ORIENTAL JOURNAL OF CHEMISTRY
An International Open Access, Peer Reviewed Research Journal
www.orientjchem.org
ISSN: 0970-020 X
CODEN: OJCHEG
2026, Vol. 42, No.(2):
Pg. 612-625

Synthesis, Characterization, and Biological Applications of Phenyl Hydrazine Derivatives- A Review

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http://dx.doi.org/10.13005/ojc/420222

(Received: June 24 , 2025; Accepted: February 23, 2026)

ABSTRACT

This review highlights the synthesis, characterization, and biological potential of phenyl hydrazine derivatives, focusing on anti-inflammatory, anticancer, antimicrobial, antimalarial, and antioxidant activities. Phenyl hydrazine derivatives were analyzed using advanced methods such as FTIR, ^{13}C NMR, and ^{1}H NMR spectroscopy to achieve precise structural elucidation. Anti-inflammatory activity was examined via molecular docking analysis with inflammatory proteins and in vivo testing using the carrageenan-induced rat paw oedema model. The anticancer potential of these derivatives was evaluated against MCF-7 breast cancer and Caco-2 colorectal carcinoma cell lines, showing higher cytotoxicity than doxorubicin and cisplatin. Additionally, their antimicrobial activity was assessed against Gram-positive and Gram-negative bacteria such as *E. coli* and *S. aureus*, demonstrating broad-spectrum antimicrobial activity.

Key words: Phenyl Hydrazine, Anti-Inflammatory, Anticancer, Antimicrobial, Antimalarial, Antioxidant, Antiviral.

INTRODUCTION

Phenyl hydrazine and its derivatives were formerly established to exhibit numerous biological activities mainly anti-inflammatory, Anti-cancer, antimicrobial activities. Thus, the search for new multi-functional therapeutic compounds has gradually increased in recent years due to the rising number of inflammatory conditions[7,14], cancer[6,7,10,20], microbes as antioxidant[6], as antimalarial[11] and as antiviral[2]. Inflammation is also considered as a part of body's defense mechanism against injuries or infections though chronic inflammation is responsible for various diseases such as cancer, cardiovascular diseases

and autoimmune diseases. This linked the demand for the synthesis of new anti-inflammatory agents that are able to interact with active inflammatory processes more selectively and with fewer side-effects. The ability of phenyl hydrazine derivatives also drew interests that it has anticancer properties. Cancer is among the most fatal diseases worldwide, and hence it requires that there must be new therapeutic agents that are efficient in targeting the tumor cells without affecting normal cells. Phenyl hydrazine derivatives have the efficacy for the cytotoxicity toward the cancerous cells of various types of cancer, especially in the breast and colon cancers[20], where cisplatin originally used induces many side effects. These derivatives' ability to suppress cancer cell growth, together with their reduced cytotoxic effects, makes them favorable targets for future oncomolecular drug development. Apart from the anti-inflammatory and anticancer effects, the phenyl hydrazine derivatives have been observed to have remarkable antimicrobial activities and this comes in handy given the present world crisis of increased antimicrobial resistance. New bacterial resistant strains have developed very quickly, making many of the conventional antibiotics almost useless, therefore there is demand for new antimicrobial agents. Phenyl hydrazine derivatives with the above novel molecular structure have excellent antifungal and antibacterial properties that combat gram-positive and gram-negative bacterial infections. The other properties consist of anti-oxidant, anti-viral, and anti-malarial where phenyl hydrazine moiety showed its effectiveness as a metal chelating agent and chelate promoter for SARS Cov-2 inhibition (COVID-19)[2] andwas found to be effective against Plasmodium Falciparum[11] – Malaria causing parasite.

Anti-Inflammatory Activity

Inflammation, a key physiological reaction to infections and tissue injury, begins with mechanisms that repair tissue and eliminate pathogens, aiding in restoring homeostasis at the affected areas. Synthesis of p-phenylenediamine-phenylhydrazine-formaldehyde terpolymer was carried out and polymer was analyzed using FTIR, ^{13}C and ^{1}H NMR spectroscopy.The signals appeared at 6.6–7.6 (δ) ppm is assigned to all the protons of aromatic ring. The signal showed at 10.4 (δ) ppm is assigned to the –NH bridge in the terpolymeric ligand. The signal observed at 4.8 (δ) ppm is assigned to the Ar-N-CH2 linkages. The signal appeared at 2.5 (δ) ppm is assigned to the methylene group in the terpolymer. IR spectrum shows the corresponding peaks at 118.81, 112.36, 113.98, 119.17, 115.16 and 115.89 (δ) ppm with respect to C1–C6 of the aromatic ring of p-phenylenediamine. The peak appeared at 129.41, 128.80, 119.37, 129.28, 129.98 and 137.33 (δ) ppm, is assigned to the C1–C6 of the aromatic ring of phenyl hydrazine. The peak appeared at 40.58 (δ) ppm is assigned to the –CH2 group in the terpolymer.DFT was used to determine the HOMO-LUMO energies and other electronic quantities of the product employing the Gaussian 09 software. Also, to predict the biological activity of the synthesized polymer, the molecular docking was carried out against three inflammatory proteins. Some of them include 6JD8, 4CYF, and 5TKB. Commercial drug-Ibuprofen was employed as reference drug to assess the efficiency of the investigated compound[14].

