Al-Imam Muhammad ibn Saud Islamic University
College of Science
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In situ synthesis and characterization of the Fe(III), Co (II), Cu(II), Zn(II), Mn(II), and Ni(II) metal complexes of Schiff bases ligand

A graduation research project

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By

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Under supervision

of

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Title:

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Introduction

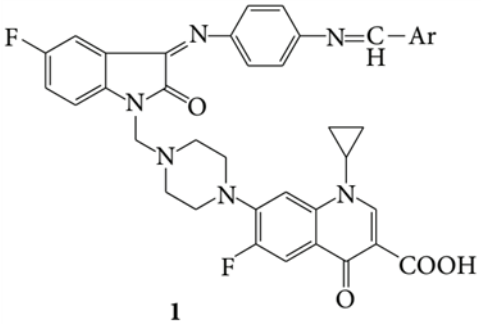
Schiff bases are the compounds carrying imine or azomethine (–C=N–) functional group. These are the condensation products of primary amines with carbonyl compounds and were first reported by Hugo Schiff [1, 2]. Schiff bases form an important class of the most widely used organic compounds and have a wide variety of applications in many fields including analytical, biological, and inorganic chemistry. Schiff bases have gained importance in medicinal and pharmaceutical fields due to a broad spectrum of biological activities like anti-inflammatory, analgesic, antimicrobial, anticonvulsant, antitubercular, anticancer, antioxidant, anthelmintic, and so forth [3-7]. The nitrogen atom of azomethine may be involved in the formation of a hydrogen bond with the active centers of cell constituents and interferes in normal cell processes [8]. Apart from biological activities, Schiff bases are also used as catalysts, intermediates in organic synthesis, dyes, pigments, polymer stabilizers [2], and corrosion inhibitors [9]. Studies enlightened that metal complexes show greater biological activity than free organic compounds [10]. Augmentation of biological activity was reported by implementation of transition metals into Schiff bases [11]. Schiff bases played an influencing role in development of coordination chemistry and were involved as key point in the development of inorganic biochemistry and optical materials [12]. Schiff bases have been utilized as synthons in the preparation of a number of industrial and biologically active compounds like formazans, 4-thiazolidinines, benzoxazines, and so forth, via ring closure, cycloaddition, and replacement reactions [13]. Schiff base derivatives in various processes promoted the researchers for designing of novel heterocyclic/aryl Schiff bases for development of new environmental-friendly technology [14]. In view of the importance of Schiff bases, in the present work we report the synthesis of a novel Schiff base ligands (E)-2-((2-phenylhydrazono)methyl)phenol, (Z)-2-(2-hydroxybenzylidene)hydrazine-1-carbothioamide and (E)-N-(4-nitrophenyl)-1-phenylmethanimine and their metal complexes.

Review of Literature

A series of some novel 5-substituted Schiff and Mannich bases of isatin derivatives, that is, 7-(4-((3-(4-(substituted benzylideneamino) phenylimino)-5-fluoro-2-oxindolin-1-yl)methyl)piperazin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid, 1(a–l), (Figure 1) were synthesized and characterized for in vitro antibacterial activity.

Antimicrobial activity of synthesized compounds was assessed by minimum inhibitory concentration (MIC) in comparison with standard antimicrobial drugs, that is, ciprofloxacin and ketoconazole. Compound 1c was reported to be more active than both of the standard drugs against tested microorganisms which proves the significance of substituted electron-donating groups in improving the antimicrobial activity [15]. A novel series of Schiff bases, that is, 6-bromo-2-[2-(2,6-dichlorophenyl)amino]benzyl-3-(substituted benzylideneamino)-quinazolin-4(3H)-one, 2(a–k), (Figure 2) has been synthesized and subjected to antimicrobial activity [16]. Evaluation was carried out for the in vitro antimicrobial activity by cup plate method. For this, S. aureus, P. aeruginosa, B. subtilis, and C. albicans were employed. Penicillin G and amphoteric in B were taken as standard drugs. Results revealed that all compounds have moderate to poor antifungal activity and good antibacterial activity [16]. A novel series of pyrazole-based Schiff bases, 3(a–j), (Figure 3) 4-[(3-substituted-1H-pyrazol-3-yl)methyleneamino]-5-substituted-4H-1,2,4-triazole-3-thiols, was synthesized and screened for antibacterial activity against the microbial strains of S. aureus, P. aeruginosa, B. subtilis, and E. coli. From the results, compound 3f was found to be equally as active as standard drug ceftriaxone against P. aeruginosa, B. subtilis, and E. coli and most active against S. aureus [17]. Synthesis of new open (4–6) (Figure 4-6) and macrocyclic (7) (Figure 7) Schiff bases has been done and evaluated for the antimicrobial activity. Open Schiff bases were synthesized by the condensation of salicylaldehyde and o-vanillin with 4,4 diaminodiphenylmethane, 4,4 diamino diphenyl sulphide, and diethyl ester of terephthalic acid, respectively. Macrocyclic Schiff bases were reported as the condensation product of 1,6-bis(2-formylphenyl)hexane with thiocarbohydrazide. In order to test the biological activity of the synthesized compounds, four microorganisms (K. pneumoniae, E. coli, S. aureus, and S. typhimurium) were employed. All the synthesized compounds were found to be moderate to strongly active [18]. A few novel solid complexes, 8, (Figure 8) of La(III), Ce(III), Pr(III), Nd(III), Sm(III), and Gd(III) with Schiff base, that is, 9,(Figure 9) 4-hydroxy-3-(1-[2-(2-hydroxybenzylidene)-amino-phenylimino]-ethyl)-6-methyl-pyran-2-ones, were synthesized and screened for the antibacterial activity against S. aureus, E. coli, and Bacillusspecies and antifungal activity against A. niger, Trichoderma ,and F. oxysporum. Results revealed that the complexes were biologically active and have exhibited enhanced antimicrobial activity than the free ligand (Schiff base) [19]. Some novel Schiff bases, macrocyclic tetradentate nitrogen donor (N4) 6,7,14,15-tetrahydroxy-1,4,9,12-tetraazacyclohexadecane-5,8,13,16-tetrone ligand-based metal complexes, 11, (Figure 11) from10, (Figure 10) were synthesized and screened for the in vitro antifungal activity and toxicity studies. Minimum inhibitory

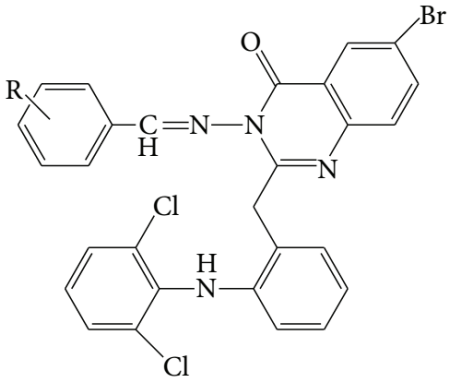
concentration (MIC) along with ergosterol composition assay against C. albicans (ATCC 10261), C. glabrata (ATCC 90030), and C. tropicalis (ATCC 750) was performed. The antimicrobial results indicated that all the synthesized compounds were found to be active against all fungal strains. It was observed that Ni(II) complex and Co(II) complex drastically reduced ergosterol content of cell membrane followed by the Cu(II) complex and the ligand itself [20].



