# Design and Biological Assessment of a Novel Thiadiazol-Imidazole Based bimetallic complex with Antimicrobial and Anti-Inflammatory Potential

Pooja Shinde [1], Willy Shah [2], Sunil Gadakh [3], Shraddha Parab [4], Suhas Janwadkar [5], Dilip Yadav [6], Bhavesh Shinde [7]

[1,3,4,5,6,7] *Department of Chemistry, S. D. Arts, V. S. A. Commerce & M. H. M. Science college, Palghar-401404, Maharashtra, India.*

[2] *Anna Saheb Vartak College of Arts, Kedarnath Malhotra College of commerce, E. S. Andrades, College of science, Vasai Road, Vasai-Mumbai-401202, Maharashtra, India.*

***Abstract*—A bimetallic complex was synthesized using a novel reagent, compound-A, derived from azole compound methyl imidazole and [N{3-(5-amino-2-thione-1,3,4-thiadiazole)}]. The synthetic pathway involved a condensation reaction between [N{3-(5-amino-2-thione-1,3,4-thiadiazole)}-methyl imidazole] and a substituted triazine carboxamide derivative, resulting in the formation of compound-A. This novel reagent was then used to form a bimetallic complex through coordination with copper metal under appropriate stoichiometric conditions. The structures of both Compound-A and its bimetallic complex were characterized using UV, IR, EDS, SEM, and NMR techniques. Preliminary biological evaluations revealed that the compound exhibits significant antimicrobial (both antibacterial and antifungal) as well as anti-inflammatory activities.**

***Index Terms*—Bimetallic complex, Thiadiazole derivative, Methyl imidazole, Coordination chemistry, antimicrobial activity, Anti-inflammatory agent**

## I. INTRODUCTION

Coo Coordination compound, also known as complex compound, are chemical complex where a central metal ion or atom is bound to group of molecule or ions called ligands [1]. Bimetallic complex is coordinated molecule that contain two metal coordinates to a Di nucleating ligand. There is new trend in the recent past to use bimetallic complex due to promising bioactivity. In a bimetallic complex, the presence of second metal centre may show an increase in antimicrobial properties of the complex as compared to monometallic complex. Two metal centres will contribute according to their chemical properties.[2] The bimetallic complex can be either be homometallic having two similar metal centre or heterobimetallic having two different metal centre. Bimetallic complexes are playing most important role in recent Canario because of their desirable functional properties. Two metal centres can facilitate cooperative multi-electron process with transition metal ions.[3][4] The metal centres of the bimetallic complex tend to cooperate by changing the reactivity and or physical properties of the complexes therein Each metal may contribute individually or collectively to the overall properties of the complexes.[5] Metal complex with Amino-1,3,4-thiadiazole derivative are well known as compound of a wide range of anticancer activity and antibacterial, anti-inflammatory property that have been prepared from their azole and addition of two metal centre in this surely giving increasing in activities like antibacterial, anti-inflammatory and anticancer. [6][7]1.3,4-Thiadiazole are also important classes of azole with important biological properties as there are many example in the literature including antifungal[8,9] and anti-inflammatory drugs[10,11],antimicrobials [12,13] antiviral [14,15] and Anti-cancer drugs.[16] Anti-depressant drugs.[17] Imidazole's play an important role in medicinal chemistry, because many of its derivatives have demonstrated significant biological activity.[18,19] Pyridine derivatives are a family of heterocyclic nitrogenous compounds possessing many of applications in the discovery of anticancer drug. This synthetic category serves as the potent class of compounds in the treatment of many types of tumours

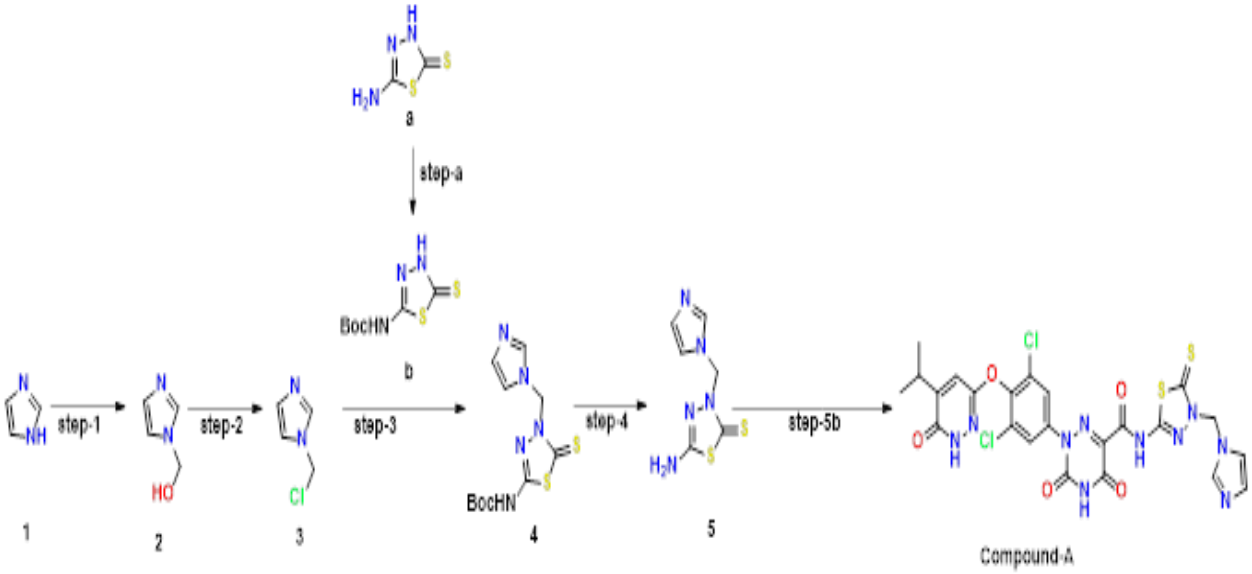
as breast cancer, myeloid leukaemia, pancreatic cancer, liver cancer. [27] The applications of Pyridine and its derivatives compel chemists, pharmacists and material scientists to introduce compounds containing this heterocycle with viable applications.[28] Complexes of copper in oxidation state +2 were found to show significant antioxidant and anti-free radical activity. [20,29] Bimetallic copper complexes are potential models for several important biological systems containing a couple of sites [22] and have been studied extensively. [23–26]. Copper complexes of imidazo [l,2-a] pyridine derivatives and/or analogues thereof for use in the treatment of cancer, particularly breast cancer, colorectal cancer, and leukemia.[30] The Copper Complexes that use thiazole and benzothiazole as ligand and that report efficient antimicrobial activity against different bacteria and fungi.[31]

Denaturation of proteins is one of the phenomenon's that result in the disturbance of stability and structure of the protein. The chemistry of proteins has always been important owing to the abundance of these biomolecules in the living system. With all this in mind, the present study was undertaken to design and synthesize a novel fused heterocyclic compound, referred to as compound-A, utilizing a newly developed reagent under optimized conditions. The molecular architecture of compound-A incorporates multiple pharmacologically relevant moieties, including imidazole, thiadiazole, pyridazine, and triazine rings, which are known to contribute to a wide range of biological activities. In addition to the free ligand, its corresponding copper(II) complex (compound-A–Cu(II)) was also synthesized to explore potential metal coordination effects on biological activity. Both compound-A and its metal complex were thoroughly characterized using standard analytical and spectroscopic techniques. Furthermore, a comprehensive evaluation of their biological properties was conducted to assess their potential as therapeutic agents.

