DESIGN AND CONSTRUCTION OF NEW METAL-ORGANIC FRAMEWORK FOR ANTIBACTERIAL STUDIES

M.Sc. Thesis

By

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DEPARTMENT OF CHEMISTRY INDIAN INSTITUTE OF TECHNOLOGY, INDORE

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DESIGN AND CONSTRUCTION OF NEW METAL-ORGANIC FRAMEWORK FOR ANTIBACTERIAL STUDIES

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of

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by

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INDIAN INSTITUTE OF TECHNOLOGY INDORE

CANDIDATE'S DECLARATION

I hereby certify that the work which is being presented in the thesis entitled **DESIGN AND CONSTRUCTION OF NEW METAL-ORGANIC FRAMEWORK FOR ANTIBACTERIAL STUDIES** in the partial fulfillment of the requirements for the award of the degree of **MASTER OF SCIENCE** and submitted to the **DEPARTMENT OF CHEMISTRY, Indian Institute of Technology Indore**, is an authentic record of my own work carried out during the time period from August 2021 to May 2022 under the supervision of Dr. Shaikh M. Mobin, Associate professor, Department of Chemistry, IIT Indore.

The matter presented in this thesis has not been submitted by me for the award of any other degree at this or any other institute.

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Dedicated to my beloved family and friends......

Abstract

This report summarizes the synthesis of two linkers 5-(1-oxoisoindolin-2-yl)isophthalic acid (H₂L) and 5-((2-carboxybenzyl)oxy)isophthalic acid (H₃L). A substitution reaction was employed between diethyl-5-((2-cyanobenzyl)amino)isophthalate and 2-cyanobenzyl bromide in dry acetonitrile solvent using the alkaline medium to synthesize lactam based H₂L linker. Moreover, the synthesis H₃L linker was done by the substitution reaction of diethyl 5-((2-cyanobenzyl)oxy)isophthalate with 2-cyanobenzyl bromide. Both linkers H₂L and H₃L have been characterized by mass spectrometry, ¹H, and ¹³C NMR spectroscopy. The H₂L linker was reacted with 4,4'-azopy in the presence of Zn(NO₃)₂.6H₂O under solvothermal conditions which gave rise to a Zn-MOF. This was characterized by SC-XRD, PXRD, SEM, EDS, TGA, and UV spectroscopy. Further, Ag was incorporated into the pores of Zn-MOF to get Ag@Zn-MOF which was characterized by PXRD, SEM, EDS, TGA, and UV spectroscopy. Also, the antibacterial studies were done for Zn-MOF and its composite against *E. coli* bacteria.

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NOMENCLATURE

Å	angstrom
0	degree
g	gram
λ	lambda
μ	micro
mm	millimeter
mmol	millimole
%	percentage
π	pi
S	second
σ	sigma
θ	theta
V	volume

ACRONYMS

4,4'-azopy	4,4'-azopyridine
CH ₃ CN	Acetonitrile
AMR	Anti-microbial resistance
С	Carbon
CO_2	Carbon dioxide
СР	Coordination polymer
CDCl ₃	Deuterated chloroform
DMSO-d ₆	Deuterated dimethyl sulphoxide
EDS	Energy-dispersive X-ray spectroscopy
FE-SEM	Field emission scanning electron microscopy
Н	Hydrogen
MOF	Metal-organic framework
MDR	Multi-drug resistance
Ν	Nitrogen
NMR	Nuclear magnetic resonance
1D	One-dimensional
0	Oxygen
PBS	Phosphate-buffered saline
K_2CO_3	Potassium carbonate
PXRD	Powder X-ray diffraction
Ag	Silver
SC-XRD	Single crystal X-ray diffraction
NaOH	Sodium hydroxide
Na ₂ SO ₄	Sodium sulphate
TGA	Thermogravimetric analysis
3D	Three-dimensional
2D	Two-dimensional
H ₂ O	Water
Zn	Zinc

Chapter 1

Introduction

Bacterial contamination¹ has led to the emergence of epidemics which is of global concern. It is one of the most challenging issues being faced by the world. Millions of people have lost their lives due to the contamination of bacteria in food and the environment. Antibiotics act as powerful tools to fight against bacteria. Due to their excessive usage, bacteria have got antibacterial resistance also called Anti-Microbial Resistance (AMR).¹ Also, Multidrug Resistance (MDR)¹ has been shown by a variety of bacteria. Due to these problems, the development of novel and effective antimicrobial agents is a prime necessity.

For the development of such antibacterial agents, three divisions are done. Organic or inorganic compounds and salts represent 1st Generation agents, simple metals and their oxides represent 2nd Generation agents, while agents with topology come under 3rd Generation antibacterial agents.²

Metal-Organic Frameworks (MOFs)³⁻⁶ are one of the 3rd generation antibacterial agents. They are highly porous and have a large specific surface area⁷ which makes them one of the perfect candidates for applications in catalysis,^{8,9} separation,¹⁰ gas storage,¹¹ sensing,^{12,13} food preservation,¹⁴ biomedical^{15,16} and water treatment.¹⁷

1.1. Metal-organic frameworks (MOFs)

Metal-organic frameworks (MOFs) are highly porous crystalline polymers composed of metal ions or metal clusters and multidentate organic ligands.¹⁸ These components are linked via coordination bonds to form continuous frameworks. The ultrahigh porosity and large surface area make them one of the best candidates for their utilization in food technology, environmental and biological aspects. They show better sieve character and have high thermal stability. Recently, the applicability of MOFs has been reported extensively in biomedical fields^{15,16} like antibacterial activities, drug delivery,^{19,20} bio-imaging,^{21,22,23} and bio-sensing.^{12,13} Moreover, various nanomaterials having antibacterial properties are being incorporated into MOFs in composite form to enhance the desired outcome.

