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Synthesis, Characterization, and Antioxidant Activities of N-(Diphenylmethyene) hydrazine carbothiohydrazide a new Schiff Bases Derived from Substituted benzophenones and their Complexes

Dr. Sanjay Kumar
Department of Chemistry, Patna University, Patna

I. INTRODUCTION

The use of metals for medicinal purposes has been exploited since very ancient times; for instance, silver has been used as a disinfectant agent for water and milk for thousands of years[1] Similarly, the application of gold in medicine can be dated back to 2500 BC and throughout the entire history of humanity it is possible to find traces of several applications of this noble metal to treat various diseases[2]. Indeed, in the 19th century the complex dicyanoaurate(I) ($K[Au(CN)_2]$) was proposed by Koch for its bacteriostatic properties to fight tubercle bacillus, while in the 20th century, gold complexes were introduced to treat rheumatoid arthritis, leading to the approval of Auranofin by FDA in 1985. This latter compound is today the reference compound for gold complexes and, on the ground of the so-called repurposing strategy, has been proposed as promising anticancer agent and entered several clinical trials in US, some of which are still ongoing [3,4].

Beyond silver and gold, several bismuth, antimony and mercury compounds have been employed to combat bacterial and parasitic diseases. In this view, bismuth salts and antimony complexes have been proposed and used for eradication of Helicobacter pylori infection, and against leishmaniasis respectively [5]. Also, arsenic, in the form of trioxide (As_2O_3), is nowadays one of the reference drugs for the treatment of acute promyelocytic leukemia [6]. Several inorganic complexes are also used for diagnostic medicine as in the case of gadolinium-based contrast agents, ^{99m}Tc compounds for myocardial perfusion imaging [7] and ^{64}Cu for PET imaging [8].

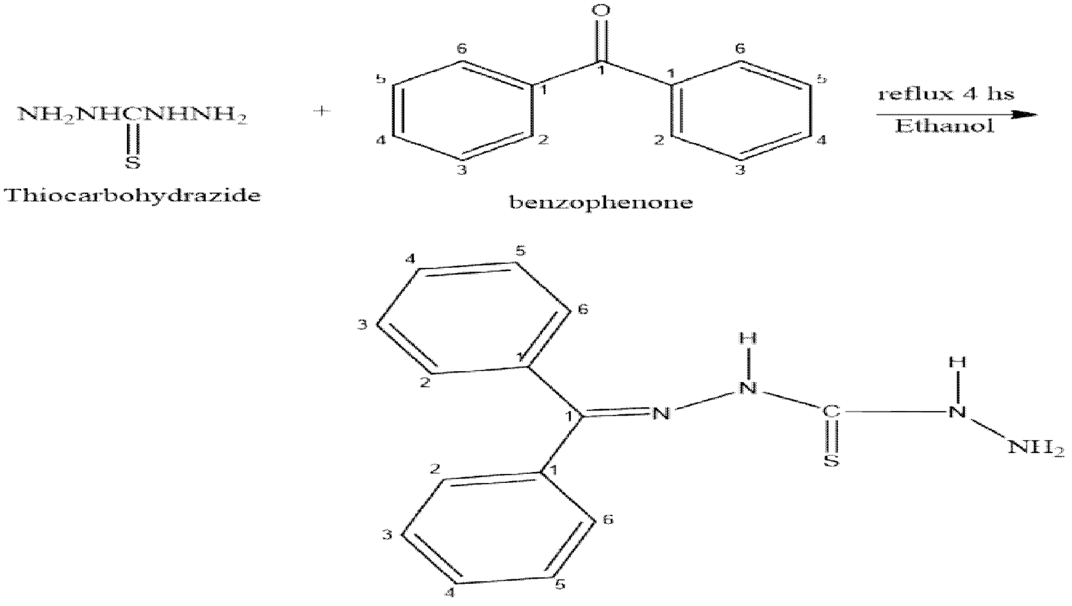
However, the most important impulse to the research of metal-based drugs with medicinal properties came from the serendipitous discovery of the antitumor features of cisplatin by Rosenberg and Loretta Van Camp in 1965 [9]. Cisplatin was approved in 1978 by the FDA, and this event triggered enormous efforts by scientists in search of innovative and ameliorated inorganic anticancer drugs, leading to the approval worldwide of carboplatin and oxaliplatin analogs. This makes platinum-based drugs an essential arsenal for first- and second-line anticancer chemotherapy used in about 50% of clinical protocols [10].