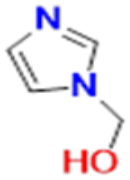
## II. EXPREMENTAL

All reagent and solvents were used as purchase from commercial suppliers without purification, N{3-(5-amino-2-thione-1,3,4-thidiazole), Imidazole, Copper chloride, purchased from sigma Aldrich. Infrared spectra studies recorded with non-destructive method on diamond surface on PerkinElmer UATR two in the range of 4000–450 cm−1 FTIR Spectrophotometer. Metal contains and presence studied by SEM-EDS Analyser also ligand and complexes studied, 1H NMR, UV spectra. NMR spectra were recorded by also bruker and UV recorded by shimadazu 1800.

Synthesis Scheme:



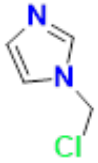

Step-1: Synthesis of (1H-imidazol-1-yl) methanol (2).



2

The mixture of Imidazole, paraformaldehyde and triethylamine were heated with stirring in an oil bath at 80 °C till the solid completely melted to give a viscous residue. Progress of reaction was monitored on TLC (TLC phase:100% EtOAc or 10% MeOH in DCM, KMnO4 or Ninhydrin as a stain). After complete consumption SM (Imidazole on TLC), Cool the reaction mass to RT and then at 0 °C, white solid obtained was the (1H-imidazol-1-yl) methanol (2) matches with CAS number: 51505-76-1 used for next with TLC confirmation.

Step-2: Synthesis of of 1-(chloromethyl)-1H-imidazole (3).



3

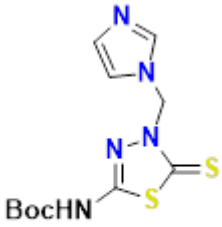
The Solid of int-2 was cooled to 0 °C under nitrogen atmosphere. To this solid SOCl2 was added drop-wise and carefully (Exothermic reaction observed) under stirring and maintaining the temp at 0 °C. After complete addition of SOCl2, Reaction mass was then stirred at 0 °C for 15 minutes. Reaction mass was then heated 100 °C for 3-4h under nitrogen. Progress of reaction was monitored on TLC. After complete consumption of SM on TLC (TLC phase:100% EtOAc or 10% MeOH in DCM, KMnO4 or Ninhydrin as a stain), SOCl2 from reaction mass evaporated under vacuum, Toluene was added to the reaction mass and again distil it to full dryness, Repeat the same procedure for toluene one more time. Dry the obtained brown gum for another 30 Minutes that gives 1-(chloromethyl)-1H-imidazole (3) used as it is for next step without further purification and analysis.

Step-a: Synthesis of tert-butyl (5-thioxo-4,5-dihydro-1,3,4-thiadiazol-2-yl) carbamate (b):

b

To a solution of 5-amino-1,3,4-thiadiazole-2(3H)-thione (4) (9.5 g, 71.4 mmol, 1.0 eq) in a tBuOH:$H_2O$ mixture (90 mL:90 mL), NaOH (1.63 g, 71.4 mmol, 1.0 eq) was added at 0 °C, followed by the dropwise addition of $Boc_2O$ (27.1 g, 71.4 mmol, 1.0 eq) at the same temperature. The reaction mixture was then stirred at room temperature for 16–20 hours. The reaction mass was acidified with a citric acid solution to adjust the pH to 4–5, resulting in the formation of a white precipitate. The precipitate was filtered, washed with water, and dried thoroughly under vacuum or at 50–60 °C to remove residual moisture, yielding tert-butyl (5-thioxo-4,5-dihydro-1,3,4-thiadiazol-2-yl) carbamate (4) (15.0 g, 90% yield).

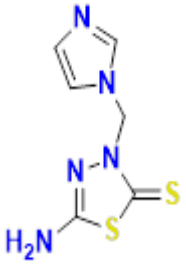
Step-3: Synthesis of tert-butyl(4-((1H-imidazol-1-yl)methyl)-5-thioxo-4,5-dihydro-1,3,4- thiadiazol-2-yl) carbamate (4)



4

To the solution of Intermediate-b in DMF was added TEA followed by the addition of Int3 (Solution in DMF) at rt. Reaction mass was then heated to 80 °C for 16h. Progress of reaction was monitored on TLC (TLC phase:100% EtOAc, UV). After complete consumption of int-b on TLC cold water was added to reaction mass and compound was extracted on 10% MeOH: DCM 2-3 times. Combined organic layer was wash with cold water and finally with saturated NaCl solution, Separated organic layer was evaporated under vacuum to get the crude Obtained crude was then purified by column chromatography (0-4% MeOH in DMF, 60-120 mesh silica gel), Obtained eluent was evaporated under vacuum to gives yellow colored solid as tert-butyl (4-((1H-imidazol-1-yl) methyl)- 5-thioxo-4,5-dihydro-1,3,4-thiadiazol-2-yl)carbamate.

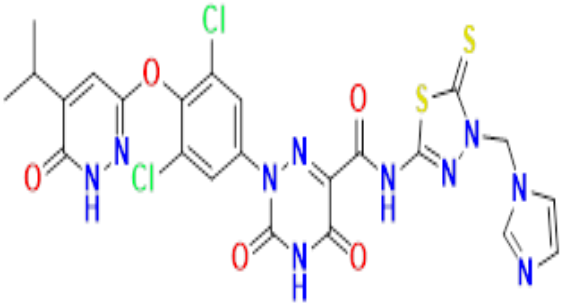
Step-4: 3-((1H-imidazol-1-yl)methyl)-5-amino-1,3,4-thiadiazole-2(3H)-thione (5):



5

To a solution of Synthesis of tert-butyl(4-((1H-imidazol-1-yl)methyl)-5-thioxo-4,5-dihydro-1,3,4-thiadiazol-2-yl) carbamate (4) (5.0 g) in dry DCM, 4M dioxane HCl was added dropwise at 0 °C under a nitrogen atmosphere. The reaction mixture was stirred at room temperature for 2 hours. After completion, the solvent was evaporated under vacuum to obtain the crude product. The crude was then triturated in diethyl ether, yielding an off-white solid identified as 3-((1H-imidazol-1-yl)methyl)-5-amino-1,3,4-thiadiazole-2(3H)-thione (5) (3.5 g, 97% yield).

