



UNIVERSITI PUTRA MALAYSIA

**SYNTHESIS, CHARACTERIZATION AND BIOACTIVITY OF NEW
PHOSPHOROUS CONTAINING SCHIFF BASES PREPARED FROM
DITHIOCARBAZATE DERIVATIVES AND THEIR METAL
COMPLEXES**

ISAM HUSSAIN T. AL-KARKHI

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**DOCTOR OF PHILOSOPHY
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By

ISAM HUSSAIN T. AL-KARKHI

**Thesis Submitted to the School of Graduate Studies, Universiti Putra Malaysia,
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January 2011



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SYNTHESIS, CHARACTERIZATION AND BIOACTIVITY OF NEW PHOSPHOROUS CONTAINING SCHIFF BASES PREPARED FROM DITHIOCARBAZATE DERIVATIVES AND THEIR METAL COMPLEXES

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ISAM HUSSAIN T. AL-KARKHI

January 2011

Chairman: Dr. Mohamed Ibrahim Mohamed Tahir (D. Phil.)

Faculty: Science

Twelve novel phosphorous containing Schiff bases derived from the four isomeric dithiocarbazates which are methyl hydrazinecarbodithioate (SMDTC), phenyl hydrazinecarbodithioate (SBDTC), 2-methylbenzyl hydrazinecarbodithioate (S2MBDTC) and 4-methylbenzyl hydrazinecarbodithioate (S4MBDTC) with 2-(diphenylphosphino) benzaldehyde (DPPB), (triphenylphosphanylidene) acetaldehyde (TPPA) and (triphenylphosphanylidene)propan-2-one (TPPP). Metal complexes of Cd(II), Co(III), Cu(II), Ni(II) and Zn(II) were synthesized from these twelve Schiff bases to obtain sixty metal complexes. All these novel compounds have been successfully synthesized and characterized by various physico-chemical and spectroscopic techniques. The structures of nine Schiff bases and two transition metal complexes were successfully determined *via* X-ray crystallographic analysis.



Four novel Schiff bases were coordinated in their metal complexes through nitrogen, sulfur and phosphorous donor atoms (PNS tridentate ligands), while the other eight Schiff bases coordinated through nitrogen and sulfur donor atoms (NS bidentate ligands). The cobalt complexes $\text{Co}(\text{SMDPB})_2 \text{NO}_3 \cdot 3\text{H}_2\text{O}$ had distorted octahedral geometry, coordinating *via* the triphenylphosphine phosphorous, azomethine nitrogen and thiolate sulphur atoms of the Schiff bases. The nickel complex has square planar geometry and coordinated *via* azomethine nitrogen and thiolate sulphur atoms of the Schiff base, while the λ^5 phosphorous do not coordinate.

All the seventy two novel compounds have been evaluated for their biological activities against certain pathogenic microbial and two breast cancer cell lines, MCF-7 (human breast carcinoma cells with positive estrogen receptor) and MDA-MB231 (human breast carcinoma cells with negative estrogen receptor). The complexes were mostly antibacterial, but were less active against the fungal strains tested. The Schiff bases in this study show a weak activity except for S2MBDTPA which shows a moderate activity. Complexation of these Schiff bases with the transition metal ions will enhance and increased the activity significantly. It was also found that the complexes contain λ^5 P shows more activity than λ^3 P. The complexes were generally more active against the MCF-7 cell line as compared to the MDA-MB231 cell line. Most of the metal complexes exhibited higher bioactivity compared to their ligands in the complexes.



Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan untuk ijazah Doctor Falsafah.

**SINTESIS, PENCIRIAN DAN AKTIVITI BIOLOGI BES SCHIFF BARU
MENGANDUNGI FOSFORUS YANG DISEDIAKAN DARIPADA
TERBITAN DITHIOKARBAZAT DAN KOMPLEKS-KOMPLEKS
LOGAMNYA**

Oleh

ISAM HUSSAIN T. AL-KARKHI

January 2011

Pengerusi: Dr. Mohamed Ibrahim Mohamed Tahir (D. Phil.)

Fakulti: Sains

Dua belas bes Schiff novel yang mengandungi fosforus dan gabungan empat isomerik ditiokarbazat iaitu metilhidrazinkarboditioat (SMDTC), fenilhidrazinkarboditioat (SBDTC), 2-metilbenzilhidrazinkarboditioat (S2MBDTC) dan 4-metilbenzilhidrazinkarboditioat (S4MBDTC) dengan 2-(difenilfosfino)benzaldehyd(DPPB), (trifenilfosfanilidin)asetaldehyd (TPPA) dan (trifenilfosfanilidin)propan-2-on (TPPP). Kompleks logam Cd(II), Co(II), Cu(II), Ni(II) dan Zn(II) telah disintesis daripada duabelas bes Schiff tersebut untuk mendapatkan enam puluh kompleks logam, kesemua sebatian novel telah berjaya disintesis dan dicirikan dengan pelbagai teknik-teknik fisiko-kimia dan spektroskopi. Struktur sembilan bes Schiff dan dua kompleks logam peralihan telah berjaya ditentukan melalui analisis kristalografi sinar-X.

Empat bes Schiff novel terkoordinat didalam kompleks logam mereka melalui atom penderma nitrogen, sulfur dan fosforus (ligan tridentat PNS), sementara lapan bes Schiff yang lair berkoordinat melalui atom perderma nitrogen dan sulfur (ligan bidentat NS). Kompleks kobalt $\text{Co}(\text{SMDPB})_2 \text{NO}_3 \cdot 3\text{H}_2\text{O}$ mempunyai geometri oktahedron terherot, dikoordinat melalui atom fosforus trifenilfosfin, nitrogen azometin dan sulfur tiolat pada bes Schiff. Kompleks nikel mempunyai geometri satah segiempat sama dan berkoordinat melalui atom nitrogen azometin dan sulfur tiolat pada bes Schiff, sementara fosforus λ^5 tidak terkoordinat.

Kesemua tujuh puluh dua sebatian novel tersebut telah dinilai untuk aktiviti biologi terhadap beberapa mikrob patogen dan dua titisan sel kanser payudara MCF-7 (sel karsinoma payudara manusia dengan penerima estrogen positif) dan MDA-MB231 (sel karsinoma payudara penerima estrogen negatif). Kebanyakan kompleks antibakteria tetapi kurang aktif terhadap strain kulat yang diuji. Bes Schiff dalam kajian ini menunjukkan aktiviti yang lemah kecuali S2MBDTPA dimana menunjukkan aktiviti yang moderat. Pengkompleksan bes Schiff ini dengan ion logam peralihan akan meningkatkan aktiviti dengan signifikan lebih dan. Kompleks mengandugi $\lambda^5\text{P}$ menunjukkan aktiviti yang teloh can $\lambda^3\text{P}$. Kompleks secara umumnya lebih aktif terhadap titisan sel MCF-7 jiba dibandingkan dengan titisan sel MDA-MB231. Kebanyakan kompleks logam menunjukkan bioaktiviti yang lebih tinggi berbanding dengan ligan didalamnya.