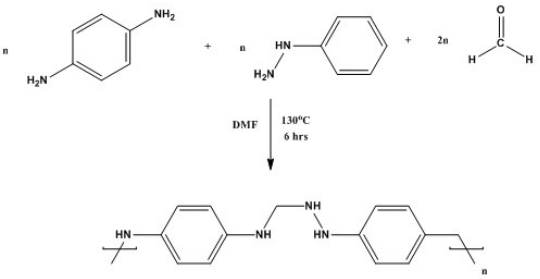


Fig. 1. Synthesis of PPHF Polymer 14

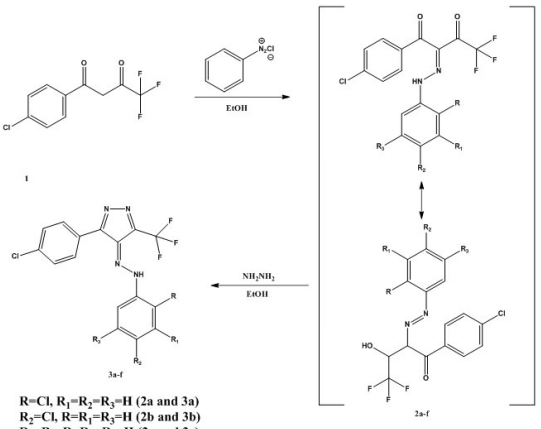


Fig. 2: Synthesis of the designed arylhydrazone and pyrazole derivative[7]

The novel pyrazole and arylhydrazone compounds were created using 1-(4-chlorophenyl)-4,4,4-trifluorobutane-1,3-dione. The carrageenan-induced rat paw oedema paradigm was used to evaluate the in vivo anti-inflammatory properties of the newly synthesized compounds. Additionally, an in vitro COX inhibition experiment was used to examine the inhibitory effect on ovine COX-1 and COX-2. Furthermore, molecular docking studies were conducted to examine the COX-2 inhibitors and active inhibitor[7].

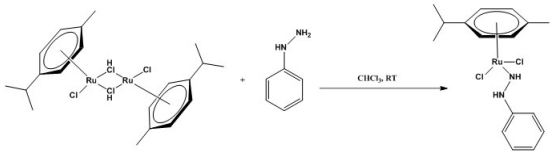


Fig. 3: Synthesis of Ruthenium Complex[3]

Table 1: In-vitro anticancer screening of compounds 2–9 against human breast cancer cell line (MCF-7)

Compound No.	IC_{50} (μg/mL)	IC_{50} (μM)
2	48.2	173.83
3	38.0	116.56
4	34.9	111.50
5	23.5	60.72
6	40.9	128.61
7	38.0	104.11
8	28.6	85.12
9	38.9	109.58

Anti-cancer or Anti-tumor activity

Anticancer potential of Ruthenium (II) complexes has caught considerable attention and excitation of investigations on oncology in the past decades since the introduction of metal-based chemotherapeutics. In this work, new ruthenium complexes were synthesized and analyzed by IR, Proton and Carbon NMR spectra[3].

The paper reports that the novel hydrazone compound 1-(5-bromo-2,3-dimethoxybenzylidene)-2-(pyridine-2-yl) hydrazine (5Br2DM2PH) exhibits potent anticancer activity against human breast (MCF-7) and colon (Caco-2) cancer cell lines.

The MTT assay was used to determine the in vitro cytotoxic effect of 5Br2DM2PH on the cancer cell lines MCF-7 and Caco-2. The molecule is more potent than the chemotherapy medication cisplatin, according to the results.

Table 2: Minimum inhibitory concentration (MIC) in μmol/mL of compound

Compound	*C. albicans*	*C. krusei*	*C. parapsilosis*	*C. glabrata*
1	0.39	0.195	0.39	1.56
Fluconazole	0.195	—	1.56	1.56

Table 3: Analytical and physical data of heterochelates

Compounds	Formula Weight	Color (% Yield)	C	H	Mn	N	O	S
$[Mn(L_1)_2Ac.H_2O].2Ac.1.5$ HδO	1047	Greenis h yellow (71)	49.86 (49.84)	4.44 (4.40)	6.08 (6.00)	15.32 (15.29)	17.49 (17.47)	7.08 (7.00)
$[Mn(L_1)_1Ac.H_2O].2Ac.3H$δO	1043	Brown (73)	50.93 (50.90)	4.73 (4.70)	5.85 (5.82)	14.87 (14.84)	16.98 (16.95)	6.82 (6.79)
$[Mn(L_1)_2 Ac.H_2O].Ac.1.5H$δO	1044	Cream (69)	51.94 (51.90)	5.01 (4.98)	5.69 (5.65)	14.43 (14.41)	16.49 (16.46)	6.64 (6.60)
$[Mn(L_1)_2 Ac_1H_2O]_1H_2O$	1046	Light yellow (68)	55.48 (55.44)	4.29 (4.26)	5.31 (5.28)	13.49 (13.47)	15.41 (15.38)	6.21 (6.17)
$[Mn(L_1)$δ$Ac.H_2O].Ac.0.5H_2O$	1184	Dark yellow (73)	51.08 (51.02)	3.78 (3.75)	4.89 (4.86)	14.91 (14.87)	19.87 (19.82)	5.71 (5.67)

Table 4. Antimicrobial effects of the ligands and their heterochelates

S. No. Ref. Drug (Penicillin)	Compounds PEnicillin	Gram +ve (*Bacillus megaterium*) 35	Gram –ve (*E. coli)* 20
1	L_1	17	10
2	L_1	10	06
3	L_1	06	07
4	L_1	20	30
5	L_1	15	20
6	$MnL_1\delta$	06	05
7	$MnL_1\delta$	15	20
8	MnLδ	23	15
9	MnLδ	13	11
10	MnLδ	08	08

Table 5: Antimicrobial Effect of Ligands and Metal Complexes (Zone of Inhibition in mm)

