ejpmr, 2016,3(8), 321-325

SJIF Impact Factor 3.628

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Research Article

ISSN 2394-3211

EJPMR

MICROWAVE ASSISTED SYNTHESIS AND ANTI INFLAMMATORY ACTIVITY OF SCHIFF BASE COMPLEXES DERIVED FROM META CHLORO ANILINE AND SALICYLALDEHYDE

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Article Received on 24/05/2016 **Article Revised on 13/06/2016** **Article Accepted on 03/07/2016**

ABSTRACT

The ligand, (2-((3-chlorophenylamino)methyl)Phenol) was synthesized by microwave method and used for the preparation of Zn (II),Co (II),Fe (II),Cu (II),Mg(II) complexes these were identified by melting point ,TLC and characterised using infrared and UV Visible spectroscopy. The infrared spectra data of this ligand and its metal complexes show that the ligand is a bidentate molecule which coordinated to the metal ions through the azomethine nitrogen and to the adjacent alkenic carbon atom. Anti inflammatory activity was conducted for all synthesized compounds by using Inhibition of albumin denaturation method (In vitro method) diclofenac sodium as reference standard.

KEY WORDS: Ligand, metal, synthesis, Schiff base, Diclofenac.

INTRODUCTION

A significant growing attention in the synthesis of new metal complexes as drugs and symptomatic agents is presently observed in the field of medicinal inorganic chemistry.[1] A lot of research work in this field is mainly focused on the speciation of metal ions in the biological media based on the possible interaction of different metal ions with different bio molecules, which may lead to the development of new therapeutics or diagnostic agents.[2,3] Several reports revealed that a wide variety of metallic elements play a vital role in biological systems.[4-6] The characteristic property of metals is that they readily lose electrons from the familiar elemental/metallic states to form positively charge ions, which tend to be readily soluble in biological fluids and the metal in this cationic form play a role in the biological system. Metal ions are electron deficient, but most of the bio molecules such as DNA and proteins are electron rich. The general tendency of the attraction of these oppositely charged species will make these ions bind and interact with various bio molecules.[7] Biological activity of complexes derived from hydrazones has been widely studied and found to have numerous biological activities: antibacterial, antitumor, anti malarial and anti tuberculosis effects. Schiff bases are a significant group of organic compounds that have biological activities and diverse applications because of their antibacterial, antivirus activities, metal complexation and other Pharmacological activities.[8]

MATERIALS AND METHODS

All the starting chemicals and solvents were of analytical grade and used without further purification. The hydrated metal salts were obtained from Loba.

General method for the preparation of (Schiff base) Ligand-I {(2-((3-chlorophenylamino) methyl)Phenol)}

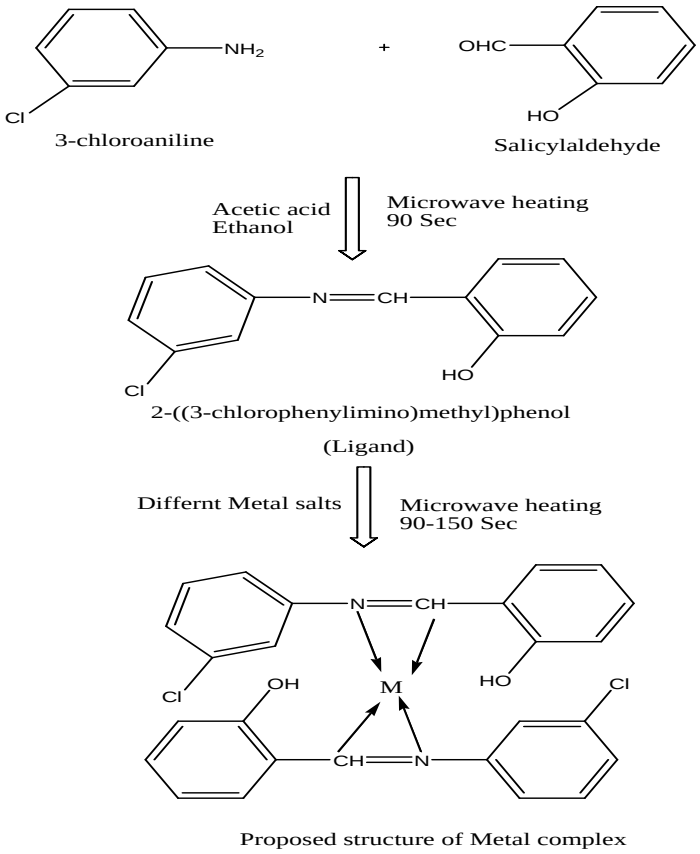
m-chloro aniline, 0.1mol was dissolved in 100 ml of ethanol containing few drops of glacial acetic acid. The salicylalehyde, 0.1 mol was added to the reaction mixture. It was heated in microwave for 90 seconds cooled and then poured into crushed ice. The solid obtained was filtered, washed with water and re crystallized with acetone. Mobile phase for TLC Chloroform: Ethanol (3:7).