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I certify that an Examination Committee met on date of viva to conduct the final examination of Isam Hussain T. Al-Karkhi on his Doctor of Philosophy thesis entitled “Synthesis, Characterization and Bioactivity of New Phosphorous Containing Schiff Bases Prepared from Dithiocarbazate Derivatives and Their Transition Metal Complexes” in accordance with Universities and University Colleges Act 1971 and the Constitution of the Universiti Putra Malaysia [P.U.(A) 106] 15 March 1998. The Committee recommends that the student be awarded the Doctor of Philosophy.

Members of the Examination Committee were as follows:

Nor Azah Yusof, PhD
Associate Professor
Faculty of Science
Universiti Putra Malaysia
(Chairperson)

Sidik Silong, PhD
Associate Professor
Faculty of Science
Universiti Putra Malaysia
(Internal Examiner)

Abdul Halim Abdullah, PhD
Associate Professor
Faculty of Science
Universiti Putra Malaysia
(Internal Examiner)

Ali Morsali, PhD
Associate Professor
Tarbiat Modares University
Iran
(External Examiner)

SHAMSUDDIN SULAIMAN, PhD
Professor and Deputy Dean
School of Graduate Studies
Universiti Putra Malaysia

Date: 11 April 2011



This thesis was submitted to the Senate of Universiti Putra Malaysia and has been accepted as fulfilment of the requirement for the degree of Doctor of Philosophy. The members of the Supervisory Committee were as follows:

Mohamed Ibrahim Mohamed Tahir, D. Phil., PhD

Senior Lecturer
Faculty of Science
Universiti Putra Malaysia
(Chairman)

Karen Anne Crouse, PhD

Professor
Faculty of Science
Universiti Putra Malaysia
(Member)

Rozita Rosli, PhD

Assoc. Prof.
Faculty of Medical and Health Science
Universiti Putra Malaysia
(Member)

HASANAH MOHD GHAZALI, PhD

Professor and Dean
School of Graduate Studies
University Putra Malaysia

Date: 24 March 2011



DECLARATION

I declare that the thesis is my original work except for the quotations and citations, which have been duly acknowledged. I also declare that this it has not been previously, and is not concurrently, submitted for any other degree at Universiti Putra Malaysia or at any other institutions.

ISAM HUSSAIN T. AL-KARKHI

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LIST OF TABLES

Table	Page
2.1 Substrates used for the synthesis of various iminophosphine ligands.	36
2.2 FT-IR for ligands HL ¹ – HL ² and its acetate palladium(II) complexes	40
2.3 Antimigratory activity of NSC 295642 and its analogs	50
3.1 Preparation of Schiff bases derived from DPPB and their abbreviations	57
3.2 Preparation of Schiff bases derived from TPPA and their abbreviations	58
3.3 Preparation of Schiff bases derived from TPPP and their abbreviations	59
4.1 Analytical data and physical properties of the Schiff Bases and their metal complexes.	73
4.2 Infrared data of the Schiff bases and metal complexes	81
4.3 ¹ H NMR Data of SMDTPB, SBDTPB, S2MBDTPB, S4MBDTPB, SMDTPA, SBDTPA, S2MBDTPA, S4MBDTPA, SMDTPP, SBDTPP, S2MBDTPP, S4MBDTPP Schiff bases	88
4.4 ¹³ C NMR Data of SMDTPB, SBDTPB, S2MBDTPB, S4MBDTPB, SMDTPA, SBDTPA, S2MBDTPA, S4MBDTPA, SMDTPP, SBDTPP, S2MBDTPP, S4MBDTPP Schiff bases	89
4.5 Suggested fragmentation for SMDPB, SBDPB, S2MBDPB & S4MBDPB	92
4.6 Suggested fragmentation for SMDTPA, SBDTPA, S2MBDTPA & S4MBDTPA	95
4.7 Suggested fragmentation for SMDTPP, SBDTPP, S2MBDTPP & S4MBDTPP	99
4.8 Magnetic susceptibility and molar conductivity measurements of the metal complexes.	105



4.9	Electronic Spectral Data for the Schiff Bases and Their Transition Metal Complexes	114
4.10	Different bond angles and bond lengths of the nine Schiff bases	119
4.11	Selected Bond Lengths (Å) and Bond Angles (°) for SMDPB	122
4.12	Selected Bond Lengths (Å) and Bond Angles (°) for SMDTPA	123
4.13	Selected Bond Lengths (Å) and Bond Angles (°) for SMDTPP	124
4.14	Selected Bond Lengths (Å) and Bond Angles (°) for SBDPB	125
4.15	Selected Bond Lengths (Å) and Bond Angles (°) for SBDTPA	126
4.16	Selected Bond Lengths (Å) and Bond Angles (°) for SBDTPP	127
4.17	Selected Bond Lengths (Å) and Bond Angles (°) for S2MBDPB	128
4.18	Selected Bond Lengths (Å) and Bond Angles (°) for S2MBDTPA	129
4.19	Selected Bond Lengths (Å) and Bond Angles (°) for S4MBDPB	130
4.20	Selected Bond Lengths (Å) and Bond Angles (°) for Co (SMDPB) ₂ NO ₃ .H ₂ O Metal Complex	134
4.21	Selected Bond Lengths (Å) and Bond Angles for Ni (S2MBDTPA) ₂ Metal Complex	135
4.22	Qualitative Antimicrobial and Antifungal screening result of the Schiff bases and their Transition Metal Complexes	144
4.23	Quantitative Antimicrobial Analysis of the Schiff bases and their Transition Metal Complexes screening results –MIC.	147
4.24	Cytotoxic Data of the Isomeric Dithiocarbazates, their Schiff bases and their Transition Metal complexes.	156



LIST OF FIGURES

Figure	Page
1.1 Some of common phosphorous compounds.	2
1.2 General structure of dithiocarbazate	3
1.3 Reaction pathway for the synthesis of potassium dithiocarbazate	3
1.4 Different Dithiocarbazate used in this study	4
1.5 Cone angle of phosphine-ligand	7
1.6 Different cone angle	8
1.7 Some of phosphine ligands.	8
1.8 The four TQMP4 cadmium complexes	10
2.1 Hemoglobin	21
2.2 A- Structure of Cisplatin and Carboplatin.	22
B- Auranofin and Myocrisin.	
C- Satraplatin, Picoplatin and Iproplatin.	
2.3 The $[\text{Rh}(\text{Bipy})_2\text{Chrisy}]^{+3}$ metalloinercalaor	23
2.4 Compounds that stop the synthesis of DNA.	29
2.5: Some compounds that cause damage to the DNA.	30
2.6 Compounds causes' breakdown of the mitotic spindles.	31



