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Article

Synthesis, Molecular Docking, Antibacterial, and Antifungal Studies of Co (II) and Cu (II) Complexes of N^1, N^2-Bis((1,3-Diphenyl-1*H*-pyrazol-4-yl) Methylene) Ethane-1,2-Diamine

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ABSTRACT

1,3-Diphenyl pyrazole terminated ligand N^1,N^2-Bis((1,3-diphenyl-1*H*-pyrazol-4-yl)methylene)ethane-1,2-diamine and its cobalt and copper complexes were synthesized. The compounds were characterized by elemental analysis, Ultraviolet–visible, Fourier transform infrared ^{1}HNMR, and ^{13}NMR spectroscopic techniques. The spectroscopic data support the structure of the compounds. The *in vitro* antimicrobial activities against some bacterial and some fungal strains of the synthesized compounds were analyzed and compared with the standard drugs. The result showed that the metal complexes are good candidates as antimicrobial agents than the ligand at the same concentration. The molecular docking studies were carried out using the online software Arguslab 4.0.1 and revealed that both the ligand and its complexes exhibiting a possible interaction with the proteins fibroblast growth factor receptors, c-Met, and vascular endothelial growth factor.

Key words: 1,3-Diphenyl pyrazole derivatives, Metal complexes, Antibacterial study, Antifungal activity, Molecular docking studies.

1. INTRODUCTION

Well-known five–membered heterocyclic compounds are oxadiazoline, pyrazoles, and pyrazoline. Nowadays, scientists are having more interest in pyrazole and its derivatives due to their broad spectrum of biological activities such as nitric oxide synthases inhibitor [1], monoamine oxidase inhibitor [2], antibacterial [3], and antiamoebic [4]. Among this derivatives, *N*-phenyl pyrazole derivative play an important role in antitumor screening [5] as well as potent antimicrobial activity [6]. Furthermore, several hydrazide-hydrazone derivatives also have been claimed to possess interesting biological activities such as antibacterial, antifungal, anticonvulsant, anti-inflammatory, antimalarial, analgesic, and anticancer activities [7]. From the literature, it was observed that a variety of transition metal complexes containing pyrazole and its derivatives are showing excellent biological activities. The increased activities were well studied and due to the different chemical nature of the nitrogen atom in the pyrazole moiety. Schiff bases having chelation with oxygen, nitrogen, etc., donors and their metal complexes have been used as drugs and reported to possess a wide variety of biological activities against bacteria, fungi, and a certain type of tumors and also, they have many biochemical, clinical, and pharmacological properties [8-11]. Imine or azomethine groups are present in various natural, naturally derived, and non-natural compounds. The imine group present in such compounds has been shown to be critical to their biological activities. Transition metal complexes with diamine also have a wide range of applications, mainly biological.

We expect that the presence of pyrazole ring together with diamine moiety and imino bond may influence the *in vitro* antibacterial and antifungal activities of the transition metal complexes. In continuation of our research work directed toward the development of simple and efficient synthesis of biologically active heterocyclic metal complexes, herein we report the synthesis pyrazole-4-carboxaldehyde by treating acetophenone with DMF/$POCl_3$ complex and functionalized by diamine giving corresponding azomethane derivative. Using this azomethine derivative Co and Cu complexes were synthesized and their antimicrobial activities investigated. Compounds were characterized using Fourier transform infrared (FT-IR) and nuclear magnetic resonance (NMR) data. Biological activities such as antimicrobial, anti-bacterial, and anti-fungal were assessed. Molecular docking studies were also carried out.

2. EXPERIMENTAL SECTION

2.1. Materials and Methods

All chemicals and reagents used in the synthesis were of analytical grade and procured from Sigma-Aldrich and Merck. All reagents were commercial products of analytical grade and were used directly without purification except where they were especially noted. Melting points were taken on a Yanaco MP-S3 microscopic melting point apparatus. The FT-IR spectra were recorded in KBr pellets on a Brucker Equinox-55 FT-IR apparatus. The ^{1}H- NMR spectra were recorded on an INOVA- 400 (using TMS as internal standard, DMSO-*d*6 as solvent).

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2.2. Synthesis of Ligand

2.2.1. 1,3-Diphenyl pyrazol-4-carboxaldehyde (A)

Acetophenone (0.1 mol) and phenyl hydrazine (0.1 mol) were heated on a water bath to reflux for 1 h. The hot mixture was dissolved in 40 ml of rectified spirit and shaken well to induce crystallization. The mixture was cooled in ice, filtered, and washed with 12 ml of rectified spirit. The residue was dried in a vacuum desiccator and recrystallized.

Dimethyl formamide (0.36 mol) and phosphoryl chloride (0.36 mol) were cooled separately at 0°C. The Vilsmeier - Haack reagent was prepared by mixing these two cold solutions. Acetophenone phenyl hydrazone (0.3 mol) was dissolved in 20 ml dimethyl formamide and added drop wise to Vilsmeier - Haack reagent with continuous shaking warmed at room temperature and then refluxed for 6 h. After cooling at room temperature, the mixture was basified with a cold saturated potassium carbonate solution. The precipitate was filtered, strongly washed with water, recrystallized, and dried in vacuum. Thin-layer chromatography (TLC) analysis was carried out to check the purity of the compound (Figure 1).