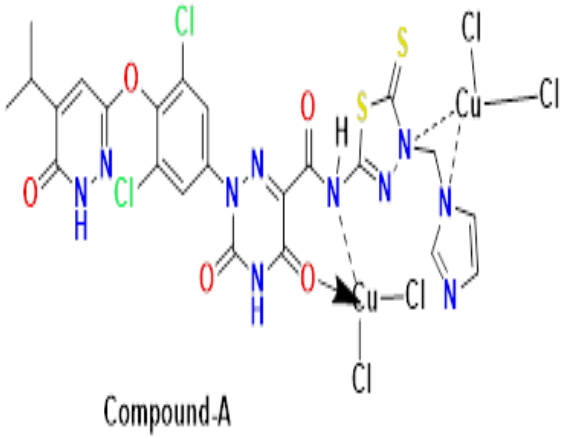
Step-5a:(Z)-N-(4-((1H-imidazol-1-yl)methyl)-5-thioxo-4,5-dihydro-1,3,4-thiadiazol-2-yl)-1-cyclopropyl-8-methyl-7-(5-methyl-6-(methylimino)-1,6-dihydropyridin-3-yl)-4-oxo-1,4-dihydroquinoline-3-carboxamide (Compound-A):



Compound-A

To a solution of 1-cyclopropyl-8-methyl-7-[5-methyl-6-(methylamino)pyridin-3-yl]-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (4.45 g, 23.4 mmol, 1.00 eq) in dry dimethylformamide (45 mL), hexafluorophosphate azabenzotriazole tetramethyl uronium (HATU) (13.3 g, 35.1 mmol, 1.5 eq) was added at 0 °C under a nitrogen atmosphere. The reaction mixture was stirred at 0 °C for 15 minutes, 3-((1H-imidazole-1-yl)methyl)-5-amino-1,3,4-thiadiazole-2(3H)-thione (7.25 g, 23.4 mmol, 1.00 eq) and N, N-Diisopropylethylamine (9.08 g, 70.38 mmol, 3.00 eq) were added to the reaction mixture, and it was stirred at 0 °C for 2 hours. Upon completion, cold water was added to the reaction mixture. The resulting solid was filtered, washed with water, and then with n-pentane. The solid was dried under vacuum to yield (Z)-N-(4-((1H-imidazol-1-yl)methyl)-5-thioxo-4,5-dihydro-1,3,4-thiadiazol-2-yl)-1-cyclopropyl-8-methyl-7-(5-methyl-6-(methylimino)-1,6-dihydropyridin-3-yl)-4-oxo-1,4-dihydroquinoline-3-carboxamide.

Step-6: Synthesis of Homobimetallic Cu(II) Complex:



Compound-A

The ethanolic solution of (Z)-N-(4-((1H-imidazol-1-yl)methyl)-5-thioxo-4,5-dihydro-1,3,4-thiadiazol-2-yl)-1-cyclopropyl-8-methyl-7-(5-methyl-6-(methylimino)-1,6-dihydropyridin-3-yl)-4-oxo-1,4-dihydroquinoline-3-carboxamide was added to an ethanolic solution of Copper Chloride in appropriate stoichiometry with stirring. This mixture was refluxed for 3 hours. The product was filtered off, washed with hot ethanol, followed by water, and dried under vacuum.

Mixing of reagent and metal solution to form a colourful precipitate was observed. This precipitate was dried and recrystallized to remove impurities

Biological activities:

Procedure:

In vitro anti-inflammatory activity by Protein denaturation method:

The reaction mixture (1 mL) consisted of 0.1 mL of egg albumin (from fresh hen's egg), 0.5 mL of Phosphate buffered saline (PBS, pH 6.4) and 0.4 mL of Sample A and Sample B at the concentration 1mg/ml. similar volume of double-distilled water served as control. Then the mixtures were incubated at (37 degree Celsius ±2) in an incubator for 15 min and then heated at 70 degree Celsius for 5 min. After cooling, their absorbance was measured at 660 nm by using vehicle as blank. Diclofenac sodium at concentration 1 mg/ml) was used as reference drug and treated similarly for determination of absorbance. The percentage inhibition of protein denaturation was calculated by using the following formula, % inhibition = absorbance of control - absorbance of test / absorbance of control x 100. Anti-inflammatory activity of different formulation by Protein denaturation.

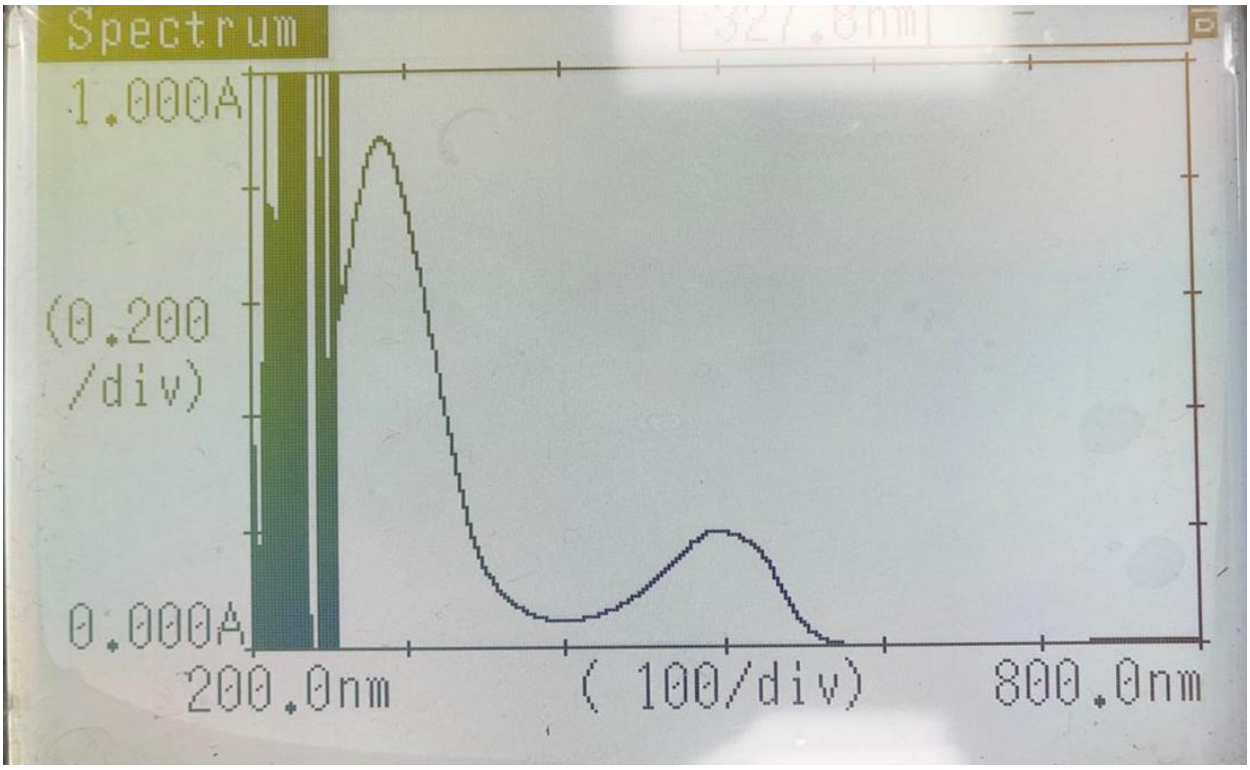
Procedure:
Antibacterial activity against E. coli, Bacillus subtilis, S Aurus, Salmonila Typibacteria by well diffusion method:
The inoculums of the micro-organism were prepared from the bacterial cultures. 15 ml of nutrient agar (Hi media) medium was poured in clean sterilized Petri plates and allowed to cool and solidify. 100 µl of broth of bacterial strain was pipette out and spread over the medium evenly with a spreading rod till it dried properly. Once the agar was hardened, then Sample Slides was placed on the plate in the manner and the plates were incubated at 370C for 24 h. Antibacterial activity was evaluated by measuring the diameters of the zone of inhibitions (ZI).