2.7	Mechanism of acid-catalyzed imine formation	35
2.8	Synthesis of iminophosphine	36
2.9	General reduction and alkylation of iminophosphine ligands	37
2.10	Series of iminophosphine could be synthesized	38
2.11	Schiff base Tautomerism	39
2.12	2-(diphenylphosphino)benzaldehyde selenosemicarbazone	39
2.13	Schematic presentation of ligand and acetate palladium(II) complex	40
2.14	New iminophosphine ligands & metal complexes	41
2.15	Structure of P, S- heterodonor ligand (L1) and Pd(L1)Cl ₂ complex	42
2.16	The Schiff base of 2-diphenylphosphino) benzaldehydethio semicarbazone (PNS) and the palladium(II) complex	43
2.17	PNNS ligand and rhenium(V) complex	44
2.18	ORTEP diagram of rhenium(V) complex.	45
2.19	ORTEP diagram of [SnEt ₂ (PyTSC)(S ₂ PPh ₂)]	46
2.20	Bioactive gold(I) phosphine complexes.	47
2.21	Synthesis of phosphunt-thioate-gold complex.	47
2.22	Structure of NSC 295642. (L ₁), L ₂ & L ₃	48
2.23	Metal(II)–ligand complexes tested for antimigratory activity.	49
2.24	Palladium (II) complexes bearing 1,2-bis(diphenylphosphino) ethane (dppe) (19 and 20).	51



2.25: Iminophoshine-Au anticancer.	52
4.1 Structure of the isomeric dithiocarbazates	68
4.2: Structure of the different ketones and aldehydes used	68
4.3: Synthesis equations of the novel Schiff bases	69
4.4: Thione-Thiol tautomerism in Schiff bases	70
4.5: Expected structures of the transition metal complexes	70
4.6: General structure of 2,4-thiadiazoles formed during synthesis (Dotted lines indicate varying positions of the methyl group).	71
4.7: Coordination Sites of the Schiff Bases	79
4.8: Fragmentation of DPPB series	91
4.9: Fragmentation of TPPA series	94
4.10: Fragmentation of TPPP series	98
4.11 Packing arrangement triclinic Schiff bases (Hydrogen bonds have been removed for clarity)	117
4.12: Packing arrangement of monoclinic Schiff bases (Hydrogen bonds have been removed for clarity)	118
4.13 Structure of the Schiff base derived from 2-quinoline carboxaldehyde and S-methyldithiocarbazate	120
4.14: Crystal structure confirmation of the Schiff base	121
4.15 ORTEP Diagram of the SMDPB Schiff base.	122
4.16 ORTEP Diagram of the SMDTPA Schiff base	123

4.17	ORTEP Diagram of the SMDTPP Schiff base	124
4.18	ORTEP Diagram of the SBDPB Schiff base	125
4.19	ORTEP Diagram of the SBDTPA Schiff base	126
4.20	ORTEP Diagram of the SBDTPP Schiff base	127
4.21	ORTEP Diagram of the S2MBDPB Schiff base	128
4.22	ORTEP Diagram of the S2MBDTPA Schiff base	129
4.23	ORTEP Diagram of the S4MBDPB Schiff base	130
4.24:	Packing arrangement of $\text{Co}(\text{SMDPB})_2 \cdot \text{NO}_3 \cdot 3\text{H}_2\text{O}$ (Along axis-c)	131
4.25:	Packing arrangement of $\text{Ni}(\text{S2MBDTPA})_2$ (Along axis-c)	133
4.26	ORTEP Diagram of the $\text{Co}(\text{SMDPB})_2 \text{NO}_3 \cdot \text{H}_2\text{O}$ Metal Complex	134
4.27	ORTEP Diagram of $\text{Ni}(\text{S2MBDTPA})_2$ Metal Complex	135
4.28	Structure of salicylaldehyde and the aminobenzylamine	141
4.29	Cinnamaldehyde	142
4.30	Schiff bases of S2- & S4-methylbenzyl dithiocarbazate (methyl groups <i>ortho</i> and <i>para</i> respectively).	143
4.31	<i>o</i> -phenhydramine, <i>p</i> -phenhydramine and S2MBDTC, SMDTC	149
4.32	Pyridine -2- carboxaldehyde, 2- acetylpyridine, TPP & TPA	150
4.33	Thiophene & Pyridine compounds	151



4.34: Comparing activity of SMDTC series against MCF-7 & MDA-MB231	153
4.35: Comparing activity of SBDTC series against MCF-7 & MDA-MB231	153
4.36: Comparing activity of S2MBDTC series against MCF-7 & MDA-MB231	154
4.37: Comparing activity of S4MBDTC series against MCF-7 & MDA-MB231	154



LIST OF FIGURES AND TABLES IN APPENDICES

Figure/Table	Page
Figure A1: IR spectra comparison of SMDTC, DPPB and SMDPB	186
Figure A2: IR spectrum of SMDPB	186
Figure A3: IR spectra comparison of SMDPB and Cd(SMDPB) ₂	187
Figure A4: IR spectra comparison of SMDPB and Co(SMDPB) ₂ .NO ₃ .3H ₂ O	187
Figure A5: IR spectra comparison of SMDPB and Cu(SMDPB) ₂	188
Figure A6: IR c SMDPB and Ni(SMDPB) ₂	188
Figure A7: IR spectra comparison of SMDPB and Zn(SMDPB) ₂	189
Figure A8: IR spectrum of SBDTPB	189
Figure A9: IR spectrum of Cd(SBDTPB) ₂	190
Figure A10: IR spectrum of Co(SBDTPB) ₂ .NO ₃	190
Figure A11: IR spectrum of Cu(SBDTPB) ₂	191
Figure A12: IR spectrum of Ni(SBDTPB) ₂	191
Figure A13: IR spectrum of Zn(SBDTPB) ₂	192
Figure A14: IR spectrum of S2MBDTPB	192
Figure A15: IR spectrum of Cd(S2MBDTPB) ₂	193
Figure A16: IR spectrum of Co(S2MBDTPB) ₂	193



