Synthesis, characterization and biological studies of oxovanadium(IV) and zinc(II) complexes of mixed ligands of sulfadiazine and dithiocarbamate

Ayodele Temidayo ODULARU

Department of Chemistry

Faculty of Science and Agriculture

University of Fort Hare

Together in Excellence

January 2016

Synthesis, characterization and biological studies of oxovanadium(IV) and zinc(II) complexes of mixed ligands of sulfadiazine and dithiocarbamate

By

Ayodele Temidayo ODULARU (Student Number: 201106223)

B. Sc. (Hons), M.Sc. Chemistry (Ibadan, Nigeria)

Being a thesis submitted to the Faculty of Science and Agriculture in fulfilment of the requirements for the award of the degree of

Doctor of Philosophy

of the

University of Fort Hare.

Supervisor: Professor P. A. Ajibade

January 2016

.

Declaration by Candidate on Plagiarism

I, Ayodele Temidayo **Odularu**, declare that:

1. The research in this thesis, except where otherwise indicated, is my original research.
2. This thesis has not been submitted for any degree or examination at other university.
3. This thesis does not contain any other person data unless specifically acknowledged as being sourced from them.
4. This thesis does not contain any other persons' writing, unless specifically acknowledged as being sourced from other researchers. Where other written sources have been quoted, then:
    a. Their words have been re-written but the general information attributed to them has been properly referenced.
    b. In all instances where the exact words of other authors have been used, then their writing has been placed in italics and inside quotation marks, and referenced.
5. This thesis does not contain text or graphics from the internet copied and pasted, unless specifically acknowledged, and the source being detailed in the thesis and in the references section.

A.T. Odularu_____ Ayodele Temidayo Odularu

Date 12 April, 2016

.

Certification

This is to certify that this research is a record of original work carried out by Ayodele Temidayo **Odularu** under my supervision in the Inorganic Materials Research laboratory of the Department of Chemistry, University of Fort Hare in fulfilments of the requirements for the award of Doctor of Philosophy degree in Chemistry.

_____ _____

Date Supervisor

P. A. Ajibade
Professor of Inorganic Materials Chemistry
B. Sc (Hons), MSc (Ibadan);
PhD (UniZul); MRSC (London)

.

Dedication

This research is dedicated to Almighty Jehovah, The Merciful.

.

Acknowledgements

First to be acknowledged is, THE Holiest One, The Most High Jehovah, The All Knowing, Greatest of The Greatest, The I Am that I Am, The Creator, The Wisest God of gods, The Original Chemist, Whose help, presence, guidance and mercies saw me throughout this research programme.

My appreciation goes to my Supervisor, Professor P. A. Ajibade, for the provision of funding, opportunity and privilege to work in his research area. I seize this medium to say, "Sir, I am extremely indebted to you". The funding body, Govan Mbeki Research and Development Foundation, (GMRDC), thank you very much for the financial assistance provided for the research through supervisor linked bursary. In addition to this, I thank, University of Fort Hare, my Institution which anchored the funding body and created the enabling environment for the period of study.

My sincere appreciation goes to my parents and siblings for your prayers, love and motivation. The Good Jehovah will continue to bless you mightily. Amen. This medium serves as a means to acknowledge all members of staff of Chemistry Department, University of Fort Hare. I also appreciate my colleagues in Inorganic Material Research (IMR) group. My utmost appreciation goes to Appointments and Promotions (Academic) Committee of Crawford University for their support to me and their approval of my doctoral research study in South Africa.

I am indebted to Professor Ondari, Daddy Khayundi, Aunt Maria Smith, Sis. Caroline Kukubo, Pastor (Dr.) Wilfred Otang Mbeng, Professor Luigi Casella and Dr. Eliana Lo Presti (University of Pavia, Italy), Professor Albert Bolhuis (University of Bath, United Kingdom), Dr. Laura Santagostini (Milano University, Italy), Prof. Dr. Michal Dusek (Academy of Sciences, Czech Republic), Mrs Benedicta Ajibade, Bro. Patrick Ajibade, Bro. Idowu Seriki, Bro. Ayodele Ladokun, Dr. Mbiji Mahlangu, Professor Horst Puschmann, Mrs Mzambo, Miss Fasi and Mrs Magalela, for their contribution in diverse ways in the course of my study.

.

Table of Contents

Declaration by Candidate on Plagiarism....iii
Certification....iv
Dedication....v
Acknowledgements....vi
Table of Contents....vii
List of Figures....xii
List of Tables....xiv
List of Schemes....xvi
Abbreviations and Symbols....xix
Research Outputs....xxiv
Abstract....xxv
CHAPTER 1....1
1.0 Introduction and literature review....1
1.1 Metal-based drugs....1
1.2 Medicinal uses of metals and their compounds....1
1.3 Rationale for the choice of metals in the current study....5
1.4 Vanadium....5
1.4.1. Chemistry of vanadium metal....5
1.4.2 Vanadium compounds and their biological applications....6
1.4.3 Vanadium as insulin-mimetic agent....7
1.4.4 Vanadium as anticancer agent....9
1.4.4.1 Different oxidation states of vanadium and DNA damage....9
1.4.5 Vanadium as antimicrobial agent....10
1.4.6 Health impacts and toxicity of vanadium....10
1.5 Zinc....11
1.5.1. The chemistry of zinc....11
1.5.2. Biological relevance and the use of zinc compounds as insulin-mimetic agents....11
1.5.3 Zinc and its compounds as anticancer and antimicrobial agents....12
1.5.4 Health impacts and toxicity of zinc....12
1.6 Ligands....13

.

1.6.1 Heterocyclic bidentate ligands....13
1.6.2 Sulfadiazine and its relevance to medicine....13
1.6.3 Dithiocarbamate and its relevance to medicine....14
1.7 Metal complexes....15
1.7.1 Metal complexes and their therapeutic applications....18
1.7.1.1 Antiarthritic agents....18
1.7.1.2 Anticancer agents....18
1.8 Types of cancer....18
1.8.1 Chronological order and methods of treatment for cancer....19
1.8.1.1 Surgery....19
1.8.1.2 Radiation therapy....19
1.8.1.3 Biology therapy....19
1.8.1.4 Alternative therapy....19
1.8.1.5 Chemotherapy....20
1.8.2 Aims of cancer therapy....22
1.8.2.1 Anticancer agents....22
1.8.2.2 Classification of anticancer drugs and subdivisions....22
1.8.3 The subdivisions of major anticancer drugs are....22
1.8.3.1 Hormonal drugs....22
1.8.3.2 Targeted drugs....23
1.8.3.3 Cytotoxic drugs....23
1.8.4 Challenges and side effects of anticancer drugs....23
1.8.5 Rationale for cytotoxic drugs....23
1.9 Antimicrobial agents....25
1.9.1 Antibiotic treatment....25
1.9.2 Antifungal treatment....26
1.9.3 Antiviral treatment....26
1.9.4 Types of antimicrobial test....26
1.9.5 Antimicrobial resistance and tests for the resistance detection....26
1.9.6 Control of microorganisms....26
1.10 Problem statement....28
1.11 Hypotheses....28
1.9 Aims of the research....28
CHAPTER 2....30
2. Experimental....30
2.1 Experimental materials, laboratory instrumentation, syntheses and characterization of Ligands....30

.

2.1.1 Standard (Traditional) method....30
2.1.2 One-pot synthesis....31
2.2 Experimental materials and instrumentation....31
2.2.1 Experimental materials....31
2.2.2 Solvents....32
2.3 Physical measurements....32
2.3.1 Melting point (MP)....32
2.3.2 Molar conductivity (MC)....32
2.3.3 Elemental analysis (EA)....32
2.3.4 Fourier transforms infrared spectroscopy (FT-IR)....33
2.3.5 Ultraviolet-Visible spectroscopy (Electronic spectroscopy)....33
2.3.6 Nuclear Magnetic Resonance (NMR)....33
2.4. Synthesis and characterization of ligands of dithiocarbamates....34
2.4.1 Materials and instrumentation....34
2.4.2 Sodium sulfadiazine, $C_{10}H_9N4NaO_2S$....34
2.5. General methods for the syntheses of ligands of dithiocarbamates....34
2.5.1 Ammonium salts of dithiocarbamates from aliphatic, cyclic aliphatic and aromatic amines....35
2.5.2 Sodium salts of dithiocarbamates from aliphatic, cyclic aliphatic and aromatic amines....35
2.5.3 Ammonium salts of dithiocarbamates from aliphatic amines....36
2.5.4. Sodium salts of dithiocarbamates from aliphatic amines....41
2.5.5. Sodium salt of dithiocarbamates from cyclic aliphatic amines....45
2.6 Results and discussion....51
2.6.1 Physicochemical characterization studies of ligands (sodium sulfadiazine and derivatives of dithiocarbamates)....51
2.6.2 Elemental Analysis....55
2.6.3 Molecular spectroscopy....56
2.7 Conclusion....68
CHAPTER 3....69
3. Synthesis of oxovanadium(IV) complexes of mixed sulfadiazine and dithiocarbamates....69
3.1 Introduction....69
3.2 Materials and Methods....71
3.2.1 Experimental materials....71
3.2.2 Instrumentation....72

.

3.3 Methods....72
3.3.1 Synthesis of oxovanadium(IV) complexes from sodium sulfadiazine (L_1) and derivatives of dithiocarbamate (L_2-DTC)....72
3.4 Results and discussion....84
3.4.1 Syntheses....84
3.4.2 Elemental Analysis....86
3.4.3 Molecular Spectroscopy....88
3.4 Conclusion....98
CHAPTER FOUR....99
4. Preparation and spectral characterization of zinc(II) complexes of mixed sulfadiazine and dithiocarbamate....99
4.1. Introduction....99
4.2 Materials and Methods....100
4.2.1 Experimental materials and instrumentation....100
4.2.2 Methods....102
4.3 Results and discussion....121
4.3.1 Syntheses....121
4.3.2 Spectral studies (Elemental Analysis (EA), Fourier Transform Infra-red spectroscopy (FT-IR), Ultraviolet-Visible Spectroscopy (UV-Vis) and Nuclear Magnetic Resonance (NMR)....122
4.3.3 Molecular Spectroscopy....125
4.4 Conclusion....142
CHAPTER FIVE....143
5. Anticancer and antimicrobial activities of oxovanadium(IV) and zinc(II) complexes....143
5.1 Introduction....143
5.1.1 *In vivo* techniques....143
5.1.2 *Ex vivo* techniques....143
5.1.3 *In vitro* techniques....144
5.2. *In vitro* anticancer screening of dithiocarbamate ligands and some mixed ligand metal complexes of oxovanadium(IV) and zinc(II) ions....144
5.2.1 Materials and reagents and equipment using cytotoxicity assay of Water Soluble Tetrazolium Salt, (WST-1)....144
5.2.2 Results and discussion on *in vitro* WST-1 assay cytotoxicity studies....146
5.3 *In vitro* cytotoxicity (SRB) assay cancer screening of some oxovanadium(IV) and zinc(II) complexes....147
5.3.1 Assay Background....147

.

5.3.2 Materials and method. 148
5.3.3 Results and discussion on *in vitro* SRB assay cytotoxicity studies. 148
5.4 *In vitro* cancer screening 150
5.4.1 Sulforhodamine B (SRB) assay background of *in vitro* cancer screening 150
5.4.2 Materials and method 151
5.4.3 *In vitro* cancer screening studies. 151
5.5. Antibacterial studies 154
5.5.1 Materials and methods for antibacterial studies. 154
5.5.2 Minimum Inhibitory Concentration (MIC) 154
5.6 *In vitro* studies. 156
5.6.1 Antibacterial studies 157
5.6.2 Minimum Inhibition Concentration (MIC) 164
5.7 Conclusion 167
CHAPTER SIX 169
6. Summary of results, conclusion and future prospects 169
6.2 Conclusion 171
6.3 Future prospects.. 171
6.4 Chemical characterization 171
6.5 Other microbiological activities. 172
6.6 Cytotoxity test 172
6.7 Insulin mimetic activities 172
REFERENCES 173

.

List of Figures

Figure 1.1: The mechanism of action of vanadium as insulin mimetic agent 8

Figure 1.2: Chemical structure of sodium sulfadiazine. 14

Figure 1.3: Molecular structures of $VO(N_2S_4)$, $VO(S_2O_2)$, $VO(S_4)$, and $VO(O_4)$.....16

Figure 1.4: Molecular structures of synthesized zinc(II) complexes of N_2O_2, S_2O_2, N_4 and O_4.....17

Figure 1.5: History of cancer chemotherapy from 1900-2015 21

Figure 1.6: Paclitaxel (Taxol) 23

Figure 1.7: Mustard gas Figure 1.8: Nitrogen mustard.....24

Figure 1.9: Historical use of antimicrobial agents..... 27

Figure 2.1: Canonical forms of dithiocarbamate moiety.....57

Figure 2.2: Infra- red spectrum of SFZ in the FT-IR.....60

Figure 2.3: Infra- red spectrum of cy-DTC in the FT-IR.....61

Figure 2.4: Infra- red spectrum of an-DTC in the FT-IR.....61

Figure 2.5: UV-Vis spectrum of he-DTC in solvents of dimethylsulfoxide (d), methanol (m) and water (w).....63

Figure 2.6: UV-Vis spectrum of cy-DTC in solvents of dimethylsulfoxide (d), methanol (m) and water (w).....63

Figure 2.7: The UV-Vis spectrum of et-DTC in solvents of dimethylsulfoxide (d), methanol (m) and water (w).....64

Figure 2.8: The 1H NMR of sodium sulfadiazine in ppm in DMSO-d6solvent.....65

Figure 2.9: The ^{13}C NMR of sodium sulfadiazine in ppm in DMSO-d6solvent 67

Figure: 2.10: The ^{1}H NMR of cy-DTC in ppm in DMSO-d6 solvent.....67

Figure 2.11: The ^{13}C NMR of me-DTC in ppm in DMSO-d6solvent 68

Figure 3.1: The three diagrams are (a) square bipyramidal, (b) square pyramidal and (c) trigonal bipyramidal.....70

Figure 3.2: The FT-IR of [VO(SFZ)(cy-DTC)] and the corresponding ligands.....94

Figure 3.3: The FT-IR of merged SFZ, me-DTC and [VO(SFZ)(me-DTC)] and the corresponding ligands.....95

Figure 3.4: The UV-Vis spectra of oxovanadium(IV) complexes and their corresponding ligands of SFZ, cy-DTC and [[VO(SFZ)(cy-DTC)].....96

Figure 3.5: The UV-Vis spectra of oxovanadium(IV) complexes and their corresponding ligands of SFZ, cy-DTC and [[VO(SFZ)(me-DTC)].....97

.

Figure 4.1: Merged FT-IR spectra of SFZ, cy-DTC and [Zn(SFZ)(cy-DTC)].....127
Figure 4.2: Merged FT-IR spectra of SFZ, me-DTC and [Zn(SFZ)(me-DTC)] 127
Figure 4.3: UV-Vis spectra of SFZ, cy-DTC and [Zn(SFZ)(cy-DTC)] 129
Figure 4.4: UV-Vis spectra of SFZ, me-DTC and [Zn(SFZ)(me-DTC)] 129
Figure 4.5: The ^{1}H NMR of [Zn(SFZ)(bt-DTC)] in ppm in DMSO-d_6 solvent.....137
Figure 4.6: The ^{13}C NMR of [Zn(SFZ)(bt-DTC)] in ppm in DMSO-d_6 solvent. 142

.

List of Tables

Table 1.1: Summary of metal-based drugs. 2

Table 2.1: Physicochemical characterization data of sodium sulfadiazine and derivatives of dithiocarbamates.....53

Table 2.2: Analytical data for elemental analysis of ammonium and sodium salts of ligands of dithiocarbamates.....56

Table 2.3: The FT-IR frequencies (cm^{-1}) for sodium sulfadiazine.....59

Table 2.4: The FT-IR wavenumbers (cm^{-1}) of derivatives of dithiocarbamates 61

Table 3.1: Physicochemical characterization studies of all oxovanadium(IV) complexes of sodium sulfadiazine and derivatives of dithiocarbamates.....85

Table 3.2: Elemental analysis of oxovanadium(IV) complexes of mixed ligands of sodium sulfadiazine and derivatives of dithiocarbamates.....87

Table 3.3: FT-IR frequencies (cm^{-1}) for sodium sulfadiazine ligated oxovanadium(IV) complexes and dithiocarbamates ligated oxovanadium(IV) complexes.....91

Table 4.1: Elemental analyses of zinc(II) complexes of mixed ligands of sodium sulfadiazine and derivatives of dithiocarbamate.....123

Table 4.2: The ^{1}H NMR of sodium sulfadiazine ligated zinc(II) complexes and dithiocarbamate ligated zinc(II) complexes in ppm in DMSO-d6 solvent.....132

Table 4.3: The ^{13}C NMR of zinc(II) complexes in ppm in DMSO-d6 solvent.....138

Table 5.1: Secondary screening results for both cell lines (KMST-6 and HT-29) and their selectivity indices.....147

Table 5.2: The in vitro cytotoxicity screening for oxovanadium(IV) and zinc(II) complexes.....149

Table 5.3: The Council for Scientific and Industrial Research (CSIR) standard criteria for *in vitro* cancer screening according to IC_{50}.....150

Table 5.4: In vitro cancer screening of oxovanadium(IV) and zinc(II) complexes.....153

Table 5. 5: The Council for Scientific and Industrial Research (CSIR) standard criteria for *in vitro* cancer screening according to IC_{50}.....154

Table 5.6: Zone of inhibition for antibacterial susceptibility test for ligands of sodium sulfadiazine and derivatives of dithiocarbamate.....159

Table 5.7: Zone of inhibition for antibacterial susceptibility test of vanadyl (IV) sulfate and oxovanadium (IV) complexes of sodium sulfadiazine and derivatives of dithiocarbamate.....161

Table 5.8: Zone of inhibition for antibacterial susceptibility test of zinc(II) chloride, zinc(II) complexes of sodium sulfadiazine and derivatives of dithiocarbamate...163

.

Table 5.9: MIC of sample compounds of oxovanadium(IV) and zinc(II) complexes.....165

.

List of Schemes

Scheme 2.1. Synthesis of ammonium *N*-butyl dithiocarbamate (bu-DTC).....36
Scheme 2.2. Synthesis of ammonium *N*-hexyl dithiocarbamate (he-DTC).....37
Scheme 2.3. Synthesis of ammonium *N*-ethanol dithiocarbamate (eh-DTC).....37
Scheme 2.4. Synthesis of ammonium *N*-cyclohexyl dithiocarbamate (cy-DTC).....38
Scheme 2.5. Synthesis of ammonium *N*-aniline dithiocarbamate (an-DTC).....38
Scheme 2.6. Synthesis of ammonium *N*-methyl-*N*-phenyl dithiocarbamate (me-DTC).....39
Scheme 2.7. Synthesis of ammonium *N*-ethyl-*N*-phenyl dithiocarbamate (et-DTC).....39
Scheme 2.8. Synthesis of ammonium *N*-para-*N*-chlorophenyl dithiocarbamate (me-DTC)...40
Scheme 2.9. Synthesis of sodium methyl dithiocarbamate (mt-DTC).....41
Scheme 2.10. Synthesis of sodium ethyl dithiocarbamate (el-DTC).....41
Scheme 2.11. Synthesis of sodium butyl dithiocarbamate (bt-DTC).....42
Scheme 2.12. Synthesis of sodium hexyl dithiocarbamate (hx-DTC).....42
Scheme 2.13 a. Synthesis of sodium diethyl dithiocarbamate (de-DTC).....43
Scheme 2.13 b. Sodium diethyl dithiocarbamate (*de-DTC).....43
Scheme 2.14. Synthesis of sodium hydrazine hydrate dithiocarbamate (hh-DTC).....44
Scheme 2.15. Synthesis of sodium ethanol dithiocarbamate (ea-DTC).....44
Scheme 2.16. Synthesis of sodium cyclohexyl dithiocarbamate (cc-DTC).....45
Scheme 2.17. Synthesis of sodium aniline dithiocarbamate (ai-DTC).....46
Scheme 2.18. Synthesis of sodium phenyl hydrazine dithiocarbamate (hy-DTC).....46
Scheme 2.19. Synthesis of sodium ortho toluidine dithiocarbamate (to-DTC).....47
Scheme 2.20. Synthesis of sodium *N*-methyl-*N*-phenyl dithiocarbamate (ml-DTC).....47
Scheme 2.21. Synthesis of sodium *N*-ethyl-*N*-phenyl dithiocarbamate (ey-DTC).....48
Scheme 2.22. Synthesis of sodium *N*-*para*-Toluidine Dithiocarbamate (tl-DTC).....49

.

Scheme 2.23. Synthesis of sodium *N*-*para*-chlorophenyl dithiocarbamate (ch-DTC).....49

Scheme 2.24. Synthesis of sodium *N*-*para*-anisidine dithiocarbamate (as-DTC).....50

Scheme 2.25. Synthesis of sodium *N*-Ethyl-*m*-toluidine (tu-DTC).....50

Scheme 3.1. Synthesis of oxovanadium(IV) complex of [VO(SFZ)(cy-DTC)].....73

Scheme 3.2. Synthesis of oxovanadium(IV) complex of [VO(SFZ)(an-DTC)].....73

Scheme 3.3. Synthesis of oxovanadium(IV) complex of [VO(SFZ)(me-DTC)].....74

Scheme 3.4. Synthesis of oxovanadium(IV) complex of [VO(SFZ)(bt-DTC)].....75

Scheme 3.5. Synthesis of oxovanadium(IV) complex of [VO(SFZ)(hx-DTC)].....76

Scheme 3.6. Synthesis of oxovanadium(IV) complex of [VO(SFZ)(de-DTC)].....76

Scheme 3.7. Synthesis of oxovanadium(IV) complex of [VO(SFZ)(hh-DTC)].....77

Scheme 3.8. Synthesis of oxovanadium(IV) complex of [VO(SFZ)(ai-DTC)].....78

Scheme 3.9. Synthesis of oxovanadium(IV) complex of [VO(SFZ)(hy-DTC)].....79

Scheme 3.10. Synthesis of oxovanadium(IV) complex of [VO(SFZ)(to-DTC)].....80

Scheme 3.11. Synthesis of oxovanadium(IV) complex of [VO(SFZ)(ch-DTC)].....81

Scheme 3.12. Synthesis of oxovanadium(IV) complex of [VO(SFZ)(as-DTC)].....82

Scheme 3.13. Synthesis of oxovanadium(IV) complex of [VO(SFZ)(tl-DTC)].....83

Scheme 3.14. Synthesis of oxovanadium(IV) complex of [VO(SFZ)(tu-DTC)].....84

Scheme 4.1. Synthesis of zinc(II) complex of [Zn(SFZ)(bu-DTC)].....103

Scheme 4.2. Synthesis of zinc(II) complex of [Zn(SFZ)(he-DTC)].....104

Scheme 4.3. Synthesis of zinc(II) complex of [Zn(SFZ)(an-DTC)].....105

Scheme 4.4. Synthesis of zinc(II) complex of [Zn(SFZ)(me-DTC)].....106

Scheme 4.5. Synthesis of zinc(II) complex of [Zn(SFZ)(et-DTC)].....107

Scheme 4.6. Synthesis of zinc(II) complex of [Zn(SFZ)(cl-DTC].....108

Scheme 4.7. Synthesis of zinc(II) complex of [Zn(SFZ)(mt-DTC)].....109

Scheme 4.8. Synthesis of zinc(II) complex of [Zn(SFZ)(bt-DTC)].....110

Scheme 4.9. Synthesis of zinc(II) complex of [Zn(SFZ)(hx-DTC)].....111

Scheme 4.10. Synthesis of zinc(II) complex of [Zn(SFZ)(de-DTC)].....112

Scheme 4.11. Synthesis of zinc(II) complex of [Zn(SFZ)(*de-DTC)].....113

Scheme 4.12. Synthesis of zinc(II) complex of [Zn(SFZ)(ea-DTC)].....114

Scheme 4.13. Synthesis of zinc(II) complex of [Zn(SFZ)(cc-DTC)].....115

Scheme 4.14. Synthesis of zinc(II) complex of [Zn(SFZ)(hy-DTC)].....116

Scheme 4.15. Synthesis of zinc(II) complex of [Zn(SFZ)(to-DTC)].....117

Scheme 4.16. Synthesis of zinc(II) complex of [Zn(SFZ)(ml-DTC)].....118

.

Scheme 4.17. Synthesis of zinc(II) complex of [Zn(SFZ)(ey-DTC)].....119
Scheme 4.18. Synthesis of zinc(II) complex of [Zn(SFZ)(as-DTC)].....120
Scheme 4.19. Synthesis of zinc(II) complex of [Zn(SFZ)(tu-DTC)].....121

.

Abbreviations and Symbols

Abbreviations

Ar- Aromatic

DMF- *N*, *N*-Dimethylformamide

DMSO- Dimethylsulfoxide

EA-Elemental Analysis

FT-IR-Fourier Transforms Infra-red Spectroscopy

h- hour

L- ligand, L_1: ligand 1, L_2: ligand 2.

M P- Melting Point

MIC- Minimum Inhibition Concentration

mmol- millimole

mol-mole

NMR- Nuclear Magnetic Resonance

THF- Tetrahydrofuran

UV-Vis - Ultraviolet-Visible

ZOI-Zone of Inhibition

Symbol

δ - Chemical shift in ppm

Other abbreviations

Ligands

ai-DTC- Sodium *N*-aniline dithiocarbamate

an-DTC- Ammonium *N*-aniline dithiocarbamate

.

as-DTC; Sodium *N*-*para*-anisidine dithiocarbamate

bt-DTC; Sodium *N*-butyl dithiocarbamate

bu-DTC- Ammonium *N*-butyl dithiocarbamate

cc-DTC; Sodium *N*-cyclohexyl dithiocarbamate

ch-DTC; Sodium *N*- para chloro *N*-phenyl dithiocarbamate

cl-DTC- Ammonium *N*-para chloro *N*-phenyl dithiocarbamate

cy-DTC; Ammonium *N*-cyclohexyl dithiocarbamate

de-DTC; Sodium *N*-diethyl dithiocarbamate

*de-DTC; Sodium *N*-diethyl dithiocarbamate

ea-DTC-Sodium *N*-ethanol dithiocarbamate

eh-DTC- Ammonium *N*-ethanol dithiocarbamate

el-DTC- Sodium *N*-ethyl dithiocarbamate

et-DTC- Ammonium *N*-ethyl *N*-phenyl dithiocarbamate

ey-DTC- *N*-ethyl *N*-phenyl dithiocarbamate,

he-DTC- Ammonium *N*-hexyl dithiocarbamate

hh-DTC, Sodium *N*-hydrazine hydrate dithiocarbamate

hy-DTC- Sodium *N*-phenyl hydrate dithiocarbamate

hx-DTC- Sodium *N*-hexyl dithiocarbamate

me-DTC; Ammonium *N*-methyl *N*-phenyl dithiocarbamate

ml-DTC- Sodium *N*-methyl *N*-phenyl dithiocarbamate

mt-DTC- Sodium *N*-methyl dithiocarbamate

SFZ; Sodium sulfadiazine

tl-DTC- Sodium *N*-para-toluidine dithiocarbamate

to-DTC-Sodium *N*-*ortho*-toluidine dithiocarbamate

.

tu-DTC-Sodium *N*-ethyl-*m*-toluidine dithiocarbamate

*de-DTC- Sodium diethyl dithiocarbamate- Readily available and not synthesized.

Oxovanadium(IV) complexes of sodium sulfadiazine and derivatives of dithiocarbamates

[VO(SFZ)(ai-DTC)] - Oxovanadium(IV) complex of sodium sulfadiazine and sodium *N*-aniline dithiocarbamate

[VO(SFZ)(an-DTC)] - Oxovanadium(IV) complex of sodium sulfadiazine and ammonium *N*-aniline dithiocarbamate

[VO(SFZ)(as-DTC)] - Oxovanadium(IV) complex of sodium sulfadiazine and sodium *N*-*para*-anisidine dithiocarbamate

[VO(SFZ)(bt-DTC)]- Oxovanadium(IV) complex of sodium sulfadiazine and sodium *N*-butyl dithiocarbamate

[VO(SFZ)(bu-DTC)] - Oxovanadium(IV) complex of sodium sulfadiazine and ammonium *N*-butyl dithiocarbamate

[VO(SFZ)(cc-DTC)] - Oxovanadium(IV) complex of sodium sulfadiazine and *N*-cyclohexyl dithiocarbamate

[VO(SFZ)(ch-DTC)] - Oxovanadium(IV) complex of sodium sulfadiazine and sodium *N*-*para*-chlorophenyl dithiocarbamate

[VO(SFZ)(cl-DTC)] - Oxovanadium(IV)complex of sodium sulfadiazine and ammonium *N*-para chloro *N*-phenyl dithiocarbamate

[VO(SFZ)(cy-DTC)] - Oxovanadium(IV) complex of sodium sulfadiazine and ammonium *N*-cyclohexyl dithiocarbamate

[VO(SFZ)(el-DTC)] - Oxovanadium(IV) complex of sodium sulfadiazine and sodium *N*-ethyl dithiocarbamate

[VO(SFZ)(hh-DTC)] - Oxovanadium(IV) complex of sodium sulfadiazine and sodium *N*-hydrazine hydrate dithiocarbamate,

.

[VO(SFZ)(hx-DTC)] - Oxovanadium(IV) complex of sodium sulfadiazine and sodium *N*-hexyl dithiocarbamate

[VO(SFZ)(hy-DTC)] - Oxovanadium(IV) complex of sodium sulfadiazine and sodium *N*-phenyl hydrate dithiocarbamate

[VO(SFZ)(me-DTC)] - Oxovanadium(IV) complex of sodium sulfadiazine and ammonium *N*-methyl *N*-phenyl dithiocarbamate

[VO(SFZ)(ml-DTC)] - Oxovanadium(IV) complex of sodium sulfadiazine and sodium *N*-methyl *N*-phenyl dithiocarbamate

[VO(SFZ)(tl-DTC)] - Oxovanadium (IV) complex of sodium sulfadiazine and sodium *N*-*para* chlorophenyl dithiocarbamate.

[VO(SFZ)(to-DTC)] - Oxovanadium(IV) complex of sodium sulfadiazine and sodium *N*-*ortho*-toluidine dithiocarbamate,

[VO(SFZ)(tu-DTC)] - Oxovanadium(IV) complex of sodium sulfadiazine and *N*-*para*-sodium *N*-ethyl-*m*-toluidine dithiocarbamate.

Zinc(II) complexes of sodium sulfadiazine and derivatives of dithiocarbamates

[Zn(SFZ)(an-DTC)] - Zinc(II) complex of sodium sulfadiazine and ammonium *N*-aniline dithiocarbamate

[Zn(SFZ)(as-DTC)] - Zinc (II) complex of sodium sulfadiazine and sodium *N*-*para*-anisidine dithiocarbamate

[Zn(SFZ)(bt-DTC)] - Zinc(II) complex of sodium sulfadiazine and sodium *N*-butyl dithiocarbamate

[Zn(SFZ)(bu-DTC)] - Zinc(II) complex of sodium sulfadiazine and ammonium *N*-butyl dithiocarbamate

[Zn(SFZ)(cl-DTC)] - Zinc(II) complex of sodium sulfadiazine and ammonium *N*-para chloro *N*-phenyl dithiocarbamate

[Zn(SFZ)(cc-DTC] - Zinc(II) complex of sodium sulfadiazine and sodium *N*-cyclohexyl dithiocarbamate

[Zn(SFZ)(de-DTC)] - Zinc(II) complex of sodium sulfadiazine and sodium *N*-diethyl dithiocarbamate,

.

[Zn(SFZ)(*de-DTC)] - Zinc(II) complex of sodium sulfadiazine and sodium *N*-diethyl dithiocarbamate

[Zn(SFZ)(ea-DTC)] - Zinc(II) complex of sodium sulfadiazine and sodium *N*-ethanol dithiocarbamate

[Zn[SFZ)(et-DTC)] - Zinc(II) complex of sodium sulfadiazine and ammonium *N*-ethyl *N*-phenyl dithiocarbamate

[Zn(SFZ)(ey-DTC)] - Zinc(II) complex of sodium sulfadiazine and *N*-ethyl *N*-phenyl dithiocarbamate

Zn[(SFZ)(he-DTC)] - Zinc(II) complex of sodium sulfadiazine and ammonium *N*-hexyl dithiocarbamate

[Zn(SFZ)(hx-DTC)] - Zinc(II) complex of sodium sulfadiazine and sodium *N*-hexyl dithiocarbamate

[Zn(SFZ)(hy-DTC)] - Zinc(II) complex of sodium sulfadiazine and sodium *N*-phenyl hydrate dithiocarbamate

[Zn(SFZ)(ml-DTC)] - Zinc(II) complex of sodium sulfadiazine and sodium *N*-methyl *N*-phenyl dithiocarbamate

[Zn(SFZ)(tl-DTC)]; Zinc(II) complex of sodium sulfadiazine and sodium *N-para*-chlorophenyl dithiocarbamate

[Zn(SFZ)(to-DTC] - Zinc(II) complex of sodium sulfadiazine and sodium *N-ortho*-toluidine dithiocarbamate

[Zn(SFZ)(tu-DTC)]; Zinc(II) complex of sodium sulfadiazine and *N-para*-sodium *N*-ethyl-*m*-toluidine dithiocarbamate.

.

Research Outputs

41st South African Chemical Institute (SACI), East London, South Africa.

Odularu, A.T. and Ajibade, P. A. "Synthesis and Spectral Studies of Vanadium(IV) and Zinc(II) Complexes, December 1st- 6th, 2013.

.

Abstract

The research involves the synthesis, characterization and biological studies of oxovanadium(IV) and zinc(II) complexes of mixed sulfadiazine and dithiocarbamates ligands. Twenty-five dithiocarbamates ligands were synthesized and characterized with elemental analysis, FT-IR, UV-Vis, ^{1}H NMR and ^{13}C NMR spectroscopy. The dithiocarbamate ligands were used with the sulfadiazine to synthesize mixed ligands complexes of oxovanadium(IV) and zinc(II). The oxovanadium(IV) and zinc(II) complexes were characterized with analytical and spectroscopic techniques. Results from molar conductivity confirmed the non-electrolytic nature of both the oxovanadium(IV) and zinc(II) complexes. The FT-IR spectra studies of the complexes confirmed bidentate coordination of sulfonamide nitrogen and pyrimidinyl nitrogen atoms of sulfadiazine to the metal ions, and the dithiocarbamate ligands acted as bidentate chelating ligands through sulfur atoms.

The coordination in both metal complexes was N_2S_2 modes. Studies from UV-Vis spectra for mixed oxovanadium(IV) and zinc(II) complexes gave blue shifts (hypsochromic shifts) in comparison with the respective ligands through N-C=S and S-C=S absorption bands. The conclusion drawn from the UV-Vis studies were proposed structures distorted octahedral geometries for the oxovanadium(IV) complexes and tetrahedral geometries for zinc(II) complexes. The presence of phenyl groups in chemical shifts' results in aromatic zinc(II) complexes (7.78- 6.38), ppm, the absence in aliphatic zinc(II) complexes, pyrimidine $C_4H_2N_2$-H (8.60-8.10 ppm), and =$CHSO_2NNa$ (11.81-11.19 ppm) in ^{1}H NMR, presence of ^{13}C-SO_2NNa (164.39-130.41 ppm) and $N^{13}CS_2$(207.00-179.32 ppm) moieties indicated the presence of the functional group still present and the impact of coordination of ligands to zinc(II) ions. Zinc(II) complexes of [Zn(SFZ)(tu-DTC)] [Zn(SFZ)(ml-DTC)] had the least chemical shift at a resonance of (179.32 ppm), while [Zn(SFZ)(ml-DTC)] has the highest resonance value with a signal for $N^{13}CS_2$ moiety.

Four ligands of dithiocarbamates, ten mixed ligands of oxovanadium(IV) and eleven zinc(II) complexes were screened for cytotoxicity and anticancer activities. They were evaluated for *in vitro* cancer activities against six cancer cell lines; *KMST-6 (a non-cancerous cell line),*

.

HT-29 (colon), W1-38 (fibroblast cell), TK-10 (renal), UACC-62 (melanoma) and MCF-7 (breast). The four ligands and four zinc(II) complexes showed potentials and potencies for cytotoxicity activities against KMST-6 and HT-29, except [Zn(SFZ)(me-DTC)]. Inactive or slightly active oxovanadium(IV) and zinc(II) complexes screened against W1-38, TK-10 UACC-62 and MCF-7 had inhibition concentration 50, IC_{50}, of greater than 50 greater than 100. Six oxovanadium(IV) and three zinc(II) complexes showed potentials and potencies for cytotoxicity activities against W1-38. Four oxovanadium(IV) and two zinc(II) complexes showed potentials and potencies for cytotoxicity activities against TK-10. Eight oxovanadium(IV) and three zinc(II) complexes showed potentials and potencies for cytotoxicity activities against UACC-62. Eight oxovanadium(IV) and three zinc(II) complexes showed potentials and potencies for cytotoxicity activities against MCF-7. Results from studies showed that [VO(SFZ)(hx-DTC)] and [VO(SFZ)(cl-DTC)] as potent cytotoxicity and anticancer chemotherapeutic agents. Cisplatin, Emetine and Parthenolide were used as standard drugs and dimethylsulfoxide as negative control.

Sodium sulfadiazine, derivatives of dithiocarbamates and both complexes of oxovanadium(IV) and zinc(II) were screened for their *in vitro* antibacterial potencies against two Gram positive (*Staphylococcus aureus* (MRSA252))and *Enterococcus faecalis* (BS385)) and Gram negative (*Escherichia coli* (MC4100))and *Pseudomonas aeruginosa* (PA01)) bacterial strains. Sodium sulfadiazine was found to have good activity against *Staphylococcus aureus* and Escherichia *coli* but most of the dithiocarbamates ligands were not active before coordination but some became more inactive or more active in various complexes of oxovanadium(IV) and zinc(II) ions. Meropenem, Tetracycline and Vancomycin were used as standard drugs and dimethylsulfoxide as negative control. The minimal inhibitory concentration (MIC) results proved that oxovanadium(IV) complexes had higher antibacterial activities than zinc(II) complexes. The oxovanadium(IV) complexes with MIC of high activities (32 µg/ml) are [VO(SFZ)(bt-DTC)],[VO(SFZ)(hx-DTC)], [VO(SFZ)(ch-DTC)] and [VO(SFZ)(hh-DTC)]. The results showed that oxovanadium(IV) complexes are better than their zinc(II) counterparts. These dual anticancer and antibacterial potentials and potencies of oxovanadium(IV) complexes can be further evaluated as potential chemotherapeutic agents.

.

CHAPTER 1

1.0 Introduction and literature review

1.1 Metal-based drugs

Development of metal based drugs started in the era when drawbacks were discovered in organic based pharmaceutical drugs. These drawbacks might be due to side effects and challenges of antineoplastic resistance and multiple drug resistance (MDR). Development of metal based drugs is an aspect of chemistry called, "***Medicinal Inorganic Chemistry***". Medicinal inorganic chemistry is of enormous importance in both drug discovery and development of metal-based drugs to treat different ailment of the human body [1]. The wide-ranging topics included in medicinal inorganic chemistry are: (i) the clarification of the general roles of both endogenous and exogenous metal ions in living cells at molecular level; (ii) the scheme of metal chelating agents to treat excess metal ion, pollution from toxic metal ions and hindrance of metalloproteins; (iii) the discovery of the function of metal ions in protein misfolding of the pathogens; (iv) the study of the functions of metal ions; (v) ***the development of metal-based drugs to treat human ailments*** [2].

1.2 Medicinal use of metals and their compounds

The functions of metal ions and the development of metal-based drugs to human diseases in medicinal inorganic chemistry had created room for metalloids, main group metals and transition metals as potentials for anticancer and antimicrobial agents [2]. Metalloids are semi metals that possess partially metallic and non-metallic properties [3, 4]. Metalloids in the periodic table are boron, silicon, germanium, arsenic, antimony, as well as, tellurium. They exhibit different levels of medicinal and toxic properties. Descending down group V of the periodic table, the properties of the elements change. Nitrogen and phosphorus are non-metals; arsenic and antimony are metalloids, while bismuth is a metal. Among the various properties of transition metals is the ability to exhibit different oxidation states [2, 5-6]. This is very vital in medicinal inorganic chemistry because the metal ions can interact to form covalent bonds with biomolecules. This further helps in the development of metal-based drugs with potential therapeutic, pharmacological and medical applications [2, 4-5, 7]. Other cogent reasons which make metal based drugs better than organic-based drugs, apart from varying oxidation states are their abilities to vary coordination numbers and the geometries

.

[8], as well as, perform catalytic and structural functions [9]. There had been well documented metals possessing potentials for potent anticancer and antimicrobial activities. These are antimony, arsenic, boron, cobalt, copper, gallium, germanium, gold, iron, manganese, molybdenum, nickel, niobium, platinum, palladium, rhodium, ruthenium, titanium, vanadium and zinc [10-11]. Table 1.1 gives the summary of metals that can be used as anticancer and antimicrobial agents.

Table 1.1: Summary of metal-based drugs**.**

Element	Compounds	Uses	References
Ag	Silver(I) complexes; Silver sulfadiazine	Antibacterial, Anticancer	12- 19
Al	Aluminium hydroxide	Antacid	19
As	Silver complexes, Salvarsan, Melarsen,	Anticancer, Antimicrobial	19-32
	Tryparsamide		
Au	Gold(I) thiolates	Antitumor, Antimicrobial	19, 33-44
	Auranofin	Antiarthritic	19
	Au(I) diphosphine complex	Antiviral	19
B	Boranes	Anticancer, Antimicrobial	19, 45-46
Ba	Barium sulphate	X-ray contrast	19
Bi	Bismuth complexes	Antacid, Anticancer	19,47-52
	Bismuth citrate, Ranitidine	Antimicrobial, Antiulcer	19,47-52
Br	Sodium bromide	Sedative	19
Co	Cobalt complexes	Anticancer, Antimicrobial	53-59
	Coenzyme B_{12}	Supplement	19
Cr	Chromium complexes	Antidiabetic	19
Cu	Copper complexes	Anticancer, Antimicrobial	60-74

.

	Copper histidine complex	Supplement for Menke's	19
		disease treatment	19
Fe	Fe(II) and Fe(III) complexes	Anticancer, Antimicrobial	75-85
	Sodium nitroprusside	Vasodilator	19
	Fe(III) desferrioxmine chelates	Antimicrobial	19
Ga	Gallium(III) complexes	Anticancer, Antimicrobial	86-93
Ge	Organogermanium	Anticancer, Antimicrobial	94-102
Gd	Gd metallotexaphyrins	MRI contrast agent, PDT,	19
		Radiopharmaceuticals	
Hg	Mereurochome	Antiseptic	19
Ir	Iridium complexes	Anticancer, Antimicrobial	103-112
La	Lanthanum complexes	Anticancer, Antimicrobial	113-118
Li	LiCl, Li_2CO_3	Manic Depression	19, 119
	Lithium complexes	Anticancer	120-121
Lu	Lutetium complexes	PDT	19
Mg	MgO Magnesium(II) complexes	Antacid, Laxative Anticancer, Antimicrobial	19 122-123
Mn	Mn(II) and Mn(III) chelates	Anticancer, Antimicrobial	124-137
Mn	Mn-SOD complexes	Superoxide Scavengers	19
		MRI contrast agent	
Mo	Molybdenum complexes	Anticancer, Antimicrobial	138-142
Na	$Na^{131}I$	Diagnosis of Thyroid	19
Nb	Niobium(II) complexes	Anticancer, Antimicrobial	143-149
Ni	Nickel(II) complexes	Anticancer, Antimicrobial	150-154

.

Os	Osmium(II) complexes	Anticancer, Antimicrobial	155-165
Pd	Palladium complexes	Anticancer, Antimicrobial	166-171
Pt	Platinum compounds and complexes	Anticancer, Antimicrobial	19,172-178
Rh	Rhodium chelates	Anticancer, Antimicrobial	179-188
Ru	Ru(II) and Ru(III) complexes	Anticancer, Antimicrobial	19,189-213
Sb	Antimony complexes	Anticancer, Antimicrobial	214-218
Sb	Pentostam, *N*-Methylglucamine,	Antileishmanial	19, 214
	Antimonate		
Se	Ebselen	Synthetic antioxidant	19
		Anti-inflammatory	
		Neuroprotective agent	
	PhenylAminoalkyl selenide	Antihypertensive	19
	Selenazofurin	Antineoplastic	19
		Antiviral	
	Selenotifen	Anti-allergic agent	19
	Selenium complexes	Anticancer, Antimicrobial	219-226
Ta	Tantalum complexes	Anticancer, Antimicrobial	227-230
Tc	^{99m} Tc(V) Propyleneamine oxime	Diagnostic imaging	19
Ti	Titanium complexes;	Anticancer, Antimicrobial	19
	Titanocenedichloride, Bis(β-Diketonato),	Anticancer, Antidiabetic	231-247
V	Vanadium complexes	Anticancer, Antidiabetic	19, 248
	Bis (maltolato)oxovanadium(IV),	Antimicrobial	260
	Bis(glycinato)oxovanadium(IV)		

.

	Bis(methylpicolinato)oxovanadium(IV)		
W	Polyoxometallates	Anti-HIV activity	19
Zn	ZnO	Skin ointment	19
	Zn(II) bicyclam complexes	Antiviral	19
	Zinc citrate	Supplement	19
	Zinc complexes	Anticancer, Antimicrobial	261-273
Zr	Zr(II) glycinato	Antiperspirant	19
	Zr complexes	Anticancer, Antimicrobial	274-278

1.3 Rationale for the choice of metals in the current study

Vanadium and zinc are transition metals. This is based on the fact drawn from the classification of elements into metals, metalloids and non-metals [3]. They are also referred as biometals and essential trace elements because both vanadium and zinc have a mass of less than 1 gram in human body [3]. Both belong to d block section of the periodic table because of their electron configurations and they are applied in chemical and industrial processes as catalysts [4]. The rationale for the choice of the vanadium and zinc is based on first of all, both being biometals, as well as, availability, bioavailability, antioxidant properties, low toxic levels and importantly, ability to interact with biomolecules due to variable oxidation states of vanadium [260, 262, 279].

1.4 Vanadium

1.4.1 Chemistry of vanadium metal

Vanadium has variable oxidation states ranging from -3 to +5 with the exception of -2 [280-281]. Among these oxidation states of vanadium, the commonest are +2, +3, +4 and +5. The +1 oxidation state is scarce to see. The ease of oxidation and reduction of +2 oxidation state makes it unstable in biological organisms [282]. The oxidation states of vanadium which are thermodynamically and physiologically stable, as well as, physiologically relevant are V^{3+}, V^{4+} and V^{5+} [283]. According to hard acids hard bases (HSAB) principle, vanadium can be

.

categorized as a hard acid, but the higher the oxidation state the harder the acid [284]. This is applicable to vanadium oxidation states III to V. From Pearson's principle of HSAB principle, he concluded that a strong bond would form between a hard acid and a hard base and a strong bond would form between a soft acid and a soft base [285-286]. Vanadium's oxidation states of +3, +4 and +5 bond readily with oxygen, nitrogen and sulphur to form complexes [282].

1.4.2 Vanadium compounds and their biological applications

Mukherjee et al and Tavman ratified vanadium as an essential trace element with anti-diabetic and anti-carcinogenic properties after eighteen years of misconception that it was carcinogenic and slightly toxic [280, 287]. Vanadium is an ultra-trace element in mammals and human beings. Athletes and muscle body builders use vanadium in the form of vanadyl sulfate as an everyday supplement. In 1911, a German chemist, Martin Henze, found a high concentration of vanadium existing as vanadium(III), being coupled with a certain level of sulfate in the blood cells of some ascidians [288-289]. Vanadium is accumulated up to 500 mg/kg in dry weight in macro fungi species such as *Amanita muscaria* and peculiar species [280]. Vanadium is found in algae, invertebrates, as well as, plants and accumulates firmly at a concentration range of 10^5 to 10^7 times above the concentration in sea water [290-291]. Inkling for the use of vanadium compounds as insulin-mimetic agents among nutritionists arose when they discovered vanadium element was an essential element in some marine animals [292-293]. In 1931, twenty years after Martin Henze discovery. Ter Meulen's researched on toadstools (*Amanita muscaria*) He found that they contained high levels of vanadium, about 3.3 mg/kg in the species [294]. Bayer and Kneifel in 1972 isolated pale blue compound of vanadium, called *amavadin* and found to consist a 1:2 complex of vanadium, and pro-ligand (S, S)-2, 2'-(hydroxyimino) dipropionic acid,((S, S)-hidpaHa) [294]. Fly agaric builds up vanadium in form of *amavadin* [294]. In 1977, L. J. Cantley was able to detect the impact of vanadate as an effective inhibitor of adenosine triphosphates [295- 296], Further investigation to support the synthesis of vanadium compounds were the two classes of natural vanadium enzymes, namely; vanadium-nitrogenase and vanadate-dependent haloperoxidases [297-299]. In 1983, H. Vilter isolated the enzyme of vanadium, *bromoperoxidase*, in the marine algae [296]. Sussex nitrogen fixation group was also able to isolate some nitrogen-fixing micro-organisms such as azobacter which used *vanadium*

.

nitrogenase where vanadium replaced molybdenum or iron, giving slight different properties to vanadium nitrogenise in 1986 [296].

1.4.3 Vanadium as insulin-mimetic agent

Another driving force to vanadium coordination chemistry was the medical uses observed when vanadate, peroxovanadate, vanadyl and other vanadium complexes influenced insulin-mimetic properties. [300-306]. Deficiency of vanadium in birds and mammals leads to retarded growth and reduced reproduction [307]. The mechanism by which vanadium mimics the activity of insulin is still not clear [308-310]. Vanadium has glycemic control because of its insulin mimetic properties in liver, skeletal muscle and adipose tissue in both in vivo and in vitro model of animals , thereby, preventing phosphotyrosine phosphatase (PTP) enzyme system [311]. The three key properties essential to the insulin mimetic actions of vanadium compounds are lability, redox chemistry and stability [306]. The mechanism of action of vanadium as insulin mimetic agent is shown in Figure 1.1.

.

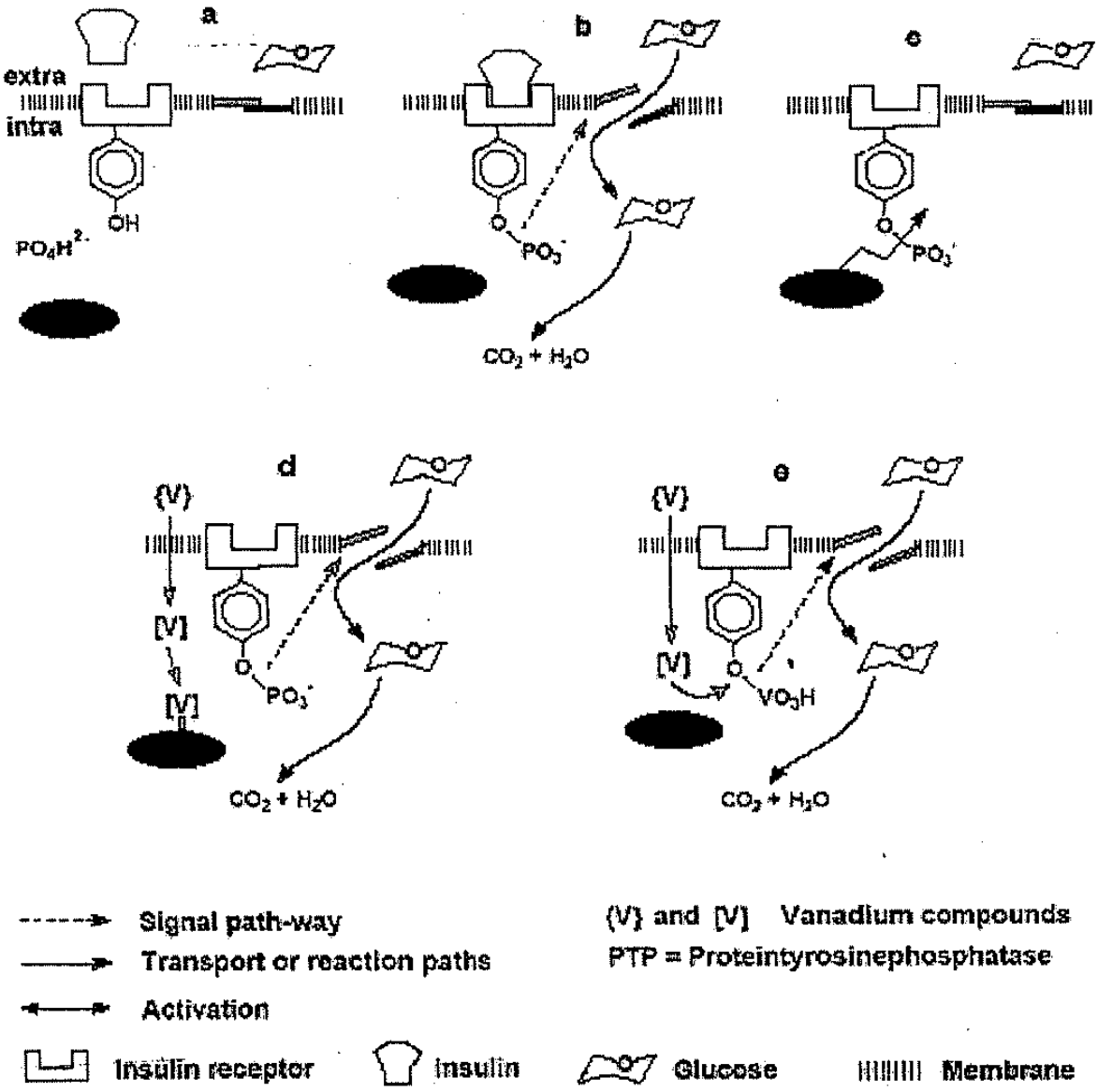


Figure 1.1: The mechanism of action of vanadium as insulin mimetic agent [305]**.**

(a) Starting situation; (b) Insulin docks to the membrane receptor and induces tyrosine phosphorylation, which in turn triggers glucose intake; (c) Protein-tyrosine-phosphatase hydrolyses the phosphate-tyrosine bond and thus interrupts signal transduction in the absence of (or resistence against) insulin; (d) Vanadate inhibits PTP; signal transduction remains intact through autophosphorylation of tyrosine; (e) Alternatively, tyrosine is vanadylated.

1.4.4 Vanadium as anticancer agent

In the early era of the 20th century, assumptions of metal complexes having potentials of antitumour activities arose [243]. In 1931, inorganic compounds were studied for their antitumour activities [243]. In 1964, the successful discovery of anticancer activities of cis-$PtCl_2$ $(NH_3)_2$ (cisplatin) inspired other researchers to study and explore anticancer potentials of metals and their compounds [175]. In 1965, vanadium salts showed active antineoplatic effects, while in 1967, vanadium showed inactiveness when tested with unstructured rat tumours [243]. In 1983, English et al extended the study of vanadium as anticancer agent [312], while in 1984, Thompson et al tested vanadyl sulfate against mammary carcinogenesis by chemical induction and it proved very potent [313-314]. On a daily basis, vanadium intake is meant to be between 10 μg and 2 mg [314-315]. A health organization such as Food and Drug Administration, USA, is yet to establish a recommended daily allowance of vanadium [314]. There is proof on the potentials of sodium metavanadate, $NaVO_3$, to stimulate transformation in gene expression, even with the lack of vanadium for various cells' divisions during *in vitro* studies [314].

1.4.4.1 Different oxidation states of vanadium and DNA damage

Inorganic ions of vanadium or organic vanadium compounds such as peroxidovanadium(V) complexes had been reported to be injurious to DNA [314]. The main target of the anticancer therapy is DNA of cancer cells, therefore, there is a need to evaluate the scope of vanadium's interrelationship with DNA by measurement of the hyperchromicity in DNA spectra [314]. A high measurement of vanadium containing compounds' interaction with DNA signifies promising antiproliferative actions [314]. The capability of vanadium and its compounds and complexes to interrelate with DNA are due to genotoxicity and additional genetic consequences of vanadium [316, 317]. In recent studies, different oxidation states that are biologically inclined (+3, +4 and +5) stimulated such consequences as *in vivo* activities in human blood leukocytes [317]. The results revealed that all the three oxidation states generated genotoxic effect, while vanadium(IV) caused double-strand DNA breaks which were linked with subsequent chromosomal aberrations [317]. A further study confirmed that the different aforementioned oxidation states of vanadium stimulated *cytotoxicity,* and also, vanadium with valency of +4 had the ability to induce clastogenic effects. Vanadium(V) was

.

proved to possess low genotoxic activity when high prescribed amount was tested in vivo, which might be due to its low bioavailability [318]. In addition, the outcome detected *in vitro*, might not be detected *in vivo* and vice versa. There is a necessity for comparative bioavailability, toxicity and transportation studies of vanadium in their various oxidation states in order to get specific information on vanadium-DNA interrelationships [314].

1.4.5 Vanadium as antimicrobial agent

Apart from the insulin-mimetic activities and anticancer activities of vanadium, it also exhibit antimicrobial activities in different oxidation states [318-319].

1.4.6 Health impacts and toxicity of vanadium

It was noted that workers exposed to vanadium compounds, vanadium(IV) oxide to be specific, suffered from eyes, nose and throat irritation, when inhaled it can cause bronchitis and pneumonia [320]. The uptake of vanadium is high through ingestion. The acute toxicity symptoms are eyes, nasal cavities, throat and lung irritations [320]. The other health hazards linked to the exposure are cardiac and vascular diseases, inflammation of the stomach and intestines, damage to the nervous system liver and kidney bleeding, skin rashes, severe trembling and paralysis, nose bleeding, throat pains and body weakening [320]. Symptoms of overexposure are nasopharyngitis, cough, rapid heartbeat, lung changes, chronic bronchitis, greenish-black tongue and allergic skin rash [320]. Vanadium ions can be found to be abundant in a few organisms, possibly as a toxin. Moderate toxicity is present in vanadium compounds. Experimental studies revealed that vanadium can affect the reproductive system of male animals and accumulates in the placenta of female animals [321]. Vanadium compounds possess the following toxic effects: hepatotoxicity, nephrotoxicity, gastrointestinal discomfort, teratogenicity reproductive toxicity and developmental toxicity [322- 323].Researchers revealed that the toxic nature of vanadium depends on oxidation state, concentration and the type of coordination environment [324]. Safety and maintenance of biological activities have an estimated concentration of $< 1.0 \times 10^{-5}$M, while those above 1.0×10^{-3} M are toxic for the use at chronic cases [305].The easy storage of vanadium in bones is possible because it is similar to phosphate [325]. Other side effects apart from the

.

aforementioned are diarrhoea, limited food and fluid uptake, dehydration and decreased body weight [325].

1.5 Zinc

1.5.1 The chemistry of zinc

Zinc is the first member of group 12 at the end of the first row transition metals in the modern periodic table and has an electronic configuration of [Ar] $3d^{10}4s^2$. It is, therefore, said to be a d block element or a post-transition metal because the metal forms Zn^{2+} by losing the two electrons from $4s^2$. The Zn^{2+}ion now has an electronic configuration of [Ar] $3d^{10}$ with a full d orbital. The commonest oxidation state is +2, while others are +1 and 0. Zinc is different from vanadium because it is not redox in nature like vanadium. Zinc, when as a metal or divalent is diamagnetic with a completely filled d^{10} electronic configuration. Zinc forms complexes with no ligand-field stabilization energy [326]. Soft polarizable ligands such as cyanides, iodides, isonitriles, phosphines and thioethers coordinate readily with zinc when the complexes are synthesized [327]. Literature also revealed that, zinc is a chalcophile metallic element and prefers to bond with sulphur compared to oxygen [328]. According to hard acids hard bases (HSAB) principle, zinc can either be categorized as a hard acid or a borderline (intermediate acid), whereas, nitrogen is a borderline base and sulfur a soft base. From Pearson's principle of HSAB principle, he concluded that a strong bond would exist between a hard acid and a hard base and a strong bond would exist between a soft acid and a soft base [284].

1.5.2 Biological relevance and the use of zinc compounds as insulin-mimetic agents

The rationale for opting for zinc(II) ion for insulin-mimetic activities was due to the availability, being the 24th most abundant element in the earth crust, safe and relatively low toxic level compared with other metal ions [329]. Zinc is a vital trace element in the systems of all living things and very fundamental in many metalloproteins and metalloenzymes, being functional in about 300 enzymes [330-333]. About 2-4 g of zinc is present in humans [334]. It has a low toxic report and it had been known for long that, there existed a biochemical relationship between insulin and zinc [335]. The three essential roles zinc performs biologically are catalytic, regulatory and structural [336]. Diabetes mellitus has been linked with imbalances in zinc homeostasis [336-338]. Ever since 1934, zinc has been found to be an essential component of insulin crystals. This led to the proposition that zinc would be related

.

to insulin mimetic activities [334]. Later studies show the essential role of zinc in diabetes mellitus. Zinc performs an essential role in the synthesis of insulin, secretion of insulin, transportation of glucose by insulin and protection of the receptor cells [338-342]. The three main classifications of zinc compounds based on their uses as insulin mimetic agents are: (i) Inorganic zinc compounds (ii) Organic and chelated zinc complexes (iii) Other *recent* zinc compounds are peptide –bound zinc complexes.

1.5.3 Zinc and its compounds as anticancer and antimicrobial agents

The essence of zinc in physiological processes such as gene transcription, phagocytic actions of macrophages and stabilization of biological membranes cannot be underestimated [343]. Apart from antioxidant and anti-inflammatory properties of zinc, it also served as anticancer agent [343]. Study revealed zinc as an important constituent of DNA-binding proteins with zinc fingers, copper/zinc superoxide dismutase and some proteins taken part in DNA repair [344]. Zinc plays an essential function in antioxidation, DNA repair and transcription [344]. Zinc is needed in human diet and an approximation of 15 mg per day is allowed [345]. Insufficiency in the daily allowance of zinc affects the single and double-strand DNA breakage and modified oxidation of DNA enhance the development of cancer [344]. Literature revealed the relevance of zinc in cancer biology. The current progress in the research of zinc as anticancer agent is promising, though it is still at the infant stage [344]. The application of metals as antimicrobial agents had been known for centuries and this signified the advances in the history of medicine [346]. The success of cisplatin as an antibacterial agent before being used as an anticancer agent is an example [346]. Zinc as a metal also exhibits antimicrobial activities [346-349].

1.5.4 Health impacts and toxicity of zinc

Zinc is very essential for proper performance of the immune system; therefore, zinc homeostasis affects the function and development of immune system and metallothioneins [350]. An excess concentration of zinc is very harmful [351]. Excess zinc can lead to disturbance of the protein metabolism, respiratory disorder, pancreas damage, nausea, anaemia, stomach cramps, skin irritations, vomiting, arteriosclerosis liver and kidney diseases

.

[351-352]. Large concentration of zinc is also unsafe for unborn and new born children when they are fed with the milk from infected mothers [353].

1.6 Ligands

Ligands are ions or molecules with lone pairs of electrons that form bonds with metals to form coordination complexes [354]. Ligands are sometimes referred to as Lewis bases and metal ions as Lewis acids.

Literature revealed that chelating ligands with oxygen (O), nitrogen (N) and sulphur (S) donor atoms (coordination modes) possess biological activities [355-360]. For this study, ligands containing nitrogen and sulfur coordination modes were used because recent studies now focused on hard and soft donors based [359], especially in biomimetic studies [361].

1.6.1. Heterocyclic bidentate ligands

The interesting characteristics of heterocyclic ligands are numerous. These include their low molecular weights, which make them applicable in the agricultural, dyes and pharmaceutical industries. They are easy to synthesize [362]. Their possession of lone pair of electrons and hydroxyl groups contribute to enhance their abilities to dissolve in water [362]. The derivatives of heterocyclic bidentate ligands enable alteration in the balance between hydrophilicity and hydrophobicity [362]. This research focused on the heterocyclic bidentate ligands of ***sodium sulfadiazine and the derivatives of dithiocarbamates.***

1.6.2 Sulfadiazine and its relevance to medicine

Sulfonamides

Sulfonamides are derivatives of sulfanilamide. Sulfonamides act as substrate analogue when they undergo inhibiting competition with para-aminobenzoic acid (PABA), which helps in enzymatic reactions to produce bacterial folic acid. They have a moiety of $–SO_2NH$. They also act as coenzyme to synthesize amino acids, purine and pyrimidine [363]. Sulfonamides are referred to as systemic antibacterial drugs [364]. They also possess antifungal properties [365-366] and can be classified according to where they are placed for actions [367]. They include sulfanilamide, sulfapyridine, sulfathiazole, sulfamerazine, sulfadimidine, sulfalene sulfamethizole and *sulfadiazine*. They are also referred to as sulfa drugs [368-370].

.

Sulfadiazine is a low toxic, short-acting sulfonamide and most effective for treating infections of bacteria by preventing the manufacture of folic acid in the cell of the bacteria [371-372]. Silver sulfadiazine is useful as an antifungal agent [367], while, zinc sulfadiazine and cerium sulfadiazine are used as therapeutic agents for treating topical burn [365, 372]. The medical application is also found in the treatment of urinary tract infections. Sulfadiazine can be combined with other sulphonamides to treat patients with Acquired Immune Deficiency Syndrome (AIDS), as well as, combination therapy with pyrimethamine to treat malaria [373].Sodium sulfadiazine is a white to off white crystalline powder soluble in water, methanol and ethanol [374-375], as well as, cyclohexane [376]. It is stable under normal conditions. Figure 1.2 shows the chemical structure of sodium sulfadiazine.

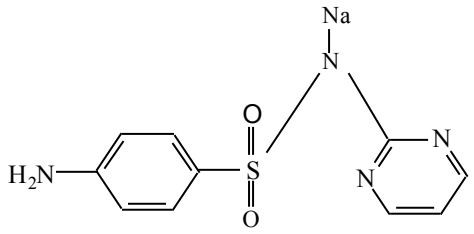


Figure 1.2: Chemical structure of sodium sulfadiazine**.**

1.6.3 Dithiocarbamate and its relevance to medicine

Dithiocarbamates are very versatile organosulfur and mono-anionic-chelating ligands that form stable complexes with actinides, lanthanides, non-transition and transition elements [377-380]. The general formula is (R_1R_2) N-(C=S) SX, where R can be substituted by an alkyl, alkylene, aryl or similar other group and X by a metal ion. Dithiocarbamates lipophilic nature enables them to bind with metals in symmetrical, monodentate and anisobidentate modes [377, 380]. Dithiocarbamate was discovered in the 1930s, and the first commercial application was as fungicides during World War II [380]. Simple preparation of dithiocarmates is mostly from primary or secondary amines, though, the type of cation influences the solubility in water and organic solvents [377]. The versatility of dithiocarbamates and the derivatives have been applied in different fields of agriculture (fungicides and pesticides) [381-382], material science; nanochemistry [383], biology (antifungal and antibacterial studies) [384-385] and medicine [384-386]. Other applications are, as catalysts or accelerators in the vulcanization of sulfur [387], antioxidant [387],

.

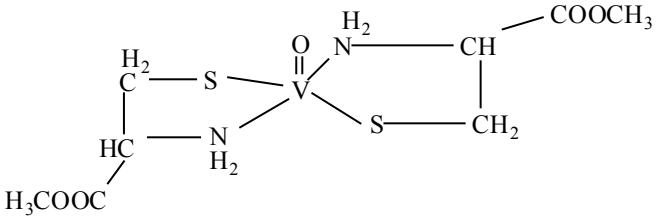
photochemistry and synthesis of ionic liquids [386, 388-393]. Metal ions are well coordinated to *N, N*-disubstituted and *N*-substituted dithiocarbamates [386,388-394]. This is due to the chelating properties of the dithiocarbamates, which leads to the yield of good geometries of their metal complexes [386, 390-392, 394].

1.7 Metal complexes

Metal complexes can also be referred to as metal coordination compounds. Metal complexes are composed of a central metal or ion and ligands [395-396]. Coordination number is the number of ligands that bond to the central metal or ion [396]. A *homoleptic complex* is synthesized when the same types of ligands are ligated to the metal and a *heteroleptic complex* is formed when different types of ligands are chelated to the central metal [388, 397-401]. The diversed applications of metal complexes are analytical, biomedical, synthetic and therapeutic [395]. Some oxovanadium(IV) complexes of different coordination modes like $VO(N_2S_4)$, $VO(S_2O_2)$, $VO(S_4)$, and $VO(O_4)$ have been developed. The molecular structures are shown in Fig. 1.3. Alternatively, different coordinating donors of N_2O_2, S_2O_2, N_4 and O_4 were synthesized for zinc(II) complexes. The molecular structures are shown in Fig. 1.4.

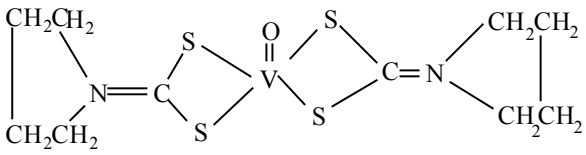
.

N_2S_2 coordination mode



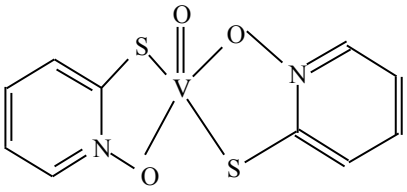
$VO(cysm)_2$

S_4 coordination mode



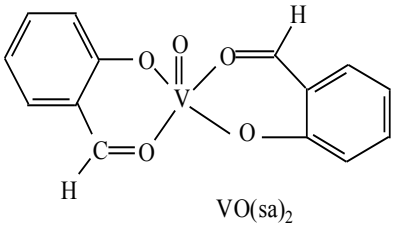
$VO(pdc)_2$

S_2O_2 coordination modes

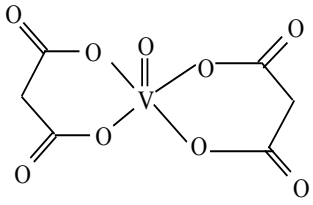


$VO(opt)_2$

O_4 coordination modes



$VO(sa)_2$

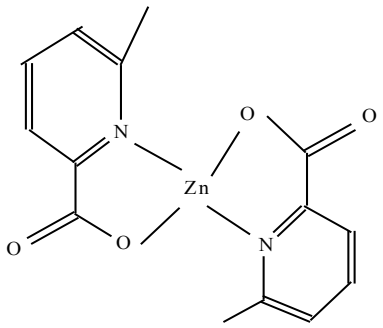


$VO(mal)_2$

Figure 1.3: Molecular structures of $VO(N_2S_4)$, $VO(S_2O_2)$, $VO(S_4)$, and $VO(O_4)$**.**

.

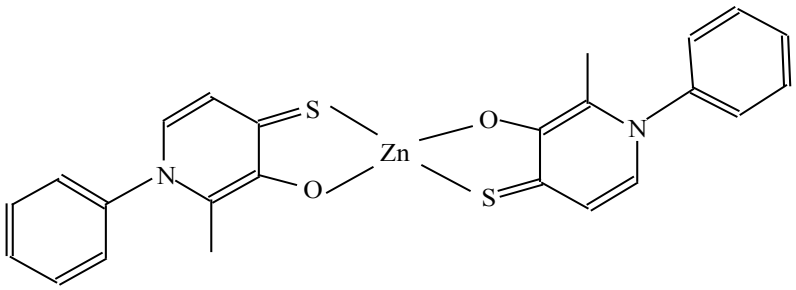
N_2O_2 Coordination mode



$Zn(6MPA)_2$

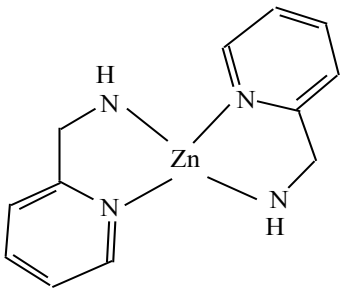
(bis(6-methylpicolinato)Zn(II)

S_2O_2 Coordination Mode



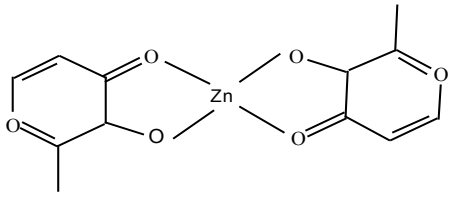
$Zn(ptp)_2$

N_4 Coordination mode



$Zn(ptp)_2$

O_4 Coordination mode



(bis(maltolato)Zn(II)-$Zn(mal)_2$

Figure 1.4: Molecular structures of synthesized zinc(II) complexes of N_2O_2, S_2O_2, $N_4$and O_4.

.

1.7.1 Metal complexes and their therapeutic applications [395]

The therapeutic applications of metal complexes can be categorised into antiarthritic agents, anticancer agents and antimicrobial agents.

1.7.1.1 Antiarthritic agents: Metal complexes such as auranofin and some gold(I) complexes of homololeptic and heteroleptic ligands are known [395, 402]. They also act as anticancer and antimicrobial agents [403-414].

1.7.1.2 Anticancer agents: Cancer is the second leading disease after cardiovascular disease in the world [415] and developing countries like Nigeria and South Africa are not exception [416-417]. It had been in existence from the primitive days of early men and the number is on the increase till this contemporary era [418]. Between 370-460 B. C., Greek physician Hippocrates was credited for the name of cancer, which was coined from two Greek terms,"carcinos" and "carcinoma" meaning "crab", and which described the non-ulcer forming and ulcer forming lumps. Cancer is a group of 200 diseases typified by abnormal growth of cells which do not undergo apoptosis like normal cells. They cause a lot of harm to the body when they form malignant growth forming lumps or tumours, with the exception of leukaemia. Factors that contribute to cancer are exposure to chemicals, dietary and environmental factors, radiation and viral infections [419]. Tumours from cancer can be benign or malignant.

1.8. Types of cancer

Different types of cancer are carcinoma, sarcoma and leukaemia.

Carcinoma is the commonest and has the highest percentage of cancer reports. Examples are breast cancer, colon cancer and lung cancer. Sarcoma starts in connective tissues of bone, cartilage, fat, muscle and tendons. Other groups of cancer not belonging to carcinoma and sarcoma belong to the class of leukaemia.

.

1.8.1 Chronological order and methods of treatment for cancer

There are several approaches to treatment of cancer. Some of them are surgery, radiation therapy biologic therapy, alternative therapy and chemotherapy.

1.8.1.1 Surgery

Surgery depends on the nature and complexity of the cancer. Surgery is applied to get rid of lumps and cancerous tissues. Before 1940, there was no sufficient evidence to support treatment of cancer, but surgery was used for treatment after 1940 and before 1955. It was often combined with either chemotherapy or radiation therapy.

1.8.1.2 Radiation therapy (Radiotherapy)

Radiation therapy (Radiotherapy): From 1955-1965, radiation therapy was used as treatment. Radiant energy was used to shrink the tumours of the DNA cells of cancer, thereby, preventing it from proliferation. Normal cells can be damaged during this process of radiation therapy but are flexible, and therefore, resuscitated. It can be used as a combination therapy with chemotherapy and surgery.

1.8.1.3 Biologic therapy (Targeted therapy/immunotherapy and gene therapy)

Biologic therapy is also known as targeted therapy, where drugs are directed at the cancerous tumours to either prevent the growth of the cancer tumours or to hinder blood flow to the cancer tumours, which make to starve. It can also be used as combination therapy with other drugs. Immunotherapy and gene therapy are both referred to as biologic therapy [420-421].

1.8.1.4 Alternative therapy (Complementary therapy)

Alternative therapy can also be referred to as complementary therapy.
They are treatments used along with standard medical treatments, which include ayuredic medicine, conventional Chinese medicine, diets, herbal therapies, homeopathy, meditation, relaxation, psychological therapies, spiritual therapies and support therapies.

.

1.8.1.5 Chemotherapy

Chemotherapy is the use of drugs such as paracetamol or penicillin to treat diseases, but majority prefer to refer to chemotherapy as a class of cancer treatment that involves the use of chemical substances [422]. There are two terms used in medicine to refer to cancer therapy, namely antineoplastic therapy (anti-cancer) and cytotoxic therapy (cell killing) [422]. The abbreviations for these are chemo, CTX or CTx. Early in 1900, famous German chemist, Paul Ehrlich produced drugs to treat diseases [395, 423]. Paul Ehrlich is known as the founder of modern drug therapy and he was the first person to coin the term, "chemotherapy", and gave the definition as the use of chemicals to treat diseases [395, 423]. He was a pioneer in the efficiency of animal models to evaluate several chemicals to verify their potentials and potencies against diseases [423]. In 1908, the screening exercise that involved the use of rabbit models for syphilis resulted to the progress of arsenicals to treat diseases. Till 1960s, radiotherapy and surgery took over cancer therapy. Treatment by chemotherapy may involve a drug at a time, known as, *single-agent chemotherapy* or numerous drugs at once, known as *combination chemotherapy or polychemotherapy* [424]. Photochemotherapy or photodynamic therapy activity is a chemotherapy that uses drugs that change to cytotoxic activities on exposure to light [425]. The first application was in the treatment of micro-organisms, but after 1965, chemotherapy was used as a method to treat cancer, and therefore, referred to as *anticancer drugs*. Chemotherapy is not targeted at specific part like surgery, but functions by focusing on fast multiplying cancer cells. They can cause side effects such as hair loss and stomach upset. It can also be used as a combination therapy with biologic or radiation therapy. Figure 1.5 depicts the history of cancer chemotherapy from 1900-2015.

.