1

1	Ar	1	Ar
a	$-C_6H_5$	**g**	$-4CH_3-C_6H_4$
b	$-4Cl-C_6H_4$	**h**	$-3,4,5(OCH_3)_3-C_6H_4$
c	$-4OH-C_6H_4$	**i**	$-4OH, 5-OCH_3-C_6H_4$
d	$-4OCH_3-C_6H_4$	**j**	$-5NO_2-C_6H_4$
e	$-4NO_2-C_6H_4$	**k**	$-4N(CH_3)_2-C_6H_4$
f	$-6OH-C_6H_4$	**l**	$-CH=HC-C_6H_4$

FIGURE 1



2	R	2	R
a	$2-NO_2$	**g**	$4-OCH_3$
b	$3-NO_2$	**h**	$3,4,5-(OCH_3)_3$
c	2-OH	**i**	$2-OH, 4-OCH_3$
d	4-OH	**j**	$4-N(CH_3)_2$
e	2-Cl	**k**	$2-OH, 4-N(C_2H_5)_2$
f	4-Cl		

FIGURE 2

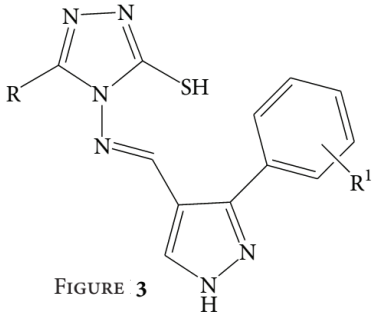


FIGURE 3

3	R	R^1	3	R	R^1
a	$-C_2H_5$	H	**f**	H	H
b	$-C_2H_5$	$4-OCH_3$	**g**	H	$4-OCH_3$
c	$-C_2H_5$	4-F	**h**	H	4-F
d	$-C_2H_5$	4-Cl	**i**	H	4-Cl
e	$-C_2H_5$	$2,4-Cl_2$	**j**	$-C_3H_7$	4-F

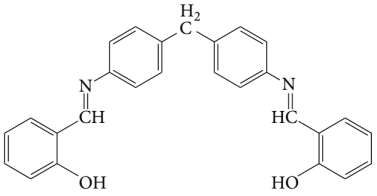


Figure 4

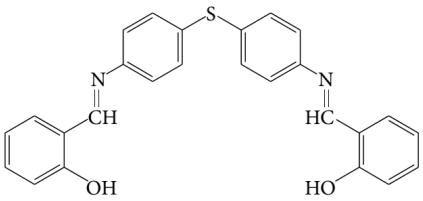


Figure 5

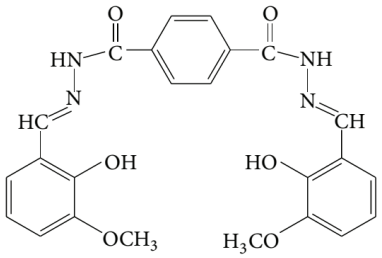


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Figure 6

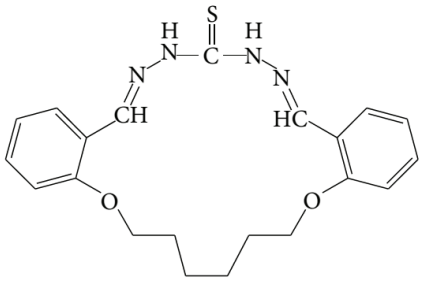

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Figure 7

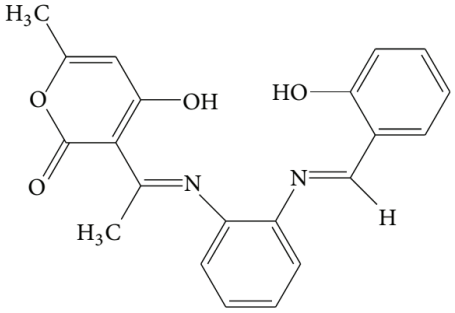

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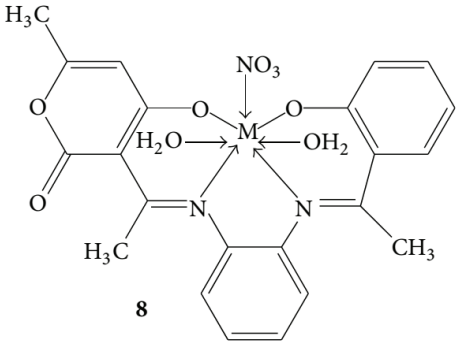
Figure 9



8

M = La(III), Ce(III), Pr(III), Nd(III), and Sm(III)

Figure 8

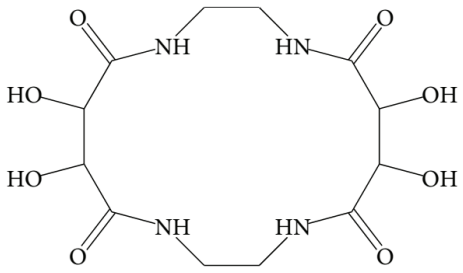


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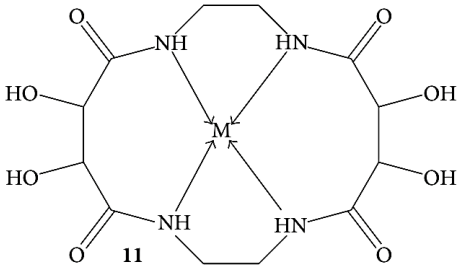
Figure 10

A series of novel keto-enamine Schiff bases, 12(a–h), (Figure 12) derived from 8-hydroxyquinoline was synthesized and subjected for in vitro antioxidant, in vivo antidyslipidemic, and post heparin lipolytic activity. Compound12d, which was formed from nucleophilic substitutions of 7-methyl aminomethylene-8-oxo-7,8-dihydroquinoline-5-carbaldehyde with p-toluidine, was found to be the most potent antidyslipidemic agent [21]. A novel series of keto-enamine Schiff bases,13(a–h), (Figure 13) derived from benzocoumarin was synthesized from 7-hydroxy-4-methyl-2-oxo-2H-benzo [H] chromene-8,10-

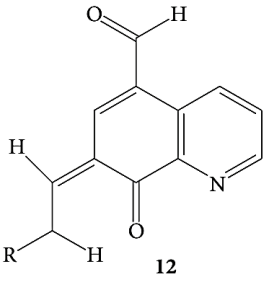
dicarbaldehyde. The compounds were evaluated in vitro for their antioxidant and in vivo for their antidyslipidemic activity. Triton WR-1339 was employed to induce hyperlipidemia. The results revealed that the compounds 13a, 13e, and 13i displayed significant lowering of total cholesterol, phospholipids, and triglycerides in the plasma. Gemfibrozil was used as a standard to compare the results [22]. A series of new Schiff bases, 14(a– e) (Figure 14) containing 4(3H)-quinazoline ring system was synthesized by the condensation reaction of 3-amino-2-methyl-4(3H) quinazolinone (AMQ) with different substituted aromatic aldehydes in methanol. The compounds were also evaluated for their anthelmintic, antioxidant, and antimicrobial activities. Indian adult earthworms (P. posthuma) were employed for the anthelmintic activity. Piperazine citrate was used as a reference standard while DMSO as a control for comparison. Results revealed that all the synthesized compounds were moderately active except compound 14c which was found to be the most potent anthelmintic agent due to presence of chloro group. Chloro group may improve the conductance of worm muscle membrane that causes reduction in hyperpolarization and excitability which leads to flaccid paralysis that results in expulsion of worm by peristaltic movement [23]. A series of twelve new N-substituted-2-hydroxyacetophenonimine derivatives, 15 (a–l) (Figure 15) was synthesized by conventional as well as microwave method. Synthesized compounds were evaluated for their antinemic activity by calculating LC50 values of different synthesized imines against J 2s of M. incognita. Carbofuran was employed as a standard. Although all the compounds possessed activity against M. incognita, N-hexyl-2-hydroxyacetophenonimine(15j),Nhexyl-2-hydroxypropiophenonimine(15k),andN-propyl-2-hydroxypropiophenonimine(15l) were found to possess significant activity with LC50 values of 99.60, 74.46, 109.53 mgL^{-1} , respectively, as compared to other imines. The above observations enlightened that bioactivity increased with increase in chain length up to 6 carbon atoms whereas further increase in chain length decreased the activity [24]. 2.4. Antitubercular Activity. A novel series of forty-four, 17 (i–xxxxiv), (Figure 17) Schiff bases of isonicotinic acid hydrazide (INH) was synthesized by structural modification of 16 (Figure 16) in which hydrazine unit was chemically blocked at N2 position by deactivating acetylation by Narylaminoacetyl transferase (NATs) enzyme. The deactivation phenomenon seems to be associated with rise of resistance. Synthesized Schiff bases were blocked toward the enzymatic deactivation process. The results revealed that compound 17(xv) was found to be the most potent antitubercular agent with MIC 0.05μg/mL and log P 4.04 [25]. A series of Schiff bases of indoline-2,3-dione derivatives and nalidixic acid carbohydrazides,18(a–n)(Figure 18)was synthesized and screened for antitubercular activity against four