Figure A17: IR spectrum of $\text{Cu}(\text{S2MBDTPB})_2$	194
Figure A18: IR spectrum of $\text{Ni}(\text{S2MBDTPB})_2$	194
Figure A19: IR spectrum of $\text{Zn}(\text{S2MBDTPB})_2$	195
Figure A20: IR spectrum of S4MBDTPB	195
Figure A21: IR spectrum of $\text{Cd}(\text{S4MBDTPB})_2$	196
Figure A22: IR spectrum of $\text{Co}(\text{S4MBDTPB})_2 \cdot \text{NO}_3$	196
Figure A23: IR spectrum of $\text{Cu}(\text{S4MBDTPB})_2$	197
Figure A24: IR spectrum of $\text{Ni}(\text{S4MBDTPB})_2$	197
Figure A25: IR spectrum of $\text{Zn}(\text{S4MBDTPB})_2$	198
Figure A26: IR spectra comparison of SMDTPA and TPPA	198
Figure A27: IR spectrum of SMDTPA	199
Figure A28: IR spectrum of $\text{Cd}(\text{SMDTPA})_2$	199
Figure A29: IR spectrum of $\text{Co}(\text{SMDTPA})_2 \cdot \text{NO}_3$	200
Figure A30: IR spectrum of $\text{Cu}(\text{SMDTPA})_2$	200
Figure A31: IR spectrum of $\text{Ni}(\text{SMDTPA})_2$	201
Figure A32: IR spectrum of $\text{Zn}(\text{SMDTPA})_2$	201
Figure A33: IR spectra comparison of SBDTPA and TPPA	202
Figure A34: IR spectrum of SBDTPA	202
Figure A35: IR spectra comparison of SBDTPA and $\text{Cd}(\text{SBDTPA})_2$	203

Figure A36: IR spectra comparison of SBDTPA and $\text{Co}(\text{SBDTPA})_2 \cdot \text{NO}_3$	203
Figure A37: IR spectra comparison of SBDTPA and $\text{Cu}(\text{SBDTPA})_2$	204
Figure A38: IR spectra comparison of SBDTPA and $\text{Ni}(\text{SBDTPA})_2$	204
Figure A39: IR spectra comparison of SBDTPA and $\text{Zn}(\text{SBDTPA})_2$	205
Figure A40: IR spectra comparison of S2MBDTPA and S2MBDTC	205
Figure A41: IR spectrum of S2MBDTPA	206
Figure A42: IR spectrum of $\text{Cd}(\text{S2MBDTPA})_2$	206
Figure A43: IR spectrum of $\text{Co}(\text{S2MBDTPA})_2 \cdot \text{NO}_3$	207
Figure A44: IR spectrum of $\text{Cu}(\text{S2MBDTPA})_2$	207
Figure A45: IR spectrum of $\text{Ni}(\text{S2MBDTPA})_2$	208
Figure A46: IR spectrum of $\text{Zn}(\text{S2MBDTPA})_2$	208
Figure A47: IR spectra comparison of S4MBDTC and S4MBDTPA	209
Figure A48: IR spectrum of S4MBDTPA	209
Figure A49: IR spectrum of $\text{Cd}(\text{S4MBDTPA})_2$	210
Figure A50: IR spectrum of $\text{Co}(\text{S4MBDTPA})_2 \cdot \text{NO}_3$	210
Figure A51: IR spectrum of $\text{Cu}(\text{S4MBDTPA})_2$	211
Figure A52: IR spectrum of $\text{Ni}(\text{S4MBDTPA})_2$	211
Figure A53: IR spectrum of $\text{Zn}(\text{S4MBDTPA})_2$	212
Figure A54: IR spectra comparison of SMDTPP and TPPP	212

Figure A55: IR spectrum of SMDTPP	213
Figure A56: IR spectrum of Cd(SMDTPP) ₂	213
Figure A57: IR spectrum of Co(SMDTPP) ₂ .NO ₃	214
Figure A58: IR spectrum of Cu(SMDTPP) ₂	214
Figure A59: IR spectrum of Ni(SMDTPP) ₂	215
Figure A60: IR spectrum of Zn(SMDTPP) ₂	215
Figure A61: IR spectra comparison of SBDTPP and TPPP	216
Figure A62: IR spectrum of SBDTPP	216
Figure A63: IR spectrum of Cd(SBDTPP) ₂	217
Figure A64: IR spectrum of Co(SBDTPP) ₂ .NO ₃	217
Figure A65: IR spectrum of Cu(SBDTPP) ₂	218
Figure A66: IR spectrum of Ni(SBDTPP) ₂	218
Figure A67: IR spectrum of Zn(SBDTPP) ₂	219
Figure A68: IR spectra comparison of S2MBDTPP and S2MBDTC	219
Figure A69: IR spectrum to S2MBDTPP	220
Figure A70: IR spectrum of Cd(S2MBDTPP) ₂	220
Figure A71: IR spectrum of Co(S2MBDTPP) ₂ .NO ₃	221
Figure A72: IR spectrum of Cu(S2MBDTPP) ₂	221
Figure A73: IR spectrum of Ni(S2MBDTPP) ₂	222



Figure A74: IR spectrum of Zn(S2MBDTPP) ₂	222
Figure A75: IR spectra comparison of S4MBDTPP, TPPP and S4MBDTC	223
Figure A76: IR spectrum of S4MBDTPP	223
Figure A77: IR spectrum of Cd(S4MBDTPP) ₂	224
Figure A78: IR spectrum of Co(S4MBDTPP) ₂ .NO ₃	224
Figure A79: IR spectrum of Cu(S4MBDTPP) ₂	225
Figure A80: IR spectrum of Ni(S4MBDTPP) ₂	225
Figure A81: IR spectrum of Zn(S4MBDTPP) ₂	226
Figure B1: ¹ H NMR spectrum of SMDPB	227
Figure B2: ¹³ C NMR spectrum of SMDPB	227
Figure B3: ¹ H NMR spectrum of SBDPB	228
Figure B4: ¹³ C NMR spectrum of SBDPB	228
Figure B5: ¹ H NMR spectrum of S2MBDPB	229
Figure B6: ¹³ C NMR spectrum of S2MBDPB	229
Figure B7: ¹ H NMR spectrum of S4MBDPB	230
Figure B8: ¹³ C NMR spectrum of S4MBDPB	230
Figure B9: ¹ H NMR spectrum of SMDTPA	231
Figure B10: ¹³ C NMR spectrum of SMDTPA	231
Figure B11: ¹ H NMR spectrum of SBDTPA	232

Figure B12: ^{13}C NMR spectrum of SBDTPA	232
Figure B13: ^1H NMR spectrum of S2MBDTPA	233
Figure B14: ^{13}C NMR spectrum of S2MBDTPA	233
Figure B15: ^1H NMR spectrum of S4MBDTPA	234
Figure B16: ^{13}C NMR spectrum of S4MBDTPA	234
Figure B17: ^1H NMR spectrum of SMDTPP	235
Figure B18: ^{13}C NMR spectrum of SMDTPP	235
Figure B19: ^1H NMR spectrum of SBDTPP	236
Figure B20: ^{13}C NMR spectrum of SBDTPP	236
Figure B21: ^1H NMR spectrum of S2MBDTPP	237
Figure B22: ^{13}C NMR spectrum of S2MBDTPP	237
Figure B23: ^1H NMR spectrum of S4MBDTPP	238
Figure B24: ^{13}C NMR spectrum of S4MBDTPP	238
Figure C1: Mass spectrum of SMDPB	239
Figure C2: Mass spectrum of SBDPB	239
Figure C3: Mass spectrum of S2MBDPB	240
Figure C4: Mass spectrum of S4MBDPB	240
Figure C5: Mass spectrum of SMDTPA	241
Figure C6: Mass spectrum of SBDTPA	241