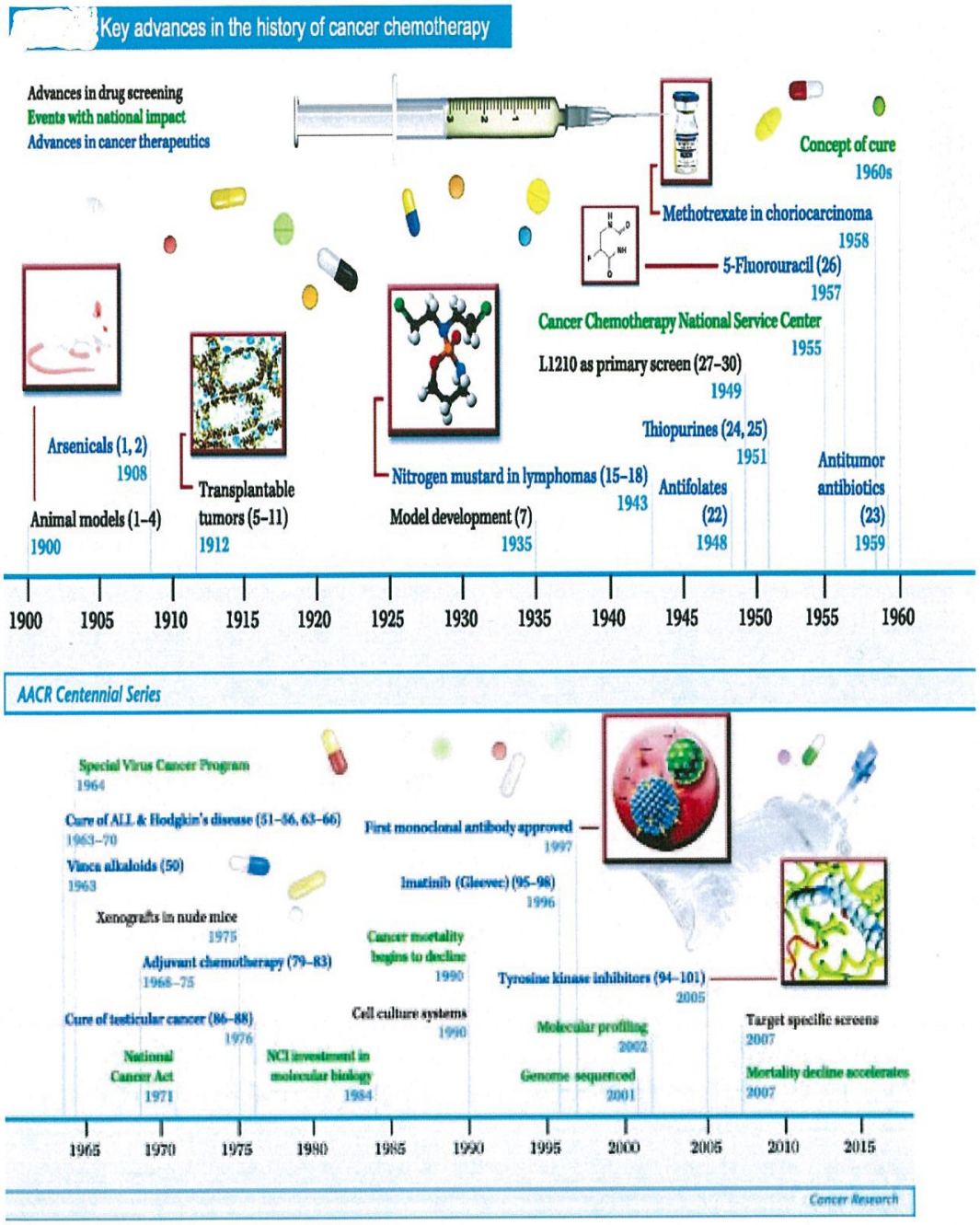


Figure 1.5: History of cancer chemotherapy from 1900-2015

(http://.farmacia.unich.it/farmacologia/didattica/chemioterapia/antimitoticibn.pdf)**.**

.

1.8.2 Aims of cancer therapy

The aims of cancer therapy are for cure or to prolong remission, palliation and adjuvant chemotherapy [426-429].

1.8.2.1 Anticancer agents (Anticancer drugs), classification and challenges and side effects

Anticancer drugs or anticancer agents are either extracts from plants or chemotherapeutic drugs that can kill cancer cells or modify their growth.

1.8.2.2 Classification of anticancer drugs and subdivisions

The major classifications of anticancer drugs are: (a) hormonal drugs (b) targeted drugs and (c) cytotoxic drugs.

1.8.3 The subdivisions of major anticancer drugs are:

1.8.3.1 Hormonal drugs

(i) Glucocorticods (Prednisolone), (ii) Estrogens (Fosfetrol, Ethinylestradiol), (iii) Selective estrogen receptor modulators (Tamoxifen), (iv) Selective estrogen receptors down-regulators (Fulvestrant), (v). Aromatise inhibitors (Letrozole, Anastrozole), (vi) Antiandrogen (Flutamide), (vii) 5-α-Reductase Inhibitor (Finasteride), (viii) GuRH analogues (Nafarelin, Triotorelin), (ix). Progestins (Hydroxyprogesterone acetate).

1.8.3.2 Targeted drugs

Targeted drugs: (i) Tyrosine proteinkinase inhibitors (Imatinib, Nilotinib), (ii) EGF receptor inhibitor (Gefitinib, Erlotinib), (iii) Angiogenesis inhibitors (Bevacizumah), (iv) Proteasome inhibitor (Bortezomib), (v) Unarmed monoclonal antibody (Rituximab, Trastuzumab).

1.8.3.3 Cytotoxic drugs (i) Alkylating agents, (ii) Platinum compounds (Cisplatin, Carboplatin, Oxaliplatin), (iii) Antimetabolites, (iv) Microtubule damaging agents (Vincristine, Vinblastine, Vinorelbine, Paclitaxel, Docetaxel) (v) Topoisomerase-2-

.

inhibitor(etoposide) (vi) Topoisomerase-1-inhibitor (Topotican, Irinotecan), (vii) Antibiotics (Actimycin O, Doxorubicin, Daunorubicin, Epirubicin, Bleomycins, Mitomycin C (viii) Miscellaneous (Hydroxyurea, L-Asparaginase, Trietinoin, Arsenic Oxide). Figure 1.6 is the chemical structure of paclitaxel.

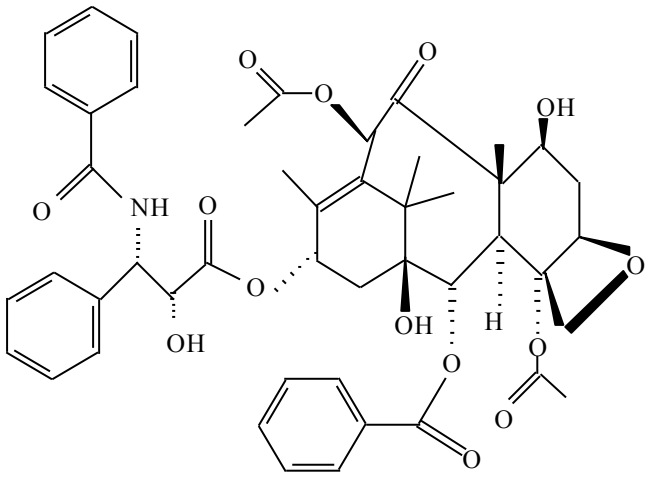


Figure 1.6. Paclitaxel (Taxol).

1.8.4 Challenges and side effects of anticancer drugs

These are challenges in supply of reagents and synthesis, wrong formulation, unsatisfactory patent and licensing, extreme near the beginning toxicity, unproductive methods and plan of management, lasting changeable toxicities and setback in implementation of clinical-trials.

1.8.5 Rationale for cytotoxic drugs

Cytotoxic drugs can be cell cycle nonspecific (CCNS), such as mustine, cyclophospamide, chlorambucil, carmustine, cisplatin and L-Asparaginase, or cell cycle specific (CCS). Studies on the impact of mustard gas during World War I, gave rise to the development of first anticancer chemical and with further development led to synthesis of the first anticancer drug, nitrogen mustard, approved by Food and Drug Administration (FDA) in 1949, while the analogues, cyclophospamide and iphosphamide, were approved by FDA in 1959 and 1988

.

respectively. Mustard gas and nitrogen mustard chemical structures are shown in Figure 1.7 and Figure 1.8.

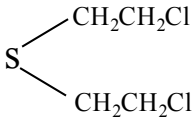


Figure 1.7: Mustard gas**.**

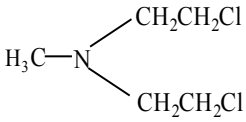


Figure 1.8: Nitrogen mustard**.**

Between 1844 and 1845, cisplatin was first synthesized and referred to as peyrone's chloride [429]. Alfred Werner deduced the structure in 1893, a portion of it which made him to win a nobel prize in 1913[429]. Between 1965 and 1969, Barnett Rosenberg discovered the anticancer activity of cisplatin (first generation), which was approved by FDA in 1978. FDA did approve other derivatives of cisplatin, such as carboplatin (second generation) and oxaliplatin (third generation) in 1989 and 1996 respectively. The side effects of cisplatin and its derivatives are nausea, nephrotoxicity and vomiting [430]. These side effects had led to considering other metals such as copper [431-433], vanadium [260] and zinc [434], as well as, others which have anticancer activities. Among the three major classifications of anticancer drugs, cytotoxic agents are opted for because of the distinct prospects experienced at each stage of the drug discovery and development processes [435].

Colorimetric assays are applied in cytotoxic studies to measure the effect of cytotoxicity and viability cells [436, 437].There are many colorimetric assays like MTT (3-[4-5-dimethylthiazol-2-yl]-25-diphenyltetrazolium bromide, PI (Propidium Iodide), Alamar Blue Assay, LDH(Lactose Dehydrogenase) Celltiter GLO, WSTs (Water Soluble Tetrazolium Salts) Sulforhodamine B.

• MTT (3-[4-5-dimethylthiazol-2-yl]-25-diphenyltetrazolium bromide): This colorimetric assay is a destructive method and acts on enzymes of the mitochondria.

• PI (Propidium Iodide): This assay is used as DNA strain for flow cytometry to assess cell viability and distinguishes among apoptotic, necrotic and normal cells.

• Alamar Blue assay: This also involves mitochondrial activity and a non-destructive method permitting some cells on identical cells.

.

• LDH (Lactose Dehydrogenase) assay: This colorimetric assay measures only damaged cells. Celltiter-Glo: This is a destructive method that causes cell lysis and releases luminescence relative to quantity of ATP. It, therefore, requires ATP standard curve.

• WSTs (Water Soluble Tetrazolium Salts): They are series of water soluble dyes for MTT Assays. WST1 is more advantageous than MTT because of their reduction outside the plasma cells, combination with PMS electron mediator and result of a water-soluble formazan. Other advantages of WST1 assays over MTT are first, direct reading, unlike MTT which requires solubilization step. Secondly, a more efficient signal than MTT and finally, reduce to cells. These advantages of WST1 assays over MTT led to the rational for these cytotoxic studies.

• Sulforhodamine B assay: This is a sensitive assay that is stable and it promotes green chemistry.

1.9. Antimicrobial agents

Antimicrobial agents are chemical substances that possess potentials in diluted solutions to undergo biocidal actions (kill) or biostatic actions (inhibit growth) of microbes. Antimicrobials can be grouped into antibiotics, antifungal, antiparasitic, antiprotozoal and antiviral. The aim of antimicrobial treatment is to inhibit the growth or kill microorganisms and not negatively harming the host animal. Figure 1.9 shows the historical use of antimicrobial agents.

1.9.1 Antibiotic treatment

Antibiotic treatment is only applicable to bacteria and gives a broad description of their spectrum of action. Bacteria can be gram-positive or gram-negative. Antibiotics of narrow spectrum works on either gram-positive or gram-negative bacteria, while antibacterial broad-spectrum work on both gram- positive and gram negative bacteria. Antibiotics can be classified as bactericidal (killing of bacteria) or bacteriostatic (inhibition of the growth and replication of bacteria). Different means by which antibiotics work are by inhibiting the cell wall synthesis, damaging the cell wall, inhibiting the synthesis of protein, interfering with metabolism and impairing the nucleus acids. This had led to different classes of antibiotics, namely; cell wall agents (penicillin, polymyxin B), protein synthesis agents (tetracycline, chloramphenicol), antimetabolites (sulphonamides), nucleic acid agents (fluoroquinolone) and miscellaneous agents (nitrofuran, nitroimiazole, and rifampin).

.

1.9.2 Antifungal treatment

Antifungal treatment involves the use of chemicals to treat fungi diseases. The two types of fungal diseases are superficial (ringworm) and systemic (blastomycosis). The diagnosis involves fungal media or serologic tests. Different groups of antifungal agents are polyene (nystatin, amphotericin B), imidazole (ketoconazole, itraconazole) and antimetabolic (flucytosine).

1.9.3 Antiviral treatment

Antiviral treatment: Viruses attack internal cells and change the host cell's metabolism. Antiviral actions involve the use of antiviral drugs to protect the host cell from different viral penetration (interferons) or the inhibiting virus from producing DNA or RNA (Acyclovir).

1.9.4 Types of antimicrobial test

Antimicrobial tests are antimicrobial efficiency test (AFT) and antimicrobial susceptibility test (AST) [438]

1.9.5 Antimicrobial resistance and tests for the resistance detection

Microorganisms resist drugs and this call for tests in detecting the resistances. These tests are (i) Dilution methods (agar and broth), (2). Disk-diffusion method, (3). E-test, (4). Automated methods, (5) Mechanism-specific tests such as beta-lactamase detection test and chromogenic cephalosporin test and (6) Genotypic methods such as PCR and DNA hybridization methods

1.9.6 Control of microorganisms

Microorganisms can be controlled by asepsis, disinfection and sterilization. Figure 9 shows the historical events in the use of antimicrobial agents (antibiotics) from 1928-2012.

.

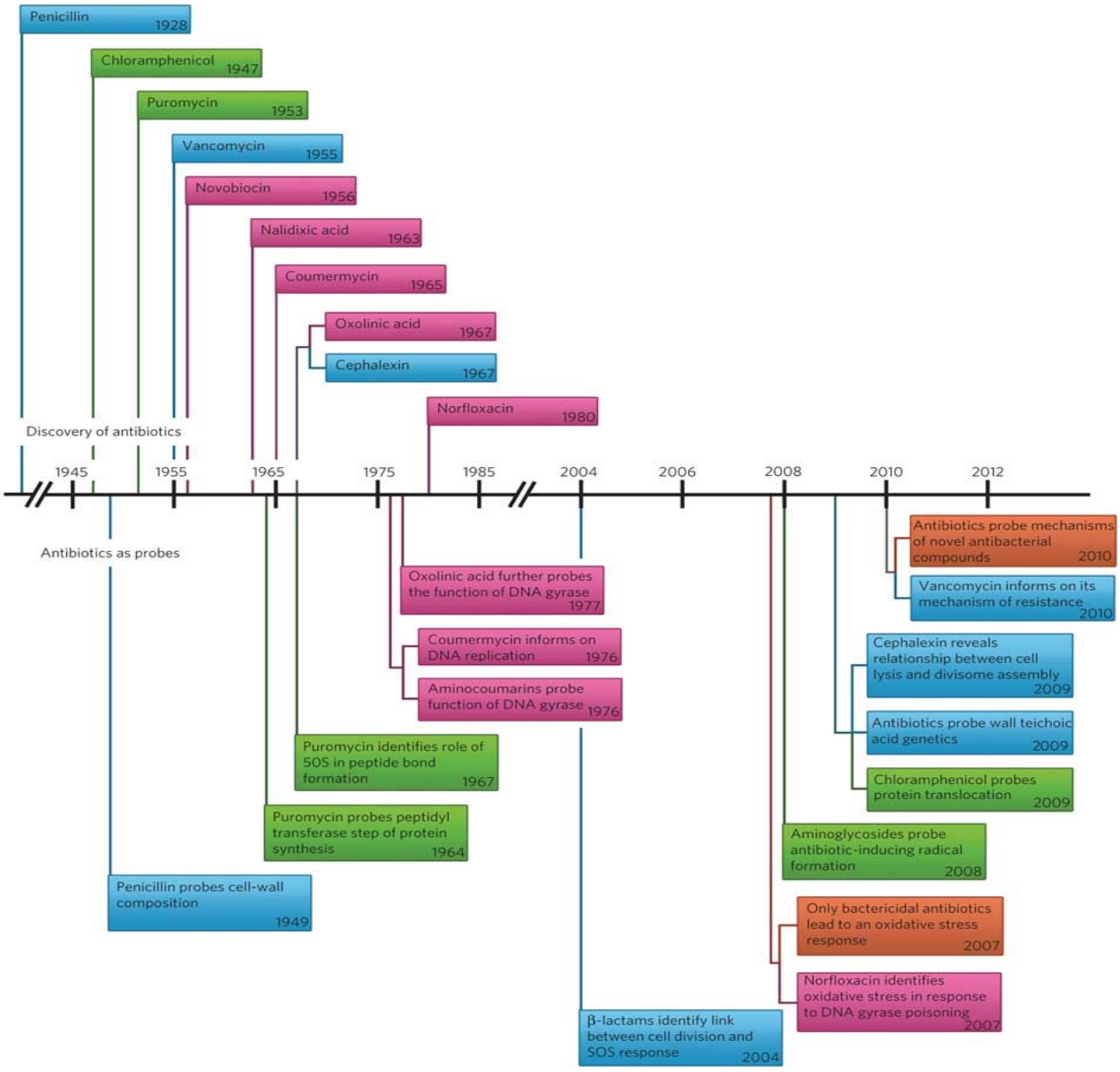


Figure 1.9: Historical events of the use of antimicrobial agents (antibiotics) from 1928-2012***.(http://www.nature.com/chembio/journaL/v7/n7/full/ nchembio.590.html).***

.

1.10 Problem statement

The treatments for of cancer and resistance micro-organisms to pharmaceutical drugs have There is insufficient evidence to support the effectiveness of pharmaceutical drugs with no drawback to treat challenges of antineoplatic resistance and multiple drug resistance. This research focused on the heterocyclic bidentate ligands of sulfadiazine and derivatives of dithiocarbamates of vanadyl and zinc ions, for the purpose of generating non-toxic, low molecular weight, neutral, high synthetic yield stable complexes and balanced ratio of the solubility of the hydrophilicity to lipophilicity as conditions for synthesizing good anticancer and antimicrobial agents.

1.11 Hypotheses

Oxovanadium(IV) complexes of mixed sulfadiazine and dithiocarbamates are less active, of the same activity or more active than zinc(II) complexes of the same mixed ligands.

1.12 Aims of the research

The research was aimed to assess the synergistic properties and potentials of oxovanadium(IV) and zinc(II) complexes of ligands of sulfadiazine and dithiocarbamates thereby, evaluating the chemotherapeutic potentials for *anticancer and antibacterial activities*. The derivatives of dithiocarbamates for this study were prepared through functionalization of the dithiocarbamate ligands. The dithiocarbamate ligands were synthesized from primary and secondary aliphatic, cyclic aliphatic and aromatic amines. The potentials and potencies of ligands, oxovanadium(IV) and zinc(II) complexes were evaluated by screening using *in vitro* approaches of anticancer and antimicrobial activities.

Objectives leading to achieving the aims were:

- to synthesize derivatives of dithiocarbamates
- to synthesize oxovanadium(IV) and zinc(II) complexes from mixed ligands of sodium sulfadiazine and derivatives of dithiocarbamates
- to characterize both ligands with physicochemical characterization techniques (melting point, solubility and conductivity tests) and chemical characterization

.

techniques of Elemental Analysis (EA), Fourier Transform Infra-red Spectroscopy (FT-IR), Ultra-Violet Visible (UV-Vis Spectroscopy), Nuclear Magnetic Resonance (^{1}H and ^{13}C NMR)

- to characterize oxovanadium(IV) and zinc(II) complexes with physicochemical characterization techniques (melting point, solubility and conductivity tests) and chemical characterization techniques of Elemental Analysis (EA), Fourier Transform Infra-red Spectroscopy (FT-IR), Ultra-Violet Visible (UV-Vis Spectroscopy), Nuclear Magnetic Resonance (^{1}H and ^{13}C NMR)
- to screen four dithiocarbamates, oxovanadium(IV) complexes and zinc(II) complexes for biological activities by screening with a standard drug of Emetine by carrying out *in vitro* cytotoxicity tests which entailed KMST-6 (non-cancerous cell line), HT-29 (colon) and W1-38 cell line (normal Human Fetal Lung Fibroblast) using Sulforhodamine B (SRB) assay
- to screen oxovanadium(IV) complexes and zinc(II) complexes for anticancer activities with a standard drug of Parthenolide and human cancer cell lines of TK10 (renal), UACC62 (melanoma) and MCF7 (breast) cancer cells using Sulforhodamine B (SRB) assay
- to screen sodium sulfadiazine, dithiocarbamates and their oxovanadium(IV) complexes and zinc(II) complexes for antimicrobial activities with four antibacterial strains of *Staphylococcus aureus* (MRSA252), *Enterococcus faecalis* (BS385), *Escherichia coli* (MC4100) and *Pseudomonas aeruginosa* (PA01).
- to compare the biological activities of ligands, oxovanadium(IV) and zinc(II) complexes.

.

CHAPTER 2

2. EXPERIMENTAL

2.1 Experimental materials, laboratory instrumentation, syntheses and characterization of ligands

This chapter describes the experimental materials, laboratory instrumentation, syntheses and characterization of ligands used for this research. These are some of the measures used to achieve the aims and objectives of this research. Detailed experiments for oxovanadium(IV) and zinc(II) complexes are described in subsequent chapters respectively.

The experimental materials and laboratory instrumentation listed below with the exception of vanadium(IV) oxide hydrate and anhydrous zinc(II) chloride were used for the syntheses and characterization of ligands of dithiocarbamates. For this research, sodium sulfadiazine and derivatives of dithiocarbamates are the reagents referred to as mixed ligands. Sodium sulfadiazine was used as commercially available, but, all the derivatives of dithiocarbamates were synthesized. The derivatives of dithiocarbamates were obtained by the efficient process of *functionalization* [439-442]. The aim of *functionalization* is to explore the chemotherapeutic and biological potentials and potencies syntheses of these derivatives of dithiocarbamates in anticancer and antimicrobial studies [442]. For derivatives of dithiocarbamates, there are two methods of synthesis, namely, *standard (traditional) methods* and the second is a recent method known as *one- pot synthesis*.

2.1.1 Standard (Traditional) method

The standard (traditional) method is also referred to as conventional method [443-444] or classical method [445]. This method involves the reaction of amines with toxic and expensive reagents, such as, isothiocyanates, thiophosgene and chlorothioformates, and finally addition of thiols [443-448]. This method also entails acidic reaction, low to high temperature, long duration of reaction, and also leads to poor yields, which are unsafe and cause environmental hazards [443-448].

.

2.1.2 One-pot synthesis

The second method applies the ***principles of green chemistry*** [441, 444, 448-449]. The procedure used for all the syntheses of derivatives of dithiocarbamates was multicomponent reaction by ***one pot synthesis,*** because the synthesis is simple, convenient, facile, efficient and environmentally friendly [439, 443-453]. The multicomponent reaction involves composition of amine, carbon disulfide and a base at a temperature less than 4^{o} C. For the multicomponent reaction, the amines used were aliphatic, cyclic aliphatic and aromatic types of primary and secondary amines. The derivatives of dithiocarbamates are divided into two forms, which are aliphatic based dithiocarbamates and aromatic based dithiocarbamates. For both aliphatic and aromatic based dithiocarbamates, the syntheses involved the use of primary amines, cyclic primary amines, secondary amines and aromatic amines. Two types of inorganic bases used for this study were liquid ammonia (weak base) and sodium hydroxide (strong base). The inorganic bases were added to preserve the important amines [454], for the facile conversion of the amines to their corresponding dithiocarbamates [455] and for the best favourable reactions [454-455]. To promote green chemistry, green solvents such as deionised water were used as the reaction media [456-459]. The one-pot synthesis for this research followed a sequence of primary amines, cyclic primary amines, secondary amines and aromatic amines. This chapter focuses on the experimental materials, laboratory instrumentation, syntheses, characterization, results, discussion and conclusion of ligands of derivatives of dithiocarbamates. Characterization, results, discussion and conclusion of sodium sulfadiazine was also done.

2.2 Experimental materials and instrumentation

2.2.1 Experimental materials

All the materials and chemical reagents used for this research were of analytical grade and all were used as received from the chemical industries without purification.

Sulfadiazine sodium salt, Vanadium(IV) oxide hydrate (Sigma-Aldrich, USA), *P*-Anisidine (Sigma Aldrich, Germany), Anhydrous zinc(II) chloride, Carbon disulfide, *O*-Toluidine (Associated Chemical Enterprises (Pty) Ltd, RSA), Aniline, Butyl amine, Diethyl amine, Hexyl amine, Methyl amine, *P*-Toluidine (Merck, Germany), Sodium Hydroxide (Merck, R.S.A.), Ammonia solution Cyclohexylamine, Ethanolamine, Ethyl amine, *P*-Chloro aniline (BDH Laboratory Reagents, England), Phenyl hydrazine (Hopkin and Williams, Chadwell Health Essex, England), N-Ethyl-*M*-Toluidine (Fluka Analytical/ Sigma Aldrich, U. S. A.).

.

Hydrazine hydrate

2.2.2 Solvents

Deionized water (In house), Acetone, Acetonitrile, Diethyl ether, Methanol, Toluene (Merck, RSA), Dimethylformamide, Dimethylsulfoxide (Merck, Germany) and Absolute Ethanol (Supplied by EC Labs).

2.3 Physical measurements

2.3.1 Melting point (MP)

Melting point was taken with STUART melting point SMP11 and was uncorrected. For this research, melting point was carried out with a thermometer of a minimum of 0 ^{o}C to a maximum of 400 ^{o}C to determine the purity of synthesized ligands and metal complexes, as well as, determining the level of coordination between the ligands and synthesized complexes.

2.3.2 Molar conductivity (MC)

Molar conductivity data of both ligands and metal complexes were measured with a CRISON EC- Meter Basic 30+. Molar conductivities of both ligands and metal complexes of oxovanadium(IV) and zinc(II) in dimethylsulfoxide to determine the ionic content and their non-electrolytic nature, with exception of mt-DTC and el-DTC, whose molar conductivities were done in deionised water, due to their very strong solubility in deionised water [460-463].The instrument was first calibrated with buffer solutions of 147 μS/ cm, 1413 μS/ cm and 12.88 μS/ cm before measuring the molar conductivity of the samples.

2.3.3 Elemental analysis (EA)

Elemental analyses of carbon, hydrogen, nitrogen and sulfur were determined using FLASH 2000 Thermoscientific elemental Analyzer and EAS 1108, FISONS Instruments S. P. A. (Italy). Elemental analysis was carried out at Chemistry Department, University of Kwa-Zulu Natal, South Africa and Chemistry Department, University of Montreal, Canada. The aim of

.

using this technique was to elucidate the structures and check the purities of the synthesized ligands and metal complexes [464].

2.3.4 Fourier transforms infrared spectroscopy (FT-IR)

IR spectra were recorded on a Perkin-Elmer 2000 FT-IR spectrophotometer in the range of 370-4000 cm^{-1}. The aims of using FT-IR for this research were to determine the presence of the moieties and also for observing the coordination activities between the ligands and their respective metal complexes.

2.3.5 Ultraviolet-Visible spectroscopy (Electronic spectroscopy)

Electronic spectra were obtained with a Perkin-Elmer Lambda 25 UV-Vis Spectrometer. Ultraviolet-visible spectroscopy was applied to determine the presence of the chromophores of the ligands and metal complexes in dimethylsulfoxide (DMSO), as well as, methanol and deionised water. The sample solutions were analyzed with cuvettes made of quartz with path length of 1 cm. Ultraviolet-visible spectroscopy provides additional information on the stereochemistry and the level of coordination between the ligands and metal complexes.

2.3.6 Nuclear Magnetic Resonance (NMR)

Nuclear magnetic resonance (NMR) data were recorded on Bruker Ultrashield 400 NMR spectrometer operating at frequencies of 400.1 MHz for ^{1}H and ^{13}C NMR at 100.6 MHz, and Varian ^{Unity}*Inova* 600 NMR spectrometer operating at frequencies of 600 MHz for ^{1}H and at 150 MHz for ^{13}C NMR frequency. Both were performed at University of Johannesburg, South Africa and University of Stellenbosch, South Africa respectively.

Nuclear magnetic resonance is used as a diagnostic tool to identify the presence of moieties in sulfadiazine, synthesized ligands of dithiocarbamates and the coordination in the corresponding oxovanadium(IV) and zinc(II) complexes [464-465] . Chemical shifts were recorded in parts per million (ppm). The solvent used was deuterated dimethylsulfoxide (DMSO- d_6 ^{1}H NMR 2.49 ppm (residual signal for DMSO- d_6); 3.50 ppm (residual signal for

.

water); ^{13}C NMR; 39.50 ppm. Tetramethylsilane (TMS) is the internal standard or a reference standard used to calibrate before the sample solution. Tetramethylsilane is also recorded in ppm.

2.4 Synthesis and characterization of ligands of dithiocarbamates

2.4.1 Materials and instrumentation

All the materials and instrumentation under Section 2.2. of this chapter were used for the synthesis of ligands of dithiocarbamates with the exception of sulfadiazine sodium salt (Sigma-Aldrich, USA), vanadium(IV) oxide hydrate (Sigma-Aldrich, USA), anhydrous zinc(II) chloride (Associated Chemical Enterprises (Pty) Ltd, RSA).

2.4.2. Sodium sulfadiazine, SFZ ($C_{10}H_9N_4NaO_2S$)

White solid. Formula Molecular weight: 272.26 g. Percentage Yield: 99%. M. P.> 300 ^oC, Molar Conductivity: 8.16 Ω^{-1} cm^2 mol^{-1}, Anal. Calcd. for $C_{10}H_9N_4O_2S$ (%) C: 44.12; H: 3.33; N: 20.58; S: 11.78. Selected FT-IR (KBr disc), $\nu(cm^{-1})$: 3415 $(NH_2)_{as}$ 3299 $(NH_2)_s$ 3237 (SO_2NH); 1544 (C=N); 1240 $(SO_2)_{as}$; 1130$(SO_2)_s$. Selected λ_{max} in DMSO solvent (nm): 274 (π-π^* N-C=S), 319, 323, 386 (n-π^* S-C=S). ^1H NMR (DMSO-d_6, 400Hz, ppm): δ 5.36 (NH_2); δ 6.38-6.46 (C_6H_5-H); δ7.46-7.48 (N=CH); δ 8.10 (pyrimidine $C_4H_2N_2$-H ring), ^{13}C NMR (DMSO-d_6, 100.6 MHz, ppm) δ 109.20; 111.91 (C_6H_5-H), δ 128.25; (N=^{13}CH), δ 133.20 (^{13}C-NH_2), δ 143.97 (pyrimidine$^{13}C_4H_2N_2$-H ring); δ157.29, 164.39; ($^{13}CSO_2NNa$).

2.5. General methods for the syntheses of ligands of dithiocarbamates

The general method of syntheses of ligands of dithiocarbamates was divided into two categories which were based on the nature of inorganic base. They are (i) ammonium salts of dithiocarbamates from aliphatic, cyclic aliphatic and aromatic amines and (ii) sodium salts of dithiocarbamates from aliphatic amines, cyclic aliphatic amines and aromatic amines.

.

2.5.1 Ammonium salts of dithiocarbamates from aliphatic, cyclic aliphatic and aromatic amines

(i). Ammonium salts of dithiocarbamates from aliphatic amines (ammonium *N*-butyl dithiocarbamate, ammonium *N*-hexyl dithiocarbamate, ammonium *N*-ethanol dithiocarbamate)

(ii). Ammonium salt of dithiocarbamates from cyclic aliphatic amines (ammonium *N*-cyclohexyl dithiocarbamate)

(iii). Ammonium salt of dithiocarbamates from aromatic amines (ammonium *N*-aniline dithiocarbamate, ammonium *N*-methyl-*N*-phenyl dithiocarbamate, ammonium *N*-methyl-*N*-phenyl dithiocarbamate and ammonium *N*-para- chlorophenyl dithiocarbamate).

All the ligands were prepared according to literature with some modifications [442-447, 493-500].

2.5.2 Sodium salts of dithiocarbamates from aliphatic, cyclic aliphatic and aromatic amines

(i). Sodium salts of dithiocarbamates from aliphatic amines (sodium *N*-methyl dithiocarbamate, sodium *N*-ethyl dithiocarbamate, sodium *N*-butyl dithiocarbamate, sodium *N*-hexyl dithiocarbamate, sodium *N*-diethyl dithiocarbamate, sodium hydrazine hydrate dithiocarbamate sodium *N*-ethanol dithiocarbamate).

(ii). Sodium salt of dithiocarbamates from cyclic aliphatic amines (sodium *N*-cyclohexyl dithiocarbamate).

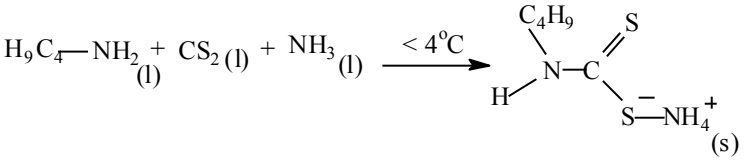
(iii). Sodium salt of dithiocarbamates from aromatic amines (sodium phenyl hydrazine dithiocarbamate, sodium *N*-aniline dithiocarbamate, sodium *N*-ortho-toluidine dithiocarbamate, sodium *N*-methyl-*N*-phenyl dithiocarbamate, sodium *N*-ethyl-*N*-phenyl dithiocarbamate, sodium *N*-para-chlorophenyl dithiocarbamate, sodium *N*-para-anisidine dithiocarbamate, sodium *N*-para-toluidine dithiocarbamate, sodium *N*-ethyl-meta-toluidine dithiocarbamate, sodium *N*-para-chlorophenyl dithiocarbamate).

.

2.5.3 Ammonium salts of dithiocarbamates from aliphatic amines

2.5.3.1 Synthesis of ammonium *N*-butyl dithiocarbamate (bu-DTC)

N-butyl aniline (4.94 mL, 0.1 mol), conc. aqueous ammonia (30.00 mL, 0.1 mol) and carbon disulphide (6.00 mL, 0.1 mol) were used as starting materials. The reaction mixture was magnetically stirred for 3 h. A white solid was obtained. Molecular weight: 166.30 g. Percentage Yield: 52%. M. P. 70 ^{o}C. Molar Conductivity: 3.99 Ω^{-1} cm^2 mol^{-1}. Anal. Calcd for bu-DTC (%) C: 36.11; H: 8.49; N: 16.85; S: 36.56. Found (%) C: 35.81; H: 10.75; N: 15.27; S: 41.80. Selected FT-IR (KBr disc), ν (cm^{-1}): 1509 (C-N), 1042 (C=S). Selected λ_{max} in DMSO solvent (nm): π-π^*(N-C=S) 302, n-π^*(S-C=S) 324. ^{1}H NMR (DMSO-*d*$_6$, 400.1 MHz, ppm): δ 1.00-1.04 (m –CH_3- C_4H_9) δ 2.78-2.81; (α -CH_2- C_4H_9), δ 3.20-3.40 (s C_2HN); δ 6.90, 7.60-7.90 (N-H). ^{13}C NMR (DMSO-d_6, 100.6 MHz, ppm) δ 13.55-18.86 (–CH_3 C_4H_9) δ 29.07-31.03; 47 (-β CH_2) δ 44.03; (α -CH_2- C_4H_9), δ 56.10 (NH_2C); δ 204.00, 214.00 (NCS_2).

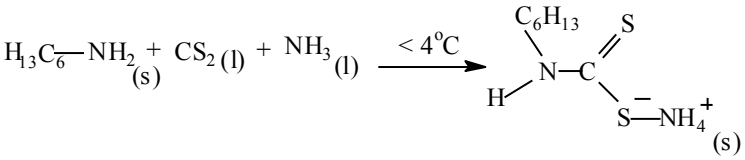


Scheme 2.1. Synthesis of ammonium *N*-butyl dithiocarbamate (bu-DTC)**.**

2.5.3.2 Synthesis of ammonium *N*-hexyl dithiocarbamate (he-DTC)

N-hexyl aniline (12.98 mL, 0.1mol), conc. aqueous ammonia (30.00 mL, 0.1 mol) and carbon disulphide (6.00 mL, 0.1 mol) were used as starting materials. The reaction mixture was magnetically stirred for 3 h in an ice bath at ambient temperature. A white solid was obtained. Molecular weight: 194.35 g. Percentage Yield: 65%. M. P. 52-54 ^{o}C, Molar Conductivity: 2.63 Ω^{-1} cm^2 mol^{-1}. Anal. Calcd for he-DTC (%) C: 43.71; H: 8.38; N: 14.56; S: 33.34. Found (%) C: 45.25; H: 10.49; N: 11.58; S: 29.38. Selected FT-IR (KBr disc), ν (cm^{-1}): 1467 (C-N), 996 (C=S). Selected λ_{max} in DMSO solvent (nm): π-π^*(N-C=S) 297, n-π^*(S-C=S) 324. ^{1}H NMR (DMSO-*d*$_6$, 400 MHz, ppm) δ 0.84-0.87 (–CH_3); δ 1.28-1.44; (β-CH_2) δ 2.98; (α -CH_2), δ 3.29-3.33 (C_2H-N); δ 6.86-7.53 (N-H).

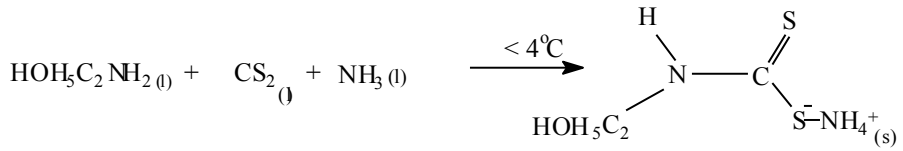
.



Scheme 2.2. Synthesis of ammonium *N*-hexyl dithiocarbamate (he-DTC).

2.5.3.3 Synthesis of ammonium *N*-Ethanol Dithiocarbamate (eh-DTC)

Ethanolamine (3.02 mL, 0.1 mol), carbon disulphide (6.00 mL, 0.1 mol) and conc. aqueous ammonia (30.00 mL, 0.1mol) were used as starting materials. The reaction mixture was magnetically stirred for 3 h in an ice bath at ambient temperature. Yellow solid precipitates were obtained. Molecular weight 155.25 g. Percentage Yield: 71%. M. P. 72 ^{o}C, Molar Conductivity: 2.95 Ω^{-1} cm^2 mol^{-1}. Anal. Calcd for eh-DTC (%) C: 23.21; H: 7.14; N: 18.04; S: 41.30; N: 18.04. Found (%) C: 30.72; H: 5.66; N: 13.89; S: 29.01. Selected FT- IR (KBr disc), ν (cm^{-1}): 1463 (C-N), 997 (C=S). Selected λ_{max} in DMSO solvent (nm): π-π^*(N-C=S) 299, n-π^*(S-C=S) 319. ^{1}H NMR (DMSO-d_6, 600 MHz, ppm): δ 0.84-0.89; 1.25-1.28; (-CH_3) δ 2.75-2.91; (α -CH_2-), δ 3.28-4.28 (C_2HN); δ 6.18-6.75; 7.45-7.72; 8.00 (N-H); δ 9.95 (OH). ^{13}C NMR (DMSO-d$_6$, 150 MHz, ppm) δ 29.46; 34.62 (–CH_3) δ 41.45, 42.84 (-γ CH_2) δ 51.47-64.17 (NH_2C); δ 157.82-159.59 (CH_2-OH); δ 173.81 (NCS_2).



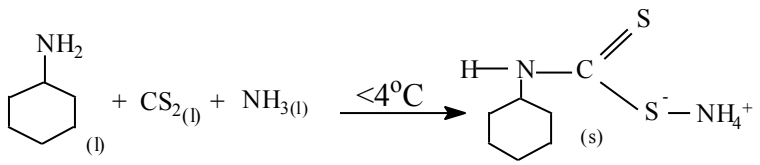
Scheme 2.3. Synthesis of ammonium *N*-ethanol dithiocarbamate (eh-DTC)**.**

2.5.3.4 Synthesis of ammonium *N*-Ethanol Dithiocarbamate (eh-DTC)

Cyclohexylamine (11.47 mL, 0.1 mol), carbon disulphide (6.00 mL, 0.1 mol) and conc. aqueous ammonia (30.00 mL, 0.1 mol) were used as starting materials. The reaction mixture was magnetically stirred for 3 h in an ice bath at ambient temperature. Pinkish-white solid precipitates were obtained. Molecular weight 192.34 g. Percentage Yield: 96%. M. P. 80 ^{o}C, Molar Conductivity: 3.74 Ω^{-1} cm^2 mol^{-1}. Anal. Calcd for cy-DTC (%) C: 43.71; H: 8.38; N: 14.56; S: 33.34. Found (%) C: 51.34; H: 8.39; N: 9.38; S: 20.57. Selected IR (KBr), ν (cm^{-1}): 1486 (C-N), 1003 (C=S). Selected λ_{max} in DMSO solvent (nm): π-π^*(N-C=S) 305, n-π^*(S-

.

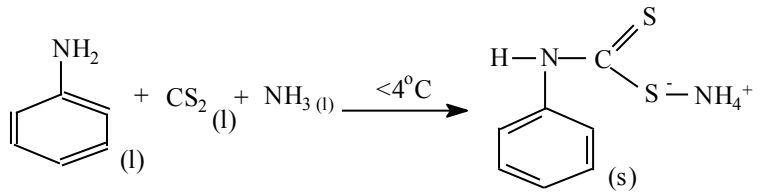
C=S) 339-351. ^{1}H NMR (DMSO-*d*$_6$, 600 MHz, ppm): δ 1.10-1.25, 1.66-1.91 (α -CH_2-), δ 4.04-4.23 (C_2HN); δ 7.15-7.18 (-C_6H_{11}) δ 7.93-7.96; 9.60-9.63 (N-H); ^{13}C NMR (DMSO-d_6, 150 MHz, ppm) δ 23.82-25.32, 30.40-39.52 (α -CH_2) δ 49.43-54.72 (NH_2C); δ 157.82-159.59 (CH_2-OH); δ 200.73, 212.08 (NCS_2).



Scheme 2.4. Synthesis of ammonium *N*-cyclohexyl dithiocarbamate (cy-DTC)**.**

2.5.3.5 Synthesis of ammonium N-aniline dithiocarbamate (an-DTC)

Aniline (9.11 mL, 0.1 mol), carbon disulphide (6.00 mL, 0.1 mol) and conc. aqueous ammonia (30.00 mL, 0.1 mol) were used as starting materials. Whitish yellow solid precipitates were obtained. Molecular weight: 186.29 g. Percentage Yield: 92%. M. P. 34-36 ^{o}C, Molar Conductivity: 1.02 Ω^{-1} cm^2 mol^{-1}; Anal. Calcd for an-DTC (%) C: 45.13; H: 5.41; N: 15.04; S: 34.42. Found (%) C: 45.32; H: 5.72; N: 14.94; S: 36.28. Selected IR (KBr), *v* (cm^{-1}): 1452 (C-N), 1023 (C=S). Selected λ_{max} in DMSO solvent (nm): π-π*(N-C=S) 318, n-π*(S-C=S) 323. ^{1}H NMR (DMSO-*d*$_6$, 400Hz, ppm): δ 3.20-3.40 (HC-N); 6.44-7.54 (Ar-^{1}H); δ7.82-7.85; 7.92-7.93; 10.13; 11.15 (N-H). ^{13}C NMR (DMSO-d_6, 150 MHz, ppm) δ 38.87-40.12 (NHC); δ 113.90-148.55 (C_6H_5-H); δ 194.00; 201.77, 218.00 (NCS_2).



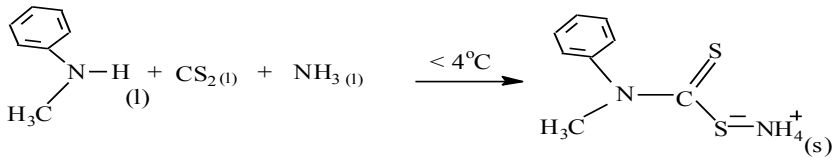
Scheme 2.5. Synthesis of ammonium *N*-aniline dithiocarbamate (an-DTC)**.**

2.5.3.6 Synthesis of ammonium of N-methyl-N-phenyl dithiocarbamate (me-DTC)

N-methyl aniline (10.82 mL, 0.1 mol), carbon disulphide (6.00 mL, 0.1 mol) and conc. aqueous ammonia (30.00 mL, 0.1 mol) were used as starting materials. Yellow solid precipitates were obtained. Molecular weight: 200.32 g. Percentage Yield: 86%. M. P. 79-80

.

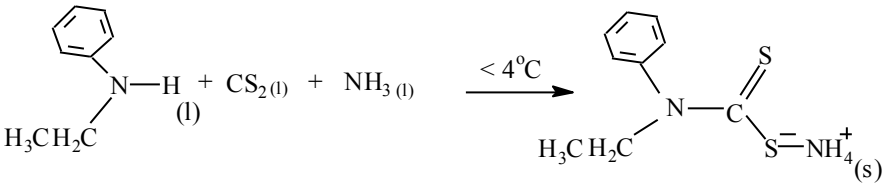
^{o}C Molar Conductivity: 1.98 Ω^{-1} cm^2 mol^{-1}. Anal. Calcd for me-DTC (%) C: 47.97; H: 6.04; N: 13.98; S: 32.01. Found (%) C: 44.68; H: 5.91; N: 14.89; S: 7.56. Selected FT-IR (KBr), *v* (cm^{-1}): 1496 (C-N), 1042 (C=S). Selected λ_{max} in DMSO solvent (nm): (N-C=S) 317, (S-C=S) 323. ^{1}H NMR (DMSO-*d*$_6$, 400Hz, ppm): δ 2.25 δ(-CH_3); 5.42 (H_2C-N); δ6.35-6.38;(Ar-^{1}H); 6.90-7.15 (N-H) ^{13}C NMR (DMSO-d$_6$, 100.6 MHz, ppm) δ 29.70 (–CH_3) δ 38.87-40.13 (NHC); δ 111.60-128.81 (C_6H_5-H); δ 149.87 (NCS_2).



Scheme 2.6. Synthesis of ammonium *N*-methyl-*N*-phenyl dithiocarbamate (me-DTC)**.**

2.5.3.7 Synthesis of ammonium *N*-ethyl-*N*-phenyl dithiocarbamate (et-DTC)

N-Ethyl aniline (12.623 mL, 0.1 mol), conc. aqueous ammonia (30.00 mL, 0.1 mol) and carbon disulphide (6.00 mL, 0.1 mol) were used as starting materials. A yellowish –white solid was obtained. Molecular weight: 214.34 g. Percentage Yield: 57%. M. P. 64-66 ^{o}C. Molar Conductivity: 1.40 Ω^{-1} cm^2 mol^{-1}. Anal. Calcd for et-DTC (%) C: 50.43; H: 6.58; N: 13.07; S: 29.91. Found (%) C: 46.71; H: 7.84; N: 12.48; S: 17.43. Selected FT-IR (KBr), *v* (cm^{-1}): 1488 (C-N), 1023 (C=S). Selected λ_{max} in DMSO solvent (nm): π-π*(N-C=S) 298, n-π*(S-C=S) 332. ^{1}H NMR (DMSO-*d*$_6$, 400Hz, ppm): δ 1.15-1.51; δ(-CH_3); δ2.96-3.34(α H_2C); 5.42 (H_2C-N); δ 6.47-6.53;(Ar-^{1}H); 6.84; 7.02-7.06 (N-H). ^{13}C NMR (DMSO-d$_6$, 100.6 MHz, ppm) δ 14.37 (–CH_3) δ 38.87-40.13 (NHC); δ 111.90-148.94 (C_6H_5-H); δ 192.68 (NCS_2).

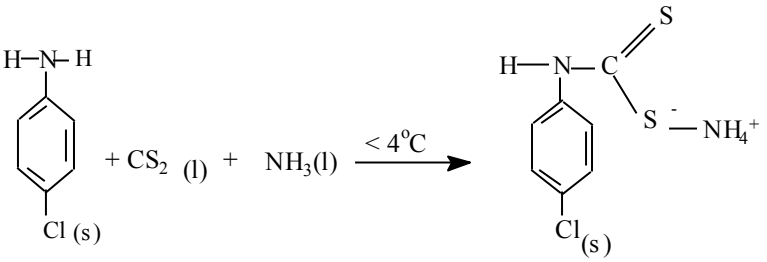


Scheme 2.7. Synthesis of ammonium *N*-ethyl-*N*-phenyl dithiocarbamate (et-DTC).

.

2.5.3.8 Synthesis of ammonium *N*-para- Chlorophenyl dithiocarbamate (cl-DTC)

N-P- Chlorophenyl dithiocarbamate (3.02 mL, 0.1 mol), carbon disulphide (6.00 mL, 0.1 mol) and conc. aqueous ammonia (30.00 mL, 0.1mol) were used as starting materials. Yellow solid precipitates were obtained. Molecular weight: 220.73 g. Percentage Yield: 91%. M. P. 120-121 ^{o}C. Molar Conductivity: 0.55 Ω^{-1} cm^2 mol^{-1}. Anal. Calcd for cl-DTC (%) C: 38.09; H: 4.11; N: 12.69; S: 29.05; Cl: 16.06; Found (%) C: 56.48; H: 5.51; N: 10.87; S: 0.11. Selected FT-IR (KBr), *v* (cm^{-1}): 1467 (C-N), 986 (C=S). Selected λ_{max} in DMSO solvent (nm): π-π^* (N-C=S) 318, n-π^* (S-C=S) 323; 356. ^{1}H NMR (DMSO-*d6*, 400Hz, ppm): δ 5.19-5.96 (H_2C-N); δ 6.34-7.21(Ar-^{1}H); 6.84; 7.02-7.06 (N-H). ^{13}C NMR (DMSO-d_6, 100.6 MHz, ppm) δ 38.87-40.13 (NHC); δ 115.22-147.55 (C_6H_5-H); δ 179.27; 181.12; 202.29 (NCS_2).



Scheme 2.8. Synthesis of ammonium *N*-para-*N*-chlorophenyl dithiocarbamate (cl-DTC)**.**

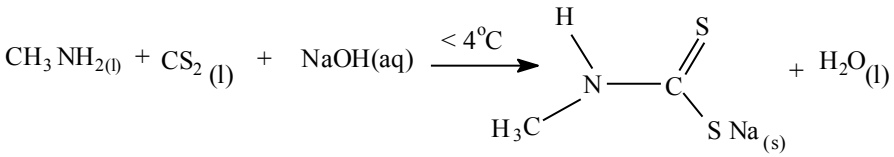
2.5.4. Sodium salts of dithiocarbamates from aliphatic amines

2.5.4.1 Synthesis of sodium methyl dithiocarbamate (mt-DTC)

In an Erlenmeyer flask (250 mL), methyl amine (4.37 mL, 0.1 mol) and carbon disulphide (6.00 mL, 0. 1 mol) were stirred for 30 min at a temperature of less than 4^{o}C, after which sodium hydroxide in a small amount of water (4 g, 0.1mol) was added dropwise to the mixture. The reaction was stirred for 3 h, while the temperature was maintained at less 4 ^{o}C. Whitish coloured crystals were formed. These were washed with diethyl ether solvent and the colour of the desired white crystals was still retained. Formula Molecular weight: 129.17 g. Percentage Yield: 88%. M. P. 56 ^{o}C. Molar Conductivity: 1.62 Ω^{-1} cm^2 mol^{-1}. Anal. Calcd for mt-DTC (%) C: 18.60; H: 3.12; N: 10.84; S: 49.64. Found (%) C: 4.57; H: 6.37; N: 0.00; S: 0.00. Selected FT-IR (Nujol), *v* (cm^{-1}): 1461 (C-N), 1016 (C=S). Selected λ_{max} in DMSO

.

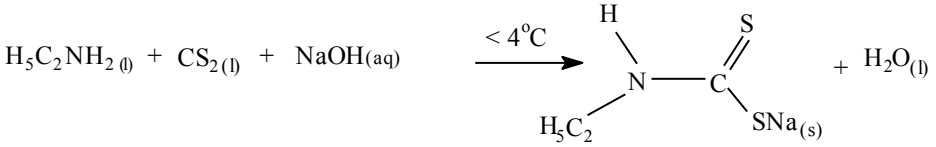
solvent (nm): (N-C=S) 265, (S-C=S) 315. ^{1}H NMR (DMSO-d_6, 400Hz, ppm): δ 2.32-2.49; 2.61(–CH_3); δ 3.53-3.55 (s CHN).



Scheme 2.9. Synthesis of sodium methyl dithiocarbamate (mt-DTC)**.**

2.5.4.2 Synthesis of sodium ethyl dithiocarbamate (el-DTC)

Ethyl amine (6.54 mL, 0.1 mol), carbon disulphide (6.00 mL, 0.1 mol) and sodium hydroxide (4.0 g, 0.1mol) were used as starting materials. The reaction mixture was magnetically stirred for 3 h in an ice bath at ambient temperature. White solid crystals were obtained. Molecular weight: 143.20 g. Percentage Yield: 97%. M. P. 80 ^{o}C. Conductivity: 0.55 Ω^{-1} cm^2 mol^{-1}. Anal. Calcd for el-DTC (%) C: 25.16; H: 4.22; N: 9.78; S: 44.78. Found (%) C: 4.42; H: 0.62; N: 0.00; S: 0.00. Selected FT-IR (Nujol), ν (cm^{-1}): 1463 (C-N), 1013 (C=S). Selected λ_{max} in DMSO solvent (nm): (N-C=S) 240, (S-C=S) 332. ^{1}H NMR (DMSO-d_6, 400Hz, ppm): δ 1.00 (-CH_3) δ 3.30 (α -CH_2), δ 3.61 (C_2HN).



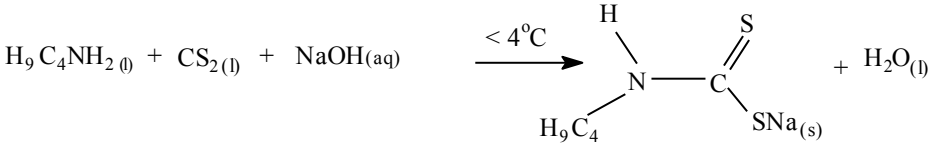
Scheme 2.10. Synthesis of sodium ethyl dithiocarbamate (el-DTC)**.**

2.5.4.3 Synthesis of sodium *N*-Butyl Dithiocarbamate (bt-DTC)

Butyl amine (9.88 mL, 0.1 mol), carbon disulphide (6.00 mL, 0.1 mol) and sodium hydroxide (4.0 g, 0.1 mol) were used as starting materials. The reaction mixture was magnetically stirred for 3 h in an ice bath at ambient temperature. Yellow liquid was obtained. Molecular weight: 171.25 g. Percentage Yield: 94%. M. P. 56-58 ^{o}C. Molar Conductivity: 2.40 Ω^{-1} cm^2 mol^{-1} Anal. Calcd for bt-DTC (%) C: 35.07; H: 5.89; N: 8.18; S: 37.44. Found (%) C: 19.01; H:

.

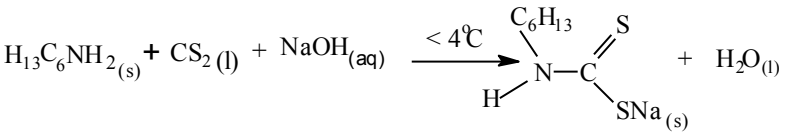
5.03; N: 4.25; S: 19.53. Selected FT-IR (KBr), *v* (cm^{-1}): 1464 (C-N), 1049 (C=S). Selected λ_{max} in DMSO solvent (nm): (N-C=S) 252, (S-C=S) 306. ^{1}H NMR (DMSO-*d*$_6$, 400Hz, ppm): δ = 0.83-0.89; 0.90-1.53(–CH_3) δ 2.78-2.81; (α -CH_2- C_4H_9), δ 3.54-3.67 (C_2HN). ^{13}C NMR (DMSO-d_6, 150 MHz, ppm) δ 13.15-13.93 (–CH_3) δ 19.25-19.86 (-γ CH_2) δ 30.38-31.24; (β -CH_2- C_4H_9), 40.20 (α -CH_2- C_4H_9), δ 44.30; 46.27 (NH_2C); δ 202.05, 214.28 (NCS_2).



Scheme 2.11. Synthesis of sodium butyl dithiocarbamate (bt-DTC)**.**

2.5.4.4 Synthesis of sodium *N*-Hexyl Dithiocarbamate (hx-DTC)

Hexyl amine (6.0708 mL, 0.05 mol), carbon disulphide (3.00 mL, 0. 05 mol) and sodium hydroxide (2.0 g, 0.05 mol) were used as starting materials. The reaction mixture was magnetically stirred for 3 h in an ice bath at ambient temperature. White solid precipitates were obtained. Molecular weight: 199.30 g. Percentage Yield: 90%. M. P. 142 °C. Conductivity: 1.39 Ω^{-1} cm^2 mol^{-1}. Anal. Calcd for hx-DTC (%) C: 42.19; H: 7.03; N: 7.03; S: 32.17. Found (%) C: 9.84; H: 9.84; N: 1.50; S: 11.96. Selected FT-IR (Nujol), *v* (cm^{-1}): 1459 (C-N), 959 (C=S). Selected λ_{max} in DMSO solvent (nm): (N-C=S) 219, (S-C=S) 318. ^{1}H NMR (DMSO-*d*$_6$, 400Hz, ppm): δ 0.82-0.85 (–CH_3); 1.20-1.26 (γ -CH_2), 1.41-1.42 (β -CH_2), δ 3.15; (α -CH_2), δ 3.60-3.62 (C_2HN).). ^{13}C NMR (DMSO-d_6, 150 MHz, ppm) δ 14.19-14.29; 18.70 (–CH_3) δ 22.39, 22.40 (-γ CH_2) δ 26.36-26.57; (β -CH_2- C_4H_9), 28.42-28.57 (α -CH_2- C_4H_9), δ 31.19-31.43 (NH_2C); δ 202.0, 214.04 (NCS_2).

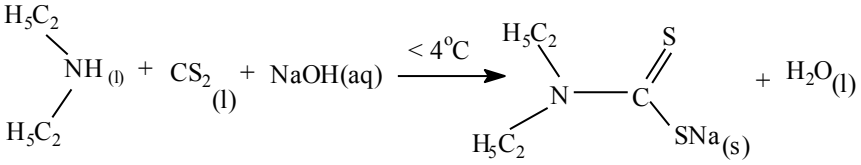


Scheme 2.12. Synthesis of sodium hexyl dithiocarbamate (hx-DTC)**.**

.

2.5.4.5 Synthesis of sodium *N*-Diethyl Dithiocarbamate (de-DTC)

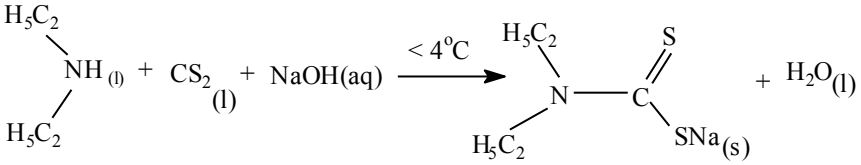
Diethyl amine (9.88 mL, 0.1 mol), carbon disulphide (6.00 mL, 0.1 mol) and sodium hydroxide (4.0 g, 0.1mol) were used as starting materials. Pinkish white crystals were obtained. Molecular weight: 171.25 g. Percentage Yield: 98%. M. P. 90-92 ^{o}C. Molar Conductivity: 5.05 Ω^{-1} cm^2 mol^{-1}. Anal. Calcd. for de-DTC (%) C: 35.07; H: 5.89; N: 8.18; S: 37.44 Found (%) C: 26.69; H: 7.27; N: 6.16; S: 23.16. Selected FT-IR (KBr), ν (cm^{-1}): 1475 (C-N), 993 (C=S). Selected λ_{max} in DMSO solvent (nm): (N-C=S) 314, (S-C=S) 323. ^{1}H NMR (DMSO-*d*$_6$, 600 MHz, ppm): δ 1.07-1.09 (–CH_3); δ 3.95-3.98 (C_2HN).). ^{13}C NMR (DMSO-d$_6$, 150 MHz, ppm) δ 12.61 (–CH_3) 46.30 (α -CH_2), δ 38.86-40.10 (NH_2C); δ 211.86 (NCS_2).



Scheme 2.13 a. Synthesis of sodium diethyl dithiocarbamate (de-DTC)**.**

2.5.4.6 Sodium salt of (already prepared) N, N- diethyl dithiocarbamate (de*-DTC)

Molecular weight: 177.25 g. Percentage Yield: 99%. M. P. 60 ^{o}C. Molar Conductivity: 2.15 Ω^{-1} cm^2 mol^{-1}. Anal. Calcd for de*-DTC (%) C: 35.07; H: 5.89; N: 8.18; S: 37.44. Found (%) C: 27.01; H: 8.34; N: 6.25; S: 29.34. Selected FT-IR (KBr), ν (cm^{-1}): 1476 (C-N), 986 (C=S). Selected λ_{max} in DMSO solvent (nm): (N-C=S) 219, (S-C=S) 303. ^{1}H NMR (DMSO-d$_6$, 400Hz, ppm): ^{1}H NMR (DMSO-*d*$_6$, 400 MHz, ppm): δ 1.05-1.08 (–CH_3); δ 4.00 (s C_2HN). ^{13}C NMR (DMSO-d$_6$, 150 MHz, ppm) δ 12.50 (–CH_3) 46.33 (α -CH_2), δ 38.86-40.13 (NH_2C); δ 211.78 (NCS_2).

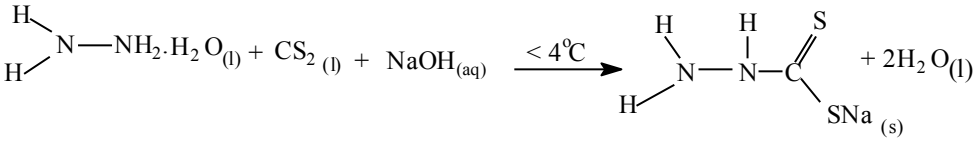


Scheme 2.13 b. Sodium diethyl dithiocarbamate (*de-DTC)**.**

.

2.5.4.7 Synthesis of sodium hydrazine hydrate dithiocarbamate (hh-DTC)

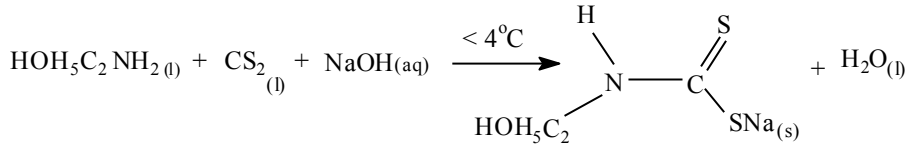
Hydrazine hydrate (4.86 mL, 0.1 mol), carbon disulphide (6.00 mL, 0.1 mol) and sodium hydroxide (4.0 g, 0.1mol) were used as starting materials. Molecular weight: 130.16 g. Percentage Yield: 87%. M. P. 42-44 ^{o}C. Molar Conductivity: 1.03 Ω^{-1} cm^2 mol^{-1}. Anal. Calcd. for hh-DTC (%) C: 9.23; H: 2.32; N: 21.52; S: 49.26. Found (%) C: 6.53; H: 4.69; N: 2.17; S: 28.41. Selected FT-IR (KBr), ν (cm^{-1}): 1462 (C-N), 1039 (C=S). Selected λ_{max} in DMSO solvent (nm): (N-C=S) 240, (S-C=S) 310. ^{1}H NMR (DMSO-d_6, 600MHz, ppm): δ 3.40; 4.40-4.54 (C_2HN); δ 8.68 (N-H). ^{13}C NMR (DMSO-d_6, 150 MHz, ppm) δ 40.43 (NH_2C); δ 181.48 (NCS_2).



Scheme 2.14. Syntheses of sodium hydrazine hydrate dithiocarbamate (hh-DTC)**.**

2.5.4.8 Synthesis of sodium *N*-ethanol dithiocarbamate (ea-DTC)

Ethanolamine (6.05 mL, 0.1 mol), carbon disulphide (6.00 mL, 0.1 mol) and sodium hydroxide (4.0 g, 0.1 mol) were used as starting materials. Yellow liquid was obtained. Molecular weight: 160.20 g. Percentage Yield: 82%. M. P. 50 ^{o}C. Molar Conductivity: 0.35 Ω^{-1} cm^2 mol^{-1}. Anal. Calcd for ea-DTC (%) C: 22.49; H: 4.40; N: 8.74; S: 40.02. Found (%) C: 14.15; H: 5.39; N: 3.90; S: 18.50. Selected FT-IR (KBr), ν (cm^{-1}): 1459 (C-N), 974 (C=S). Selected λmax in DMSO solvent (nm): π-π*(N-C=S) 239, n-π*(S-C=S) 312. ^{1}H NMR (DMSO-d_6, 400Hz, ppm): δ 1.02-1.05 (–CH_3); δ 2.00-3.43; (α -CH_2), δ 4.25-4.80 (C_2HN); δ 8.00 (N-H). ^{13}C NMR (DMSO-d_6, 150 MHz, ppm) δ 18.62 (–CH_3) δ 29.56; 33.12; 33.14; 38.20; 38.98(-γ CH_2) δ 42.95-69.89 (NH_2C); δ 122.13, 158.19, 158.29 (CH_2-OH); δ 188.69, 198.26 (NCS_2).



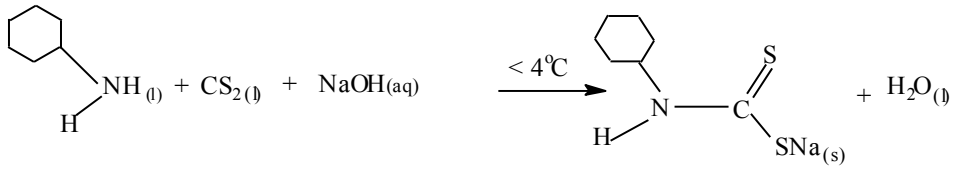
Scheme 2.15. Synthesis of sodium ethanol dithiocarbamate (ea-DTC)**.**

.

2.5.5. Sodium Salt of Dithiocarbamates from Cyclic Aliphatic Amines

2.5.5.1 Synthesis of sodium *N*-cyclohexyl dithiocarbamate (cc-DTC)

Cyclohexyl amine (11.47 mL, 0.1 mol), carbon disulphide (6.00 mL, 0.1 mol) and sodium hydroxide (4.0 g, 0.1mol) were used as starting materials. The reaction mixture was magnetically stirred for 3 h in an ice bath at ambient temperature. White solid precipitates were obtained. Molecular weight: 197.29 g. Percentage Yield: 99%. M. P. 188-190 ^{o}C. Molar Conductivity: 3.43 Ω^{-1} cm^2 mol^{-1}. Anal. Calcd.for cc-DTC(%) C: 42.62; H: 6.13; N: 7.10; S: 32.50. Found (%) C: 19.47; H: 6.32; N: 3.17; S: 18.87. Selected FT-IR (KBr), ν (cm^{-1}): 1462 (C-N), 985 (C=S). Selected λ_{max} in DMSO solvent (nm): π-π^*(N-C=S) 220, n-π^*(S-C=S) 336. ^{1}H NMR (DMSO-d_6, 600Hz, ppm): δ 3.34-3.54; 4.03-4.13 (C_2HN); δ 0.69-1.83(Cyclic hexyl); δ 7.76-7.78; 9.62 (N-H). ^{13}C NMR (DMSO-d_6, 150 MHz, ppm) δ 25.05-25.43, 32.05 (α -CH_2) δ 54.27 (NH_2C); 212.94 (NCS_2).



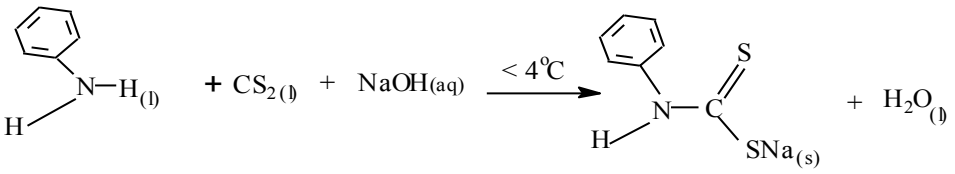
Scheme 2.16. Synthesis of sodium cyclohexyl dithiocarbamate (cc-DTC)**.**

2.5.6. Sodium Salt of Dithiocarbamates from Aromatic Amines

2.5.6.1 Synthesis of sodium aniline dithiocarbamate (ai -DTC)

Aniline (9.11 mL, 0.1 mol), carbon disulphide (6.00 mL, 0.1 mol) and sodium hydroxide (4.0 g, 0.1 mol) were used as starting materials. The reaction mixture was magnetically stirred for 3 h in an ice bath at ambient temperature. Whitish yellow crystals were obtained. Molecular weight: 191.24 g. Percentage Yield: 90%. M. P. 72 ^{o}C. Molar Conductivity: 1.09 Ω^{-1} cm^2 mol^{-1}. Anal. Calcd for ai-DTC (%) C: 43.96; H: 3.16; N: 7.32; S: 33.53; Na: 12.02. Found (%) C: 64.31; H: 4.85; N: 11.98; S: 13.19. Selected FT-IR (KBr), ν (cm^{-1}): 1460 (C-N), 1008 (C=S). Selected λ_{max} in DMSO solvent (nm): π-π^*(N-C=S) 246, n-π^*(S-C=S) 317. ^{1}H NMR (DMSO-d_6, 400Hz, ppm) δ 3.33-3.47 (CH-N); δ 6.87-7.16; 7.17-7.19 (Ar-H); δ 7.83-7.85; 10.03-10.09 (N-H). ^{13}C NMR (DMSO-d_6, 150 MHz, ppm) δ 121.80-122.07; 127.47-128.23; 142.47 (C_6H_5-H); δ 215.94 (NCS_2).

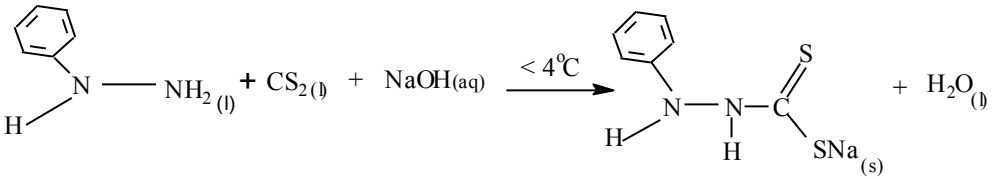
.



Scheme 2.17. Synthesis of sodium aniline dithiocarbamate (ai-DTC)**.**

2.5.6.2 Synthesis of sodium phenyl hydrazine dithiocarbamate (hy-DTC)

Phenyl hydrazine (9.83 mL, 0.1 mol), carbon disulphide (6.00 mL, 0.1 mol) and sodium hydroxide (4.0 g, 0.1mol) were used as starting materials. The reaction mixture was magnetically stirred for 3 h in an ice bath at ambient temperature. Reddish-black solid precipitates were obtained. Molecular weight: 206.26 g. Percentage Yield: 93%. M. P. 36-38 ^{o}C. Molar Conductivity: 2.98 Ω^{-1} cm^2 mol^{-1}. Anal. Calcd for hy-DTC (%) C: 40.76; H: 3.42; N: 13.58; S: 31.09. Found (%) C: 27.32; H: 3.42; N: 15.04; S: 34.42. Selected FT-IR (KBr), *v* (cm^{-1}): 1426 (C-N), 1025 (C=S). Selected λ_{max} in DMSO solvent (nm): π-π^*(N-C=S) 225, n-π^*(S-C=S) 318. ^{1}H NMR (DMSO-*d*$_6$, 400Hz, ppm) δ 7.33-7.36 (C_2H-N); δ 7.42-7.46; 7.65-7.67 (N-H). ^{13}C NMR (DMSO-d$_6$, 150 MHz, ppm) δ 127.30-128.76, 139.45 (C_6H_5-H); δ 178.44, 184.58 (NCS_2).



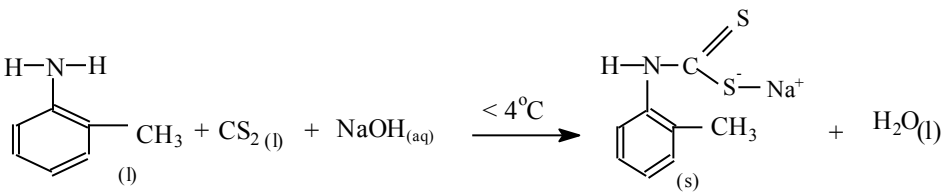
Scheme 2.18. Synthesis of sodium phenyl hydrazine dithiocarbamate (hy-DTC)**.**

2.5.6.3 Synthesis of sodium ortho-toluidine dithiocarbamate (to-DTC)

O-Toluidine (10.72 mL, 0.1 mol), carbon disulphide (6.00 mL, 0.1 mol) and sodium hydroxide (4.0 g, 0.1 mol) were used as starting materials. The reaction mixture was magnetically stirred for 3 h in an ice bath at ambient temperature. White solid precipitates were obtained. Molecular weight: 205.27 g. Percentage Yield: 82%. M. P. 56-58 ^{o}C Molar Conductivity: 0.47 Ω^{-1} cm^2 mol^{-1}. Anal. Calcd for to-DTC (%) C: 46.81; H: 3.93; N: 6.82; S:

.

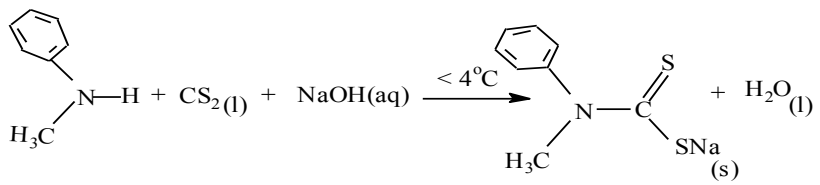
31.24. Found (%) C: 71.00; H: 6.93; N: 11.42; S: 8.51. Selected FT-IR (KBr), *v* (cm^{-1}): 1496 (C-N), 1006 (C=S). Selected λ_{max} in DMSO solvent (nm): (N-C=S) 245-259, (S-C=S) 304. ^1H NMR (DMSO-*d*$_6$, 600Hz, ppm): 2.04; 2.25; 2.50-2.51; 3.31 (–CH_3); δ 3.31; 3.44; 4.74 (CH-N); δ 6.45-7.16; δ 7.17-7.27; 9.14 (N-H). ^{13}C NMR (DMSO-d_6, 150 MHz, ppm) δ 113.94-146.49 (C_6H_5-H) δ 181.17 (NCS_2).



Scheme 2.19. Synthesis of sodium ortho toluidine dithiocarbamate (to-DTC)**.**

2.5.6.4 Synthesis of sodium N-methyl-N-phenyl dithiocarbamate (ml-DTC)

N-Methyl-*N*-Phenyl (10.82 mL, 0.1 mol), carbon disulphide (6.00 mL, 0.1 mol) and sodium hydroxide (4.0 g, 0.1 mol) were used as starting materials. The reaction mixture was magnetically stirred for 3 h in an ice bath at ambient temperature. White precipitates were obtained. Molecular weight: 205.27 g. Percentage Yield: 90%. M. P. 150°C. Molar Conductivity: 1.86 Ω^{-1} cm^2 mol^{-}1. Anal. Calcd. for ml-DTC (%) C: 46.81; H: 3.93; N: 6.82; S: 31.24. Found (%) C: 35.43; H: 3.83; N: 5.12; S: 18.08. Selected FT-IR (KBr), *v* (cm^{-1}): 1469 (C-N), 1038 (C=S). Selected λ_{max} in DMSO solvent (nm): π-π*(N-C=S) 233, n-π*(S-C=S) 260-285. ^1H NMR (DMSO-*d*$_6$, 400Hz, ppm) 1.03-1.05; 2.50-2.65 (–CH_3); δ 3.72-3.73; 3.93; (α -CH_2), δ 3.14; -3.39-3.45 (CH-N); δ 6.51-6.52 (Ar-H); δ 6.85-6.91; 7.06-7.27; 7.49-7.59; 8.00 (N-H). ^{13}C NMR (DMSO-d_6, 150 MHz, ppm) δ 45.84 (NHC); δ 111.63-130.02, 150.67 (C_6H_5-H) δ 215.94 (NCS_2).

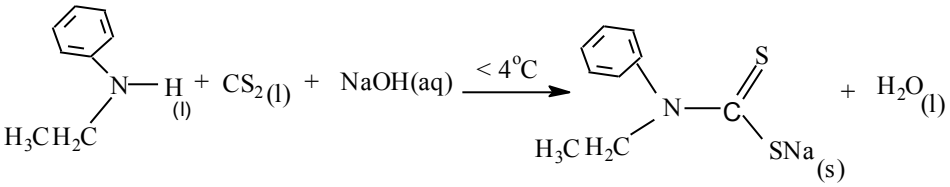


Scheme 2.20. Synthesis of sodium *N*-methyl-*N*-phenyl dithiocarbamate (ml-DTC)**.**

.

2.5.6.5 Synthesis of sodium *N*-ethyl-*N*-phenyl dithiocarbamate (ey-DTC)

N-Ethyl-*N*-Phenyl dithiocarbamate (12.58 mL, 0.1 mol), carbon disulphide (6.00 mL, 0.1 mol) and sodium hydroxide (4.0 g, 0.1mol) were used as starting materials. The reaction mixture was magnetically stirred for 3 h in an ice bath at ambient temperature. Pinkish-white solid precipitates were obtained. Molecular weight: 219.29 g. Percentage Yield: 85%. M. P. 70-72 ^{o}C. Molar Conductivity: 8.10 Ω^{-1} cm^2 mol^{-1}. Anal. Calcd. for ey-DTC (%) C: 49.29; H: 4.60; N: 6.39; S: 29.24. Found (%) C: 66.17; H: 5.99; N: 9.92; S: 6.86. Selected FT-IR (KBr), *v* (cm^{-1}): 1462 (C-N), 1002 (C=S). Selected λ_{max} in DMSO solvent (nm): π-π^*(N-C=S) 238, n-π^*(S-C=S) 315. ^{1}H NMR (DMSO-*d*$_6$, 400Hz, ppm): 1.14-1.16 (–CH_3); δ 2.50-2.63; (α -CH_2), δ 3.54-3.60, 4.28 (C_2H-N); δ 7.18-7.20 (Ar-H); δ 7.24-7.27 (N-H). ^{13}C NMR (DMSO-d_6, 150 MHz, ppm) δ 55.20 (NH_2C); δ 113.40,-125.5, 132.72, 137.48 (C_6H_5-H); δ 140.57 (NCS_2).