Metals complexes offer an extremely versatile and reliable tool for the development of improved medicinal compounds. Indeed, it is possible to finely tune the chemical properties of these complexes by controlling the metal center oxidation state and selecting the most appropriate ligands for each application. Thus, it is not surprising that the challenge in the development of innovative and improved metal-based drugs largely overlaps with the development of innovative and ameliorated ligands for the functional metal element.

Among several ligands, thiosemicarbazones (TSCs), are a very attractive class of metal-chelating ligands, able to coordinate many transition metals through the sulfur as well as the azomethinic nitrogen atoms [11]. They can act as N, S-multidentate ligands, and moreover, it is possible to modulate the binding properties/stoichiometries through the insertion of other heteroatoms into the backbone structure (i.e., phenolic or pyridyl moieties). They have a great variety of biological properties, both as free ligands and as metal complexes, and several studies have been published reporting on thiosemicarbazone-based complexes with medicinal applications [12-21].

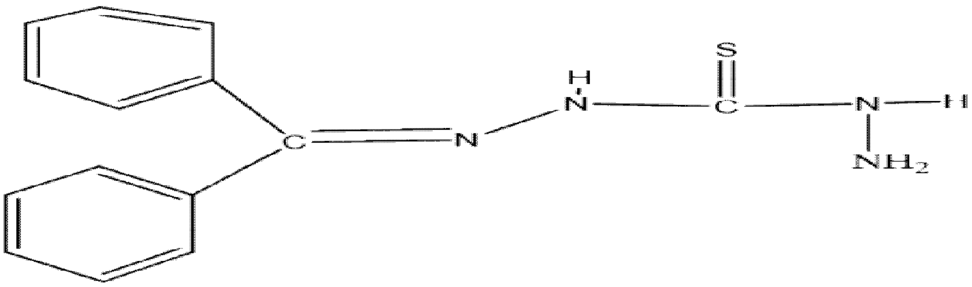
Beyond TSCs, in recent years, there has been growing interest in the coordination chemistry of thiocarbohydrazones (TCHs) compounds that share the general formula depicted in Scheme 1a–c and that can be considered the higher homologues of TSCs (Scheme 1d).

The first synthesis of these systems is dated 1925 and described the condensation of ketones and aldehydes with thiocarbohydrazide [22]. The earliest employ of this derivatives relied the hetero-ring closure of the aldehyde derived thiocarbohydrazones [22-24].
The condensation of benzophenone with thiocarbohydrazide in ethanol acidified with a few drop of glacial acetic acid results in the formation of thiocarbohydrazone,N (diphenylmethenelene) hydrazine thiocarbohydrazide (DTCH).



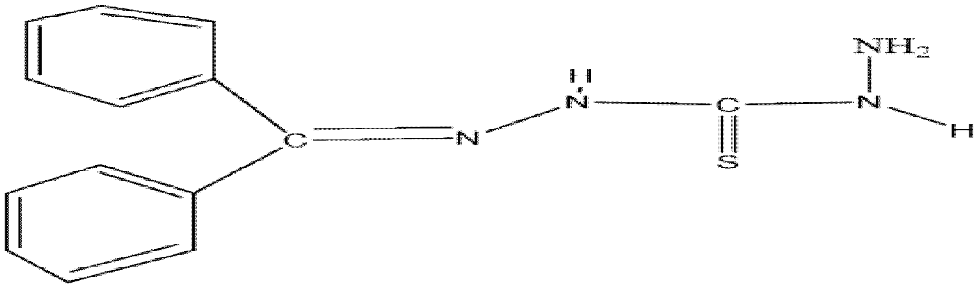
N'-(diphenylmethylene)hydrazinecarbothiohydrazide

N-(Diphenylmethyene) hydrazine carbothiohydrazide (DTCH) has different donor sites and it can exist in the following orientations of donor sites (A and B) also.



