SYNTHESIS AND ANTIMIC ROBIAL STUDY OF SOME TRANSITION METAL COMPLEXES OF PICOLINIC ACID HYDRAZIDE

Balachandhiran[1], V S Sangeetha[2], V.Bhakyajothi[3], P.Saraswathi[4]

Assistant professor,

[1]Department of chemistry ,Dhanalakshmi Srinivasan College of Arts & Science for Women(Autonomous)

Perambalur

Abstract

An approach was presented during this text for organizing of has been carried out for the synthesis of (E)-3,4-dichlorobenzylidene picolino hydrazide using 3,4 - trimethoxybenzaldehyde and thio semicarbazide. This work is very effective medicinal hydrazide derivatives are synthesized from Schiff base route. The structure of the ligand TLC and its complexes were carried various spectral studies. The spectrophotometric data just like the transmittance was cogitated within the 350-2500 nm regions and were found. Fourier transform infrared investigation was wont to characterize the grown crystal and assigning the modes of vibrations and to identify the presence of functional groups.

Introduction

Compounds with the structure of –C=N–(azomethine group) are referred to as Schiff bases, which are usually synthesized by condensation of primary amines and active carbonyl groups. Schiff bases are a crucial class of compounds within the medicinal and therefore the pharmaceutical field. More- over, Schiff bases have found application in drug development for the treatment of hypertension, HIV infection and are shown to exhibit a broad range of biological activities, including antifungal, antibacterial, antimalarial, antiproliferative, antiinflammatory, antiviral, and antipyretic properties(1).

A Schiff base (-C=N-R) may be a nitrogen analog of an aldehydes or ketones during which the C=O group is replaced by amine group. it's usually formed by condensation of an aldehydes or ketones with a primary amine and that they are explained with schemes. Tuberculosis (TB) is presently considered the foremost dangerous infective disease world- wide and one among the main AIDS associated infections. at the present , consistent with statistics, TB kills four people every minute somewhere within the world and accounts for about two million deaths per annum. it's estimated that one-third of the world's population is currently infected with the TB bacillus and 30 million people will die within the next 10 years. For the event of latest antimycobacterial compounds Turan-Zitouni et al.(8) synthesized new thiazolylhydrazone derivatives by the reaction of thiosemicarbazide with acetophenone derivatives. Hydrazones possess an azometine -NHN=CH- proton that has found wide utility in organic synthesis. 1-2 While hydrazones have traditionally been employed as moiety for the derivatization and characterization of carponyl compounds, in recent years the N-N linkage has been used as a key structural motif in

various bioactive agents.(9) Hydrazide-Hydrazone derivatives containing –NHN=CH- moiety represent an over whelming and rapid developing field in modern medicinal chemistry. Reported data indicade that hydrazide derivatives have significant biological activities like anti-inflammatory

METERIALS AND METHODS

Characterization techniques used:

Some physical methods were wont to elucidate the bonding and structure of the synthesized ligands and complexes and to verify the expected properties. While the ligands were characterized by usual methods like analytical technique like TLC, molar conductance, magnetic susceptibility and spectral techniques like IR, UV-Visible, NMR and mass spectral techniques, it differs for complexes counting on the character of the ligands and therefore the metal ions involved. The presence of paired or unpaired electrons of the metal ions imparts the magnetic behavior of the complexes. All the chemicals used were of Merck and Sigma Aldrich products, available commercially in AR grade. The purchased chemicals were used with none further purification.The physicochemical techniques employed for this study is discussed below.

TLC:

Thin Layer Chromatography has been used as an analytical tool, especially in chemistry due to its high speed of separation and its applicability during a sizable amount of chemical compounds. The high sensitivity of TLC is employed to see the purity of the samples. With the assistance of TLC, it's possible to understand whether a reaction is complete and had followed the expected course. Thin Layer Chromotography was made by dipping a glass plate in slurry of colloid G, prepared by shaking colloid G with chloroform-methanol (2:1) mixture at temperature . The homogeneity of the compounds was monitored by this TLC plates and visualized by UV lamp-NHN=CH- proton that has found wide utility in organic synthesis. 1-2 While hydrazones have traditionally been employed as moiety for the derivatization and characterization of carponyl compounds, in recent years the N-N linkage has been used as a key structural motif in various bioactive agents.(9) Hydrazide-Hydrazone derivatives containing –NHN=CH- moiety represent an over whelming and rapid developing field in modern medicinal chemistry. Reported data indicade that hydrazide derivatives have significant biological activities like anti-inflammatory

METERIALS AND METHODS

Characterization techniques used:

Some physical methods were wont to elucidate the bonding and structure of the synthesized ligands and complexes and to verify the expected properties. While the ligands were characterized by usual methods like analytical technique like TLC, molar conductance, magnetic susceptibility and spectral techniques like IR, UV-Visible, NMR and mass spectral techniques, it differs for complexes counting on the character of the ligands and therefore the metal ions involved. The presence of paired or unpaired electrons of the metal ions imparts the magnetic behavior of the complexes.