Color: Pale yellow, yield: 73%, melting point 115°C. FT- IR $cm^{-1:}$ 1670 (C=O str), 2839 (C-H str aldehyde), 1525 (ArC=C str), 1057 (ArCH deformation), 1600 (C=Nstr), 1298 (C-N str), 3329 (sharp small peak,aldehydic CH) and 3126 (CH stretching of N=CH); ^{1}HNMR δ: 10.00 (s, 1H of CHO), 9.33(s, 1H, H5 of pyrazole), 7.4–8.01 (all other H of the molecule): ^{13}CNMR: 109 ppm −142 ppm (all aromatic carbons).

2.2.2. N^1, N^2-Bis((1,3-diphenyl-1H-pyrazol-4-yl) methylene) ethane-1,2-diamine (BDMED)

1, 3-Diphenyl pyrazole - 4 - carboxaldehyde (0.01 mol) was dissolved in boiling ethanol and then 0.2 ml of glacial acetic acid and ethylene diamine (0.005 mol) were added and heated to reflux for 7.0 h. After cooling N^1, N^2-Bis((1,3-diphenyl-1*H*-pyrazol-4-yl) methylene) ethane-1,2-diamine was obtained, filtered, dried, and recrystallized (Figure 2).

Color: Yellow, yield: 53%, melting point 186°C. FT-IR $cm^{-1:}$ 3046 (Ar-CH stretching), 1515 (ArC=C stretching), 1660 (C=N), 1285 (C-N), 1369 (Ph-N stretching), 2827 (CH stretching of N=CH), 1211 (N-CH_2 stretching), ^{1}HNMR δ:10.05 (s, 2H of H5 of pyrazole), 9.33 (s,2H, H of HC=N), 7.93–8.03 (m, 10H, C-Ph group), 7.45–7.61 (m, 10H of N-Ph group), 3.35 (s, 4H, N-CH_2CH_2-N) ^{13}CNMR: 109 ppm–142 ppm (all aromatic carbons), 51.7 (aliphatic carbons).Cal. for C34H28N6:C,78.44, H, 5.42, N,16.14, Found: C, 77.03; H,5.42; N,17.03.

2.3. Synthesis of Metal Complexes

2.3.1. Synthesis of Cu(BDMED)Cl_2

The ligand BDMED (1mmol) was dissolved in a boiling ethanol - dichloroethane mixture. A hot solution of $CuCl_2.2H_2O$ (1 mmol) in ethanol was added drop wise to the above boiling solution with constant stirring and refluxed the whole mixture for 5 h with continuous stirring using a magnetic stirrer. It is then concentrated to half the volume and kept at room temperature. Then greenish microcrystals were separated out which was filtered, washed with ethanol followed by ether, and dried in a desiccator (Figure 3).

Color: Dark green, yield 61%, melting point >300°C, ^{1}HNMR δ: 10.35 (s, 4H of H5 of pyrazole), 9.42 (s,4H, H of HC=N), 7.85–8.16 (m, 20H, C-Ph group), 7.62–7.85 (m, 20H of N-Ph group), 4.13 (s, 8H, N-CH_2CH_2-N) ^{13}CNMR: 109 ppm–142 ppm (all aromatic carbons), 48.17 (aliphatic carbons).

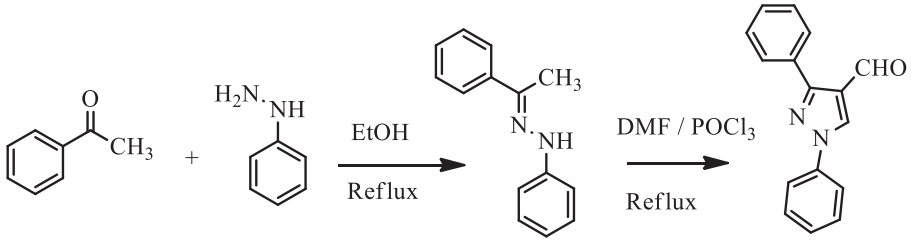

Figure 1: Synthesis of 1,3-diphenyl pyrazol-4-carboxaldehyde (A).

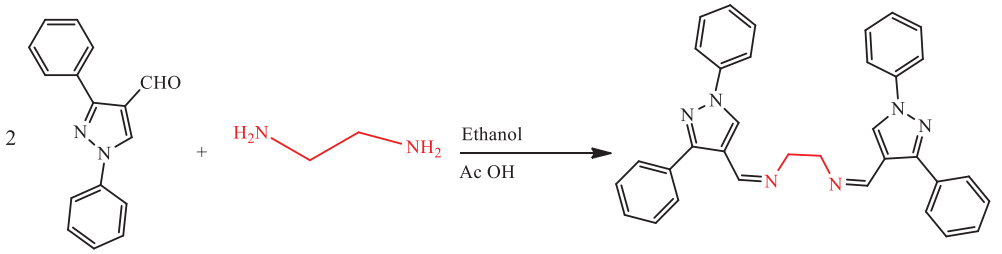

Figure 2: Synthesis of BDMED.