1.2. Synthesis of metal-organic frameworks

- Generally, Reticular Chemistry²⁴ (choosing molecular building blocks for the conceptual design approach) is employed to get the desired structure for a particular application.
- The conventional synthesis of MOFs occurs by a solvothermal method²⁵ where metal salt, linker, co-linker, and solvents are put after optimization in an autoclave at high temperature in the solvothermal oven.
- Other methods like the Solvent evaporation method,²⁶ Diffusion method,²⁷ Microwave method,²⁸ and electrochemical methods²⁹ are also employed.
- Their synthesis is done under relatively mild conditions in contrast to naturally occurring zeolites.
- Due to the incorporation of various organic linkers having different functional groups, MOFs can exhibit wonderful required properties like chirality, hydrophilicity, and hydrophobicity.
- The preference for MOFs over well-known nano-porous materials like carbon nanotubes and zeolites is due to the potential to tune the functionality and structure directly during synthesis.

1.3. Dimensionality in metal-organic frameworks

The dimensionality and structure of MOFs are determined by the coordination behavior of metal salt and the linker. MOFs are 1D, 2D, and 3D based on the flexibility of metal to bond with the linker and co-linker.

1D MOFs are considered to be the most basic coordination array. Generally, zig-zag, linear, and ladder chain CPs are reported in the literature. They have excellent electrical, magnetic, and optical properties.

Self-assembly facilitates the coordination of ligand moieties (three or four) as linkers between the metal ion centers, ensuing in two-dimensional (2D) MOFs.

Commonly, anionic or neutral linkers are used to synthesize **3D MOFs**. Because neutral ligands reduce the porosity of the framework by trapping anions inside the cavity, anionic ligands are primarily used for highly porous MOFs. Anionic multidentate ligands such as carboxylate enable the formation of metal clusters known as secondary building units (SBUs), which are extremely rigid in nature.

1.4. Applications of metal-organic frameworks

The unique combination of crystallinity, large surface area, strong metal to ligand interaction, and variable pore size make MOFs a very special and fascinating class of porous materials. MOFs show a wide range of applications in drug delivery,^{19,20} catalysis,^{8,9} storage of gases,¹¹ sensing,^{12,13} electrochemistry, and so on.

1.4.1 Gas storage and separation

Effective storage of gases requires high pressure tanks and multistage compressors. This implementation is very difficult for practical usage due to high cost. So, MOFs have come across as a safer and cheap solution for gas storage. Due to their high surface area, and variable pore size MOFs are one of the most promising materials for this application in comparison to various other porous materials.

MOF-177 shows a gravimetric uptake of H_2 of 7.5 wt% at 77 K and 70 bar due to its high surface area and large pore volume. Also, MOF-5 (IRMOF-1) has H_2 uptake of 7.1 wt% at 40 bar and 77 K. Various other MOFs like HKUST-1, MIL-101, MOF-210, PCN-12, NU-100, MOF-205, and NOTT-102 are also known for H_2 storage.

 CO_2 level is also being reduced by using MOFs by capturing it and converting into useful cyclic carbonates. A zinc-based MOF, MOF-210³⁰ has CO_2 uptake of 2400 mg g⁻¹ which is 74.2 wt% at 50 bar and 298 K. MOF-200 also shows high CO_2 uptake as that of MOF-210 under experimental conditions.

1.4.2 Magnetism and its applications

When 3d transition metal nodes having paramagnetism are combined with suitable diamagnetic organic linkers, MOFs so formed are found to have magnetism and such MOFs are referred to as magnetic metal organic frameworks (MMOFs). MOFs made out of 3d metals have made important contributions to the development of molecular magnets.³²⁻³⁷ Close-shell ligands with weak magnetic interactions, such as oxo, cyano, azido bridges, and polycarboxylic ligands,³⁸ are ideal candidates for this. Magnetic MOFs could possibly be used in the environmental sector to remove arsenic.

1.4.3 Sensing

Due to presence of aromatic rings of linkers, various MOFs have been found to be photoluminescent. This is due to the luminescence caused by absorbing the UV-visible light. Such MOFs show a wide application in projection television, fluorescent tubes, pH sensors,⁹ high-technology optics and small-molecule sensors.^{39,40} Bimodal (or multicoloured) light emitters can be made from LnMOFs doped with several Ln³⁺ ions.

1.4.4 Catalysis

MOFs serve as excellent candidate for heterogenous catalysis. MOFs with metal centres that are not totally blocked by organic ligands or unsaturated, i.e., labile ligands are good catalysts because labile ligands are generally solvent molecules that leave a free coordination position on the metal when they are removed. HKUST-1⁴¹ when activated thermally leaves a vacant coordination site due to loss of water molecule.

