DECLARATION

I, SEENA THOMACHAN hereby declare that the thesis, entitled “Synthesis, Characterization and Biological Applications of Transition metal chelates of 1,7-Diarylheptanoids” submitted to the University of Calicut, in partial fulfillment of the requirements for the Degree of Doctor of Philosophy in Chemistry, is an authentic record of the research work carried out by me under the supervision and guidance of Dr. John V. D, Associate Professor (Rtd), Department of Chemistry, Christ College, Irinjalakuda, Kerala and further that no part thereof has been presented before for any other Degree.

SEENA THOMACHAN
ACKNOWLEDGEMENT

I express my heartfelt gratitude and deep indebtedness to my supervising teacher, Dr. John V. D, Associate Professor, Christ College, Irinjalakuda, Kerala for his inspiring and intellectual guidance, healthy criticism, whole hearted support, personal care, attention and immense patience of the great scholar that made me confident throughout the course of this investigation. Actually, no words can express my deep feelings towards him.

I am extremely grateful to Rev. Fr. Jose Thekkan C.M.I, Principal, Christ College for providing opportunity to opt Christ College as research centre, sincere support and help extended to me during my research work.

I wish to extend my sincere thanks to Dr. Mathew Paul Ukken, Head, Department of Chemistry, Christ College, and former heads of department, Prof. Rappai, Prof. T.I. Johnson and Prof. Babu Antony for their support and encouragement throughout the course of my work.

I am extremely grateful to all the teaching and non-teaching staff of Department of Chemistry, Christ College, Irinjalakuda, for their whole hearted co-operation.

I am extremely thankful to the Principal and Staff, Sreerama Govt. Polytechnic College, Thriprayar for the sincere support and help extended to me in this tough venture. I express my heartfelt gratitude to my friends Dhivya, Athira, Shanu, Sreejith, Saneesh and Srutheej for the generous encouragement and whole hearted support till the exciting finish of my investigation.

I am sincerely grateful to my fellow research scholars, especially to my co-worker S.Sindhu for their valuable advice and timely help during the tenure of my study.

I am extremely thankful to Dr. Ramdaskuttan, Professor, Amala Cancer Research Institute, Thrissur and Biotechnology department, St.Mary’s College, Thrissur and St.Josephs College, Irinjalakuda for the valuable suggestion and help in antitumor, antimicrobial studies.

I wish to extend my thanks to STIC, Kochi, SAIF, IIT, Mumbai, CDRI Lucknow, NIIST Thiruvananthapuram and St. Thomas College, Thrissur for the instrumental facilities made available to me for analysis.

Words are not enough to thank my beloved parents and my family members for their love prayers, support and encouragement for the successful completion of thesis. I express my
heartfelt gratitude to my husband Joju Sebastian and my children Rohith and Tom for their enthusiastic support, constructive guidance that made me confident in taking up the challenging field of research.

Finally, a word of thanks to the spirit of truth for the providential care bestowed on me during the investigation.

SEENA THOMACHAN
DEDICATED

TO

MY FAMILY
PREFACE

The use of plants and their active principles in the prevention and treatment of chronic diseases is based on experience of traditional system of medicine. The potential of medicinal plants as source for new drugs is still largely unexplored. Now a days there is wide spread interest in drugs derived from plants. This interest primarily stems from the belief that green medicine is safe and dependable compared to synthetic drugs. One among the few medicinal plants that has been the subject of scientific investigation is the Turmeric (*Curcuma longa* Linn). Turmeric and its active chemical constituents, curcuminoids have been reported to possess a wide spectrum of biological actions such as antinflammatory, antioxidant, anticancer, antidiabetic, antiallergic, antiviral, antiprotozoal, antibacterial and antifungal activities. Curcumin, the bioactive yellow orange pigment is the most important fraction which is responsible for the biological activities of turmeric. The utility of curcumin is limited by its colour, lack of water solubility and relatively low invivo bioavailability. Structurally curcuminoids are 1,7-diaryl heptanoids. They are a group of naturally occurring 1,3-diketones in which diketo function is directly attached to olefinic groups. It has three chemical entities in its structure, two aromatic ring systems containing o-methoxy phenolic groups connected by a seven carbon linker consisting of an $\alpha$- $\beta$ unsaturated $\beta$-diketone moiety. They are ideally suited to act as chelating ligands towards a variety of metals and to form complexes similar to diketones. Literature review has revealed the enhanced biochemical activities of synthetic analogues of curcuminoids and their metal complexes especially as cytotoxic, antibacterial and antifungal agents. The present study is mainly on the synthesis and characterization of a series of curcuminoid analogues (1,7-diaryl heptanoids) and their metal complexes with Cu(II), Zn(II), Ni(II) and VO(IV). The cytotoxic, antitumour, antibacterial and antifungal activities of these compounds and their metal complexes were also studied. The thesis is divided into four parts.
Part I. Introduction

