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SYNTHESIS, PHYSICO-CHEMICAL ANALYSIS AND BIOLOGICAL STUDIES OF POTENT MANNICH BASE [(4-CHLORO-PHENYL)-MORPHOLIN-4-YL-METHYL] THIOUREA

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ABSTRACT

The organic action of Mannich bases, a primarily heterogeneous class of synthetic mixtures that are created from different substrates through the presentation of an amino methyl work through the Mannich response, is overviewed, with accentuation on the connection among structure and natural action. The survey covers broadly the writing reports that have uncovered Mannich bases as anticancer and cytotoxic activity, or mixtures with possible antibacterial and antifungal movement somewhat recently. The review contains additionally an intensive inclusion of anticonvulsant, calming, pain relieving and cell reinforcement exercises of Mannich bases.

The oddity of the current work is the blend of some N-Mannich bases. Using the above compound as ligand, metal complexes were prepared and their designs were developed by essential assessments, IR, UV-vis spectra, molar conductivity and alluring second examinations. Further, the ligand and the metal complexes were gone after for antimicrobial activity and atomic docking studies to consider the association of Morpholine subordinates against the receptor Extended Spectrum Beta Lactamase (ESBL) of protein activity. The antibacterial exercises of the recently blended mixtures were assessed and corresponded with their physicochemical properties. Antimicrobial examinations uncovered that metal structures have higher activity and discovered to be more strong than those of the metal salts and

ligands. The sub-nuclear docking results propose a decent hydrogen security association among GLN and HIS shows the higher loving of ligand than standard. Docking study showed a solid hydrophobic collaboration. Strong Vander wall's interactions are additionally seen with the carbon of ketone, nitrogen of amine and sulphur of thiourea. The review gives in the end a concise outline of the capability of Mannich bases as inhibitors of different chemicals or ligands for a few receptors.

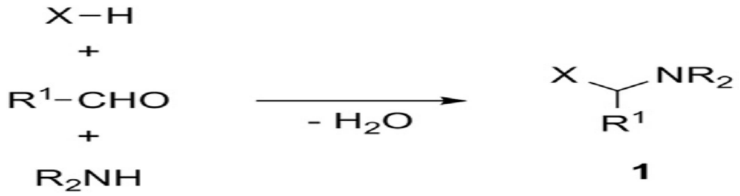
Keywords: Morpholine, Beta Lactamase, Atomic docking

INTRODUCTION

The classical Mannich reaction, a three-component condensation between structurally diverse substrates (XeH) containing at least one active hydrogen atom, an aldehyde component (generally R1-CHO) and an amine reagent leads to a class of compounds generally known as Mannich bases 1 **(Scheme 1)**. Because Mannich bases may be regarded as derivatives of the substrate obtained through substitution by an amino alkyl moiety, Mannich reactions are also known as amino alkylation reactions. In the particular instance when formaldehyde is employed as aldehyde component, the substrate is converted into the corresponding Mannich base through an aminomethylation process. Although primary amines

and even ammonia (in the form of an ammonium salt) may be employed as amine reagents in aminomethylations or aminoalkylations, secondary aliphatic amines (R2NH) are the most commonly encountered as amine reagents in the Mannich reaction. As formaldehyde is used to a great extent as aldehyde component in the Mannich reaction, the structural diversity of Mannich bases stems primarily from the miscellaneous types of the substrates that can be subjected to aminomethylation, and secondarily from the variety of amine reagents that can be potentially employed in the Mannich reaction.

A general classification of the most common types of Mannich bases with respect of the substrates from which they derive and the nature of the atom substituted by the aminomethyl function is given in **Figure 1**.