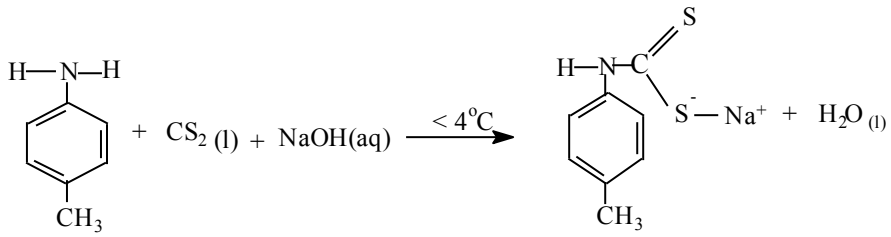


Scheme 2.21. Synthesis of sodium *N*-ethyl-*N*-phenyl dithiocarbamate (ey-DTC)**.**

2.5.6.6 Synthesis of sodium *N*-*p*-toluidine dithiocarbamate (tl-DTC)

N-p-Toluidine (10.72 mL, 0.1 mol), carbon disulphide (6.00 mL, 0.1 mol) and sodium hydroxide (4.0 g, 0.1mol) were used as starting materials. The reaction mixture was magnetically stirred for 3 h in an ice bath at ambient temperature. White solid precipitates were obtained. Molecular weight: 205.27 g. Percentage Yield: 84%. M. P. 62-64 ^{o}C. Molar Conductivity: 3.17 Ω^{-1} cm^2 mol^{-1}. Anal. Calcd for tl-DTC (%) C: 46.81; H: 3.93; N: 6.82; S: 31.24. Found (%) C: 40.55; H: 5.04; N: 6.08; S: 20.91. Selected FT-IR (KBr), *v* (cm^{-1}): 1474 (C-N), 1005 (C=S). Selected λ_{max} in DMSO solvent (nm): π-π^*(N-C=S) 218, n-π^*(S-C=S) 322. ^{1}H NMR (DMSO-*d*$_6$, 400Hz, ppm): 1.02-1.07 (–CH_3); δ 6.45-6.47 (Ar-H); δ 6.80-7.11, 7.38-7.40; 7.71-7.73. 10.28 (N-H). ^{13}C NMR (DMSO-d_6, 150 MHz, ppm) δ (–CH_3) 24.12 (α -CH_2); δ 54.27 (NH_2C); δ 126.02-128.77; 137.48 (C_6H_5-H); δ 140.57 (NCS_2).

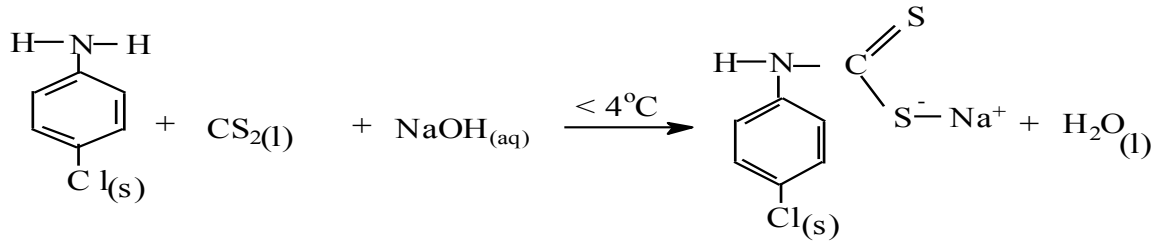
.



Scheme 2.22. Synthesis of sodium *N-para*-toluidine Dithiocarbamate (tl-DTC)**.**

2.5.6.7 Synthesis of sodium N-para-chlorophenyl dithiocarbamate (ch-DTC)

N-p-chlorophenyl (8.92 mL, 0.1 mol), carbon disulphide (6.00 mL, 0.1 mol) and sodium hydroxide (4.0 g, 0.1mol) were used as starting materials. The reaction mixture was magnetically stirred for 3 h in an ice bath at ambient temperature. White solid precipitates were obtained. Molecular weight: 225.69 g. Percentage Yield: 97%. M. P. 66-68 ^{o}C. Molar Conductivity: 0.58 Ω^{-1} cm^2 mol$^-$. Anal. Calcd for ch-DTC (%) C: 37.25; H: 2.23; N: 6.21; S: 28.41. Found (%) C: 55.98; H: 4.89; N: 10.93; S: 0.00. Selected FT-IR (KBr), ν (cm^{-1}): 1465 (C-N), 994 (C=S). Selected λ_{max}in DMSO solvent (nm): π-π^*(N-C=S) 249, n-π^*(S-C=S) 301. ^{1}H NMR (DMSO-d_6, 400Hz, ppm): δ 3.30, 5.20 (CH-N); δ 6.53-6.56 (Ar-H); δ 6.98-7.04 (N-H). ^{13}C NMR (DMSO-d$_6$, 150 MHz, ppm) δ = δ 115.17-128.49 (C_6H_5-H); δ 147.68 (NCS_2).



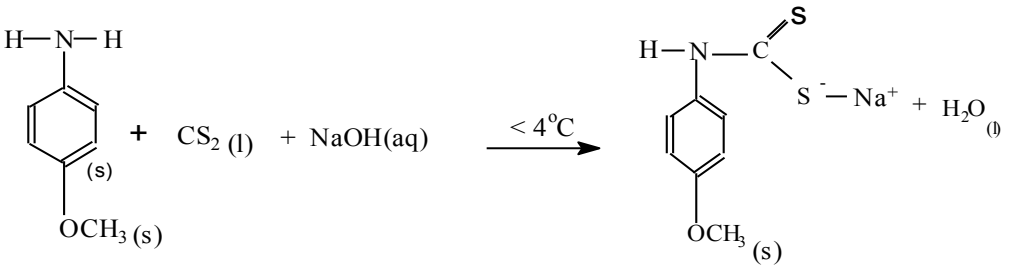
Scheme 2.23. Synthesis of sodium *N*-para-chlorophenyl dithiocarbamate (ch-DTC)**.**

2.5.6.8 Sodium N-*p*-Anisidine Dithiocarbamate (as-DTC)

N-p-Anisidine (11.51 mL, 0.1 mol), carbon disulphide (6.00 mL, 0.1 mol) and sodium hydroxide (4.0 g, 0.1 mol) were used as starting materials. The reaction mixture was magnetically stirred for 3 h in an ice bath at ambient temperature. Grey precipitates were obtained. Molecular weight: 221.27 g. Percentage Yield: 91%. M. P. 90-92 ^{o}C. Molar Conductivity: 3. 13 Ω^{-1} cm^2 mol^{-1}. Anal. Calcd for as-DTC (%) C: 43.43; H: 3.64; N: 6.33; S: 28.98. Found (%) C: 53.50; H: 5.10; N: 8.24; S: 12.61. Selected FT-IR (KBr), ν (cm^{-1}): 1466

.

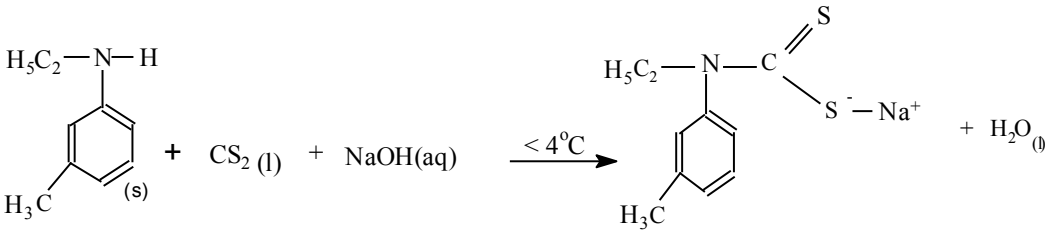
(C-N), 1031 (C=S). Selected λ_{max} in DMSO solvent (nm): π-π^*(N-C=S) 248, n-π^*(S-C=S) 315. ^{1}H NMR (DMSO-*d*$_6$, 600Hz, ppm): δ 2.50 (–CH_3); δ 3.36, 3.73 (CH-N); δ 6.45-6.47 (Ar-H); δ 7.36-7.38; 9.85, 9.93 (N-H). ^{13}C NMR (DMSO-d_6, 150 MHz, ppm) δ 55.20 (NH_2C); δ 113.40, 125.84, 132.72, (C_6H_5-H); δ 156.18 (C_6H_5-OCH_3) δ 179.77 (NCS_2).



Scheme 2.24. Synthesis of sodium *N*-para-anisidine dithiocarbamate (as-DTC)**.**

2.5.6.9 Synthesis of sodium *N*-ethyl-m-toluidine (tu-DTC)

N-ethyl-m-toluidine (14.13 mL, 0.1 mol), carbon disulphide (6.00 mL, 0.1 mol) and sodium hydroxide (4.0 g, 0.1mol) were used as starting materials. The reaction mixture was magnetically stirred for 3 h in an ice bath at ambient temperature. Whitish-yellow solid precipitates were obtained. Molecular weight: 233.32. Percentage Yield: 89%. M. P. 100°C: Molar Conductivity: 4.77 Ω^{-1} cm^2 mol^{-1}. Anal. Calcd for tu-DTC (%) C: 51.48; H: 5.18; N: 6.00; S: 27.48. Found (%) C: 40.01; H: 5.91; N: 4.60; S: 21.28. Selected FT-IR (KBr), *v*(cm^{-1}): 1451 (C-N), 1001 (C=S). Selected λmax in DMSO solvent (nm): π-π^*(N-C=S) 243, n-π^*(S-C=S) 301. ^{1}H NMR (DMSO-*d*$_6$, 400Hz, ppm): δ 1.02-1.07 (–CH_3); δ 2.26-2.51; (α -CH_2), δ 3.32-3.51; 4.23-4.30 (CH-N); δ 6.82-6.85; 6.91-6.93; 7.12-7.17 (Ar-H) ^{13}C NMR (DMSO-d_6, 150 MHz, ppm) 12.90 (–CH_3) 20.99 (α -CH_2); δ 50.97 (NH_2C); δ 125.68-128.85; 137.23; 148.76, (C_6H_5-H); 214.93. (NCS_2).



Scheme 2.25. Synthesis of sodium *N*-ethyl-m-toluidine (tu-DTC)**.**

.

2.6 Results and discussion

2.6.1. Physicochemical characterization of ligands (sodium sulfadiazine and derivatives of dithiocarbamates)

2.6.1.1 Colour

Sodium sulfadiazine has a white colour, since the sodium present is a non-transition element, therefore, no d orbital. All the synthesized ligands of ammonium and sodium dithiocarbamates used for this study had dirty mostly white, yellow and enhanced white colours to confirm that chemical reaction occurred. Two ligands, namely; cy-DTC and hy-DTC had pinkish white and dark red colours respectively.

2.6.1.2 Molecular mass

The highest formula molecular mass for the ligands was sodium sulfadiazine, with formula molecular mass of 272.25. For all the derivatives of dithiocarbamates, hh-DTC had the lowest formula molecular mass of 130.16, while tu-DTC had the highest formula molecular mass of 233.32.

2.6.1.3 Stability

Sodium sulfadiazine was kept and stored at room temperature, for stability and to retain the white colour because of its air sensitive nature. For the derivatives of dithiocarbamates, they were all stored in the refrigerator to retain the stability of the ligands most especially the ammonium dithiocarbamates that were not thermally stable [385]. Ligand, hx-DTC appeared in liquid state.

2.6.1.4 Percentage Yield

The percentage yield of sodium sulfadiazine was not done, since it was bought. The asaay was stated on the bottle label as ≥98 %. All the synthesized dithiocarbamates had a minimum percentage yield of 52% and a maximum percentage yield of 99%. This indicated a good to excellent percentage yield of the ligands.

2.6.1.5 Solubility

Deionised water dissolved all the ligands, with the exception of eh-DTC, being insoluble. Ligands of as-DTC, bu-DTC, el-DTC and mt-DTC were slightly soluble and as-DTC was partially soluble in deionized water. The ligands of as-DTC, eh-DTC, el-DTC and mt-DTC

.

were insoluble in methanol. Dimethylsulfoxide (DMSO) dissolved most of the ligands, except for ligands of eh-DTC and hy-DTC, which were partially soluble. Both mt-DTC and el-DTC were insoluble in DMSO. Other solvents used to test solubility were methanol, ethanol, ethyl acetate, chloroform, dichloromethane, acetonitrile, tetrahydrofuran, dimethylformamide, diethyl ether, acetone, hexane, heptane, benzene and toluene.

2.6.1.5 Temperature (^{o}C)

Sodium sulfadiazine had the highest temperature at >300 ^{o}C, followed by tu-DTC with a temperature of 233.32. The ligand with the lowest decomposition temperature was an-DTC with 34-36 ^{o}C. Most of the ligands decomposed, except for an-DTC and de-DTC, which melted.

2.6.1.6 Molar conductivity ($\Omega^{-1}cm^{2}$ mol^{-1})

Molar conductivities of sodium sulfadiazine and all derivatives of dithiocarbamates were below 20 $ohms^{-1}cm^{2}$ mol^{-1} in dimethylsulfoxide (DMSO), which proved the nonelectrolytic and monomeric nature of the ligands [465]. The results of the physicochemical characterization studies involving colour, formula molecular mass, percentage yield, solubility, melting point and molar conductivity are depicted in Table 2.1. below.

.

Table 2.1: Physicochemical characterization data of sodium sulfadiazine and derivatives of dithiocarbamates**.**

Ligands	**Colour**	**Formula Molecular Mass**	**Stability at Room and Cold Temperature**	**Percentage Yield (%)**	**Solubility**	**Temperature (^oC)**	**Molar Conductivity in DMSO and water ($\Omega^{-1}cm^2\ mol^{-1}$)**
SFZ	White	272.26	Solid	99	DMSO, Methanol, Water	>300	8.16
bu-DTC	White	166.30	Solid	52	DMSO, Methanol, Water (Partial)	70	3.99
he-DTC	Yellow	194.35	Solid	65	DMSO, Methanol, Water	52-54	2.63
eh-DTC	Yellow	155.25	Solid	71	DMSO, Methanol, Water (Insoluble)	72	2.95
cy-DTC	Pinkish white	192.34	Solid	96	DMSO, Methanol, Water (Partial)	80	3.74
an-DTC	White	186.29	Solid	92	DMSO, Methanol, Water	34-36	1.02
me-DTC	Yellow	200.32	Solid	86	DMSO, Methanol, Water	79-80	1.98
et-DTC	Yellow	214.34	Solid	57	DMSO, Methanol, Water	64-65	1.40
cl-DTC	Dirty white	220.73	Solid	91	DMSO, Methanol, Water	120-121	0.55

mt-DTC	White	129.17	Solid	88	DMSO, Methanol (Partial) Water	56	1.62
el-DTC	White	143.20	Solid	97	DMSO, Methanol (Insoluble),Water	80	0.90
bt-DTC	White	171.25	Solid	94	DMSO, Methanol, Water	56-58	2.40
hx-DTC	Yellow liquid	199.30	Liquid	90	DMSO, Methanol, Water	142	1.39
de-DTC	White	171.25	Solid	98	DMSO, Methanol, Water	91-92	5.05
*de-DTC	White	171.25	Solid	99	DMSO, Methanol, Water	60	2.15
hh-DTC	Yellow	130.16	Solid	87	DMSO, Methanol, Water	42-44	1.03
ea-DTC	Yellow	160.20	Solid	82	DMSO, Methanol, Water	50	0.35
cc-DTC	Dirty white	197.29	Solid	99	DMSO, Methanol, Water	188-190	3.43
ai-DTC	White	191.24	Solid	90	DMSO, Methanol, Water	72	1.09
hy-DTC	Reddish black	206.26	Solid	93	DMSO(Partially), Methanol, Water	36-38	2.98
to-DTC	Dirty white	205.27	Solid	82	DMSO, Methanol, Water (Partial)	56-58	0.47
ml-DTC	White	205.27	Solid	90	DMSO, Methanol, Water	150	1.86
ey-	Dirty	219.29	Solid	85	DMSO, Methanol	70-72	8.10

DTC	white				(Insoluble), Water		
tl-DTC	White	205.27	Solid	84	DMSO, Methanol, Water	62-64	3.17
ch-DTC	Dirty white	225.69	Solid	97	DMSO, Methanol, Water	66-68	0.58
as-DTC	Dirty white	221.27	Solid	91	DMSO, Methanol Water (Slight)	110	3.13
tu-DTC	White	233.32	Solid	89	DMSO, Methanol, Water	100	4.77

2.6.2 Elemental Analysis

Elemental analysis was used to check the purity by determining the percentage composition of carbon, hydrogen, nitrogen and sulfur. Homogeneity of all the samples for elemental analysis was done by ensuring they were of fine and uniform grains. The variation observed in the analytical data could be due to unstable ammonium salts of dithiocarbamates at room temperature [466]. For stable salts of dithiocarbamates at room temperature, variations could be due to the effects of effects of hydrate or moisture [467], deionised water used in most syntheses, separation of water and sulfur might be incomplete. On the other hand, elemental analyzer for CHN is more optimized than CHNS elemental analyzer [467]. Incomplete combustion is also a possibility for variation in results of analytical data for elemental analysis [468].

2.6.3 Molecular spectroscopy

Molecular spectroscopy includes Fourier transform infra-red spectroscopy (FTIR), ultraviolet-visible spectroscopy (UV-Vis) and nuclear magnetic resonance (NMR).

2.6.3.1. Fourier Transform Infra-Red Spectroscopy (FT-IR)

The FT-IR of sodium sulfadiazine, as well as, all derivatives of dithiocarbamates was taken from upper FTIR region of 4000 cm^{-1} to a lower FT-IR region of 370 cm^{-1}.

2.6.3.1.1. Fourier Transform Infra-Red Spectroscopy (FT-IR) of sodium sulfadiazine

The structure of sodium sulfadiazine was depicted in Figure 1.2. of Chapter one.

The FT-IR data of sodium sulfadiazine (SFZ) is shown in Table 2.2. Bands appearing between 3500 and 3400 cm^{-1} are due to ν $(NH)_{as}$ and $\nu(NH)_s$ of amino (NH_2)group of sodium sulfadiazine [371]. The asymmetrical ν $(NH)_{asy}$ and symmetrical $\nu(NH)_{sym}$ vibrations of amino (-NH) group had 3422, 3482 and 3310 cm^{-1} respectively. The sulfonamidic $(SO_2N$-) group of sodium sulfadiazine had an absorption peak at 3251 cm^{-1}. Azomethine, ν(C=N) group of free sodium sulfadiazine ligand vibrated at 1626 cm^{-1} and 1549 cm^{-1}. Absorption peaks for $\nu(SO_2)_{as}$ and $\nu(SO_2)_s$ were 1244 cm^{-1} and 1138 cm^{-1}, 1102 cm^{-1} respectively. The stretching vibration for (S-N) group was 1024 cm^{-1}.

Table 2.2: The FT-IR frequencies (cm^{-1}) for sodium sulfadiazine**.**

Ligand (L_1)	**$\nu(NH)_{as}$**	**$\nu(NH)_s$**	**$\nu(SO_2N)$**	**ν(C=N)**	**$\nu(SO_2)_{as}$**	**$\nu(SO_2)_s$**	**ν(S-N)**
SFZ	3422(s) 3482(s)	3310(m)	3251(s)	1626(s) 1549(w)	1244(s)	1138(s) 1102(s)	1024(s)

2.6.3.1.2 Fourier Transform Infra-Red Spectroscopy (FT-IR) of derivatives of dithiocarbamates

All dithiocarbamates, either as ligands or complexes exhibit three important absorption bands in Fourier Transform Infra-red Spectroscopy (FT-IR). The relevance of FT-IR in this study had already been stated in Section 2.3.5. Figure 2.1 depicts the four canonical forms of dithiocarbamato (NCS_2) moiety. The first two structures are monodentate forms of coordination bonding, while structures III and IV are forms of bidentate mode of coordinate bonding [469]. The three distinct important spectra bands occur at 1450-1550 cm^{-1}, attributed to ν(C- -N), that is, thioureide band, 950-1050 cm^{-1} attributed to the ν(C-S) and 300-400 cm^{-1} attributed to ν(M-S). [387-389, 470-471]. For this chapter, the ν(C- -N) and ν(C-S) are applicable while all three features are applicable to chapter three and chapter four respectively.

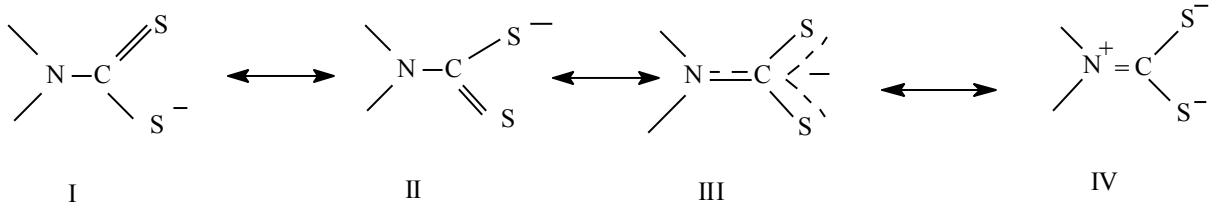


Figure 2.1: Canonical forms of dithiocarbamate moiety**.**

2.6.3.1.3 The NH stretching amino group (amino asymmetrical and symmetrical amino group $(NH)_{as/s}$)

Free ligands of dithiocarbamate have numerous absorption broad bands of -NH stretching vibrations in the region of 3300-3150 cm^{-1}[472]. The effect of hydrogen bonding on solid state samples results into a low wavenumber of N-H stretching vibrations [472]. Primary amines depict two sharp bands; secondary amines depict one band and no absorption for tertiary amines. Most $–NH_2$ asymmetric stretching vibrations appeared with broad bands at 3600-3000 cm^{-1} due to the presence of –OH stretching vibrations of water of coordination from its use during the syntheses of most ligands [473-475]. All asymmetric amino groups had minimum of 3411 cm^{-1} and maximum of 3479 cm^{-1}, while all symmetric amino groups had minimum of 3204 cm^{-1} and 3415 cm^{-1}.The –NH bending vibrations had assignment of a band of 1576 cm^{-1} and 1638 cm^{-1}.

2.6.3.1.4 The *v*(C--N) 1450-1550 cm^{-1}

The *v*(C-N) vibration group of the *–NCS₂* moiety of dithiocarbamates is otherwise known as thioureide bond. Aforementioned is the absorption band 1450-1550 cm^{-1}, which falls between the absorption band *v*(C-N) of 1250-1350cm^{-1} and the absorption band of *v*(C=N) vibration, (1640-1690 cm^{-1}) [383, 387-389], which implied partial double bond character and partial delocalization of electron density the dithiocarbamate moiety. The absorption band region for all thioureide groups was from 1426 cm^{-1} and 1509 cm^{-1}.

2.6.3.1.5 The *v*(C-S) 950-1050 cm^{-1}

The *v*(C-S) vibration group of the *–NCS₂* moiety of dithiocarbamates is typically characterized by $v(C\text{-}S)_{as}$ and $v(C\text{-}S)_{s}$ [383]. A single band in the region of 950-1050 cm^{-1} suggests symmetrical and bidentate coordination of dithiocarbamate moiety and a double band would suggest asymmetrical and monodentate coordination of dithiocarbamate moiety [389, 476-477]. All the asymmetric and symmetric CS_2 bands appeared in the region from 959-1049 cm^{-1} and 689-793 cm^{-1} respectively. Table 2.3 shows the FT-IR spectral bands of derivatives of dithiocarbamates.

Table 2.3: The FT-IR wavenumbers (cm^{-1}) of derivatives of dithiocarbamates**.**

Ligands(L_2)	***ν*(N-H)$_{as}$**	***ν*(N-H)$_s$**	***ν*(N-H)$_b$**	***ν*(C-N)**	***ν*(C=S)**	***ν*(CS_2)$_{as}$**	***ν*(CS_2)$_s$**
bu-DTC	$3414_{(s)}$	$3285_{(s)}$	$1617_{(s)}$	$1509_{(s)}$	$1150_{(s)}$	$1042_{(s)}$	$789_{(w)}$
he-DTC	$3413_{(s)}$	$3209_{(s)}$	$1617_{(s)}$	$1467_{(s)}$	$1136_{(m)}$	$996_{(m)}$	$789_{(m)}$
eh-DTC	$3447_{(m)}$	$3213_{(w)}$	$1642_{(w)}$	$1463_{(s)}$	$1165_{(w)}$	$997_{(w)}$	$774_{(m)}$
cy-DTC	$3461_{(s)}$	$3325_{(w)}$	$1588_{(w)}$	$1486_{(s)}$	1158	$1003_{(m)}$	$779_{(w)}$
an-DTC	$3424_{s)}$	$3224_{(s)}$	1631 $_{(s)}$	$1452_{(m)}$	$1157_{(w)}$	$1023_{(s)}$	$760_{(s)}$
me-DTC	$3414_{(s)}$	$3236_{(s)}$	$1618_{(s)}$	$1496_{(m)}$	$1185_{(m)}$	$1042_{(m)}$	$757_{(s)}$
et-DTC	$3479_{(s)}$	$3415_{(s)}$	$1617_{(s)}$	$1488_{(s)}$	$1125_{(s)}$	$1023_{(s)}$	$797_{(s)}$
cl-DTC	$3420_{(w)}$	$3208_{(w)}$	$1628_{(w)}$	$1467_{(m)}$	$1097_{(w)}$	$986_{(w)}$	$769_{(w)}$
mt-DTC	$3457_{(s)}$	-	$1667_{(w)}$	$1461_{(m)}$	$1161_{(w)}$	$1016_{(w)}$	$775_{(m)}$
el-DTC	$3467_{(w)}$	$3249_{(w)}$	$1648_{(w)}$	$1463_{(m)}$	$1167_{(w)}$	$1013_{(w)}$	$773_{(m)}$
bt-DTC	$3455_{(m)}$	$3209_{(w)}$	$1634_{(w)}$	$1464_{(s)}$	$1155_{(w)}$	$1049_{(w)}$	$772_{(m)}$
hx-DTC	$3457_{(s)}$	$3219_{(s)}$	$1652_{(s)}$	$1459_{(s)}$	$1115_{(w)}$	$959_{(m)}$	$732_{(s)}$
de-DTC	$3411_{(s)}$	$3279_{(w)}$	$1627_{(s)}$	$1475_{(s)}$	$1129_{(m)}$	$993_{(s)}$	$689_{(w)}$
*de-DTC	$3412_{(s)}$	$3237_{(s)}$	$1617_{(s)}$	$1476_{(m)}$	$1133_{(m)}$	$986_{(w)}$	$780_{(w)}$
hh-DTC	$3457_{(m)}$	$3217_{(s)}$	$1647_{(s)}$	$1462_{(s)}$	$1151_{(m)}$	$1039_{(m)}$	$728_{(s)}$
ea-DTC	$3448_{(s)}$	$3222_{(s)}$	$1652_{(s)}$	$1459_{(s)}$	$1157_{(m)}$	$974_{(m)}$	$732_{(s)}$
cc-DTC	$3422_{(w)}$	$3316_{(w)}$	1640 $_{(m)}$	$1462_{(s)}$	$1162_{(w)}$	$985_{(m)}$	$750_{(m)}$
ai-DTC	$3466_{(w)}$	$3221_{(m)}$	$1601_{(w)}$	$1460_{(s)}$	$1122_{(s)}$	$1008_{(w)}$	$759_{(m)}$
hy-DTC	$3432_{(s)}$	-	$1647_{(m)}$	$1426_{(s)}$	$1126_{(m)}$	$1025_{(s)}$	$759_{(m)}$
to-DTC	$3386_{(s)}$	$3247_{(s)}$	$1617_{(s)}$	$1496_{(s)}$	$1176_{(w)}$	$1006_{(m)}$	$751_{(w)}$
ml-DTC	$3385_{(s)}$	$3204_{(s)}$	$1632_{(s)}$	$1469_{(s)}$	$1171_{(w)}$	$1038_{(w)}$	$761_{(s)}$

ey-DTC	3445$_{(w)}$	3341$_{(m)}$	1676$_{(s)}$	1462$_{(s)}$	1149$_{(w)}$	1002$_{(w)}$	739$_{(s)}$
tl-DTC	3427$_{(s)}$	-	1602$_{(s)}$	1474$_{(m)}$	1135$_{(s)}$	1005$_{(s)}$	756$_{(w)}$
ch-DTC	3464$_{(s)}$	3293$_{(s)}$	1646$_{(s)}$	1465$_{(s)}$	1143$_{(s)}$	994$_{(s)}$	760$_{(m)}$
as-DTC	3434$_{(s)}$	3221$_{(s)}$	1611$_{(s)}$	1466$_{(s)}$	1102$_{(s)}$	1031$_{(s)}$	786$_{(s)}$
tu-DTC	3434$_{(s)}$	3251$_{(s)}$	1634$_{(s)}$	1459$_{(m)}$	1122$_{(w)}$	1001$_{(s)}$	793$_{(s)}$

s= strong; m= medium; w= weak

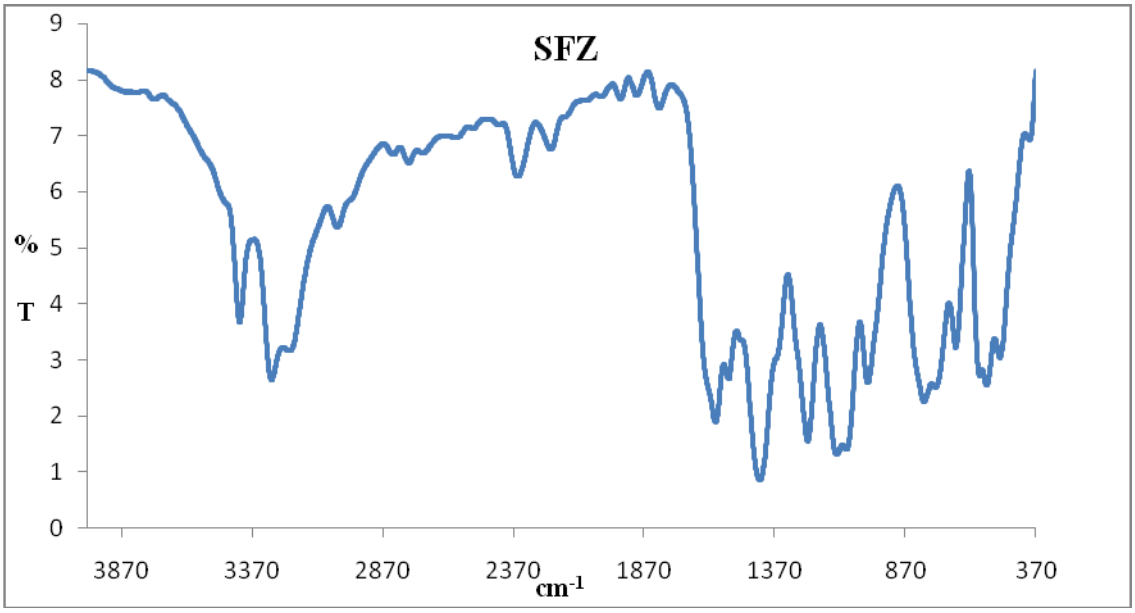


Figure 2.2: FT-IR spectrum of SFZ**.**

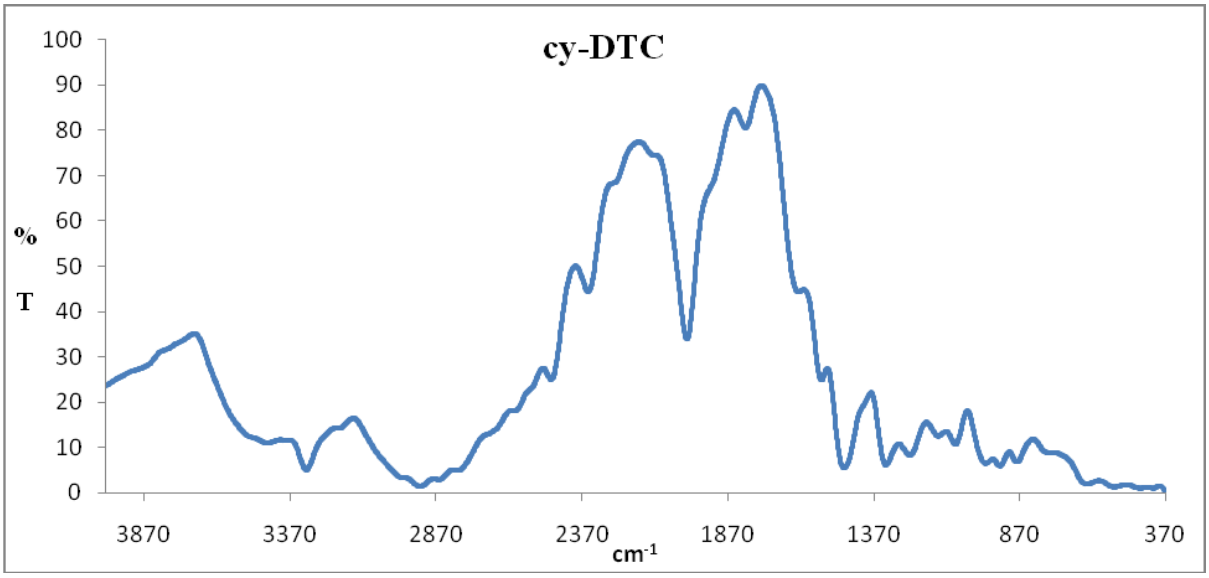


Figure 2.3: FT-IR spectrum of cy-DTC**.**

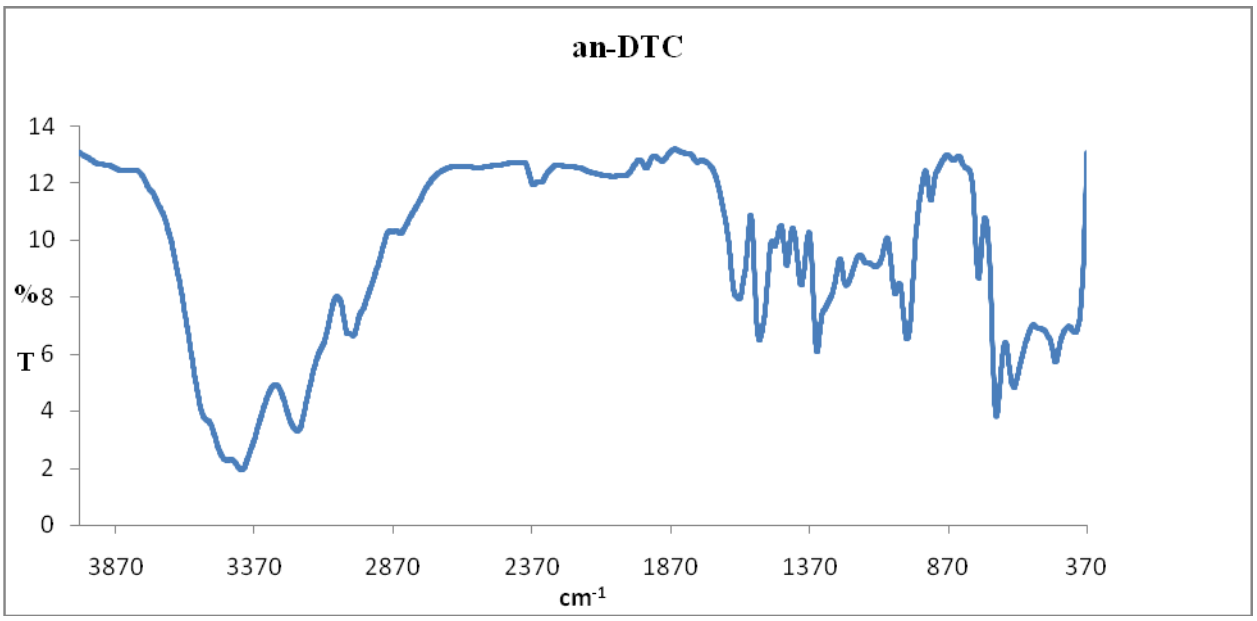


Figure 2.4: FT-IR spectrum of an-DTC**.**

2.6.3.2 Ultraviolet-Visible (UV-Vis) spectroscopic studies

The aim of carrying out ultra-violet visible spectroscopic studies on sodium sulfadiazine was to confirm the presence of $–SO_2N$ moiety of sodium sulfadiazine of π-π^* and n-π^*transitions [371]. It is typical of chromophores in NCS_2 dithiocarbamates to show three absorption bands [478]. A band out of three is overlapped by intense bands of π-π^* transitions of benzene [478]. The recording of the electronic spectra was done between 10^{-3} and 10^{-5} M solutions of dimethylsulfoxide (DMSO), methanol and water solvents. The use of DMSO solvent was to find out if there would be a d-d transition. Each solution was transferred for absorption measurements in a 1 cm^3 cuvette (quartz cell). This was read after taking the blank containing corresponding solvent for baseline correction in a Perkin-Elmer Lambda 25 UV-Vis double beam spectrometer with a minimum wavelength of 200 nm and a maximum wavelength of 600 nm at ambient temperature for methanol and deionised water. The band range was from 200 - 1000 nm for DMSO solvent. Apart from the effect of substituents on the electronic spectra of dithiocarbamates, solvent also plays important function in dithiocarbamates [479]. At room temperature where the ligands' transitions were observed, ligands of dithiocarbamate showed similar spectra data from solvents of methanol and distilled water [478]. Dimethylsulfoxide, DMSO, was used as solvent to confirm d-d transitions of all the ligands [478]. Some of the dithiocarbamate ligands were coloured which were evident in the d-d transitions [he-DTC, eh-DTC, cy-DTC, et-DTC, hx-DTC, ea-DTC and hy-DTC]. Other L_2 samples that were colourless exhibited d-d transition with the exception of an-DTC, me-DTC, ml-DTC, as well as, L_1.The absorption bands of π-π^* and n-π^* below 300-350 nm are due to intra-ligand transitions [480-481]. In dithiocarbamates, the *N—C=S* and *S—C=S* chromophores in the $–NCS_2$ moiety of the dithiocarbamate were confirmed. The UV-Vis spectra of he-DTC, cy-DTC and et-DTC in solvents of DMSO, methanol and water are shown in Figures 2.5, 2.6 and 2.7 respectively.

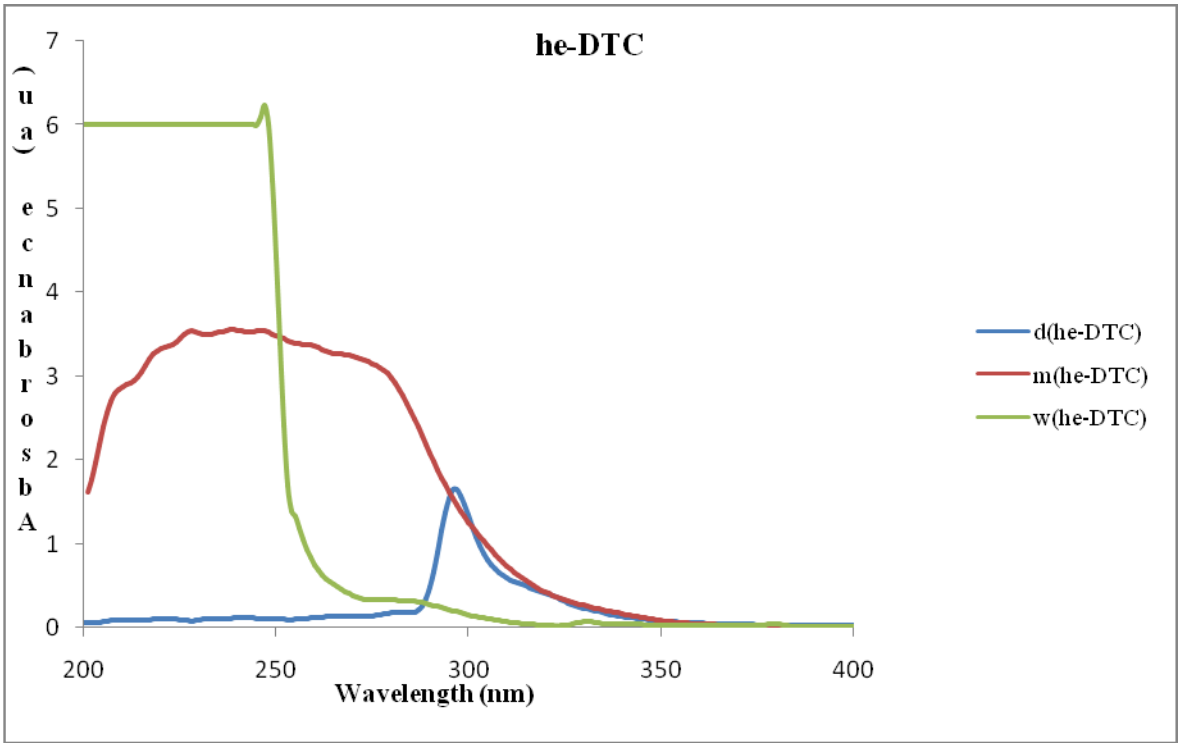


Figure 2.5: UV-Vis spectrum of he-DTC in solvents of dimethylsulfoxide (d), methanol (m) and water (w).

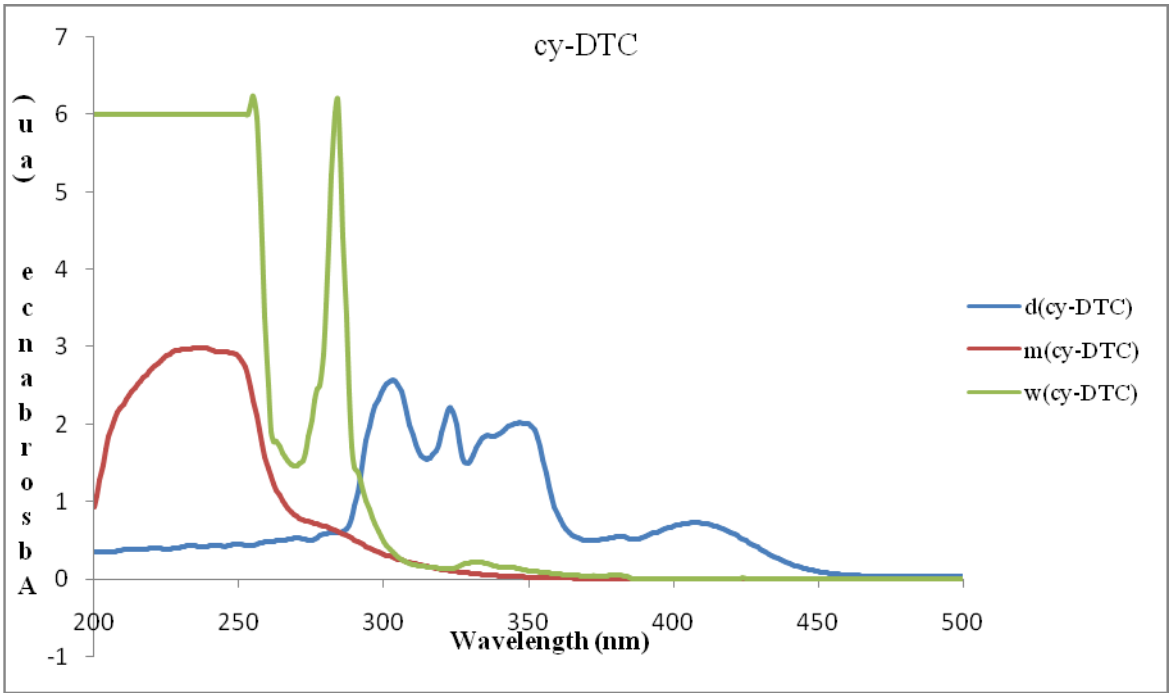


Figure 2.6: The UV-Vis spectrum of cy-DTC in solvents of dimethylsulfoxide (d), methanol (m) and water (w).

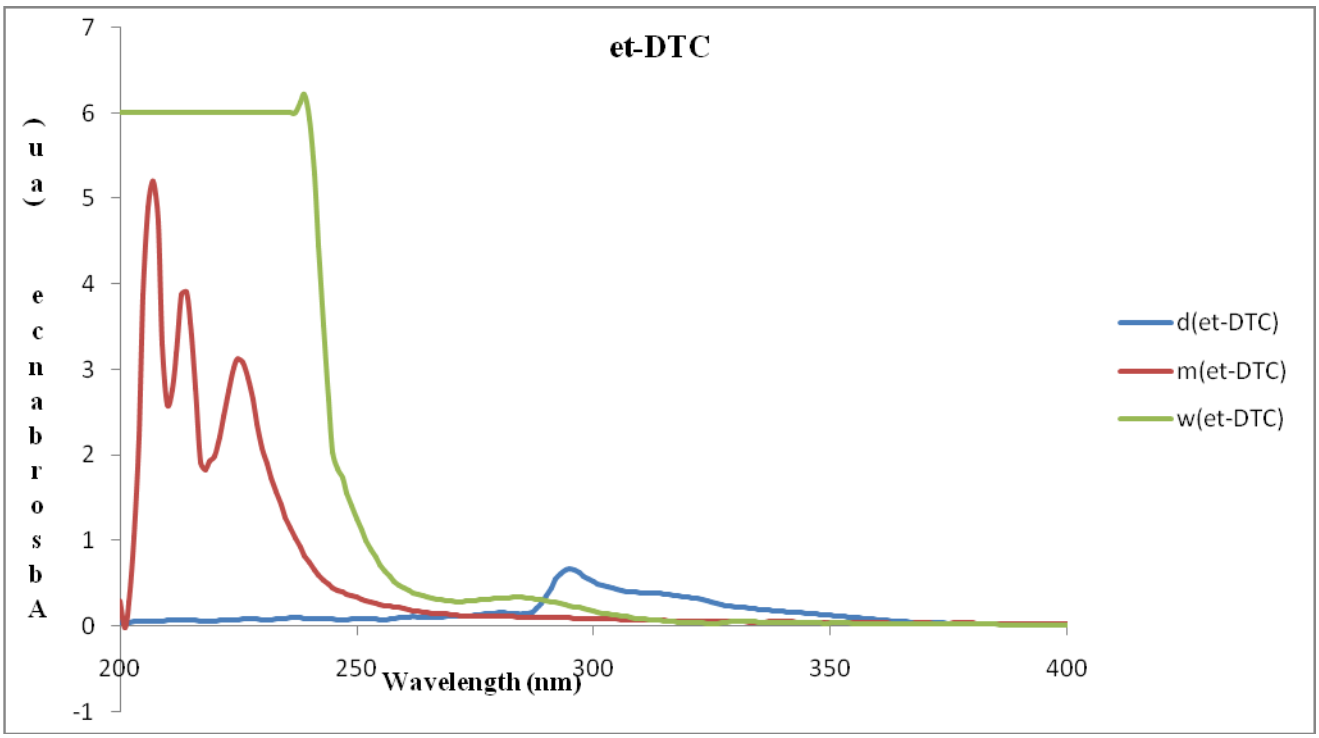


Figure 2.7: The UV-Vis spectrum of et-DTC in solvents of dimethylsulfoxide (d), methanol (m) and water (w).

2.6.3.3 Nuclear Magnetic Resonance (NMR)

Nuclear magnetic resonance (NMR) is a diagnostic tool to identify carbon- hydrogen frameworks within a molecule. It, therefore, does the identification of functional groups in organic compounds, organometallic compounds and metal complexes. Most moieties of sodium sulfadiazine and derivatives of dithiocarbamates both show diagnostic nuclear magnetic resonance (NMR) spectroscopic properties. The two mostly used NMR spectroscopies are ^{1}H NMR and ^{13}C NMR. Proton (^{1}H) NMR gives the number and type of hydrogen atoms in a molecule, while carbon 13 (^{13}C) NMR gives the type of carbon atoms in the molecule.

For sodium sulfadiazine and derivatives of dithiocarbamates, the proton NMR, (^{1}H NMR) and carbon 13 NMR, (^{13}C NMR) resonance spectra were obtained from deuterated DMSO, (DMSO-d_6), with the exception of mt-DTC and el-DTC. Both mt-DTC and el-DTC samples were insoluble in DMSO-d_6. This led to the proton nuclear resonance being done in

deuterated water, D_2O. The chemical shifts of both ^1H NMR and ^{13}C NMR were expressed in ppm relative to the internal tetramethylsilane, TMS for both sodium sulfadiazine and derivatives of dithiocarbamates.

2.6.3.3.1 Proton (^1H) NMR

The amino proton absorbed at 5.36 ppm while aromatic protons resonated in the region of 6.38-6.46 ppm. The azomethine proton absorbed at chemical shift of 7.48-7.68 ppm. Protons of pyrimidine ring (3H pyrimidine $C_4H_2N_2$-H ring) resonated at a chemical shift of 8.10 ppm. The functional group, C-NSO_2Na had no proton so ^1H NMR value for proton was not given. For all the derivatives of dithiocarbamates, the resonance values ranged from a minimum of 0.81 to 3.39 ppm for all methyl and methylene groups of aliphatic, cyclic and aromatic compounds. The H_2N-C peaks appeared from 3.28 ppm to 5.28 ppm. All compounds possessing phenyl (Ar-^1H) group had the protons that resonated at chemical shifts of 6.35-7.36 ppm. Resonance values of 6.18-11.54 ppm belonged to the NH_2 group present. Hydroxyl group for eh-DTC was also observed at 9.95 ppm. Difficulties arose during the nuclear magnetic resonances of mt-DTC and el-DTC even when both dissolved in water. This might be due to proton exchange [523]. The ^1H NMR of sodium sulfadiazine in ppm in DMSO-*d_6* solvent is shown in Figure 2.8.

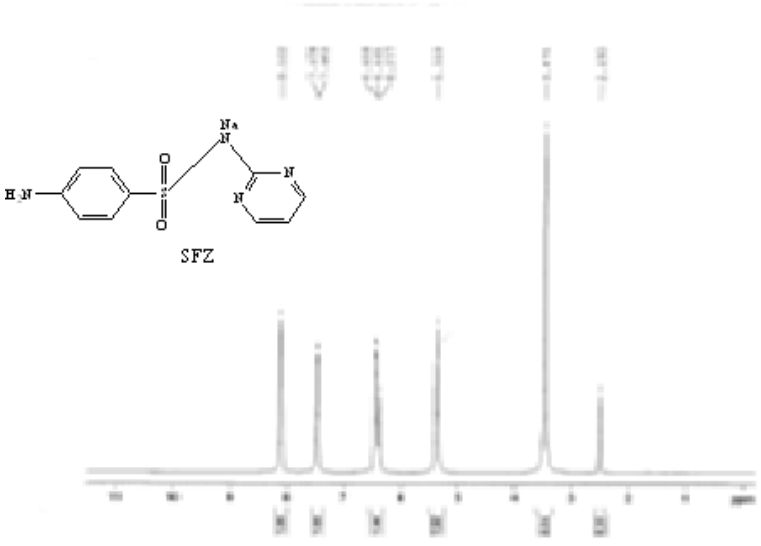


Figure 2.8: The ^1H NMR of sodium sulfadiazine in ppm in DMSO-*d6* solvent**.**

2.6.3.3.2 Carbon 13 (^{13}C) NMR

The aryl proton, Ar-H has a chemical shift of δ 109.20-111.91 ppm. Azomethine carbon with δ 128.25 and amino attached carbon had a resonance at δ 133.20. The pyrimidine ring carbon attached at amino group had a resonance at δ 143.97, while ^{13}C-NNa resonated at a region of δ 151.39-164.39.

Peaks with chemical shifts of δ 13.55- 46.33 ppm were observed for all the methyl and methylene groups in the^{13}C NMR spectra of all aliphatic, cyclic and aromatic compounds. The azomethine group and HCN appeared in the region of δ 31.19-69.89 ppm. All phenyl groups had resonance from δ111.60-148.76 ppm.

According to Gary et al, the most important group, CS_2 of the thione, NCS_2 moiety, resulting from the successful synthesis of all the dithiocarbamates' moieties had resonance values from δ 185- 220 ppm [483]. Electronegativity and resonance effects can bring differences in the resonance values of dithiocarbamates [484]. Most derivatives of dithiocarbamates had resonance peaks from δ 179.81-215.94 ppm, which indicated successful synthesis. Few exceptions can be found in me- DTC (δ 149.87 ppm), ey-DTC (δ 140.57 ppm) and ch-DTC (δ 147.68 ppm). This might be due to overlapping with phenyl groups present, since they successfully resonated in ^{1}H NMR. The ^{13}C NMR of sodium sulfadiazine in ppm in DMSO-*d6*solvent is shown in Figure 2.9.

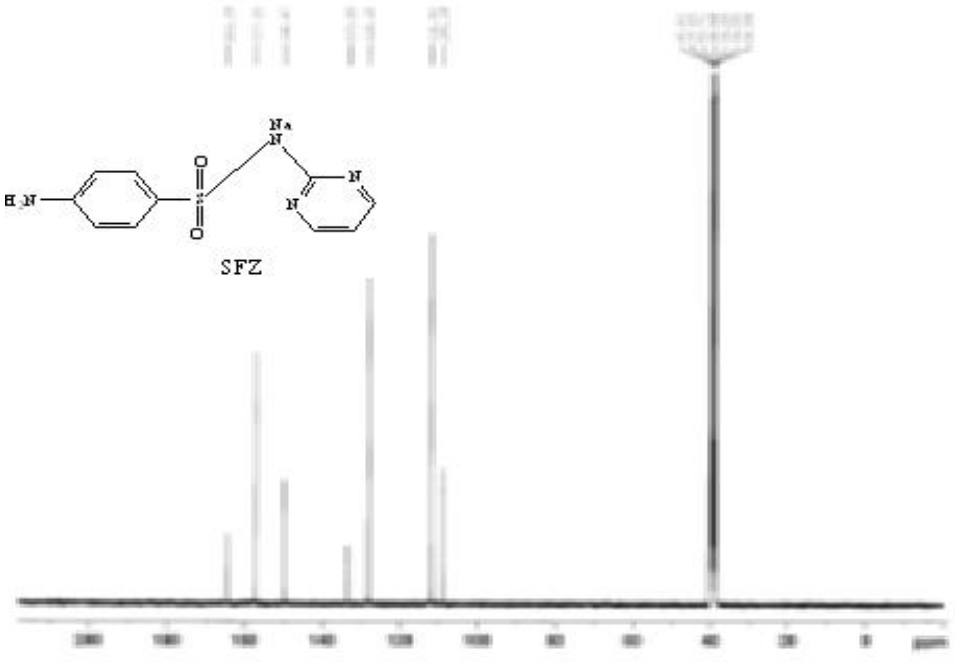


Figure 2.9: The ^{13}C NMR of sodium sulfadiazine in ppm in DMSO-d_6 solvent**.**

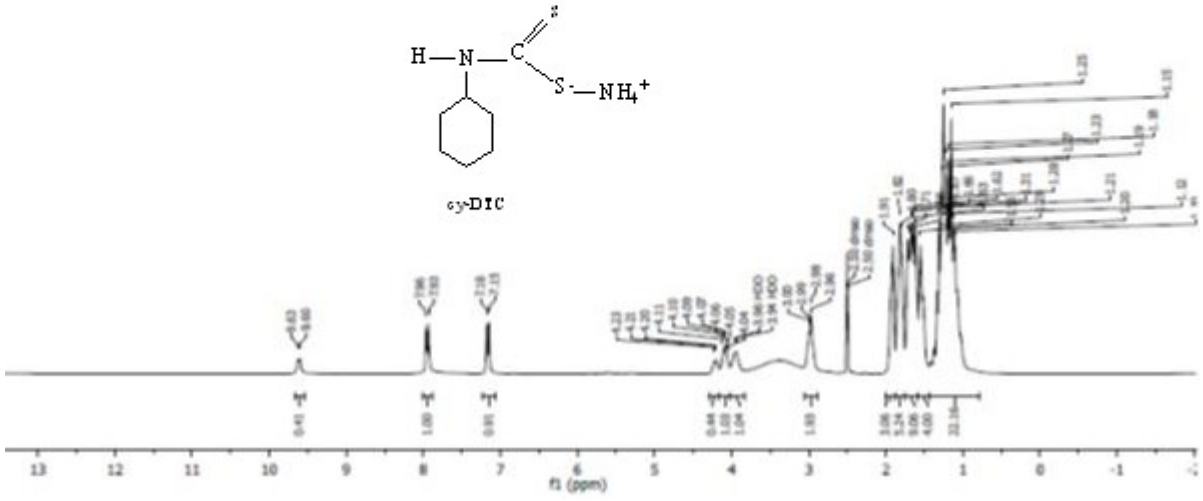


Figure 2.10: The ^{1}H NMR of cy-DTC in ppm in DMSO-d_6 solvent**.**

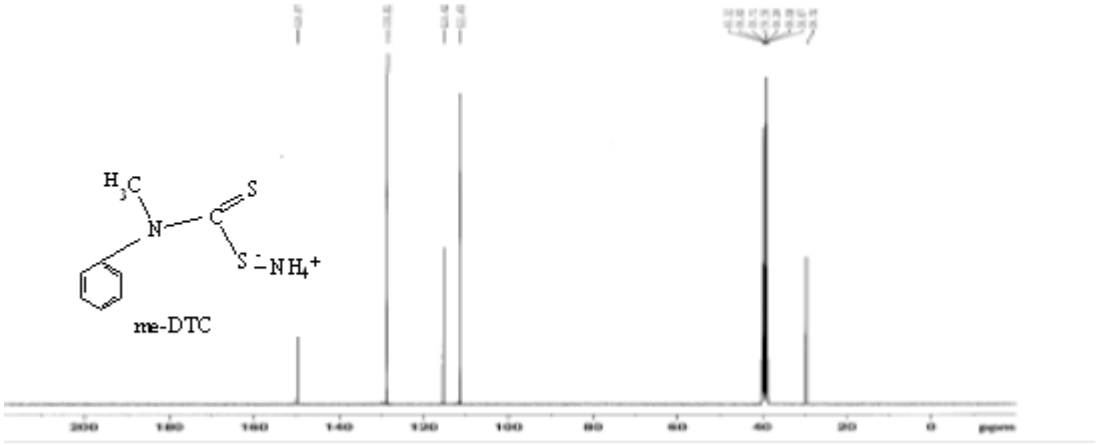


Figure 2.11: The ^{13}C NMR of me-DTC in ppm in DMSO-$d_6$solvent**.**

2.7. Conclusion

The syntheses of derivatives of ammonium and sodium salts of aliphatic, cyclic and aromatic dithiocarbamates were done using one-pot synthesis. Sodium sulfadiazine and all the synthesized dithiocarbamates were all subjected to physicochemical and spectroscopic characterizations. Molar conductivities of both ligands established their non-electrolytic nature. The functional groups(moieties) and structures of sodium sulfadiazine and derivatives of dithiocarbamates were confirmed with Fourier transforms infra-red spectroscopy, ultra-violet visible spectroscopy and nuclear magnetic resonance. The characterization techniques proved the successful syntheses of derivatives of ammonium and sodium salts of aliphatic, cyclic and aromatic dithiocarbamates were done using one pot synthesis.

CHAPTER 3

3. Synthesis and characterization of oxovanadium(IV) complexes of mixed sulfadiazine and dithiocarbamate

3.1. Introduction

This chapter focuses on synthesis of oxovanadium(IV) complexes and their spectra characterizations. Different coordination donors of NN, NO, SS, SO, OO and *NS* had been studied to coordinate with vanadyl ion and were successfully characterized. These ideas of coordination were coined from the two natural enzymes of vanadium (vanadium-nitrogenase and vanadate dependent haloperoxidases), sea squirts (ascidiaceae), as well as, mushrooms (amavadin) mainly from +3 to +5 oxidation states of vanadium [485-489]. In the environment, the oxidation states; +3, +4 and +5 of vanadium are most stable among the other oxidation states of -1, 0, 1 and 2 [490,491]. Vanadium exists as oxophilic in the higher oxidation states of +4 and +5 to form big diversed oxido compounds and complexes in both solid and aqueous media [490].

Vanadyl ion is a hard acid and prefers to bond with hard bases. According to Pearson's Concept of HSAB in 1963 and his 1967 article written with Professor Jon Songstad, hard acids preferably react with hard bases and soft acids react with soft bases [492]. A paper written by Professor Ralph G. Pearson in 1966 said there was a possibility of a hard acid forming stable complexes with soft bases and vice versa [492]. Oxovanadium(IV) ions are the most stable diatomic ion [493] acidic hydrated salt of vanadyl (IV) sulfate. Ligands have the abilities to stabilize vanadium in its highest oxidation states [494].The chemistry of oxovanadium(IV) complexes is made up coordination of ligands with stable oxovanadium(IV) ion to give four plausible geometries of square bipyramidal, square pyramidal and trigonal bipyramidal [495-496] as shown in Figure 3.1, and distorted octahedral [497]. These geometries correspond to four coordinates (tetravalent), five coordinates (square bipyramidal, square pyramidal and trigonal bipyramidal) and six coordinates (distorted octahedral). The six coordinated oxovanadium(IV) complex can form polymers due to intermolecular bonding of ---V=O---V=O--- [498]. Kasahara *et al* said green coloured products of their synthesized oxovanadium(IV) complexes were monomeric square

pyramidal while the orange coloured products were polymeric [499]. This research involved the coordination of sodium sulfadiazine and derivatives of dithiocarbamate of *NS* donors respectively with oxovanadium(IV) ions to yield different isolated precipitates of oxovanadium(IV) complexes. The synthesized oxovanadium(IV) complexes were characterized using molar conductivity, elemental analysis, UV-Vis and FT-IR.

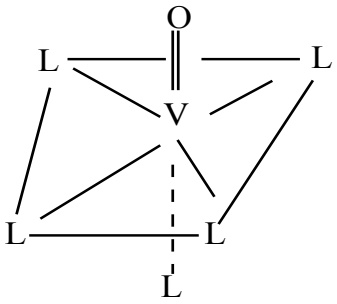


Figure 3.1: (a) square bipyramidal**.**

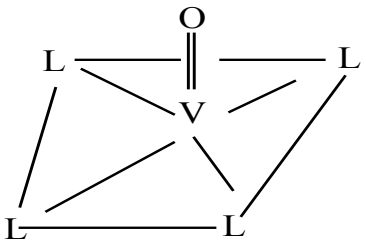


Figure 3.1: (b) Square pyramidal**.**

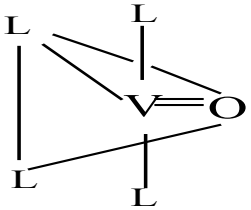


Figure 3.1: (c) Trigonal bipyramidal**.**

3.2. Materials and Methods

3.2.1 Experimental materials

All the materials and chemical reagents used for this research were of analytical grade and all were used as received without purification from the chemical industries. Apart from sulfadiazine sodium salt and vanadium(IV) oxide hydrate, others were synthesized.

Sulfadiazine sodium salt, vanadium(IV) oxide hydrate (Sigma-Aldrich, USA), cy-DTC; ammonium *N*-cyclohexyl dithiocarbamate; an-DTC; ammonium *N*-aniline dithiocarbamate; me-DTC; ammonium *N*-methyl *N*-phenyl dithiocarbamate; bt-DTC; sodium *N*-butyl dithiocarbamate, hx-DTC; sodium *N*-hexyl dithiocarbamate, de-DTC; sodium *N*-diethyl dithiocarbamate, hh-DTC, sodium *N*-hydrazine hydrate dithiocarbamate, ai-DTC sodium *N*-aniline dithiocarbamate, hy-DTC sodium *N*-phenyl hydrate dithiocarbamate, to-DTC, sodium *N*-*ortho*-toluidine dithiocarbamate; sodium *N*-para-toluidine dithiocarbamate, ch-DTC; sodium *N*- para chloro *N*-phenyl dithiocarbamate, as-DTC; sodium anisidine dithiocarbamate, tl-DTC; Sodium *N*-*para*-toluidine dithiocarbamate, tu-DTC; sodium *N*-ethyl-*m*-toluidine dithiocarbamate.

3.2.1.1 Solvents

Deionized water (In house), methanol (Merck, RSA), absolute ethanol (Supplied by EC Labs), toluene (Merck, RSA), acetone (Merck, RSA), diethyl ether (Merck, RSA), dimethylsulfoxide (Merck, Germany) dimethylformamide (Merck, Germany), acetonitrile (Merck, RSA) and 55% trioxonitrate (V) acid ((Associated Chemical Enterprises (Pty) Ltd, Johannesburg, RSA).

3.2.2 Instrumentation

Sample masses were weighed on Sartorius Electronic Balance (Maximum Capacity (110 g), One open-end capillary tube melting points were done on a STUART SMP11 melting point apparatus and recorded uncorrected. Molar conductivities of oxovanadium(IV) complexes were recorded on a CRINSON EC- Meter BASIC 30+ conductivity meter. Elemental analyses for carbon, hydrogen, nitrogen and sulfur were performed on a FLASH 2000 Thermoscientific Elemental Analyzer. Electronic spectra (UV-Vis spectra) for all oxovanadium(IV) complexes were measured using a Perkin-Elmer Lambda 25 UV-Vis

Spectrometer. Fresh solutions of the synthesized oxovanadium(IV) complexes were prepared and transferred into 1 cm^3 cuvette (quartz cell) for electronic absorption measurement. The recording of the electronic spectra was done between 10^{-3} and 10^{-5} M solutions of dimethylsulfoxide (DMSO). The reading was taken after calibration for baseline correction in the double beam spectrometer. The reading was done in the wavelength interval between 200 nm and 1000 nm. The FT- IR spectra were recorded from a KBr disc in the range of 370-4000 cm^{-1} on a Perkin-Elmer 2000 FT-IR spectrophotometer.

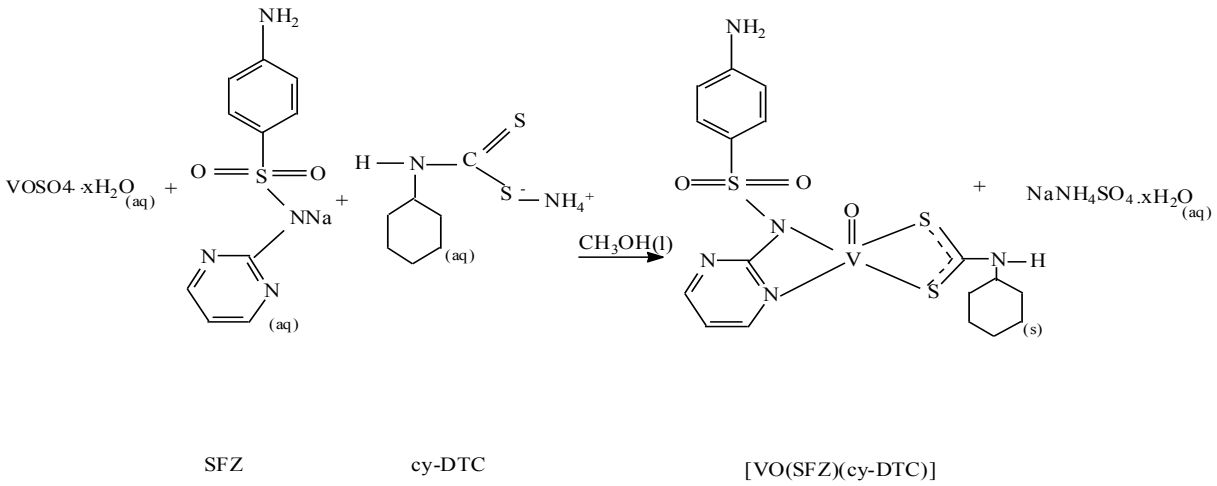
3.3 Methods

3.3.1 Synthesis of oxovanadium(IV) complexes from sodium sulfadiazine (L_1) and derivatives of dithiocarbamate ($L_{2\text{-DTC}}$)

Vanadyl(IV) complexes were synthesized using similar procedure according to the literature with some modifications [364, 385-393].

3.3.3.1 Synthesis of oxovanadium(IV) complex [VO(SFZ)(cy-DTC)]

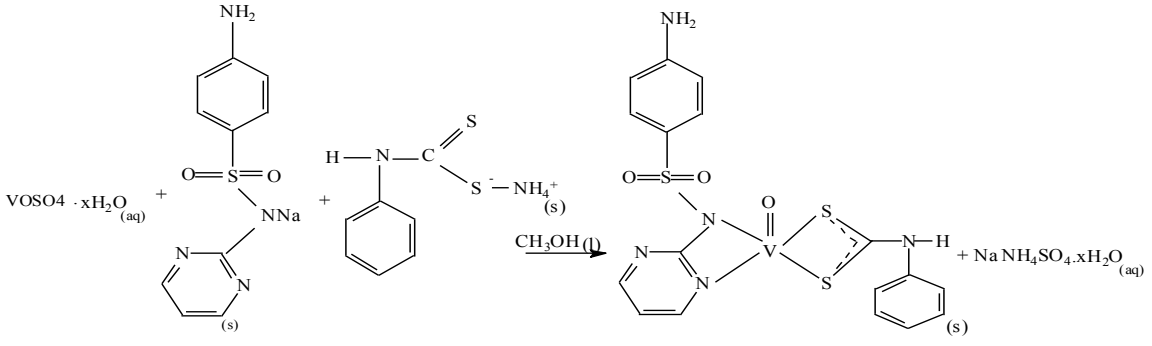
Vanadium(IV) oxide sulfate hydrate (0.2445 g, 1.5 mmol), solution of sodium sulfadiazine, L_1, (0.4085 g, 1.5 mmol) in methanol (100 mL) and ammonium cyclohexyl dithiocarbamate, L_2, (0.2885 g, 1.5 mmol,) were magnetically stirred for 3 h at room temperature. A green solid precipitate was formed, filtered, washed with deionized water (3 x 5 mL) and dried over silica gel in a desiccator. Molecular weight: 490.51 g. Percentage Yield: 85%. M. P. 140 ^oC. Molar Conductivity (DMSO): 1.10 Ω^{-1} cm^2 mol^{-1}; Anal. Calcd. for [VO(SFZ)(cy-DTC)](%) C: 41.63; H: 4.32; N: 14.28; S: 19.61, Found: C: 48.24; H: 3.40; N: 26.45; S: 11.21. Selected FT-IR bands (KBr), (cm^{-1}): 3157 (SO_2NH), 1627 (C=N), 1498 (C-N), 948 $(CS_2)_{as}$. Selected λ_{max} in DMSO solvent (nm): (π- π^* N-C=S) 322; (n- π^* S-C=S) 362; Band I: 834, 721; Band II: 614; Band III: 398.



Scheme 3.1. Synthesis of oxovanadium(IV) complex [VO(SFZ)(cy-DTC)]**.**

3.3.1.2 Synthesis of oxovanadium(IV) complex [VO(SFZ)(an-DTC)]

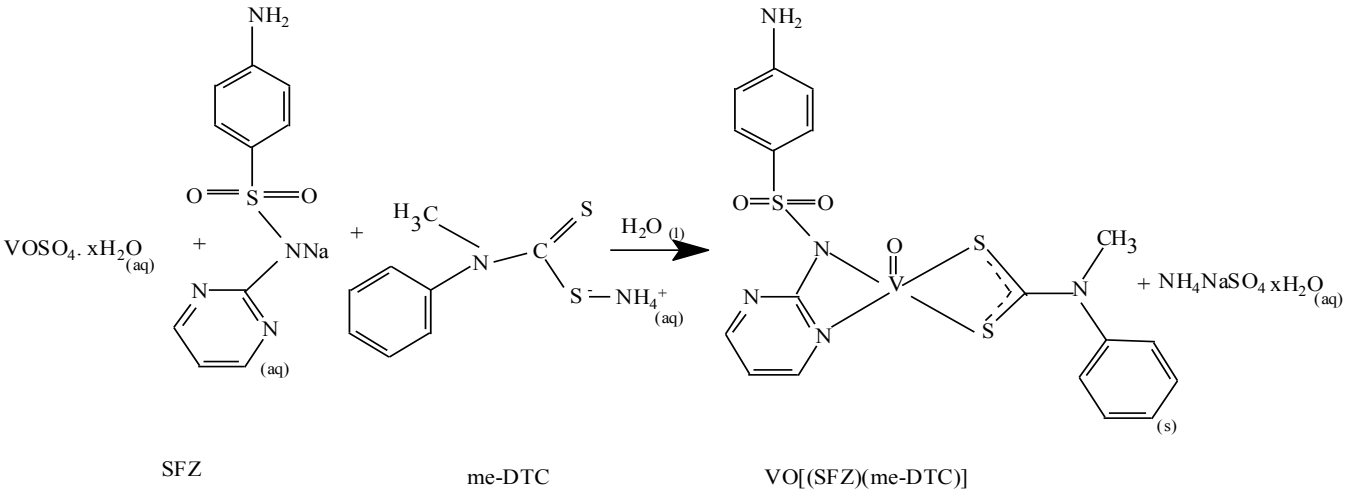
To vanadium(IV) oxide sulfate hydrate (0.2445 g, 1.5 mmol), a solution of sodium sulfadiazine, L_1, (0.4085 g, 2 mmol) in methanol (100 mL) was added dropwise. Ammonium *N*-aniline dithiocarbamate, $L_{2an\text{-}DTC}$, (0. 2795 g, 1.5 mmol,) in methanol (20 mL) was simultaneously added and magnetically stirred for 3 h at room temperature. A green solid precipitate was formed, filtered, washed with deionized water (3 x 5 mL) and dried over silica gel in a desiccator. Molecular weight: 484.49 g. Percentage Yield: 72%. M. P. 206-208 ^{o}C. Molar Conductivity (DMSO): 0.01 Ω^{-1} cm^2 mol^{-1}. Anal. Calcd. for [VO(SFZ)(an-DTC)] (%) C: 42.15; H: 3.12; N: 14.46; S: 19.85, Found (%) C: 41.54; H: 3.94; N: 18.23; S: 18.03. Selected FT-IR (KBr), (cm^{-1}): 3120 (SO_2NH), 1574 (C=N), 1530 (C-N), 1016$(CS_2)_{as}$. Selected λ_{max} in DMSO solvent (nm): (π- π^*) 322; (n- π^*) 354; Band I: 848, 732; 713, Band II: 588; Band III: 402.



Scheme 3.2. Synthesis of oxovanadium(IV) complex [VO(SFZ)(an-DTC)]**.**

3.3.1.3 Synthesis of oxovanadium(IV) complex [VO(SFZ)(me-DTC)]

Vanadium(IV) oxide sulfate hydrate (0.2445 g, 1.5 mmol), solution of sodium sulfadiazine, L_1, (0.4085 g, 1.5 mmol) in deionized water (100 mL) and ammonium *N*- methyl *N*- phenyl dithiocarbamate ammonium *N*-butyl dithiocarbamate, $L_{2me\text{-}DTC}$, (0.3005 g, 1.5 mmol,) were magnetically stirred for 3 h at room temperature. A green solid precipitate was formed, filtered, washed with deionized water (3 x 5 mL) and dried over silica gel in a desiccator. Molecular weight: 498.49 g. Percentage Yield: 52%. M. P. 208 ^oC. Molar Conductivity (DMSO): 2.02 Ω^{-1} cm^2 mol^{-1}. Anal. Calcd. for [VO(SFZ)(me-DTC)](%) C: 43.37; H: 3.44; N: 14.05; S: 19.29, Found C: 46.03; H: 3.55; N: 19.04; S: 10.54. Selected FT-IR (KBr), (cm^{-1}): 3157 (SO_2NH), 1628 (C=N), 1478 (C-N), 954$(CS_2)_{as}$. Selected λ_{max} in DMSO solvent (nm): (π- π^* N-C=S) 322; (n- π^* S-C=S) 348; Band I: 812, 718; Band II: 593; Band III: 402.

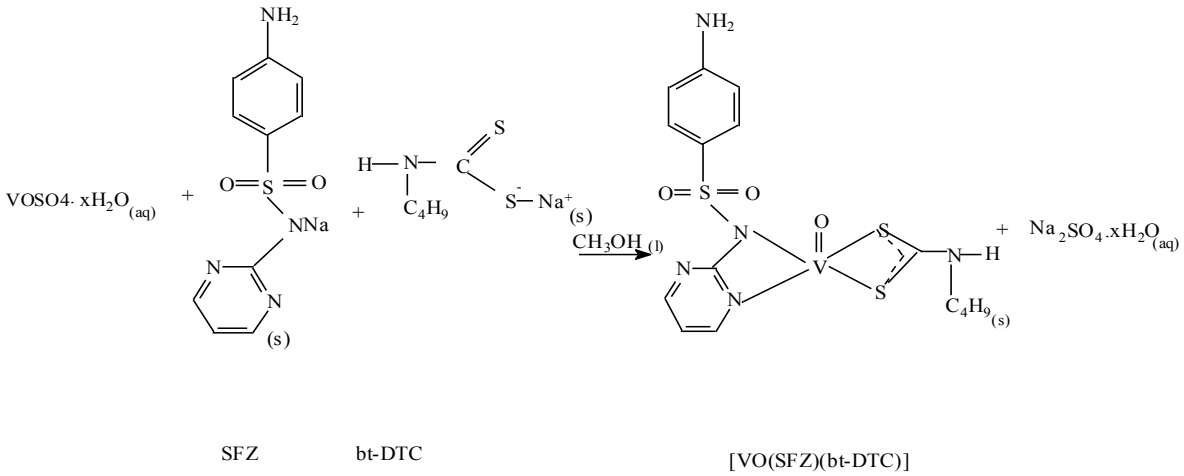


Scheme 3.3. Synthesis of oxovanadium(IV) complex [VO(SFZ)(me-DTC)]**.**

3.3.1.4 Synthesis of oxovanadium(IV) complex [VO(SFZ)(bt-DTC)]

Vanadium(IV) oxide sulfate hydrate (0.2445 g, 1.5 mmol), solution of sodium sulfadiazine, L_1, (0.4085 g, 1.5 mmol) in methanol (100 mL) and *N*-butyl dithiocarbamate, $L_{2bt\text{-}DTC}$, (0.2570 g, 1.5 mmol,). The reaction mixture was magnetically stirred for 3 h at room temperature. A light green solid precipitate was formed, filtered, washed with deionized water (3 x 5 mL) and dried over silica gel in a desiccator. Molecular weight: 464.47 g. Percentage Yield: 82%. M. P. 212 ^oC. Molar Conductivity (DMSO): 0.00 Ω^{-1} cm^2 mol^{-1}.Anal. Calcd. for [VO(SFZ)(bt-DTC)] (%) C: 38.79; H: 4.12; N: 15.08; S: 20.71, Found (%) C:

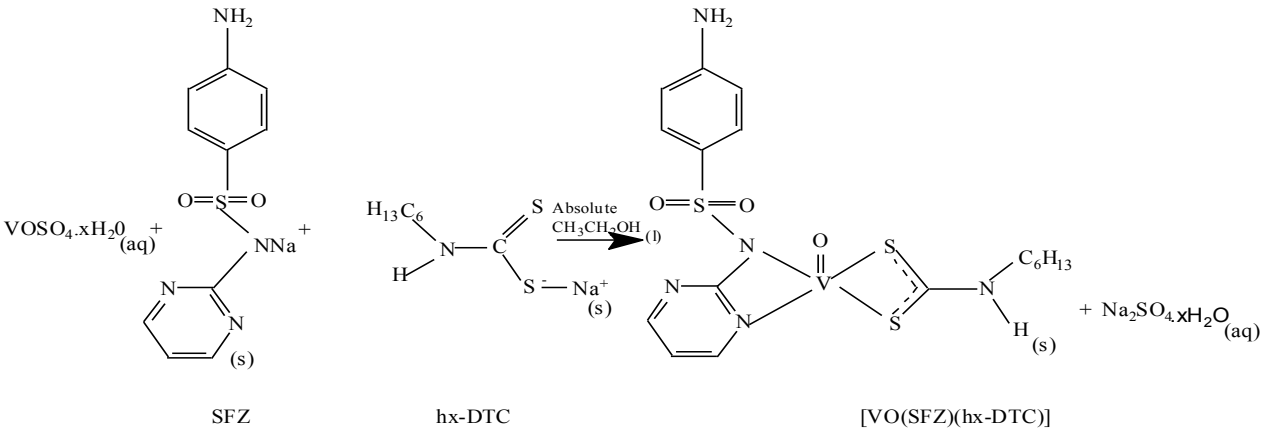
37.10; H: 2.93; N: 17.20; S: 11.62. Selected FT-IR (KBr), (cm^{-1}): 3113 (SO_2NH), 1589 (C=N), 1497 (C-N), 946$(CS_2)_{as}$. Selected λ_{max} in DMSO solvent (nm): (π- π^* N-C=S) 298, (n- π^* S-C=S) 332; Band I: 843, 736; Band II: 606; Band III: 413.



