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Synthesis of Novel 2-Amino Thiazole Derivatives and Salicyaldehyde based Ligand to have Biological Activity

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Abstract - In inorganic chemistry, Schiff bases and complexes come in a variety of forms. Therefore, the discovery of new organic and inorganic compounds with remarkable anti-fungal, anti-bacterial, and anticancer characteristics represents a major advancement in biochemistry, pharmacy, and medicine. All of the chemicals that were employed in this study were A.R. grade. The following materials provided by SD's fine chemical Ltd. and Merck chemicals, Mumbai were utilised impurification: methanol, calcium hydroxide, sodium acetate, thiourea, ethylacetoacetate, benzoyl chloride, acetyl chloride, 1,4-dioxane, and sulfuric acid. Additionally, this Schiff base may combine with the ions of several transition metals, such as Ni(II), Cu(II), Co(II), and Cd(II), to create complexes. In addition to chemical analysis, conductivity, and magnetic tests, we further characterized the complexes using electronic and infrared spectroscopy in order to examine their structures. Every compound's antibacterial activity was evaluated. In the agar cup test method, all of the Schiff base metal complexes had a moderate level of antibacterial activity. Spectroscopic data suggests that these complexes are all of type $ML_2(H_2O)_2$ (M=Mn, Fe, Co, Ni, and Cu).

Keywords: 2-Amino Thiazole, Salicyaldehyde, Schiff Base, Antimicrobial Activity, Metal complex

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INTRODUCTION

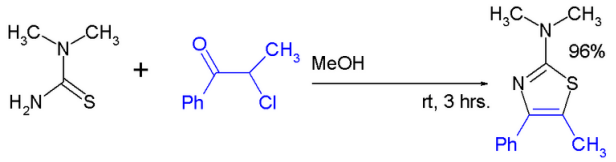
The condensation of an aldehyde or a ketone produces a Schiff base. Aldimines are formed by the carbonyl group of an aldehyde, while ketoimines are formed by the carbonyl group of a ketone. Tsumaki (1983) described the [Co(sal_2-en) Complex], which gained attention due to its capacity to undergo reversible adduct formation with molecular oxygen, as an example of a chelate that is known to be produced when various metal ions interact with Schiff bases. It was first noticed that the complex might oxygenate. The mechanism of oxygenation, however, remained a mystery until the development of cutting-edge physical methods. 2-Salicylaldehyde and 2,2-bis(P-methoxyphenylamine) complexed with Mn(II), Co(II), and Cu(II) were used to create and characterise a new Schiff base ligand. Next, complexes of Cr(III), Fe(III), Co(II), and Ni(II) with a Schiff base generated from 4-dimethylamino benzaldehyde and primary amines will be synthesized and characterized. The results of the chemical analysis indicated that complexes with Cr(III) and Fe(III) atoms formed an octahedral structure, while complexes with Co(II) and Ni(II) atoms formed a square planar geometry. A Schiff base was synthesized by combining salicylaldeyde, histidine, and complexes of these two with divalent transition metal ions. The complexes were examined using elemental analysis, which revealed a metal to ligand ratio of 1:1. Agricultural, industrial, medicinal, and other sectors all make use of Schiff base complexes of transition metals. An example of an element that is involved in oxygen metabolism is [Co($acac_2$-en)] in dimethylformamide, pyridine, and substituted pyridines. The refining of petroleum makes use of transition metal complexes with 1, 10-phenanthroline and 2, 2-bipyridine. Figments made of Schiff bases, which are generated by condensing 1-formyl-2-hydroxy-3- naphthoic arylamide with O-hydroxyl or O-methoxy aniline complexes of Co(II), Ni(II), Cu(II), and Zn(II), are helpful. Some forms of leukaemia have shown potent activity against oxovanadium complexes. There have been reports of biological activity in transition metal complexes produced from various amino acids.