Figure C7: Mass spectrum of S2MBDTPA	242
Figure C8: Mass spectrum of S4MBDTPA	242
Figure C9: Mass spectrum SMDTPP	243
Figure C10: Mass spectrum of SBDTPP	243
Figure C11: Mass spectrum of S2MBDTPP	244
Figure C12: Mass spectrum of S4MBDTPP	244
Figure D1: UV-Vis spectrum of (SMDPB) ₂ x 10 ⁻⁵ M	245
Figure D2: UV-Vis spectrum of Cd(SMDPB) ₂ x 10 ⁻⁵ M	245
Figure D3: UV-Vis spectrum of Co(SMDPB) ₂ .NO ₃ .3H ₂ O x 10 ⁻⁵ M	245
Figure D4: UV-Vis spectrum of Cu(SMDPB) ₂ x 10 ⁻⁵ M	245
Figure D5: UV-Vis spectrum of Ni(SMDPB) ₂ x 10 ⁻³ M	245
Figure D6: UV-Vis spectrum of Zn(SMDPB) ₂ x 10 ⁻⁴ M	245
Figure D7: UV-Vis spectrum of SBDPB x 10 ⁻⁵ M	246
Figure D8: UV-Vis spectrum of Cd(SBDPB) ₂ x 10 ⁻⁵ M	246
Figure D9: UV-Vis spectrum of Co(SBDPB) ₂ .NO ₃ x 10 ⁻³ M	246
Figure D10: UV-Vis spectrum of Co(SBDPB) ₂ .NO ₃ x 10 ⁻³ M	246
Figure D11: UV-Vis spectrum of Cu(SBDPB) ₂ x 10 ⁻⁵ M	246
Figure D12: UV-Vis spectrum of Ni(SBDPB) ₂ x 10 ⁻³ M	246
Figure D13: UV-Vis spectrum of Ni(SBDPB) ₂ x 10 ⁻⁴ M	247

Figure D14: UV-Vis spectrum of $\text{Zn}(\text{SBDPB})_2 \times 10^{-4} \text{ M}$	247
Figure D15: UV-Vis spectrum of $\text{S2MBDPB} \times 10^{-4} \text{ M}$	247
Figure D16: UV-Vis spectrum of $\text{Cd}(\text{S2MBDPB})_2 \times 10^{-5} \text{ M}$	247
Figure D17: UV-Vis spectrum of $\text{Co}(\text{S2MBDPB})_2 \cdot \text{NO}_3 \times 10^{-3} \text{ M}$	247
Figure D18: UV-Vis spectrum of $\text{Cu}(\text{S2MBDPB})_2 \times 10^{-4} \text{ M}$	247
Figure D19: UV-Vis spectrum of $\text{Cu}(\text{S2MBDPB})_2 \times 10^{-5} \text{ M}$	248
Figure D20: UV-Vis spectrum of $\text{Ni}(\text{S2MBDPB})_2 \times 10^{-4} \text{ M}$	248
Figure D21: UV-Vis spectrum of $\text{Zn}(\text{S2MBDPB})_2 \times 10^{-4} \text{ M}$	248
Figure D22: UV-Vis spectrum of $\text{S4MBDPB} \times 10^{-4} \text{ M}$	248
Figure D23: UV-Vis spectrum of $\text{Cd}(\text{S4MBDPB})_2 \times 10^{-5} \text{ M}$	248
Figure D24: UV-Vis spectrum of $\text{Co}(\text{S4MBDPB})_2 \cdot \text{NO}_3 \times 10^{-3} \text{ M}$	248
Figure D25: UV-Vis spectrum of $\text{Co}(\text{S4MBDPB})_2 \cdot \text{NO}_3 \times 10^{-4} \text{ M}$	249
Figure D26: UV-Vis spectrum of $\text{Cu}(\text{S4MBDPB})_2 \times 10^{-3} \text{ M}$	249
Figure D27: UV-Vis spectrum of $\text{Cu}(\text{S4MBDPB})_2 \times 10^{-4} \text{ M}$	249
Figure D28: UV-Vis spectrum of $\text{Ni}(\text{S4MBDPB})_2 \times 10^{-3} \text{ M}$	249
Figure D29: UV-Vis spectrum of $\text{Ni}(\text{S4MBDPB})_2 \times 10^{-5} \text{ M}$	249
Figure D30: UV-Vis spectrum of $\text{Zn}(\text{S4MBDPB})_2 \times 10^{-5} \text{ M}$	249
Figure D31: UV-Vis spectrum of $\text{SMDTPA} \times 10^{-4} \text{ M}$	250
Figure D32: UV-Vis spectrum of $\text{Cd}(\text{SMDTPA})_2 \times 10^{-4} \text{ M}$	250

Figure D33: UV-Vis spectrum of $\text{Co}(\text{SMDTPA})_2 \times 10^{-3} \text{ M}$	250
Figure D34: UV-Vis spectrum of $\text{Co}(\text{SMDTPA})_2 \cdot \text{NO}_3 \times 10^{-4} \text{ M}$	250
Figure D35: UV-Vis spectrum of $\text{Cu}(\text{SMDTPA})_2 \times 10^{-3} \text{ M}$	250
Figure D36: UV-Vis spectrum of $\text{Cu}(\text{SMDTPA})_2 \times 10^{-4} \text{ M}$	250
Figure D37: UV-Vis spectrum of $\text{Ni}(\text{SMDTPA})_2 \times 10^{-4} \text{ M}$	251
Figure D38: UV-Vis spectrum of $\text{Zn}(\text{SMDTPA})_2 \times 10^{-4} \text{ M}$	251
Figure D39: UV-Vis spectrum of $\text{SBDTPA} \times 10^{-4} \text{ M}$	251
Figure D40: UV-Vis spectrum of $\text{Cd}(\text{SBDTPA})_2 \times 10^{-4} \text{ M}$	251
Figure D41: UV-Vis spectrum of $\text{Co}(\text{SBDTPA})_2 \cdot \text{NO}_3 \times 10^{-3} \text{ M}$	251
Figure D42: UV-Vis spectrum of $\text{Co}(\text{SBDTPA})_2 \cdot \text{NO}_3 \times 10^{-4} \text{ M}$	251
Figure D43: UV-Vis spectrum of $\text{Cu}(\text{SBDTPA})_2 \times 10^{-3} \text{ M}$	252
Figure D44: UV-Vis spectrum of $\text{Cu}(\text{SBDTPA})_2 \times 10^{-4} \text{ M}$	252
Figure D45: UV-Vis spectrum of $\text{Ni}(\text{SBDTPA})_2 \times 10^{-4} \text{ M}$	252
Figure D46: UV-Vis spectrum of $\text{Zn}(\text{SBDTPA})_2 \times 10^{-4} \text{ M}$	252
Figure D47: UV-Vis spectrum of $\text{S2MBDTPA} \times 10^{-4} \text{ M}$	252
Figure D48: UV-Vis spectrum of $\text{Cd}(\text{S2MBDTPA})_2 \times 10^{-4} \text{ M}$	252
Figure D49: UV-Vis spectrum of $\text{Co}(\text{S2MBDTPA})_2 \cdot \text{NO}_3 \times 10^{-3} \text{ M}$	253
Figure D50: UV-Vis spectrum of $\text{Cu}(\text{S2MBDTPA})_2 \times 10^{-4} \text{ M}$	253
Figure D51: UV-Vis spectrum of $\text{Ni}(\text{S2MBDTPA})_2 \times 10^{-3} \text{ M}$	253