Scheme 1: General representation of the Mannich reaction

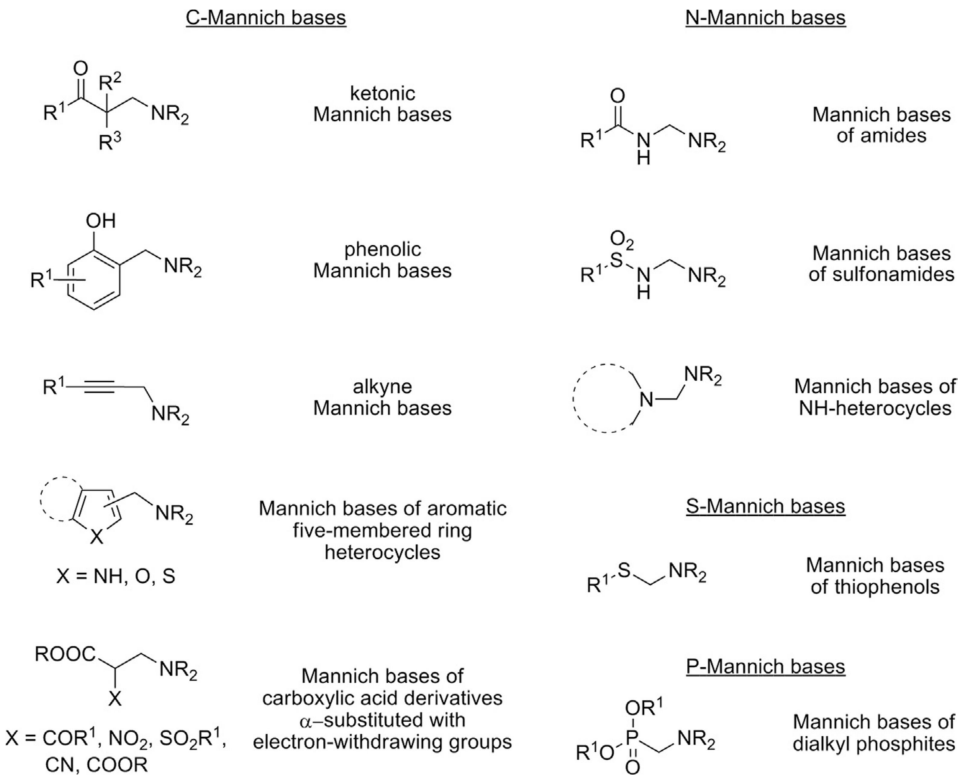


Figure 1: Examples of various types of Mannich bases

Mannich bases have found numerous practical applications in the treatment of natural macromolecular materials such as leather, paper and textiles, the production of synthetic polymers, as additives used by the petroleum industry, as products used in water treatment, analytical reagents, cosmetics, dyes, etc. **[1]**.

Aminomethylation may increase the hydrophilic properties of drugs through the introduction of a polar function in their structure, the long-known rolicycline being one of the most common examples **[2]**.

The lipophilic properties of a drug could be tailored through a Mannich reaction if the appropriate amine reagent is employed **[3]**. In addition, the aminomethylated drugs could act as prodrugs, releasing the active substance under controlled hydrolytic conditions via deaminomethylation **[4]** or deamination **[5]**.

Anticancer and cytotoxic activity

Anticancer properties and cytotoxicity of ketonic Mannich bases (with an emphasis on Mannich bases derived from acetophenones **[6]** and of structurally related α,β-unsaturated ketones **[7]** were reviewed 15 years ago. These two groups of compounds were shown to exert their cytotoxic action through the alkylation of cellular thiols such as glutathione or cysteine, and may be useful in sensitizing tumor cells to antineoplastic agents, and even reverse drug resistance **[8]**. It is

therefore no surprise that compounds having both a ketonic Mannich base moiety and an activated unsaturated carbon carbon double bond in their structure (for example, Mannich bases of chalcones) have been considered as candidates for the evaluation of the sequential cytotoxicity theory **[9]**.

Docking study

Computational methodologies have become a crucial component of many drug discovery programs, from hit identification to lead optimization. One key methodology is docking of small molecules to protein binding sites, pioneered during the early 1980s. The docking process involves the prediction of ligand conformation and orientation (or posing) within a targeted binding site. The two aims of docking studies are accurate structural modeling and correct prediction of activity. Docking studies have become a scientific approach for the study of macromolecular structures and interactions. Macromolecular modeling by docking studies provides most detailed possible view of drug–receptor interaction and has created a new rational approach to drug design, where the structure of drug is designed based on its fit to three dimensional structures of a receptor site. On the basis of docking scores one can predict the amount of activity that will be shown by compounds. To conform the mechanism of antifungal activity of synthesized compounds, docking of synthesized compounds was performed. For docking study Vlife MDS 3.5 was used **[10]**.

MATERIALS AND METHODS:

The dissolving motivations behind the consolidated blends were settled using a condensing point mechanical gathering and are uncorrected. Completing of the response and the prudence of the organized compound were discovered by TLC using the dissolvable structure Chloroform and Methanol and the spots were recognize using UV-Chamber. The fused compound were depicted using MB 3000 game plan FT-IR Spectrophotometer by KBr-pellet procedure **[11]**. 1H-NMR spectra was recorded on AMX-400 NMR spectrophotometer at 400 MHz using DMSO-d6 as the dissolvable and tetra methyl silane (TMS) as an internal standard. The blend shifts are clarified in δ ppm. Mix of the moderate and target blends was developed by the means portrayed in the **Schemes 2 and 3**.