N'-(diphenylmethylene)hydrazinecarbothiohydrazide

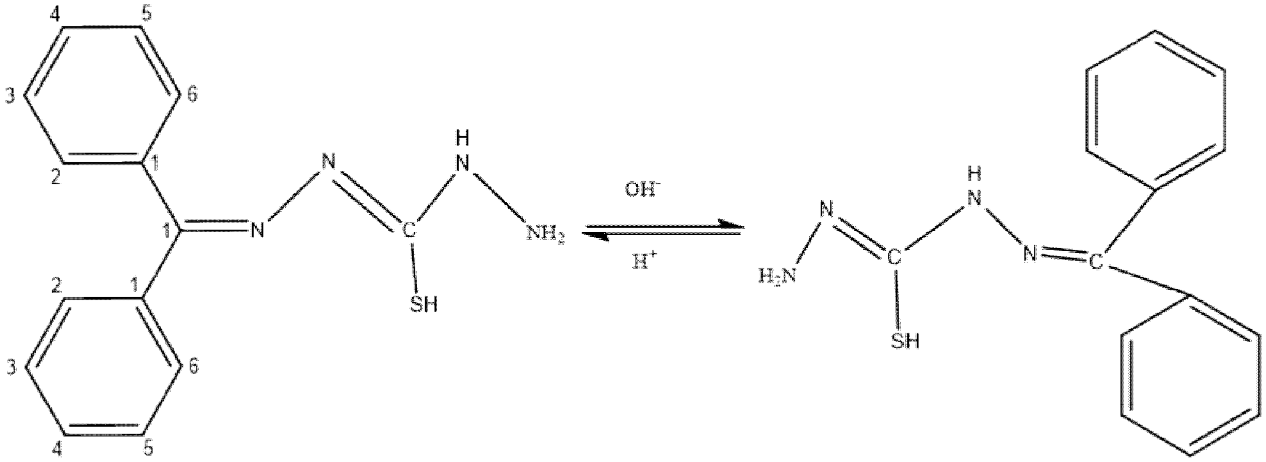
(A)



N'-(diphenylmethylene)hydrazinecarbothiohydrazide

(B)

Due to the bulky size of diphenylketone, the hydrozone formed DTCH is expected to get stabilises with only one ketone molecule. As expected bis(diphenylmethyle) thiohydrazide could be obtained by rigorous refluxing in ethanol in slightly acidic medium. The ligand DTC contains thiocarbohydrazide in two or three orientation of –NH-NH_2 and thiocarbonyl group (>C=S).The molecule in neutral or acidic medium expected exist in thione tautomer. The thiol tautomer will be expected to be formed in basic medium(as shown below).



(*Z*)-2-(diphenylmethylene)hydrazine-1-carbohydrazonothioic acid

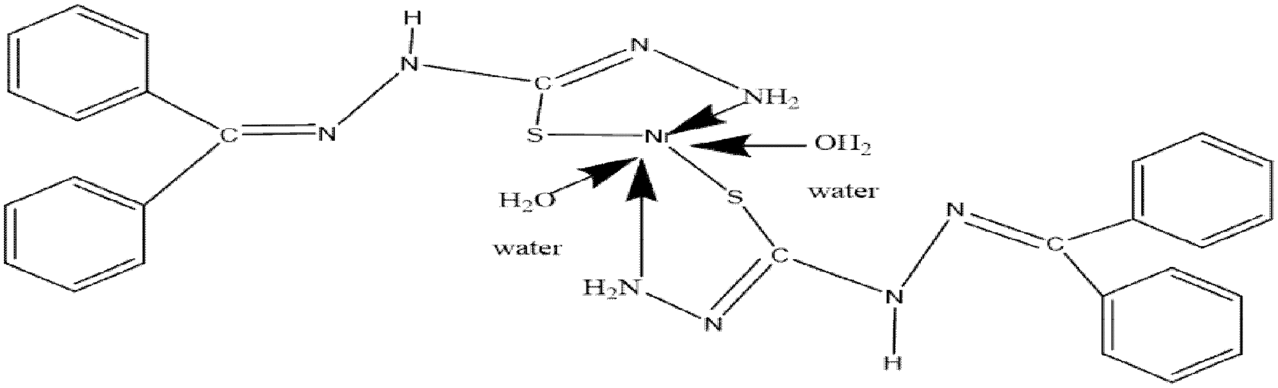
In neutral or slightly acidic medium it is expected that the ligand will coordinate as bidental neutral molecule. The orientation of third donor sites to coordinate with the same metal as tridentate donor molecule is improbable due to steric reason.The ligand has been used to prepare complexes of Cu(II),Ni(II),Zn(II),Cd(II),Co(II) and Mn(II) .It has been found that the ligand fails to form pure Mn(II) complexes both in neutral and basic medium.

EXPERIMENTAL

Preparation of complexes with Co(II) and Ni(II) with DTCH.