Mycobacteriumstrains (M. xenopi, M. cheleneo, M. intraccllulave, and M. smegmatis) using isonicotinic acid hydrazide as a standard drug. Agar dilution method was opted for screening the activity. From the results, compound 18fwas found to be the most potent antitubercular agent with MIC 0.625μg/mL which is 20 times higher than the MIC of standard drug (12.5μg/mL) [26]. Synthesis of six D-mannitol-derived Schiff bases, 19(a–f) (Figure 19) 1,6-dideoxy-1,6-bis-([(E)-arylmethylidene]amino)-D-mannitol was carried out and synthesized compounds were evaluated for their in vitro antitubercular activity against M. tuberculosisH37 Rv by employing microplate Alamar Blue assay (MABA). Compounds19e, 19d, and19f have shown significant inhibitory activity when compared with standard drug ethambutol (first-line drug) due to presence of nitro group while chlorine-containing compounds (19a, 19b, and 19c) have shown resistance. MIC values for19e, 19d, and19f were found to be 12.5, 25.0, and 25μg/mL, respectively [27].



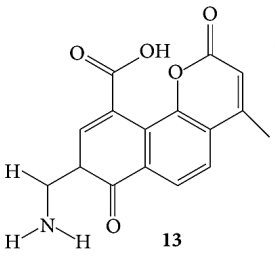
M = Cu(II), Co(II), and Ni(II)

FIGURE 11



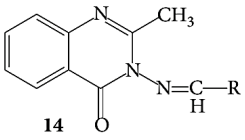
12	R
a	Ethyl
b	Isopropyl
c	t-Butyl
d	4-Methyl phenyl
e	Benzyl
f	2-Morpholine ethyl
g	2-Morpholine propyl
h	Isoheptyl

FIGURE 12



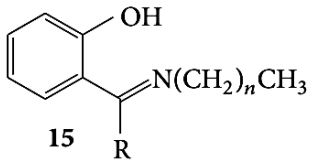
13	R
a	-CHO
b	t-Butyl
c	Isopropyl
d	Methyl
e	Heptyl
f	Ethyl
g	Propyl
h	Butyl
i	2-Morpholilno ethyl

FIGURE 13



14	R	14	R
a	HO	d	NO_2
b	N	e	O, OH
c	Cl, Cl		

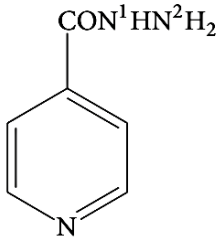
FIGURE 14



15

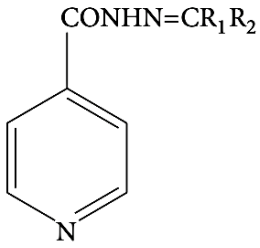
15	R	*n*	15	R	*n*
a	CH_3	17	**g**	C_2H_5	8
b	C_2H_5	17	**h**	CH_3	6
c	CH_3	15	**i**	C_2H_5	6
d	C_2H_5	15	**j**	CH_3	5
e	CH_3	14	**k**	C_2H_5	5
f	C_2H_5	10	**l**	C_2H_5	2

FIGURE 15



16

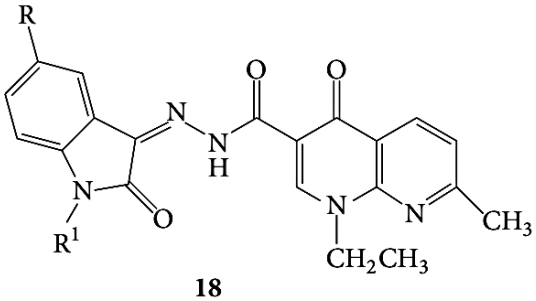
FIGURE 16



17

17	R_1	R_2
xv	H	4-(CH=NNHCOC_5H_4N)C_6H_4

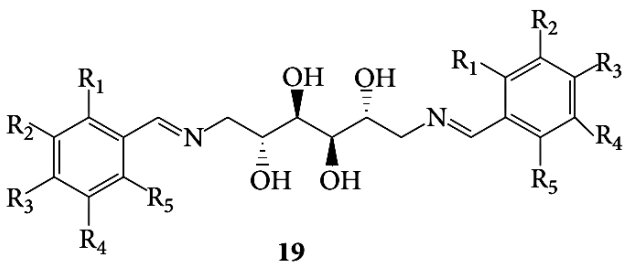
FIGURE 17



18

18	R	R^1	18	R	R^1
a	H	H	**h**	Br	H
b	H	CH_3	**i**	Br	CH_3
c	H	C_2H_5	**j**	Br	C_2H_5
d	H	C_3H_7	**k**	Br	C_3H_7
e	H	$-CH_2CH=CH_2$	**l**	Br	$-CH_2CH=CH_2$
f	H	$-CH_2C_6H_5$	**m**	Br	$-CH_2C_6H_5$
g	H	OH	**n**	Br	OH