All the chemicals used were of Merck and Sigma Aldrich products, available commercially in AR grade. The purchased chemicals were used with none further purification.The physicochemical techniques employed for this study is discussed below.

TLC:

Thin Layer Chromatography has been used as an analytical tool, especially in chemistry due to its high speed of separation and its applicability during a sizable amount of chemical compounds. The high sensitivity of TLC is employed to see the purity of the samples. With the assistance of TLC, it's possible to understand whether a reaction is complete and had followed the expected course. Thin Layer Chromotography was made by dipping a glass plate in slurry of colloid G, prepared by shaking colloid G with chloroform-methanol (2:1) mixture at temperature . The homogeneity of the compounds was monitored by this TLC plates and visualized by UV lamp

Spectral methods:

Infrared spectroscopy:

Most of the spectra give sufficient information about the structure of the compound. The Infra Red spectrum is one among the spectra. The absorption of Infra-Red radiations causes the varied bands during a molecule to stretch and bend with reference to each other .The IR spectroscopy is widely used as a characterization technique for metal complexes. the essential theory involved is that the stretching modes of the ligands changes upon complexation thanks to weakening or strengthening of the bonds involved within the bond formation leading to subsequent change within the position of the bands appearing within the IR Spectrum. The changes within the structural features of the ligands are observed as changes in bands observed, mainly within the fingerprint region (4000-400 cm-1). The bands thanks to the metal ligand bonds are mainly observed within the far IR region (600-100 cm-1). within the present study, IR spectra of the compounds were recorded using Perkin Elmer spectrum RXI using KBr pellets at frequency range 4000-400 cm-1at ACIC, St. Joseph′s College (Autonomous), Trichirapalli and Shimadzu FT IR 400 Spectrophotometer, frequency range 4000-400 cm-1 using KBr disc at St

Joseph's College, Trichy.

Nuclear resonance spectroscopy:

Proton NMR:

NMR may be a study of transitions between the magnetically inducted spin states. it's concerned with the magnetic properties of atomic nuclei with an integral value I. this system consists of exposing the protons in an organic molecule to a strong field. The protons will process at different frequencies. Now, these processing protons are irradiating with steady changing frequencies and observe the frequencies at which absorptions occur. The signals obtained like the absorption is understood as NMR Spectrum. Studying a molecule by NMR spectroscopy enables us to record differences within the magnetic properties of varied magnetic nuclei present and to deduce the positions of this nucleus within the molecule. One can deduce what percentage different sorts of environments there are within the molecule and also which atoms are present in neighboring groups. Usually, the amount of atoms present in each of those environments is measured. Therefore, the diagnostic features of the NMR Spectra are the amount of signals, position of signals, splitting pattern of signals and area of signals. 1H NMR of the ligands were recorded using Bruker 300 MHz Avance –II FT-NMR Spectrometer with DMSO-d6 because the solvent and TMS as internal standard at SASTRA University, Tanjore.

SYNTHESIS OF (3,4-DICHLORO BENZALDEHYDE) PYRIDINE DICARBOXYLIC ACID HYDRAZIDE

CHEMICALS REQUIRED:

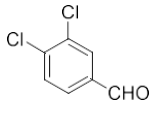
3,4 dichlobenzaldehyde (0.8750mol) =2.5

Pyridinedicarboxylicacidhydrazide(0.6857)=1.4

Ethonal=10ml

water=10ml

3,4, dicholoro benzaldehyde and pyridine di acid hydrazide absorb 1;1 molar ratio.1.4g of pyridinedi acid hydrazide(0.6857mole) was taken during a round bottom flask and 40ml of ethanol was added .To this solution.10ml ethanolic solution of two .5g of 3,4dicholoro benzaldehyde(0.8750mole) was added and stirred well for one hour by keeping the reaction mixture on a magnetic stirrer. After one hour a crude solid was obtained (scheme3).this crude solid was washed with water two to 3 times and dried then finally washed with ether and kept in over monitored by this TLC plates and visualized by UV lamp



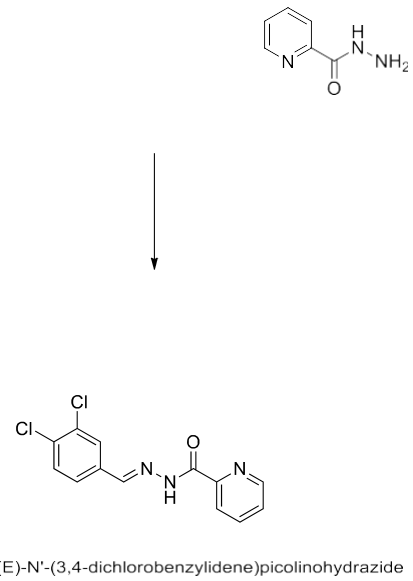


Figure 1. schematic representation of synthesis of hydrazide

Solubility Test:

Solubility of compound was tested using water, methanol, ethanol, hexane, dichloromethane, benzene, ester , chloroform and DMSO. 1mg of compound was added to 10ml of solvent and solubility was tested under three different conditions like cold condition and hot condition like the boiling point of the solvent.