Figure D52: UV-Vis spectrum of Ni(S2MBDTPA) ₂ x 10 ⁻⁴ M	253
Figure D53: UV-Vis spectrum of Zn(S2MBDTPA) ₂ x 10 ⁻³ M	253
Figure D55: UV-Vis spectrum of S4MBDTPA x 10 ⁻⁴ M	253
Figure D55: UV-Vis spectrum of Cd(S4MBDTPA) ₂ x 10 ⁻⁴ M	254
Figure D56: UV-Vis spectrum of Co(S4MBDTPA) ₂ .NO ₃ x 10 ⁻³ M	254
Figure D57: UV-Vis spectrum of Cu(S4MBDTPA) ₂ x 10 ⁻³ M	254
Figure D58: UV-Vis spectrum of Cu(S4MBDTPA) ₂ x 10 ⁻⁴ M	254
Figure D59: UV-Vis spectrum of Ni(S4MBDTPA) ₂ x 10 ⁻³ M	254
Figure D60: UV-Vis spectrum of Zn(S4MBDTPA) ₂ x 10 ⁻⁴ M	254
Figure D61: UV-Vis spectrum of SMDTPP x 10 ⁻⁴ M	255
Figure D62: UV-Vis spectrum of Cd(SMDTPP) ₂ x 10 ⁻⁴ M	255
Figure D63: UV-Vis spectrum of Co(SMDTPP) ₂ .NO ₃ x 10 ⁻³ M	255
Figure D64: UV-Vis spectrum of Co(SMDTPP) ₂ .NO ₃ x 10 ⁻⁴ M	255
Figure D65: UV-Vis spectrum of Cu(SMDTPP) ₂ x 10 ⁻³ M	255
Figure D66: UV-Vis spectrum of Cu(SMDTPP) ₂ x 10 ⁻⁴ M	255
Figure D67: UV-Vis spectrum of Ni(SMDTPP) ₂ x 10 ⁻³ M	256
Figure D68: UV-Vis spectrum of Zn(SMDTPP) ₂ x 10 ⁻⁴ M	256
Figure D69: UV-Vis spectrum of SBDTPP x 10 ⁻⁴ M	256
Figure D70: UV-Vis spectrum of Cd(SBDTPP) ₂ x 10 ⁻⁴ M	256

Figure D71: UV-Vis spectrum of $\text{Co}(\text{SBDTPP})_2 \cdot \text{NO}_3 \times 10^{-3} \text{ M}$	256
Figure D72: UV-Vis spectrum of $\text{Cu}(\text{SBDTPP})_2 \times 10^{-3} \text{ M}$	256
Figure D73: UV-Vis spectrum of $\text{Cu}(\text{SBDTPP})_2 \times 10^{-4} \text{ M}$	257
Figure D74: UV-Vis spectrum of $\text{Ni}(\text{SBDTPP})_2 \times 10^{-3} \text{ M}$	257
Figure D75: UV-Vis spectrum of $\text{Ni}(\text{SBDTPP})_2 \times 10^{-4} \text{ M}$	257
Figure D76: UV-Vis spectrum of $\text{Zn}(\text{SBDTPP})_2 \times 10^{-3} \text{ M}$	257
Figure D77: UV-Vis spectrum of $\text{S2MBDTPP} \times 10^{-4} \text{ M}$	257
Figure D78: UV-Vis spectrum of $\text{Cd}(\text{S2MBDTPP})_2 \times 10^{-3} \text{ M}$	257
Figure D79: UV-Vis spectrum of $\text{Co}(\text{S2MBDTPP})_2 \cdot \text{NO}_3 \times 10^{-3} \text{ M}$	258
Figure D80: UV-Vis spectrum of $\text{Co}(\text{S2MBDTPP})_2 \cdot \text{NO}_3 \times 10^{-4} \text{ M}$	258
Figure D81: UV-Vis spectrum of $\text{Cu}(\text{S2MBDTPP})_2 \times 10^{-3} \text{ M}$	258
Figure D82: UV-Vis spectrum of $\text{Cu}(\text{S2MBDTPP})_2 \times 10^{-4} \text{ M}$	258
Figure D83: UV-Vis spectrum of $\text{Ni}(\text{S2MBDTPP})_2 \times 10^{-3} \text{ M}$	258
Figure D84: UV-Vis spectrum of $\text{Ni}(\text{S2MBDTPP})_2 \times 10^{-4} \text{ M}$	258
Figure D85: UV-Vis spectrum of $\text{Zn}(\text{S2MBDTPP})_2 \times 10^{-3} \text{ M}$	259
Figure D86: UV-Vis spectrum of $\text{S4MBDTPP} \times 10^{-3} \text{ M}$	259
Figure D87: UV-Vis spectrum of $\text{Cd}(\text{S4MBDTPP})_2 \times 10^{-4} \text{ M}$	259
Figure D88: UV-Vis spectrum of $\text{Co}(\text{S4MBDTPP})_2 \cdot \text{NO}_3 \times 10^{-3} \text{ M}$	259
Figure D89: UV-Vis spectrum of $\text{Cu}(\text{S4MBDTPP})_2 \times 10^{-3} \text{ M}$	259