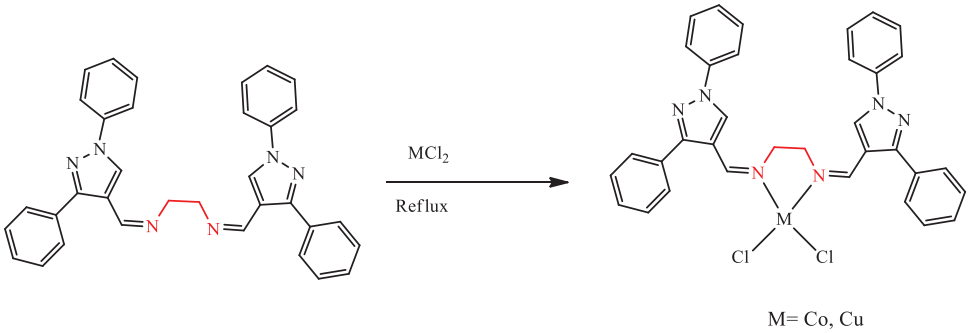

Figure 3: Synthesis of $M(BDMED)_2Cl_2$.

2.3.2. Synthesis of Co(BDMED)Cl_2

The ligand BDMED (1 mmol) was dissolved in ethanol: dichloroethane mixture by boiling. A hot solution of $CoCl_2.6H_2O$ (1 mmol) in ethanol was prepared. This metal salt solution was added drop wise to the boiling solution of the ligand with constant stirring and refluxed the whole mixture for 5 h with continuous stirring using a magnetic stirrer. The completion of the reaction was monitored by the TLC experiment. It is then concentrated to half the volume and kept at room temperature for 2 days. Then a purple colored precipitate was formed, filtered, washed with ethanol followed by ether, and dried in a desiccator. It was then recrystallized from ethyl acetate: dichlorobenzene (2:1) mixture, yellowish-green colored needle like crystals are obtained (Figure 3).

Color: Yellowish green, yield 58%, melting point >300°C, ^{1}HNMR δ: 10.21 (s, 4H of H5 of pyrazole), 9.38 (s,4H, H of HC=N), 7.81–8.09 (m, 20H, C-Ph group), 7.58–7.76 (m, 20H of N-Ph group), 4.25 (s, 8H, N-CH_2CH_2-N) ^{13}CNMR: 109 ppm–142 ppm (all aromatic carbons), 47.17 (aliphatic carbons).

2.4. Biological Studies

The synthesized metal complexes and its ligand have been screened for biological properties by adopting standard protocols available in the literature [12]. Antibacterial activity (*in vitro*) of the synthesized compounds was studied against the representative panel of bacteria such as *Escherichia coli* MTCC443, *Pseudomonas aeruginosa* MTCC-1688 as Gram-negative bacteria, and *Staphylococcus aureus* MTCC-96 and *Streptococcus pyogenes* MTCC-442 as Gram-positive bacteria, using ciprofloxacin as the standard antibacterial drug. Antifungal activity was screened against two fungal species, *Candida albicans* MTCC-227 and *Aspergillus niger* MTCC-282, and fluconazole was used as the standard antifungal drug. The minimal inhibitory concentration (MIC) of all the synthesized compounds was determined by the broth microdilution method according to National Committee for Clinical Laboratory Standards (NCCLS) [13]. All the synthesized compounds were screened for antibacterial and antifungal activities against bacteria and fungi used in the present protocol and the results are tabulated in Table 1.

2.5. Molecular Docking Studies

The binding interaction of all the synthesized compounds with three different proteins, vascular endothelial growth factor (VEGF), fibroblast growth factor receptors (FGFR), and c-Met were studied. We chose the Arguslab 4.0.1 version software for docking to prepare input files. The molecular docking study was performed by considering the protein to be rigid and the docking molecule as flexible where all rotatable bonds of the compound were considered. Before running the docking all the miscellaneous residues, water molecules, and heterocyclic compounds present in the protein were removed from its crystallographic structure to activate the binding site only for the synthesized compounds and subsequently adding hydrogen atoms to the protein. The structure of the synthesized compound was drawn and optimized using the above software. The calculation box was generated and centered on the binding site residues with 60 × 60 × 60 grid points in XYZ direction. The docking calculations were run with standard precision with default values. In general, the docking setup was validated by the compound having protein binding with cells. In literature similar works on quinazoline derivatives with thienopyrimidines used EGFR and VEGFR receptors and the co-crystallized ligand Eriotinib and Tivozanib [14] has been recently reported. The base structure selected from the protein data bank with identified proteins of the present study utilized to determine the compound interaction with active site in the protein.

3. RESULTS AND DISCUSSION

1,3-Diphenyl pyrazole carboxaldehyde was prepared by the Vilsmeier – Haack reaction which on condensation with ethylene diamine yielded BDMED. The reaction of the ligand BDMED with $CuCl_2.2H_2O$ and $CoCl_2.6H_2O$ (1:1 ratio) in ethanol and dichloroethane afford a green complex of Cu(BDMED)Cl_2 and yellowish green Co(BDMED)Cl_2, respectively, in good yields which were characterized by different spectroscopic techniques such as FT-IR, ^{1}HNMR, ^{13}CNMR, and elemental analysis. This was according to the percentage composition of C, H, and N obtained from the elemental analysis, which showed good agreement with the experimental data (Table 2).

3.1. FT-IR Spectroscopy

The IR spectra of the complexes showed several strong bands in the range of 1211–3543 cm^{-1} indicated ArC-H, ArC=C, C=N, Ph-N, N=CH, and N-CH_2 stretching. For Cu complex Cu-N stretching frequency was found at 690 cm^{-1} and for Co complex, it was at 687 cm^{-1}. In addition, υ (N-N) stretching band was observed with medium intensity in the region of 1062–1089. On complexation a strong band at 1686 of BDMED was due to the C=N stretching shifted by 7–21 cm^{-1}. The shifting was the direct evidence for the formation of a complex of azomethane N with metal, M-N [15]. The peaks of the complexes are shifted to higher or lower frequencies indicating the participating of azomethine N in coordination, as shown in Table 3.