Nature places a premium on the thiazole ring. As an example, the oxidative decarboxylation of α-keto acids requires thiamine, a coenzyme. Penicillin, one of the earliest and most significant broad-spectrum antibiotics, also contains a tetrahydrothiazole in its structure. Important medications include thiazoles and thiazolamines. The presence of a thiazole ring in a molecule makes its possible biological action

readily apparent. Similarly, 2-aminothiazoles are used as intermediate products in the manufacture of antibiotics and dyes, and they are recognised as physiologically active chemicals with a wide spectrum of action. In pharmacology, 2-aminothiazole derivatives find extensive usage. Aminothiazole has antioxidant and antibacterial properties. Hydrocarbon fuels, minerals, synthetic lubricating oils, solid paraffin, polyolefins, and vegetable fats may all benefit from the antioxidant properties of certain substituted aminothiazole derivatives. When added to lubricating lubricants, triazine derivatives with substituents that include 2-aminothiazole fragments effectively prevent corrosion, wear, and scuffing.

2-Aminothiazole

A heterocyclic amine with a thiazole core is 2-aminothiazole. Another name for it is a cyclic isothiourea. It dissolves in water, alcohols, and diethyl ether, and it has a pyridine-like aroma. Almost exclusively, 2-aminothiazole is of interest to academics. A sulfathiazole ("sulfa drugs"). As a thyroid inhibitor, 2-aminothiazole may be used to treat hyperthyroidism. Sulfuryl chloride, 2-aminothiazole, and paraldehyde are the three main ingredients in its preparation. A common way to make 2-aminothiazoles is to combine thiourea with an alpha-halo ketone, much like the parent compound.



A 2-acylamino-ketone combines with phosphorus pentasulfide in a modification of the Robinson-Gabriel synthesis. The field of medical chemistry makes use of synthetic aminothiazoles, which are molecules that include the parent 2-aminothiazole as a component. As an example, there are many instances such as abafungin, acotiamide, amiphenazole, amthamine, avatrombopag, aztreonam, cefepime, cefixime, ceftizoxime, ceftiofur, ceftibuten, cefpirome, famotidine, meloxicam, and pramipexole.

LITERATURE REVIEW

Singh, Nrendra & Sutar, Niranjan & Kumar, Sushil & Sharma, Umesh. (2012) The antimicrobial and antifungal activities of many 2-aminothiazoles derivatives were evaluated in vitro against various microbes. Simple methods have been used to carry out synthesis with good isolated yields. Infrared spectroscopy, nuclear magnetic resonance, and elemental analysis all verified the original compounds' structures and purity. Using the disk-diffusion technique, both the antibacterial and antifungal activities of each compound were examined against Bacillus subtilus (+ve), E. coli (-ve), Candida albicans (+ve), and Aspergillus niger (-ve) at concentrations of 50 and 100µg/ml. Some of the chemicals seem to be showing promising action based on these early findings.

Khalifa, Mohamed. (2018) Precursors to compounds with biological activity, such as aminothiazole nuclei and their derivatives, have a long history of use. 2-Aminothiazole is a heterocyclic amine that serves as a building block for numerous compounds. These compounds include sulphur drugs, biocides, fungicides, synthetic fibre dyes, chemical reaction accelerators, and antibiotics. A large number of 2-aminothiazoles have been substituted with different groups for various pharmaceutical purposes, and they also reduce corrosion on mild steel. This paper presents an overview of the synthetic usefulness, reactions, and biological activity of 2-amino-4-substituted-thiazoles.