Diaquo bis [diphenyl ketone thio carbo hydrazone Co(II)] and Diaquo bis [diphenyl ketone thio carbo hydra zone Ni(II)] $[M(DTCH)_2(H_2O)_2]$

Procedure:- About 0.1 milli mole metal chloride was dissolved in 20 ml aqueous ethanol and treated with 0.21 milli mole of ligand (DTCH) in hot ethanol. The mixed solution were heated on steam bath for fifteen minutes and p^H of the solution was raised by adding dilute ammonia drop wise when the complex was digested on steam bath for ten to fifteen minutes and allow to cool at room temperature. The complex were filtered on a Buckner funnel and washed with cold aqueous ethanol (20%) and dried in a desiccator for two to three days. The dried sample were analysed and their magnetic moment value were recorded on Gouy balance at room temperature. The analytical results magnetic moment value of complexes are recorded in Table-A.



bis(((*Z*)-(2-(diphenylmethylene)hydrazineyl)(hydrazineylidene)methyl)thio)nickel

TABLE - A

ANALYTICAL RESULTS AND COLOUR OF THE COMPLEXES

S. No.	Complex	% Element: Found/ (Calc .)						μ_{eff}
		COLOUR	M	C	N	S	H	$30\text{-}31^{0}$C in B.M
1	[DTCH] LIGAND	Yellow		62.17	21.05	11.25	5.16	Diamagnetic
2	$[Ni(DTCH)_2(H_2O)_2]$	Yellowish brown	19.37	51.23	17.65	9.78	1.79	3.42

TABLE — B

SOLUBILITY AND ELECTCRICAL CONDUCTANCE DATA (31^{o} C)

Complex	Qualitative value in solvents				Molar conductance value Ohm $^{-1}$mol^{-1} cm^{2}{DMF}
	Water	Methanol	Benzene	DMF	
[DTCH]	INS	SL S	Sl S	FS	12
$[Ni(DTCH)_2(H_2O)_2]$	INS	SL S	SIS	FS	6

TABLE-IR

I.R. SPECTRAL BANDS OF LIGAND

S.No	Band Positions in cm^{-1}	Assignments
1	3228.69	√(NH_2)
2	3149.69	√(NH)
3	3103.53	√(NH_2)
4	2924.77	√(C-H) phenyl ring
5	1603.79	√(C=N)
6	1498.49	δ(NH) Thioamide I
7	1443.34	δ(C-H) phenyl group skeletal
8	1319.59	δ(C-H)
9	1297.25	√(C-C)
10	1235.63	√(N-N)
11	1216.48	√(C-N)
12	1198.06	√(C-N)
13	1069.40	√(C=S)
14	953.65	δ(C-C) Phenyl rings + Phenyl rings(Ph-C)
15	917.96	δ(C-C) Phenyl rings + Phenyl rings(Ph-C)
16	826.67	δ(C-C) Phenyl rings + Phenyl rings(Ph-C)
17	768.36	Ortho substituted δ(C-H) vibration
18	692.28	Ortho substituted δ(C-H) vibration
19	668.36	δ(C-C)+ δ(N-N)+ring deformation vibration
20	650.02	δ(C-C)+ δ(N-N)+ring deformation vibration
21	626.07	δ(C-C)+ δ(N-N)+ring deformation vibration
22	454.83	δ(C-C)+ δ(N-N)+ring deformation vibration
23	419.48	δ(C-C)+ δ(N-N)+ring deformation vibration

TABLE-IR$_3$

I.R. SPECTRAL BANDS OF COMPLEX

S.No	Band Positions in cm^{-1}	Assignments
1	3421.09	√(H_2O)
2	3246.34	√(NH_2)
3	3171.12	√(NH)
4	3029.90	√(C-H) phenyl ring
5	2930.86	√(C-H) phenyl ring
6	1635.68	√(C=N) ketoimine
7	1484.29	δ(NH) thioamide I
8	1441.05	phenyl ring skeletal vibration
9	1313.88	δ(C-H) phenyl ring
10	1297.42	Phenyl ring skeletal vibration.
11	1270.07	Thioamide II
12	1231.66	Phenyl ring skeletal vibration
13	1191.92	Phenyl ring skeletal vibration
14	1124.50	√(N-N) Phenyl ring skeletal vibration
15	1015.81	√(C-N) Phenyl ring skeletal vibration
16	952.06	√(C=S)
17	907.78	Phenyl ring skeletal vibration
18	824.61	Ortho substituted phenyl ring
19	773.37	Ortho substituted phenyl ring
20	758.55	δ(C-H) vibration
21	724.94	√(C-S) deprotonated thiol
22	682.58	Ring deformation vibration
23	655.73	Ring deformation vibration
24	625.21	Ring deformation vibration
25	482.63	Ring deformation vibration
26	454.63	Ring deformation vibration
27	419.62	√(M-N) $_{+}$√(M-O)