TLC analysis

The crude sample was recrystallised from ethanol. The purity of the compound was checked by Thin Layer Chromatography (TLC) using polar and non polar solvents and compounds were detected under UV.

Analytical techniques

Elemental Analysis:

Our objective is to detect the presence of nitrogen, sulphur, chlorine, bromine and iodine in organic compounds by Lassaigne's test. A small piece of dry sodium was melted during a fusion tube. Then 0.1g of solid substance was added to the molten sodium. it had been heated gently initially , then to red hotness. Quickly plunged hotdog end of tube into 10mL water during a china dish. it's stirred well with broken end of tube, boiled and filtered

Test for nitrogen:

Few crystals of ferrous sulphatewas added with 1ml of fusion extract. it had been boiled, cooled then added two-ml of diluted vitriol . cyanide is converted to sodium ferrocyanide on treating with ferrous sulphate. The green colour solution developed, it indicates the presence of nitrogen.

$$Na + \underset{\text{(From organic compound)}}{C + N} \xrightarrow{\text{Fuse}} NaCN$$

$$FeSO_4 + 2NaOH \rightarrow \underset{\text{(Green ppt.)}}{Fe(OH)_2} + Na_2SO_4$$

$$Fe(OH)_2 + \underset{\text{(From Sodium extract)}}{2NaCN} \rightarrow Fe(CN)_2 + 2NaOH$$

$$Fe(CN)_2 + 4NaCN \rightarrow \underset{\text{Sod. ferrocyanide}}{Na_4[Fe(CN)_6]}$$

$$3Na_4[Fe(CN)_6] + 4FeCl_3 \rightarrow \underset{Ferric\ ferrocyanide}{Fe_4[Fe(CN)_6]_3} + 12NaCl$$

$$Na_2S + (CH_3COO)_2Pb \rightarrow \underset{\text{Black precipitate}}{PbS} + 2CH_3COONa$$

Test for halogen

One-ml of dilute aqua fortis is mixed with one-ml of fusion extract. it's boiled, cooled then added 1ml of nitrate solution. The halide ions chloride, bromide and iodide ions are giving white, straw and yellow precipitate respectively but the compound THC doesn't formany precipitate which is sparingly soluble in ammonia water pale. Hence we've conclude the sampleTHC has absence of halogen is confirmed.

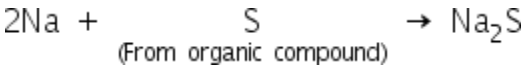
4.4.1.3. Test for sulphur.

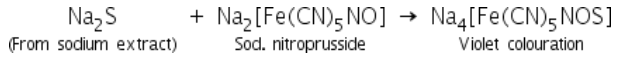
4.4.1.3. 1.Lead acetate test

Sodium sulphide formed during the preparation of Lassaigne's extract reacts with sugar of lead to yield lead sulphide as black precipitate.

4.4.1.3. 2. **Sodium nitroprusside test**

During the preparation of Lassaigne's extract, sulphur from the organic compound reacts with sodium to form sodium sulphide. It gives a purple colour with sodium nitroprusside due to the formation of sodium thionitroprusside.





From this test conclude the synthesized compound has both nitrogen and sulphur is present in it.

4.5.Antibacterial activity

Sterile Mueller Hinton agar plat was prepared and the test pathogen *Staphylococcus aureus* were swabbed on agar plates. 100µL of hydrazide derivative (1mg/ml) weas loaded on sterile disc and

placed over the surface of agar plate. Plates were incubated for 24h and zone of inhibition was recorded and compared with positive control.

4.6 Minimum inhibitory concentration

Minimum inhibitory concentration (MIC) decided using the micro broth dilution method. two-fold serial dilutions of the extracts were prepared (200, 100, 50,25,12.5, 6.25 and 1.12 µg/ml) during a eppendorf tubes. All the tubes inoculated with 25µL of S.aereus and incubation of the vials was administered at 37o C for 18-24 hours under aeerobic condition. After incubation, micotire wells were observed for any visible growth by the addition of 20µL resazurin indicator and further incubated for 30min. The bacterial suspensions were used as positive control and extracts in broth were used as negative control. The MIC was interpreted because the lowest concentration of the extract that didn't show any visible growth with non oxidized indicator in comparison to regulate tubes.