S. No.	Compounds Ref. Drug (Penicillin)	Gram-Positive (*Bacillus megaterium*) 35	Gram-Negative(*E. coli*) 28
1	Lδ	17	10
2	Lδ	10	06
3	Lδ	06	07
4	Lδ	20	24
5	Lδ	15	20
6	Lδ	13	17
7	MLδ	19	15
8	MLδ	11	09
9	MLδ	10	08
10	MLδ	23	26
11	MLδ	19	20
12	MLδ	17	19

Table 6: Elemental analysis results for copper complexes

Complex	Molecular weight(g/mlo)	%C Calc.	%N Found	%H Calc.	Found	Calc.	Found
1	681	52.86	52.42	12.33	12.12	3.23	3.14
2	931	56.71	52.21	6.01	5.82	4.73	4.68

Cytotoxicity Results

16.8 µM was the IC50 value (concentration needed for half -maximal inhibition of cellular growth) for MCF-7 breast cancer cells. The IC50 value for Caco-2 colon cancer cells was 11.8 µM. Cisplatin's IC50 values are 81.4 µM for the colon cancer cell line Caco-2 and 76 µM for the human breast cancer cell line MCF-7. It shows 5Br2DM2PH has a stronger anticancer effect compared to cisplatin, a widely used chemotherapy drug, on both breast and colon cancer cell lines[20].

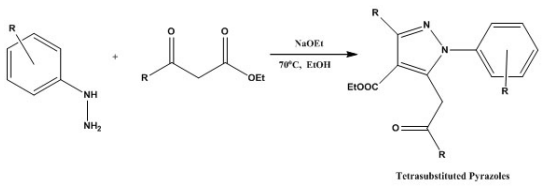


Fig. 5. Synthesis of Tetra substituted Pyrazoles[5]

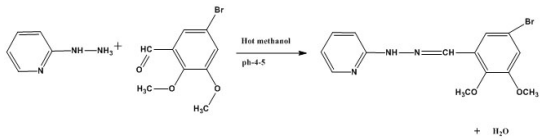


Fig. 4. Synthesis of 2-Pyridine hydrazinyl Schiff Base[20]

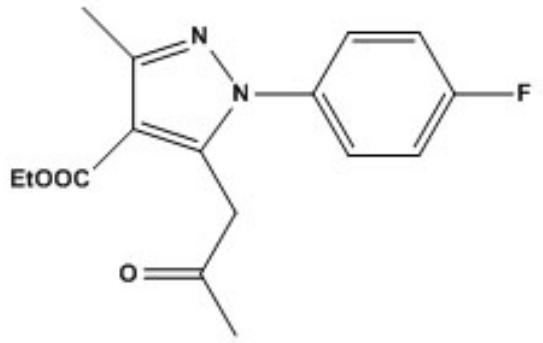


Fig. 6. 4-Fluoro substituted Pyrazole[5]

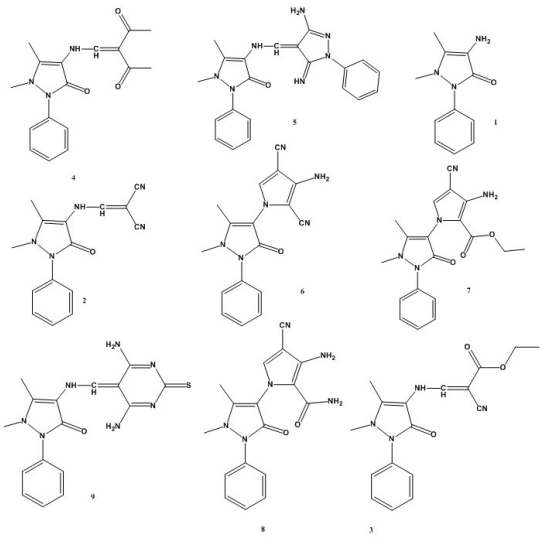
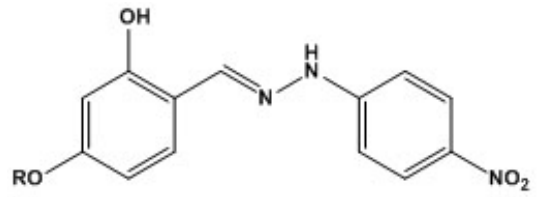


Fig. 7. Pyrazole derivatives derived from 4-Amino antipyrine[10]

The pyrazole is one of the essential nitrogen-containing heterocycles abundant in agrochemicals, catalysis and serves as an important pharmacophore for synthesizing natural products and commercial drugs. Interestingly, these important scaffolds display various biological properties, including Antiviral, analgesic, Estrogen Receptor Agonistic and cannabinoid receptor antagonistic properties. They can also act as ligands in coordination compounds and are employed as optical brighteners, UV protection components, and supramolecular assembly units. In addition to their medicinal actions, these polysubstituted pyrazoles, are used as ligands in cross coupling reactions and very recently as dyes[5].

Substituting the R group of phenyl hydrazine ring with different atoms will give different derivatives of pyrazoles with corresponding applications. Here by changing the R group with fluorine F then the pyrazole derivative formed will have anti-cancer properties.

The Newly synthesized pyrazole derivatives from 4-amino antipyrine as an intermediate were analyzed through IR, Proton and carbon-13 NMR techniques. A series of highly active compounds having IC50 values ranging from 30.68 to 60.72 µM, were all produced and tested as cytotoxic activity against the breast cancer cell line MCF7 after comparing with standard drug Doxoribucin which has the IC_{50} value of 71.8 µM[10].



