg/mL)

		5	1 0			
Microbes	10	5	2.5	1.25	0.625	
S. aureus	-	-	o+	+	++	
S. pyogenes	-	-	0+	+	++	
P. eruginosa	R					
P. mirabilis	R					
C. kusei	-	-	o+	+	++	
M. distortum	R					
M. muceller	-	-	-	o+	+	
P. chrysogenum	-	-	-	o+	+	

- = No turbidity, o+ = MIC, + = Turbidity, ++ = Moderate growth, R= Resistant

Mn(II) complex shows superior antimicrobial activity (Table 6) against *S. aureus*, *P. aeruginosa*, *P. mirabilis* (bacteria) as well as *C. krusei*, *M. distortum* and *P. chrysogenum* (fungi). Co(II) complex on the other hand, showed best antifungal activity towards *M. muceller* and *P. chrysogenum* 

(Table 7) both with MIC of value 1.25  $\mu$ g/mL. From Table 8, it was noticed that while Mn(II) acetylacetonate acts both as bactericidal and fungicidal, Co(II) acetylacetonate is more fungicidal (Table 9), both with MBC/MFC value of 2.5  $\mu$ g/mL

Table 8: MBC/MFC	C values of Mn(I	I) acetyl	lacetonate on som	e pathogens	$(\mu g/mL)$
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Microbes	10	5	2.5	1.25	0.625	
S. aureus	-	o+	+	++	+++	
S. pyogenes	R					
P. eruginosa	-	-	o+	+	++	
P. mirabilis	-	-	o+	+	++	
C. kusei	-	o+	+	++	+++	
M. distortum	-	-	o+	+	++	
M. mceller	-	o+	+	++	+++	
P. chrysogenum	-	o+	+	++	+++	

- = No colony growth, o+ = MBC/MFC, + = Scanty colony growth, ++ = Moderate colony growth, +++ = Heavy colony growth

Microbes	10	5	2.5	1.25	0.625
S.aureus	-	o+	+	++	+++
S.pyogenes	-	o+	+	++	+++
P. eruginosa	R				
P. mirabilis	R				
C. kusei	-	o+	+	++	+++
M.distortum	R				
M.muceller	-	-	o+	+	++
P.chrysogenum	-	-	o+	+	++

**Table 9:** MBC/MFC values of Co(II) acetylacetonate on some pathogens (µg/mL)

A remarkable increase in the antimicrobial activity of the prepared complexes was observed relatively to the free ligand. The enhancement of the antimicrobial activity occurs due to synergy between the metal and ligand. This behaviour is explained on the basis of overtone concept of cell permeability and Tweedy's chelation theory (Ketan, et al., 2012; Emmanuel, et al., 2013). The overtone's concept explained that, cell membrane is made up of lipid layers that facilitate the passage of only lipid-soluble materials. In this regard, lipophilicity is an important factor that controls the antimicrobial activity. Tweedy's chelation theory on the other hand, explained that, the polarity of the metal ion is reduced by the overlap of ligand and metal orbitals. The overlap brings about partial sharing of positive charge of the metal ion with the donor atoms of the ligand. Hence the delocalisation of  $\pi$ -electrons increases on the chelate ring and improves the lipophilicity of the complexes. The increment in lipophilicity increases the penetration of the complex into cell lipid's membrane and blocks the metal binding sites on the enzymes of the microorganism. This might disturb the process of cell respiration and protein synthesis, therefore, inhibiting the growth and eventually death of the organism (Ketan, et al., 2012; Aderoju, et al., 2014; Aurora, at al., 2014). Contrary to this, some of the microbes are resistant to the metal complexes. The resistance could be due to lack of metal complex affinity for cellular components. Besides some microbes have genes that produce a metal ion-specific efflux protein or protein complex that limit the access of antimicrobial agents to its active site or enzyme(s) that is capable of altering antibiotics into a form less toxic to the organism cell (Jon and Lisa, 2014; Antonia et al., 2014). However, even though the prepared antibiotics have shown bio-activity, the potency is less compared to that of the standard drugs (ciprofloxacin and fulcin) used for combating these pathogens.

# Conclusion

The Mn(II) and Co(II) complexes were synthesised by using acetylacetone as a ligand. These complexes were characterised by various physio-chemical methods. Antimicrobial activity studies revealed that the metal complexes have a bio-activity on the tested microbes except *S. pyogenes, P. erginosa* and *P. mirabilis*. The bioactivity of the metal complexes is greater compared to its free ligand. The enhancement in the activity may be due to increased lipophilicity of the complexes. However, the potency of the prepared antibiotics is less compared to the standard drugs (ciprofloxacin and fulcin).

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