Scheme 3.4. Synthesis of oxovanadium(IV) complex [VO(SFZ)(bt-DTC)]**.**

3.3.1.5 Synthesis of oxovanadium(IV) complex [VO(SFZ)(hx-DTC)]

Vanadium(IV) oxide sulfate hydrate (0.2445 g, 1.5 mmol), solution of sodium sulfadiazine, L_1, (0.4085 g, 1.5 mmol) in methanol (100 mL) and sodium hexyl dithiocarbamate, $L_{2hx\text{-}DTC}$, (0.2990 g, 1.5 mmol,) were magnetically stirred for 3 h at room temperature. Green solid precipitate was formed, filtered, washed with distilled water (3 x 5 mL) and dried with silica gel in a desiccator. Molecular weight: 492.52 g. Percentage Yield: 64%. M. P. 208 ^oC. Molar Conductivity (DMSO): 0.00 Ω^{-1} cm^2 mol^{-1}. Anal. Calcd. for [VO(SFZ)(hx-DTC)](%) C: 41.46; H: 4.71; N: 14.22; S: 19.53. Found (%) C: 37.57; H: 2.60; N: 18.05; S: 7.37. Selected FT-IR (KBr), ν (cm^{-1}): 3114 (SO_2NH), 1586 (C=N), 1500 (C-N), 945$(CS_2)_{as}$. Selected λ_{max} in DMSO solvent (nm): (π- π^* N-C=S) 319, 322; (n- π^* S-C=S) 355; Band I: 851, 709; Band II: 616; Band III: 432.

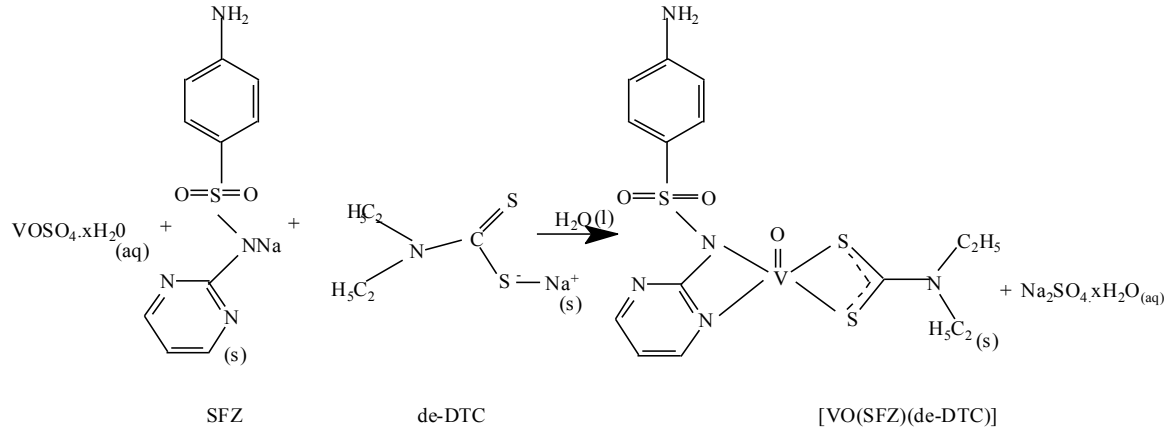


Scheme 3.5. Synthesis of oxovanadium(IV) complex [VO(SFZ)(hx-DTC)]**.**

3.3.1.6 Synthesis of oxovanadium complex [VO(SFZ)(de-DTC)]

Vanadium (IV) oxide sulfate hydrate (0.2445 g, 1.5 mmol), solution of sodium sulfadiazine, L_1, (0.4085 g, 1.5 mmol) in deionized water (100 mL) and sodium *N,N*-diethyl dithiocarbamate, L_2, (0.2570 g, 1.5 mmol,) were magnetically stirred for 3 h at room temperature. A green solid precipitate was formed, filtered, washed with deionized water (3 x 5 mL) and dried over silica gel in a desiccator. Molecular weight: 464.67 g. Percentage Yield: 82%. M. P. 218-220 ^{o}C. Molar Conductivity: 0. 02 Ω^{-1} cm^2 mol^{-1}, Anal. Calcd for [VO(SFZ)(de-DTC)] (%) C: 38.79; H: 4.12; N: 15.08; S: 20.71. Found (%) C: 43.18; H: 4.26; N: 18.54; S: 13.94. Selected FT-IR (KBr), *v* (cm-^{1}): 3130 (SO_2NH), 1599 (C=N), 1500 (C-N), 951 $(CS_2)_{as}$. Selected λ_{max} in DMSO solvent (nm): (π- π^* N-C=S) 319, 322; (n- π^* S-C=S) 358, 361; Band I: 852, 741; Band II: 616; Band III: 394.

.

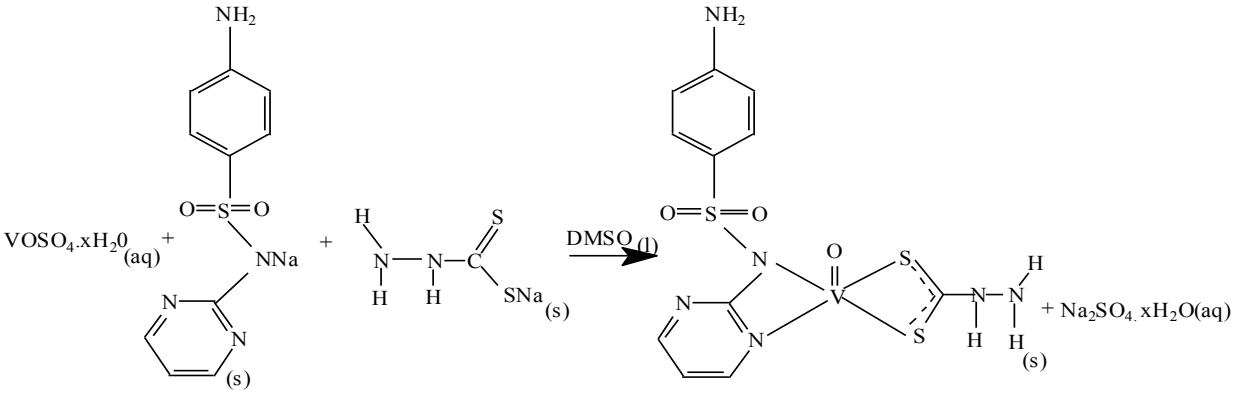


Scheme 3.6. Synthesis of oxovanadium(IV) complex of [VO(SFZ)(de-DTC)]**.**

3.3.1.7 Synthesis of oxovanadium(IV) complex [VO(SFZ)(hh-DTC)]

Vanadium(IV) oxide sulfate hydrate (0.2445 g, 1.5 mmol), solution of sodium sulfadiazine, L_1, (0.4085 g, 1.5 mmol) in methanol (100 mL) and hydrazine hydrate dithiocarbamate, $L_{2hh\text{-}DTC}$, (0.1953 g, 1.5 mmol,) were magnetically stirred for 3 h at room temperature. A yellow solid precipitate was formed filtered, washed with deionized water (3 x 5 mL) and dried over silica gel in a desiccator. Molecular weight: 423.38. Percentage Yield: 58%. M. P.: 220 ^oC. Molar Conductivity (DMSO): 0.11 Ω^{-1} cm^2 mol^{-1}; Anal. Calcd. for [VO(SFZ)(hh-DTC)](%) C: 31.21; H: 2.86; N: 19.85; S: 22.75. Found (%) C: 43.80; H: 3.61; N: 21.81; S: 19.34. Selected FT-IR (KBr), (cm^{-1}): 1488 (C-N), 1023$(CS_2)_{as}$. Selected λ_{max} in DMSO solvent (nm): (π- π^* N-C=S) 250, 319, 322; (n- π^* S-C=S) 351, 356; Band I: 837, 721; Band II: 592; Band III: 399.

.

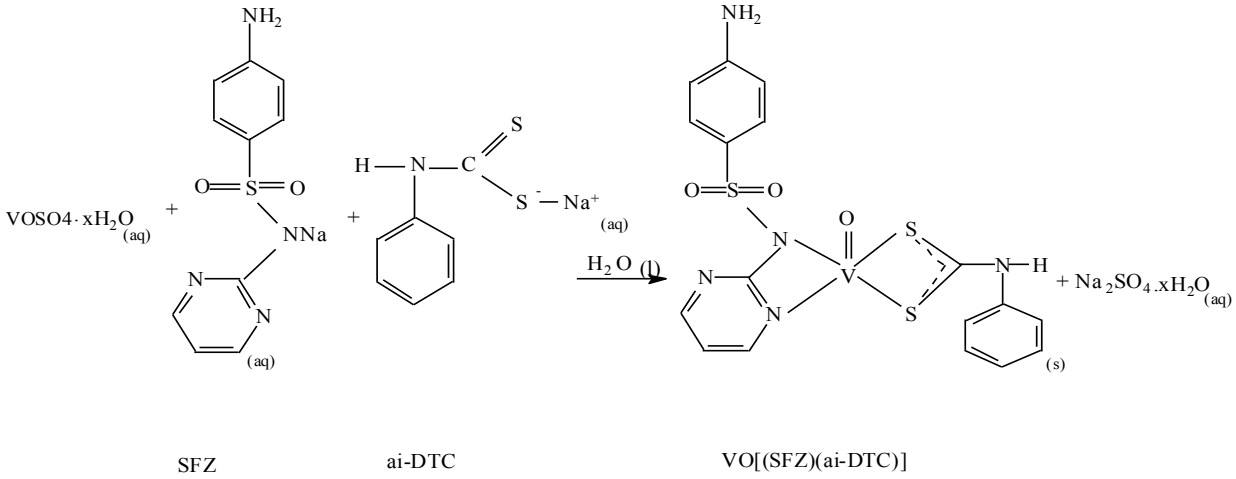


Scheme 3.7. Synthesis of oxovanadium(IV) complex [VO(SFZ)(hh-DTC)]**.**

3.3.1.8 Synthesis of oxovanadium(IV) complex [VO(SFZ)(ai-DTC)]

Vanadium(IV) oxide sulfate hydrate (0.2445 g, 1.5 mmol), solution of sodium sulfadiazine, L_1, (0.4085 g, 1.5 mmol) in methanol (100 mL) and aniline dithiocarbamate $L_{2ai\text{-}DTC}$, (0.2868 g, 1.5 mmol,) were magnetically stirred for 3 h at room temperature. A brownish green solid precipitate was formed, filtered, washed with deionized water (3 x 5 mL) and dried over silica gel in a desiccator. Molecular weight: 484.46 g. Percentage Yield: 75%. M. P. 250 ^oC. Molar Conductivity (DMSO): 0.74 Ω^{-1} cm^2 mol^{-1}. Anal. Calcd. for [VO(SFZ)(ai-DTC)] (%) C: 42.15; H: 3.12; N: 14.46; S: 19.85. Found (%) C: 41.34; H: 3.23; N: 13.56; S: 8.84. Selected FT-IR (KBr), ν (cm^{-1}): 3150 (SO_2NH), 1624 (C=N), 1507 (C-N), 951$(CS_2)_{as}$.

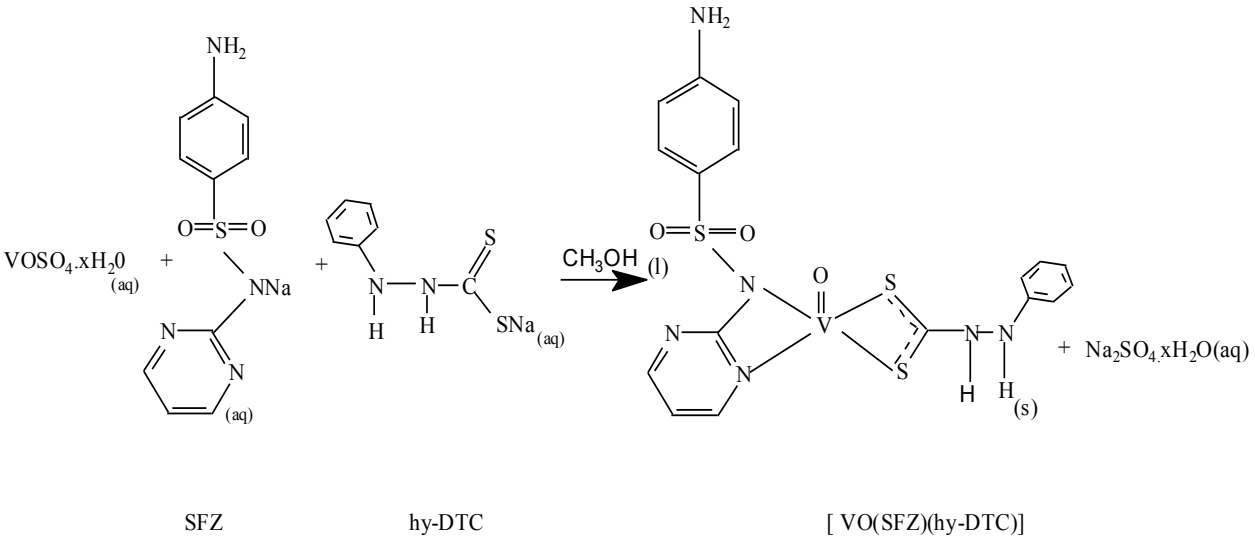
Selected λ_{max} in DMSO solvent (nm): (π- π^*N-C=S) 319, 322; (n- π^* S-C=S) 355; Band I: 828, 738; Band II: 617; Band III: 396.



Scheme 3.8. Synthesis of oxovanadium(IV) complex [VO(SFZ)(ai-DTC)]**.**

3.3.1.9. Synthesis of oxovanadium(IV) complex [VO(SFZ)(hy-DTC)]

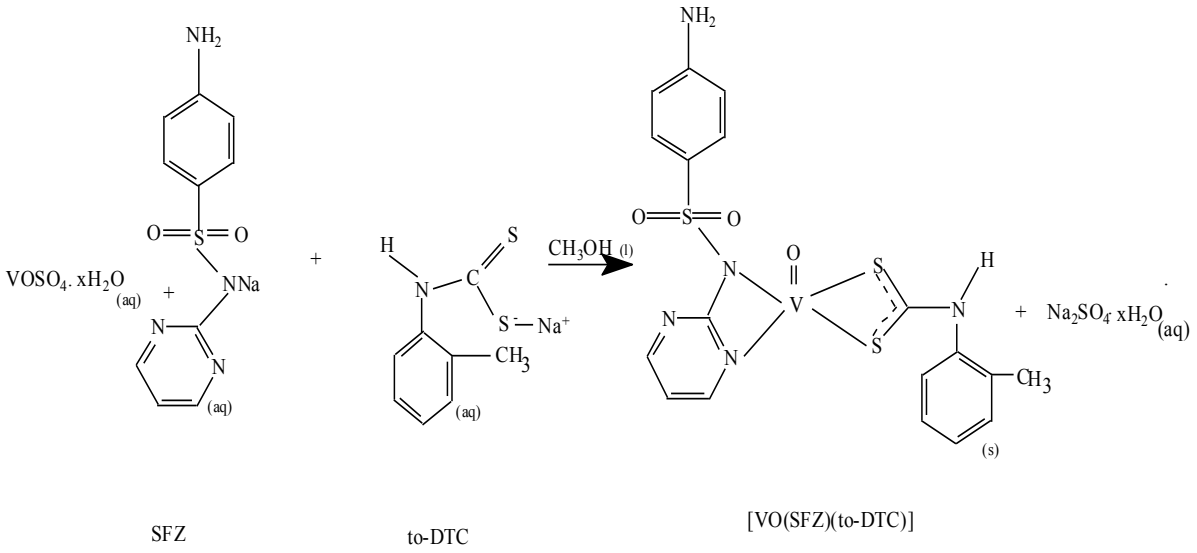
Vanadium (IV) oxide sulfate hydrate (0.2445 g, 1.5 mmol), solution of sodium sulfadiazine, L_1, (0.4085 g, 1.5 mmol) in methanol (100 mL) and sodium phenyl hydrazine dithiocarbamate, $L_{2hy\text{-}DTC}$, (0.3095 g, 1.5 mmol,) were magnetically stirred for 3 h at room temperature. A brown solid precipitate was formed, filtered, washed with deionized water (3 x 5 mL) and dried over silica gel in a desiccator. Molecular weight: 499.47 g. Percentage Yield: 80%. M. P. 222 ^oC. Molar Conductivity: 0.68 Ω^{-1} cm^2 mol^{-1}. Anal. Calcd. for [VO(SFZ)(ai-DTC)] (%) C: 40.88; H: 3.23; N: 16.83; S: 19.29, Found (%) C: 41.19; H: 2.83; N: 15.18; S: 15.44. Selected FT-IR (KBr), ν (cm^{-1}): 3160 (SO_2NH), 1645 (C=N), 1503 (C-N), 951$(CS_2)_{as}$. Selected λ_{max} in DMSO solvent (nm): (π- π^* N-C=S) 315, 319, 322; (n- π^* S-C=S) 338 Band I: 861, 715; Band II: 602; Band III: 400.



Scheme 3.9. Synthesis of oxovanadium(IV) complex [VO(SFZ)(hy-DTC)]**.**

3.3.1.10 Synthesis of oxovanadium (IV) complex [VO(SFZ)(to-DTC)]

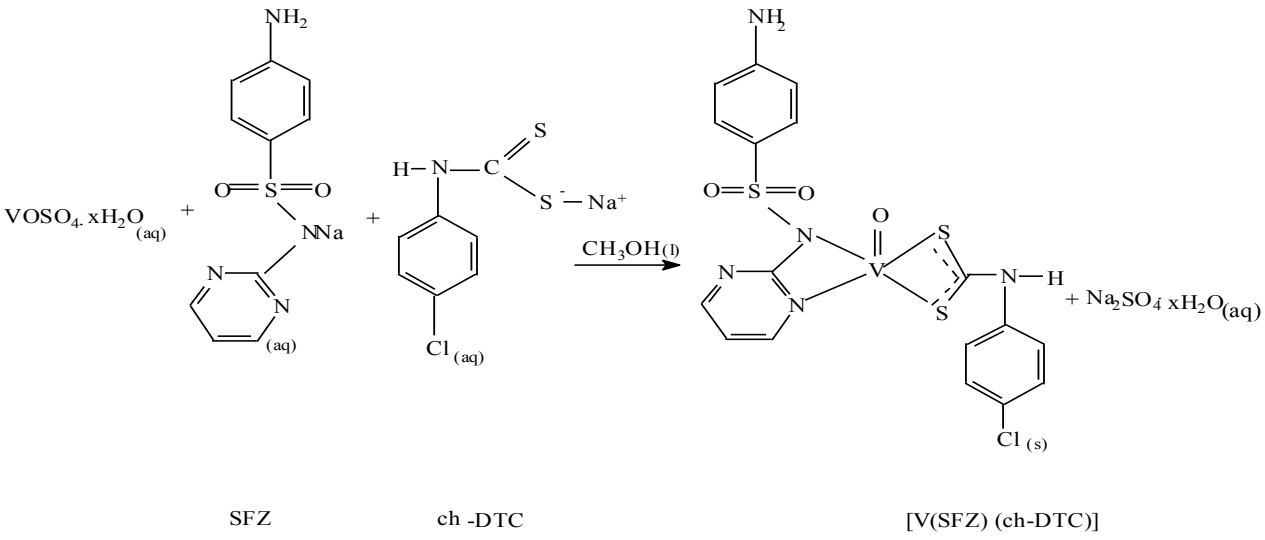
Vanadium(IV) oxide sulfate hydrate (0.2445 g, 1.5 mmol), solution of sodium sulfadiazine, L_1, (0.4085 g, 1.5 mmol) in methanol (100 mL) and sodium ortho toluidine dithiocarbamate$L_{2to\text{-}DTC}$, (0.3080 g, 1.5 mmol,) were magnetically stirred for 3 h at room temperature. A deep green solid precipitate was filtered, washed with deionized water (3 x 5 mL) and dried over silica gel in a desiccator. Molecular weight: 498.49 g. Percentage Yield: 67%. M. P. 210 ^{o}C Molar Conductivity (DMSO): 1.75 Ω^{-1} cm^2 mol^{-1}.Anal. Calcd. for [VO(SFZ)(to-DTC)](%) C: 43.37; H: 3.44; N: 14.05; S: 20.71. Found (%) C: 49.03; H: 3.70; N: 17.34; S: 7.09. Selected FT-IR (KBr), ν (cm^{-1}): 3139 (SO_2NH), 1646 (C=N), 1500 (C-N), 948 $(CS_2)_{as}$. Selected λ_{max} in DMSO solvent (nm): (π- π^* N-C=S) 316, 322; (n- π^* S-C=S) 336; Band I: 833, 719; Band II: 609; Band III: 395.



Scheme 3.10. Synthesis of oxovanadium(IV) complex [VO(SFZ)(to-DTC)]**.**

3.3.1.11 Synthesis of oxovanadium(IV) complex [VO(SFZ)(ch-DTC)]

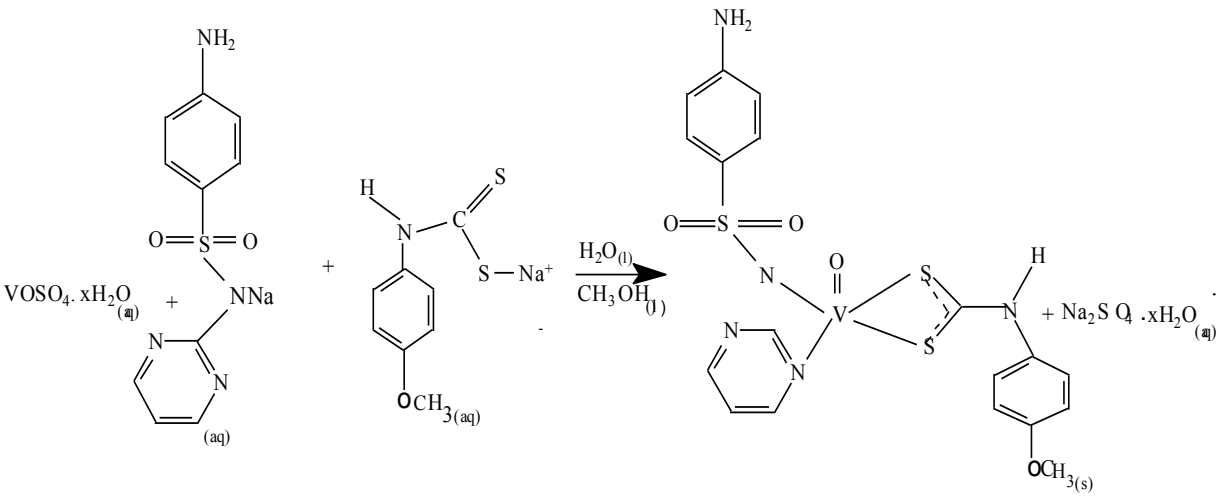
Vanadium (IV) oxide sulfate hydrate (0.2445 g, 1.5 mmol), solution of sodium sulfadiazine, L_1, (0.4085 g, 1.5 mmol) in methanol (100 mL), sodium 4-chlorodithiocarbamate $L_{2ch\text{-}DTC}$, (0.3386 g, 1.5 mmol,) were magnetically stirred for 3 h at room temperature. A brown solid precipitate was formed, filtered, washed with deionized water (3 x 5 mL) and dried over silica gel in a desiccator. Molecular weight: 518.90 g. Percentage Yield: 76%. M. P. 240-242 ^{o}C Molar Conductivity (DMSO): 0.02 Ω^{-1} cm^2 mol^{-1}. Anal. Calcd. for [VO(SFZ)(ch-DTC)](%) C: 39.35; H: 2.72; N: 13.50; S: 18.54. Found (%) C: 45.06; H: 3.61; N: 20.37; S: 9.59. Selected FT-IR (KBr), ν (cm^{-1}): 3140 (SO_2NH), 1645 (C=N), 1502 (C-N), 1004$(CS_2)_{as}$. Selected λ_{max} in DMSO solvent (nm): (π- π^* N-C=S) 308, 317, 322; (n- π^* S-C=S) 342, 351, 360, 363; Band I: 812, 699; Band II: 616; Band III: 404.



Scheme 3.11. Synthesis of oxovanadium(IV) complex [VO(SFZ)(ch-DTC)]**.**

3.3.1.12 Synthesis of oxovanadium(IV) complex of [VO(SFZ)(as-DTC)]

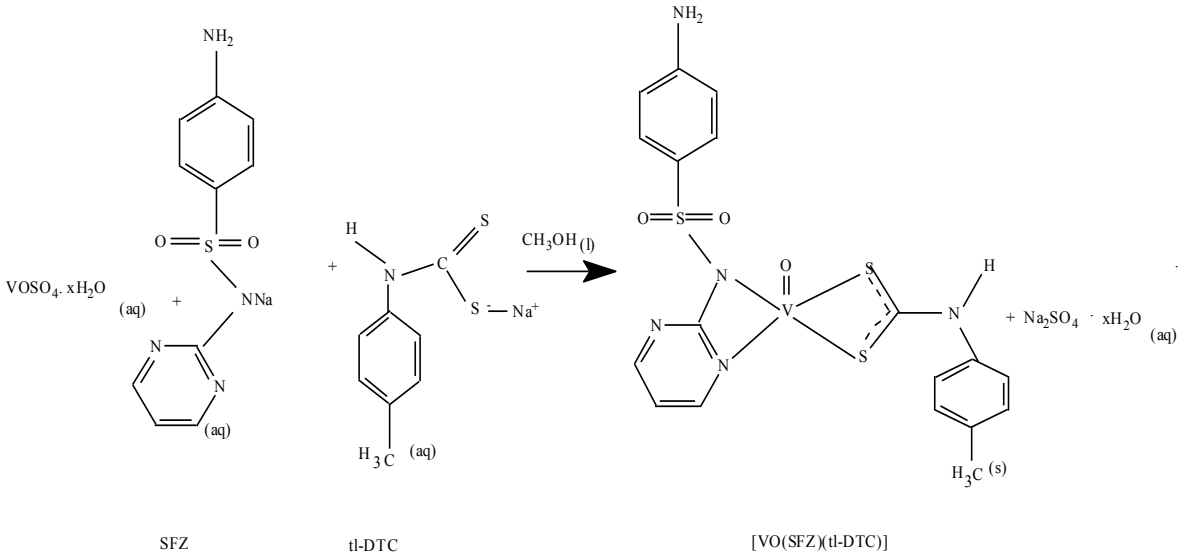
Vanadium(IV) oxide sulfate hydrate (0.2445 g, 1.5 mmol), solution of sodium sulfadiazine, L_1, (0.4085 g, 1.5 mmol) in methanol (100 mL) and sodium anisidine dithiocarbamate $L_{2as\text{-}DTC}$, (0.3320 g, 1.5 mmol were magnetically stirred for 3 h at room temperature. A green solid precipitate was formed, filtered, washed with deionized water (3 x 5 mL) and dried over silica gel in a desiccator. Molecular weight: 514.49 g. Percentage Yield: 73%. M. P. 232-234 ^{o}C. Molar Conductivity (DMSO): 0.00 Ω^{-1} cm^2 mol^{-1}. Anal. Calcd. for [VO(SFZ)(as-DTC)](%) C: 42.02; H: 3.33; N: 13.61; S: 18.69. Found (%) C: 47.29; H: 3.96; N: 15.18; S: 6.33. Selected FT-IR (KBr), ν (cm^{-1}): 3119 (SO_2NH), 1646 (C=N), 1502 (C-N), 945$(CS_2)_{as}$. Selected λ_{max} in DMSO solvent(nm): (π- π^* N-C=S) 312, 319, 322; (n- π^* S-C=S) 357, 367; Band I: 800, 718; Band II: 694, 599; Band III: 570.



Scheme 3.12. Synthesis of oxovanadium(IV) complex of [VO(SFZ)(as-DTC)]**.**

3.3.1.13 Synthesis of oxovanadium(IV) complex [VO(SFZ)(tl-DTC)]

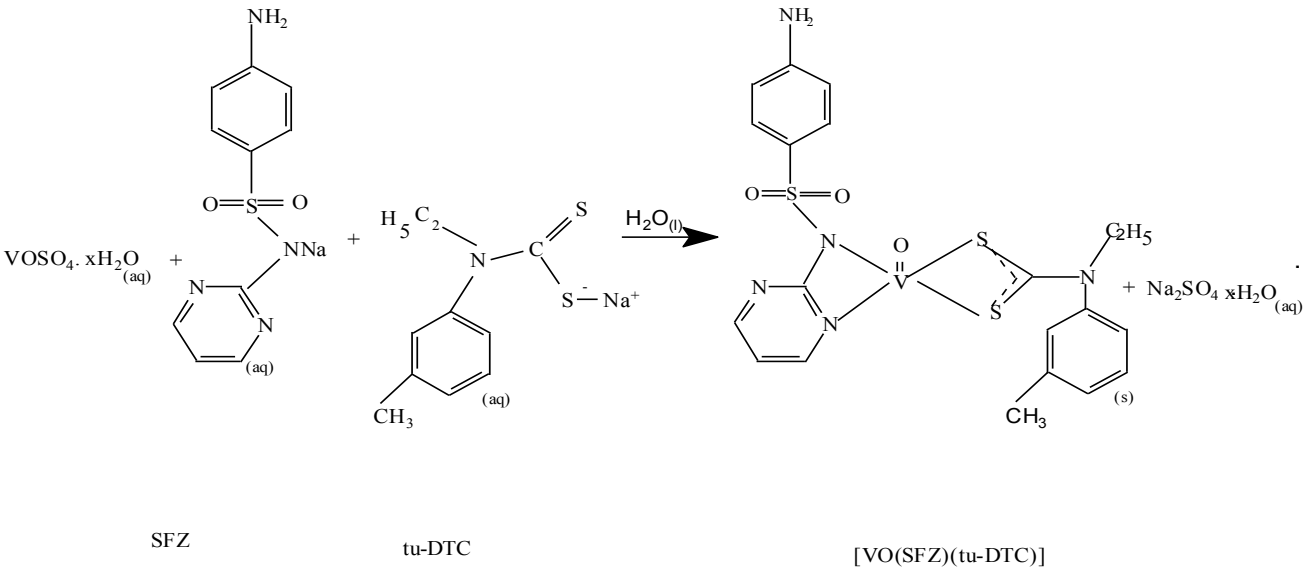
Vanadium(IV) oxide sulfate hydrate (0.2445 g, 1.5 mmol), solution of sodium sulfadiazine, L_1, (0.4085 g, 1.5 mmol) in methanol (100 mL) and sodium para toluidine dithiocarbamate $L_{2tl\text{-}DTC}$, (0.3080 g, 1.5 mmol,) were magnetically stirred for 3 h at room temperature. A brown solid precipitate was formed, filtered, washed with deionized water (3 x 5 mL) and dried with silica gel in a desiccator. Molecular weight: 498.49 g. Percentage Yield: 77%. M. P. 212 ^{o}C. Molar Conductivity (DMSO): 0.01 Ω^{-1} cm^2 mol^{-1}.Anal. Calcd. for [VO(SFZ)(tl-DTC)](%) C: 43.37; H: 3.33; N: 14.05; S: 19.29. Found (%) C: 48.25; H: 3.87; N: 19.10; S: 7.17. Selected FT-IR (KBr), ν (cm^{-1}): 3150 (SO_2NH), 1646 (C=N), 1501 (C-N), 951(CS_2)$_{as}$. Selected λ_{max} in DMSO solvent (nm): (π- π^* N-C=S) 317, 322; (n- π^* S-C=S) 352; Band I: 830, 812; Band II: 694, 593; Band III: 561.



Scheme 3.13. Synthesis of oxovanadium(IV) complex [VO(SFZ)(tl-DTC)]**.**

3.3.1.14 Synthesis of oxovanadium(IV) complex of [VO(SFZ)(tu-DTC)]

Vanadium(IV) oxide sulfate hydrate (0.2445 g, 1.5 mmol), solution of sodium sulfadiazine, L_1, (0.4085 g, 1.5 mmol) in methanol (100 mL) and sodium *meta* ethyl toluidine. $L_{2tu\text{-}DTC}$, (0.3498 g, 1.5 mmol,) were magnetically stirred for 3 hat room temperature. A greenish brown solid precipitate was formed, filtered, washed with deionized water (3 x 5 mL) and dried over silica gel in a desiccator. Molecular weight: 526.54 g. Percentage Yield: 72%. M. P. 190-192 ^{o}C Molar Conductivity (DMSO): 1.38 Ω^{-1} cm^2 mol^{-1}; Anal. Calcd. for [VO(SFZ)(tu-DTC)](%) C: 45.62; H: 4.02; N: 13.30; S: 18.27. Found (%) C: 47.47; H: 4.19; N: 16.84; S: 10.03. Selected FT-IR (KBr), ν (cm^{-1}): 3116 (SO_2NH), 1646 (C=N), 1498 (C-N), 945$(CS_2)_{as}$. Selected λ_{max} in DMSO solvent (nm): (π- π^* N-C=S) 312, 317, 322, (π- π^* S-C=S) 344; Band I: 812; Band II: 706, 572; Band III: 405.



Scheme 3.14. Synthesis of oxovanadium(IV) complex of [VO(SFZ)(tu-DTC)]**.**

3.3 Results and discussion

3.3.1 Syntheses

The synthesized oxovanadium(IV) complexes were precipitated from the reactions of solutions of mixed sulfadiazine, derivatives of dithiocarmates and oxovanadium(IV) salt. The different precipitates possessed various colours of light green, green, brown and yellow as evidence of chemical reactions to have taken place. The *para* substituted derivatives of mixed ligands of oxovanadium (IV) complexes were brown in colour, namely; ([VO(SFZ)(ch-DTC)] and [VO(SFZ)(tl-DTC)]). The other complexes of oxovanadium (IV) had different levels of green colour typical of oxovanadium(IV) complexes, except for [VO(SFZ)(hh-DTC)] which appeared yellow. The highest formula molecular mass for oxovanadium(IV) complexes had a formula molecular mass of 526.54 for [VO(SFZ)(tu-DTC)]. The lowest formula molecular mass was [VO(SFZ)(hh-DTC)] with formula molecular mass of 423.38. Oxovanadium(IV) complexes were stable, though kept and stored in a desiccator over silica gel at room temperature. Among the synthesized oxovanadium(IV) complexes 52% was the minimum percentage yield and the maximum percentage yield was 85%. This indicated a good to excellent percentage yield of oxovanadium(IV) complexes. Dimethylsulfoxide (DMSO) and dimethylformamide (DMF) dissolved all oxovanadium(IV) complexes of sodium sulfadiazine and derivatives of dithiocarbamates. They were mostly insoluble in

deionized water. The lowest temperature was [VO(SFZ)(cy-DTC)], with 140 ^{o}C, while the highest was for [VO(SFZ)(ai-DTC)] at 250 ^{o}C. The non-electrolytic nature of all oxovanadium(IV) complexes of sodium sulfadiazine and derivatives of dithiocarbamates was confirmed with values less 20 ohms^{-11}cm^{2} mol^{-1} [500]. The physicochemical characterization studies of all oxovanadium(IV) complexes are depicted in Table 3.1. below.

Table 3.1: Physicochemical characterization studies of all oxovanadium(IV) complexes of sodium sulfadiazine and derivatives of dithiocarbamates**.**

Oxovanadium(IV) Complexes	Colour	Formula Molecular Mass	Percentage Yield (%)	Solubility	Temperature (^{o}C)	Molar Conductivity (Ω^{-1}cm^{2} mol^{-1})
$VOSO_4$	Blue		99	DMSO DMF	88-90	1.65
[VO(SFZ)(cy-DTC)]	Green	490.51	85	DMSO DMF	140	1.10
[VO(SFZ)(an-DTC)]	Green	484.46	72	DMSO DMF	206-208	0.01
[VO(SFZ)(me-DTC)]	Green	498.49	52	DMSO DMF	208	2.02
[VO(SFZ)(bt-DTC)]	Green	464.47	82	DMSO DMF	212	0.00
[VO(SFZ)(de-DTC)]	Green	464.47	82	DMSO DMF	218-220	0.02
[VO(SFZ)(hx-	Green	492.52	64	DMSO	248	0.00

DTC)]				DMF		
[VO(SFZ)(hh-DTC)]	Yellow	423.38	58	DMSO DMF	220	0.11
[VO(SFZ)(ai-DTC)]	Light green	484.46	75	DMSO DMF	250	0.74
[VO(SFZ)(hy-DTC)]	Yellow	499.47	80	DMSO DMF	222	0.68
[VO(SFZ)(to-DTC)]	Deep green	498.49	67	DMSO DMF	210	1.75
[VO(SFZ)(ch-DTC)]	Brown	518.90	76	DMSO DMF	240-242	0.02
[V(SFZ)(as-DTC)]	Green	514.49	73	DMSO DMF	232-234	0.00
[VO(SFZ)(tl-DTC)]	Brown	498.49	77	DMSO DMF	212	0.01
[VO(SFZ)(tu-DTC)]	Green	526.54	72	DMSO DMF	190-192	1.38

3.3.2 Elemental Analysis

Elemental analysis was also used to check the purities of the oxovanadium(IV) complexes by determining the percentage composition of carbon, hydrogen, nitrogen and sulfur. Following guidelines of homogeneous samples for elemental analysis, variations were still observed in the results. These might be due to effect of hydrate or moisture, incomplete separation of water from sulfur and incomplete digestion [501-502].

Table 3.2: Elemental analysis of oxovanadium(IV) complexes of mixed ligands of sodium sulfadiazine and derivatives of dithiocarbamates**.**

Metal complex	Chemical formula	Analytical data (%)			
		C	H	N	S
		Calculated			
		Found			
[VO(SFZ)(cy-DTC)]	$C_{17}H_{21}N_5S_3O_3V$	41.63	4.32	14.28	19.61
		48.24	3.40	26.45	11.21
[VO(SFZ)(an-DTC)]	$C_{17}H_{15}N_5S_3O_3V$	42.15	3.12	14.46	19.85
		41.54	3.94	18.23	18.03
[VO(SFZ)(me-DTC)]	$C_{18}H_{17}N_5S_3O_3V$	43.37	3.44	14.05	19.29
		46.03	3.55	19.04	10.54
[VO(SFZ)(bt-DTC)]	$C_{15}H_{19}N_5S_3O_3V$	38.79	4.12	15.08	20.71
		37.10	2.93	17.20	11.62
[VO(SFZ)(hx-DTC)]	$C_{17}H_{23}N_5S_3O_3V$	41.46	4.71	14.22	19.53
		37.57	2.60	18.05	7.37
[VO(SFZ)(de-DTC)]	$C_{15}H_{19}N_5S_3O_3V$	38.79	4.12	15.08	20.71
		43.18	4.26	18.54	13.94
[VO(SFZ)(hh-DTC)]	$C_{11}H_{12}N_6S_3O_3V$	31.21	2.86	19.85	22.75
		43.80	3.61	21.81	19.34
[VO(SFZ)(ai-DTC)]	$C_{17}H_{15}N_5S_3O_3V$	42.15	3.12	14.46	19.85
		41.34	3.23	13.56	8.84
[VO(SFZ)(hy-	$C_{17}H_{16}N_6S_3O_3V$	40.88	3.23	16.83	19.29

DTC)]		41.19	2.83	15.18	15.44
[VO(SFZ)(to-DTC)]	$C_{18}H_{16}N_5S_3O_3V$	43.37	3.44	14.05	20.71
		49.03	3.70	17.34	7.09
[VO(SFZ)(ch-DTC)]	$C_{17}H_{14}N_5S_3O_3ClV$	39.35	2.72	13.50	18.54
		45.06	3.61	20.37	9.59
[VO(SFZ)(as-DTC)]	$C_{18}H_{17}N_5O_4S_3V$	42.02	3.33	13.61	18.69
		47.29	3.96	15.18	6.33
[VO(SFZ)(tl-DTC)]	$C_{18}H_{17}N_5O_3S_3V$	43.37	3.44	14.05	19.29
		48.25	3.87	19.10	7.17
[VO(SFZ)(tu-DTC)]	$C_{20}H_{21}N_5S_3O_3V$	45.62	4.02	13.30	18.27
		47.47	4.19	16.84	10.03

3.3.3 Molecular Spectroscopy

In this chapter, the two molecular spectroscopic techniques used to characterize the synthesized oxovanadium(IV) complexes were Fourier Transform Infra-Red (FT-IR) and Ultra-violet Visible (UV-Vis) Spectroscopy.

3.3.3.1 Fourier Transform Infra-Red (FT-IR) Spectroscopy of mixed sulfadiazine and dithiocarbamate with oxovanadium(IV) complexes

The FT-IR for oxovanadium(IV) was also taken from upper region of 4000 cm^{-1} to a lower FT-IR region of 370 cm^{-1}. In this chapter, the relevance of FT-IR was used to determine the coordinating ability of the donors of the mixed ligands to the oxovanadium(IV) ion. This was done for each oxovanadium(IV) complex and then compared with the corresponding ligand.

The asymmetrical and symmetrical stretching modes of amino group, NH_2, of all oxovanadium(IV) complexes had absorption bands between 3558 and 3250 cm^{-1} as compared

to SFZ, with absorption bands at 3415 and 3482-3310 cm^{-1} respectively. Differences were observed between the spectra of oxovanadium(IV) complexes and sodium sulfadiazine. These differences might be due to either different forms of vibrations of coordinated water, lattice water or hydrogen bonding between the oxovanadium complexes entailing the NH_2 and SO_2 groups [371, 503]. Sulfonamide nitrogen (-SO_2N) atom in the oxovanadium(IV) complexes and they all absorbed at either lower or higher frequencies (3262-3112 cm^{-1}) compared to the free ligand (3251 cm^{-1}). Azomethine group, -C=N, had higher and lower frequencies (1651-1579 cm^{-1}) than the free ligand of sodium sulfadiazine (1628, 1577 cm^{-1}). SO_2 asymmetrical and symmetrical stretching modes absorbed at higher wavenumbers, (1333 cm^{-1}, 1160 cm^{-1})) while (S-N) absorbed at lower wavenumbers (1057 cm^{-1}) in all oxovanadium(IV) complexes when compared with the free ligand, (1374, 1244, 1138, 1102 cm^{-1}) (1024 cm^{-1}) respectively. All the modifications of NH_2, -SO_2N, -C=N, SO_2 and S-N confirmed the coordination of azomethine nitrogen and sulfonamide nitrogen atom to the oxovanadium (IV) ion [363-364, 371, 503-504]. All oxovanadium(IV) complexes had metal coordination stretching, (V-N) from 550-636 cm^{-1}.

In all the dithiocarbamates, the thioureide band appeared in the region from 1530-1476 cm^{-1} for all the oxovanadium(IV) complexes. They all had higher wavenumbers than the ligands of dithiocarbamates 1496-1426cm^{-1}, with a difference of 34-50 cm^{-1} in the wavenumber compared with the ligand. The general stretching frequency for $(CS_2)_{as}$ is 1050-950 cm^{-1}. The asymmetrical $(CS_2)_{as}$ that had shifted slightly for a difference of 1-5 cm^{-1} for all synthesized oxovanadium(IV) complexes when compared with the stretching frequencies of the general with vibration frequencies from a region of 1049-945 cm^{-1}. The wavenumbers of the oxovanadium(IV) complexes were less than the corresponding ligands, with the exception of [VO(SFZ)(hh-DTC)] [VO(SFZ)(ch-DTC)] and[VO(SFZ)(as-DTC)] with lower differences of 4cm^{-1}, 10 cm^{-1} and 3 cm^{-1} as compared to hh-DTC, ch-DTC and as-DTC, respectively. Most of the $(CS_2)_{as}$ vibrational frequencies had overlap with the ν(V=O) vibrational frequencies as evident in Table 3.3.

The multiple covalent bond of oxovanadium species, VO, has a general stretching frequency for the FT-IR of oxovanadium (IV), ν(V=O), in the region of 940-1020 cm^{-1} [505], 960±50 cm^{-1} [506] or 985±50 cm^{-1} [507]. All the synthesized oxovanadium(IV) complexes had

absorption frequencies, ν(V=O), in the region of 1016-942 cm^{-1}, which were within the general stretching frequencies. The ν(V=O) of inorganic salt of vanadyl(IV) sulfate hydrate was 1015 cm^{-1}[505]. It was earlier said of their overlap with ν $(CS_2)_{as}$ absorption frequency bands. Another band shift between 855-803 cm^{-1} indicated the presence of coordinated water in some oxovanadium(IV) complexes. [505]. This can also be explained as traces of ----O=V-----V=O interaction of polymeric nature [508].The V-S wavenumber of the oxovanadium(IV) complexes appeared in the region of 456-407 cm^{-1}. They were similar to the results obtained by Sharma M et al, where their *ν*(V-S) had absorption stretching frequencies from 431-416 cm^{-1}[509].

Data from FT-IR spectra of all the oxovanadium(IV) complexes proved the successful coordination of the mixed ligands of N_2S_2 coordination mode to the oxovanadium (IV) ion.

Table 3.3: FT-IR frequencies (cm^{-1}) for sodium sulfadiazine ligated oxovanadium(IV) complexes and dithiocarbamates ligated oxovanadium(IV) complexes**.**

Ligand (L_1)	$\nu(N\text{-}H)_{as}$	$\nu(N\text{-}H)_s$	$\nu(SOONH)$	$\nu(C=N)$	$\nu(SOO)_{as}$	$\nu(SOO)_s$	$\nu(S\text{-}N)$	$\nu(V\text{-}N)$
SFZ	$3422_{(s)}$ $3482_{(s)}$	$3310_{(s)}$	$3251_{(s)}$	$1549_{(w)}$ $1628_{(s)}$	$1244_{(s)}$ $1374_{(w)}$	$1138_{(s)}$ $1102_{(s)}$	$1024_{(s)}$	
Oxovanadium(IV) Complexes								
[VO(SFZ)(cy-DTC)]	$3549_{(s)}$ $3481_{(s)}$ $3424_{(s)}$	$3251_{(w)}$	$3157_{(w)}$	$1627_{(s)}$	$1286_{(w)}$	$1158_{(s)}$	$1021_{(w)}$	$571_{(m)}$
[VO(SFZ)(an-DTC)]	$3435_{(s)}$ $3479_{(s)}$ $3559_{(s)}$	$3299_{(s)}$	$3120_{(w)}$	$1574_{(m)}$	$1327_{(s)}$	$1138_{(s)}$	$1016_{(s)}$	$559_{(m)}$
[VO(SFZ)(me-DTC)]	$3427_{(s)}$ $3485_{(s)}$ $3554_{(s)}$	$3265_{(m)}$	$3120_{(w)}$	$1628_{(m)}$	$1333_{(m)}$	$1159_{(w)}$	$1032_{(w)}$	$627_{(m)}$
[VO(SFZ)(bt-DTC)]	$3427_{(s)}$ $3380_{(s)}$ $3552_{(s)}$	$3364_{(s)}$ $3271_{(m)}$	$3113_{(m)}$	$1589_{(s)}$	$1326_{(s)}$	$1156_{(s)}$	$1006_{(w)}$	$555_{(s)}$
[VO(SFZ)(hx	$3425_{(s)}$	$3318_{(s)}$	$3114_{(m)}$	$1586_{(s)}$	$1326_{(s)}$	$1156_{(s)}$	$1000_{(m)}$	$551_{(m)}$

-DTC)]	3477$_{(s)}$ 3556$_{(s)}$							
[VO(SFZ)(de-DTC)]	3428$_{(s)}$	3270$_{(w)}$	3130$_{(w)}$	1599$_{(s)}$	1326$_{(m)}$	1154$_{(s)}$	1035$_{(w)}$	555$_{(s)}$
[VO(SFZ)(hh-DTC)]	3426$_{(s)}$	3313$_{(m)}$	3109$_{(m)}$	1587$_{(s)}$	1299$_{(m)}$	1158$_{(s)}$	1052$_{(w)}$	
[VO(SFZ)(cc-DTC)]	3421$_{(s)}$ 3485$_{(s)}$ 3557$_{(s)}$	3250$_{(w)}$	3160$_{(w)}$	1622$_{(m)}$	1327$_{(s)}$	1156$_{(s)}$	1009$_{(w)}$	602$_{(w)}$
[VO(SFZ)(ai-DTC)]	3428$_{(s)}$ 3480$_{(s)}$ 3550$_{(s)}$	3284$_{(w)}$	3150$_{(w)}$	1624$_{(m)}$	1330$_{(m)}$	1160$_{(s)}$	1024$_{(m)}$	597$_{(w)}$
[VO(SFZ)(hy-DTC)]	3431$_{(s)}$ 3448$_{(s)}$ 3558$_{(s)}$	3294$_{(w)}$	3160$_{(w)}$	1645$_{(m)}$	1332$_{(m)}$	1159$_{(s)}$	1057$_{(w)}$	565$_{(w)}$
[VO(SFZ)(to-DTC)]	3427$_{(s)}$ 3480$_{(s)}$	3367$_{(w)}$ 3269$_{(w)}$	3139$_{(w)}$	1646$_{(s)}$	1328$_{(s)}$	1158$_{(s)}$ 1136$_{(m)}$	1024$_{(w)}$	574$_{(m)}$
[VO(SFZ)(ch-DTC)]	3428$_{(s)}$	3254$_{(w)}$	3140 $_{(s)}$	1645$_{(s)}$	1328$_{(s)}$	1158$_{(s)}$	1025$_{(s)}$	555$_{(s)}$
[VO(SFZ)(as	3424$_{(s)}$	3244$_{(s)}$	3119$_{(s)}$	1646$_{(s)}$	1329$_{(s)}$	1158$_{(s)}$	1038$_{(m)}$	555$_{(s)}$

-DTC)]	3482$_{(s)}$ 3554$_{(s)}$							
[VO(SFZ)(tl-DTC)]	3424$_{(s)}$ 3486(s)	3287$_{(s)}$	3150$_{(w)}$	1646$_{(s)}$	1331$_{(s)}$	1158$_{(s)}$	1028$_{(w)}$	570$_{(s)}$
[VO(SFZ)(tu-DTC)]	3424$_{(s)}$ 3482$_{(s)}$ 3554$_{(s)}$	3311$_{(s)}$	3116$_{(s)}$	1646$_{(s)}$	1327$_{(s)}$	1157$_{(s)}$	1006$_{(w)}$	553$_{(s)}$

Ligands(L_2)	*v*(C-N)	*v*(CSS)$_{as}$	*v*(V=O)	*v*(V-S)
cy-DTC	1486$_{(s)}$	1003$_{(m)}$		
[VO(SFZ)(cy-DTC)]	1498(s)	948$_{(s)}$	948$_{(s)}$, 845$_{(m)}$	414$_{(m)}$
an-DTC	1452$_{(m)}$	1023$_{(s)}$		
[VO(SFZ)(an-DTC)]	1530$_{(w)}$	1016 $_{(s)}$	1016$_{(s)}$, 803$_{(s)}$	426$_{(m)}$
me-DTC	1496$_{(m)}$	1042$_{(m)}$		
[VO(SFZ)(me-DTC)]	1478$_{(w)}$	954$_{(m)}$	954$_{(m)}$	414$_{(s)}$
bt-DTC	1464$_{(s)}$	1049$_{(w)}$		
[VO(SFZ)(bt-DTC)]	1497$_{(s)}$	946$_{(s)}$	946$_{(m)}$, 846$_{(m)}$	432$_{(m)}$
hx-DTC	1459$_{(s)}$	959$_{(m)}$		
[VO(SFZ)(hx-DTC)]	1482$_{(s)}$1500$_{(s)}$	945$_{(s)}$	945$_{(s)}$, 845 $_{(m)}$	456$_{(m)}$
de-DTC	1475$_{(s)}$	993$_{(s)}$		
[VO(SFZ)(de-DTC)]	1500$_{(s)}$	951$_{(m)}$	951$_{(m)}$ 845$_{(w)}$	434$_{(m)}$
[VO(SFZ)(hh-DTC)]	1495$_{(s)}$	1043$_{(s)}$	943$_{(s)}$, 844$_{(s)}$	390$_{(m)}$
cc-DTC	1462$_{(s)}$	985$_{(m)}$		
[VO(SFZ)(cc-DTC)]	1498$_{(s)}$	946$_{(s)}$	946$_{(br,s)}$,.846$_{(br,s)}$	410$_{(s)}$

ai-DTC	$1460_{(s)}$	$1008_{(w)}$		
[VO(SFZ)(ai-DTC)]	$1507_{(s)}$	$951_{(m)}$	$951_{(m)}$,$850_{(w)}$	$414_{(s)}$
hy-DTC	$1426_{(s)}$	$1025_{(s)}$		
[VO(SFZ)(hy-DTC)]	$1503_{(s)}$	$951_{(s)}$	$951_{(s)}$, $855_{(w)}$	$413_{(w)}$
to-DTC	$1496_{(s)}$	$1006_{(m)}$		
[VO(SFZ)(to-DTC)]	$1500_{(s)}$	$948_{(s)}$	$948_{(s)}$, $848_{(m)}$	$446_{(s)}$
ch-DTC	$1465_{(s)}$	$994_{(s)}$		
[VO(SFZ)(ch-DTC)]	$1502_{(s)}$	$1004_{(s)}$	$1004_{(s)}$, $847_{(w)}$	$443_{(s)}$
as-DTC	$1466_{(s)}$	$1031_{(s)}$		
[VO(SFZ)(as-DTC)]	$1502_{(s)}$	$1034_{(m)}$	$945_{(m)}$, $853_{(w)}$	$447_{(s)}$
tl-DTC	$1474_{(m)}$	$1005_{(s)}$		
[VO(SFZ)(tl-DTC)]	$1501_{(s)}$	$951_{(m)}$	$951_{(m)}$, $853_{(w)}$	$442_{(s)}$
tu-DTC	$1459_{(m)}$	$1001_{(s)}$		
[VO(SFZ)(tu-DTC)]	$1498_{(m)}$	$945_{(s)}$	$945_{(s)}$, $847_{(w)}$	$423_{(s)}$

br= broad; m= medium; s= strong; w=weak

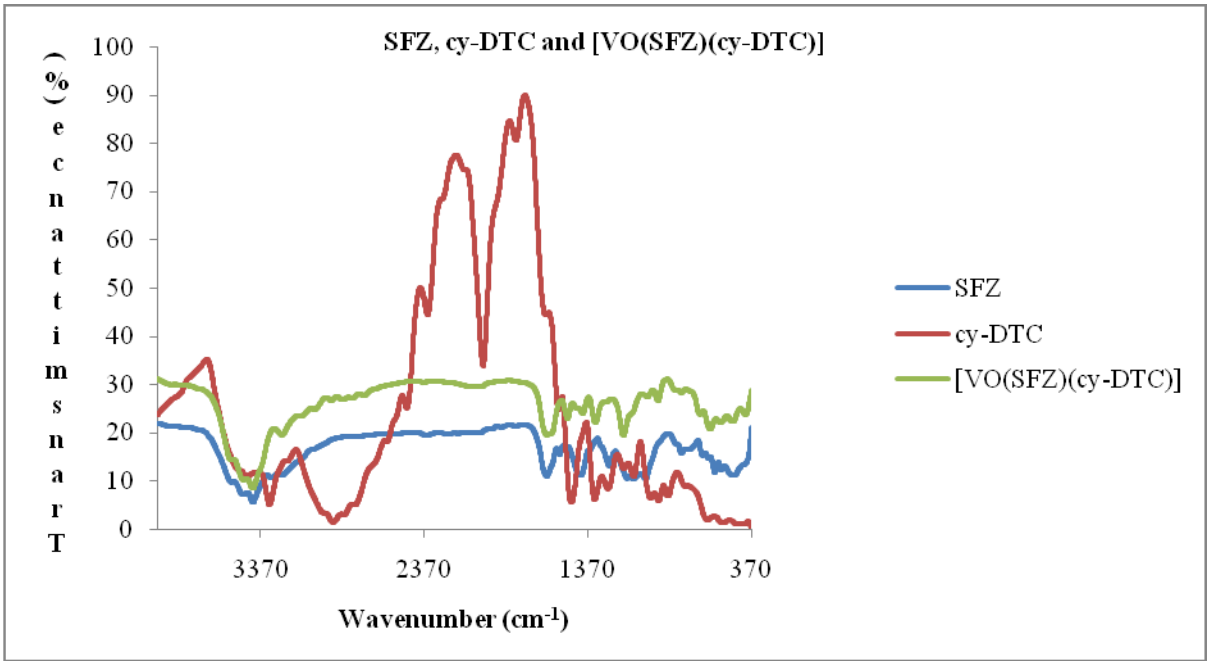


Figure 3.2: The FT-IR of [VO(SFZ)(cy-DTC)] and the corresponding ligands.

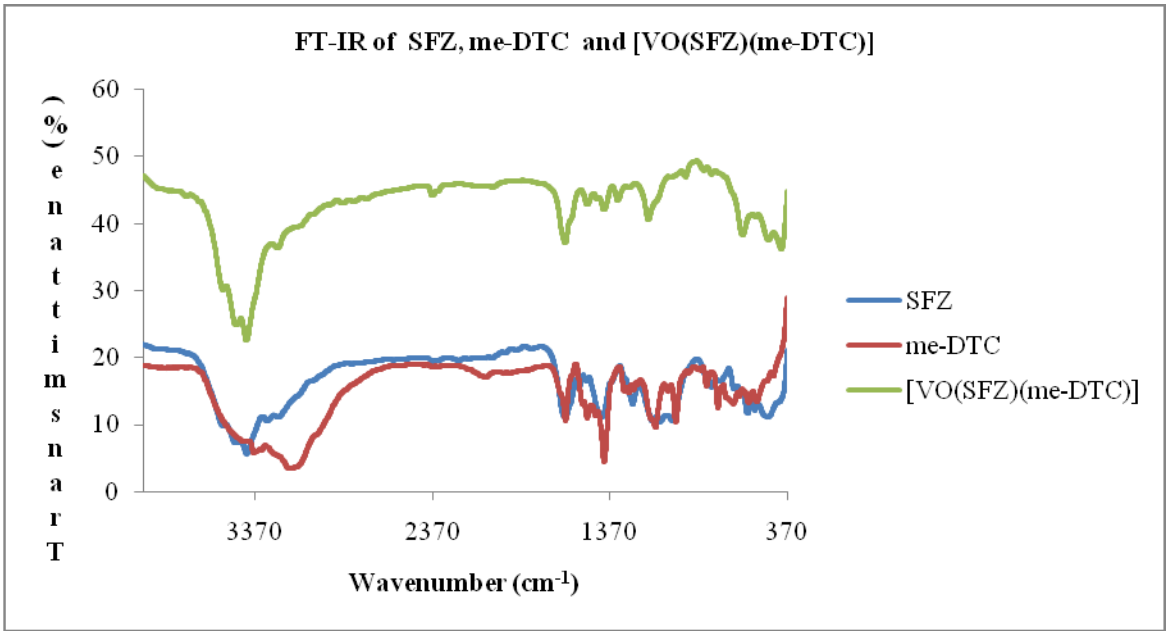


Figure 3.3: The FT-IR of [VO(SFZ)(me-DTC)] and the corresponding ligands.

3.3.3.2 Electronic spectra studies of oxovanadium(IV) complexes

Studies on the electronic spectra of the oxovanadium(IV) complexes were done to assess the mode of coordination if there would be a blue or red shift, as well as, the determination of the geometries of all the oxovanadium(IV) complexes. Absorption in the wavelength region between 250-300 nm can be due to functional group of conjugated alkenes, C=C, benzene or phenyl ring of the mixed ligands and the corresponding oxovanadium(IV) complexes [510-511]. In addition, all the complexes of oxovanadium with absorption bands of below 300-350 nm were due to intra-ligand transitions from mixed ligands of sodium sulfadiazine *(-CH=N-)* and all derivatives of dithiocarbamates (*N-C=S* and *S-C=S*) as reported for uncomplexed ligands [510, 512, 513]. Absorption bands above 350 nm and below 400 nm can be further due to the presence of the azomethine group *(-CH=N-)* and lone pair of electrons on sulfur atom in *S-C=S* of dithiocarbamate group [511-514]. Metal to ligand charge transfer (MLCT) in all oxovanadium (IV) complexes have absorptions above 400 nm of d-d transition [511]. Overlapping might occur since both ligands (L_1 and L_2) had π-$\pi^*$and n-π^*, so they had the same results as presented in Table 3.5. All the complexes of oxovanadium(IV) had blue hypsochromic shifts when compared with the mixed ligands. At room temperature, there are three absorption bands, known as band I (900-526 nm), band II (689-526 nm) and band III (476-333 nm). According to Ballhausen and Gray Scheme, band I was assigned to $^2B_2 \rightarrow {}^2E$ ($b_2 \rightarrow e_2^*$), band II assigned to $^2B_2 \rightarrow {}^2B_1$ ($b_2 \rightarrow e_1^*$) and band III assigned to $^2B_2 \rightarrow {}^2A_1$ ($b_2 \rightarrow a_1^*$) transitions [511, 515]. Studies on electronic spectroscopy of all oxovanadium(IV) complexes revealed coordination of DMSO solvent in the sixth position which is trans to the V=O bond in order to retain the dimeric nature [511]. They all formed six coordinate complexes, since the d-d transition showed low absorption above 700 nm [511]. For five coordinate complexes, there is no d-d transition above 700 nm [511].

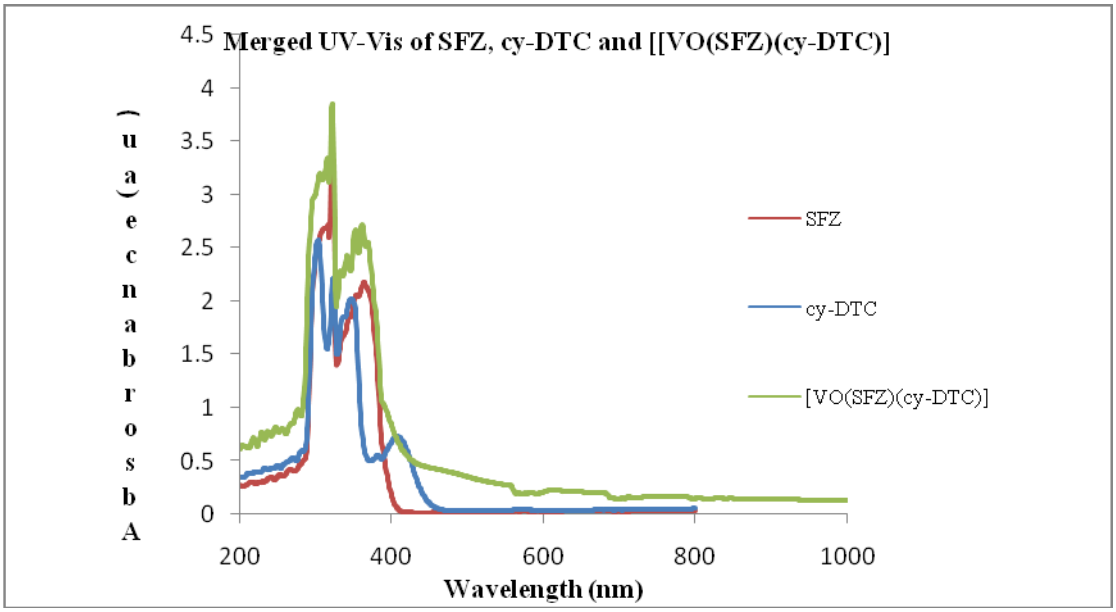


Figure 3.4: The UV-Vis spectra of oxovanadium(IV) complexes and their corresponding ligands of SFZ, cy-DTC and [[VO(SFZ)(cy-DTC)].

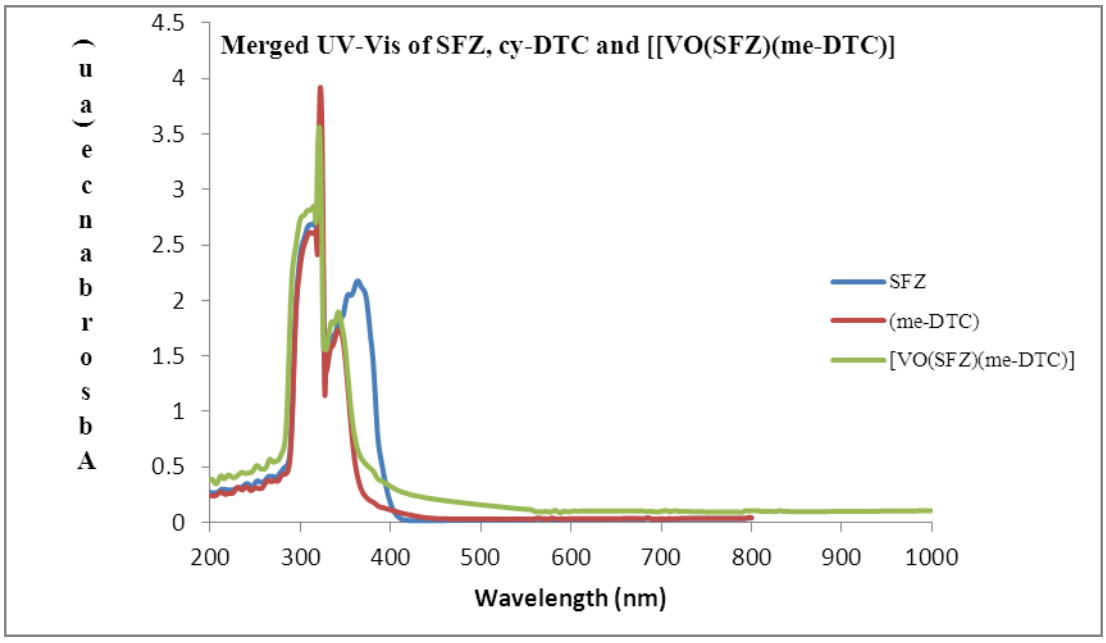


Figure 3.5: The UV-Vis spectra of SFZ, cy-DTC and [VO(SFZ)(me-DTC)].

3.3.3.3 Nuclear Magnetic Resonance (^{1}H NMR and ^{13}C NMR)

Both ^{1}H NMR and ^{13}C NMR were not carried out for all the oxovanadium(IV) complexes due to their paramagnetic nature.

3.4. Conclusion

Apart from the blue colour of inorganic salt of vanadyl sulfate hydrate, the changes observed in the colour of the complexes confirmed coordination. The different colours were light green, green, deep green, brown and yellow. They were all stable at room temperature and the colours were still retained after ten months. They all appeared as solid and were soluble in dimethylformamide (DMF) and dimethylsulfoxide (DMSO). All the oxovanadium(IV) complexes were non electrolytes.

For the spectroscopic characterization studies, FT-IR proved the successful coordination of the mixed ligands with oxovanadium(IV) ion. The wavenumbers of oxovanadium(IV) ions were observed between 1016-942 cm^{-1}, which confirmed ligands coordination with oxovanadium(IV) ions. Six coordinate complexes might be formed as absorption band region from 855-803 cm^{-1} indicating polymeric forms were detected as elements of water coordination. The coordination was N_2S_2 modes.

Studies on electronic spectroscopies of all oxovanadium(IV) complexes revealed coordination of DMSO solvent in the sixth position which is trans to the V=O bond in order to retain the dimeric nature. They all formed six coordinate complexes, since the d-d transition showed low absorption above 700 nm. In addition to the above, d-d transitions above 700 nm confirmed six coordinate complexes for all the oxovanadium(IV) complexes on the basis of UV-Vis spectroscopic data. For five coordinate complexes, there is no d-d transition above 700 nm.

CHAPTER FOUR

4. Preparation and spectral characterization of zinc(II) complexes of mixed sulfadiazine and dithiocarbamate

4.1 Introduction

Zinc is a d block element, but it is said to be a non-transition element because it possesses a filled d^{10} electron configuration, as an element or ion, when it appears as Zn^{2+} [516]. Zinc is a borderline acid in classification of hard acids and hard bases from Pearson's concept of HSAB principle [516]. It is typical of zinc to appear as a sulfide, most especially, as the zinc ore, ZnS (zinc blende). In biological systems, zinc performs multifaceted actions [517]. The d^{10} electron configurations of Zn^{2+} ions enable them to form complexes with flexible coordinating environment and diverse geometries ranging from tetrahedral, several distorted polyhedral to octahedral structures [518].

Coordination compounds show different distinct properties due to metal ions and the types of ligands these metal ligands are ligated to [519]. These coordination compounds are referred to as metal complexes [520]. The donor ligands in these metal complexes have unique properties and other potentials they can use to enhance or inhibit the properties of metal ions to give useful metal complexes in the areas of industries, medicine and biology [516, 520-523]. On the other way round, metals can influence the potentials of ligands in metal complexes [524]. HSAB classification also revealed ligands such as nitrogen and phenylamine as borderline bases, amine as hard base and sulfides as soft bases [516].

Recently, coordination chemistry of zinc has been the focus. Zinc in form of Zn(II) in hydrolytic enzymes can act as nucleophiles which react with substrates of electrophiles [517]. The central actions of Zn(II) with flexibility and coordination abilities in hydrolytic enzymes and deoxyribonucleic acid (DNA) have helped to implement very effective and fast catalytic reactions [517, 525]. Zinc also behaves catalytically and structurally in proteins, most especially in zinc finger family, which entailed binding of nucleic acid and gene regulation [526].

In geometry and stereochemistry of zinc(II) complexes, they can form stable structures as four coordinates (tetrahedral/square–planar), five coordinates (trigonal pyramidal) or six coordinates (octahedral) complexes. For zinc finger protein, histidine and cysteine are

covalently coordinated to zinc(II) ion to form tetrahedral structure [526]. In photoluminescence, a lot of square planar zinc(II) complexes show effective quantum properties [527]. Five coordinated intermediates dominate the geometry and stereochemistry of similarly prepared related biological ligands in zinc complexes [524, 528, 529]. Zinc in metalloenzymes possess ligands with donor atoms of nitrogen (imidazolyl), oxygen(aqueous) and sometimes sulfur (cysteinal) which coordinate with zinc ion to form five-coordinate trigonal bipyramidal zinc substrate [525]. Zinc(II) complexes also exist in square pyramidal geometry depending on the type of ligands [527]. Octahedral structures occur when zinc complexes are present in aqueous solution and also in proteins [526].

Zinc complexes with different coordination donors of N_4, O_4, S_4, N_2O_2, S_2O_2, N_2O_2, and N_2S_2 had been synthesized and characterized successfully. Research revealed that great interest had been found with zinc complexes with mixed ligands of *N* and *S* coordination modes due to their distinctive structural and spectroscopic characteristics for metal chelating sites in some metalloenzymes and metalloproteins [529].For this research, mixed ligands of sodium sulfadiazine of nitrogen donor and derivatives of dithiocarbamates of sulfur donor were coordinated with zinc ion from anhydrous zinc chloride salt to yield both aliphatic and phenyl complexes of zinc(II) ion. In this chapter, the write-up involves the syntheses of nineteen zinc(II) complexes from their corresponding mixed ligands with coordination modes of N_2S_2. The mixed ligands and zinc(II) complexes were characterized using physico-chemical parameters and molecular spectroscopy to probe the successful syntheses and presence of the moieties in the ligands and the complexes. The aim of this research was to synthesize heteroleptic zinc(II) complexes from their corresponding mixed ligands of sodium sulfadiazine and derivatives of dithiocarbamate.

4.2 Materials and Methods

4.2.1 Experimental materials and instrumentation

4.2.1.1 Experimental materials

All the materials and chemical reagents used for this research as obtained from the chemical industries were of analytical grade and all were, therefore, used as received without purification. All reagents were synthesized, except for sulfadiazine sodium salt and anhydrous zinc(II) chloride.

Sulfadiazine sodium salt (Sigma-Aldrich, USA), anhydrous zinc(II) chloride (Associated Chemical Enterprises (Pty) Ltd, RSA),bu-DTC; ammonium *N*-butyl dithiocarbamate, he-DTC; ammonium hexyl dithiocarbamate, cy-DTC; ammonium *N*-cyclohexyl dithiocarbamate, an-DTC; ammonium *N*-aniline dithiocarbamate; me-DTC; ammonium *N*-methyl *N*-phenyl dithiocarbamate; et-DTC; Ammonium *N*-ethyl *N*-phenyl dithiocarbamate, cl-DTC; ammonium *N*- para chloro *N*-phenyl dithiocarbamate, mt-DTC; sodium *N*-methyl dithiocarbamate, bt-DTC; sodium *N*-butyl dithiocarbamate, hx-DTC; sodium *N*-hexyl dithiocarbamate; de-DTC; sodium *N*-diethyl dithiocarbamate, *de-DTC; sodium *N*-diethyl dithiocarbamate(synthesized), ea-DTC; sodium *N*-ethanol dithiocarbamate cc-DTC; sodium *N*-cyclohexyl dithiocarbamate, hy-DTC sodium *N*-phenyl hydrate dithiocarbamate, to-DTC, sodium *N*-*ortho*-toluidine dithiocarbamate, ml-DTC; sodium *N*-methyl *N*-phenyl dithiocarbamate ;ey-DTC; sodium *N*-ethyl *N*-phenyl dithiocarbamate, ch-DTC; sodium *N*-para chloro *N*-phenyl dithiocarbamate, as-DTC; sodium anisidine dithiocarbamate, tl-DTC; sodium *N*-*para*-anisidine dithiocarbamate, tu-DTC; sodium *N*-ethyl-*m*-toluidine dithiocarbamate.

4.2.1.2 Solvents

Deionized water (In house), Acetone, Acetonitrile, Diethyl ether, Methanol, Toluene (Merck, RSA), Absolute Ethanol (Supplied by EC Labs), Dimethylformamide, Dimethylsulfoxide (Merck, Germany).

4.2.1.3 Instrumentation

Sample masses were weighed on Sartorius Electronic Balance (Maximum Capacity (110 g), one open-end capillary tube melting points were carried out on a STUART SMP11 melting point apparatus and recorded uncorrected. Molar conductivities of oxovanadium (IV) complexes were obtained from a CRINSON EC- Meter BASIC 30+ conductivity meter. Elemental analyses for carbon, hydrogen, nitrogen and sulfur were done on a FLASH 2000 Thermoscientific Elemental Analyzer. Electronic spectra (UV-Vis spectra) for all the zinc(II) complexes were carried out at room temperature by using a Perkin-Elmer Lambda 25 UV-Vis Spectrometer. The recording of the electronic spectra was done between 10^{-3} and 10^{-5} M solutions of dimethylsulfoxide (DMSO). The reading was taken after calibration for baseline

correction in the double beam spectrometer in the wavelength interval between 200 nm and 1000 nm. The FT- IR spectra were recorded from a KBr disc in the range of 4000-370 cm^{-1} on a Perkin-Elmer 2000 FT-IR spectrophotometer. NMR spectra were obtained on a Bruker Avance 400 NMR spectrometer operating at frequencies of 400.1 MHz for ^{1}H and ^{13}C NMR at 100.6 MHz. The temperature of the NMR measurements was 303 K. NMR samples were prepared by dissolving the zinc(II) complexes using DMSO-d_6 as solvent. University of Stellenbosch, South Africa (Varian ^{Unity}*Inova* 600 NMR spectrometer operating at frequencies of 600 MHz for ^{1}H and at 150 MHz for ^{13}C NMR frequency. The chemical shifts were expressed in ppm in relation to internal standard of TMS.

4.2.2 Methods

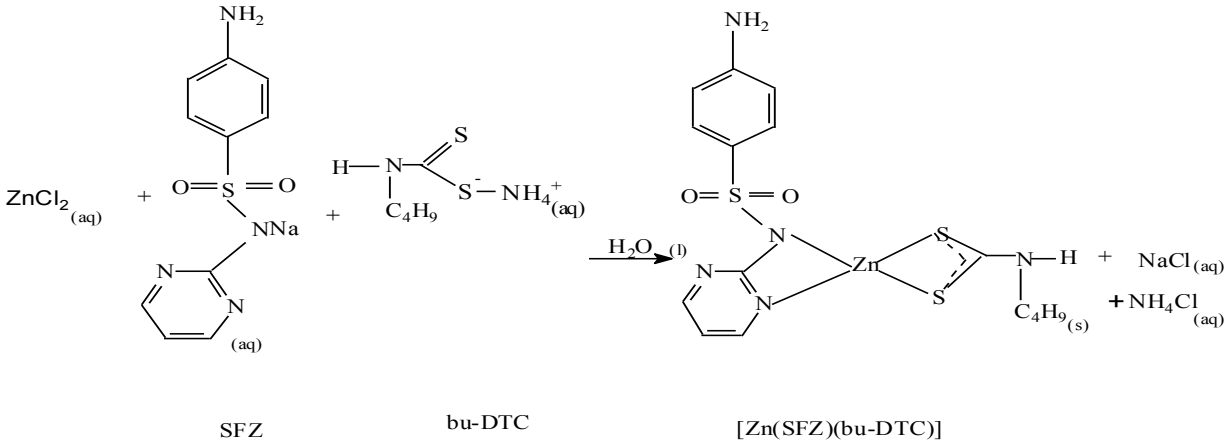
Preparation of zinc(II) complexes from sodium sulfadiazine (L_1) and derivatives of dithiocarbamate ($L_{2\text{-}DTC}$)

The zinc compounds were prepared following a literature procedure with some modifications [364, 385-393].