Combination assay

The testing was performed in 1 ML eppndorf tubes Twofold dilutions of every antibacterial compounds were prepared. First, 100 µl of Mueller-Hinton broth was added into 36 wells of a 96-well microtiter plate. Then, 50 µl of every dilutions of extract was added horizontally into six rows, and 50 µl of every dilutions of antibiotic was added vertically into six columns. the ultimate volume was 200 µl. the ultimate concentration range corresponded to 1/32 MIC – MIC. Each well contained unique combination of plant extract and antibiotic concentration. Ten microlitres of every 106 CFU/ml bacterial suspension and 10 µl of resazurin solution were added. The microtiter plates were incubated for twenty-four h at 37°C. the mixture of the compounds during which resazurin color change didn't appear (growth inhibition) is taken as effective MIC for the mixture . Each test included growth control and sterility control.

In vitro interactions between antimicrobial agents were determined and quantified by calculating the fractional inhibitory concentration index (FICI) using the subsequent formula: FICI=MICa together /MICa + MICb in combination/ MICb

RESULT AND DISCUSSION

5.1 A completely unique monosubstituted dipicolinic acid hydrazide derivative 3,4-Dichloro Benzaldehyde) Pyridine Dicarboxylic Acid Hydrazide was synthesized by schiff base reaction. Formation of discrete white powdere redisolved and crystaliesed compound (plate 1) was used for further characterization. The Hydrazide base derivatives are soluble in common organic solvents. The analytical data and physical properties of the Substituted chloro pyridine Hydrazides solubility listed in Table No. 1. Under RT it found to be soluble in water and hexane only but under hot condition the results were the other way around it's insoluble in predicament and hexane but soluble in methanol, ethanol(plate 2). the basic analsis(table 2) showed Presence of nitrogen, halogen, chlorine. The crystalised compound shows purity and detected by TLC. Single fraction was detected under 365 nm and therefore the Rf value isn't varied among solvent and located to be on the brink of 0.84-0.95(plate 3). the basic analysis reveals presence of nitrogen halogen and chlorine

Plate 1. Compound

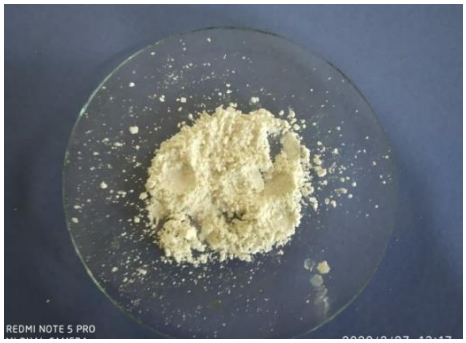


Plate 2. Solubility of compound

plate 3. TLC of synthesized hydrazide

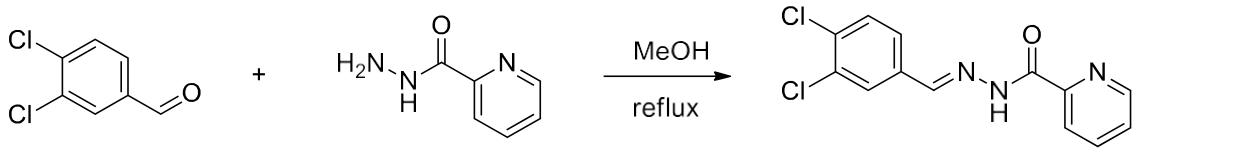
Table 1.solubility and R_f value of compound Vs solvent

S.no.	**Solvents**	**Room temperature**	**Hot condition**	**Rf value**
1	Water	Soluble	Insoluble	-
2	Methanol	InSoluble	Soluble	0.94
3	Ethanol	Insoluble	Soluble	0.93
4	Hexane	Soluble	Insoluble	-
5	Benzene	Insoluble	Soluble	0.91
6	Ethyl acetate	Insoluble	Soluble	0.92
7	Chloroform	Insoluble	Soluble	0.79
8	Dimethylsulphoxide	Insoluble	Soluble	o.94
9	Dichloromethane	Insoluble	Soluble	0.84

Table 2. Elemental analysis of hydrazide derivative

Test	Report
Test for nitrogen	Presence of nitrogen
Test for halogen	Presence of halogen
Test for sulphur	Absence of sulphur
Test for chlorine	Presence of chlorine
Test for bromine	Absence of bromine
Test for iodine	Absence of iodine

Spectral Characterization



(*E*)-*N*'-(3,4-dichlorobenzylidene)picolinohydrazide

Spectral Characterization:

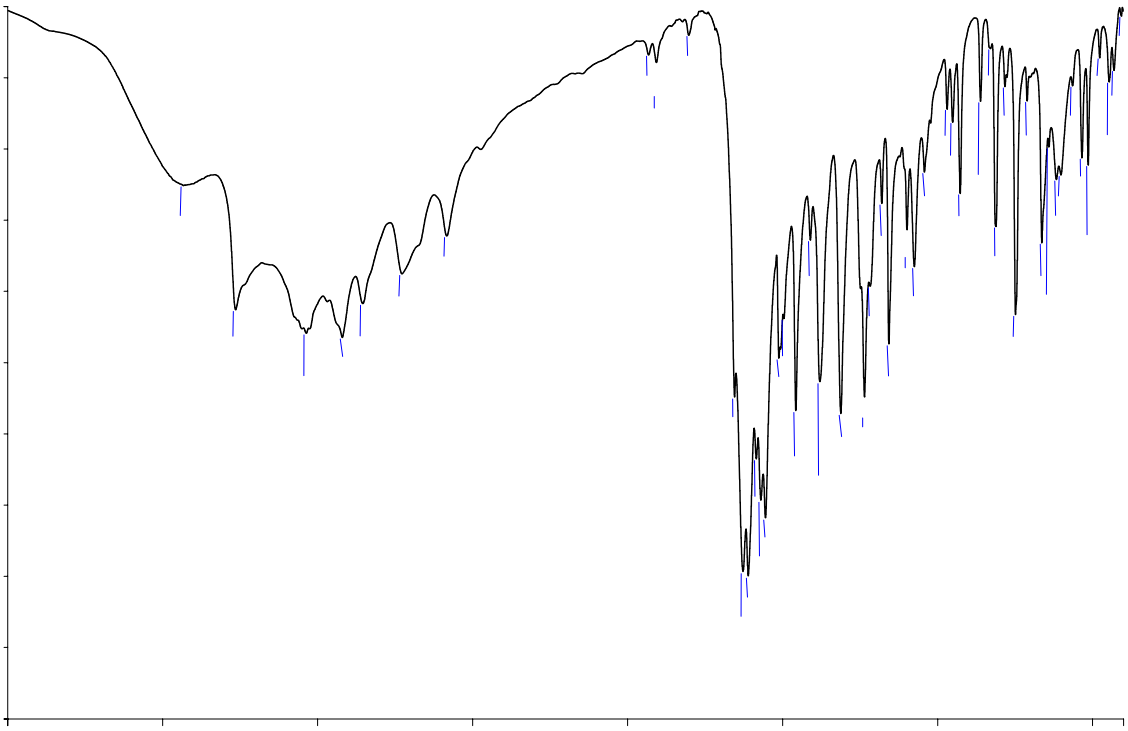
FT-IR Spectral studies:

In order to review of functional group of the synthesized Schiff base, the IR spectrum was compared with the overall functional ranges. The IR spectrum of Schiff base showed characteristic broad band at 3433 cm-1 are often attributed to ν(N-H) and aromatic ν(ArC-H) stretching vibrations appeared at 3037 cm-1. it's indicated, the Schiff base also having intermolecular O…H hydrogen bonding. The weak force was depends on the concentration of the answer . during this spectrum was recorded with very dilute sample. Another distinctive vibration expected for N-N observed at 1932 cm-1. Generally group stretching vibrations appears at 1680-1700 cm-1 but during this case appeared at 1627 cm-1; this is often thanks to amide group present within the compound which decreases the carbonyl functional group. The newly generated C=N stretching vibration appeared at 1456 cm-1 along side other finger print region signal and every one other peaks are good agreement with the proposed structure. The FT-IR spectral data are given in table 3 and figure 1.

Table 3 Important IR bands of Schiff base with their assignments.

Vibrations	**ν(N-H)**	**ν(ArC-H)**	**ν(N-N)**	**ν(C=O)**	**ν(C=N)**
Peak (cm^{-1})	**3433**	**3037**	**1932**	**1627**	**1456**

Figure 1. FTIR spectrum of (*E*)-*N*'-(3,4-dichlorobenzylidene)picolinohydrazide



NMR spectra analysis:

In ^{1}H NMR spectrum, the proton attached to C2 & C7 carbon showed as a singlet at δ = 8.26 and 8.31 ppm. It had been the unique proton appeared as a pointy singlet without multiplicity and wont to calibrate other peaks. The characteristic amine N-H was appeared as broad singlet at δ = 7.86 ppm. The three protons attached on the phenyl ring were appeared as two doublets at δ = 7.59 and 7.67 ppm and one singlet as discussed early. On the opposite hand, the four protons related to pyridine ring were identified as two doublets at δ = 8.36 & 8.68 ppm and two multiplets at δ = 7.80 & 8.08 ppm. The detailed assignments of protons were given in table 2 and figure 2. 1H NMR spectrums showed signals within the range 8.3 ppm, and these signals were the evidence of the secondary amide bonding to the ligand [42].