1.4.5 Biomedical applications

MOFs have been widely used for biomedical applications nowadays. Because of their increased stability, massive porosity, and high pore volume,⁴⁴ the MIL family of MOFs is an excellent candidate for storing and regulated release of biologically essential chemicals. For employing targeted drug delivery, non-toxic metal-organic frameworks are used. Various Febased MOFs like MIL-8, MIL-88A, MIL-101 and MIL-100 have the ability to entrap antiretroviral and antitumor drugs.

1.4.5.1 Antibacterial/Antimicrobial applications of MOFs

The classification of bacteria is done in two types on the basis of their cell wall structure which are Gram-negative bacteria (-) and Gram-positive (+). The peptidoglycan layer of cell wall in Gram (+) is more thick than that of Gram (-) bacteria.⁴⁵ Due to this, they have different types of tolerance towards antibacterial agents. Most of the studies reveal the high sensitivity of gram (-) bacteria in comparison to Gram (+) bacteria against MOFs.

The need for MOFs-derived carriers came into play due to the non-targeted approach, uncontrolled release, and lesser efficacy of conventional delivery agents. pH is one of the important stimuli which triggers the drug release at the site of inflammation. MOFs containing anti-cancerous drugs are typically designed in a way that drug release occurs due to exposure to an acidic environment.



Figure 1: Schematic summary of the possible antibacterial/antimicrobial applications of MOFs⁴⁶

1.4.5.2 Mechanism of regulation of antibacterial activities

There have been reports of various mechanisms of MOFs being used as antibacterial agents, which are as follows -:

- Antibacterial metal ions like Ag⁺, Zn²⁺, Cu²⁺, and Hg₂²⁺ are generally employed for synthesizing MOFs which can be released at the site of action.⁴⁷ Metal ions released by metal nanoparticles have the ability to cross the cell membrane, which results in cell death
- Antibacterial framework of the linker can also be incorporated in MOF which can be released when needed⁴⁸
- Reactive Oxygen Species (ROS) is generated when NPs are irradiated with light^{49,50}



Figure 2: The probable mechanisms for antibacterial activity of MOFs

• Loading of various drugs having antibacterial agents in the pores which get released due to the exposure of stimuli like pH, light, temperature, etc.^{51,52}



Figure 3: Illustration mechanism of drug loading and unloading⁵³

• Usage of all mechanisms in a single run to get their synergistic effect

1.5 Organization of the thesis

The purpose of this project is to synthesize lactam and oxygen functionalized linkers for the construction of Zn-based MOF and its doping with silver. After doping, their antibacterial properties were studied.

Chapter 2: In this chapter, we have discussed about the past and present works on various MOFs for the antibacterial applications.

Chapter 3: This chapter includes materials, instrumentation and experimental procedures which were used to synthesize linkers, Zn-MOF and Ag@Zn-MOF.

Chapter 4: This chapter includes the characterization of linkers, Zn-MOF and Ag@Zn-MOF and the results obtained using these compounds.

Chapter 5: In this chapter, we have concluded all the results of our work and their future aspects.

Chapter 2

Literature review

There are various reports of metal centres being used for synthesizing MOFs, which ultimately lead to the stimulation of antibacterial properties. MOFs having an Ag metal centre were tested for the 1st time for antimicrobial activities. They have attracted researchers by the potential to use them for human welfare.⁵⁶

The following table shows some MOFs where metal salt acts as a source to work against bacteria-:

MOF	Metal	Ligand	Type of bacteria	Antibacterial activity	Reference
Ag ₃ (3-phosphonobenzoate)	Ag	3-Phosphonobenzoate	E. coli, S. aureus, and P. aeruginosa	E. coli: MBC = 30 µM S. aureus: MBC = 50 to 75 µM P. aeruginosa: MBC = 20 to 30 µM	Berchel et al., 2011
[(AgL)N0 ₃]:2H ₂ O [(AgL)CF ₃ SO ₃]:2H ₂ O [(AgL)Cl04]:2H ₂ O	Ag	Tris-(4-pyridylduryl) borane	E. coli and S. aureus	E. coli: MIC = 300 to 308 µM; ZOI = 13 mm S. aureux: MIC = 293 to 307 µM; ZOI = 16 mm	Liu et al., 2010
$ \begin{array}{l} \left[A \xi_{0}(\mu \cdot PTA)_{0}(\mu \cdot \operatorname{suc}) \right]_{n} \cdot \operatorname{2nh}_{0} O \\ \left[A \xi_{0}(\mu \cdot PTA)_{0}(\mu \cdot \operatorname{adip}) \right]_{n} \cdot \operatorname{2nh}_{0} O \\ \left[A \xi_{0}(\mu \cdot \Gamma A)(\mu \cdot \operatorname{mal}) \right]_{n} \end{array} \end{array} $	Ag	1,3,5-triaza-7- phosphaaDamantane Flexible aliphatic Dicarboxylic acids	E. coli, S. aureus, P. aeruginosa, and C. albicans	E. coli: MIC = 6 to 7 µM S. aureus: MIC = 6 to 40 µM P. aeruginous: MIC = 6 to 20 µM C. albicans: MIC = 30 to 50 µM	Jaros et al., 2014
[Ag(N0,/μ ₂ -PTAd0)] _n [Ag ₂ (μ ₂ -S0 ₄ (μ ₅ -PTAd0)(H ₂ 0)] _n	Ag	1,3,5-triaza-7- phosphaadamantane-7- oxide	E. coli, S. aureus, P. aeruginosa, and C. albicans	E. coli: MIC= 6 to 7 µM S. aureus: MIC= 20 to 30 µM P. aeruginose: MIC= 6 to 7 µM C. abbicans: MIC= 20 to 30 µM	Kirillov et al., 2011
[Ag ₂ (0-IPA)(H ₂ O)(H ₃ O)] [Ag ₅ (PYDC) ₂ (0H)]	Ag	5-Hydroxyisophthalic acid Pyridine-3, 5-dicarboxylic acid	E. coli and S. aureus	E. coli: MIC= 5 to 15 ppm; ZOI= 17 to 20 mm S. aureus: MIC = 10 to 20 ppm; ZOI= 14 to 16 mm	Lu et al., 2014
Zn-MOF nanocubes	Zn	Terephthalic acid	P. aeruginosa	MIC = 25μ M; ZOI = 9 mm	Pezeshkpour et al., 2018
[Za(kipy)(OH_j) ²⁺]_{15}[CIO4 ⁻] ₅ (bipy) ₃ (H_2O)	Zn	4,4'-Bipyridine	E. coli and S. epidermidis	E. coli: MIC= 5.3 ppm S. <i>epidermidis</i> : MIC= 3.8 ppm Fluorescence microscopy: High level of oxidative stress was caused	Colinas et al., 2018
$[Za_{1,5}(CH_5CO_2)_5(bipy)$ $_2^+][CO_4^-]+H_5O_5(bipy)$	Zn	4,4'-Bipyridine	E. coli and S. epidermidis	E. coit: MIC= 6.1 ppm S. <i>epidermidis</i> : MIC = 4.6 ppm Fluorescence microscopy: High level of oxidative stress was caused	Colinas et al., 2018
[Ni(NPTA)(4,4'-bipy)(H ₂ O)] _n	N	3-Nitrophthalic acid; 4,4'-bipyridine	E. coli and S. aureus	<i>E. coli</i> : ZOI = 14 mm <i>S. aureus</i> : ZOI = 12 mm	Lu et al., 2014
[Co ₄ (H_O) ₂ (TDM)(H_O) ₈]	ප	Tetrakis [(3,5-dicarboxyphenyl)- oxamethyl] methane	E. coli	MBC = 10 to 15 ppm EDS elemental mapping: Rupture of the bacteria membrane	Zhuang et al., 2012
n[Cu(AIP)_(PIY)(H_2O)_]4H_2O	5	5-Aminoisophthalic acid 2,3 Diamino-5- bromopyridine	E. coli, S. aureus, P. aeruginosa, and Klebsiella sp.	E. coli: Z01 = 28 mm S. aureus: Z01 = 25 mm P. aeruginosa: Z01 = 32 mm Klebsiella sp.: Z01 = 18 mm	Sheta et al., 2018

Table 1: Summary of antibacterial activities of metal ions of various MOFs¹

Also, it was seen that metal ions along with linkers in the MOF show a synergistic effect to combat against the bacteria. Tamames-Tabar et al. synthesized a novel bioactive MOF (BioMIL-5) using Zn^{2+} metal and azelaic acid (AzA). AzA is widely used as an antibacterial agent in dermatology.⁵⁷ Due to the combination of Zn^{2+} and AzA, the poor absorption of AzA was solved which helped in relieving pain.

Compound	Ligand	Metal	Type of bacteria	Antibacterial activity	Reference
BioMIL-5	Azelaic acid	Zn	S. aureus and S. epidermidis	S. aureus: MIC = 1.7 mM; MBC = 4.3 mM S. epidermidis: MIC = 1.7 mM; MBC = 4.3 mM	[57]
MSN-Sul@ carMOF	Carbenicillin	Fe	MRSA	Confocal laser scanning microscopy: Biofilm destruction	[58]
$\begin{array}{l} [Zn(\mu-4-\\hzba)_2]_2\\ \cdot 4(H_2O)_n \end{array}$	4- hydrazinebenzoate	Zn	S. aureus	$ZOI = 14.6 \pm 3.1 \text{ mm}$ EC50 = 24.2 ± 3.4 µM	[48]

Table 2: Summarized antibacterial action by ligands of various MOFs¹

The reports of biocompatible metal ions being used in MOFs as composites can be seen frequently. Mostly, Ag nanoparticles are used as composites of MOFs.⁵⁹

Duan et al.,⁵⁸ and Abd El Salam et al.⁶⁰ reported the better antibacterial effects of MOFs composites having Ag nanoparticles than alone Ag nanoparticles. This happens due to the cluster of metal ions of MOFs. Abd El Salam et al.,⁶⁰ and Duan et al.⁶¹ concluded in their report that the enhanced activity is due to the disruption of cytomembrane's permeability which leads to the outflow of intracellular contents.