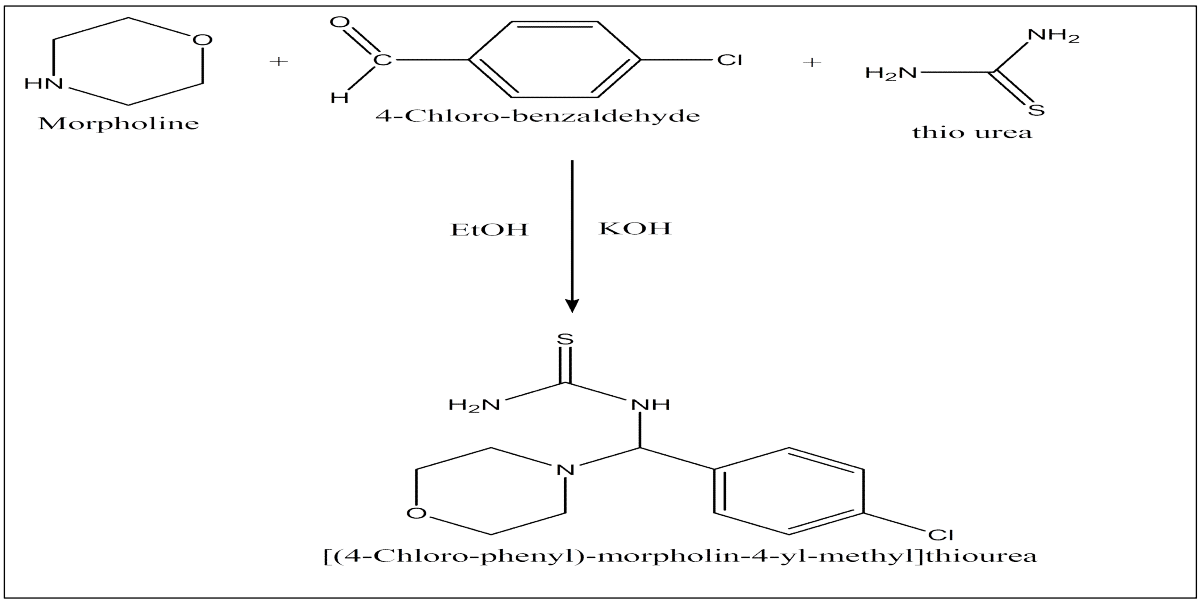
Synthesis of Mannich Base - [(4-Chloro-phenyl)-Morpholin-4-yl-methyl]Thiourea

10 m moles (1.70 g) of Morpholine were broken up in a 15 mL of Ethanol in a 100 mL 2 neck round base carafe furnished with a reflux condenser ensured by a calcium chloride drying tube and a fast fit

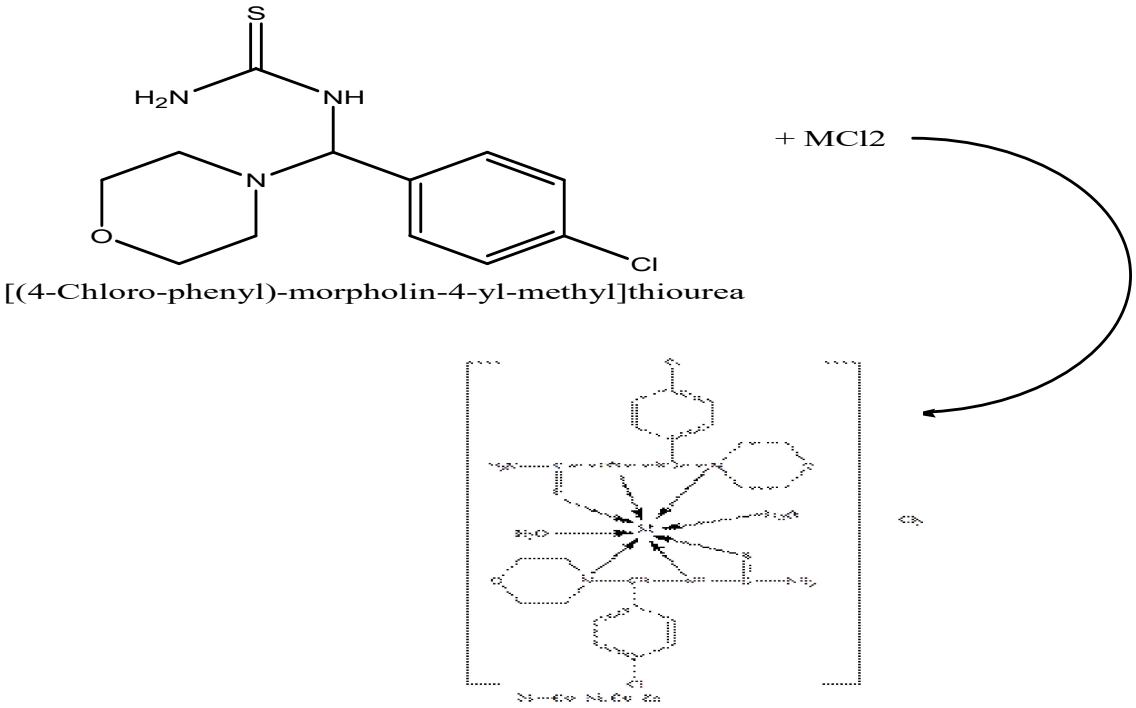
thermometer, then, at that point 1.5 g of thiourea and 10 m mole (1.36 g) of 4-Chlorobenzaldehyde were disintegrated with consistent mixing, to this response blend 0.2 to 0.4 mL HCl were added with cooling on an ice shower **[12]**. Yellow shading strong isolates soon after the expansion of HCl. The combinations was mixed for 1-2 hours at room temperature. The response combination was refluxed on a water shower at 90-95˚C for3-4 hours, the response blend was inspected by TLC with time to time till fulfilment **[13]**. The overabundance of dissolvable was eliminated under decreased pressing factor, the item was washed with water and 95% ethanol individually.

Synthesis of transition metal complexes:

A solution of 0.1 M of MCl2 (M=Co, Ni, Cu and Zn) in methanol and 0.2 M of [(4-Chloro-phenyl)- Morpholin-4-yl-methyl]Thiourea in ethanol were added to a round-lined carafe and mixed well with using appealing stirrer for two hours **[14]**. The complex outlined was isolated, washed with refined water and hardened from absolute alcohol.