General method for the preparation of final compounds (Metal Complexes)

To a stirred solution of step I, product (0.01 M) added 0.005 M. of inorganic metal salts and stirred for 5 minutes and subjected for microwave for 90-150 sec based on the different metal substances. After cooling product was separated from beaker, dried over sunlight and re crystallized by using different solvents. Different solvents are mentioned in Tab.No.1.

Tab.No.1: Different solvents used for re crystallization

S. No	Name of the metal salt	Recrystallization
1.	Zinc chloride	Ethanol
2.	Cobalt chloride	Chloroform
3.	Ferrous chloride	Acetone
4.	Copper twins	Ethanol
5.	Magnesium chloride	Ethanol, Acetone



Proposed structure of Metal complex

Scheme

Procedure for different metal complexes

Actually we prepared 5 different metal complexes by using single ligand, procedure is as follows:

1. **Preparation of (Ligand +Zn) L_2Zn:** To a stirred solution of step I, product (0.01 M) added 0.005 M. of inorganic metal salts and stirred for 5 minutes and subjected for microwave for 150 sec.
2. **Preparation of (Ligand +Co) L_2Co:** To a stirred solution of step I, product (0.01 M) added 0.005 M. of inorganic metal salts and stirred for 5 minutes and subjected for microwave for 140sec.
3. **Preparation of (Ligand +Fe) L_2Fe:** To a stirred solution of step I, product (0.01 M) added 0.005 M. of inorganic metal salts and stirred for 5 minutes and subjected for microwave for 90 sec.
4. **Preparation of (Ligand +Cu) L_2Cu:** To a stirred solution of step I, product (0.01 M) added 0.005 M. of inorganic metal salts and stirred for 5 minutes and subjected for microwave for 150 sec.
5. **Preparation of (Ligand +Mg) L_2Mg:** To a stirred solution of step I, product (0.01 M) added 0.005 M. of inorganic metal salts and stirred for 5 minutes and subjected for microwave for 60 sec. summary of synthesized compounds is shown in Tab. No 2, and Thin layer chromatography is shown in Tab. No.3.

Tab.No.2 Summary of synthesizing compounds

S.NO	Code	Mol. Formula	Mol.Wt	Colour	Melting Point	Solubility
1.	L	$C_{13}H_{10}NClO$	231.5	Yellow crystals	112°C	Chloroform
2.	L_2Zn	$(C_{13}H_{10}NClO)_2Zn$	531	Orange Yellow shiny crystasls	108°C	Acetone
3.	L_2Co	$C_{13}H_{10}NClO)_2co$	521	Shiny orange crystals	100°C	Ethanol, Acetone
4.	L_2Fe	$C_{13}H_{10}NClO)_2Fe$	518	Black crystals	92°C	Ethanol
5.	L_2cu	$C_{13}H_{10}NClO)_2Cu$	526	Pale Yellow crystals	70°C	Chloroform
6.	L_2Mg	$C_{13}H_{10}NClO)_2Mg$	484	Shiny pale yellow crystals	98°C	Chloroform