Compound	Nanoparticles	Combination type	Type of bacteria	Antibacterial activity	Reference
Ag NPs@ HKUST- 1@ CFs	Ag NPs	In situ reduction (simultaneous synthesis)	S. aureus	Standard plate count: 99.41% of growth inhibition	[61]
MIL- 88B(Fe)- Ag/TiO2 nanotubes/ Ti plates	Ag NPs	In situ reduction (Growing on MOFs)	E. coli	ZOI: Effectively photocatalytically kill bacteria under UV light	[62]
Ag- CuTCPP MOFs	Ag NPs	In situ reduction	E. coli, S. aureus, B. subtilis	E. coli: MIC = 12.50 μ M; MBC = 25.00 μ M S. aureus: MIC = 6.25 μ M; MBC = 12.50 μ M B. subtilis: MIC = 6.25 μ M; MBC = 12.50 μ M Mixed strains: MIC = 12.50 μ M; MBC = 25.00 μ M SEM: Disruption of bacteria surface	[63]
Ag@ZIF-8	Ag nanowires	ZIF-8 were located on Ag nanowires	B. subtilis and E. coli	Kinetic test: Efficiently slow down the growth Growth inhibition assay: At the concentration of 10 mM <i>B. subtilis</i> : MIC = 200 µM E. coli: MIC = 300 µM	[65]
Ag@MOF- 5	Ag NPs	Dispersed in MOFs	E. coli	Rapid inactivation of >91% bacteria in only 70 min of time under visible light irradiation	[64]
Ag@NH ₂ - MOP(Ti)	Ag NPs	Doped nanoparticles with MOFs	ND	ZOI: High activity in killing bacteria under Xenon Lamp	[66]
Ag-NPs @ Ni-MOF	Ag NPs	Ag-NPs and Ni- MOF were mixed together	B. subtilis, E. coli, P. aeruginosa, and C. albicans	Growth inhibition assay: At the concentration of 2.5 μ M of approximately 5 × 107 CFU/mL microbial cells MIC = 0.025 μ M; MBC = 2.5 μ M	[60]

Table 3: Summarized antibacterial applications of MOF composites having nanoparticles¹

Chapter 3

Experimental section

3.1 Chemicals and reagents:

All of the reagents used were commercially available and were used without further purification. Sigma-Aldrich supplied Zn(NO₃)₂.6H₂O, 2-cyanobenzyl bromide, and 5-aminoisophthalic acid (98%) and were used as received. Rest other chemicals like K₂CO₃, KOH, HCl, and solvents were obtained from Finar Chemicals (India). Prior to use, all the solvents were dried.

3.2 Instrumentation:

The purified products were verified using NMR spectra recorded in CDCl₃ and DMSO-d₆ using a Bruker Advance 500 Spectrometer at 500 MHz (¹H) with tetramethylsilane as an internal standard on a Bruker Advance 500 Spectrometer. All chemical shift values are listed in parts per million on the scale (ppm). The CDCl₃ and DMSO-d₆ residual solvent peaks were 7.26 and 2.50 ppm, respectively. The multiplicities of desired peaks were denoted as given s (singlet), d (doublet), dd (doublet of doublet), t (triplet), q (quartet), m (multiplet).

3.3 Synthetic schemes:

3.3.1 Synthesis of diethyl-5-((2-cyanobenzyl)amino)isophthalate (DCAI)⁵⁴

Diethyl 5-aminobenzene-1,3-dicarboxylate (2.0 g, 8.40 mmol), dry K_2CO_3 (1.6 g, 12.3 mmol) were taken in an RB flask and dry acetonitrile (200 mL) was added to the mixture. The mixture was stirred for 4 h at 80 °C in an N₂ atmosphere (Scheme 1). Then, 2-cyanobenzyl bromide (1.7 g, 8.40 mmol) was added to the mixture and it was again refluxed for 48 h by maintaining the N₂ atmosphere. After completion of 48 h, the reaction mixture was cooled to normal temperature. Then, it was poured in 100 mL of ice-cold water. The appearance of white precipitates took place and these precipitates were collected by filtration using filter paper and then air-dried. Yield: 65% (1.2 g).

3.3.2 Synthesis of 5-(1-oxoisoindolin-2-yl)isophthalic acid (H₂L)

The above-obtained compound, DCAI (2.0 g, 5.17 mmol) was hydrolyzed with 6 N KOH solution (25 mL) and methanol (25 mL) for 24 h at 70 °C under reflux conditions (Scheme 1). After its completion, the reaction mixture was cooled to around 5 °C. Then, neutralization of the solution was done using 6N HCl solution which results in the formation of pale-yellow precipitate. These precipitates were filtered, washed several times with water and then, air-dried. Yield: 80% (1.4 g).



Scheme 1: Schematic representation for the synthesis of DCAI and H₂L

3.3.3 Synthesis of diethyl 5-(2-cyanophenethyl)isophthalate (o-decpi)

Diethyl 5-hydroxybenzene-1,3-dicarboxylate (2.0 g, 8.40 mmol), dry K₂CO₃ (1.6 g, 12.30 mmol) were taken in an RB flask and dry acetonitrile (200 mL) was added to the mixture. The mixture was stirred for 4 h at 80 °C in an N₂ atmosphere (Scheme 2). Then, 2-cyanobenzyl bromide (1.7 g, 8.40 mmol) was added to the mixture and was again refluxed for 48 h by maintaining the N₂ atmosphere. After completion of 48 h, it was cooled to normal temperature. Then, it was poured in 100 mL of ice-cold water. The appearance of white precipitate took place and these precipitates were collected by filtration using filter paper and then air-dried. Yield: 86% (2.8 g).