Procedure:
Antifungal activity against Candida albicans A.Nigar(Agar well plate diffusion Method) well diffusion method:
For the determination of zone of inhibition Antifungal activity Stock solution for antifungal activity: For antifungal study sample concentration of 5mg and10 mg stored in a refrigerator till further used. Antifungal activities of the sample were evaluated by means of agar well diffusion assay.The assay was carried out according to the method of (Hufford et al., 1975). Sabourauddextrose agar (Hi media) was used for the growth of fungus. Media with acidic pH (pH 5.5to 5.6) containing relatively high concentration of glucose (40%) is prepared by mixing (SDA) Sabouraud dextrose and distilled water and autoclaved at 121oC for 15 minutes.Twenty five ml of molten (450C) SDA medium was aseptically transferred into each100mm×15mm sterile Petri dish. For counting of spore (fungi) were suspended in normal saline to make volume up to1ml and then counted with help of heamocytometer (neubar chamber). Once the agar was hardened,6mm wells were bored using a sterile cork borer. Then 0.1ml (100µl) from each stock solution of the sample having final concentration of 5 mg and 10mg was placed in each the well and the plates were incubated for 72 hour at 29oC. The antifungal activity was measured as the diameter (mm) of clear zone of growth inhibition. (Umadevi et al., 2003).

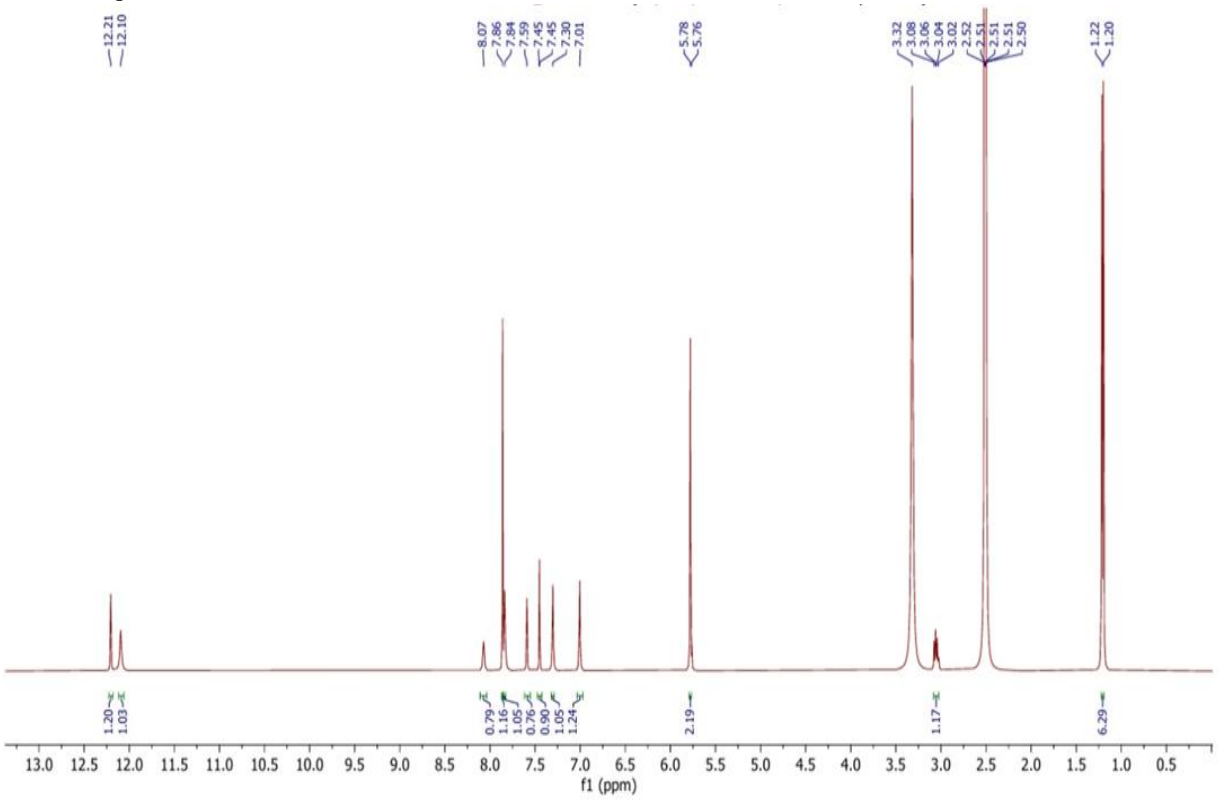
## III. RESULT AND DISSUASION

Ultraviolet visible spectroscopy [UV], Infrared radiation [IR] and protonated nuclear magnetic resonance[1H NMR] spectral data, biological activities like Anti- Microbial (fungal/bacterial), Anti–Inflammatory of (Z)-N-(4-((1H-imidazol-1-yl)methyl)-5-thioxo-4,5-dihydro-1,3,4-thiadiazol-2-yl)-1-cyclopropyl-8-methyl-7-(5-methyl-6-(methylimino)-1,6-dihydropyridin-3-yl)-4-oxo-1,4-dihydroquinoline-3-carboxamide.and(Z)-N-(4-((1H-imidazol-1-yl)methyl)-5-thioxo-4,5-dihydro-1,3,4-thiadiazol-2-yl)-1-cyclopropyl-8-methyl-7-(5-methyl-6-(methylimino)-1,6-dihydropyridin-3-yl)-4-oxo-1,4-dihydroquinoline-3-carboxamide-Cu (II) Bimetallic complex.