Al-Qadsy et al (2023) Synthesis, Characterization, and Molecular Docking Studies of Novel Ni(II) and Zn(II) Complexes with (E)-2-((5-Bromothiazol-2-yl)imino)methyl)phenol Ligand: Antimicrobial Activity. Brief summary: Two novel complexes, Ni(II) and Zn(II), have been synthesised using the usual approach based on the Schiff base ligand (E)-2-((5-bromothiazol-2-yl) imino) methyl) phenol. These complexes aim to address the issues associated with antibiotic resistance by bacteria. Both conventional and efficient, environmentally benign, microwave-assisted methods were used to synthesise the Schiff base ligand (HL) from salicylaldehyde and 5-(4-bromophenyl)thiazol-2-amine. Nuclear magnetic resonance (NMR), thermogravimetric analysis (TGA), elemental analyses, fluorescence time-of-flight (FTIR) spectroscopy, ultraviolet-visible spectroscopy, and magnetic susceptibility were all used to assess the ligand and complicated compounds. Three Gram-positive bacteria (Staphylococcus aureus ATCC 25923, Methicillin-resistant Staphylococcus aureus ATCC 43300 and Enterococcus faecalis ATCC 29212) and three Gram-negative bacteria (Pseudomonas aeruginosa ATCC 27853, Escherichia coli ATCC 25922 and Klebsiella pneumoniae ATCC 700603) were tested for antibacterial activity by analysing the ligand and its complexes. The results show that the ligand and its complexes are effective against some bacteria, but the Ni(II) complex surpassed all other drugs, including the popular antibiotic Streptomycin, with MIC values ranging from 1.95 to 7.81 µg/mL. The docking investigation also proved the antibacterial findings were true, since the Ni complex exhibited a higher binding affinity for E. coli NAD synthetase (−7.61 kcal/mol), according to the data.

Adnan, Shaimaa. (2021) New heterocycle chemicals are synthesised in this research in a multi-step process. An azo derivative is formed by reacting 2-Amino-5-nitrothiazole with salicylaldehyde at 0^{o} C in acidic conditions. Then, a chalcone derivative is obtained by reacting (1) with 4-hydroxyacetophenone (2). In the third step, react (2) with various compounds such as hydrazine hydrate,

phenylhydrazine, 2,4-dinitrophenylhydrazine, hydroxylamine hydrochloride, urea, thiourea, ethyl cyanoacetate, malononitrile, and guanidine. This reaction will produce pyrazole derivatives, isoxazole derivatives, oxazine derivatives, thiazine derivatives, and pyridine derivatives. The compounds were identified using various techniques such as FT-IR spectra, ^{1}H-NMR, ^{13}C-NMR, CHN, Rf-TLC reaction, measurement liquefaction point, and following experimental results. After that, we looked at how eleven different chemicals affected two different types of microbes.

Sumrra, et al (2021) The current research supports investigating Schiff base ligands generated from aminothiazoles using both computational and experimental methods. Spectroscopic techniques (UV-Vis, FT-IR, ^{1}H-NMR and ^{13}C-NMR), mass spectrometry, elemental analysis, and density function theory (DFT) have all been used to experimentally study the electronic and structural features of ligands. By means of computational simulations using the B3LYP/6-31 + G(d,p) functional of DFT, the optimised geometrical structures of ligands, geometric parameters, MEP surfaces, and FMO energies were investigated. It was determined that ligands were bioactive by looking at global reactivity characteristics calculated from FMO energy gaps. In a 1:2 molar ratio, the developed ligands were chelated with 3d-transition metals, including VO(IV), Cr(III), Fe(II), Co(II), Ni(II), Cu(II), and Zn(II). The creation of octahedral geometry surrounding all the divalent and trivalent metal centres was verified by the spectral and magnetic data, while the square-pyramidal geometry of the tetravalent vanadyl centres was also established. Two Gram-negative (Salmonella typhimurium and Escherichia coli) and two Gram-positive (Bacillus subtilis and Staphylococcus aureus) bacteria were tested for their in vitro antibacterial capability against all of the chemicals that were synthesised. Their antibacterial activity was equivalent to that of a typical antibiotic (streptomycin), and the results of the experiment showed strong action. The compounds' ability to scavenge radicals using diphenyl picryl hydrazide was used to determine their antioxidant potential. All of the metal chelates showed more bioactivity than the free ligands, according to the data. The primary cause of their increased bioactivity was the chelation. Based on these findings, thiazole metal-based compounds may have potential as antibacterial and antioxidant agents.