3.2. ^{1}H and ^{13}C-NMR Spectroscopies

^{1}H NMR data of the ligand are recorded in $CDCl_3$. The aromatic protons are observed in the region of 8.03–7.45 ppm. The proton of the H of HC=N was observed at 9.33 ppm as a singlet. Within their respective complexes, the above proton is shifted by 0.27–0.99 up field [16]. In ^{13}CNMR, the HC=N was signal shifted to downfield in complexes due to the various electron densities, indicating the coordination of lone pairs on nitrogen to the metal. Other carbons in these compounds resonated almost at the same frequency as those in that of the ligand.

Table 1: Antimicrobial screening data for the ligand and its complex in terms of diameter of zone of inhibition (mm) 1000 µg/ml.

Compound	*Staphylococcus aureus*	*Escherichia coli*	*Pseudomonas aeruginosa*	*Streptococcus pyogenes*	*Aspergillus niger*	*Candida albicans*
BDMED	18	9	6	10	5	9
Co(BDMED)$_2$	33	21	23	28	14	22
Cu(BDMED)$_2$	21	29	23	19	19	32
Ciprofloxacin	36	33	26	31	-	-
Fluconazole		-	-	-	22	37

([a] 25–40 mm significantly active, 12–25 mm moderately active, <12 less active)

Table 2: Analytical data and physical properties of the compound.

Compound	MP (°C)	Color	Yield (%)	Exp (Calc)%		
				C	H	N
BDMED	127	Yellow	53	78.44 (77.03)	5.42 (5.42)	16.14 (17.03)
Co(BDMED)2Cl2	>300	Yellowish green	58	69.74 (69.36)	4.82 (4.82)	14.35 (13.93)
Cu(BDMED)2Cl2	>300	Dark green	61	69.47 (68.10)	4.80 (4.80)	14.30 (14.01)

Table 3: Spectral data of the ligand and its metal complexes (cm^{-1}).

Compound	ArC-H	ArC=C	C=N	Ph-N	C-H of N=CH	C-N	N-CH_2	M-N	M-Cl
BDMED	3046	1515	1686	1369	2827	1285	1211		
$Co(BDMED)_2$	3543	1600	1667	1363	2437		1198	690	330
$Cu(BDMED)_2$	3334	1598	1681	1398	2444		1050	687	310

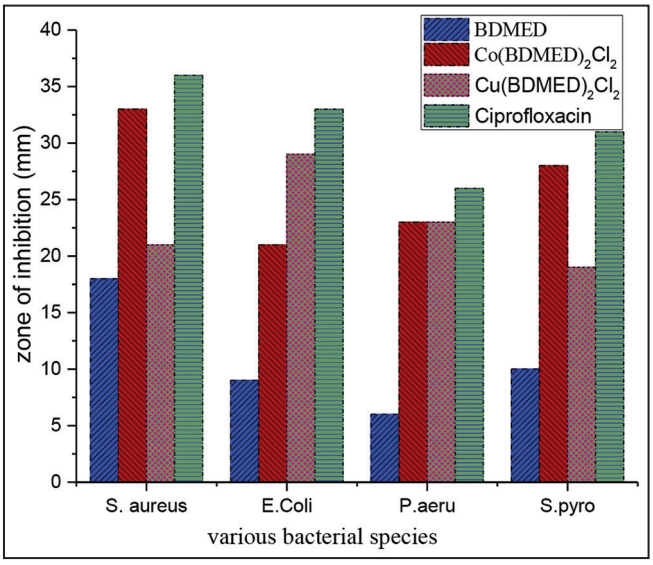

Figure 4: Bar chart showing antibacterial activities of the compounds in terms of diameter of zone of inhibition.

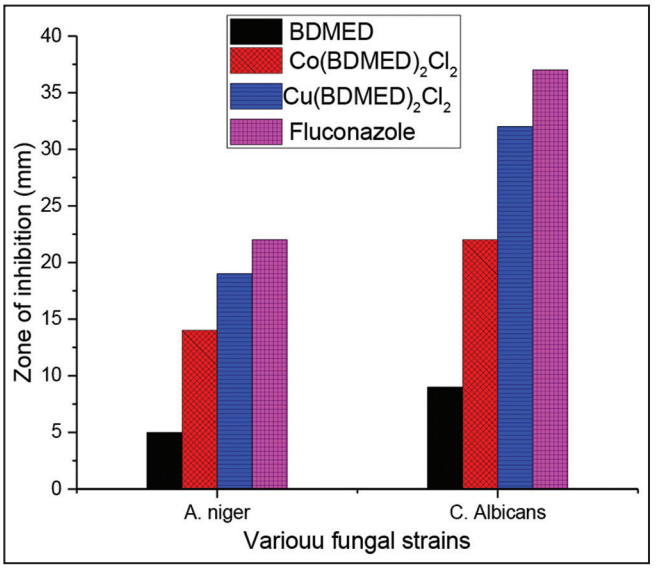

Figure 5: Bar chart showing antifungal activities of the compounds in terms of diameter of zone of inhibition.