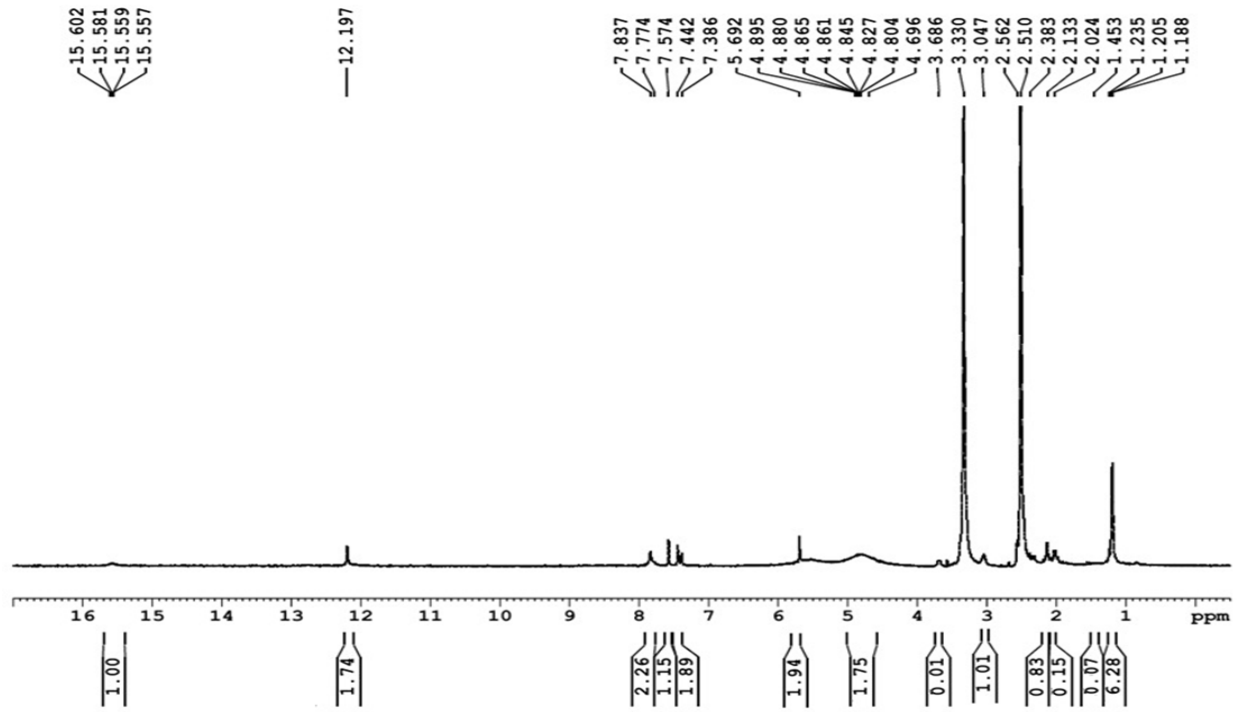
UV Spectra: The UV -Visible data can be used as supporting evidence for structural Elucidation [32]. The UV and visible spectra of several Reagent and based metal complex have been studied and show the graph in this paper. The electronic absorption spectrum of Reagent synthesised in DMSO solvent in the UV visible region show the peaks at various intensity band 240nm to 330nm, i.e π-π and n-π * was observed in this graph.




H1 NMR Spectra:

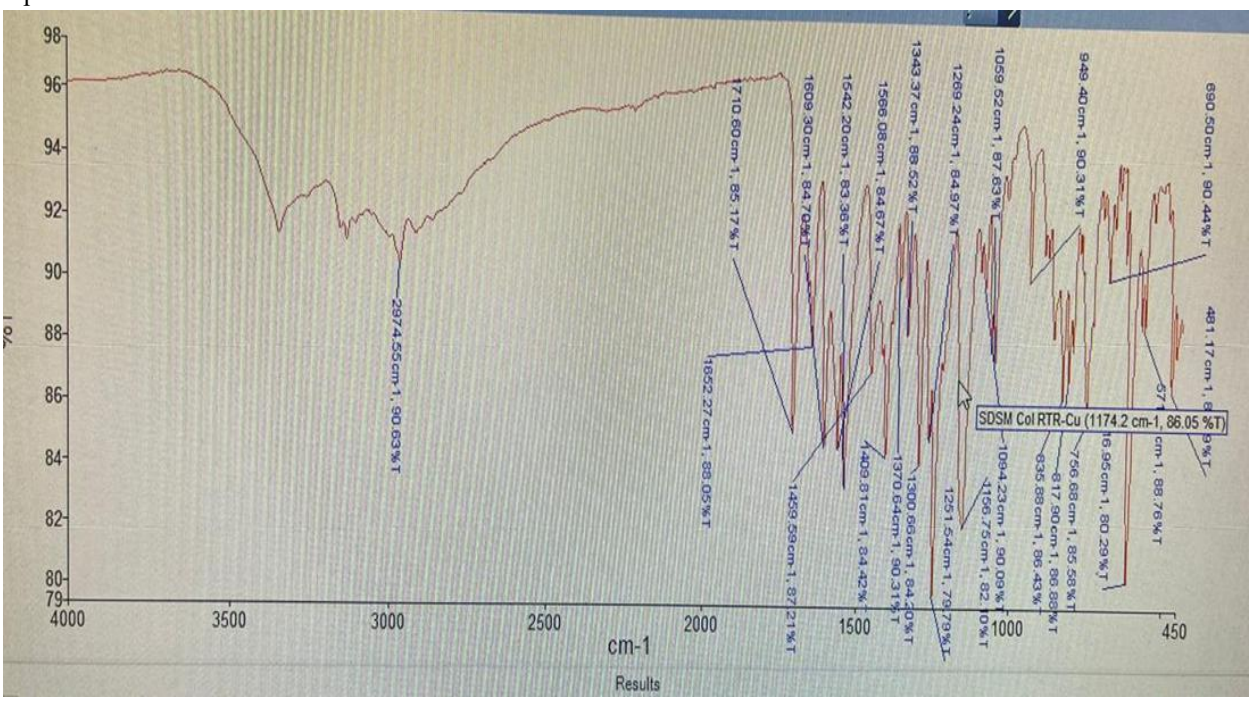



1H NMR (400 MHz, DMSO-$d_6$): 12.21 (s, 1H), 12.10 (s, 1H), 8.07 (s, 1H), 7.84 (m, 2H), 7.59 (s, 1H), 7.45 (m, 1H), 7.30 (s, 1H), 7.01 (s, 1H), 5.76 (s, 2H), 3.06 (m, 1H), 1.21 (d, J=8Hz, 6H)