4.2.2.1 Synthesis of zinc(II) complex of [Zn(SFZ)(bu-DTC)]

Sodium sulfadiazine (0.4085 g, 1.5 mmol) and ammonium *N*-butyl dithiocarbamate ($L_{2bu\text{-}DTC}$)

(0.2495 g, 1.5 mmol) were added together and magnetically stirred at room temperature for 30 min, followed by dropwise addition of a solution of zinc chloride (0.2044 g, 1.5 mmol) in distilled water (30 mL). The reaction mixture was further stirred for 2 h 30 min and the resultant white precipitate was filtered, washed thoroughly with deionized water (3 x 5 mL) and dried over silica gel in a desiccator. Molecular weight: 462.91 g. Percentage Yield: 54%. M. P.140-142^{o}C. Molar Conductivity: 1.80 Ω^{-1} cm^2 mol^{-1}. Anal. Calcd for [Zn(SFZ)(bu-DTC)] (%) C: 38.92; H: 4.14; N: 15.13; S: 20.18.Found: C: 35.99; H: 4.55; N: 11.82; S: 25.07. Selected FT-IR (KBr), ν (cm^{-1}): 3235 (SO_2NH), 1652 (C=N), 1519 (C-N), 974$(CS_2)_{as}$. Selected λ_{max} in DMSO solvent(nm): 266, 296 (π-π^* N-C=S) 376, 378; (n-π^* N-C=S). Selected^{1}H NMR (DMSO-d_6, 600Hz, ppm): δ 5.95 (C_2HN); δ 8.60 ($C_4H_4N_2$-H) δ 10.00 (N-H); δ 11.24 (=$CHSO_2NNa$). Selected ^{13}C NMR (DMSO-d_6, 150 MHz, ppm); δ 29.85 ($^{13}CH_2$), δ 13.59 ($^{13}CH_3$).

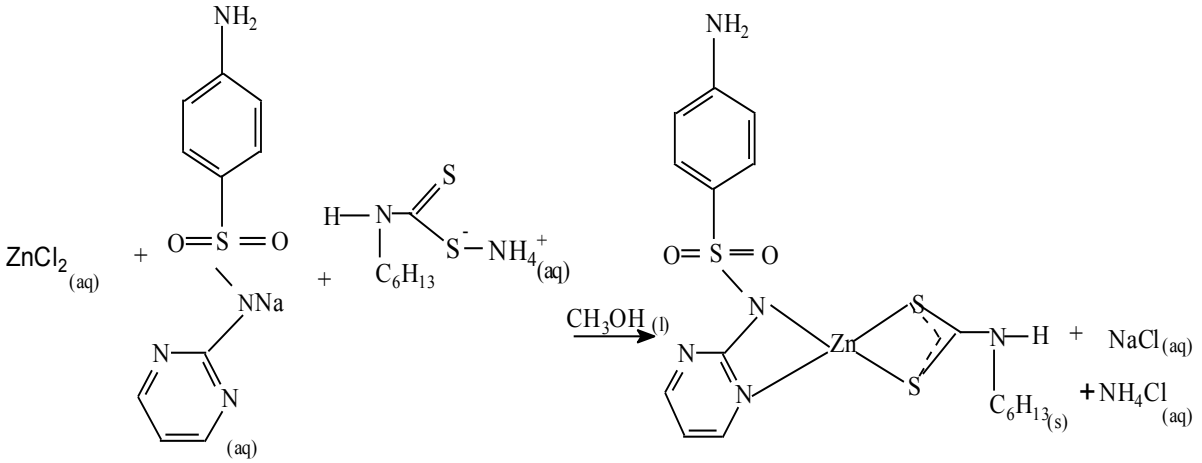


Scheme 4.1. Synthesis of zinc(II) complex of [Zn(SFZ)(bu-DTC)]**.**

Other zinc(II) complexes were synthesized using the same procedure for syntheses of zinc complexes derived from sodium salt of sulfadiazine and ammonium hexyl dithiocarbamate (he-DTC), ammonium *N*-cyclohexyl dithiocarbamate (he-DTC),ammonium *N*-cyclohexyl dithiocarbamate (cy-DTC), ammonium *N*-aniline dithiocarbamate (an-DTC), ammonium *N*-methyl *N*-phenyl dithiocarbamate (me-DTC), ammonium *N*-ethyl *N*-phenyl dithiocarbamate et-DTC), ammonium *N*- para chloro *N*-phenyl dithiocarbamate (cl-DTC), sodium *N*-methyl dithiocarbamate (me-DTC), sodium *N*-butyl dithiocarbamate (bt-DTC), sodium *N*-hexyl dithiocarbamate (hx-DTC), sodium *N*-diethyl dithiocarbamate (de-DTC), sodium *N*-diethyl dithiocarbamate (*de-DTC), sodium *N*-ethanol dithiocarbamate (ea-DTC), sodium *N*-cyclohexyl dithiocarbamate (cc-DTC),sodium *N*-phenyl hydrate dithiocarbamate (hy-DTC), sodium *N*-*ortho*-toluidine dithiocarbamate (to-DTC), sodium *N*-methyl *N*-phenyl dithiocarbamate(ml-DTC),sodium *N*-ethyl *N*-phenyl dithiocarbamate (ey-DTC),sodium *N*-para chloro *N*-phenyl dithiocarbamate (ch-DTC), sodium anisidine dithiocarbamate (as-DTC), sodium *N*-*para*-anisidine dithiocarbamate, sodium *N*-ethyl-*m*-toluidine dithiocarbamate (tu-DTC).

4.2.2.2 Synthesis of zinc(II) complex of [Zn(SFZ)(he-DTC)]

Sodium sulfadiazine (0.4085 g, 1.5 mmol), ammonium N-hexyl dithiocarbamate ($L_{2he\text{-}DTC}$) (0.2915 g, 1.5 mmol) and $ZnCl_2$ (0.2044 g, 1.5 mmol) were magnetically stirred for 3 h at room temperature. A white solid was formed, filtered, washed thoroughly with deionized water (3 x 5 mL) and dried over silica gel in a desiccator. Molecular weight: 490.96 g. Percentage Yield: 60%. M. P. 240-242^{o}C. Molar Conductivity: 0.80 Ω^{-1} cm^2 mol^{-1}. Anal. Calcd for [Zn(SFZ)(he-DTC)] (%) C: 41.59; H: 4.72; N: 14.26; S: 19.59. Found: C: 44.81; H: 3.83; N: 20.14; S: 13.58. Selected FT-IR (KBr), ν (cm^{-1}): 3234 (SO_2NH), 1617, 1638 (C=N), 1498 (C-N), 995 (C=S). Selected λ_{max} in DMSO solvent, (nm): 266, 269 (π-π^* N-C=S) 374, 390; (n-π^* N-C=S). Selected ^{1}H NMR (DMSO-*d*$_6$, 600Hz, ppm): δ 5.95 (C_2HN); δ 8.45 ($C_4H_4N_2$-H) δ 9.93 (N-H); δ 11.19 (=$CHSO_2NNa$). Selected ^{13}C NMR (DMSO-*d*$_6$, 150 MHz, ppm); δ111.97-115.33 (Ar-C) δ 129.80-152.80 (NH_2C); δ 158.02(-SO_2N=C).

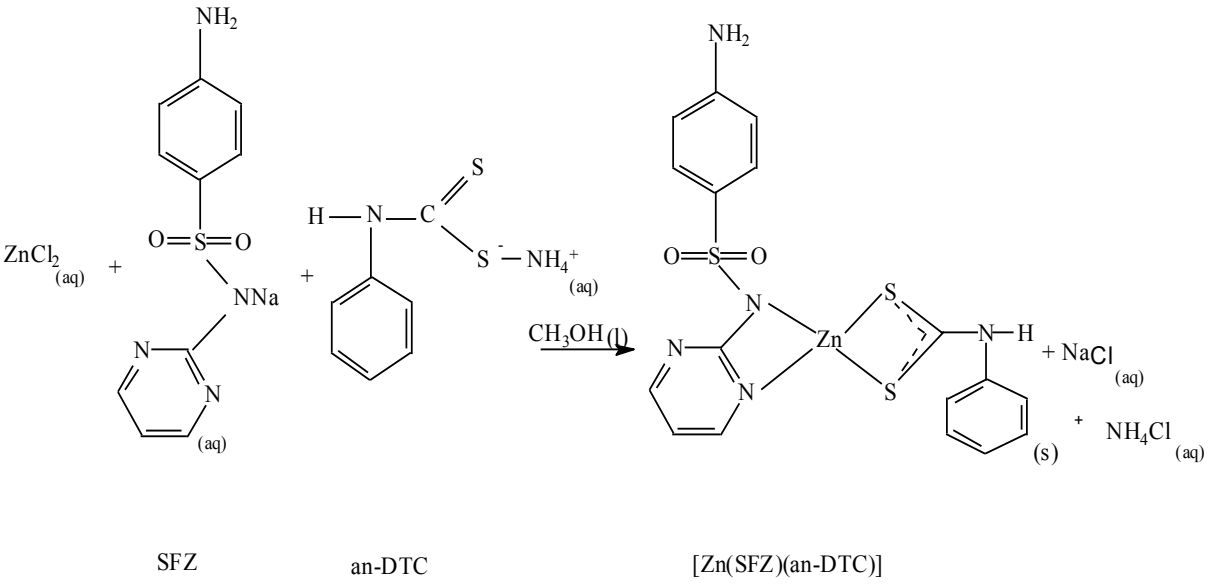


Scheme 4.2. Synthesis of zinc(II) complex of [Zn(SFZ)(he-DTC)]**.**

4.2.2.3 Synthesis of zinc(II) complex of [Zn(SFZ)(an-DTC)]

Aqueous sodium sulfadiazine (0.4085 g, 1.5 mmol) in distilled water (50 mL) was added dropwise to a solution of ammonium salt of aniline dithiocarbamate ($L_{2an\text{-}DTC}$) (0.2790 g, 1.5 mmol) in distilled water (20 mL). The reaction was magnetically stirred at room temperature for 30 min, followed by dropwise addition of a solution of zinc chloride (0.2044 g, 1.5 mmol) in distilled water (30 mL). The reaction was stirred further for 2 h 30 min, and the resultant white precipitate was filtered, washed thoroughly with water (3 x 5 mL) and dried over silica gel in a desiccator. Molecular weight: 482.90 g. Percentage Yield: 68%. M. P. 180 ^{o}C. Molar

Conductivity: 0.18 Ω^{-1} cm^2 mol^{-1}. Anal. Calcd for [Zn(SFZ)(an-DTC)](%) C: 42.28; H: 3.13; N: 14.50; S: 19.92. Found (%) C: 52.59; H: 3.55; N: 20.20; S: 7.44. Selected FT-IR (KBr), ν (cm-[1]): 3279 (SO_2NH), 1653; 1590 (C=N), 1509 (C-N), 1017 (C=S).Selected λ_{max} in DMSO solvent, (nm): 231, 252, 292 (π-π^* N-C=S) 374, 379; (n-π^* N-C=S). Selected ^{1}H NMR (DMSO-*d_6*, 600Hz, ppm): δ 5.95 (C_2HN); δ 6.54 (Ar-H); δ 8.44 ($C_4H_4N_2$-H) δ 9.70 (N-H); δ 11.72 (=$CHSO_2NNa$). Selected ^{13}C NMR (DMSO-*d_6*, 150 MHz, ppm); δ123.34-128.03 (Ar-C) δ 129.59 (NH_2C); δ 139.11(SO_2N=C); δ 179.32; 192.00 (NCS_2).



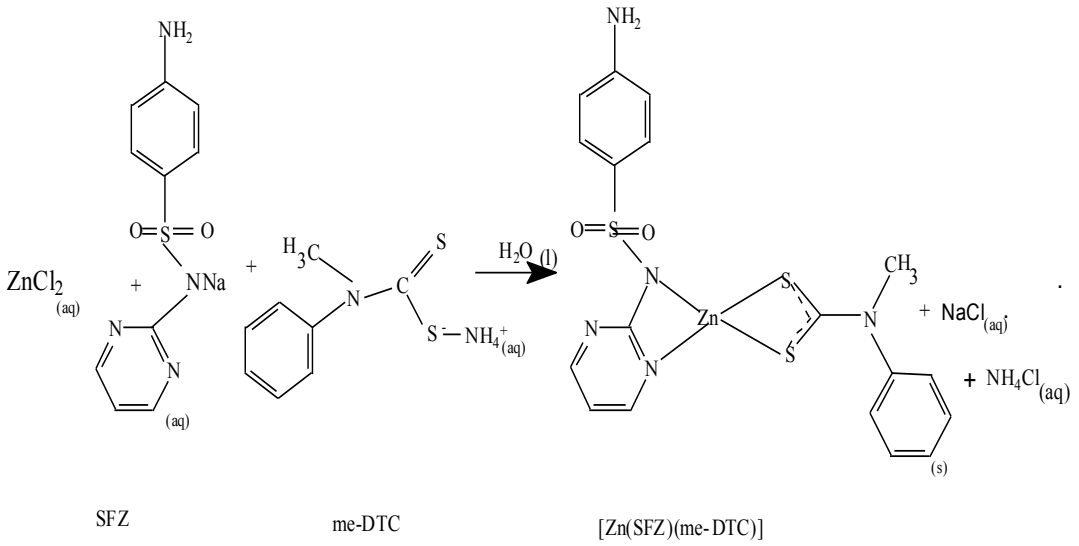
SFZ an-DTC [Zn(SFZ)(an-DTC)]

Scheme 4.3. Synthesis of zinc(II) complex of [Zn(SFZ)(an-DTC)]**.**

4.2.2.4 Synthesis of zinc(II) complex of [Zn(SFZ)(me-DTC)]

Sodium sulfadiazine (0.4085 g, 1.5 mmol), ammonium N-methyl-N-phenyl dithiocarbamate ($L_{2me\text{-}DTC}$)(0.3005 g, 1.5 mmol) and $ZnCl_2$ (0.2044 g, 1.5 mmol) were magnetically stirred for 3 h at room temperature. A white solid was formed, filtered, washed thoroughly with deionized water (3 x 5 mL) and dried over silica gel in a desiccator. Molecular weight: 496.93 g. Percentage Yield: 52%. M. P. 210-212^{o}C. Molar Conductivity: 0.02 Ω^{-1} cm^2 mol^{-1}. Anal. Calcd for [Zn(SFZ)(me-DTC)] (%) C: 43.51; H: 3.45; N: 14.09; S: 19.36. Found (%) C: 27.01; H: 8.34; N: 6.25; S: 29.34.Selected FT-IR (KBr), ν (cm-[1]):3266 (SO_2NH), 1589

(C=N), 1497 (C-N), 1034 (C=S). Selected λ_{max} in DMSO solvent, (nm): 265, 276 (π-π^* N-C=S) 373, 384; (n-π^* N-C=S).Selected ^{1}H NMR (DMSO-d_6, 600Hz, ppm): δ 4.75 (C_2HN); δ 6.55 (Ar-H); δ 8.45 ($C_4H_4N_2$-H) δ 9.11 (N-H); δ 11.31 (=$CHSO_2NNa$). Selected ^{13}C NMR (DMSO-d_6, 150 MHz, ppm); δ125.49-127.85 (Ar-C) δ 129.92 (NH_2C); δ 130.41; 137.42(-SO_2N=C); δ 180.68; 192.24 (NCS_2).

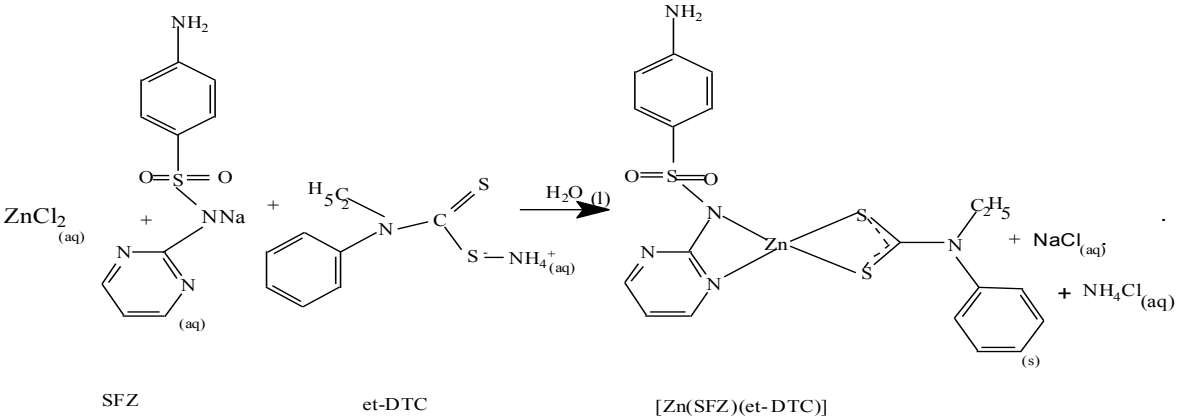


Scheme 4.4. Synthesis of zinc(II) complex of [Zn(SFZ)(me-DTC)]**.**

4.2.2.5 Synthesis of zinc(II) complex of [Zn(SFZ)(et-DTC)]

Sodium sulfadiazine (0.4085 g, 1.5 mmol), ammonium N-ethyl-N-phenyl dithiocarbamate ($L_{2et\text{-}DTC}$) (0.3215 g, 1.5 mmol) and $ZnCl_2$ (30 mL, 1.5 mmol) were magnetically stirred for 3 h at room temperature. A white solid was formed filtered, washed thoroughly with deionized water (3 x 5 mL) and dried over silica gel in a desiccator. Molecular weight: 510.95 g. Percentage Yield: 60%. M. P. 212-214^{o}C. Molar Conductivity: 0.79 Ω^{-1} cm^2 mol^{-1}. Anal. Calcd for [Zn(SFZ)(et-DTC)](%) C: 44.66; H: 3.75; N: 13.71; S: 18.82. Found (%) C: 46.27; H: 3.99; N: 7.52; S: 24.34.Selected FT-IR (KBr), ν (cm^{-1}): 3236 (SO_2NH), 1581 (C=N), 1435 (C-N), 1502 (C=S). Selected λ_{max} in DMSO solvent, (nm): 256, 300 (π-π^* N-C=S) 372, 384; (n-π^* N-C=S) Selected ^{1}H NMR (DMSO-d_6, 600Hz, ppm): δ 4.12 (C_2HN); δ 6.55 (Ar-H);) δ

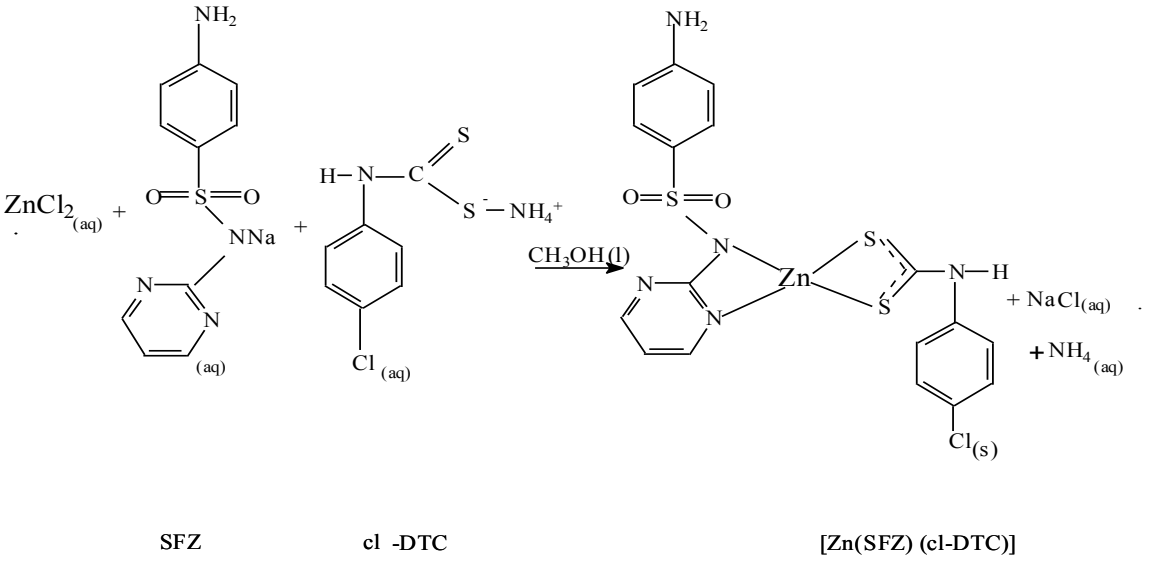
9.15 (N-H), Selected ^{13}C NMR (DMSO-d_6, 150 MHz, ppm); δ126.95-127.85 (Ar-C) δ 129.25 (NH_2C); δ 144.93(-SO_2N=C); δ 206.35 (NCS_2).



Scheme 4.5. Synthesis of zinc(II) complex of [Zn(SFZ)(et-DTC)]**.**

4.2.2.6 Synthesis of zinc(II) complex of [Zn(SFZ)(cl-DTC)]

Sodium sulfadiazine (0.4085 g, 1.5 mmol), ammonium N-chloro-*N*-phenyl dithiocarbamate ($L_{2cl\text{-}DTC}$) (0.3311 g, 1.5 mmol) and $ZnCl_2$ (0.2044 g, 1.5 mmol) were magnetically stirred for 3 h at room temperature. A white solid was formed washed thoroughly with deionized water (3 x 5 mL) and dried over silica gel in a desiccator. Molecular weight: 517.34 g. Percentage Yield: 62%. M. P. 190-192^oC Molar Conductivity: 0.01 Ω^{-1} cm^2 mol^{-1}. Anal. Calcd for [Zn(SFZ)(et-DTC)](%) C: 39.47; H: 3.73; N: 13.54; S: 18.59. Found (%) C: 57.58; H: 3.36; N: 20.00; S: 8.51. Selected FT-IR (KBr), ν (cm^{-1}): 3247 (SO_2NH), 1575, 1590 (C=N), 1506, 1481 (C-N), 1040 (C=S). Selected λ_{max} in DMSO solvent, (nm): 253, 282 (π-π^* N-C=S) 374, 383; (n-π^* N-C=S). Selected ^1H NMR (DMSO-d_6, 600Hz, ppm): δ 5.98 (C_2HN); δ 6.52-6.54 (Ar-H); δ 8.45 ($C_4H_4N_2$-H) δ 9.92 (N-H); δ 11.81 (=$CHSO_2NNa$). Selected ^{13}C NMR (DMSO-d_6, 150 MHz, ppm); δ115.07 (Ar-C) δ 129.80-138.22 (NH_2C); δ 139.34(-SO_2N=C); δ 210.00 (NCS_2).

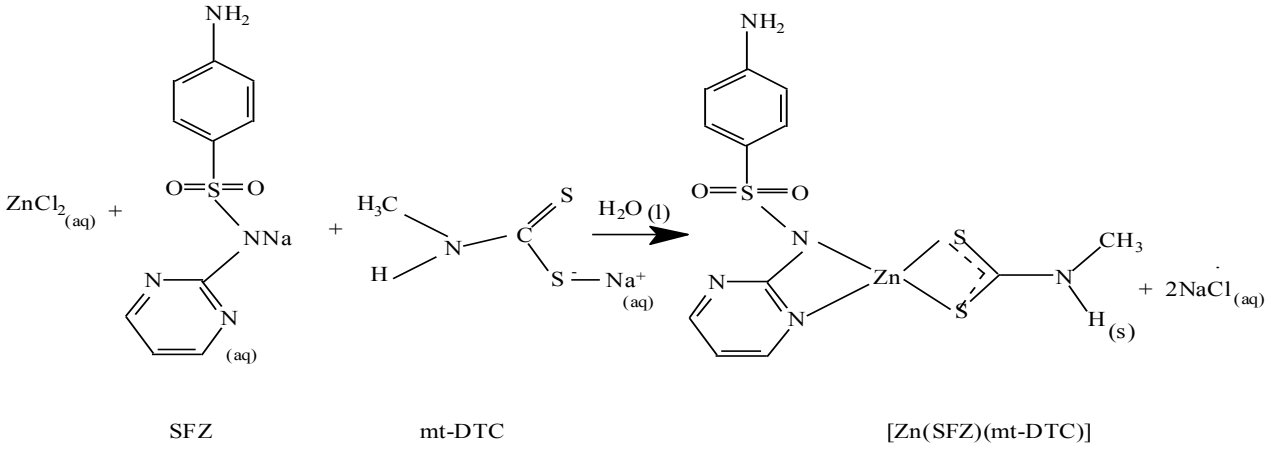


Scheme 4.6. Synthesis of zinc(II) complex of [Zn(SFZ)(cl-DTC)]**.**

4.2.2.7 Synthesis of zinc(II) complex of [Zn(SFZ)(mt-DTC)]

Sodium sulfadiazine (0.4085 g, 1.5 mmol), sodium methyl dithiocarbamate ($L_{2mt\text{-}DTC}$)

(0.1937 g, 1.5 mmol) and $ZnCl_2$ (0.2044 g, 1.5 mmol) were magnetically stirred for 3 h at room temperature. A dirty-white solid was formed, washed thoroughly with deionized water (3 x 5 mL) and dried over silica gel in a desiccator. Molecular weight: 420.83 g. Percentage Yield: 74%. M. P. 230-231^{o}C. Molar Conductivity: 0.98 Ω^{-1} cm^2 mol^{-1}. Anal. Calcd for [Zn(SFZ)(mt-DTC)] (%) C: 34.25; H: 3.11; N: 16.64; S: 22.85. Found (%) C: 34.05; H: 3.13; N: 14.99; S: 7.79. Selected FT-IR (KBr), ν (cm-^{1}): 3271 (SO_2NH), 1590 (C=N), 1498 (C-N), 946 (C=S). Selected λ_{max} in DMSO solvent, (nm): 260, 282 (π-π^* N-C=S) 378, 383; (n-π^* N-C=S). Selected^{1}H NMR (DMSO-*d*$_6$, 600Hz, ppm): δ 5.98 (C_2HN); δ 6.55-6.57 (Ar-H); δ 8.47 ($C_4H_4N_2$-H). Selected ^{13}C NMR (DMSO-*d*$_6$, 150 MHz, ppm); δ112.14, 115.48, 124.94 (Ar-C) δ 129.79 (NH_2C); δ 152.99; 157.26; 158.22(-SO_2N=C).

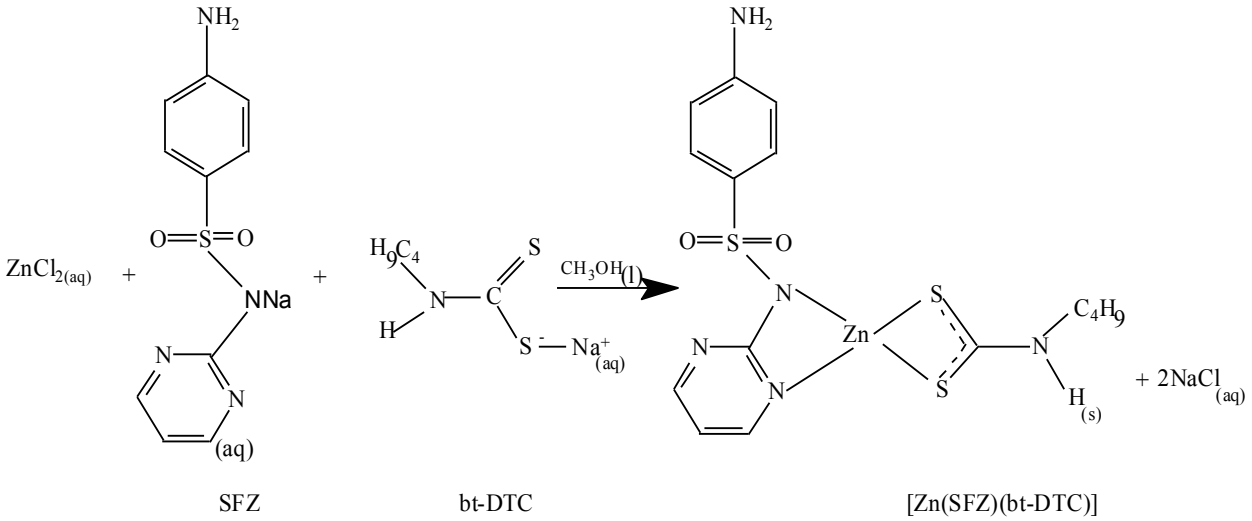


Scheme 4.7. Synthesis of zinc(II) complex of [Zn(SFZ)(mt-DTC)]**.**

4.2.2.8 Synthesis of zinc(II) complex of [Zn(SFZ)(bt-DTC)]

Sodium sulfadiazine (0.4085 g, 1.5 mmol), sodium butyl dithiocarbamate (L_{2bt})

(0.2569 g, 1.5 mmol) and $ZnCl_2$ (0.2044 g, 1.5 mmol) were magnetically stirred for 3 h at room temperature. A white solid was formed washed thoroughly with deionized water (3 x 5 mL) and dried over silica gel in a desiccator. Molecular weight: 462.91 g. Percentage Yield: 72%, M. P. 224-226^{o}C. Molar Conductivity: 0.35 Ω^{-1} cm^2 mol^{-1}. Anal. Calcd for [Zn(SFZ)(bt-DTC)] (%) C: 38.92; H: 4.14; N: 15.13; S: 19.32. Found (%) C: 37.21; H: 3.74; N: 15.83; S: 13.51. Selected FT-IR (KBr), ν (cm^{-1}): 3266 (SO_2NH), 1591 (C=N), 1501, 1477 (C-N), 1050 (C=S). Selected λ_{max} in DMSO solvent, (nm): 252 (π-π^* N-C=S) 378, 383; (n-π^* N-C=S).Selected ^{1}H NMR (DMSO-d_6, 600Hz, ppm): δ 5.96 (C_2HN); δ 6.55-6.56 (Ar-H); δ 8.46 ($C_4H_4N_2$-H). Selected ^{13}C NMR (DMSO-d_6, 150 MHz, ppm); δ112.13 (Ar-C) δ 129.76 (NH_2C); δ 158.21(-SO_2N=C); δ 179.32; 192.00 (NCS_2).



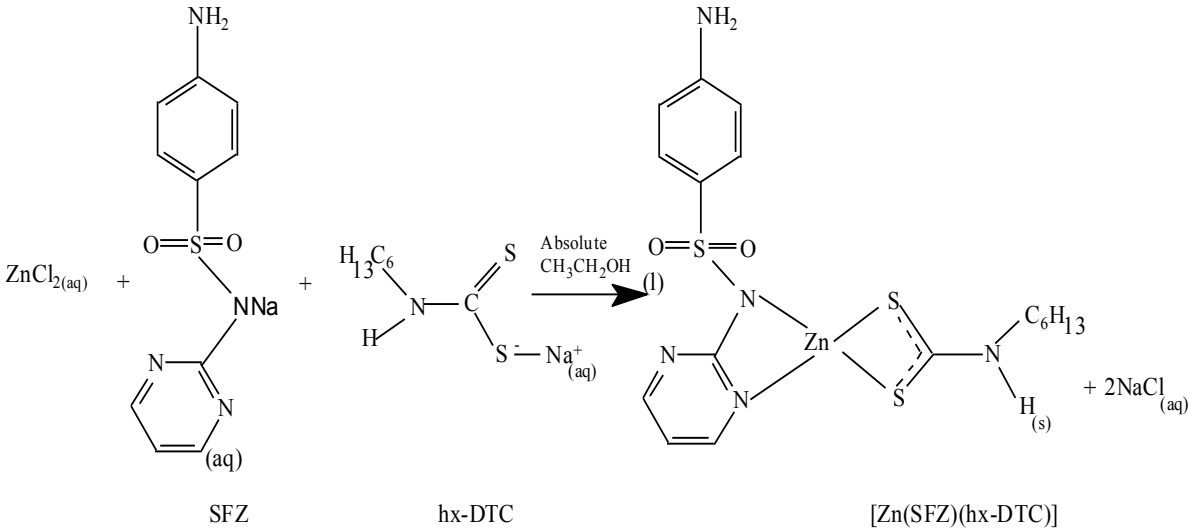
Scheme 4.8. Synthesis of zinc(II) complex of [Zn(SFZ)(bt-DTC)]**.**

4.2.2.9 Synthesis of zinc(II) complex of [Zn(SFZ)(hx-DTC)]

Sodium sulfadiazine (0.4085 g, 1.5 mmol), sodium *N*-hexyl dithiocarbamate ($L_{2hx\text{-}DTC}$)

(0.1952 g, 1.5 mmol) and $ZnCl_2$ (0.2044 g, 1.5 mmol) were magnetically stirred for 3 h at room temperature. A white solid was formed washed thoroughly with deionized water (3 x 5 mL) and dried over silica gel in a desiccator. Molecular weight: 490.96 g. Percentage Yield: 71%. M. P. 236-238ºC. Molar Conductivity: 0.01 Ω^{-1} cm^2 mol^{-1}. Anal. Calcd (%) for [Zn(SFZ)(hx-DTC)] C: 41.59; H: 4.72; N: 14.26; S: 19.59. Found: C: 37.62; H: 3.88; N: 15.43; S: 13.20 .Selected FT-IR (KBr), ν (cm^{-1}): 3298 (SO_2NH), 1650, 1590 (C=N), 1501,1477 (C-N), 1046 (C=S). Selected λ_{max} in DMSO solvent, (nm): 268, 277 (π-π^* N-C=S) 375, 384; (n-π^* N-C=S).Selected ^{1}H NMR (DMSO-d_6, 600Hz, ppm): δ 3.70 (C_2HN); δ 6.55-6.57 (Ar-H); δ 8.47 ($C_4H_4N_2$-H) δ 7.61-7.62 (N-H); δ 11.24 (=$CHSO_2NNa$). Selected ^{13}C NMR (DMSO-d_6, 150 MHz, ppm); δ112.10 (Ar-C) δ 129.77 (NH_2C); δ 152.96, 158.19

(-SO_2N=C).

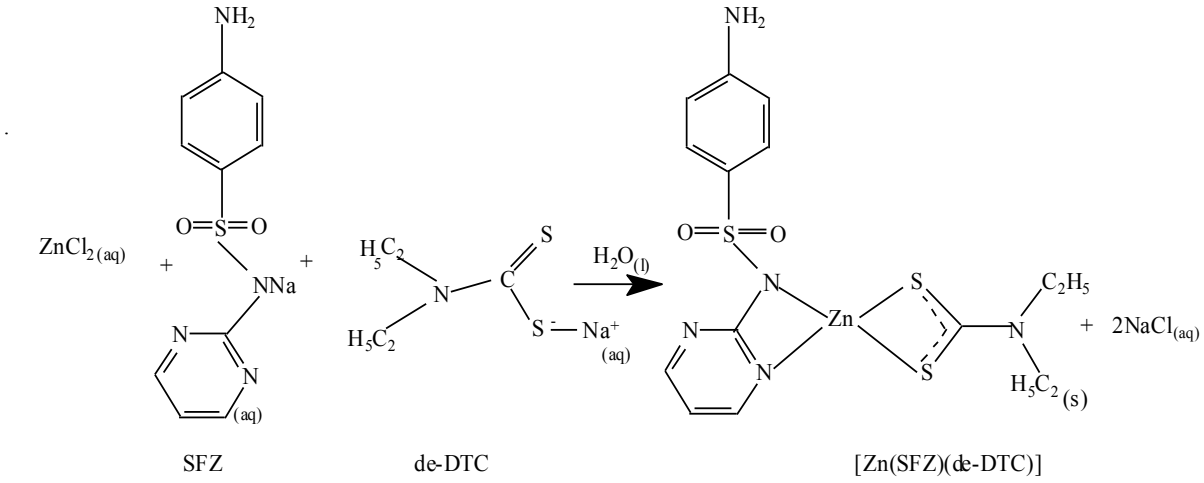


Scheme 4.9. Synthesis of zinc(II) complex of [Zn(SFZ)(hx-DTC)]**.**

4.2.2.10 Synthesis of zinc(II) complex of [Zn(SFZ)(de-DTC)]

Sodium sulfadiazine (0.4085 g, 1.5 mmol), sodium ethyl dithiocarbamate ($L_{2de\text{-}DTC}$)

(0.2569 g, 1.5 mmol) and $ZnCl_2$ (0.2044 g, 1.5 mmol) were magnetically stirred for 3 h at room temperature. A white solid was formed washed thoroughly with deionized water (3 x 5 mL) and dried over silica gel in a desiccator. Molecular weight: 462.91 g. Percentage Yield: 80%. M. P. 190-191^{o}C. Molar Conductivity: 0.09 Ω^{-1} cm^2 mol^{-1}. Anal. Calcd (%) C: 38.92; H: 4.14; N: 15.13; S: 20.78. Found (%) C: 34.27; H: 3.96; N: 13.01; S: 17.45.Selected FT-IR (KBr), ν (cm-^{1}): 3267 (SO_2NH), 1590 (C=N), 1500 (C-N), 951 (C=S). Selected λ_{max} in DMSO solvent, (nm): 263, (π-π^* N-C=S) 316, 322, 356; (n-π^* N-C=S), d-d: 417, 457.Selected^{1}H NMR (DMSO-*d*$_6$, 600Hz, ppm): δ 5.98 (C_2HN); δ 6.55-6.56 (Ar-H); δ 8.33 ($C_4H_4N_2$-H) δ 8.43 (N-H); δ 11.24 (=$CHSO_2NNa$). Selected ^{13}C NMR (DMSO-d$_6$, 150 MHz, ppm); δ112.11 (Ar-C) δ 129.74 (NH_2C); δ 158.19(-SO_2N=C), δ 202.31 (NCS_2).

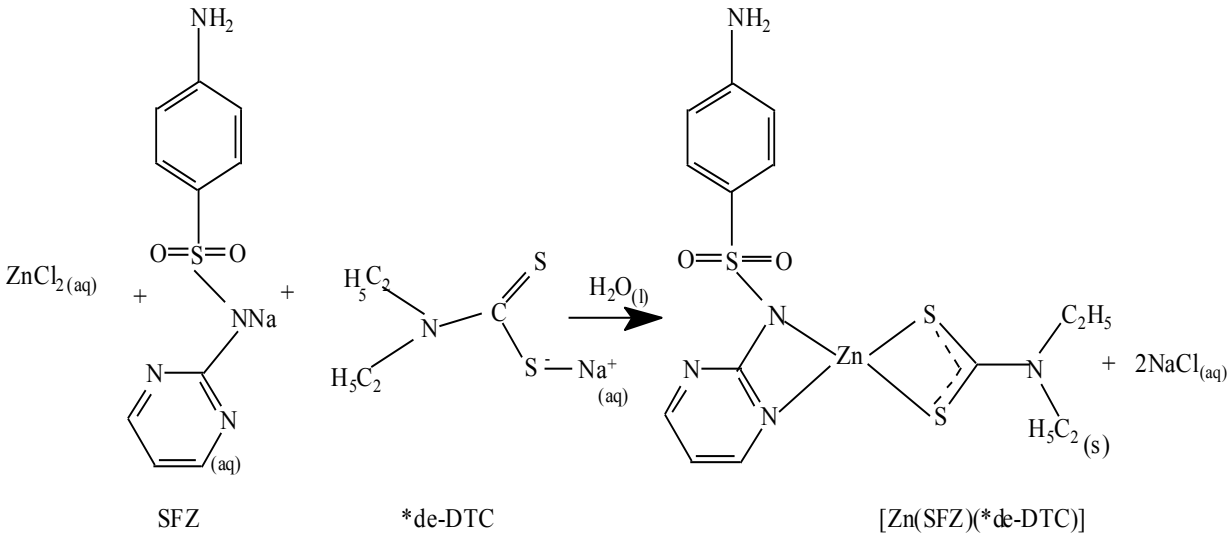


Scheme 4.10. Synthesis of zinc(II) complex of [Zn(SFZ)(de-DTC)]**.**

4.2.2.11 Synthesis of zinc(II) complex of [Zn(SFZ)(*de-DTC)]

Sodium sulfadiazine (0.4085 g, 1.5 mmol), sodium ethyl dithiocarbamate ($L_{2*de\text{-}DTC}$)

(0.2569 g, 1.5 mmol) and $ZnCl_2$ (0.2044 g, 1.5 mmol) were magnetically stirred for 3 h at room temperature. A white solid was formed, washed thoroughly with deionized water (3 x 5 mL) and dried over silica gel in a desiccator. Molecular weight: 462.91 g. Percentage Yield: 75%. M. P. 210-212ºC. Molar Conductivity: 0.59 Ω^{-1} cm^2 mol^{-1}. Anal. Calcd for [Zn(SFZ)(*de-DTC)](%) C: 38.92; H: 4.14; N: 15.13; S: 20.78. Found C: 42.04; H: 3.43; N: 13.19; S: 16.83. Selected FT-IR (KBr), ν (cm^{-1}): 3290 (SO_2NH), 1638, 1618 (C=N), 1492 (C-N), 970 (C=S). Selected λ_{max} in DMSO solvent, (nm): 236, 254-290 (π-π^* N-C=S) 375, 382, (n-π^* N-C=S), 383-800; d-d) Selected ^{1}H NMR (DMSO-d_6, 600Hz, ppm): δ 5.75 (C_2HN); δ 6.51-6.80 (Ar-H); δ 7.34-7.59 ($C_4H_4N_2$-H) δ 8.33 (N-H); δ 11.24 (=$CHSO_2NNa$). Selected ^{13}C NMR (DMSO-d_6, 150 MHz, ppm); δ111.97 (Ar-C) δ 129.45 (NH_2C); δ 171.87; 157.89(-SO_2N=C), δ 202.24 (NCS_2).

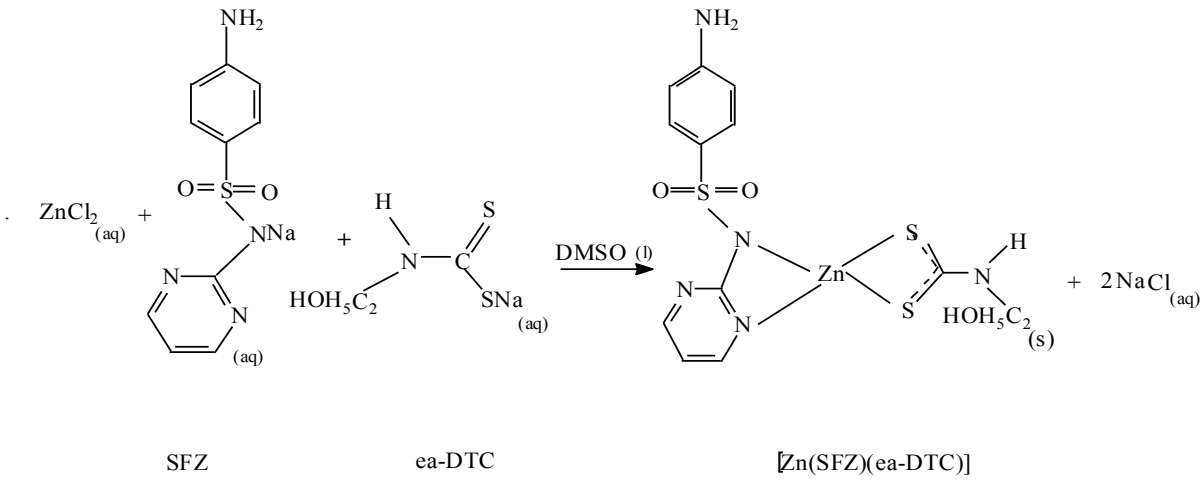


Scheme 4.11. Synthesis of zinc(II) complex of [Zn(SFZ)(*de-DTC)].

4.2.2.12 Synthesis of zinc(II) complex of [Zn(SFZ)(ea-DTC)]

Sodium sulfadiazine (0.4085 g, 1.5 mmol), sodium ethanol dithiocarbamate ($L_{2ea\text{-}DTC}$)

(0.2403 g, 1.5 mmol) and $ZnCl_2$ (0.2044 g, 1.5 mmol) were magnetically stirred for 3 h at room temperature. A white solid was formed, washed thoroughly with deionized water (3 x 5 mL) and dried over silica gel in a desiccator. Molecular weight: 451.86 g. Percentage Yield: 52%. M. P. 218^{o}C. Molar Conductivity: 1.55 Ω^{-1} cm^2 mol^{-1}. Anal. Calcd for [Zn(SFZ)(ea-DTC)] (%) C: 34.56; H: 3.57; N: 15.50; S: 21.29. Found (%) C: 32.29; H: 3.06; N: 14.59; S: 9.37.Selected FT-IR (KBr), ν (cm-^{1}): 3292 (SO_2NH), 1596 (C=N) 1502 (C-N), 1038 (C=S). Selected λ_{max} in DMSO solvent, (nm): 230, 257, 281 (π-π^* N-C=S) 375, 385; (n-π^* N-C=S) Selected^{1}H NMR (DMSO-*d*$_6$, 600Hz, ppm): δ 5.98 (C_2HN); δ 6.55-6.57; 6.99 (Ar-H); δ 7.61-7.62 ($C_4H_4N_2$-H) δ 8.46-8.47 (N-H). Selected ^{13}C NMR (DMSO-*d*$_6$, 150 MHz, ppm); δ112.16; 115.49 (Ar-C) δ 129.80 (NH_2C); δ 152.99; 158.24(-SO_2N=C).

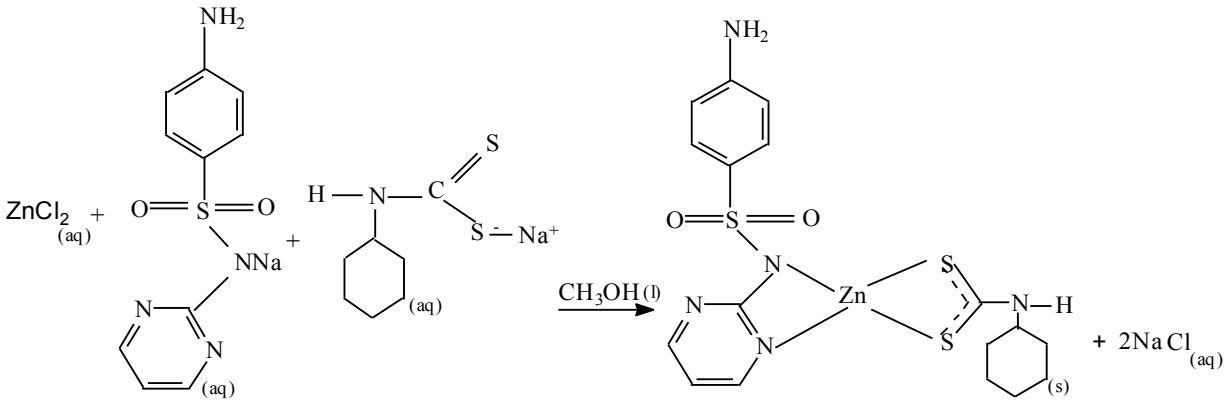


Scheme 4.12. Synthesis of zinc(II) complex of [Zn(SFZ)(ea-DTC)]**.**

4.2.2.13 Synthesis of zinc(II) complex of [Zn(SFZ)(cc-DTC)]

Sodium sulfadiazine (0.4085 g, 1.5 mmol), sodium ethyl dithiocarbamate ($L_{2cc\text{-}DTC}$)

(0.2959 g, 1.5 mmol) and $ZnCl_2$ (0.2044 g, 1.5 mmol) were magnetically stirred for 3 h at room temperature. . A white solid was formed, washed thoroughly with deionized water (3 x 5 mL) and dried over silica gel in a desiccator. Molecular weight: 489.93 g. Percentage Yield: 84%. M. P. 239-240ºC. Molar Conductivity: 0.04 Ω^{-1} cm^2 mol^{-1}. Anal. Calcd for [Zn(SFZ)(cc-DTC)] (%) C: 41.67; H: 4.53; N: 14.29; S: 19.63. Found (%) C: 43.05; H: 3.57; N: 17.63; S: 12.59.Selected FT-IR (KBr), ν (cm^{-1}): 3263 (SO_2NH), 1590 (C=N),: 1498 (C-N), 946 (C=S). Selected λ_{max} in DMSO solvent, (nm): 264, 274 (π-π^* N-C=S) 374, 384; (n-π^* N-C=S) Selected ^{1}H NMR (DMSO-d_6, 600Hz, ppm): δ 5.99 (C_2HN); δ 6.55-6.57; 6.99 (Ar-H); δ 7.61-7.62 ($C_4H_4N_2$-H) δ 8.46-8.47 (N-H); δ 9.86 (=$CHSO_2NNa$). Selected ^{13}C NMR (DMSO-d_6, 150 MHz, ppm); δ112.14 (Ar-C) δ 129.89 (NH_2C); δ 158.23(-SO_2N=C), δ 202.73 (NCS_2).



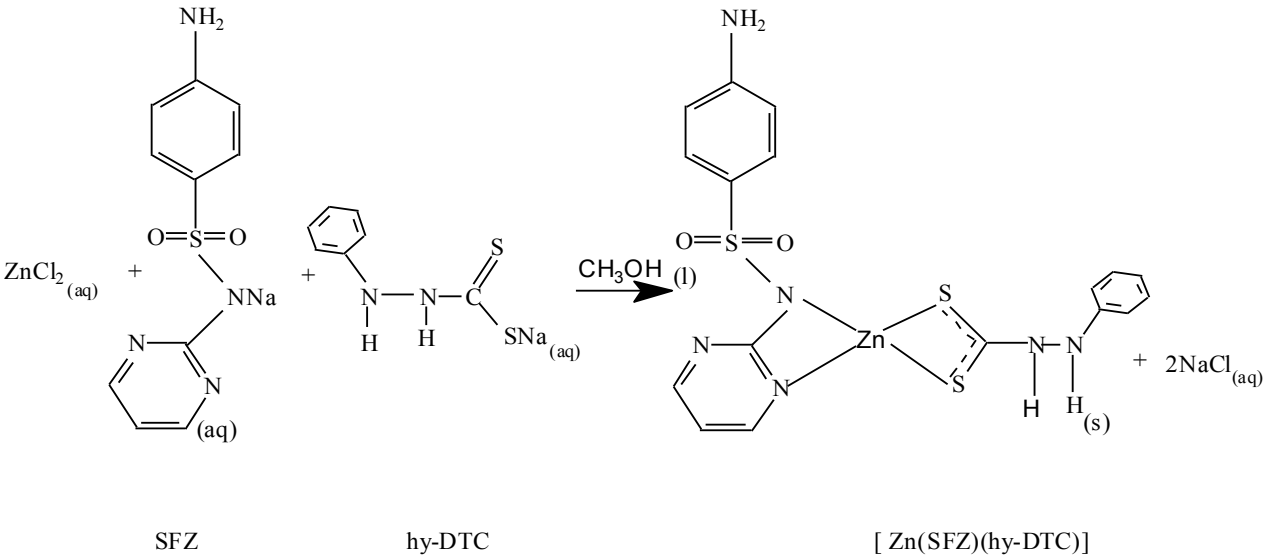
SFZ cc-DTC [Zn(SFZ)(cc-DTC)]

Scheme 4.13. Synthesis of zinc(II) complex of [Zn(SFZ)(cc-DTC)]**.**

4.2.2.14 Synthesis of zinc(II) complex of [Zn(SFZ)(hy-DTC)]

Sodium sulfadiazine (0.4085 g, 1.5 mmol), sodium hydrazine dithiocarbamate ($L_{2hy\text{-}DTC}$)

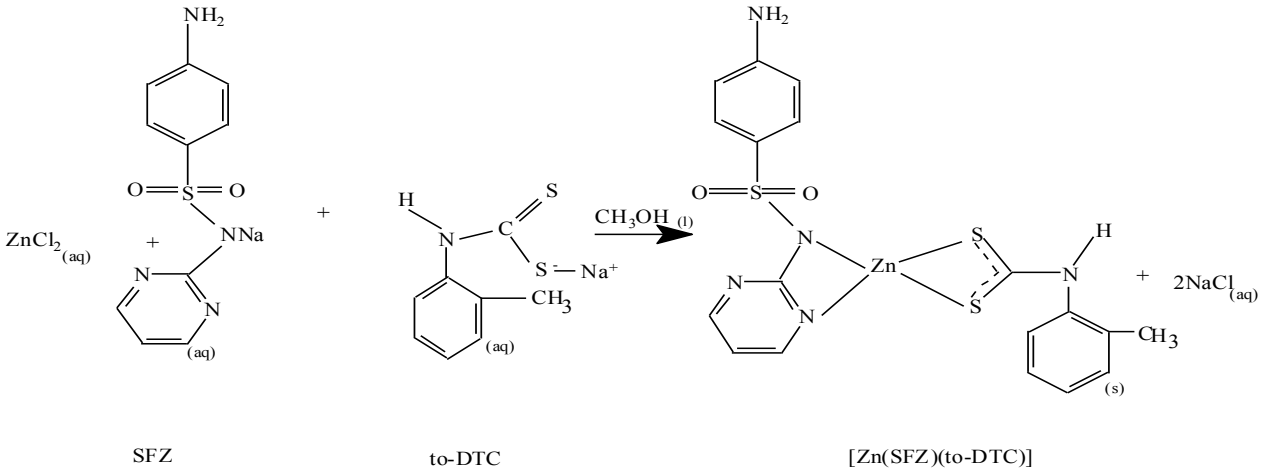
(0.3094 g, 1.5 mmol) and $ZnCl_2$ (0.2044 g, 1.5 mmol) were magnetically stirred for 3 h at room temperature. A white solid was formed, washed thoroughly with deionized water (3 x 5 mL) and dried over silica gel in a desiccator. Molecular weight: 497.91 g. Percentage Yield: 60%. M. P. 220ºC. Molar Conductivity: 6.36 Ω^{-1} cm^2 mol^{-1}. Anal. Calcd for [Zn(SFZ)(hy-DTC)] (%) C: 41.01; H: 3.24; N: 16.88; S: 19.32. Found (%) C: 37.54; H: 3.29; N: 15.46; S: 15.19. Selected FT-IR (KBr), ν (cm-^{1}): 3270 (SO_2NH), 1621 (C=N), 1499 (C-N), 1048 (C=S). Selected λ_{max} in DMSO solvent, (nm): 225, 235 (π - π^* N-C=S) 374, 382; (n - π^* N-C=S). Selected ^{1}H NMR (DMSO-d_6, 600Hz, ppm): δ 5.98 (C_2HN); δ 6.55-6.57; 6.98 (Ar-H); δ 7.46-7.67 ($C_4H_4N_2$-H) δ 8.46 (N-H); δ 1.24 (=$CHSO_2NNa$). Selected ^{13}C NMR (DMSO-d_6, 150 MHz, ppm); δ112.14 (Ar-C) δ 129.81 (NH_2C); δ 158.22(-SO_2N=C).



Scheme 4.14. Synthesis of zinc(II) complex of [Zn(SFZ)(hy-DTC)]**.**

4.2.2.15 Synthesis of zinc(II) complex of [Zn(SFZ)(to-DTC)]

Sodium sulfadiazine (0.4085 g, 1.5 mmol), sodium *ortho* toluidine ethyl dithiocarbamate ($L_{2to\text{-}DTC}$) (0.3079 g, 1.5 mmol) and $ZnCl_2$ (0.2044 g, 1.5 mmol) were magnetically stirred for 3 h at room temperature. A dirty-brown solid was formed, washed thoroughly with deionized water (3 x 5 mL) and dried over silica gel in a desiccator. Molecular weight: 497.93. Percentage Yield: 72%. M. P. 224ºC. Molar Conductivity: 0.40 Ω^{-1} cm^2 mol^{-1}. Anal. Calcd for [Zn(SFZ)(to-DTC)](%) C: 43.42; H: 3.64; N: 14.06; S: 19.32. Found (%) C: 43.88; H: 4.18; N: 15.39; S: 9.61.Selected FT-IR (KBr), ν (cm^{-1}): 3266 (SO_2NH), 1590 (C=N), 1499, 1488 (C-N), 1048 (C=S). Selected λ_{max} in DMSO solvent, (nm): 235, 264, 284 (π-π^* N-C=S) 376, 384; (n-π^* N-C=S) Selected ^{1}H NMR (DMSO-d_6, 600Hz, ppm): δ 5.98 (C_2HN); δ 6.55-6.57, 6.99 (Ar-H); δ 7.17-7.24,, 7.61-7.62 ($C_4H_4N_2$-H) δ 8.47 (N-H); δ 9.14 (=$CHSO_2NNa$). Selected ^{13}C NMR (DMSO-d_6, 150 MHz, ppm); δ112.14 (Ar-C) δ 129.79; 130.31 (NH_2C); δ 158.22(-SO_2N=C), δ 207.00 (NCS_2).

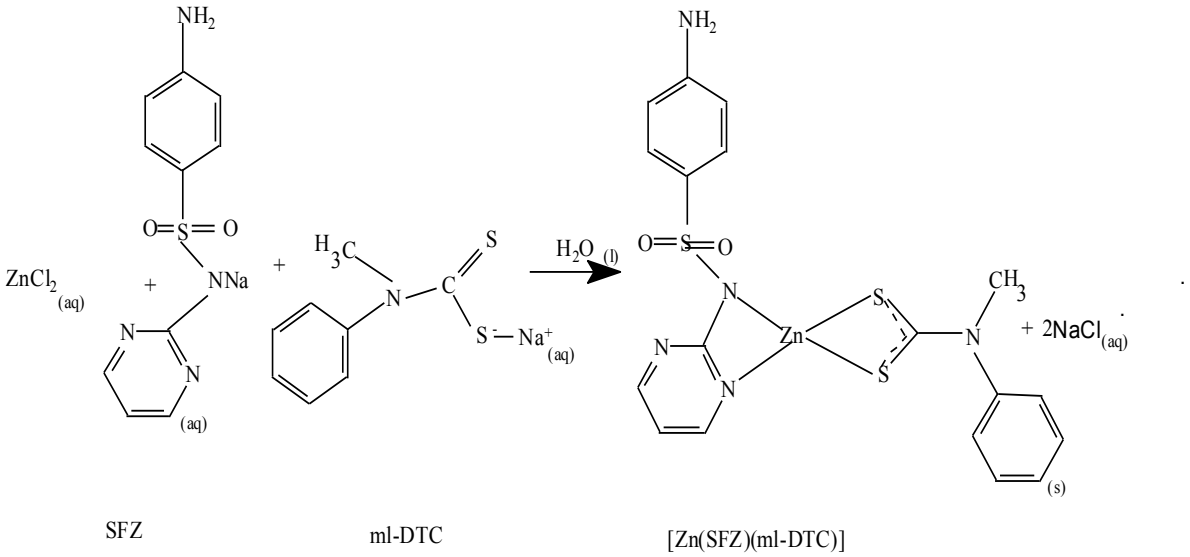


Scheme 4.15. Synthesis of zinc(II) complex of [Zn(SFZ)(to-DTC)]**.**

4.2.2.16 Synthesis of zinc(II) complex of [Zn(SFZ)(ml-DTC)]

Sodium sulfadiazine (0.4085 g, 1.5 mmol), sodium ethyl dithiocarbamate ($L_{2ml\text{-}DTC}$)

(0.3079 g, 1.5 mmol) and $ZnCl_2$ (0.2044 g, 1.5 mmol) were magnetically stirred for 3 h at room temperature. A dirty-white solid was formed. Molecular weight: 496.93 g. Percentage Yield: 78%. M.P. 206-208ºC. Molar Conductivity: 0.02 Ω^{-1} cm^2 mol^{-1}. Anal. Calcd for [Zn(SFZ)(ml-DTC)] (%) C: 43.51; H: 3.45; N: 14.09; S: 19.36. Found (%) C: 40.41; H: 3.62; N: 13.07; S: 15.95.Selected FT-IR (KBr), ν (cm-^{1}): 3263 (SO_2NH), 1587 (C=N), 1494 (C-N), 1000 (C=S). Selected λ_{max} in DMSO solvent, (nm): 231, 265, 275 (π-π^* N-C=S) 375, 385; (n-π^* N-C=S) Selected ^{1}H NMR (DMSO-d_6, 600Hz, ppm): δ 5.98 (C_2HN); δ 6.55-6.56 (Ar-H); δ 7.34-7.43 ($C_4H_4N_2$-H) δ 7.61-7.62; 8.45 (N-H); δ 11.26 (=$CHSO_2NNa$). Selected ^{13}C NMR (DMSO-d_6, 150 MHz, ppm); δ112.08 (Ar-C) δ 129.20; 129.70 (NH_2C); δ 158.18(-SO_2N=C), δ 181.77 (NCS_2).

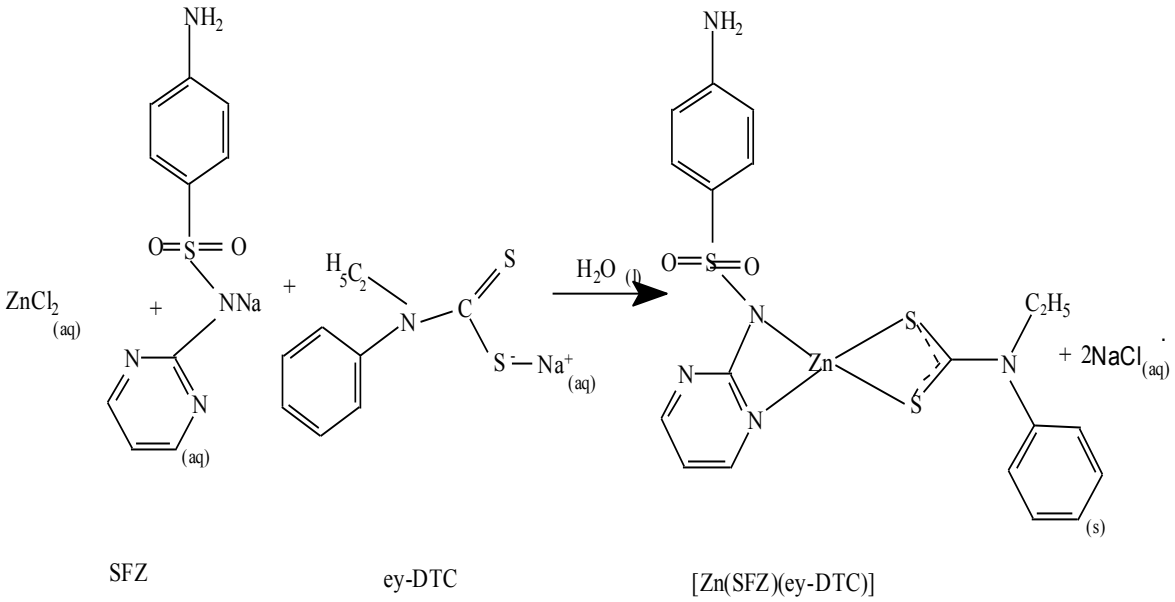


Scheme 4.16. Synthesis of zinc(II) complex of [Zn(SFZ)(ml-DTC)].

4.2.2.17 Synthesis of zinc(II) complex of [Zn(SFZ)(ey-DTC)]

Sodium sulfadiazine (0.4085 g, 1.5 mmol), sodium ethyl dithiocarbamate ($L_{2ey\text{-}DTC}$)

(0.3289 g, 1.5 mmol) and $ZnCl_2$ (0.2044 g, 1.5 mmol) were magnetically stirred for 3 h at room temperature. A white solid was formed washed thoroughly with deionized water (3 x 5 mL) and dried over silica gel in a desiccator. Molecular weight: 510.95 g. Percentage Yield: 82%. M. P. 220-222ºC. Molar Conductivity: 0.03 Ω^{-1} cm^2 mol^{-1}. Anal. Calcd for [Zn(SFZ)(ey-DTC)] (%) C: 44.66; H: 3.75; N: 13.71; S: 18.82. Found: C: 44.38; H: 4.26; N: 14.16; S: 9.37. Selected FT-IR (KBr), ν(cm^{-1}): 3296 ($NHSO_2$), 1591 (C=N), 1502 (C-N), 1025 (C=S). Selected λ_{max} in DMSO solvent, (nm): 232, 264 (π - π^* N-C=S) 370, 374, 384; (n - π^* N-C=S). Selected ^{1}H NMR (DMSO-*d_6*, 600Hz, ppm): δ 5.98 (C_2HN); δ 6.55-6.57 (Ar-H); δ 7.20-7.25; 7.61-7.62 ($C_4H_4N_2$-H) δ 8.46-8.47 (N-H); δ 9.10 (=$CHSO_2NNa$). Selected ^{13}C NMR (DMSO-d_6, 150 MHz, ppm); δ112.10 (Ar-C) δ 129.75 (NH_2C); δ 158.18(-SO_2N=C), δ 181.77 (NCS_2).

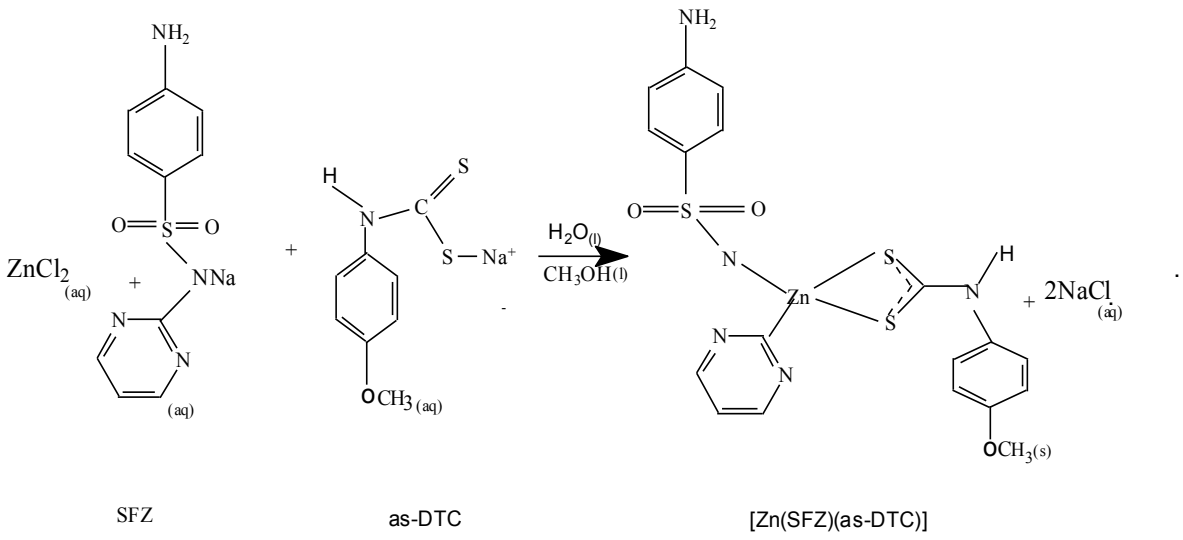


Scheme 4.17. Synthesis of zinc(II) complex of [Zn(SFZ)(ey-DTC)].

4.2.2.18 Synthesis of zinc(II) complex of [Zn(SFZ)(as-DTC)]

Sodium sulfadiazine (0.4085 g, 1.5 mmol), sodium ethyl dithiocarbamate ($L_{2as\text{-}DTC}$)

(0.3319 g, 1.5 mmol) and $ZnCl_2$ (0.2044 g, 1.5 mmol) were magnetically stirred for 3 h at room temperature. A dirty-white solid was formed. Molecular weight: 512.92 g. Percentage Yield: 77%. M. P. 220-221^{o}C. Molar Conductivity: 0.36 Ω^{-1} cm^2 mol^{-1}. Anal. Calcd for [Zn(SFZ)(as-DTC)] (%) C: 42.15; H: 3.34; N: 13.65; S: 18.75. Found (%) C: 41.76; H: 3.47; N: 14.92; S: 11.70.Selected FT-IR (KBr), ν (cm^{-1}): 3292 (SO_2NH), 1592 (C=N), 1496 (C-N), 1001 (C=S). Selected λ_{max} in DMSO solvent, (nm): 215, 235 (π - π^* N-C=S) 376; 382 (n - π^* N-C=S) 564600, 688-800(d-d).Selected ^{1}H NMR (DMSO-d_6, 600Hz, ppm): δ 5.98 (C_2HN); δ 6.56-6.57; 6.99 (Ar-H); δ 7.39-7.62 ($C_4H_4N_2$-H) δ 8.47 (N-H); δ 9.24 (=$CHSO_2NNa$). Selected ^{13}C NMR (DMSO-d_6, 150 MHz, ppm); δ112.14; 115.49 (Ar-C) δ 129.79 (NH_2C); δ 158.22(-SO_2N=C), δ 179.78 (NCS_2).

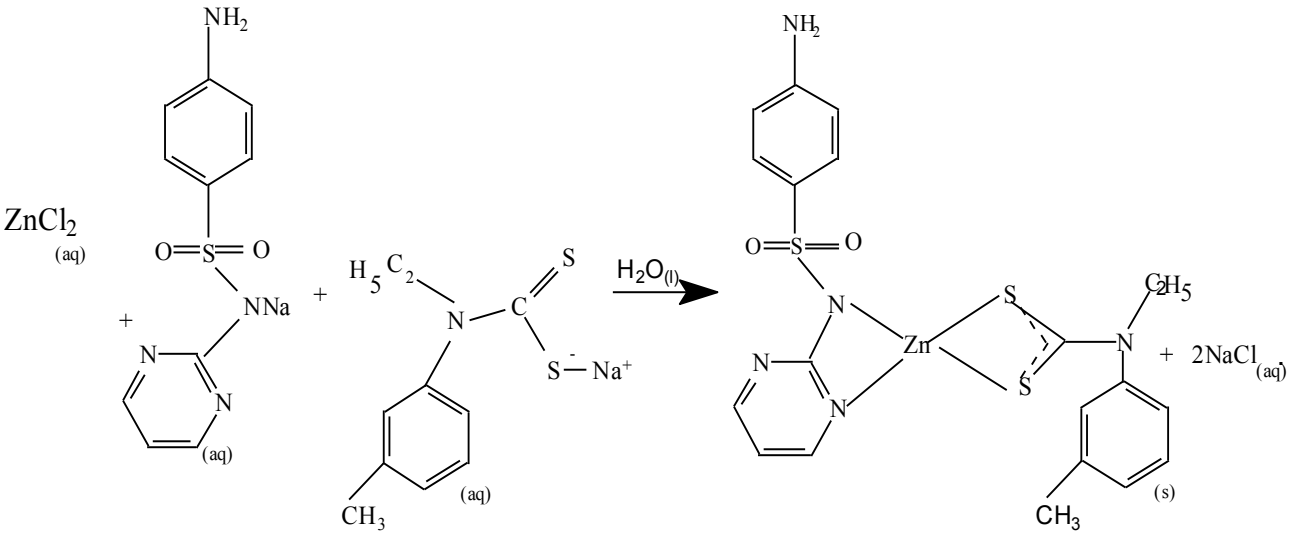


Scheme 4.18. Synthesis of zinc(II) complex of [Zn(SFZ)(as-DTC)]**.**

4.2.2.19 Synthesis of zinc(II) complex of [Zn(SFZ)(tu-DTC)]

Sodium sulfadiazine (0.4085 g, 1.5 mmol), sodium ethyl dithiocarbamate ($L_{2tu\text{-}DTC}$)

(0.3500 g, 1.5 mmol) and $ZnCl_2$ (0.2044 g, 1.5 mmol) were magnetically stirred for 3 h at room temperature. A white solid was formed washed thoroughly with deionized water (3 x 5 mL) and dried over silica gel in a desiccator. Molecular weight: 524.98 g. Percentage Yield: 82%. M. P. 200-201ºC. Molar Conductivity: 0.01 Ω^{-1} cm^2 mol^{-1}. Anal. Calculated for [Zn(SFZ)(tu-DTC)] (%) C: 45.76; H: 4.03; N: 13.34; S: 18.32. Found (%) C: 42.58; H: 4.00; N: 12.71; S: 15.62. Selected FT-IR (KBr), ν (cm-^{1}): 3270 (SO_2NH), 1592 (C=N), 1464 (C-N), 1001 (C=S). Selected λ_{max} in DMSO solvent, (nm): 235, 262 (π - π^* N-C=S) 368, 374, 384; (n - π^* N-C=S). Selected ^{1}H NMR (DMSO-*d*$_6$, 600Hz, ppm): δ 5.97 (C_2HN); δ 6.55-6.57 (Ar-H); δ 7.05-7.31, 7.61-7.62 ($C_4H_4N_2$-H) δ 8.46 (N-H). Selected ^{13}C NMR (DMSO-*d*$_6$, 150 MHz, ppm); δ112.12 (Ar-C) δ 129.75 (NH_2C); δ 158.19(-SO_2N=C), δ 206.18 (NCS_2).



Scheme 4.19. Synthesis of zinc(II) complex of [Zn(SFZ)(tu-DTC)]**.**

4.3. Results and discussion

4.3.1. Syntheses

All the zinc(II) complexes were prepared using solutions of mixed sulfadiazine and derivatives of dithiocarmates to ligate to zinc(II) chloride salt solution. The products of all reactions were in form of precipitates. Most of the precipitates formed were white in colour, few were dirty white in colour ([Zn(SFZ)(mt-DTC)], [Zn(SFZ)(ml-DTC)] and [Zn(SFZ)(as-DTC)]) while [Zn(SFZ)(hy-DTC)] appeared pink in colour. The different extents of the white colour of the precipitates justified the full d ten electron configuration and non-transition nature of zinc and its compounds with the exception of [Zn(SFZ)(hy-DTC)]. All the zinc(II) complexes were kept and stored over silica gel in a desiccator at room temperature. For the molecular masses, [Zn(SFZ)(mt-DTC)] had the lowest molecular mass of 420.83 g and highest formula molecular mass of 602.08 g was for [Zn(SFZ)(cl-DTC)]. A maximum percentage yield of 84% was observed in [Zn(SFZ)(cc-DTC)] while a minimum percentage yield of 52% was observed in [Zn(SFZ)(me-DTC)]. This indicated a good to excellent percentage yield of zinc(II) complexes. Solubility tests were carried out on sample solutions of nineteen zinc(II) complexes with polar protic (ethanol, methanol and water), polar aprotic (acetone, dichloromethane, dimethylformamide and tetrahydrofuran) and non-

polar solvents (chloroform, diethyl ether, ethyl acetate and hexane. The sample solutions were insoluble. Further solubility test of the zinc(II) complexes in dimethylsulfoxide (DMSO) solvent showed partially soluble and soluble results. Among the zinc(II) complexes, [Zn (SFZ) (bu-DTC)] had the lowest melting point/decomposition with 140-142^{o}C, while [Zn(SFZ)(he-DTC)] had the highest melting point/ decomposition temperature at 240-242 ^{o}C. All zinc (II) complexes had molar conductivities of less than 20 $\Omega^{-1}cm^{2}$ mol^{-1}. [Zn(SFZ)(hx-DTC)] and [Zn(SFZ)(tu-DTC)] molar conductivity of 0.01 $\Omega^{-1}cm^{2}$ mol^{-1}, while [Zn(SFZ)(hy-DTC)] had the highest molar conductivity of 6.36 $\Omega^{-1}cm^{2}$ mol^{-1}.

4.3.2. Spectral studies

4.3.2.1. Elemental Analysis (E. A.)

Variations observed in the analytical data for elemental analysis might be due to effect of contamination during the syntheses of dithiocarbamates, effect of hydrate or moisture, incomplete separation of water from sulfur and incomplete digestion. [11, 501, 502]. Table 4.1 the elemental analyses of zinc(II) complexes of mixed ligands of sodium sulfadiazine and derivatives of dithiocarbamate.

Table 4.1: Elemental analyses of zinc(II) complexes of mixed ligands of sodium sulfadiazine and derivatives of dithiocarbamate

Sample Codes	Chemical Formulae	Analytical Data (%)			
		C	H	N	S
		Calculated			
		Found			
[Zn(SFZ)(bu-DTC)]	$C_{15}H_{19}N_5S_3O_2Zn$	38.92	4.14	15.13	20.78
		35.99	4.55	11.82	25.07
[Zn(SFZ)(he-DTC)]	$C_{17}H_{23}N_5S_3O_2Zn$	41.96	4.72	14.26	19.59
		44.81	3.83	20.14	13.58
[Zn(SFZ)(an-DTC)]	$C_{17}H_{15}N_5S_3O_3Zn$	42.28	3.13	14.50	19.92
		40.58	2.44	8.10	30.55
[Zn(SFZ)(me-DTC)]	$C_{18}H_{17}N_5O_2S_3Zn$	43.51	3.45	14.09	19.36
		43.65	3.40	8.50	25.08
[Zn(SFZ)(et-DTC)]	$C_{19}H_{19}N_5S_3O_2Zn$	44.83	3.76	13.71	18.82
		46.27	3.99	7.52	24.34
[Zn(SFZ)(cl-DTC)]	$C_{17}H_{14}N_5S_3O_3ClZn$	39.47	2.73	13.54	18.59
		39.90	3.47	18.32	8.93
[Zn(SFZ)(mt-DTC)]	$C_{12}H_{13}N_5O_2S_3Zn$	34.25	3.11	16.64	22.85
		34.05	3.13	14.99	7.79
[Zn(SFZ)(bt-DTC)]	$C_{15}H_{19}N_5O_2S_3Zn$	38.92	4.14	15.13	20.78
		37.21	3.74	15.83	13.51

[Zn(SFZ)(hx-DTC)]	$C_{15}H_{19}N_5O_2S_3Zn$	41.92 37.62	4.72 3.74	14.26 15.43	19.59 13.20
[Zn(SFZ)(de-DTC)]	$C_{15}H_{19}N_5O_2S_3Zn$	38.92 34.27	4.14 3.96	15.13 13.01	20.78 17.45
[Zn(SFZ)(*de-DTC)]	$C_{15}H_{19}N_5O_2S_3Zn$	38.92 42.04	4.14 3.43	15.13 13.19	20.78 16.83
[Zn(SFZ)(ea-DTC)]	$C_{13}H_{15}N_5S_3O_3Zn$	34.56 32.29	3.57 3.06	15.50 14.59	21.29 9.37
[Zn(SFZ)(cc-DTC)]	$C_{17}H_{23}N_5S_3O_2Zn$	41.67 43.05	4.53 3.57	14.29 17.63	19.63 12.59
[Zn(SFZ)(hy-DTC)]	$C_{17}H_{16}N_6S_3O_2Zn$	41.01 37.54	3.24 3.29	16.88 15.46	19.32 15.19
[Zn(SFZ)(to-DTC)]	$C_{18}H_{16}N_5S_3O_2Zn$	43.42 43.88	3.64 4.18	14.06 15.39	19.32 9.61
[Zn(SFZ)(ml-DTC)]	$C_{18}H_{17}N_6S_3O_2Zn$	43.51 40.41	3.45 3.62	14.09 13.07	19.36 15.95
[Zn(SD)(ey-DTC)]	$C_{19}H_{19}N_5S_3O_2Zn$	44.66 44.38	3.75 4.26	13.71 14.16	18.82 9.37
[Zn(SFZ)(as-DTC)]	$C_{18}H_{17}N_5O_2S_3Zn$	42.15 41.76	3.34 3.46	13.65 14.92	18.75 11.70
Zn(SFZ)(tu-DTC)]	$C_{20}H_{21}N_5S_3O_2Zn$	45.76 42.58	4.03 4.00	13.34 12.71	18.32 15.62

4.3.3 Molecular Spectroscopy (Fourier Transform Infra-red spectroscopy (FT-IR), Ultraviolet-Visible Spectroscopy (UV-Vis) and Nuclear Magnetic Resonance (NMR)

In this chapter, the two molecular spectroscopies applied to study the synthesized nineteen zinc complexes were Fourier Transform Infra-Red (FT-IR) Spectroscopy and Electronic Spectroscopy (UV/Vis) Spectroscopy.