3 a-f

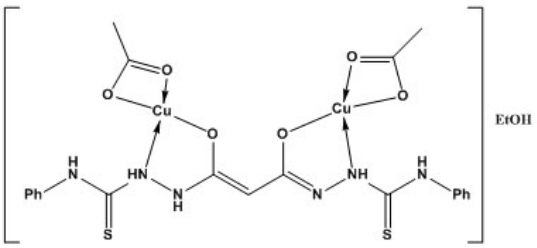


Fig. 8. Copper Complex of 3a-f[6]

Anti-Oxidant Properties

A new p-nitrophenyl hydrazone derivatives (3a–f) were synthesized and characterized as well as evaluated for the presence of antioxidants. The preparation of these compounds involves refluxing (p-nitrophenyl) hydrazine with 4-substituted salicylaldehydes. The Molecular structures of compounds were determined through mass spectra, 1H, Carbon NMR, and infrared spectral studies. Tests were conducted to assess the anti-oxidant properties

Table 7: In-vitro antibacterial activity values of the synthesized hydrazone Schiff base and Cu(II) complexes

	Zone of Inhibition (mm)	Zone of Inhibition (mm)		
	S. aureus	***E. coli***	***K. pneumoniae***	***P. aeruginosa***
1	6	8	6	7
2	6	6	6	6
3	6	6	6	6
4	9	10	15	6
5	8	6	6	6
+Ve. Control	24	23	11	14
–Ve. Control	6	6	6	6

Table 8: IR spectral data (cm^{-1}) of synthesized compounds

Compound	C–N (1360-1800)	C=C (1400-1600)	C=N (1650-1700)	CH (Al, 2850–3000)	CH (Ar, 3000–3100)	N–H (3300–3500)
1 (dpa)	1118	1373	1650	2940	1339	3233
2 (bpd)	1136	1371	1643	2936	3152	3298
3 (dhd)	1139	1381	1660	2971	3120	3232
4 (bdh)	1136	1337	1655	2971	3099	3233

Table 9: Antibacterial activity (zone of inhibition, mm) of synthesized compounds

Compound	***Staphylococcus aureus***	***E. coli***	**Inhibition Zone (mm)**
Control (Ceftriaxone)	25	22	18
1 (dpa)	8	7	10
2 (bpd)	9	8	9
3 (dhd)	8	7	8
4 (bdh)	9	8	9

Table 10: Molecular docking results of synthesized metal complexes

Pharmaceutical Name	**Binding Percentage[a]**	**Score ± SD (kcal/mol)[b]**	**RMSD (L–H)**
Ni Complex	22	–5.9 to –6.0	29.46 – 32.52
Zn Complex	22	–6.2 to –7.2	0.00 – 4.22

Table 11: Antimicrobial Effects of the Ligands (L_1–L_6) and their Cr(III) Complexes, Zone of Inhibition (mm)

S. No.	Compound	Gram-positive (***Bacillus subtilis***)	Gram-negative (***E. coli***
Ref. Drug	Penicillin	35	23
1	$L_1\delta$	12	7
2	$L_1\delta$	10	6
3	$L_1\delta$	13	8
4	$L_1\delta$	15	10
5	$L_1\delta$	20	13
6	$L_1\delta$	17	10
7	$[Cr(L_1)_2(H_2O)_2]Cl.H_2O$	15	10
8	$[Cr(L_2)_2(H_2O)_2]Cl.2H_2O$	17	12
9	$[Cr(L_3)_2(H_2O)_2]Cl.2H_2O$	18	15
10	$[Cr(L_4)_2(H_2O)_2]Cl.2H_2O$	22	17
11	$[Cr(L_5)_2(H_2O)_2]Cl.2H_2O$	27	20
12	$[Cr(L_6)_2(H_2O)_2]Cl.2H_2O$	25	18

of these hydrazone derivatives in the areas of free radical scavenging, reducing power, metal chelation, and overall antioxidant capacity. All the compounds exhibited appreciable anti-oxidant activity, among them compound 3a which bears the shortest chain length has shown maximum activity and it was consistent in all assays[6].

Antifungal and Antibacterial Properties

Using Proton and Carbon NMR, and Electron spray ionization based mass analysis, these compounds—1-(1-(4-Chlorophenyl)-2-(phenylsulfonyl)ethylidene)-2-phenylhydrazine were produced, described, and examined.IR ν3341 (NH) cm^{-1}; ^1H NMR (DSMO-d_6) ν5.17 (s, 2H, CH_2), 6.82–6.85 (m, 1H, ArH), 7.12 (d, *J* = 7.5 Hz, 2H, ArH), 7.23–7.26 (m, 2H, ArH), 7.32 (d, *J* = 8 Hz, 2H, ArH), 7.53–7.56 (m, 2H, ArH), 7.59–7.63 (m, 1H, ArH), 7.71 (d, *J* = 8.5 Hz, 2H, ArH), 9.81 (s, D_2O exchangeable, 1H, NH); ^{13}C NMR (DSMO-d_6) ν51.54, 113.00, 120.06, 127.26, 127.88, 128.12, 128.93, 128.97, 131.88, 133.93, 136.50, 139.26, 144.46; MS (ESI) *m*/*z* 384.7 The synthetic compound's anticandidal activity were monitored against 4 species of Candida—*C. albicans*, *C. krusei*, *C. parapsilosis*, and *C. glabrata*—and contrasted with that of the common anticandidal medication, fluconazole. The synthesized chemical likewise exhibits a comparable binding relationship with fluconazole at the active site of CYT P450 14δsterol demethylase, according to the docking result. Furthermore, the molecule possess the strong cytotoxicity against the MCF10A human breast cell line, which is normally non-tumorogenic[9].