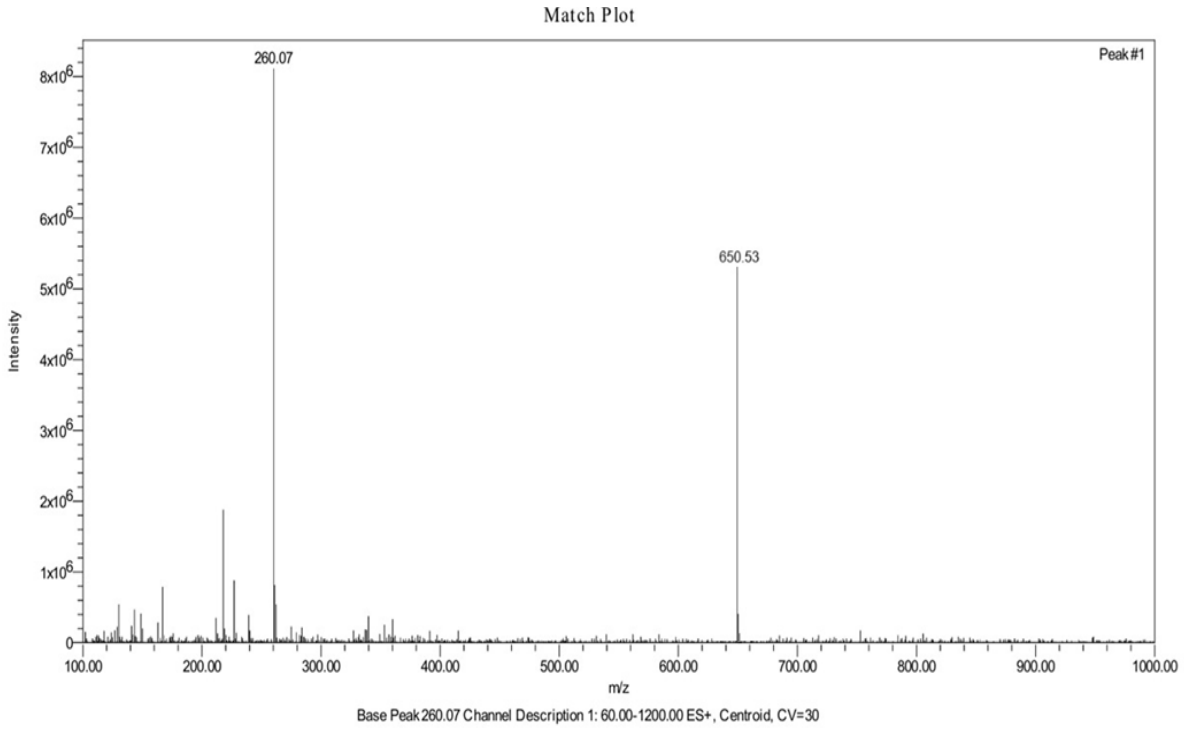



IR Spectra: (Z)-N-(4-((1H-imidazol-1-yl) methyl)-5-thioxo-4,5-dihydro-1,3,4-thiadiazol-2-yl)-1-cyclopropyl-8-methyl-7-(5-methyl-6-(methylimino)-1,6-dihydropyridin-3-yl)-4-oxo-1,4-dihydroquinoline-3-carboxamide-(Cu)2(II)-Cl4.

A spectral band at 1269.24 cm-1 which is attributed to C-O bond, bond at 1710 cm-1 represent of C=O bond, band at 1609.30 cm-1 which is attributed to HC=N bond, bond at 571 cm-1 represent of M-N bond , bond at 481.17 cm-1 represent of M-Cl bond.



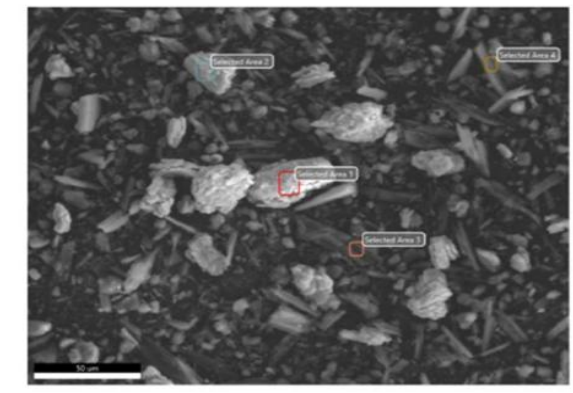

Mass Spectra:

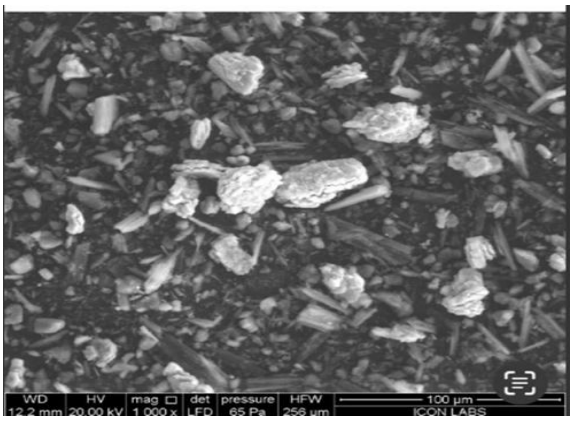


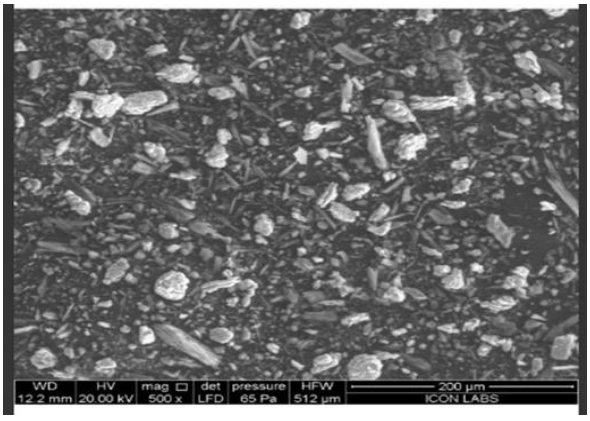

Mass (ESI): m/z calculated for $C_{23}H_{18}Cl_2N_{10}O_5S_2$: 650.49 $[M+1]^+$, found: 649.49

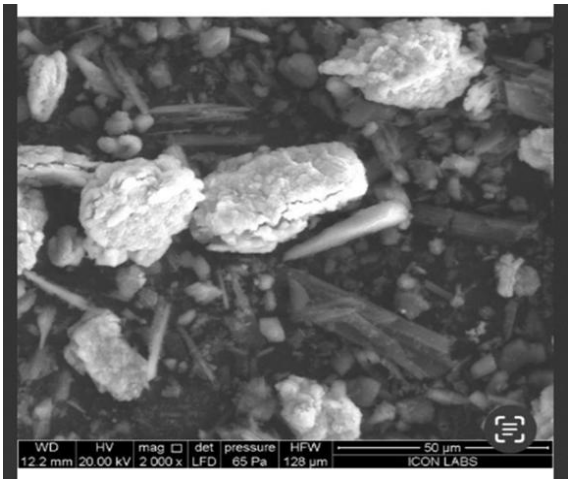
EDS-SEM:

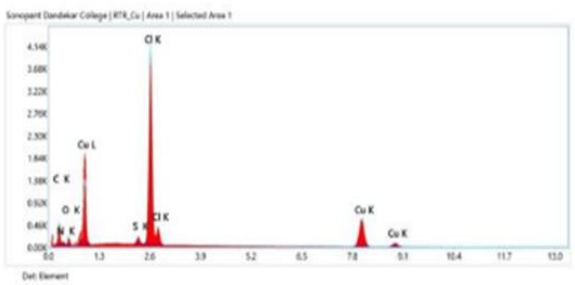
RTR_Cu





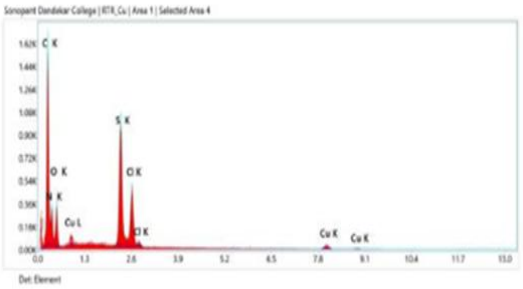






eZAF Quant Result

| Element | Weight % | Atomic % | Net Int. |
|---|---|---|---|
| C K | 50.0 | 71.3 | 116.2 |
| N K | 6.8 | 8.3 | 23.2 |
| O K | 5.8 | 6.2 | 51.0 |
| S K | 0.6 | 0.3 | 56.2 |
| Cl K | 18.6 | 9.0 | 1499.0 |
| Cu K | 18.2 | 4.9 | 319.8 |



eZAF Quant Result

| Element | Weight % | Atomic % | Net Int. |
|---|---|---|---|
| C K | 61.2 | 68.1 | 406.5 |
| N K | 20.8 | 19.8 | 81.1 |
| O K | 11.6 | 9.7 | 93.4 |
| S K | 3.5 | 1.5 | 362.9 |
| Cl K | 2.0 | 0.8 | 179.0 |
| Cu K | 0.8 | 0.2 | 17.4 |