3.3. Biological Studies

3.3.1. Antibacterial studies

It was observed from the literature imine base of 1 µg/1 µl and was highly active against both Gram-positive and Gram-negative bacteria. The stock solution was prepared by dissolving the compounds in DMSO. The MIC was determined. A suspension of the tested microorganism (0.1 ml) was spread over the nutrient agar taken in a petri plate. Antibacterial activity (*in vitro*) of the synthesized compounds was studied against the representative panel of bacteria such as *E. coli*, *P. aeruginosa*, *S. aureus,* and *S. pyogenes* using ciprofloxacin as the standard antibacterial drug. The antimicrobial screening data (Table 1) showed that the ligand exhibited antibacterial properties. It was observed that the metal chelates had higher inhibitory effects than that of the free ligands. The antibacterial activities could be explained by Overton and Tweedy's chelation theory [17,18]. The lipid membrane that surrounds the cell of bacteria allows the passage of only lipid-soluble materials. According to Overton's concept of cell permeability, the important factor that controls antibacterial activity is the liposolubility of the complex molecule. On chelation, due to the overlap of the ligand orbital and partial sharing of the metal ion's positive charge, the polarity of the metal ion will be reduced to a greater extent [19]. It also increases the delocalization of π-electrons across the entire chelate ring and increases the lipophilicity of the complexes. Hence, increased lipophilicity enhances the penetration of the complexes into the lipid membrane and blocks the metal-binding sites in the enzymes of microorganisms [17,18]. Metal complexes act as potent bactericidal agents, thus killing more of the bacteria than the ligands due to the chelation of the ligands with metal. The ligand can penetrate the cell wall of the bacteria by coordination of metal ion through nitrogen donor atom which leads to the damage of outer cell membrane of bacteria causing its death and consequently decrease the bacterial growth [19]. In our case, $Co(BDMED)Cl_2$ was found to be more active against *S. aureus* and *S. pyogenes* than $Cu(BDMED)Cl_2$, activity against *E. Coli* was more for copper complex than the cobalt complex and both were equally active against *P. aeruginosa*.

3.3.2. Antifungal studies

The antifungal activity data indicate that complexes show an appreciable activity against *C. albicans* and *A. niger* and Fluconazole was taken as the standard [20]. Both the metal complexes exhibited almost similar activity on the fungi. The ligand imine base, however, has exhibited lower activity than its metal complexes (Table 1).

3.4. Molecular Docking Studies

The molecular docking study was carried out to understand potency of the structure of the compound and its interaction with proteins. Here, we used three different proteins; tertiary structures of VEGF2 (crystal structure of VEGFR2 kinase domain in complex with a pyrrazolone inhibitor PDB Id: 3U6J), FGFR1 (crystal structure of activated receptor tyrosine kinase in complex with substrates PDB Id: 3GQI), and c-Met (structure of the kinase domain of c-Met bound to XL880 (GSK1363089) PDB Id: 3LQ8) were downloaded from PDB database. Using AutoDock, active site-based docking was adopted; the compounds were made to bind inside the active site of VEGF2 kinase, FGFR1 kinase, and c-Met proteins kinase. These approaches were done to check the possibility of binding of compounds in the whole protein and specifically inside the protein binding site. The selection of the binding site was based on the co-crystal ligand molecule in the target protein structure [21-23]. During docking, many conformations were generated for each compound. From these, the conformation having the lowest binding energy and better interaction with active site residues was considered as the active conformation for each compound. H-bond interaction, binding energy, and orientation of the docked compound within the active site were also analyzed.

It is observed that the ligand and its metal complexes showing better binding energy in the range of −11–−13.02 kcal/mol for VEGF2, −9–−11 kcal/mol for FGFR1, and −8–−14 kcal/mol for c-Met. The ligand BEMED has shown the highest docking energy >−13 kcal/mol in c-Met protein. Figures 6-8 show the binding of the compounds inside the binding cavity of VEGF2, FGFR1, and c-Met, respectively. It is observed that ligand and its copper and cobalt metal complexes formed H-bond interaction with the active residues. In compound BDMED, 514 LYS of FGFR1 formed H-bond with N of N-phenyl residue, 868 LYS of VEGF2 formed H bond with VEGF2, and in c -Met protein, there was no H bond. The cobalt complex forming four different H bonding with the protein FGFR1 such as 633 GLU with N-phenyl, 632 THR with imino N, 542 LYS with N-phenyl, and 632 THR with N-phenyl. In the protein c-Met it forms eight H bonds such as 1221 ALA with imino N, 1210 CYS with imino N, 1202 HIS with N of the pyrazole ring, 1202 HIS with N-phenyl, 1210 CYS with N-phenyl, 1210 CYS with imino N, 1209 ASN with N-phenyl, and 1208 ARG with N-phenyl. With the protein VEGF2 it formed three different H bonds such as 1045 CYS with N-phenyl, 1045 CYS with imino N, and 1030 ALA with N-phenyl. Copper complex forming three different H bonds with the protein FGFR1as 1045 CYS with N-phenyl, 1045 CYS with N of the pyrazole ring, and 1030 ALA with N-phenyl; with the protein c-met it formed seven H bonds as 1202 HIS with N-phenyl, 1202 HIS with N-phenyl, 1221 ALA with imino N, 1210 CYS with imino N, 1210 CYS with imino N, 1210 CYS with N-phenyl, 1165 LEU with Nphenyl,