The medicinal properties of Turmeric have been attributed mainly due to Curcumin, the bioactive yellow orange pigment. Curcumin has already been the subject of several clinical trials and has been reported to possess medicinal properties. Curcumin is one of the most potent and multi targeting phytochemical against a variety of diseases. Synthetic chemical modifications of curcumin have been studied intensively to identify compounds with similar or enhanced properties of curcumin. Fourteen curcuminoid analogues structurally related with natural curcumin were synthesized in the present work. In the synthesized compounds the α,β unsaturated diketo moiety is retained as such without modification and the phenyl ring part in natural curcumin has been modified. The phenyl ring part has been substituted with heterocyclic rings, polynuclear rings, substituted polynuclear rings trisubstituted and disubstituted phenyl rings with substituents different from that of natural curcumin. The structural and spectral properties were studied by UV, IR, $^1$H NMR, $^{13}$C NMR, 2D-COSY NMR, Mass Spectral techniques etc. Research in the field of coordination chemistry of biologically important ligands and their synthetic analogues has gained considerable momentum in recent years. It has been revealed that the biological significance of these ligands is enhanced by complex formation with metal ions. Curcuminoids are excellent chelating ligands which can bind with metal ions to form stable metal complexes. Metal complexation of these α,β –unsaturated 1,3-diketones has led to effective changes in their biological activities including antitumour, antibacterial and antifungal activity. In the present investigation transition metal ions namely $\text{Cu}^{2+}, \text{Zn}^{2+}, \text{Ni}^{2+}$ and $\text{VO}^{2+}$ were complexed with synthetic curcuminoid analogues. Biological activities investigated in the present work include Cytotoxic activity, antibacterial activity and antifungal activity of synthesized compounds.
Part II. Literature Review

This part includes the review of literature related with the chemical and biological studies of curcuminoids, its allied derivatives and metal chelates. The biological activities of curcuminoids like antiinflammatory, antioxidant, antiprotozoal, nematocidal, anti-bacterial antiviral, antitumour activity etc are discussed in this part. The importance of synthetic analogues of curcumin and the metal complexes as biologically significant agents have been well established. Studies related with the cytotoxic nature of curcuminoid analogues and their metal chelates have been extensively discussed in this part. The enhanced pharmacological significance of the compounds due to complexation has also been revealed in this part. This part explains the necessity of synthesis of curcumin analogues and their metal chelates and their biological significance.

Part III. Materials, Methods and Experimental techniques

This part is a general description on various chemicals and methods employed, instruments used and various experimental techniques. The methods used for the synthesis of curcuminoid analogues, their transition metal chelates and purification of compounds are given. Various spectral techniques involved in characterization of the compounds have been explained. The biological studies conducted include In Vitro cytotoxic study, In Vivo antitumour study, effect of compounds on solid tumour, Antibacterial and Antifungal studies. Materials, cell lines, animals, chemicals, methods etc employed in the studies are given.

Part IV. Synthesis, Characterization and Biochemical activities of 1,7-diaryl heptanoids

This part is divided into six chapters. Each chapter is further divided into five sections.

Chapter I. The chapter deals with the Synthesis, Characterization and Biochemical activities of methyl substituted 1,7-diaryl heptanoids and their Transition metal chelates.

Section I: Synthesis and Characterization of 1,7-bis(2-methyl phenyl)hepta-1,6-diene-3,5-dione(1a) and 1,7-bis(2,5-dimethyl phenyl) hepta-1,6-diene-3,5-dione(1b).
Section II: Synthesis and Characterization of Transition metal chelates of 1,7-bis(2-methyl phenyl) hepta-1,6-diene-3,5-dione(1a) and 1,7-bis(2,5-dimethyl phenyl) hepta-1,6-diene-3,5-dione(1b) with Cu(II), Zn(II), Ni(II) and VO(IV). ESR Spectrum of Cu(II) complex is also included.

Section III: Antitumour studies of Methyl substituted 1,7-diaryl heptanoids and the transition metal chelates. The studies include Invitro cytotoxic study of ligands and their metal complexes [Cu(II), Zn(II), Ni(II) and VO(IV)] by Trypan blue dye exclusion method. In vivo antitumour studies were conducted in mice with the ligand 1,7-bis(2,5-dimethyl phenyl)-1,6-heptadiene-3,5-dione (1b) and its Cu(II) & VO(IV) complexes. The ligands 1a and 1b and their copper complexes were used to find the effect on solid tumour development in mice.