Phenyl pyrazolines, isoxazoles containing heterocycles were also prepared from chalcones derived from s-triazine. The chalcones were synthesized by reacting the substituted acetophenone in DMF with different aromatic aldehyde. These chalcones were then subjected to further reactions: the treatment with phenyl hydrazine hydrochloride

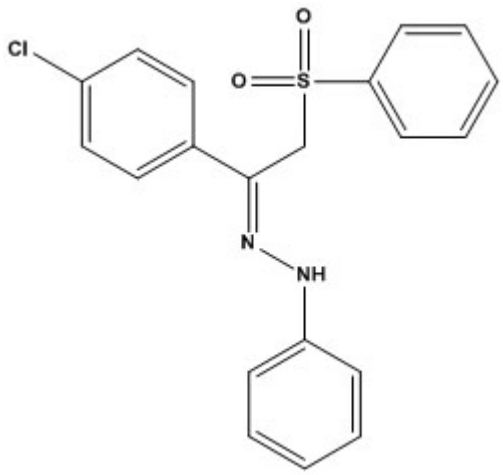


Fig. 9: 1-(1-(4-Chlorophenyl)-2-(phenylsulfonyl) ethylidene)-2-phenylhydrazine[9]

produced phenyl pyrazolines while reaction with hydroxylamine hydrochloride afforded isoxazoles the reactions being carried out in alkaline conditions. The obtained compounds were characterized using IR spectroscopy and by elemental analysis of their empirical formula by Proton and Carbon NMR. All of the recently produced compound's antibacterial properties were evaluated against various bacterial and fungal stains[16].

In the current study, 2,3-diaryloxirane-2,3-dicarbonitriles underwent various chemical transformation with various nucleophiles including hydrazine, methyl hydrazine, phenylhydrazine, hydroxylamine, thiosemicarbazide and 2-amino-5-phenyl-1,3,4-thiadiazole led to the formation of pyrazole. The pyrazoles were further subjected to reaction with aromatic aldehydes and/or methyl glycinate to afford Schiff bases and pyrazolo[3,4-b]-pyrazinone derivative were also observed. Further reaction of Schiff bases with ammonium acetate and/or hydrazine hydrate resulted to imidazolopyrazole and pyrazolotriazine system. When the reaction of the pyrazolo[3,4-b]-pyrazinone with chloroacetic acid and/or diethyl malonate was carried out, the obtained compound was a tricyclic compound and a triketone. Also, the compound was treated with active methylene reagents including acetylacetone and/or cyclopentanone to form adducts and on heating with ammonium acetate, the compound gave 3-pyridone derivatives[4].

In this work, some new Phenyl hydrazine Schiff base and its Copper (II) and Zinc (II) complexes were prepared and characterized using UV-Visible, Infrared and NMR techniques. Gram-negative, bacteria Pseudomonas aeruginosa and gram-positive bacteria, E. coli and Staphylococcus aureus were shown to be susceptible to these chemicals. Overall, the copper (II) complex was found to be most efficient with bacterial inhibition

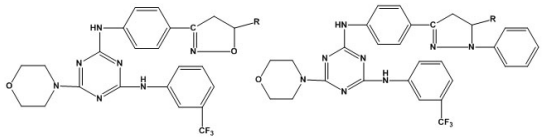


Fig. 10: Phenyl pyrazolines[16]

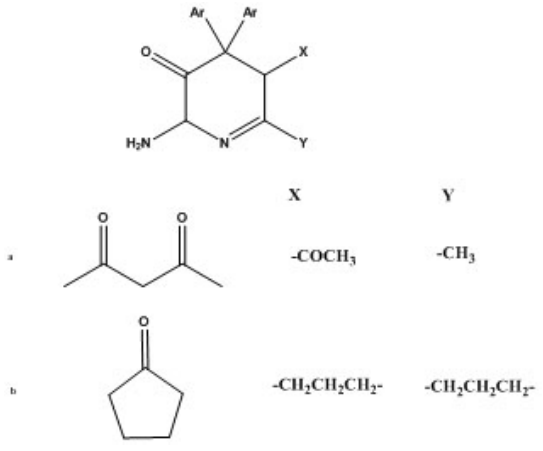


Fig. 11: 3-pyridone derivatives[4]

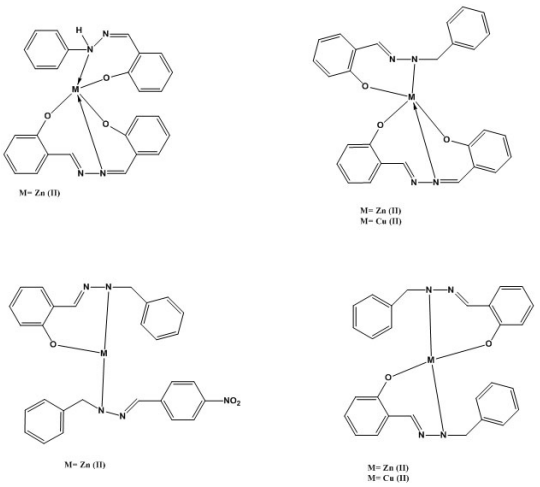


Fig. 12. Phenyl hydrazine Schiff base and its Cu(II) and Zn(II) complexes[12]

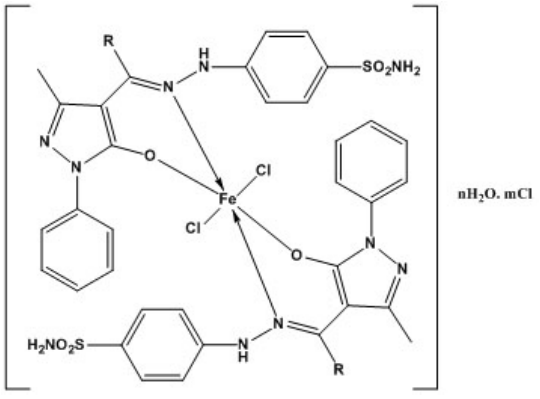


Fig. 13: p-Sulfonamide Phenyl Hydrazine-Pyrazolone Fe Complex[18]

compared with the zinc (II) complex and individual ligands[12].