4.3.3.1 Fourier Transform Infra-Red Spectroscopy (FT-IR) of mixed ligands of zinc(II) complexes

4.3.3.1.1 FT-IR frequencies (cm^{-1}) of sulfadiazine ligated zinc(II) complexes

The FT-IR for zinc(II) complexes was also taken from upper region of 4000 cm^{-1} to a lower FT-IR region of 400 cm^{-1} as it was done for ligands. FT-IR was applied to determine the coordination of the mixed ligands to zinc(II) ion.

Amino group asymmetrical and symmetrical stretching modes (NH_2), of all zinc(II) complexes had absorption bands between higher absorption vibration bands in the region of 3548 and 3416 cm^{-1} as compared to SFZ, (L_1), which had 3482 and 3310 cm^{-1} respectively. The differences might be due to either different forms of vibrations of coordinated water, lattice water or hydrogen bonding between zinc(II) complexes entailing the NH_2 and SO_2 groups [371-373]. The sulfonamide nitrogen (-SO_2N) atom in the zinc(II) complexes was observed with higher absorption frequency values compared to the free ligand at 3251cm^{-1} with exception of some lower vibration values with [Zn(SFZ)(bu-DTC)], [Zn(SFZ)(he-DTC)], [Zn(SFZ)(et-DTC)]and [Zn(SFZ)(cl-DTC)]. Azomethine group, -C=N, had both higher and lower frequencies (1653-1575 cm^{-1}) than the corresponding free ligand of sodium sulfadiazine (1628, 1549 cm^{-1}). All SO_2 asymmetrical stretching modes absorbed at either higher or lower wavenumbers than the corresponding ligands. For symmetrical stretching modes, all the absorption values were greater than those of their corresponding ligands. S-N absorbed at lower wavenumbers (996 - 940 cm^{-1}) in all zinc(IV) complexes when compared

with the free ligand, (1024 cm^{-1}). For Zn-N, the nitrogen donor bond to zinc was observed from a region 577-549cm^{-1}.All the modifications of NH_2, -SO_2N, -C=N, SO_2 and S-N confirmed the coordination of sulfonamide nitrogen atom to the zinc(II) ion [363-364, 371-373, 530].

4.3.3.1.2 FT-IR frequencies (cm^{-1}) of dithiocarbamate ligated zinc(II) complexes

4.3.3.1.2.1 Variations in FT-IR Absorption frequencies (C-N), *ν*(C=S) and ν(Zn-S) in mixed donor ligands of zinc(II) complexes

As mentioned in chapter two, there are three important infra red bands in dithiocarbamate. These are thioureide band, *ν* (C-N), from 1450-1550 cm^{-1}, dithiocarbamate band, *ν* (C=S) from 950-1050 cm^{-1} and ν (Zn-S) from 300-400 cm^{-1}.

In all the complexes of zinc(II) ion, the frequencies of thioureide bands *ν* (C-N) and dithiocarbamate band *ν* (C=S), were either higher or lower than those of their corresponding ligands.

In all the nineteen complexes, only [Zn(SFZ)(me-DTC)] and [Zn(SFZ)(et-DTC)] had lower thioureide frequency bands than the ligands with a range difference of 1 cm^{-1} and 14-52 cm^{-1}, respectively. This indicated monodentate coordination, while the other seventeen zinc(II) complexes had bidentate coordination [531, 532].

In all dithiocarbamate bands, seven zinc(II) complexes, namely; [Zn(SFZ)(he-DTC)], [Zn(SFZ)(cl-DTC)], [Zn(SFZ)(hx-DTC)], [Zn(SFZ)(*de-DTC)], [Zn(SFZ)(hy-DTC)], [Zn(SFZ)(as-DTC)] and [Zn(SFZ)(to-DTC)] with had higher frequencies differences of 18, 40, 13, 27, 44, 37 and 38 cm^{-1} respectively from the corresponding ligands. This indicated bidentate coordination, while the other eleven zinc(II) complexes with lower absorption frequencies than the corresponding ligands [531, 532]. For, ν(Zn-S), the region was from 456 - 370cm^{-1}. Differences in *ν*(C-N), *ν*(C=S) and *ν*(Zn-S) proved both coordination of the sulfur donor to zinc(II) ion.

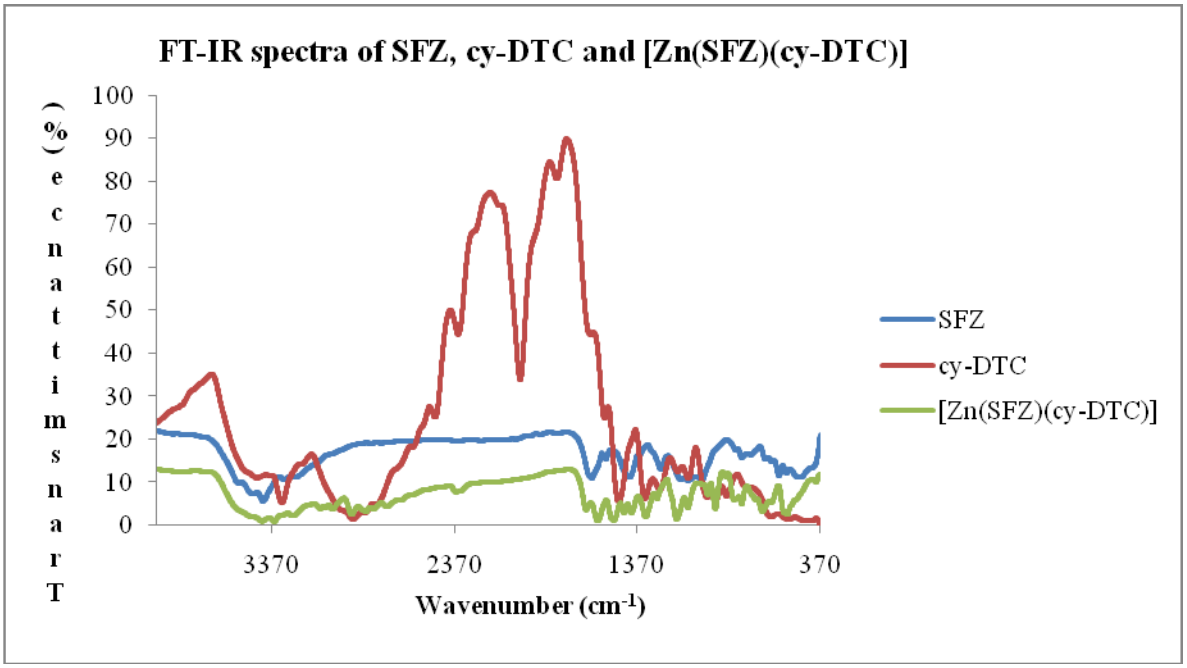


Figure 4.1: FT-IR spectra of SFZ, cy-DTC and [Zn(SFZ)(cy-DTC)].

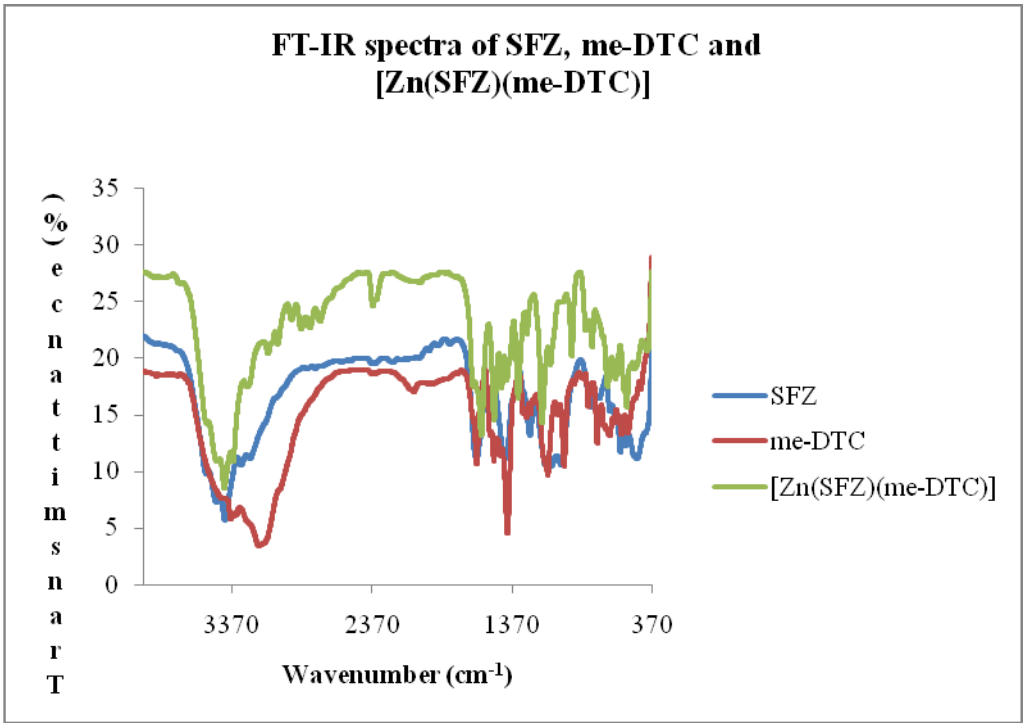


Figure 4.2: FT-IR spectra of SFZ, me-DTC and [Zn(SFZ)(me-DTC)].

4.3.3.2 Electronic spectroscopies of zinc(II) complexes of mixed sulfadiazine and dithiocarbamate

Sodium sulfadiazine and dithiocarbamates both had π - π^* and n - π^* transitions as can be observed in Table 4.2. All zinc(II) complexes had a blue shifts (hypsochromic shifts) in comparison with the corresponding ligands, except in [Zn(SFZ)(mt-DTC)], where it was a red shift to mt-DTC.

One to more than one splitting were observed in the absorption bands indicating non-equivalence of the C-S bands in the zinc(II) complexes.[Zn(SFZ)(mt-DTC)] had no splitting.

Shoulders of d-d transitions were observed in some zinc(II) complexes. These eight zinc(II) complexes were [Zn(SFZ)(me-DTC)],[Zn(SFZ)(et-DTC)],[Zn(SFZ)(hx-DTC)],[Zn(SFZ)(de-DTC)],[Zn(SFZ)(*de-DTC)], [Zn(SFZ)(hh-DTC)], [Zn(SFZ)(as-DTC)] and [Zn(SFZ)(hy-DTC)]. These shoulders of d-d transitions might be due to pronounced effects of sulfur present in the mixed donor ligands in the sodium sulfadiazine (SFZ) and dithiocarbamates (SFZ).

Another factor should be solvent impact when the coordination could contribute to the d-d transitions. The geometries of the aforementioned could be five coordinate complexes.

All the zinc(II) complexes with no d-d transition could be square planar or tetrahedral structures [533]. Tetrahedral geometries could be suggested for all zinc(II) complexes because their spectral bands were less than 400nm and also due to their possessions of d^{10} electronic configurations [534].

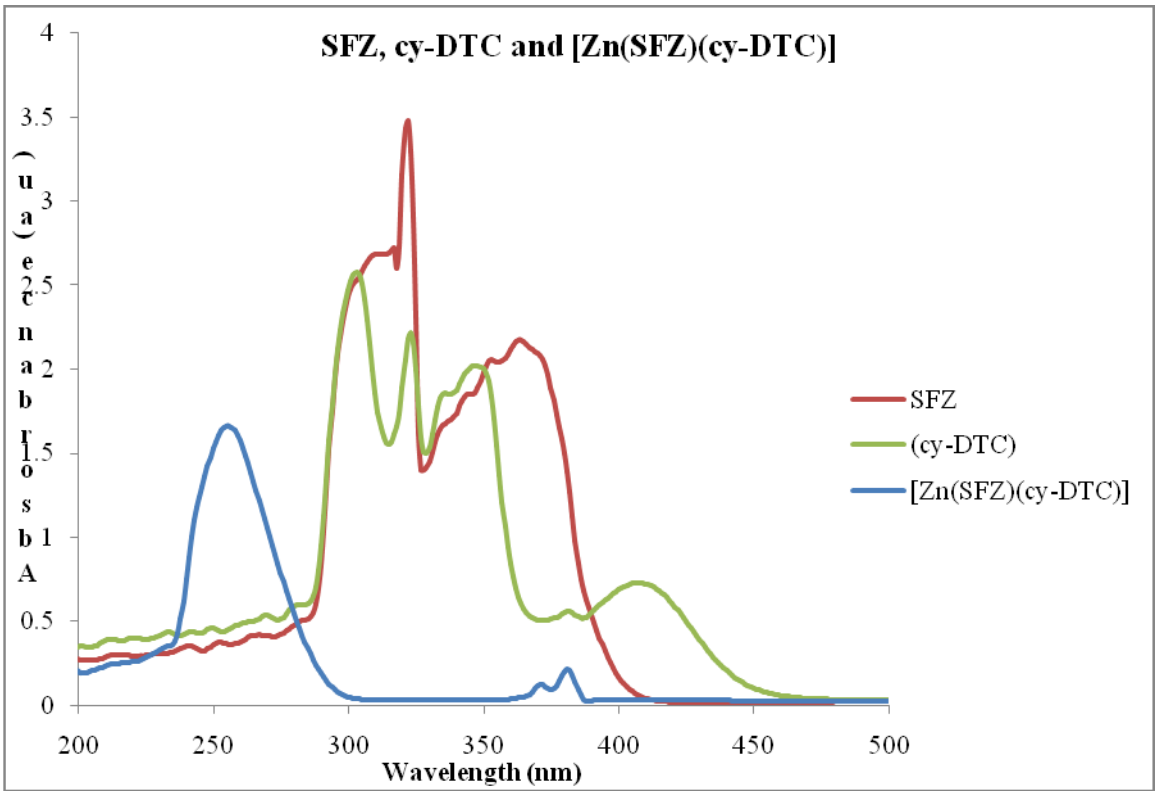


Figure 4.3: The UV-Vis spectra of SFZ, cy-DTC and [Zn(SFZ)(cy-DTC)].

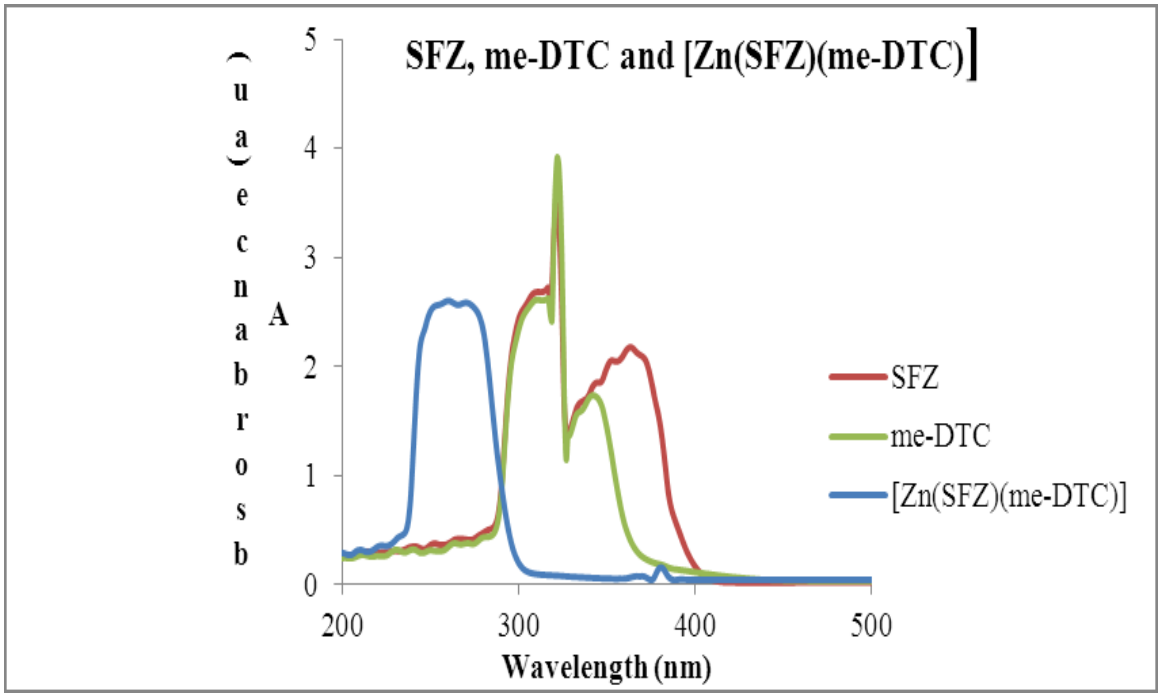


Figure 4.4: The UV-Vis spectra of SFZ, me-DTC and [Zn(SFZ)(me-DTC)].

4.3.3.3 Proton (^{1}H) NMR and Carbon 13 (^{13} C) NMR Spectra of zinc(II) complexes of mixed sulfadiazine and dithiocarbamate

Proton(^{1}H) NMR and Carbon 13, (^{13}C) NMR spectra of all zinc(II) complexes were obtained from deuterated DMSO (DMSO-d_6)solvents. The chemical shifts of all zinc(II) complexes of all zinc(II) complexes were expressed in ppm relative to internal TMS, as applied to the ligands.

4.3.3.3.1 ^{1}H NMR Spectra (Methyl and methylene, N-H, Azomethine proton, Pyrimidine ring and Phenyl (Ar-^{1}H) groups)

Methyl groups of zinc(II) complexes had similar chemical shifts with their corresponding ligands. These include: bt-DTC; 0.83-0.89 ppm and [Zn(SFZ)(bt-DTC)];0.86-0.89 ppm, hx-DTC; 0.82-0.85 ppm and [Zn(SFZ)(hx-DTC)]; 0.85 ppm, de-DTC; 1.07-1.09 ppm and [Zn(SFZ)(bt-DTC)];1.19.-1.22 ppm, *de-DTC; 1.05-1.08 ppm and [Zn(SFZ)(*de-DTC)];0.80-1.30 ppm, to-DTC; 2.04; 2.25; 2.50-2.51 ppm and [Zn(SFZ)(to-DTC)];2.24 ppm and ey-DTC; 1.14-1.16 ppm and [Zn(SFZ)(bt-DTC)]; 1.14-1.17 ppm. The above results revealed the non-coordinating nature of methyl groups. All the methylene groups of aforementioned ligands had values of chemical shifts similar to corresponding zinc(II) complexes, therefore, did not coordinate with zinc(II) ion. The amino proton of all zinc(II) complexes with the exception of [Zn(SFZ)(cl-DTC)] resonated at higher ppm than the ligand at δ 5.36 ppm. The azomethine proton absorbed either at higher or lower chemical shifts than the ligands. Protons of pyrimidine ring (3H pyrimidine $C_4H_2N_2$-H ring) of all zinc(II) complexes resonated at higher chemical shifts than the corresponding ligand. All zinc(II) complexes possessing phenyl (Ar-^{1}H) groups had higher values of chemical shifts than the ligands.

4.3.3.3.2 ^{13} C NMR Spectra (Methyl and methylene, azomethine -(NCH_2), aromatic Carbon (Ar-C), pyrimidine ring, ^{13}C-SO_2Na and thione (-NCSS) groups)

Methyl group being absent in L_1 was displayed in some zinc(II) complexes, due to some being present in the ligands. For L_2, there were similarities in the values of chemical shifts

between L_2 and their corresponding zinc(II) complexes. These include: bu-DTC; 13.55 ppm and [Zn(SFZ)(bu-DTC)]; 13.59 ppm. (bt-DTC; 13.15-13.93 ppm and [Zn(SFZ)(bt-DTC)]; 13.64 ppm). (de-DTC; 12.61 ppm and [Zn(SFZ)(de-DTC)]; 12.02 ppm. The similarities indicated no coordination with the metal ion. Others with methyl groups had the zinc(II) complexes lower than L_2 (hx-DTC; 14.19-14.29 ppm and [Zn(SFZ)(me-DTC)]; 17.39; 17.42 ppm. (me-DTC; 29.70 ppm and [Zn(SFZ)(me-DTC)]; 17.39; 17.42 ppm. ((ml-DTC; 29.75 ppm and [Zn(SFZ)(ml-DTC)]; 29.80 ppm (tl-DTC; 20.55, 20.57 ppm and [Zn(SFZ)(tl-DTC)]; 20.54 ppm.

Some showed no chemical shift for the methyl groups, for example, ea-DTC with 18.62 ppm but none for the corresponding zinc(II) complex. The methylene groups of aforementioned ligands and their corresponding zinc(II) complexes were similar, therefore, did not coordinate with zinc(II) ion. For the azomethine group -(NCH_2), zinc(II) complexes had resonance values of -NCH_2 higher than the corresponding ligands (de-DTC; 43.30 ppm and [Zn(SFZ)(de-DTC)]; 48.88 ppm.(*de-DTC; 46.33 ppm and [Zn(SFZ)(*de-DTC)]; 48.96 ppm, (tu-DTC; 50.97 ppm and [Zn(SFZ)(tu-DTC)]; 53.43 ppm and (et-DTC; 38.87 ppm and [Zn(SFZ)(et-DTC)]; 53. 49 ppm. There was no resonance for ea-DTC, while for the complex [Zn(SFZ)(ea-DTC)], the chemical shift appeared at 40.43 ppm. In case of aromatic carbon (Ar-C), all carbon atoms present in aromatic zinc(II) complexes had their Ar-H resonance values higher than the corresponding ligands. The pyrimidine ring of the zinc(II) complexes absorbed at resonance lower than the ligands. The ^{13}C-SO_2NNa of the zinc(II) complexes resonated at either higher or lower chemical shifts than the ligands. The presence of thione group (-NCS_2) moiety indicates the presence of the functional group still present and the impact of coordination. The values were higher than the corresponding ligands except in some zinc(II) complexes. These zinc(II) complexes were [Zn(SFZ)(cc-DTC)]; 202.73 ppm, with ligand cc-DTC; 212.94 ppm, and *para* substituted [Zn(SFZ)(tu-DTC)]; at 206.18 ppm, with ligand tu-DTC; 214.93 ppm, and *para* substituted [Zn(SFZ)(to-DTC)] 181.16 ppm, with ligand to-DTC; 181.17 ppm, [Zn(SFZ)(as-DTC)];179.76 ppm, with ligand as-DTC; 179.77 ppm, [Zn(SFZ)(de-DTC)];202.31 ppm, with ligand de-DTC; 211.78 ppm, [Zn(SFZ)(ml-DTC)];207.00 ppm, with ligand ml-DTC; 215.94 ppm.

Despite the fact that aliphatic and *para* substituted dithiocarbamates had thione groups. The regions were absent in some zinc(II) complexes. These include [Zn(SFZ)(bu-DTC)], [Zn(SFZ)(cy-DTC)], [Zn(SFZ)(ml-DTC)], [Zn(SFZ)(ey-DTC)], [Zn(SFZ)(bt-DTC)],

[Zn(SFZ)(hx-DTC)],[Zn(SFZ)(hh-DTC)]and[Zn(SFZ)(hy-DTC)]. No chemical shift of –NCS_2 was observed for both ligand and zinc(II) complex of [Zn(SFZ)(ea-DTC)].

Table 4.2: The ^{1}H NMR of sodium sulfadiazine ligated zinc(II) complexes and dithiocarbamate ligated zinc(II) complexes in ppm in DMSO-d_6 solvent**.**

^{1}H NMR	N-H	Ar-H(C_6H_5-H)	N=CH	(3H pyrimidine C_4H_2N-H ring)	=C-HSO_2NNa
SFZ (L_1)	5.36	6.38-6.46	7.46-7.48	8.10	
[Zn(SFZ)(bu-DTC)]	5.60	6.50	7.50	8.60	11.24
[Zn(SFZ)(he-DTC)]	5.95	6.55-6.97	7.27-7.59	8.45	11.19
[Zn(SFZ)(an-DTC)]	5.94	6.98	7.18-7.50	8.44	11.72
[Zn(SFZ)(me-DTC)]	5.95	6.98	7.18-7.59	8.45	11.31
[Zn(SFZ)(et-DTC)]		7.26	7.43	8.25	
[Zn(SFZ)(cl-DTC)]	5.19	6.98-7.00	7.35-7.56	8.45	11.81
[Zn(SFZ)(mt-DTC)]	5.98	6.99	7.61-7.62	8.47	
[Zn(SFZ)(bt-DTC)]	5.96	6.98	7.62-7.62	8.46	
[Zn(SFZ)(hx-	5.98	6.99	7.61-	8.47	11.24

DTC)]			7.62		
[Zn(SFZ)(de-DTC)]	5.96	6.97	7.61-7.62	8.45	
[Zn(SFZ)(*de-DTC)]	5.75	6.51-6.80	7.43-7.60	8.33	11.24
[Zn(SFZ)(ea-DTC)]	5.98	6.55-6.57	7.61-7.62	8.46-8.47	
[Zn(SFZ)(cc-DTC)]	5.99	6.55-6.57	7.61-7.62	8.46-8.47	
[Zn(SFZ)(hy-DTC)]	5.98	6.98	7.61-7.62	8.46	11.24
[Zn(SFZ)(to-DTC)]	5.98	6.99	7.61-7.62	8.47	
[Zn(SFZ)(ml-DTC)]	5.98	6.99	7.61-7.62	8.45	11.26
[Zn(SFZ)(ey-DTC)]	5.98	6.99	7.61-7.62	8.46-8.47	
[Zn(SFZ)(as-DTC)]	5.98	6.99	7.39-7.62	8.47	
[Zn(SFZ)(tu-DTC)]	5.97	6.99	761-7.62	8.46	

^{1}H NMR	δ (-CH_3)	δ (γ $^{1}H_2C$)	δ (β CH_2)	δ (α H_2C)	$^{1}H_2C$-N	Ar-^{1}H	N-H
an-DTC					4.98	6.44-7.54	7.82-7.85

							10.13 11.15
[Zn(SFZ)(an-DTC)]					5.95	6.54	9.70
me-DTC	2.25				5.42	6.35-6.38	6.90-7.15
[Zn(SFZ)(me-DTC)]	2.04-2.32				-NCH 4.75	6.55	9.11
et-DTC	1.15-1.51			2.96-3.34	5.42	6.47-6.53	6.84 7.02-7.06
[Zn(SFZ)(et-DTC)]	1.14			4.11	4.12	6.55	9.15
cl-DTC					5.18-5.94	6.52-7.21	10.23
[Zn(SFZ)(cl-DTC)]					5.98	6.52-6.54	9.92
mt-$DTC_{(D2O)}$	2.32-2.49 2.61				3.53-3.55	-	
[Zn(SFZ)(mt-DTC)]				5.98	6.55.6.57	-	
bt-DTC	0.83-0.89			3.31-3.39	3.54-3.67	-	7.50 7.97

[Zn(SFZ)(bt-DTC)]	0.86-0.89			1.28-1.29 1.49-1.52	5.96	6.55-6.56	
hx-DTC	0.82-0.85	1.20-1.26	1.41-1.42-1.52	3.15	3.60-3.62		7.97-7.99 9.54
[Zn(SFZ)(hx-DTC)]	0.85-0.87	1.28-1.50			3.70	6.55-6.57	
de-DTC	1.07-1.09				3.95-3.98		
[Zn(SFZ)(de-DTC)]	1.19-1.22				5.98		9.14
*de-DTC	1.05-1.08				4.00		
[Zn(SFZ)(*de-DTC)]	0.80 1.30				3.64		
ea-DTC	1.02-1.05			2.00-3.43	4.25-4.80		8.00
[Zn(SFZ)(ea-DTC)]					5.98		
cc-DTC				Cyclic hexyl 0.69-1.83	3.34-3.54; 4.03-	7.76-7.78	9.62

					4.13		
[Zn(SFZ)(cc-DTC)]				Cyclic hexyl 1.05-1.83	3.65	6.55-6.57	9.86
hy-DTC						7.33-7.36	7.65-7.67
[Zn(SFZ)(hy-DTC)]					5.98	6.55-6.57	
to-DTC	2.04 2.25				NC-H: 3.31	6.45-7.16	7.17-7.27 9.14
[Zn(SFZ)(to-DTC)]	2.24				5.98	6.55-6.57	9.14
ml-DTC	1.03-1.052.50-2.65				NC-H: 3.14: 3.39-3.45	6.51-6.52	6.85-6.91 7.06-7.27
[Zn(SFZ)(ml-DTC)]					NC-H:3.64	6.55-6.56	
ey-DTC	1.14-1.16			2.50-2.63	3.54-3.60 4.28	7.18-7.20	7.24-7.27
[Zn(SFZ)(ey-DTC)]	1.14-1.17			2.59-2.62	5.98	6.55-6.57	9.10
as-DTC	2.50				NC-H: 3.36 3.73	6.84-6.87	7.36-7.38 9.85

							9.93
[Zn(SFZ)(as-DTC)]					NC-H: 5.97	6.55-6.57	9.93
tu-DTC	1.02-1.07			2.26-2.51	3.32-3.51; 4.23-4.30	6.82-6.85 6.91-6.93	
[Zn(SFZ)(tu-DTC)]	1.14-1.16			C_2H_5: 2.32	4.10-4.11	6.55-6.57	

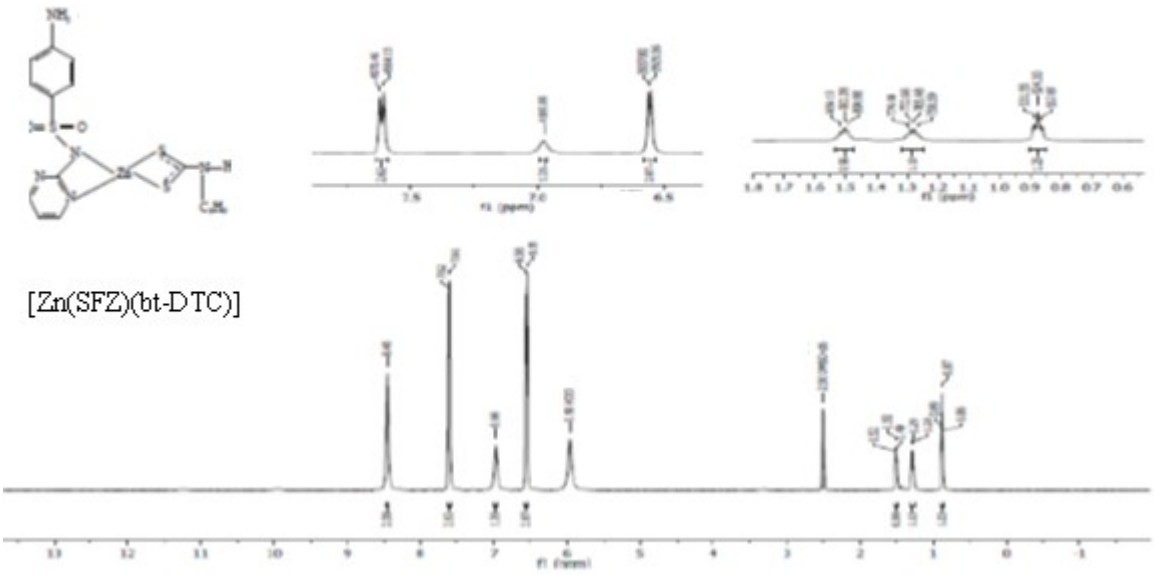


Figure 4.5: The ^{1}HNMR spectrum of [Zn(SFZ)(bt-DTC)] in ppm in DMSO-d_6 solvent**.**

Table 4.3: The ^{13}C NMR of zinc(II) complexes in ppm in DMSO-d_6 solvent.

^{13}C NMR	δ (-$^{13}CH_3$)	δ (γ $H_2{}^{13}C$)	δ (β $^{13}CH_2$)	δ (α $H_2{}^{13}C$)	N^{13}CH$_2$	^{13}Ar-H	N=^{13}CH	^{13}C-NH$_2$	$^{13}C_4H_2N_2$-H	^{13}C-SO$_2$Na	N^{13}CS$_2$
SFZ(L_1)						109.20 111.91	128.25	133.20	143.97	157.29 164.39	
DTC(L_2)											
[Zn(SFZ)(bu-DTC)]	13.59			19.48	29.85						
Zn(SFZ)(he-DTC)]	14.00				22.00	111.97 115.33			129.60	158.02 152.80	
[Zn(SFZ)(an-DTC)]						123.34	124.10	127.66 128.08	129.59	139.11	179.32 192.00
[Zn(SFZ)(me-	17.39 17.42					125.49-125.7	126.20-126.8	127,35-127.4	129.92	130.41-137.4	180.68 192.2

DTC)]						4	6	0		2	4
[Zn(SFZ)(et-DTC)]	12.13				53.49	126.95	126.95	127.88	129.25	144.93	205.36
[Zn(SFZ)(cl-DTC)]						123.34 124.10	125.58	127.66 128.08	129.59	139.11	179.32 194.00
[Zn(SFZ)(mt-DTC)]											
[Zn(SFZ)(el-DTC)]											
[Zn(SFZ)(bt-DTC)]	13.64					112.13			129.76	158.21	
[Zn(SFZ)(hx-DTC)	13.89	22.00	25.96	27.73	30.88	112.10			129.77	152.96 158.1	

]										9	
[Zn(SFZ)(de-DTC)]	12.02				48.88	112.11			129.74	158.19	202.31
[Zn(SFZ)(*de-DTC)]	12.00				48.96	111.97			129.45	151.87 157.89	202.24
[Zn(SFZ)(ea-DTC)]						112.16 115.49			129.80	152.99 158.24	
[Zn(SFZ)(cc-DTC)]				24.67 24.95	31.20	112.14			129.80	158.23	202.73
[Zn(SFZ)(hy-DTC)]						112.14	125.78	127.94 128.51	129.81	139.28 158.22	
[Zn(SFZ)(to-DTC)	17.80					112.14	126.14 126.5	128.24	129.79 130.3	135.07 137.8	181.16

]							8		1	0 152.58 158.22	
[Zn(SFZ)(ml-DTC)]					47.03	112.08	125.91 127.70	128.80	129.20 129.73	158.16	207.00
[Zn(SFZ)(as-DTC)]						112.14 115.49	125.37	128.35 128.44	129.79	138.31 152.99 157.26 158.22	179.78
[Zn(SFZ)(tu-DTC)]	12.15			20.81	53.45	112.12	123.98 127.22	128.50 128.99	129.75	138.76 144.92 158.19	206.18

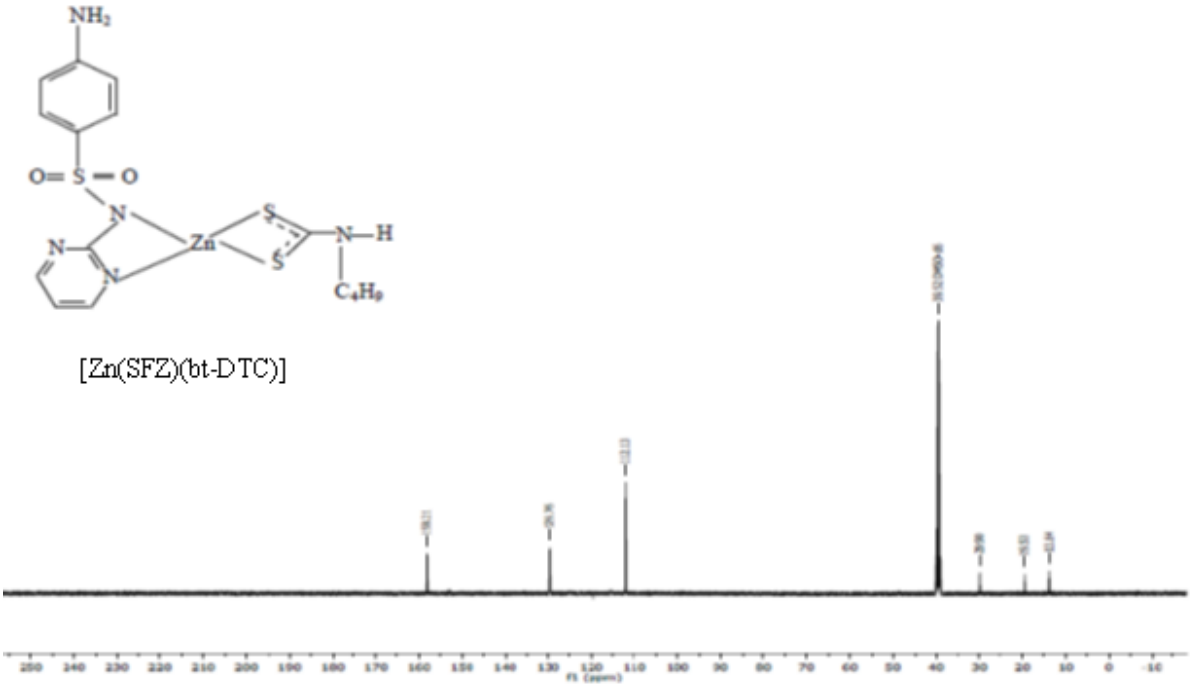


Figure 4.6: The ^{13}CNMR spectrum of [Zn(SFZ)(bt-DTC)] in ppm in DMSO-d_6 solvent**.**

4.4 Conclusion

Zinc(II) complexes of mixed sulfadiazine and dithiocarbamate ligands were synthesized and subjected to spectral characterization. One of the physicochemical parameters, that is, molar conductivity, confirmed the non-electrolytic natures were of all the zinc(II) complexes. Spectroscopic data from FT-IR and UV-Vis confirmed the coordination of the mixed donor ligands of N_2S_2 coordination modes to zinc(II) complexes. Results from electronic spectra gave likely structures of tetrahedral, square-planar and five-coordinate zinc(II) complexes. Resonance values of ^{1}H NMR and ^{13} C NMR for all zinc(II) complexes confirmed most of the successful coordination of the mixed ligand of sulfadiazine and dithiocarbamate to zinc(II) ion.

CHAPTER FIVE

5. Anticancer and antimicrobial activities of oxovanadium(IV) and zinc(II) complexes

5.1 Introduction

Biological assays are simply referred to as," bioassays" [535]. They are biological assessment test methods that involve the use of animal or plant (*in vivo*) cell or tissue (*in vitro*) to determine the potency of physical, chemical or biological agent [535]. In a bioassay, the response of a specific amount of the test sample is measured and compared with relevant standard in a biological system within specific time and standard conditions [535]. Bioassay can be qualitative if it does not involve statistical tools and quantitative if it involves numerals and statistical tools [535]. The principle of bioassay is to determine what, how much and how long the test sample would generate a less, equal or higher biological response compared to that of the standard [535]. The advantages of bioassays over other assay methods are to determine concentration and potency of test sample, when no suitable bioassay is available. Other uses are to test sample substance with different chemical compositions that have the same biological activities, to efficiently estimate complex chemical compounds which cannot be analyzed by simple assay, to standardize drugs, vaccines, toxins, poisons and to determine specificity of a chemical compound against ailment for rapid recovery [535]. Bioassay techniques can be divided into *in vivo* techniques, *ex vivo* techniques and *in vitro* techniques [535].

5.1.1 *In vivo* techniques

These techniques involve the use of living animals such as rodents in order to directly study the biological response of the test compound screened in a biological system [535].

5.1.2 *Ex vivo* techniques

These techniques involve the use of cells or tissue in a biological system in order to study the effect of test compound screened under standard conditions, in which the cell or tissue survives outside the body within specific time [535].

5.1.3 *In vitro* techniques

These techniques involve the use of cultured cells in a biological system in order to study the effect of test compound screened under standard conditions. Here, cultured cells use nutrition to survive [535].

In this chapter, this research employs the use of *in vitro* techniques in order to test the synthesized compounds for their anticancer and antibacterial activities [536, 537]. This chapter highlights the different methods used to determine the anticancer and antimicrobial activities of some of the compounds, the discussion on the results obtained from the biological assays are presented. The evaluations of the biological potentials of the compounds were carried out in three different laboratories. The experimental procedures and results obtained for anticancer screening is presented in Section 5.2. They were evaluated for their potentials as anticancer (cytotoxic activities) and antibacterial agents. Conclusion was drawn from the results of the various tests.

5.2 *In vitro* anticancer screening of dithiocarbamate ligands and some mixed ligand metal complexes of oxovanadium(IV) and zinc(II) ions

In vitro anticancer screening exercises were carried out at the Department of Biotechnology, University of the Western Cape, South Africa with WST-1 assay (Roche Diagnostics, GmbH, Mannheim, Germany) and at The Council for Scientific and Industrial Research (CSIR), Pretoria, South Africa with Sulforhodamine B (SRB) assay.

5.2.1 Materials and reagents and equipment using cytotoxicity assay of Water Soluble Tetrazolium Salt, (WST-1)

Incubator (37^{o}C), centrifuge, micro plate, microscope, hemacytometer, multichannel pipette (10, 50, 100 µl), sterile pipette tips, cisplatin and 96-well micro plates.

5.2.1.1 Cytotoxicity (WST-1) assay experiment

Culture medium, e.g. RPMI 1640 containing 10% heat-inactivated FCS, 2 mL-glutamine and actinomycin C1 (actinomycin D), 1 µg/ml, WST-1 assay from Roche Diagnostics, cisplatin,

dimethyl sulfoxide (DMSO), KMST-6 (Non-cancerous fibroblast), HT-29 (Human colon cancer adenocarcinoma). Professor Denver Hendricks (Department of Clinical and Laboratory Medicine, University of Cape Town-South Africa) supplied the cell lines (and HT-29).

Negative control - DMSO.

Positive control (Reference cancer drug)-Cisplatin.

Some samples of ligands and mixed ligand zinc(II) complexes.

5.2.1.2 Cell culture

HT-29 and KMST-6 were maintained in Dulbecco's Modified Eagle's medium containing 10% foetal bovine serum and 1% penicillin-streptomycin at a temperature of 37^{o}C humidified incubator with 5% carbon (IV) oxide saturation. All reagents for cell culture were provided by Invitrogen Ltd. (CA, USA).

5. 2.1.3 Cytotoxicity (WST-1) assay

WST-1 based colorimetric assay is used only for *in vitro* analyses [538, 539]. It involves nonradioactive quantification of cell proliferation, cell viability and *cytotoxicity*. The screening took place in two stages. The first stage involved the selection of active compounds and the second stage, *secondary screening*, required the determination of the inhibition concentration value, IC_{50} value, of the active compound. IC_{50} value is the inhibition concentration value, where concentration of the growth of the cell lines got reduced by 50%. The WST-1 colorimetric assay was used to evaluate the growth inhibitory effects of sodium sulfadiazine, derivatives of dithiocarbamates, oxovanadium(IV) and zinc(II) complexes. They were screened for cytotoxic activities as potential anticancer drugs. Culture of the cells was done using 96 well cell culture plates of a density of 200 000 cells/well. After 24 h, the culture medium was removed and substituted with culture medium which contained increasing concentrations (6.25- 50 μM) of the sample compounds. Stock solutions of the compounds were prepared in dimethylsulfoxide, DMSO, whereas, the working solutions were prepared in culture medium. Untreated cells were used as a negative control, while Cisplatin was used for positive control. All treatments were done in triplicates for 24 h, ensue

the treatment, 10 µL of WST-1 reagent was added to the wells and the cell plates were incubated at 37ºC for 4 h. BMG Labtech POLAR star Omega micro plate reader was used to determine the absorbance/optical density of the wells. Percentage of cell viability was calculated by comparing the absorbance of the test samples with the absorbance of the control (untreated) samples, as described by the manufacturer. The primary screening of derivatives of dithiocarbamates and some zinc(II) complexes was done with non-cancerous fibroblast cell line, KMST-6 and human colon cancer line, HT-29. Secondary screening involving IC_{50} was done for sample compounds. The IC_{50} value of the cell growth was less than 50% and can be said to be active with a concentration of 20 µM.

5.2.2 Results and discussion on *in vitro* WST-1 assay cytotoxicity studies

Some dithiocarbamate ligands (with the exception of sodium sulfadiazine) and some zinc(II) complexes were tested on two cancer cell lines (a non-cancerous cell line, KMST-6, and a cancerous cell line, HT-29 for primary screening. The results are displayed in Table 5.1. A concentration of less than 20 µM and lowest IC_{50} results indicate very active compounds [11]. Both ligands and zinc complexes were not very active against the resistant KMST-6 cell line, with a display of IC_{50} greater than 50. These were also reflected in the control and standard with IC_{50} above 50. For HT-29 cell line, the primary screening proved both ligands and zinc complexes as active compounds with concentrations less than 20 µM, therefore, all showed cytotoxic activities, with the exception of [Zn(SFZ)(me-DTC)]. Measuring the selectivity of the compounds with available data, the selectivity indices were calculated. They showed all forms of selectivity because they were within the range of 1-8.

5.2.2.1 Selectivity Index [11]

The aim of selectivity index is to further see if the samples can go into the next phase of drug development (drug discovery). To obtain results for selectivity index, IC_{50} of KMST-6 (µM) must be divided by IC_{50} of HT-29 (µM).

For example, [Zn(SFZ)(me-DTC)], 50/31.60 (100) = 1.58

Table 5.1: Secondary screening results for both cell lines (KMST-6 and HT-29) and their selectivity indices**.**

Compounds	$IC_{50}$for KMST-6 (μM)	$IC_{50}$for HT- 29 (μM)	Selectivity Index
an-DTC	> 50	< 6.25	8
et-DTC	> 50	< 6.25	8
bu-DTC	> 50	11.06	4.52
de*-DTC	> 50	18.06	2.77
[Zn(SFZ)(me-DTC)]	> 50	31.60	1.58
[Zn(SFZ)(et-DTC)]	> 50	< 6.25	8
[Zn(SFZ)(cl-DTC)]	> 50/ 64.773	15.87	4.08
[Zn(SFZ)(bu-DTC)]	> 50	< 6.25	8
[Zn(SFZ)(he-DTC)]	> 50	< 6.25	8
Cisplatin	82.10	76.61	1
DMSO (Control)	100	100	1

Slight selectivity: Selective Index of 0-2; Moderate selectivity: Selective Index of 2-6; Active selectivity: > 6.

5.3 *In vitro* cytotoxicity (SRB) assay cancer screening of some oxovanadium(IV) and zinc(II) complexes

5.3.1 Assay Background

The cytotoxic effects of the compounds were tested by Sulforhodamine B (SRB) assay on the WI38 cell line.The SRB assay was developed by Skehan and colleagues to measure drug-induced cytotoxicity and cell proliferation. Its principle is based on the ability of the protein dye sulforhodamine B (Acid Red 52) to bind electrostatically in a pH-dependent manner to protein basic amino acid residues of trichloroacetic acid-fixed cells. Under mild acidic conditions it binds to the fixed cellular protein, while under mild basic conditions it can be

extracted from cells and solubilized for measurement. The SRB Assay is performed at CSIR in accordance with the protocol of the Drug Evaluation Branch, NCI, and the assay has been adopted for this screen.

5.3.2 Materials and method

The W1-38 cell line- normal Human Fetal Lung Fibroblast from ECACC was routinely maintained as a monolayer cell culture at 37ºC, 5% CO_2, 95% air and 100% relative humidity in EMEM containing 10% foetal bovine serum, 2 mL-glutamine and 50 µg/ml gentamicin.

For screening experiment, the cells (21-50 passages) were inoculated in a 96-well microtiter plates at plating densities of 10 000 cells/well and were incubated for 24 h. After 24 h the cells were treated with the experimental drugs which were previously dissolved in DMSO and diluted in medium to produce 5 concentrations. Cells without drug addition served as control. The blank contains complete medium without cells. Emetine was used as a standard.

The plates were incubated for 48 h after addition of the compounds. Viable cells were fixed to the bottom of each well with cold 50% trichloroacetic acid, washed, dried and dyed by SRB. Unbound dye was removed and protein-bound dye was extracted with 10 mM Tris base for optical density determination at the wavelength 540 nm using a multiwell spectrophotometer. Data analysis was performed using GraphPad Prism software. 50% of cell growth inhibition (IC_{50}) was determined by non-linear regression.

5.3.3 Results and discussion on *in vitro* SRB assay cytotoxicity studies

After successful syntheses and chemical characterization of mixed oxovanadium(IV) and zinc(II) complexes. Sulforhodamine B assay was used to determine the *in vitro* cytotoxities of these metal complexes [544]. Results for the *in vitro* cytotoxities' tests can be seen in Table 5.2. The interpretations of the results were based on The Council for Scientific and Industrial Research (CSIR) standard criteria in Table 5.3. Four oxovanadium(IV) and one zinc(II) complexes: [VO(SFZ)(to-DTC)], [VO(SFZ)(tu-DTC)], [VO(SFZ)(ml-DTC)], [VO(SFZ)(ey-DTC)] and [Zn(SFZ)(to-DTC)] were of low hazard to cancer cell line of W1-38. Weak hazard was discovered in zinc(II) complex of [Zn(SFZ)(as-DTC)] . In the case of moderate hazards on cancer cell line of W1-38, six oxovanadium(IV) complexes and two zinc(II)

complexes : [VO(SFZ)(tl-DTC)], [VO(SFZ)(as-DTC)] [VO(SFZ)(cc-DTC)], [VO(SFZ)(hx-DTC)], [VO(SFZ)(bt-DTC)] and [VO(SFZ)(cl-DTC)], [Zn(SFZ)(tu-DTC)] and [Zn(SFZ)(hy-DTC)] were noted. None of the mixed ligand metal complexes was of high hazard and none had IC_{50} less than the standard drug of emetine. Based on observation, both [VO(SFZ)(to-DTC)] and [Zn(SFZ)(to-DTC)] were of low hazards, while [VO(SFZ)(cc-DTC)] and [Zn(SFZ)(cc-DTC)] were of moderate hazards.

Table 5.2: The *in vitro* cytotoxicity screening for oxovanadium(IV) and zinc(II) complexes**.**

Compound	IC_{50} for W1-38 (μM)
[VO(SFZ)(to-DTC)]	> 100
[VO(SFZ)(tu-DTC)]	> 100
[VO(SFZ)(tl-DTC)]	29.9
[VO(SFZ)(as-DTC)]	33.9
[VO(SFZ)(cc-DTC)]	16.3
[VO(SFZ)(ml-DTC)]	> 100
[VO(SFZ)(el-DTC)]	> 100
[VO(SFZ)(hx-DTC)]	23.3
[VO(SFZ)(bt-DTC)]	21.9
[VO(SFZ)(cl-DTC)]	31.9
[Zn(SFZ)(to-DTC)]	> 100
[Zn(SFZ)(tl-DTC)]	> 100
[Zn(SFZ)(tu-DTC)]	24.4
[Zn(SFZ)(as-DTC)]	71.7
[Zn(SFZ)(cc-DTC)]	22.1
[Zn(SFZ)(hy-DTC)]	> 100

Emetine	0.05

Table 5.3: The Council for Scientific and Industrial Research (CSIR) standard criteria for *in vitro* cancer screening according to IC_{50}**.**

IC_{50} (μM)	Status
> 100	Low hazard
< 100	Weak hazard
> 50	Weak hazard
< 50	Moderate hazard
> 10	Moderate hazard
< 10	High hazard

5.4. *In vitro* cancer screening

5.4.1. Sulforhodamine B (SRB) assay background of *in vitro* cancer screening [540-542]

The growth inhibitory effects of the compounds were tested in a 3-cell line panel consisting of TK10 (renal), UACC62 (melanoma) and MCF7 (breast) cancer cells by Sulforhodamine B (SRB) assay.The SRB assay was developed by Skehan and colleagues to measure drug-induced cytotoxicity and cell proliferation [543]. Its principle is based on the ability of the protein dye Sulforhodamine B (Acid Red 52) to bind electrostatically in a pH-dependent manner to protein basic amino acid residues of trichloroacetic acid-fixed cells. Under mild acidic conditions it binds to the fixed cellular protein, while under mild basic conditions it can be extracted from cells and solubilized for measurement. The SRB Assay is performed at CSIR in accordance with the protocol of the Drug Evaluation Branch, NCI, and the assay has been adopted for this screen.

5.4.2 Materials and method

The human cell lines TK10, UACC62 and MCF7 was obtained from NCI in the framework a collaborative research program between CSIR and NCI. Cell lines was routinely maintained as a monolayer cell culture at 37ºC, 5% CO_2, 95% air and 100% relative humidity in RPMI containing 5% fetal bovine serum, 2 mM L-glutamine and 50 µg/ml gentamicin.

For screening experiment, the cells (3-19 passages) were inoculated in a 96-well micro titer plates at plating densities of 7-10 000 cells/well and were incubated for 24 h. After 24 h the cells were treated with the experimental drugs which were previously dissolved in DMSO and diluted in medium to produce 5 concentrations. Cells without drug addition served as control. The blank contains complete medium without cells. Parthenolide was used as a standard.

The plates were incubated for 48 h after addition of the compounds. Viable cells were fixed to the bottom of each well with cold 50% trichloroacetic acid, washed, dried and dyed by SRB. Unbound dye was removed and protein-bound dye was extracted with 10mM Tris base for optical density determination at the wavelength 540 nm using a multiwell spectrophotometer.

Data analysis was performed using GraphPad Prism software. 50% of cell growth inhibition (IC50) was determined by non-linear regression.

5.4.3 The *in vitro* cancer screening studies

Ten oxovanadium(IV) and six zinc(II) complexes were screened for *in vitro* cancer activities, against three cancer cell lines. These cancer cell lines are TK10 (renal), UACC62 (melanoma) and MCF7 (breast). Parthenolide was used as the standard drug and the control as dimethylsulfoxide.

The anticancer activities of these sixteen mixed ligand complexes standard and control were determined with SRB assay on the three cancer cells [543]. The results obtained can be seen in Table 5.4. The explanation of the results was based on CSIR criteria in Table 5.5. For cancer cell line of TK-10 (renal), two oxovanadium(IV) complexes: [VO(SFZ)(ml-DTC)], [VO(SFZ)(ey-DTC)] and three zinc(II) complexes: [Zn(SFZ)(to-DTC)], [Zn(SFZ)(tu-DTC)] and [Zn(SFZ)(hy-DTC)] were inactive. Four oxovanadium(IV) complexes: [VO(SFZ)(to-DTC)], [VO(SFZ)(tu-DTC)], [VO(SFZ)(as-DTC)] [VO(SFZ)(bt-DTC)] and one zinc(II)

complex of [Zn(SFZ)(as-DTC)] gave weak activities against TK-10. Moderate activities against TK-10 were observed in four oxovanadium(IV) complexes: [VO(SFZ)(tl-DTC)], [VO(SFZ)(cc-DTC)], [VO(SFZ)(hx-DTC)], [VO(SFZ)(cl-DTC)], and two zinc(II) complexes of [Zn(SFZ)(tu-DTC)] and [Zn(SFZ)(cc-DTC)]. No metal had a potent activity and higher than the standard drug.

In the case of the cancer cell line of UACC62 (melanoma), an oxovanadium(IV) complex of [VO(SFZ)(ml-DTC)] and zinc(II) complexes of Zn(SFZ)(to-DTC)], [Zn(SFZ)(tu-DTC)] and [Zn(SFZ)(hy-DTC)] were inactive. An oxovanadium(IV) complex of [VO(SFZ)(ey-DTC)] was found with weak activity. Moderate activities were observed in seven oxovanadium(IV) complexes of [VO(SFZ)(to-DTC)], [VO(SFZ)(tu-DTC)], [VO(SFZ)(tl-DTC)], [VO(SFZ)(as-DTC)], [VO(SFZ)(cc-DTC)], [VO(SFZ)(hx-DTC)], [VO(SFZ)(bt-DTC)] and three zinc(II) complexes of [Zn(SFZ)(tu-DTC)], [Zn(SFZ)(as-DTC)] and [Zn(SFZ)(cc-DTC)]. Oxovanadium(IV) complex of [VO(SFZ)(cl-DTC)] had very high activity.

For the cancer cell line of MCF-7 (breast), two zinc(II) complexes: [Zn(SFZ)(ml-DTC)] and [Zn(SFZ)(ml-DTC)] were inactive. Two oxovanadium(II) complexes: [VO(SFZ)(ml-DTC)] [VO(SFZ)(ey-DTC)] and one zinc(II) complex of [Zn(SFZ)(hy-DTC)] had weak activities. Moderate activities were observed in six oxovanadium(IV) complexes: [VO(SFZ)(to-DTC)], [VO(SFZ)(tu-DTC)], [VO(SFZ)(tl-DTC)], [VO(SFZ)(as-DTC)], [VO(SFZ)(cc-DTC)] [VO(SFZ)(bt-DTC)] and zinc(II) complexes: [Zn(SFZ)(tu-DTC)], [Zn(SFZ)(as-DTC)] and [Zn(SFZ)(cc-DTC)]. Oxovanadium(IV) complexes of [VO(SFZ)(hx-DTC)] and [VO(SFZ)(cl-DTC)] were of high activities. The IC_{50} of the standard drug, Parthenolide is higher than all the compounds. According to CSIR criteria, a sample is categorized to have potent activity if the parameter IC_{50} for two or three cancer cell lines is less than 10 μM. Oxovanadium(IV) complex of potent activity is [VO(SFZ)(hx-DTC)] has IC50 of 6.97 μM, which is less than 10 μM, but only against MCF7 cancer cell line. The only compound found in this category is [VO(SFZ)(cl-DTC)]. This might be due to a study that chloro- substituents are biologically active against breast, colon and lung cancer cell lines [545].

Table 5.4: *In vitro* cancer screening of oxovanadium(IV) and zinc(II) complexes**.**

Compound	IC50 for TK-10 (μM)	IC50 for UACC-62 (μM)	IC50 for MCF-7 (μM)
[VO(SFZ)(to-DTC)]	59.13	47.97	38.21
[VO(SFZ)(tu-DTC)]	81.22	49.81	33.34
[VO(SFZ)(tl-DTC)]	30.65	15.84	15.43
[VO(SFZ)(as-DTC)]	73.23	49.14	33.27
[VO(SFZ)(cc-DTC)]	28.27	12.51	12.80
[VO(SFZ)(ml-DTC)]	> 100	> 100	62.36
[VO(SFZ)(ey-DTC)]	> 100	> 64.02	50.65
[VO(SFZ)(hx-DTC)]	11.15	15.18	6.97
[VO(SFZ)(bt-DTC)]	75.95	49.98	28.75
[VO(SFZ)(cl-DTC)]	36.00	5.92	7.10
[Zn(SFZ)(to-DTC)]	> 100	> 100	> 100
[Zn(SFZ)(tl-DTC)]	> 100	> 100	102.00
[Zn(SFZ)(tu-DTC)]	22.71	24,53	16.08
[Zn(SFZ)(as-DTC)]	66.52	32.03	23.10
[Zn(SFZ)(cc-DTC)]	23.19	18.28	13.60
[Zn(SFZ)(hy-DTC)]	> 100	> 100	80.37
Parthenolide	4.64	11.37	3.52

Table 5.5: The Council for Scientific and Industrial Research (CSIR) standard criteria for *in vitro* cancer screening according to IC_{50}**.**

IC_{50} (μM)	Status
> 100	Inactive
< 100	Weak activity
> 50	Weak activity
< 50	Moderate activity
> 10	Moderate activity
< 10	Potent activity

5.5. Antibacterial studies

5.5.1. Materials and methods for antibacterial studies

5.5.1.1. Bacterial strains, disc susceptibility tests and growth conditions

The antibacterial screening exercise was carried out at the Department of Pharmacy and Pharmacology in University of Bath, United Kingdom.

Antimicrobial susceptibility test was carried out on four bacterial strains used. They were *Staphylococcus aureus* (MRSA252), *Enterococcus faecalis* (BS385), *Escherichia coli* (MC4100) *and Pseudomonas aeruginosa* (PA01). Bacterial strains were maintained on Tryptone Soy Agar (TSA; Oxoid). The media used fresh Mueller Hinton broth.

Bacterial cell lines of *S. aureus*, *E. coli, E. faecalis* and *P. aeruginosa* cultures were grown in Mueller Hinton (MH; Oxoid) broth to an optical density (at 600 nm) of approximately 1, and then diluted to 10^6 cells/mL in fresh MH broth. 100μl of this was placed on MH agar plates. Next, 6 mm paper disks (Whatman 3MM chromatography paper), loaded with 50 μg of compound (stock solutions 10mg/mL in DMSO), were deposited on top of the agar. The plates were then incubated at 37ºC, and after 24 h the zone of inhibition around the disks was recorded.

There is no standard amount in disks that applies to all antibiotics. Some are use at 30 μg but many others are used at different concentrations. Disks contain 1, 2, 5, 10, 15 or 30 μg depending on the antibiotic. The amount used is based on what is workable; if a disk would give an enormous zone of inhibition at 30 μg, then it would be better to go lower. Similarly, if an antibiotic has rather low activity, a higher amount is needed. Well, there is no certainly for a concentration higher than 30 μg. More generally, for new compounds, it may be desirable to test initially at fairly high concentrations in order to check if there is activity at all.

5.5.1.2. Antibacterial screening activities [11]

The aim was to explore the antibacterial potencies and potentials of sodium sulfadiazine, derivatives of dithiocarbamates, oxovanadium(IV) and zinc(II) complexes to inhibit bacterial growth by screening against four bacterial strains of *Staphylococcus aureus* (MRSA252), *Enterococcus faecalis* (BS385), *Escherichia coli* (MC4100) and *Pseudomonas aeruginosa (*PA01). The results had been displayed in Figures 5.6 to 5.8 for zone of inhibition (ZOI) of ligands, oxovanadium(IV) and zinc(II) complexes respectively. The solvent, dimethylsulfoxide, (DMSO) was used as a negative control, which showed no activity against all the four bacterial strains. The positive control was 30 μg of tetracycline for *Staphylococcus aureus* and 28 μg *Escherichia coli*. Other positive controls used were vancomycin and meropenem for *Enterococcus faecalis* and *Pseudomonas aeruginosa* respectively. Both ligands and metal complexes were screened *in vitro* against two Gram positive bacteria (*Staphylococcus aureus* and *Enterococcus faecalis)* and Gram negative bacteria (Escherichia *coli* and *Pseudomonas aeruginosa).* Well diffusion method was used, while the nutrient medium was agar.

5.5.2. Activity Index [11]

The activity of both ligands and metal complexes could not be compared to the antibiotic, tetracycline, because of the variances in the masses for Staphylococcus *aureus* and *Escherichia coli*. Each sample had a mass of 50 μg per disc, while tetracycline of commercial disc used in hospitals had 30 μg. As aforementioned, no activity index could be done. 50 μg

per disc used were vancomycin and meropenem for *Enterococcus faecalis* and *Pseudomonas aeruginosa* respectively.

% Activity Index=A/B*100

where A is ZOI of sample compound

B is ZOI of standard (positive control)

For hx-DTC=22.5/22*100=102%

[VO(SFZ)(hhDTC)], activity index=22/22*100=100%

$ZnCl_2$=27/22*100=123%

5.5.3 Minimum Inhibitory Concentration (MIC)

Minimum inhibitory concentration is the lowest drug concentration where a visible inhibition in the growth of the microorganisms can be identified (546, 547). The minimum inhibitory concentrations (MIC) values for the compounds were determined with a micro dilution broth method using MH broth as described (546, 547). MIC gives the inhibition screening concentration of sample compounds. MIC serves as a secondary screening after the *in vitro* primary antibacterial screening test had been done to give ZOI of sample compounds.

For the MIC secondary screening, nineteen sample compounds were screened against *Staphylococcus aureus*, fifteen samples against *Enterococcus faecalis*, twenty sample compounds *Escherichia coli* and fifteen sample compounds against *Pseudomonas aeruginosa*. All selected sample compounds for MIC had zone of inhibition of above 11 mm.

5.6 *In vitro* studies

This section looks into *in vitro* cytotoxicity and antibacterial studies of sodium sulfadiazine, dithiocarbamate ligands, oxovanadium(IV) and zinc(II) complexes.

5.6.1 Antibacterial studies

The results for the zone of inhibition of antibacterial activities for all the ligands are shown in Table 5.6. Four bacterial strains of *Staphylococcus aureus* (MRSA252), *Enterococcus faecalis* (BS385), *Escherichia coli* (MC4100) and *Pseudomonas aeruginosa* (PA01) were considered for the antibacterial activities.

All the ligands were inactive against the bacterial cell line of *Pseudomonas aeruginosa*. For *Escherichia coli*, only SFZ (17 mm), eh-DTC (6.7 mm), he-DTC (6.7 mm) and hx-DTC (18.7 mm) were active while the other ligands were inactive. In reference to gram- positive bacterial strain of *Enterococcus faecalis*, only three ligands were active while the other ligands were inactive. These ligands are he-DTC (6.5 mm), ea-DTC (6.5 mm) and hx (22.5 mm). Ligand of hx-DTC is 0.5 mm higher than the positive standard, vancomycin. The other gram positive bacterial strain; *Staphylococcus aureus*, had more than half of the ligands active against it. The ligands were SFZ (17 mm), cy-DTC (8 mm), he-DTC (11.3 mm), ch-DTC (6.7 mm), tl-DTC (9.3 mm), ai-DTC(8 mm), to-DTC(6.5 mm), as-DTC (6.5 mm), de-DTC (16 mm), mt-DTC (7.3 mm), el-DTC(6.2 mm), hy-DTC (6.7 mm), bt-DTC(8.7 mm), ea-DTC (12.7 mm), hx-DTC (40 mm), ey-DTC(8 mm) and hh-DTC(10.7 mm).Ligand of hx-DTC is 10 mm higher than the positive standard, tetracycline. Among all the ligands, hx-DTC had the highest zone of inhibition against all bacterial strains, with the exception of *Pseudomonas aeruginosa*. Ligand of hx-DTC can be said to have a broad spectrum because of its activity against both gram positive and gram negative.

Table 5.7 shows results for the zones of inhibition of vanadyl(IV) sulfate and fourteen mixed oxovanadium(IV) complexes of sodium sulfadiazine and derivatives of dithiocarbamate. Vanadyl(IV) sulfate was inactive to the four bacterial strains. Six oxovanadium(IV) complexes were still inactive against *Pseudomonas aeruginosa* like their corresponding ligands, while eight oxovanadium(IV) complexes were active against *Pseudomonas aeruginosa*. Eight oxovanadium(IV) complexes underwent synergism compared to their corresponding ligands. For the bacterial strain of *Escherichia coli*, three inactive oxovanadium(IV) complexes, namely; [VO(SFZ)(to-DTC)], [VO(SFZ)(as-DTC)] and [VO(SFZ)(tu-DTC)] were not active like their corresponding ligands. The other eleven oxovanadium(IV) complexes were active against *Escherichia coli* and synergistic mechanisms were observed in comparison with their corresponding dithiocarbamate ligands. All oxovanadium(IV) complexes had antagonistic effect against *Escherichia coli* as

compared with ligand of SFZ, with zone of inhibition of 16.3 mm The only exemption is [VO(SFZ)(bt-DTC)] with zone of inhibition of 17 mm. Oxovanadium(IV) complexes of [VO(SFZ)(ai-DTC)], [VO(SFZ)(bt-DTC)], [VO(SFZ)(to-DTC)], [VO(SFZ)(as-DTC)] [VO(SFZ)(tl-DTC)] and [VO(SFZ)(tu-DTC)] were inactive against *Enterococcus faecalis*, while the other oxovanadium(IV) complexes were active. Oxovanadium(IV) complex of [VO(SFZ)(hx-DTC)] of zone of inhibition of 12 mm had an antagonistic mechanism compared to the corresponding ligand, hx-DTC with zone of inhibition of 22.5 mm. All the oxovanadium(IV) complexes were active *Staphylococcus aureus*, with the exception of [VO(SFZ)(ai-DTC)] and [VO(SFZ)(to-DTC)]. Oxovanadium(IV) complex of [VO(SFZ)(hx-DTC)] with zone of inhibition of 19.7 mm had an antagonistic mechanism against *Staphylococcus aureus* compared with the corresponding ligand , hx-DTC with zone of inhibition of 40 mm. For the ligand of SFZ, with zone of inhibition of 17 mm against *Staphylococcus aureus*, others had antagonistic mechanisms except for [VO(SFZ)(an-DTC)],[VO(SFZ)(hx-DTC)] and [VO(SFZ)(to-DTC)] with zones of inhibition of 20.7 mm, 19.7 mm and 40 mm respectively. Oxovanadium(IV) complex of [VO(SFZ)(hh-DTC)] with zone of inhibition of 22 mm had the same with zone of inhibition as the positive standard, vancomycin. Eight oxovanadium(IV) complexes were broad spectrum antibacterial oxovanadium agents.

According to Table 5.5, there were results for zones of inhibition for anhydrous zinc(II) chloride and nineteen zinc(II) complexes of mixed sodium sulfadiazine and derivatives of dithiocarbamate. Anhydrous zinc(II) chloride was active to all the four bacterial cell lines. Among these nineteen complexes of zinc(II), only three zinc(II) complexes were inactive against *Pseudomonas aeruginosa* like their corresponding DTC ligand ([Zn(SFZ)(de*-DTC)],[Zn(SFZ)(et-DTC)] and [Zn(SFZ)(hy-DTC)]. Three zinc(II) complexes had antagonistic mechanisms compared to anhydrous zinc(II) chloride([Zn(SFZ)(cl-DTC)],[Zn(SFZ)(ea-DTC)] and [Zn(SFZ)(hy-DTC)]) while [Zn(SFZ)(he-DTC)] had the same value of zone of inhibition as 9 mm as anhydrous zinc(II) chloride. All the zinc complexes with the exception of ([Zn(SFZ)(cl-DTC)], [Zn(SFZ)(ea-DTC)] and [Zn(SFZ)(hy-DTC)] had synergistic mechanisms compared to their corresponding dithiocarbamate ligands.

For the bacterial strain of *Escherichia coli*, all the zinc(II) complexes had synergism when compared with anhydrous zinc(II) chloride of 9.3 mm, The exempted zinc(II) complexes were [Zn(SFZ)(tl-DTC)] and [Zn(SFZ)(to-DTC)] with zones of inhibition of 8.7 mm and 9.0

mm respectively. All the zinc(II) complexes had antagonistic effects with the exception of zinc(II) complexes of [Zn(SFZ)(cl-DTC)] and [Zn(SFZ)(hx-DTC)] when compared with ligand of SFZ. There were synergistic effects for all zinc(II) complexes with the exception of ([Zn(SFZ)(hx-DTC)] when compared with the ligand of dithiocarbamates. The zone of inhibition of the positive standard, tetracycline, is highest when compared to the zones of inhibition of anhydrous zinc(II) chloride and zinc(II) complexes. Antagonism was encountered for all activities of zinc(II) complexes when compared to the zone of inhibition of anhydrous zinc(II) chloride against *Enterococcus faecalis*. Nine zinc(II) complexes were inactive like their corresponding ligands of SFZ and DTC. For the ligands of DTCs, [Zn(SFZ)(hx-DTC)] had a lower zone of inhibition of 12 mm than the ligand, hx-DTC of 22 mm. The remaining nine zinc(II) complexes had synergism when compared with the corresponding ligands of SFZ and DTCs. None of the zinc(II) complexes had values higher than the positive standard, vancomycin. Four zinc(II) complexes of [Zn(SFZ)(bu-DTC)], [Zn(SFZ)(bt-DTC)], [Zn(SFZ)(hx-DTC)], and [Zn(SFZ)(cc-DTC)] had higher zones of inhibition than the zone of inhibition for $ZnCl_2$ with their activities against *Staphylococcus aureus*. Only zinc complex of [Zn(SFZ)(hx-DTC)]among the nineteen zinc(II) complexes had synergism due to its higher zone of inhibition than the ligand of SFZ. Zinc(II) complexes of [Zn(SFZ)(de-DTC)], [Zn(SFZ)(hx-DTC)] and [Zn(SFZ)(to-DTC)] had antagonism compared to their corresponding ligands, while the other sixteen zinc(II) complexes had synergism. None of the zinc(II) complexes had higher values than the positive control., tetracycline, but most had potentials for activities against *Staphylococcus aureus*.

Table 5.6: Zone of inhibition for antibacterial susceptibility test for ligands of sodium sulfadiazine and derivatives of dithiocarbamate**.**

Ligands	*Staphylococcus aureus* MRSA252 (mm)	*Enterococcus faecalis* BS385 (mm)	*Escherichia coli* MC4100(mm)	*Pseudomonas aeruginosa* PA01 (mm)
SFZ	17	ND	16.3	ND
me-DTC	0	ND	0	ND
cy-DTC	8	ND	0	ND

an-DTC	0	ND	0	ND
cl-DTC	0	ND	0	ND
eh-DTC	0	ND	6.7	ND
et-DTC	0	ND	0	ND
he-DTC	11.3	6.5	6.7	ND
cc-DTC	0	ND	0	ND
ch-DTC	6.7	ND	0	ND
tl-DTC	9.3	ND	0	ND
tu-DTC	0	ND	0	ND
ai-DTC	8	ND	0	ND
to-DTC	6.5	ND	0	ND
as-DTC	6.5	ND	0	ND
de-DTC	16	ND	0	ND
mt-DTC	7.3	ND	0	ND
el-DTC	6.2	ND	0	ND
hy-DTC	6.7	ND	0	ND
bt-DTC	8.7	ND	0	ND
ea-DTC	12.7	6.5	0	ND
hx-DTC	40	22.5	18.7	ND
ml-DTC	0	ND	0	ND
ey-DTC	8	ND	0	ND
hh-DTC	10.7	ND	0	ND
Vancomycin		22		

Meropenem				30
Tetracycline	30		28	
DMSO	0	0	0	0

ND=Non Detectable; 0 is equivalent to ND. Positive standards/controls: Vancomycin; Meropenem; Tetracycline. Negative control: DMSO (Dimethylsulfoxide).

Table 5.7: Zone of inhibition for antibacterial susceptibility test of vanadyl (IV) sulfate and oxovanadium(IV) complexes of sodium sulfadiazine and derivatives of dithiocarbamate**.**

Compounds	*Staphylococcus aureus* MRSA 252 (mm)	*Enterococcus faecalis* BS 385 (mm)	*Escherichia coli* MC4100 (mm)	*Pseudomonas aeruginosa* PA01 (mm)
$VOSO_4$	0	NA	0	NA
[VO(SFZ)(me-DTC)]	12.7	15.5	13.3	12
[VO(SFZ)(cy-DTC)]	8	10.5	14.7	11
[VO(SFZ)(an-DTC)]	20.7	16.5	14.7	10
[VO(SFZ)(bt-DTC)]	16.8	14.5	17.0	12
[VO(SFZ)(hx-DTC)]	19.7	12	15.7	10
[VO(SFZ)(de-DTC)]	8.0	NA	8.70	NA
[VO(SFZ)(hh-DTC)]	14.3	22	14.3	13.5
[VO(SFZ)(ai-DTC)]	0	NA	8.0	NA
[VO(SFZ)(hy-DTC)]	12.7	19	9.3	9.5
[VO(SFZ)(to-DTC)]	0	NA	0	NA
[VO(SFZ)(ch-DTC)]	13.7	16.5	15.0	13.5
[VO(SFZ)(as-DTC)]	7.30	NA	0	NA

[VO(SFZ)(tl-DTC)]	40	NA	14.3	NA
[VO(SFZ)(tu-DTC)]	7.0	NA	0	NA
Meropenem				30
Vancomycin		22		
Tetracycline	30		28	
DMSO	0	0	0	0

NA=Not Applicable. Positive standards/controls:Vancomycin;Meropenem;Tetracycline. Negative control: DMSO (Dimethylsulfoxide)

Table 5.8: Zone of inhibition for antibacterial susceptibility test of zinc(II) chloride, zinc(II) complexes of sodium sulfadiazine and derivatives of dithiocarbamate**.**

Compounds	*Staphylococcus aureus* MRSA 252 (mm)	*Enterococcus faecalis* BS 385 (mm)	*Escherichia coli*MC4100 (mm)	*Pseudomonas aeruginosa* PA01 (mm)
$ZnCl_2$	13	27	9.3	9.0
[Zn(SFZ)(bu-DTC)]	16.3	NA	13.0	11.0
[Zn(SFZ)(he-DTC)]	7.7	9.0	15.0	9.0
[Zn(SFZ)(an-DTC)]	7.0	NA	10.0	13.0
[Zn(SFZ)(me-DTC)]	11.7	9.0	16.7	10.0
[Zn(SFZ)(et-DTC)]	6.7	NA	0.0	NA
[Zn(SFZ)(cl-DTC)]	6.7	11.0	12.7	7.0
[Zn(SFZ)(mt-DTC)]	11	13.5	12.70	13.0
[Zn(SFZ)(bt-DTC)]	16	11	16	10.5
[Zn(SFZ)(hx-DTC)]	17.8	12	16.8	10.0
[Zn(SFZ)(de-DTC)]	10.3	12.5	12.70	11.5
[Zn(SFZ)(de*-DTC)]	7.7	NA	12.7	NA
[Zn(SFZ)(ea-DTC)]	9.0	NA	13.0	8.0
[Zn(SFD)(cc-DTC)]	15	11.5	12.7	7.0
[Zn(SFZ)(hy-DTC)]	7	NA	13.7	NA
[Zn(SFZ)(to-DTC)]	0.0	NA	9.0	9.5
[Zn(SFZ)(ml-DTC)]	10.7	NA	13.0	13
[Zn(SFZ)(ey-DTC)]	10.0	NA	14	13

[Zn(SFZ)(as-DTC)]	11.0	9.0	12.0	10.5
[Zn(SFZ)(tu-DTC)]	9.0	8.0	10.3	10.5
Meropenem				30
Vancomycin		22		
Tetracycline	30		28	
DMSO	0	0	0	0

NA=Not Applicable. Positive standards/controls: Vancomycin; Meropenem; Tetracycline. Negative control: DMSO (Dimethylsulfoxide).

5.6.2 Minimum Inhibition Concentration (MIC)

The minimum inhibition concentrations (MIC) of vanadyl(IV) sulfate and anhydrous zinc(II) chloride were both > 128 µg/ml . This indicated they had best activities against *Pseudomonas aeruginosa*. All oxovanadium(IV) complexes and zinc(II) complexes also showed best activities with MIC values of 128 and > 128 µg/mL against *Pseudomonas aeruginosa*, with the exception of two zinc(II) complexes of [Zn(SFZ)(hx-DTC)] and [Zn(SFZ)(hx-DTC)]. The two had most active inhibition of MIC value of 64 µg/mL. Of all the compounds screened against *Escherichia coli* MC4100, the most active and potent was SFZ lignd, with MIC value of 64 µg/mL. Samples of oxovanadium(IV) and zinc(II) complexes had best activities with MIC values at128 and > 128 µg/mL. In the MIC secondary screening against *Enterococcus faecalis*, four oxovanadium(IV) complexes with each having MIC results of 32 µg/mL were of highest activities. They were [VO(SFZ)(bt-DTC)], [VO(SFZ)(hx-DTC)], [VO(SFZ)(hh-DTC)] and [VO(SFZ)(ch-DTC)]. Two zinc(II) complexes each having 64 µg/mL had most active inhibition of MIC against *Enterococcus faecalis*. These were [Zn(SFZ)(mt-DTC)] and [Zn(SFZ)(hx-DTC)] . Minimum Inhibition Concentration (MIC) results can be found in Table 5.9.