FIGURE 18



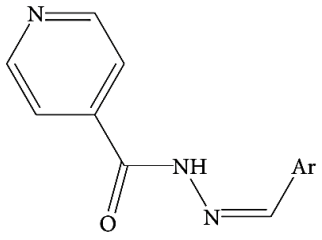
19

19	R_1	R_2	R_3	R_4	R_5
a	Cl	H	H	H	H
b	H	Cl	H	H	H
c	H	H	Cl	H	H
d	NO_2	H	H	H	H
e	H	NO_2	H	H	H
f	H	H	NO_2	H	H

FIGURE 19

Schiff bases of isonicotinoyl hydrazone, N-[(1Z)-(substituted aromatic)methylidene]pyridine-4-carbohydrazides, 20(a–k) (Figure 20) were synthesized by green route of microwave synthesis and sonication. Synthesized compounds were evaluated for in vivo antidepressant and nootropic activities. The results revealed that the test compounds substituted with nitro, halogen, and dimethoxy groups exhibited significant antidepressant and nootropic activities. N-[(1Z)-(2,5dimethoxyphenyl)methylidene]pyridine-4-carbohydrazide was found to exhibit the highest antidepressant activity [28]. A series of Schiff bases of phthalimide, 4-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-N-(substituted phenyl)methylene/ethylidene benzohydrazide, 21(a–i) (Figure 21) was synthesized and evaluated for anticonvulsant and neurotoxic activities [29]. From the results, it was concluded that all the compounds were found to be active and less toxic than phenylo in which was employed as a standard drug. Compound 21l substituted with nitro group at ortho position of distal aryl ring was reported as the most potent anticonvulsant agent [29]. Synthesis of a series of 3,3([6-(2,3-dichlorophenyl)-1,2,4-triazine-3,5-diyl]dinitrolo)bis-(substituted-1,3-dihydro-2Hindol-2-one), 22(Figure 22) of lamotrigine with isatin and substituted isatin was carried out and screened for the anticonvulsant activity. MES (maximal electroshock seizure) test method was opted to carry out the anticonvulsant activity by incorporation of lamotrigine and phenobarbitone sodium as standard drugs. Results revealed that the synthesized compounds possessed better anticonvulsant activity than the standard lamotrigine [30]. Some novel 3-aryl-4(3H)-quinazolinones-2-carboxaldehydes and their corresponding Schiff bases, 23 (Figure 23) and thiosemicarbazone derivatives, have been synthesized. Compounds showed anticonvulsant, analgesic, and cytotoxic potential due to thiosemicarbazone side chain at position ending with a free amino group and fluorine atom [31]. A novel series of Schiff bases containing sydnone that is, 3-[1-(4-isobutylphenyl)ethyl]-4-(3-substituted-4-sydnonylidene) amino 5-mercapto-1,2,4-triazoles, 24(a–c), (Figure 24) was synthesized and screened for their anti-inflammatory and analgesic activities. Results revealed that compound 24c, 3-[1-(4-isobutylphenyl)ethyl]-4-[3-(panisyl)-4-sydnonylidene] amino 5-mercapto-1,2,4-triazole, exhibited good anti-inflammatory and analgesic activities as compared to24aand24bwhich indicated that presence of electron-releasing group in sydnone has resulted in better anti-inflammatory and analgesic activities [32]. Synthesis of novel Schiff base analogues of 4-amino-1,5-dimethyl-2-phenylpyrazol-3-one,25(a–m),(Figure 25)was carried out. Synthesized compounds were screened for the anti-inflammatory and antioxidant activities. Compound 25f was found to be the most potent anti-inflammatory agent and antioxidant. The anti-inflammatory activity of 25f was evaluated in terms of its potential of

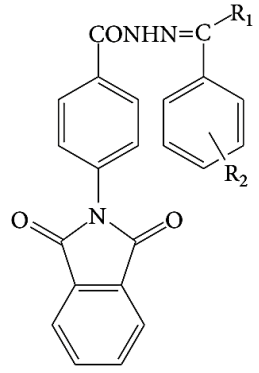
nitric oxide (NO) production inhibition in LPS-pretreated RAW 264.7 cells using the Griess method. Lipopolysaccharide (LPS), an endotoxin which is derived from the cell wall of Gram-negative bacteria, can induce multiple signaling pathways to stimulate the production of inflammatory modulators involving NO, PGE2 , TNF-α, and interleukins. The results indicated that 50μg/mL of 25f inhibited the LPS-stimulated COX-2 mRNA levels [33]. A series of S-substituted phenacyl 1,3,4-oxadiazoles and Schiff bases26(a–k)(Figure 26) derived from 2-[(2,6-dichloroanilino) phenyl] acetic acid (diclofenac acid) was synthesized and screened for the analgesic, anti-inflammatory, and nonulcerogenic activities. Acetic-acid-induced writhing test and carrageenan-induced rat paw edema method were employed for analgesic and anti-inflammatory activities, respectively. From the studies it was concluded that synthesized compounds were devoid of gastrointestinal toxicities. Among all the synthesized compounds, N-(4-bromobenzylidene)-[2-(2,6-dichloroaniline)benzyl carbazide] 26k was found to be the most potent anti-inflammatory agent. The analgesic effect of26k(68.66%) was found to be better than that of diclofenac sodium (64.65%) [34].



20

20	R	20	R
a	2-OHC_6H_5	**g**	4-$OCH_3C_6H_4$
b	4-OHC_6H_5	**h**	4-OH, 3-$OHCH_3C_6H_3$
c	4-ClC_6H_4	**i**	2-C_4H_3O
d	4-$NO_2C_6H_5$	**j**	4-$(CH_3)_2NC_6H_4$
e	2-$NO_2C_6H_4$	**k**	4-$(CH_3)_2NC_6H_4$
f	4-FC_6H_4		

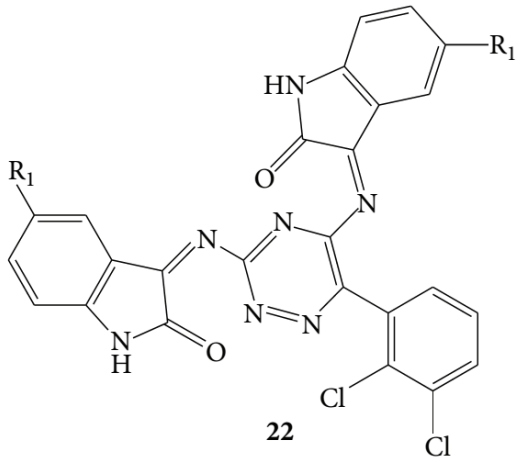
FIGURE 20



21

21	R_1	R_2	21	R_1	R_2
a	H	4-OH	**g**	CH_3	4-Cl
b	H	3,4$(OCH_3)_2$	**h**	CH_3	4-NO_2
c	H	3-NO_2	**i**	CH_3	4-OCH_3
d	CH_3	2-OH	**j**	CH_3	2,4-$(Cl)_2$
e	CH_3	4-OH	**k**	CH_3	2-OH, OCH_3
f	CH_3	4-CH_3	**l**	CH_3	2-NO_2