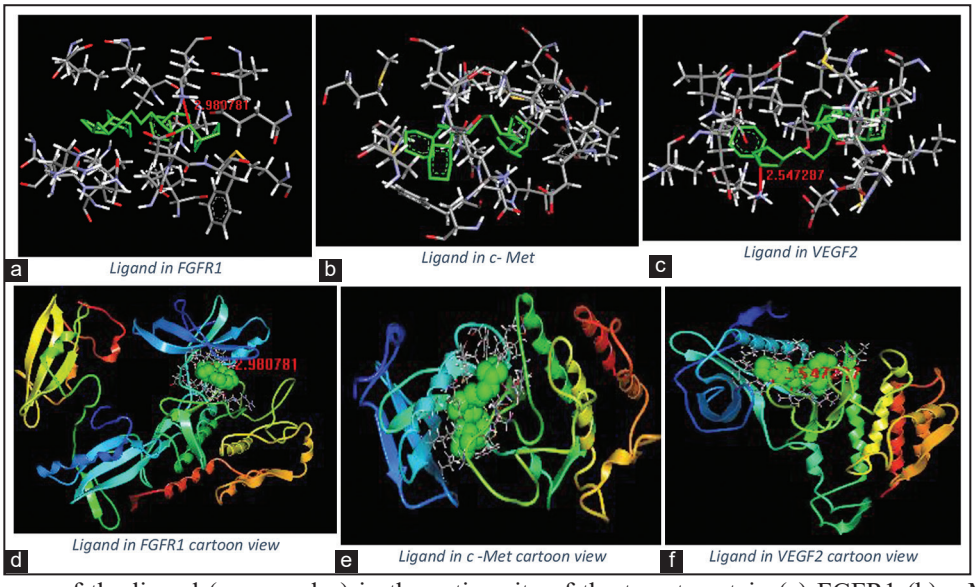

Figure 6: Binding pose of the ligand (green color) in the active site of the target protein (a) FGFR1 (b) c-Met, (c) VEGF2 (H bonding showed in red color) and in (d-f) protein as cartoon ribbon form. (a) Ligand in FGFR1, (b). ligand in c- Met, (c) ligand in VEGF2, (d) ligand in FGFR1 cartoon view, (e) ligand in c -Met cartoon view, (f) ligand in VEGF2 cartoon view.

Table 4: Binding energy of the compound and H-bond length calculated using Argus lab 4.0.1.

Compound	Best ligand pose energy (Kcal/mol)			H-bond length (A°)		
	FGFR1	c-Met	VEGF2	FGFR1	c-Met	VEGF2
BDMED	−10.76	−13.35	−11.59	2.98	-	2.54
$Co(BDMED)_2Cl_2$	−9.45	−8.87	−12.76	1.60, 2.28, 2.46, 2.67	1.01, 1.62, 1.86, 1.93, 2.33, 2.57, 2.85, 2.95	1.65, 2.06, 2.52
$Cu(BDMED)_2Cl_2$	−9.57	−9.04	−13.02	1.76, 2.45, 2.67	1.36, 1.42, 1.81, 1.98, 2.38, 2.40, 2.60	1.09, 2.95

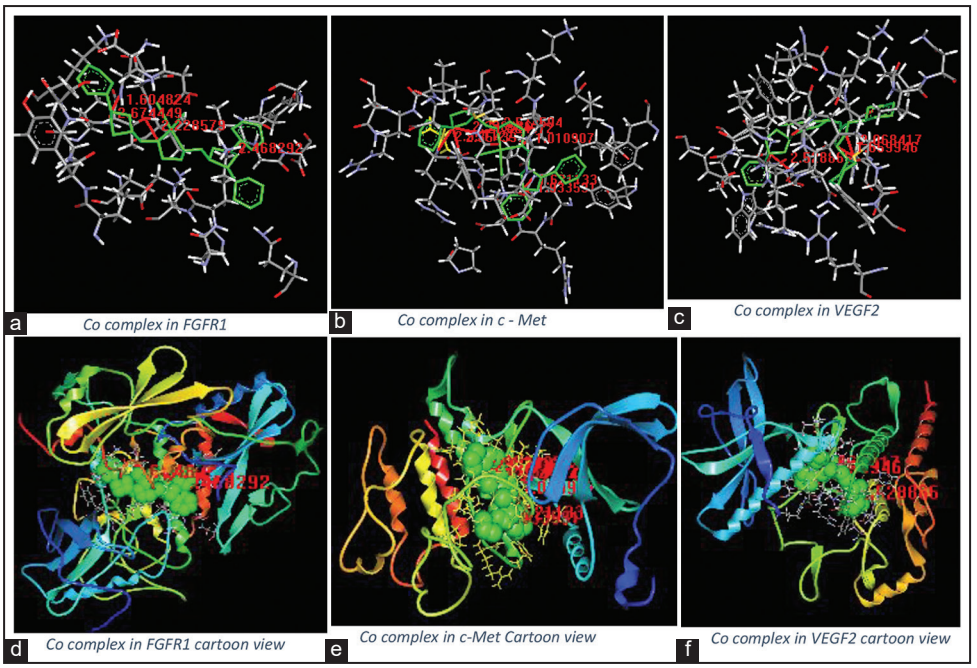

Figure 7: Binding pose of the Cobalt complex (green color) in the active site of the target protein (a) FGFR1 (b) c-Met, (c) VEGF2 (H bonding showed in red color) and in (d-f) protein as cartoon ribbon form. (a) Co complex in FGFR1, (b) Co complex in c – Met, (c) Co complex in VEGF2, (d) Co complex in FGFR1 cartoon view, (e) Co complex in c-Met Cartoon view, (f). Co complex in VEGF2 cartoon view.