Table 5.9: MIC of sample compounds of oxovanadium(IV) and zinc(II) complexes**.**

Compounds	*S.aureus* MRSA252 MIC(μg/mL)	Compounds	*E. faecalis* BS385 MIC (μg/mL)
SFZ	64		
$VOSO_4$	>128	$VOSO_4$	>128
[VO(SFZ)(an-DTC)]	128		
[VO(SFZ)(me-DTC)]	>128	[VO(SFZ)(me-DTC)]	>128
[VO(SFZ)(bt-DTC)]	128	[VO(SFZ)(bt-DTC)]	32
[VO(SFZ)(hx-DTC)]	>128	[VO(SFZ)(hx-DTC)	32
[VO(SFZ)(ch-DTC)]	>128	[VO(SFZ)(ch-DTC)]	32
		[VO(SFZ)(hh-DTC)]	32
Compounds	*E. coli* MC4100 MIC (μg/mL)	Compounds	*P.aeruginosa* PA01 MIC (μg/mL)
SFZ	64		
$VOSO_4$	>128	$VOSO_4$	>128
[VO(SFZ)(an-DTC)]	128		
[VO(SFZ)(me-DTC)]	>128	[VO(SFZ)(me-DTC)]	>128
[VO(SFZ)(bt-DTC)]	128	[VO(SFZ)(bt-DTC)]	>128

[VO(SFZ)(hx-DTC)]	>128	[VO(SFZ)(ch-DTC)]	>128
[VO(SFZ)(cy-DTC)]	>128		
[VO(SFZ)(ch-DTC)]	128		
[VO(SFZ)(hh-DTC)]	128	[VO(SFZ)(hh-DTC)]	128
[VO(SFZ)(tl-DTC)]	>128		
Anhydrous $ZnCl_2$	>128	Anhydrous $ZnCl_2$	>128
		[Zn(SFZ)(an-DTC)]	>128
[Zn(SFZ)(hx-DTC)]	128	[Zn(SFZ)(hx-DTC)]	64
[VO(SFZ)(ea-DTC)]	>128	[VO(SFZ)(mt-DTC)]	64
[Zn(SFZ)(me-DTC)]	>128	[Zn(SFZ)(de-DTC)]	128
		[Zn(SFZ)(hh-DTC)]	>128

Weak inhibition of MIC: >500 μg/mL; Moderate inhibition of MIC: 250-500 μg/mL; Best active inhibition of MIC: 100-250 μg/mL; Most active inhibition of MIC: 50-100 μg/mL; Highest activity of MIC: 1-50 μg/mL.

5.7 Conclusion

The use of WST-1 assay on synthesized ligands of derivatives of dithiocarbamates and zinc complexes of mixed ligands of sodium sulfadiazine and derivatives of dithiocarbamates showed cytotoxic activities against human colon cancer cell HT-29 with a concentration less than 20 μM, except [Zn (SFZ)(me-DTC)]. They all showed no cytotoxic activity towards non-cancerous human fibroblast cell line, KMST-6 with all possessing IC_{50} above 50. Both [Zn (SFZ)(cl-DTC)] and [Zn (SFZ)(de-DTC)] showed moderate selectivity. With the exception of [Zn (SFZ)(me-DTC)], the results proved that they were all good enough to enter secondary screening.

Cytotoxities' tests on mixed oxovanadium(IV) and zinc(II) complexes were carried out with SRB assay revealed moderate hazards of [VO(SFZ)(cc-DTC)] with IC_{50} of 16.3 μM and [Zn(SFZ)(cc-DTC)] with IC_{50} of 22.1 μM.

Results from anticancer studies on mixed oxovanadium(IV) and zinc(II) complexes using SRB assay confirmed the potent activities of [VO(SFZ)(hx-DTC)] and [VO(SFZ)(cl-DTC)], but [VO(SFZ)(cl-DTC)] is more potent than [VO(SFZ)(hh-DTC)].

The *in vitro* antibacterial susceptibility screening test of both ligands and complexes were carried out. All ligands were not active against the bacterial strain of *Pseudomonas aeruginosa*. Oxovanadium(II) complexes: [VO(SFZ)(hh-DTC)] and [VO(SFZ)(ch-DTC)] were the best active oxovanadium(IV) compounds, each having a ZOI of 13.5 mm. Against most bacterial strain of *Enterococcus faecalis*, hx-DTC had the highest activity with ZOI of 22.5 mm. The most active oxovanadium complex was [VO(SFZ)(hh-DTC)] with ZOI of 22 mm. The most active zinc(II) complex was [Zn(SFZ)(mt-DTC)] with ZOI of 13.5 mm. Ligand hx-DTC had the highest activity with zone of inhibition of 40 mm against *Staphylococcus aureus*. For the complexes, most active complexes were [VO(SFZ)(tl-DTC) with ZOI of 40 mm and [Zn(SFZ)(hx-DTC) with ZOI of 17.8 mm. In the case of *Escherichia coli* MC4100, hx-DTC was found to be the most active, with ZOI of 18 mm, while [VO(SFZ)(bt-DTC)] had ZOI of 17 mm was the most active oxovanadium(IV) complex and [Zn(SFZ)(me-DTC)] was the most active zinc(II) sample compound.

In comparison, MIC values for oxovanadium(IV) complexes had four that were of high activities (32 µg/ml). These are [VO(SFZ)(bt-DTC)],[VO(SFZ)(hx-DTC)], [VO(SFZ)(ch-DTC)]and [VO(SFZ)(hh-DTC)].Only one zinc(II) complex of [Zn(SFZ)(bu-DTC)] had highest activity of 32 µg/mL .

CHAPTER SIX

6. Summary of results, conclusion and future prospects

6.1 Summary of results

In this research study, the syntheses, characterizations and biological activities of oxovanadium(IV) and zinc(II) complexes from mixed sodium sulfadiazine and dithiocarbamates are described. This thesis is made up of six chapters.

Chapter one dealt with chemistry of vanadium, zinc, oxovanadium(IV) and its compounds, zinc(II) and its compounds, as well as, their main biological applications as anticancer and antimicrobial agents. Chemistry of the mixed ligands of sodium sulfadiazine and dithiocarbamates and the relevance to medicine were discussed. Studies also involved cancer and micro-organisms and the chemotherapy. This chapter also highlights the problem statement, hypothesis and the aims and objectives. A prior into subsequent chapters was also done.

In chapter two, twenty five ligands which are derivatives of dithiocarbamates were synthesized and characterized with physicochemical and spectroscopic studies (Elemental analysis, FT-IR, ultra-violet visible spectroscopy, UV-Vis and NMR). Results from molar conductivity confirmed the non-electrolytic nature of the ligands, as well as the other ligand; sodium sulfadiazine. Nuclear magnetic resonance confirmed the presence of moieties in both ligands.

Synthesis and characterization techniques which include physicochemical studies, molecular absorption spectrophotometry (FT-IR and Ultra-violet visible spectroscopy) of fourteen oxovanadium(IV) complexes mixed ligands of sodium sulfadiazine and derivatives of dithiocarbamates were covered in chapter three. Results from FT-IR gave the presence of oxovanadium ion and the presence of water of crystallization as hexahydrate in all

oxovanadium(IV) complexes. The FT-IR and UV-Vis confirmed the N_2S_2 coordination of ligands to oxovanadium(IV) ions. Sodium sulfadiazine coordinated through the sulfonamide nitrogen atom, while dithiocarbamates coordinated through the dithiocarbamato sulfur atom to the oxovanadium(IV) ion. Most oxovanadium(IV) complexes could be said to possess octahedral distorted geometries (six- coordinate geometries) from FT-IR and UV-VIS studies.

Chapter four described the syntheses of nineteen zinc(II) complexes of mixed ligands of sodium sulfadiazine and derivatives of dithiocarbamates. This chapter also considered characterization of mixed zinc(II) complexes using physicochemical studies and spectroscopic studies (Elemental analysis, FT-IR, UV-Vis and nuclear magnetic resonance, NMR) of zinc(II) complexes As in oxovanadium(IV) complexes, the FT-IR and UV-Vis confirmed the N_2S_2 coordination of ligands to zinc(II) ions. Sodium sulfadiazine coordinated through the sulfonamide nitrogen atom, while dithiocarbamates coordinated through the dithiocarbamato sulfur atom to zinc(II) ion. Nuclear magnetic resonance confirmed the presence of moieties of both ligands to zinc(II) ion and the impact of coordination with zinc(II) ion. UV-VIS confirmed the tetrahedral geometries of most zinc(II) complexes.

Biological evaluation of the ligands, oxovanadium(IV) and zinc(II) complexes were discussed in chapter five. The biological evaluation entailed cytotoxicity, anticancer and antibacterial activities. The compounds for cytotoxicity tests using WST-1 assay had good anticancer potencies except [Zn(SFZ)(me-DTC)], with a concentration higher than 20 µM. Sulforhodamine (SRB) assay was used on sixteen mixed oxovanadium(IV) and zinc(II) complexes for cytotoxicity evaluation. Results revealed moderate hazards of [VO(SFZ)(cc-DTC)] and [Zn(SFZ)(cc-DTC)] on W1-38 cell line. Anticancer studies on mixed oxovanadium(IV) and zinc(II) complexes with SRB assay confirmed the potent activities of [VO(SFZ)(hx-DTC)] and [VO(SFZ)(cl-DTC)]. For antibacterial activities, the sample compounds which entailed the ligands, oxovanadium(IV) and zinc(II) complexes were most active and best active. None was with a weak activity of MIC value of 500 µg/mL. Oxovanadium(IV) complexes had more antibacterial potencies and potentials than zinc(II) complexes.

6.2 Conclusion

The aims and objectives of this research were to synthesize, characterize and evaluate dithiocarbamate ligands, mixed oxovanadium(IV) and zinc(II) complexes as anticancer and antimicrobial chemotherapeutic agents. No significant difference existed in non-electrolytic status among ligands, oxovanadium(IV) complexes and zinc(II) complexes. The FT-IR supported bidentate N_2S_2 coordination modes in mixed oxovanadium(IV) and zinc(II) complexes. On the other hand, there is a significant difference in the geometries. Mixed oxovanadium(IV) complexes were proposed to be of distorted octahedral geometries (6 coordinate geometries) and mixed zinc(II) complexes were proposed to be of tetrahedral geometries (4 coordinate geometries). Another significant difference to note were the higher MIC and IC_{50} of mixed oxovanadium(II) complexes compared to zinc(II) complexes. The hypothesis that oxovanadium(IV) complexes are less active or of the same activities as mixed zinc(II) complexes were not supported, but the hypothesis that mixed oxovanadium(IV) complexes are more active than mixed zinc(II) complexes was supported for the results of this research. Mixed oxovanadium(IV) complexes are better anticancer and antibacterial agents than zinc(II) complexes because of more mixed oxovanadium(IV) complexes of potent activities.

6.3 Future prospects

The future work to be done still involves some chemical characterization methods and biological activities.

6.4 Chemical characterization

Crystal structures of oxovanadium(IV) and zinc(II) complexes could not be achieved through crystal growth. More efforts with different solvents shall be tried to grow the crystals. While crystal growth will be in place, the samples of these compounds would be subjected to the characterization technique of magnetic susceptibility to obtain the geometries of these samples.

Microwave synthesis will be employed and compared with one pot synthesis used to synthesize dithiocarbamate ligands, mixed oxovanadium(IV) complexes and zinc(II) complexes.

6.5 Other microbiological activities

The antibacterial test shall be done for other bacterial strains of two gram positive (*Bacillus pumilis* and *Bacillus cereus*) and two gram negative bacteria *(Proteus vulgaris* and *Klebsiella pneumonia*).The antifungal and antiviral screening activities of the mixed donor ligands, oxovanadium(IV) and zinc(II) complexes will be done to find out if they have antifungal and antiviral potencies and potentials.

6.6 Cytotoxity test

The robustness of assay performance is important in drug discovery. This will amount to considering high throughput screening (HTS) assay for the mixed complexes.

6.7 Insulin mimetic activities

Ligands, oxovanadium(IV) and zinc(II) complexes should be screened for their insulin mimetic activities.

REFERENCES

1. Storr, T.; Thompson, K. H.; Orvig, C. Design of Targeting Ligands in Medicinal Inorganic Chemistry. *Chem. Soc. Rev.* **2006**, *35*, 534-544.

2. Barrios, A. M., Cohen, S. M.; Lim, M. H. Medicinal Inorganic Chemistry: A Web Themed Issue. *Chem. Commun.* **2013**, *49*, 5910-5911.

3. Mamtani, R.; Stern, P.; Cheema, S. Metals and Diseases: A Global Primary Health Care Perspective. *J. Toxicol.* **2011**, *2011,* 1-11.

4. Warra, A. A. Transition Metal Complexes and Their Application in Drugs and Cosmetics-A Review. *J. Chem. Pharm. Res* .**2011**, *3*, 951-958.

5. Rivasdeen, A.; Loganathan, R.; Palaniandavar, M. Akbarsha, A. Novel Coordination Complexes of a Few Essential Trace Metals: Cytotoxic Properties and Lead Identification for Drug Development of Cancer. *Perspective in Cancer Prevention-Translational Cancer Res*. **2014**, 133-143.

6. Jungwirth, U.; Kowol, C. R.; Keppler, B. K.; Hartinger, C. G. Berger, W.; Heffeter, P. Anticancer Activity of Metal Complexes: Involvement of Redox Processes. *Antiox. Redox Signal.* **2011**, *15,* 1085-1127.

7. Liguori, P. L.; Valentini, A.; Palma, M.; Bellusci, A.; Bernardini, S.; Ghedini, M.; Panno, M. L.; Pettinari, C.; Marchetti, F.; Crispini, A.; Pucci, D. Non-Classical Anticancer Agents: Synthesis and Biological Evaluation of Zinc(II) Heteroleptic Complexes. *Dalton Trans.* **2010**, *39*, 4205-4212.

8. Graf. N.; Lippard, S. J. Redox Activation of Metal-Based Prodrugs as a Strategy for Drug Delivery. *Adv. Drug Deliv. Rev.* **2012**, *64*, 993-1004.

9. Frezza, M. Hindo, S.; Chen, D.; Davenport, A.; Schmitt, S.; Tomco, D.; Dou, Q. P. Novel Metals and Metal Complexes as Platforms for Cancer Therapy. *Curr Pharm Des*. **2010**, *16*, 1813-1825.

10. Jungwirth, U.; Kowol, C. R.; Keppler, B. K.; Hartinger, C. G.; Berger, W.; Heffeter, P. Anticancer Activity of Metal Complexes: Involvement of Redox Processes. *Antioxid. Redox Signal.* **2011**, *15*, 1085-1127.

11. Buczkowska, M. K. Synthesis, Characterization, Antitumor and Antibacterial Activities of Heterocyclic Transition Metal Complexes. PhD Thesis, Ernst-Moritz-Arndt-Universität Greifswald, May, 2011.

12. Medvetz, D. A.; Hindi, K.M.; Panzner, M. J.; Ditto, A. J.; Yun, Y. H.; Youngs, W. J. Anticancer Activity of Ag(I) N-Heterocyclic Carbene Complexes Derived from 4, 5-Dichloro-1 H-Imidazole. *Metal-Based Drugs.* **2008**, *2008*, 1-7.

13. Iqbal, M. A.; Haque, R. A.; Nasri, S. F.; Mjid, A. A.; Ahamed, M. B. K.; Farsi, E.; Fatima, T. Potential of Silver against Human Colon Cancer (Synthesis, Characterization and Crystal Structures of Xylyl (Ortho, Meta, & Para) Linked Bisbenzimidazolium Salts and Ag (I)-NHC Complexes: *In vitro* Anticancer Studies). *Chem. Central J.* **2013**, *7*, 1-17.

14. Sriram, M. I.; Kanth, S. B. M.; Kalishwaralal, K.; Gurunathan, S. Antitumor Activity of Silver Nanoparticles in Dalton's Lymphoma Ascites Tumor Model. *Int. J. Nanomed.* **2010**, *5*, 753-762.

15. Sondi, I.; Slopek-Sondi, B. Silver Nanoparticles as Antimicrobial Agent: A Case Study on *E. coli* as a Model for Gram-Negative Bacteria. *J. Colloid Interface Sci.***2004**, *275*, 177-182.

16. Lansdown, A. B. G. A Pharmacological and Toxicological Profile of Silver as an Antimicrobial Agent in Medical Devices. *Adv. Pharmacolog. Sci.* **2010**, *2010*, 1-16.

17. Rai, M.; Yadav, A.; Gade, A. Silver Nanoparticles as a New Generation of Antimicrobials. *Biotech. Adv.* **2009**, *27*, 76-83.

18. Jung, W. O.; Koo, H. C.; Kim, K. W.; Shin, S.; Kim, S. O.; Park, Y. O. Antibacterial Activity and Mechanism of Action of the Silver Ion in *Staphylococcus aureus* and *Escherichia coli. Appl. Environ. Microbio.* **2008**, *74*, 2171-2178.

19. Sekhon, B. S.; Gandhi, L. Medical Uses of Inorganic Compounds. *Reson.* **2006**, 75-90.

20. Salemo, M.; Garnier-Suillerot, A. Resistance to Arsenic and Antimony-Based Drugs. *Bioinorg. Chem. Appl.* **2003**, *1*, 189-198.

21. Sharma, P.; Perez, D.; Cabrera, A.; Rosas, N. Arias, J. L. Perspectives of Antimony Compounds in Oncology. *Acta Pharmacol Sin.* **2008**, *29,* 881-890.

22. Sathiyajith, C. W. Investigations towards New Multidentate Ligands as Potential Multidentate Imaging Agents. Ph.D. Thesis. The University of Wales, Cardiff. Oct. 2010.

23. Tiekink, E. R. T. Antimony and Bismuth Compounds in Oncology. *Crit. Rev. Oncol/Hematol*, **2002**, *42*, 217-224.

24. Yadav, R. P. Metals in Oncology: An Overview. *Academic Voices*. **2012**, *2*, 54-58.

25. Menezes, J. B.; Silva, T. A.; Grillo, L. A. M.; Dornelas, C. B. Therapeutic Arsenal against Leishmaniases: A Review. *IJTDH*, **2015**, *5*, 101-122.

26. Gibaud, S.; Jaouen, G.; Arsenic-Based Drugs: From Fowler's Solution to Modern Anticancer Chemotherapy. *Top Organomet Chem.* **2010**, *32*, 1-20.

27. Chen, S.; Yan, X.; Chen, Z. Arsenic in Therapy. *Encyclo. Metallopro.* 2013, 131-135.

28. Olaku, O.; White, J. D. Herbal Therapy Use by Cancer Patients: A Literature Review on Case Reports. *Eur. J. Cancer.* **2011**, *47*, 508-514.

29. Zhu, J.; Chen, Z.; Lallemand-Breitenbach, V.; Thé, H. How Acute Promyelocytic Leukaemia Revived Arsenic. *Nature Rev. Cancer*, **2002**, *2*, 705-714.

30. Edmonds, M. The Evolution of Chemistry and Medicine in the 18th and 19th Centuries. *Chem. New Zealand*. **2012**, 123-126.

31. Waxman, S.; Anderson, K. C. History of the Development of Arsenic Derivatives in Cancer Therapy. *Oncol*. **2001**, *6*, 3-10.

32. Mechanisms of Action of Arsenic Trioxide. Miller, W. H.; Schipper, H. M.; Lee, J.S.; Waxman, S. *Cancer Res.* **2002**, *62*, 3893-3903.

33. Fricker, S. P. Medical Uses of Gold Compounds: Past, Present and Future. *Gold Bull*. **1996**, *29*, 53-60.

34. Messori, L.; Marcon, G.; Orioli, P. Gold(III) Compounds as New Family of Anticancer Drugs. *Bioinorg. Chem. Appl.* 2003, *1*, 177-187.

35. Milacic. V.; Fregona, D.; Dou, Q. P. Gold Complexes as Prospective Metal-based Anticancer Drugs. *Histol Histopathol.* **2008**, *23*, 101-108.

36. Ronconi, L.; Fregona, D. The Midas Touch in Cancer Chemotherapy: from Platinum-to-Gold-Dithiocarbamate Complexes. *Dalton Trans.* **2009**, *28*, 10670-10680.

37. Marzano, C.; Roncoli, L.; Chiara, F.; Giron, M. C.; Faustineli, I.; Cristofori, P.; Trevisan, A.; Fregona, D. Gold (III)-dithiocarbamate Anticancer Agents: Activity, Toxicology and Histopathological Studies in Rodents. *Int. J. Cancer.* **2011**, *129*, 487-496.

38. Nardon, C.; Boscutti, G.; Fregona, D. Beyond Platinums: Gold Complexes as Anticancer Agents. *Anticancer Res.* **2014**, *34*, 487-492.

39. Nardon, C.; Schmitt, S. M.; Yang, H.; Zuo, J.; Fregona, D.; Dou, Q. P. Gold(III)-Dithiocarbamate Peptidomimetics in the Forefront of the Targeted Anticancer Therapy: Preclinical Studies against Human Breast Neoplasia. *Plos One*, **2014**, *9,* 1-10.

40. Cattaruzza, L.; Fregona, D.; Mongiat, M.; Ronconi, L.; Fassina, A.; Colombatti, A. Aldinucci, D. Antitumour Activity of Gold(III)-dithiocarbamate Derivatives on Prostate Cancer Cells and Xenografts. *Int. J. Cancer.* **2011**, *128*, 206-215.

41. Novelli, F.; Recine, M.; Sparatore, F.; Juliano, C. Gold(I) complexes as antimicrobial agents. *Farmaco*. **1999**, *54*, 232-236.

42. Glišić, B. D.; Djuran, M. I. Gold Complexes as Antimicrobial Agents: an Overview of Different Biological Activities in Relation to the Oxidation State of thr Gold and the Ligand Structure. *Dalton Trans*. **2014**, *43*, 5950-5969.

43. Bertrand, B.; Casini, A. A Golden Future in Medicinal Inorganic Chemistry: the Promise of Anticancer Gold Organometallic Compounds. *Dalton Trans.* **2014**, *43*, 4209-4219.

44. Milacic, V.; Fregona, D.; Dou, Q. P. Gold Complexes as Prospective Metal-based Anticancer Drugs. *Histol Histopathol.* **2008**, *23*, 101-108.

45. Scorei, R. I.; Radu, P. Boron-Containing Compounds as Preventive and Chemotherapeutic Agents for Cancer. *Anti-Cancer Agents Med. Chem*. **2010**, *10*, 346-351.

46. Baker, S. J.; Ding, C. Z.; Akama, T.; Zhang, Y.; Hernandez, V.; Xia, Y. Therapeutic Potential of Boron-Containing Compounds. *Future Med. Chem.* **2009**, *1*, 1276-1788.

47. Yang, N.; Sun, H. Biocoordination Chemistry of Bismuth: Recent Advances. *Coord. Chem Rev.* **2007**, *251*, 2354-2366.

48. Sadler, P. J.; Li, H.; Su, H. Coordination Chemistry of Metals in Medicine: Target Sites for Bismuth. *Coord. Chem. Rev*. **1999**, *185-186*, 689-709.

49. Stavila, V.; Davidovich R. L.; Gulea, A.; Whitmire, K. H. Bismuth(III) Complexes with Aminopolycarboxylate and Polyaminopolycarboxylate Ligands: Chemistry and Structure. *Coord. Chem. Rev.* **2006**, *250*, 2782-2810.

50. Li, H.; Lai, C. S.; Wu, J.; Ho, P. C.; Vos, D.; Tiekink, E. R. T. Cytotoxicity, Qualitative Structure-Activity Relationship (QSAR), and Anti-tumor Activity of Bismuth Dithiocarbamate Complexes. *J. Inorg. Biochem.* **2007**, *101*, 809-816.

51. Tiwari, V. K.; Shukla, S. K.; Chauhan, V. S.; Kant, R.; Sushma, R.; Tewari, I.C. Antimicrobial, antitumour and Gastroprotective Studies of Some New Water Soluble Organic Derivatives of Bismuth. *Int. J. Pharm. Anal.* **2010**, *2*, 09-14.

52. Bothwell, J. M.; Krabbez, S. W.; Mohan, R. S. Applications of Bismuth(III) Compounds in Organic Synthesis. *Chem. Soc. Rev.* **2011**, *40*, 4649-4707.

53. Osinsky, S. P.; Levitin, I. Y.; Sigan, A. L.; Bubnovskaya, L. N.; Canusevich, I. I.; Campanella, L.; Wardman, P. Redox-Active Cobalt Complexes as Promising Antitumor Agents. *Russ. Chem. Bull. Int. Ed*. **2003**, *52*, 2636-2645.

54. Chang, E. C.; Simmers, C.; Knight, D. A. Cobalt Complexes as Antiviral and Antibacterial Agents. *Pharmaceut.* **2010**, *3*, 1711-1728.

55. Chohan, Z. H.; Arif, M.; Akhtar, M. A. Supuran. Metal- Based Antibacterial and Antifungal Agents: Synthesis, Characterization and In Vitro Biological Evaluation of Co(II), Cu(II), Ni(II) and Zn(II) Complexes with Amino Acid-Derived Compounds. *Bioinorg. Chem. App.* **2006**, *2006*, 1-13.

56. Singh, K.; Kumar, Y.; Puri, P.; Sharma, C.; Aneja, K. R. Thermal, Spectral, Fluorescence and Antimicrobial of Cobalt, Nickel, Copper and Zinc Complexes Derived from 4-[(5-Bromo-Thiphen-2-ylmethylene)-amino]-3-mercapto-6-methyl-5-oxo-{1, 2, 4] triazines. *Int. J. Inorg. Chem*. **2012**, *2012*, 1-9.

57. Saha, S.; Dhanasekarani, D.; Chandraleka, S.; Panneerselvam, A. Synthesis, Characterization and Antimicrobial Activity of Cobalt Metal Complex against Multidrug Resistant Bacterial and Fungal Pathogens. *Phy. Chem. Tech.* **2009**, *7*, 73-80.

58. Aiyelabola, T. O.; Ojo, I. A.; Adebajo, C. A.; Ogunlusi, A. O.; Oyetunji, O.; Akinkunmi, E. O.; Adeoye, A. O. Synthesis, Characterization and Antimicrobial Activities of Some Metal(II) Amino Acids' Complexes. *Adv. Bio.Chem.* **2012**, *2*, 368-273.

59. Ahmad, M.; Afza, M. Tabassum, S.; Kalińska, B.; Mrozinski, J.; Bharadwaj, P. Synthesis and Structure Elucidation of a Cobalt (II) Complex as Topoisomerase I Inhibitor: In vitro DNA binding, nuclease and RBC Hemolysis. *Euro. J. Med. Chem.* **2014**, *74*, 683-693.

60. Goodman, V. L.; Brewer, G. J.; Merajver, S. D. Copper Deficiency as an Anti-cancer Strategy. *Endocrine-Related Cancer*. **2004**, *11*, 255-263.

61. Wang, F.; Jiao, P.; Qi, M.; Frezza, M.; Dou, Q. P.; Yan, B. Turning Tumor-Promoting Copper into an Anti-Cancer Weapon via High-Throughput Chemistry. *Curr. Med. Chem.* **2010**, *17*, 2685-2698.

62. Grass, G.; Rensing, C.; Solioz, M. Metallic Copper as Antimicrobial Surface. *Appl. Env. Microbio.* **2011**, *77*, 1541-1547.

63. Iakovidis, I.; Delmaris, I.; Piperakis, S. M. Copper and Its Complexes in Medicine: A Biochemical Approach. *Mol. Bio. Int.* **2011**, *2011*, 1-13.

64. Plotek, M.; Durek, K.; Kyziol, A. Selected Copper(I) Complexes as Potential Anticancer Agent. *Chemik.* **2013**, *67*, 1181-1190.

65. Singh. A. P.; Kaushik, N. K.; Verma, A. K.; Gupta, R. Synthesis, Structure and Anticancer Activities of Copper(II) Complexes of *N*-Benzyl-2-(Diethyl amino) Acetanide and (2-Diethylamino)-*N*-Phenylethylacetanide. *Ind. J. Chem.* **2011**, *50a*, 474-483.

66. Santini, C.; Pellei, M.; Gandin, V.; Poschia, M.; Tisalo, F.; Marzano, C. Advances in Copper Complexes as Anticancer Agents. *Chem. Rev*. **2014**, *114*, 815-852.

67. Liu, H.; Yan, W.; Zhou, W.; Xu, Y.; Xie, J.; Li, Mengying. Crystal Structures and Antimicrobial Activities of Copper(II) Complexes. *Inorg. Chimica Acta.* **2013**, *405*, 387-394.

68. Ibrahim, S. A.; Yang H.; Seo, C. W. Antimicrobial Activity of Lactic Acid and Copper on Growth of *Salmonella* and *Escherichia coli* 0157:H7 in Laboratory Medium and Carrot Juice. *Food Chem*. **2008**, *109*, 135-143.

69. Stănilă, A.; Braicu, C.; Stănilă, S.; Pop, R. M. Antibacterial Activity of Copper and Cobalt Amino Acids Complexes. *Not Bot Horti Agrobo*, **2011**, *39,* 124-129.

70. Leite, G. C.; Padoveze, M. C.; Copper as an Antimicrobial Agent in Healthcare: An Integrative Literature Review. *J. Infect. Control*. **2012,** *1,* 33-36.

71. Prisakar, V. I.; Tsapkov, V. I.; Buracheéva, S. A.; Byrké and Gulya, A. P. Synthesis and Antimicrobial Activity of Coordination Compounds of Copper with Substituted Salicylaldehyde Thiosemicarbazones. *Pharm. Chem. J.* **2005**, *39,* 313-315.

72. Gyawali, R.; Ibrahim, S. A. Synergistic Effect of Copper and Lactic Acid against *Salmonella* and *Escherichia coli* O157: H7: A Review. *Emir. J. Food Agric.* **2012**, *24*, 1-11.

73. Faúndez, G.; Troncoso, M.; Navarrete, P. Figueroa, G. Antimicrobial Activity of Copper Surfaces against Suspensions of *Salmonella enteric* and *Campylobacter jejuni*. *BMC Microbio.* **2004**, *4*, 1-7.

74. Osowole, A. A.; Ott, I. Synthesis, Characterization, In-vitro Anticancer and Antimicrobial Properties of Some Metal(II) Complexes of 4-[(2, 3-dihydro-1H-inden-4-ylimino) methyl] Benzene-2, 4-diol. *Int. Res. J. Pure & Appl. Chem*. **2012**, *2*, 156-169.

75. Lieu, P. T.; Heiskala, M.; Peterson, P. A.; Yang, Y. The Roles of Iron in Health and Disease. *Mol. Aspects Med.* **2001**, *22*, 1-87.

76. Ott, I.; Gust, R. Non Platinum Metal Complexes as Anti-cancer Drugs. *Arch. Pharm. Chem. Life Sci.* **2007**, *340*, 171-126.

77. Saleem, K.; Wani, W. A.; Hague, A.; Lone, M. N.; Hsieh, M. F.; Jairaipuri, M. A.; Ali, I. Synthesis, DNA Binding, Hemolysis Assays and Anticancer Studies of Copper(II), Nickel(II) and Iron(III) Complexes of a Pyrazoline-based Ligand. Future Med. Chem. **2013**, *5*, 135-146.

78. Burger, R. M.; Projan, O. S. J.; Horwitz, S. B.; Peisachoa, J. The DNA Cleavage Mechanism of Iron-Bleomycin Kinetic Resolution of Strand Scission from Base Propenal Release. *J. Bio. Chem.* **1986**, *261*, 15955-15959.

79. Zikmund-Fisher, B. J.; Ubel, P. A.; Smith, D. A.; Derry, H. A.; McClure, J. B.; Stark, A.; Pitsch, R. K.; Fagerlin, A. Communicating Side Effect Risks in a Tamoxifen Prophylaxis

Decision Aid: The Debiasing Influence of Pictographs. *Patient Educ. Couns.***2008**, *73*, 209-214.

80. Pigeon, P.; Top, S.; Vessières, A.; Huché, M.; Görmen, M.; Arbi, M. E.; Plamont, M.; McGlinchey, M. J.; Jaouen, G. A New Series of Ferrocifen Derivatives, Bearing Two Aminoalkyl Chains, with Strong Antiproliferative Effects on Breast Cancer Cells. *New J. Chem.* **2011**, *35*, 2212-2218

81. Rafique, S.; Idrees, M.; Nasim, A.; Akbar, H.; Athar, A. Transition Metal Complexes as Potential Therapeutic Agents. *Biotech. Mol. Biol. Rev.* **2010**, *5*, 38-45.

82. Qui, D.; Huang, Z.; Zhou, T.; Shen, C; Hide, R. C. *In vitro* Inhibition of Bacteria Growth by Iron Chelators. *FEMS Microbiol. Let.* **2011**, *314*, 107-111.

83. Richards, A. D.; Rodger, A.; Hannon, M. J.; Bolhuis, A. Antimicrobial Activity of Iron Triple Helicate. *Int. J. Antimicrob. Agents*, **2009**, *33*, 469-472.

84. Nagajothi, A. Kiruthika, A.; Chitra, S.; Parameswari, K. Fe(III) Complexes with Schiff Base Ligands: Synthesis, Characterization, Antimicrobial Studies. *Res. J. Chem. Sci*. **2013**, *3*, 35-43.

85. Haque, M. D. E.; Hossen, M. D. F.; Islam, M. D. S.; Norman, A. S. M. Biological Screening of Some Ferrocene Derivative Metal Complexes. *Int. J. Agric. Bio.* **2006**, *8*, 774-777.

86. Chitambar, C. R. Gallium-containing Anticancer Compounds. *Future Med. Chem.* **2012**, *4*, 1257-1272.

87. Gomez-Ruiz, S.; Gallego, B.; Kaluderović, W. R.; Kommera, H.; Hey-Hawkins, E.; Paschke, R.; Kaluderović, G. N. Novel Gallium(III) Complexes Containing Phthaloyl Derivatives of Neutral Amino acids with Apoptotic Activity in Cancer Cells. *J. Organomet. Chem.* **2009**, *694*, 2191-2197.

88. Hannon, M. J. Metal-based Anticancer Drugs: From a Past Anchored in Platinum Chemistry to a Post-genomic Future of Diverse Chemistry and Biology. *Pure Appl. Chem.* **2007**, *79*, 2243-2261.

89. Bernstein, L. R. Mechanism of Therapeutic Activity for Gallium. *Pharm. Rev.* **1998**, *50*, 665-682.

90. Shakya, R.; Peng, F.; Liu, J.; Heeg, M. J.; Verani, C. N. Synthesis, Structure and Anticancer Activity of Gallium(III) Complexes with Asymmetric Tridentate Ligands; Growth Inhibition and Apoptosis Induction of Cisplatin-Resistant Neuroblastoma Cells. *Inorg. Chem.* **2006**, *45*, 6263-6268.

91. Collery, P.; Mohsen, A.; Kermadoret, A. D'Angelo, J.; Morgant, G.; Desmaele, D.; Tomas, A.; Collery, T.; Wei, M.; Badawi, A. Combination of Three Metals for the Treatment of Cancer: Gallium, Rhenium and Platinum 1. Determination of the Optimal Schedule of Treatment. *Anticancer Res.* **2012**, *32*, 2769-2782.

92. Timerbaev, A. R. Advances in Developing Tris(8-Quinolinolato) Gallium(III) as an Anticancer. *Metallomics.* **2009**, *1*, 193-198.

93. Biot, C.; Castro, W.; Botte, C. Y.; Navarro, M. The Therapeutic Potential of Metal-Based Antimalarial Agents: Implications for the Mechanism of Action. *Dalton Trans.* **2012**, *41*, 6335-6349.

94. Kaplan, B. J.; Parish, W. W.; Andrus G.M.; Simpson, J. S. Field, C. J. Germany Facts about Germanium Sesquioxide: 1. Chemistry and Anticancer Properties. *J. Altern. Complement Med.* **2004**, *10*, 337-344.

95. Zhang, C. L.; Li, T. H.; Niu, S. H.; Wang, R. F.; Fu, Z. L.; Guo, F. Q.; Yang, M. Synthesis and Evaluation of Novel Organogermanium Sesquioxides as Antitumor Agents. *Biol. Chem. Appl.* **2009**, 2009, 1-8.

96. Ogwapit, S. M. Analysis of Ge-132 and Development of a Simple Oral Anticancer Formulation. *Biosci. Hori.* **2011**, *4*, 128-139.

97. Pi, J. Z.; Luo, J.; Yang, P.; Cai, J. Synthesis and biological evaluation of Germanium(IV)-Polyphenol Complexes as Potential Anti-cancer Agents. *Bioorg. Med. Chem. Lett*. **2013**, *23*, 2902-2908.

98. Jeyaraman, V.; Sellappa, S. *In-vitro* Anticancer Activity of Organic Germanium on Human Breast Cancer Cell Line (MCF-7). *J. Current Pharm. Res.* **2011**, *5*, 39-41.

99.Yang, F.; Jin, H.; Pi, J.; Jiang, J. H.; Liu, L.; Bai, H. H.; Yang, P. H.; Cai, J. Y. Anti-tumor Activity Evaluation of Novel Chrysin-organogermanium(IV) Complex in MCF-7 Cells. *Biorg. Med. Chem. Let.* **2013**, *23*, 5541-5544.

100. Köpf- Maier, P.; Janiak, C.; Shumann, H. Antitumor Properties of Organometallic Metallocene Complexes of Tin and Germanium. *J. Cancer Res. Clin. Oncol.* **1988**, *114*, 502-506.

101. Sellappa, S. Antibacterial Properties of Organic Germanium against Some Human Pathogens. *Int. J. Pharma. Bio. Sci.* **2011**, *2*, 854-859.

102. Sijpesteijn, A. K.; Rijkens, F.; Luijten, J. G. A.; Willemsens, L. C. On the Antifungal and Antibacterial Activity of Some Trisubstituted Organogermanium, Organotin and Organolead Compounds. *Antonie van Leeuwen.* **1962**, *28,* 346-356.

103. Ludwig, G.; Mijatović. S.; Randelović, I., Bulatović, M.; Miliković, D.; Maksimović-Iyanić, D.; Korb, M.; Lang, H.; Steinborn, D.; Kaluderović, G. N. Biological Activity of Neutral and Cationic Iridium(III) Complexes with kP and kP, kS coordinated $Ph_2PCH_2S(O)xPh$(x=0-2) Ligands. *Eur. J. Med. Chem.* **2013**, *69*, 216-222.

104. Liu, Z.; Sadler, P. J. Organoiridium Complexes: Anticancer Agents and Catalysts. *Acc. Chem. Res.* **2014**, *47*, 1174-1185.

105. Dave, S.; Bansal, N. Application of Schiff Bases as Therapeutic Agent-A Review. *Int. J. Curr. Pharmaceut. Res.* **2013**, *5*, 1-7.

106. Almodares, Z.; Lucas, S. J.; Crossley, B. D.; Basri, A. M.; Pask, C. M.; Hebden, A. J.; Phillips, R. M.; Mc Gowan, P. C. Rhodium, Iridium and Ruthenium Half-Sandwich Picolinamide Complexes as Anticancer Agents. *Amer. Chem. Soc.; Inorg. Chem.* **2014**, *53*, 727-735.

107. Geldmacher, Y.; Oleszak, M.; Sheldrick, W. S. Rhodium(III) and Iridium(III) Complexes as Anticancer Agents. *Inorg. Chimica Acta*. **2012**, *393*, 84-102.

108. Lucas, S. J.; Lord, R. M.; Wilson, R. L.; Phillips, R. M.; Sridharan, V.; McGowan, P. C. Synthesis of Iridium and Ruthenium Complexes with (N, N), (N, O) and (O, O) Coordinating Bidentate Ligands as Potential Anti-cancer Agents. *Dalton Trans.* **2012,** *41*, 13800-13802.

109. Buckley, R. G. Rhodium, Iridium and Palladium Compounds as Experimental Anticancer Drugs. *Metal Comp. Cancer Ther.* **1994**, 92-108.

110. Gasser, G.; Ott, I.; Metzler-Nolte, N. Organometallic Anticancer Agents. *J. Med. Chem.* **2011**, *54*, 3-25.

111. Sharma, V. K.; Srivastava, A.; Srivastava, S. Synthetic, Structural and Antifungal Studies of Coordination Compounds of Ru(III), Rh(III) and Ir(III) with Tetradentate Schiff Bases. *J. Serb. Chem. Soc.* **2006**, *71*, 917-928.

112. Pandrala, M.; Li, F.; Festerl, M.; Mulyana, Y.; Warner, J. M.; Wallace, L.; Keene, F. R.; Collins, J. G. Chlorido-Containing Ruthenium(II) and Iridium(III) Complexes as Antimicrobial Agents. *Dalton Trans*. **2013**, *42*, 4686-4694.

113. Heffeter, P.; Jakupec, M. A.; Körner, W.; Wild, S.; Von Keyserlingk, N. G.; Elbing, L.; Zorbas, H.; Koryneyska, A.; Knasmüller, S.; Sutterlüty, H.; Micksche, M.; Keppler, B. K.; Berger, W. Anticancer Activity of the Lanthanum Compound [Tris (1, 10-Phenanthroline) Lanthanum(III) Trithiocyanate (KP 772; FFC24). *Biochem. Pharmacol.* **2006**, *71*, 426-440.

114. Heffeter, P.; Jakupec, M. A.; Körner, W.; Chika, P.; Dornetshuber, R.; Elbing, L.; Sutterlüty, H.; Micksche, M.; Keppler, B. K.; Berger, W. Multidrug-Resistant Cancer Cells

Are Preferential Targets of the New Antineoplatic Lanthanum Compound KP772 (FFC24). *Biochem. Pharmacol.* **2007**, *73*, 1873-1886.

115. Wang, Z. M.; Lin, H. K.; Zhu, S. R.; Liu, T. F.; Zhou, Z. F.; Chen, Y. F. Synthesis, Characterization and Cytotoxicity of Lanthanum(III) Complexes with Novel 1, 10-Phenanthroline-2, 9-Bis-Alpha-Amino Acid Conjugates. *Anticancer Drug Des.* **2000**, *15,* 405-411.

116. Durgo, K.; Halec, I.; Šola, I.; Franekić, J. Cytotoxic and Genotoxic Effects of the Quercetin/Lanthanum Complex on Human Cervical Carcinoma Cells *In Vitro.Arh. Hig Rada Toksikol,* **2011**, *62*, 221-227.

117. Alghool, S.; Abd El-Halim, H, F.; El-Sadek, M. S.; Yahia, I. S.; Wahab, L. A. Synthesis, Thermal Characterization and Antimicrobial Activity of Lanthanum, Cerium and Thorium Complexes of Amino Acid Schiff Base Ligand. *J. Therm. Anal. Calor*. **2012**, *109*, 2628-2634.

118. Andotra, S.; Kalgotra, N.; Pandey, S. K. Syntheses, Characterization, Thermal and Antimicrobial Studies of Lanthanum(III) Tolyl/Benzyldithiocarbonates. *Bioinorg. Chem. Applic.* **2014**, *2014*, 1-12.

119. Malhi, G. S.; Tanious, M.; Das, P.; Berk, M. The Science and Practice of Lithium Therapy. *Aust. N. Z. J. Psych*. **2012**. *46*, 192-211.

120. Mahdi, J. G.; Mahdi, E. J. Al-Hazzaa A.; Pepper, C. J. The Effect of Hydroxybenzoate Lithium Complexes in Inducing Apoptosis in HT-1080 Human Fibrosarcoma Cells. *J. Cancer Res.* **2013**, *2013*, 1-8.

121. Yuldasheva, G. A.; Zhidomirov, G. M.; Ilin, A. I. The Antitumor Activity of Molecular Iodine Complexes with Lithium Halogenides and Bioorganic Ligands when Applied in Combination with Doxorubicin. *J. Antivir Antiretroviral*. **2014**, *6*, 050-053.

122. Hossain, M. S.; Hossain, M. A.; Islam, R.; Alam, A. H. M. K.; Zahan, E.; Sarkar, S.; Faroque, M. A. Antimicrobial and cytotoxic activities of 2-Aminobenzoic Acid and 2-Aminophenol and Their Coordination Complexes with Magnesium(Mg-II). *Pak. J. Biol. Sci*. **2004**, *7*, 25-27.

123. Zhang, N.; Fan, Y.; Bi C.; Zuo, J., Zhang, P.; Zhang, Z.; Zhu, Z. Synthesis, Crystal Structure of Magnesium(II) Complexes with Schiff Bases. *J. Coord. Chem.* **2013**, *66*, 1933-1944.

124. Maurya, R. C.; Bohre, P.; Sahu, S.; Martin, M.H.; Sharma, A. K. Manganese (II) Chelates of Bioinorganic and Medicinal Relevance: Synthesis, Characterization, Antibacterial Activity and 3D-Molecular Modeling of Some Penta-Coordinated Manganese(II) Chelates in

O, N-Donor Coordination Matrix of ß-Diketoenolates and Picolinate. *Arab. J. Chem*. **2011**, 1-10.

125. Morzyk-Ociepa, B.; Kobot, M.; Różżcka-Sokolowska, Gielzak-Koćwin, K.; Filli-Psurska, B.; Wietrzyk, J.; Michalska, D. Crystal Structure, Infrared and EPR Spectra and Anticancer Activities *In vitro* of the Novel Manganese(II) Complexes of Indolecarboxylic Acids. *Poly.* **2014**, *67*, 464-470.

126. Tan, Z.; Tan, F.; Zhao, L.; Li, J. The Synthesis, Characterization and Application of Ciprofloxacin Complexes and Its Coordination with Copper, Manganese and Zirconium Ions. *J. Crystal. Proc. Tech.* **2012**, *2*, 55-63.

127. Geraghty, M.; Cronin, J. F.; Devereux, M.; McCann M. Synthesis and Antimicrobial Activity of Copper(II) and Manganese(II) Alpha, Omega-dicarboxylate Complexes. *Biomet.* **2000**, *13,* 1-8.

128. Aiyelabola, T.; Ojo, I.; Akinkunmi, O. Structural and Antimicrobial Studies of Coordination Compounds of Phenylalanine and Glycine. *Int. J. Chem.* **2012**, *4*, 49-59.

129. Rao, P. G.; Rahganatham, P.; Srinivasan, K.K.; Sharada, N.R. Enhancement of Antimicrobial Activity of Sulfa Drugs by Metallic Ions. Current Sci. **1979**, *48*, 99-101.

130. Revanasiddappa, H. D.; Shivakumar, L.; Prasad, K. S.; Vijay, B.; Jayalakshmi, B. Synthesis, Structural Characterization and Antimicrobial Activity Evaluation of Manganese(II) Complexes with Biologically Important Drugs. *Chem. Sci. J.* **2012**, *CSJ-64*, 1-10.

131. Khajuria, R.; Syed, A.; Kumar, S.; Pandey, S. K. Spectroscopic, Thermal, Electrochemical and Antimicrobial Studies of Mononuclear Manganese(II) Ditolydithiophosphates. *Bioinorg. Chem. Appl.* **2013**, *2013*, 1-13.

132. Osowole, A. A.; Akpan, E. J. Synthesis, Spectroscopic Characterisation *In Vitro* Anticancer and Antimicrobial Activities of Some Metal(II) Complexes of 3-{4, 6-Dimethoxy Pyrimidinyl} Iminomethyl Napthalen-2-ol. *Euro. J. App. Sci.* **2012**, *4*, 14-20.

133. Hossain, M. S.; Anwar-ul-Islam, M. K.; Sarkar, S. *In vitro* Antimicrobial and *In vivo* Cytotoxic Activity of Three Coordination Complexes Synthesized by Mixed Ligands. *Pak. J. Biol. Sci.* **2004**, *7*, 1113-1116.

134. Birada, V. D.; Mruthyunjayaswamy, B. H. M. Synthesis, Characterization and Antimicrobial Activity Studies of Some Transition Metal Complexes Derived from 3-Chloro-N-[2-hydroxyphenyl)Methylene]-6-Methoxy-1-Benzothiophene-2-Carbohydrazide. *Hindawi Publ. Corp.; Scientific. World J.* **2013**, *2013*, 1-10.

135. Ansari, K. I.; Grant, J. D.; Kasiri, S.; Woldemarian, G.; Subhrangsu, B. S.; Mandal, S. S. Manganese(III)-Salens Induce Tumor Selective Apoptosis in Human Cells. *J. Inorg. Biochem.* **2009**, *103,* 818-826.

136. Shanker, K.; Ashok, M.; Reddy, P. M.; Rohini, R.; Ravinder, V. Spectroscopic Characerization and Antibacterial Activities of Mn(III) Complexes Containing the Tetradentate Aza Schiff Base Ligands. *Int. J. Chem. Tech. Res.* **2009**, *1,* 777-783.

137. Sushama, P. G.; Dorothy, M. A.; Alaudeen, M. Antimicrobial and Antifungal Activity of Mn(III) Complexes of 2, 5-Dihydroxy-3-undecyl-1, 4-benzoquinone Derivative. *Asian J. Chem*. **2007**, *19,* 3403-3406.

138. Nair, M. L. H.; Thankamani, D. Synthesis and Characterization of Oxomolybdenum (V) and Dioxomolybdenum(VI) Complexes with Schiff Base Derived from Isonicotinoylhydrazide. *Ind. J. Chem.* **2009**, *48A*, 1212-1218.

139. Patil, S. K.; Naik, V. M.; Mallur, N. B. Synthesis, Spectral and Antibacterial Studies of Oxomolybdenum(V) and Dioxomolybdenum(VI) Complexes with 2-Imidazolylmercaptoacetohydrazone. *Der Pharma Chemica.* **2012**, *4*, 1812-1818.

140. Saraswati, K.; Kant, R. Synthesis, Characterization and Biological Activity of Some Molybdenum(VI) Complexes. *Der Pharma Chemica.* **2013**, *5*, 347-356.

141. Pereira, C.C.L.; Diogo, C. V.; Burgeiro, A.; Oliveira, P. J.; Marques, M. P. M.; Braga, S. S.; Paz, F. A. A.; Pillinger, M.; Gonçalves, I. S. Complex Formation between Heptakis (2, 6-di-*O*-methyl)-Cyclodextrin and Cyclopentadienyl Molybdenum(II) Dicarbonyl Complexes; Structural Studies and Cytotoxicity Evaluations. *Organomet.* **2008**, *27*, 4948-4956.

142. Köpf-Maier, P.; Köpf. H. Organometallic Titanium, Vanadium, Niobium, Molybdenum and Rhenium Complexes-Early Transition Metal Antitumour Drugs. *Met. Comp. Cancer Ther.* **1994**, 109-146.

143. Mokdsi, G.; Harding, M. M. A ^{1}H HMR Study of the Interaction of Antitumour Metallocenes with Glutathione. *J. Inorg. Biochem.* **2001**, *86*, 611-616.

144. Thomadaki, H.; Lymberopoulou-Karaliota, A.; Maniatakou, A.; Scorillas, A. Synthesis, Spectroscopic Study and Anticancer Activity of a Water-Soluble Nb(V) Peroxo Complex. *J. Inorg. Biochem.* **2011**, *105*, 155-163.

145. Stachtea, X.; Karamanos, N.; Klouras, N.; Enhanced Antitumour Activity of Cyclopentadienyl-Substituted Metallocene Dihalides in Human Breast and Colon Cancer Cells. Anticancer Res. 2009, 29, 3227-3232.

146. Hayatifar, M.; Marchetti, F; Pamplona, G.; Zacchini, S. Synthesis, X-ray, Characterization and Reactivity of α-Aminoacidato Ethoxide Complexes of Niobium(V) and Tantalum(V). Inorg. Chem. 2013, 52, 4017-4025.

147. Rindhe, S. S.; Karale, B. K.; Gupta, R. C.; Rode, M. A. Synthesis, Antimicrobial and Antioxidant Activity of Some Oxindoles, *Indian J. Pharm. Sci.* **2011**, *73*, 292-296.

148. Revanasiddappa, H. D.; Vijaya, B.; Shvakumar, L.; Prasad, S. Synthesis, Structural Characterization and Antimicrobial Activity Evaluation of New Binuclear Niobium(V) Tartrate Complexes with Biologically Important Drugs. *ISRN Inorg. Chem*. **2013**, *2013*, 1-7.

149. Shi, Y.; Harvey, I.; Campopiano, D.; Sadlers, P. J. Niobium Uptake and Release by Bacterial Ferric Ion Binding Protein. *Bioinorg. Chem. Appl.* **2010**, 2010, 1-11.

150. Kasprzak, K. S.; Diwan, B. A.; Konishi, N.; Misra, N.; Rice, J. M. Initiation by Nickel Acetate and Promotion by Sodium Barbital of Renal Cortical Epithelial Tumors in Male F344 Rats. *Carcinogen*. **1990**, *11*, 647-652.

151. Wu, H.; Sun, t.; Liu, B.; Kou, F.; Yuan, F. J. J.; Bai, Y. Synthesis, Crystal Structure, and DNA-Structure Studies of a Nickel(II) Complex with the Bis (2-Benzimidazolymethyl)amine Ligand. *Bioinorg. Chem. Appl.* **2012**, 2012, 1-7.

152. Karmaker, P. G.; Khan, A. R.; Karim, M. S. Antimicrobial Activities of Copper, Cobalt and Nickel Cyanex Complexes. *J. Agrofor Environ*. **2010**, *3,* 15-18.

154. Diwan, B. A.; Kasprzak, K. S.; Rice, J. M. Transplacental Carcinogenic Effects of Nickel (II) Acetate in The Renal, Cortex, Renal Pelvis and Adenophypophysis in F344/NCr Rats. *Carcinogen*. **1992**, *13*, 1351-1357.

154. Kumar, A.; Verma, U.; Chauhan, S. Antimicrobial Activity of Nickel(II) Coordinated Compounds, *G. J. B. B*. **2012**, *1*, 310-313.

155. Van Rijt, S. H.; Peacock, A. F. A.; Sadler, P. J. Osmium Arenes: A New Class of Potential Anti-Cancer Agents. *Plat. Other Heavy Met. Comp. Cancer Chem.* **2009**, 73-79.

156. Ni, W.; Man, W.; Cheung, T.; Sun, R. W.; Shu, Y.; Lam, Y.; Che, C.; Lau, T. Osmium(VI) Complexes as a New Class of Potential Anti-Cancer Agents. Chem. Comm. 2011, 47, 2140-2142.

157. Van Rigt, S. H.; Peacock, A. F. A.; Russell, D. L. Sadler, P. Johnstone, R. D. L.; Parsons, S.; Sadler, P. J. Organometallic Osmium(II) Arene Anticancer Complexes Containing Picolinate Derivatives. *Inorg. Chem.* **2009**, *48*. 1753-1762.

158. Peacock, A. F. A.; Sadler, P. J. Medicinal Organometallic Chemistry: Designing Metal Arene Complexes as Anticancer Agents. *Chem. Asian. J.* **2008**, *3*, 1890-1899.

159. Stepananko, I. N.; Büchel, G. E.; Keppler, B. K. Osmium Complexes with Azole Heterocycles as Potential Antitumor Drugs. Encyc. Metalloproteins. 2013, 1596-1614.
160. Fu, Y.; Soni, R.; Romano, M. J.; Pizarro, A. M.; Salassa, L.; Clarkson, G. J.; Hearn, J. M.; Habtemariam, A.; Wills, M.; Sadler, P. J. Mirror-Image Organometallic Osmium Arene Iminopyridine Halido Complexes Exhibit Similar Potent Anticancer Activity. *Chem. Euro. J*, **2013**, *19*, 15199-15209.
161. Liu, H.; Sadler, P. J. Metal Complexes as DNA Intercalators. *Acc. Chem. Res.* **2011**, *44*, 349-359.
162. Henke, H.; Kandioller, W.; Hanif, M.; Keppler, B.; Hartinger, C. G. Organometallic Ruthenium and Osmium Compounds of Pyridin-2-and-4-ones as Potential Anticancer Agents. *Chem. Biodiv.* **2012**, *9*, 1718-1727.
163. Elsome, A. M.; Hsmilton-Miller, J.M.; Brumfitt, W.; Noble, W. C. Antimicrobial Activities In vitro and In vivo of Transition Element Complexes Containing Gold(I) and Osmium(VI). *J. Antimicrob. Chemother.* **1996**, *37*, 911-918.
164. Kilpin, K. J.; Crot, S.; Riedel, T.; Kitchen, J. A.; Dyson, P. J. Ruthenium(II) and Osmium(II) 1, 2, 3-Triazolylidene Organometallics: A Preliminary Investigation into Biological Activity of 'Click' Complexes. Dalton Trans. 2014, 43, 1443-1448.
165. Panda, B. K. Synthesis, Characterization and Photophysical Properties of Quinol-8-olato Chelated Osmium (II) Organometallics Bearing a Pendant Imine-Phenol Motif and Electrogeneration of Trivalent Analogue. *Open J. Inorg. Chem.* **2012**, *2*, 49-57.
166. Elhusseiny, A. F.; Hassan, H. H. Antimicrobial and Antitumour of Platinum and Palladium Complexes of Novel Spherical Aramides Nanoparticles Containing Flexibilizing Linkages: Structure-Property Relationship. *Spectrochim. Acta A. Mol. Biomol. Spectrosc.* **2013**, 103, 232-245.
167. Abu-Surrah, A. S.; Al-Sa'doni, H. H.; Abdalla, M. Y. Palladium-Based Chemotherapeutic Agents: Routes toward Complexes with Good Antitumor Activity. *Cancer Ther*, **2008**, *6*, 1-10.
168. Ulukaya, E.; Frame, F. M.; Cevatemre, B.; Pellacani, D.; Walker, H.; Mann, V. N.; Simms, M. S.; Stowes, M. J.; Yilmaz, V. T.; Maitland, N. J. Differential Cytotoxic Activity of a Novel Palladium-Based Compound on Prostate Call Lines, Primary Prostate Epithelial Cells and Prostate Stem Cells. *Plos One*. **2013**, *8*, 1-13.
169. Abu-Surrah, A.; Kettunen, M. Platinum Group Antitumor Chemistry: Design and Development of New Anticancer Drugs Complementary to Cisplatin. *Curr. Med. Chem.* **2006**, *13*, 1337-1357

170. Serebryanskaya, T. V.; Yung T.; Bogdanov, A. A.; Shchebet, A.; Johnsen, S. A.; Lyakhov, A. S.; Ivashkevich, L. S.; Ibrahimava, Z. A; Garbuzenco, T. S.; Kolesnikova, T. S.; Melnova, N. I.; Gaponik, P. N.; Ivashkevich, O. A. Synthesis, Characterization and Biological Evaluation of New Tetrazole-Based Platinum(II) and Palladium(II) Chlorido Complexes-Potent Cisplatin Analogues and Their Trans Isomers. *J. Inorg. Biochem*. **2013**, *120*, 44-53.

171. Ahmad, S.; Rüffer, T.; Lang, H.; Nadeem, S.; Tirmizi, S. A.; Saleem, M.; Anwar, A. Synthesis, Crystal Structure, and Antimicrobial Studies of Trans-[$Pd(PPh_3)_2$(Imidazolidine-2-Thione)$_2$]$Cl_2.3.5H_2O$. *Russ. J. Coord. Chem.* **2010**, *36*, 520-524.

172. Ray, S.; Mohan, R.; Singh, J. K.; Samantaray, M. K.; Shaikh, M. M.; Panda, D.; Ghosh, P. Anticancer and Antimicrobial Metallopharmaceutical Agents Based on Palladium, Gold and Silver N-Heterocyclic Carbene Complexes. *J. Am. Chem. Soc.* **2007**, *129,* 15042-15053.

173. Alderden, R. A.; Hall, M. D.; Hambley, T. W. The Discovery and Development of Cisplatin. *J. Chem. Edu.* **2006**. *83*, 728-734.

174. Barnard, C. F. J. Platinum Anti-Cancer Agents Twenty Years of Continuing Development. *Plat. Metal Rev.* **1989**, *33*, 162-167.

175. Lewis, R. From Basic Research to Cancer Drug; The Story of Cisplatin. *The Scientist.* **2009**, *13*, 11.

176. Kostova, I. Platinum Complexes as Anticancer Agents. *Recent Pat. Anti-Cancer Discov.* **2006**, *1*, 1-22.

177. Johnstone, T. C.; Wilson, J. J.; Lippard, S. J. Monofunctional and Higher-Valent Platinum Anticancer Agents. *Inorg. Chem.* **2013**, *52*, 12234-12249.

178. Rosenberg, B.; Van Camp, L.; Krigas, T. Inhibition of Cell Division in *Escherichia coli* by Electrolysis Product from a Platinum Electrode. *Nature*, **1965**, *205*, 698-699.

179. McConnell, J. R.; Rananaware, D. P.; Ramsey, D. M.; Buys, K. N.; Cole, M. L.; McAlpine, S. R. A Potential Rhodium Cancer Therapy: Studies of a Cytotoxic Organorhodium (I) Complex that Binds DNA. *Bioorg. Med. Chem. Let.* **2013**, *23*, 2527-2531.

180. Giraldi, T.; Sava, G.; Bertoli, G.; Mestroni, G.; Zassinovich, G. Antitumor Action of Two Rhodium and Ruthenium Complexes in Comparison with Cis-Diamminedichloroplatinum(II). *Cancer Res.***1977**, *37*, 2662-2666.

181. Parson, C.; Smith, V.; Krauss, C.; Banerjee, H. N.; Reilly, C.; Krause, J. A.; Wachira, J. M.; Giri, D.; Winstead, A.; Mandal, S. K. The Effect of Novel Rhenium Compounds on Lymphosarcoma, PC-3 Prostate and Myeloid Leukemia Cancer Cell Lines and an

Investigation on the DNA Binding Properties of One of These Compounds through Electronic Spectroscopy. *J. Bioprocess Biotech.* **2013**, *4*, 1-5.

182. Gupta, G.; Garci, A.; Murray, B. S.; Dyson, P. J.; Fabre, G.; Trouillas, P.; Giannini, F.; Furrer, J.; Suss-Fink, G.; Therrien, B. Synthesis, Molecular Structure, Computational Study and In vitro Anticancer Activity of Dinuclear Thiolato-Bridged Pentamethylcyclopentadienyl Rh(III) and Ir(III) Complexes. *Dalton Trans*. **2013**, *4*2, 15457-15463.

183. Leung, C. H.; Zhong, H. J.; Chan, D. S. H.; Ma, D. L. Bioactive Iridium and Rhodium Complexes as Therapeutic Agents. *Coord. Chem. Rev.* **2013**, *257*, 1764-1776.

184. Geldmacher, Y.; Oleszak, M.; Sheldrick, W. S. Rhodium(III) and Iridium(III) Complexes as Anticancer Agents. *Inorg. Chim. Acta.***2012**, *393*, 84-102.

185. Bieda, R.; Kitanovic, I.; Alborzinia, H.; Meyer, A.; Ott, I.; Wolfl, S.; Sheldrick, W. S. Antileukemic Activity and Cellular Effects of Rhodium(III) Crown Thiaether Complexes. *Biomet.* **2011**, *24*, 645-661.

186. Oehninger, L.; Kuster, L. N.; Schmidt, C.; Munoz-Castro, A.; Prokop, A.; Ott, I. A Chemical-Biological Evaluation of Rhodium(I) *N*-Heterocyclic Carbene Complexes as Prospective Anticancer *Drugs*. *Chem-A Euro. J.* **2013**, *19*, 17871-17880.

187. Ruiz, J.; Rodriguez, V.; Cutillas, N.; Samper, K. G.; Capdevila, M.; Palacios, O.; Espinosa, A. Novel C, *N*-Chelate Rhodium(III) and Iridium(III) Antitumour Complexes Incorporating a Lipophilic Steroidal Conjugate and Their Interaction with DNA. *Dalton Trans.* 2012, *41*, 12847-12856.

188. Gillard, R. D.; Lekkas, E. Complex Compounds with Rhodium(III) of Enantiomers of Nicotine. *Tran. Met. Chem.* **2000**, *25*, 617-621.

189. Nazarov, A. A.; Hartinger, C. G.; Dyson, P. J. Opening the Lid on Piano-Stool Complexes: An Account of Ruthenium(II) Arene Complexes with Medical Applications. *J. Organomet. Chem.* **2014**, 751, 251-260.

190. Allardyce, C. S.; Dyson, P. J. Ruthenium in Medicine: Current Clinical Uses and Future Prospects. *Plat. Met. Rev.* **2001**, *45*, 62-69.

191. Bratsos, I.; Jedner, S.; Gianferrara, T.; Alessio, E. Ruthenium Anticancer Compounds: Challenges and Expectations. *Chimia*, **2007**, *61*, 692-697.

192. Kostova, I. Ruthenium Complexes as Anticancer Agents. *Curr. Med. Chem.* **2006**, *13*, 1085-1107.

193. Sharma, A.R.; Gangrade, D. M.; Bakshi, S. D.; John, J. S. Ruthenium Complexes:-Potential Candidate for Anti-Tumour Activity. *Int. J. Chem. Tech Res.* **2014**, *6*, 828-837.

194. Laxmi, T.; Praveen, K.; Singhai, A. K. Role of Chelates in Treatment of Cancer. *Ind. J. Cancer,* **2007**, *44*, 62-71.

195. Ruiz, J.; Vicente, C.; Haro, C.; Bautista, D. A Novel Ruthenium(II) Arene Based Intercalator with Potent Anticancer Activity. *Dalton Trans*. **2009**, 5071-5073.

196. Naik Kumar, K. H.; Bhimareddy, A.; Nagaraja, N. Ruthenium Metal Complexes and Their Biological Approach-A Short Review. *IJPSR*, **2014**, *5*, 758-773.

197. Ang, W. H.; Dyson, P. J. Classical and Non-Classical Ruthenium-Based Anticancer Drugs: Towards Targeted Chemotherapy. *J. Inorg. Chem*. **2006**. 4003-4018.

198. Santamaria, R.; Irace, C.; D'Errico, G.; Montesarchio, D.; Paduano, L. Perspectives and Potential Applications of Ruthenium-Based Nanocarriers for Cancer Therapy. *J. Pharm. Drug Dev.* **2013**, *1*, 1-4.

199. Gobec, M.; Kljun, J.; Sošič, I.; Mlinarič-Raščan, I.; Uršič, M.; Gobec, S.; Turel, I. Structural Characterization and Biological Evaluation of a Clioquinol-Ruthenium Complex with Copper-Independent Antileukemic Activity. *Dalton Trans.* **2014**, *43*, 9045-9051.

200. Pandrala, M.; Li, F.; Feterl M.; Mulyana, Y.; Warner, J. M.; Wallace, L.; Keene, R. F.; Collins, J. G. Chlorido-Containing Ruthenium(II) and Iridium(III) Complexes as Antimicrobial Agents. *Dalton Trans*. **2013**, *42*, 4686-4694.

201. Warad, I.; Eftaiha, A. F.; Al-Nuri, M. A.; Husein, A. I.; Assal, M.; Abu-Obaid, A.; Al-Zaqri, N.; Hadda, T. B.; Hammouti, B. Metal Ions as Antitumour Complexes-Review. *J. Mater, Environ. Sci.* **2013**, *4*, 542-557.

202. Turel, I.; Kljun, J.; Perdih, E.; Morozova, E.; Byl, J. A. W.; Osherof, N. First Ruthenium Organometallic Complex of Antibacterial Agent Crystal Structure and Interactions with DNA. *Inorg. Chem*. **2010**, *49*, 10750-10752.

203. Kiruthika, M.; Elayaperumal, R.; Vennila, T. Synthesis and Antifungal Potential of a Ruthenium (II) Complex. *Der Chemica Sinica*. **2012**, *3*, 1175-1180.

204. Prasad, K. S.; Kumar, L. S.; Revanasiddappa, H. D.; Vijay, B.; Jayalakshmi, B. Synthesis, Characterization and Antimicrobial Activity of Cu(II), Co(II), Ni(II), Pd(II) and Ru(III) Complexes with Clomiphene Citrate. *Chem. Sci. J.* **2011**, *28*, 1-11.

205. Li, F.; Feterl, M.; Mulyana, Y.; Warner J. M.; Collins, G.; Keene, F. R. *In vitro* Susceptibility and Cellular Uptake for a New Class of Antimicrobial Agents. *J. Antimicrobial Chemother.* **2012**, *67*, 2686-2695.

206. Thota, S.; Karki, S. S.; Bhukya, B. R. Synthesis, Characterization and Antibacterial Activity of Some Mononuclear Ru(II) Complexes. *Int. J. Pharm. Pharmaceut. Sci.* **2009**, *1*. 62-70.

207. Scolaro, C.; Chaplin, A. B.; Hartinger, C. G.; Bergamo, A.; Cocchietto, M.; Keppler, B. K.; Sava, G.; Dyson, P.J. Turning the Hydrophobicity of Ruthenium (II)-Arene (RAPTA) Drugs to Modify Uptake, Bimolecular Interactions and Efficacy. *Dalton Trans*. **2007**, 5065-5072.

208. Govender, P.; Antonels, N. C.; Mattsson, J.; Renfrew, A. K.; Dyson, P. J.; Moss, J. R.; Therrien, B.; Smith, G. S. Anticancer Activity of Multinuclear Arene Ruthenium Complexes Coordinated to Dendritic Polypyridyl Scaffolds. *J. Organomet. Chem.* **2009**, *694*, 3470-3476.

209. Süss-Fink, G. Arene Ruthenium Complexes as Anticancer Agents. *Dalton Trans*. **2010**, *39*, 1673-1688.

210. Murray, B. S.; Menin, L.; Scopelliti, R.; Dyson, P. J. Conformational Control of Anticancer Activity: Thee Application of Arene-Linked Dinuclear Ruthenium(II) Organometallics. *Chem. Sci.* **2014**, *5*, 2536-2545.

211. Adeniyi, A. A.; Ajibade, P. A. An Insight into the Anticancer Activities of Ru(II) Based Metallocompounds Using Docking Methods. *Mol.* **2013**, *18,* 10829-10856.

212. Adeniyi, A. A.; Ajibade, P. A. The Spectroscopic and Conductive Properties of Ru(II) Complexes with Potential Anticancer Properties. *J. Spec.* **2014**, *2014*, 1-14.

213. Motswainyana, W. M.; Ajibade, P. A. Anticancer Activities of Mononuclear Ruthenium(II) Coordination Complexes. *Adv. Chem.* **2014**, *2014*, 1-21.

214. Halder, A. K.; Sen, P.; Roy, S. Use of Antimony in the Treatment of Leishmaniasis: Current Status and Future Directions. *Mol. Bio. Int.* **2011**, *2011*, 1-23.

215. Salemo, M.; Garnier-Suillerot, A. Resistance to Arsenic and Antimony-Based Drugs. *Bioinorg. Chem. Appl.***2003**, *1*, 189-198.

216. Sharma, P.; Perez, D.; Cabrera, A.; Rosas, N. Arias, J. L. Perspectives of Antimony Compounds in Oncology. *Acta Pharmacol Sin.* **2008**, *29,* 881-890.

217. Sathiyajith, C. W. Investigations towards New Multidentate Ligands as Potential Multidentate Imaging Agents. Ph.D. Thesis. The University of Wales, Cardiff. Oct. 2010.

218. Tiekink, E. R. T. Antimony and Bismuth Compounds in Oncology. *Crit. Rev. Oncol/Hematol*. **2002**, *42*, 217-224.

219. Novotny, L.; Rauko, P.; Kombian, S. B.; Edafiogho, I. O. Selenium as a Chemoprotective Anti-Cancer Agent: Reality or Wishful Thinking? *Neoplasma*. **2010**, *57*, 385-391.

220. Cao, S.; Durrani, F. A.; Rustum, Y. M. Selective Modulation of the Therapeutic Efficiency of Anticancer Drugs by Selenium Containing Compounds against Human Tumor Xenografts. *Clin. Cancer Res.* **2004**, *10*, 2561-2569.

221. Al-Mudhaffar, D. M. H. Some Amino Acid Derivatives Containing Selenium Part (II): Anticancer Activity and of Their Cu(II)-Complexes. *Int. J. App. Sci. Tech.* 2013, *3*, 78-86.

222. Martins, I. L.; Miranda, J. P.; Oliveira, N. G.; Fernandes, A. S.; Gonçalves, S.; Antunes, A. M. M. Synthesis and Biological Activity of 6-Selenocaffeine: Potential Modulator of Chemotherapeutic Drugs in Breast Cancer Cells. *Mol*. **2013**, *18*, 5252-5264.

222. Zeng, L.; Li, Y.; Li, T.; Cao, W.; Yi, Y.; Geng, W.; Sun, Z.; Xu, H. Selenium-Platinum Coordination Compounds as Novel Anticancer Drugs: Selectively Killing Cancer Cells via a Reactive Oxygen Species (ROS)-Mediated Apoptosis Route. *Chem. Asian J.* **2014**, *9*, 2295-2302.

223. Buttrus, N. H.; AL-Ani, W. N.; AL-Omari. Synthesis, Characterization and Biological Studies of Selenium Dithiocarbamates and Their Ni^{2+} and Cu^{2+} Complexes. *Raf. Jour. Sci.* **2007**, *18*, 38-47.

224. Verma, P. A Review on Synthesis and Their Antibacterial Activity of Silver and Selenium Nanoparticles against Biofilm Forming *Staphylococcus Aureus.World J. Pharm Pharmaceut. Sci.* **2015**, *4*, 652-677.

225. Radhakrishma, P. M.; Sharadamma, K. C.; Vagdevi, H. M.; Abhilekha, P. M.; Mubeen, S. R. Synthesis and Antibacterial Activity of Novel Organoselenium Compounds. *Int. J. Chem*. **2010**, *2*, 149-154.

226. Attai, A. H.; El-Shemawy, A. I.; Koura, F. A.; Refat, M. S. Synthesis and Characterization of Some Selenium Nanometric Compounds: Spectroscopic, Biological and Antioxidant *Assessments. World J. Nano Sci. Eng.* **2014**, *4*, 58-69.

227. Hall, I. H.; Lackey, C. B.; Kistler, T. D.; Durham, R. W.; Russell, J. M.; Grímes, R. N. Antitumor Activity of Mono- and Dimetallic Transition Metal Carborane Complexes of Ta, Fe, Co, Mo or W. *Anticancer Res.* **2000**, *20*, 2345-2354.

228. Hall, I. R. H.; Tolmie, C. E.; Jo Barnes, B.; Curtis, M. A.; Russell, J. M.; Finn, M. Grimes R. N. Cytotoxicity of Tantalum (V) and Niobium (V) Small Carborane Complexes and Mode of Action in P388 Lymphocytic Leukemia Cells. *Appl. Oganomet. Chem.* **2000**, *14*, 108-118.

229. Chen, M.; Hein, S.; Le, D.; Feng, W.; Foss, M. Kjems, J.; Besenbacher, F.; Zou, X.; Bünger, C. Free Radicals Generated by Tantalum Implants Antagonize the Cytotoxic Effect of Doxorubicin. *Int. J. Pharm*. **2013**, *448*, 214-220

230. Huang, H.; Chang, Y.; Chen, H.; Chou, Y.; Lai, C.; Chen, M. Y. C. Antibacterial Properties and Cytocompatibility of Tantalum Oxide Coatings with Different Silver Contents. *Vac. Sci. Technol. A*. **2014**, *32*, 1-10.

231. Kostova, I. Titanium and Vanadium Complexes as Anticancer Agents. *Anticancer Agents Med. Chem.* **2009**, *9*, 827-842.

232. Allen, O. R.; Gott, A. L.; Hartley, J. A.; Hartley, J.M.; Knox, r. j.; McGowan, P. C. Functionalised Cyclopentadienyl Titanium Compounds as Potential anticancer Drugs. *Dalton Trans.* **2007**, 5082-5090.

233. Caruso, F.; Rossi, M.; Pettinari, C. Anticancer Titanium Agents. *Expert Opinion Theraupeut. Patents.*2001, *11*, 969-979.

234. Pampillón, C.; Mendoza, O.; Sweeney, N.J.; Strohfeldt, K.; Tacke, M. Diarylmethyl Substituted Titanocenes: Promising Anti-cancer Drugs. *Poly.* **2006**, *25*, 2101-2108.

235. Sweeney, N.J.; Gallagher, W. M.; Müller-Bunz, H.; Pampillón, C.; Strohfeldt, K.; Tacke, M. Heteroaryl Substituted Titanocenes as Potential Anti-cancer Drugs. *J. Inorg. Biochem*. **2006**, *100*, 1479-1486.

236. Vessières, A.; Plamont, M.; Cabestaing, C.; Claffey, J.; Dieckmann, S. Proliferative and Anti-proliferative Effects of Titanium- and Iron-Based Metallocene Anti-Cancer Drugs. *J. Organomet. Chem.* **2009**, *694*, 874-879.

237. Tacke, M.; Cuffe, L. P.; Gallagher, W. M.; Lou, Y.; Mendoza, O.; Müller-Bunz, H.; Rehmann, F. K.; Sweeney, N. Methoxy-phenyl Substituted Ansa-Titanocenes as Potential Anti-cancer Drugs Derived from Fulvenes and Titanium Dichlorides. *J. Inorg. Biochem*. **2004**, *98*, 1987-1994.

238. Rehmann, F. K.; Rous, A. J.; Mendoza, O.; Sweeney, N.J.; Gallagher, W. M.; Tacke, M. A Trimethoxyphenyl Substituted Ansa-Titanocene: a Possible Anti-Cancer Drug. *Poly.* **2004**, *24*, 1250-1255.

239. Boyles, J. R.; Baird, M. C.; Campling, B. G.; Jain, N. Enhanced Anti-cancer Activities of Some Derivatives of Titanocene Dichloride. *J. Inorg. Biochem.* **2001**, *84*, 159-162.

240. Ravera, M.; Cassino, C.; Monti, E.; Gariboldi, M.; Osella, D. Enhancement of the Cytotoxicity of Titanocene Dichloride by Aging in Organic Co-Solvent. *J. Inorg. Biochem.* **2005**, *99*, 2264-2269.

241. Pampillón, C.; Sweeney, N.J.; Strohfeldt, K.; Tacke, M. Synthesis and Cytotoxicity Studies of New Dimethylamino-Functionalised and Heteroaryl-Substituted Titanocene Anti-cancer Drugs. *J. Organomet. Chem.* **2007**, *692*, 2153-2159.