Sulphonamide phenyl hydrazone derivatives were synthesized and their thermal and biological characteristics were investigated. The ligands and the heterochelates of iron (III) complex were characterized with the help of diverse spectroscopic analysis such as ^{1}H NMR, IR, elemental analysis, thermal analysis, and mass spectral analysis. According to the biological tests carried out against Gram Positive as well as negative bacteria revealed that hetero-chelates exhibit moderate antibacterial performance, suggesting deep exploration of the topic[18].

Further, it investigates the catalytic, synthetic and thermal and biological properties of sulphonamide phenyl hydrazone derivatives. Several ligands and Manganese (III) based heterochelates were prepared using various acyl chloride reagents. Evaluation of ligands were done using Infrared technique, Proton NMR, and elemental analysis; the hetero-chelates were characterized by thermal methods; TGA/DTG, DSC and mass spectroscopy. The bacterial inhibition of these compounds were checked in test tube against Gram positive as well as gram negative bacteria; the results encourages future research[17].

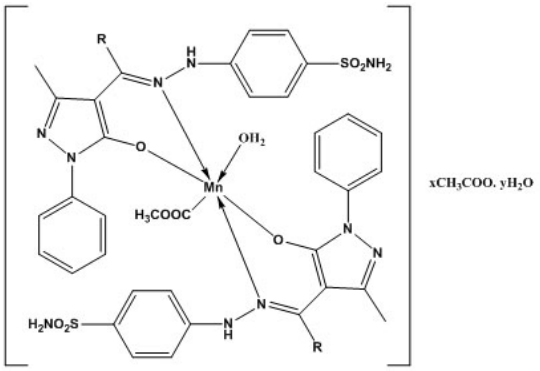


Fig. 14: p-Sulfonamide Phenyl Hydrazine-Pyrazolone Mn Complex[17]

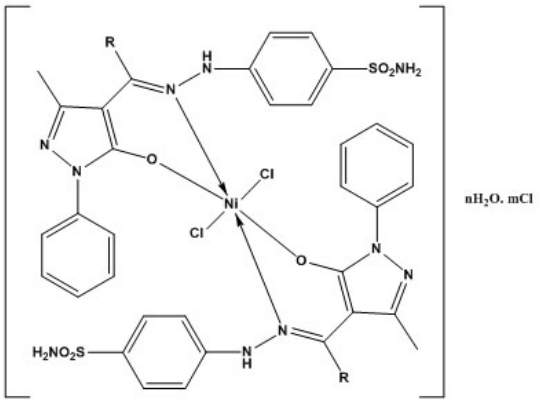


Fig. 15: p-Sulfonamide Phenyl Hydrazine-Pyrazolone Ni Complex[19]

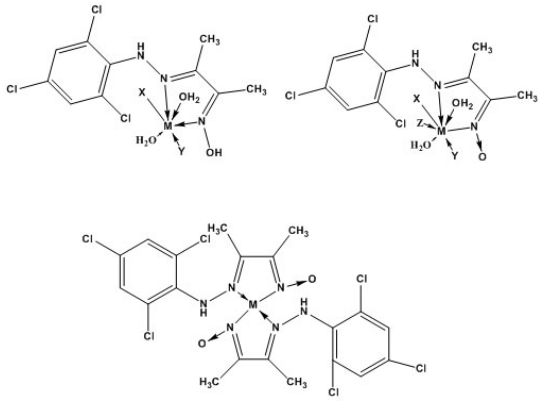


Fig. 16: Mononuclear complexes based on 3-(2-(2,4,6-trichlorophenyl) hydrazono) butan-2-one oxime as a ligand[15]

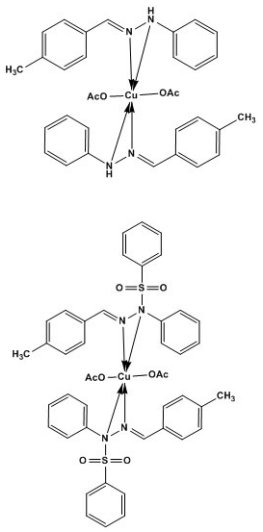


Fig. 17: Hydrazone derivatives[1]

The thermal and biological characteristics of newly synthesized Ni (II) complexes with pyrazolone ligands were evaluated. These ligands were synthesized from a range of 4-acyl pyrazolones. The newly formed compounds were also investigated with Proton and Carbon NMR, Infrared technique, UV-vis spectra and elemental analysis. The generated Ni (II) complexes were described using thermal analysis profiles TGA/DTG and DSC, elemental analysis, and UV-Vis and IR spectra. Antibacterial and antimalarial activities of the synthesized compounds were determined and the results obtained showed some positive acts that call for further studies[19].

The entire set of new mononuclear complexes based on 3-(2-(2,4,6-trichlorophenyl) hydrazono) butan-2-one oxime as a ligand having transition metal ions of Cd(II), Zn(II), Cu(II), Ni(II), Co(II), Fe(II), Mn(II), and VO(II). The complexes were studied by several physicochemical techniques. Quantum Molecular calculations explicate the binding site of the ligand, and electronic parameters of both free-ligand and its complexes. Coordination occurred through imine nitrogen of hydrazone group and the nitrogen atom of oxime group, forming complexes via ML and M2L methods. They were identified as a quite rich geometrical architecture displaying different geometrical configurations. As mentioned above the ESR spectra of the $Cu^2\delta$ complexes exhibited axial symmetry and the paramagnetic electron was there in the $d(x^2-y^2)$ orbital revealing substantial covalency of bonding. Thermogravimetric analysis revealed that the complexes decomposed into 4 stages, beginning with the loss of coordinated H_2O molecules and dehydration, followed by complete decomposition to form metal oxides. While the free ligand showed no antimicrobial activity. Some of its metal complexes demonstrated varying levels of antimicrobial effectiveness[15].