Scheme – 2 – Synthesis of [(4-Chloro-phenyl)-Morpholin-4-yl-methyl]Thiourea



[(4-Chloro-phenyl)-morpholin-4-yl-methyl]thiourea

Scheme – 3 – Synthesis of transition metal complexes

Biological activity

Antimicrobial tests

Invitro antimicrobial activities of the ligand, buildings and free metal particles were surveyed by the plate spread system against the microorganisms, for instance, Staphylococcus aureus, Bacillus subtilis, Escherichia coli, Pseudomonas aeruginosa, Aspergillus niger, Rhizoctonia bataicola. Ampicillin and Amphotericin B were used as standard for microorganisms and parasites **[15]**. The microbial isolates were kept up on agar slant at 4˚C. The strains were sub refined on new fitting agar plate in an incubator for 18 h going before any microbial test. The enhancement agar medium was masterminded and sanitized by means of autoclaving at 121˚C, 15 lbs pressure for 15 min and a while later aseptically purged the medium into the sterile petri plates and allowed to set the bacterial stock culture and these are cleaned on each petri plates by sterile buds. By then wells were made by well shaper **[16]**. The Kirby Bauer Agar (KBA) medium was used for the scattering inspects confirmation and Nutrient stock was used as microbial advancement medium. This strategy was repeated for each petri plate, by then the petri plates were agonized at 37˚C for about 24h. In the wake of bring forth, the plates were looked for the zone of limitation. The effect made by the model was differentiated and the effect conveyed by the positive control. Supplement agar (NA) was used for the sanctioning of

Bacillus species, while NA alone was used for various tiny life forms. Every one of the antimicrobial tests were noticed obviously and UV-spectrophotometric partner and the examinations were acted in triplicate **[17]**.

Atomic docking

Protein preparation [18]

Auto Dock is a set-up of automated docking gadget. It is planned to expect how little particles, for instance, substrates or drug up-and-comers, bind to a receptor of realized 3D construction. The protein recuperated from PDB data set. The protein design of Extended-territory β-lactamase (PDB ID: 4LEN). All water particles ousted from all protein structure and included with Kollmann charges was given out. The essentialness restricted protein was then saved in PDB plan. Using MGLTools-1.4.6 nonpolar hydrogens were mixed, Auto Dock atom type AD4 and Gasteiger charges were given out ultimately saved in protein.pdbqt plan **[19]**.

Ligand preparation

Construction of ligands were drawn using Chem Sketch, improved with 3D-calculation and the two-dimensional designs of made were changed over into 3-D construction using the open Babel plan molecule converter and saved in PDB position for Auto Dock closeness **[20]**. MGLTools-1.4.6. The Scripps Research Institute was used to change over ligand.pdb records to ligand.pdbqt archives.

Docking protocol-MGL tools [21]

Structure limit reports (protein.gpf) and docking limit records (ligand.dpf) have made using MGLTools-1.4.6. Receptor networks were created using 80x80x60 system centers in xyz with cross section isolating of 0.375 Å. Structure box was engaged co cemented ligand map types were made using autogrid4. Docking of macromolecule was performed using a test free essentialness limit and Lamarckian Genetic Algorithm, with a hidden people of 250 discretionarily situated individuals, a biggest number of 106 imperativeness appraisals, a change speed of 0.02, and a half and half speed of 0.80. 100 independent docking runs were performed for each ligand **[22]**. Results differentiating by 2.0 Å in positional root-mean square deviation (RMSD) were gathered and addressed by the result with the best free essentialness of definitive.

Docking protocol-Hex tools [23]

The nuclear docking between the target receptor and ligand was performed by Hex gadget. This mechanical assembly is intended for keen docking and can prepared to run in any functioning system. There are pushed frames in this instrument and it gives the imperativeness regards to every one of the models. The model can envision

in any constructions with docked limits **[24]**. The design for the ligand CMT can be envisioned in the phenol watcher and docked with the construction of Ebola disease and the target receptor for harm. The ligand structure was drawn by Chemsketch and presented to docking. Both the constructions were docked and demonstrated essentialness regards, for instance, E-max, E-min, E-shape, and E-complete. These still up in the air. The Net blames for number of headings not really settled. Finally, the results were taken a gander at reliant upon the docking limits **[25]**.

RESULTS AND DISCUSSION

Chemistry

The Mannich base was integrated by utilizing the strategy depicted in before writing. Every one of the mixtures were acquired in acceptable amounts. The finishing of the response was affirmed by TLC **[26]**. The dissolving point of the blended mixtures was estimated by utilizing open slim cylinder technique. Every one of the combined mixtures gave palatable IR, ^{1}H-NMR and ^{13}C-NMR spectra were steady with the relegated structures. Blend method of the Mannich base and the metal complex was laid out in **Schemes 2 and 3**. The physicochemical information of the mixtures are introduced in **Table 1**.