Table 2. NMR spectroscopic data (δ) of (*E*)-*N*'-(3,4-dichlorobenzylidene) picolinohydrazide

S. No	Position Assignment	^{1}H (δ, ppm)	^{13}C(δ, ppm)
1	1	--	133.2
2	2	8.26, s	130.6
3	3	--	133.5
4	4	--	135.7
5	5	7.67, d	130.3
6	6	7.59, d	128.7
7	7	8.31, s	146.8
8	8	--	--
9	9	7.86, br	--
10	10	--	157.6
11	1’	--	--
12	2’	--	151.3
13	3’	8.36, d	122.1
14	4’	8.08, m	137.5
15	5’	7.80, m	126.7
16	6’	8.68, d	147.6

UV ANALYSIS:

Figure 4 shows UV-visible absorption spectra of (E)-N'-(3,4 dichlorobenzylidene)picolinohydrazide in DMSO which exhibit absorption bands at 256 nm. Normally, pyridine absorbs at visible region and its linked with other azo unit reduces its absorption. The longer wavelength bands are often attributed to the π-π* transitions of the (E)-N'-(3,4-dichlorobenzylidene) picolinohydrazide Biological activity.

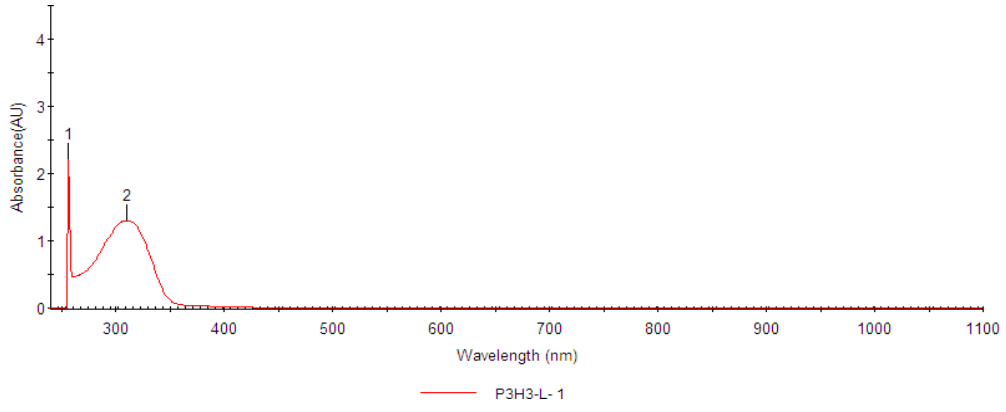


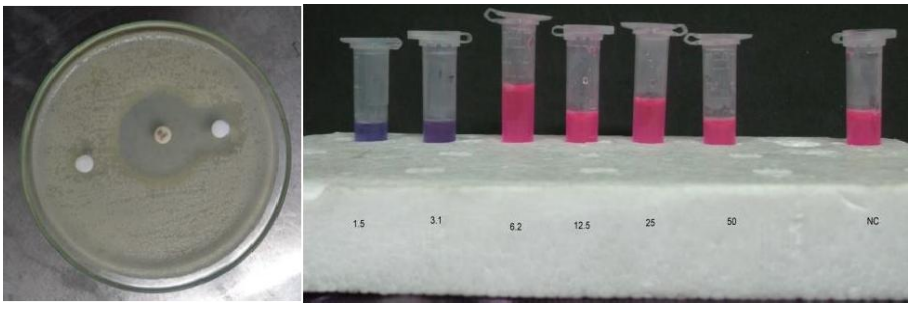
Figure 4. UV spectrum of (*E*)-*N*'-(3,4-dichlorobenzylidene)picolinohydrazide

Biological activity

Compound analyzed during this study were obtained within the condensation reaction of appropriate acid hydrazides. The results of our study indicated that examined compounds exhibited a good spectrum of antimicrobial activity against tested reference bacteria which is immune to methicillin. The metR S.aureus found to be sensitive to hydrazide derivative and therefore the the zone of inhibition is 22 mm where as immune to methicillin and sensitive to sublactam antibiotic. It showed very strong, mainly bactericidal effect towards Staphylococcus spp. The activity data expressed as MIC recorded as 1.5µg. an equivalent substances showed simultaneously the widest spectrum of antimicrobial activity against all tested reference Gram-positive and Gram-negative bacteria and fungi (40). Interpretation of the FICI was as follows: FICI ≤ 0.5 synergy; FICI > 0.5–1 additivity; FICI > 1–4 indifference and FICI > 4 antagonism. The FIC 0.6 INDICATES additive property of drug. The newly synthesized hydrazide is in a position to mix with the lipophilic layer so as to reinforce the membrane permeability of the Gram-positive bacteria. The lipid membrane surrounding the cell favours the passage of only lipid soluble (43)Table 3.Minimum inhibitory concentration of synthesized compound