RESEARCH METHODOLOGY

Experimental

The compounds used in this investigation were all of the A.R. grade. These substances were used unfiltered: iodine, hydrochloric acid, sulfuric acid, thiourea, ethylacetoacetate, sodium acetate, calcium hydroxide, benzoyl chloride, acetyl chloride, 1,4-dioxane, and methanol (provided by SD's fine chemical Ltd and Merck chemicals., Mumbai). After distillation, the alcohol was extracted using pure ethanol sourced from the alembic Chemical Works Co. Ltd. in Baroda. Preparation of Schiff base metal complexes was carried out using metal acetates of Mn(II), Co(II), Ni(II), Cu(II), and Fe(III) from SD's fine chemical Ltd, Qualigens-Glaxo, Mumbai, and Merck chemicals., Pune, respectively.

2-Aminothiazoles as Anticancer Agents

In order to overcome resistance, clinical administration of large dosages of anticancer medications results in significant toxicities. According to the reviewed literature, the anticancer effects of heterocyclic thiazole derivatives were tested by integrating them with other moieties. Figure 1 shows the synthetic protocol for paeonol-2-aminothiazole-phenylsulfonyl derivatives 4. The first step was to treat paeonol (1) with thiourea and iodine in refluxing ethyl alcohol to produce the corresponding 2-aminothiazole scaffold 2. Then, scaffold 2 was treated with substituted phenylsulfonyl chloride 3 to yield compound 4. We tested seven different cancer cell lines and fibroblast cells (BALB/3T3) for the cytotoxic effects of several paeonol-2-aminothiazole-phenylsulfonyl derivatives 4. Among the cancer cell lines studied, the F and OCH_3 derivatives of the thiazole-paeonolphenylsulfonyl scaffold exhibited the most cytotoxic and powerful effects. Scheme 2 details the design and synthesis of new cinnamic acid amide scaffolds 9 that include thiazoles. Based on the anticancer activity data, compound 9 (R^1 = R^2 = H, R^3 = OCOMe) has some promising properties for a medication that combines coagulant and platelet actions.

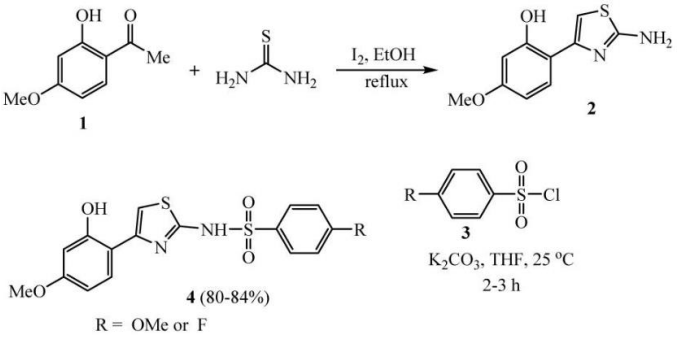


Figure 1: Creating different paeonol-2-aminothiazole-phenylsulfonyl compounds 4

Antimicrobial Evaluation Test

The agar well diffusion technique was used to test the complexes for their antibacterial activity against several kinds of bacteria, including gram-positive Escherichia coli and Shigella dysenteriae as well as gram-negative Streptococcus agalactiae and Bacillus cereus, all of which are known to be harmful to humans. A proper procedure was followed to prepare the medium and bacterial suspension. The antibacterial activity was evaluated in vitro using the diffusion method. In accordance with the prior research, the bacteria were cultured in nutritional concoction at 37°C for a duration of 24 hours. Diffusion on solid media was used to evaluate the

complexes. A sterile paper disc with a diameter of 5 mm was soaked with 50 µg cm^{-3} of dimethylformamide (DMF) and their bimetallic complexes, and then put in nutritional agar. After that, the plates were left to incubate for one day. In order to record the data, the growth inhibition (% zones of inhibition) around the disc was measured.

The process of creating and studying metal complexes

Complexes were prepared by mixing an aqueous solution of metal acetate (0.05 M) with a 1:4 dioxane solution of ligand (0.05 M) in the presence of an acetate buffer (pH=6.5). The mixture was digested on a sand bath for 30 minutes, cooled, and filtered to remove any excess precipitate. Subsequently, it was washed with water to remove excess metal ions and methanol to remove unreacted Schiff bases, respectively.