Section IV: Antibacterial studies of methyl substituted 1,7-diaryl heptanoids and their Cu(II), Zn(II) and Ni(II) metal complexes.

Section V: Antifungal studies of methyl substituted 1,7-diaryl heptanoids and their Zn(II) and VO(IV) metal complexes.

Chapter II. The chapter deals with the Synthesis, Characterization and Biochemical activities of 1,7-dithiophenyl heptanoids and their Transition metal chelates.

Section I: Synthesis and Characterization of 1,7-di(thiophen-2-yl)hepta-1,6-diene-3,5-dione (2a) and 1,7-bis(3-methyl thiophen-2-yl) hepta-1,6-diene-3,5-dione (2b).

Section II: Synthesis and Characterization of Transition metal chelates of 2a and 2b with Cu(II), Zn(II), Ni(II) and VO(IV).

Section III: Antitumour studies of 1,7-dithiophenyl heptanoids and the transition metal chelates. The studies include Invitro cytotoxic study of ligands and their metal complexes [Cu(II), Zn(II), Ni(II) and VO(IV)] by Trypan blue dye exclusion method towards DLA and EAC cell lines. In vivo antitumour studies were conducted in mice with the ligands 2a and 2b.
and their Cu(II) complexes. The effect of ligands 2a and 2b and their copper complexes on solid tumour development in mice were also studied.

Section IV: Antibacterial studies of 1,7-dithiophenyl heptanoids and their Zn(II),Ni(II) and VO(IV) metal complexes.

Section V: Antifungal studies of 1,7-dithiophenyl heptanoids and their Zn(II) and VO(IV) metal complexes.

Chapter III. The chapter deals with the Synthesis, Characterization and Biochemical activities of chloro substituted 1,7-diaryl heptanoids and their Transition metal chelates.

Section I: Synthesis and Characterization of 1,7-bis(4-chloro phenyl) hepta-1,6-diene-3,5-dione(3a),1,7-bis(4-chloro phenyl) hepta-1,6-diene-3,5-dione(3b), 1,7-bis(4-chloro phenyl) hepta-1,6-diene-3,5-dione(3c). They were characterized by UV, IR, $^1$H NMR, $^{13}$C NMR and Mass spectral techniques.

Section II: Synthesis and Characterization of Transition metal chelates of 3a, 3b and 3c with Cu(II),Zn(II),Ni(II) and VO(IV).

Section III: Cytotoxic and Antitumour studies of chloro substituted 1,7-diphenyl heptanoids and their transition metal chelates. The studies include Invitro cytotoxic study of ligands and their metal complexes [Cu(II),Zn(II),Ni(II) and VO(IV)]by Trypan blue dye exclusion method towards DLA and EAC cell lines. In vivo antitumour studies were conducted in mice with the ligand 1,7-bis(4-chloro phenyl) hepta-1,6-diene-3,5-dione(3a) and their Cu(II) and Zn(II) complexes.

Section IV: Antibacterial studies of chloro substituted 1,7-diphenyl heptanoids and their Zn(II),Cu(II) and VO(IV) metal complexes.

Section V: Antifungal studies of chloro substituted 1,7-diphenyl heptanoids and their VO(IV) metal complexes.
**Chapter IV.** The chapter deals with the Synthesis, Characterization and Biochemical activities of 1,7-diaryl heptanoids with di and tri substituted phenyl ring and their Transition metal chelates.

Section I: Synthesis and Characterization of 1,7-bis(3-ethoxy-4-hydroxyphenyl)hepta-1,6-diene-3,5-dione(4a), 1,7-bis(2,4-dihydroxy phenyl)hepta-1,6-diene-3,5-dione(4b), and 1,7-bis(3,4,5-trimethoxy phenyl)hepta-1,6-diene-3,5-dione(4c). They were characterized by UV, IR, \(^1\)H NMR, \(^{13}\)C NMR, 2D COSY and Mass spectral techniques.

Section II: Synthesis and Characterization of Transition metal chelates of 4a, 4b and 4c with Cu(II), Zn(II), Ni(II) and VO(IV). The metal chelates were also characterised by various spectral techniques.

Section III: Cytotoxic and Antitumour studies of curcuminoid analogues with di and tri substituted aryl rings and their transition metal chelates. The studies include Invitro cytotoxic study of ligands and their metal complexes [Cu(II), Zn(II), Ni(II) and VO(IV)] by Trypan blue dye exclusion method towards DLA and EAC cell lines. *In vivo* antitumour studies were conducted in mice with the ligands 1,7-bis(2,4-dihydroxyphenyl)hepta-1,6-diene-3,5-dione(4b), 1,7-bis(3,4,5-trimethoxy phenyl)hepta-1,6-diene-3,5-dione(4c) and their Cu(II) complexes.