3.3.4 Synthesis of 5-(2-Carboxybenzyloxy)isophthalic acid (H₃L)

The above-obtained compound, o-decpi (2.0 g, 5.17 mmol) was hydrolyzed with 6 N KOH solution (25 mL) and methanol (25 mL) for 72 h at 90 °C under reflux conditions (Scheme 2). After its completion, it was cooled to around 5 °C. Then, neutralization of the solution was done using 6N HCl solution which results in the formation of white precipitate. These precipitates were filtered, washed several times with water and then, air-dried. Yield: 80% (1.3 g).



Scheme 2: Schematic representation for the synthesis of o-decpi and H₃L

3.3.5 Synthesis of Zn-MOF:

 $Zn(NO_3)_2 \cdot 6H_2O$ (60 mg, 0.20 mmol), linker H₂L (15 mg, 0.60 mmol), co-linker 4,4'azopy (15 mg, 0.60 mmol), DMF (1 mL), NaOH (1 M, 20 µL), and DI water (1 mL) were dissolved in a 5 mL Teflon vessel and heated for 72 h at 100 °C in a heating furnace. After the reaction's completion, we got golden-colored and needle-shaped crystals of Zn-MOF. The MOF was filtered from the mother liquor and then, washed with DI water four to five times, then 2-3 times with acetone. These crystals were, then soaked in acetone for 5 days so as to remove water and DMF from their pores for their activation. The acetone was changed every day for better activation. After five days, the acetone was removed and the MOF was vacuum-dried to be fully activated.



Scheme 3: Schematic representation for the synthesis of Zn-MOF

3.3.6 Synthesis of Ag@Zn-MOF:

Zn-MOF (0.005 g) and $AgBF_4$ (0.002 g) were added to 15 mL dichloromethane (DCM), then stirred for 12 h at 400 rpm in dark. After 12 h, there was a change in the color of the solution. The resultant solution was centrifuged to get the desired Ag@Zn-MOF.



Scheme 4: Schematic representation for the synthesis of Ag@Zn-MOF

Chapter 4

Results and discussion

Zn-MOF was synthesized by the solvothermal reaction of zinc nitrate and H₂L with 4,4'-py as co-linker in H₂O in an alkaline medium at 130 °C. The presence of bidentate ligand and the tendency of Zn to form MOFs have led to the formation of this Zn-MOF. The linker H₂L was characterized by mass spectrometry and NMR spectroscopy. The MOF was characterized by SC-XRD, bulk purity by PXRD, surface morphology by SEM analysis, Elemental mapping by EDS, absorbance by UV spectroscopy, and thermal stability by TGA analysis.

4.1 Characterization of DCAI:

DCAI has been characterized by mass spectrometry, ¹H and ¹³C NMR. ¹H NMR (500 MHz, CDCl₃) δ =8.81 (s, *J* = 0.9 Hz, 2H, Ar-H), 8.43 (s, 1H, N-H), 7.76 (d, *J* = 4.6 Hz, 1H, Ar-H), 7.58-7.55(d, 1H, Ar-H), 7.52-7.49 (m, 2H, Ar-H), 5.00(s, 2H,-CH₂-N), 4.46-4.41(q, 4H, -CH₂-), 1.43(t, 6H, -CH₃) ppm (**Figure 5**); ¹³C NMR (126 MHz, CDCl₃) δ =166.95, 140.61, 133.13, 132.51, 128.78, 125.54, 123.93, 123.65, 50.92 ppm (**Figure 6**); ESI-MS: m/z [M+nH]⁺ = 353.1514 (**Figure 4**).







Figure 5: ¹H NMR spectrum of DCAI



Figure 6: ¹³C NMR spectrum of DCAI

4.2 Characterization of H₂L:

Lactum-based linker was characterized by ¹H, ¹³C NMR & mass Spectrometry¹H NMR (500 MHz, DMSO-d₆) δ =8.73 (s, 2H, Ar-H), 8.27 (s, 1H, -NH), 7.81 (m, 1H), 7.96 – 7.75 (t, *J* = 11.7, 6.7 Hz, 2H), 7.57 (dd, *J* = 9.7, 3.8 Hz, 1H), 5.15 (s, 2H) ppm (**Figure 8**); ¹³C NMR (126 MHz, DMSO-d₆) δ =167.59, 166.95, 141.62, 140.61, 133.12, 132.50, 128.77, 125.54, 123.93, 123.65, 50.91 ppm (**Figure 9**); ESI-MS: m/z [M+K]⁺ = 336.0245 (**Figure 7**).







Figure 8: ¹H NMR spectrum of H₂L



Figure 9: ¹³C NMR spectrum of H₂L

4.3 Characterization of o-decpi:

o-decpi linker is characterized by the ¹H, ¹³C & mass spectrometry. ¹H NMR (500 MHz, CDCl₃) δ =8.32 (s, 1H), 7.84 (d, *J* = 1.3 Hz, 2H), 7.74 – 7.70 (m, 1H), 7.65 (dd, *J* = 15.1, 11.1, 4.1 Hz, 2H), 7.46 (td, *J* = 7.6, 1.2 Hz, 1H), 5.32 (s, 2H), 4.40 (q, *J* = 7.1 Hz, 4H), 1.40 (t, *J* = 7.1 Hz, 6H) ppm (**Figure 11**); ¹³C NMR (126 MHz, CDCl₃) δ =165.49, 158.18, 139.62, 133.11, 132.37, 128.81, 123.79, 119.97, 116.95, 111.59, 77.33, 77.07, 76.82, 68.08, 61.51, 14.30 ppm (**Figure 12**); ESI-MS: m/z [M+nK]⁺ = 392.1127 (**Figure 10**).