II. RESULTS AND DISCUSSION

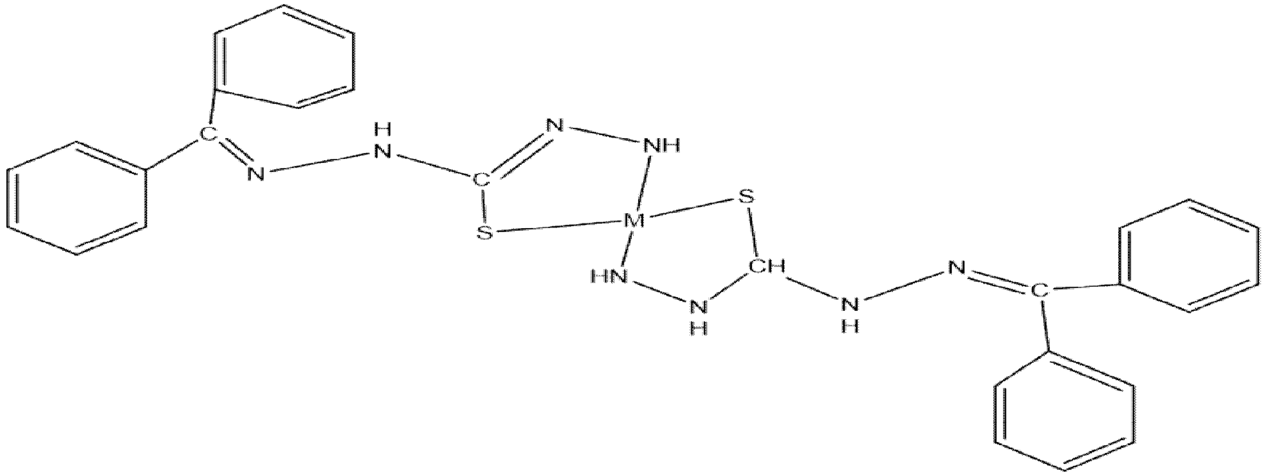
Diphenylketone thiocarbohydrazone (DTCH).

N-(diphenylmethylene) hydrazine carbothiohydrazide contain two bulky phenyl group adjacent to hydrazinoyl methylene (>C=N-) nitrogen and it is expected that (>C=N-) should be reluctant to form coordinate bond with metal atom. The thiol sulphur and terminal hydrazine nitrogen (NH_2) is suitable site to form chelate ring with metal atom. The elemental analysis of complexes of bivalent metal atom Co(II),Ni(II),Cu(II),Zn(II),Cd(II) and Hg(II) corresponds to composition $M(DTC)_2$ .nH_2O(n=2 or zero). The complexes are almost insoluble in cold and hot water but slightly dissolve in hot ethanol and methanol. These complexes however dissolve in appreciably in Dimethyl formamide and dimethyl sulphoxide. The electrical conductance value of these complexes were determined qualitatively to as certain it's non ionic character. The electrical conductance value at 31-32^{0}c in dimethyl formide were found almost negligible (6-8 ohm^{-1}cm^{-2}) supporting their non-ion character. The magnetic susceptibility of these complexes were determined by Gouy process at room temperature (31.5-32^{o}c) as expected Zn(II),Cd(II) and Hg(II)(d^{10}electronic system) complexes are diamagnetic and Co(II),Ni(II) and Cu(II) complexes are paramagnetic system. The magnetic susceptibility value of Co(II) complex $[Co(DTC)_2(H_20]$ was found 4.86B.M and that of Ni(II) complexes $[Ni(DTC)_2(H_2O)]$ value was 3.42 BM. TheMagnetic moment of Co(II) and Ni(II) within the range expected for octahedral complexes of respective metal ion.