Section IV: Antibacterial studies of 1,7-diphenyl heptanoids with di and tri substituted phenyl ring and their Zn(II), Cu(II) and VO(IV) metal complexes.

Section V: Antifungal studies of 1,7-diphenyl heptanoids with di and tri substituted phenyl ring and their VO(IV) metal complexes.

**Chapter V.** The chapter deals with the Synthesis, Characterization and Biochemical activities of 1,7-dianthracenyl heptanoids and their Transition metal chelates.
Section I: Synthesis and Characterization of 1,7-bis(9-anthracenyl)hepta-1,6-diene-3,5-dione(5a). The ligand was characterized by UV, IR, $^1$H NMR, $^{13}$C NMR and Mass spectral techniques.

Section II: Synthesis and Characterization of Transition metal chelates of 5a with Cu(II), Zn(II), Ni(II) and VO(IV). The metal chelates were also characterised by various spectral techniques.

Section III: Cytotoxic and Antitumour studies of curcuminoid analogues with anthracenyl ring and its transition metal chelates. The studies include Invitro cytotoxic study of ligand and its metal complexes [Cu(II), Zn(II), Ni(II) and VO(IV)] by Trypan blue dye exclusion method towards DLA and EAC cell lines. In vivo antitumour studies were conducted in mice with the ligand and its Cu(II) and VO(IV) complexes. Invivo cytotoxic study on solid tumour development was conducted with the ligand and its Cu(II) complex.

Section IV: Antibacterial studies of 1,7-dianthracenyl heptanoid and their Zn(II), Cu(II) and VO(IV) metal complexes.

Section V: Antifungal studies of 1,7-dianthracenyl heptanoids and their VO(IV) metal complexes.

Chapter VI. The chapter deals with the Synthesis, Characterization and Biochemical activities of curcuminoid analogues with naphthyl and substituted naphthyl ring and their Transition metal chelates.

Section I: Synthesis and Characterization of 1,7-dinaphthyl-1,6-heptadiene-3,5-dione(6a), 1,7-bis(2-methoxynaphthyl)1,6-heptadiene-3,5-dione(6b), 1,7-bis(2-hydroxynaphthyl)1,6-heptadiene-3,5-dione(6c). They were characterized by UV, IR, $^1$H NMR, $^{13}$CNMR, 2D COSY and Mass spectral techniques. Thermogravimetric and magnetic studies were done.
Section II: Synthesis and Characterization of Transition metal chelates of 6a, 6b and 6c with Cu(II), Zn(II), Ni(II) and VO(IV). The metal chelates were also characterised by various spectral techniques. ESR Spectrum of Cu(II) complex is included.

Section III: Cytotoxic and Antitumour studies of curcuminoid analogues with substituted naphthyl rings and their transition metal chelates. The studies include Invitro cytotoxic study of ligands and their metal complexes [Cu(II), Zn(II), Ni(II) and VO(IV)]by Trypan blue dye exclusion method towards DLA and EAC cell lines. In vivo antitumour studies were conducted in mice with the ligands 1,7-bis(2-methoxynaphthyl)1,6-heptadiene-3,5-dione (6b), 1,7-bis(2-hydroxynaphthyl)1,6-heptadiene-3,5-dione (6c) and their Cu(II) complexes.

Section IV: Antibacterial studies of 1,7-dinaphthyl heptanoids and their Zn(II), Cu(II) and VO(IV) metal complexes.

Section V: Antifungal studies of 1,7-dinaphthyl heptanoids and their VO(IV) metal complexes.
LIST OF PUBLICATION


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ABBREVIATIONS

ROS  —  Reactive Oxygen Species
COX-2 — Cyclooxygenase 2
LOX  —  Lipoxygenase
NF-κB — Nuclear Factor kappa B
cPLA  —  Cytosolic Phospholipase
HBC  —  Hydrazinobenzoylcurcumin
DMC  —  Demethoxy curcumin
BDMC — BisDemethoxy curcumin
iNOS — inducible nitric oxide synthetase
GST  —  Glutathione S-transferase
AD   —  Alzheimer’s disease
DMSO — Dimethyl Sulphoxide
EAC  —  Ehrlich Ascites Carcinoma
COSY — Correlation Spectroscopy
DLA  —  Daltons Lymphoma Ascites
ILS  —  Increase in life span
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