Figure D90: UV-Vis spectrum of $\text{Cu}(\text{S4MBDTPP})_2 \times 10^{-4} \text{ M}$	259
Figure D91: UV-Vis spectrum of $\text{Ni}(\text{S4MBDTPP})_2 \times 10^{-3} \text{ M}$	260
Figure D92: UV-Vis spectrum of $\text{Ni}(\text{S4MBDTPP})_2 \times 10^{-4} \text{ M}$	260
Figure D93: UV-Vis spectrum of $\text{Zn}(\text{S4MBDTPP})_2 \times 10^{-4} \text{ M}$	260
Table E1: Crystallographic Data and Structure Refinement Details for SMDPB	261
Table E2: Crystallographic Data and Structure Refinement Details for SMDTPA	266
Table E3: Crystallographic Data and Structure Refinement Details for SMDTPP	271
Table E4: Crystallographic Data and Structure Refinement Details for SBDTPP	276
Table E5: Crystallographic Data and Structure Refinement Details for SBDTPA	283
Table E6: Crystallographic Data and Structure Refinement Details for SBDTPP	289
Table E7: Crystallographic Data and Structure Refinement Details for S2MBDPB	295
Table E8: Crystallographic Data and Structure Refinement Details for S2MBDTPA	301
Table E9: Crystallographic Data and Structure Refinement Details for S4MBDPB	307
Table E10: Crystallographic Data and Structure Refinement Details for $\text{Co}(\text{SMDPB})_2 \text{ NO}_3 \cdot \text{H}_2\text{O}$	313
Table E11: Crystallographic Data and Structure Refinement Details for $\text{Ni}(\text{S2MBDTPA})_2$	322



LIST OF ABBREVIATIONS

DTC	Dithiocarbazate
K-DTC	Potassiun-Dithiocarbazae
SMDTC	methylhydrazinecarbodithioate
SBDC	benzylhydrazinecarbodithioate
S2MBDTC	2-methylbenzylhydrazinecarbodithioate
S4MBDTC	4-methylbenzylhydrazinecarbodithioate
HIV	Human Immunodeficiency Virus
TQMP4, L	8-[(pyridin-4-yl)methylthio] quinoline
DNA	Deoxyribonucleic acid
RNA	Ribonucleic acid
NLO	Non-Linear Optical properties
DPPB	2-(diphenylphosphino) benzaldehyde
TPPA	(triphenylphosphoranylidene) acetaldehyde
TPPP	1-(triphenyl phosphoranylidene)-2-propanone
SMDPB	(<i>E</i>)-methyl 2-(2-(diphenylphosphino)benzylidene) hydrazinecarbodithioate
SBDPB	(<i>E</i>)-phenyl 2-(2-(diphenylphosphino)benzylidene) hydrazinecarbodithioate



S2MBDPB	(<i>E</i>)-2-methylbenzyl 2-(2-(diphenylphosphino)benzylidene)hydrazinecarbodithioate
S4MBDPB	(<i>E</i>)-4-methylbenzyl 2-(2-(diphenylphosphino)benzylidene)hydrazinecarbodithioate
SMDTPA	Methyl (<i>2E</i>)-2-[2-(triphenyl- λ^5 -phosphanylidene)ethylidene]hydrazinecarbodithioate
SBDTPA	Phenyl (<i>2E</i>)-2-[2-(triphenyl- λ^5 -phosphanylidene)ethylidene]hydrazinecarbodithioate
S2MBDTPA	2-methylphenyl (<i>2E</i>)-2-[2-(triphenyl- λ^5 -phosphanylidene)ethylidene]hydrazinecarbodithioate
S4MBDTPA	4-methylphenyl (<i>2E</i>)-2-[2-(triphenyl- λ^5 -phosphanylidene)ethylidene]hydrazinecarbodithioate
SMDTPP	Methyl(<i>2E</i>)-2-[1-(triphenyl- λ^5 -phosphanylidene)propan-2-ylidene]hydrazinecarbodithioate
SBDTPP	Phenyl(<i>2E</i>)-2-[1-(triphenyl- λ^5 -phosphanylidene)propan-2-ylidene]hydrazinecarbodithioate
S2MBDTPP	2-methylbenzyl(<i>2E</i>)-2-[1-(triphenyl- λ^5 -phosphanylidene)propan-2-ylidene]hydrazinecarbodithioate
S4MBDTPP	4-methylbenzyl(<i>2E</i>)-2-[1-(triphenyl- λ^5 -phosphanylidene)propan-2-ylidene]hydrazinecarbodithioate
TSC	Thiosemicarbazone
HPyTSC	Pyridine-2-aldehyde thiosemicarbazonato
HS(S)PPh ₂	Dithiodiphenylphosphine
MTB	Mycobacterium tuberculosis



REMA	Repetitive Excess Mixed Anhydride
TB	Tubercles Bacillus
IC ₅₀	Inhibition concentration at 50%
MIC	Minimum inhibitory concentration in $\mu\text{g cm}^{-3}$
MTT	3-(4,5)-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide
ORTEP	Oak Ridge Thermal Ellipsoid Program
QSAR	Quantitative Structure-Activity Relationship
CHNS	Carbon, Hydrogen, Nitrogen, Sulphur
MCF-7	human breast cancer cell line with positive estrogen receptor
MDA-MB-231	Human breast carcinoma cells with negative estrogen receptor
MRSA	Methicillin resistant <i>staphylococcus</i>
B29	<i>Bacillus subtilis</i> wild type
60690	<i>Pseudomonas aeruginosa</i>
S.C	<i>Salmonella choleraesuis</i>
C.A	<i>Candida albicans</i>
398	<i>Aspergillus ochraceous</i>
20341	<i>Saccaromyces cerevisiae</i>

ICP-AES	Inductively Coupled Plasma-Atomic Emission Spectroscopic Analyses
UATR	Universal ATR (Attenuated Total Reflection Spectroscopy)
DMEM	Dulbecco's Modified Eagle Medium
dppm	(diphenylphosphino) methane
dppe	(diphenylphosphino) ethane
PBS	Phosphate buffered saline
FBS	Fetal bovine serum
NA	Nutrient Agar
PDA	Potato Dextrose Agar
HeLA	Cervical Cancer cells
ER	Estrogen
RNR	Ribonucleotide Reductase

TABLE OF CONTENTS

	Page
ABSTRACT	iii
ABSTRAK	v
ACKNOWLEDGEMENT	vii
APPROVAL	x
DECLARATION	xi
LIST OF TABLES	xii
LIST OF FIGURES	xiv
LIST OF FIGURES AND TABLES IN APPENDICES	xvii
LIST OF ABBREVIATIONS	xxx
CHAPTER	
INTRODUCTION	1
1.1 Dithiocarbazate derivatives	2
1.2 Properties of Sulphur and Nitrogen as Donor Ligands	5
1.3 Phosphine ligands	7
1.4 Metal complexes	9
1.5 Biologically applicable Transition Metal Ions	10
1.5.1 Cadmium	10
1.5.2 Cobalt	11
1.5.3 Copper	12
1.5.4 Nickel	13
1.5.5 Zinc	14
1.5.6 Research problem	15
Objectives	16
LITERATURE REVIEW	17
2.1 Organophosphorous chemistry	19
2.2 Analogies Between the chemistry of phosphorous Compounds and that of related Element (N.S.C.).	20
2.3 Bioinorganic chemistry and biological activity	20
2.4 Bacteria, fungi and antimicrobial activity	24
2.5 Cancer therapy	26
2.5.1 Therapeutic inorganic complexes	27
2.5.2 Cancer Chemotherapy	28
2.5.3 Categories of Chemotherapy Drugs	29
2.5.4 Synthetic drugs	31