Concentration	50	25	12.5	6.2	3.1	1.5	FIC
MIC A	+	+	+	+	-	+	
MIC B	+	+	+	-	+	+	
MIC A+B	+	+	+	+	-	-	0.4
MIC B+A	+	+	+	-	-	-	0.24

Plate 3. Antibacterial and MIC Study



CONCLUSION

It deals with synthesis and characterization 3,4 dichloro benzaldehyde) pyridine dicarboxylic acid hydrazide. the basic analysis shows the presence of nitrogen is confirmed by using sodium fusion extract.The FT-IR spectral study information. The frequencies around ν 3393 and 1603 cm-1 confirm the presence of amide group and thiocarbonyl group. The 1H and 13C NMR spectral studies of the ligand THC. The signals appeared in both the spectra give the precise position of every proton and carbon respectively needless to say . In mass spectral study of the ligand THCis discussed. The compounds we obtained were identified on the idea of 1H NMR and 13C NMR spectroscopy. The in vitro screening of antimicrobial properties of synthesized compounds revealed a good spectrum of antimicrobial activity.schiff bases derived from of mono hydrazide showed higher antibacterial activity than the quality and also found to be synergistic with betlactam inhibitor indicate that the compound is extremely promising antibacterial agent. In my future, I even have do the biological studies like antimicrobial activities, anti-cancer activities and anti-oxidant activities for synthesized THC

BIBLOGRAPHY

1. Silva GAA, Costa LMM, Brito FCF, Miranda ALP, Barreiroa EJ, Fragaa CAM. Bioorg. Med. Chem. 2004, 12, 3149–3158.
2. Ha S. T., Ong L. K., Ong S. T. *Chinese Chemical Letters*, vol. 20, no. 7, pp. 767–770, 2009.
3. Lingala, S., R. Nerella and K.R.S.S. Rao,. Pharm. Chem., 2011, 3: 344-352.
4. Cai, S., K. Sato, T. Shimizu, S. Yamabe, M. Hiraki, C. Sano and H. Tomioka, J. Antimicrob. Chemother,2006. ., 57: 85-93.
5. Przybylski P, Huczynski A, Pyta K, Brzezinski B and Bartl F 2009 Journal Org. Chem. 13 124
6. Sztanke K,. Pasternak K, Rzymowska J., Sztanke M., Kandefer Szerszen M. , Bioorg. Med. Chem. 15 (2007) 2837
7. Vicini P, Zani F, Cozzini P, Doytchinova I. Hydrazones of 1,2-benzisothiazole hydrazides: sy[2002]. GAA Silva;
8. Turan-Zitouni, G.; Zdemer, A.O.; Kaplancikli, Z.A.; Benkli, K.; Chevallet, P.; Akalin, G. Synthesis and antituberculosis activity of new thiazolylhydrazone derivatives. Eur. J. Med. Chem., 2008, 43, 981-985.
9. J. A. Fallas, L. González, and I. Corral, “Density functional theory rationalization of the substituent effects in trifluoromethyl-pyridinol derivatives,” *Tetrahedron*, vol. 65, no. 1, pp. 232–293, 2009.
10. Rollas S., Gülerman N., Erdeniz H. Synthesis and antimicrobial activity of some new hydrazones of 4-fluorobenzoic acid hydrazide and 3-acetyl-2,5-disubstituted-1,3,4-oxadiazolines. Farmaco. 2002;57:171–174.

11. FathyA.Yessin and Amal F.Seleim.*journal of pharma chemistry*.(2013),5(3);1-7.

12.T.A yousef,G.M abuAL-Zahab,M.A.A safaan.*Journal of molecular chemistry*,(2019);564-575.

13. Maisara Abdul Kadir, Nafisah Mansor& Uwaisulqarni M. Iomsan.*Journal of organic chemistry*,(2017),46(5);725-731.

14.p.Kanchana,Bhuvaneswari V,A.sangeetha.*journal of chemistry application*,(2014),6;121-131.

15. Dongfang Xu,Yanming Xu, Ningning cheng,Xianan Zhou,yang shi$Qizhuang He.*journal of coordination chemistry*,(2010),63(10);2360-2369.

16. Maria Carla Bosco, Annamaria Rapisarda, Stefano Massazza, Giovanni Melillo, Howard Young and Luigi Varesio.*journal of immunology*,(2000),164(6);3283-3291.