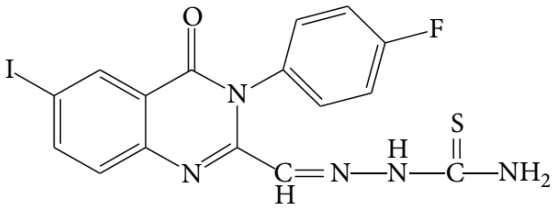
FIGURE 21



22

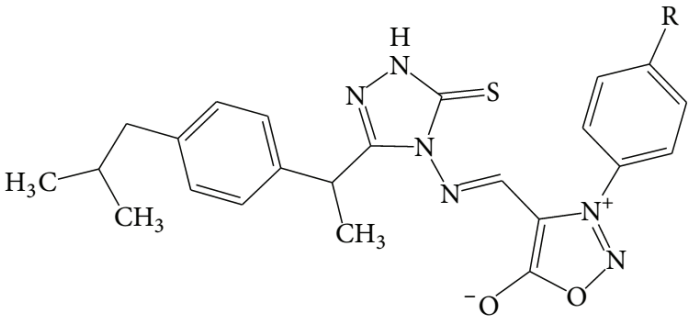
22	R_1
1	-H
2	-Cl

Figure 22



23

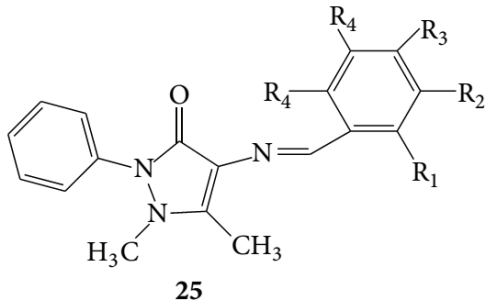
Figure 23



24

24	R
a	H
b	CH_3
c	OCH_3

Figure 24



25

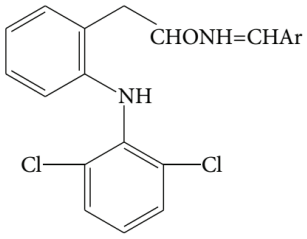
25	R_1	R_2	R_3	R_4	R_5
f	H	OH	OH	H	H

Figure 25

A novel series of fluoroquinolone C-3 heterocycles (IV), that is, s-triazole Schiff 27(a–k) (Figure 27) and mannich bases derivatives of ofloxacin was synthesized and evaluated for in vitro antitumor activity against a murine leukemia cell line (L1210), a human leukocytoma cell line (HL60), and a Chinese hamster ovary cell line (CHO) using the MTT assay. From the observed results it was concluded that a free phenol group containing compounds 27c, 27g ,and 27h exhibited more potent activity than the other test compounds [35]. A series of thirteen quinolin-2(1H)-one-derived Schiff bases 28(a–m) (Figure 28) and their Cu(II) 29(a–m) (Figure 28) complexes was synthesized. Selected compounds were screened for their in vitro anticancer and antifungal activities. Human hepatic carcinoma cell line, Hep-G2 was employed for screening of the anticancer potential. Cisplatin was used as a standard drug for the comparison. Screened compounds were found to be active antifungal agents and compound (7E)-7-(3-ethoxy-2-hydroxybenzylideneamino)-4-methylquinolin-2(1H)-one was reported as a potent cytotoxic agent which enlightened the good potential of Cu(II) complexes of Schiff base ligands as therapeutic agents [36]. A series of three Schiff bases 4-(([3-(4-substituted phenyl)-1H-pyrazol-4-yl] methylene)amino)-5-[(substituted phenoxy)methyl]-1,2,4-triazole-3- thiol,30(a–c)(Figure 29) was evaluated for their in vivo antitumor activity against Ehrlich-ascites-carcinoma-(EAC-) bearing Swiss albino mice. Schiff bases were used in two different doses, that is, 50 mg/kg and 100 mg/kg of the body weight of mice. Mean survival time (MST) and percentage increase in lifespan (% ILS), that is, total number of days an animal survived from the day of tumor inoculation were calculated. Body weights of all animals were measured on days 0, 3, 5, 7, 10, 12, and 14 [37]. The results revealed that cisplatin (3.5 mg/kg, i.p. single dose) significantly enhanced MST of EAC-infected mice. Among the three Schiff bases 4-(([3-(4-fluorophenyl)-1H-pyrazol-4-yl]methylene)amino)-5-[(2-methylphenoxy)methyl]-1,2,4-triazole-3-thiol,30c,atthedoseof 100 mg/kg body weight was found to enhance the mean survival time of tumor-bearing mice. MST and deviated hematological parameters of infected mice were found to be normal after treatment with 30c. A series of substituted-N-[(1E)-substituted phenylmethylidene]benzohydrazide analogs, 31(a–n)(Figure 30) was synthesized and evaluated for their in vitro antioxidant, anti-inflammatory, and antimicrobial activities. The antioxidant activity of all the synthesized compounds was evaluated by the phosphomolybdenum method. Compounds 31c, 31d, and 31f were reported to show good antioxidant activity due to presence of 4-nitro, 4-methyl, and 3-nitro groups, respectively, whereas31ahaving 4-hydroxy group did not possess such activity. From the results, it can be concluded that substitutions like nitro and alkyl lead to enhancement in antioxidant activity through one-electron transfer mechanism [38]. A new Schiff base ligand

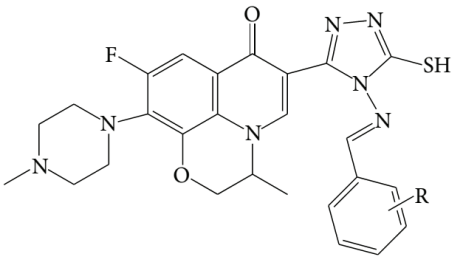
N-(2-hydroxylacetophenone)-3-oxapentane-1,5-diamine (HL), 32, and its Ni complex, [Ni2 (L)2(NO3)2], 33, were synthesized and evaluated for antioxidation and DNA-binding properties. The complex showed inhibitory activity and the suppression ratio of OH radical increases with increase in the concentration of the complex. Mannitol and vitamin C were employed as the standard antioxidants for comparison. According to the results the 50% inhibitory concentration (IC50) value of 33 was found to be 8.1±0.078μM whereasIC50 for mannitol was 9.6μM and 32 was devoid of antioxidant activity. Both 32and33bind to DNA in intercalation mode but the binding strength of 33was found to be better than 32 [39]. A series of 3-(benzylideneamino)-2-phenylquinazoline-4(3H)-one, 34(a–l) (Figure 31) was synthesized and evaluated for their cytotoxicity and antiviral activity. Compounds having 2-hydroxy substitution showed better antiviral activity [40]. A series of thiazolines and azetidinones was synthesized by reaction of Schiff bases, 35(a–i), (Figure 32) (intermediate reaction) with thioglycolic acid and chloral acetyl chloride, respectively. Schiff bases were evaluated for antibacterial and antiviral (against HIV-I) potential. All the compounds were found to be good HIV-I inhibitors except 35f and 35g [41]. Schiff bases of 2-phenyl-3-(amino substituted arylidene)quinazoline-4-(3H)-ones, 36(a-b) (Figure 33) were synthesized and evaluated for antihyperlipidemic activity. Hyperlipidemia was induced in rats by atherogenic diet. After 45 days, levels of serum total cholesterol (TC) and LDL cholesterol were recorded to be 231.6±1.435 mg/dL and 164.53 ±1.26 mg/dL which were comparatively higher than normal rat serum TC (71.36± 1.195 mg/dL) and LDL-C (100.66 ± 0.88 mg/dL) levels whereas serum HDL-C level was found to be lower (19.012± 0.66 mg/dL) as compared to the normal level (50.66 ± 0.88 mg/dL). Results revealed that36areduced TC and LDL-C levels to 172.41 ±41 mg/dL and 91.10±0.97 mg/dL and raised serum HDL-C level to 60.07 ±0.67 mg/dL whereas36b reducedserumTCandLDL-Clevelsto93.63 ±1.292 and 81.35±0.81 mg/dL and raised serum HDL-C level to 59.40± 0.45 mg/dL at the dose of 200 mg/kg, p.o., once daily [42]. A series of oxovanadium complexes with mixed ligands, a bidentate NN ligand,37, and a tetradentate ONO-donor Schiff base ligand, 38 (Figure 34) was synthesized and evaluated for protein tyrosine phosphate (PTP) inhibition. PTP1B has been identified as key enzyme related to insulin resistance. Thus the inhibition of PTP1B has emerged out as an important approach to enhance insulin sensitivity. The kinetic analysis results revealed that oxovanadium complexes displayed potent reversible competitive inhibition PTP1B with IC50 values in low nanomolar range [43]. A series of twenty-seven bis-Schiff base of isatin, 39 (i–xxvii) (Figure 35) was synthesized and evaluated for their in vitro anti glycation activity. Compounds 39(xx) and 39 (xxi) substituted with nitro groups at para and ortho positions,

respectively, were found to be the most potent antiglycation agents with IC50 (257.61 ±5.63μM) and 243.95±4.59μM better than IC50 (294.46 ±1.50μM) of rutin which was employed as standard. The 3,4-dihydroxy analog 39 (vii) was found as the third most potent antiglycationa gent with IC50 (291.14±2.53μM) [44].