Physical and spectral data of the synthesized compound

FTIR Spectra (Figure 2)

The ligand and its metal structures were penniless somewhere around IR spectroscopy. The results were used to investigate ionic and covalent bonds related with coordination blends. IR spectroscopy recommends that when metal molecule solidifies with the ligand to outline complex, its vibrational spectra expected to change. The striking features of IR scope of a ligand and structures are given in the **Table 2.**

^{1}H- NMR Spectra

The broad band appears at 3353cm^{-1} is consigned to stretching out of amide NH. The broad band in the area 2340cm^{-1} is a direct result of fragrant C-H broadening. The band appearing at 1975cm^{-1} is apportioned to (C-H) aliphatic expanding. The band appearing at 1446cm^{-1} is designated to C-N expanding. The band appearing at 761cm^{-1} is given out to C-Cl expanding **(Figure and Table 3)**.

The compound shows a singlet δ 2.2 which is because of the NH proton (1H). The compound shows products at δ 7.9-7.7ppm, are appointed to the fragrant protons. The Morpholine protons are in the scope of δ 3.4-3.3ppm. The singlet δ 4.9ppm which is expected to the aliphatic CH.

^{13}C-NMR spectra of [(4-Chloro-phenyl)-Morpholin-4-yl-methyl]Thiourea (Figure and Table 4)

The phenyl ring shows its range 132.8-129.2 (4C) is due to the presence of aromatic carbons. The compound shows at 85.9δ which is due to aliphatic carbon group. The compound shows at 54.4δ (4C) which is due Morpholine ring carbons.

Antimicrobial Studies

The results of the antimicrobial activity of the CMT and its complexes are presented in **Table 5**. From the table, it is observed that the metal complexes are more active than the free ligand and their standards. The increase in antimicrobial activity is due to faster diffusion of metal complexes as a whole through the combined activity of the metal and the ligand **[27]**.

Query Molecule

Docking study of Cu (II) complex of CMT with ESBL

Figure 5, 6 uncovers that the amino destructive form ups SER237 was locked in with participation's with compound Cu (II) the unique site of ESBL. The amino destructive stores SER237 was locked in with participation's with compound Cu (II) the unique site of ESBL. The length of hydrogen bond molded 2.125å. The IC50 assessments of this compound have 4.1 μm and low docking score (- 5.16). Docking score of the complexed inhibitor was viewed as - 5.16, with RMSD of 0.486. The sub-nuclear sections fuse characteristics and quality.items, yet also other creation substances in living cells **[28]**.

Docking study of Co (II) complex of CMT with ESBL

Figure 7, Uncovers that the amino destructive stores GLN192 and HIS192 were related with participation's with compound Co (II) the powerful site of ESBL. The amino destructive form ups GLN192 and HIS192 were related with collaboration's with compound Co (II) the powerful site of ESBL. From the table it was seen that the length of hydrogen bond outlined 2.111å and 2.146å. The IC50 assessments of this compound have 2.1(μm) and low docking score (- 5.6). The participation of attempted metal particles with regular ligands shows better antibacterial development diverged from free ligand a choice for new drugs with Beta Lactam conveying pathogenic organisms. Studies show that metal structures with copper particles invade even more successfully through the bacterial cell divider, due to denature protein with sulphydrile bundle **[29]** and crushing the bacterial cell divider.

Table 1: Physicochemical data

Compounds	Molecular Formula	Melting Point	Elemental Analysis – Percentage Calculated (Found)						Molar Conductance (Ω^{-1} cm^2 mol^{-1} in 10^{-3}
			C	H	N	O	S	Cl	
CMT	$C_{12}H_{16}ClN_3OS$	172˚C	50.43 (50.11)	5.64 (5.26)	14.70 (13.56)	5.60 (5.10)	11.22 (10.54)	12.41 (12.25)	--
Co(II)-CMT	$[C_{12}H_{16}ClN_3OSCo]Cl_2$	176 ˚C	49.41 (48.20)	5.52 (5.21)	13.52 (12.58)	5.82 (5.45)	11.15 (10.59)	12.35 (12.16)	192
Ni(II)-CMT	$[C_{12}H_{16}ClN_3OSNi]Cl_2$	179 ˚C	49.33 (47.89)	5.21 (5.10)	13.28 (11.56)	5.80 (5.65)	11.10 (11.5)	12.29 (12.16)	181
Cu(II)-CMT	$[C_{12}H_{16}ClN_3OSCu]Cl_2$	183 ˚C	49.25 (48.56)	5.28 (5.16)	12.28 (11.56)	5.89 (5.72)	10.9 (10.2)	12.15 (12.10)	184
Zn(II)-CMT	$[C_{12}H_{16}ClN_3OSZn]Cl_2$	186 ˚C	48.55 (47.26)	5.19 (5.12)	12.17 (11.56)	5.55 (5.46)	10.54 (10.21)	12.10 (12.2)	156