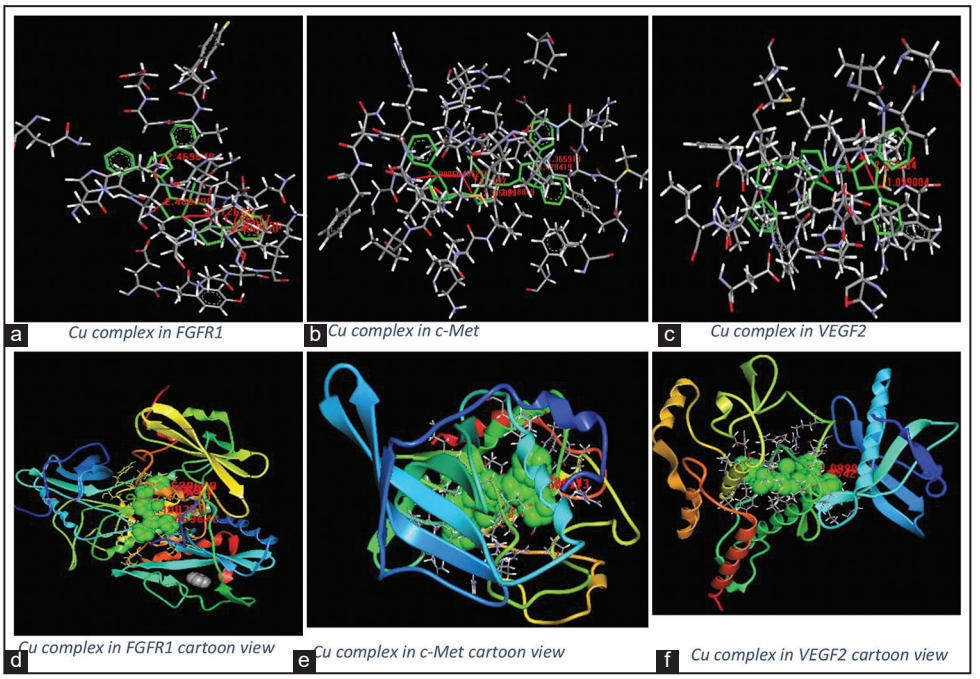

Figure 8: Binding pose of the copper complex (green color) in the active site of the target protein (a) FGFR1 (b) c-Met, (c) VEGF2 (H bonding showed in red color), and in (d-f) protein as cartoon ribbon form. (a) Cu complex in FGFR1, (b) Cu complex in c-Me, (c) Cu complex in VEGF2, (d) Cu complex in FGFR1 cartoon view, (e) Cu complex in c-Met cartoon view, (f) Cu complex in VEGF2 cartoon view.

and with the protein VEGF2, the formed two H bonds were 1045 CYS with N-phenyl (both end). H bond length are shown in Table 4.

4. CONCLUSION

The title compounds N^1,N^2-Bis((1,3-diphenyl-1*H*-pyrazol -4-yl) methylene)ethane-1,2-diamine and its (1:1) complexes containing copper and cobalt core have been synthesized and thoroughly characterized with the aim to design antimicrobial agents. The metal complexes were characterized by Ultraviolet–visible, IR, NMR, and elemental analysis. The antimicrobial activity results show that the metal complexes are more active than its ligand N^1, N^2-bis((1,3-diphenyl-1*H*-pyrazol-4-yl) methylene) ethane-1,2-diamine. This indicated that the presence of chelation dominantly affects the overall biological activities of the compounds. Molecular docking studies revealed that

the ligand and its metal compounds interact with the active binding site of the proteins FGFR, c-Met, and VEGF and minimum ligand pose binding energy of all the synthesized compounds also tabulated.

5. ACKNOWLEDGMENT

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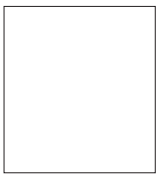
6. CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