26

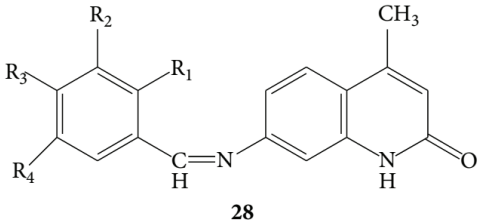
FIGURE 26



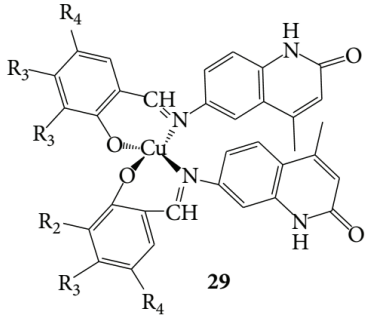
27

27	R	27	R
a	H	**g**	3-OH, 4-CH_3O
b	4-CH_3O	**h**	4-OH, 3-CH_3O
c	2-OH	**i**	4-Cl
d	2-CH_3O	**j**	4-F
e	3,4-OCH_2O	**k**	4-NO_2
f	3,4,5-$(CH_3O)_3$		

FIGURE 27



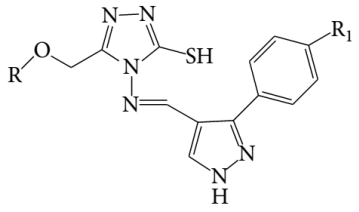
28



29

28, 29	R_1	R_2	R_3	R_4
d	OH	OC_2H_5	H	H

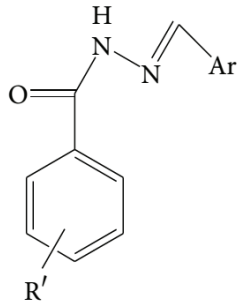
FIGURE 28



30

30	R	R_1
a	4-Methylbenzene	Cl
b	4-Methylbenzene	F
c	2-Methylbenzene	F

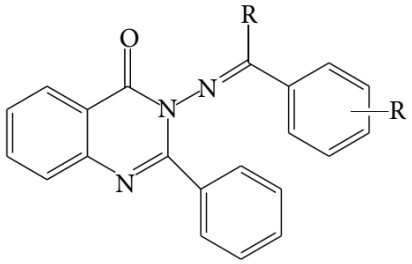
FIGURE 29



31

31	R′	Ar	31	R′	Ar
a	4-Cl	2-OHC_6H_4	**g**	2-COC_6H_5	-C_6H_4
b	4-Cl	3-OCH_3, 4-OHC_6H_3	**h**	2-COC_6H_5	4-ClC_6H_4
c	4-Cl	4-$NO_2C_6H_4$	**i**	2-COC_6H_5	4-$NO_2C_6H_4$
d	4-Cl	4-$CH_3C_6H_4$	**j**	2-COC_6H_5	4-$CH_3C_6H_4$
e	4-Cl	2-$OHC_{10}H_6$	**k**	2-COC_6H_5	3-OCH_3, 4-OHC_6H_3
f	4-Cl	3-$NO_2C_6H_4$	**l**	2-COC_6H_5	4-OHC_6H_4
			m	2-COC_6H_5	2-$NO_2C_6H_4$
			n	2-COC_6H_5	2-OHC_6H_4

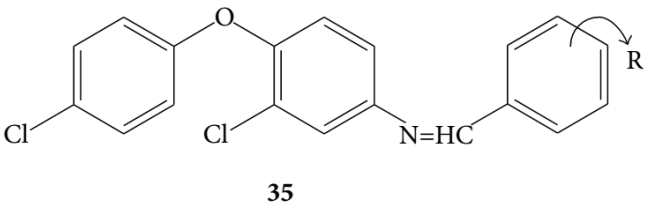
Figure 30



34

34	R	R′	34	R	R′
a	H	2-OH	**g**	H	4-OH
b	H	2-NO_2	**h**	CH_3	H
c	H	4-OCH_3	**i**	CH_3	4-OH
d	H	4-$N(CH_3)_2$	**j**	H	4-Cl
e	CH_3	4-Cl	**k**	H	3-OH, 4-OCH_3
f	H	H	**l**	H	2-OCH_3

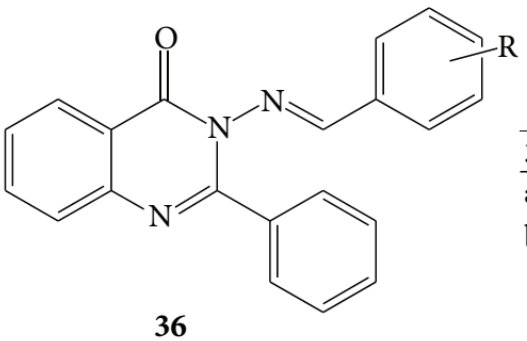
Figure 31



35

35	R
a	H
b	2-OH
c	4-OH
d	4-OH, 3-OCH_3
e	-CH=CH-C_6H_5
f	4-Cl
g	4-NO_2
h	4-OCH_3
i	3,4,5-$(OCH_3)_3$

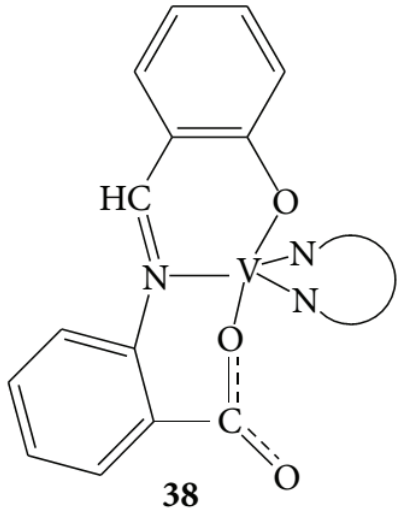
Figure 32



36

36	R
a	2-OH
b	4-OH, 3-OMe

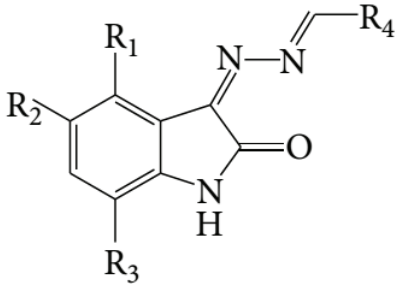
Figure 33



38

Bipyridine, phenanthroline, dipyridoquinoxaline, dipyridophenazine, and methyldipyridophenazine

Figure 34



39

39	R_1	R_2	R_3	R_4
xx	H	H	H	4-$NO_2C_6H_4$
xxi	H	H	H	2-$NO_2C_6H_4$
vii	H	H	H	3,4-$(OH)_2C_6H_3$

Figure 35

Experimental Part

In this part the student started to learn by the synthesis of an already prepared ligand and its metal complexes for comparison reasons [45] then a two new ligands and ten metal complexes were prepared.

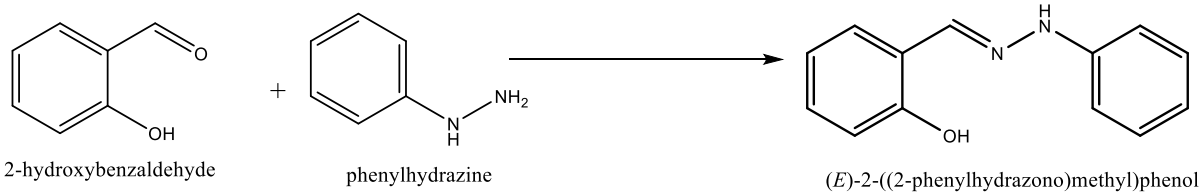
Materials

All the reagents employed for the preparation of the ligand and its complexes were of the best grade available and used without further purification. Preparation of ligands:

Preparation of ligands

The Ligand, H_2L^1

Ethanol solution (10 mL) of 2-hydroxybenzaldehyde (1.00 g, 8.19 mmol) was added dropwise to ethanol solution (10 mL) of phenylhydrazine (0.89 g, 8.19 mmol) over 15 min with stirring and continue stirring for 0.5 h. The yellow precipitate (see Figure 36) was then filtered off, washed with methanol, and dried in a vacuum desiccator over P4O10 (1.23 g, 71% yield). IR (KBr): ν(OH) 3291 (br), ν(NH) 3282(Sh), ν(C=N) 1621(s), ν(C-O) 1252 (m). Elemental analysis for $C_{13}H_{12}N_2O$ (212.25): calcd. C 73.56, H 5.70, N 13.20; found C 73.66, H 5.94, N 13.12.