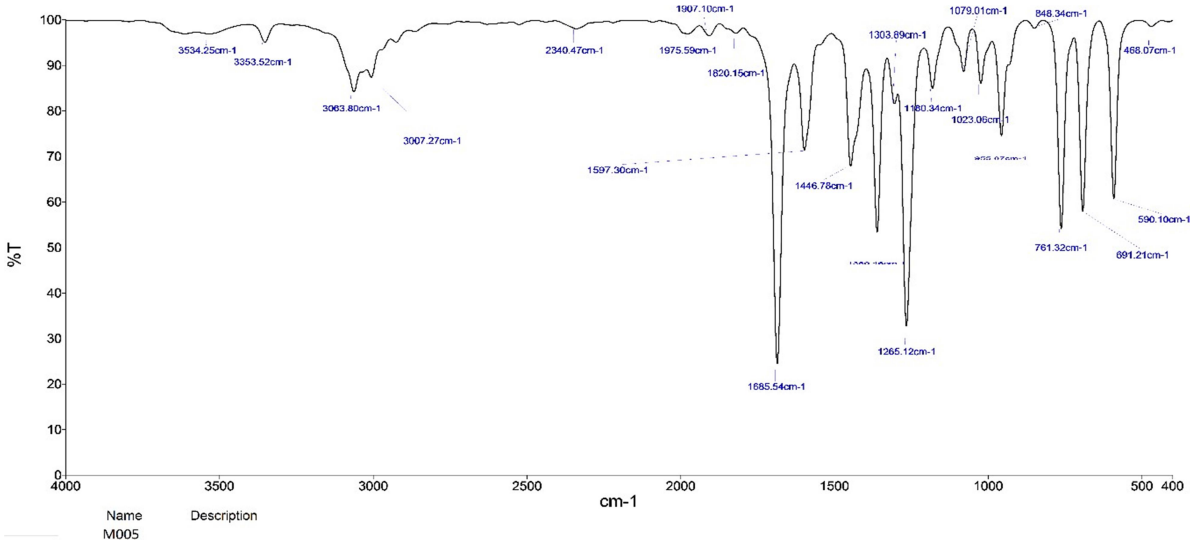


Figure 2: FTIR spectra of [(4-Chloro-phenyl)-Morpholin-4-yl-methyl]Thiourea

Table 2: IR SPECTRAL DATA OF (MORPHOLIN-4-YL-PHENYL-METHYL)-THIOUREA

FUNCTIONAL GROUP	FREQUENCY cm^{-1}
N - H Stretching	3353
Aromatic C-H stretching	2340
C-H aliphatic stretching	1975
C-N stretching	1446
C-Cl	761

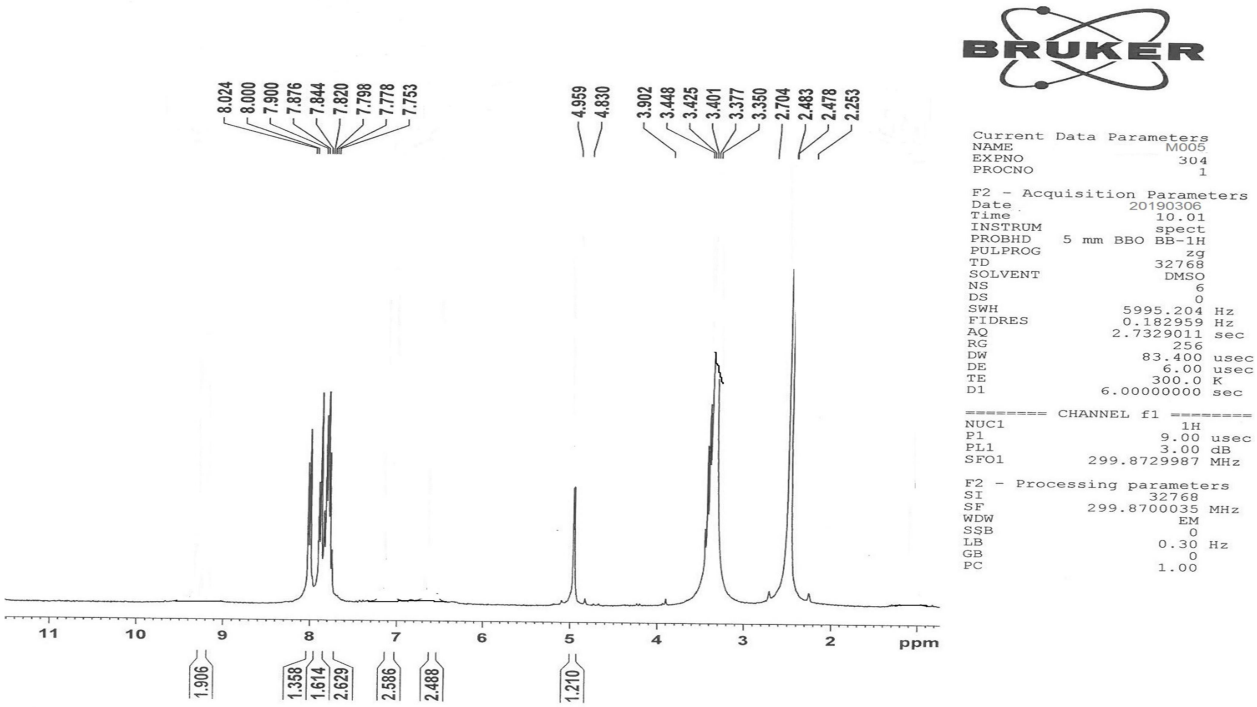


Figure 3: ^{1}H-NMR spectra of [(4-Chloro-phenyl)-Morpholin-4-yl-methyl]Thiourea

Table – 3 – ^{1}H-NMR SPECTRAL DATA OF (MORPHOLIN-4-YL-PHENYL-METHYL)-THIOUREA

GROUP ASSIGNMENT	CHEMICAL SHIFT (δ ppm)
NH Proton (1H,s)	2.2
Phenyl Protons (4H,m)	7.9-7.7
Aliphatic CH	4.9
Morpholine ring Protons (m)	3.4-3.3