The formation of the various hydrazone derivatives such as phenylhydrazine, 4-methoxybenzaldehyde, 4-nitrobenzaldehyde

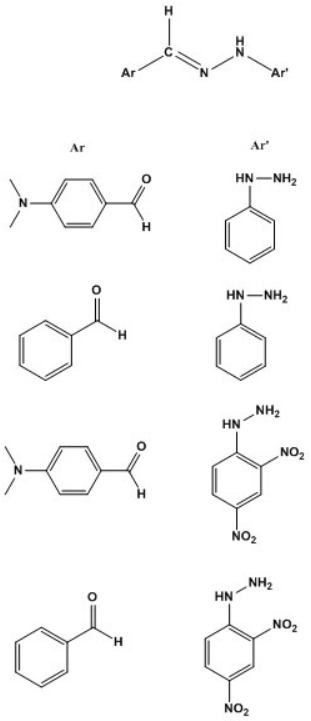


Fig. 18: Schiff bases were prepared from phenylhydrazine (1) and 2,4-dinitrophenylhydrazine (2) with different aldehydes[8]

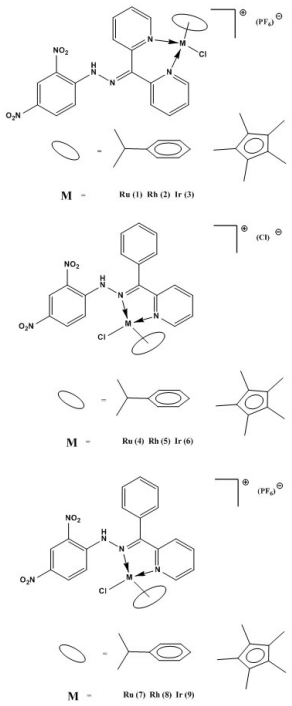


Fig. 19: Hydrazone complexes[13]

and benzenesulfanohydrazones and their Cu(II) complexes were carried out.The infrared spectra showed sharp absorption at 1616 cm-1 attributed to azomethine groups (C=N). The sharp absorption at 3013 cm-1 was assigned to H-C=N band of the azomethine group. From the IR spectra results it was found that the Schiff base ligands are bidentate in nature binding through azomethine nitrogen and another nitrogen atom.

Bacterial susceptibility testing revealed that the Cu(II) complex of compound 2 has a stronger antibacterial interference with Klebsiella pneumoniae with 15mm of antibacterial zone, compared to ceftriaxone with inhibition zone of 11mm which may be as a result of increased lipophilicity of Cu(II) complex of compound 2[1].

A novel set of Schiff bases are prepared by reacting phenylhydrazine (1) and 2,4-dinitrophenylhydrazine (2) with different aldehydes. Here the reactions took place with complimentarily high purity and efficiency towards the yields. The structures of the synthesized compounds were further verified using elemental analysis, Mass Analysis, IR, electronic spectral analysis. These compounds were also assessed in light of their ability to inhibit microorganisms growth[8].

The preparation and study of a number of hydrazone based mononuclear complexes of general formula [(arene)MLCl]PF6, where M=Ru, Rh, Ir were carried out. They were further characterized by X-ray crystallography and established a piano stool geometry with ligand behaving as NN' chelation. The Ligand in some complexes can chelate through the two nitrogen atoms of pyridine to form a 6-membered

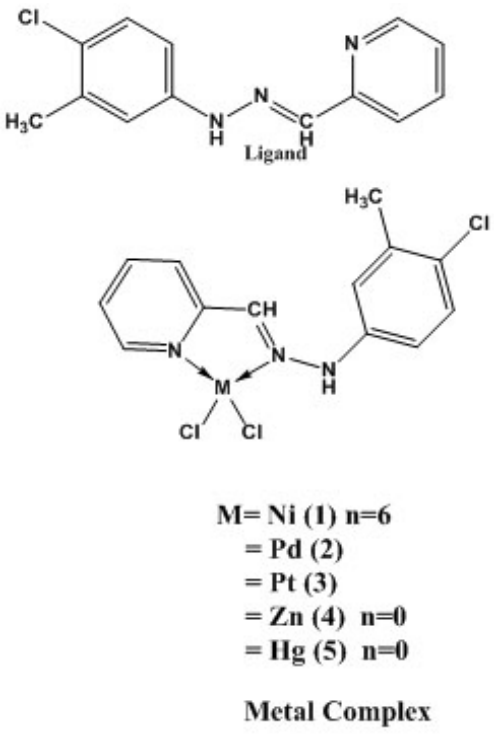


Fig. 20: Proposed structure of Ligand and Metal complex[2]

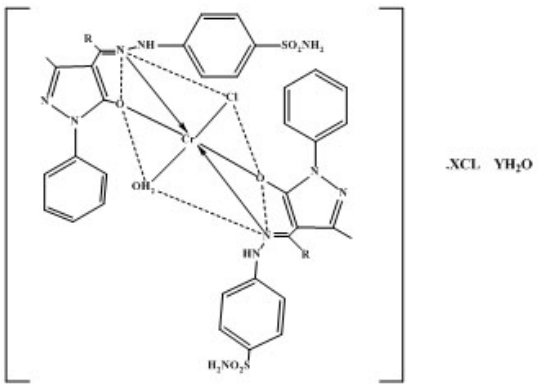


Fig. 21: Proposed structure of Cr(III) complexes[21]