2-hydroxybenzaldehyde phenylhydrazine (*E*)-2-((2-phenylhydrazono)methyl)phenol

Figure 36: Preparation of the ligand H_2L^1

The Ligand, H_4L^2

Ethanol solution (10 mL) of 2-hydroxybenzaldehyde (1.34 g, 10.97 mmol) was added dropwise to ethanol solution (50 mL) of thiosemicarbazide (1.00 g, 10.97 mmol) with stirring and then 3 drops of sulfuric acid were add and continue refluxing for 2 h. The yellow precipitate (see Figure 37) was then filtered off, washed with methanol, and dried in desiccator over P4O10 (1.23 g, 71% yield).

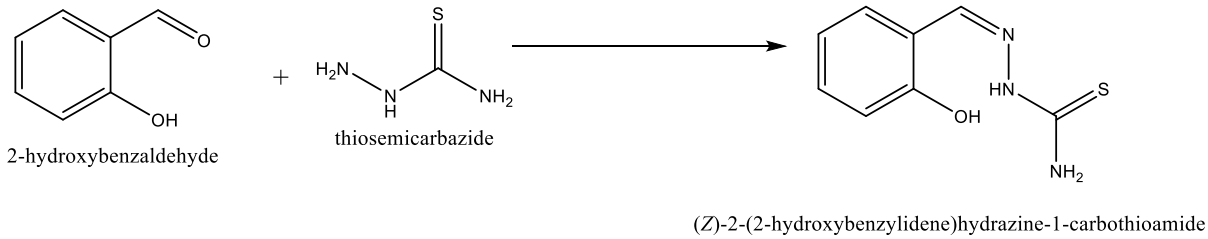


Figure 37: Preparation of the ligand H_4L^2

The Ligand, L^3

Few drops of acetic acid were added to hot (60 ^oC) methanol solution (30 mL) of benzaldehyde (1.00 g, 7.24 mmol) then methanol solution (40 mL) of 4-nitroaniline (0.77 g, 7.24 mmol) was added dropwise. The solvent was evaporated to 50 mL. The yellow solution is left to precipitate in the refrigerator for 24 h. The precipitate (see Figure 38) was then filtered off, washed with methanol, and dried in desiccator over P_4O_{10} (1.23 g, 71% yield).

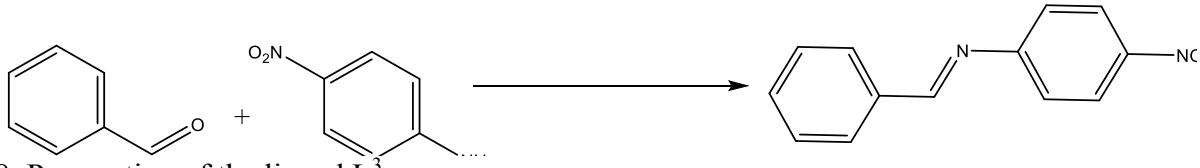


Figure 38: Preparation of the ligand L^3

Preparation of metal complexes

$[HL^1FeCl_3(H_2O)].3H_2O$:

Ethanol solution (10 mL) of 2- hydroxybenzaldehyde (0.25 g, 2.05 mmol) was added drowsily to ethanol solution (10 mL) of phenylhydrazine (0. 22 g, 2.05 mmol). After 5 min a methanol solution (20 mL) of $FeCl_3.6H_2O$ (0.55 g, 2.05 mmol) was drowsily added with stirring. A few drops of trimethyl amine were added to allow precipitation. The precipitate was then filtered off, washed with methanol and dried in desiccator over P_4O_{10} (0.68 g, 74% yield).

$[HL^1NiCl_2(H_2O)_2].H_2O$:

Ethanol solution (12 mL) of 2- hydroxybenzaldehyde (0.27 g, 2.29 mmol) was added drowsily to ethanol solution (12 mL) of phenylhydrazine (0.25 g, 2.29 mmol). After 5 min a methanol solution (20 mL) of $NiCl_2.6H_2O$ (0.55 g, 2.29 mmol) was drowsily added with stirring. A few drops of trimethyl amine were added to allow precipitation. The precipitate

was then filtered off, washed with methanol and dried in a vacuum desiccator over P_4O_{10} (0.72 g, 73 % yield).

$[HL^1CoCl_2(H_2O)_2].3H_2O$:

Ethanol solution (13 mL) of 2- hydroxybenzaldehyde (0.28 g, 2.29 mmol) was added drowsily to ethanol solution (13 mL) of phenylhydrazine (0.25 g, 2.29 mmol). After 5 min a methanol solution (22 mL) of $CoCl_2.6H_2O$ (0.55 g, 2.29 mmol) was drowsily added with stirring. A few drops of trimethyl amine were added to allow precipitation. The precipitate was then filtered off, washed with methanol and dried in a vacuum desiccator over P_4O_{10} (0.72 g, 73 % yield).

Complex 3:

Methanol solution (20 mL) of 2-hydroxybenzaldehyde (1.34 g, 10.97 mmol) was added drowsily to methanol solution (50 mL) of thiosemicarbazide (1.00 g, 10.97 mmol). After 5 min a methanol solution (100 mL) of $Cu(CH_3COO)_2.H_2O$ (2.19 g, 10.97 mmol) was drowsily added with stirring. The precipitate was then filtered off, washed with methanol and dried in desiccator over P_4O_{10} (3.08 g, 68% yield).

Complex 4:

Methanol solution (20 mL) of 2-hydroxybenzaldehyde (0.67 g, 5.49 mmol) was added drowsily to methanol solution (50 mL) of thiosemicarbazide (0.50 g, 5.49 mmol). After 5 min a methanol solution (120 mL) of $FeCl_3.6H_2O$ (1.48 g, 5.49 mmol) was drowsily added with stirring. A few drops of trimethyl amine were added to allow precipitation. The precipitate was then filtered off, washed with methanol and dried in desiccator over P_4O_{10} (1.40 g, 65% yield).

Complex 5:

Methanol solution (20 mL) of 2-hydroxybenzaldehyde (0.67 g, 5.49 mmol) was added drowsily to methanol solution (50 mL) of thiosemicarbazide (0.50 g, 5.49 mmol). After 5 min a methanol solution (120 mL) of $Co(CH_3COO)_2.4H_2O$ (1.37 g, 5.49 mmol) was drowsily added with stirring. The precipitate was then filtered off, washed with methanol and dried in desiccator over P_4O_{10} (1.64 g, 77% yield).

Complex 6:

Methanol solution (20 mL) of 2-hydroxybenzaldehyde (0.67 g, 5.49 mmol) was added drowsily to methanol solution (50 mL) of thiosemicarbazide (0.50 g, 5.49 mmol). After 5 min a methanol solution (120 mL) of $NiCl_2.6H_2O$ (1.30 g, 5.49 mmol) was drowsily added with stirring. A few drops of trimethyl amine were added to allow precipitation. The precipitate was then filtered off, washed with methanol and dried in desiccator over P_4O_{10} (1.33 g, 67% yield).