Figure 10: ESI-MS spectrum of o-decpi



Figure 11: ¹H NMR spectrum of o-decpi



Figure 12: ¹³C NMR spectrum of o-decpi

4.5 Characterization of H₃L:

Oxygen-based H₃L linker is characterized by the following ¹H, ¹³C and mass spectrometry. ¹H NMR (500 MHz, DMSO-d₆) δ =8.11 (s, 1H), 7.95 (d, *J* = 7.7 Hz, 1H), 7.70 (t, *J* = 5.5 Hz, 3H), 7.61 (t, *J* = 7.5 Hz, 1H), 7.46 (t, *J* = 7.3 Hz, 1H), 5.56 (s, 2H) ppm (**Figure 14**); ¹³C NMR (126 MHz, DMSO-d₆) δ =168.71, 167.00, 158.92, 138.07, 133.64, 132.53, 130.98, 130.32, 128.33, 123.02, 119.59, 68.63 ppm (**Figure 15**); ESI-MS: m/z [M+nNa]⁺=339.0523 (**Figure 13**).



Figure 13: ESI-MS spectrum of H₃L



Figure 14: ¹H NMR spectrum of H₃L



Figure 15: ¹³C NMR spectrum of H₃L

4.6 Characterization of Zn-MOF:

SC-XRD studies reveal that Zn-MOF crystallizes in a triclinic space group *P-1*. Figure 16 shows the asymmetric unit of the Zn-MOF, which contains one Zn (II) ion, one H_2L unit, and a 4,4'-azopy molecule. It also exhibits the coordination of each Zn (II) ion with three O atoms of two different H_2L molecules and one N atom of 4,4'-azopy linker.

Zn(II) metal ions in the MOF formed distorted octahedral geometry.

Two adjacent Zn(II) ions forming a metallacycle ring where both the Zn(II) ions are separated by 4.079 Å which extended to create a 1D layers which are pillared by azo-dpe molecule forming a 2D framework containing square shaped voids along the *c*-axis. Also, C–H···O type hydrogen bond interactions form a self-assembled 3D network.

Parameters	Zn-MOF
Crystal System	Triclinic
Empirical formula	C26H17N5O5Zn
Space Group	P-1
a (Å)	10.0192(9)
b (Å)	13.3441(15)
c (Å)	14.680(2)
α (°)	100.841(10)
B (°)	100.374(9)
γ (°)	92.200(8)
Volume (Å ³)	1890.9(4)
Z	2
Final R indices (R_1^a, wR_2^b) [I>2 σ (I)]	9.97, 23.70
R indices (R_1^a, wR_2^b) (all data)	22.33, 29.36

Table 4: Cell parameters of Zn-MOF

^a
$$R_1 = \Sigma(|Fo| - |Fc|) / \Sigma |Fo|$$
. ^b $R_2 = [\Sigma \{w(Fo^2 - Fc^2)^2\} / \Sigma \{w(Fo^2)^2\}]^{1/2}$



Figure 16: Asymmetric unit of Zn-MOF

Figure 17: The consecutive representation of **Zn-MOF** from the c-axis

PXRD Analysis:

Bulk purity of the Zn-MOF was confirmed by PXRD analysis. As most of the peaks matched with the simulated pattern which was obtained from SC-XRD, we can interpret that the bulk reproduced had the same crystal structure as of data interpreted by SC-XRD.



Figure 18: PXRD analysis of Zn-MOF

FE-SEM Analysis:

The particle size distribution and shape of Zn-MOF crystals were measured using a field emission scanning electron microscope (FE-SEM), as shown in fig. 19. These images clearly show the cuboidal type of structure of our MOF.



Figure 19: FE-SEM analysis of Zn-MOF

EDS analysis:

EDS analysis was done over an area of 5 μ m to check the elements present in the MOF. It was found that this MOF contains Zn, C, N, O and H in different proportions.

Element	Zn	С	Ν	0
At%	1.5	67.9	12.6	18.0
Wt%	7.2	59.1	12.8	20.9

|--|



Figure 20: EDS analysis of Zn-MOF

UV Analysis:

The photophysical properties of Zn-MOF was studied using electronic absorption spectroscopy. A solution of 0.1 mg/mL was used. The UV-vis spectrum (Figure 21) of Zn-MOF displayed an intense absorption band at 270.5 nm.



Figure 21: UV spectrum of Zn-MOF

Thermal analysis:

TGA was done to check the thermal stability of our MOF. By analyzing the data, it was found that in the first step, 30-300 °C around 10.00 weight % was lost due to the presence of H_2O molecules and other solvent molecules which are present in the framework. In the second step, 320-500 °C, breakage of covalent bonds led to the decrease of 47.92 weight % and finally in the third step, 500-600 °C, the disintegration of the framework took place by

14.23 weight % which indicates that all the elements have reached in elemental state, thereby putting no effect on further increasing the temperature.