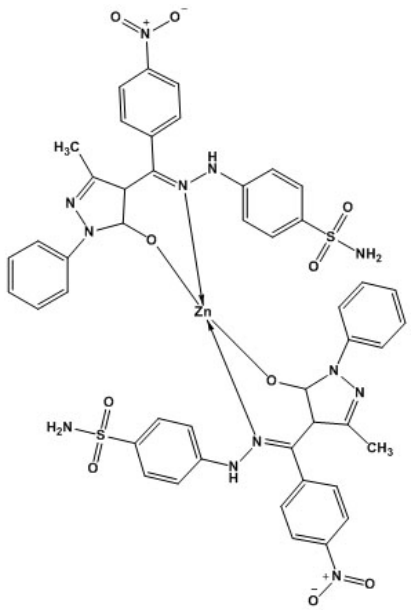


Fig. 22: Zn(II) complexes from 4-acyl pyrazolone ligands[22]

metallocycle while in other complexes, it only coordinates through one nitrogen of hydrazone and one pyridine nitrogen that also forms a five-membered metallocycle. Antibacterial efficacy of the complexes was evaluated against both Gram-negative as well as Gram-positive bacteria and all complexes inhibited bacterial growth[13].

The two-fold suppression of the primary protease (M_{pro}) and the NSP10/NSP16 methyltransferase complex as potential therapeutic targets for COVID-19 was determined. The focus is on a newly synthesized Schiff-base ligand formed from the condensation of (4-chloro-3-methyl phenyl) hydrazine and 2-pyridine-carboxaldehyde, along with +2 complexes of Ni, Pd, Pt, Zn, and Hg. Characterization of these compounds was carried out using Infrared, Proton and Carbon NMR, and elemental analysis. The infrared spectrum of the Schiff-base (Cmpy) ligand showed a band at 3240 cm^{-1} due to the stretching vibration of the NH group, and a new band displayed at 1606 cm^{-1} due to the ϑ(C=N) azomethine group, whereas the ϑ(C=N) of the pyridyl ring displayed at 1689 cm^{-1}.The ^1H NMR spectrum of the Cmpy ligand showed four singlet peaks at ϑH = 11.25 ppm, 7.80 ppm, 7.65 ppm, and 2.38 ppm attributed to the protons of the NH, CH=N, H8, and CH_3 group, respectively. In the ^1H NMR spectra of the M(II) complexes, the azomethine proton signals at 7.80–7.85 ppm (s, 1H) for complexes. Antibacterial testing revealed that the Zn complex exhibited maximum activity against *Pseudomonas aeruginosa* and *Staphylococcus aureus*. Molecular docking studies shows that ligand and its Ni and Zn complexes had excellent binding energies with Mpro and NSP16, ranging from –5.9 to –7.2 kcal/mol. The metal complexes displayed 100% binding affinity with the active site of the NSP16 receptor, marking the first reported use of these metal complexes as two-fold suppressors of M_{pro} and NSP16 in SARS-CoV-2[2].

Chromium (III) complexes of pyrazolone phenylhydrazone ligands were synthesized, characterized and its anti-microbial efficacy was analyzed. The compounds were characterized using NMR, mass, IR, UV-visible spectral studies and thermal analysis. In the IR spectra of ligands (L1-L5), sharp peak is observed in the 1531-1560 cm^{-1}range, corresponding to the acyclic azomethine group. In the complexes, where the ligands coordinate to the metal through the nitrogen atom, a reduction in electron density in the azomethine link is expected, resulting in the appearance of a peak in the 1512-1535 cm^{-1}range37 The electronic properties and chemical reactivity was determined by using computational studies employing DFT studies. The antibacterial examination presented here demonstrated significant activity against both Gram-positive as well as negative microorganisms, indicating the possibility of these complexes to be used as virucidal agents[21].

In the present investigation, new Zn(II) complexes from 4-acyl pyrazolone ligands were synthesized and fully described. With increased efficiency, structure and stability of synthesized products were supported by NMR, IR, UV-visible spectroscopy, and thermal analysis (TGA/DTG, DSC). These complexes were tested for antibacterial activity, and have shown promising results, making them useful as stable modules for material science and in medicine[22].

Anti-Malarial Property

A novel series of fluoro-substituted pyrazolylpyrazolines was synthesized with good to excellent yields (77–88%) using pyrazole chalcones and substituted phenyl hydrazine hydrochlorides under microwave irradiation. The synthesized compounds were tested for antibacterial, antifungal, antituberculosis, and antimalarial activities and demonstrated strong antimalarial activity against *Plasmodium falciparum*, outperforming quinine (IC50 0.268)[11].

CONCLUSION

The review sheds the light on the preparation, analytical assessment, and bioactivity assessment of the different phenyl hydrazine derivatives with the ability to work in various therapeutic classifications such as anti-inflammatory, anti-cancer and anti-microbial fields. These derivatives were proved by in vitro and in vivo biological activities to have good activity and high selectivity for anti-inflammatory agents as well as anti-cancer cell proliferation. Indeed, the molecular docking and DFT studies proved to give important and valuable information regarding their interaction with target proteins. The anti-cancer activity especially towards the breast, colon and human liver cancer cell has made it a

prominent chemotherapeutic agent in the treatment of cancer similar to that of cisplatin. Furthermore, suppression of their growth as antimicrobial or antifungal agents against diverse pathogens such as fungi, bacteria, and protozoa will also exhibit an account of their effectiveness towards looming antibiotic resistance.

ACKNOWLEDGEMENT

The authors express their sincere gratitude to the Department of Chemical Science, Parul Institute of Applied Sciences, Parul University, Vadodara, Gujarat, India, for providing the essential facilities and continuous academic support.

CONFLICT OF INTEREST

This review was conducted independently and no conflict of interest exists from any funding agency.

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