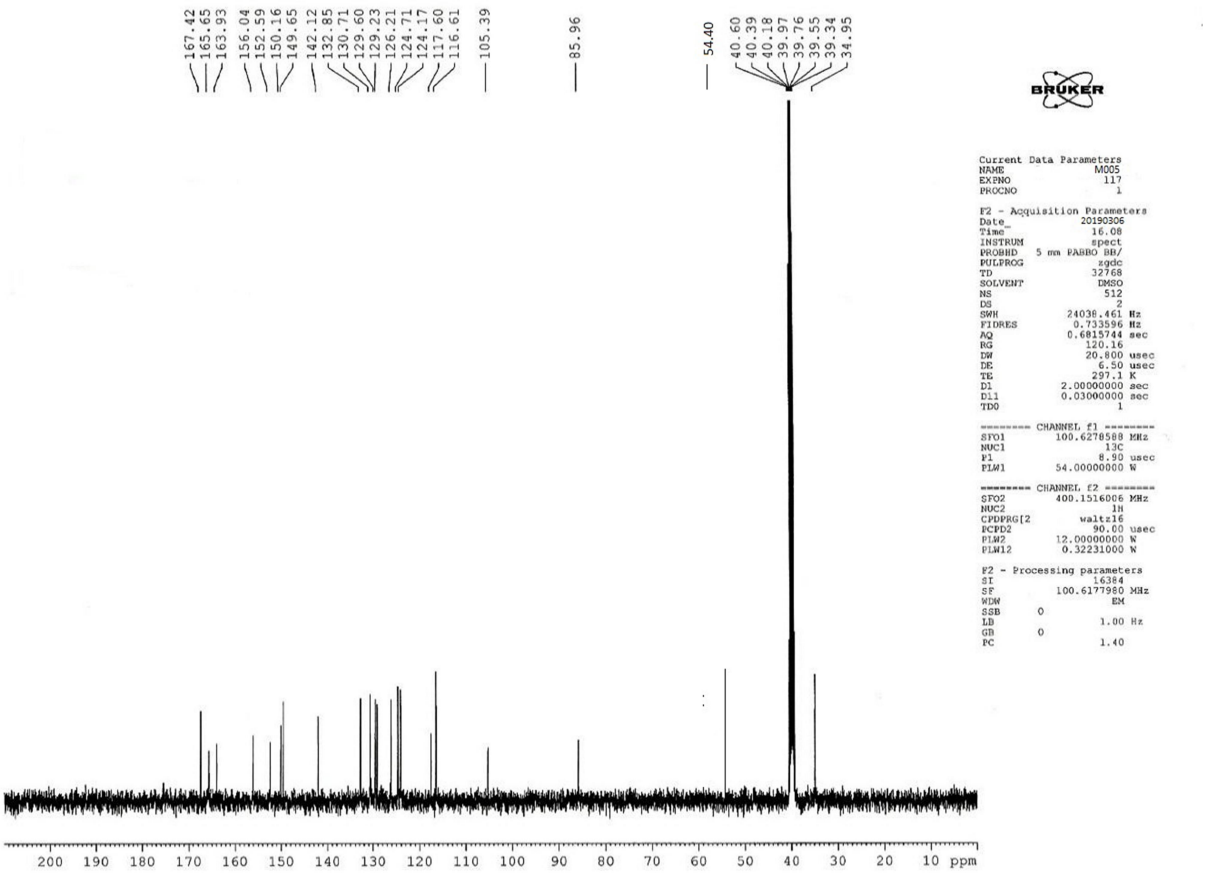


Figure 4: ^{13}C-NMR spectra of [(4-Chloro-phenyl)-Morpholin-4-yl-methyl]Thiourea

Table 4: ^{13}C-NMR SPECTRAL DATA OF (MORPHOLIN-4-YL-PHENYL-METHYL)-THIOUREA

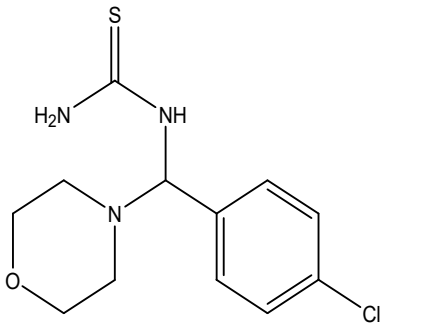
GROUP ASSIGNMENT	CHEMICAL SHIFT (δ ppm)
Phenyl Carbons	132.8-129.2
Aliphatic Carbon	85.9
Morpholine Ring Carbons	54.4