The magnetic moment value ofCu(II) complexes $[Cu(DTC)_2(H_2O](1.85B.M)$ was also similar to octahedral copper(II) complexes. The complexes are stable at room temperature and up to temperature (110-120^{o}c). On heated aqua complexes $[M(DTC)_2(H_2O)[M=Co(II),Ni(II)$ and $Cu(II)]$ starts losing water and become almost anhydrous at (160-180^{o}c). The retaletion of water molecule by complexes below 120^{o}c suggested the co-ordination nature of water molecule. The presence of water molecule in complexes is also supported by a broad band near 3320-3430 cm^{-1} in IR spectra of complexes. The complexes on heating above 230-250^{o}c started decomposition suggested that hydrazine part get detached from phenyl part. The infrared spectra of complexes and free ligands were determined in KBr optics. The IR spectrum of ligands shows NH_2 and NH stretching bands at 3228, 3149 and 2924 cm^{-1}. The phenyl ring C-H stretch assigned to a band at 3103 cm^{-1}.The methylene part √(C=N) stretch of the ligand is observed at 1443, 1319,1249 and 1235 cm^{-1}.are attributed to skeletal vibrations of phenyl ring. The I.R bands located at 1216,1198,1069,1067 and 919 cm^{-1}are attributed √(C-N), √(N-N) and √(K-C) vibration of free ligand molecule. The I.R band at 952 cm^{-1} of free ligand is assigned to thiol group √(C=S) vibration which disappear in its complexes and shifted to lower frequency. The IR bands of ligand located at 826,768,692,668 cm^{-1} are assigned to phenyl ring out of plane (C-H) stretches and IR bands at 1635 cm^{-1} (Fig-IR-2) which is due to √(C=N) band to higher wave number supported it is free and not the bonding site of ligand molecule. The $\delta(NH_2)$ of ligand located at 1498cm^{-1} is shifted to lower frequency and observed near 1484cm^{-1} suggested to coordinated nature of terminal hydrazine NH_2 nitrogen. The IR bands of free ligands has been found shifted to some extent in complexes (prominent bands are shown in IR Table$^{1-5}$).The electronic spectrum of ligand in ethanol shows three electronic transitions located at 213, 254 and 312cm^{-1} assigned to σ-σ*,π-π* and n-π* transition. The n-π* transition located at 312cm^{-1} is fairly weak as it is spin forbidden transition. The electronic absorption spectrum of complexes shows strong absorption below 420cm^{-1} attributable from charge transfer transition and no d-d transition could be located definitely in solution.

III. CONCLUSIONS

Thus on basis of electric conductance, magnetic susceptibility and I.R. spectral studies the following structures are tantively suggested for the complexes $M(DTCH)_2.nH_2O$



(M=Zn^{++},Cd^{++}or Hg^{++})

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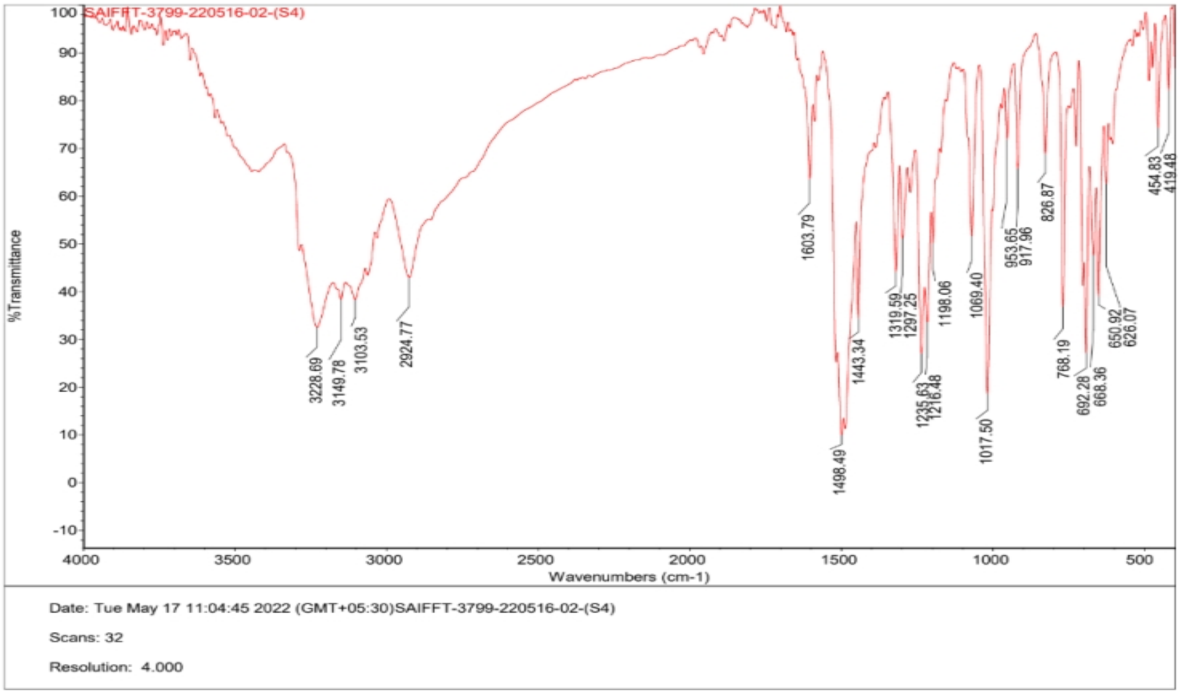