242. Sweeney, N.J.; Mendoza, O.; Müller-Bunz, H.; Pampillón, C.; Rehmann, F. K.; Strohfeldt, K.; Tacke, M. Novel Benzyl Substituted Titanocene Anti-cancer Drugs. *J. Organomet. Chem.* **2005**, *690*, 4537-4544.

243. Kaushal, R.; Kumar, N.; Chaudhary, A.; Arora, S.; Awasthi, P. Synthesis, Spectral Characterization, and Antiproliferative Studies of Mixed Ligand Titanium Complexes of Adamantylamine. *Bioinorg. Chem. Appl.* **2014**, *2014*, 1-12.

244. Titanium(IV) Complexes: Cytotoxicity and Cellular Uptake of Titanium(IV) Complexes on CaCO-$_2$ Cell Line. *Toxicol. In Vitro.* 2010, *24*, 178-183.

245. Kaushal, R.; Kumar, N.; Awasthi, P.; Nehra, N.Synthesis, Characterization, and Antibacterial Study of Titanium Complexes. *Turk. J. Chem.* 2013, *37*, 936-945.

246. Chang, Y.; Huang, H.; Lai, C.; Hsu, J.; Shieh, T.; Wu, A. Y.; Chen, C. Analyses of Antibacterial Activity and Cell Compatibility of Titanium Coated with a Zr-C-N Film. *Plos One*, 2013, *8*, 1-6.

247. Ahmad, R.; Sardar, M. TiO_2 Nanoparticles as an Antibacterial Agents against E. coli. *Int. J. Innovative Res. Sci. Eng. Tech.* **2013**. *2*, 3567-3574.

248. Evangelou, A. M. Vanadium in Cancer Treatment. *Critical Rev. Oncol. /Hematol.* **2002**, *42*, 249-265.

249. Abakumova, O. Y.; Podobed, O. V.; Belayeva, N. F. Tochilkin, A. I. Anticancer Activity of Oxovanadium Compounds. *Biomedic. Chem.***2012**, *6*, 164-170.

250. Zhang, Y.; Wang, X.; Fang, W.; Cai, X.; Chu, F.; Liao, X.; Lu, J. Synthesis and In Vitro Antitumor Activity of Two Mixed-Ligand Oxovanadium (IV) Complexes of Schiff Base and Phenanthroline. *Bioinorg. Chem Applic.* **2013**, *2013*, 1-14.

251. Prasad, P.; Pant, I.; Khan, I.; Kondaiah, P.; Chakravarty, A.R. Mitochondria-Targeted Photoinduced Anticancer Activity of Oxidovanadium (IV) Complexes of Curcumin in Visible Light. *Eur. J. Inorg. Chem.* **2014**, 2420-2431.

252. Léon, I. E.; Butenko, N.; Di Virgilio, A. L.; Miglia, C. L.;. Baran, E. J.; Cavaco, I.; Etcheverry, S. B. Vanadium and Cancer Treatment: Antitumoral Mechanism of Three Oxidovanadium(IV) Complexes on a Human Osterosarcoma Cell Line *J. Inorg. Biochem.* **2014**, *134*, 106-117.

253. Narla, R. K.; Dong, Y.; D'Cruz, O. J.; Navara, C.; Uckin, F. M. Bis (4, 7-Dimethyl-1, 10-Phenanthroline) Sulfatooxovanadium(IV) as a Novel Apoptosis-Inducing Anticancer Agent. *Clin. Cancer Res.* **2000**, *6*, 1546-1556.

254. D'Cruz, O. J.; Uckun, F. M. Metvan: A Novel Oxovanadium(IV) Complex with Broad Spectrum Anticancer Activity. *Exp. Opin. Invest. Drugs.* **2002**, *11*, 1829-1836.

255. Qi, W.; Qin, Y.; Qi, Y.; Guo, L.; Li, J. *In Vitro* Antitumour Activity of a Keggin Vanadium-Substituted Polyoxomolybdate and Its ctDNA Binding Properties. *J. Chem*. **2015**, *2015*, 1-6.

256. Korbecki, J.; Baranowska-Basiacka, I.; Gutowska, I.; Chlubek, D. Biochemical and Medical Importance of Vanadium Compounds. *ABP*, **2012**, *59*, 195-200.

257. Ostad, S. N.; Emadi, S. M.; Tavajohi, S.; Amani, V.; Abedi, A. Oxovanadium(IV) Compounds of Cis-[VOCl (N-N) $_2$]$^+$ (N-N= 4, 4' and 5, 5'-Dimethyl-2, 2'-Bipyridine); Crystal Structure and Biological Activity. *Bull. Korean Chem. Soc.* **2012**, *33*, 3391-3394.

258. Winter, J. M.; Moore, B. S. Exploring the Chemistry and Biology of Vanadium-Dependent Haloperoxidases. *JBC*, **2009**, *284*, 18577-18581.

259. Shahzadi, S.; Ali, S.; Parvez, M.; Badshah, A.; Ahmed, E.; Malik, A. Synthesis, Spectroscopy and Antimicrobial Activity of Vanadium(III) and Vanadium(IV) Complexes Involving Schiff Bases Derived from Tranexamic Acid and X-Ray Structure of Zwitter Ions of Tranexamic Acid. *Russian J. Inorg. Chem*. **2007**, *52*, 386-393.

260. Sharma, S.; Sharma, N. Biological Activity of Bis(Nicotinohydroxamato) Oxidovanadium(IV) Complex. *Der Chemica Sinica*. **2013**, *4*, 87-96.

261. Liguori, P. F.; Valentini, A.; Palma, M.; Bellusci, A.; Bernardini, S.; Ghedini, M.; Panno, M. L.; Pettinari, C.; Marchetti, F.; Crispini, A.; Pucci, D. Non- Classical Anticancer Agents: Synthesis and Biological Evaluation of Zinc(II) Heteroleptic Complexes. *Dalton Trans.* **2010**, *39*, 4205-4212.

262. Mendiguchia, B.S.; Pucci, D.; Mastropietro, T. F. Non-Classical Anticancer Agents: On the Way to Water Soluble Zinc(II) Heteroleptic Complexes. *Dalton Trans.* **2013**, *42*, 6768-6774.

263. Magda, D.; Lecane, P.; Zhong, W.; Hu, W.; Thiemann, P.; Ma, X.; Dranchak, P. K.; Wang, X.; Lynch, V.; Wei, W.; Csokai, V.; Hacia, J. G.; Sessler, J. L. Synthesis and Anticancer Properties of Water-Soluble Zinc Ionophores. *Cancer Res.* **2008**, *68*, 5318-5325.

264. Cvek, B.; Milacic, V.; Taraba, J.; Dou, Q. P. Ni(II), Cu(II) and Zn(II) Diethyldithiocarbamate Complexes against the Proteasome in Breast Cancer Cells. *J. Med. Chem.* **2008**, *51*. 6256-6258.

265. Singh, B.; Mishra, J.; Pradhan, A. Physicochemical Microbial and Pharmacological Studies of Zn(II) - Melphalan Complex. *Int. J. Chem. Tech. Res.* **2012**, *4*, 546-552.

266. Satoh, M.; Kondo, Y.; Mita, M.; Nakagawa, I.; Naganuma, A.; Imura, N. Prevention of Carcinogenicity of Anticancer Drugs by Metallothionein Induction. *Cancer Res.***1993**, *53*, 4767-4768.

267. Mahboobi, H.; Viarengo, A.; Colangelo, D.; Osella, D. Effect of Metal-Based Anticancer Drugs on Wild Type and Metallothionein Null Cell Lines. *Biomet*, **2003**, *16*, 403-409.

268. Arakelova, E.; Khachatryan, A. Avjyan, K.; Farmazyan, Z.; Mirzoyan, A.; Savchenko, L.; Ghazaryan, S.; Arsenyan, F. Zinc Oxide Nanocomposites with Antitumor Activity. *Nat. Sci.* **2010**, *2*, 1341-1348.

269. Modi, G. Increased Anticancer Activity of Curcumin-Zn(II) Complex by Species Sensitive Method. *Der Chemica Sinica*, **2011**, *2*, 91-99.

270. Arakelova, E. R.; Grigoryan, S. G.; Arsenyan, F. G.; Babayan, N. S.; Grigoryan, R. M.; Sarkisyan, N. K. *In vitro* and *In vivo* Anticancer Activity of Nanosize Zinc Oxide Composites of Doxorubicin. *Int. J. Med. Dentistry, Pharmaceut. Health Eng.* **2014**, *8*, 33-38.

271. Braha, S.; Gafitanu, E.; Alexandrescu, G.; Groll, M.; Gherasim, P. Antimicrobial Activities of Organic Zinc Compounds. *Rev. Med. Chir. Soc. Med. Nat.* **1992**, *96*, 249-252.

272. Zaidi, M. I.; Wattoo, F. H.; Wattoo, M. H. S. Antibacterial Activities of Nicotine and Its Zinc Complex. *Afr. J. Microbio. Res*. **2012**, *6*, 5134-5137.

273. Yamgar, R. S.; Nivid, Y.; Nalawade, S.; Mandewale, M.; Atram, R. G.; Sawant, S. Novel Zinc(II) Complexes of Heterocyclic Ligands as Antimicrobial Agents: Synthesis, Characterization, and Antimicrobial Studies. *Bioinorg. Chem. Appl.* **2014**, *2014*, 1-10.

274. Kostova, I.; Momekov, G. New Zirconium(IV) Complexes of Coumarins with Cytotoxic Activity. *Eur. J. Med. Chem*. **2006**, *41*, 717-726.

275. Allen, O. R.; Knox, R. J.; McGowan, P. C. Functionalised Cyclopentadienyl Zirconium Compounds as Potential Anticancer Drugs. *Dalton Trans*. **2008**, 5293-5295.

276. Pradhaban, G.; Kaliaraj. G. S.; Vishwakarma, V. Antibacterial Effects of Silver-Zirconia Composite Coatings Using Pulsed Laser Deposition onto 316L SS for Bio Implants. *Prog. Biomater.* **2014**, *3*, 123-130.

277. Nasrin, J.; Islam, M. S. Synthesis, Structural and Biological Activity of Peroxo Complexes of Zirconium(IV) Containing Organic Acid and Amine Bases. *J. Appl. Sci.* **2007**, *7*, 434-441.

278. Bajju, G. D.; Devi, G.; Ktoch, S.; Bhagat, M.; Deepmala, Ashu, Kundan, S.; Anandi, S. K. Synthesis, Spectroscopic and Biological Studies on New Zirconium(IV) Porphyrins with Axial Ligand. *Bioinorg. Chem. Appl.* **2013**, *2013*, 1-15.

279. Florea, A.; Büsselberg, D. Occurrence, Use and Potential Toxic Effects of Metals and Metal Compounds. *BioMet.* **2006**, *19*, 419-427.

280. Mukherjee, B.; Patra, B.; Mahapatra, S.; Banerjee, P.; Tiwari, A.;Chatterjee, M. Vanadium- an element of a typical biological significance. *Tox. Let.* 2004, *150*, 135–143.

281. Rehder, D. Biological and Medicinal Aspects of Vanadium. *Inorg. Chem. Comm.*, **2003**, *6*, 604-617.

282. Pretorius, C. A Solution and Solid State Study of Vanadium Complexes. M.Sc Dissertation, University of Free State, January, 2012.

283. Gorzsás, A. Vanadate and Peroxovanadate Complexes of Biomedical Relevance-A Speciation Approach with Focus on Diabetes. M. Sc. (Thesis), Umea University, Sweden, April 2005.

284. Beerbower, A and William B. J. The HSAB Principle and Extended Solubility Theory *Inorganica Chimica Acta.,* **1983***, 75,* 193-197.

285. Gamovskii, A. D.; Osipov, O. A.; Bulgarevich, S. B. The Principle of Hard and Soft Acids and Bases and the Problems of Competitive Coordination in Complex Compounds. *Russ. Chem. Rev.* **1972**, *41*, 341-359.

286. Chandrakumar, K. R. S.; Souray, P. A Systematic Study on the Reactivity of Lewis Acid-Base Complexes through the Local Hard-Soft Acid-Base Principle. *J. Phys. Chem A.* **2002**, *106*, 11775-11781.

287. Tavman, A. Vanadium(III) Complexes of 1, 2- Bis-(5-H/Methyl/Chloro/Nitro-1H-Banzimidazol-2-yl)-1, 2-Ethanediols. *J. Serb. Chem. Soc.* **2006**, *71*, 521-528.

288. Kütter, V. T.; Montes-Baύon, M.; Sella, S. M.; Sanz-Medel, A.; Silva-Filho, E. A. Vanadium-Binding Protein in Marine Plankton from Tropical South Atlantic Ocean. *J. Braz. Chem. Soc.* **2014**, *25*, 1116-1123.

289. Rehder, D. The Future of/for Vanadium. *Dalton Trans*. **2013**, *42*, 11749-11761.

290. Dadfarnia, S.; Shabani, A. M. H.; Mirshamsi, A. Solidified Floating Organic Drop Microextraction and Spectrophotometric Determination of Vanadium in Water Samples. *Turk. J. Chem.* **2011**, 35, 625-636.

291. Crans, D. C.; Smee, J. J.; Gaidamauskas, E.; Yang, L. The Chemistry and Biochemistry of Vanadium and the Biological Activities Exerted by Vanadium Compounds. *Chem Rev.* **2004**, *104*, 849-902.

292. Levina, A.; Lay, P. A. Metal-Based Anti-Diabetic Drugs: Advantages and Challenges. *Dalton Trans*, **2011**, *40*, 11675-11686.

293. Yamaguchi, M.; Wakasugi, K.; Saito, R.; Adachi, Y.; Yoshikawa, Y.; Sakurai, H.; Katoh, A. Synthesis of Vanadyl and Zinc(II) Complexes of 1-Hydroxy-4, 5, 6 Substituted 2 (1H)-Pyrimidinones and Their Insulin-Mimetic Activities. *J. Inorg. Biochem*. **2006**, *100*, 260-269.

294. Berry, R. E.; Armstrong, E. A.; Beddoes, R. L.; Collison, D.; Ertok, S. N.; Helliwell, M.; Garner, C. D. The Structural Characterization of Amavadin. *Angew Chem. Int. Ed.* **1999**, *38*, 795-797.

295. Pezza, R. J.; Villarreal, M. A.; Montich, G. G.; Argaraña, C. E. Vanadate Inhibits the ATPase Activity and DNA Binding Capability of Bacterial MutSB. A Structural Model for the Vandate-MutS. A Structural Model for the Vanadate-MutS Interaction at the Walker A Motif. *Nucleic Acids Res.***2002**, *30*, 4700-4708.

296. Rehder, D. Bioinorganic Vanadium Chemistry. John Wiley Sons. Inc. New York. **2008** - (Bioinorganic Chemistry, ISBN: 978-0-470-06516-7) 1-224.

297. Maurya, M. R. Structural Models of Vanadate-Dependent Haloperoxidases and Their Reactivity. *J. Chem. Sci.* **2006**, *118*, 503-511.

298. Winter, J. M.; Moore, B. S. Biology of Vanadium-Dependent Haloperoxidases. *J. Biol. Chem.* **2009**, *284*, 18577-18581.

299. Cui, Y. M.; Cai, Y. J.; Chen, W. Synthesis and Crystal Structures of Schiff Base Oxovanadium (V) Complexes [VO(Bhm)(OCH_3)(CH_3OH)] and [VO_2(Bpp)] *Russian J. Coord. Chem.* **2011**, *37*, 908-815.

300. Crans, D. C.; Mahroof-Tahir, M.; Keramidas, A. D. Vanadium Chemistry and Biochemistry of Relevance for Use of Vanadium Compounds as Antidiabetic Agents. *Mol. Cell. Biochem.* **1995**, *153*, 17-24.

301. Germinario, R. J.; Colby-Germinario, S. P.; Posner, B. I.; Nahm, K. Different Forms of Vanadate on Sugar Transport in Insulin Target and Nontarget Cells. *J. Biomed. Biotech.* **2002**, *2*, 22-30.

302. Thompson, K. H.; Orvig, C. Design of Vanadium Compounds as Insulin Enhancing Agents. *J. Chem. Soc. Dalton Trans.* 2000, 2885-2892.

303. Thompson, K. H.; McNeill, J. H.; Orvig, C. Vanadium Compounds as Insulin Mimics. *Chem. Rev.* **1999**, *99*, 2561-2571.

304. Walmsley, R. S. An Investigation into the Antidiabetic and Catalytic Properties of Oxovanadium(IV) complexes. PhD Thesis, Rhodes University, S A, December 2011.

305. Nejo, A. A. Metal(II) Schiff Base Complexes and the Insulin-Mimetic Studies on the Oxovanadium (IV) Complexes. PhD Thesis Uni. of Zululand, S A, June 2009.

306. Shaver, A.; Ng, J. B.; Hall, D. A.; Posner, B. I. The Chemistry of Peroxovanadium Compounds Relevant to Insulin Mimesis. *Mol. Cell. Biochem*. **1995**, *153*, 5-15.

307. Gummow, B. Vanadium: Environmental Pollution and Health Effects. *Elsev.* **2011**, 628-636.

308. Cam, M. C.; Brownsey, R.W.; McNeill, J. H. Mechanisms of Vanadium Action: Insulin-Mimetic or Insulin-Enhancing Agent? *Can. J. Physiol. Pharma.* **2000**, *78*, 829-847.

309. Balasubramanyam, M.; Mohan, V. Orally Active Insulin Mimics: Where Do We Stand Now? *J. Biosci.* **2001**, *26*, 383-390.

310. Tsiani, E.; Fantus, I. G. Vanadium Compounds Biological Actions and Potential as Pharmacological Agents. *TEM.* **1997**, 8, 51-58.

311. White, M. F. The IRS-Signalling System: A Network of Docking Proteins that Mediate Insulin Action. *Mol. Cell. Biochem*. **1998**, *182*, 3-11.

312. English, L.; Macara, J. G.; Cantley, L. C. Vanadium Stimulates (Na, K) ATPase in Friend Erythroleukemia Cells and Blocks Erythropoiesis. *J. Cell. Biol.* **1983**, *97*, 1299-1302.

313. Thompson, H. J.; Chasteen, D. N.; Neeker, L. Dietary Vanadyl(IV) Sulfate Inhibits Chemically-Induced Mammary Carcinogenesis. *Carcinogen.* **1984**, *5*, 849-851.

314. Novotny, L.; Kombian, S. B. Vanadium: Possible Use in Cancer Chemoprevention and Therapy. *J. Cancer Res. Updates*. **2014**, *3*, 97-102.

315. Badmaev, V.; Prakash, S.; Majeed, M. Vanadium: A Review of Its Potential Role in the Fight against Diabetes. *J. Altern. Complement Med.* **1999**, *5*, 273-291.

316. Ciranni, R.; Antonetti, M. Migliore, L. Vanadium Salts Induce Cytogenetic Effects in *In Vivo* Treated Mice. *Mutat. Res.* **1995**, *343*, 53-60.

317. Rodŕiguez-Mercado, J. J.; Mateos-Nava, R. A.; Altamirano-Lozano, M. A. DNA Damage Induction in Human Cells Exposed to Vanadium Oxides *In Vitro*. *Tox. In Vitro*. **2011**, *25*, 1996-2002.

318. Sharma, S.; Sharma, N. Synthesis, Characterization, Electrochemistry and Antimicrobial Activities of Bis (Hydroxamato) Oxidovanadium(IV) Complexes. *Der Chemica Sinica*. 2013, 4, 108-119.

319. Baysse, C.; De Vos, D.; Naudet, Y.; Vandermonde, A.; Ochsner, U.; Meyer, J.; Budzikiewicz, H.; Scha, M.; Fuch, R.; Cornelis, P. Vanadium Interferes with Siderophoremediated Iron Intake in *Pseudomonas Aeruginosa*. *Microbio*. **2000**, *146*, 2425-2434.

320. Barceloux, D. G. Vanadium. *J. Toxicol. Clin. Tox.* **1993**, *37*, 265-278.

321. Shrivastava, S.; Anjana, J.; Shukia, S.; Mathur, R. Chelation Therapy and Vanadium: Effect on Reproductive Organs in Rats. *Ind. J. Experim. Bio.***2007**, *45*, 515-523.

322. Domingo, J. L. Vanadium: A Review of the Reproductive and Developmental Toxicity. *Reprod. Tox.* **1996**, *10*, 175-182.

323. Srivastava, A. K.; Mehdi, M. Z. Insulino-Mimetic and Anti-Diabetic Effects of Vanadium Compounds. *Diab. Med.* **2004**, 22, 2-13.

324. Baran, E. J. Model Studies Related to Vanadium Biochemistry: Recent Advances and Perspectives. *J. Braz. Chem. Soc.* **2003**, *14*, 878-888.

325. Dikanov, S. A.; Liboiron, B. D.; Orvig, C. VO^{2+} Hydroxyapatite Complexes as Models for Vanadyl Coordination to Phosphate in Bone. *Mol. Phys.* **2013**, *111*, 2967-2979.

326. Roberts, D. A.; Ford, R. G.; Sparks, D. L. Kinetics and Mechanisms of Zn Complexation on Metal Oxides Using EXAFS Spectroscopy. *J.Colloid. Interface Sci.* **2003**, *263*, 364-376.

327. Sharma, N.; Prakash, R.; Chaturvedi, K. Spectroscopic and Antimicrobial Studies of Mixed Ligand Complexes of Transition Metal (II) Ions with Nitro Quinoline and Dibenzoyl Methane. *Sci. Revs. Chem. Comm.* **2012**, *2*, 108-114.

328. Core, D. P.; Kesler, S. E.; Essene, E. J. Copper and Zinc in Silicate and Oxide Minerals in Igneous Rocks from the Bingham-Park City Belt, Utah: Synchrotron X-Ray- Fluorescence Data. *Canad. Mineral*. **2005**, *43,* 1781-1796.

329. Plum, L. M.; Rink L.; Hasse, H. The Essential Toxin: Impact of Zinc on Human Health. *Int. J. Environ. Res. Public Health.* **2010**, 7, 1342-1365.

330. Eide, D. J. Zinc Transporters and the Cellular Trafficking of Zinc. *Biochemical et Biophysic. Acta.* **2006**, *1763*, 711–722.

331. Kelleher, S. L.; McCormick, N. H.; Velasquez, V.; Lopez, V. Zinc in Specialized Secretory Tissues: Roles in the Pancreas, Prostate, and Mammary Gland, *Adv. Nutr.* **2011**, *2,* 101–111.

332. Hambidge M. Human Zinc Deficiency. *J. Nutr.* **2000**, *130*, 1344S-1349S.

333. Ali, S. F. A.; Imtiaz, N; Mehdi, S. U. Analysis of Zinc in Human Blood Using Flame Atomic Absorption Spectroscopy (FAAS). *2nd Int. Conf. Med., Biol. Pharm. Sci.* **2012**, Singapore.

334. Vijayaraghavan, K.; Pillai, S. I.; Subramanian, S. P. Design, Synthesis and Characterization of Zinc-3 Hydroxyl Flavones, A Novel Zinc Metallocomplex for the Treatment of Experimental Diabetes in Rats. *Euro. J. Pharm.* **2012**, *680*, 122-129.

335. Garnovskii, A. D.; Sennikova, E.V.; Kharisov, B. I. Coordination Aspects in Modern Inorganic Chemistry, *Open Inorg. Chem. J.* **2009**, *3*, 1-20.

336. Yoshikawa, Y.; Ueda, E.; Kojima, Y.; Sakurai, H.The action mechanism of zinc(II) Complexes with Insulinomimetic Activity in Rat Adipocytes. *Life Sci.* **2004**, *75*, 741–751.

337. Janet C. King, 2 David M. Shames and Leslie R. Woodhouse, Zinc Homeostasis in Humans1 J. *Nutr.* **2000**, *130*, 1360S—1366S

338. Ma, Z.; Jacobsen, F.E.; Giedroc, D. P. Metal Transporters and Metal Sensors: How Coordination Chemistry Controls Bacterial Metal Homeostasis. *Chem Rev*. **2009**, *109*, 4644–4681.

339. Sakurai. H.; Kojima Y.; Yoshikawa Y.; Kenji K., Yasui, H. Antidiabetic Vanadium(IV) and Zinc Complexes. *Coord. Chem. Rev*. **2002**, *226*, 187-198.

340. Sakurai, H.; Katoh, A.; Yoshikawa, Y. Chemistry and Biochemistry of Insulin-Mimetic Vanadium and Zinc Complexes, Trial for Treatment of Diabetes Mellitus. *Bull. Chem. Soc. Jpn*. **2006**, *79*, 1645-1664.

341. Myers, S. A.; Nield, A.; Myers, M. Zinc Transporters, Mechanisms of Action and Therapeutic Utility: Implications for Type 2 Diabetes Mellitus *J. Nut. Met.* **2012**, 2012, 1-13.

342. Chausmer, A. B. Zinc, Insulin and Diabetes. *J. Amer. Coll. Nut.* **1998**. *17*, 109–115.

343. Brandt, S. The Clinical Effects of Zinc as a Topical or Oral Agent on the Clinical Response and Pathophysiologic Mechanisms of Acne: A Systematic Review of the Literature. *J. Drugs Dermatol.* **2013**, *12*, 542-545.

344. Dhawan, D. K.; Chadha, V. D. Zinc: A Promising Agent in Dietary Chemoprevention of Cancer. *Ind. J. Med. Res.* **2010**, *132*, 676-682.

345. Tapiero, H. Tew, K. D. Trace Elements in Human Physiology and Pathology: Zinc and Metallothioneins. *Biomed Pharmacother.* **2003**, *57*, 399-411.

346. Yamgar, R. S.; Nivid, Y.; Nalawade, S.; Mandewale, M.; Atram, R. G.; Sawant, S. Novel Zinc (II) Complexes of Heterocyclic Ligands as Antimicrobial Agents: Synthesis, Characterization, and Antimicrobial Studies. *Bioinorg. Chem. Appl.* **2014**, *2014*, 1-10.

347. Zaidi, M. I.; Wattoo, F. H.; Wattoo, M. H. S. Antibacterial Activities of Nicotine and Its Zinc Complex. *Afr. J. Microbio. Res*. **2012**, *6*, 5134-5137.

348. Braha, S.; Gafitanu, E.; Alexandrescu, G.; Groll, M.; Gherasim, P. Antimicrobial Activities of Organic Zinc Compounds. *Rev. Med. Chir. Soc. Med. Nat.***1992**, *96*, 249-252.

349. Arabi, F.; Imandar, M.; Negahdary, M.; Imandar, M.; Noughabi, M. T.; Akbari-dastjerdi, H.; Fazilati, M. Investigation Anti-Bacterial Effect on Zinc Oxide Nanoparticles Upon Life of Listeria Monocytogenes. *Annals Biol. Res*. **2012**, *3*, 3679-3685.

350. Mocchegiani, E. Zinc and Ageing: Third Zincage Conference. *Immunity Age.* 2007, *4*, 1-7.

351. Prasad, A. S. Impact of the Discovery of Human Zinc Deficiency on Health. *J. Am. Coll. Nut.***2009**, *28*, 257–265.

352. Mestek, O; Zima, T.; Suchánek M.; Tesar V.; Merta, M. Determination of Copper, Selenium and Zinc in Human Blood by Inductively Coupled Mass Spectrometry: The Sources of Uncertainty and Variability of Results. *Sb. Lek*., **2000**, *101*, 1-10.

353. Paula, R. L. Ecotoxicity and Pollutant Concentrations of Wastewater from Mineral Processing. B.Sc (Thesis) Tampere Uni. of App. Sci. Finland, June 2013.

354. Crabtree, R. H. (Ed.) The Organometallic Chemistry of the Transition Metals. **2005**, John Wiley & Sons. Inc., New Jersey.

355. Monga, V.; Thompson, K.H.; Yuen, V.G.; Sharma, V.; Patrick, B.O.; McNeill, J.H.; Orvig, C.Vanadium Complexes with Mixed O, S Anionic Ligands Derived from Maltol: Synthesis, Characterization, and Biological Studies. *Inorg Chem.* **2005**. *44*, 2678-88.

356. Yaul, S. R.; Yaul, G. B.P.; Aswar, A. S. Synthesis and Characterization of Transition Metal Complexes with N, O- Chelating Hydrazone Schiff Base Ligand. *Amer.-Eur. J. Sci. Res.* **2009**, *4*, 229-234.

357. Raman, N.; Jeyamurugan, R. Synthesis, Characterization and DNA Interaction of Mononuclear Copper (II) and Zinc(II) Complexes Having a Hard-Soft NS donor ligand. *J. Coord. Chem.* **2009**, *62*, 2375-2387.

358. Miessler, Gary L.; Donald, A. T. *Inorg. Chem.,***1999**. ISBN 0138418918, 9780138418915, 642.

359. Bakir, S. R. Synthesis, Spectral Study and Biological Activity of Some Metal Ions Complexes with Bidentate Ligands. *J. Al-Nahrain Uni.***2012**, 15, 30-42.

360. Tian, Y.; Duan, C.; Lu, Z.; You, X. Preparation, Characterization of Metal Complexes Containing a NS Donor Ligand Derived from S-Benzyldithiocarbazate and p-Nitrobenzaldehyde. X-ray Crystal Structure of the Nickel (II) Chelate. *Tran. Met. Chem.***1996**, *21*, 254-257.

361. Contreras, R. R.; Fontai, B.; Bahsas, A.; Suarez, T.; Reyes, M.; Bellandis, F.; Nava, F.; Cancines, P. Synthesis of Copper, Nickel and Cobalt Complexes Containing a New N_2S_2 ligand: Benzyl- N, N'-Alkylbis (2-Amino-1-Cyclopentenecarbodithioate). *Tran. Met. Chem.,***2004**, *29*, 51-55.

362. Katoh, A.; Matsumura,Y.; Yoshikawa, Y.; Yasui, H.; Sakurai, H. Evaluation of Insulin-Mimetic Activities of Vanadyl and Zinc (II) Complexes from the View Point of Heterocyclic Bidentate Ligands. *Inorg. Biochem*. **2009**, *103*, 567-574.

363. Tella, A. C.; Obaleye, J. A. Metal Complexes as Antibacterial Agents: Synthesis, Characterization and Antibacterial Activity of Some 3d Metal Complexes of Sulphadimidine. *Orbital Elec. J. Chem.* **2010**, *202*, 11-26.

364. Ajibade, P.A.; Idemudia, G. I.; Okoh, A. I. Synthesis, Characterization and Antibacterial Studies of Metal Complexes of Sulfadiazine with N-Alkyl-Phenyldithiocarbamate. *Bull. Chem. Soc. Ethiop.* **2013**, *27*, 77-84.

365. Lee, A. R.; Hung, W. H. Zinc Sulfadiazines: Novel Topical Antimicrobial Agents for Burns. *J. Pharm Pharmacol.* **1995**, *47*, 503-6.

366. Cao Z.; Sun X.; Sun, Y. Rechargeable Antibacterial and Antifungal Polymeric Silver Sulfadiazine. *J. Bio. Comp. Poly.* **2009**, *24*, 350-367.

367. Mastrolorenzo, A.; Scozzafava, A.; Supuran, C. T. Antifungal Activity of Sliver and Zinc Complexes of Sulfa Drug Derivatives Incorporating Arylsufonylureido Moieties. *Euro. J. Pharm. Sci.* **2000**, *11*, 99-107.

368. Bult, A.; Hulsing, N.; Weyland, J. W.; Zinc and Cerium Sulfadiazine, Zinc Sulfathiazole Real Compounds or Physical Mixtures. *Pharm. Weekblad. Sci. Ed.* **1980**, 2, 190-195.

369. Narang, K. K.; Gupta, J. K. Sulfa Drug Complexes of Zinc(II), Cadmium(II) and Mercury(II). *Tran. Met. Chem.*, **1977**, *2*, 181-183.

370. Ghoneim, M. M.; Mabrouk, E. M.; Hassanein, A. M.; El-Attar, M. A.; Hesham, E. A.; Voltammetric and Potentiometric Studies of Some Sulfa Drug-Schiff Base Compounds and Their Metal Complexes. *Centr. Euro. J. Chem.* **2007**, 898-911.

371. Golzar Hossain, G.M.; Amoroso, A. J.; Banu, A.; Malik, K. M. A. Syntheses and

Characterization of Mercury Complexes of Sulfadiazine, Sulfamerazine and Sulfamethazine. *Poly.* **2007**, *26*, 967-974.

372. Ajibade, P. A.; Kolawole, G. A.; Synthesis, Characterization, Antiplasmodial and Antitrypanosomal Activity of Some Metal(III) Complexes of Sulfadiazine. *Bull. Chem. Soc. Ethiop*. **2008**, *22*, 261-268.

373. Ajibade, P.A.; Kolawole, G.A.; O'Brien, P.; Helliwell. M.; Raftery, J. Cobalt(II) Complexes of the Antibiotic Sulfadiazine, the X-ray Single Crystal Structure of $[Co(C_{10}H_9N_4O_2S)\ (CH_3OH)_2]$. *Inorg. Chim. Acta.* **2006**, *359*, 3111-3116.

374. Delgado, D. R. Martinez, F.; Fakhree, M. A. A. Jouyban, A. Study of the Solubility of Some Sodium Sulfonamides in Ethanol + Water Co-Solvent Mixtures and Correlation with the Jouyban Acree Model. *Biomed. Int*. **2011**, 2, 5-11.

375. Delgado, D. R.; Martinez, R. F. The Thermodynamic Study of the Solubility of Sodium Sufadiazine in Some Ethanol + Water Cosolvent Mixtures. ISSN 0121-4004, **2010**, 17, 2.

376. Martinez, F.; Avila, C. A.; Gomez, A. Thermodynamic Study of the Solubility of Some Sulfonamides in Cyclohexane. *J. Braz. Chem. Soc.* **2003**, *14*, 808-808.

377. Hogarth, G. Metal-Dithiocarbamate Complexes: Chemistry and Biological Activity. *Mini. Rev. Chem.* **2012**, *12*, 1202-1215.

378. Ekennia, A. C. Antibacterial Application of Novel Mixed-Ligand Dithiocarbamate Complexes of Nickel (II). *IOSR J. Appl. Chem.* **2013**, *5*, 36-39.

379. Rath, N. C.; Rasaputra, K. S.; Liyanage, R.; Huff, G. R,; Huff, M. E. Dithiocarbamate Toxicology-An Appraisal, Pesticide in Modern World-Effects of Pesticides Exposure. Stoytcheva, M. (Ed), ISSN: 978-953-307-454-2, **2011**.

380.Ahamad, M. M.; Rao, R. M.; Kumar, E. V. M.; Begun, J. T. M.; Sreeramulu, J. Synthesis, Characteristics and Biological Evaluation of Dithiocarbamate metal. *J.Chem. Pharm. Res*. **2012**, *4*, 1601-1605.

381. Pitchaimani, P.; Lo, K. M.; Elango, K. P. Synthesis, Spectral Characterization, Crystal Structures and Catalytic Activity of a Series of Lanthanide(III) Azepane Dithiocarbamate Complexes. *Poly*. **2013**, *54*, 60-66.

382. Madalageri, P. M.; Kotresh, O. Synthesis and Biological Evaluation of Some Novel Substituted 4- Chloroquinolin 2-(1H)-One Dithiocarbamates. *Der Pharma Chemica.* **2012**, *4*, 2187-2193.

383. Nabipour, H. Synthesis of a New Dithiocarbamate Cobalt Complex and Its Nanoparticles with the Study of Their Biological Activities. *Int. J. Nano. Dim.* **2011**, *1*, 225-232.

384. Shockravi, A.; Kamali, M. Sorkhei, F.; Jafari R. A Simple and Efficient Synthesis and Dynamic NMR Studies of New Podands of Dithiocarbamates Formed from Bis (Naphthyl) derivatives. *Het. Chem.***2011**, *2*, 659-668.

385. Kolehmainen, E.; Koivukorpi, J. Synthesis of Both Ionic Species of Ammonium Dithiocarbamate Derived Cholic Acid Moieties. *Molecules*, **2011**, *16*, 6306-6312.

386. Jayaraju, A.; Ahamad, M. M.; Rao, M. R.; Sreeramulu, J. Synthesis, Characterization and Biological Evaluation of Novel Dithiocarbamate Metal Complexes. *Der Pharma Chemica*. **2012**, *4*, 1191-1194.

387. Sharma, R.; Kaushik, N. K. Thermal Studies on Some Organotin(IV) Complexes with Piperidine and 2-Aminopyridine Dithiocarbamates. *J. Chem. Anal. Cal.* **2004**, *78*, 953-964.

388. Onwudiwe, D. C. and Ajibade, P. A .Synthesis, Characterization and Thermal Studies of Zn(II), Cd(II) and Hg(II) Complexes of *N*-Methyl-*N*-Phenyldithiocarbamate: The Single Crystal Structure of $[(C_6H_5)\ (CH_3)\ NCS_2]_4Hg_2$. *Int. J. Mol. Sci.* **2011**, *12*, 1964-1978.

389. Onwudiwe, D. C. and Ajibade, P. C. Synthesis and Crystal Structure of Bis (*N*-Alkyl-*N*-Phenyldithiocarbamato) Mercury(II). J. Chem. *Crystallogr.* **2011**, 41, 980–985.

390. Grainger, R. S. and Innocenti, P. New Applications of Dithiocarbamates in Organic Synthesis. *Het. Chem.* **2007**, *18*, 568-571.

391. Nyamen, L. D.; Rajasekhar Pullabhotla, V.S.R.; Nejo, A. A.; Ndifon, P. T.; Warner, J. H, Revaprasadu, N. Synthesis of anisotropic PbS Nanoparticles Using Heterocyclic Dithiocarbamate Complexes. *Dalton Trans.* **2012**, *41*, 8297-8302.

392. Jing, X.; Liu, F.; Yang, X.; Ling, P.; Li, L.; Long, C.; Li, A. Adsorption Performances and Mechanisms of the Newly Synthesized N, N-Di (Carboxymethyl) Dithiocarbamate Chelating Resin Toward Divalent Heavy Metal Ions from Aqueous Media. *J. Hazardous Mat.* **2009**, *167*, 589–596.

393. Tarique M. Cr(III), Mn(II), Fe(III) ,Co(II), Ni(II), Cu(II) and Zn(II) Complexes with Diisobutyldithiocarbamato Ligand. *E-J.Chem.* **2011**, *8*, 2020-2023.

394. Yoshikawa, Y.; Adachi, Y.; Sakurai, H. A New Type of Orally Active Anti-Diabetic Zn (II)-Dithiocarbamate Complex. *Life Sci.***2007**, *80*, 759–766.

395. Jain, S.; Longia, S; Ramnani, V. K. Metal Complexes as Magic Bullet-An Overview. *People's J. Scientif. Res.* **2009**, *2*, 37-40.

396. Sabale, P. M.; Patel, J.; Patel, Y. Metal Complexes: Current Trends and Future Potential. *IJPCBS*. **2012**, *2*, 251-265.

397. Ruppa, K. B. P.; Desmangles, N.; Gambarotta, S.; Yap, G.; Rheingold, A. L. Preparation and Characterization of a Homoleptic Vanadium(III) Amide Complex and Its Transformation into Terminal Chalcogenide Derivatives [(3, 5-Me_2Ph) and]$_3$ VdE (E) S, Se; Ad) Adamantyl). *Inorg. Chem.* **1997**, *36*, 1194-1197.

398. Choukroun, R.; Moumboko, P. Chevalier, S.; Etienne, M.; Donnadieu, B. Cationic Homoleptic Vanadium(II), (IV) and (V) Complexes Arising from Protonolysis of [V (Net_2)$_4$] *Chem. Int. Ed.* **1998**, *37*, 3169-3172.

399. Sharma, M.; Sachar, R. Syntheses and Characterization of the Adducts of Bis (N, N-Diethyldithiocarbamato) Oxovanadium(IV) with Substituted Pyridines. *Oriental J. Chem.* **2009**, *25*, 215-218.

400. Doadrio, A. L.; Sotelo, J.; Fernádez-Ruano, A. Synthesis and Characterization of Oxovanadium(IV) Dithiocarbamates with Pyridine. *Quim. Nova*. **2002**, *25*, 522-528.

401. Khattak, Z. A. K.; Zia-ur Rehman; Khan, A.; Badshah, A.; Fettouhi, M.; Fazal, A. Self-Assembled Heteroleptic Zn(II) Dithiocarbamate-Based 2D-Interwoven Supramolecular Giant Macrocycles and Their Redox Properties. *Hetero. Chem* .**2014**, *00*, 1-7.

402. Wood, P. L.; Khan, M. A.; Moskal, J. R. Mechanism of Action and Sodium Aurothiomalate: Restoration of Cellular Free Thiols and Sequestration of Reactive Aldehydes. *Euro. J. Pharmacol.* **2008**, *580*, 48-54.

403. Fricker, S. P. Medical Uses of Gold Compounds: Past, Present and Future. *Gold Bull.* **1996**, *29*, 53-60.

404. Messori, L.; Marcon, G.; Orioli, P. Gold(III) Compounds as New Family of Anticancer Drugs. *Bioinorg. Chem. Appl.* **2003**, *1*, 177-187.

405. Milacic. V.; Fregona, D.; Dou, Q. P. Gold Complexes as Prospective Metal-based Anticancer Drugs. *Histol Histopathol.* **2008**, *23*, 101-108.

406. Ronconi, L.; Fregona, D. The Midas Touch in Cancer Chemotherapy: from Platinum-to-Gold-Dithiocarbamate Complexes. *Dalton Trans.* **2009**, *28*, 10670-10680.

407. Marzano, C.; Roncoli, L.; Chiara, F.; Giron, M. C.; Faustineli, I.; Cristofori, P.; Trevisan, A.; Fregona, D. Gold (III)-dithiocarbamate Anticancer Agents: Activity, Toxicology and Histopathological Studies in Rodents. *Int. J. Cancer.* **2011**, *129*, 487-496.

408. Nardon, C.; Boscutti, G.; Fregona, D. Beyond Platinums: Gold Complexes as Anticancer Agents. *Anticancer Res*. **2014**, *34*, 487-492.

409. Nardon, C.; Schmitt, S. M.; Yang, H.; Zuo, J.; Fregona, D.; Dou, Q. P. Gold(III)-Dithiocarbamate Peptidomimetics in the Forefront of the Targeted Anticancer Therapy: Preclinical Studies against Human Breast Neoplasia. *Plos One*. **2014**, *9,* 1-10.

410. Cattaruzza, L.; Fregona, D.; Mongiat, M.; Ronconi, L.; Fassina, A.; Colombatti, A. Aldinucci, D. Antitumour Activity of Gold (III)-dithiocarbamate Derivatives on Prostate Cancer Cells and Xenografts. *Int. J. Cancer.* **2011**, *128,* 206-215.

411. Novelli, F.; Recine, M.; Sparatore, F.; Juliano, C. Gold(I) complexes as antimicrobial agents. *Farmaco*, **1999**, *54*, 232-236.

412. Glišić, B. D.; Djuran, M. I. Gold Complexes as Antimicrobial Agents: an Overview of Different Biological Activities in Relation to the Oxidation State of the Gold and the Ligand Structure. *Dalton Trans*. **2014**, *43*, 5950-5969.

413. Bertrand, B.; Casini, A. A Golden Future in Medicinal Inorganic Chemistry: the Promise of Anticancer Gold Organometallic Compounds. *Dalton Trans.* **2014**, *43*, 4209-4219.

414. Milacic, V.; Fregona, D.; Dou, Q. P. Gold Complexes as Prospective Metal-based Anticancer Drugs. *Histol Histopathol.* **2008**, *23*, 101-108.

415. Ma, X.; Yu, H. Global Burden of Cancer. Yale J. Biol. Med. 2006, 79, 85-94.

416. Beck, S. L.; Falkon, G. Prevalence and Management of Cancer in South Africa. *Pain*. **2001**, *94*, 75-84.

417. Nissinen, A.; Berrios, X.; Puska, P. Community-Based Noncommunicable Disease Interventions: Lessons from Developed Countries for Developing Ones. *Bull. World Health Org.* **2001**, *79*, 963-970.

418. Nobili, S.; Lippi, D.; Witort, E.; Donnini, M.; Bausi, L; Mini, E; Capaccioli, S. Natural Compounds for Cancer Treatment and Prevention. *Pharmacol. Res.* **2009**, *59*, 365-378.

419. Agarwal, N.; Majee, C.; Chakraborthy, G. S. Natural Herbs as Anticancer Drugs. *Int. J. Pharm. Tech. Res.* **2012**, *4*, 1142-1153.

420. Rosenberg, S A. Immunotherapy and Gene Therapy of Cancer 1. Cancer Res. 1991, 51, 5074-5079.

421. Rosenberg, S A. The Immunotherapy and Gene Therapy of Cancer Res. *Clin. Oncol.* 1992, *10*, 180-199.

422. Chemotherapy. http://www.wikidoc.org/index.php/Chemotherapy (accessed April 29, 2015).

423. DeVita, V. T.; Chu, E. A History of Cancer Chemotherapy. *Cancer Res.*2008, *68*, 6843-6853.

424. Pronzato, P.; Rondini, M. First Line Chemotherapy of Metastatic Breast Cancer. *Annals Oncol.* **2006**, *17*, 165-168.

425. Pasparakis, G.; Manouras, T.; Vamvakaki, M.; Argitis, P. Harnessing Photochemical Internalization with Dual Degradable Nanoparticles for Combinatorial Photo-Chemotherapy. *Nature Comm.* **2014**, *5*, 1-9.

426. Balis, F. M. The Goal of Cancer Treatment. *Oncol*. 1998, *3*, 5.

427. Connors, T. Anticancer Drug Development: The Way Forward. *Oncol.* **1996**, *1*, 2-3.

428. Khan, F. A.; Aktar, S. S.; Sheikh, M. K. Cancer Treatment-Objectives and Quality of Life Issues. *Malay. J. Med. Sci.* **2005**, *12*, 3-5.

429. Kauffman, G. B. Michele Peyrone (1813-1883), Discovery of Cisplatin, Plat. Met. Rev. 2010, 54, 250-256.

430. Taguchi, T.; Razzaque, M. S. Cisplatin-Associated Nephrotoxicity and Pathological Events Cell. *Stress Response Renal Diseases*. **2005**, *148*,106-120.

431. Telpouskhovskaia, M. A.; Rodriguez-Rodriguez, C.; Scott, L. E.; Page, B. D. G.; Patrick, B. O.; Orvig, C. Synthesis, Characterization and Cytotoxicity Studies of Cu(II), Zn(II) and Fe(III) Complexes of N-Derivatised 3-Hydroxy-4-pyridiones. *J. Inorg. Biochem.* **2014**, *132*, 59-66.

432. Shi, Y.; Toms, B. B.; Dixit, N.; Kumari, N.; Mishra, L.; Goodisman, J.; Dabrowiak, J. C. Cytotoxicity of Cu(II) and Zn(II) 2, 2 Bipyridyl Complexes: Dependence of IC_{50} on Recovery Time. *Chem. Rev. Toxicol.* **2010**, *23*, 1417-1426.

433. Nath, P.; Dhumwad, S. D. Synthesis, Characterization, Antimicrobial, DNA Binding and Cytotoxic Studies of Co(II), Ni(II), Cu(II) and Zn(II) Complexes of Quinoline-Adenine Schiff Bases. *Der Pharma Chemica*, **2014**, *6*, 253-261.

434. Qui, X.; Li, S.; Shi, A.; Li, Q.; Zhai, B. Synthesis, Characterization and Cytotoxic Activity of a Zinc(II) Complexes of the Schiff Base Derived from S-Benzyldithiocarbazate. *Chin. J. Struct. Chem.* **2012**, *31*, 555-561.

435. Giannicchi, I.; Brissis, R.; Ramos, D.; Lapuente, J.; Lima, J. C.; Cort, A. D. Rodriguez, L. Substituent Effects in the Biological Properties of Zn-Salophen Complexes. *Inorg. Chem.* **2013**, *52*, 9245-9253.

436. Narang, A. S.; Desai, D. S. Anticancer Drug Development Unique Aspects of Pharmaceutical Agents. *Pharm. Perspect. Cancer Theraupeut.* **2009**, 49-52.

437. Castro-Garza, J. H.; Barrio-Garcia, H. B.; Cruz-Vega, D. E.; Said-Fernández, S.; Carranza-Rosalles, P.; Molina-Torres, C. A.; Vera-Cabrera, L. Use of a Colorimetric Assay to Measure Differences in Cytotoxicity of Mycobacterium Tuberculosis Strains. *J Med. Microbiol*. 2007, 56, 733-737.

438. Jorgensen, J. H.; Ferraro, M. J. Antimicrobial Susceptibility Testing: A Review of General Principles and Contemporary Practices. *Clin. Infect. Dis.* **2009**, *49*, 1749-1755.

439. Ghabraie, E.; Moghimi, H.; Balalaie, S.; Bararjanian, M.; Rominger, F.; Bijanzadeh, H. R. Efficient Synthesis of Functionalized Dithiocarbamate Derivatives through One-Pot Three-Component Reaction and Evaluation of Their Antimicrobial Activities. *J. Iran. Chem.Soc.* **2013**, *10*, 725-732.

440. Goubert-Renaudin, S.; Gaslain, F.; Marichal C.; Lebeau B.; Schneider, R. I.; Walcarius, A. Synthesis of Dithiocarbamate-Functional Mesoporous Silica-Based Materials: Interest of One-Step Grafting. *New J. Chem*. **2009**, *33*, 528-537.

441. Movassagh, B.; Shokri, B. A Facile and Efficient One-Pot Regioselective Synthesis of 2-hydroxyalkyl dithiocarbamates under Catalyst-Free Conditions. *Int. J. Org. Chem.* **2012**, *2*, 248-253.

442. Bardajee, G. R.; Sadraei, S.; Taimoory, S.; Abtin, E. One-Pot Synthesis of Dithiocarbamates under Solvent-Free Conditions in the Presence of KF/Al_2O_3. *Asian J. Biochem. Pharmaceut. Res.* **2011**, *1*, 178-184.

443. Aryanasab, F.; Saidi, M. R. Transition Metal-Free Addition of Alkynes: One- Pot Regioselective Synthesis of S-Vinyl Dithiocarbamates under Solvent-Free Conditions. *Monatsh Chem*. **2012**, *143*, 1171-1174.

444. Chatterjee, T.; Bhadra, S.; Ranu, B. C.; Transition Metal-Free Procedure for the Synthesis of S-Aryl Dithiocarbamates Using Aryl Diazonium Fluoroborate in Water at Room Temperature. *Green Chem*. **2011**, *13*, 1837-1842.

445. Parada-Aliste, J.; Megia-Fernandez, A.; Torre-Gonzalez, D. D.; Hernandez-Mateo, F.; Santoyo-Gonzalez, F. Synthesis of *S*- and *N*- Functionalized Dithiocarbamates from Cyclic Sulfates. *Eur. J. Org. Chem.* **2013**, 3578-3763.

446. Azizi, N.; Gholibeglo, E.; Nayeri, S. D. An Efficient Synthesis of Dithiocarbamates under Ultrasound Irritation in Water. *Monatsh Chem*. **2012**, *143*, 1171-1174.

447. Sha, Q.; Wei, Y. One-Pot Synthesis of S-Alkyl Dithiocarbamates via the Reaction of *N*-tosylhydrazones, carbon disulfide and amines. *Org. Biomol. Chem.* **2013**, *11*, 5615-5620.

448. Halimehjani, A. Z.; Marjani, K.; Ashouri, A. Synthesis of Dithiocarbamate by Markovnikov Addition Reaction in Aqueous Medium. *Green Chem*. **2010**, *12*, 1306-1310.

449. Srivastava, K. P.; Singh, S.; Kumar, S. Green Chemical Synthesis and Photochemical Reactions of Symmetrical Phthaloic Bis-amine Dithiocarbamic Anhydrides. *Der Chemica Sinica*. **2013**, *4*, 24-31.

450. Ghorbani-Vaghei, R.; Amin, M.; Veisi, H. A New and Facile Protocol for the Synthesis of Dithiocarbamate-Linked 3, 4-Dihydro-2H-pyran using N-Halo Catalysts under Mild Conditions Reaction. *Bull. Korean Chem. Soc*. **2012**, *33*, 4047-4051.

451. Bardajee, G. R.; Sadraei, S.; Taimoory, S.; Abtin, E. One-Pot Synthesis of Dithiocarbamates under Solvent-Free Conditions in the Presence of KF/Al_2O_3. *Asian J. Biochem. Pharmaceut. Res.* **2011**, *1*, 178-184.

452. Nabipour, H.; Ghammamy, S.; Ashuri, S; Aghbolaghc, Z. S. Synthesis of a New Dithiocarbamate Compound and Study of Its Biological Properties. *Org. Chem. J.* **2010**, *2*, 75-80.

453. Ghabraie, E.; Moghimi, H.; Balalaie, S.; Bararjanian, M. Efficient Synthesis of Functionalized Dithiocarbamate Derivatives through One-Pot Three-Component Reaction and Evaluation of Their Antimicrobial Activities. *J. Iran Chem. Soc.* **2013**, *10*, 725-732.

454. Kanchi, S.; Singh, P.; Bisetty, K. Dithiocarbamates as Hazardous Agent: A Critical Review on Progress in Environmental Chemistry for Inorganic Species Studies of 20^{th} Century. *Arabian J. Chem.* **2014**, *7*, 11-25.

455. Sun, N.; Li, B.; Shao, J.; Mo, W.; Hu, B.; Shen, Z.; Hu, X. A General and Facile One-Pot Process of Isothiocyanates from Amines under Aqueous Conditions. *Bellstein J. Org. Chem*. **2012**, *8*, 61-70.

456. Halimehjani, Z. A.; Katayoun, M.; Ashouri, A. Synthesis of Dithiocarbamate by Markovnikov Reaction in Aqueous Medium. *Green Chem.* **2010**, *12*, 1306-1310.

457. Aryanasab, F.; Halimehjani, A. Z.; Saidi, M. R. Dithiocarbamate as an Efficient Intermediate for the Synthesis of 2-Amino-1, 2, 3-Thiadiazoles in Water. *Tetrahed. Let.* **2010**, *51*, 790-792.

458. Capello, C.; Fisher, U.; Hungerbu¨hler. What Is a Green Solvent? A Comprehensive Framework for the Envionmental Assessment of Solvents. *Green Chem.* **2007**, *9*, 927-934.

459. Jessop, P. G. Searching for Green Solvents. *Green Chem*. **2011**, *13*, 1391-1398.

460. Girolami, G. S.; Rauchfuss, T. B.; Angelici, R. J. Synthesis and Technique in Inorganic Chemistry, *A Lab. Manual*, 3rd ed.; University Science Books: Sausalito, CA, **1999**.

461. Coury, L. Conductance Measurements Part 1: Theory. *Curr. Separat*. 1999, *18*, 91-96.

462. Szirtes, L.; Megyeri, J.; Kuzmann, E. Klencs´ar, Z. Electrical Conductivity of Transition Metal Containing Crystalline Zirconium Phosphate Materials. *Solid State Ionics.* **2001**, *145*, 257–260.

463. Refat, M.; El-Deen, I. M.; Zein, M. A.; Adam, A. M. A.; Kobeasy, M. Spectroscopic, Structural and Electrical Conductivity Studies of Co(II), Ni(II) and Cu(II) Complexes Derived from 4-Acetylpyridine with Thiosemicarbazide. *Int. J. Electrochem. Sci.* **2013**, *8*, 9894-9917.

464. Fadeeva, V. P.; Tikhova, V. D.; Nikulicheva, O. N. Elemental Analysis of Organic Compounds with the Use of Automated CHNS Analyzers. *J. Analytic. Chem.* **2008**, *63*, 1094-1106.

465. Olagboye, S. A., Hassan, G. F. Synthesis, Characterization and Biocidal Evaluation of Azole Based Ligands Metal Complexes. *Int. J. App. Sci. Biotechnol.* **2013**, *1*, 258-265.

466. Onwudiwe, D. C.; Ajibade, P. A. Synthesis and Characterization of Metal Complexes of *N*-Alkyl-*N*-Phenyl Dithiocarbamates. *Poly*. **2010**, *29*, 1431-1436.

467. CHN Elemental Microanalysis. http:// www.ucl.ac.uk/pharmacy/facilities/research-services/chn-elemental-microanalysis.(accessed Dec. 18, 2014).

468. Peta, P. G. 2400 Series 2 CHNS/O Analyser. http:// www.google.co.za/url?url=http://qub.ac.uk/schools/SchoolofChemistryandChemicalEngineering/FileStore/InternalForms/ASEPAnalyticalServicesand Environmental Projects/Filet upload, 404656 (accessed Dec. 18, 2014).

469. Siddiqi, K. S.; Shahab, A. A.; Lutfullah, N.; Chebude, Y. Template Synthesis of Symmetrical Transition Metal Dithiocarbamates. *J. Braz. Chem. Soc.***2006**, *17*, 107-112.

470. Ajibade, P. A.; Onwudiwe, D. C.; Moloto, M. J. Synthesis of Hexadecylamine Capped Nanoparticles Using Group 12 Complexes of N-Alkyl-N-Phenyl Dithiocarbamates as Single-Source Precursors. *Poly*. **2011**, *30*, 246-252.

471. Raya, I.; Baba, I.; Yamin, B. M. New Mixed Ligands Complexes of Samarium(III) with Dithiocarbamates and 1, 10- Phenanthroline. *Mal. J. Anal. Sci.* **2006**, *10*, 93-98.

472. Uddin, M. S.; Chowdhury, D. A.; Islam, M. T. Studies on Some Dioxouranium(VI) Complexes with Dithiocarbamate Ligands. *CMU. J. Nat. Sci.* **2014**, *13*, 1-9.

473. Venugopal, K.; Musthaq, A. M, Jaya, R. A.; Rameshbabu, K., Noorjahan, B. T.; Sreeramulu. Chemical Synthesis, Characterization and Antibacterial Activity of 2-Amino-2-Ethyl 1, 3 Propanediol and It's Cu(II), Ru(III) Complexes. *URJC*, **2014**, *2*, 8-15.

474. Munir, C.; Hassan, S. T.; Ahmad, N. Complexes of Fe(III), Co(II) and Zn(II) with Thiocarbamyldithiocarbamate and Their Antibacterial Activity. *J. Chem. Soc. Pak.* **1987**, *9*, 463-471.

475. Mathur, P. N.; Parashar, K.; Shrivastava, S. Synthesis of a Novel Metal Chelating Ion Exchange Resin Specific for Zinc. *Indian J. Chem*. **2000**, *39A,* 1327-1330.

476. Tarique, M.; Aslam, M. Bi and Trivalent Metal Complexes of Dithiocarbamates Derived from 2, 6-Diacetylpyridine. *Oriental J. Chem.* **2008**, *24*, 267-270.

477. Garg, B. S.; Singh, A. L.; Dixit, R. Mixed Ligand Complexes of Manganese (III) with Dithiocarbamate and Glycine/Acetylacetone, Ligands: Magnetic, Spectra and Thermal Studies. *Tran. Met. Chem*. **1998**, *13*, 351-355.

478. Su, C.; Tang, N.; Gan, X.; Cai, L. Synthesis and Characterization of Light Lanthanide Complexes with Monosubstituted Dithiocarbamates. *Synth. React. Inorg. Met. Org. Chem.* **1997**, *27*, 291-300.

479. Oktavee, D.; Síleš, B.; Štefanec, J.; Korgovă, E.; Garajok, J. The Electronic Spectra of Nickel (II) Bis(Dithiocarbamate) Chelates. *Collect. Czech. Chem. Comm.* **1980**, *5*, 791-799,

480. Manohar, A, Ramalingam, K.; Karpagaveli, K. Mixed Ligand Complexes Involving Bis(Dithiocarbamate)Nickel(II) and Phosphorus Donors: Synthesis, Spectral, Thermal Studies and BVS Investigations. *IJCRG.* **2012**, *4*, 1383-1391.

481. Gopal, K. V.; Jyothi, P. S.; Raju, P. A. G.; Rameshbabu, K.; Sreeramulu. Synthesis and Characterization of 2-Amino Pyridine Dithiocarbamate Ligand and It's Cu(II), Co(II) Metal Complexes. *J. Chem. Pharm. Res* .**2013**, *5*, 50-69.

482. Examination of Proton NMR Spectra. http://www.oneonta.edu/faculty/knauerbr/221lects/nmr.pdf.(accessed Jan. 8, 2015).

483. Gaal, V.; H. L. M.; Diesveld, J. W.; Pijpers, F. W.; Van der Linder, J. G. M. Carbon-13 Nmr Spectra of Dithiocarbamates Chemical Shifts, Carbon- Nitrogen Stretching Vibration Frequencies, and Bonding in the NCS Fragment. *Inorg. Chem.***1979**, *18*, 3251-3260.

484. Kamaludin, N. F.; Awang, N.; Baba, I. Synthesis, Characterization and Crystal Structure of Organotin(IV) *N*-Butyl *N*- Phenyldithiocarbamate Compounds and their Cytotoxicity in Human Leukemia Cell Lines. *Pakistan J. Bio. Sci.* 2013, *16*, 12-21.

485. Krakowiat, J.; Lunberg, D.; Persson, I. A Coordination Chemistry Study of Hydrated and Solvated Cationic Vanadium Ions in Oxidation States +III, +IV and +V in Solution and Solid State. *Inorg. Chem.***2012**, *51,* 9598-9609.

486. Liu, S.; Gao, S. Synthesis, Crystal Structure and Spectral Properties of VO (acetyl acetone benzoyl hydrazone) (8-quinolinol). *Poly.***1988**, *17,* 81-84.

487. Rehder, D. Biological and Medicinal Aspects of Vanadium. *Inorg. Chem. Comm.* 2003, *6,* 604–617.

488. Rehder, D. The Coordination Chemistry of Vanadium as Related to Its Biological Functions. *Coord. Chem Rev,* **1999**, 182, 297-322.

489. Hakimelahi, R. Stability and Molecular Structure of Some Vanadium Complexes Effective in Biological Systems: a Quantum Mechanical Study. *Int. J. Env. Eng.* **2011**, *2,* 1-5.

490. Kundu, S.; Mondal, D.; Bhattacharya, K.; Endo, A.; Sanna, D.; Garibba, E.; Chaudhury, M. Nonoxido Vanadium (IV) Compounds Involving Dithiocarbazate-Based Tridentate ONS Ligands: Syntheses, Electronic and Molecular Structure, Spectroscopic and Redox Properties. *Inorg. Chem.* **2015**, *54*, 6203-6215.

491. Zorzano, A. Palacin, M.; Marti, L.; Garcia-Vicente, S. Arylalkylamine Vanadium Salts as New Anti-Diabetic Compounds. *J.Inorg. Biochem.* **2009**, *103*, 559.566.

492. Ritter, S. Hard and Soft Acids and Bases. *Sc. Tech.***2003**, *81,* 50.

493. Rajeswari, M.; Shivakumar, S.; Ramesh, H.; Mageswari, K.; Rajappa, A.; Savithri, S. Single Crystal EPR Optical Studies of Vanadyl (II) Doped in Tetraaqua (1, 10-Phenanthroline –K2 N, N') Magnesium (II) Dinitrate. *IJCPS*, **2014**, *2*, 944-952.

494. Majhi, P. K. Synthesis and Characterization of Oxovanadium Featuring O- and N-Donor Environment. M.Sc. Dissertation. National Institute of Technology, Rourkela, India, May 2009.

495. Cornman, R. C.; Geiser-Bush, K. M.; Rowley, S. P.; Boyle, P. D. Structural and Electron Paramagnetic Resonance Studies of the Square Pyramidal to Trigonal Bipyramidal Distortion of Vanadyl Complexes Containing Sterically Crowded Schiff Band Ligands. *Inorg. Chem.* **1997**, *36*, 6401-6408.

496. Cocco, M. T.; Onnis, V.; Ponticelli, G.; Meier, B.; Rehder, D.; Garribba, E.; Micera, G. Synthesis, Characterisation and Insulin-Mimetic Activity of Oxovanadium (IV) Complexes with Amidrazone Derivatives. *J. Inorg. Biochem*. **2007**, *101*, 19-29.

497. Sharma, M.; Sachar, R. Synthesis and Characterization of the Adducts of bis (N, N-Diethyldithiocarbamato) Oxovanadium (IV) with Substituted Pyridines. *Oriental J. Chem.* **2009**, *25*, 215-218.

498. Mubarak, A. T. Supramolecular Structures of Oxovanadium(IV) Polymeric Complexes Containing Quinoline Azodyes. *Designed Mono. Poly.* 2005, *8*, 1-10.

499. Kasahara, R.; Tsuchimoto, M.; Ohba, S.; Nakajima, K.; Ishida, H.; Kojima, H. Interconversion Between Polymeric and Monomeric Forms of Oxovanadium(IV) Complexes with Tetradentate Schiff Base Ligands Derived from (*R, R*)- 2, 4- Pentanediamine. *Inorg. Chem*. **1996**, *35*, 7661-7665.

500. Olagboye, S. A., Hassan, G. F. Synthesis, Characterization and Biocidal Evaluation of Azole Based Ligands Metal Complexes. *Int. J. App. Sci. Biotechnol.* **2013**, *1*, 258-265.

501. CHN Elemental Microanalysis. http:// www.ucl.ac.uk/pharmacy/facilities/research-services/chn-elemental-microanalysis.(accessed Dec. 18, 2014).

502. Peta, P. G. 2400 Series 2 CHNS/O Analyser. http:// www.google.co.za/url?url=http://qub.ac.uk/schools/SchoolofChemistryandChemicalEngineering/FileStore/InternalForms/ASEPAnalyticalServices and Environmental Projects/ (accessed Dec. 18, 2014).

503. Ajibade, P. A.; Kolawole, G. A.; O'Brien, P. Metal Complexes of 4-Amino-N-(2-Pyrimidinyl)benzene Sulfonamide: Synthesis, Characterization and Antiprotozoal Studies. *Syn. React. Inorg., Met.-Org Nano-Met. Chem.* **2007**, *37*, 653-659.

504. García-Raso, A.; Fiol, J.J.; Martorell, G.; López-Zafra A.; Quirós M. Metallation of 2-Sulfanilamidopyrimidine (Sulfadiazine). X-Ray Diffraction Structure and Solution Behaviour of Bis(Sulfadiazinato) Mercury(II) Bis(Dimethylsulfoxide). *Poly*. **1997**, *16*, 613-621.

505. Selbin, J. Oxovanadium (IV) Complexes. *Coord. Chem. Rev.*1966, *1*, 293-314.

506. Ajibade, P. A.; Kolawole, G. A.; O'Brien, P. Metal Complexes of 4-Amino-N-(2-Pyrimidinyl)benzene Sulfonamide: Synthesis, Characterization and Antiprotozoal Studies. *Syn. React. Inorg., Met.-Org Nano-Met. Chem.* **2007**, *37*, 653-659.

507. Wazalwar, S. S.; Bhave, N. S.; Dikundwar, A. G.; Ali. P. Microwave Assisted Synthesis and Antimicrobial Study of Schiff Base Vanadium(IV) Complexes of Phenyl Esters of Amino Acids. *Syn. Reac. Inorg., Met-Org. Nano-Met. Chem.* **2011**, 41, 459-464.

508. Maurya, R. C.; Sutradhar, D.; Martin, M. H.; Roy, S.; Chourasia, J.; Sharma, A. K.; Vishwakama, P. Oxovanadium(IV) Complexes of Medical Relevance: Synthesis, Characterization and 3D Molecular Modelling and Analysis of Some Oxovanadium (IV) Complexes in O, N-Donor Coordination Matrix of Sulfa Drug Schiff Bases Derived from a 2-Pyrazolin-5-one Derivative. *Arab. J. Chem*. **2015**, *8*, 78-92.

509. Sharma, M.; Sachar, R. Synthesis and Characterization of the Adducts of Bis-(*N, N*-Diethyldithiocarbamato) Oxovanadium (IV) with Substituted Pyridines. *Oriental J. Chem.* **2009**, *25*, 215-218.

510. Elsayed, B. A.; Elhenawy, A. A.; Sultanah, A. S. A. Synthesis, Characterization, Antibacterial and Cytotoxic Studies on Some Novel Transition Metal Complexes of Schiff Base Ligand Derived from Sulfadiazine with Molecular Orbital Calculations. *Int. J. Chem. Mat. Res.* **2014**, *2*, 1-16.

511. Uzma, M. A. Synthesis and Characterization of the Complexes of Vanadium with Hydrazide. Potential Antidiabetic Agent. PhD Thesis. 2006, Uni. of Karachi, Pakistan.

512. Manohar, A, Ramalingam, K.; Karpagaveli, K. Mixed Ligand Complexes Involving Bis(Dithiocarbamate)Nickel(II) and Phosphorus Donors: Synthesis, Spectral, Thermal Studies and BVS Investigations. *IJCRG.* **2012**, *4*, 1383-1391.

513. Gopal, K. V.; Jyothi, P. S.; Raju, P. A. G.; Rameshbabu, K.; Sreeramulu. Synthesis and Characterization of 2-Amino Pyridine Dithiocarbamate Ligand and It's Cu(II), Co(II) Metal Complexes. *J. Chem. Pharm. Res.* **2013**, *5*, 50-69.

514. Chauhan, H. P. S.; Carpenter, J.; Joshi, S. Synthetic Aspects, Spectral, Thermal Studies and Antimicrobial Screening on Bis(N, N-Dimethyl dithiocarbamato-S, S)Antimony(III) Complexes with Oxo or Thio Donor Ligands. *Spectrochim. Acta Part A: Mol. Biomol. Spec.* **2014**, *130*, 230-237.

515. Mishra, A. P.; Pandey, L. R.; Jain, R. K. Microwave Synthesis, Reactivity, Spectral and Thermal Analysis of Some Binary/ Mixed Ligand Oxovanadium(IV) Complexes. *Chem. Sci. Trans.* **2012**, *1*, 121-133.

516. Haas, K. L.; Franz, K. J. Application of Metal Coordination Chemistry to Explore and Manipulate *Cell Biology. Chem. Rev*. **2009**, *109*, 4921-4960.

517. Sanyal, R.; Guha, A.; Ghosh, T.; Mondal, T. K.; Zangrando, E.; Das, D. Influence of the Coordination Environment of Zinc(II) Complexes of Designed Mannich Ligands on Phosphatase Activity: A Combined Experimental and Theoretical Study. *Inorg. Chem*. **2014**, *53*, 85-96.

518. Shit, S.; Chakraborty, J.; Samanta, B.; Rosair, G. M.; Mitra, S. Synthesis, Structure and Florescence Properties of a Trinuclear Zn(II) Complexes with *N, N, O*-Donor Schiff Base Ligands and Bridging Acetates. *Z. Naturforsch*. **2009**, *64b*, 403-408.

519. Mahapatra, B. B.; Panda, S. K. Coordination Compounds of Co(II), Ni(II), Zn(II), Cd(II) and Hg(II) with Tridentate ONS Donor Azo Dye Ligands. *Biokem.* **2010**, *22*, 0795-08080.

520. Rehman, S.; Ikran, M.; Rehman, S.; Ul Islam, N.; Jan, N. Synthesis and Characterization of Ni(II), Cu(II) and Zn(II) Tetrahedral Transition Metal Complexes of Modified Hydrazine. *J. Med. Chem. Soc.* **2011**, *55*, 164-167.

521. Al-Obaidi, O. H. Synthesis, Characterization and Antimicrobial Screening Mixed-Ligand Cu(II) and Zn(II) Complexes: DNA Binding Studies on Cu(II) Complexes. *Open. J. Inorg. Non-Metal. Mat.* **2013**, *2*, 59-64.

522. Gull, P.; Al-Thabaiti, S. A.; Hashmi, A.A. Design, Characterization and Antimicrobial Activity of Cu(II), Co(II) and Zn(II) Complexes with Schiff Base from 1, 2-Diphenylethane-1, 2-Dione and N-(1-Naphthyl) Ethylenediamine. *Int. Multidisciplin. Curr. Res.* **2014**, *2*, 1142-1147.

523. Bharti, S. K.; Singh, S. K. Metal Based Drugs: Current Use and Future Potential. *Der Pharm. Let.* **2009**, *1*, 39-511.

524. Sarkar, K.; Sen, K. Some Drugs in Action: Metal Ions Do Influence the Activity. *IJPRSR*, **2015**, *6*, 1-13.

525. Bhattacharyya, S.; Kumar, S. B.; Dutta, S. K.; Tiekink, E. R. T.; Chaudhury, M. Zinc(II) and Copper(II) Complexes of Pentacoordinating (N_4S) Ligands with Flexible Pyrazolyl Arms: Synthesis, Structure, and Redox and Spectroscopic Properties. *Inorg. Chem.* **1996**. *35*, 1967-1973.

526. Dudev, T.; Lim, C. Tetrahedral vs Octahedral Zinc Complexes with Ligands of Biological Interest: A DFT/CDM Study. *J. Am. Chem. Soc.* **2000**, *122*, 11146-11153.

527. Lin, H.; Huang, C.; Shi, C.; Liao, Y.; Chen, C.; Lin, Y.; Liu, Y. Synthesis of Alkynylated Photo-luminescent Zn(II) and Mg(II) Schiff Base Complexes. *Dalton Trans.* **2007**, 781-791.

528. Niklas, N.; Walter, O.; Hampel, F.; Alsfasser, R.; Can Aromatic Interactions Control Geometry of Zinc Complexes? Structural Evidence and a Possible Mechanism for the

Conversion of Trigonal-bipyramidal to Octahedral Compounds. *J. Chem. Soc. Dalton Trans.* **2002**, 3367-3373.

529. Shaban, S. Y.; Puchta, R.; Van Eldik, R. Five Coordinate Zinc(II) Complexes Containing Sterically Demanding Bio-Mimetic N_3S_2 Ligands: Syntheses, Characterization and DFT Calculations. *Z. Naturforsch*. **2010**, *65b*, 251-257.

530. Yuan, R.; Xiong, R.; Chen, Z.; Zhang, P.; Ju, H.; Dai, Z.; Guo, Z.; Fun, K.; You, X. Crystal Structure of Zinc(II) 2-Sulfanilamidopyrimidine: A widely Used Topical Burn Drug. *J. Chem. Soc. Dalton Trans.* **2001**, 774-776.

531. Fabretti, A. C.; Franchini, G. C.; Preti, C.; Zannini, P. Transition Metal Complexes with 2-Methyl-, 3-Methyl-, and 4-Methyl- Piperidine Dithiocarbamate as Ligands. *Tran. Met. Chem.* **1985**, *10*, 284-287.

532. Zedan, S. W. Binuclear Complexes of Co(II), Ni(II), Cu(II) and Zn(II) with Mixed Ligand Triethylenetetraamine Dithiocarbamate and Glycine. *Coll. Basic. Edu. Res. J* .**2010**, *10*, 530-542.

533. Amirnasr, M.; Bagheri, M.; Farrokhpour, H.; Schenk, K. J.; Mereiter, K. New Zn(II) Complexes with N_2S_2 Schiff Base Ligands. Experimental and Theoretical Studies of the Role of Zn(II) in Disulfide Thiolate-Exchange. *Poly*. **2014**, 71, 1-7.

534. Konstantinović, S..; Radovanović, B.; Cakić, V.; Vasić, V. Synthesis and characterization of Co(II), Ni(II), Cu(II) and Zn(II) complexes with 3-salicylidenehydrazone-2-indolinone. *J. Serb. Chem. Soc.* **2003**, *68*, 641-647.

535. Panuganti, S. J. Principles Involved in Bioassay by Different Methods: A Mini-Review. *RRJOB*. **2015**, *3*, 1-18.

536. Li, A. P. Preclinical *In vitro* Screening Assays for Drug-Like Properties. *Drug Discov.* **2005**, *2*, 179-185.

537. Brandon, E. F. A.; Raap, C. D.; Meijerman, I.; Beijnen, J. H.; Schellens, J. H. M. An Update on *In Vitro* Test Methods in Human Hepatic Drug Biotransformation Research: Pros and Cons. *Tox. App. Pharm.* **2003**, *189*, 233-246.

538. Nogueira, D. R.; Mitjans, M.; Rolim, C. M. B.; Vinardell, M. P. Mechanisms Underlying Cytotoxicity Induced by Engineered Nanomaterials: A Review of *In Vitro* Studies. *Nanomat.* **2014**, *4*, 454-484.

539. Yin, L.; Wang, W.; Wang, Y.; Xu, Y.; Yang, Y. Simultaneous Application of BrdU and WST-1 Measurements for Detection of the Proliferation and Viability of Airway Smooth Muscle Cells. *Biol. Res.* **2014**, *47*, 47-75.

540. Ejidike, I. P.; Ajibade, P. A. Synthesis, Characterization and *In vitro* Antioxidant and Anticancer Studies of Ruthenium(III) Complexes of Symmetric and Asymmetric Tetradentate Schiff Bases. *J. Coord. Chem.* **2015**, *68*, 2552-2564.

541. Agbo, E. N.; Makhafola, T. J.; Choong, Y. S.; Mphahlele, M. J.; Ramasami, P. Synthesis, Biological Evaluation and Molecular Docking Studies of 6-Aryl-2-Styrylquinzolin-4(3H)-Ones. *Mol.* **2016**, *21*, 1-15.

542. Vichai, V.; Kirtikara, K. Sulforhodamine B Colorimetric Assay for Cytotoxicity Screening. *Nature Prot.* **2006**, *1*, 1112-1116.

543. Voigt, W. Sulforhodamine B Assay and Chemosensitivity. *Methods Mol. Med.* **2005**, *110*, 39-48.

544. Osman, S. A.; Mousa, H.A.; Yosef, H. A. A.; Hafez, T. S.; El-Sawy, A. A.; Abdallah, M. M.; Hasssan, A. S. Synthesis, Characterization and Cytotoxicity of Mixed Ligand Mn(II), Co(II) and Ni(II) Complexes. *J. Serb. Chem. Soc.* **2014**, *79*, 953-964.

545. Salahuddin, Shaharyar, M.; Mazumber, A. Benzimidazole: A Biologically Active Compounds. *Asian J. Chem*. **2012**, *30,* 1-17.

546. Andrews, J. M. Determination of Minimum Inhibitory Concentrations. *J. Antimic. Chemother.* **2001**, *48*, 5-16.

547. Akbor; M.A., Islam, M. S.; Akhter, N.; Ahmed, S.; Siraj, S. Studies on Antibacterial and Antifungal Activities and Minimum Inhibitory Concentrations of Mixed Ligand Transition Metal Complexes of Dibasic Acids as Primary and Heterocyclic Bases as Secondary Ligands. *Bangl. J. Sci. Ind. Res.* **2011**, *46*, 365-368.