7. REFERENCES

1. M. Abid, A. R. Bhat, F. Athar, A. Azam, (2009) Synthesis, spectral studies and antiamoebic activity of new 1-N-substituted thiocarbamoyl-3-phenyl-2-pyrazolines, ***European Journal of Medicinal Chemistry***, **44:** 417-425.
2. P. Arora, V. Arora, H. S. Lamba, D. Wadhwa, (2012) Importance of heterocyclic chemistry: A Review. ***International Journal of Pharmaceutical Sciences and Research***, **3:** 2947-2954.
3. F. Azam, S. Singh, S, L. Khokhra, O. Prakash, (2007) Synthesis of Schiff bases of naphtha[1,2-d]thiazol-2-amine and metal complexes of 2-(2'-hydroxy) benzylideneaminonaphthothiazole as potential antimicrobial agents. ***Journal of Zhejiang University Science B***, **8:** 446-452.
4. A. Balbi, M. Anzaldi, M. Mazzei, M. Miele, M. Bertolotto, L. Ottonello, F. Dallegri, (2006) Synthesis and biological evaluation of novel heterocyclic ionone-like derivatives as anti-inflammatory agents. ***Bioorganic and Medicinal Chemistry***, **14:** 5152-5160.
5. M. D. Carrión, L. C. L. Cara, M. E. Camacho, V. Tapias, G. Escames, D. Acuña-Castroviejo, A. Espinosa, M. A. Gallo, A. Entrena, (2008) Pyrazoles and pyrazolines as neural and inducible nitric oxide synthase (nNOS and iNOS) potential inhibitors (III), ***European Journal of Medicinal Chemistry***, **43:** 2579-2591.
6. S. Dadiboyena, E. J. Valente, A. T. Hamme, (2009) A novel synthesis of 1,3,5-trisubstituted pyrazoles through a spiro-pyrazoline intermediate via a tandem 1,3-dipolar cycloaddition/elimination, ***Tetrahedron Letters***, **50:** 291-294.
7. M. M. de Oliveira Cabral, (2007) Biological activity of yangambin on the postembryonic development of *Chrysomya megacephala* (*Diptera*: *Calliphoridae*), ***Journal of Medical Entomology***, **44:** 249-255.
8. H. Beraldo, D. Gambino, (2004) The Wide pharmacological versatility of semi-carbazones, thiosemicarbazones and their metal complexes. Mini-reviews, ***Medicinal Chemistry***, **4:** 31-39.
9. P. K. Panchal, P. B. Pansuriya, M. N. Patel, (2008) *In-vitro* biological evaluation of some ONS and NS Donor Schiff' s bases and their metal complexes, ***Journal of Enzyme Inhibition Medicinal Chemistry***, **21:** 453-458.
10. D. X. West, C. S. Carlson, C. P. Galloway, (1990) The chemical and antifungal properties of copper (II) comlplexes of 2-acetylpyrazineNmethyl, N-dimethyl and 3-hexamethyleneiminylthiosemicarbazone, ***Transition Metal Chemistry***, **15:** 91.
11. H. A. Tang, L. F. Wang, R. D. Yang, (2003) Synthesis characterization and antibacterial activities of manganese (II), cobalt (II), nickel (II), copper (II) and zinc (II) complexes with soluble vitamin K_3 thiosemicarbazone, ***Transition Metal chemistry***, **88:** 395-398.
12. R. Sheikh, (2014) Microwave assisted synthesis, spectral and antifungal studies of 2-phenyl-N,N'-bis(pyridin-4-ylcarbonyl) butanediamide ligand and its metal complexes, ***The Scientific World Journal***, **19:** 40461.
13. C. F. Carson, K. A. Hammer, T. V. Riley, (1995) Broth micro-dilution method for determining the susceptibility of *Escherichia coli* and *Staphylococcus aureus* to the essential oil of *Melaleuca alternifolia* (tea tree oil), ***Microbios***, **82:** 181-185.
14. A. E. S. Mghwary, E. M. Gedawy, A. M. Kamal, S. M. Abuel-Maaty, (2019) Novel thienopyrimidine derivatives as dual EGFR and VEGFR-2 inhibitors: design, synthesis, anticancer activity and effect on cell cycle profile, ***Journal of Enzyme Inhibition Medicinal Chemistry***, **34:** 838.
15. Shilpi Gupta, M. K. Maheshwar, (2013) Synthesis, Spectral and Structural Studies of Some Copper(II) Complexes of N,N'-Bis(2-methyl-N-methylbenzimidazolyl)hexanediamide ligand, ***Chemical Science Transaction***, **2:** 927-935.
16. K. K. Narang, V. P. Singh, (1993) Synthesis and characterization of cobalt (II), nickel (II), copper (II) and Zinc (II) complexes with acetylacetone bis-isonicotinoylhydrazone, ***Transition Metal chemistry***, **18:** 287-290.
17. B. G. Tweedy, (1964) Plant extracts with metal ions as potential antimicrobial agents, ***Phytopathology***, **55:** 910-914.
18. D. Sakthilatha, R. Rajavel, (2013) synthesis, characterization and biological studies of homobimetallic Schiff base Cu(II) and Ni(II) complexes, ***Chemistry Science Transaction***, **2:** 711-726.
19. A. Rattan, (2000) ***Antimicrobials in Laboratory Medicine***, New Delhi: BI Churchill Livingstone Pvt., Ltd., p85.
20. H. Von Pechmann, C. Duisberg, (1883) Zeolite catalysed synthesis of coumarin derivatives, ***Chem. Berg,*** **16:** 2119.
21. G. M. Morris, R. Huey, W. Lindstrom, M. F. Sanner, R. K. Belew, D. S. Goodsell, A. J. Olson, (2009) Autodock4 and autodocktools4: Automated docking with selective receptor flexibility, ***Journal of Computational Chemistry, 30:*** 2785.
22. R. A. Friesner, J. L. Banks, R. B. Murphy, T. A. Halgren, J. J. Klicic, D.T. Mainz, M. P. Repasky, E. H. Knoll, M. Shelley, J. K. Perry, D. E. Shaw, P. Francis, P. S. Shenkin, (2004) Glide: A new approach for rapid, accurate docking and scoring. 1. method and assessment of docking accuracy, ***Journal of Medicinal Chemistry, 47:*** 1739.
23. T. A. Halgren, R. B. Murphy, R. A. Friesner, H. S. Beard, L. L. Frye, W. T. Pollard, J. L. Banks, (2004) Glide: A new approach for rapid, accurate docking and scoring. 2. enrichment factors in database screening, ***Journal of Medicinal Chemistry, 47:*** 1750.

***Bibliographical Sketch**



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