2.6 Imminophosphine Ligands	33
2.7 Thione – thiol Tautomerism	38
2.8 FT-IR $\nu(\text{C-P})$ Stretching Modes	39
2.9 Transition metal complex with iminophosphine ligands	41
2.10 Phosphorus, Nitrogen and Sulphur Donor Ligands	42
as Multidentate Ligands	
2.10.1 Bidentate ligands	42
2.10.2 Tridentate Ligands	43
2.10.3 Tetradentate ligands	44
MATERIALS AND METHODS	54
3.1 Chemicals	54
3.1.1 Reagents	54
3.1.2 Solvents	54
3.2 Preparation of Substituted Dithiocarbazate Compounds	55
3.2.1 Phenylhydrazinecarbodithioate (SBDTC)	55
3.2.2 Methyhydrazinecarbodithioate (SMDTC)	55
3.2.3 (2 or 4)-Methylphenylhydrazinecarbodithioate	56
3.3 Preparation of Schiff Bases	56
3.3.1 Preparation of Schiff Bases derived from (2-(diphenylphosphino)benzaldehyde with four dithiocarbazate isomers	56
3.3.2 Preparation of Schiff Bases derived from (triphenylphosphoranylidene) acetaldehyde with four dithiocarbazate isomers	57
3.3.3 Preparation of Schiff Bases derived from (1-triphenylphosphoranylidene-2-propanone) with four dithiocarbazate isomers	58
3.4 Preparation of Metal Complexes	59
3.5 Physical Measurements and Elemental Analyses	60
3.5.1. Melting Points	60
3.5.2 Carbon, Hydrogen, Nitrogen and Sulphur (CHNS) Elemental Analyses	60
3.5.3 Mass Spectroscopic Analyses	60
3.5.4 ^1H and ^{13}C Nuclear Magnetic Resonance Spectroscopic (NMR) Analyses	61
3.5.5 Molar Conductivity Analyses	61
3.5.6 Magnetic Susceptibility Measurements	62
3.5.7 Inductively Coupled Plasma-Atomic Emission Spectroscopic Analyses	62
3.5.8 Ultraviolet/ Visible Spectroscopic Analyses	63
3.5.9 Fourier Transform Infrared Spectroscopic (FT-IR) Analyses	63
3.6 Cytotoxic Assay	64
3.6.1 Cell Culture	64
3.6.2 Treatments and Sample Dilutions	64
3.6.3. MTT Assay	65
3.7 Single Crystal X-ray Determination using Enraf-Nonius Kappa CCD Diffractometer at Oxford	66

3.8 Determination of Biological Activities	66
3.9 Qualitative Antimicrobial Assay	67
RESULTS AND DISCUSSION	68
4.1 Physico-Chemical Data Analyses of the Schiff Bases and Their Metal Complexes	71
4.2 Fourier-Transform Infrared Data for the Schiff Bases and Their Transition Metal Complexes	77
4.3 ¹ H and ¹³ C Nuclear Magnetic Resonance (NMR) Spectroscopy Analyses	84
4.3.1 ¹ H NMR Spectral Analysis	84
4.3.2 ¹³ C NMR Analysis	86
4.4 Mass Spectral Analysis	90
4.5 Molar Conductance and Magnetic Data Analyses of the Schiff bases and Their Metal Complexes	101
4.6 Electronic Spectral Analysis for the Schiff Bases and Their Transition Metal Complexes	107
4.7. X-Ray Crystallographic Analysis	117
1. (<i>E</i>)-methyl 2-(2-(diphenylphosphino)benzylidene) Hydrazincarbodithioate (SMDPB) Schiff base of methylhydrazinecarbodithioate (SMDTC)	122
2. methyl (<i>2E</i>)-2-[2-(triphenyl-λ ⁵ -phosphanylidene) ethylidene]hydrazine carbodithioate (SMDTPA) Schiff base of methylhydrazinecarbodithioate (SMDTC)	123
3. methyl(<i>2E</i>)-2-[1-(triphenyl-λ ⁵ -phosphanylidene) propan-2-ylidene]hydrazine carbodithioate (SMDTPP) Schiff base of methylhydrazinecarbodithioate (SMDTC)	124
4. (<i>E</i>)-benzyl 2-(2-(diphenylphosphino)benzylidene) hydrazincarbodithioate(SBDPB) Schiff base of benzylhydrazinecarbodithioate (SBDTC)	125
5. phenyl (<i>2E</i>)-2-[2-(triphenyl-λ ⁵ -phosphanylidene) ethylidene]hydrazine carbodithioate (SBDTPA) Schiff base of benzylhydrazinecarbodithioate (SBDTC)	126
6. benzyl(<i>2E</i>)-2-[1-(triphenyl-λ ⁵ -phosphanylidene) propan-2-ylidene]hydrazine carbodithioate (SBDTPP) Schiff base of benzylhydrazinecarbodithioate (SBDTC)	127
7. (<i>E</i>)-2-methylbenzyl 2-(2-(diphenylphosphino) benzylidene) hydrazine carbodithioate (S2MBDPB) Schiff base of 2-methylbenzylhydrazine carbodithioate (S2MBDTC)	128
8. 2-methylphenyl (<i>2E</i>)-2-[2-(triphenyl-λ ⁵ -phosphanylidene)ethylidene] hydrazine carbodithioate (S2MBDTPA) Schiff base of 2-methylbenzylhydrazine carbodithioate (S2MBDTC)	129
9. (<i>E</i>)-4-methylbenzyl 2-(2-(diphenylphosphino) benzylidene) hydrazine carbodithioate (S4MBDPB) Schiff base of S-Benzylthiocarbamate (S4MBDTC)	130
Metal complexes	
1. Co (SMDPB) ₂ NO ₃ ·H ₂ O	134
2. Ni (S2MBDTPA) ₂	135



4.8 Biological activity	136
4.9 Cytotoxic activities	148
CONCLUSION	158
REFERENCES	164
APPENDICES	186
A- INFRARED SPECTRA	186
B- NMR SPECTRA	227
C- MASS SPECTRA	239
D- UV-VISIBLE SPECTRA	245
E- X-RAY CRYSTALLOGRAPHIC ANALYSIS	260
LIST OF PUBLICATIONS	331
BIODATA OF THE STUDENT	332