Tab. No.3: Summary of Thin layer chromatography and Their R_f values

S.No	Code	Mobile Phase	R_f value
1	L	Choroform: Acetone	0.65
2	L_2Zn	Acetone : Ethanol	0.54
3	L_2Co	Ethanol: Chloroform	0.64
4	L_2Fe	Ethanol: Chloroform	0.70
5	L_2cu	Choroform: Acetone	0.60
6	L_2Mg	Choroform: Acetone	0.62

Analytical methods for identification of synthesize compounds

Different absorbance values were obtained in UV-Visible spectroscopy which is performed for their identification with respect of formation of metal complex at specific wave number (342). Compounds were characterized by IR spectroscopy , here Imine (Schiff base or Ligand) was identified at 1580Cm^{-1} but after fusing slight change in the value 1620-1640 based on this phenomenon confirmed the reaction procedure and time, IR values and UV- Visible values are shown in **Tab. No.4 and 5.**

Tab. No.4: Summary of UV- Visible Spectral Data

S.No	Ligand/Complex	Wave length (nm)	Absorption maxima
1	L	342	0.360
2	L_2Zn	341,342,343,344	0.450
3	L_2Co	342	0.521
4	L_2Fe	342	0.211
5	L_2cu	342	0.434
6	L_2Mg	342,343	0.622

Tab. No.5: IR Values for synthesized compounds

S.No	Code	Molecular formula	IR Values (Cm^{-1})
1	Ligand (Schiff Bases)	$C_{13}H_{10}NClO$	Aromatic CH Str- 3040 Phenolic OH- 3600 Aromatic NH Str-(Broad)-3300-3400 Aromatic C-Cl- 700 Imine (-N=CH-)-**1580**
2	L_2Zn	$(C_{13}H_{10}NClO)_2Zn$	Aromatic CH Str-2920.23 Phenolic OH-3600 Aromatic NH Str- (Narrow)- 3421-3464 Aromatic C-Cl-752 Imine (-N=CH-)**1620**
3	L_2Co	$C_{13}H_{10}NClO)_2co$	Aromatic CH Str- 2920.23 Phenolic OH- Aromatic NH Str-(Narrow)-3433.29 Aromatic C-Cl- 752.24 Imine (-N=CH-)1620.21
4	L_2Fe	$C_{13}H_{10}NClO)_2Fe$	Aromatic CH Str-2924.09 Phenolic OH-3741.90 Aromatic NH Str-3441.01 Aromatic C-Cl-752.24 Imine (-N=CH-) **1627.92**
5	L_2cu	$C_{13}H_{10}NClO)_2Cu$	Aromatic CH Str-2920.23 Aromatic NH Str (Narrow)-3448.72 Aromatic C-Cl-752.24 Imine (-N=CH-) **1620.21**
6	L_2Mg	$C_{13}H_{10}NClO)_2Mg$	Aromatic CH Str-2920.23 Phenolic OH-3930.2 Aromatic NH Str-3347.2 Aromatic C-Cl-752.24 Imine (-N=CH-)-**1620.21**

Anti Inflammatory activity

Anti inflammatory activity was performed for synthesizing compounds using Inhibition of albumin denaturation method.

Procedure

Albumin denaturation assay was conducted as described by Biswakanth et al.[9] with slight modifications. The reaction mixture consisted of samples (Mg, Cu, Zn, Fe,Co) at single concentration (100 µg/ml) and 1 % bovine serum albumin (BSA) fraction prepared in saline phosphate buffer (pH = 7.4). The pH of the reaction mixture was adjusted to 6.8 using small amounts of glacial acetic acid. The test tubes were incubated at 72 ° C for 5 min and then cooled for 10 min. The absorbance of these solutions was determined using a spectrophotometer at a wavelength of 660 nm. The experiment was performed in triplicate. The percentage inhibition of precipitation (denaturation of the protein) was determined on a percentage basis relative to the control using the formula:

Percentage of inhibition denaturation = 100 – ($Absorbance_{sample}$/$Absorbance_{control}$) x 100

- Test solution (0.5 mL) consist of 0.45 mL of BSA (5 % w/v aqueous solution) and 0.05 mL of test solution (100 µg/mL).
- Test control solution (0.5 mL) consists of 0.45 mL of BSA (5 % w/v aqueous solution) and 0.05 mL of distilled water.
- Product control solution (0.5 mL) consists of 0.45 mL of distilled water and 0.05 mL of test solution (100 µg/mL).
- Standard solution (0.5 mL) consists of 0.45 mL of BSA (5 % w/v aqueous Solution and 0.05mL of Diclofenac sodium 100 µg/mL). The anti inflammatory results of synthesized metal complexes are shown in Tab. No.6.