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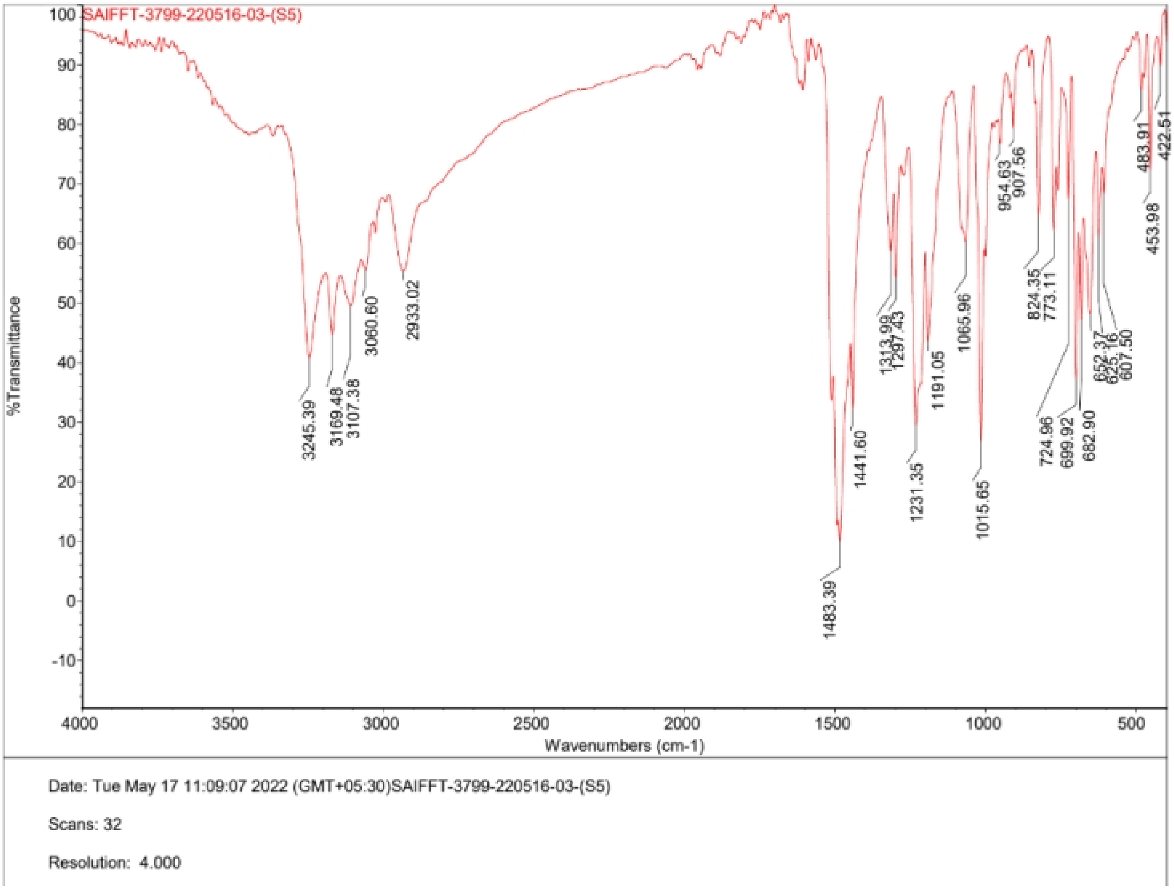

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