Table 5: Antimicrobial activity of the ligand and its metal complexes

Complex	Inhibition zone(mm)			
	Staphylococcus aureus	*Escherichia Coli*	*Pseudomonas aeruginosa*	*Bacillus subtilis*
CMT	11	12	12	10
Co-CMT	19	16	14	15
Ni-CMT	12	11	10	11
Cu-CMT	14	13	15	14
Zn-CMT	13	12	10	12
Ampicillin	11	11	11	10
DMSO	--	--	--	--
Metal Salt	13	15	14	11

Table 6: Atomic Docking data of metal ligand with Extended Spectrum Beta Lactamase

S. No.	Compound name	Docking Score	Inhibitory Concentration	H-bond interaction	Distance
1	Compound Cu	-5.16	4.1	SER237 N-H…O	2.125
2	Compound Co	-5.6	2.1	GLN192 N-H…O HIS197 N-H…O	2.146 2.111
3	Ciprofloxacin	-3.9	364	SER235 N-H…O SER130 N-H…O	1.958 1.793



[(4-Chloro-phenyl)-morpholin-4-yl-methyl]thiourea

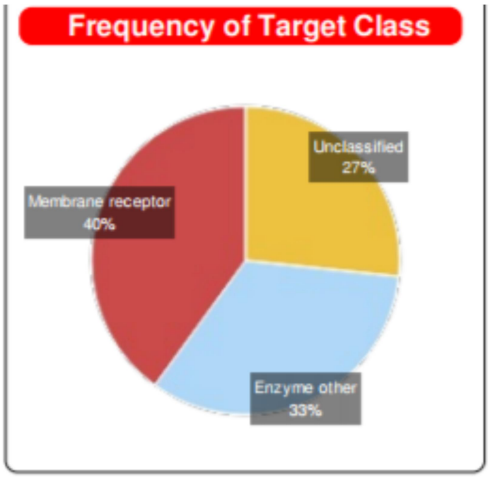


Figure 5: Target Site prediction against Homo Sapiens

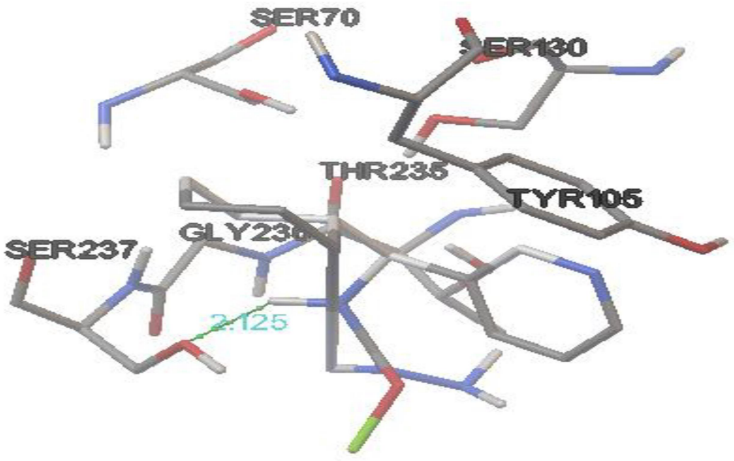


Figure 6: Extended Spectrum Beta Lactamase with CMT-Cu (II)

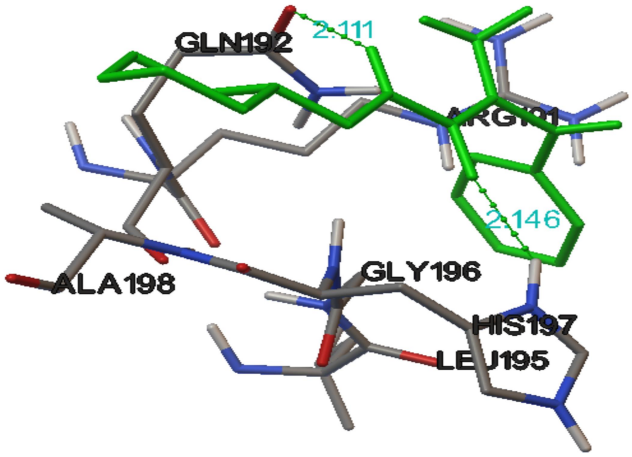


Figure 7: Extended Spectrum Beta Lactamase with CMT-Co (II)

CONCLUSION

The ligand, CMT and its metal buildings have been consolidated and portrayed by fundamental assessment, IR, ^{1}H-NMR, ^{13}C-NMR and brand name assessments. Antimicrobial screening of ligand and the metal buildings exhibited their superb activity. The zone of deterrent of metal edifices are also high than the free ligand. The healing assurance of the analyzed metal (II) edifices were found to show higher antimicrobial development than the ligand. Limiting energies of the ESBL protein-ligand (sedate) affiliations are basic to portray how fit the medicine connections to the goal macromolecule **[29]**. We have attempted to discover ESBL inhibitors by performing sub-nuclear docking and sub-nuclear components focuses on ESBL with Morpholine subordinate. Our docking re-order achieved a close by target protein structure, which supports our disclosures. The blends Co (II) and compound Cu (II) were significantly interfacing with ESBL **[30]**. That dynamically preliminary considers are relied upon to find the association among MIC and coordinated effort imperativeness.

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CONFLICT OF INTEREST

The authors don't have any conflict of interest.

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