Complex 7:

Methanol solution (20 mL) of 2-hydroxybenzaldehyde (0.67 g, 5.49 mmol) was added drowsily to methanol solution (50 mL) of thiosemicarbazide (0.50 g, 5.49 mmol). After 5 min a methanol solution (120 mL) of $Zn(NO_3)_2.6H_2O$ (1.63 g, 5.49 mmol) was drowsily added with stirring. A few drops of trimethyl amine were added to allow precipitation. The precipitate was then filtered off, washed with methanol and dried in desiccator over P_4O_{10} (1.36 g, 59% yield).

Complex 8:

Methanol solution (20 mL) of 2-hydroxybenzaldehyde (0.67 g, 5.49 mmol) was added drowsily to methanol solution (50 mL) of thiosemicarbazide (0.50 g, 5.49 mmol). After 5 min a methanol solution (120 mL) of $Mn(CH_3COO)_2 \cdot 4H_2O$ (1.34 g, 5.49 mmol) was drowsily added with stirring. The precipitate was then filtered off, washed with methanol and dried in desiccator over P_4O_{10} (1.68 g, 73% yield).

Complex 9:

Methanol solution (20 mL) of 2-hydroxybenzaldehyde (1.00 g, 7.24 mmol) was added drowsily to methanol solution (25 mL) of thiosemicarbazide (0.77 g, 7.24 mmol). After 5 min a methanol solution (120 mL) of $Cu(CH_3COO)_2.H_2O$ (1.45 g, 7.24 mmol) was drowsily added with stirring. The precipitate was then filtered off, washed with methanol and dried in desiccator over P_4O_{10} (2.51 g, 78% yield).

Complex 10:

Methanol solution (20 mL) of 2-hydroxybenzaldehyde (1.00 g, 7.24 mmol) was added drowsily to methanol solution (25 mL) of thiosemicarbazide (0.77 g, 7.24 mmol). After 5 min a methanol solution (150 mL) of $FeCl_3.6H_2O$ (1.96 g, 7.24 mmol) was drowsily added with stirring. A few drops of trimethyl amine were added to allow precipitation. The precipitate

was then filtered off, washed with methanol and dried in desiccator over P_4O_{10} (2.18 g, 68% yield).

Complex 11:

Methanol solution (20 mL) of 2-hydroxybenzaldehyde (1.00 g, 7.24 mmol) was added drowsily to methanol solution (25 mL) of thiosemicarbazide (0.77 g, 7.24 mmol). After 5 min a methanol solution (150 mL) of $Co(CH_3COO)_2.4H_2O$ (1.80 g, 7.24 mmol) was drowsily added with stirring. The precipitate was then filtered off, washed with methanol and dried in desiccator over P_4O_{10} (2.51 g, 76% yield).

Complex 12:

Methanol solution (20 mL) of 2-hydroxybenzaldehyde (1.00 g, 7.24 mmol) was added drowsily to methanol solution (25 mL) of thiosemicarbazide (0.77 g, 7.24 mmol). After 5 min a methanol solution (150 mL) of $NiCl_2.6H_2O$ (1.72 g, 7.24 mmol) was drowsily added with stirring. A few drops of trimethyl amine were added to allow precipitation. The precipitate was then filtered off, washed with methanol and dried in desiccator over P_4O_{10} (2.11 g, 71% yield).

Complex 13:

Methanol solution (20 mL) of 2-hydroxybenzaldehyde (1.00 g, 7.24 mmol) was added drowsily to methanol solution (25 mL) of thiosemicarbazide (0.77 g, 7.24 mmol). After 5 min a methanol solution (150 mL) of $Zn(NO_3)_2.6H_2O$ (2.15 g, 7.24 mmol) was drowsily added with stirring. A few drops of trimethyl amine were added to allow precipitation. The precipitate was then filtered off, washed with methanol and dried in desiccator over P_4O_{10} (1.87 g, 55% yield).

Results and Discussion

All the synthesized compounds are colored, solid, stable at room temperature, non-hygroscopic, insoluble in water and poorly soluble in common organic solvents such as $CHCl_3$, but soluble in MDF and DMSO. The synthesis of a known ligand and some of its complexes almost gave the same results as published. Due to the limited time and facilities not all compounds were fully characterized. IR spectra of the ligands and its metal complexes were to be recorded to confirm their structures. The assignments of the characteristic vibrational frequencies of the complexes to be were made by comparison with the vibrational

frequencies of the free ligand. For ligand 1 and 2 they can coordinate through the imine group, the thioketone and hydroxyl group giving a tridentate ligand. The hydroxyl group can coordinate as a neutral group or a subsequent deprotonation of the phenolic proton prior to coordination can talk place [46-50]. If complexes included water molecules. The broad bands in the 3550-3350 cm^{-1} region are due to coordinated water or water of crystallization. The bands for water of crystallization are different from those of coordinated water. The presence of water molecules within the coordination sphere in the hydrated complexes is supported by the presence of bands in the 3432-3448 , 1600-1610, 940-955 and 620-632 cm-1 regions due to OH stretching, HOH deformation, H_2O rocking and H_2O wagging, respectively [51]. The absence of coordinated water molecules in complexes was confirmed from the absence of the rocking, twisting and wagging vibrational modes which are normally activated in 970-930 cm-1 and 660-600 cm^{-1} regions [52]. The presence of ν(M-Cl) is supported by the presence of a weak intensity ν(M-Cl) band in 347-368 cm^{-1} range indicating a terminal Chloro ligands [53, 54]. Extensive IR spectral studies reported on metal aceto complexes indicate that the acetate ligand may coordinate to a metal center in either a monodentate, bidentate or bridging manner [52]. The $\nu_{asym.}(CO_2)$ and $\nu_{sym.}(CO_2)$ of the free acetate ions are at 1560 cm^{-1} and 1416 cm^{-1}, respectively [52]. In monodcntate coordination ν(C=O) is found at higher energy than $\nu_{asym.}(CO_2)$ and ν(C-O) is lower than $\nu_{sym.}(CO_2)$. As a result, the separation between the two ν(CO) bands is much larger in monodentate complexes than the free ion [52]. The ESR spectra of polycrystalline samples of copper(II) complexes at room temperatures (298 K) will have axial shape if $g// > g^{\perp}$ characteristic of complexes with $^2B_1(d_{x2}\text{-}y2)$ orbital ground state. [54] The average g values were calculated according to the equation: $gav = 1/3[g// + 2\ g^{\perp}]$. Complexes exhibit $g// < 2.3$, suggests covalent characters around the copper in present complexes. Kivelson and Neiman [56] have reported that a g// value greater than 2.3 indicates ionic character. The g-values were related by the expression, [22, 53] $G = (g//-2)/(g^{\perp}-2)$, if $G > 4.0$ then local tetragonal axes were aligned parallel or only a slightly misaligned, if $G < 4.0$, significant exchange coupling is present. The g///A// is taken as an indication for the stereochemistry of the copper(II) complexes. Addison [58] has suggested that this ratio may be an empirical indication of the tetrahedral distortion of the square planar geometry. The values of g///A// quotient in the range 105–135 cm^{-1} are expected for copper complexes within perfectly square based geometry and those higher than 150 cm^{-1} for tetrahedrally distorted complexes.

Summary and Conclusion

The referenced synthesis of ligand 1 and its metal complexes almost showed identical results. The newly prepared ligands 2 and 3 were stable and gave good yield. The synthesis of metal complexes gave colored and stable compounds insoluble in water and organic solvents bur soluble in polar solvents such as DMSO. The air stability and insolubility of metal complexes in water gave indication of their ability to be used in industry.

Recommendations

A more detailed study of current compound for testing in industrial applications is recommended was further study of similar compounds to study the effect of substitution on the overall properties of such compounds.

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