17. Peter comba,Maik jokob,Katharina Ruck,Hubert Wadepohl.*journal of organic chemistry*.(2018)481;98-105.

18. Krishna,K.Rama,Ananta,M.venkata Subba.*journal of Indian chemistry*.(2012),51(4);571-579.

19. Hisanori ueri,Trevor K.Ellis,Collin H.Martin,Vadim A.Soloshonok.*journal of European chemistry*.(2003),10;1954-1957.

20. Prarthana devi,SarahM.Barry,Kate M.Houlihan,Michael J.Murphy,Peter Turner,Paul Jensen&Peter J.Rutledge.*journal of organic chemistry*.(2015),37(4);542-551.

21. Jim C. Spain, Shirley F. Nishino, Bernard Witholt, Loon-Seng Tan, Wouter A. Duetz, *Journal Environmental Microbiology*(2003),69(7);4037-4042.

22. Di Li And Guo-Qing Zhong.*Journal Of Scientific World*,(2014),14;1-7

23. Mohareb R.M ,Sharkawy ,K.A Hussein M.M And Sehrawi H.M. *Journal Of Pharmaceutical Sciences*,(2010). 2(4);185-196.

24. Afzal Basha Shaik Rajendra Prasad Yejella,and Shahanaaz Shaik.*jounal of medicinal chemistry*(2017) 1-14

25. Semih Kurban , Nahide Gulsah Deniz , Cigdem Sayil , Mustafa Ozyurek , Kubilay Guclu , Maryna Stasevych , Viktor Zvarych , Olena Komarovska-Porokhnyavet , and Volodymyr Novikov.*journal of heteroatom chemistry*,(2019)1-12

26. kandemirli fatma,shvets nathaly,rollas sevim,anatholy dimoglo,oruc elcin,unsalan seda,.*journal of medicinal chemistry*(2006),41(11);1253-1261.(16)

27. Mansur Nassiri Koopaei, Mohammad Javad Assarzadeh,,Ali Almasirad,, Seyedeh Farnaz Ghasemi-Niri,, Mohsen Amini,,Abbas Kebriaeezadeh,,Nasser Nassiri Koopaei, Maryam Ghadimi, and Arash Tabeijournal .*journal of pharmaceutical research*,(2013),12(4);721-727.

28. Haitao wang,Binglian bai,dongmai pang,zhong fei zou,li xuan,fan li.*journal of liquid crystals*(2008),33(4);333-338

29. sheng-huei Hsiao,li-min chang.*journal of polymer chemistry*,(2000),38(9);1599-1608

30.Grant.R.S,CogganS.E,SmytheG.A.*Journal of tryptophan research*,(2009) 2;71-79.

31.A.PadmajaT.PayaniG. DinneswaraReddyV.Padmavathi,*journal of medicinal chemistry,(*2009),44(11);4557-4566.

32. Ahmed Ozdemir,Gulhan turan-zitouni,Zafer asim kaplancikli,yagmur Tunali.*journal of medicinal chemistry*,(2009)24(3);825-831.

33. Basim Hatim Al-Zaidi, Mohammed Mujbel Hasson, Ahmad Hussein Ismail.*journal of pharmaceutical science.(*2019).9(4);45-57.

34. Anant Prakash, Devjani Adhikari,*journal of chem Tech research*,(2011),3(4);1891-1896.

35. Rafat M.Mohareb,Daisy H.Fleita ola K.Sakka.*journal of medicinal chemistry*(2011),16(1);16-27.

36. Roghayyeh asgharzadeh,Gholamhassan imanzadeh,Zahra soltanzadeh.*journal of green chemistry*(2017).10(2);80-87

37. PeterComba,MaikJakob,KatharinaRück,HubertWadepohl.*Journal of medicinal chemistry*.(2018),48198-105.

38. Rapisarda A,Reffo G,Massazzas, pastorino S, Varesio. *journal of medicine chemistry*.(2003);55-65.

39. Oladipo I (2013*). Journal of Pharmaceutical and Biological Sciences*. 1. 34-39.

40. Kumar D., Kumar N.M., Ghosh S., Shah K.. Bioorg. Med. Che. Lett. 2012;22:212–215.
41. Clinical Laboratory Standard Institute (CLSI), *Reference Method for Broth Dilution Antifungal Susceptibility Testing of Yeasts*, Approved Standards, CLSI Document M27-2A, CLSI, Philadelphia, Pa, USA, 2nd edition, 2002.
42. Geary W. J. *Coordination Chemistry Reviews*, vol. 7, no. 1, pp. 81–122, 1971.
43. Mulligan M. E., K. A. Murray-Leisure, B. S. Ribner. *American Journal of Medicine*, vol. 94, no. 3, pp. 313–328, 1993.