Physical parameters of the Metal complexes:

| Parameter | | Reagent | Complex |
|---|---|---|---|
| Molecular Formula | | $C_{23}H_{18}Cl_2N_{10}O_5S_2$ | $C_{23}H_{18}Cl_2N_{10}O_5S_2$-Cu(II).$Cl_4$ |
| Molecular Weight | | 649.49 | 918.39 |
| Colour | | Red | Reddish Brown |
| Element % | H | 42.53 | 30.05 |
| | C | 2.79 | 2.08 |
| | N | 21.57 | 15.24 |
| | O | 12.32 | 8.70 |
| | S | 9.87 | 6.97 |
| | Cl | 10.92 | 23.14 |
| | Cu | --- | 13.82 |

Powder XRD:

The powder XRD pattern of the Cu (II) bimetallic complex recorded in the range (2θ = 0-80o) was shown in Fig. XRD pattern of the bimetallic complex shows the sharp crystalline peaks indicating its crystalline phase. The average crystallite size (dXRD) of the complex was calculated using Scherer's formula. The bimetallic complex has an average crystallite size of 70 nm.

Biological Study:

Antibacterial Activity of the Given Sample Against Escherichia coli and Staphylococcus aureus Using the Well Diffusion Method

| Sr. No | Sample | Concentration (mg/ml) | Zone diameter (mm) E. coli | Zone diameter (mm) Stap. Aureus |
|---|---|---|---|---|
| 1 | Control | - | - | |
| 2 | Standard (streptomycin) | 1 mg | 30 | 28 |
| 3 | Reagent | 5 mg | 11 | 04 |
| 4 | Bimetallic complex | 10 mg | 13 | 06 |

Antifungal activity against Candida albicans via Agar well plate diffusion Method:

| Sr. No. | Sample | Concentration. (mg/ml) | Zone diameter (mm) against Candida albicans |
|---|---|---|---|
| 1 | Control | - | 18 |

| | | | |
|---|---|---|---|
| 2 | Reagent | 5 | 04 |
| 3 | Reagent | 10 | 12 |
| 4 | Bimetallic complex | 5 | 06 |
| 5 | Bimetallic complex | 10 | 13 |

In Vitro Anti-Inflammatory Activity by Protein Denaturation Method:

| Sr. No. | Compounds | Conc. | O.D. | Mean | % inhibition |
|---|---|---|---|---|---|
| 1 | Blank | - | 1.50<br>1.45<br>1.48 | 1.47 | - |
| 2 | Standard (Diclofenac sodium) | 1mg/ml | 0.13<br>0.14<br>0.15 | 0.14 | 90.47 |
| 3 | Reagent | 1mg/ml | 0.26<br>0.26<br>0.29 | 0.24 | 80.62 |
| 4 | Bimetallic complex | 1mg/ml | 0.29<br>0.27<br>0.24 | 0.26 | 82.31 |

## IV. CONCLUSION

In conclusion, the novel Cu(II) metal complex of Compound-A was successfully synthesized and subsequently converted into the desired target molecules. The structure of Compound-A was confirmed using various spectral techniques, and its biological activities were thoroughly evaluated.

Anti-inflammatory activity:

Compound-A and its bimetallic complex exhibited significant in vitro anti-inflammatory activity using the protein denaturation inhibition assay at a concentration of 1 mg/mL. The results demonstrated that both the reagent and the bimetallic complex of Compound-A showed superior anti-inflammatory effects compared to the standard drug diclofenac sodium.

Antibacterial activity:

Compound-A and its bimetallic complex were tested against bacterial strains including E. coli, Bacillus subtilis, Staphylococcus aureus, and Salmonella typhi at a concentration of 10 mg/mL. The results revealed good antibacterial activity, with efficacy comparable to or exceeding that of the standard antibiotic.

Antifungal activity:

Similarly, Compound-A and its bimetallic complex showed promising antifungal activity, indicating broad-spectrum antimicrobial potential.

Overall, the findings suggest that Compound-A, particularly in its bimetallic Cu(II) complex form, holds considerable promise as a multi-functional therapeutic agent with anti-inflammatory, antibacterial, and antifungal properties.

## V. ACKNOWLEDGEMENT

The authors gratefully acknowledge SimSon Life Sciences Pvt. Ltd. and Biocyte Research & Development Pvt. Ltd. for providing the necessary facilities to carry out the spectral and biological activity studies. We also extend our sincere thanks to the Department of Chemistry, Sonopant Dandekar College, Palghar, Maharashtra – 401404, for their continuous encouragement, support, and assistance throughout the course of this research work.

## REFERENCES

[1] Inoragnic -Chemistry -by- James-e_House,ISBN 978-0-12-356786-4.
[2] Bimetallic complexes; A mini review of their synthesis, and potential antitumor activities, Hillary Kipruto Tanui.
[3] D.G. McCollum, G. P. A. Yap, L. Liable Sands ans A.L. Rheingold, Inorg.Chem.,1997,36,2230-2235.

[4] C. Incarvito, A. L. Rheingold, A.L Gavilova, C.J. Qin and B Bosnich, Inorg. Chem, 2001, 40, 4101-4108.

[5] Iqbal H, Ali S, Shahzadi S, et al. Synthesis and Characterization of hetero-bimetallic complexes with 2-mercapto-5-methyl-benzilidazole; theoretical study abd biological activities J Coord Chem 2015;68:2434-2448.

[6] Mathew, V., et al., Studies on synthesis and pharmacological activities of 3, 6-disubstituted-1, 2, 4-triazolo [3, 4-b]-1, 3, 4-thiadiazoles and their dihydro analogues. European journal of medicinal chemistry, 2007. 42(6): p. 823-840.

[7] Mehnaz Kamal, Ashok k. Shyakya 1, 3, 4-Thiadiazole as antimicrobial agent: a review October 2011 International Journal of Biomedical Research 2(1):41-61

[8] Li, Q., et al. Synthesis and antifungal activity of thiadiazol -functionalized chitosan derivatives. Carbohydrate research, 2013. 373: p.103-107.