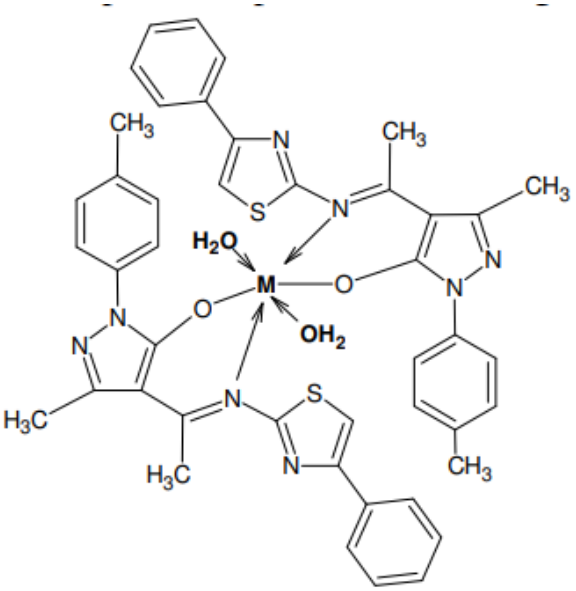
RESULTS AND DISCUSSION

TGA study of complexes including Mn(II), Fe(III), Co(II), Ni(II), and Cu(II)

Thermograms of these metal complexes reveal a three-step breakdown process (refer to Table 1). There is no evidence of lattice water in any of the metal complexes as their weight remains constant at temperatures below 120 °C. Within the temperature range of 140-210 °C, the first step of breakdown is achieved. The loss of two coordinated water molecules correlates to the percentage of weight loss in this range. Between 210 and 400 °C, the second stage of breakdown occurs. Two Schiff base ligands have a combined weight loss that falls within this range. At temperatures between 400 and 900 °C, the third stage of decomposition may be achieved. A percentage drop in weight within this range correlates to a percentage drop in metal oxide residue. Metal complexes falling into this group may undergo the following breakdown mechanisms: The complexes of Mn(II), Fe(III), Co(II), Ni(II), and Cu(II) investigated here all belong to the $[ML_2.(H_2O)_2]$ group, according to TGA and analytical data. These structures are suggested for the ligand-complexes based on the findings of elemental analysis, infrared spectra, electronic spectra, TGA analysis, and magnetic susceptibility tests (Figures 2 & 3).

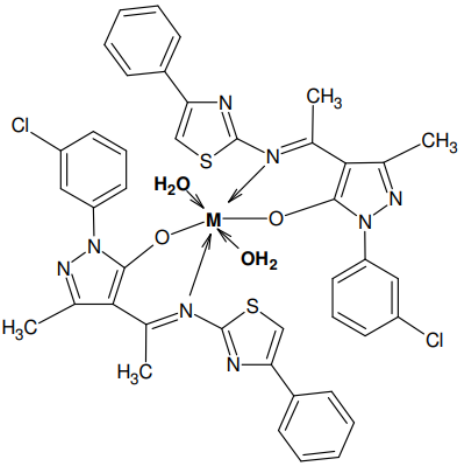
Table 1. Analysis of ligands and their metal complexes using thermodynamics (control-DMF)