Figure 22: TGA analysis of Zn-MOF

4.7 Characterization of Ag@Zn-MOF:

PXRD Analysis -:

After doping with Ag, the crystal structure was examined whether it has changed or not, by PXRD. By interpreting the data and comparing the peaks with as-synthesized Zn-MOF, we can infer that the bulk purity was maintained even after doping with Ag. There is slight reduction in the crystallinity due to the enrichment of amorphicity of the composite, so formed.



Figure 23: PXRD analysis of Ag@Zn-MOF

FE-SEM analysis -:

The particle size distribution and shape of Zn-MOF crystals were measured using a field emission scanning electron microscope (FE-SEM), as shown in fig. 24. These images clearly show the cuboidal type of structure of our MOF. The morphology was intact even after doping with Ag.



Figure 24: FE-SEM analysis of Ag@Zn-MOF

EDS mapping -:

EDS mapping was done over an area of 3 μ m to check the elements present in the MOF. It was found that the composite contains Zn, Ag, C, N, O and H in different proportions.



Table 25: EDS mapping of Ag@Zn-MOF



Figure 26: UV Spectra of Zn-MOF & Ag@Zn-MOF

The photophysical properties of Zn-MOF and its composite Ag@Zn-MOF were studied using electronic absorption spectroscopy. A solution of 0.1 mg/mL was used to study these properties. The UV-vis spectra of Zn-MOF and Ag doped Zn-MOF displayed absorption bands between 250-450 nm. The Ag@Zn-MOF exhibited intense absorption bands at 270.5 nm and 420.3 nm respectively. This absorption peak at 420.3 nm confirms the presence of silver. Further, we discovered that Ag@Zn-MOF had a redshift in UV-vis absorption spectroscopy. The UV data indicates that the primary structure is intact even after doping with Ag.

Thermal analysis:-

Thermogravimetric plots infer that more thermal degradation has taken place due to the incorporation of Ag. The weight loss percentage is almost similar to that of Zn-MOF upto 2^{nd} step. The change in weight loss percentage is around 7.62% between Zn-MOF and its composite Ag@Zn-MOF. The reason for shift is because of doping with Ag. The primary

interactions (bonds) between Zn metal, linker and co-linker sites get weakened as Ag also interacts with the donor sites after incorporation.



Figure 27: TGA Analysis of Ag@Zn-MOF

4.8 Antibacterial studies of Zn-MOF and Ag@Zn-MOF

4.8.1 Turbidity Assay of Zn-MOF and its composite Ag@Zn-MOF

The in vitro antibacterial studies were performed using the *E. coli* DH5 α bacterial strain. To ensure the sterility, all the labware was autoclaved at 121 °C for 15 minutes. *Escherichia coli* was cultured in Luria broth in an orbital shaker at 37 °C with continuous shaking at 220 rpm and harvested till the exponential growth phase was reached. The OD of the resuspended bacterial pallet in PBS was measured at 600 nm (OD₆₀₀) and was adjusted to 0.1 by using PBS to form a fresh inoculum. Addition of 10 µL inoculum to the 5mL of Luria broth was done to perform the experiments. The inhibition of *E. coli* growth study was

tested using four treatments; 1.) positive control where only inoculum and bacterial cells were incubated, 2.) negative control containing only inoculum, 3.) Broth having bacteria, inoculum and Zn-MOF (1 mg/mL), 4.) broth containing bacteria, inoculum and Ag@Zn-MOF (1 mg/mL). The optical density of these samples was measured using UV-vis spectrometer at wavelength 600 nm after every 30 minutes for 8 h and a graph was plotted (Fig. 28).



Figure 28: Growth curves of Escherichia coli on treatment with Zn-MOF and its composite Ag@Zn-MOF

The results obtained from the growth curves indicate that Ag@Zn-MOF has better antibacterial property in comparison to Zn-MOF. This can be attributed due to the excellent antimicrobial properties of silver.

Biocompatibility of our Zn-MOF and its composite is yet to be done in the future with healthy cell lines using MTT Assay. This will check the cell viability of our MOF and will be helpful in opening the new aspects for antibacterial activities in MOFs.

Chapter 5

Conclusion and Future Scope

Two ligands namely, 5-(1-oxoisoindolin-2-yl)isophthalic acid (H₂L) and 5-((2carboxybenzyl)oxy)isophthalic acid (H₃L) were synthesized and characterized by NMR spectroscopy and Mass spectrometry. We synthesized a Zn-MOF using H₂L as linker and 4,4'-azopy as co-linker under solvothermal conditions. Also, post-synthetic modification was done to Zn-MOF. Ag⁺ ions were incorporated into the pores of Zn-MOF by treatment with AgBF₄ to get Ag@Zn-MOF. Single Crystal XRD, PXRD, SEM, TGA, EDS, and UV techniques were done for the characterization of our MOF and its composite. Also, antibacterial application has been investigated against *E. coli* bacteria using the MOF and its composite. The results showed that Ag-doped MOF had better inhibition towards *E. coli* in comparison to Zn-MOF alone.

There has been a tremendous growth in synthesizing MOFs which has opened lots of paths for the future. Some gaps are still there in completely understanding their crystal structure, stability and various factors which affect their formation and destruction. MOFs having biological properties will act as a boon for the upcoming generations as these are one of the best and economical candidates for nanotechnology. Commercialization of MOFs-based drugs has given a promising and exciting in the area of science.

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