[9] Zou.Y., et al., New triazole derivative as antifungal agents: synthesis via click reaction, in vitro evaluation and molecular docking studies. Bioorganic & medicinal chemistry letters, 2012 22 (8): p.2959-2962.

[10] Rajak, H., M.D. Kharya, and P. Mishra, Synthesis of some novel oxadiazole and oxadiazoline analogues for their anti-inflammatory activity. Yakugaku Zasshi, 2007. 127(10): p. 1757-1764.

[11] Karabasanagouda, T., A.V. Adhikari, and N.S. Shetty, Synthesis and antimicrobial activities of some novel 1, 2, 4-triazolo [3, 4-b]-1, 3, 4-thiadiazoles and 1, 2, 4-triazolo [3, 4-b]-1, 3, 4-thiadiazines carrying thioalkyl and sulphonyl phenoxy moieties. European journal of medicinal chemistry, 2007. 42(4): p. 521-529.

[12] Sadek, B. and K.M.S. Fahelelbom, Synthesis, characterization, and antimicrobial evaluation of oxadiazole congeners. Molecules, 2011. 16(6): p. 4339-4347.

[13] Dong, W.-L., et al., Synthesis and antiviral activity of new acrylamide derivatives containing 1, 2, 3-thiadiazole as inhibitors of hepatitis B virus replication. European journal of medicinal chemitry, 2010. 45(5): p. 1919-1926.

[14] Mohammad Yusuf, Riaz A. Khan, Bahar Ahmed. Synthesis and anti-depressant activity of 5-amino-1,3,4-thiadiazole-2-thione imines and thiobenzyl derivatives. Bioorganic & Medicinal Chemistry Volume 16, Issue 17,1 September 2008, Pages 8029-8034.

[15] Sondavid K. Nandanwar, Prof. Hak Jun Kim Anticancer and Antibacterial Activity of Transition Metal Complexes 04 February 2019.

[16] Mohammad Yusuf, Riaz A. Khan, Bahar Ahmed. Synthesis and anti-depressant activity of 5-amino-1,3,4-thiadiazole-2-thione imines and thiobenzyl derivatives. Bioorganic & Medicinal Chemistry Volume 16, Issue 17,1 September 2008, Pages 8029-8034.

[17] Delia Hernández Romero, Víctor E. Torres Heredia, Oscar García-Barradas, Ma.Elizabeth Márquez López & Esmeralda Sánchez Pavón. Synthesis of Imidazole Derivatives and Their Biological Activities. Journal of Chemistry and Biochemistry December 2014, Vol. 2, No. 2, pp. 45-83.

[18] Amita Verma, Sunil Joshi, and Deepika Singh Hindawi, Imidazole: Having Versatile Biological Activities. Publishing Corporation Journal of Chemistry Volume 2013, Article ID 329412.

[19] R. M.S.Pereira, N. E. D. Andrades, N. Paulino, et al., "Synthesis and characterization of a metal complex containing naringin and Cu, and its antioxidant, antimicrobial, anti in□ammatory and tumor cell cytotoxicity," Molecules, vol. 12, no. 7, pp. 1352–1366, 2007.

[20] Adam Lewis, Molly Mc,ZDonald, Stphanie Scarbach, Stefan Hanaway, Melissa plooster, kyle Peters, Kristin M.Fax , Lynne Cassimeris, Joseph M. Tanski, Laurie A. Tyler, the chemical biology of Cu (II) complexes with imidazole or thiazole containing ligands: Synthesis, crystal structure and comparative biological activity. Journal of Inorganic Biochemistry, Volume 157, April 2016, Pages 52-61.

[21] M. Mohan, N. K. Gupta, and M. Kumar, "Synthesis, magnetic and electrochemical properties of binuclear copper (II) complexes of pyridoxal hydrazones," Inorganica Chimica Acta, vol.197, no. 1, pp. 39–40, 1992.

[22] S. K. Mandal and K. Nag, "Dinuclear metal complexes. Part 3. Preparation and properties of hydroxo-bridged dicopper(II) complexes," Journal of the Chemical Society, Dalton Transactions, no. 10, pp. 2141–2149, 1984.

[23] P. K. Coughlin and S. J. Lipard, "A monohydroxobridged, strongly in antiferromagnetically coupled dicopper(II) center a binucleating macrocycle. Comparisons with binuclear coppersites in biology," Journal of the American Chemical Society, vol.103, no. 11, pp. 3228–3228, 1981.

[24] R. N. Patel, N. Singh, K. K. Shukla, V. L. N. Gundla, and U.K. Chauhan, "Synthesis, spectra and biomimetic properties of copper (II) copper (II) and copper (II)-zinc (II) binuclear complexes with CuN5 chromophores," Spectrochimica Acta Part A,vol. 61, no. 11-12, pp. 2603–2610, 2005.

[25] R. R. Gagne, R. P. Kreh, and J. A. Dodge, "Unusual structural and reactivity types for copper(I). Synthesis and structural and redox properties of binuclear copper(I) complexes which are probably three coordinates in solution and experience inter molecular metal metalinteractions in the solid state," Journal of the American Chemical Society, vol. 101, no. 23, pp. 6917–6927,1979.

[26] Mohamed Ayman AlYEl-Zahabi, Reda G Yousef, Ibrahim H Eissa, Alaa Elwan PYRIDINE DERIVATIVES AS ANTICANCER AGENTS: FDA-APPROVED DRUGS AND PROMISING REPORTED COMPOUNDS, Al-Azhar Journal of Pharmaceutical Sciences, Volume 68, Issue 2-serial Number 2 September 2023, Pages 64-81.

[27] Prof. Ezzat Khan, Pyridine Derivatives as Biologically Active Precursors; Organics and Selected Coordination Complexes, Chemistry Europe, Volume 6, Issue1, April 8, 2021, Page 3041-3064.

[28] I. B. Afanasev, E. A. Ostrskhovitchm, E. V. M. Chik, C. A. Ibraginova, andL.G. Korkina,"Doestheantitumo rcyclopropy lpyrroloindole antibiotic CC-1065 cross-link DNA in tumor cells?" Biochemical Pharmacology, vol. 61, no. 1, pp. 67–72, 2001.

[29] Inventor Charles Bernard De Koning, Leonie HARMSE, Jean DAM Imidazo[1,2-a] pyridine complexes with anticancer activity. Patent No: WO2017178992A1, 19th Oct 2017.

[30] Raul Colorado-Peralta, Jose luis Olivares-Romera, Sharon Rosete-Luna, Oscar Garcia-Barradas, Viviana Reyes-Marquez, Delia Hernandez-Romero, David Morales-Morales, Copper_ Coordinated Thiazoles and Benzothiazoles: A Perfect Alliance in the serach for Compound with Antibacterial and Antifungal activity. Inorganics 2023, 25th April 2023, 11(5) , 185.

[31] Infrared Spectra of Metallic Complex. I. The Effect of Coordination on the Infrared Spectra of ammine, Rhodanato and Azido Complex Junnosuko Fujita, Kazuo Nakamoto and Masahisa Kobayashi J.Am. Chem. Soc. 1956, 78, 14, 3295-3297 Publication Date: July, 1956.