Compounds	Mass loses observed (Calculated)		
	Stage-I [140-210 °C]	Stage-II [210-400 °C	Stage-III [400-900 °C]
$[Mn(Ligand\text{-}L)_2.2H_2O]$	4.11 (4.16)	86.84 (86.96)	9.06 (9.11)
$[Fe(Ligand\text{-}L)_2.2H_2O]$	4.10 (4.15)	86.78 (86.87)	9.24 (9.21)
$[Co(Ligand\text{-}L)_2.2H_2O]$	4.21 (4.14)	88.44 (88.49)	8.48 (8.61)
$[Ni(Ligand\text{-}L)_2.2H_2O]$	4.06 (4.14)	89.27 (89.35)	6.65 (6.75)
$[Cu(Ligand\text{-}L)_2.2H_2O]$	4.08 (4.12)	86.84 (87.02)	8.96 (9.10)
$[Mn(Ligand\text{-}L_1)_2.2H_2O]$	3.92 (3.97)	87.33 (87.54)	8.76 (8.70)
$[Fe(Ligand\text{-}L_1)_2.2H_2O]$	3.86 (3.96)	87.34 (87.45)	8.75 (8.79)
$[Co(Ligand\text{-}L_1)_2.2H_2O]$	3.98 (3.95)	88.08 (88.04)	8.11 (8.22)
$[Ni(Ligand\text{-}L_1)_2.2H_2O]$	3.96 (3.95)	89.76 (89.82)	6.38 (6.44)
$[Cu(Ligand\text{-}L_1)_2.2H_2O]$	3.88 (3.93)	87.54 (87.59)	8.65 (8.69)
Assignment	Loss of two coordinated water molecules	Loss of two Schiff base ligand molecules	Metal Oxide



Where M= Mn(II), Fe(III), Co(II), Ni(II) and Cu(II)

Figure 2. Metal complexes of ligand-L



Where M= Mn(II), Fe(III), Co(II), Ni(II) and Cu(II)

Figure 3. Metal complexes of ligand-L_1

Evaluation of Elements and Conductivity

Tables 2 and 3 detail the complexes' physical characteristics and elemental analyses, respectively. The complexes' suggested empirical formula was well-supported by the analytical results. All of the complexes are non-electrolyte according to their conductance values. All of the complexes do not include any anions outside of the coordination sphere, according to the calculated values.

Table 2. The complexes and ligand (Schiff base) elemental analysis

Ligand and Complexes	% Carbon		% Hydrogen		% Nitrogen	
	Calculated	Found	Calculated	Found	Calculated	Found
SB(C12H10N2O) Orangered crystal	72.72	72.58	5.03	4.95	14.13	14.01
[Ni(C12H10N2O)2]	63.32	62.41	4.38	4.12	12.30	11.74
[Cu(C12H10N2O)2]	62.66	61.51	4.34	4.03	12.17	11.85
[Co(C12H10N2O)2]	63.31	62.47	4.38	3.81	12.30	11.51
[Mn(C12H10N2O)2]	56.66	56.05	3.92	3.11	11.01	10.51

Where, SB = Schiff base.

Table 3. Complex and ligand physical characteristics

Complexes	Colour	Melting point or decomposition tem. (± 5°C)	% Yield	Molar conductance (ohm^{-2} cm^2 mol^{-1})
[Ni(C12H10N2O)2]	Green	280(above)	62	15.3
[Cu(C12H10 N2O)2]	Black	149	59	15.5
[Co(C12H10 N2O)2]	Brown	80	61	17.1
[Mn(C12H10 N2O)2]	yellow	184	65	14.2
SB (C12H10N2O)	Orange red crystal	65		

Where, SB = Schiff base.

CONCLUSION

We can say that the A heterocyclic amine with a thiazole core is 2-aminothiazole. Another name for it is a cyclic isothiourea. It dissolves in water, alcohols, and diethyl ether, and it has a pyridine-like aroma. Based on spectroscopic data, it seems that all Schiff base metal complexes are of the $ML_2.(H_2O)_2$ type, where M=Mn, Fe, Co, Ni, and Cu. When tested against harmful bacteria (Escherichia coli, Bacillus subtilis, Staphylococcus aureus, Acinetobacter niger, and Staphylococcus cerevisiae), the produced metal complexes showed more antibacterial activity than the uncomplexed Schiff base ligand. Coordination with metal ions increased the activity of Schiff base complexes. In terms of biological activity, the complexes are arranged as follows: Cu(II), Fe(III), Mn(II), Ni(II), and Co(II). The tetrahedral structure of all the complexes was verified by the electronic spectrum data.

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