Tab.No 6: Effect of synthetic compounds on BSA denaturation inhibitory activity, percentage inhibition compared to diclofenac sodium.

Test compound	Absorbance	Concentration	Inhibition percentage
L_2Zn	0.72	100 µg/ml	18%
L_2Co	0.69		32%
L_2Fe	0.68		34%
L_2cu	0.66		38%
L_2Mg	0.69		21%
Diclofenac sodium	0.36		56%
Control	0.826		

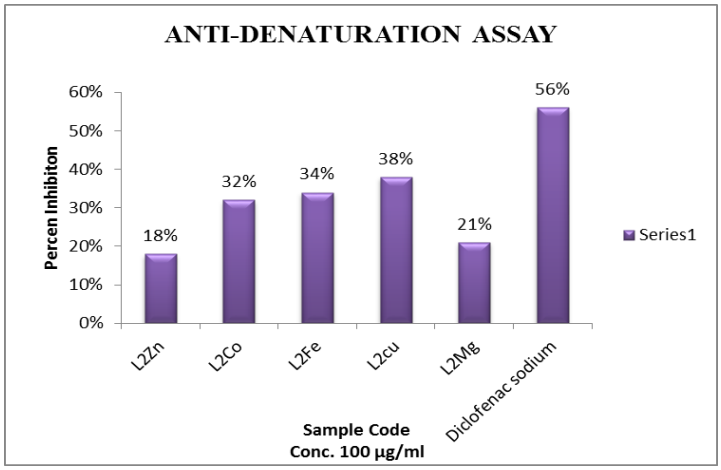


Fig. No 1: Albumin -denaturation assay of Synthesized compounds

RESULTS AND DISCUSSION

The new microwave assisted synthetic procedure was developed, title compounds were synthesized by the two step process, where in first step m-Chloroanilie was fused with Salicyladehyde (o- hydroxy benzaldehyde) in few drops of acetic acid and ethanol to get Shiff base (Imine or Ligand) , in second step various metal salts in half the concentration was fused with ligand and finally got metal complexes. Final compounds were re crystallized by different solvents. Compounds were identified by their colour, Melting point, Rf Values. (Thin layer chromatography) UV-Visible Spectroscopy and FT- IR studies. Synthesized compounds showed different melting and Rf values including Ligand. Different absorbance values were obtained in UV-Visible spectroscopy which is performed for their identification with respect of formation of metal complex at specific wave number (342). Compounds were characterized by Ir spectroscopy, here Imine (Schiff base or Ligand) was identified at $1580Cm^{-1}$ but after fusing slight change in the value 1620-1640 based on this phenomenon confirmed the reaction procedure and time. Finally synthesized compounds were screened for their in vitro anti inflammatory activity by Anti Denaturation

Assay method using diclofenac sodium as standard compound at specific concentration 100 µg/ml, among the synthesized compounds L_2Cu was shown good anti inflammatory activity when compared to standard, remaining compounds shown moderate anti inflammatory activity.

CONCLUSION

Microwave assisted synthesis of Metal complexes was developed where microwave irradiation offers significant improvements over existing procedures and thus helps facile entry into a synthesis of variety of metal complexes with short duration of time with good yields without formation of undesirable side products. All synthesized compounds were identified by their Physical and spectral studies and screened their anti inflammatory activity by Agar Denaturation method.

ACKNOWLEDGEMENTS

I thankful to Management and Principal of Annamacharya College of Pharmacy for providing me necessary facilities to carry out this research work.

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